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Scientists Reveal How Genetic Mutations May Cause Type 1 Diabetes

By Mika Ono

Scientists from The Scripps Research Institute have provided an answer to the 40-year-old mystery of how certain genetic mutations lead to Type 1 diabetes. This new molecular understanding could lead to novel therapies for Type 1 diabetes and other autoimmune diseases.

The study appears in the May print edition of the Journal of Clinical Investigation.

"People have been looking for the mechanism linking HLA and autoimmunity for 40 years," said Scripps Research Professor Luc Teyton, who led the study with Scripps Research Professor Ian Wilson. "This study provides a big leap forward in understanding and suggests a critical new target to intervene in type 1 diabetes."

Teyton notes that his lab has been trying to solve the mystery of autoimmune mechanisms and related conditions like celiac disease for some 25 years.

A Life-Threatening Condition

This new study focuses on Type 1, or insulin-dependent diabetes, a rapidly progressive disease of the young that leads to high blood sugar, coma, and death if not treated with replacement insulin.

Type 1 diabetes occurs when the body's immune system attacks insulin-producing β cells in the pancreas. Without insulin, the glucose in the bloodstream increases dramatically; early symptoms are unusual thirst, increased output of urine, fatigue, and unusual hunger accompanied by weight loss.

Currently, the only therapy available is to compensate for the destruction of the body's insulin-producing cells by injecting insulin on an ongoing basis.

While genes predispose people to many different types of diseases in many different ways, specific genetic variations are an especially strong predictor of the development of type 1 diabetes. Three genetic variations in particular (HLA-DQ2, HLA-DQ8, and HLA-DR0405)—all located in the region of the genome called HLA for "human leukocyte antigen"—are known to dramatically increase risk of coming down with the condition.

These three genes encode molecules that present peptides (protein fragments) to the body's T cells. T cells then determine whether the peptide being presented is dangerous and needs to be eliminated from the body—as in the case of foreign invaders such as bacteria or viruses—or whether the peptide is "self," part of the host and something the immune system needs to leave alone. However, in the context of type 1 diabetes, T cells aggressively attack the body's own cells.

The scientists wanted to know on a molecular level how mutations in the immune surveillance machinery could lead to type 1 diabetes.

"We were interested in trying to understand why certain MHC molecules (which are molecules in mice analogous to HLA molecules in humans) are linked to autoimmune disease, particularly type 1 diabetes," said Research Associate Adam Corper of the Wilson lab, who was first author of the paper with Kenji Yoshida of the Teyton lab. "In particular, we wanted to know why a single residue at position 57 on the β chain of HLA molecules seems to be linked to the disease."

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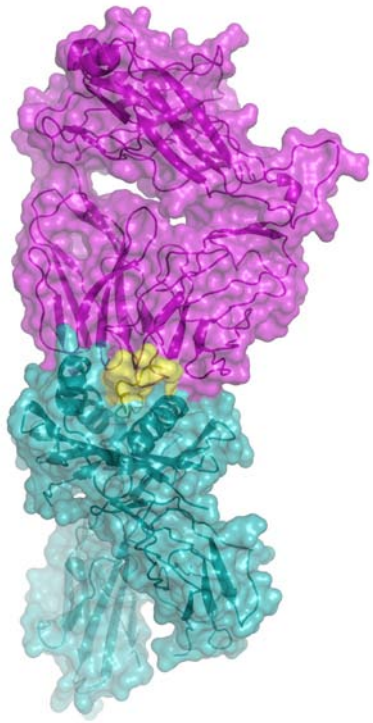

As part of its quest to discover how certain genetic mutations lead to Type 1 diabetes, the Scripps Research team determined the structure of a T cell receptor and MHC molecule in complex. Here, the surfaces of the two molecules are illustrated as partially transparent, with a ribbon trace of the backbone underneath. The TCR is shown in purple, the MHC in cyan, and the peptide bound by the MHC in yellow.

Scientists Find New Link

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Breaking Tolerance

In the new research, the team used a series of structural and biophysical studies to answer that question.

Previously, Teyton and Wilson labs had determined the structure of a "diabetogenic" MHC molecule and found that mutations to position 57 caused only subtle changes. It did not, as some had speculated, cause the molecule to become unstable and non-functional.

Now, in the new study the researchers found that diabetes-causing mutations changed the charge at one end of the MHC peptide-binding groove. In individuals not predisposed to type 1 diabetes, MHC molecules usually have a negatively charged residue at position 57. In contrast, disease-causing MHC molecules have a neutral residue at position 57 and consequently the surrounding region is more positively charged.

The result of this molecular change was that the mutated MHC molecules selected a unique subset of T cells that bound to it strongly, with "higher affinity." These T cells may overreact and potentially misidentify "self" peptides as dangerous rather than harmless.

"We found that the MHC region around position 57 can be seen by the T cell receptor," said Teyton. "That's the big novelty of the paper—for the first time, we show that it is not only essential for peptide binding, but also critical for the selection of T cells. Finally, we have an idea of why those particular MHC molecules are associated with disease."

Corper added, "What we have here is potentially a way of breaking 'tolerance'—the mechanism where the immune system doesn't respond to self. Obviously, if that breaks down you get autoimmune disease."

The team is now investigating potential antibody or small molecule therapies that could target and correct mutated MHC.

In addition to Teyton, Wilson, Corper, and Yoshida (currently assistant professor at Meijo University, Japan), the authors of the paper, "The diabetogenic murine MHC class II molecule I-Ag7 is endowed with a switch which modulates TCR affinity," include Rana Herro of Scripps Research and Bana Jabri of the University of Chicago. See http://www.jci.org/articles/view/41502

The study was supported by the National Institutes of Health.

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Inaugural Event Showcases Research Talent of Scripps Florida Postdocs and Graduate Students

By Eric Sauter

Scores of visitors, some from as far away as Miami, and representatives of more than 50 scientific vendors came together at Scripps Florida on April 20 for ResearchFest 2010. The first in what is expected to become an annual event, the gathering highlighted the work of the institute's graduate students and postdoctoral fellows, showcasing the scientific talent being developed at Scripps Florida.

The day-long event was sponsored by the Scripps Florida Society of Research Fellows.

"Congratulations to our postdoc community for organizing and running the very popular and successful ResearchFest event," said Harry Orf, Scripps Florida vice president for scientific operations. "We received many positive comments from faculty, staff, and participating vendors. The atmosphere was lively all day, great science and products were on exhibit, and excellent presentations were given. The success of the event bodes well for making it an annual occurrence and an integral part of our culture."

"The event went extremely well," said Laura Solt, the society's new president, a co-founder of Women in Science at Scripps Florida, and research associate in the Burris lab. "We had people from Max Planck and FAU and some who even drove up from the University of Miami to attend."

In addition to about 50 scientific posters, the event featured lectures by four postdoctoral fellows: Solt; Antonio L. Amelio of the Conkright laboratory; Emmanuel Sturchler of the McDonald laboratory; Seth Tomchik of the Ron Davis lab.

Solt seemed surprised by the number of vendors who signed up and paid to attend, but she noted they all seemed pleased to be there and looked forward to coming back next year. The event raised more than $10,000 for the society, which will be put to good use in the coming year.

"Some of the money will be used to fund next year's ResearchFest," Solt said, "and some will be used to jumpstart a postdoctoral speaker series."

Solt credited a number of people for the day's success, including Mike Tarselli from the Micalizio lab, Heidi Walsh from the Smith lab, and Kapil Lokare from the Periana lab.

"There's no other comparable event like this being held in south Florida," said Tarselli, "which explains why people came up from Miami to attend."

The society also received financial help from its counterpart, the Society of Fellows in La Jolla, and broad support from the Scripps Florida administration, Tarselli noted.

Visitors, vendors, and members of the Scripps Research community all turned out for ResearchFest 2010.

Starting Out

The Scripps Florida Society of Research Fellows was founded in 2007 by Antonio L. Amelio, a research fellow recruited to the Conkright laboratory in early 2006, well before the new campus was built. The Scripps Florida society marks the second scientific organization founded by Amelio to serve the needs of junior scientists, the first being the College of Medicine Graduate Student Organization launched while he was a doctoral student at the University of Florida.

"I think it's important to stress that these scientific organizations are created to serve the needs of developing scientists," Amelio said.

The Scripps Florida Society of Research Fellows sponsored a pair of well-attended lectures last year, given by Professor Bernard Roizman of the University of Chicago, who spoke on targeting herpes simplex virus for therapy of malignant glioma, and Professor Arnold Levine of the Institute for Advanced Study in Princeton, New Jersey, who offered his views on single nucleotide polymorphisms in the p53 pathway.

In addition to hosting scientific lectures, the society also offers a number of practical seminars during its Lunch n' Learn series, including tips on automobile purchases, first-time home buying, and estate planning.

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Inaugural Event

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Amelio said he was particularly interested in building a forum for graduate students and postdocs that would address issues surrounding their professional and career development needs.

"We want to help scientists understand the various paths open to them, that it isn't just a choice between research and academics," Amelio said. "There are lots of other opportunities out there."

Laura Solt thinks that this year's ResearchFest event – and the ones that will come after it – will help junior scientists learn how to network, get collaborative projects going, and develop their careers. It's also a way to help them get noticed by the larger scientific world.

"This is a good way to reach out to the larger scientific community and show what we do at Scripps Florida," she said. "When you think of research centers, you generally think of places like Cambridge or Berkeley, not South Florida. We want to show people how well we're doing here."

Judging from Tuesday's results, they are doing quite well indeed.

Send comments to: mikaono@scripps.edu

New NIH Grant Funds Development of New Tests for Potential Obesity and Diabetes Treatment

By Eric Sauter

The Scripps Research Institute has been awarded a $1.3 million grant by the National Institutes of Health (NIH) to develop a series of tests at its Florida campus to help explore the potential of a protein that has emerged as a highly attractive target for the treatment of obesity and Type 2 diabetes.

Patricia McDonald, an associate scientific director in the Translational Research Institute at Scripps Florida and an assistant professor in the Department of Molecular Therapeutics, is the principal investigator for the three-year project funded by the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

"Because obesity and diabetes are two of the most serious health problems facing us, the need for novel treatments has never been greater," McDonald said. "Some recent studies in animal models have shown that activating the G protein-coupled receptor GPR119 improves glucose homeostasis or balance, while positively affecting both food intake and weight gain. This funding will help us design new assays that will explore the overall potential of GPR119 – and may one day lead to more effective treatments."

G protein-coupled receptors (GPCRs) are the largest and most diverse protein family in the human genome. They transduce or convert extracellular stimuli including neurotransmitters, light, hormones, lipids, and peptides into intracellular signals through a number of signaling pathways. Approximately one third, and perhaps as many as half, of currently marketed drugs are designed to target these receptors.

GPR119 is expressed predominantly in the pancreas and gut of humans and rodents and in the rat brain. When activated, the receptor promotes secretion of a specific hormone, called Glucagon-Like Peptide-1 (GLP-1), in the intestines, which in turn increases insulin secretion from the pancreas; both are key components in regulating the balance of glucose in the body. Although some modulators of GPR119 have been discovered, they do not necessarily mimic the receptor's natural ligand and have thus turned out to be mostly unsuitable for use in studying the receptor's biology and function.

"In terms of treating metabolic disease through modulation of GPCRs," McDonald said, "an obvious candidate such as the GLP-1 receptor has been a historically difficult target to track with small molecules, but GPR119 is much more amenable to modulation, plus it also regulates the GLP-1 axis, which is what makes it such a potentially valuable target in diabetes and obesity. We chose this particular receptor for those reasons – and the fact that it's being studied extensively by the pharmaceutical industry."

McDonald hopes that once the new assays are developed, and molecular probes created, the process will lead to the identification of small molecule compounds that can be used therapeutically. The probes themselves might even have potential in this regard.

"We'll be studying these probes to see if they have any drug-like properties, particularly if they show any significant activity against the GPR119 receptor," she said. "The obvious goal would be to improve a probe's therapeutic qualities – oral bioavailability, for example – while keeping its high level of activity, a process that can be a lot more difficult than it sounds."

Expanding Knowledge in the Field

With the human genome sequenced, science now has a good handle on just how many GPCRs exist – at least 1,000 or more. Of those, McDonald said, scientists have a good understanding of what approximately 200 of them actually do and what activates them; another 600 or so are involved in taste and smell. The remaining receptors are known as orphan receptors, whose function and natural ligands have yet to be discovered (also a receptor class that the McDonald lab is actively pursuing).

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"Because obesity and diabetes are two of the most serious health problems facing us, the need for novel treatments has never been greater," said Assistant Professor Patricia McDonald, principal investigator of the new grant.

Grant Funds Development of New Tests

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"We want to look at developing assay environments that are more physiologically relevant to the disease state in question," she said, "to make them more akin to what's really going on in the whole animal. We hope that the in vitro pharmacology that we uncover in GPR119 will help bridge the gap between the limits of cell-based assays and in vivo studies. That's why this funding is so important to eventually find more effective treatments for diabetes and obesity."

In her work, McDonald collaborates with the medicinal chemists at Scripps Florida.

"When small molecule candidates demonstrate some sort of efficacy in our cell-based assays, we work very closely with the chemists to improve their efficacy," she said. "The chemists modify these molecules and then they cycle back to the biologists and our assays for further evaluation. It's a very symbiotic relationship."

Send comments to: mikaono@scripps.edu

In Brief

Karsten Sauer Wins Leukemia and Lymphoma Society Award

Associate Professor Karsten Sauer has won a five-year Scholar Award from The Leukemia and Lymphoma Society for highly qualified individuals "who have demonstrated their ability to conduct original research bearing on leukemia, lymphoma and myeloma." The Sauer lab's research program combines broad functional genomics approaches with traditional, hypothesis-driven research to identify and functionally characterize novel genes with important roles in lymphocyte development and function, and in blood cancers. In particular, the lab focuses on the molecular mechanisms through which soluble inositol phosphates and protein kinases mediate lymphocyte receptor signaling. More details can be found on the Sauer lab website (www.scripps.edu/ims/sauer).

SF-SRF Announces ResearchFest Prize Winners

The Scripps Florida Society of Research Fellows (SF-SRF) has announced the winners from the inaugural ResearchFest on April 20.

POSTDOCTORAL FELLOW POSTER PRESENTATION AWARDS

- First prize: Jiali Li with Shawn Browning, Sukhvir Mahal, and Anja Oelschlegel, presenting "Selection Of Drug Resistant Variants From Cloned Prion Populations." The prize was a gift card for the Palm Beach Hilton Hotel.
- Second prize: Monica A. Istrate with Scott A. Busby, Juliana J. Conkright, Michael J. Conkright, and Patrick R. Griffin, presenting "Role of ARA70 as a LRH-1 Coactivator for Modulation of the Aromatase Promoter II: Implications for Targeting Estrogen-Dependent Breast Cancer." The prize was a VISA gift card sponsored by DiscoveRx.
- Third Prize: Xin Qi with Tom Kodadek, presenting "Novel Chemical Screens to Target GPCRs." The prize was an iPod Shuffle.

GRADUATE STUDENT POSTER PRESENTATION AWARDS

- Cristin Gavin with Maria D. Rubio and Gavin Rumbaugh, presenting "Actin-Myosin Dynamics Contribute to Fear Memory Consolidation in the Lateral Amygdala." The prize was a VISA gift card sponsored by DiscoveRx.
- Cullen Schmid with Laura M. Bohn, presenting "Functional Selectivity at the Serotonin 2A Receptor: Differential Signaling by Serotonin and Dimethylated Tryptamines." The prize was a VISA gift card sponsored by DiscoveRx

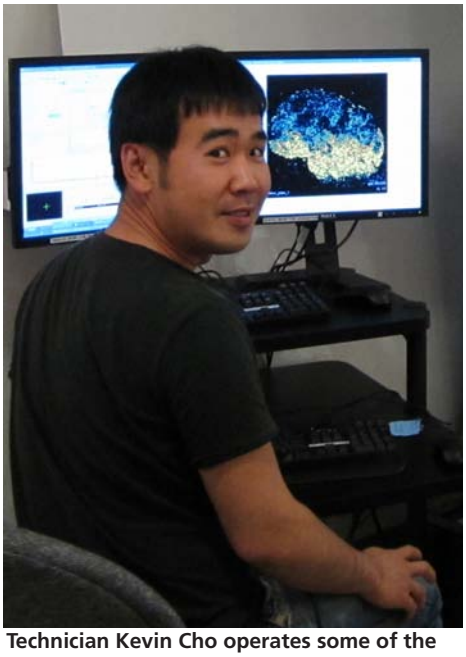
ORAL PRESENTATION AWARD

- Antonio L. Amelio of the Conkright lab, who spoke on "Emerging Roles for the CRTC Activators in Oncogenesis." The prize was a gift card to Christine Lee's Restaurant.

New Imaging Instrumentation and Technology Extends Mass Spec Center's Capabilities

The Scripps Center for Mass Spectrometry has recently extended its capabilities in metabolomic tissue imaging and protein identification. The new AB SCIEX 5800 TOF/TOF equipment is funded by grants from the National Institutes of Health and the Department of Energy. According to Gary Siuzdak, who heads the Scripps Center for Mass Spectrometry, the new equipment allows the center "to continue its efforts in one of the most interesting areas being developed in mass spectrometry—mass-based tissue imaging."

The imaging capabilities of the 5800 TOF/TOF add to a set of technologies developed at the Center for Mass Spectrometry called Nanostructure Initiator Mass Spectrometry (NIMS) (reported in Nature 1999, Nature 2007, Anal. Chem. 2009). Tissue slices are placed on a NIMS surface and laser-induced image acquisition is created



Technician Kevin Cho operates some of the new instrumentation in the Scripps Center for Mass Spectrometry.

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In Brief

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from the respective mass spectral data. Mass spec data acquisition is customizable to a user's experimental conditions, in which a whole tissue section can be imaged over the course of hours. This new technique has facilitated spatially resolved molecular profiling of analytes such as cholesterol in mouse brain cross-sections. These spatial differences can be used to track areas of altered metabolite concentration such as in specific disease models.

The TOF/TOF instrumentation also allows the center to offer a high-throughput alternative to nano-LC/MS/MS analysis. Pre-digested gel samples can be submitted using the center's online sample submission form. The samples can be submitted individually in separate vials or brought to the lab using an industry standard 96- or 384-sample plate format. The individual peptides can then be spotted onto MALDI target plates. Data-dependent MALDI-MS/MS is acquired in a high-throughput fashion, and peak lists are generated and searched on the center's proteomics search engines for protein identification. Along with existing instrumentation, the new MALDI-TOF/TOF allows the center to offer a full range of protein identification and characterization options. Peptide mass fingerprinting in mass spec-only mode can be used for very highly purified protein samples, MALDI-TOF/TOF with data-dependent MS/MS can be used for samples of medium complexity, and nano-LC-MS/MS is still available for samples of higher complexity.

Career Workshop Series: Spring Grantsmanship and Funding Fest 2010

The Society of Fellows and Office of Career and Postdoctoral Services is hosting events in the Spring Grantsmanship and Funding Fest on the La Jolla campus on Wednesday, May 12. The program features:

- Miles Fabian, program director at National Institute of General Medical Sciences, speaking on "Funding Opportunities from the NIH," from 10 to 11 AM.
- A panel discussion on "K99/R00" from 1:30 to 3 PM. In addition to Fabian, panelists include moderator Lars Bode, assistant professor of pediatrics at UCSD, and K99 recipients Cortney Henderson of UCSD, and Jeff Lee and Nicole Steinmetz of Scripps Research.

The events will be held in the in the Keck Amphitheater, Beckman Building. No RSVP is necessary and refreshments will be provided.

Scripps Research Volunteers Support Home Start

A cadre of volunteers from Scripps Research helped Home Start put on its Blue Ribbon Gala fundraiser on April 24, celebrating the organization's 38 years of service to San Diego and honoring National Child Abuse Prevention Month.

"I'd say about one third of all the volunteers at the event were from Scripps," said Marcia McRae, administrative manager for MIND and one of the evening's Scripps Research volunteers with Floriska Chizer and spouse Clyde Byas, Mishelle McClanahan-Shinn and spouse Tim Shinn, Joshua Pierce and spouse Joan Pierce, and Deirdra Tomasso (LeBlanc).

Volunteers helped with a variety of tasks at the gala, including checking in the approximately 250 guests, answering questions about the silent auction, acting as runners for the live auction, monitoring tables, selling raffle tickets, handing out prizes, and helping with final clean up.

The Scripps Research Institute publishes News&Views weekly throughout the academic year.

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