nature biotechnology

# Back to the future

**Investment in basic research is needed to let all regenerative therapies flourish.**

In the late 19th century, Thomas Hunt Morgan established that a planarian flatworm can be cut into 279 pieces, each of which will regenerate an entire worm. Some species of salamanders can regrow limbs, tails, hearts and other structures, although closely related species cannot. Most animals can heal wounds, but the ability to regenerate entire body parts, although widespread, is scattered across the Metazoan phylogenetic tree by evolutionary mechanisms that we do not understand. In humans, the capacity for regeneration is relatively limited. The liver is a remarkable exception; resect two-thirds of it and the lost tissue will be replaced in a week or two. Blood cells turn over rapidly, as do skin and gut epithelial cells. But many tissues and organs, including the heart, brain, spinal cord and cartilage, do not recover spontaneously from serious tissue loss.

Regenerative medicine, the focus of this issue, aims to enhance regeneration using any available means—cell therapies, primarily, but also approaches based on tissue engineering, biomaterials, small molecules, proteins and genes. In many ways cells and engineered tissues seem best suited to the task. Cells are the living building blocks of tissues. Stem and progenitor cells of the appropriate lineage can give rise to any cell type required for repair. And we know that cell therapy works: hematopoietic stem cells transplanted into a recipient can engraft in the foreign bone marrow and regenerate the full repertoire of blood cells for life.

Enthusiasm for cell therapies has also been fueled by breakthroughs in stem cell biology, particularly the derivation of human embryonic stem cells in 1998 and of induced pluripotent stem (iPS) cells in 2007. Because iPS cells can be made from the somatic cells of any patient, in principle they enable immune-matched therapies with any needed cell type. Pluripotent stem cells are not directly useful for therapies as they form teratomas *in vivo*, but steady progress on differentiation protocols has brought this field to the point of early-stage clinical trials.

For all of its promise, however, cell therapy outside of the hematopoietic system faces formidable challenges. By its very nature, the identity of a cell is inseparable from its tissue microenvironment. Extricating cells from their native milieu and placing them in plasticware induces wholesale changes in their gene-expression and proteomic profiles. We know very little about how to formulate media to support cells *in vitro*; during manufacture of cell therapies, cell loss can be upwards of 50%. Moreover, cell populations are heterogeneous, and their composition is continually changing. Analytic tools for defining this variability are lacking, so our understanding of cell products is woefully inadequate.

Another murky area is how a cell product interacts with the environment in the transplantation site. More often than not, the environment is a hostile one, characterized by tissue damage, ischemia, inflammation and scarring. If the cells are allogeneic, they will be attacked by the patient's immune system without effective immunosuppression. Cells usually die in large numbers soon after transplantation and often migrate away from the region targeted for repair. If they survive in place, they must proliferate, differentiate into the correct cell types, integrate anatomically with the host, elicit the growth of new blood vessels and nerves, and restore organ function. In addition, they must not form tumors or harmful tissue of an undesired type.

Once a cell therapy has been validated in animal models, clinical translation brings a new set of challenges. Animal studies are generally conducted using cells and processes that don't meet regulatory standards for current good manufacturing practice (cGMP) and for chemistry, manufacturing and controls (CMC). The manufacturing process is usually unsuitable to produce enough cells for large-scale clinical trials, let alone the post-approval market. And the studies required by regulators to demonstrate safety and efficacy—such as studies of cell engraftment, integration, potency, mechanism of action, longevity, immunogenicity and toxicity—are more complex than those for other drugs.

For regenerative medicine to realize its full potential, this journal supports increased funding to address these challenges. In addition, efforts should be redoubled to define and harmonize the technical, ethical, regulatory and legal requirements of this nascent field. But it will be just as important—if not more important—for funders to continue supporting basic research.

More than a century after the experiments of Morgan, many fundamental questions surrounding regeneration remain unanswered. Insights gained from basic research on stem cells, the stem cell niche, differentiation, reprogramming, tissue development, genomics, cell culture, immunology and imaging—and even on worms and amphibians—will be critical to tackling the translational challenges surrounding the manufacture, efficacy and safety of cell therapies.

But research on these areas will also have a broader impact. It will lift efforts to develop the full breadth of approaches encompassed by regenerative medicine—not only cell therapies but also tissue engineering, biomaterials and small-molecule and protein drugs. Capitalizing on new technologies, such as microfluidic organs-on-chips and 3D bioprinting, will galvanize our ability to screen drugs and understand their effects on cells and tissues.

Regenerative medicine is more than just cell therapy. Some of biotech's most successful recombinant proteins *are* regenerative medicines, even if they are not widely regarded as such. Neupogen (granulocyte colony-stimulating factor) and Epogen (erythropoietin beta) are hematopoietic regenerative therapies for neutropenia and anemia, respectively.

The promise of regenerative medicine lies in its ability to seed a broad array of therapeutic options for diseases that have no options. And for naysayers who remain unconvinced that regenerative medicine can deliver blockbuster products, it already has: Neupogen and Epogen are among the most successful biologic drugs in history. They turned Amgen from a Californian upstart into one of the most successful pharmaceutical companies in the world.

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