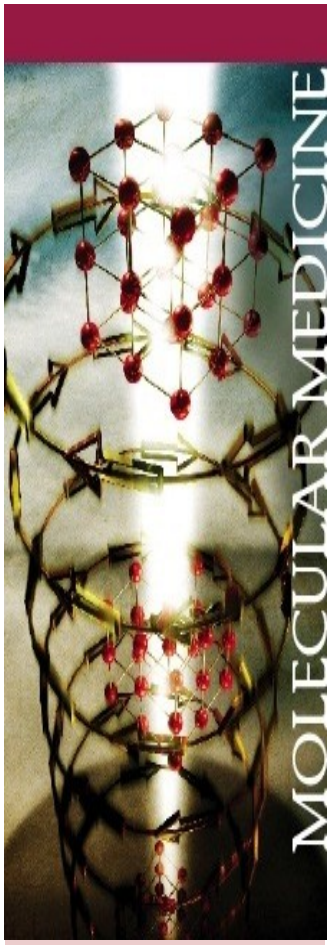

CENTER FOR
MOLECULAR MEDICINE AND GENETICS

December 2014

Leonard Lipovich wins Director's New Innovator Award from National Institutes of Health

The National Institutes of Health has selected Wayne State University School of Medicine researcher Leonard Lipovich, Ph.D., Associate Professor of Molecular Medicine and Genetics and of Neurology, for its coveted Director's New Innovator Award, a five-year, $2.3 million grant he will use from the National Cancer Institute to test a hypothesis that could lead to breakthrough methodologies to improve human health.

Leonard Lipovich, PhD

The project will identify primate-specific long non-coding ribonucleic acids, or lncRNAs, that are functional in cell growth and cell death, within the framework of human estrogen receptor positive breast cancer. The goal of the project, which has broad relevance to other nuclear hormone receptor pathways in human disease, is to reveal the extent to which non-conserved RNA genes contribute to cancer pathogenesis in humans.

Lipovich is the first researcher from Wayne State University to receive the competitive award. The New Innovator Award mechanism was created by the NIH to support exceptionally creative new investigators who propose highly innovative, high-risk projects that have the potential for unusually high impact. Approximately 40 New Innovator awardees are selected each year. The small number of awards, along with the relatively high award amounts and the unconventional nature of the funded research, makes the program considerably more exclusive than the NIH's more common R01 funding mechanism.

The grant award, "Life, Death and Function: The Primate-Specific Long Non-Coding RNA Transcriptome," will test whether evolutionarily young lncRNA genes – present in humans and some or all nonhuman primates, but absent in non-primates – are directly functional in positioning human estrogen receptor alpha positive breast cancer cells along the apoptosis-proliferation axis.

Long non-coding RNA is abundant in human cells. Their genes often lack sequence conservation even between closely related species, in contrast to protein-coding genes, which are highly conserved across even distant evolutionary lineages. Over the past several years, the Lipovich lab has been highlighting the primate-specificity of lncRNAs in diverse disease systems.

Dr. Lipovich pointed out that targeting primate-specific lncRNAs (pslncRNAs) therapeutically should result in fewer side effects than disrupting conserved pathways as is caused by cancer drugs currently in use. For selective chemotherapeutic agents that kill only breast cancer cells but not normal cells, pslncRNAs constitute a promising class of targets. The reason: these RNAs are young and have not yet had the time to deeply embed themselves in conserved protein-based networks over evolutionary time. Drug side effects may be a consequence of perturbing those conserved networks, Dr. Lipovich added.

"This is nothing less than a paradigm shift in cancer biology," Dr. Lipovich said. "Ever since Richard Nixon's lost 'War on Cancer,' proteins – and mouse models – have dominated the study of cancer. Here, we systematically interrogate the contribution of non-protein-coding genes to cancer, with a focus on those that do not even exist in commonly used animal models."

Since joining the School of Medicine faculty in 2007, Dr. Lipovich has been working to build an internationally collaborative, cutting edge research program. He is the only Wayne State faculty member to be selected by The Royal Society to chair one of its International Scientific Meetings, the lncRNA meeting that will take place near London in September, 2015. Dr. Lipovich is a funded co-investigator of ENCODE, or Encyclopedia of DNA Elements, the international consortium that serves as the official successor to the original Human Genome Project. He is also in his second decade of working with the Japan-based Functional Annotation of the Mammalian Genome, or FANTOM project, and this year he joined the CHARGE, or Cohorts for Heart and Aging Research in Genomic Epidemiology consortium, bringing all these major efforts to Wayne State through his laboratory.

"I have been arguing ever since the late 1990s, when I was a graduate student, that primate-specific, non-coding RNA genes are not junk, and

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Inside this issue:

WAYNE STATE UNIVERSITY
SCHOOL OF MEDICINE

GO-GIRL Program Seeks to Diversify Field of Genetic Counseling

Angela Trepanier, MS, CGC

Erin Carmany, MS, CGC

The Center's Genetic Counseling Graduate Program, led by Assistant Professors Angela Trepanier and Erin Carmany, recently hosted Wayne State's GO-GIRL Program. With an overall long-term goal of increasing the diversity of the genetic counseling profession, the Genetic Counseling camp for GO-GIRLS - which saw 60 girls participate - was held on August 5, 2014.

The GO-GIRL program, an acronym for Gaining Options – Girls Investigate Real Life, seeks to increase the competence and confidence of adolescent girls in the areas of mathematics, technology, scientific thinking, and communication by engaging them in experiences that promote an interest in STEM (Science, Technology, Engineering and Mathematics) and build their capacity to pursue STEM related careers.

After an introduction for students previously unfamiliar with the field of genetic counseling, the seminar was composed of two sessions. The first was a "Speed dating" session, in which participants had the opportunity to chat for five minutes with each of six genetic counselors about their jobs, challenging cases, their thoughts about the profession, and the pros and cons of being a genetic counselor. Second, students got to conduct mock genetic counseling sessions, which demonstrated the field in professional practice. Students were assigned to the role of genetic counselor, patient, or support person and were given information about how to play the various roles. Then, under the guidance of a genetic counselor, the students went through the steps of a genetic counseling session - finding out the patients' goals and prior knowledge, taking a family medical history, providing the patient with genetic risk information, and facilitating genetic testing. Participants got to see what it is like to help people make difficult decisions about testing for conditions like hereditary breast and ovarian cancer or Huntington disease and what it is like to be the patient facing such decisions. It was truly an all hands on deck operation—Trepanier, Carmany, Program Instructor Melissa Hicks, Academic Services Officer Michelle Cichon, and the Karmanos Institute's Alicia Salkowski and Robin Gold—were all present and responsible for leading and conducting the sessions, as well as writing scripts for discussion among the students on subjects such as hereditary diseases. Several genetic counseling students participated as well.

Trepanier says she hopes to foster an appreciation for genetic counseling's unique blend of counseling and science. In addition to participating in an intensive, hands-on seminar, female students benefit from interacting with professionals and academic peers in an open, inclusive, and fun atmosphere. Trepanier believes that the only way to eventually diversify the field is to reach out to potential counselors at a young age, so students can learn the intricacies of the field, with the hopes of eventually reaching out themselves and serving their communities as genetic counselors. The collaboration with the School of Education's GO-GIRLS program provided an excellent opportunity to accomplish this goal. The program also serves a Community outreach function for all parties, with the Genetic Counseling program educating and empowering potential students who will in turn educate and empower others in their community, all while highlighting Wayne State University's Genetic Counseling program as a practical and medically important career choice.

The GO-GIRLS program was initially funded through a grant from the National Science Foundation and has received support from the Michigan Department of Education, the RGK Foundation, Wayne State University, and private contributions. The program is currently seeking funding to not only continue the program at Wayne State University but also to expand it to reach participants at additional grade levels. For more information, please contact Wayne State's principal investigator, Dr. Sally Roberts, or visit the program's website at http://gogirls.wayne.edu.

Speakers Scheduled to Date for Winter Seminar Series

February 5, 2015	Charles A. Easley, IV, PhD, Instructor of Cell Biology, Laboratory of Translational Cell Biology, Emory University School of Medicine
Feb 19, 2015	Richard Levy, MD, Professor of Anesthesiology and Pediatrics, Columbia University Medical Center
March 5, 2015	Laurie S. Kaguni, PhD, University Distinguished Professor of Biochemistry and Molecular Biology and Director of the MSU Center for Mitochondrial Science and Medicine, Michigan State University
April 2, 2015	Gene Yeo, PhD, MBA, Associate Professor of Cellular and Molecular Medicine, University of California, San Diego
May 14, 2015	George Perry, PhD, Assistant Professor of Anthropology and Biology, Pennsylvania State University

Hüttemann Lab Branches to Lung Cancer Research

The lab of Maik Hüttemann, Associate Professor of Molecular Medicine and Genetics and of Biochemistry and Molecular Biology, has continued its translational research into lung cancer biomarkers.

Maik Hüttemann, PhD

Dr. Hüttemann first set out to investigate expression levels of the lung-specific mitochondrial gene *COX4i2* with greater accuracy In 2011. This was done in conjunction with detecting the expression level of *COX4i1*, a version of the gene present in all cell types, as a control for the test. He and his students and collaborators have been developing novel techniques known as probe ligation and rolling circle amplification to detect levels of both *COX4i1* and *COX4i2*. Differences between the expression levels of these two genes may indicate the development of cancer and, importantly, at the earliest stages.

The techniques entail Hüttemann's lab using synthetic DNA segments, or "probes," that recognize and attach to the target gene. Using DNA polymerase and a circular DNA template in tandem, the polymerase amplifies the target of the gene-specific probes over 1000-fold.

Hüttemann's group is currently working to further develop the techniques into a robust working assay in the lab. Once this is achieved, the next step will be to test it using clinical specimens from lung cancer patients, alongside matched control samples.

Improving the ability to measure the levels of the COX genes may result in a test for the early screening of lung cancer. "Only 15 percent of lung cancers are detected in time to do something about it," Hüttemann said. "Our hope with this assay is to develop a robust screening method. In particular, individuals at high risk for developing lung cancer, including smokers, would benefit from such a test." Although lung cancer is Hüttemann's primary interest in this project, he also aims to develop the assay as a platform technology to screen for any gene.

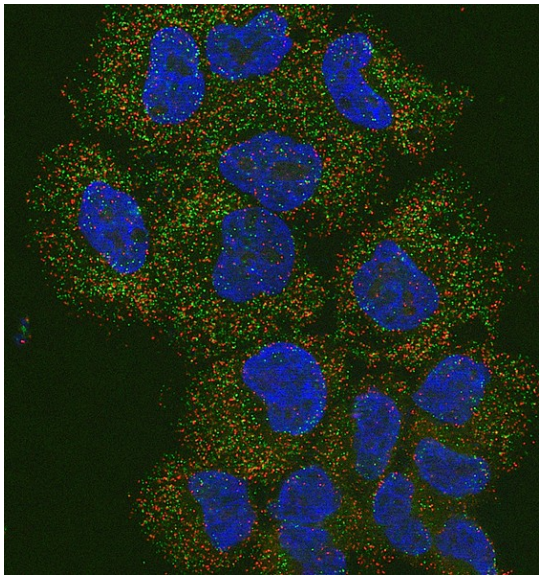
Since the initial design of the test, the lab has made significant strides in regards to consistency and replicability, as well as reducing background noise and false signals. The lab can now apply a standard protocol to most types of specimen, with eyes toward publication within the next year.

One of the major goals for the project was the ability to perform the entire assay in one working day. Providing a workable kit in a clinical setting has to account for ease of use and speed, and being able to collect a sample from the patient in the morning and have an answer by the evening makes an ideal situation. Currently, a fully functional assay takes about 8 hours from the time the cells are placed on the slide, until the time visible signal can be detected. The assay itself is workable in most clinical environments because it only requires a heating block and simple salt buffers in conjunction with specific enzymes to perform every step up until detection.

In order to expand the number of situations where the assay is applicable a collaboration has begun with the laboratory of Dr. Vinod B. Shidham, MD, Professor and Director of Cytopathology, Wayne State Department of Pathology. The collaboration aims to adapt the fluorescent assay towards a chromogenic one. In this setup, rather than using probes that require fluorescent microscopy to visualize the result, recognition probes would be chemically linked to active enzymes, which then use an artificial substrate to produce a signal visible with transmitted light. The amount of color that stains the tissue will be proportional to the amount of signal present, and the color development will be done in a multiplexed manner (that is, both signals can be detected at once by the amount of red, blue, or purple stain that results). This is an important development because one of the most common types of sample obtained from pathologists, flash-frozen paraffin-embedded tissue, is often considered incompatible with fluorescent microscopy due to very high background signals.

The lab is designing the kit with the intention of being able to perform the same protocol regardless of sample type, having to simply adjust the final visible signal step to fit the type of microscopy used. This will also serve as proof of concept for using the assay as a platform for other types of single cell expression analyses.

Dr. Hüttemann's office is located at 3214 Scott Hall and he can be reached at 313-577-9150.



In the figure the signal amplification assay has been performed on cultured human cells that highly express COX4i2. *The green signal represents the lung-specific marker (*COX4i2*), whereas the red signal represents the ubiquitously-expressed control marker. Lung cancer samples will show red signal while the green will be absent.*

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that they can cause human disease," he said. "I am profoundly and emphatically grateful for this opportunity to finally address exactly the problem that I've spent the past 15 years studying – the functional and mechanistic contribution of primate-specific long non-coding RNA genes to human phenotypic uniqueness, including human diseases that lack non-primate animal models."

Dr. Lipovich's office is located at 3208 Scott Hall and can be reached at 313-577-9683.

(Based on an article by Andrea Westfall)

Drs. Kurkinen and Goustin Present Poster that Challenges Alzheimer's Research Status Quo

Markku Kurkinen, PhD

Dr. Markku Kurkinen, Professor of Molecular Medicine and Genetics and of Pathology, and Dr. Anton Goustin, Part-Time Faculty of Molecular Medicine and Genetics, and Dr. Jerzy Leszek of Wroclaw Medical University, recently presented, "Why 'Amyloid Cascade' Is a Misguided Hypothesis of Alzheimer's Dementia Etiology" at the Alzheimer's Association International Conference, July 12-17, 2014, Copenhagen, Demark. Alzheimer's dementia (AD) refers to disorders of the mind characterized by a slowly progressing and irreversible memory loss, mental decline, remarkable personality changes and loss of self. Advanced or old age is the only important risk factor for developing AD. Other risks include head trauma, stroke, cerebrovascular and cardiovascular events, neuropsychiatric conditions, obesity, diabetes, and the APOE4 gene.

The 'amyloid cascade' hypothesis says that AD begins with the extracellular accumulation of Aβ peptides in brain amyloids, causing reactive inflammation and immune responses, synaptic loss and neuronal cell death. The 'amyloid cascade' hypothesis has dominated AD research and clinical trials for 25 years. Brain amyloids can be detected at post-mortem autopsy or by PET brain imaging of living individuals. The 'amyloid cascade' hypothesis is based on the genetics of some rare forms of inherited AD caused by dominant mutations in APP, PS1 or PS2 genes which all increase Aβ peptides production and amyloids formation in the brain. However, Dr. Kurkinen points out that studies on deceased individuals have revealed that as many as 30% of them, cognitively normal in life, are found at autopsy to have brain amyloid deposits typical of severely-demented patients. He points out that clinical drug trials featuring companies such as Eli Lilly, Bristol-Myers Squibb, and Pfizer that targeted APP processing and Aß

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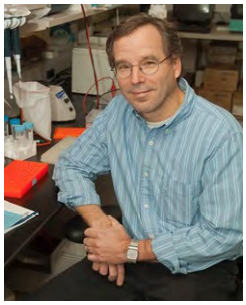
New Faculty Profiles: James Granneman and Karli Rosner

This fall two new members joined the Center for Molecular Medicine and Genetics faculty. Dr. James Granneman is Professor of Molecular Medicine and Genetics and of Internal Medicine. Dr. Granneman is also the Director of Wayne State's Center for Integrative Metabolic and Endocrine Research, a joint research effort of the Departments of Pathology and of Internal Medicine (Endocrinology) that was established to address the world-wide epidemic of obesity and diabetes.



James Granneman, PhD

Dr. Granneman's research focuses on targeting adipose tissue and adipose tissue receptors for treatment of obesity-related disorders, like diabetes and cardiovascular disease. His current work addresses two areas. The first seeks to identify mechanisms that promote catabolic remodeling of adipose tissue; that is, how to turn typical white fat from a tissue that stores excess energy to one that burns it. This work ranges from PET and FMRI imaging in humans (with Dr. Otto Muzik, Department of Pediatrics), to cell lineage tracing and cell-specific gene targeting in mouse models.

The second area of research addresses how muscle and fat cells mobilize lipid energy for local and systemic use. Inappropriate mobilization of fatty acids by fat and muscle can lead to insulin resistance and diabetes. The long-term goal of this work is to validate new preclinical drug candidates for development as obesity and diabetes therapeutics. The research uses several complex techniques. One, molecular imaging, addresses fundamental mechanisms of fat storage and mobilization in eukaryotic cells. This work has been expanded to include comparative/evolutionary analysis of lipid droplet proteins in zebrafish (in collaboration with Dr. Ryan Thummel, Department of Anatomy and Cell Biology) and ultra-high throughput compound screening and preclinical drug development (in collaboration with Dr. William Roush, Scripps Research Institute, and his CMMG colleague, Dr. Jeffrey Tseng). Dr. Granneman is currently PI/PD of 4 NIH research or training grants, and a VA Merit Award. He is co-PI of the multidisciplinary Diabetes Obesity Team Science (DOTS) initiative through the WSU OVPR. His office and laboratory are located in room 103 of the Lande building at 550 E. Canfield.

The second new faculty member is Dr. Karli Rosner, a dermatologist who is Assistant Professor of Dermatology and of Molecular Medicine and Genetics. In addition, Dr. Rosner is the Director of Dermatology Research in the WSU Department of Dermatology, and works at the Laboratory of Molecular Dermatology (LMD) he established at the Barbara Ann Karmanos Cancer Institute. One of his current main projects for the LMD is melanoma gene therapy by targeted gene constructs, in which he is seeking to develop a melanoma-targeted construct containing a high killing efficiency gene. A second project seeks diagnostic melanoma biomarkers by high-throughput antigen cloning and detection on arrays. The goals are both to identify new melanoma biomarkers and develop a highly sensitive melanoma-targeted blood test. The third project is on the role of mobile genetic elements in the etiology of melanoma, in which he is attempting to identify such elements that potentially begin the malignant transformation of benign melanocytes.

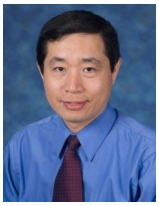
Karli Rosner, MD, PhD

Dr. Rosner recently developed a personalized cancer therapy treatment based on a naturally occurring genetically modified human enzyme, DNase1, to trick cancer cells into killing themselves. Wayne State University protected this innovation with a patent application. More information can be found in the article, "Engineering a waste management enzyme to overcome cancer resistance to apoptosis: adding DNase1 to the anti-cancer toolbox" in the Jan. 14 online edition of *Cancer Gene Therapy,* a Nature Publishing Group journal.

Dr. Rosner's office is located in the Prentis Building at 110 E. Warren Ave, Room 2216, Tel: 313-578-4430.

Faculty Accomplishments

Samavati, Trepanier, Zhang and Gow Honored



Lobelia Samavati, MD, Associate Professor of Internal Medicine and of Molecular Medicine and Genetics, received the 2014 Research Excellence Award from the School of Medicine. Dr. Samavati's major research focus is to understand the molecular pathways underlying inflammatory diseases including sarcoidosis. As a disease model, she studies both clinical and laboratory aspects of sarcoidosis and interstitial lung disease. She has been awarded several grants for this work; most recently she received a $400,000 award from the NIH to study "The Role and Regulation of MKP-1 in Sarcoidosis."

Angela Trepanier, MS, CGC, Assistant Professor of Molecular Medicine and Genetics, received the School of Medicine 2014 Teaching Award. A former president of the National Society of Genetic Counselors, she directs the Center's Genetic Counseling program.

Kezhong Zhang, PhD, Associate Professor of Molecular Medicine and Genetics and of Immunology and Microbiology, and Director of the Summer Undergraduate Research Program, received the School of Medicine 2014 Teaching Award. Dr. Zhang studies inflammation and endoplasmic reticulum protein misfolding.

Alexander Gow, PhD, Professor of Molecular Medicine and Genetics and of Neurology and of Pediatrics, and a member of the CMMG Faculty since 2000, has accepted an appointment as Associate Director of the Center. Dr. Gow is an accomplished scientist who specializes in research related to neurodegenerative diseases. He has been funded continuously by the Multiple Sclerosis Society since 1996, and has received contracts from private industry to conduct pre-clinical trials as well as grants from the National Institutes of Health to study cell death in the brain.

Continued from Pg. 4

peptides clearance have all failed. Thus, Dr. Kurkinen suggests another path is needed since there are no AD survivors and because the current drug trials and treatments have failed.

Dr. Goustin adds that there are emerging alternatives to 'amyloid cascade' hypothesis that may deserve more attention. He illustrated that familial (inherited) forms of AD are driven by the dysregulation of a single pathway involving three genes —APP and two proteases that cleave APP including presenilins 1 and 2 (PS1, PS2). The majority of AD cases are sporadic (non-familial) late-onset AD (LOAD); these have been analyzed through genomic-wide association studies (GWAS), including the analysis of single-nucleotide-polymorphisms (SNPs) in the human genome. One gene stands out in penetrance — the gene encoding apolipoprotein E (ApoE), which is active both in the periphery (chiefly liver hepatocytes) and in the brain (chiefly by astrocytes, with receptors on neurons). There is no successful mechanistic linkage between ApoE and the 'amyloid cascade.' The other 30+ AD risk genes for late-onset AD do not link to either the APP or ApoE pathways, but cluster in pathways regulating membrane-trafficking, chronic inflammation, and bioenergetics. Dr. Goustin argues that more research needs to mechanistically merge these non-amyloid risk genes into the etiology of AD, free of the 'amyloid cascade' hypothesis. AD researchers were excited recently by news from the Mayo Clinic lab of Dr. Edward Goetzl, who has developed a predictive blood test for AD based on the ratio of serine-to-tyrosine phosphorylation of IRS-1 (insulin receptor substrate) associated with brain insulin resistance.

Anton Goustin, PhD

Dr. Kurkinen, who is on sabbatical in England for the Fall, 2014 semester, working with Dr. Alexei Verkhratsky of the University of Manchester, hopes to discover whether the ApoE genotype, whose APOE2 and APOE4 variants protect and predispose for AD, respectively, affects glutamate uptake and metabolism by astrocytes. He hopes that if this direction is successful it could contribute to developing a new AD hypothesis that could lead to effective treatments during the course of the disease.

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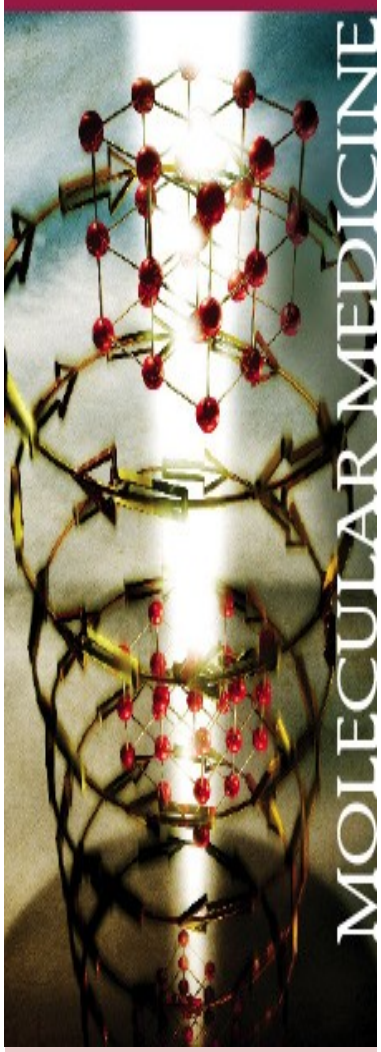

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