

A Multi-Disciplinary Approach to Stem Cells



T. Keith Blackwell, M.D., Ph.D., Head of the Section on Developmental and Stem Cell Biology, uses the microscopic nematode (worm) *C. elegans*—to study the regulation of genes that are important for the development of oocytes (egg cells) and the early embryo. By studying how these genes are regulated, Dr. Blackwell and colleagues hope to discover how these cells differentiate into various types of cells. They believe these regulatory mechanisms will provide knowledge that may make it possible to reprogram human stem cells to develop into different types of cells—including insulin-producing cells.



C. Ronald Kahn, M.D., Head of the Section on Obesity and Hormone Action, studies the developmental origins of fat, including how stem cells (both mesenchymal and embryonic) become different kinds of fat cells and how the process can be modified to impact insulin sensitivity and potential treatments or preventative measures for obesity.



Rohit N. Kulkarni, M.D., Ph.D., Section on Cellular and Molecular Physiology, is exploring the possible presence of “beta-cell stem cells” within adult islets, which are different from duct cells or traditional stem cells. Dr. Kulkarni hypothesizes these beta-cell stem cells may be able to respond to insulin resistant states or other stimuli by replicating and thus increase the beta cell mass and insulin secretion. Dr. Kulkarni is also part of the HSCI team developing approaches to enhance beta cell replication. In other studies Dr. Kulkarni’s laboratory is investigating the mechanisms that allow the regeneration of glucagon-producing islet alpha cells.



George L. King, M.D., Director of Research and Head of the Section on Vascular Cell Biology, studies how the mobilization of adult stem cells may be abnormal in the setting of insulin resistance and diabetes, which could lead to the decreased blood vessel formation within the myocardium (heart muscle) seen in people with diabetes.



Mary R. Loeken, Ph.D., Section on Developmental and Stem Cell Biology, focuses on the underlying causes of birth defects in diabetic pregnancy. Embryonic stem cells can be used to study the precise biochemical and molecular mechanisms by which high glucose and oxidative stress prevent the activation of embryonic genes. In addition to providing information to prevent or repair birth defects resulting from diabetic pregnancy, study of embryonic stem cells may help to explain the pathogenesis of diabetic complications, and lead to improved treatments. Dr. Loeken’s laboratory has also developed more efficient methods of isolating new embryonic stem cells.



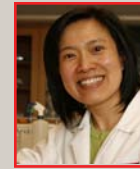
Diane J. Mathis, Ph.D., and Christophe O. Benoist, M.D., Ph.D., Heads of Section on Immunology and Immunogenetics, study immunological tolerance. In this particular context, their research group is attempting to molecularly pinpoint defects in the development of the immune system of diabetes patients by expanding blood-forming cells derived from the blood of patients and maturing them in organocultures or in genetically engineered mice.



Arun J. Sharma, Ph.D., Section on Islet Transplantation and Cell Biology focuses on regulating conversion of embryonic stem cells into definitive endoderm, a lineage that gives rise to pancreas, and on isolation and characterization of embryonic pancreatic progenitor cells.



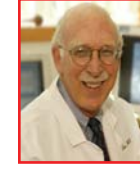
Steven E. Shoelson, M.D., Ph.D., Head of the Section on Cellular and Molecular Physiology. The Shoelson lab has been identifying and characterizing adipocyte precursors. These studies should identify the molecular/genetic switches that determine white vs. brown adipocytes and differences between fat depots such as abdominal vs. subcutaneous, which may have relevance to the pathology of insulin resistance and type 2 diabetes.



Yu-Hua Tseng, Ph.D., Section on Obesity and Hormone Action studies brown fat development and the role of insulin and other growth factors during this process using murine and human mesenchymal stem cells. Brown fat is specialized for energy expenditure, thus understanding how brown fat is formed would assist the development of drugs that promote brown fat differentiation and ultimately facilitate the release of extra energy in humans, thereby providing a new avenue to the prevention and treatment of obesity and its many metabolic complications.



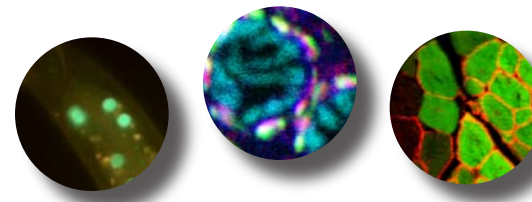
Amy J. Wagers, Ph.D., Section on Developmental and Stem Cell Biology, studies the migration and function of blood-forming stem cells, which are being used to treat such diseases as leukemia, lymphoma and immune deficiency. Blood cell transplantation may someday help people with diabetes better tolerate islet transplants without the need for prolonged use of powerful immunosuppressive drugs. In addition, transplantation of blood-forming stem cells may prove useful in strategies to halt the autoimmune process that causes type 1 diabetes.



Gordon C. Weir, M.D., Head of the Section on Islet Transplantation and Cell Biology, along with the section’s Senior Investigator, **Susan Bonner-Weir, Ph.D.**, have been working with embryonic stem cells and adult precursor cells that have the capacity to become insulin-secreting cells. Much of Dr. Weir’s research studies the genetic make-up and functioning



of pancreatic beta cells in the body, which could provide a blueprint for helping stem cells differentiate into insulin-producing cells. Dr. Bonner-Weir and colleagues have shown that new islets can be formed from adult precursor cells called duct cells that have been isolated from the human pancreas. These findings offer hope that such duct cells might one day be used to provide islets for transplantation, obviating the need for immunosuppressive drugs if the transplanted islets could be derived from the patient’s own body.



Stem Cells and Diabetes

Harnessing the developmental potential of stem cells holds great promise to provide regenerative therapies for diabetes. Joslin Diabetes Center is determined to utilize the regenerative potential of these cells to find new methods for preventing and treating diabetes and its many complications.

Joslin researchers are investigating:

- Could embryonic or adult stem cells be cultivated and manipulated in such a way that they differentiate into insulin-producing cells? What regulatory genes must be turned on or off to make this happen?
- Could transplanting blood-forming stem cells be used in methods to achieve immunological tolerance and so help enable people with diabetes to better tolerate islet transplants?
- Could new methods that incorporate blood-forming stem cell transplants be useful for halting the autoimmune process that leads to type 1 diabetes?
- Could blood-forming stem cells or other stem cells be used to repair tissues damaged by diabetes, such as blood vessels?
- Can blood-forming stem cells be expanded from the blood of diabetes patients and be used to identify the underlying defect(s) in immunological tolerance?
- How do diabetes and hyperglycemia block the differentiation of stem cells in tissues damaged by diabetic complications?

Joslin and the Harvard Stem Cell Institute



As a member of the Harvard Stem Cell Institute (HSCI), Joslin works with an interactive community of stem cell scientists working at the institutes affiliated with Harvard, and has access to the many resources and mechanisms for collaborations that HSCI provides. Joslin faculty hold a variety of leadership positions at HSCI:

Diane J. Mathis, Ph.D., Head of the Section on Immunology and Immunogenetics and **Amy Wagers, Ph.D., an investigator in Developmental and Stem Cell Biology**, are on the Executive Committee of HSCI.

T. Keith Blackwell, M.D., Ph.D., Head of the Section on Developmental and Stem Cell Biology, is co-organizer of the HSCI laboratory research presentation conferences.

Gordon C. Weir, M.D., Head of the Section on Islet Transplantation and Cell Biology, heads the HSCI diabetes program, and **Rohit N. Kulkarni, M.D., Ph.D., an investigator in Cellular and Molecular Physiology**, is co-PI on the program.

Susan Bonner-Weir, Ph.D., an investigator in Islet Transplantation and Cell Biology, heads the HSCI membership committee.

Christophe Benoist, M.D., Ph.D., Head of the Section on Immunology and Immunogenetics, serves on the grants committee.

Drs. Bonner-Weir, Blackwell, Mathis, Wagers and Weir are principal faculty members at HSCI, and Drs. Khan, King, Kulkarni, Loeken and Sharma are affiliate faculty.

Joslin Diabetes Center is the global leader in diabetes research, care and education. Founded in 1898 by Dr. Elliott P. Joslin, we are an independent nonprofit institution affiliated with Harvard Medical School.

Joslin Research is a highly collaborative team of more than 300 people with 44 faculty level investigators undertaking the largest research program aimed at preventing and curing type 1 and type 2 diabetes and their long-term complications.

Joslin Clinic, affiliated with Beth Israel Deaconess Medical Center in Boston, the nationwide network of Joslin Affiliated Programs, and the hundreds of Joslin educational programs offered each year for clinicians, researchers and patients, enable Joslin to develop, implement and share innovations that immeasurably improve the lives of people with diabetes.

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Harnessing the Power of Stem Cells