March 11, 2014

Intrexon Corporation BUY

Target Price Change : Biotechnology

Intrexon Completes An Important Acquisition

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Stock Symbol	**NYSE: XON**
Current Price	$27.27
12 mos. Target Price	$45.00
Market Cap	$2,645.0 mln
Shares O/S	97.0 mln
Avg Daily Vol. (3 mos.)	536,253 shs.
52- Week Price Low/High	$16.00 - $38.50
P/B	7.0x
Dividend Yield	0.0%

EPS

	FY 13E	FY 14E	FY 15E
Q1 (Mar)	(0.47)A	(10.00)E	—
Q2 (Jun)	(0.07)A	(0.09)E	—
Q3 (Sep)	0.16A	(0.09)E	—
Q4 (Dec)	(0.05)E	(0.02)E	—
	(0.38)E	(0.30)E	(0.07)E

The synthetic biology specialist acquired Medistem, a pioneer in the development of endometrial regenerative cells. The $26 million deal was consummated via an exchange of $0.27 in cash and approximately 0.0392 XON shares for each Medistem share.

The acquisition adds a new dimension to the Intrexon toolbox for delivering DNA-based medicines. Medistem's cells are adult-derived stem cells that can be genetically modified to produce specific therapeutic agents to treat cancer, inflammatory conditions, and rare diseases caused by a genetic anomaly. The unique property of stem cells that render this acquisition so important is their natural proclivity to hone into areas of inflammation and tissue damage. As a result, they will provide Intrexon and its collaborators with the ability to deliver DNA-based therapeutics locally to diseased sites. The stem cells also release exosomes that can also be used to deliver therapeutic agents to up- or down-regulate the immune system or to intervene against a disease in other ways. We believe Intrexon was also attracted by Medistem's patent portfolio and the fact that its technology yields a readily available source of stem cells that can be expanded cost effectively.

New collaborations are afoot. Intrexon entered into an agreement with the seventh largest generic drug manufacturer in the United States to reduce the cost of producing an undisclosed active pharmaceutical ingredient. In addition, interest from the environment and energy/chemical industries has begun to pick up, prompting the Company to expand its team dedicated to the environment sector.

We like the Medistem deal. The cost was minor compared to the number of potential indications, sizes of patient populations, and potential returns on the investment via the delivery of DNA-based therapies. We are raising our price target to $40 for Intrexon shares in recognition of the new opportunities that the acquisition provides. Intrexon remains a Griffin BUY recommendation.

Investment Thesis

Intrexon continues to secure strategic assets that expand its capabilities for the creation and delivery of new molecules for therapeutic purposes. The latest deal garnered technologies that are well suited for delivering DNA-based medicines to sites of inflammation and general tissue damage. It also offers a means of influencing the immune system in ways that Intrexon did not have previously. As a result, we consider Medistem to be an important addition to the Intrexon portfolio.

How quickly will the investment community recognize Intrexon's leading position in an industry that is likely to drastically change the world? That's a good question, but one that is likely to be answered over time in steps, some large and some small. Intrexon has assembled a technology toolbox that is already far ahead of any would-be competitors, and it has the right business model to maximize the market penetration, and hence, the commercial value of its expertise. Numerous collaborations have been consummated with small companies in the healthcare, food, and environment industries and lately large, multinational corporations have entered into agreements. Each deal is structured to cover Intrexon's immediate expenses and to yield a healthy return over the long run via royalty payments. Thus, we are impressed with the Company's progress in developing its capabilities and in generating interest in the solutions that synthetic biology has to offer.

In recognition of the importance of the Medistem deal, we are raising our price target on Intrexon to $40 and maintaining our BUY recommendation.

Medistem – A Significant Acquisition

Intrexon has acquired Medistem for approximately $26 million in stock and cash to gain expertise in the fields of stem cells and cellular therapies. The deal gives the Company two platforms for the delivery system of DNA-based medicines, Endometrial Regenerative Cells (ERCs) and exosomes that are released from the cells.

Medistem's ERCs are well-characterized universal adult stem cells that secrete enzymes (e.g., matrix metalloproteases 3 and 10) and angiopoietin-2 involved in angiogenesis.[1] In addition, they release common cytokine growth factors, including granulocyte macrophage colony stimulating factor (GM-CSF), platelet-derived growth factor-BB (PDGF-BB), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and epidermal growth factor (EGF). But they also express immune modulatory genes, such as pregnancy associated glycoprotein 1, neuronal pentraxin, and decay-accelerating factor, that are involved in innate and T-cell immunity as well as inflammation.[2] Unlike embryonic stem cells, they do not appear to pose the risk of teratoma development.[1,3] The cells do, however, appear to have a limitation, which is their ability to survive when implanted *in vivo*. Two studies have shown that few ERCs survive 14 days post-implantation, regardless of whether they are administered intravenously, intracerebrally, or as part of an implanted device.[4,5]

On the other hand, ERCs have several characteristics that render them very attractive drug delivery vehicles. First, they are readily available from menstrual blood, easily and economically expanded in culture, and equivalent to an "off-the-shelf" allogeneic therapy. Medistem developed an FDA-approved production protocol that generates 20,000 doses of 100 million cells each from a single donation. The company also secured or filed for patents on the preparation and use of these cells and ERC-derived exosomes that may be used directly for inducing immune tolerance, treating inflammatory diseases, and as a delivery vehicle for DNA-based medicines.[6,7,8] (Exosomes are

[1] Meng, X, et al. Endometrial regenerative cells: a novel stem cell population. J Transl Med (2007); 5: 57.

[2] Wang, H, et al. Comparison of endometrial regenerative cells and bone marrow stromal cells. J Transl Med (2012); 10: 207.

[3] Lin, J, et al. Plasticity of human menstrual blood stem cells derived from endometrium. J Zhejiang Univ Sci B (2011); 12(5): 372.

[4] Borlongan, CV, et al. Menstrual blood cells display stem cell-like phenotypic markers and exert neuroprotection following transplantation in experimental stroke. Stem Cells Dev (2010); 19(4): 439.

[5] Ulrich, D, et al. Human endometrial mesenchymal stem cells modulate the tissue response and mechanical behavior of polyamide mesh implants for pelvic organ prolapse repair. Tissue Eng Part A (2014); 20(3-4): 785.

[6] U.S. Patent Application No. US 2013/0156726 A1, Endometrial stem cells and methods of making and using same.

[7] U.S. Patent Application No. US 2013/0195899 A1, Therapeutic immune modulation by stem cell secreted exosomes.

nanoparticles in the range of 40 nm – 100 nm in size that are secreted from a variety of tissues including tumors, platelets, and immune cells for intercellular communication.) We believe these properties underpinned Intrexon's decision to acquire Medistem so that it may use the cells and exosomes for drug delivery purposes.

Given Intrexon's intent, it is not surprising that Medistem's clinical development program has been halted. The one trial that had already treated eight patients with congestive heart failure in Russia will be used to collect data on the safety of the ERCs. A Phase 1 study that was designed to investigate the cells for critical limb ischemia will not be initiated. In addition, we note that the intended use of Medistem's technologies will not interfere with the Mesoblast-Ziopharm-Intrexon collaboration involving genetically modified stem cells for cancer indications. Just how ERCs may be used in the oncology setting has not been revealed yet, but management sees distinct differences in the application of the Medistem and Mesoblast cells.

Perhaps, more important is the potential use of ERCs for non-malignant indications. We did a brief review of the scientific literature for publications in which menstrual or umbilical cord stem cells were used. The results of our search, which are presented in Table 1, suggest the cells are attracted to a broad range of diseased tissues.

Table 1. Examples of Stem Cell Applications

Application	Stem Cell Source	References
Cardiac muscle regeneration	Endometrial	Hida, N, et al.[9]
Post-stroke recovery	Endometrial	Borlongan, CV et al.[4]
Multiple sclerosis	Endometrial	Zhong, Z, et al.[10]
Duchenne muscular dystrophy	Endometrial	Cui, CH, et al.[11]
Rheumatoid arthritis	Umbilical cord	Wang,L, et al.[12]
Autism	Umbilical cord	Ichim, TE, et al.[13]

Research has shown that mesenchymal stem cells can be genetically engineered without loss of their stem cell properties, notably their ability to migrate into the vicinity of a tumor where they are able to deliver a DNA-based medicine *in vivo*.[14] Specifically, human mesenchymal stem cells were modified to express and secrete the cytokine tumor necrosis factor apoptosis ligand (TRAIL). As shown in Figure 1, administration of the TRAIL-secreting cells to mice bearing Ki67+ve glioma cells resulted in a reduction in the number of malignant cells (left graph) and an increase in the number of cells undergoing apoptosis (right graph) when compared to animals that received mesenchymal stem cells expressing a red fluorescent marker.

[8] U.S. Patent Application No. US 2013/0273011 A1, Stem cells and stem cell generated nanoparticles for treatment of inflammatory conditions and acute radiation syndrome.

[9] Haida, N, et al. Novel cardiac precursor-like cells from human menstrual blood-derived mesenchymal cells. Stem Cells (2008); 26(7): 1695.

[10] Zhong, A, et al. Feasibility investigation of allogeneic endometrial regenerative cells. J Transl Med (2009); 7: 15.

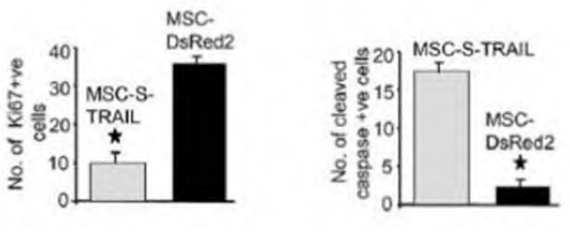
[11] Cui, CH, et al. Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation. Mol Biol Cell (2007); 18(5): 1586.

[12] Wang, L, et al. Human umbilical cord mesenchymal stem cell therapy for patients with active rheumatoid arthritis: safety and efficacy. Stem Cells Dev (2013); 22(24): 3192.

[13] Ichim, TE, et al. Stem cell therapy for autism. J Transl Med (2007); 5: 30.

[14] Sasportas, LS, et al. Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. Proc Natl Acad Sci (2009); 106(12): 4822.

Figure 1. Effect of Engineered Stem Cells Secreting TRAIL on Gliomas[14]



This suggests that Medistem's ERCs should prove very useful in delivering DNA-based therapies crafted with Intrexon's technologies.

At this juncture, it is not possible to know whether the ERCs or their exosomes will prove to be more important commercially. We note that the nanoparticles normally carry a variety of compounds, including proteins, messenger RNA, and microRNA, from their originating cells. As such, they figure importantly in cellular communication since most cells release exosomes to carry signals locally and/or systemically in support of normal physiological processes or pathological conditions. Indeed, exosomes transfer immunologically relevant molecules that activate T cells, induce tolerance and stimulate dendritic cell maturation.[15,16,17] They also transfer pathogens and pathogenic proteins, including prions and α-synuclein, a molecule that contributes to neurodegeneration related to Parkinson's disease.[18,19]

Exosomes may be used to carry antitumor cytokine(s) or other molecules to alter the status of the immune system. Several studies have provided preclinical proof of concept data supporting this approach. Table 2 provides examples of exosomes carrying immunomodulatory payloads.

Table 2. Examples of Exosomes Carrying Immunomodulatory Compounds

Immunomodulatory Compounds	Indication	References
Interleukin-2	Cancer	Yang, Y, et al.[20]
Tumor-related antigens	Melanoma and Lewis lung cancer	Tian, X, et al.[21]
Proangiogenic factors, incl. VEGF	Acute kidney injury	Choi, HY, et al.[22]
Interleukin-4	Inflammatory diseases – arthritis and delayed-type hypersensitivity	Kim, SH, et al.[23]
siRNA against BACE1	Alzheimer's disease	Alvarez-Erviti, L, et al.[24]

As shown by the diversity of compounds carried by exosomes and the nature of the medical indications shown in the Tables 1 and 2, genetically modified ERCs and their exosomes have broad potential medical and commercial

[15] Skokos, D, et al. Mast cell-dependent B and T lymphocyte activation is mediated by the secretion of immunologically active exosomes. J Immunol (2001); 166(2): 868.

[16] Karlsson, M, et al. "Tolerasomes" are produced by intestinal epithelial cells. Eur J Immunol (2001); 31(): 2892.

[17] Skokos, D, et al. Mast cell-derived exosomes induce phenotypic and functional maturation of dendritic cells and elicit specific immune responses in vivo. J Immunol (2003); 170(6): 3037.

[18] Emmanouilidou, E, et al. Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival. J Neurosci (2010); 30(20): 6838.

[19] Vella, LJ, et al. Packaging of prions into exosomes is associated with a noel pathway of PrP processing. J Pathol (2007); 211(5): 582.

[20] Yang, Y, et al. Increased induction of antitumor response by exosomes derived from interleukin-2 gene-modified tumor cells. J Cancer Res Clin Oncol (2007); 133(6): 389.

[21] Tian, X, et al. A membrane vesicle-based dual vaccine against melanoma and Lewis lung cancer. Biomaterials (2012); 33(26): 6147.

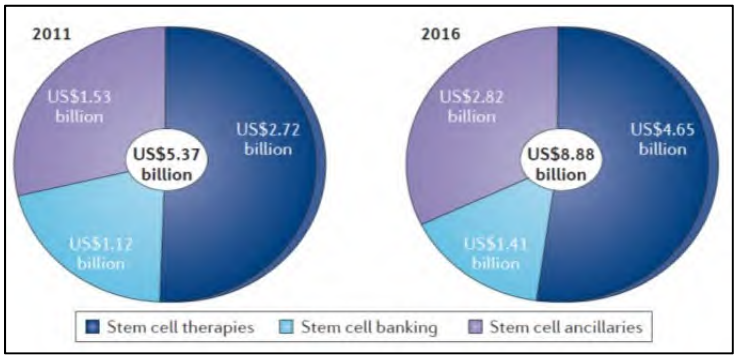
[22] Choi, HY, et al. Microparticles from kidney-derived mesenchymal stem cells act as carriers of proangiogenic signals and contribute to recovery from acute kidney injury. PLoS ONE (2014); 9(2): e87853.

[23] Kim, SH, et al. Effective treatment of inflammatory disease models with exosomes derived from dendritic cells genetically modified to express IL-4. J Immunol (2007); 179(4): 2242.

[24] Alvarez-Erviti, L, et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol (2011); 29(4): 341.

applications. This probably won't alter a recent assessment of the stem cell market's growth between 2011 and 2016 (see Figure 2), since it will take time for DNA-based medicines to gain regulatory approval.[25] However, we believe living biotherapeutics, such as those under development at Intrexon and its collaborators, will accelerate the growth of the market and alter its composition starting in the second half of this decade.

Figure 2. The Stem Cell Market – 2011 to 2016 [25]



A New Collaboration Is Consummated …

Intrexon announced a new exclusive channel collaboration with Amneal Pharmaceuticals, the seventh largest manufacturer of generic drugs in the United States. The agreement will provide the privately owned drug company with access to Intrexon's technologies to reduce the cost of producing an undisclosed active pharmaceutical ingredient. Amneal's current product catalog consists of 215 small-molecule drugs, but no biologicals. Synthetic biology has the potential to lower the cost of producing both types of drugs through more efficient cell cultures and improved purification processes.

… And More Are Expected

The Company recently added an executive with experience in the environment sector to increase its business development efforts. The pesticide deal signed with Rentokil last September has stimulated interest from other corporations in that area, perhaps because compounds that are safer for humans and the environment are an important goal of the pesticide industry and synthetic biology offers a new approach to creating such compounds. Meanwhile, Intrexon reports that discussions are advancing with potential collaborators in the energy/chemical industry based on microbes it has genetically engineered to produce high-value compounds (e.g., isobutanol and isoprene) from natural gas.

[25] Syed, BA, and Evans, JB. Stem cell therapy market. Nat Rev (2013); 12(3): 185.

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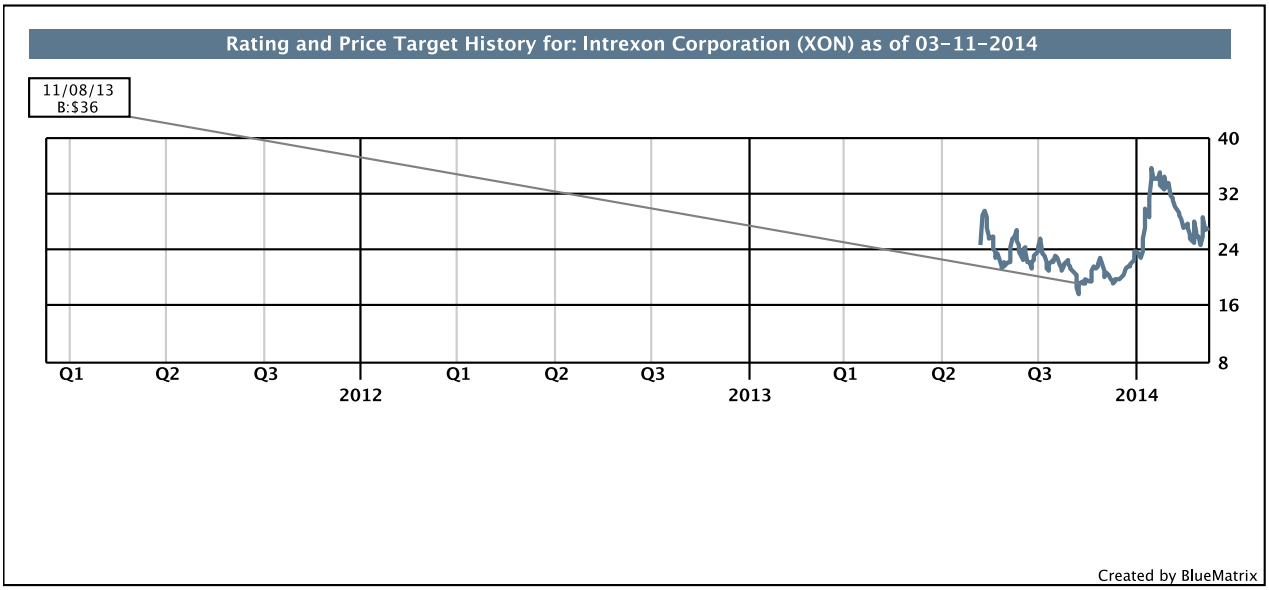

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