IGS NEWSLETTER

SPRING 2016

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
INSTITUTE FOR GENOME SCIENCES

801 W BALTIMORE ST, BALTIMORE MD 21201 | WWW.IGS.UMARYLAND.EDU | 410.706.1481

Greetings Colleagues,

Genomics is defined as the branch of science that studies the genome – the genetic material of a human or other species – to better understand the workings of an organism, and what happens when genes interact with each other and the environment. Genome projects having always been high-throughput, applying large scale DNA sequencing technologies and bioinformatics tools to make sense of the enormous amounts of data that are generated. Genome projects have also been very systematic in their approaches – often making use of standard operating procedures, working within defined levels of error, and delivering results with a careful eye towards cost. Fifteen years ago, genome studies tended to be reductionist – often with the goal of generating a complete genome sequence. Science has entered a new era – in which a systems-level understanding of biological processes has become a new goal. Whether it be Precision Medicine, the BRAIN initiative, the Human Microbiome Project, or the National Cancer Moonshot, we now understand that in order to make the important discoveries of the 21st century we must take a holistic view of health and disease. Genomics will continue to play a key role in all of these endeavors, but as just one set of tools in an ever-expanding tool kit.

The stories that are featured in our Spring Newsletter provide great examples of how genome data have launched exciting collaborative studies that bridge disciplines and bring new perspectives to basic and clinical research questions. Here in Baltimore, and around the world, IGS faculty and staff continue to push the frontiers of science to tackle some of our most urgent public health concerns.

I hope that you will mark your calendars for our 4th Annual Frontiers in Genomics Lecture that will be given by Atul Butte, MD, PhD on June 15, 2016. Dr. Butte is the Director of the Institute of Computational Health Sciences at the University of California, San Francisco. He has been a champion of making scientific data publically accessible. He has also founded three data-driven companies and brings first-hand experience to the challenges of translating enormous amounts of data into new diagnostics and therapies.

Finally, I hope that you will take time to read Dr. Anne Estes's column. She is a post-doctoral fellow at IGS, who is firmly committed to advancing the public's understanding of her work on the microbiome through her blog, *Mostly Microbes*, and as a contributor to other science blogs. She is a passionate believer in the power of social media to inform and educate a diversity of people.

As always, I welcome your feedback,

Claire M. Fraser, PhD

Dean's Endowed Professor in the School of Medicine
Professor of Medicine, Microbiology and Immunology
Director, Institute for Genome Sciences
University of Maryland School of Medicine

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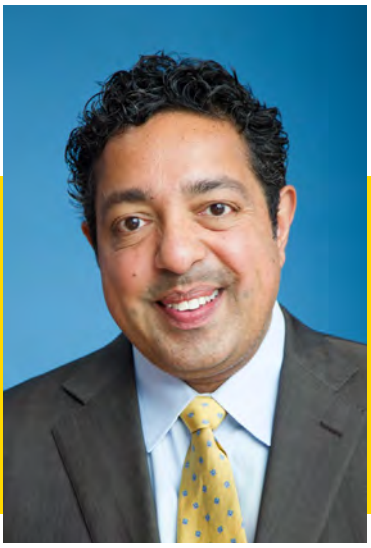
UPCOMING

Save the Date: June 15th 2016



Our speaker for the 4th Annual Frontiers in Genomics will be Atul Butte, MD, PhD, from the University of California, San Francisco.

Atul Butte, MD, PhD is the inaugural Director of the Institute of Computational Health Sciences (ICHS) at the University of California, San Francisco, and a Professor of Pediatrics and a well-known expert in Health Informatics. He serves as the Executive Director for Clinical Informatics across the six University of California Medical Schools and Medical Centers, thus is responsible for millions of electronic medical records.

Dr. Butte trained in Computer Science at Brown University, worked as a software engineer at Apple and Microsoft, received his MD at Brown University, trained in Pediatrics and Pediatric Endocrinology at Children's Hospital Boston, then received his PhD from Harvard Medical School and MIT. Dr. Butte has authored nearly 200 publications, with research repeatedly featured in Wired Magazine, the New York Times, and the Wall Street Journal. In 2013, Dr. Butte was recognized by the White House as an Open Science Champion of Change for promoting science through publicly available data. Other recent awards include his election into the Institute of Medicine in 2015 (now known as the National Academy of Medicine), the 2014 E. Mead Johnson Award for Research in Pediatrics, the 2013 induction into the American Society for Clinical Investigation, the 2012 FierceBiotech IT "Top 10 Biotech Techies", and the 2011 National Human Genome Research Institute Genomic Advance of the Month.

Dr. Butte is also a founder of three investor-backed data-driven companies: Personalis, providing clinical interpretation of whole genome sequences, Carmenta (acquired by Progenity), discovering diagnostics for pregnancy complications, and NuMedii, finding new uses for drugs through open molecular data. Dr. Butte is also the principal investigator of the California Initiative to Advance Precision Medicine, and the principal investigator for ImmPort, the clinical and molecular data repository for the National Institute of Allergy and Infectious Diseases.

His talk at the Frontiers in Genomics is entitled "**Translating a Trillion Points of Data into Therapies, Diagnostics, and New Insights into Disease**."

June 15th, 2016

Fourth Annual Frontiers in Genomics

"Translating a Trillion Points of Data into Therapies, Diagnostics, and New Insights into Disease"

Refreshments at 10:30am

Slide presentation by Agilent & Lecture from 10:45–12:30

Discover Auditorium, Bio Park II

801 W. Baltimore St, Baltimore MD 21201

Attendance is free, but an RSVP is required

RSVP:
igs-event@som.umaryland.edu

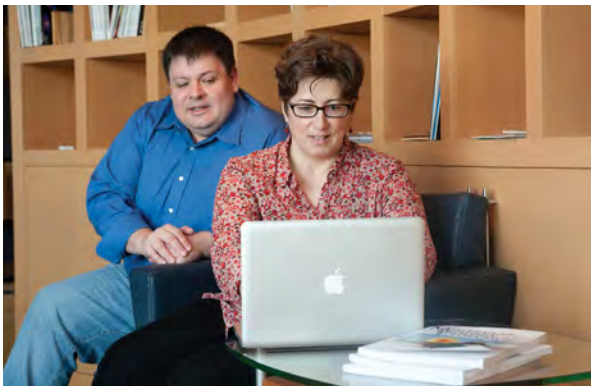
This article ran as a cover story in the *Medicine Bulletin* magazine, Volume 100 Number 3. Reproduction rights have been granted by the Medical Alumni Association of the University of Maryland, Inc.

Paired for Results:

Translational Genomics Improving World Health by Rita M. Rooney

Take two of the world's most debilitating diseases. Set them against the combined capabilities of two of the most highly esteemed medical research programs worldwide. Such a premise might well lead one to the partnership between Maryland's Institute for Genome Sciences (IGS) and Institute for Global Health (IGH), and their joint battle against malaria and cholera.

Fighting malaria with genomic research



Dr. David Rasko, Dr. Joana Silva

The IGS team is working with Christopher V. Plowe, MD, Professor, Departments of Medicine, Epidemiology and Public Health, Microbiology and Immunology, who is a Howard Hughes Medical Institute investigator, and the founding director of IGH. A new malaria vaccine, developed and tested through a partnership with Sanaria, is part of the aligned IGS/IGH team's current research. The vaccine has had 100 percent success among Maryland volunteers who were experimentally infected with malaria compared with those in the control group, who got malaria.

Plowe is collaborating closely with Joana Carneiro Silva, PhD, Associate Professor, Department of Microbiology and Immunology at IGS. She points to the significance of the specific parasites in vaccine development, "By characterizing the genome in the parasite, we can understand factors of translational importance including those that make good drug or vaccine targets, and how to identify those genes," she says.

She reminisces about her time at The Institute for Genomic Research (TIGR), where the most virulent human malaria parasite, *Plasmodium falciparum*, was first sequenced. "At the time, it took six years to put together its genomes," she says. "Today, with state-of-the-art technology available at IGS, this can be accomplished in a matter of weeks."

Commenting on the ultimate success of her work with Plowe and others on the research team, Silva points to genetic variation in malaria parasites that make it difficult to develop a universal successful vaccine. She points to the different strains present in Africa and Asia, as examples. "Malaria is an extremely diverse parasite," she says. "Until it is known how alike or unlike parasites are to each other, and which specific genes are important in determining vaccine efficacy or drug failure, sequencing remains a critically important endeavor."

Plowe counters by referring to the work Silva and her group perform as "sequencing magic, starting with a small amount of malaria from patients' blood, we get considerably more information, and it's significantly more cost-effective, than was possible just a few years ago," he says.

cont. from pg. 3

He adds that the alliance between the partners is a strong one. He says he previously had little knowledge of genomics. When he started to absorb some of the research just a few years ago, he found it was difficult even to find a common vocabulary. "I think there was a cultural divide between the two disciplines," he says. "But Claire Fraser deserves enormous credit for recognizing that the way for her work to have the greatest impact is to reach out to people working on problems with real world needs." He admits that, except for a vague notion that his malaria research could benefit from interaction, he wasn't sure what their needs were or how the two disciplines might effectively interact. Today, he says Silva has become a secondary member of IGH who meets with members every week.

Silva agrees, calling their shared work both collaborative and integrated. "We are very close to publication," she reports. "We now have 12 completely new genomes and are waiting for nine more."

Genomic attack on cholera

With only 50 cases of cholera in the United States during the last decade, the catastrophic disease is of little danger to Americans, however, it is a devastating presence to people in underdeveloped countries. Infection with *Vibrio cholerae*, the causative agent of cholera, results in diarrhea and a rapidly dehydrating situation among adults and children, which can be life-threatening.

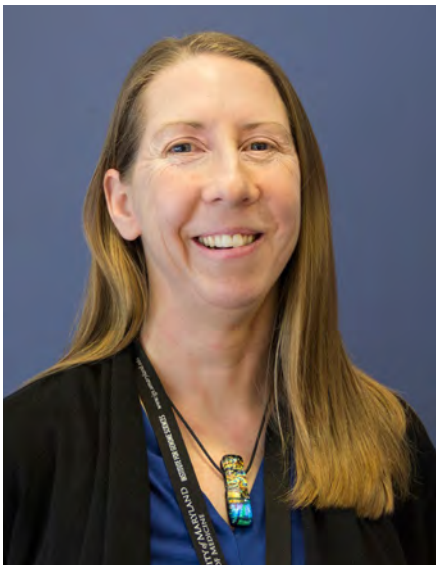
An IGH/IGS team, led by Wilbur Chen, MD, Associate Professor of Medicine at IGH, and David A. Rasko, PhD, Associate Professor, Department of Microbiology and Immunology and IGS, are working on several vaccine projects funded by NIH. Claire Fraser, PhD, Director of IGS, refers to the IGS/IGH's joint cholera project as the first study to use genomics to examine the impact of immunization and exposure to cholera on the resident microbes in the gastrointestinal tract, and vice-versa. Just like malaria, they are exploring the genome sequence diversity of *Vibrio cholerae* as a means to understand and improve vaccine efficacy. The IGH/IGS team is conducting a unique study among healthy volunteers that can only be performed at a few places worldwide. Volunteers are randomized to receive either the vaccine or a placebo, and later are infected with *V. cholerae*, while being monitored in the University of Maryland, Baltimore inpatient research ward.

"From a genomic standpoint, we are looking at characterizing the genetic changes in *V. cholerae* as it travels through the body of vaccinated and non-vaccinated volunteers, but also evaluate the impact of the gastrointestinal microbiota on these changes and the expression of genes the pathogen activates during the infection" says Rasko. This challenge trial affords a unique opportunity because in non-vaccinated volunteers, it mimics a natural infection, but one for which the team controls the infecting pathogen genomic characteristics. Understanding the factors that drive genetic changes in the host is critical to improving vaccine formulation to maximize its efficacy and minimize its side effects.

IGH has pioneered volunteer challenge studies for four decades and is using these contemporary challenges to evaluate the efficacy of a single-dose oral cholera vaccine, developed by James B. Kaper, PhD, Professor and Chair, Department of Microbiology and Immunology, Senior Associate Dean for Academic Affairs. If this vaccine is FDA-approved, it will be the first cholera vaccine licensed in the U.S.

Looking back 20 years to the beginning of microbial genomics, a field that Fraser and colleagues pioneered at TIGR, she says that the rationale at that time was that sequencing the genomes of important human pathogens would lead to breakthroughs in disease diagnosis or therapeutics, as well as in understanding differences in virulence across isolates. A rationalization that is finally becoming a reality with the work IGS does at the University of Maryland School of Medicine. Additional translational projects are underway between IGS and other University of Maryland programs, including one with tremendous potential that examines the potential modulation of the outcomes following organ transplantation by the gut microbiome, where certain types of gut microbiomes would be associated with better outcomes while others with a higher probability of rejection.

As for the satisfaction of seeing that kind of success emanating from a hypothetical concept, Fraser says, "It doesn't get much better than that." Her reflection seems to make a strong statement on behalf of future collaborations between genomics and translational medicine.



A Peek
Behind the Curtain

Anne M. Estes, PhD

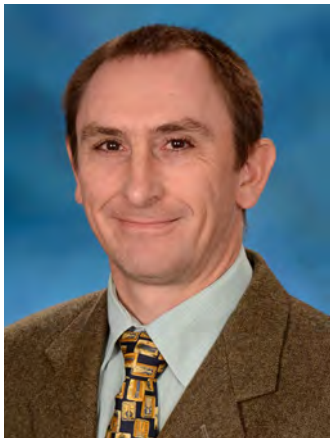
Not all bacteria make you sick. This idea can be a hard sell to a public constantly bombarded with commercials for everything from antibacterial soaps and toothpaste to clothes and toys. However, research suggests that killing all microbes may make us sicker instead of healthier. As a post-doctoral fellow at IGS, I interact with leading scientists, both in residence and visiting, whose research on the human microbiome and genomics is changing the way we view human health and disease. I feel that their research findings often get trapped in scientific journals or overhyped or misunderstood by the media and lay public. Science blogging and social media outlets allow me to make microbiome research findings accessible, so that everyone from grandparents to preschoolers can understand why microscopic organisms are essential for our health.

Science blogging provides opportunities to teach a diverse international audience spanning multiple interests, backgrounds, and training about the importance of microorganisms. My personal science blog, **Mostly Microbes**, provides a reputable voice and resources in these early days of human microbiome **research** when the promise and excitement for improving human health can get exaggerated and misinformation quickly spread. *Mostly Microbes* features reviews of latest human microbiome research, as well as reputable books on microbes for **adults** and **kids**, activities for the **classroom** or household, and microbiome "friendly" recipes. As a scientist who is also a mom, I talk to my kids about microbes – maybe too much. The girls and I have made **yogurt** together, a **video** about healthy eating and the gut microbiome, Winogradsky gradients, and more. Translating microbiome research findings to kids under eight really helps me focus my point, while getting them excited about a very different world they certainly don't learn about in school.

As an invited, contributing blogger to other blogs, I can extend the scientific conversation to professionals, such as childbirth educators, nutritionists, building scientists, and architects. The Lamaze International blog, ***Science and Sensibility***, provides information to child birth educators, such as midwives, nurses, and doulas, to use in their classes. These childbirth professionals are extremely excited about the potential for **translating basic microbiome** research on birth and first foods to the bedside. I provide a balanced perspective on the microbiome research to the childbirth community to help child birth educators and parents make more informed choices about their health and that of their children. Conversations with these childbirth educators has taught me now to be a better educator and communicator and alerted me to additional issues in the delivery room that influence how I read the literature.

I am also a contributing blogger to ***microBEnet*** where I write about the **influence of buildings on birth** and early childhood. *microBEnet* is an academic blog about the literature of the built microbiome from Jonathan Eisen's lab at the University of California, Davis and funded by the Sloan Foundation. My childhood was spent rummaging around my family's plumbing, electrical, HVAC company, sealing ductwork on job sites, and hearing conversations about air flow at the dinner table. With that background and the knowledge that we spend over 90% of our time indoors, I enjoy following the microbiome of the built environment. Childbirth is a time where the built environment and human microbiome worlds intersect. Research suggests that this initial microbial inoculum, either from the mother or the environment may be important for long term human health. So most of my posts to *microBEnet* focus on the influence of buildings with birth and early childhood.

While there are many comments about blogging and social media being a waste of time for academics, I've found great value in communicating science to a diversity of people. It keeps me up on the literature, both recent findings and emerging methods, helps me focus my thoughts and connect seemingly different fields together, and expands my scientific network. Additionally, in these days of decreased funding, increasing public distrust of scientists and misunderstanding of the process of science, I blog to give the public a peek behind the curtain of science. I firmly believe that people fear what they do not understand – whether those fears are of microscopic organisms or the scientific process. Hopefully, the blogging I do reveals scientists as the passionate, curious people they are and that not all microbes make you sick.



Application of **Functional Genomics** to Bacterial Pathogens

Dr. Tettelin, an Associate Professor in Microbiology and Immunology at the University of Maryland School of Medicine, came to IGS in 2007 from The Institute for Genomic Research (TIGR). He pioneered the fields of reverse vaccinology and pan-genomics, working closely with collaborators at what is now GlaxoSmithKline. Throughout his career, he has been interested in using comparative genomics to understand bacterial diversity and virulence, and has studied host-pathogen interactions to identify vaccine candidates and drug targets to cure disease. Over the past year, he has begun several innovative collaborations with medical investigators who are applying genomics tools to their work.

Chronic obstructive pulmonary disease (COPD) afflicts almost 24 million Americans and is the third leading cause of death in the U.S. The presence of bacterial pathogens in the airways in COPD is common and increases with advancing disease. Dr. Timothy F. Murphy, the Senior Associate Dean for Clinical and Translational Research at the University of Buffalo, and an internationally recognized expert in respiratory tract bacterial infections, has been studying COPD for the past 18 years, particularly trying to elucidate the dynamics of bacterial colonization and infection of the respiratory tract in adults with COPD. Dr. Murphy and his team began working with Dr. Tettelin in 2015 to help determine the difference between bacteria in patients whose lungs get cleared of infection and patients who have bacteria staying in their lungs for months or even years. Dr. Tettelin is helping the team analyze the genomes of persistent bacterial isolates collected serially over time to understand the genomic changes they undergo associated with their persistence. The research project will also examine the effect of immune selective pressure on candidate vaccine antigens.

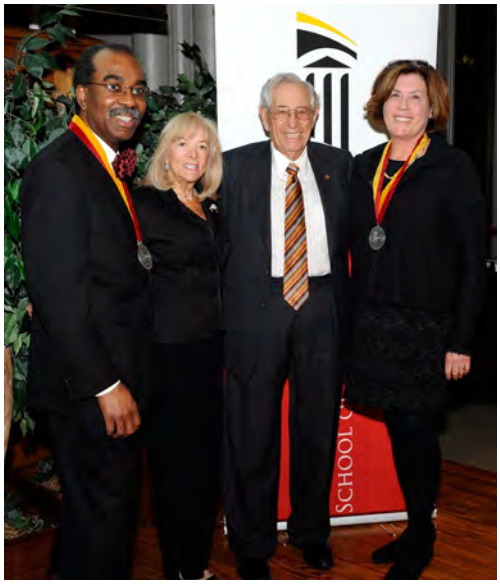
Another one of Dr. Tettelin's interesting collaborations is with Dr. Carlos Orihuela, an Associate Professor in Microbiology at the University of Alabama, Birmingham. Dr. Orihuela is an expert in the mechanisms of *Streptococcus pneumoniae* pathogenesis. *S. pneumoniae* is responsible for >1.5 million deaths a year worldwide, many of which are the result of an adverse cardiac event during infection. Dr. Orihuela noticed that cardiac lesions filled with bacteria formed during *S. pneumoniae* infections and this is associated with heart failure. Dr. Tettelin is working with the team to apply genomics and bioinformatics tools to examine the host-pathogen interactions that occur during cardiac lesion formation and to identify potential targets for intervention. They have noticed that microbubbles can form in the heart, and sometimes bacteria will bury themselves in biofilms which render them more resistant to treatments. Tettelin's sequence-based transcriptomic analysis is allowing the team to examine the host and bacterial responses at the same time and understand the mechanisms of host-pathogen interaction and microlesion formation.

Dr. Tettelin is also involved in an NIH Intramural project with Drs. Steve Holland, Adrian Zelazny and Elizabeth Sampaio where they are studying the evolution and adaptation of non-tuberculosis strains of mycobacteria associated with different diseases of the lung. The collaborative team is also trying to delineate genomic mutations that allow the bacterium to become resistant to antibiotics.

Dr. Tettelin has been an active developer and contributor of several of the bioinformatics tools used at IGS, particularly with **Sybil**, a web-based tool for visualizing and mining comparative genomic data, which has been very useful for these projects. This Sybil system is freely available to the public via the **CloVR** cloud virtual resource developed at IGS that packages all the tools necessary for researchers to perform comparative genome analyses without the need for bioinformatics and IT expertise.

"After spending so many years pioneering genomic applications to vaccinology and new bioinformatics tools, it's very gratifying to collaborate with medical researchers who have been experts in their own field and now want to apply genomic tools and perform more precise and in-depth analyses," said Dr. Tettelin.

Sybil: **view paper** **view application** CloVR: **view paper** **view application**



Dean Reece, Susan Fischell, Dr. Robert Fischell, Dr. Claire Fraser

Claire Fraser Named the Inaugural **Dean's Endowed Professor**

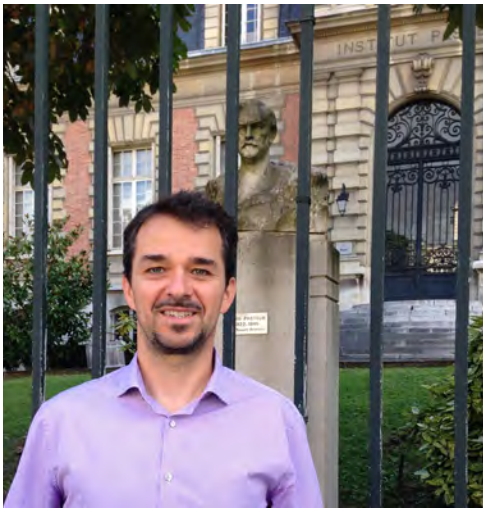
Claire Fraser, PhD, was presented with the inaugural Dean's Endowed Professorship in the School of Medicine on December 7, 2015. The ceremony, which took place in Westminster Hall, also honored ***Robert E. Fischell****, ScD, and his wife* ***Susan R. Fischell*** *for their generous support. The couple funded the professorship but chose not to put it in their names.*

Endowed professorships provide faculty with critical resources needed to sustain and expand promising research, launch innovative clinical initiatives, and educate and train future physicians. The University of Maryland School of Medicine has more than 70 endowed chairs and professorships.

"It is because of endowed professorships like this that we can recruit faculty members of great significance to these positions," said **E. Albert Reece**, MD, PhD, MBA, Vice President for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean of the School of Medicine.

Dr. Fraser has played a seminal role in the sequencing and analysis of human, animal, plant and microbial genomes to better understand the role that genes play in development, evolution, physiology and disease. She led the teams that first sequenced the genomes of several microbial organisms, including important human and animal pathogens, and as a consequence helped to initiate the era of comparative genomics. Her current research interests are focused on the structure and function of the human gut microbiota.

Dr. Fischell is a physicist, inventor and holder of more than 200 U.S. and foreign patents on medical devices and spacecraft. With the active assistance of his wife Susan, his inventions have led to the creation of several biotechnology companies. These inventions include a rechargeable implantable pacemaker that can be programmed with radio waves (Pacesetter Systems, Inc., now St. Jude Medical), which he and his team later helped miniaturize to save even more lives; the implantable insulin pump (now a product of Medtronic MiniMed); numerous coronary stents used to open clogged arteries (IsoStent, Inc., which merged with Cordis, a Johnson & Johnson company); and two feedback systems that provide early warning signs of both epileptic seizures (NeuroPace, Inc.) and heart attacks (Angel Medical Systems, Inc.). In 2005, Dr. Fischell was awarded a $100,000 TED prize to pursue his work on the design of a device to cure migraines without medication. That device (eNeura, Inc.) received FDA approval in May 2014. Dr. Fischell also was a co-inventor on a device to treat epilepsy that received FDA approval in November 2013.



Jacques Ravel Receives Pretigious International Science Award

Research Focuses on the Intersection of Women's Health and the Microbiome

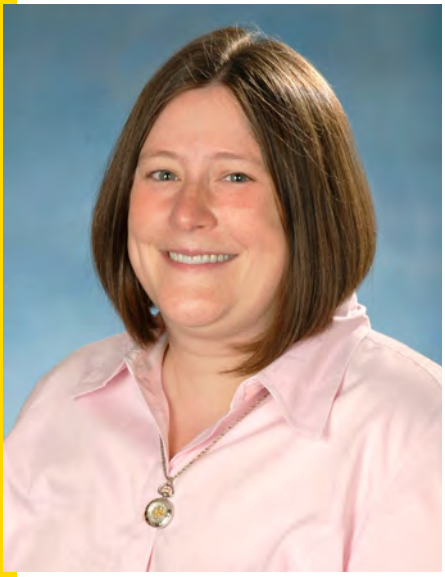
Jacques Ravel, PhD, Professor of Microbiology and Immunology at the University of Maryland School of Medicine and Associate Director for IGS, has been named a 2015-2017 Blaise Pascal International Research Chair, one of the most prestigious European science awards. He is spending this year working at the Institut Pasteur in Paris, and divides his time between Paris and Baltimore.

Dr. Ravel focuses on the human microbiome and its role in women's health. In his research, he develops and applies modern genomic technologies and systems biology approaches to decipher the functional relationships between the human host, the microbiome and susceptibilities to obstetrics and gynecological outcomes and sexually transmitted infections.

While at the Institut Pasteur, Dr. Ravel is working with Philippe J. Sansonetti, MS, MD, Professor of Microbiology at the Pasteur Institute and the Collège de France in Paris, a member of the U.S. National Academy of Sciences, and a microbiologist who is interested in intestinal pathogens. Working with Dr. Sansonetti, Dr. Ravel will address the following central question: "Can a pathogen, to be successful, become a commensal, by subverting the fine-tuned balance between the host and the microbiome?" They will try to better understand how *Chlamydia*, which is pathogenic in some parts of the body, can live in the gastrointestinal tract without triggering problems.

"Being able to work at the Institut Pasteur, and with Dr. Sansonetti is a fantastic opportunity. For over 100 years, the Institut has been a leader in the battle against infectious diseases," said Dr. Ravel. "Having immersed myself in genomics over the past 15 years, the Chair Blaise Pascal is giving me a rare opportunity to re-engage myself with my original research focus in microbiology and interact with global leaders in microbiology, cell biology and immunology focused on the role of the human microbiome in infectious diseases."

The Blaise Pascal International Research Chairs were established in 1996 to honor foreign scientists in all disciplines. Dr. Ravel is one of two Blaise Pascal Chairs selected this year.



Dr. Julie Hotopp Featured in Dr. Francis Collins' Newsletter

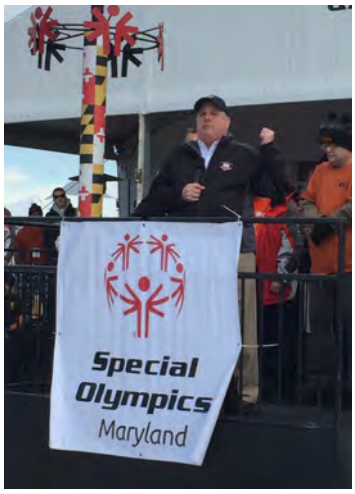
In a February 18th article called "Creative Minds: Bacteria, Gene Swaps, and Human Cancer," NIH Director Dr. Francis Collins wrote about Dr. Julie Hotopp's research:

"When Julie Dunning Hotopp was a post-doctoral fellow in the early 2000s, bacteria were known for swapping bits of their DNA with other bacteria, a strategy known as lateral gene transfer. But the offloading of genes from bacteria into multicellular organisms was thought to be rare, with limited evidence that a bacterial genus called *Wolbachia*, which invades the cells of other organisms and takes up permanent residence, had passed off some of its DNA onto a species of beetle and a parasitic worm. Dunning Hotopp wondered whether lateral gene transfer might be a more common phenomenon than the evidence showed.

Click to read more

She and her colleagues soon discovered that *Wolbachia* had engaged in widespread lateral gene transfer with eight species of insects and nematode worms, possibly passing on genes and traits to their invertebrate hosts [1]. This important discovery put Dunning Hotopp on a research trail that now has taken a sharp turn toward human cancer and earned her a 2015 NIH Director's Transformative Research Award. This NIH award supports exceptionally innovative research projects that are inherently risky and untested but have the potential to change fundamental research paradigms in areas such as cancer and throughout the biomedical sciences...."

Congratulations to Dr. Hotopp for this wonderful recognition of her research.



Governor Hogan

Super Plungers

Lynn Schriml – Special Olympics Volunteer

MSP Polar Bear Plunge – January 29-30th, 2016

The "Maryland State Police Polar Bear Plunge" is a charity event to benefit the 7,169 athletes of Special Olympics Maryland. This year over 6,000 daring folks and over 2,000 students took a dip in the wintry waters of the Chesapeake Bay to raise funds to support Special Olympics events and athletes. In its 20th year, this year's event raised over $2.2 million dollars bringing total funds raised to over $30 million dollars over its history.

Dr. Lynn Schriml volunteered this year on the media team for Friday's military and police plunge and Saturday's main plunge events helping to coordinate media interviews and taking photos of plungers, sponsors and volunteers including Governor Hogan kicking off the police plunge and taking a team picture with the Super Plungers.

Lynn has volunteered with the Special Olympics Maryland (SOMD) for the past 15 years. She has volunteered at multiple Special Olympics sporting events in Maryland including at swim meets, basketball tournaments, bocce, summer games and cycling competitions.

Dr. Schriml is a faculty member in the Institute for Genome Science at the University of Maryland School of Medicine, and also holds an academic appointment as Assistant Professor in the Department of Epidemiology and Public Health at the School of Medicine.

University of Maryland School of Medicine Researchers Identify **Most Dangerous Strains** of Often-Deadly Bacteria

New Approach Could Lead To Fewer Deaths and New Treatments

Dr. Tracy Hazen

A multi-disciplinary group of researchers at the University of Maryland School of Medicine (UM SOM) have for the first time elucidated the genetic makeup of various strains of *Escherichia coli*, which every year kills hundreds of thousands of people around the world.

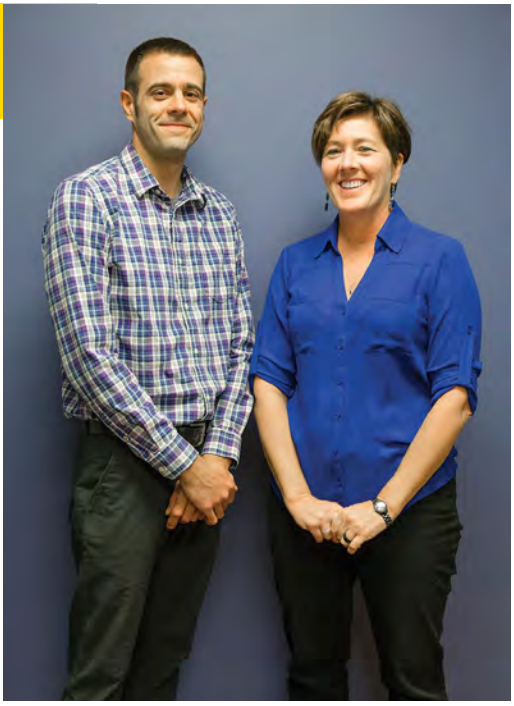
The paper, which appears in the latest issue of *Nature Microbiology*, focused on the analysis of the genomes of Enteropathogenic *Escherichia coli* (EPEC), which are the strains of the bacteria that cause diarrhea. Globally, there are nearly 1.7 billion cases of diarrheal disease every year and diarrhea kills ~760,000 children under the age of five each year.

The scientists, led by Drs. **Tracy Hazen**, Research Associate, Microbiology and Immunology at UM SOM and **David Rasko**, PhD, Associate Professor of Microbiology and Immunology at UM SOM, as well as Michael Donnenberg, Professor of Medicine at UM SOM, identified certain strains that are typically much more lethal than others. Dr. Rasko and his colleagues, including researchers in The Gambia, Mali, Kenya, Mozambique, India, Pakistan and Bangladesh, examined the genomes of 70 strains of EPEC, which were obtained from infected children enrolled in the Global Enterics Multi-Center study (GEMS) a multi-institutional project funded by the Bill and Melinda Gates Foundation and led by the University of Maryland School of Medicine Center for Vaccine Development. EPEC isolates were obtained from cases associated with children's death, diarrheal symptoms but recovery, or no symptoms.

The comparative analysis identified a set of genes that were more prevalent in lethal isolates when compared to the other groups of isolates. Some of these genes appear to be known virulence genes, while others were not and might highlight novel virulence pathways. The findings represent a resource that will help researchers better characterize the functions of these novel virulence factors and may ultimately lead to improvements in the identification and the development of effective treatments for these more dangerous versions of the pathogen, ultimately reducing the death toll associated with diarrheal diseases.

"These findings really help us map the associations between the bacterial content and these illnesses in a new way. This kind of research would not have been possible a few years ago," says Dr. Rasko. "But with recent new sequencing approaches, we can make these kinds of exciting discoveries." Rasko described the research as "genomic epidemiology," a new way of doing public health science that integrates the most cutting edge genomic technologies with an extensive knowledge of the pathogenic bacteria, both of which exist at the University of Maryland School of Medicine.

GRC UPDATE



As we begin 2016, we're looking forward to another exciting year for the Genomics Resource Center (GRC) and the application of genomic technologies to human health. The GRC team attended the yearly Advances in Genome Biology and Technology (AGBT) conference in Orlando, FL, where scientists meet and discuss a wide range of genomic-related topics. This year, the focus was on advances in single-cell sequencing, cancer mutation analysis, *de novo* human genome assembly using multiple long read technologies, and the introduction of new sequencing platforms from 10X Genomics and Pacific Biosciences. It was a busy four-day conference!

On the technology side, 10X Genomics introduced the new Chromium platform, enabling rapid pseudo-long read sequencing of human genomes, exomes, and up to 48,000 single cells in one Illumina HiSeq sequencing run. Illumina's Jay Flatley gave a plenary talk focused on the potential of their future platform, called Firefly. Expected to be available in late 2017, the new platform has the potential to further reduce cost and instrument footprint, and represent a major advancement for the industry leading sequencing manufacturer. Finally, Jonas Korlach from Pacific Biosciences described several early data sets from the recently released Sequel System. With average read lengths between 5-10kb, the new platform still has ways to go to equal the read lengths of the RS II, the current version of the instrument, but with up to 5 Gbp yield per run, the potential for larger, more cost-effective projects is already coming to fruition.

In fact, the GRC took delivery of its first Sequel instrument on February 29 - leap day! We're looking forward to what this new platform can do as we generate even more long reads for this extra long year!

Please check out our **blog** or email us: **grc-info@som.umaryland.edu**!

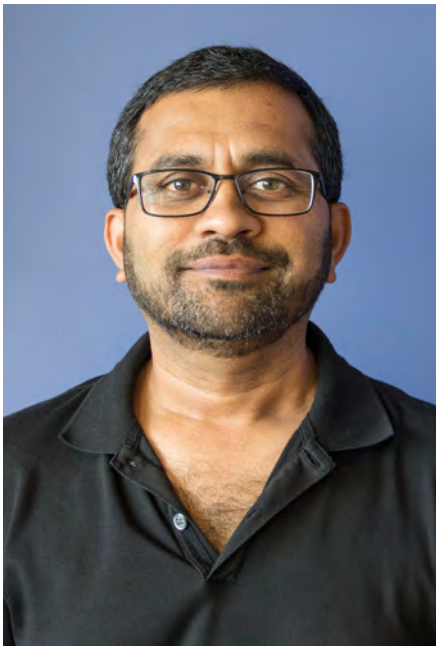
Q&A

How long does a project with GRC take?

It all depends on the project. Small projects can be completed in as few as three weeks. We've also completed large-scale, multi-year projects and everything in between. Time is always of the essence with science and we work hard to complete each project as quickly as possible without sacrificing quality.

Do you offer sequencing using Oxford Nanopore? When will the Sequel be operational?

We are part of the Oxford Nanopore MinION Early Access Programme and currently have two MinION devices in our R&D lab. While we continue to evaluate and develop on this platform, it is not yet part of our GRC sequencing services. On the other hand, while we expect the PacBio Sequel system will take some months to install, validate, and optimize, we anticipate offering Sequel services as soon as possible. If you are interested in this new, cutting-edge platform, please **email us**!



IRC with Anup Mahurkar

Executive Director, Software Engineering & IT

This newsletter issue features Dr. Tettelin's research, and we mention one of his projects using **Sybil**. I'd like to detail Sybil as an example of how we develop software and work with medical researchers who need certain applications.

What is Sybil?

Sybil is a web-based tool for visualizing and mining comparative genomic data generated by the **IGS Comparative Pipeline**, a pipeline used for comparing multiple genomes from the same species or closely related species. The tool has been implemented for a variety of organisms, both prokaryotes and eukaryotes.

Sybil provides a rich set of interfaces for browsing and analyzing comparative data. Sybil allows users to search for specific genes or gene clusters of interest and visualize their genomic context. Sybil also gives users the ability to identify core genes, genes shared across a phylogeny, and accessory genes from all or a subset of the available genomes. Most recently a Sybil site has been released to the public for comparison of complete ***Streptococcus pneumoniae* genomes**. The *S. pneumoniae* Sybil instance promises to be an important tool in accelerating vaccine discovery in developing nations. The software also includes utilities for rendering publication quality images in SVG and PDF formats. Sybil is open source and freely available with documentation and demo databases available for download.

Why was Sybil developed and/or how do medical researchers use it?

Sybil is used in conjunction with the IGS Comparative Pipeline, which provides a mechanism to compare multiple genomes at the nucleotide or protein levels to identify similarities and differences in genomes. This genome comparison can be done within a species or among closely related species. Comparison within a species allows researchers to understand strain level similarities and differences and identify shared genes and unique genes. These shared genes become putative vaccine targets that would be effective against as wide a range of strains as possible. The unique genes of strains can be used for strain identification and detection.

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PUBLICATION LIST

Shelburne SA, Ajami NJ, Chibucos MC, Beird HC, Tarrand J, Galloway-Pena J, Albert N, Chemaly RF, Ghantoji SS, Marsh L, Pemmaraju N, Andreeff M, Shpall EJ, Wargo JA, Rezvani K, Alousi A, Bruno VM, Futreal PA, Petrosino JF, Kontoyiannis DP: Implementation of a Pan-Genomic Approach to Investigate Holobiont-Infecting Microbe Interaction: A Case Report of a Leukemic Patient with Invasive Mucormycosis. *PLoS ONE* 2015, **10**(11):e0139851.

Mustapha MM, Marsh JW, Krauland MG, Fernandez JO, de Lemos AP, Dunning Hotopp JC, Wang X, Mayer LW, Lawrence JG, Hiller NL, Harrison LH: Genomic Epidemiology of Hypervirulent Serogroup W, ST-11 *Neisseria meningitidis*. *EBioMedicine* 2015, **2**(10):1447-1455.

Sinha R, Abnet CC, White O, Knight R, Huttenhower C: The microbiome quality control project: baseline study design and future directions. *Genome Biology* 2015, 16:276.

Breshears LM, Edwards VL, Ravel J, Peterson ML: *Lactobacillus crispatus* inhibits growth of *Gardnerella vaginalis* and *Neisseria gonorrhoeae* on a porcine vaginal mucosa model. *BMC Microbiology* 2015, 15(1):276.

Oruganty K, Talevich EE, Neuwald AF, Kannan N: Identification and classification of small molecule kinases: insights into substrate recognition and specificity. *BMC Evolutionary Biology* 2016, **16**(1):7.

Scholz CF, Bruggemann H, Lomholt HB, Tettelin H, Kilian M: Genome stability of *Propionibacterium acnes*: a comprehensive study of indels and homopolymeric tracts. *Scientific Reports* 2016, 6:20662.

Gulia-Nuss M, Nuss AB, Meyer JM, Sonenshine DE, Roe RM, Waterhouse RM, Sattelle DB, de la Fuente J, Ribeiro JM, Megy K, Thimmapuram J, Miller JR, Walenz BP, Koren S, Hostetler JB, Thiagarajan M, Joardar VS, Hannick LI, Bidwell S, Hammond MP, Young S, Zeng Q, Abrudan JL, Almeida FC, Ayllon N, Bhide K, Bissinger BW, Bonzon-Kulichenko E, Buckingham SD, Caffrey DR, Caimano MJ, Croset V, Driscoll T, Gilbert D, Gillespie JJ, Giraldo-Calderon GI, Grabowski JM, Jiang D, Khalil SM, Kim D, Kocan KM, Koci J, Kuhn RJ, Kurtti TJ, Lees K, Lang EG, Kennedy RC, Kwon H, Perera R, Qi Y, Radolf JD, Sakamoto JM, Sanchez-Gracia A, Severo MS, Silverman N, Simo L, Tojo M, Tornador C, Van Zee JP, Vazquez J, Vieira FG, Villar M, Wespiser AR, Yang Y, Zhu J, Arensburger P, Pietrantonio PV, Barker SC, Shao R, Zdobnov EM, Hauser F, Grimmelikhuijzen CJ, Park Y, Rozas J, Benton R, Pedra JH, Nelson DR, Unger MF, Tubio JM, Tu Z, Robertson HM, Shumway M, Sutton G, Wortman JR, Lawson D, Wikel SK, Nene VM, Fraser CM, Collins FH, Birren B, Nelson KE, Caler E, Hill CA: Genomic insights into the *Ixodes scapularis* tick vector of Lyme disease. *Nature Communications* 2016, 7:10507.