

## Hüttemann lab identifies mechanism that could halt dying process in the mitochondria of kidney

The lab of Dr. Maik Hüttemann has identified a mechanism that could halt the dying process in the mitochondria of kidney cells, specifically the cytochrome c heme protein.

Dr. Hüttemann, Associate Professor of Molecular Medicine and Genetics, and of Immunology, Biochemistry, and Molecular Biology, likens the finding to the concept of a battery. “Batteries can be discharged, which leads to a lack of energy; they can be overcharged, specifically under conditions of cell stress, where they generate toxic ‘free radicals,’ that trigger cell death processes, and there is the healthy charge in the middle: plenty of energy but very little free radicals.”



Dr. Maik Hüttemann

Or think of a car engine hooked up to a dead battery, an engine running in the red, or one contented-

ly purring along in the middle.

Dr. Hüttemann initially wanted to study cytochrome c oxidase, a protein complex that plays a key role in the generation of adenosine triphosphate (ATP) via electron transport. However, the study of cytochrome c oxidase is a massive undertaking, so much so that securing funding can be challenging. Thus, Dr. Hüttemann broadened his focus to cytochrome c, “a small but very important protein because it makes life and death decisions for the cell.”

Cytochrome c is one of the components of the electron transport chain (ETC) in mitochondria and catalyzes redox reactions. It is also involved in apoptosis – the programmed cell death process. In early apoptosis, mitochondrial reactive oxygen species (ROS) production is stimulated.

Cytochrome c “is not only crucial for the production of the vast majority of the cell’s energy in the mitochondria – the powerhouses of the cell – but it’s also a ticking bomb,” said Dr. Hüttemann. “Once it’s released from the mitochondria it starts apoptosis, which is also of medical importance. For example, in another ongoing project in the lab, we study apopto-

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## CMMG Faculty amass awards



Feldman

Finley

Zhang

Granneman

Hüttemann

Luca

Pique-Regi

2016 Research Excellence Award – **Francesca Luca**

2016 President’s Award for Excellence in Teaching – **Russell Finley, Jr.**

2016-2017 Career Development Chair’s Award – **Kezhong Zhang**

2017 Outstanding Graduate Mentor – **Roger Pique-Regi**

2017 President’s Award for Excellence in Teaching – **Gerald Feldman**

2017 Charles H. Gershenson Distinguished Faculty Fellowship – **Maik Hüttemann**  
 – **James Granneman**

*Charles H. Gershenson Distinguished Faculty Fellowship Awards were created to recognize and provide support for members of the faculty whose continuing*

*achievements and current activities in scholarship, research or in the fine and performing arts, are nationally distinguished.*

*The fellowships are part of the benefaction to the University by Charles H. Gershenson who formerly served on the Board of Governors. The term of each fellowship is two years. There have been approximately 78 fellowships awarded since their inception in 1985.*



## Genetic Counseling Masters Program a success

In April, the Center for Molecular Medicine and Genetics graduated the fifteenth class in its Genetic Counseling Graduate Program.



Angela Trepanier,  
MS, CGC

"We're proud of what is still a relatively young program," says Angela Trepanier, MS, CGC, Associate Professor of Molecular Medicine and Genetics and program director.

The program enjoys a 97 percent pass rate on the genetic counseling certification

exam, easily surpassing the national average of 80 percent. The matriculation rate is 97 percent as well.

The program, which began in 2001, has graduated 71 counselors.

Job placement is 100 percent. All of the April graduates had jobs lined up by February.

"Those who want jobs get them, basically," says Trepanier. "For the last couple of years, given a shortage of genetic counselors and many open positions, most students have secured strong salaries and signing bonuses or tuition remission."

According to the Bureau of Labor Statistics ([www.bls.gov/ooh/healthcare/genetic-counselors.htm](http://www.bls.gov/ooh/healthcare/genetic-counselors.htm)), the median pay for genetic counselors (as of May 2016) is \$74,120 per year. The job outlook for the 2014-24 period is 29 percent, dubbed "much faster than average" by the Bureau. That's compared to 10 percent estimated growth for other healthcare and technical occupations over the same period.

The two-year program is expanding, too, accepting eight candidates this fall, from a field of 111 applicants.

The program is just one of 41 in the U.S. and Canada and is fully accredited by the Accreditation Council for Genetic Counseling. Of Michigan's 128 certified genetic counselors, ~30% are WSU graduates. Not only are WSU alumni an important part of the Michigan workforce, but they are also involved in advocating for quality genetic counseling services in the state through the Michigan Association of Genetic Counselors (MAGC). In fact, four program alumni hold prominent positions on the MAGC board of directors: Lindsay Dohany (Class of 2007), President; Bridget O'Connor (Class of 2011), VP; Mary DeGrandchamp (Class of 2014), Treasurer; and Mary Mobley (Class of 2012), Genetic Services Chair.

Those who oversee the program serve as dedicated examples, and faculty from all over the city and state take part. "We have a great, committed group of professionals who

participate in training and program development," Trepanier says. This group includes Trepanier herself, along with Erin Carmany, MS, Associate Program Director of the Genetic Counseling Program and Assistant Professor of Molecular Medicine and Genetics, and Gerald L. Feldman, MD, PhD, Medical Director, Genetic Counseling Graduate Program and Professor of Molecular Medicine and Genetics, and of Pediatrics, and of Pathology. Together, the program directors and faculty strive to achieve the program's mission which is to train a highly qualified, competent, and culturally diverse genetic counseling workforce to enhance access to services in Michigan and beyond. A second part of the mission is to ensure students graduate with a strong foundation in genomics that allows them to adapt to the rapidly involving landscape of genomic medicine.

That the area's population is so diverse – coming from all walks of life and a variety of ethnicities – only serves to strengthen the Wayne State program. Students have excellent opportunities to learn other perspectives. According to the National Society of Genetic Counselors ([www.nsgc.org](http://www.nsgc.org)), "Genetic counselors are professionals who have specialized education in genetics and counseling to provide personalized help patients may need as they make decisions about their genetic health." According to NSGC, there are more than 4,000 certified genetic counselors nationwide.

Genetic counselors are schooled in two distinct disciplines – medical genetics and counseling – and are involved in assessing genetic risks, providing information about identified risks, and offering support to families who are affected by or at risk for genetic

disorders. They counsel families facing difficult decisions on healthcare matters, including questions on how family and medical histories may affect them and which genetic tests would provide the best and most useful information.

Genetic counselors can work in a clinic or hospital setting, and may specialize in a variety of areas, including prenatal, pediatric, cancer, cardiovascular, and neurology. They typically work alongside physicians, including medical (MD) geneticists. But there are a growing number of opportunities outside of clinical practice including positions with genetic testing laboratories, universities, insurance companies, and state health departments.

To be accepted, Trepanier says, candidates must stand out. Having a strong grade-point average is important, along with a solid science background. Most candidates have a degree in biology or related science. Counseling advocacy experience is required since genetic counselors have to be comfortable working with people who are in distress. A lifelong love of learning doesn't hurt either, as the field is growing, guided by new technology and discoveries.

"Genetic counseling is a wonderful profession," says Trepanier. "Not only is it ever-changing, but given the relatively small number of genetic counselors, there are many opportunities to take the lead in shaping where the profession goes. For me, this has been an unanticipated benefit of being part of the field."

For more information about the genetic counseling program or how to apply go to [www.genetics.wayne.edu/education/ms-genetic-counseling](http://www.genetics.wayne.edu/education/ms-genetic-counseling).



## Gow lab begins to see results from MS pathology study

Dr. Alexander Gow has entered into the final stretch of a three-year grant from the National Multiple Sclerosis Society, which is beginning to yield results.

Dr. Gow is a Charles H. Gershenson Distinguished Fellow, Professor of Molecular Medicine and Genetics, and of Pediatrics, and of Neurology, and Associate Director of the Center.



His grant is titled *Dr. Alexander Gow* "Neurodegeneration with metabolic stress in oligodendrocytes, the cells that synthesize myelin in the brain." A main goal is to characterize a novel preclinical mouse model of multiple sclerosis that recapitulates many pathological features in the brains of MS patients, including changes in behavior over time (i.e., memory, mood, and depression-like endophenotypes) and damage to cortical/gray matter regions of the brain associated with critical thinking. The construction of the mouse model, named the "Obiden mouse" by Gow's lab, allows a more detailed study for future application to MS patients and the development of treatments to reduce disease severity.

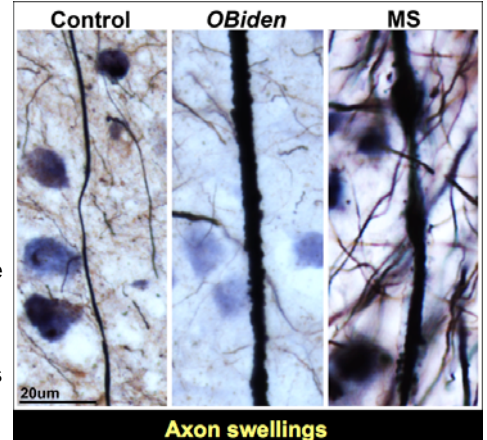
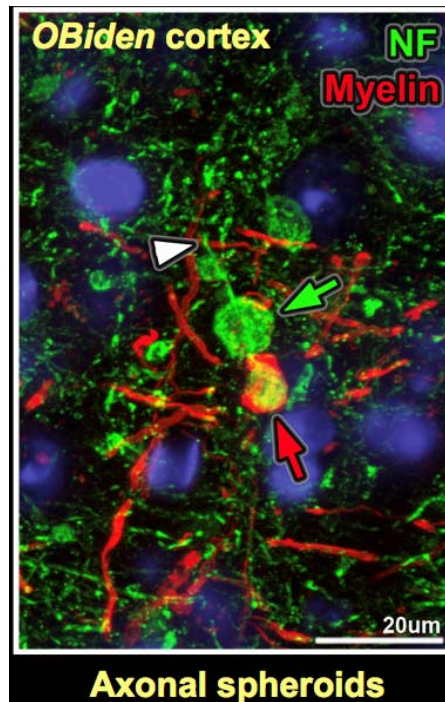
From the early to mid phases of MS, disease symptoms are accompanied by considerable damage to the brain in the forms of autoimmune lesions, or periventricular atrophy and cognitive deficits. Most studies to date have focused on finding disease modifying therapies for the autoimmune component of MS, and have tended to leave aside cognitive changes, which can be the most debilitating and frustrating aspects for patients and caregivers. Several important findings have come to light in recent years, including the revelation that strong immunosuppression of patients for several years only modestly slows disease progression, and that damage to cortical brain regions is much more widespread than has been appreciated.

Dr. Gow's study tackles both of these issues by using a novel model of MS pathology that does not involve autoimmune stimulation to generate disease symptoms. Rather, metabolic stress is activated in oligodendrocytes to cause dysfunction and death of these cells, which is a potential disease mechanism

that has gained experimental support from several laboratories, including his own. The knock-on effects of this primary pathology include neuronal pathology and cell death leading to periventricular tissue atrophy. Dr. Gow's lab also is seeking to determine if this non-immune-mediated "Obiden" mouse model can recapitulate MS pathology and provide evidence of behavioral changes and cognitive decline, which appears to be the case.

Finally, the lab is testing a drug treatment strategy designed to protect oligodendrocytes and neurons from the degenerative changes associated with inducing primary metabolic stress in oligodendrocytes.

Now, in year three, the study has started to see results. The drug Rapamycin, which has immunosuppressant functions and for this study targets metabolic pathways in cells, appears to be effective at changing behavior of control mice but not the Obiden mutants. With both groups of mice on the drug, the control group, when on Rapamycin, becomes more active. The Obiden mice, by contrast, experience less of an effect from the drug. It also appears the female Obiden mice benefit more from the drug, possibly because females tend to experience a milder form of MS, so the drug would logically have more impact.



"The known activity of the drug implicates a critical pathway for cell function and survival that may not be functioning optimally in the mutants. If so, the study could identify a biomarker for disease in the mice," says Dr. Gow.

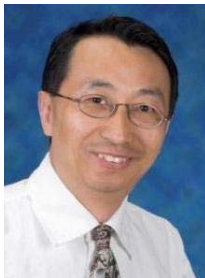
Dr. Gow states that, although autoimmune activity is unquestionably important to the symptoms and progression of MS pathology, there is increasing evidence to suggest that autoimmune attack on the CNS may be a secondary event rather than a primary cause of disease.

For example, it is clear that MS progression to disability continues despite almost complete cessation of new immune lesion formation using steroids or, more recently in several large clinical trials, antibodies to block immune cell entry into the CNS. These data are consistent with autoimmune-mediated exacerbation rather than etiology of the disease in a significant proportion of cases. MS etiology must therefore be reconsidered, and new preclinical nonimmune model systems tested and developed to enlighten disease pathophysiology, which has been a stated goal of NMSS since the 2002 French-American joint MS conference in Nice, France.

Dr. Gow's study uses one form of metabolic stress, namely the accumulation of a mutant form of myelin protein in the endoplasmic reticulum of adult mature oligodendrocytes, to analyze this possibility *in vivo*. In addition, this study will determine if reducing cell metabolism moderates pathology stemming from primary oligodendrocyte metabolic stress, including axonal pathology, neurophysiological, neurochemical, and behavioral/cognitive changes.

## Heng's 'genome chaos' theory gains traction among cancer researchers

The "genome chaos" theory of Dr. Henry Heng, Professor of Molecular Medicine and Genetics and of Pathology, continues to gain acceptance within the cancer research community.



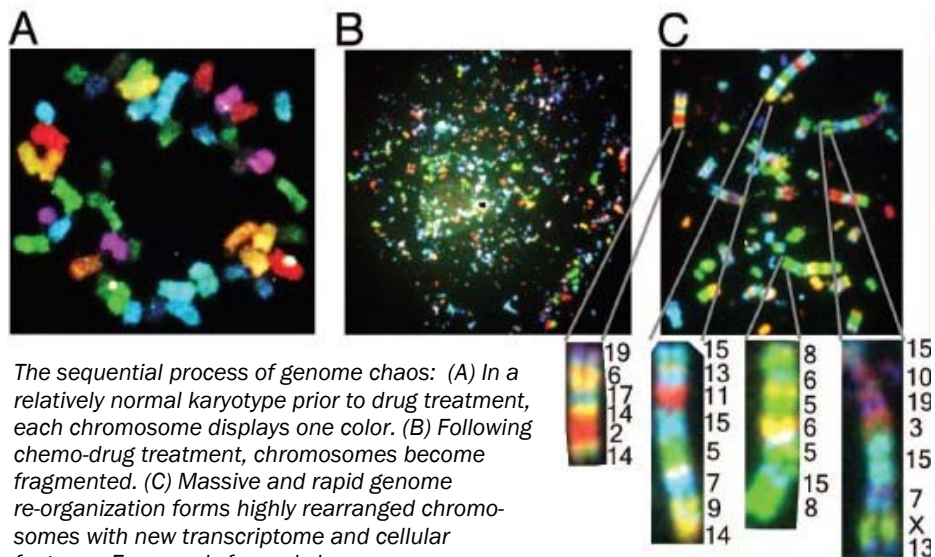
Dr. Henry Heng

According to Dr. Heng, one of the biggest surprises from the cancer genome sequencing project was the rediscovery of the chaotic genome. These rapidly and massively re-organized genomes were originally described by Dr. Heng's

laboratory here at Wayne State more than a decade ago. Now, chaotic genomes have been detected in nearly all types of cancer. Furthermore, in some cancer types, chaotic genomes have been found in the majority of cases. Many terms have been used to describe these fragmented and stitched chromosomes, including "chromothripsis," "chromplexity," "chromoanagenesis," "chromoanagenesis," "chromosome catastrophes," and "structural mutations." According to Dr. Heng, the invention of different buzzwords for the same biological phenomenon reflects the significance of these genome-level alterations, as they may offer a new mechanism of cancer formation: a non-traditional, punctuated-genome evolution.

The concept of genome chaos has also captured public imagination. Articles with titles such as "Monster Cancer Chromosome," "Chromosome Chaos," "Frankenstein DNA," and "Monster Fuels Cancer" point to a developing interest by major newspapers and leading popular science journals.

"Just a few years back, it would have been impossible to convince the research community to accept this concept," says Dr. Heng. His journey began decades ago, when he discovered multiple types of genome alterations in cancer cells, including chromosomal fragmentation. Since he joined the Center for Molecular Medicine and Genetics, his group has confirmed the dynamic relationships between stress, these fragmented and stitched chromosomes, and rapid genomic evolution (by re-shattering and creating the new genomes using the same DNA materials). Specifically, these extensive chromoso-



The sequential process of genome chaos: (A) In a relatively normal karyotype prior to drug treatment, each chromosome displays one color. (B) Following chemo-drug treatment, chromosomes become fragmented. (C) Massive and rapid genome re-organization forms highly rearranged chromosomes with new transcriptome and cellular features. Four newly formed chromosomes are listed, and the number indicates the chromosome origin. As a result of genome re-organization, the chromosomal coding is no longer the same in comparison to before treatment (modified from *Cell Cycle*, 13: 528-537).

mal changes have been linked to high levels of chromosomal instability (CIN), the punctuated cancer evolutionary phase, and tumorigenicity. In these initial studies, terms like "karyotypic chaos" and "genome chaos" were used. According to Dr. Heng, it is clear that these stochastic genome changes are essential for cancer evolution, as well as drug resistance. Linking genome chaos to cancer challenges the gene mutation theory of cancer, where stepwise accumulations of gene mutations over time is the key. "The implication is significant," says Dr. Heng.

The importance of genome chaos to cancer evolution was unfortunately not immediately appreciated, says Dr. Heng. In the face of massive changes, it is hard to identify impacted genes, and the stochastic nature of this process does not provide a common molecular pathway. Due to the drastic nature of these changes, they could be dismissed as merely in vitro artifacts. These chaotic genomes must be eliminated by cell death mechanisms in patients, many researchers argue, as it is difficult to document such radical variations via average profiling methods. Moreover, according to current evolutionary thinking, these massive genome alterations would not be survivable, since most big genetic changes are harmful, according

to Dr. Heng.

The concept of genome chaos is now ready to be generally accepted, as new molecular tools have discovered and confirmed its presence in a large number of clinical examples. According to Dr. Heng, this new phenomenon helps to explain the aggressiveness and complexity of cancer. However, the mechanism of genome chaos cannot be understood only by comparing DNA sequences, especially when chaotic genomes represent the stochastic genome alterations that occur during the punctuated phase of cancer evolution.

To fully appreciate the importance of genome chaos, Dr. Heng suggests that research should not only focus on the impacted genes, but also should incorporate the new concept of genome topology-defined system inheritance. Using the chaotic genome as an example, his group has linked genome chaos to transcriptome dynamics, the success of outliers, and evolutionary potential. Furthermore, these studies of genome chaos have led to the establishment of the genome theory of cancer evolution. According to this theory:

1) New karyotypes define new system inheritance, as similar gene content can result in different inheritance by simply changing the

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sis in cancer. Cancer cells acquire mechanisms to get around apoptosis, which is a major problem in cancer therapy."

"We believe that we have identified a mechanism, again through a specific chemical modification of our protein, which prevents it from participating in the cell death cascade, which we think is pretty exciting."

The chemical modification is called phosphorylation. In biology, it is called a posttranslational modification and it plays a critical role in many cellular processes, regulating enzyme function.

"The phosphorylation that we found on our protein in the kidney is important because it regulates the activity of the protein. It kind of tells the protein that the cell is happy and regulates its activity, similar to being in cruise mode when you drive your car and you're staying within the speed limit. The problem arises when cells face stress such as a temporary lack of blood flow, nutrients, and oxygen. Such stress leads to the loss of the phosphorylation, and once oxygen and nutrients get back into the tissue, the proteins are maximally active. Now, you're pushing down the gas pedal all the way, which usually doesn't end well."

At that level the reactive oxygen species, or free radicals, surge out of control. At that extreme it results in cell death – this is when the damage from a stroke or

heart attack occurs, to cite one illustration. On the other end, ATP is lacking, and the slow decay can cause acute inflammation or sepsis.

"We have a pretty good understanding of how energy is produced in our cells," Dr. Hüttemann said. "But what we don't know is how this process is regulated and how it responds to different energy demands and stress situations. For example, think of a muscle cell during a sprint versus at rest. Energy need and production are vastly different in these conditions."

According to Dr. Hüttemann, "this is the first report of a chemical modification of a protein in the entire aerobic energy production pathway for which we have collected functional and structural information, as well as identified the enzyme called a kinase that carries out the chemical modification on the protein.

"The kinase itself is very interesting," he said. "It's called AMP kinase, which has a built-in energy sensor and is famous for adjusting the activity of metabolic enzymes based on the energetic state of the cell. Our study is the first to show that AMP kinase targets a mitochondrial protein."

"The subject is not just of academic significance, but biological significance," he concluded. "With this study, we are pioneering a major contribution to understanding what happens in disease and cell death."

**2017 Faculty Promotions**

**Maik Hüttemann, PhD** will be promoted from Associate Professor to Professor in 2017



Hüttemann

**Kezhong Zhang, PhD** will be promoted from Associate Professor to Professor in 2017



Zhang

**Continued from Pg. 4**

genomic topology (or relationships among gene interaction). Despite the traditional focus on gene coding, chromosomal coding represents the true blueprint. In fact, the order of gene or other DNA sequences on chromosomes is a new type of genomic information. For example, the main function of sex in organismal evolution is to preserve the karyotype, thus preserving system inheritance (by making sure that the order of genes is the same);

2) Genome chaos is often associated with macro-cellular evolution (punctuated evolution), where rapid and massive genome fragmentation and re-organization is needed for survival; this differs from stepwise, micro-cellular evolution, which involves the accumulation of small changes (e.g. at the gene/epigene level);

3) Transcriptome dynamics are linked to evolutionary potential and provide an explanation as to why different molecular pathways can be detected in winning cells after selection. This concept is well-illustrated using multiple level landscape models. In this model, ge-

nomical alterations can be divided into global landscapes (big mountains representing karyotypes) and local landscapes (small hills representing gene mutations and epigene status). Any karyotype-level change will impact the transcriptome dynamics involving many genes or pathways.

4) Recent studies of cell population outliers have demonstrated the power of the individual chaotic genome in macro-cellular evolution, which explains why evolution can succeed despite the massive cell death coupled with genome chaos. While unstable, these genomes can rapidly evolve until stable clones emerge and thrive, representing the only chance for survival under crisis. This sheds light on a key paradox of current aggressive therapeutic strategies, where high initial cell death consistently results in drug resistance. Despite early massive tumor cell killing, surviving populations after drug-induced genome chaos emerge and drive population growth and disease progression; and

5) Genome alterations play important roles for normal cellular adaptation but, as a trade-

off, too many of them will lead to diseases including cancer.

With these recent discoveries, Dr. Heng insists that the research community reconsider its current framework, research strategies, and practices regarding gene-based research in cancer. Considering the heterogeneity and large-scale genomic changes that are key characteristics of the disease, the real impact of specific gene mutations in cancer becomes limited. By and large, cancer gene mutations represent moving targets. A new strategy must be adopted that integrates multiple level landscape models, which will not only account for the fitness contributed from gene mutations/epigenetic changes, but also the survival landscape determined by genome re-organization-mediated macro-evolution. System inheritance, or the genetic blueprint, is not only about new mutations and dosages of individual genes, but the new karyotype-defined genome system. More detailed information about the genome theory of cancer evolution can be found in Dr. Heng's book, *Debating Cancer: The Paradox in Cancer Research*.

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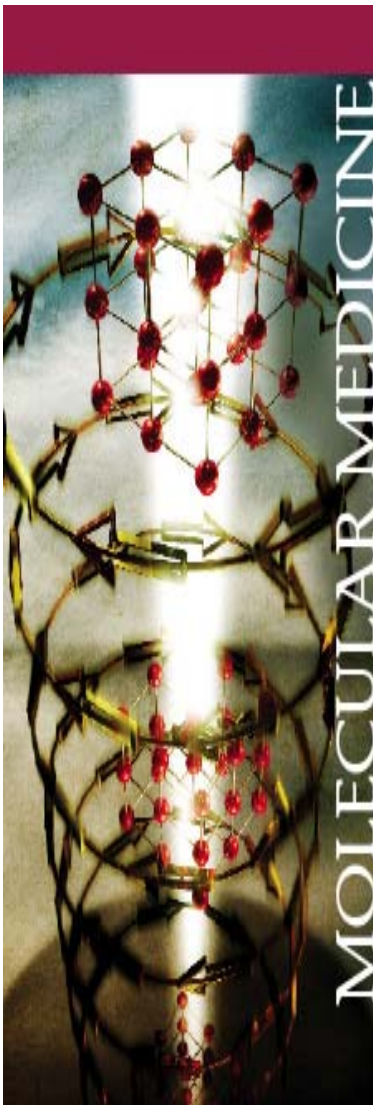
Michelle Cichon, MS, CGC

**Administrative Staff:**

Lydia Knight, MM/HRM  
Suzanne Shaw, ALA  
Aleesa Toman, MBA  
David K. Wissbrun, MBA

**Newsletter Written  
and Edited by:**

Heidi Bitsoli



Wayne State University  
School of Medicine  
3127 Scott Hall  
540 East Canfield Avenue  
Detroit, Michigan 48201

Phone: 313.577.5323

Fax: 313.577.5218

Web: [www.genetics.wayne.edu](http://www.genetics.wayne.edu)

Email: [info@genetics.wayne.edu](mailto:info@genetics.wayne.edu)

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