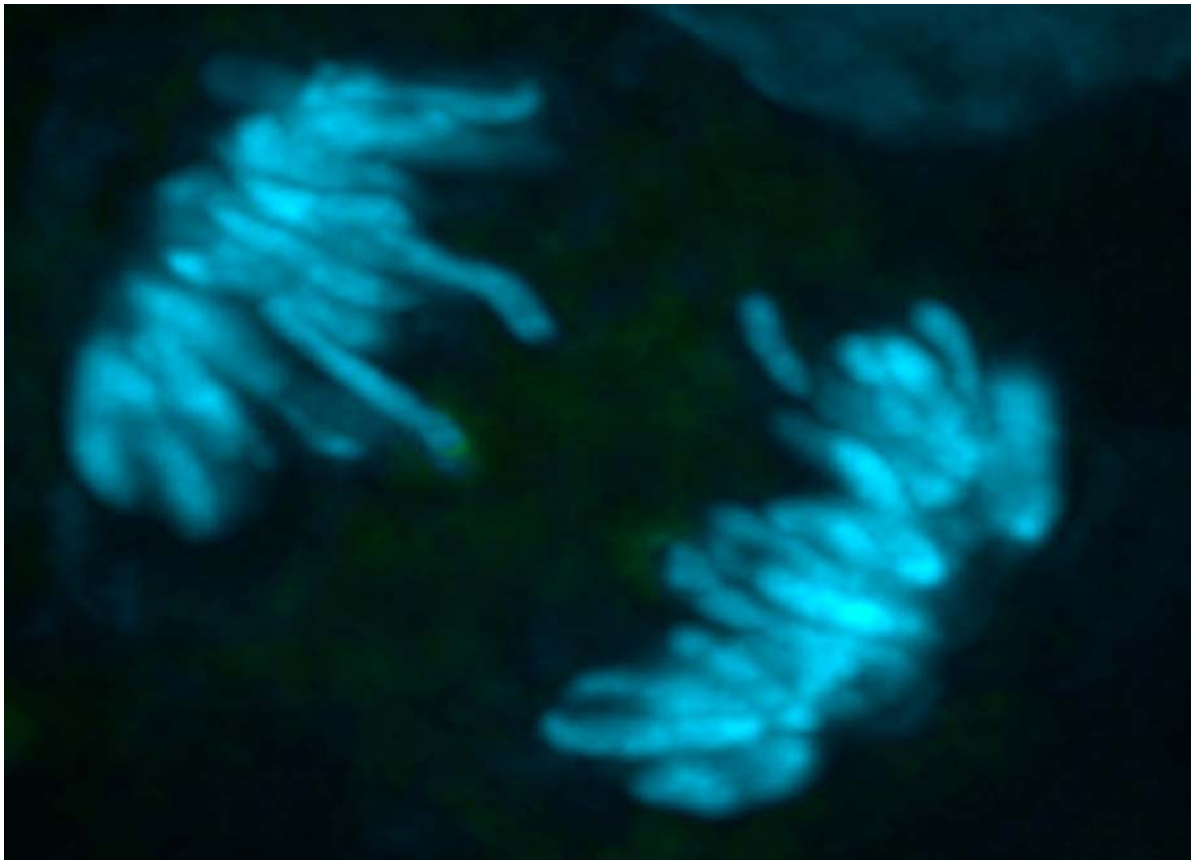
Regenerative Medicine: Cures, Market Potential and Commercialization



Cellular Mitosis Courtesy JCB

A White Paper by:

ALTURUS
Biomedicine

Introduction. Current national healthcare costs are in excess of $2.0 trillion annually[1], or 13% of the GDP, and may reach 25% of the U.S. GDP by 2040. The majority of these costs come from recurring treatment of chronic diseases that arise as a result of organ failure due to irreversible damage of terminally differentiated cells. Almost 1 out of every 2 American adults have at least one chronic disease; 7 out of 10 deaths are due to chronic disease.[2] Regenerative Medicine overcomes this problem as it potentially cures rather than treats diseases. As well, it will significantly reduce healthcare costs by sharply decreasing or eliminating recurring treatments.

Regenerative Medicine. Regenerative Medicine is broadly defined as a multidisciplinary approach to restoring, or providing new tissues for damaged ones. As a field, it incorporates many, if not all, aspects of modern biomedical science to create and/or replace damaged tissues or organs. Restorative Medicine addresses the restoration of function through bioartificial devices (e.g., brain-device interfaces), bioengineering (exoskeletons for paraplegics) and other organ-device applications (eye implants to restore vision). For simplicity, regenerative/restorative medicine and other innovative medical solutions are captured herein by using the term "regenerative medicine". Adult stem cell[3] therapy and its related fields such as stem cell-based devices are currently leading the race for regenerative medicine-based cures for a number of intractable diseases (see below).

A recent successful tissue transplant demonstrates the power of regenerative medicine and stem cells[4]. In March 2010, Harvard Bioscience announced the launch of its regenerative medicine product, the "In Breath" bioreactor[5]. In 2008, this bioreactor was used to grow a replacement lung bronchus (airway) in a patient whose own bronchus was damaged by disease. In a landmark transplantation surgery, a human trachea was removed from a cadaver and denuded of cells - leaving behind only the extracellular tissue scaffold. The bioreactor was used to colonize the scaffold with the patient's own adult stem cells. After 4 days in the bioreactor, the newly tissue/stem cell engineered trachea was implanted in the patient, replacing her defective left main bronchus (compare circles in Figure 1). The patient was reported

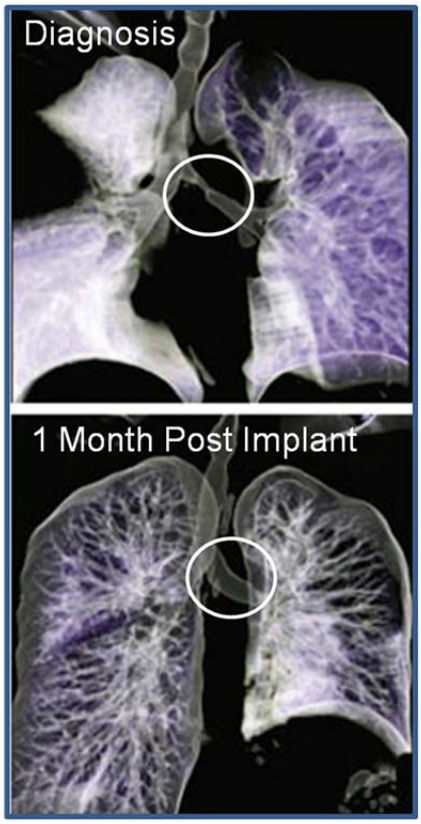


Figure 1. Regenerative Medicine: Restoration of a Diseased Airway. See Text *The Lancet 372:2023. 2008*

[1] McKinsey Global Institute "Accounting for the cost of US Healthcare: A new look at why Americans spend more. McKinsey & Company, 2008

[2] http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5311a1.htm

[3] "Adult stem cells" and "Stem cells" are used interchangeably in this document. Embryonic Stem cells are only used where cited. MRM does not anticipate using Embryonic Stem Cells.

[4] Paolo Macchiarini; Philipp Jungebluth; Tetsuhiko Go; M Adelai Clinical transplantation of a tissue-engineered airway The Lancet 372 , 2023. 2008

[5] http://www.globenewswire.com/newsroom/news.html?d=186144

as making full recovery with no immune rejection problems, as the transplant was essentially her own tissue.

Regenerative medicine field is a nascent, but fast-growing commercial industry that is predicted to have high market value[6]. In response to strong market demand, the industry has a robust pipeline of therapeutic candidates in various phases of preclinical and clinical trials. Several major pharmaceutical companies, GlaxoSmithKline, Pfizer, Novartis, Novo Nordisk, Roche, and Teva, have or will enter the stem cell market in the next five years. Moreover, strategic partnerships between pharmaceutical and stem cell research companies are sharply increasing, given pharmaceutical industry needs for innovative, competitive therapies.

Regenerative Medicine Market and Unmet Need. Current national healthcare costs are in excess of $2.0 trillion annually[7], or 13% of the GDP, and may reach 25% of the U.S. GDP by 2040. The majority of these costs come from recurring treatments of diseases that arise as a result of organ failure due to irreversible damage of terminally differentiated cells. Regenerative Medicine overcomes this problem as it potentially cures rather than treats diseases. As well, it will significantly reduce healthcare costs by sharply decreasing or eliminating recurring treatments.

MARKET POTENTIAL. The market potential for regenerative medicine therapies is driven by a strong unmet need and powerful market drivers. A recent US report[8] from Dept. of Health and Human Services (DHHS) stated "*This revolutionary technology has the potential to develop therapies for previously untreatable diseases and conditions. Examples of diseases that regenerative medicine can cure include diabetes, heart disease, renal failure, osteoporosis and spinal cord injuries. The current world market for replacement organ therapies is in excess of $350 billion and the projected US market for regenerative medicine in 2025 is estimated at $500 billion*". The stem cell market (a subset of the regenerative medicine market) is also strong. Global sales reached $410 million in 2008, and are estimated to grow to $4.68 billion by 2014 (Figure 2)[9]. Confirming this, analyst Robin Young, projects that the U.S. stem cell therapy market will generate well over $8.5 billion in revenue by 2017 and estimates that stem cells will be used therapeutically in as many as 2 million annual procedures[10].

Regenerative Medicine therapies are rapidly moving into the clinic. From 2005 to 2008, the overall number of clinical trials increased[11]. Specifically, the number of Phase I trials increased about 85% and the number of Phase II trials increased about 42%. The number of Phase III and Phase IV trials decreased due to trial failure. This perhaps reflects the early nature of these therapies, as they would have started the clinical path 7 – 10 years ago.

---

[6] Stem Cell Research: Market Trends, Investment Trends, and Pipeline Analysis. February, 2010. Report GBIHC009MR. GBI Research.

[7] McKinsey Global Institute "Accounting for the cost of US Healthcare: A new look at why Americans spend more. McKinsey & Company, 2008

[8] The U.S. Department of Health and Human Services report, "2020 Vision -- A Future for Regenerative Medicine"

[9] Advances in the Stem Cell Industry: The Future Impact of Innovation, and an Evaluation of the Commercial Landscape. www.companiesandmarkets.com/r.ashx?id=3CP03OFNH168616

[10] 2/2/8/2008 Press Release: NeoStem Reports Positive Stem Cell Industry Research Trends From The Journal of the American Medical Association and Third Annual Stem Cell Summit.

[11] Stem Cell Research: Market Trends, Investment Trends, and Pipeline Analysis. February, 2010. Report GBIHC009MR. GBI Research.

Pharmaceutical companies are exploring the use of stem cells in drug discovery in order to accelerate the development of novel drug molecules. The industry also lacks human material for preclinical safety assessment. Two of the leading causes of pre-clinical failure of new compounds are hepatoxicity (liver) and cardiotoxicity (heart). For example, one pharmaceutical company estimated that clinical failures based on liver toxicity cost the company more than $2 billion over the last decade[12]. Human stem cell-derived hepatocytes and cardiomyocytes therefore are expected to result in the creation of new assays to assess adverse effects early in the development phase.

It is clear that there remains a critical "funding gap" in establishing regenerative medicine/stem cell companies. The capital needs for establishing and running such companies are high. Although the current political environment is supportive, funding needs remain urgent. At present, venture capital firms are cautious about investing in stem cell companies. Seed round and other institutional investments are scarce. Current NIH funding for companies, while helpful, is difficult to obtain, slow and insufficient to cover costs. Increased federal focus is being placed on basic academic research in regenerative medicine. For example, the DHHS recently proposed the formation of the Federal Initiative for Regenerative Medicine (FIRM) with a goal of "tissues on demand" in 20 years[8]; however, this initiative is yet to be funded.

INDUSTRY BUSINESS MODELS. There are various business models in the stem cell industry; a common model is a hybrid one wherein the stem cell company sells reagents and/or cells (research tools) while also developing proprietary therapies. Therapy-based companies are predicted to realize the highest profits[13], although the time to reach market is considerably longer. Therapy-based companies are the most prevalent (~70%) of regenerative medicine companies, followed by those selling R&D tools (~25%) and then by miscellaneous advisory/service provider firms. Despite its current growth rate and ongoing clinical trials, the field lacks necessary infrastructure. In particular, there is an urgent need for large-scale cell-production facilities and products to service them.

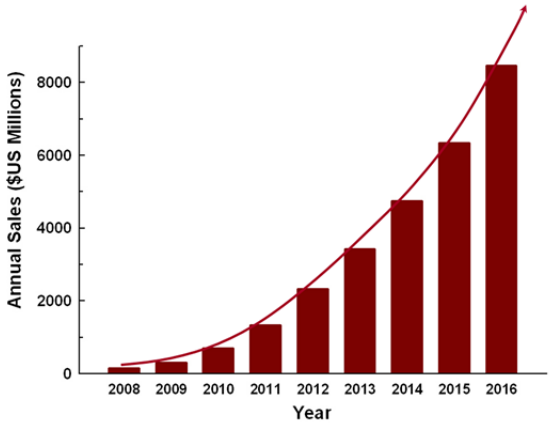


Figure 2. Six-year Stem Cell Market Projection. (See Text).

As with drug development, partnerships between large pharmaceutical companies and research-based stem cell companies will be important to the regenerative medicine industry. Typically, pharmaceutical firms fund the research and development of the therapy in return for a negotiated part of, or the entire resultant products(s). The stem cell research company receives an upfront fee, licensing fee(s), and potential milestone and royalty payments. GlaxoSmithKline, Johnson & Johnson, Novartis and Roche have become active in the regenerative medicine industry through investments and/or partnerships. In 2008, Pfizer became the first large pharmaceutical company to start operating a dedicated, internal global research program, known

[12] Technology Review, 107:58-65, 2004.

[13] Stem Cell Research: Market Trends, Investment Trends, and Pipeline Analysis. February, 2010. Report GBIHC009MR. GBI Research.

as "Pfizer Regenerative Medicine." Examples of recent key partnerships between pharmaceutical and research companies are:

- Novartis and Epistem. (2009): Novartis provides research funding for stem cell drug targets. Epistem will receive up to $45 million in milestone payments and undisclosed tiered royalties for each drug developed from those targets.
- Novo Nordisk and Cellartis. (2008): Novo Nordisk acquires the exclusive rights to further develop and commercialize potential products for the treatment of diabetes. Cellartis will receive milestone payments of more than €100 million (Euros) if a product is successfully commercialized.
- Pfizer and Novocell. (2008): Pfizer funds Novocell's research, which concentrates on turning human embryonic stem cells into pancreas cells to treat diabetes. Novocell received an upfront fee, researching funding, and potential milestone payments. Amounts were not disclosed.
- GlaxoSmithKline and Harvard Stem Cell Institute. (2008): A five-year, $25 million+ collaborative agreement where GSK supports Harvard SCI for innovative and early stage research in stem cell biology.

Recommendations from Industry and Academic Thought Leaders. In assessing the market potential of regenerative medicine, Alturus Biomedicine interviewed eight leaders in the field. As might be expected with such a broad-based industry, opinions varied. Nonetheless, certain recurring themes were evident and these help guide the formation of this plan.

There was an almost universal feeling that effective cell-based therapies were 10+ years off. This was felt to be due to an expected increase rigor in regulatory requirements and the complexities of developing the therapies. Clearly, some of the current clinical trials will yield positive results in the next five years, particularly in more readily addressable diseases like macular degeneration of the eye. More complex diseases require both improved infrastructure and clinical protocols; each takes development time.

A number of near-term opportunities exist. It was felt that there is an urgent need for enabling technology, such large scale production capacity. There is also a need for biological and small molecules that regulate the fate of stem cells, as the ability to produce one cell type from a multitude of potentialities is crucial to the field.

As these discussion ranged over a lot of territory, some of the comments were not germane to the present analysis. Nonetheless, a number of salient comments did occur that are helpful as background (comments paraphrased):

- "widely available GMP production facilities are needed"
- "Enabling (cell fate) technologies are needed"
- "There is no further need for libraries of stem cells; the field is overrun"
- "There is no longer a real need to derive human embryonic cell lines, as over 180 human embryonic cell lines exist…iPS cells obviate this need"
- "Service companies are a poor model… hybrid companies work better"
- "Stem cell IP is complex...clear rights are needed"

Competitive Landscape. The stem cell industry undergoes intense and rapid technology change

and is predominantly a competition market. The competitive environment is a mix of regenerative medicine/stem cell companies, biopharmaceutical companies, academic research institutions, and governmental agencies. Companies focused on the development of drugs and therapies often target the same diseases. Most of companies compete strongly against each other based on their intellectual property portfolio and the efficacy of products.

The US accounts for 90% of the current worldwide market in regenerative medicine. However, other countries are making inroads and may grow faster than the US market. Stem cell research is an integral part of both developing cell-based therapeutics and is necessary for its commercialization; a fact now recognized by most major countries of the world. The US has led this field for decades and this intellectual prowess has translated into its current worldwide lead in the market. Nonetheless, there are now more than 300 companies worldwide are actively developing stem cell therapies, and over 70 disease indications are under investigation

Another indication that the US presence in regenerative medicine is in danger of being eclipsed is the fact that more than 40% of the regenerative medicine firms founded since the year 2000 have been outside of the U.S. Increasingly, patients are traveling from developed nations to countries where they can readily obtain stem cell therapies. These nations include China, Thailand, Germany, the Dominican Republic, Costa Rica, Israel, and Argentina. Such activities demonstrate an urgent unmet need and a public acceptance, if not desire, for regenerative medicine therapies.

As mentioned, regenerative medicine shows considerable diversity in company types. It is necessary to evaluate those companies based on their primary area of business, e.g., stem cell therapies vs. R&D Tools. Although there are several hundred companies in the field, only a handful are industry leaders:

- Aastrom Biosciences. (Device-based Cell Therapy & R&D Tools). Developing autologous cell products based on proprietary device-based tissue repair cell technology. Aastrom's Tissue Repair Cell (TRC) products are currently in clinical trials for cardiac and vascular regeneration applications.
- Advanced Cell Technology (Cell Therapy). ACT specializes in the development of cellular therapy for the treatment of rare and common diseases by applying stem cell-based technologies and other proprietary methods in the area of regenerative medicine.
- ArunA Biomedical. (R&D Tools). Uses cellular technology combined with proprietary growth- media to make cell line kits for drug discovery and basic research. ArunA's cell lines are renewable and readily grown into large populations needed for today's high throughput research.
- Athersys. (Cell Therapy & R&D Tools). Clinical-stage biopharmaceutical company with a pipeline of therapeutics to treat significant and life-threatening diseases. Lead programs are in the areas of obesity, myocardial infarction, and bone marrow transplant.
- Cellular Dynamics International (CDI). (R&D Tools) CDI is collaborating with several pharmaceutical partners to develop and deploy a number of cell types derived from induced pluripotent stem (iPS) cells to aid drug discovery and toxicity testing.
- Fate Therapeutics. (Drug Discovery) The company is using stem cell biology to develop therapeutics based on modulating cell fate. The Company's first therapeutic candidate entered clinical trials in early 2009 in hematopoietic stem cell support.
- Geron. (Cell Therapy & Drug Development). The company is advancing an anti-cancer drug and a cancer vaccine through multiple clinical trials in different cancers. Geron is the first company approved by the FDA for a clinical study on human embryonic stem cell-based therapy in humans.
- International Stem Cell Corporation (ISCC). (Cell Therapy). ISCC has developed a process to derive stem cells similar to Embryonic Stem Cells without the need for fertilized embryos, thus avoiding ethical issues.

- iPerian. (Drug Discovery). Plans to use precise human disease models to find new molecular targets and develop proprietary therapeutic small molecule or biologic drugs for its own pipeline to treat specific diseases.
- Neostem. (Cell Therapy). First to provide adult stem cell collection and storage services to the general population and are developing therapeutics in the adult stem cell area.
- Osiris Therapeutics (Cell Therapy). Stem cell therapy company focused on developing products to treat serious medical conditions in the inflammatory, orthopedic, and cardiovascular areas. Several products are under development including two formulations of mesenchymal stem cells.
- Progenitor Cell Therapy. (R&D Tools). Client-based cell therapy services that support the development of cellular therapy by providing compliant cell manufacturing and consulting services.
- Stematix. (R&D Tools). Regenerative medicine technology and solutions provider, accelerating the global use of stem cell therapy.
- Stem Cells. (Cell Therapy & R&D Tools). Engaged in stem cell therapeutics and enabling technologies for use in stem cell-based research and drug discovery. Cellular medicine programs target diseases of the central nervous system and liver.
- Stem Gent. (R&D Tools). Provides proprietary reagents and tools developed and proven for reproducibility by some of the world's leading stem cell scientists.

Stem Cell Classifications. Stem Cells are named based on their tissue source. In general, there are three types: embryonic stem cells, cord blood stem cells and adult stem cells. These cells differ in their ability to generate differing types of tissues (potentiality), self-renewal capacity and ability to function in vivo.

Embryonic stem cells are produced from surplus embryos of in vitro fertilization procedures (in the case of humans) donated for research purposes with informed consent of the donors. Embryonic stem cells are the most flexible and versatile among the different stem cell types. They hold immense potential and promise for a wide range of disease conditions. Embryonic stem cells are distinguished by two properties: pluripotency and capability to replenish themselves (self-renew) in-definitely. Pluripotency is defined as the ability to differentiate into all cell types in the body. These characteristics allow allows embryonic stem cells to be employed as powerful research tools, as well as being the basis for cellular therapies. However, the development of replacement therapies using embryonic stem cell-derived cells is burdened with social and religious controversy regarding the use of human embryos, as well as issues involving immune rejection of the transplanted cells.

Cord blood stem cells represent a transitional state between embryonic and adult stem cells. Cord blood stem cells are derived from umbilical cord blood, after the umbilical cord has been detached from the newborn. Cord blood contains stem cells, including blood-forming stem cell s, which can be used to treat blood diseases and genetic disorders. Usually, cord blood derived stem cells are used in allogeneic (between individuals) stem cell transplantation. Patients transplanted with these cells are less likely to face the problem of Graft versus Host Disease (GvHD). While clinically proven and useful, their limited number (in a sample) poses problems in terms of adult transplantation, as does delayed engraftment.

Adult stem cells are derived from adult tissue samples. They are predominantly multi-potent cells that generate most cell types (Figure 3). Adult stem cells have been utilized for over 35 years in the form of bone marrow transplantation. As a result, adult stem cell research is more advanced relative to other types of stem cells and novel technologies have been developed to utilize them. Adult stem cell research is not controversial and a number of adult stem cell therapies are expected to be launched in approximately 10 years.

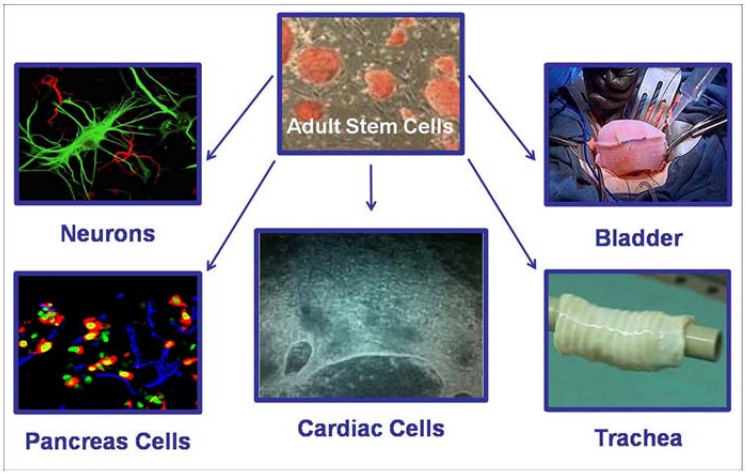


Figure 3. Adult Human Stem Cells Make Tissues and Organs

An important milestone in stem cell technology occurred in 2007 when Japanese researchers reprogrammed adult human tissue cells (e.g., skin fibroblasts) into a stem cell state, using defined genetic factors[14]. These cells are called induced pluripotent stem (iPS) cells and ar e believed to be near-identical in nature to the pluripotent, embryonic stem cells. This is an important advance in stem cell science and commercialization, as iPS cells offer an alternative to the controversial use of embryonic cells. Moreover, iPS cells are autologous (patient-specific) thus overcoming the problem of immune rejection issues.[15] iPS cells can also be used in drug discovery, safety testing, and enable testing in a wider range of cell types.[16]

The discovery of iPS cells also removed a roadblock for pharmaceutical company involvement, as many were concerned about using embryonic stem cells, given the controversy. Research on iPS calls continues at a breathtaking pace. Recently, iPS cells have been used to generate cellular models of disease (”disease in a culture dish”) which were then used to screen and evaluate drug candidates[17].

Conclusion. Given the potential to cure and not just ameliorate disease, regenerative medicine represents the future of medicine; now and in the foreseeable future. The field is new and ripe with business opportunities for those knowledgeable in both the intricate science and commercial pitfalls of the area. Alturus Biomedicine and its experts stand ready to strengthen and advance companies wishing to capitalize on our expertise.

[14] K. Takahashi and S. Yamanaka Cell 126, 663–676, August
[15] The Journal of Clinical Investigation. Vol. 120, No. 1. January 2010. www.jci.org
[16] The National Institutes of Health resource for stem cell research: stemcells.nih.gov/info/basics/basics6.asp
[17] Nature Biotechnology. Vol. 27, No. 11. November 2009.