



Stem Cell Based Regenerative Medicine: Is Russia Taking the Lead?

A Case Study from St. Petersburg

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Abstract

The recent scientific breakthroughs in genetics have lead to a thriving stem cell industry transforming the way medicine is practiced. This article discusses these developments and presents a case study of Russian research institute in St. Petersburg which is doing state of the art stem cell trials providing successful treatment of blood vessel disease and bone fractures. The potential impact of stem cell technology on regenerative medicine is discussed, the potential convergence of nanoparticle science and its contribution to stem cell research is discussed, and the dynamics of the stem cell industry is presented.

Keywords: Stem Cells, Nanoparticles, Regenerative Medicine, Russia

1. Introduction

In the later parts of 20th century breakthroughs in medical sciences fundamentally changed the science of medicine by the discovery of the human genome. The Human Genome Project was lead by Dr. James D. Watson at the U.S. National Institute of Health who lead an international effort to discover the constitution of the human genome. The project started in 1990, the first findings were published in 2000 (ScienceDaily, 2000), and the complete sequence of the human genome was published in 2003. The human genome has the potential to create a whole range of industries with explosive growth potential for global businesses as they have an opportunity to get a solid competitive position at the early stage of the industry's life cycle (Porter, 1980) and exploit the "blue oceans" (Kim and Maugorgne, 2005) created by this scientific discovery. Moreover nations may gain comparative advantage by creating a favorable business conditions for these new medical industries (Porter, 1990).

The solution to the human genome riddle leads to the potential to manipulate the genetic makeup of humans to eliminate wide range of genetic diseases. For an example research has been done on the treatment of diabetes, asthma, migraine, schizophrenia and many other diseases (Kim, 2002). The range of diseases treated and prevented by genetic manipulation will increase rapidly in the 21st century (Rowley & Martin, 2009). Furthermore the understanding of genetics may make it possible to manipulate the generic make up of the disease itself and make it less threatening or harmless to people. One such promising development is in the manipulation of the genes of the malaria parasites *Plasmodium vivax*, the leading cause of malaria in people outside Africa and the more difficult malaria parasite *Plasmodium falciparum* together these parasites kill and afflict nearly 500 million people annually (Economist, October, 9, 2008).

The Human Genome Project opened up the plausible creation of super-humans through manipulation of their genes and this development may adversely impact developing nations that do not have the technology to do this. However for every threat there is a corresponding opportunity so global business can leapfrog the historical development of medical sciences by instituting beneficial investment climate for genetic research and focusing research and development efforts and investment in the exciting field of genetic engineering, which is one the most promising areas in stem cell regenerative medicine.

This article reviews the convergence of genetics, stem cell science, and nanoparticle technology, discusses the dynamics of the stem cell industry's potential for explosive growth potential, and Russia's plausible lead in the field. The article

presents a qualitative case study of breakthrough stem cell trials conducted in St. Petersburg, Russia. Qualitative case studies facilitate the intensive investigation of phenomena as the researcher does an in-depth investigation and spends extensive resources to understand it (Stake, 2005; Saunders et. al., 2003; Thomas 1994; Pettigrew, 1992). Qualitative case studies have been used by business researchers to describe development and processes in business organizations. Penrose (1960) studied a single firm- the Hercules Engine Company, to formulate a theory of the competitive advantage of organizations, and Chandler (1962) studied the historical development of several organizations in new and rapidly growing industries that had radical impact on world society. Moreover the case study research method has been applied to the new industries as researchers have noted it suitable to situation where there is a need for an intensive study of contemporary events and experimental controls and manipulations of independent and dependent variables is not feasible (Benbasat, Goldstein, & Mead, 1987; Browne, 2005; Siggelkow, 2007). As the stem cell therapy industry is at its embryonic stage, the stem cell therapy in St. Petersburg case provided a potential instrumental- and critical case (Stake, 2005) which would be used to test and demonstrate phenomena as advocated by Yin (2003) and done by Brower (1999) who discussed the business development potential of the stem cell science, and Hambor (2008) who discussed the designing and manufacturing of stem cells on a large scale in a modern production facility for the purpose of testing drugs specific to particular organs. Additionally Platt (1988) states that single cases may be used to form general propositions and Easton (1998) and Yin (2003) argue although single cases will not describe populations its findings are transferable to other cases.

The article develops as follows: next the potential impact of stem cell technology on regenerative medicine is discussed. Second is the example of successful trials of treating degenerative blood vessel diseases and bone fracture with stem cells. Third, the potential convergence of nanoparticle science and its contribution to stem cell research is discussed. Forth, the dynamics of the stem cell industry is presented. Finally, the conclusions are drawn.

2. Stem Cell Technology's Potential Impact on Medicine

Stem cell technology's impact on longevity and health is likely to transcend our conception of medicine and the treatment of degenerative diseases. Stem cell research is one of the most promising areas of biotechnology and promises to lead to a whole new approach in dealing with and treating diseases. Stem cell research opens up the option of treating diseases with regenerative stem cells that have the ability to take on the makeup of damaged cells in the body and replace them. The process is continuous throughout the life of the patient.

Stem cells are a unique form of cells that are unspecialized and are able to take on the characteristics of other cells such as kidney- or bone cells. Thus stem cells have the ability to be the basic repair blocks of the body and they have opened up a whole new area in medicine called regenerative medicine. Stem cells come of two main types: embryonic stem cells and adult stem cells. In 1998, Thomson (1998) and his colleagues at the University of Wisconsin-Madison discovered how to isolate human embryo stem cells and how to grow them in the laboratory. Since the main focus of the research has been on learning how stem cells are able to renew themselves and be undifferentiated for many years and what causes the stem cells to transfer into specialized cells such as heart cells. A critical element in the use of stem cell based therapies in treatment of diseases such as Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis, is the discovery of the 'signal' that encourages stem cells to transfer from being undifferentiated to become the targeted cure cell. Palona et al. (2006) and her team of researchers at the University of Nagasaki discovered an effective process to manipulate the signaling in thyroid cancer cells and opened up the plausibility of treating thyroid cancer by turning off the signals which encouraged the thyroid cancer cells to multiply and do harm to the patient. This discovery opens up the plausibility of signaling stem cells to transform into the targeted organ or tissue to repair it. According to the Repair Stem Cell Institute, stem cell therapies were available for the treatment of more than 200 diseases in 2009 as shown in the list in table 1 in the appendix.

3. Russian Leadership in Stem Cell Therapy

As Director of Research in the Stem Cell Bank "POKROVSKI" and Center for Cell and Gene Therapy based in Saint Petersburg State Medical Institution, one of the authors was responsible for developing isolation and culture systems for human bone marrow stem cells and played a major role in several clinical trials. In these trials, stem cells were taken from the patient, manipulated, and used to treat humans with diseased arteries in the legs and severe leg bone fractures. Twenty one patients with artery diseases called: arteriosclerosis obliterans (ASO) or thromboangitis obliterans (TSO, also known as Buerger's disease) and nine patients with non-knitting fractures of long tubular bones were treated. The patients who entered the trials had not responded to conventional medical therapies.

The method used to treat the patients was as follows: 750 ml of bone marrow was aspirated from the posterior iliac bone crest under general anesthesia and anticoagulated with heparin. Mononuclear cells were concentrated to 25-30 mL by volume reduction technique with the kit CS- 490.1 and Sepax main processing unit from Biosafe (Eysins, Switzerland). The initial and final products were subject to total CD 34+ cell counts using a Beckman Coulter from Cytomics (FC 500, USA) for viability and sterility controls. The mononuclear cells were injected into the gastrocnemius muscle of the ischemic leg within less than two hours after isolation and concentration. About 50 injections of 0.7 mL of mononuclear

cells each were made. The depth of injections was a bit different (1-2 cm deep into the gastrocnemius muscle) and varied according to the thickness of subcutaneous fat. The patients were examined each week for the first month and then ones per month for the next 5 months. Digital subtraction angiography was performed before and 24 weeks after the procedure in a standardized manner to obtain identical imaging conditions.

After treatment and six months of observations for each patient, the following results were achieved. Nine of the 21 patients with ASO or TSO had complete remission of leg pain and 17 had improvement in skin ulcers. Most importantly, in many patients, the treatment stimulated durable formation of new blood vessels and amputation could be avoided. The fracture patients also experienced a positive effect following the stem cell therapy and new bone tissue could be observed within the fractures.

However, from the trial results in St. Petersburg, it was not possible to determine and prove if the observed formation of new blood vessels and the creation of new bone material were due to the effect of the injected stem cells and/or if the preexisting cells themselves were generating the new blood vessels or bone. In order to make progress in this field, there is a pressing need to develop a safe, non-invasive method to enable the stem cells to be tracked following transplantation to the patient. This is an important goal, not only because if achieved, it will help to understand the mechanisms whereby stem cells mediate their positive effects; but also, it is important from a safety perspective, as it will be necessary to determine if transplanted stem cells migrate to sites other than the target organ, a situation that could lead to detrimental side effects for the patient.

In order to address this tremendously important question, a technology for tracking the injected stem cells is needed in order to develop an effective a stem cell tracking system. The convergence of nanotechnology with stem cell science is a promising prospect for tracking stem cells in the body. Hence the potential of nanoparticles and their use in stem cell science is discussed next.

4. Convergence: Nanoparticles for Labeling Stem Cells

A critical prerequisite for the development of regenerative medicine based on stem cells science is the ability to track the injected stem cell in the body of the patient to observe if the injected stem cells actually migrate to the target organ or tissue needing repair. Various stem cell tracking technologies have been developed but, all of them have their limitations.

However the convergence of nanotechnology with regenerative medicine shows promising prospects as nanoparticles can be used to mark stem cells by inserting the nanoparticles into the stem cells facilitating the tracking of the stem cells as the nanoparticles can be detected by technologies such as Magnetic Resonance Imaging (MRI). To increase our understanding of the mechanisms involved, it is necessary to find a way to monitor the behavior of the stem cells following transplantation by developing a non-invasive method for tracking the stem cells that will not cause harm to the patient.

Over recent years, superparamagnetic iron oxide nanoparticles (SPIONs) have emerged as an attractive system for tracking stem cells in the body. The main advantage of SPIONs is that they enable stem cells to be tracked non-invasively using MRI (Guzman, 2007; Zhu, J. et al., 2006) and, some SPIONs, such as Feridex/Endorem, have now been approved for human use by the FDA. Most importantly SPIONs do not appear to have any or little adverse effects on stem cell viability or differentiation potential. Thus they appear harmless to the cells and the patient. However it is now recognized that SPIONs lose their ability to track stem cells by giving a signal of their location after a period of time. While cell division and migration accounts for some loss of signal, a major cause of poor label retention is degradation of the SPIONs within the cellular environment. To overcome these problems, there is a pressing need to devise improved methods for coating SPIONs to protect their magnetic core from natural deterioration in the body whilst retaining biocompatibility and signaling capability.

Researchers are in the process of developing a new stem cell tracking technology based on superparamagnetic iron oxide nanoparticles, or 'SPIONs'. The main advantage of SPIONs is that because of their nanoscale dimensions, they can be easily introduced into cells without detrimental side-effects, and their magnetic properties enable them to be imaged using MRI. Furthermore, because iron is a natural substance in the human body, being an essential component of the oxygen-carryng molecule- haemoglobin, it is unlikely to cause any harm to patients. However the SPIONs can be difficult to detect as they deteriorate in the body due to natural processes. We suggest using a novel technology to coat the SPIONs so that they are not degraded too quickly, enabling the stem cells to be tracked for extended periods inside the patient. To test the effectiveness of the technology, we propose stem cells will be labeled with SPIONs and transplanted into an organ culture system. The advantage of using this organ culture system is that it avoids the need for using living animals to test the technology. The cultures will be monitored daily using various imaging methods, including computerized tomography, or CT, a technology where images of body structures are created by a computer from X-ray images.

In order to realize the potential of stem cell treatments another convergence needs to take place among the government, legislators, business community, and investors and, the stem cell community needs to deal effectively with threats from conventional medicine, pharmaceutical industry, religious groups, and the public opinion. This is discussed in the next section.

5. Stem Cell Industry Dynamics

Global business has the opportunity to develop the stem cell industry and to get into the industry at the early stage to get a head start in the explosive growth potential of this promising technological breakthrough that has the potential to transfer our knowledge of the medical sciences and replace many conventional medicine practices and treatment therapies. A convergence of efforts from government, legislators, business community, and investors is needed to develop the scientific competence and capacity that forms a fundamental basis for the development of effective stem cell based regenerative medicine industry.

First, the government needs to provide the funding for primary research into stem cell science and facilitate the distribution of the knowledge gained. Furthermore funding is needed to develop the necessary number of competent stem cell scientist at universities and research institutes to establish the country's core competence, which forms a basis for a competitive advantage as considered a principle prerequisite for effective strategy formulation by Hamel and Prahalad (1994).

Second, a favorable legislative environment needs to be enacted that balances the public concerns and limits restrictions of stem cell research and funding. Although fundamental stem cell research was pioneered in the USA, it was not until Pr. Obama lifted a ban on federal funding of research on new embryonic stem cell lines that the legal environment changed in favor of applied stem cell research. Similar restrictive attitudes remain as barriers to commercial development in many countries in Europe such as in Italy, France, Spain, Austria, and Germany. However several countries in Europe have enacted stem cell friendly legislations. Sweden and the United Kingdom have strong commitment to stem cell research both financially and by relatively favorable legislation. However Russia has achieved a comparative advantage because of its liberal laws on stem cell research and therapies (see eg De Trizio & Brennan, 2004; UKSCI, 2009; Rowley & Martin, 2009).

Third, the business community needs to develop effective growth strategies to cash in on the opportunities generated by the stem cell technology and the respective spin-off industries this science has generated. Placzek, et al. (2008) consider poor business- and production management as a prime impediment for the development of commercially viable stem cell products, this concern is echoed by other researchers in the field who call for more effective strategy formulation for businesses in the stem cell industry (Brower, 1999, p. 139), improved distribution system (Rowley & Martin, 2009, p. 8), and increased business pragmatism (Seay, 2008, p. 145).

Fourth, investors' attention needs to be drawn to the stem cell industry by promotion and tax incentives needs to be initiated because of the long term investment needed to reach commercialization of stem cell products. Stem cell companies have not gone unnoticed by the financial community and investors are exploring and investing in promising stem cell firms. According to Russ Urban of SpeculatingStocks.com, "Stem cells are extremely powerful and can dramatically change how we treat various diseases," and as in indication of the commercial potential of stem cell regenerative medicine, Speculating Stocks began in its analysis and information sharing on stem cell stocks in October 2008 (PRWeb, 2008).

As noted by Learned, et al. (1965) and Porter (1980) for every business opportunity there is a corresponding threat and, the stem cell industry is no exception and the future of the industry is to a large extent dependence on the effective handling of the following important stakeholders (Drucker, 1955; 1974). First the stem cell industry has to gain public acceptance of its contribution to the health care system and this depends largely on the way the stem cell industry handles its public relations and potential conflict of interest depends in large measure on the naming of the various techniques done by the stem cell industry and at all cost must blunders like happened to the genetic modified food industry be avoided. Terms like GMO must be avoided and acceptable terms for the stem cell treatments must be developed. A recent report from Australia indicates a significant increase in the public support for stem cell research as 82% of respondents are in favor of stem cell research and its potential benefits which is a stark contrast to the public opinion in Italy which has one of the restrictive embryonic stem cell regulation in the (UKSCI, 2009). The HCD Research Inc. conducted a poll on March 9th after Pr. Obama's speech and asked consumers and doctors "How much do you agree with federal funding for embryonic stem cell research?" Consumers and doctors who replied as follows: complete agreement 55%, somewhat agreed 29%, not at all 17% which can be considered good total acceptance rate for stem cell research. However one must note the stark contrast between democrats and independents vs republicans (Reuters, March 11, 2009).

Second, the conventional medicine profession's perception of the threat of obsolescence of conventional medicine must be minimized or the conventional medicine profession will use its considerable political power to hinder developments and funding of the stem cell industry.

Third, the pharmaceutical industry perception of the same obsolescence is equally threatening to the stem cell industry. Thus effective coping strategies must be developed to deal with this threat.

Forth, the concerns of the religious community must be dealt with by the stem cell industry and the concerns are equally shared by the Christian and Muslim communities. Albeit the concerns are different; in the Muslim community's the main concern is the use of pigs or pig derived products as for research or treatment as all contact with pigs is strictly prohibited. The Christian community and Pro-life advocates have reasoned that the human embryo is a living human being and should not be used in research. For an example, on 19th of July, 2006, President George W. Bush vetoed the Stem Cell Research Enhancement Act. Hence the veto upheld previous legislation prohibiting the use of federal money for stem cell research on non-existing lines of embryonic stem cells. The new USA President Obama ended the ban on stem cell funding by an executive order on March 22, 2009. As in the case of the genetics, the ethical issues relating to human stem cell research, particularly on human embryonic stem cells, has triggered heated debates in the United States and in Europe.

In practice the net effect of the restrictions on funding for stem cell research and the related research activities has been the transfer of the stem cell research to countries offering more hospitable climate for the research firms. Therefore breakthrough discoveries in stem cell research are being made in research centers in Japan, Israel, France, Russia, Peoples Republic of China and other countries, which have friendly climate towards this kind of research. Moreover leading scientist are leaving countries like the United Kingdom to work in countries with more favorable working environment for the stem cell research as indicated by the headline news that one of UK's leading stem cell scientist Professor Colin McGuckin, professor of medicine at Newcastle University, was leaving the UK for a favorable working conditions in France where he can focus on his patients' and staffs' welfare (Waggoner, 2008). The importance of recruiting and retaining the highest caliber cadre of competent knowledge workers has been recognized by management researchers (Drucker, 1993; Porter, 1990). Figure 1 shows the stem cell industry's business dynamics.

<Insert Figure 1 here>

6. Conclusions

Already, the stem cell science has drastically impacted the practice of medicine and our perception thereof. The stem cell industry has tremendous growth potential for global businesses willing to take the risk of investing in this industry and the profit potential deriving from an early foothold is great. However the stem cell industry has to balance stakeholders' concerns and overcome several barriers to reach its full potential. The convergence of genetic-, stem cell-, and nanoparticle sciences furthers technological advances in the stem cell industry and facilitates accurate measurement of the effectiveness of stem cell based regenerative medicine therapies.

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Table 1. Stem Cell Therapies 2009

Absence Of The Septum Pellucidum	Glucose Transfer Disorders	Lupus	Optic Nerve Hypoplasia	Rett Syndrome
Acquired Ataxia	Glycogen Storage Disease Type II	Lymphoma	Osteoarthritis	Rheumatoid Arthritis
Acquired Epileptiform Aphasia	Guillain-Barr Syndrome	Machado-Joseph Disease	Osteogenesis Imperfecta	Sarcoidosis
Acute Disseminated Encephalomyelitis	Heart Disease	Macular Degeneration	Parkinson's	Scaphoid Nonunion
Agenesis Of The Corpus Callosum	Hepatic Cirrhosis	MDS	Peripheral Artery Disease	Schizencephaly
Alcardi Syndrome	Hereditary Ataxias	Meningitis	Peripheral Nerve Injuries	SCI
ALS	Hodgkin's Disease	Microcephaly	Peripheral Vascular Disease	SCID
Alzheimer's	Huntington's Disease	Motor Neuron Disease	Perisylvian	Septo-Optic Dysplasia
Amyotrophic Lateral Sclerosis	Hypertonia	Multiple Myeloma	Polymicrogyria	Sequelae
Angina	Hypotonia	Multiple Sclerosis	Pompe Disease	Severe Aplastic Anemia
Ataxia	Including Type C	Multisystem Atrophy	Post Polio Syndrome	Severe Combined Immune Deficiency
Autism	Infantile Osteopetrosis	Muscular Dystrophy	Primary Lateral Sclerosis	Sickle Cell Anemia
Autoimmune Diseases	Infantile Spasms	Myelodysplastic Syndrome	Progressive Muscular Dystrophy	Spastic Tetraparesis
Batten Disease	Inflammatory Bowel Diseases	Myoclonic Encephalopathy Of Infants	Psoriatic Arthritis	Spina Bifida
Becker's Muscular Dystrophy	Ischemic Heart Disease	Myoclonus	Pulmonary Fibrosis	Spinal Amiotrophy
Bell's Palsy	Ischemic Optic Neuropathy	Myopathies	Pulmonary Hypertension	Spinal Cord Injury
Bone Fractures	Kennedy's Disease	Neurofibromatosis	Retinitis Pigmentosa	Spinal Muscular Atrophy
Brachial Plexus Birth Injuries	Kidney Disease	Neurological - Other	Retinopathy of Prematurity	Spinocerebellar Ataxia
Brachial Plexus Injury	Lack Of Cardiac Mobility	Neuronal Ceroid Lipofuscinosis	Rett Syndrome	Spinocerebellar Atrophy
Brain Conditions/Diseases	Landau-Kleffner Syndrome	Neurotoxicity	Rheumatoid Arthritis	Spinocerebellar Degeneration
Brain Injury	Leber's Hereditary Optic Neuropathy	Non Hemorrhagic Brain Vascular Accident	Sarcoidosis	Stroke
Brown-Sequard Syndrome	Leukemia	Non Hodgkin's Lymphoma	Scaphoid Nonunion	Systemic Lupus Erythematosus
Bulbospinal Muscular Atrophy	Leukemia Lissencephaly Liver	Ohtahara Syndrome	Schizencephaly	Tendonitis
Cancer	Lissencephaly	Olivopontocerebellar Atrophy	SCI	Thalassemia

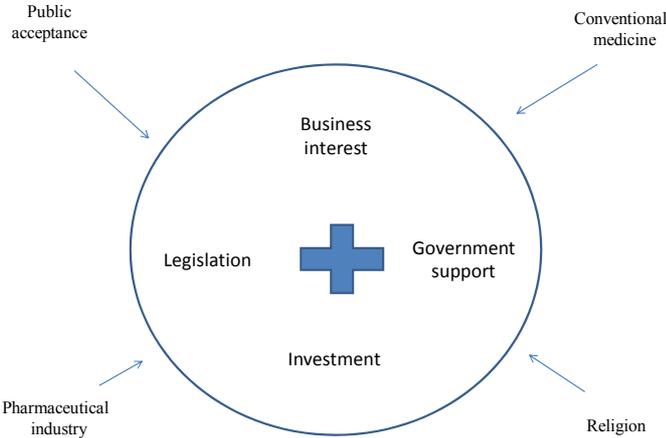


Figure 1. The Dynamics of the Stem Cell Industry and Threats