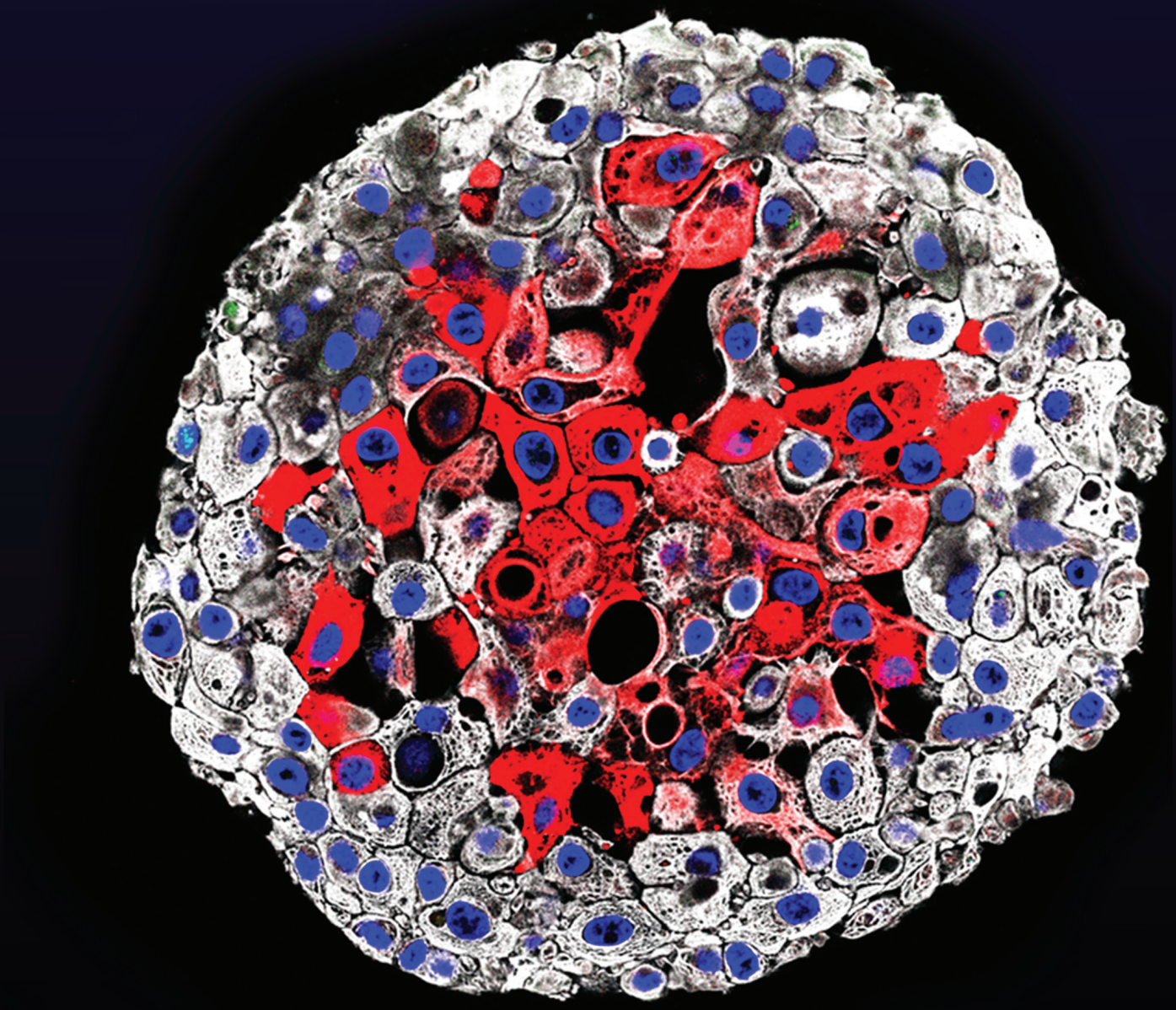
Department of Systems Biology

Columbia University Irving Medical Center



Research Highlights
2017-2018

Bladder Cancer Organoids Mimic Patient Tumors

Introducing Columbia's Program for Mathematical Genomics

Targeting the Engine Room of the Cancer Cell

World's Smallest Tape Recorder is Built from Microbes

COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER
Department of Systems Biology

Highlights 2018

Table of Contents

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

PAGE 3

Organoids Created from Patients' Bladder Cancers Could Guide Treatment
Innovative patient-specific bladder cancer organoids have the ability to mimic many of the characteristics of actual tumors. In the future, the use of organoids may guide the personalized treatment of patients.

PAGE 4

At the Intersection of Math and Genomics
The Program for Mathematical Genomics is a new research hub at Columbia University that brings together computer scientists, mathematicians, evolutionary biologists and physicists to uncover new quantitative techniques aimed at fundamental biomedical problems.

PAGE 4

Prize for Excellence in Human Genetics Goes to Tuuli Lappalainen
Dr. Lappalainen is the recipient of the 2018 Leena Peltonen Prize for her contributions in advancing the field of human genomics.

PAGE 5

Targeting the Engine Room of the Cancer Cell
A highly innovative computational framework that can support personalized cancer treatment by matching individual tumors with the drugs or drug combinations that are most likely to kill them.

PAGE 7

World's Smallest Tape Recorder is Built from Microbes
Researchers have figured out a way to convert a natural bacterial immune system into a microscopic data recorder, enabling a new class of technologies that use bacterial cells for everything from disease diagnosis to environmental monitoring.

PAGE 8

New Insights on How the Reprogramming Factor LIN28 Regulates its Targets
A study in *Molecular Cell,* led by the laboratory of Dr. Chaolin Zhang, sheds light on a critical RNA-binding protein that is widely researched for its role in stem cell biology and its ties to cancer progression in multiple tissues.

PAGE 9

Integrating Single-Cell Sequencing with Live Cell Imaging
Learn about a novel platform for linking optical imaging with high-throughput single-cell sequencing devised by researchers in the laboratory of Dr. Peter Sims.

PAGE 10

Faculty Spotlight
A Q+A with Dr. Laura Landweber discussing her research in genome-wide DNA rearrangements in ciliates, particularly *Oxytricha,* and their role in contributing to human diseases.

PAGE 12

Electronic Health Record Analysis Shows Which Diseases Run in Families
A new study that analyzed data from millions of electronic health records estimate the heritability of hundreds of different traits and conditions.

PAGE 13

Postdoc Suying Bao Named Precision Medicine Fellow
The two-year fellowship aims to train postdocs to use genomics and complex clinical data to improve personalized clinical care and outcomes.

PAGE 14

Around the Department
Selected awards and grants from DSB faculty, researchers, and students, and notable departmental updates

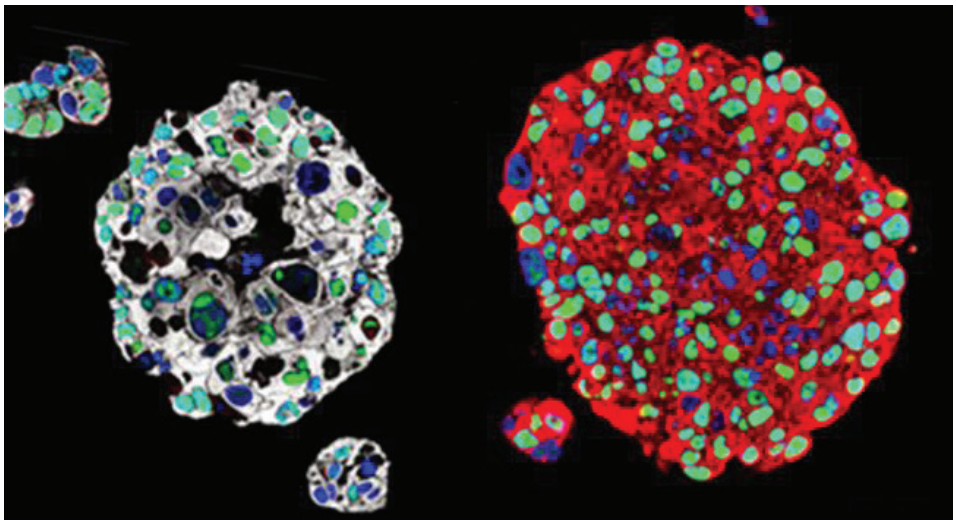
PAGE 15:

Photo Gallery
Cancer genomics and mathematical data analysis topics were explored during a two-day conference February 7 to 8, 2018, co-hosted by the National Cancer Institute centers at Columbia University Irving Medical Center, Cornell University and Memorial Sloan Kettering Cancer Center.

On the Cover:
Bladder cancer organoid lines mimic the individual patient tumors from which they were established. Using these organoids can potentially guide personalized treatment of bladder cancer patients. (Article on page 3; Image Courtesy of Dr. Michael Shen)

Organoids Created from Patients' Bladder Cancers Could Guide Treatment

Custom 3-D mini-tumors mimic individual patient's cancer



Organoids created from the bladder cancers of patients mimic the characteristics of each patient's tumor and may be used in the future to identify the best treatment for each patient. (Image Courtesy of Dr. Michael Shen)

Columbia University Irving Medical Center (CUIMC) and NewYork-Presbyterian researchers have created patient-specific bladder cancer organoids that mimic many of the characteristics of actual tumors. The use of organoids, tiny 3-D spheres derived from a patient's own tumor, may be useful in the future to guide treatment of patients.

The study was published in the April 5, 2018, online edition of *Cell*.

In precision medicine, molecular profiling of an individual patient's tumor is used to identify genetic mutations that drive that individual's cancer. That knowledge may help physicians select the best drug to fight the cancer, but the analysis does not always predict how a patient will respond to specific therapies.

"The great advantage of organoids is that they are essentially avatars of a patient's tumor," said study leader Michael M. Shen, PhD, professor of medicine, genetics & development, urology, and systems biology at Columbia University Vagelos College of Physicians and Surgeons. "Having these personalized laboratory models, which we can make in a matter of weeks, will let us test multiple different drugs on the tumor and help us bring precision medicine to individuals with bladder cancer."

Dr. Shen, who is also a member of NewYork-Presbyterian/CUIMC's Herbert Irving Comprehensive Cancer Center, began developing bladder cancer organoids about four years ago. A major challenge in creating any type of organoid is determining the unique mixture of nutrients, growth factors, and tissue culture techniques that will transform patient tumor cells into miniature tumor organoids in a petri dish. The exact conditions can vary greatly from one type of cancer to another.

In the current study, organoids were made from the tumor cells of 22 patients with invasive bladder cancer.

The researchers were able to make organoids from three patients both before and after treatment. "This offers a new way to study the molecular mechanisms associated with drug response and drug resistance," said Dr. Shen.

Bladder cancer is the fifth most common cancer in the United States, yet it is one of the least understood because few animal models reflect the biology of the disease.

"The creation of bladder cancer organoids is an important advance in the field," said study co-author James M. McKiernan, MD, the John K. Lattimer Professor of Urology and chair of urology at Columbia, and urologist-in-chief at NewYork-Presbyterian/Columbia. "This should greatly improve our understanding of the genomics of bladder cancer, how these tumors respond to drugs, and how they develop drug resistance. Ultimately, this may allow us to develop new therapies for the disease and predict an individual patient's response to treatment."

The researchers are planning to test the organoids' predictive abilities in "co-clinical" trials, in which patients and their corresponding organoids are treated with the same drug. "This would establish whether organoids can be used to predict how an individual patient will respond to a specific therapy," said Dr. Shen. "At present, it's very difficult to know beforehand exactly which drugs may be most effective for a given patient."

The current standard of care for patients with bladder cancer that has not invaded muscle is surgery to remove the tumor plus immunotherapy or chemotherapy. These tumors have a high recurrence rate, requiring repeat treatment. Some of these tumors progress to invade the bladder muscle, a form that is harder to treat and more lethal.

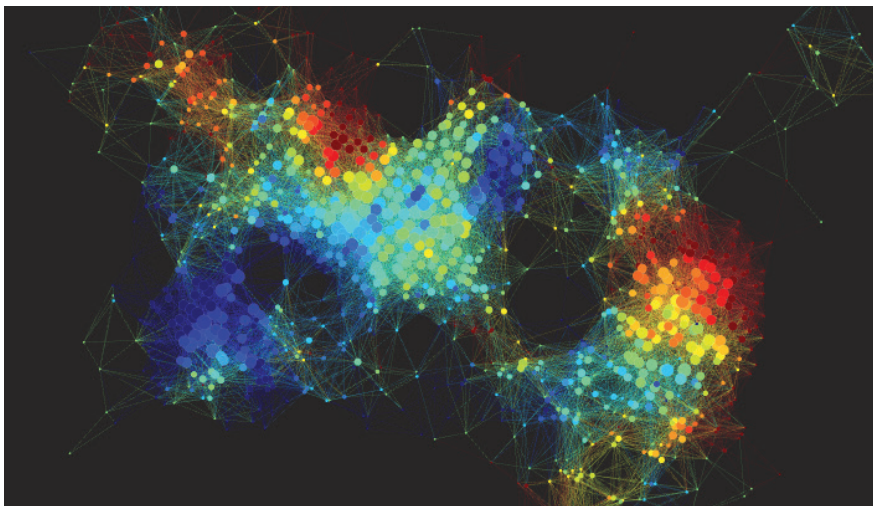
Patients with muscle-invasive cancer are typically advised to undergo bladder-removal surgery and chemotherapy. "Since bladder removal has such a profound effect on quality of life, most patients seek to avoid it," said Dr. Shen. "We desperately need better, more targeted therapies for both types of bladder cancer."

—Reprinted with permission by Columbia News

REFERENCES:

Lee SH, Hu W, Matulay JT, Silva MV, Owczarek TB, Kim K, Chua CW, Barlow LJ, Kandoth C, Williams AB, Bergren SK, Pietzak EJ, Anderson CB, Benson MC, Coleman JA, Taylor BS, Abate-Shen C, McKiernan JM, Al-Ahmadie H, Solit DB, Shen MM. *Tumor Evolution and Drug Response in Patient-Derived Organoid Models of Bladder Cancer.* Cell. 2018 Apr 5;173(2):515-528.e17.

At the Intersection of Math and Genomics



Topology data analysis of cancer samples. (Image courtesy of Rabadan Lab)

The new Program for Mathematical Genomics (PMG) is aiming to address a growing—and much-needed—area of research. Launched in the fall of 2017 by Raul Rabadan, PhD, a theoretical physicist in the Department of Systems Biology, the new program is serving as a research hub at Columbia University where computer scientists, mathematicians, evolutionary biologists and physicists can come together to uncover new quantitative techniques to tackle fundamental biomedical problems.

"Genomic approaches are changing our understanding of many biological processes, including many diseases, such as cancer," said Dr. Rabadan, professor of systems biology and of biomedical informatics. "To uncover the complexity behind genomic data, we need quantitative approaches, including data science techniques, mathematical modeling, statistical techniques, among many others, that can extract meaningful information in a systematic way from large-scale biological systems."

This new program is being built upon collaborative research opportunities to explore and develop mathematical techniques for biomedical research, leading to a deeper understanding of areas such as disease evolution, drug resistance, and innovative therapies. Inaugural members include faculty across several disciplines: statistics, computer science, engineering and pathology, to name a few. The program also is providing education and outreach to support and promote members' work, including joint discussion groups, the development of cross-campus courses, and scientific meetings.

In its first year, PMG co-hosted a two-day symposium in February on cancer genomics and mathematical data analysis. Guest speakers from Columbia University, Memorial Sloan Kettering and Cornell University presented a comprehensive overview of quantitative methods for the study of cancer through genomic approaches. (See page 15 for a photo gallery of the symposium.)

Dr. Rabadan, who joined Columbia University in 2008, also directs the Center for Topology of Cancer Evolution and Heterogeneity. Prior to coming to Columbia, he conducted research as a string theorist at CERN and was the Martin A. and Helen Chooljian Member at The Simons Center for Systems Biology at Princeton University. His work uncovers patterns of evolution in biological systems, focusing on RNA viruses and cancer.

"We are very excited to establish a program that will spotlight critical work in genomic analysis," said Dr. Rabadan. "PMG will help advance research in this rapidly growing field, providing a better understanding of diseases to identify potential treatments."

Tuuli Lappalainen Receives Leena Peltonen Prize for Excellence in Human Genetics

Tuuli Lappalainen, PhD, assistant professor of systems biology and core faculty member at New York Genome Center (NYGC), is the recipient of the 2018 Leena Peltonen Prize for Excellence in Human Genetics. The award was presented to Dr. Lappalainen on June 16, 2018, in Milan, Italy, at the 52nd Annual European Society of Human Genetics meeting, the largest human genetics conference in Europe. The award is funded by the Leena Peltonen Memorial Fund in the Paulo Foundation.

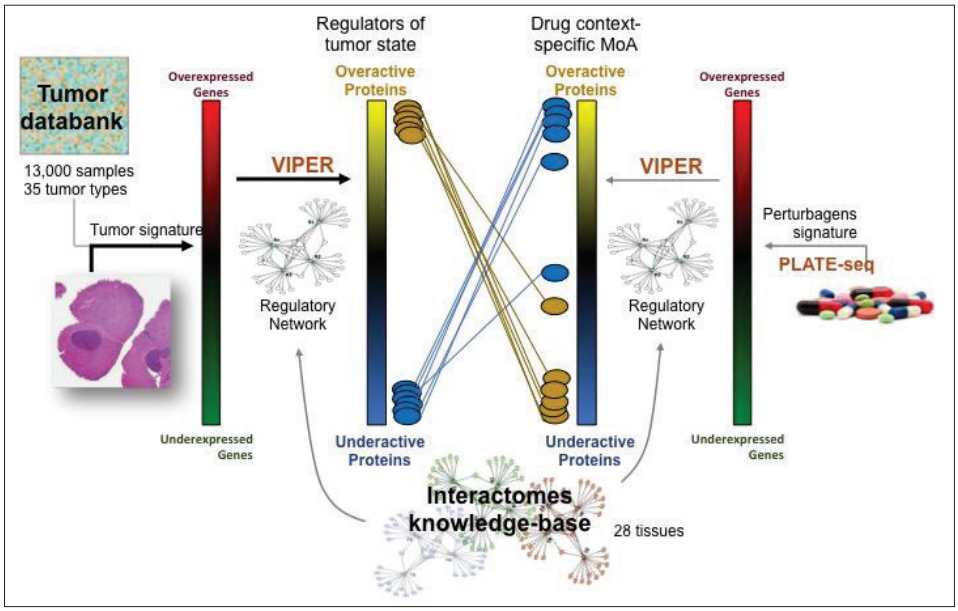
Dr. Lappalainen's research focus is on functional genetic variation in human populations. She and her research group at NYGC study regulatory variation affecting the transcriptome, as well as cellular mechanisms underlying genetic associations to diseases. The work of her research group links computational and population genomics to experimental molecular biology. Widely published in her field, Dr. Lappalainen has made important contributions to several international research consortia in human genomics, including the Genotype Tissue Expression (GTEx) Project, the 1000 Genomes Project, and the Geuvadis Consortium.

The prize Dr. Lappalainen received honors the memory of Dr. Leena Peltonen, a world-renowned human geneticist from Finland who passed away in 2009. A visionary in medical genetics, Dr. Peltonen contributed to the identification of disease genes for human diseases in the Finnish and other populations. Her outstanding achievements inspired many young researchers in the field of medical genetics, including Dr. Lappalainen, who grew up in Finland, earning her PhD in genetics at the University of Helsinki in 2009, followed by postdoctoral research at the University of Geneva and Stanford University.

"Tuuli's commitment to international collaboration as well as her philosophy of empowering and inspiring the next generation of genomic researchers mirrors Leena Peltonen's values and vision for advancing the field," said a member of the award's nominating committee, Samuli Ripatti, PhD, professor of Biometry Public Health, University of Helsinki, Institute for Molecular Medicine Finland (FIMM), Broad Institute of MIT, and Harvard.

"As a female Finnish scientist who was inspired by Leena Peltonen's important contributions to human genetic research, it's truly a great honor and especially meaningful to me to receive this award," noted Dr. Lappalainen.

Targeting the Engine Room of the Cancer Cell



Schematic diagram for the OncoTreat clinical pipeline. The pipeline consists of a series of pre-computed components, including a reference set of more than 13,000 tumor expression profiles representing 35 different tumor types, a collection of 28 tissue context-specific interactomes and a database of context-specific mechanism of action (MoA) for >400 FDA-approved drugs and investigational compounds in oncology. The transcriptome of the perturbed cell lines is profiled at low cost by PLATE-Seq. The process begins with the expression profile of a single patient sample, which is compared against the tumor databank to generate a tumor gene expression signature. This signature is interpreted by VIPER using a context-matched interactome to identify the set of most dysregulated proteins, which constitute the regulators of the tumor cell state – tumor checkpoint. These proteins are then aligned against the drugs' and compounds' MoA database, to prioritize compounds able to invert the activity pattern of the tumor checkpoint. (Image courtesy of Califano Lab.)

Researchers at Columbia University Irving Medical Center (CUIMC) have developed a highly innovative computational framework that can support personalized cancer treatment by matching individual tumors with the drugs or drug combinations that are most likely to kill them.

The study, which was published June 18, 2018, in *Nature Genetics,* by Dr. Andrea Califano of CUIMC and Dr. Irvin Modlin of Yale University and Wren Laboratories LLC, co-senior author on the study, with collaborators from 17 research centers worldwide, details a proof of concept for a novel analytical platform applicable to any cancer type and validates its predictions on gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The latter represent a rare class of tumors of the digestive system that, when metastatic, are associated with poor survival.

In a comprehensive analysis of samples from 212 patients, the team first identified a new class of drug-targets, called master regulators, which are rarely, if ever, mutated in cancer patients, and then predicted the drugs that can specifically invert their activity. Surprisingly, even though tumors were analyzed on an individual patient basis, the algorithm predicted the same top drug – Entinostat – for almost half of the metastatic patients. More importantly, when tested in a xenograft transplant of the tumor in a mouse, this drug induced dramatic shrinking of the tumor, while drugs predicted to have partial or no effect were also validated to produce results in line with predictions. These data led to rapid IND (Investigational New Drug) approval by the FDA for a metastatic GEP-NET clinical trial that is open and recruiting patients at Columbia University.

The innovative approach, OncoTreat, is now available as a New York State Department of Health approved test through the Department of Pathology and Cell Biology at CUIMC. The test was co-developed with DarwinHealth, a precision oncology company born out of work from the Califano lab. It is the only such test designed to predict drugs that are optimally matched to individual patient tumors for 10 different aggressive tumor subtypes of ovarian, breast, pancreas, prostate, bladder, and lung cancer, as well as meningioma, sarcoma, glioblastoma, and GEP-NETs.

"This manuscript represents a first proof of concept of what may become a valuable new tool to deliver an effective and systematic precision medicine approach to cancer patients that may complement what we are currently doing with genetic mutations," says Dr. Califano, who also is the Clyde and Helen Wu Professor of Chemical and Systems Biology at CUIMC.

"Using novel systems biology methodologies, which combine the use of supercomputers with large-scale pharmacological assays, we can computationally predict and prioritize drugs and drug combinations that will most effectively kill cancer cells," he explains. "Such an approach is especially promising for patients with aggressive tumors, who lack actionable mutations, fail to respond to targeted inhibitors or immune-checkpoint inhibitors, or relapse following initial response to a standard of care drug or drug combination. These patients, who unfortunately represent the majority of the aggressive tumor cases, present few, if any, effective therapeutic options. We hope that OncoTreat may offer the oncologist new alternatives when they run out of approved therapies, alternatives that are predicated on an increasingly mechanistic understanding of cancer cell regulation and response to drugs rather than on educated guesswork."

"Using novel systems biology methodologies, which combine the use of supercomputers with large-scale pharmacological assays, we can computationally predict and prioritize drugs and drug combinations that will most effectively kill cancer cells."—*Dr. Andrea Califano*

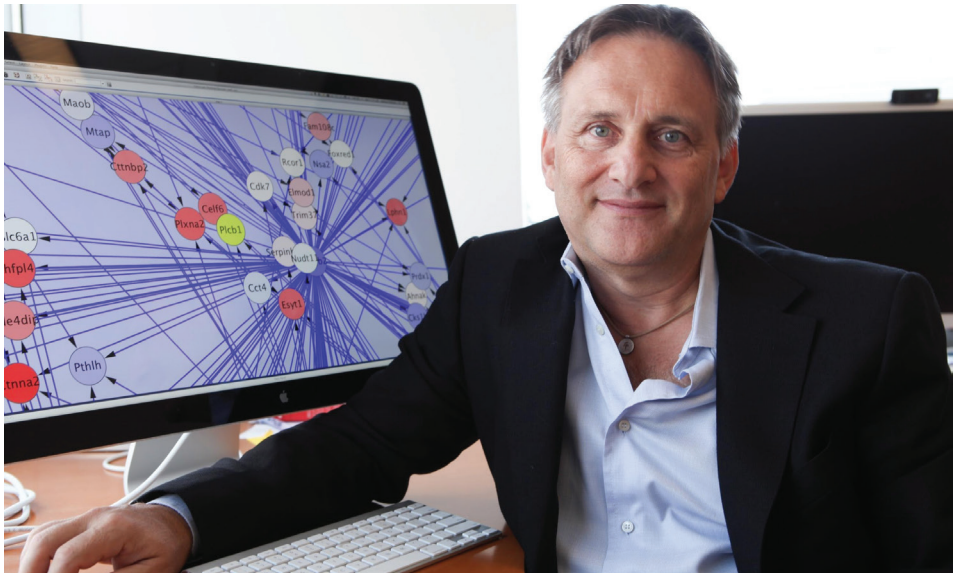
Dr. Modlin, who had initially proposed the concept of addressing Neuroendocrine tumors using the innovative strategy developed by Dr. Califano, commented that the successful demonstration of the efficacy of a pre-treatment molecular identification strategy was a significant advance on previous practice where treatment agents were used based upon serendipitous selection rather than objective molecular evidence. This work combined with the use of molecular signature tools in blood to monitor real-time efficacy of therapy on disease are likely to change the face of therapeutic management in many diseases.

OncoTreat's Precision Medicine Approach

The OncoTreat framework centers on identifying and analyzing actionable proteins in cancer patients, independent of their genetic mutations. Called master regulators (MR), these proteins are organized into small regulatory modules—so-called tumor checkpoints—which are responsible for regulating and ensuring the stability of tumor cells. Master regulators and tumor checkpoints can be efficiently and systematically elucidated using the VIPER algorithm developed by the Califano Lab and published in an earlier *Nature Genetics* manuscript; critically, these analyses allow tracking their activity through metastatic progression, relapse, and development of drug resistance. These computational models were built based on mathematical concepts from information theory and Bayesian statistics and have been extensively validated over the past decade.

MR proteins represent a novel class of tumor vulnerabilities and potential therapeutic targets that are being increasingly adopted by pharmaceutical companies. Extensive research has demonstrated that shutting down the activity of these proteins is catastrophic for tumor cells, making it virtually impossible for them to survive and grow in their environment. In this study, drug compounds are prioritized based on their ability to revert the coordinated activity of 50 such master regulator proteins, as identified by the analysis of tumor samples. Predicted activity reversal was surveyed from an analysis of drug assays both in cell lines and *in vivo,* in PDX mice models.

"Master regulators—a new Achilles' heel of cancer—represent the engine room of the cancer cell, where the effects of all tumorigenic mutations come together. What OncoTreat is able to do is attack this convergence point with a therapeutic intervention," says collaborator Gary Schwartz, MD, division chief of hematology and oncology at CUIMC and associate director of the Herbert Irving Comprehensive Cancer Center. "By collapsing this tumor bottleneck, blocking this Achilles' heel, the cancer can no longer survive. This method is so innovative, requiring a lot of mathematical modeling and understanding. It's a whole new approach to cancer therapeutics, taking us in an entirely new direction."



Dr. Andrea Califano (Photo: Chris Williams)

Califano and team validated the OncoTreat approach on a cohort of 212 gastroenteropancreatic neuroendocrine tumors, a deliberate choice since GEP-NETs are rare and poorly characterized, making them one of the more challenging tumors to research. Their analysis identified several MR proteins, including key immune function modulators, whose role as critical tumor dependencies was experimentally confirmed. The GEP-NET cells were screened against a library of 107 compounds, and found that the drug, Entinostat, proved to successfully invert the activity of the top 50 MR proteins in 42 percent of GEP-NET patients, providing the rationale for the follow up clinical trial.

"It is certainly our hope that this may provide a short cut to identify viable candidates for phase 2 trials in this and other malignancies," says coauthor Edward Gelmann, MD, professor of medicine and of pathology and cell biology at CUIMC.

In addition to its potential therapeutic value, OncoTreat provides novel insight into the mechanisms and maintenance of GEP-NETs. In future work, Califano and collaborators intend to expand this approach to cover more than 80% of human malignancies and to develop clinical trials that will test the predictions in patients.

The *Nature Genetics* paper is titled "A Precision Oncology Approach to the Pharmacological Targeting of Mechanistic Dependencies in Neuroendocrine Tumors". The study was funded by the Falconwood Foundation.

REFERENCES:

Alvarez MJ, Subramaniam PS, Tang LH, Grunn A, Aburi M, Rieckhof G, Komissarova EV, Hagan EA, Bodei L, Clemons PA, Dela Cruz FS, Dhall D, Diolaiti D, Fraker DA, Ghavami A, Kaemmerer D, Karan C, Kidd M, Kim KM, Kim HC, Kunju LP, Langel Ü, Li Z, Lee J, Li H, LiVolsi V, Pfragner R, Rainey AR, Realubit RB, Remotti H, Regberg J, Roses R, Rustgi A, Sepulveda AR, Serra S, Shi C, Yuan X, Barberis M, Bergamaschi R, Chinnaiyan AM, Detre T, Ezzat S, Frilling A, Hommann M, Jaeger D, Kim MK, Knudsen BS, Kung AL, Leahy E, Metz DC, Milsom JW, Park YS, Reidy-Lagunes D, Schreiber S, Washington K, Wiedenmann B, Modlin I, Califano A. *A Precision Oncology Approach to the Pharmacological Targeting of Mechanistic Dependencies in Neuroendocrine Tumors.* Nat Genet. 2018 Jun 18. Jul; 50(7); 979-989.

Alvarez MJ, Shen Y, Giorgi FM, Lachmann A, Ding BB, Ye BH, Califano A. *Functional Characterization of Somatic Mutations in Cancer Using Network-based Inference of Protein Activity.* Nat Genet. 2016 Aug;48(8):838-47.

World's Smallest Tape Recorder is Built from Microbes

Using the CRISPR acquisition system, the Wang Lab has built a "tape recorder" that enables bacteria to record their interactions with the environment and time-stamp these events. (Image courtesy of Wang Lab)

Through a few clever molecular hacks, researchers at Columbia University Irving Medical Center (CUIMC) have converted a natural bacterial immune system into a microscopic data recorder, laying the groundwork for a new class of technologies that use bacterial cells for everything from disease diagnosis to environmental monitoring.

The researchers modified an ordinary laboratory strain of the ubiquitous human gut microbe *Escherichia coli,* enabling the bacteria to not only record their interactions with the environment but also time-stamp the events.

"Such bacteria, swallowed by a patient, might be able to record the changes they experience through the whole digestive tract, yielding an unprecedented view of previously inaccessible phenomena," says Harris Wang, PhD, assistant professor of systems biology and of pathology & cell biology at CUIMC and senior author on the new work, published in *Science.* Other applications could include environmental sensing and basic studies in ecology and microbiology, where bacteria could monitor otherwise invisible changes without disrupting their surroundings.

Dr. Wang and members of his laboratory created the microscopic data recorder by taking advantage of CRISPR-Cas, an immune system in many species of bacteria. CRISPR-Cas copies snippets of DNA from invading viruses so that subsequent generations of bacteria can repel these pathogens more effectively. As a result, the CRISPR locus of the bacterial genome accumulates a chronological record of the bacterial viruses that it and its ancestors have survived. When those same viruses try to infect again, the CRISPR-Cas system can recognize and eliminate them.

"The CRISPR-Cas system is a natural biological memory device," says Dr. Wang. "From an engineering perspective that's actually quite nice, because it's already a system that has been honed through evolution to be really great at storing information."

CRISPR-Cas normally uses its recorded sequences to detect and cut the DNA of incoming phages. The specificity of this DNA cutting activity has made CRISPR-Cas the darling of gene therapy researchers, who have modified it to make precise changes in the genomes of cultured cells, laboratory animals, and even humans. Indeed, more than a dozen clinical trials are now underway to treat various diseases through CRISPR-Cas gene therapy.

But Ravi Sheth, a graduate student in Dr. Wang's laboratory, saw unrealized potential in CRISPR-Cas's recording function. "When you think about recording temporally changing signals with electronics, or an audio recording … that's a very powerful technology, but we were thinking how can you scale this to living cells themselves?" says Sheth.

To build their microscopic recorder, Sheth and other members of the Wang lab modified a piece of DNA called a plasmid, giving it the ability to create more copies of itself in the bacterial cell in response to an external signal. A separate recording plasmid, which drives the recorder and marks time, expresses components of the CRISPR-Cas system. In the absence of an external signal, only the recording plasmid is active, and the cell adds copies of a spacer sequence to the CRISPR locus in its genome. When an external signal is detected by the cell, the other plasmid is also activated, leading to insertion of its sequences instead. The result is a mixture of background sequences that record time and signal sequences that change depending on the cell's environment. The researchers can then examine the bacterial CRISPR locus and use computational tools to read the recording and its timing.

The paper, which appeared in *Science* on November 23, 2017, proves the system can handle at least three simultaneous signals and record for days.

"Now we're planning to look at various markers that might be altered under changes in natural or disease states, in the gastrointestinal system or elsewhere," says Dr. Wang.

Synthetic biologists have previously used CRISPR to store poems, books, and images in DNA, but this is the first time CRISPR has been used to record cellular activity and the timing of those events.

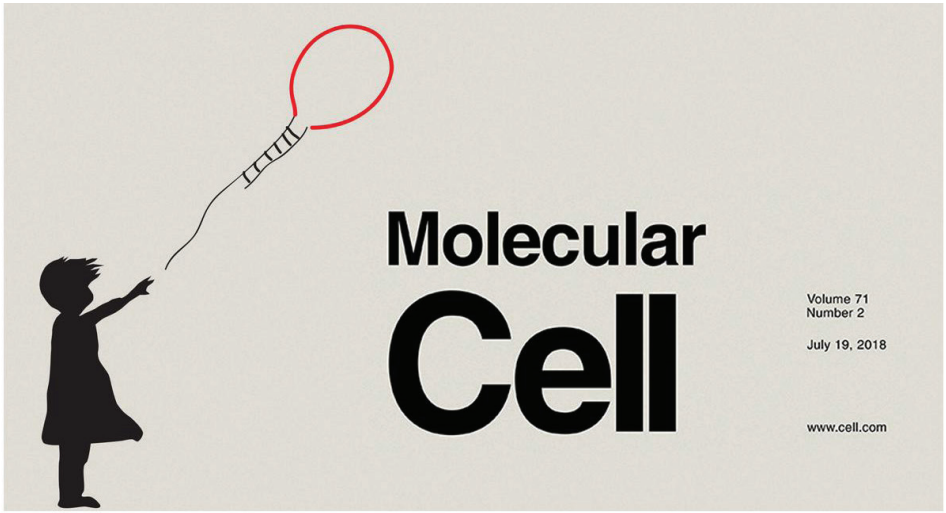
The paper is titled "Multiplex recording of cellular events over time on CRISPR biological tape." The other contributors are Sung Sun Yim and Felix L. Wu (CUIMC). The study was funded by grants from the Department of Defense, Office of Naval Research, the National Institutes of Health, and the Sloan Foundation.

—Reprinted with permission by Columbia News

REFERENCES:

Sheth RU, Yim SS, Wu FL, Wang HH. *Multiplex Recording of Cellular Events Over Time on CRISPR Biological Tape.* Science. 2017 Dec 15;358(6369):1457-1461.

New Insights on How the Reprogramming Factor LIN28 Regulates its Targets



Cover artwork for *Molecular Cell,* Vol. 71, Issue 2; Let-7 microRNA partially escapes recognition and suppression by LIN28. Art by Dmytro Ustianenko, with inspiration from the mural, Balloon Girl (2002) by Banksy.

A new study, led by Chaolin Zhang, PhD, assistant professor of systems biology, sheds light on a critical RNA-binding protein that is widely researched for its role in stem cell biology and its ties to cancer progression in multiple tissues. The paper appeared July 19, 2018, as the cover story of *Molecular Cell*.

Researchers have been focusing on understanding Let-7's various functions due to evidence that links the loss of Let-7 to the development of aggressive cancers. It has also been uncovered that Let-7 has to be suppressed, by LIN28, for the self-renewal of stem cells.

The LIN28 RNA-binding protein, initially found in worms about 15 years ago, is specifically expressed in stem cells. It became well known because the protein is one of the four factors that were used to "reprogram" skin cells to induced pluripotent stem cells, or iPSCs, a breakthrough that was awarded the Nobel Prize in 2012. More recently, it was determined that the LIN28 RNA-binding protein can also be reactivated in cancer to drive tumor growth and progression. Due to its critical importance in developmental and cancer biology, scientists want to understand the role LIN28 plays at the molecular level. This new study provides some understanding of how the LIN28 protein suppresses a specific family of microRNAs, called Let-7, which are selectively lost in cancer.

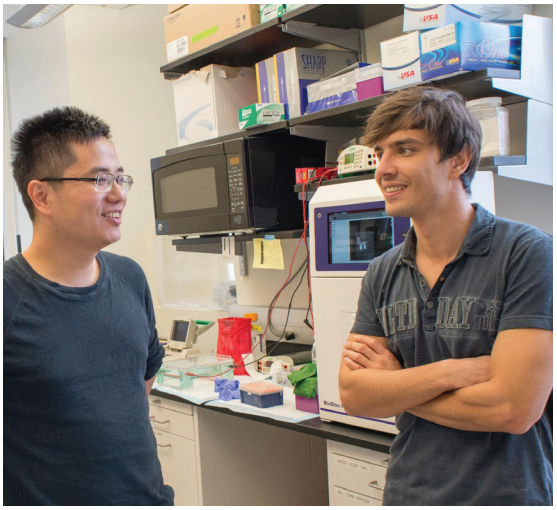
"Let-7 microRNAs are the major downstream targets controlled by LIN28 identified so far. While LIN28 is mostly found in stem cells, Let-7 is only detected in differentiated cells because of stem cell-specific suppression by LIN28. However, the interplay between the two is still not well understood," says Dr. Zhang, who is also a member of Columbia University's Center for Motor Neuron Biology and Disease. "This study contributes to our understanding of how LIN28 suppresses Let-7, as well as provides a refined model for this important, rather complex molecular pathway."

MicroRNAs, also referred to as miRNAs, are a class of small regulatory RNAs that are involved in essentially all cellular processes. Let-7 miRNA family, the focus of this particular work, is an ancient family of miRNAs whose expression is required for proper developmental timing and tumor suppressor function.

Researchers have been focusing on understanding Let-7's various functions due to evidence that links the loss of Let-7 to the development of aggressive cancers. It has also been uncovered that Let-7 has to be suppressed (by LIN28) for the self-renewal of stem cells. Interestingly, in humans and other mammalian species, there are 12 Let-7 family members that were generated by genomic duplications during evolution and fixed ever since. These members are thought to have the same functions and are all suppressed by LIN28 through the same mechanism. Still, the reason for 12 different copies remains a mystery.

In the study, Dr. Zhang and collaborators analyzed specific binding sites of LIN28 using their own computational method that maps protein-RNA interactions at the single-nucleotide level, mapping tens of thousands of LIN28 binding sites in mRNA derived from CLIP data (CLIP is a biochemical assay used in the field that enables the analysis of protein interactions with RNA on a genome-wide scale).

Their analyses revealed an entirely new RNA sequence pattern (aka motif) recognized by LIN28 in addition to another sequence motif that was previously known to bind LIN28. Careful characterization demonstrated that the new motif was recognized through a protein domain in LIN28 called cold-shock domain (CSD), while the other known motif was recognized through the zinc knuckle domain (ZKD) of LIN28. Excitingly, when the study's authors re-examined LIN28 binding sites in the precursor forms of Let-7



Dr. Chaolin Zhang (left) with Dmytro Ustianenko

miRNAs, they found that only half of Let-7 family members have CSD binding sites, and the other half do not, and because of this, LIN28 binds to the latter group much more weakly.

"When we examined the protein-RNA interaction data we found a striking difference in how robustly LIN28 will bind to Let-7 miRNA depending on whether they have this new sequence motif. This leads us to believe—and validate—that not all members of the Let-7 family are equally suppressed by LIN28," says Dr. Dmytro Ustianenko, a postdoctoral scientist in the Zhang lab and lead author of the study. "I have been working on this pathway since the start of my PhD, and I am very excited to add another small piece to the solution of this complex puzzle."

The researchers say their finding could lead to a new set of questions. "The selective suppression of Let-7 through this molecular switch provides a fine tuning mechanism. We found that some Let-7 family members partially escaped from suppression in stem cells and cancer. This implies a potential new role of LIN28 and Let-7 in pluripotent and cancer stem cells," notes Drs. Zhang and Ustianenko. The exact nature of such function still needs to be investigated in a future study, which could lead to a better understanding as to why some cancers are more aggressive than others.

The study was funded by the National Institute of Neurological Disorders and Stroke and the National Institute of General Medical Sciences.

REFERENCES:

Ustianenko D, Chiu HS, Treiber T, Weyn-Vanhentenryck SM, Treiber N, Meister G, Sumazin P, Zhang C. *LIN28 Selectively Modulates a Subclass of Let-7 MicroRNAs.* Mol Cell. 2018 Jul 19;71(2):271-283.e5

Picture This: Integrating Single-Cell Sequencing with Live Cell Imaging

The field of single-cell RNA sequencing is moving at a fast clip. Adding to its rapid advance is a novel platform for linking optical imaging with high-throughput single-cell sequencing devised by researchers in the Sims Lab at Columbia's Department of Systems Biology.

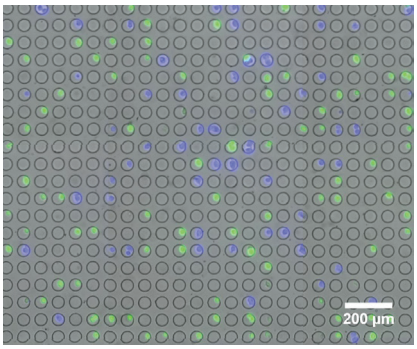
The new technology, developed by Peter Sims, PhD, assistant professor of systems biology, and postdoctoral research scientist, Jinzhou Yuan, PhD, enables live cell imaging and RNA sequencing simultaneously of the same individual cell on a large scale and at low cost. Jointly awarded a $1.5 million grant funded by the National Institutes of Health's SBIR program, the Sims Lab and Cell Microsystems are collaborating to build and test the device, with the goal of bringing to market a fully integrated system capable of imaging thousands of single cells and preparing them for genomic analysis.

The proposed system will integrate Cell Microsystems' proprietary CellRaft Technology with the Sims Lab's novel approaches to tracking single cells with so-called optical barcodes.

In single-cell RNA sequencing, "State-of-the-art technology now allows us to routinely process thousands of individual cells and obtain their genome-wide mRNA expression profiles," notes Dr. Yuan. "However, cells that share similar expression profiles at the mRNA level may be distinct from each other based on features obtainable by optical microscopy, such as morphology, motility, and fluorescent labels. A more comprehensive description of each cell obtained by both imaging and sequencing may help us further refine cell type and state."

"We're leveraging a 400-year-old method—microscopic imaging—and refining it to link nicely with high-throughput sequencing," says Dr. Sims. "Imaging cells is key. There are a lot of features of a cell you can't infer without images, such as shape, size, and behavior."

Drs. Sims and Yuan devised their optical barcoding method, called SCOPE-Seq, to be implemented in a microwell array-based platform, which analyzes thousands of individual cells in parallel, enabling it to detect thousands of genes per cell, maintain high expression profile purity, and link optical phenotypes and expression profile of the same cell with high accuracy.



Microwell array flow cell device loaded with fluorescently-labeled live cells. (Image courtesy of Sims Lab)

In future work, the SCOPE-Seq technique could be applied to study the molecular mechanism of drug resistance or to associate dynamic protein expression patterns with genome-wide mRNA expression profile of individual cells.

The Sims Lab is an early contributor to the emerging, fast-growing field of automated single-cell RNA sequencing, which has made it possible to analyze tens of thousands of cells but at the same time obtain characteristics and genomics data from each individual cell. This technique is also making it possible to discover new cell types. The Sims group applies cutting-edge microscopy, next-generation sequencing, and microfabrication to enable unbiased, genome-wide measurements in wide-ranging biological systems.

Under this new NIH grant, Cell Microsystems and the Sims Lab will work closely together to build a user-friendly version of the SCOPE-Seq system coupled with Cell Microsystems' cost-effective method to isolate and recover single cells for direct analysis; ultimately turning their platform into a single-button solution. Additionally, the new optical barcoding approach is contributing to the Human Cell Atlas Project, a global effort to identify and characterize each individual cell type of the human body, with the support of the Chan Zuckerberg Initiative.

Says Sims, "We are excited to work towards commercializing this new platform, which will enable researchers to obtain more comprehensive pictures of individual cells with the scalability for high-throughput applications."

FACULTY SPOTLIGHT
Q&A with Dr. Laura Landweber

Laura Landweber, PhD, loves a challenge. So it's no surprise that she has built a scientific career unraveling the hows and whys of a unique single-cell organism known for its biological complexity.

An evolutionary biologist whose work sits at the interface of genetics and molecular biology, Dr. Landweber, for nearly 20 years, has focused much of her research on *Oxytricha trifallax,* a microbial organism that is prevalent in ponds, feeds on algae and has a highly complex genome architecture, making it an attractive, albeit challenging, model organism to study. Compared to humans, with 46 chromosomes containing some 25,000 genes, *Oxytricha* is known to comprise many thousands of chromosomes, in the ballpark of 16,000 tiny "nanochromosomes". Yet not only is it complex in sheer numbers of chromosomes but the information carried in those individual chromosomes can be scrambled, like information compression, and the process of development in *Oxytricha* must descramble this information so that it can be converted into RNA and proteins.

"DNA can be flipped and inverted in *Oxytricha* and the cellular machinery actually knows how to restore order," says Dr. Landweber. "Hence, it's this wonderful paragon for understanding genome integrity and the maintenance and establishment of genome integrity."

Even more perplexing, in cell division, *Oxytricha* reproduces asexually when it wants to produce more in number, and it reproduces sexually when it needs to rebuild its genome. It also has the ability to "clean up" its genome, so to speak, eliminating nearly all of the non-coding DNA, or so-called junk DNA. Much of why *Oxytricha* presents such an intricate genomic landscape remains a mystery, and for Dr. Landweber, the leading expert on this single-celled protist, that wide-open field for potential discovery is what got her hooked.

"We're learning from *Oxytricha* a lot about the range of plasticity of genomes and the evolution of genomes, and that our notion of what is a genome doesn't have to be based on the few model systems that have been studied so far," she notes. "Most eukaryotes that are studied are animals, but the greater diversity found on our planet is still in the microbial eukaryotic world."

Dr. Landweber joined Columbia in 2016, after serving on the faculty at Princeton University for over 20 years. The first course she taught at Princeton was rather unconventional, a freshman seminar titled "Jurassic Park: Myth or Reality," to engage new undergraduates in science subjects from an interdisciplinary standpoint. She says, "It was great fun to discuss the science behind the movie, when both genome sequencing and the study of ancient DNA were new and controversial."


Laura Landweber

This spring at Columbia, she will be teaching a graduate/undergraduate seminar on RNA biology, focused on the ancient and modern RNA worlds. The course will begin with a discussion about the origin of life and conclude with the many types of small and large RNAs that flood modern cells.

Early in her tenure at Princeton, Dr. Landweber attended a lecture given by the late David Prescott, PhD, from the University of Colorado-Boulder. Dr. Prescott, at the time, had been studying chromosomes in *Oxytricha*, and uncovered its unique and complicated genetic makeup that intrigued Dr. Landweber, and set her on the research path she is on today.

Studying this corner of the eukaryotic world provides the Landweber lab with a plethora of research directions. A two-part lab, both experimental and computational, the Landweber group is currently exploring topics of genome rearrangement, and the roles of small and long non-coding RNAs in programming genome rearrangement, as well as genome evolution and molecular evolution. Several of the basic biology discoveries made in *Oxytricha* have been shown to extend to other organisms.

Dr. Landweber has joint appointments in the Department of Biochemistry and Molecular Biophysics, the Department of Systems Biology and the Department of Biological Sciences. She has been the recipient of a Guggenheim fellowship, an NSF CAREER Award and the Blavatnik Award for Young Scientists. She recently served as president of the Society for Molecular Biology & Evolution.

Q: *Oxytricha continues to mystify because of its bizarre genome architecture. You mentioned also that it can "clean up" its genome. What does this mean exactly and what can be gleaned from this?*

A: *Oxytricha* has the ability to take its genome, which is sort of an informational mess, put it back together and establish these conventional chromosomes. Or, it can establish chromosomes that encode conventional information. It smashes its genome into roughly a quarter million DNA pieces and then rebuilds it. Why does it do that? We of course don't have the answer yet to that basic question, but one of the motivating factors is to understand why nature allowed a system like this to become so exaggerated and complex. It would be a nice direction to go into in the future to see how the process of *Oxytricha*'s genome rearrangement can inform us about the landscape of possible genome rearrangements gone awry, like in some cancers, for instance.

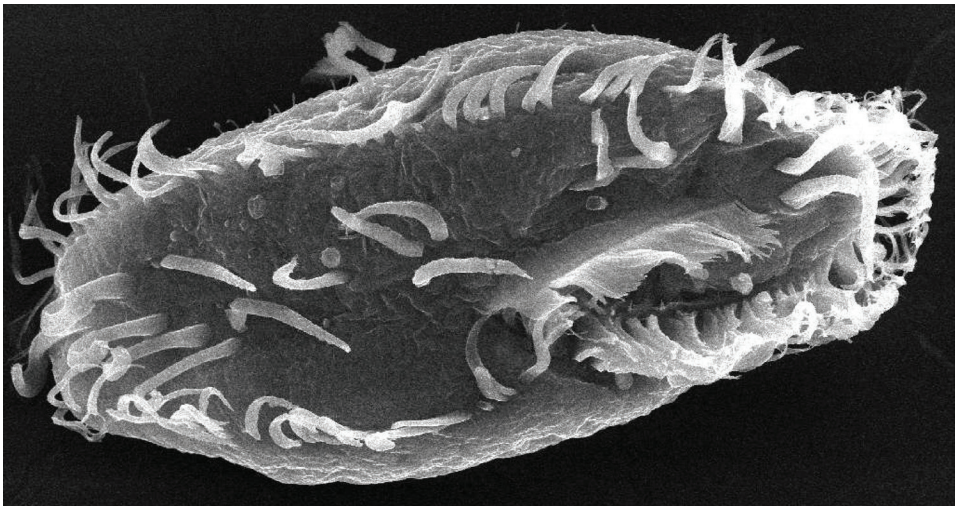
Q: *What is one theory?*

A: We think it could be runaway evolution. One of the key things we study in *Oxytricha* is that it has this error-correcting machinery available to it. And, because it can correct errors, it has the ability to buffer the consequences of its mutational burden. And so if mutations happen, they can be erased at the stage of genome assembly during development.

A lot of the pathways that it uses to do this are just variations of pathways that all eukaryotes possess, or nearly all eukaryotes. In that regard, *Oxytricha* has tweaked some fundamental molecular biology for its benefit to become a really good proofreader, and that sure would be useful as a tool in the future for engineering healthier cells.

Q: *Is that possible?*

A: Probably down the road. For now, we're focused on discovery, the basic science research.



Oxytricha. (Credit: Bob Hammersmith.)

Q: *You've been investigating Oxytricha for roughly two decades. What continues to intrigue you?*

A: I'm still amazed at how accurately this system can be executed considering how many possible points of failure there are. There's a quarter of a million DNA pieces that have to be joined correctly and if a few of those are joined incorrectly then the cell may not survive. Like any cell, it might be able to tolerate some error but it's amazing to me that this process of development that can take just a few days, can bash a genome into a quarter million pieces and put it back together with fidelity, and it does this on the basis of cross checking. It checks its own nascent genome against either mom's or dad's reference genome from the previous generation—it has this wonderful cross-talk between generations mediated by RNA molecules.

Q: *What's the most surprising thing, thus far, you've learned from your research?*

A: Maybe that [Jean-Baptiste] Lamarck was partly right. Lamarck has a bad reputation for this notion of the transfer of acquired traits. Our work was coming out at the same time as other studies demonstrating that RNA can be a bona fide vehicle for the transmission of acquired characters across generations. Discoveries that we published in 2008 and 2012, as well as results from other labs, demonstrated that RNA can transmit information across generations. And that was pretty exciting. Not that we set out to prove that Lamarck had some merit, but it was becoming vogue again to think that inheritance can depend not only on the DNA genome but on cytoplasmic factors which can include RNA.

Beyond that, we've learned that non-coding RNAS inherited from the parents' cytoplasm, not just messenger RNAs, provide a crucial instructions set to the offspring. We published in *Nature* in 2008 that long non-coding RNAs can guide genome rearrangement. Then in 2012, we found that a set of millions of smaller RNAs, just 27 nucleotides long, can mark the parts of the genome that it needs to keep, thereby instructing the next generation offspring on how to rebuild their genome. In creating that new genome of 16,000 chromosomes the organism can throw out nearly all of the non-coding DNA, or junk, that it doesn't need anymore, at least for several asexual generations, and it knows which pieces to keep on the basis of those that are marked by small RNAs, like the post-it notes that mark what stays and what goes. And then the long RNAs that we discovered in 2008 provide the information about the order and orientation to assemble those tiny pieces of DNA.

Q: *How do you incorporate systems biology approaches in your research?*

A: There are so many pieces to this Jigsaw puzzle. The *Oxytricha* genome itself begins at about a billion nucleotides. That gets shattered to roughly a quarter of a million stretches of DNA and the intervening segments are destroyed, so this is systems biology in the sense that we are dealing with problems of large numbers and the cell has to determine, for instance, which of these pieces to keep, which ones to eliminate. And then, there are many millions of 27-nucleotide piRNAs involved in the discrimination of sense and nonsense, and ultimately there are steps that detect and correct error that has crept into this system during post-zygotic development.

We use a lot of computational resources and tools because we're doing comparative genomics not just across species but even within a single cell. A single cell in *Oxytricha* has two genomes; And so, to understand the genome architecture of just that one cell, we have to understand and decrypt the genome of both its germline nucleus, which is the archive of all of the information, and the somatic rearranged nucleus, which is the one that has expressed and has captured all the relevant information out of the archive.

Another angle that inspired me to move into this system, besides being awestruck by it, was an analogy to computation. There are parallels in this system to processes of both encryption and decryption, with evolution supplying the encryption of information in DNA, followed by a developmental decryption algorithm that restores the coding capacity of its genome and generates useful chromosomes. Our goal is to reverse engineer how the cell can execute these algorithmic ways of processing its genome. Most genomes don't require nearly as much processing as *Oxytricha*'s does.

Q: *What is your group working on now?*

A: On the computational front we're really exploring comparative genomes, on both developmental and evolutionary time-scales. We have a good understanding of the genome architecture and how complex it is in *Oxytricha,* but from the evolutionary perspective, even if this genome is a Rube Goldberg-like device, the question is how it got that way. So, to understand how this came into being, we have to crawl back on the evolutionary tree and look at antecedents or earlier diverged representatives of life on our planet that are a little bit simpler than *Oxytricha*. We're using a lot of the methods that are on the horizon for tools for genome sequencing to probe these other microbial eukaryotes to try to figure out both how and when *Oxytricha*'s genome became scrambled, and became so highly complex.

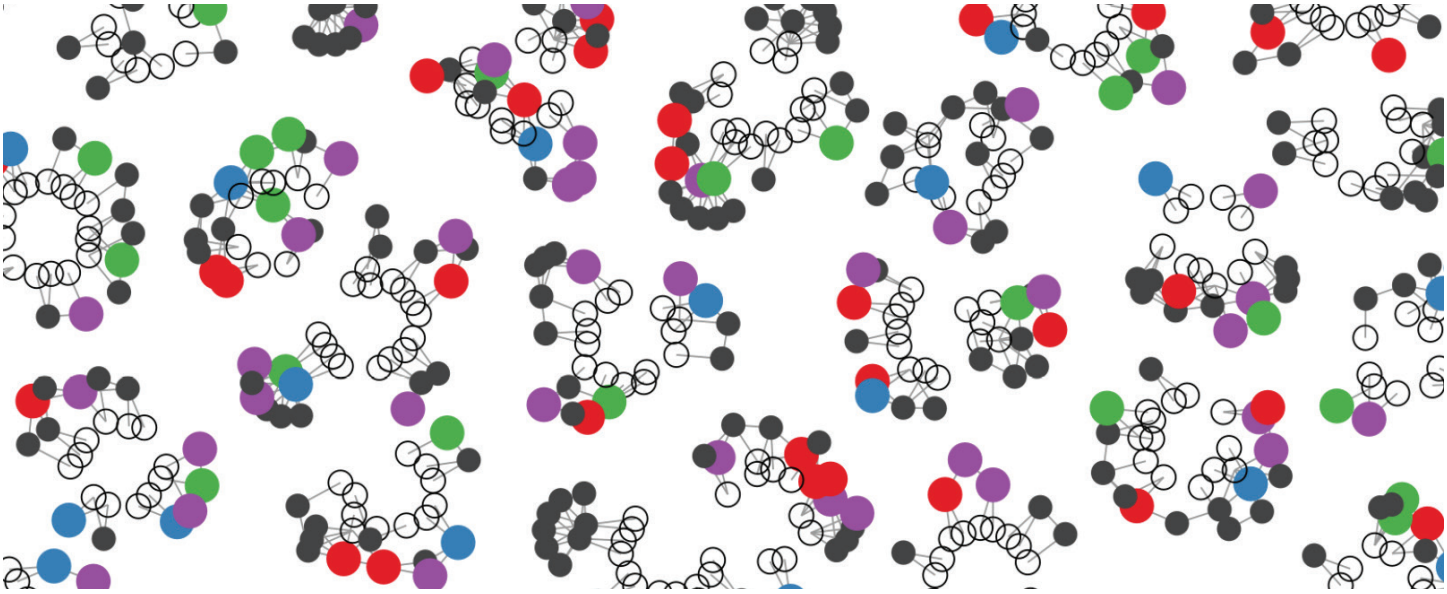
—Melanie A. Farmer

REFERENCES:

Nowacki M, Vijayan V, Zhou Y, Schotanus K, Doak TG, Landweber LF. *RNA-mediated Epigenetic Programming of a Genome-Rearrangement Pathway.* Nature. 2008 Jan 10; 451(7175): 153-8.

Fang W, Wang X, Bracht JR, Nowacki M, Landweber LF. *Piwi-Interacting RNAs Protect DNA Against Loss During Oxytricha Genome Rearrangement.* Cell. 2012 Dec 7; 151(6): 1243-55.

Electronic Health Record Analysis Shows Which Diseases Run in Families



Familial relationships inferred from electronic health records can be used to study the genetics of diseases. Each subgraph in this image is a family reconstructed from EHR data: Each node represents an individual and the colors represent different health conditions. (Image courtesy of Dr. Nicholas Tatonetti)

Acne is highly heritable, passed down through families via genes, but anxiety appears more strongly linked to environmental causes, according to a recent study that analyzed data from millions of electronic health records to estimate the heritability of hundreds of different traits and conditions.

The findings, published May 17, 2018, in *Cell* by researchers at Columbia University Irving Medical Center and NewYork-Presbyterian could streamline efforts to understand and mitigate disease risk—especially for diseases with no known disease-associated genes.

"Knowledge of a condition's heritability—how much the condition's variability can be attributed to genes—is essential for understanding the biological causes of the disease and for precision medicine," says study co-leader Nicholas Tatonetti, PhD, the Herbert Irving Assistant Professor of Biomedical Informatics at Columbia University Vagelos College of Physicians and Surgeons and faculty of the Department of Systems Biology. "It is clinically useful for estimating disease risk, customizing treatment, and tailoring patient care."

> "Knowledge of a condition's heritability…is essential for understanding the biological causes of the disease and for precision medicine."—*Dr. Nicholas Tatonetti*

But estimating heritability usually involves difficult and time-consuming studies of family members, especially twins.

Instead, Dr. Tatonetti and his colleagues thought heritability could be estimated more easily by using data that is routinely included in hospitals' electronic health records. Upon admission, patients are usually asked to provide emergency contacts, often family members who are also patients at the same hospital. "It occurred to us that this information could be used to infer family relationships and, combined with each patient and each contact's health data, give us heritability estimates faster and less expensively than traditional methods," Dr. Tatonetti says.

In the current study, the researchers analyzed data from 5.5 million electronic health records of patients and their emergency contacts at three academic medical centers: NewYork-Presbyterian/Columbia University Irving Medical Center, NewYork-Presbyterian/Weill Cornell Medical Center, and Mount Sinai Health System. To protect privacy, patient and contact identities were removed from the data before the information was provided to the researchers.

They used algorithms to infer 7.4 million family relationships among patients and contacts and then analyzed the incidence of some 500 different traits and conditions reported in the electronic health records to generate heritability estimates. "One algorithm identified the family relationships and a second computed heritability estimates for every available trait," says study co-leader David K. Vawdrey, PhD, assistant professor of biomedical informatics at Columbia University Vagelos College of Physicians and Surgeons and vice president of the Value Institute at NewYork-Presbyterian Hospital.

The researchers' heritability estimates were similar across all three medical

centers and were consistent with previously published estimates. For many of the conditions, however, heritability had never been estimated, and researchers found a few surprises. HDL cholesterol is significantly more heritable than LDL cholesterol, even after accounting for the use of lipid-lowering statin medications. Respiratory diseases in general appear more heritable among African-Americans, and sinus infections are highly heritable across all populations studied.

"The one about sinus infections surprised me personally," says Dr. Tatonetti. "My family has a lot of oral history about being predisposed to sinus infections. I didn't really believe it before, but this analysis may change my mind!"

The approach also promises to diversify the study of heritability. "Many heritability studies have focused on very specific populations, usually white Europeans," says lead author Fernanda Polubriaginof, a PhD candidate in biomedical informatics at Columbia. "Because we used data from a very diverse group of patients in New York City, we were able to stratify disease risk for different ethnicities in ways that hadn't been done before."

An artistic representation of the digital transformation process of paper medical records that enables this new study by the Tatonetti Lab. (Image courtesy of Dr. Nicholas Tatonetti)

The study was funded by the National Institutes of Health, the Herbert Irving Scholars Award, the AWS Cloud Credits for Research program, and the Open Science Grid (which is supported by the National Science Foundation and the U.S. Department of Energy's Office of Science).

—Reprinted with permission by Columbia News

REFERENCES:

Polubriaginof FCG, Vanguri R, Quinnies K, Belbin GM, Yahi A, Salmasian H, Lorberbaum T, Nwankwo V, Li L, Shervey MM, Glowe P, Ionita-Laza I, Simmerling M, Hripcsak G, Bakken S, Goldstein D, Kiryluk K, Kenny EE, Dudley J, Vawdrey DK, Tatonetti NP. *Disease Heritability Inferred from Familial Relationships Reported in Medical Records.* Cell. 2018 Jun 14;173(7):1692-1704.e11.

Systems Biology Postdoc Suying Bao Named Precision Medicine Fellow

Suying Bao, a postdoctoral research scientist in the laboratory of Dr. Chaolin Zhang, has been named an inaugural Precision Medicine Research fellow by Columbia's Irving Institute of Clinical and Translational Research. The two-year fellowship aims to train postdocs to use genomics and complex clinical data to improve personalized and tailored clinical care and clinical outcomes.

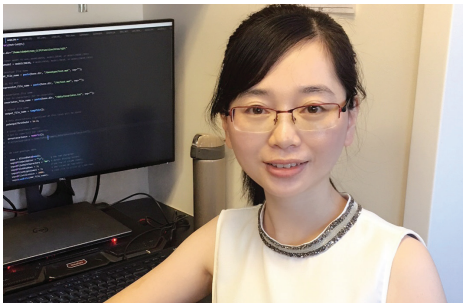
This fellowship "will provide me with more opportunities to translate my findings from basic science research into clinical application," says Bao, "and pave my way towards an independent researcher in this field."

Bao's expertise lies in RNA regulation at the interface of systems biology, ranging from the specificity of protein-RNA interaction to function of specific splice variants. RNA regulation is critical in proper cellular function; gaining deeper insights into this complex molecular mechanism will promote the development of precision medicine therapies.

In this project, Bao is aiming to develop new approaches to identify causal noncoding regulatory variants (RVs) modulating post-transcriptional gene expression regulation, such as RNA splicing and stability. "A majority of genetic variants associated with human diseases reside in noncoding genomic regions with regulatory roles," notes Bao. "Thus, elucidating how these noncoding regulatory variants contribute to gene expression variation is a crucial step towards unraveling genotype-phenotype relationships and advancing precision medicine for common and complex diseases."

To identify these RVs, she will leverage massive datasets of high-throughput profiles of gene expression and protein-RNA interactions generated from large cohorts of normal and disease human tissues and cell lines by multiple consortia, such as ENCODE, GTEx and CommonMind, and develop innovative computational methods of data mining.

This is the first year the Precision Medicine Research fellowship has been awarded. The two-year program will include required lectures in precision medicine as well as coursework in systems biology, genomics, statistics, ethics and/or medical informatics. Bao joined the Zhang lab in 2017 after completing her PhD in genetics and bioinformatics at the University of Hong Kong. She received her BSc in bioinformatics from Harbin Medical University.



Suying Bao

The Zhang Lab in the Department of Systems Biology at Columbia concentrates on the study of the nervous system and its underlying molecular mechanisms. The group focuses on the function of post-transcriptional gene regulation, in particular a level of molecular regulation called alternative RNA splicing, in the nervous system.

Around the Department, 2017-2018

Selected Grants and Awards

Cory Abate-Shen, PhD, has received a five-year grant from the National Cancer Institute for "Preclinical Analyses of Advanced Prostate Cancer in Genetically Engineered Mice".

Inaugural Chan Zuckerberg Initiative grants, which support the global Human Cell Atlas effort, were awarded to **Andrea Califano**, Dr, **Raul Rabadan,** PhD and **Peter Sims,** PhD.

Harmen Bussemaker, PhD, and **Tuuli Lappalainen,** PhD, received an inaugural Roy and Diana Vagelos Precision Medicine Pilot award for "Elucidating the tissue-specific molecular mechanisms underlying disease associations through integrative analysis of genetic variation and molecular network data". Dr. Bussemaker was the keynote lecturer at EPFL/ETHZ summer school on Shaping the Future of Bioengineering, Davos, Switzerland. Dr. Lappalainen has also received a new grant from the National Heart, Lung, and Blood Institute for "Integration of Omics Data to Improve Interpretation of Genetic Risk Variants in Lung Disease".

Andrea Califano, Dr, has received new grants from the Price Family Foundation targeting gastric and esophageal cancer and the Lustgarten Foundation to test a new precision medicine approach to the treatment of metastatic pancreatic cancer. He also received a new five year grant from Hyundai Hope on Wheels for pediatric cancer research.

Oliver Hobert, PhD, has received a new grant from the National Institute of Neurological Disorders and Stroke for "A Nervous System-Wide Analysis of C. Elegans Homeobox Gene Function".

Brian Ji, an MD/PhD student in the Vitkup Lab, won the award for Best Oral Presentation at the Biennial Integrated Retreat held July 22-24, 2018, at the Glen Cove Mansion in Long Island.

Laura Landweber, PhD, has received a five-year grant from the National Institute of General Medical Sciences for "Understanding Complex Gene Editing Systems and RNA Biology in Oxytricha ."

Kam Leong, PhD, has been awarded a new grant by the National Center for Advancing Translational Sciences for "Integrated Microphysical System of Cerebral Organoid and Blood Vessel for Disease Modeling and Neuropsychiatric Drug Screening".

Amir Momen-Roknabadi, postdoctoral research scientist in the Tavazoie Lab, has received an NIH F32 Fellowship award.

Molly Przeworski, PhD, received the Distinguished Columbia Faculty Award for exceptional teaching. The annual award recognizes faculty for outstanding scholarship, University citizenship and professional involvement.

Raul Rabadan, PhD, has been awarded a Philip A. Sharp Innovation in Collaboration award from Stand Up to Cancer. The award, with collaborator Dr. Dan Landau of Weill Cornell Medicine, is for "Cupid-seq—high throughput transcriptomic spatial mapping of immune-tumor interactions in the micro-environment."

Columbia University Irving Medical Center recently joined Project GENIE, a consortium by the American Association for Cancer Research that is building an international cancer registry through data sharing. From DSB, Project GENIE is being co-led by **Raul Rabadan**, PhD, with collaborators **Cory Abate-Shen,** PhD, and **Andrea Califano,** Dr.

Michael Shen, PhD, is the recipient of the JPB Foundation Bladder Cancer Research Innovation award by BCAN, the Bladder Cancer Advocacy Network, for his work, "Modeling bladder cancer metastasis using human patient-derived tumor organoids".

Yufeng Shen, PhD, has received a new five-year grant from NICHD to study the genetics of birth defect. He has also received two five-year grants for "Integrating cancer genomics data in genetic studies and diagnosis of developmental disorders", from NIGMS, and "Developmental Mechanisms of Trachea-Esophageal Birth Defects", from NICHD. Dr. Shen is also co-PI of two X01 funded programs by the NIH Gabriella Miller Kids First Pediatric Research program.

Peter Sims, PhD, has received a five-year grant from the National Institute of Neurological Disorders and Stroke for "Single-Cell Analysis of the Infiltrative Margins of Glioblastoma and Post-treatment Recurrence."

Milan Stojanovic, PhD, has been awarded a new grant from the National Institute of Biomedical Imaging and Bioengineering for "Graft Engineering of Allogeneic Hematopoietic Stem Cell Products with Molecular Cascades".

Nicholas Tatonetti, PhD, has been awarded a five-year grant from the National Cancer Institute for "Advanced Development and Dissemination of EMERSE for Cancer Phenotyping from Medical Records". Dr. Tatonetti was also named Director of Clinical Informatics at the Institute for Genomic Medicine.

Dennis Vitkup, PhD, and **Harris Wang,** PhD, are co-PIs on a new NIH R01 for the study, "Ecological dynamics and metabolic interactions in the gut microbiome across space and time".

Harris Wang, PhD, has been named a 2018 Schaefer Research Scholar and received funding for a project to systematically determine new mechanisms by which specific members of the human microbiome metabolize and alter drugs and pharmaceuticals. He also received new grants from the NIH, Defense Advanced Research Projects Agency, the DoD University Research Instrumentation Program and the Burroughs Wellcome Fund.

Sebastien Weyn, PhD, a former member of the Chaolin Zhang Lab and DSB graduate, received the Titus M. Coan Prize for Excellence in Research. Weyn was recognized for outstanding basic cell and molecular research.

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

Andrew Blumberg, *Visiting Faculty*
Tal Korem, *Assistant Professor*
Laura Landweber, *Professor*

PHD GRADUATES

Congratulations to our Recent Grads!

Jonathan Chang (Vitkup lab)
Ding Hongxu (Califano lab)
Judith Kribelbauer
(Mann and Bussemaker labs)
Erik Ladewig (Rabadan lab)
Chioma Madubata (Rabadan lab)
Sebastien Weyn (Zhang lab)

NEW IN DSB ADMINISTRATION

Ndola Carlest, *Grants & Finance*
Melanie A. Farmer, *Communications*
Lila Lande, *Scientific Administrator* (Califano lab)
Bryant Mota, *Information Technology*
Maria Neagoe, *Department Administrator*
Tatiana Suero, *Grants & Finance*

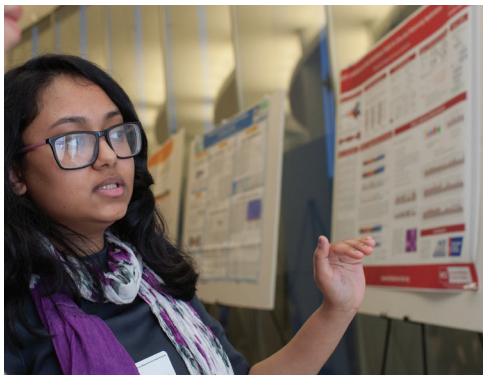
Gallery

The Cancer Genomics and Mathematical Data Analysis Symposium, co-hosted by the National Cancer Institute centers at Columbia, Cornell University and Memorial Sloan Kettering, featured talks on cancer precision medicine, the evolutionary dynamics of cancer and response to treatment, cancer heterogeneity and identifying cancer vulnerabilities on an individual cell basis. (Photos by Lydia Lee Photography)

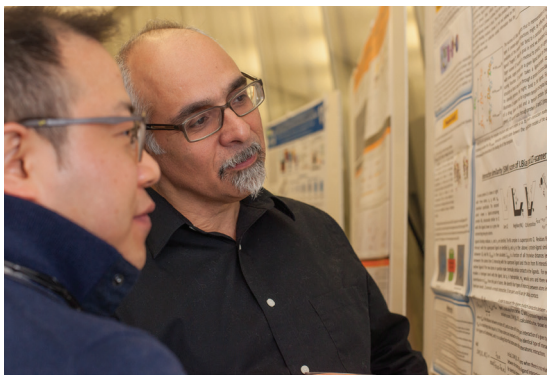
Dr. Raluca Gordon, assistant professor of bioinformatics at Duke University.

Dr. Antonio Iavorone, MD (left, co-director, the Center for Topology and Cancer Evolution and Heterogeneity) with Dr. Peter Sims (Systems Biology).

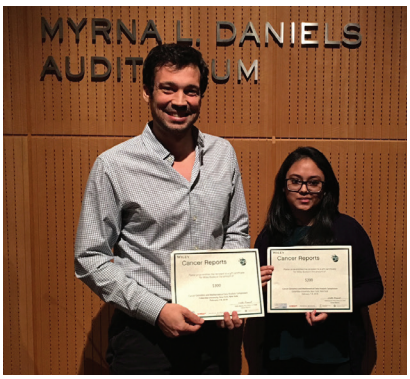
Michael Stokes (left) of the Stockwell Lab with Eugene Douglass of the Califano Lab.



Kamrun Begum of the Honig lab won second place prize in poster competition.

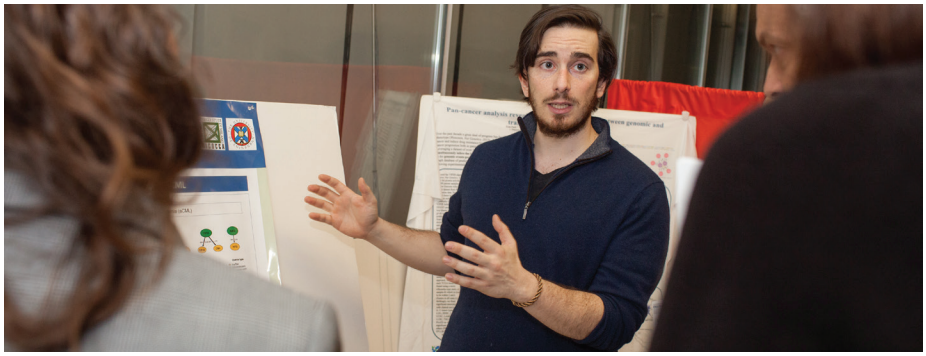


Dr. Aris Floratos (right), assistant professor of systems biology at Columbia, with researcher Howook Hwang of the Honig Lab.



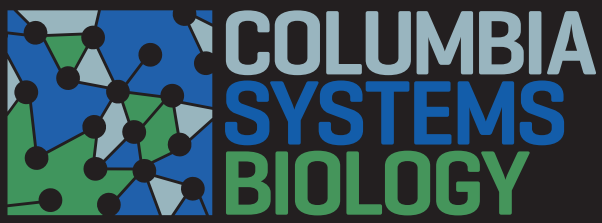
Poster prizewinners: Columbia University's Luis Arnes (left) pictured with Kamrun Begum.

Dr. Raul Rabadan, professor of systems biology at Columbia.



James Bannon of NYU's Courant Institute, a poster prizewinner.

COLUMBIA UNIVERSITY
IRVING MEDICAL CENTER



Columbia University Department of Systems Biology
Irving Cancer Research Center
1130 St. Nicholas Avenue
New York, NY 10032

Melanie A. Farmer
Editor
mf2362@cumc.columbia.edu

To learn more about our research and programs,
visit **systemsbiology.columbia.edu.**