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Replacing Insulin is Top-Ranked of 10 Breakthroughs for Developing World Health Foreseen from "Regenerative Medicine"

Medical, Scientific Experts Forecast Greatest Ways of Improving Health in Poor Countries From Emerging Stem Cell and Related Technologies

Researchers ***Heather L. Greenwood, Peter A. Singer, Gregory P. Downey, Douglas K. Martin, Halla Thorsteinsdóttir and Abdallah S. Daar*** *are available for advance interviews Sept. 7-11. Please call to schedule a time. Media can preview the study, "Regenerative Medicine and the Developing World," to be published in the peer-reviewed journal PloS Medicine Sept. 11, online at www.plos.org/press/plme-03-09-daar.pdf*

Eliminating the need for costly insulin injections for diabetics, regenerating heart muscle after it fails, and improving resistance to disease by engineering immune cells top a list of 10 potential breakthroughs for health in developing countries seen emerging from the new world of regenerative medicine, according to a study published today in the prestigious journal *Public Library of Science (PLoS) Medicine*.

Conducted by University of Toronto researchers (from the McLaughlin Centre for Molecular Medicine, the Canadian Program on Genomics and Global Health, and the U of T Joint Centre for Bioethics), the study says regenerative medicine has the potential to help developing countries address a suite of disastrous health problems, foremost among them a diabetes epidemic.

However, the study notes that in developed countries, where most of the cutting-edge science research occurs today, health-related priorities differ greatly from those of developing countries, which therefore should develop their own expertise and capacity.

“Though largely neglected by the field of regenerative medicine to date, we suggest that developing countries could potentially benefit from advances in regenerative medicine to address the epidemic of non-communicable disease and other pressing health needs,” the authors say.

Regenerative medicine combines know-how from diverse disciplines to repair, replace or regenerate cells, tissues or organs impaired by congenital defects, disease, trauma and other causes. It moves beyond traditional transplant and replacement therapies to include the use of stem cells, soluble molecules, genetic engineering, tissue engineering, and advanced cell therapy.

There is increasing research in regenerative medicine in both developed and developing countries. Already regenerative medicine has produced a skin substitute (Apligraf), a bone regenerating therapy (Osteocel) and other medical breakthroughs. An eye institute in India (L.V. Prasad) has used adult stem cell therapy to repair the corneas of over 125 blind patients; an estimated 60% of blindness in poor communities is treatable. Regenerative medicine holds the promise of more affordable treatments than corneal grafts and of offsetting shortages of donor material.

The study, the first of its kind:

- Identifies and prioritizes applications of regenerative medicine that could effectively improve health in developing countries;
- Assesses the feasibility of building developing countries’ capacity in regenerative medicine; and
- Offers recommendations for developed and developing countries alike.

An international panel of experts was involved in the study to identify the 10 most promising applications of regenerative medicine for improving health in developing countries. 35 of 44 experts in the study placed atop their list: “Novel methods of insulin replacement and pancreatic islet cell regeneration for diabetes.”

Many panellists noted the heavy health, social and economic burdens that result from widespread diabetes in developing countries. Controlling that disease would consequently reduce complications such as blindness, heart disease, chronic kidney disease and diabetic ulcers, they noted, adding that repeated insulin treatments are costly and therefore inaccessible to many developing country patients.

The 2nd-ranked application, regenerating failed heart muscle using the patient’s own cells, is being successfully tested in several countries and will help address fast-rising rates of heart

disease in developing countries. In addition to saving lives, such therapies could reduce the cost of treating heart failure by avoiding immune rejection and costly immunosuppressive regimens.

The 3rd-ranked application: using engineered immune cells and novel vaccination strategies to improve immunity from infectious disease, would assist countless developing country victims, many of them their societies' youngest members. These technologies could improve a person's ability to fight off infection and new strains of HIV/AIDS, tuberculosis, hepatitis, malaria and other common diseases.

The full Top 10 list follows (maximum possible total score: 440)

Ranking (Score)*	Applications of Regenerative Medicine	Examples Identified by the Panelists
1 (415)	Novel methods of insulin replacement and pancreatic islet regeneration for diabetes	• Bone marrow stem cell transplantation for pancreatic regeneration • Microencapsulation (e.g. poly-lactide-co-glycolide) for immunoisolation of transplanted islets • Cultured insulin-producing cells from embryonic stem cells, pancreatic progenitor cells, or hepatic stem cells • Genetically engineered cells to stably express insulin and contain a glucose-sensing mechanism
2 (358)	Autologous cells for the regeneration of heart muscle	• Myocardial patch for cardiac regeneration • Direct injection of autologous bone marrow mononuclear cells for cardiac repair • Stromal cell injection for myocardial regeneration • Localized angiogenic factor therapy through controlled release systems or gene therapy
3 (339)	Immune system enhancement by engineered immune cells and novel vaccination strategies for infectious disease	• Genetically engineered immune cells to enhance or repair immune function • Single-injection DNA vaccines
4 (272)	Tissue engineered skin substitutes, autologous stem or progenitor cells, intelligent dressings, and other technologies for skin loss due to burns, wounds, and diabetic ulcers	• Bilayered living skin constructs (e.g. Apligraf) • Engineered growth factors (e.g. rbbFGF, rhEGF) applied in conjunction with topical treatments (e.g. SD-Ag-Zn cream) • Intelligent dressings composed of a slow-releasing growth hormone polymer • Epithelial cell sprays
5 (238)	Biocompatible blood substitutes for transfusion requirements	• Polyhemoglobin blood substitutes for overcoming blood shortages and contamination issues
6 (200)	Umbilical cord blood banking for future cell replacement therapies and other applications	• Preserved umbilical cord blood stem cells to provide future cell replacement therapies for diseases such as diabetes, stroke, myocardial ischemia, and Parkinson's disease • Pooled cord blood for the treatment of leukemia
7 (157.5)	Tissue engineered cartilage, modified chondrocytes, and other tissue engineering technologies for traumatic and degenerative joint disease	• Matrix-induced Autologous Chondrocyte Implantation (MACI) for cartilage repair • Tissue engineered cartilage production using mesenchymal stem cells
8 (121.5)	Gene therapy and stem cell transplants for inherited blood disorders	• Genetically-engineered hematopoietic stem cells to restore normal blood production in β-thalassemic patients
9 (105.5)	Nerve regeneration technologies using growth factors, stem cells, and synthetic nerve guides for spinal cord and peripheral nerve injuries	• Synthetic nerve guides to protect regenerating nerves • Embryonic stem cell therapy for spinal cord regeneration • Growth factor-seeded scaffolds to enhance and direct nerve regeneration

10 (80)	Hepatocyte transplants for chronic liver diseases or liver failure	• Microencapsulation of hepatocytes to prevent immunological reaction • Derivation of hepatocytes for transplantation from embryonic stem cells • Transdifferentiation of hepatocytes for transplantation from bone marrow cells

About the study

Some 44 international experts and clinicians from relevant fields – three quarters of them from developing countries – were canvassed using three rounds of the Delphi technique to reach consensus on the 10 most promising applications of regenerative medicine for improving health in developing countries.

They used six criteria in their rankings:

- Burden: Will the application address some of the most pressing health needs of developing countries?
- Impact: Will the application be an improvement over existing treatment options and have a clear impact towards improving health in developing countries?
- Feasibility: Can the application reasonably be developed and deployed within a 10 year timeframe?
- Affordability: Will the application be affordable to develop and/or use in developing countries?
- Acceptability: Is the application safe, and socially, ethically, and legally acceptable?
- Indirect Benefits: Does the application provide benefits, such as capacity building or economic benefits, which could indirectly improve health in developing countries?

Huge Numbers of Potential Patients Worldwide

A report from the US National Academies of Science, *Stem Cells and the Future of Regenerative Medicine*, estimates over 100 million potential US patients could benefit from such stem cell-based therapies, including victims of cardiovascular disease, auto-immune diseases, diabetes, cancer, neurodegenerative diseases and burns.

Chronic diseases, the primary targets of regenerative medicine, affect people at a younger age in developing than developed countries. They are also much more likely to be prevalent in the poor and have resulted in more deaths in 2005 than infectious disease, maternal and perinatal conditions, and nutritional deficiencies *combined*.

The authors say low and middle income countries as a group report 80% of all chronic disease deaths, over 95% of deaths due to infectious disease, and almost 90% of deaths due to injury and trauma.

Even though developing countries suffer more than developed countries from the medical problems targeted by regenerative medicine, "there has been no attempt to understand systematically how regenerative medicine could contribute to improving health in developing countries," the authors say.

Building Capacity in Developing Countries for Regenerative Medicine

While developed countries share large interests in treatments for such chronic illnesses as diabetes and heart disease, the developed world is relatively less concerned about finding applications to combat infectious diseases -- immune system enhancement and biocompatible blood substitutes that can be sterilized to avoid costly screening measures, for example.

"Whether developing countries choose to build capacity in regenerative medicine themselves or whether they wait to adopt therapies developed first elsewhere may depend both on their economic position and on the level of research attention a particular regenerative medicine application is receiving in industrialized nations. However, as highlighted in the 2005 report of the UN Task Force on Science, Technology, and Innovation, domestic innovation by developing countries is important as it is more likely to be targeted towards local health needs and can be a contributor to health and economic development," the authors say.

"In addition, previous studies of the health biotechnology sectors in developing countries have shown that local innovation in science and technology can lead to more affordable treatments for the populations of developing countries. India's Shantha Biotechnics, for instance, has developed a recombinant hepatitis B vaccine that sells for only $US O.40 per dose as compared to imported vaccines which sell for $US 8-10 per dose."

Leaders among developing countries in their level of regenerative medicine activity are India, China and Brazil.

The authors say the study results represent a potential guide for the policy formulation at international and bilateral aid agencies, and within developing countries.

And they recommend:

- An initiative on Grand Challenges in Non-communicable Diseases, modelled on the success of Grand Challenges in Global Health initiative, sponsored in part by the Bill and Melinda Gates Foundation. The initiative would work to remove the barriers -- behavioural, scientific, and technological – to preventing and managing non-

communicable diseases. Establishment of such an initiative would encourage the regenerative medicine community to develop products and approaches that are applicable, affordable, and accessible to the developing world.

- That governments of developing countries evaluate regenerative medicine technologies and investigate potential collaborations with both industrialized and developing countries as a way to build national capacity.

- That industrialized country governments devote a portion of research and development spending to challenges facing developing countries. Such a commitment would provide the means to pursue the proposed Grand Challenges in Non-communicable Diseases initiative and provide incentives to develop regenerative medicine therapies that are relevant, accessible and affordable to the developing world.

"The threat of non-communicable diseases in developing countries has been largely ignored by the international community but these are now reaching epidemic proportions in many places, creating a difficult burden for poor nations. As with many other health technologies, for example vaccines, it is people in the developing world, where 90% of humankind lives, that may ultimately derive the most benefit," says senior responsible author Abdallah Daar, Director of Ethics and Policy of the U of T McLaughlin Centre for Molecular Medicine.

"While there are no easy solutions to the complex challenges facing developing countries, these technologies offer real promise in the field of health. It is a young field and there's great opportunity to shape it now while it is developing." says Heather Greenwood of the Canadian Program on Genomics and Global Health.

Says co-author Halla Thorsteinsdottir of the CPGGH: “Our recent study of developments in regenerative medicine indicate that researchers in, for example, India, are taking regenerative medicine very seriously and there are government policies meant to energize research in this field,”

Adds Peter Singer, Senior Scientist at the McLaughlin Centre for Molecular Medicine, who has been researching the commercialization of health technologies in developing countries and the many innovations being pursued by the private and academic sectors in China: “Just like cell phones have completely revolutionized communication in the developing world, biotechnology -- and in particular regenerative medicine -- could in the future provide new ways to deal with old health problems plaguing millions of people."

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Background:

University of Toronto Joint Centre for Bioethics
Innovative. Interdisciplinary. International. Improving health care through bioethics.

The JCB is a partnership among the University of Toronto and 15 health care organizations. It provides leadership in bioethics research, education, and clinical activities. Its vision is to be a model of interdisciplinary collaboration in order to create new knowledge and improve practices with respect to bioethics. The JCB does not advocate positions on specific issues, although its individual members may do so.

For more information: www.utoronto.ca/jcb/

Canadian Program on Genomics and Global Health

Recognized worldwide as a leading program on innovation and global health, the mission of the CPGGH is to harness the advances of innovative technology for global health equity. Its vision is to optimize global health benefits and minimize the social risks of advances in innovation through careful evaluation of the associated social and economic impacts.

For more information: www.utoronto.ca/jcb/genomics

The R. Samuel McLaughlin Centre for Molecular Medicine was established to improve health through the application of molecular advances to clinical care. With $150 million in funding, the Centre is a joint initiative of the University of Toronto and four affiliated hospital-based research institutions (Hospital for Sick Children, Mount Sinai Hospital, Sunnybrook and Women's College Health Sciences Centre and University Health Network). The centre seeks to become a global leader in translational research.

For more information: www.mcmm.ca/

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