New Grant

Chemotaxis to Islets Based on Cellular Insulin Receptor Expression (NIH/NIDDK)

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Type 1 insulin-dependent diabetes affects some 15 million people worldwide, with three million in the US. More than 15,000 children and 15,000 adults are diagnosed with type 1 diabetes each year in the US. Furthermore, the incidence of Type 1 Diabetes for children under fourteen years of age is estimated to increase by 3% annually worldwide. In Type 1 diabetes, pancreatic beta cells, the only cells in the body that secrete insulin, are destroyed. Because insulin controls the usage of sugar in the body, which allows cells to be fed, glucose levels in the blood and urine rise when insulin is not present, leading to the clinical symptoms of diabetes. Diabetes is controlled by insulin injection; however, secondary complications of diabetes include heart disease, blindness, kidney failure, poor circulation and wound healing, and increased risk of infection. The healthcare cost for Type 1 Diabetes in the US is close to $15 billion each year.

The immune system, which includes white blood cells or lymphocytes, is responsible for recognizing and destroying foreign invaders such as bacteria and viruses. Normally, the immune system does not respond to any self-components. In autoimmune disease, however, the immune system recognizes some self-tissue as “foreign” and destroys it as a result; this is what happens in type 1 diabetes. In a process called insulitis, lymphocytes enter the islets of Langerhans in the pancreas, where the beta cells, the only cells in the body that produce insulin, live. The lymphocytes destroy the beta cells. Once they are destroyed, the body can no longer make insulin and it must be provided by injections. The nonobese diabetic (NOD) mouse is an accepted animal model that is used to study human insulin-dependent diabetes. Diabetes is genetically inherited in NOD mice, and they spontaneously become diabetic by three to six months of age. The process of cellular movement of lymphocytes into the pancreas begins at 4-6 weeks of age, and by 3 to 6 months of age, when approximately 90% of the beta cells are destroyed, not enough insulin can be made in response to the intake of glucose. As a result, glucose levels rise in the system and the animals become diabetic.

Why do lymphocytes move into the pancreas? Insulin binds the insulin receptor and a signal is given to transport glucose so that cells can be fed, and this overall operation maintains homeostasis. However, along with binding insulin and signaling for glucose transport, the insulin receptor is also a chemotactic molecule for insulin. Therefore, cells that have many insulin receptors on their cell surface can physically move toward
insulin. If lymphocytes have receptors for insulin on their surface, insulin secretion might draw lymphocytes to the pancreas and into the islets. When lymphocytes obtained from diabetic NOD mice are transferred into young (6-8 weeks old) non-diabetic NOD mice, the recipient mice develop insulitis and become diabetic within three weeks. This is called adoptive transfer. Significantly, when lymphocytes expressing insulin receptors are removed from the total lymphocyte population, the remaining cells are no longer able to transfer insulitis or diabetes in the NOD mouse. Furthermore, when only lymphocytes expressing the insulin receptor are transferred, these cells can cause insulitis and diabetes in a shortened period of time. Therefore, our data indicate that lymphocytes expressing insulin receptor are involved in the development of diabetes. We wish to further characterize these lymphocytes and confirm that insulin receptor expression is important for cellular movement into the pancreas. By characterizing these cells, methods may be developed to prevent the movement of lymphocytes into the pancreas, thus preventing beta cell destruction and the development of insulin-dependent diabetes.

Therefore, the hypothesis for this new NIH/NIDDK grant is that T cells (a type of lymphocyte) with a high density of insulin receptor expression can migrate to the pancreas in response to an insulin gradient. We have made transgenic mice wherein an insulin receptor with a FLAG tag (to distinguish from endogenous insulin receptor) was placed behind the CD3 promoter and enhancer (CD3 is on all T cells) in normal strains of mice (C57BL6 and FVB) that do not spontaneously become diabetic to determine if T cells engineered to express exogenous insulin receptor can move into the pancreas. We have evidence for insulitis in the transgenic mice by 10 months of age (see figure 1[left] below). The animals do not become diabetic. We are still in the process of staining for FLAG expression.

We would like to bring this back to the NOD mouse and determine whether insulin receptor over-expression on all T cells in NOD mice will lead to a shortened time to diabetes development. This will be tested in a Cre-lox system. We are in the process of making the lox mice expressing a FLAG tagged Green Fluorescent Protein (GFP) mouse insulin receptor. NOD mice, with Cre expression in all T cells, are already available commercially. It is also possible that the Cre-lox system can be used to prevent diabetes development by delivering regulatory T cells, over-expressing insulin receptor, to the pancreas.

Finally, we would like to be able to test whether insulin receptor expression on T cells in human type 1 diabetes patients is important for diabetes development. With our clinical consultant, Dr. Blumer, we will be examining peripheral blood from Type 1 diabetes patients. The lymphocytes will be injected into humanized mice, wherein human cells from diabetic patients can traffic into the pancreas and cause diabetes. Insulin receptor positive cells will be separated from insulin receptor negative T cells prior to injection in order to determine the importance of insulin receptor expression.

If insulin receptor overexpression is identified as important for cellular movement into the pancreas, then immunotherapy directed at the chemotactic portion of the insulin receptor molecule will be tested in the future to block cell movement. Blocking T cell movement should prevent beta cell destruction and the development of diabetes.
Workshop for MPH Students

Sadik Khuder, Ph.D.
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The JCCTR hosted a workshop for MPH Students interested in careers in clinical research on Wednesday, November 19. The workshop consisted of informing students about the process of coordinating clinical trials, applying for IRB approvals, regulatory compliance and budgeting.

Holly Burtch reviewed the federal regulations, Good Clinical Practices, research misconduct and how to effectively coordinate clinical trials.

Kelly Walter reviewed the IRB website and discussed CITI training and HIPPA certification, what IRB reviewers need from an application, the elements of a protocol, and documents needed for submission, specifically with respect to investigator initiated studies.

Danielle Mockensturm talked about how to set up a clinical trial budget, fair market value, and its effect on clinical trial budget negotiations.

The students involved in the workshop had spent three months with the JCCTR working on clinical research to fulfill the 275 hours of training required by the MPH degree program. The internship covers the basics of clinical research; study design, data collection and management, statistical analysis and reporting. A review of existing literature and learning about new research tools pertinent to clinical research are also included in the program.

JCCTR supports professional development of clinical researchers by offering resources and services that are relevant to the needs and interests of MPH students, and which lead to success in clinical research. Our service is designed for students who wish to gain basic training in clinical research before graduation and for those having experience in clinical research aiming to broaden their role in the design, management, analysis, and reporting components.

RSP Corner

NIH eRA Commons Update
Rick Francis, Ph.D., C.R.A.

The NIH continues to add new functionality to the eRA Commons site. This year the Commons has seen updates to the Advanced Search function; the addition of the Inclusion Management System (IMS) to report inclusion of women and minorities in clinical research; and new closeout capabilities.

New Features on Closeout

Grantees will receive more notifications, with emphasis on notices on overdue or incomplete closeouts. Grantees will be able to submit additional information through a feature called “Final Report Additional Material” or FRAM. In addition, it will be easy to identify grants that will be closing soon through a new “quick query” on the eRA Commons home screen (i.e. NOT requiring Commons login).

Changes in Quick Queries

On Monday, November 24, 2014, an announcement was issued regarding the changes in Quick Queries, and this is very useful indeed, as these queries can be run without logging in. That’s quick! Here is what is available now:

![Welcome to Commons Quick Queries](image)

A new search tool, Grants Pending Closeout, will return a list of NIH Research grants due for Closeout for your organization over the selected last number of days. Pro tip: The UTHSC IPF is 0229501, but you can always search for it through a quick query.

You can access all the queries from the eRA Commons home page (no log in required) using Commons Quick Queries link under Additional Links along the right side of the page.

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