IGS

INSTITUTE FOR GENOME SCIENCES

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UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
INSTITUTE FOR GENOME SCIENCES

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Greetings Colleagues,

On March 12, 2020, in what seems like a lifetime ago, Governor Hogan sent all Maryland residents home, except for essential workers. At IGS, we grabbed our laptops and our briefcases and left our offices. We could never have anticipated or predicted how this year would develop!

While most of us familiarized ourselves with the logistics of quarantining and meeting via Zoom, a small team of dedicated IGS faculty and staff led by Dr. Jacques Ravel and Mr. Mike Humphrys began working closely with the University of Maryland Pathology Associates (UMPA), led by Dr. Sanford Stass, to launch a large-scale SARS-CoV-2 Testing Initiative on behalf of the State of Maryland. In a very short period of time, with campus support from Dean Reece, Dr. Bruce Jarrell and Dr. David Marcozzi, and with financial support from Governor Hogan, IGS repurposed and expanded its microbiome laboratory infrastructure to build a high-throughput testing operation capable of processing thousands of patient samples per day. We have been running this operation 24 hours a day, 7 days a week for more than 5 months and our team now numbers over 100 people. We will continue for as long as testing is required, and we are gratified that we have a role to play in safeguarding the health and safety of our fellow citizens. These are extraordinary times and I salute the entire COVID-19 testing team. In the past few months, I've directly seen the level of your dedication and work ethic, and I am humbled by your collegial spirit.

In the midst of the pandemic and the anti-science rhetoric that is swirling around us every day, we know that scientific research is even more important than ever. Consequently, I am thrilled to share news about many new IGS grants and publications that have come from our collective efforts over the summer – with some of us coming into Baltimore and some of us working remotely as hard as we ever have. I applaud your commitment to new research breakthroughs.

Here are some highlights in this issue:

- Maryland Genomics and many IGS heroes' extraordinary work with the COVID Testing Initiative **(pg. 7)**
- Scott Devine's dedication to graduate, medical and postdoctoral education **(pg. 3)**
- Owen White and Seth Ament's new SCORCH grant **(pg. 15)**
- Hervé Tettelin's role with a new book about the pangenome **(pg. 12)**
- David Serré's new RO1 grant and work in Cambodia **(pg. 11)**
- Ronna Hertzano' new work with proteins in the ear **(pg. 13)**
- We also congratulate our faculty who have recently been promoted **(pg. 19)**

I hope that you are as inspired by the stories in this issue as I am. In these challenging times, please stay safe, strong and continue your excellent work.

Sincerely,

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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Influencing Future Researchers and Physicians: IGS Involvement with GPILS

Many long-term benefits were anticipated with the launch of the Institute for Genome Sciences (IGS) in 2007 at the University of Maryland School of Medicine (UMSOM). One of IGS's priorities was increasing collaborative genomic and medical research. Another outcome envisioned was the long-term benefit of having the Institute develop new curriculum for the medical and graduate schools, as many were pioneers in genomics. As Dean of one of the nation's preeminent teaching hospitals, Dr. E. Albert Reece anticipated that IGS faculty would apply their expertise to creating cutting edge genomics and informatics courses for SOM's medical students and residents, as well as the students in Graduate Program in Life Sciences (GPILS) at UMB.

Over the years, IGS' involvement with course development and teaching has enhanced the quality of student research, and more broadly the education of graduate students, post-doctoral and medical fellows as well as residents. The ability to have hands-on access to current bioinformatics applications and analysis, and leading genomic research programs has contributed to the successful recruiting of top-tier students to SOM and UMB programs.

UMB offers a broad selection of seven different doctoral granting programs in the Graduate Program in Life Sciences (GPILS), and Molecular Medicine is one the largest Program. There are four research tracks within Molecular Medicine: Cancer Biology, Genome Biology, Molecular and Cellular Physiology and Applied Pharmacology and Toxicology.

Molecular Medicine involves numerous interdepartmental faculty from UMB schools. Toni Antalis, PhD, Professor, Physiology, in the Center for Vascular & Inflammatory Diseases (CVID) is the Director of the Molecular Medicine program.

Scott E. Devine, PhD, Associate Professor, Medicine was recruited to IGS in 2009 from Emory University in Atlanta, where he developed many of their educational programs. Dr. Devine soon became the Track Leader of the newly created Genome Biology research track. Over the years, he and other faculty from the IGS have introduced bioinformatics and genomics analyses to the curriculum, and now several hands-on analysis training courses are offered.

Clinical bioinformatics, which combines clinical informatics, bioinformatics, medical informatics, information technology, and omics science has become increasingly vital in the diagnosis, treatment, and predictive prognosis of patients with cancer. The National Cancer Institute (NCI) is interested in having graduate students, faculty and postdoctoral students learn hands-on bioinformatic analysis. The National Institutes of Health (NIH) has recognized the importance of bioinformatics and genomics for all disease research, cancer being one of the most prominent. To continue expanding the school cancer biology training program, Dr. Antalis obtained a prestigious T32 Training grant from NIH that helps fund graduate and post-graduate student placements in various laboratories. "NCI's interest in expanding bioinformatics training is that cancer is a genetic disease, and as more tumors

Scott E. Devine, PhD
Associate Professor
Medicine
Institute for Genome Sciences

are studied with genomic sequencing, it is important to be able to customize analyses," said Dr. Devine.

In 2011, Dr. Devine has worked with Michelle Gwinn-Giglio, PhD, Lynn Schriml, PhD, Joana Carneiro da Silva, PhD, and several other faculty and scientists at IGS to develop and continuously update two important full semester courses for GPILS: the three credit GPILS 716 (Genomics and Bioinformatics) and the 2 credit GPILS 718 (Programming for Bioinformatics). Additionally, in 2019, IGS faculty created a mini-course called "Cancer Genomics and Bioinformatics" to further address the students' need for hands-on bioinformatics skills. Luke Tallon, Executive Scientific Director of the Genomic Resource Center, and Anup Mahurkar, Executive Director, Bioinformatics Software Engineering, and their teams have been contributing their expertise with genome sequencing and computational analysis to these courses.

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Michelle Gwinn-Giglio is Director of the three credit GPILS 716 course, which is a semester-long, team-taught class which introduces the basics of bioinformatics from an entry level perspective. Students do not need any prerequisite classes before enrolling in this course. They are taught how to use existing software and tools and to start analyzing research data. By the end of the class, students are more familiar with tools and can analyze data.

"One of the most important accomplishments of GPILS 716 is to bridge that gap for students with no bioinformatics background at all, and bring them to a level where they can analyze large genomics datasets on their own using existing tools," explains Dr. Devine.

Ten years ago, researchers could send their DNA samples to a core facility and facilities would return the data sequenced. Today, genomic scientists cannot get the data back in a readable format, unless they know their way around bioinformatics tools running on systems such as Linux, and even that can be cumbersome as the data has become more extensive.

Bioinformatics is more widely used in biomedical research, and it has become increasingly important for researchers to understand how to set up their own parameters and to be able to design their own bioinformatic analysis. Recognizing this, Dr. Devine has constructed ways that students can steadily progress in understanding the process of genomic data analysis. In designing GPILS 716 and 718, the faculty wanted students to have the experience of working with software that would allow them to realistically analyze "mock" data that would be similar to real data. By analyzing real-life data, the students would learn critical skills to prepare them to handle their own research data.

Anup Mahurkar and Erik Anderson, IT Support Assistant, and IGS IT department, set up a server to "mock" realistic patient sequencing. This process involves extensive IT preparation to set up this parallel data site. As part of the course, the students learn basic skills in the programming languages Python, MySQL and R, as well as other software programs that are used in bioinformatics. More importantly, they learn how to run their own custom programs and analysis.

"This is a very innovative program at UMB," explained Dr. Devine. "My colleagues at other universities have told me that teaching medical and graduate students how to handle bioinformatics analysis is a needed skill that is rarely taught. Once they learn off-the-shelf software, they can learn how to customize their analysis to find specific information."

An important part of this hands-on curriculum is teaching students how to identify mutations in tumors. The Greenebaum Cancer Center has a tissue bank with thousands of samples stored, and the students can select various samples to study. They can sequence the genomes of tumors and matched normal control tissues, and also perform transcriptomics (where the complete set of RNA transcripts that are produced by the genome are quantified by sequencing).

Molecular Medicine, the umbrella program, hosts between 80 – 90 students per year. Boosting recruitment and growing the program has been a big emphasis for the IGS faculty. The national recruitment effort is extensive, as SOM reaches out to chairs and other faculty of biology and computer science departments at major universities.

Dr. Antalis notes that the genomics program at UMB is a big draw with recruitment. "IGS has transformed our genomics training. There are more applicants applying specifically because of that track, and it has enhanced the reputation of our University. Dr. Devine is a great ambassador for this program," she said.

The genome sciences curriculum has contributed to the **Greenebaum Cancer Center** become designated a P30 Cancer Center through an NIH grant and has helped Dr. Antalis receive a prestigious T32 grant, which helps with institutional training.

"The caliber of graduate, post-graduate, medical students, fellows, and residents coming out of these programs has been outstanding," said Dr. Devine. The students' publications have been in leading scientific journals, and our students routinely build upon their training here and move on to prestigious scientific or medical careers. About half of the students have continued in the academic research environment and about half have continued into diverse alternative careers, which have included science journalism (being awarded with an AAAS Fellowship), working with Federal laboratories such as the FDA, or working with industry. A few students have branched into patent law, focusing on biotechnical or biomedical discoveries, where a modern science background is needed.

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Dr. Devine feels the strength of IGS is that these programs rely on a real team effort. **"We have a very harmonious group, who work well together, and mentor junior faculty with many people working behind the scenes. The leadership at IGS has created a great environment for research, education, and service."**

MORE INFORMATION

https://www.medschool.umaryland.edu/profiles/Devine-Scott/

Open Standards, Open Source Software, Open Collaborations: IGS and the NIH Common Fund

Since 2019, the Institute for Genome Sciences has been a leading institution in the **NIH Common Fund Data Ecosystem (CFDE)** , which is a program where Common Fund datasets are being organized and stored in a digital cloud environment.

In 2020, IGS began its second year of the CFDE, continuing to work remotely with the other global participating organizations. The Ecosystem has been working and communicating remotely since its 2019 launch, so the workflow has continued without a pause during the quarantine.

Participating institutions include Oxford in the UK, several institutions in California (UCD, USC, UCSD), and on the East Coast (Icahn School of Medicine at Mt. Sinai; Research Triangle Institute), as well as the University of Chicago. IGS is the prime institution and Owen White, PhD, serves as the Principal Investigator (PI) of the entire project. Dr. White is Associate Director, Informatics at the Institute for Genome Sciences and Professor, Epidemiology & Public Health at the School of Medicine.

The purpose of the project is to facilitate better sharing and improved tagging within huge datasets and to move the datasets to the cloud environment for improved access by many researchers. IGS and other institutions are building a portal and working on the organization of the data storage and coordination.

Dr. White was the PI of the Human Microbiome Project (HMP) Data Analysis and Coordination Center (DACC), which ran from 2009 – 2014 to develop datasets and tools

IGS CFDE Team

Definition

The NIH Common Fund programs address emerging scientific opportunities and pressing challenges in biomedical research that no single NIH Institute or Center (IC) can address on its own, but are of high priority for the NIH as a whole. The Common Fund is a unique resource at NIH, serving as an incubator where high-risk, innovative endeavors with the potential for extraordinary impact can be supported. Common Fund programs are short-term, goal-driven strategic investments, with deliverables intended to catalyze research across multiple biomedical research disciplines.

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that the community could use to evaluate which biological properties of the microbiome affect human health. Since then and as part of CFDE, Dr. White and the bioinformatics team from IGS have been actively involved in transitioning the storage of HMP data into the cloud, for improved query capability and access.

The Common Fund Data Ecosystem (CFDE) links multiple data platforms and is intended to provide a central access point for Common Fund datasets, tools, and other digital objects. This CFDE portal links multiple data platforms that have been established through Common Fund programs and creates cloud workspaces for users to access and analyze data across the different platforms.

"While users may continue to access an individual dataset via the platform created for that dataset, the CFDE will foster new discoveries and support different types of analyses by enabling queries of multiple datasets simultaneously. The CFDE will provide user support through automated help tools, online courses, webinars, and in-person training events," said Dr. White.

During the years of the HMP grant, IGS had a "custodian" role with the data. That dynamic has been transitioning to a data analysis model. In fact, IGS has been tracking "best practices" from the HMP experience, outlining the transition of archiving big datasets, documenting the ways that data was collected and the tools used for building analyses pipelines. These processes will be invaluable for the other Data Coordination Centers (DCCs), which are now "retiring" large datasets that will still be used in the future. The Library of Integrated Network-based Cellular Signatures or LINCS is expected to be the next center to transition to cloud-storage using the lessons learned during the transition of HMP to the CFDE.

One of the challenges of a project involving multiple institutions with various areas of specialties is coordinating everyone's perspectives into a cohesive "whole."

"The CFDE is working on a huge problem across many different data providers, and there are differing opinions about which aspect of the data is a priority," said Dr. White. "Working together, we better understand the needs of different users and organize the storage and access for those needs."

In the next few years of the project, the consortium will improve the analysis tools, while adding new information providers.

"The CFDE is working on a huge problem across many different data providers, and there are differing opinions about which aspect of the data is a priority," said Dr. White. "Working together, we better understand the needs of different users and organize the storage and access for those needs."

– Dr. Owen White

Taking the Lead in Testing:

The Institute for Genome Sciences Sets Up a New Large-Scale SARS-CoV-2 Testing Facility at UMSOM

With support on campus from Dean Reece, Dr. Jarrell and Dr. David Marcozzi and backed by a $2.5 million grant from the State of Maryland, the Institute for Genome Sciences (IGS) and the University of Maryland Pathology Associates (UMPA) launched a large-scale SARS-CoV-2 Testing Initiative that expanded testing capability to better serve Marylanders.

The new initiative has been led by Claire Fraser, PhD, the Dean's Endowed Professor and Director of the Institute for Genome Sciences and Sanford Stass, MD, Professor and Chair of both the UMSOM Department of Pathology and Department of Medical and Research Technology. The facility is an expansion of the Microbiome Service Laboratory (MSL). MSL Core Director, Michael Humphrys, has had valuable experience working as a CDC laboratory scientist and his expertise has been critical to this effort. The MSL team working with the Genomic Resource Center staff led by Dr. Lisa Sadzewicz and Luke Tallon, repurposed and reprogrammed the robotic platforms to handle specific tasks related to COVID-19 testing, a task that they started in late February after it became clear that the virus was spreading beyond China. The machines had previously been used for research studies to characterize the bacteria that compose the human microbiome.

In April 2020, the State of Maryland, through a grant, enabled the purchase of additional robots and the expansion of the facility testing capacity. The collaboration between an established pathology laboratory (UMPA) and the Institute for Genome Sciences' expertise in high-throughput genomic processes, has been highly successful in building and operating the facility that has progressively ramped up its capacity to about 15,000 tests per day. The facility is located at the Institute for Genome Sciences on the second floor of the Health Sciences Facility III (HSF III).

The Informatics Resource Center (IRC), led by Anup Mahurkar and Owen White, PhD, developed the informatics infrastructure that enable sample tracking through the facilities and interfacing with the clinical diagnostic laboratory for reporting results to clients.

All tests are performed in a CLIA-certified (Clinical Laboratory Improvement Amendments of 1988, 42 U.S.C. §263a), high-complexity laboratory environment. CLIA certification ensures that the laboratory meets federal standards applicable to all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent or treat disease.

Analyzing test samples from patients suspected of having COVID-19 is a complex, multi-step process that first involves transferring a portion of the sample to an inactivation solution and extracting its RNA, which contains the

SARS-CoV-2 Testing at UMSOM

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virus genetic code. The RNA is then converted to DNA and amplified using qPCR according to protocols developed and validated by the laboratory. Automation of these steps is critical to the laboratory ability to test thousands of samples per day.

"We have now implemented a reconfiguration of the MSL to establish this high-throughput testing capability," said Jacques Ravel, PhD, Professor of Microbiology and Immunology and Associate Director of Genomics, IGS. "Working closely with the Department of Pathology, the UMPA laboratory we were able to obtain regulatory approval to enable us to perform all aspects of the tests at IGS."

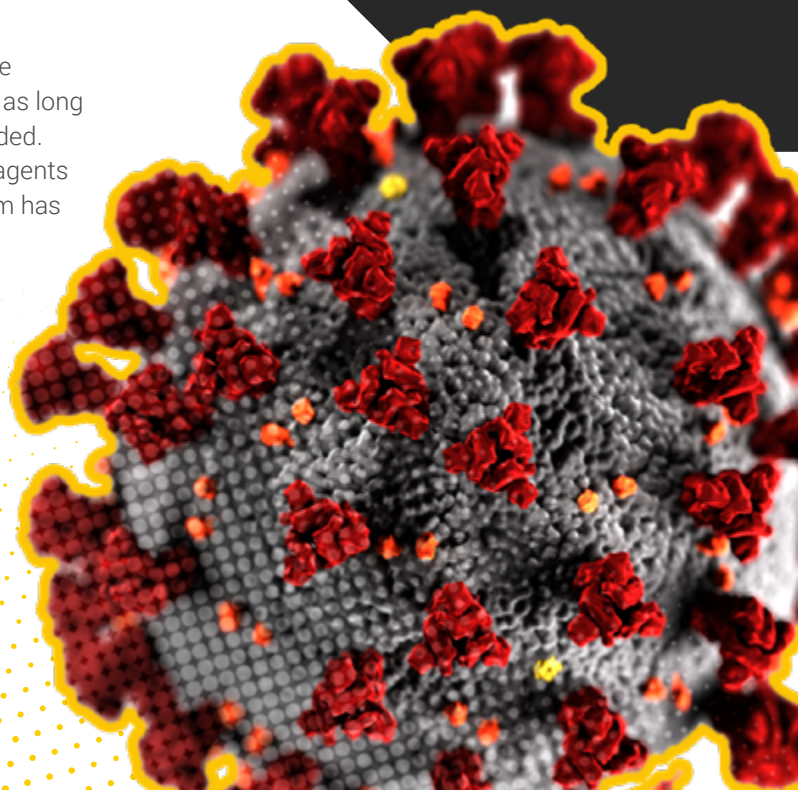
The testing laboratory supports several populations throughout the State, including the staff and residents within nursing homes, assisted living facilities, correctional facilities and detention centers, as well as colleges, universities and community testing sites.

"This initiative is a results of a huge team effort at IGS and UMPA. Its success highlights the incredible hard work and dedication of the IGS staff. We are so proud to contribute to the fight against COVID-19 in Maryland," says Claire Fraser, PhD. "It has greatly improved our capabilities to reach deeper into the community and help provide expanded testing which is desperately needed to help bring the epidemic under control in the State of Maryland. The enhanced testing capability has also been leveraged to ensure sustained COVID-19 surveillance across the State of Maryland."

"The State was in dire need of increased coronavirus testing and the SOM already had the early infrastructure in place, in terms of our technology and scientific expertise to help close the testing gap," notes University of Maryland School of Medicine (UMSOM) Dean E. Albert Reece, MD, PhD, MBA. **"The funding provided enabled us to better track the spread of the virus and provide swifter diagnoses and treatments to those in need."**

COVID-19 testing is going to remain a major operation at IGS for the foreseeable future, and plans are being drawn to sustain operation as long as support for the State of Maryland public health response is needed. To achieve this, it involves continued sourcing large amounts of reagents and supplies from around the world, something the expanding team has become expert at doing.

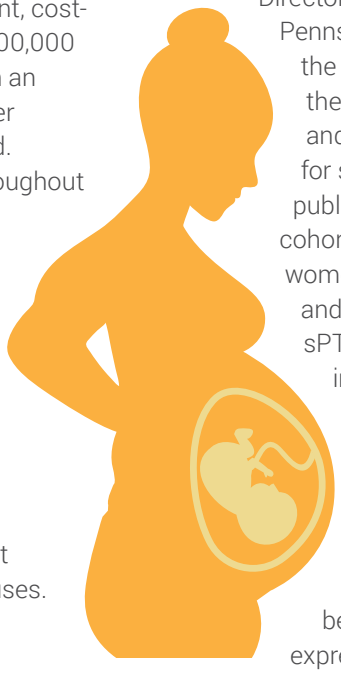
SARS-CoV-2 Testing at UMSOM



Addressing the Health Disparity in Preterm Birth:

Evaluating the contribution of the host-microbiota interaction on pregnancy outcomes and racial disparity in the US

According to the World Health Organization, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation) worldwide annually, and this number is rising. Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015. Three-quarters of these deaths could be prevented with current, cost-effective interventions. In the United States, 400,000 infants are born preterm each year resulting in an infant mortality rate that is worse than 26 other economically developed countries in the world. Preterm birth risk is not evenly distributed throughout American society, resulting in massive racial disparities. Indeed, 2019 March of Dime research reports that in the United States, the preterm birth rate among Black women is 49% higher than the rate among all other women. This disparity is poorly understood, and more research and novel interventions are desperately needed.



Over 75% of preterm births (PTBs) are termed spontaneous (sPTB), resulting in giving birth at early gestational time points without clear causes. Our lack of understanding of the mechanisms and overall pathogenesis that promotes sPTB results in limited successful interventions. It is widely accepted that genetic variation does not explain racial differences in PTB risk, hence other biological factors must have some obligatory role for disparities in PTB. While contractions of the uterus and changes in the structure of the cervix (cervical remodeling) are necessary to the birthing process to be initiated, the reasons these are triggered prematurely remain elusive. Foundational work led by **Jacques Ravel, PhD**, Professor, Microbiology & Immunology, SOM and Associate Director, Genomics, IGS, has provided key information for women's reproductive health, and specifically has characterized the composition of the communities of microbes (the microbiota) that occupy the cervicovaginal space. Dr. Ravel's comprehensive studies in non-pregnant women have led to the classification of cervicovaginal microbiota into five major kinds which he coined "community state types (CSTs)". Subsequent research has demonstrated that select CSTs are associated with various pathologies such as sexually transmitted infections, bacterial vaginosis, and urinary tract infections. Yet, the data on the association of these CSTs with spontaneous PTB (sPTB) has been limited with existing studies confounded by small sample sizes, lack of racial diversity and inconsistent phenotyping of the preterm birth.

Dr. Ravel has been collaborating with Michal Elovitz, MD, Director, Prematurity Prevention Program, University of Pennsylvania Medicine. Together, they are researching the role of interactions between the microbiota and the genital epithelium in altering preterm birth risk, and that in Black women, a population at high risk for sPTB. With funding from the NIH, they recently published the results of a comprehensive study of a cohort of 2000 racially and ethnically diverse pregnant women. This study provided conclusive data that CSTs and specific bacteria are strongly associated with sPTB. Furthermore, they found that local cervicovaginal immune responses to these bacteria modify the risk of sPTB associated with high-risk CSTs, suggesting that the cervicovaginal microbial-immune profiles are of critical importance for sPTB risk. Providing possible insight into the known racial disparity with sPTB, their data demonstrated that Black women are more likely to be colonized with high-risk CSTs and have differential expression of the immune mediators that modify the risk of sPTB. The study was published in the journal *Nature Communications*. Further, the work led to the filing of a patent for novel diagnostics to predict women at risk of sPTB.

Drs. Ravel and Elovitz, received an additional 5 years of funding to their NIH R01 grant to continue their groundbreaking work. While their findings suggest an opportunity for therapeutic interventions to reduce sPTB, recent advances support that only by understanding the totality of an ecosystem and the subsequent host response can the greatest impact on health and disease be realized. They will rely on IGS' expertise on multi-omics and biomathematical modeling developed in Dr. Ravel's

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laboratory to characterize the cervicovaginal microbiota-host interactions in pregnant women. The purpose of their new project is to define the causes for the large racial disparities in spontaneous preterm birth (sPTB) for Black women. The project will explore a role for cervicovaginal microbiome in contributing to changes in cervical cells activity, metabolic and immune response that identify Black women at a greater risk for sPTB. Specifically, the team will explore 1/ whether select CSTs are associated with molecular evidence of premature cervical remodeling and 2/ whether high-risk cervicovaginal microbiota-immune profiles are present prior to pregnancy and/or does becoming pregnant shift a women's microbiota to a favorable or unfavorable state.

Addressing these gaps in knowledge will provide novel information as to potential new windows for intervention as well as identifying novel modifiers associated with a high-risk cervicovaginal microbiota-immune state which could lead to a reduction of sPTB in Black women.

Jacques Ravel, PhD
Professor
Microbiology and Immunology
Institute for Genome Sciences

Michal Elovitz, MD
Director, Prematurity
Prevention Program Penn Medicine

MORE INFORMATION

https://www.medschool.umaryland.edu/profiles/Ravel-Jacques

https://www.pennmedicine.org/providers/profile/michal-elovitz

http://ravel-lab.org/

The Serre Lab's Malarial Research in Cambodia

By combining controlled field studies with genomic analyses of the malarial parasite, *Plasmodium vivax*, Dr. Serre and his team are taking an innovative approach to research questions about this important infectious disease.

Over the last eight years, **David Serre, PhD**, Associate Professor, Microbiology & Immunology, University of Maryland School of Medicine and Institute for Genome Sciences, has focused his research on *Plasmodium vivax*, a single-celled parasite transmitted by mosquitoes that is responsible every year for more than 8.5 million clinical malaria cases worldwide. While *P. vivax* is less lethal that *P. falciparum*, it cannot be grown in the laboratory and is more difficult to study.

In recent years, WHO and NIH have focused new attention on *P. vivax* because its unique life cycle makes it resilient to elimination measures, and while the levels of *P. falciparum* have been globally reduced over the past 10 years, *P. vivax* prevalence has remained high.

One challenging aspect of *P. vivax* is that the parasite can become dormant and stay for weeks or months in its host's liver. Then, at a future time, the parasite can reactivate and cause blood infections and malaria episodes. With their previous field study, Dr. Serre and his collaborators at the Institut Pasteur in Cambodia showed that those liver relapses were more frequent than previously thought and would likely be the main challenge of vivax malaria elimination, and not, as in *P. falciparum*, the emergence and spread of antimalarial resistance. This observation was particularly worrying since there is no good drug targeting liver parasites: the only WHO-approved drug for treating liver-stage malaria, primaquine, has severe side effects in people lacking a specific red blood cell enzyme, resulting in an increased risk of anemia. Unfortunately, about 40% of the Cambodian population carries a partially deficient copy of this enzyme and primaquine is therefore rarely used in Cambodia.

Dr. Serre will continue the next phase of his malaria research in Cambodia with a new multi-year award from the National Institute of Allergy and Infectious Diseases (NIAID), on a tightly designed clinical trial paired with genomic analyses (grant number R01AI146590). The study has several research goals.

First, Dr. Serre and his team will use genome sequencing approaches to differentiate relapses of liver parasites from new infections caused by mosquito bites, to determine how often dormant liver parasites reactivate and if a specific stimulus is triggering this reactivation. The study could highlight features (biomarkers) indicative that an apparently asymptomatic individual carries parasites in its liver and help elimination of this disease.

Next, the team will conduct a clinical trial to test the efficacy of primaquine on *P. vivax*; primaquine is already FDA-approved but this study will focus on how efficacious and safe different doses are on individuals living in endemic areas. To run their study, the team will bring study participants from malaria-endemic areas to the provincial capital city (where there are little or no mosquitoes) for the entire study period, to avoid having participants become re-infected.

This will be a tightly controlled field study, and the Serre Lab will be collaborating with the same institutions in Cambodia with which they worked before – the National Center for Malaria Control in Phnom Penh and with the Institut Pasteur in Cambodia.

David Serre, PhD
Associate Professor
Microbiology and Immunology
Institute for Genome Sciences

Serre Lab Scenes

MORE INFORMATION

https://www.medschool.umaryland.edu/profiles/David-Serre/

https://www.igs.umaryland.edu/labs/serre/

The Pangenome – New Reference Book

"*The Pangenome: Diversity, Dynamics and Evolution of Genomes*", a new reference free open access book about the pangenome was published by Springer in May 2020. The book was edited by **Hervé Tettelin, PhD**, Professor, Microbiology & Immunology, IGS at the UMSOM and Duccio Medini, PhD, Head of Data Science and Digital Innovation at GSK Vaccines Research and Development.

(*far left*) **Dr. Hervé Tettelin, TIGR at the time, now IGS, Dr. Brigitte Gaume, (NIH at the time)/UMB-Johns Hopkins (now), Dr. Vega Masignani, Chiron/Novartis/GSK, Dr. Rino Rappuoli, Head Vaccine Research, Chiron/Novartis/GSK, Matthew Lewis, TIGR at the time/now OpGen**

Drs. Tettelin, Medini, and colleagues are credited with coining the term "pangenome" in 2005. In simple terms, the pangenome is the realization that the pool of genetic material present across the organisms of a given species often greatly exceeds the material available to each of the individual genomes. Pangenomics, first developed during comparative analyses of a few bacterial genomes, has evolved into a novel discipline at the intersection of biology, computer science, and applied mathematics.

This is the first reference book written on the topic of pangenomics, published 15 years after the term was coined. Pangenomics is an early example of big data applied in biology—in which a mathematical model that was developed to address a practical question in vaccinology – ended up transforming established concepts. Since then, the development of next-generation sequencing and computational technologies has afforded the generation of pangenomes from thousands of isolates and non-cultured samples of many microbial species, first, and then of eukaryotes encompassing all the kingdoms of life, which has extended the original hypothesis beyond the most ambitious expectations.

The first chapter entitled: "The Pangenome: A Data-Driven Discovery in Biology", co-authored by Drs. Medini, Donati*, Rappuoli†, and Tettelin, explains the concept of the pangenome and how the authors' hypothesis evolved from their studies of vaccinology. Other book sections and chapters cover the breadth of knowledge and perspectives about the impact of the pangenome concept and tools on genomic diversity, evolutionary biology, metagenomics, epigenomics, antibiotic resistance, and more. The chapter entitled "Meta-Pangenome: At the Crossroads of Pangenomics and Metagenomics" was contributed by Bing Ma, PhD, Michael France, PhD and Jacques Ravel, PhD, Associate Director, Genomics at IGS.

"This book is the culmination of 15 years of sustained research on the pangenome around the world. The concept has impacted so many fields of biology that we felt it was time to provide the community at large with a one-stop reference on the topic," said Hervé Tettelin, PhD, Professor, Microbiology & Immunology, IGS.

*Claudio Donati, PhD, (former GSK), Computational Biology Unit, Research and Innovation Centre, Fondazione Edmund Mach, San Michele all'Adige, Italy

†Rino Rappuoli, PhD, GSK Vaccines R&D, Siena, Italy

MORE INFORMATION

https://www.medschool.umaryland.edu/profiles/Tettelin-Herve/

UM School of Medicine Researchers Identify Role of Crucial Protein in Development of New Hair Cells Needed for Hearing

Understanding Hair Cell Development is Critical for Developing Future Treatments

Researchers at the University of Maryland School of Medicine (UMSOM) have conducted a study that has determined the role that a critical protein plays in the development of hair cells. These hair cells are vital for hearing. Some of these cells amplify sounds that come into the ear, and others transform sound waves into electrical signals that travel to the brain. Ronna Hertzano, MD, PhD, Associate Professor in the Department of Otorhinolaryngology Head and Neck Surgery at UMSOM, Affiliate Faculty at IGS and Maggie Matern, PhD, who performed this work while a graduate student in the Hertzano Laboratory, now a postdoctoral fellow at Stanford University, demonstrated that the protein, called GFI1, may be critical for determining whether an embryonic hair cell matures into a functional adult hair cell or develops to a cell that resembles a nerve cell or neuron.

The study was published in the journal *Development*, and was conducted by physician-scientists and researchers at the UMSOM Department of Otorhinolaryngology Head and Neck Surgery and the UMSOM Institute for Genome Sciences (IGS), in collaboration with researchers at the Sackler School of Medicine at Tel Aviv University in Israel.

Hearing relies on the proper functioning of specialized cells within the inner ear called hair cells. When the hair cells do not develop properly or are damaged by environmental stresses like loud noise, it results in a loss of hearing function. In the United States, the prevalence of hearing loss doubles with every 10-year increase in age, affecting about half of all adults in their 70s and about 80 percent of those who are over age 85. Researchers have been focusing on describing the developmental steps that lead to a functional hair cell, in order to potentially generate new hair cells when old ones are damaged. The Hertzano laboratory, a highly collaborative group, specializes in identifying the key regulatory proteins in hair cell development and understanding their function. These studies use a combination of advanced genomics methodologies with techniques to isolate specific cell types from the ear. Some of their recent findings include the roles of Zeb1, RFX and IKZF2 transcription factors in hair cell development.

To conduct her latest study, Dr. Hertzano and her team utilized cutting-edge methods to study gene expression in the hair cells of genetically modified newborn mice that did not produce GFI1. They demonstrated that, in the absence of this vital protein, embryonic hair cells failed to progress in their development to become fully functional adult cells. In fact, the genes expressed by these cells indicated that they were likely to develop into neuron-like cells.

Dr. Ronna Hertzano
Associate Professor
Otorhinolaryngology-Head & Neck Surgery
School of Medicine
Institute for Genome Sciences

"Our findings explain why GFI1 is critical to enable embryonic cells to progress into functioning adult hair cells," said Dr. Hertzano. "These data also explain the importance of GFI1 in experimental protocols to regenerate hair cells from stem cells. These regenerative methods have the potential of being used for patients who have experienced hearing loss due to age or environmental factors like exposure to loud noise."

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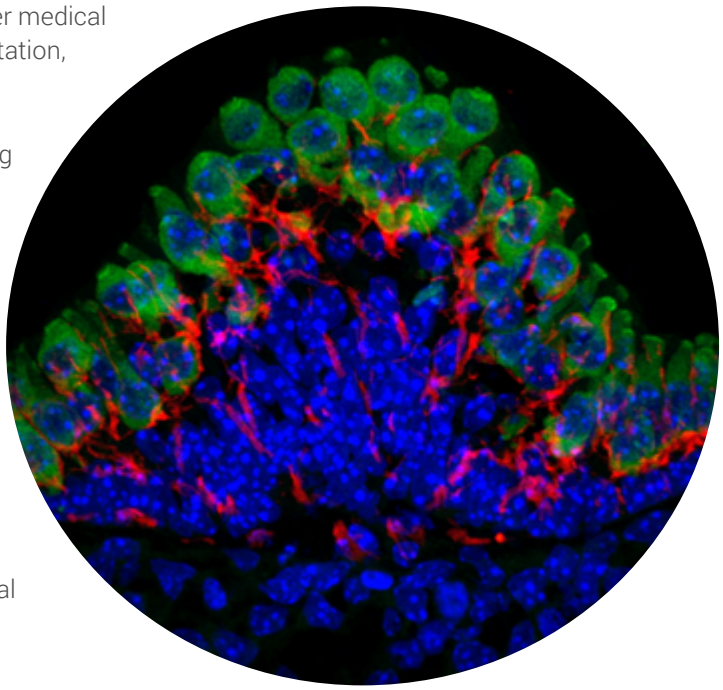
Dr. Hertzano first became interested in GFI1 while completing her medical degree and doctorate at Tel Aviv University. As part of her dissertation, she discovered that the hearing loss resulting from mutations in another protein called POU4F3 appeared to largely result from a loss of GFI1 in the hair cells. Since then, she has been conducting studies to discover the role of GFI1 and other proteins in hearing. Other research groups in the field are now testing these proteins to determine whether they can be used as a "cocktail" to regenerate lost hair cells and restore hearing.

"Hearing research has been going through a Renaissance period, not only from advances in genomics and methodology, but also thanks to its uniquely collaborative nature among researchers," said Dr. Herzano.

The new study was funded by the National Institute on Deafness and Other Communication Disorders (NIDCD) which is part of the National Institutes of Health (NIH) and the Binational Scientific Foundation (BSF).



Sensory hair cells (green, MYO6 protein) and their neuronal connections (red, DCX protein) of a one-day old mouse vestibular crista.

MORE INFORMATION

https://www.medschool.umaryland.edu/profiles/Hertzano-Ronna/

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https://umgear.org/

UM School of Medicine Researchers Receive Federal Funding for Data Center for HIV and Substance Use Disorders

Research Could Lead to New Understanding of Interplay Between Cognitive Disorders and Opioid Abuse Linked to Persistent HIV Infections

Researchers at the University of Maryland School of Medicine (UMSOM) have received a nearly $7 million grant to be disbursed over five years from the National Institute on Drug Abuse (NIDA), which is part of the National Institutes of Health (NIH). The grant awarded to the Institute for Genome Sciences (IGS) at UMSOM will be used to establish an online data coordination center to enable researchers to store and access data sets generated by a program called Single Cell Opioid Responses in the Context of HIV (SCORCH).

These data sets include genetic data (in the form of RNA-sequencing and epigenomic) for several brain regions involved in persistent HIV infection and abuse of illicit drugs like opioids, cocaine and methamphetamine.

"Our research is designed to determine which cells and overlapping areas of the brain are involved in both neurocognitive deficits associated with HIV infections and opioid use disorder," said Principal Investigator **Owen White, PhD**, Professor, Epidemiology & Public Health at UMSOM and Associate Director, Informatics, at the Institute for Genome Sciences (IGS) at UMSOM.

Adds co-investigator **Seth Ament, PhD**, Assistant Professor of Psychiatry and faculty member at IGS at UMSOM: **"Evaluation of the data sets will help us map out the brain circuitry and molecular mechanisms that link these two seemingly disparate conditions to help us determine overlapping pathways that can be potentially targeted with the same treatments."**

Both researchers have played key roles in establishing the Neuroscience Multi-Omic Data Archive (**NeMO**), a database that contains genetic information relevant to the diversity of cell types in the brain and their dysregulation in brain diseases. SCORCH is a national consortium that leverages NeMO as well as other NIDA-funded databases established to study HIV and substance abuse disorders.

HIV-infected patients suffer more frequently from chronic pain often due to neurological conditions caused by their infection. Doctors traditionally treated this pain with opioids, which led over time to more HIV-infected individuals developing opioid use disorder. Persistent HIV infections can also cause cognitive problems including anxiety, depression, confusion and even full-blown dementia. A major impediment to developing better treatments for opiate abuse and addiction, as well as for neurological symptoms in HIV, is the lack of knowledge regarding the action of drugs and of the virus on select cell subtypes in the heterogeneous central nervous system. The SCORCH program will close these gaps by using complex data sets to better understand, on a

Owen White, PhD
Professor
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Institute for Genome Sciences

Seth Ament, PhD
Assistant Professor
Psychiatry
Institute for Genome Sciences

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molecular level, the interplay between opioid use disorder and HIV-related cognitive impairment.

The team will collect data through the SCORCH project consortium, which includes investigators at the UMSOM, the Broad Institute, and the Yale Cancer Center. The information incorporated into the NeMO-SCORCH data center will, in part, enable understanding of genomic regions associated with brain abnormalities and disease.

SCORCH researchers will study post-mortem human brain tissue of individuals with opioid disorder and HIV-associated cognitive impairment, using new technologies for "single-cell" genomics to quantify gene expression patterns in millions of single-cells. The roles of the SCORCH data center will be to organize data from the consortium, make it accessible to researchers around the world, and conduct integrative data analysis to provide insight into how each brain cell type changes in the context of opioid use disorder and HIV.

In addition to Drs. White and Ament, other co-investigators from UMSOM on this project include Linda Chang, MD, MS, Professor Diagnostic Radiology and Nuclear Medicine, UMSOM; Ronna Hertzano, MD, PhD, Associate Professor of Otorhinolaryngology - Head & Neck Surgery, UMSOM; Mary Kay Lobo, PhD, Professor, Anatomy and Neurobiology, UMSOM; Michelle G. Giglio, PhD, Associate Professor, Medicine, IGS, UMSOM; and Anup Mahurkar, Executive Director of Software Engineering & Information Technology at IGS.

"Our research is designed to determine which cells and overlapping areas of the brain are involved in both neurocognitive deficits associated with HIV infections and opioid use disorder,"

– Dr. Owen White

MORE INFORMATION

https://www.medschool.umaryland.edu/profiles/White-Owen/

https://www.medschool.umaryland.edu/profiles/Seth-Ament/

https://www.igs.umaryland.edu/labs/ament/

AIM-HI: Precision Therapy for Neonatal Opioid Withdrawal Syndrome UMCP & UMB Fund New Collaborative Research to Advance Medical Science

The University of Maryland, Baltimore (UMB) and the University of Maryland, College Park (UMD) are funding new cross-campus research to help solve big health care challenges through the collaborative expertise in medicine and artificial intelligence within both institutions.

Known as AIM-HI (Artificial Intelligence and Medicine for High Impact), the program was launched a year ago by Laurie Locascio, PhD, in partnership with the Deans from both campuses and support from both presidents. Dr. Locascio is Vice President for Research for both UMD and UMB.

"The AIM-HI program unites unique strengths from both campuses in pursuit of breakthrough efforts that will impact and improve human health," said Dr. Laurie Locascio. These teams of investigators are partnering to address major healthcare challenges. I have big expectations for what these teams will be able to accomplish and the impact that it will have on Marylanders and around the world."

"The AIM-HI program represents some of our best research collaboration, leveraging our strengths to address real-world healthcare challenges. Not only will this partnering of expertise in medicine and computer science yield new knowledge and new treatments, but it will also lead to countless new collaborations, as we all see what is possible when we work together," said UMB President Bruce Jarrell.

One of the four AIM-HI 2020 awardee groups is focusing on "Precision Therapy for Neonatal Opioid Withdrawal Syndrome", a coordinated effort to enable precision therapy for Neonatal Opioid Withdrawal Syndrome (NOWS). NOWS is a multi-system disorder in infants exposed to opioid drugs during pregnancy. Infants born with NOWS experience neurobehavioral, gastrointestinal, and metabolic withdrawal signs, with long-term developmental consequences that remain poorly understood. Due to the opioid crisis, the incidence of NOWS has increased >4-fold nationally and now affects more than 1% of newborns in the United States.

The following UMB/UMD faculty are PIs of this grant:

- **Seth Ament, PhD** (Coordinating PI), Assistant Professor, Institute for Genome Sciences and Department of Psychiatry, UMSOM
- **Dina El-Metwally, MB, BCh, PhD**, Associate Professor, Department of Pediatrics, UMSOM and Medical Director, Neonatal Intensive Care Unit, UMMC
- **Amber Beitelshees, PharmD/MPH**, Associate Professor, Department of Medicine, UMSOM
- **Asaf Keller, PhD**, Professor and Chair, Department of Anatomy and Neurobiology, UMSOM
- **Margret Bjarnadottir, PhD**, Assistant Professor, Management Science and Statistics, University of Maryland College Park
- **Ritu Agarwal, PhD**, Interim Dean, Distinguished University Professor, Robert H. Smith Dean's Chair of Information Systems, and Co-Director, CHIDS, University of Maryland College Park

As Director of the Neonatal Intensive Care Unit at the University of Medical Center, Dr. El-Metwally is directly responsible for providing clinical care to hundreds of opioid-exposed infants. In addition, treatment protocols developed by Dr. El-Metwally and her team at UMMC are applied across the University of Maryland Medical System and affiliated hospitals, that collectively care

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for several hundred additional NOWS cases each year. Dr. El-Metwally will be responsible for recruiting families into the study and collecting clinical phenotypes and biological samples. Dr. Beitelshees (UMB, Program in Personalized and Genomic Medicine) is an expert in pharmacogenomics/precision medicine and epidemiology and will be responsible for the primary analysis of clinical data. Dr. Ament (UMB, Institute for Genome Sciences) is an expert in genomics and will be responsible for the generation and primary analysis of multi-omic data. Dr. Bjarnadottir (UMCP, Management Science and Statistics) is an expert in machine learning and decision making; she will apply advanced machine learning and artificial intelligence algorithms to heterogeneous clinical and genomic data and combined with decision modeling will formulate decisions support models to be applied to improve clinical care. Drs. Keller (UMB, Chair of Anatomy and Neurobiology) and Agarwal (UMCP, Distinguished University Professor of Information Systems) are university leaders in neuroscience and digital health technologies, respectively, who will provide mentorship and overall project guidance. Addressing the urgent clinical challenge of NOWS requires this truly multidisciplinary effort, drawing on the collective strengths of the two campuses.

"While several of the PIs have worked together previously, this is an exciting new cross-campus collaboration that has formed as a direct consequence of the AIM-HI competition. In the last two months, they have already begun to successfully share data and ideas," said E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, UM Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine.

Currently there is a lack of scientific knowledge to optimize the treatment of infants with NOWS. This study aims to fill that scientific gap, in order to improve our ability to predict which opioid-exposed babies will require treatment and better define what that treatment should be, accounting for clinical and genetic factors to improve outcomes. The researchers will mine ten years of retrospective data from the electronic health records of infants with NOWS treated at the University of Maryland Medical Center (UMMC) and have begun the creation of a prospectively sampled cohort with genetic samples. AIM-HI funding allows the investigators to grow this cohort and expand it to additional hospitals in the region, which collectively treat an estimated 1,000 infants with NOWS each year. These data sources will provide a unique opportunity to use cutting-edge artificial intelligence and machine learning technology in a diverse cohort in order to address a huge public health problem that has arisen from the opioid epidemic.

The group will address three critical questions: To what extent do combined demographic, clinical (including drug exposure), and genomic factors predict NOWS symptoms and treatment outcomes? How do investigators optimize machine learning processes and model building to maximize the benefit to all sub-groups in a diverse, vulnerable study population? How can large scale data and mathematical modeling improve decision making?

The investigators will apply advanced machine learning methods to predict NOWS symptoms and treatment outcomes in the study population. In their data, there are sub-group differences both in the predictors (e.g., SNPs that are more common in one ancestry), and in the presentation of clinical phenotypes. They will therefore apply data driven optimization and empirical modeling to develop machine learning models that simultaneously optimize outcomes for different subgroups balancing local vs. global learning. Finally, building on the observations and insights from the prediction models, they will build and validate decision support models that aim to optimize decisions based on multi-objective criteria, including symptom severity and cumulative pharmacological treatment.

Inclusion of diverse populations is critical to achieve equitable outcomes. However, previous epidemiological and genetic studies of NOWS were conducted in cohorts >90% white. The University of Maryland Medical System (UMMS) and its neighboring hospitals are well-positioned to address this need, as they serve a diverse population with approximately 30% of infants admitted for NOWS being African American.

AIM-HI supports research with strong potential to contribute major scientific discoveries, secure sizable additional external funding and, ultimately, to lead to meaningful improvements in the quality of the lives of people in Maryland, the region and the nation through improved patient care or treatment.

Congratulations to the following faculty on their promotions!

Vincent Bruno, PhD, Associate Professor, Microbiology & Immunology, has been awarded tenure.

Joana Carneiro da Silva, PhD, Microbiology & Immunology, has been promoted to Professor.

Rebecca Brotman, PhD, MPH, Epidemiology & Public Health, has been promoted to Professor.

David Serre, PhD, Associate Professor, Microbiology & Immunology, has been awarded tenure.

Timothy O'Connor, PhD, Medicine (Endocrinology), was promoted to Associate Professor.

Farewell to Emmanuel Mongodin: On to NIH!

We wish the best to Emmanuel Mongodin, PhD, who has been working with IGS since our launch in 2007. Emmanuel started a new job as a Program Officer at the National Heart, Lung, and Blood Institute, the largest institute at NIH. "He brings a wealth of expertise in genomics to his new role and our loss will be NIH's gain!" said Claire Fraser, PhD, Director of IGS.

For many at IGS, their association with Emmanuel goes back a long way to time together at TIGR. He helped to build IGS and has developed exciting research collaborations on transplantation, and water genomics.

We wish him well at NIH!

IGS Newsletter is produced by the Institute for Genome Sciences at the University of Maryland School of Medicine.

Jacques Ravel, PhD, *Scientific Editor*
Sarah Pick, *Editor*
Lance Nickel, *Designer*
Riham Keryakos, *Contributor*

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