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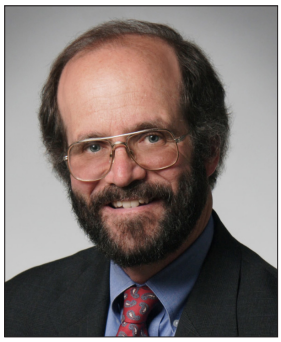

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Stem Cell Science and Regenerative Biology: Tools for Building New Treatments

Deneen M. Wellik, PhD; Robert N. Golden, MD

Advances in medicine are dramatically improving patient outcomes. Solid tumors can be removed, the progression of heart disease can be slowed, and the ability to more effectively treat diabetes continues to advance, yet progress in regenerating diseased, damaged, or resected tissue has been limited. Advanced lung, heart, kidney, and liver disease too often lead to end-of-life care. There are no effective treatments to repair tissue damage following myocardial infarction or stroke. Muscular dystrophies remain progressive, debilitating diseases.

Stem cell and regenerative biology research drives the mission of the Stem Cell and Regenerative Medicine Center at University of Wisconsin–Madison and the Department of Cell and Regenerative Biology at the UW School of Medicine and Public Health (SMPH). Our vision includes gaining knowledge about how stem cells behave and translating those insights into new treatments. Current efforts focus on coaxing existing stem and progenitor cells to respond to catastrophic tissue damage, loss, or disease. Progress on this research frontier offers great potential for advancing clinical care.

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STEM CELL AND REGENERATIVE BIOLOGY RESEARCH IN WISCONSIN

UW–Madison has a storied history in stem cell research. One game-changing breakthrough was the 2007 demonstration that isolated human skin cells could be reprogrammed to return to a "stem cell-like" state. These "induced pluripotent stem cells" (iPSCs) can differentiate into the major cell types required to form a new organ. This discovery was immediately recognized for its potential to harness these cells to generate replacement tissue.

Labs at UW–Madison and around the world have found ways to coax iPSCs into hundreds of specific cell types. Breakthroughs were made possible following decades of basic developmental biology research that defined the signaling factors required for cell differentiation. Generating specific cell types from iPSCs relies on recapitulating these signals, including strict requirements for the order, concentration, and timing of treatment with these factors. The most notable successes in this approach include stem cell-based islet replacement therapy for Type 1 diabetes, a field that has advanced into clinical trials. This disease is caused primarily by the loss of a single cell type, pancreatic beta cells. Many research groups have focused on how iPSCs can be differentiated into beta cells, or at least into pancreatic progenitor cells that can mature further after transplantation. The latter process utilizes the body's ability to develop a new blood supply to the transplant and direct continued differentiation to functional beta cells. Clinical trials have reported encouraging results, allowing some patients to discontinue insulin treatment. More work is needed to decrease the risk of rejection of transplanted cells.

Replacing damaged or diseased organs requires the generation of complex structures that incorporate different cell types into functional tissue. One approach involves creating "organoids"—small, three-dimensional versions of organs that contain several differentiated cell types relevant for organ function. Organoids have been successfully generated for many tissue and organ types, including brain, kidney, and heart. While current organoids are not yet advanced enough for transplantation, they are already valuable for modeling for diseases, screening for drugs, and understanding the cell-to-cell interactions that are required for organ function. Colleagues at the SMPH are modeling brain organoids generated from human cells with Down syndrome and comparing neural development of these organoids to those generated from human cells without the trisomy abnormality of Down syndrome. Because patients with Down syndrome also have a greater risk for diabetes, iPSCs also may be used to create pancreatic organoids that could increase our understanding of the differentiation processes in pancreatic tis-

sues. In other labs, retinal organoids are being utilized for reproducing several key retina cell types. Recent work suggests that retina neural and ganglion cells generated by these methods can reestablish functional connectivity after transplantation.

Numerous challenges remain in the development of iPSC-based therapies. Producing the countless kinds of cells that make up a functional, complex organ requires a large, sustained effort. Successful generation and transplantation of a fully functional organ from an iPSC line theoretically would require generating iPSCs from each patient. Generating new iPSC lines from every human patient and completing the laborious and complicated process of new organ generation are daunting tasks. Researchers are actively exploring other means of avoiding rejection following transplantation by using human leukocyte antigen matches or iPSCs from compatible "super donors."

WHAT ARE THE "HOTTEST" NEW AREAS IN STEM CELL AND REGENERATIVE BIOLOGY?

Discoveries from the earliest era of regenerative biology research are opening doors to future advancements. In the 1950s, scientists found that salamanders can regenerate an entire limb after surgical removal; and in the 1990s, several groups reported that fish are capable of regenerating fins and hearts. In recent decades, advanced microscopy and molecular approaches led to the identification of progenitor cells in non-mammalian organisms that permit such regeneration. Surprisingly, these cells are not as special as this remarkable regenerative ability suggests. In the case of the regenerating limb or fin, existing reserve connective tissue of the injured limb is recruited via regenerative signaling to form a new "blastema," stem/progenitor cells that grow and undergo redifferentiation to replace the missing limb. Thus the "stem cells" are the normal stromal cells found in all limb tissues that can be reactivated for regeneration. In the fish heart, cardiomyocytes that undergo de-differentiation begin proliferating and subsequently replace the damaged heart tissue.

Parallel research in humans and other mammalian species has shown that most of our organs maintain similar reserves of organ-specific stem/progenitor cells. These cells can be induced to proliferate and give rise to the different cell types required for rebuilding an organ. Unfortunately, the potential for this restorative process in mammals is much lower than for other organisms. Scientists have learned much about the identity of reserve bone cells that are capable of extensive proliferation and regeneration of skeletal tissue; these are the cells we rely on for healing a fractured bone. Muscle stem cells also are capable of repairing moderately damaged muscle. However, if a limb is amputated or severely damaged, these reserve bone and muscle progenitors are incapable of mounting the level of repair and regeneration required for full replacement. Recent observations suggest this limitation is not due to a lack of regenerative capacity. Rather, there are two main roadblocks to human regeneration: our immune system and our metabolism. Humans have developed complex immune systems compared to other non-mammalian species. This highly evolved immune system serves us well in combatting viral or bacterial infections, but the strong inflammatory response triggered by severe injury or disease appears to block robust regenerative responses. Recent data also suggest that metabolic state has a tremendous influence on regenerative responses. Many regenerative systems across species rely on glycolysis, a relatively inefficient metabolic state that produces energy in cells quickly without requiring oxygen. Adult mammals, however, largely switch their metabolic profile to fatty acid oxidation, a slower but more efficient means of producing energy. While this metabolic change is ideal for overall health, it is incompatible with the cellular demands of regeneration. Developing ways to overcome this inhibitory effect of metabolism on regenerative capacity is one of the most exciting new areas of research.

The overall research trajectory in regenerative biology is extremely impressive. We are learning more each day about the control switches that regulate inflammatory responses and metabolism. And we continue to develop basic knowledge regarding how tissues and organs develop and regenerate normally. Ten years ago, available information suggested that regenerative organisms retained different kinds of cells compared to mammals, a limitation that would be difficult to address. Current research supports the idea that cells capable of mounting a full regenerative response exist in almost all human organs, including the brain. Researchers are focusing on understanding how these reserve stem/progenitor cells can be activated, and how we can block the inflammatory and metabolic responses that mute regeneration. These are not easy problems to solve, but the exceedingly rapid emergence of new findings provides great hope for the future.

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CONCLUSION

Regenerative biology does not have a dedicated institute at the National Institutes of Health (NIH), and federal funding in this area is insufficient to support all the promising avenues. While the NIH supports important work in this area, there is no centralized, coordinated approach. Expanded investment in stem cell research and regenerative biology will accelerate our progress in developing new healing modalities across the broad spectrum of human illness.

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