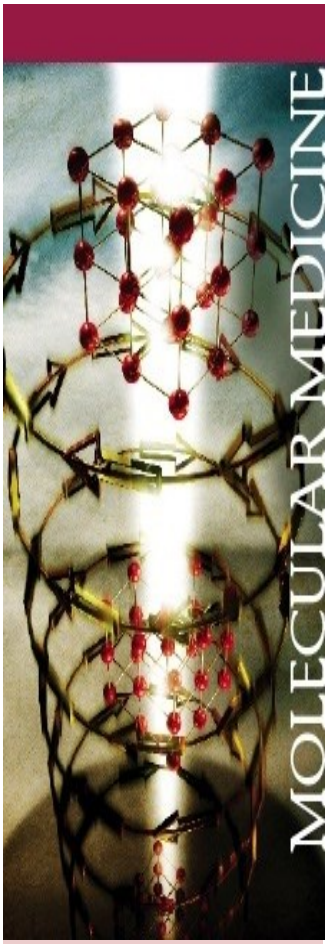


CENTER FOR
MOLECULAR MEDICINE AND GENETICS

Spring 2019

Center celebrates 20 years of ground-breaking science

The Center for Molecular Medicine and Genetics celebrated its 20th anniversary as an interdisciplinary biomedical center for basic and translational research and education.

The Center's director, Dr. Lawrence I. Grossman (the Henry L. Brasza Professor of Molecular Medicine and Genetics), describes it as "interdisciplinary by design, built around modern molecular genetics, and comprising basic researchers, physician-scientists, computational scientists, and genetic counselors. This mix allows us to run the gamut from basic research to clinical genetics to translation to the bedside and, in some cases, all the way to a biotech company."

The foundation of the Center lies with its faculty and the research programs they pursue. Dr. Grossman explains that "our underlying goal is excellence in molecular genetics, molecular medicine, and genomics to increase the understanding, diagnosis, treatment and prevention of human disease. Our daily goal is to do this in a stimulating, supportive environment where we also have fun."

"First and foremost," Dr. Grossman says, "the Center has emphasized ground-breaking science." In a previous time, the late Morris Goodman (Distinguished Professor and Professor of Anatomy and Cell Biology and of Molecular Medicine and Genetics) was a pioneer in molecular evolution who is credited with laying the foundations of molecular phylogenetics. Goodman's assertion that chimpanzees and gorillas are genetically more closely related to humans than to other apes was controversial at the time but was later validated when technology caught up and DNA sequencing became possible. Goodman, who was (and remains) the only WSU faculty member to be elected to the US National Academy of Sciences, continued his ground break-

20 Years, Continued on Pg. 5

Inside this issue:

Nobel winner Dr. Baltimore honored with Palade award

The Center reached a significant milestone in 2018, marking its 20th anniversary as a Wayne State University center. To celebrate and reflect on several successful decades of research, education, clinical excellence, and service to the greater Detroit community, the Center partnered with the George E. Palade endowment to invite David Baltimore for a visit and seminar.

Dr. David Baltimore

Dr. Baltimore, President Emeritus and Robert Andrews Millikan Professor of Biology at the California Institute of Technology and a Nobel Prize laureate, is a co-discoverer of the reverse transcriptase enzyme, which copies RNA into DNA, which thereby advanced our knowledge about the interaction between tumor viruses and the genetic material of the cell. He presented the George E. Palade Distinguished Lecture on September 25, 2018 at the Wayne State University School of Medicine and was also honored with the George E. Palade Gold Medal Award. Dr. Baltimore won the 1975 Nobel Prize in Physiology or Medicine with Renato Dulbecco and Howard Temin for their discoveries. He was previously the Founding Director of the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology and President of the Rockefeller University. He received the National

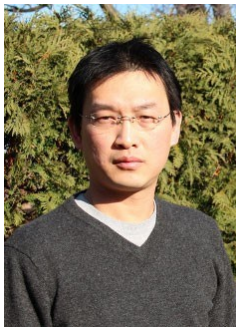
Palade, Continued on Pg. 5

Tseng lab uses computing cluster to render 3D models of protein structures, and characterize drug pharmacokinetics

Dr. Yan Yuan (Jeffrey) Tseng's lab is working on a powerful computing cluster that he has built for 3D modeling of protein structures that are designed to create and test drug therapies.

"My research is focused on developing accurate and efficient methods of computational geometry and applying these methods and molecular dynamics simulations to obtain structural and mechanistic insights into protein structure, function, and evolution," Dr. Tseng, Assistant Professor of Molecular Medicine and Genetics, and of Biochemistry, Microbiology, and Immunology, explains. "I pursue biophysical and evolutionary analyses, and I work with chemical biologists, neurobiologists and cancer biologists to study protein structure and function. In particular, I design geometric algorithms to identify drugable sites and conduct structure-based drug screening with my collaborators for novel drug discoveries." Dr. Tseng has been promoted to Associate Professor with tenure starting August 19th of this year.

His research has focused on identifying functional surfaces of proteins to "detect and characterize (1) structural variations between protein duplicates, (2) nonsynonymous single nucleotide polymorphisms (nsSNPs) in genome-wide association studies, and (3) Protein Surface Classification (PSC)."



Dr. Jeffrey Tseng

For the project, Tseng has constructed a database called SplitPocket (http://pocket.med.wayne.edu) to identify functional surfaces of proteins from their structure coordinates. The result is identification of more than 35,000 protein binding pockets. "Using the Alpha Shape Theory, we previously developed an analytical approach to identify protein functional surfaces by the geometric concept of a split pocket," he says, "which is a pocket split by a binding ligand. This integrated webserver of functional surfaces provides a source of spatial patterns to serve as templates for predicting the functional surfaces of unbound structures involved in binding activities. These spatial patterns should also be useful for protein functional inference, structural evolution, and drug design."

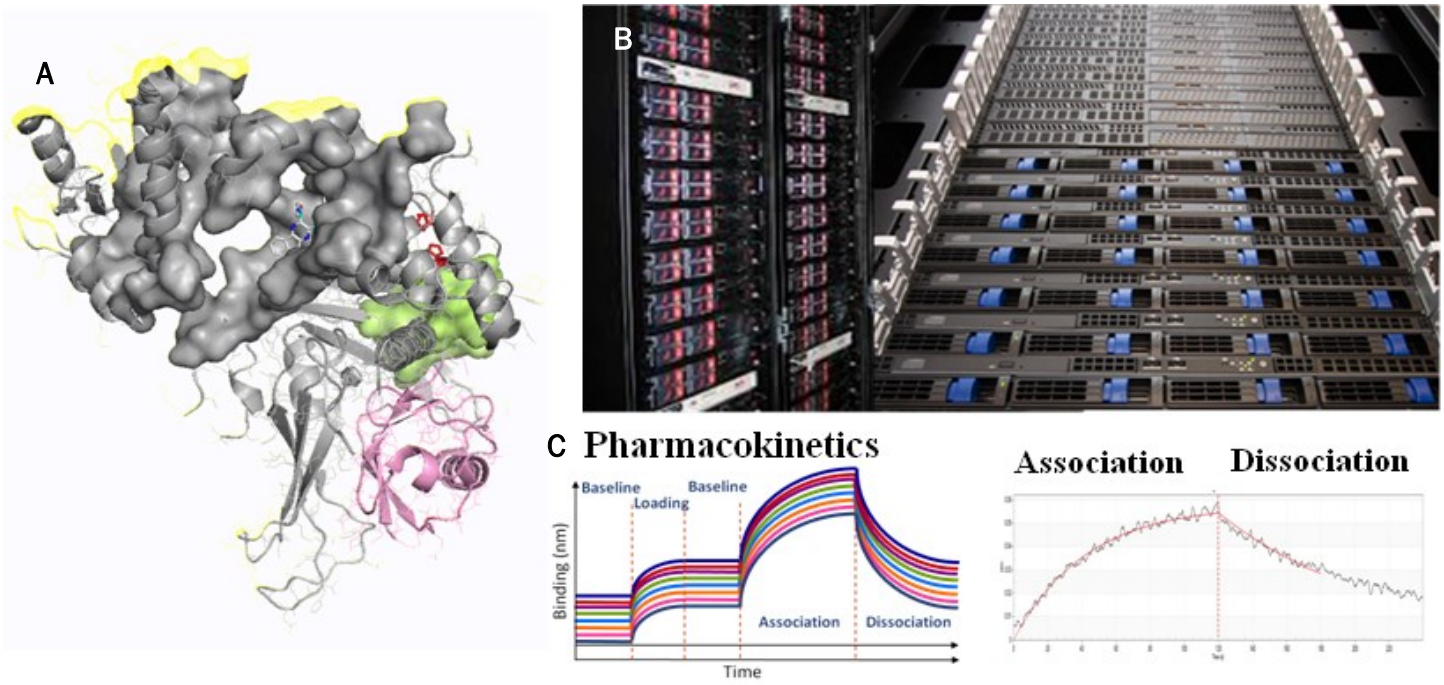
To test these methods, Dr. Tseng is collaborating with several principal investigators (PIs), including the Center's Dr. James Granneman and Dr. William Roush at Scripps Research Institute. The findings allowed them to secure two NIH R01 grants in 2015 and 2016 from NIDDK.

Dr. Tseng was also awarded an NIH R01 grant in 2017 from NCI to study genome-wide cancer-related variants with Dr. Jie Liang at the University of Illinois in Chicago and his Center colleague Dr. Kezhong Zhang.

"Each project has several interrelated objectives that require special scientific and technical approaches to achieve our goals," he explains.

Since he joined WSU, Dr. Tseng has worked steadily on analysis of protein conformational diversity and on methods of analysis. "I have developed GPU-accelerated molecular dynamics techniques for dynamic shape analy-

Dr. Tseng, continued on Pg. 3



(A) 3D structural model on protein USP22 used to analyze potential antagonist with (B) High-throughput computing Linux clusters with 2048 CPU cores and 64 GPUs for 3D structural modeling and molecular simulations. (C) SPR (Surface Plasmon Resonance) and BLI (Bio-Layer Interferometry) technology for novel drug screening and characterization of pharmacokinetics at CMMG research center.

Aras' team seeks treatment options for viruses by studying their effects on mitochondria

The laboratory of Siddhesh Aras, MBBS, PhD, Assistant Professor (Research) of Molecular Medicine and Genetics, is studying how viruses affect cellular energy, and is working on treatments to halt the path of destruction these invaders inflict on host cells.

Viruses typically target the mitochondria, leeching energy from the host cell. Ongoing research in the Aras lab is focused towards a better understanding of how a virus hijacks the cellular energy machinery.

Each virus poses its own challenges, and Dr. Aras aims to find more effective mechanism-based treatment options.

HIV, for example, has drug treatments available but no cure, and with the existing remedies there are caveats. In the case of HIV research, Dr. Aras' team is testing cell models, using central nervous system neurons to see the effects of viral infection and therapy. "Antivirals have a toxic effect on host mitochondria (to put it broadly)," he says. "We're evaluating the pathway by which the virus affects the mitochondria and the way the antiviral affects it." Dr. Aras' lab has grant funding from the National Institutes of Health in the form of a two-year R21 grant to study HIV.

"Our hypothesis is that most treatments target the virus," Dr. Aras explains. "We thought, why not target something in the cells, like for example prevent the virus from getting energy to multiply?"

Dr. Siddesh Aras

In addition to HIV, Dr.Aras is also studying two other viruses – Hepatitis C and Zika.

Zika, a relatively new threat, has no cure. "It's an upcoming infection, and the World Health Organization has declared it a public health emergency," Dr. Aras says.

Hepatitis C is of interest because it has only one treatment available, and it's very expensive.

What's special about both these viruses is that they require a specific gene in the host cell, namely Mitochondria Nuclear Retrograde Regulator 1 (MNRR1), that Dr.Aras has been working on for the past 8 years. In the absence of MNRR1, both these viruses fail to replicate in host cells. A central question is, how does MNRR1 facilitate viral replication?

"We want to understand the pathway the virus uses for energy from the host. Is there an important target in the mitochondria? Can we identify a common lynchpin target to circumvent the virus?"

In other words, what are the functional mitochondrial pathways different between normal versus virally infected cells? With the mapped pathway, when a specific virus infects the cells, it would be possible to target only the infected cells.

Dr. Aras would like to study and work on a number of viruses to identify a common pathway. One of interest is Epstein-Barr virus. With >90 percent of the world's population testing positive for it, "the virus is a good model to study how viral infections affect the mitochondria because it has a latent stage (quiescent) and an lytic (active) stage. "We can do more teasing out of the pathway using Epstein-Barr as a model," he says.

Besides hoping for some real inroads toward treating troublesome and life-threatening viral infections, Dr. Aras would like to use the findings toward cancer treatment, specifically those caused by viruses.

Dr. Tseng, Continued from Pg. 2

sis of proteins, with the goal of gaining biological insights into protein functions," he says. He has also carried out geometric computations on cancer-related proteins using thousands of computing cores in high-performance clusters he's built in his lab. "To gauge the performance of our computational methods, my lab has extensively been involved in the development of a large scale and automatic pipeline of screening compounds to discover potent drugs. I successfully integrated the methods of computational geometric predictions with real-time pharmacokinetics based on Surface plasmon resonance (SPR), Bio-Layer Interferometry technology, and for experimental validation and characterization of protein-protein interactions and novel drug discoveries in my lab."

Looking ahead, Tseng says, "Identifying cancer variants in coding regions and understanding their roles can help to develop novel diagnoses, to identify therapeutic targets, and to formulate effective treatment strategies.

"We assess protein dynamic surfaces and map a significant portion of somatically acquired cancer-related coding variants to precomputed protein functional surfaces by integrating multiple sources of data (COSMIC, TCGA, dbGAP, and 6,000 exome ESP)," he continues. "Geometric, evolutionary, and biophysical properties of these functional surfaces will be computed, and a predictive model will be developed for discoveries of additional unknown cancer-related genetic variants and their higher-order cooperative units. Building upon our protein surface analysis using computational geometry as well as analysis of molecular evolution, our lab will provide unique computational capabilities that can help to elucidate the structural and functional basis of known cancer genetic variants, to assess their biochemical roles for novel mechanistic insight, and to leverage known experimental data to discover high confidence cancer genetic variants."

The research carried out in the Tseng laboratory encompasses surface alignment, surface mapping of protein functions, structural characterization of disease-associated SNPs, protein surface classification, protein structural evolution, patterns of cancer-related

Dr. Tseng, Continued on Pg. 6

Krawetz contributes to U.S. report on effects of the Gulf War on generational health

Wayne State University School of Medicine reproductive medicine researcher Stephen Krawetz, PhD is among the national experts from 16 institutions selected to serve a two-year term on a National Academies of Sciences, Engineering and Medicine committee that prepared a comprehensive report on the reproductive effects of wartime exposures on Gulf War veterans and their children.

Dr. Stephen Krawetz

> *"Exposures across the life course, beginning in utero, can have an impact on health, including that of future children. Those exposures … may interact with one another and be influenced by a person's genome and epigenome."*
>
> **— Gulf War and Health, Volume 11**

Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War" was published Nov. 28. A full copy is available at nationalacademies.org/GulfWarHealth11

The report concludes that no toxicant had sufficient evidence of a causal association between exposure and reproductive or developmental effects. "Nor did any toxicant have limited/suggestive evidence of no association between exposure and reproductive or developmental effects," the report states.

However, Dr. Krawetz and his colleagues end the report by proposing and outlining a health monitoring and research program to help determine if veterans' descendants are at risk for health effects resulting from the veterans' deployment. The program would including the monitoring of veterans' and their descendants' health over time, epidemiologic studies to examine health outcomes of concern, and basic and translational research to help address data and knowledge gaps.

"Exposures across the life course, beginning in utero, can have an impact on health, including that of future children. Those exposures ... may interact with one another and be influenced by a person's genome and epigenome. Such changes are being studied, but at present there is not enough evidence to link any deployment exposures to epigenetic effects," the report concludes.

A reproductive medicine scientist, Dr. Krawetz is the associate director of WSU's C.S. Mott Center for Human Growth and Development, and the Charlotte B. Failing Professor of Fetal Therapy and Diagnosis in the Department of Obstetrics and Gynecology, and Professor of Molecular Medicine and Genetics.

Researchers from the Farber Cancer Institute, Harvard T.H. Chan School of Public Health, Emory University, the University of Maryland and more, were brought together to address a specific Statement of Task. Nearly 700,000 U.S. troops were deployed to the Persian Gulf region during the height of Operation Desert Shield and Operation Desert Storm. In any war, deployed service members may be exposed to hazardous agents and situations, including pesticides and solvents, chemical and biological agents, mandatory vaccines, oil-well smoke, dust, high ambient temperatures and heat stress, depleted uranium and pyridostigmine bromide, a prophylactic agent against nerve agent exposure.

The committee began its deliberations with public meetings to hear from VA representatives, academic researchers, interested veterans and veterans' service organizations. It also gathered information from the National Institute of Environmental Health Sciences and its National Toxicology Program, the U.S. Centers for Disease Control and Prevention, and the Department of Defense. Actual tasks were driven by the published literature and the committee's expertise.

In 1998, Congress directed the Department of Veterans Affairs to contract with the National Academies of Sciences, Engineering and Medicine to evaluate the scientific and medical literature regarding associations between illness and exposure to the toxic agents, environmental and wartime hazards, and preventive medicines and vaccines associated with Gulf War service. Since then, the National Academies has prepared 11 volumes of the Gulf War and Health series, focused on the health of Gulf War veterans. The latest assesses the available evidence on the reproductive systems of Gulf War and Post-9/11 conflicts, and provides guidance to VA on future research. The report also lists potential ways researchers may determine if there are health issues in the children or grandchildren of veterans of any era related to their parents' or grandparents' deployment exposures.

The National Academies of Science, Engineering and Medicine is a Washington, D.C.-based independent organization that provides objective advice on issues affecting people's lives worldwide.

20 Years, Continued from Pg. 1

ing work in the Center until his death, in November of 2010, at age 86.

Current research covers a wide range of basic and translational projects. Examples are the role of mitochondria in infectious disease, in various mitochondrial diseases, in hypoxia and oxygen sensing, and in cancer; gene regulation during cardiovascular, hematopoietic, and eye development, and in spermatogenesis; intracellular stress signaling and inflammation and its role in neurodegenerative diseases; functional genomics of long noncoding-RNA transcripts; computational methods and statistical genetic models; gene -environment interactions and complex traits; genomic instability; adipose tissue cell and molecular biology; obesity and diabetes; cancer genetic studies of familial cancers; mechanisms in sarcoidosis and interstitial lung disease; multilevel statistical modeling and model selection in high dimensional data; regulatory networks that control cell proliferation; protein structure and function, with an emphasis on modeling disease associated mutations; and use of molecular technologies in the diagnosis of genetic diseases.

Some of these basic research directions have stimulated translational applications. Two current examples are work from the laboratory of Maik Hüttemann (Professor of Molecular Medicine and Genetics and of Biochemistry, Microbiology and Immunology) on preventing ischemia-reperfusion injury. Dr. Hüttemann's laboratory has been developing infrared light technology capable of halting cellular damage caused by this injury before it can take root; the lab is currently developing a medical device that could be used in hospitals and clinics. A second example stems from the work of Lobelia Samavati (Associate Professor of Internal Medicine and of Molecular Medicine and Genetics) whose basic research has led to a tool for disease diagnosis that was initially applied to cystic fibrosis (both applications are described in the Center's Summer 2018 newsletter).

In addition to its research strength, the Center is home to strong educational programs that include tracks to earn a PhD, MD-PhD, and MS in molecular genetics and genomics. The Center's clinical division includes an MS program in genetic counseling, as well as clinical residency and fellowship training programs in genetics and genomics. Most recently, the MS program in molecular genetics and genomics was developed by CMMG faculty members and approved by the University. Several students have already earned that degree in the few years of the program's existence.

The genetic counseling graduate program continues to excel. "We're proud of what is still a relatively young program," says Professor Angela Trepanier (Associate Professor (Professor as of Aug. 19, 2019) of Molecular Medicine and Genetics, and program director). The need for genetic counselors has doubled in the past decade and is forecast to double again within the next 10 years. The field's surge is due to rapid growth of clinical genomic testing and to non-patient facing genetic counseling job opportunities with genetic testing laboratories, insurance companies, and others. Due to growing demand, job openings continue to outpace the number of qualified genetic counselors. "The Center is doing its part," Prof. Trepanier explains, "by enrolling six to eight new students each year and is developing additional plans for expanding enrollment capacity."

As a university center at Wayne State, the Center is positioned to take advantage of opportunities not only in the School of Medicine but also via its partnership with the WSU Division of Research. Its grant portfolio exceeds $30 million and in recent years research expenditures have exceeded $6 million annually. In the academic year 2018-19 the Center was engaged in faculty recruitment and hired Dr. Shengyi (Iris) Sun, from the University of Texas Southwestern Medical Center, who will arrive on July 1 of this year as Assistant Professor of Molecular Medicine and Genetics and of Biochemistry, Microbiology and Immunology. The Center is located in the University's Scott Hall building on the WSU/DMC medical campus. It occupies over 28,000 square feet, with both open and closed laboratory space, equipment and procedure rooms, offices, conference rooms and interactions areas, as well as a server room.

As Palade laureate Dr. Bhanu Jena (Professor of Physiology and Center member) summarizes, "The Center has made tremendous contributions to not only science and education but has had a positive impact on the medical school as well as the entire University."

Palade, Continued from Pg. 1

Medal of Science from President Bill Clinton in 1999.

For the Palade lecture, Dr. Baltimore spoke on the "Fine Control of Gene Expression by Retaining Introns." Treatment of cells with proinflammatory stimuli like tumor necrosis factor turns on a gene program that greatly alters the cells' properties. Central to that program is activation of the transcription factor NF- kB. Dr. Baltimore's work has demonstrated that, although NF-kB-mediated transcriptional activation happens within 5 minutes of treatment, the induced program activates over many hours. This has led to the realization that the splicing of the pre-mRNA gene transcripts from individual genes is spread over time and is controlled at least partially by bottleneck introns that are slow to splice. The splicing of bottleneck introns involves a specific splicing factor, the function of which Dr. Baltimore is in the process of determining.

In 1968, he was recruited by Nobel laureate Salvador Luria to the Department of Biology at MIT as an associate professor of Microbiology. There, he extended his work and examined two RNA tumor viruses. He then discovered reverse transcriptase, the enzyme that transcribes DNA from RNA. In doing so, he discovered a distinct class of viruses – later named retroviruses – that use an RNA template to catalyze the synthesis of DNA. This overturned a central belief of genetic theory, garnering him the Nobel Prize at age 37.

Dr. Bhanu Jena, the George E. Palade University Professor and Distinguished Professor of the Wayne State University School of Medicine's Department of Physiology and member of the Center for Molecular Medicine and Genetics, presented Dr. Baltimore with the George E. Palade Gold Medal Award. Dr. Jena himself received the award in 2005.

The award and lecture are named for the man considered the father of modern cell biology, George Palade, who also shared the Nobel Prize for Physiology or Medicine, in 1974, with Professors Albert Claude and Christian de Duve. Dr. Palade was honored for his pioneering studies in the 1950s and 1960s that defined the structure and func-

Palade, Continued on Pg. 6

Palade, Continued from Pg. 5

tion of cellular components, including the ribosome, secretory vesicles, and the endoplasmic reticulum.

In 2003, WSU President Irvin Reid established the award and lecture at the School of Medicine. The first recipient was Professor Palade's student, Professor Günter Blobel, himself also a Nobel Prize winner (1999, in Physiology or Medicine, for his discovery in the 1970s and 1990s that "proteins have intrinsic signals that govern their transport and localization in the cell"). Since its inception, the award has been given to five Nobel Prize winners.

An interesting sidelight to the 2018 Palade awards was the presence at the event of two previous winners – besides Dr. Jena, Dr. Walter F. Boron, Professor and Chairman of Physiology and Biophysics at Case Western Reserve University and 2010 Palade award recipient for "pioneering work on pH regulation in cells," was in attendance.

That Dr. Baltimore attended to accept the award and deliver a lecture "shows respect for the Center's accomplishments, that Dr. Baltimore is a friend of CMMG," Dr. Jena said.

Dr. Tseng, Continued from Pg. 3

mutations and molecular dynamic simulations. The lab overall has been engaged in developing theory, methodology, interdisciplinary concepts, bioinformatics approaches, and advanced computational skills to great extents.

The Tseng lab is equipped with a Linux cluster consisting of 96 Titan GPUs, 80-cores Xeon blades (16,00 Hyperthreads), cluster processors with 2048 CPU cores of 3.0 GHz and 2TB server memory, and additionally supported by more than 5,000 cores of a grid network in the Grid Center of the Computer and Information Technology unit. The lab also has numerous Linux, Mac, and Windows workstations for development of new approach and algorithm design.

"Our lab has been building multiple high-throughput cluster computers with thousands of cores and 64-GPU-accelerated clusters," Dr. Tseng says, "and is also launching a highly-anticipated service of real-time pharmacokinetics based on Bio-Layer Interferometry technology for novel drug discovery and the identification of the network of protein-protein interactions. Our lab has been also maintaining multiple web-servers that provide resources such as SplitPocket, PSC, and databases such as fPOP and PSD for investigators who represent a wide range of research and academic disciplines from over 100 institutions. Users freely access these servers hosted in my lab in the Center more than 300 times monthly."

Faculty and trainee accomplishments

Cynthia Kalita, PhD (Luca & Pique-Regi labs) successfully defended her PhD thesis in December 2018. Further, Ms. Kalita had a portion of her thesis published in *Genome Research.*

Neeraja Purandare, PhD (Grossman lab) successfully defended her PhD thesis in September 2018.

James Granneman, PhD was awarded the School of Medicine 2018 College Teaching Award.

Jeffrey Tseng, PhD was awarded the School of Medicine 2018 College Research Excellence Award.

Michael Tainsky, PhD was awarded the School of Medicine 2018 College Teaching Award.

Hasini Kalpage (Hüttemann lab) was awarded 1st place for oral presentation at the 2018 CP Lee Graduate Student Research Presentation Day.

Jenna Isherwood (Ruden lab) was awarded an honorable mention in poster presentation at the 2018 CP Lee Graduate Student Research Presentation Day.

Sophia Chaudhry (Tainsky lab) served as Chair of the 2018 CP Lee Graduate Student Research Presentation Day.

Michelle Cichon, MS, CGC was named to the Accreditation Council for Graduate Medical Education (ACGME) Coordinator Advisory Group for a 3-year term.

Christos Strubakos, PhD a student in the Department of Physiology, co-mentored by Dr. Thomas Sanderson and Dr. Maik Hüttemann, successfully defended his PhD thesis in August 2018.

Anthony Findley (Luca and Pique-Regi labs) was awarded a 4 year NIH F30 MD-PhD Fellowship. Anthony was also awarded an AHA pre-doctoral fellowship. However, he will have to turn down the AHA to accept the NIH fellowship.

Junmei Wan (Hüttemann lab research associate) successfully defended her Master's thesis in December 2018. Junmei was part of the Biochemistry, Molecular Biology and Immunology MS program.

Francesca Luca, PhD and Roger Pique-Regi, PhD served as organizers of the Presidential Sesquicentennial Symposium: Genes, Urban Environments and Health. This event was co-organized by Genomics@Wayne, RoBUST, the School of Social Work, and CURES. It focused on genomics and the impact of urban environments on human health - September 2018.

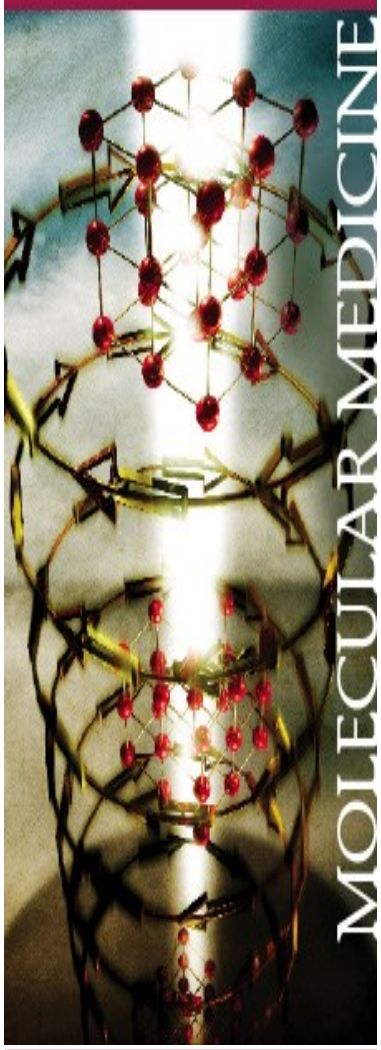
Francesca Luca, PhD and Roger Pique-Regi, PhD were awarded 2-year support from the WSU Division of Research for a postdoctoral fellow position, via the Division's November 2018 Faculty Competition for Postdoctoral Fellows.

Hasini Kalpage (Hüttemann lab) was awarded a Competitive Graduate Research Assistant fellowship for the 2019-2020 academic year. This is her second consecutive year receiving the award.

Sophia Chaudhry (Tainsky lab) was awarded a Competitive Graduate Research Assistant fellowship for the 2019-2020 academic year.

Francesca Luca, PhD was awarded a 2019-2020 Career Development Chair Award by Wayne State President M. Roy Wilson.

Kezhong Zhang, PhD was named a Charles H. Gershenson Distinguished Faculty Fellow by Wayne State President M. Roy Wilson.



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