Biographical Sketch

Dr. Blackwell is a Senior Investigator and Head of the Section on Developmental and Stem Cell Biology at Joslin as well as Associate Professor of Pathology at Harvard Medical School. He received his medical and doctoral degrees from Columbia University, where he studied with Frederick W. Alt, Ph.D., a leader in immunobiology and cancer biology. He trained as a postdoctoral fellow with the late Harold Weintraub, M.D., Ph.D., a pioneer in gene regulation and cellular differentiation.

Dr. Blackwell received the Searle Scholar Award as an outstanding junior faculty member in 1995 while a Junior Investigator at the Center for Blood Research and Harvard Medical School; in 2001 he became an Investigator at the Center for Blood Research. He joined Joslin in early 2004 to head the Section on Developmental and Stem Cell Biology.

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Stem cells have the potential to transform the future of medicine. Many scientists believe that stem cell research holds significant potential to help people with a variety of diseases, including type 1 diabetes. Embryonic stem cells are undifferentiated precursor cells that function like blank slates, capable of replication and able to develop into any type of cell in the body, including insulin-producing islet cells. The ultimate self-renewing type of stem cells are germ cells, which become egg or sperm cells. Germ stem cells are "multipotent," able to develop into any cell in an entire organism.

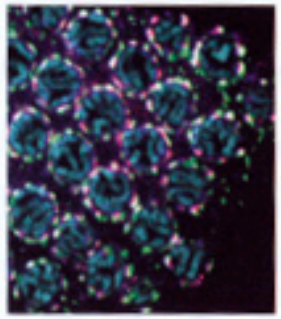
In January 2004, Joslin Diabetes Center established the Section on Developmental and Stem Cell Biology, headed by T. Keith Blackwell, M.D., Ph.D. Under Dr. Blackwell's leadership, the section is assembling a core group of developmental biologists who are exploring the potential therapeutic value of stem cells for type 1 diabetes and certain diabetic complications.

Within the section, the Blackwell laboratory works primarily on two projects, each addressing an important problem in diabetes. One area is oxidative stress, the cellular and tissue damage caused by elevated levels of free radicals (a byproduct of metabolism). Oxidative stress also can result from chemical toxins and elevated glucose levels found in patients with diabetes.

Oxidative stress is an underlying cause of diabetic vascular disease, which gives rise to various diabetic complications. Understanding how to mount defenses against oxidative stress is likely to be of clinical benefit in treating diabetes, heart attack and stroke and in preventing cancer.

In the second area, the Blackwell laboratory is using a simple model organism—the microscopic nematode (worm), *Caenorhabditis elegans*—to study specialized gene regulation mechanisms that are important for the development of oocytes (egg cells) and the early embryo. These gene regulation mechanisms may shed light on the powerful multipotent nature of the germ cell and on other specialized gene regulation mechanisms, such as those that store RNAs and proteins in these cells and allow them to follow differentiation programs appropriately.

Based on previous research, Dr. Blackwell and his colleagues believe that the gene regulatory mechanisms in *C. elegans* stem cells may make significant contributions toward determining how to reprogram human stem cells to adopt particular differentiation pathways, including becoming insulin-producing cells. In the future, Dr. Blackwell would like to apply the knowledge gained in the *C. elegans* research to an investigation of the same regulatory mechanisms in mouse and human stem cells.

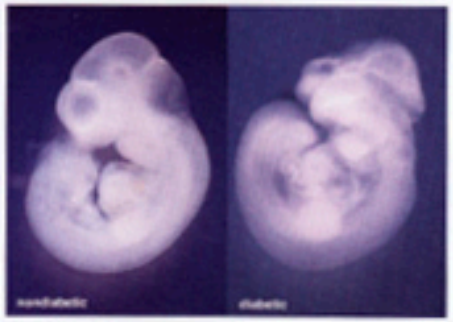


Germline stem cells, showing detection of RNA-binding proteins (green and red) surrounding the nucleus (blue).

It has long been recognized that birth defects occur 2 to 5 times more frequently in the pregnancies of women who have diabetes. Until recently, the reasons for this were unknown. The laboratory of Mary R. Loeken, Ph.D., showed that the malformations are caused by abnormal expression of the genes in the early embryo that control formation of organs such as the brain, spinal cord and heart. These findings were obtained using a mouse model of diabetic pregnancy that was developed by Dr. Loeken. She and her colleagues demonstrated that the abnormally high glucose levels in the mother's blood are delivered to the embryo, and when the embryo cells break down the excess glucose, it blocks the activation of certain embryo genes.

Most of Dr. Loeken's research has focused on expression of one particular gene, *Pax-3*, which is needed for proper formation of the brain, spinal cord and heart. Dr. Loeken has shown that oxidative stress, resulting from excess glucose metabolism by the embryo, blocks expression of *Pax-3*. In trying to understand why blocking expression of *Pax-3* leads to congenital malformations, the Loeken lab showed that the Pax-3 protein is necessary for formation of these structures because it prevents cells from dying. While further research is necessary, Dr. Loeken's findings may lead to new methods to prevent high glucose damage to embryo gene expression and to identify which women may be at increased risk for having a baby with a birth defect. Furthermore, these findings may be applicable to understanding the relationship between high glucose and abnormal gene expression in other diabetic complications such as nephropathy and vasculopathy.

Building on these findings, the current work of the Loeken laboratory is focusing on three major questions: What are the biochemical pathways by which increased glucose metabolism generates oxidative stress and interferes with gene expression? How does *Pax-3* prevent cell death? And which genes increase or decrease risk for the adverse effects of maternal diabetes on embryo gene expression? Experiments to answer these questions will use the diabetic mouse model of pregnancy, genetically engineered mutant mouse strains, and embryonic stem cells. Experiments using embryonic stem cells provide a cell culture model to study how the *Pax-3* gene is induced during embryonic development, and how glucose metabolism blocks its induction. The stem cell model complements the mouse model and can be used for molecular and proteomic analysis of the signals by which glucose metabolism affects embryo gene expression.



Normal embryo from a nondiabetic mouse (left) and embryo with a neural tube defect from a diabetic mouse (right).

Biographical Sketch

Dr. Loeken is an Investigator in the Section on Developmental and Stem Cell Biology at Joslin and an Assistant Professor of Medicine at Harvard Medical School. She received her doctoral degree in Reproductive Endocrinology at the University of Maryland Medical School and did her postdoctoral training in Molecular Virology at the National Cancer Institute. In 1992, she was named a Capps Scholar in Diabetes Research at Harvard Medical School, from which she also received a Scholars in Medicine Award in 1998. She is an expert on the study of birth defects resulting from diabetic pregnancy, and she serves on numerous grant review panels and the editorial board of the journal *Diabetes*.

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