Supplementary table 1: Immune metagenes

|  |  |
| --- | --- |
| Inhibitory immune checkpoint genes | CD276, VTCN1, BTLA, CTLA4, LAG3, CD274, C10orf54, TNFRSF14, PDCD1LG2, ADORA2A, PDCD1, IDO1, HAVCR2, LAIR1, LGALS9, PVRL3, TIGIT |
| Stimulatory immune checkpoint genes | CD2, CD226, CD27, CD28, CD40, CD40LG, CD58, CD70, CD86, ICOS, ICOSLG, SLAMF1, TNFRSF18, TNFRSF25, TNFRFS4, TNFRFS8, TNFRFS9, TNFSF14, TNFSF15, TNFSF18, TNFSF4, TNFSF8, TNFSF9 |
| T-cell activation genes | CCL2, CCL3, PTPRC, ICOS, GZMK, CXCL10, CXCL9, CCL4, CD8A, IRF1, HLA-DMA, HLA-DMB, HLA-DRA, HLA-DOA, HLA-DRB1, HLA-DOB |
| T-cell cytolytic activity | GZMA, PRF1 |
| Macrophage activity | ITGAM, ADGRE1, CD68, CSF1R, LGALS3, ITGAX, IL4R, CD163 |
| Natural killer cells | KLRF1, KLRC1, KLRD1 |
| Lymphocyte-specific protein tyrosine kinase genes | ARHGAP15, ARHGAP25, CCL5, CCR2,CCR7, CD2, CD247, CD27, CD3D, CD48, CD53, CORO1A, CSF2RB, EVI2B, FGL2, GIMAP4, GIMAP5, GMFG, GZMA, GZMK, HCLS1, IL10RA, IL2RG, IL7R, INPP5D, IRF8, ITK, KLRK1, LCK, LCP2, LPXN, LTB, PIK3CD, PLAC8, PRG1, PRKCB1, PTPRC, RAC2, SAMSSN1, SCYA5, SELL, SD2D1A, SLA, SLAMF1, STAT4, TNFRSF7, TRBC1 |
| MHC I | HLA-A, HLA-B, HLA-C, HLA-F, HLA-G, HLA-J |
| MHC II | HLA-DMA, HLA-DQB1, HLA-DRA, HLA-DRB4 |
| B-cells | CD79B, BTLA, FCRL3, BANK1, CD79A, BLK, RALGPS2, FCRL1, HVCN1, BACH2 |
| Dendritic cells | LILRA4, CLEC4C, PLD4, PHEX, IL3RA, PTCRA, IRF8, IRF7, GZMB, CXCR3 |
| Chemokines | CCL2, CCL3, CCL4, CCL5, CCL11, CXCL9, CXCL10, CXCL11 |
| CD8 | CD8A, CD8B |

Supplementary table 2a

MOD1: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | BH | q-value | Count | Bonf |
| REACTOME\_CELL\_CYCLE\_MITOTIC | 78/694 | 325/8904 | 3.11E-20 | 3.46E-17 | 2.70E-17 | 78 | 3.46E-17 |
| REACTOME\_CELL\_CYCLE | 89/694 | 421/8904 | 4.69E-19 | 2.61E-16 | 2.04E-16 | 89 | 5.21E-16 |
| REACTOME\_DNA\_REPLICATION | 45/694 | 192/8904 | 1.02E-11 | 3.78E-09 | 2.96E-09 | 45 | 1.13E-08 |
| KEGG\_DNA\_REPLICATION | 18/694 | 36/8904 | 2.17E-11 | 6.03E-09 | 4.72E-09 | 18 | 2.41E-08 |
| REACTOME\_DNA\_REPAIR | 30/694 | 112/8904 | 1.03E-09 | 2.30E-07 | 1.80E-07 | 30 | 1.15E-06 |
| KEGG\_CELL\_CYCLE | 32/694 | 128/8904 | 1.91E-09 | 3.53E-07 | 2.76E-07 | 32 | 2.12E-06 |
| REACTOME\_MITOTIC\_M\_M\_G1\_PHASES | 37/694 | 172/8904 | 9.14E-09 | 1.45E-06 | 1.14E-06 | 37 | 1.02E-05 |
| REACTOME\_MITOTIC\_G1\_G1\_S\_PHASES | 31/694 | 137/8904 | 4.32E-08 | 6.01E-06 | 4.70E-06 | 31 | 4.81E-05 |
| REACTOME\_CYTOSOLIC\_TRNA\_AMINOACYLATION | 12/694 | 24/8904 | 5.17E-08 | 6.38E-06 | 4.99E-06 | 12 | 5.74E-05 |
| REACTOME\_G2\_M\_CHECKPOINTS | 16/694 | 45/8904 | 1.18E-07 | 1.12E-05 | 8.73E-06 | 16 | 0.00013168 |
| REACTOME\_DNA\_STRAND\_ELONGATION | 13/694 | 30/8904 | 1.21E-07 | 1.12E-05 | 8.73E-06 | 13 | 0.00013454 |
| REACTOME\_MITOTIC\_PROMETAPHASE | 23/694 | 87/8904 | 1.22E-07 | 1.12E-05 | 8.73E-06 | 23 | 0.0001353 |
| PID\_FOXM1\_PATHWAY | 15/694 | 40/8904 | 1.30E-07 | 1.12E-05 | 8.73E-06 | 15 | 0.00014508 |
| REACTOME\_PROCESSING\_OF\_CAPPED\_INTRON\_CONTAINING\_PRE\_MRNA | 30/694 | 140/8904 | 2.57E-07 | 2.04E-05 | 1.60E-05 | 30 | 0.00028579 |
| KEGG\_RNA\_DEGRADATION | 18/694 | 59/8904 | 2.79E-07 | 2.07E-05 | 1.62E-05 | 18 | 0.00031044 |
| KEGG\_MISMATCH\_REPAIR | 11/694 | 23/8904 | 3.38E-07 | 2.35E-05 | 1.84E-05 | 11 | 0.00037603 |
| REACTOME\_MRNA\_PROCESSING | 31/694 | 161/8904 | 1.91E-06 | 0.00012494 | 9.77E-05 | 31 | 0.00212394 |
| REACTOME\_EXTENSION\_OF\_TELOMERES | 11/694 | 27/8904 | 2.44E-06 | 0.0001458 | 0.000114 | 11 | 0.00271289 |
| REACTOME\_CELL\_CYCLE\_CHECKPOINTS | 26/694 | 124/8904 | 2.49E-06 | 0.0001458 | 0.000114 | 26 | 0.0027702 |
| REACTOME\_ACTIVATION\_OF\_ATR\_IN\_RESPONSE\_TO\_REPLICATION\_STRESS | 13/694 | 38/8904 | 3.04E-06 | 0.00016926 | 0.00013235 | 13 | 0.00338525 |
| KEGG\_AMINO\_SUGAR\_AND\_NUCLEOTIDE\_SUGAR\_METABOLISM | 14/694 | 44/8904 | 3.40E-06 | 0.00017182 | 0.00013434 | 14 | 0.00378 |
| KEGG\_NUCLEOTIDE\_EXCISION\_REPAIR | 14/694 | 44/8904 | 3.40E-06 | 0.00017182 | 0.00013434 | 14 | 0.00378 |
| REACTOME\_MRNA\_DECAY\_BY\_3\_TO\_5\_EXORIBONUCLEASE | 7/694 | Nov-04 | 4.24E-06 | 0.00020503 | 0.00016032 | 7 | 0.0047158 |
| REACTOME\_S\_PHASE | 23/694 | 109/8904 | 8.43E-06 | 0.00039038 | 0.00030524 | 23 | 0.00936907 |

Supplementary table 2b

MOD2: Enriched pathways

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | | BH | | q-value | Count | Bonf |
| PID\_IL12\_2PATHWAY | 25/515 | 63/8904 | 2.00E-15 | | 2.05E-12 | | 1.74E-12 | 25 | 2.05E-12 |
| PID\_NFAT\_TFPATHWAY | 16/515 | 47/8904 | 3.52E-09 | | 1.81E-06 | | 1.53E-06 | 16 | 3.61E-06 |
| REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM | 40/515 | 270/8904 | 2.93E-08 | | 1.00E-05 | | 8.51E-06 | 40 | 3.01E-05 |
| REACTOME\_INTERFERON\_SIGNALING | 27/515 | 159/8904 | 3.57E-07 | | 9.16E-05 | | 7.78E-05 | 27 | 0.00036627 |
| REACTOME\_INTERFERON\_ALPHA\_BETA\_SIGNALING | 16/515 | 64/8904 | 4.56E-07 | | 9.36E-05 | | 7.96E-05 | 16 | 0.00046823 |
| PID\_CD8\_TCR\_DOWNSTREAM\_PATHWAY | 16/515 | 65/8904 | 5.74E-07 | | 9.81E-05 | | 8.33E-05 | 16 | 0.00058849 |
| BIOCARTA\_ASBCELL\_PATHWAY | 7/515 | Dec-04 | 1.28E-06 | | 0.00018726 | | 0.00015908 | 7 | 0.00131083 |
| BIOCARTA\_NKT\_PATHWAY | 10/515 | 29/8904 | 2.83E-06 | | 0.00036321 | | 0.00030854 | 10 | 0.00290569 |
| PID\_IL2\_STAT5\_PATHWAY | 10/515 | 30/8904 | 4.03E-06 | | 0.00042206 | | 0.00035853 | 10 | 0.0041352 |
| KEGG\_CYTOKINE\_CYTOKINE\_RECEPTOR\_INTERACTION | 35/515 | 267/8904 | 4.11E-06 | | 0.00042206 | | 0.00035853 | 35 | 0.00422057 |
| KEGG\_TYPE\_I\_DIABETES\_MELLITUS | 12/515 | 44/8904 | 4.74E-06 | | 0.00042939 | | 0.00036476 | 12 | 0.00486072 |
| BIOCARTA\_TH1TH2\_PATHWAY | 8/515 | 19/8904 | 5.08E-06 | | 0.00042939 | | 0.00036476 | 8 | 0.00521637 |
| PID\_CD40\_PATHWAY | 10/515 | 31/8904 | 5.64E-06 | | 0.00042939 | | 0.00036476 | 10 | 0.0057917 |
| BIOCARTA\_IL2RB\_PATHWAY | 11/515 | 38/8904 | 6.28E-06 | | 0.00042939 | | 0.00036476 | 11 | 0.00644081 |
| KEGG\_ALLOGRAFT\_REJECTION | 11/515 | | | 38/8904 | 6.28E-06 | 0.00042939 | 0.00036476 | 11 | 0.00644081 |
| KEGG\_P53\_SIGNALING\_PATHWAY | 15/515 | | | 69/8904 | 6.87E-06 | 0.00044044 | 0.00037415 | 15 | 0.0070471 |
| REACTOME\_IMMUNOREGULATORY\_INTERACTIONS\_BETWEEN\_A\_LYMPHOID\_AND\_A\_NON\_LYMPHOID\_CELL | 15/515 | | | 70/8904 | 8.28E-06 | 0.0005 | 0.00042475 | 15 | 0.00850001 |

Supplementary table 2c

MOD3: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | Count | bonf |
| REACTOME\_INTERFERON\_ALPHA\_BETA\_SIGNALING | 23/201 | 64/8904 | 2.50E-22 | 1.74E-19 | 1.43E-19 | 23 | 1.74E-19 |
| REACTOME\_INTERFERON\_SIGNALING | 32/201 | 159/8904 | 5.54E-22 | 1.93E-19 | 1.58E-19 | 32 | 3.86E-19 |
| REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM | 34/201 | 270/8904 | 1.27E-16 | 2.97E-14 | 2.43E-14 | 34 | 8.90E-14 |
| REACTOME\_INTERFERON\_GAMMA\_SIGNALING | 13/201 | 63/8904 | 1.04E-09 | 1.82E-07 | 1.49E-07 | 13 | 7.27E-07 |
| PID\_CD8\_TCR\_DOWNSTREAM\_PATHWAY | 11/201 | 65/8904 | 1.82E-07 | 2.21E-05 | 1.81E-05 | 11 | 0.00012701 |
| PID\_FOXM1\_PATHWAY | 9/201 | 40/8904 | 1.90E-07 | 2.21E-05 | 1.81E-05 | 9 | 0.00013255 |
| PID\_NFAT\_TFPATHWAY | 9/201 | 47/8904 | 8.25E-07 | 8.23E-05 | 6.74E-05 | 9 | 0.00057607 |
| REACTOME\_ANTIVIRAL\_MECHANISM\_BY\_IFN\_STIMULATED\_GENES | 10/201 | 66/8904 | 1.93E-06 | 0.00016826 | 0.00013779 | 10 | 0.00134609 |
| PID\_TCR\_CALCIUM\_PATHWAY | 7/201 | 29/8904 | 2.76E-06 | 0.00021367 | 0.00017497 | 7 | 0.00192307 |
| PID\_AP1\_PATHWAY | 10/201 | 70/8904 | 3.35E-06 | 0.000234 | 0.00019161 | 10 | 0.00233996 |
| REACTOME\_CELL\_CYCLE | 25/201 | 421/8904 | 8.35E-06 | 0.00052964 | 0.00043371 | 25 | 0.00582607 |
| PID\_IL12\_2PATHWAY | 9/201 | 63/8904 | 1.05E-05 | 0.00061019 | 0.00049967 | 9 | 0.00732229 |
| REACTOME\_CELL\_CYCLE\_MITOTIC | 21/201 | 325/8904 | 1.32E-05 | 0.00070612 | 0.00057823 | 21 | 0.00917954 |

Supplementary table 2d

MOD4: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | Count | bonf |
| REACTOME\_INTERFERON\_SIGNALING | 24/211 | 159/8904 | 2.88E-13 | 2.10E-10 | 1.75E-10 | 24 | 2.10E-10 |
| REACTOME\_INTERFERON\_ALPHA\_BETA\_SIGNALING | 16/211 | 64/8904 | 1.00E-12 | 2.51E-10 | 2.09E-10 | 16 | 7.33E-10 |
| REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM | 30/211 | 270/8904 | 1.03E-12 | 2.51E-10 | 2.09E-10 | 30 | 7.53E-10 |
| PID\_NFAT\_TFPATHWAY | 11/211 | 47/8904 | 8.41E-09 | 1.54E-06 | 1.28E-06 | 11 | 6.15E-06 |
| PID\_IL12\_2PATHWAY | 12/211 | 63/8904 | 2.12E-08 | 3.09E-06 | 2.57E-06 | 12 | 1.55E-05 |
| REACTOME\_INTERFERON\_GAMMA\_SIGNALING | 11/211 | 63/8904 | 2.13E-07 | 2.60E-05 | 2.16E-05 | 11 | 0.00015587 |
| PID\_AP1\_PATHWAY | 11/211 | 70/8904 | 6.48E-07 | 6.77E-05 | 5.63E-05 | 11 | 0.00047363 |
| KEGG\_CYTOKINE\_CYTOKINE\_RECEPTOR\_INTERACTION | 21/211 | 267/8904 | 1.29E-06 | 0.0001178 | 9.80E-05 | 21 | 0.00094238 |
| PID\_CD8\_TCR\_DOWNSTREAM\_PATHWAY | 10/211 | 65/8904 | 2.59E-06 | 0.00021036 | 0.00017508 | 10 | 0.0018932 |
| BIOCARTA\_NKT\_PATHWAY | 7/211 | 29/8904 | 3.81E-06 | 0.00027818 | 0.00023154 | 7 | 0.00278183 |
| PID\_CD40\_PATHWAY | 7/211 | 31/8904 | 6.16E-06 | 0.00040924 | 0.00034061 | 7 | 0.0045016 |
| PID\_ATF2\_PATHWAY | 9/211 | 59/8904 | 8.93E-06 | 0.00054422 | 0.00045296 | 9 | 0.00653064 |

Supplementary table 2e

MOD5: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | Count | bonf |
| REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM | 34/173 | 270/8904 | 9.76E-19 | 6.08E-16 | 4.64E-16 | 34 | 6.08E-16 |
| REACTOME\_INTERFERON\_SIGNALING | 27/173 | 159/8904 | 2.18E-18 | 6.78E-16 | 5.18E-16 | 27 | 1.36E-15 |
| REACTOME\_INTERFERON\_ALPHA\_BETA\_SIGNALING | 19/173 | 64/8904 | 4.56E-18 | 9.48E-16 | 7.24E-16 | 19 | 2.84E-15 |
| PID\_FOXM1\_PATHWAY | 11/173 | 40/8904 | 1.54E-10 | 2.01E-08 | 1.53E-08 | 11 | 9.58E-08 |
| REACTOME\_INTERFERON\_GAMMA\_SIGNALING | 13/173 | 63/8904 | 1.61E-10 | 2.01E-08 | 1.53E-08 | 13 | 1.00E-07 |
| PID\_AP1\_PATHWAY | 13/173 | 70/8904 | 6.49E-10 | 6.74E-08 | 5.15E-08 | 13 | 4.04E-07 |
| PID\_IL12\_2PATHWAY | 12/173 | 63/8904 | 2.23E-09 | 1.98E-07 | 1.52E-07 | 12 | 1.39E-06 |
| PID\_NFAT\_TFPATHWAY | 10/173 | 47/8904 | 1.64E-08 | 1.28E-06 | 9.78E-07 | 10 | 1.02E-05 |
| PID\_TCR\_CALCIUM\_PATHWAY | 8/173 | 29/8904 | 5.24E-08 | 3.62E-06 | 2.77E-06 | 8 | 3.26E-05 |
| PID\_CD8\_TCR\_DOWNSTREAM\_PATHWAY | 10/173 | 65/8904 | 4.21E-07 | 2.62E-05 | 2.00E-05 | 10 | 0.00026198 |
| REACTOME\_ANTIVIRAL\_MECHANISM\_BY\_IFN\_STIMULATED\_GENES | 9/173 | 66/8904 | 4.58E-06 | 0.00025952 | 0.0001982 | 9 | 0.00285473 |
| KEGG\_P53\_SIGNALING\_PATHWAY | 9/173 | 69/8904 | 6.67E-06 | 0.00034649 | 0.00026462 | 9 | 0.00415789 |
| PID\_IL2\_1PATHWAY | 8/173 | 55/8904 | 9.66E-06 | 0.00046277 | 0.00035342 | 8 | 0.00601602 |

Supplementary table 2f

MOD6: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | Count | bonf |
| REACTOME\_INTERFERON\_SIGNALING | 25/173 | 159/8904 | 2.94E-16 | 1.70E-13 | 1.49E-13 | 25 | 1.70E-13 |
| REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM | 29/173 | 270/8904 | 3.29E-14 | 8.61E-12 | 7.55E-12 | 29 | 1.91E-11 |
| REACTOME\_INTERFERON\_ALPHA\_BETA\_SIGNALING | 16/173 | 64/8904 | 4.46E-14 | 8.61E-12 | 7.55E-12 | 16 | 2.58E-11 |
| REACTOME\_INTERFERON\_GAMMA\_SIGNALING | 11/173 | 63/8904 | 2.78E-08 | 4.02E-06 | 3.53E-06 | 11 | 1.61E-05 |
| REACTOME\_ANTIVIRAL\_MECHANISM\_BY\_IFN\_STIMULATED\_GENES | 10/173 | 66/8904 | 4.87E-07 | 5.64E-05 | 4.95E-05 | 10 | 0.00028219 |

Supplementary table 2g

MOD7: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | Count | bonf |
| PID\_NFAT\_TFPATHWAY | 8/128 | 47/8904 | 2.88E-07 | 0.00017836 | 0.0001505 | 8 | 0.00017836 |
| PID\_AP1\_PATHWAY | 8/128 | 70/8904 | 6.55E-06 | 0.00203035 | 0.00171322 | 8 | 0.00406071 |

Supplementary table 2h

MOD8: Enriched pathways

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | GeneRatio | BgRatio | pvalue | p.adjust | qvalue | Count | bonf |
| PID\_NFAT\_TFPATHWAY | 7/77 | 47/8904 | 1.31E-07 | 2.67E-05 | 2.20E-05 | 7 | 5.26E-05 |
| PID\_AP1\_PATHWAY | 8/77 | 70/8904 | 1.32E-07 | 2.67E-05 | 2.20E-05 | 8 | 5.34E-05 |
| PID\_TCR\_CALCIUM\_PATHWAY | 5/77 | 29/8904 | 4.28E-06 | 0.00057529 | 0.00047484 | 5 | 0.00172587 |
| PID\_IL12\_STAT4\_PATHWAY | 5/77 | 33/8904 | 8.33E-06 | 0.00083934 | 0.00069278 | 5 | 0.00335735 |
| PID\_CD8\_TCR\_DOWNSTREAM\_PATHWAY | 6/77 | 65/8904 | 1.89E-05 | 0.00152471 | 0.00125848 | 6 | 0.00762355 |