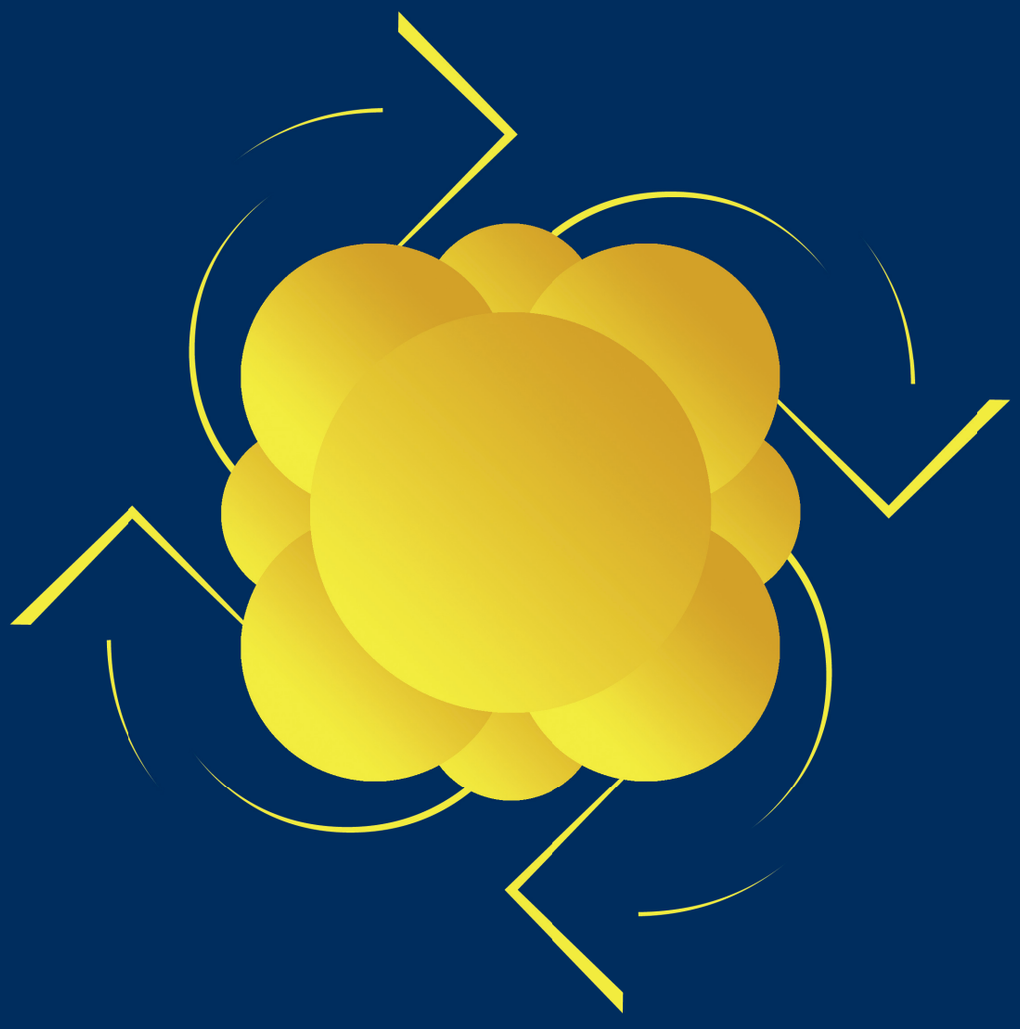
Lipodystrophy in 2014

Leptin and Beyond



University of Michigan · October 17-19, 2014

Sponsored by AstraZeneca, ISIS Pharmaceuticals and the Michigan Metabolomics and Obesity Center (MMOC)

North Campus Research Complex
2800 Plymouth Road
Ann Arbor, Michigan

http://mmoc.med.umich.edu/lipodystrophy

SYMPOSIUM ANNOUNCEMENT
AUGUST 29, 2014

This year marks a milestone in the history of Lipodystrophy Syndromes as there is now an approved form of therapy for the most severe forms of the disease. In addition, 2014 marks the 20th year after the discovery of leptin. The last 20 years have been exciting for both fields during which the research paths have been intertwined repeatedly.

We believe that this is a great time to convene the community of clinicians treating patients with lipodystrophy and patients and families afflicted with these disorders, together with researchers working on adipocyte biology, leptin action and novel metabolic therapeutics development. The purpose of this meeting is to come up with a bold research agenda for the next 10 years, with ambitious goals of discovering new disease mechanisms and developing novel treatments to cover more ground for the unmet medical need. In order to achieve this, we are making sure that we hear the perspectives of all stakeholders. Therefore, we have reached out to a diverse group of participants to get together from October 17th through 19th, 2014 for meeting we call **"Lipodystrophy in 2014: Leptin and Beyond."**

We hope to capture participation from the entire international community and plant the seeds to form an International Clinical Research Network dedicated to the Study of Lipodystrophy (SOLID).

This meeting is catalyzed by an educational grant from Astra Zeneca. ISIS Pharmaceuticals provided additional support. We are delighted that we can bring future funding perspectives from NIDDK and the Office of Rare Diseases. The symposium is also supported by the Michigan Nutrition Obesity Research Center (MNORC) and will serve as its 2014 Annual Symposium.

The scientific program is being chaired by Dr. Phillip Gorden (NIDDK) and Dr. Abhimanyu Garg (UTSW) who have been pioneers in this field for the past 30 years. The meeting program features great scientists from around the world who have contributed to the field. The participation form such diverse geography makes this meeting quite unique. Another unique aspect is the broad participation from the patient community. We believe that the discussions will be fruitful for a collaborative future in the field that will continue to develop novel treatments for the lipodystrophy syndromes and shed light on regulation of adiposity and metabolism in humans.

We look forward to welcoming everyone in Ann Arbor, Michigan this fall.

On Behalf of Scientific Organization Committee,

Elif A. Oral, M.D.
Associate Professor of Internal Medicine
Metabolism, Endocrinology and Diabetes Division
Brehm Center for Diabetes
Department of Internal Medicine
University of Michigan

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FROM OUR CHAIR

The lipodystrophies are a heterogeneous group of conditions that were initially described as clinical syndromes. In the current era of molecular genetic technologies, our colleagues at this meeting have been able to refine these clinical syndromes into specific genetic conditions. In addition, acquired forms of lipodystrophy have been described. Together, these various syndromes are associated with severe metabolic dysfunction which does not respond well to conventional treatment.

A seminal scientific event occurred 20 years ago with the discovery of leptin by Jeff Friedman. This discovery provided the mechanism by which the body senses energy balance. The translation of leptin into a clinical therapy for lipodystrophy depended on the understanding that leptin deficiency is the major mediator of metabolic dysfunction in these patients. The conceptual basis that leptin replacement would correct the metabolic abnormalities of lipodystrophy came from animal models in the laboratories of Brown and Goldstein, and the laboratory of Marc Reitman at the NIH. This led to the first clinical experiment at the NIH by Elif Oral which ultimately led to FDA approval of metreleptin for generalized forms of lipodystrophy; similar studies led to government approval in Japan.

Both the descriptive phase of the lipodystrophy and its treatment represent the finest example of international collaboration in the United States, Japan, and Europe, and one of the best examples of government and industry collaboration in the public interest.

Phillip Gorden, M.D.
Director Emeritus and Senior Investigator
National Institute of Diabetes and Digestive and Kidney Disease
National Institutes of Health

SCIENTIFIC ORGANIZATION COMMITTEE

Phillip Gorden, M.D.
NIDDK, NIH
Co-Chair

Abhimanyu Garg, M.D.
UT Southwestern Medical Center
Co-Chair

David Araújo-Vilar, M.D., Ph.D.
Universidad de Santiago

Rebecca J. Brown, M.D.
NIDDK, NIH

Charles F. Burant, M.D., Ph.D.
University of Michigan

Ormond A. MacDougald, Ph.D.
University of Michigan

Martin G. Myers, M.D., Ph.D.
University of Michigan

Elif A. Oral, M.D.
University of Michigan

David Savage, M.D.
University of Cambridge

Simeon Taylor, M.D., Ph.D.
University of Maryland

IN COLLABORATION WITH

Lipodystrophy United

Lipodystrophy Connect

SPONSORS

The National Institutes of Health and the University of Michigan wish to acknowledge the following sponsors for *Lipodystrophy in 2014: Leptin and Beyond*:

ACKNOWLEDGMENT

As Sir Archibald Garrod put it in the Annual Oration delivered before the Medical Society of London on May 21, 1928 (shared with me by my colleague, a distinguished rare disease researcher here at the University of Michigan, Dr. James Shayman) *"We may feel sure that, in the future as in the past, there will be many who will try to solve the problems of the commoner diseases, the control of which is of such vital interest to the community at large. Let us hope that there will always be some who will seek to guess the riddles and to learn the lessons of the rarer maladies."*

This meeting is put together by a group of scientists and physicians who have been mystified by a cluster of rare diseases called the lipodystrophy syndromes. Hopefully those who attend our meeting "Lipodystrophy in 2014: Leptin and Beyond" will see why we are so intrigued by these conditions and why we seek to understand the puzzles of these conditions!

This meeting could not have been possible without the countless hours put in by two very dedicated individuals: Priya Wiersba and Grace Wu. Priya coordinated all aspects of the meeting and Grace provided the experienced oversight and the Michigan Metabolomics and Obesity Center's infrastructure. I am truly grateful for their hard work and smiles. I also would like to thank the rest of the administrative staff at the Division of Metabolism Endocrinology and Diabetes (Liz Cole, Sonja Hughbanks, Annette Murphy and Lisa Gilbert) as they all shared in the volume of the phone calls and e-mails. Chandani Wiersba provided an extra set of hands whenever they were needed. Robin Wylie designed and created amazing graphics for the posters, booklet covers and the website which he also constructed and maintained. Amy Garber helped to put the word out in the community and guided us through videography. Susan Schaefgen and Teresa Maldonado from University Conference Services helped with registration and meeting logistics. Bill Vlisides from the City of Ann Arbor guided us to important city resources to enable the meeting. Phil Krall from North Campus Research Complex team helped to identify our meeting location. The Medical School Information Services is providing much needed technical support. It literally takes a whole village to have a scientific meeting!

I also would like to express my deep appreciation to the AstraZeneca Medical Affairs and Education teams whose belief in the concept of this meeting led to the successful funding of the meeting. If we have a successful scientific platform today, it is because of their trust in us and commitment to the treatment of patients with lipodystrophy. Isis Pharmaceuticals also provided further support to the meeting. All of the members of the Scientific Organization Committee worked diligently to ensure that we reached out to the players in the field. I am especially indebted to Drs. Alan Saltiel and Simeon Taylor who provided much needed scientific guidance. Dr. Chuck Burant provided the resources of the entire MMOC at our disposal and funding to allow patient travel. Of course, all of our distinguished speakers ignite the sparks needed to make this meeting a success.

We would like to thank Dr. Jeffrey Friedman whose discovery of leptin clearly left such a large mark on the field and led to the successful treatment of many of our patients.

Finally, I would like to thank all of our patients who have volunteered in the studies of lipodystrophy so willingly to enable the unlocking of some of the genetic mysteries and the development of the treatment programs at various centers for lipodystrophy: this meeting is put together with you and for you.

Elif A. Oral, M.D.
October 12, 2014
Ann Arbor, Michigan

Day One, Daytime Program: October 17, 2014
North Campus Research Complex
2800 Plymouth Road, Ann Arbor, MI 48105

12:00 pm – 1:30 pm **Registration and Networking**
Building 18

1:30 pm – 1:45 pm **Welcome**
Research Auditorium
Steve Groft, NCATS
Charles Burant, University of Michigan

1:45 pm – 2:20 pm **Overview of Lipodystrophy Syndromes**
Research Auditorium
Abhimanyu Garg, UT Southwestern

2:20 pm – 4:30 pm **Session One: Pathways in Disease Development**
Research Auditorium
Chair: Alan Saltiel, University of Michigan

2:20 - 3:00 *Pathways from Lipodystrophy to clinical disease*
Robert Semple, University of Cambridge, UK

3:00 - 3:30 *The unknown world of seipin*
Jocelyn Magre, Universite de Nantes, France

3:30 - 4:00 *Organising adipogenesis: Seipin as a molecular scaffold*
Justin Rochford, University of Abardeen, UK

4:00 - 4:30 *Nuclear lamins in health and disease*
Stephen Young, UCLA

4:30 pm – 4:45 pm **Break**
Atrium

4:45 pm – 5:45 pm **Late-Breaking Key Note Lecture**
Research Auditorium
Chair: Alan Saltiel, University of Michigan

New genes and pathways in regulation of adipogenesis, obesity and metabolic syndrome
Arya Mani, Yale University

5:45 pm – 6:45 pm **Poster Session and Welcome Reception**
Dining Hall

6:45 pm – 7:00 pm **Shuttles from NCRC to Sheraton Ann Arbor**

Day One, Evening Program: October 17, 2014
Sheraton Ann Arbor
3200 Boardwalk, Ann Arbor, MI 48108

7:30 pm – 9:30 pm **Dinner Symposium**
Grande Ballroom
Chair: Steven Groft, NCATS

Panel Discussion: The Advantages and Challenges of Forming a Clinical Research Network for Rare Diseases: Are We Up for It?

What does the network bring to the table?
Steven Groft, NCATS

European network and perspective
David Araújo-Vilar, Universidad de Santiago, Spain

Lipodystrophy Connect
Debbie Jae, PatientCrossroads

The charge
Elif A. Oral, University of Michigan

Day Two, Daytime Program: October 18, 2014
North Campus Research Complex
2800 Plymouth Road, Ann Arbor, MI 48105

7:00 am – 8:00 am **Registration and Networking**
Building 18

8:00 am – 10:00 am **Session One: Adipogenesis and Adipocytokines (Not Leptin)**
Research Auditorium
Chair: Carol Haft, NIDDK

8:00 - 8:30 *Transcriptional networks regulating browning of human adipocytes*
Susanne Mandrup, University of Southern Denmark

8:30 - 9:00 *Bone marrow adiposity and lipodystrophy*
Cliff Rosen, Tufts University

9:00 - 9:30 *Marrow adipose tissue: Metabolism and endocrine functions*
Ormond MacDougald, University of Michigan

9:30 - 10:00 *A subcutaneous adipose tissue-liver axis in the control of hepatic gluconeogenesis*
Shannon Reilly, University of Michigan

10:00 am – 10:15 am **Break**
Atrium

10:15 am – 11:40 am **Focus Lectures**
Research Auditorium
Chair: Carol Haft, NIDDK

10:15 - 11:00 *Inventing new medicines. FGF21 story*
Alexei Kharitonenkov, Indiana University, Bloomington

11:00 - 11:40 *Pathophysiological aspects of genetic and acquired lipodystrophy syndromes*
Jacqueline Capeau, UPMC INSERM, France

11:40 am – 12:30 pm **Lunch**
Dining Hall

12:30 pm – 2:00 pm **Session Two: Models of Disease**
Research Auditorium
Chair: Ormond MacDougald, University of Michigan

12:30 - 1:00 *Phenotyping the Agpat2 knock-out lipodystrophic mice: some new observations*
Anil Agarwal, UT Southwestern

1:00 - 1:30 *Mechanisms underlying sex differences in adiposity*
Karen Reue, UCLA

1:30 - 2:00	*Genome editing in pluripotent cells to generate human models of lipodystrophy* Chad Cowan, Harvard
2:00 pm – 4:00 pm	**Session Three: Clinical Challenges** *Research Auditorium* Chair: Abhimanyu Garg, UT Southwestern
2:00 - 2:30	*Reproductive challenges: a great model for PCO-S* Andrea Dunaif, Northwestern University
2:30 - 3:00	*Non-alcoholic steatohepatitis: Is there a benefit to study the rare?* Arun Sanyal, Virginia Commonwealth University
3:30 - 4:00	*NASH and obethicolic acid* Abhimanyu Garg, UT Southwestern
3:30 - 4:00	*Multisystemic lipodystrophy syndromes: when there is more than lipodystrophy* David Araújo-Vilar, Universidad de Santiago, Spain
4:00 pm – 4:15 pm	**Break** *Atrium*
4:15 pm – 5:45 pm	**Session Four: Treatment of Lipodystrophy Syndromes (All about Leptin)** *Research Auditorium* Chair: Phillip Gorden, NIDDK
4:15 - 4:55	*Overview of lipodystrophy treatment with metreleptin* Rebecca Brown, NIDDK
4:55 - 5:15	*Leptin therapy in lipodystrophy: UT Southwestern experience* Vinaya Simha, Mayo Clinic
5:15 - 5:45	*Translational research of leptin for lipodystrophy in Japan* Ken Ebihara, Jichi Medical University, Japan
5:45 pm – 6:45 pm	**Poster Session** *Dining Hall*
6:45 pm – 7:00 pm	**Shuttles from NCRC to Sheraton Ann Arbor**

Day Two, Evening Program: October 18, 2014
Sheraton Ann Arbor
3200 Boardwalk, Ann Arbor, MI 48108

7:30 pm – 9:30 pm **Dinner Symposium**
Grande Ballroom
Chair: Elif A. Oral, University of Michigan

Panel Discussion: All about Patients

A unique personal perspective on FPLD
Samantha Pulliam, Harvard

Discussion on patient priorities
Elaine Cochran, NIDDK

How to grow a voice for Lipodystrophy United
Andra Stratton, Lipodystrophy United

Open patient platform

Day Three, Daytime Program: October 19, 2014
North Campus Research Complex
2800 Plymouth Road, Ann Arbor, MI 48105

7:00 am – 7:30 am	**Registration and Networking** *Building 18*
7:30 am – 7:40 am	**Welcome and Goals for the Day** *Research Auditorium* Simeon Taylor, University of Maryland
7:40 am – 8:10 am	**Session One: Some more on Leptin** *Research Auditorium* Chair: Simeon Taylor, University of Maryland
7:40 - 8:10	*Novel molecules on the leptin pathway* Martin Myers, University of Michigan
8:10 am – 8:40 am	**Short Talks** *Research Auditorium* Chair: Simeon Taylor, University of Maryland
8:10 - 8:25	*One year metreleptin improves insulin secretion in patients with lipodystrophy syndromes* Camille Valtier et al, INSERM, France
8:25 - 8:40	*Lessons from treatment of children with congenital leptin deficiency with metreleptin* Martin Wabitsch, Universitätsklinikum Ulm, Germany
8:40 am – 8:55 am	**Break** *Atrium*
8:55 am – 10:25 am	**Session Two: Unmet Medical Need Beyond Leptin** *Research Auditorium* Chair: Simeon Taylor, University of Maryland
8:55 - 9:25	*Antisense drugs: apoC3 inhibition, a novel treatment for dyslipidemia* Andres Digenio, ISIS Pharmaceuticals
9:25 - 9:55	*Antisense drugs: ANGPTL3, DGAT2 and PTP-1B inhibition, potential new metabolic therapies* Teresa Brandt, Vickie Alexander, Andres Digenio, ISIS Pharmaceuticals
9:55 - 10:25	*Designer combination hormonal therapies* Matthias Tschöp, IDO, Germany
10:25 am – 10:30 am	**Break** *Atrium*

10:30 am – 11:30 am **Short Talks**

Research Auditorium

Chairs: Jennifer Wyckoff and Tae-Hwa Chun, University of Michigan

10:30 - 10:45 *Hypothalamic tumors mimicking acquired generalized lipodystrophy*
Nivedita Patni et al, UT Southwestern

10:45 - 11:00 *Prevalence and mechanisms of polycystic ovarian syndrome in familial partial lipodystrophy, Dunnigan variety*
Chandna Vasandani et al, UT Southwestern

11:00 - 11:15 *The brown fat enriched secreted factor Nrg-4 preserves metabolic homeostasis through attenuating hepatic lipogenesis*
Guo-Xiao Wang, University of Michigan

11:15 - 11:30 *Forced PPARg1 expression confers adipogenic competence to BSCL type 1 and type 2 human dermal fibroblasts*
Rosa M. Moro et al, CIEMAT Centre for biomedical research on rare diseases, Spain

11:30 am – 12:10 pm **Focus Lecture**

Research Auditorium

Chair: James Shayman, University of Michigan

Lessons from an accomplished warrior: NEPTUNE as a case study for ORD CRN
Matthias Kretzler, University of Michigan

12:10 pm – 12:30 pm **Agenda for the Year & Concluding Remarks**

Research Auditorium

Phillip Gorden, NIDDK

BIOGRAPHIES

Anil K. Agarwal, Ph.D.
Professor
UT Southwestern

Dr. Agarwal earned his doctoral degree while working at Central Drug Research Institute, Lucknow, India. He received further training at the Population Council, The Rockefeller University, New York, and Cornell Medical College (now Weill Cornell Medical College), New York. Since then, Dr. Agarwal has been studying the molecular genetics and biology of rare diseases. He, along with his colleagues, discovered that *11β-HSD2* was the cause of Apparent Mineralocorticoid Excess (AME), characterized by hypertension usually diagnosed in early childhood. He went on to discover several genetic loci found in patients affected with lipodystrophy, a disease characterized by a loss of adipose tissue. Chief among these are *AGPAT2* (congenital generalized lipodystrophy), *PPARγ* (partial lipodystrophy), *Zmpste24* (Mandibulo-acral dysplasia), and *PSMB8* (JMP; an autoinflammatory syndrome characterized by joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy). Dr. Agarwal also developed an animal model of lipodystrophy to study, at the molecular level, the pathophysiology of lipodystrophy and its associated clinical phenotype in an animal model (hepatic steatosis and diabetes) and, more specifically, the molecular mechanism of loss of adipose tissue.

Vickie Alexander, Ph.D.
Director, Clinical Development
ISIS Pharmaceuticals, Inc.

Vickie Alexander earned her Ph.D. in Pharmacology and Toxicology at the University of California, Irvine and conducted her post-doctoral research at the Salk Institute in the area of mammalian growth and development. She continued her research as an Assistant Professor at the University of California, San Diego School of Medicine with a focus on neuroendocrine functions and later joined the pharmaceutical industry to direct hematology and oncology clinical research trials. Dr. Alexander currently works in cardiovascular and metabolic therapeutic areas as Director, Clinical Development at Isis Pharmaceuticals.

David Araújo-Vilar, M.D., Ph.D.
Professor of Medicine
University of Santiago de Compostela (Spain)

David Araújo-Vilar is a Professor of Medicine (Medical Genetics and Endocrinology) at the School of Medicine of the University of Santiago de Compostela (USC), Spain. He is a Clinical Endocrinologist at the University Clinical Hospital of Santiago de Compostela (CHUS). Dr. Araújo-Vilar is also a Responsible Physician of the Spanish Reference Centre for Rare Lipodystrophic Syndromes (CHUS). He is the Team Leader of the UETeM-Molecular Pathology Group at the Institute of Biomedical Research (CIMUS) of the USC. David Araújo-Vilar is the coordinator of the Executive Board of the European Consortium of Lipodystrophies. He is also a member of the Scientific Adviser Committee of the Spanish Federation of Rare Diseases.

Rebecca J. Brown, M.D.
Assistant Clinical Investigator
NIDDK, NIH

Dr. Rebecca Brown received her B.A. degree from Rice University, and her M.D. from Mayo Medical School, followed by pediatric residency training at Rainbow Babies and Children's Hospital. In 2005, she came to the National Institutes of Health (NIH) for fellowship training in pediatric endocrinology, and she has remained in the NIH intramural research program since that time. Her current research interests focus on pathophysiology and clinical therapeutics for rare disorders of extreme insulin resistance, including lipodystrophy, mutations of the insulin receptor, and autoimmune conditions affecting insulin signaling. She is particularly interested in understanding the mechanisms of action of the adipokine, leptin, in improving metabolic disease in lipodystrophy.

Charles Burant, M.D., Ph.D.
Dr. Robert C and Veronica Atkins Professor of Metabolism,
Professor of Internal Medicine
University of Michigan

Charles Burant is Professor of Internal Medicine, Section of Metabolism, Endocrinology, and Diabetes. He holds the Robert C. and Veronica Atkins Professor of Metabolism endowed chair. His clinical interests are in the care of patients with obesity, type 2 diabetes, and related conditions. Burant's research program integrates molecular phenotyping (genomics, transcriptomics, proteomics, and transcriptomics) with dietary, clinical, and biobehavioral phenotypes to understand the development of obesity, insulin resistance, and diabetes in both people and in animal models.
Burant directs the Michigan Metabolomics and Obesity Center (MMOC), the umbrella organization for the NIH-funded Nutrition Obesity Research Center and Michigan Regional Comprehensive Metabolomics Resource Core. These centers provide infrastructure for human and animal studies related to metabolic diseases.
Burant earned his B.S. in biochemistry at the University of Wisconsin, Madison, in 1979. He earned an M.S. in environmental toxicology at the University of Wisconsin, Madison, in 1981. He earned an M.D. in medicine at the Medical University of South Carolina in 1987. He earned a Ph.D. in molecular and cell biology at the Medical University of South Carolina in 1987.

Jacqueline Capeau, M.D, Ph.D.
Professor of Cell Biology and Metabolism
Pierre and Marie Curie University (France)

Jacqueline Capeau is a Professor of Cell Biology and Metabolism at the Pierre and Marie Curie Faculty of Medicine (University Pierre and Marie Curie, Paris6), Paris, France and a scientific advisor for the Vice-President of this University. Her current responsibilities include Head of the Department of Biochemistry and Hormonology at the Tenon Hospital and Head of a coordinated group on "Complications of Antiretroviral Treatment and Aging" for the French National Agency against AIDS and Viral Hepatitis (ANRS). Regarding research, Jacqueline Capeau is working on genetic lipodystrophies and acquired lipodystrophies seen in HIV-infected patients together with ageing and age-related comorbidities in these patients. The main research approaches are complementary between basic science and clinical trials to decipher the pathophysiology of fat hypertrophy and related complications and to improve therapeutics in HIV-infected patients. She has over 268 full publications, has been regularly invited to speak at international meetings and is member of the organizing committee of 2 international meetings on HIV-related comorbidities and aging.

Elaine K. Cochran
Nurse Practitioner
NIDDK, NIH

Elaine Cochran is a pediatric nurse practitioner and lead association investigator for 3 active research protocols at the NIDDK for syndromes of severe insulin resistance. She has worked with Dr. Phillip Gorden for the past 14 years with patient with lipodystrophy receiving leptin hormone replacement therapy. She authored over 40 manuscripts on patients with extreme forms of insulin resistance, patients receiving leptin hormone replacement therapy, and the administration of U-500 insulin. She has presented nationally and internationally on these topics as well.

Chad A. Cowan, Ph.D.
Associate Professor, Department of Stem Cell and Regenerative Biology; Principal Faculty, Harvard Stem Cell Institute
Harvard University

Chad Cowan received his B.A. and B.S., with honors, from the University of Kansas. He received his Ph.D. from the University of Texas Southwestern at Dallas, garnering the Nominata award for most outstanding thesis. He subsequently completed a Damon Runyon postdoctoral fellowship with Professor Douglas Melton at Harvard University. He was named a Stowers Medical Investigator in 2006 and in 2008, he became an Assistant Professor at Harvard University. He is currently an Associate Professor at Harvard University in the Department of Stem Cell and Regenerative Biology and Massachusetts General Hospital, with appointments in the Center for Regenerative Medicine, Cardiovascular Research Center and Center for Human Genetics Research. He is an Associate Member of the Broad Institute and a Principal Faculty member of the Harvard Stem Cell Institute where he directs the Diabetes Disease Program and the iPS Cell Core Facility. Professor Cowan has led or been a member of several large efforts to utilize stem cells to better understand disease, including the NHLBI's Next Gen iPS Cell Project and the Progenitor Cell Biology Consortium. In 2013, Professor Cowan received a Transformative Research Award from the NIH to create isogenic human pluripotent stem cell-based models of human disease mutations. More recently, Professor Cowan has focused on using genome-editing tools as therapeutics and as a co-founder of CRISPR Therapeutics hopes to see these discoveries translated into treatments or cures.

Andres Digenio, M.D., Ph.D.
Executive Director, Clinical Development
ISIS Pharmaceuticals, Inc.

Dr. Andres Digenio serves as Executive Director in Clinical Development at Isis Pharmaceuticals where he supports novel antisense treatments for cardio-metabolic conditions. In previous positions he conducted research with CETP inhibitors, CB1 blockers and GLP-1 agonists. His main clinical interests include the pharmacological and lifestyle management of lipids, obesity and diabetes. Before joining industry he was Assistant Professor of Medicine in the Department of Cardiology at Vanderbilt University and the Medical Director of a large primary and secondary prevention center in Johannesburg, South Africa.

Andrea E. Dunaif, M.D.
Charles F. Kettering Professor of Endocrinology and Metabolism
Northwestern University

Andrea Dunaif, M.D., is the Charles F. Kettering Professor of Endocrinology and Metabolism, and Vice Chair for Research in the Department of Medicine at the Feinberg School of Medicine, Northwestern University. Formerly, she was Chief of the Division of Endocrinology, Metabolism and Molecular Medicine at the Feinberg School of Medicine for 10 years. Before joining Northwestern in 2001, Dr. Dunaif held faculty appointments at the Mount Sinai School of Medicine, Pennsylvania State University College of Medicine and Harvard Medical School. Dr. Dunaif is an internationally recognized expert in endocrinology and women's health. Her research on polycystic ovary syndrome (PCOS has shown that it is a leading risk factor for type 2 diabetes mellitus. Further, this research has revolutionized the treatment of PCOS with insulin sensitizing drugs. Dr. Dunaif has more than 125 original scientific publications and has edited four books. She has received numerous awards and honors including the Endocrine Society's highest award for clinical research, the Clinical Investigator Award. She is a past president of the Endocrine Society, a former associate editor of The Journal of Clinical Endocrinology and Metabolism and Obesity.

Ken Ebihara, M.D.
Associate Professor, Division of Endocrinology and Metabolism
Jichi Medical University (Japan)

Dr. Ebihara obtained his M.D. in 1994 from Tohoku University School of Medicine in Sendai, Japan. In 1996, Dr. Ebihara joined Dr. Kazuwa Nakao's lab at Kyoto University Graduate School of Medicine in Kyoto, Japan and started his leptin study. He obtained a Ph.D. in 2000. Since then, as a staff scientist, he had been studying leptin in Kyoto University. Based on the achievement of his basic study, in 2002, he first started leptin therapy in patients with lipodystrophy in Japan. From 2009 to July 2014, he was an associate professor in Translational Research Center, Kyoto University Hospital. In August 2014, he moved to the Division of Endocrinology and Metabolism, Jichi Medical University in Shimotsuke, Japan as an associate professor.

Abhimanyu Garg, M.D.
Professor of Internal Medicine
Chief, Division of Nutrition and Metabolic Diseases
UT Southwestern

Abhimanyu Garg, M.D. is a professor of Internal Medicine and is Chief, Division of Nutrition and Metabolic Diseases at UT Southwestern. He holds a Distinguished Chair in Human Nutrition Research. Dr. Garg received his M.B.B.S. and M.D. degrees from the All India Institute of Medical Sciences, New Delhi, India. He completed his endocrine training at the University of Alabama at Birmingham. In 1985, Dr. Garg joined UT Southwestern as a fellow in Endocrinology and Metabolism. He has carefully characterized the phenotype of various disorders of adipose tissue, called lipodystrophies, which has led to discovery of many novel genes for these disorders. Dr. Garg's group identified deficiency of AGPAT2 enzyme, which is critical for triglyceride and phospholipid biosynthesis, as the cause of congenital generalized lipodystrophy, type 1. His group also linked peroxisome proliferator-activated receptor-γ (PPARG) gene, the key adipocyte differentiation transcription factor, to familial partial lipodystrophy. His team has also identified the second locus for mandibuloacral dysplasia, i.e., zinc metalloproteinase (ZMPSTE24), that is responsible for post translational processing of prelamin A to its mature form lamin A. Recently, he uncovered molecular genetic basis of a novel autoinflammatory lipodystrophy to be proteasome subunit, beta-type 8 (*PSMB8*). He demonstrated that patients with generalized lipodystrophy have profound leptin deficiency and proposed that leptin deficiency might contribute to the metabolic complications in the disorder. This led him to initiate a collaborative trial with the NIDDK that demonstrated dramatic improvement in hyperglycemia, dyslipidemia, and fatty liver with leptin therapy.

Phillip Gorden, M.D.
Director Emeritus and Senior Investigator
NIDDK, NIH

Dr. Phillip Gorden received his B.A. degree from Vanderbilt University, and an MD degree from Vanderbilt University School of Medicine. He then spent 5 years in medical residency, and completed an endocrine and metabolism fellowship at Yale University School of Medicine. In 1966, he came to the National Institutes of Health (NIH), as a clinical investigator. His early studies include the heterogeneity of polypeptide hormones, including the pro-insulin-like components of plasma, and clinical descriptions of diseases of extreme insulin resistance; particularly as related to the insulin receptor. From 1976 to 1978 he was a visiting professor in the laboratory of Lelio Orci, M.D. in Geneva, Switzerland. Following his return to the NIH, he served as a major branch chief, and as clinical director of the National Institute of Diabetes Digestive and Kidney Diseases (NIDDK). In 1999 Dr. Gorden returned full time to the intramural program of NIDDK, where he is focused on developing therapeutic strategies for the extreme forms of insulin resistance, such as lipodystrophy and autoantibodies to the insulin receptor. He has received a number of national and international awards, including lectureships and honorary degrees, and has published over 370 scientific papers.

Stephen C. Groft, Pharm.D.
Senior Advisor to the Director
NCATS, NIH

Steve is currently a Senior Advisor to the Director, National Center for Advancing Translational Sciences at NIH. He served as the Director of the Office of Rare Diseases Research (ORDR) in the National Center for Advancing Translational Sciences at the National Institutes of Health (NIH). His major focus has been on stimulating research with rare diseases and developing information about rare diseases and conditions for health care providers and the public. To help identify research opportunities and establish research priorities, the ORDR co-sponsored over 1400 rare diseases-related scientific conferences with the NIH research Institutes and Centers and the extramural research community, including patient advocacy groups. Previous activities included the development of common and unique data elements for patient registries for rare diseases, transferring information to the Rare Diseases Community through a public information center on genetic and rare diseases, developing an international rare diseases research consortium (IRDiRC), establishing and maintaining the Rare Diseases Clinical Research Network, and assisting in the development of a special emphasis research network with senior clinical staff for patients with undiagnosed diseases at NIH's Clinical Research Center Hospital and at academic centers in the United States.
Steve received the B.S. degree in Pharmacy in 1968 and the Doctor of Pharmacy degree from Duquesne University in 1979.

Carol Haft, Ph.D.
Senior Advisor for Cell Biology in the Division of Diabetes, Endocrinology, and Metabolic Diseases
NIDDK, NIH

Dr. Carol Haft is a Senior Advisor for Cell Biology in the Division of Diabetes, Endocrinology and Metabolic Diseases in the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health (NIH) in Bethesda, Maryland. She oversees a large portfolio of grant applications focused in two major areas, adipocyte biology and protein trafficking and processing in metabolic diseases. As a program director in NIDDK, she interacts with investigators looking to submit projects, help them to revise projects following peer review, make funding recommendations, and assess the scientific progress of funded applications. Dr. Haft also advises the director of NIDDK about research opportunities, understudied areas, and emerging areas; holds workshops in focused areas; develops initiatives in emerging areas; and acts as a talent scout.

Debbie Jae, M.S.
Director of Programs
PatientCrossroads

Debbie Jae, M.S. is Director of Programs at PatientCrossroads. Debbie oversees the daily operations of multiple private patient registries. She works directly with researchers, pharmaceutical companies, government institutions, advocacy groups and patients. She has a Master's degree in Genetic Counseling, experience working in a large academic hospital, small clinics, and for laboratories, as well as experience in the medical device industry. She relies on all of her training and past experience to serve the needs of patients and researchers alike to collect the data needed to find treatments that work.

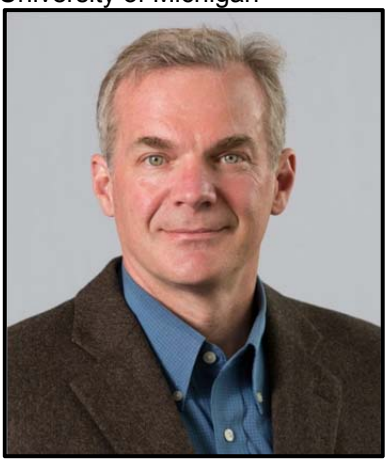
Alexei Kharitonenkov, Ph.D.
Professor
Indiana University, Bloomington

Throughout Dr. Alexei Kharitonenkov's career in Science, he was privileged to study various aspects of Biology spanning the variety of disciplines from cellular biochemistry and signal transduction to the matters of *in vivo* pharmacology in rodents, non-human primates and man. His research tenures at the prestigious Research Centers such as Moscow State University, Max-Planck-Institute for Biochemistry, Lilly Research Laboratories, and now in the Chemistry Department of the IUB helped his skills and expertise to mature. Being coached by the world-class experts such as Profs. Axel Ullrich and Richard DiMarchi was critical to Dr. Kharitonenkov's development as an independent investigator and aided him to acquire deep passion for Life Sciences. While leading a lab and then the research group in Diabetes Research at Lilly he discovered FGF21, a novel metabolic hormone, and championed this target from the initial metabolic hit in the *in vitro* screen to the evaluation of its therapeutic utility in clinic. His current research interests lie within the translational aspects of metabolism with the intent to expand the boundaries of metabolic drug discovery in collaboration with Richard DiMarchi's group.

Matthias Kretzler, M.D.
Warner-Lambert/Parke-Davis Professor of Internal Medicine/Nephrology and Computational Medicine and Bioinformatics
University of Michigan

Dr. Kretzler is the Warner-Lambert/Parke-Davis Professor of Internal Medicine/Nephrology and Computational Medicine and Bioinformatics. He leads the Nephrotic Syndrome Research Network (NEPTUNE) in the Rare Disease Clinical Research Network III and the director of the Data Coordinating Center of the UM1 CureGN glomerular disease network. He leads the Applied Systems Biology Core in the Director of the O'Brien Renal Center at UMichigan and is an investigator in the CKD-H3 Africa Network, Eurenomics and NEPTUNE-China. He focuses with his research team on the analysis of molecular mechanism of glomerular damage. Using integrated biology approaches transcriptional networks in glomerular diseases are defined in human cohorts and integrated with genetic information, complex clinical and environmental data sets. The large-scale data integration across the genotype-phenotype continuum aims to reach a more holistic understanding of glomerular disease and has already resulted in the initiation of trials with targeted therapies in glomerular diseases in the setting of the NEPTUNE.

Ormond MacDougald, Ph.D.
John A. Faulkner Collegiate Professor of Physiology
University of Michigan



Dr. Ormond MacDougald earned his B.Sc. from the University of Guelph, and his M.S. and Ph.D. from Michigan State University. After completing his postdoctoral training at Johns Hopkins University School of Medicine, he began his academic career at the University of Michigan, where he currently holds the John A. Faulkner Collegiate Professorship of Physiology. The longstanding focus of his lab is the regulation of adipocyte differentiation and metabolism.

Jocelyne Magré, Ph.D.
Senior Researcher – Inserm
L'Institut du Thorax, Université de Nantes (France)

Jocelyne Magré is a senior researcher at the Inserm, L'Institut du Thorax (Nantes, France) - Team 5 "Molecular Investigations of Dyslipidemias". She received her Ph.D. in 1988 in Cellular and Molecular Biology (Pierre and Marie Curie University, Paris) with a thesis entitled "Studies of the mechanism of Insulin Resistance in a syndrome with major InsulinResistance: Lipoatrophic Diabetes" performed under the responsibility of Jacqueline Capeau. She then performed a post-doctoral training at the Joslin Diabetes Center (Harvard Medical School, Boston, MA) in C. Ronald Kahn's laboratory from 1988 to 1991 where she extended her expertise in the field of Insulin Resistance and got experience in DNA analysis. In 1991, Jocelyne got a tenure position at Inserm as a research scientist and worked with Jacqueline Capeau on the rare syndromes of severe insulin resistance. She more precisely handled the genetics of Berardinelli-Seip Congenital Lipodystrophy. Within the frame of collaboration with M.Ds and Mark Lathrop's laboratory (Centre de Genotypage, Evry, France) for the genome screening, they identified *BSCL2*, the seipin gene in 2001. They identified mutations in *AGPAT2* or *BSCL2* in most patients with BSCL and also discovered the implication of Caveolin 1 and Perilipin as new causative-genes in various forms of lipodystrophies. In 2011, she joined the Inserm laboratory at "l'Institut du Thorax" in Nantes (France) to phenotype *Bscl2*$^{-/-}$ mice in collaboration with some members of her new team directed by Bertrand Cariou, in particular, Xavier Prieur. In parallel, she is conducting a new research project that aims to define the genetic basis of various forms of dyslipidemia, more particularly hypobetalipoproteinemia.

Susanne Mandrup, Ph.D.
Professor, Department of Biochemistry and Molecular Biology
University of Southern Denmark

Susanne Mandrup has been Professor at Department of Biochemistry and Molecular Biology, University of Southern Denmark since 2008. She obtained her Ph.D. in Biochemistry from Odense University in 1992 and worked among others as a post doc in Prof. M. Daniel Lane's group, Department of Biological Chemistry, Johns Hopkins University, Baltimore 1995-96. In 1996 she was recruited back to Odense as Assistant Professor. The research in the Mandrup group focuses on understanding the molecular cross-talk between transcriptional regulation and metabolism in adipocytes and pancreatic β-cells, and in the transcriptional network regulating adipocyte differentiation. Her group runs its own sequencing platform and combines genome-wide studies of transcription factor binding, epigenetic marks and chromatin structure with detailed molecular analyses of the cross-talk between transcriptional regulators.

Arya Mani, M.D.
Associate Professor of Medicine (Cardiology) and of Genetics
Yale University

Arya Mani is an Associate Professor of Medicine and Genetics, and the Director of Yale Cardiovascular Genetics Program. He has graduated from Johannes Gutenberg University in Mainz, Germany and has completed his Internal Medicine residency, chief residency and cardiology fellowship as well as a 4 year postdoctoral fellowship in human genetics under mentorship of Richard Lifton at Yale University School of Medicine. His research focuses on the genetic causes of cardiovascular disorders and the molecular and cell biological underpinnings of the pathophysiology of these disorders. His lab has identified a number of genetic mutations that underlie different cardiovascular diseases. These mutations cause vascular remodeling, from patent ductus arteriosus to atherosclerosis. His investigations have also led to identification of genes that regulate body weight, glucose and lipid metabolism. He is currently working on identification of optimal targets for drug development for atherosclerosis.

Martin Myers, Jr., M.D., Ph.D.
Marilyn H. Vincent Professor of Diabetes Research; Director, Michigan Diabetes Research Center
University of Michigan

Dr. Martin Myers, Jr., is Professor of Internal Medicine, Division of Metabolism, Endocrinology & Diabetes; Professor of Molecular & Integrative Physiology; the Marilyn H. Vincent Professor of Diabetes Research; and Director of the Michigan Diabetes Research Center at the University of Michigan. Dr. Myers received his bachelor's degree from Princeton University, and his M.D. and Ph.D. from Harvard University. Dr. Myers's first independent research program was at the Joslin Diabetes Center/Harvard Medical School. He joined the University of Michigan faculty in 2004 and was named the Marilyn H. Vincent Professor of Diabetes Research in 2008. The Myers lab studies leptin action along two broad themes: Mechanisms of intracellular signaling, and the neural basis of leptin action. Revealing these mechanisms may reveal potential targets for therapeutic intervention in obesity and diabetes. Dr. Myers has received numerous awards for his research achievements, including the Jerome Conn Award and the Basic Science Research Award from the University of Michigan, as well as Outstanding Scientific Achievement Awards from The Obesity Society and from the American Diabetes Association, and the Ernst Oppenheimer Award from the Endocrine Society. Research in the Myers lab is funded by grants from the National Institutes of Health, the American Diabetes Association, and the American Heart Association.

Elif A. Oral, M.D.
Associate Professor of Medicine
University of Michigan

Dr. Elif Oral, M.D., is an Associate Professor in the Division of Metabolism, Endocrinology and Diabetes (MEND) at The University of Michigan. She completed her medical education in her home country of Turkey at the University of Istanbul. In 1996, she completed her residency in Internal Medicine at Sinai Hospital of Detroit (Michigan). She then pursued a Fellowship in Endocrinology, Metabolism and Diabetes at the National Institutes of Health where she also chose to stay as a Senior Fellow under the mentorship of Drs. Simeon Taylor and Phillip Gorden in the Diabetes Branch of NIDDK. Since joining The University of Michigan in 2002 as an Assistant Professor of Medicine, along with her regular faculty responsibilities, Dr. Oral also completed a Masters of Science Degree in Clinical Research Design and Biostatistics at the School of Public Health. Her clinical interests are in insulin resistance, obesity, lipid disorders, and diabetes. Her research focuses on the importance of adipocytes in human metabolism and adipocyte hormones such as leptin. She is best known for her work showing the remarkable efficacy of leptin in rare lipodystrophy syndromes. These studies provided the basis for her current studies investigating the effects of leptin in treatment of non-alcoholic fatty liver disease.

Samantha Pulliam, M.D.
Patient; Assistant Professor, Department of Obstetrics and Gynecology
Massachusetts General Hospital

Dr. Samantha Pulliam is an Assistant Professor in the department of Obstetrics and Gynecology at Massachusetts General Hospital, where she directs the fellowship in Female Pelvic Medicine and Reconstructive Surgery. She was diagnosed with Familial Partial Lipodystrophy in 2005. She has been a part of a clinical trial involving Leptin for over three years at the University of Michigan.

Shannon Reilly, Ph.D.
Postdoctoral Fellow
University of Michigan

Dr. Shannon Reilly obtained her Ph.D. from Harvard University and received the Edgar Haber Award for her research into the role of the nuclear receptor corepressor SMRT in metabolic disease, which was performed in the laboratory of Chih-Hao Lee within the Department of Genetic and Complex Diseases. Since 2011, Reilly has been investigating the role of the noncanoical IKKs in metabolic disease in Alan Saltiel's laboratory at the Life Sciences Institute at the University of Michigan. Her 2013 publication in *Nature Medicine* described the metabolic benefits of inhibiting the noncanoical IKKs with amlexanox in obese rodents. Reilly's current work is focused on the short-term effects of amlexanox treatment and elucidating the molecular mechanism(s) of its metabolic effects. Additionally, Saltiel and Reilly are collaborating with Dr. Elif Oral from the Department of Internal Medicine at the University of Michigan to perform clinical trials to determine if amlexanox could be repurposed for the treatment of metabolic disease.

Karen Reue, Ph.D.
Professor, Department of Human Genetics
UCLA

Karen Reue received her B.S. from the University of Arizona, and Ph.D. from UCLA. After post-doctoral studies at the Rockefeller University, she returned to UCLA, where she is currently a professor in the Department of Human Genetics. Her research focuses on the identification of genes affecting obesity and metabolic disease. Using positional cloning of spontaneous mutant genes, her laboratory isolated the lipin gene family (required for fat cell differentiation) and Diet1 (a regulator of plasma cholesterol levels). Recent work includes the investigation of mechanisms underlying sex differences in obesity.

Justin Rochford, Ph.D.
Senior Lecturer, Rowett Institute of Nutrition and Health
University of Aberdeen (UK)

Justin Rochford is a Senior Lecturer at the Rowett Institute of Nutrition and Health (RINH) of the University of Aberdeen, UK. His laboratory studies molecular mechanisms controlling adipocyte development and function. A significant aim of the lab is to define why the protein seipin, disruption of which causes severe generalised lipodystrophy in humans, is critical for adipose tissue development. The lab also investigates how seipin and other proteins of interest such as γ-synuclein may influence the metabolic functions of mature adipocytes. Justin's training included post-doctoral work at the University of Cambridge, UK with Steve O'Rahilly investigating altered intracellular signalling in patients with severe insulin resistance. He subsequently developed a group focussed on adipogenesis, initially as a British Heart Foundation Intermediate Fellow, then as a Medical Research Council (MRC) New Investigator. His laboratory moved to the RINH in 2013. By better defining how new adipocytes develop and the metabolic function of mature fat cells the lab aims to identify potential novel therapeutic targets that may treat obesity and associated metabolic diseases.

Clifford J. Rosen, M.D.
Professor of Medicine
Tufts University

Dr. Clifford J. Rosen, M.D. is the Director of Clinical and Translational Research and a Senior Scientist at Maine Medical Center's Research Institute. He is a Professor of Medicine at Tufts University School of Medicine. He was the first Editor-in-Chief of the Journal of Clinical Densitometry, is the current Editor-in-Chief of The Primer in Metabolic Bone Diseases, and is the Associate Editor for New England Journal of Medicine. His publications include more than 369 peer-reviewed manuscripts, covering both clinical and basic bone biology.
Dr. Rosen has overseen numerous phase II and III clinical trials, funded both privately and through the NIH. He is a member of the FDA Advisory Panel on Endocrinologic and Metabolic Drugs and a former chairperson of that committee. He also has served on two Institute of Medicine Committees, and was Chair of the NIH Review Panel for Skeletal Biology and Bone Diseases for 2002-2004. He is the current Chair of the Clinical Trials Review Panel for NIAMS. He was a previous member of the NIAMS Scientific Advisory Board and served as president of the American Society for Bone and Mineral Research in 2002-2003. Dr. Rosen's research interests include the genetic regulation of IGF-I, skeletal metabolism and stem cell fate, PTH as an anabolic therapy, and the relationship between marrow adipogenesis and osteoblastogenesis.

Arun J. Sanyal, M.B.B.S., M.D.
Professor of Medicine; Executive Director, Education Core, CCTR
Virginia Commonwealth University

Dr. Sanyal has a long standing interest in chronic liver disease and its outcomes. He has served as a chair of the National Institute of Health (NIH) NASH Research Network and is the current Chair of the Liver Study Section at NIH. He is also a past president of the American Association for the Study of Liver Disease (AASLD), where he served for many years. He is actively involved in global health initiatives both as a scientist, a lecturer, and publisher in leading medical and scientific journals. In addition, Dr. Sanyal is an author and co-author of textbooks that are being circulated globally. A deep commitment to liver disease research and to global health initiatives has made Dr. Sanyal a much sought-after speaker and brought him to the forefront of symposiums all over the world.

Robert Semple, M.B., Ph.D.
Wellcome Trust Senior Research fellow, Clinical Science
University of Cambridge (UK)

Dr. Semple is a Wellcome Trust Senior Research Fellow and Honorary Consultant Endocrinologist at the University of Cambridge, UK. He read Biochemistry and Medicine at the University of Cambridge before internal medical posts in London. He returned to Cambridge for specialist training in Diabetes and Endocrinology, interrupted by doctoral studies with Prof Stephen O'Rahilly, focussing on genetic regulation of adipose tissue metabolism. For the past 12 years he has focussed on rare disorders of insulin action and growth. His research aims to identify novel genetic defects underlying insulin resistance and related conditions, to discriminate these clinically/biochemically, and thereby to accelerate diagnosis and to enhance treatment of affected patients. This work has played a key part in the establishment of a National NHS Severe Insulin Resistance Service in Cambridge.

Vinaya Simha, M.B.B.S., M.D.
Assistant Professor, Department of Internal Medicine; Senior Associate Consultant, Division of Endocrinology
Mayo Clinic

Dr. Vinaya Simha, M.B.B.S., M.D. is a Senior Associate Consultant in the Division of Endocrinology, and Assistant Professor, Department of Internal Medicine at Mayo Clinic, Rochester, MN. He completed his medical school and post-graduation in human physiology at Kasturba Medical College, Mangalore and the All India Institute of Medical Sciences, New Delhi in India before coming to the United States for Internal Medicine Residency at Brooklyn Jewish Hospital. He completed his Fellowship training in Endocrinology, and in Nutrition and Metabolic Diseases at UT Southwestern Medical Center, Dallas. He served on the faculty at UT Southwestern and in Texas Tech University Health Sciences Center before moving to Mayo Clinic in 2012. He is board certified in Internal Medicine, Endocrinology and Clinical Lipidology. His research interests include lipodystrophy and the role of body fat distribution on glucose and lipid homeostasis and he has many publications in the field of lipodystrophy and leptin-replacement therapy.

Andra Stratton
President
Lipodystrophy United

Andra Stratton is a patient advocate with an extensive background in organizational development and human resources. After her diagnosis, she united with other lipodystrophy patients and co-founded Lipodystrophy United, the global patient foundation. As President of LU since inception two years ago, she has been responsible for working to educate patients and physicians and increase awareness of all types of lipodystrophy. She is active in online social media groups with patients and acts as a liaison between patients and lipodystrophy stakeholders. Andra has represented the lipodystrophy community in large and small venues including serving as an active participant in rare disease conferences, lobbying with other advocates in Washington DC, speaking to physicians in the US and in Spain and serving as a governing board member for LD Connect, the global patient registry. In addition to her role as a patient and advocate, Andra is a single mother of two pre-teen daughters.

Simeon Taylor, M.D., Ph.D.
Professor of Medicine
University of Maryland School of Medicine

Dr. Simeon Taylor received his education at Harvard University (B.A., M.D., and Ph.D.) and his clinical training at Massachusetts General Hospital (Internal Medicine and Endocrinology). In 1979, he moved to the U. S. National Institutes of Health where he was Chief of the Diabetes Branch, NIDDK (1989-2000). At NIH, his research focused on mechanisms of insulin resistance, genetics of insulin resistant diabetes, and investigating innovative therapies including metreleptin to treat lipoatrophic diabetes. His contributions were recognized by the Outstanding Service Award of the U.S. Public Health Service and the Outstanding Scientific Achievement Award of the American Diabetes Association. In 2000, he moved to the pharmaceutical industry. In his role as Vice President of Cardiovascular and Metabolic Disease Research at Bristol-Myers Squibb, he made substantial contributions to R&D leading to four approved drugs: saxagliptin, dapagliflozin, metreleptin, and apixaban. Most recently, he has returned to academia as an Adjunct Professor in the Division of Diabetes, Endocrinology, and Nutrition at the University of Maryland School of Medicine.

Matthias Tschöp, M.D.
Research Director; Chair of Metabolic Diseases
Technische Universität München (Germany)

Matthias Tschöp is the Research Director of the Helmholtz Diabetes Center, serves as the Chair of Metabolic Diseases at Technische Universität München and is the first physician to receive the prestigious Alexander-von-Humboldt Professorship. Prof. Tschöp discovered the orexigenic, adipogenic, and metabolic effects of the “hunger hormone” ghrelin as well as its secretory control by nutrients. He also discovered how specific CNS circuits directly “remote control” lipid metabolism of fat tissue and liver to modulate circulating cholesterol, fatty acids and triglycerides. Together with the chemist Richard DiMarchi, Tschöp discovered and functionally characterized a series of novel gut hormone-based single molecule combinatorial therapeutics, which are currently in clinical development for the treatment of diabetes and obesity. Most recently, DiMarchi and Tschöp engineered and validated peptides capable of delivering small molecules to distinct cell populations. Prof. Tschöp has received numerous awards, including the 2010 NIH/NIDDK Scholar Award, the 2011 Outstanding Scientific Achievement Award of the American Diabetes Association, the Paul-Martini-Prize for Clinical Pharmacology in 2014 and the Erwin Schrödinger Prize, the highest German Award for interdisciplinary biomedical research (2014). He was elected into the German National Academy of Sciences (Leopoldina) in 2013.

Stephen G. Young, M.D.
Distinguished Professor of Medicine and Human Genetics
UCLA

Stephen G. Young, M.D. is a Distinguished Professor of Medicine and Human Genetics at the University of California, Los Angeles (UCLA). Early in his career, Young defined the role of apolipoprotein (apo-) B in lipoprotein metabolism and atherosclerosis. In recent years, Dr. Young’s work at UCLA has worked on two research areas—mechanisms underlying plasma triglyceride metabolism and functions of nuclear lamins in health and disease. His laboratory identified an endothelial cell protein, GPIHBP1, that is crucial for transporting lipoprotein lipase to the capillary lumen. His research team also led the way in understanding the importance of posttranslational modifications of nuclear lamins in health and disease. Dr. Young has published numerous papers in top scientific journals, lectured at national and international meetings, and been awarded various prizes, including the Ernst Jung Prize in Medicine in 2010.

ABSTRACTS

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Prevalence and Mechanisms of Polycystic Ovarian Syndrome in Familial Partial Lipodystrophy, Dunnigan Variety

Chandna Vasandani, PhD, Darshana Purohit, MD, Beverley Adams-Huet, MS, Abhimanyu Garg, MD
UT Southwestern Medical Center, Dallas, Texas, USA

Introduction: Familial partial lipodystrophies (FPL) are rare monogenic disorders of the adipose tissue characterized by marked loss of subcutaneous (sc) fat from the extremities resulting in a muscular appearance. Mutations in four loci, lamin A/C (*LMNA*), peroxisome proliferator activated receptor gamma (*PPARG*), v-AKT murine thymoma oncogene homolog 2 (*AKT2*) and perilipin 1 (*PLIN1*) cause autosomal dominant FPL, while a mutation in cell death-inducing DNA, fragmentation factor a-like effector c (*CIDEC*) has been reported in a patient with autosomal recessive variety. FPL, Dunnigan (FPLD) is the most common variety of FPL, and is due to missense mutations in *LMNA* that encodes nuclear lamina proteins, lamins A and C. FPLD patients are predisposed to metabolic complications of insulin resistance such as diabetes, hypertriglyceridemia, low levels of high density lipoprotein (HDL)-cholesterol, and atherosclerotic heart disease, especially in females. However, whether affected women with FPLD have an increased prevalence of PCOS is not well-established. Therefore, the objective of this study was to determine the prevalence and underlying mechanisms of PCOS in postpubertal, premenopausal females with FPLD using the National Institutes of Health criteria.

Results: Of the 47 women with FPLD, age 14-50 years, twenty one percent of women with FPLD had PCOS. Compared to the non-PCOS group, PCOS women had higher body mass index (23.9 ± 3.5 vs. 26.9 ± 3.0 kg/m^2, respectively; p=0.007), upper body fat (19 ± 3% vs. 22 ± 4%, respectively; p= 0.03), and sum of truncal skinfolds thickness (55 ± 20 mm vs. 77 ± 20 mm, respectively; p=0.02) but not the sum of peripheral skinfold thickness (25 ± 8 mm vs. 27 ± 7 mm, respectively; p=0.23). The PCOS group also had an increased prevalence of diabetes (29% vs. 70%, respectively; p=0.03) and acanthosis nigricans (41% vs. 89%, respectively; p=0.02).

General Characteristics and co-morbidities in FPLD women with and without PCOS

Subjects	n	PCOS (n=10)	n	Non-PCOS(n=37)	P value
Mean Age (years)	10	33.7 ± 7.5	37	32.1 ± 11.3	0.87
BMI (kg/m²)	10	26.9 ± 3.0	32	23.9 ± 3.5	0.007
Diabetes (n; %)	10	7 (70%)	35	10 (29%)	0.03
Upper body fat % (n)	9	22.4 ± 3.6	14	19.0 ± 2.8	0.03
Sum of Truncal skinfolds*	6	76.7 ± 19.8	14	55.3 ± 19.6	0.02
Sum of Peripheral skinfolds*	7	26.7 ± 6.5	14	24.4 ± 7.8	0.23
Acanthosis Nigricans (n, %)	9	8 (89%)	37	15 (41%)	0.02

Results are presented as mean ± SD. P-values are from the Wilcoxon Rank Sum test for numerical variables and the Fisher Exact test for categorical variables. BMI, body mass index. * Skinfolds are in (mm)

Conclusion: Women with FPLD have a high prevalence of PCOS compared to 6-8% prevalence observed in the general population. This increased prevalence of PCOS is associated with excess truncal adiposity and insulin resistance but not the severity of fat loss from the extremities.

Hypothalamic tumors mimicking acquired generalized lipodystrophy.

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Introduction: A rare presentation of hypothalamic tumors in infants and young children is profound emaciation and generalized loss of subcutaneous (sc) adipose tissue, also known as 'diencephalic syndrome'. Similar loss of sc fat can be observed in children with "idiopathic subtype of acquired generalized lipodystrophy (AGL)". Precise diagnosis may be challenging early in the course of the disease, especially in the absence of metabolic abnormalities. We report 2 cases who presented with generalized loss of sc fat, initially suggestive of AGL, who subsequently developed central precocious puberty and were diagnosed with hypothalamic tumors.

Case 1: A 10-month-old Caucasian male presented with inability to gain weight since 5 months of age despite increased appetite. Physical examination revealed generalized loss of sc fat with sparing of the palms and soles, prominent musculature and sc veins and hepato-splenomegaly. Initial laboratory data showed normal fasting glucose, hemoglobin A1c (HbA1c), lipid panel and transaminases. At 4 ½ years age, his 2 hours post prandial glucose was 166 mg/dL, total body fat estimated by DEXA scan was 11.7% and full body magnetic resonance imaging (MRI) revealed generalized loss of sc fat but no evidence of fatty liver. At 6 years of age, he started developing pubic hair and on examination he had early tanner 2 pubic hair and tanner 2 testes. His bone age was advanced to 10 years and he had pubertal levels of testosterone, LH, FSH with normal androstenedione, dehydroepiandrosterone-sulfate and 17-hydroxyprogesterone. Brain MRI showed hypothalamic chiasmatic mass measuring 2.7x2.9x2.2 cm. The mass was surgically removed and histopathology revealed it to be a pilocytic astrocytoma. Postoperatively, patient gained weight from 22.4 kg to 40 kg over a 2 year period.

Case 2: A 5.5-year-old Caucasian male from Brazil presented with poor weight gain since age of 3 years. Examination revealed generalized loss of sc fat with apparent muscular hypertrophy in extremities, coarse scalp hair, but no acanthosis or hepato-splenomegaly. Laboratory data showed normal blood glucose, HbA1c, lipid panel and transaminases. In view of normal metabolic work up, differential diagnosis of diencephalic syndrome was suggested. An MRI brain showed a solid lesion measuring 2.6x2.4x1.9 cm in the optic chiasmatic region. Tumor biopsy showed "Fibrillar Diffuse Astrocytoma, WHO grade II" and patient was treated with chemotherapy. After treatment initiation, the patient gained weight from 15 kg to 22 kg over a one year period. At 6 year 4 month of age, enlargement of the penis, deepening of the voice and axillary hair were noted and the patient was started on LHRH analog. MRI at 7 years and 1 month showed reduction in tumor size.

Discussion: Diencephalic syndrome is typically observed in children less than 2 years of age with hypothalamic-chiasmatic tumors. Older children with similar brain tumors typically present with obesity, central precocious pubertyand diabetes insipidus [1-3]. Patient 1 had some features consistent with AGL, such as, increased appetite, hepato-splenomegaly and glucose intolerance, which have not been reported in diencephalic syndrome. Patient 2 had no abnormal metabolic parameters. Interestingly, both of our patients had atypical presentation, i.e., presence of central precocious puberty and increased age.

The cause of loss of sc fat in children with hypothalamic tumors remains unknown. Multiple etiologies like excessive metabolic expenditure [1, 4], destruction of known modifying (afferent) pathways to hypothalamus [2], lipolysis by elevated GH levels or β-lipotropin hormone [3, 5] and possible role of leptin and ghrelin [6, 7] have been postulated. There is also a possibility of hypersecretion of hormones or cytokines by the tumor affecting metabolism or tumor-induced autoantibody formation which may induce AGL.

Conclusion: Generalized loss of sc fat in young children without concomitant metabolic abnormalities should prompt investigation for hypothalamic tumors.

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One-year metreleptin treatment improves insulin secretion in patients with lipodystrophic syndromes

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ABSTRACT

Context: Recombinant methionyl human leptin (Metreleptin) therapy was shown to improve hyperglycemia, dyslipidemia and insulin sensitivity in patients with lipodystrophic syndromes. Its effects on insulin secretion remain unclear.

Objective: To study the effects of one-year metreleptin therapy on insulin secretion.

Design and Setting: The study was conducted during a compassionate program of metreleptin therapy in a French University Hospital.

Patients: Fourteen patients with diabetes and hypoleptinemia due to partial or generalized lipodystrophies.

Main Outcome Measures: Insulin secretion, adjusted to insulin sensitivity, was directly measured at baseline and after one-year metreleptin treatment, using clamp procedures. Metabolic effets of metreleptin including distribution of adipose tissue were also studied.

Results: Mean BMI (23.9 ± 2.2 kg/m^2, ± SEM), HbA1c (8.8 ± 1.4 %) and serum triglycerides (5.2 ±1.1 mmol/l) significantly decreased within one month of subcutaneous metreleptin, then remained stable. However, HbA1c did not improve in two women with partial lipodystrophies who did not lose weight during therapy. Insulin sensitivity (M value during euglycemic hyperinsulinemic clamp), insulin secretion during graded glucose infusion, and acute insulin response to intravenous glucose adjusted to insulin sensitivity (disposition index), significantly increased after one-year metreleptin therapy. Visceral, but not subcutaneous abdominal fat, assessed by CT-scan, decreased. Changes indisposition index were related to fat mass amount and distribution.

Conclusions: Metreleptin therapy improved not only insulin sensitivity, but also insulin secretion in patients with diabetes due to lipodystrophic syndromes, supporting its overall beneficial effect on lipotoxicity, which probably also decreases in the pancreas.

Lessons from treatment of children with congenital leptin deficiency with metreleptin

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Congenital leptin deficiency (CLD) is a rare, autosomal recessive disease caused by mutations in the leptin gene. Patients with CLD are presented with severe, early-onset obesity due to impaired satiety and intense hyperphagia and show multiple metabolic, hormonal and immunological abnormalities. In humans, eight distinct leptin mutations characterized by undetectable to low serum leptin levels have been identified so far. Mechanistically, defects in the synthesis and/or secretion of the hormone have been proposed and demonstrated for some of these mutations.

Upon substitution therapy with metreleptin to compensate the lack of leptin, patients lose weight, reduce their body fat mass and show a complete normalization of the metabolic, hormonal and immunological alterations. Our group in Ulm has further characterize metreleptin effects in CLD patients by demonstrating that:

- the long lasting benefit of metreleptin substitution is associated with activation changes in homeostatic, hedonic and frontal control regions
- metreleptin is needed for a timely maturation of the hypothalamic/pituitary/gonadal axis in humans with CDL
- metreleptin substitution induces pituitary growth hormone release and IGF-1 production
- metreleptin results in a rapid and strong reduction of liver triglyceride content and resolves hepatic steatosis in humans with CDL

Patients with CLD therefore show a severe dysfunction of white adipose tissue resulting metabolic and hormonal abnormalities which can be successfully treated by substitution with metreleptin.

Forced PPARγ1 expression confers adipogenic competence to BSCL type 1 and type 2 human dermal fibroblasts despite AGPAT2 and seipin loss-of-function.

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Berardinelli-Seip congenital lipodystrophy (BSCL) comprises several inherited disorders characterized by severe generalized adipose tissue atrophy, metabolic alterations and deficiency of adipokines. Inactivation of 1-acylglycerol-3-phosphate-O- acyltransferase 2 (AGPAT2) or seipin due to mutations in *AGPAT2* or *BSCL2* genes constitute the molecular defects responsible to type 1 and type 2 BSCL, respectively. Recent evidences indicate that functions of both AGPAT2 and seipin may go beyond those of glycerolipids biosynthesis and fat vesicle formation, filling and fusion in adipocytes, but may have additional roles affecting other metabolic and signalling pathways critical for adipogenesis, including PPARgamma transcription factor activation. In the present study we show that both BSCL1 and BSCL2 dermal fibroblasts made permissive for adipogenic stimuli by PPARγ1 overexpression, become fully capable of adipose differentiation, bypassing the requirement of functional *AGPAT2* or *BSCL2* genes. Data including lipid accumulation, mRNA expression of adipogenic markers and leptin secretion, demonstrated that PPARγ1-reprogrammed BSCL1 and BSCL2 fibroblasts undergo adipogenic differentiation in the same way than PPARγ1-reprogrammed healthy donor-derived dermal fibroblasts. No major differences were found in terms of insulin-dependent AKT activation between PPARγ1-expressing and GFP-expressing BSCL cells. Lipid profiling showed that differentiated, PPARγ1-reprogrammed control and BSCL fibroblasts exhibit a lipid composition similar to that of differentiated healthy donor-derived mesenchymal stem cells. Preliminary *in vivo* studies demonstrate the safety of grafted PPARg1-reprogrammed dermal fibroblasts in immunodeficient mice. Our results provide new evidence for a main role of AGPAT2 and seipin as essential controllers of PPARγ function and a proof-of-concept for PPARg1-based *ex vivo* gene therapy for the major forms of BSCL.

The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuating hepatic lipogenesis

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Brown fat activates uncoupled respiration to defend against cold and contributes to systemic metabolic homeostasis. To date, the metabolic action of brown fat has been primarily attributed to its role in fuel oxidation and uncoupling protein 1 (UCP1)-mediated thermogenesis. Whether brown fat engages other tissues through secreted factors remains largely unexplored. Here we show that Neuregulin 4 (Nrg4), a member of the EGF family of extracellular ligands, is highly expressed in adipose tissues, enriched in brown fat, and markedly increased during brown adipocyte differentiation. Adipose tissue Nrg4 expression was reduced in rodent and human obesity. Gain- and loss-of-function studies in mice demonstrated that Nrg4 protects against diet-induced insulin resistance and hepatic steatosis through attenuating hepatic lipogenic signaling. Mechanistically, Nrg4 activates ErbB3/ErbB4 signaling in hepatocytes and negatively regulates *de novo* lipogenesis mediated by LXR/SREBP1c in a cell-autonomous manner. These results establish Nrg4 as a brown fat-enriched endocrine factor with therapeutic potential for the treatment of obesity-associated disorders, including type 2 diabetes and non-alcoholic fatty liver disease.

EXOGENOUS LEPTIN RE-PARTITIONS COMPONENTS OF BODY MASS DURING GROWTH AND RECOVERY FROM WEIGHT LOSS. [1]Borer KT, [2]Devlin M, [3]Jepsen K, [4]Li L, [5]Yang J, [1]Schools of Kinesiology, [2]Literature, Arts & Sciences, and [3]Medicine at the University of Michigan, [4]East China Normal University, Shanghai and [5]Beijing Sport University, Beijing, PR China.

INTRODUCTION. Adipokine leptin is hypothesized to regulate body fat mass through a negative feedback from an expanding white adipose tissue mass that proportionally oversecretes the hormone and inhibits hypothalamic feeding circuits and hunger and increases thermogenesis (1). However, exogenous leptin administration does not reduce obesity or hunger (2), but it does so after weight and fat loss in weight-reduced hypoleptinemic humans (3). Leptin administration also can facilitate growth of bone and lean body mass during the phase of rapid developmental growth without an effect on food intake (4). We hypothesized that leptin allows recovery from weight loss in adulthood and re-partitioning of components of body weight during statural growth. We tested this hypothesis by administering murine leptin during last four weeks of food restriction and 21% weight loss to sexually mature and slowly growing golden hamsters (Mesocricetus auratus) and animals that were stimulated by voluntary exercise to display catch-up growth. We observed changes in feeding and body composition during ad-libitum re-alimentation after exercise and weight loss (5)

METHODS. Four groups of 46-54 day old sexually mature female hamsters were matched by weight, length and body composition to two sedentary and two exercising groups for a 42-day exposure to 70% food restriction (FR) and voluntary exercise (EX) or sedentary condition (SED) and for sc infusion of murine leptin (2.8 ug/h) or buffer through Alzet 2ML4 osmotic minipumps during the last 4 w of FR (groups LEPSED and LEPEX vs CONSED and CONEX, respectively). The measurements included total body length and body composition by NMR at the start and the end of FR and at the end of 60 days of ad-libitum re-alimentation (REAL). Blood for serum leptin measurements by ELISA (Millipore) was collected at the same three times by either retro-orbital bleeds or during final decapitation. Final femoral size, mineral density and robusticity (cortical area/bone length) were measured by µCT. Data were analyzed by mixed-model ANOVA (SAS) and one-way ANOVA with Newman-Keuls multiple comparison tests.

RESULTS. **Weight changes**. FR resulted in approximately 21% weight loss in all four group, and the loss was maintained through the 28 days of sc leptin or saline administration. After day 11 of REAL, weight regain was significantly greater in exercised (EX) than in sedentary (SED) hamsters ($F=26.8$, $df=3,34$, $p<0.001$), The inhibitory effect of leptin on LEPSED relative to CONSED weight recovery were not significant. **Growth.** Final body length increased by 1.3 cm in LEPEX and by 1 cm in CONEX and CONSED, compared to only 0.6 cm in LEPSED (Treatment* time $F=5.43$, $df=3,68$, $p= 0.0001$). The femora of EX hamsters were ~ 1 mm longer that those of SED groups ($F=8.3$, $df=3,37$, $p=0.0003$). Their robusticity (total area/length) was greatest in LEPEX hamsters ($F=3.06$,$p=0.041$). **). Lean body mass (LBM)** change. SED hamsters lost 10.1%, and EX 6.5% of LBM during FR, After REAL, LBM gain was 30.4% and 26.5% in LEPEX and CONEX, significantly more that the 10.1-10.3% in the SED groups (Group*time $F=3.34$, $df=6,68$, $p=0.006$).Post-FR increase in LEPEX LBM was greater than in the other 3 groups ($t=3.43$, $p<0.0001$). **Body fat change**. SED groups lost 69% of body fat during FR, andEX lost 79%. During REAL, body fat regain was 100% in CONSED, 106% CONEX and only 86.8% in LEPSED and 93.3%, LEPEX or about 13% less after leptin exposure ($F=3.01$, $df-34$, $p=0.044$). **Food intake (FI),** absolute (g) and relative (g/100 body weight), was higher during exercise. Relative FI significantly increased during the first 10 days of REAL with no effect of prior leptin exposure. **Serum leptin** concentration was less than 1 ng/ml at the start and the end of REAL and 15.9 ± 3.7 and 17.5 ± 4.8 ng/ml in LEPSED and LEPEX groups during leptin infusion.

CONCLUSIONS. Supra-physiological leptin exposure during last 4 weeks of a 21% weight loss consisting of 10% loss of LBM and 69% to 79% body fat loss re-partitioned components of body mass in sedentary hamsters recovering from weight loss and exercised hamsters displaying rapid catch-up growth. Leptin was permissive to lean body mass accretion in growing but not non-growing animals, but was similarly restrictive to fat mass recovery when body mass stabilized at the post-deprivation plateau. This suggests that leptin administration during weight-loss maintenance may be an effective hormonal approach toward lasting body fat reduction.

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Effect of leptin-replacement therapy on acanthosis nigricans in congenital generalized lipodystrophy

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Context: Patients with lipodystrophy have severe insulin resistance and often suffer from acanthosis nigricans (AN). Although it has been reported that leptin-replacement therapy effectively improves metabolic abnormalities in lipodystrophy, the effect of leptin on AN is not fully understood.

Objective: The aim of this study is to investigate the effect of leptin-replacement therapy on AN in patients with lipodystrophy.

Patients and Intervention: Leptin-replacement therapy was performed in two patients with congenital generalized lipodystrophy (CGL) due to seipin mutation for 24 months.

Main Outcome Measures: Changes of glucose and lipid metabolism, serum insulin-like growth factor binding protein (IGFBP)-1 and IGFBP-2 levels and skin findings were evaluated.

Results: Both of patients showed severe insulin resistance, hyperinsulinemia and AN. After the initiation of leptin-replacement therapy, plasma insulin levels were immediately decreased accompanied by the improvement of insulin sensitivity. Pigmentations over the neck, axilla, cubital fossa and trunk were gradually reduced. In one patient, they were almost disappeared after 24 months. During this time, increase of IGFBP-1 and IGFBP-2 levels was observed.

Conclusions: Leptin-replacement therapy improved AN accompanied by decrease of plasma insulin and increase of serum IGFBPs levels. Our findings suggest the involvement of not only insulin but also IGF system in the effect of leptin on AN.

The human lipodystrophy gene product, seipin plays physiological roles in the brain development and spermatogenesis in addition to the adipogenesis

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Berardinelli-Seip congenital lipodystrophy (BSCL) is a disease characterized by a near total lack of adipose tissue from birth. BSCL patients frequently develop severe insulin resistance, hypertriglyceridemia, and fatty liver. Among known BSCLs, BSCL2 is the most common but most severe variety. However, the molecular function of seipin, a protein encoded by *BSCL2* remains unclear. *BSCL2* mRNA is highly expressed in the brain and testis in addition to the adipose tissue in human. BSCL2 patients often exhibit mild mental retardation, suggesting physiological roles of seipin in non-adipose tissues. Since tissue-specific *BSCL2* mRNA expression pattern is different between mouse and human but is similar between rat and human, we generated a *Bscl2*/seipin knockout (SKO) rat using the method with ENU (*N*-ethyl-*N*-nitrosourea) mutagenesis. SKO rat showed impairment of spatial working memory with reduction of whole brain weight and azoospermia in addition to generalized lipodystrophy. We therefore analyzed brain volume and semen in human BSCL2 patients. We will report here the physiological role of seipin in the brain and testis in addition to the white adipose tissue. SKO rat provided us a powerful tool for studying the pathophysiological roles of seipin.

Hematopoietic Cells Define Sex Differences in Obesity Induced Inflammation

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Background: Women of reproductive age are protected from metabolic disease compared to post-menopausal women and males. Most murine studies are skewed towards the use of male mice to study obesity-induced metabolic dysfunction because of a similar protection in female mice. **Objective:** To understand if sex differences in obesity-induced inflammation contributes to differences in metabolic disease risk.

Design/Methods: Male and female C57Bl/6J mice were fed a high fat diet (HFD) for 6 weeks or 16 weeks and assessed for glucose metabolism and leukocyte activation in bone marrow, blood, and adipose tissue. Competitive bone marrow experiments using male and female bone marrow were performed to assess differences between sexes in myeloid responses to obesity. Colony forming unit (CFU) assays were used to assess progenitor capacity to produce myeloid leukocytes from male and female bone marrow. Bone marrow derived cell culture systems were used to detail inflammatory profiles of male and female mice marrow cells through qPCR. **Results**: With both short term and long term HFD, male mice demonstrated increased weight gain and $CD11c^+$ adipose tissue macrophage content compared to female mice despite similar degree of adipocyte hypertrophy. Male mice were noted to have significant impairments in glucose tolerance compared to females. Competitive bone marrow transplant studies demonstrated that obesity induced a preferential contribution of male hematopoietic cells to circulating leukocytes and adipose tissue macrophages compared to female cells independent of the sex of the recipient. CFU assay investigations showed that male marrow was able to produce more granulocyte and macrophage colonies after fatty acid stimulation and after HFD exposure compared to female marrow. **Conclusion**: Sex differences in obesity-induced leukocyte activation are due to cell intrinsic differences in hematopoietic cell activation in response to obesogenic cues.

Disruption of Insulin Receptor Signaling in the Pituitary Gland Alters Peripheral Glucose Metabolism and Adiposity in Male Mice

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Introduction: Individuals with excess fat (obesity) or decreased fat (lipodystrophy) have common clinical features including insulin resistance, dyslipidemia, and steatohepatitis. Therefore, a spectrum of changes in adipose tissue may be regulated by similar mechanisms that contribute to the pathophysiology of insulin resistance and diabetes. Transgenic mouse models of lipodystrophy and insulin resistance provide critical research tools to identify new genes and/or signaling pathways that may play an important role in the pathophysiology of these disorders.

Objective: To disrupt insulin receptor signaling in the pituitary gland of mice and examine effects on body weight, peripheral glucose metabolism, and adiposity.

Methods: Pituitary insulin receptor knockout mice (PitIRKO) were generated using the Cre/lox system. Wild-type mice and PitIRKO mice were fed a control diet or high-fat diet for 16 weeks, and body weight was measured at 4-week intervals. Tissues were isolated from mice to prepare whole cell extracts and RNA for Western blot analysis and real-time PCR analysis, respectively. Intraperitoneal glucose and insulin tolerance tests were performed in mice on control and high-fat diets. Tissues (heart, liver, kidney, and adipose depots) were isolated from male mice and weighed. Histological analysis of adipose tissues was also performed and the Cell Profiler software was used to determine adipocyte cell size.

Results: Wild-type and PitIRKO female mice showed comparable changes in body weight on both control and high-fat diets. In contrast, PitIRKO male mice had a 12% to 16% decrease in weight gain compared to wild-type male mice that was independent of changes in food consumption or pituitary hormone gene expression. Wild-type and PitIRKO female mice had normal glucose tolerance and responses to exogenous insulin. In contrast, PitIRKO male mice on a high-fat diet developed fasting hyperglycemia with more severe resistance to exogenous insulin compared to wild-type male mice on a high-fat diet. Further investigation showed that changes in body weight observed in PitIRKO male mice correlated with decreased adiposity. Adipose tissue isolated from PitIRKO male mice also displayed heterogeneity in cell size and showed a significant increase in cells with a smaller diameter compared to adipose tissue isolated from wild-type male mice.

Conclusions: Disruption of insulin receptor signaling in the pituitary gland of male mice impairs weight gain and glucose metabolism secondary to decreased adiposity; and thus provides a new mouse model of lipodystrophic diabetes suggesting a unique link between the pituitary gland and adipose tissue.

Absence of oocyte glycogen synthase kinase 3 during late oogenesis and the peri-conception period does not alter fertility but negatively influences offspring health through cardiovascular defects

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Glycogen synthase kinase-3 (Gsk3) is a constitutively active serine threonine kinase with i) two isoforms (Gsk3a and Gsk3b) having unique and overlapping functions, ii) multiple molecular intracellular mechanisms involving phosphorylation of diverse substrates, and iii) implications in pathogenesis of many diseases. Insulin causes inactivation of Gsk3 and mammalian oocytes have a functional insulin-signaling pathway whereby prolonged elevated insulin during follicle/oocyte development causes altered oocyte chromatin remodeling. Periconceptional diabetes and chronic hyperinsulinemia are associated with congenital malformations and onset of adult diseases of cardiovascular origin. Objectives were to produce transgenic mice that recapitulated the hyperinsulinemic state with reduced or no oocyte Gsk3 activity during late oogenesis and determine effects on fertility, fetal development, and offspring health. Whole body Gsk3a and oocyte specific Gsk3b knockout mice (oGsk3a-/-b-/-) were generated. Reproductive and offspring developmental outcomes of oGsk3a-/-b-/- were compared to whole body Gsk3a knockout mice (Gsk3a-/-bf/f) outcomes with Student's t test or Mann-Whitney's U test. Eight weeks old Gsk3a-/-bf/f and oGsk3a-/-b-/- females were mated with wild type FBV-NJ males. Age at first conception [Gsk3a-/-bf/f (n=4): 66±9 d; and oGsk3a-/-b-/- (n=8): 77±8 d; p=0.4] and primiparous litter size [Gsk3a-/-bf/f (n=4): 10±1 pups; and oGsk3a-/-b-/- (n=8): 9±1 pups; p=0.4] were similar between genotypes. Time required to achieve pregnancy following post-pubertal female placement with males [Gsk3a-/-bf/f (n=8): median= 0 d, first quartile (Q1)= 0 d (Q1) and third quartile (Q3)= 3.5 d; oGsk3a-/-b-/- (n=14): median= 0.25 d, Q1= 2.5 d and Q3= 7d; p=0.2] and multiparous litter size [Gsk3a-/-bf/f (n=13 litters): 9±1 pups; and oGsk3a-/-b-/- (n=18 litters): 8±1 pups; p=0.2] were comparable between genotypes. However, 24 hours death rate was significantly higher in litters from oGsk3a-/-b-/- females [(n=18 litters) median: 60.3%, Q1: 43% and Q3: 93.7%] than in those from Gsk3a-/-bf/f females [(n=13 litters) median: 0%, Q1: 0% and Q3: 11%; p<0.001]. Histopathology findings in oGsk3a-/-b-/- female-derived pups were severe atrial and great pulmonary vessels dilation, ischemic nephrosis, liver congestion, and atelectasis, yet not observed in Gsk3a-/-bf/f female-derived pups. Ventricle length was similar between pups derived from both genotypes; yet ventricular width was larger in oGsk3a-/-b-/- female-derived pups [(n=5) 2.6±0.1 mm] than in Gsk3a-/-bf/f female-derived pups [(n=5) 2.1±0.1 mm; p=0.02]. Atrial length [Gsk3a-/-bf/f (n=3): 1.1±0.2 mm and oGsk3a-/-b-/- (n=4): 3.3± 0.2mm; p=0.001)] and atrial width [Gsk3a-/-bf/f (n=3): 1.2±0.2 mm and oGsk3a-/-b-/- (n=4): 3.3± 0.1mm; p=0.002)] were different between genotypes. Cardiomyocyte size was similar between groups [Gsk3a-/-bf/f (n=5)=79±6.4 µm2 and oGsk3a-/-b-/- (n=5)=95±6.4 µm2; p=0.1]; however, cardiomyocyte number/area was greater in pups derived from oGsk3a-/-b-/- females (n=4; 8.6±0.4 nuclei/100 µm2) than from Gsk3a-/-bf/f (n=5; 7±0.2 nuclei/100 µm2; p=0.03). Absence of oocyte Gsk3 in the periconceptional period does not alter fertility yet causes offspring cardiac hyperplasia, cardiovascular defects, and significant neonatal death. These results support a developmental mechanism by which periconceptional hyperinsulinemia actions at the oocyte can impact offspring cardiovascular development and function.

The Roles of CD36 and CD47 in Thrombospondin1-Dependent Obesity and Diabetes

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Thrombospondin-1 (THBS1 or TSP-1) plays a major role in high-fat diet induced obesity, insulin resistance, and muscle fibrosis (Inoue et al., *Endocrinology 2013*). CD36 and CD47 are the downstream targets of thrombospondin-1. Using *Cd36* and *Cd47* knockout mouse models, we aimed to determine whether CD36, CD47, or both together mediates THBS1-dependent regulation of obesity and diabetes. [Methods and Results] Eight-week-old male C57BL/6J mice (*WT*) and age- and sex-matched *Cd36*$^{-/-}$ (*Cd36KO*) or *Cd47*$^{-/-}$ (*Cd47KO*) mice were fed low-fat chow diet (LFD), short-term 45% high-fat diet (HFD) (3 weeks), or long-term 45% HFD (6–8 weeks). On LFD, no significant difference in weight was observed between *WT* and *Cd36KO* mice (WT 24.9 ± 0.4 g, KO 24.1 ± 0.5 g). During 3-week-HFD, however, *WT* mice gained 17% of the starting weight, whereas *Cd36KO* gained only 6%. Oxygen consumption — VO_2 (ml/kg lean body mass/hr), respiratory exchange ratio (RER), or total physical activity, during 3-week-HFD was not different between *WT* and *Cd36KO* mice. On the other hand, *Cd47KO* mice displayed no significant difference in weight compared to age- and sex-matched *WT* mice on either LFD or HFD. Consistent with the weight reduction observed, the fat pads isolated from *Cd36KO* mice weighed 40% less relative to those from *WT* mice; however, the fat pads from *Cd47KO* mice weighed the same as those from *WT* mice. *WT* mice developed fasting hyperglycemia and impaired glucose tolerance after 8 weeks of HFD. *Cd36KO* mice displayed significantly lower fasting blood glucose and insulin levels as well as significantly better glucose metabolism (fasting glucose, *WT* 261 ± 14 mg/dL vs. *Cd36KO* 181 ± 9 mg/dL; fasting insulin, 56 ± 7 mU/L vs. 15 ± 3 mU/L). On the other hand, after 6 weeks of HFD, *Cd47KO* mice displayed significantly higher fasting glucose as well as elevated peak and 2 hour glucose levels during I.P. glucose tolerance test (fasting, *WT* 106 ± 5 mg/dL vs. *Cd47KO* 132 ± 5 mg/dL; at 15 minutes, 166 ± 6 vs. 232 ± 9; at 2 hour, 97 ± 10 vs. 130 ± 4).

[Conclusion] THBS1 exerts pleiotropic effects on multiple target organs. Our study suggests that the loss of *Cd36* is beneficial for obesity and diabetes, whereas the loss of *Cd47* leads to the significant impairment of glucose metabolism while exerting a minimal effect on diet-induced weight gain. These results suggest the presence of complex interplay between CD36 and CD47 as the effectors of THBS1 in the pathogenesis of obesity and diabetes.

Active Self-Microencapsulation of Leptin in Poly(lactic-co-glycolic acid) Microspheres

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One of the current treatments for lipodystrophy patients includes a daily subcutaneous injection of the protein leptin to decrease triglyceride levels and improve insulin levels; however, daily injections often lead to poor patient compliance due to the need for multiple, possibly painful, injections. The use of the synthetic polymer poly(lactic-*co*-glycolic acid) (PLGA) for controlled release of drugs is promising because of its biocompatible and biodegradable nature and PLGA is in use in over a dozen FDA approved controlled-release products. PLGA microspheres for controlled release of drugs are ideal because they allow for easier delivery of low solubility and poor bioavailability drugs, such as peptides and proteins, and may reduce the number of injections needed by patients. Injectable self-healing microspheres of PLGA containing high molecular weight dextran sulfate (HDS) as a trapping agent were used to encapsulate human recombinant methionyl leptin from aqueous solution. The overall goal of these studies is to achieve high loading and encapsulation efficiency of leptin into microspheres prepared by a novel aqueous encapsulation method and then slowly release stable protein over multiple weeks. Drug-free microspheres of ester terminated 50:50 PLGA were formulated using a water-in-oil-in-water (w/o/w) double emulsion solvent evaporation method and sieved to collect microspheres of size 20-90 μm, suitable for subcutaneous injection. The basic salt, zinc carbonate, was added to the inner water phase as a modulator of microsphere pH during PLGA degradation and an osmotic modulator to facilitate continuous leptin release *in vitro*. Active encapsulation of leptin, using the trapping agent HDS, was performed by incubating 10 mg of porous microspheres in 250 μl leptin loading solution (2mg/ml leptin in 10 mM sodium acetate) in a water bath at 25^{o}C for 48 h. Loaded microspheres were then incubated above the hydrated PLGA glass transition temperature at 43^{o}C with mild agitation for 50 h to allow for microsphere pore healing. The amount of protein encapsulated in the polymer was determined using high performance liquid chromatography (HPLC) analysis of loading solution remaining after incubation to determine leptin mass loss from the initial loading solution. Surface morphology and size of microspheres before and after leptin loading was observed by scanning electron microscopy. *In vitro* release of leptin from microspheres was analyzed in phosphate buffered saline + 0.02% Tween 80 (PBST, pH 7) at 37^{o}C; release media was completely removed and replaced at specific time points and analyzed by HPLC to determine the concentration of leptin present in release media. Initial loading studies exhibited successful encapsulation of leptin (3.65 ± 0.1% w/w loading; 72 ± 2% encapsulation efficiency; mean ± SEM (n=3)) and sustained release over 3 weeks. Future work on this project will be done to improve the loading and encapsulation efficiency and to optimize stability and release of the protein from the self-healing PLGA microspheres.

Clinical Features and Metabolic Derangements in Acquired Generalized Lipodystrophy (AGL) and Acquired Partial Lipodystrophy (APL)

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Introduction: AGL and APL are rare types of lipodystrophies with loss of fat in most patients due to autoimmune mechanisms. Patients with AGL lose subcutaneous (sc) fat from all over the body, while APL patients lose sc fat mainly from the face, neck, upper extremities and upper trunk while the abdomen and lower extremities are spared. Both AGL and APL are markedly heterogeneous in clinical presentation and there is paucity of data regarding the clinical features, metabolic complications and natural history. Therefore, we report demographic data and prevalence of other morbidities and metabolic complications in patients from the Lipodystrophy Registry at UT Southwestern from 1993 to date.

Results:

	AGL	n	APL	n
Total number of patients	65		80	
Male/ Female ratio	1:2.5	65	1:6.7	77
Caucasian/ Others	43/ 4	47	59/1	60
Age (y) **	14 (1.5-68)	65	29.5 (6-67)	74
Age of onset (y) **	4 (0.3-16)	25	7 (3-35)	45
BMI (kg/m^2) *	18 ± 3	24	21.6 ± 4	30
History of Diabetes mellitus (%)	21 (55.3%)	38	6 (10.3%)	58
Hypertension (%)	10 (31.3%)	32	14 (25.9%)	54
Heart Disease (%)	5 (15.6%)	32	2 (3.9%)	51
Kidney problems (%)	2 (7.4%)	27	11 (20.4%)	54
Leptin levels (ng/mL) *	3.3 ± 3.5	16	5.8± 2.7	20
HbA1c (%)*	6.1 ± 1.9	26	5.3 ±0.5	31
Fasting Glucose (mg/dL) *	111.1 ± 52.3	33	85.7±29.4	41
Fasting Triglycerides (mg/dL) **	325 (80-1418)	33	109 (36-490)	42

* Values are mean ± SD ** Values are median with minimum and maximum values

While both AGL and APL are more common in females, APL is particularly so with M:F ratio of 1:6.7. Both disorders are predominantly observed in Caucasians. Median age of onset of fat loss in AGL was 4 years as compared to 7 years in APL. Diabetes affects more than half of patients with AGL, but only 10% of patients with APL. Serum triglyceride concentrations were also markedly high and serum leptin levels markedly low in AGL patients. On the other hand, 20% of APL patients had renal disease, membranoproliferative glomerulonephritis (MPGN) or proteinuria, likely due to circulating autoantibody, C3 nephritic factor. One APL patient is on hemodialysis and another received renal transplantation. One patient with AGL died of hepatocellular carcinoma and another had skin cancer. Breast cancer was diagnosed in one patient with APL.

Conclusion:
We conclude that AGL patients are more predisposed to metabolic complications such as diabetes and hypertriglyceridemia. Hypoleptinemia may contribute to pathogenesis of metabolic derangements in AGL patients. The major cause of morbidity in APL patients is renal failure.

Clinical Features and Metabolic Derangements in Congenital Generalized Lipodystrophy (CGL)

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Introduction: There are 4 distinct subtypes of CGL: CGL1 with *AGPAT2* mutations, CGL2 with *BSCL2* mutations, CGL3 with *CAV1* mutation *and CGL4 with PTRF* mutations. There is paucity of data on phenotypic differences between the various subtypes, especially related to their metabolic complications. Therefore, we report demographic data and prevalence of other morbidities and metabolic complications in patients from the Lipodystrophy Registry at UTSW ascertained from 1986 till date.

Results: Of a total of 124 CGL pedigrees, 69 have CGL1, 36 have CGL2 and 3 have CGL4. None of our patients has *CAV1* mutation. Sixteen pedigrees remain unexplained and suggest further genetic heterogeneity and additional loci for CGL.

	CGL1 (*AGPAT2*)	**n**	**CGL2 (*BSCL2*)**	**n**	**CGL4 (*PTRF*)**	**n**
n (F/M)	88(62/26)		45 (22/23)		5 (3/2)	
Race Caucasian African American Asians/PacIs Native Americans Not reported	 27 31 5 2 23	88	 21 0 10 0 14	45	 5 0 0 0 0	5
Age at ascertainment (y) mean ± SD	15.3 ± 13.4	84	11.9 ± 8.7	44	7.4 ± 5.7	5
Diabetes (%)	31 (57.4%)	54	13 (56.5%)	23	0 (0 %)	3
Hypertension (%)	19 (38%)	50	3 (15.8%)	19	0 (0%)	3
Leptin levels (ng/mL)*	0.73 (0.04-3.33)	23	0.3 (0.0-0.7)	14	0.17 (0.07-0.27)	2
Fasting glucose (mg/dL)*	114 (46-581)	35	126 (55-368)	14	87 (86-95)	3
Hemoglobin A1c (%)*	7.2 (4.7-13.8)	27	7.5 (4.9-12.3)	10	5.1 (4.3-5.3)	3
Fasting triglycerides (mg/dL)*	364 (38-4515)	42	319 (60-2430)	20	142 (86-268)	3

N: total number of patients, F: female, M: male, y: years, PacIs: Pacific islanders.
*median (minimum and maximum values)

Conclusions: CGL1 is the most prevalent subtype of CGL, followed by CGL2 and CGL4. Patients of African origin interestingly only have *AGPAT2* mutations, whereas Caucasians, Asians and others can have any subtype. CGL1 is more prevalent in females than males, in contrast to CGL2 and CGL4 which have nearly equal M:F ratio. Marked diabetes and hypertriglyceridemia are seen in CGL1 and CGL2, but not in CGL4. Hypertension may be more prevalent in CGL1 compared to CGL2 and CGL4. Coronary heart disease developed in 3 patients with CGL1, and in 1 patient with CGL2. All CGL4 patients had catecholaminergic polymorphic ventricular tachycardia (CPVT) and had myopathy with elevated creatine kinase levels. Next generation sequencing may reveal additional loci for unexplained CGL patients.

Clinical features and Metabolic Derangements in Familial Partial Lipodystrophy (FPLD)

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FPLD are rare autosomal dominant disorders characterized by the selective loss of body fat from the extremities. To date, 5 distinct subtypes of FPLD are known: type 1 or Kobberling-type (FPLD1) and type 2 or Dunnigan-type (FPLD2) first described as clinical syndromes, and subsequent subtypes were described on the basis of genetic mutations discovered. The molecular basis of FPLD1 is not known. FPLD2, the most common subtype, is due to missense mutations in lamin A/C (*LMNA*) gene. FPLD3 is associated with heterozygous mutations in *PPARG* gene. FLPD4, caused by heterozygous mutations in *PLIN1* gene, has only been reported in three families. A heterozygous mutation in *AKT2* gene was reported in a single family with FPLD5. One patient with autosomal recessive FPLD had a homozygous nonsense mutation in *CIDEC* gene.

There is paucity of data regarding phenotypic and metabolic differences between various types of FPLD. Therefore, we compared demographic data and prevalence of other morbidities and metabolic complications in 378 patients with a clinical diagnosis of FPLD from our Lipodystrophy Registry ascertained from 1990 till date.

	FPLD2 (*LMNA*)	***n***	**FPLD3 (*PPARG*)**	***n***	**FPLDX (Unknown)**	***n***
Number of Patients (F/M)	192/56	248	11/3	14	95/21	116
Race		248		14		116
Caucasians	178 (72%)		13 (93%)		69 (59%)	
Black	14 (6%)		0 (0%)		4 (3%)	
As/PacIs	14 (6%)		0 (0%)		3 (3%)	
Native American	16 (6%)		0 (0%)		5 (4%)	
Not reported	26 (10%)		1 (7%)		35 (30%)	
Mean Age (y)	36.1 ± 16.7	243	34.6 ± 19.6	12	45.0 ± 15.5	110
Age of Onset (y)	18.3 ± 12.2	57	11 y, 42 y	2	16.7 ± 12.7	15
BMI (kg/m^2)	26.3 ± 6.2	212	25.1 ± 4.6	7	32.4 + 7.5	90
Diabetes Mellitus (%)	90 (43.3%)	208	5 (55.6%)	9	54 (71.1%)	76
Hypertension (%)	83 (39.3%)	211	5 (50.0%)	5	42 (54.5%)	77
Coronary Heart Disease (%)	20 (9.9%)	202	1 (14.3%)	7	7 (9.7%)	72
Leptin Level (ng/mL)	3.88 (0.24, 49.2)	127	5.71 (4.9, 15.7)	3	6.73 (0.86, 55.8)	40
HbA1c (%)	6.4 ± 1.8	172	6.4 ± 1.5	6	7.1 ± 1.7	83
Fasting Glucose (mg/dL)	118 ± 57	183	121 ± 50	6	133 ± 63	89
Fasting Triglycerides (mg/dL)	207 (41, 9040)	187	214 (60, 2104)	6	224 (36, 2965)	90

Abbreviations; F, female; M, male; As, Asian; PacIs, Pacific Islanders; BMI, body mass index; Data reported as mean ± SD or median (minimum and maximum values)

All FPLDs are more prevalent in females suggesting that the diagnosis in males may be missed because of subtler changes in phenotype compared to females.FPLD2 was the most prevalent subtype responsible for 65.8% of patients, followed by FPLD3 with 14 patients, but we have so far not observed any FPLD patient with *AKT2*, *PLIN1* or *CIDEC* mutations. The molecular basis of 116 FPLD patients (30.7%) remains unknown. These FPLDX patients are older, have higher BMI, increased prevalence of diabetes mellitus, and have higher HbA1c and fasting glucose levels than patients with FPLD2 and FPLD3. Clinical features and metabolic derangements in FLPD2 and FLPD3 are very similar. Morbidity and mortality in FPLD is mainly from diabetes mellitus and its long-term complications, recurrent pancreatitis secondary to hypertriglyceridemia, long-standing steatosis resulting in cirrhosis, and coronary heart disease. Early recognition of the phenotype is essential to initiate intervention to treat the metabolic derangements frequently seen in these patients.

Clinical Variability of Familial Partial Lipodystrophy Type 2 Caused by *LMNA* R482W Mutation Discovered in 3 Unrelated Families in Moscow Region

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Background: Familial partial lipodystrophy type 2 (FPLD2, Dunnigan variety) is the most common type of inherited partial lipodystrophies. It is characterized by abnormal subcutaneous fat redistribution and different metabolic abnormalities, which intensity may vary. So this condition can be hard to distinguish from common metabolic syndrome or metabolic changes in type 2 diabetes or PCOS. Here we present 3 unrelated families with different clinical manifestations of this disease with same genotype.

Materials and methods: We sequenced 8-12 exons of *LMNA* gene in 10 unrelated patients with FPLD and found heterozygous missense mutation R482W of *LMNA* gene, previously described for FPLD2[*], in 3 patients.

Family 1: A 20 y.o. woman first presented with abnormal subcutaneous fat redistribution, muscular appearance, acanthosis nigricans, history of diabetes mellitus since 18 y.o., with significant insulin resistance (insulin daily dosage up to 200 U and combined therapy with no effect). Despite different therapeutic strategies, glycemic control was poor: HbA1c 15.4% (< 6.5%), glycemic levels during the day 13.0-25.0 mmol/l (3.9-6.1); ALAT 222 U/l (10-40), ASAT 149 U/l (10-40), total cholesterol 452 mg/dl (<175), triglycerides 953 mg/dl (<150), insulin 49 mcm/ml (5-25), leptin 6.4 ng/ml (3.7-11.1). US-scan: hepatic steatosis, hepatomegaly, splenomegaly. Later the disease was genetically confirmed in her youngest sister (8 y.o.) who starts to develop slight fat redistribution (muscular extremities) and Acanthosis nigricans. In last 2 years the patient had 2 spontaneous abortions. The same mutation was found in their father, who has not any obvious signs of fat redistribution and in his 60 y.o. has only mild dyslipidemia and fasting hyperglycemia.

Family 2: A 29 y.o. woman presented with similar changes in appearance as Patient 1 since 13 y.o. Since the age of 18 she had dysmenorrhea due to PCOS, impaired glucose tolerance, non-alcoholic steatohepatitis, mild arterial hypertension. In the age of 26 ovarian wedge resection was performed successfully, and in 28 y.o. patient delivered a healthy baby. During the pregnancy she developed gestational diabetes, controlled with diet and insulin in 3rd trimester. A year after delivery: HbA1c 6.0% (<6.5%), starving glycemia 5.7 mmol/l (3.9-6.1), glycemic level after OGTT 8.1 mmol/l (<7.8); ALAT 35 U/l (10-40), ASAT 31 U/l (10-40), total cholesterol 246 mg/dl (<175), triglycerides 2120 mg/dl (<150), insulin 68.6 mcm/ml (5-25), leptin 3.9 ng/ml (3.7-11.1). US-scan: hepatic steatosis, hepatomegaly. Patient's younger sister (26 y.o.) had the same appearance, fasting hyperglycemia and leptin level 3.2 ng/ml.

Family 3. A 66 y.o. woman presented with abnormal subcutaneous fat redistribution (lack of subcutaneous fat, especially on extremities) and hypermuscular appearance. She was diagnosed with arterial hypertension in the age of 55, dyslipidemia and type 2 diabetes in 60, controlled with OAD (DPP-4 inhibitor + Metformin). She is a mother of a healthy daughter and never had any gynecological problems. Her leptin level was 4.2 ng/ml (3.7-11.1). In family history there were 2 generations of diabetes mellitus and a grandmother with hypermuscular appearance.

Conclusion. In all 3 families, despite the significant clinical differences, we found the same heterozygous missense mutation R482W of *LMNA* gene. Those 3 families demonstrate clinical variability of Dunnigan type FPLD caused by same mutation: from developed typical clinical picture of the syndrome to a very mild form of metabolic syndrome, even inside 1 family. This indicates that many mild forms of FPLD may remain undiagnosed, giving false impression of extreme rareness of this pathology, and careful examination of subcutaneous fat redistribution is needed in all the patients with any component of metabolic syndrome.

*[1]Shackleton S. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. Nature Genet. 2000; 24: 153-156.

Results of body composition study by dual-energy x-ray absorptiometry, using fat mass ratio as primary diagnostic tool in familial partial lipodystrophy.

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Background. Familial partial lipodystrophy (FPLD) is a rare genetic condition associated with different metabolic disorders, like insulin resistant diabetes mellitus, severe dyslipidaemia, hepatic steatosis and cirrhosis, cardiovascular disease and cardiomyopathy, kidney disease. Up to date there are no settled clinical diagnostic criteria, so the diagnosis is usually based on the results of genetic testing, mostly sequencing of *LMNA* gene, associated with Dunnigan syndrome. However, in many cases mutations are not found, which requires additional expensive diagnostic procedures (like fat tissue MRI) and search for new genes, associated with FPLD. Recently, dual-energy x-ray absorptiometry (DXA) was suggested as a tool for FPLD diagnostics, with a cut-off point of trunk/extremities fat mass ratio (FMR) of 1.2.

Objective. The objective of this study was to assess the possibility of FPLD diagnostics by dual energy X-ray absorptiometry (DXA).

Methods. 10 female patients with partial lipodystrophy phenotype and typical metabolic abnormalities and 10 healthy female controls, matched for BMI and age, were studied. All participants had body fat distribution evaluated by DXA “Total body” program (GE Healthcare Lunar iDXA, USA) with FMR assessing. Genetic testing (sequencing of *LMNA*, exons 8-12) was carried out.

Results. DXA results analysis revealed that in all studied patients FMR was significantly higher than cut-off point of 1.2, suggested in previous international studies, and its value was 2.4 ± 0.8, which is typical for FPLD, unlike in control group, where FMR was significantly lower, 0.8 ± 0.3. In 4 patients missense mutation of *LMNA* was found (*R482W*), and so FPLD patients were divided in 2 groups: *LMNA*+ and *LMNA* -. There were no statistically significant differences in FMR values for patients of both groups: 2.36 ± 0.46 for *LMNA*+ and 2.4 ± 0.8 for *LMNA*- ($p < 0.001$). This result suggests that FPLD is present in both study groups and further genetic testing is needed in *LMNA* negative patients.

Conclusion. This study demonstrates the possibility of body fat distribution assessment by DXA, using FMR for initial diagnostics of FPLD.

[1]Valerio CM et al. Diabetol Metab Syndr. 2012 Aug 31;4(1):40. doi: 10.1186/1758-5996-4-40.

The complexity of familial partial lipodystrophy: efforts in identifying causal variants through exome sequencing in a family study

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Familial partial lipodystrophy (FPLD) syndromes may present with reproductive symptoms such as masculinization and menstrual irregularity as well as metabolic complications. We evaluated a 32-year-old woman with severe hirsutism and irregular menses who was referred because of concern about an androgen secreting neoplasm. On physical examination, she had an FPLD2 (Dunnigan's) phenotype. Laboratory evaluation was noteworthy for a number of testosterone levels over 200 ng/dL, fasting glucose 114 mg/dL and postchallenge glucose 234 mg/dL. Her total triglyceride levels and liver function tests were normal. Despite our presumptive diagnosis of FPLD2, her referring physician proceeded with ovarian exploration and bilateral ovarian wedge resection. The pathology showed ovarian stromal hyperthecosis. After surgery, she lost weight and had resumption of regular menses. Subsequently, we evaluated her parents. Her father had type 2 diabetes, coronary artery disease and features of FPLD2.

We performed next generation exome sequencing on the proband and her parents. Sequencing was performed on the Illumina platform at BGI and results were aligned using BWA with build 37 as the reference genome. The standard workflow available through the Genome Analysis Toolkit (GATK) was utilized to prepare analysis-ready variants combining the trio family and annotated using ANNOVAR. *In silico* analyses yielded 19,329 quality variants with exonic gene locations and called in all individuals. Of these, 25 nonsynonymous variants were found to have a paternal autosomal dominant mode of inheritance (MAF<0.01) and 9 nonsynonymous variants with an autosomal recessive mode of inheritance (MAF<0.05) including a deleterious SNV within *ACOXL*, a gene involved in lipid metabolism. A candidate gene approach was used to evaluate variants within genes related to adipogenesis and previously known FPLD-associated genes (*AKT1, AKT2, APOE, CAV1-3, CD36, CEBPA, CEBPB, CIDEC, DGAT1, GSK3B, KLF5, KLF15, LMNA, LPIN1, LPIN2, LPL, LXR, PLIN1, PLIN2, PPARG, PTRF, SIRT1* and *SREBF1*).

The patient and her parents were heterozygous for a variant within *LMNA*, rs4641 (MAF=0.23). This common SNV, located at the exon 10 splice site region, has been previously shown to lower transcript levels of lamin A and C and may contribute to the FPLD phenotype. The proband and father were also heterozygous for a missense variant within *CAV2*, rs8940 (MAF=0.15). The father was found to have a pathogenic missense variant within *CAV3*, rs72546668 (MAF=0.01), which has been previously shown to be associated with dilated cardiomyopathy, hyperCKemia, limb girdle muscular dystrophy and rippling muscle disease. Collectively, our analyses have revealed variants that may be contributing to the proband's and father's phenotypes. However, given that these variants are relatively common, we expect that there are additional variants contributing to their rare phenotypes. Thus, these unknown variants may map to yet unidentified FPLD genes and/or noncoding regulatory elements.

Metreleptin treatment in acquired generalized lipodystrophy: consistent metabolic effects in three patients presenting with distinct autoimmune conditions.

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Background: Acquired generalized lipodystrophy (AGL) is a rare heterogeneous disorder characterized by fat loss, associated with severe insulin resistance, diabetes, dyslipidemia, and leptin deficiency. While metreleptin therapy has been shown to improve metabolic abnormalities in lipodystrophy patients, the effect in AGL patients with active autoimmune diseases warrants further characterization. Between 3/2009 and 9/2014, 3 pediatric patients with AGL and unusual presentations received metreleptin, an experimental medication, in an ongoing open-label expanded access program (sponsored by Amylin Pharmaceuticals, Inc.) at University of Michigan.

Clinical Cases: AGL-1 (9 y, female) presented with severe hypertriglyceridemia, uncontrolled diabetes and hyperphagia associated with active juvenile dermatomyositis. During 5 years of metreleptin treatment, triglycerides decreased from 10,623 mg/dL to a low of 111 mg/dL (n<150 mg/dl), and HbA1c decreased from 9.1% to a low of 6.7% (n<5.8%) while daily insulin dose fluctuated. Functional capacity improved and muscle inflammation (evaluated by extremity MRI) was no longer present at 2, 3 and 5 years while metabolic benefits were sustained.

AGL-2 (16 y, female) presented with difficult to control diabetes and insulin resistance. She had a diagnosis of Graves' disease prior to development of AGL. After 3 years of metreleptin, HbA1c decreased from 10.2% to 5.0%, triglycerides decreased from 1,845 to 253 mg/dL and aminotransferases decreased (ALT 259 to 54 U/L). Despite high anti-GAD autoantibody she was able to discontinue insulin (>300 units/day) as well as pioglitazone and has not reverted back to the diabetic state.

AGL-3 (9 y, male) presented with autoimmune hepatitis and AGL. He did not have diabetes but had hypertriglyceridemia (354 mg/dL), hyperphagia leading to aggressive night-time food-seeking behavior, and markedly abnormal aminotransferases (ALT 419 U/L, n<35 U/L; AST 208 U/L, n<30 U/L). After 3 years of metreleptin, triglycerides decreased to 45 mg/dL and ALT/AST to 84/57 U/L. Importantly, food intake normalized and aggressive behavior resolved.

Clinical Lessons: These cases demonstrated that the presentation of AGL can be quite heterogeneous and associated with diverse autoimmune diseases. Metreleptin therapy resulted in substantial improvements in metabolic abnormalities, liver function tests, and/or hyperphagia without evidence of worsening of the associated autoimmune disease.

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Earlier data-cut previously presented at Endocrine Society in 2012, President's Poster Session.

A case of acquired generalized lipodystrophy and Graves' ophthalmopathy.

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Background: Lipodystrophy syndromes are characterized by loss of adipose tissue (primarily subcutaneous) and are associated with metabolic abnormalities including insulin resistance, hypertriglyceridemia and hepatic steatosis. Patients with acquired generalized lipodystrophy (AGL) may also have autoimmune diseases. A case of a pediatric patient with acquired generalized lipodystrophy (AGL) and typical metabolic complications is presented. Unique to her case is the presence of Graves' disease and ophthalmopathy.

Clinical Case:

A 16-year-old girl with AGL, which was diagnosed at age 11, presented to be treated with recombinant leptin. She had diabetes with marked insulin resistance requiring over 300 units of insulin per day, hypertriglyceridemia and abnormal liver function tests. She also had a history of Graves' disease which was diagnosed at age 6. She received radioiodine ablation treatment and has subsequently received replacement levothyroxine. Her parents had noticed puffiness surrounding her eyes.

Her physical examination was significant for generalized loss of body fat (Image 1) and the presence of clinical exophthalmos (Image 2).

Laboratory studies were significant for a hemoglobin A1C of 10.2% (normal < 6.5%), triglycerides of 1845 mg/dL (normal < 150 mg/dL), ALT of 259 U/L (normal < 35 U/L), AST 145 U/L (normal < 30 U/L), TSH 5.37 mIU/L (normal 0.3-5.5 mIU/L) and TSI of 4.4 (normal < 1.3 TSI index).

An MRI of the orbits with and without contrast was performed which showed asymmetric enlargement and enhancement of the left inferior and left medial rectus muscles and possible mild swelling of the right inferior rectus muscle consistent with Graves' eye disease. Fat in the retro-ocular region appeared largely well preserved despite near total absence of body fat. Due to intermittent nonadherence with levothyroxine she has had elevated TSH for extended periods of time and this is slowly worsening exophthalmos. At some point, she may require orbital decompression and fat tissue may become available for investigations.

Discussion:

The metabolic abnormalities that are associated with lipodystrophy are related to the absence of fat. Further investigation into the pathways leading to preservation of retro-orbital fat in this patient may provide additional insight into the pathophysiology and future treatment of lipodystrophy.

BUS SCHEDULE

Friday, October 17

Indian Trails Coach Buses

Morning
Charter Bus #1 Departure schedule from Sheraton to North Campus Research Center (NCRC)
11:20a, 12:20p, 1:20p, 2:20p, 3:20p, 4:20p
Charter Bus #2 Departure schedule from Sheraton to NCRC
11:40a, 12:40p, 1:40p

Evening
Charter Buses #1 and #2 will arrive at NCRC at 5:30p. One bus will load at a time and will depart at the direction of Conference Services staff. Buses will continue to make trips from NCRC until 7:30p. Bus #2 is released after last trip from NCRC.
Bus #1 will make a trip or two from Sheraton to Courtyard, Holiday Inn South and/or NCRC as needed from 9:30p to 10:30p.

Saturday, October 18

University of Michigan Blue Buses

Morning
Bus #1 Departure schedule from Sheraton to NCRC
6:30a, 7:30a, 8:30a, 9:30a
Bus #2 Departure schedule from Sheraton to NCRC
7:00a, 8:00a, 9:00a, 10:00a

Evening
Buses #1 and #2 will arrive at NCRC at 5:30p. One bus will load at a time and will depart at the direction of Conference Services staff. Buses will continue to make trips from NCRC until 7:30p. Bus #2 is released after last trip from NCRC.
Bus #1 will make a trip or two from Sheraton to Courtyard, Holiday Inn South and/or NCRC as needed from 9:30p to 10:30p.

Sunday, October 19

University of Michigan Blue Buses

Morning
Bus #1 Departure schedule from Sheraton to NCRC
6:00 a, 7:00a, 8:00a, 9:00a, 10:00a
Bus #2 Departure schedule from Sheraton to NCRC
6:30a, 7:30a, 8:30a, 9:30a

Afternoon
Bus #1 Departure schedule from NCRC to South Hotels
11:00a, 12:00p, 1:00p
Bus #2 Departure schedule from NCRC to South Hotels
11:30a, 12:30p, 1:30p

DIRECTIONS FROM NCRC TO SHERATON

Google

Drive 9.8 miles, 11 min

Directions from **North Campus Research Complex** to **Sheraton Ann Arbor Hotel**

North Campus Research Complex
2800 Plymouth Rd, Ann Arbor, MI 48109

Get on **US-23 S**

1.3 mi / 2 min

1. Head **east** on **Plymouth Rd** toward **Huron Pkwy**

0.8 mi

2. Turn **right** to merge onto **US-23 S**

0.4 mi

Continue on **US-23 S**. Take **I-94 W** to **S State St**. Take exit **177** from **I-94 W**

8.2 mi / 8 min

3. Merge onto **US-23 S**

4.9 mi

4. Take exit **35** to merge onto **I-94 W** toward **Chicago**

3.0 mi

5. Take exit **177** for **State St**

0.3 mi

Take **Victors Way** to **Boardwalk Dr**

0.4 mi / 1 min

6. Turn **right** onto **S State St**

338 ft

7. Take the 1st **right** onto **Victors Way**

0.2 mi

8. Turn **left** onto **Boardwalk Dr**
   Destination will be on the left

0.1 mi

Sheraton Ann Arbor Hotel
3200 Boardwalk Dr, Ann Arbor, MI 48108

ıese directions are for planning purposes only. You may find that construction
ɔjects, traffic, weather, or other events may cause conditions to differ from the map
sults, and you should plan your route accordingly. You must obey all signs or
ıtices regarding your route.

Map data ©2014 Google

CONTACT INFORMATION

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Join

ldconnect.org today!

One of the most important steps towards finding effective treatments for lipodystrophy (LD) is to uncover the ways in which the diseases behave, the symptoms that are commonly seen and how those symptoms progress. This requires the collection of as much information as possible about all people affected by LD. LD Connect will serve as that database–the critical link between the patient community and the scientific community.

Join THE LD CONNECT Registry to:

- Tell us about your experience with LD and learn about the experiences with others
- Share information in a program that protects your privacy
- Provide valuable quality-of-life information that can be used to advocate on behalf of the LD community
- Help the research community launch clinical trials and studies We need to hear YOUR VOICE and we hope you will decide to join LD Connect. Every individual who joins makes a vital contribution toward helping all of those affected by lipodystrophy.

Your information may result in future treatments for all types of Lipodystrophy

Lipodystrophy United

Sponsored by : AstraZeneca

Lipodystrophy Connect

Who Can Participate

- Patients
- Family members
- Healthcare providers
- Investigators & researchers
- Stakeholders interested in Lipodystrophy

Who We Are

As its name implies, Lipodystrophy Connect represents the coming together of a wide range of entities and individuals who recognize the value in pooling their combined expertise and information. The Governing Board of Lipodystrophy Connect comes from leaders in the non-profit sector, government agencies, academic institutions and the pharmaceutical industry. Regardless of their individual backgrounds, the thought leaders of Lipodystrophy Connect share a common goal to increase the community's ability to help one another through improved communication, and by doing so, to help the millions of people affected by Lipodystrophy.