REGENERATIVE MEDICINE

promising answers in the face of an ageing population

As the population ages, the scientific and medical communities are working to solve the challenges this changing demographic will place on society. Companies involved in the promising field of regenerative medicine are now on the cutting edge as it strives to promote longevity without disability.

By Dr Doros Platika

Regenerative medicine offers hope and promise to the current challenges being faced as demographics change and our population ages. It can provide solutions that traditional medicine cannot, including replacing cells killed by strokes, growing a new liver to replace a failed one (potentially avoiding sourcing and rejection problems) and creating pancreatic islet cells for diabetics who cannot manufacture them. A number of companies have risen to the challenge that regenerative medicine offers, hoping to find effective cures and treatments by regenerating and replacing tissues that are no longer viable.

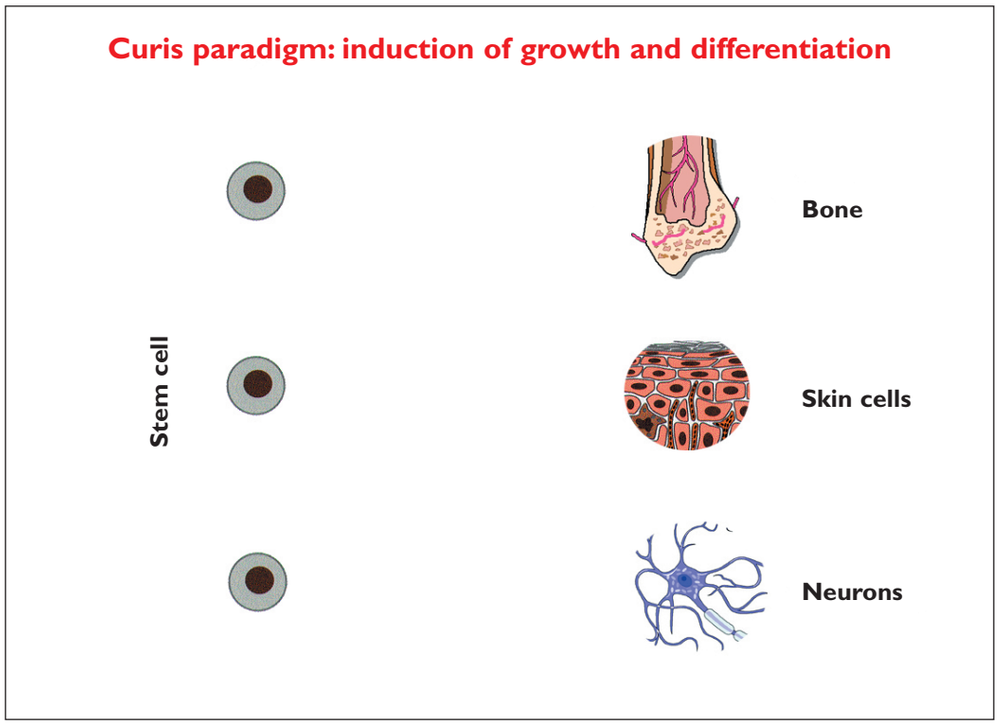
Degenerative disorders pose a serious threat to society. Often there is no effective therapy, only palliative treatments. According to the US Census Bureau[1], 53 million people will be over the age of 65 in the US by 2020 – up from 35 million in 2000. As the population ages and fertility drops globally, the number of adults able to support an ageing population has shrunk to nearly unsustainable levels. Knowing this, we can anticipate that our ageing population will pose enormous socio-economic problems[2].

In addition, debilitating conditions that afflict our youth, such as juvenile diabetes and spinal trauma, will also pose a further burden to society. Young patients suffering from such conditions may now live for decades due to previous medical advances, but often in seriously disabled states. While the number of young people with lost function are not growing as rapidly as the numbers of those in the ageing population, caring for such a young population for such lengthy periods of time will cause insurmountable healthcare costs. The long-term financial challenge may bring about tremendous ethical and emotional dilemmas for the patients, their family members and society.

These factors support the social and economic needs for regenerative medicine treatments; a regenerative medicine market exists and continues to grow. A number of biotech companies and academic labs are rising to the challenge and advancing the body's own ability to repair and regenerate diseased and damaged tissues and organs.

As an example of one approach, Curis brings the core components of regenerative medicine (developmental biology, functional genomics and stem cells) under one roof. Extensive expertise in the area of developmental biology – the study of the mechanisms that are activated as an organism develops from a single cell to a fully differentiated, complete system – permits the identification of the key factors in a signalling pathway that are activated during organ development or repair[3]. This approach generates products that range from the natural growth factors to small molecule agonist and antagonist. When combined with stem cells, the ability to induce differentiation results in tissue engineering products.

As can be seen from the above example, the field



of regenerative medicine has been made possible by rapid advances in a number of fields such as genomics, stem cell biology and bioinformatics. Below is a brief review of how these fields are converging and contributing to a potential revolution in drug discovery.

Opportunities in the post-genomic era

The genomics era has generated much raw data and excitement. The challenge in the post-genomic era is to convert this data into useful information that can be applied to drug discovery. One approach has been in the area of customised medicine, or 'pharmacogenomics', in which pharmaceutical companies, after genomic analysis of identified sub-sets of patients, design drugs for people who may be allergic, or non-responsive, to the standard therapeutics.

A second approach has been to compare the genes activated in normal tissue with the genes active in diseased organs. Using this approach researchers are identifying thousands of genes associated with diseases. The challenge is to sort through the many differences and identify the ones that are validated targets for drug discovery.

A third approach in mining the genome is to identify the handful of genes that are critical to organ development and repair through developmental biology and bioinformatics. The initial product opportunity from this approach is the protein growth factor itself. Such growth factors are among the blockbuster products of biotechnology. Amgen's (Thousand Oaks, CA) has led the way in this category with erythropoietin (EPOGEN®) for the treatment of anaemia associated with cancer chemotherapy and chronic renal failure and NEUPOGEN®, granulocyte colony stimulating factor (G-CSF), to prevent infections in patients undergoing chemotherapy or marrow transplant. Biogen (Cambridge, MA), Curis (Cambridge, MA), Genentech (San Francisco, CA) Genetics Institute (Cambridge, MA), Human Genome Sciences (Rockville, MD), Eli Lilly (Indianapolis, IN) and Regeneron (Tarrytown, NY) are just a few of the companies mining the genome for proteins that help the body repair damage.

In addition to identifying genes that code for growth factors that can become products themselves, the third approach to mining the genome identifies the pathway that is responsible for the control of growth and differentiation. Validated assays can then be created and combined with high throughput screening (HTS) to search for small molecule agonists to mimic the activities of the normally occurring molecule. The same approach can

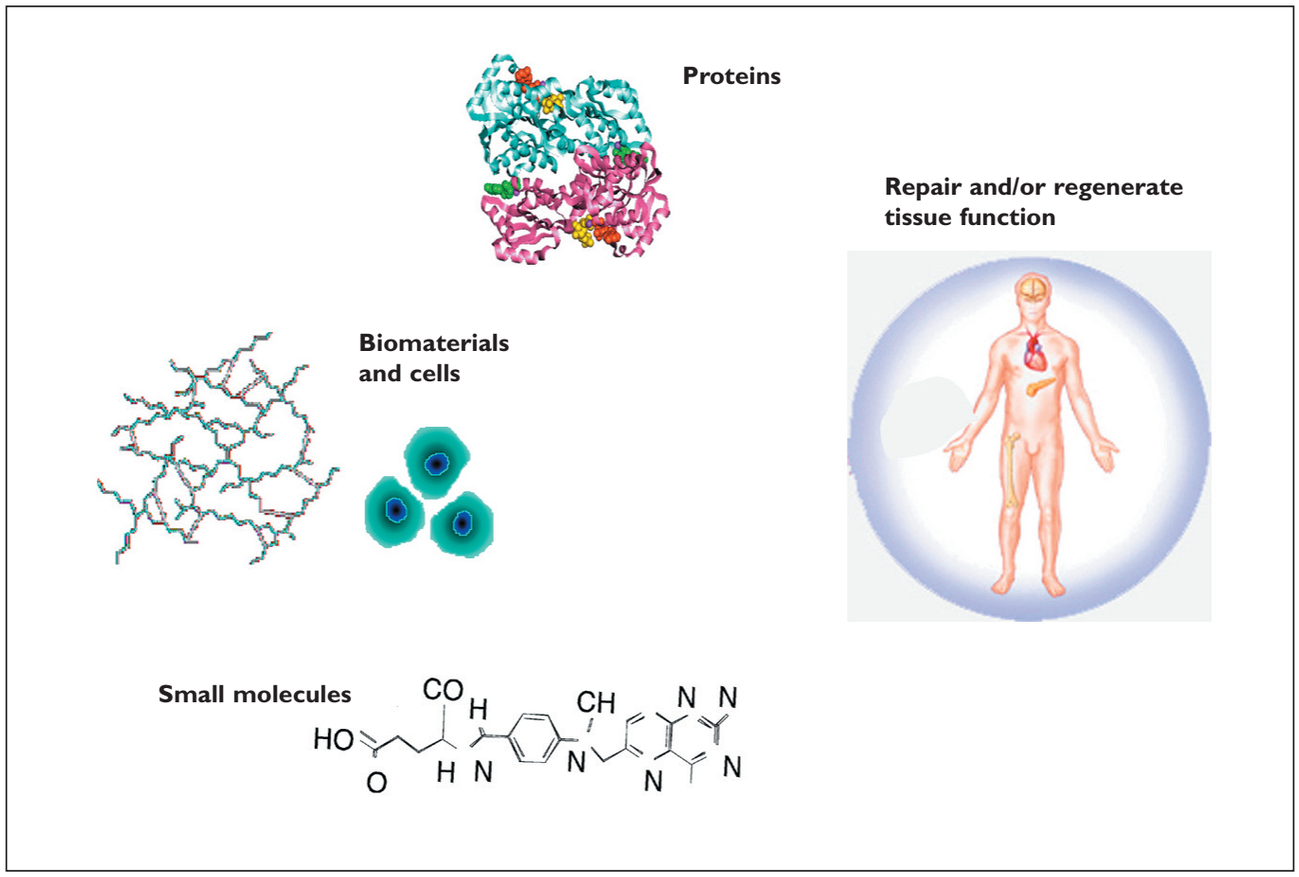
be used to search for antagonists or inhibitors of the pathways in order to treat the inappropriate growth seen with malignancy.

Both protein and small molecule products have advantages and liabilities for drug makers. Protein products have a much lower risk of toxicity than do small molecules products. Proteins, however, have greater delivery problems, whereas small molecule drugs can be taken orally and can be more cost-effective to formulate and manufacture. Companies such as Millennium Pharmaceuticals (Cambridge, MA), Exelixis (San Francisco, CA) and Curis employ automated screening systems to evaluate potential small molecule drug targets. Using this approach, Curis has identified small molecules inhibitors of pathways involved in skin (basal cell carcinoma), brain (medulloblastoma), prostate, bladder and colon cancers. Curis has also identified small molecule agonists that may have the potential to stimulate hair growth in balding men or to restore nerve function in diabetic neuropathy and nerve trauma.

Stem cell use in regenerative medicine

Sometimes, however, just providing the body with the missing growth factor is not sufficient because the factor targets a receptor on a type of cell that is missing. In type 1 diabetes (juvenile diabetes), for example, patients are lacking the functional pancreatic islet cells that produce insulin. Recently published data in the *New England Journal of Medicine*[4] illustrates how infusing islet cells into type 1 diabetics allowed the patients to attain sustained insulin independence. Unfortunately, there are not sufficient islets available to make this approach practical for the vast majority of juvenile diabetics. One potential solution is to use insights generated by the study of islet cell development and differentiation to create functional islets out of stem cells. Curis and other groups have made significant progress in this area.

Stem cells, according to the National Institutes of Health Stem Cell Primer[5], are "cells that have the ability to divide for indefinite periods in culture and to give rise to specialised cells". Stem cells, therefore, can be made to create the cell types that



may be missing in a patient. There are two options for researchers wishing to use human stem cells to create regenerative therapies: embryonic stem cells and adult stem cells.

Embryonic stem cells

Embryonic stem cells are totipotent, that is, capable of giving rise to all types of cell lineages, as well as being self-renewing. Geron (Menlo Park, CA) and Advanced Cell Technology (Worcester, MA), for example, are examining the possibility of using these cells for use in human regenerative medicine. While the medical benefits derived from this research may be many, the use of embryonic stem cells raises issues about the sourcing of the cells. The US Department of Health and Human Services is currently reviewing federal funding guidelines of embryonic stem cell research. Many companies, as well as third party advocacy groups, are urging the federal government to allow this funding to continue based on the potential to find cures through the use of human embryonic stem cells[6].

Adult stem cells

Adult stem cells in blood have been shown to act as progenitors that can make more of the same tissues from which they originated. Blood stem cells, with or without growth factors, have been used in bone marrow transplants to regenerate the blood system after extensive cancer chemotherapy and radiation. Other examples of progenitor adult stem cell technology can be found at Organogenesis Inc (Canton, MA) and Advanced Tissue Sciences (La Jolla, CA) where scientists are creating new skin for wound repair and burn victims. Curis uses adult cells to produce Chondrogel, a structural tissue product comprised of cartilage cells placed in a biodegradable gel for endoscopic injection into an area where structural deficiency may be corrected by tissue augmentation. Chondrogel is currently in a pivotal Phase III clinical tests for vesicoureteral reflux, a pediatric indication. Curis has also initiated clinical trials with Vascugel, a matrix and endothelial cell product to prevent blockage (restenosis and thrombosis) following coronary artery bypass graft surgery.

Even more exciting is recent data suggesting that adult stem cells from blood, skin and muscle can be used to create other tissues types such as neuronal (brain) tissue. Adult stem cells may be able to be induced to behave very much like embryonic stem cells, acting as pluripotent cells with the ability to become many different types of cells. Adult stem cells may eventually replace failed cells, developing into functional tissue. One of the challenges facing researchers is to find an easily accessible source of adult stem cells. Aegera's (Toronto and Montreal, Canada) observations regarding the use of skin stem cells may provide a commercially viable and easily accessible source. To have clinical utility, human adult stem cells still need to demonstrate that they can be expanded and differentiated with the same efficiency as embryonic stem cells. It is not yet clear if adult stem cell can replace embryonic stem cells for all or even most indications. The work with the embryonic stem cells will be critical to providing the insights that may allow adult stem cell therapies to become a viable commercial reality.

Animal-derived stem cells

Some companies are exploring alternatives to the use of human embryonic or human adult stem cells. Advanced Cell Technology, Alexion Pharmaceuticals, Inc (New Haven, CT), BioTransplant Incorporated (Charlestown, MA) and Diacrin (Charlestown, MA) are examining the use of animal-derived embryonic, fetal and adult stem cells to regenerate lost functions in humans. Diacrin has ongoing clinical trials in Parkinson's Disease and stroke using porcine-derived fetal neuronal stem cells. The use of animal stem cells bypasses the ethical questions of using human stem cells and provides an unlimited source of cells. Animal stem cells do raise the additional challenges of the possible introduction of animal pathogens and the need for strong immunosuppression to avoid rejection. The recent 'mad cow' scare in Europe has accentuated these issues.

Here and now

The goal of regenerative medicine is not only to restore normal function in the young and old, but also to disassociate disability from ageing and improve quality of life. As it does this, regenerative medicine will also serve to lower healthcare costs and the related emotional hardship that degenerative diseases can have on patients and their families. The field is not some distant science fiction fantasy. In addition to products that have been mentioned above such as EPOGEN and NEUPOGEN, there are many others that are on the market or about to enter the market. Products on the market include Organogenesis' Apligraf skin substitute and Genzyme's (Cambridge, MA) Carticel for cartilage repair. Currently, Stryker Corporation's (Kalamazoo, MI) OP-1 (licensed from Curis), a bone morphogenic protein that stimulates bone formation, has received advisory panel recommendations for approval in Europe and Australia for the treatment of non-union bone fractures. Investigators at the Boston Children's Hospital are conducting clinical studies to regrow bladders in children. These are but a few examples of the tremendous progress made by industry and academia in this promising field. In addition, the mining of the human genome should accelerate the process and generate a vast number of novel targets for future development.

In a society whose ageing population is demanding increased functionality, a superior quality of life, and lower healthcare costs, regenerative medicine may prove to be the answer to many of these challenging demands. Medical science is already rushing to create ways to help the body repair and replace damaged and diseased cells, tissues and organs – genomics and regenerative medicine is a scientific revolution that is here to stay. DDW

***Doros Platika, MD**, is President and Chief Executive Officer of Curis, Inc, of Cambridge MA. Dr Platika held the same position at Ontogeny, which merged with Creative BioMolecules and Reprogenesis, to form Curis in 2000.*

References

1 US Census Bureau, www.census.gov
2 Longman, PJ. How global ageing will challenge the world's economic well-being. US News & World Report, March 1, 1999; 30-39.
3 Rhodes, SJ and Smith, RC. Using the power of developmental biology for drug discovery. Drug Discovery Today, 1998; 3: 361-369.
4 Shapiro, AMJ, Lakey, JRT, Ryan, EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. New England Journal of Medicine 2000; 343: 230-238.
5 National Institutes of Health, Stem Cell Primer, www.nih.gov/stemcell/primer.htm, May 20, 2000.
6 Letter to President Bush, www.washingtonpost.com. February 2000.