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METHODS OF TREATING BRAIN INJURY

Abstract

The present invention generally relates to compositions and methods useful for treating a brain injury such as stroke, optic neuropathy, traumatic brain injury, and cerebral palsy. The methods include administering HMCs obtained by in vitro differentiation of pluripotent stem cells and/or extracellular vesicles (EVs) derived from such HMCs (HMC-EVs) into a subject.

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Background/Summary

RELATED APPLICATION [0001] This application is a national phase filing under 35 C.F.R. § 371 of and claims priority to PCT Patent Application No. PCT/US2023/027882, filed on Jul. 17, 2023, which claims the benefit of priority to U.S. Provisional Application No. 63/390,044, filed on Jul. 18, 2022, the entire contents of which are incorporated herein by reference.

FIELD OF THE DISCLOSURE
[0002] The instant presently disclosed subject matter relates to methods of treating a brain injury using mesenchymal stem cells and/or extracellular vesicles secreted from the mesenchymal stem cells.
BACKGROUND OF THE DISCLOSURE
[0003] Brain injuries are complex and can have multiple severe clinical outcomes. An acquired brain injury is an injury to the brain that is not hereditary, congenital, degenerative, or induced by birth trauma. The injury results in a change to the brain's neuronal activity, which affects the physical integrity, metabolic activity, or functional ability of nerve cells in the brain. There are two main types of acquired brain injury: traumatic and non-traumatic.
[0004] Traumatic brain injury (TBI) is a major cause of death and disability in the United States. More than 1.7 million individuals suffer annually from TBI in US. A TBI is caused by an external force, such as a bump, blow, or jolt to the head that disrupts the normal function of the brain. The severity of a TBI may range from “mild” (i.e., a brief change in mental status or consciousness) to “severe” (i.e., an extended period of unconsciousness or memory loss after the injury). TBIs contribute to about 30% of all injury deaths. (Taylor et al. MMWR Surveill. Summ. 2017; 66(No. SS-9):1-16). Every day, about 153 people in the United States die from injuries that include TBI. Id. Those who survive a TBI can face effects that last a few days, or the rest of their lives. Effects of TBI can include impaired thinking or memory, movement, sensation (e.g., vision or hearing), or emotional functioning (e.g., personality changes, depression).
[0005] Approximately 20%-40% of people with TBI experience related vision disorders (Houston K E, et al., *Am J Phys. Med. Rehabil.* 2017, 96: e70-4). This can include blurred vision, visual field loss, and decreased visual acuity. These symptoms can occur acutely or chronically depending on injury type, location, and severity. TBI can affect diverse parts of the visual system ranging from the optic nerve and tract, lateral geniculate nucleus, and optic radiations, resulting in a variety of visual problems (Barnett B P, el al., *Curr Treat Options Neurol.*, 2015:17:329). One known site of afferent pathway damage is via the optic nerve and tract. Structurally, the optic nerve is vulnerable to compression, traction, crush, laceration, and avulsion injuries. Rapid acceleration, or deceleration, of the head may indirectly lead to optic nerve traction or axonal shearing, which can result in optic neuropathy.
[0006] Several treatment options to date for TBI include hyperbaric oxygen therapy, noninvasive brain stimulation, task-oriented functional electrical stimulation, and behavioral therapies (Dang et al. Neural Plasticity 2017; Volume 2017, Article ID 1582182, 6 pages). However, there is still a need for improved treatments for TBI.
[0007] Non-traumatic brain injury is usually caused by damage to the brain by internal factors, such as lack of oxygen, exposure to toxins, pressure from tumor, etc. Stroke is an example of non-traumatic brain injury. Stroke is the fifth leading cause of death in the United States, and nearly 800,000 people have a stroke each year. Stroke occurs when a blockage or bleed of the blood

vessels either interrupts or reduces the supply of blood to the brain. When this happens, the brain does not receive enough oxygen or nutrients, and brain cells start to die. A person experiencing a stroke needs immediate emergency treatment, such as drugs that break down clots and prevent continued formation of clots. Although strokes can be treatable, some can lead to disability or death.

[0008] Cerebral palsy occurs as a result of a brain injury sustained during fetal development or birth. Cerebral palsy is caused by damage to the motor cortex of the brain, which affects muscle control and coordination, including an individual's ability to move, grasp objects, and talk. It is a leading cause of disability in young children and affects about 500,000 children and adults. There is currently no known cure for cerebral palsy.

[0009] Nerve and brain cells damaged in brain injuries are generally irreparable because brain tissue cannot regenerate. Stem cell therapies have shown some promise in neuroregenerative treatments. However, there is still a need for improved treatments for brain injuries.

SUMMARY OF THE DISCLOSURE

[0010] The presently disclosed subject matter provides mesenchymal stem cells (MSCs, or also referred to herein as “HMCs”) obtained by in vitro differentiation of pluripotent stem cells, and extracellular vesicles (“EVs”) secreted from the HMCs (HMC-EVs) of the presently disclosed subject matter, and their use in methods of treating brain injuries. Specifically, the inventors of the presently disclosed subject matter have discovered that the HMCs and HMC-EVs of the presently disclosed subject matter are distinct from MSCs and EVs derived from other sources, e.g., adipose tissue-derived MSCs, bone marrow-derived MSCs, and/or umbilical cord blood-derived MSCs. Specifically, the HMCs of the presently disclosed subject matter have a distinct expression profile when compared to other MSCs, e.g., adipose tissue-derived MSCs, bone marrow-derived MSCs, and/or umbilical cord blood-derived MSCs. Proteins/genes that are involved in neuroprotection and cell viability/survival pathways are upregulated in the HMCs of the presently disclosed subject matter, suggesting that the HMCs of the presently disclosed subject matter are able to confer neuroprotective effects, and provide neurotrophic factors, i.e., factors involved in supporting neuronal survival, growth, health and/or recovery. Likewise, the HMC-EVs of the presently disclosed subject matter share a similar profile as the HMCs from which they were secreted. Similar signaling pathways enriched in the HMCs are also enriched in the HMC-EVs when compared to other tissue-derived MSCs and EVs. This distinct profile renders the HMCs and the HMC-EVs to be particularly useful and effective in treating disease, such as brain injuries. Examples of brain injuries treatable with the HMCs and/or HMC-EVs of the presently disclosed subject matter include stroke, traumatic brain injury, acquired brain injury, anoxic brain injury, diffuse axonal brain injury, focal brain injury, subdural hematoma, brain aneurysm, coma, optic neuropathy, and cerebral palsy.

[0011] Accordingly, in one aspect, the presently disclosed subject matter provides a method of treating a brain injury in a subject suffering from, or suspected of suffering from, a brain injury, the method comprising administering to the subject an effective amount of EVs secreted from HMCs (HMC-EVs) obtained by in vitro differentiation of pluripotent stem cells, thereby treating the brain injury in the subject.

[0012] In some embodiments, the brain injury is selected from the group consisting of stroke, traumatic brain injury, optic neuropathy, cerebral palsy, acquired brain injury, anoxic brain injury, diffuse axonal brain injury, focal brain injury, subdural hematoma, brain aneurysm, and coma. In some embodiments, the brain injury is stroke. In some embodiments, the brain injury is optic neuropathy.

[0013] In some embodiments, the method comprises increasing oligodendrocyte and precursor cells in the brain following administration of the HMC-EVs into the subject. In some embodiments, the method comprises preserving myelin in the brain following administration of the HMC-EVs into the subject. In some embodiments, the method comprises preventing oxidative damage in neurons

following administration of the HMC-EVs into the subject. In some embodiments, the method comprises preventing neuronal death due to glutamate excitotoxicity injury following administration of the HMC-EVs into the subject. In some embodiments, the method comprises reducing tissue loss in the brain following administration of the EVs into the subject. In some embodiments, the method comprises reducing cell death in the brain following administration of the HMC-EVs into the subject. In some embodiments, the method comprises stimulating pathways involved in the development of neuronal lineage following administration of the HMC-EVs into the subject.

[0014] In some embodiments, the HMC-EVs are administered systemically. In some embodiments, the HMC-EVs are administered intracerebrally. In some embodiments, the HMC-EVs are administered intrathecally. In some embodiments, the HMC-EVs are administered intracisternally. In some embodiments, the HMC-EVs are administered intraperitoneally.

[0015] In some embodiments, the subject is a human.

[0016] In some embodiments, the HMCs are obtained by in vitro differentiation of human pluripotent stem cells. In some embodiments, the pluripotent stem cells are further differentiated into hemangioblasts. In some embodiments, the pluripotent stem cells are embryonic stem cells. In some embodiments, the pluripotent stem cells are induced pluripotent stem cells. In some embodiments, the induced pluripotent stem cells are produced by contacting a cell with one or more reprogramming factors.

[0017] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 9 at a higher level compared to EVs secreted from umbilical cord blood-derived MSCs (UCB-MSC-EVs).

[0018] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 10 at a lower level compared to UCB-MSC-EVs.

[0019] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 11 at a higher level compared to EVs secreted from bone marrow-derived MSCs (BM-MSC-EVs).

[0020] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 12 at a lower level compared to BM-MSC-EVs.

[0021] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 13 at a higher level compared to EVs secreted from adipose tissue-derived MSCs (AD-MSC-EVs).

[0022] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 14 at a lower level compared to AD-MSC-EVs).

[0023] In some embodiments, the HMC-EVs express at least one of the proteins in Table 15 at a higher level compared to UCB-MSC-EVs.

[0024] In some embodiments, the HMC-EVs express at least one of the proteins in Table 16 at a lower level compared to UCB-MSC-EVs.

[0025] In some embodiments, the HMC-EVs express at least one of the proteins in Table 17 at a higher level compared to BM-MSC-EVs.

[0026] In some embodiments, the HMC-EVs express at least one of the proteins in Table 18 at a lower level compared to BM-MSC-EVs.

[0027] In some embodiments, the HMC-EVs express at least one of the proteins in Table 19 at a higher level compared to AD-MSC-EVs.

[0028] In some embodiments, the HMC-EVs express at least one of the proteins in Table 20 at a lower level compared to AD-MSC-EVs.

[0029] In some embodiments, the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0030] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3,

FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB, PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0031] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2R1A, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A11, SLC44A1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0032] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to EVs secreted from BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0033] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0034] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 21 at a higher level compared to the HMCs.

[0035] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 22 at a lower level compared to the HMCs.

[0036] In some embodiments, about 1×10.sup.6 to about 1×10.sup.13 HMC-EVs are administered to the subject. In some embodiments, about 10×10.sup.10 or about 30×10.sup.10 HMC-EVs are administered to the subject.

[0037] In some embodiments, the HMC-EVs are administered in a pharmaceutical composition.

[0038] In some embodiments, the pharmaceutical composition comprises (a) a buffer, maintaining the solution at a physiological pH; (b) at least 2 mM or at least 0.05% (w/v) glucose; and (c) an osmotically active agent maintaining the solution at a physiological osmolarity.

[0039] In some embodiments, the glucose is D-glucose (Dextrose). In some embodiments, the osmotically active agent is a salt. In some embodiments, the osmotically active agent is a magnesium salt, phosphate salt, sulfate salt, chloride salt, poorly absorbed disaccharides, such as lactulose, sugar alcohols, such as mannitol and sorbitol, and polyethylene glycol, or a combination thereof. In some embodiments, the osmotically active agent is CaCl2), KCl, NaCl, KH2PO4, Na3HPO4, MgCl2, MgSO4, HEPES, NaHCO.sub.3, or a combination thereof. In some embodiments, the salt is sodium chloride.

[0040] In some embodiments, the method further comprises administering to the subject an effective amount of HMCs obtained by in vitro differentiation of pluripotent stem cells.

[0041] In one aspect, the presently disclosed subject matter provides a method of treating a brain injury in a subject suffering from, or suspected of suffering from, a brain injury, the method comprising administering to the subject an effective amount of HMCs obtained by in vitro differentiation of pluripotent stem cells, thereby treating the brain injury in the subject.

[0042] In some embodiments, the brain injury is selected from the group consisting of stroke, traumatic brain injury, cerebral palsy, acquired brain injury, anoxic brain injury, diffuse axonal brain injury, focal brain injury, subdural hematoma, brain aneurysm, optic neuropathy, and coma.

[0043] In some embodiments, the brain injury is stroke.

[0044] In some embodiments, the brain injury is optic neuropathy.

[0045] In some embodiments, the method comprises preserving myelin in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises suppressing neuroinflammatory responses following administration of the HMCs into the subject. In some embodiments, the method comprises reducing microglial and astrocyte activation in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises stimulating pathways involved in cell survival following administration of the HMCs into the subject. In some embodiments, the method comprises stimulating expression of a neuroprotective gene in the brain following administration of the HMCs into the subject. In some embodiments, the neuroprotective gene is selected from the group consisting of heat shock protein family B member 1 (HSPB1), insulin-like growth factor 1 (IGF2), and secreted phosphoprotein 1 (SPP1). In some embodiments, the method comprises stimulating pathways involved in synaptic transmission in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises stimulating pathways involved in the development of neuronal lineage following administration of the HMCs into the subject. In some embodiments, the method comprises reducing apoptosis following administration of the HMCs into the subject.
[0046] In some embodiments, the brain injury is traumatic brain injury.
[0047] In some embodiments, the method comprises reducing tissue loss in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises reducing cell death in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises increasing neurogenesis following the administration of the HMCs into the subject. In some embodiments, the method comprises reducing the presence of microglia and macrophages in the cortex and striatum following the administration of the HMCs into the subject. In some embodiments, the method comprises reducing inflammation of the spleen following the administration of the HMCs into the subject. In some embodiments, the method comprises migration of HMCs across the blood-brain barrier to the cortex, striatum, and/or hippocampus.
[0048] In some embodiments, the brain injury is cerebral palsy.
[0049] In some embodiments, the method comprises reducing apoptosis in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises reducing lesion size in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises reducing microglial and astrocyte activation in the brain following administration of the HMCs into the subject. In some embodiments, the method comprises preserving myelin of the corpus callosum following administration of the HMCs into the subject. In some embodiments, the method comprises at least a partial rescue of Olig2 in the brain following administration of the HMCs into the subject.
[0050] In some embodiments, the HMCs are administered systemically. In some embodiments, the HMCs are administered intracerebrally. In some embodiments, the HMCs are administered intrathecally. In some embodiments, the HMCs are administered intracisternally. In some embodiments, the HMCs are administered intraperitoneally. In some embodiments, the mesenchymal stem cells are human cells.
[0051] In some embodiments, the subject is a human.
[0052] In some embodiments, the pluripotent stem cells are further differentiated into hemangioblasts. In some embodiments, the pluripotent stem cells are embryonic stem cells. In some embodiments, the pluripotent stem cells are induced pluripotent stem cells. In some embodiments, the pluripotent stem cells are human pluripotent stem cells.
[0053] In some embodiments, the HMCs have been passaged no more than 5 times in vitro before administration into the subject.
[0054] In some embodiments, the HMCs express at least one of the genes in Table 3 at a higher level compared to bone marrow-derived MSCs (BM-MSCs).
[0055] In some embodiments, the HMCs express at least one of the genes in Table 4 at a lower

level compared to BM-MSCs.
[0056] In some embodiments, the HMCs express at least one of the genes in Table 5 at a higher level compared to umbilical cord blood-derived MSCs (UCB-MSCs).
[0057] In some embodiments, the HMCs express at least one of the genes in Table 6 at a lower level compared to UCB-MSCs.
[0058] In some embodiments, the HMCs express at least one of the genes in Table 7 at a higher level compared to adipose tissue-derived MSCs (AD-MSCs).
[0059] In some embodiments, the HMCs express at least one of the genes in Table 8 at a lower level compared to AD-MSCs.
[0060] In some embodiments, the HMCs express, in a basal state, mRNA encoding interleukin-6 (IL-6) at a level less than ten percent of the IL-6 mRNA level expressed by BM-MSCs, in a basal state, and wherein the HMCs express, in a basal state, mRNA encoding CD24 at a level that is greater than the CD24 mRNA level expressed by BM-MSCs in a basal state.
[0061] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of CALR, UBB, PKM, CXCL8, C15orf48, PSME2, TPM3, ANKRD1, PFN1, SRGN, ACTB, MDK, TAGLN2, CFL1, HSP90AA1, HSPA8, CXCL12, UCHL1, HMGA2, HMGA1, HN1, PTMA, SP90AB1, PRDX1, GSTP1, KRT18, IGFBP4, CALD1, COL4A1, COL4A2, and GAPDH at a higher level compared to adipose tissue-derived MSCs (AD-MSCs).
[0062] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of TMSB4X, ACTG1, GSTP1, KRT18, IGFBP5, NPY, KRT8, PRDX6, MDK, DKK3, UCHL1, TUBB3, HN1, PTMA, HSP90AB1, HMGA1, HSPA8, TAGLN2, ANKRD1, PFN1, CYBA, and UBB at a higher level compared to AD-MSCs.
[0063] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of SERPINE1, ACTA2, TPM2, CTGF, SERPINE2, CRYAB, ELN, MFGE8, ANXA2, POSTN, VIM, MFAP5, ISLR, THBS1, TIMP3, DKK1, COL6A3, COL6A1, TPT1, BCYRN1, COL1A1, SPARC, TPM1, BGN, COL1A2, COL3A1, TGFBI, CRLF1, COMP, NEAT1, MT-CO3, MT-CO2, MT-ATP8, MT-CYB, MT-CO1, MT-ATP6, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-ND3, MT-ND1, MT-ND2, GREM1, TMSB4X, ITGB1, LMNA, H2AFZ, FTL, EEF1G, NPM1, EEF1A1, RACK1, ACTG1, and TPM4 at a lower level compared to AD-MSCs.
[0064] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of SERPINE1, S100A6, CD59, POSTN, VIM, MFAP5, ISLR, THBS1, COL6A3, TIMP3, ELN, ANXA2, COL1A1, BCYRN1, CCDC80, COL6A1, COL6A2, BGN, COL1A2, COL3A1, TGFB1, CRLF1, COMP, and GREM1 at a lower level compared to AD-MSCs.
[0065] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of MT1X, MT1G, TMSB10, CCL8, INHBA, CTSB, SERPINB2, ADM, APOL1, FTH1, CCL2, CCL5, CSF1, IL1B, IGFBP3, P4HB, DCN, FSTL1, ANXA5, LOX, CD63, CTSZ, FN1, LGALS1, LDHA, RCN3, MMP2, and TIMP1 at a lower level compared to AD-MSCs.
[0066] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of PPIA, NPM1, HNRNPA1, IGFBP5, KRT19, KRT18, GSTP1, TUBB, TUBA1B, KRT8, HN1, PTMA, TUBA1C, HSPA8, HMGA1, CFL1, MYL6, ACTB, UCHL1, TAGLN2, MDK, GREM1, MMP1, and CTSC at a higher level compared to bone marrow-derived MSCs (BM-MSCs).
[0067] In some embodiments, the HMCs express at least one of the genes selected from the group consisting of ANXA2, TPT1, VIM, COL6A1, BGN, COL6A2, CTGF, TIMP3, ACTA2, COL3A1, SPARC, ITGB1, SERPINH1, TPM2, TGFBI, COL1A1, TPM1, COL6A3, TPM4, SERPINE2, CALD1, COL1A2, TAGLN, MYL9, MT-RNR2, POSTN at a lower level compared to BM-MSCs.
[0068] In some embodiments, the HMCs express at least one of the miRNA in Table 21 at a lower level compared to the HMC-EVs secreted from the HMCs.
[0069] In some embodiments, the HMCs express at least one of the miRNA in Table 22 at a higher level compared to the HMC-EVs secreted from the HMCs.

[0070] In some embodiments, about 1×10.sup.6 to about 1×10.sup.13 HMCs are administered to the subject.
[0071] In some embodiments, the HMCs are administered in a pharmaceutical composition.
[0072] In some embodiments, the pharmaceutical composition comprises (a) a buffer, maintaining the solution at a physiological pH; (b) at least 2 mM or at least 0.05% (w/v) glucose; and (c) an osmotically active agent maintaining the solution at a physiological osmolarity.
[0073] In some embodiments, the glucose is D-glucose (Dextrose). In some embodiments, the osmotically active agent is a salt. In some embodiments, the salt is sodium chloride.
[0074] In another aspect, the presently disclosed subject matter provides a method of treating a brain injury in a subject suffering from, or suspected of suffering from, a brain injury, the method comprising administering to the subject an effective amount of EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, and an effective amount of HMCs obtained by in vitro differentiation of pluripotent stem cells, thereby treating the brain injury in the subject.
[0075] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of CALR, UBB, PKM, CXCL8, C15orf48, PSME2, TPM3, ANKRD1, PFN1, SRGN, ACTB, MDK, TAGLN2, CFL1, HSP90AA1, HSPA8, CXCL12, UCHL1, HMGA2, HMGA1, HN1, PTMA, SP90AB1, PRDX1, GSTP1, KRT18, IGFBP4, CALD1, COL4A1, COL4A2, and GAPDH at a higher level compared to AD-MSCs.
[0076] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of TMSB4X, ACTG1, GSTP1, KRT18, IGFBP5, NPY, KRT8, PRDX6, MDK, DKK3, UCHL1, TUBB3, HN1, PTMA, HSP90AB1, HMGA1, HSPA8, TAGLN2, ANKRD1, PFN1, CYBA, and UBB at a higher level compared to AD-MSCs.
[0077] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of PPIA, NPM1, HNRNPA1, IGFBP5, KRT19, KRT18, GSTP1, TUBB, TUBA1B, KRT8, HN1, PTMA, TUBA1C, HSPA8, HMGA1, CFL1, MYL6, ACTB, UCHL1, TAGLN2, MDK, GREM1, MMP1, and CTSC at a higher level compared to BM-MSCs.
[0078] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of SERPINE1, ACTA2, TPM2, CTGF, SERPINE2, CRYAB, ELN, MFGE8, ANXA2, POSTN, VIM, MFAP5, ISLR, THBS1, TIMP3, DKK1, COL6A3, COL6A1, TPT1, BCYRN1, COL1A1, SPARC, TPM1, BGN, COL1A2, COL3A1, TGFBI, CRLF1, COMP, NEAT1, MT-CO3, MT-CO2, MT-ATP8, MT-CYB, MT-CO1, MT-ATP6, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-ND3, MT-ND1, MT-ND2, GREM1, TMSB4X, ITGB1, LMNA, H2AFZ, FTL, EEF1G, NPM1, EEF1A1, RACK1, ACTG1, and TPM4 at a lower level compared to AD-MSCs.
[0079] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of SERPINE1, S100A6, CD59, POSTN, VIM, MFAP5, ISLR, THBS1, COL6A3, TIMP3, ELN, ANXA2, COL1A1, BCYRN1, CCDC80, COL6A1, COL6A2, BGN, COL1A2, COL3A1, TGFB1, CRLF1, COMP, and GREM1 at a lower level compared to AD-MSCs.
[0080] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of MT1X, MT1G, TMSB10, CCL8,

INHBA, CTSB, SERPINB2, ADM, APOL1, FTH1, CCL2, CCL5, CSF1, IL1B, IGFBP3, P4HB, DCN, FSTL1, ANXA5, LOX, CD63, CTSZ, FN1, LGALS1, LDHA, RCN3, MMP2, and TIMP1 at a lower level compared to AD-MSCs.

[0081] In one aspect, the presently disclosed subject matter provides a composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of ANXA2, TPT1, VIM, COL6A1, BGN, COL6A2, CTGF, TIMP3, ACTA2, COL3A1, SPARC, ITGB1, SERPINH1, TPM2, TGFBI, COL1A1, TPM1, COL6A3, TPM4, SERPINE2, CALD1, COL1A2, TAGLN, MYL9, MT-RNR2, POSTN at a lower level compared to BM-MSCs.

[0082] In some embodiments, the HMCs further express at least one of the genes in Table 3 at a higher level compared to BM-MSCs.

[0083] In some embodiments, the HMCs further express at least one of the genes in Table 4 at a lower level compared to BM-MSCs.

[0084] In some embodiments, the HMCs further express at least one of the genes in Table 5 at a higher level compared to UCB-MSCs.

[0085] In some embodiments, the HMCs further express at least one of the genes in Table 6 at a lower level compared to UCB-MSCs.

[0086] In some embodiments, the HMCs further express at least one of the genes in Table 7 at a higher level compared to AD-MSCs.

[0087] In some embodiments, the HMCs further express at least one of the genes in Table 8 at a lower level compared to AD-MSCs.

[0088] In one aspect, the presently disclosed subject matter provides a pharmaceutical composition comprising the HMCs of the presently disclosed subject matter, and a pharmaceutically acceptable carrier.

[0089] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs of the presently disclosed subject matter.

[0090] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 9 at a higher level compared to UCB-MSC-EVs.

[0091] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 10 at a lower level compared to UCB-MSC-EVs.

[0092] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 11 at a higher level compared to BM-MSC-EVs.

[0093] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 12 at a lower level compared to BM-MSC-EVs.

[0094] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 13 at a higher level compared to AD-MSC-EVs.

[0095] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 14 at a lower level compared to AD-MSC-EVs.

[0096] In some embodiments, the HMC-EVs express at least one of the proteins in Table 15 at a higher level compared to UCB-MSC-EVs.

[0097] In some embodiments, the HMC-EVs express at least one of the proteins in Table 16 at a lower level compared to UCB-MSC-EVs.

[0098] In some embodiments, the HMC-EVs express at least one of the proteins in Table 17 at a higher level compared to BM-MSC-EVs.

[0099] In some embodiments, the HMC-EVs express at least one of the proteins in Table 18 at a lower level compared to BM-MSC-EVs.

[0100] In some embodiments, the HMC-EVs express at least one of the proteins in Table 19 at a higher level compared to AD-MSC-EVs.

[0101] In some embodiments, the HMC-EVs express at least one of the proteins in Table 20 at a lower level compared to AD-MSC-EVs.

[0102] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 21 at a higher level compared to the HMCs.
[0103] In some embodiments, the HMC-EVs express at least one of the miRNA in Table 22 at a lower level compared to the HMCs.
[0104] In some embodiments, the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to EVs secreted from BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
[0105] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3, FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB, PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
[0106] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2RIA, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A11, SLC44A1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
[0107] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
[0108] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
[0109] In one aspect, the presently disclosed subject matter provides a pharmaceutical composition comprising the HMC-EVs of the presently disclosed subject matter, and a pharmaceutically acceptable carrier.
[0110] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 9 at a higher level compared to UCB-MSC-EVs.
[0111] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 10 at a lower level compared to UCB-MSC-EVs.
[0112] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 11 at a higher level compared to BM-MSC-EVs.
[0113] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 12 at a lower level compared to BM-MSC-EVs.

[0114] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 13 at a higher level compared to AD-MSC-EVs.
[0115] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 14 at a lower level compared to EVs secreted from AD-MSC-EVs.
[0116] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 15 at a higher level compared to UCB-MSC-EVs.
[0117] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 16 at a lower level compared to UCB-MSC-EVs.
[0118] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 17 at a higher level compared to BM-MSC-EVs.
[0119] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 18 at a lower level compared to BM-MSC-EVs.
[0120] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 19 at a higher level compared to AD-MSC-EVs.
[0121] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 20 at a lower level compared to AD-MSC-EVs.
[0122] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 21 at a higher level compared to the HMCs.
[0123] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 22 at a lower level compared to the HMCs.
[0124] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
[0125] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3, FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB,

PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0126] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF 11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2RIA, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A11, SLC44A1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0127] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0128] In one aspect, the presently disclosed subject matter provides a population of HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0129] In one aspect, the presently disclosed subject matter provides a pharmaceutical composition comprising the HMC-EVs of the presently disclosed subject matter, and a pharmaceutically acceptable carrier.

[0130] The presently disclosed subject matter also provides a method of determining neurite outgrowth of an HMC and/or HMC-EV population. The method comprises (a) preparing a mixed neuronal culture from an isolated cerebral cortex, (b) plating the HMC and/or HMC-EV population on a permeable membrane, (c) applying strain on the mixed neuronal culture, (d) overlaying the strained mixed neuronal culture with the permeable membrane of step (b), and (e) measuring neurite outgrowth of the mixed neuronal culture. In an embodiment, step (d) is cultured in a media substantially lacking in serum. In another embodiment, the method further comprises determining gene expression of the mixed neuronal culture in the presence and absence of the HMC and/or HMC-EV population. In another embodiment, the strain is a physical scratch made in the mixed neuronal culture. In another embodiment, the strain is vacuum pressure and positive air pressure applied to the mixed neuronal culture. In another embodiment, the strain may be applied at 15% to 0% stretching oscillations.

[0131] The presently disclosed subject matter also provides a method of determining neurite outgrowth of an HMC and/or HMC-EV population. The method comprises preparing a mixed neuronal culture from an isolated cerebral cortex, (b) plating the HMC and/or HMC-EV population on a permeable membrane, (c) applying strain on the mixed neuronal culture, (d) overlaying the strained mixed neuronal culture with the permeable membrane of step (b), and (e) measuring neurite outgrowth of the mixed neuronal culture. In an embodiment, the method further comprises determining gene expression of the mixed neuronal culture in the presence and absence of the HMC and/or HMC-EV population. In another embodiment, the strain is a physical scratch made in the mixed neuronal culture. In another embodiment, the strain is vacuum pressure and positive air

pressure applied to the mixed neuronal culture. In another embodiment, the strain is applied at 15% to 0% stretching oscillations.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

[0132] FIG. **1**. shows results of the elevated body swing test (EBST) in rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV).

[0133] FIG. **2** shows forelimb akinesia in rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV).

[0134] FIG. **3** shows paw grasp in rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV).

[0135] FIG. **4**A shows H&E staining of the brains of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **4**B shows a bar graph of the TBI impact area in the rats as measured by H&E staining.

[0136] FIG. **5**A shows Nissl staining of the peri-impact cortex of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **5**B shows a bar graph of the percentage of live cells in the peri-impact cortex of the rats as determined by Nissl staining. FIG. **5**C shows Nissl staining of the striatum in the rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **5**D shows a bar graph of the percentage of live cells in the striatum of the rats as determined by Nissl staining. FIG. **5**E shows Nissl staining of the hippocampus of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **5**F shows a bar graph of the percentage of live cells in the hippocampus of the rats as determined by Nissl staining.

[0137] FIG. **6**A shows doublecortin (DCX) staining of the cortex of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **6**B shows a bar graph of the DCX cell count in the cortex area of the rats. FIG. **6**C shows DCX staining of the striatum of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **6**D shows a bar graph of the DCX cell count in the striatum area of the rats. FIG. **6**E shows DCX staining of the hippocampus of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **6**F shows a bar graph of the DCX cell count in the hippocampus area of the rats.

[0138] FIG. **7**A shows Iba1 staining in the cortex of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **7**B shows a bar graph of the Iba1 cell count in the cortex of the rats.

[0139] FIG. **7**C shows Iba1 staining in the striatum rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **7**D shows a bar graph of the Iba1 cell count in the striatum of the rats.

[0140] FIG. **8**A shows OX6 staining of the cortex of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **8**B shows a bar graph of the OX6 cell count in the cortex of the rats.

[0141] FIG. **8**C shows OX6 staining of the striatum of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **8**D shows a bar graph of the OX6 cell count in the striatum of the rats.

[0142] FIG. **9**A shows 1L6 staining in the spleens of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV).

FIG. **9**B shows a bar graph of the 1L6 staining intensity in the spleens of the rats.
[0143] FIG. **10**A shows TNF-alpha staining in the spleens of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **10**B shows a bar graph of the TNF-alpha staining intensity in the spleens of the rats.
[0144] FIG. **11**A shows HuNu staining in the cortex of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **11**B shows a bar graph of the HuNu cell count in the cortex of the rats. FIG. **11**C shows HuNu staining in the striatum of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **11**D shows a bar graph of the HuNu cell count in the striatum of the rats. FIG. **11**E shows HuNu staining in the hippocampus of rats induced with TBI by controlled cortical impact (CCI) and administered with HMCs or vehicle intracerebrally (IC) or intravenously (IV). FIG. **11**F shows a bar graph of the HuNu cell count in the hippocampus of the rats.
[0145] FIG. **12**A shows migration of unstimulated hESC-MSCs ("HMC"), BM-MSCs, and UCB-MSCs into a gap of about 500 μm wide at 0 hrs and 6 hrs. FIG. **12**B shows a bar graph of the number of unstimulated and stimulated cells that had migrated into the gap.
[0146] FIG. **13** shows images of neurite outgrowth staining at days 1 and 7 post-scratch and co-culture of hESC-MSCs ("HMC") with a mixed neuronal culture.
[0147] FIG. **14**A shows TUNEL ranking of each rat tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **14**B shows a bar graph of the average TUNEL ranking of each group of rats tested. TUNEL ranking was as follows: 1=no structural damage and No TUNEL; 2=structural damage and Low TUNEL; 3=structural damage and Medium TUNEL; 4=structural damage and High TUNEL; 5=extreme damage/tissue gone. A comparison of the rats in the Sham vs HI groups showed a t-test of 0.006284 and Mann-Whitney of 0.0256; Sham vs Lot B groups showed a t-test of 0.148904 and Mann-Whitney of 0.2; and HI vs Lot B groups showed a t-test of 0.101453 and Mann-Whitney of 0.1841.
[0148] FIG. **15** shows H&E staining of the brains of rats tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy.
[0149] FIG. **16**A shows images of Iba-1 staining in peri-infarct tissue of rats tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **16**B shows the mean signal intensity of Iba-1 staining in each rat tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **16**C shows the average mean signal intensity of Iba-1 staining in each group of rats tested. A comparison of the rats in the Sham vs HI groups showed a t-test of 0.039335 and Mann-Whitney of 0.065; Sham vs Lot B groups showed a t-test of 0.129562 and Mann-Whitney of 0.1949; and HI vs Lot B groups showed a t-test of 0.353204 and Mann-Whitney of 0.4418.
[0150] FIG. **17**A shows images of GFAP staining in peri-infarct tissue of rats tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **17**B shows the mean signal intensity of GFAP staining in each rat tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **17**C shows the average mean signal intensity of GFAP staining in each group of rats tested. A comparison of the rats in the Sham vs HI groups showed a t-test of 0.011749 and Mann-Whitney of 0.0047; Sham vs Lot B groups showed a t-test of 0.070012 and Mann-Whitney of 0.0207; and HI vs Lot B groups showed a t-test of 0.57941 and Mann-Whitney of 0.7984.
[0151] FIG. **18**A shows images of MBP staining in the corpus callosum in rats tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **18**B shows the mean signal intensity of MBP staining in each rat tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **18**C shows the average mean signal intensity of MBP staining in each group of rats tested. A comparison of the rats in the Sham vs HI groups showed a t-test of 0.012963 and Mann-Whitney of 0.007; Sham vs Lot B groups showed a t-test of 0.189251 and Mann-Whitney of 0.3282; and HI vs Lot B groups showed a t-test of 0.172857 and Mann-Whitney of 0.2345.
[0152] FIG. **19**A shows images of Olig2 staining in the hippocampus of the ipsilesional hemisphere

of rats tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy.
[0153] FIG. **19**B shows the mean signal intensity of Olig2 staining in the SVZ, cortex, hippocampus, and region mean of each rat tested in the in vivo neonatal hypoxia-ischemia model of cerebral palsy. FIG. **19**C shows the average mean signal intensity of Olig2 staining in the SVZ, cortex, hippocampus, and region mean of each group of rats tested. A comparison of the rats in Lot B vs HI for Olig2 staining in the SVZ showed a t-test of 0.3962; in the cortex a t-test of 0.4399; in the hippocampus a t-test of 0.5435; and the region mean showed a t-test of 0.3597.
[0154] FIG. **20** depicts the results of the body swing test in rats having middle cerebral artery occlusion (MCAO) stroke and receiving HMCs via three routes of administration: intravenous (IV), intracerebral (IC) and intrathecal (IT) administration. Two-way ANOVA with Tukey's MCT was used for statistical analysis, *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
[0155] FIG. **21** depicts the results of the forelimb placement, the hindlimb placement, and the body swing test in rats having middle cerebral artery occlusion (MCAO) stroke and receiving HMCs and HMC-EVs via intravenous, intracerebral and intracisternal administration. Two-way ANOVA Tukey's MCT was used for statistical analysis, *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
[0156] FIG. **22** depicts the results of the forelimb placement, the hindlimb placement, and the body swing test in rats having middle cerebral artery occlusion (MCAO) stroke and receiving HMC-EVs via intracisternal administration. Two-way ANOVA with Tukey's MCT was used for statistical analysis, *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
[0157] FIG. **23** depicts the results of the forelimb placement, the hindlimb placement, and the body swing test in rats having middle cerebral artery occlusion (MCAO) stroke and receiving HMC-EVs via intrathecal administration. Two-way ANOVA with Turkey's MCT was used for statistical analysis, *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001.
[0158] FIG. **24**A shows images of MBP staining in the cortex and striatum in rats having MCAO stroke and receiving HMCs (obtained from C-GS1 and N-line cells) via IV administration. FIG. **24**B shows the average signal intensity of MBP staining in the cortex of rats tested in the vivo MCAO stroke model. FIG. **24**C shows the average signal intensity of MBP staining in the striatum of rats tested in the vivo MCAO stroke model. For sham vs Vehicle groups: Welch's test was used for statistical analysis, ***p<0.001. For vehicle vs treatment groups: one-way ANOVA with Dunnet's multiple comparisons test was used for statistical analysis, *p<0.05, **p<0.01, and ***P<0.001.
[0159] FIG. **25**A shows images of Iba1 staining in the cortex and striatum in rats having MCAO stroke and receiving HMCs (obtained from C-GS1 and N-line cells) via IV administration. FIG. **25**B shows the average signal intensity of Iba1 staining in the cortex of rats tested in the vivo MCAO stroke model. FIG. **25**C shows the average signal intensity of Iba1 staining in the striatum of rats tested in the vivo MCAO stroke model. For sham vs Vehicle groups: Welch's test was used for statistical analysis, ***p<0.001. For vehicle vs treatment groups: one-way ANOVA with Dunnet's multiple comparisons test was used for statistical analysis, *p<0.05, **p<0.01, and ***P<0.001.
[0160] FIG. **26**A shows images of GFAP staining in the cortex and striatum in rats having MCAO stroke and receiving HMCs (obtained from C-GS1 and N-line cells) via IV administration. FIG. **26**B shows the average signal intensity of GFAP staining in the cortex of rats tested in the vivo MCAO stroke model. FIG. **26**C shows the average signal intensity of GFAP staining in the striatum of rats tested in the vivo MCAO stroke model. For sham vs Vehicle groups: Welch's test was used for statistical analysis, ***p<0.001. For vehicle vs treatment groups: one-way ANOVA with Dunnet's multiple comparisons test was used for statistical analysis, *p<0.05, **p<0.01, and ***P<0.001.
[0161] FIG. **27**A shows images of MBP staining in rats having MCAO stroke and receiving HMC-EVs (obtained from N-line cells, treated with IFNgamma for 96 hours at 50 ng/mL) via

intracisternal administration. FIG. **27**B shows the average signal intensity of MBP staining in rats tested in the vivo MCAO stroke model. cc: corpur callosum; ec: external capsule; cg: cingulate gyrus. For vehicle vs treatment groups: Bonferroni comparisons was used for statistical analysis, **p<0.01.

[0162] FIG. **28**A shows images of Iba1 staining in rats having MCAO stroke and receiving HMC-EVs (obtained from N-line cells, treated with gamma interferon for 96 hours at 50 ng/mL) via intracisternal administration. FIG. **28**B shows the average signal intensity of Iba1 staining in rats tested in the vivo MCAO stroke model. cc: corpur callosum; ec: external capsule; cg: cingulate gyrus. For vehicle vs treatment groups: Bonferroni comparisons was used for statistical analysis, **p<0.01.

[0163] FIG. **29**A shows images of GFAP staining in rats having MCAO stroke and receiving HMC-EVs (obtained from N-line cells, treated with gamma interferon for 96 hours at 50 ng/mL) via intracisternal administration. FIG. **29**B shows the average signal intensity of GFAP staining in rats tested in the vivo MCAO stroke model. cc: corpur callosum; ec: external capsule; cg: cingulate gyrus. For vehicle vs treatment groups: Bonferroni comparisons was used for statistical analysis, **p<0.01.

[0164] FIG. **30**A shows images of Olig2 staining in rats having MCAO stroke and receiving HMC-EVs (obtained from N-line cells, treated with gamma interferon for 96 hours at 50 ng/mL) via intracisternal administration. FIG. **30**B shows the average signal intensity of Olig2 staining in rats tested in the vivo MCAO stroke model. cc: corpur callosum; ec: external capsule; cg: cingulate gyrus. For vehicle vs treatment groups: Bonferroni comparisons was used for statistical analysis, **p<0.01.

[0165] FIG. **31**A shows images of NG2 staining in rats having MCAO stroke and receiving HMC-EVs (obtained from N-line cells, treated with gamma interferon for 96 hours at 50 ng/mL) via intracisternal administration. FIG. **30**B shows the average signal intensity of NG2 staining in rats tested in the vivo MCAO stroke model. cc: corpur callosum; ec: external capsule; cg: cingulate gyrus. For vehicle vs treatment groups: Bonferroni comparisons was used for statistical analysis, **p<0.01.

[0166] FIG. **32** is a schematic of the study design for the in vitro oxygen glucose deprivation (OGD) assay for modeling stroke.

[0167] FIG. **33**A shows TUNEL staining and imaging of primary rat neurons treated with or without HMCs following 0 hr, 1 hr, 2 hr and 3 hr oxygen glucose deprivation (OGD) injury.

[0168] FIG. **33**B shows the average TUNEL quantification of primary rat neurons treated with or without MSCs following 0 hr, 1 hr, 2 hr and 3 hr OGD injury.

[0169] FIGS. **34**A-F depict the pathway enrichment analysis of the differential expression between neurons subjected to 3 hours of oxygen glucose deprivation injury and grown on HMC-enriched and control media. FIGS. **34**A-B depict the pathways enriched by the differential expression. FIGS. **34**C-F depict the differential expression between OGD neurons grown on HMC-enriched and control media for Gene Oncology terms. FIG. **34**C shows the upregulation of pathways involved in cell viability, neuroprotection, and synaptic transmission in OGD neurons grown on HMC-enriched culture. FIG. **34**D shows upregulation of genes involved in neuroprotection in OGD neurons grown on HMC-enriched culture. FIG. **34**E shows the downregulation of pathways involved in apoptosis in OGD neurons grown on HMC-enriched culture. FIG. **34**F shows downregulation of genes involved in apoptosis or general response to cell death in OGD neurons grown on HMC-enriched culture.

[0170] FIG. **35**A depicts the in vitro OGD assay RNAseq analysis of primary rat neurons treated with or without HMCs following 0 hr, 1 hr, 2 hr and 3 hr oxygen glucose deprivation (OGD) injury. FIG. **35**B depicts the qPCR analysis of primary rat neurons treated with or without HMCs following 0 hr, 1 hr, 2 hr and 3 hr oxygen glucose deprivation (OGD) injury. Two-way ANOVA with Sidak multiple comparison test was used for statistical analysis: *p<0.05, **p<0.01, and

****p<0.0001.
[0171] FIG. **36**A shows attenuation of cell death by HMC-EVs. Percentage of cell death was determined as the number of PI+ cells out of the total Hoechst+ cells. Two-way ANOVA was used for statistical significance analysis. ****p<0.0001. FIG. **36**B shows dose-dependent attenuation of cell death by HMC-EV treatment. Percentage of cell death was determined as the number of PI+ cells out of the total Hoechst+ cells. One-way
[0172] FIG. **37** shows maintenance of the mitochondrial membrane potential in HMC-EV treated cells undergoing nuclear swelling. HMC-EV treatment sustained cells in the nuclear swelling stage after glutamate-induced injury.
[0173] FIG. **38** shows the principal component analysis of transcriptomes of HMCs (obtained from N-line cells), and adipose tissue-derived MSCs shows that HMCs are distinct from adipose tissue-derived MSCs in both basal and inteferon-gamma stimulated state. AMSC-B-1,2,3: adipose tissue-derived MSCs collected from 3 different adult donors, 2 technical replicate samples for each biological replicates. AMSC-S-1,2,3: adipose tissue-derived MSCs, but stimulated with gamma interferon. NHMC-B: 3 technical replicates of MSCs derived from N-line cells, basal state. NHMC-S: MSCs derived from N-line cells, but stimulated with gamma interferon.
[0174] FIG. **39** depicts the weights of different genes contributing to the second principal component which determines the variance between HMCs (obtained from N-line cells) and adipose tissue-derived MSCs.
[0175] FIG. **40** depicts the hierarchical clustering map demonstrating that HMCs (obtained from N-line cells) are distinct from adipose tissue-derived MSCs in both basal and gamma interferon-stimulated states. AB1, AB2, AB3—adipose tissue-derived MSCs collected from 3 different adult donors, 2 technical replicates per donor; basal cell state. AS1, AS2, AS3-adipose tissue-derived MSCs, stimulated with gamma interferon. NB—MSCs derived from N-line cells, basal states, 3 technical replicates. NS—MSCs derived from N-line cells, stimulated with gamma interferon.
[0176] FIG. **41** depicts the basal HMC-specific cluster of genes.
[0177] FIG. **42** depicts the basal adipose tissue-derived MSC-specific cluster of genes.
[0178] FIG. **43** depicts the pathway enrichment of differential expression pattern between HMCs (obtained from N-line cells) and adipose tissue-derived MSCs showing noticeable HMC-specific up-regulation of several pathways (denoted by arrows) involved in the development of neuronal lineage including axon guidance, CREB signaling in neurons, and synaptogenesis signaling.
[0179] FIG. **44** depicts the top 15 most strongly differentially expressed genes contributing to activation of neuronal CREB signaling in HMCs (obtained from N-line cells).
[0180] FIG. **45** depicts the top 15 most strongly upregulated genes contributing to the enrichment of axon guidance pathway in HMCs (obtained from N-line cells).
[0181] FIG. **46** depicts the top 15 most strongly expressed genes contributing to activation of synaptogenesis signaling pathway in HMCs (obtained from N-line cells).
[0182] FIG. **47** depicts the top 15 most up-regulated genes contributing to activation of neuroinflammation signaling pathway in HMCs (obtained from N-line cells).
[0183] FIG. **48** shows the principal component analysis of transcriptomes of HMCs obtained from N-line cells, HMCs obtained from GMP1 cells, and adipose tissue-derived MSCs. AMSC-B-1,2,3—adipose tissue-derived MSCs collected from 3 different adult donors, basal state, 2 technical replicate samples for each biological replicate. AMSC-S-1,2,3—adipose tissue-derived MSCs collected from 3 different adult donors, but stimulated with gamma interferon. NHMC-B—HMCs derived from N-line cells, basal state. NHMC-S—HMCs derived from N-line cells, but stimulated with gamma interferon. GMP-B—HMC derived from GMP1 cell line, basal state. GMP-S—HMC derived from GMP1 cell line, but stimulated with gamma interferon.
[0184] FIG. **49** depicts the hierarchical clustering map demonstrating that HMCs (obtained from N-line cells) and HMCs (obtained from GMP1 cells) are distinct from adipose tissue-derived MSCs in both basal and gamma interferon-stimulated cell states. AB1, AB2, AB3—adipose tissue-derived

MSCs collected from 3 different adult donors, 2 technical replicates per donor; basal cell state. AS1, AS2, AS3—adipose tissue-derived MSCs collected from 3 different adult donors, stimulated with gamma interferon. NB—HMCs derived from N-line cells, basal state, 3 technical replicates. NS—HMCs derived from N-line cells, stimulated with gamma interferon. GB—HMC derived from GMP1 cell line, basal state, 3 technical replicates. GS—HMC derived from GMP1 cell line, stimulated with gamma interferon.

[0185] FIG. **50** depicts the HMC-specific cluster of genes.

[0186] FIG. **51** depicts the basal adipose tissue-derived MSC-specific cluster of genes.

[0187] FIG. **52** depicts the stimulated adipose tissue-derived MSC-specific cluster of genes.

[0188] FIG. **53**A depicts the pathway enrichment of differential expression pattern between HMCs (obtained from GMP1 cells) and adipose tissue-derived MSCs showing noticeable HMC-specific up-regulation of several pathways involved in the development of neuronal lineage including axon guidance, CREB signaling in neurons, and synaptogenesis signaling.

[0189] FIG. **53**B depicts the top canonical pathways that are differentially regulated in HMCs. FIG. **53**C depicts exemplary regulators being activated and inhibited in HMCs.

[0190] FIG. **54**A depicts the pathway enrichment of differential expression pattern between HMCs (obtained from N-line cells) and adipose tissue-derived MSCs showing noticeable HMC-specific up-regulation of several pathways involved in the development of neuronal lineage including axon guidance, CREB signaling in neurons, and synaptogenesis signaling.

[0191] FIG. **54**B depicts the top canonical pathways that are differentially regulated in HMCs. FIG. **54**C depicts exemplary regulators being activated and inhibited in HMCs.

[0192] FIG. **55** shows the principal component analysis of transcriptomes of HMCs (obtained from N-line cells) and bone marrow-derived MSCs shows that HMCs are distinct from bone marrow-derived MSCs in both basal and inteferon-gamma stimulated states. BM-B—bone marrow-derived MSCs collected from 3 different adult donors, basal states, 2 technical replicate samples for each biological replicate. BM-S—bone marrow-derived MSCs, but stimulated with gamma interferon. N-B—3 technical replicates of HMCs derived from N-line cells, basal state. N-S—HMCs derived from N-line cells, but stimulated with gamma interferon.

[0193] FIG. **56** depicts the weights of different genes contributing to the second principal component which determines the variance between HMCs and bone marrow-derived MSCs.

[0194] FIG. **57** depicts the hierarchical clustering map demonstrating that HMCs (obtained from N-line cells) are distinct from bone marrow-derived MSCs in both basal and gamma interferon-stimulated cell states. BMB1, BMB2, BMB3—bond marrow-derived MSCs collected from 3 different adult donors, 2 technical replicates per donor; basal cell state. BMS1, BMS2, BMS3—bond marrow-derived MSCs, stimulated with gamma interferon. NB—HMCs derived from N-line cells, basal states, 3 technical replicates. NS—HMCs derived from N-line cells, stimulated with gamma interferon.

[0195] FIG. **58** depicts the basal HMC-specific cluster of genes.

[0196] FIG. **59** depicts the basal bone marrow-derived MSC-specific cluster of genes.

[0197] FIG. **60** depicts the pathway enrichment of differential expression pattern between HMCs (obtained from N-line cells) and bone marrow-derived MSCs showing noticeable HMC-specific up-regulation of several pathways (denoted by arrows) involved in the development of neuronal lineage such as CREB signaling in neurons.

[0198] FIG. **61** depicts the top 15 most strongly differentially expressed genes contributing to activation of neuronal CREB signaling in HMCs (obtained from N-line cells).

[0199] FIG. **62** depicts the top 15 most strongly upregulated genes contributing to activation of synaptogenesis signaling in HMCs (obtained from N-line cells).

[0200] FIG. **63**A depicts the pathway enrichment of differential expression pattern between HMC-EVs and EVs secreted from bone marrow-derived MSCs (BM-MSC-EVs). Pathways that are upregulated in HMC-EVs have a positive z-score and are represented by orange bars. Pathways

that are downregulated in HMC-EVs have a negative z-score and are represented by blue bars. White/gray bars represent pathways that are enriched in HMC-EVs, i.e., proteins contributing to these pathways are enriched. FIG. **63**B depicts the disease or functional annotation of proteins that have higher expression levels in HMC-EVs when compared to BM-MSC-EVs. FIG. **63**C depicts the disease or functional annotation of proteins that have lower expression levels in HMC-EVs when compared to BM-MSC-EVs. An activation z-score above 2 or below −2 is considered as the threshold value.

[0201] FIG. **64**A depicts the pathway enrichment of differential expression pattern between HMC-EVs and EVs secreted from adipose tissue-derived MSCs (AD-MSC-EVs). Pathways that are upregulated in HMC-EVs have a positive z-score and are represented by orange bars. Pathways that are downregulated in HMC-EVs have a negative z-score and are represented by blue bars. White/gray bars represent pathways that are enriched in HMC-EVs, i.e., proteins contributing to these pathways are enriched. FIG. **64**B depicts the disease or function annotational of proteins that have higher expression levels in HMC-EVs when compared to AD-MSC-EVs. FIG. **64**C depicts the disease or function annotational of proteins that have lower expression levels in HMC-EVs when compared to AD-MSC-EVs. An activation z-score above 2 or below −2 is considered as the threshold value.

[0202] FIG. **65**A depicts the pathway enrichment of differential expression pattern between HMC-EVs and EVs secreted from umbilical cord blood-derived MSCs (UCB-MSC-EVs). Pathways that are upregulated in HMC-EVs have a positive z-score and are represented by orange bars. Pathways that are downregulated in HMC-EVs have a negative z-score and are represented by blue bars. White/gray bars represent pathways that are enriched in HMC-EVs, i.e., proteins contributing to these pathways are enriched. FIG. **65**B depicts the disease or function annotational of proteins that have higher expression levels in HMC-EVs when compared to UCB-MSC-EVs. FIG. **65**C depicts the disease or function annotational of proteins that have lower expression levels in HMC-EVs when compared to UCB-MSC-EVs. An activation z-score above 2 or below −2 is considered as the threshold value.

DETAILED DESCRIPTION

Definitions

[0203] “Pluripotent cells”, “pluripotent stem cells,” and “PSCs” as used herein, refer broadly to a cell capable of prolonged or virtually indefinite proliferation in vitro while retaining their undifferentiated state, exhibiting a stable (preferably normal) karyotype, and having the capacity to differentiate into all three germ layers (i.e., ectoderm, mesoderm and endoderm) under the appropriate conditions. Typically pluripotent cells (a) are capable of inducing teratomas when transplanted in immunodeficient (SCID) mice; (b) are capable of differentiating to cell types of all three germ layers (e.g., ectodermal, mesodermal, and endodermal cell types); and (c) express at least one hES cell marker (such as Oct-4, alkaline phosphatase, SSEA 3 surface antigen, SSEA 4 surface antigen, NANOG, TRA 1 60, TRA 1 81, SOX2, REX1). Exemplary pluripotent cells may express Oct-4, alkaline phosphatase, SSEA 3 surface antigen, SSEA 4 surface antigen, TRA 1 60, and/or TRA 1 81. Additional exemplary pluripotent cells include but are not limited to embryonic stem cells, induced pluripotent cells (iPS) cells, embryo-derived cells, pluripotent cells produced from embryonic germ (EG) cells (e.g., by culturing in the presence of FGF-2, LIF and SCF), parthenogenetic ES cells, ES cells produced from cultured inner cell mass cells (ICM), ES cells produced from a blastomere, and ES cells produced by nuclear transfer (e.g., a somatic cell nucleus transferred into a recipient oocyte). Exemplary pluripotent cells may be produced without destruction of an embryo. For example, induced pluripotent cells may be produced from cells obtained without embryo destruction. As a further example, pluripotent cells may be produced from a biopsied blastomere (which can be accomplished without harm to the remaining embryo); optionally, the remaining embryo may be cryopreserved, cultured, and/or implanted into a suitable host. Pluripotent cells (from whatever source) may be genetically modified or otherwise modified

to increase longevity, potency, homing, or to deliver a desired factor in cells that are differentiated from such pluripotent cells (for example, MSCs, and hemangioblasts). As non-limiting examples thereof, the pluripotent cells may be genetically modified to express Sirt1 (thereby increasing longevity), express one or more telomerase subunit genes optionally under the control of an inducible or repressible promoter, incorporate a fluorescent label, incorporate iron oxide particles or other such reagent (which could be used for cell tracking via in vivo imaging, MRI, etc., see Thu et al., Nat Med. 2012 Feb. 26; 18(3):463-7), express bFGF which may improve longevity (see Go et al., J. Biochem. 142, 741-748 (2007)), express CXCR4 for homing (see Shi et al., Haematologica. 2007 Jul; 92(7):897-904), express recombinant TRAIL to induce caspase-mediated apoptosis in cancer cells like Gliomas (see Sasportas et al., Proc Natl Acad Sci USA. 2009 Mar. 24; 106(12):4822-7), etc.

[0204] “Embryo” or “embryonic,” as used herein refers broadly to a developing cell mass that has not implanted into the uterine membrane of a maternal host. An “embryonic cell” is a cell isolated from or contained in an embryo. This also includes blastomeres, which may be obtained as early as the two-cell stage, and aggregated blastomeres.

[0205] “Embryonic stem cells” (ES cells or ESC) encompasses pluripotent cells produced from embryonic cells (such as from cultured inner cell mass cells or cultured blastomeres). Frequently such cells are or have been serially passaged as cell lines. Embryonic stem cells may be used as a pluripotent stem cell in the processes of producing hemangioblasts as described herein. For example, ES cells may be produced by methods known in the art including derivation from an embryo produced by any method (including by sexual or asexual means) such as fertilization of an egg cell with sperm or sperm DNA, nuclear transfer (including somatic cell nuclear transfer), or parthenogenesis. As a further example, embryonic stem cells also include cells produced by somatic cell nuclear transfer, even when non-embryonic cells are used in the process. For example, ES cells may be derived from the ICM of blastocyst stage embryos, as well as embryonic stem cells derived from one or more blastomeres. Such embryonic stem cells can be generated from embryonic material produced by fertilization or by asexual means, including somatic cell nuclear transfer (SCNT), parthenogenesis, and androgenesis. As further discussed above (see “pluripotent cells), ES cells may be genetically modified or otherwise modified to increase longevity, potency, homing, or to deliver a desired factor in cells that are differentiated from such pluripotent cells (for example, MSCs, and hemangioblasts).

[0206] ES cells may be generated with homozygosity or hemizygosity in one or more HLA genes, e.g., through genetic manipulation, screening for spontaneous loss of heterozygosity, etc. day ES cells may be genetically modified or otherwise modified to increase longevity, potency, homing, or to deliver a desired factor in cells that are differentiated from such pluripotent cells (for example, MSCs and hemangioblasts). Embryonic stem cells, regardless of their source or the particular method used to produce them, typically possess one or more of the following attributes: (i) the ability to differentiate into cells of all three germ layers, (ii) expression of at least Oct-4 and alkaline phosphatase, and (iii) the ability to produce teratomas when transplanted into immunocompromised animals. Embryonic stem cells that may be used in embodiments of the presently disclosed subject matter include, but are not limited to, human ES cells (“hESC” or “hES cells”) such as CT2, MA01, MA09, ACT-4, No. 3, H1, H7, H9, H14 and ACT30 embryonic stem cells. Additional exemplary cell lines include NED1, NED2, NED3, NED4, NED5, and NED7. See also NIH Human Embryonic Stem Cell Registry. An exemplary human embryonic stem cell line that may be used is MA09 cells. The isolation and preparation of MA09 cells was previously described in Klimanskaya, et al. (2006) “Human Embryonic Stem Cell lines Derived from Single Blastomeres.” Nature 444: 481-485. The human ES cells used in accordance with exemplary embodiments of the presently disclosed subject matter may be derived and maintained in accordance with GMP standards.

[0207] Exemplary hES cell markers include, but are not limited to: alkaline phosphatase, Oct-4,

Nanog, Stage-specific embryonic antigen-3 (SSEA-3), Stage-specific embryonic antigen-4 (SSEA-4), TRA-1-60, TRA-1-81, TRA-2-49/6E, Sox2, growth and differentiation factor 3 (GDF3), reduced expression 1 (REX1), fibroblast growth factor 4 (FGF4), embryonic cell-specific gene 1 (ESG1), developmental pluripotency-associated 2 (DPPA2), DPPA4, telomerase reverse transcriptase (hTERT), SALL4, E-CADHERIN, Cluster designation 30 (CD30), Cripto (TDGF-1), GCTM-2, Genesis, Germ cell nuclear factor, and Stem cell factor (SCF or c-Kit ligand). Additionally, embryonic stem cells may express Oct-4, alkaline phosphatase, SSEA 3 surface antigen, SSEA 4 surface antigen, TRA 1 60, and/or TRA 1 81.

[0208] The ESCs may be initially co-cultivated in any culture media known in the art that maintains the pluripotency of the ESCs, with or without feeder cells, such as murine embryonic feeder cells (MEF) cells or human feeder cells, such as human dermal fibroblasts (HDF). The MEF cells or human feeder cells may be mitotically inactivated, for example, by exposure to mitomycin C, gamma irradiation, or by any other known methods, prior to seeding ESCs in co-culture, and thus the MEFs do not propagate in culture. Additionally, ESC cell cultures may be examined microscopically and colonies containing non ESC cell morphology may be picked and discarded, e.g., using a stem cell cutting tool, by laser ablation, or other means. Typically, after the point of harvest of the ESCs for seeding for embryoid body formation no additional MEF cells or human feeder cells are used.

[0209] Alternatively, hES cells may be cultured under feeder-free conditions on a solid surface such as an extracellular matrix e.g. by any method known in the art, e.g., Klimanskaya et al., Lancet 365:1636-1641 (2005). Accordingly, the hES cells used in the methods described herein may be cultured on feeder-free cultures.

[0210] “Embryo-derived cells” (EDC), as used herein, refers broadly to pluripotent morula-derived cells, blastocyst-derived cells including those of the inner cell mass, embryonic shield, or epiblast, or other pluripotent stem cells of the early embryo, including primitive endoderm, ectoderm, and mesoderm and their derivatives. “EDC” also including blastomeres and cell masses from aggregated single blastomeres or embryos from varying stages of development, but excludes human embryonic stem cells that have been passaged as cell lines.

[0211] “Potency”, as used herein, refers broadly to the concentration, e.g., number of cells (such as hemangioblast-derived MSCs) that produces a defined effect. Potency may be defined in terms of effective concentration (EC50), which does not involve measurements of maximal effect but, instead, the effect at various locations along the concentration axis of dose response curves. Potency may also be determined from either graded (EC50) or quantal dose-response curves (ED50, TD50 and LD50); however, potency is preferably measured by EC50. The term “EC50” refers to the concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum effect after some specified exposure time. The EC50 of a graded dose response curve therefore represents the concentration of a compound where 50% of its maximal effect is observed. The EC50 of a quantal dose response curve represents the concentration of a compound where 50% of the population exhibit a response, after a specified exposure duration. The EC50 may be determined using animal studies in which a defined animal model demonstrates a measurable, physiological change in response to application of the drug; cell-based assays that use a specified cell system, which on addition of the drug, demonstrate a measurable biological response; and/or enzymatic reactions where the biological activity of the drug can be measured by the accumulation of product following the chemical reaction facilitated by the drug. Preferably, an immune regulatory assay is used to determine EC50. Non-limiting examples of such immune regulatory assays include intracellular cytokine, cytotoxicity, regulatory capacity, cell signaling capacity, proliferative capacity, apoptotic evaluations, and other assays.

[0212] “Mesenchymal stem cells” (MSCs) as used herein refers to multipotent stem cells with self-renewal capacity and the ability to differentiate into osteoblasts, chondrocytes, and adipocytes, among other mesenchymal cell lineages. Unless otherwise specifically noted, MSCs of the

presently disclosed subject matter are MSCs generated from in vitro differentiation of pluripotent stem cells, and which may be referred to herein as HMCs. In an embodiment, the HMCs may be generated by in vitro differentiation of pluripotent stem cells followed by differentiation to hemangioblasts, which are then differentiated into HMCs. HMCs may be identified by the expression of one or more markers as further described herein. HMCs may also have any of the characteristics described in WO 2013/082543, U.S. Pat. Nos. 8,962,321, and 8,961,956, the entire contents of which are hereby incorporated herein by reference.

[0213] HMCs may be genetically modified or otherwise modified to increase longevity, potency, homing, or to deliver a desired factor in the HMCs or cells that are differentiated from such HMCs. As non-limiting examples thereof, the HMCs may be genetically modified to express Sirt1 (thereby increasing longevity), express one or more telomerase subunit genes optionally under the control of an inducible or repressible promoter, incorporate a fluorescent label, incorporate iron oxide particles or other such reagent (which could be used for cell tracking via in vivo imaging, MRI, (see Thu et al., Nat Med. 2012 Feb. 26; 18(3):463-7), express bFGF which may improve longevity (see Go et al., J. Biochem. 142, 741-748 (2007)), express CXCR4 for homing (see Shi et al., Haematologica. 2007 July; 92(7):897-904), express recombinant TRAIL to induce caspase-mediated apoptosis in cancer cells like Gliomas (see Sasportas et al., Proc Natl Acad Sci USA. 2009 Mar. 24; 106(12):4822-7).

[0214] As used herein, the term “extracellular vesicle” or “EV” refers to lipid bound vesicles secreted by cells into the extracellular space. The three main subtypes of EVs are microvesicles (MVs), exosomes, and apoptotic bodies, which are differentiated based upon their biogenesis, release pathways, size, content, and function (Zaborowski M. P., et al. *Bioscience.* 2015; 65:783-797). Generally extracellular vesicles range in diameter from 20 nm to 5000 nm, and can comprise various macromolecular payload either within the internal space (i.e., lumen), displayed on the external surface of the extracellular vesicle, and/or spanning the membrane. Said payload can comprise nucleic acids, e.g., microRNAs (miRNA), long non-coding RNAs (lncRNA), mRNAs, DNA fragments; proteins, carbohydrates, lipids, small molecules, and/or combinations thereof. By way of example and without limitation, extracellular vesicles include apoptotic bodies, fragments of cells, vesicles derived from cells by direct or indirect manipulation (e.g., by serial extrusion or treatment with alkaline solutions), vesiculated organelles, and vesicles produced by living cells (e.g., by direct plasma membrane budding or fusion of the late endosome with the plasma membrane). Extracellular vesicles can be derived/secreted from a living or dead organism, explanted tissues or organs, prokaryotic or eukaryotic cells, and/or cultured cells.

[0215] “Optic neuropathy”, as used herein, includes any disease, disorder or condition that involves damage to the optic nerve. Optic neuropathy includes hereditary (e.g., autosomal dominant optic atrophy (Kjer's disease) and maternally inherited Leber's hereditary optic neuropathy) and non-hereditary optic neuropathy (e.g., ischemic optic neuropathy). In one embodiment, optic neuropathy is glaucoma/glaucomatic optic neuropathy.

[0216] “Therapy,” “therapeutic,” “treating,” “treat” or “treatment”, as used herein, refers broadly to treating a disease, arresting or reducing the development of the disease or its clinical symptoms, and/or relieving the disease, causing regression of the disease or its clinical symptoms. “Therapy”, “therapeutic,” “treating,” “treat” or “treatment” encompasses prophylaxis, prevention, treatment, cure, remedy, reduction, alleviation, and/or providing relief from a disease, signs, and/or symptoms of a disease. “Therapy”, “therapeutic,” “treating,” “treat” or “treatment” encompasses an alleviation of signs and/or symptoms in patients with ongoing disease signs and/or symptoms. “Therapy”, “therapeutic,” “treating,” “treat” or “treatment” also encompasses “prophylaxis” and “prevention”. Prophylaxis includes preventing disease occurring subsequent to treatment of a disease in a patient or reducing the incidence or severity of the disease in a patient. The term “reduced”, for purpose of therapy, “therapeutic,” “treating,” “treat” or “treatment” refers broadly to the clinical significant reduction in signs and/or symptoms. “Therapy”, “therapeutic,” “treating,”

“treat” or “treatment” includes treating relapses or recurrent signs and/or symptoms. “Therapy”, “therapeutic,” “treating,” “treat” or “treatment” encompasses but is not limited to precluding the appearance of signs and/or symptoms anytime as well as reducing existing signs and/or symptoms and eliminating existing signs and/or symptoms. “Therapy”, “therapeutic,” “treating,” “treat” or “treatment” includes treating chronic disease (“maintenance”) and acute disease. For example, treatment includes treating or preventing relapses or the recurrence of signs and/or symptoms.

[0217] As used herein, the term “effective amount,” is intended to include the amount of HMCs and/or HMC-EVs that, when administered to a subject having a brain injury, is sufficient to effect treatment of the disease (e.g., by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The “effective amount” may vary depending on the nature of the HMC and/or HMC-EVs, how the HMC and/or HMC-EVs are administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

[0218] An “effective amount” also includes an amount of HMC and/or HMC-EVs that produces some desired effect at a reasonable benefit/risk ratio applicable to any treatment. The HMC and/or HMC-EVs employed in the methods of the presently disclosed subject matter may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

[0219] “Normalizing a pathology”, as used herein, refers to reverting the abnormal structure and/or function resulting from a disease to a more normal state. Normalization suggests that by correcting the abnormalities in structure and/or function of a tissue, organ, cell type, etc. resulting from a disease, the progression of the pathology can be controlled and improved. For example, following treatment with the HMCs of the presently disclosed subject matter the abnormalities of the brain as a result of brain injury, e.g., traumatic brain injury, may be improved, corrected, and/or reversed.

[0220] “Induced pluripotent stem cells” or “iPSCs” or “iPS cells” as used herein refer to pluripotent stem cells generated by reprogramming a somatic cell. iPSCs may be generated by expressing or inducing expression of a combination of factors (“reprogramming factors”). iPS cells may be generated using fetal, postnatal, newborn, juvenile, or adult somatic cells. iPS cells may be obtained from a cell bank. Alternatively, iPS cells may be newly generated (by processes known in the art) prior to commencing differentiation to MSCs or another cell type. The making of iPS cells may be an initial step in the production of differentiated cells. iPS cells may be specifically generated using material from a particular patient or matched donor with the goal of generating tissue-matched MSC cells. iPS cells can be produced from cells that are not substantially immunogenic in an intended recipient, e.g., produced from autologous cells or from cells histocompatible to an intended recipient. As further discussed above (see “pluripotent cells”), pluripotent cells including iPS cells may be genetically modified or otherwise modified to increase longevity, potency, homing, or to deliver a desired factor in cells that are differentiated from such pluripotent cells (for example, MSCs and hemangioblasts).

[0221] As a further example, induced pluripotent stem cells may be generated by reprogramming a somatic or other cell by contacting the cell with one or more reprogramming factors. For example, the reprogramming factor(s) may be expressed by the cell, e.g., from an exogenous nucleic acid added to the cell, or from an endogenous gene in response to a factor such as a small molecule, microRNA, or the like that promotes or induces expression of that gene (see Suh and Blelloch, Development 138, 1653-1661 (2011); Miyoshi et al., Cell Stem Cell (2011), doi:10.1016/j.stem.2011.05.001; Sancho-Martinez et al., Journal of Molecular Cell Biology (2011) 1-3; Anokye-Danso et al., Cell Stem Cell 8, 376-388, Apr. 8, 2011; Orkin and Hochedlinger, Cell 145, 835-850, Jun. 10, 2011, each of which is incorporated by reference herein in its entirety). Reprogramming factors may be provided from an exogenous source, e.g., by being added to the culture media, and may be introduced into cells by methods known in the art such as through

coupling to cell entry peptides, protein or nucleic acid transfection agents, lipofection, electroporation, biolistic particle delivery system (gene gun), microinjection, and the like. In certain embodiments, factors that can be used to reprogram somatic cells to pluripotent stem cells include, for example, a combination of Oct4 (sometimes referred to as Oct 3/4), Sox2, c-Myc, and Klf4. In other embodiments, factors that can be used to reprogram somatic cells to pluripotent stem cells include, for example, a combination of Oct-4, Sox2, Nanog, and Lin28. In other embodiments, somatic cells are reprogrammed by expressing at least 2 reprogramming factors, at least three reprogramming factors, or four reprogramming factors. In another embodiment, somatic cells are reprogrammed by expressing Oct4, Sox2, MYC, Klf4, Nanog, and Lin28. In other embodiments, additional reprogramming factors are identified and used alone or in combination with one or more known reprogramming factors to reprogram a somatic cell to a pluripotent stem cell. iPS cells typically can be identified by expression of the same markers as embryonic stem cells, though a particular iPS cell line may vary in its expression profile.

[0222] The induced pluripotent stem cell may be produced by expressing or inducing the expression of one or more reprogramming factors in a somatic cell. In an embodiment, the somatic cell is a fibroblast, such as a dermal fibroblast, synovial fibroblast, or lung fibroblast, or a non-fibroblastic somatic cell. In an embodiment, the somatic cell is reprogrammed by expressing at least 1, 2, 3, 4, 5 reprogramming factors as described above. In another embodiment, expression of the reprogramming factors may be induced by contacting the somatic cells with at least one agent, such as a small organic molecule agent, that induces expression of reprogramming factors.

[0223] The somatic cell may also be reprogrammed using a combinatorial approach wherein the reprogramming factor is expressed (e.g., using a viral vector, plasmid, and the like) and the expression of the reprogramming factor is induced (e.g., using a small organic molecule.) For example, reprogramming factors may be expressed in the somatic cell by infection using a viral vector, such as a retroviral vector or a lentiviral vector. Also, reprogramming factors may be expressed in the somatic cell using a non-integrative vector, such as an episomal plasmid or mRNA. See, e.g., Yu et al., Science. 2009 May 8; 324(5928):797-801, which is hereby incorporated by reference in its entirety. When reprogramming factors are expressed using non-integrative vectors, the factors may be expressed in the cells using electroporation, transfection, or transformation of the somatic cells with the vectors.

[0224] Once the reprogramming factors are expressed in the cells, the cells may be cultured by any method known in the art. Over time, cells with ES characteristics appear in the culture dish. The cells may be chosen and subcultured based on, for example, ES morphology, or based on expression of a selectable or detectable marker. The cells may be cultured to produce a culture of cells that resemble ES cells—these are putative iPS cells. iPS cells typically can be identified by expression of the same markers as other embryonic stem cells, though a particular iPS cell line may vary in its expression profile. Exemplary iPS cells may express Oct-4, alkaline phosphatase, SSEA3 surface antigen, SSEA4 surface antigen, TRA160, and/or TRA181.

[0225] To confirm the pluripotency of the iPS cells, the cells may be tested in one or more assays of pluripotency. For example, the cells may be tested for expression of ES cell markers; the cells may be evaluated for ability to produce teratomas when transplanted into SCID mice; the cells may be evaluated for ability to differentiate to produce cell types of all three germ layers. Once a pluripotent iPS cell is obtained it may be used to produce hemangioblast and MSC cells.

[0226] “Hemangioblasts” or “HBs” as used herein refer to multipotent cells and serve as the common precursor to both hematopoietic and endothelial cell lineages. During embryonic development, they are believed to arise as a transitional cell type that emerges during early mesoderm development and colonizes primitive blood islands (Choi et al. Development 125 (4): 725-732 (1998). Once there, hemangioblasts are capable of giving rise to both primitive and definitive hematopoietic cells, HSCs, and endothelial cells (Mikkola et al, J. Hematother. Stem Cell Res 11(1): 9-17 (2002).

[0227] Hemangioblasts may be derived in vitro from both mouse PSCs (Kennedy et al, Nature (386): 488-493 (1997); Perlingeiro et al, Stem Cells (21): 272-280 (2003)) and human PSCs (ref. 14, 15, Yu et al., Blood 2010 116: 4786-4794). Other studies claim to have isolated hemangioblasts from umbilical cord blood (Bordoni et al, Hepatology 45 (5) 1218-1228), circulating CD34− lin− CD45− CD133− cells from peripheral blood (Ciraci et al, Blood 118: 2105-2115), and from mouse uterus (Sun et al, Blood 116 (16): 2932-2941 (2010)). Both mouse and human PSC-derived hemangioblasts have been obtained through the culture and differentiation of clusters of cells grown in liquid culture followed by growth of the cells in semi-solid medium containing various cytokines and growth factors (Kennedy, Perlingeiro, ref 14, 15); see also, U.S. Pat. No. 8,017,393, which is hereby incorporated by reference in its entirety. In an embodiment, hemangioblasts may be generated in vitro from pluripotent stem cells according to the methods described in, for example, U.S. Pat. Nos. 9,938,500; 9,410,123; and WO 2013/082543, all of which are incorporated herein by reference in their entireties. The term hemangioblasts also includes the hemangio-colony forming cells described in U.S. Pat. No. 8,017,393 (incorporated herein by reference in its entirety), which in addition to being capable of differentiating into hematopoietic and endothelial cell lineages, are capable of becoming smooth muscle cells and which are not positive for CD34, CD31, KDR, and CD133. In another embodiment, the hemangioblasts are positive for the blood markers CD43 and CD45 and express low levels or are negative for the pericyte markers CD146, PDGRb, and/or NG2.

[0228] Hemangioblasts useful in the methods described herein may be derived or obtained from any of these known methods or any method described herein. For example, embryoid bodies may be formed by culturing pluripotent cells under non-attached conditions, e.g., on a low-adherent substrate, in a “hanging drop”, or through the Able Biott spin bioreactor. In these cultures, PSCs can form clumps or clusters of cells denominated as embryoid bodies. See Itskovitz-Eldor et al., Mol Med. 2000 February; 6(2):88-95, which is hereby incorporated by reference in its entirety. Typically, embryoid bodies initially form as solid clumps or clusters of pluripotent cells, and over time some of the embryoid bodies come to include fluid filled cavities, the latter former being referred to in the literature as “simple” EBs and the latter as “cystic” embryoid bodies. Id. The cells in these EBs (both solid and cystic forms) can differentiate and over time produce increasing numbers of cells. Optionally EBs may then be cultured as adherent cultures and allowed to form outgrowths. Likewise, pluripotent cells that are allowed to overgrow and form a multilayer cell population can differentiate over time.

[0229] In one embodiment, hemangioblasts are generated by the steps comprising (a) culturing a PSC line for 2, 3, 4, 5, 6 or 7 days to form clusters of cells (embryoid bodies; EBs), and (b) inducing said clusters of cells or EBs to differentiate into hemangioblasts. In a further embodiment, the clusters of cells or EBs in step (b) of are cultured in a cytokine-rich serum-free methylcellulose based medium. In an embodiment, hemangioblasts are generated by inducing differentiation of any pluripotent cell as described herein.

[0230] In one embodiment, the clusters of cells or EBs are cultured for at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 days in culture in a serum free methylcellulose medium comprising one or more ingredients selected from the group comprising penicillin/streptomycin (pen/strp), EX-CYTE® growth supplement (a water-soluble concentrate comprising 9.0-11.0 g/L cholesterol and 13.0-18.0 g/L lipoproteins and fatty acids at pH 7-8.4), Flt3-ligand (FL), vascular endothelial growth factor (VEGF), thrombopoietin (TPO), basic fibroblast growth factor (bFGF), stem cell derived factor (SCF), granulocyte macrophage colony stimulating factor (GM-CSF), interleukin 3 (IL3), and interleukin 6 (IL6), and producing hemangioblasts. In a preferred embodiment of the instant presently disclosed subject matter, hemangioblasts are harvested between 6-14 days, of being cultured in, for example, serum-free methylcellulose plus one or more of the ingredients of the previous embodiment. In a preferred embodiment, the one or more ingredients may be present in said medium at the following concentrations: Flt3-ligand (FL) at 50

ng/ml, vascular endothelial growth factor (VEGF) at 50 ng/ml, thrombopoietin (TPO) at 50 ng/ml, and basic fibroblast growth factor (bFGF) at 20-30 ng/ml, 50 ng/ml stem cell derived factor (SCF), 20 ng/ml granulocyte macrophage colony stimulating factor (GM-CSF), 20 ng/ml interleukin 3 (IL3), and 20 ng/ml interleukin 6 (IL6).

In vitro Generation of Mesenchymal Stem Cells

[0231] An embodiment of the instant presently disclosed subject matter comprises methods of producing mesenchymal stem cells (hereinafter, “HMCs”) by in vitro differentiation of hemangioblasts. The hemangioblasts may be obtained by any of the methods described herein. In an embodiment, the hemangioblasts are obtained by in vitro differentiation of pluripotent stem cells. Pluripotent stem cells can be cultured on feeders (e.g., human dermal fibroblasts, or mouse embryonic fibroblasts), or in feeder-free conditions. In some embodiments, hemangioblasts are cultured in feeder-free conditions then plated on an extracellular matrix. In another embodiment, said extracellular matrix is selected from the group consisting of laminin, fibronectin, vitronectin, proteoglycan, entactin, collagen, collagen I, collagen IV, heparan sulfate, a soluble preparation from Engelbreth-Holm-Swarm (EHS) mouse sarcoma cells, Matrigel, and a human basement membrane extract. In a still further embodiment, said extracellular matrix may be derived from any mammalian, including human, origin.

[0232] In another embodiment, hemangioblasts are re-plated and cultured for at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 days forming a preparation of HMCs. In an embodiment, initial plating of hemangioblasts onto substrate-coated tissue culture dishes may be done at a concentration of about 50,000 to about 100,000 cells/cm.sup.2. During culturing of hemangioblasts, a portion of hemangioblasts adheres to the culture plate and begins to differentiate into HMCs. Adherent cells are passaged every 3-6 days or more than 6 days, e.g., about 6-10 days, or about 10-15 days, depending on their growth rate, plating density, and perceived degree of confluence. For passaging, harvest density may be about 5,000 to about 20,000 cells/cm.sup.2, or about 20,000 to about 40,000 cells/cm.sup.2. After the cells are harvested, cells are counted and may be replated at a density of between about 2500 to about 6000 cells/cm.sup.2. In one embodiment, HMCs are generated by the steps comprising (a) culturing ESCs for 8-12 days and producing hemangioblasts, (b) harvesting hemangioblasts, (c) re-plating the hemangioblasts of step (b), and (d) culturing the hemangioblasts of step (c) for between 14-30 days.

[0233] In one embodiment, the hemangioblasts are harvested, re-plated and cultured in liquid medium under feeder-free conditions wherein no feeder layer of cells such as mouse embryonic fibroblasts, OP9 cells, or other cell types known to one of ordinary skill in the art are contained in the culture. In a preferred embodiment, hemangioblasts are cultured on an extracellular matrix. In a further preferred embodiment, hemangioblasts are cultured on an extracellular matrix, wherein said matrix comprises a soluble preparation from Engelbreth-Holm-Swarm (EHS) mouse sarcoma cells that gels at room temperature to form a reconstituted basement membrane (Matrigel). In a still further preferred embodiment, hemangioblasts are formed according to the steps comprising (a) culturing said hemangioblasts on an extracellular matrix for at least 7 days, (b) transferring the hemangioblasts of step (a) to non-coated tissue culture plate and further culturing said hemangioblasts of step (b) for between about 7 to 14 days. The hemangioblasts may be cultured in the presence of one or more of the factors selected from the group consisting of: transforming growth factor beta (TGF-beta), epidermal growth factor (EGF), insulin-like growth factor 1, bovine fibroblast growth factor (bFGF), and/or platelet-derived growth factor (PDGF). In an embodiment, the extracellular matrix is selected from the group consisting of Human Basement Membrane Extract (BME) (e.g., Cultrex BME, Trevigen) or an EHS matrix, laminin, fibronectin, vitronectin, proteoglycan, entactin, collagen (e.g., collagen I, collagen IV), and heparan sulfate. Said extracellular matrix or matrix components may be of mammalian, or more specifically human, origin. In one embodiment, hemangioblasts are cultured in a liquid medium comprising serum on

an extracellular matrix protein-coated plate, wherein the culture medium may comprise ingredients selected from αMEM (Sigma-Aldrich) supplemented with 10-20% fetal calf serum (αMEM+20% FCS), αMEM supplemented with 10-20% heat-inactivated human AB serum, and IMDM supplemented with 10-20% heat inactivated AB human serum.

[0234] In another embodiment, hemangioblasts are cultured in a medium comprising serum or a serum replacement, such as αMEM supplemented with 20% fetal calf serum. In another embodiment, hemangioblasts are cultured in a serum-free medium.

[0235] In a further embodiment, hemangioblasts are cultured on an extracellular matrix for about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 days. In a still further embodiment of the instant presently disclosed subject matter, HMCs are generated by the steps comprising (a) culturing hemangioblasts on an extracellular matrix for about 7 days, (b) transferring the hemangioblasts of step (a) to an uncoated tissue culture dish and culturing the hemangioblasts for an additional 9-100 days, about 9, 10, 11, 12, 13,14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 days. In yet another embodiment, HMCs are generated by the steps comprising (a) culturing hemangioblasts on an extracellular matrix for about 7 days, (b) transferring the hemangioblasts of step (a) to a coated tissue culture dish and culturing the hemangioblasts for an additional 9-100 days, about 9, 10, 11, 12, 13,14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 days.

[0236] In an embodiment of the instant presently disclosed subject matter, hemangioblasts are differentiated from PSCs by following the steps comprising: (a) culturing PSCs in the presence of vascular endothelial growth factor (VEGF) and/or bone morphogenic protein 4 (BMP-4) (by way of non-limiting examples) to form clusters of cells or EBs; (b) culturing said clusters of cells or EBs in the presence of at least one growth factor (e.g., basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), bone morphogenic protein 4 (BMP-4), stem cell factor (SCF), Flt 3L (FL), thrombopoietin (TPO), and/or tPTD-HOXB4) in an amount sufficient to induce the differentiation of said clusters of cells or EBs into hemangioblasts; and (c) culturing said hemangioblasts in a medium comprising at least one additional growth factor (e.g., insulin, transferrin, granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO), stem cell factor (SCF), vascular endothelial growth factor (VEGF), bone morphogenic protein 4 (BMP-4), and/or tPTD-HOXB4), wherein said at least one additional growth factor is provided in an amount sufficient to expand said clusters of cells in said culture, and wherein copper is optionally added to any of the steps (a)-(c).

[0237] In an embodiment of the instant presently disclosed subject matter, HMCs are generated by culturing hemangioblasts, wherein said hemangioblasts are differentiated from PSCs by following the steps comprising: (a) culturing PSCs in the presence of vascular endothelial growth factor (VEGF) and bone morphogenic protein 4 (BMP-4) within 0-48 hours of initiation of said culture to form clusters of cells or EBs; (b) culturing said clusters of cells or EBs in the presence of at least one growth factor selected from the group comprising basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), bone morphogenic protein 4 (BMP-4), stem cell factor (SCF), Flt 3L (FL), thrombopoietin (TPO), and tPTD-HOXB4 in an amount sufficient to induce the differentiation of said clusters of cells or EBs into hemangioblasts; and (c) culturing said hemangioblasts in a medium comprising at least one additional growth factor selected from the group consisting of insulin, transferrin, granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO), stem cell factor (SCF), vascular endothelial growth factor (VEGF), bone morphogenic protein 4 (BMP-4), and tPTD-HOXB4, wherein said at least one additional growth factor is provided in an amount sufficient to expand hemangioblasts in said culture.

[0238] In another embodiment, HMCs are generated by the steps comprising: (a) harvesting hemangioblasts after at least 6, 7, 8, 9, 10, 11, 12, 13, or 14 days of inducing PSCs to differentiate

into said hemangioblasts, and (b) harvesting HMCs that are generated within about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 days of inducing said hemangioblasts from step (a) to differentiate into said mesenchymal cells.

[0239] In yet another embodiment, a preparation of at least 80, 85, 90, 95, 100, 125 or 125 million HMCs are generated from about 200,000 hemangioblasts within about 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days of culturing the hemangioblasts, wherein said preparation of HMCs comprises less than about 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% human embryonic stem cells. In still another embodiment, at least 80, 85, 90, 100, 125 or 150 million HMCs are generated from about 200,000 hemangioblasts within about 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 days of culturing the hemangioblasts.

Extracellular Vesicles Secreted from Mesenchymal Stem Cells

[0240] The presently disclosed subject matter also provides extracellular vesicles isolated, derived, secreted, or released from a cell, e.g., the HMCs of the presently disclosed subject matter.

[0241] As used herein, the term “extracellular vesicle” or “EV” refers to lipid bound vesicles secreted by cells into the extracellular space. The three main subtypes of EVs are microvesicles (MVs), exosomes, and apoptotic bodies, which are differentiated based upon their biogenesis, release pathways, size, content, and function (Zaborowski M. P., et al. *Bioscience.* 2015; 65:783-797). Generally extracellular vesicles range in diameter from 20 nm to 5000 nm, and can comprise various macromolecular payload either within the internal space (i.e., lumen), displayed on the external surface of the extracellular vesicle, and/or spanning the membrane. Said payload can comprise nucleic acids, e.g., microRNAs (miRNA), long non-coding RNAs (lncRNA), mRNAs, DNA fragments; proteins, carbohydrates, lipids, small molecules, and/or combinations thereof. By way of example and without limitation, extracellular vesicles include apoptotic bodies, fragments of cells, vesicles derived/secreted from cells by direct or indirect manipulation (e.g., by serial extrusion or treatment with alkaline solutions), vesiculated organelles, and vesicles produced by living cells (e.g., by direct plasma membrane budding or fusion of the late endosome with the plasma membrane). Extracellular vesicles can be derived/secreted from a living or dead organism, explanted tissues or organs, prokaryotic or eukaryotic cells, and/or cultured cells.

[0242] As used herein, the term “exosome” refers to a cell-derived small vesicle comprising a membrane that encloses an internal space (i.e., lumen), and which is formed from said cell by direct plasma membrane budding or by fusion of the late endosome with the plasma membrane (Yáñez-Mó M., et al. *J. Extracell. Vesicles.* 2015; 4:27066). Specifically, exosomes are involved in protein sorting, recycling, storage, transport, and release. Exosomes are generally between 20-300 nm in diameter. Exosomes are secreted by all cell types and have been found in plasma, urine, semen, saliva, bronchial fluid, cerebral spinal fluid (CSF), breast milk, serum, amniotic fluid, synovial fluid, tears, lymph, bile, and gastric acid.

[0243] Exosomes have been found to participate in cell-cell communication, cell maintenance, and tumor progression. In addition, exosomes have been found to stimulate immune responses by acting as antigen-presenting vesicles (Bobrie A., et al., *Traffic.* 2011; 12:1659-1668). In the nervous system, exosomes haven been found to help promote myelin formation, neurite growth, and neuronal survival, thus playing a role in tissue repair and regeneration (Faure J., et al. *Mol. Cell. Neurosci.* 2006; 31:642-648). At the same time, exosomes in the central nervous system (CNS) have been found to contain pathogenic proteins, such as beta amyloid peptide, superoxide dismutase, and alpha synuclein that may aid in disease progression (Fevrier B., et al., *Proc. Natl. Acad. Sci. USA.* 2004; 101:9683-9688). Exosomes have also been shown as carriers for disease markers. The use of exosomes as carriers of biomarkers is ideal because these vesicles are found in bodily fluids, such as blood and urine, which allows for minimally to non-invasive “liquid biopsy”

type methods to diagnose and even monitor a patient's response to treatment.
[0244] In addition to their natural role in cell-cell interactions, exosomes can be loaded with different cargos, e.g., drugs and exogenous nucleic acids or proteins, and deliver this cargo to different cells. The cargo can be conjugated to an extracellular vesicle, embedded within an extracellular vesicle, encapsulated within an extracellular vesicle, or otherwise carried by an extracellular vesicle, or any combination thereof. Thus, as used herein, a reference to a cargo being "present" in an extracellular vesicle or its lumen is understood to include any of the foregoing means of carrying the cargo.
[0245] A cargo can be an endogenous cargo, an exogenous cargo, or a combination thereof. Examples of cargos that can be conjugated, embedded, encapsulated within or otherwise carried by an extracellular vesicle described herein include, without limitation, nucleic acid molecules (e.g., DNA, cDNA, antisense oligonucleotides, mRNA, inhibitory RNAs (e.g., antisense RNAs, miRNAs, small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), and agomiRs), antagomiRs, primary miRNAs (pri-miRNAs), long non-coding RNAs (lncRNAs), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), and microbial RNAs), polypeptides (e.g., enzymes, antibodies), lipids, hormones, vitamins, minerals, small molecules, and pharmaceuticals, or any combination thereof. Importantly, exosomes, are natural carriers for miRNAs and other non-coding RNAs, and the direct membrane fusion with the target cell allows contents to be delivered directly into the cytosol. This makes exosomes an excellent delivery system for small molecules (Lai R. C., et al. *Biotechnol. Adv.* 2013; 31:543-551).
[0246] Microvesicles are EVs that form by direct outward budding, or pinching, of the cell's plasma membrane. The size of microvesicles typically range from 100 nm up to 1000 nm in diameter. The route of microvesicles formation is not well understood, however, it is thought to require cytoskeleton components, such as actin and microtubules, along with molecular motors (kinesins and myosins), and fusion machinery (SNAREs and tethering factors) (Cai H., et al. *Dev. Cell.* 2007; 12:671-682). The number of microvesicles produced depends on the donor cell's physiological state and microenvironment (Zaborowski M. P., et al. *Bioscience.* 2015; 65:783-797). Likewise, it has been previously demonstrated that the number of microvesicles consumed depends on the physiological state and microenvironment of recipient cells. Like exosomes, microvesicles are involved in cell-cell communication between local and distant cells. The ability of these EVs to alter the recipient cell has been well demonstrated (Harding C. V., et al., *J. Cell Biol.* 2013; 200:367-371; White I. J., et al., *EMBO J.* 2006; 25:1-12). The uniqueness of EVs is that they have the ability to package active cargo (proteins, nucleic acids, and lipids) and deliver it to another cell, neighboring or distant, and alter the recipient cell's functions with its delivery.
[0247] Apoptotic bodies are released by dying cells into the extracellular space. They are reported to range in size from 50 nm up to 5000 nm in diameter, with the size of most apoptotic bodies tending to be on the larger side (Borges F., et al. *Braz. J. Med. Biol. Res.* 2013; 46:824-830). These bodies form by a separation of the cell's plasma membrane from the cytoskeleton as a result of increased hydrostatic pressure after the cell contracts (Wickman G., et al. *Cell Death Differ.* 2012; 19:735-742). The composition of apoptotic bodies is in direct contrast with exosomes and microvesicles. Unlike exosomes and microvesicles, apoptotic bodies contain intact organelles, chromatin, and small amounts of glycosylated proteins (Borges F., et al., *Braz. J. Med. Biol. Res.* 2013; 46:824-830; Thery C., et al. *J. Immunol.* 2001; 166:7309-7318).
Methods for Isolating Extracellular Vesicles
[0248] The EVs of the presently disclosed subject matter can be isolated, secreted, derived, or separated, from a medium or other source material, e.g., the HMCs of the presently disclosed subject matter, using routine methods known in the art (see, for example the techniques described in Taylor et al., Serum/Plasma Proteomics, Chapter 15, "Extracellular vesicle Isolation for Proteomic Analyses and RNA Profiling," Springer Science, 2011; and Tauro et al., Methods 56 (2012) 293-304, and references cited therein) and as described in the Examples section below. The

most commonly used method involves multiple centrifugation and ultracentrifugation steps.
[0249] Physical properties of EVs (e.g., HMC-EVs) may be employed for EV isolation, purification or enrichment, including separation on the basis of electrical charge (e.g., electrophoretic separation), size (e.g., filtration, molecular sieving, etc), density (e.g., regular or gradient centrifugation), Svedberg constant (e.g., sedimentation with or without external force, etc). Alternatively, or additionally, isolation may be based on one or more biological properties, and include methods that may employ surface markers (e.g., for precipitation, reversible binding to solid phase, FACS separation, specific ligand binding, non-specific ligand binding, immuno-magnetic capture of EVs using magnetic beads coated with antibodies directed against proteins exposed on EV membranes, etc.).
[0250] Methods based on the use of volume-excluding polymers, such as PEG, have been recently described by a number of different groups (U.S. Pat. Appl. 20130273544, U.S. Pat. Appl. 20130337440). Two such products are ExoQuick (System Biosciences, Mountain View, USA) and Total Exosome Isolation Reagent (Life Technologies, Carlsbad, USA). These polymers work by tying up water molecules and forcing less-soluble components such as extracellular vesicles, as well as proteins out of solution, allowing them to be collected by a short, low-speed centrifugation.
[0251] In some embodiments, isolation, purification, and enrichment can be done in a general and non-selective manner (typically including serial centrifugation). Alternatively, isolation, purification, and enrichment can be done in a more specific and selective manner (e.g., using producer cell-specific surface markers). For example, specific surface markers may be used in immunoprecipitation, FACS sorting, affinity purification, or bead-bound ligands for magnetic separation.
[0252] In some embodiments, tangential flow filtration may be used to isolate or purify the EVs (e.g., HMC-EVs).
[0253] In some embodiments, size exclusion chromatography can be utilized to isolate or purify the EVs (e.g., HMC-EVs). Size exclusion chromatography techniques are known in the art. In some embodiments, density gradient centrifugation can be utilized to isolate the EVs. In some embodiments, the isolation of EVs (e.g., HMC-EVs) may involve ion chromatography, such as anion exchange, cation exchange, or mixed mode chromatography. In some embodiments, the isolation of EVs (e.g., HMC-EVs) may involve desalting, dialysis, tangential flow filtration, ultrafiltration, or diafiltration, or any combination thereof. In some embodiments, the isolation of EVs (e.g., HMC-EVs) may involve combinations of methods that include, but are not limited to, differential centrifugation, size-based membrane filtration, concentration and/or rate zonal centrifugation. In some embodiments, the isolation of EVs (e.g., HMC-EVs) may involve one or more centrifugation steps. The centrifugation may be performed at about 50,000 to 150,000-g. The centrifugation may be performed at about 50,000×g, 75,000×g, 100,000×g, 125,000×g, or 150,000×g. In another embodiment, EVs (e.g., HMC-EVs) are separated from nonmembranous particles, using their relatively low buoyant density (Raposo et al., 1996; Escola et al., 1998; van Niel et al., 2003; Wubbolts et al., 2003). Kits for such isolation are commercially available, for example, from Qiagen, InVitrogen and SBI. Methods for loading EVs with a therapeutic agent are known in the art and include lipofection, electroporation, as well as any standard transfection method.
[0254] In some embodiments, the presently disclosed subject matter provides methods for isolating HMC-EVs secreted from HMCs obtained by in vitro differentiation of pluripotent stem cells. The method comprises providing HMCs obtained by in vitro differentiation of pluripotent stem cells, and isolating extracellular vesicles. The HMC-EVs may be isolated by any method known in the art or as described herein. In some embodiments, the HMC-EVs are isolated by tangential flow filtration. In some embodiments, the HMC-EVs are isolated by ultracentrifugation. In some embodiments, the HMC-EVs are isolated by cation exchange chromatography. In some embodiments, the HMC-EVs are isolated by anion exchange chromatography.

Characteristics and Compositions of HMCs and/HMC-EVs

[0255] The presently disclosed subject matter further provides compositions comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, and/or extracellular vesicles secreted from the HMCs (HMC-EVs) of the presently disclosed subject matter. In an embodiment, the HMCs are obtained by in vitro differentiation of hemangioblasts. Expression levels of certain phenotypic markers may be determined by any method known in the art, such as immunohistochemistry. Expression of certain genes may be determined by any method known in the art, such as RT-PCR and RNA-Seq.

[0256] In an embodiment, the HMCs of the presently disclosed subject matter express at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 markers selected from the group comprising CD9, CD13, CD29, CD44, CD73, CD90, CD105, CD166, and HLA-ABC. A still further embodiment, the HMCs of the presently disclosed subject matter express at least 2, at least 3, at least 4, at least 5 or at least 6 markers selected from the group consisting of CD9, CD13, CD29, CD44, CD73, CD90 and CD105, and wherein said HMCs s do not express CD2, CD3, CD4, CD5, CD7, CD8, CD14, CD15, CD16, CD19, CD20, CD22, CD33, CD36, CD38, CD61, CD62E and CD133. In another embodiment, the HMCs of the presently disclosed subject matter express at least 1, at least 2, at least 3, at least 4, at least 5 or at least 6 markers selected from the group consisting of AIRE-1, IL-11, CD10, CD24, ANG-1, and CXCL1.

[0257] In an embodiment, the composition comprises HMCs, wherein about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% of the HMCs express CD9, CD13, CD29, CD44, CD73, CD90, CD105, CD166, and HLA-abc after about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days in culture. In an embodiment of the instant presently disclosed subject matter at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% of the HMCs in a composition of the presently disclosed subject matter express at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 markers selected from the group consisting of CD9, CD13, CD29, CD44, CD73, CD90, CD105, CD166, and HLA-ABC and lack expression of CD2, CD3, CD4, CD5, CD7, CD8, CD14, CD15, CD16, CD19, CD20, CD22, CD33, CD36, CD38, CD61, CD62E, CD133 and Stro-1 after about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days in culture. The HMCs in a composition of the presently disclosed subject matter may further express at least 1, at least 2, at least 3, at least 4, at least 5 or at least 6 markers selected from the group consisting of AIRE-1, IL-11, CD10, CD24, ANG-1, and CXCL1.

[0258] In an embodiment, the composition comprises HMCs, wherein at least 30% of the HMCs are positive for CD10. Additionally, at least 60% of the HMCs may be positive for markers CD73, CD90, CD105, CD13, CD29, CD44, and CD166 and HLA-ABC. In an exemplary embodiment, less than 30% of the HMCs may be positive for markers CD31, CD34, CD45, CD133, FGFR2, CD271, Stro-1, CXCR4 and TLR3.

[0259] In another embodiment, the composition comprises HMCs, wherein at least 50% of the HMCs are positive for CD105 or CD73 within about 7-20 (e.g., 15) days of culture. In a preferred embodiment of the instant presently disclosed subject matter, at least 50% of the HMCs are positive for CD105 or CD73 after about 7-15 days of culture. In a further embodiment of the instant presently disclosed subject matter, at least 80% of the HMCs are positive for CD105 and CD73 within about 20 days of culture. In still a further embodiment of the instant presently disclosed subject matter, at least 80% of a composition of HMCs are positive for CD105 and CD73 within about 20 days of culture.

[0260] In an embodiment, the composition comprises HMCs, wherein at least 20%, 30%, 40%, or 50% of said HMCs may be positive for (i) at least one of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73 and CD90; (ii) at least one of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73, CD90, CD105, CD13, CD29, CD44, CD166, CD274, and HLA-ABC; (iii) CD105, CD73 and/or CD90 or (iv) any combination thereof. At least 20%, 30%, 40%, or 50% of said HMCs may be positive for (i) at least two of CD105, CD73 and/or CD90 (ii) at least two of

CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73 and CD90; or (iii) all of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73, CD90, CD105, CD13, CD29, CD44, CD166, CD274, and HLA-ABC. At least 20%, 30%, 40%, or 50% of said HMCs (i) may be positive for CD105, CD73 and CD90; (ii) positive for CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73, CD90, CD105, CD13, CD29, CD 44, CD166, CD274, and HLA-ABC and/or (ii) may be negative for or less than 5% or less than 10% of the cells express CD31, 34, 45, 133, FGFR2, CD271, Stro-1, CXCR4, and/or TLR3. At least 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of said HMCs may be positive for (i) one or more of CD105, CD73 and CD90 (ii) one or more of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73 and CD90; or (iii) one or more of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73, CD90, CD105, CD13, CD29, CD 44, CD166, CD274, and HLA-ABC.

[0261] In another embodiment, the composition comprises HMCs, wherein at least 20%, 30%, 40%, or 50% of said HMCs (i) may be positive for all of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73, CD90, CD105, CD13, CD29, CD 44, CD166, CD274, and HLA-ABC and (ii) may be negative for or less than 5% or less than 10% of the cells express CD31, 34, 45, 133, FGFR2, CD271, Stro-1, CXCR4 and/or TLR3.

[0262] In a further embodiment, the composition comprises HMCs, wherein at least 20%, 30%, 40%, or 50% of said HMCs may be positive for (i) all of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73 and CD90; or (ii) all of CD73, CD90, CD105, CD13, CD29, CD44, CD166, CD274, and HLA-ABC.

[0263] In yet another embodiment, the composition comprises HMCs, wherein at least 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of said HMCs may be positive for (i) at least one of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73 and CD90; or (ii) at least one of CD73, CD90, CD105, CD13, CD29, CD 44, CD166, CD274, and HLA-ABC.

[0264] In another embodiment, the HMCs may not express or less than 5% or less than 10% of the HMCs may express at least one of CD31, 34, 45, 133, FGFR2, CD271, Stro-1, CXCR4, or TLR3.

[0265] In addition to the characteristics described above, the HMCs of the presently disclosed subject matter may possess phenotypes of younger cells as compared to adult-derived MSCs. In one embodiment, the HMCs are capable of undergoing at least or about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, or more population doublings in culture. In contrast, adult-derived MSCs typically undergo 2-3 doublings in culture. In another embodiment, the HMCs of the presently disclosed subject matter have longer telomere lengths, greater immunosuppressive effects, fewer vacuoles, divide faster, divide more readily in culture, higher CD90 expression, are less lineage committed, or combinations thereof, compared to adult-derived MSCs. In another embodiment, the HMCs of the presently disclosed subject matter have increased expression of transcripts promoting cell proliferation (i.e., have a higher proliferative capacity) and reduced expression of transcripts involved in terminal cell differentiation compared to adult-derived MSCs.

[0266] In an embodiment, the HMCs are “early passage” HMCs and may be passaged no more than 1, 2, 3, 4, 5, 6, 7, or 8 times. In an embodiment, early passage HMCs are passaged no more than 4 times. In another embodiment, the early passage HMCs are passaged no more than 5 times. In another embodiment, the early passage HMCs are passaged no more than 6 times. In addition to the HMCs characteristics described above, early passage HMCs may, in a resting or basal state, express mRNA encoding interleukin-6 (IL-6) at a level which may be less than ten percent of the IL-6 mRNA level expressed by BM-MSCs or AD-MSCs in a resting or basal state. VEGF mRNA levels may also be downregulated in early passage HMCs, in a resting or basal state, compared to BM-MSCs in a resting or basal state. In another embodiment, the HMCs may, in a resting or basal state, express mRNA encoding CD24 at a level that is greater than the CD24 mRNA level expressed by BM-MSC or AD-MSC preparations in a resting or basal state. Other mRNA levels that may be upregulated in early passage HMCs, in a resting or basal state, compared to BM-MSCs, in a resting or basal state, include AIRE, ANGPT1 (ANG-1), CXCL1, CD10, and IL-11.

Additionally, the early passage HMCs, in a resting or basal state, may be negative for one or more of mRNAs encoding ANGPT2, CD31, CD34, CD45, HLA-G, IL2RA, IL3, IL12B.
[0267] In a further embodiment, the early passage HMCs express one or more markers selected from the group consisting of CD13, CD29, CD44, CD73, CD90, CD105, CD166, and HLA-ABC, as determined by immunohistochemistry. In another embodiment, the early passage HMCs are negative for one or more markers selected from the group consisting of CD31, CD34, CD45, CXCR4, HLA-DR, FGFR2, TLR3, CD106, CD133, and CD271, as determined by immunohistochemistry.
[0268] In an embodiment, expression levels of CD10 is upregulated in early passage HMCs compared with the expression levels of CD10 in BM-MSCs, as determined by immunohistochemistry. In another embodiment, expression levels of CD10 in early passage HMCs may be about the same the expression levels of CD10 in BM-MSCs. In another embodiment, expression levels of Stro-1 is downregulated in early passage HMCs of the presently disclosed subject matter compared with the expression levels of Stro-1 in BM-MSCs, as determined by immunohistochemistry. In a specific embodiment, a composition comprises early passage HMCs, wherein about 5-10% of the early passage HMCs express Stro-1.
[0269] In a further embodiment, the HMCs of the presently disclosed subject matter express higher levels of certain genes compared to BM-MSCs, UCB-MSCs, or AD-MSCs. For example, the HMCs of the presently disclosed subject matter may express higher levels of any of the genes listed in Table 3 compared to BM-MSCs, and/or any of the genes listed in Table 5 compared to UCB-MSCs, and/or any of the genes listed in Table 7 compared to AD-MSCs. In another embodiment, the HMCs of the presently disclosed subject matter may express lower levels of any of the genes listed in Table 4 compared to BM-MSCs, and/or any of the genes listed in Table 6 compared to UCB-MSCs, and/or any of the genes listed in Table 8 compared to AD-MSCs.
[0270] In an embodiment, genes associated with increased migration and chemotaxis, such as MMP9 is expressed at a higher level in the HMCs of the presently disclosed subject matter compared to BM-MSCs or UCB-MSCs. In another embodiment, Lgr5, a marker of multipotent stem cells, is expressed at a higher level in the HMCs of the presently disclosed subject matter compared to BM-MSCs or UCB-MSCs. In a further embodiment, CD24 is expressed at a higher level in the HMCs of the presently disclosed subject matter compared to BM-MSCs and IL-6 is expressed at a lower level in the MSCs of the presently disclosed subject matter compared to BM-MSCs. In yet another embodiment, neuro-related genes, such as NGF, NTF-4, NTRK-2, NTRK-3, and DCC (Netrin-1), are expressed at a higher level in the HMCs of the presently disclosed subject matter compared to BM-MSCs or UCB-MSCs. MSCs of the presently disclosed subject matter may be selected or purified based on any of the genes that are differentially expressed.
[0271] In some embodiments, the HMCs of the presently disclosed subject matter may express lower levels of any of the miRNA listed in Table 21 compared to HMC-EVs. In some embodiments, the HMCs of the presently disclosed subject matter may express higher levels of any of the miRNA listed in Table 22 compared to HMC-EVs.
[0272] In a further embodiment, the HMC-EVs of the presently disclosed subject matter express higher levels of certain miRNA, genes, or proteins compared to BM-MSCs-EVs, UCB-MSCs-EVs, or AD-MSCs-EVs.
[0273] In some embodiments, the HMC-EVs of the presently disclosed subject matter may express higher levels of any of the miRNAs listed in Table 9 compared to UCB-MSCs-EVS, and/or any of the miRNAs listed in Table 11 compared to BM-MSC-EVs, and/or any of the miRNAs listed in Table 13 compared to AD-MSC-EVs. In another embodiment, the HMC-EVs of the presently disclosed subject matter may express lower levels of any of the miRNAs listed in Table 10 compared to UCB-MSCs-EVS, and/or any of the miRNAs listed in Table 12 compared to BM-MSC-EVs, and/or any of the miRNAs listed in Table 13 compared to AD-MSC-EVs. In some embodiments, the HMC-EVs of the presently disclosed subject matter may express higher levels of

any of the proteins listed in Table 15 compared to UCB-MSCs-EVS, and/or any of the proteins listed in Table 17 compared to BM-MSC-EVs, and/or any of the miRNA listed in Table 19 compared to AD-MSC-EVs. In another embodiment, the HMC-EVs of the presently disclosed subject matter may express lower levels of any of the proteins listed in Table 16 compared to UCB-MSCs-EVS, and/or any of the proteins listed in Table 18 compared to BM-MSC-EVs, and/or any of the proteins listed in Table 20 compared to AD-MSC-EVs.

[0274] In some embodiments, the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0275] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3, FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB, PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0276] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2RIA, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A11, SLC44A1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0277] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0278] In some embodiments, the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

[0279] In some embodiments, the HMC-EVs of the presently disclosed subject matter may express higher levels of any of the miRNAs listed in Table 21 compared to the HMCs of the presently disclosed subject matter. In some embodiments, the HMC-EVs of the presently disclosed subject matter may express lower levels of any of the miRNAs listed in Table 22 compared to the HMCs of the presently disclosed subject matter.

[0280] In an embodiment, genes associated with or involved in the development of neuronal lineage including axon guidance, CREB signaling in neurons, synaptogenesis signaling, or neuroinflammation signaling, are expressed at a higher level in the HMCs of the presently disclosed subject matter compared to AD-MSCs or BM-MSCs.

[0281] In another embodiment, the HMCs of the presently disclosed subject matter have a distinct expression profile when compared to mature MSCs, e.g., AD-MSCs or BM-MSCs or UCB-MSCs. Specifically, the HMCs of the presently disclosed subject matter are able to confer neuroprotective effects, and provide neurotrophic factors, i.e., factors involved in supporting neuronal survival, growth, health and recovery. Likewise, the HMC-EVs of the presently disclosed subject matter share a similar profile as the HMCs from which they were derived. Similar signaling pathways enriched in the HMCs are also enriched in the HMC-EVs when compared to other tissue-derived MSCs and EVs.

[0282] In an embodiment, the composition comprising HMCs of the presently disclosed subject matter is substantially purified with respect to pluripotent stem cells. In a further embodiment, a composition of HMCs of the presently disclosed subject matter is substantially purified with respect to pluripotent stem cells such that said composition comprises at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% HMCs. The pluripotent stem cells may be any pluripotent stem cells described herein.
[0283] The composition may comprise less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% pluripotent stem cells. The composition may be devoid of pluripotent stem cells.
[0284] In some embodiments, the composition comprising HMC-EVs of the presently disclosed subject matter is substantially purified with respect to the HMCs. In a further embodiment, a composition of HMC-EVs of the presently disclosed subject matter is substantially purified with respect to HMCs such that said composition comprises at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% HMC-EVs.
[0285] The composition may comprise less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% HMCs.
[0286] In another embodiment of the instant presently disclosed subject matter, a composition of HMCs and/or HMC-EVs generated by any one or more of the processes of the instant presently disclosed subject matter does not form a teratoma when introduced into a host.
[0287] In an exemplary aspect, the present disclosure provides a composition comprising at least 10.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8 or 10.sup.9 HMCs. In a specific embodiment, the composition comprises 10.sup.6 HMCs and less than one percent of any other cell type, wherein the mesenchymal stem cells have replicative capacity to undergo at least 10 population doublings in cell culture with less than 25 percent of the cells undergoing cell death, senescing or differentiating into non-HMC cells by the tenth population doubling.
[0288] The HMCs may have replicative rates to undergo at least 10 population doublings in cell culture in less than 25 days. The HMCs may have a mean terminal restriction fragment length (TRF) that may be longer than 8 kb. The HMCs may have a statistically significant decreased content and/or enzymatic activity, relative to mesenchymal stem cell preparations derived from bone marrow that have undergone five population doublings, of proteins involved in one or more of (i) cell cycle regulation and cellular aging, (ii) cellular energy and/or lipid metabolism, and (iii) apoptosis. The HMCs may have a statistically significant increased content and/or enzymatic activity of proteins involved in cytoskeleton structure and cellular dynamics relating thereto, relative to mesenchymal stem cell preparations derived from bone marrow. The HMCs may not undergo more than a 75 percent increase in cells having a forward-scattered light value, measured by flow cytometry, greater than 5,000,000 over 10 population doublings in culture.
[0289] In an embodiment of the instant presently disclosed subject matter, a preparation of the subject HMCs (e.g., generated by culturing hemangioblasts) is provided, wherein said preparation comprises substantially similar levels of p53 and p21 protein, or wherein the levels of p53 as compared to p21 are 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times greater. In an embodiment of the instant presently disclosed subject matter, a pharmaceutical preparation of the subject HMCs (e.g., generated by culturing hemangioblasts) is provided, wherein said pharmaceutical preparation comprises substantially similar levels of p53 and p21 protein, or wherein the levels of p53 as compared to p21 are 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times greater.

[0290] In an embodiment, the presently disclosed subject matter provides a composition comprising HMCs, wherein the comprises a substantially similar percentage of HMCs positive for p53 and p21 protein, or wherein the percentage of HMCs positive for p53 as compared to p21 are 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times greater.

[0291] In one embodiment, the present disclosure provides a composition comprising at least about 10.sup.3 to about 10.sup.13 HMC-EVs. In another embodiment, the present disclosure provides a composition comprising at least 10.sup.3, 10.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, or 10.sup.13 HMC-EVs.

Methods of Determining Neurite Outgrowth of HMC and/or HMC-EV Populations.

[0292] The presently disclosed subject matter also provides a method of determining effects of the HMC and/or HMC-EVs on neurons, such as neurite outgrowth. In an aspect, the presently disclosed subject matter provides a method of determining neurite outgrowth of an HMC and/or HMC-EV population. In an embodiment, the method comprises (a) preparing a mixed neuronal culture from an isolated cerebral cortex, (b) plating the HMC and/or HMC-EV population on a permeable membrane, (c) applying strain on the mixed neuronal culture, (d) overlaying the strained mixed neuronal culture with the permeable membrane of step (b), and (e) measuring neurite outgrowth of the mixed neuronal culture. In an embodiment, the method further comprises determining gene expression of the mixed neuronal culture in the presence and absence of the HMC and/or HMC-EV population. In another embodiment, the strain is a physical scratch made in the mixed neuronal culture. In another embodiment, the strain is vacuum pressure and positive air pressure applied to the mixed neuronal culture. In yet another embodiment, the strain may be applied at 15% to 0% stretching oscillations. In an embodiment, the stretching oscillations may be applied at 15%, 12.5%, 10%, 7.5%, 5%, 2.5%, or 0% cycles.

Pharmaceutical Preparations Comprising HMCs and HMC-EVs

[0293] Pharmaceutical preparations of the instant presently disclosed subject matter may comprise any of the HMCs or compositions of HMCs described herein, and/or HMC-EVs. Pharmaceutical preparations comprising HMCs and/or HMC-EVs of the presently disclosed subject matter may be formulated with a pharmaceutically acceptable carrier. For example, HMCs and/or HMC-EVs of the presently disclosed subject matter may be administered alone or as a component of a pharmaceutical formulation, wherein said HMCs and/or HMC-EVs may be formulated for administration in any convenient way for use in medicine. One embodiment provides a pharmaceutical preparation of HMCs and/or HMC-EVs comprising said HMCs and/or HMC-EVs in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions selected from the group consisting of: dispersions, suspensions, emulsions, sterile powders optionally reconstituted into sterile injectable solutions or dispersions just prior to use, antioxidants, buffers, bactericides, solutes or suspending and thickening agents.

[0294] Exemplary pharmaceutical preparations of the present disclosure may be any formulation suitable for use in treating a human patient, such as pyrogen-free or essentially pyrogen-free, and pathogen-free.

[0295] The preparation comprising HMCs and/or HMC-EVs used in the methods described herein may be transplanted in a suspension, gel, colloid, slurry, or mixture. Also, at the time of injection, cryopreserved HMCs and/or HMC-EVs may be resuspended with commercially available balanced salt solution to achieve the desired osmolality and concentration for administration by injection (i.e., bolus or intravenous).

[0296] One aspect of the presently disclosed subject matter relates to a pharmaceutical preparation suitable for use in a mammalian patient, comprising at least 10.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, or 10.sup.13 HMCs and/or HMC-EVs and a pharmaceutically acceptable carrier. Yet another aspect of the presently disclosed subject matter provides a cryogenic cell bank comprising at least 10.sup.8, 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12 or even 10.sup.13 HMCs and/or HMC-EVs. Still another aspect of the presently

disclosed subject matter provides a pharmaceutical preparation free of or substantially free of non-human cells and/or non-human animal products, comprising at least 10.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8 10.sup.9, 10.sup.10, 10.sup.11, 10.sup.12, or 10.sup.13 HMCs and/or HMC-EVs and less than 1% of any other cell type, more preferably less than 0.1%, 0.01% or even 0.001% of any other cell type.

[0297] Concentrations for administration of pharmaceutical preparations of HMCs and/or HMC-EVs may be at any amount that is effective and, for example, substantially free of PSCs. For example, the pharmaceutical preparations may comprise the numbers and types of HMCs and/or HMC-EVs described herein. In a particular embodiment, the pharmaceutical preparations of HMCs and/or HMC-EVs comprise about 1×10.sup.6 to about 1×10.sup.7, about 1×10.sup.7 to about 1×10.sup.8, about 1×10.sup.8 to about 1×10.sup.9, about 1×10.sup.9 to about 1×10.sup.10, about 1×10.sup.10 to about 1×10.sup.11, about 1×10.sup.11 to about 1×10.sup.12, or about 1×10.sup.12 to about 1×10.sup.13 of the HMCs and/or HMC-EVs for systemic administration to a host in need thereof or about 1×10.sup.4 to about 1×10.sup.3, about 1×10.sup.3 to about 1×10.sup.6, 1×10.sup.6 to about 1×10.sup.7, about 1×10.sup.7 to about 1×10.sup.8, about 1×10.sup.8 to about 1×10.sup.9, about 1×10.sup.9 to about 1×10.sup.10, about 1×10.sup.10 to about 1×10.sup.11, about 1×10.sup.11 to about 1×10.sup.12, or about 1×10.sup.12 to about 1×10.sup.13 of said HMCs and/or HMC-EVs for local administration to a host in need thereof.

Methods of Treating Brain Injury

[0298] The HMCs and/or HMC-EVs and pharmaceutical preparations comprising HMCs and/or HMC-EVs described herein may be used for treating brain injury, e.g., stroke, or optic neuropathy. In particular, the instant presently disclosed subject matter provides methods for treating or preventing brain injuries described herein comprising administering an effective amount of HMCs and/or HMC-EVs, wherein the HMCs are obtained by in vitro differentiation of pluripotent stem cells. In another embodiment, the HMCs are obtained by in vitro differentiation of hemangioblasts.

[0299] In an embodiment, brain injury is selected from traumatic brain injury, acquired brain injury, anoxic brain injury, diffuse axonal brain injury, focal brain injury, subdural hematoma, brain aneurysm, coma, stroke, optic neuropathy, and cerebral palsy. In a particular embodiment, the brain injury is traumatic brain injury. In another embodiment, the brain injury is cerebral palsy. In yet another embodiment, the brain injury is stroke. In another embodiment, the brain injury is optic neuropathy.

[0300] The HMCs and/or HMC-EVs of the instant presently disclosed subject matter may be administered systemically or locally. The HMCs and/or HMC-EVs may be administered using modalities known in the art including, but not limited to, injection via intravenous, intracranial, intrathecal, intracerebral, intracisternal, intramuscular, intraperitoneal, intravitreal, or other routes of administration, or local implantation, dependent on the particular pathology being treated.

[0301] The HMCs and/or HMC-EVs of the instant presently disclosed subject matter may be administered via local implantation, such as intracranial implantation, wherein a delivery device is utilized. Delivery devices of the instant presently disclosed subject matter are biocompatible and biodegradable. A delivery device of the instant presently disclosed subject matter can be manufactured using materials selected from the group comprising biocompatible fibers, biocompatible yarns, biocompatible foams, aliphatic polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, tyrosine derived polycarbonates, poly(iminocarbonates), polyorthoesters, polyoxaesters, polyamidoesters, polyoxaesters containing amine groups, poly(anhydrides), polyphosphazenes, biopolymers; homopolymers and copolymers of lactide, glycolide, epsilon-caprolactone, para-dioxanone, trimethylene carbonate; homopolymers and copolymers of lactide, glycolide, epsilon-caprolactone, para-dioxanone, trimethylene carbonate, fibrillar collagen, non-fibrillar collagen, collagens not treated with pepsin, collagens combined with other polymers, growth factors, extracellular matrix proteins, biologically relevant peptide fragments, hepatocyte growth factor, platelet-derived growth factors, platelet rich plasma,

insulin growth factor, growth differentiation factor, vascular endothelial cell-derived growth factor, nicotinamide, glucagon like peptides, tenascin-C, laminin, anti-rejection agents, analgesics, anti-oxidants, anti-apoptotic agents anti-inflammatory agents and cytostatic agents. In some embodiments, the HMCs and/or HMC-EVs are delivered through a slow release device, e.g., transdermal microneedle patch.

[0302] The particular treatment regimen, route of administration, and adjuvant therapy may be tailored based on the particular pathology, the severity of the pathology, and the patient's overall health. Administration of the HMCs and/or HMC-EVs may be effective to reduce the severity of the manifestations of a pathology or and/or to prevent further degeneration of the manifestation of a pathology.

[0303] In some embodiments, administration of the HMCs results in preservation of myelin. In some embodiments, administration of the HMCs results in suppression of neuroinflammatory response in a subject. In some embodiments, administration of the HMCs results in reduction of microglial and astrocyte activation in the brain. In some embodiments, administration of the HMCs results in stimulation and/or activation of pathways involved in cell survival. In some embodiments, administration of the HMCs results in stimulation of expression of a neuroprotective gene in the brain. In some embodiments, the neuroprotective gene is selected from the group consisting of heat shock protein family B member 1 (HSPB1), insulin-like growth factor 1 (IGF2), and secreted phosphoprotein 1 (SPP1). In some embodiments, administration of the HMCs results in stimulation and/or activation of pathways involved in synaptic transmission in the brain. In some embodiments, administration of the HMCs results in reduction of apoptosis. In some embodiments, administration of the HMCs results in stimulation and/or activation of pathways involved in development of neuronal lineage, e.g., axon guidance, BREB signaling in neurons, or synaptogenesis signaling.

[0304] In some embodiments, administration of HMC-EVs results in an increase in the oligodendrocyte and precursor cells in the brain. In some embodiments, administration of HMC-EVs results in preservation of myelin in the brain. In some embodiments, administration of HMC-EVs results in suppression of neuroinflammatory response in the subject. In some embodiments, administration of HMC-EVs results in reduction of microglial and astrocyte activation in the brain. In some embodiments, administration of HMC-EVs results in prevention or reduction of oxidative damage in neurons. In some embodiments, administration of extracellular HMC-EVs results in prevention or reduction of neuronal death due to glutamate excitotoxicity injury.

[0305] A treatment modality of the presently disclosed subject matter may comprise the administration of a single dose of HMCs and/or HMC-EVs. Alternatively, treatment modalities described herein may comprise a course of therapy where HMCs and/or HMC-EVs are administered multiple times over some period of time. Exemplary courses of treatment may comprise weekly, biweekly, monthly, quarterly, biannually, or yearly treatments. Alternatively, treatment may proceed in phases whereby multiple doses are required initially (e.g., daily doses for the first week), and subsequently fewer and less frequent doses are needed.

[0306] The HMCs and/or HMC-EVs may be administered separately or in combination. In some embodiments, the methods comprise administering to the subject an effective amount of HMCs. In other embodiments, the methods comprise administering to the subject an effective amount of HMC-EVs. In another embodiment, the methods comprise administering to the subject an effective amount of HMCs and an effective amount of HMC-EVs.

[0307] The HMCs and HMC-EVs can be administered simultaneously or sequentially. In one embodiment, the HMCs and the HMC-EVs are mixed together before administering to the subject. In another embodiments, the subject receives an effective amount of HMCs, followed by an effective amount of HMC-EVs. Alternatively, the subject receives an effective amount of HMC-EVs, followed by an effective amount of HMCs.

[0308] In one embodiment, the HMCs and/or HMC-EVs are administered to a patient one or more

times periodically throughout the life of a patient. In a further embodiment of the instant presently disclosed subject matter, the HMCs and/or HMC-EVs are administered once per year, once every 6-12 months, once every 3-6 months, once every 1-3 months, or once every 1-4 weeks. Alternatively, more frequent administration may be desirable for certain conditions or disorders. In an embodiment of the instant presently disclosed subject matter, the HMCs and/or HMC-EVs are administered via a device once, more than once, periodically throughout the lifetime of the patient, or as necessary for the particular patient and patient's pathology being treated. Similarly contemplated is a therapeutic regimen that changes over time. For example, more frequent treatment may be needed at the outset (e.g., daily or weekly treatment). Over time, as the patient's condition improves, less frequent treatment or even no further treatment may be needed.

[0309] In some embodiments, about 20 million, about 40 million, about 60 million, about 80 million, about 100 million, about 120 million, about 140 million, about 160 million, about 180 million, about 200 million, about 220 million, about 240 million, about 260 million, about 280 million, about 300 million, about 320 million, about 340 million, about 360 million, about 380 million, about 400 million, about 420 million, about 440 million, about 460 million, about 480 million, about 500 million, about 520 million, about 540 million, about 560 million, about 580 million, about 600 million, about 620 million, about 640 million, about 660 million, about 680 million, about 700 million, about 720 million, about 740 million, about 760 million, about 780 million, about 800 million, about 820 million, about 840 million, about 860 million, about 880 million, about 900 million, about 920 million, about 940 million, about 960 million, or about 980 million MSCs and/or MSC-EVs are administered into the subject. In some embodiments, about 1 billion, about 2 billion, about 3 billion, about 4 billion or about 5 billion HMCs and/or HMC-EVs or more are administered. In some embodiments, the number of HMCs and/or HMC-EVs ranges from between about 20 million to about 4 billion, between about 40 million to about 1 billion, between about 60 million to about 750 million, between about 80 million to about 400 million, between about 100 million to about 350 million, and between about 175 million to about 250 million.

[0310] The methods described herein may further comprise the step of monitoring the efficacy of treatment or prevention using methods known in the art.

EXAMPLES

[0311] The following examples are not intended to limit the presently disclosed subject matter in any way.

Example 1—Generating HMCs from Hemangioblasts

[0312] Hemangioblasts were generated from single-blastomere derived human ESC line, MA09 (Klimanskaya et al., Nature 444 (2006) 481-485). First, a 10 cm plate was coated with 0.1% gelatin and irradiated MEF was added at a concentration of about 25,000 cells/cm.sup.2 in MEF media (high glucose DMEM+10% FCS) the day before adding ESCs to the plate. The MEF media was then aspirated, rinsed with PBS, and replaced with Reprocell Primate media (Reprocell) plus 10 ng/mL bFGF. A split of MA09 cells were added to the dish and fed with fresh media daily. The MA09s were cultured in Reprocell Primate Media plus 10 ng/mL bFGF until about 90% confluent. The MA09s were then harvested with 0.05% trypsin/EDTA or Reprocell dissociation buffer (Reprocell). After the cells detached, the cells were rinsed and collected. The cells were spun down at 300×g for 10 min. The supernatant was aspirated and the cell pellet was resuspended in Stemline II (Sigma) (plus pen/strep and L-glutamine) plus 50 ng/mL VEGF and 50 ng/mL BMP4. The MA09 ESCs were plated in 2×10 cm ultra low adherence plate (Corning) in 15 ml Stemline II medium (Sigma) supplemented with 50 ng/ml of VEGF and 50 ng/ml of BMP-4 (R & D or Peprotech) and incubated at 37° C. with 5% CO.sub.2. After 40-48 hours, half of the medium (1.5 ml) was replaced with fresh Stemline II medium supplemented with 50 ng/ml of VEGF, 50 ng/ml of BMP-4, and 40-45 ng/ml bFGF so that the final concentration of bFGF ends up being 20-22.5 ng/ml bFGF, and continued incubation for an additional 40-48 hours (i.e., 3.5-4 days total).

[0313] Clusters of cells (embryoid bodies; EBs) were dissociated and plated as single cells in serum-free semisolid blast-colony growth medium (BGM). Specifically, clusters of cells were dissociated with trypsin for 2-5 min. or until clumps start to break up. The cell suspension was pipetted up and down and then DMEM+10% FCS was added to inactivate the trypsin. Cells were then passed through a 40 μm or 70 μm strainer to obtain a single cell suspension. Cells were then counted and resuspended in Stemline II medium at 1-1.5×10.sup.6 cells/ml.
[0314] The single cell suspension was mixed with hemangioblast (HB) Growth Medium (H4536 based medium recipe: base medium methylcellulose product H4536 (StemCell Technologies) plus penicillin/streptomycin (pen/strp), Excyte growth supplement (Millipore), and the cytokines, Flt3-ligand (FL) at 50 ng/ml, vascular endothelial growth factor (VEGF) at 50 ng/ml, thrombopoietin (TPO) at 50 ng/ml, and basic fibroblast growth factor (bFGF) at 20-30 ng/ml) for a final concentration of about 1×10.sup.5 cells/ml with a brief vortex, and allowing the bubbles to settle. The cell mixture was then transferred to 4×10 cm ultra low adherence plates by using a syringe (30 ml) attached with an 18G needle, and incubated at 37° C. with 5% CO.sub.2 for 8-12 days. HBs will begin to appear within 3 or 4 days and continue to populate the plates and may be harvested between days 7-12 of culture. The HBs were harvested on day 9 of culture and frozen down.
[0315] The frozen HBs were thawed and replated onto Matrigel-coated tissue culture plates in MSC medium [α-MEM without nucleosides (Hyclone), 20% Defined FBS—Heat Inactivated (Hyclone), 1× Glutamax (Gibco), 1×MEM non-essential amino acids (Gibco), and 1× penicillin/streptomycin]. The cells were cultured for about 4-5 days and then passaged, and repeated for up to three passages (P3) to generate HMCs. The P3 HMCs (“MARP12” cells) were frozen down for further use.
Example 2—Traumatic Brain Injury (TBD In Vivo Study
[0316] The HMCs obtained according to Example 1 were thawed and cultured in MSC medium described above for about 4 days in 37° C., 5% CO.sub.2 in T225 culture flasks at about 4500 cells/cm.sup.2. To harvest the cells for administration, the cells were washed with PBS, dissociated from the flasks with trypsin, and the trypsin was inactivated with addition of MSC medium. The cells were collected in 50 ml conical tubes and centrifuged at 300×g for 10 min. The supernatant was aspirated and 1 ml of GS2 buffer [for 552.2 mL of GS2: 0.9% Sodium Chloride Irrigation USP (408.6 mL); 5% Dextrose/0.9% Sodium Chloride, Injection USP (33.2 mL), and BSS Irrigation Solution (110.4 mL)], which is described in WO 2017/031312 and is incorporated herein by reference in its entirety, was added to each tube. The cells were strained through a 100 μm cell strainer and centrifuged at 300×g for 5 min. The supernatant was aspirated and resuspended in GS2. The cells obtained are passage 4 (P4) HMCs.
[0317] Mild-to moderate experimental traumatic brain injury (TBI) was induced in 56 Sprague Dawley Rats by controlled cortical impact (CCI) (Lee et al., Theranostics 9:1029-1046 (2019)). Cells were injected locally by intracerebral (IC) transplantation or systemically (iv) into the rats and sacrificed at early or late time points according to Table 1.
TABLE-US-00001 TABLE 1 Groups Animals Time-points End-points EARLY IC Local 7 Treatment with cells Cortical and Administration or vehicle 7 days Hippocampal cell Vehicle (3 ul-10 ul post CCI. loss- H&E GS2) Animals sacrificed 7 staining and CA3 IC Local 7 days post treatment neuron counting Administration MSCs (14 days post CCI). Microgliosis- (400,000 cells in 3 ul- DCX, OX6. 10 ul GS2) IBA-1 staining I.V. (jugular vein) 7 IHC for human Admin Vehicle (500 ul cells GS2) Swing Test I.V. (jugular vein) 7 Bederson Test Admin MSCs (4 × 10.sup.6 cells in 500 ul GS2) LATE IC Local 7 Treatment with cells All end points as Administration or vehicle 7 days Early groups Vehicle (3 ul-10 ul) post CCI. IC Local 7 Behavioral testing Administration every 7 days from MSCs (400,000 cells Day 0 (CCI) to Day in 3 ul-10 ul) 56 plus baseline. I.V. (jugular vein) 7 Animals sacrificed Admin Vehicle (500 ul at Day 56. GS2) I.V. (jugular vein) 7 Admin MSCs (4 × 10.sup.6 cells in 500 ul GS2)
[0318] The rats were studied according to the following schedule:

Early

[0319] Day −1: Swing test and Bederson test for baseline [0320] Day 0: Controlled Cortical Impact performed on all groups [0321] Day 7: All groups treated with cells or vehicle, locally or intravenously; Swing test and Bederson test post treatment for all groups [0322] Day 14: Swing and Bederson Tests for all groups; All groups sacrificed; H&E staining, CA3 neuron counting, DCX, OX6, IBA-1 staining, IHC for human cells on all groups

Late

[0323] Day −1: Swing Test and Bederson Test for baseline for all groups [0324] Day 0: Controlled Cortical Impact performed on all groups [0325] Day 7: All groups treated with cells or vehicle, locally or intravenously; Swing and Bederson tests post treatment for all groups [0326] Day 14: Swing and Bederson tests for all groups [0327] Day 28: Swing and Bederson tests for all groups [0328] Day 35: Swing and Bederson tests for all groups [0329] Day 42: Swing and Bederson tests for all groups [0330] Day 49: Swing and Bederson tests for all groups [0331] Day 56: Swing and Bederson tests for all groups; All groups sacrificed; H&E staining, CA3 neuron counting, DCX, OX6, IBA-1 staining, IHC for human cells on all groups.

Results from Behavioral Tests

[0332] The CCI in vivo TBI model causes significant behavioral deficits of the rats up to 56 days post-injury. Intracerebral (IC) transplantation of the HMCs significantly rescued against behavior deficits compared to their respective vehicles, including elevated body swing test (EBST) from day 14 to 42 after transplantation (FIG. **1**), forelimb akinesia starting at day 28 up to day 56 after transplantation (FIG. **2**), and paw grasp from day 14 to day 56 after transplantation (FIG. **3**). Intravenous (IV) transplantation of the HMCs also significantly rescued against behavior deficits compared to their respective vehicles, including EBST from day 14 up to day 56 after transplantation (FIG. **1**), forelimb akinesia starting at day 42 to day 56 after transplantation (FIG. **2**), and paw grasp at day 28 after transplantation (FIG. **3**). These findings support the use of HMCs for treatment of TBI.

Results from Histology

[0333] The CCI in vivo model causes significant histopathological effects in the rats post-injury. IV and IC transplantation of the HMCs demonstrated neuroprotective effects compared to their respective vehicles. For example, H&E staining showed a reduction in tissue loss compared to vehicle (FIGS. **4**A-B), Nissl staining demonstrated a neuroprotective effect of HMC administration by reducing cell death (FIGS. **5**A-F), and doublecortin (DCX) staining showed a slight increase in neurogenesis following the administration of HMCs post-injury (FIGS. **6**A-F).

[0334] IV and IC transplantation of the HMCs also significantly reduced the activation of microglia and macrophages compared to their respective vehicles. Iba1 (FIGS. **7**A-D) and OX6 (FIGS. **8**A-D) staining demonstrated that the HMCs reduced the presence of microglia and macrophages, respectively, in the cortex and striatum post-injury.

[0335] Further, IV and IC transplantation of the HMCs significantly reduced inflammatory markers in the spleen compared to their respective vehicles. A reduction in I16 (FIGS. **9**A-B) and TNF-alpha (FIGS. **10**A-B) staining in the spleen demonstrates the HMCs reduced inflammation post-injury.

[0336] IV and IC transplantation of the HMCs also resulted in migration of HMCs across the blood brain barrier (BBB) to the cortex, striatum, and hippocampus as shown by HuNu staining (FIGS. **11**A-F).

[0337] These finding support the use of HMCs for treatment of TBI.

Example 3—In Vitro Migration Assay of HMCs

[0338] HMCs were generated from the same bank of frozen hemangioblasts described in Example 1. Three separate lots of HMCs were generated, frozen at P4, thawed and cultured for 4 days, and the passage 5 (P5) cells were harvested according to the method described in Example 1. MSCs isolated from bone marrow (BM-MSCs) and umbilical cord blood (UCB-MSCs) were used as

controls. Each of the HMCs, BM-MSCs, and UCB-MSCs were seeded into two wells of an ibidi insert with a defined gap in between and allowed to adhere overnight. Inserts were removed, leaving a 500 μm gap. Cells were washed and MSC media (described in Example 1) was added to the chamber, with or without stimulation with 25 ng/mL TNF-α+50 ng/mL IFN-γ. Cells were incubated for 6 hours at 37° C. Pictures were then taken of the non-stimulated cells (FIG. **12**A) and cells that had migrated into the center of the gap (middle ˜250 μm) were counted visually (FIG. **12**B), using ImageJ, an open source image processing program (Schneider et al., *Nature Methods* 9:671-675 (2012)). As can be seen from FIGS. **12**A-B, the HMCs (hESC-MSCs) had a greater capacity for cell migration than BM-MSCs or UCB-MSCs.

Example 4—In Vitro Neurite Outgrowth/Neuron Migration in the Presence of HMCs

[0339] Rat primary mixed neuronal cultures were prepared from whole brains of E18 Sprague Dawley rat pups obtained from BrainBits, LLC (Springfield, IL). The midbrain, cerebellum, and hippocampus were removed to isolate the cerebral cortex. Cells were dissociated from the tissue and cultured for 14 days to allow for maturation. Although tissue is from an embryonic rat pup, the neurons have been shown to display mature receptor and electrophysiological profiles after 14 days in culture. The mixed neuronal culture was used in an adapted migration assay to study neuroregeneration and as an in vitro TBI model (Darbinyan et al., Methods Mol. Biol. 1078:45-54 (2013); Ali et al., High Content Screening with Primary Neurons. 2013 Oct 15. In: Sittampalam GS, Coussens NP, Brimacombe K, et al., editors. Assay Guidance Manual. Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences (2004)).

[0340] On day 0, the mixed neuronal culture was plated. On day 9, MARP12 cells that were frozen and thawed as described in Example 1 were plated in flasks for expansion. At Day 13, MARP12 cells were harvested and plated on transwell inserts for about a 10:1 ratio of neuron to MARP12 cells in MSC media. At day 14, two scratches were made per well in the mixed neuronal culture prepared as described above (Liang et al., Nat. Protoc. 2:329-333 (2007). The MSC media in the transwell was changed to neuronal media (Neurobasal™ Plus (Thermo Fisher); 1× Gentamicin; 1× GlutaMAX™ (ThermoFisher); 1× B27™ Plus (Thermo Fisher)) to remove all traces of serum, and the transwell inserts containing MARP12 cells were added to wells containing the mixed neuronal cultures. As shown in FIG. **13**, co-culture with MARP12 (hESC-MSCs or HMC) encouraged neurite outgrowth and increased migration.

[0341] RNA-seq data can also show that the presence of the co-cultured HMCs and/or HMC-EVs can affect gene expression in the neurons. Neurons are dissociated from the cortex of brains of E18 Sprague-Dawley rats and plated at a density of 1.2×10.sup.6 cells per well on 6-well BioFlex culture plates (FlexCell Int.) that are coated with poly-D-lysine (Sigma). The neurons are supplemented with Neurobasal Plus/B27 Plus media (Gibco) and maintained for 14 days in vitro (DIV) at 37° C. in a humidified CO.sub.2 incubator. Half media changes are performed every 3 days. For HMC treatment, HMCs are cultured for 4 days in α-MEM media (α-MEM (Hyclone) with 1× GlutaMAX (Gibco), 1×MEM-NEAA (Gibco), and Pen-strep (Gibco)) and then harvested and plated on transwell inserts (Corning) at a density of 1.2×10.sup.5 cells per insert. After one day in culture, the α-MEM media is changed to Neurobasal Plus/B27 Plus media for 1 hour, and the inserts are then added to the 6-well plates containing the neurons at DIV14. For EV treatment, EVs were purified from HMCs (HMC-EVs) by tangential flow filtration. HMC-EVs are added to the plates containing the neurons. TNF-α is then added at a concentration of 100 ng/mL where appropriate and the plates are then placed on the FlexCell FX-6000. The culture is subjected to 15%-0/o stretching oscillations (15%, 12.5%, 10%, 7.5%, 5%, 2.5%, and 0% cycles) overnight. The neurons are then removed from the BioFlex plate, pelleted, washed with PBS, and subjected to RNA isolation via the RNeasy Mini Kit (Qiagen). RNA (300 ng) is then submitted to BGI Americas for RNAseq analysis, and data is analyzed by Rosalind software (https://rosalind.onramp.bio/). Cutadapt is used to trim the reads, and FastQC is used to assess quality scores. STAR is used to align the reads to the *Rattus norvegicus* genome build rn5. HTseq is

used to quantify the individual sample reads, and they are normalized via Relative Log Expression (RLE) using DESeq2 R library.

Example 5—In Vivo Neonatal Hypoxia-Ischemia Model of Cerebral Palsy

[0342] The HMCs of the presently disclosed subject matter were tested in an in vivo neonatal hypoxia-ischemia (HI) model of cerebral palsy. HMCs used were MARP12 cells described in Example 1 that were thawed and passaged as passage 5 (P5) cells for four days upon which time, the cells were harvested, rinsed and formulated for injection. To establish the in vivo model for cerebral palsy, the common carotid artery in post-natal day (PND) 7 Sprague Dawley male rat pups was ligated to induce ischemia. Following recovery, pups were subjected to a hypoxic episode, followed by normoxia for 25 additional minutes. Pups in the sham control group received an equivalent exposure, except that normoxia rather than hypoxia was presented. At 7 days following surgery and hypoxic exposure (i.e. PND14), pups were humanely euthanized, with blood, cerebrospinal fluid (CSF), and brain tissue harvested for further testing. The pups were treated according to Table 2.

TABLE-US-00002 TABLE 2 Treatment Groups Maximum # Group Treatment per Group Purpose Lot B HI 8 Test MARP12 article 1 × 10.sup.6 cells 6 hours post-hypoxia via IP injection HI HI, Vehicle Control 8 Control Sham Sham Control 8 Control

End Points Assessed

[0343] CSF and blood used for ELISAs for inflammatory panel and others depending on amount of sample.

[0344] Brain tissue analyzed for: [0345] Cell death—TUNEL; [0346] Infarct volume—H&E; [0347] Iba-1—microglial activation in peri-infarct tissue; [0348] GFAP—Astrocyte activation in peri-infarct tissue; [0349] Olig2—Oligodendrocyte precursor cells in hippocampus [0350] MBP—Myelin Basic Protein for mature oligodendrocytes in corpus callosum; and hippocampus.

Results

[0351] TUNEL staining as shown in FIGS. **14**A-B suggests a neuroprotective effect by MARPS12 (Lot B) with reduced cell death. Further, H&E staining as shown in FIG. **15** suggests a neuroprotective effect by MARPS12 (Lot B) with reduced lesion size. A reduction in microglial activation via Iba-1 staining as shown in FIGS. **16**A-C suggests an anti-inflammatory effect by MARPS12 (Lot B). A mild reduction in astrocyte activation via GFAP staining as shown in FIGS. **17**A-C also suggests an anti-inflammatory effect by MARPS12 (Lot B). Preservation of myelin in the corpus callosum via MBP staining as shown in FIGS. **18**A-C suggests a beneficial role of MARPS12 on oligodendrocytes. Moreover, FIGS. **19**A-C suggest that Olig2 expression is partially rescued by administration of MARPS12.

[0352] These results support the use of HMCs in the treatment of cerebral palsy.

Example 6—RNAseq Analysis of HMC Vs BM-MSC Vs UCB-MSC

[0353] HMCs were generated from the same bank of frozen hemangioblasts described in Example 1. Three separate lots of HMC were generated and passaged up to five passages (P5) according to the method described in Example 1. RNA seq analysis was performed on the three lots of HMC under basal conditions. MSCs isolated from bone marrow (BM-MSCs) (9 lots) and umbilical cord blood (UCB-MSCs) (9 lots) under basal conditions were used as controls.

[0354] Table 3 shows genes that were more highly expressed in the HMCs compared with BM-MSCs. Table 4 shows genes that were more highly expressed in BM-MSCs compared with the HMCs. Table 5 shows genes that were more highly expressed in HMCs compared with UCB-MSCs. Table 6 shows genes that were more highly expressed in UCB-MSCs compared with the HMCs. HMCs of the presently disclosed subject matter may be selected or purified based on any of the genes that are differentially expressed.

TABLE-US-00003 TABLE 3 Genes more highly expressed in HMCs compared with BM-MSCs Log Gene Fold Fold Name Description Change Change p-Adj KCNN2 potassium channel_calcium activated 3376.7 11.7214 9.68E−96 intermediate/small conductance subfamily N alpha_member 2

GATA4 GATA binding protein 4 3374.36 11.7204 3.92E−74 FAR2P1 fatty acyl CoA reductase 2 pseudogene 1 2722.47 11.4107 2.85E−33 GATA3 GATA binding protein 3 2000.99 10.9665 9.13E−69 NKX2-5 NK2 homeobox 5 1763.59 10.7843 1.21E−69 VAT1L vesicle amine transport 1-like 1436.96 10.4888 1.73E−168 NRK Nik related kinase 1233.89 10.269 1.08E−36 NETO1 neuropilin (NRP) and tolloid (TLL)-like 1 1185.6 10.2114 9.67E−53 BCHE butyrylcholinesterase 1128.82 10.1406 1.24E−46 OCA2 oculocutaneous albinism II 1052.28 10.0393 5.00E−52 GABRA5 gamma-aminobutyric acid (GABA) A 1034.77 10.0151 7.33E−112 receptor_alpha 5 DPPA4 developmental pluripotency associated 4 1029.48 10.0077 6.22E−74 KIF26A kinesin family member 26A 990.004 9.95129 7.81E−55 RELN reelin 942.435 9.88025 1.16E−43 LOC440416 NA 908.838 9.82788 1.42E−77 SNCA synuclein_alpha (non A4 component of 880.69 9.78249 5.86E−40 amyloid precursor) GABRB1 gamma-aminobutyric acid (GABA) A 830.623 9.69805 1.47E−40 receptor_beta 1 SNRPN small nuclear ribonucleoprotein polypeptide 778.66 9.60485 3.61E−42 N CACNG4 calcium channel_voltage-dependent_gamma 757.788 9.56565 2.68E−56 subunit 4 LRRTM1 leucine rich repeat transmembrane 717.547 9.48693 4.54E−44 neuronal 1 LINGO2 leucine rich repeat and Ig domain 620.437 9.27714 4.01E−40 containing 2 TNNT2 troponin T type 2 (cardiac) 594.602 9.21578 1.04E−36 ZNF804A zinc finger protein 804A 586.802 9.19673 6.40E−56 ST6GAL2 ST6 beta-galactosamide alpha-2_6- 576.929 9.17225 7.18E−88 sialyltranferase 2 COL4A5 collagen_type IV_alpha 5 576.757 9.17182 2.11E−82 LIN28B lin-28 homolog B (C. elegans) 563.605 9.13854 2.92E−39 MMP9 matrix metallopeptidase 9 554.502 9.11505 1.92E−42 SLC7A2 solute carrier family 7 (cationic amino 520.325 9.02327 3.31E−149 acid transporter_y+ system)_member 2 COL4A6 collagen_type IV_alpha 6 497.261 8.95786 1.25E−97 FENDRR FOXF1 adjacent non-coding developmental 488.058 8.93091 1.86E−46 regulatory RNA DSC2 desmocollin 2 478.415 8.90212 2.20E−39 KCTD8 potassium channel tetramerization domain 459.857 8.84504 3.51E−38 containing 8 ARAP2 ArfGAP with RhoGAP domain_ankyrin 455.472 8.83122 4.05E−38 repeat and PH domain 2 DIO2 deiodinase_iodothyronine_type II 450.443 8.8152 1.78E−98 CDH10 cadherin 10_type 2 (T2-cadherin) 448.881 8.81019 7.16E−25 SHC3 SHC (Src homology 2 domain containing) 447.61 8.8061 3.60E−90 transforming protein 3 SULT1E1 sulfotransferase family 1E_estrogen- 447.155 8.80463 2.93E−34 preferring_member 1 CPXM1 carboxypeptidase X (M14 family)_member 445.688 8.79989 1.94E−75 1 FGF20 fibroblast growth factor 20 428.96 8.7447 9.75E−34 LINC00890 long intergenic non-protein coding RNA 890 382.729 8.58018 1.14E−32 BAI3 adhesion G protein-coupled receptor B3 364.764 8.51082 8.84E−35 L1CAM L1 cell adhesion molecule 361.67 8.49853 1.36E−94 CACNG8 calcium channel_voltage-dependent_gamma 359.757 8.49088 1.88E−29 subunit 8 SULT1C4 sulfotransferase family_cytosolic_1C_member 324.225 8.34085 4.13E−29 4 TRIM55 tripartite motif containing 55 319.183 8.31824 9.79E−22 HOXB13 homeobox B13 313.091 8.29044 4.19E−32 DSG2 desmoglein 2 309.567 8.27411 3.18E−14 ELFN2 extracellular leucine-rich repeat and 301.134 8.23426 1.62E−92 fibronectin type III domain containing 2 CTD-2297D10.2 uncharacterized LOC101929176 300.946 8.23336 5.57E−22 TRPC5 transient receptor potential cation 297.627 8.21736 6.17E−23 channel_subfamily C_member 5 WT1 Wilms tumor 1 297.142 8.21501 4.53E−32 TMEM63C transmembrane protein 63C 296.544 8.2121 1.88E−36 RERG RAS-like_estrogen-regulated_growth 292.372 8.19166 3.31E−32 inhibitor CCND2 cyclin D2 288.586 8.17286 2.31E−48 NKX2-3 NK2 homeobox 3 287.642 8.16813 4.09E−28 SAMD5 sterile alpha motif domain containing 5 281.787 8.13846 2.29E−79 STMN2 stathmin 2 281.654 8.13778 7.49E−14 TMEM200C transmembrane protein 200C 277.722 8.1175 9.71E−27 SOX17 SRY (sex determining region Y)-box 17 277.509 8.11639 2.49E−29 MGAT3 mannosyl (beta-1_4-)-glycoprotein beta- 269.263 8.07287 3.27E−96 1_4-N-acetylglucosaminyltransferase FLT1 fms-related tyrosine kinase 1 266.319 8.05701 1.95E−173 NKAIN4 Na+/K+ transporting ATPase interacting 4 260.054 8.02267 3.36E−39 SYTL5 synaptotagmin-like 5 257.406 8.0079 8.81E−79 MDGA2 MAM domain containing 252.998 7.98298 4.70E−26 glycosylphosphatidylinositol anchor 2 GATA3-AS1 GATA3 antisense RNA 1

249.784 7.96454 3.99E−22 LGI1 leucine-rich_glioma inactivated 1 248.088 7.95471 5.19E−26 PKP2 plakophilin 2 247.539 7.95151 2.82E−15 KLHL4 kelch-like family member 4 238.045 7.89509 3.70E−63 GPR143 G protein-coupled receptor 143 235.692 7.88076 5.07E−44 ADAMTS18 ADAM metallopeptidase with 219.386 7.77733 5.32E−25 thrombospondin type 1 motif_18 CHRM2 cholinergic receptor_muscarinic 2 218.008 7.76824 1.34E−14 TMEM40 transmembrane protein 40 216.144 7.75585 2.22E−25 NIPAL4 NIPA-like domain containing 4 213.309 7.7368 6.44E−119 SEMA3D sema domain_immunoglobulin domain 212.776 7.73319 4.51E−37 (Ig)_short basic domain_secreted_(semaphorin) 3D PHOX2A paired-like homeobox 2a 212.508 7.73137 1.17E−27 PRAC1 prostate cancer susceptibility candidate 1 200.695 7.64886 3.28E−20 CSMD3 CUB and Sushi multiple domains 3 191.196 7.57891 4.33E−23 B3GAT1 beta-1_3-glucuronyltransferase 1 189.606 7.56686 7.70E−26 TRIM58 tripartite motif containing 58 189.244 7.5641 4.32E−32 ANO4 anoctamin 4 186.743 7.54491 2.59E−41 GPR20 G protein-coupled receptor 20 186.668 7.54433 9.67E−22 EEF1A2 eukaryotic translation elongation factor 1 186.624 7.54399 9.79E−37 alpha 2 HOXD11 homeobox D11 184.825 7.53002 4.91E−37 LHX1 LIM homeobox 1 183.385 7.51873 6.08E−21 DCC DCC netrin 1 receptor 177.536 7.47197 2.29E−36 SHC2 SHC (Src homology 2 domain containing) 177.418 7.47101 3.45E−36 transforming protein 2 FIRRE firre intergenic repeating RNA element 175.85 7.4582 2.53E−19 HAND2-AS1 HAND2 antisense RNA 1 (head to head) 173.707 7.44051 7.94E−44 MAB21L2 mab-21-like 2 (C. elegans) 171.99 7.42618 5.59E−25 TMC6 transmembrane channel-like 6 171.467 7.42179 1.23E−42 KDR kinase insert domain receptor 171.259 7.42004 8.29E−26 C2CD4C C2 calcium-dependent domain containing 167.398 7.38714 1.53E−42 4C CXXC4 CXXC finger protein 4 164.691 7.36362 1.29E−19 LGR5 leucine-rich repeat containing G protein-163.206 7.35055 4.04E−44 coupled receptor 5 DSC3 desmocollin 3 162.352 7.34298 1.77E−10 IL1RAPL1 interleukin 1 receptor accessory protein- 158.417 7.30758 2.79E−17 like 1 VANGL2 VANGL planar cell polarity protein 2 153.694 7.26392 2.36E−55 ABCB1 ATP-binding cassette_sub-family B 147.802 7.20752 3.07E−26 (MDR/TAP)_member 1 AADAC arylacetamide deacetylase 140.148 7.13081 7.12E−17 FSTL5 follistatin-like 5 139.259 7.12163 2.68E−15 MED15P9 mediator complex subunit 15 pseudogene 9 138.438 7.1131 5.39E−10 GCNT2 glucosaminyl (N-acetyl) transferase 2_I- 133.285 7.05837 1.16E−15 branching enzyme (I blood group) SULT1B1 sulfotransferase 132.429 7.04907 8.14E−21 family_cytosolic_1B_member 1 GPR87 G protein-coupled receptor 87 132.396 7.04872 3.45E−10 LIN28A lin-28 homolog A (C. elegans) 130.54 7.02835 7.46E−19 KRT8 keratin 8_type II 130.494 7.02784 2.19E−255 SLC35F3 solute carrier family 35_member F3 129.889 7.02114 4.02E−18 MYRF myelin regulatory factor 127.908 6.99896 8.88E−97 TIE1 tyrosine kinase with immunoglobulin- 125.933 6.97651 3.53E−48 like and EGF-like domains 1 FAT3 FAT atypical cadherin 3 125.595 6.97264 2.69E−61 C8orf49 chromosome 8 open reading frame 49 119.914 6.90586 2.72E−18 GABRA4 gamma-aminobutyric acid (GABA) A 119.403 6.89969 1.79E−15 receptor_alpha 4 PCDH7 protocadherin 7 119.262 6.89799 3.97E−83 ST6GALNAC3 ST6 (alpha-N-acetyl-neuraminyl-2_3-beta- 118.478 6.88848 2.53E−23 galactosy1-1_3)-N-acetylgalactosaminide alpha-2_6-sialyltransferase 3 PPP2R2B protein phosphatase 2_regulatory subunit 118.228 6.88543 3.56E−74 B_beta C6orf141 chromosome 6 open reading frame 141 117.977 6.88236 2.95E−18 SFMBT2 Scm-like with four mbt domains 2 116.043 6.85851 2.63E−33 SPINK5 serine peptidase inhibitor_Kazal type 5 115.386 6.85032 1.10E−08 SLC6A15 solute carrier family 6 (neutral amino 112.26 6.8107 6.07E−17 acid transporter)_member 15 FXYD6 FXYD domain containing ion transport 108.606 6.76296 1.75E−17 regulator 6 DNAH11 dynein_axonemal_heavy chain 11 107.843 6.75279 8.79E−60 SCG2 secretogranin II 106.966 6.74101 4.54E−67 SEMA3E sema domain_immunoglobulin domain 106.595 6.736 9.68E−18 (Ig)_short basic domain_secreted_(semaphorin) 3E GAL galanin/GMAP prepropeptide 105.543 6.72169 4.15E−52 NPY neuropeptide Y 104.525 6.70771 1.51E−15 KCNH2 potassium channel_voltage gated eag 102.046 6.67308 9.32E−33 related subfamily H_member 2 SYTL1 synaptotagmin-like 1 99.8984

6.64239 1.73E−47 HOPX HOP homeobox 98.9453 6.62856 1.74E−17 GPR37 G protein-coupled receptor 37 (endothelin 98.1407 6.61678 8.32E−36 receptor type B-like) CLSTN2 calsyntenin 2 97.1573 6.60225 6.01E−51 SLCO4A1 solute carrier organic anion transporter 96.0211 6.58528 3.70E−20 family_member 4A1 LUZP2 leucine zipper protein 2 95.3037 6.57446 1.86E−13 ERP27 endoplasmic reticulum protein 27 87.6213 6.45321 5.22E−15 TAGLN3 transgelin 3 87.0661 6.44404 8.10E−50 CACNA1H calcium channel_voltage-dependent_T 86.7024 6.438 2.39E−85 type_alpha 1H subunit NOVA1 neuro-oncological ventral antigen 1 85.9586 6.42557 1.21E−09 IGSF3 immunoglobulin superfamily_member 3 85.2324 6.41333 5.56E−38 P2RY14 purinergic receptor P2Y_G-protein 84.4116 6.39937 7.54E−13 coupled_14 SLC5A4 solute carrier family 5 (glucose 83.7995 6.38887 6.99E−15 activated ion channel)_member 4 NDST3 N-deacetylase/N-sulfotransferase 83.6463 6.38623 3.11E−20 (heparan glucosaminyl) 3 HOXD10 homeobox D10 83.2622 6.37959 6.03E−24 FOXF1 forkhead box F1 82.2857 6.36257 9.91E−08 HAND1 heart and neural crest derivatives 80.2556 6.32653 1.20E−12 expressed 1 CTTNBP2 cortactin binding protein 2 77.8222 6.28211 1.15E−09 ADAMTS16 ADAM metallopeptidase with 77.6573 6.27905 1.53E−57 thrombospondin type 1 motif_16 ELOVL2 ELOVL fatty acid elongase 2 77.076 6.26821 6.48E−39 HOXB9 homeobox B9 76.7162 6.26146 2.85E−09 PLCXD3 phosphatidylinositol-specific phospholipase 74.8868 6.22664 3.68E−13 C_X domain containing 3 SCN5A sodium channel_voltage gated_type V 74.3881 6.217 3.97E−24 alpha subunit TRIL TLR4 interactor with leucine-rich repeats 73.8563 6.20665 1.44E−14 HIST1H2BH histone cluster 1_H2bh 73.8405 6.20634 2.65E−21 MYL7 myosin_light chain 7_regulatory 73.5177 6.20002 3.16E−17 TEPP testis_prostate and placenta expressed 73.0296 6.19041 2.06E−15 HOXB8 homeobox B8 73.018 6.19018 6.99E−44 LIPG lipase_endothelial 72.8496 6.18685 1.62E−38 SLCO6A1 solute carrier organic anion transporter 72.6328 6.18255 3.74E−10 family_member 6A1 IGDCC3 immunoglobulin superfamily_DCC 72.6258 6.18241 1.28E−22 subclass_member 3 GABRG3 gamma-aminobutyric acid (GABA) A 72.1476 6.17288 4.13E−11 receptor_gamma 3 GRIA1 glutamate receptor_ionotropic_AMPA 1 71.9404 6.16873 1.08E−37 C8orf4 chromosome 8 open reading frame 4 71.2481 6.15478 9.53E−24 FABP4 fatty acid binding protein 4_adipocyte 70.9554 6.14884 1.96E−09 PLEKHG4B pleckstrin homology domain containing_family 70.7746 6.14516 8.93E−52 G (with RhoGef domain) member 4B IP6K3 inositol hexakisphosphate kinase 3 69.7939 6.12503 1.34E−16 PDE9A phosphodiesterase 9A 67.1097 6.06845 1.00E−15 KLHDC8A kelch domain containing 8A 66.2124 6.04903 1.29E−09 FLJ16779 uncharacterized LOC100192386 65.8988 6.04218 5.66E−07 CCDC160 coiled-coil domain containing 160 64.6832 6.01532 1.22E−11 SPP1 secreted phosphoprotein 1 63.3767 5.98588 2.40E−37 PCDH17 protocadherin 17 63.0227 5.9778 1.49E−10 HOTTIP HOXA distal transcript antisense RNA 62.4396 5.96439 3.67E−19 OXTR oxytocin receptor 62.3043 5.96126 1.14E−36 SH2D3C SH2 domain containing 3C 62.2667 5.96039 2.83E−68 USP43 ubiquitin specific peptidase 43 61.9104 5.95211 1.62E−26 KC6 keratoconus gene 6 61.6005 5.94487 4.37E−07 CACNG7 calcium channel_voltage-dependent_gamma 61.5198 5.94298 1.74E−114 subunit 7 SLC44A5 solute carrier family 44_member 5 60.9756 5.93016 4.59E−63 COL18A1 collagen_type XVIII_alpha 1 60.1278 5.90996 0.00E+00 LINC00491 long intergenic non-protein coding RNA 491 60.0324 5.90767 6.94E−12 TBX1 T-box 1 60.0149 5.90725 1.38E−30 GALNT14 polypeptide N- 59.4424 5.89342 9.44E−16 acetylgalactosaminyltransferase 14 CLEC1A C-type lectin domain family 1_member A 59.3592 5.8914 1.45E−09 CALY calcyon neuron-specific vesicular protein 59.309 5.89018 1.54E−21 CD93 CD93 molecule 58.2498 5.86418 9.02E−15 HIF3A hypoxia inducible factor 3_alpha subunit 58.2328 5.86376 2.36E−19 LPAR4 lysophosphatidic acid receptor 4 58.2304 5.8637 4.90E−18 TBX20 T-box 20 57.7408 5.85152 1.78E−06 TNRC6C-AS1 TNRC6C antisense RNA 1 57.652 5.8493 4.12E−13 CHMP4C charged multivesicular body protein 4C 56.3561 5.8165 1.76E−18 CADM1 cell adhesion molecule 1 56.3186 5.81554 1.11E−89 SDK1 sidekick cell adhesion molecule 1 55.5517 5.79576 9.60E−52 MMP10 matrix metallopeptidase 10 55.3001 5.78921 4.28E−11 MERTK MER proto-oncogene_tyrosine kinase 55.1428 5.7851 2.56E−26

DPY19L2P1 DPY19L2 pseudogene 1 55.0725 5.78326 1.10E−82 GPRC5B G protein-coupled receptor_class C_group 54.6061 5.77099 2.76E−17 5_member B VWDE von Willebrand factor D and EGF domains 54.0424 5.75602 1.37E−13 CIDEA cell death-inducing DFFA-like effector a 53.9432 5.75337 4.10E−11 RASGRF1 Ras protein-specific guanine nucleotide- 53.6193 5.74468 1.80E−21 releasing factor 1 CACNG6 calcium channel_voltage-dependent_gamma 53.5476 5.74275 8.41E−09 subunit 6 FAM189A1 family with sequence similarity 189_member 53.2323 5.73423 5.88E−18 A1 IL2RB interleukin 2 receptor_beta 52.6777 5.71912 9.40E−31 C1orf106 chromosome 1 open reading frame 106 52.1675 5.70508 8.35E−35 CRHBP corticotropin releasing hormone binding 52.0357 5.70143 5.66E−12 protein HBD hemoglobin_delta 51.5443 5.68774 4.43E−11 MGAT4C MGAT4 family_member C 49.6272 5.63306 4.86E−10 RBM20 RNA binding motif protein 20 49.1418 5.61888 3.22E−14 KCNA1 potassium channel_voltage gated shaker 49.1238 5.61835 9.02E−12 related subfamily A_member 1 SEMA3A sema domain_immunoglobulin domain 48.3221 5.59461 4.17E−74 (Ig)_short basic domain_secreted_(semaphorin) 3A SORCS3 sortilin-related VPS10 domain 48.1716 5.59011 3.21E−08 containing receptor 3 SLC22A31 solute carrier family 22_member 31 47.946 5.58334 8.45E−22 ZCCHC16 zinc finger_CCHC domain containing 16 47.7911 5.57867 2.49E−08 SHISA3 shisa family member 3 47.5212 5.5705 9.76E−18 VGF VGF nerve growth factor inducible 47.2303 5.56164 2.03E−20 CPVL carboxypeptidase_vitellogenic-like 47.0731 5.55683 3.13E−08 FAM213A family with sequence similarity 46.8767 5.5508 2.15E−17 213_member A HTR1D 5-hydroxytryptamine (serotonin) receptor 46.5442 5.54053 1.25E−28 1D_G protein-coupled PCDHA12 protocadherin alpha 12 45.8017 5.51733 7.82E−06 NTSR1 neurotensin receptor 1 (high affinity) 44.7576 5.48406 6.68E−10 FAM69B family with sequence similarity 69_member 43.6101 5.44659 2.53E−96 B LRRN4 leucine rich repeat neuronal 4 42.0904 5.39542 3.90E−26 LOC644919 uncharacterized LOC644919 40.994 5.35734 1.75E−09 COL9A3 collagen_type IX_alpha 3 40.5677 5.34226 3.87E−50 GIPC3 GIPC PDZ domain containing 40.4621 5.3385 4.22E−140 family_member 3 CYTL1 cytokine-like 1 40.3604 5.33487 2.91E−20 GBX2 gastrulation brain homeobox 2 39.8398 5.31614 1.15E−07 C2orf91 chromosome 2 open reading frame 91 38.997 5.28529 7.95E−09 TTLL6 tubulin tyrosine ligase-like family 38.9764 5.28453 1.48E−08 member 6 IFLTD1 lamin tail domain containing 1 38.9187 5.28239 3.52E−12 CECR2 cat eye syndrome chromosome 38.553 5.26877 3.66E−08 region_candidate 2 PDGFB platelet-derived growth factor beta 38.5383 5.26822 6.45E−21 polypeptide SSTR1 somatostatin receptor 1 37.612 5.23312 1.10E−06 RGS5 regulator of G-protein signaling 5 37.382 5.22427 1.21E−127 MMP23B matrix metallopeptidase 23B 37.1557 5.21551 2.07E−27 ISL1 ISL LIM homeobox 1 36.8768 5.20464 1.70E−14 ABI3 ABI family_member 3 36.724 5.19865 2.86E−20 ZPLD1 zona pellucida-like domain containing 1 36.7237 5.19864 2.13E−11 PDE3B phosphodiesterase 3B_cGMP-inhibited 36.6545 5.19592 7.16E−22 BEST3 bestrophin 3 36.5693 5.19256 3.02E−12 B4GALNT4 beta-1_4-N-acetyl-galactosaminy1 36.2902 5.18151 1.97E−21 transferase 4 LRRC17 leucine rich repeat containing 17 36.1996 5.1779 9.35E−27 KCNA6 potassium channel_voltage gated shaker 36.0306 5.17115 1.91E−15 related subfamily A_member 6 NRXN3 neurexin 3 36.0153 5.17054 4.93E−26 MGC2889 uncharacterized protein MGC2889 35.8955 5.16573 7.62E−08 ADAMTS20 ADAM metallopeptidase with 35.2102 5.13792 1.38E−08 thrombospondin type 1 motif_20 HUNK hormonally up-regulated Neu-associated 34.6857 5.11627 3.50E−14 kinase MTUS1 microtubule associated tumor suppressor 1 34.2018 5.096 3.01E−24 LOC101929086 NA 34.028 5.08865 8.77E−07 DACT2 dishevelled-binding antagonist of beta- 33.744 5.07656 1.56E−06 catenin 2 ACTG2 actin_gamma 2_smooth muscle_enteric 33.0521 5.04667 1.30E−11 WNT2 wingless-type MMTV integration site family 32.8017 5.0357 8.54E−08 member 2 TTR transthyretin 32.3991 5.01788 2.02E−06 SFRP1 secreted frizzled-related protein 1 32.2615 5.01174 6.51E−40 GRPR gastrin-releasing peptide receptor 32.2049 5.00921 3.28E−29 CCDC88C coiled-coil domain containing 88C 32.1773 5.00797 8.98E−23 LOC440910 uncharacterized LOC440910 32.1351 5.00608 7.01E−06 CYP2S1 cytochrome P450_family

32.1307 5.00588 3.24E−59 2_subfamily S_polypeptide 1 LRRN1 leucine rich repeat neuronal 1
32.0926 5.00417 1.17E−06 C7 complement component 7 32.0613 5.00276 2.19E−13 NDRG2
NDRG family member 2 32.0118 5.00053 1.08E−55 ZDHHC8P1 zinc finger_DHHC-type
containing 8 31.9831 4.99924 3.17E−14 pseudogene 1 LRFN5 leucine rich repeat and fibronectin
31.9362 4.99712 8.06E−09 type III domain containing 5 NR0B1 nuclear receptor subfamily
0_group 31.7781 4.98996 1.35E−05 B_member 1 FAM105A family with sequence similarity
31.7613 4.9892 2.11E−17 105_member A MMP1 matrix metallopeptidase 1 31.7026 4.98653
3.12E−12 GABRQ gamma-aminobutyric acid (GABA) A 31.1647 4.96184 4.24E−07
receptor_theta C9orf47 chromosome 9 open reading frame 47 31.1247 4.95999 1.13E−14 HAND2
heart and neural crest derivatives 30.8252 4.94604 7.86E−05 expressed 2 ARHGDIB Rho GDP
dissociation inhibitor (GDI) beta 30.6697 4.93874 1.46E−162 KCNMB4 potassium channel
subfamily M regulatory 30.6622 4.93839 3.00E−36 beta subunit 4 LOC728392 uncharacterized
LOC728392 30.6522 4.93792 1.84E−102 NUTM2F NUT family member 2F 30.1029 4.91183
3.45E−07 GRIP1 glutamate receptor interacting protein 1 30.0545 4.90951 8.20E−33 AIM1L
absent in melanoma 1-like 29.8554 4.89992 5.19E−08 WT1-AS WT1 antisense RNA 29.8471
4.89952 8.31E−07 PNMA3 paraneoplastic Ma antigen 3 29.7352 4.8941 4.99E−14 TPSG1 tryptase
gamma 1 29.473 4.88132 9.37E−08 MOV10L1 Mov10 RISC complex RNA helicase like 1
29.1231 4.86409 5.72E−36 HOXD13 homeobox D13 29.089 4.8624 1.15E−08 KAL1 anosmin 1
29.0122 4.85859 2.64E−42 KNDC1 kinase non-catalytic C-lobe domain 28.744 4.84519 3.37E−33
(KIND) containing 1 ADAM23 ADAM metallopeptidase domain 23 28.5026 4.83302 8.82E−19
TYRP1 tyrosinase-related protein 1 28.363 4.82594 1.51E−22 SP140 SP140 nuclear body protein
28.3 4.82273 3.34E−28 LOC100652770 NA 28.1835 4.81678 1.28E−05 ZNF467 zinc finger
protein 467 28.1178 4.81341 7.48E−14 GPR115 adhesion G protein-coupled receptor F4 27.9129
4.80286 1.95E−08 PNMT phenylethanolamine N-methyltransferase 27.911 4.80276 1.28E−05
LINC00648 long intergenic non-protein coding RNA 648 27.9067 4.80254 8.86E−06 FAM95C
family with sequence similarity 95_member 27.6934 4.79147 1.23E−06 C LOC101928340 NA
27.633 4.78832 1.36E−05 FAM162B family with sequence similarity 27.3855 4.77534 4.42E−06
162_member B ASXL3 additional sex combs like transcriptional 27.0169 4.75579 9.59E−06
regulator 3 EBI3 Epstein-Barr virus induced 3 26.9236 4.7508 8.48E−11 LYPLAL1-AS1
LYPLAL1 antisense RNA 1 (head to head) 26.8861 4.74879 2.75E−22 ANKRD18B ankyrin repeat
domain 18B 26.6734 4.73733 4.75E−11 LLGL2 lethal giant larvae homolog 2 (Drosophila)
26.6686 4.73707 5.18E−26 SRSF12 serine/arginine-rich splicing factor 12 26.1794 4.71036
1.89E−31 DLK1 delta-like 1 homolog (Drosophila) 26.1428 4.70834 1.22E−08 TMPRSS11B
transmembrane protease_serine 11B 26.0476 4.70308 1.68E−05 IGF2BP3 insulin-like growth
factor 2 mRNA binding 26.0092 4.70095 1.08E−69 protein 3 F11R F11 receptor 25.9993 4.7004
2.83E−29 TNNI1 troponin I type 1 (skeletal_slow) 25.984 4.69955 1.41E−06 MAGEB17
melanoma antigen family B17 25.5824 4.67708 4.62E−06 PPARG peroxisome proliferator-
activated 25.1998 4.65534 1.06E−11 receptor gamma PLCB2 phospholipase C_beta 2 25.1225
4.65091 8.52E−26 HRASLS HRAS-like suppressor 25.1096 4.65017 3.45E−05 JPH1 junctophilin
1 25.0058 4.64419 3.39E−06 EPHA7 EPH receptor A7 24.8508 4.63522 3.06E−05 PCYT1B
phosphate cytidylyltransferase 24.7382 4.62867 4.96E−06 1_choline_beta KIAA1211 KIAA1211
24.6733 4.62488 5.54E−17 ARL14 ADP-ribosylation factor-like 14 24.6274 4.62219 5.67E−05
VIP vasoactive intestinal peptide 24.5153 4.61561 1.86E−06 LHX2 LIM homeobox 2 24.445
4.61147 2.21E−08 C4BPB complement component 4 binding 24.4286 4.6105 1.18E−07
protein_beta RSPO4 R-spondin 4 24.3298 4.60465 2.80E−14 YBX2 Y box binding protein 2
24.2681 4.60099 1.18E−07 THSD7A thrombospondin_type I_domain containing 24.2192 4.59808
2.09E−50 7A SDK2 sidekick cell adhesion molecule 2 24.0776 4.58962 1.10E−06 HS6ST2
heparan sulfate 6-O-sulfotransferase 2 23.8949 4.57863 3.22E−06 PCDHB2 protocadherin beta 2
23.8823 4.57787 1.41E−32 PCDH10 protocadherin 10 23.6912 4.56628 1.50E−07 ICOSLG
inducible T-cell co-stimulator ligand 23.6241 4.56219 5.57E−19 IGF2BP1 insulin-like growth

factor 2 mRNA binding 23.6132 4.56152 4.59E−76 protein 1 KCNF1 potassium channel_voltage gated modifier 23.6097 4.56131 4.19E−11 subfamily F_member 1 GDF7 growth differentiation factor 7 23.5935 4.56032 9.44E−06 EFNA2 ephrin-A2 23.46 4.55213 3.31E−12 CXADR coxsackie virus and adenovirus receptor 23.1897 4.53541 1.38E−08 GLB1L2 galactosidase_beta 1-like 2 23.1096 4.53042 4.28E−14 IGFBP5 insulin-like growth factor binding protein 5 22.9538 4.52066 8.23E−28 KRT79 keratin 79_type II 22.9042 4.51754 5.91E−08 IL33 interleukin 33 22.8265 4.51264 5.10E−05 CPA6 carboxypeptidase A6 22.6992 4.50457 1.90E−05 RGS1 regulator of G-protein signaling 1 22.6241 4.49979 0.000116 GPR63 G protein-coupled receptor 63 22.6204 4.49955 4.35E−10 DOC2GP double C2-like 22.592 4.49774 1.08E−10 domains_gamma_pseudogene FAM110D family with sequence similarity 22.2782 4.47756 2.13E−08 110_member D ART5 ADP-ribosyltransferase 5 22.0036 4.45967 6.14E−06 CD163L1 CD163 molecule-like 1 21.9861 4.45852 6.41E−25 ATCAY ataxia_cerebellar_Cayman type 21.9716 4.45757 1.81E−05 CNTN5 contactin 5 21.7124 4.44045 0.000119 LONRF2 LON peptidase N-terminal domain and ring 21.3584 4.41673 3.34E−16 finger 2 AFAP1L2 actin filament associated protein 1-like 2 21.2551 4.40974 1.28E−12 LRP1B low density lipoprotein receptor-related 21.1326 4.4014 0.000136 protein 1B HOXA13 homeobox A13 21.1285 4.40112 1.71E−11 LCP1 lymphocyte cytosolic protein 1 (L-plastin) 21.0927 4.39867 1.38E−11 TNFSF4 tumor necrosis factor (ligand) 21.0743 4.39741 4.65E−65 superfamily_member 4 AQP7P3 aquaporin 7 pseudogene 3 21.0438 4.39532 0.000248 METTL24 methyltransferase like 24 20.8515 4.38208 1.27E−05 SULT4A1 sulfotransferase family 4A_member 1 20.8356 4.38098 3.22E−20 PDE6B phosphodiesterase 20.8092 4.37915 5.14E−22 6B_cGMP-specific_rod_beta AQP7P1 aquaporin 7 pseudogene 1 20.7323 4.37381 9.27E−07 GUCY1A3 guanylate cyclase 1_soluble_alpha 3 20.6716 4.36958 3.47E−05 PCAT1 prostate cancer associated transcript 1 20.6577 4.36861 0.000117 (non-protein coding) OTOS otospiralin 20.6125 4.36545 3.94E−07 AQP5 aquaporin 5 20.6021 4.36472 5.95E−07 HES4 hes family bHLH transcription factor 4 20.5841 4.36346 5.75E−14 ADAMTS3 ADAM metallopeptidase with 20.527 4.35945 3.83E−34 thrombospondin type 1 motif_3 C1orf94 chromosome 1 open reading frame 94 20.4524 4.3542 3.40E−05 LOC101928303 uncharacterized LOC101928303 20.4496 4.354 1.54E−05 MOB3B MOB kinase activator 3B 20.3551 4.34732 1.05E−12 ITIH3 inter-alpha-trypsin inhibitor heavy chain 3 20.3247 4.34516 1.58E−13 SUCNR1 succinate receptor 1 20.1055 4.32952 0.000611 ST8SIA2 ST8 alpha-N-acetyl-neuraminide alpha-2_8- 19.9714 4.31986 1.02E−05 sialyltransferase 2 PCDHA11 protocadherin alpha 11 19.8527 4.31126 1.11E−07 S1PR5 sphingosine-1-phosphate receptor 5 19.7582 4.30438 5.60E−39 LRRC4C leucine rich repeat containing 4C 19.7054 4.30052 3.88E−23 GPRIN2 G protein regulated inducer of neurite 19.63 4.29499 1.04E−07 outgrowth 2 ANXA3 annexin A3 19.3198 4.27201 6.49E−38 UCP2 uncoupling protein 2 (mitochondrial_proton 19.1933 4.26253 9.86E−33 carrier) PRAC2 prostate cancer susceptibility candidate 2 18.9331 4.24284 0.000291 MAP3K9 mitogen-activated protein kinase kinase 18.9294 4.24256 2.16E−25 kinase 9 MYH14 myosin_heavy chain 14_non-muscle 18.9226 4.24204 3.05E−09 SLITRK5 SLIT and NTRK-like family_member 5 18.887 4.23932 0.000287 RAMP2-AS1 RAMP2 antisense RNA 1 18.881 4.23886 2.61E−14 FRAS1 Fraser extracellular matrix complex 18.7633 4.22984 7.69E−22 subunit 1 DCHS1 dachsous cadherin-related 1 18.7224 4.22669 1.91E−85 PCBP3 poly(rC) binding protein 3 18.6032 4.21748 5.50E−08 DENND2A DENN/MADD domain containing 2A 18.5959 4.21691 2.08E−28 CYTH4 cytohesin 4 18.4855 4.20832 2.05E−05 SYT3 synaptotagmin III 18.4219 4.20335 4.79E−10 BEGAIN brain-enriched guanylate kinase-associated 18.3092 4.1945 5.24E−14 SYT13 synaptotagmin XIII 18.3031 4.19402 1.84E−07 PRKCQ protein kinase C_theta 18.3006 4.19382 1.34E−08 ALPK3 alpha-kinase 3 18.0415 4.17325 8.05E−43 INPP5D inositol polyphosphate-5-phosphatase D 18.0215 4.17165 1.99E−10 CLEC14A C-type lectin domain family 14_member A 17.9653 4.16714 2.07E−10 GRAP GRB2-related adaptor protein 17.9383 4.16497 9.76E−14 MYCT1 myc target 1 17.8007 4.15386 5.96E−17 SPINT1 serine peptidase inhibitor_Kunitz type 1 17.6879 4.14469 1.47E−10 LINC00951 long intergenic non-protein coding

RNA 951 17.6694 4.14318 0.000391 SLC1A7 solute carrier family 1 (glutamate 17.6269 4.13971 5.10E−21 transporter)_member 7 PLN phospholamban 17.6175 4.13894 2.23E−05 CDH8 cadherin 8_type 2 17.6042 4.13785 5.23E−06 SCN2A sodium channel_voltage gated_type II 17.5982 4.13736 1.84E−07 alpha subunit OR2H2 olfactory receptor_family 2_subfamily 17.4823 4.12782 5.83E−06 H_member 2 TNNI3 troponin I type 3 (cardiac) 17.2932 4.11213 8.76E−06 SNCB synuclein_beta 17.2161 4.10569 2.97E−05 PRSS16 protease_serine_16 (thymus) 17.1239 4.09794 1.53E−05 NNAT neuronatin 17.1189 4.09752 9.80E−78 ZBTB46 zinc finger and BTB domain containing 46 17.1106 4.09682 1.95E−29 SLC6A12 solute carrier family 6 (neurotransmitter 17.0269 4.08974 0.000365 transporter)_member 12 EPB41L3 erythrocyte membrane protein band 4.1- 17.0146 4.0887 0.001336 like 3 IL1A interleukin 1_alpha 16.9791 4.08569 6.19E−09 GRIN2A glutamate receptor_ionotropic_N-methyl 16.9785 4.08564 2.15E−06 D-aspartate 2A HBE1 hemoglobin_epsilon 1 16.9763 4.08545 3.06E−05 LIPH lipase_member H 16.9375 4.08215 0.000383 EMCN endomucin 16.9336 4.08182 1.72E−05 NTRK3 neurotrophic tyrosine kinase_receptor.sub.— 16.9244 4.08103 4.31E−17 type 3 TMEFF2 transmembrane protein with EGF-like and 16.918 4.08049 3.89E−06 two follistatin-like domains 2 N4BP3 NEDD4 binding protein 3 16.7396 4.06519 5.46E−10 LINC00460 long intergenic non-protein coding RNA 460 16.6098 4.05396 1.41E−09 SCARF1 scavenger receptor class F_member 1 16.605 4.05355 2.79E−51 SMCO3 single-pass membrane protein with coiled- 16.529 4.04693 1.48E−13 coil domains 3 FBXL16 F-box and leucine-rich repeat protein 16 16.4858 4.04315 1.21E−14 SLC16A12 solute carrier family 16_member 12 16.4363 4.03881 2.11E−10 IRX4 iroquois homeobox 4 16.3644 4.03249 0.00015 F2RL1 coagulation factor II (thrombin) receptor- 16.3467 4.03093 1.05E−12 like 1 PLCH2 phospholipase C_eta 2 16.2672 4.02389 1.91E−20 EPCAM epithelial cell adhesion molecule 16.2263 4.02026 8.21E−19 TNFRSF9 tumor necrosis factor receptor 16.1981 4.01775 4.31E−20 superfamily_member 9 CCDC3 coiled-coil domain containing 3 16.1881 4.01686 2.55E−20 SOX8 SRY (sex determining region Y)-box 8 16.1306 4.01173 3.37E−09 PTPN6 protein tyrosine phosphatase_non-receptor 16.1207 4.01084 2.13E−21 type 6 PDGFRL platelet-derived growth factor receptor-like 16.015 4.00135 1.75E−28 CBLN2 cerebellin 2 precursor 15.984 3.99856 0.001124 NLRP2 NLR family_pyrin domain containing 2 15.9836 3.99852 2.37E−11 EXPH5 exophilin 5 15.9414 3.99471 3.32E−10 CNTN1 contactin 1 15.9247 3.99319 9.80E−09 ACHE acetylcholinesterase (Yt blood group) 15.8565 3.987 2.21E−18 GPR112 adhesion G protein-coupled receptor G4 15.7991 3.98177 5.31E−06 FAM84B family with sequence similarity 15.7964 3.98152 6.39E−95 84_member B PARM1 prostate androgen-regulated mucin-like 15.771 3.9792 2.10E−09 protein 1 B3GNT5 UDP-GlcNAc:betaGal beta-1_3-N- 15.7637 3.97853 2.55E−29 acetylglucosaminyltransferase 5 MCF2L MCF.2 cell line derived transforming 15.7588 3.97809 6.13E−05 sequence-like F10 coagulation factor X 15.7575 3.97797 3.70E−17 RAB26 RAB26_member RAS oncogene family 15.7496 3.97724 1.59E−23 OR51E2 olfactory receptor_family 51_subfamily 15.7274 3.97521 0.000128 E_member 2 ANXA13 annexin A13 15.6535 3.96841 0.000199 SLC12A5 solute carrier family 12 (potassium/chloride 15.6414 3.9673 3.07E−10 transporter)_member 5 ARHGEF26 Rho guanine nucleotide exchange factor 15.637 3.96689 6.21E−18 (GEF) 26 CLDN1 claudin 1 15.6055 3.96398 8.58E−16 HMGA2 high mobility group AT-hook 2 15.5802 3.96164 3.74E−38 SYT9 synaptotagmin IX 15.5294 3.95693 0.000275 COX6B2 cytochrome c oxidase subunit VIb 15.4751 3.95188 3.39E−15 polypeptide 2 (testis) SLC9A4 solute carrier family 9_subfamily A 15.4171 3.94646 0.00011 (NHE4_cation proton antiporter 4)_member 4 SLITRK6 SLIT and NTRK-like family_member 6 15.4144 3.94621 0.001369 DOCK8 dedicator of cytokinesis 8 15.414 3.94617 0.000138 GPR126 adhesion G protein-coupled receptor G6 15.3514 3.9403 5.60E−39 LOC100130238 uncharacterized LOC100130238 15.2641 3.93207 2.52E−05 SULT1C2 sulfotransferase 15.2025 3.92624 4.89E−05 family_cytosolic_1C_member 2 NIPAL1 NIPA-like domain containing 1 15.1915 3.92519 9.10E−12 GNA14 guanine nucleotide binding protein (G 15.1356 3.91987 5.65E−26 protein)_alpha 14 PRKCQ-AS1 PRKCQ antisense RNA 1 15.0898 3.9155 2.20E−14

LOC102800447 uncharacterized LOC102800447 15.0873 3.91526 9.37E−06 KCNS1 potassium voltage-gated channel_modifier 15.0747 3.91406 3.97E−16 subfamily S_member 1 LOC100126784 uncharacterized LOC100126784 15.0471 3.91141 1.38E−33 LPHN3 adhesion G protein-coupled receptor L3 14.9638 3.9034 0.000136 TMIGD2 transmembrane and immunoglobulin domain 14.9566 3.90271 0.001397 containing 2 VSTM1 V-set and transmembrane domain containing 14.8319 3.89063 0.001267 1 CDH3 cadherin 3_type 1_P-cadherin (placental) 14.8271 3.89016 2.48E−20 PRKCZ protein kinase C_zeta 14.7712 3.88472 2.05E−20 MAP2 microtubule-associated protein 2 14.7558 3.88321 4.24E−17 PIK3AP1 phosphoinositide-3-kinase adaptor protein 1 14.7409 3.88175 5.73E−06 TNFSF18 tumor necrosis factor (ligand) 14.7276 3.88045 0.001118 superfamily_member 18 MIR4697HG MIR4697 host gene 14.6591 3.87372 3.42E−07 GP6 glycoprotein VI (platelet) 14.6537 3.87319 0.000236 LINC01021 long intergenic non-protein coding RNA 14.6366 3.87151 2.94E−08 1021 PLAC8 placenta-specific 8 14.5941 3.86731 2.84E−39 TMEM88 transmembrane protein 88 14.5881 3.86672 9.16E−19 ENTPD8 ectonucleoside triphosphate 14.5833 3.86625 0.000548 diphosphohydrolase 8 PPARGC1A peroxisome proliferator-activated receptor 14.5566 3.8636 9.48E−07 gamma_coactivator 1 alpha SH3GL2 SH3-domain GRB2-like 2 14.4701 3.855 1.65E−06 SCN9A sodium channel_voltage gated_type IX 14.4341 3.85141 9.10E−23 alpha subunit CPNE7 copine VII 14.4104 3.84904 1.53E−18 NRARP NOTCH-regulated ankyrin repeat protein 14.4019 3.84819 6.33E−13 CERS4 ceramide synthase 4 14.3768 3.84567 1.43E−21 FCHO1 FCH domain only 1 14.3756 3.84555 1.82E−20 C19orf81 chromosome 19 open reading frame 81 14.3156 3.83952 4.03E−09 PGM5 phosphoglucomutase 5 14.3137 3.83932 5.56E−07 LINC01082 long intergenic non-protein coding RNA 14.2988 3.83782 0.002369 1082 HIST1H2BG histone cluster 1_H2bg 14.2247 3.83033 5.47E−11 LOC100507006 uncharacterized LOC100507006 14.1543 3.82317 0.002106 LMTK3 lemur tyrosine kinase 3 14.1398 3.82169 2.65E−37 QPRT quinolinate phosphoribosyltransferase 14.1045 3.81808 6.47E−60 TMEM35 transmembrane protein 35 14.0929 3.8169 7.46E−19 SEMA6B sema domain_transmembrane domain 14.0663 3.81417 1.78E−13 (TM)_and cytoplasmic domain_(semaphorin) 6B AADACP1 arylacetamide deacetylase pseudogene 1 14.0634 3.81387 9.06E−05 CDH5 cadherin 5_type 2 (vascular endothelium) 14.0396 3.81143 3.35E−05 ZNF521 zinc finger protein 521 13.9425 3.80142 3.49E−07 ZYG11A zyg-11 family member A_cell cycle 13.8672 3.7936 3.38E−14 regulator LINC00880 long intergenic non-protein coding RNA 880 13.826 3.78931 3.87E−06 DENND1C DENN/MADD domain containing 1C 13.8021 3.78682 9.80E−07 LOC101927746 uncharacterized LOC101927746 13.6537 3.77122 1.42E−10 TRPV6 transient receptor potential cation 13.6524 3.77108 0.000789 channel_subfamily V_member 6 CAMK1G calcium/calmodulin-dependent protein 13.5132 3.7563 8.50E−09 kinase IG ELOVL2-AS1 ELOVL2 antisense RNA 1 13.4665 3.7513 0.000246 CYFIP2 cytoplasmic FMR1 interacting protein 2 13.3884 3.74291 8.57E−94 NOS1AP nitric oxide synthase 1 (neuronal) adaptor 13.3866 3.74272 3.46E−07 protein TRHDE thyrotropin-releasing hormone degrading 13.2802 3.73121 1.32E−13 enzyme LSAMP-AS1 LSAMP antisense RNA 1 13.2538 3.72833 0.000305 SPOCK3 sparc/osteonectin_cwcv and kazal-like 13.2293 3.72566 0.0022 domains proteoglycan (testican) 3 MPZL2 myelin protein zero-like 2 13.2262 3.72533 0.001202 LAMA5 laminin_alpha 5 13.2086 3.72341 1.87E−24 LOC101929690 NA 13.2059 3.72311 1.65E−16 F7 coagulation factor VII (serum prothrombin 13.1548 3.71752 0.001195 conversion accelerator) LOC101927482 uncharacterized LOC101927482 13.1233 3.71406 3.80E−09 ACSM4 acyl-CoA synthetase medium-chain family 13.0723 3.70844 0.00141 member 4 KLHL6 kelch-like family member 6 13.0632 3.70744 0.000927 MUC22 mucin 22 13.0296 3.70372 0.001228 FGF13 fibroblast growth factor 13 13.018 3.70244 0.004351 F3 coagulation factor III 12.9766 3.69784 1.07E−10 (thromboplastin_tissue factor) TMSB15A thymosin beta 15a 12.9458 3.69441 1.02E−14 KSR1 kinase suppressor of ras 1 12.9175 3.69125 1.82E−74 CERS1 ceramide synthase 1 12.9124 3.69068 5.47E−10 TNIK TRAF2 and NCK interacting kinase 12.8675 3.68566 2.39E−15 PKIB protein kinase (cAMP-

dependent_catalytic) 12.7595 3.6735 9.98E−05 inhibitor beta C1orf226 chromosome 1 open reading frame 226 12.7485 3.67225 1.48E−05 DEF6 DEF6 guanine nucleotide exchange factor 12.7046 3.66728 3.26E−28 RCVRN recoverin 12.6679 3.6631 0.001865 IL31RA interleukin 31 receptor A 12.6668 3.66298 1.03E−08 SOWAHB sosondowah ankyrin repeat domain family 12.6359 3.65946 5.40E−07 member B MIR2682 microRNA 2682 12.6238 3.65808 2.24E−37 SH2D5 SH2 domain containing 5 12.6064 3.65608 1.12E−31 ST6GALNAC5 ST6 (alpha-N-acetyl-neuraminyl-2_3-beta- 12.5647 3.65131 6.63E−05 galactosyl-1_3)-N-acetylgalactosaminide alpha-2_6-sialyltransferase 5 TNFRSF10C tumor necrosis factor receptor superfamily 12.5125 3.6453 1.63E−21 member 10c_decoy without an intracellular domain GJA3 gap junction protein_alpha 3_46kDa 12.427 3.63541 2.24E−05 ELAVL2 ELAV like neuron-specific RNA binding 12.3924 3.63138 2.84E−06 protein 2 ERC2 ELKS/RAB6-interacting/CAST family 12.358 3.62737 3.63E−05 member 2 CAPN11 calpain 11 12.356 3.62714 0.0006 C7orf69 chromosome 7 open reading frame 69 12.3522 3.6267 1.28E−17 KIF17 kinesin family member 17 12.3375 3.62498 1.04E−21 ZBED2 zinc finger_BED-type containing 2 12.2674 3.61676 1.51E−06 TTYH2 tweety family member 2 12.2659 3.61658 1.79E−86 ST18 suppression of tumorigenicity 18_zinc 12.2605 3.61595 0.000105 finger GRB14 growth factor receptor-bound protein 14 12.2588 3.61574 2.43E−31 EDN2 endothelin 2 12.2511 3.61484 2.03E−06 KCP kielin/chordin-like protein 12.2016 3.609 4.14E−05 MESTIT1 MEST intronic transcript 1_antisense RNA 12.1456 3.60236 0.000424 CLGN calmegin 12.1193 3.59923 2.73E−09 IL18 interleukin 18 12.101 3.59706 6.08E−15 ANKRD18A ankyrin repeat domain 18A 12.0977 3.59666 1.23E−05 UPB1 ureidopropionase_beta 12.0815 3.59473 0.000346 CARD11 caspase recruitment domain 12.066 3.59287 4.03E−13 family_member 11 KLHL23 kelch-like family member 23 12.0564 3.59173 0.003407 ABCD2 ATP-binding cassette_sub-family D 12.0107 3.58625 0.000115 (ALD)_member 2 ITGAX integrin_alpha X (complement component 3 11.9821 3.58281 0.003088 receptor 4 subunit) CDH18 cadherin 18_type 2 11.9667 3.58095 0.004769 NOX4 NADPH oxidase 4 11.9252 3.57594 7.16E−28 TMEM125 transmembrane protein 125 11.9135 3.57452 0.000735 PPARGC1B peroxisome proliferator-activated receptor 11.8045 3.56127 4.66E−06 gamma_coactivator 1 beta F2 coagulation factor II (thrombin) 11.7803 3.5583 9.71E−05 CAMSAP3 calmodulin regulated spectrin-associated 11.777 3.5579 0.001984 protein family_member 3 LOC100996579 uncharacterized LOC100996579 11.7569 3.55544 0.000352 FBXO2 F-box protein 2 11.7289 3.55199 2.38E−28 ZNF663P zinc finger protein 663_pseudogene 11.713 3.55004 1.20E−05 KCNK3 potassium channel_two pore domain 11.7019 3.54867 9.68E−15 subfamily K_member 3 OGDHL oxoglutarate dehydrogenase-like 11.6171 3.53818 1.44E−11 HTR1B 5-hydroxytryptamine (serotonin) receptor 11.5855 3.53425 0.006255 1B_G protein-coupled NPW neuropeptide W 11.5805 3.53363 8.71E−28 RND2 Rho family GTPase 2 11.5602 3.53109 2.29E−19 POU2F3 POU class 2 homeobox 3 11.4708 3.51989 0.000573 BAIAP3 BAI1-associated protein 3 11.4524 3.51758 4.89E−11 PCDHA9 protocadherin alpha 9 11.4289 3.51461 0.00541 INA internexin neuronal intermediate filament 11.406 3.51172 1.76E−19 protein_alpha LINC01012 long intergenic non-protein coding RNA 11.3526 3.50495 0.000134 1012 FLT4 fms-related tyrosine kinase 4 11.3474 3.50429 9.13E−06 FAR2P2 fatty acyl CoA reductase 2 pseudogene 2 11.298 3.49799 1.10E−05 PALM3 paralemmin 3 11.2908 3.49708 3.25E−22 LINC00887 long intergenic non-protein coding RNA 887 11.2675 3.4941 9.65E−05 HSD17B14 hydroxysteroid (17-beta) dehydrogenase 14 11.261 3.49326 8.14E−10 ZNF853 zinc finger protein 853 11.2476 3.49155 5.44E−17 TYROBP TYRO protein tyrosine kinase binding 11.2225 3.48832 0.004002 protein FCGBP Fc fragment of IgG binding protein 11.193 3.48453 2.53E−08 LOC349160 uncharacterized LOC349160 11.1929 3.48451 0.00353 C10orf91 chromosome 10 open reading frame 91 11.1722 3.48184 1.42E−05 PCDH9 protocadherin 9 11.1083 3.47356 4.97E−14 CD101 CD101 molecule 11.0942 3.47174 3.83E−07 PCDHA4 protocadherin alpha 4 11.0596 3.46723 7.10E−06 LINC00858 long intergenic non-protein coding RNA 858 11.0374 3.46433 0.007369 SPACA4 sperm acrosome associated 4 10.9188 3.44874 0.005785 C14orf39

chromosome 14 open reading frame 39 10.9121 3.44786 1.16E−15 JUP junction plakoglobin 10.8918 3.44517 1.02E−41 KIF21B kinesin family member 21B 10.847 3.43922 4.67E−31 NPPB natriuretic peptide B 10.8154 3.43502 6.87E−06 GALNTL6 polypeptide N- 10.803 3.43336 0.001067 acetylgalactosaminyltransferase-like 6 PCDHGB6 protocadherin gamma subfamily B_6 10.7364 3.42444 5.77E−09 KIAA1257 KIAA1257 10.7286 3.42339 0.00706 DNM1 dynamin 1 10.7235 3.42271 6.95E−21 CRB2 crumbs family member 2 10.6856 3.4176 7.06E−05 ECSCR endothelial cell surface expressed 10.64 3.41143 4.77E−18 chemotaxis and apoptosis regulator SRRM4 serine/arginine repetitive matrix 4 10.595 3.40531 3.37E−08 SLC27A2 solute carrier family 27 (fatty acid 10.5673 3.40153 8.96E−05 transporter)_member 2 ATRNL1 attractin-like 1 10.5349 3.39711 1.52E−13 PEG10 paternally expressed 10 10.4808 3.38968 2.60E−13 NFAM1 NFAT activating protein with ITAM motif 1 10.3784 3.37551 0.00437 BLACAT1 bladder cancer associated transcript 1 10.3481 3.37129 0.000494 (non-protein coding) HSD17B2 hydroxysteroid (17-beta) dehydrogenase 2 10.3443 3.37077 0.006844 MEX3A mex-3 RNA binding family member A 10.2924 3.36351 0.00E+00 LOC100129617 uncharacterized LOC100129617 10.2675 3.36001 7.93E−06 IGLON5 IgLON family member 5 10.2593 3.35886 4.35E−05 AQP1 aquaporin 1 (Colton blood group) 10.2493 3.35746 2.90E−52 ERBB4 erb-b2 receptor tyrosine kinase 4 10.2334 3.35521 0.003618 MGAT5B mannosyl (alpha-1_6-)-glycoprotein beta- 10.2166 3.35284 1.50E−28 1_6-N-acetyl- glucosaminyltransferase_isozyme B EPHB6 EPH receptor B6 10.2139 3.35246 6.39E−10 CTAGE11P CTAGE family_member 11_pseudogene 10.2083 3.35167 0.000199 HOXB-AS3 HOXB cluster antisense RNA 3 10.1938 3.34962 6.77E−33 LOC102723854 uncharacterized LOC102723854 10.1809 3.3478 7.33E−06 KCNN3 potassium channel_calcium activated 10.1753 3.347 7.11E−05 intermediate/small conductance subfamily N alpha_member 3 DCDC2 doublecortin domain containing 2 10.1005 3.33636 0.00503 ZFP92 ZFP92 zinc finger protein 10.0974 3.33591 4.67E−05 UPK1A-AS1 UPK1A antisense RNA 1 10.0951 3.33558 0.004621 HIST1H2BE histone cluster 1_H2be 10.0917 3.3351 6.66E−05 RIMS2 regulating synaptic membrane exocytosis 2 10.0667 3.33152 0.001381 WSCD1 WSC domain containing 1 10.0653 3.33132 0.000557 LOC100507534 uncharacterized LOC100507534 10.0514 3.32933 2.13E−05 FSIP2 fibrous sheath interacting protein 2 10.0377 3.32735 4.93E−09 FGD4 FYVE_RhoGEF and PH domain containing 10.0126 3.32375 5.09E−57 4 CTSC cathepsin C 10.0114 3.32357 3.86E−17 RASL10A RAS-like_family 10_member A 10.0097 3.32333 3.46E−05 JSRP1 junctional sarcoplasmic reticulum protein 1 9.98879 3.32031 0.000419 ERVMER34-1 endogenous retrovirus group 9.96811 3.31732 0.002564 MER34_member 1 ITGA2 integrin_alpha 2 (CD49B_alpha 2 subunit 9.96486 3.31685 3.74E−13 of VLA-2 receptor) LOC101927043 uncharacterized LOC101927043 9.94692 3.31425 5.99E−05 PROZ protein Z_vitamin K-dependent plasma 9.93142 3.312 9.36E−09 glycoprotein NR2F2-AS1 NR2F2 antisense RNA 1 9.92254 3.31071 1.80E−45 PLAC1 placenta-specific 1 9.91313 3.30934 6.64E−08 NMNAT3 nicotinamide nucleotide adenylyltransferase 9.90969 3.30884 1.04E−05 3 TMEM51 transmembrane protein 51 9.9007 3.30753 1.11E−35 ZIC2 Zic family member 2 9.89967 3.30738 0.006266 LOC100507600 uncharacterized LOC100507600 9.83537 3.29798 3.68E−35 AR androgen receptor 9.7898 3.29128 3.71E−23 ALOX15 arachidonate 15-lipoxygenase 9.71686 3.28049 0.006396 ROR2 receptor tyrosine kinase-like orphan 9.70407 3.27859 9.56E−11 receptor 2 MBP myelin basic protein 9.66694 3.27306 5.54E−07 LEMD1-AS1 LEMD 1 antisense RNA 1 9.66353 3.27255 0.000186 TMEM151B transmembrane protein 151B 9.66085 3.27215 0.000879 EGLN3 egl-9 family hypoxia-inducible factor 3 9.65482 3.27125 5.65E−06 SGIP1 SH3-domain GRB2-like (endophilin) 9.64934 3.27043 1.12E−11 interacting protein 1 OVCH2 ovochymase 2 (gene/pseudogene) 9.61196 3.26483 4.28E−22 PRKAR2B protein kinase_cAMP- 9.57233 3.25887 1.50E−16 dependent_regulatory_type II_beta PURG purine-rich element binding protein G 9.549 3.25535 1.64E−07 KRT19 keratin 19_type I 9.51392 3.25004 3.57E−18 NFE2L3 nuclear factor_erythroid 2-like 3 9.51267 3.24985 7.63E−18 FILIP1 filamin A interacting protein 1 9.49936 3.24783 1.05E−06 MYOCD myocardin 9.48028 3.24493 3.68E−49 KCNQ1 potassium

channel_voltage gated KQT-like 9.44205 3.2391 0.003517 subfamily Q_member 1 ACTBL2 actin_beta-like 2 9.43662 3.23827 3.82E−08 NUP62CL nucleoporin 62kDa C-terminal like 9.4291 3.23712 0.007505 POTEF POTE ankyrin domain family_member F 9.42244 3.2361 7.58E−23 FAM83E family with sequence similarity 9.41016 3.23422 0.000192 83_member E CPA4 carboxypeptidase A4 9.39003 3.23113 1.67E−160 FAM183A family with sequence similarity 9.38463 3.2303 0.000142 183_member A DUSP9 dual specificity phosphatase 9 9.37663 3.22907 1.19E−05 MYOM3 myomesin 3 9.30657 3.21825 4.91E−08 BCL11A B-cell CLL/lymphoma 11A (zinc finger 9.29523 3.21649 8.22E−07 protein) GEM GTP binding protein overexpressed in 9.27688 3.21364 4.53E−64 skeletal muscle TRABD2A TraB domain containing 2A 9.25383 3.21005 3.80E−23 SPTBN2 spectrin_beta_non-erythrocytic 2 9.25318 3.20995 5.85E−33 ZP1 zona pellucida glycoprotein 1 (sperm 9.24959 3.20939 9.78E−05 receptor) VTRNA1-3 vault RNA 1-3 9.24312 3.20838 0.001629 FNDC9 fibronectin type III domain containing 9 9.23524 3.20715 0.004547 PPAP2C phosphatidic acid phosphatase type 2C 9.21574 3.2041 1.87E−06 SERPINB7 serpin peptidase inhibitor_clade B 9.21146 3.20343 1.69E−16 (ovalbumin)_member 7 LOC645752 golgin A6 family_member A pseudogene 9.19169 3.20033 0.0005 SLC4A9 solute carrier family 4_sodium bicarbonate 9.19029 3.20011 0.000273 cotransporter_member 9 SLC37A1 solute carrier family 37 (glucose-6- 9.18838 3.19981 3.01E−24 phosphate transporter)_member 1 FSTL4 follistatin-like 4 9.12858 3.19039 0.009879 NTF4 neurotrophin 4 9.11094 3.1876 9.13E−10 DRP2 dystrophin related protein 2 9.0987 3.18566 6.82E−39 ILDR2 immunoglobulin-like domain containing 9.06646 3.18054 0.001062 receptor 2 HBEGF heparin-binding EGF-like growth factor 9.04249 3.17672 3.30E−40 MDFI MyoD family inhibitor 9.03672 3.1758 3.42E−14 MED12L mediator complex subunit 12-like 9.0187 3.17292 3.30E−16 TMCC3 transmembrane and coiled-coil domain 8.99436 3.16902 2.07E−08 family 3 FBXL13 F-box and leucine-rich repeat protein 13 8.97206 3.16544 1.13E−16 LOC100652824 NA 8.96603 3.16447 2.05E−07 NSG1 neuron specific gene family member 1 8.91305 3.15592 8.80E−18 KRT18 keratin 18_type I 8.89023 3.15222 2.87E−11 DOC2A double C2-like domains_alpha 8.88388 3.15119 1.98E−07 LOC642366 uncharacterized LOC642366 8.88142 3.15079 0.000859 NOS3 nitric oxide synthase 3 (endothelial cell) 8.85572 3.14661 1.46E−09 LPPR3 lipid phosphate phosphatase-related protein 8.84382 3.14467 9.86E−23 type 3 DACH2 dachshund family transcription factor 2 8.83978 3.14401 0.008437 C16orf74 chromosome 16 open reading frame 74 8.82148 3.14102 8.22E−22 CAMK4 calcium/calmodulin-dependent protein 8.81329 3.13968 6.34E−10 kinase IV EMID1 EMI domain containing 1 8.80797 3.13881 8.00E−06 SSPO SCO-spondin 8.79778 3.13714 1.54E−09 ST6GAL1 ST6 beta-galactosamide alpha-2_6- 8.79705 3.13702 1.44E−24 sialyltranferase 1 RHOJ ras homolog family member J 8.78103 3.13439 3.91E−10 ZBTB8B zinc finger and BTB domain containing 8B 8.77744 3.1338 0.002569 PIK3R3 phosphoinositide-3-kinase_regulatory 8.73344 3.12655 1.04E−59 subunit 3 (gamma) TRPC5OS TRPC5 opposite strand 8.72582 3.12529 0.003814 HS3ST1 heparan sulfate (glucosamine) 3-O- 8.69744 3.12059 5.29E−07 sulfotransferase 1 LRMP lymphoid-restricted membrane protein 8.64011 3.11105 9.22E−05 CASC9 cancer susceptibility candidate 9 8.63556 3.11029 0.006985 (non-protein coding) EPPK1 epiplakin 1 8.63311 3.10988 1.71E−19 LGALS9 lectin_galactoside-binding_soluble_9 8.63095 3.10952 5.69E−10 TNNT1 troponin T type 1 (skeletal_slow) 8.59573 3.10362 2.35E−65 CASKIN1 CASK interacting protein 1 8.58239 3.10138 1.29E−09 EFNA1 ephrin-A1 8.58233 3.10137 1.97E−06 EPHA4 EPH receptor A4 8.53032 3.0926 8.89E−171 FUT1 fucosyltransferase 1 (galactoside 2-alpha- 8.52772 3.09216 2.02E−08 L-fucosyltransferase_H blood group) CD274 CD274 molecule 8.52725 3.09208 5.00E−85 ADAMTS15 ADAM metallopeptidase with 8.52394 3.09152 2.67E−62 thrombospondin type 1 motif_15 MYH15 myosin_heavy chain 15 8.51272 3.08962 2.63E−11 ZBED9 zinc finger_BED-type containing 9 8.47087 3.08251 2.57E−06 ZFR2 zinc finger RNA binding protein 2 8.46688 3.08183 0.008776 SLC5A12 solute carrier family 5 8.45837 3.08038 1.56E−12 (sodium/monocarboxylate cotransporter)_member 12 HIST1H4E histone cluster 1_H4e 8.45198 3.07929 3.48E−05 SLC28A3 solute carrier family 28 (concentrative 8.43864 3.07701

5.17E−19 nucleoside transporter)_member 3 TLR2 toll-like receptor 2 8.42117 3.07402 1.85E−06 MIR450A2 microRNA 450a-2 8.42064 3.07393 0.009071 TRHDE-AS1 TRHDE antisense RNA 1 8.39482 3.0695 5.85E−07 FAM49A family with sequence similarity 8.39209 3.06903 4.98E−09 49_member A DTX4 deltex 4_E3 ubiquitin ligase 8.35054 3.06187 7.50E−11 FRZB frizzled-related protein 8.34771 3.06138 2.64E−24 LOC644838 uncharacterized LOC644838 8.33025 3.05836 0.000163 XKR6 XK_Kell blood group complex subunit- 8.3224 3.057 1.57E−09 related family_member 6 SERTAD4 SERTA domain containing 4 8.32131 3.05681 9.53E−05 OR10A3 olfactory receptor_family 10_subfamily 8.313 3.05537 0.000849 A_member 3 GNGT2 guanine nucleotide binding protein (G 8.2804 3.0497 3.49E−05 protein)_gamma transducing activity polypeptide 2 MIR548AO microRNA 548ao 8.26864 3.04765 4.29E−06 SLC29A2 solute carrier family 29 (equilibrative 8.25295 3.04491 7.15E−27 nucleoside transporter)_member 2 BAI1 adhesion G protein-coupled receptor B1 8.24089 3.0428 2.23E−05 SAMD12 sterile alpha motif domain containing 12 8.23158 3.04117 7.76E−74 GUCA1A guanylate cyclase activator 1A (retina) 8.22605 3.0402 4.66E−05 EFR3B EFR3 homolog B 8.1885 3.0336 9.94E−28 LRCH2 leucine-rich repeats and calponin homology 8.18147 3.03236 5.11E−15 (CH) domain containing 2 ZDHHC11 zinc finger_DHHC-type containing 11 8.15639 3.02793 9.38E−08 ICAM5 intercellular adhesion molecule 8.12 3.02148 3.39E−16 5_telencephalin PYY2 peptide YY_2 (pseudogene) 8.11848 3.02121 2.82E−06 GNG4 guanine nucleotide binding protein 8.10724 3.01921 0.0006 (G protein)_gamma 4 RASEF RAS and EF-hand domain containing 8.09471 3.01698 1.21E−05 ANKRD1 ankyrin repeat domain 1 (cardiac muscle) 8.08955 3.01606 9.99E−26 SBK1 SH3 domain binding kinase 1 8.07314 3.01313 3.63E−07 KISS1 KiSS-1 metastasis-suppressor 8.05001 3.00899 8.23E−06 PTPN7 protein tyrosine phosphatase_non-receptor 8.04404 3.00792 3.46E−05 type 7 KIAA1804 mixed lineage kinase 4 8.03986 3.00717 0.000206 LCT lactase 8.03117 3.00561 0.002301 IQSEC3 IQ motif and Sec7 domain 3 8.01843 3.00332 0.000208 CXCL14 chemokine (C-X-C motif) ligand 14 7.97918 2.99624 4.67E−05 SLC6A16 solute carrier family 6_member 16 7.97901 2.99621 1.02E−14 PLCXD2 phosphatidylinositol-specific phospholipase 7.96315 2.99334 0.000163 C_X domain containing 2 THBD thrombomodulin 7.94661 2.99034 8.69E−13 NRGN neurogranin (protein kinase C 7.94254 2.9896 6.09E−13 substrate_RC3) MAPK15 mitogen-activated protein kinase 15 7.91544 2.98467 1.72E−10 TSPEAR-AS1 TSPEAR antisense RNA 1 7.9002 2.98189 6.21E−08 TMEM52 transmembrane protein 52 7.89862 2.9816 2.09E−10 MIR503 microRNA 503 7.89796 2.98148 2.97E−09 FBP2 fructose-1_6-bisphosphatase 2 7.86867 2.97612 8.34E−08 OR5E1P olfactory receptor_family 5_subfamily 7.86818 2.97603 8.61E−06 E_member 1 pseudogene GS1-24F4.2 uncharacterized LOC100652791 7.85456 2.97353 7.22E−06 CX3CL1 chemokine (C-X3-C motif) ligand 1 7.85156 2.97298 0.00914 PLA2G3 phospholipase A2_group III 7.82435 2.96797 0.00959 STK32B serine/threonine kinase 32B 7.81351 2.96597 1.02E−33 NR2F2 nuclear receptor subfamily 2_group 7.81139 2.96558 1.03E−214 F_member 2 DPF3 D4_zinc and double PHD fingers_family 3 7.8095 2.96523 5.87E−13 MGARP mitochondria-localized glutamic acid-rich 7.79257 2.9621 1.73E−30 protein BTBD11 BTB (POZ) domain containing 11 7.74567 2.95339 2.81E−07 SYNPO2L synaptopodin 2-like 7.73698 2.95177 5.43E−09 SEP3 septin 3 7.66853 2.93895 3.40E−06 SORL1 sortilin-related receptor_L(DLR class) A 7.65048 2.93555 1.07E−09 repeats containing MYOZ3 myozenin 3 7.63792 2.93318 4.21E−27 MIR7851 microRNA 7851 7.62655 2.93103 0.007612 CNGA1 cyclic nucleotide gated channel alpha 1 7.61086 2.92806 0.002809 ZCCHC5 zinc finger_CCHC domain containing 5 7.60021 2.92604 1.23E−07 C14orf105 chromosome 14 open reading frame 105 7.59084 2.92426 0.009166 ZNF488 zinc finger protein 488 7.5507 2.91661 1.69E−05 HES7 hes family bHLH transcription factor 7 7.52379 2.91146 0.000368 CCDC81 coiled-coil domain containing 81 7.51863 2.91047 3.24E−22 TCEAL7 transcription elongation factor A (SII)-like 7 7.5155 2.90987 2.66E−13 FRMPD4 FERM and PDZ domain containing 4 7.50957 2.90873 6.14E−17 CA11 carbonic anhydrase XI 7.49039 2.90504 4.39E−62 GAD1 glutamate decarboxylase 1 (brain_67 kDa) 7.48758 2.9045 1.51E−05 MARCHF3 membrane-associated ring finger (C3HC4) 7.47296 2.90168

3.24E−35 3_E3 ubiquitin protein ligase MIR503HG MIR503 host gene 7.46654 2.90044 8.97E−11 NRTN neurturin 7.46587 2.90031 0.005609 PKNOX2 PBX/knotted 1 homeobox 2 7.43731 2.89478 2.23E−05 TMEM156 transmembrane protein 156 7.42052 2.89152 0.001671 HHEX hematopoietically expressed homeobox 7.41281 2.89002 1.56E−37 OBSCN obscurin_cytoskeletal calmodulin and titin- 7.37136 2.88193 4.80E−11 interacting RhoGEF SDPR serum deprivation response 7.36482 2.88065 2.55E−23 PKDCC protein kinase domain 7.35375 2.87848 2.89E−30 containing_cytoplasmic LOC101926963 uncharacterized LOC101926963 7.30888 2.86965 1.84E−07 PPP1R9A protein phosphatase 1_regulatory subunit 7.30716 2.86931 0.00519 9A CAMK2N1 calcium/calmodulin-dependent protein 7.29749 2.8674 9.32E−95 kinase II inhibitor 1 MTL5 metallothionein-like 5_testis-specific 7.29061 2.86604 1.26E−23 (tesmin) COLEC10 collectin sub-family member 10 (C-type 7.27986 2.86391 9.04E−10 lectin) MAMDC2 MAM domain containing 2 7.27224 2.8624 4.49E−08 CGN cingulin 7.26227 2.86042 0.002144 KIF25 kinesin family member 25 7.2597 2.85991 0.005232 GFRA2 GDNF family receptor alpha 2 7.16685 2.84134 9.87E−06 TSPEAR thrombospondin-type laminin G domain and 7.16581 2.84113 0.008624 EAR repeats HIST1H2AE histone cluster 1_H2ae 7.15846 2.83965 7.07E−08 MAST1 microtubule associated serine/threonine 7.10823 2.82949 7.37E−06 kinase 1 PCP2 Purkinje cell protein 2 7.10074 2.82797 0.000883 RAC3 ras-related C3 botulinum toxin substrate 3 7.09951 2.82772 9.54E−62 (rho family_small GTP binding protein Rac3) JAG2 jagged 2 7.0975 2.82731 1.53E−11 AFF3 AF4/FMR2 family_member 3 7.08737 2.82525 2.06E−15 FGFBP3 fibroblast growth factor binding protein 3 7.0854 2.82485 8.65E−52 NAALAD2 N-acetylated alpha-linked acidic dipeptidase 7.07799 2.82334 5.08E−12 2 TMEM184A transmembrane protein 184A 7.0749 2.82271 1.54E−20 PM20D2 peptidase M20 domain containing 2 7.06216 2.82011 5.26E−17 RAB38 RAB38_member RAS oncogene family 7.05771 2.8192 1.03E−08 RET ret proto-oncogene 7.05135 2.8179 0.000163 HTRA4 HtrA serine peptidase 4 7.04583 2.81677 7.74E−07 LINC01096 long intergenic non-protein coding RNA 7.04232 2.81605 0.008893 1096 SRCRB4D scavenger receptor cysteine rich 7.02593 2.81269 1.07E−17 family_4 domains SERTAD4-AS1 SERTAD4 antisense RNA 1 7.01377 2.81019 0.000178 AMN amnion associated transmembrane protein 7.0109 2.8096 1.99E−05 NAP1L2 nucleosome assembly protein 1-like 2 7.00682 2.80876 6.17E−07 P2RX6P purinergic receptor P2X_ligand gated ion 7.0057 2.80853 8.55E−05 channel_6 pseudogene PADI2 peptidyl arginine deiminase_type II 6.99644 2.80662 3.36E−09 NEDD4L neural precursor cell 6.96899 2.80095 5.91E−83 expressed_developmentally down-regulated 4-like_E3 ubiquitin protein ligase RASGEF1A RasGEF domain family_member 1A 6.96098 2.79929 0.001206 MIR3648 microRNA 3648-1 6.95794 2.79866 8.24E−06 MIR1204 microRNA 1204 6.93017 2.79289 1.30E−05 SNORD116-28 small nucleolar RNA_C/D box 116-28 6.92906 2.79266 1.24E−07 RBP7 retinol binding protein 7_cellular 6.87958 2.78232 3.79E−08 PIK3C2B phosphatidylinositol-4-phosphate 6.85849 2.77789 1.86E−34 3-kinase_catalytic subunit type 2 beta SLC4A11 solute carrier family 4_sodium borate 6.83969 2.77393 3.99E−10 transporter_member 11 ISYNA1 inositol-3-phosphate synthase 1 6.83556 2.77306 1.30E−19 SALL2 spalt-like transcription factor 2 6.82534 2.7709 4.21E−10 MIR3687 microRNA 3687-1 6.81026 2.76771 1.02E−06 SOX5 SRY (sex determining region Y)-box 5 6.76692 2.7585 0.001343 FOXL1 forkhead box L1 6.74075 2.75291 4.01E−101 AC093375.1 NA 6.73959 2.75266 0.000186 PLXDC1 plexin domain containing 1 6.7358 2.75185 3.23E−10 APOE apolipoprotein E 6.71948 2.74835 8.58E−16 HID1 HID1 domain containing 6.71478 2.74734 1.31E−07 SSUH2 ssu-2 homolog (C. elegans) 6.71431 2.74724 0.006498 ABCA12 ATP-binding cassette_sub-family A 6.69391 2.74285 0.000933 (ABC1)_member 12 OLFM2 olfactomedin 2 6.68636 2.74122 4.43E−22 GCA grancalcin_EF-hand calcium binding 6.68066 2.73999 2.21E−23 protein MAGEL2 melanoma antigen family L2 6.67399 2.73855 6.63E−39 LINC00920 long intergenic non-protein coding RNA 920 6.67311 2.73836 7.44E−08 SLC40A1 solute carrier family 40 (iron-regulated 6.66535 2.73668 8.07E−16 transporter)_member 1 MUC19 mucin 19_oligomeric 6.65242 2.73388 0.001879 GRAP2 GRB2-related adaptor protein 2 6.62458 2.72783 8.63E−06 HOXB6 homeobox

B6 6.60748 2.7241 3.58E−47 ITPRIPL1 inositol 1_4_5-trisphosphate receptor 6.59508 2.72139 4.78E−18 interacting protein-like 1 LOC100996351 uncharacterized LOC100996351 6.59097 2.72049 0.00819 F2RL2 coagulation factor II (thrombin) receptor- 6.56193 2.71412 5.61E−09 like 2 WDR65 cilia and flagella associated protein 57 6.5512 2.71176 5.50E−05 AP1M2 adaptor-related protein complex 1_mu 2 6.55007 2.71151 4.62E−09 subunit PLP1 proteolipid protein 1 6.54975 2.71144 3.53E−11 SLC6A17 solute carrier family 6 (neutral amino acid 6.54662 2.71075 2.30E−09 transporter)_member 17 SALL1 spalt-like transcription factor 1 6.52818 2.70668 0.000106 TRIM17 tripartite motif containing 17 6.51882 2.70461 1.10E−25 CXorf57 chromosome X open reading frame 57 6.51832 2.7045 3.14E−11 ELF3 E74-like factor 3 (ets domain transcription 6.46482 2.69261 0.000323 factor_epithelial-specific) CNIH2 cornichon family AMPA receptor auxiliary 6.44915 2.68911 1.14E−22 protein 2 C15orf48 chromosome 15 open reading frame 48 6.44795 2.68884 6.06E−08 LINGO1 leucine rich repeat and Ig domain 6.43861 2.68675 1.73E−08 containing 1 CLDN11 claudin 11 6.42987 2.68479 8.10E−12 PLEKHG3 pleckstrin homology domain containing_family 6.42773 2.68431 4.08E−37 G (with RhoGef domain) member 3 GPR132 G protein-coupled receptor 132 6.41763 2.68204 5.59E−06 LINC01239 long intergenic non-protein coding RNA 6.4166 2.68181 1.45E−07 1239 SPTB spectrin_beta_erythrocytic 6.40669 2.67958 3.70E−15 LINC00649 long intergenic non-protein coding RNA 649 6.4051 2.67922 7.95E−05 ST6GALNAC1 ST6 (alpha-N-acetyl-neuraminyl-2_3-beta- 6.38785 2.67533 0.004035 galactosyl-1_3)-N-acetylgalactosaminide alpha-2_6-sialyltransferase 1 STOX2 storkhead box 2 6.38108 2.6738 2.61E−05 HOXB5 homeobox B5 6.37811 2.67313 7.00E−11 HBQ1 hemoglobin_theta 1 6.37449 2.67231 0.003817 SORBS1 sorbin and SH3 domain containing 1 6.36597 2.67038 5.94E−12 DHDH dihydrodiol dehydrogenase (dimeric) 6.35821 2.66862 0.000693 MYOZ2 myozenin 2 6.34034 2.66456 2.49E−07 MMP23A matrix metallopeptidase 23A (pseudogene) 6.31994 2.65991 0.000145 PDE10A phosphodiesterase 10A 6.31801 2.65947 4.38E−05 HEY1 hes-related family bHLH transcription factor 6.30572 2.65666 1.47E−10 with YRPW motif 1 CTXN1 cortexin 1 6.30309 2.65606 2.29E−39 EDN1 endothelin 1 6.30056 2.65548 2.72E−51 PKD1L1 polycystic kidney disease 1 like 1 6.29078 2.65324 2.76E−09 LRRC7 leucine rich repeat containing 7 6.28608 2.65216 0.003815 LIMS3-LOC44089 LIMS3-LOC440895 readthrough 6.2829 2.65143 8.95E−10 PLEKHA6 pleckstrin homology domain 6.27972 2.6507 7.09E−06 containing_family A member 6 POU3F1 POU class 3 homeobox 1 6.26698 2.64777 0.002473 AMH anti-Mullerian hormone 6.25002 2.64386 7.65E−10 PCLO piccolo presynaptic cytomatrix protein 6.23941 2.64141 3.62E−08 MYOZ1 myozenin 1 6.21502 2.63576 3.95E−05 CCDC78 coiled-coil domain containing 78 6.21145 2.63493 3.59E−10 CCDC85A coiled-coil domain containing 85A 6.16961 2.62518 2.43E−05 PRKX protein kinase_X-linked 6.1588 2.62265 1.00E−48 VEPH1 ventricular zone expressed PH domain-6.15552 2.62188 7.39E−69 containing 1 DDX26B DEAD/H (Asp-Glu-Ala-Asp/His) box 6.12322 2.61429 2.74E−09 polypeptide 26B COCH cochlin 6.1044 2.60985 0.000474 MYH10 myosin_heavy chain 10_non-muscle 6.09616 2.6079 3.63E−52 PDGFD platelet derived growth factor D 6.08687 2.6057 4.95E−06 LINC00704 long intergenic non-protein coding RNA 704 6.08522 2.60531 5.99E−05 PHACTR1 phosphatase and actin regulator 1 6.07599 2.60312 0.000104 COL6A4P2 collagen_type VI_alpha 4 pseudogene 2 6.06232 2.59987 0.005576 TFAP2A transcription factor AP-2 alpha (activating 6.06161 2.5997 9.93E−06 enhancer binding protein 2 alpha) COL17A1 collagen_type XVII_alpha 1 6.0569 2.59858 1.18E−08 LRP4 low density lipoprotein receptor-related 6.05648 2.59848 3.47E−20 protein 4 DUSP4 dual specificity phosphatase 4 6.04855 2.59659 0.006571 MAP3K15 mitogen-activated protein kinase kinase 6.03494 2.59334 2.05E−05 kinase 15 RAMP2 receptor (G protein-coupled) activity 6.03469 2.59328 4.50E−09 modifying protein 2 DOK6 docking protein 6 6.0139 2.5883 4.14E−06 CELF2 CUGBP_Elav-like family member 2 6.00548 2.58628 4.06E−05 GRASP GRP1 (general receptor for 6.00448 2.58604 4.24E−16 phosphoinositides 1)-associated scaffold protein ERICH5 glutamate-rich 5 6.00407 2.58594 3.75E−07 MFNG MFNG O-fucosylpeptide 3-beta-N- 5.99858

2.58462 0.001964 acetylglucosaminyltransferase ETS2 v-ets avian erythroblastosis virus E26
5.99193 2.58302 1.91E−71 oncogene homolog 2 C21orf90 TSPEAR antisense RNA 2 5.99164
2.58295 2.26E−09 GABRA3 gamma-aminobutyric acid (GABA) A 5.98931 2.58239 0.002658
receptor_alpha 3 FZD9 frizzled class receptor 9 5.9784 2.57976 2.07E−24 PGM5P2
phosphoglucomutase 5 pseudogene 2 5.96739 2.5771 1.46E−09 FAM179A family with sequence
similarity 5.96437 2.57637 0.000582 179_member A GPR183 G protein-coupled receptor 183
5.9604 2.57541 2.09E−10 WFDC10B WAP four-disulfide core domain 10B 5.95318 2.57366
0.007524 SP6 Sp6 transcription factor 5.94353 2.57132 2.26E−07 AMOT angiomotin 5.94114
2.57074 1.51E−12 MAP2K6 mitogen-activated protein kinase kinase 6 5.93744 2.56984 2.54E−26
TMEFF1 transmembrane protein with EGF-like and 5.92769 2.56747 0.001063 two follistatin-like
domains 1 TPPP tubulin polymerization promoting protein 5.92005 2.56561 2.81E−08 HIST1H3G
histone cluster 1_H3g 5.91648 2.56474 0.0055 RASL10B RAS-like_family 10_member B
5.91378 2.56408 3.58E−48 TNFRSF18 tumor necrosis factor receptor 5.91054 2.56329 6.13E−10
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3.09E−75 LOC400863 NA 5.90477 2.56188 0.00776 MLLT11 myeloid/lymphoid or mixed-
lineage 5.89863 2.56038 4.89E−56 leukemia; translocated to_11 NAV2 neuron navigator 2 5.89552
2.55962 5.06E−31 UPK1B uroplakin 1B 5.88932 2.5581 0.001333 CORO1A coronin_actin
binding protein_1A 5.87232 2.55393 2.46E−16 AQP3 aquaporin 3 (Gill blood group) 5.86447
2.552 1.66E−18 OLFML2A olfactomedin-like 2A 5.84118 2.54626 1.29E−12 CBX2 chromobox
homolog 2 5.83693 2.54521 1.72E−76 KIT v-kit Hardy-Zuckerman 4 feline sarcoma 5.83693
2.54521 4.23E−07 viral oncogene homolog CSDC2 cold shock domain containing C2_RNA
5.83673 2.54516 5.32E−26 binding CXorf28 long intergenic non-protein coding RNA 5.83592
2.54496 0.000425 1546 TBX5 T-box 5 5.82909 2.54327 0.002357 CDKL2 cyclin-dependent
kinase-like 2 (CDC2- 5.82222 2.54157 3.15E−06 related kinase) TLE4 transducin-like enhancer of
split 4 5.79352 2.53444 7.60E−234 BRSK2 BR serine/threonine kinase 2 5.79187 2.53403
2.45E−11 MIR1206 microRNA 1206 5.79059 2.53371 0.009759 CHRNA5 cholinergic
receptor_nicotinic_alpha 5 5.76748 2.52794 4.07E−05 (neuronal) DLL3 delta-like 3 (Drosophila)
5.75549 2.52494 9.19E−08 IL1B interleukin 1_beta 5.73006 2.51855 4.35E−05 CDK18 cyclin-
dependent kinase 18 5.69833 2.51054 2.31E−08 PODN podocan 5.69782 2.51041 2.97E−22
MEIS2 Meis homeobox 2 5.69502 2.5097 9.78E−81 SLC35F2 solute carrier family 35_member F2
5.68338 2.50675 2.12E−11 MAP3K7CL MAP3K7 C-terminal like 5.6811 2.50617 6.77E−23 LTK
leukocyte receptor tyrosine kinase 5.67763 2.50529 0.000247 FILIP1L filamin A interacting
protein 1-like 5.66777 2.50278 9.35E−14 CASC8 cancer susceptibility candidate 8 5.664 2.50182
0.003796 (non-protein coding) ADM5 adrenomedullin 5 (putative) 5.64225 2.49627 4.68E−07
UNC13A unc-13 homolog A (C. elegans) 5.61934 2.4904 4.82E−06 ZNF702P zinc finger protein
702_pseudogene 5.57754 2.47963 1.14E−08 TFEC transcription factor EC 5.56777 2.4771
0.006309 MAML3 mastermind-like transcriptional coactivator 3 5.55493 2.47377 2.57E−13
STMN3 stathmin-like 3 5.53717 2.46915 6.59E−20 GRIP2 glutamate receptor interacting protein 2
5.51064 2.46222 0.0023 RHOU ras homolog family member U 5.50972 2.46198 2.42E−08
POU2F2 POU class 2 homeobox 2 5.49592 2.45836 9.51E−29 PMAIP1 phorbol-12-myristate-13-
acetate-induced 5.49059 2.45696 3.86E−10 protein 1 FRMD5 FERM domain containing 5 5.48929
2.45662 7.37E−40 PTN pleiotrophin 5.48074 2.45437 1.09E−11 LOC101929555 uncharacterized
LOC101929555 5.45251 2.44692 0.004989 ASRGL1 asparaginase like 1 5.44303 2.44441
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coding RNA 319 5.4347 2.4422 0.002249 ST3GAL5 ST3 beta-galactoside alpha- 5.43357 2.4419
3.42E−46 2_3-sialyltransferase 5 GDF6 growth differentiation factor 6 5.4242 2.43941 1.21E−06
MTRNR2L10 MT-RNR2-like 10 5.42292 2.43907 0.002039 CSRP2 cysteine and glycine-rich
protein 2 5.41166 2.43607 2.13E−32 PRSS35 protease_serine_35 5.40914 2.4354 4.82E−10
CDCA7 cell division cycle associated 7 5.39476 2.43156 1.46E−12 RPS6KA1 ribosomal protein
S6 5.38501 2.42895 1.51E−94 kinase_90 kDa_polypeptide 1 RUNDC3B RUN domain containing

3B 5.34867 2.41918 2.30E−05 RGS2 regulator of G-protein signaling 2 5.34004 2.41685 3.99E−54 KRTAP5-1 keratin associated protein 5-1 5.33882 2.41652 0.006121 LINC01358 long intergenic non-protein coding RNA 5.33737 2.41613 0.000225 1358 PLS1 plastin 1 5.33723 2.41609 8.64E−12 RASGRP2 RAS guanyl releasing protein 2 (calcium 5.33552 2.41563 2.81E−05 and DAG-regulated) ALOXE3 arachidonate lipoxygenase 3 5.32968 2.41405 1.76E−06 TNFRSF21 tumor necrosis factor receptor 5.3223 2.41205 5.50E−09 superfamily_member 21 SYNGR1 synaptogyrin 1 5.29258 2.40397 9.94E−21 RGS9 regulator of G-protein signaling 9 5.27003 2.39781 0.007409 ZMYND8 zinc finger_MYND-type containing 8 5.25281 2.39309 4.51E−28 CASS4 Cas scaffolding protein family member 4 5.25179 2.39281 0.001735 C20orf166-AS1 C20orf166 antisense RNA 1 5.23613 2.3885 0.002467 FGFR4 fibroblast growth factor receptor 4 5.22833 2.38635 7.16E−06 MARCKSL1 MARCKS-like 1 5.22101 2.38433 4.46E−162 TMEM179 transmembrane protein 179 5.21053 2.38143 0.006078 NPAS2 neuronal PAS domain protein 2 5.18732 2.37499 7.68E−06 LPPR4 lipid phosphate phosphatase-related 5.15317 2.36546 3.99E−05 protein type 4 RGS20 regulator of G-protein signaling 20 5.15188 2.3651 5.03E−27 RPL13AP20 ribosomal protein L13a pseudogene 20 5.14696 2.36372 9.02E−08 GPRC5C G protein-coupled receptor_class C_group 5.13644 2.36077 1.12E−15 5_member C PARD6G par-6 family cell polarity regulator gamma 5.11031 2.35341 9.22E−67 SLC7A14 solute carrier family 7_member 14 5.09623 2.34943 4.24E−08 NES nestin 5.09319 2.34857 4.94E−05 CADM4 cell adhesion molecule 4 5.07578 2.34363 4.33E−30 EBF4 early B-cell factor 4 5.07114 2.34231 4.29E−07 MEIS1-AS3 MEIS1 antisense RNA 3 5.0691 2.34173 0.006678 LYPD1 LY6/PLAUR domain containing 1 5.06204 2.33972 9.67E−12 DMRTA1 DMRT-like family A1 5.04649 2.33528 0.000332 MKRN7P makorin ring finger protein 7_pseudogene 5.02265 2.32845 0.001418 CHRNB2 cholinergic receptor_nicotinic_beta 2 5.0166 2.32671 0.002487 (neuronal) RTN4R reticulon 4 receptor 5.01187 2.32535 1.61E−06 NUTM2G NUT family member 2G 5.0032 2.32285 8.01E−13

TABLE-US-00004 TABLE 4 Genes more highly expressed in BM MSCs compared with HMCs Gene Fold Log Fold Name Description Change Change p-Adj MEG3 maternally expressed 3 (non-protein coding) −35629.9 −15.1208 7.46E−116 FLG filaggrin −6300.72 −12.6213 1.68E−64 DYNLT3 dynein_light_chain_Tctex-type 3 −4479.74 −12.1292 2.88E−63 CAT catalase −4286.84 −12.0657 2.94E−75 EMX2OS EMX2 opposite strand/antisense RNA −2329.98 −11.1861 5.58E−51 EYA2 EYA transcriptional coactivator and −2121.1 −11.0506 2.10E−69 phosphatase 2 CTSF cathepsin F −2093.35 −11.0316 1.29E−47 IRX3 iroquois homeobox 3 −2000.16 −10.9659 6.67E−128 FNDC1 fibronectin type III domain containing 1 −1635.26 −10.6753 1.84E−202 EMX2 empty spiracles homeobox 2 −1529.98 −10.5793 4.66E−55 EN1 engrailed homeobox 1 −1434.27 −10.4861 2.82E−42 COMP cartilage oligomeric matrix protein −1343.15 −10.3914 1.95E−89 S100A6 S100 calcium binding protein A6 −1267.09 −10.3073 1.14E−203 TEKT4P2 tektin 4 pseudogene 2 −1262.44 −10.302 1.48E−38 HSPB2 heat shock 27 kDa protein 2 −1165.07 −10.1862 1.34E−39 GSTT1 glutathione S-transferase theta 1 −1164.58 −10.1856 1.18E−39 LYNX1 Ly6/neurotoxin 1 −1153.42 −10.1717 4.51E−38 NFASC neurofascin −1132.03 −10.1447 3.32E−253 LINC00839 long intergenic non-protein coding RNA 839 −1026.77 −10.0039 1.19E−37 ZNF662 zinc finger protein 662 −965.023 −9.91442 9.55E−46 BHMT2 betaine--homocysteine S-methyltransferase 2 −925.315 −9.8538 5.90E−36 SCUBE1 signal peptide_CUB domain_EGF-like 1 −872.185 −9.76849 1.92E−39 FGFR2 fibroblast growth factor receptor 2 −810.535 −9.66273 1.40E−137 ANKRD20A5P ankyrin repeat domain 20 family_member −768.537 −9.58597 4.90E−33 A5_pseudogene CES1 carboxylesterase 1 −764.679 −9.57871 5.24E−33 CHI3L1 chitinase 3-like 1 (cartilage glycoprotein-39) −703.37 −9.45814 8.98E−130 FLG-AS1 FLG antisense RNA 1 −667.864 −9.38341 1.10E−29 ISLR immunoglobulin superfamily containing −627.765 −9.29408 0.00E+00 leucine-rich repeat LOC400043 uncharacterized LOC400043 −617.438 −9.27015 6.34E−56 LINC01133 long intergenic non-protein coding RNA 1133 −608.212 −9.24843 8.34E−91 CYP4F35P cytochrome P450_family −601.512 −9.23245

4.19E−29 4_subfamily F_polypeptide 35_pseudogene GREM2 gremlin 2_DAN family BMP antagonist −598.256 −9.22462 2.08E−126 ANKRD30B ankyrin repeat domain 30B −579.225 −9.17798 1.31E−29 PPP1R14C protein phosphatase 1_regulatory (inhibitor) −552.557 −9.10998 2.51E−29 subunit 14C FPR1 formyl peptide receptor 1 −489.04 −8.93381 3.56E−27 LINC01268 long intergenic non-protein coding RNA 1268 −449.046 −8.81072 1.71E−74 KRT14 keratin 14_type I −443.758 −8.79363 7.01E−63 TDRD9 tudor domain containing 9 −436.358 −8.76937 6.87E−26 ZNF300P1 zinc finger protein 300 pseudogene 1 −420.677 −8.71657 1.01E−30 (functional) FAM225A family with sequence similarity 225_member −400.542 −8.64581 1.47E−25 A (non-protein coding) FAM180A family with sequence similarity 180_member −380.312 −8.57104 7.93E−67 A CCDC36 coiled-coil domain containing 36 −352.867 −8.46298 4.80E−24 CH25H cholesterol 25-hydroxylase −352.664 −8.46215 1.70E−23 CCKAR cholecystokinin A receptor −324.76 −8.34323 2.32E−22 KRBOX1 KRAB box domain containing 1 −322.749 −8.33427 4.54E−23 CCDC144B coiled-coil domain containing 144B −315.525 −8.30161 6.20E−23 (pseudogene) LINC00856 long intergenic non-protein coding RNA 856 −313.304 −8.29142 9.69E−23 CSTA cystatin A (stefin A) −310.748 −8.2796 1.38E−47 FAM225B family with sequence similarity 225_member −301.418 −8.23562 2.28E−22 B (non-protein coding) LINC00865 long intergenic non-protein coding RNA 865 −301.073 −8.23397 2.20E−22 CMKLR1 chemerin chemokine-like receptor 1 −281.601 −8.13751 4.31E−19 ENPP2 ectonucleotide −271.077 −8.08256 3.42E−71 pyrophosphatase/phosphodiesterase 2 FMOD fibromodulin −269.205 −8.07256 3.90E−23 SDR42E1 short chain dehydrogenase/reductase family −252.017 −7.97738 2.21E−20 42E_member 1 ITGBL1 integrin_beta-like 1 (with EGF-like repeat −244.002 −7.93075 6.52E−295 domains) IBSP integrin-binding sialoprotein −240.491 −7.90984 1.41E−19 FAM20A family with sequence similarity 20_member A −235.186 −7.87766 1.62E−85 MKRN3 makorin ring finger protein 3 −228.014 −7.83298 1.04E−19 NKAPL NFKB activating protein-like −218.076 −7.76869 2.56E−19 C5orf63 chromosome 5 open reading frame 63 −214.955 −7.74789 2.78E−24 MYBPH myosin binding protein H −214.733 −7.7464 6.31E−26 CPXM2 carboxypeptidase X (M14 family)_member 2 −211.34 −7.72342 4.82E−22 CECR7 cat eye syndrome chromosome −207.364 −7.69602 2.50E−18 region_candidate 7 (non-protein coding) PCDHGB3 protocadherin gamma subfamily B_3 −206.449 −7.68964 2.56E−18 LINC00968 long intergenic non-protein coding RNA 968 −205.155 −7.68057 1.65E−129 FAM66B family with sequence similarity 66_member B −202.202 −7.65965 3.81E−18 PENK proenkephalin −200.898 −7.65032 3.99E−22 KIAA1644 KIAA1644 −194.503 −7.60365 9.45E−107 MEOX2 mesenchyme homeobox 2 −193.912 −7.59926 3.51E−16 COX7A1 cytochrome c oxidase subunit VIIa polypeptide −191.832 −7.5837 2.42E−46 1 (muscle) LOC284757 NA −189.246 −7.56412 1.36E−21 SGCD sarcoglycan_delta (35 kDa dystrophin- −183.534 −7.5199 1.79E−85 associated glycoprotein) DDX43 DEAD (Asp-Glu-Ala-Asp) box polypeptide 43 −181.828 −7.50643 9.97E−20 LOC101927642 N −181.224 −7.50163 3.36E−22 LRRK2 leucine-rich repeat kinase 2 −180.898 −7.49903 1.38E−17 NUPR1 nuclear protein_transcriptional regulator_1 −178.489 −7.47969 8.60E−126 LOC101929369 NA −157.878 −7.30267 7.09E−25 DLX6-AS1 DLX6 antisense RNA 1 −154.645 −7.27282 2.04E−21 PCDHGA3 protocadherin gamma subfamily A_3 −154.162 −7.2683 5.13E−16 HAS1 hyaluronan synthase 1 −153.647 −7.26348 9.36E−40 M1AP meiosis 1 associated protein −150.851 −7.23698 9.94E−21 HLA-DPA1 major histocompatibility complex_class −147.269 −7.20231 3.20E−14 II_DP alpha 1 DNAJA4 DnaJ (Hsp40) homolog_subfamily −142.774 −7.15759 3.81E−82 A_member 4 PCDHGA12 protocadherin gamma subfamily A_12 −142.64 −7.15623 3.66E−41 MEG8 maternally expressed 8 (non-protein coding) −142.207 −7.15185 1.69E−15 KRT16 keratin 16_type I −140.972 −7.13926 3.82E−67 NRXN2 neurexin 2 −140.865 −7.13817 6.15E−187 PTGES prostaglandin E synthase −140.439 −7.1338 0.00E+00 C5AR2 complement component 5a receptor 2 −139.462 −7.12373 4.43E−15 ECM2 extracellular matrix protein 2_female organ −138.933 −7.11825 6.04E−93 and adipocyte specific FGF7 fibroblast growth factor 7 −138.746 −7.1163 5.19E−71 SLC39A4 solute carrier

family 39 (zinc −138.362 −7.1123 7.14E−41 transporter)_member 4 OAS2 2′-5′-oligoadenylate synthetase 2_69/71 kDa −136.733 −7.09522 2.01E−31 HOXC-AS1 HOXC cluster antisense RNA 1 −135.946 −7.08689 8.21E−20 LINC00506 long intergenic non-protein coding RNA 506 −135.81 −7.08545 3.96E−15 CRYAB crystallin_alpha B −133.344 −7.05901 0.00E+00 CKM creatine kinase_muscle −131.62 −7.04023 5.91E−15 HYDIN HYDIN_axonemal central pair apparatus −130.426 −7.02709 8.10E−26 protein CYP1B1 cytochrome P450_family 1_subfamily −128.476 −7.00536 6.34E−95 B_polypeptide 1 LINC01018 long intergenic non-protein coding RNA 1018 −126.369 −6.9815 7.56E−52 NAALADL1 N-acetylated alpha-linked acidic dipeptidase- −126.097 −6.97839 8.44E−96 like 1 FMO3 flavin containing monooxygenase 3 −125.887 −6.97599 2.41E−17 KCNJ15 potassium channel_inwardly rectifying −125.648 −6.97324 5.50E−29 subfamily J_member 15 KRT34 keratin 34_type I −123.593 −6.94945 1.45E−238 LSP1 lymphocyte-specific protein 1 −123.36 −6.94673 1.62E−77 ADAMTSL3 ADAMTS-like 3 −122.924 −6.94162 2.78E−14 LOC101927740 uncharacterized LOC101927740 −122.513 −6.93679 4.46E−31 LOC441666 zinc finger protein 91 pseudogene −121.086 −6.91989 3.57E−14 LINC01114 long intergenic non-protein coding RNA 1114 −120.579 −6.91384 4.38E−14 SPESP1 sperm equatorial segment protein 1 −118.239 −6.88556 3.68E−13 LTF lactotransferrin −116.299 −6.8617 9.29E−14 ZNF572 zinc finger protein 572 −113.357 −6.82473 8.77E−14 ENPP4 ectonucleotide −112.876 −6.81859 4.04E−25 pyrophosphatase/phosphodiesterase 4 (putative) ANKRD29 ankyrin repeat domain 29 −111.733 −6.80391 3.07E−41 ZNF736 zinc finger protein 736 −110.633 −6.78964 1.31E−13 COL10A1 collagen_type_X_alpha 1 −104.652 −6.70945 4.29E−16 DDO D-aspartate oxidase −103.847 −6.69832 4.62E−13 LOC400644 NA −103.675 −6.69592 3.54E−13 PID1 phosphotyrosine interaction domain containing −103.642 −6.69546 9.95E−50 1 LINC00654 long intergenic non-protein coding RNA 654 −103.64 −6.69544 6.70E−33 INSRR insulin receptor-related receptor −101.301 −6.6625 9.58E−13 FOXQ1 forkhead box Q1 −100.715 −6.65413 1.23E−12 LOC150381 NA −100.34 −6.64875 1.90E−34 CRLF1 cytokine receptor-like factor 1 −98.9591 −6.62876 1.19E−124 ZNF208 zinc finger protein 208 −98.7165 −6.62522 1.48E−12 HOXD8 homeobox D8 −97.5297 −6.60777 1.81E−139 ZNF454 zinc finger protein 454 −97.3285 −6.60479 8.60E−21 GPNMB glycoprotein (transmembrane) nmb −97.0778 −6.60107 1.59E−129 NDNF neuron-derived neurotrophic factor −95.3473 −6.57512 1.41E−64 KRTAP1-5 keratin associated protein 1-5 −94.974 −6.56946 6.22E−138 HTR1F 5-hydroxytryptamine (serotonin) receptor −94.3421 −6.55983 1.89E−12 1F_G protein-coupled ZFP3 ZFP3 zinc finger protein −93.8497 −6.55228 1.48E−85 FGF14 fibroblast growth factor 14 −93.5198 −6.5472 3.27E−59 HOXD-AS2 HOXD cluster antisense RNA 2 −92.3698 −6.52935 5.39E−47 FAM106A family with sequence similarity 106_member −90.6541 −6.5023 3.74E−12 A SFRP2 secreted frizzled-related protein 2 −90.2641 −6.49608 6.67E−12 WISP3 WNT1 inducible signaling pathway protein 3 −89.3459 −6.48133 1.32E−29 SORBS2 sorbin and SH3 domain containing 2 −85.5325 −6.4184 1.14E−65 HRNR hornerin −85.3134 −6.4147 1.35E−11 ANGPT4 angiopoietin 4 −85.0978 −6.41105 2.39E−14 PSG5 pregnancy specific beta-1-glycoprotein 5 −83.3795 −6.38162 4.75E−178 HOXD3 homeobox D3 −82.3393 −6.36351 2.07E−25 PAPPA2 pappalysin 2 −81.7037 −6.35233 2.07E−13 LOC728819 NA −81.3742 −6.3465 1.77E−11 TGFA transforming growth factor_alpha −80.5845 −6.33243 4.10E−11 DEPTOR DEP domain containing MTOR-interacting −77.9318 −6.28414 2.95E−62 protein DMGDH dimethylglycine dehydrogenase −77.6697 −6.27928 4.55E−26 PTGDR prostaglandin D2 receptor (DP) −77.4445 −6.27509 4.87E−11 LOC102724678 NA −77.2241 −6.27098 4.89E−14 C20orf197 chromosome 20 open reading frame 197 −75.3602 −6.23573 3.84E−36 RUNX3 runt-related transcription factor 3 −75.1822 −6.23232 5.89E−122 IRX5 iroquois homeobox 5 −75.1677 −6.23204 1.97E−163 TAS1R1 taste receptor_type 1_member 1 −75.1036 −6.23081 5.60E−11 ELANE elastase_neutrophil expressed −74.1873 −6.2131 8.13E−11 NINJ2 ninjurin 2 −72.5478 −6.18086 1.67E−36 FAM198A family with sequence similarity 198_member −72.4965 −6.17984 1.80E−10 A CXADRP3 coxsackie virus and adenovirus receptor −72.3675 −6.17727 1.33E−10 pseudogene 3

COL14A1 collagen type XIV_alpha 1 −72.2227 −6.17438 1.61E−32 CLEC3B C-type lectin domain family 3_member B −71.9035 −6.16799 2.18E−42 TMEM178B transmembrane protein 178B −71.2387 −6.15459 3.10E−19 ITIH5 inter-alpha-trypsin inhibitor heavy chain −71.1864 −6.15353 5.61E−10 family_member 5 PRPH2 peripherin 2 (retinal degeneration_slow) −70.98 −6.14934 4.07E−39 ELN elastin −70.9303 −6.14833 1.39E−152 KCTD12 potassium channel tetramerization domain −70.8271 −6.14623 1.23E−114 containing 12 DOK5 docking protein 5 −70.5136 −6.13983 1.22E−40 LOC100287846 patched 1 pseudogene −70.372 −6.13693 1.78E−10 PTPN20B protein tyrosine phosphatase_non-receptor −70.0489 −6.13029 1.79E−10 type 20 WISP2 WNT1 inducible signaling pathway protein 2 −69.2811 −6.11439 4.45E−40 DLX3 distal-less homeobox 3 −66.5059 −6.05541 1.41E−18 CCDC89 coiled-coil domain containing 89 −66.2524 −6.0499 1.20E−23 FPR2 formyl peptide receptor 2 −66.0346 −6.04515 3.24E−10 ITGB2 integrin_beta 2 (complement component 3 −65.6849 −6.03749 1.16E−93 receptor 3 and 4 subunit) PPAPDC3 phosphatidic acid phosphatase type 2 domain −65.2393 −6.02767 1.66E−153 containing 3 ELOVL3 ELOVL fatty acid elongase 3 −65.1824 −6.02641 1.24E−28 SERPING1 serpin peptidase inhibitor_clade G (C1 −64.6895 −6.01546 7.96E−157 inhibitor)_member 1 ST8SIA1 ST8 alpha-N-acetyl-neuraminide alpha-2_8- −62.1154 −5.95688 1.66E−16 sialyltransferase 1 PCDHGA4 protocadherin gamma subfamily A_4 −61.6851 −5.94685 6.57E−22 TP53TG3D TP53 target 3D −61.6052 −5.94498 1.08E−09 PRSS30P protease_serine_30_pseudogene −61.4529 −5.94141 8.51E−10 GSTM5 glutathione S-transferase mu 5 −61.3317 −5.93856 5.36E−13 P2RY6 pyrimidinergic receptor P2Y_G-protein −60.6271 −5.92189 1.09E−69 coupled_6 EGFLAM EGF-like_fibronectin type III and laminin G −60.2517 −5.91293 5.44E−38 domains TNFRSF11B tumor necrosis factor receptor −59.9164 −5.90488 1.45E−102 superfamily_member 11b ALS2CR11 amyotrophic lateral sclerosis 2 (juvenile) −59.6645 −5.8988 8.62E−50 chromosome region_candidate 11 USP32P2 ubiquitin specific peptidase 32 pseudogene 2 −59.5653 −5.8964 1.88E−39 KRT81 keratin 81_type II −59.3033 −5.89004 3.27E−15 DCHS2 dachsous cadherin-related 2 −59.2162 −5.88792 2.11E−11 XG Xg blood group −59.1707 −5.88681 2.16E−69 MAFB v-maf avian musculoaponeurotic fibrosarcoma −58.753 −5.87659 9.71E−55 oncogene homolog B LIPC lipase_hepatic −57.1242 −5.83603 1.35E−09 ZNF439 zinc finger protein 439 −56.9337 −5.83121 8.44E−49 SLC22A15 solute carrier family 22_member 15 −56.5498 −5.82145 6.31E−63 TDRD1 tudor domain containing 1 −56.2293 −5.81325 5.08E−09 GRM6 glutamate receptor_metabotropic 6 −56.1432 −5.81104 2.31E−11 P2RY2 purinergic receptor P2Y_G-protein coupled_2 −55.9967 −5.80727 1.68E−34 ACSM5 acyl-CoA synthetase medium-chain family −55.4867 −5.79407 2.02E−09 member 5 SPAG17 sperm associated antigen 17 −55.2572 −5.78809 2.69E−16 LOC101927468 uncharacterized LOC101927468 −54.9269 −5.77944 2.23E−09 SYT8 synaptotagmin VIII −53.8752 −5.75155 2.03E−16 HOXC4 homeobox C4 −53.6672 −5.74597 6.76E−89 HOXC10 homeobox C10 −52.9838 −5.72748 1.87E−217 SNORD114-10 small nucleolar RNA C/D box 114-10 −52.8042 −5.72258 4.03E−09 BARX1 BARX homeobox 1 −52.6707 −5.71893 1.83E−10 LINC00664 long intergenic non-protein coding RNA 664 −52.6383 −5.71804 8.69E−09 RGL3 ral guanine nucleotide dissociation stimulator- −52.0505 −5.70184 3.35E−52 like 3 ZNF257 zinc finger protein 257 −51.9283 −5.69845 1.02E−08 AKR1C2 aldo-keto reductase family 1_member C2 −51.819 −5.69541 9.97E−51 HCAR1 hydroxycarboxylic acid receptor 1 −51.5214 −5.6871 1.14E−08 ZDHHC15 zinc finger_DHHC-type containing 15 −51.0571 −5.67404 1.28E−08 HSPB7 heat shock 27 kDa protein family_member 7 −50.9821 −5.67192 1.96E−97 (cardiovascular) IFI44L interferon-induced protein 44-like −50.8431 −5.66798 3.99E−46 POMC proopiomelanocortin −50.2343 −5.6506 4.12E−10 DLX5 distal-less homeobox 5 −50.0851 −5.64631 3.03E−53 EPGN epithelial mitogen −48.8136 −5.60921 2.21E−36 HAGLR HOXD antisense growth-associated long non- −47.4406 −5.56805 2.98E−24 coding RNA NOTUM notum pectinacetylesterase homolog −47.2843 −5.56329 7.00E−23 (*Drosophila*) ISM1 isthmin 1_angiogenesis inhibitor −46.9645 −5.5535 1.98E−17 SFRP4 secreted frizzled-related protein 4 −46.9411 −5.55278 4.74E−13 DLX6

distal-less homeobox 6 −46.9268 −5.55234 7.46E−74 CCL28 chemokine (C-C motif) ligand 28 −46.8501 −5.54998 7.28E−19 APBB1IP amyloid beta (A4) precursor −46.7936 −5.54824 3.06E−66 protein-binding_family B_member 1 interacting protein NRN1 neuritin 1 −46.7933 −5.54823 2.76E−96 ATP1A2 ATPase_Na+/K+ transporting_alpha 2 −45.6518 −5.5126 6.32E−08 polypeptide SLC2A5 solute carrier family 2 (facilitated −45.6069 −5.51118 2.46E−27 glucose/fructose transporter)_member 5 SAMD9L sterile alpha motif domain containing 9-like −45.4488 −5.50617 7.48E−108 EPYC epiphycan −45.3506 −5.50305 2.66E−08 REM1 RAS (RAD and GEM)-like GTP-binding 1 −45.0583 −5.49372 3.23E−08 CYP19A1 cytochrome P450_family 19_subfamily −45.004 −5.49198 2.28E−08 A_polypeptide 1 SEPSECS-AS1 SEPSECS antisense RNA 1 (head to head) −44.8986 −5.4886 2.63E−08 IFI30 interferon_gamma-inducible protein 30 −43.4309 −5.44065 2.99E−288 HOXC5 homeobox C5 −43.3641 −5.43843 2.23E−39 TMEM233 transmembrane protein 233 41.9538 −5.39073 1.91E−07 METTL7B methyltransferase like 7B −41.948 −5.39053 1.51E−23 DOK7 docking protein 7 −41.8052 −5.38561 2.21E−15 TNNT3 troponin T type 3 (skeletal_fast) −41.6502 −5.38025 4.62E−16 LINC00944 long intergenic non-protein coding RNA 944 −41.6467 −5.38013 9.97E−08 HOXC8 homeobox C8 −40.9363 −5.35531 2.64E−147 RBP4 retinol binding protein 4_plasma −40.7777 −5.34971 4.34E−23 FAM27A family with sequence similarity 27_member C −40.5416 −5.34133 7.17E−08 KRT86 keratin 86_type II −40.3929 −5.33603 3.14E−18 IFI44 interferon-induced protein 44 −40.0664 −5.32432 2.25E−105 LCNL1 lipocalin-like 1 −39.8641 −5.31702 5.71E−20 HRCT1 histidine rich carboxyl terminus 1 −39.6602 −5.30962 4.53E−64 APOL1 apolipoprotein L_1 −39.6399 −5.30888 7.88E−165 ZIC4 Zic family member 4 −39.6291 −5.30849 4.67E−17 HCG4 HLA complex group 4 (non-protein coding) −39.4647 −5.30249 1.68E−07 MRAP2 melanocortin 2 receptor accessory protein 2 −39.3374 −5.29783 1.34E−11 CABP1 calcium binding protein 1 −39.2854 −5.29592 3.55E−09 LOC100133445 NA −39.1418 −5.29064 1.58E−07 SYN3 synapsin III −39.0654 −5.28782 1.56E−07 C11orf70 chromosome 11 open reading frame 70 −38.8235 −5.27886 1.39E−124 LINC00482 long intergenic non-protein coding RNA 482 −38.7606 −5.27652 1.27E−07 ADAMTS5 ADAM metallopeptidase with thrombospondin −37.5963 −5.23252 3.03E−51 type 1 motif 5 APOC3 apolipoprotein C-III −37.5229 −5.2297 2.14E−07 ERG v-ets avian erythroblastosis virus E26 −37.4574 −5.22718 3.45E−16 oncogene homolog PCDHGA6 protocadherin gamma subfamily A_6 −37.3744 −5.22398 2.20E−28 CIITA class II_major histocompatibility −37.3343 −5.22243 9.56E−09 complex_transactivator ADIRF adipogenesis regulatory factor −37.096 −5.21319 1.00E−21 SP7 Sp7 transcription factor −36.5771 −5.19287 5.75E−07 PEG3 paternally expressed 3 −36.3802 −5.18508 3.42E−07 BHMT betaine--homocysteine S-methyltransferase −36.3023 −5.18199 3.42E−07 RARRES3 retinoic acid receptor responder (tazarotene −36.2603 −5.18032 3.07E−34 induced) 3 ERMN ermin_ERM-like protein −36.1008 −5.17396 6.53E−41 KRTAP1-1 keratin associated protein 1-1 −35.9286 −5.16706 3.30E−74 ABI3BP ABI family_member 3 (NESH) binding −35.9144 −5.16649 7.26E−68 protein ALX1 ALX homeobox 1 −35.5028 −5.14986 7.73E−28 HOMER2 homer scaffolding protein 2 −35.447 −5.14759 7.88E−50 HSD17B7P2 hydroxysteroid (17-beta) dehydrogenase 7 −35.1909 −5.13713 4.15E−18 pseudogene 2 IFITM10 interferon induced transmembrane protein 10 −35.0208 −5.13014 7.03E−87 PSG1 pregnancy specific beta-1-glycoprotein 1 −34.8641 −5.12367 1.04E−06 ASTL astacin-like metallo-endopeptidase (M12 −34.4342 −5.10577 1.51E−08 family) CTLA4 cytotoxic T-lymphocyte-associated protein 4 −34.2089 −5.0963 3.13E−10 TNFAIP8L3 tumor necrosis factor_alpha-induced protein −34.1767 −5.09494 2.09E−38 8-like 3 CSF2RB colony stimulating factor 2 −34.0391 −5.08912 1.02E−25 receptor_beta_low-affinity (granulocyte-macrophage) SUSD3 sushi domain containing 3 −33.8605 −5.08153 4.41E−21 KLF8 Kruppel-like factor 8 −33.676 −5.07365 6.76E−09 KLF4 Kruppel-like factor 4 (gut) −33.4045 −5.06197 3.52E−163 HAS2 hyaluronan synthase 2 −33.3869 −5.06121 1.19E−56 LOC100132891 NA −33.1397 −5.05049 2.09E−48 EYA4 EYA transcriptional coactivator and −33.1124 −5.0493 5.02E−18 phosphatase 4 LOC100996609 NA −33.0553 −5.04681 3.10E−06 C16orf54

chromosome 16 open reading frame 54 −32.8202 −5.03651 8.70E−07 ITGB2-AS1 ITGB2 antisense RNA 1 −32.6077 −5.02714 1.02E−25 LINC00884 long intergenic non-protein coding RNA 884 −32.4197 −5.0188 7.78E−09 PCDHGA7 protocadherin gamma subfamily A_7 −32.4112 −5.01842 3.70E−20 TMEM155 transmembrane protein 155 −31.9076 −4.99583 7.65E−43 ITGAL integrin_alpha L (antigen CD11A −31.8094 −4.99138 1.12E−06 (p180)_lymphocyte function-associated antigen 1; alpha polypeptide) SIX2 SIX homeobox 2 −31.7605 −4.98916 1.28E−134 ABCA8 ATP-binding cassette_sub-family A −31.5103 −4.97775 1.79E−37 (ABC1)_member 8 ZNF578 zinc finger protein 578 −30.6722 −4.93886 6.76E−29 OOEP oocyte expressed protein −30.5166 −4.93152 3.47E−06 DUXAP10 double homeobox A pseudogene 10 −30.303 −4.92139 4.16E−09 TEKT4 tektin 4 −29.2438 −4.87006 4.86E−06 SYNDIG1 synapse differentiation inducing 1 −29.2011 −4.86795 1.73E−31 ZIC1 Zic family member 1 −28.9793 −4.85695 8.42E−15 RFX8 RFX family member 8_lacking RFX DNA −28.8092 −4.84846 4.93E−29 binding domain PTGDS prostaglandin D2 synthase 21 kDa (brain) −28.8045 −4.84822 2.95E−20 MR1 major histocompatibility complex_class I- −28.6716 −4.84155 3.59E−47 related PCDHGA5 protocadherin gamma subfamily A_5 −28.5837 −4.83712 1.02E−25 LTBP2 latent transforming growth factor beta binding −28.4538 −4.83055 7.30E−60 protein 2 LINC00478 mir-99a-let-7c cluster host gene −28.3982 −4.82773 5.37E−12 IL6 interleukin 6 −28.1909 −4.81716 7.58E−67 LINC00922 long intergenic non-protein coding RNA 922 −28.1849 −4.81685 7.58E−06 FBLN7 fibulin 7 −28.1669 −4.81593 8.77E−28 PAX8-AS1 PAX8 antisense RNA 1 −28.1127 −4.81315 9.03E−07 BRINP1 bone morphogenetic protein/retinoic acid −28.0874 −4.81185 9.33E−111 inducible neural-specific 1 IGJ joining chain of multimeric IgA and IgM −28.0393 −4.80938 5.41E−10 PCDHGA11 protocadherin gamma subfamily A_11 −28.0007 −4.80739 1.55E−40 KANK4 KN motif and ankyrin repeat domains 4 −27.9921 −4.80695 6.94E−06 C15orf54 chromosome 15 open reading frame 54 −27.7757 −4.79575 5.79E−13 ZNF492 zinc finger protein 492 −27.703 −4.79197 1.66E−07 SNTG2 syntrophin_gamma 2 −27.6039 −4.7868 5.38E−22 HOXC9 homeobox C9 −27.5876 −4.78595 9.32E−28 CPN2 carboxypeptidase N_polypeptide 2 −27.5662 −4.78483 2.28E−08 PP12613 uncharacterized LOC100192379 −27.2393 −4.76762 8.38E−08 ANGPTL1 angiopoietin-like 1 −27.2239 −4.7668 5.53E−11 PODNL1 podocan-like 1 −27.1105 −4.76078 3.88E−88 LOC101926935 uncharacterized LOC101926935 −27.0989 −4.76016 4.72E−06 LOC388849 uncharacterized LOC388849 −26.899 −4.74948 3.25E−48 CD300C CD300c molecule −26.7809 −4.74313 5.77E−06 ASB5 ankyrin repeat and SOCS box containing 5 −26.5086 −4.72839 1.84E−16 CCNYL2 cyclin Y-like 2_pseudogene −26.4971 −4.72776 6.12E−06 ZFYVE28 zinc finger_FYVE domain containing 28 −26.4622 −4.72586 3.11E−64 SERINC2 serine incorporator 2 −26.3179 −4.71797 5.05E−126 COL15A1 collagen_type XV_alpha 1 −26.0413 −4.70273 9.51E−07 SLC30A3 solute carrier family 30 (zinc −25.8968 −4.6947 2.23E−07 transporter)_member 3 COL5A3 collagen_type V_alpha 3 −25.7264 −4.68518 1.17E−31 LOC100505718 NA −25.717 −4.68465 7.80E−12 FLG2 filaggrin family member 2 −25.5466 −4.67506 1.48E−05 SYBU syntabulin (syntaxin-interacting) −25.4087 −4.66725 4.29E−21 LINC00578 long intergenic non-protein coding RNA 578 −25.2589 −4.65872 2.57E−07 SLC12A1 solute carrier family 12 −25.254 −4.65844 9.59E−06 (sodium/potassium/chloride transporter)_member 1 OASL 2′-5′-oligoadenylate synthetase-like −25.1755 −4.65395 2.35E−07 OLAH oleoyl-ACP hydrolase −25.0589 −4.64725 8.67E−06 KRT9 keratin 9_type I −25.0061 −4.64421 6.79E−07 PPAP2B phosphatidic acid phosphatase type 2B −24.7585 −4.62985 4.73E−24 TM4SF20 transmembrane 4 L six family member 20 −24.584 −4.61965 7.35E−16 PCDHGA2 protocadherin gamma subfamily A_2 −24.557 −4.61806 1.82E−17 AMPH amphiphysin −24.4871 −4.61395 3.66E−81 KCNK15 potassium channel_two pore domain −24.4564 −4.61214 2.64E−14 subfamily K_member 15 HOXA10-AS HOXA10 antisense RNA −24.4528 −4.61193 7.23E−30 INSC inscuteable homolog (*Drosophila*) −24.452 −4.61188 1.62E−05 MIR4257 microRNA 4257 −24.4166 −4.60979 1.11E−05 HOXC6 homeobox C6 −24.4007 −4.60885 1.41E−36 RTP4 receptor (chemosensory) transporter protein 4 −24.3581

−4.60633 1.95E−05 GAS1 growth arrest-specific 1 −24.0511 −4.58803 9.44E−50 EBF1 early B-cell factor 1 −23.9491 −4.5819 3.55E−143 SNTB1 syntrophin_beta 1 (dystrophin-associated −23.9123 −4.57968 1.73E−74 protein A1_59 kDa_basic component 1) ANPEP alanyl (membrane) aminopeptidase −23.8821 −4.57786 0.00E+00 C10orf105 chromosome 10 open reading frame 105 −23.8719 −4.57724 4.12E−07 PCDHGB1 protocadherin gamma subfamily B_1 −23.7715 −4.57116 4.31E−13 COMT catechol-O-methyltransferase −23.7198 −4.56802 8.63E−144 CYP7B1 cytochrome P450_family 7_subfamily −23.7073 −4.56726 5.30E−07 B_polypeptide 1 KLHL33 kelch-like family member 33 −23.6812 −4.56567 1.63E−05 KLHL13 kelch-like family member 13 −23.596 −4.56047 1.50E−44 RAET1E retinoic acid early transcript 1E −23.5653 −4.55859 1.34E−06 ABCC3 ATP-binding cassette_sub-family C −23.5388 −4.55697 1.55E−32 (CFTR/MRP)_member 3 PRR34 proline rich 34 −23.4808 −4.55341 5.23E−12 LOC100130992 uncharacterized LOC100130992 −23.2829 −4.5412 2.47E−26 ISLR2 immunoglobulin superfamily containing −23.2065 −4.53646 4.26E−05 leucine-rich repeat 2 PLAC9 placenta-specific 9 −23.1863 −4.5352 7.53E−79 ATE1-AS1 ATE1 antisense RNA 1 −22.9836 −4.52253 9.59E−06 ZMYND15 zinc finger_MYND-type containing 15 −22.9796 −4.52228 3.63E−15 PRL prolactin −22.9438 −4.52003 1.60E−05 GPAT2 glycerol-3-phosphate acyltransferase −22.8257 −4.51259 2.15E−15 2_mitochondrial SYT11 synaptotagmin XI −22.6805 −4.50338 6.30E−20 RTN4RL1 reticulon 4 receptor-like 1 −22.6662 −4.50247 8.59E−07 PDK4 pyruvate dehydrogenase kinase_isozyme 4 −22.5842 −4.49724 6.18E−13 IGF1 insulin-like growth factor 1 (somatomedin C) −22.4869 −4.49101 4.74E−21 COL8A2 collagen_type VIII_alpha 2 −22.4439 −4.48825 3.73E−22 C12orf56 chromosome 12 open reading frame 56 −22.4084 −4.48597 9.34E−08 CHRDL2 chordin-like 2 −22.3783 −4.48403 1.55E−06 MIR10B microRNA 10b −22.2523 −4.47588 2.37E−05 IL18R1 interleukin 18 receptor 1 −22.2043 −4.47277 1.27E−08 OMD osteomodulin −22.1734 −4.47076 2.63E−05 C9orf170 chromosome 9 open reading frame 170 −22.1436 −4.46882 9.24E−07 HOXD4 homeobox D4 −22.1291 −4.46787 3.19E−29 LINC01060 long intergenic non-protein coding RNA 1060 −22.1154 −4.46698 4.42E−05 LOC100130539 NA −22.0684 −4.46391 4.11E−14 ASPG asparaginase −22.0317 −4.46151 3.52E−05 LOC729296 uncharacterized LOC729296 −21.9806 −4.45816 2.94E−05 SPATA41 spermatogenesis associated 41 (non-protein −21.9421 −4.45563 1.98E−06 coding) LRRN4CL LRRN4 C-terminal like −21.936 −4.45523 4.64E−41 MYOC myocilin_trabecular meshwork inducible −21.9193 −4.45413 5.99E−05 glucocorticoid response POSTN periostin_osteoblast specific factor −21.9072 −4.45333 2.31E−13 FOXF2 forkhead box F2 −21.8768 −4.45133 2.78E−103 LYPD5 LY6/PLAUR domain containing 5 −21.8023 −4.44641 3.63E−05 ALX4 ALX homeobox 4 −21.7607 −4.44365 8.25E−14 HTR7 5-hydroxytryptamine (serotonin) receptor −21.6032 −4.43317 4.24E−12 7_adenylate cyclase-coupled MCOLN3 mucolipin 3 −21.5099 −4.42693 1.84E−11 NXF3 nuclear RNA export factor 3 −21.506 −4.42667 9.32E−10 MFAP5 microfibrillar associated protein 5 −21.467 −4.42405 6.48E−64 MALRD1 MAM and LDL receptor class A domain −21.4603 −4.4236 3.91E−05 containing 1 ADAMTS4 ADAM metallopeptidase with thrombospondin −21.4536 −4.42315 1.39E−43 type 1 motif_4 ZNF528 zinc finger protein 528 −21.4192 −4.42083 8.50E−35 SLC8A3 solute carrier family 8 (sodium/calcium −21.3959 −4.41926 7.10E−05 exchanger)_member 3 NDUFA4L2 NADH dehydrogenase (ubiquinone) 1 alpha −21.3677 −4.41736 2.98E−19 subcomplex_4-like 2 TRABD2B TraB domain containing 2B −21.2105 −4.40671 1.19E−09 SIM1 single-minded family bHLH transcription −21.2004 −4.40602 9.35E−06 factor 1 FAM19A5 family with sequence similarity 19 (chemokine −21.1652 −4.40362 3.42E−44 (C-C motif)-like)_member A5 FAM50B family with sequence similarity 50_member B −21.0535 −4.39599 1.01E−50 KCNN4 potassium channel_calcium activated −20.9584 −4.38946 2.97E−46 intermediate/small conductance subfamily N alpha_member 4 HTR2A 5-hydroxytryptamine (serotonin) receptor −20.9571 −4.38937 0.00011 2A_G protein-coupled PM20D1 peptidase M20 domain containing 1 −20.5974 −4.36439 8.81E−05 LOC100506834 uncharacterized LOC100506834 −20.5877 −4.36371 6.39E−17 PLD5 phospholipase D family_member 5 −20.5811 −4.36325 0.000159

NR4A2 nuclear receptor subfamily 4_group −20.3715 −4.34848 1.39E−29 A_member 2 BACH2 BTB and CNC homology 1_basic leucine −20.2688 −4.34119 2.14E−28 zipper transcription factor 2 CRIP1 cysteine-rich protein 1 (intestinal) −20.2183 −4.33759 1.77E−45 ANGPTL5 angiopoietin-like 5 −20.2061 −4.33672 7.79E−05 USP32P1 ubiquitin specific peptidase 32 pseudogene 1 −20.1748 −4.33448 6.91E−06 PLSCR4 phospholipid scramblase 4 −20.0422 −4.32497 1.83E−45 BACE2 beta-site APP-cleaving enzyme 2 −20.0121 −4.3228 5.29E−71 CYP1B1-AS1 CYP1B1 antisense RNA 1 −19.9626 −4.31923 2.92E−13 SLC14A2 solute carrier family 14 (urea −19.7333 −4.30256 7.17E−05 transporter)_member 2 POU5F1 POU class 5 homeobox 1 −19.6359 −4.29542 1.68E−08 KCND3 potassium channel_voltage gated Shal related −19.5189 −4.2868 1.65E−06 subfamily D_member 3 RHBDL2 rhomboid veinlet-like 2 (*Drosophila*) −19.5079 −4.28599 2.69E−35 CCDC67 coiled-coil domain containing 67 −19.222 −4.26469 8.79E−05 ADAMTS2 ADAM metallopeptidase with thrombospondin −19.1384 −4.2584 4.81E−197 type 1 motif_2 ENTPD1-AS1 ENTPD1 antisense RNA 1 −19.1196 −4.25698 6.87E−05 MLKL mixed lineage kinase domain-like −19.1013 −4.2556 1.91E−88 BMPR1B bone morphogenetic protein receptor_type IB −18.9871 −4.24695 1.35E−21 LINC00028 long intergenic non-protein coding RNA 28 −18.9553 −4.24453 7.98E−05 MYOT myotilin −18.7318 −4.22742 4.74E−10 ADRA2C adrenoceptor alpha 2C −18.6355 −4.21998 3.71E−27 HOXC-AS2 HOXC cluster antisense RNA 2 −18.5603 −4.21415 1.91E−13 TIMP3 TIMP metallopeptidase inhibitor 3 −18.3901 −4.20086 7.89E−33 C21orf119 URB1 antisense RNA 1 (head to head) −18.3392 −4.19686 6.85E−48 ANKRD7 ankyrin repeat domain 7 −18.2307 −4.1883 0.000179 ANKRD20A9P ankyrin repeat domain 20 family_member −18.175 −4.18388 0.000271 A9_pseudogene NFE2 nuclear factor_erythroid 2 −18.1645 −4.18305 1.53E−41 ASS1 argininosuccinate synthase 1 −18.1342 −4.18064 1.34E−73 BTLA B and T lymphocyte associated −18.1274 −4.1801 1.28E−05 SLC14A1 solute carrier family 14 (urea −18.1032 −4.17817 4.65E−33 transporter)_member 1 (Kidd blood group) ANKRD6 ankyrin repeat domain 6 −18.0164 −4.17124 1.65E−85 DMBT1 deleted in malignant brain tumors 1 −17.9852 −4.16874 0.000133 LINC00271 long intergenic non-protein coding RNA 271 −17.9802 −4.16834 1.18E−05 OR2S2 olfactory receptor_family 2_subfamily −17.9513 −4.16602 0.000215 S_member 2 (gene/pseudogene) SNED 1 sushi_nidogen and EGF-like domains 1 −17.8528 −4.15808 8.57E−101 LOC392232 transient receptor potential cation −17.7659 −4.15104 0.000183 channel_subfamily A_member 1 pseudogene KCNT2 potassium channel sodium activated −17.5312 −4.13185 3.15E−18 subfamily T_member 2 RORA RAR-related orphan receptor A −17.4834 −4.12791 1.46E−114 TNFSF9 tumor necrosis factor (ligand) −17.4353 −4.12394 2.78E−21 superfamily_member 9 ADH1C alcohol dehydrogenase 1C (class I)_gamma −17.4236 −4.12297 0.000163 polypeptide FBXO39 F-box protein 39 −17.3262 −4.11488 0.000153 ZNF595 zinc finger protein 595 17.2323 −4.10704 1.79E−30 LMO7DN LM07 downstream neighbor −17.2099 −4.10517 2.90E−17 PI16 peptidase inhibitor 16 −17.1836 −4.10296 2.92E−11 EPDR1 ependymin related 1 −17.0851 −4.09467 8.65E−36 HLA-DRA major histocompatibility complex_class −17.078 −4.09407 0.000417 II_DR alpha C10orf54 chromosome 10 open reading frame 54 −17.0211 −4.08925 2.39E−93 ZNF311 zinc finger protein 311 −17.0103 −4.08834 2.37E−10 LINC01119 long intergenic non-protein coding RNA 1119 −16.956 −4.08372 7.58E−67 RASSF9 Ras association (RalGDS/AF-6) domain −16.9475 −4.083 4.43E−41 family (N-terminal) member 9 HLA-DRB1 major histocompatibility complex_class −16.872 −4.07656 2.00E−08 II_DR beta 1 HMOX1 heme oxygenase 1 −16.8711 −4.07648 2.77E−128 MIRLET7BHG MIRLET7B host gene −16.8548 −4.07509 2.54E−22 TRPM3 transient receptor potential cation −16.8294 −4.07291 2.12E−13 channel_subfamily M_member 3 CCDC64B coiled-coil domain containing 64B −16.8047 −4.07079 10.000407 HOXA9 homeobox A9 −16.7153 −4.0631 4.84E−53 BATF basic leucine zipper transcription factor_ATF- −16.7105 −4.06268 0.000383 like IGFBPL1 insulin-like growth factor binding protein-like −16.6703 −4.05921 1.29E−35 1 KCNH1 potassium channel_voltage gated eag related −16.6561 −4.05798 2.27E−18 subfamily H_member 1 LPO lactoperoxidase −16.5886 −4.05212 1.79E−05 ADCY4 adenylate

cyclase 4 −16.5671 −4.05025 4.41E−19 ANKRD65 ankyrin repeat domain 65 −16.3912 −4.03485 8.58E−49 OLFML1 olfactomedin-like 1 −16.3551 −4.03167 2.87E−21 C11orf96 chromosome 11 open reading frame 96 −16.2548 −4.02279 3.34E−22 TLE2 transducin-like enhancer of split 2 −16.2491 −4.02229 3.65E−36 LOC653602 uncharacterized LOC653602 −16.2049 −4.01836 2.06E−10 EVA1C eva-1 homolog C (*C. elegans*) −16.2023 −4.01813 2.64E−72 SATB2-AS1 SATB2 antisense RNA 1 −16.0753 −4.00677 0.000254 GBP5 guanylate binding protein 5 −16.0594 −4.00535 6.57E−06 IL1R1 interleukin 1 receptor_type I −16.0375 −4.00338 5.75E−80 MIR656 microRNA 656 −15.983 −3.99847 0.000289 KCNK2 potassium channel_two pore domain −15.9332 −3.99396 2.10E−31 subfamily K_member 2 TNFRSF14 tumor necrosis factor receptor −15.913 −3.99213 5.69E−44 superfamily_member 14 PCDHGA1 protocadherin gamma subfamily A_1 −15.866 −3.98787 5.58E−09 CCL20 chemokine (C-C motif) ligand 20 −15.8653 −3.9878 6.53E−09 LOC284412 uncharacterized LOC284412 −15.8392 −3.98543 5.86E−07 TNFAIP6 tumor necrosis factor_alpha-induced protein 6 −15.7201 −3.97454 7.00E−12 ACAN aggrecan −15.6611 −3.96911 3.97E−83 VTRNA1-2 vault RNA 1-2 −15.6195 −3.96528 3.85E−10 RGN regucalcin −15.609 −3.96431 3.76E−23 NR4A1 nuclear receptor subfamily 4_group −15.5795 −3.96158 3.99E−95 A_member 1 TNS4 tensin 4 −15.5521 −3.95904 9.17E−22 CFB complement factor B −15.4426 −3.94884 5.90E−31 TMEM119 transmembrane protein 119 −15.4262 −3.94731 2.09E−59 MIR4271 microRNA 4271 −15.3448 −3.93968 0.000385 ABCC9 ATP-binding cassette_sub-family C −15.294 −3.93489 6.82E−35 (CFTR/MRP)_member 9 AGMO alkylglycerol monooxygenase −15.2848 −3.93403 0.000102 RIPK3 receptor-interacting serine-threonine kinase 3 −15.1926 −3.9253 1.71E−31 SLPI secretory leukocyte peptidase inhibitor −15.1322 −3.91955 0.000432 MIR23A microRNA 23a −15.1079 −3.91723 0.000424 EBF3 early B-cell factor 3 −15.0595 −3.9126 2.02E−102 RGS22 regulator of G-protein signaling 22 −15.059 −3.91255 7.45E−05 PRUNE2 prune homolog 2 (*Drosophila*) −15.0164 −3.90847 3.38E−83 A2M alpha-2-macroglobulin −15.0025 −3.90713 4.18E−14 LRRC15 leucine rich repeat containing 15 −14.8862 −3.8959 1.94E−16 LOC101927650 uncharacterized LOC101927650 −14.8779 −3.8951 4.42E−05 LINC00870 long intergenic non-protein coding RNA 870 −14.8421 −3.89162 0.000319 LANCL3 LanC lantibiotic synthetase component C-like −14.8372 −3.89115 1.68E−08 3 (bacterial) SLC6A1 solute carrier family 6 (neurotransmitter −14.7885 −3.8864 0.000151 transporter) member 1 SNORD113-4 small nucleolar RNA_C/D box 113-4 −14.7598 −3.8836 0.000496 APOL6 apolipoprotein L_6 −14.7294 −3.88063 2.08E−62 CRIP3 cysteine-rich protein 3 −14.6825 −3.87603 5.54E−07 ADPRH ADP-ribosylarginine hydrolase −14.6571 −3.87353 6.54E−66 PLA2G5 phospholipase A2_group V −14.6359 −3.87144 0.001334 LINC00877 long intergenic non-protein coding RNA 877 −14.4527 −3.85327 0.000505 FIBIN fin bud initiation factor homolog (zebrafish) −14.4064 −3.84864 2.26E−27 LIPI lipase_member I −14.3906 −3.84705 0.000612 LINC01121 long intergenic non-protein coding RNA 1121 −14.3857 −3.84656 0.000775 ABCA6 ATP-binding cassette_sub-family A −14.3797 −3.84596 2.42E−16 (ABC1)_member 6 LINC00961 long intergenic non-protein coding RNA 961 14.3653 −3.84452 4.16E−29 MLIP muscular LMNA-interacting protein −14.299 −3.83784 6.43E−05 TP63 tumor protein p63 −14.2856 −3.83649 4.77E−08 MEDAG mesenteric estrogen-dependent adipogenesis −14.2853 −3.83646 3.66E−98 FOSB FBJ murine osteosarcoma viral oncogene −14.261 −3.834 3.25E−18 homolog B CCDC144A coiled-coil domain containing 144A −14.2522 −3.83311 3.88E−05 ZNF704 zinc finger protein 704 −14.252 −3.83309 3.01E−11 FZD1 frizzled class receptor 1 −14.1041 −3.81804 2.20E−37 NPR3 natriuretic peptide receptor 3 −14.0506 −3.81256 2.04E−32 LRRC6 leucine rich repeat containing 6 −13.9759 −3.80487 1.02E−33 LAMA4 laminin_alpha 4 −13.9682 −3.80407 3.57E−32 FLJ22447 uncharacterized LOC400221 −13.9582 −3.80304 6.71E−23 ANKFN1 ankyrin-repeat and fibronectin type III domain −13.9499 −3.80218 9.52E−11 containing 1 LOC101927524 NA −13.947 −3.80188 0.000913 C3 complement component 3 −13.9125 −3.79831 7.27E−21 TCHH trichohyalin −13.8398 −3.79075 0.000751 TMSB4Y thymosin beta 4_Y-linked −13.839 −3.79067 0.001604 PON3 paraoxonase 3 −13.7218 −3.7784

0.00108 KRT83 keratin 83_type II −13.7094 −3.77709 0.00026 AGT angiotensinogen (serpin peptidase −13.702 −3.77631 2.67E−25 inhibitor_clade A_member 8) CEMIP cell migration inducing protein_hyaluronan −13.667 −3.77262 4.15E−30 binding MIR4297 microRNA 4297 −13.6626 −3.77216 0.001069 PSORS1C3 psoriasis susceptibility 1 candidate 3 (non- −13.5703 −3.76238 0.001055 protein coding) ITGA8 integrin_alpha 8 −13.5429 −3.75946 2.41E−67 LOC102546299 uncharacterized LOC102546299 −13.5364 −3.75877 1.02E−06 GSTM1 glutathione S-transferase mu 1 −13.5248 −3.75754 0.001586 MIR6730 microRNA 6730 −13.49 −3.75382 9.36E−05 DHX58 DEXH (Asp-Glu-X-His) box polypeptide 58 −13.4889 −3.7537 5.11E−29 CXCL16 chemokine (C-X-C motif) ligand 16 −13.4676 −3.75142 1.20E−38 GJB5 gap junction protein_beta 5_31.1 kDa −13.4535 −3.74991 0.000119 SCIN scinderin −13.4499 −3.74952 3.34E−08 CSGALNACT1 chondroitin sulfate N- −13.4328 −3.74769 1.50E−70 acetylgalactosaminyltransferase 1 LOC101928882 uncharacterized LOC101928882 −13.4233 −3.74667 0.001191 MSC musculin −13.4205 −3.74637 2.37E−56 WEE2 WEE1 homolog 2 (*S. pombe*) −13.4086 −3.74509 0.001064 NR1I2 nuclear receptor subfamily 1_group −13.3169 −3.73519 0.000887 I_member 2 OAS1 2′-5′-oligoadenylate synthetase 1_40/46 kDa −13.282 −3.7314 3.02E−07 LINC01116 long intergenic non-protein coding RNA 1116 −13.2627 −3.7293 2.01E−69 VMO1 vitelline membrane outer layer 1 homolog −13.2306 −3.72581 7.39E−16 (chicken) CD4 CD4 molecule −13.2111 −3.72368 9.20E−251 SLAMF9 SLAM family member 9 −13.208 −3.72334 5.08E−17 COL12A1 collagen_type XII_alpha 1 −13.1992 −3.72238 1.82E−30 TBX15 T-box 15 −13.1967 −3.7221 2.80E−169 LOC102724224 NA −13.1605 −3.71814 3.31E−26 EYA1 EYA transcriptional coactivator and −13.1442 −3.71635 9.67E−11 phosphatase 1 HOXA1 homeobox A1 13.0858 −3.70993 3.29E−34 IL21R interleukin 21 receptor −13.0523 −3.70623 5.45E−25 AKR1C3 aldo-keto reductase family 1_member C3 −13.0514 −3.70613 4.31E−71 ELFN1-AS1 ELFN1 antisense RNA 1 −13.0005 −3.70049 0.001132 GIMAP2 GTPase_IMAP family member 2 −12.977 −3.69789 0.000193 EPHA3 EPH receptor A3 −12.9631 −3.69634 4.89E−09 AMDHD1 amidohydrolase domain containing 1 −12.8293 −3.68137 2.56E−06 DHRS3 dehydrogenase/reductase (SDR family) −12.8017 −3.67826 3.71E−99 member 3 HOTAIRM1 HOXA transcript antisense RNA_myeloid- −12.6644 −3.66271 7.70E−17 specific 1 LOC643733 caspase 4_apoptosis-related cysteine peptidase 12.6634 −3.66259 0.001868 pseudogene PLEKHS1 pleckstrin homology domain −12.6564 −3.6618 0.0018 containing_family S member 1 ALDH3A1 aldehyde dehydrogenase 3 family_member A1 −12.5614 −3.65093 0.001122 FAM124A family with sequence similarity 124A −12.5491 −3.64951 3.37E−13 APOL4 apolipoprotein L_4 12.5159 −3.64569 4.34E−05 LOC344887 NmrA-like family domain containing 1 −12.445 −3.63749 8.59E−08 pseudogene MKX mohawk homeobox −12.4443 −3.63741 3.59E−45 GPR1 G protein-coupled receptor 1 −12.4127 −3.63374 8.62E−69 C1S complement component 1_s subcomponent −12.3465 −3.62603 5.89E−122 WBP2NL WBP2 N-terminal like −12.3298 −3.62408 0.00032 ADAMTS1 ADAM metallopeptidase with thrombospondin −12.2866 −3.61901 1.75E−51 type 1 motif_1 PTPRQ protein tyrosine phosphatase_receptor type_Q −12.2197 −3.61114 6.07E−15 ADRA1D adrenoceptor alpha 1D −12.2063 −3.60955 3.37E−33 MIR4768 microRNA 4768 −12.1847 −3.607 5.42E−07 BPIFB4 BPI fold containing family B_member 4 −12.181 −3.60656 0.002036 GCNT1 glucosaminyl (N-acetyl) transferase 1_core 2 −12.1357 −3.60118 7.82E−213 THBS1 thrombospondin 1 −12.1223 −3.59959 8.45E−26 KLF15 Kruppel-like factor 15 −12.1204 −3.59936 5.06E−08 ICAM2 intercellular adhesion molecule 2 −12.0635 −3.59258 1.67E−16 LINC00264 long intergenic non-protein coding RNA 264 −12.0558 −3.59166 0.002903 HAR1B highly accelerated region 1B (non-protein −12.0333 −3.58896 0.000378 coding) KRT32 keratin 32_type I −11.9989 −3.58483 0.000268 TRPA1 transient receptor potential cation −11.9929 −3.58411 1.13E−09 channel_subfamily A_member 1 CACNA1C- CACNA1C antisense RNA 1 −11.9457 −3.57842 3.11E−05 AS1 RXFP1 relaxin/insulin-like family peptide receptor 1 −11.9372 −3.57739 0.00163 HSPA7 heat shock 70 kDa protein 7 (HSP70B) −11.9275 −3.57622 0.002637 ZSWIM2 zinc

finger_SWIM-type containing 2 −11.9 −3.57289 5.58E−09 POM121L9P POM121 transmembrane nucleoporin-like −11.8915 −3.57186 2.42E−12 9_pseudogene PLA2R1 phospholipase A2 receptor 1_180 kDa −11.8505 −3.56687 6.96E−87 LOC100506258 uncharacterized LOC100506258 −11.8385 −3.56541 7.21E−08 MIR27A microRNA 27a −11.8194 −3.56308 0.00043 XAF1 XIAP associated factor 1 −11.8067 −3.56153 1.34E−19 C21orf15 cytochrome P450_family 4_subfamily −11.7779 −3.55801 0.00238 F_polypeptide 29_pseudogene FIBCD1 fibrinogen C domain containing 1 −11.7398 −3.55333 1.37E−52 TLX2 T-cell leukemia homeobox 2 −11.7162 −3.55043 0.000158 PSG2 pregnancy specific beta-1-glycoprotein 2 −11.7126 −3.54999 0.001543 PCDHGB5 protocadherin gamma subfamily B_5 −11.6849 −3.54657 1.84E−09 RNF212 ring finger protein 212 −11.6282 −3.53956 1.92E−84 HERC2P10 hect domain and RLD 2 pseudogene 10 −11.6193 −3.53845 7.54E−07 SHCBP1L SHC SH2-domain binding protein 1-like −11.585 −3.53418 0.001762 FKBP9P1 FK506 binding protein 9 pseudogene 1 −11.5254 −3.52674 2.78E−17 MAB21L3 mab-21-like 3 (*C. elegans*) −11.5082 −3.52459 0.002871 C9orf64 chromosome 9 open reading frame 64 −11.5027 −3.5239 1.20E−22 TDRD12 tudor domain containing 12 −11.4976 −3.52326 0.003909 FXYD3 FXYD domain containing ion transport −11.4449 −3.51663 0.002241 regulator 3 PCDHB15 protocadherin beta 15 −11.4199 −3.51348 4.29E−16 HTATSF1P2 HIV-1 Tat specific factor 1 pseudogene 2 −11.4056 −3.51167 1.54E−18 KRTAP1-3 keratin associated protein 1-3 −11.405 −3.5116 0.000615 ESR1 estrogen receptor 1 −11.4016 −3.51116 1.74E−09 TDRD6 tudor domain containing 6 −11.3952 −3.51035 5.09E−06 SLC4A4 solute carrier family 4 (sodium bicarbonate −11.3712 −3.50731 6.76E−68 cotransporter)_member 4 IL26 interleukin 26 −11.2376 −3.49026 1.05E−06 LIN7A lin-7 homolog A (*C. elegans*) −11.1763 −3.48237 1.60E−19 C2orf88 chromosome 2 open reading frame 88 −11.153 −3.47936 6.65E−36 PRRX2 paired related homeobox 2 −11.1516 −3.47918 4.79E−30 CASC1 cancer susceptibility candidate 1 −11.132 −3.47664 8.72E−06 HTR6 5-hydroxytryptamine (serotonin) receptor 6_G −11.1213 −3.47525 9.95E−05 protein-coupled STAT4 signal transducer and activator of transcription −11.0841 −3.47042 3.13E−15 4 MEIS3P1 Meis homeobox 3 pseudogene 1 −11.0567 −3.46685 5.16E−15 PCAT5 prostate cancer associated transcript 5 (non- −11.0216 −3.46226 0.003735 protein coding) LEP leptin −10.9642 −3.45473 0.002439 SETBP1 SET binding protein 1 −10.9298 −3.4502 1.13E−13 CEACAM22P carcinoembryonic antigen-related cell adhesion −10.913 −3.44797 0.003652 molecule 22_pseudogene C4orf32 chromosome 4 open reading frame 32 −10.8864 −3.44445 2.30E−28 LINC00943 long intergenic non-protein coding RNA 943 −10.8536 −3.4401 0.004493 ZNF541 zinc finger protein 541 −10.8222 −3.43592 0.001083 CC2D2B coiled-coil and C2 domain containing 2B −10.8072 −3.43392 0.002733 LOC340113 uncharacterized LOC340113 −10.7923 −3.43193 0.003322 RAB3IL1 RAB3A interacting protein (rabin3)-like 1 −10.7393 −3.42483 1.25E−78 LEPR leptin receptor −10.7172 −3.42186 3.94E−24 CACNA1C calcium channel_voltage-dependent_L −10.6935 −3.41866 8.21E−37 type_alpha 1C subunit LMO7-AS1 LMO7 antisense RNA 1 −10.6495 −3.41271 8.67E−21 C1R complement component 1_r subcomponent −10.6162 −3.4082 3.20E−139 SLC9A9 solute carrier family 9_subfamily A −10.6078 −3.40705 3.19E−37 (NHE9_cation proton antiporter 9)_member 9 LOC102724927 uncharacterized LOC102724927 −10.5947 −3.40527 1.19E−20 DPT dermatopontin −10.5809 −3.40339 0.005268 EMP1 epithelial membrane protein 1 −10.5387 −3.39763 3.56E−26 ZNF676 zinc finger protein 676 −10.5336 −3.39693 0.00396 LIMCH1 LIM and calponin homology domains 1 −10.5325 −3.39678 3.84E−19 PLXNA4 plexin A4 −10.5205 −3.39513 1.94E−23 MT1M metallothionein 1M −10.5182 −3.39481 3.35E−15 TENM2 teneurin transmembrane protein 2 −10.5068 −3.39325 2.22E−96 WISP1 WNT1 inducible signaling pathway protein 1 −10.468 −3.38792 2.62E−25 LOC391322 D-dopachrome tautomerase-like −10.3516 −3.37178 9.00E−12 CMAHP cytidine monophospho-N-acetylneuraminic −10.3496 −3.37151 5.26E−27 acid hydroxylase_pseudogene MIR92B microRNA 92b −10.3491 −3.37144 0.004725 IL7 interleukin 7 −10.3346 −3.36941 7.43E−15 KRT33B keratin 33B_type I −10.3158 −3.36678 3.78E−29 FAM109B family with sequence similarity 109_member −10.2915 −3.36338 1.99E−239 B TGM5

transglutaminase 5 −10.2562 −3.35843 0.006672 PAX8 paired box 8 −10.2492 −3.35744 0.000304 SOCS2 suppressor of cytokine signaling 2 −10.2112 −3.35208 2.28E−77 MEGF6 multiple EGF-like-domains 6 −10.2066 −3.35143 5.05E−52 ALOX15P1 arachidonate 15-lipoxygenase pseudogene 1 −10.2064 −3.3514 0.004495 LINC00982 long intergenic non-protein coding RNA 982 −10.1965 −3.35 3.29E−20 ZNF560 zinc finger protein 560 −10.1806 −3.34775 2.83E−07 FOS FBJ murine osteosarcoma viral oncogene −10.1784 −3.34744 4.35E−15 homolog ASPN asporin −10.1769 −3.34723 3.42E−05 CNTNAP2 contactin associated protein-like 2 −10.1411 −3.34214 4.27E−07 ESM1 endothelial cell-specific molecule 1 −10.1294 −3.34047 8.19E−14 CTSW cathepsin W −10.1277 −3.34023 0.000387 NFIX nuclear factor I/X (CCAAT-binding −9.99031 −3.32053 2.37E−35 transcription factor) GCKR glucokinase (hexokinase 4) regulator −9.97447 −3.31824 1.31E−20 HOXC11 homeobox C11 −9.96673 −3.31712 8.15E−41 B4GALNT1 beta-1_4-N-acetyl-galactosaminyl transferase −9.96445 −3.31679 2.03E−47 1 LRRC2-AS1 LRRC2 antisense RNA 1 −9.9483 −3.31445 0.004436 ALDH1L2 aldehyde dehydrogenase 1 family_member L2 −9.92626 −3.31125 3.37E−31 DOCK9-AS2 DOCK9 antisense RNA 2 (head to head) −9.92564 −3.31116 4.99E−08 ROCK1P1 Rho-associated_coiled-coil containing protein −9.8439 −3.29923 0.000897 kinase 1 pseudogene 1 LTC4S leukotriene C4 synthase −9.83353 −3.29771 4.10E−27 HOXA7 homeobox A7 −9.7738 −3.28892 5.73E−17 PCDHGA8 protocadherin gamma subfamily A_8 −9.76602 −3.28777 3.68E−30 TECTB tectorin beta −9.74931 −3.2853 0.006826 LINC00965 long intergenic non-protein coding RNA 965 −9.72515 −3.28172 0.005153 S100P S100 calcium binding protein P −9.7143 −3.28011 0.002216 TTTY10 testis-specific transcript_Y-linked 10 (non- −9.70481 −3.2787 0.008667 protein coding) ALDH3B1 aldehyde dehydrogenase −9.68338 −3.27551 8.63E−125 3 family_member B1 C1orf158 chromosome 1 open reading frame 158 −9.65944 −3.27194 0.006341 LOC101927755 uncharacterized LOC101927755 −9.65536 −3.27133 3.78E−06 MSR1 macrophage scavenger receptor 1 −9.65375 −3.27109 2.50E−11 TNFSF11 tumor necrosis factor (ligand) −9.64439 −3.26969 0.004874 superfamily_member 11 C5orf38 chromosome 5 open reading frame 38 −9.64305 −3.26949 2.16E−35 CFI complement factor I −9.63697 −3.26858 2.03E−37 TCF7 transcription factor 7 (T-cell specific_HMG- −9.60729 −3.26413 4.99E−36 box) CD80 CD80 molecule −9.60576 −3.2639 0.004995 MIR6071 microRNA 6071 −9.6027 −3.26344 0.007925 LCN1 lipocalin 1 −9.59651 −3.26251 2.06E−05 IL1R2 interleukin 1 receptor_type II −9.58634 −3.26098 0.000578 LOC100506895 uncharacterized LOC100506895 −9.56291 −3.25745 1.66E−05 A2ML1 alpha-2-macroglobulin-like 1 −9.54662 −3.25499 0.0002 AFF2 AF4/FMR2 family_member 2 −9.53809 −3.2537 4.80E−45 NKG7 natural killer cell granule protein 7 −9.51933 −3.25086 0.002237 SIGLEC10 sialic acid binding Ig-like lectin 10 −9.46584 −3.24273 0.002419 TRIM4 tripartite motif containing 4 −9.44283 −3.23922 3.32E−58 ZG16B zymogen granule protein 16B −9.43708 −3.23834 8.22E−07 CCDC158 coiled-coil domain containing 158 −9.40514 −3.23345 3.13E−10 FGL2 fibrinogen-like 2 −9.40299 −3.23312 0.000861 LOC101927688 NA −9.39908 −3.23252 9.42E−05 INHBB inhibin_beta B −9.38645 −3.23058 8.02E−123 HOXA10 homeobox A10 −9.35158 −3.22521 1.51E−123 FHAD1 forkhead-associated (FHA) phosphopeptide −9.33345 −3.22241 1.89E−06 binding domain 1 OSR2 odd-skipped related transciption factor 2 −9.30935 −3.21868 1.36E−05 SNORD114-26 small nucleolar RNA_C/D box 114-26 −9.27939 −3.21403 0.008533 NKX6-1 NK6 homeobox 1 −9.26352 −3.21156 1.76E−15 DNER delta/notch-like EGF repeat containing −9.25472 −3.21019 2.07E−06 LDHAL6B lactate dehydrogenase A-like 6B −9.24985 −3.20943 0.001253 C11orf86 chromosome 11 open reading frame 86 −9.24556 −3.20876 5.32E−05 VSTM4 V-set and transmembrane domain containing 4 −9.21485 −3.20396 2.42E−29 HOXA3 homeobox A3 −9.19985 −3.20161 1.76E−26 HOXC-AS3 HOXC cluster antisense RNA 3 −9.18303 −3.19897 4.60E−08 NPY6R neuropeptide Y receptor Y6 (pseudogene) −9.17883 −3.19831 0.009703 HSD11B1 hydroxysteroid (11-beta) dehydrogenase 1 −9.17323 −3.19743 0.008005 LINC01220 long intergenic non-protein coding RNA 1220 −9.16738 −3.19651 0.001771 MB21D1 Mab-21 domain containing 1 −9.16484

−3.19611 1.32E−26 RNF43 ring finger protein 43 −9.14802 −3.19346 0.001612 HEYL hes-related family bHLH transcription factor −9.14321 −3.1927 0.000477 with YRPW motif-like TNIP3 TNFAIP3 interacting protein 3 −9.14295 −3.19266 1.78E−12 SMCR9 NA −9.12902 −3.19046 0.009476 SNORD114-1 small nucleolar RNA_C/D box 114-1 −9.11006 −3.18746 0.007346 CCRL2 chemokine (C-C motif) receptor-like 2 −9.04819 −3.17763 0.005581 GOLGA8O golgin A8 family_member O −9.00421 −3.1706 4.43E−05 MIR615 microRNA 615 −8.99835 −3.16966 0.009703 KLF17 Kruppel-like factor 17 −8.98289 −3.16718 3.70E−05 BST1 bone marrow stromal cell antigen 1 −8.96697 −3.16462 4.52E−64 MIR199A1 microRNA 199a-1 −8.87877 −3.15036 0.000581 SERP2 stress-associated endoplasmic reticulum −8.87533 −3.1498 1.63E−47 protein family member 2 S100B S100 calcium binding protein B −8.87514 −3.14977 9.46E−08 ZNF726 zinc finger protein 726 −8.84578 −3.14499 8.39E−07 COL16A1 collagen_type XVI_alpha 1 −8.83647 −3.14347 1.43E−59 TMEM30B transmembrane protein 30B −8.83133 −3.14263 1.45E−07 FLJ46906 uncharacterized LOC441172 −8.81866 −3.14056 1.58E−13 SCRT1 scratch family zinc finger 1 −8.77945 −3.13413 0.007849 GDAP1L1 ganglioside induced differentiation associated −8.77622 −3.1336 0.000269 protein 1-like 1 TRPM2 transient receptor potential cation −8.76959 −3.13251 4.32E−08 channel_subfamily M_member 2 CSMD1 CUB and Sushi multiple domains 1 −8.74592 −3.12861 0.00292 FTCDNL1 formiminotransferase cyclodeaminase N- −8.73253 −3.1264 4.10E−05 terminal like RIMS1 regulating synaptic membrane exocytosis 1 −8.72987 −3.12596 5.39E−29 MIR409 microRNA 409 −8.70721 −3.12221 0.008342 RCN3 reticulocalbin 3_EF-hand calcium binding −8.69955 −3.12094 3.55E−43 domain LOC101927354 uncharacterized LOC101927354 −8.68551 −3.11861 2.09E−06 PLA2G16 phospholipase A2_group XVI −8.68226 −3.11807 8.21E−118 SLC1A3 solute carrier family 1 (glial high affinity −8.64838 −3.11243 8.42E−16 glutamate transporter)_member 3 CARD16 caspase recruitment domain family_member −8.61225 −3.10639 2.92E−14 16 LOC101927667 NA −8.61094 −3.10617 1.92E−05 DAPK1 death-associated protein kinase 1 −8.59746 −3.10391 1.87E−56 ANGPT1 angiopoietin 1 −8.57235 −3.09969 2.50E−11 ACOX2 acyl-CoA oxidase 2_branched chain −8.56189 −3.09793 4.59E−28 GHDC GH3 domain containing −8.55483 −3.09674 3.85E−76 IGFBP1 insulin-like growth factor binding protein 1 −8.53103 −3.09272 0.004458 PDE7B phosphodiesterase 7B −8.52488 −3.09168 3.28E−45 MACROD2 MACRO domain containing 2 −8.51166 −3.08944 7.31E−06 RSPO2 R-spondin 2 −8.50788 −3.0888 0.009007 KCNJ9 potassium channel_inwardly rectifying −8.42934 −3.07542 0.003859 subfamily J_member 9 LOC101059948 uncharacterized LOC101059948 −8.42554 −3.07477 8.21E−06 GPR68 G protein-coupled receptor 68 −8.42543 −3.07475 5.26E−24 SOX9-AS1 SOX9 antisense RNA 1 −8.3768 −3.0664 0.001328 RDH5 retinol dehydrogenase 5 (11-cis/9-cis) −8.36862 −3.06499 9.26E−19 NLRP3 NLR family_pyrin domain containing 3 −8.32102 −3.05676 1.57E−20 SLC22A3 solute carrier family 22 (organic cation −8.31762 −3.05617 7.45E−15 transporter)_member 3 G0S2 G0/G1 switch 2 −8.30817 −3.05453 4.71E−17 LOC100505739 NA −8.29372 −3.05202 0.00648 C21orf67 long intergenic non-protein coding RNA 1547 −8.28844 −3.0511 1.50E−39 CHST15 carbohydrate (N-acetylgalactosamine 4-sulfate −8.23107 −3.04108 4.79E−40 6-O) sulfotransferase 15 HOXD1 homeobox D1 −8.22674 −3.04032 0.005994 HOXA2 homeobox A2 −8.20418 −3.03636 3.98E−13 TRIB3 tribbles pseudokinase 3 −8.18805 −3.03352 3.54E−51 LOC100129722 NA −8.18147 −3.03236 1.67E−05 CCIN calicin −8.17223 −3.03073 1.07E−17 ITGB8 integrin_beta 8 −8.16131 −3.0288 8.36E−29 HIST2H2BA histone cluster 2_H2ba (pseudogene) −8.13657 −3.02442 8.34E−11 PIWIL2 piwi-like RNA-mediated gene silencing 2 −8.13177 −3.02357 1.37E−05 ID4 inhibitor of DNA binding 4_dominant −8.11865 −3.02124 7.49E−94 negative helix-loop-helix protein EVI2B ecotropic viral integration site 2B −8.11263 −3.02017 2.32E−16 LOC375196 uncharacterized LOC375196 −8.07711 −3.01384 3.53E−06 WEE2-AS1 WEE2 antisense RNA 1 −8.07107 −3.01276 2.72E−12 GYPE glycophorin E (MNS blood group) −8.04454 −3.00801 0.006375 OXT oxytocin/neurophysin I prepropeptide −8.04393 −3.0079 0.001064 LOC102724550 NA −8.03317 −3.00597 1.79E−11 FAM87A family with sequence similarity 87_member A

−8.0081 −3.00146 0.004949 VLDLR-AS1 VLDLR antisense RNA 1 −7.96365 −2.99343 8.01E−16 NECAB2 N-terminal EF-hand calcium binding protein 2 −7.9535 −2.99159 1.90E−11 ACSS3 acyl-CoA synthetase short-chain family −7.94006 −2.98915 1.83E−60 member 3 LOC284798 uncharacterized LOC284798 −7.92994 −2.98731 0.006819 MYO18B myosin XVIIIB −7.92143 −2.98576 0.004941 UBE2QL1 ubiquitin-conjugating enzyme E2Q family-like −7.91692 −2.98494 2.09E−05 1 MFSD7 major facilitator superfamily domain −7.85287 −2.97322 9.43E−57 containing 7 PNMA2 paraneoplastic Ma antigen 2 −7.81074 −2.96546 8.09E−11 FXYD1 FXYD domain containing ion transport −7.79906 −2.9633 1.83E−11 regulator 1 PGF placental growth factor −7.75142 −2.95446 1.58E−176 RAD21-AS1 RAD21 antisense RNA 1 −7.75109 −2.9544 0.001458 ZFP57 ZFP57 zinc finger protein −7.72037 −2.94867 0.002055 CRNDE colorectal neoplasia differentially expressed −7.70092 −2.94503 3.84E−139 (non-protein coding) BAALC brain and acute leukemia_cytoplasmic −7.68764 −2.94254 2.92E−09 LURAP1L leucine rich adaptor protein 1-like −7.65939 −2.93723 1.58E−119 NOV nephroblastoma overexpressed −7.65419 −2.93625 3.00E−29 CALHM2 calcium homeostasis modulator 2 −7.65409 −2.93623 2.60E−57 TEC tec protein tyrosine kinase −7.64428 −2.93438 2.13E−10 LOC101928036 NA −7.62586 −2.9309 3.39E−06 MACC1 metastasis associated in colon cancer 1 −7.61276 −2.92842 0.000151 FGR FGR −7.51472 −2.90972 0.007795 proto-oncogene_Src family tyrosine kinase GPR85 G protein-coupled receptor 85 −7.50577 −2.908 3.58E−33 MIR24-2 microRNA 24-2 −7.48909 −2.90479 6.35E−05 HTRA1 HtrA serine peptidase 1 −7.43493 −2.89432 3.38E−46 CD97 adhesion G protein-coupled receptor E5 −7.39628 −2.8868 5.45E−18 OXCT1-AS1 OXCT1 antisense RNA 1 −7.39459 −2.88647 0.000781 LOC101928891 uncharacterized LOC101928891 −7.38977 −2.88553 6.18E−09 SVILP1 supervillin pseudogene 1 −7.37176 −2.88201 0.002022 LINC00619 long intergenic non-protein coding RNA 619 −7.36349 −2.88039 1.40E−11 PITX1 paired-like homeodomain 1 −7.33329 −2.87446 1.60E−40 DDIT4 DNA-damage-inducible transcript 4 −7.32445 −2.87272 2.85E−30 DAPK2 death-associated protein kinase 2 −7.3142 −2.8707 1.43E−19 PCDHGB2 protocadherin gamma subfamily B_2 −7.27169 −2.86229 2.78E−16 PDE2A phosphodiesterase 2A cGMP-stimulated −7.25291 −2.85856 3.93E−05 SLC38A5 solute carrier family 38_member 5 −7.21735 −2.85147 1.83E−60 TRPC6 transient receptor potential cation −7.20945 −2.84989 7.86E−05 channel_subfamily C_member 6 ITGA10 integrin_alpha 10 −7.19378 −2.84675 1.86E−15 CXCL3 chemokine (C-X-C motif) ligand 3 −7.19218 −2.84643 5.23E−06 CFD complement factor D (adipsin) −7.19049 −2.84609 3.15E−27 FAM78B family with sequence similarity 78_member B −7.18386 −2.84476 1.29E−05 C2orf73 chromosome 2 open reading frame 73 −7.17794 −2.84357 0.003713 ITGA7 integrin_alpha 7 −7.17232 −2.84244 5.49E−11 VDR vitamin D (1_25-dihydroxyvitamin D3) −7.15926 −2.83981 4.27E−46 receptor LOC100506188 uncharacterized LOC100506188 −7.15311 −2.83857 5.64E−11 LOC100240734 uncharacterized LOC100240734 −7.12801 −2.8335 0.004573 PRG4 proteoglycan 4 −7.11523 −2.83091 7.94E−17 LOC102723769 uncharacterized LOC102723769 −7.11064 −2.82998 0.008421 SLC30A2 solute carrier family 30 (zinc −7.10237 −2.8283 0.000171 transporter)_member 2 MISP mitotic spindle positioning −7.10183 −2.82819 7.07E−08 MTSS1 metastasis suppressor 1 −7.09096 −2.82598 1.40E−16 FAM178B family with sequence similarity 178_member −7.09027 −2.82584 6.79E−05 B C15orf59 chromosome 15 open reading frame 59 −7.08467 −2.8247 1.37E−32 FAM167A family with sequence similarity 167_member −7.08197 −2.82415 2.71E−20 A LOC101929234 uncharacterized LOC101929234 −7.06216 −2.82011 3.24E−07 CSF1R colony stimulating factor 1 receptor −7.04705 −2.81702 5.45E−12 PRSS12 protease_serine_12 (neurotrypsin_motopsin) −7.04642 −2.81689 4.76E−14 HCG4B HLA complex group 4B (non-protein coding) −7.03246 −2.81403 0.000191 CYB561 cytochrome b561 −7.01533 −2.81051 5.12E−66 TMEM150C transmembrane protein 150C −6.98447 −2.80415 2.34E−33 LY75 lymphocyte antigen 75 −6.98326 −2.8039 0.003764 VCAM1 vascular cell adhesion molecule 1 −6.97542 −2.80228 6.95E−17 ZNF667-AS1 ZNF667 antisense RNA 1 (head to head) −6.9484 −2.79668 1.23E−19 ALPK1 alpha-kinase 1 −6.94238 −2.79543 6.99E−35 ZNF354C zinc

finger protein 354C −6.93824 −2.79457 2.95E−06 ZNF396 zinc finger protein 396 −6.93516 −2.79393 3.40E−07 NDRG1 N-myc downstream regulated 1 −6.93439 −2.79377 5.51E−30 ZNF829 zinc finger protein 829 −6.92479 −2.79177 2.09E−50 C10orf11 chromosome 10 open reading frame 11 −6.92354 −2.79151 9.83E−19 KRT31 keratin 31_type I −6.92349 −2.7915 0.000395 NTRK1 neurotrophic tyrosine kinase_receptor_type 1 −6.91726 −2.7902 0.00105 PRDM6 PR domain containing 6 −6.89452 −2.78545 1.36E−05 KCNJ8 potassium channel_inwardly rectifying −6.89323 −2.78518 1.33E−44 subfamily J_member 8 FZD5 frizzled class receptor 5 −6.88306 −2.78305 1.81E−09 KLF9 Kruppel-like factor 9 −6.87905 −2.78221 1.75E−17 GGT5 gamma-glutamyltransferase 5 −6.87896 −2.78219 1.66E−19 LOC115110 uncharacterized LOC115110 −6.8771 −2.7818 0.002611 SCRG1 stimulator of chondrogenesis 1 −6.86286 −2.77881 2.32E−19 OTUD7A OTU deubiquitinase 7A −6.86253 −2.77874 0.001651 C15orf65 chromosome 15 open reading frame 65 −6.85963 −2.77813 4.91E−26 AGBL2 ATP/GTP binding protein-like 2 −6.85255 −2.77664 1.04E−09 NR4A3 nuclear receptor subfamily 4_group −6.83504 −2.77295 6.82E−11 A_member 3 FOXC1 forkhead box C1 −6.78684 −2.76274 6.06E−51 VCAN versican −6.7773 −2.76071 6.67E−20 MILR1 mast cell immunoglobulin-like receptor 1 −6.74767 −2.75439 1.29E−07 KLF2 Kruppel-like factor 2 −6.74019 −2.75279 2.40E−150 ESPNL espin-like −6.73748 −2.75221 0.000167 JHDM1D-AS1 JHDM1D antisense RNA 1 (head to head) −6.73137 −2.7509 5.34E−41 CFH complement factor H −6.70659 −2.74558 9.08E−17 MIR4664 microRNA 4664 −6.70241 −2.74468 0.002155 SLC1A1 solute carrier family 1 (neuronal/epithelial high −6.69944 −2.74404 2.47E−45 affinity glutamate transporter_system Xag)_member 1 HOXA-AS3 HOXA cluster antisense RNA 3 −6.67751 −2.73931 8.73E−21 RADIL Ras association and DIL domains −6.66867 −2.7374 2.59E−11 HOXA4 homeobox A4 −6.66258 −2.73608 6.22E−18 NAT2 N-acetyltransferase 2 (arylamine N- −6.64993 −2.73334 0.001906 acetyltransferase) LINC00936 long intergenic non-protein coding RNA 936 −6.6138 −2.72548 1.61E−28 LINC00595 long intergenic non-protein coding RNA 595 −6.60954 −2.72455 7.72E−07 COLEC12 collectin sub-family member 12 −6.60904 −2.72444 1.14E−34 CST6 cystatin E/M −6.59403 −2.72116 8.41E−10 SMOC1 SPARC related modular calcium binding 1 −6.58603 −2.71941 1.06E−12 BEX1 brain expressed_X-linked 1 −6.55884 −2.71344 1.73E−78 ADM2 adrenomedullin 2 −6.55079 −2.71167 2.80E−43 NXPH4 neurexophilin 4 −6.54045 −2.70939 3.69E−35 IL1RL2 interleukin 1 receptor-like 2 −6.52881 −2.70682 5.90E−11 LOC101060542 uncharacterized LOC101060542 −6.52261 −2.70545 0.001517 ENG endoglin −6.51701 −2.70421 3.07E−110 RNLS renalase_FAD-dependent amine oxidase −6.49167 −2.69859 3.94E−23 OLFML3 olfactomedin-like 3 −6.48659 −2.69746 1.13E−28 KLHDC7B kelch domain containing 7B −6.47549 −2.69499 3.22E−12 SLC38A3 solute carrier family 38_member 3 −6.47092 −2.69397 1.15E−10 CRISPLD2 cysteine-rich secretory protein LCCL domain −6.43576 −2.68611 5.56E−22 containing 2 DUSP2 dual specificity phosphatase 2 −6.41158 −2.68068 1.10E−41 PER3 period circadian clock 3 −6.39746 −2.6775 3.51E−25 TYMP thymidine phosphorylase −6.38732 −2.67521 3.10E−35 GSTO2 glutathione S-transferase omega 2 −6.38254 −2.67413 6.70E−56 LOC730102 quinone oxidoreductase-like protein 2 −6.37736 −2.67296 2.98E−80 pseudogene STAC2 SH3 and cysteine rich domain 2 −6.37007 −2.67131 4.20E−16 PMP22 peripheral myelin protein 22 −6.35777 −2.66852 4.22E−47 CCR7 chemokine (C-C motif) receptor 7 −6.35495 −2.66788 4.47E−19 HECW1 HECT_C2 and WW domain containing E3 −6.33265 −2.66281 4.22E−09 ubiquitin protein ligase 1 PKP1 plakophilin 1 −6.32077 −2.6601 6.21E−08 BICC1 BicC family RNA binding protein 1 −6.30488 −2.65647 3.68E−11 C11orf87 chromosome 11 open reading frame 87 −6.27715 −2.65011 1.73E−10 ANKH ANKH inorganic pyrophosphate transport −6.27311 −2.64918 2.02E−12 regulator CCPG1 cell cycle progression 1 −6.25517 −2.64505 4.34E−25 NIM1K NIMI serine/threonine protein kinase −6.23474 −2.64033 1.29E−12 ISL2 ISL LIM homeobox 2 −6.23427 −2.64022 3.68E−11 TLR3 toll-like receptor 3 −6.21748 −2.63633 5.43E−09 C2 complement component 2 −6.20031 −2.63234 2.07E−11 ERAP2 endoplasmic reticulum aminopeptidase 2 −6.19296 −2.63063 0.001254 ANKRD2 ankyrin repeat domain 2

(stretch responsive −6.18177 −2.62802 1.59E−05 muscle) EPB41L4B erythrocyte membrane protein band 4.1 like 4B −6.18018 −2.62765 9.12E−16 WFDC1 WAP four-disulfide core domain 1 −6.17248 −2.62585 1.42E−09 PCK2 phosphoenolpyruvate carboxykinase 2 −6.16803 −2.62481 3.91E−40 (mitochondrial) ENPP1 ectonucleotide −6.15146 −2.62093 2.52E−13 pyrophosphatase/phosphodiesterase 1 PRDM1 PR domain containing 1_with ZNF domain −6.14605 −2.61966 1.49E−53 FAM149A family with sequence similarity 149_member −6.14052 −2.61836 1.20E−10 A MIR452 microRNA 452 −6.09565 −2.60778 0.000336 SLC22A23 solute carrier family 22_member 23 −6.09117 −2.60672 2.51E−12 LY6K lymphocyte antigen 6 complex_locus K −6.0611 −2.59958 1.18E−06 CLIC3 chloride intracellular channel 3 −6.05757 −2.59874 3.33E−15 RCAN2 regulator of calcineurin 2 −6.05401 −2.59789 3.03E−11 BEST1 bestrophin 1 −6.04964 −2.59685 1.30E−32 FRK fyn-related Src family tyrosine kinase −6.03846 −2.59418 0.002353 CEBPA CCAAT/enhancer binding protein −6.03373 −2.59305 3.36E−13 (C/EBP)_alpha MROH9 maestro heat-like repeat family member 9 −6.01986 −2.58973 0.000743 RRN3P2 RRN3 homolog_RNA polymerase I −6.01819 −2.58933 2.73E−09 transcription factor pseudogene 2 CASC2 cancer susceptibility candidate 2 (non-protein −6.01098 −2.5876 5.05E−20 coding) TPD52L1 tumor protein D52-like 1 −5.99812 −2.58451 5.88E−10 C5orf49 chromosome 5 open reading frame 49 −5.98948 −2.58243 2.76E−12 SLC16A4 solute carrier family 16_member 4 −5.97807 −2.57968 4.74E−35 ACTC1 actin alpha cardiac muscle 1 −5.9597 −2.57524 4.39E−07 ZMYND12 zinc finger_MYND-type containing 12 −5.95437 −2.57395 3.45E−05 TEX41 testis expressed 41 (non-protein coding) −5.94699 −2.57216 0.003728 ALPK2 alpha-kinase 2 −5.93591 −2.56947 6.22E−18 TIMP4 TIMP metallopeptidase inhibitor 4 −5.9332 −2.56881 1.17E−06 VEGFC vascular endothelial growth factor C −5.92954 −2.56792 2.29E−109 SNX29P2 sorting nexin 29 pseudogene 2 −5.92732 −2.56738 0.000105 DOK1 docking protein 1_62 kDa (downstream of −5.91866 −2.56527 1.07E−31 tyrosine kinase 1) MEIOB meiosis specific with OB domains −5.91689 −2.56484 0.000871 CADPS2 Ca++-dependent secretion activator 2 −5.91427 −2.5642 2.11E−06 LOC729041 NA −5.8972 −2.56003 5.46E−05 QPCT glutaminyl-peptide cyclotransferase −5.89426 −2.55931 1.37E−28 HOXA5 homeobox A5 −5.89393 −2.55923 1.56E−22 SOX18 SRY (sex determining region Y)-box 18 −5.88099 −2.55606 4.33E−11 GOLGA8S golgin A8 family_member S −5.87724 −2.55514 0.008437 EMR2 adhesion G protein-coupled receptor E2 −5.868 −2.55287 0.001436 GOLGA8M golgin A8 family_member M −5.86394 −2.55187 0.001897 LOXL3 lysyl oxidase-like 3 −5.85931 −2.55073 1.05E−25 CD70 CD70 molecule −5.8535 −2.5493 0.000669 CRHR2 corticotropin releasing hormone receptor 2 −5.85204 −2.54894 0.004334 TUSC1 tumor suppressor candidate 1 −5.83742 −2.54533 4.43E−32 OPCML opioid binding protein/cell adhesion molecule- −5.80964 −2.53845 7.19E−05 like RASD1 RAS_dexamethasone-induced 1 −5.78987 −2.53353 2.46E−15 RASIP1 Ras interacting protein 1 −5.77736 −2.53041 0.003568 C8orf34 chromosome 8 open reading frame 34 −5.77396 −2.52956 2.92E−19 LINC00341 long intergenic non-protein coding RNA 341 −5.77043 −2.52868 2.78E−24 THPO thrombopoietin −5.72561 −2.51743 1.25E−05 KRT38 keratin 38_type I −5.71245 −2.51411 0.008435 LOC100506746 uncharacterized LOC100506746 −5.69261 −2.50909 2.59E−10 ACTR3C ARP3 actin-related protein 3 homolog C −5.68878 −2.50812 0.000316 (yeast) GPR78 G protein-coupled receptor 78 −5.67866 −2.50555 0.002572 HAS2-AS1 HAS2 antisense RNA 1 −5.65148 −2.49863 9.77E−20 CACNA1G calcium channel_voltage-dependent_T −5.62588 −2.49208 0.000806 type_alpha 1G subunit C8orf31 chromosome 8 open reading frame 31 −5.62472 −2.49178 1.44E−19 DNAJC6 DnaJ (Hsp40) homolog_subfamily −5.60949 −2.48787 1.16E−20 C_member 6 PSTPIP1 proline-serine-threonine phosphatase −5.60114 −2.48572 1.32E−09 interacting protein 1 WDR96 cilia and flagella associated protein 43 −5.58242 −2.48089 1.59E−05 DMKN dermokine −5.58029 −2.48034 2.46E−06 ASIC4 acid sensing (proton gated) ion channel family −5.57596 −2.47922 8.95E−06 member 4 LOC100132352 NA −5.56955 −2.47756 1.56E−18 CCDC170 coiled-coil domain containing 170 −5.55397 −2.47352 5.97E−15 VEGFA vascular endothelial growth factor A −5.53138 −2.46764 1.95E−13 SLC6A9 solute carrier family 6

(neurotransmitter −5.53119 −2.46759 4.84E−36 transporter_glycine)_member 9 EIF4EBP3 eukaryotic translation initiation factor 4E −5.51362 −2.463 1.18E−06 binding protein 3 MMP2 matrix metallopeptidase 2 −5.50976 −2.46199 6.16E−19 SLC15A3 solute carrier family −5.50923 −2.46185 2.06E−21 15 (oligopeptide transporter)_member 3 MIR3074 microRNA 3074 −5.49504 −2.45813 0.000669 LINC00707 long intergenic non-protein coding RNA 707 −5.48766 −2.45619 0.004664 SNHG5 small nucleolar RNA host gene 5 −5.47478 −2.4528 6.87E−05 IRAK3 interleukin-1 receptor-associated kinase 3 −5.45792 −2.44835 7.59E−26 AK4 adenylate kinase 4 −5.44824 −2.44579 8.23E−19 GALNT1 polypeptide N-acetylgalactosaminyltransferase −5.43526 −2.44235 5.15E−11 1 NR1D1 nuclear receptor subfamily 1_group −5.43255 −2.44163 3.99E−26 D_member 1 SOCS2-AS1 SOCS2 antisense RNA 1 −5.42758 −2.44031 3.48E−10 CLMP CXADR-like membrane protein −5.42382 −2.43931 9.55E−08 LOC101929125 uncharacterized LOC101929125 −5.40416 −2.43407 4.93E−05 ZNF568 zinc finger protein 568 −5.39982 −2.43291 4.37E−64 PTER phosphotriesterase related −5.39925 −2.43276 1.36E−11 GOLGA6L4 golgin A6 family-like 4 −5.39256 −2.43097 1.00E−05 CASP1 caspase 1_apoptosis-related cysteine peptidase −5.39103 −2.43056 3.33E−15 LINC01152 long intergenic non-protein coding RNA 1152 −5.38774 −2.42968 0.000239 EFHD1 EF-hand domain family_member D1 −5.38662 −2.42938 0.000127 TMTC1 transmembrane and tetratricopeptide repeat −5.37588 −2.4265 4.69E−09 containing 1 HOTAIR HOX transcript antisense RNA −5.34882 −2.41922 2.75E−14 PRKD1 protein kinase D1 −5.34804 −2.41901 1.67E−75 LOC102724316 NA −5.31861 −2.41105 3.64E−148 FAM69A family with sequence similarity 69_member A −5.31555 −2.41022 1.23E−95 ODF3L2 outer dense fiber of sperm tails 3-like 2 −5.30963 −2.40861 1.50E−05 LOC101928414 uncharacterized LOC101928414 −5.29808 −2.40547 0.006814 PLCL1 phospholipase C-like 1 −5.29555 −2.40478 9.84E−08 NCF2 neutrophil cytosolic factor 2 −5.27361 −2.39879 2.58E−15 LOC101241902 chromosome 4 open reading frame 46 −5.27046 −2.39793 1.49E−06 pseudogene PRR15 proline rich 15 −5.26802 −2.39726 1.01E−05 SERPINE2 serpin peptidase inhibitor_clade E −5.26685 −2.39694 5.29E−24 (nexin_plasminogen activator inhibitor type 1)_member 2 CYP4V2 cytochrome P450_family 4_subfamily −5.25992 −2.39504 1.24E−15 V_polypeptide 2 DENND2C DENN/MADD domain containing 2C −5.2427 −2.39031 5.92E−07 SBSN suprabasin −5.24263 −2.39029 7.29E−08 PDGFRA platelet-derived growth factor receptor_alpha −5.20862 −2.3809 2.21E−168 polypeptide MYOM1 myomesin 1 −5.19942 −2.37835 4.14E−07 COL6A3 collagen_type VI_alpha 3 −5.19621 −2.37746 6.71E−55 MIR6775 microRNA 6775 −5.18477 −2.37428 0.000735 LINC00921 long intergenic non-protein coding RNA 921 −5.15046 −2.3647 1.26E−14 LINC01352 long intergenic non-protein coding RNA 1352 −5.13232 −2.35961 7.17E−06 NXPH3 neurexophilin 3 −5.12915 −2.35872 6.51E−10 LOC100507557 uncharacterized LOC100507557 −5.12826 −2.35847 7.49E−14 DHRS4L1 dehydrogenase/reductase (SDR family) −5.11906 −2.35588 0.004779 member 4 like 1 TXNRD2 thioredoxin reductase 2 −5.07937 −2.34465 1.58E−31 PCDHA3 protocadherin alpha 3 −5.07779 −2.3442 0.000773 ALDH1A3 aldehyde dehydrogenase 1 family_member A3 −5.0685 −2.34156 1.92E−06 PPFIA2 protein tyrosine phosphatase_receptor type_f −5.06538 −2.34067 4.69E−05 polypeptide (PTPRF)_interacting protein (liprin)_alpha 2 TLE3 transducin-like enhancer of split 3 −5.06183 −2.33966 9.92E−78 CLDN23 claudin 23 −5.05927 −2.33893 0.000316 STEAP1 six transmembrane epithelial antigen of the −5.04544 −2.33498 3.27E−44 prostate 1 ADAMTS9-ADAMTS9 antisense RNA 2 −5.04177 −2.33393 4.23E−06 AS2 ANK2 ankyrin 2_neuronal −5.03583 −2.33223 6.76E−28 FCRLA Fc receptor-like A −5.02004 −2.3277 8.25E−08 UNC5C unc-5 netrin receptor C −5.01017 −2.32486 1.67E−05 ATOH8 atonal bHLH transcription factor 8 −5.0049 −2.32334 6.40E−56

TABLE-US-00005 TABLE 5 Genes more highly expressed in HMCs compared to UCB-MSCs Log Fold Fold Name Description Change Change p-Value LRRN1 leucine rich repeat neuronal 1 3423.37 11.7412 7.84E−104 NKX2-5 NK2 homeobox 5 1581.96 10.6275 6.39E−97 IGFBP2 insulin-like growth factor binding 1184.37 10.2099 2.47E−103 protein 2_ 36 kDa DCC DCC netrin

1 receptor 891.771 9.80053 1.60E−76 NETO1 neuropilin (NRP) and tolloid 852.709 9.73591
3.52E−68 (TLL)-like 1 IGSF1 immunoglobulin superfamily_ member 1 611.14 9.25536 7.03E−52
LOC440416 NA 540.215 9.07739 3.70E−139 FLJ16779 uncharacterized LOC100192386 430.748
8.7507 3.08E−52 NKAIN4 Na+/K+ transporting ATPase interacting 369.492 8.5294 9.57E−49 4
OCA2 oculocutaneous albinism II 359.59 8.49021 2.24E−89 NLGN4X neuroligin 4_ X-linked
350.92 8.455 1.14E−41 RSPO4 R-spondin 4 313.369 8.29172 2.78E−76 LIN28B lin-28 homolog
B (C. elegans) 307.263 8.26333 2.37E−52 KCTD8 potassium channel tetramerization 297.083
8.21472 1.55E−48 domain containing 8 IRX2 iroquois homeobox 2 237.351 7.89088 1.80E−48
PLAC8 placenta-specific 8 207.368 7.69605 2.30E−74 CLSTN2 calsyntenin 2 201.99 7.65814
4.29E−113 CACNG4 calcium channel_ voltage-dependent_ 174.326 7.44564 5.03E−71 gamma
subunit 4 PHOX2A paired-like homeobox 2a 169.602 7.40601 2.70E−36 ITGA8 integrin_ alpha 8
169.257 7.40307 4.76E−40 CHRDL1 chordin-like 1 159.108 7.31386 2.02E−44 UNC5C unc-5
netrin receptor C 150.173 7.23048 7.96E−46 NLRP2 NLR family_ pyrin domain containing 2
147.386 7.20346 3.25E−30 PRAC1 prostate cancer susceptibility candidate 1 136.827 7.09621
3.19E−25 PCDHB2 protocadherin beta 2 130.227 7.02488 3.62E−25 TRPC5 transient receptor
potential cation 127.06 6.98937 3.76E−30 channel_ subfamily C_ member 5 PPARGC1A
peroxisome proliferator-activated 124.471 6.95967 4.68E−32 receptor gamma_ coactivator 1 alpha
NRK Nik related kinase 122.669 6.93863 5.98E−41 ABCB1 ATP-binding cassette_ sub-family B
122.107 6.932 2.34E−39 (MDR/TAP)_ member 1 PALM paralemmin 112.71 6.81647 2.44E−94
LRRTM1 leucine rich repeat transmembrane 112.66 6.81583 1.31E−68 neuronal 1 LOC642366
uncharacterized LOC642366 109.152 6.77019 7.96E−38 KCNK3 potassium channel_ two pore
domain 107.071 6.74242 5.85E−41 subfamily K_ member 3 SIX1 SIX homeobox 1 105.882
6.72631 1.43E−71 SLC44A5 solute carrier family 44_ member 5 105.792 6.72509 3.28E−75
OVCH2 ovochymase 2 (gene/pseudogene) 105.433 6.72018 2.03E−45 PRDM16 PR domain
containing 16 104.665 6.70963 2.54E−63 MGAM maltase-glucoamylase 100.991 6.65809
1.29E−46 GCNT2 glucosaminyl (N-acetyl) transferase 2_ 99.6577 6.63891 5.38E−48 I-branching
enzyme (I blood group) TNRC6C- TNRC6C antisense RNA 1 99.3178 6.63398 1.80E−33 AS1
ANO1 anoctamin 1_calcium activated chloride 97.8208 6.61207 3.23E−44 channel GATA3-
GATA3 antisense RNA 1 97.6731 6.60989 1.41E−29 AS1 EBF3 early B-cell factor 3 95.5471
6.57814 5.38E−33 SPINK5 serine peptidase inhibitor_ Kazal type 5 91.5539 6.51655 6.26E−18
FXYD6 FXYD domain containing ion transport 86.0701 6.42744 1.97E−22 regulator 6 SLITRK1
SLIT and NTRK-like family_ member 1 84.3333 6.39803 2.73E−28 DPPA4 developmental
pluripotency associated 4 83.2928 6.38012 2.54E−16 NKX2-6 NK2 homeobox 6 77.2391 6.27126
9.65E−21 SYT13 synaptotagmin XIII 75.1088 6.23091 2.59E−17 LGR5 leucine-rich repeat
containing G protein- 74.3515 6.21629 1.30E−16 coupled receptor 5 LHX2 LIM homeobox 2
73.4001 6.19771 1.19E−30 CYTIP cytohesin 1 interacting protein 72.9805 6.18944 4.02E−19
BMP2 bone morphogenetic protein 2 72.9274 6.18839 2.01E−33 CST1 cystatin SN 71.2699
6.15522 1.75E−18 AFF3 AF4/FMR2 family_ member 3 70.7339 6.14433 4.25E−45 TMEM132B
transmembrane protein 132B 66.6337 6.05818 1.53E−33 ADAMTS18 ADAM metallopeptidase
with 65.9833 6.04403 1.11E−27 thrombospondin type 1 motif_ 18 C8orf4 chromosome 8 open
reading frame 4 65.9737 6.04382 5.03E−27 CDH10 cadherin 10_ type 2 (T2-cadherin) 64.672
6.01507 2.27E−20 PDE1C phosphodiesterase 1C_ calmodulin- 64.3452 6.00776 1.34E−91
dependent 70 kDa PLCXD3 phosphatidylinositol-specific 63.3025 5.98419 3.70E−17
phospholipase C_ X domain containing 3 SH2D3C SH2 domain containing 3C 63.288 5.98386
5.85E−27 P2RY14 purinergic receptor P2Y_ G-protein 62.0216 5.9547 7.33E−17 coupled_ 14 VIT
vitrin 61.9138 5.95219 1.55E−29 TLR4 toll-like receptor 4 61.5135 5.94283 1.08E−28 PKIB
protein kinase (cAMP-dependent_ 61.1347 5.93392 5.81E−30 catalytic) inhibitor beta C5orf38
chromosome 5 open reading frame 38 60.5666 5.92045 3.12E−23 KCNA1 potassium channel_
voltage gated shaker 60.5552 5.92018 9.27E−20 related subfamily A_ member 1 CDH3 cadherin
3_ type 1_ P-cadherin 58.9647 5.88178 4.90E−23 (placental) CD24 CD24 molecule 58.1703

5.86221 1.21E−27 PCDHA12 protocadherin alpha 12 57.8257 5.85364 3.85E−17 LINC00491 long intergenic non-protein coding RNA 56.8741 5.8297 9.86E−16 491 COL22A1 collagen_ type XXII_ alpha 1 56.2589 5.81401 6.75E−16 LHX1 LIM homeobox 1 55.9249 5.80542 4.65E−21 CYP27C1 cytochrome P450_ family 27_ subfamily 55.3101 5.78947 1.14E−14 C_ polypeptide 1 CRHBP corticotropin releasing hormone binding 53.735 5.74779 3.46E−16 protein RERG RAS-like_ estrogen-regulated_ growth 53.574 5.74346 2.81E−21 inhibitor LOC644919 uncharacterized LOC644919 52.9644 5.72695 1.01E−28 FRMPD3 FERM and PDZ domain containing 3 52.182 5.70548 6.36E−29 GABRG3 gamma-aminobutyric acid (GABA) A 51.9283 5.69845 8.06E−15 receptor_ gamma 3 CHST15 carbohydrate (N-acetylgalactosamine 4- 51.5446 5.68775 9.64E−69 sulfate 6-O) sulfotransferase 15 C14orf39 chromosome 14 open reading frame 39 51.4707 5.68568 1.34E−32 SLC5A12 solute carrier family 5 50.7533 5.66543 6.50E−28 (sodium/monocarboxylate cotransporter)_ member 12 ST8SIA2 ST8 alpha-N-acetyl-neuraminide alpha- 50.7101 5.6642 2.57E−15 2_8-sialyltransferase 2 SFRP1 secreted frizzled-related protein 1 48.7693 5.6079 1.72E−51 SLCO6A1 solute carrier organic anion transporter 48.3763 5.59623 1.56E−13 family_ member 6A1 KIAA0040 KIAA0040 48.2565 5.59265 3.37E−16 FBP2 fructose-1_6-bisphosphatase 2 48.0722 5.58713 1.41E−20 ANKRD1 ankyrin repeat domain 1 (cardiac 47.3197 5.56437 3.90E−29 muscle) TMEM40 transmembrane protein 40 47.1841 5.56023 1.11E−27 SLC1A7 solute carrier family 1 (glutamate 46.3199 5.53356 6.47E−25 transporter)_ member 7 PODN podocan 46.2856 5.53249 5.78E−87 SFMBT2 Scm-like with four mbt domains 2 46.1078 5.52694 2.44E−28 NKX3-2 NK3 homeobox 2 45.6483 5.51249 4.78E−22 SHC2 SHC (Src homology 2 domain 45.3695 5.50365 6.32E−54 containing) transforming protein 2 SLCO2A1 solute carrier organic anion transporter 44.7573 5.48405 3.12E−23 family_ member 2A1 MYCT1 myc target 1 44.739 5.48346 1.75E−22 FIRRE firre intergenic repeating RNA element 43.2066 5.43318 2.76E−15 TNNI1 troponin I type 1 (skeletal_ slow) 42.8853 5.42241 2.00E−23 BCL11B B-cell CLL/lymphoma 11B (zinc finger 42.833 5.42065 2.47E−14 protein) ISL1 ISL LIM homeobox 1 42.4758 5.40857 2.02E−12 CLEC1A C-type lectin domain family 1_ member 42.2799 5.4019 5.81E−13 A TSPAN11 tetraspanin 11 41.6233 5.37932 1.52E−37 KRTAP1-1 keratin associated protein 1-1 41.5841 5.37796 1.11E−23 HS6ST2 heparan sulfate 6-O-sulfotransferase 2 41.4563 5.37352 1.08E−21 PCDHA4 protocadherin alpha 4 40.8944 5.35383 5.99E−17 WSCD1 WSC domain containing 1 40.5031 5.33996 6.93E−22 MED15P9 mediator complex subunit 15 39.4893 5.30339 3.88E−11 pseudogene 9 PLP1 proteolipid protein 1 39.4054 5.30032 4.24E−21 NIPAL4 NIPA-like domain containing 4 39.3494 5.29827 1.36E−59 FAR2P1 fatty acyl CoA reductase 2 pseudogene 1 39.2938 5.29623 4.11E−11 LINC01096 long intergenic non-protein coding RNA 38.8828 5.28106 7.17E−14 1096 MMP9 matrix metallopeptidase 9 38.4633 5.26541 1.22E−50 VAV3 vav 3 guanine nucleotide exchange 38.3209 5.26006 8.17E−19 factor C7 complement component 7 38.2986 5.25922 2.82E−18 TBX15 T-box 15 37.8573 5.2425 4.62E−19 CASC9 cancer susceptibility candidate 9 (non- 37.6386 5.23414 3.36E−15 protein coding) DIO2 deiodinase_ iodothyronine_ type II 36.187 5.1774 2.13E−67 LIPG lipase_ endothelial 36.1381 5.17545 3.51E−58 GCNT4 glucosaminyl (N-acetyl) transferase 4_ 36.0191 5.17069 1.91E−24 core 2 MYH14 myosin_ heavy chain 14_ non-muscle 35.5979 5.15372 6.48E−15 A2M alpha-2-macroglobulin 35.1412 5.13509 4.63E−16 LINC01021 long intergenic non-protein coding RNA 34.8127 5.12154 2.04E−23 1021 FAM65B family with sequence similarity 65_ 34.4156 5.10499 7.07E−43 member B GNA14 guanine nucleotide binding protein (G 34.2393 5.09758 2.18E−36 protein)_ alpha 14 FAT3 FAT atypical cadherin 3 33.7873 5.07841 2.67E−22 LINC00982 long intergenic non-protein coding RNA 33.7057 5.07492 1.23E−12 982 TCEAL2 transcription elongation factor A (SII)- 33.0111 5.04488 2.67E−17 like 2 ZCCHC16 zinc finger_ CCHC domain containing 32.9462 5.04204 6.15E−12 16 GPR112 adhesion G protein-coupled receptor G4 32.5887 5.0263 2.27E−11 PCDHB4 protocadherin beta 4 31.9594 4.99817 3.18E−18 CACNA1H calcium channel_ voltage-dependent_ T 31.9406 4.99732 9.26E−41 type_alpha 1H subunit SCARF1 scavenger receptor class F_ member 1 31.5437 4.97928 3.39E−90

SHISA3 shisa family member 3 31.1437 4.96087 5.28E−15 KCNF1 potassium channel_ voltage gated 30.8845 4.94881 1.67E−15 modifier subfamily F_ member 1 B3GAT1 beta-1_3-glucuronyltransferase 1 30.6098 4.93592 3.57E−20 EXOC3L2 exocyst complex component 3-like 2 30.5731 4.93419 9.95E−36 TRIM55 tripartite motif containing 55 30.4766 4.92963 5.00E−118 PLXDC1 plexin domain containing 1 30.4333 4.92758 1.81E−26 TBX1 T-box 1 30.343 4.92329 8.72E−30 SMOC1 SPARC related modular calcium binding 30.1614 4.91463 2.44E−17 1 EFHD1 EF-hand domain family_ member D1 29.6463 4.88978 4.18E−27 CD93 CD93 molecule 29.3736 4.87645 2.59E−14 KISS1 KiSS-1 metastasis-suppressor 28.5813 4.837 4.19E−12 OR10A3 olfactory receptor_ family 10_ 28.1094 4.81298 4.22E−10 subfamily A_ member 3 LRRC4C leucine rich repeat containing 4C 27.9941 4.80705 7.72E−18 BEX1 brain expressed_ X-linked 1 26.7397 4.74091 9.64E−24 TNNT2 troponin T type 2 (cardiac) 26.4701 4.72629 2.05E−21 RBM20 RNA binding motif protein 20 25.9298 4.69654 2.80E−25 TMC6 transmembrane channel-like 6 25.8548 4.69236 1.86E−27 TMEM200C transmembrane protein 200C 25.7952 4.68903 2.92E−12 LINGO1 leucine rich repeat and Ig domain 25.5052 4.67272 1.30E−100 containing 1 CNNM1 cyclin and CBS domain divalent metal 25.5017 4.67252 1.63E−28 cation transport mediator 1 PCDHA11 protocadherin alpha 11 24.9492 4.64092 7.22E−10 FAM19A5 family with sequence similarity 19 24.8579 4.63563 4.90E−20 (chemokine (C-C motif)-like)_ member A5 DACT2 dishevelled-binding antagonist of beta- 24.8207 4.63347 2.24E−09 catenin 2 BRINP1 bone morphogenetic protein/retinoic 24.5667 4.61863 4.07E−10 acid inducible neural-specific 1 CDH5 cadherin 5_ type 2 (vascular 24.4423 4.61131 1.18E−09 endothelium) ZMAT1 zinc finger_ matrin-type 1 24.4046 4.60908 6.07E−14 SHISA2 shisa family member 2 24.293 4.60247 5.61E−17 NUTM2F NUT family member 2F 24.1311 4.59282 4.34E−10 NNAT neuronatin 23.7076 4.56728 1.98E−30 LGI1 leucine-rich_ glioma inactivated 1 23.391 4.54788 5.91E−13 MAP2 microtubule-associated protein 2 23.3814 4.54729 6.52E−74 KC6 keratoconus gene 6 23.3338 4.54435 1.16E−14 LPPR3 lipid phosphate phosphatase-related 23.2252 4.53762 8.02E−25 protein type 3 PARVG parvin_gamma 22.8769 4.51582 6.30E−11 EXTL 1 exostosin-like glycosyltransferase 1 22.7777 4.50955 3.33E−26 BAI3 adhesion G protein-coupled receptor B3 22.6455 4.50115 1.26E−13 ITIH3 inter-alpha-trypsin inhibitor heavy chain 22.6251 4.49985 1.71E−35 3 LOC339166 uncharacterized LOC339166 22.4073 4.4859 5.90E−12 GJA5 gap junction protein_alpha 5_40 kDa 22.3805 4.48417 2.27E−09 TTR transthyretin 22.3757 4.48386 4.57E−10 LOC440910 uncharacterized LOC440910 22.3751 4.48382 1.60E−08 NOVA1 neuro-oncological ventral antigen 1 22.1041 4.46624 4.48E−09 PCDH17 protocadherin 17 22.0883 4.46521 1.44E−12 ERP27 endoplasmic reticulum protein 27 21.8318 4.44836 2.90E−15 SLC37A1 solute carrier family 37 (glucose-6- 21.6711 4.4377 1.39E−33 phosphate transporter)_ member 1 MMP23B matrix metallopeptidase 23B 21.3419 4.41562 7.23E−22 SHOX2 short stature homeobox 2 21.0896 4.39846 6.22E−14 PDE9A phosphodiesterase 9A 20.9168 4.38659 8.62E−14 GPR37 G protein-coupled receptor 37 20.6854 4.37054 2.43E−16 (endothelin receptor type B-like) KRTAP4- keratin associated protein 4-12 20.5994 4.36453 1.38E−09 12 ABCB4 ATP-binding cassette_ sub-family B 20.596 4.36429 7.71E−14 (MDR/TAP)_ member 4 LOC283299 uncharacterized LOC283299 20.5908 4.36393 7.84E−11 CXXC4 CXXC finger protein 4 20.5032 4.35778 4.39E−12 LOC101928340 NA 20.221 4.33778 3.54E−08 GRIN2A glutamate receptor_ ionotropic_N- 20.0934 4.32865 7.56E−09 methyl D-aspartate 2A FCGBP Fc fragment of IgG binding protein 20.0563 4.32598 5.12E−16 LOC102467080 uncharacterized LOC102467080 20.0368 4.32458 7.29E−32 KIT v-kit Hardy-Zuckerman 4 feline sarcoma 19.7848 4.30632 1.51E−14 viral oncogene homolog ANO5 anoctamin 5 19.7803 4.30599 3.21E−08 SALL1 spalt-like transcription factor 1 19.6367 4.29548 1.26E−19 EMCN endomucin 19.4577 4.28227 6.72E−10 PLXNA4 plexin A4 19.3804 4.27653 7.04E−24 NR0B1 nuclear receptor subfamily 0_ group B_ 19.2784 4.26891 1.26E−08 member 1 MDGA2 MAM domain containing 19.1619 4.26017 2.68E−24 glycosylphosphatidylinositol anchor 2 FAM49A family with sequence similarity 49_ 19.0858 4.25443 4.32E−58 member A KSR2 kinase suppressor of ras 2 18.8714 4.23813

4.77E−09 AIF1L allograft inflammatory factor 1-like 18.8237 4.23448 2.05E−21 DAAM2 dishevelled associated activator of 18.6607 4.22193 2.05E−45 morphogenesis 2 IGDCC3 immunoglobulin superfamily_ DCC 18.5723 4.21508 1.08E−10 subclass_ member 3 GDF7 growth differentiation factor 7 18.421 4.20328 3.48E−08 MGAT4C MGAT4 family_ member C 18.3217 4.19548 1.72E−08 LDB3 LIM domain binding 3 18.287 4.19275 1.11E−40 DENND2A DENN/MADD domain containing 2A 18.2434 4.1893 3.62E−27 OR5E1P olfactory receptor_ family 5_ subfamily 18.1705 4.18353 4.88E−09 E_ member 1 pseudogene SYTL5 synaptotagmin-like 5 18.1419 4.18125 8.91E−19 TNFSF18 tumor necrosis factor (ligand) 18.1251 4.17992 1.85E−11 superfamily_ member 18 RELN reelin 17.9466 4.16564 5.93E−14 IRX1 iroquois homeobox 1 17.9075 4.16249 1.27E−07 LARGE like-glycosyltransferase 17.8339 4.15655 1.82E−39 FAM69B family with sequence similarity 69_ 17.7295 4.14808 1.72E−47 member B SULT1C4 sulfotransferase family_ cytosolic_ 1C_ 17.4646 4.12636 2.56E−07 member 4 EMID1 EMI domain containing 1 17.2871 4.11162 1.05E−20 MGAT3 mannosyl (beta-1_4-)-glycoprotein beta- 17.2126 4.10539 9.53E−45 1_4-N-acetylglucosaminyltransferase ILDR2 immunoglobulin-like domain containing 16.8161 4.07177 4.49E−08 receptor 2 PLCB2 phospholipase C_ beta 2 16.794 4.06987 9.31E−33 EPCAM epithelial cell adhesion molecule 16.6721 4.05936 2.18E−19 EPB41L3 erythrocyte membrane protein band 4.1- 16.6397 4.05656 6.17E−13 like 3 LICAM L1 cell adhesion molecule 16.6355 4.05619 8.47E−30 BEX5 brain expressed_ X-linked 5 16.586 4.05189 1.99E−07 GFRA2 GDNF family receptor alpha 2 16.5833 4.05166 1.29E−08 DLX5 distal-less homeobox 5 16.5784 4.05123 1.62E−07 DLX1 distal-less homeobox 1 16.5368 4.04761 7.18E−31 GRIA1 glutamate receptor_ ionotropic_ AMPA 16.5334 4.04731 7.77E−11 1 GRAP GRB2-related adaptor protein 16.4563 4.04057 2.92E−19 BBOX1 butyrobetaine (gamma)_ 2-oxoglutarate 16.3933 4.03503 7.12E−09 dioxygenase (gamma-butyrobetaine hydroxylase) 1 ADAMTS20 ADAM metallopeptidase with 16.3915 4.03488 7.59E−12 thrombospondin type 1 motif_ 20 CXCL12 chemokine (C-X-C motif) ligand 12 16.3253 4.02904 4.11E−138 UNC13A unc-13 homolog A (C. elegans) 16.2647 4.02367 1.32E−14 RGS1 regulator of G-protein signaling 1 16.2524 4.02258 5.09E−07 DLX6 distal-less homeobox 6 16.1897 4.017 5.02E−07 GRB14 growth factor receptor-bound protein 14 16.1678 4.01505 4.61E−15 HUNK hormonally up-regulated Neu-associated 15.9866 3.99879 6.11E−14 kinase HEPH hephaestin 15.8794 3.98908 4.82E−07 SLC6A16 solute carrier family 6_ member 16 15.8359 3.98513 1.45E−22 RGMA repulsive guidance molecule family 15.6927 3.97202 8.19E−18 member a GPR87 G protein-coupled receptor 87 15.6778 3.97065 8.41E−26 PADI2 peptidyl arginine deiminase_ type II 15.645 3.96763 4.81E−15 PTPN6 protein tyrosine phosphatase_ non- 15.6183 3.96517 2.28E−20 receptor type 6 SUCNR1 succinate receptor 1 15.5191 3.95597 6.46E−07 PALMD palmdelphin 15.5141 3.95551 1.40E−49 MERTK MER proto-oncogene_ tyrosine kinase 15.509 3.95503 5.72E−14 KCNC3 potassium channel_ voltage gated Shaw 15.4779 3.95214 7.69E−11 related subfamily C_ member 3 PCDHB3 protocadherin beta 3 15.4368 3.9483 6.91E−09 CILP2 cartilage intermediate layer protein 2 15.2364 3.92945 1.66E−32 MAF v-maf avian musculoaponeurotic 15.2303 3.92887 8.06E−17 fibrosarcoma oncogene homolog NTRK2 neurotrophic tyrosine kinase_ receptor_ 15.1355 3.91986 1.08E−07 type 2 SEMA3E sema domain_immunoglobulin domain 15.0925 3.91576 6.08E−10 (Ig)_ short basic domain_ secreted_ (semaphorin) 3E C21orf90 TSPEAR antisense RNA 2 15.0718 3.91378 1.82E−12 PCDHB9 protocadherin beta 9 15.0096 3.90781 6.79E−14 SIX2 SIX homeobox 2 14.933 3.90043 1.73E−07 CALY calcyon neuron-specific vesicular 14.8895 3.89622 9.05E−19 protein PCAT1 prostate cancer associated transcript 1 14.6893 3.87669 4.25E−08 (non-protein coding) GPRC5C G protein-coupled receptor_ class C_ 14.6602 3.87383 3.58E−07 group 5_member C NRN1 neuritin 1 14.6458 3.87242 1.36E−11 RIMS1 regulating synaptic membrane 14.6198 3.86985 2.43E−22 exocytosis 1 LINC01012 long intergenic non-protein coding RNA 14.5829 3.86621 6.92E−09 1012 SH3GL2 SH3-domain GRB2-like 2 14.5492 3.86287 5.63E−09 SYT3 synaptotagmin III 14.5396 3.86192 3.33E−12 IL1RAPL1 interleukin 1 receptor accessory protein- 14.538 3.86176 4.34E−13 like 1 PART1

prostate androgen-regulated transcript 1 14.5131 3.85928 9.40E−12 (non-protein coding) PCDHB10 protocadherin beta 10 14.4383 3.85183 4.97E−17 SRSF12 serine/arginine-rich splicing factor 12 14.4059 3.84859 4.43E−16 TRH thyrotropin-releasing hormone 14.405 3.8485 1.44E−06 EPHB1 EPH receptor B1 14.3437 3.84235 3.08E−13 CD70 CD70 molecule 14.1423 3.82194 1.66E−06 SPP1 secreted phosphoprotein 1 14.1278 3.82046 7.35E−19 DOC2GP double C2-like domains_ gamma_ 14.0595 3.81347 4.24E−10 pseudogene TSPEAR- TSPEAR antisense RNA 1 14.0479 3.81228 4.84E−31 AS1 THBD thrombomodulin 14.0129 3.80868 1.12E−10 RGS5 regulator of G-protein signaling 5 14.0103 3.80842 1.90E−40 CYP26B1 cytochrome P450_ family 26_ subfamily 13.9621 3.80344 3.95E−15 B_ polypeptide 1 LINC01139 long intergenic non-protein coding RNA 13.882 3.79514 1.74E−20 1139 NAPIL2 nucleosome assembly protein 1-like 2 13.8587 3.79272 2.85E−10 MTUS1 microtubule associated tumor suppressor 13.7747 3.78395 3.49E−09 1 DSP desmoplakin 13.7042 3.77655 2.30E−31 AR androgen receptor 13.6558 3.77144 1.35E−28 COL4A3 collagen_ type IV_ alpha 3 13.5989 3.76542 1.62E−19 (Goodpasture antigen) PTH1R parathyroid hormone 1 receptor 13.588 3.76426 3.24E−11 CELSR1 cadherin_ EGF LAG seven-pass G-type 13.4867 3.75347 6.06E−22 receptor 1 CCND2 cyclin D2 13.4595 3.75055 6.45E−07 LINC00951 long intergenic non-protein coding RNA 13.4392 3.74838 2.58E−06 951 AZU1 azurocidin 1 13.4366 3.7481 8.77E−10 SULT1C2 sulfotransferase family_ cytosolic_ 1C_ 13.4353 3.74796 2.68E−06 member 2 LPAR4 lysophosphatidic acid receptor 4 13.4176 3.74606 8.11E−12 INA internexin neuronal intermediate 13.3079 3.73421 5.90E−76 filament protein_ alpha MYOZ3 myozenin 3 13.1452 3.71646 6.32E−75 AQP7P3 aquaporin 7 pseudogene 3 13.0872 3.71009 3.62E−07 FOXC1 forkhead box C1 13.0634 3.70746 2.10E−53 LRRC7 leucine rich repeat containing 7 13.0529 3.7063 1.25E−08 FZD3 frizzled class receptor 3 13.0287 3.70362 7.46E−27 NCALD neurocalcin delta 12.9782 3.69802 4.24E−13 LSAMP- LSAMP antisense RNA 1 12.9224 3.6918 3.76E−06 AS1 IRX4 iroquois homeobox 4 12.8313 3.6816 1.79E−06 PURG purine-rich element binding protein G 12.8256 3.68095 6.03E−10 AMH anti-Mullerian hormone 12.7728 3.675 1.24E−21 RIPPLY3 ripply transcriptional repressor 3 12.6992 3.66667 2.22E−08 LOC101927482 uncharacterized LOC101927482 12.6952 3.66621 1.78E−15 C1orf94 chromosome 1 open reading frame 94 12.664 3.66266 8.39E−07 FOXA1 forkhead box A1 12.6375 3.65964 3.26E−07 FSTL5 follistatin-like 5 12.6272 3.65846 4.81E−08 KCNJ2 potassium channel_ inwardly rectifying 12.5831 3.65341 1.16E−07 subfamily J_ member 2 XIRP1 xin actin binding repeat containing 1 12.4469 3.63772 1.58E−06 TMEM246 transmembrane protein 246 12.3385 3.62509 2.04E−11 LIPH lipase_ member H 12.2843 3.61874 5.47E−06 AQP7P1 aquaporin 7 pseudogene 1 12.1751 3.60586 2.31E−09 CASKIN1 CASK interacting protein 1 12.1053 3.59757 3.92E−15 ACHE acetylcholinesterase (Yt blood group) 12.0642 3.59266 1.51E−17 C14orf105 chromosome 14 open reading frame 105 12.0171 3.58702 5.90E−06 TNFRSF10C tumor necrosis factor receptor 11.8486 3.56665 8.74E−46 superfamily_ member 10c_ decoy without an intracellular domain FAM43B family with sequence similarity 43_ 11.7047 3.54901 5.63E−10 member B CBLN2 cerebellin 2 precursor 11.6961 3.54795 9.91E−06 FRZB frizzled-related protein 11.6693 3.54465 2.01E−47 PTCHD4 patched domain containing 4 11.6421 3.54128 6.59E−16 DMRTA1 DMRT-like family A1 11.6186 3.53836 6.83E−16 ZSCAN1 zinc finger and SCAN domain 11.609 3.53717 4.18E−08 containing 1 EPHA7 EPH receptor A7 11.5942 3.53533 3.06E−07 GABRA4 gamma-aminobutyric acid (GABA) A 11.5797 3.53353 3.25E−06 receptor_ alpha 4 AFAP1L2 actin filament associated protein 1-like 2 11.5445 3.52914 2.57E−11 RAPIGAP2 RAP1 GTPase activating protein 2 11.44 3.51602 4.39E−15 CSDC2 cold shock domain containing C2_ RNA 11.4326 3.51508 5.86E−15 binding CGB8 chorionic gonadotropin_beta 11.3511 3.50476 1.28E−08 polypeptide 8 ARHGEF16 Rho guanine nucleotide exchange factor 11.3114 3.4997 2.42E−17 (GEF) 16 PCDH1 protocadherin 1 11.2726 3.49475 1.68E−17 NPPC natriuretic peptide C 11.2664 3.49396 1.28E−06 ANGPTL4 angiopoietin-like 4 11.2516 3.49206 4.55E−35 ATP2B2 ATPase_ Ca++ transporting_ plasma 11.1335 3.47684 9.53E−10 membrane 2 RNF182 ring finger protein 182 11.1267 3.47595 1.49E−10 CCDC160 coiled-coil domain containing 160 11.0566

3.46683 6.35E−12 DACH2 dachshund family transcription factor 2 11.0356 3.46409 2.10E−06 PTPRN2 protein tyrosine phosphatase_ receptor 11.0305 3.46342 6.05E−07 type_ N polypeptide 2 IGFBP5 insulin-like growth factor binding 11.0117 3.46097 1.68E−06 protein 5 COL4A4 collagen_ type IV_ alpha 4 11.0069 3.46033 6.39E−108 TMEM74B transmembrane protein 74B 10.9141 3.44812 2.86E−09 OCLN occludin 10.9085 3.44738 7.88E−18 PTGIS prostaglandin I2 (prostacyclin) synthase 10.8909 3.44505 4.07E−17 CIDEA cell death-inducing DFFA-like effector a 10.8757 3.44303 3.21E−07 VANGL2 VANGL planar cell polarity protein 2 10.8126 3.43464 2.88E−06 DOCK8 dedicator of cytokinesis 8 10.7905 3.43169 1.37E−06 CCDC88C coiled-coil domain containing 88C 10.7762 3.42978 1.47E−08 NMNAT3 nicotinamide nucleotide 10.7424 3.42524 1.21E−20 adenylyltransferase 3 TCF15 transcription factor 15 (basic helix-loop- 10.7253 3.42295 1.61E−07 helix) ITGB6 integrin_ beta 6 10.6645 3.41475 7.14E−08 SCUBE3 signal peptide_CUB domain_ EGF-like 10.622 3.40899 5.25E−30 3 SOX17 SRY (sex determining region Y)-box 17 10.6119 3.40761 2.79E−06 IL2RB interleukin 2 receptor_ beta 10.6028 3.40637 7.12E−29 ATCAY ataxia_ cerebellar_ Cayman type 10.5981 3.40573 8.13E−07 FMN1 formin 1 10.5973 3.40562 2.24E−36 EFNA2 ephrin-A2 10.5791 3.40314 1.56E−08 MAGEB17 melanoma antigen family B17 10.5548 3.39983 2.63E−06 CERS1 ceramide synthase 1 10.5375 3.39746 3.22E−09 DLK1 delta-like 1 homolog (Drosophila) 10.5276 3.39611 5.93E−11 DCHS1 dachsous cadherin-related 1 10.5002 3.39234 2.11E−108 SFTAIP surfactant associated 1_ pseudogene 10.3743 3.37494 1.05E−20 FOXG1 forkhead box G1 10.3464 3.37105 2.17E−05 ADAMTS7P1 ADAMTS7 pseudogene 1 10.3038 3.3651 2.14E−08 LEMD1- LEMD 1 antisense RNA 1 10.2887 3.36299 6.84E−08 AS1 C6orf141 chromosome 6 open reading frame 141 10.1422 3.3423 1.99E−14 EDN1 endothelin 1 10.1099 3.3377 8.53E−77 RAB9B RAB9B_ member RAS oncogene family 10.1049 3.33698 1.44E−32 SLC29A2 solute carrier family 29 (equilibrative 10.0911 3.33501 3.03E−28 nucleoside transporter)_ member 2 GABRA5 gamma-aminobutyric acid (GABA) A 10.09 3.33486 8.12E−06 receptor_ alpha 5 RIMBP2 RIMS binding protein 2 10.0289 3.32609 4.37E−06 HTR1D 5-hydroxytryptamine (serotonin) 10.0216 3.32504 1.09E−17 receptor 1D_ G protein-coupled GAL3ST3 galactose-3-O-sulfotransferase 3 9.99031 3.32053 4.84E−09 OXTR oxytocin receptor 9.97952 3.31897 8.27E−11 SESN3 sestrin 3 9.97647 3.31853 8.95E−11 CCDC148 coiled-coil domain containing 148 9.92199 3.31063 1.51E−15 EPHA5 EPH receptor A5 9.84984 3.3001 4.99E−08 CTTNBP2 cortactin binding protein 2 9.84806 3.29984 1.31E−11 NLRP10 NLR family_ pyrin domain containing 9.83285 3.29761 6.88E−08 10 ANO4 anoctamin 4 9.81113 3.29442 1.05E−10 KLHL6 kelch-like family member 6 9.78275 3.29024 4.00E−05 ALPK3 alpha-kinase 3 9.782 3.29013 1.59E−25 THRB thyroid hormone receptor_ beta 9.77116 3.28853 3.43E−05 TMEM63C transmembrane protein 63C 9.76168 3.28713 1.95E−42 MLN motilin 9.75086 3.28553 5.19E−06 LINC01082 long intergenic non-protein coding RNA 9.74789 3.28509 3.83E−05 1082 GBX2 gastrulation brain homeobox 2 9.63377 3.2681 1.35E−05 PCYT1B phosphate cytidylyltransferase 1_ 9.59964 3.26298 8.46E−13 choline_ beta KRTAP4-9 keratin associated protein 4-9 9.55569 3.25636 5.02E−05 LOC90246 uncharacterized LOC90246 9.53148 3.2527 1.42E−28 PCDH19 protocadherin 19 9.51511 3.25022 1.59E−09 PCDHGB6 protocadherin gamma subfamily B_ 6 9.49593 3.24731 1.93E−10 FAM92B family with sequence similarity 92_ 9.43459 3.23796 1.44E−05 member B NTN4 netrin 4 9.42825 3.23699 6.41E−12 TPSG1 tryptase gamma 1 9.3604 3.22657 4.47E−05 PCDHA9 protocadherin alpha 9 9.32536 3.22116 5.91E−05 FAM110D family with sequence similarity 110_ 9.3129 3.21923 1.47E−44 member D GATA3 GATA binding protein 3 9.25004 3.20946 2.07E−05 ELN elastin 9.21082 3.20333 3.62E−29 NTNG1 netrin G1 9.15722 3.19491 6.47E−05 VIP vasoactive intestinal peptide 9.13168 3.19088 6.52E−05 LHX9 LIM homeobox 9 9.10507 3.18667 8.09E−07 MYOZ1 myozenin 1 9.05729 3.17908 1.14E−07 FAM84A family with sequence similarity 84_ 9.04907 3.17777 9.59E−08 member A APOE apolipoprotein E 9.04199 3.17664 2.45E−19 LOC102723344 uncharacterized LOC102723344 9.02815 3.17443 6.68E−08 RUNDC3B RUN domain containing 3B 8.95349 3.16245 6.26E−06 C5orf46 chromosome 5 open reading frame 46 8.91071 3.15554 1.80E−27

LYVE1 lymphatic vessel endothelial hyaluronan 8.90262 3.15423 7.29E−06 receptor 1
LINC00547 long intergenic non-protein coding RNA 8.88271 3.151 5.29E−05 547 SPINT2 serine
peptidase inhibitor_ Kunitz type_ 8.85505 3.1465 2.28E−25 2 GDF6 growth differentiation factor
6 8.82209 3.14112 1.43E−27 DACH1 dachshund family transcription factor 1 8.79004 3.13587
9.43E−05 HAP1 huntingtin-associated protein 1 8.77075 3.1327 5.15E−12 LOC149684
uncharacterized LOC149684 8.74792 3.12894 2.96E−06 BMP3 bone morphogenetic protein 3
8.74477 3.12842 1.07E−08 ALDH5A1 aldehyde dehydrogenase 5 family_ 8.72285 3.1248
1.65E−24 member A1 KIAA1211 KIAA1211 8.72013 3.12435 9.95E−10 MAP3K7CL MAP3K7
C-terminal like 8.71361 3.12327 1.40E−59 AQP5 aquaporin 5 8.67359 3.11663 1.39E−06
LINC00887 long intergenic non-protein coding RNA 8.67191 3.11635 5.11E−07 887 ACSM4 acyl-
CoA synthetase medium-chain 8.67101 3.1162 3.26E−05 family member 4 SLC12A5 solute carrier
family 12 8.66692 3.11552 1.95E−16 (potassium/chloride transporter)_ member 5 PPP1R14A
protein phosphatase 1_ regulatory 8.62037 3.10775 6.73E−17 (inhibitor) subunit 14A KCNMB1
potassium channel subfamily M 8.61667 3.10713 2.55E−10 regulatory beta subunit 1 SLC5A4
solute carrier family 5 (glucose activated 8.5971 3.10385 4.58E−06 ion channel)_ member 4
ZNF423 zinc finger protein 423 8.58459 3.10175 5.59E−15 CHRNA7 cholinergic receptor_
nicotinic_ alpha 7 8.57015 3.09932 1.97E−05 (neuronal) FGF11 fibroblast growth factor 11
8.53766 3.09384 2.45E−58 CYTL1 cytokine-like 1 8.52908 3.09239 4.27E−35 GPR20 G protein-
coupled receptor 20 8.52654 3.09196 1.94E−09 LOC100507600 uncharacterized LOC100507600
8.52406 3.09154 7.30E−09 SERTAD4 SERTA domain containing 4 8.52388 3.09151 5.96E−15
PROC protein C (inactivator of coagulation 8.49091 3.08592 3.83E−07 factors Va and VIIIa)
JAM2 junctional adhesion molecule 2 8.48856 3.08552 7.86E−12 PCDHB16 protocadherin beta
16 8.48268 3.08452 7.41E−18 GRIK1- GRIK1 antisense RNA 1 8.45011 3.07897 2.75E−05 AS1
CGB2 chorionic gonadotropin_ beta 8.43343 3.07612 0.00012 polypeptide 2 CDH8 cadherin
8_type 2 8.4109 3.07226 8.44E−05 GPLD1 glycosylphosphatidylinositol specific 8.40962 3.07204
5.72E−12 phospholipase D1 ZNF521 zinc finger protein 521 8.40507 3.07126 9.51E−26 FAM83E
family with sequence similarity 83_ 8.38046 3.06703 6.69E−06 member E SBK3 SH3 domain
binding kinase family_ 8.31767 3.05618 7.17E−05 member 3 WT1 Wilms tumor 1 8.30932
3.05473 4.77E−05 HID 1 HID1 domain containing 8.25518 3.0453 1.09E−27 ERC2 ELKS/RAB6-
interacting/CAST family 8.21762 3.03872 1.91E−06 member 2 ESPN espin 8.21625 3.03848
2.65E−06 WT1-AS WT1 antisense RNA 8.19435 3.03463 6.39E−05 APBB1IP amyloid beta (A4)
precursor protein- 8.191 3.03404 8.22E−12 binding_ family B_ member 1 interacting protein
PIEZO2 piezo-type mechanosensitive ion channel 8.18754 3.03343 4.71E−09 component 2
AC093375.1 NA 8.15554 3.02778 0.000116 POTEF POTE ankyrin domain family_ member
8.1373 3.02455 1.74E−28 F JSRP1 junctional sarcoplasmic reticulum 8.12772 3.02285 4.78E−06
protein 1 DRD1 dopamine receptor D1 8.11798 3.02112 5.53E−05 SYT9 synaptotagmin IX
8.04426 3.00796 7.24E−06 KRT7 keratin 7_ type II 8.02866 3.00516 1.44E−64 LINC00858 long
intergenic non-protein coding RNA 8.00705 3.00127 0.000153 858 ABCA13 ATP-binding
cassette_ sub-family A 7.98465 2.99723 3.12E−07 (ABC1)_ member 13 IGF1 insulin-like growth
factor 1 7.97768 2.99597 0.000181 (somatomedin C) PALD1 phosphatase domain
containing_paladin 7.96188 2.99311 1.28E−08 1 SOWAHB sosondowah ankyrin repeat domain
7.95753 2.99232 3.29E−05 family member B TMEM35 transmembrane protein 35 7.92494 2.9864
1.78E−38 ACTC1 actin_ alpha_ cardiac muscle 1 7.9239 2.98621 3.75E−16 CACNG6 calcium
channel_ voltage-dependent_ 7.87156 2.97665 5.54E−34 gamma subunit 6 PPL periplakin 7.86982
2.97633 1.32E−14 TRPC5OS TRPC5 opposite strand 7.86845 2.97608 0.00015 ABLIM1 actin
binding LIM protein 1 7.82169 2.96748 2.65E−19 FOXL2 forkhead box L2 7.82115 2.96738
8.54E−08 TMOD1 tropomodulin 1 7.7731 2.95849 0.000143 FOXE3 forkhead box E3 7.72208
2.94899 5.15E−05 LINC00890 long intergenic non-protein coding RNA 7.70423 2.94565
9.71E−23 890 PLN phospholamban 7.69819 2.94452 3.81E−08 CAPN11 calpain 11 7.69782
2.94445 4.09E−08 MAGEL2 melanoma antigen family L2 7.68668 2.94236 5.71E−12 LINC00622

long intergenic non-protein coding RNA 7.67023 2.93927 4.03E−13 622 RASL10A RAS-like_ family 10_ member A 7.61561 2.92896 4.24E−05 C11orf87 chromosome 11 open reading frame 87 7.60006 2.92601 2.64E−06 LINC00840 long intergenic non-protein coding RNA 7.5575 2.91791 3.57E−06 840 SCG2 secretogranin II 7.55457 2.91735 7.95E−22 PXDNL peroxidasin-like 7.5359 2.91378 8.38E−06 RASSF2 Ras association (RalGDS/AF-6) domain 7.49563 2.90605 3.11E−57 family member 2 VGF VGF nerve growth factor inducible 7.4909 2.90514 1.11E−12 NLGN1 neuroligin 1 7.46018 2.89921 7.92E−06 GRPR gastrin-releasing peptide receptor 7.45051 2.89734 8.69E−29 ARL14 ADP-ribosylation factor-like 14 7.44819 2.89689 1.18E−05 RENBP renin binding protein 7.40233 2.88798 2.31E−06 TRIML2 tripartite motif family-like 2 7.37534 2.88271 0.00029 FGD4 FYVE_ RhoGEF and PH domain 7.33934 2.87565 1.76E−20 containing 4 BIRC7 baculoviral IAP repeat containing 7 7.33522 2.87484 0.000137 CADM4 cell adhesion molecule 4 7.33024 2.87386 9.04E−38 ANKS1B ankyrin repeat and sterile alpha motif 7.32308 2.87245 1.49E−05 domain containing 1B LOC100130899 uncharacterized LOC100130899 7.31958 2.87176 0.00027 DCDC2 doublecortin domain containing 2 7.30194 2.86828 0.000282 CD101 CD101 molecule 7.30179 2.86825 3.82E−06 KIF21B kinesin family member 21B 7.29992 2.86788 1.17E−68 EEF1A2 eukaryotic translation elongation factor 7.24763 2.85751 1.16E−22 1 alpha 2 CASC15 cancer susceptibility candidate 15 (non- 7.23774 2.85554 6.66E−07 protein coding) DCLK1 doublecortin-like kinase 1 7.22426 2.85285 2.25E−15 SOX18 SRY (sex determining region Y)-box 18 7.2107 2.85014 1.24E−08 CTNND2 catenin (cadherin-associated protein)_ 7.20676 2.84935 0.000304 delta 2 NHS Nance-Horan syndrome (congenital 7.20476 2.84895 5.32E−08 cataracts and dental anomalies) LOC100128531 uncharacterized LOC100128531 7.18551 2.84509 0.000395 RGS9 regulator of G-protein signaling 9 7.17555 2.84309 2.06E−15 NCF2 neutrophil cytosolic factor 2 7.16358 2.84068 1.39E−06 LINC00649 long intergenic non-protein coding RNA 7.15772 2.8395 2.36E−08 649 PCDHB8 protocadherin beta 8 7.13874 2.83567 7.07E−05 CLEC4GP1 C-type lectin domain family 4_ member 7.12243 2.83237 0.000363 G pseudogene 1 PCBP3 poly(rC) binding protein 3 7.12199 2.83228 1.76E−13 CSMD3 CUB and Sushi multiple domains 3 7.11932 2.83174 5.68E−13 SERPINA9 serpin peptidase inhibitor_ clade A 7.01897 2.81126 0.000456 (alpha-1 antiproteinase_ antitrypsin)_ member 9 ELAVL2 ELAV like neuron-specific RNA 7.01328 2.81009 8.89E−05 binding protein 2 LBH limb bud and heart development 6.9804 2.80331 5.82E−57 KCNN2 potassium channel_ calcium activated 6.96663 2.80046 4.14E−14 intermediate/small conductance subfamily N alpha_ member 2 SEMA3F sema domain_ immunoglobulin domain 6.94267 2.79549 1.50E−60 (Ig)_ short basic domain_ secreted_ (semaphorin) 3F BEND5 BEN domain containing 5 6.89538 2.78563 0.000319 P2RX6P purinergic receptor P2X_ ligand gated 6.89509 2.78557 1.13E−07 ion channel_6 pseudogene LRMP lymphoid-restricted membrane protein 6.89452 2.78545 9.07E−08 CNTNAP3B contactin associated protein-like 3B 6.89089 2.78469 0.000117 ZCCHC18 zinc finger_ CCHC domain containing 6.88597 2.78366 2.72E−16 18 RASSF10 Ras association (RalGDS/AF-6) domain 6.87391 2.78113 0.000516 family (N-terminal) member 10 ZIC2 Zic family member 2 6.86139 2.7785 0.000395 CYGB cytoglobin 6.84267 2.77456 3.13E−31 TYROBP TYRO protein tyrosine kinase binding 6.83154 2.77221 0.00043 protein LOC100507006 uncharacterized LOC100507006 6.81583 2.76889 0.000275 THSD7A thrombospondin_ type I_ domain 6.81361 2.76842 1.62E−06 containing 7A MIR4321 microRNA 4321 6.7899 2.76339 0.000527 DYSF dysferlin 6.78731 2.76284 6.21E−23 SYTL1 synaptotagmin-like 1 6.7575 2.75649 1.41E−09 ADCY10P1 adenylate cyclase 10 (soluble) 6.74884 2.75464 2.20E−09 pseudogene 1 JAG2 jagged 2 6.73398 2.75146 1.38E−15 COL6A5 collagen_ type VI_ alpha 5 6.72302 2.74911 0.000601 PAQR6 progestin and adipoQ receptor family 6.72195 2.74888 1.92E−09 member VI FSTL4 follistatin-like 4 6.71483 2.74735 0.000619 UPB1 ureidopropionase_ beta 6.71129 2.74659 1.91E−06 LZTS1 leucine zipper_ putative tumor 6.70896 2.74609 9.30E−74 suppressor 1 CNGA1 cyclic nucleotide gated channel alpha 1 6.70645 2.74555 1.88E−05 KCNH1 potassium channel_ voltage gated eag 6.69549 2.74319 1.61E−09 related subfamily H_ member 1

RGPD1 RANBP2-like and GRIP domain 6.66165 2.73588 9.04E−06 containing 1 SPINK1 serine peptidase inhibitor_ Kazal type 1 6.66082 2.7357 0.000649 ECSCR endothelial cell surface expressed 6.65985 2.73549 3.50E−17 chemotaxis and apoptosis regulator MYL4 myosin_ light chain 4_ alkali; atrial_ 6.65547 2.73454 4.43E−07 embryonic ADCY4 adenylate cyclase 4 6.64339 2.73192 1.28E−05 ZMAT4 zinc finger_ matrin-type 4 6.62004 2.72684 6.04E−10 DUSP15 dual specificity phosphatase 15 6.59183 2.72068 0.000655 SHROOM2 shroom family member 2 6.57527 2.71705 1.20E−61 RAPGEF5 Rap guanine nucleotide exchange factor 6.54952 2.71139 9.33E−06 (GEF) 5 CTAGE6 CTAGE family_ member 6 6.54925 2.71133 0.00016 Clorf106 chromosome 1 open reading frame 106 6.53003 2.70709 6.55E−41 TIE1 tyrosine kinase with immunoglobulin- 6.49856 2.70012 4.16E−36 like and EGF-like domains 1 GZMA granzyme A (granzyme 1_ cytotoxic T- 6.47226 2.69427 0.000623 lymphocyte-associated serine esterase 3) RHOV ras homolog family member V 6.46433 2.6925 1.72E−06 LINC01002 long intergenic non-protein coding RNA 6.42043 2.68267 2.59E−05 1002 LEPREL1 prolyl 3-hydroxylase 2 6.40243 2.67862 8.05E−55 KRTAP5-1 keratin associated protein 5-1 6.40017 2.67811 0.000735 TLR2 toll-like receptor 2 6.37577 2.6726 0.000277 PALM2 paralemmin 2 6.34878 2.66648 3.95E−17 LINC00704 long intergenic non-protein coding RNA 6.317 2.65924 7.01E−06 704 LOC100652824 NA 6.31166 2.65802 3.63E−11 AADACP1 arylacetamide deacetylase pseudogene 1 6.301 2.65558 0.000388 TLL2 tolloid-like 2 6.29999 2.65535 2.58E−12 ENTPD3 ectonucleoside triphosphate 6.28582 2.6521 4.00E−05 diphosphohydrolase 3 ATRNL1 attractin-like 1 6.28468 2.65184 2.86E−06 LINC01239 long intergenic non-protein coding RNA 6.2672 2.64782 1.04E−05 1239 ZIC1 Zic family member 1 6.26702 2.64778 0.000977 UPK1A uroplakin 1A 6.24976 2.6438 2.79E−05 LOC100507534 uncharacterized LOC100507534 6.2293 2.63907 1.20E−05 PDZD2 PDZ domain containing 2 6.22718 2.63858 3.38E−32 SEMA6B sema domain_ transmembrane domain 6.21709 2.63624 9.15E−14 (TM)_ and cytoplasmic domain_ (semaphorin) 6B MEGF10 multiple EGF-like-domains 10 6.21063 2.63474 0.000763 LINC01197 long intergenic non-protein coding RNA 6.20461 2.63334 0.000813 1197 SPATA31E1 SPATA31 subfamily E_ member 1 6.19447 2.63098 0.000662 A2M-AS1 A2M antisense RNA 1 (head to head) 6.19176 2.63035 2.13E−05 CECR2 cat eye syndrome chromosome region_ 6.19017 2.62998 0.000364 candidate 2 DNAH8 dynein_ axonemal_ heavy chain 8 6.18036 2.62769 0.000829 GPR183 G protein-coupled receptor 183 6.17916 2.62741 2.62E−18 PRICKLE1 prickle homolog 1 6.17192 2.62572 3.61E−10 MEI4 meiotic double-stranded break formation 6.16504 2.62411 0.000297 protein 4 GNAO1 guanine nucleotide binding protein (G 6.16397 2.62386 1.09E−18 protein)_ alpha activating activity polypeptide O PCDHA2 protocadherin alpha 2 6.15846 2.62257 0.000939 FGFBP3 fibroblast growth factor binding protein 6.15599 2.62199 1.51E− 3 120 PTPN7 protein tyrosine phosphatase_ non- 6.13465 2.61698 9.90E−05 receptor type 7 BAALC brain and acute leukemia_ cytoplasmic 6.12976 2.61583 5.89E−17 ZFHX2 zinc finger homeobox 2 6.12963 2.6158 1.58E−11 LAMC2 laminin_ gamma 2 6.12581 2.6149 6.63E−12 PPARG peroxisome proliferator-activated 6.12428 2.61454 2.53E−11 receptor gamma LOC729737 uncharacterized LOC729737 6.11478 2.6123 3.85E−11 RASGRF1 Ras protein-specific guanine nucleotide- 6.1072 2.61051 8.10E−24 releasing factor 1 ACVR1C activin A receptor_ type IC 6.08514 2.60529 1.32E−07 ST6GAL2 ST6 beta-galactosamide alpha-2_6- 6.08295 2.60477 1.66E−19 sialyltranferase 2 FAM162B family with sequence similarity 162_ 6.08193 2.60453 0.000742 member B MYOZ2 myozenin 2 6.07679 2.60331 2.14E−10 ZIC5 Zic family member 5 6.06955 2.60159 0.000829 SLC7A9 solute carrier family 7 (amino acid 6.05199 2.59741 5.05E−07 transporter light chain_ bo_+ system)_ member 9 GPR143 G protein-coupled receptor 143 6.04486 2.59571 1.54E−18 WNT16 wingless-type MMTV integration site 6.03971 2.59448 4.60E−08 family_ member 16 LINC00222 long intergenic non-protein coding RNA 6.03009 2.59218 0.000545 222 PIFO primary cilia formation 6.0247 2.59089 1.19E−09 MDFI MyoD family inhibitor 6.02437 2.59081 4.67E−15 SGIP1 SH3-domain GRB2-like (endophilin) 6.0134 2.58818 1.29E−15 interacting protein 1 FSIP2 fibrous sheath interacting protein 2 6.0124 2.58794 4.68E−06 ACAN aggrecan 6.00973 2.5873 1.06E−08

LOC400863 NA 6.00885 2.58709 7.71E−05 C11orf88 chromosome 11 open reading frame 88 5.97741 2.57952 9.46E−15 TSPAN18 tetraspanin 18 5.96437 2.57637 9.71E−07 VSTM2L V-set and transmembrane domain 5.96346 2.57615 1.08E−12 containing 2 like LINC00460 long intergenic non-protein coding RNA 5.95206 2.57339 6.68E−09 460 HOXB8 homeobox B8 5.94534 2.57176 7.30E−22 LINC00086 small integral membrane protein 10 like 5.9242 2.56662 1.98E−08 2A CDHR1 cadherin-related family member 1 5.92223 2.56614 0.001148 BMF Bcl2 modifying factor 5.92087 2.56581 2.33E−12 RUNX3 runt-related transcription factor 3 5.91292 2.56387 0.00036 SCN5A sodium channel_ voltage gated_ type V 5.88809 2.5578 8.62E−07 alpha subunit GLRA4 glycine receptor_ alpha 4 5.88793 2.55776 0.001253 PTPRR protein tyrosine phosphatase_ receptor 5.87154 2.55374 1.05E−06 type_ R NTF4 neurotrophin 4 5.87053 2.55349 3.68E−12 MCF2 MCF.2 cell line derived transforming 5.86829 2.55294 2.85E−05 sequence TF transferrin 5.84908 2.54821 3.31E−06 ATP2B3 ATPase_ Ca++ transporting_ plasma 5.84714 2.54773 1.90E−06 membrane 3 CD37 CD37 molecule 5.83422 2.54454 7.82E−09 LAPTM5 lysosomal protein transmembrane 5 5.82008 2.54104 3.89E−31 RAMP2- RAMP2 antisense RNA 1 5.81049 2.53866 1.81E−09 AS1 IGLON5 IgLON family member 5 5.80401 2.53705 6.67E−05 SLC6A17 solute carrier family 6 (neutral amino 5.79641 2.53516 3.43E−15 acid transporter)_ member 17 GIPC3 GIPC PDZ domain containing family_ 5.7752 2.52987 6.08E−59 member 3 ASXL3 additional sex combs like transcriptional 5.77324 2.52938 0.000148 regulator 3 PCDHAC1 protocadherin alpha subfamily C_ 1 5.77243 2.52918 0.001215 GRIK4 glutamate receptor_ ionotropic_ kainate 5.77079 2.52877 8.42E−06 4 IRF6 interferon regulatory factor 6 5.7632 2.52687 8.02E−09 KRT23 keratin 23_ type I 5.75905 2.52583 2.56E−07 ST6GALNAC1 ST6 (alpha-N-acetyl-neuraminyl-2_3- 5.75581 2.52502 0.001081 beta-galactosyl-1_3)-N-acetylgalactosaminide alpha-2_6- sialyltransferase 1 CYP2E1 cytochrome P450_ family 2_ subfamily 5.7484 2.52316 5.32E−07 E_ polypeptide 1 SIPA1L2 signal-induced proliferation-associated 1 5.74103 2.52131 4.32E−53 like 2 CACNA2D3 calcium channel_ voltage-dependent_ 5.73638 2.52014 2.26E−05 alpha 2/delta subunit 3 CCDC3 coiled-coil domain containing 3 5.72514 2.51731 1.02E−07 PTGS1 prostaglandin-endoperoxide synthase 1 5.72137 2.51636 6.83E−12 (prostaglandin G/H synthase and cyclooxygenase) RGS7 regulator of G-protein signaling 7 5.71709 2.51528 1.57E−07 LINC01260 long intergenic non-protein coding RNA 5.71614 2.51504 0.00024 1260 LOC102724849 uncharacterized LOC102724849 5.71392 2.51448 2.09E−07 LRRN4 leucine rich repeat neuronal 4 5.71217 2.51404 4.42E−15 SP140 SP140 nuclear body protein 5.71063 2.51365 6.75E−14 C19orf81 chromosome 19 open reading frame 81 5.70956 2.51338 4.55E−05 KLHL4 kelch-like family member 4 5.69849 2.51058 1.19E−08 CD163L1 CD163 molecule-like 1 5.67893 2.50562 8.29E−08 TUBA3E tubulin_ alpha 3e 5.66777 2.50278 0.001189 FGF13 fibroblast growth factor 13 5.66568 2.50225 0.00092 GSC goosecoid homeobox 5.6614 2.50116 1.08E−05 CGB5 chorionic gonadotropin_ beta 5.64166 2.49612 0.000597 polypeptide 5 PCDHB5 protocadherin beta 5 5.63693 2.49491 8.16E−06 SRCRB4D scavenger receptor cysteine rich family_ 5.63486 2.49438 2.65E−19 4 domains ZAP70 zeta-chain (TCR) associated protein 5.62596 2.4921 0.000113 kinase 70 kDa CCDC81 coiled-coil domain containing 81 5.6037 2.48638 6.86E−14 KIAA1456 KIAA1456 5.60048 2.48555 1.55E−20 NFATC2 nuclear factor of activated T-cells_ 5.59757 2.4848 1.37E−19 cytoplasmic_ calcineurin-dependent 2 MUC19 mucin 19_ oligomeric 5.59536 2.48423 0.000489 KCNJ6 potassium channel_ inwardly rectifying 5.59284 2.48358 0.001973 subfamily J_ member 6 MTRNR2L10 MT-RNR2-like 10 5.58513 2.48159 9.04E−05 ZBTB46 zinc finger and BTB domain containing 5.57495 2.47896 1.21E−23 46 PCDHB14 protocadherin beta 14 5.56515 2.47642 2.03E−06 IGSF3 immunoglobulin superfamily_ member 3 5.56368 2.47604 1.39E−14 NOVA2 neuro-oncological ventral antigen 2 5.5601 2.47511 4.01E−06 DRP2 dystrophin related protein 2 5.54662 2.47161 1.49E−37 PRTG protogenin 5.53752 2.46924 1.84E−09 KIF26A kinesin family member 26A 5.53717 2.46915 3.41E−08 LINC01013 long intergenic non-protein coding RNA 5.52759 2.46665 0.000302 1013 KNDC1 kinase non-catalytic C-lobe domain 5.52062 2.46483 1.87E−08 (KIND) containing 1

PAK3 p21 protein (Cdc42/Rac)-activated 5.51324 2.4629 5.54E−32 kinase 3 TMEM52B transmembrane protein 52B 5.51278 2.46278 0.002149 HOXB13 homeobox B13 5.48937 2.45664 1.06E−05 COL23A1 collagen_ type XXIII_ alpha 1 5.4837 2.45515 0.001602 DNM3 dynamin 3 5.48298 2.45496 5.19E−11 PAX9 paired box 9 5.46356 2.44984 0.002241 SETBP1 SET binding protein 1 5.45784 2.44833 5.88E−06 FGF16 fibroblast growth factor 16 5.4399 2.44358 0.002308 DUSP26 dual specificity phosphatase 26 5.43809 2.4431 0.002181 (putative) BEX2 brain expressed X-linked 2 5.43259 2.44164 1.45E−09 FAM84B family with sequence similarity 84_ 5.4242 2.43941 3.53E−13 member B SDK2 sidekick cell adhesion molecule 2 5.40851 2.43523 1.06E−10 KBTBD11 kelch repeat and BTB (POZ) domain 5.40671 2.43475 1.16E−10 containing 11 GRHL3 grainyhead-like transcription factor 3 5.40217 2.43354 8.32E−07 ZBED2 zinc finger_ BED-type containing 2 5.40094 2.43321 9.10E−07 TMC8 transmembrane channel-like 8 5.3717 2.42538 0.001867 C2CD4C C2 calcium-dependent domain 5.37103 2.4252 1.38E−10 containing 4C NBL1 neuroblastoma 1_ DAN family BMP 5.3578 2.42164 0.000893 antagonist ARL4C ADP-ribosylation factor-like 4C 5.34848 2.41913 5.53E−19 MS4A4A membrane-spanning 4-domains_ 5.33327 2.41502 0.001852 subfamily A_ member 4A GLB1L2 galactosidase_ beta 1-like 2 5.32363 2.41241 3.97E−12 FAM131B family with sequence similarity 131_ 5.31858 2.41104 1.09E−19 member B LOC643542 uncharacterized LOC643542 5.31821 2.41094 0.00023 TMEM151B transmembrane protein 151B 5.30974 2.40864 0.002088 LMO2 LIM domain only 2 (rhombotin-like 1) 5.30653 2.40777 0.000314 IGDCC4 immunoglobulin superfamily_ DCC 5.29724 2.40524 5.68E−72 subclass_ member 4 OPCML opioid binding protein/cell adhesion 5.28436 2.40173 5.06E−05 molecule-like CACNG8 calcium channel_ voltage-dependent_ 5.27975 2.40047 1.83E−16 gamma subunit 8 RORB RAR-related orphan receptor B 5.24415 2.39071 0.002129 HAND1 heart and neural crest derivatives 5.22167 2.38451 1.82E−06 expressed 1 SULT4A1 sulfotransferase family 4A_ member 1 5.21208 2.38186 1.47E−06 HLA-B major histocompatibility complex_class 5.20569 2.38009 1.09E−26 I_ B KCNN3 potassium channel_ calcium activated 5.20126 2.37886 0.000383 intermediate/small conductance subfamily N alpha_ member 3 CRLF1 cytokine receptor-like factor 1 5.15671 2.36645 1.13E−11 ATP8A1 ATPase_ aminophospholipid transporter 5.15531 2.36606 1.96E−07 (APLT)_ class I_ type 8A_ member 1 TRIM9 tripartite motif containing 9 5.15374 2.36562 0.000187 KCNA7 potassium channel_ voltage gated shaker 5.15228 2.36521 2.72E−05 related subfamily A_ member 7 TAGLN3 transgelin 3 5.14806 2.36403 4.16E−08 PRKCG protein kinase C_ gamma 5.13449 2.36022 1.20E−05 SPON1 spondin 1_ extracellular matrix protein 5.12098 2.35642 5.19E−09 PKD1L2 polycystic kidney disease 1-like 2 5.12063 2.35632 0.000127 (gene/pseudogene) PKNOX2 PBX/knotted 1 homeobox 2 5.11513 2.35477 0.000112 LOC100129203 uncharacterized LOC100129203 5.10379 2.35157 0.001332 DOK6 docking protein 6 5.07399 2.34312 4.34E−05 TNFSF4 tumor necrosis factor (ligand) 5.05892 2.33883 1.26E−10 superfamily_ member 4 CHDH choline dehydrogenase 5.05647 2.33813 0.000408 CAMSAP3 calmodulin regulated spectrin-associated 5.04422 2.33463 0.000936 protein family_ member 3 NEDD4L neural precursor cell expressed_ 5.03796 2.33284 8.36E−17 developmentally down-regulated 4-like_ E3 ubiquitin protein ligase ZNF702P zinc finger protein 702_ pseudogene 5.02959 2.33044 2.26E−06 PPP1R1C protein phosphatase 1_ regulatory 5.01083 2.32505 0.000132 (inhibitor) subunit 1C CPE carboxypeptidase E 5.00021 2.32199 2.22E−05

TABLE-US-00006 TABLE 6 Genes more highly expressed in UCB-MSCs compared to HMCs Log Fold Fold Name Description Change Change p-Value MEG3 maternally expressed 3 (non-protein −17630.7 −14.1058 7.58E−194 coding) CAT catalase −1511.12 −10.5614 1.14E−99 DYNLT3 dynein_ light_ chain_ Tctex-type 3 −1417.76 −10.4694 5.79E−88 ALDH1A1 aldehyde dehydrogenase 1 family.sub.— −1170.82 −10.1933 5.05E−179 member A1 S100A6 S100 calcium binding protein A6 −895.544 −9.80662 5.29E−222 GSTT1 glutathione S-transferase theta 1 −681.793 −9.41319 2.12E−66 CTSF cathepsin F −302.374 −8.24019 7.74E−45 CMKLR1 chemerin chemokine-like receptor 1 −284.33 −8.15142 2.15E−43 FLG-AS1 FLG antisense RNA 1

−246.966 −7.94817 1.08E−41 KRBOX1 KRAB box domain containing 1 −229.441 −7.84198 4.89E−41 LYNX1 Ly6/neurotoxin 1 −199.238 −7.63835 7.06E−36 FMOD fibromodulin −191.276 −7.57951 1.15E−56 ZNF662 zinc finger protein 662 −174.724 −7.44893 1.18E−40 LMO3 LIM domain only 3 (rhombotin-like 2) −170.074 −7.41002 8.31E−49 CNTN3 contactin 3 (plasmacytoma associated) −162.07 −7.34047 1.38E−64 CXCL1 chemokine (C-X-C motif) ligand 1 −149.21 −7.2212 2.41E−66 (melanoma growth stimulating activity_ alpha) IRX3 iroquois homeobox 3 −148.228 −7.21167 1.60E−65 LINC01133 long intergenic non-protein coding −143.929 −7.16921 8.35E−65 RNA 1133 CCDC36 coiled-coil domain containing 36 −142.12 −7.15097 7.50E−32 LOC400043 uncharacterized LOC400043 −135.246 −7.07944 2.84E−43 CXCL6 chemokine (C-X-C motif) ligand 6 −134.778 −7.07444 4.76E−46 LOC101929369 NA −133.058 −7.05591 2.42E−39 C5orf63 chromosome 5 open reading frame 63 −130.609 −7.02911 1.23E−35 ANGPTL1 angiopoietin-like 1 −129.967 −7.022 1.55E−47 MEG8 maternally expressed 8 (non-protein −128.676 −7.0076 1.67E−30 coding) BHMT2 betaine--homocysteine S- −114.938 −6.84471 8.37E−28 methyltransferase 2 RTN1 reticulon 1 −109.648 −6.77673 6.25E−56 FLG filaggrin −100.449 −6.65032 8.20E−26 PCDHGA12 protocadherin gamma subfamily A_ 12 −99.7593 −6.64038 2.95E−35 PI16 peptidase inhibitor 16 −98.0204 −6.61501 2.34E−34 FOXQ1 forkhead box Q1 −97.2354 −6.60341 5.15E−25 SLC39A4 solute carrier family 39 (zinc −96.9111 −6.59859 2.72E−45 transporter)_ member 4 HOXC8 homeobox C8 −91.8113 −6.5206 3.45E−183 SDR42E1 short chain dehydrogenase/reductase −88.1232 −6.46145 5.13E−25 family 42E_ member 1 ZNF300P1 zinc finger protein 300 pseudogene 1 −86.6483 −6.4371 5.64E−28 (functional) PID1 phosphotyrosine interaction domain −86.3803 −6.43263 1.87E−48 containing 1 ABCA8 ATP-binding cassette_ sub-family A −82.6607 −6.36913 5.15E−87 (ABC1)_ member 8 NAALADL 1 N-acetylated alpha-linked acidic −81.0517 −6.34077 5.70E−89 dipeptidase-like 1 GSTM5 glutathione S-transferase mu 5 −78.262 −6.29024 7.38E−25 LOC150381 NA −78.0664 −6.28663 2.48E−40 SPESP1 sperm equatorial segment protein 1 −75.344 −6.23542 7.37E−22 COX7A1 cytochrome c oxidase subunit VIIa −71.77 −6.16531 8.83E−41 polypeptide 1 (muscle) CHI3L1 chitinase 3-like 1 (cartilage −71.6066 −6.16202 2.08E−36 glycoprotein-39) PLD5 phospholipase D family_ member 5 −71.5604 −6.16109 3.57E−22 PAX8-AS1 PAX8 antisense RNA 1 −70.7006 −6.14365 6.52E−60 LINC00473 long intergenic non-protein coding −65.782 −6.03962 8.00E−37 RNA 473 TNFAIP6 tumor necrosis factor_ alpha-induced −65.3624 −6.03039 6.10E−32 protein 6 CCDC89 coiled-coil domain containing 89 −65.2389 −6.02766 3.85E−33 NKAPL NFKB activating protein-like −63.0638 −5.97874 1.55E−20 PTGES prostaglandin E synthase −61.3844 −5.9398 7.12E−283 IQGAP2 IQ motif containing GTPase activating −61.2161 −5.93584 7.26E−46 protein 2 HOXC-AS1 HOXC cluster antisense RNA 1 −61.0945 −5.93297 3.56E−23 CXCL3 chemokine (C-X-C motif) ligand 3 −60.7166 −5.92402 3.01E−21 DNAJA4 DnaJ (Hsp40) homolog_ subfamily A.sub.— −59.1739 −5.88689 4.13E−60 member 4 LINC00654 long intergenic non-protein coding −54.5633 −5.76986 3.95E−29 RNA 654 MYH13 myosin_ heavy chain 13_ skeletal −53.4523 −5.74018 1.10E−19 muscle CCDC144B coiled-coil domain containing 144B −51.3236 −5.68155 5.35E−18 (pseudogene) CXCL5 chemokine (C-X-C motif) ligand 5 −51.2493 −5.67946 9.87E−32 PCDHGB3 protocadherin gamma subfamily B_ 3 −51.168 −5.67717 4.94E−18 AARD alanine and arginine rich domain −50.3978 −5.65529 1.45E−27 containing protein CARD16 caspase recruitment domain family.sub.— −50.1007 −5.64676 1.07E−63 member 16 GAS1 growth arrest-specific 1 −49.8734 −5.6402 4.77E−129 LOC100240735 uncharacterized LOC100240735 −49.8499 −5.63952 5.09E−18 CSF3 colony stimulating factor 3 −49.1343 −5.61866 1.33E−16 (granulocyte) HOXC10 homeobox C10 −48.8217 −5.60945 2.74E−104 CXCL8 chemokine (C-X-C motif) ligand 8 −48.64 −5.60407 1.22E−37 NUPR1 nuclear protein_ transcriptional −48.4841 −5.59944 2.59E−81 regulator_ 1 ZNF572 zinc finger protein 572 −48.1552 −5.58962 1.69E−17 HSPB2 heat shock 27kDa protein 2 −47.9112 −5.58229 1.64E−17 HOXD8 homeobox D8 −47.1374 −5.5588 8.90E−63 GBP4 guanylate binding protein 4 −45.9041 −5.52055 4.74E−42 LRRK2 leucine-rich repeat kinase 2

−45.7497 −5.51569 6.91E−16 FAM66B family with sequence similarity 66.sub.— −44.8352 −5.48656 1.09E−16 member B ISLR immunoglobulin superfamily −44.685 −5.48172 1.83E−95 containing leucine-rich repeat PCDHGA3 protocadherin gamma subfamily A_ 3 −44.2636 −5.46805 1.12E−16 ZNF736 zinc finger protein 736 −43.1447 −5.43111 3.45E−16 HSD17B7P2 hydroxysteroid (17-beta) −42.9582 −5.42486 2.52E−30 dehydrogenase 7 pseudogene 2 LRRTM3 leucine rich repeat transmembrane −42.6848 −5.41565 4.82E−30 neuronal 3 HGF hepatocyte growth factor (hepapoietin −42.505 −5.40956 8.03E−36 A; scatter factor) ADAMTS4 ADAM metallopeptidase with −42.3714 −5.40502 9.49E−138 thrombospondin type 1 motif_ 4 ZNF257 zinc finger protein 257 −41.6912 −5.38167 4.49E−16 GRID2 glutamate receptor_ ionotropic_ delta 2 −41.5991 −5.37848 1.54E−18 FGF7 fibroblast growth factor 7 −41.044 −5.3591 1.97E−25 PRSS30P protease_ serine_ 30_ pseudogene −40.9168 −5.35462 1.00E−15 LINC00506 long intergenic non-protein coding −40.2244 −5.33 1.00E−15 RNA 506 HOXC5 homeobox C5 −37.8836 −5.2435 2.08E−41 ADIRF adipogenesis regulatory factor −37.6375 −5.2341 1.34E−31 ZFP3 ZFP3 zinc finger protein −37.3196 −5.22186 1.35E−56 HYDIN HYDIN_ axonemal central pair −37.0798 −5.21256 8.40E−18 apparatus protein TDO2 tryptophan 2_3-dioxygenase −36.9156 −5.20616 2.68E−25 CD200 CD200 molecule −36.3481 −5.18381 0.00E+00 HOXC4 homeobox C4 −36.3086 −5.18224 1.34E−75 ANXA10 annexin A10 −35.674 −5.1568 2.34E−121 LOC284757 NA −35.3454 −5.14345 3.92E−16 ZNF311 zinc finger protein 311 −34.811 −5.12147 4.19E−40 CASP1 caspase 1_ apoptosis-related cysteine −34.3279 −5.10131 1.32E−90 peptidase C1QTNF7 C1q and tumor necrosis factor related −33.2599 −5.05571 1.08E−13 protein 7 SNORD114-10 small nucleolar RNA_ C/D box 114-10 −32.3322 −5.0149 1.14E−13 PCDHGA11 protocadherin gamma subfamily A_ 11 −32.1396 −5.00628 9.50E−53 HOXD-AS2 HOXD cluster antisense RNA 2 −31.947 −4.99761 3.44E−26 PITX1 paired-like homeodomain 1 −31.6427 −4.9838 1.10E−119 ZNF492 zinc finger protein 492 −31.3026 −4.96821 1.68E−14 HOXC6 homeobox C6 −31.295 −4.96786 4.21E−45 HOXC9 homeobox C9 −31.2237 −4.96457 1.02E−30 KCNJ13 potassium channel_ inwardly −30.8716 −4.94821 4.29E−17 rectifying subfamily J_ member 13 IL1B interleukin 1_ beta −29.6829 −4.89156 1.93E−46 C11orf86 chromosome 11 open reading frame 86 −29.6418 −4.88956 1.78E−20 CSGALNACT1 chondroitin sulfate N- −29.5941 −4.88724 2.37E−57 acetylgalactosaminyltransferase 1 FPR1 formyl peptide receptor 1 −29.0064 −4.8583 1.23E−12 LOC728819 NA −28.0926 −4.81212 2.57E−12 MLC1 megalencephalic leukoencephalopathy −28.0634 −4.81062 4.15E−21 with subcortical cysts 1 CXCL2 chemokine (C-X-C motif) ligand 2 −27.977 −4.80617 4.71E−24 CEACAM22P carcinoembryonic antigen-related cell −27.7945 −4.79673 4.37E−12 adhesion molecule 22_ pseudogene ZNF454 zinc finger protein 454 −27.2796 −4.76975 2.00E−15 TDRD9 tudor domain containing 9 −26.7334 −4.74057 4.26E−12 FAM198A family with sequence similarity 198.sub.— −26.5826 −4.73241 8.07E−12 member A IL21-AS1 IL21 antisense RNA 1 −26.2061 −4.71183 9.27E−12 LINC00478 mir-99a-let-7c cluster host gene −25.7904 −4.68876 1.29E−17 ZNF439 zinc finger protein 439 −25.5938 −4.67772 2.02E−40 KLHDC7B kelch domain containing 7B −25.3659 −4.66482 2.63E−32 EN1 engrailed homeobox 1 −25.0474 −4.64659 1.53E−10 SLC22A15 solute carrier family 22_ member 15 −24.8777 −4.63678 1.45E−62 LOC283683 uncharacterized LOC283683 −24.4078 −4.60927 2.99E−14 DOK5 docking protein 5 −24.0441 −4.58761 9.96E−25 LINC00922 long intergenic non-protein coding −23.9592 −4.58251 4.59E−11 RNA 922 LINC00865 long intergenic non-protein coding −23.941 −4.58141 3.99E−11 RNA 865 PF4V1 platelet factor 4 variant 1 −23.5142 −4.55546 3.02E−10 MLKL mixed lineage kinase domain-like −23.4787 −4.55328 3.66E−225 HOXC-AS2 HOXC cluster antisense RNA 2 −23.2705 −4.54043 1.46E−23 STAB1 stabilin 1 −23.2547 −4.53945 1.35E−19 PTGFR prostaglandin F receptor (FP) −23.1644 −4.53384 1.80E−46 HDC histidine decarboxylase −23.0207 −4.52486 1.88E−10 IFI44 interferon-induced protein 44 −22.9589 −4.52098 1.56E−41 LINC00578 long intergenic non-protein coding −22.9554 −4.52076 1.06E−12 RNA 578 CSTA cystatin A (stefin A) −22.5737 −4.49657 1.31E−16 GPNMB glycoprotein (transmembrane) nmb −22.3879 −4.48465 4.97E−49 OR51E2 olfactory receptor_

family 51.sub.— −22.3769 −4.48394 6.76E−26 subfamily E_ member 2 LINC00856 long intergenic non-protein coding −22.3207 −4.48031 2.48E−10 RNA 856 CFB complement factor B −21.9633 −4.45702 8.87E−137 POMC proopiomelanocortin −21.6878 −4.43881 3.18E−11 LOC101927468 uncharacterized LOC101927468 −21.205 −4.40633 3.00E−10 CD7 CD7 molecule −21.1331 −4.40143 4.15E−27 BMPER BMP binding endothelial regulator −20.9432 −4.38841 4.46E−52 GSDMA gasdermin A −20.921 −4.38688 1.37E−11 SUSD3 sushi domain containing 3 −20.5652 −4.36213 1.29E−21 IL1A interleukin 1_ alpha −20.5136 −4.35851 3.30E−31 ELOVL3 ELOVL fatty acid elongase 3 −20.3658 −4.34808 3.34E−18 PCDHGA6 protocadherin gamma subfamily A_ 6 −20.2761 −4.34171 6.62E−25 IGJ joining chain of multimeric IgA and −19.8671 −4.31231 3.70E−12 IgM SEPSECS-AS1 SEPSECS antisense RNA 1 (head to −19.8668 −4.31229 1.20E−09 head) PPP4R4 protein phosphatase 4_ regulatory −19.4997 −4.28538 3.86E−40 subunit 4 CCL20 chemokine (C-C motif) ligand 20 −19.484 −4.28422 1.44E−14 DEPTOR DEP domain containing MTOR- −19.4709 −4.28325 9.47E−33 interacting protein ANKRD7 ankyrin repeat domain 7 −19.4419 −4.2811 1.58E−09 C3 complement component 3 −19.2979 −4.27037 2.08E−21 APOL1 apolipoprotein L_ 1 −19.0488 −4.25163 3.81E−37 ITGBL1 integrin_ beta-like 1 (with EGF-like −18.9388 −4.24327 1.78E−180 repeat domains) PCDHGA4 protocadherin gamma subfamily A_ 4 −18.6151 −4.2184 1.07E−14 SLC19A3 solute carrier family 19 (thiamine −18.5448 −4.21294 5.33E−16 transporter)_ member 3 CCL5 chemokine (C-C motif) ligand 5 −18.4312 −4.20408 2.95E−11 MIR656 microRNA 656 −18.4149 −4.2028 3.88E−09 MYH1 myosin_ heavy chain 1_ skeletal −18.0365 −4.17285 5.52E−09 muscle_ adult PDPN podoplanin −17.8868 −4.16082 2.51E−17 ZNF560 zinc finger protein 560 −17.6976 −4.14548 6.02E−17 HRNR hornerin −17.6899 −4.14485 1.10E−08 CNKSR2 connector enhancer of kinase −17.623 −4.13939 1.51E−09 suppressor of Ras 2 C21orf119 URB1 antisense RNA 1 (head to head) −17.6194 −4.13909 2.07E−45 SNORD114-1 small nucleolar RNA_ C/D box 114-1 −17.5184 −4.1308 6.92E−09 PCDHGA7 protocadherin gamma subfamily A_7 −17.5156 −4.13057 2.41E−19 SLC22A3 solute carrier family 22 (organic cation −17.5078 −4.12993 1.29E−63 transporter)_ member 3 LOC100507540 NA −17.3144 −4.1139 3.58E−11 ZNF595 zinc finger protein 595 −17.2473 −4.1083 3.38E−37 LOC100506834 uncharacterized LOC100506834 −17.2068 −4.10491 2.84E−25 DDX43 DEAD (Asp-Glu-Ala-Asp) box −17.0631 −4.09281 1.50E−09 polypeptide 43 SAMD9L sterile alpha motif domain containing −16.9705 −4.08496 9.90E−44 9-like ZNF578 zinc finger protein 578 −16.7751 −4.06825 6.41E−26 FAM20A family with sequence similarity 20.sub. — −16.5262 −4.04668 3.43E−12 member A ALDH1A3 aldehyde dehydrogenase 1 family.sub.— −16.4835 −4.04295 1.93E−28 member A3 LINC00839 long intergenic non-protein coding −16.3055 −4.02729 6.19E−08 RNA 839 LOC101926935 uncharacterized LOC101926935 −16.0385 −4.00347 2.44E−08 HSPA2 heat shock 70kDa protein 2 −15.5047 −3.95463 1.15E−64 SGCD sarcoglycan_ delta (35kDa dystrophin- −15.4663 −3.95106 8.53E−25 associated glycoprotein) AKR1C2 aldo-keto reductase family 1_ member −15.1928 −3.92532 5.86E−18 C2 FAM106A family with sequence similarity 106.sub.— −15.175 −3.92362 6.49E−08 member A SPON2 spondin 2_ extracellular matrix protein −15.051 −3.91179 5.07E−25 CNTNAP2 contactin associated protein-like 2 −14.8446 −3.89187 1.63E−17 BRINP3 bone morphogenetic protein/retinoic −14.776 −3.88518 3.70E−10 acid inducible neural-specific 3 ZNF280A zinc finger protein 280A −14.7238 −3.88008 1.26E−07 SYT11 synaptotagmin XI −14.71 −3.87873 2.65E−18 IL13RA2 interleukin 13 receptor_ alpha 2 −14.6618 −3.87399 7.77E−08 HTR2A 5-hydroxytryptamine (serotonin) −14.6491 −3.87274 9.16E−08 receptor 2A_ G protein-coupled FDCSP follicular dendritic cell secreted protein −14.606 −3.86849 1.59E−07 PF4 platelet factor 4 −14.5247 −3.86044 1.20E−07 LRRN4CL LRRN4 C-terminal like −14.4001 −3.84801 1.50E−36 COMT catechol-O-methyltransferase −14.3741 −3.8454 4.90E−145 HOXA1 homeobox A1 −14.3096 −3.83891 5.13E−52 PDE7B phosphodiesterase 7B −14.2867 −3.8366 4.03E−98 RAD21-AS1 RAD21 antisense RNA 1 −14.2782 −3.83574 9.85E−11 CBLC Cbl proto-oncogene C_ E3 ubiquitin −14.2299 −3.83085 1.46E−08 protein ligase PRSS3 protease_ serine_ 3 −14.22 −3.82985

2.89E−19 STXBP5L syntaxin binding protein 5-like −14.064 −3.81393 3.06E−22 AMPH amphiphysin −14.0368 −3.81114 9.92E−48 FAM50B family with sequence similarity 50.sub.— −13.9849 −3.8058 9.58E−38 member B MYH8 myosin_ heavy chain 8_ skeletal −13.9336 −3.8005 3.09E−08 muscle_ perinatal PRPH2 peripherin 2 (retinal degeneration.sub.— −13.832 −3.78994 3.29E−13 slow) ARHGAP20 Rho GTPase activating protein 20 −13.8103 −3.78767 5.09E−20 SPOCK3 sparc/osteonectin_ cwcv and kazal-like −13.79 −3.78555 1.19E−13 domains proteoglycan (testican) 3 HOXA10-AS HOXA10 antisense RNA −13.646 −3.77041 1.07E−23 GREM2 gremlin 2_ DAN family BMP −13.637 −3.76945 7.24E−18 antagonist C11orf70 chromosome 11 open reading frame 70 −13.5827 −3.7637 1.23E−56 PCDHGA8 protocadherin gamma subfamily A_8 −13.484 −3.75318 2.54E−63 SLC9A9 solute carrier family 9_ subfamily A −13.3834 −3.74237 2.92E−41 (NHE9_ cation proton antiporter 9).sub.— member 9 ZNF528 zinc finger protein 528 −13.3712 −3.74106 3.29E−35 HOXC11 homeobox C11 −13.3183 −3.73534 5.42E−20 HOTAIR HOX transcript antisense RNA −13.2446 −3.72733 1.66E−23 HOXA9 homeobox A9 −12.9587 −3.69585 2.40E−46 GALNT12 polypeptide N- −12.9507 −3.69496 6.77E−23 acetylgalactosaminyltransferase 12 PDE2A phosphodiesterase 2A_ cGMP- −12.9165 −3.69114 2.56E−12 stimulated PRSS12 protease_ serine_ 12 (neurotrypsin.sub.— −12.9162 −3.69111 2.60E−84 motopsin) LINC00707 long intergenic non-protein coding −12.9156 −3.69104 9.57E−21 RNA 707 CHRDL2 chordin-like 2 −12.9061 −3.68998 8.82E−08 PCDHGA5 protocadherin gamma subfamily A_ 5 −12.7366 −3.67091 3.66E−17 PPAPDC3 phosphatidic acid phosphatase type 2 −12.6247 −3.65818 4.50E−56 domain containing 3 ST6GALNAC5 ST6 (alpha-N-acetyl-neuraminy1-2_3- −12.604 −3.65581 1.09E−65 beta-galactosy1-1_3)-N-acetylgalactosaminide alpha-2_6- sialyltransferase 5 LIN7A lin-7 homolog A (*C. elegans*) −12.5604 −3.65081 2.64E−53 PTPRQ protein tyrosine phosphatase_ receptor −12.554 −3.65008 5.16E−36 type_ Q FAM27A family with sequence similarity 27.sub.— −12.3804 −3.62999 9.74E−07 member C CNTN5 contactin 5 −12.3042 −3.62108 8.87E−13 IL1RN interleukin 1 receptor antagonist −12.2859 −3.61893 9.35E−07 HS6ST3 heparan sulfate 6-O-sulfotransferase 3 −12.2168 −3.61079 9.07E−07 SNORD113-4 small nucleolar RNA_ C/D box 113-4 −12.116 −3.59884 9.47E−07 PRSS21 protease_ serine_ 21 (testisin) −12.0628 −3.59249 1.80E−06 TEKT4P2 tektin 4 pseudogene 2 −12.0135 −3.58658 2.77E−06 SYBU syntabulin (syntaxin-interacting) −11.9685 −3.58117 1.77E−17 P2RX1 purinergic receptor P2X_ ligand gated −11.86 −3.56803 1.82E−23 ion channel_ 1 IRX5 iroquois homeobox 5 −11.7574 −3.5555 1.53E−33 ENTPD1-AS1 ENTPD1 antisense RNA 1 −11.7407 −3.55345 1.43E−06 RBM47 RNA binding motif protein 47 −11.7375 −3.55305 6.27E−62 RFX8 RFX family member 8_ lacking RFX −11.7343 −3.55266 5.37E−18 DNA binding domain DHX58 DEXH (Asp-Glu-X-His) box −11.6685 −3.54455 1.82E−36 polypeptide 58 ESPNL espin-like −11.6038 −3.53652 1.55E−21 SPATA41 spermatogenesis associated 41 (non- −11.5983 −3.53584 2.01E−07 protein coding) SH3GL3 SH3-domain GRB2-like 3 −11.5783 −3.53335 5.54E−17 NDUFA4L2 NADH dehydrogenase (ubiquinone) 1 −11.5191 −3.52595 3.08E−25 alpha subcomplex_ 4-like 2 GGT5 gamma-glutamyltransferase 5 −11.506 −3.52432 1.42E−80 ASS1 argininosuccinate synthase 1 −11.4005 −3.51103 4.39E−41 LOC645638 NA −11.3763 −3.50796 8.68E−27 SLPI secretory leukocyte peptidase inhibitor −11.303 −3.49863 2.64E−06 AGBL2 ATP/GTP binding protein-like 2 −11.295 −3.49761 3.66E−16 HOXD4 homeobox D4 −11.2388 −3.49041 1.49E−21 TMEM155 transmembrane protein 155 −11.2145 −3.48729 1.59E−14 SMIM21 small integral membrane protein 21 −11.171 −3.48168 2.91E−06 C9orf170 chromosome 9 open reading frame 170 −11.1377 −3.47738 4.33E−07 ECM2 extracellular matrix protein 2_ female −11.0978 −3.4722 1.52E−29 organ and adipocyte specific CHRNA9 cholinergic receptor_ nicotinic_ alpha −11.0708 −3.46869 6.89E−07 9 (neuronal) PCDHGA2 protocadherin gamma subfamily A_ 2 −11.0172 −3.46168 8.04E−11 NAT2 N-acetyltransferase 2 (arylamine N- −10.9863 −3.45764 5.16E−10 acetyltransferase) EMX2 empty spiracles homeobox 2 −10.9733 −3.45593 3.76E−07 PDIA2 protein disulfide isomerase family A.sub.— −10.9385 −3.45134 6.66E−10 member 2 OGN

osteoglycin −10.9193 −3.44881 1.20E−07 LTF lactotransferrin −10.8719 −3.44253 4.86E−06 GRM6 glutamate receptor_ metabotropic 6 −10.8433 −3.43873 1.06E−06 PRR34 proline rich 34 −10.8229 −3.43601 9.05E−09 USP32P2 ubiquitin specific peptidase 32 −10.7465 −3.42579 1.18E−07 pseudogene 2 GPAT2 glycerol-3-phosphate acyltransferase −10.6944 −3.41879 1.94E−10 2_ mitochondrial PTGS2 prostaglandin-endoperoxide synthase 2 −10.678 −3.41657 4.22E−30 (prostaglandin G/H synthase and cyclooxygenase) C9orf64 chromosome 9 open reading frame 64 −10.6157 −3.40813 5.46E−28 LINC00884 long intergenic non-protein coding −10.5556 −3.39994 8.61E−07 RNA 884 GUCY1B3 guanylate cyclase 1_ soluble_ beta 3 −10.5296 −3.39638 6.23E−36 DMRT2 doublesex and mab-3 related −10.4519 −3.3857 9.81E−06 transcription factor 2 GBP5 guanylate binding protein 5 −10.4326 −3.38302 4.00E−07 MYOT myotilin −10.3531 −3.37199 4.38E−10 PCDHGB1 protocadherin gamma subfamily B_ 1 −10.3161 −3.36682 8.50E−10 EPGN epithelial mitogen −10.2797 −3.36172 3.50E−09 MME membrane metallo-endopeptidase −10.2755 −3.36114 5.88E−25 ST3GAL6- ST3GAL6 antisense RNA 1 −10.269 −3.36023 1.58E−12 AS1 ATP8B4 ATPase_ class I_ type 8B_ member 4 −10.242 −3.35643 9.62E−16 TSTD1 thiosulfate sulfurtransferase −10.231 −3.35488 2.07E−13 (rhodanese)-like domain containing 1 LOC102724927 uncharacterized LOC102724927 −10.1447 −3.34265 1.27E−18 LIPC lipase_ hepatic −10.1202 −3.33917 9.64E−06 RAETIE retinoic acid early transcript 1E −10.1052 −3.33702 4.21E−07 EMX2OS EMX2 opposite strand/antisense RNA −10.0321 −3.32655 1.01E−05 LINC00540 long intergenic non-protein coding −9.99412 −3.32108 1.10E−05 RNA 540 RSPO2 R-spondin 2 −9.98734 −3.3201 9.05E−06 PDE4B phosphodiesterase 4B_ cAMP-specific −9.96763 −3.31725 4.87E−44 LCNL1 lipocalin-like 1 −9.96645 −3.31708 4.54E−26 HOTAIRM1 HOXA transcript antisense RNA.sub.— −9.94899 −3.31455 2.93E−11 myeloid-specific 1 DMGDH dimethylglycine dehydrogenase −9.88328 −3.30499 4.90E−09 SIGLEC10 sialic acid binding Ig-like lectin 10 −9.87917 −3.30439 1.40E−06 ELANE elastase_ neutrophil expressed −9.78058 −3.28992 1.22E−05 CD55 CD55 molecule_ decay accelerating −9.66681 −3.27304 1.09E−17 factor for complement (Cromer blood group) TNFRSF8 tumor necrosis factor receptor −9.66205 −3.27233 3.99E−08 superfamily_ member 8 MB21D1 Mab-21 domain containing 1 −9.5886 −3.26132 2.18E−34 IL1R1 interleukin 1 receptor type_ I −9.54616 −3.25492 5.60E−97 SNTG2 syntrophin_ gamma 2 −9.4908 −3.24653 5.86E−14 ANPEP alanyl (membrane) aminopeptidase −9.46866 −3.24316 1.64E−113 HP09025 uncharacterized LOC100652929 −9.45076 −3.24043 1.87E−05 PAX8 paired box 8 −9.40977 −3.23416 5.17E−15 IL 1R2 interleukin 1 receptor_type II −9.39713 −3.23222 4.46E−07 HOXA10 homeobox A10 −9.37189 −3.22834 2.63E−96 ST8SIA4 ST8 alpha-N-acetyl-neuraminide −9.36728 −3.22763 1.55E−42 alpha-2_8-sialyltransferase 4 PIWIL2 piwi-like RNA-mediated gene −9.31522 −3.21959 1.57E−10 silencing 2 COL14A1 collagen_ type XIV_ alpha 1 −9.30515 −3.21803 2.33E−09 DHRS3 dehydrogenase/reductase (SDR family) −9.29774 −3.21688 2.28E−115 member 3 MR1 major histocompatibility complex.sub.— −9.27785 −3.21379 5.21E−24 class I-related HOXA11 homeobox A11 −9.21868 −3.20456 5.28E−303 VTN vitronectin −9.19685 −3.20114 6.40E−52 C1QTNF1 C1q and tumor necrosis factor related −9.16344 −3.19589 1.36E−28 protein 1 ABCA6 ATP-binding cassette_ sub-family A −9.06131 −3.17972 9.25E−09 (ABC1)_ member 6 CHRM3 cholinergic receptor_ muscarinic 3 −9.03134 −3.17494 2.72E−05 GPR85 G protein-coupled receptor 85 −9.02571 −3.17404 7.36E−43 CCL7 chemokine (C-C motif) ligand 7 −9.01627 −3.17253 1.82E−13 KLF4 Kruppel-like factor 4 (gut) −8.9928 −3.16877 2.83E−34 MALRD1 MAM and LDL receptor class A −8.91837 −3.15678 3.50E−05 domain containing 1 SLC27A2 solute carrier family 27 (fatty acid −8.91108 −3.1556 1.64E−10 transporter)_ member 2 DIRAS3 DIRAS family_ GTP-binding RAS- −8.838 −3.14372 9.46E−137 like 3 CRYAB crystallin_ alpha B −8.83359 −3.143 1.22E−23 LINC00968 long intergenic non-protein coding −8.82888 −3.14223 2.73E−11 RNA 968 LAMA2 laminin_ alpha 2 −8.81329 −3.13968 1.53E−37 MCTP2 multiple C2 domains_ transmembrane −8.79577 −3.13681 2.25E−19 2 MIR199A1 microRNA 199a-1 −8.77312 −3.13309 2.25E−06 FGF14 fibroblast growth factor 14 −8.76655 −3.13201 2.54E−13

PIWIL3 piwi-like RNA-mediated gene −8.74695 −3.12878 4.15E−05 silencing 3 PRG2 proteoglycan 2_ bone marrow (natural −8.69683 −3.12049 3.14E−08 killer cell activator_ eosinophil granule major basic protein) NMU neuromedin U −8.66945 −3.11594 4.96E−05 PTPN20B protein tyrosine phosphatase_ non- −8.55964 −3.09755 4.66E−05 receptor type 20 XAF1 XIAP associated factor 1 −8.55869 −3.09739 3.21E−18 ABCC3 ATP-binding cassette_ sub-family C −8.55857 −3.09737 3.88E−29 (CFTR/MRP)_ member 3 HSPA7 heat shock 70kDa protein 7 (HSP70B) −8.55436 −3.09666 4.67E−05 SYN3 synapsin III −8.54843 −3.09566 4.78E−05 JAKMIP2 janus kinase and microtubule −8.53996 −3.09423 2.50E−07 interacting protein 2 TMCC3 transmembrane and coiled-coil domain −8.52719 −3.09207 1.37E−26 family 3 IL22RA1 interleukin 22 receptor_ alpha 1 −8.46823 −3.08206 1.47E−05 ATE1-AS1 ATE1 antisense RNA 1 −8.42987 −3.07551 5.34E−05 KCND2 potassium channel_ voltage gated Shal −8.41096 −3.07227 1.61E−10 related subfamily D_ member 2 MIR410 microRNA 410 −8.40927 −3.07198 5.23E−05 LINC00664 long intergenic non-protein coding −8.4 −3.07039 5.69E−05 RNA 664 MKRN3 makorin ring finger protein 3 −8.37959 −3.06688 6.58E−05 ANKRD2 ankyrin repeat domain 2 (stretch −8.36891 −3.06504 2.42E−14 responsive muscle) COL8A2 collagen_ type VIII_ alpha 2 −8.26996 −3.04788 8.49E−24 CFHR1 complement factor H-related 1 −8.24809 −3.04406 7.97E−12 TRPV3 transient receptor potential cation −8.2018 −3.03594 8.67E−13 channel_ subfamily V_member 3 GAL3ST1 galactose-3-O-sulfotransferase 1 −8.17971 −3.03205 7.89E−05 PCDHGB5 protocadherin gamma subfamily B_ 5 −8.17002 −3.03034 3.34E−09 TFPI2 tissue factor pathway inhibitor 2 −8.1526 −3.02726 4.98E−24 LPO lactoperoxidase −8.10836 −3.01941 1.89E−05 EVI2B ecotropic viral integration site 2B −8.07532 −3.01352 5.75E−10 FRMPD1 FERM and PDZ domain containing 1 −8.0519 −3.00933 3.56E−05 B4GALNT1 beta-1_4-N-acetyl-galactosaminyl −8.04934 −3.00887 1.81E−22 transferase 1 TRPA1 transient receptor potential cation −8.02538 −3.00457 1.88E−06 channel_ subfamily A_ member 1 ASB2 ankyrin repeat and SOCS box −7.95317 −2.99153 5.28E−17 containing 2 HOXD3 homeobox D3 −7.92077 −2.98564 8.03E−07 POM121L9P POM121 transmembrane nucleoporin- −7.87866 −2.97795 1.58E−09 like 9_ pseudogene PSG5 pregnancy specific beta-1-glycoprotein −7.82847 −2.96873 1.32E−09 5 LOC654342 lymphocyte-specific protein 1 −7.8218 −2.9675 3.42E−73 pseudogene HOXA3 homeobox A3 −7.76922 −2.95777 1.04E−15 HOXC-AS3 HOXC cluster antisense RNA 3 −7.75002 −2.9542 6.68E−09 CDSN corneodesmosin −7.74895 −2.954 7.46E−07 PLEKHA7 pleckstrin homology domain −7.71957 −2.94852 1.05E−16 containing_ family A member 7 GRIK2 glutamate receptor_ ionotropic.sub.— −7.70925 −2.94659 2.40E−44 kainate 2 FXYD1 FXYD domain containing ion −7.67911 −2.94094 3.54E−13 transport regulator 1 TRIM4 tripartite motif containing 4 −7.65127 −2.9357 3.26E−64 PP12613 uncharacterized LOC100192379 −7.61931 −2.92966 3.85E−05 KDR kinase insert domain receptor −7.59337 −2.92474 1.08E−31 MIR10B microRNA 10b −7.59337 −2.92474 0.000142 TSPAN32 tetraspanin 32 −7.56594 −2.91952 7.50E−09 TRPM3 transient receptor potential cation −7.55714 −2.91784 3.49E−09 channel_ subfamily M_ member 3 RGL3 ral guanine nucleotide dissociation −7.55567 −2.91756 7.95E−09 stimulator-like 3 CXCL14 chemokine (C-X-C motif) ligand 14 −7.54181 −2.91491 5.44E−10 RBM46 RNA binding motif protein 46 −7.53465 −2.91354 0.000159 KCNQ3 potassium channel_ voltage gated −7.52817 −2.9123 4.08E−20 KQT-like subfamily Q_ member 3 FAM225A family with sequence similarity 225.sub.— −7.51587 −2.90994 0.000168 member A (non-protein coding) TRIM29 tripartite motif containing 29 −7.49381 −2.9057 4.35E−15 PRDM1 PR domain containing 1_ with ZNF −7.48966 −2.9049 5.11E−33 domain HIST2H2BA histone cluster 2_ H2ba (pseudogene) −7.48011 −2.90306 1.97E−12 SUSD2 sushi domain containing 2 −7.47804 −2.90266 2.34E−06 HPD 4-hydroxyphenylpyruvate dioxygenase −7.46064 −2.8993 4.25E−10 GPR115 adhesion G protein-coupled receptor −7.46028 −2.89923 2.61E−26 F4 PHYHIP phytanoyl-CoA 2-hydroxylase −7.44742 −2.89674 6.50E−21 interacting protein SPN sialophorin −7.40741 −2.88897 1.04E−09 FAM109B family with sequence similarity 109.sub.— −7.38363 −2.88433 1.52E−90 member B LOC101926892 uncharacterized LOC101926892 −7.34595 −2.87695 0.000183 CASC1

cancer susceptibility candidate 1 −7.33019 −2.87385 4.51E−06 PRND prion protein 2 (dublet) −7.32328 −2.87249 0.000189 KCNT2 potassium channel_ sodium activated −7.26433 −2.86083 3.16E−13 subfamily T_ member 2 GBP7 guanylate binding protein 7 −7.24964 −2.85791 0.000204 TYMP thymidine phosphorylase −7.24643 −2.85727 1.99E−51 P4HA3 prolyl 4-hydroxylase_ alpha −7.23127 −2.85425 1.01E−28 polypeptide III MX2 MX dynamin-like GTPase 2 −7.22406 −2.85281 1.96E−43 ATP6V0A4 ATPase_ H+ transporting_ lysosomal −7.16531 −2.84103 3.08E−06 V0 subunit a4 IL6 interleukin 6 −7.16268 −2.8405 6.92E−09 SCRG1 stimulator of chondrogenesis 1 −7.14171 −2.83627 3.06E−33 ENPP4 ectonucleotide −7.11247 −2.83035 2.30E−06 pyrophosphatase/phosphodiesterase 4 (putative) GCH1 GTP cyclohydrolase 1 −7.09022 −2.82583 2.11E−20 LOC102724224 NA −7.07054 −2.82182 5.08E−15 ZNF726 zinc finger protein 726 −7.05854 −2.81937 2.09E−07 TNFRSF11B tumor necrosis factor receptor −7.05683 −2.81902 6.55E−11 superfamily_ member 11b ZNF829 zinc finger protein 829 −7.04715 −2.81704 2.15E−54 TULP2 tubby like protein 2 −7.04485 −2.81657 1.07E−05 LOC101929319 uncharacterized LOC101929319 −7.03261 −2.81406 0.000119 HSPB6 heat shock protein_ alpha-crystallin- −7.01854 −2.81117 1.15E−21 related_ B6 LAMA1 laminin_ alpha 1 −7.0143 −2.8103 9.37E−45 LUZP2 leucine zipper protein 2 −7.00954 −2.80932 7.61E−31 LOC101928161 uncharacterized LOC101928161 −7.00255 −2.80788 6.81E−24 CCDC64B coiled-coil domain containing 64B −6.98897 −2.80508 0.000297 CRHR2 corticotropin releasing hormone −6.98839 −2.80496 1.30E−06 receptor 2 TIMP3 TIMP metallopeptidase inhibitor 3 −6.988 −2.80488 2.42E−17 OASL 2′-5′-oligoadenylate synthetase-like −6.98369 −2.80399 0.000202 SGCG sarcoglycan_ gamma (35kDa −6.94816 −2.79663 9.02E−14 dystrophin-associated glycoprotein) GYPE glycophorin E (MNS blood group) −6.91309 −2.78933 0.000146 TMEM215 transmembrane protein 215 −6.8823 −2.78289 0.00033 RADIL Ras association and DIL domains −6.86181 −2.77859 2.72E−30 LRRIQ3 leucine-rich repeats and IQ motif −6.8524 −2.77661 1.68E−06 containing 3 NR5A2 nuclear receptor subfamily 5_ group −6.85041 −2.77619 0.00012 A_ member 2 PABPC4L poly(A) binding protein_ cytoplasmic −6.84818 −2.77572 4.78E−29 4-like PLSCR4 phospholipid scramblase 4 −6.843 −2.77463 9.90E−72 LOC100132891 NA −6.83817 −2.77361 1.07E−10 LOC100240734 uncharacterized LOC100240734 −6.83201 −2.77231 1.59E−05 PRDM6 PR domain containing 6 −6.76711 −2.75854 3.35E−06 DNAJC12 DnaJ (Hsp40) homolog_ subfamily C.sub.— −6.76134 −2.75731 4.24E−23 member 12 ADAM33 ADAM metallopeptidase domain 33 −6.74519 −2.75386 6.75E−10 ANXA8 annexin A8 −6.73118 −2.75086 2.82E−18 ZFYVE28 zinc finger_ FYVE domain containing −6.72083 −2.74864 3.30E−17 28 RRN3P2 RRN3 homolog_ RNA polymerase I −6.70557 −2.74536 3.86E−14 transcription factor pseudogene 2 LINC00271 long intergenic non-protein coding −6.69285 −2.74262 0.000178 RNA 271 LINC01116 long intergenic non-protein coding −6.69169 −2.74237 1.07E−40 RNA 1116 KCNIP3 Kv channel interacting protein 3.sub.— −6.68459 −2.74084 4.54E−17 calsenilin SLC30A3 solute carrier family 30 (zinc −6.68237 −2.74036 0.000188 transporter)_ member 3 KCNE4 potassium channel_ voltage gated −6.67672 −2.73914 2.01E−26 subfamily E regulatory beta subunit 4 LOC101927650 uncharacterized LOC101927650 −6.66004 −2.73553 0.000222 MEG9 maternally expressed 9 (non-protein −6.64975 −2.7333 1.07E−11 coding) SPAG17 sperm associated antigen 17 −6.63263 −2.72958 2.02E−05 RNF112 ring finger protein 112 −6.62601 −2.72814 4.94E−13 BACH2 BTB and CNC homology 1_ basic −6.60624 −2.72383 3.20E−09 leucine zipper transcription factor 2 M1AP meiosis 1 associated protein −6.59279 −2.72089 0.000184 HOXA7 homeobox A7 −6.5864 −2.71949 7.83E−11 PPP1R14C protein phosphatase 1_ regulatory −6.57354 −2.71667 0.000573 (inhibitor) subunit 14C LINC01081 long intergenic non-protein coding −6.53252 −2.70764 0.000487 RNA 1081 MOCOS molybdenum cofactor sulfurase −6.52985 −2.70705 4.40E−12 HOXA4 homeobox A4 −6.49257 −2.69879 4.09E−14 ATP2B1 ATPase_ Ca++ transporting_ plasma −6.48124 −2.69627 8.06E−35 membrane 1 ALDH3B1 aldehyde dehydrogenase 3 family.sub.— −6.47078 −2.69394 9.21E−80 member B1 NKG7 natural killer cell granule protein 7 −6.43206 −2.68528 0.000222 S100A4 S100

calcium binding protein A4 −6.42248 −2.68313 3.30E−18 LOC441666 zinc finger protein 91 pseudogene −6.41349 −2.68111 0.00069 CRISPLD2 cysteine-rich secretory protein LCCL −6.38028 −2.67362 2.78E−11 domain containing 2 SLC38A5 solute carrier family 38_ member 5 −6.37595 −2.67264 7.82E−40 KRT34 keratin 34_ type I −6.35852 −2.66869 2.57E−05 APOL6 apolipoprotein L_ 6 −6.33252 −2.66278 1.01E−35 DPP10 dipeptidyl-peptidase 10 (non- −6.31845 −2.65957 7.29E−06 functional) KLF15 Kruppel-like factor 15 −6.30523 −2.65655 6.85E−06 IL33 interleukin 33 −6.28503 −2.65192 1.04E−11 HOXA-AS3 HOXA cluster antisense RNA 3 −6.27515 −2.64965 1.92E−19 MIR541 microRNA 541 −6.22835 −2.63885 0.000695 ANXA8L1 annexin A8-like 1 −6.21916 −2.63672 9.58E−20 STRA6 stimulated by retinoic acid 6 −6.21395 −2.63551 3.82E−20 PM20D1 peptidase M20 domain containing 1 −6.20921 −2.63441 0.000794 GPR1 G protein-coupled receptor 1 −6.19666 −2.63149 2.05E−28 IL21R interleukin 21 receptor −6.16645 −2.62444 2.53E−09 LOC284889 NA −6.15198 −2.62105 2.12E−09 FLJ45974 NA −6.10766 −2.61062 0.000858 ABCA9 ATP-binding cassette_ sub-family A −6.09827 −2.6084 8.73E−07 (ABC1)_ member 9 C12orf56 chromosome 12 open reading frame 56 −6.09688 −2.60807 0.000122 AKRIB10 aldo-keto reductase family 1_ member −6.09206 −2.60693 1.09E−07 B10 (aldose reductase) MYBPH myosin binding protein H −6.06324 −2.60009 0.000347 HSD11B1 hydroxysteroid (11-beta) −6.05896 −2.59907 0.001014 dehydrogenase 1 LOC391322 D-dopachrome tautomerase-like −6.05149 −2.59729 1.82E−07 LIPI lipase_ member I −6.03465 −2.59327 0.000958 ICAM4 intercellular adhesion molecule 4 −6.03072 −2.59233 1.43E−11 (Landsteiner-Wiener blood group) RTP4 receptor (chemosensory) transporter −5.97637 −2.57927 0.00098 protein 4 LOC100507642 uncharacterized LOC100507642 −5.96305 −2.57605 2.82E−29 C4BPB complement component 4 binding −5.95421 −2.57391 5.64E−14 protein_ beta EVA1C eva-1 homolog C (*C. elegans*) −5.94217 −2.57099 2.18E−23 MIR615 microRNA 615 −5.8772 −2.55513 0.001088 ASIC5 acid sensing (proton gated) ion channel −5.87676 −2.55502 0.001107 family member 5 TRIM61 tripartite motif containing 61 −5.85513 −2.5497 1.21E−16 OLFML3 olfactomedin-like 3 −5.84576 −2.54739 2.66E−32 ALPK 1 alpha-kinase 1 −5.8373 −2.5453 4.75E−37 LINC00936 long intergenic non-protein coding −5.81396 −2.53952 1.41E−32 RNA 936 LINC00570 long intergenic non-protein coding −5.80852 −2.53817 0.001211 RNA 570 LOC340515 NA −5.80538 −2.53739 0.001211 GALNT18 polypeptide N- −5.78501 −2.53232 1.74E−19 acetylgalactosaminyltransferase 18 HOXA11-AS HOXA11 antisense RNA −5.778 −2.53057 4.63E−102 HRCT1 histidine rich carboxyl terminus 1 −5.77227 −2.52914 9.88E−32 RASIP1 Ras interacting protein 1 −5.75398 −2.52456 8.49E−17 FPR2 formyl peptide receptor 2 −5.74597 −2.52255 0.001275 IFI44L interferon-induced protein 44-like −5.74306 −2.52182 9.82E−09 CCDC147- CFAP58 antisense RNA 1 (head to −5.73952 −2.52093 4.88E−09 AS1 head) LDHAL6B lactate dehydrogenase A-like 6B −5.7328 −2.51924 0.000211 KCTD12 potassium channel tetramerization −5.71221 −2.51405 6.98E−12 domain containing 12 GNG2 guanine nucleotide binding protein (G −5.71055 −2.51363 8.51E−23 protein)_ gamma 2 KLHL33 kelch-like family member 33 −5.70418 −2.51202 0.001368 ADAMTS1 ADAM metallopeptidase with −5.69596 −2.50994 5.60E−24 thrombospondin type 1 motif_1 SCIN scinderin −5.69008 −2.50845 3.26E−08 INSC inscuteable homolog (*Drosophila*) −5.68555 −2.5073 0.001391 DLGAP1 discs_ large (*Drosophila*) homolog- −5.66922 −2.50315 0.000493 associated protein 1 ZNF354C zinc finger protein 354C −5.66871 −2.50302 2.85E−06 ODAM odontogenic_ ameloblast asssociated −5.65223 −2.49882 0.001552 LPXN leupaxin −5.65203 −2.49877 1.59E−27 NOV nephroblastoma overexpressed −5.63045 −2.49325 3.30E−06 HAND2-AS1 HAND2 antisense RNA 1 (head to −5.60856 −2.48763 2.11E−115 head) BCL2A1 BCL2-related protein A1 −5.60848 −2.48761 0.000262 ENPP2 ectonucleotide −5.60393 −2.48644 9.74E−09 pyrophosphatase/phosphodiesterase 2 CKM creatine kinase_ muscle −5.5897 −2.48277 0.001639 PTGDR prostaglandin D2 receptor (DP) −5.57391 −2.47869 0.001624 SLC7A7 solute carrier family 7 (amino acid −5.57314 −2.47849 9.34E−50 transporter light chain_ y + L system).sub.— member 7 DAW1 dynein assembly factor with WDR −5.55902 −2.47483 1.25E−12 repeat domains 1 OVCH1-AS1 OVCH1

antisense RNA 1 −5.55493 −2.47377 0.001707 LRRTM2 leucine rich repeat transmembrane −5.53203 −2.46781 3.28E−08 neuronal 2 KCNE3 potassium channel_ voltage gated −5.51951 −2.46454 1.51E−14 subfamily E regulatory beta subunit 3 IRAK3 interleukin-1 receptor-associated −5.51068 −2.46223 3.63E−10 kinase 3 OGFRL 1 opioid growth factor receptor-like 1 −5.50247 −2.46008 1.39E−99 HOXA6 homeobox A6 −5.50015 −2.45947 8.54E−12 C1S complement component 1_ s −5.47793 −2.45363 2.03E−35 subcomponent CYSLTR2 cysteinyl leukotriene receptor 2 −5.47489 −2.45283 0.000616 PODNL1 podocan-like 1 −5.47322 −2.45239 5.63E−51 RBM11 RNA binding motif protein 11 −5.4681 −2.45104 0.001847 NID2 nidogen 2 (osteonidogen) −5.45103 −2.44653 3.65E−43 BTBD11 BTB (POZ) domain containing 11 −5.44775 −2.44566 4.29E−45 KIF6 kinesin family member 6 −5.44126 −2.44394 0.000483 LYPD5 LY6/PLAUR domain containing 5 −5.42409 −2.43938 0.001979 GCNT1 glucosaminyl (N-acetyl) transferase 1.sub.— −5.42224 −2.43889 2.28E−139 core 2 LOC375196 uncharacterized LOC375196 −5.42074 −2.43849 7.01E−06 LOC101928200 NA −5.3954 −2.43173 6.53E−14 ADAMTS9 ADAM metallopeptidase with −5.39529 −2.4317 1.31E−12 thrombospondin type 1 motif_ 9 LINC00870 long intergenic non-protein coding −5.3923 −2.4309 0.002006 RNA 870 MIR6730 microRNA 6730 −5.39211 −2.43085 0.000806 CP ceruloplasmin (ferroxidase) −5.37483 −2.42622 0.001242 SULT1E1 sulfotransferase family 1E_ estrogen- −5.35869 −2.42188 8.47E−05 preferring_ member 1 ROR2 receptor tyrosine kinase-like orphan −5.35832 −2.42178 2.45E−10 receptor 2 MFSD7 major facilitator superfamily domain −5.34533 −2.41828 1.30E−20 containing 7 NECAB2 N-terminal EF-hand calcium binding −5.33837 −2.4164 3.15E−09 protein 2 IP6K3 inositol hexakisphosphate kinase 3 −5.33649 −2.41589 3.69E−24 INHBE inhibin_ beta E −5.3237 −2.41243 5.12E−18 ALDH1L2 aldehyde dehydrogenase 1 family.sub.— −5.30804 −2.40818 1.83E−18 member L2 HOXA2 homeobox A2 −5.30253 −2.40668 3.64E−08 RCN3 reticulocalbin 3_ EF-hand calcium −5.29984 −2.40595 2.01E−34 binding domain NOL4 nucleolar protein 4 −5.2921 −2.40384 0.001181 ISLR2 immunoglobulin superfamily −5.28928 −2.40307 0.002359 containing leucine-rich repeat 2 DHRS4L1 dehydrogenase/reductase (SDR family) −5.27818 −2.40004 7.20E−08 member 4 like 1 HOXA5 homeobox A5 −5.27503 −2.39918 7.07E−11 EHHADH enoyl-CoA_ hydratase/3-hydroxyacyl −5.26119 −2.39539 1.38E−16 CoA dehydrogenase LOC101928891 uncharacterized LOC101928891 −5.25839 −2.39462 4.53E−08 MGC27382 uncharacterized MGC27382 −5.25791 −2.39449 0.002301 SLC12A8 solute carrier family 12_ member 8 −5.24943 −2.39216 1.29E−29 CTHRC1 collagen triple helix repeat containing −5.23947 −2.38942 1.59E−40 1 SNORD127 small nucleolar RNA_ C/D box 127 −5.22474 −2.38536 0.001157 BST1 bone marrow stromal cell antigen 1 −5.2242 −2.38521 6.04E−21 APOA1 apolipoprotein A-I −5.2238 −2.3851 1.64E−06 LINC01169 long intergenic non-protein coding −5.21414 −2.38243 0.001091 RNA 1169 LINC00163 long intergenic non-protein coding −5.21393 −2.38237 0.000343 RNA 163 FHAD1 forkhead-associated (FHA) −5.1735 −2.37114 3.98E−12 phosphopeptide binding domain 1 PDC phosducin −5.16569 −2.36896 0.001012 HMOX1 heme oxygenase 1 −5.15739 −2.36664 5.29E−29 FAM27E3 family with sequence similarity 27.sub.— −5.15367 −2.3656 9.91E−07 member E3 HAS1 hyaluronan synthase 1 −5.14635 −2.36355 9.44E−07 LINC00052 long intergenic non-protein coding −5.13691 −2.3609 5.40E−09 RNA 52 EYA2 EYA transcriptional coactivator and −5.12816 −2.35844 0.000837 phosphatase 2 CABP1 calcium binding protein 1 −5.1219 −2.35668 0.001407 PCDHGA1 protocadherin gamma subfamily A_ 1 −5.11598 −2.35501 6.54E−05 TXNRD2 thioredoxin reductase 2 −5.10008 −2.35052 2.65E−45 USP32P1 ubiquitin specific peptidase 32 −5.02757 −2.32986 0.001626 pseudogene 1 DPP4 dipeptidyl-peptidase 4 −5.00486 −2.32333 2.66E−16

Example 7—In Vivo Middle Cerebral Artery Occlusion (MCAO) Stroke Model

[0355] The HMCs and HMC-EVs of the presently disclosed subject matter were tested in an in vivo model of middle cerebral artery occlusion (MCAO) stroke.

[0356] HMCs were generated from the same bank of frozen hemangioblasts described in Example 1.

[0357] For HMC-EVs, early passage (passage 4) HMCs were thawed, washed, counted, and plated in Corning CellBIND flasks at a density of 5,000 cells/cm.sup.2 in RoosterBio RoosterNourish-MSC-XF media. Cells were grown for 96 hours to a confluence of approximately 70-90% for acclimation to the media and cell expansion. At 96 hours, cells were removed from flasks with TripLE dissociation, live cells were counted, and replated at 5,000 cells/cm.sup.2 in new flasks and fresh media at passage 5. At this passage media can be collected after 96 hours for EV isolation. Cells can be passaged again up to passage 7 for larger volumes of media collection. After media aas harvested for EV isolation, it was clarified to remove cells and debris with differential, low-speed centrifugation at 300×g for 10 minutes and 2,000×g for 20 minutes followed by 0.2 μm vacuum filtration. EVs were isolated from the clarified media using tangential flow filtration (TFF) on the Repligen KR2i system outfitted with a hollow fiber, 300 kDa pore, mPES membrane filter. The approximately 100 nm pore size of filter removed small impurities and retained the EVs. Combined, the clarification and TFF parameters were such that particles between 100 nm and 200 nm in size were isolated. The media was first concentrated by a factor of approximately 10× before it was diafiltered with DPBS to improve sample purity and remove non-EV associated proteins during the TFF process. The diafiltered media was further concentrated so that the final product was concentrated by a factor of approximately 100x. The resulting isolated and concentrated EVs in DPBS were then ready for downstream analyses and could also be further purified using chromatography techniques.

In Vivo Effects of HMCs and HMC-EVs on Locomotor Skills

[0358] MCAO animal models were generated as described herein. Briefly, one day prior to surgical injury, the Body Swing Test was performed to establish the baseline performance using male Sprague-Dawley rats (300-400 g). For each, the rat was held approximately one inch from the base of its tail. It was then elevated to an inch above a surface of a table. The rat was held in the vertical axis, defined as no more than 100 to either the left or the right side. A swing was recorded whenever the rat moved its head out of the vertical axis to either side. The rat must have returned to the vertical position for the next swing to be counted. Thirty total swings were counted. A normal rat typically has an equal number of swings to either side. Following focal ischemia, the rat tends to swing to the contralateral (left) side. After one day of testing, focal cerebral infarcts were made by permanent occlusion of the proximal right middle cerebral artery (MCA) using a modification of the method of Tamura et al. The rats were anesthetized with 1-3% isoflurane in the mixture of N.sub.2O:O.sub.2 (2:1), and were maintained with 1.5-2% isoflurane in the mixture of N.sub.2O:O.sub.2 (2:1). The temporalis muscle was bisected and reflected through an incision made midway between the eye and the eardrum canal. The proximal MCA was exposed through a subtemporal craniectomy without removing the zygomatic arch and without transecting the facial nerve. The artery was then occluded by microbipolar coagulation from just proximal to the olfactory tract to the inferior cerebral vein. Body temperature was maintained at 37.0±1° C. throughout the entire procedure. Cefazolin (40 mg/kg) was given intraperitoneally (i.p.) before MCAO to prevent infections. Buprenorphine, s.c, (˜0.1 mg/kg Simbadol) was given before the MCAO surgery as analgesia. For Sham conditions, animals underwent the same procedure described above without the middle cerebral artery being coagulated.

[0359] Treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%). For HMC treatments, the cells were stored in liquid nitrogen until the day of use. Cells were thawed in a 37° C. water bath, counted, and diluted in the vehicle, Plasma-Lyte A. For HMC-EV treatments, EV aliquots were stored at −80° C. until the day of use. EVs were thawed on ice and either diluted in the vehicle, DPBS, or used as prepared.

[0360] On day 1 and day 7 after the MCAO (24 hours and 7 days+/−10.sup.0/a), animals were anesthetized with 1-3% isoflurane in the 02 and were maintained with 1.5-2% isoflurane in 02. Jugular vein injections were performed by using a 1 ml syringe with a 25G (3/4″) needle attached, 0.5 ml vehicle or cells were injected into the jugular vein. The injection site was compressed for

about 1 minute to ensure there was no bleeding. Local injection were performed by using a 50 microliter Hamilton syringe with a 26G needle attached, 10 microliters of vehicle, cells, or EVs were injected to the peri infarct area in 3 locations at 3 to 4 microliters per site. Intrathecal injections were performed using a 25G hypodermic needle and an insulin syringe (0.5 mL), 40 microliters of vehicle, cells, or EVs were injected between the last lumbar vertebra and the 1st sacral vertebrae (L6-S1).

[0361] The Body Swing Test was performed on day 1, 7, 14, 21, and 28 post-injury, and animals were sacrificed after testing 28 days post-injury. At twenty-eight days (Day 28) after MCAO, rats were anesthetized deeply with ketamine/xylazine (91 mg/kg ketamine, 9 mg/kg xylazine, respectively). After the rats were in the deep anesthetized stage, they were perfused transcardially with normal saline (with heparin 2 unit/ml) followed by 4% paraformaldehyde. Brains were removed and stored in 4% paraformaldehyde for 24 hours then changed to 1×PBS and stored in 0-4° C. All data were expressed as mean f S.E.M. The Body Swing Test data was analyzed by two-way ANOVA and Tukey's multiple comparison test. Significance is represented as *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

[0362] The effects of the HMCs and HMC-EVs of the presently disclosed subject matter on locomotion were evaluated in MCAO models.

[0363] HMC cells were injected via three routes of administrations including intravenous (IV), intracerebral (IC) and intrathecal (IT) administration. Cells were dosed at 4 million in 0.5 mL per IV jection; 400,000 in 10 microliters per IC injection; and 500,000 or 1 million in 40 microliters per IT injection. As shown in FIG. **20**, all treatment groups demonstrated improvement in recovering deficits in the Body Swing Test, with the IV and IC treatments having the most significance.

[0364] In another study, animals were subjected to the MCAO injury as described above. Cell treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%) using HMCs, specifically HMCs derived from C-GS1 cells (C-GS1-HMC) and N-lot QR57 cells (N-HMC). The dosing of the cells was 4 million in 0.5 mL per IV injection. Extracellular vesicle (EV) treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%) using EVs derived from N-HMCs (N-HMC-EVs). The dosing of the EVs was 10×10.sup.10 for intracerebral and intracisternal. All treatment groups demonstrated significant improvement in the limb placement tests (FIG. **21**). In the Body Swing Test, all treatment groups provided recovery, with the C-GS1-HMCs, N-HMCs, and N-HMC-EVs via intracerebral injections demonstrating significant increases.

[0365] In a separate study, treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%) using N-HMC-EVs (N-lot p6 and p7 treated with IFNgamma for 96 hours at 50 ng/ml). The dosing of the EVs was 10×10.sup.10 or 30×10.sup.10 total for N-HMC-EVs (stimulated N-lot) via intracisternal injections. All groups provided significant improvement in all three behavioral tests, with the most significant improvement demonstrated in the forelimb placement test and the body swing test (FIG. **22**).

[0366] In yet another study, treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%) using HMC-EVs (N-lot) or HE-VPC-EVs. The dosing of the exosomes was 10×10.sup.10, 30×10.sup.10, and 10×10.sup.11 for HMC-EVs and 10×10.sup.10 for VPC-EVs via intrathecal injections. HMC-EV depleted injections were performed as a negative control. All groups provided significant improvement in all three behavioral tests, with the most significant improvement demonstrated in the forelimb placement test and the body swing test (FIG. **23**).

[0367] Accordingly, the HMCs of the presently disclosed subject matter and HMC-EVs were efficacious in an MCAO stroke model via intravenous, intrathecal, intracerebral and/or intracisternal administrations, and both HMC and EV treatments provided improved locomotor recovery in behavioral tests.

In Vivo Effects of HMC on Histopathological Outcome

[0368] The effects of the HMCs of the presently disclosed subject matter on histopathological outcome were assessed. Specifically, animals were subjected to the MCAO injury as described above. Cell treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%) using HMCs, specifically HMCs derived from C-GS1 cells (C-GS1-HMCs) and N-lot QR57 cells (N-HMCs). The dosing of the cells was 4 million in 0.5 mL per IV injection.

[0369] Sham, vehicle, and cell treatment groups were prepared for histopathological analysis for white matter loss (MBP), and markers for neuroinflammation such as microglial activation (Iba-1) and astrocyte activation (GFAP).

[0370] FIG. **24** shows preservation of myelin with HMC cell treatment in striatum. Specifically, for MBP, there was a statistically significant difference between the sham and vehicle, but there was no statistically significant difference between the vehicle and treatment groups in the ipsi part of the cortex. There was a statistically significant difference between the vehicle and N-line cell treatment groups in the contralateral cortex, however, there was no statistically significant difference between the groups in the ipsi and as well as sham and vehicle in the contra part of the cortex. There was a statistically significant difference between the sham and vehicle for both ipsi and contra in striatum, vehicle and both cell treatment groups only in ipsi part of the striatum. There was no statistically significant difference between the groups in the contra part of striatum.

[0371] FIG. **25** shows reduced microglial activation following HMC administration. Specifically, for Iba-1, there was a statistically significant difference between the sham and for both ipsi and contra part of cortex, vehicle and cell treatment groups only in ipsi part of cortex. There was no statistically significant difference between the vehicle and treatment groups in the contra part of cortex. There was a statistically significant difference between the sham and vehicle for both ipsi and cotra part of striatum, vehicle and C-GS1 cell treatment groups in the ipsi part of striatum. There was no statistically significant difference between the vehicle and treatment groups in the contra part of striatum.

[0372] FIG. **26** shows reduction of astrocyte reactivity upon HMC treatment. Specifically, for GFAP, there was a statistically significant difference between the sham and vehicle as well as vehicle and cell treatment groups for both ipsi and contra part of cortex. There was a statistically significant difference between the sham and vehicle as well as vehicle and cell treatment groups for both ipsi and contra part of striatum.

[0373] Accordingly, these results demonstrated that the MSCs of the presently disclosed subject matter not only increased preservation of myelin, thus white matter, but also resulted in robust reduction of neuroinflammation markers by reducing the number of reactive astrocytes and microglia.

In vivo effects of HMC-EVs on histopathological outcome

[0374] The effects of HMC-EVs on histopathological outcome were also assessed. Specifically, animals were subjected to the MCAO injury as described above. Treatments were administered on day 1 and day 7 after the MCAO surgery (24 hours and 7 days+/−10%) using HMC-EVs (N-lot p6 and p7 treated with IFNgamma for 96 hours at 50 ng/ml). The dosing of the EVs was 10×10.sup.10 or 30×10.sup.10 total for HMC-EVs (stimulated N-lot) via intracisternal injections.

[0375] Sham, vehicle, and cell treatment groups were prepared for histopathological analysis for MBP, Iba-1, GFAP, Olig-2, and NG2. FIG. **27** shows preservation of myelin with intracisternal delivery of EVs. Specifically, MBP IF staining showed a stable stained area in all treatment groups in the range of 0.81-0.88. The mean ratio of the vehicle group was the lowest (0.64). The differences between the vehicle group and all the treatment groups were significant.

[0376] FIG. **28** shows the effects of HMC-EV treatment on microglial activation. Specifically, Iba-1 IF staining showed the same mean ratio (R/L) of the number of positive cells in the vehicle group and in the HMC-EV 10.sup.10 and HMC-EV 30.sup.10 treatment groups (˜2.5).

[0377] FIG. **29** shows the effects of intracisternal HMC-EV delivery on astrocyte reactivity.

Specifically, GFAP IF staining did not reveal any differences between the control and all treatment groups and showed stable mean ratios (R/L) of the number of positive stained cells.

[0378] FIG. **30** shows that intracisternal delivery of HMC-EVs increased oligodentrocytes. Specifically, Olig-2 IF staining revealed highest mean ratio (R/L) of positive stained cells in all exosome treatment groups (compare to the vehicle group). The differences between the Vehicle group and HMC-EV 10.sup.10 and HMC-EV 30.sup.10 were significant.

[0379] FIG. **31** shows that intracisternal delivery of HMC-EVs increased oligodentrocyte precursor cells. Specifically, NG2 IF staining revealed a statistically significant increase in the mean ratio (R/L) of positive stained area in HMC-EV 10.sup.10 and HMC-EV 30.sup.10 compared to the vehicle group.

[0380] Accordingly, these results demonstrated that HMC-EVs increased preservation of myelin. In addition, EV treatment also increased oligodentrocytes and oligodentrocyte-precursor cells.

Example 8—In Vitro Oxygen Glucose Deprivation Stroke Model

[0381] The neuroprotective effect of MSCs of the presently disclosed subject matter was examined in vitro. An oxygen glucose deprivation (OGD) assay which combines hypoxic conditions with glucose-deprived media was used to model stroke in vitro.

[0382] The overview of the assay is shown in FIG. **32**. For primary neuronal culture, embryonic day 18 (E18) rat cortex samples (#SDECX), sourced from Sprague Dawley rats, were ordered from Brain Bits, LLC (Springfield, IL). The cortices were washed in dissection media (DM) three times. DM consists of 50 mL 10×HBSS (w/o Ca and Mg; Gibco 14185-052), 500 μL Gentamicin, 5 mL pyruvate (Gibco: 11360070), 5 mL Hepes (Gibco 15630080) 10 mM final, 15 mL Glucose 30 mM Final (1M stock), and 425 mL water. After washing, DM was aspirated and the tissue was then minced into equal sized pieces with scalpel. A DM, papain, and DNase I solution was prepared while washing tissue by measuring 1 mL DM, 40 uL papain (Worthington LS003126), and 2.5 uL DNase I (DNase (Sigma #DN-25) per brain; activating the papain with incubation in a 37° C. water bath for 30 minutes; and sterile filter using a 0.22 micron filter. The DM, activated papain, and DNase I solution was added to the cortex samples and incubated at 37° C. for 30 minutes to dissociate the tissue.

[0383] During this time, neuronal media (NMO) was also prepared and incubated at 37° C. NMO consists of Neurobasal plus media with 1× B27 plus added fresh (Neurobasal Plus and B27; Life Tech Corp A3653401), 1× Glutamax (Gibco #35050-061), and gentamycin sulfate (MP Biomedical #0916760-CF). Dissociation pipets were prepared by fire polishing Pasteur pipets with sequentially smaller tip diameters (1=just flame polish, 2=3/4 of original diameter, 3=1/2 of original diameter. After the 30 minutes incubation, the tissue was removed from the water bath. The DM/papain/DNase I solution was gently aspirated and 5 mL of pre-warmed NMO with freshly added B27 was added. The tissue was allowed to settle, and the NMO was gently pipetted off. The tissue was washed again with 5 mL fresh NMO (with B27), and this was repeated for a total of 3 washes. After the last wash, the NMO was removed. The tissue was dissociated by gently triturating the brain tissue through a fire-polished Pasteur pipet, starting with the largest pipet. This was performed by adding 3 mL of NMO, gently triturate 4-5X, and dispensing tissue against wall of tube to prevent bubble formation as neurons trapped in bubbles will die. After the remaining tissue settled, the supernatant was removed and added to a fresh 50 mL falcon tube. This was repeated for all pipet sizes and the cell mixture was then passed through a 70 micron cell strainer. Cells were counted and diluted to 600,000 cells per mL. Cells were plated on tissue culture plates precoated with poly-D-lysine (PDL). For a 6-well plate, 2 mL was added for a total of 1.2 million cells per well. For a 24-well plate, 0.5 mL was added for a total of 300,000 cells per well. Cultures were then fed with ½ media changes every 3rd day to prevent metabolic byproduct accumulation. After one week, the cells were then subjected to the OGD assay.

[0384] Five days before the endpoint processing for the neurons, N-lot HMC were thawed in a 37° C. water bath with gentle swirling. Once thawed, cells were pipetted dropwise into pre-warmed

MSC media (alpha MEM without nucleosides (Hyclone, #SH30568.01), 20% Defined FBSHeat Inactivated (Hyclone, #SH30070.03HI), 1× Glutamax (Gibco #35050-061), 1×MEM NEAA (Gibco #11140-050), 1× Pen/Strep (Gibco #15140-120)). Cells were then centrifuged at 300×g for 5 min, resuspended, and counted. 1 million MSCs were plated in a T225 flask using 50 mL of MSC media and allowed to persist in culture for 4 days. HMCs were then harvested by first aspirating the media. The flask was washed with 10 mL of PBS, the PBS was aspirated, 3 mL of TrypLE Express (Gibco, #12604021) was added, and the cells were incubated at 37° C. for 4-6 minutes. Following the incubation, the cells were washed with MSC media, collected into a 50 mL conical tube, the plate was washed with MSC media to remove remaining cells, the cells were centrifuged for 5 minutes at 300×g. The cells were then resuspended in MSC media and counted. HMCs were then plated in transwell inserts in MSC media to achieve a 1:10 ratio of HMCs to neurons (for 6-well transwell inserts, 120,000 HMCs were plated per well, and for 24-well transwell inserts, 30,000 HMCs were plated per well). The HMCs were allowed to recover for 24 hours, and the MSC media was replaced with NMO to remove traces of FBS. The HMCs were incubated in NMO media for 24 hours until their use for recovery in the oxygen glucose deprivation (OGD) assay.

[0385] For the OGD assay, OGD media was used to deprive the neurons of glucose. OGD media consisted of 1 mM CaCl.sub.2), 5 mM KCl, 137 mM NaCl, 0.4 mM KH2PO4, 0.3 mM Na.sub.3HPO.sub.4, 0.5 mM MgCl.sub.2, 0.4 mM MgSO.sub.4, 25 mM HEPES, 4 mM NaHCO.sub.3, 1× Pen/Strep diluted in 450 mL DI water. The pH was adjusted to 7.3 and water was added for a final volume of 500 mL. The media was then sterile filtered using a 0.2 μm filter. One day prior to initiating the OGD experiment, OGD media was placed in T75 vented flasks and incubated in a hypoxia chamber (C-Chamber with ProOx C21 Oxygen CO.sub.2 Single Chamber Controller, BioSpherix, Parish, NY) overnight to allow for diffusion of oxygen out of the media. The next day, the OGD media was removed from hypoxia chamber and neurons were washed once with OGD media to remove traces of NMO. OGD media was removed and a complete media change with OGD media was performed just prior to adding cells to chamber, i.e. media for 3 hr OGD duration was changed, but media for 2 hr time point was not changed until just before adding cells to chamber, etc. This ensures that the recovery time was the same for all conditions. Neurons were incubated in the hypoxia chamber with OGD media for 1, 2, or 3 hours. Once finished, the neurons were removed and complete media change with NMO media (+B27) was performed. For noninjured controls, NMO was replaced with OGD media, but neurons were not incubated in hypoxia chamber. OGD media in the non-injured controls was replaced with NMO at the same time as the injured cells. HMC co-culture conditions were performed for both non-injured controls and injured cells. Immediately after the OGD media was replaced with NMO, the transwell inserts with HMCs were added in the co-culture conditions. Recovery from the OGD injury was allowed to persist for 24 hours in an incubator under normal cell culture conditions. The neurons were either collected for RNA isolation, or fixed and subjected to TUNEL staining.

In Vitro OGD Assay TUNEL Analysis

[0386] Primary neuronal culture was generated from embryonic day 18 (E18) rat cortex samples, sourced from Sprague Dawley rats, that were ordered from Brain Bits, LLC (Springfield, IL) as described above. HMC co-culture conditions using a transwell insert (no direct contact) at a ratio of 1:10 HMCs to neurons were performed using N-lot cells, and initiated immediately after OGD injury for a total duration of 24 hrs.

[0387] To assess the effects of HMC co-culture to prevent neuronal cell death caused by the OGD assay, TUNEL staining, imaging, and quantification was performed. After the OGD assay, the transwells were removed in co-culture conditions, and the neurons were first fixed with 4% paraformaldehyde. To fix the cells, the NMO was removed and 4% paraformaldehyde was applied to each well and incubated at room temperature for 10 minutes. After the fixation, the cells were then washed 3× with PBS and permeabilized with 0.02% Triton-X in PBS for 10 minutes at room temperature. The cells were then washed 3× with PBS. The positive control was designated and

treated with DNase I (Sigma #4536282001) in DNase I Reaction Buffer (20 mM Tris-HCl, pH 8.4, 2 mM MgCl.sub.2, 50 mM KCl) for 30 minutes at room temperature at 370 for 30 minutes. The positive control was then washed 3× in PBS.

[0388] To achieve TUNEL staining, the TUNEL Label Mix (Sigma #11767291910) and TUNEL Enzyme kit (Sigma #11767305001) was used according to the manufacturer's protocol with slight variation. In general, two kits were used per experiment and diluted in PBS to accommodate the larger volume for 24-well plates. The instructions suggest to use the kit directly with a volume of 50 uL per well, but to ensure coverage of a 24-well plate, PBS was used to dilute the sample for 150 uL per well. For negative control, TUNEL labeling reagent without TUNEL enzyme diluted in PBS was used. For all samples, 200 μL of DAPI staining solution (VWR #10791-650) was added to the combined solution. TUNEL labeling reagent with TUNEL enzyme dilution was added to desired wells, and samples were incubated for 1 hr at 37° C. Samples were washed 3× with PBS. Imaging was performed on the Leica DMi8 microscope and quantification was performed using the Leica LAS X Navigation software. For each condition, 3 wells were stained and 9 images per well were taken and quantified, producing 27 images per condition to be analyzed. TUNEL staining and analysis demonstrated significant increase in cell death with increasing OGD injury duration.

[0389] As shown in FIG. **33**, HMC co-culture prevented cell death in primary rat neurons following OGD injury. Neuroprotective effects of HMC cells in ischemic injury do not require direct contact with neurons, function via paracrine effect onto target neurons.

[0390] Accordingly, the in vitro analysis demonstrated that HMCs of the presently disclosed subject matter can protect from ischemic injury (i.e., oxygen glucose deprivation) in isolated neuronal culture preparations, demonstrating a benefit of direct access to central nervous system in stroke.

RNAseq Analysis of Oxygen-Glucose Deprived Rat Neurons

[0391] Primary rat neuronal culture was subjected to oxygen glucose deprivation (OGD) for various durations (e.g., 0, 1, 2 and 3 hours injury duration). Neurons were subsequently co-cultured with HMCs for 24 hours after OGD treatment. RNA samples were collected 24 hours after OGD treatment. RNA-seq analysis was performed to examine transcriptome and pathway enrichment following OGD in vivo injury with or without subsequent HMC co-culture.

[0392] For RNA isolation, neurons were collected by washing with PBS, scraping, and centrifuging in a microcentrifuge tube at 500 g for 5 minutes. The PBS was aspirated and the cell pellet was either snap frozen and placed at −80° C. or immediately processed through the RNeasy RNA isolation kit (Qiagen #74104) following the manufacturer's protocol. RNA was quantified using a Nano Drop and all samples were normalized to 50 ng/uL and 1 ug total was submitted to GeneWiz for RNAseq analysis with the goal of analyzing the changes in gene expression in response to the OGD injury and HMC co-culture. The conditions were Control, Control with HMCs, 1 hr OGD, 1 hr OGD with MSCs, 2 hr OGD, 2 hr OGD with MSCs, 3 hr OGD, and 3 hr OGD with HMCs. For each condition, 3 biological replicates were provided.

[0393] Library preparation was performed using the NEB Ultra II RNA library preparation kit followed by Illumina sequencing. For each sample, 20-30 million reads were achieved. Bioinformatic analysis was performed, and RNAseq data was analyzed. Reads were trimmed using cutadapt1. Quality scores were assessed using FastQC2. Reads were aligned to the *Rattus norvegicus* genome build rn6 using STAR3. Individual sample reads were quantified using HTseq4 and normalized via Relative Log Expression (RLE) using DESeq2 R library5. Read Distribution percentages, violin plots, identity heatmaps, and sample MDS plots were generated as part of the QC step using RSeQC6. DEseq2 was also used to calculate fold changes and p-values and perform optional covariate correction. Clustering of genes for the final heatmap of differentially expressed genes was done using the PAM (Partitioning Around Medoids) method using the fpc R library7. Hypergeometric distribution was used to analyze the enrichment of pathways, gene ontology, domain structure, and other ontologies. The topGO R library8, was used to determine local

similarities and dependencies between GO terms in order to perform Elim pruning correction. Several database sources were referenced for enrichment analysis, including Interpro, NCBI, MSigDB REACTOME, WikiPathways. Enrichment was calculated relative to a set of background genes relevant for the experiment. Although numerous gene expression changes were observed, genes involved in neuroprotection were highlighted.

[0394] The therapeutic effect of HMC-enriched culture for OGD neuron growth was observed for neurons subjected to 3 hours of OGD damage. Pathway enrichment analysis of the differential expression between neurons subjected to 3 hours of OGD damage and grown on HMC-enriched and control media was performed using Qiagen Ingenuity Pathway Analysis framework. As shown in FIGS. **34**A-C, pathways enriched by this differential expression include (a) STAT3 pathway (p-value: 4×10.sup.−11), deactivated in HMC-cultured OGD neurons, (b) CREB signaling in neurons (p-value: 4.4×10.sup.−8), and (c) numerous inflammatory activity pathways downregulated in HMC-cultured OGD neurons (e.g., IL-6 signaling, IL-10 signaling, Th1/2 activation pathway).

[0395] Enriching differential expression between OGD neurons grown on HMC-enriched and control media for Gene Ontologyterms (FIGS. **34**C-F) in turn shows increase in cell viability of OGD neurons grown on HMC-enriched culture (FIG. **34**C), direct neuroprotective effect (FIG. **34**C, genes involved in upregulation of neuroprotection are presented on FIG. **34**D) and upregulation of pathways involved in synaptic transmission (FIG. **34**C). Simultaneously, pathways involved in apoptosis (FIG. **34**E, genes downregulated by the effect of HMC-enriched growth culture are presented on FIG. **34**F) and general response to cell death are strongly downregulated. This reflects the relation between full differential expression and the displacement of the molecular marker of OGD damage induced by the presence of HMC-enriched growth medium.

[0396] To validate these increases in gene expression, the same RNA samples used for RNAseq analysis were used for qPCR analysis. To perform qPCR analysis, Taqman probes (ThermoFisher Scientific) were designed and used with the Taqman Fast Advanced Master Mix (ThermoFisher Scientific #4444556) and samples were analyzed on the QuantStudio Flex 7 RT-PCR system (Applied Biosystems #4485698). The three biological replicates for each sample were run in duplicate, and the analysis demonstrates the similar increase in gene expression with the presence of HMCs. Statistical significance was achieved through 2-way ANOVA and Sidak multiple comparison test (* $p<0.05$, ** $p<0.01$, **** $p<0.0001$).

[0397] As shown in FIG. **35**, qPCR analysis verified RNAseq results of genes involved in cell viability and neuroprotection. Specifically, HMC cells stimulated expression of neuroprotective genes in neuron undergoing ischemic injury, such as heat shock protein family B member 1 (HSPB1), insulin-like growth factor 1 (IGF2), and secreted phosphoprotein 1 (SPP1), also known as osteopontin.

Example 9—In Vitro Oxidative Damage Model

[0398] The HMC-EVs of the presently disclosed subject matter were tested in an in vitro oxidative damage model. Briefly, neurons were subject to H.sub.2O2 oxidative damage, and treated with HMC-EVs at a dose of about 10,000, 30,000 or 100,000 EVs/cells. Percentage of cell death was determined as the number of propidium iodide (PI)-positive cells out of the total cell number.

[0399] As shown in FIG. **36**, HMC-EV treatment resulted in a dose-dependent attenuation of cell death. A significant rescue from cell death by HMC-EVs was observed at 30K and 100K doses. The overall cell death rate was about 44% lower than the control group without EV treatment.

[0400] Accordingly, these results demonstrated that HMC-EVs can prevent oxidative injury in neurons.

Example 10—In vitro Glutamate Excitotoxicity Model

[0401] The HMC-EVs of the presently disclosed subject matter were tested in an in vitro glutamate excitotoxicity (high doses of L-glutamate) model. Briefly, neurons were exposed to various concentrations of L-glutamate (about 0, 30, 300 and 3000 uM), and treated with HMC-EVs at a dose of about 50,000 EVs/cells. Percentage of cell death was determined as the number of

propidium iodide (PI)+ cells out of the total cell number.
[0402] As shown in FIG. **37**, HMC-EV treatment sustained cells in the nuclear swelling stage after glutamate-induced injury and maintained viability. Staining with TMRM (cell permeant dye that accumulates in active mitochondria with intact membrane potentials) showed that HMC-EV treatment also maintained mitochondrial activity in injured cells.
[0403] Accordingly, these results demonstrated that HMC-EVs prevent neuronal death due to glutamate excitotoxic injury.
Example 11—RNAseq analysis of HMCs vs Bone Marrow-MSC vs Adipose Tissue-MSC
[0404] RNAseq analysis was performed for the HMCs of the presently disclosed subject matter under both basal and stimulated conditions. HMCs were generated from both N-line (N-HMCs) and GMP-1 (GMP-HMCs) cell line, and 3 technical replicate samples were prepared for each condition. MSCs isolated from adipose tissue and bone marrow were also analyzed and compared with the HMCs of the presently disclosed subject matter. AD-MSCs were collected from 3 different adult donors, and 2 technical replicate samples were prepared for each biological replicate. BM-MSCs were also collected from 3 different adult donors.
HMCs Vs. Adipose Tissue Derived MSCs
[0405] Principal component analysis of transcriptomes of HMCs (obtained from the N-cell line) and AD-MSCs shows that HMCs are distinct from the latter in both basal and interferon-gamma stimulated state (FIG. **38**). The first principal component largely describes the effect of stimulation with gamma interferon, while the second principal component describes the difference between HMCs and AD-MSCs.
[0406] Weights of different genes contributing to the second principal component which determines the variance between HMCs and AD-MSCs. Of a particular note is down-regulation of collagen genes (COLlA1, COL3A1 etc.), mitochondrial function genes and TGF Beta 1 (one of the main factors promoting angiogenesis) in HMCs as compared to AD-MSCs demonstrating a certain degree of immaturity of HMCs (FIG. **39**).
[0407] Hierarchical clustering demonstrates similarity between biological/technical replicate samples of the same biological type as well as clear difference between HMCs and AD-MSCs, in both basal cell states and cell states stimulated with gamma interferon (FIG. **40**).
[0408] As shown in FIG. **41**, genes in this cluster were up-regulated in HMCs (both basal and INFN gamma-stimulated) as compared to AD-MSCs. The genes included: CALR, UBB, PKM, CXCL8, C15orf48, PSME2, TPM3, ANKRD1, PFN1, SRGN, ACTB, MDK, TAGLN2, CFL1, HSP90AA1, HSPA8, CXCL12, UCHL1, HMGA2, HMGA1, HN1, PTMA, SP90AB1, PRDX1, GSTP1, KRT18, IGFBP4, CALD1, COL4A1, COL4A2 and GAPDH. Differential expression of these genes between HMCs and AD-MSCs was consistent across biological and technical replicates according to the hierarchical clustering map.
[0409] Functional annotation of biological pathways enriched in the cluster on FIG. **41** was performed using Reactome (https://reactome.org/). The top pathway enriched by the corresponding genes was associated with axon guidance. Other significantly enriched pathways included cellular stress response and developmental biology (related to the relative immaturity of HMCs).
[0410] As shown in FIG. **42**, genes in this cluster were down-regulated in HMCs (both basal and INFN gamma-stimulated) as compared to AD-MSCs. The genes included: SERPINE1, ACTA2, TPM2, CTGF, SERPINE2, CRYAB, ELN, MFGE8, ANXA2, POSTN, VIM, MFAP5, ISLR, THBS1, TIMP3, DKK1, COL6A3, COL6A1, TPT1, BCYRN1, COL1A1, SPARC, TPM1, BGN, COL1A2, COL3A1, TGFBI, CRLF1, COMP, NEAT1, MT-CO3, MT-CO2, MT-ATP8, MT-CYB, MT-CO1, MT-ATP6, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-ND3, MT-ND1, MT-ND2, GREM1, TMSB4X, ITGB1, LMNA, H2AFZ, FTL, EEF1G, NPM1, EEF1A1, RACK1, ACTG1, and TPM4. Differential expression of these genes between HMCs and AD-MSCs was consistent across biological and technical replicates according to the hierarchical clustering map.
[0411] Functional annotation of biological pathways enriched in the cluster on FIG. **42** was

performed using Reactome (https://reactome.org/). The top pathways enriched by the corresponding genes were associated with respiratory electron transport and mitochondrial function in general as well as collagen biosynthesis.

[0412] Canonical pathway enrichment of differential gene expression signature between HMCs and AD-MSCs shows noticeable HMC-specific up-regulation of several pathways (denoted by red arrows) involved in the development of neuronal lineage including axon guidance, CREB signaling in neurons, synaptogenesis signaling etc. (FIG. **43**). These results suggest that HMCs have a distinct expression profile when compared to AD-MSCs, and HMCs may confer neuroprotective effects, and provide neurotrophic factors, factors involved in supporting neuronal health and recovery.

[0413] Lists of genes-contributors to the activated pathways establishing this difference are shown in FIGS. **44-47**.

[0414] FIG. **44** depicts the top 15 most strongly differentially expressed genes contributing to activation of neuronal CREB signaling in HMCs. Expr Log Ratio denotes base 10 logarithm of the fold change between average TPM expression of a gene in HMCs and its average TPM expression in adipose tissue-derived MSCs, i.e., the Expr Log Ratio higher than 2 implies gene expression increase by a factor larger than 100.

[0415] FIG. **45** depicts the top 15 most strongly upregulated genes contributing to the enrichment of axon guidance pathway in HMCs. Although activation pattern of axonal guidance signaling pathway has not been determined by Qiagen Ingenuity Pathway Analysis, the pathway was enriched with p-value ˜1.38e-4 in HMCs as compared to AD-MSCs.

[0416] FIG. **46** depicts the top 15 most strongly expressed genes contributing to activation of synaptogenesis signaling pathway in HMCs. Enrichment p-value 1.14e-3, activation pattern z-score 3.578, the highest among all pathways differentially upregulated in HMCs.

[0417] FIG. **47** depicts the top 15 most up-regulated genes out of contributing to activation of neuroinflammation signaling pathway in HMCs. Pathway enrichment p-value 4.97e-3, activation z-score 1.508.

[0418] HMCs were also generated from a different pluripotent stem cell, i.e., GMP1 cells. Principal component analysis of transcriptomes of GMP1-HMC was also performed and compared with HMC derived from N-line cells (N-HMCs) and AD-MSCs under both basal and stimulated conditions (FIG. **48**).

[0419] Hierarchical clustering analysis showed that GMP1-HMCshad similar profiles to the N-HMCs (FIG. **49**). As shown in FIG. **50**, genes in this cluster were up-regulated in N-HMCsand GMP1-HMCs (both basal and INFN gamma-stimulated) as compared to AD-MSCs. The genes included: TMSB4X, ACTG1, GSTP1, KRT18, IGFBP5, NPY, KRT8, PRDX6, MDK, DKK3, UCHL1, TUBB3, HN1, PTMA, HSP90AB1, HMGA1, HSPA8, TAGLN2, ANKRD1, PFN1, CYBA, and UBB. Differential expression of these genes between N-HMC, GMP1-HMC, and adipose tissue-derived MSC lines was consistent across biological and technical replicates according to the hierarchical clustering map.

[0420] Functional annotation of biological pathways enriched in the cluster on FIG. **50** was performed using Reactome (https://reactome.org/). The top pathway enriched by the corresponding genes was associated with axon guidance. Other significantly enriched pathways included cellular stress response and developmental biology.

[0421] As shown in FIG. **51**, genes in these cluster were down-regulated in N-HMCs and GMP1-HMCs in basal condition as compared to AD-MSCs. The genes included: SERPINE1, S100A6, CD59, POSTN, VIM, MFAP5, ISLR, THBS1, COL6A3, TIMP3, ELN, ANXA2, COL1A1, BCYRN1, CCDC80, COL6A1, COL6A2, BGN, COL1A2, COL3A1, TGFB1, CRLF1, COMP, and GREM1. Differential expression of these genes between N-HMC, GMP1-HMC, and AD-MSC lines was consistent across biological and technical replicates according to the hierarchical clustering map.

[0422] As shown in FIG. **52**, genes in these cluster were down-regulated in N-HMCs and GMP1-HMCs in INFN gamma-stimulated condition as compared to AD-MSCs. The genes included: MT1X, MT1G, TMSB10, CCL8, INHBA, CTSB, SERPINB2, ADM, APOL1, FTH1, CCL2, CCL5, CSF1, IL1B, IGFBP3, P4HB, DCN, FSTL1, ANXA5, LOX, CD63, CTSZ, FN1, LGALS1, LDHA, RCN3, MMP2, and TIMP1. Differential expression of these genes between N-HMC, GMP1-HMC, and AD-MSC lines was consistent across biological and technical replicates according to the hierarchical clustering map.
[0423] Functional annotation of biological pathways enriched in the cluster on FIGS. **51** and **52** was performed using Reactome (https://reactome.org/). The top pathways enriched by the corresponding genes were associated with extracellular matrix organization in general as well as collagen biosynthesis.
[0424] Similarly, canonical pathway enrichment of differential gene expression signature between N-HMCs, GMP1-HMCs, and AD-MSCs shows noticeable HMC-specific up-regulation of several pathways (denoted by red arrows) involved in the development of neuronal lineage including axon guidance, CREB signaling in neurons, synaptogenesis signaling etc. (FIGS. **53**A-C and **54**A-C). Thus, N-HMC and GMP1-HMCs shared a similar profile and both showed axon guidance enrichment.
[0425] Accordingly, it is concluded that the HMCs of the presently disclosed subject matter are distinct from AD-MSCs. Specifically, the MSCs of the presently disclosed subject matter have a distinct expression profile when compared to AD-MSCs, and may confer neuroprotective effects, provide neurotrophic factors, i.e., factors involved in supporting neuronal survival, growth, health and recovery.
HMC Vs. Bone Marrow Derived MSC
[0426] Principal component analysis of transcriptomes of HMCs (obtained from N-cell line) and BM-MSCs shows that HMCs are distinct from the latter in both basal and INFN-gamma stimulated state. The 1.sup.st principal component largely describes the effect of stimulation with gamma interferon, while the 2.sup.nd principal component describes the difference between HMCs and BM-MSCs (FIG. **55**).
[0427] Weights of different genes contributing to the 2.sup.nd principal component which determines the variance between HMCs and BM-MSCs. Of a particular note is down-regulation of collagen genes (COL1A1, COL1A2, COL3A1, COL6A2 etc.), mitochondrial function genes and TGF Beta 1 (one of the main factors promoting angiogenesis) in HMCs as compared to BM-MSCs demonstrating a certain degree of immaturity of HMCs as compared to the latter (FIG. **56**).
[0428] Hierarchical clustering demonstrates similarity between biological replicate samples of the same type as well as clear difference between HMCs and BM-MSCs, in both basal cell states and cell states stimulated with gamma interferon (FIG. **57**).
[0429] Genes in this cluster were up-regulated in HMCs (both basal and INFN gamma-stimulated) as compared to BM-MSCs (FIG. **58**). The genes included: PPIA, NPM1, HNRNPA1, IGFBP5, KRT19, KRT18, GSTP1, TUBB, TUBA1B, KRT8, HN1, PTMA, TUBA1C, HSPA8, HMGA1, CFL1, MYL6, ACTB, UCHL1, TAGLN2, MDK, GREM1, MMP1, and CTSC. Differential expression of these genes between HMCs and BM-MSCs was consistent across biological and technical replicates according to the hierarchical clustering map.
[0430] Functional annotation of biological pathways enriched in the cluster on FIG. **58** was performed using Reactome (https://reactome.org/). Among the top pathways enriched by the corresponding genes there is axon guidance. Other significantly enriched pathways included cellular stress response and developmental biology (related to the relative immaturity of HMCs).
[0431] Genes in this cluster were down-regulated in HMCs (both basal and INFN gamma-stimulated) as compared to BM-MSCs (FIG. **59**). The genes included: ANXA2, TPT1, VIM, COL6A1, BGN, COL6A2, CTGF, TIMP3, ACTA2, COL3A1, SPARC, ITGB1, SERPINH1, TPM2, TGFBI, COL1A1, TPM1, COL6A3, TPM4, SERPINE2, CALD1, COL1A2, TAGLN,

MYL9, MT-RNR2, POSTN. Differential expression of these genes between HMCs and BM-MSCs was consistent across biological and technical replicates according to the hierarchical clustering map.

[0432] Functional annotation of biological pathways enriched in the cluster on FIG. **59** was performed using Reactome (https://reactome.org/). The top pathways enriched by the corresponding genes were associated with collagen biosynthesis/assembly (demonstrating similarities between BM-MSCs and AD-MSCs).

[0433] Canonical pathway enrichment of differential gene expression signature between HMCs and BM-MSCs again shows an HMC-specific up-regulation of pathways involved in the development of neuronal lineage such as CREB signaling in neurons (FIG. **60**).

[0434] FIG. **61** depicts the top 15 most strongly differentially expressed genes contributing to activation of neuronal CREB signaling in HMCs as compared to BM-MSCs. FIG. **62**. depicts the top 15 most strongly upregulated genes contributing to activation of synaptogenesis signaling in HMCs as compared to BM-MSCs.

[0435] Accordingly, it is concluded that, the HMCs of the presently disclosed subject matter are distinct from BM-MSCs. Specifically, the HMCs of the presently disclosed subject matter have a distinct expression profile, and provide neuroprotective effects when compared to BM-MSCs.

TABLE-US-00007 TABLE 7 Genes more highly expressed in HMCs compared with AD-MSCs

Gene name	Description	Fold Change	Log Fold Change	p-Adj
LOC400655	uncharacterized LOC400655	298.97	8.2239	2.40E−39
BAI3	adhesion G protein-coupled receptor B3	234.52	7.8735	2.09E−44
SHISA2	shisa family member 2	197.93	7.6288	9.51E−133
CYYR1	cysteine/tyrosine-rich 1	190.66	7.5749	1.02E−30
PAX7	paired box 7	181.34	7.5025	4.73E−29
SYT14	synaptotagmin XIV	181.02	7.5000	1.15E−39
ELAVL2	ELAV like neuron-specific RNA binding protein 2	158.73	7.3105	4.28E−80
DCC	DCC netrin 1 receptor	157.22	7.2966	3.12E−59
WDR72	WD repeat domain 72	156.71	7.2920	6.07E−32
TMEM40	transmembrane protein 40	137.10	7.0991	3.16E−33
TTTY15	testis-specific transcript_Y-linked 15 (non-protein coding)	123.88	6.9528	1.15E−131
HRH2	histamine receptor H2	112.31	6.8114	2.57E−22
CA8	carbonic anhydrase VIII	103.90	6.6990	3.78E−28
TFAP2A	transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)	101.18	6.6608	1.12E−48
ZDHHC8P1	zinc finger_DHHC-type containing 8 pseudogene 1	97.79	6.6115	2.23E−75
DENND2A	DENN/MADD domain containing 2A	83.16	6.3778	2.98E−72
HOPX	HOP homeobox	78.67	6.2978	1.14E−29
SYT13	synaptotagmin XIII	72.13	6.1726	1.68E−29
KC6	keratoconus gene 6	71.51	6.1602	1.97E−21
KDM5D	lysine (K)-specific demethylase 5D	68.12	6.0899	1.32E−90
UTY	ubiquitously transcribed tetratricopeptide repeat containing.sub.— Y-linked	67.39	6.0744	1.17E−124
SULT1C4	sulfotransferase family_cytosolic.sub.— 1C_member 4	67.28	6.0721	1.62E−18
MAB21L2	mab-21-like 2 (*C. elegans*)	64.72	6.0161	1.10E−13
ZIC2	Zic family member 2	64.55	6.0124	5.67E−45
LOC644919	uncharacterized LOC644919	63.85	5.9965	5.51E−22
USP9Y	ubiquitin specific peptidase 9_Y-linked	62.40	5.9634	5.67E−57
MSX2	msh homeobox 2	60.69	5.9233	1.33E−41
GATA3	GATA binding protein 3	59.60	5.8973	2.70E−62
RIPK4	receptor-interacting serine-threonine kinase 4	59.03	5.8833	1.18E−61
PKIB	protein kinase (cAMP-dependent.sub.— catalytic) inhibitor beta	58.55	5.8717	1.61E−22
GAL3ST3	galactose-3-O-sulfotransferase 3	58.19	5.8627	1.39E−21
CASC9	cancer susceptibility candidate 9 (non-protein coding)	56.08	5.8095	1.34E−24
TGFB2	transforming growth factor_beta 2	53.17	5.7324	2.52E−45
L1CAM	L1 cell adhesion molecule	53.09	5.7305	2.84E−117
TXLNGY	taxilin gamma pseudogene_Y-linked	50.60	5.6610	3.79E−98
EIF1AY	eukaryotic translation initiation factor 1A_Y-linked	50.17	5.6487	3.91E−55
RPS4Y1	ribosomal protein S4_Y-linked 1	48.25	5.5925	6.04E−33
PCDHA2	protocadherin alpha 2	47.12	5.5582	5.20E−33
LINC00648	long intergenic non-protein coding RNA 648	46.20	5.5298	2.25E−16
SNRPN	small nuclear ribonucleoprotein polypeptide N	45.49	5.5075	2.85E−23
PRKY	protein kinase_Y-linked.sub.—	44.67	5.4813	5.09E−58
TTTY14	testis-specific transcript_Y-linked 14 (non-protein coding)	44.52	5.4764	3.51E−12
PCDHB5	protocadherin beta 5	43.99		

5.4592 7.71E−125 SDK2 sidekick cell adhesion molecule 2 43.14 5.4310 3.20E−46 CDH3 cadherin 3_type 1_P-cadherin 43.08 5.4289 7.17E−39 (placental) FZD10-AS1 FZD10 antisense RNA 1 (head to 42.97 5.4251 2.77E−12 head) CD24 CD24 molecule 41.69 5.3818 2.94E−211 C7orf69 chromosome 7 open reading frame 40.57 5.3422 1.20E−33 69 NETO1 neuropilin (NRP) and tolloid (TLL)- 40.16 5.3277 1.29E−66 like 1 SOX11 SRY (sex determining region Y)- 40.07 5.3244 5.46E−13 box 11 SLC7A2 solute carrier family 7 (cationic 39.40 5.3002 3.79E−13 amino acid transporter_y + system).sub.— member 2 NLGN4X neuroligin 4_X-linked 38.78 5.2773 2.05E−11 MDFI MyoD family inhibitor 38.75 5.2762 1.58E−226 GABRB1 gamma-aminobutyric acid (GABA) 38.15 5.2535 1.20E−15 A receptor_beta 1 LOC100507600 uncharacterized LOC100507600 36.76 5.1999 1.30E−19 DDX3Y DEAD (Asp-Glu-Ala-Asp) box 36.52 5.1908 1.14E−21 helicase 3_Y-linked IGF2-AS IGF2 antisense RNA 35.47 5.1486 1.14E−10 GPRC5C G protein-coupled receptor_class 35.30 5.1415 3.14E−44 C_group 5_member C MSLN mesothelin 35.29 5.1412 1.09E−10 LPAR4 lysophosphatidic acid receptor 4 35.24 5.1392 2.90E−22 EFNA1 ephrin-A1 34.82 5.1217 2.55E−31 MUM1L1 melanoma associated antigen 33.17 5.0516 1.14E−10 (mutated) 1-like 1 C7 complement component 7 32.85 5.0377 1.03E−09 NLGN4Y neuroligin 4_Y-linked 32.76 5.0340 1.43E−14 PCDHA12 protocadherin alpha 12 32.56 5.0249 1.18E−11 TFAP2A-AS1 TFAP2A antisense RNA 1 32.47 5.0211 1.24E−17 CDH18 cadherin 18_type 2 32.36 5.0160 6.15E−13 DPY19L2P1 DPY19L2 pseudogene 1 31.57 4.9804 2.43E−15 GABRA3 gamma-aminobutyric acid (GABA) 30.86 4.9475 4.71E−18 A receptor_alpha 3 CLDN1 claudin 1 30.81 4.9454 8.36E−18 CYP27C1 cytochrome P450_family 27.sub.— 30.78 4.9439 1.65E−17 subfamily C_polypeptide 1 IGSF9B immunoglobulin superfamily.sub.— 30.52 4.9316 8.19E−25 member 9B C5orf46 chromosome 5 open reading frame 30.22 4.9175 1.02E−09 46 C1orf94 chromosome 1 open reading frame 30.16 4.9148 1.70E−10 94 NEDD4L neural precursor cell expressed.sub.— 29.64 4.8895 4.58E−81 developmentally down-regulated 4- like_E3 ubiquitin protein ligase MLC1 megalencephalic 29.14 4.8650 2.64E−10 leukoencephalopathy with subcortical cysts 1 DLX1 distal-less homeobox 1 29.04 4.8601 3.14E−116 PAX3 paired box 3 28.76 4.8457 6.05E−156 PCDHAC2 protocadherin alpha subfamily C_2 28.62 4.8388 2.47E−22 MAGEL2 melanoma antigen family L2 28.59 4.8374 4.18E−21 PLCH2 phospholipase C_eta 2 28.36 4.8256 3.33E−11 NR0B1 nuclear receptor subfamily 0_group 28.35 4.8253 3.16E−17 B_member 1 CCNJL cyclin J-like 28.31 4.8232 5.67E−16 SORCS1 sortilin-related VPS10 domain 27.98 4.8064 6.23E−10 containing receptor 1 VANGL2 VANGL planar cell polarity protein 27.96 4.8054 3.88E−14 2 SALL1 spalt-like transcription factor 1 27.92 4.8035 1.31E−18 LOC102467080 uncharacterized LOC102467080 27.08 4.7594 9.43E−11 CRISPLD1 cysteine-rich secretory protein 26.77 4.7424 1.83E−16 LCCL domain containing 1 TMEM132D transmembrane protein 132D 26.14 4.7082 9.35E−11 PRKCQ-AS1 PRKCQ antisense RNA 1 25.48 4.6711 2.53E−17 CACNG4 calcium channel_voltage- 25.36 4.6644 1.76E−08 dependent_gamma subunit 4 KIAA1211 KIAA1211 25.20 4.6553 2.27E−31 ANXA3 annexin A3 25.16 4.6532 2.77E−46 NMNAT3 nicotinamide nucleotide 25.10 4.6493 3.46E−09 adenylyltransferase 3 SLAMF7 SLAM family member 7 24.98 4.6427 8.99E−13 GPR20 G protein-coupled receptor 20 24.72 4.6275 9.88E−11 OLFML2A olfactomedin-like 2A 24.60 4.6206 4.62E−40 IP6K3 inositol hexakisphosphate kinase 3 24.54 4.6172 1.08E−10 LMX1B LIM homeobox transcription factor 24.37 4.6070 7.25E−15 1_beta IGF2 insulin-like growth factor 2 24.24 4.5992 3.10E−08 KCNK3 potassium channel_two pore 24.24 4.5991 3.99E−08 domain subfamily K_member 3 ZFY zinc finger protein_Y-linked 23.97 4.5833 1.42E−09 CLSTN2 calsyntenin 2 23.89 4.5781 6.01E−11 GNAZ guanine nucleotide binding protein 23.80 4.5728 1.11E−90 (G protein)_alpha z polypeptide GCNT2 glucosaminyl (N-acetyl) transferase 23.61 4.5616 2.98E−28 2_I-branching enzyme (I blood group) PCDHB15 protocadherin beta 15 23.53 4.5564 2.81E−46 PCDHA10 protocadherin alpha 10 23.47 4.5527 3.83E−16 C11orf88 chromosome 11 open reading frame 23.47 4.5527 3.83E−11 88 MGAT5B mannosyl (alpha-1_6-)-glycoprotein 23.21 4.5366 6.99E−73 beta-1_6-N-acetyl-glucosaminyltransferase_isozyme B OVCH2 ovochymase 2 (gene/pseudogene) 23.17 4.5344

2.35E−11 ATRNL1 attractin-like 1 23.05 4.5266 8.08E−18 TEX15 testis expressed 15 22.84 4.5138 2.28E−12 SHROOM2 shroom family member 2 22.83 4.5131 4.36E−10 ECEL1P2 endothelin converting enzyme-like 22.60 4.4985 6.48E−10 1_pseudogene 2 SDK1 sidekick cell adhesion molecule 1 22.28 4.4780 1.76E−24 EPHB2 EPH receptor B2 22.27 4.4773 2.63E−18 MIR4697HG MIR4697 host gene 22.12 4.4675 2.04E−17 ABCA13 ATP-binding cassette_sub-family A 21.72 4.4407 2.93E−17 (ABC1)_member 13 C21orf88 B3GALT5 antisense RNA 1 21.46 4.4238 1.23E−09 LIN28B lin-28 homolog B (*C. elegans*) 21.46 4.4233 1.04E−19 LINC01158 long intergenic non-protein coding 21.14 4.4018 1.41E−08 RNA 1158 RASGRF1 Ras protein-specific guanine 21.12 4.4004 1.98E−13 nucleotide-releasing factor 1 GRIA1 glutamate receptor_ionotropic.sub.— 20.59 4.3639 6.29E−25 AMPA 1 LINC00491 long intergenic non-protein coding 20.56 4.3619 1.12E−08 RNA 491 PCDHB2 protocadherin beta 2 20.19 4.3355 1.69E−71 ZNF853 zinc finger protein 853 19.98 4.3202 6.14E−46 SERPINA5 serpin peptidase inhibitor_clade A 19.89 4.3138 1.54E−10 (alpha-1 antiproteinase.sub.— antitrypsin)_member 5 CA3 carbonic anhydrase III 19.47 4.2832 1.71E−07 PLEKHA6 pleckstrin homology domain 19.34 4.2734 1.17E−22 containing_family A member 6 LOC283299 uncharacterized LOC283299 19.22 4.2642 2.33E−08 NRK Nik related kinase 18.95 4.2444 2.17E−47 LINC00460 long intergenic non-protein coding 18.91 4.2414 3.71E−08 RNA 460 MYO5C myosin VC 18.88 4.2390 1.38E−12 ANK1 ankyrin 1_erythrocytic 18.61 4.2182 1.01E−25 NIPAL4 NIPA-like domain containing 4 18.46 4.2066 8.70E−10 SAMD5 sterile alpha motif domain 18.35 4.1981 6.95E−07 containing 5 SOWAHD sosondowah ankyrin repeat domain 18.22 4.1874 3.96E−18 family member D CIDEA cell death-inducing DFFA-like 18.04 4.1732 1.37E−06 effector a SHF Src homology 2 domain containing 17.93 4.1643 9.93E−91 F GABRQ gamma-aminobutyric acid (GABA) 17.93 4.1639 8.84E−09 A receptor theta NFE2L3 nuclear factor_erythroid 2-like 3 17.87 4.1596 4.45E−50 CRHBP corticotropin releasing hormone 17.49 4.1285 2.10E−08 binding protein SPTBN2 spectrin_beta_non-erythrocytic 2 17.41 4.1219 3.91E−106 INA internexin neuronal intermediate 17.37 4.1188 1.25E−22 filament protein_alpha VAX1 ventral anterior homeobox 1 17.32 4.1144 8.06E−07 CDKL2 cyclin-dependent kinase-like 2 17.11 4.0971 2.86E−12 (CDC2-related kinase) GLIS1 GLIS family zinc finger 1 17.08 4.0943 6.84E−149 IRF6 interferon regulatory factor 6 16.81 4.0711 7.61E−11 POU3F3 POU class 3 homeobox 3 16.77 4.0680 1.72E−10 LOC339975 uncharacterized LOC339975 16.72 4.0639 3.00E−08 RASL10B RAS-like_family_10_member B 16.67 4.0590 1.14E−52 KLHL4 kelch-like family member 4 16.57 4.0502 7.55E−23 EN2 engrailed homeobox 2 16.46 4.0405 3.11E−07 FBXO2 F-box protein 2 16.33 4.0291 9.42E−23 CADM1 cell adhesion molecule 1 16.17 4.0152 1.30E−11 SIPA1L2 signal-induced proliferation-16.14 4.0125 1.24E−23 associated 1 like 2 PAK3 p21 protein (Cdc42/Rac)-activated 16.08 4.0071 3.73E−38 kinase 3 EPHA5-AS1 EPHA5 antisense RNA 1 15.99 3.9993 2.38E−06 OPRD1 opioid receptor_delta 1 15.91 3.9915 6.44E−06 NIPAL1 NIPA-like domain containing 1 15.83 3.9846 1.07E−09 SRSF12 serine/arginine-rich splicing factor 15.68 3.9709 2.27E−10 12 NNAT neuronatin 15.59 3.9623 2.99E−19 FAM69B family with sequence similarity 69.sub.— 15.49 3.9532 1.53E−83 member B DUSP8 dual specificity phosphatase 8 15.45 3.9493 7.39E−44 MAMDC2-AS1 MAMDC2 antisense RNA 1 15.38 3.9433 1.48E−08 MEX3A mex-3 RNA binding family member 15.32 3.9375 9.15E−96 A PLEKHG4B pleckstrin homology domain 15.18 3.9241 2.31E−23 containing_family G (with RhoGef domain) member 4B EYA1 EYA transcriptional coactivator and 15.07 3.9137 1.31E−09 phosphatase 1 TIE1 tyrosine kinase with 15.03 3.9096 1.41E−17 immunoglobulin-like and EGF-like domains 1 ARSE arylsulfatase E (chondrodysplasia 14.84 3.8914 1.74E−36 punctata 1) FAM110D family with sequence similarity 14.73 3.8807 1.42E−17 110_member D PLCXD3 phosphatidylinositol-specific 14.68 3.8759 1.26E−05 phospholipase C_X domain containing 3 SLC44A5 solute carrier family 44_member 5 14.68 3.8753 1.15E−06 PCSK1N proprotein convertase 14.66 3.8737 1.93E−06 subtilisin/kexin type 1 inhibitor IL31RA interleukin 31 receptor A 14.62 3.8701 1.26E−08 PCDHGB6 protocadherin gamma subfamily B.sub.— 14.54 3.8620 5.59E−70 6 WSCD1 WSC domain containing 1 14.47

3.8555 6.83E−06 KLHL23 kelch-like family member 23 14.36 3.8442 8.90E−08 KCNF1 potassium channel_voltage gated 14.35 3.8430 2.97E−06 modifier subfamily F_member 1 TFAP2C transcription factor AP-2 gamma 14.26 3.8339 9.30E−08 (activating enhancer binding protein 2 gamma) CD163L1 CD163 molecule-like 1 14.13 3.8202 9.04E−28 RAMP1 receptor (G protein-coupled) activity 13.96 3.8033 1.04E−07 modifying protein 1 C10orf126 chromosome 10 open reading frame 13.61 3.7662 2.35E−05 126 CPXM1 carboxypeptidase X (M14 family).sub.— 13.60 3.7657 1.95E−58 member 1 SPINK5 serine peptidase inhibitor_Kazal 13.56 3.7614 4.59E−06 type 5 NCRNA00185 testis-specific transcript_Y-linked 13.51 3.7558 2.44E−05 14 (non-protein coding) JAKMIP2 janus kinase and microtubule 13.39 3.7428 7.95E−12 interacting protein 2 SLC7A14 solute carrier family 7_member 14 13.38 3.7415 1.86E−30 B4GALNT4 beta-1_4-N-acetyl-galactosaminyl 13.35 3.7385 2.93E−10 transferase 4 ETNK2 ethanolamine kinase 2 13.22 3.7248 1.53E−135 SH2D3C SH2 domain containing 3C 13.17 3.7196 8.57E−08 MAP3K9 mitogen-activated protein kinase 12.93 3.6923 2.32E−23 kinase kinase 9 SHC2 SHC (Src homology 2 domain 12.84 3.6829 1.46E−08 containing) transforming protein 2 PTGER4 prostaglandin E receptor 4 (subtype 12.81 3.6794 1.54E−59 EP4) EPHA5 EPH receptor A5 12.70 3.6673 1.03E−18 LINC01012 long intergenic non-protein coding 12.64 3.6596 9.52E−06 RNA 1012 IL2RB interleukin 2 receptor_beta 12.64 3.6595 1.10E−07 GATA3-AS1 GATA3 antisense RNA 1 12.62 3.6581 2.67E−06 RIMS2 regulating synaptic membrane 12.60 3.6551 2.86E−22 exocytosis 2 ADAMTS3 ADAM metallopeptidase with 12.60 3.6549 1.02E−64 thrombospondin type 1 motif_3 PIEZO2 piezo-type mechanosensitive ion 12.55 3.6495 2.89E−08 channel component 2 GLP2R glucagon-like peptide 2 receptor 12.46 3.6393 3.38E−06 GPRC5D G protein-coupled receptor_class 12.45 3.6382 4.22E−06 C_group 5_member D GBX2 gastrulation brain homeobox 2 12.44 3.6366 1.28E−07 TMEM255A transmembrane protein 255A 12.34 3.6257 8.27E−14 LOC100506314 uncharacterized LOC100506314 12.33 3.6240 5.74E−19 LHX8 LIM homeobox 8 12.31 3.6221 4.39E−06 NOMO3 NODAL modulator 3 12.30 3.6210 8.51E−148 LINC00858 long intergenic non-protein coding 12.25 3.6152 5.74E−05 RNA 858 C2CD4C C2 calcium-dependent domain 12.22 3.6110 4.68E−14 containing 4C COL4A6 collagen_typeIV_alpha 6 12.20 3.6084 4.19E−05 CD6 CD6 molecule 12.18 3.6059 8.90E−07 EFNB2 ephrin-B2 12.06 3.5922 1.23E−06 FOXF1 forkhead box F1 11.99 3.5840 9.88E−22 B3GNT5 UDP-GlcNAc:betaGal beta-1_3-N- 11.97 3.5812 6.07E−128 acetylglucosaminyltransferase 5 LINC00470 long intergenic non-protein coding 11.89 3.5720 4.17E−07 RNA 470 ADARB2 adenosine deaminase_RNA- 11.83 3.5640 2.75E−05 specific_B2 (non-functional) IGFBP2 insulin-like growth factor binding 11.82 3.5635 5.62E−05 protein 2_36 kDa LRP1B low density lipoprotein receptor- 11.82 3.5626 5.67E−05 related protein 1B DUSP4 dual specificity phosphatase 4 11.81 3.5624 2.18E−42 TRHDE-AS1 TRHDE antisense RNA 1 11.78 3.5588 1.62E−05 TFAP2B transcription factor AP-2 beta 11.77 3.5565 1.86E−05 (activating enhancer binding protein 2 beta) BIRC7 baculoviral IAP repeat containing 7 11.72 3.5505 3.89E−05 TMCC3 transmembrane and coiled-coil 11.70 3.5482 4.68E−07 domain family 3 LINC00649 long intergenic non-protein coding 11.69 3.5470 3.31E−20 RNA 649 GDF5 growth differentiation factor 5 11.64 3.5409 3.92E−09 BEND5 BEN domain containing 5 11.55 3.5293 3.37E−09 AFAP1L2 actin filament associated protein 1- 11.44 3.5157 1.02E−16 like 2 SALL2 spalt-like transcription factor 2 11.40 3.5109 3.93E−27 FZD10 frizzled class receptor 10 11.35 3.5045 6.53E−05 DPPA4 developmental pluripotency 11.30 3.4989 1.23E−04 associated 4 MECOM MDS1 and EVI1 complex locus 11.26 3.4925 7.73E−06 RBP1 retinol binding protein 1_cellular 11.22 3.4885 9.69E−27 PPARGC1A peroxisome proliferator-activated 11.21 3.4872 5.02E−05 receptor gamma_coactivator 1 alpha TMEM200C transmembrane protein 200C 11.15 3.4784 1.09E−04 PCDHA11 protocadherin alpha 11 11.14 3.4777 8.36E−07 PCDHA3 protocadherin alpha 3 11.13 3.4768 2.60E−10 LRFN5 leucine rich repeat and fibronectin 11.07 3.4686 5.35E−09 type III domain containing 5 SCGB3A2 secretoglobin_family 3A_member 10.82 3.4361 1.56E−04 2 SCN2B sodium channel_voltage gated.sub.— 10.81 3.4348 1.58E−04 type II beta subunit HMGA2

high mobility group AT-hook 2 10.78 3.4309 4.79E−14 TLL1 tolloid-like 1 10.77 3.4296 3.71E−22 PM20D2 peptidase M20 domain containing 2 10.77 3.4292 2.19E−22 PURG purine-rich element binding protein 10.72 3.4228 1.15E−06 G KLHL38 kelch-like family member 38 10.68 3.4173 2.07E−06 HIST1H2BH histone cluster 1_H2bh 10.68 3.4170 1.17E−12 ITGB6 integrin_beta 6 10.56 3.4000 9.77E−09 AFF3 AF4/FMR2 family_member 3 10.55 3.3986 3.23E−81 ZBED2 zinc finger_BED-type containing 2 10.49 3.3907 1.64E−06 TRHDE thyrotropin-releasing hormone 10.40 3.3789 5.13E−05 degrading enzyme APBA2 amyloid beta (A4) precursor protein- 10.39 3.3775 2.69E−08 binding_family A_member 2 PCDHA4 protocadherin alpha 4 10.36 3.3733 2.60E−08 SMIM1 small integral membrane protein 1 10.27 3.3608 6.15E−07 (Vel blood group) PIK3R3 phosphoinositide-3-kinase.sub.— 10.19 3.3496 2.71E−34 regulatory subunit 3 (gamma) KALRN kalirin_RhoGEF kinase 10.03 3.3267 1.54E−34 LOC728463 NA 10.01 3.3241 2.74E−04 PTN pleiotrophin 9.96 3.3165 2.92E−06 CLDN6 claudin 6 9.95 3.3142 3.72E−07 ASXL3 additional sex combs like 9.93 3.3111 1.05E−04 transcriptional regulator 3 KBTBD11 kelch repeat and BTB (POZ) domain 9.86 3.3023 2.00E−06 containing 11 GALNT14 polypeptide N- 9.86 3.3022 1.82E−09 acetylgalactosaminyltransferase 14 LOC440173 uncharacterized LOC440173 9.86 3.3022 1.39E−04 TLE4 transducin-like enhancer of split 4 9.85 3.2996 2.87E−71 NOX4 NADPH oxidase 4 9.81 3.2948 1.77E−23 EPHX4 epoxide hydrolase 4 9.73 3.2823 1.50E−05 DIO2 deiodinase_iodothyronine_type_II 9.68 3.2755 2.14E−05 DNAJC6 DnaJ (Hsp40) homolog_subfamily 9.60 3.2634 7.55E−24 C_member 6 SLC16A12 solute carrier family 16_member 12 9.60 3.2630 2.76E−06 BCL11A B-cell CLL/lymphoma 11A (zinc 9.49 3.2467 4.04E−15 finger protein) ZNF608 zinc finger protein 608 9.45 3.2402 2.33E−16 PPAP2C phosphatidic acid phosphatase type 9.37 3.2285 1.22E−17 2C IGSF3 immunoglobulin superfamily.sub.— 9.29 3.2164 2.26E−38 member 3 COL18A1 collagen_type XVIII_alpha 1 9.20 3.2021 2.63E−16 ZNF732 zinc finger protein 732 9.18 3.1988 3.05E−16 NAALAD2 N-acetylated alpha-linked acidic 9.18 3.1979 4.47E−06 dipeptidase 2 EXOC3L2 exocyst complex component 3-like 2 9.16 3.1959 8.87E−09 JUP junction plakoglobin 9.14 3.1926 3.22E−24 MSR1 macrophage scavenger receptor 1 9.12 3.1888 4.36E−07 TRIM58 tripartite motif containing 58 9.03 3.1745 3.32E−25 TMSB15A thymosin beta 15a 9.02 3.1728 2.04E−17 MAPK15 mitogen-activated protein kinase 15 9.00 3.1707 1.35E−05 CELSR1 cadherin_EGF LAG seven-pass G- 9.00 3.1705 1.83E−15 type receptor 1 SEMA3D sema domain_immunoglobulin 8.96 3.1630 2.81E−06 domain (Ig)_short basic domain.sub.— secreted_(semaphorin) 3D SH3RF2 SH3 domain containing ring finger 2 8.93 3.1586 5.06E−16 MYPN myopalladin 8.81 3.1391 5.10E−11 PKD1L1 polycystic kidney disease 1 like 1 8.80 3.1377 1.21E−05 PCDHA13 protocadherin alpha 13 8.76 3.1317 4.55E−04 PKNOX2 PBX/knotted 1 homeobox 2 8.76 3.1317 7.68E−07 ZIC5 Zic family member 5 8.74 3.1277 3.70E−05 LOC90246 uncharacterized LOC90246 8.72 3.1251 4.62E−14 SLC12A5 solute carrier family 12 8.68 3.1175 1.98E−09 (potassium/chloride transporter).sub.— member 5 PCDHB10 protocadherin beta 10 8.67 3.1168 2.00E−16 TMEM63C transmembrane protein 63C 8.65 3.1130 1.86E−09 LYN LYN proto-oncogene_Src family 8.65 3.1127 9.22E−41 tyrosine kinase CHMP4C charged multivesicular body protein 8.61 3.1057 6.67E−06 4C GPRIN2 G protein regulated inducer of 8.56 3.0977 1.13E−05 neurite outgrowth 2 TNS3 tensin 3 8.56 3.0972 3.01E−30 DOCK3 dedicator of cytokinesis 3 8.55 3.0955 4.29E−21 CPA4 carboxypeptidase A4 8.54 3.0935 1.85E−05 C1orf106 chromosome 1 open reading frame 8.53 3.0928 6.67E−10 106 LOC339862 uncharacterized LOC339862 8.51 3.0891 2.74E−04 SLC6A6 solute carrier family 6 8.47 3.0819 6.02E−44 (neurotransmitter transporter).sub.— member 6 LPPR3 lipid phosphate phosphatase-related 8.43 3.0762 2.23E−10 protein type 3 BMF Bc12 modifying factor 8.43 3.0758 4.14E−79 MDK midkine (neurite growth-promoting 8.43 3.0749 3.83E−52 factor 2) SBK1 SH3 domain binding kinase 1 8.38 3.0668 8.81E−06 ZNF676 zinc finger protein 676 8.36 3.0643 2.95E−04 SIM2 single-minded family bHLH 8.32 3.0570 6.97E−17 transcription factor 2 COL24A1 collagen_type XXIV_alpha 1 8.31 3.0555 2.37E−06 C14orf39 chromosome 14 open reading frame 8.29 3.0520 9.36E−04 39 RTL1 retrotransposon-like 1 8.29 3.0513 2.60E−06

TUBB2B tubulin_beta 2B class IIb 8.29 3.0508 1.38E−04 PDZD2 PDZ domain containing 2 8.23 3.0409 1.60E−15 SEMA6B sema domain_transmembrane 8.22 3.0388 2.53E−15 domain (TM)_and cytoplasmic domain_(semaphorin) 6B KCTD8 potassium channel tetramerization 8.21 3.0380 8.62E−04 domain containing 8 FAM213A family with sequence similarity 8.19 3.0336 3.82E−06 213_member A HRASLS HRAS-like suppressor 8.18 3.0326 2.51E−07 TRIML2 tripartite motif family-like 2 8.14 3.0253 8.36E−16 CNIH2 cornichon family AMPA receptor 8.09 3.0166 1.42E−47 auxiliary protein 2 OCA2 oculocutaneous albinism II 8.01 3.0011 4.47E−04 RNF165 ring finger protein 165 8.01 3.0010 2.48E−04 PTPRN2 protein tyrosine phosphatase.sub. — 8.00 3.0000 3.98E−34 receptor type_N polypeptide 2 PIK3C2B phosphatidylinositol-4-phosphate 3- 7.99 2.9979 4.89E−53 kinase_catalytic subunit type 2 beta NFE2 nuclear factor_erythroid 2 7.96 2.9927 1.85E−04 PRND prion protein 2 (dublet) 7.95 2.9901 1.26E−03 EGLN3 egl-9 family hypoxia-inducible 7.91 2.9828 7.72E−07 factor 3 SLC38A3 solute carrier family 38_member 3 7.88 2.9781 6.75E−04 IGF2BP3 insulin-like growth factor 2 mRNA 7.87 2.9762 5.96E−05 binding protein 3 RAB27B RAB27B_member RAS oncogene 7.84 2.9712 1.03E−11 family LINC00333 long intergenic non-protein coding 7.84 2.9702 4.05E−04 RNA 333 CYTL1 cytokine-like 1 7.81 2.9650 3.54E−05 FENDRR FOXF1 adjacent non-coding 7.78 2.9597 5.21E−04 developmental regulatory RNA WNK3 WNK lysine deficient protein kinase 7.76 2.9568 6.00E−09 3 CDH10 cadherin 10_type 2 (T2-cadherin) 7.73 2.9498 2.09E−11 GPRIN3 GPRIN family member 3 7.71 2.9468 1.31E−03 DOK2 docking protein 2_56 kDa 7.70 2.9440 2.85E−05 TTYH2 tweety family member 2 7.70 2.9440 1.49E−48 SLC2A12 solute carrier family 2 (facilitated 7.66 2.9377 3.75E−16 glucose transporter)_member 12 DYSF dysferlin 7.65 2.9362 6.16E−12 NRARP NOTCH-regulated ankyrin repeat 7.65 2.9355 6.67E−10 protein CELSR2 cadherin_EGF LAG seven-pass G- 7.65 2.9354 4.02E−13 type receptor 2 RAD21L1 RAD21 cohesin complex component 7.65 2.9350 4.40E−04 like 1 RAP1GAP2 RAP1 GTPase activating protein 2 7.63 2.9309 1.35E−09 OGDHL oxoglutarate dehydrogenase-like 7.56 2.9179 1.33E−16 IGFBP7-AS1 IGFBP7 antisense RNA 1 7.51 2.9092 7.05E−06 PIANP PILR alpha associated neural protein 7.46 2.8994 2.59E−15 TRABD2A TraB domain containing 2A 7.46 2.8991 7.41E−83 FSIP2 fibrous sheath interacting protein 2 7.46 2.8986 1.04E−03 RASSF4 Ras association (RalGDS/AF-6) 7.42 2.8915 7.70E−31 domain family member 4 ABCA4 ATP-binding cassette_sub-family A 7.34 2.8764 8.46E−09 (ABC1)_member 4 PPP1R3A protein phosphatase 1_regulatory 7.33 2.8734 2.01E−03 subunit 3A ZBTB46 zinc finger and BTB domain 7.32 2.8724 1.25E−30 containing 46 CYP2S1 cytochrome P450_family 2.sub.— 7.29 2.8668 2.98E−09 subfamily S_polypeptide 1 DIRC3 disrupted in renal carcinoma 3 7.26 2.8600 9.57E−08 COL9A3 collagen_type IX_alpha 3 7.24 2.8559 4.41E−10 MAMDC2 MAM domain containing 2 7.20 2.8474 5.15E−18 GIPC3 GIPC PDZ domain containing 7.20 2.8471 6.98E−09 family_member 3 DPYSL4 dihydropyrimidinase-like 4 7.18 2.8445 3.72E−06 DLX2 distal-less homeobox 2 7.17 2.8429 1.60E−37 TRIM67 tripartite motif containing 67 7.16 2.8401 5.57E−07 ADAMTS18 ADAM metallopeptidase with 7.13 2.8348 1.91E−03 thrombospondin type 1 motif_18 IGDCC4 immunoglobulin superfamily_DCC 7.12 2.8317 2.14E−18 subclass_member 4 EFNA2 ephrin-A2 7.12 2.8313 1.23E−04 CPVL carboxypeptidase_vitellogenic-like 7.11 2.8292 1.50E−08 PCDHA8 protocadherin alpha 8 7.09 2.8261 1.57E−03 DBNDD1 dysbindin (dystrobrevin binding 7.09 2.8253 2.34E−11 protein 1) domain containing 1 DNER delta/notch-like EGF repeat 7.08 2.8239 7.46E−15 containing NPW neuropeptide W 7.07 2.8226 7.31E−25 GNGT2 guanine nucleotide binding protein 7.03 2.8129 8.59E−07 (G protein)_gamma transducing activity polypeptide 2 CDC42BPG CDC42 binding protein kinase 7.02 2.8124 4.40E−12 gamma (DMPK-like) FBN2 fibrillin 2 7.01 2.8089 1.27E−29 TPSG1 tryptase gamma 1 6.97 2.8020 1.48E−03 KCND1 potassium channel_voltage gated 6.96 2.7996 8.82E−34 Shal related subfamily D_member 1 KRT80 keratin 80_type II 6.95 2.7979 1.69E−16 ST6GAL1 ST6 beta-galactosamide alpha-2_6- 6.90 2.7872 3.42E−59 sialyltranferase 1 EPPK1 epiplakin 1 6.89 2.7849 2.02E−06 HS6ST2 heparan sulfate 6-O-sulfotransferase 6.89 2.7836 2.41E−03 2 OBSCN obscurin_cytoskeletal

calmodulin 6.88 2.7826 2.91E−28 and titin-interacting RhoGEF CCDC68 coiled-coil domain containing 68 6.88 2.7825 1.73E−22 ZNF185 zinc finger protein 185 (LIM 6.87 2.7805 1.15E−04 domain) PCDHB9 protocadherin beta 9 6.84 2.7748 1.21E−09 SH3GL2 SH3-domain GRB2-like 2 6.84 2.7736 3.07E−03 LINC00707 long intergenic non-protein coding 6.81 2.7680 5.48E−04 RNA 707 GABRA5 gamma-aminobutyric acid (GABA) 6.78 2.7620 2.28E−24 A receptor_alpha 5 KRT8 keratin 8_type II 6.78 2.7605 1.07E−07 RNF43 ring finger protein 43 6.76 2.7576 3.24E−03 SLC35F3 solute carrier family 35_member F3 6.74 2.7536 7.42E−05 SNCA synuclein_alpha (non A4 6.68 2.7395 2.22E−03 component of amyloid precursor) CGN cingulin 6.65 2.7323 3.68E−05 LOC100131289 uncharacterized LOC100131289 6.62 2.7260 1.55E−03 LOC100128885 uncharacterized LOC100128885 6.60 2.7219 8.13E−11 LOC653712 intraflagellar transport 122 homolog 6.59 2.7198 5.35E−18 (*Chlamydomonas*) pseudogene LLGL2 lethal giant larvae homolog 2 6.58 2.7171 2.79E−10 (*Drosophila*) TRIM62 tripartite motif containing 62 6.54 2.7097 7.99E−154 AMZ1 archaelysin family metallopeptidase 6.54 2.7088 1.81E−70 1 PDE3B phosphodiesterase 3B_cGMP- 6.54 2.7085 2.17E−05 inhibited IGDCC3 immunoglobulin superfamily_DCC 6.51 2.7021 1.17E−03 subclass_member 3 RAB38 RAB38_member RAS oncogene 6.48 2.6951 2.73E−05 family SFMBT2 Scm-like with four mbt domains 2 6.47 2.6930 1.62E−13 MEST mesoderm specific transcript 6.42 2.6817 3.56E−05 MAP2K6 mitogen-activated protein kinase 6.31 2.6583 5.33E−06 kinase 6 TOX thymocyte selection-associated high 6.21 2.6352 1.98E−05 mobility group box GARNL3 GTPase activating Rap/RanGAP 6.21 2.6336 2.42E−05 domain-like 3 TRIM16L tripartite motif containing 16-like 6.20 2.6334 1.13E−18 ABI3 ABI family_member 3 6.20 2.6330 3.20E−33 SHC4 SHC (Src homology 2 domain 6.20 2.6326 3.82E−11 containing) family_member 4 BFSP1 beaded filament structural protein 1.sub.— 6.17 2.6255 3.20E−22 filensin FAXC failed axon connections homolog 6.17 2.6251 2.70E−16 TBX1 T-box 1 6.16 2.6234 1.74E−03 PLS1 plastin 1 6.15 2.6195 8.36E−16 RGS9 regulator of G-protein signaling 9 6.14 2.6177 9.91E−08 NLRP3 NLR family_pyrin domain 6.13 2.6164 2.52E−04 containing 3 LOC101928775 uncharacterized LOC101928775 6.13 2.6148 5.43E−03 FAM84B family with sequence similarity 84.sub.— 6.09 2.6074 4.97E−08 member B VSTM1 V-set and transmembrane domain 6.09 2.6073 5.51E−03 containing 1 RNF150 ring finger protein 150 6.09 2.6064 1.69E−03 KIF21B kinesin family member 21B 6.06 2.6002 2.72E−25 ZNF702P zinc finger protein 702_pseudogene 6.05 2.5959 1.47E−10 ITPRIPL1 inositol 1_4_5-trisphosphate 6.04 2.5955 1.98E−19 receptor interacting protein-like 1 ANKRD18B ankyrin repeat domain 18B 6.02 2.5907 1.70E−03 SIX1 SIX homeobox 1 6.02 2.5889 8.50E−09 RUNX3 runt-related transcription factor 3 6.00 2.5848 1.62E−12 TNFRSF21 tumor necrosis factor receptor 5.98 2.5803 2.24E−24 superfamily_member 21 SUSD5 sushi domain containing 5 5.98 2.5795 1.27E−03 GRIP1 glutamate receptor interacting 5.96 2.5744 5.40E−05 protein 1 MEGF10 multiple EGF-like-domains 10 5.94 2.5704 5.12E−03 MGC2889 uncharacterized protein MGC2889 5.94 2.5696 4.80E−03 EDARADD EDAR-associated death domain 5.92 2.5663 2.25E−13 FBXO16 F-box protein 16 5.91 2.5642 6.29E−08 VASH2 vasohibin 2 5.90 2.5606 5.92E−08 PCDHAC1 protocadherin alpha subfamily C_1 5.88 2.5560 3.37E−03 ADM5 adrenomedullin 5 (putative) 5.88 2.5552 4.05E−10 FAM160A1 family with sequence similarity 5.86 2.5510 2.61E−03 160 member A1 EFNB3 ephrin-B3 5.86 2.5500 5.60E−13 STK32B serine/threonine kinase 32B 5.85 2.5482 1.91E−83 MYOZ1 myozenin 1 5.82 2.5412 4.63E−04 EGF epidermal growth factor 5.82 2.5398 8.06E−07 FRRS1L ferric-chelate reductase 1-like 5.81 2.5387 5.23E−03 CSRP2 cysteine and glycine-rich protein 2 5.81 2.5386 1.37E−56 FAM83F family with sequence similarity 83.sub.— 5.78 2.5323 2.50E−03 member F LOC101929690 NA 5.78 2.5321 1.50E−03 EPB41L4B erythrocyte membrane protein band 5.78 2.5303 1.25E−26 4.1 like 4B APOE apolipoprotein E 5.76 2.5265 5.10E−11 PCDHGC4 protocadherin gamma subfamily C.sub.— 5.76 2.5249 8.40E−12 4 GPR162 G protein-coupled receptor 162 5.72 2.5166 1.36E−08 SLC29A2 solute carrier family 29 5.71 2.5131 7.20E−15 (equilibrative nucleoside transporter)_member 2 GULP1 GULP_engulfment adaptor PTB 5.70 2.5107 9.81E−17 domain containing 1 AC093375.1 NA 5.69 2.5079 6.38E−03

PIFO primary cilia formation 5.68 2.5048 3.68E−03 GALNT3 polypeptide N- 5.67 2.5039 1.41E−05 acetylgalactosaminyltransferase 3 CBX2 chromobox homolog 2 5.67 2.5031 4.47E−37 PROC protein C (inactivator of coagulation 5.67 2.5029 8.18E−07 factors Va and VIIIa) CHD7 chromodomain helicase DNA 5.66 2.5004 1.63E−18 binding protein 7 VAC14-AS1 VAC14 antisense RNA 1 5.66 2.5001 3.38E−05 ISYNA1 inositol-3-phosphate synthase 1 5.65 2.4986 1.68E−21 FBXL16 F-box and leucine-rich repeat 5.64 2.4961 1.63E−07 protein 16 NKAIN4 Na+/K+ transporting ATPase 5.64 2.4951 3.47E−03 interacting 4 HID1 HID1 domain containing 5.63 2.4927 1.59E−04 SYT12 synaptotagmin XII 5.62 2.4907 4.24E−03 BEGAIN brain-enriched guanylate kinase- 5.61 2.4875 1.29E−07 associated OCIAD2 OCIA domain containing 2 5.60 2.4850 9.91E−54 FSD1 fibronectin type III and SPRY 5.59 2.4817 1.01E−24 domain containing 1 SCD5 stearoyl-CoA desaturase 5 5.58 2.4813 1.61E−13 PTCHD4 patched domain containing 4 5.57 2.4767 6.76E−04 OR2W3 olfactory receptor_family 2.sub.— 5.55 2.4735 4.87E−07 subfamily W_member 3 PNMT phenylethanolamine N- 5.55 2.4733 3.44E−03 methyltransferase ZNF208 zinc finger protein 208 5.51 2.4630 1.91E−04 MYOZ3 myozenin 3 5.50 2.4595 1.47E−20 CPT1B carnitine palmitoyltransferase 1B 5.50 2.4587 5.67E−03 (muscle) KCNMA1 potassium channel_calcium 5.48 2.4541 1.81E−67 activated large conductance subfamily M alpha_member 1 PALMD palmdelphin 5.47 2.4521 8.82E−05 SYNGR1 synaptogyrin 1 5.46 2.4485 1.69E−91 DRP2 dystrophin related protein 2 5.46 2.4482 5.80E−23 CAPN14 calpain 14 5.42 2.4384 3.28E−03 SOX17 SRY (sex determining region Y)- 5.39 2.4314 8.94E−03 box 17 PTGES3L prostaglandin E synthase 3 5.39 2.4308 2.45E−04 (cytosolic)-like KCTD4 potassium channel tetramerization 5.38 2.4287 2.05E−04 domain containing 4 PCDHA6 protocadherin alpha 6 5.38 2.4282 3.90E−03 LOC101927497 uncharacterized LOC101927497 5.37 2.4259 7.44E−07 TMEM184A transmembrane protein 184A 5.35 2.4201 5.40E−18 DOCK4 dedicator of cytokinesis 4 5.35 2.4184 6.49E−25 THEMIS thymocyte selection associated 5.34 2.4177 1.06E−02 HEY1 hes-related family bHLH 5.34 2.4169 1.31E−06 transcription factor with YRPW motif 1 MKRN3 makorin ring finger protein 3 5.34 2.4156 9.13E−13 JAG2 jagged 2 5.33 2.4144 2.59E−09 LOC101927482 uncharacterized LOC101927482 5.33 2.4137 2.19E−04 RND2 Rho family GTPase 2 5.32 2.4121 2.31E−15 DSC2 desmocollin 2 5.32 2.4107 1.56E−03 CTXN1 cortexin 1 5.31 2.4095 1.48E−11 LOC100128076 protein tyrosine phosphatase 5.31 2.4080 2.30E−04 pseudogene KCNS1 potassium voltage-gated channel.sub.— 5.30 2.4048 1.77E−19 modifier subfamily S_member 1 KCNMB4 potassium channel subfamily M 5.29 2.4042 4.48E−16 regulatory beta subunit 4 MCTP1 multiple C2 domains.sub.— 5.28 2.4012 5.81E−06 transmembrane 1 SLC2A14 solute carrier family 2 (facilitated 5.26 2.3962 5.86E−04 glucose transporter)_member 14 MTL5 metallothionein-like 5_testis- 5.25 2.3921 1.23E−09 specific (tesmin) SLC16A4 solute carrier family 16_member 4 5.24 2.3905 2.14E−63 CARD10 caspase recruitment domain family.sub.— 5.23 2.3856 3.39E−28 member 10 TMEM108 transmembrane protein 108 5.21 2.3821 2.63E−05 NETO2 neuropilin (NRP) and tolloid (TLL)- 5.19 2.3764 5.94E−37 like 2 CLDN16 claudin 16 5.16 2.3679 1.34E−02 SLC29A4 solute carrier family 29 5.15 2.3656 1.71E−23 (equilibrative nucleoside transporter)_member 4 ZBED9 zinc finger_BED-type containing 9 5.15 2.3652 6.60E−10 SLC22A31 solute carrier family 22_member 31 5.15 2.3641 3.24E−03 CCND2 cyclin D2 5.13 2.3600 2.48E−26 BEX1 brain expressed_X-linked 1 5.13 2.3592 1.18E−02 PPM1H protein phosphatase_Mg2+/Mn2+ 5.13 2.3592 5.26E−07 dependent_1H C7orf61 chromosome 7 open reading frame 5.13 2.3588 7.21E−06 61 RGPD1 RANBP2-like and GRIP domain 5.13 2.3586 4.05E−03 containing 1 GPR143 G protein-coupled receptor 143 5.13 2.3576 9.43E−03 TNFRSF10C tumor necrosis factor receptor 5.10 2.3515 4.48E−07 superfamily_member 10c_decoy without an intracellular domain MSI2 musashi RNA-binding protein 2 5.10 2.3502 1.21E−79 HIST1H3F histone cluster 1_H3f 5.09 2.3485 1.42E−02 TRIM55 tripartite motif containing 55 5.07 2.3425 9.83E−05 LPAR3 lysophosphatidic acid receptor 3 5.07 2.3411 5.33E−03 LEPREL1 prolyl 3-hydroxylase 2 5.03 2.3313 5.14E−05 KCNN3 potassium channel_calcium 5.01 2.3251 7.84E−06 activated intermediate/small conductance subfamily N

alpha.sub.— member 3

TABLE-US-00008 TABLE 8 Genes more highly expressed in AD-MSCs compared with HMCs Log Fold Fold Gene name Description Change Change p-Adj TWIST2 twist family bHLH transcription factor −615.13 −9.265 2.6E−153 2 FGL2 fibrinogen-like 2 −521.90 −9.028 1.5E−52 PI16 peptidase inhibitor 16 −505.64 −8.982 1.6E−78 EMX2OS EMX2 opposite strand/antisense RNA −429.80 −8.748 4.3E−56 XIST X inactive specific transcript (non- −416.10 −8.701 2.3E−269 protein coding) ISLR immunoglobulin superfamily −316.46 −8.306 1.1E−26 containing leucine-rich repeat MEOX2 mesenchyme homeobox 2 −302.76 −8.242 2.2E−45 HAGLR HOXD antisense growth-associated −273.46 −8.095 7.7E−39 long non-coding RNA FAM180A family with sequence similarity 180.sub.— −260.12 −8.023 3.2E−51 member A LINC00856 long intergenic non-protein coding −254.50 −7.992 2.9E−36 RNA 856 EMX2 empty spiracles homeobox 2 −246.43 −7.945 9.7E−54 TNXB tenascin XB −240.63 −7.911 7.3E−140 HAS1 hyaluronan synthase 1 −233.59 −7.868 4.5E−47 HAS2 hyaluronan synthase 2 −209.41 −7.710 8.3E−139 TBX5-AS1 TBX5 antisense RNA 1 −202.78 −7.664 1.8E−41 BHMT2 betaine-- homocysteine S- −195.84 −7.614 8.1E−82 methyltransferase 2 HOXC5 homeobox C5 −185.04 −7.532 1.1E−52 COMP cartilage oligomeric matrix protein −182.83 −7.514 3.3E−35 DOK5 docking protein 5 −182.49 −7.512 2.7E−154 CSTA cystatin A (stefin A) −181.14 −7.501 5.4E−32 CCDC36 coiled-coil domain containing 36 −179.59 −7.489 3.7E−42 TPTEP1 transmembrane phosphatase with −175.65 −7.457 1.4E−29 tensin homology pseudogene 1 XG Xg blood group −174.60 −7.448 1.6E−37 KRT14 keratin 14_ type I −170.06 −7.410 9.0E−29 NDNF neuron-derived neurotrophic factor −169.92 −7.409 1.6E−46 HTR2A 5-hydroxytryptamine (serotonin) −160.86 −7.330 1.2E−34 receptor 2A_ G protein-coupled PSG5 pregnancy specific beta-1-glycoprotein −160.55 −7.327 8.1E−76 5 DCLK3 doublecortin-like kinase 3 −158.45 −7.308 3.7E−29 KCND2 potassium channel_ voltage gated Shal −148.30 −7.212 4.1E−28 related subfamily D_ member 2 LINC01133 long intergenic non-protein coding −139.87 −7.128 1.6E−31 RNA 1133 CNTN3 contactin 3 (plasmacytoma associated) −137.81 −7.107 1.3E−66 GPAT2 glycerol-3-phosphate acyltransferase −137.06 −7.099 5.4E−37 2_ mitochondrial HOXC6 homeobox C6 −136.95 −7.098 0.0E+00 KRBOX1 KRAB box domain containing 1 −136.24 −7.090 9.5E−54 ITGBL1 integrin_ beta-like 1 (with EGF-like −135.06 −7.077 0.0E+00 repeat domains) PCDHGA12 protocadherin gamma subfamily A_ 12 −134.87 −7.075 1.8E−210 DMGDH dimethylglycine dehydrogenase −130.82 −7.031 5.0E−36 SGCG sarcoglycan_ gamma (35 kDa −130.78 −7.031 1.1E−29 dystrophin-associated glycoprotein) HOXD3 homeobox D3 −130.60 −7.029 3.0E−26 HOXD8 homeobox D8 −127.97 −7.000 8.4E−156 EGFLAM EGF-like_ fibronectin type III and −127.49 −6.994 2.4E−43 laminin G domains HOXD9 homeobox D9 −118.10 −6.884 1.1E−41 MASP1 mannan-binding lectin serine peptidase −115.18 −6.848 3.1E−29 1 (C4/C2 activating component of Ra- reactive factor) OLFM1 olfactomedin 1 −113.80 −6.830 2.5E−110 ADRA2A adrenoceptor alpha 2A −109.79 −6.779 2.0E−49 HOXD4 homeobox D4 −109.17 −6.770 1.2E−47 ARHGAP20 Rho GTPase activating protein 20 −108.16 −6.757 2.8E−48 PRR15 proline rich 15 −107.72 −6.751 2.2E−148 PENK proenkephalin −103.97 −6.700 1.4E−30 MMP3 matrix metallopeptidase 3 −101.89 −6.671 7.5E−36 SFRP4 secreted frizzled-related protein 4 −100.96 −6.658 1.1E−22 SIM1 single-minded family bHLH −100.64 −6.653 6.4E−36 transcription factor 1 TEKT4P2 tektin 4 pseudogene 2 −98.84 −6.627 1.6E−37 MYH2 myosin_ heavy chain 2_ skeletal −98.26 −6.619 9.2E−25 muscle_ adult EN1 engrailed homeobox 1 −98.11 −6.616 7.5E−95 TBX5 T-box 5 −94.95 −6.569 7.2E−31 HOXC10 homeobox C10 −94.63 −6.564 1.4E−43 ABCC9 ATP-binding cassette_ sub-family C −89.87 −6.490 7.9E−81 (CFTR/MRP)_ member 9 HOXC-AS2 HOXC cluster antisense RNA 2 −89.25 −6.480 1.4E−29 USP32P1 ubiquitin specific peptidase 32 −87.52 −6.452 3.3E−25 pseudogene 1 FMOD fibromodulin −87.47 −6.451 1.1E−75 ABCA8 ATP-binding cassette_ sub-family A −87.45 −6.450 3.1E−33 (ABC1)_ member 8 PDE1A phosphodiesterase 1A_ calmodulin- −86.65 −6.437 3.6E−56 dependent COL15A1 collagen_ type XV_ alpha 1 −86.33 −6.432 1.7E−142 HOXC4 homeobox C4 −85.68

−6.421 4.2E−84 GSC goosecoid homeobox −85.63 −6.420 2.9E−28 IL13RA2 interleukin 13 receptor_ alpha 2 −84.87 −6.407 1.1E−21 LINC00968 long intergenic non-protein coding −83.09 −6.377 4.8E−35 RNA 968 HOXD-AS2 HOXD cluster antisense RNA 2 −82.83 −6.372 1.6E−67 PAPPA2 pappalysin 2 −82.24 −6.362 6.6E−35 HOXC8 homeobox C8 −81.56 −6.350 0.0E+00 CCDC144B coiled-coil domain containing 144B −79.34 −6.310 5.6E−35 (pseudogene) TMEM233 transmembrane protein 233 −74.43 −6.218 2.6E−19 HOXC9 homeobox C9 −74.28 −6.215 2.5E−275 FAM225B family with sequence similarity 225.sub.— −74.15 −6.212 1.9E−18 member B (non-protein coding) FGF7 fibroblast growth factor 7 −72.94 −6.189 8.8E−55 C2orf88 chromosome 2 open reading frame 88 −69.58 −6.121 5.1E−41 NFASC neurofascin −67.27 −6.072 2.8E−158 HSPB2 heat shock 27 kDa protein 2 −66.67 −6.059 1.7E−95 HOXA10-AS HOXA10 antisense RNA −64.54 −6.012 5.4E−28 HOXA7 homeobox A7 −63.72 −5.994 1.8E−32 USP32P2 ubiquitin specific peptidase 32 −63.62 −5.991 3.0E−24 pseudogene 2 MCF2L MCF.2 cell line derived transforming −62.47 −5.965 6.2E−44 sequence-like DCN decorin −60.95 −5.929 9.3E−243 PRSS12 protease_ serine_ 12 (neurotrypsin.sub.— −59.56 −5.896 6.0E−143 motopsin) LAMA2 laminin_ alpha 2 −59.38 −5.892 2.7E−151 RARRES2 retinoic acid receptor responder −59.19 −5.887 8.3E−25 (tazarotene induced) 2 EYA2 EYA transcriptional coactivator and −58.85 −5.879 4.3E−18 phosphatase 2 LINC01018 long intergenic non-protein coding −58.61 −5.873 3.3E−16 RNA 1018 CLEC11A C-type lectin domain family 11.sub.— −58.21 −5.863 0.0E+00 member A CRLF1 cytokine receptor-like factor 1 −57.83 −5.854 7.2E−39 TRH thyrotropin-releasing hormone −57.47 −5.845 6.7E−16 LOC400043 uncharacterized LOC400043 −56.54 −5.821 4.9E−49 ASPN asporin −56.26 −5.814 2.0E−26 PRG4 proteoglycan 4 −56.25 −5.814 3.7E−24 LYNX1 Ly6/neurotoxin 1 −56.17 −5.812 5.7E−40 HOTAIRM1 HOXA transcript antisense RNA.sub.— −55.20 −5.787 1.6E−63 myeloid-specific 1 NUPR1 nuclear protein_ transcriptional −53.82 −5.750 2.4E−182 regulator_ 1 CECR7 cat eye syndrome chromosome region.sub.— −53.72 −5.747 9.2E−17 candidate 7 (non-protein coding) GREM2 gremlin 2_ DAN family BMP −52.48 −5.714 5.2E−78 antagonist ADAMTSL3 ADAMTS-like 3 −52.02 −5.701 2.5E−16 KCNE4 potassium channel_ voltage gated −51.90 −5.698 2.1E−145 subfamily E regulatory beta subunit 4 PODN podocan −51.36 −5.683 7.4E−182 PRDM6 PR domain containing 6 −50.92 −5.670 2.9E−21 HOXA9 homeobox A9 −50.65 −5.663 1.7E−69 HSPB7 heat shock 27 kDa protein family.sub.— −50.60 −5.661 0.0E+00 member 7 (cardiovascular) MFAP5 microfibrillar associated protein 5 −47.76 −5.578 2.6E−241 WISP2 WNT1 inducible signaling pathway −46.57 −5.541 3.2E−16 protein 2 PPAPDC3 phosphatidic acid phosphatase type 2 −46.47 −5.538 9.0E−97 domain containing 3 KCNJ8 potassium channel_ inwardly −46.17 −5.529 1.5E−148 rectifying subfamily J_ member 8 PRSS30P protease_ serine_ 30_ pseudogene −46.12 −5.527 3.5E−14 NINJ2 ninjurin 2 −45.86 −5.519 2.8E−29 TECTB tectorin beta −44.68 −5.482 1.1E−13 IRX5 iroquois homeobox 5 −44.28 −5.468 8.4E−64 CADPS Ca++-dependent secretion activator −44.19 −5.466 2.2E−24 LIMCH1 LIM and calponin homology domains −44.02 −5.460 7.0E−23 1 NR3C2 nuclear receptor subfamily 3_ group −44.00 −5.459 3.2E−17 C_ member 2 CCDC89 coiled-coil domain containing 89 −43.76 −5.452 7.3E−53 DUXAP10 double homeobox A pseudogene 10 −43.60 −5.446 1.3E−63 S1PR1 sphingosine-1-phosphate receptor 1 −43.42 −5.440 1.0E−30 FNDC1 fibronectin type III domain containing −43.32 −5.437 7.2E−18 1 HOXA6 homeobox A6 −43.04 −5.428 1.5E−16 MIRLET7BHG MIRLET7B host gene −42.02 −5.393 1.7E−61 IRX3 iroquois homeobox 3 −41.92 −5.390 2.6E−99 WNT2 wingless-type MMTV integration site −41.90 −5.389 4.3E−12 family member 2.sub.— HAS2-AS1 HAS2 antisense RNA 1 −41.88 −5.388 2.6E−25 LOC643355 uncharacterized LOC643355 −41.85 −5.387 1.2E−13 SYBU syntabulin (syntaxin-interacting) −41.62 −5.379 7.3E−101 MB myoglobin −41.60 −5.378 1.8E−13 GYPE glycophorin E (MNS blood group) −41.46 −5.374 3.2E−17 CLEC2B C-type lectin domain family 2 −41.02 −5.358 1.1E−17 member B HOXC-AS1 HOXC cluster antisense RNA 1 −40.92 −5.355 4.6E−20 MALL mal_ T-cell differentiation protein-like −40.81 −5.351 6.2E−43 HOXA11 homeobox A11 −40.54 −5.341 3.4E−48 RFX8 RFX family member 8_ lacking RFX

−40.47 −5.339 1.3E−55 DNA binding domain BMPER BMP binding endothelial regulator −39.88 −5.318 1.2E−59 KCTD12 potassium channel tetramerization −39.69 −5.311 2.0E−40 domain containing 12 CH25H cholesterol 25-hydroxylase −39.23 −5.294 5.3E−13 ERG v-ets avian erythroblastosis virus E26 −38.73 −5.275 3.9E−13 oncogene homolog CCL26 chemokine (C-C motif) ligand 26 −38.66 −5.273 3.4E−27 HOXA10 homeobox A10 −38.54 −5.268 1.7E−144 POMC proopiomelanocortin −38.34 −5.261 9.8E−12 LOC100996609 NA −38.33 −5.260 1.6E−17 TDRD9 tudor domain containing 9 −38.08 −5.251 1.9E−13 LOC100506834 uncharacterized LOC100506834 −37.86 −5.243 2.5E−12 HOXB7 homeobox B7 −37.72 −5.237 5.8E−95 KRT34 keratin 34_ type I −37.35 −5.223 7.0E−63 FRMPD1 FERM and PDZ domain containing 1 −37.23 −5.218 1.9E−12 BHMT betaine--homocysteine S- −37.16 −5.216 3.8E−12 methyltransferase FAM198A family with sequence similarity 198.sub.— −36.59 −5.194 1.9E−12 member A PSTPIP1 proline-serine-threonine phosphatase −36.30 −5.182 3.6E−19 interacting protein 1 HOXB-AS3 HOXB cluster antisense RNA 3 −35.85 −5.164 7.0E−51 TRABD2B TraB domain containing 2B −35.59 −5.153 1.7E−13 GALNT12 polypeptide N- −34.90 −5.125 6.8E−63 acetylgalactosaminyltransferase 12 C8orf31 chromosome 8 open reading frame 31 −34.72 −5.118 1.0E−23 ZNF300P1 zinc finger protein 300 pseudogene 1 −34.71 −5.117 2.1E−51 (functional) TNFRSF11B tumor necrosis factor receptor −34.56 −5.111 2.2E−27 superfamily_ member 11b PLBD1 phospholipase B domain containing 1 −34.51 −5.109 7.9E−33 PPP1R14C protein phosphatase 1_ regulatory −34.18 −5.095 1.5E−18 (inhibitor) subunit 14C MROH9 maestro heat-like repeat family −34.17 −5.095 1.7E−11 member 9 HOXD1 homeobox D1 −34.15 −5.094 7.3E−15 HOXA4 homeobox A4 −33.55 −5.068 2.5E−30 LUM lumican −33.14 −5.050 1.5E−72 HOXB5 homeobox B5 −33.04 −5.046 2.2E−39 MR1 major histocompatibility complex.sub.— −32.88 −5.039 3.7E−63 class I-related TSKS testis-specific serine kinase substrate −32.74 −5.033 6.0E−15 SPATA22 spermatogenesis associated 22 −32.55 −5.025 1.9E−11 GIPC2 GIPC PDZ domain containing family.sub.— −32.43 −5.019 3.5E−34 member 2 FGF14 fibroblast growth factor 14 −31.99 −5.000 6.2E−30 HOXB6 homeobox B6 −31.84 −4.993 1.9E−126 HOXB4 homeobox B4 −31.80 −4.991 3.2E−58 BAIAP2L2 BAI1-associated protein 2-like 2 −31.62 −4.983 5.1E−35 HOXB3 homeobox B3 −31.37 −4.971 2.0E−77 TP53TG3D TP53 target 3D −31.36 −4.971 6.5E−11 HOXA3 homeobox A3 −31.31 −4.969 2.0E−13 POSTN periostin_ osteoblast specific factor −30.78 −4.944 1.8E−38 IRAK3 interleukin-1 receptor-associated −30.66 −4.938 6.7E−68 kinase 3 TNFSF9 tumor necrosis factor (ligand) −30.57 −4.934 3.9E−47 superfamily_ member 9 BEAN1 brain expressed_ associated with −30.15 −4.914 2.3E−12 NEDD4_ 1 HOXC11 homeobox C11 −29.68 −4.891 5.8E−12 LRRK2 leucine-rich repeat kinase 2 −29.57 −4.886 2.4E−26 NRN1 neuritin 1 −29.56 −4.886 2.1E−133 LOC388780 uncharacterized LOC388780 −29.54 −4.884 1.1E−10 C3orf80 chromosome 3 open reading frame 80 −29.33 −4.874 1.7E−18 PINLYP phospholipase A2 inhibitor and −29.27 −4.871 1.9E−27 LY6/PLAUR domain containing PLAC9 placenta-specific 9 −29.00 −4.858 7.1E−184 CHST8 carbohydrate (N-acetylgalactosamine −28.41 −4.828 1.1E−11 4-0) sulfotransferase 8 LOC100240735 uncharacterized LOC100240735 −28.35 −4.825 1.5E−12 TSHZ2 teashirt zinc finger homeobox 2 −28.01 −4.808 6.3E−14 PRR34 proline rich 34 −27.65 −4.789 3.7E−10 DNASE1L3 deoxyribonuclease I-like 3 −27.53 −4.783 2.5E−09 COL10A1 collagen_ type X_ alpha 1 −27.42 −4.777 7.4E−12 FPR1 formyl peptide receptor 1 −27.04 −4.757 2.4E−12 KCND3 potassium channel_ voltage gated Shal −26.98 −4.754 7.2E−41 related subfamily D_ member 3 MRAP2 melanocortin 2 receptor accessory −26.90 −4.750 2.8E−09 protein 2 MIR10B microRNA 10b −26.66 −4.737 5.5E−10 DLX3 distal-less homeobox 3 −26.66 −4.737 2.4E−18 PCSK9 proprotein convertase subtilisin/kexin −26.34 −4.719 2.0E−20 type 9 ANGPTL1 angiopoietin-like 1 −26.14 −4.708 6.3E−15 CLIC3 chloride intracellular channel 3 −26.07 −4.704 4.0E−17 OSR2 odd-skipped related transciption factor −26.05 −4.703 8.5E−19 2 SORCS2 sortilin-related VPS10 domain −25.91 −4.696 5.3E−28 containing receptor 2 HOXB2 homeobox B2 −25.67 −4.682 1.6E−154 LOC728613 programmed cell death 6 pseudogene −25.51 −4.673 2.8E−41 ADAMTS4 ADAM

metallopeptidase with −25.45 −4.670 1.8E−57 thrombospondin type 1 motif_ 4 NGFR nerve growth factor receptor −25.08 −4.648 3.5E−13 KCNK2 potassium channel_ two pore domain −24.80 −4.632 8.3E−98 subfamily K_ member 2 GAS1 growth arrest-specific 1 −24.65 −4.623 1.3E−61 ABCA9 ATP-binding cassette_ sub-family A −24.63 −4.622 6.9E−09 (ABC1)_ member 9 THRB thyroid hormone receptor_ beta −24.45 −4.612 4.6E−19 M1AP meiosis 1 associated protein −24.10 −4.591 3.3E−14 SLC7A8 solute carrier family 7 (amino acid −24.02 −4.586 2.4E−12 transporter light chain_ L system).sub.— member 8 ENPP2 ectonucleotide −23.98 −4.584 2.7E−26 pyrophosphatase/phosphodiesterase 2 LOC102724224 NA −23.97 −4.583 2.7E−28 GABBR2 gamma-aminobutyric acid (GABA) B −23.97 −4.583 3.3E−09 receptor_ 2 RASSF9 Ras association (RalGDS/AF-6) −23.96 −4.583 4.4E−22 domain family (N-terminal) member 9 TRIM29 tripartite motif containing 29 −23.93 −4.581 6.4E−09 GGT8P gamma-glutamyltransferase 8 −23.83 −4.574 5.7E−09 pseudogene FBLN5 fibulin 5 −23.70 −4.567 0.0E+00 HOXA5 homeobox A5 −23.63 −4.563 1.1E−12 EYA4 EYA transcriptional coactivator and −23.47 −4.553 2.6E−11 phosphatase 4 GPC3 glypican 3 −23.38 −4.547 1.5E−10 HTR1F 5-hydroxytryptamine (serotonin) −23.32 −4.543 1.6E−08 receptor 1F_ G protein-coupled LOC101928370 uncharacterized LOC101928370 −23.01 −4.525 7.4E−10 HOXA2 homeobox A2 −23.01 −4.524 1.3E−09 LOC102800310 NA −22.91 −4.518 2.1E−08 RHBDL2 rhomboid_ veinlet-like 2 (Drosophila) −22.89 −4.517 7.4E−46 ACTC1 actin_ alpha_ cardiac muscle 1 −22.82 −4.512 1.5E−88 ACOX2 acyl-CoA oxidase 2_ branched chain −22.68 −4.503 3.9E−55 RAET1E retinoic acid early transcript 1E −22.54 −4.494 1.5E−13 TNFAIP8L3 tumor necrosis factor_ alpha-induced −22.53 −4.494 4.3E−87 protein 8-like 3 LRRC15 leucine rich repeat containing 15 −22.43 −4.487 1.4E−10 IL33 interleukin 33 −22.38 −4.484 2.2E−12 PTPN20B protein tyrosine phosphatase_ non- −22.28 −4.477 1.3E−08 receptor type 20 RIPK3 receptor-interacting serine-threonine −22.28 −4.477 5.6E−19 kinase 3 CHI3L1 chitinase 3-like 1 (cartilage −22.22 −4.474 8.4E−13 glycoprotein-39) CNKSR2 connector enhancer of kinase −22.19 −4.472 1.5E−19 suppressor of Ras 2 ZFYVE28 zinc finger_ FYVE domain containing −22.16 −4.470 3.9E−42 28 HMOX1 heme oxygenase 1 −22.07 −4.464 3.1E−113 FLG-AS1 FLG antisense RNA 1 −22.02 −4.461 3.8E−08 SGCD sarcoglycan_ delta (35 kDa dystrophin- −21.92 −4.454 4.1E−20 associated glycoprotein) CD36 CD36 molecule (thrombospondin −21.67 −4.437 4.8E−08 receptor) GPR133 adhesion G protein-coupled receptor −21.65 −4.436 1.1E−59 D1 PTGIS prostaglandin I2 (prostacyclin) −21.63 −4.435 9.9E−125 synthase PCDHGA4 protocadherin gamma subfamily A_ 4 −21.59 −4.432 4.0E−22 RAI2 retinoic acid induced 2 −21.54 −4.429 5.9E−10 LCN1 lipocalin 1 −21.52 −4.428 3.8E−09 ANKRD6 ankyrin repeat domain 6 −21.48 −4.425 1.2E−26 ADIRF adipogenesis regulatory factor −21.09 −4.398 1.3E−21 ISLR2 immunoglobulin superfamily −21.04 −4.395 1.1E−26 containing leucine-rich repeat 2 FLG filaggrin −21.04 −4.395 2.0E−08 IBSP integrin-binding sialoprotein −20.92 −4.387 1.0E−07 ELN elastin −20.70 −4.371 1.1E−56 SALL4 spalt-like transcription factor 4 −20.68 −4.370 1.2E−13 TRPV3 transient receptor potential cation −20.62 −4.366 3.7E−28 channel_ subfamily V_ member 3 PTGS1 prostaglandin-endoperoxide synthase 1 −20.61 −4.365 0.0E+00 (prostaglandin G/H synthase and cyclooxygenase) FGF18 fibroblast growth factor 18 −20.56 −4.361 2.0E−17 ZNF662 zinc finger protein 662 −20.47 −4.356 3.3E−35 KCNJ15 potassium channel_ inwardly −20.33 −4.346 1.0E−35 rectifying subfamily J_ member 15 LINC01354 long intergenic non-protein coding −20.07 −4.327 1.1E−09 RNA 1354 LGI2 leucine-rich repeat LGI family.sub.— −20.02 −4.323 5.3E−13 member 2 TIMP3 TIMP metallopeptidase inhibitor 3 −19.80 −4.308 4.6E−92 EDA ectodysplasin A −19.58 −4.292 7.3E−24 FAM225A family with sequence similarity 225.sub.— −19.26 −4.267 1.1E−11 member A (non-protein coding) ALS2CR11 amyotrophic lateral sclerosis 2 −19.16 −4.260 8.9E−24 (juvenile) chromosome region.sub.— candidate 11 COX7A1 cytochrome c oxidase subunit VIIa −19.02 −4.249 1.1E−46 polypeptide 1 (muscle) HCG4 HLA complex group 4 (non-protein −18.90 −4.240 1.3E−07 coding) KLF14 Kruppel-like factor 14 −18.65 −4.221 2.2E−07 APOD apolipoprotein D −18.62 −4.219 1.8E−07 NOV nephroblastoma overexpressed −18.58 −4.215 2.0E−49 CLEC14A C-type lectin

domain family 14.sub.— −18.57 −4.215 2.3E−07 member A CGREF1 cell growth regulator with EF-hand −18.43 −4.204 5.5E−55 domain 1 NTF3 neurotrophin 3 −18.40 −4.201 9.1E−29 FOLR3 folate receptor 3 (gamma) −18.29 −4.193 1.6E−09 LOC100132077 uncharacterized LOC100132077 −18.27 −4.192 1.8E−25 WNT11 wingless-type MMTV integration site −18.08 −4.177 6.9E−15 family_ member 11 CLIC6 chloride intracellular channel 6 −17.89 −4.161 8.0E−17 PRSS3 protease_ serine_ 3 −17.80 −4.154 1.5E−09 PSG2 pregnancy specific beta-1-glycoprotein −17.77 −4.152 5.8E−07 2 MFSD7 major facilitator superfamily domain −17.75 −4.150 3.3E−51 containing 7 PIWIL4 piwi-like RNA-mediated gene −17.71 −4.147 1.3E−23 silencing 4 MEGF6 multiple EGF-like-domains 6 −17.69 −4.145 9.3E−50 LINC01116 long intergenic non-protein coding −17.69 −4.145 3.0E−41 RNA 1116 TLX2 T-cell leukemia homeobox 2 −17.25 −4.108 7.0E−10 GRID1 glutamate receptor_ ionotropic_ delta 1 −17.25 −4.108 6.6E−07 DLGAP1 discs_ large (Drosophila) homolog- −17.21 −4.105 4.3E−07 associated protein 1 SPESP1 sperm equatorial segment protein 1 −17.05 −4.092 1.2E−09 NAALADL1 N-acetylated alpha-linked acidic −16.94 −4.083 1.2E−101 dipeptidase-like 1 IL22RA1 interleukin 22 receptor_ alpha 1 −16.93 −4.081 6.4E−07 SNORD114-10 small nucleolar RNA_ C/D box 114-10 −16.91 −4.080 5.8E−07 PSG1 pregnancy specific beta-1-glycoprotein −16.89 −4.078 7.5E−07 1 LOC100130872 uncharacterized LOC100130872 −16.85 −4.075 4.2E−26 LPXN leupaxin −16.83 −4.073 2.6E−133 GSTM5 glutathione S-transferase mu 5 −16.82 −4.072 1.5E−13 NDUFA4L2 NADH dehydrogenase (ubiquinone) 1 −16.80 −4.071 6.2E−10 alpha subcomplex_ 4-like 2 MYH13 myosin_ heavy chain 13_ skeletal −16.76 −4.067 1.1E−06 muscle PCDHGA2 protocadherin gamma subfamily A_ 2 −16.75 −4.066 2.3E−29 HOXB-AS1 HOXB cluster antisense RNA 1 −16.48 −4.043 3.4E−24 ZFP92 ZFP92 zinc finger protein −16.47 −4.042 1.1E−08 GLYATL2 glycine-N-acyltransferase-like 2 −16.44 −4.039 9.7E−10 LIPC lipase_ hepatic −16.34 −4.031 9.3E−07 BMPR1B bone morphogenetic protein receptor.sub.— −16.32 −4.029 4.9E−22 type IB PTGES prostaglandin E synthase −16.31 −4.028 1.5E−35 S100P S100 calcium binding protein P −16.14 −4.013 1.4E−06 LINC00595 long intergenic non-protein coding −16.01 −4.001 7.2E−08 RNA 595 SLC1A2 solute carrier family 1 (glial high −15.96 −3.996 9.5E−08 affinity glutamate transporter).sub.— member 2 AGMO alkylglycerol monooxygenase −15.91 −3.992 1.7E−07 BMP6 bone morphogenetic protein 6 −15.87 −3.988 7.5E−15 SLC1A1 solute carrier family 1 −15.85 −3.987 8.9E−14 (neuronal/epithelial high affinity glutamate transporter_ system Xag).sub. — member 1 IGF1 insulin-like growth factor 1 −15.78 −3.980 5.4E−11 (somatomedin C) IFNE interferon_ epsilon −15.73 −3.976 1.1E−14 SHCBP1L SHC SH2-domain binding protein 1- −15.70 −3.972 1.2E−06 like OPCML opioid binding protein/cell adhesion −15.69 −3.972 1.3E−13 molecule-like DKK1 dickkopf WNT signaling pathway −15.64 −3.967 1.5E−120 inhibitor 1 ASTL astacin-like metallo-endopeptidase −15.62 −3.965 1.6E−06 (M12 family) LDLRAD4 low density lipoprotein receptor class −15.61 −3.964 1.1E−19 A domain containing 4 P2RY6 pyrimidinergic receptor P2Y_ G- −15.57 −3.960 2.6E−11 protein coupled_ 6 FAM87B family with sequence similarity 87.sub.— −15.49 −3.953 1.2E−15 member B PLEKHH2 pleckstrin homology domain −15.47 −3.952 2.2E−64 containing_ family H (with MyTH4 domain) member 2 ALK anaplastic lymphoma receptor tyrosine −15.46 −3.951 1.8E−06 kinase MKX mohawk homeobox −15.44 −3.948 3.9E−07 MT1A metallothionein 1A −15.39 −3.944 3.1E−16 SHANK1 SH3 and multiple ankyrin repeat −15.31 −3.937 2.7E−18 domains 1 LOC150381 NA −15.30 −3.936 1.4E−30 ZNF503 zinc finger protein 503 −14.98 −3.905 8.3E−59 ZMYND12 zinc finger_ MYND-type containing −14.96 −3.903 8.4E−10 12 A4GALT alpha 1_4-galactosyltransferase −14.91 −3.898 4.6E−49 HOXA1 homeobox A1 −14.87 −3.894 1.0E−21 ADRA2C adrenoceptor alpha 2C −14.85 −3.892 2.6E−15 GALNT13 polypeptide N- −14.70 −3.878 4.4E−06 acetylgalactosaminyltransferase 13 RASIP 1 Ras interacting protein 1 −14.68 −3.875 2.8E−21 CCDC85A coiled-coil domain containing 85A −14.61 −3.869 2.0E−10 PLCL1 phospholipase C-like 1 −14.56 −3.864 8.5E−11 KLF8 Kruppel-like factor 8 −14.54 −3.862 1.3E−15 FAM20A family with sequence similarity 20.sub.— −14.53 −3.861 1.4E−18 member A HOXA-AS3 HOXA

cluster antisense RNA 3 −14.51 −3.859 2.2E−10 LMO3 LIM domain only 3 (rhombotin-like 2) −14.44 −3.852 2.8E−07 LOC100133669 uncharacterized LOC100133669 −14.39 −3.847 7.4E−10 SLC22A3 solute carrier family 22 (organic cation −14.37 −3.845 4.1E−18 transporter)_ member 3 SSTR1 somatostatin receptor 1 −14.28 −3.835 1.7E−08 SBSN suprabasin −14.27 −3.835 1.1E−43 LY96 lymphocyte antigen 96 −14.24 −3.832 1.9E−48 FAM46C family with sequence similarity 46.sub.— −14.18 −3.826 1.1E−08 member C ATP8B4 ATPase_ class I_ type 8B_ member 4 −14.07 −3.814 5.2E−06 LINC00702 long intergenic non-protein coding −14.02 −3.810 3.3E−16 RNA 702 ANPEP alanyl (membrane) aminopeptidase −14.00 −3.807 1.8E−57 MIR31HG MIR31 host gene −13.99 −3.806 1.7E−100 ESPNL espin-like −13.85 −3.791 1.8E−09 FLJ12825 uncharacterized LOC440101 −13.84 −3.791 3.6E−11 KLF4 Kruppel-like factor 4 (gut) −13.73 −3.779 1.2E−61 KCNK15 potassium channel_ two pore domain −13.67 −3.773 3.9E−08 subfamily K_ member 15 IL1RN interleukin 1 receptor antagonist −13.65 −3.771 2.0E−07 CACNB4 calcium channel_ voltage-dependent.sub.— −13.65 −3.771 8.5E−07 beta 4 subunit PPAP2B phosphatidic acid phosphatase type 2B −13.65 −3.770 1.3E−64 NEFM neurofilament_ medium polypeptide −13.53 −3.758 1.3E−06 KLF17 Kruppel-like factor 17 −13.51 −3.756 1.1E−07 CNGA3 cyclic nucleotide gated channel alpha 3 −13.50 −3.755 9.6E−10 ROS1 ROS proto-oncogene 1 _ receptor −13.44 −3.749 4.4E−09 tyrosine kinase PTX3 pentraxin 3_ long −13.36 −3.740 4.2E−21 BRINP1 bone morphogenetic protein/retinoic −13.33 −3.736 1.0E−05 acid inducible neural-specific 1 RGL3 ral guanine nucleotide dissociation −13.23 −3.726 8.6E−06 stimulator-like 3 DEPTOR DEP domain containing MTOR- −13.21 −3.723 1.2E−48 interacting protein ADH1C alcohol dehydrogenase 1C (class I).sub.— −13.16 −3.718 1.1E−05 gamma polypeptide ADAMTS2 ADAM metallopeptidase with −13.14 −3.716 3.0E−156 thrombospondin type 1 motif_ 2 CASP10 caspase 10_ apoptosis-related cysteine −13.13 −3.715 2.2E−31 peptidase LINC00398 long intergenic non-protein coding −13.13 −3.714 9.1E−06 RNA 398 TFPI2 tissue factor pathway inhibitor 2 −13.09 −3.710 7.5E−08 PLXDC2 plexin domain containing 2 −13.07 −3.708 1.7E−08 SYT7 synaptotagmin VII −12.97 −3.697 1.5E−22 GPC6 glypican 6 −12.96 −3.696 4.6E−51 GGT5 gamma-glutamyltransferase 5 −12.94 −3.694 9.6E−10 INMT indolethylamine N-methyltransferase −12.89 −3.688 6.5E−06 PTGDS prostaglandin D2 synthase 21 kDa −12.86 −3.685 3.5E−09 (brain) CHRD chordin −12.79 −3.677 1.0E−38 PLA2G5 phospholipase A2_ group V −12.73 −3.670 7.8E−08 PTGER3 prostaglandin E receptor 3 (subtype −12.66 −3.662 3.5E−15 EP3) RGS22 regulator of G-protein signaling 22 −12.64 −3.660 1.4E−05 CARD6 caspase recruitment domain family.sub.— −12.59 −3.654 5.0E−75 member 6 ANKRD30B ankyrin repeat domain 30B −12.58 −3.653 4.9E−07 NPY4R neuropeptide Y receptor Y4 −12.46 −3.639 9.9E−07 P2RY2 purinergic receptor P2Y_ G-protein −12.42 −3.635 1.2E−06 coupled_ 2 HRCT1 histidine rich carboxyl terminus 1 −12.41 −3.634 1.9E−08 CCDC144A coiled-coil domain containing 144A −12.37 −3.629 1.8E−07 MEIS1 Meis homeobox 1 −12.33 −3.624 5.6E−85 DLEU7 deleted in lymphocytic leukemia_ 7 −12.30 −3.620 8.7E−07 ZNF385D zinc finger protein 385D −12.27 −3.617 3.7E−16 HOXB8 homeobox B8 −12.26 −3.616 9.9E−27 PCDHGA9 protocadherin gamma subfamily A_ 9 −12.25 −3.614 3.0E−23 DHRS3 dehydrogenase/reductase (SDR family) −12.17 −3.605 2.7E−43 member 3 C4BPB complement component 4 binding −12.16 −3.604 3.4E−05 protein_ beta ANKRD2 ankyrin repeat domain 2 (stretch −12.15 −3.603 2.0E−19 responsive muscle) PHYHIP phytanoyl-CoA 2-hydroxylase −12.15 −3.603 3.2E−10 interacting protein PPP2R2C protein phosphatase 2_ regulatory −12.11 −3.598 5.3E−07 subunit B_ gamma AKR1C2 aldo-keto reductase family 1_ member −12.09 −3.596 3.6E−174 C2 THNSL2 threonine synthase-like 2 (*S.* −12.08 −3.594 5.4E−27 *cerevisiae*) PID1 phosphotyrosine interaction domain −12.07 −3.593 1.8E−117 containing 1 PSORS1C1 psoriasis susceptibility 1 candidate 1 −12.03 −3.588 9.8E−07 CPXM2 carboxypeptidase X (M14 family).sub.— −11.97 −3.581 6.1E−11 member 2 TNFAIP6 tumor necrosis factor_ alpha-induced −11.96 −3.580 4.6E−09 protein 6 DMRT2 doublesex and mab-3 related −11.93 −3.577 1.1E−08 transcription factor 2 PCDHGB3 protocadherin gamma subfamily B_ 3 −11.87 −3.569 7.2E−18 TMTC2 transmembrane and tetratricopeptide −11.84

−3.566 2.1E−61 repeat containing 2 C2orf81 chromosome 2 open reading frame 81 −11.84 −3.565 7.5E−65 KANK4 KN motif and ankyrin repeat domains −11.81 −3.562 2.8E−05 4 SEL1L2 sel-1 suppressor of lin-12-like 2 (*C.* −11.80 −3.561 3.2E−05 *elegans*) HOXC13 homeobox C13 −11.80 −3.561 4.5E−05 NR4A2 nuclear receptor subfamily 4_ group −11.74 −3.554 1.2E−18 A_ member 2 FLRT2 fibronectin leucine rich transmembrane −11.74 −3.553 3.3E−14 protein 2 SCRG1 stimulator of chondrogenesis 1 −11.71 −3.550 1.5E−41 LTBP2 latent transforming growth factor beta −11.70 −3.549 9.9E−194 binding protein 2 SPON1 spondin 1_ extracellular matrix protein −11.65 −3.543 1.8E−84 SYNDIG1 synapse differentiation inducing 1 −11.63 −3.540 2.2E−09 MMRN2 multimerin 2 −11.57 −3.532 6.7E−17 EDNRB endothelin receptor type B −11.55 −3.530 4.5E−05 GRIA3 glutamate receptor_ ionotropic.sub.— −11.54 −3.528 2.1E−38 AMPA 3 SOD3 superoxide dismutase 3_ extracellular −11.53 −3.527 1.7E−09 SAMD3 sterile alpha motif domain containing 3 −11.37 −3.507 9.7E−08 SUSD3 sushi domain containing 3 −11.32 −3.500 3.7E−30 PCOLCE2 procollagen C-endopeptidase enhancer −11.28 −3.496 7.1E−65 2 C1QL3 complement component 1_ q −11.23 −3.489 6.5E−11 subcomponent-like 3 SUSD2 sushi domain containing 2 −11.21 −3.487 1.5E−06 C1S complement component 1_ s −11.20 −3.485 5.1E−125 subcomponent PRELP proline/arginine-rich end leucine-rich −11.17 −3.481 8.7E−25 repeat protein CDA cytidine deaminase −11.15 −3.479 2.5E−53 PTPRD protein tyrosine phosphatase_ receptor −11.09 −3.471 5.5E−07 type_ D ZDHHC15 zinc finger_ DHHC-type containing 15 −10.98 −3.456 6.4E−06 APOA1 apolipoprotein A-I −10.96 −3.454 1.2E−08 FHAD1 forkhead-associated (FHA) −10.96 −3.454 2.0E−08 phosphopeptide binding domain 1 HIST1H1E histone cluster 1_ H1e −10.93 −3.450 5.6E−05 LOC100507642 uncharacterized LOC100507642 −10.92 −3.449 3.1E−13 CFD complement factor D (adipsin) −10.91 −3.448 2.5E−23 LOC100507540 NA −10.91 −3.447 4.6E−20 RTN1 reticulon 1 −10.90 −3.447 4.4E−07 ADH1B alcohol dehydrogenase 1B (class I).sub.— −10.85 −3.440 7.8E−05 beta polypeptide CCL28 chemokine (C-C motif) ligand 28 −10.83 −3.437 1.6E−05 HOTAIR HOX transcript antisense RNA −10.79 −3.432 3.2E−06 LOC100505718 NA −10.76 −3.427 1.3E−08 RNF212 ring finger protein 212 −10.63 −3.411 2.9E−16 FIBCD1 fibrinogen C domain containing 1 −10.61 −3.407 1.3E−28 EFCAB1 EF-hand calcium binding domain 1 −10.60 −3.406 2.2E−08 LOC101059948 uncharacterized LOC101059948 −10.56 −3.400 9.5E−06 PCDH18 protocadherin 18 −10.53 −3.397 1.0E−39 CPNE8 copine VIII −10.51 −3.394 1.5E−80 TIMP1 TIMP metallopeptidase inhibitor 1 −10.49 −3.390 0.0E+00 TINAGL 1 tubulointerstitial nephritis antigen-like −10.39 −3.377 7.6E−06 1 C10orf11 chromosome 10 open reading frame 11 −10.27 −3.360 2.1E−06 PCDHGB5 protocadherin gamma subfamily B_ 5 −10.25 −3.358 3.2E−102 P2RX1 purinergic receptor P2X_ ligand gated −10.24 −3.356 2.2E−05 ion channel_ 1 RPLP0P2 ribosomal protein_ large_ P0 −10.22 −3.353 2.0E−07 pseudogene 2 HOXA11-AS HOXA11 antisense RNA −10.22 −3.353 1.2E−11 COL21A1 collagen_ type XXI_ alpha 1 −10.22 −3.353 5.8E−05 ESM1 endothelial cell-specific molecule 1 −10.20 −3.351 1.5E−06 FAM106A family with sequence similarity 106.sub.— −10.19 −3.350 1.1E−04 member A GHDC GH3 domain containing −10.17 −3.347 6.2E−96 LOC654342 lymphocyte-specific protein 1 −10.15 −3.344 6.6E−147 pseudogene GAS7 growth arrest-specific 7 −10.07 −3.332 2.5E−36 FAM124A family with sequence similarity 124A −10.06 −3.331 1.3E−05 ITGB2-AS1 ITGB2 antisense RNA 1 −10.06 −3.330 1.1E−06 ZNF280A zinc finger protein 280A −10.04 −3.328 1.4E−04 MEDAG mesenteric estrogen-dependent −10.04 −3.327 5.5E−17 adipogenesis DNAH2 dynein_ axonemal_ heavy chain 2 −9.99 −3.320 4.8E−05 WNT4 wingless-type MMTV integration site −9.96 −3.317 4.4E−05 family_ member 4 COL12A1 collagen_ type XII_ alpha 1 −9.89 −3.306 8.1E−35 DMKN dermokine −9.87 −3.303 6.9E−14 SLC1A7 solute carrier family 1 (glutamate −9.83 −3.297 3.5E−06 transporter)_ member 7 COL8A2 collagen_ type VIII_ alpha 2 −9.80 −3.292 6.4E−09 MYOM3 myomesin 3 −9.77 −3.288 9.5E−28 EPDR1 ependymin related 1 −9.76 −3.287 2.2E−30 TMEM155 transmembrane protein 155 −9.71 −3.279 1.1E−08 PODNL1 podocan-like 1 −9.71 −3.279 5.8E−47 PITX1 paired-like homeodomain 1 −9.68 −3.275 2.3E−25 IL20RA interleukin 20 receptor_ alpha −9.68 −3.274

5.1E−05 GPR4 G protein-coupled receptor 4 −9.67 −3.274 5.5E−05 GPX3 glutathione peroxidase 3 −9.67 −3.273 5.3E−09 C5orf27 long intergenic non-protein coding −9.67 −3.273 2.3E−05 RNA 1554 CYP1B1 cytochrome P450_ family 1.sub.— −9.64 −3.269 3.2E−14 subfamily B_ polypeptide 1 TEK TEK tyrosine kinase_ endothelial −9.63 −3.267 1.4E−61 KRT13 keratin 13_ type I −9.60 −3.263 5.5E−06 NEFL neurofilament_ light polypeptide −9.58 −3.260 4.5E−07 BDKRB1 bradykinin receptor B1 −9.55 −3.256 7.0E−39 LINC01140 long intergenic non-protein coding −9.53 −3.253 4.2E−17 RNA 1140 SEMA7A semaphorin 7A_ GPI membrane −9.53 −3.252 2.6E−85 anchor (John Milton Hagen blood group) PCDHGA7 protocadherin gamma subfamily A_ 7 −9.47 −3.244 3.5E−20 ZNF503-AS2 ZNF503 antisense RNA 2 −9.44 −3.239 5.5E−25 MMP12 matrix metallopeptidase 12 −9.43 −3.238 2.5E−05 ANKRD37 ankyrin repeat domain 37 −9.43 −3.238 3.0E−38 KRT81 keratin 81_ type II −9.40 −3.233 4.2E−26 AADAC arylacetamide deacetylase −9.40 −3.232 6.1E−05 PARP15 poly (ADP-ribose) polymerase family.sub.— −9.33 −3.223 9.8E−08 member 15 FAM90A1 family with sequence similarity 90.sub.— −9.33 −3.222 2.4E−04 member A1 OXCT2 3-oxoacid CoA transferase 2 −9.33 −3.222 4.6E−06 SLC22A15 solute carrier family 22_ member 15 −9.29 −3.215 1.2E−47 SAA1 serum amyloid A1 −9.26 −3.212 2.6E−04 ANKRD65 ankyrin repeat domain 65 −9.25 −3.210 6.6E−07 UBE2QL1 ubiquitin-conjugating enzyme E2Q −9.24 −3.208 5.9E−05 family-like 1 LHB luteinizing hormone beta polypeptide −9.22 −3.205 5.5E−06 SLC9A9 solute carrier family 9_ subfamily A −9.19 −3.200 3.1E−26 (NHE9_ cation proton antiporter 9).sub.— member 9 PRDM8 PR domain containing 8 −9.18 −3.198 5.7E−119 MAGOH2 mago homolog 2_ pseudogene −9.17 −3.197 3.2E−04 ICAM2 intercellular adhesion molecule 2 −9.16 −3.195 1.2E−07 NECAB2 N-terminal EF-hand calcium binding −9.13 −3.191 1.1E−06 protein 2 MDGA1 MAM domain containing −9.13 −3.191 9.3E−99 glycosylphosphatidylinositol anchor 1 BCL6B B-cell CLL/lymphoma 6_ member B −9.09 −3.185 1.6E−05 HSD11B1 hydroxysteroid (11-beta) −9.09 −3.184 1.2E−05 dehydrogenase 1 DIRAS3 DIRAS family_ GTP-binding RAS- −9.05 −3.177 7.7E−06 like 3 MOB3B MOB kinase activator 3B −9.03 −3.175 6.7E−19 ITM2A integral membrane protein 2A −9.02 −3.173 3.8E−04 CRYAB crystallin_ alpha B −9.01 −3.171 1.1E−11 HLA-F-AS1 HLA-F antisense RNA 1 −9.00 −3.170 2.2E−17 LINC00578 long intergenic non-protein coding −8.99 −3.168 3.2E−04 RNA 578 DUSP2 dual specificity phosphatase 2 −8.95 −3.163 6.4E−84 FAM228A family with sequence similarity 228.sub.— −8.94 −3.161 1.2E−04 member A PLSCR4 phospholipid scramblase 4 −8.94 −3.160 1.0E−65 CD97 adhesion G protein-coupled receptor −8.87 −3.148 3.3E−70 E5 KCNE1 potassium channel_ voltage gated −8.84 −3.144 1.2E−07 subfamily E regulatory beta subunit 1 PCSK1 proprotein convertase subtilisin/kexin −8.79 −3.135 3.2E−06 type 1 ZNF558 zinc finger protein 558 −8.78 −3.134 1.3E−52 CXCL6 chemokine (C-X-C motif) ligand 6 −8.77 −3.132 3.5E−05 KCNS3 potassium voltage-gated channel.sub.— −8.73 −3.125 7.4E−13 modifier subfamily S_ member 3 CD14 CD14 molecule −8.67 −3.116 4.4E−07 FLJ38576 uncharacterized LOC651430 −8.66 −3.114 6.1E−05 VTN vitronectin −8.65 −3.113 4.3E−04 EBF2 early B-cell factor 2 −8.64 −3.111 7.4E−20 MIR503 microRNA 503 −8.61 −3.107 1.4E−11 CHRDL2 chordin-like 2 −8.57 −3.099 5.2E−04 ACADL acyl-CoA dehydrogenase_ long chain −8.56 −3.098 5.3E−04 HCRTR1 hypocretin (orexin) receptor 1 −8.54 −3.095 3.8E−05 KCNC4-AS1 KCNC4 antisense RNA 1 (head to −8.51 −3.088 7.1E−05 head) PVRL4 poliovirus receptor-related 4 −8.49 −3.085 1.0E−07 FRY furry homolog (*Drosophila*) −8.47 −3.082 7.6E−11 ITIH5 inter-alpha-trypsin inhibitor heavy −8.45 −3.080 6.6E−04 chain family_ member 5 GSTO2 glutathione S-transferase omega 2 −8.42 −3.075 3.8E−22 LOC101927524 NA −8.42 −3.074 6.3E−04 PODXL podocalyxin-like −8.37 −3.065 2.3E−09 STXBP5L syntaxin binding protein 5-like −8.36 −3.063 1.1E−04 NR4A1 nuclear receptor subfamily 4_ group −8.36 −3.063 2.6E−72 A_ member 1 CD55 CD55 molecule_ decay accelerating −8.32 −3.057 2.0E−67 factor for complement (Cromer blood group) FMO3 flavin containing monooxygenase 3 −8.28 −3.049 2.1E−04 ZG16B zymogen granule protein 16B −8.26 −3.047 5.1E−05 CHN2 chimerin 2 −8.24 −3.043 7.0E−12 FPR2 formyl peptide receptor 2 −8.18 −3.033 2.0E−04 COL5A3 collagen_ type V_ alpha 3 −8.18 −3.032 3.6E−13 TNFRSF14 tumor

necrosis factor receptor −8.18 −3.031 5.1E−10 superfamily_ member 14 PAQR9 progestin and adipoQ receptor family −8.17 −3.031 2.5E−05 member IX LOC101927229 uncharacterized LOC101927229 −8.17 −3.030 5.0E−04 MME membrane metallo-endopeptidase −8.12 −3.022 1.3E−12 FZD1 frizzled class receptor 1 −8.11 −3.020 6.2E−29 COL6A6 collagen_ type VI_ alpha 6 −8.11 −3.020 2.1E−04 PRG2 proteoglycan 2_ bone marrow (natural −8.11 −3.020 5.6E−04 killer cell activator_ eosinophil granule major basic protein) PLD5 phospholipase D family_ member 5 −8.09 −3.016 9.1E−04 CCDC64B coiled-coil domain containing 64B −8.06 −3.011 7.9E−04 MIR503HG MIR503 host gene −8.05 −3.010 9.4E−18 SULF1 sulfatase 1 −8.05 −3.009 1.7E−31 SDHAP3 succinate dehydrogenase complex.sub.— −8.05 −3.009 9.2E−13 subunit A_ flavoprotein pseudogene 3 DACT1 dishevelled-binding antagonist of beta- −8.05 −3.009 3.6E−50 catenin 1 C3 complement component 3 −8.02 −3.004 3.9E−15 ABI3BP ABI family_ member 3 (NESH) −8.00 −3.001 4.3E−87 binding protein ANKH ANKH inorganic pyrophosphate −7.97 −2.994 6.5E−31 transport regulator RADIL Ras association and DIL domains −7.96 −2.992 1.5E−25 ZNF454 zinc finger protein 454 −7.93 −2.987 2.7E−06 KRTAP1-5 keratin associated protein 1-5 −7.93 −2.986 4.6E−05 SUPT20HL1 suppressor of Ty 20 homolog (*S.* −7.92 −2.986 4.5E−04 *cerevisiae*)-like 1 DPT dermatopontin −7.88 −2.979 1.1E−03 CHST15 carbohydrate (N-acetylgalactosamine −7.88 −2.978 1.1E−22 4-sulfate 6-O) sulfotransferase 15 OLFML1 olfactomedin-like 1 −7.86 −2.974 5.2E−07 MT1M metallothionein 1M −7.85 −2.973 1.3E−28 AKR1C1 aldo-keto reductase family 1_ member −7.84 −2.971 2.0E−88 C1 TLE2 transducin-like enhancer of split 2 −7.84 −2.970 5.6E−41 PIGZ phosphatidylinositol glycan anchor −7.83 −2.969 5.9E−32 biosynthesis_ class Z KRT16 keratin 16_ type I −7.82 −2.967 2.2E−09 CAPN3 calpain 3 −7.78 −2.960 3.0E−18 LOC100506385 NA −7.78 −2.960 4.5E−14 TBX18 T-box 18 −7.74 −2.952 3.1E−119 SOCS2-AS1 SOCS2 antisense RNA 1 −7.73 −2.950 7.4E−13 DLX4 distal-less homeobox 4 −7.71 −2.947 1.1E−03 PF4V1 platelet factor 4 variant 1 −7.71 −2.947 1.1E−03 LOC729041 NA −7.70 −2.944 4.7E−04 XYLT1 xylosyltransferase I −7.69 −2.944 7.1E−65 C1R complement component 1_ r −7.69 −2.942 2.3E−23 subcomponent XAF1 XIAP associated factor 1 −7.68 −2.940 1.7E−30 RBPMS2 RNA binding protein with multiple −7.67 −2.939 2.0E−22 splicing 2 SLC22A23 solute carrier family 22_ member 23 −7.67 −2.938 1.0E−29 RAB3IL1 RAB3A interacting protein (rabin3)- −7.66 −2.937 4.6E−55 like 1 MPV17L MPV17 mitochondrial membrane −7.64 −2.933 7.0E−07 protein-like CSF3 colony stimulating factor 3 −7.64 −2.933 1.2E−03 (granulocyte) TRPM2 transient receptor potential cation −7.62 −2.931 3.4E−05 channel_ subfamily M_ member 2 KRT33B keratin 33B_ type I −7.61 −2.929 1.3E−14 EID3 EP300 interacting inhibitor of −7.60 −2.927 2.7E−30 differentiation 3 CES1 carboxylesterase 1 −7.59 −2.925 9.9E−04 ACSL5 acyl-CoA synthetase long-chain family −7.59 −2.924 3.7E−14 member 5 CTSK cathepsin K −7.58 −2.922 1.6E−18 LINC00654 long intergenic non-protein coding −7.54 −2.914 2.0E−26 RNA 654 F8 coagulation factor VIII_ procoagulant −7.53 −2.913 2.6E−23 component MAGEB17 melanoma antigen family B17 −7.52 −2.911 1.5E−03 SLIT3 slit guidance ligand 3 −7.52 −2.911 4.7E−230 ZXDA zinc finger_ X-linked duplicated A −7.52 −2.911 1.3E−44 HAR1A highly accelerated region 1A (non- −7.49 −2.905 2.9E−04 protein coding) IFI27 interferon_ alpha-inducible protein 27 −7.47 −2.902 4.2E−34 SPOCK1 sparc/osteonectin_ cwcv and kazal-like −7.47 −2.901 3.8E−50 domains proteoglycan (testican) 1 FLJ43879 FLJ43879 protein −7.46 −2.900 1.4E−03 GPR150 G protein-coupled receptor 150 −7.46 −2.898 1.1E−13 DDO D-aspartate oxidase −7.45 −2.898 1.6E−03 JOSD2 Josephin domain containing 2 −7.44 −2.895 1.4E−100 ANKRD35 ankyrin repeat domain 35 −7.43 −2.893 2.1E−41 LINC00482 long intergenic non-protein coding −7.41 −2.889 1.5E−03 RNA 482 TDRD1 tudor domain containing 1 −7.38 −2.883 6.7E−04 VCAN versican −7.37 −2.882 3.8E−166 OGN osteoglycin −7.37 −2.882 8.3E−04 S100A4 S100 calcium binding protein A4 −7.35 −2.878 5.2E−09 SHANK2 SH3 and multiple ankyrin repeat −7.35 −2.877 1.8E−35 domains 2 POU5F1 POU class 5 homeobox 1 −7.35 −2.877 3.4E−13 CALB2 calbindin 2 −7.34 −2.876 3.3E−04 ECM2 extracellular matrix protein 2_ female −7.34 −2.875 3.9E−08 organ and adipocyte specific WNT9A wingless-type MMTV integration site −7.32 −2.872 9.3E−05

family_ member 9A LCE2A late cornified envelope 2A −7.32 −2.872 1.8E−03 IGFBP3 insulin-like growth factor binding −7.32 −2.871 8.2E−48 protein 3 ANK2 ankyrin 2_ neuronal −7.28 −2.864 9.4E−61 ELOVL3 ELOVL fatty acid elongase 3 −7.28 −2.863 5.0E−07 MAB21L1 mab-21-like 1 (*C. elegans*) −7.27 −2.863 9.4E−28 ADCY4 adenylate cyclase 4 −7.27 −2.862 2.0E−07 RORA RAR-related orphan receptor A −7.27 −2.861 1.2E−17 MFAP4 microfibrillar-associated protein 4 −7.25 −2.857 1.3E−27 ZDHHC23 zinc finger_ DHHC-type containing 23 −7.22 −2.852 9.9E−25 SLC2A9 solute carrier family 2 (facilitated −7.20 −2.848 5.5E−11 glucose transporter)_ member 9 SLC14A1 solute carrier family 14 (urea −7.19 −2.847 1.8E−03 transporter)_ member 1 (Kidd blood group) LRRC6 leucine rich repeat containing 6 −7.17 −2.842 1.2E−08 C15orf59 chromosome 15 open reading frame 59 −7.16 −2.839 2.0E−08 PRRX2 paired related homeobox 2 −7.15 −2.838 6.5E−295 C11orf91 chromosome 11 open reading frame 91 −7.15 −2.838 2.6E−16 LRRN4CL LRRN4 C-terminal like −7.12 −2.832 7.3E−09 FLRT1 fibronectin leucine rich transmembrane −7.12 −2.832 4.3E−13 protein 1 PSG3 pregnancy specific beta-1-glycoprotein −7.11 −2.830 1.9E−03 3 CR1L complement component (3b/4b) −7.11 −2.829 8.4E−04 receptor 1-like ABCA6 ATP-binding cassette_ sub-family A −7.06 −2.820 1.5E−04 (ABC1)_ member 6 ADRA2B adrenoceptor alpha 2B −7.06 −2.819 2.0E−03 TPTE2P6 transmembrane phosphoinositide 3- −7.05 −2.817 2.1E−03 phosphatase and tensin homolog 2 pseudogene 6 MYH15 myosin_ heavy chain 15 −7.04 −2.815 9.5E−13 ZFP3 ZFP3 zinc finger protein −7.03 −2.813 2.4E−44 THEM6 thioesterase superfamily member 6 −7.02 −2.811 1.5E−13 MOXD1 monooxygenase_ DBH-like 1 −7.01 −2.809 5.1E−14 FBLN7 fibulin 7 −7.00 −2.808 9.6E−18 LOC728819 NA −7.00 −2.808 8.2E−05 EPHA1-AS1 EPHA1 antisense RNA 1 −6.99 −2.806 2.2E−03 PRL prolactin −6.99 −2.805 2.3E−03 PSG4 pregnancy specific beta-1-glycoprotein −6.96 −2.799 1.3E−03 4 LOC646762 uncharacterized LOC646762 −6.96 −2.798 4.4E−40 MIR497HG mir-497-195 cluster host gene −6.95 −2.796 9.7E−10 PTER phosphotriesterase related −6.94 −2.795 3.8E−37 ADAM12 ADAM metallopeptidase domain 12 −6.94 −2.794 2.2E−231 ADH6 alcohol dehydrogenase 6 (class V) −6.93 −2.794 1.3E−04 FAM66D family with sequence similarity 66.sub.— −6.91 −2.790 1.3E−07 member D GUCY1A2 guanylate cyclase 1_ soluble_ alpha 2 −6.90 −2.787 8.6E−04 MAPK13 mitogen-activated protein kinase 13 −6.87 −2.781 3.9E−55 PLCL2 phospholipase C-like 2 −6.87 −2.780 1.7E−41 POU3F2 POU class 3 homeobox 2 −6.86 −2.778 9.8E−04 DDX43 DEAD (Asp-Glu-Ala-Asp) box −6.84 −2.774 2.6E−05 polypeptide 43 HIST2H2BA histone cluster 2_ H2ba (pseudogene) −6.84 −2.774 1.8E−12 IVL involucrin −6.83 −2.772 2.7E−03 DOK7 docking protein 7 −6.82 −2.770 1.7E−04 MUC13 mucin 13_ cell surface associated −6.81 −2.767 2.8E−03 FAM198B family with sequence similarity 198.sub.— −6.79 −2.763 2.1E−31 member B TRAPPC3L trafficking protein particle complex 3- −6.78 −2.761 2.7E−03 like PIWIL2 piwi-like RNA-mediated gene −6.77 −2.760 1.3E−03 silencing 2 RNF112 ring finger protein 112 −6.76 −2.757 5.0E−11 LINC01060 long intergenic non-protein coding −6.75 −2.756 2.7E−12 RNA 1060 PCDHGB8P protocadherin gamma subfamily B_ 8 −6.75 −2.754 5.8E−04 pseudogene SOST sclerostin −6.74 −2.753 1.8E−03 FAM167B family with sequence similarity 167.sub.— −6.72 −2.749 2.2E−17 member B IL21R interleukin 21 receptor −6.72 −2.748 4.0E−64 DDIT4L DNA-damage-inducible transcript 4- −6.71 −2.746 2.3E−05 like C19orf81 chromosome 19 open reading frame 81 −6.71 −2.745 2.8E−03 AGTR1 angiotensin II receptor_ type 1 −6.70 −2.745 1.8E−09 SCUBE3 signal peptide_ CUB domain_ EGF- −6.69 −2.742 9.5E−81 like 3 PDE2A phosphodiesterase 2A_ cGMP- −6.69 −2.742 3.8E−04 stimulated MMP8 matrix metallopeptidase 8 −6.67 −2.739 5.0E−04 SHOX2 short stature homeobox 2 −6.66 −2.737 6.0E−41 DPY19L2P3 DPY19L2 pseudogene 3 −6.64 −2.731 3.0E−03 NPAS1 neuronal PAS domain protein 1 −6.63 −2.730 4.2E−17 FAM87A family with sequence similarity 87.sub.— −6.63 −2.729 3.3E−03 member A CEMIP cell migration inducing protein.sub.— −6.61 −2.725 3.4E−07 hyaluronan binding C1QTNF3 C1q and tumor necrosis factor related −6.58 −2.718 1.0E−05 protein 3 ADAMTSL1 ADAMTS-like 1 −6.58 −2.718 5.1E−33 TSPEAR-AS1 TSPEAR antisense RNA 1 −6.55 −2.713 1.1E−03 ASCL2 achaete-scute family bHLH −6.52 −2.705 5.9E−04

transcription factor 2 MYH3 myosin_ heavy chain 3_ skeletal −6.51 −2.703 3.2E−13 muscle_ embryonic RPSAP52 ribosomal protein SA pseudogene 52 −6.50 −2.701 4.2E−06 KCNJ2-AS1 KCNJ2 antisense RNA 1 (head to −6.49 −2.697 3.6E−03 head) LINC00961 long intergenic non-protein coding −6.47 −2.695 2.7E−08 RNA 961 LINC01123 long intergenic non-protein coding −6.45 −2.689 1.1E−06 RNA 1123 TBX15 T-box 15 −6.44 −2.688 4.9E−09 MCOLN3 mucolipin 3 −6.43 −2.686 3.8E−03 ROR2 receptor tyrosine kinase-like orphan −6.43 −2.684 2.4E−04 receptor 2 DPP4 dipeptidyl-peptidase 4 −6.40 −2.678 2.3E−07 GPC4 glypican 4 −6.39 −2.677 4.1E−08 RBP4 retinol binding protein 4_ plasma −6.39 −2.675 1.6E−06 CDH1 cadherin 1_ type 1 −6.37 −2.671 3.0E−05 COL14A1 collagen_ type XIV_ alpha 1 −6.37 −2.671 6.3E−05 SNCG synuclein_ gamma (breast cancer- −6.36 −2.669 2.5E−08 specific protein 1) TSPAN2 tetraspanin 2 −6.35 −2.667 4.0E−13 PSG7 pregnancy specific beta-1-glycoprotein −6.35 −2.667 3.9E−03 7 (gene/pseudogene) LINC00161 long intergenic non-protein coding −6.34 −2.664 4.4E−03 RNA 161 ANXA8L1 annexin A8-like 1 −6.33 −2.662 5.9E−07 FAM129A family with sequence similarity 129.sub.— −6.31 −2.658 3.5E−51 member A GPR1 G protein-coupled receptor 1 −6.30 −2.656 5.4E−55 TEX36 testis expressed 36 −6.28 −2.650 4.5E−03 CCL20 chemokine (C-C motif) ligand 20 −6.28 −2.650 1.6E−03 LOC101929234 uncharacterized LOC101929234 −6.27 −2.648 2.3E−03 ANXA8 annexin A8 −6.25 −2.644 7.9E−08 ANO1 anoctamin 1_ calcium activated −6.24 −2.641 3.2E−05 chloride channel MFSD6 major facilitator superfamily domain −6.22 −2.638 1.6E−28 containing 6 LOC101929369 NA −6.22 −2.637 7.4E−08 ARHGEF35 Rho guanine nucleotide exchange −6.21 −2.635 3.3E−19 factor (GEF) 35 GPAM glycerol-3-phosphate acyltransferase.sub.— −6.21 −2.634 6.0E−09 mitochondrial PRSS35 protease_ serine_ 35 −6.20 −2.632 7.7E−07 IFI44 interferon-induced protein 44 −6.19 −2.630 1.1E−22 TACR1 tachykinin receptor 1 −6.18 −2.627 4.8E−03 COL16A1 collagen_ type XVI_ alpha 1 −6.17 −2.624 1.7E−108 FAIM2 Fas apoptotic inhibitory molecule 2 −6.16 −2.623 2.6E−07 TULP2 tubby like protein 2 −6.15 −2.621 1.6E−03 HERC3 HECT and RLD domain containing E3 −6.14 −2.618 1.5E−34 ubiquitin protein ligase 3 SLC47A1 solute carrier family 47 (multidrug and −6.12 −2.614 4.4E−05 toxin extrusion)_ member 1 SLC30A3 solute carrier family 30 (zinc −6.11 −2.612 1.7E−03 transporter)_ member 3 LOX lysyl oxidase −6.10 −2.609 1.2E−104 ACE angiotensin I converting enzyme −6.10 −2.608 1.7E−15 PPP4R4 protein phosphatase 4_ regulatory −6.09 −2.605 1.1E−03 subunit 4 RDH5 retinol dehydrogenase 5 (11-cis/9-cis) −6.08 −2.604 1.3E−05 CTD- BEAN1 antisense RNA 1 −6.08 −2.604 5.1E−03 2258A20.5 OTOF otoferlin −6.08 −2.604 1.1E−03 ZFP42 ZFP42 zinc finger protein −6.08 −2.603 1.8E−04 PCSK6 proprotein convertase subtilisin/kexin −6.07 −2.601 3.4E−08 type 6 FAM13A-AS1 FAM13A antisense RNA 1 −6.06 −2.600 7.2E−06 HS3ST3A1 heparan sulfate (glucosamine) 3-O- −6.06 −2.599 3.0E−17 sulfotransferase 3A1 PRKG2 protein kinase_ cGMP-dependent.sub.— −6.06 −2.598 3.3E−03 type II KCNT2 potassium channel_ sodium activated −6.05 −2.597 1.4E−07 subfamily T_ member 2 PAMR1 peptidase domain containing −6.05 −2.596 2.5E−09 associated with muscle regeneration 1 MEG3 maternally expressed 3 (non-protein −6.03 −2.593 1.5E−24 coding) NFIX nuclear factor I/X (CCAAT-binding −6.03 −2.591 1.6E−91 transcription factor) EPHA3 EPH receptor A3 −6.02 −2.590 5.2E−04 MAP3K8 mitogen-activated protein kinase −6.02 −2.590 6.3E−21 kinase kinase 8 LINC01204 long intergenic non-protein coding −6.00 −2.585 9.8E−22 RNA 1204 PTGIR prostaglandin I2 (prostacyclin) −6.00 −2.584 1.7E−93 receptor (IP) LOR loricrin −5.99 −2.582 5.9E−03 NTNG1 netrin G1 −5.98 −2.580 1.1E−05 LMO7DN LMO7 downstream neighbor −5.98 −2.579 2.1E−03 UNC13A unc-13 homolog A (*C. elegans*) −5.97 −2.579 1.6E−08 FREM1 FRAS1 related extracellular matrix 1 −5.97 −2.578 3.2E−03 CYP26B1 cytochrome P450_ family 26.sub.— −5.97 −2.577 9.4E−05 subfamily B_ polypeptide 1 LRRC38 leucine rich repeat containing 38 −5.96 −2.576 6.1E−03 PDPN podoplanin −5.95 −2.574 1.3E−03 RECK reversion-inducing-cysteine-rich −5.94 −2.571 1.1E−165 protein with kazal motifs UNC5B unc-5 netrin receptor B −5.94 −2.570 1.4E−06 GOLGA8K golgin A8 family_ member K −5.93 −2.569 6.0E−03 ADAMTS1 ADAM metallopeptidase with −5.93 −2.568 2.0E−06 thrombospondin type 1 motif_ 1 C3orf55 PQ loop

repeat containing 2-like −5.92 −2.566 5.6E−27 NR1D1 nuclear receptor subfamily 1_ group −5.91 −2.564 1.5E−82 D_ member 1 HERC2P4 hect domain and RLD 2 pseudogene 4 −5.91 −2.563 2.2E−10 ADD2 adducin 2 (beta) −5.90 −2.561 6.5E−03 SLC1A3 solute carrier family 1 (glial high −5.89 −2.559 5.4E−12 affinity glutamate transporter).sub.— member 3 KLHL33 kelch-like family member 33 −5.89 −2.558 1.2E−04 ANGPTL4 angiopoietin-like 4 −5.89 −2.558 7.5E−09 MILR1 mast cell immunoglobulin-like −5.89 −2.557 8.7E−04 receptor 1 SLC17A9 solute carrier family 17 (vesicular −5.88 −2.556 4.0E−34 nucleotide transporter)_ member 9 HSPB6 heat shock protein_ alpha-crystallin- −5.88 −2.556 1.1E−209 related_ B6 MIR3613 microRNA 3613 −5.87 −2.554 6.3E−03 TSIX TSIX transcript_ XIST antisense RNA −5.86 −2.552 6.5E−03 P2RX5 purinergic receptor P2X_ ligand gated −5.81 −2.540 9.3E−06 ion channel_ 5 CRIP1 cysteine-rich protein 1 (intestinal) −5.81 −2.540 7.2E−122 CALHM3 calcium homeostasis modulator 3 −5.81 −2.537 6.7E−03 TIMP4 TIMP metallopeptidase inhibitor 4 −5.79 −2.533 4.2E−17 C11orf70 chromosome 11 open reading frame 70 −5.77 −2.528 7.6E−23 PDGFRA platelet-derived growth factor −5.77 −2.527 3.2E−11 receptor_ alpha polypeptide TBX4 T-box 4 −5.76 −2.527 1.3E−03 SORCS3 sortilin-related VPS10 domain −5.75 −2.524 7.3E−03 containing receptor 3 SPATA41 spermatogenesis associated 41 (non- −5.72 −2.516 3.4E−03 protein coding) LOC101927905 uncharacterized LOC101927905 −5.72 −2.516 5.5E−07 ANKRD20A5P ankyrin repeat domain 20 family.sub.— −5.70 −2.512 2.7E−03 member A5_ pseudogene IL1R1 interleukin 1 receptor_ type I −5.70 −2.511 1.1E−64 LURAP1L leucine rich adaptor protein 1-like −5.70 −2.511 4.5E−16 GDNF-AS1 GDNF antisense RNA 1 (head to head) −5.69 −2.509 2.5E−18 LOC100505739 NA −5.69 −2.509 7.6E−03 MRO maestro −5.68 −2.506 7.6E−03 RAP1GAP RAP1 GTPase activating protein −5.68 −2.505 2.6E−05 PDE4C phosphodiesterase 4C_ cAMP-specific −5.68 −2.505 7.3E−05 HSD3B7 hydroxy-delta-5-steroid −5.67 −2.504 3.0E−57 dehydrogenase_ 3 beta- and steroid delta-isomerase 7 PRLR prolactin receptor −5.66 −2.501 3.2E−03 ADAMTSL2 ADAMTS-like 2 −5.66 −2.500 2.3E−03 SLC38A5 solute carrier family 38_ member 5 −5.66 −2.500 3.7E−60 C4BPA complement component 4 binding −5.65 −2.499 7.9E−03 protein_ alpha SLC38A4 solute carrier family 38_ member 4 −5.65 −2.498 2.4E−27 MESP2 mesoderm posterior bHLH −5.64 −2.496 6.0E−05 transcription factor 2 LINC01268 long intergenic non-protein coding −5.63 −2.494 4.5E−03 RNA 1268 NPR1 natriuretic peptide receptor 1 −5.63 −2.494 2.7E−03 COL3A1 collagen_ type III_ alpha 1 −5.63 −2.493 4.8E−26 FAM107A family with sequence similarity 107.sub.— −5.62 −2.490 2.5E−03 member A FAM149A family with sequence similarity 149.sub. — −5.61 −2.489 1.6E−26 member A HCG4B HLA complex group 4B (non-protein −5.61 −2.488 4.9E−04 coding) CHN1 chimerin 1 −5.61 −2.488 7.7E−47 TMTC1 transmembrane and tetratricopeptide −5.60 −2.486 1.6E−10 repeat containing 1 NEAT1 nuclear paraspeckle assembly −5.59 −2.484 8.4E−11 transcript 1 (non-protein coding) IGFL3 IGF-like family member 3 −5.59 −2.482 8.7E−03 MFAP3L microfibrillar-associated protein 3-like −5.58 −2.480 1.9E−93 PTGS2 prostaglandin-endoperoxide synthase 2 −5.58 −2.479 2.1E−05 (prostaglandin G/H synthase and cyclooxygenase) LINC00312 long intergenic non-protein coding −5.56 −2.476 1.5E−04 RNA 312 PLA2G2A phospholipase A2_ group IIA −5.55 −2.473 9.1E−03 (platelets_ synovial fluid) RGMA repulsive guidance molecule family −5.54 −2.470 1.0E−05 member a CCDC158 coiled-coil domain containing 158 −5.53 −2.468 4.2E−03 EMP1 epithelial membrane protein 1 −5.53 −2.468 1.3E−33 MT1G metallothionein 1G −5.53 −2.467 4.5E−10 ITGB8 integrin_ beta 8 −5.53 −2.467 4.5E−10 ZNF311 zinc finger protein 311 −5.53 −2.466 2.1E−09 HSD3B1 hydroxy-delta-5-steroid −5.50 −2.458 9.6E−03 dehydrogenase_ 3 beta- and steroid delta-isomerase 1 F10 coagulation factor X −5.48 −2.454 1.1E−08 LINC00478 mir-99a-let-7c cluster host gene −5.47 −2.453 5.2E−04 DOK6 docking protein 6 −5.46 −2.450 2.5E−08 MIR193A microRNA 193a −5.46 −2.448 6.1E−04 RASL11B RAS-like_ family 11_ member B −5.45 −2.446 7.0E−05 AKR1C3 aldo-keto reductase family 1_ member −5.44 −2.445 5.2E−11 C3 FAS Fas cell surface death receptor −5.44 −2.444 1.8E−61 KY kyphoscoliosis peptidase −5.44 −2.443 3.2E−15 AGAP11 ankyrin repeat and GTPase domain Arf −5.43 −2.442 9.8E−06 GTPase activating protein 11 PRRG4 proline rich Gla

(G-carboxyglutamic −5.43 −2.441 2.1E−04 acid) 4 (transmembrane) MUC12 mucin 12_ cell surface associated −5.43 −2.441 6.6E−03 CYP21A2 cytochrome P450_ family 21.sub.— −5.42 −2.439 1.0E−02 subfamily A_ polypeptide 2 IL6 interleukin 6 −5.41 −2.436 1.2E−05 ANKRD29 ankyrin repeat domain 29 −5.40 −2.433 1.7E−05 NFIA nuclear factor I/A −5.39 −2.431 8.0E−25 TENM2 teneurin transmembrane protein 2 −5.39 −2.430 1.3E−03 LOC101928200 NA −5.38 −2.427 3.0E−05 CAMK2B calcium/calmodulin-dependent protein −5.37 −2.426 8.0E−03 kinase II beta CDC20B cell division cycle 20B −5.35 −2.420 1.1E−02 FPR3 formyl peptide receptor 3 −5.35 −2.419 1.1E−02 MIR10A microRNA 10a −5.33 −2.415 1.1E−02 TTC3P1 tetratricopeptide repeat domain 3 −5.33 −2.414 4.5E−08 pseudogene 1 LY86 lymphocyte antigen 86 −5.33 −2.414 1.1E−02 HRNR hornerin −5.32 −2.412 1.1E−02 SERPING1 serpin peptidase inhibitor_ clade G (C1 −5.31 −2.409 1.4E−15 inhibitor)_ member 1 NRG1 neuregulin 1 −5.31 −2.409 7.4E−09 ALDH1A3 aldehyde dehydrogenase 1 family.sub.— −5.31 −2.408 3.9E−05 member A3 IL20RB interleukin 20 receptor beta −5.30 −2.407 1.7E−11 MMP10 matrix metallopeptidase 10 −5.30 −2.406 5.2E−05 ZNF704 zinc finger protein 704 −5.29 −2.403 1.2E−04 OR2S2 olfactory receptor_ family 2.sub.— −5.29 −2.403 2.4E−03 subfamily S_ member 2 (gene/pseudogene) RSPO3 R-spondin 3 −5.27 −2.398 7.5E−04 BEND7 BEN domain containing 7 −5.27 −2.397 9.5E−22 C21orf90 TSPEAR antisense RNA 2 −5.26 −2.396 1.2E−02 SBSPON somatomedin B and thrombospondin.sub.— −5.26 −2.395 9.7E−04 type 1 domain containing EEF1DP3 eukaryotic translation elongation factor −5.26 −2.395 3.2E−04 1 delta pseudogene 3 LY6K lymphocyte antigen 6 complex_ locus −5.25 −2.392 5.2E−03 K ENPP4 ectonucleotide −5.25 −2.392 5.9E−10 pyrophosphatase/phosphodiesterase 4.sub.— (putative) EVPL envoplakin −5.24 −2.390 9.7E−03 SFN stratifin −5.23 −2.386 8.8E−03 CYP4V2 cytochrome P450_ family 4 −5.22 −2.385 4.0E−15 subfamily V_ polypeptide 2 GJB5 gap junction protein beta 5 31.1 kDa −5.22 −2.384 1.2E−02 SERPINB2 serpin peptidase inhibitor_ clade B −5.21 −2.382 5.0E−05 (ovalbumin)_ member 2 C2 complement component 2 −5.21 −2.382 2.0E−06 LMO2 LIM domain only 2 (rhombotin-like 1) −5.21 −2.381 5.2E−05 ELTD1 adhesion G protein-coupled receptor −5.20 −2.379 1.3E−48 L4 ESR1 estrogen receptor 1 −5.20 −2.378 1.3E−02 MYH8 myosin_ heavy chain 8_ skeletal −5.20 −2.378 1.2E−02 muscle_ perinatal GDNF glial cell derived neurotrophic factor −5.19 −2.376 9.7E−59 KRT222 keratin 222_ type II −5.18 −2.374 1.2E−02 SNTB1 syntrophin_ beta 1 (dystrophin- −5.18 −2.372 1.0E−05 associated protein A1_ 59 kDa_ basic component 1) PRUNE2 prune homolog 2 (*Drosophila*) −5.17 −2.371 5.6E−03 PCDHGA5 protocadherin gamma subfamily A_ 5 −5.16 −2.368 1.2E−05 LBX2 ladybird homeobox 2 −5.16 −2.367 2.8E−09 LINC01119 long intergenic non-protein coding −5.16 −2.367 2.6E−11 RNA 1119 SLC4A4 solute carrier family 4 (sodium −5.15 −2.365 4.2E−83 bicarbonate cotransporter)_ member 4 SEL1L3 sel-1 suppressor of lin-12-like 3 (*C.* −5.15 −2.364 1.7E−90 *elegans*) HSPA7 heat shock 70 kDa protein 7 (HSP70B) −5.14 −2.363 3.1E−04 PRKD1 protein kinase D1 −5.13 −2.358 2.6E−50 ADPRH ADP-ribosylarginine hydrolase −5.13 −2.358 5.5E−30 GPR116 adhesion G protein-coupled receptor −5.11 −2.354 1.4E−02 F5 NKPD1 NTPase_ KAP family P-loop domain −5.11 −2.354 7.5E−03 containing 1 CNTD2 cyclin N-terminal domain containing 2 −5.11 −2.354 1.1E−04 GAL galanin/GMAP prepropeptide −5.10 −2.351 7.0E−16 ENPP1 ectonucleotide −5.09 −2.349 6.2E−07 pyrophosphatase/phosphodiesterase 1 SERINC2 serine incorporator 2 −5.09 −2.347 4.9E−18 ASS1 argininosuccinate synthase 1 −5.08 −2.344 5.7E−09 PITX2 paired-like homeodomain 2 −5.07 −2.343 7.4E−05 LINC00933 long intergenic non-protein coding −5.07 −2.342 4.4E−03 RNA 933 C11orf96 chromosome 11 open reading frame 96 −5.06 −2.340 2.3E−03 APOBEC3G apolipoprotein B mRNA editing −5.04 −2.332 7.4E−21 enzyme_ catalytic polypeptide-like 3G MBP myelin basic protein −5.02 −2.329 5.9E−14 RGS7BP regulator of G-protein signaling 7 −5.02 −2.329 1.5E−02 binding protein ACKR4 atypical chemokine receptor 4 −5.02 −2.327 7.8E−05 TYMP thymidine phosphorylase −5.01 −2.324 2.4E−31 MAB21L3 mab-21-like 3 (*C. elegans*) −5.01 −2.324 1.5E−02 DENND2C DENN/MADD domain containing 2C −5.00 −2.323 2.7E−07 FLJ46906 uncharacterized LOC441172 −5.00 −2.321 6.7E−21 PSG11 pregnancy specific

beta-1-glycoprotein −5.00 −2.321 1.5E−02 11

Example 12. miRNA Nanostring nCounter Analysis of HMC-EVs Vs BM-MSC-EVs Vs UCB-MSC-EVs Vs AD-MSC-EVs

[0436] HMCs were generated from the same bank of frozen hemangioblasts described in Example 1. HMCs were generated and passaged up to six passages (P6) according to the method described in Example 1. Extracellular vesicles (EVs) were purified from HMCs (HMC-EVs) by tangential flow filtration (TFF). miRNA profiling was performed using Nanostring nCounter Analysis system for three lots of HMC-EVs under basal conditions. EVs isolated from bone marrow (BM-MSC-EVs) (3 lots), umbilical cord blood (UCB-MSC-EVs) (3 lots), and adipose tissue (AD-MSC-EVs) under basal conditions were used as controls.

[0437] Table 9 shows miRNAs that were more highly expressed in the HMC-EVs compared with UCB-MSC-EVs. Table 10 shows miRNAs that were more highly expressed in UCB-MSC-EVs compared with the HMC-EVs. Table 11 shows miRNAs that were highly expressed in HMC-EVs compared with BM-MSC-EVs. Table 12 shows miRNAs that were more highly expressed in BM-MSC-EVs compared with the HMC-EVs. Table 13 shows miRNAs that were highly expressed in HMC-EVs compared with AD-MSC-EVs. Table 14 shows miRNAs that were more highly expressed in AD-MSC-EVs compared with the HMC-EVs. HMC-EVs of the presently disclosed subject matter may be selected or purified based on an of the miRNAs that are differentially expressed.

TABLE-US-00009 TABLE 9 miRNAs with higher expression in HMC-EVs compared to UCB-MSC-EVs miRNA ID Fold Difference p-Value hsa-miR-125b-5p 3.90 0.000 hsa-miR-100-5p 3.50 0.004 hsa-miR-21-5p 2.59 0.025 hsa-miR-199a-3p + hsa-miR-199b-3p 2.57 0.000 hsa-miR-23a-3p 2.37 0.013 hsa-miR-181a-5p 2.16 0.007 hsa-miR-199b-5p 2.07 0.000 hsa-miR-125a-5p 2.05 0.008 hsa-miR-1204 1.96 0.035 hsa-miR-106a-5p + hsa-miR-17-5p 1.73 0.013 hsa-let-7e-5p 1.68 0.017 hsa-miR-450a-5p 1.67 0.014

TABLE-US-00010 TABLE 10 miRNAs with higher expression in UCB- MSC-EVs compared to HMC-EVs miRNA ID Fold Difference p-Value hsa-miR-1252-5p −2.04 0.00 hsa-miR-376c-3p −2.00 0.01 hsa-miR-196b-5p −1.93 0.02 hsa-miR-4755-5p −1.83 0.00 hsa-miR-211-3p −1.81 0.05 hsa-miR-548d-3p −1.66 0.05 hsa-miR-671-3p −1.66 0.03 hsa-miR-1297 −1.56 0.01 hsa-miR-134-5p + hsa-miR-6728-5p −1.55 0.05 hsa-mir-498 −1.52 0.01 hsa-miR-128-1-5p −1.52 0.01 hsa-miR-1269b −1.51 0.01

TABLE-US-00011 TABLE 11 miRNAs with higher expression in HMC-EVs compared to BM-MSC-EVs miRNA ID Fold Difference p-Value hsa-miR-320e 13.68 0.035 hsa-miR-125b-5p 4.81 0.000 hsa-miR-100-5p 4.38 0.001 hsa-miR-181a-5p 3.42 0.007 hsa-miR-23a-3p 3.03 0.006 hsa-miR-21-5p 2.95 0.012 hsa-miR-199a-3p + hsa-miR-199b-3p 2.86 0.007 hsa-let-7a-5p 2.30 0.032 hsa-miR-221-3p 2.18 0.005 hsa-miR-199b-5p 2.07 0.000 hsa-miR-29a-3p 1.67 0.019 hsa-miR-125a-5p 1.64 0.034 hsa-let-7g-5p 1.54 0.025

TABLE-US-00012 TABLE 12 miRNAs with higher expression in BM- MSC-EVs compared to HMC-EVs miRNA ID Fold Difference p-Value hsa-miR-1469 −2.34 0.026 hsa-miR-892b −2.29 0.004 hsa-miR-664b-5p −2.27 0.003 hsa-miR-151b −2.20 0.012 hsa-miR-219a-2-3p −2.16 0.035 hsa-miR-485-3p −2.14 0.010 hsa-miR-134-5p + hsa-miR-6728-5p −2.07 0.008 hsa-miR-195-5p −2.05 0.014 hsa-miR-508-3p −2.03 0.004 hsa-miR-5010-5p −2.01 0.032 hsa-miR-629-5p −1.99 0.018 hsa-miR-518d-3p −1.99 0.035 hsa-miR-18b-5p −1.98 0.037 hsa-miR-147a −1.92 0.048 hsa-miR-196b-5p −1.90 0.013 hsa-miR-486-3p −1.88 0.032 hsa-miR-1258 −1.85 0.023 hsa-miR-548aa + hsa-miR-548t-3p −1.81 0.034 hsa-miR-584-5p −1.81 0.047 hsa-miR-3202 −1.80 0.012 hsa-miR-663a −1.80 0.034 hsa-miR-517a-3p −1.80 0.013 hsa-miR-329-3p −1.80 0.019 hsa-miR-1248 −1.76 0.035 hsa-miR-628-3p −1.76 0.013 hsa-miR-499b-5p −1.75 0.038 hsa-miR-1279 −1.74 0.017 hsa-miR-873-3p −1.74 0.048 hsa-miR-514a-5p −1.73 0.008 hsa-miR-127-5p −1.72 0.048 hsa-miR-491-3p −1.71 0.019 hsa-miR-548k −1.71 0.013 hsa-miR-566 −1.70 0.036 hsa-miR-520c-3p −1.69 0.036 hsa-miR-591 −1.68 0.012 hsa-miR-129-5p −1.67 0.013 hsa-miR-6503-3p −1.66 0.011 hsa-

miR-1183 −1.65 0.003 hsa-miR-1178-3p −1.65 0.046 hsa-miR-885-3p −1.65 0.019 hsa-miR-6721-5p −1.62 0.013 hsa-miR-4536-5p −1.61 0.033 hsa-miR-617 −1.61 0.027 hsa-miR-510-5p −1.59 0.031 hsa-mir-498 −1.59 0.017 hsa-miR-142-5p −1.59 0.006 hsa-miR-378d −1.58 0.014 hsa-miR-3131 −1.58 0.016 hsa-miR-578 −1.57 0.041 hsa-miR-450a-2-3p −1.57 0.002 hsa-miR-620 −1.57 0.024 hsa-miR-3613-3p −1.57 0.012 hsa-miR-1234-3p −1.57 0.049 hsa-miR-1269b −1.57 0.029 hsa-miR-940 −1.56 0.007 hsa-miR-4787-5p −1.55 0.019 hsa-miR-378h −1.55 0.005 hsa-miR-654-5p −1.53 0.028 hsa-miR-92b-3p −1.51 0.044

TABLE-US-00013 TABLE 13 miRNAs with higher expression in HMC-EVs compared to AD-MSC-EVs miRNA ID Fold Difference p-Value hsa-miR-125b-5p 5.73 0.004 hsa-miR-4454 + hsa-miR-7975 4.31 0.001 hsa-miR-100-5p 4.03 0.002 hsa-miR-181a-5p 3.39 0.001 hsa-miR-21-5p 3.20 0.021 hsa-miR-199a-3p + hsa-miR-199b-3p 3.06 0.011 hsa-miR-23a-3p 2.69 0.007 hsa-miR-125a-5p 2.22 0.024 hsa-miR-29a-3p 2.14 0.024 hsa-miR-450a-5p 2.11 0.004 hsa-miR-25-3p 2.02 0.000 hsa-miR-221-3p 1.99 0.009 hsa-miR-106a-5p + hsa-miR-17-5p 1.79 0.001 hsa-miR-199b-5p 1.76 0.027 hsa-miR-214-3p 1.65 0.034

TABLE-US-00014 TABLE 14 miRNAs with higher expression in AD-MSC EVs compared to HMC-EVs miRNA ID Fold Difference p-Value hsa-miR-194-5p −2.54 0.023 hsa-miR-665 −2.05 0.025 hsa-miR-219a-2-3p −1.95 0.046 hsa-miR-4536-3p −1.91 0.049 hsa-miR-18b-5p −1.87 0.039 hsa-miR-124-3p −1.83 0.042 hsa-miR-127-5p −1.83 0.016 hsa-miR-628-3p −1.83 0.026 hsa-miR-2110 −1.80 0.022 hsa-miR-566 −1.77 0.027 hsa-miR-4755-5p −1.76 0.025 hsa-miR-509-3p −1.76 0.003 hsa-miR-578 −1.71 0.029 hsa-miR-1248 −1.66 0.030 hsa-miR-1252-5p −1.63 0.034 hsa-miR-28-5p −1.63 0.005 hsa-miR-128-1-5p −1.62 0.014 hsa-miR-1183 −1.62 0.004 hsa-miR-1296-3p −1.61 0.045 hsa-miR-1285-5p −1.61 0.015 hsa-miR-485-3p −1.60 0.032 hsa-miR-514a-5p −1.59 0.039 hsa-mir-498 −1.58 0.024 hsa-miR-330-5p −1.56 0.020 hsa-miR-10a-5p −1.55 0.038 hsa-miR-888-5p −1.55 0.013 hsa-miR-183-5p −1.52 0.049 hsa-miR-760 −1.51 0.016 hsa-miR-6721-5p −1.51 0.019 hsa-miR-664b-5p −1.50 0.025

Example 13. Proteome Profiling for HMC-EVs Vs BM-MSC-EVs Vs UCB-MSC-EVs Vs AD-MSC-EVs

[0438] HMCs were generated from the same bank of frozen hemangioblasts described in Example 1. HMCs were generated and passaged up to six passages (P6) according to the method described in Example 1. Extracellular vesicles (EVs) were purified from HMCs (HMC-EVs) by tangential flow filtration (TFF). Proteome profiling by standard mass spectrometry analysis was performed for three lots of HMC-EVs under basal conditions. EVs isolated from bone marrow (BM-MSC-EVs) (3 lots), umbilical cord blood (UCB-MSC-EVs) (3 lots), and adipose tissue (AD-MSC-EVs) under basal conditions were used as controls.

[0439] T-test statistical analysis was used to identify proteins with significant differences in abundance between EV types. Table 15 shows proteins that were more highly abundant in the HMC-EVs compared with UCB-MSC-EVs. Table 16 shows proteins that were more highly abundant in UCB-MSC-EVs compared with the HMC-EVs. Table 17 shows proteins that were more highly abundant in HMC-EVs compared with BM-MSC-EVs. Table 18 shows proteins that were more highly abundant in BM-MSC-EVs compared with the HMC-EVs. Table 19 shows proteins that were more highly abundant in HMC-EVs compared with AD-MSC-EVs. Table 20 shows proteins that were more highly abundant in AD-MSC-EVs compared with the HMC-EVs. HMC-EVs of the presently disclosed subject matter may be selected or purified based on any of the proteins that are differentially abundant.

[0440] The proteomics data was subsequently analysed to determine how the overall protein expression profile may affect different signaling pathways. FIG. **63**A depicts the pathway enrichment of differential expression pattern between HMC-EVs and BM-MSC-EVs. FIG. **64**A depicts the pathway enrichment of differential expression pattern between HMC-EVs and AD-MSC-EVs. FIG. **65**A depicts the pathway enrichment of differential expression pattern between HMC-EVs and EVs secreted from umbilical cord blood-derived MSCs (UCB-MSC-EVs). As

shown in FIGS. **63**A, **64**A and **65**A, certain pathways are up-regulated (see orange bars) in HMC-EVs as compared to EVs secreted from other tissue-derived MSCs, such as pathways involved in LXR/RXR activation, acute phase response signaling, B cell receptor signaling, and systemic lupus erythematosus in B cell signaling pathway. In addition, proteins contributing to certain pathways, for example, IL-15 signaling, claritin-mediated endocytosis signaling, and FXR/RXR activation, are also enriched (see white and gray bars). etc

[0441] Diseases or functional annotation of proteins that are differentially expressed in HMC-EVs and EVs secreted from tissue-derived MSCs are also analyzed. FIG. **63**B depicts the functional annotation of proteins that are upregulated in HMC-EVs when compared to BM-MSC-EVs. FIG. **63**C depicts the functional annotation of proteins that are downregulated in HMC-EVs when compared to BM-MSC-EVs. FIG. **64**B depicts the functional annotation of proteins that are upregulated in HMC-EVs when compared to AD-MSC-EVs. FIG. **64**C depicts the functional annotation of proteins that are downregulated in HMC-EVs when compared to AD-MSC-EVs. FIG. **65**B depicts the functional annotation of proteins that are upregulated in HMC-EVs when compared to UCB-MSC-EVs. FIG. **65**C depicts the functional annotation of proteins that are downregulated in HMC-EVs when compared to UCB-MSC-EVs. An activation z-score above 2 or below −2 is considered as the threshold value. The analysis suggests that proteins involved in cell viability/survival, cellular movement, cell-to-cell signalizing and interaction pathways are upregulated in HMC-EVs, whereas proteins involved in cell death or apoptosis are downregulated in HMC-EVs.

TABLE-US-00015 TABLE 15 Proteins significantly more abundant in HMC-EVs compared to UCB-MSC EVs Name log 2 fold difference p-value SLC2A1 5.55 1.62E−05 MFGE8 5.07 2.17E−04 MAMDC2 4.72 2.05E−03 H3-3A 4.31 2.35E−04 MARCKSL1 4.11 1.78E−04 KIF11 4.08 3.76E−05 PRSS23 3.97 2.13E−02 SLC3A2 3.95 2.18E−03 CD81 3.85 2.02E−03 TSPAN14 3.84 7.49E−05 CD99 3.79 3.63E−03 MDGA1 3.78 1.66E−03 RPS18 3.76 5.81E−04 CAV1 3.70 1.10E−03 KRT4 3.69 3.30E−04 MVP 3.57 7.81E−04 KPNA2 3.47 1.25E−03 HLA-A 3.47 1.10E−02 TRIM5 3.46 6.75E−04 KRAS 3.46 1.36E−04 ANXA5 3.35 2.75E−03 GNG12 3.32 8.10E−05 S100A11 3.31 2.61E−03 H4-16 3.22 2.39E−05 PCDH1 3.19 2.16E−03 ITGAV 3.17 1.55E−03 H3-7 3.11 7.29E−04 TNC 3.09 2.30E−02 VAT1 3.09 2.25E−04 RAP2A 3.06 2.12E−03 UCHL1 3.01 3.08E−03 FDPS 3.01 2.08E−03 H2AC20 3.01 4.80E−03 RPS4X 3.00 4.96E−03 BASP1 2.99 2.49E−06 CKM 2.97 1.41E−03 B2M 2.89 1.16E−02 TSPAN9 2.89 8.06E−04 RPS3A 2.83 3.59E−03 RPS13 2.82 4.48E−03 MMP14 2.78 2.06E−06 GNAI2 2.77 2.88E−05 YWHAQ 2.77 4.56E−03 PDIA3 2.75 7.76E−03 RALA 2.75 5.45E−03 RPS3 2.74 1.77E−03 EPB41L3 2.70 1.75E−03 SLC44A1 2.70 2.09E−03 ARL8A 2.69 5.53E−03 H1-3 2.69 1.27E−03 NIBAN2 2.64 2.11E−05 ITGA2 2.63 5.60E−06 TUBB3 2.63 1.77E−02 BBS1 2.62 5.29E−03 MAPK3 2.61 4.10E−03 YWHAB 2.58 5.14E−03 H2BC15 2.58 1.87E−05 TRPM2 2.52 9.52E−03 GALE 2.49 2.26E−04 CA2 2.49 2.81E−04 H2AC21 2.48 1.22E−02 TTYH3 2.45 1.23E−05 PDGFRB 2.44 2.84E−05 CD47 2.41 5.97E−05 DTD1 2.41 3.62E−03 GP9 2.39 2.26E−03 TAGLN2 2.38 1.02E−02 GNAQ 2.37 4.97E−03 PPP2R1A 2.37 2.16E−02 ALDOC 2.36 1.08E−03 RPS15A 2.35 8.55E−03 MERTK 2.35 4.34E−03 MDH1 2.34 1.63E−05 TPT1 2.27 1.35E−03 EIF5A 2.21 2.70E−02 LYN 2.20 2.74E−02 VCAN 2.18 7.73E−09 CYFIP1 2.18 5.89E−03 APBB2 2.18 1.93E−02 SDCBP 2.16 1.56E−06 LAP3 2.16 2.08E−02 KRT13 2.15 3.25E−02 LRRC59 2.13 5.62E−03 RPL13 2.13 4.00E−04 CD36 2.12 2.49E−05 SRSF8 2.08 2.45E−05 TSPAN33 2.03 4.53E−03 TPTE2 2.03 2.17E−02 HLA-A 2.02 1.02E−02 EPHB2 1.93 9.56E−03 FAH 1.93 4.25E−03 FUCA1 1.90 3.24E−04 MARCKS 1.89 2.79E−05 GP1BB 1.88 2.91E−04 CD276 1.88 1.48E−03 ACLY 1.86 2.15E−02 YWHAE 1.86 1.50E−02 PLAA 1.85 2.05E−02 UBE2L3 1.85 2.75E−02 WARS1 1.83 9.19E−04 AOC3 1.83 3.71E−05 BGN 1.82 1.55E−07 AGRN 1.82 8.24E−06 SLC44A2 1.78 3.13E−02 RPL11 1.77 1.77E−02 FARP1 1.73 5.55E−03 ITGA3 1.72 6.48E−07 ANXA2 1.71 3.90E−05 STX11 1.71 4.14E−05 TBC1D2 1.71 1.96E−02 PGAP1 1.71 5.86E−06 RPL14 1.68 1.27E−02 RPL10A 1.66 9.01E−06 CD63 1.66 5.06E−05 CPN2 1.63

4.56E−06 RPS25 1.62 8.88E−03 BLVRA 1.62 3.32E−03 PPP2CB 1.62 2.58E−04 LGALS1 1.59 1.48E−05 S100A6 1.51 2.82E−07 MEIOB 1.51 4.95E−06 NME2 1.51 2.23E−03 OSMR 1.50 2.78E−02 SEPTIN5 1.49 6.58E−03 MYL12B 1.49 1.38E−03 FN3KRP 1.49 9.63E−03 CDH5 1.48 4.17E−05 ITGA2B 1.48 1.11E−05 HLA-B 1.47 1.33E−04 BMP1 1.46 4.26E−02 CLIC4 1.45 1.31E−03 BST1 1.45 1.05E−03 ITGB1 1.45 6.19E−11 STRADB 1.44 2.93E−04 MOB1B 1.43 5.59E−03 SDC1 1.43 4.81E−03 B4GALT1 1.42 3.27E−03 ITGA6 1.38 2.40E−09 RPL4 1.36 3.19E−02 ITGA4 1.33 4.40E−04 COL4A2 1.33 3.97E−07 PDCD6IP 1.32 1.34E−07 MSN 1.32 1.34E−07 PF4 1.32 2.10E−03 STXBP2 1.31 1.64E−02 ARF6 1.30 3.43E−02 EDIL3 1.29 1.12E−02 COTL1 1.29 1.54E−02 ITGA5 1.28 1.34E−05 QSOX1 1.28 3.43E−04 RALB 1.28 1.71E−04 NAGLU 1.28 6.87E−04 GNB1 1.28 3.11E−03 PDE4DIP 1.27 2.47E−04 CBR1 1.27 3.98E−03 ROBO4 1.26 8.58E−04 FBLN1 1.25 1.33E−02 STOM 1.25 2.40E−05 SRPX 1.25 4.98E−04 GSTM2 1.24 1.05E−04 ZNF607 1.23 7.88E−05 KIT 1.21 8.09E−05 LAMP1 1.21 7.48E−03 SEPTIN2 1.21 3.37E−04 CDC42 1.20 2.49E−03 ANXA6 1.19 3.38E−05 TANK 1.17 1.89E−05 UBA52 1.17 2.31E−04 COL18A1 1.17 1.41E−02 PAFAH1B1 1.15 3.38E−02 NUTF2 1.15 5.64E−04 TPI1 1.14 3.11E−07 LRP1 1.14 1.21E−04 SERPINA10 1.14 8.66E−03 MYO1F 1.13 2.84E−03 VNN1 1.12 1.99E−04 RPSA 1.12 1.82E−04 ARPC5 1.12 2.29E−02 CTBS 1.11 1.26E−07 MON2 1.11 1.38E−05 LUM 1.10 1.24E−03 RPS12 1.08 5.10E−03 PGLYRP2 1.08 5.38E−05 APOC4 1.08 9.84E−04 BANF1 1.08 1.55E−02 PRG4 1.07 3.13E−02 SERPINE2 1.07 1.26E−02 AHSG 1.07 2.87E−07 DYNLL1 1.06 3.53E−06 RAC1 1.06 3.65E−04 PRKAR1A 1.06 2.75E−03 SH3BGRL3 1.05 1.10E−03 CD9 1.04 7.31E−08 CLPP 1.04 9.54E−03 DEFA3 1.03 2.28E−02 CCT4 1.03 1.79E−04 HSPA4L 1.03 5.99E−04 EFEMP1 1.02 2.90E−02 GLIPR2 1.02 1.07E−03 ITGB3 1.02 1.86E−05 FUCA2 1.01 1.66E−02 PROCR 1.01 9.71E−05 CFHR1 1.00 1.67E−04 YWHAZ 1.00 3.72E−06

TABLE-US-00016 TABLE 16 Proteins significantly more abundant in UCB-MSC EVs compared to HMC-EVs Name log 2 fold difference p-value TMEM198 −5.16 3.92E−10 CAT −5.16 1.45E−06 SPON2 −4.11 5.60E−05 DOK4 −4.09 3.21E−05 LRAT −3.88 3.31E−05 ADIPOQ −3.85 3.79E−04 PTX3 −3.69 7.69E−06 CHST9 −3.52 5.30E−07 CEP290 −3.46 3.05E−03 FAM151B −3.41 1.76E−02 IGHV1-45 −3.36 1.71E−02 MSH6 −3.22 7.41E−03 SNTG1 −3.11 4.29E−06 AKAP9 −2.92 3.94E−06 MUC16 −2.91 2.71E−03 ALB −2.87 5.77E−04 LRRTM2 −2.79 8.46E−05 SURF1 −2.77 1.45E−02 CDSN −2.76 1.11E−02 PSMA6 −2.73 7.91E−05 F11 −2.68 4.35E−08 ALOX5 −2.63 3.36E−06 SEMA7A −2.52 1.92E−02 TAS2R33 −2.50 2.27E−03 IGHV3-38-3 −2.48 1.14E−03 TYMP −2.47 7.15E−06 MMRN2 −2.47 1.11E−02 PAK6 −2.46 4.81E−03 LDLR −2.46 1.24E−02 KRT17 −2.45 3.78E−02 CCIN −2.45 1.39E−03 RGS14 −2.39 5.06E−03 TRIM4 −2.38 7.42E−03 CFHR5 −2.38 1.71E−02 AP3B2 −2.34 1.05E−02 TIMP3 −2.34 3.57E−04 L1CAM −2.31 3.56E−06 IGHV3OR16-13 −2.27 3.03E−02 ABI3 −2.24 1.71E−03 BLMH −2.20 3.37E−03 S100A9 −2.19 3.76E−06 LAMB4 −2.16 1.42E−02 LTF −2.15 2.62E−02 ERC1 −2.14 1.10E−02 APLP2 −2.12 6.31E−03 ZSWIM9 −2.11 7.12E−03 OLFML3 −2.10 1.82E−02 CTHRC1 −2.10 1.79E−05 CD109 −2.07 1.92E−02 IGLV6-57 −2.04 4.16E−04 REG1A −2.02 1.27E−02 CCBE1 −2.02 1.36E−02 OAF −2.01 2.28E−05 NEO1 −1.97 2.41E−02 NBEAL2 −1.92 1.99E−02 PIWIL2 −1.84 3.95E−05 SBSN −1.82 4.12E−02 CAPN5 −1.80 1.04E−08 TRIM7 −1.76 1.08E−06 ZNF804B −1.73 1.35E−03 LYVE1 −1.72 4.57E−04 ACTR1A −1.70 1.16E−02 IGHG2 −1.67 9.34E−10 DSC1 −1.66 2.60E−04 PDZK1P1 −1.63 8.47E−04 FHL1 −1.61 1.39E−02 PSMA7 −1.58 1.94E−07 DBH −1.55 1.42E−03 IGHV3-74 −1.53 2.05E−05 PRXL2B −1.53 2.10E−07 C18orf63 −1.51 5.55E−06 IGHG1 −1.48 2.23E−09 PSMA4 −1.45 3.77E−03 UBTD1 −1.45 2.11E−06 PIEZO1 −1.44 1.14E−05 MYCBP2 −1.43 1.76E−02 NYAP2 −1.43 2.19E−06 CCDC110 −1.42 1.18E−05 ZNF800 −1.41 1.95E−07 VEGFA −1.41 3.31E−02 FBRSL1 −1.41 1.61E−04 GTF2IRD2 −1.39 1.99E−06 PPM1F −1.39 4.41E−02 HGFAC −1.37 5.90E−03 IGLV3-1 −1.36 8.16E−04 CD99L2 −1.36 6.57E−06 L1TD1 −1.35 4.40E−11 KRT16 −1.34 2.76E−03 XPNPEP2 −1.34 2.62E−05 IGHA2 −1.32 7.71E−04 ADA −1.30 2.88E−07 ALB −1.30 1.22E−02 IGLV2-18 −1.29 2.05E−02 IGHV4-4 −1.28 2.45E−09 COLEC11 −1.27 1.39E−02 PKP1 −1.24 1.57E−03 MYH3

−1.23 4.39E−02 TGFB1 −1.23 2.74E−06 IGHV1-69 −1.23 1.28E−04 IGLV3-21 −1.22 2.11E−08 DDX55 −1.20 9.05E−10 IGHA1 −1.20 5.28E−11 ANO7 −1.20 1.08E−07 MPP1 −1.19 1.11E−03 GPR179 −1.19 4.94E−06 WDR46 −1.19 1.08E−04 SYMPK −1.18 2.74E−05 TNFAIP6 −1.13 1.92E−06 RACK1 −1.13 2.93E−04 LOXL2 −1.12 3.21E−02 A2M −1.12 3.96E−07 S100A8 −1.11 4.92E−06 IGKV3D-20 −1.11 6.86E−06 ITIH1 −1.10 1.87E−09 GDI1 −1.09 9.12E−06 IGHV5-10-1 −1.06 4.68E−05 CYLC2 −1.05 2.35E−05 IGHD −1.04 1.81E−04 VTI1B −1.04 8.83E−04 VCP −1.03 9.97E−07 USP4 −1.03 1.72E−04 ATAD2 −1.03 1.41E−05 TF −1.03 4.24E−08 F13B −1.03 7.08E−05 ITIH3 −1.02 1.71E−06 IGLV3-25 −1.02 1.38E−07 CCT6A −1.01 1.46E−02 CFH −1.00 2.81E−06 IGLV3-27 −1.00 2.68E−06

TABLE-US-00017 TABLE 17 Proteins significantly more abundant in HMC-EVs compared to BM-MSC EVs Name log 2 fold difference p-value GDF10 9.24 9.5E−08 L1TD1 7.45 0.004719 CD82 7.27 6.06E−07 ZNF607 7.18 6.84E−07 KRT78 6.83 2.14E−07 H2AC20 6.53 1.75E−06 IGKV1-17 6.46 5.34E−05 GATA5 6.34 2.64E−06 H3-3A 6.10 5.68E−05 GOLGB1 5.73 4.16E−06 CCT4 5.39 4.42E−06 DYNLL1 5.38 0.000324 ARHGDIA 5.36 0.000256 B4GALT1 5.26 2.07E−05 LTBP3 5.17 0.008415 CORO1A 5.15 6.22E−10 ADGRG6 5.14 1.64E−07 PRDM5 5.11 3.57E−06 STAC2 5.10 4.11E−05 IGLV2-14 5.10 0.000465 ROBO4 5.04 7.26E−09 MBTD1 5.03 8.28E−06 CHMP4B 4.98 0.002437 IGHV5-10-1 4.93 0.000306 FAM76A 4.93 2.98E−06 C4B_2 4.86 0.000418 OBSCN 4.81 5.91E−05 N4BP1 4.79 0.002836 VCP 4.76 0.000141 MYEF2 4.65 0.014568 EXOC1 4.62 1.8E−07 IGHV4-4 4.61 0.000758 SLC2A1 4.38 4.24E−06 SPARC 4.33 6.11E−08 FBLN1 4.32 2.04E−07 NBPF4 4.30 0.014757 BASP1 4.29 0.002139 MYO1F 4.22 4.22E−06 PIK3CA 4.14 0.000126 STRADB 4.11 0.00015 MERTK 4.10 7.49E−05 DENND1B 4.08 0.000505 COL4A1 4.08 8.57E−05 SLTM 4.05 1.03E−05 LGALS1 4.03 0.010051 CFHR1 4.03 3.92E−05 TSPAN14 3.92 3.45E−05 MARCKSL1 3.91 1.26E−05 CAV1 3.83 7.42E−05 ZNF879 3.81 5.73E−05 MIF 3.78 0.00036 MVP 3.78 2.82E−06 STXBP2 3.77 2.93E−05 TAGLN2 3.77 2.81E−11 MOB1B 3.77 0.000694 TSKU 3.76 0.001976 PMVK 3.72 0.000187 TNC 3.71 0.000233 GPX3 3.68 2E−06 GOT1L1 3.68 6.05E−06 EDIL3 3.68 1.24E−06 SNX14 3.63 0.00065 MYL12B 3.63 0.000851 KRT4 3.61 0.000113 COL5A2 3.59 0.002899 PRAMEF10 3.57 2.37E−05 ITGA2 3.51 1E−05 CDH5 3.48 0.000121 APBB2 3.48 0.005607 CCN2 3.47 0.000961 ALOX12 3.45 0.001648 SLC3A2 3.45 0.000745 IGLV1-40 3.44 0.000266 YWHAB 3.44 0.002303 H3-7 3.42 0.004263 TIMP1 3.42 0.008573 GNB2 3.41 0.009415 VAT1 3.40 4.14E−05 PLCH1 3.39 1.03E−07 IGKV1D-16 3.39 0.000314 SMG1 3.38 9.29E−08 CALR 3.38 0.005623 RPS18 3.37 0.000232 CYP11B1 3.37 0.00017 RPSA 3.35 0.008587 IGHV3-64 3.33 0.001246 CDH13 3.31 8.2E−09 PDIA3 3.30 0.000169 MMP14 3.26 0.026749 PCDH1 3.25 9.86E−05 MFGE8 3.23 0.00748 IGHV1-18 3.22 3.63E−06 IGHG4 3.21 0.000498 TSPAN9 3.21 0.000157 ALDOC 3.21 5.46E−07 BIN2 3.20 0.035938 STN1 3.19 0.00191 GNAQ 3.18 0.002647 GANAB 3.17 6.5E−05 ADA 3.14 0.030644 PF4 3.13 7.99E−08 ARPC5 3.09 0.000116 HLA-A 3.09 0.006161 APRT 3.07 0.000978 PAFAH1B1 3.07 1.37E−05 PGAP1 3.06 8.7E−05 PRG4 3.06 1.28E−05 CAP1 3.02 1.92E−08 COL18A1 3.02 0.015049 ATP6V1E1 3.02 0.004046 IGLV2-18 3.01 0.000485 KPNA2 3.01 0.001586 ANXA6 3.00 7E−06 TRIM5 2.97 0.006958 CD99 2.96 0.001694 HSPB1 2.92 0.000978 PXDN 2.92 1.47E−06 H4-16 2.92 8.26E−05 PON3 2.91 2.32E−05 BLVRA 2.90 0.016521 CLIC4 2.88 0.001057 RPL18 2.87 4.68E−05 YWHAE 2.87 0.001475 EEF1D 2.87 0.001449 UCHL1 2.85 0.00102 SDCBP 2.85 6.09E−07 KIF3B 2.84 0.000319 APOC4 2.83 2.48E−05 GPR108 2.83 0.000693 MDGA1 2.79 0.013423 SFRP1 2.79 0.035069 LCP2 2.79 4.89E−05 ANXA5 2.78 5.76E−05 FGD6 2.77 0.001047 DSP 2.76 2.7E−05 TTYH3 2.76 0.005149 MMP2 2.75 0.001 AEBP1 2.75 0.00897 RPS3A 2.74 2.67E−06 RPLP2 2.74 0.000334 GNG12 2.72 0.003946 FDPS 2.72 0.013411 DSG1 2.72 3.89E−07 YWHAQ 2.71 0.001864 IGKV1-16 2.69 0.006457 LAMP1 2.69 0.003596 ENG 2.68 0.000983 TPM3 2.67 1.31E−06 MYO3A 2.67 0.022487 CAPN1 2.67 0.004755 MAMDC2 2.64 0.014581 MYH13 2.63 0.010167 CCDC110 2.61 0.025959 UNC13D 2.61 6.39E−05 AZGP1 2.59 8.12E−08 IGLV7-46 2.59 2.12E−05 MFAP2 2.58 0.000225 KRAS 2.57 0.000972 ESD 2.57 0.005135 DSTN 2.54

0.006875 BST1 2.52 0.018602 CNTFR 2.51 0.006624 IGHV1-46 2.50 1.45E−05 MYLK 2.49 0.000117 H2AC21 2.47 0.001132 HSP90AA1 2.45 1.04E−08 COL9A1 2.44 0.003595 ARPC1B 2.44 0.002084 TGM2 2.43 0.00205 SLC44A2 2.43 0.012886 TPP1 2.41 0.002061 EPB41L1 2.39 0.026857 PACSIN2 2.38 3.55E−05 CCNB3 2.36 0.001287 FHL1 2.36 0.002402 GP9 2.35 0.003498 SDC4 2.35 6.41E−05 COP1 2.33 0.000435 S100A13 2.32 0.00412 GMPR 2.32 0.006239 RAB8B 2.31 0.001874 CKM 2.31 0.011772 TMC8 2.31 0.026692 RAC2 2.27 3.6E−10 F13A1 2.26 2.5E−07 CD34 2.25 0.002686 PLOD1 2.25 0.000714 ARHGAP1 2.24 0.009884 CCT7 2.24 0.007496 LRRC59 2.23 0.006427 GNB1 2.21 8.13E−05 TSPAN33 2.21 0.014502 TUBA8 2.20 0.00438 GDI2 2.20 0.001214 GPX1 2.19 4.02E−05 UBE2D3 2.19 0.019397 AGRN 2.19 1.05E−05 HIP1 2.18 0.013348 DNAH14 2.18 0.034721 PTPRJ 2.17 0.010632 EPB41L3 2.17 0.004269 KIT 2.17 1.47E−07 EEF1G 2.16 0.001644 COMP 2.15 0.000843 COPS5 2.15 0.006709 CROCC 2.14 0.017985 PDGFRB 2.14 0.024622 MARCKS 2.13 9.55E−05 SEPTIN7 2.12 0.029813 TRIM7 2.11 0.017447 MPP1 2.11 0.028828 ARF3 2.11 4.97E−05 PEBP1 2.11 7.82E−05 RPL4 2.11 0.015036 CD81 2.11 0.022106 UTRN 2.10 0.013306 PARVB 2.07 3.93E−06 UBA1 2.07 0.00192 FLT1 2.07 0.000237 FGA 2.06 3.05E−08 STX11 2.05 0.005538 SYMPK 2.05 0.029327 RPS4X 2.05 0.000531 ACTN4 2.03 0.000159 ENO1 2.03 1.17E−07 RPL13 2.02 0.036252 TGFB1 2.02 0.010422 IGKV3D-15 2.01 0.03058 MTHFD1 1.98 0.033147 PDCD6IP 1.98 9.8E−05 LOXL2 1.98 0.002378 RALA 1.97 0.030452 ITGB1 1.96 8E−11 LAMC2 1.95 0.000129 VASN 1.95 1.91E−06 CAPZA2 1.95 0.001251 IDE 1.95 6.78E−05 EIF5A 1.95 0.000575 ACTR2 1.94 6.37E−07 RPL14 1.94 0.001723 LAP3 1.94 5.36E−05 PLAA 1.92 0.003494 CYFIP1 1.92 0.025712 CAMP 1.91 0.023111 UBE2L3 1.90 0.011389 ZNF800 1.90 0.022228 RPS25 1.90 0.00532 RPL11 1.89 0.012891 CD63 1.88 0.001159 IGFALS 1.88 1.01E−05 IGHV3-20 1.87 0.002723 YWHAZ 1.86 0.001333 SAR1A 1.85 0.003235 CALU 1.85 0.000369 DNAJB2 1.84 0.016971 GAPDH 1.84 7.75E−06 EGFR 1.83 9.58E−05 IGKV6D-21 1.80 0.017376 ITGA3 1.80 2.31E−09 KRT16 1.80 0.006106 IGLV8-61 1.76 0.00018 CAPNS1 1.75 0.016719 RPS3 1.74 0.005878 NT5E 1.74 0.013852 PKM 1.71 0.002702 FLNA 1.70 5.52E−07 TUBB3 1.70 0.017002 ANXA7 1.66 0.004786 IGHV2-5 1.66 0.001333 HRNR 1.65 0.00186 RPS15A 1.65 0.003786 ARF6 1.62 0.005927 PDIA3 1.62 0.001716 H2BC15 1.61 0.000244 FUCA1 1.60 8.36E−06 C1QA 1.60 0.00089 GLIPR2 1.60 0.000144 DDX55 1.59 0.035084 PDLIM7 1.59 1.72E−05 SERPINE1 1.59 0.00105 CALM3 1.59 0.026876 NPTX1 1.58 0.023521 NIBAN2 1.58 0.007383 PPBP 1.57 0.000391 HK1 1.57 0.031509 FCN3 1.57 0.000268 MYL6 1.57 0.000755 PTGES3 1.56 0.023852 GPR179 1.55 0.004002 PRDX6 1.55 7.44E−05 VCAN 1.54 0.003195 MSN 1.54 1.34E−05 C1RL 1.52 4.62E−07 RAB8A 1.52 0.000118 HTRA1 1.51 0.027976 C1QB 1.51 0.000215 S100A4 1.51 0.034502 IGHV3-64D 1.51 0.001005 DTD1 1.50 0.007098 THBS2 1.50 0.023918 PATJ 1.50 5.49E−05 CFH 1.50 0.00065 HSPA5 1.49 2.24E−05 UBA52 1.49 0.006603 HLA-A 1.49 0.027277 IGKV3-7 1.49 6.84E−05 RAP2A 1.48 0.01951 CNTNAP5 1.48 0.020994 APOA1 1.47 7.05E−05 CD59 1.46 0.017075 TGFBI 1.46 0.000145 EHD3 1.45 6.79E−07 TMTC2 1.45 0.000856 CD276 1.45 0.003687 IGLV3-21 1.45 6.09E−05 PLXDC2 1.43 2.54E−06 SP5 1.43 0.033692 AHCY 1.42 0.010938 IGHG3 1.41 0.003373 PTPRG 1.41 5.65E−06 SERPINC1 1.40 1.47E−05 C1R 1.40 0.000988 HABP2 1.40 0.000584 FN1 1.40 0.0248 C1S 1.40 2.03E−05 FBN1 1.38 5.52E−05 CDC42 1.38 1.69E−05 INF2 1.37 0.007261 HBA1 1.37 2.11E−05 PCYOX1 1.37 0.015589 HBD 1.37 0.00225 SELENOP 1.37 3.88E−05 C8B 1.36 0.000264 C9 1.36 1.91E−05 TUBB1 1.36 1.06E−05 PI16 1.35 0.000586 EMILIN1 1.35 0.027038 LYN 1.35 0.008809 VPS13A 1.33 0.001477 IGLV1-47 1.32 0.001108 COTL1 1.31 0.018812 CLTC 1.31 0.00392 IGHV3-33 1.31 0.005984 CPB2 1.30 1.11E−06 F12 1.30 8.18E−05 TUBA1B 1.30 3.08E−09 IGLV4-69 1.29 0.000486 RAB7A 1.29 0.016284 NAA25 1.28 0.001563 F2 1.28 0.000124 CLEC3B 1.28 0.01992 C1QC 1.25 0.000596 APP 1.24 0.001311 SERPINA1 1.23 2.47E−07 DENND2A 1.21 0.033105 GSTP1 1.20 4.84E−07 NID2 1.20 0.014748 RNASE11 1.19 0.03571 COL6A2 1.19 0.020663 NUTF2 1.19 0.000436 YWHAG 1.18 9.65E−06 PEPD 1.18 3.67E−06 PPP1CA 1.17 0.017239 ILK 1.16 0.022235 EHD1 1.15 0.001047 APCS 1.15 1.05E−05

RALB 1.15 4.1E−05 IGHV3-73 1.14 0.00507 IGHA2 1.13 0.000613 CD36 1.12 8E−07 HRG 1.12 9.25E−05 GALE 1.12 0.034543 VASP 1.11 0.002503 ACE 1.09 4.32E−05 TUBB 1.09 0.000838 TPI1 1.09 3.71E−05 RAC1 1.07 0.000549 ANXA2 1.07 8.86E−08 FAH 1.07 0.023699 TUBB4B 1.06 4.98E−06 GSN 1.06 2.88E−06 EIF4A1 1.05 4.7E−06 COL5A1 1.04 5.41E−05 FERMT3 1.03 4.1E−07 ITGA2B 1.03 0.001339 PROS1 1.02 0.002371 HSP90B1 1.00 0.015352 LGALS3BP 1.00 0.003375

TABLE-US-00018 TABLE 18 Proteins significantly more abundant in BM-MSC EVs compared to HMC-EVs Name log 2 fold difference p-value DMXL1 −9.78 4.91E−13 PXYLP1 −7.74 1.34E−08 PTGFRN −7.55 1.38E−14 CSHL1 −4.51 6.52E−03 RNH1 −4.24 3.53E−02 AASS −3.91 7.86E−03 APOL1 −3.85 4.66E−12 RPL15 −3.72 8.13E−03 IRF6 −3.48 1.71E−02 TMEM198 −3.29 1.49E−03 RAB1B −3.10 8.69E−03 ASPM −2.91 2.21E−02 SULT1A1 −2.79 1.21E−08 GP5 −2.69 5.64E−08 CAT −2.63 3.53E−02 KYAT3 −2.54 6.63E−06 CCT2 −2.46 1.87E−07 TAS2R33 −2.41 3.11E−03 FGG −2.33 3.66E−10 ABI3BP −2.30 7.93E−08 ARMCX5 −2.25 2.54E−02 IGLV6-57 −2.23 2.66E−03 ADIPOQ −2.23 2.36E−02 WNT5B −2.23 2.45E−02 IGKV1D-39 −2.18 1.61E−05 CUX1 −2.10 1.19E−02 LILRA3 −2.06 2.74E−03 PPM1F −2.01 1.70E−02 GM2A −2.01 1.32E−02 CEP290 −2.01 2.08E−02 IGLV3-1 −2.01 6.15E−03 CTSK −1.94 1.70E−02 IGHV3-38 −1.78 1.08E−03 CCDC80 −1.77 1.88E−02 DOCK9 −1.72 1.45E−04 LAMA4 −1.71 1.52E−02 NAP1L4 −1.60 1.91E−04 APOA2 −1.59 3.14E−04 NBEAL2 −1.58 2.65E−02 KRT81 −1.48 2.99E−02 AASDHPPT −1.46 1.29E−02 PAICS −1.45 2.47E−06 FBLN5 −1.45 6.53E−04 MUC16 −1.44 3.66E−02 PRXL2C −1.42 1.97E−05 IGLV4-60 −1.40 3.26E−02 AKR7A2 −1.39 2.67E−04 SRR −1.30 1.57E−02 CYLC2 −1.26 1.37E−05 COL3A1 −1.20 3.78E−03 GMFG −1.19 2.10E−02 PDLIM1 −1.16 8.70E−05 SPOCK1 −1.04 1.69E−04 ITIH1 −1.00 1.51E−02

TABLE-US-00019 TABLE 19 Proteins significantly more abundant in HMC-EVs compared to AD-MSC EVs Name log 2 fold difference P-Value SEPTIN5 6.88 3.98E−08 B2M 6.71 1.29E−07 H3-3A 6.61 9.60E−04 PRSS23 6.46 1.73E−08 SLC2A1 5.40 1.62E−07 IGKV3D-20 5.14 9.44E−05 RAB6B 5.13 2.00E−04 APBB2 5.11 1.32E−06 LTBP3 5.01 3.28E−03 PGAP1 5.00 1.75E−04 TAGLN2 4.69 1.16E−10 CD81 4.64 6.54E−07 SRSF8 4.55 3.60E−05 BSG 4.54 1.65E−02 ENG 4.52 6.54E−05 NT5E 4.49 2.13E−03 RPS3A 4.39 1.21E−06 S100A11 4.38 3.93E−05 CA2 4.30 8.95E−04 CD99 4.29 2.10E−07 ESD 4.24 1.58E−03 TSPAN14 4.20 7.38E−05 RPS4X 4.13 1.15E−04 CAV1 4.13 1.15E−05 FSCN1 4.12 2.04E−02 ARF4 4.10 2.53E−03 ITGA2 4.10 4.84E−05 ANXA5 4.08 1.59E−04 RPS18 4.07 1.04E−03 BLVRA 4.07 2.14E−03 VAT1 4.06 1.27E−04 MAMDC2 4.05 3.48E−03 KIF11 4.00 8.93E−03 GNAQ 3.99 4.47E−05 CKM 3.99 2.49E−03 YWHAQ 3.99 1.25E−02 CD36 3.99 8.04E−04 MARCKSL1 3.94 2.00E−05 ARHGDIB 3.90 8.12E−03 RAB27B 3.89 2.15E−03 GNAI2 3.88 3.08E−03 H3-7 3.85 2.02E−03 KRAS 3.77 1.12E−03 ARHGDIA 3.69 3.75E−03 MFGE8 3.63 1.01E−07 MEIOB 3.63 3.25E−03 CDC42 3.63 6.84E−05 SH3BGRL3 3.62 2.31E−03 STXBP2 3.59 4.95E−04 STX11 3.58 8.41E−05 ARL8A 3.56 2.66E−06 TRPM2 3.53 6.82E−04 CCN2 3.52 4.52E−04 H2BC15 3.48 3.02E−07 MERTK 3.46 2.22E−03 YWHAB 3.46 8.75E−03 ALDOC 3.44 1.72E−07 TUBB3 3.44 2.51E−03 FDPS 3.40 2.12E−03 SFRP1 3.39 1.70E−03 TSPAN33 3.39 1.54E−04 PCDH1 3.38 1.50E−02 MBTD1 3.37 3.98E−02 SLTM 3.37 8.65E−03 COL4A2 3.35 1.76E−06 MARCKS 3.34 5.03E−06 FUCA1 3.34 5.42E−08 TSPAN9 3.33 3.04E−04 CD47 3.31 1.77E−04 DTD1 3.29 4.19E−05 KPNA2 3.29 5.32E−05 MDGA1 3.27 5.41E−04 BCL9 3.24 6.32E−03 HIP1 3.23 2.83E−03 IGLV2-23 3.23 2.68E−02 TTYH3 3.23 1.38E−04 TNC 3.22 4.36E−02 LAMP1 3.21 3.34E−03 HLA-A 3.18 1.74E−02 PPP2R1A 3.18 2.11E−03 MDH1 3.17 3.10E−04 MYO3A 3.14 1.89E−02 PGD 3.13 3.38E−02 RPS12 3.12 4.41E−04 PXDN 3.11 5.32E−06 YWHAE 3.10 1.50E−03 PRXL2C 3.10 1.99E−02 GNG12 3.10 1.59E−03 ARPC5 3.08 4.69E−03 LRRC59 3.05 2.84E−03 PF4 3.05 2.00E−06 SLC44A1 3.05 1.83E−07 TPI1 3.03 6.86E−06 CCNB3 3.03 1.22E−03 CD63 3.02 1.40E−05 GP9 3.01 5.73E−04 PSTPIP2 2.99 5.92E−06 HP 2.97 8.61E−04 PPP2CB 2.96 8.89E−03 H2AC20 2.96 1.77E−02 BST1 2.96 1.45E−02 SLC3A2 2.94 4.64E−02 ACACA 2.94 4.53E−03 MTPN 2.93 1.85E−02 EPB41L3 2.93 2.63E−03 MMP14 2.89 2.18E−05 RPS3 2.87 1.26E−03

BMP1 2.87 3.15E−02 FCGR3A 2.86 4.72E−03 COP1 2.86 3.04E−02 UCHL1 2.85 1.26E−05 PEBP1 2.85 6.66E−04 SLC44A2 2.85 5.32E−03 SDCBP 2.82 1.40E−06 PLXDC2 2.81 2.13E−04 RAB11FIP1 2.80 1.23E−04 RNASE11 2.80 9.39E−03 MYL12B 2.77 1.88E−03 RPL10A 2.76 3.20E−05 SMG1 2.75 2.02E−08 ITGA3 2.73 2.01E−05 PDIA3 2.72 3.30E−03 H4-16 2.71 5.73E−04 AGRN 2.71 3.35E−05 AOC3 2.71 4.15E−04 ARPC2 2.69 1.06E−02 ITGA2B 2.69 3.15E−06 VCAN 2.69 1.80E−05 COTL1 2.67 1.88E−03 RPL13 2.66 1.16E−02 RICTOR 2.64 1.71E−02 DYNLL1 2.64 8.64E−04 H1-3 2.63 1.03E−03 H2AC21 2.63 1.64E−02 TPP1 2.62 7.50E−03 RAB14 2.61 4.68E−04 PDGFRB 2.61 2.90E−02 RPL14 2.61 3.28E−05 TUBA8 2.59 4.67E−03 ADGRG6 2.59 4.04E−03 KRT4 2.58 7.61E−03 MYO1F 2.57 1.00E−02 EPHB2 2.56 1.62E−03 RALA 2.56 4.82E−04 RPS25 2.55 1.54E−02 MAPK3 2.55 7.18E−03 STOM 2.53 4.63E−05 CTBS 2.51 6.65E−05 SERPINA10 2.50 1.92E−02 GNB4 2.50 2.35E−02 ANXA6 2.49 1.01E−05 CD276 2.49 2.99E−03 GLIPR2 2.49 6.02E−05 BBS1 2.48 2.48E−02 BASP1 2.48 4.27E−02 MVP 2.47 3.35E−02 FAH 2.47 8.09E−03 CD34 2.47 2.04E−03 NAGLU 2.47 4.76E−04 PTPRG 2.47 1.09E−03 THY1 2.45 1.37E−06 PRG4 2.42 8.78E−06 RPS15A 2.42 1.07E−02 FREM3 2.42 1.08E−04 MOB1B 2.42 9.08E−03 FLG2 2.42 2.52E−02 SEPTIN2 2.39 1.29E−04 PTGDS 2.38 1.39E−03 IL1RAP 2.38 4.95E−04 NIBAN2 2.38 2.82E−04 LGALS1 2.37 1.45E−06 GSTM1 2.37 6.30E−03 EEF1D 2.36 3.60E−06 SPARC 2.35 3.57E−02 UBE2L3 2.34 5.48E−03 CBR1 2.34 4.64E−02 RAP2A 2.34 7.67E−03 TANK 2.34 1.89E−05 S100A6 2.32 5.70E−03 CRISP3 2.29 3.53E−05 ANXA2 2.28 2.47E−07 MON2 2.28 6.21E−06 APOC4 2.28 4.38E−04 MTHFD1 2.27 3.08E−02 DEFA3 2.27 5.03E−03 NPM1 2.26 1.08E−02 C1QA 2.25 5.27E−05 ACLY 2.24 3.88E−02 ITGB3 2.24 4.84E−07 CPN2 2.23 5.77E−08 RPS13 2.22 3.10E−03 ARHGAP1 2.20 4.63E−02 HYOU1 2.20 2.88E−02 IGLV7-43 2.19 3.58E−02 GNB1 2.19 2.91E−05 ZNF607 2.19 7.60E−04 TGM2 2.18 9.01E−03 CORO1A 2.18 4.53E−05 CD9 2.18 2.71E−06 STRADB 2.16 3.17E−02 GATA5 2.16 3.73E−05 YBX3 2.16 4.51E−02 EHD1 2.15 2.63E−03 LUM 2.13 5.69E−05 CNDP2 2.12 3.00E−03 ITGA4 2.10 5.79E−04 RNF149 2.09 2.50E−04 SRPX 2.09 1.32E−09 HSP90AB1 2.09 4.04E−05 LAP3 2.08 4.83E−04 ITGB1 2.05 1.72E−07 HSPA4L 2.05 1.89E−04 TPTE2 2.05 1.85E−02 QSOX1 2.04 3.25E−04 PLOD1 2.04 5.58E−02 SERPINA11 2.04 1.85E−02 EEF1G 2.02 8.25E−03 DENND2A 2.01 5.43E−03 RPSA 2.01 7.73E−06 PRKAR1A 2.01 3.58E−03 LCAT 2.01 9.99E−08 C1QB 2.00 1.60E−05 PROCR 2.00 4.29E−06 MYH13 1.98 1.77E−02 NME2 1.95 1.43E−03 PGLYRP2 1.95 7.91E−09 SDC4 1.94 2.60E−03 PTPN6 1.94 2.68E−04 C1RL 1.93 1.91E−04 AFM 1.92 4.17E−06 B4GALT1 1.92 9.83E−03 CNTFR 1.92 4.02E−04 HSPE1-MOB4 1.92 3.09E−02 COL18A1 1.91 1.23E−02 ARF6 1.91 7.99E−03 ACOT7 1.91 4.52E−04 ROBO4 1.90 1.22E−03 CAPZA2 1.90 5.23E−02 CLIC4 1.90 3.52E−03 RAB8B 1.89 1.57E−02 PFN1 1.89 5.10E−06 APRT 1.88 1.18E−02 RBP4 1.87 4.24E−04 ACTR3 1.87 2.56E−02 MYL6 1.86 2.32E−04 CD82 1.86 1.27E−03 PDCD6IP 1.86 3.88E−06 ARHGAP6 1.86 2.73E−02 ADCY5 1.86 1.09E−04 SDC1 1.85 3.15E−05 C1QC 1.85 1.71E−04 ITGA6 1.82 6.75E−06 GMPR 1.82 2.99E−02 VNN1 1.82 2.85E−05 TUBA4A 1.82 7.14E−03 GPNMB 1.81 1.32E−02 GGH 1.81 6.85E−05 NUTF2 1.80 6.20E−04 CDH5 1.79 3.11E−04 INF2 1.79 2.52E−02 OSMR 1.78 2.41E−04 AHSG 1.77 2.67E−07 RPL4 1.76 2.48E−02 PDE4DIP 1.75 1.35E−07 RALB 1.74 1.20E−05 TBC1D2 1.74 2.92E−02 EHD3 1.73 1.45E−04 EIF3K 1.73 1.38E−02 C1R 1.73 5.18E−05 IGHG4 1.71 3.10E−04 LGALSL 1.71 1.49E−06 LIPT1 1.71 4.62E−02 WDR48 1.70 4.83E−05 FARP1 1.70 8.11E−03 RAB11B 1.69 2.80E−02 UNC13D 1.69 2.60E−02 PAFAH1B1 1.69 9.85E−04 IGKV6D-21 1.68 5.48E−04 ARPC1B 1.67 3.51E−03 LCP2 1.67 9.04E−03 TUBB1 1.67 5.82E−04 CDH13 1.64 3.23E−03 AHCY 1.64 1.06E−02 SLC22A23 1.64 3.11E−04 GANAB 1.63 3.25E−06 SELL 1.63 2.53E−07 PRPH2 1.63 2.30E−05 PYGB 1.62 1.12E−04 CLIC1 1.62 3.58E−04 MYO15A 1.60 1.45E−04 TMC8 1.60 1.06E−02 LOXL2 1.60 8.00E−04 APOE 1.58 3.45E−04 RPL11 1.57 1.32E−02 RAP1B 1.57 2.29E−03 FGA 1.56 8.45E−05 RAB8A 1.56 4.90E−03 GSTO1 1.56 1.40E−03 LRG1 1.55 1.69E−04 UBA52 1.54 7.44E−05 HLA-A 1.54 4.79E−02 CD14 1.54 3.09E−04 CALM3 1.53 1.38E−04 RHOA 1.53 8.42E−05 ITGA5 1.51 2.00E−06 HPX 1.51 5.50E−05 APOA2 1.50 2.40E−02 NEBL 1.50

6.28E−03 CCT4 1.50 1.65E−04 LRP1 1.49 1.91E−04 TEX35 1.49 1.11E−04 ARPC4 1.48 2.63E−04 LPA 1.48 7.69E−05 OBSCN 1.47 3.86E−03 ACE 1.47 6.26E−03 CALR 1.46 9.54E−03 HP 1.46 4.00E−04 TUBB4B 1.45 4.15E−07 MAPRE2 1.45 6.84E−04 ILK 1.43 1.31E−06 LAMC2 1.43 1.05E−02 YWHAG 1.43 1.25E−03 SERPINA6 1.42 8.01E−07 FUCA2 1.41 3.97E−04 PCOLCE 1.41 2.17E−03 POTEJ 1.40 9.12E−04 MCAM 1.40 6.43E−05 MYH9 1.40 1.46E−05 LBP 1.40 2.72E−03 DSTN 1.38 7.18E−05 DYNC1H1 1.38 1.11E−05 YWHAZ 1.38 1.22E−06 FERMT3 1.37 6.62E−06 PPIA 1.37 6.55E−05 APMAP 1.35 1.77E−02 PI16 1.34 7.66E−07 A1BG 1.33 5.52E−08 DNAJB2 1.33 2.80E−02 EDIL3 1.33 2.07E−03 PSMB4 1.33 3.52E−02 APP 1.33 4.69E−05 CAP1 1.33 1.24E−04 PRKDC 1.31 1.33E−04 CACNA2D1 1.31 1.64E−03 SYK 1.31 5.47E−03 AKR7A2 1.30 2.85E−04 COL1A2 1.29 4.13E−03 FN1 1.29 2.43E−03 ZNF879 1.29 1.30E−02 RAB10 1.27 1.34E−04 SRC 1.26 2.09E−03 PVR 1.26 2.61E−03 APCS 1.26 1.19E−04 WARS1 1.26 5.38E−02 CNN2 1.25 2.34E−02 PKM 1.25 1.66E−03 PFKP 1.25 2.58E−04 GAPDH 1.25 3.31E−03 IGFALS 1.24 2.59E−02 ALDOA 1.23 4.07E−05 BCHE 1.23 1.05E−04 ALOX12 1.23 4.37E−02 HSPB1 1.23 9.90E−04 CD59 1.23 4.25E−04 CSF1R 1.22 3.24E−03 PRDX6 1.22 1.01E−03 MIF 1.22 2.05E−04 COL6A2 1.22 6.03E−06 MTAP 1.21 5.61E−03 COL6A3 1.21 1.03E−04 F10 1.21 1.34E−03 BANF1 1.21 8.40E−04 F13A1 1.19 1.39E−04 APOA4 1.19 9.01E−06 FGG 1.18 6.87E−07 SAR1A 1.17 9.11E−03 ARPC3 1.17 7.77E−04 ADAMTS12 1.16 4.03E−02 EEF2 1.15 7.16E−05 VTN 1.15 5.04E−04 C1S 1.15 1.22E−06 CETP 1.15 4.16E−03 ADH5 1.14 5.04E−03 HABP2 1.14 2.65E−02 SYNE1 1.13 5.60E−04 TIMM13 1.13 6.67E−05 APOC4-APOC2 1.13 2.40E−02 APOC3 1.13 1.88E−02 HP 1.13 1.14E−04 SPP2 1.12 2.41E−05 PPBP 1.12 2.83E−05 CC2D2B 1.12 1.48E−02 COL1A1 1.12 8.40E−04 AHNAK 1.12 2.44E−03 TPX2 1.11 4.00E−03 FBN2 1.11 1.06E−02 APOC1 1.11 1.22E−03 IGHM 1.11 1.29E−03 MASP2 1.10 3.47E−03 PGK1 1.10 1.05E−03 DIAPH1 1.09 4.53E−02 AGT 1.09 4.53E−06 CCT3 1.09 3.36E−02 DPP4 1.08 1.78E−06 CPB2 1.08 4.46E−03 PEPD 1.07 5.39E−09 BGN 1.07 6.47E−05 IDE 1.07 4.31E−05 DNAJC12 1.06 1.42E−04 PTGES3 1.06 4.09E−02 APOH 1.05 6.15E−06 CCT2 1.05 9.47E−04 ACTB 1.05 6.98E−08 MTA2 1.05 6.42E−03 MRC2 1.05 1.19E−02 TUBA1B 1.03 2.86E−04 CD5L 1.02 3.55E−04 CFHR1 1.02 1.07E−03 CTSD 1.01 1.49E−03 FCGBP 1.01 9.17E−04 ARF3 1.00 6.70E−04 CAPZB 1.00 1.91E−03

TABLE-US-00020 TABLE 20 Proteins significantly more abundant in AD-MSC EVs compared to HMC-EVs Name log 2 fold difference P-Value TMEM198 −6.91 6.10E−12 ARMCX5 −6.41 1.83E−02 SH3BGRL −4.93 2.45E−06 CAT −4.70 4.13E−07 CEP290 −4.35 2.28E−09 TAS2R33 −4.18 4.86E−03 ALB −4.13 3.11E−05 KRT81 −4.04 2.94E−07 ADIPOQ −3.99 3.32E−04 SEMA7A −3.95 5.59E−07 SPON2 −3.94 3.38E−04 CHST9 −3.93 2.60E−08 IGHV1-45 −3.90 7.40E−03 CD109 −3.78 2.49E−09 NEO1 −3.70 5.61E−06 IQGAP2 −3.68 4.59E−07 SURF1 −3.66 3.77E−09 SEPTIN6 −3.58 2.10E−08 LTF −3.57 6.82E−03 ZNF800 −3.56 8.17E−09 ERC1 −3.46 6.65E−05 ITPR3 −3.44 7.92E−07 MSH6 −3.37 2.76E−03 OLFML3 −3.30 7.36E−03 ALB −3.24 8.12E−06 HAUS6 −3.23 1.89E−03 PAK6 −3.16 2.33E−03 PRDX2 −3.16 1.33E−05 AKAP9 −3.12 5.02E−04 HAUS8 −3.11 9.58E−07 ALOX5 −3.08 9.38E−07 PRKACB −3.07 5.34E−03 CDSN −3.05 2.49E−03 SLC9A4 −3.04 1.49E−08 LRRTM2 −3.00 1.13E−04 ALX4 −2.99 1.46E−06 GPR179 −2.97 1.08E−07 CYLC2 −2.93 5.87E−07 DSC1 −2.91 2.21E−08 NBEAL2 −2.90 4.83E−05 DDX55 −2.78 7.01E−11 SYMPK −2.77 7.34E−08 L1TD1 −2.77 5.98E−08 QDPR −2.76 1.82E−04 C6 −2.76 2.19E−12 RGS14 −2.72 2.47E−03 CNDP1 −2.68 4.27E−10 LRAT −2.62 5.70E−03 LAMB4 −2.61 1.47E−04 F11 −2.59 9.76E−08 RPS6KA4 −2.55 7.87E−03 MOGS −2.51 3.62E−02 IGLV6-57 −2.50 6.55E−03 CCDC178 −2.50 9.07E−03 ATP10A −2.49 1.15E−04 SLC24A4 −2.49 7.62E−03 PHF24 −2.47 1.84E−05 SNX14 −2.44 3.37E−06 DCN −2.43 2.90E−04 IGHV1-8 −2.43 1.58E−02 VCP −2.41 9.84E−06 OAF −2.39 1.15E−03 COG2 −2.39 3.26E−02 TRIM4 −2.38 7.87E−03 GTF2IRD2 −2.37 1.81E−08 TRIM7 −2.35 4.33E−06 NID2 −2.33 3.79E−06 RPL13A −2.30 3.89E−02 TNFAIP6 −2.30 1.08E−05 IGLL1 −2.25 1.61E−03 GMFG −2.21 4.87E−03 DBH −2.21 3.65E−02 SERPINB12 −2.20 3.30E−02 PSMA7 −2.18 1.94E−08 TIMP2 −2.17 1.70E−03 IGHV5-51 −2.11 3.25E−07 RACK1 −2.09 8.66E−06 APLP2 −2.05

5.38E−03 IGHV1-69D −2.02 6.38E−03 KRT16 −2.02 1.24E−04 IGHV2-26 −2.00 7.32E−05 CAPN5 −2.00 6.65E−07 PSMA6 −1.97 5.32E−02 IGHG1 −1.97 1.83E−07 IGHG2 −1.95 2.21E−07 CCT6A −1.93 3.26E−05 GP6 −1.93 1.75E−02 C18orf63 −1.88 9.55E−06 ANO7 −1.88 3.89E−08 IGLV4-60 −1.87 3.29E−02 XYLT1 −1.84 3.86E−03 FAM180A −1.81 7.96E−04 LYVE1 −1.81 1.23E−02 ERFL −1.78 2.65E−09 CRTAP −1.78 1.15E−02 MYCBP2 −1.76 4.22E−03 SCIN −1.75 6.38E−08 FBLN5 −1.73 1.16E−02 ITGAV −1.73 1.17E−04 KIF5C −1.71 5.47E−09 ZNF488 −1.70 1.01E−04 ITIH1 −1.70 1.95E−06 PDZK1P1 −1.70 7.05E−04 SBSN −1.69 1.58E−02 FBRSL1 −1.68 1.87E−04 CHL1 −1.67 3.00E−04 TF −1.66 1.67E−05 COL3A1 −1.66 5.22E−02 MMP1 −1.63 4.10E−04 GRIN2C −1.62 2.48E−02 CAMP −1.61 4.54E−05 BLMH −1.58 5.24E−04 ADA −1.55 2.61E−06 ALB −1.54 3.86E−07 TIMP3 −1.53 1.81E−03 HK1 −1.49 9.51E−07 LCN1 −1.47 4.32E−03 TGM1 −1.44 4.86E−02 COMP −1.44 1.07E−05 SLC26A11 −1.40 2.30E−03 IGLV3-9 −1.39 8.77E−08 IGLV3-21 −1.39 4.11E−07 VPS13A −1.37 2.81E−05 IGHV1-69 −1.35 4.84E−05 PRXL2B −1.34 2.79E−02 IGHA2 −1.33 3.04E−03 CPQ −1.33 1.19E−08 PAICS −1.31 2.83E−04 ABCC4 −1.28 5.62E−07 IGHV3-74 −1.28 6.09E−05 IGKV1D-16 −1.26 2.09E−03 DNAH11 −1.26 1.07E−04 IGKV1D-39 −1.25 2.39E−02 ZGRF1 −1.24 1.53E−06 TGFB1 −1.21 1.31E−04 DCD −1.20 1.97E−04 KRT9 −1.20 4.97E−09 IGHV4-4 −1.20 9.57E−03 XPNPEP2 −1.19 3.50E−03 PKP1 −1.16 9.92E−05 RASGRP2 −1.16 8.93E−04 CLEC3B −1.15 9.25E−04 LRP1B −1.14 3.59E−02 IGKV3D-15 −1.13 2.04E−05 ATAD2 −1.13 2.38E−03 IGHV5-10-1 −1.12 6.47E−05 TPM4 −1.11 3.11E−06 KRT2 −1.10 9.67E−08 IGHD −1.10 8.57E−06 IGHV3-43 −1.09 2.07E−04 PATJ −1.09 9.49E−03 ZNF425 −1.08 5.60E−02 IGHV1OR15-1 −1.08 3.68E−03 CCDC180 −1.04 1.48E−04 EIF4A1 −1.03 3.56E−04 IGLV3-25 −1.03 1.36E−06 F13B −1.02 2.69E−02 MSN −1.01 3.22E−06 CSTA −1.01 6.82E−07 FAM47E-STBD1 −1.00 4.16E−05

Example 14. smRNAseq Profiling for HMC Cells Vs HMC-EVs

[0442] HMCs were generated from the same bank of frozen hemangioblasts described in Example 1. HMCs were generated and passaged up to six passages (P6) according to the method described in Example 1. Extracellular vesicles (EVs) were purified from HMCs (HMC-EVs) by tangential flow filtration (TFF). smRNAseq profiling was performed for HMC-EVs (n=3) and HMCs (n=3).

[0443] Table 21 shows smRNAs that were more highly abundant in the HMC-EVs compared with HMCs. Table 22 shows smRNAs that were more highly abundant in the HMCs compared with HMC-EVs.

TABLE-US-00021 TABLE 21 miRNAs with higher levels in HMC-EVs compared to HMCs miRNA ID Fold difference P value hsa-miR-1290 −3237.80 0 hsa-miR-122-5p −2697.49 6.83E−40 hsa-miR-223-3p −1451.47 1.70E−20 hsa-miR-338-5p −1191.28 1.44E−19 hsa-miR-451a −672.00 3.99E−26 hsa-miR-320c −513.86 0 hsa-miR-1246 −485.03 0 hsa-miR-320d −447.23 0 hsa-miR-9-3p −333.60 1.98E−12 hsa-miR-139-3p −282.32 4.45E−12 hsa-miR-150-5p −268.41 8.85E−12 hsa-miR-423-5p −253.84 0 hsa-miR-4516 −241.56 4.44E−11 hsa-miR-4433b-5p −235.62 5.88E−11 hsa-miR-223-5p −222.70 9.27E−11 hsa-miR-3138 −213.62 3.87E−17 hsa-miR-4433b-3p −184.67 9.31E−10 hsa-miR-11400 −170.22 1.16E−09 hsa-miR-486-5p −159.91 0 hsa-miR-4738-3p −135.10 7.01E−10 hsa-miR-5010-5p −130.91 1.30E−08 hsa-miR-144-3p −126.67 2.43E−08 hsa-miR-664a-5p −124.89 0 hsa-miR-432-5p −122.75 0 hsa-miR-6809-5p −117.30 1.35E−07 hsa-miR-320b −110.63 0 hsa-miR-4659b-3p −99.06 2.55E−06 hsa-miR-139-5p −89.21 4.42E−08 hsa-miR-142-5p −82.36 0 hsa-miR-320e −79.30 4.88E−14 hsa-miR-363-3p −76.09 2.75E−27 hsa-miR-1273h-5p −75.36 2.36E−06 hsa-miR-3679-5p −67.01 2.62E−24 hsa-miR-584-5p −63.66 0 hsa-miR-2110 −62.37 0 hsa-miR-6877-5p −59.41 5.22E−05 hsa-miR-6862-5p −58.09 4.50E−05 hsa-miR-766-5p −55.73 2.21E−08 hsa-miR-4446-3p −51.85 6.66E−06 hsa-miR-5187-5p −49.91 0.000222 hsa-miR-544b −47.93 0.000163 hsa-miR-320a-3p −47.66 0 hsa-miR-6515-5p −46.42 1.83E−05 hsa-miR-342-5p −43.34 2.57E−20 hsa-miR-338-3p −43.19 0.000301 hsa-miR-3154 −41.01 0.000725 hsa-miR-193b-5p −40.02 0 hsa-miR-628-3p −39.55 0 hsa-miR-4429 −36.37 0.000548 hsa-miR-6837-5p −36.33 7.33E−05 hsa-miR-7849-3p −35.48 0.004653 hsa-miR-122-3p −34.71 0.001147 hsa-miR-6866-5p −32.18 0.001507 hsa-miR-6735-5p −31.29 0.00492 hsa-miR-

4743-5p −30.88 0.001291 hsa-miR-3177-3p −30.77 5.76E−21 hsa-miR-7854-3p −28.89 1.52E−05 hsa-miR-6852-5p −28.85 5.35E−12 hsa-miR-126-5p −28.31 0 hsa-miR-1908-5p −26.94 2.76E−17 hsa-miR-323b-3p −26.80 0 hsa-miR-2276-3p −26.68 0.005841 hsa-miR-142-3p −26.63 0.000857 hsa-miR-3175 −26.50 0.002484 hsa-miR-5189-5p −26.30 0.001287 hsa-miR-616-3p −26.22 2.88E−05 hsa-miR-144-5p −26.09 0.000808 hsa-miR-4667-5p −25.94 0.000963 hsa-miR-483-5p −25.40 0 hsa-miR-877-5p −23.99 0 hsa-miR-204-3p −23.92 0.012059 hsa-miR-126-3p −23.32 0 hsa-miR-7856-5p −23.28 0.004825 hsa-miR-1273h-3p −23.10 0.004919 hsa-let-7b-5p −22.10 0 hsa-miR-433-3p −21.75 1.59E−09 hsa-miR-3161 −20.29 0.010391 hsa-miR-146a-5p −20.17 0 hsa-miR-1-3p −20.10 0 hsa-miR-6131 −19.93 0.010871 hsa-miR-1262 −18.98 1.96E−18 hsa-miR-10399-5p −18.72 5.36E−15 hsa-miR-5584-5p −18.07 0.013828 hsa-miR-3126-5p −17.58 7.88E−06 hsa-miR-4804-5p −17.11 1.74E−05 hsa-miR-335-5p −17.04 0 hsa-miR-95-3p −16.80 0.005371 hsa-miR-148a-3p −16.41 0 hsa-miR-23b-5p −15.34 6.38E−39 hsa-miR-10b-3p −15.11 0.002094 hsa-miR-3125 −14.93 0.001865 hsa-miR-3187-3p −14.48 7.00E−05 hsa-miR-760 −14.46 1.14E−07 hsa-miR-942-3p −14.12 1.30E−06 hsa-miR-10526-3p −13.89 0.008759 hsa-miR-548j-3p −13.31 0.014203 hsa-miR-3960 −13.13 0.004868 hsa-miR-5189-3p −13.00 0.011457 hsa-miR-4647 −12.61 0.004701 hsa-miR-3622a-5p −12.43 0.001639 hsa-miR-4662a-5p −12.21 2.37E−08 hsa-miR-1299 −12.13 0.000244 hsa-miR-10a-3p −10.83 5.92E−08 hsa-miR-1270 −10.52 6.89E−38 hsa-let-7c-5p −10.37 0 hsa-miR-3944-5p −9.06 0.00445 hsa-miR-3605-5p −8.98 2.29E−17 hsa-miR-3120-3p −8.97 0.003762 hsa-miR-1180-3p −8.79 7.93E−34 hsa-miR-758-5p −8.33 2.17E−05 hsa-miR-3928-3p −8.18 6.01E−05 hsa-miR-7706 −8.02 2.68E−21 hsa-miR-10399-3p −7.86 0.012167 hsa-miR-182-5p −7.30 0 hsa-miR-485-5p −7.05 1.78E−11 hsa-miR-574-5p −6.67 0 hsa-miR-505-5p −6.42 2.25E−07 hsa-miR-1843 −6.34 3.29E−18 hsa-miR-3934-5p −6.20 7.24E−07 hsa-miR-543 −6.20 6.64E−15 hsa-miR-654-5p −5.92 1.94E−06 hsa-miR-421 −5.90 1.68E−44 hsa-miR-23a-5p −5.90 0.002561 hsa-miR-548e-3p −5.88 1.03E−24 hsa-miR-4645-3p −5.71 0.010916 hsa-miR-25-5p −5.55 1.87E−12 hsa-miR-196b-5p −5.35 0.009427 hsa-miR-3140-3p −5.18 0.010278 hsa-miR-1301-3p −5.16 2.63E−36 hsa-miR-4435 −5.13 0.006987 hsa-miR-889-3p −5.02 0 hsa-miR-744-5p −5.01 0 hsa-miR-148a-5p −4.74 8.33E−05 hsa-miR-486-3p −4.74 0.005596 hsa-miR-125a-3p −4.61 7.80E−30 hsa-miR-323a-3p −4.60 1.49E−25 hsa-miR-1292-5p −4.44 0.000159 hsa-miR-10b-5p −4.38 0 hsa-miR-365b-5p −4.37 0.000148 hsa-miR-193a-5p −4.35 2.27E−29 hsa-miR-10527-5p −4.35 0.002016 hsa-miR-134-5p −4.20 2.31E−25 hsa-miR-423-3p −4.02 2.84E−34 hsa-miR-3129-5p −4.00 8.78E−05 hsa-miR-942-5p −3.96 7.75E−05 hsa-miR-16-2-3p −3.80 1.32E−22 hsa-miR-101-3p −3.75 0 hsa-miR-495-3p −3.74 1.64E−07 hsa-miR-92b-5p −3.67 0.000132 hsa-miR-369-3p −3.62 5.98E−06 hsa-miR-1197 −3.51 0.003072 hsa-miR-382-5p −3.49 2.65E−15 hsa-miR-1285-3p −3.42 7.67E−06 hsa-miR-30a-3p −3.13 3.03E−18 hsa-miR-656-3p −3.10 2.82E−05 hsa-miR-589-5p −2.99 0 hsa-miR-128-3p −2.99 0 hsa-miR-409-3p −2.95 0 hsa-miR-215-5p −2.83 0.000243 hsa-miR-378i −2.81 0.003797 hsa-miR-382-3p −2.78 4.02E−08 hsa-miR-185-5p −2.52 0 hsa-let-7d-5p −2.50 5.51E−43 hsa-let-7e-5p −2.48 0 hsa-miR-576-3p −2.45 9.25E−09 hsa-miR-652-3p −2.41 4.86E−09 hsa-miR-10a-5p −2.34 3.29E−25 hsa-miR-1304-3p −2.29 1.16E−05 hsa-miR-28-3p −2.25 0 hsa-miR-92a-3p −2.15 6.94E−09 hsa-let-7d-3p −2.15 0.000249 hsa-miR-330-3p −2.07 3.20E−11 hsa-miR-629-5p −1.84 0.000424 hsa-miR-424-3p −1.82 5.89E−08 hsa-miR-30e-3p −1.78 2.84E−06 hsa-miR-378a-3p −1.78 7.49E−23 hsa-miR-146b-5p −1.71 2.30E−20 hsa-miR-654-3p −1.68 4.70E−19 hsa-miR-224-5p −1.64 1.42E−13 hsa-miR-106b-3p −1.59 1.10E−08

TABLE-US-00022 TABLE 22 miRNAs with higher levels in HMC cells compared to HMC-EVs miRNA ID Fold difference P value hsa-miR-5701 347.64 9.55E−14 hsa-miR-500a-5p 93.58 3.69E−08 hsa-miR-145-5p 78.86 0 hsa-miR-7974 76.40 2.30E−11 hsa-miR-4521 71.20 3.38E−07 hsa-miR-137-3p 55.66 1.57E−09 hsa-miR-152-5p 54.93 2.47E−06 hsa-miR-1260a 46.60 0 hsa-miR-483-3p 44.67 1.22E−05 hsa-miR-12135 42.22 2.94E−05 hsa-miR-548i 42.02 2.14E−05 hsa-miR-140-5p 41.64 1.64E−13 hsa-miR-5100 36.65 5.81E−05 hsa-miR-190a-5p 31.23 0.000258 hsa-miR-153-3p 31.17 0.000223 hsa-miR-27a-5p 29.93 4.85E−28 hsa-miR-500b-5p 27.87 0.000394

hsa-let-7c-3p 27.31 0.000354 hsa-miR-4286 25.72 1.00E−34 hsa-miR-374b-3p 25.68 0.000161 hsa-miR-218-5p 24.79 1.43E−13 hsa-miR-331-3p 19.83 9.12E−41 hsa-miR-301b-3p 19.57 0.002357 hsa-miR-188-3p 19.51 0.002865 hsa-miR-18a-5p 18.74 4.22E−10 hsa-miR-874-5p 18.67 0.003373 hsa-miR-105-5p 18.22 0.003366 hsa-miR-31-3p 17.35 3.79E−06 hsa-let-7a-2-3p 16.87 0.001668 hsa-miR-21-3p 16.43 9.09E−13 hsa-miR-210-5p 16.37 0.005401 hsa-miR-2277-5p 16.24 0.002077 hsa-miR-450a-1-3p 15.87 0.007502 hsa-miR-296-5p 15.50 0.008142 hsa-miR-1260b 14.94 0 hsa-miR-193a-3p 14.50 0.009837 hsa-miR-212-3p 14.40 0.010622 hsa-miR-130a-5p 14.39 0.000405 hsa-miR-542-3p 14.09 5.25E−39 hsa-miR-125a-5p 13.32 0 hsa-miR-7-5p 13.03 0 hsa-miR-4497 13.02 0.015303 hsa-miR-454-3p 12.59 1.99E−08 hsa-miR-21-5p 12.45 0 hsa-miR-570-3p 11.59 0.009332 hsa-miR-424-5p 11.54 0 hsa-miR-132-5p 11.48 4.52E−07 hsa-miR-125b-5p 11.40 0 hsa-miR-7977 11.37 3.36E−44 hsa-miR-34b-3p 11.18 0.010197 hsa-miR-93-5p 10.73 0 hsa-miR-199a-5p 10.58 0 hsa-miR-197-3p 10.19 3.63E−29 hsa-miR-210-3p 9.66 2.56E−05 hsa-miR-221-5p 9.28 0 hsa-miR-582-5p 9.09 1.82E−10 hsa-miR-99b-5p 8.87 0 hsa-miR-3940-3p 8.72 0.000688 hsa-miR-103a-3p 8.70 0 hsa-miR-34a-5p 8.49 4.14E−33 hsa-miR-143-5p 8.47 3.58E−38 hsa-miR-31-5p 8.34 0 hsa-miR-24-2-5p 8.30 2.00E−22 hsa-miR-452-5p 8.25 6.71E−22 hsa-miR-874-3p 8.15 9.71E−42 hsa-miR-145-3p 8.03 0 hsa-miR-143-3p 7.80 0 hsa-miR-365a-3p 7.70 0 hsa-miR-365b-3p 7.70 0 hsa-miR-3613-5p 7.52 2.97E−06 hsa-miR-33b-3p 7.50 0.001136 hsa-miR-708-5p 7.45 0 hsa-miR-17-3p 7.22 8.22E−05 hsa-miR-1296-5p 7.12 2.14E−05 hsa-miR-27a-3p 7.11 0 hsa-miR-17-5p 6.83 0 hsa-miR-2682-5p 6.75 1.73E−06 hsa-miR-148b-5p 6.70 6.49E−05 hsa-let-7a-3p 6.38 4.34E−42 hsa-miR-576-5p 6.38 0.000384 hsa-miR-181a-3p 6.36 0 hsa-miR-665 6.33 9.58E−06 hsa-miR-3130-5p 6.30 0.015272 hsa-let-7i-3p 6.19 0.010866 hsa-miR-30e-5p 5.99 0 hsa-miR-30a-5p 5.99 0 hsa-let-7i-5p 5.79 0 hsa-let-7g-5p 5.79 0 hsa-miR-335-3p 5.60 0 hsa-miR-425-5p 5.56 0 hsa-miR-4454 5.55 6.45E−30 hsa-miR-20a-5p 5.46 0 hsa-miR-34a-3p 5.45 0.010285 hsa-miR-29a-3p 5.42 0 hsa-miR-362-5p 5.39 1.42E−15 hsa-miR-708-3p 5.37 9.33E−20 hsa-miR-342-3p 5.25 0 hsa-miR-193b-3p 5.19 1.77E−23 hsa-miR-301a-5p 5.12 3.39E−05 hsa-miR-15b-5p 5.08 0 hsa-miR-34c-5p 5.07 0 hsa-miR-345-5p 5.06 1.40E−45 hsa-miR-4636 4.99 0.010845 hsa-miR-374b-5p 4.80 1.90E−33 hsa-miR-12136 4.80 0.012744 hsa-miR-4326 4.71 1.35E−05 hsa-miR-374a-3p 4.69 1.22E−39 hsa-miR-29c-5p 4.54 0.01528 hsa-miR-15a-5p 4.46 1.46E−11 hsa-miR-103a-2-5p 4.43 7.59E−06 hsa-miR-450a-5p 4.42 0 hsa-miR-411-5p 4.31 3.39E−35 hsa-miR-3158-3p 4.22 0.000646 hsa-miR-3117-3p 4.20 0.00018 hsa-miR-409-5p 4.16 0 hsa-miR-548w 4.11 0.007376 hsa-miR-532-3p 4.06 1.86E−05 hsa-miR-106a-5p 4.06 0.000408 hsa-miR-374a-5p 4.03 1.22E−19 hsa-miR-9903 4.03 0.014869 hsa-miR-181b-3p 3.99 1.83E−09 hsa-miR-214-3p 3.83 0 hsa-miR-99a-5p 3.83 0 hsa-miR-671-5p 3.80 5.71E−07 hsa-let-7e-3p 3.76 0.00696 hsa-miR-100-5p 3.74 0 hsa-miR-106b-5p 3.71 1.27E−09 hsa-miR-339-5p 3.70 1.04E−08 hsa-miR-16-5p 3.69 0 hsa-miR-376c-3p 3.63 0.007115 hsa-miR-582-3p 3.52 0.007728 hsa-miR-561-5p 3.51 0.000356 hsa-miR-30b-5p 3.50 0 hsa-miR-500a-3p 3.24 3.86E−32 hsa-miR-381-3p 3.17 9.94E−05 hsa-miR-130b-5p 3.17 0 hsa-miR-130a-3p 3.09 3.31E−07 hsa-let-7f-1-3p 3.09 0.008094 hsa-miR-194-5p 3.08 3.68E−11 hsa-miR-502-3p 3.08 4.76E−14 hsa-miR-32-5p 3.07 0.015461 hsa-miR-5094 3.06 0.007148 hsa-miR-125b-2-3p 2.98 1.04E−07 hsa-miR-625-3p 2.95 1.48E−11 hsa-miR-379-5p 2.91 1.68E−09 hsa-miR-484 2.82 0 hsa-miR-138-5p 2.80 1.76E−16 hsa-miR-148b-3p 2.78 0 hsa-miR-27b-3p 2.75 0 hsa-miR-19b-3p 2.66 1.11E−19 hsa-miR-30c-5p 2.63 3.60E−34 hsa-miR-22-3p 2.63 3.16E−33 hsa-miR-221-3p 2.62 0 hsa-miR-183-5p 2.58 0.000322 hsa-miR-214-5p 2.56 3.02E−05 hsa-miR-2355-5p 2.55 0.000159 hsa-miR-29b-3p 2.48 2.65E−05 hsa-miR-149-5p 2.40 2.02E−05 hsa-miR-4677-3p 2.34 6.76E−06 hsa-miR-98-5p 2.32 1.53E−19 hsa-miR-361-3p 2.30 3.19E−06 hsa-miR-181a-2-3p 2.29 2.46E−17 hsa-miR-370-3p 2.26 4.89E−07 hsa-miR-140-3p 2.19 1.90E−25 hsa-miR-574-3p 2.16 2.43E−06 hsa-miR-127-3p 2.13 1.73E−28 hsa-miR-28-5p 2.11 8.76E−18 hsa-miR-181c-3p 2.03 8.80E−09 hsa-miR-24-3p 2.02 1.08E−28 hsa-miR-136-3p 2.00 1.84E−06 hsa-miR-107 2.00 0.000144 hsa-miR-199b-5p 1.99 7.66E−26 hsa-miR-26b-5p 1.91 1.80E−17 hsa-miR-191-5p 1.87 1.08E−22 hsa-miR-450b-5p 1.81 1.76E−07 hsa-miR-30d-5p 1.69 2.65E−42 hsa-miR-339-3p 1.66 0.008601 hsa-miR-23b-3p 1.64

3.63E−18 hsa-miR-769-5p 1.51 0.000511

[0444] While the foregoing description and figures represent exemplary embodiments of the present disclosure, it will be understood that various additions, modifications and substitutions may be made therein without departing from the spirit and scope and range of equivalents of the accompanying claims. In particular, it will be clear to those skilled in the art that the presently disclosed subject matter may be embodied in other forms, structures, arrangements, and with other elements, materials, and components, without departing from the spirit or essential characteristics thereof. In addition, numerous variations in the methods/processes described herein may be made within the scope of the present disclosure without departing from the principles described herein. The presently disclosed embodiments are therefore to be considered in all respects as illustrative and not restrictive. The appended claims should be construed broadly, to include other variants and embodiments of the disclosure, which may be made by those skilled in the art without departing from the scope and range of equivalents.

Claims

1. A method of treating a brain injury in a subject suffering from, or suspected of suffering from, a brain injury, the method comprising administering to the subject an effective amount of extracellular vesicles (EVs) secreted from mesenchymal stem cells (HMCs) obtained by in vitro differentiation of pluripotent stem cells, thereby treating the brain injury in the subject.

2. The method of claim 1, wherein the brain injury is selected from the group consisting of stroke, optic neuropathy, traumatic brain injury, cerebral palsy, acquired brain injury, anoxic brain injury, diffuse axonal brain injury, focal brain injury, subdural hematoma, brain aneurysm, and coma.

3. The method of claim 2, wherein the brain injury is stroke.

4. The method of any one of claims 1-3, wherein the method comprises increasing oligodendrocyte and precursor cells in the brain following administration of the EVs secreted from the HMCs (HMC-EVs) into the subject.

5. The method of any one of claims 1-3, wherein the method comprises preserving myelin in the brain following administration of the HMC-EVs into the subject.

6. The method of any one of claims 1-3, wherein the method comprises preventing oxidative damage in neurons following administration of the HMC-EVs into the subject.

7. The method of any one of claims 1-3, wherein the method comprises preventing neuronal death due to glutamate excitotoxicity injury following administration of the HMC-EVs into the subject.

8. The method of any one of claims 1-3, wherein the method comprises reducing tissue loss in the brain following administration of the HMC-EVs into the subject.

9. The method of any one of claims 1-3, wherein the method comprises reducing cell death in the brain following administration of the HMC-EVs into the subject.

10. The method of any one of claims 1-3, wherein the method comprises stimulating pathways involved in the development of neuronal lineage following administration of the HMC-EVs into the subject.

11. The method of any one of claims 1-10, wherein the HMC-EVs are administered systemically.

12. The method of any one of claims 1-10, wherein the HMC-EVs are administered intracerebrally.

13. The method of any one of claims 1-10, wherein the HMC-EVs are administered intrathecally.

14. The method of any one of claims 1-10, wherein the HMC-EVs are administered intracisternally.

15. The method of any one of claims 1-10, wherein the HMC-EVs are administered intraperitoneally.

16. The method of any one of claims 1-15, wherein the subject is a human.

17. The method of any one of claims 1-16, wherein the HMCs are obtained by in vitro differentiation of human pluripotent stem cells.

18. The method of any one of claims 1-17, wherein the pluripotent stem cells are further

differentiated into hemangioblasts.
19. The method of any one of claims 1-18, wherein the pluripotent stem cells are embryonic stem cells.
20. The method of any one of claims 1-18, wherein the pluripotent stem cells are induced pluripotent stem cells.
21. The method of claim 20, wherein the induced pluripotent stem cells are produced by contacting a cell with one or more reprogramming factors.
22. The method of any one of claims 1-21, wherein the HMC-EVs express at least one of the miRNA in Table 9 at a higher level compared to EVs secreted from umbilical cord blood-derived mesenchymal stem cells (UCB-MSC-EVs).
23. The method of any one of claims 1-22, wherein the HMC-EVs express at least one of the miRNA in Table 10 at a lower level compared to UCB-MSC-EVs.
24. The method of any one of claims 1-23, wherein the HMC-EVs express at least one of the miRNA in Table 11 at a higher level compared to EVs secreted from bone marrow-derived mesenchymal stem cells (BM-MSC-EVs).
25. The method of any one of claims 1-24, wherein the HMC-EVs express at least one of the miRNA in Table 12 at a lower level compared to BM-MSC-EVs.
26. The method of any one of claims 1-25, wherein the HMC-EVs express at least one of the miRNA in Table 13 at a higher level compared to EVs secreted from adipose tissue-derived mesenchymal stem cells (AD-MSC-EVs).
27. The method of any one of claims 1-26, wherein the HMC-EVs express at least one of the miRNA in Table 14 at a lower level compared to AD-MSC-EVs.
28. The method of any one of claims 1-27, wherein the HMC-EVs express at least one of the proteins in Table 15 at a higher level compared to UCB-MSC-EVs.
29. The method of any one of claims 1-28, wherein the HMC-EVs express at least one of the proteins in Table 16 at a lower level compared to UCB-MSC-EVs.
30. The method of any one of claims 1-29, wherein the HMC-EVs express at least one of the proteins in Table 17 at a higher level compared to BM-MSC-EVs.
31. The method of any one of claims 1-30, wherein the HMC-EVs express at least one of the proteins in Table 18 at a lower level compared to BM-MSC-EVs.
32. The method of any one of claims 1-31, wherein the HMC-EVs express at least one of the proteins in Table 19 at a higher level compared to AD-MSC-EVs.
33. The method of any one of claims 1-32, wherein the HMC-EVs express at least one of the proteins in Table 20 at a lower level compared to AD-MSC-EVs.
34. The method of any one of claims 1-33, wherein the HMC-EVs express at least one of the miRNA in Table 21 at a higher level compared to the HMCs.
35. The method of any one of claims 1-34, wherein the HMC-EVs express at least one of the miRNA in Table 22 at a lower level compared to the HMCs.
36. The method of any one of claims 1-35, wherein the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
37. The method of any one of claims 1-36, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3, FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB, PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or

AD-MSC-EVs.
38. The method of any one of claims 1-37, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2R1A, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A 11, SLC44A1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
39. The method of any one of claims 1-38, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
40. The method of any one of claims 1-39, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
41. The method of any one of claims 1-40, wherein about 1×10.sup.6 to about 1×10.sup.3 HMC-EVs are administered to the subject.
42. The method of any one of claims 1-41, wherein about 10×10.sup.10 or about 30×10.sup.10 HMC-EVs are administered to the subject.
43. The method of any one of claims 1-42, wherein the HMC-EVs are administered in a pharmaceutical composition.
44. The method of claim 43, wherein the pharmaceutical composition comprises (a) a buffer, maintaining the solution at a physiological pH; (b) at least 2 mM or at least 0.05% (w/v) glucose; and (c) an osmotically active agent maintaining the solution at a physiological osmolarity.
45. The method of claim 44, wherein the glucose is D-glucose (Dextrose).
46. The method of claim 44, wherein the osmotically active agent is a salt.
47. The method of claim 46, wherein the salt is sodium chloride.
48. The method of any one of claims 1-47, further comprising administering to the subject an effective amount of HMCs obtained by in vitro differentiation of pluripotent stem cells.
49. A method of treating a brain injury in a subject suffering from, or suspected of suffering from, a brain injury, the method comprising administering to the subject an effective amount of mesenchymal stem cells (HMCs) obtained by in vitro differentiation of pluripotent stem cells, thereby treating the brain injury in the subject.
50. The method of claim 49, wherein the brain injury is selected from the group consisting of stroke, optic neuropathy, traumatic brain injury, cerebral palsy, acquired brain injury, anoxic brain injury, diffuse axonal brain injury, focal brain injury, subdural hematoma, brain aneurysm, and coma.
51. The method of claim 50, wherein the brain injury is stroke.
52. The method of any one of claims 49-51, wherein the method comprises preserving myelin in the brain following administration of the HMCs into the subject.
53. The method of any one of claims 49-51, wherein the method comprises suppressing neuroinflammatory responses following administration of the HMCs into the subject.
54. The method of any one of claims 49-51, wherein the method comprises reducing microglial and astrocyte activation in the brain following administration of the HMCs into the subject.
55. The method of any one of claims 49-51, wherein the method comprises stimulating pathways involved in cell survival following administration of the HMCs into the subject.

56. The method of any one of claims 49-51, wherein the method comprises stimulating expression of a neuroprotective gene in the brain following administration of the HMCs into the subject.
57. The method of claim 56, wherein the neuroprotective gene is selected from the group consisting of heat shock protein family B member 1 (HSPB1), insulin-like growth factor 1 (IGF2), and secreted phosphoprotein 1 (SPP1).
58. The method of any one of claims 49-51, wherein the method comprises stimulating pathways involved in synaptic transmission in the brain following administration of the HMCs into the subject.
59. The method of any one of claims 49-51, wherein the method comprises stimulating pathways involved in the development of neuronal lineage following administration of the HMCs into the subject.
60. The method of any one of claims 49-51, wherein the method comprises reducing apoptosis following administration of the HMCs into the subject.
61. The method of claim 50, wherein the brain injury is traumatic brain injury.
62. The method of claim 61, wherein the method comprises reducing tissue loss in the brain following administration of the HMCs into the subject.
63. The method of claim 61 or 62, wherein the method comprises reducing cell death in the brain following administration of the HMCs into the subject.
64. The method of any one of claims 61-63, wherein the method comprises increasing neurogenesis following the administration of the HMCs into the subject.
65. The method of any one of claims 61-64, wherein the method comprises reducing the presence of microglia and macrophages in the cortex and striatum following the administration of the HMCs into the subject.
66. The method of any one of claims 61-65, wherein the method comprises reducing inflammation of the spleen following the administration of the HMCs into the subject.
67. The method of any one of claims 61-66, wherein the method comprises migration of HMCs across the blood-brain barrier to the cortex, striatum, and/or hippocampus.
68. The method of claim 50, wherein the brain injury is cerebral palsy.
69. The method of claim 68, wherein the method comprises reducing apoptosis in the brain following administration of the HMCs into the subject.
70. The method of claim 68 or 69, wherein the method comprises reducing lesion size in the brain following administration of the HMCs into the subject.
71. The method of any one of claims 68-70, wherein the method comprises reducing microglial and astrocyte activation in the brain following administration of the HMCs into the subject.
72. The method of any one of claims 68-71, wherein the method comprises preserving myelin of the corpus callosum following administration of the HMCs into the subject.
73. The method of any one of claims 68-72, wherein the method comprises at least a partial rescue of Olig2 in the brain following administration of the HMCs into the subject.
74. The method of any one of claims 49-73, wherein the HMCs are administered systemically.
75. The method of any one of claims 49-73, wherein the HMCs are administered intracerebrally.
76. The method of any one of claims 49-73, wherein the HMCs are administered intrathecally.
77. The method of any one of claims 49-73, wherein the HMCs are administered intracisternally.
78. The method of any one of claims 49-73, wherein the HMCs are administered intraperitoneally.
79. The method of any one of claims 49-78, wherein the mesenchymal stem cells are human cells.
80. The method of any one of claims 49-79, wherein the subject is a human.
81. The method of any one of claims 49-80, wherein the pluripotent stem cells are further differentiated into hemangioblasts.
82. The method of any one of claims 49-81, wherein the pluripotent stem cells are embryonic stem cells.
83. The method of any one of claims 49-82, wherein the pluripotent stem cells are induced

pluripotent stem cells.
84. The method of any one of claims 49-83, wherein the pluripotent stem cells are human pluripotent stem cells.
85. The method of any one of claims 49-84, wherein the HMCs have been passaged no more than 5 times in vitro before administration into the subject.
86. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes in Table 3 at a higher level compared to bone marrow-derived MSCs (BM-MSCs).
87. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes in Table 4 at a lower level compared to BM-MSCs.
88. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes in Table 5 at a higher level compared to umbilical cord blood-derived MSCs (UCB-MSCs).
89. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes in Table 6 at a lower level compared to UCB-MSCs.
90. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes in Table 7 at a higher level compared to adipose tissue-derived MSCs (AD-MSCs).
91. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes in Table 8 at a lower level compared to AD-MSCs.
92. The method of any one of claims 49-85, wherein the HMCs express, in a basal state, mRNA encoding interleukin-6 (IL-6) at a level less than ten percent of the IL-6 mRNA level expressed by BM-MSCs in a basal state and wherein the HMCs express, in a basal state, mRNA encoding CD24 at a level that is greater than the CD24 mRNA level expressed by BM-MSCs in a basal state.
93. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of CALR, UBB, PKM, CXCL8, C15orf48, PSME2, TPM3, ANKRD1, PFN1, SRGN, ACTB, MDK, TAGLN2, CFL1, HSP90AA1, HSPA8, CXCL12, UCHL1, HMGA2, HMGA1, HN1, PTMA, SP90AB1, PRDX1, GSTP1, KRT18, IGFBP4, CALD1, COL4A1, COL4A2, and GAPDH at a higher level compared to AD-MSCs.
94. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of TMSB4X, ACTG1, GSTP1, KRT18, IGFBP5, NPY, KRT8, PRDX6, MDK, DKK3, UCHL1, TUBB3, HN1, PTMA, HSP90AB1, HMGA1, HSPA8, TAGLN2, ANKRD1, PFN1, CYBA, and UBB at a higher level compared to AD-MSCs.
95. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of SERPINE1, ACTA2, TPM2, CTGF, SERPINE2, CRYAB, ELN, MFGE8, ANXA2, POSTN, VIM, MFAP5, ISLR, THBS1, TIMP3, DKK1, COL6A3, COL6A1, TPT1, BCYRN1, COL1A1, SPARC, TPM1, BGN, COL1A2, COL3A1, TGFBI, CRLF1, COMP, NEAT1, MT-CO3, MT-CO2, MT-ATP8, MT-CYB, MT-CO1, MT-ATP6, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-ND3, MT-ND1, MT-ND2, GREM1, TMSB4X, ITGB1, LMNA, H2AFZ, FTL, EEF1G, NPM1, EEF1A1, RACK1, ACTG1, and TPM4 at a lower level compared to AD-MSCs.
96. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of SERPINE1, S100A6, CD59, POSTN, VIM, MFAP5, ISLR, THBS1, COL6A3, TIMP3, ELN, ANXA2, COL1A1, BCYRN1, CCDC80, COL6A1, COL6A2, BGN, COL1A2, COL3A1, TGFB1, CRLF1, COMP, and GREM1 at a lower level compared to AD-MSCs.
97. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of MT1X, MT1G, TMSB10, CCL8, INHBA, CTSB, SERPINB2, ADM, APOL1, FTH1, CCL2, CCL5, CSF1, IL1B, IGFBP3, P4HB, DCN, FSTL1, ANXA5, LOX, CD63, CTSZ, FN1, LGALS1, LDHA, RCN3, MMP2, and TIMP1 at a lower level compared to AD-MSCs.
98. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of PPIA, NPM1, HNRNPA1, IGFBP5, KRT19, KRT18, GSTP1,

TUBB, TUBA IB, KRT8, HN1, PTMA, TUBA1C, HSPA8, HMGA1, CFL1, MYL6, ACTB, UCHL1, TAGLN2, MDK, GREM1, MMP1, and CTSC at a higher level compared to BM-MSCs.
99. The method of any one of claims 49-85, wherein the HMCs express at least one of the genes selected from the group consisting of ANXA2, TPT1, VIM, COL6A1, BGN, COL6A2, CTGF, TIMP3, ACTA2, COL3A1, SPARC, ITGB1, SERPINH1, TPM2, TGFBI, COL1A1, TPM1, COL6A3, TPM4, SERPINE2, CALD1, COL1A2, TAGLN, MYL9, MT-RNR2, POSTN at a lower level compared to BM-MSCs.
100. The method of any one of claims 49-85, wherein the HMCs express at least one of the miRNA in Table 21 at a lower level compared to the HMC-EVs.
101. The method of any one of claims 49-85, wherein the HMCs express at least one of the miRNA in Table 22 at a higher level compared to the HMC-EVs.
102. The method of any one of claims 49-101, wherein about 1×10.sup.6 to about 1×10.sup.13 HMCs are administered to the subject.
103. The method of any one of claims 49-102, wherein the HMCs are administered in a pharmaceutical composition.
104. The method of claim 103, wherein the pharmaceutical composition comprises (a) a buffer, maintaining the solution at a physiological pH; (b) at least 2 mM or at least 0.05% (w/v) glucose; and (c) an osmotically active agent, maintaining the solution at a physiological osmolarity.
105. The method of claim 104, wherein the glucose is D-glucose (Dextrose).
106. The method of claim 104, wherein the osmotically active agent is a salt.
107. The method of claim 106, wherein the salt is sodium chloride.
108. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of CALR, UBB, PKM, CXCL8, C15orf48, PSME2, TPM3, ANKRD1, PFN1, SRGN, ACTB, MDK, TAGLN2, CFL1, HSP90AA1, HSPA8, CXCL12, UCHL1, HMGA2, HMGA1, HN1, PTMA, SP90AB1, PRDX1, GSTP1, KRT18, IGFBP4, CALD1, COL4A1, COL4A2, and GAPDH at a higher level compared to AD-MSCs.
109. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of TMSB4X, ACTG1, GSTP1, KRT18, IGFBP5, NPY, KRT8, PRDX6, MDK, DKK3, UCHL1, TUBB3, HN1, PTMA, HSP90AB1, HMGA1, HSPA8, TAGLN2, ANKRD1, PFN1, CYBA, and UBB at a higher level compared to AD-MSCs.
110. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of PPIA, NPM1, HNRNPA1, IGFBP5, KRT19, KRT18, GSTP1, TUBB, TUBA1B, KRT8, HN1, PTMA, TUBA1C, HSPA8, HMGA1, CFL1, MYL6, ACTB, UCHL1, TAGLN2, MDK, GREM1, MMP1, and CTSC at a higher level compared to BM-MSCs.
111. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of SERPINE1, ACTA2, TPM2, CTGF, SERPINE2, CRYAB, ELN, MFGE8, ANXA2, POSTN, VIM, MFAP5, ISLR, THBS1, TIMP3, DKK1, COL6A3, COL6A1, TPT1, BCYRN1, COL1A1, SPARC, TPM1, BGN, COL1A2, COL3A1, TGFBI, CRLF1, COMP, NEAT1, MT-CO3, MT-CO2, MT-ATP8, MT-CYB, MT-CO1, MT-ATP6, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-ND3, MT-ND1, MT-ND2, GREM1, TMSB4X, ITGB1, LMNA, H2AFZ, FTL, EEF1G, NPM1, EEF1A1, RACK1, ACTG1, and TPM4 at a lower level compared to AD-MSCs.
112. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of SERPINE1, S100A6, CD59, POSTN, VIM, MFAP5, ISLR, THBS1, COL6A3, TIMP3, ELN, ANXA2, COL1A1, BCYRN1, CCDC80, COL6A1, COL6A2, BGN, COL1A2, COL3A1, TGFB1, CRLF1, COMP, and GREM1 at a lower level compared to AD-MSCs.

113. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of MT1X, MT1G, TMSB10, CCL8, INHBA, CTSB, SERPINB2, ADM, APOL1, FTH1, CCL2, CCL5, CSF1, IL1B, IGFBP3, P4HB, DCN, FSTL1, ANXA5, LOX, CD63, CTSZ, FN1, LGALS1, LDHA, RCN3, MMP2, and TIMP1 at a lower level compared to AD-MSCs.
114. A composition comprising HMCs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMCs express at least one of the genes selected from the group consisting of ANXA2, TPT1, VIM, COL6A1, BGN, COL6A2, CTGF, TIMP3, ACTA2, COL3A1, SPARC, ITGB1, SERPINH1, TPM2, TGFBI, COL1A1, TPM1, COL6A3, TPM4, SERPINE2, CALD1, COL1A2, TAGLN, MYL9, MT-RNR2, POSTN at a lower level compared to BM-MSCs.
115. The composition of any one of claims 108-114, wherein the HMCs further express at least one of the genes in Table 3 at a higher level compared to BM-MSCs.
116. The composition of any one of claims 108-114, wherein the HMCs further express at least one of the genes in Table 4 at a lower level compared to BM-MSCs.
117. The composition of any one of claims 108-114, wherein the HMCs further express at least one of the genes in Table 5 at a higher level compared to UCB-MSCs.
118. The composition of any one of claims 108-114, wherein the HMCs further express at least one of the genes in Table 6 at a lower level compared to UCB-MSCs.
119. The composition of any one of claims 108-114, wherein the HMCs further express at least one of the genes in Table 7 at a higher level compared to AD-MSCs.
120. The composition of any one of claims 108-114, wherein the HMCs further express at least one of the genes in Table 8 at a lower level compared to AD-MSCs.
121. A pharmaceutical composition comprising the HMCs of any one of claims 108-114, and a pharmaceutically acceptable carrier.
122. A population of HMC-EVs of any one of claims 108-114.
123. The population of EVs of claim 122, wherein the HMC-EVs express at least one of the miRNA in Table 9 at a higher level compared UCB-MSC-EVs.
124. The population of EVs of claim 122 or 123, wherein the HMC-EVs express at least one of the miRNA in Table 10 at a lower level compared to UCB-MSC-EVs.
125. The population of EVs of any one of claims 122-124, wherein the HMC-EVs express at least one of the miRNA in Table 11 at a higher level compared to BM-MSC-EVs.
126. The population of EVs of any one of claims 122-125, wherein the HMC-EVs express at least one of the miRNA in Table 12 at a lower level compared to BM-MSC-EVs.
127. The population of EVs of any one of claims 122-126, wherein the HMC-EVs express at least one of the miRNA in Table 13 at a higher level compared to AD-MSC-EVs.
128. The population of EVs of any one of claims 122-127, wherein the HMC-EVs express at least one of the miRNA in Table 14 at a lower level compared to AD-MSC-EVs.
129. The population of EVs of any one of claims 122-128, wherein the HMC-EVs express at least one of the proteins in Table 15 at a higher level compared to UCB-MSC-EVs.
130. The population of EVs of any one of claims 122-129, wherein the HMC-EVs express at least one of the proteins in Table 16 at a lower level compared to UCB-MSC-EVs.
131. The population of EVs of any one of claims 122-130, wherein the HMC-EVs express at least one of the proteins in Table 17 at a higher level compared to BM-MSC-EVs.
132. The population of EVs of any one of claims 122-131, wherein the HMC-EVs express at least one of the proteins in Table 18 at a lower level compared to BM-MSC-EVs.
133. The population of EVs of any one of claims 122-132, wherein the HMC-EVs express at least one of the proteins in Table 19 at a higher level compared to AD-MSC-EVs.
134. The population of EVs of any one of claims 122-133, wherein the HMC-EVs express at least one of the proteins in Table 20 at a lower level compared to AD-MSC-EVs.
135. The population of EVs of any one of claims 122-134, wherein the HMC-EVs express at least

one of the miRNA in Table 21 at a higher level compared to the HMCs.
136. The population of EVs of any one of claims 122-135, wherein the HMC-EVs express at least one of the miRNA in Table 22 at a lower level compared to the HMCs.
137. The population of EVs of any one of claims 122-136, wherein the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
138. The population of EVs of any one of claims 122-137, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3, FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB, PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
139. The population of EVs of any one of claims 122-138, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2R1A, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A 11, SLC44A 1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
140. The population of HMC-EVs of any one of claims 122-139, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
141. The population of HMC-EVs of any one of claims 122-140, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
142. A pharmaceutical composition comprising the HMC-EVs of any one of claims 122-141, and a pharmaceutically acceptable carrier.
143. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNAs in Table 9 at a higher level compared to UCB-MSC-EVs.
144. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNAs in Table 10 at a lower level compared to UCB-MSC-EVs.
145. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNAs in Table 11 at a higher level compared to BM-MSC-EVs.
146. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNAs in Table 12 at a lower level compared to BM-MSC-EVs.
147. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells,

wherein the HMC-EVs express at least one of the miRNAs in Table 13 at a higher level compared to AD-MSC-EVs.

148. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 14 at a lower level compared to AD-MSC-EVs.

149. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 15 at a higher level compared to UCB-MSC-EVs.

150. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 16 at a lower level compared to UCB-MSC-EVs.

151. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 17 at a higher level compared to (BM-MSC-EVs.

152. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 18 at a lower level compared to BM-MSC-EVs.

153. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 19 at a higher level compared to AD-MSC-EVs.

154. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins in Table 20 at a lower level compared to AD-MSC-EVs.

155. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNAs selected from the group consisting of hsa-miR-125b-5p, hsa-miR-181a-5p, hsa-miR-199b-5p, hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-125a-5p, hsa-miR-106a-5p+hsa-miR-17-5p and hsa-miR-221-3p at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

156. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ALDOC, ANXA5, APBB2, BASP1, CAV1, CD81, CD99, CKM, EPB41L3, FDPS, GNAQ, GNG12, GP9, H2AC20, H2AC21, H3-3A, H3-7, H4-16, HLA-A, ITGA2, KPNA2, KRAS, KRT4, LRRC59, MAMDC2, MARCKSL1, MDGA1, MERTK, MFGE8, MMP14, MVP, PCDH1, PDGFRB, PDIA3, RPL13, RPS18, RPS3A, RPS4X, SDCBP, SLC2A1, SLC3A2, TAGLN2, TNC, TSPAN14, TSPAN33, TSPAN9, TTYH3, UCHL1, VAT1, YWHAB, and YWHAQ at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

157. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADGRG6, AGRN, ANXA6, APOC4, ARHGAP1, ARGHDIA, ARL8A, ARPC5, B2M, BBS1, BLVRA, BST1, CA2, CCN2, CCNB3, CD34, CD36, CD47, CORO1A, DTD1, EEF1D, EEF1G, ENG, ESD, GNAI2, GNB1, H1-3, H2BC15, HIP1, KIF11, LAMP1, LAP3, LGALS1, LTBP3, MAPK3, MARCKS, MBTD1, MDH1, MOB1B, MYL12B, MYO1F, MYO3A, NIBAN2, PEBP1, PF4, PGAP1, PLOD1, PPP2R1A, PRSS23, PXDN, RALA, RAP2A, RPS13, RPS3, RPSA, S100A11, SLC44A1, SLC44A2, SLTM, SMG1, SPARC, SRSF8, STRADB, STX11, STXBP2, TGM2, TPP1, TPTE2, TRIM5, TRPM2, TUBA8, TUBB3, VCAN, YWHAE, and ZFN607 at a higher level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

158. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of ADIPOQ, CAT, CEP290, IGLV6-57, TAS2R33, and TMEM198 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.

159. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the proteins selected from the group consisting of AKAP9, ALB, ALOX5, APLP2, CD109, CDSN, CHST9, ERC1, F11, ARMCX5, LAMB4, LRRTM2, LTF, MSH6, OAF, OLFML3, PAK6, RGS14, SEMA7A, SURF1, and TRIM4 at a lower level compared to BM-MSC-EVs, UCB-MSC-EVs, and/or AD-MSC-EVs.
160. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 21 at a higher level compared to the HMCs.
161. A population of HMC-EVs obtained by in vitro differentiation of pluripotent stem cells, wherein the HMC-EVs express at least one of the miRNA in Table 22 at a lower level compared to the HMCs.
162. A pharmaceutical composition comprising the HMC-EVs of any one of claims 143-161, and a pharmaceutically acceptable carrier.
163. A method of determining neurite outgrowth of an HMC population comprising: (a) preparing a mixed neuronal culture from an isolated cerebral cortex; (b) plating the HMC population on a permeable membrane; (c) applying strain on the mixed neuronal culture; (d) overlaying the strained mixed neuronal culture with the permeable membrane of step (b); and (e) measuring neurite outgrowth of the mixed neuronal culture.
164. The method of claim 163, further determining gene expression of the mixed neuronal culture in the presence and absence of the HMC population.
165. The method of claim 163, wherein the strain is a physical scratch made in the mixed neuronal culture.
166. The method of claim 163, wherein the strain is vacuum pressure and positive air pressure applied to the mixed neuronal culture.
167. The method of claim 163, wherein the strain is applied at 15% to 0% stretching oscillations.