NEW CELLS FOR OLD: THE EMERGING POTENTIAL OF PLURIPOTENT STEM CELLS IN REGENERATIVE MEDICINE

Replacing diseased or injured cells is a primary ambition of regenerative medicine. New advances in the development of pluripotent stem cells could benefit the treatment of three diseases in particular, EACH AFFECTING MILLIONS OF PEOPLE WORLDWIDE.

When disease or old age ravage the body, it would be great to turn back the clock by swapping out the damaged cells, replacing them with new ones, like for like. Pluripotent stem cells (PSCs) self-replicate and have the potential in the human body to develop into almost any cell type. As such, they have long held potential in the development of regenerative medicines. But obtaining a steady supply of PSCs proved challenging for a number of reasons.

In 2006, researchers introduced a method to reprogram adult cells into a pluripotent state. These induced pluripotent stem cells (iPSCs) could then be coaxed to differentiate into different cell types. Fifteen years on, iPSC technology has become the basis for many drug development efforts, and it could one day change the outlook for millions of people.

iPSC-based therapies could replace, for example, the neurons that die off in Parkinson's disease or the retinal tissue damaged by macular degeneration. Or perhaps they could obviate the need for a heart transplant. The technology is a marked change for big pharma. "This is a completely different way of looking at medicine—replacing diseased cells rather than drugging them. And we're right on that precipice," says Seth Ettenberg, Chief Executive Officer of BlueRock Therapeutics, a biotechnology company headquartered in Cambridge, MA, and a Bayer subsidiary. "It's an incredibly exciting time for the field."

Several questions remain, however, including where to get the cells. The allogeneic approach uses mass-produced iPSCs derived from healthy donor blood cells to deliver off-the-shelf treatments; typically, however, these cells generate an immune response when transplanted. The alternative is to generate iPSCs from the patient's own cells, but this autologous approach takes longer and costs more. With both approaches, the question remains of how to deliver the iPSC-derived cells, and how to ensure they survive and function.

Using tools such as gene-editing, researchers are seeking to answer these questions and make iPSC-based treatments more effective. The past few years have seen significant progress in the development of treatments for three widespread diseases, among others.

New developments in cardiovascular disease

Cardiovascular disease is a leading cause of death in the developed world. Heart transplantation dramatically improves survival, but supply is scarce. "There's a huge shortage of heart donors, and the gap is growing," says Christine Mummery, a developmental biologist at Leiden University in the Netherlands. It's a grim irony that success in treating cancer is feeding this problem. "Chemotherapy can have negative effects on the heart. People who are cured of cancer might develop heart failure years later."

iPSC-based models could help to identify how individual cancer patients might respond to medication, and to minimize side effects. "We make iPSC models from cardiovascular patients' cells, and use them to look at the toxic effects of drugs," says Mummery, "and we're close to getting regulators to accept this as an alternative to mouse models, which aren't very predictive at all."

Human iPSCs can differentiate into cardiomyocytes, the beating muscle cells whose death can result in heart failure. Cardiomyocytes can improve heart function when transplanted into infarcted rat hearts[1]. The process of differentiation can be inefficient and technically complex, and survival rates of transplanted cells are low. As well, iPSC-based therapies for cardiovascular disease have some unique challenges.

"One of the problems is that the derived cells are fetal-like and beat strongly. They can cause arrhythmias when transplanted," says Mummery. "As the cells mature, they lose the ability to beat by themselves and need a pacemaker. As with any transplantation, the problem is getting the cells to have a dialogue with the host."

Mummery and her colleagues are developing methods to mature differentiated heart cells. "When we started, our cardiomyocytes mimicked those in a human fetus after 16 weeks of gestation," she says. "We can now make them postnatal, so they're still not fully mature."

"THIS IS A COMPLETELY DIFFERENT WAY OF LOOKING AT MEDICINE"
Seth Ettenberg, Chief Executive Officer, BlueRock Therapeutics

iPSC-based models of heart disease are furthest along. Development of treatments, by engineering sheets of heart cells or directly reprogramming other heart cells, is still in the

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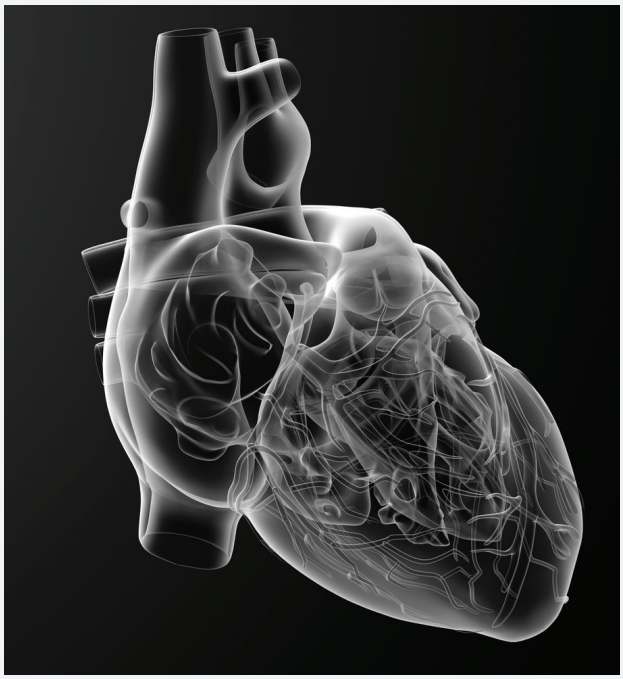

There is a shortage of donor hearts that is expected to only get worse.

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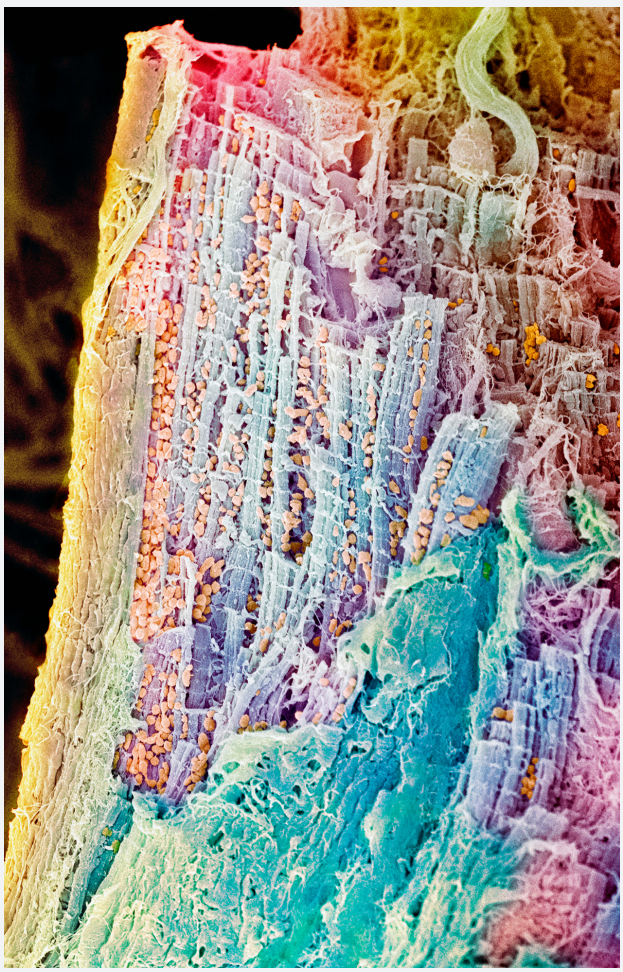


iPSCs can be differentiated to cardiomyocytes, which are the heart's beating cells, but researchers need to fine tune them before they can be tested in patients.

preclinical or very early clinical stages, and many years away from routine use [2]. But with such a big medical need, regenerative medicine has a lot to offer.

Implications in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder that affects more than ten million people worldwide, characterized by the progressive loss of dopamine-producing midbrain neurons, which causes tremors and other motor and neurological symptoms. Mainstay treatments can alleviate symptoms, but do not halt disease progression.

Researchers hope that iPSC-based therapies could replace the neurons killed as Parkinson's disease progresses. Dopamine-producing neurons derived from iPSCs have been shown to improve behaviour in a rat model of PD[3]. In one patient, dopamine cells from autologous iPSCs seemed to stabilize or even slightly improve motor symptoms 18-24 months after transplantation[4].

The brain is a difficult organ to access, however. "Cells will be administered to the midbrain via neurosurgery using devices designed to ensure cells are not damaged during delivery," says Stefan Frank, associate director of Bayer's iPSC platform strategy. "The cells then need to stay there, survive and integrate."

Therapeutic delivery and survival are specialities of Asklepios BioPharmaceutical. The Bayer subsidiary is developing viral vectors to take genetic instructions into the midbrain. One such gene encodes GDNF, a growth factor that promotes survival of dopamine-producing neurons. Animal models have shown that delivery of GDNF into the midbrain improves integration of human stem cell-derived neurons[5].

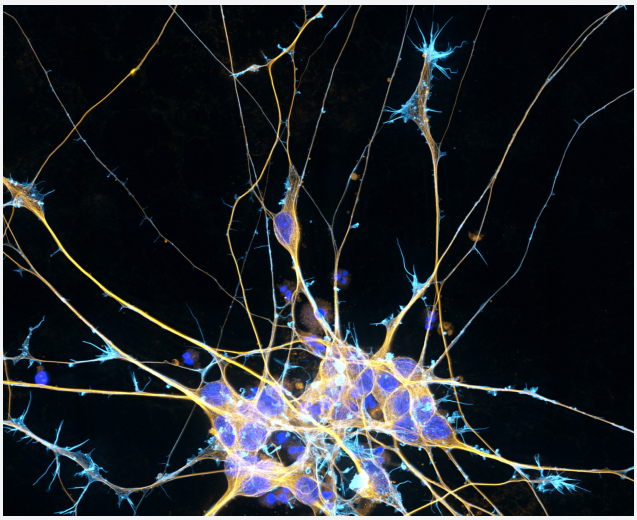
BlueRock, meanwhile, is in clinical trials with pluripotent stem cell-derived midbrain dopaminergic neurons. "Parkinson's is a disease that we have no cure for," says Ettenberg. "We're talking about replacing lost cells to restore neural circuit function." If successful, this approach could herald the end of symptomatic treatment, leaving patients free from tremors and other PD-related problems.

Applications in macular degeneration

One of the most advanced regenerative treatments is for age-related macular degeneration (AMD). A key occurrence in AMD is the progressive loss of the retinal pigment epithelium, a single layer of cells that protects and regulates the light-sensitive photoreceptor cells above. AMD mainly affects people over the age of 65, and is responsible for nearly nine percent of global blindness.

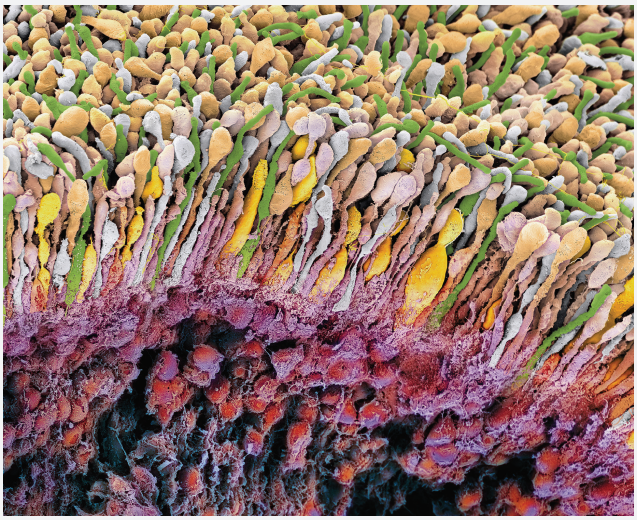
Wet AMD, specifically, is associated with over-production of vascular endothelial growth factor (VEGF), causing abnormal growth of, and leakage from, retinal blood vessels. While this disease can be treated with injections of anti-VEGF drugs, that does not stop underlying degeneration. Recurrence is common if treatment is discontinued.

The eye is easier to access surgically than the brain, and, like the brain, it is said to be immunoprivileged; its local immune system is less likely to attack foreign cells or tissues. Furthermore, the adult mammalian retina retains some regenerative capacity, raising the hope that new cells can be encouraged to grow from intrinsic progenitor cells. Nevertheless, despite more than a decade of studies, it has proven difficult to develop cell therapies for AMD.



Dr Torsten Wittmann / Science Photo Library

Neurons, derived from stem cells, have potential to replace those lost to Parkinson's disease. But delivering the cells, and ensuring they survive and integrate, are still big challenges.



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One goal of regenerative medicine is to replace the retinal cells lost in macular degeneration.

In 2017, ophthalmologist and stem cell researcher, Masayo Takahashi, and her colleagues at RIKEN, in Japan, showed that a sheet of patient-derived retinal pigment epithelium cells, differentiated from iPSCs, survived for a year after implantation in two patients[6].

When it comes to using allogeneic material, Takahashi's team is careful to select candidates for treatment. They look for patients whose immune system is compatible with the 'super donor' of their cell line. "The HLA [human leukocyte antigen] genes are a match for 17 percent of Japan's population, who could be treated with this single cell line without any immunosuppression," she says.

The technology has progressed to the point that personalized iPSC-based treatments for AMD—and other eye diseases—might be used widely in the near future. "Maybe within five years—and definitely within 10 years—we can prepare standardized treatments in Japan's main hospitals," Takahashi says.

The pluripotential of next-generation treatments

iPSC technology, gene editing and viral delivery strategies are combined at Bayer under its cell and gene therapy platform, launched at the end of 2020. The platform enables development of innovative treatments to enhance regenerative medicine strategies. For example, Bayer researchers are developing gene circuits to precisely engineer iPSCs such that they can sense and respond to specific disease markers around them.

Ettenberg describes a partnership between BlueRock and Senti Biosciences, a company backed by a Series B investment from Leaps by Bayer, the impact investment arm of Bayer AG. The aim is to develop "inducible genetic switches" to give cells the ability to sense their environment and act only if certain conditions are met. "CRISPR gene-editing technology," Ettenberg says, "allows us to modify the genomes of cells to improve their therapeutic potential when engrafted, or to allow cells from a foreign donor to be tolerated by a patient."

Gene editing can also be used to improve cardiomyocyte therapy by, for example, altering the expression of ion channels to reduce the risk of arrhythmias[7].

As for autologous versus allogeneic cells, that is still an open question, and involves trading risk of immune rejection with time and cost. But it may not be necessary to choose. "These two paradigms will likely co-exist," says Frank. As with many aspects of personalized medicine, it will involve selecting the right approach for each individual.

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