DERC UC San Diego ■ UC Los Angeles ■ Cedars-Sinai ■ Salk Institute

APRIL 30, 2009

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

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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."

NEW DERC WEBSITE LAUNCHED

The UCSD/UCLA DERC has a new website at

http://DERC.UCSD.EDU

Please bookmark the site to find information about the UCSD/UCLA/Salk/Cedars-Sinai DERC, including web pages for each Core, information about the Research Programs, the Pilot and Feasibility grants, links to seminar announcements, meeting announcements, a very useful membership directory, and other important services and activities of YOUR Diabetes and Endocrinology Research Center.

2009 DERC P&F Grants Awarded

Pilot and Feasibility Projects in Endocrinology and Diabetes

Pilot & Feasibility Program, Director: Pinchas Cohen

As part of the recently renewed 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 available each year. The Pilot and Feasibility grant program supports 4-5 grantees at approximately $30,000-$40,000 per year. 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 in the years following their award.

THE UCSD/UCLA DERC is Proud to Announce the 2009 P&F AWARDEES:

Mina Desai, Associate Professor, Department of Obstetrics and Gynecology, Geffen School of Medicine at UCLA and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
Development of Insulin Resistance and Adiposity via PPAR Dysregulation

Anthony Heany, Associate Professor, Associate Professor, David Geffen School of Medicine at UCLA, Co-Director, Pituitary & Neuroendocrine Tumor Program, Departments of Medicine & Neurosurgery, Cedars-Sinai
Role of GLUT5 in Pathogenesis of Metabolic Syndrome

Karen Herbst, Assistant Professor, Department of Medicine, University of California, San Diego
Blockade of Receptor Cleavage in Diabetes Mellitus with an MMP Inhibitor

Andrea Hevener, Assistant Professor, Endocrinology, Diabetes, and Hypertension, Department of Medicine, David Geffen School of Medicine at UCLA
The Impact of Myeloid-Specific ERα Expression on Inflammation, Insulin Action and Adiposity

Congratulations to Marc Montminy, DERC member, on his 2009 Election to the National Academy of Sciences

MARC R. MONTMINY, Professor, Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, Calif.

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

Contact information for DERC Cores and Programs:

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Transgenic and Knockout Mouse CORE:
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MEETING ANNOUNCEMENT

Clinical Investigation Institute/Nature Medicine
Bench to Bedside: Metabolism
October 8-10, 2009

http://www.nature.com/natureconferences/ctri2009/index.html

Special Pricing for DERC P & F Faculty and UC faculty
On or Before 9/8/09 Only $150
On or After 9/9/09 $195

As part of our Enrichment activities, the DERC will help host a scientific meeting co-sponsored by Nature Medicine and UCSD next Fall in La Jolla. This Nature Medicine meeting is focused on Diabetes and Metabolism and begins the evening of October 8th, ending at Noon at Saturday October 10th. On Saturday afternoon, (October 10th), the DERC will put on its own scientific presentations, based on the work of P&F recipients. The program for this meeting is outstanding and all DERC members, including all P&F recipients, are encouraged to attend the full meeting starting Thursday evening. The Western region DERCs (Baylor, UCSD/UCLA, University of Colorado, and University of Washington) have organized into a subgroup and through the Regional DERC Director's committee, we have already arranged for P&F recipients from the other Western Centers to attend this meeting.

This activity has been approved for AMA PRA Category 1 Credit

For more information visit http://cme.ucsd.edu/b2b2009

Speakers Include:

Michael Brown (U Texas)
Helen Hobbs (U Texas)
Gokhan Hotamisligil (Harvard)
Peter Libby (Harvard)
Michael Karin (UCSD)
Steve Shoelson (Joslin Diabetes Center)
Paresh Dandona (SUNY Buffalo)
Gerry Shulman (Yale)
Ira Goldberg (Columbia)
Phil Scherer (U Texas)
Barbara Kahn (Harvard)
Chris Newgard (Duke)
Tony Lam (Toronto)
Zofia Zukowska (Georgetown)
Daniel Drucker (Toronto)
David Cummings (U Wash)
Francesco Rubino (Cornell Medical Center-NYC)

Hilton La Jolla Torrey Pines
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http://www1.hilton.com/en_US/hi/hotel/SANTPHH-Hilton-La-Jolla-Torrey-Pines-California/index.do

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The Transgenic and Knock-Out Mouse CORE

CORE Director: Pamela L. Mellon, Ph.D.

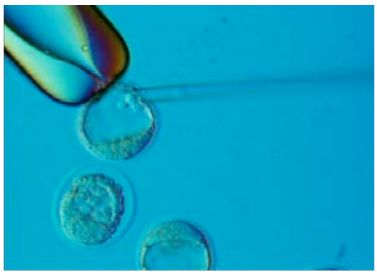
Professor of Reproductive Medicine and Neurosciences

The DERC Transgenic and Knock-out Core is a state-of-the-art facility that has an outstanding track record in the production of genetically altered subjects. Transgenic subjects carrying new or novel genes are created by microinjection of DNA into the pronuclei of fertilized eggs. Knock-out mice lacking specific genes of interest are created by homologous recombination in embryonic stem cells followed by injection into blastocysts to create chimeric subjects. Highly experienced personnel produce transgenic and knock-out mice for UCSD investigators at very reasonable cost and with very short lead times. The Core provides embryonic stem cell recombination, knockout mice, transgenic mice (both standard and BAC transgenics), embryo freezing, and pathogen-free embryonic rederivation to the DERC community at discounted rates. This UCSD-based Core Facility has been in operation since 1992.

SERVICES

Pronuclear Injection for the creation of transgenic mice
Gene Targeting in embryonic stem (ES) cells
Blastocyst injection for the creation of chimeric mice from ES cells
Chromosome counting for ES cells
Embryo rederivation for the creation of pathogen-free mice
Ovary transplants
Embryo cryopreservation

Success rates: The key measures of success of a transgenic and knockout mouse production facility are the measures of quality and quantity of mice produced. We have a very high success rate for the production of transgenic and knock-out mice which approaches 100% success. Major jobs include: 1) blastocyst injection for the creation of chimeric knock-out mice, 2) microinjection of embryos for the creation of transgenic mice, 3) production of homologously recombined embryonic stem cells for the production of knock-out mice and 4) embryo cryopreservation. In the past year we have performed 63 transgenic jobs. We have an average of 14.7% integration for approximately 8 positive founder animals per job and performed 35 pronuclear injection jobs in 2008. We also inject BACs to make transgenic mice carrying BAC DNA. Twenty-six transgenic jobs were BAC injections with a 8.9% integration frequency for an average of 5.4 positive founders per job. We have performed 54 embryonic stem cell targeting jobs resulting in an average recombination efficiency of 2.85% for an average of 56. homologously recombined clones per job. We have performed 29 blast injection jobs with an average of 12.3 pups per job with an average of 5.9 chimeric animals (~50%) resulting for each job. All of these (for which we have reports from the scientists) have gone germline. Our embryo freezing service is also very successful. In addition to these three primary services, the core continues to provide chromosome counting, embryo rederivation, and ovary transplantation services to an ever-increasing number of investigator/subscribers throughout the DERC community.



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Krauss RM, Mangravite LM, Smith JD, Medina MW, Wang D, Guo X, Rieder MJ, Simon JA, Hulley SB, Waters D, Saad M, Williams PT, Taylor KD, Yang H, Nickerson DA,Rotter JI. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. Circulation. 2008 117:1537-44.

Medina, M.W., Gao, F., Ruan, W., Rotter, J.I., Krauss, R.M.: Alternative splicing of HMGCR is associated with plasma LDL cholesterol response to simvastatin. Circulation, 118355-62

Solinas, G., Vilcu, C., Neels, J. G., Bandyopadhyay, G. K., Luo, J. L., Naugler, W., Grivennikov, S., Wynshaw-Boris, A., Scadeng, M., Olefsky, J. M., and Karin, M. (2007). JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. Cell Metab 6, 386-97.

Narkar, V.A., M. Downes, T.R. Yu, E. Embler, Y-X. Wang, E. Banayo, M.M. Milhaylova, M.C. Nelson, Y Zou, H. Juguilon, H. Kang, R.J. Shaw and R.M. Evans. 2008. AMPK and PPARδ Agonists are Exercise Mimetics. Cell 134:405-15

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, three projects highlighted here represent different areas of scientific endeavor, which reflect emerging issues in the overall fields.

POLYMORPHISMS THAT CAN PREDICT STATIN RESPONSIVENESS Two papers from Jerry Rotter and Ron Krause address the pharmacogenetics of statin responsiveness in hypercholesterolemic patients. As is well known, statins have been used to lower LDL cholesterol and reduce risk for cardiovascular disease for many years and have been extraordinarily successful. They are among the most highly prescribed medicines in the world and their entry into the clinic has been responsible for saving countless lives. HMG CoA is the target of statin therapy and these investigators hypothesized that variations in the HMG CoA reductase gene might be responsible for the well-known variation in statin therapy outcomes across populations. By mapping the gene for polymorphisms in a group of patients treated with statins, specific haplotypes were associated with greater statin responsiveness and these haplotype-related effects were most pronounced in blacks. Some of these polymorphisms were associated with alternate splicing of the HMG CoA reductase mRNA and particular spliced forms were associated with poor statin-induced hypocholesterolemic responses. These are powerful studies since they show genetic influences on drug responsiveness in a situation involving one of the most commonly prescribed and beneficial therapies that exist.

OBESITY ONLY CAUSES INSLUIN RESISTANCE IF ACCOMPANIED BY INFLAMMATION In a collaboration between Jerrold Olefsky and Michael Karin's labs at UCSD, the role of macrophage-mediated inflammation in causing insulin resistance was examined. JNK/AP1 comprises a major intracellular macrophage inflammatory pathway, and the goal was to study the role of macrophage JNK1 depletion on tissue inflammation and insulin sensitivity (3). These studies were performed by conducting BMTs from whole body JNK1 KOs into irradiated wild type C57BL6 mice, followed by 8 weeks for bone marrow reconstitution and 12 weeks on HFD. With this approach, the chimeric animals display KO of JNK1 in macrophages (as well as in all bone marrow derived myeloid cells) but have normal JNK1 expression in all non-myeloid tissue compartments (e.g. muscle, adipose tissue, and liver). Although all myeloid cell types show JNK1 depletion, they hypothesize it is most likely the macrophage which is responsible for the phenotypes observed. The data showed that deletion of macrophage JNK1 led to improved glucose tolerance, a reduction in hyperinsulinemia and protection from HFD-induced systemic insulin resistance in muscle, liver, and adipose tissue. Importantly, on the HFD, the chimeric macrophage JNK1 KO animals developed the expected full degree of obesity. Therefore, in this animal model, obesity dissociates from insulin resistance demonstrating that, without the macrophage-driven inflammatory component, obesity per se, does not cause insulin resistance. On the HFD, the chimeric JNK1 KO animals also developed the full degree of hepatic steatosis, but did not display hepatic insulin resistance. The bone marrow-derived macrophage in liver is the Kupffer cell, and, in these chimeric mice, the Kupffer cells were null for JNK1, and hepatic markers of inflammation were also markedly reduced. Thus, in the absence of the inflammatory component, hepatic insulin resistance does not develop, despite the expected diet-induced increase in hepatic lipid accumulation.

THE EXERCISE PILL Ron Evan's lab at the Salk Institute treated wild type and PPARδ knock-out mice with PPARδ ligands, exercise training, and the AMP kinase activator, ACAR, or various combinations. The PPARδ agonist led to a characteristic gene profile related to oxidative metabolism. Importantly, they found that PPARδ agonist treatment did not change exercise endurance. However, when PPAR agonists were given to exercise trained mice, they found enhanced muscle remodeling (increased proportion of Type 1 fibers, increased mitochondrial biogenesis, and a gene expression pattern typical of exercise training). Importantly, the dual treatment led to a synergistic response to increased running endurance. Thus, exercise training sensitized these animals to PPARγ agonism by exposing cryptic PPARγ target gene sites. Since exercise training stimulates AMP kinase, they combined PPARδ treatment with the AMP kinase activator, ACAR, and found synergistic effects between the two, similar to those seen in exercise-trained animals treated with the PPARγ agonist. Thus, AMP kinase activation increases the transcriptional activity of PPARγ agonist leading to the synergistic effects on gene expression, muscle remodeling, and exercise endurance. Stimulation of AMP kinase can induce exercise related genes and enhance running endurance in sedentary mice and the AMP kinase in PPARδ pathways can be synergistically targeted to enhance training adaptation and increase endurance, even in the absence of exercise. These studies hold the potential to use pharmacologic means to harvest the health benefits of exercise without the need for extensive and strenuous physical activity. This could be of great benefit to patients whose physical activity is restricted by health related issues.