Research Highlights
2019-2020

Addressing the Global Pandemic
New Tumor-Specific Molecular Interaction Maps
Capture Complexity of Cancer Networks
Dynamics of Gut Bacteria Follow Ecological Laws
Ancient Part of Immune System May Underpin Severe COVID
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By early spring, the highly contagious novel coronavirus ripped through communities and challenged medical resources, particularly in epicenters like New York City. The surge in positive cases at the time summoned clinical communities to the front lines of the pandemic, and simultaneously it galvanized the scientific community to quickly collaborate across multiple disciplines and problem-solve a cure.

Several faculty in the Department of Systems Biology rapidly came together to address the novel SARS-CoV-2 virus. There has since been an incredible outpouring of rapid response by academic researchers to aid in a cure or uncover the fundamental biology driving the novel coronavirus.

“This is an unprecedented time in history, when scientists from all fields who are not necessarily experts in virology are forming teams with exceptional complementary talent to address one of the greatest challenges our society has ever faced,” said Systems Biology Department Chair Andrea Califano, Dr. at the time. “The current situation creates a unique and unprecedented commitment to a shared goal without institutional, geographic, or expertise boundaries.”

A sample of COVID-19 research from systems biology faculty:

**CRISPR-based Therapeutics**

Coronavirus genomes comprise single-stranded RNA, and the novel coronavirus, SARS-CoV-2 that leads to COVID-19, is part of a family of viruses that include SARS and MERS—two devastating infectious diseases that surfaced in the last 20 years. Xuebing Wu, PhD, assistant professor of systems biology, is an expert in RNA research and studies RNA-centric gene regulation in mammalian cells. He is working on developing a CRISPR-based approach for killing the SARS-CoV-2 virus, and potentially also the infected surrounding cells.

CRISPR is a natural bacterial immune system that scientists have begun to use as a revolutionary tool to alter genomes. Dr. Wu and his collaborators have already developed a similar CRISPR-based technique to eliminate cancer cells, and intend to apply this method to target COVID-19. The hope is that this research can aid in the speedier development of a therapeutic, not just for this novel strain but for future variants of SARS-CoV-2.

**Data-driven Solutions**

In a study published in *Cell*, Sagi Shapira, PhD, and Barry Honig, PhD, faculty in the Department of Systems Biology, developed P-HPSTer, a computational method that leverages the supercomputing infrastructure at Columbia to identify key interactions between all human-infecting viruses (including coronaviruses) and the cells they infect. In addition to studying vaccine design, they are using the information to identify FDA-approved drugs that may be repurposed and immediately deployed. In a study published in *Cell Systems*, Drs. Shapira and Honig applied similar methods to map virus-encoded mimics of host protein structures across thousands of viruses and hosts that are part of Earth’s virome. They identified, among their findings, over 150 human proteins that are mimicked by coronaviruses, providing clues about cellular processes driving the pathogenesis of the ongoing COVID-19 pandemic. In a study published in *Nature Medicine*, Dr. Shapira collaborated with Nicholas Tatonetti, PhD, associate professor of systems biology and of biomedical informatics, to leverage these clues in an analytical and computational framework to demonstrate that genetic and functional dysregulation in immune complement and coagulation pathways are risk factors of morbidity and mortality associated with COVID-19. Their ongoing efforts are extending these approaches to identify key genetic and functional determinants of disease susceptibility in the context of other emerging pathogens. (See related article on page 9)

Andrea Califano, Dr., is a pioneer in the field of systems biology and founding chair of Columbia’s Department of Systems Biology. He has developed sophisticated algorithms to identify key master regulator proteins in tumors and enable the prioritization of FDA-approved drugs that could treat and kill cancer in various tumor types. He is now applying these validated methods to study the biology of coronaviruses and their ability to hijack the machinery of human host cells.

Dr. Califano and his collaborators have already analyzed gene expression profile data generated from SARS-CoV-infected and mock-infected epithelial cells to identify the proteins responsible for maintaining the transcriptional state of infection response. (SARS-CoV is closely related to the current novel coronavirus SARS-CoV-2 and produces a similar response in patients.) They’ve applied the computational method, OncoTreat, developed by the Califano lab, to identify several promising drugs to potentially treat these infections, including drugs used to treat rheumatoid arthritis as well as several kinase and transport protein inhibitors. Dr. Califano and his
team have now generated gene expression profiles from nasopharyngeal cells of COVID-19 infected and negative control and are repeating the analysis. They are also collaborating with Dr. Wellington Cardoso, professor of medicine at Columbia University, to screen a larger number of drugs in physiologically relevant cells, beyond those selected for oncology, and to validate their ability to revert the effect of the virus on the host.

Dr. Califano also is collaborating with Dr. Sagi Shapira to use these gene expression profiles to identify RNA-based biomarkers from nasal swab tests that can predict the need for hospitalization and intensive care. The researchers will analyze patient cell samples from swab tests by using rapid-turnaround, next-generation sequencing methods that capture both the infection status and complex immune response profiles. Using Dr. Califano’s computational methods, the researchers hope to identify master regulator-based markers to predict clinical outcomes based on the transcriptional profiles of easily accessible samples. The hope is to be able to rapidly inform doctors how to best triage COVID-19 patients upon diagnosis.

COVID-19 Genomics

Raul Rabadan, PhD, professor of systems biology and director of the Program for Mathematical Genomics at Columbia, is an expert in uncovering patterns of evolution in biological systems—in particular, RNA viruses and cancer. He has developed computational methods to study cancer genetics and to elucidate biological understanding of how tumors evolve over time, in such complex cancers as leukemia, pancreatic ductal adenocarcinoma and glioblastoma. Dr. Rabadan and his collaborators are now applying these methods to assess individuals’ predispositions to COVID-19. Why do some patients who test positive for COVID-19 experience severe symptoms and complications—some cases their illness results in death—while other COVID positive patients do not?

Dr. Rabadan and his group are taking a deep dive into the genetics of COVID-19, with the hope of identifying biomarkers of COVID-19 severity and that can lend to immediate management of patients at risk, including cancer patients. They are already leveraging their cancer genomics expertise and algorithms to analyze the UK Biobank data (comprising 500,000 individuals, with genetic and clinical data) as well as transcriptomic data from COVID-19 patients. “This effort will help us to better understand the SARS-CoV-2 mechanism of action,” says Dr. Rabadan, “and to define risk groups with greater precision, in particular those with other conditions.”

Exploring Untapped Data

Nicholas Tatonetti, PhD, associate professor of systems biology, has teamed up with colleagues Noemie Elhadad and Lena Mamykina in biomedical informatics, and collaborators in urban policy and affairs and infectious disease on a data-collection app and website for tracking the impact of the COVID-19 pandemic in New York City.

CovidWatcher, which launched in April works as a crowd-sourcing research platform that surveys users—both healthy and potentially exposed to COVID-19—about their exposure to the virus, symptoms, and access to medical care. The data will be used not only as a decision tool to advise patients if they should seek help but also to enable healthcare officials to deploy resources at New York City “hot spots”, or where they are needed most. The ultimate goal is to prevent future spread.

“There has been no ability yet to track and obtain this kind of data from New Yorkers,” says Dr. Tatonetti, who also directs clinical informatics at Columbia’s Institute for Genomic Medicine. “Our live surveys, for instance, could help find out where New Yorkers are in the city that are having symptoms, even before they may or not may become infected with the virus. Then, we can redistribute this data to hospital sites to help them prepare for what’s coming their way.”

Dr. Tatonetti and other faculty across Columbia have been quickly transforming their research to address COVID-19. The collaborative energy from the scientific community has been “incredible to witness,” he says, underscoring that right now, research is moving quickly but there is still very much a sense of a shared vision and goals.

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Systems Biology

COVID Volunteers

Miles Richardson, DSB graduate student and early CRAC team organizer

At the peak of the COVID-19 pandemic, four members of the Systems Biology Department were especially active in the Columbia-wide volunteer project, Columbia Researchers Against Coronavirus or CRAC. They were graduate student Nick Giangreco, postdoctoral research scientist Amir Momen-Roknabadi, postdoctoral research scientist Panos Oikonomou, and graduate student Miles Richardson.

Richardson says his main role as chief organizational officer of the group was searching for and finding problems, and fixing them. “The progress we make as scientists,” he says, “is often abstract and indirect, divorced from the society that we serve. So I jumped at this opportunity to help—which ended up dominating the next three months of my life.”

Giangreco was the data and analytics lead on a global effort to design an open-source tool to support people affected by COVID-19. “The project,” he says, “symbolizes the connectedness of people and shared experiences, the urge to help out our neighbors in need, and the amazing ability of smart people to put their talents and skills together for the common good.”
Through cancer researchers have made considerable headway in elucidating signaling and regulatory pathways, current representations fail to capture the full complexity of the mechanisms that mediate the effects of both genetic and pharmacological perturbations. More specifically, prior efforts to identify signaling and regulatory pathways do not capture their cross-tissue differences (context-dependence), are based largely on interactions reported in the literature, and do not effectively reflect their role in mediating oncoprotein-specific signals. Some researchers have recently begun to incorporate cell line-, tumor-, or tissue-specific information in efforts to produce findings that are context-specific, but comprehensive, proteome-wide depictions of human interactomes across different tissue contexts remain elusive.

In a paper published in *Nature Biotechnology* on Sept. 14, 2020, Andrea Califano, Dr, chair of Systems Biology; Diana Murray, PhD, research scientist in Systems Biology; and Barry Honig, PhD, professor of Systems Biology, and their co-authors propose a fundamentally different representation of the signaling and regulatory machinery needed to modulate the function of a specific protein of interest in a specific tissue context, i.e., a protein mechanism of action. This novel representation is called a signaling map, or SigMap.

The paper presents OncoSig, an integrative machine learning (ML) framework for the systematic protein-centric reconstruction of tumor-specific SigMaps. The SigMaps reported are centered on virtually all known oncoproteins and contextualized to more than 20 tumor contexts. OncoSig is trained on integrated information derived from predicted physical protein-protein interactions, inferred from 3D structural data; and transcriptional and post-transcriptional interactions, from gene-expression and mutational profiles in large-scale repositories such as The Cancer Genome Atlas (TCGA).

The researchers first generated a KRAS-specific SigMap for lung cancer (the KRAS oncogene is commonly mutated in lung cancer). The SigMap not only included known KRAS interactors reported in published pathways, but also identified many novel synthetic lethal proteins that were subsequently validated in 3D spheroid models at a validation rate exceeding 80%; it also identified crosstalk with Rab and Rho pathway proteins. OncoSig generates a single integrated score that represents the probability that a protein belongs to a specific SigMap. Using lung adenocarcinoma as an example, of the 40 highest-scoring proteins predicted in the KRAS SigMap, 20 were already known, and 16 of the remaining 20 were experimentally validated. “This is an extraordinary validation rate,” says Dr. Califano.

SigMaps might also be used to identify pharmacologically accessible candidate targets for many mutated oncoproteins, including KRAS, thus providing a valuable tool for guiding hypothesis-based studies to validate their disease-related relevance.

“This is fundamentally a new methodology,” says Dr. Califano, “and its usefulness should extend well beyond cancer. Pathways and networks are central to how cells recognize one another and communicate. One reason we are more advanced in dealing with cancer than with, say, Alzheimer’s disease, is that the cells of other diseases don’t proliferate. It’s much easier to culture cancer cells—proliferating is what they like to do. But SigMaps can also be constructed for proteins unrelated to cancer, greatly expanding the value of the algorithm.”

“Advances in ML methodology have enabled us to integrate these very different sources of input,” says Dr. Honig. “The complexity of SigMaps is daunting, but biology is complex, and sometimes it is important to embrace that complexity.”

**REFERENCE**

Dynamics of Gut Bacteria Follow Ecological Laws

The seemingly chaotic bacterial soup of the gut microbiome is more organized than it first appears and follows some of the same ecological laws that apply to birds, fish, tropical rainforests, and even complex economic and financial markets, according to a paper published in *Nature Microbiology* by systems biology researchers.

One of the main challenges facing researchers who study the gut microbiome is its sheer size and amazing organizational complexity. Many trillions of bacteria, representing thousands of different species, live in the human intestinal tract, interacting with each other and the environment in countless and constantly changing ways.

The study’s discovery of multiple principles of gut bacterial dynamics should help researchers to understand what makes a gut microbiome healthy, how it may become perturbed in disease and unhealthy diets, and also suggest ways we could alter microbiomes to improve health.

**Gut microbiome dynamics remain poorly understood**

Although current DNA sequencing technologies make it possible to identify and track bacteria in the gut over time, “the biological processes governing the short- and long-term changes in the gut’s microbiome remain very poorly understood,” says the study’s senior author, Dennis Vitkup, PhD, professor of systems biology and of biomedical informatics at Columbia University Vagelos College of Physicians and Surgeons.

As a first step in identifying the factors that describe microbial communities in the gut, Dr. Vitkup and his co-authors, graduate students Brian W. Ji and Ravi U. Sheth and research scientists Purushottam Dixit and Konstantine Tchourine, looked for mathematical relationships describing dynamical changes of the gut microbiome of four healthy people followed for a year. They also analyzed microbiome data obtained for mice fed either high fiber or high fat diets every day for several weeks.

With this data, the researchers explored statistical connections between various aspects of microbiome dynamics, such as fluctuations and abundances of various bacteria over time, or the average times different microbes continuously reside in the human gut. “Up to now, it has been an open question whether there are any natural laws describing dynamics of these complex bacterial communities,” Dr. Vitkup says.

**Chaotic fluctuations follow statistical laws**

As expected, they discovered large fluctuations in the composition and daily changes of the human and mouse gut microbiomes. But strikingly, these apparently chaotic fluctuations followed several elegant ecological laws.

“Similar to many animal ecologies and complex financial markets, a healthy gut microbiome is never truly at equilibrium,” Dr. Vitkup says. “For example, the number of a particular bacterial species on day one is never the same on day two, and so on. It constantly fluctuates, like stocks in a financial market or number of animals in a valley, but these fluctuations are not arbitrary. In fact, they follow predictable patterns described by Taylor’s power law, a well-established principle in animal ecology that describe how fluctuations are related to the relative number of bacteria for different species.”

Other discovered laws of the gut microbiome also followed principles frequently observed in animal ecologies and economic systems, including the tendency of gut bacteria abundances to slowly but predictably drift over time and the tendency of species to appear and disappear from the gut microbiome at predictable times.

“It is amazing that microscopic ecological communities—which are about six orders of magnitude smaller than macroscopic ecosystems analyzed previously—appear to be governed by a similar set of mathematical and statistical principles,” says Dr. Vitkup.

**Laws allow identification of abnormal bacterial behavior**

These universal principles should help researchers to better understand what processes govern the microbial dynamics in the gut. Using the statistical laws, the Columbia researchers were able to identify particular bacterial species with abnormal fluctuations. These wildly fluctuating bacteria were associated with documented periods of gut distress or travel to foreign countries in humans providing data for the study. Thus, this approach may immediately allow researchers to understand and identify which specific bacteria are out of line and behave in a potentially harmful fashion.

Using mice data, the researchers also observed that microbiomes associated with unhealthy high fat diets drift in time significantly faster compared with microbiomes feeding on healthier high fiber diets. This demonstrates that ecological laws can be applied to understand how various dietary changes may affect and perhaps alleviate persistent microbiome instabilities.

**Gut microbiome as miniature ecological laboratory**

The study by Columbia researchers also opens an exciting opportunity to use the gut microbial communities as a model system for exploring general ecological relationships. “Ecologists have debated for years why and how these natural ecological laws arise, without any clear answers,” says Dr. Vitkup. “Previous ecological research has been mostly limited to observational studies, which can take decades to perform for animals and plants. And some key experiments, such as additions or removal of particular species simply cannot be performed.”

The gut microbiome, in contrast, provides an ideal miniature laboratory, where researchers could easily manipulate different variables, such as the number and composition of microorganisms, and then explore various aspects of environmental influences. “One of our next goals is to understand the origin of these general ecological laws using gut microbiota,” Dr. Vitkup says.

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REFERENCES

Network-Based Approach for Predicting Response to Cancer Treatment

Histone deacetylases (HDACs) play a central role in regulating gene expression, by modulating how tightly histones bind chromatin. In cancer, their aberrant activation can lead to the repression of tumor-suppressing genes. Thus, one strategy for treating cancer is the use of HDAC inhibitors, which change the epigenetic state of the cell and re-enable tumor suppression programs. Clinical use of pan-HDAC inhibitors has been limited, however, due to their toxicity, and researchers have been seeking to develop more selective inhibitors that target individual HDACs. In addition, otherwise promising inhibitors have had disappointing clinical results for lack of predictive biomarkers to identify those patients in a cancer cohort most likely to respond.

In a prior collaboration, Drs. Andrea Califano, Jose Silva, and Jiyang Yu predicted that the HDAC6-specific inhibitor ricolinostat would be effective in a subset of breast cancer patients identified by the aberrant activity of this protein (Putcha et al., 2015), as measured by VIPER, an algorithm developed in the Califano lab (Alvarez et al., 2016). Now, in a paper published online on medRxiv on April 28, 2020 (Zeleke et al. 2020) and currently in review, Drs. Califano, Kevin Kalinsky, Yu, and Silva report the results of the first clinical study of ricolinostat in breast cancer, showing remarkable agreement between patient clinical response and HDAC6 activity in their tumors, as also measured by VIPER.

A focus of Dr. Califano’s research program at Columbia University Irving Medical Center has been the identification and characterization of master regulator proteins in cancer. These are proteins that coordinate the regulatory programs that control cancer establishment and progression. As such, they are ideal targets for pharmacological intervention. Until recently, most cancer research has focused on mutations in individual cancer-causing genes. Because master regulators are rarely mutated, genomics is not an efficient way to identify them. Instead, the Califano lab develops algorithms such as VIPER, which leverage the structure of regulatory networks to identify master regulators. Using VIPER, Dr. Califano’s lab has identified 24 master regulator modules whose activity is responsible for the vast majority of cancers represented in the Cancer Genome Atlas (TCGA).

“One oncologist still have to deal with the exceptionally large number of genetic mutation patterns that cause individual cancers,” says Dr. Califano, chair of the Department of Systems Biology. “These would potentially require thousands of distinct drugs. But by specifically targeting the master regulator modules, you may need only a few dozen drugs.” Indeed, Dr. Califano’s methodology has the potential not only to identify master regulators but to identify potential treatments to target them.

Prior to the clinical trial reported in this study, the Silva and Califano labs had identified HDAC6 as a master regulator of inflammatory breast cancer, a rare but highly aggressive form of the disease, as well as of an additional 30% of aggressive breast cancers. They did so using an algorithm that can quantify the activity of proteins, including HDAC6, in individual tumors. Furthermore, HDAC6 inhibitors were found to synergize with paclitaxel-based chemotherapy. The algorithm can now be used to assign an HDAC6 score to each patient, to determine the likelihood of their response to HDAC6 inhibitors—thus providing a much-needed predictive biomarker.

When analysis of approximately 3,000 primary human breast cancers showed that around 30% of them had high HDAC6 scores, the researchers designed the phase Ib clinical trial reported in this study to evaluate the safety of combining ricolinostat (an HDAC6 inhibitor) and nabpaclitaxel for treatment of patients with metastatic breast cancer. They found not only that the two agents could be safely combined, but that the patient’s HDAC6 score was highly effective in predicting progression-free survival following treatment with the two agents in HR+/HER2- cancers. Though the biomarker was available at the time the study was designed, the FDA required the study to be conducted across the entire spectrum of breast cancer, independent of HDAC6 activity. In this way, the potential value of the biomarker could be assessed retrospectively. Thus, though the aim of the trial was to study the effectiveness of breast cancer treatment with ricolinostat in combination with nabpaclitaxel, Dr. Califano and his colleagues were also able to determine that the HDAC6 score was highly predictive of clinical response.

“When Drs. Silva and Yu expanded the analysis to other cancers,” says Dr. Califano, “we found other types of tumors with high HDAC6 scores, including common malignancies such as prostate and colorectal cancer, as well as less common but highly lethal ones such as melanoma and glioblastoma. Thus, our methodology may help to extend the use of HDAC6 inhibitors to treat cancers other than breast.”

REFERENCES


Researchers have identified a genetic signature in localized prostate cancer that can predict whether the cancer is likely to spread, or metastasize, early in the course of the disease and whether it will respond to anti-androgen therapy, a common treatment for advanced disease. The new gene signature may also be useful for evaluating responses to treatment and for developing new therapies to prevent or treat advanced prostate cancer.

“If we could know in advance which patients will develop metastases, we could start treatments earlier and treat the cancer more aggressively,” says the study’s senior author, Cory Abate-Shen, PhD, chair of the Department of Molecular Pharmacology and Therapeutics, the Michael and Stella Chernow Professor of Urologic Sciences (in Urology), and professor of pathology & cell biology (in the Herbert Irving Comprehensive Cancer Center), and professor of systems biology at Columbia University Vagelos College of Physicians and Surgeons.

“Conversely, patients whose disease is likely to remain confined to the prostate could be spared from getting unnecessary therapy.”

The study was published in Nature Cancer.

Existing tests can’t identify aggressive cancers

Prostate cancer is the second-leading cause of cancer death among men in the United States; about 33,330 men are expected to die of the disease this year.

Most prostate cancers remain confined to the prostate and can be successfully managed by active surveillance or local therapy (mainly surgery or radiotherapy), with five-year survival rates above 99%. But once prostate cancer spreads, it is considered incurable, and five-year survival rates drop to approximately 30%.

“The problem is that with existing tests, it’s hard to know which cancers are which,” says the study’s lead author, Juan M. Arriaga, PhD, associate research scientist in molecular pharmacology and therapeutics at Columbia University Vagelos College of Physicians and Surgeons.

“We miss a lot of aggressive cancers that should have been treated earlier, and we overtreat some slow-growing cancers that probably would not have spread.”

New gene signature first identified in new mouse model

To identify a more accurate method of predicting advanced prostate cancer, the researchers first created a mouse model of prostate cancer that accurately reflects the human form of the disease, including how the cancer spreads to the bone, the tissue most often affected by prostate cancer metastases.

Using this first-of-its-kind mouse model, the researchers discovered that bone metastases have a different molecular profile than that of primary tumors. “By focusing on those differences, we were able to identify 16 genes that drive localized prostate cancer to metastasize,” Dr. Abate-Shen says.

16 genes predict metastasis in patients

The genetic signature, called META-16, was then tested on biopsies from several hundred patients with localized prostate cancer. The outcomes of those patients were blinded to the researchers.

The Columbia team found that META-16 was highly effective at predicting time to metastasis and response to anti-androgen therapy (which is used to suppress androgen, the male hormone, which promotes tumor progression).

The team is currently refining the test, which they then hope to evaluate in a prospective clinical trial.

In theory, META-16 could also be used to develop therapies against metastatic prostate cancer.

“The genes in our signature are not only correlated with metastasis, they appear to be driving metastasis,” Dr. Arriaga says. “That means that if we can suppress the activity of those genes, we might be able to prevent the cancer from spreading or at least improve outcomes.”

REFERENCE

Ancient Part of Immune System May Underpin Severe COVID

One of the immune system’s oldest branches, called complement, may be influencing the severity of COVID disease, according to a new study from researchers at the Vagelos College of Physicians and Surgeons at Columbia University Irving Medical Center.

Among other findings linking complement to COVID, the researchers found that people with age-related macular degeneration—a disorder caused by overactive complement—are at greater risk of developing severe complications and dying from COVID.

The connection with complement suggests that existing drugs that inhibit the complement system could help treat patients with severe COVID-19. The study, led by systems biology faculty Sagi Shapira, PhD, MPH, with Nicholas Tatonetti, PhD, was published in Nature Medicine.

The authors also found evidence that clotting activity is linked to COVID severity and that mutations in certain complement and coagulation genes are associated with hospitalization of COVID patients.

“Together, these results provide important insights into the pathophysiology of COVID-19 and paint a picture for the role of complement and coagulation pathways in determining clinical outcomes of patients infected with SARS-CoV-2,” says Dr. Shapira.

Findings stem from study of coronavirus mimicry

The idea to investigate the role of coagulation and complement in COVID-19 began with a sweeping survey of viral mimicry across all viruses on Earth—over 7,000 in all.

“Viruses have proteins that can mimic certain host proteins to trick the host’s cells into aiding the virus with completing its life cycle,” Dr. Shapira says. “Beyond the fundamental biological questions that we were interested in addressing, based on our previous work and the work of others, we suspected that identifying those mimics could provide clues about how viruses cause disease.”

Coronaviruses, the survey found, are masters of mimicry, particularly with proteins involved in coagulation and proteins that make up complement, one of the oldest branches of the human immune system.

Complement proteins work a bit like antibodies and help eliminate pathogens by sticking to viruses and bacteria and marking them for destruction. Unchecked, these systems can also be quite detrimental,” says Dr. Shapira.

“Together, these results provide important insights into the pathophysiology of COVID-19 and paint a picture for the role of complement and coagulation pathways in determining clinical outcomes of patients infected with SARS-CoV-2,” says Dr. Shapira.

Macular degeneration associated with greater COVID mortality

If complement and coagulation influence severity of COVID, people with pre-existing hyperactive complement or coagulation disorders should be more susceptible to the virus.

That led Drs. Shapira and Tatonetti to look at COVID patients with macular degeneration, an eye disease caused by overactive complement, as well as common coagulation disorders like thrombosis and hemorrhage.

Among 11,000 COVID patients who came to Columbia University Irving Medical Center with suspected COVID-19, the researchers found that over 25% of those with age-related macular degeneration died, compared to the average mortality rate of 8.5%, and roughly 20% required intubation. The greater mortality and intubation rates could not be explained by differences in the age or sex of the patients.

“Complement is also more active in obesity and diabetes,” Dr. Shapira says, “and may help explain, at least in part, why people with those conditions also have a greater mortality risk from COVID.”

People with a history of coagulation disorders also were at increased risk of dying from SARS-CoV-2 infection.

Coagulation and complement pathways activated

The researchers then examined how gene activity differed in people infected with the coronavirus.

That analysis revealed a signature in COVID-19 patients indicating that the virus engages and induces robust activation of the body’s complement and coagulation systems.

“We found that complement is one of the most differentially expressed pathways in SARS-CoV-2-infected patients,” says Dr. Tatonetti, who also is an associate professor of biomedical informatics. “As part of the immune system, you would expect to see complement activated, but it seems over and above what you’d see in other infections like the flu.”
Some coagulation and complement genes associated with hospitalization

More evidence linking severe COVID with coagulation and complement comes from a genetic analysis of thousands of COVID patients from the U.K. Biobank, which contains medical records and genetic data from half a million people.

The authors found that variants of several genes that influence complement or coagulation activity are associated with more severe COVID-19 symptoms that required hospitalization.

“These variants are not necessarily going to determine someone’s outcome,” Dr. Shapira says. “But this finding is another line of evidence that complement and coagulation pathways participate in the morbidity and mortality associated with COVID-19.”

Targeting coagulation and complement

Physicians treating COVID patients have noticed coagulation issues since the beginning of the pandemic, and several clinical trials are underway to determine the best way to use existing anti-coagulation treatments.

Complement inhibitors are currently used in relatively rare diseases, but at least one clinical trial is testing the idea with COVID patients.

“I think our findings provide a stronger foundation for the idea that coagulation and complement play a role in COVID,” Dr. Tatonetti says, “and will hopefully inspire others to evaluate this hypothesis and see if it’s something that can be useful for fighting the ongoing pandemic.”

Q&A: Raul Rabadan, PhD, and Understanding the Coronavirus

Raul Rabadan, PhD, is an expert in uncovering patterns of evolution in highly dynamic biological systems, including in complex diseases like cancer. As the author of Understanding Coronavirus, published by Cambridge University Press in June, Dr. Rabadan, who originally began his academic career in mathematical physics, has set out to provide readers an accessible overview that quells misinformation about the novel virus, its origin, causes, and spread.

Dr. Rabadan is professor of systems biology and of biomedical informatics. He directs Columbia’s Program for Mathematical Genomics of cancer and COVID-19 research. For instance, some of these genomic changes follow certain rules that can hopefully help us to develop better treatments or vaccines. Scheduled to be on sabbatical earlier this year, Dr. Rabadan instead remained quarantined with his family in New York City, shifting his attention to the new book and his own ongoing work in the genomics of cancer and COVID-19 research.

Q: You were early to pivot your cancer-focused research to address SARS-CoV-2. What motivated you to focus on the virus?

A: I have been working on viruses and cancers for the last 15 years. The relation between viruses and cancers is fascinating. Around 20% of all cancers in the world are related to viruses, including some lymphomas, nasopharyngeal carcinomas, cervical and liver cancers, among many others. Many fundamental discoveries about the mechanisms of oncogenesis have been found through their relation with viruses.

Coronaviruses have not been linked to cancers but cancers and viruses share fundamental and abstract principles. They are both very fast-evolving systems and this evolution can be read through changes in their genomes. These changes follow certain rules that can be uncovered and modeled with the right set of approaches. Understanding these rules can hopefully help us to develop better ways of combating the associated diseases. For instance, some of these genomic changes in cancers and viruses could be associated

REFERENCES


to resistance to therapy. Reading and interpreting these changes could help to optimize therapeutic approaches.

Q: How does your expertise in cancer, bioinformatics, and systems biology dovetail with virology research?
A: When I came to Columbia in 2008 I was very active in trying to understand the origins of pandemic viruses, mostly influenza pandemics. These pandemics occur every 30 years or so, and the last one was the H1N1 influenza of 2009. I was fascinated with understanding the genomic changes of a virus. In 2009, I was working on how influenza viruses infecting pigs and birds could generate new genetic combinations that enable them to infect and propagate in humans. We developed computational methods to identify genetic changes in these rapidly evolving systems. Many of these approaches were the seeds of the genomic work I have carried out with many colleagues at Columbia in cancer evolution since 2010.

My research is focused on understanding fast evolving biological systems by reading and modeling these changes in their genomes. Mathematical frameworks to identify relevant changes could lead to understanding basic mechanisms of evolution that can be applied to different biological systems. Learning from one system can help develop approaches to understand others.

Q: What compelled you to write the book?
A: The first semester of 2020 was supposed to be my first sabbatical since I started at Columbia in 2008. With all sabbatical plans canceled I was absorbed in research related to the new coronavirus. As I was taking notes on scientific results I realized that there was a significant amount of confusing ideas, probably due to the fast pace of events involving the outbreak. Last year, I published a book on mathematical methods that we developed for analyzing genomic data. Talking to the editors of that book at Cambridge University Press, I was motivated to organize notes and ideas to provide a landscape of what we currently know about the novel coronavirus: How is it related to other coronaviruses, including SARS; what do we know about its origins; how is it evolving; and how does it relate to previous pandemics?

In some ways, this book is a natural extension of work that I began several years ago. Shortly after I joined Columbia, and following the H1N1 flu pandemic, I organized a course on Mathematical Modeling of Infectious Diseases aimed at graduate students with an interest in a quantitative understanding of infectious diseases, and viruses in particular. Many of the notes used in the book came from this course: viruses and their genomes, recent and past outbreaks and pandemics, how genomic information could be used to learn about the viruses and their hosts. These notes provided a framework to conceptualize the current pandemic.

Q: What do you hope readers will take away from this book?
A: The main goal is to conceptualize the current events we are living. There are many reference points in the horizon of our experience that can help to frame the current situation, and there are many things that still need to be learned. Previous pandemics have taught us about epidemiology and public health measures. The outbreak propelled research into coronaviruses, about their origin, associated diseases, and even therapies. Common circulating coronaviruses, viruses that are associated with mild respiratory infections, are also very interesting, as they have been with us for some time and they also have a zoonotic origin, meaning they can be transmitted from animals to humans. Although we can learn from these other outbreaks, the comparisons between these episodes can also have some dangers. For instance, the comparison with seasonal influenza has been quite misused, and is a poor metaphor for the current COVID-19 pandemic. I thought it could be useful for some people to learn about all these topics to help conceptualize the current situation.

Q: What have you and your lab uncovered about the virus up to this point? What are you currently working on?
A: We are working on several aspects of the virus. COVID-19 is a disease caused by the virus SARS-CoV-2, but while an infection in an individual could be asymptomatic in another it could be deadly. In other words, COVID-19, the infectious disease, is a product of the virus and the individual. My work is mostly on genomics, and in this case, we are characterizing the genome of the virus and the genome of the infected individuals. Some of the questions we are trying to answer are related to the origins of the virus: Where is it coming from? How is it evolving? Other sets of questions relate to the severity of the disease: Why do some patients have mild cases and others severe outcomes? There is an increasing amount of data that could help to address these questions.

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The Department of Systems Biology is pleased to welcome Mohammed AlQuraishi, PhD, who joined Columbia University Irving Medical Center in September as an assistant professor and as a member of the Program for Mathematical Genomics.

Prior to joining Columbia, Dr. AlQuraishi served as a fellow of systems pharmacology and systems biology at Harvard Medical School. He completed his PhD in genetics and master’s in statistics from Stanford University. At Santa Clara University, he earned two bachelor’s degrees in biology and in computer engineering.

Dr. AlQuraishi’s lab focuses on two biological perspectives: the molecular and systems levels. On the molecular side, the AlQuraishi lab is developing machine learning models for predicting protein structure and function, protein-ligand interactions, and learned representations of proteins and proteomes. On the systems side, his group is applying these models in a proteome-wide fashion to investigate the organization, combinatorial logic, and computational paradigms of signal transduction networks, and investigate how these networks vary in human populations, and how they are dysregulated in human diseases, particularly cancer.

Dr. AlQuraishi’s expertise in the foundations of biology; the principles, patterns, and mechanisms that underlie living organisms, as well as innovative computational methods, position him uniquely as a PI in the Program for Mathematical Genomics. His expertise is essential for understanding the functional role of mutations across many diseases, including cancer and heritable and infectious diseases.
For individuals with rare diseases, getting a diagnosis is often a long and complicated odyssey. Over the past few years, this has been greatly improved by genome sequencing that can pinpoint the mutation that breaks a gene and leads to a severe disease. However, this approach is still unsuccessful in the majority of patients, largely because of our inability to read the genome to identify all mutations that disrupt gene function.

In a study published in *Science*, researchers from New York Genome Center, Columbia University, and Scripps Research Institute propose a solution to this problem. Building a new computational method for analyzing genomes together with transcriptome data from RNA-sequencing, they can now identify genes where genetic variants disrupt gene expression in patients and improve the diagnosis of rare genetic disease.

The new method introduced in this study, Analysis of Expression Variation or ANEVA, first takes allele-specific expression data from a large reference sample of healthy individuals to understand how much genetic regulatory variation each gene harbors in the normal population. Then, using the ANEVA Dosage Outlier Test, researchers can analyze the transcriptome of any individual — such as a patient — to find a handful of genes where he or she carries a genetic variant with an unusually large effect compared to what healthy individuals have. By applying this test to a cohort of muscle dystrophy and myopathy patients, the researchers demonstrated the performance of their method and diagnosed additional patients where previous methods of genome and RNA analysis had failed to find the broken genes.

The study was led by Pejman Mohammadi, PhD, a former postdoctoral scientist at the New York Genome Center and Columbia University and now an assistant professor at the Scripps Research Institute, and supervised by Tuuli Lappalainen, PhD, core faculty member at the New York Genome Center and an associate professor of systems biology at Columbia University. Their method is implemented in software released with the paper and can be applied to any rare disease patients where RNA-sequencing and genetic data exists.

--New York Genome Center
Pew-Stewart Scholar Dr. Xuebing Wu Focuses on Therapeutic Targets in Breast Cancer

Xuebing Wu, PhD, has been selected as a Pew-Stewart Scholar for his innovative approaches to cancer research.

The Pew Charitable Trusts and the Alexander and Margaret Stewart Trust named five early-career researchers to its prestigious Pew-Stewart Scholars Program for cancer research. This talented class of scholars will receive four years of funding to advance groundbreaking research into the development, diagnosis, and treatment of the disease.

Dr. Wu is an assistant professor of medicine and of systems biology and a member of the Herbert Irving Comprehensive Cancer Center at Columbia University Irving Medical Center. His research seeks to bridge the discovery of basic mechanisms of gene regulation with the development of novel therapeutics for human diseases, focusing on cancer and cardiometabolic diseases.

As a Pew-Stewart scholar, Dr. Wu will investigate the dysregulation of messenger RNA structure in the development of breast cancer.

One of the least understood ways of controlling genes is by changing the shape of the messenger RNA (mRNA), an intermediate carrier of the genetic information stored in genes. Messenger RNA serves as the template for making proteins, but its molecules are like a string of sticky beads that can fold into complex shapes and block protein production. A group of molecular helpers called helicases can unwind those structures and thus control gene expression.

“Intriguingly, many helicases have shown abnormal activities in breast cancer and other cancers but at this moment we don’t yet know what these helicase do to other genes,” says Dr. Wu. “We are developing new technologies that will tell us the shape of all mRNAs in the cell, and help us understand how they change in breast cancer and how they respond to various treatment. We hope that our study will tell us the inner workings of breast cancer and help guide us in designing new, improved therapeutic targets in breast cancer.”

At the center of Dr. Wu’s interests is understanding the fundamental principles of gene regulation in human cells through integrative genomics approaches. His previous work has uncovered important roles of RNA sequence and structure signals in controlling the expression and evolution of the mammalian genome. Dr. Wu and collaborators have been increasingly turning their attention to genomic technologies such as the revolutionary CRISPR/Cas system and a high throughput analysis technology called massively parallel reporter assays (MPRA), as well as novel computational tools and deep learning models to study gene regulation at a global scale.

The Pew Charitable Trust announced a total of 22 early-career researchers for its scholars program in the biomedical sciences. At Columbia, Dr. Wu joins fellow faculty members, Dr. Samuel Sternberg (biochemistry and molecular biophysics) and Dr. Miguel Villavicencio Camarillo (neuroscience) as a new Pew scholar.

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Molly Przeworski, PhD, was selected a Pew-Stewart scholar

Molly Przeworski, PhD, specializes in population genetics research

Molly Przeworski, PhD, Elected to the National Academy of Sciences

Molly Przeworski, PhD, professor of biological sciences and of systems biology, has been elected to the prestigious National Academy of Sciences (NAS). Announced on April 27, Dr. Przeworski joins two fellow Columbia University Irving Medical Center faculty members named to the 2020 class, recognized for their distinguished and continuing achievements in original research.

Dr. Przeworski’s work aims to understand how natural selection has shaped patterns of genetic variation and to identify the causes and consequences of variation in recombination and mutation rates in humans and other organisms. Earlier this year, she was also elected to the American Academy of Arts & Sciences, which recognizes and celebrates excellence of scientists, artists, scholars, and leaders in the public, non-profit, and private sectors.

A member of Columbia’s Program for Mathematical Genomics, Dr. Przeworski is the recipient of the Distinguished Columbia Faculty Award, the Howard Hughes Medical Institute Early Career Scientist award, the Rosalind Franklin Young Investigator award, the Friedrich Wilhelm Bessel Research award, and an Alfred P. Sloan fellowship.

The NAS has elected 120 members and 26 international members to its new class.
Around the Department, 2019-2020
Grants, Awards, and More

Cory Abate-Shen, PhD, received a Life Science Accelerator pilot grant for “Development of ATAD2 Inhibitors as a Novel Treatment for Metastatic Prostate Cancer.”

Harmen Bussemaker, PhD, received a Columbia Life Science Accelerator award for “Data-Driven Design of Biologics for the Next Generation of Drug Discovery.”

Andrea Califano, Dr., and Andrew Lassman, MD, the John Harris Associate Professor of Neurology at Columbia University Irving Medical Center, received an award from the William Rhodes and Louise Titzer-Rhodes Center for Glioblastoma at NewYork-Presbyterian Hospital for “Precision Biology for Newly Diagnosed Glioblastoma—A Translational Pilot Clinical Trial.”

Andrea Califano, Dr., and Peter Sims, PhD, along with Hanina Hibshoosh, MD, professor of pathology and cell biology; Kevin Kalinsky, MD (formerly at CUIMC); and Gordana Vunjak-Novakovic, PhD, University Professor at Columbia, received a grant from the National Cancer Institute for development of a “cancer patient on a chip” for invasive human breast cancer.

In a study reported in Nature Scientific Reports, Andrea Califano, Dr.; Brent Stockwell, PhD, Columbia’s Departments of Biological Sciences and of Chemistry; and coauthors at Columbia and Harvard Medical School screened neuroblastoma (NBL) tumor subtypes for selectively lethal compounds, to identify metabolic dependencies that underpin each subtype, in particular, the mesenchymal NBL subtype. These biosynthetic pathways, which are essential to cell viability, represent vulnerabilities that they hope to exploit therapeutically.

Scientists in the laboratories of Andrea Califano, Dr., and IBM’s Gustavo Stolovitzky, PhD, demonstrated that the transcriptomic response of cells to a combination of two drugs is more than the sum of responses to the individual drugs. Motivated by this observation, they designed an algorithm able to predict synergistic drug combinations based on the gene expression of monotherapies. Results of this study were published in the journal eLife. The paper also presents a conceptual framework for the molecular underpinnings of the drug synergy.

Elise Flynn, PhD student in the Lappalainen lab, received an F31 fellowship, and MD/PhD student Molly Martorella, an F30 fellowship, both from the National Human Genome Research Institute.

Tuuli Lappalainen, PhD, and Harmen Bussemaker, PhD, were awarded an R01 from the National Institute of Mental Health for “Integrative Analysis of Genetic Variation and Transcription Factor Networks to Elucidate Mechanisms of Mental Health Disorders.”

Dr. Lappalainen has joined the Editorial Board of Cell, and the scientific advisory boards of the Jackson Laboratory and the Wellcome Trust Centre for Human Genetics, Oxford, UK. She also served on the external panel for the quinquennial review of the Human Genetics and Cellular Genetics programs at the Wellcome Sanger Institute, and she co-led the final phase of analysis of the GTEx Consortium, with multiple papers published in Science and other journals in September 2020.

Michael Murphy, a postdoc in the Xuebing Wu lab, received a postdoctoral fellowship from the American Heart Association.

Raul Raban, PhD, received National Cancer Institute grants for “Dissecting the Glia Immune Microenvironment Using Random Matrix Theory” and for “Peripheral T-Cell Lymphomas.”

Sagi Shapira, PhD, and Nicholas Tatonetti, PhD, received a COVID-19 pilot grant from Columbia’s Herbert Irving Comprehensive Cancer Center for “Identification of Adverse SARS-CoV-2 Infection Outcome Determinants.”

Peter Sims, PhD, received a pilot grant from the Herbert Irving Comprehensive Cancer Center and Columbia Engineering for collaborative cancer biology-engineering research.

Dennis Vitkup, PhD, received a grant from the National Institutes of Health/National Institute of Mental Health for “Discovery and Analysis of Brain Circuits and Cell Types Affected in Autism and Schizophrenia.” He also received a grant from the National Institute of General Medicine for “Systems Biology of Protein and Phenotypic Evolution.”

Harris Wang, PhD, received a Hirschl Trust Research Scientist Award from the Irma T. Hirschl Trust for “Next-Generation Gut Biome Modulators of Host Behavior and Cognition,” as well as a National Science Foundation grant for “The Rules of Microbiota Colonization of the Mammalian Gut” and for the project “Towards Life with a Reduced Protein Alphabet.” He also received a Columbia Life Science Accelerator Pilot Grant for “A Multimodal Oral Non-Viral CRISPR-Cas Medical Countermeasure to Enhance Ionizing Radiation Resilience and Survival.”

Xuebing Wu, PhD, received a National Institute of Health Director’s New Innovator Award (DP2) for his project “Genome-Wide Studies of the Noncoding Functions and Mechanisms of Human mRNAs”; he was also named a Highly Cited Researcher in 2019 by Web of Science.

Chaolin Zhang, PhD, received a Vagelos Precision Medicine Pilot Grant for “Unbiased Screen of Proximal and Distal Splicing Regulatory Elements Towards Drug Discovery.”
IN THE MEDIA
An article in Science, “Computer Algorithms Find Tumors’ Molecular Weak Spots,” discusses the work of Andrea Califano, Dr, and his research group on the identification of master regulators, i.e., genes that orchestrate regulatory programs involved in cancer pathology. A *Nature Outlook* article on genetically targeted cancer therapy, “Beyond the Genome,” also discusses Dr. Califano’s research on master regulators, as well as on algorithms to suggest treatments.

COVID-19 ACTIVITIES (Related: Systems Biology Faculty Address the Global Pandemic, Page 3)
At the beginning of the COVID-19 pandemic, Andrea Califano, Dr, along with Stephen Goff, PhD, Departments of Microbiology and Immunology and of Biochemistry and Molecular Biophysics; Eric Greene, PhD, Department of Biochemistry and Molecular Biophysics; and Andrew Marks, MD, Departments of Physiology and Cellular Biophysics and of Molecular Physiology (in Medicine), organized a series of weekly virtual symposia on the virus for researchers and clinicians. The symposia, which started in April, covered a broad range of scientific, clinical, economic, and social aspects of the pandemic, and attracted hundreds of attendees.

Wellington Cardoso, MD, PhD, director of the Columbia Center for Human Development, and Andrea Califano, Dr, are conducting a study to identify and pharmacologically target key regulators of the epithelial response to COVID-19 infection in the respiratory tract, aiming to reduce viral load and transmission. The research is supported by supplemental funding to Dr. Cardoso’s Outstanding Investigator Award (R35 grant) from the National Institutes of Health, for “Mechanisms Controlling Expansion and Lineage Specification of Airway Progenitors in Development and Disease.”

PHD GRADUATES
*Congratulations to our recent grads!*
Tom Blazejewski (Wang lab)
Margot Brandt (Lappalainen lab)
Jimin Park (Wang lab)
Ravi Sheth (Wang lab)

NEWLY TENURED FACULTY IN SYSTEMS BIOLOGY
Congratulations to Drs. Lappalainen, Sims, and Wang, of the Department of Systems Biology, who have been awarded tenure and promoted to associate professor.

Tuuli Lappalainen, PhD, joined Columbia University Irving Medical Center in 2014. She holds a joint appointment in the Department of Systems Biology and the New York Genome Center. Her research links computational and population genomics to experimental molecular biology, with a focus on characterizing functional genetic variation in human populations and its contribution to traits and diseases. The overall goal of her research program is to uncover general rules of the genomic sources of human variation and to push discoveries and methods from her research projects toward clinical applications. Dr. Lappalainen has made important contributions to several international research consortia in human genomics, including co-leading the final phase of the Genotype-Tissue Expression (GTEx) project.

Harris Wang, PhD, joined Columbia University Irving Medical Center in 2013. He has a joint appointment in the Department of Systems Biology and the Department of Pathology and Cell Biology. His research primarily focuses on applying systems and synthetic biology approaches to understand the organizing principles that govern the structure and function of microbial communities, with a focus on the mammalian gut microbiome. His laboratory pioneers new experimental and computational approaches, combined with *in vitro* cultures, mice models, and clinical specimens, to make entirely new types of microbiome measurements and functional perturbations to study and engineer gut microbiota. His work employs a variety of high-throughput techniques including CRISPR-Cas gene editing, *de novo* DNA synthesis, and next-generation DNA sequencing towards unlocking the therapeutic potential of the microbiome.

Peter Sims, PhD, joined Columbia University Irving Medical Center in 2012. He has a joint appointment in the Department of Systems Biology and the Department of Biochemistry and Molecular Biophysics. He has served as Director of Systems Biology Graduate Studies since 2016 and Director of the Columbia Single Cell Analysis Core since 2017. Dr. Sims’s primary focus is the development of single-cell approaches to systems biology. Researchers in his lab develop new tools for single-cell and cell type-specific analysis, focusing mainly on transcriptional and translational regulation. They use cutting-edge microscopy, next-generation sequencing, and microfabrication to enable unbiased, genome-wide measurements of biological samples. They apply these tools broadly to problems in cancer biology, immunology, and neuroscience.
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To learn more about our research and programs, visit systemsbiology.columbia.edu.

Front cover:
Illustration of the novel SARS-CoV-2 (Credit: Nicoletta Barolini)

Back cover:
Image artistically depicts the complexity of gut microbiota. A recent study by the Vitkup lab revealed fundamental macroecological laws that could help researchers better understand the gut microbiota dynamics and its role in human health and disease. (Credit: Irina Titkova)