Interactions

Nicholas Chia, PhD

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MAYO CLINIC & ILLINOIS ALLIANCE
FOR TECHNOLOGY–BASED HEALTHCARE

IHSI INTERDISCIPLINARY HEALTH SCIENCES INITIATIVE AT ILLINOIS

Interactions

highlights the collaborative activities of the Mayo Clinic & Illinois Alliance for Technology-Based Healthcare.

Inside

Director's Message

President Barack Obama unveiled the Precision Medicine Initiative in his annual State of the Union address in early 2015. His goal with the initiative is to radically change the medical care delivered to patients in the U.S.

"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time," the President said.

While the scientific and medical communities await word on Congressional funding of this new federal initiative, thankfully, the promise of personalized healthcare is already becoming reality. Institutions like the University of Illinois at Urbana-Champaign and Mayo Clinic have been concerned with individualized medicine for some time, and their work is having a real impact in cancer treatment—not to mention the prevention and detection of a myriad of other health conditions.

The Mayo Clinic and Illinois Alliance for Technology-Based Healthcare, now five years old, continues to grow and flourish. Whether you are new to the alliance or the realm of precision medicine, or if you have been connected for years, we invite you to keep reading.

In *Interactions*, our inaugural print publication, we'll tell you about the collaborative activities of the alliance from May 2014 to May 2015. From researcher Nicholas Chia and his path from Illinois to Mayo Clinic and his continued interactions, to the $9.3M NIH award to build a Knowledge Engine for Genomics (KnowEnG), our investigators are making progress toward precision medicine outcomes.

You'll also learn about the innovative educational opportunities the alliance inspires. The next generation of biomedical scientists is upon us. Annually, more Illinois undergraduates participate in Mayo Clinic's summer research fellowship program (SURF) than any other university. Two Illinois Community Health PhD students were mentored during their summer research experience at Mayo Clinic. More than fifty people participated in the 2014 Computational Genomics Course.

Precision medicine is more than a trendy concept. It is being realized daily, through the interactions of clinicians, researchers, and students. Precision medicine is moving from promise to practice.

So I'll segue to Mayo Clinic's 2015 Individualizing Medicine Conference: From Promise to Practice, in Rochester, Minnesota from September 20-23. We hope you are making plans to attend. Visit mayoillinois.org to register and learn more.

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Director, Mayo Clinic and Illinois Alliance for Technology-Based Healthcare

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Modeling an Innovative Research Alliance

by Margret Berg Miller

Nicholas Chia: analyzing how the human body's trillions of microbes predict and indicate certain types of cancer.

Meet Nicholas Chia, PhD, former University of Illinois postdoc fellow turned associate director of Mayo Clinic's Center for Individualized Medicine's Microbiome Program and Department of Surgery consultant. If you'd told Chia during his postdoc days that he would wind up at Mayo Clinic, he would have laughed you out of the lab. He is by no means a surgeon—to date, he's never set foot in an operating room.

You see, Dr. Chia is actually a physicist.

Research scientist to clinical consultant

While Chia's education is in physics—he earned his bachelor's from Georgetown and his PhD in Physics from The Ohio State University—he claims to have never really studied physics or worked on a physics problem, per se, since his days as an undergrad at Georgetown. His graduate work dealt with statistics and sequence alignment, teaching him how to manage rare events, big data, and computational challenges, which built a foundation for things to come.

After graduate school, Chia landed at the University of Illinois at Urbana-Champaign as a postdoc under renowned biophysicists Carl Woese and Nigel Goldenfeld, modeling microbial dynamics in evolution and studying the origins of life. While working at the Institute for Genomic Biology at Illinois, Bryan White asked him to help analyze a new pyrosequencing data set from the microbial communities in the bovine rumen. The technical knowledge Chia picked up in graduate school aided him as his research interests turned toward microbial evolution and microbiomes. Then, thanks to the Mayo Clinic and Illinois Alliance, Chia was introduced to the idea of microbiome research in a clinical setting.

Fast forward to Rochester, Minnesota. Now on board at Mayo Clinic, Chia went from working with a theoretical physics group studying the origins of life to working in a major medical center, attempting to apply theoretical physics knowledge to medicine. Besides his leadership of the Microbiome Program and consulting for the Department of Surgery, he also has an academic appointment as assistant professor of biophysics. Chia has become an expert on the human microbiome—particularly in modeling microbial community and metabolic dynamics—and was recently awarded an R01 from the National Institutes of Health (NIH) to study the effects of the gut microbiome on colorectal cancer.

Dr. Chia's transition from academic research to clinical research has not been without challenges, however. Being completely new to a medical center research environment, Chia has had a learning curve to overcome. Understanding clinical flow and how to interrupt the flow to get patient consent and collect samples was brand new, but key to knowing what is and isn't practical for research projects. Chia feels in some ways that it may have been easier for him to pick up on how to get things done at Mayo because he's learned everything from scratch. Interestingly, he's also found that physicists and surgeons have a lot in common—they both tend to be very direct and expect results quickly—so he feels right at home. Chia says he's managed the transition well by keeping an open mind. As a result, his work at Mayo Clinic is flourishing.

Innovative methods for researching the microbiome

Chia's experience at Illinois enabled him to take a different approach to studying the microbiome and colorectal cancer (CRC). His lab at Mayo Clinic uses a systems biology and modeling-heavy approach that allows them to model the metabolisms of all the individual microbes in the gut and then build a predictive model of what happens over a period of time. His lab uses this model to predict which metabolites and toxins will be generated, how stable the microbiome is, and what the population fluctuations look like. The biggest difference in their approach, compared to a typical approach, is looking at a dynamic model versus a snapshot of a specific point in time. The dynamic model allows a better capture of overall exposure to toxic compounds. In the case of CRC, Chia's lab is mainly focusing on the role of proton balance in the gut and the effects of hydrogen sulfide exposure on colon cells.
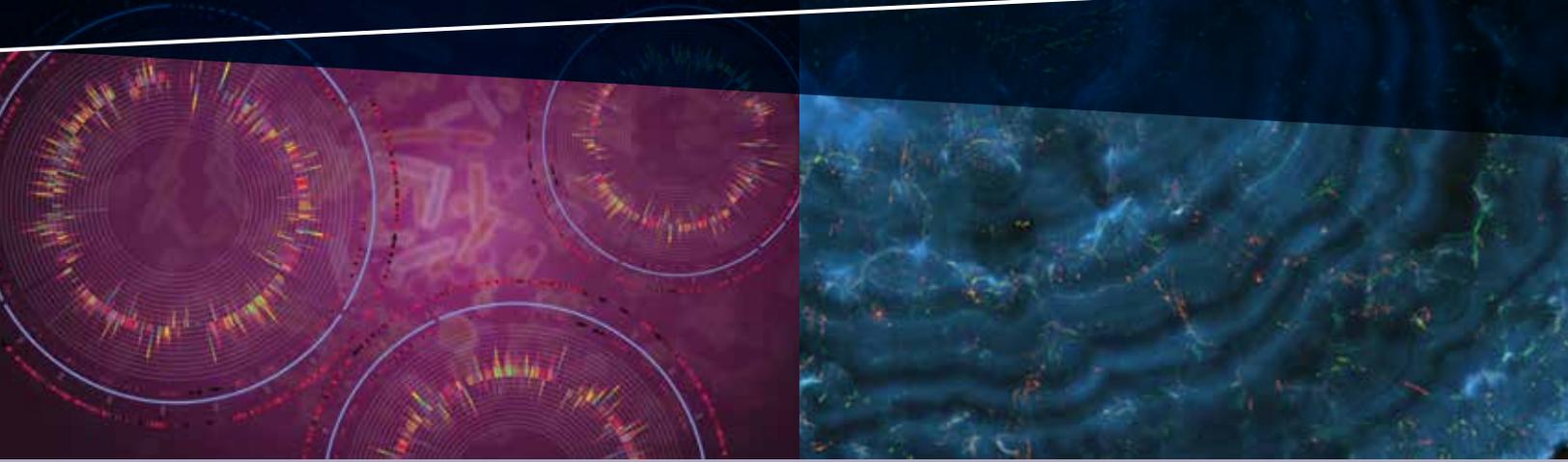
The colorful graphic on the left is a conceptualized illustration of genomic analysis. On the right, Dr. Chia's work shows a microscopic view of sections of kidney stones after being treated with florescent probes, showing bacteria (green) and fungi (red).

Hydrogen sulfide is known to be one of the toxic metabolic byproducts generated within the colon that may contribute to carcinogenic DNA damage. It's also known that some microbes, like sulfate reducing bacteria (SRB), contribute to hydrogen sulfide production. However, there are also microbes in the colon, such as methanogenic archaea, that help remediate hydrogen sulfide accumulation by competing with SRBs for protons (H+), and could play a protective role in keeping the colon healthy. By modeling the changes in the microbiome over time, Chia's lab will be able to determine if a person is at a greater risk of developing CRC due to large spikes of toxic metabolites or if chronic exposure is the more likely culprit.

Chia's experience at Illinois enabled him to take a different approach to studying the microbiome and colorectal cancer.

Translating scientific discovery to preventive medicine

The research project, funded by Chia's R01 from the NIH, is titled "Microbial Metabolic Toxicity Drives Colon Cancer." In addition to gastrointestinal cancer clinical researchers at Mayo Clinic, the research team includes Nigel Goldenfeld and Bryan White—Chia's former postdoc advisors—as Illinois collaborators. Through this alliance facilitated project, Chia aims to better understand the environmental components of CRC and settle certain questions about the role of diet, the environment, and other compounds involved in carcinogenesis. But the goal isn't necessarily to cure colorectal cancer.

"Instead of moving to detection and treatment, I really want to get us toward prevention—which is the next step—to not have this problem to begin with. And it's a very western problem. What is it about our diet that is causing this? Is it something we can prevent? Obviously, if we figure this out it would mean there may be behavioral changes needed to change our chances of colorectal cancer, much like how we put on sunscreen [to prevent skin cancer]," Chia says.

He believes this research should be able to tell us what some of the causes of CRC are and how to prevent or ameliorate them by getting rid of certain microbes or adding in beneficial microbes that could compete with the so-called "bad" microbes. He feels strongly that the best intervention is going to be through changing people's diets, rather than through probiotic or prebiotic supplementation.

"One of the things I worry about [with probiotic or prebiotic supplements] is the dosages necessary to bring about some kind of permanent change," Chia says. He does admit, however, that getting people to change their eating habits is easier said than done.

Chia's lab will be sequencing the metagenomes of human stool samples and assembling all the individual genomes within the metagenomes, down to organisms, with 0.5% abundance. The genomes may not be complete, but they should be complete enough to build a metabolic model for each organism. This endeavor requires an enormous amount of sequencing. Chia says his lab is actually "overdoing it," until they optimize the sequencing technique.

The group will also be building new computational tools to create more reliable metabolic models from the genomes, then combining the metabolic models into a community metabolic model. The community metabolic model will allow each of the individual microbes to act independently and change in relative abundance—as if they were being monitored in real time.

Through ongoing interaction, Nick Chia and his collaborators are a dynamic model of the boundless advantages of active university-clinical partnerships in the age of genomic research. ✚

(Bio)Marking New Territory in Precision Medicine

by Abigail Bobrow

Researchers from Mayo Clinic and the University of Illinois embarked on a mission to expand upon existing biomarker identification during the first Mayo Clinic and Illinois Alliance Biomarker Discovery Workshop, held in Urbana.

Dr. George Vasmatzis, director of the Biomarker Discovery Program within the Center for Individualized Medicine (CIM) at Mayo Clinic, helped organize the workshop. Mayo Clinic has been involved in biomarker discovery for several years, and Vasmatzis realized the collaboration with Illinois could take things to a new, level.

But what is a biomarker, and why would a person want to discover one? The term 'biomarker' is broad, comprising all measurable indicators of a biological state or condition. Biomarker examples include specific molecules or proteins, an imaging agent, or even a genome sequencing test that has the ability to inform physicians of a possible clinical dilemma. The identification of a biomarker gives physicians the ability to make more informed decisions concerning a patient's care.

Biomarkers can be predictive, identifying a malignancy like cancer, or prognostic, indicating what the likely outcome for a patient will be with one therapeutic intervention or another. Biomarkers can even go so far as determining that a treatment is not effective.

"Individuals have individual disease. Each disease acts differently from one another. So that's where biomarkers can tell you how you need to treat the individual patient," said Vasmatzis. "We think through the Mayo Clinic collaboration with Illinois that we can become leaders in biomarker discovery, utilizing multidisciplinary teams and bringing technologies and tools for those teams to discover new biomarkers and address important clinical questions."

> The term 'biomarker' is broad, comprising all measurable indicators of a biological state or condition.

Illinois' Rashid Bashir, the Abel Bliss Professor of Electrical and Computer Engineering and Bioengineering, was also a workshop organizer and also recognizes the enormous potential inherent in a multidisciplinary collaboration with Mayo Clinic.

"Mayo is a top-ranked institution with world-class faculty and clinicians doing clinical research and healthcare delivery. Mayo can provide for a great opportunity for our faculty and students to do clinical translation work in bioengineering," Bashir said.

Students and researchers, no matter how brilliant, are not expected to be experts in every field biomarker research encompasses.

"Students working in this area (biomarker discovery) can come in from a wide range of backgrounds—both computation and experimental. They can take classes in bioinformatics and computational medicine, genomic technologies, imaging, micro and nanotechnologies, and molecular and cellular biotechnologies," Bashir said.

Vasmatzis, Bashir, and Illinois associate professor of chemistry Ryan Bailey devised three "grand challenges" to encourage collaboration and focus between the two institutions, within their varied backgrounds of expertise.

Grand Challenge	Examples	Time Scale
1. Detection of Biomolecules from Body Fluids	Early Detection miRNA Epigenetics Cancer Cells	Early detection of disease
2. Molecular Imaging from Tissue Samples	Digital Pathology Cytogenetics Cytotranscriptomics Next Gen FISH	Surgery and intervention
3. 3D Cancer Tumor Chip-Avatars	Cell Culture Arrays Therapeutic Trajectories Replace Mouse-avatars	Personalized drug therapy

Projects Awarded Seed Funding

The Mayo Clinic and Illinois Alliance awarded funding to these four collaborative research proposals that originated from the Biomarker Discovery Workshop. Each project addresses one of the three grand challenges:

Chip-Based Engineered Tumor Microenvironments for Glioma Therapy
Research Team: Brendan Harley (UI), Daniel Ma (Mayo), Jann Sarkaria (Mayo)

Glioblastoma multiforme (GBM) is a common and aggressive form of brain cancer with poor clinical prognosis. In vivo models and pathology metrics are commonly used to develop and assess new treatment strategies, but are complex, expensive, and cannot be used to optimize patient-specific therapies. We are developing a scalable biomaterial tool that will facilitate rapid in vitro assessment of biopsy-derived cells (not cell lines) response to inhibitor cocktails.

Moving Toward Model Systems for Cancer Therapeutic Biomarker Testing
Research Team: Irina Kovtun (Mayo), Farhad Kosari (Mayo), R. Jeffrey Karnes (Mayo), John Cheville (Mayo), Gregory Underhill (UI), Hyunjoon Kong (UI), Taher Saif (UI), Brendan Harley (UI)

Identification of the best individualized treatment options for most tumors especially in patients with advanced disease is often limited because of the lack of appropriate tumor models. Generation of mouse models

which are often the system of choice, remain costly and lengthy. The goal of this work is to develop 2-D and 3-D culture systems which recapitulate specific tumor context and allow simultaneous testing of tens of drugs and their combinations. We will test this approach using prostate and lung tumor cells and biomarkers we have recently identified in these cancers. Achieving these goals will require synergistic collaboration between Mayo Clinic and Illinois. Mayo Clinic investigators will provide clinical and biological expertise, as well as tumor cells of interest, and UI investigators will provide expertise in biomimetic culture systems.

Novel Biomarkers and Point-of-Care Methods for Latent Tuberculosis Infection
Research Team: Patricio Escalante (Mayo), Yi Lu (UI), Ryan Bailey (UI), Rashid Bashir (UI)

Accurate detection of the latent form of tuberculosis (TB) infection remains a major clinical and public health problem worldwide. During this project, a team of investigators from the University of Illinois at Urbana-Champaign and Mayo Clinic will develop and test novel and state-of-the-art point-of-care methods to accurately detect and stratify latent TB infection. This study has the potential to provide new diagnostic tools to identify specific immune biomarkers of latent TB with a high likelihood to progress to active

tuberculosis, enabling clinicians to improve the management of TB in resource-limited settings.

Translational Molecular Imaging Technologies for Quantitative Prostate Tumor Pathology
Research Team: John Cheville (Mayo), R. Jeffrey Karnes (Mayo), Stephen Murphy (Mayo), Rohit Bhargava (UI), Andrew Smith (UI)

Approximately 240,000 men in the US are diagnosed with prostate cancer each year; most men diagnosed today have low-risk tumors, where the most appropriate care may not be aggressive therapy. However, we do not have a specific diagnostic assay that can identify low-risk prostate cancers from aggressive tumors. In the absence of this diagnostic capability, patients with low-risk cancers are often given costly and unnecessarily harmful treatments. This project aims to develop a robust clinical test based on quantum dot genome profiling technologies to assay copy number variations and rearrangements in a biomarker panel of five genes with prognostic significance in prostate cancer. To develop this assay, Mayo Clinic's expertise in the field of biomarker discovery will be joined with the state-of-the-art biomarker detection technologies at the University of Illinois.

At the workshop, researchers were asked to submit funding proposals integrating Mayo Clinic's clinical and Illinois' engineering strengths. The research had to address the following four goals: collaboration between the institutions, discovery and validation of new biomarkers, facilitating the development of new clinical tests, and the translation and commercialization of new technologies.

Brendan Harley, associate professor in chemical and biomolecular engineering, attended the workshop and is working on two of the four projects chosen for funding following the workshop.

"The workshop gave me a much broader sense of the types of questions that are of direct clinical relevance. While I already knew about a number of collaborative opportunities, getting the scope of how the research may transfer to impact patients was really important," Harley said.

That future impact for patient populations could be massive. "I think the potential in biomarkers is much bigger than what we can see or even imagine, especially when we develop this participation with Illinois in such a way as to quickly translate discoveries and implement new technologies," Vasmatzis said. ✚

Harnessing the Power of Big Data: A Revolution in Genomic Data Analysis

by Claudia Lutz, Carl R. Woese Institute for Genomic Biology

Internet search engines like Google allow us to search and parse the collective knowledge of the world—they anticipate the user's questions, remember preferences, deliver information quickly and clearly. Why can't researchers trying to discover the most effective disease treatment employ the same analytical power to the challenges of their work?

To a team of biologists, computer scientists, and bioinformaticians from the University of Illinois at Urbana-Champaign and Mayo Clinic, this question sounds like an exciting opportunity. Supported by one of the first awards from a recently established National Institutes of Health (NIH) initiative, the group has begun work on a tool, the Knowledge Engine for Genomics, that interprets new results by leveraging community knowledge of how genes interact with each other.

Converting Big Data to better knowledge

The effort aims to address one component of a broad and pressing issue faced by the biomedical research field. Rapid advances in laboratory technology have made it possible for investigators to collect once unheard-of amounts of data in a single experiment, whether those data are high-resolution brain images, interactions within a social network, or expression levels of thousands of genes.

The problem with such large-scale experiments is the resulting data sets—termed "Big Data"—are only valuable if they can be translated into more knowledge, and the tools used to handle all this information haven't improved quickly enough.

To address this issue, the NIH created the Big Data to Knowledge (BD2K) initiative in 2012. The goals of the initiative are to promote the development of better methods to manage very large data sets, develop better analytical tools, train researchers in the use of those tools, and shift the culture of the scientific community to make these and related activities more successful.

As part of the first wave of BD2K funding announced in October 2014, the University of Illinois at Urbana-Champaign and Mayo Clinic received a $9.34M, 4-year award to create one of 11 new Centers of Excellence for Big Data Computing. The center focuses on a specific class of Big Data: the rapidly growing body of genomic and transcriptomic data produced by genome-wide, high-throughput experimental technologies.

University of Illinois computer scientist Jiawei Han is the center's program director. Other Mayo Clinic and Illinois Alliance principal investigators are computer scientist Saurabh Sinha; physicist and bioengineer Jun Song; and Richard Weinshilboum, MD, director of the Mayo Clinic Center for Individualized Medicine's Pharmacogenomics Translational Program. C. Victor Jongeneel, director of the High-Performance Biological Computing Group (HPCBio) at Illinois, is executive director.

"By integrating multiple analytical methods derived from the most advanced data mining and machine learning research, KnowEnG will transform the way biomedical researchers analyze their genome-wide data," said Program Director Jiawei Han, describing the software tool under development. "The center will leverage the latest computational techniques used to mine corporate or Internet data to enable the intuitive analysis and exploration of biomedical Big Data."

The center combines the expertise of many units across the U of I campus, including the Carl R. Woese Institute for Genomic Biology (IGB), the Department of Computer Science, the Coordinated Science Laboratory, the College of Engineering, and the National Center for Supercomputing Applications (NCSA). As a leader of biomedical research and structured data collection, Mayo Clinic plays a vital role in design, testing, and refinement. The Breast Cancer Genome-Guided Therapy (BEAUTY) study at Mayo Clinic will be the first to benefit from the KnowEnG technology.

Saurabh Sinha, PhD

Richard Weinshilboum, MD

C. Victor Jongeneel, PhD

A tool to harness community knowledge

Results of biomedical genomic studies often come in the form of a list of genes—genes that differ in sequence or activity in healthy and diseased individuals, for example. Researchers would like to translate that list of genes into a better understanding of how disease works: How does a particular disease compare to other diseases at a cellular level? Are there specific functions inside the cell that are most affected? How are they affected? This type of knowledge could help predict disease risk, or lead to new ideas for treatment.

Traditional tools used to interpret genomic data have relied on making comparisons between a researcher's gene list, and a database containing a specific type of information about genes. It is up to the researcher to identify what comparisons will be helpful, and integrate the outputs of many different analytical tools into a coherent interpretation.

Newer tools aggregate different types of gene-related information from multiple sources, but the difficult task of synthesizing how these relate to a specific list of genes is still up to the researcher. When completed, KnowEnG will be unique in its integration of many disparate sources of gene-related data into one enormous network, a comprehensive guide against which a researcher's specific results can then be compared. "We'd like to take community knowledge and datasets in this richer representation, this format of a network of gene-gene relationships, gene-gene functional relationships, protein-protein relationships and so on, and allow the user to do their analysis in the context of that community knowledge," said Sinha, who leads the research arm of the project. The team is also designing KnowEnG to accommodate future growth in size and scope of the network, as the scientific community continues to learn about the relationships among genes.

In addition to development of KnowEnG, the center is developing a training framework that empowers researchers to use the new tool and engage in bioinformatics research,

regardless of their prior computational knowledge. The center has also begun participation in a nation-wide consortium, composed of all the BD2K Centers of Excellence established by the NIH initiative, to exchange insights, contribute to standards for tool development, and help set broad goals for the future of work on Big Data.

"Ideally, undergraduates would be trained in both biology and computer science" before engaging in biomedical genomics research, said Song, who leads the training and community activities of the center. Because most of today's biomedical researchers did not have access to extensive formal training in computation, Song explained, the center's training resources will be carefully designed to build users' understanding of computational questions in a visual, intuitive way.

Strengthening interdisciplinary connections

The center relies on communication between interface design experts at Illinois and biomedical researchers at Mayo Clinic, who represent KnowEnG's intended users. Feedback among these center members ensures that the completed tool will be valuable, intuitive, and customizable for use in a broad array of experimental contexts.

"A major challenge is to understand the language and culture of each group so that we can communicate effectively, and make the tools that are developed at Illinois accessible to the biomedical audience," said Weinshilboum, who oversees the evaluation of KnowEnG's functionality. "The biomedical staff will communicate back to Illinois about what is helpful in terms of advancing their research and their understanding."

Mayo Clinic researchers will test the mettle of initial versions of KnowEnG, employing it in two large-scale investigations of the genomics of cancer treatment. KnowEnG's success in constructing functional

conclusions from patients' genetic background, gene expression, responses to treatment, and many other measures will provide important benchmarks of performance during its development.

"All the institutional signals are agreeing; the computer scientists are really excited about doing this, and the biologists also behind it," said Jongeneel, reflecting on the culture of collaboration that has made the center's conception possible. "We have a fantastic relationship with Mayo."

Analysis of several biological experiments at Illinois will also be used to gauge performance. Cell and developmental biologist Lisa Stubbs, along with Sinha, will use KnowEnG in a project investigating the relationship between gene regulation and social behavior in animal models and humans. Stubbs is also the leader of the Gene Networks of Developmental and Neural Plasticity Research Theme at the IGB, which is the official host of the center.

Altogether, the project promises both incredible intellectual challenges, and the possibility of great advances in genomics and Big Data.

"There's a lot to do, and obvious challenges to overcome, and we're looking forward to those challenges," said Sinha. "What I'm most excited about is the actual possibility that this could be a tool which everybody in the world uses." ✚
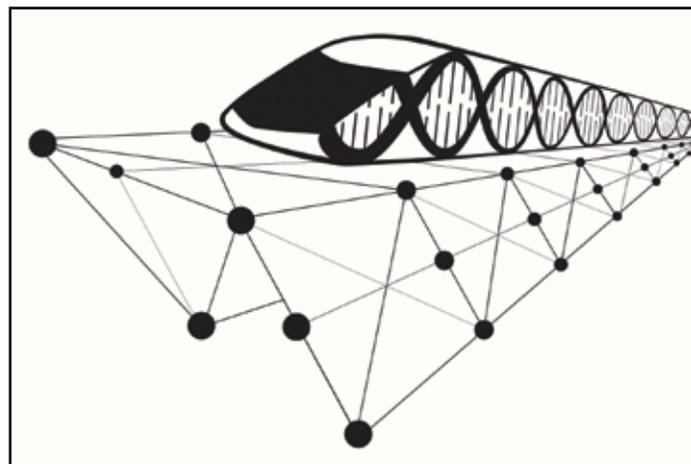
Update: Microbiome Characteristics Determined in Healthy Pregnancies

by Margret Berg Miller

Study lays groundwork for connecting vaginal microbiome abnormalities to pregnancy complications

Continuing to assess the vaginal microbiome, Bryan White, PhD, director of the Mayo Clinic and Illinois Alliance for Technology-Based Healthcare and professor of animal sciences at Illinois, and Dr. Douglas Creedon, obstetrician and gynecologist at Mayo Clinic, led a team of scientists from the University of Illinois at Urbana-Champaign, Mayo Clinic, and the J. Craig Venter Institute in an investigation of vaginal microbiomes over the course of uncomplicated pregnancies. Results of the study were published in the journal *PLOS One.*

> Knowing what is normal sets the stage for further investigation of whether the microbiome has a causal role in pregnancy complications, such as preterm birth.

Titled "Pregnancy's Stronghold on the Vaginal Microbiome," the article represents one of the first research collaborations initiated by the Mayo Clinic and Illinois Alliance, applying cutting-edge technology to understand the fundamental problems in maternal-fetal health.

"This work would never have been completed without the alliance. It took the collaboration and expertise of the team at U of I who know the microbiome and the clinical perspective and material from Mayo to make this project a reality. I think it has been a great example of the power and potential of such cooperation and hope the work continues to flourish," said Creedon.

This research is expected to have a great impact on obstetrical and perinatal care, as it has established a baseline for a "normal" vaginal microbiome during pregnancy. Knowing what is normal sets the stage for further investigation of whether the microbiome has a causal role in pregnancy complications, such as preterm birth.

As Dr. Marina Walther-Antonio, lead author on the paper, explained, "This study is significant for obstetrics. It provides a comparative platform researchers studying pregnancy complications suspected of having a microbial cause, like preterm labor, can use for identifying potential microbiome dysbiosis associated with the vaginal microbiome during pregnancy."

In this longitudinal study, researchers found that in uncomplicated pregnancies, the vaginal microbiome is made up of few bacterial species and is typically dominated by one or two Lactobacillus species. And unlike non-pregnant women whose vaginal

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Recent Grants and Publications

Grants

- Droplet Microfluidic Platform for Ultralow Input Epigenetics. Ryan Bailey (UI), Tamas Ordog (Mayo). 2014. NIH-NCI-R21.

- Big Data to Knowledge Center of Excellence. Jiawei Han (UI), Richard Weinshilboum (Mayo). 2014. NIH-U54.

- I/UCRC Planning Grant: Computing and Genomics – An Essential Partnership for Biology Breakthroughs. Ravi Iyer (UI), Gene Robinson (UI), Liewei Wang (Mayo). 2014. NSF Planning Grant.

- Microbial Metabolic Toxicity Drives Colon Cancer. Nigel Goldenfeld (UI), Bryan White (UI), Nicholas Chia (Mayo). 2014. NIH-R01.

microbiomes fluctuate with the menstrual cycle, a pregnant woman's microbiome stays relatively stable from the first trimester until the time of delivery. Walther-Antonio went on to say that, "any deviations from this profile may be interpreted as indicative of potential microbial dysbiosis and possible increased risk for complication."

The team's findings did not come without hurdles to jump. "One of the greatest challenges we faced was the recruitment of patients to participate in the study. These studies take a very long time since the pregnancy and sample collection take nine months to complete, and not all of the subjects become pregnant at the same time. Preterm births only occur in about 20 percent of pregnancies, so we also needed larger participant groups for statistical validation," said White.

The authors plan to continue their collaboration, with the goal of finding biomarkers in participants who deviated from the baseline microbiome. They anticipate these biomarkers may be used to diagnose and treat potential pregnancy complications before becoming clinically symptomatic.

Publications

- Allen JM, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins HR, White BA, Fryer JD, Woods JA. 2015. Voluntary and forced exercise differentially alter the gut microbiome in C57BL/6J mice. J Appl Physiol. 118(8): 1059-66.

- Jeraldo P, Kalari K, Chen X, Bhavsar J, Mangalam A, White B, Nelson H, Kocher JP, Chia N. 2014. IM-TORNADO: A Tool for Comparison of 16S Reads from Paired-End Libraries. PLoS One. 9(12): e114804.

- Benedict MN, Mundy MB, Henry CS, Chia N, Price ND. 2014. Likelihood-Based Gene Annotations for Gap Filling and Quality Assessment in Genome-Scale Metabolic Models. PLoS Comput Biol. 10(10): e1003882

- Kang SS, Jeraldo PR, Kurti A, Berg Miller ME, Cook MD, Whitlock K, Goldenfeld N, Woods JA, White BA, Chia N, Fryer JD. 2014. Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Mol Neurodegener. 9:36.

- Walther-António MRS, Jeraldo P, Berg Miller ME, Yeoman CJ, Nelson KE, Wilson BA, White BA, Chia N, Creedon DJ. 2014. Pregnancy's Stronghold on the Vaginal Microbiome. PLoS ONE 9:e98514.

- Ranadive SM, Cook M, Kappus RM, Yan H, Lane AD, Woods JA, Wilund KR, Iwamoto G, Vanar V, Tandon R, Fernhall B. 2014. Effect of acute aerobic exercise on vaccine efficacy in older adults. Med Sci Sports Exerc 46:455–461.

- Bagaria SP, Ray PS, Sim M-S, Ye X, Shamonki JM, Cui X, Giuliano AE. 2014. Personalizing Breast Cancer Staging by the Inclusion of ER, PR, and HER2. JAMA Surg 149:125–129.

- Blancas-Mejía LM, Tischer A, Thompson JR, Tai J, Wang L, Auton M, Ramirez-Alvarado M. 2014. Kinetic control in protein folding for light chain amyloidosis and the differential effects of somatic mutations. J Mol Biol 426:347–361.
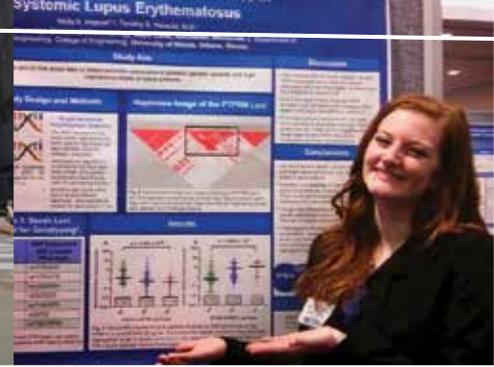
Molly Imgruet, two-time SURF from Illinois. A bioengineering major, Molly worked in Mayo Clinic's immunology department lab. She is currently pursuing an MD/PhD.

SURF's Up: The Next Wave of Biomedical Scientists

by Margret Berg Miller

Illinois students maximize their summer experiences

The Summer Undergraduate Research Fellowship (SURF) program is a major success story for the Mayo Clinic and Illinois Alliance. During the past five years, 30 students from the Urbana campus have been part of the SURF program at Mayo Clinic. In fact, a record number of Illinois students applied and were accepted to the program in 2014, with eleven Illinois students selected out of a total of 138 participants. Illinois was the university with the largest number of SURF students in the nation. This strong representation would not be possible without the Mayo Clinic and Illinois Alliance, which guarantees that five fellowships are reserved specifically for Urbana campus students.

The SURF program itself is an incredibly valuable experience for any undergraduate student. Each student is matched to a research lab at Mayo Clinic and is completely immersed in his or her own research project, the results of which are presented during a poster session at the end of the summer.

Chemical and biomolecular engineering student Kevin Erning explained his experience in Dr. Timothy Nelson's lab. "I really appreciated that Tim treated me like a graduate student and didn't just give me a to-do list for my SURF project. Instead, he constantly encouraged and pushed me to design my own project and consider how it would fit the big picture goal for our group."

Get to know Illinois' 2015 SURF class at mayoillinois.org. 🔍

Outside of research projects, undergrads find many other opportunities to take advantage of while at the Mayo Clinic. Annette Merkel, a student in molecular and cellular biology, recommends attending as many seminars as possible. "Mayo Clinic has so many chances to get involved that you can find something you are interested in just by attending a new seminar."

Some of these opportunities involve shadowing various researchers or clinicians. Past SURFs often speak fondly of their shadowing experiences at Mayo Clinic. Many advise the next group of SURFs to take full advantage of these shadowing opportunities as they arise. George Mastarakos, junior in biochemistry, heeded this advice when he jumped at the chance to shadow a neurosurgeon.

"Shadowing a neurosurgeon was the most interesting experience I had while at Mayo. I was fortunate enough to sit in on a live craniotomy in which Dr. Frederick Meyers resected a brain tumor. Having never shadowed a surgeon thus far in my medical journey, it was an elucidating experience of the surgery field," Mastarakos said.

During the ten-week program, SURFs not only get a taste of what graduate school is like, they also get to build relationships with researchers, clinicians, and other SURFs, developing bonds that have the potential to last long into their scientific careers. These types of relationships are increasingly important in an era where it is the norm to work as a part of a multidisciplinary research team.

Jonathan Bacos, junior in molecular and cellular biology, says one of his favorite aspects from the summer was meeting and developing relationships with the diverse group of SURF students who traveled to Rochester, Minnesota, from all over the nation. "I gained a lot of new friends who I still remain in contact with and hope to continue networking with as we are integrated into the professional scientific community."

Overwhelmingly, students in the SURF program highly recommend it to anyone considering graduate school or pursuing an MD/PhD. For many of them, the experience has helped solidify their career trajectory, and all would agree it's a worthwhile experience. The only complaint is that it goes by faster than expected.

"Ten weeks sounds like a long time, but it goes by remarkably fast," says Mastarakos. His advice to future participants? "Start research off with a bang and immerse yourselves in the Mayo culture right from the beginning so that you make the most of your summer."

More information, including SURF student profiles, can be found at mayoillinois.org, under "Undergraduate Student Opportunities" in the Education section. Specific information about the SURF Program and how to apply can be found at the Mayo Clinic website, mayoclinic.org. ✚

Mentoring Important for Illinois PhD Students

Alliance connects new research opportunities for community health students

by Margret Berg Miller

As any graduate student knows, a faculty advisor's connections to industry leaders can often result in opportunities for said advisor's students. Such was the case for University of Illinois Community Health PhD students Mary Christoph and Zinnia Zhang, who participated in a summer research opportunity in the Department of Health Sciences Research at Mayo Clinic. The research experience was jointly organized by Dr. Hillary Klonoff-Cohen, director of the Master's in Public Health Program at Illinois, and Dr. James Cerhan, chair of the Department of Health Sciences Research and head of epidemiology at Mayo Clinic.

Christoph and Zhang spent ten weeks at Mayo Clinic in Rochester, MN, working on research projects in the Epidemiology Division of the Department of Health Sciences Research. They were placed with mentors based on their interests and the goals of their practicum. Though Christoph and Zhang were both paired with mentors in the area of epidemiology, their research projects were very different.

While at Mayo, Zhang evaluated the internal and external validity of an ovarian cancer case-control study conducted by Dr. Ellen Goode, professor of epidemiology at Mayo Clinic. To complete her assessment, Zhang used the methodology outlined in an article by Dr. Cerhan titled, "Design and validity of a clinic-based case-control study on the molecular epidemiology of lymphoma." In a clinic-based case-control study it is important to evaluate whether the results are true for the target population, which in Zhang's case would be the subjects in the ovarian cancer study (internal validity), and whether the results of the study can be generalized to patient populations outside of Mayo Clinic (external validity). Zhang intends for her evaluation of the ovarian cancer study to be part of her doctoral dissertation.

Christoph's work at Illinois focuses on how nutrition and eating behaviors influence adolescent obesity. Adolescent obesity has become a major public health concern, since children and adolescents who are obese are more likely to be obese as adults, putting them at greater risk for type 2 diabetes, heart disease, and certain types of cancer. At Mayo Clinic, she examined how different measures of adiposity are correlated with atherosclerosis-related adhesion proteins in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. MESA is a longitudinal medical research study sponsored by the National Heart, Lung and Blood Institute of the NIH. She worked under the guidance of Dr. Suzette Bielinski and a collaborator at the University of California, San Diego during her stay in Rochester. Christoph is compiling her research results into a manuscript she intends to submit for publication.

Both PhD students found the clinical research experience at Mayo Clinic to be invaluable to their graduate program work and to their future clinical and translational research endeavors.

"I cannot overstate how much I appreciate this opportunity and would recommend it to others," Christoph said. "The competence, professionalism, and excellence of the researchers that I have been able to meet and collaborate with (at Mayo) are unparalleled. Not only have I improved my analytical skills and knowledge of clinical measures of heart disease and obesity, I have learned how successful collaborations and large cohort studies are managed and designed." ✚
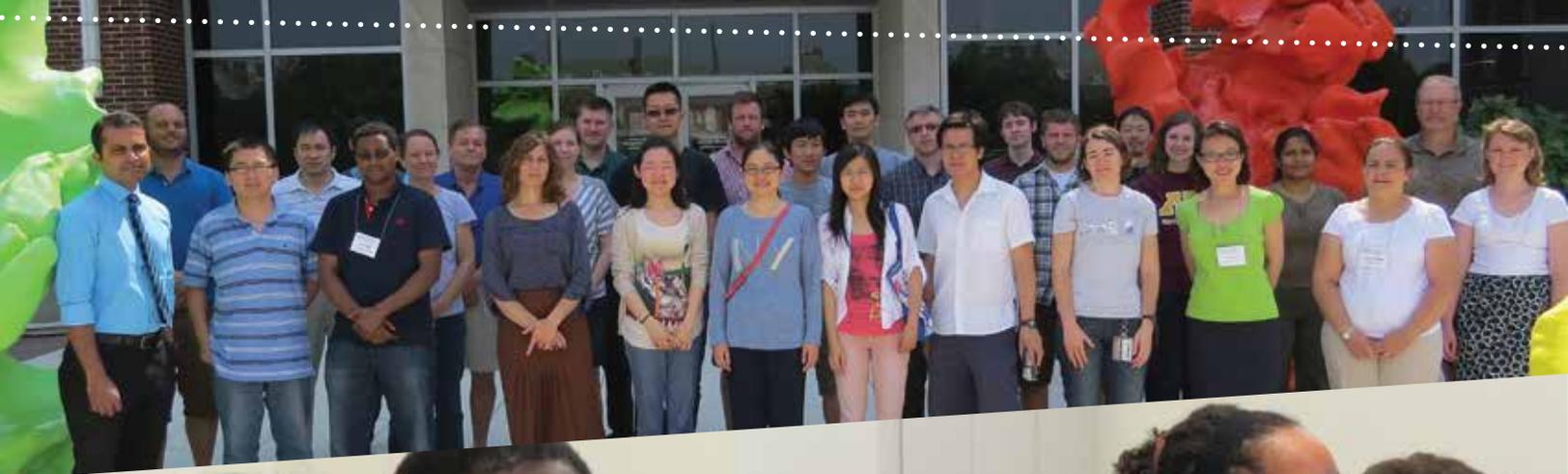
High Tech, High Touch

Course immerses participants in the emerging study of computational genomics

by Ashley Lawrence

Designed by Mayo Clinic and Illinois Alliance steering committee member Dr. Saurabh Sinha, the 2014 Computational Genomics Course was an intense week of exploring the latest methodologies and technologies of computational genomics for clinical application.

Learn more at go.illinois.edu/ computationalgenomics

For the second year, the course was held at the Institute for Genomic Biology (IGB) on the University of Illinois' Urbana campus. Building on a successful 2013 course, the number of participants doubled to more than 50 attendees. Illinois faculty, postdocs and students filled all available seats at the IGB , and Mayo Clinic allied health staff and fellows participated in the course remotely from Rochester.

Illinois teaching assistant Casey Hanson traveled to Rochester to provide support for remote participants.

From Monday to Saturday, a lecture from Illinois faculty was followed by a lab session where participants were given exercises and had hands-on experience performing high-level data analyses.

"Basically, what happened was everyone received a set of instructions on how to solve these exercises that they all had to follow. They were all doing the exercise at the same time in the lab. If someone got stuck, the whole classes couldn't move ahead until that person had done the step," explained Sinha. "Each and every person made mistakes and got to learn. No one was left behind. I think it was very much appreciated," he said. ✛

Illinois Students Excel at Conference

by Ashley Lawrence

The Individualizing Medicine Conference, jointly developed by Mayo Clinic and the University of Illinois at Urbana-Champaign, is the premier conference on precision medicine. Each year, clinicians and scientists from around the world—including a contingent from Urbana—travel to Rochester to learn the latest discoveries in genome-based healthcare.

New for 2014, three Illinois broadcast journalism students were chosen to attend the event and assist Mayo Clinic public affairs staff in producing daily video segments. Each student was responsible for writing scripts, interviewing conference speakers, and shooting B-roll video.

"We created packages (full video stories) for the clinic, under strict deadline which greatly improved my ability to turnover a story," said UI College of Media student Katie Welch. "The researchers enjoyed having media present, because they are passionate about their work and had a strong desire to share it with people."

Along with full-length speaker sessions, 2014 IM Conference videos, written and produced by Illinois students, can be viewed at www.individualizingmedicineconference.mayo.edu.
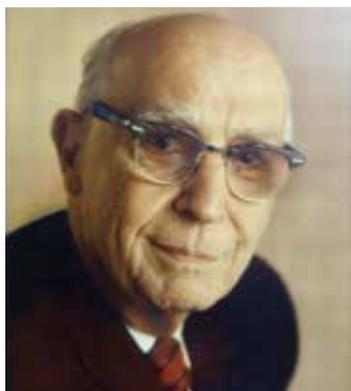
Gianturco Fellowship

Thanks to a generous gift from The Gianturco Family Foundation to the Mayo Clinic and Illinois Alliance for Technology-Based Healthcare, 15 Illinois postdocs and graduate students were able to register for the 2014 Individualizing Medicine Conference free of charge.

The Gianturco Fellowship is offered by in memory of Dr. Cesare Gianturco, who was born in Italy in 1905 and was a radiologist who came to America to be a Fellow at Mayo Clinic from 1930-1934. Gianturco later moved on to teach at the University of Illinois, was a co-founder of Carle Hospital and Clinic, and held numerous patents. +

INDIVIDUALIZING MEDICINE CONFERENCE 2015

HOSTED BY MAYO CLINIC CENTER FOR INDIVIDUALIZED MEDICINE

September 20-23, 2015

It's not too late to attend the premier conference on precision medicine.

Register today at **www.individualizingmedicineconference.mayo.edu**.

Contact Margret Berg Miller at meberg@illinois.edu for more information.
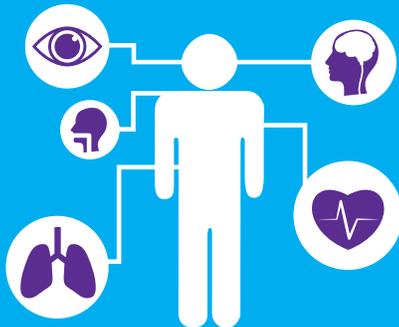
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What Is the Mayo Clinic & Illinois Alliance?

The Mayo Clinic and Illinois Alliance for Technology-Based Healthcare is a group of faculty researchers, scientists, physicians, and students at Mayo Clinic and the University of Illinois at Urbana-Champaign who collaborate in a broad spectrum of health-related research. Established in 2010, the alliance combines the strengths of both institutions **to facilitate unique educational programs and advance clinical and translational research and technology innovation.**

The Mayo Clinic & Illinois Alliance Purpose

The alliance advances the promise of individualized medicine. Precision (or, individualized) medicine is uniquely informed by an individual's genomic make up, environment, and lifestyle. The promises of precision medicine include **better diagnoses, earlier interventions, customized treatment plans, and more-efficient drug therapies.** Combining expertise in genomics, computing, and nanotechnology, **the Alliance pushes precision medicine forward.**

Disease and Health Conditions Focus

Mayo Clinic and Illinois Alliance research and technology development teams are focusing on advances in myriad health areas. These are current research areas, though the list is continually expanding.

- **Cancer**—glioblastoma, prostate, colorectal, and breast cancers
- **Autoimmune Diseases**—multiple sclerosis, rheumatoid arthritis, and celiac
- **General Health Conditions**—reproductive health, obesity, aging, and heart failure

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