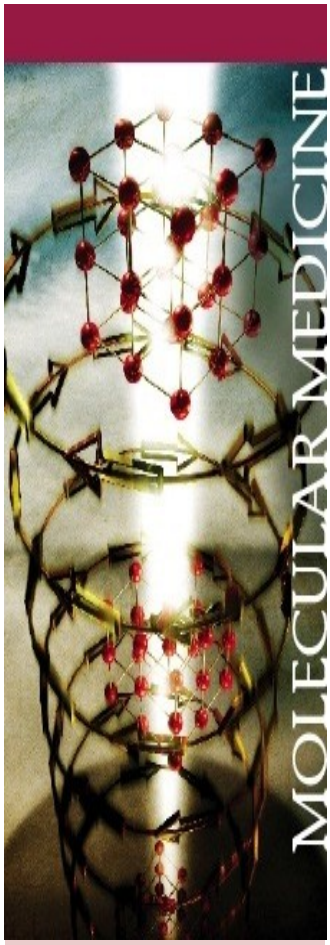
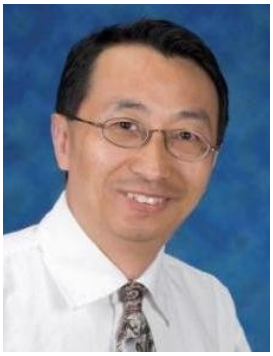


CENTER FOR
MOLECULAR MEDICINE AND GENETICS

September, 2012

Seeing the Forest for the Trees: Critiquing Genetic Theory



Henry Heng, PhD.

Dr. Henry Heng, Associate Professor of Molecular Medicine and Genetics and of Pathology, is taking a unique approach to genetic theory. According to Heng, modern genetics might need a complete overhaul to understand the complex workings of the genome.

Heng says that geneticists have focused far too much on individual genes and not enough on the genome as a whole. Genes, he says, only represent parts of the genetic system and are fundamentally different from the entire genome. "A list of materials needed to build a building does not instruct builders how to make that building," Heng says. He proposes that genome context, which is made by not only the information coded in DNA sequences but also the information hidden in the genome topology, is the key to complex diseases such as cancer.

Traditionally, in looking for the cause of complex diseases, geneticists have looked at individual genes. As technologies have advanced, scientists have moved to looking for defects in all of the 20,000 genes in the human genome and trying to find a consensus pattern of gene mutations and a pattern of alteration of the pathways that those genes function in for each type of cancer. However, Heng says that the full answer is not in mutations of specific genes or pathways, as most cancer patients do not share the same gene mutations. Instead, Heng focuses on large scale genome change such as chromosomal rearrangements and changes in the number of chromosomes, as these changes are nearly universal in cancer.

He explains that the difference between the traditional view of genetics and his genome theory is that traditional gene based genetics is like looking at two different houses, systems, and blaming a few bricks for the differences in architecture. Instead, the entire genome, the whole house, needs to be studied.

Heng says his group first considered this line of thinking while studying gene and chromosome change in cancer models. "Traditional models of cancer say that we should find a straightforward, stepwise pattern of gene and chromosomal change," he says, "but what we found was something far different. We found that the genomic makeup of cancer cells was changing randomly and sometimes very rapidly." He observed that specific genes were contributory in some isolated exceptional cases, but the common mechanism of cancer progression was evolution driven by random chromosome change, which he calls 'genome replacement mediated macro-cellular-evolution.' This led his lab to believe that cancer is a disease of the genome rather than individual genes.

Recently, Heng has also observed that in cells subjected to stress, chromosomes, actually break apart and rearrange themselves in different, often complex, random combinations in a process called genome chaos, possibly causing a variety of diseases, including cancer, and driving resistance to treatment. "The ability of the cancer genome to adaptively evolve is incredible," Heng says with an air of remorse, "If cancer followed the stepwise models of progression, we would be much better at treating it."

Unsurprisingly, the scientific community at large initially had a hard time accepting Heng's theories. However, this has not dissuaded Heng. He understands that it will take time, and a great deal of study, for his theories to take root. Following 10 years of fighting the mainstream, his viewpoints are now catching on. In addition to participating in various think tank meetings, his group has been frequently invited to write perspectives and book chapters, as well as editing special issues for different journals.

Heng will be publishing a book titled "4D-Genomics: Genome Dynamics and Constraint" later this year to introduce his genome theory.

Inside this issue:

WAYNE STATE UNIVERSITY
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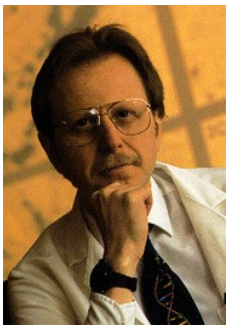
Identifying Male Infertility



Stephen Krawetz, PhD.

Dr. Stephen Krawetz, Charlotte B. Failing Professor of Obstetrics and Gynecology and Professor of Molecular Medicine and Genetics, may have found an inexpensive and more accurate way to identify male infertility.

Typically, male fertility is tested through what Krawetz called, "subjective characteristics," such as sperm shape, swimming speed and trajectory, concentration, etc.

Research from the Krawetz laboratory has now found that these subjective characteristics vary widely in fertile males; thus, using them as the defining points of fertility could prove unreliable. Then, in comparing how these aspects vary in order to find a pattern, the Krawetz laboratory observed that there was only a 50% correlation among them, making accurate testing using these characteristics almost impossible.

Krawetz hopes his research will change this by looking at the problem from a different angle, the RNA. Krawetz has tested a concept of using the RNAs present in spermatozoa to test male fertility, changing the testing parameters from subjective to objective. Using a battery of RNAs, there appears to be a greater than 90% correlation with male fertility.

It was originally difficult for the Krawetz laboratory to get anything published on this research, as it had been widely established that sperm held no RNA. Krawetz said he was encouraged, however, by research done by a colleague in England, Dr. David Miller of the University of Leeds, who, independently and previously unknown to Krawetz, and using different techniques, found similar results.

Krawetz said that, initially, there was great interest in male fertility testing, though using DNA microarrays or sequencing would be too expensive with current sequencing costs of roughly one thousand dollars per test. Instead, the laboratory is using PCR based testing, reducing the cost of each test to $20 - $100.

Currently, Krawetz's group is in the process of translating this research to a future clinic. Hopefully this research will lead to treatment opportunities in the near future for male infertility. The group is eager to continue this work, as interest for it has been high. Krawetz said that new discoveries are continuing to unfold. For instance, during deep sequencing of the small RNAs, Krawetz's lab observed that miR-34c, the most abundant micro RNA found in sperm, appeared to be critical for first embryonic cleavage in mice. Micro RNAs are post-transcriptional regulators that bind to complementary sequences on target messenger RNAs, usually resulting in gene silencing.

Krawetz said, "this represents a major advance," and that, "there's much more interesting things to come out of this, stay tuned!"

New Faculty Member Profile: Francesca Luca, PhD

Francesca Luca, PhD.

The Center welcomed Dr. Francesca Luca as Assistant Professor of Molecular Medicine and Genetics and of Obstetrics and Gynecology in January of this year.

Luca originally was graduated with a PhD in Molecular Bio-pathology from the University of Calabria in southern Italy in 2006. Her thesis revolved around population genetics, specifically the populations of the Mediterranean area and Eastern Europe, to infer the contribution of recent migrations to the peopling of Europe.

She moved to the U.S. in August, 2006 and did her postgraduate work at the University of Chicago. Luca said she made the move from Italy because she felt she could do better research here in America. Luca said that, "Italy is a very good place to get training as an undergrad," but after she got her PhD, she decided she had to go abroad to further her research.

After finishing her postdoctoral work, Luca decided to join Wayne State University because she was eager to add a translational aspect to her work. She said, "I think the environment here at Wayne State, and at CMMG most importantly, makes it ideal," for her research.

Luca plans on continuing her work in population genetics. Specifically, she plans on characterizing the interaction between genetics and environmental conditions. One of her current projects involves studying the effects of estrogen treatment on cellular phenotypes to determine if there is a genetic basis for estrogen-related diseases. She was recently a co-author of a study on genetic variation in cellular response to glucocorticoid treatment in *PLoS Genetics*. Luca is confident that her research will be able to show a link between genotype and cellular phenotype in certain environments.

Her office is located in Room 3317 Scott Hall.

Tough Questions in Mitochondrial Disease

John Kamholz, MD, PhD

Dr. John Kamholz is trying to find the answers for diagnosing mitochondrial disease.

For the past few years, Dr. Kamholz, Professor of Neurology and of Molecular Medicine and Genetics, along with Center colleagues Drs. Lawrence Grossman and Maik Hüttemann, have been working to put together a mitochondrial disease clinic to discover new and accurate methods of diagnoses and pursue possible treatment plans, both of which are still few in number.

Dr. Kamholz says that one of the problems of diagnosing mitochondrial diseases is the variety of ways they can appear. Symptoms of mitochondrial disease range from vision impairment to seizures. Kamholz jokingly referred to it as "the Chinese restaurant menu syndrome," as patients will usually have a mix of symptoms from several different categories. The usual way to diagnose a mitochondrial disease, according to Dr. Kamholz, is to find a patient with a multifactorial disease that cannot otherwise be explained.

The focus of the clinic is the diagnosis and, in the future, treatment of diseases that are caused directly by mitochondrial malfunction. Dr. Kamholz says that the clinic is also interested in diseases where mitochondria may play a secondary role, such as Huntington's disease, but that these are not the main focus.

The clinic administers an anaerobic stress test to help identify whether the patient's body is properly utilizing oxygen. Improper oxygen utilization can imply a problem with the patient's mitochondria. By monitoring a patient's exhalations during testing, the clinic can measure oxygen intake and identify whether the problem lies in the lungs. Dr. Lobelia Samavati, Assistant Professor of Medicine and of Molecular Medicine and Genetics, is working with Dr. Kamholz in patient diagnosis by providing input on pulmonary testing.

Blood and muscle tests are also used to identify whether there is an excess of lactate in the patients after testing. Normally the human body produces lactate when cells receive too little oxygen, such as during intense exercise when the body's oxygen levels go down, and are forced to produce energy anaerobically. In patients whose cells have trouble turning food into energy, possibly as a result of a mitochondrial disease, lactate levels are much higher than they would normally be.

The clinic also depends a great deal on collaboration between several departments and individuals, including Dr. Samavati, as well as performing genetic histories on their patients to help determine if a patient's disease is inherited. Since mitochondria are inherited maternally, diseases that are common on the mother's side of the family are more likely to be mitochondrial in origin.

However, even with all of this testing, it is still difficult to accurately determine whether a disease is mitochondria-based. Dr. Kamholz said that the only way to accurately identify a mitochondrial disease is to find a genetic defect that is known to cause it. "Anything else is not going to specifically identify something like that," he added.

Apart from difficulty in diagnoses, the problem with mitochondrial disease is the lack of treatment. According to the United Mitochondrial Disease Foundation, an organization that supports mitochondrial disease research across the U.S., there are no known cures for mitochondrial disorders. Kamholz says that current treatments revolve around dietary and vitamin supplements, which help alleviate some symptoms but don't cure the disease.

Lobelia Samavati, MD

Drs. Kamholz and Samavati both agree, however, that even without treatments for mitochondrial disease, their clinic makes a large difference in their patients' lives. Many patients can go from hospital to hospital, meeting with several different doctors and getting just as many different diagnoses, none of them being for mitochondrial disease due to the lack of research and awareness on the subject.

A patient undergoing the anaerobic stress test

Being able to accurately identify the problem is a huge emotional help. "Human beings want to know what is wrong with them," Dr. Samavati said. She added that people would rather know they have an incurable disease than to go on with the stress of having no answers.

The Lake House: Helping Those Touched By Cancer

Wayne Lancaster, PhD

Dr. Wayne Lancaster, Professor of Molecular Medicine and Genetics and of Obstetrics and Gynecology, has worked for years with cancer. While it's easy to see the physical impact of cancer, very little effort is spent on the emotional impact. Dr. Lancaster has seen how people, those afflicted and those whose loved ones are afflicted, have been hurt by cancer on a psychological level. That is why he became a member of the executive board of The Lake House.

Started on May 1, 2011, The Lake House provides help to those whose lives have been affected by cancer, whether they've been diagnosed themselves, or if they have a family member or loved one who has suffered from it. The House prides itself as "A gathering place for those touched by cancer."

According to Dr. Lancaster, the House's creation was first inspired in part by Gilda's Club, another cancer support group with locations in Grand Rapids and Royal Oak; that has been a great help to cancer victims in those areas. People who live in Southeastern Michigan, however, had no such support. The Lake House was built to help those in the Wayne and Macomb counties.

The Lake House is a non-profit organization that provides free support to its members. Though, as president and founding member Ted Huebner said, "free service is expensive."

The Lake House depends on private donations, silent auctions, and grants for financial support, as well as help from volunteers.

Dr. Lancaster believes that the house has been a huge success despite its slow start. Initially only a few people were members of the House, simply because most didn't know about it. As Huebner said, "It's like any start-up organization."

However, since word spread, the House's attendance has been on the upswing. Huebner added, "Once people get in here and once we connect with them, then we've been very successful."

The Lake House's website states that a report from the National Institute of Health in 2007 showed that the mental and emotional difficulties of cancer (anxiety, depression, fear, etc.) can cause "additional suffering, weakened adherence to prescribed treatments and threaten patients' return to health."

School of Medicine Assistant Dean of Research, Dr. Daniel Walz and Dr. Jeffrey Zonder of the Karmanos Cancer Institute are also members of the House's advisory boards, as well as former Center graduate student Dr. Jayson Field, who is a gynecologic oncologist at Beaumont Hospital.

The Lake House is located at 26701 Little Mack in St. Clair Shores. You can find more information about it at www.milakehouse.org, or join them on Facebook at facebook.com/milakehouse.

Recent Faculty Accomplishments

Jeffrey Loeb, MD, PhD

Dr. Jeffrey A. Loeb, Professor of Neurology and of Molecular Medicine and Genetics, and Associate Director of the Center, has been selected to receive the 2012 Charles H. Gershenson Distinguished Faculty Fellowship. The Distinguished Faculty Fellowship is awarded to recognize and reward those whose work in their respective fields is nationally distinguished, and who show remarkable scholarly prowess.

Dr. Loeb will receive the Fellowship on July 1st, which includes a total of $13,000 in funds for the next two years. This award marks a continuous holding of one of these fellowships by a Center member: Dr. Alexander Gow, Professor of Molecular Medicine and Genetics and of Pediatrics and of Neurology, has been a Gershenson Distinguished Fellow since 2010.

Maik Hüttemann, PhD

Dr. Maik Hüttemann, Associate Professor of Molecular Medicine and Genetics and of Biochemistry and Molecular Biology, has been selected to receive a 2012 President's Award for Excellence in Teaching. The award is given to faculty members who excel in their given field and who show exceptional expertise in their classroom performance.

These professors show deep dedication to the education of their students, and this award recognizes that. Dr. Hüttemann will be presented with the award at the Wayne State University Academic Recognition Ceremony held April 26 at the McGregor Memorial Conference Center, where he will receive a plaque and $2,500.

Leonard Lipovich, PhD

Dr. Leonard Lipovich, Assistant Professor of Molecular Medicine and Genetics and of Neurology, has received an NIH U01 grant from the Encyclopedia of DNA Elements (ENCODE). ENCODE is a research consortium started by the US National Human Genome Research Institute (NHGRI). The goal of ENCODE is the discovery and cataloging of all functional elements of the human genome and is NHGRI's successor to the Human Genome Project.

This grant makes Dr. Lipovich the first member of Wayne State's faculty to receive an ENCODE grant. Becky Cai and Emily Wood, members of Lipovich's lab, will also be supported by the ENCODE grant.

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Monica Uddin, PhD

Dr. Monica Uddin, Assistant Professor of Molecular Medicine and Genetics and of Psychiatry and Behavioral Neurosciences, was awarded the 2012 Eli Robins, Samuel Guze award for early career promise by the American Psychopathological Association. She also received a postdoctoral fellowship from the Office of the Vice President for Research.

Dr. Henry Heng, Associate Professor of Molecular Medicine and Genetics and of Pathology, received a grant from the National Chronic Disease Foundation.

Dr. Li Li, Associate Professor of Internal Medicine and of Molecular Medicine and Genetics and Dr. Kezhong Zhang, Assistant Professor of Molecular Medicine and Genetics and of Immunology and Microbiology, were awarded the Shared Postdoctoral fellowship offered by the Center

Incoming 2012 Genetic Counseling Students

Amanda Bartenbaker, from Michigan State University

Kelly Burgess, from Michigan State University

Sarah Campian, from Saginaw Valley State University

Lisa Gillis, from York University

Ashley Port, from Grand Valley State University

Mary Schultz, from Oakland University

Genetic Counseling Masters Degrees Conferred in 2012

Mary Mobley

Tessa Paling

Ashley Reeves

Renee Tousignant

Shirley Yao

Nikki Hajduk

Doctoral Degrees in 2012

Jianbin Shen

"Identifying SM22 as a key player in arterial diseases"

Lab: Li Li, PhD

Incoming 2012 MBG Students

Gregory Moyerbrailean, from Michigan State University

Whitney Lee, from Southern Utah University

Students, Postdocs Receive Recognition

PhD student Shruti Bagla (laboratory of Jeffrey Loeb, MD, PhD) and PhD student Paul Albosta (laboratory of Russell Finley Jr., PhD) were awarded the 2012-2013 Thomas C. Rumble University Graduate Fellowship

PhD student Graham Johnson (laboratory of Stephen Krawetz, PhD) was awarded the MBG Discretionary WSU/SOM Graduate Research Assistantship for 2012-2013.

PhD student Emily J. Wood (laboratory of Leonard Lipovich, PhD) won two international honors during her 2nd year in the program. In October 2011, she received a $1000 travel scholarship to attend and speak at the FANTOM5 Consortium, Phase II Meeting in Yokohama, Japan. In April 2012, she received a $1200 Keystone Scholarship from the Keystone Symposium: Non-Coding RNAs, in Snowbird, Utah where she presented a poster.

PhD student Daniel Radecki (laboratory of Alexander Gow, PhD) has been invited to give an oral presentation at the Neuroscience 2012 Conference in October, 2012.

PhD student Batoul Abdallah (laboratory of Henry Heng, PhD) gave an oral presentation, "Non-clonal chromosomal aberrations as genomic markers of ovarian cancer," at the Michigan Alliance for Reproductive Technology research symposium held on May 23, 2012.

Genetic Counseling student Ashley Reeves received a $500 award from the National Society of Genetic Counselors Prenatal Interest Group to conduct her study: "Information preferences regarding informed consent models for genetic carrier screening."

Genetic Counseling student Mary Mobley received a $500 award from the Michigan Association of Genetic Counselors to conduct her study: "An Educational Needs Assessment of Primary Care Physicians in the Genomic Era."

MD, PhD student Levent Sipahi (laboratory of Derek Wildman, PhD) received a Sigma Xi grant for his work on the epigenetic regulation of posttraumatic stress disorder.

Danielle Senador, PhD (laboratory of Jeffrey Loeb, MD, PhD), received a post-doctoral research grant from the Epilepsy Foundation for her study: "Interictal Spiking as a Model for Epileptogenesis and Co-morbidities."

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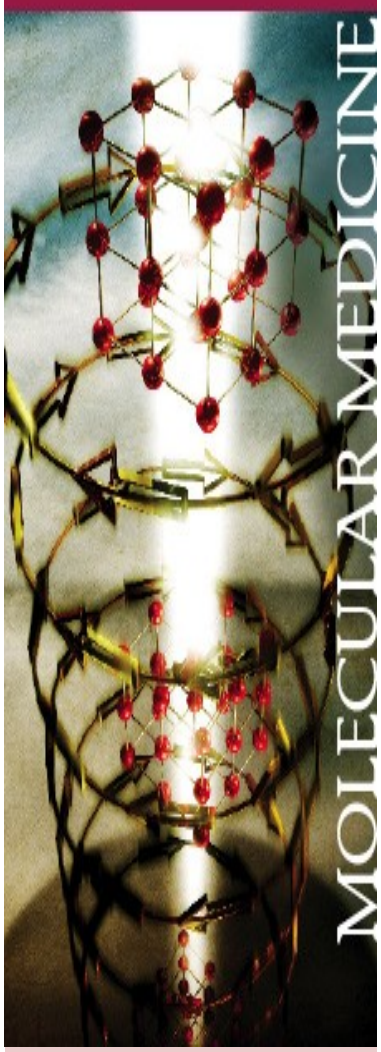

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