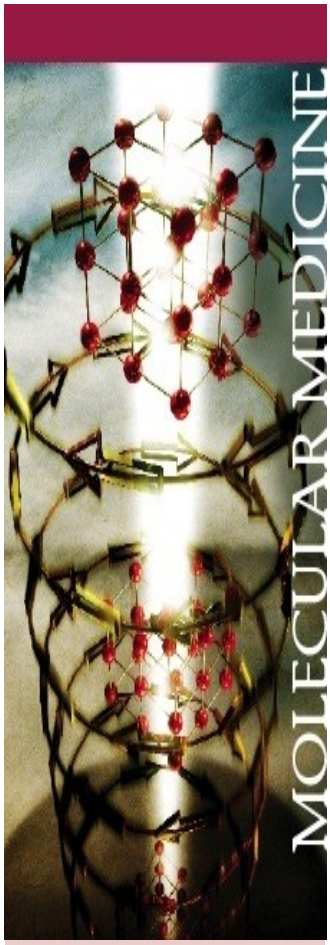


CENTER FOR
MOLECULAR MEDICINE AND GENETICS

August, 2014

# Luca and Pique-Regi Collaborative Labs Produce Novel Results

## Inside this issue:



*Roger Pique-Regi, PhD*

*Francesca Luca, PhD*

What began as a concept between labs of two distinct research fields has quickly turned into a successful, grant-funded practice – and its framework has almost unlimited application potential.

Dr. Francesca Luca and Dr. Roger Pique-Regi (Assistant Professors of Molecular Medicine and Genetics and, respectively, of Obstetrics and Gynecology and of Clinical and Translational Science) have been combining their strengths to form an interdisciplinary research group to get a better molecular understanding of the genetic and environmental determinants of complex traits in humans. As a result of their collaborative philosophy, they were recently awarded a grant from the American Heart Association for "Functional genomics characterization of genetic variation associated with cardiovascular disease" and an R01 grant by the National Institutes of Health for "Functional Characterization of the Genetic and Environmental Determinants of Complex Traits." Dr. Pique-Regi noted that several NIH funding opportunity announcements were specifically looking for the sort of collaboration their labs are engaged in, and that Dr. Luca's focus on an environmental element in their research has likely allowed them to stand out from the pack of applicants. Many of the funding opportunities are requiring applicants to develop novel analytical tools as well, a challenge that Dr. Pique-Regi is eager to embrace.

Dr. Luca's work revolves around the study of population genomics, a field she has been investigating since her graduation from the University of Calabria in 2006 and her post-doctoral experience at the University of Chicago. She is particularly interested in understanding how genotypes interact with environmental exposures in determining an individual's phenotype.

Dr. Pique-Regi's work is more focused on developing computational methods and statistical models. By working together the two labs are designing experiments jointly with new analytical methods. This allows making the results gathering and data analysis from laboratory experiments far more efficient in order to answer the underlying biological questions.

According to Dr. Luca, most data analysis is taken into account only after the experiments have been completed, meaning it may become difficult to answer the original question if the study was not designed properly. Collaboration from the very beginning of a project ensures that this doesn't become a problem later on, and helps give the labs a framework as to how to set up their experiments. There is also the added benefit of having collaborators nearby for any sort of troubleshooting. Dr. Luca said that it was far easier to accomplish things in the lab when the person she needed to talk to was only a few steps away, as opposed to an entirely different laboratory or institution. The interdisciplinary nature of the Center for Molecular Medicine and Genetics fosters such an environment where collaborators of different disciplines can be within arm's reach of each other.

As part of their collaborative group, students and research staff share joint meetings and thus are made familiar with both labs to ensure synergy exists. Also, both Dr. Luca and Dr. Pique-Regi interview each new member that's brought into the labs, so there's a sense of familiarity right from the beginning of their work.

Omar Davis, the lab-manager and senior member of the Luca lab, helped Dr. Luca and Dr. Pique-Regi get started with their experimental plans when they joined the Center, and recently played a key role in developing a new high throughput experimental protocol. However, the collaborative group was re-

Continued on Pg. 4

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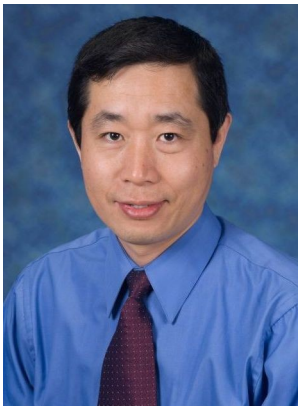
# CMMG Summer Program Gives Undergraduates Intensive Research Experience



*Kezhong Zhang, PhD*

The Center for Molecular Medicine and Genetics offers an opportunity for budding scientists to gain research experience. While they are still undergraduates.

The Summer Undergraduate Research Program (often referred to as SURP) was started in the year 2000. Dr. Kezhong Zhang, Associate Professor of Molecular Medicine and Genetics and of Immunology and Microbiology, is in his second year serving as the director of the program. The program is open to sophomore and junior undergraduate students, and the application process is intensely competitive – for this summer's program the Center received almost 40 applications for only 7 available positions. The pre-requirements for application are a 3.0 GPA, 2 letters of recommendation, a personal statement describing background and research goals, and a curriculum vitae.

Once accepted, undergraduate students can look forward to a truly captivating experience. The 12-week program, running from June through August also includes a $2500 stipend. Once they arrive students are matched with a faculty member commensurate with their previous research experience and studies, then given an intensive training course in the labs. They are assigned to work under a senior lab member, typically a post-doctoral Fellow or Graduate research assistant. At the end of the program students present their research at the Presentation Seminar which is hosted by the School of Medicine and includes SURP participants from other departments; the presentations consist of individual 5-10 minute lectures concerning the research conducted over the summer. However, the most rewarding part of the program is the opportunity to engage in intensive, hands-on research which leaves them with a professional understanding of laboratory research.

However, the benefits of the program don't end in August – for many former students, SURP provides an invaluable platform from which to continue their research. Some recent student achievements include: Jonte Jefferson of Hampton University was accepted to the elite Howard Hughes Medical Institute after working in the lab of Dr. Maik Hüttemann (Associate Professor of Molecular Medicine and Genetics and of Biochemistry & Molecular Biology); Mary Jean Higgins of Lafayette College was recently awarded the prestigious Barry M. Goldwater Scholarship after working in the lab of Dr. Li Li (Professor of Internal Medicine and of Molecular Medicine and Genetics); Nathan Vengalil had his SURP project selected for presentation at the 2014 National Conference in Undergraduate Education (NCUR) at the University of Kentucky after working in the lab of Dr. Derek Wildman (Associate Professor of Molecular Medicine and Genetics and of Obstetrics and Gynecology). In addition, other students have gone on to become professional research assistants and Graduate Research Assistants in the Center for Molecular Medicine and Genetics.

For more information on the SURP, please visit http://genetics.wayne.edu/edunew/surp/past-surp.php.

**Meet the 2014 SURP Students**

Matthew Wexler
Michigan State University, Microbiology
Brandon Duprey
Michigan State University, Human Biology
Alwin David
Michigan State University, Osteopathic Medicine
Sawsan Edriss
Wayne State University, Pre-Medicine
Robert Brice Calco
Kalamazoo College, Undeclared
Gregg Udeh-Ubaka
Wayne State University, Biology
Jamie L. Maurice
Michigan State University, Clinical Lab Science

# Lipovich Presents Research at Gordon Conference

*Leonard Lipovich, PhD*

Wayne State University School of Medicine Faculty Member Leonard Lipovich, PhD, Associate Professor of Molecular Medicine and Genetics and of Neurology, can count himself as being part of the forefront of the field of human genetics and genomics after presenting a talk titled "Primate-specific long non-coding RNA genes regulate cellular states in human disease" at the Gordon Research Conference on Human Genetics and Genomics held at Bryant University, Smithfield, R.I.

The Gordon Conference, held from July 7-11, is a biannual, competitive conference, with attendance limited to those scientists emerging at the forefront of their fields. The conference brings together international leaders in the field of human genetics and genomics to discuss what has been learned and where the field is heading. Dr. Lipovich, presenting his work on non-coding ribonucleic acids, joined speakers from Yale University, Harvard Medical School, the Whitehead Institute at the Massachusetts Institute of Technology, the University of Oxford, England, and others who focus on advancing the study, organization and function of the genome. This includes non-coding regions, new insights into human genetic diversity, and case studies of sequencing approaches applied to both rare and common diseases.

The conference began in the late 1920s when Dr. Neil E. Gordon of Johns Hopkins University recognized the difficulty in establishing effective

Continued on Pg. 4

# Zhang's Lab Discovers A Novel Regulator of Lipid Metabolism

Metabolic syndrome is a common metabolic disorder that includes glucose intolerance and dyslipidemia, and its prevalence has increased dramatically in the past two decades. Patients suffering from metabolic syndrome are at high risk of developing type 2 diabetes, which, in addition to hyperglycemia, is often associated with hypertriglyceridemia. Recent work in the lab of Dr. Ren Zhang, Assistant Professor of Molecular Medicine and Genetics and of Internal Medicine, has identified a novel lipid regulator, named lipasin, which is a potential drug target for treating both dyslipidemia and diabetes.

RNA-seq is a technique that enables detection of novel transcripts and other changes such as single nucleotide variants; it is more sensitive than microarray and thus was used to identify novel nutritionally regulated genes in mice treated with fasting, refeeding or a high-fat diet. "This uncharacterized gene, official symbol being Gm6484, got our attention because it is predominately expressed in liver and fat, and because it is very sensitive to nutritional stimuli," Dr. Zhang said. "Fasting reduces it, and even 10 minutes after feeding, its levels are drastically increased. So we thought it must be doing something important in terms of metabolism." He added, "The protein turns out to be a hormone secreted from the liver. We overexpressed the gene in mouse liver, and serum triglyceride levels were dramatically increased. We named the gene lipasin, because it inhibits lipoprotein lipase activity, and because it is a circulating factor."

Dr. Zhang's project exemplifies how competitive biological research can be. "Because the gene was so new that it did not even have a name, we once thought we were the only lab working on it. But it turned out that at least 4 other groups were also working on this gene, independently, yet without knowledge of each other. We were the first to report its function in triglyceride metabolism. Within a couple of months, all the groups published the data on this gene by focusing on different aspects, and gave the gene many different names, such as RIFL, betatrophin, and Angptl8," he explained.

The betatrophin story, reported by a Harvard group in the journal *Cell*, claims that betatrophin, another name for lipasin, can very potently and specifically stimulate expansion of pancreatic beta cells. This discovery drew significant attention because it can potentially lead to a therapeutic strategy to restore functional insulin-secreting beta cell mass for both type 1 and type 2 diabetes patients.

A logical next step is to examine circulating lipasin levels in patients. In a *Scientific Reports* paper, Dr. Zhang's lab showed that circulating lipasin was increased in human type 2 diabetes and obesity. Dr. Zhang explained that because lipasin overexpression increases triglycerides, this result immediately suggests a potential mechanism for hypertriglyceridemia that is often associated with type 2 diabetes and obesity. In a recent paper published in *Diabetologia*, Dr. Zhang's lab resolved a discrepancy among determined lipasin levels in different studies by pointing out that lipasin undergoes proteolytic regulation. Utilizing multiple ELISAs (a test that uses antibodies and color change to identify substances) his lab is able to detect different lipasin fragments.

*Ren Zhang, PhD*

"Small molecule inhibitors of lipasin are promising triglyceride-lowering drugs, and elucidation of lipasin functions will significantly improve our understanding on how triglycerides are metabolized in humans," Dr. Zhang said.

The lipasin story also provides to the observer a window on how science sometimes progresses, with multiple discoveries going on in parallel and then merging into a more complete picture.

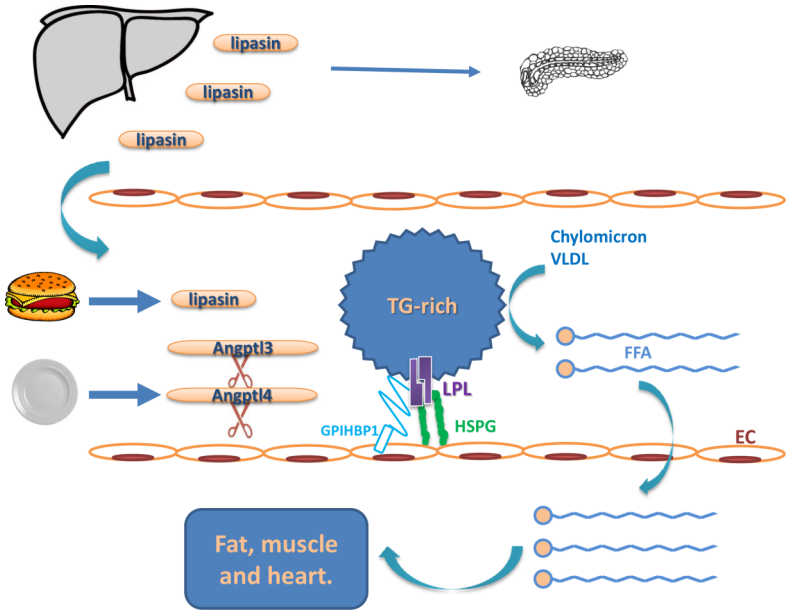



*Fig. 1. Roles of lipasin in regulating triglyceride metabolism and in promoting pancreatic beta-cell proliferation. Lipasin is secreted from the liver into the circulation, and its expression is dramatically induced by food intake and suppressed by fasting. Lipasin, Angptl3 and Angptl4 are coordinated to regulate lipid metabolism by inhibiting the activity of lipoprotein lipase (LPL) at different physiological conditions (feeding vs. fasting) and pathological conditions (lean vs. obesity). Angptl3, angiopoietin-like 3; Angptl4, angiopoietin-like 4; EC, endothelial cell; GPIHBP1, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1; FFA, free fatty acid; HSPG, heparan sulfate proteoglycans; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very low-density lipoprotein.*

### Lab Collaboration, Continued from Pg. 1

cently expanded with new students and staff. Greg Moyerbrailean earned recognition as a first year rotational student for having presented posters at the Cold Springs Harbor Biology of Genomes meeting, and now Dr. Luca and Dr. Pique-Regi are jointly his PhD advisors. Chris Harvey, with an MS in Biostatistics from the University of Michigan, brings his data analysis expertise to the group. Adnan Alazizi, MPS from the University of Toledo, recently joined the group to replace Omar Davis as lab-manager, while Elizabeth Doman was recently hired as a Research Assistant after having spent two summers in the Luca Lab as a SURP student. Finally the group is completed by Jamie Maurice, a current SURP student, by Rich Soliven and Jet Mair, both Research Assistants in the Luca Lab. Donovan Watza, who was a Research Assistant in the Luca Lab, has joined the MD-PhD program at the WSU School of Medicine.

Currently, Drs. Luca and Pique-Regi are preparing to publish the research they've accomplished thus far. Greg Moyerbrailean is the first author of a recently submitted paper that will release a comprehensive catalog of genetic variants predicted to affect gene regulation. Meanwhile, they are also working hard to bring together investigators interested in functional and computational genomics across campus and from neighbor research institutions. They are organizing monthly meetings of the Functional & Computational Discussion Group attended by PIs, Post-Docs and students, with the goal of fostering collaborations.

### Lipovich Presents, Continued from Pg. 2

lines of communication between scientists in the same field, as well as those in more interdisciplinary research areas. Since then it has promoted discussions and the free exchange of ideas at the outer research limits of the biological, chemical and physical sciences. Scientists with common professional interests come together for a week of intense discussion and examination of the most advanced aspects of their field.

In addition to his presentation at the Gordon Conference, it has been an eventful year for Dr. Lipovich. In March, he co-authored a paper in *Nature*, "A Promoter Level Mammalian Expression Atlas," with the FANTOM group in Japan. In June, he was invited to lecture for the inauguration of the new computational biology center at KAUST in Saudi Arabia. Dr. Lipovich is also the sole faculty member from Wayne State to be participating in all three major international consortia that succeeded the original human genome project: ENCODE, FANTOM, and CHARGE. Dr. Lipovich's office can be found at 3228 Scott Hall.

# New Faculty Profile: Jeffrey Tseng, PhD

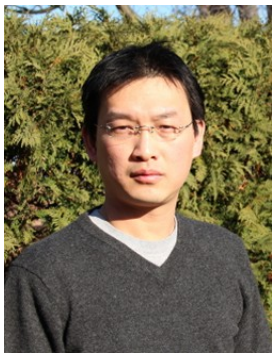
Jeffrey Tseng, PhD, Assistant Professor of Molecular Medicine and Genetics and of Biochemistry and Molecular Biology, joined the Center in October of 2013. Coming to Wayne State by way of the University of Chicago, Dr. Tseng's research revolves around the analysis of the structural geometry of protein surfaces, and how those structures may provide insights into both the molecular function and structural evolution of proteins.

Dr. Tseng's main research goal is to develop methods for studying the structure and function of proteins. There are four steps to his approach which is called computational structural biology: First, he has been developing computational geometric methods to characterize protein binding (functional) surfaces, which are the local spatial regions that actually perform the biological functions. Second, utilizing his expertise in identification and characterization of protein functional surfaces he seeks to collaborate with research groups who are interested in directed protein evolution and drug discovery. In doing so, he has developed a geometric strategy for identifying the binding surface of a bound structure: splitpocket, a pure and analytical geometric concept for identifying the binding surfaces of proteins to reveal their spatial patterns by which duplicated proteins have evolved to new functions. Third, to measure the evolutionary pressure on functionally important residues, he has applied phylogenetic methods to assess the physiochemical constraints that have been acting on binding residues and folding nuclei during evolution. Fourth, he has worked on a medically important but highly-challenging subject: identification of non-synonymous changes that may have deleterious effects on human health.

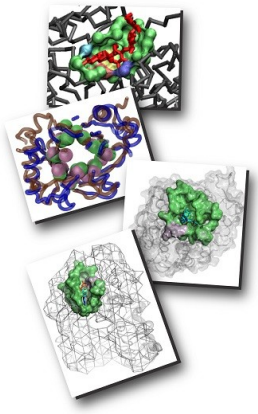
*Cluster orchards for high performance computing and simulations*

After almost two years of getting settled and set up, Dr. Tseng says that he has found his experience in the Center for Molecular Medicine and Genetics to be highly rewarding, both professionally and personally. In particular, he notes how the disparate research conducted by his colleagues at the Center allows for insights into his own research.

Dr. Tseng's office is located 3206 Scott Hall, and his references and research can be accessible at http://pocket.med.wayne.edu/ytseng/.



*Jeffrey Tseng, PhD*



# Faculty Accomplishments

## Gow, Hüttemann and Lipovich Win SOM Award

**2013 School of Medicine Research Excellence Award recipients:**

Alexander Gow, PhD, Professor of Molecular Medicine and Genetics and of Pediatrics and of Neurology

Maik Hüttemann, PhD, Associate Professor of Molecular Medicine and Genetics and of Biochemistry and Molecular Biology

Leonard Lipovich, PhD, Associate Professor of Molecular Medicine and Genetics and of Neurology

## Trepanier Receives President's Award

Angela Trepanier, MS, CGC, Assistant Professor of Molecular Medicine and Genetics and Director of the CMMG Genetic Counseling MS Program was awarded the 2014 Wayne State University President's Award in Teaching.

## Kamholz Appointed to Associate Director

John Kamholz, MD, PhD, Professor of Molecular Medicine and Genetics and of Neurology, has been a long-time member of the CMMG Faculty and we are pleased to announce that he will be serving as Associate Director of the Center. Dr. Kamholz is a physician-scientist who has extensive experience in both laboratory and clinical studies, and also with clinical trials. This experience will be invaluable to the Center as we continue to make translational science a key mission.

# 2013-2014 Seminar Series

**The Center for Molecular Medicine and Genetics hosts a bi-monthly seminar series each academic year. The series features renowned scholars from institutions around the nation and the world. Guest speakers who participated in 2013-2014 are listed below.**

Luis Barreiro, PhD
Assistant Professor
University of Montreal

Antonios Barrientos, PhD
Associate Professor
University of Miami

Ben Brown, PhD
Staff Scientist
Lawrence Berkeley Nat. Laboratory

Donald Conrad, PhD
Assistant Professor
Washington University

Brian Ference, MD, MPhil, MSc, FACC
Director, Cardiovasular Genomic Research Center and Assistant Professor
Wayne State University

Andrey Kozlov, PhD
Group Leader
Ludwig Boltzmann Institute, AU

Ann-Hwee Lee, PhD
Associate Professor
Cornell University

Bradford Lowell, MD, PhD
Professor
Harvard University

Lynne Maquat, PhD
J. Lowell Orbison Endowed Chair and Professor
University of Rochester

Christopher Mason, PhD
Assistant Professor
Cornell University

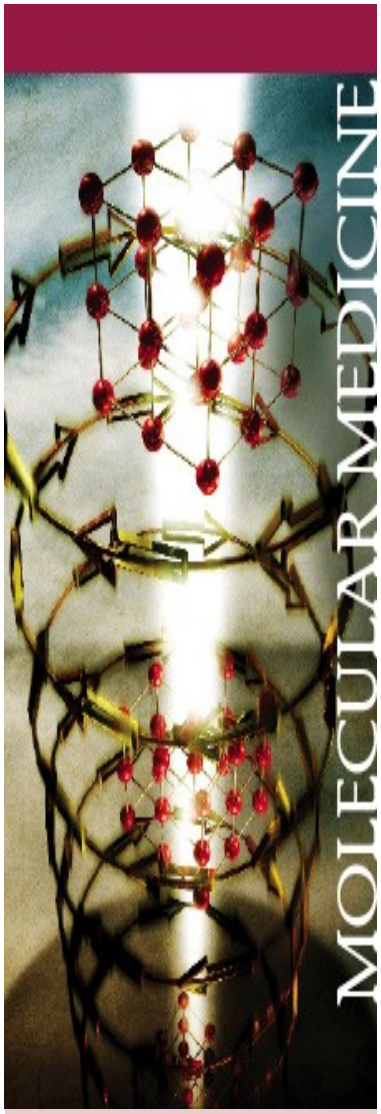
Olivia Merkel, PhD
Assistant Professor
Wayne State University

Carlos Moraes, PhD
Professor and Ester Lichtenstein Endowed Chair
University of Miami

Gabriel Nunez, MD
Paul de Kruif Endowed Professor
University of Michigan

Dennis R. Petersen, PhD
Professor
University of Colorado

Jenny Tung, PhD
Assistant Professor
Duke University

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MS in Genetic Counseling

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Erin Carmany, MS, CGC
Gerald L. Feldman, MD, PhD
Russell L. Finley, Jr., PhD
Alexander Gow, PhD
James Granneman, PhD
Lawrence I. Grossman, PhD
Henry H.Q. Heng, PhD
Maik Hüttemann, PhD
John Kamholz, MD, PhD
Gregory Kapatos, PhD
Markku Kurkinen, PhD
Wayne D. Lancaster, PhD
Leonard Lipovich, PhD
Francesca Luca, PhD
Roger Pique-Regi, PhD
Angela Trepanier, MS, CGC
Jeffrey Tseng, PhD
Monica Uddin, PhD
Jiemei Wang, MD, PhD
Derek Wildman, PhD
Kezhong Zhang, PhD
Ren Zhang, PhD

**Joint Faculty**

Samiran Ghosh, PhD
Stephen A. Krawetz, PhD
Susan Land, PhD
Li Li, PhD
Richard E. Miller, MD
Karli Rosner, MD, PhD
Lobelia Samavati, MD
Michael Tainsky, PhD

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