Denise Myshko

BEYOND Stem CELLS

It may seem like science fiction: a trachea grown from stem cells and implanted into a human being. But it's not; this is an actual account of the power of stem cells and regenerative medicine.

The 36-year-old patient, who had been suffering from late-stage tracheal cancer, received his new trachea in June at Karolinska University Hospital in Stockholm. The artificial trachea was made from a spongy plastic polymer scaffold scaled to the same dimensions as the patient's trachea and then was seeded with the stem cells in a bioreactor.

"The bioreactor is the size of a shoe box; it has a long spindle and rotates at about one revolution per minute," says David Green, president of Harvard Biosciences, which created the bioreactor. "As it rotates, the scaffold gets good oxygenation as it passes through the air, as well as good contact with the stem cells. This allows the stem cells to slowly deposit on the inside and the outside of the scaffold to start growing in the pores of the plastic. It took about two days to complete before it was surgically implanted into the patient."

This procedure marks an important milestone in regenerative medicine, which aims to repair, replace, or regenerate organs and tissues. Regenerative medicine addresses a variety of research areas, including cell therapy, tissue engineering, biomaterials engineering, growth factors, and transplantation science.

Regenerative medicine is a rapidly evolving interdisciplinary field in healthcare that translates fundamental knowledge in biology, chemistry, and physics into materials, devices, systems, and therapeutic strategies, according to the Alliance for Regenerative Medicine.

This is the first time a completely artificial organ was regenerated outside of the body. Mr. Green suggests that within a few years, there will be clinical adoption of simple organ transplants, such as the trachea.

"After tracheas, more complex organs such as lung, heart, liver, kidney, and pancreas will be able to be regenerated," he says. "We're working with researchers who are planning to do clinical trials in both the larger, more complicated organs and the simple organs. This is the first step, but it is a very important first step."

Experts say breakthroughs in biomedical tools and technologies such as preclinical imaging have made these advances possible.

"Stem cell research has improved our understanding of these cells and how to manage and differentiate them for the intended tissues or cell types," says Vivek Shinde Patil, Ph.D., manager of technical applications at Caliper Life Sciences. "Developments in chemical engineering and nanotechnology, as well as the science of biologically active molecules have yielded biocompatible and biodegradable materials to provide the right scaffold or environment to guide stem cells in forming the desired tissue or organs."

FAST FACT

REGENERATIVE MEDICINE REVENUE WORLDWIDE WILL REACH $8.84 BILLION IN 2021.

Source: Visiongain

Indeed, regenerative medicine research has advanced tremendously in the last few decades.

"Advances have been realized both within the therapeutic realm as well as in the technologies being used to develop, characterize, and validate the applications of regenerative medicine," Dr. Patil says.

REGENERATIVE MEDICINE HOLDS THE PROMISE OF TRANSFORMING THE WAY RESEARCHERS DISCOVER AND PRODUCE MEDICINES.

Opportunities for Biopharma

Leading experts say regenerative medicine presents exciting opportunities for pharma and biotech companies. Companies such as Geron, La Jolla Pharmaceutical, Shire, Tengion, Pfizer, and Sanofi, to name a few, are pursuing regenerative medicine.

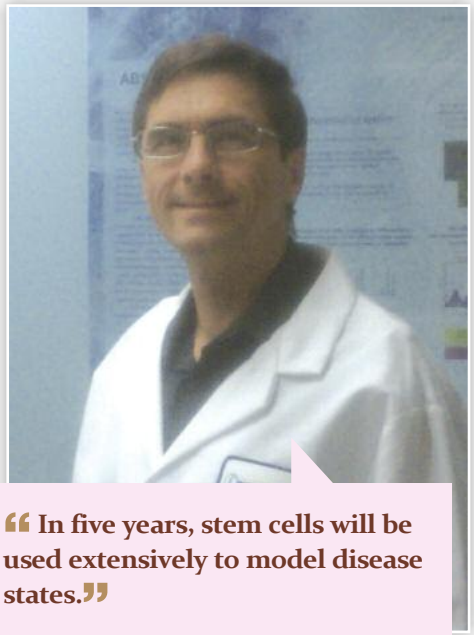
According to a September 2010 report from TriMark Publications, about 230 pharmaceutical companies in the United States, Japan, Germany, United Kingdom, and Sweden are focusing on drug discovery and development using stem cells. Some companies are developing drugs to be used in regenerative medicine.

"There are challenges in realizing the potential of regenerative medicine in the near term, and focused and sustained translational research partnership between academia and industry is needed to address these challenges," says Sridar Natesan, Ph.D., head of external innovation and partnering and site head for Cambridge at Sanofi. "Nevertheless, as regenerative medicine continues to advance, it opens up completely new avenues for pharmaceutical companies to develop novel medicines for several diseases that remain incurable today. Many efforts that are currently under way in this field, when they are demonstrated at the clinical level to be effective, are likely to lead to development of cures for many diseases, not just drugs to treat symptoms of disease."

The therapeutic benefits of regenerative medicine are limitless, Dr. Patil says.

"Different disciplines, including stem cell research and tissue engineering that form the

> "In a few years, there will be clinical adoption of transplants of simple organs that have been regenerated outside of the body."
>
> **DAVID GREEN** / Harvard Biosciences



> "In five years, stem cells will be used extensively to model disease states."
>
> **JEFFREY JANUS** / International Stem Cell

underlying basis of regenerative medicine, have the potential to treat everything from organ damage to congenital defects," Dr. Patil says. "For example, significant advances in the science of skin regeneration have now made it possible to develop and grow artificial skin grafts in a lab for treatment of burn victims. Tracheal transplants and tissue engineered organs, such as the bladder, are some examples currently in human clinical trials. Other therapeutic applications include the use one day of stem cells to treat and repair central nervous system diseases, such as ischemia and cerebral palsy, cardiovascular diseases, as well as autoimmune diseases, including type 1 diabetes."

The opportunity for biopharma will be the ability to use stem cells to produce drugs that are difficult to make in bacteria or yeast, says Jeffrey Janus, director, senior VP, operations, for International Stem Cell Corp. and president and CEO of Lifeline Cell.

"In five years, these cells will be used extensively in the industry as disease models," he says. "Embryonic stem cells or parthenogenic stem cells can be made to have a genetic disease and then researchers can use that as a model to address the disease in a test tube. Drug companies can then test their drugs to see if they are effective using this model. The cells are also useful to test for toxicity."

Mr. Green says in the future there may even come a time when entire organs can be regenerated and used as an alternative to animal testing.

"If we could manufacture human hearts, re-

Uncertain Regulatory Environment

On May 12, 2011, a bill was introduced in the U.S. House of Representatives to launch a national strategy for the development of regenerative medicines.

The bill, co-sponsored by Reps. Brian Bilbray (R-CA) and Diana DeGette (D-CO), is called the Regenerative Medicine Promotion Act of 2011, and seeks to establish funding priorities for research and development of regenerative medicine products and to develop a regulatory environment to ensure rapid approval of safe and effective products.

The bill calls for a report to be issued by the Comptroller General to identify all ongoing federal programs regarding regenerative medicine, as well as for the establishment of a Regenerative Medicine Coordinating Council. The Council's function would be to prepare a national strategy to support regenerative medicine research and development, and to prioritize funding for such activities.

The bill also sets up several grant programs through the National Institutes of Health to fund research and development, including grants for academic or nonprofit groups, grants for academic-industry collaboration, and grants for private companies through the existing Cures Acceleration Network.

According to Vivek Shinde Patil, Ph.D., manager of technical applications at Caliper Life Sciences, funding and regulatory oversight are needed to advance research into regenerative medicine.

"Having a dialogue around ethical issues, educating the public about regenerative medicine and its benefits, and addressing controversies surrounding stem cell research are clearly warranted," he says. "Furthermore, increased public and private funding would help attract even more bright, top-ranking researchers into the field and create the type of strategic research momentum we will need to accelerate the science and bring its promise to fruition."

To approve these types of products, regulators need to have the expertise and the ability to understand what the clinicians are doing, says Kelli Tanzella, Ph.D., senior manager, regulatory affairs for the Americas, Life Technologies.

"There are questions that need to be answered: what are the requirements for safe and effective use, is there going to be a requirement to follow the good tissue practices, and who is going to be required to follow the guidelines," she asks. "The path is not really clear, which makes it difficult for those companies looking to get approval for an IND."

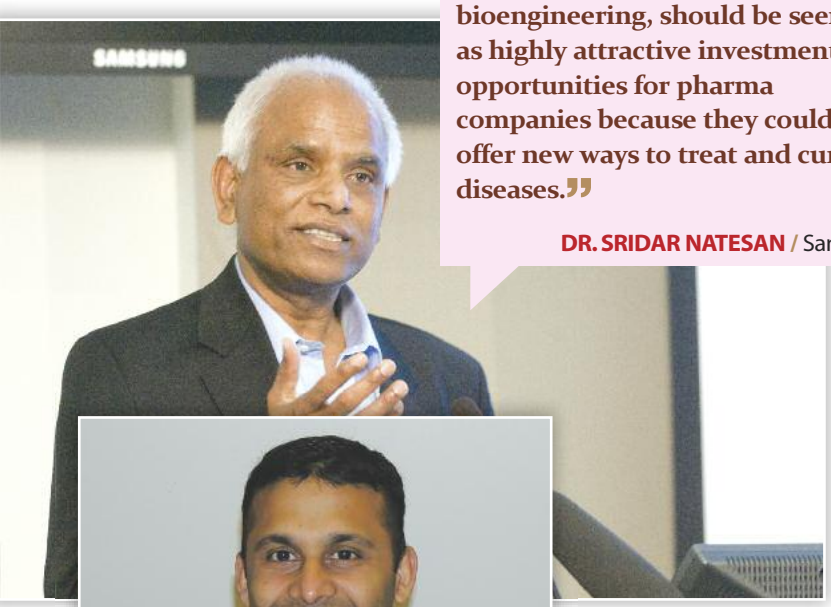
Dean Tozer, senior VP, Advanced BioHealing, says the legislation was put forth to help clarify and bring more definition to how the agency views regenerative medicine.

"This is an effort to clarify that regenerative medicines are a unique class of technologies that need to have their own expertise in the regulatory groups," he says. "Other countries around the world, particularly in Europe, are embracing these technologies more aggressively. The legislation, from our perspective — we are a founding member of the Alliance for Regenerative Medicine — was to help facilitate the conversation with the FDA, the CMS, and with various other organizations in Washington, D.C. Regulators have been very receptive and would like a mandate to better address these technologies."

For example, he says, Dermagraft's venous leg ulcer indication will be reviewed by the FDA as a medical device under a PMA to the product's current indication for diabetic foot ulcers. In Europe the company intends to file Dermagraft as a medicinal product.

Mr. Tozer points out that regulations are evolving.

"In this space, many of the technologies coming to fruition are stem cell technologies and are being reviewed by the biologics group at the FDA, which wasn't always the case," he says. "Regulators are starting to understand these products better and believe it may be more appropriate to have them reviewed by the biologics group."



> "The field of regenerative medicine, particularly cell therapy, tissue and bioengineering, should be seen as highly attractive investment opportunities for pharma companies because they could offer new ways to treat and cure diseases."
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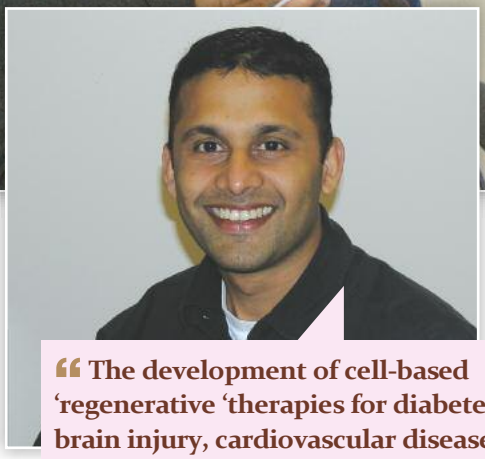
> **DR. SRIDAR NATESAN** / Sanofi



> "The development of cell-based 'regenerative 'therapies for diabetes, brain injury, cardiovascular disease and so on, in my mind, represents the next frontier in treating human disease."
>
> **DR. VIVEK SHINDE PATIL** / Caliper Life Sciences

> "Regenerative medicine represents a new breed of medicine, a new breed of commercial capabilities, and a new breed of research."
>
> **DEAN TOZER** / Advanced BioHealing

searchers could use these to test for cardiovascular side effects before they go into full-scale trials," he says. "Perhaps we could weed out drugs that have serious side effects."

Market Potential

According to a February 2011 report from Business Insights, the first regenerative cell therapies to have significant market value within the next five years will be based on allogeneic adult cells, and they will target tissues that are naturally sheltered from patients' immune systems.

Regenerative medicine revenue worldwide was $82 million in 2010 and will reach $8.84 billion in 2021, according to a July 2011 report from Visiongain. The regenerative medicine market will grow rapidly this decade, driven by the approval of new tissue engineered products, stem cell treatments, and gene therapies. Growth will be most rapid in emerging markets, Visiongain's analysis shows.

Dean Tozer, senior VP of Advanced BioHealing, says there is interest from big pharma in acquiring or partnering with regenerative medicine companies.

"These technologies are very promising and could in the very near future be the fourth leg of healthcare: biotech, device, pharma, and regenerative medicine," he says. "Regenerative medicine is going to become its own area."

In May, Shire acquired Advanced BioHealing, the maker of a diabetic foot ulcer treatment, for $750 million. Advanced BioHealing's Dermagraft is a bio-engineered skin substitute.

The company launched Dermagraft in the United States in 2007 after acquiring it from Smith & Nephew. Dermagraft now is being studied for venous leg ulcers. Mr. Tozer says the company plans to file for this indication with the FDA in the first quarter of 2012 and with the EMA in 2013.

Sanofi is pursuing most of its regenerative medicine approaches through partnerships, Dr. Natesan says.

"We have external partnerships in several therapeutic areas," Dr. Natesan says. "For example, more than a year ago, we formed a partnership with the Juvenile Diabetes Research Foundation to focus on identifying molecules or approaches to beta cell generation. We also have created an internal stem cell initiative that covers all therapeutic areas within the company."

A more recent collaboration is Sanofi's partnership with Audion Therapeutics. In June, the company entered into a research collaboration to develop potential small molecule treatments for hearing loss.

Dr. Natesan says the agreement with Audion is part of the company's focus on aging.

"The regenerative medicine approach for hearing loss is one of our focus areas," he says. PV

EXPERTS

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