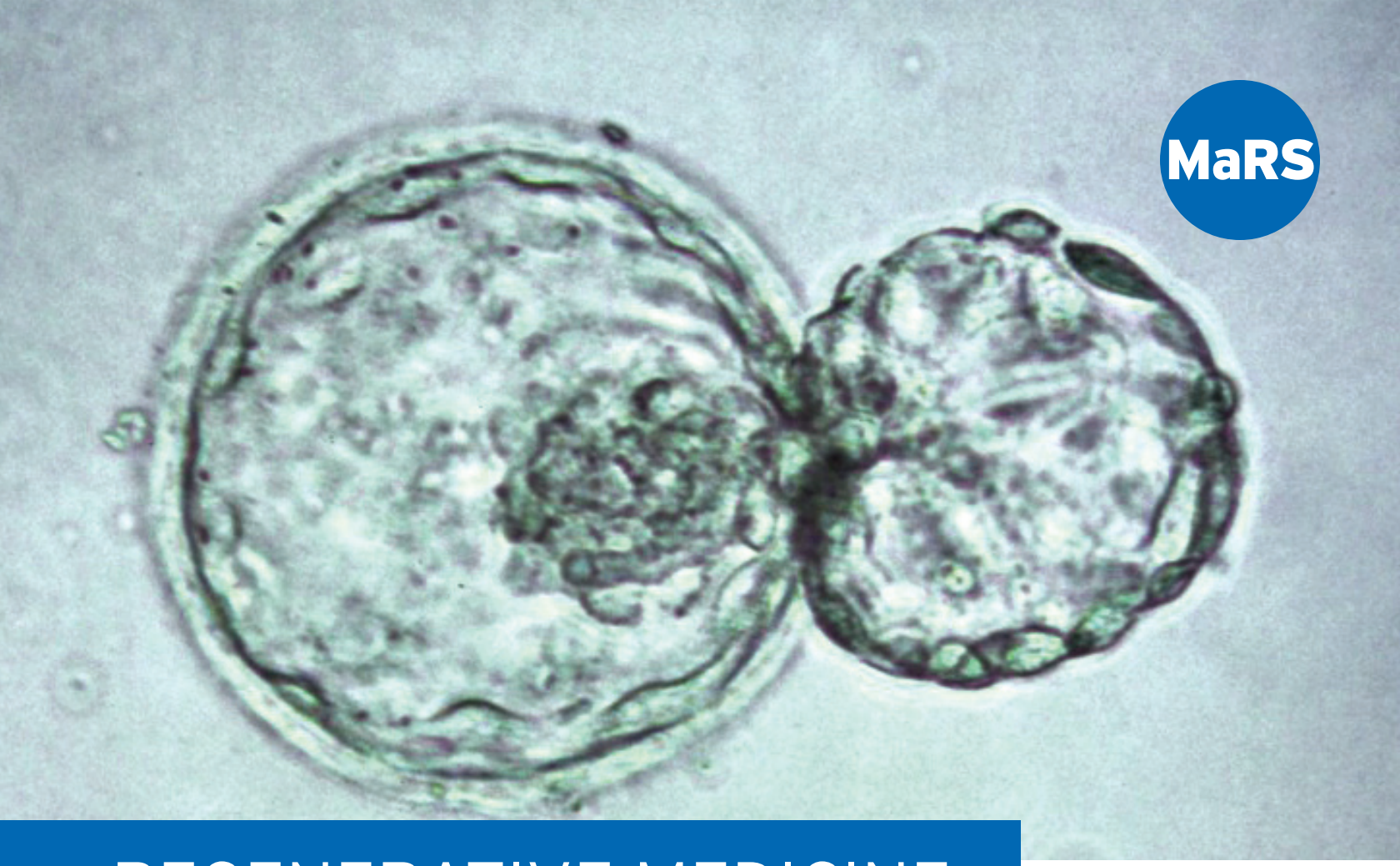


REGENERATIVE MEDICINE

Industry Briefing

Commercial opportunities and Ontario's strengths

2009

Industry Briefing

Regenerative Medicine

Executive Summary

After 30 years of research, many regenerative medicine technologies are in development and approaching commercialization. Clinical programs are underway worldwide and patients can look forward to numerous innovative solutions to pressing global health issues in the years ahead. A swelling wave of scientific discovery funded by major government initiatives has helped create unprecedented momentum in this exciting field.

The current market for regenerative medicine is estimated at between USD$2-5 billion. U.S. sales of commercially available stem cell therapies alone were $15.2M in 2007, and $16.5M during the first two quarters of 2008. It is projected that the stem cell market including therapeutics, blood cord banking and drug development tools will achieve annual growth of 29.2% resulting in sales of more than $11 billion by 2020.

Many leading multinational pharmaceutical companies have made a commitment to the field as evidenced through internal discovery programs and by establishing major research collaborations with leading academic groups worldwide.

The maturation of the industry is also reflected by a high number of clinical development activities. The U.S. National Institutes of Health is tracking over 900 clinical trials involving adult stem cells for therapeutic applications such as heart disease, diabetes, severe burns, bone regrowth, and vision impairments. Moreover, several FDA approved cell therapies for immune disorders and repopulation of bone marrow following chemotherapy are already on the market. In addition, several companies are working on products derived from embryonic stem cells that should reach the clinic in the next five years. Venture capital investors also see near-term revenue opportunities for companies making tools for the industry or using stem cells for drug discovery and development.

Canadian medical researchers have been at the vanguard of regenerative medicine since the 1960s. Given the rapid maturation of the regenerative medicine industry, the time is ripe to transform Canadian scientific leadership into commercial outcomes.

This industry briefing gives an overview of the global commercial landscape in regenerative medicine and relative strengths in Ontario.

Table of Contents

Industry Briefing
Regenerative Medicine

Introduction

Regenerative medicine is an emerging field that aims to repair, replace, and/or regenerate damaged tissues and organs in vivo (in the living body) by stimulating previously irreparable organs into healing themselves. The U.S. National Institutes of Health (NIH) includes tissue engineering, biomaterials, and cellular therapeutics (stem cell therapy) under the umbrella of regenerative medicine (Appendix I).

Regenerative medicine holds the potential to treat previously incurable chronic diseases and conditions including Alzheimer's disease, Parkinson's disease, diabetes, heart disease, renal failure, osteoporosis and spinal cord injuries, to name a few. The most obvious societal benefit of regenerative medicine is the possibility of significantly reduced healthcare costs from such treatments.

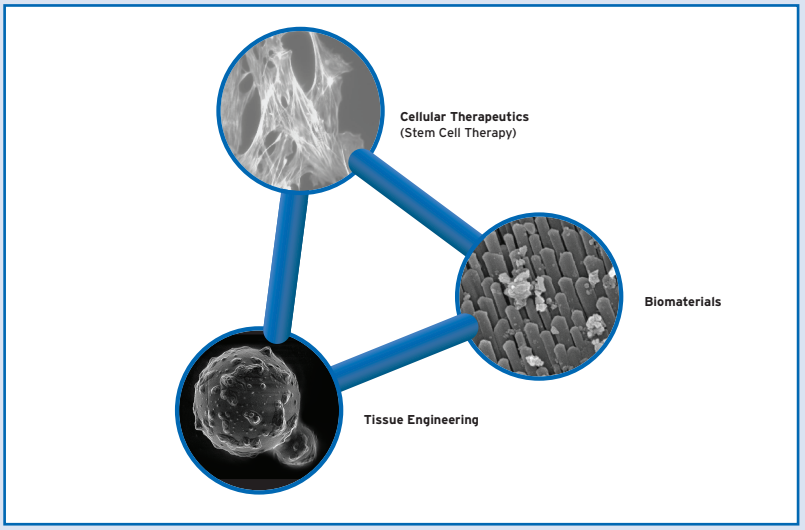
Regenerative medicine is a truly multidisciplinary field, bringing together biology, physics, chemistry, and applied engineering and blending the therapeutic effects of biological entities (cells, proteins) with the precision and stability of engineered biomaterials.

Although the roots of regenerative medicine go back 30 years, the field is in its commercial infancy for several reasons:

- Cell-based biological products represent both new technology and a business model that is different from traditional drug or device development. While devices such as artificial joints have resulted in significant benefits to patients, the device approach does not address the underlying causes of disease, namely the decline or failure of normal tissue or organ function.
- Start-up biotech and cell therapy companies lack the financial means and the clinical, regulatory, and manufacturing capabilities necessary to establish a sustainable product portfolio and technology pipeline.

Thus, there is an opportunity for new entrants in the field to use Canada's proven global strengths in fundamental scientific research and commercialization strategy to lay a foundation for global leadership in this emerging industry.

Scope: This report discusses the three fields within regenerative medicine: tissue engineering, biomaterials, and cellular therapeutics (stem cell therapy). The report will not discuss the roles of growth factors, bioartificial organs and gene therapy. The primary focus here is an overview of the global commercial opportunities in regenerative medicine and Ontario's relative strengths in particular.



Industry Briefing
Regenerative Medicine

Cellular Therapeutics, Tissue Engineering and Biomaterials

Research into stem cells, both embryonic and adult, is at the heart of regenerative medicine. Although embryonic stem cells have the potential to differentiate into any type of specialized cell, their use in scientific research is the subject of fierce ethical debate. Now a major breakthrough by two independent research teams could put the debate over embryonic stem cell research to rest entirely. In November 2007, a Japanese team led by Shinya Yamanaka and an American team led by James Thomson each announced that they had successfully created embryonic-like stem cells, named iPS cells (induced pluripotent stem cells), from adult human skin cells. Their findings, published in Cell and Science respectively, open the door for a revolution in regenerative medicine research.

Similar to stem cell therapies, tissue engineering and biomaterials are also garnering much attention. Tissue engineering at its most basic level populates 3D tissue scaffolding (biomaterials) with cells to generate functional organ constructs. Tissue engineering aims to solve the recent critical shortage of organs with the creation of viable bioartificial organs.

Over one third of global regenerative medicine companies are now involved in biomaterials development. Biomaterials refers to any natural or synthetic material that interfaces with living tissue and/or biological fluids. Polymers, metals (titanium, stainless steel, cobalt-chromium alloys), ceramics (alumina, zirconia, silicon nitride), and composite materials which can be developed into biocompatible materials are presently used in hip and dental implants and cardiac stents. These biomaterials can be modified to incorporate biological activity, such as growth factors and cells, to speed healing or aid in transplantation.

Applications for tissue engineering and biomaterials were originally limited to prosthetic devices and surgical manipulation of tissues but now include the following fields:

- Bone tissue engineering
- Cardiac tissue engineering
- Liver tissue engineering
- Corneal tissue engineering
- Wound healing
- Tissue engineered blood vessel
- Development of biomaterial scaffolds

Although tissue engineering and biomaterials are emerging fields, it is not too soon to identify clusters of academic strength and to follow progress within the discipline. As in stem cell research, Ontario boasts a number of prominent researchers in tissue engineering, including Michael Sefton, John Davies, Yu-Ling Cheng, Molly Shoichet, Peter Zandstra, and Kimberly Woodhouse. Six of the world's top 20 researchers in biomaterials are located in Toronto, Ontario.

Brief history of tissue engineering

Experimentation in tissue engineering and biomaterials began in Boston in the early 1970s when new cartilage was generated using chrondrocytes seeded onto bone and implanted in mice. Although these first forays were unsuccessful, researchers hypothesized that innovative biocompatible materials could act as scaffolds for generating new tissue. Friendenstein's critical observation in 1970 that bone marrow stromal cells could become bone and cartilage in vitro, led to experiments to generate skin substitutes, using a collagen matrix to support the growth of dermal fibroblasts. Sheets of keratinocytes were transferred onto burn patients. These pioneering experiments in tissue engineering were led by notable scientists such as Joseph Vacanti, Robert Langer, John Burke, Iannas Yannos, Howard Green, and Eugene Bell.

In the 1990s, Chris Brewer and Mark Saltzman established the Tissue Engineering Institute at Yale University. Other tissue engineering centres were established in Seattle (Steven Kim), Toronto (Michael Sefton), Shanghai (Yi Lin Cao) and Mexico City (Clemente Ibarra).

Outside North America, pathologist and stem cell biologist Julia Polak spearheaded an effort in tissue engineering at Imperial College, London. German scientists Una Chen, R. Hetzer and Christof Brelsch collaborated with the Boston-based labs to launch tissue engineering efforts of their own. In 1997, Boston's Vacanti laboratory also partnered with Koichi Tanaka's Kyoto University laboratories and Minora Ueda at the University of Nagoya. Raymund Horch and Bjorn Stark led a tri-country effort by Germany, Switzerland, and France.

The Tissue Engineering Society was founded in 1996 by Bostonians Joseph Vacanti and Charles Vacanti with the stated goal of sharing information among all these international centres. The first meeting occurred in 1996 with 300 attendees from 13 countries. Toronto scientists led by John Davies hosted the 2003 meeting of international TES. As the field of tissue engineering evolved and expanded, it grew to include regenerative medicine and thus TES was eventually renamed the Tissue Engineering Regenerative Medicine International Society (TERMIS).

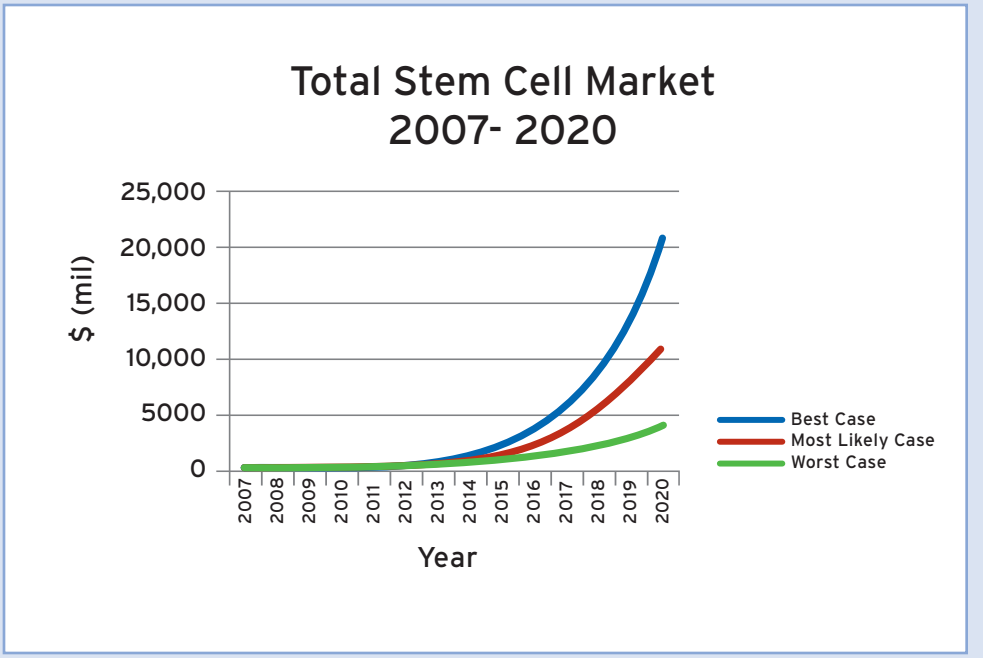
Industry Briefing
Regenerative Medicine

Regenerative Medicine Market

The current market for regenerative medicine is estimated at between USD$2-5 billion.It is projected that the total stem cell market including therapeutics, blood cord banking and drug development tools will achieve annual growth of 29.2% resulting in sales of more than $11 billion by 2020 (figure 1). U.S. sales of commercially available stem cell therapies alone were $15.2M in 2007, and $16.5M during the first two quarters of 2008.

Companies involved in cell therapy number more than 500 as of 2008. Of these, over 100 are involved in stem cell therapy. The number of stem cell patents issued globally has exploded from 111 in 2003 to 539 in 2007. Notably, more than 40% of the regenerative medicine firms founded since 2000 have been based outside the U.S., supported by national initiatives in countries such as the U.K., Canada, Australia, South Korea, Singapore, China, Sweden, and Israel.

Regenerative medicine is expected to begin bringing complex skin, cartilage, and bone substitutes to market within two years. Tissue and organ patches to regenerate damaged tissues and organs such as the heart and kidneys will appear on the market within 5-10 years. And within 20 years, with continued public funding and support, the goal of "tissues on demand" is realistic. Proactive efforts to advance regenerative medicine today open a window of opportunity for companies and nations, including Canada, to create a tremendous new global industry driven by new global leaders.



Source: Kalorama 2008

A crucial new tool for drug developers will be stem cell-based development drug discovery technologies to create more cost-efficient stem cell cultures but also to be used in the crucial pre-clinical testing phase to identify potential problems that could arise during clinical trials. The increasing use of these tools would save developers hundreds of millions of dollars in direct testing fees as well as indirect costs related to drug recalls. Invitrogen holds the leading market position in the molecular biology and cell culture markets and offers more than 1200 products for growing and differentiating stem cells. The company recently launched KNOCKOUT(TM) SR XenoFree Media for use in the culture of human embryonic stem cells. Invitrogen and Applied Biosystems completed a merger in November 2008, forming Life Technologies. For 2008, Life Technologies had revenues of $1.62 billion compared to revenues of $1.28 billion for Invitrogen in 2007.

Industry Briefing

Regenerative Medicine

Market Drivers

The following market drivers have created a new global race for regenerative medicine dominance.

- Rising healthcare costs and aging populations:
  - Healthcare costs in the U.S. were $2.4T or 16.6% GDP in 2008.
  - By 2040, the senior citizen population will double in the U.S. to about 70 million and about 25% of GDP could be devoted to healthcare by that time.
- Ever-increasing demand for a limited number of organs due to end stage organ failure:
  - 18 people in the U.S. die each day waiting for an available organ.
- Technological innovations in biomaterials, nanotechnology, drug delivery, cell therapies and combinations thereof are fueling the development of regenerative products.

Market Opportunities

In the area of injured tissues, researchers are attempting to use cellular therapeutics to repair bone fractures and knee joints, injured muscles (including damaged heart muscles), and damaged organs such as the liver, kidney, skin, and pancreas. Genetic disorders including Duchenne Muscular Dystrophy and Gauche's Disease and cancers such as leukemia and lymphoma, will also benefit from cellular therapies. The fastest-growing fields, which will have the easiest entry into the market, are projected to be orthopedics and wound healing.

Current consensus is that commercial products will appear in the market in the following order:

1. Orthopedics
2. Cardiology
3. Wound healing
4. Diabetes
5. Neurodegenerative diseases

1. ORTHOPEDICS

The orthopedic market, including spine, bone grafts, and bone substitutes, comprise a $1.2B opportunity in the U.S, a figure that is projected to grow at nearly 15% per year, or more than twice as fast as the overall orthopedic market. In 2002, more than one million procedures utilized some form of graft. According to leading investment-banking firm WR Hambrecht & Co., the number of surgical procedures using orthobiologics, bone graft substitutes in particular, will continue to increase.

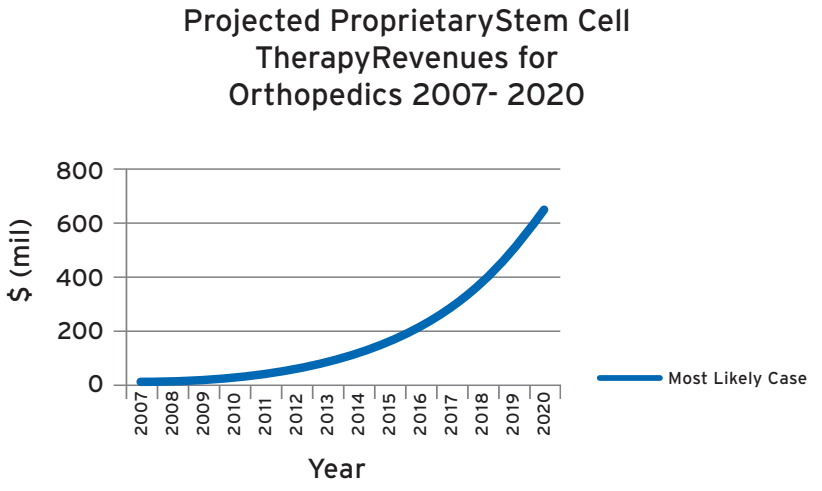
According to the U.S. Centers for Medicare and Medicaid Services, approximately 900,000 surgeries requiring bone restructuring or regeneration are performed annually, with the most common being spinal fusion (about 450,000 surgeries performed annually in the U.S.).

The current standard of care is bone autograft, a procedure in which the patient's own bone is harvested prior to surgery, then grafted to the damaged bone. However, complications due to the additional autograft surgery and limited quantity of material available for harvesting remain serious shortcomings to the autograft approach. Regenerative medicine therapy favourably compares to autograft and other available alternatives: non-viable bone (procured from cadavers and available only in limited quantities) and synthetic materials.

Industry Briefing

Regenerative Medicine

The leading stem cell therapeutic company focusing on the orthopedics market is Osiris Therapeutics, a public company since 2006 (NASDAQ) with a market capitalization of about $540M. Sales for the first two quarters in 2008 were $16.5M, up 7.8% over 2007 for their one product on the market, Osteocel. Osteocel is the first bone matrix product to provide all three bone growth properties: osteoconduction, osteoinduction, and osteogenesis. In the third quarter of 2008, Osteocel was sold to NuVasive Inc., a medical device company focused on spinal disorders. Osiris currently has two candidates in clinical trials. Prochymal, an intravenously administered formulation of mesenchymal cells, is in phase III trials for Crohn's disease and acute and steroid refractory Graft versus Host disease. Chondrogen, an injectable formulation of mesenchymal cells, is in phase II trials for arthritis of the knee. In November 2008 Genzyme Corporation partnered with Osiris for the commercialization of both products.



Source: Kalorama 2008

2. CARDIOLOGY

The total cost of treatment of coronary heart disease in the U.S. alone is estimated to be $165B per year. As of 2006, 16.8 million Americans are afflicted with coronary heart disease, 7.9 million with myocardial infarction and 9.8 million with angina pectoris. In 2006 approximately 1.3 million angioplasties and 448,000 coronary artery bypass graft operations were performed in the U.S. In 2004-2005, Ontario hospitals treated 48,520 inpatients with heart failure, 14% of whom died during their stay. Inpatient days for patients with heart failure (596,273) led to 90% occupancy of acute care hospital beds in the province at a cost of $367M. The most promising area for regenerative medicine is the treatment of myocardial infarction, since stem cells can stimulate injured myocardial tissue to repair and regenerate. More than seven million Americans experience a heart attack each year, requiring an estimated $33B in treatment. To date, 50 clinical trials involving 3,200 patients and 12 companies have investigated stem cell coronary treatments. In March 2007, Osiris Therapeutics and Mytogen released results from separate studies demonstrating that stem cells improve the pumping of diseased hearts. In May 2007, Baxter announced that a similar therapy decreased chest pain in 24 people. Overall, according to a meta-analysis published this year in the Archives of Internal Medicine, stem cell therapy provides patients with coronary heart disease with benefits above and beyond conventional therapy.

3. WOUND HEALING

Almost 2 million surgical procedures performed in the U.S. (7.9 million globally) require wound healing. Globally, 500,000 surgeries were performed to treat diabetic ulcers; 500,000 surgeries to treat venous ulcers, 45,000 burn surgeries; and 940,000 plastic surgeries are performed each year. The cost of dressings alone exceeds $5B per year. In Ontario, care for 4,192 chronic care patients with pressure ulcers cost the province $92,540 in 2005. The most common application for regenerative medicine is for the treatment of burns. The need to cover burns is immediate and skin grafts are essential for treatment. Skin grafts usually involve taking both the upper epidermal and underlying dermal layer from an unburned site on the patient's body or cadaver donor. Using regenerative medicine, the problems of scarring, infection, and poor adhesion can be significantly reduced.

4. DIABETES

The number of people with diabetes globally will likely double between 2003-2030. The U.S. alone will have over 30 million diabetics by 2030. The number of Ontarians with diabetes has increased by 69% over the last 10 years - and is projected to grow from 900,000 to 1.2 million by 2010.

One promising avenue of treatment is surgical transplantation of pancreatic islet cells; however, the procedure currently requires 600,000 functional islet cells from 2 donor pancreases. Whole organ transplant of the pancreas is another option. However, the supply of available organs is nowhere near the present demand. In 2005, there were 925,000 pancreas whole organ transplant surgical procedures performed in the U.S. and 3.4 million globally.

Regenerative medicine offers the possibility of implanting islet stem cells that would eliminate the need for any organ transplant or major surgical procedure. 2007 saw major developments in this area. Vitro Diagnostics claimed to have found a method of producing stem cell-derived islets that are structurally equivalent to islets derived from the pancreas. Two independent research teams based at Harvard and the University of Pennsylvania reported that adult pancreatic cells could maintain islet population without specialized progenitor cells. Geron Corporation and collaborators at the University of Alberta successfully differentiated human embryonic stem cells into islet-like clusters that secrete insulin in response to elevated glucose levels, demonstrating the feasibility of producing therapeutic cell types from human embryonic stem cells (hESCs).

5. NEURODEGENERATIVE DISEASES

Neurodegenerative diseases take a staggering toll on society. Every year, 795,000 people in the U.S. suffer a stroke, while 5 million have some degree of stroke-induced partial paralysis. 1.5 million people in the U.S. have Parkinson's disease with 52,000 new diagnoses each year. Over 5 million Americans are afflicted with Alzheimer's disease. Each year, 200,000 new cases of epilepsy are diagnosed, adding to the ranks of over 2 million existing epileptics. Traumatic brain injury affects 1.4 million Americans annually. The Centers for Disease Control estimates that at least 5.3 million Americans currently have long-term or lifelong need for help to perform activities of daily living as a result of TBI. Approximately 247,000 people in the U.S. live with spinal cord injuries, with 11,000 new cases occurring every year. There are 11,000 new cases of Multiple Sclerosis (MS) each year in the U.S. as well, adding to 400,000 people already living with the condition.

In the recent past, most neurodegenerative diseases and central nervous system injuries were regarded as permanent and irreparable. However, regenerative medicine offers the possibility of regenerating nerves and brain cells to cure central nervous system (CNS) injuries and neurodegenerative diseases. Regenerative medicine is already using biomaterial scaffolds, drug induced stimulation, bridges to aid nerve regeneration and neural stem cell injections to treat Parkinson's, MS, and Alzheimer's.

The possibilities here are many and varied.

Industry Briefing
Regenerative Medicine

Financing Landscape

The most prominent public initiative thus far has been the creation of the California Institute for Regenerative Medicine (CIRM) through Proposition 71, a ballot initiative approved by 59% of voters in 2004 that authorized the state to sell $3B in bonds over 10 years to fund stem cell research. The CIRM has committed more than $554 million to date. In May 2008, CIRM announced $271 million to help build 12 stem cell research facilities.

According to the U.S. Department of Health and Human Services more than $4B in private capital has been invested in regenerative medicine to date. The first dedicated regenerative medicine venture capital fund was launched in 2006. California-based Proteus Fund is a $225M fund focusing on cell therapies, tissue engineering, tools & devices and aesthetic medicines. The commercial potential of combining biomaterials with stem cells has rejuvenated interest in biomaterials companies especially by the venture capital industry.

Recent Deals in Regenerative Medicine

COMPANY	TECHNOLOGY	VC DEALS, 2008	NUMBER OF FIRMS INVOLVED	DEAL VALUE (U.S. MIL)	DATE
OncoMed Pharmaceuticals	Develops a series of therapies for solid tumors	2	8	$17.5, $43.13	January 2008, July 2008
BrainCells	Develops therapies for depression, mood disorders and other central nervous system diseases by using small molecule therapeutics to target neurogenesis	2	8	$30, $20.6	February 2008, April 2008
Five Prime Therapeutics	Develops and discovers therapeutic proteins and antibodies for treatment of clinical indications in oncology, immunology, diabetes, and regenerative medicine	1	8	$40.28	May 2008
Pieris AG	Develops Anticalins for therapeutic and diagnostic use	1	5	$38	March 2008
Tyrx Pharma	Commercializes implantable combination drug-device products utilizing biomaterials	1	2	$25	February 2008
Aldagen	Company products can identify and isolate adult stem and progenitor cells which can be administered to regenerate or repair tissue	1	10	$18.40	April 2008
Histogenics	Company aims to combine device technology with tissue engineering expertise to streamline the methodology of exogenous cell tissue growth	1	5	$13.10	September 2008
Fate Therapeutics	Investigating the use of small molecule drugs to coax adult stem cells into their embryonic state	1	4	$12.9	April 2008
iZumi Bio	Using the power of induced pluripotent stem (iPS) cells to transform drug discovery and enable the promise of regenerative medicine	1	2	not disclosed	June 2008

Source: Thomson Reuters 2008

Industry Briefing

Regenerative Medicine

Recent Highlights Among Regenerative Medicine Companies

DATE	SUMMARY
10/8/08	Stem Cell Sciences plc, a biotechnology company, has signed a license agreement with Cambridge Enterprise Limited, a wholly-owned subsidiary of the University of Cambridge, which gives Stem Cell Sciences access to certain technologies created by Austin Smith for reprogramming adult cells into stem cells. Both the companies are based in the UK. The agreement relates specifically to patents and know-how for technologies used to generate induced pluripotent stem cells or iPS cells from mammalian cells.
9/22/08	Cellerant Therapeutics, Inc., a US-based biotechnology company engaged in the development of hematopoietic stem cell-based cellular and antibody therapies for blood disorders and cancer, has been awarded a $13.5 million contract from the Biomedical Advanced Research and Development Authority (BARDA) of the Department of Health and Human Services for the development of a treatment for acute radiation syndrome (ARS). Cellerant would receive $3.4 million in the first year and, depending on development progress, up to $10.1 million in additional funds over three years.
9/3/08	Neurologix, Inc., a US-based biotechnology company, has exclusively licensed the worldwide rights, excluding China, for the use of the XIAP gene (x-linked inhibitor of apoptosis protein) from Aegera Therapeutics, Inc., a Canada-based clinical stage company focused on oncology and neuropathic pain, for therapeutic or prophylactic purposes in the treatment of Huntington's disease.
8/21/08	Embryome Sciences, Inc., a US-based wholly-owned subsidiary of BioTime, Inc., has signed a license agreement with Advanced Cell Technology, Inc. (ACT), a biotechnology company. Under this agreement, Embryome Sciences licenses portfolio of patents and patent applications from Advanced Cell Technology relating to induced pluripotent stem cells ("iPS") and embryonic stem cell differentiation technology. The license is for the commercialization of products in human therapeutic and diagnostic product markets. The technology licensed by Embryome Sciences covers methods for the transformation of cells of the human body, such as skin cells, into an embryonic and pluripotent state.
8/7/08	Chromos Molecular Systems, Inc. has entered into an arrangement agreement with Calyx Bio-Ventures Inc., a wholly-owned subsidiary of Chromos, and Modatech Systems Inc. Upon completion of the arrangement, Calyx would be the holder of all of the assets, property and undertaking of Chromos, together with additional cash of $2.35 million. In particular, Calyx would own all of Chromos intellectual property and all of the outstanding shares of Chromos subsidiaries, as well as 29% of the outstanding shares of Agrisoma Biosciences Inc.
8/1/08	Bioheart, Inc., a company engaged in the discovery, development, and commercialization of cell-based therapy products, has signed a non-binding letter of intent to acquire the worldwide rights to the POCKETECG device, from MEDICALGORITHMICS, Ltd., a high-technology company focused on development of solutions and systems for signal and data processing in cardiac monitoring, heart sounds and electrophysiology of the heart. Under the terms of the agreement, Bioheart and MEDICALGORITHMICS are expected to conduct their due diligence review within the next 60-90 days.
7/24/08	NuVasive, Inc., a medical device company, has acquired the Osteocel biologics business from Osiris Therapeutics, Inc., a biotechnology company, for $35 million in cash, plus additional milestone-based contingent payments not to exceed $50 million in either cash or stock, at NuVasives election.
7/22/08	Cryo-Save Group N.V., engaged in the collection, processing and storage of human adult stem cells, has acquired the remaining 50% of Cryo-Save Balcanica S.A., a distributor of Cryo-Save Group in the Balkans, for an initial consideration of EUR4.1 million payable in cash. Cryo-Save Group has also agreed make a deferred payment based on the performance of Cryo-Save Balcanica during a three year period. Kaupthing Bank acted as financial advisor and College Hill acted as public relations advisor to Cryo-Save Group.

Industry Briefing

Regenerative Medicine

Recent Highlights Among Regenerative Medicine Companies

DATE	SUMMARY
7/22/08	Roche Holdings, Ltd., a research-focused healthcare group in the fields of pharmaceuticals and diagnostics, has signed a definitive agreement to acquire Mirus Bio Corporation, a biotechnology company focused on the discovery and development of nucleic acid based technologies, for a consideration of $125 million. Mirus transfection reagents business would be divested into a standalone business to be known as Mirus Bio LLC. The transaction is expected to be completed during the second half of 2008.
7/11/08	Bioheart, Inc., a company focused on the discovery, development, and commercialization of cell-based therapy products, has secured worldwide non-exclusive distribution rights to the Bioheart 3370 Heart failure monitor from RTX Healthcare A/S, a developer and manufacturer of wireless medical devices.
6/18/08	MedCell Bioscience, Ltd., a regenerative medicine company, has merged with NovaThera, Ltd., a biotechnology company. The combined Company, would continue to trade under the MedCell Bioscience name, has a post merger valuation of about GBP30 million.
5/27/08	Kinetic Concepts, Inc. (KCI) has completed the acquisition of LifeCell Corporation, a provider of tissue repair products for use in reconstructive, urogynecologic, and orthopedic surgical procedures. Kinetic Concepts, Inc. (KCI), and LifeCell Corporation, have signed a definitive agreement whereby KCI would acquire LifeCell for $51.00 per share, or $1700 million in cash. The offer represents a 18% premium above the closing price of LifeCell common stock on April 4, 2008.
4/8/08	Lorus Therapeutics, Inc., through its a subsidiary GeneSense Technologies, Inc. has signed an exclusive multinational license agreement with Zor Pharmaceuticals LLC, a subsidiary of Zoticon Bioventures, Inc., to further develop and commercialize Virulizin for human therapeutic applications. The initial clinical development of Virulizin under the agreement will be in advanced pancreatic cancer. Under the terms of the agreement, GeneSense will be entitled to receive payments in excess of $10 million upon achievement of various milestone events and royalties that vary from 10-20% depending on achieving of sales of Virulizin.
2/27/08	On June 19, 2008, Stem Cell Therapy International, Inc. signed an amendment to the reorganization and stock purchase agreement with Histostem Co., Ltd., a biotechnology research company focused on stem cells. In accordance with the terms of the amendment, Stem Cell and Histostem Korea issued and delivered shares reflecting the acquisition of Histostem Korea into Escrow by Stem Cell pending resolution of outstanding litigation between Histostem Korea and Histostem, Inc.
2/27/08	On February 27, 2008, Regeneration Technologies, Inc., a processor of orthopedic and other biologic implants, and Tutogen Medical, Inc., a manufacturer of sterile biological implants made from human (allograft) and animal (xenograft) tissue, have announced the completion of merger of the two companies. The total value of the transaction is approximately $205 million. The name of the newly combined company is RTI Biologics, Inc. The stock will continue to trade on the Nasdaq Global Market under the symbol RTIX

Industry Briefing

Regenerative Medicine

Recent Highlights Among Regenerative Medicine Companies

DATE	SUMMARY
2/25/08	Organogenesis, Inc., a tissue regeneration company, has acquired NanoMatrix, Inc., a regenerative medicine company.
2/19/08	I-Flow Corporation, designer of ambulatory drug delivery systems, has acquired AcryMed, Inc.for $25 million in cash. The agreement contemplates the merger of a new subsidiary of I-Flow into AcryMed, with AcryMed being the surviving corporation as a wholly owned subsidiary of I-Flow.
1/31/08	Cryo-Save Group N.V., a stem cell bank, has agreed to acquire a 70% interest in its Hungarian distributor Sejtbank Egeszsegugyi Szolgaltato Korlatolt Felelossegu Tarsasag (Sejtbank) and Sejtbanks subsidiary Archiv Bunek s.r.o. in Czech Republic, for an initial consideration of EUR3.25 million payable in cash on completion. Cryo-Save Group has also an option to acquire a 30% of Sejtbank, for EUR1.4 million plus a performance bonus based on revenue growth.
1/17/08	Angiotech Pharmaceuticals, Inc. and Symphony Medical, Inc., which develops proprietary biopolymer and cellular-based biologic therapies, have entered into a licensing agreement to employ one of Angiotech's PEG-based biomaterials as part of a prophylactic therapy envisioned to mitigate the onset of post-operative atrial fibrillation (POAF) for patients undergoing coronary artery bypass grafting and cardiac valve surgeries. Under the terms of the agreement, Angiotech has been granted an equity position in Symphony Medical in exchange for the exclusive license of Angiotech's technology in the field of POAF. In addition, Angiotech will receive a royalty on end-user product sales should the product receive regulatory approval and is commercialized.
1/14/08	Regenetech, Inc., an adult stem cell company, is pleased to announce that it has signed a license covering the Republic of Korea for its proprietary stem cell expansion technology, cellXpansion, with Korea Stem Cell Bank Co., Ltd. (KSCB). Financial terms for the agreement were not disclosed.

Industry Briefing

Regenerative Medicine

Industry-Academia Collaborations

DATE	SUMMARY
10/23/08	Novo Nordisk, Cellartis AB, a stem cell biotechnology company, and Lund University Stem Cell Center have signed a collaborative research agreement for the development of insulin-producing cells from human stem cells. The collaboration aims to develop a cell therapy for the treatment of insulin-dependent diabetes and, in the longer term, a cure for diabetes. Under the agreement, Novo Nordisk acquires the exclusive rights to further develop and commercialize potential products for the treatment of Diabetes, while Cellartis acquires the exclusive rights to further develop and commercialize certain other products resulting from the technologies developed under the collaboration.
7/25/08	GlaxoSmithKline (GSK) will sponsor work at the Harvard Stem Cell Institute in a five-year $25M agreement. The collaboration will involve researchers conducting work in cancer, obesity, diabetes, and neurological, cardiac, and musculoskeletal diseases at Massachusetts General Hospital, Joslin Diabetes Center, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute. GSK will also help fund Harvard's "seed grant" program which supports early stage research.
6/17/08	The University of Toronto has entered into a research partnership with UCSF-affiliated Gladstone Institute to develop iPS cells. The University of Toronto has received $1M to build an iPS core facility by The Ministry of Research and Innovation.
6/12/08	Q Therapeutics, Inc. and Nicholas Maragakis, MD of Johns Hopkins University have received notification of a $0.8 million grant to be awarded from the Maryland Stem Cell Research Fund (MSCRF) to enable study of Q's human neural cell product Q-Cells(R) in preclinical models of Amyotrophic Lateral Sclerosis (ALS).
6/10/08	Pfizer and the University of California, San Francisco launched a three-year drug-discovery and development collaboration worth up to $9.5M. Efforts will be managed by UCSF's unit of QB3, the multi-campus California Institute for Quantitative Biosciences and Pfizer's newly formed division Biotherapeutics and Bioinnovation Center (BBC).
2/26/08	StemCyte, Inc. and Rutgers University have entered into a research and licensing agreement for a spinal cord injury therapy, that uses StemCyte's human umbilical cord blood (UCB) stem cells in conjunction with lithium. Under the terms of the agreement, StemCyte will provide financial sponsorship for Dr. Young's work at Rutgers' W.M. Keck Center for collaborative neuroscience and receive exclusive commercialization rights to the therapy.
2/13/08	Plasticell, Ltd, has entered into an agreement with King's College London, a college of the University of London, to exploit and market two human embryonic stem cell (hESC) lines. Under the terms of the agreement, Plasticell has obtained a licence to make, have made, use and sell the hESC lines KCL-001 and KCL-002 which were derived at King's College London by researchers based at Guy's Hospital, a UK fertility and stem cell research centre.
1/7/08	On July 7, 2008, BrainStorm Cell Therapeutics Inc, a developer of adult stem cell technologies and therapeutics in collaboration with the W.M. Keck Center for Collaborative Neuroscience at Rutgers, has completed a preclinical study to repair spinal cord injuries in animals through the transplantation of Brainstorm's neurotrophic factor (NTF) adult stem cells.

Industry Briefing

Regenerative Medicine

Acquisitions/Collaborations by Multinationals

DATE	SUMMARY
11/17/08	Pfizer announced the launch of a new research unit to be known as Pfizer Regenerative Medicine. The unit will explore the use of stem cells to develop future treatments that may prevent disability, repair failing organs and treat degenerative diseases. Pfizer Regenerative Medicine will be co-located in the biotechnology hubs of Cambridge, UK and Cambridge, Massachusetts and is expected to employ about 70 researchers.
11/4/08	Genzyme Corporation and Osiris Therapeutics, Inc., have signed an agreement for the development and commercialization of Prochymal and Chondrogen, two late-stage adult stem cell treatments. Osiris will commercialize Prochymal and Chondrogen in the US and Canada, and Genzyme will commercialize the treatments in all other countries. Genzyme will make a $130 million up-front payment to Osiris, with $75 million paid initially and $55 million to be paid on July 1, 2009. In addition, Osiris also has the potential to receive a total of up to $1,250 million in milestone payments from Genzyme.
7/21/08	Gamida Cell Ltd. has signed a licensing agreement with Amgen, Inc., for the use of a number of proprietary cytokines in the manufacturing of StemEx for Gamida Cell's pivotal registration study of StemEx and its subsequent commercialization. Under the terms of the agreement, Amgen would receive a minority equity interest in Gamida Cell in addition to royalty payments from future sales of StemEx for hematological diseases.
6/19/08	Bone Medical Limited, a biopharmaceutical development company, has signed a letter of intent with Hyundai Pharm. Co. Ltd., a pharmaceutical company, for granting a licence to sell Bone's CaPTHymone oral parathyroid hormone in South Korea. Bone Medical would qualify for an up-front payment, milestone payments related to product development, approval and launch events and payments for supply of bulk product. Bone would also receive royalties on annual sales of CaPTHymone by Hyundai in South Korea.
4/30/08	Medtronic, Inc. and Scil Technology GmbH have signed a development, licensing and supply agreement focused on the development of Scil's biologic rhGDF-5 (recombinant human Growth and Differentiating Factor 5) dental regenerative technology for use in bone regeneration for dental implant placement and treatment of periodontal disease.
4/29/08	International Stem Cell Corporation (ISCO) has signed an exclusive agreement with CellSystems Biotechnologie Vertrieb GmbH, a provider of cell culture products, to distribute laboratory-cultured models of human skin useful for testing the hazardous properties of consumer products and for dermatological and pharmaceutical research in the United States and Canada. The laboratory-cultured models of human skin, called EST-1000 and AST-2000 were developed by CellSystems and contain cells manufactured by Lifeline. These three dimensional skin cell models are used as alternative methods to animal testing in the field of Skin Corrosion, Skin Irritation, Skin Sensitization, Genotoxicity and Phototoxicity.
3/31/08	Cell Genesys, Inc. and Takeda Pharmaceutical Company Limited have formed a global alliance for the development and commercialization of GVAX immunotherapy for prostate cancer, Under the agreement, in exchange for exclusive worldwide commercial rights to GVAX immunotherapy for prostate cancer, Takeda will pay Cell Genesys an upfront payment of $50 million and additional milestone payments totaling up to $270 million relating to regulatory approval and commercialization of GVAX immunotherapy for prostate cancer in the United States, European Union and Japan.
2/19/08	Angioblast Systems, Inc. has entered into a collaborative agreement with Abbott Laboratories, Inc., a healthcare company, for the development and commercialization of angioblast's catheter-based cell therapy product for heart failure. Under the terms of the agreement, Abbott will provide funding for the collaborative New Drug (IND) submission from Angioblast to the US Food and Drug Administration (FDA) for a Phase 2 clinical trial in heart failure. In addition, Abbott has made an equity-based investment of $5 million in Angioblast.

Industry Briefing

Regenerative Medicine

Acquisitions/Collaborations by Multinationals

DATE	SUMMARY
2/12/08	Cellartis AB entered into a collaborative research agreement with Pfizer, Inc., for the development of a model system for the detection of human toxicity in vitro by using Cellartis's human ES technology. Cellartis will take the lead in the development of the human ES cell model system and will conduct validation compound testing, while Pfizer will provide expertise and capabilities in the design and optimization of the developmental toxicity prediction model.
1/16/08	Pfizer Inc., and Scil Technology GmbH have signed a licensing agreement for worldwide collaboration on Scil's cartilage specific growth factor CD-RAP. In addition to receiving royalties on the sale of any products that may be commercialised under this agreement, Scil is eligible for upfront and milestone payments of approximately $250 million depending on the achievement of various development and regulatory milestones.
1/7/08	On August 6, 2008, Genzyme Corporation, and Isis Pharmaceuticals, Inc. have started a phase III study of Mipomersen in patients with heterozygous familial hypercholesterolemia (heFH). The companies have updated the deal terms so that Isis would contribute up to $50 million in additional development funding for mipomersen, bringing Isis' development funding commitment up to $125 million. In exchange for this additional contribution, Isis has the opportunity to receive $75 million in milestone payments early.

Product Development Challenges

Tissue engineering is a young field and many technical and regulatory challenges lie ahead. Researchers are only starting to gain insight into cell interactions with scaffold materials.

While the potential of regenerative medicine is theoretically boundless, there are a number of commercial and product development unknowns:

1. REGULATORY CONSTRAINTS

While regulations vary from one country to another, a few features are common to almost all jurisdictions: most human cellular and tissue-based products are considered biologics; there is minimal regulation concerning autologous use; and manufacturers of these products must meet Good Manufacturing Practice (GMP) and Good Tissue Practice (GTP) guidelines.

In the U.S., regenerative medicine falls under the auspices of the FDA. The FDA has been developing a unified approach to the regulation of new regenerative medicine products by consolidating a number of regulatory programs into the Office of Cellular, Tissue, and Gene Therapies (OCTGT). This office is responsible for tissue, cellular therapy, gene therapy, cellular plus gene therapies, and tissue engineering. In addition, the FDA also created the Office of Combination Products (OCP) in 2002 to accelerate the regulatory review process of products that combine two or more regulated components, such as drug/device (e.g. drug-eluting stent), biologic/device (e.g. bioartificial organs), drug/biologic (e.g. recombinant proteins), or drug/device/biologic (e.g. orthopedic implant with anti-inflammatory drugs and growth factors) that are physically, chemically, or otherwise combined or mixed and produced as a single entity.

In April 2007, meanwhile, the European Union approved of a centralized regulatory process, The Advanced Therapies Regulation, for approving new tissue and cell engineering therapies, including embryonic stem cell therapies. This will supersede country-by-country guidelines, regulations, and procedures and make regulatory approval for regenerative medicine therapies faster and more efficient.

The FDA and other regulatory agencies take a proactive stance towards accelerated clinical development of regenerative medicine; as a result, stem cell therapies have reached pre-clinical and clinical trials for a number of diseases, such as Parkinson's, Huntington's disease, myocardial infarction and multiple sclerosis.

2. LEGISLATION

Most countries have adopted some form of legislation on the use of human stem cells in research. Though laws vary, human reproductive cloning is usually forbidden; creation of embryos exclusively for research purposes is usually prohibited, whereas, derivation of embryonic stem cell lines from excess in vitro fertilization embryos is usually permitted; and the utilization of adult stem cells for research purposes does not pose any ethical problem and is generally not addressed. Stances on therapeutic cloning are more divided, with about 30 countries in favour and 60 countries against. National policies in Europe differ widely with the U.K., Belgium, Spain and Sweden being the most permissive, and Germany and Italy being some of the most restrictive. More permissive countries allow for the procurement of surplus embryos and might also allow for the creation of human embryos for the procurement of stem cells (therapeutic cloning). Israel, Russia, Japan, Singapore, South Korea, China and India also allow for therapeutic cloning.

The United States' restrictive federal stem cell policy has created a window of opportunity for other countries to lead the regenerative medicine race. In June 2007 President Bush vetoed the latest attempt by Congress to ease restrictions on stem cell research funding. In the meantime, private industry, which is not affected by federal funding policies, has created new embryonic stem cell lines and a number of states encourage private investments and public/private partnerships at the state level. Eight states, California, Connecticut, Illinois, Iowa, Massachusetts, New Jersey, New York, and Rhode Island have statues that prohibit human cloning only for the purpose of initiating a pregnancy, or reproductive cloning, but allow cloning for research. President Barack Obama's recent reversal of the restrictive legislation implemented during President Bush's term opens up federal funding to scientists who work with embryonic stem cells.

3. TECHNICAL CHALLENGES

In tissue engineering and biomaterials, a number of factors require further study. Scaffold material determination, cell interactions with scaffold materials, functional integration of the tissue, and the modulation of development using humoral cues are still being optimized. In cellular therapeutics, factors controlling cell differentiation without causing cancer must be further investigated. One possible solution currently under investigation is injecting purer populations of stem cells and a lower number of them to reduce cancer formation.

A major change in recent years has been the growth of induced pluripotent stem cell (iPS cell) technology. The iPS approach allows derivation of patient-specific pluripotent cells from adult tissues. One major barrier to clinical adoption of this technology was the requirement for introduction of reprogramming genes using a retrovirus. Pioneering work by Andras Nagy (Toronto) and others has provided a new method for iPS cell establishment which offers great safety advantages. The new technology may help speed iPS cells to clinical utility.

Regenerative Medicine Global Leadership Race

Presently, the top 10 nations in regenerative medicine and specifically in stem cell therapy are the U.S., U.K., Canada, Singapore, Australia, South Korea, China, Japan, Sweden, and Israel. According to all indicators and research, success and global leadership in this emerging field of regenerative medicine will depend on a number of important criteria:

1. Government funding and support
2. World-class scientific research
3. Regulatory environment
4. Legislative constraints
5. Public awareness

Global Stem Cell Research Activity: Canada ranks among top 5 in Numbers of Scientists

Stem cell research includes embryonic, adult, hermatopoietic, and mesenchymal stem cells.
Source: Data compiled by TRAA using ISI citation analysis, research association reports, phone & e-mail interviews

TRRA
TORONTO REGION RESEARCH ALLIANCE

Industry Briefing
Regenerative Medicine

Comparison of Leading Global Nations in Regenerative Medicine

COUNTRY		PUBLIC FUNDING/YEAR (U.S. Mil)	DISTINCT STRENGTHS (+) AND WEAKNESSES (-)
U.S.		$938 (NIH, 2008)	+ largest committed funding, holds most patents, world class scientists - no federal funding for embryonic research, restrictive legislation
	CA	$495 for FY07-08 ($3,000 over 10 years committed)	
	MA	$6 committed ($1,000 committed for life sciences)	
	WI	$14M committed ($750 committed for life sciences)	
	NY	$14.5 for FY 07-08 ($600 over 11 years committed)	
	NJ	$250.7 for FY 07-08	
	CT	$30 for FY 07-08 ($100 over 10 years committed)	
	MD	$23 for 2008	
	IL	$5 for FY07-08 ($15 over 10 years committed)	
U.K.		£42 million for FY07-08	+ world class scientists, regulatory environment, U.K. stem cell bank - lack of central coordinated strategy, requires more funding
South Korea		$45 ($454 over 10 years committed)	+ central coordinated strategy, international stem cell bank will become global hub - lack of experienced scientists
Canada		$40	+ world class scientists - commercialization pipeline, clinical translation, funding
Australia		$35 (NHMRC, 2006)	+ strong gov't support, world class scientists, legalized cloning in Dec 2006 - lack of central coordinated strategy, requires more funding
Singapore		$25-29	+ strong gov't support, attracting world class stem cell conferences - lack of experienced scientists
Japan		$19.8	+ strong gov't support, preclinical focus, flagship research centers -strict regulatory
China		$6-26 ($33-126/5yr)	+ strong gov't support, focus on clinical translation, "Stem Cell and Tissue Engineering for Regenerative Medicine" project, Chinese Tissue Engineering Research and Development Centre has 14 pending patents - lack of experienced scientists, unclear regulatory environment
Sweden		$11	+ strong gov't support, has 30% of all existing embryonic stem cell lines of 2001 - looking for partnerships with Asia
Israel		$3.3-15	+ world class scientists, regulatory environment - no dedicated public funding policy

Industry Briefing
Regenerative Medicine

Canada's Global Competitiveness In Cellular Therapeutics

CRITERIA	CANADA'S GLOBAL POSITION
Government funding and support	4th
World class scientific research	1st/2nd
Regulatory constraints	ambiguous
Legislative constraints	medium
Public awareness	high

1. GOVERNMENT FUNDING AND SUPPORT:

- Canada ranks 4th globally with annual national spending between US$40-50M, largely dispersed by CIHR and the Regenerative Medicine and Nanomedicine Initiative (RMNI).

2. WORLD-CLASS SCIENTIFIC RESEARCH:

- On June 16, 2008, Ontario Premier Dalton McGuinty announced the partnership between the University of Toronto and the University of California, San Francisco (UCSF)-affiliated Gladstone Institute. Based on this partnership Canada's first iPS core facility was created with $1 million in seed funding granted by Ontario's Ministry of Research and Innovation. In an agreement announced at BIO Japan 2008, a consortium of the top Ontario scientists in regenerative medicine will be working with Dr. Shinya Yamanaka, creator of the first iPS cell, jointly located at both the Gladstone Institute and Kyoto University to share cell lines and protocols that will significantly accelerate the advancement of this revolutionary science.

- Furthermore, significant advances have already been made to improve the process of iPS cell creation. In March 2009, Dr. Andras Nagy (Mt. Sinai Hospital, Toronto) and colleagues announced a breakthrough virus-free iPS cell method which also allows for the removal of reprogramming genes.

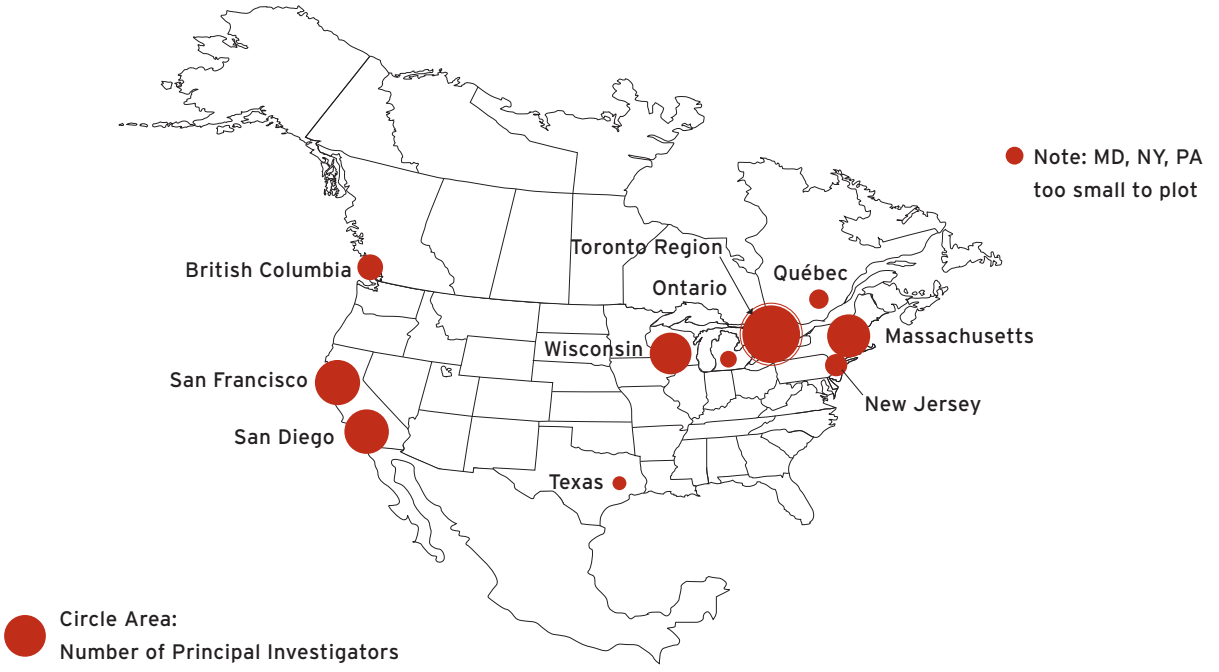
- Canada had the fastest rate of growth in external patent applications and industrial R&D investment among the G7 nations.
- Canada ranks 1st in cost competitiveness for biomedical R&D compared to other industrialized nations

i. Patents

- By any measure, Canada is a competitive player in the global stem cell patent landscape:
  - **Patent influence:** According to the 2005 Report & Recommendations of the UK Stem Cell Initiative, Canada ranks third in its share of the 16 most influential stem cell patents, behind the U.S. and the U.K.
  - **Canadian inventors (individuals):** In a core set of 4,265 PCT patent applications identified by Nature Biotechnology (NBT), 4.6% of first inventors were Canadian. The U.S. ranked first with 61% of first inventors, but Canada tied with the U.K. and Germany for distant second.
  - **Canadian assignees (organizations):** In NBT's analysis, the U.S. also dominated this category with 66% of first assignees, but Canada, the U.K. and Germany again tied for second with 4.6% of first assignees each.
  - **Patent filings within Canada:** Patent filings within a country reflect the importance of that country's market. NBT places Canada fifth in its share of the number of global stem cell patent filings between 1986-2005, behind only the global PCT filing mechanism, the U.S., Europe and Australia

- Leading Canadian assignees are Stem Cell Therapeutics (16 PCT patents), NeuroSphere Holdings (15 U.S. patents), the University of British Columbia (14 U.S. patents), AnorMed (9 PCT patents), and Robarts Research Institute (8 PCT patents).

North American Stem Cell Research Activity: Toronto region capacity is comparable to Boston and California



Source: Compiled by TRRA using ISI citation analysis, research association reports, phone & email interviews

TRRA TORONTO REGION RESEARCH ALLIANCE

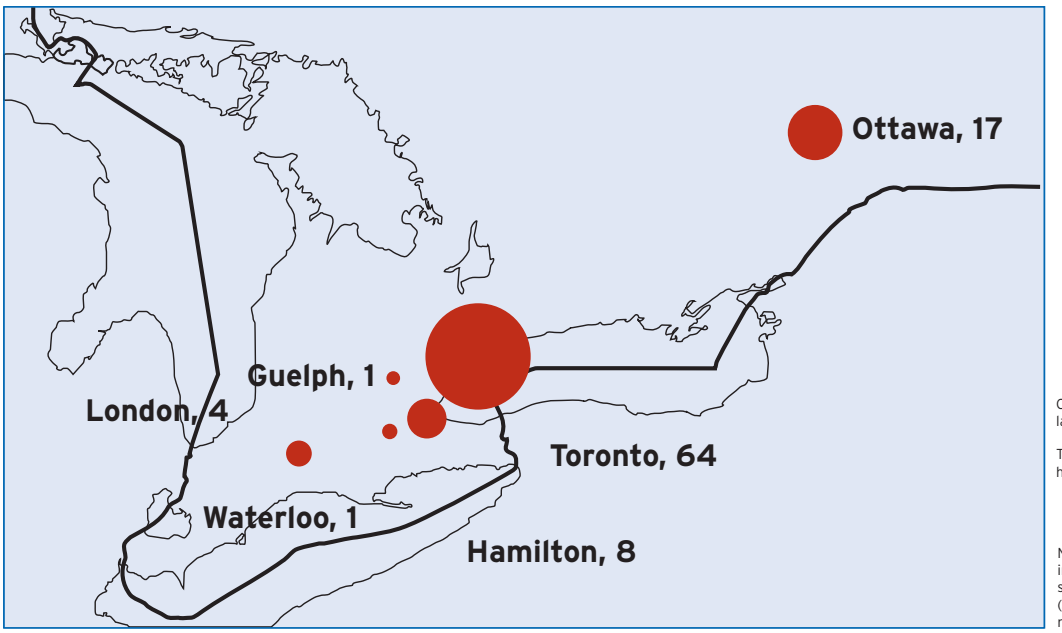
ii. Fundamental research depth and publications

- Canada published the second highest number of embryonic stem cell papers from 1991-2001, behind the U.S. (304 vs. 2,500).
- More importantly, Canadian papers are first in being referenced by later work, suggesting great international significance. When measured by citations per paper, Canadian papers (51.17 citations) fare considerably better than those of U.S. (39.1) and U.K. (30.92) authors.
- Canada boasts a long history of stem cell research. James Till and Ernest McCulloch of the Ontario Cancer Institute in Toronto were the first to identify hematopoietic stem cells in a landmark research paper in the 1960's. Based on their discovery, over one third of Canadian stem cell researchers are based in Ontario, mainly at the University of Toronto and its associated hospitals.
- Other landmark papers from Canadian researchers include those from John E. Dick, Suzanne Kamel-Reid, Alan Bernstein, and Derek Van der Kooy, all from the University of Toronto; Sam Weiss from the University of Calgary; and Peter Lansdorp and Connie Eaves from the University of British Columbia.
- In biomaterials research, six of the 20 leading researchers in North America are in Ontario.
- According to Nature Immunology, 35 classic hematopoiesis papers were written in the last half of the 20th century. Thirteen came out of Canadian labs. James Till and Ernest McCulloch, along with a host of other pioneering Canadian researchers and Ontario Cancer Institute alumni such as Gordon Keller, Lou Siminovitch, Norman Iscove, and Ronald Worton, contributed nine of the 15 classic papers published in the 1960s.
- In a major coup for Canadian research, Gordon Keller returned to Canada in 2006, leaving his position at the Mount Sinai School of Medicine in New York to head the new McEwen Centre for Regenerative Medicine at Toronto's University Health Network.

iii. Rank of world class Canadian researchers based on papers published and citations:

- 2nd-Janet Rossant, a Stem Cell Network investigator with The Hospital for Sick Children, Toronto
- 6th-Tak Wah Mak, University of Toronto
- 21st- Andras Nagy, Samuel Lunenfeld Institute, Mount Sinai Hospital, Toronto
- 22nd-Alexandra Joyner, formerly of the Ontario Cancer Institute.
    - All of the major research centres in Canada are populated by scientists steeped in Ontario's intellectually rigorous research environment. Both Alan Bernstein, head of CIHR, and Connie Eaves were at the University of Toronto, for example. This shared scholarly background provides a unique foundation for Canada's continuing stem cell research.
    - On an institutional basis, in terms of embryonic stem cell research publications, the University of Toronto places 2nd in the world, behind only Harvard but ahead of MIT, Baylor, and UCSF. Mount Sinai Hospital ranked 4th.

95 Principal investigators in Ontario performing Stem Cell Research



Over one third of this number have large research groups: 10-30 staff

Two thirds of all these investigators have research groups of 3-6 staff

Number of Principal Investigators in Ontario conducting stem cell research (area of circle proportional to number of Principal Investigators)

Source: Data compiled by TRRA usingdepartmental websites, internal interviews, UofT Faculty of medicine Annual Report, Vice Dean of Research (2008)

TRRA
TORONTO REGION RESEARCH ALLIANCE

Industry Briefing

Regenerative Medicine

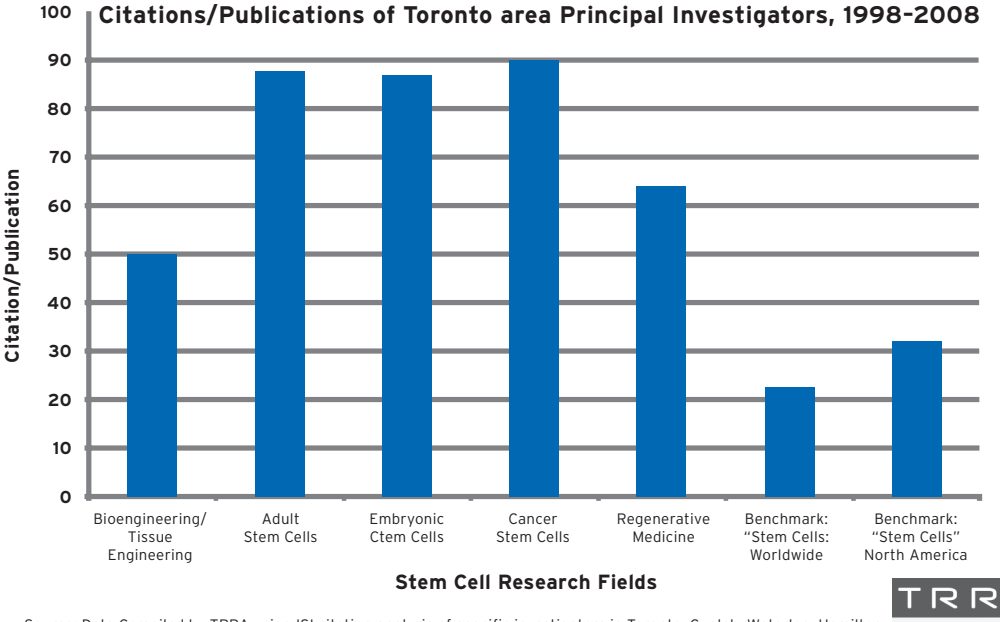
- Ontario is one of the largest biotech research centres in North America and is home to 40% of Canada's biotech companies.
- In North America, Ontario competes for research strength in regenerative medicine with major academic clusters in the U.S. While the U.S. is hampered by restrictive legislation, Canada can seize a window of opportunity to further develop its research strengths and commercialization networks.
- In May 2007, Governor of California Arnold Schwarzenegger and Premier of Ontario Dalton McGuinty announced the Cancer Stem Cell Consortium, an offshoot of the Canada-California Strategic Innovation Partnership. University of California, Berkeley's Stem Cell Center and Canada's International Regulome Consortium will partner on cancer stem cell research. The Consortium has already received its first $30M in funds from the Ontario Institute of Cancer Research and is poised to become a research powerhouse.

Braley Human Stem Cell Library, McMaster University

Housed within McMaster University's Stem Cell and Cancer Research Institute is Canada's first stem cell screening facility, the Braley Human Stem Cell Library (BHSCL). With access to a 190,000 compound library composed of commercially available and novel chemicals, advanced High Throughput Screening and Biophotonics, access to over 15 iPS cell lines, and established translational and clinical research capabilities, this screening facility has become a platform for innovations in regenerative medicine. It's screening platform is based on High Content Screening and High Content Analysis which allows for a rapid gain of knowledge about targets and compounds of interest in a cellular context.
Currently it is focusing on the discovery of novel non-viral reprogramming factors for the creation of iPS cells, creation of new adult stem cell lines, creation of a stem cell function database, development of novel methods for stem cell differentiation and the assembly of a supportive pluripotent human stem cell bank.
In development is a modular technology platform composed of automated cell culture, cellular and molecular assays, chemical and genetic modification of stem cells originated from multiple novel sources, imaging and data interpretation protocols.

Prominant Stem Cell Research Activities

Toronto Region'sExpertise is in five broad areas



Source: Data Compiled by TRRA using ISI citation analysis of specific investigators in Toronto, Guelph, Waterloo, Hamilton

TRRA TORONTO REGION RESEARCH ALLIANCE

3. REGULATORY CONSTRAINTS:

Canada's regulatory situation is similar to that of the U.S. Cellular or tissue products are classified as biological drugs and medical devices are regulated as devices. The Biologics and Genetics Therapy Directorate (BGTD) of the Health Products and Food Branch of Health Canada is presently reviewing the guidelines written in 2000 for the safety of cells, tissues, and organs for transplantation. At the moment, classifications are ambiguous. Health Canada has implied that classifications may depend on the final application of the regenerative medicine product.

4. LEGISLATION:

On March 11, 2004, the Canadian Senate adopted a legislative act known as An Act Respecting Assisted Human Reproduction and Related Research (AHR), which prohibits therapeutic cloning for research purposes only but allows for the use of unused embryos of 14 days' development or less if the donor has given an informed consent and has not been remunerated. Because there are so few excess in vitro fertilization (IVF) embryos available for research in Canada, this position might impede the pace of scientific research.

2008 AND EARLY 2009 WAS A PERIOD OF MANY NOTABLE DISCOVERIES IN ONTARIO IN REGENERATIVE MEDICINE WHICH WILL LEAD TO NEW TARGETS FOR DETECTION, THERAPY, UNDERSTANDING DISEASE ETIOLOGY, AND PREDICTIVE OUTCOMES.

Dr. Andras Nagy, Senior Investigator at the Samuel Lunenfeld Research Institute, Toronto and colleagues published a groundbreaking new approach to generating iPS cells in the March 1, 2009 issue of Nature. The new technique is virus-free and allows for the reprogramming genes to be removed after the induction phase. It is hoped that this elegant protocol will facilitate widespread adoption of iPS cells in basic and applied research and help make iPS cell therapy a near-term prospect.

Dr. G. Keller, Director of the McEwen Centre for Regenerative Medicine, led an international team with members from the US and Britain to successfully differentiate human embryonic stem cells into three types of progenitor heart cells. developed human heart cells from a KDR(+) human embryonic-stem-cell-population. Dr. Keller's group was able to induce differentiation into the three main cardiac cell types, both in vitro and in vivo, by treating cells with combinations of growth promoting factors-DKK1, FGF2, BMP4, activin A, VEGFA. It's the first study to identify a human cardiovascular progenitor cell that may give rise to the three distinct mesoderm-derived lineages required for a functional heart-cardiomyocytes, endothelial cells and vascular smooth muscle cells. This advance will accelerate the understanding of adult heart repair and soon lead to the test-tube creation of functioning heart tissue (Nature. 2008 May; 453: 524-528).

Drs C. Seguin and J. Rossant, Chief of Research for The Hospital for Sick Children, Program in Developmental and Stem Cell Biology in collaboration with Dr. A. Nagy from the Samuel Lunenfeld Research Institute at Mount Sinai Hospital and Dr. J.S. Draper of the McMaster Stem Cell and Cancer Research Institute discovered an important key to controlling stem cell development. By manipulating the expression of transcription factors, SOX7 and SOX17, they were able to control cell fate determination of human embryonic stem cells to produce stable progenitor cells capable of producing all endoderm cell types. Since these early endoderm cells can eventually become lung, liver, pancreas, and respiratory and digestive tracts and maintained their distinct profiles and self-renewal abilities through many cell culture stages, these results will lead to new tools to understand endoderm differentiation (Cell Stem Cell. 2008 August. 3:182-195).

Dr. M. Bhatia's group from McMaster University's Cancer and Stem Cell Biology Research Institute developed a test with 12 different criteria to reliably identify cancerous stem cells from healthy stem cells. Human embryonic stem cells with cancer-cell characteristics are difficult to differentiate from healthy stem cells since they both have the same expression of pluripotency markers, self-renewal properties, and potential for teratoma formation. Functional characterization of cancerous human embryonic stem cells makes the use of human embryonic stem cells for clinical applications significantly safer by reducing the risk of transplanting "healthy looking" yet cancerous rogue stem cells. (Nature Biotechnology. 2009 Jan. 27(1):91-97).

Industry Briefing

Regenerative Medicine

Table 1: Summary of Regenerative Medicine Companies and Product Development Status

173 companies currently have products in US clinical trials, comprised mainly of therapeutic treatments. These companies already have 64 products on the market compared with only 25 in 2007. There has been significant progress to bring regenerative medicine products to market with 112 products in preclinical trials (PC), 59 products in Phase 1, 96 products in Phase II, and 41 products in Phase III. These represent increases of 5% (PC), 181% (I), 111% (II), and 156% (III) respectively from 2007.

COMPANY	SYMBOL	CLINICAL STAGE				
		PC	I	II	III	M
Aastrom Biosciences Inc	ASTM	--	--	5	1	--
Access Pharmaceuticals Inc	ACCP	1	--	--	--	--
Acologix, Inc.	Private	--	1	1	--	--
Advanced Biohealing Inc	Private	--	--	1	--	--
Advanced Cell Technology Inc	ACTC	2	--	1	--	--
Aegera Therapeutics Inc.	Private	1	3	1		
Aldagen, Inc (formerly Stemco Biomedical, Inc)	Private	--	--	3	1	--
Alizyme plc	AZM (London Stock Exchange)	--	--	1	--	--
Alseres Pharmaceuticals, Inc.	ALSE	2	--	--	--	--
Amgen Inc	AMGN	--	2	3	3	4
Amorcyte Inc.	Private	--	1	--	--	--
Amoytop Biotech	Private	--	--	--	--	1
AM-PHARMA B.V.	Private	--	2	1	--	--
Angioblast Systems, Inc.	Private	3	1	2	--	--
Angiotech Pharmaceuticals Inc	ANPI	--	1	--	--	1
Apogenix GmbH	Private	1	--	--	--	--
Arteriocyte Medical Systems, Inc.	Private	4	1	--	--	--
Astellas Pharma Inc	ALPMF	--	3	--	--	1
Athersys, Inc.	ATHX	2	1	--	--	--
Axcan Pharma Inc.	Private	--	--	--	2	--
Baxter International Inc	BAX	--	--	1	--	--
Bayer Schering Pharma AG	Private	--	--	--	--	2
Benitec Ltd	BNIKF	--	1	--	--	--
Biocad	Private	--	--	--	--	1
BioCancell Therapeutics, Inc.	Private	1	--	1	--	--
BioCardia, Inc.	Private	--	2	--	--	--
Bioheart, Inc.	BHRT	1	--	--	1	--
BioMimetic Therapeutics Inc	BMTI	--	--	--	1	--
Bionovo Inc	BNVI	--	--	1	--	--
BioSante Pharmaceuticals Inc	BPAX	1	--	--	--	--
Biosyntech Inc	BSYI	2	--	--	1	--
Biothera.	Private	--	1	1	--	--
Biovitrum AB	Private	--	--	--	--	2

Industry Briefing

Regenerative Medicine

COMPANY	SYMBOL	CLINICAL STAGE				
		PC	I	II	III	M
Bolder BioTechnology, Inc.	Private	1	--	--	--	--
BrainCells, Inc.	Private	--	--	1	--	--
Bristol-Myers Squibb Company	BMY	--	--	1	--	1
Capstone Therapeutics	CAPS	1	--	--	--	--
CardioVascular BioTherapeutics Inc	CVBT	1	--	--	--	--
Celgene Corporation	CELG	1	1	2	--	2
Cell Genesys Inc	CEGE	--	--	1	--	--
Cell Therapeutics Inc	CTIC	--	--	--	--	1
Cellerant Therapeutics, Inc.	Private	2	--	--	--	--
Cellerix	Private	1	--	--	2	--
Celltran Limited	Private	--	--	1	--	--
Celsus Laboratories, Inc.	Private	1	--	--	--	--
Ceregene	Private	2	1	1		
Chemgenex Pharmaceuticals Ltd	CXSFF	--	--	--	1	--
Chemokine Therapeutics Corp	CHKT	1	1	--	--	--
Cleveland Biolabs Inc	CBLI	2	--	--	--	--
CSL Limited	CSL (Australian Stock Exchange)	--	1	--	--	--
CureTech Ltd.	Private	--	--	1	--	--
Curis Inc	CRIS	1	--	--	--	--
Cyathus Exquirere Pharmaforschungs GmbH	Private	1	--	--	--	--
Cytheris SA	Private	--	2	--	--	--
Cytori Therapeutics Inc	CYTX	1	--	--	--	--
DAIICHI SANKYO COMPANY, LIMITED	Global (Osaka and Tokyo Stock Exchange)	--	--	--	--	1
Derma Sciences Inc	DSCI	--	--	1	--	--
DRAXIS Health Inc	Private	--	1	1	--	--
Eleos Inc.	Private	--	--	1	--	--
Enkam Pharmaceuticals A	Private	--	1	--	--	--
EntreMed Inc	ENMD	--	1	--	--	--
Enzo Biochem Inc	ENZ	--	--	1	--	--
Enzon Pharmaceuticals Inc	ENZN	--	--	1	--	--
Epeius Biotechnologies Corporation	Private	1	--	--	--	--
EUSA Pharma Inc.	Private	--	1	--	--	2

Industry Briefing

Regenerative Medicine

COMPANY	SYMBOL	CLINICAL STAGE				
		PC	I	II	III	M
FivePrime Therapeutics, Inc.	Private	2	--	--	--	--
Fresenius AG	FRE (Frankfurt Stock Exchange)	--	--	--	1	--
Gamida Cell Ltd.	Private	--	1	--	1	--
Genetix Pharmaceuticals, Inc.	Private	--	--	2	--	--
Genmab A	GEN (Copenhagen Stock Exchange)	--	--	1	--	--
Gentium S.p.A	GENT	--	--	--	2	--
Genzyme Corporation	GENZ	1	--	6	3	2
Geron Corporation	GERN	8	1	1	--	--
GlaxoSmithKline plc	GSK	--	1	1	1	2
GNI Ltd.	Private	--	--	--	--	1
Hana Biosciences Inc	HNAB	--	--	1	--	--
Hangzhou Jiuyuan Gene Engineering Co. Ltd	Private	--	--	--	--	2
Histogen, Inc.	Private	2	1	--	--	--
Hospira Inc	HSP	--	--	--	--	1
ImmunoCellular Therapeutics, Ltd.	IMUC	1	--	--	--	--
Incitive Ltd	ICV (Australian Stock Exchange)	1	--	--	--	--
Intas Pharmaceuticals Ltd.	Private	--	--	--	--	1
Intercytex	ICX.L (London Stock Exchange)	--	1	2	--	--
IR Biosciences Holdings Inc	IRBS	1	--	--	--	--
Janssen-Cilag S.p.A.	Private	--	--	1	--	2
Johnson & Johnson	JNJ	--	--	1	4	2
KAKEN PHARMACEUTICAL CO., LTD.	Private	--	--	3	--	--
Keryx Biopharmaceuticals Inc	KERX	--	--	1	--	--
Kiadis Pharma B.V.	Private	--	--	1	--	--
Kuhnil Pharmaceutical Co., Ltd.	Private	--	--	--	1	--
Kuros Biosurgery AG	Private	--	--	1	--	--
Kyowa Hakko Kirin Co., Ltd. (formerly Kyowa Hakko Kogyo Co., Ltd.)	4151 (Tokyo Stock Exchange)	--	--	--	--	3
Laboratoires Pierre Fabre SA	Private	--	--	--	--	1
Living Cell Technologies Ltd.	Private	1		1		
Medistem, Inc.	MEDS	1	--	--	--	--

Industry Briefing

Regenerative Medicine

COMPANY	SYMBOL	CLINICAL STAGE				
		PC	I	II	III	M
Merck & Co Inc	MRK	--	3	--	--	1
Merck Frosst Canada Ltd.	Private	--	--	--	--	1
Mesoblast Limited	MSB (ASX Operations Pty. Ltd.)	4	1	1	--	--
MethylGene Inc	MYLGF	--	--	2	--	--
MicroIslet Inc.	MIIS	2				
Millennium: The Takeda Oncology Company	4502 (Tokyo Stock Exchange)	--	--	--	3	1
Mirna Therapeutics Inc.	Private	5	--	--	--	--
MolMed S.p.A.	Private	--	--	1	--	--
NatImmune A	Private	--	--	1	--	--
Nektar Therapeutics	NKTR	--	1	--	--	--
NeuroNova AB	Private	2	1	--	--	--
Nippon Shinyaku Co., Ltd.	4516 (Tokyo Stock Exchange)	--	--	--	--	1
Northern Therapeutics Inc.	Private	--	--	1	--	--
Norwood Immunology Limited	NIM (London Stock Exchange)	--	--	2	--	--
Novartis AG	NVS	--	--	--	--	1
Novocell, Inc.	Private	1	--	1	--	--
Novogen Ltd	NVGN	1	--	--	--	--
NsGene A/S	Private	1	1			
Oncomed Pharmaceuticals Inc	Private	--	1	--	--	--
Opexa Therapeutics Inc	OPXA	1	--	--	--	--
Organogenesis	Private	--	--	--	--	4
Orcrist Bio Inc.	Private	1	--	--	--	--
ORLING spol. s r.o.	Private	--	--	--	--	1
Orphan Australia Pty Ltd.	Private	--	--	--	--	1
Osiris Therapeutics Inc	OSIR	1	--	4	3	--
Otsuka Pharmaceutical Co., Ltd.	Private	--	--	--	--	1
Pharmagenesis Inc	Private	1	--	1	--	1
PharmaMar	Private	1	--	--	--	--
Pfizer Inc	PFE	--	--	1	--	--
Pluristem Therapeutics, Inc.	PSTI	5	--	--	--	--
Polyphor Ltd	Private	--	1	--	--	--

Industry Briefing

Regenerative Medicine

COMPANY	SYMBOL	CLINICAL STAGE				
		PC	I	II	III	M
ProCertus BioPharm Inc	Private	--	1	--	--	--
ProNeuron Biotechnologies (IS)	Private	1		1	1	
Prospect Therapeutics	Private	--	--	1	--	--
Reliance Life Sciences Pvt. Ltd.	Private	--	--	--	--	1
ReNeuron Group plc	Private	5	--	--	--	--
Repligen Corporation	RGEN	--	--	1	--	--
Roche Holdings Ltd	RHHBY	--	--	--	--	2
Rottapharm SpA	Private	2	--	--	--	--
Samaritan Pharmaceuticals Inc	SPHC	4	--	--	--	--
Sangamo BioSciences Inc	SGMO	2	--	1	--	--
Schering-Plough Corp	SGP	--	--	--	--	1
Scil Technology GmbH	Private	2	--	2	--	--
Seattle Genetics Inc	SGEN	--	2	1	--	--
Shanghai CP Guojian Pharmaceutical Co., Ltd.	Private	--	--	--	--	1
Shanghai Dongbao Biopharmaceutical Co., Ltd.	Private	--	--	--	--	1
Shionogi & Co., Ltd.	Private	--	--	--	--	2
Sigma-Tau S.p.A.	Private	--	--	--	1	--
Sinobiomed Inc.	SOBM	--	1	--	--	--
SkinMedica, Inc.	Private	--	--	--	--	1
Stem Cell Innovations Inc	SCLL	1	--	--	--	--
Stem Cell Therapeutics Corp.	Private	--	--	1	--	--
StemCells Inc	STEM	7	1	--	--	--
Stemline Therapeutics, Inc.	Private	1	1	--	--	--
Stryker Corp	SYK	--	--	--	--	1
SuperGen Inc	SUPG	--	2	--	--	--
Sygnis Pharma AG	SYGWF	1	--	--	--	--
TaiGen Biotechnology Co., Ltd.	Private	--	1	--	--	--
Taiho Pharmaceutical Co., Ltd.	Private	--	--	2	--	--
Takeda Pharmaceutical Company Limited	4502 (Tokyo, Osaka and Nagoya Stock Exchanges)	--	1	3	2	--
Targa Therapeutics Corp.	Private	--	1	--	--	--
Teva Pharmaceutical Industries Ltd	TEVA	--	--	1	2	1
TheraVitae Ltd.	Private	--	2	1	--	--

COMPANY	SYMBOL	CLINICAL STAGE				
		PC	I	II	III	M
TiGenix N.V.	Private	1	--	--	1	--
Topotarget A	Private	--	--	1	--	--
TorreyPines Therapeutics, Inc.	TPTX	--	1	--	--	--
Transition Therapeutics Inc.	TTHI	--	--	1	--	--
Tzamal Medical Group Ltd	Private	--	--	--	--	1
UCB S.A.	UCB (Euronext Brussels Stock Exchange)	--	--	--	--	1
United Therapeutics Corporation	UTHR	--	--	1	--	--
Vical Inc	VICL	--	--	1	--	--
Vion Pharmaceuticals Inc	VION	--	1	--	--	--
Viropharma Inc	VPHM	--	--	--	1	--
Wellstat Therapeutics Corporation	Private	1	--	--	--	--
Wyeth	WYE	--	--	1	1	2
XOMA Ltd	XOMA	--	--	1	--	--
Yissum Research Development Company	Private	1	--	1	--	--
Zelos Therapeutics Inc.	Private	1	--	--	--	--

NIH Definition of Regenerative Medicine

Appendix I

The National Institutes of Health (NIH) in the U.S. defines regenerative medicine as an emerging multidisciplinary field involving biology, medicine, and engineering that is likely to revolutionize the ways we improve the health and quality of life for millions of people worldwide by restoring, maintaining, or enhancing tissue and organ function. In addition to having a therapeutic application, where the tissue is either grown in a patient or outside the patient and transplanted, tissue engineering can have diagnostic applications where the tissue is made in vitro and used for testing drug metabolism and uptake, toxicity, and pathogenicity. The foundation of regenerative medicine for either therapeutic or diagnostic applications is the ability to exploit living cells in a variety of ways. Regenerative medicine research includes the following areas:

1) **Biomaterials:** including novel biomaterials that are designed to direct the organization, growth, and differentiation of cells in the process of forming functional tissue by providing both physical and chemical cues.

2) **Cells:** including enabling methodologies for the proliferation and differentiation of cells, acquiring the appropriate source of cells such as autologous cells, allogeneic cells, xenogeneic cells, stem cells, genetically engineered cells, and immunological manipulation.

3) **Biomolecules:** including angiogenic factors, growth factors, differentiation factors and bone morphogenic proteins.

4) **Engineering design aspects:** including 2D cell expansion, 3D tissue growth, bioreactors, vascularization, cell and tissue storage and shipping (biological packaging).

5) **Biomechanical aspects of design:** including properties of native tissues, identification of minimum properties required of engineered tissues, mechanical signals regulating engineered tissues, and efficacy and safety of engineered tissues.

6) **Informatics to support tissue engineering:** gene and protein sequencing, gene expression analysis, protein expression and interaction analysis, quantitative cellular image analysis, quantitative tissue analysis, in silico tissue and cell modeling, digital tissue manufacturing, automated quality assurance systems, data mining tools, and clinical informatics interfaces.

7) **Stem cell research:** Includes research that involves stem cells, whether from embryonic, fetal, or adult sources, human and non-human. It should include research in which stem cells are isolated, derived or cultured for purposes such as developing cell or tissue therapies, studying cellular differentiation, research to understand the factors necessary to direct cell specialization to specific pathways, and other developmental studies. It should not include transgenic studies, gene knockout studies or the generation of chimeric animals.

References

Fraser-Moodie, I. "The Future of Targeted Therapies" Business Insights. 2008.

"Stem Cells: Worldwide Markets for Transplantation, Blood Cord Banking and Drug Development." Kalorama. March 2008

"Technology, Talent and Capital: State Bioscience Initiatives 2008". Battelle Memorial Institute. June 2008

Burrill & Company. 2007. The Burrill Stem Cell Report.

Robin Young Consulting, RRY Publications LLC. 2007.
Stem Cell Industry 2007 Fall Update.

U.S. Department of Health and Human Services. 2005. 2020: A New Vision.
A Future for Regenerative Medicine.

MedMarket Dilgience. 2005. Tissue Engineering, Cell Therapy and Transplantation:
Products, Technologies and Market Opportunities, 2004-2014.

Biophoenix. 2006. Opportunities in Stem Cell Research and Commercialization.
Technology advances, regulatory impact and key players.

U.K. Stem Cell Initiative: Report and Recommendations. November 2005.

Science-Metrix & MNBC. 2004. Potential for Stem Cells Science and Technology in Canada:
Great promises and challenges.

Milken Institute. September 2006. Mind to Market: A Global Analysis of University Biotechnology
Transfer and Commercialization.

National Academies Press. 2002. Stem Cells and the Future of Regenerative Medicine.

Williams, D. 2005. Business models for Biomaterials in Regenerative Medicine.
Medical Device Technology. June 16(5):7-8.

Pooley, E. 2006. The stem cell revolution. Canadian Business.
November 20-December 3. pp. 31-35.

Weissman, I. 2005. Stem cell research. Paths to Cancer Therapies and Regenerative Medicine.
JAMA 294:1359-1366.

Giebel LB. 2005. Stem Cells-A Hard Sell to Investors.
Nature Biotechnology 23(7):798-800.

2005. Stem cell revolution: Big Opportunity for Investors.
BioPharm International. May.pp.18-19.

Neilssien T. 2006. Adult Stem Cells for Orthopedic and Spine Repair. IN VIVO:
The business an medicine report. Pp.48-50.

Author Unknown. "Stem Cell Research". National Conference of State Legislatures.
January 2008<http://www.ncsl.org/programs/health/genetics/embfet.htm>

Tigerstrom, B.J. The Challenges of Regulating Stem Cell-Based Products. Trends in Biotechnology.
2008. Vol.26(12):653-8

MaRS Discovery District

Contact info: John McCulloch PhD, jmcculloch@marsdd.com

MaRS Centre South Tower, 101 College Street, Suite 100, Toronto, Ontario, Canada M5G 1L7
T 416.673.8100 F 416.673.8181 www.marsdd.com