

## ESSAY

# STEM CELLS IN DISEASE MODELING AND REGENERATIVE MEDICINE—PERSPECTIVES, CHALLENGES AND REALITIES

**When human pluripotent and other stem cells became available in the late 1990s, there was hope that novel therapies might arise quickly. The last two decades have yielded novel concepts, and stem cells are now moving into application.**

## DISEASE MODELING WITH STEM CELLS AND DRUG TESTING

Two major discoveries opened the door to establishing human cell cultures for uncovering disease mechanisms: the identification of human embryonic stem cells (hESCs) and the Nobel prizewinning discovery of induced pluripotent stem cells (iPS cells). The latter allows somatic cells to simply be taken from patients and “rewound,” producing pluripotent cells that can be pushed toward diverse fates. Pluripotent hESCs and iPS cells, alongside other somatic stem cells and their derivatives, can be used to test drugs and identify potentially toxic side effects.

Reliable animal models are lacking for a number of devastating human diseases, including cystic fibrosis, fragile X and Long QT syndrome, and neurological diseases such as Parkinson’s (PD) or Huntington’s. This heightens the importance of studies on human cells obtained through genetic modifications of human pluripotent stem cells and, more recently, deriving iPS cells from patients. Stem cells harboring disease-causing mutations can be differentiated in vitro, producing cell types that are directly involved in the disease. Identifying and modeling the mechanisms that contribute to disease are crucial first steps toward new forms of treatment and prevention. New genetic engineering technologies based on the CRISPR/Cas9 system and

TALEN nucleases are precise, powerful tools to introduce or repair genetic mutations in stem cells. They can be used to produce two cell lines whose genomes differ by only a single, disease-causing gene. This huge step eliminates genetic background effects in studies of cell lines derived from different people whose genomes differ in many other ways.

Modeling a disease in cell cultures permits studying how drugs affect cells with a disease phenotype, as well as identifying other targets that do not exhibit mutations but might be modulated to improve health. Such cells will help avoid past problems: After approval, some drugs turned out to have toxic side effects on organs that were not the intended targets. Deriving specialized human cells from stem cells offers a method of testing drugs before their release that is safer and more cost-efficient, as well as reducing the amount of animal testing.

## THE PATH TO CLINICAL STEM CELL APPLICATIONS

In regenerative medicine, stem cells offer the potential to replace a patient’s degenerated cells or tissues, using his own cells that have been manipulated and grown in the lab. This strategy demands that new cells or tissues integrate themselves correctly in the body. It is also essential that methods of preparation are developed that

do not harm the recipient. Importantly, stem cell-based products have to be well-defined; control of their genetic integrity is crucial, and contamination with other cell types that may, for instance, lead to tumor formation or arrhythmias in the heart, have to be excluded. HSCs have been used for almost half a century to treat leukemias and lymphomas, and now successful treatments based on stem cells are reality for the replacement of skin grafts to treat high-degree burns, and limbal stem cells are used to repair corneal damage. Clinical trials with pluripotent stem cells have been initiated (or soon will be) for major diseases including PD, where dopaminergic neurons must be replenished; to replace disrupted nerves in spinal cord injuries, which may be successful if performed quickly; to generate pancreatic cells in diabetes, cardiomyocytes after heart attacks, and retinal pigment epithelial (RPE) cells to treat macular degeneration.

Stem cell transplantations have produced some unexpected side effects: In many cases, transplanted cells do not integrate into an organ to participate directly in its regeneration. Even so, there may be benefits, since the transplanted stem cells may support self-regeneration through cells already present in the body—a so-called bystander effect. This has been observed in mesenchymal stem/stroma cell (MSCs) treatments after cardiac infarctions and in bone and cartilage regeneration. Compared to other sources of stem cells, MSCs are currently the subject of most clinical trials worldwide. Intensive efforts are underway to identify the factors that cells secrete to trigger the bystander effect and exploit them in other types of therapies. As well as unleashing the self-healing powers of specific organs, MSCs (and possibly other stem cell-derived cell types) may modulate the immune system after degenerative events. This may powerfully influence inflammatory reactions in the aftermath of tissue damage, and thus allow organ regeneration.

## MAJOR CHALLENGES FOR APPLIED STEM CELL TREATMENTS

Applications of stem cells in regenerative therapies, disease modeling and drug development raise a number of questions that need to be discussed:

- » When can patients expect to see the first treatments for more diseases, and can developments be accelerated without compromising patient safety?
- » Will healthcare systems be ready to reimburse the cost of treatments?
- » How can the expertise of diverse players, including clinicians, scientists, and the private sector with biotech, larger pharma companies and suppliers, be best combined to promote innovation?

Basic stem cell researchers have to bridge a gap to translate their findings; regulations governing clinical and basic research are very different. Many European countries lack the “clinician scientists” who have experience in both research environments and could help bridge the gap. Patients with serious diseases are naturally anxious to see

cures arrive before it is too late, prompting untrustworthy clinics to promote “miracle cures” based on unproven therapies. An important task is to provide education and carry on realistic discussions with patients concerning the opportunities and difficulties still faced by treatments based on stem cells.

Stem cell research is costly, and innovation requires business strategies from the private sector. Novel technologies have to be made available to the whole research community, a process in which suppliers play pivotal roles. Moreover, to be accessible to researchers worldwide, stem cells need to be stored in specialized biobanks in a standardized manner, a major investment that cannot be carried by public funding alone. Regulatory requirements are established for stem cell-based products for transplantations, so-called advanced therapy medicinal products (ATMPs), to ensure patients’ safety while speeding up clinical applications. Finally, national healthcare systems need to evaluate the matter of reimbursement for future treatments. It may be difficult to cover such treatments for all patients, since production of ATMPs is expensive.

## DRIVING TRANSLATION FORWARD

Public-private partnerships worldwide are instrumental in deriving commercial applications from stem cell-based approaches. The Innovative Medicines Initiative (IMI) is Europe’s largest public-private initiative aiming to speed up the development of better, safer medicines. IMI is a joint undertaking of the European Union and the pharmaceutical industry association EFPIA. Two projects in IMI directly involve stem cell research: StemBANCC will generate and characterize stem cells to carry out biological assays for novel drugs; the European Bank for induced pluripotent Stem Cells (EBiSC) aims to establish an iPS cell bank that will be the “go-to” resource for the characterization, storage and distribution of iPS cells.

Interaction and communication between scientists, clinicians and other stakeholders require reliable networks. The German Stem Cell Network (GSCN) and other networks embedded in international structures are playing a key role here. The GSCN aims to create new synergies within all areas relevant to stem cell research in Germany, and on a global level with international partners. It provides an interface between science, education, politics and society as a whole. ▲



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