Narrative report of Research, Teaching and Clinical Contributions.
By C. Ronald Kahn, MD

Since our discovery that the insulin receptor is an insulin-stimulated membrane tyrosine kinase activity, my laboratory has focused its attention on how this early signal is converted to the final effects of insulin on metabolism and growth, how insulin signaling is altered in insulin resistant states such as type 2 diabetes and obesity, and what the impact of genetics is on these functions.

We have shown that following the activation of the receptor kinase, several intracellular substrates become tyrosine phosphorylated. The best studied of these are a family of high molecular weight proteins termed insulin receptor substrates-1, 2, 3 and 4 (IRS-1 thru -4). These phosphorylated IRS proteins serve as intracellular messengers by docking to other intracellular signaling proteins that contain SH2 domains. This links insulin to two major intracellular cascades - one mediated by the enzyme phosphatidylinositol 3-kinase (PI 3-kinase) and the other mediated by the Ras-MAP kinase pathway. These form an important point of diversion in insulin signaling and several potential points of regulation in disease.

Using a wide range of genetic, biochemical, and approaches, as well as cellular, animal and human systems, my laboratory is attempting to define the specific pathways that lead to specific insulin actions and how they are modified in insulin resistant states. We are also attempting to identify genetic alterations that might contribute to the development of type 2 diabetes in humans and rodents by gene expression using Affymetrix microarray analysis, proteomics and other techniques.

Current projects in the laboratory fall into five areas: 1) Defining the roles of each of the IRS-proteins, isoforms of PI 3-kinase and their downstream kinases, such as Akt and atypical PKCs, in insulin signaling and insulin resistance through the creation of cell lines and animal models in which these proteins are either eliminated by a genetic "knock-out" or knocked-down using RNAi. This also includes studies utilizing the technique of tissue specific gene inactivation to determine the role of insulin in various tissues of the body, including classical target tissues for insulin action such as liver, muscle and fat, as well as non-classical targets such as the brain, endothelial cell and beta cell. 2) Mechanisms of insulin resistance, including the role of regulation of

insulin receptor, IRS proteins, p85 subunits of PI 3- kinase, SOCS and Trb proteins, various adipokineș as well as other molecules that can act directly or indirectly as inhibitors of insulin action, such as the sirtuin protein deacetylases. 3) The role of insulin signaling in control of gene expression. In these studies we have made extensive use of microarrays and realtime PCR coupled with the genetic models we have created to answer questions about which components of the insulin signaling cascade are involved in which insulin actions and to dissect insulin vs. diabetes regulated events. 4) The biology of adipocytes and their special role in insulin resistance. Here we are focused on understanding not only the role of various fat depots in insulin resistance, but also what determines fat distribution and the nature of adipocyte lineages, including the formation of brown vs. white fat and subcutaneous vs. intra-abdominal fat. 5) Finally, we are also interested in the problem of aging and the relationship between insulin action, obesity and lifespan. Again we have taken advantage of some of our genetic models to define better the physiological connections between these events. We are now studying several pathways involved in the connection between aging and metabolism at the molecular level.