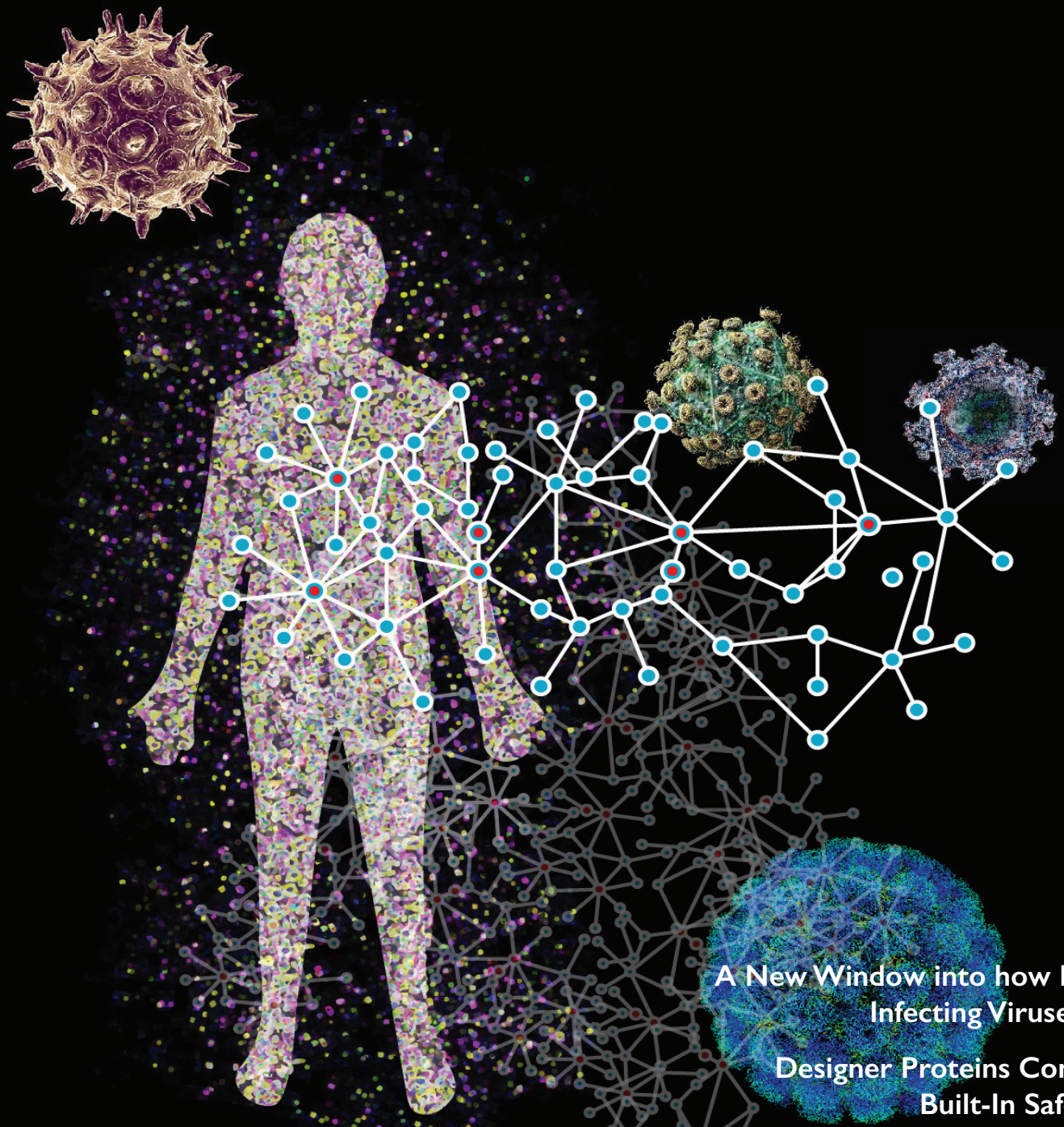
Department of Systems Biology

Columbia University Irving Medical Center



A New Window into how Human-Infecting Viruses Work

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On the Cover:
P-HIPSTer is an in silico computational framework that leverages protein structure information to identify protein-protein interactions across all fully-sequenced human-infecting viruses. This image highlights that in addition to rediscovering known biology, P-HIPSTer has yielded a series of new findings and enables discovery of a previously unappreciated universe of cellular circuits and biological principles that act on human-infecting viruses. (Article on page 3; Image Courtesy of Dr. Sagi Shapira.)

COLUMBIA UNIVERSITY
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Department of Systems Biology

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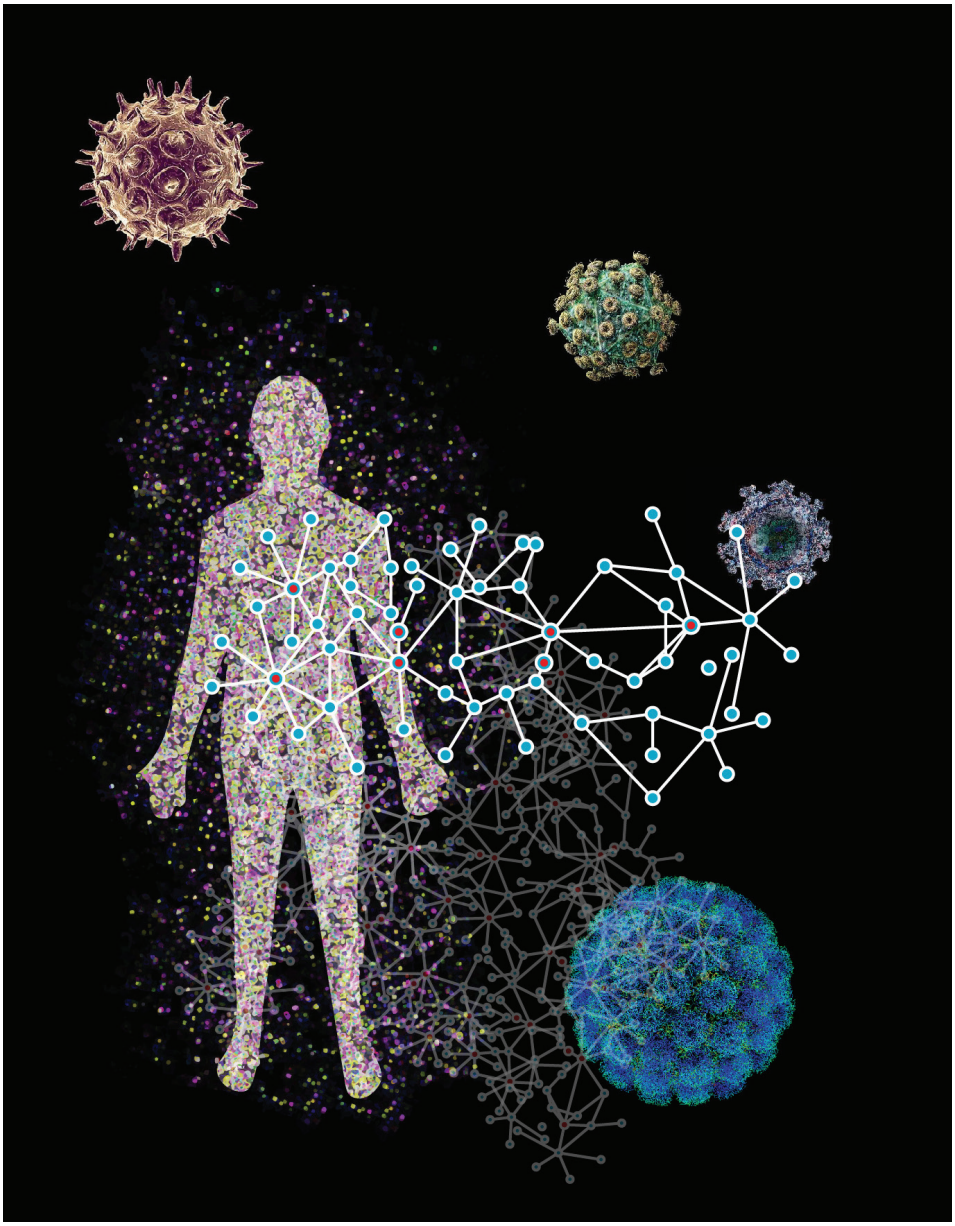
Highlights 2019

Inside this issue, learn about the latest research, noteworthy grants and milestones from the Department of Systems Biology.

RESEARCH

Detailed Map Gives Scientists a New Window into How Human-Infecting Viruses Work



P-HIPSTer is an in silico computational framework that leverages protein structure information to identify approximately 282,000 protein-protein interactions across all fully-sequenced human-infecting viruses (1001 in all). In addition to rediscovering known biology, P-HIPSTer has yielded a series of new findings and enables discovery of a previously unappreciated universe of cellular circuits and biological principles that act on human-infecting viruses. (Image Courtesy of Dr. Sagi Shapira)

Researchers at Columbia University Irving Medical Center have leveraged a computational method to map protein-protein interactions between all known human-infecting viruses and the cells they infect. The method, along with the data that it generated, has spawned a wealth of information toward improving our understanding of how viruses manipulate the cells that they infect and cause disease. Among its findings, the work uncovered a role for estrogen receptor in regulating Zika Virus (ZIKV) infection, as well as links between cancer and the human papillomavirus (HPV).

The research, led by Sagi Shapira, PhD, Assistant Professor in the Department of Systems Biology and the Department of Microbiology & Immunology at Columbia University Vagelos College of Physicians and Surgeons, was published on Aug. 29 in the journal *Cell*. Dr. Shapira's collaborators include Professors Barry Honig, PhD, of Systems Biology and of Biochemistry and Molecular Biophysics and Raul Rabadan, PhD, of Systems Biology and of Biomedical Informatics.

From seasonal influenza and chicken pox, which are largely treatable, to life-threatening emerging viruses, such as Ebola and Zika, infections can result in a wide range of clinical symptoms and outcomes. At the molecular level, viruses invade cells and manipulate them to replicate, survive, and cause disease. One way viruses co-opt cellular machinery is through protein-protein interactions within their cell host. Cells respond to infection by initiating immune responses that control and limit viral replication – these too, depend on protein-protein interactions.

To date, considerable effort has been invested in identifying these key interactions – and many of these efforts have resulted in many fundamental discoveries, some with therapeutic implications. However, limitations on cost, scalability, efficiency, and even access have limited the use of traditional methods. To address this challenge, Dr. Shapira and his collaborators developed and implemented a computational framework, termed P-HIPSTER, that infers interactions between pathogen and human proteins, the building blocks of viruses and cells.

Until now, our knowledge about many viruses that infect people is limited to their genome sequences. Yet, for most viruses little has been uncovered about the underlying biological interactions that mediate virus-human contact and give rise to disease.

"There are over 1,000 unique viruses that are known to infect people," says Dr. Shapira. "Yet, despite their unquestionable public health importance, we know virtually nothing about the vast majority of them. We just know they infect human cells. The idea behind this effort was to systematically catalogue the interactions that viruses have with the cells they infect. And, by doing so, also reveal some really interesting biology and provide the scientific community with a resource that they can use to make interesting observations of their own."

Leveraging the PrePPI algorithm (developed in Professor Honig's Laboratory), P-HIPSTer exploits protein structural information to systematically interrogate virus-human protein-protein interactions with remarkable accuracy. Dr. Shapira and his collaborators applied P-HIPSTer to all 1,001 human-infecting viruses and the approximately 13,000 proteins they encode. The algorithm predicted roughly 280,000 likely pairs of interacting proteins that represent a comprehensive catalogue of human virus protein-protein interactions with an accuracy rate of almost 80 percent.

"This is the first step towards building a comprehensive cartography of physical interactions between different organisms," Dr. Shapira says.

"There are over 1,000 unique viruses that are known to infect people, yet, despite their unquestionable public health importance, we know virtually nothing about the vast majority of them."

— Dr. Sagi Shapira

Series of New Findings: Zika, HPV, Viral Evolution

In addition to defining pan-viral protein interactions, P-HIPSTer has yielded new biological insights into Zika virus, HPV, and the impact of viruses in shaping human genetics.

Among their discoveries, the researchers found that Zika virus interacts with estrogen receptor, the protein that allows cells to effectively respond to the estrogen hormone. Importantly, they found that estrogen receptor has the potential to inhibit replication of the Zika virus. Says Dr. Shapira, "And, in fact, estrogen receptor inhibits viral replication even more than interferon, a protein that is the body's first line of defense to viral infection and our gold standard for anti-viral defense."

The finding is particularly relevant to clinical disease as pregnant women are most susceptible to Zika during their first trimester, which is when estrogen levels are at their lowest. This period also is when the fetus is most susceptible to Zika, a virus for which there is no vaccine or specific treatment and that can cause severe birth defects.

Dr. Shapira and his team also explored interactions between human papillomavirus (HPV; the leading cause of cervical cancer) and the cells that it infects. HPV is the most common sexually transmitted infection with approximately 80 percent of sexually active individuals contracting one of the 200 different types of HPV at some point in their lives.

Dr. Shapira and his team used the data generated by P-HIPSTer to identify protein-protein interactions that distinguish HPV infections associated with cancer from those that are not. In addition to providing insights into how HPV may cause disease, the finding could lead to improved diagnostics for those infected with HPV, and P-HIPSTer could potentially be used to help predict whether or not any particular virus is likely to be highly pathogenic.

The researchers also examined whether the interactions mediated by viruses have impacted human genetics. The researchers found evidence that strong selection pressure for several dozen cellular proteins has been shaped by viral infection, unlocking new insights into how our genome has been impacted by viruses.

"One of the things we can do with this data is drill down and ask whether virus infection has changed the history of human genetics," notes Dr. Shapira. "That is certainly not a novel idea but to have a catalogue of what those proteins are is significant. There are a lot of areas that we can explore now that we couldn't before."

Dr. Shapira and his team intend to apply P-HIPSTer on more complex pathogens, such as parasites and bacteria, and use it to better understand how bacteria in the human gut communicate with each other. In the future, the algorithm could also be used to explore viruses or pathogens that effect agricultural plants or livestock.

The Shapira Laboratory at Columbia University is working to decipher the genetic and molecular circuitry at the interface of host–pathogen interactions. A deeper understanding of these relationships provides important insights into cellular machinery that control basic cell biology and has broad implications in human translational immunology and infectious disease research.

The paper, "A Structure-Informed Atlas of Human-Virus Interactions", is also coauthored by: Gorka Lasso (Columbia Systems Biology and Microbiology & Immunology); Sandra V. Mayer (Columbia Systems Biology and Microbiology & Immunology); Evandro R. Winkelmann (Columbia Systems Biology and Microbiology & Immunology); Tim Chu (Columbia Systems Biology); Oliver Elliot (Columbia System Biology); Juan Angel Patino-Galindo (Columbia Systems Biology); and Kernyu Park (Columbia Biomedical Informatics).

Interactions derived by P-HIPSTer can be browsed at http://phipster.org. The study's results are available through an interactive webserver that enables both searchable queries and data download.

REFERENCES:

Lasso G, Mayer SV, Winkelmann ER, Chu T, Elliot O, Patino-Galindo JA, Park K, Rabadan R, Honig B, Shapira SD. *A Structure-Informed Atlas of Human-Virus Interactions*. Cell. 2019 Aug 23. pii: S0092-8674(19)30893-1. doi: 10.1016/j.cell.2019.08.005.

GRANT

Prostate Cancer Grant Spotlights Columbia's Aim to Deliver Precision Cancer Medicine

Columbia Team Wins $1 Million Prostate Cancer Foundation Challenge Award

Principal investigators of the Challenge Award, from left to right: Charles Drake, MD, PhD, Michael Shen, PhD, and Andrea Califano, Dr.

Columbia University Irving Medical Center experts in prostate cancer will lead a new team research project that tests a novel approach for personalized cancer treatment. The two-year project, funded by a $1 million Challenge Award from the Prostate Cancer Foundation (PCF), combines cutting-edge techniques that include computational methods for targeted drug therapy, single-cell RNA sequencing and novel cancer immunotherapy. The combined approaches are behind a proof-of-concept clinical trial for patients with lethal metastatic prostate cancer.

PCF Challenge Awards fund projects that bring together experts from a number of related fields to form a team focused on the creation of innovative, effective therapies for advanced prostate cancer. As part of Columbia's grant, the new clinical trial will take place at the James J. Peters VA Medical Center (also known as the Bronx VA), a partner of Columbia University Irving Medical Center (CUIMC) and NewYork-Presbyterian Hospital.

PCF is recognized as the leading philanthropic organization for prostate cancer research. For the team at Columbia's Herbert Irving Comprehensive Cancer Center (HICCC), receiving a Challenge Award from the foundation was more than just an exciting achievement. It underscores CUIMC's continued commitment to strengthening and expanding its expertise in prostate cancer research and care through investments in faculty recruitment, enhanced emphases on bolstering basic science research and clinical trials centered on the disease and direct engagement with PCF.

"PCF has played a role in the early stages of development of almost every drug that has been approved over the past decade in the treatment of prostate cancer. It has been very influential in the field," says Michael Shen, PhD, professor of medical sciences, of genetics and development and of systems biology at CUIMC and one of the study's principal investigators. "This is the first Challenge Award that has been awarded to Columbia, and this is a goal we have long sought to achieve."

Since its founding in 1993, PCF has raised more than $765 million and funded more than 2,000 research programs at more than 210 cancer centers and universities. Prostate cancer is the second most common cancer in men worldwide, and the eighth leading cause of cancer-related death. It is estimated that 1 in every 9 men in the United States will be diagnosed with the disease during his lifetime.

Columbia expanded its prostate cancer research with the recruitment of Charles Drake, PhD, MD, a pioneer in cancer immunotherapy who joined the University in 2016 from Johns Hopkins University. Dr. Drake, who currently directs genitourinary oncology at NewYork-Presbyterian/CUIMC and co-directs Columbia's cancer immunotherapy program, is co-principal investigator of Columbia's PCF grant and is overseeing the clinical aspects of the research, along with co-investigators Tito Fojo, MD, and Susan Bates, MD, both of whom have appointments at the Bronx VA and are also more recent recruits to Columbia.

"Getting our team together came quite naturally," Dr. Shen adds. "We already had the key investigators in place. It was really about creating a project that would exploit the specific advantages of what we each bring."

The project encompasses experimentally validated computational tools developed by Columbia's Andrea Califano, Dr, that

can identify the proteins that drive aggressive prostate cancer and predict drugs and drug combinations that can target them. It leverages Dr. Drake's specific research in the tumor microenvironment, particularly the immune component. This is combined with experiments from Dr. Shen's lab on single cell analysis of the normal and transformed prostate, coupled with mouse models established in the laboratory of Cory Abate-Shen, PhD, professor of urology, of pathology and cell biology, and of systems biology at Columbia who also is a co-investigator of the study.

"PCF interests change over time. More recently, their interest has evolved to immunotherapy and personalized cancer therapy," says Dr. Drake. "Unique to the strengths of Columbia is Andrea Califano's series of algorithms that predict medicines based on the RNA sequencing of the tumor, and the single-cell RNA sequencing that we will be doing here."

"Prostate cancer is typically devoid of targetable mutations," notes Dr. Califano, study co-PI and founding chair of Columbia's Department of Systems Biology. "What we are trying to do here is use the RNA as an entry point to therapeutic options."

Single-cell RNA sequencing is a rapidly evolving technology that obtains molecular and genomic data for each individual cell contained within the tens of thousands that can make up a biological sample. This technique is also making it possible to discover new cell types within the tumor and its surrounding environment.

The project also ties in next-generation immunostaining technology, led by co-investigator and molecular pathologist, Massimo Loda, MD. In February, Dr. Loda joined Weill Cornell as its new chair of the Department of Pathology and Laboratory Medicine, and as pathologist-in-chief at NewYork-Presbyterian and Weill Cornell Medical Center.

"The icing on the cake, so to speak, is the clinical trial ability at the VA," notes Dr. Shen.

Precision Cancer Medicine at the VA

Historically, VA patients have not had access to clinical trials or cutting-edge cancer therapies. PCF has made working with VA hospitals a priority, in order to bring personalized prostate cancer therapies to VA patients and HICCC has a long-standing commitment to serving the needs of patients in its community. Last November, PCF received a $2.5 million donation from the John and Daria Barry Foundation to establish a Precision Oncology Center of Excellence at the Manhattan campus of the VA NY Harbor Healthcare System.

The Columbia proof-of-concept trial at the Bronx VA will serve a small group of patients with an aggressive form of prostate cancer. The trial is devised so that the biopsy of patient tumors occurs when they begin their first treatment, giving the Columbia team ample time to run Dr. Califano's algorithmic framework to effectively analyze those tumor biopsies for the most effective drugs unique to each patients' cancer.

"We will have the drug predictions ready for them before their next line of treatment," says Dr. Drake. "This is a very ambitious project. What sets this research apart is we have the ability to analyze the whole tumor microenvironment when we do the single-cell RNA sequencing … There is not a lot of data on metastatic prostate cancer. Scientifically, those data will teach us things that we have yet to discover."

Jessica Hawley, MD, a young investigator who drafted the study's clinical protocol and is charged with overseeing the project's many logistics, notes that in addition to the exciting science that will be gleaned from this project, it will test the feasibility of this approach.

"This is uncharted territory. We are looking at patients as an individual and not looking at a specific sort of mutational basket where we are then fitting patients into," says Dr. Hawley, an oncology fellow at Columbia. Dr. Hawley is working closely with Dr. Prab Mundi, the point physician at the VA, to carry out Columbia's clinical trial.

"While precision oncology trials are extremely challenging logistically," adds Dr. Mundi, "they have tremendous potential of finding effective treatments for these patients that will extend survival and improve quality of life."

For Dr. Hawley, the potential outcome of this project resonates personally. Her grandfather, who passed away from metastatic prostate cancer, was a military veteran and had received part of his care at the VA system.

"I only wish things like this had been available for him," she says. "Precision oncology is the wave of the future and we are still in the early stages of learning what the best platform is to really execute the right treatment, and to do it in a safe way, too."

—Melanie A. Farmer

> "Prostate cancer is typically devoid of targetable mutations. What we are trying to do here is use the RNA as an entry point to therapeutic options."
>
> *— Dr. Andrea Califano*

PCF Challenge Award Project Title:
Master Regulators Underlying Tumor-Microenvironment Interactions in Metastatic Prostate Cancer

Principal Investigators : Michael Shen, PhD (Columbia University Irving Medical Center), Charles Drake, MD, PhD (New York-Presbyterian and Columbia University Irving Medical Center), Andrea Califano, Dr (Columbia University Irving Medical Center)

Co-Investigators : Cory Abate-Shen, PhD (Columbia University Irving Medical Center), Susan Bates, MD (James J. Peters Veterans Affairs Medical Center, Bronx), Antonio Tito Fojo, MD (James J. Peters Veterans Affairs Medical Center, Bronx), Massimo Loda, MD (Dana-Farber Cancer Institute), Francesco Cambuli, PhD (Columbia University Irving Medical Center)

RESEARCH

New Designer Proteins Come with Built-In Safeguards

By entangling two separate genes in a single stretch of DNA, the CAMEOS algorithm can prevent synthetic genes from mutating or being transferred to another organism. The blue boxes represent the prmC gene after CAMEOs; the orange boxes represent the aroB gene. (Image courtesy of the Harris Wang lab.)

By merging two genes into a single DNA sequence, CUIMC synthetic biologists have created a method that could prevent human-engineered proteins from spreading into the wild, as well as stabilize synthetic proteins so they don't change over time.

Protein engineering is a relatively young field that creates new proteins never seen before in nature. Today's protein engineers usually create synthetic proteins by making small changes to the gene that encodes a naturally occurring protein. The variety of synthetic proteins range from stain-removing enzymes that improve detergents to a long-acting insulin that is used by millions of people with diabetes.

But two big unsolved challenges for protein engineers remain: The gene encoding the synthetic protein needs to be contained, to prevent escape into other organisms; and it needs to resist mutating over time, so the protein doesn't lose its function.

Synthetic biologists at Columbia University Vagelos College of Physicians and Surgeons have developed a method, published Aug. 9 in the journal *Science*, that can address both issues.

> In devising the method, Dr. Harris Wang and team were inspired by overlapping genes in viruses. When two different genes overlap, they occupy the same sequence of DNA. But the genes are read in different frames so that two different proteins are produced.

In devising the method, the researchers were inspired by overlapping genes in viruses. When two different genes overlap, they occupy the same sequence of DNA. But the genes are read in different frames so that two different proteins are produced.

In overlapping genes, a random mutation in the sequence may not affect one gene, but it's likely that it will harm the second gene.

"Overlapping genes essentially lock in a specific DNA sequence, and we thought we could exploit this idea for synthetic biology," says Harris Wang, PhD, assistant professor of systems biology, who developed the new method with graduate student Tomasz Blazejewski and postdoctoral scientist Hsing-I Ho, PhD.

The CAMEOS technique developed by Wang, Blazejewski, and Ho starts with two distinct genes and devises ways to combine them into a single DNA sequence.

To accomplish such entanglement, bases in each gene need to be altered but without affecting the function of each

gene's protein. CAMEOS taps a database of hundreds of thousands of gene sequences to determine which base changes are likely to succeed and which are likely to fail.

The final predicted sequences are then printed and tested inside living cells using high throughput techniques that make possible the testing of thousands of different sequences in a short period of time.

"Ten years ago, we didn't have the technology that would make this possible," Wang says. "We didn't have enough sequences in the database to make informed predictions and we didn't have a way to synthesize long DNA sequences for testing our predictions."

To prevent a synthetic gene from escaping into the wild, the Columbia researchers used CAMEOS to entangle it with a gene that produces a toxic protein.

When inserted into bacterial cells engineered to make the antidote, the entangled genes produce the synthetic gene and the toxin. Other bacteria could take up the entangled gene, but that meant instant death once the toxin was created.

Similar designs "could be useful for agricultural purposes where you don't want a synthetic gene to spread to natural crops," Blazejewski says, "or in any situation when you don't want your synthetic DNA to escape from the lab."

By locking in a DNA sequence, gene entanglement also stabilizes engineered genes and prevents the synthetic protein from losing its functions (or acquiring unwanted ones).

"Instability is an issue now in industries that use vats of cells to produce engineered proteins," Ho says. "The reaction will only run for a certain amount of time before mutations take over. With CAMEOS, it may be possible to sustain the reaction for longer."

The U.S. Department of Defense, which is interested in increasing the stability of engineered proteins, helped fund the development of CAMEOS. Incorporated into microbes, engineered proteins could help protect equipment against corrosion, warn soldiers of the presence of chemical weapons, or produce fuel or drugs on demand.

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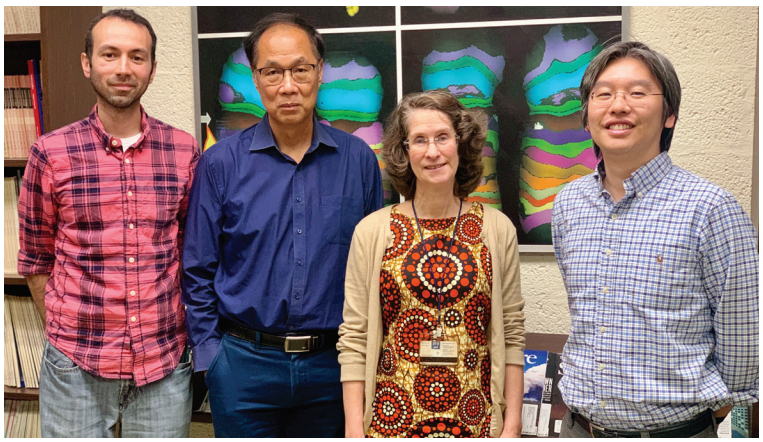
REFERENCES:

Blazejewski T, Ho HI, Wang HH. *Synthetic sequence entanglement augments stability and containment of genetic information in cells*. Science. 2019 Aug 9;365(6453):595-598. doi: 10.1126/science.aav5477.

Boosting the Body's Resilience to Radiation



Dr. Harris Wang (far right) with collaborators, from left to right: Alex Chavez, Kam Leong, and Sally Amundson; Missing from photo: David Brenner.

Harris Wang, PhD, assistant professor of systems biology at Columbia University Irving Medical Center, is leading a team of experts in radiation research, CRISPR-Cas technologies, and drug delivery on an innovative new project announced June 27 and funded by the Defense Advanced Research Projects Agency (DARPA). The up to $9.5M project focuses on pursuing a therapy to protect the body from the effects of high-dose ionizing radiation, and is part of DARPA's initiative to fund research into new strategies to combat public health and national security threats.

In humans, acute radiation syndrome primarily affects stem cells in the blood and gut, yet existing treatments only help to regenerate blood cells, and only with limited effect. There is no possibility for prophylactic administration of these drugs, and most must be delivered immediately following radiation exposure to provide any benefit. There are no existing medical countermeasures for radiation damage to the gut.

The Columbia team aims to develop an orally delivered programmable gene modulator therapeutic. The multimodal treatment the team envisions would take hold in both the gut and liver, triggering protection and regeneration of intestinal cells, while also inducing liver cells to produce protective cues that trigger the regeneration of blood cells in bone marrow.

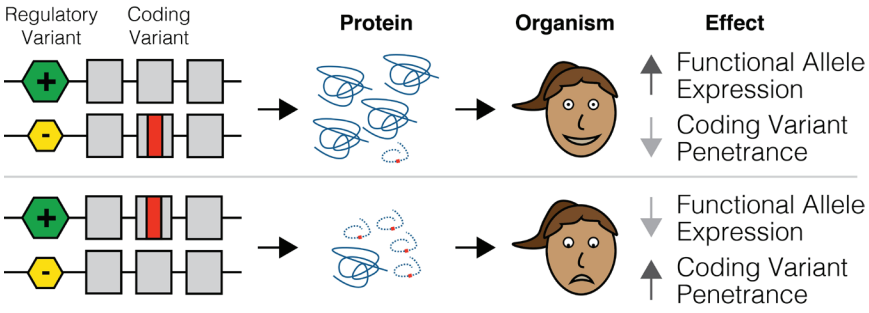
Dr. Wang, who also has a joint appointment in pathology and cell biology, is collaborating with radiation research experts David Brenner, PhD, and Sally Amundson, ScD, of Columbia's Center for Radiological Research; Alejandro Chavez, MD, PhD, of the Department of Pathology and Cell Biology, a specialist in the fast-growing CRISPR field; and Kam Leong, PhD, of Columbia Engineering, a pioneer in biomaterials, nanomedicine, and drug delivery.

Dr. Wang's team is one of five teams selected by DARPA to participate in its Preemptive Expression of Protective Alleles and Response Elements (PREPARE) program. Each team has received an award to develop new medical interventions that temporarily and reversibly modulate the expression of protective genes to specifically guard against acute threats from either ionizing radiation or influenza. Ultimately, the technology could serve as the foundation for a generalizable platform that can be rapidly adapted to other emerging public health and national security threats.

Dr. Wang and the other PREPARE teams expect to submit at least one product each to the U.S. Food and Drug Administration (FDA) for review as an investigational new drug (IND) by the end of the four-year program period.

RESEARCH

Study Explains Why Genetic Mutations Cause Disease in Some But Not All



The hypothesis of this study is illustrated with an example in which an individual is heterozygous for both a regulatory variant and a pathogenic coding variant. The two possible haplotype configurations would result in either decreased penetrance of the coding variant, if the non-mutant haplotype had high expression, or increased penetrance of the coding variant, if the non-mutant haplotype was lowly expressed. (Image courtesy of the Lappalainen lab)

Researchers at the New York Genome Center (NYGC) and Columbia University's Department of Systems Biology have uncovered a molecular mechanism behind one of biology's long-standing mysteries: why individuals carrying identical gene mutations for a disease end up having varying severity or symptoms of the disease. In this widely acknowledged but not well understood phenomenon, called variable penetrance, the severity of the effect of disease-causing variants differs among individuals who carry them.

Published in *Nature Genetics*, this study provides evidence for modified penetrance, in which genetic variants that regulate gene activity modify the disease risk caused by protein-coding gene variants. The study links modified penetrance to specific diseases at the genome-wide level, which has exciting implications for future prediction of the severity of serious diseases such as cancer and autism spectrum disorder.

NYGC Core Faculty Member and Systems Biology Assistant Professor Dr. Tuuli Lappalainen led the study alongside post-doctoral research fellow Dr. Stephane Castel.

"Our findings suggest that a person's disease risk is potentially determined by a combination of their regulatory and coding variants, and not just one or the other," Dr. Lappalainen said. "Most previous studies have focused on either looking for coding variants or regulatory variants that affect disease in these individuals or potentially looking at common variants that could affect disease. We have merged these two fields into one clear hypothesis that uses data from both of them, which was fairly unheard of before."

Variable penetrance has long posed a challenge for predicting the severity of a disease, even for diseases with a strong genetic association. Dr. Lappalainen and colleagues developed the modified penetrance hypothesis from their interest in the idea that gene variants that regulate the activation of genes could also play a role in modifying the penetrance of coding variants for the same gene.

As a first test of the modified penetrance hypothesis, they conducted an analysis of data from the Genotype-Tissue Expression (GTEx) project, a large catalog of genetic variants that affect gene expression in humans, to evaluate the interactions of regulatory and coding variants in a human population without severe genetic diseases. They found an enrichment of combinations of regulatory and coding variants, called haplotypes, that act as protective against disease by decreasing the penetrance of coding variants associated with disease development. This finding was expected in the general population, Dr. Castel explained, as a result of natural selection removing damaging gene variants from the genome over time.

To test their hypothesis in a disease-specific population of patients, the researchers analyzed data from the National Institutes of Health's The Cancer Genome Atlas (TCGA) and the Simons Simplex Collection, a permanent repository of genetic samples from 2,600 families, each of which has one child affected with an autism spectrum disorder, and unaffected parents and siblings. In the cancer patients and individuals with autism, they found an enrichment of haplotypes predicted to increase the penetrance of coding variants associated with cancer and autism spectrum disorder, respectively.

Finally, they designed an experiment using CRISPR/Cas9 genome editing technology to test the modified penetrance hypothesis with a coding variant that is known to be associated with a disease. They chose a coding variant associated with Birt-Hogg-Dubé Syndrome, a rare hereditary disease that increases the risk of certain types of tumors. They edited the SNP into a cell line on different haplotypes with a regulatory variant. The researchers were able to show that the regulatory variant indeed modified the effect of the coding disease-causing variant, consistent with expectations based on the large-scale data collections. This finding provides an important framework for scientists moving forward to experimentally test specific disease SNPs to determine if they could be affected by modified penetrance.

"Now that we have demonstrated a mechanism for modified penetrance, the long-term goal of the research is better prediction of whether an individual is going to have a disease, using their genetic data and integrating the regulatory and coding variants," Dr. Lappalainen said.

"In the future, studies of the genetic causes of severe diseases should take into account this idea that regulatory variants need to be considered alongside coding variants," Dr. Castel said. "This should eventually lead to a more fine-grained understanding of the risk of coding variants associated with disease."

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REFERENCES:

Castel SE, Cervera A, Mohammadi P, Aguet F, Reverter F, Wolman A, Guigo R, Iossifov I, Vasileva A, Lappalainen T. *Modified penetrance of coding variants by cis-regulatory variation contributes to disease risk.* Nat Genet. 2018 Sep;50(9):1327-1334. doi: 10.1038/s41588-018-0192-y. Epub 2018 Aug 20.

Making Strides in Mapping the Human Cell Atlas

In two groundbreaking research projects contributing to the Human Cell Atlas, Columbia University scientists are tasked with mapping cells in the immune system and the human spine. The global effort is aiming to identify and define every cell type of the human body and create a collection of maps for navigating the cellular basis of human health and disease.

The Columbia teams, which include co-principal investigators from the Department of Systems Biology Drs. Peter Sims and Raul Rabadan, are among the 38 collaborative science teams launching the Chan Zuckerberg Initiative's (CZI) Seed Networks for the Human Cell Atlas project announced in June. The three-year projects, receiving a total of $68 million in award funding by Seed Networks, are collaborative groups that are bringing together expertise in science, computational biology, software engineering, and medicine to support the ongoing progress of the Human Cell Atlas.

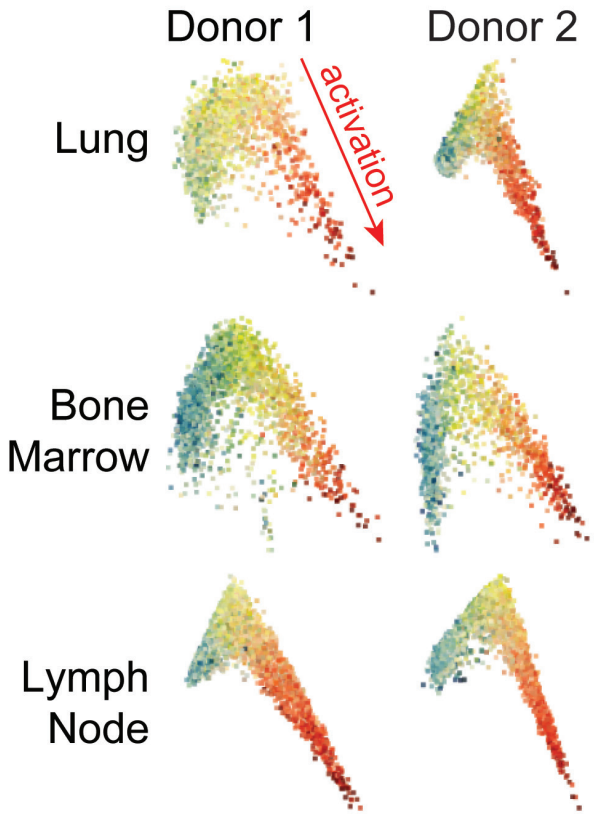
Dr. Sims, part of an international team including close collaborator Dr. Donna Farber of the Department of Surgery, is combining single-cell sequencing technologies, data analysis, and immunology expertise to better understand how the immune system ages and gain new insights into how human diseases occur.

"Understanding how the immune system ages might provide us with a unique window into how different diseases occur and how they transpire in different stages of our life," says Dr. Sims, assistant professor of systems biology and director of the Single-Cell Analysis Core at Columbia. "Single-cell analysis will be very important in this project not only because it is going to allow us to identify and track many different populations of cells simultaneously it is also going to let us monitor how they change upon stimulation."

Unlike bulk DNA/RNA sequencing, where the genomic data obtained represents an aggregate of many cells, single-cell RNA sequencing enables scientists to capture molecular and genomic data for each individual cell contained within the tens of thousands that can make up a biological sample. In cancer biology, for instance, this technique is making it possible to discover new cell types within a tumor and its surrounding environment.

A key challenge of studying the human immune system has been access to healthy organs for research. At Columbia, Dr. Farber has established a pioneering resource for acquiring healthy human tissues from organ donors and developed the expertise to isolate many different immune cell types with sufficient quality for sophisticated molecular analysis.

"Our ongoing work in investigating human immune cells in tissues could not be possible without the research protocol we've established with organ donor procurement organization, LiveOnNY," says Dr. Farber, Humphreys Professor of Surgical Sciences and professor of microbiology and immunology at Columbia. "With the Sims lab, we will transcriptionally profile the entire complement of immune cells isolated from multiple tissue sites on the single cell level, from individual organ donors over age and genetic diversity. The results from this study will reveal new insights into human immunity to better define the origin and mechanisms for disease."



Single-cell RNA-seq of T cells isolated from human tissues reveals lineage-specific activation trajectories (CD4 T cells shown here). Credit: Hanna Mendes Levitin of the Sims lab.

> "Our network of collaborations truly underscores the interdisciplinary collaborative environment at Columbia."
>
> — *Dr. Raul Rabadan*

Drs. Sims and Farber are working with multiple PIs on their new Seed Networks project, which is being co-led by Dr. Sarah Teichmann from the Sanger Institute-UK

and Dr. Nir Yosef at UC Berkeley.

Focusing on the human spine, Dr. Rabadan, professor of systems biology and founding director of Columbia's Program for Mathematical Genomics, is a co-PI of the Seed Networks project exploring sophisticated experimental and computational techniques to create an open source atlas of the human spinal cord. Working in a team with co-PIs Abbas Rizvi, PhD (Zuckerman Institute); Tom Maniatis, PhD (Zuckerman Institute, Biochemistry and Molecular Biophysics); and Liam Paninski, PhD (Zuckerman Institute, Statistics and Neuroscience), this reference guide will serve as a platform to help others develop treatments and technologies for neurodegenerative disease and spinal cord injury.

Dr. Rabadan is working closely with Dr. Paninski on the computational front. The Rabadan lab is generating innovative tools to denoise, align, analyze, and visualize multimodal single cell datasets. Dr. Paninski's group is developing highly novel and statistically robust methods to harmonize single cell observations and analyze in situ sequencing data.

> "Single-cell analysis will be very important in this project not only because it is going to allow us to identify and track many different populations of cells simultaneously it is also going to let us monitor how they change upon stimulation."
>
> — *Dr. Peter Sims*

In 2017, CZI, created by Facebook CEO Mark Zuckerberg and wife, Priscilla Chan, awarded Drs. Sims and Rabadan pilot grants in its inaugural round of funding. Dr. Sims gained support for his research in SCOPE-Seq, a novel, cost-effective method for conducting RNA sequencing coupled with live imaging of the same individual cell on a large scale, and Dr. Rabadan and his existing CZI team received a pilot grant to develop their atlas of the genetic activity of all the cells in the human spinal cord.

Additionally, Drs. Sims and Rabadan have been intensively collaborating in the last few years as part of an NCI center grant to dissect the evolution and dynamics of tumors. "Our network of collaborations," notes Dr. Rabadan, "truly underscores the interdisciplinary collaborative environment at Columbia."

The Seed Networks grantees represent 20 countries and more than 200 labs, with 45 percent of projects featuring international collaborations. The projects will generate new analysis methods, produce open source software tools, and make significant contributions of diverse data to the Human Cell Atlas Data Coordination Platform, a resource for data sharing across researchers and research institutes.

Dr. Michael Shen Wins Cancer Research Innovation Award

Dr. Michael Shen

The Bladder Cancer Advocacy Network (BCAN) has awarded Dr. Michael Shen the 2018 Bladder Cancer Research Innovation Award. The honor is given to scientists whose novel and creative research has great potential to produce breakthroughs in the management of bladder cancer.

Dr. Shen, who is professor of medicine, genetics and development, urology and systems biology at Columbia University, has used new techniques of 3D cell culture to establish "organoids" from primary bladder tumors obtained from patients. These personalized laboratory models, which the Shen lab can create in a matter of weeks, provide a new, innovative way to study the molecular mechanisms associated with drug response and drug resistance in bladder cancer patients.

The BCAN award supports the Shen lab's efforts in furthering their work in patient-derived bladder tumor organoids.

"We will employ these organoid lines to examine how specific oncogenic drivers may regulate the invasiveness and metastatic ability of muscle-invasive bladder cancer (MIBC), both in cell culture and in mouse models," says Dr. Shen. "Our goal is to use these new experimental approaches to provide molecular insights into the lethal properties of human MIBC, which will hopefully lead to improved therapeutic approaches."

Bladder cancer is the fifth most common cancer in the United States, and the primary treatment of the disease is surgery. Overall, this new project will examine central questions of bladder cancer biology using Dr. Shen's innovative approach involving patient-derived tumor organoids, and may provide the basis for future therapies for metastatic bladder cancer.

This is the fourth year BCAN has bestowed the Bladder Cancer Research Innovation Award; in 2015, fellow Columbia faculty member, Cory Abate-Shen, PhD, professor in the Departments of Urology, Medicine, Systems Biology and Pathology & Cell Biology, received the award for research into the epigenetic regulation of bladder cancer progression.

FACULTY SPOTLIGHT

Q&A with Dr. Tal Korem

Dr. Tal Korem

As a member of Columbia University's Program for Mathematical Genomics (PMG), Tal Korem, PhD, is bringing his interests in systems biology, quantitative research, and the human microbiome to areas of clinical relevance. For Dr. Korem, that clinical focus is women's reproductive health.

"There is still a lot we don't understand that relates to women's health, to fertility, and to birth outcomes, and how microbes play a role in all of this," says Dr. Korem, assistant professor of systems biology, with a joint appointment in obstetrics and gynecology at Columbia University Vagelos College of Physicians and Surgeons. A current focus of the Korem lab is preterm birth, i.e., birth that occurs prior to 37 weeks of gestation, though Dr. Korem intends to expand into other areas such as infertility and endometriosis.

Dr. Korem's interest in women's health research is personal, stemming from several impactful experiences that hit close to home.

"My aunt passed away from ovarian cancer and I have seen friends and family members struggle with idiopathic infertility," he says. "Also, witnessing the complications with the birth of my first child, which involved emergency procedures, motivated my interest in this area, and I am very excited about the potential to contribute to women's health with my own research."

Dr. Korem, a native of Tel Aviv, Israel, is the first in his family to earn a PhD, and had entered academia as a medical student. After completing his undergraduate degree, he enrolled in a MD/PhD graduate program. There, he realized that research was what he enjoyed the most. He is a trained computational biologist, and studied under Professor Eran Segal at the Weizmann Institute of Science, where his work focused on the human microbiome, a complex system of microbial communities that inhabit every body part.

In the last two decades the gut microbiome, in particular, has attracted a lot of research interest for its strong associations to human health and disease. Researchers in the Korem lab are using novel computational methods to study how different microbes combine their metabolic activities to produce metabolites that have a systemic effect on the host.

The Korem lab is now applying these methods to study cancer. Specifically, working with a global team of researchers, Dr. Korem is helping to develop a comprehensive computational framework that will identify microbial high-risk factors for pancreatic cancer. Funding for this research is provided by a grant from the Pancreatic Cancer Collective (PCC), awarded in the spring of 2018 and led by PMG Director Dr. Raul Rabadan. "We hope that the results of this work will enable better and earlier identification of individuals at risk for this lethal disease, facilitating improved treatment and prognosis," says Dr. Korem.

This academic year marks Dr. Korem's one-year anniversary as both a Columbia faculty member and first-time New Yorker. Prior to joining Columbia, he was a postdoc and graduate student at Weizmann, earning his PhD in computational biology, and at Tel Aviv University from where he received his Bsc. in medicine. In September 2019, he was named a CIFAR Azrieli Global Scholar in the Humans & the Microbiome program by CIFAR, a Canadian-based global charitable organization that targets pressing questions in science and technology. The

fellowship will support Dr. Korem's work in microbiome metabolism. CIFAR's community of fellows includes 19 Nobel laureates and more than 400 researchers from 22 countries.

Q: *Tell us what fascinates you about studying the human microbiome and a bit about your focus in this area.*

A: For the past couple of decades, we've been finding statistical associations between the microbiome and probably every disease you can think of. Like patients with electronic health records, we have come to think of the microbiome as sort of our biological health record. It is like a one-stop-shop for indications about almost everything that's wrong with a person. It's also a system that's very challenging to explore. With genetics studies for example, there is an expected way in which things progress. If I'm now finding a new mutation that has a very strong signal for some disease, then it probably means that the mutation affects the disease in some way, whether directly or indirectly.

With the microbiome, it is probably the opposite direction that is more reasonable, and that's why we've been able to find all these associations of these signatures to changes in the microbiome. This means that whenever something is changing with the physiology of the host or when we get a disease or a condition, they cause a change in the microbiome. There is also a lot of evidence that there are some effects the other way around—and trying to find the microbiome's causal effects on disease is the most interesting challenge for me and my lab. While the host affecting the microbiome gives us diagnostic understanding, the microbiome affecting the host, we hope, will lead us to novel therapeutics.

Q: *Are you oftentimes considering a clinical application in your research?*

A: We are always working on two things at the same time—one is our methodological or analytical approach to a research problem and the other is thinking about a specific clinical area. When we're working on a new computational approach, where we can apply it is at the top of our minds.

Q: *A majority of your research is in women's health. What are you currently working on?*

A: Right now our major focus is in preterm birth, and studying the link between the vaginal microbiome to this condition. It has been observed that there is a direct involvement of the vaginal microbiome in an estimated 25-40% of preterm births. But, we don't yet know enough about the link. One hypothesis is that ascending infection from the vaginal or cervical area to the uterus triggers preterm birth in some cases. Scientists have also looked at metabolic effects associated with this condition. Despite these strong links between the vaginal microbiome and preterm birth, we don't yet have good biomarkers of preterm birth and it is still hard to know whether a woman carrying a child will have this condition. Known risk factors are not predictive enough. If we can sample the vaginal microbiome in the first trimester and use it to mark really high risk women, then this could change the way this condition is treated.

There are many research groups looking into this problem. The challenge is that it likely does not link back to a single microbe but, rather, to how the microbial ecosystem works as a whole. For example, we see that microbes associated with preterm birth are different from cohort to cohort and across different ethnicities. We are aiming to identify the underlying principle that connects all of this together—a mechanism that explains why some women experience preterm birth, or how we can use this mechanism to make an early diagnosis. Our work is focused on analyzing the data, developing machine learning approaches tailored to this type of data and to various characteristics of the data, and applying different approaches that could produce better predictors than what we currently have.

Q: *You are faculty of the Program for Mathematical Genomics (PMG), a multidisciplinary center born out of the Department of Systems Biology in the fall of 2017. What drew you to PMG?*

A: When I was searching for a position, I was looking for a quantitative program or department but I also wanted to be across the street from a hospital. Right now, I'm in a hospital, and that's even better. PMG gives me the opportunity to conduct research in a place that does strong quantitative work, to be able to collaborate with people like Raul [Rabadan] and at the same time, be very connected to the clinical side. There aren't a lot of institutions that can provide both.

> "The Program for Mathematical Genomics gives me the opportunity to conduct research in a place that does strong quantitative work … and at the same time, be very connected to the clinical side. There aren't a lot of institutions that can provide both." — *Dr. Tal Korem*

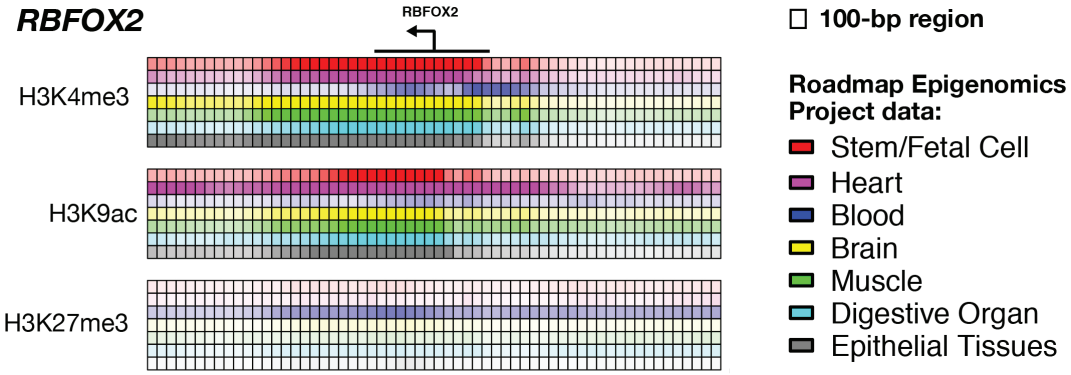
Q: *You first studied to be a doctor. What changed your mind?*

A: When I joined an MD/PhD program, I thought a PhD would be a nice addition on my way to becoming a doctor. But once I started, I realized that research really is the place for me, and decided not to go back to medical school and complete my MD. Every once in a while I wonder if I should have completed my MD, for various reasons; but ultimately I knew I wanted to be on the cutting edge of medicine, where medicine isn't working or where you don't yet know what is going on. I think that is exactly where I am today, and where my research is. Research in the microbiome area is very challenging and interesting from a quantitative standpoint, and at the same time could probably lead down the road to better, improved medical advances.

—Melanie A. Farmer

RESEARCH

Novel Method Identifies New Risk Genes for Developmental Disorders



The epigenomic profile of RBFOX2, a haploinsufficient gene recently identified as a risk gene of congenital heart disease. Each small box represents 100 bp region around transcription start sites (TSSs) and the shade of the color reflect the strength of the histone mark signal in tissues under normal conditions. RBFOX2 has large expansion of active histone marks (H3K4me3 and H3K9ac), especially in heart and epithelial tissues (purple and gray rows), and tissue-specific suppression mark (H3K27me3) in blood samples.

The genetics of developmental disorders, such as congenital heart disease and autism, are highly complex. Five hundred to 1,000 risk genes are estimated to contribute to each of these diseases. To date, only about a few dozen have been identified. To close this gap, scientists have ramped up efforts to develop computational approaches that can accurately identify genetic risk factors in ongoing genetic studies. The availability of such tools could assist greatly in gaining a deeper understanding of the root causes of these diseases.

Focusing on haploinsufficiency, a key biological mechanism of genetic risk in developmental disorders, Yufeng Shen, PhD, and his lab have developed a novel computational method for risk gene discovery. The key idea is that the expression of haploinsufficient genes must be precisely regulated during normal development, and such regulation can be manifested in distinct patterns of genomic regulatory elements. Using data from the NIH Roadmap Epigenomics Project, they showed there is a strong correlation of certain histone marks and known haploinsufficient genes. Then based on supervised machine learning algorithms, they developed a new method, called Episcore, to predict haploinsufficiency from epigenomic data representing a broad range of tissue and cell types. Finally, they demonstrate the utility of Episcore in identification of novel risk variants in studies of congenital heart disease and intellectual disability.

Haploinsufficiency means that a loss of function of one of the two copies of a particular gene could have pathological consequences. Previous studies have shown that developmental disorders are often caused by loss of function mutations in such haploinsufficient genes.

The critical challenge the Shen group had to address was to devise a way to computationally identify these haploinsufficiencies.

"We know that a lot of genes can be haploinsufficient, but we don't know which of these genes are, in any given study," says Dr. Shen, associate professor of systems biology at Columbia University Irving Medical Center (CUIMC). "So, the question we sought to answer is whether we can computationally infer which genes are haploinsufficient before we do an actual human genetic study."

Episcore can be used to predict the likelihood that a gene is haploinsufficient; Once this information is available, studies can be designed to specifically test this hypothesis and further analyze the loss of function variance only in the study dataset.

"If a gene is determined haploinsufficient and we are able to observe loss of function in the patient, then it is likely that this is a risk gene," explains Dr. Shen. "Episcore enables us to increase our chances of being able to predict which haploinsufficient gene could be a risk gene. Furthermore, we can combine this with additional statistical analyses to implicate new risk genes."

A comparison of Episcore to existing methods, using data from recent exome sequencing studies of developmental disorders, revealed that Episcore achieved better performance overall in prioritizing loss of function de novo variants, or new mutations, than current methods. According to the comparison study, one of the reasons for the superior performance is that Episcore is not biased towards well-studied genes; instead, the data used for the method are generated by high throughput technologies in a gene-agnostic manner. Some previous methods used protein-protein interaction networks or gene pathways as input, which are inevitably biased toward well-studied genes. One of the most popular competing methods, ExAC pLI, is based on depletion of rare genetic variation in the general population. The epigenomic data used by Episcore are orthogonal to population genetic data, making Episcore and ExAC pLI complementary with each other.

—Melanie A. Farmer

REFERENCES:

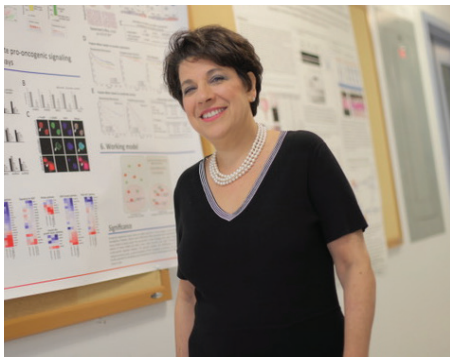
Han X, Chen S, Flynn E, Wu S, Wintner D, Shen Y. *Distinct Epigenomic Patterns are Associated with Haploinsufficiency and Predict Risk Genes of Developmental Disorders.* Nat Commun. 2018 May 30;9(1):2138. doi: 10.1038/s41467-018-04552-7.

DSB Faculty Elected to Prestigious Groups

Dr. Andrea Califano

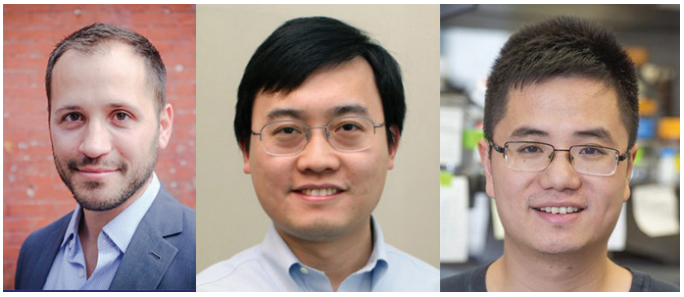
Andrea Califano, Dr., a pioneer in the field of systems biology and founding chair of the Department of Systems Biology at Columbia University Irving Medical Center (CUIMC), has been elected to the **National Academy of Medicine** (NAM). Membership in the NAM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievements and commitment to service. Dr. Califano is currently the Clyde and Helen Wu Professor of Chemical and Systems Biology in the Departments of Systems Biology, Biochemistry and Molecular Biophysics, Biomedical Informatics and Medicine. He also is director of the JP Sulzberger Columbia Genome Center.

Cory Abate-Shen, PhD, a leader in the development of mouse models for translational research in prostate and bladder cancers, has been elected a fellow of the **American Association for the Advancement of Science** (AAAS). The AAAS honors Dr. Abate-Shen for her work in mouse models to better understand how basic cellular mechanisms are co-opted in cancer and for her contributions to the field of cancer biology. Dr. Abate-Shen is chair of the Department of Pharmacology at Columbia University Irving Medical Center and the Michael and Stella Chernow Professor of Urologic Sciences, with appointments in the Departments of Systems Biology, Medicine, and Pathology & Cell Biology.



Dr. Cory Abate-Shen

DSB's Newly Tenured Faculty



Congratulations to Drs. Yufeng Shen (above, middle), Nicholas Tatonetti (above, left), and Chaolin Zhang (above, right) of the Department of Systems Biology, who have been awarded tenure and promoted to associate professor.

Yufeng Shen, PhD, joined Columbia University Irving Medical Center in 2011 as an Assistant Professor in Systems Biology and Biomedical Informatics. He directs a research group focused on studies of human biology and diseases using genomic and computational approaches. They are developing new methods to interpret genomic variations by machine learning based on biological mechanisms, and using these methods in large-scale genome sequencing studies to identify new genetic causes of human diseases, such as autism, birth defects, and cancer. His group also works on modeling of clonal and transcriptional dynamics of immune cells to improve our understanding of human adaptive immune system under normal and clinical conditions. Dr. Shen serves as an Associate Director of the JP Sulzberger Columbia Genome Center, a member of the Program for Mathematical Genomics, and an adjunct member of Columbia Center for Translational Immunology.

Dr. Nicholas Tatonetti, whose primary appointment is in the Department of Biomedical Informatics, has an interdisciplinary appointment with both the Departments of Systems Biology and Medicine. Dr. Tatonetti's lab specializes in advancing the application of data science in biology and health science. His group integrates their medical observations with systems and chemical biology models to not only explain drug effects, but also to gain further understanding of basic biology and human disease.

Dr. Chaolin Zhang and his lab focus on the function of post-transcriptional gene regulation, in particular a level of molecular regulation called alternative RNA splicing, in the nervous system. Their work, both computational and experimental, aims to characterize the regulatory networks that specify neuronal cell types, and how these networks can be compromised in certain pathologic contexts, such as neurodevelopmental and neurodegenerative diseases. Prior to joining the Department of Systems Biology in 2012, Dr. Zhang was a researcher at Rockefeller where he studied neuron-specific RNA regulatory networks by developing an integrative modeling approach that combines multiple types of high-throughput data, including transcriptome profiles and protein-RNA interaction maps.

Around the Department, 2018-2019

Selected Grants and Awards

Cory Abate-Shen, PhD, (PI, Project Leader, Core Leader) and **Michael Shen**, PhD (Project Leader and Core Leader) received a five-year P01 award from NIH/NCI for their project entitled "Modeling bladder cancer pathogenesis and tumor evolution". Dr. Abate-Shen has also received a grant from the National Cancer Institute for "Mitochondrial and Nuclear Functions of NKX3.1 in Regulating Oxidative Stress in Prostate Cancer". In March 2019, she was named chair of the Department of Pharmacology at Columbia University Irving Medical Center, an appointment she assumed on April 1.

Researchers from Columbia University Irving Medical Center received a 2018 PCF Challenge Award from the Prostate Cancer Foundation (PCF) to advance prostate cancer research. From the Department of Systems Biology, the team includes Drs. **Cory Abate-Shen**, **Andrea Califano**, and **Michael Shen**. (See the article on page 5.)

Harmen Bussemaker received a Netherlands Academy of Sciences (KNAW) Visiting Professor Fellowship, and spent his spring 2019 sabbatical at the Hubrecht Institute in the Netherlands.

Barry Honig, PhD, has received a four-year, million-dollar award from the National Science Foundation entitled "Molecular Mechanisms in Adhesion Protein Mediated Neuron-Neuron Recognition". This marks the 39th year of continuous funding from the NSF.

Tal Korem, PhD, was named a CIFAR Azrieli Global Scholar in the Humans & the Microbiome program by CIFAR, a Canadian-based global charitable organization in science and technology. (See the Faculty Q&A on page 12).

Tuuli Lappalainen was honored with the Lamport Research faculty award at the 2019 Commencement ceremony. Dr. Lappalainen is pictured here with University Trustee Andrew Barth (left) and Dean Lee Goldman of Columbia University Irving Medical Center. (Courtesy of CUIMC Communications)

Molly Przeworski, PhD, held a temporary chair called "Innovation technologique Liliane Bettencourt" at an Institute in France, College de France. She gave a series of public lectures, including "The Evolutionary Roots of Genetic Variation". In May, she delivered the keynote talk at the Biology of Genomes at Cold Spring Harbor Labs.

Stand Up to Cancer (SU2C) awarded **Raul Rabadan**, PhD, the Philip A. Sharp Innovation in Collaboration prize, jointly with collaborator Dan A. Landau, MD, PhD of Weill Cornell. Dr. Rabadan also received a two-year, $1 million grant from the Pancreatic Cancer Collective from SU2C and the Lustgarten Foundation, and an inaugural Chan Zuckerberg Initiative Seed Networks grant for a collaborative project focused on the human spinal cord. (See the article on page 10).

Yocelyn Recinos, a graduate student in the lab of Dr. Chaolin Zhang, has been awarded an NSF Graduate Research fellowship.

Michael Shen, PhD, received a five-year R01 award from NIH/NCI for his project entitled, "Analysis of Epithelial Heterogeneity in Prostate Development and Cancer"; was awarded the 2018 V Foundation for Cancer Research Translational Award for "A Co-Clinical Trial of Chemotherapy Response in Bladder Cancer Using Patient-Derived Tumor Organoids." He also is the recipient of the 2018 Bladder Cancer Research Innovation Award. (See the article on page 11.)

Yufeng Shen, PhD, has received an NIH/NHLBI grant for "Integrate Gene Expression Data to Characterize the Contribution of Rare Genetic Risk Factors to Structural Birth Defects."

Yufeng Shen, PhD, and **Chaolin Zhang,** PhD, received a grant from the Simons Foundation for "Genomic Analysis for Autism Risk Variants in SPARK."

The Mark Foundation for Cancer Research awarded **Peter Sims**, PhD, an Emerging Leader Award and will support his work to advance a novel use of single-cell RNA sequencing to develop brain cancer treatments. Dr. Sims has also received a grant from the National Human Genome Research Institute for "Fully Integrated Single-Cell Imaging and RNA-Seq Library Preparation" and was selected as an inaugural Chan Zuckerberg Initiative Seed Networks project for research on the immune system and aging. (See the article on page 10.)

Harris Wang, PhD, is leading a team of scientists on a new project by DARPA that aims to boost the body's resilience to radiation exposure. (See the article on page 8.) He has also received a Bill and Melinda Gates Foundation grant for "Azithromycin's Impact on Microbiome Re-Assembly and Re-configuration in Mice".

Xuebing Wu, PhD, has received the 2019 RNA Society/Scaringe Award, an international recognition for young scientists. The awardees were recognized at the RNA 2019 conference in June in Krakow, Poland.

Chaolin Zhang, PhD, and **Tuuli Lappalainen**, PhD, received a R01 from the National Institute of General Medical Sciences (NIGMS) to study the impact of genetic variation on protein-RNA interactions and splicing regulation.

NEW FACULTY

Alejandro Chavez, *Assistant Professor (affiliated faculty)*
David Knowles, *Assistant Professor (interdisciplinary appointment)*
Xuebing Wu, *Assistant Professor*

PHD GRADUATES

Congratulations to our Recent Grads!
Sway Chen (Wang lab)
Brian Ji (Vitkup lab)
Nathan Johns (Wang lab)

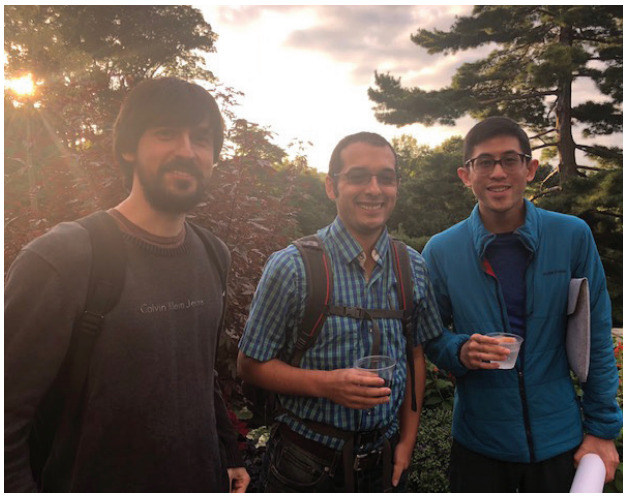
NEW IN DSB ADMINISTRATION

Margarita Kenny, *Financial Assistant*
Chris Newsome, *Graduate Program Coordinator*
Melanie Ng, *Finance Coordinator*
Paula Ralph-Birkett, *Administrative Manager* (Rabadan Lab)
Enid Vallejo-Juste, *Grants Finance Manager*

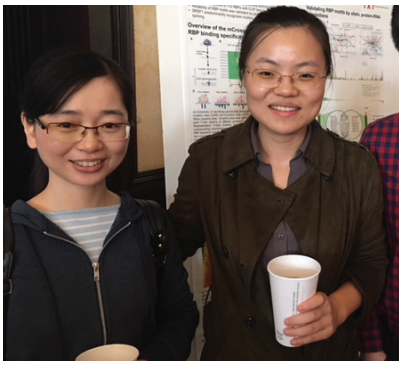
Gallery

Faculty, students, staff, researchers, and guests gathered on October 5, 2018, for the Department of Systems Biology Annual Retreat in Riverdale, NY. The day's activities included research presentations by faculty members and an opportunity for young investigators to showcase their latest projects during a poster competition.

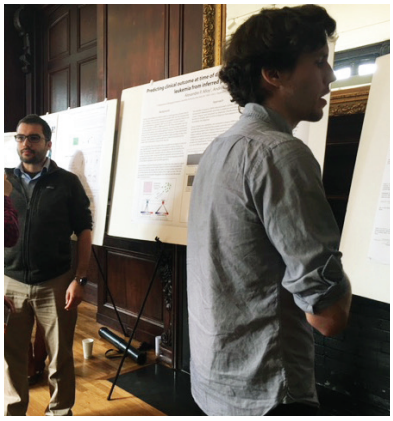
Dr. Aris Floratos gives introductory remarks.



Above: Hanna Levitin, of the Peter Sims lab, with Dr. Sagi Shapira. At left: Members of the lab of Dr. Dennis Vitkup, left to right: Konstantine Tchourine, Germán Plata, and Jon Chang.



Above: Suying Bao (left) and Huijuan Feng of the Chaolin Zhang lab. At right: Haiqing Zhao (left), Kamrun Begum (middle), and Julia de Vasconcellos Castro (right), from the lab of Dr. Barry Honig.



Above: Young investigators present their research during the poster competition.

Drs. Andrea Califano (left) and Barry Honig, the founders of Columbia's Department of Systems Biology.

Above: Members of the labs of Drs. Barry Honig and Andrea Califano, from left to right: Deepika Mathur, Somnath Tagore, Ajay Nair, and Prem Subramaniam.

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