2011 DERC P&F Grants AVAILABLE

Pilot and Feasibility Projects in Endocrinology & Diabetes

Pilot & Feasibility Program, Director: Pinchas Cohen

As part of the mission of our UCSD/UCLA DERC grant, the Pilot and Feasibility grant program will support ~4-5 grantees at approximately $30,000-$40,000 per year for 2011.

Applications DUE: March 18th 2011 to Dr. Pinchas Cohen at: hassy@mednet.ucla.edu

As part of the UCSD/UCLA DERC grant, a mechanism to fund innovative new projects that will explore the feasibility of novel testable concepts and enhance the endocrine/diabetes research scope within the institutions is again available. A special emphasis on promoting promising junior faculty involved with diabetes research is key to the UCSD/UCLA P&F mission. It is expected that P&F studies will generate preliminary data that will be used by these investigators in diabetes/endocrinology-related R01 applications following their award.

P&F grant format

Failure to meet the requirements for grant format will lead to an administrative disqualification of the proposal. The P&F grant applications should include:
(a) Face page with the title of the grant, the name, email, academic title, department, and institution of the PI, the names of additional personnel and collaborators and a 200 word abstract.
(b) Biosketches for the PI and other key personnel.
(c) The scientific proposal (5-page limit).
(d) References.

The entire grant must be submitted as a single emailed pdf file < 2 megabite in size.

If the grant includes high-resolution images, these must be reduced to meet the size requirement. Failure to provide a single pdf file or a file that is too big will result in disqualification. No budget is required, but the scope of the work should be appropriate for 1-year project and the funds cannot be used for the PI salary.

Eligibility

All eligible investigators must have faculty appointments at UCLA, Salk, Cedars, or UCSD and be independent investigators. To be eligible for a P&F grant you need to be eligible to submit an R01 as a PI at the end of the grant period. A joint appointment at an affiliated institution is allowed. Investigators eligible for pilot and feasibility funding generally will be expected to fall into three categories:
(Category 1) New investigators without current or past non-mentored NIH research support as a principal investigator (current or past support from other sources being modest).
(Category 2) Established investigators with no previous work in diabetes who wish to apply their expertise to a problem in this area.
(Category 3) Established investigators in diabetes/endocrinology research who propose testing innovative ideas that represent clear departure from ongoing research interests.

Interactions with other DERC components

It is expected that junior faculty will be able to rely on the advice and support of senior DERC investigators and will have priority access to DERC Cores, including an opportunity to discuss their projects in depth with the core directors in order to receive maximum benefits from their services. Similarly, investigators with no previous experience in diabetes/endocrinology research will be expected to have a DERC collaborator. P&F grantees will be encouraged and expected to utilize DERC core resources. However, the award is given only to the designated PI and not to collaborators.

P&F Final report and presentation at the annual retreat

A report on each pilot and feasibility study conducted will be due at the end of the study period and an update will be requested yearly for four years after the completion of the award. These brief reports will contain professional career status at the time of the award and at the time of the report; an overview of the project including its significance and salient results; a list of resulting publications; and peer-reviewed subsequent funding in the same or related areas. Funded P&F investigators will be expected to attend the annual DERC retreats as well as a meeting of Regional P&F awardees, present the results of their work in the year immediately following their award and continue to attend the annual meetings for at least three years thereafter. Travel to these meetings can be charged to the individual P&F awards.

ALL PAPERS MUST CITE P30 DK063491

Notification procedure:

After approval of the funding decisions by the DERC executive committee, funded and unfunded investigators will be notified and, when appropriate, a brief summary of the reviews will be sent to them by email (not a detailed critique). Expected activation date is 5/1/2011.

NEW WEBSITE
http://DERC.ucsd.edu

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...To Meet Your Research Needs In Diabetes, Endocrinology, and Diabetes Complications...

Please remember to cite the DERC Grant in all papers that utilize DERC Cores or are supported by the Pilot and Feasibility Awards:

"Our research utilized Core (or Research) support from the UCSD/UCLA NIDDK Diabetes and Endocrinology Research Center P30 DK063491."
**Listserv for DERC Members**

Send announcements, communications, requests, etc., to your DERC colleagues:

**DERC-L@UCSD.EDU**

If you are receiving this newsletter directly, you are already subscribed. If you would like to subscribe, please email mellonadmin@ucsd.edu. This is a moderated listserv, so messages will be prescreened such that only relevant and important messages will reach you.

**NEW WEBSITE**

http://DERC.UCSD.EDU

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**Summer Medical Student Research Program in Diabetes and Endocrinology**

The Medical Student Research Program in Diabetes is sponsored by the National Institutes of Health through the NIDDK and allows medical students to conduct research under the direction of an established scientist in the areas of diabetes, hormone action, physiology, islet cell biology or obesity at an institution with one of 17 NIDDK-funded Diabetes and Endocrinology Research Centers (DERC) or Diabetes Research and Training Centers (DRTC) during the summer between the first and second year or second and third year of medical school. The UCSD/UCLA DERC center has supported 4 medical student trainees for summer research in each of the summers of 2009 and 2010: two students at UCLA/Cedars Sinai and two at UCSD/Salk each summer, for 8 students total. This program will be continued through the summer of 2011 and likely beyond. Students must be U.S. Citizens and/or permanent residents to participate in this Program. Students spend 2-3 months working on their research project at a DERC or DRTC of their choice and receive a weekly stipend from a T32 grant. All students present a poster in Nashville, TN at a meeting in early August. Commencement dates and conclusion for the program are reasonably flexible. More information can be found at http://medicalstudentdiabetesresearch.org/

**Application deadline for summer of 2011 was January 24, 2011.**

If you have interest in hosting one of these outstanding medical students for summer research project, please contact Dr. Pamela Mellon pmellon@ucsd.edu or Dr. Hassy Cohen hassy@mednet.ucla.edu

**AWARDS**

**Field Awarded $3.8 Million for New Path to Breast Cancer Therapy**

Seth Field, MD, PhD, Associate Professor in the Department of Medicine at UC San Diego, has been awarded a five-year, $3.86 million “Era of Hope Scholar Award” from the Department of Defense Breast Cancer Research Program. The award supports individuals who have high potential for innovation in breast cancer research early in their careers, researchers considered the “best and brightest” in their field through “extraordinary creativity, vision and productivity and potential for leadership in the breast cancer research community. Field was one of two scientists selected in the global competition. His project “A New Path to Breast Cancer Therapy” will investigate the mechanism by which a lipid-binding protein called GOLPH3 contributes to cancer.

**Peter Tontonoz, UCLA,** won the 2010 Jeffery M. Hoeg Award for Basic Science and Clinical Research from the American Heart Association.

**Mark Goodarzi, Cedars-Sinai,** won the Endocrine Society Richard E. Weitzman Memorial Award, June 2010.

**Pinchas Cohen, UCLA,** In the beginning of 2010, Dr. Cohen received the NIH-Director Transformative R01 Award.
DERC Mouse Phenotyping Core

CORE Directors: Rajendra Tangirala, Ph.D., Pinchas Cohen, M.D., Andrea Hevener, Ph.D., David Hwang, Ph.D.

The goal of the Mouse Phenotyping Core is to offer expertise to DERC investigators conducting studies of mouse physiology relevant to Endocrinology and Diabetes.

Core Services:

General Physiological Services: Experimental Design Consultation; Drug Delivery Training, development and Dissemination of New Strains, Tissue Sample Collection and Morphological and Basic Histological Analyses.

Cardiovascular and Renal Physiology: Blood Pressure; Quantification of Cardiac Fibrosis; on en face atherosclerotic lesion analyses; Aortic Root atherosclerotic lesion analysis; Urine Collection/Analyses; Kidney Function Tests.

In Vivo Metabolism: Glucose tolerance tests, Insulin tolerance tests, Euglycemic clamps.

Novel Assay Development: Consultations, antigen and antibody generation, RIA and ELISA construction, validation and creation of normative data. Existing novel assay services are also provided including growth factors and mitochondrial peptides.

Components of the core highlighted in this newsletter:

1. Mouse In Vivo Metabolism

The mouse metabolic phenotyping core offers numerous services designed to assist in characterizing genetically engineered rodents. The core offers strong capabilities in assessing alterations in whole body, tissue, and primary cell metabolism and insulin action arising from genetic or dietary manipulation. Glucose intolerance and insulin resistance are defining features of the metabolic syndrome and central contributors in the pathogenesis of type 2 diabetes and atherosclerosis. The euglycemic-hyperinsulinemic clamp is the gold standard method for quantifying insulin sensitivity in humans and rodents, and the mouse phenotyping core can perform this technique, fee for service. Additionally, the core can provide comprehensive instruction in rodent vessel catheterization, blood acquisition, and approaches to radio-tracer metabolism as part of an academically-led preclinical assays to assess in vivo metabolism and insulin action. Consultation to optimize experimental design for assessment of unique rodent models exhibiting complex phenotypes can also be provided.

2. Assay Development

As genomic and proteomic methodologies are continuing to identify new markers of disease activity and responsiveness to treatments, the translation of this information to emerging clinical care is hampered by the delay of the development of appropriate assays for such novel serum markers. While a handful of newly discovered molecules are identified by the diagnostics industry and represent optimization-personalization tools for diseases such as diabetes, we are discovering and identifying scores more molecules for which the detection methodologies are cumbersome and not applicable for translational development and clinical studies. Clearly the ability to “translate” a potential marker to clinical testing as part of an academically-led preclinical animal study or a clinical research study requires such assays that are sadly often unavailable. The DERC immunoassay development lab creates novel assays to address translational needs of our research communities. Our staff has unique expertise (and previous diagnostic industry experience) in the art and science of immunoassay development against novel molecules. We help DERC investigators to rapidly develop novel immunoassays to assist investigators with planning immunoassay needs, budgeting to identify the most cost-effective means of obtaining comprehensive, accurate data for each project. We identify and obtain pre-existing kits, reagents and other materials required for each assay. In the case of new or esoteric assays, the immunoassay core lab will develop or contract the development of required new antibodies and other reagents. The immunoassay core is responsible for validating each immunoassay method prior to use in a research project. Validation will include determination of in-house performance characteristics (inter and intra assay CVs, sensitivity, specificity, linearity, etc.) and assay adjustments to improve specific performance (matrix and detection reagent testing, solid/liquid-phase conversions if required).

CONTACT INFORMATION

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RECENT MAJOR FINDINGS BY OUR MEMBERSHIP

DERC faculty members at UCSD/Salk and UCLA/Cedars represent a large, highly productive and diverse group of scientists, four projects highlighted here represent different areas of scientific endeavor, which reflect emerging issues in the overall fields.

The first advance is a paper from Ron Evans’ laboratory, which represented a collaborative effort with Dr. Rajendra Tangirala who Co-Directs the DERC Mouse Phenotyping Core at UCLA. This paper showed that the genetic repressor Bcl-6 opposes nearly 25% of TLR4+ triggered transcriptional responses and that, in its absence, a broad array of inflammatory genes are hyper-activated by LPS stimulation. Furthermore, they identified Bcl-6 itself as a positively regulated target of TLR signaling, suggesting that it may be part of the normal cycle by which acute inflammatory responses are limited. To explore Bcl-6’s function mechanistically, these investigators performed extensive ChIP-seq of Bcl-6 in quiescent and LPS-stimulated macrophages. The results revealed that Bcl-6 controls a promoter-distal cistrome and largely occurs at enhancers marked with Pu.1 and p300. Remarkably, sequencing analysis suggested thousands of NF-kB motifs in the vicinity of Bcl-6, and further ChIP-sequencing of the NF-kB activator subunit p65 identified a dramatic co-localization between Bcl-6 and NF-kB to within a nucleosome at thousands of binding sites, where they coordinately control epigenetic modifications of the local chromatin.

Although known for its oncogenic role in B-cell non-Hodgkin’s lymphomas, in which it is aberrantly expressed, these studies now define Bcl-6 as critical for the maintenance of macrophage quiescence and termination of acute inflammatory responses. This paper provided the first description not only of the Bcl-6 cistrome but also that of NF-kB. In doing so, they further identified a unique relationship in which Bcl-6 uses proximate binding-based antagonism of NF-kB to control a sub-set of the TLR-NF-kB gene network. Overall, these studies defined a new molecular architecture for controlling inflammation and identify Bcl-6 as a key genomic regulator underlying the macrophage cycle between quiescence and activation".


The second paper comes from Dr. Peter Tontonoz’s laboratory at UCLA. This paper presents two major discoveries. Firstly, the authors have identified TLE3 as the first regulated PPARδ co-activator involved in adipocyte differentiation. Although deletion of several other transcriptional proteins has been shown to impair adipogenesis, there is little evidence that any of these proteins are actually components of the developmental switch. Rather, they are common basal factors required for the action of many transcription factors, and their expression does not change during differentiation. By contrast this work shows that TLE3 is highly regulated during differentiation and is itself a target for PPARδ regulation. TLE3 selectively coactivates PPARδ and acts synergistically with PPARδ to drive adipogenesis. Thus, TLE3 is a key component of a feed-forward regulatory mechanism in adipocyte development.

The second major contribution of this paper is to solve longstanding mysteries regarding actions of the Wnt pathway in preadipocytes: how does the Wnt pathway inhibit adipogenesis and how is Wnt signaling shut off during differentiation? This group found that the mechanism of Wnt repression involves direct binding of β-catenin/TCF4 complexes to adipogenic promoters. Moreover, recruitment of TLE3 to these promoters inhibits β-catenin interaction with TCF4, thereby, providing a mechanism for relief of Wnt-mediated repression.

The dual action of TLE3 on adipocyte promoters provides an elegant mechanism for transcriptional integration of the major positive (PPARδ) and negative (Wnt) signaling pathways controlling adipocyte development.


During this past year, Dr. Olefsky’s laboratory published a key paper exploring the role of inflammatory and anti-inflammatory signals in obesity and insulin resistance. This work showed that omega 3 fatty acids (fish oils) exert potent anti-inflammatory effects in macrophages, and then went on to identify the molecular mechanisms. These workers found that a lipid sensing GPCR, termed GPR120, is the receptor/sensor for omega 3 fatty acids, and that activation of this receptor mediates robust and broad anti-inflammatory signals, capable of inhibiting Tlr4, Tlr2, and TNFα signaling. This worked through a β arrestin-2 dependent mechanism in which omega 3 fatty acid stimulation of GPR120 causes β arrestin-2 to associate with GPR120, which then internalizes. Following internalization, β arrestin-2 dissociates from the receptor complex and is now capable of...
binding to TAB1 (which is the major activator of TAK1). By binding to TAB1, β-arrestin effectively removes TAB1 from its TAK1 partner, inhibiting TAK1. Since TAK1 is the proximal kinase in both the IKKβ/NFκB, and JNK/AP1 pathway, this abruptly shuts down proinflammatory signaling. They then went on to demonstrate the in vivo relevancy of these findings by studies in GPR120 knockout animals. In this work, they showed that GPR120 KO mice were more inflamed and insulin resistant than wild type littermates. They also found that omega 3 fatty acid dietary supplementation of wild type animals on high fat diets caused a marked insulin sensitizing effect, equal to that of Rosiglitazone. In contrast, omega 3 fatty acid supplementation was without effect on insulin sensitivity in the GPR120 KO mice. Taken together, these studies demonstrate that GPR120 is the relevant receptor/sensor for omega 3 fatty acids with respect to their anti-inflammatory and insulin sensitizing properties.


A highlight of the translational research generated by DERC faculty is a collaborative work on the CRTC3 gene. Mark Montminy from the Salk Institute has been investigating CRTC3 for its role in obesity and metabolism. When he studied CRTC3+/− mice he found they were protected from diet-induced obesity and insulin resistance. He then characterized a common human variant, S72N, and found that the mutant allele had increased activity. He thus hypothesized that it would be associated with increased adiposity in humans. This prompted him to contact Jerome Rotter and Mark Goodarzi of the Common Disease Genetics research team at Cedars-Sinai. They genotyped the S72N variant in the MACAD (Mexican-American Coronary Artery Disease) cohort. In MACAD, this variant was associated with increased weight, increased BMI, and increased hip circumference. They then found that a perfect proxy for this variant was associated with adiposity traits in Mexican Americans from the MESA (Multi-Ethnic Study of Atherosclerosis) study. Finally, they also accessed data from two large consortia (each comprising >30,000 subjects) of non-Hispanic whites, CHARGE and GIANT, both of which had conducted genome-wide association studies of BMI. In contrast to the results in Mexican Americans, the S72N variant was not associated with BMI in these large cohorts, suggesting that S72N plays a specific role in Mexican Americans, a group with a particularly high rate of obesity and diabetes but not in individuals of European decent. The human genetic association results were added to the CRTC3 manuscript that Dr. Montminy had prepared, culminating in a publication in Nature. This example illustrates how the DERC was able to bring together mouse research with human genetic epidemiologic studies, resulting in the identification of a novel factor for human obesity.


Diabetes Center Annual Retreat

On December 13th 2010 the UCSD/UCLA Diabetes Center held its Annual Retreat at the Covel Commons Conference Center at UCLA. The event drew over seventy-five members from DERC institutions. After an introduction by Professor Jerry Olefsky, the DERC director, the keynote speaker, professor Peter Tontonoz of the HHMI at UCLA led the day with a lecture reviewing the control of cholesterol metabolism by nuclear receptors and the role of his newly described molecule, IDOL, which has a central role in these processes. Dr. Pinchas Cohen, a UCLA professor and associate director of the DERC spoke about the pilot and feasibility awards and compared our center to practices around the country. Dr. Dayoung Oh, the Center’s inaugural Junior Faculty Developmental Award winner, spoke about the work described in her recent Cell paper together with Dr. Olefsky, entitled: GPR120 Is an Omega-3 Fatty Acid Receptor Mediating Potent Anti-inflammatory and Insulin-Sensitizing Effects. The event featured several talks from outstanding former pilot and feasibility grant awardees and the final lecture was by Professor Jake Lusis on systems genetics approach to complex cardiovascular and metabolic traits. The event concluded with a wine and cheese reception coupled with viewing of twenty exceptional posters from young center investigators including recent feasibility grant awardees.

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SALK and CEDARS

