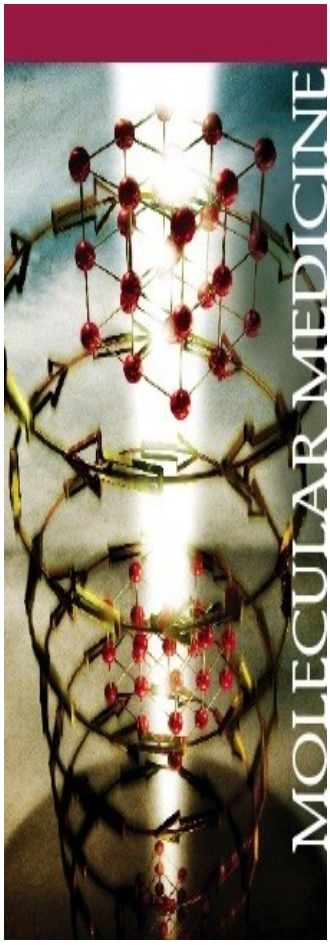


DISCOVERY. FOR LIFE.

WAYNE STATE UNIVERSITY
SCHOOL OF MEDICINE

CENTER FOR
MOLECULAR MEDICINE AND GENETICS

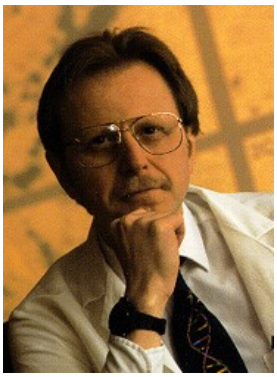
Summer/Fall 2009

Inside this issue:

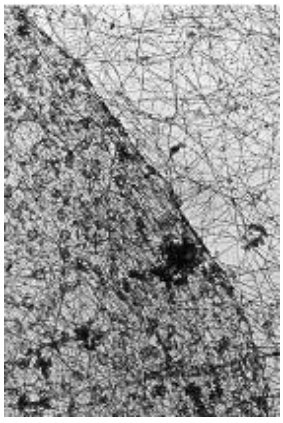
Center Researcher Uncovers the Basis of Genome and Nuclear Matrix Interaction

A team of Center researchers led by Dr. Stephen Krawetz has unraveled the basis of interactions between the human genome and nuclear matrix, suggesting a global role in the function of genome organization. The findings were published in and featured on the cover of the February 2009 *Journal of Human Molecular Genetics*.

The main researchers on this project were Stephen A. Krawetz, PhD, Charlotte B. Failing Professor of Fetal Therapy and Diagnosis, Center for Molecular Medicine and Genetics, Director of Translational Reproductive Systems, Department of Obstetrics and Gynecology, Institute for Scientific Computing; Amelia Linnemann, PhD, Center for Molecular Medicine and Genetics; and Adrian Platts, Department of Obstetrics and Gynecology and Center for Molecular Medicine and Genetics.


Stephen Krawetz, PhD

Dr. Krawetz's laboratory tries to understand how the genome is organized in the three-dimensional space of the nucleus to orchestrate gene activity. Using rapid large scale genomic techniques, the researchers defined key context dependent interactions of genes with specific regions of the nuclear matrix organizer. The interaction between the two plays a significant role in gene expression. These findings may lead to techniques which can switch on or switch off genes that are at the root of diseases or disorders.


TEMicrograph of mouse fibroblast nuclear matrix[left] and surrounding cytoplasm . Fibroblasts were detergent extracted and DNaseI treated. (Capco et al. 1982)

The research and resulting published paper formed the cornerstone of Ms Linnemann's doctoral thesis. Mr. Platts is the lab's primary biosystems informatician. Initially trained as a physicist, he is "naturally quite at home developing novel analytical tools suited to this voluminous data and the statistical rigors that are required for these large scale projects," said Dr. Krawetz.

"The contribution of these indi-

(continued on page 4)

Professors Kapatos and Wildman Win Prestigious Awards

Gregory Kapatos, PhD, Professor of Molecular Medicine and Genetics and of Pharmacology has been awarded the Gowland Hopkins Award. This prestigious honor is awarded to individuals who have made a demonstrable contribution to the field of pteridine biochemistry. Dr. Kapatos, a leader in pteridine biochemistry, received the award and was the keynote speaker at the14th International Symposium on the Chemistry and Biology of Pteridines and Folates held in Korea in June, 2009.

Derek E. Wildman, Ph.D., Assistant Professor of Molecular Medicine and Genetics and of Obstetrics and Gynecology, Member of the Perinatology Research Branch has been awarded the 2008-2009 Junior Faculty Award – Sciences - by the Wayne State University Academy of Scholars. Each year the Academy selects two junior faculty members – one in the sciences and one in the humanities - who demonstrate significant promise in their respective academic fields, to receive this significant honor.

A Message from the Director

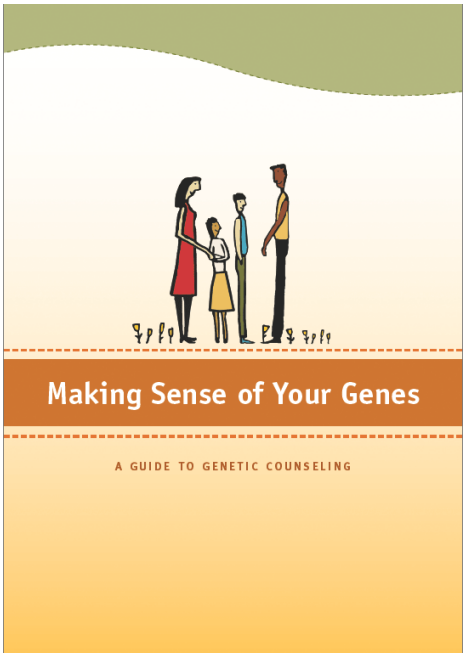
The start of a new academic year, with its arrival of a new crop of students, adds a reminder of the season and always brings a little surge of excitement and expectation, even at a place where research is the major activity, and one that goes on all year long. This year the summer was especially busy; in addition to running our Summer Undergraduate Research Program (http://genetics.wayne.edu/students/surp/past-surp.php), many faculty members were busy writing and submitting (and four eventually receiving) grant applications to compete for stimulus funding made available to NIH through the 2009 Recovery Act.

Perhaps one reason for our success in competing for funding is the ongoing vigorous and interdisciplinary research in the Center. In this issue we highlight two areas: the Krawetz lab's work on genome and nuclear matrix interaction – which was featured on the cover of the *Journal of Human Molecular Genetics* – and the Zhang lab's work on the molecular links between cell stress and metabolic disease. Although each examines a very different aspect of cellular metabolism, their work is united by seeking to better understand how cells and organisms function.

Not surprisingly, our faculty accrue honors, and several our faculty members received are also highlighted here. And, of course, this start of a school year reminds us that the process also has an end, and for some — our 2009 graduates and enrollees in both the Molecular Biology and Genetics and the Genetic Counseling graduate programs — they are celebrated here as they set out in both the academic and the medical worlds at large.

Lawrence I. Grossman, PhD
Professor of Molecular Medicine and Genetics and of Internal Medicine
Henry L. Brasza Director

Genetic Counseling Director Helps Create Groundbreaking Guide to Genetic Counseling for Patients and Doctors



Angela Trepanier MS, CGC, Director, Genetic Counseling Program, Assistant Professor of Molecular Medicine and Genetics, recently served as an advisor and reviewer for a new consumer guide to genetic counseling.

The 24-page booklet, "Making Sense of Your Genes: A Guide to Genetic Counseling," was produced by the Genetic Alliance, the National Society of Genetic Counselors and select students from the Johns Hopkins/NHGRI genetic counseling program. The guide is targeted to patients and physicians seeking to understand the process of genetic counseling.

Trepanier was asked to serve as advisor and reviewer because of her position as President of the National Society of Genetic Counselors, a title she held in 2008.

"Genetic counseling is a relatively new profession. Consequently, clinicians are often not familiar with the service provided by genetic counselors and patients referred for services do not know what to expect," Trepanier said. "This booklet will serve as a valuable resource for clinicians and patients to help them prepare for and understand what will happen during a genetic counseling session. It was an honor to be invited to work with the many students, advocates and clinicians who developed this booklet in what was truly a collaborative process."

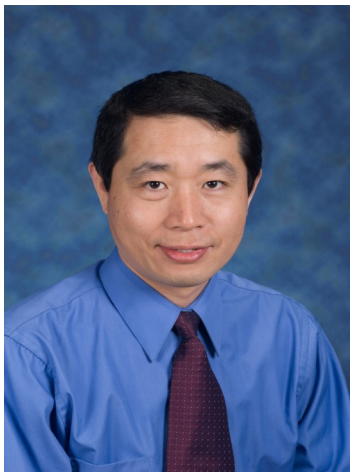
According to Trepanier, genetic counseling services are taking off because an increasing number of genetic tests are becoming available. Such tests are moving beyond the rare, single-gene disorders caused by mutations to include genome-wide searches able to identify predispositions to conditions such as heart disease, cancer and diabetes. "It is anticipated that full genome sequencing (the sequencing of every one of a person's 30,000 genes) will be available at a cost of $1,000 in the next five years," Trepanier said. "The goal is that this information will revolutionize health care in that it will someday be possible to identify what health conditions an individual will be at highest risk of developing so that a physician can personalize approaches to disease prevention."

Angela Trepanier, MS, CGC

"Someday, this information will also be useful in determining how well a person will respond to certain medications and whether he or she is at high risk for an adverse effect with particular medications," she added.

Physicians seeking copies of the booklet may review a PDF file of the publication at: http://www.hsgc.org/ or http://geneticalliance.org/ws_display.asp?filter=counseling.guide. The file can be downloaded.

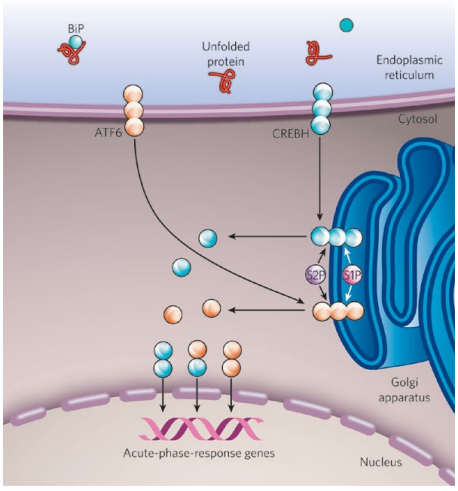
Center Researcher Furthers the Exploration of the Molecular Links Between Cell Stress and Metabolic Disease



Kezhong Zhang, PhD

Kezhong Zhang, PhD, Assistant Professor of Molecular Medicine and Genetics and of Immunology and Microbiology, is using molecular and cellular biology and animal genetics to explore the molecular links between cell stress and metabolic disease.

Metabolic disease, such as obesity, diabetes, and atherosclerosis, is the leading cause of disability and death in the United States. Generally, people believe that metabolic disease is associated with multiple, interrelated risk factors, such as abnormal fat accumulation, elevated plasma glucose, and pro-inflammatory state. However, the molecular mediators by which these risk factors initiate or propagate metabolic disorders remain elusive.



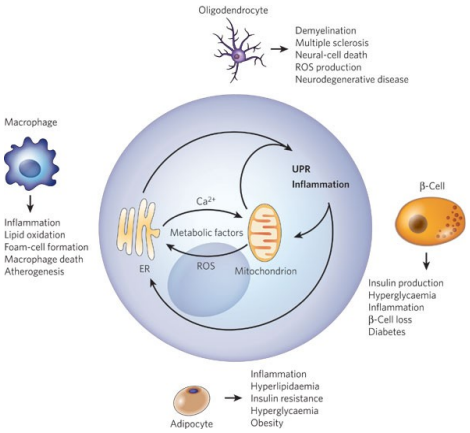
The ER-stressed-induced acute phase response

"At the cellular level, metabolic risk factors such as a high-fat diet can impose stress on a cellular compartment called the endoplasmic reticulum, a site where newly synthesized proteins are folded and assembled," Dr. Zhang said. "This stress on the endoplasmic reticulum interrupts the protein folding process, and causes the accumulation of unfolded or misfolded proteins. This induces the formation of a stress signaling pathway called the unfolded protein response. We believe that the unfolded protein response stimulates a crucial molecular network to remodel the stressed cells and alter cell physiology, leading to metabolic disorders." Dr. Zhang's laboratory tries to pinpoint the molecular regulators that sense cell stress and transmit signals to modulate lipid metabolism, the physiological process closely related to metabolic disease. The researchers use conditional gene "knock out" technology to delete the genes encoding stress sensors in specific cell types in the animal models. The animal models are then fed a high-fat diet to induce metabolic disorders. Through this approach, they have defined at least two endoplasmic reticulum-resident protein factors which can mediate stress signals and are crucial for the development of metabolic disease.

"The molecular network for stress signals is extremely complicated. Upon many pathological conditions, endoplasmic reticulum stress, mitochondrial oxidative stress, and the inflammatory response can interact to amplify the unfolded protein response. Identification of key players in the stress signal network is essential for our understanding of the molecular roots of medical evils from diabetes to heart disease, neurodegenerative disease to cancer. These approaches represent a novel research direction in molecular pathology," Dr. Zhang said.

Dr. Zhang's important, original discoveries in this area of research have been published in several top scientific journals, including *Cell*, *Nature*, *Journal of Clinical Investigation*, and *PNAS*. He has also been a receipt of the American Heart Association Scientist Development Award. Currently, his team is pushing research concerning the role and mechanism for newly-identified liver stress sensors in modulating lipid metabolism which leads to obesity. They are also collaborating with investigators at the Center to understand the interaction between endoplasmic reticulum and mitochondria in regulating stress signaling and cell physiology.

"We believe the findings from our studies will have a high impact on the diagnosis, prevention, and treatment of metabolic disease," Dr. Zhang explained. "The findings will be particularly informative in terms of potential pharmaceutical interventions targeting cell stress pathways. The stress mediators and mechanisms identified in our studies may prove crucial in developing novel therapeutic strategies to control metabolic disorders."



In specialized cells that secrete large amounts of protein, the UPR and inflammatory-response signalling can be triggered by a chronic excess of extracellular and/or intracellular metabolic factors, such as lipids, glucose, cytokines, hormones, non-esterified fatty acids and neurotransmitters. The increased protein-folding demand and the signalling involving calcium and ROS induce the UPR and inflammatory-response signalling, leading to the transcription of genes whose products mount a broader inflammatory response. An excess of metabolic factors can further boost the UPR and inflammation, contributing to impaired lipid and glucose metabolism, insulin resistance and apoptosis. This forward ER-stress–inflammation loop could also further promote inflammatory stress signalling and contribute to the metabolic deterioration that is associated with atherosclerosis, obesity, type 2 diabetes and neurodegenerative diseases.

Center Researcher Uncovers the Secret of Genome and Nuclear Matrix Interactions (continued from page 1)

viduals highlight the breadth, yet focused nature of my research program, which since its inception has been dedicated to using Systems Approaches to develop self-help therapeutics," Dr. Krawetz explained. "My laboratory strives to realize bench-to-bedside personalized medicine at Wayne State University."

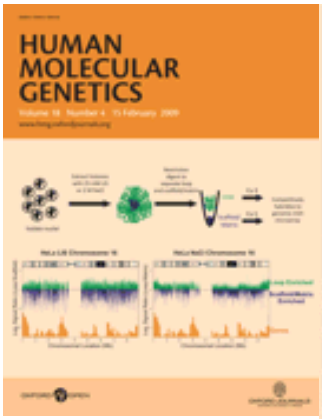
"For some time now the majority of the human genetic code has been known," Dr. Krawetz said. "But how this information is used by the body -- to choose which genes within the cell to activate or leave dormant -- still remains largely unknown. In this recent work, we have shown that structures within the cell's nucleus partner with the DNA in the functional regulation of the genome."

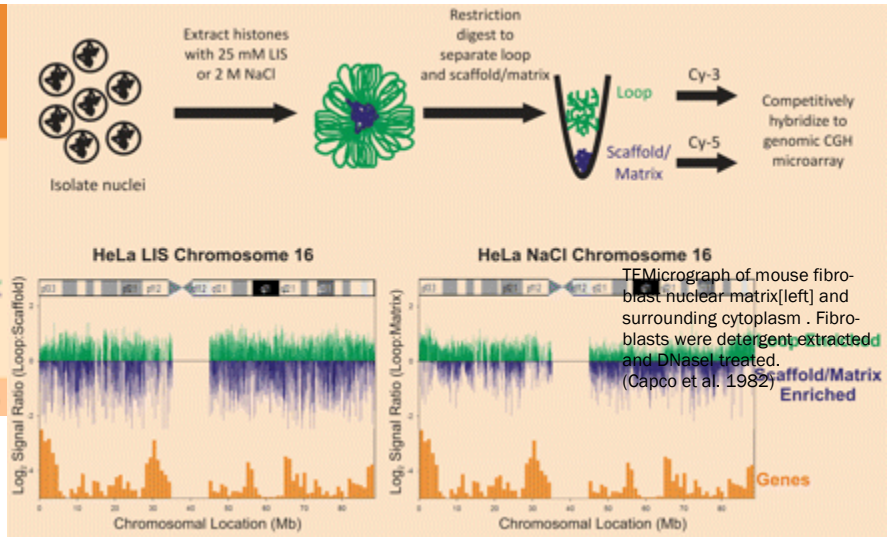
"Understanding how DNA is switched between active and dormant states opens a new door to the mechanism by which cells acquire their distinct specializations. The knowledge gained here provides the structural mechanistic link to genome reprogramming, essential in a healthy child and life.

This opens up new possibilities for indirect (epigenetic) treatment therapies for diseases, including dystrophies, premature aging, several types of cancers and reproductive fitness," said Dr. Krawetz.

Amelia Linneman, PhD

Journal of Human Molecular Genetics February 2009 Cover





TEMicrograph of mouse fibroblast nuclear matrix[left] and surrounding cytoplasm . Fibroblasts were detergent extracted and DNaseI treated. (Capco et al. 1982)

The cover highlights the unique genome organization mediated by complementary sites of nuclear scaffold and nuclear matrix attachment as revealed by array-CGH. Differential isolation of HeLa S3 nuclear matrices by 2 M NaCl and nuclear scaffolds by 25 mM LIS and analysis by array-CGH reveals distinct global profiles of scaffold/matrix attachment. Signal ratios for both loop:scaffold and loop:matrix comparative array hybridizations are displayed. Loop enrichment is shown in green and scaffold/matrix enriched regions are blue. Genes, shown in orange, are represented as density per megabase. Nuclear matrix attachment sites are concentrated in gene poor regions suggesting a global role in functional genome organization.

Doctoral Students Awarded Competitive Fellowships for 2009-2010

Graham Johnson received a Thomas C. Rumble Fellowship for the 2009-2010 year that includes tuition, stipend, and healthcare allowance. Graham is a second-year in the PhD program.

Shruti Bagla and Amy Boddy both received Housing Allowance Rewards for the 2009-2010 academic year. Shruti is a second-year and Amy is a third-year in the PhD program.

Our website is always changing, thanks in large part to our Web Programmer, Rajesh Rampilla. Rajesh graduated last year from Wayne State with a masters degree in Computer Science, and is currently a first-year student in MBA Program at Wayne State. He lives on-campus in the University Towers, and enjoys hanging out with his friends and watching Hindi movies when not at work. Check out the changes he is making to the website - including the new 'Commercialization Center' page - at:

www.genetics.wayne.edu

Doctoral Degrees Conferred in 2009

Amelia Linnemann

"Analysis of Nuclear Scaffold/Matrix Attachment: The Role of Genome Organization in Transcription"

Advisor: Stephen Krawetz, PhD

Joshua Stevens

"Mitotic Cell Death by Chromosome Fragmentation: Discovery, Characterization and Implications"

Advisor: Henry Heng, PhD

Genetic Counseling Masters Degrees Conferred in 2009

Tiara Johnson

Kelly Kenner

Mary Nyhuis

Preethi Premkumar

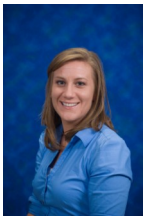
Abbey Putnam

Kate Zellmer

2009 MBG Graduate Enrollees

Batoul Abdallah from University of Michigan

Paul Albosta from Saginaw Valley State University

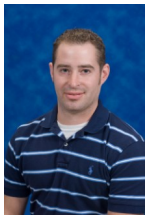


Kathleen Maheras from Alma College

Richard Smith from Brigham Young University

Dayna Testori from Oakland University

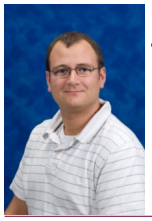
2009 Genetic Counseling Enrollees



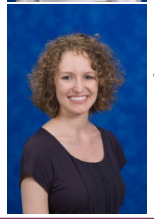
Michael "Jay" Harrison from Capital University

Sommer Hayden from Western Michigan University

Lauren Isley from Northwest Missouri State University

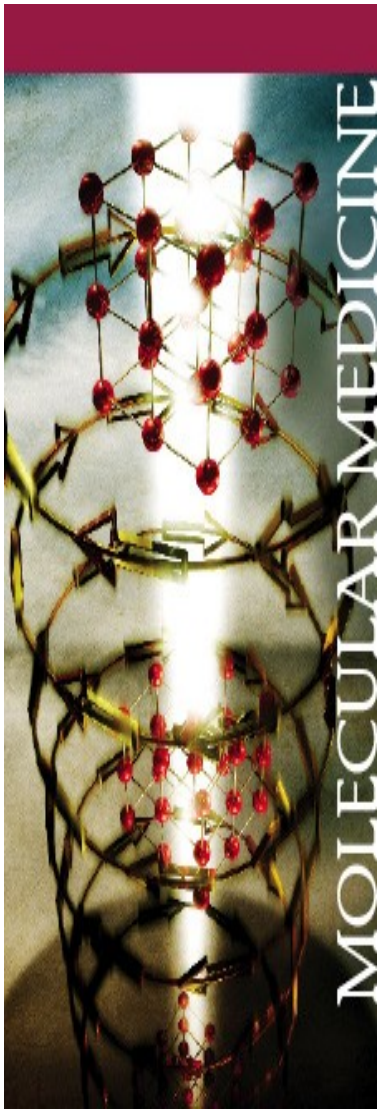


Jason Laufman from Ohio State University



Bridget O'Connor from University of Michigan

Divya Wilson Mathews from McMaster University



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MD/PhD in Molecular Biology and Genetics

MS in Genetic Counseling

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Graduate Officer: Gregory Kapatos, PhD

Division Directors

Basic Science Research: Russell L. Finley, Jr., PhD

Clinical Genetics: Gerald L. Feldman, MD, PhD

Education: Gregory Kapatos, PhD

Primary Faculty

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Gerald L. Feldman, MD, PhD
Russell L. Finley, Jr., PhD
Alexander Gow, PhD
Lawrence I. Grossman, PhD
Henry H.Q. Heng, PhD
Maik Hüttemann, PhD
Gregory Kapatos, PhD
Markku Kurkinen, PhD
Wayne D. Lancaster, PhD
Leonard Lipovich, PhD
Jeffrey A. Loeb, MD, PhD
Angela Trepanier, MS, CGC
Derek E. Wildman, PhD
Carin Yates, MS, CGC
Kezhong Zhang, PhD

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James Y. Garbern, MD, PhD
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