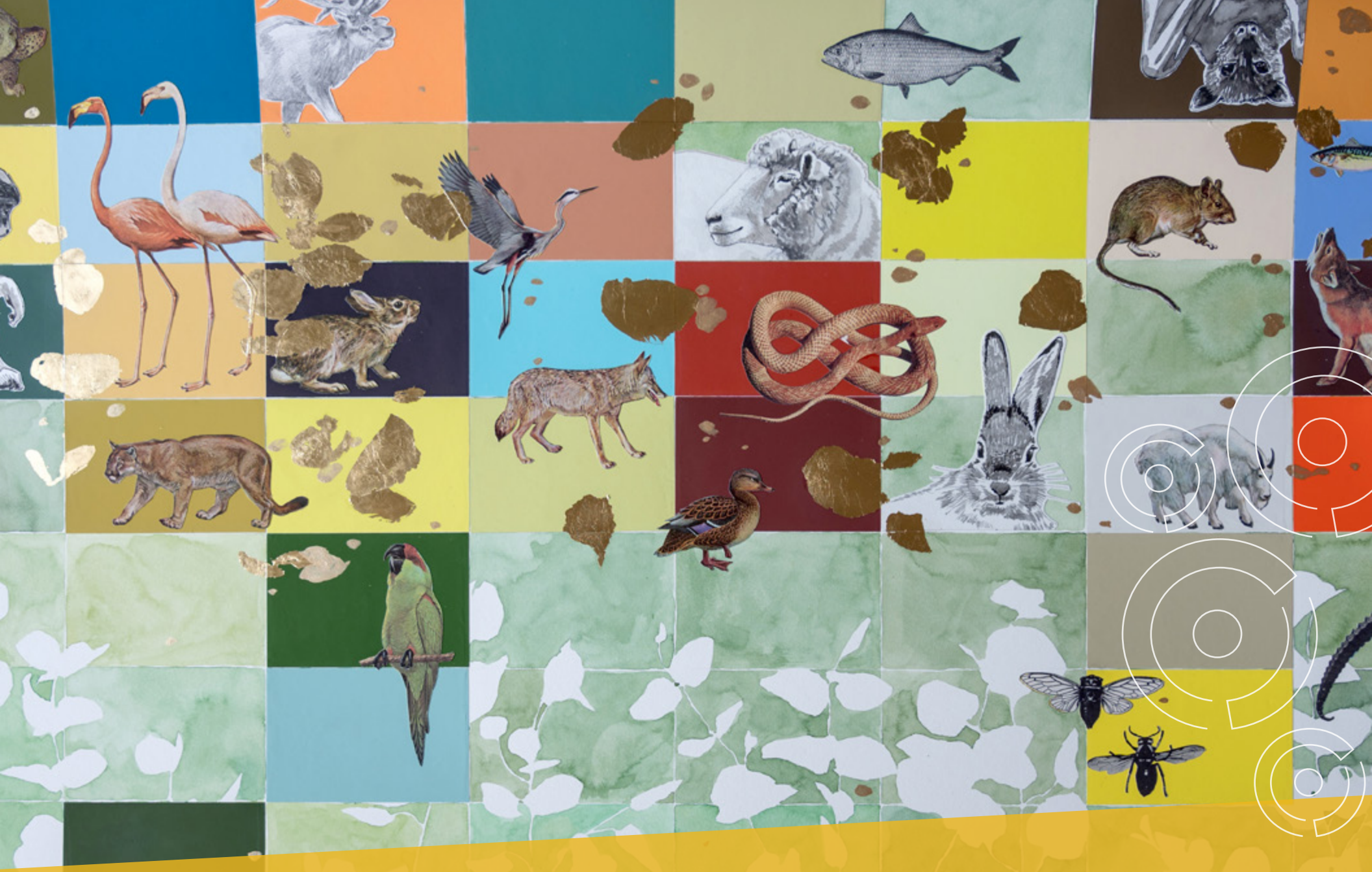


12TH ANNUAL · 2021

GoldLab SYMPOSIUM

BIOLOGY MEETS BIG DATA

May 13 & 14, 2021

SYMPOSIUM AGENDA
BIOLOGY MEETS BIG DATA

All times are in Mountain Time | MDT UTC-06:00

MAY 13

9:00-9:15am **Larry Gold**
Welcome

9:15-10am **Jack Szostak,** Harvard
Why RNA? A Rationale for RNA as the First Biopolymer of Life

10-10:45am **Nebojsa Janjic,** SomaLogic
Measuring Proteins with DNA, Twisting the Central Dogma for Better Understanding of Biology

10:45-11:30am **Emmanuel Mignot,** Stanford
Waking Up the Narcolepsy Field

11:30am-12pm *Break*

12-12:45pm **Michael Rosbash,** Brandeis
The Circadian Rhythm Story: Past, Present and Future

12:45-1:30pm **Leslie Leinwand,** University of Colorado
From Bench to Bedside: The Role of Science in Treating a Deadly Disease

1:30-2:15pm **Roy Smythe,** SomaLogic
Authority, Power, and Autonomy in Medicine

2:15-2:30pm *Break*

2:30-3:15pm **Ken Sharpe,** Emeritus, Swarthmore
Designing for Practical Wisdom: How Can Medical Organizations Encourage Practitioners to Learn the Character and Judgment they Need?

3:15-4pm **Jesse Gillis,** Cold Spring Harbor
The Transcriptional Legacy of Developmental Stochasticity

4-4:45pm **Molly Burhans,** GoodLands
It's the End of the World as We Know It (and I feel fine)

4:45-5pm **Larry Gold**
Closing Remarks

MAY 14

9-9:15am **Larry Gold**
Introduction

9:15-10am **Aaron Clauset,** University of Colorado
Prediction and Its Limits in Scientific Discovery

10-10:45am **Sendhil Mullainathan,** University of Chicago
Machine and Human Intelligence: Algorithms as a Source of Bias or Insight

10:45-11:30am **Robin Dowell,** University of Colorado
Cracking the Regulation Code

11:30am-12pm *Break*

12-1pm **Craig Mundie,** Mundie & Associates
Mira Murati, OpenAI
Larry Hunter, University of Colorado
The Evolution of Machine Intelligence

1-2:45pm **Craig, Mira, Larry**
Panel Discussion

2:45-3pm *Break*

3-3:45pm **Dan Shefet,**
Association for Accountability & Internet Democracy
Regulating AI

3:45-4:30pm **Rebecca Trumbull,**
Retired, Stanford Distinguished Careers Institute
Eric Trumbull, Retired, Actor, Professor, and Director
23 & Us

4:30-4:45pm **Larry Gold**
Closing Remarks

ABOUT THE COVER ART

Largely inspired by esoteric questions about the future of AI, this 2021 GLS piece reflects on pattern recognition, information archives, and the [infinite] unknowable variables that affect all of us. My aim was to visualize the complex meeting of biology and computational worlds without drawing a conclusion.

How will the documentation - categorized and delineated throughout the years–of our biological response, our animalistic tendencies and (un)evolved ways be re-purposed? Visions of animal taxonomy and sorting swirled. What will this human-driven archive of nature become as it is now translated digitally? Reinforced learning of animals, "intelligent" behavior turned to algorithm. As biological response is increasingly determined by algorithms, what will a modern machine predict, using our data? When life and our experience of it is juxtaposed onto an electronic platform - how does that present itself? Collaged animals, both collected from out-dated Audubon Nature Encyclopedia and hand-drawn, scatter chromatically against squares of color. They inhabit a grid, partially filled with blocks of color, an underlying pattern of eucalyptus leaves, and gold leaf obstructions.

DARIN GRASSMAN is a designer and artist based in Colorado. She holds a BFA in Painting from California College of Art in Oakland and an MA in textiles from the Royal College of Art in London. Her work spans a range of media, exploring themes of object-hood, documentation, pattern, repetition, ephemera, and aura. When she's not teaching drawing classes or gluing paper, she's out hiking and taking photos of rocks and other mundane phenomena.

DEDICATION

BILL BURHANS 1952-2019

Bill Burhans was a scientist, cancer patient, and uniquely qualified patient advocate for himself and others. He gave a wonderful talk at the 2019 GLS entitled *My Life Over and Under the Microscope as a Cancer Scientist and Patient.* Due to his cancer treatment, he was not able to attend the GoldLab Symposium in person, so out of necessity, Bill became the first GLS speaker to present virtually. Bill was ahead of his time.

During the course of his six years of treatment, Bill received the PARP inhibitor Olaparib, a treatment that was based on his own research as a basic scientist. He said, "as a scientist with expertise in DNA repair pathways, I've played an unusually active role in planning my treatment".

We are grateful to Bill for his friendship and scientific contributions. Through his work he leaves behind a legacy of wisdom and compassion. And warmth and humor…

The talk Bill gave had no emotional distance whatsoever. We sat and listened to Bill, wanting so much that he would live forever. Bill's wife Deb, the co-pilot of his talk and our newest GLS friend (along with their daughter Molly), also reminded us that Bill's treatment did take a heavy emotional toll on all of us. Bill was a teacher who made our lives better. The price was too high.

"My background as a scientist has made it possible and actually easy to look on everything that is happening to me with a much more objective eye. There is a certain amount of emotional distance between myself and my treatment that I don't think a lot of other patients would be able to have without the background I have. That's been very valuable."

BILL BURHANS

MODERATORS DAY 1

PIPPA MARRACK, PH.D.

National Jewish Health

Dr. Marrack has studied T cells, how they are created and how they operate for good or ill for more than 40 years, almost since the cells were discovered. The lab run jointly by Dr. Marrack and her husband, John Kappler, discovered the proteins that make up the T cell receptor, the proteins that allow T cells to recognize and respond to foreign invaders. Their lab also demonstrated one of the main processes that prevents T cells from attacking their own host, processes that prevent autoimmune diseases. Recently the lab has been working on vaccines, in attempts to understand how they work and how better vaccines can be created. Drs Marrack and Kappler have two children, three grandchildren, two dogs, and a very mean cat.

LEE NISWANDER, PH.D.

University of Colorado Boulder

Dr. Niswander is the Chair of Molecular, Cellular, and Developmental Biology, University of Colorado Boulder. The Niswander lab investigates mouse models of embryonic development with the overarching goal of providing insights into fundamental developmental processes, major human birth defects and potential clinical therapies. Her multi-disciplinary studies investigate the interplay among genes, environment, and epigenetic mechanisms. Her studies over the years have provided a unique perspective on the molecular mechanisms that control the formation of the central and peripheral nervous system, as well as lung, limb, and neuromuscular development. Her lab developed time-lapse imaging methods to visualize and quantify the cell and tissue behaviors during embryonic morphogenesis. Current studies focus on the common and severe birth defect wherein the neural tube fails to close, resulting in neural tube defects (NTDs, such as spina bifida), and early neural progenitor specification and differentiation, defects which can lead to microcephaly and other neurological disorders.

JACK W. SZOSTAK, PH.D.

Professor of Chemistry & Chemical Biology, Harvard University; Professor of Genetics, Harvard Medical School;
Investigator, Howard Hughes Medical Institute; Alex Rich Distinguished Investigator, Massachusetts General Hospital

ABSTRACT

Why RNA? A Rationale for RNA as the First Biopolymer of Life

RNA is ubiquitous in biology today, from its role as a primer in DNA replication to its multiple roles in protein synthesis and its even more diverse roles in regulation. Most of the viruses that continue to plague us to this day are RNA viruses, while it is RNA based vaccines that provided the first and best weapons to fight these plagues. But why RNA? Why are we immersed in the biology of RNA? The answer lies in the early history of life, and its origins in the chemistry that led to RNA as the first biopolymer of life.

Why did life begin with RNA, and not DNA, or TNA, or ANA, or any of the myriad other nucleic acids (collectively referred to as XNAs) that look as if they could transmit genetic information and fold up into aptamers and catalysts? Part of the answer comes from the recent advances in prebiotic chemistry that describe plausible pathways for the synthesis of ribonucleotides on the early earth. However, many noncanonical nucleotides would have been generated together with ribonucleotides in ratios depending on the environmental conditions. If these noncanonical nucleotides were present with ribonucleotides in some prebiotic pool, and exposed to activating chemistry, their oligomerization would have led to a highly heterogeneous collection of oligonucleotides containing different types of nucleotides. To add to the complexity, these nucleotides could have been connected by a variety of different types of backbone linkages. How could anything resembling modern RNA, with a relatively homogeneous composition, have possibly emerged from this primordial heterogeneity? It now appears that the chemistry of nonenzymatic template copying would have strongly enriched for RNA over the course of multiple cycles of replication.

Jack's laboratory has studied the chemistry of template copying using a simple model system in which an RNA primer bound to an RNA template is extended by reaction with activated ribonucleotides. In order to understand whether this copying chemistry would still work under more realistic conditions, we began to study the kinetics of copying using nonstandard nucleotides either as activated monomers, or when incorporated into the primer and template oligonucleotides. What we found surprised us: in all of the cases we have examined so far, chemical copying with ribonucleotides is faster than copying with alternative nucleotides. Furthermore, nonstandard nucleotides or backbone linkages in the template are readily copied into native RNA with ribonucleotides. Our results suggest that nonenzymatic copying served as a chemical selection mechanism that allowed relatively homogeneous RNA to emerge from a complex mixture of prebiotically synthesized nucleotides and oligonucleotides. The resulting RNA oligonucleotides could then have served as the genetic raw material for the emergence of the first RNA based protocells.

BIOGRAPHY

Dr. Szostak is a Professor of Chemistry and Chemical Biology at Harvard University, Professor of Genetics at Harvard Medical School, an Investigator of the Howard Hughes Medical Institute, and the Alex Rich Distinguished Investigator at Massachusetts General Hospital. Throughout his career Dr. Szostak has focused on nucleic acid biochemistry, including seminal work on DNA repair, telomeres and telomerase, and the laboratory evolution of aptamers and ribozymes. He is a recipient of the 1994 National Academy of Sciences Award in Molecular Biology, the 2006 Albert Lasker Basic Medical Research Award, the 2008 H.P. Heineken Prize in Biophysics and Biochemistry and the 2009 Nobel Prize in Physiology or Medicine. He is a member of the National Academy of Sciences, the American Philosophical Society, and was recently elected a Fellow of the Royal Society. Dr. Szostak's current academic research is focused on the Origin of Life.

Dr. Szostak has been closely involved with commercial aspects of biotechnology for 40 years. He holds 16 issued patents, has co-founded two biotech companies, and has served as an advisor to over a dozen biotech and pharma companies. Dr. Szostak is the scientific co-founder and Chair of the SAB of Ra Pharmaceuticals, a publicly traded company developing novel complement based therapeutics. Dr. Szostak is also the Chair of the SAB of Moderna, Inc., a publicly traded company developing mRNA therapeutics. Dr. Szostak has a strong interest in helping innovative biotech companies reach their full potential by bringing useful new therapies into medical practice.

NEBOJSA JANJIC, PH.D.

Chief Science Officer, SomaLogic, Inc.

ABSTRACT

Measuring proteins with DNA, Twisting the Central Dogma for Better Understanding of Biology.

Information in biology, according to the central dogma, flows in a defined order: DNA, the master copy that contains all genes, is transcribed to RNA, which is then translated to proteins. It is proteins, the final product of this process, that execute most of the instructions encoded in the genes. Unlike DNA, which is relatively static through life, protein composition changes dynamically as the organism goes through various stages of development, responds to a variety of stimuli, and cycles through health and illness.

Much of biology is driven by interactions among three-dimensional objects. Through shape recognition, enzymes transform their substrates, cell-surface receptors transmit signals after binding to their ligands, ions travel through pores of precise dimensions, and genes are activated by transcription factors. To better understand biology, we need a large collection of shapes with which to measure other complementary shapes. In humans, there are 20,000 genes that encode proteins. If we want to fully understand dynamic changes in the body, measuring many proteins at the same time is crucial since proteins do not work in isolation but rather operate in networks. For this task, we have employed aptamers, affinity reagents made of single-stranded DNA.

The realization that a large collection of sequences of single-stranded nucleic acids can be thought of as a large collection of shapes, from which rare molecules capable of binding to other molecules with high affinity and specificity can be selected, arose independently in two labs. This notion, initially considered to be of questionable utility, proved to be both robust and applicable to a wide range of molecular targets. Over time, aptamers have been improved through chemistry to incorporate molecular features typically found in proteins, which further expanded the range of molecular targets for which a useful aptamer can be identified. Three decades on, aptamers have found many uses in research and medicine. They have also turned out to have several unique advantages for simultaneous measurement of many proteins, which has led to better understanding of health and wellness, as well as progression to disease. The common denominator in this adventure has been the commitment to ask open-ended questions, to make and test all possible solutions, and to view biology as being more complex and surprising than we often appreciate.

BIOGRAPHY

Dr. Janjic has been the Chief Science Officer at SomaLogic since January 2009. Prior to joining SomaLogic, Dr. Janjic was a founder and CSO of Replidyne, Inc., a biotechnology company focusing on the development of novel small-molecule antibacterial agents, whose mission is continuing through a successor company, Crestone, Inc., where he currently serves as advisor and Chairman of the Board. Prior to Replidyne, he was among the initial group of scientists to join the original aptamer company, NeXagen, which became NeXstar Pharmacauticas. As Senior Director of Drug Discovery at NeXstar, he was responsible for creating a pipeline of aptamer-based drug candidates for pre-clinical and clinical development. His contributions included the discovery and early development of Macugen, the first-in-class, FDA-approved treatment for macular degeneration targeting VEGF and named Innovative Pharmaceutical Product of the Year in 2005.

Dr. Janjic received his bachelor's degree in molecular biology and doctorate in physical organic chemistry from the University of Washington in Seattle. He completed his postdoctoral training at the Scripps Research Institute in La Jolla as a Cancer Research Institute Fellow.

EMMANUEL MIGNOT, M.D.

Professor of Psychiatry and Behavioral Sciences, Stanford University

ABSTRACT

Waking Up the Narcolepsy Field

Narcolepsy has fascinated scientists for centuries, as it a unique disease where reality and REM/dreaming sleep get confused with each other. Patients experience sleepiness, vivid dreaming bordering on hallucinations, sleep paralysis and cataplexy (muscle weakness triggered by emotions). Type 1 narcolepsy affects 0.03% of the population, and most often starts in children or adolescent. When I started to work on narcolepsy in 1987, nothing was known, and it was considered exceptionally rare. Thinking that finding the cause of the disease could reveal new sleep mechanisms and that the field was without competitors, I plunged myself in this topic of research. Working with a dog model of narcolepsy that transmitted the disorder as a single autosomal gene, we positionally cloned mutations in two dog breeds in 1999, at a time the dog genome was a no men land. The study revealed mutations in a G-Protein coupled receptor called hypocretin/orexin receptor 2, a receptor for a recently discovered peptide believed to be involved in appetite (thus the misnomer "orexin"). Since then, this system has become a major target for hypnotics (blockers), and a promising new treatment of narcolepsy itself (agonists under human clinical trial)is emerging. Remarkably, patient with narcolepsy who don't have hypocretin are hypersensitive to these drugs, so that smaller dose than in normal individuals have disease reversing effects.

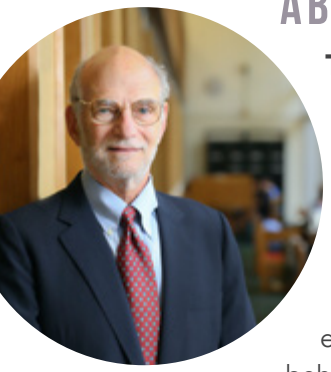
In parallel with this work, after finding that the hypocretin/orexin pathway was involved in canine narcolepsy, we discovered that in humans, the disease is not due to mutations of the receptor, but rather the result of an autoimmune disease destroying the 20,000 neurons containing hypocretin, not unlike type 1 diabetes and insulin. More studies have shown that this process is the result of T cell molecular mimicry between hypocretin itself and specific flu epitopes, with no involvement of antibodies as far as we know. This explains seasonal onset in the spring, and in a unique instance, post vaccination cases following a specific swine flu vaccine called Pandemrix. These discoveries are also opening a new field, that of CNS autoimmune mediated disorders. Indeed, many new brain diseases such as anti NMDAR, anti-LGi1, anti-GAD, anti-CASPR2 diseases are increasingly recognized and found to be amendable to immunotherapy. This field is also exploding although mechanisms behind CNS-specific immunity remain poorly understood. Autoimmunity seems to also play a role in neurodegenerative disorders such as Parkinson's disease and Alzheimer dementia. CNS immune therapies have a bright future considering the rapid progress of immunotherapy in cancer. My research is described at mignotlab.com.

BIOGRAPHY

Emmanuel Mignot, M.D., is Professor of Psychiatry and Behavioral Sciences at Stanford University. He is internationally recognized for discovering the cause of narcolepsy. His research focuses on the neurobiology, genetics, and immunology of narcolepsy, a disorder caused by hypocretin (orexin) cell loss, with an indirect interest in the neuroimmunology of other brain disorders. Currently, Dr. Mignot is interested in analyses involving statistics and machine learning of polysomnography, clinical and biological data, including the combination of EEG, wearable biosensors, and genetic datasets.

MICHAEL ROSBASH, PH.D.

Professor of Biology and the Peter Gruber Professor of Neuroscience, Brandeis University
Investigator, Howard Hughes Medical Institute



ABSTRACT

The Circadian Rhythm Story: Past, Present and Future

The last 35-40 years has seen a sea change in the field of circadian rhythms. This modern era began with work in Drosophila (fruit flies), which has been a leading genetic system for more than 100 years. Michael and his colleagues discovered the clock mechanism that underlies circadian timing, and it turned out that the genes and mechanism are conserved in all animals. This circadian system governs a large fraction of all gene expression, once again extending from fruit flies to humans, which explains why so much animal physiology (biochemistry, metabolism, endocrinology, behavior, sleep, etc.) is under temporal control. The broad reach of circadian biology indicates that it will continue to be important to many aspects of human well-being and will become increasingly relevant to medicine as more knowledge and applications accrue.

Michael will also touch on unusual and interesting features of the 150 adult fly brain clock neurons, which is of major interest to his current lab. They play an important role in regulating sleep and wake behavior. Their small numbers present a challenge, as many molecular methods of interest are biochemical and therefore difficult to apply to these neurons. (There are in contrast about 100,000 total neurons in the adult fly brain.) Insha'Allah, Michael will have sufficient time at the end of his remarks to make some philosophical and political comments about behavioral genetics as well as to address the contemporary research landscape that we all currently inhabit.

BIOGRAPHY

Dr. Rosbash is a Professor of Biology and the Peter Gruber Professor of Neuroscience at Brandeis University. He is also an Investigator of the Howard Hughes Medical Institute. He has made fundamental contributions to our understanding of the post-transcriptional regulation of gene expression, especially RNA metabolism in yeast. However, he is best known for his work in Drosophila that illuminated our current understanding of the molecular mechanisms that underlie circadian rhythms, the intrinsic clock that controls the cyclic behaviors of all animals.

Dr. Rosbash went to the Newton public schools in greater Boston and then to Caltech, graduating in 1965 with a B.S. in Chemistry. He spent the 1965-1966 academic year in Paris as a Fulbright Scholar in the lab of Marianne Grunberg-Monago. He then worked in the lab of Sheldon Penman at MIT and received a Ph.D. in Biophysics in 1970. After a brief stint at the University of St. Andrews, he was a post-doc in the lab of John Bishop in the Department of Genetics at the University of Edinburgh from 1971-1974. Dr. Rosbash joined Brandeis University in 1974. He became a Howard Hughes Medical Institute Investigator in 1989.

Dr. Rosbash and his Brandeis colleague Jeff Hall as well as Mike Young of the Rockefeller University have received numerous awards for their circadian work including the 2017 Nobel Prize in Physiology or Medicine. They most recently received the Peter Farrell Prize in Sleep Medicine (2018) from the Harvard Medical School.

LESLIE LEINWAND, PH.D.

Director of the University of Colorado's Computational Bioscience Program
Professor of Pharmacology (School of Medicine) and Computer Science (Boulder)

ABSTRACT

From Bench to Bedside: The Role of Science in Treating a Deadly Disease

Leslie was fascinated by human genetics by the time she went to college and has been passionate for decades about unraveling genetic contributions to disease. A long path that took a few twists and turns ultimately led her to a longstanding goal: to develop treatments for genetic diseases where none existed. It started with mapping genes to human chromosomes. The next phase led her to be an academic scientist. At the University of Colorado, Leslie's lab studied how certain muscle mutations lead to disease. In other words, how a small DNA change leads to an often fatal crisis in the heart. It is this kind of work, sometimes called basic research, that lays the foundation for the bridge from bench to bedside.

The disease that her lab continues to study is called familial hypertrophic cardiomyopathy, a long way of saying a big sick heart that runs in a family. This disease is most notable for killing young athletes, sometime with no prior symptoms. Geneticists identified what genes, if mutated, cause this disease. What Leslie will do today is to share how a great deal of searching led to the first FDA approved drug in 2021 by MyoKardia, the company she co-founded in 2012. MyoKardia has since been acquired by Bristol Myers Squibb. Prior to this drug, the only effective treatment for this disease was a heart transplant. In fact, familial hypertrophic cardiomyopathy is the leading cause of sudden death in young people. Once tools became available, it was possible to determine which members of a family carried that mutant gene, frequently after someone in the family suffered a cardiac arrest. Having the knowledge of your genotype is an important advance. But, what do you do with that information when there is no treatment? Many were told to stop athletic activity; others were followed by a cardiologist, but this was a very anxious way of life. Leslie's talk will tell the story of finding a treatment for a fatal genetic disease of the heart.

BIOGRAPHY

Dr. Leinwand is a Molecular, Cellular, and Developmental Biology (MCDB) Distinguished Professor and the Chief Scientific Officer of the BioFrontiers Institute at the University of Colorado Boulder. Her research focuses on the genetics and molecular physiology of inherited diseases of the heart and skeletal muscle, and how biological sex modifies heart and skeletal muscle. The study of these diseases has required multidisciplinary approaches, involving biophysics, molecular biology, mouse genetics, cardiac physiology, and the analysis of human tissues.

She co-founded Myogen, Inc., which was sold to Gilead Pharmaceuticals. More recently, she was a co-founder of Hiberna, Inc., and of MyoKardia, Inc., a company founded to develop therapeutics for inherited cardiomyopathies. Bristol Myers Squibb acquired MyoKardia in late 2020.

She received her Bachelor's degree from Cornell University and her Ph.D. from Yale University, and completed her post-doctoral training at Rockefeller University. She joined the faculty at Albert Einstein College of Medicine in New York in 1981 and remained there until moving to Colorado in 1995 to be Chair of MCDB. Dr. Leinwand is a Fellow of the AAAS, former MERIT Awardee of the NIH, Established Investigator of the American Heart Association, elected member of the American Academy of Arts and Sciences and the National Academy of Inventors, and she serves on the International Council for the International Society for Heart Research. She has been honored by the American Heart Association with its Distinguished Scientist Award.

ROY SMYTHE, M.D.

Chief Executive Officer, SomaLogic, Inc.

ABSTRACT

Authority, Power and Autonomy in Medicine

Money, science and technology have been important, but not enough to create and sustain the massive medical industrial complex. A critical additional force – one responsible for almost everything civilization has accomplished – has been necessary. That force is authority.

Authority exists between parents and children, employers and employees, governments and citizens, and between health care providers and those seeking care. At its core it is someone acting as suggested or directed by another where action would not otherwise occur. While they are two drums beating constantly in the background of civilization - one a staccato snare you willingly tap your feet to, and the other a bass drum struck on occasion with such force you feel the vibration and are compelled to move – authority and power are not the same. Power implies use of force or coercion and authority voluntary acceptance. The medical industrial complex has never had power, so society had to grant it authority. In other industries, this is the "right to sell", and in medicine - this is the "right to treat".

The medical industrial complex was built on three pillars of medical authority – informational, technical and moral. Informational authority implies it possesses knowledge laypersons cannot access or understand, technical authority technology laypersons cannot obtain or use and moral authority suggests healthcare providers are somehow divinely empowered. Medical authority has prevented individuals from actively participating in a more effective care model. However, the three pillars are crumbling.

BIOGRAPHY

Dr. Smythe is the Chief Executive Officer of SomaLogic, Inc., a leading-edge biotechnology company headquartered in Boulder, Colorado. During the course of his career, he has been an internationally recognized surgeon, biomedical scientist, academician, health system administrator, and healthcare business entrepreneur.

While in medical school at Texas A&M, he was a Charles A. Dana Foundation Scholar at the University of Pennsylvania School of Medicine and the Wharton School of Business. Following medical school, Dr. Smythe trained in general surgery, surgical oncology, and thoracic surgery and completed a postdoctoral research fellowship in molecular therapeutics at the University of Pennsylvania. His medical and translational research career then began at the University of Texas MD Anderson Cancer Center, where he was the recipient of NIH and numerous other funding awards. He subsequently chaired the Department of Surgery at Baylor Scott & White Health System and the Texas A&M Health Science Center College of Medicine, where he was the Roney Endowed Chair, and later became the Medical Director of Innovation and Executive Vice President for Institute Development before moving into expanded roles in corporate healthcare.

Dr. Smythe came to SomaLogic from Royal Philips, where he served as Global Chief Medical Officer for Strategy and Partnerships. Before joining Philips, he served as Chief Medical Officer at Valence Health, a Chicago-based healthcare company. He held the same title previously at AVIA, a healthcare technology accelerator.

A highly sought-after lecturer and the author of more than 300 papers, abstracts and essays in academic, literary and humanities publications, Dr. Smythe is also currently a member of more than 20 U.S. national learned societies.

KENNETH E. SHARPE, PH.D.

Professor Emeritus Political Science, Swarthmore College

ABSTRACT

Designing for Practical Wisdom: How Can Medical Organizations Encourage Practitioners to Learn the Character and Judgment They Need?

Good health care demands good science, good research, good drugs, good technology and medical staff with first rate technical skills. But data, technology, drugs and algorithms are not enough. Good judgement is a critical capacity that medical practitioners need if they are to successfully make tough, everyday decisions about how to care and how to work with each other in teams. At the heart of this judgment is not just academic knowledge and technical expertise but something Aristotle called phronesis, or practical wisdom. What does this practical wisdom mean concretely?

It demands being motivated by the right things: medical practitioners need to have the virtues of character that motivate them to seek the good of patients.

It demands the ability to notice, to see: the capacity to listen not only to what their patients are saying but what they are actually feeling.

It demands the ability to reflect and deliberate about the tough decisions, big and small, involved in everyday care and major illnesses—to figure out how they and their teams can diagnose and treat each person given the particular context of their lives, hopes, and fears.

It demands the will and capacity to empathize, to counsel, to deal with uncertainty, to balance empathy with detachment, to balance honesty and kindness, to balance hope with truth telling, and the courage to keep trying and learning in the face of inevitable failures.

Such practical wisdom is only learned through experience. But not any experience will do. So how do you design the right kind of experiences? How do you create systems that encourage the learning of practical wisdom? How do you design medical institutions and medical education to encourage practitioners to learn the character traits and judgment skills they need to care for us?

I've got three stories to tell: one takes place in an intensive care unit in a major Boston Hospital; one takes place in an inner-city health clinic; and one is a story about a program in a major medical center that provides palliative care. Each story will help elaborate how medical organizations can be re-designed to encourage clinicians to learn the practical wisdom they need.

BIOGRAPHY

Dr. Sharpe is Professor Emeritus of Political Science at Swarthmore College where he taught political philosophy, practical ethics, Latin American politics, and foreign policy. He has been a Visiting Professor at the University of British Columbia, at the Law School at the University of Colorado, and most regularly at Dartmouth College in the MALS program and the Government Department.

His most recent course in the MALS program (jointly taught in 2019 with Dr. Kathryn Kirkland from the Dartmouth Medical School) was "Reading Ourselves, Reading Others: How Medical Humanities Prepares Clinicians (and the rest of us) to Co-create Better Health Care."

He is author (with Professor Deborah Cantrell) of *Practicing Practical Wisdom,* (67 *Mercer Law Review* 331, 2016). He is co-author, with Professor Barry Schwartz, of *Practical Wisdom: The Right Way to Do The Right Thing* (Penguin/Riverhead, 2010). Most recently they have co-authored *Practical Wisdom and Health Care* in R.J. Sternberg et. al. *Applying Wisdom to Contemporary World Problems* (Palgrave Macmillan 2019).

Dr. Sharpe's previous books include, *Drug War Politics: The Price of Denial* (University of California Press, 1996), *The State and the Transnational Corporations: The Political Economy of the Mexican Auto Industry* (Princeton, 1985), and *Peasant Politics: Struggle in a Dominican Village* (Johns Hopkins University Press, 1977). He has also published articles in *The Washington Post, The New York Times, The Christian Science Monitor, The Los Angeles Times, The Boston Globe, The Nation, Foreign Policy Magazine,* and *The American Prospect.*

JESSE GILLIS, PH.D.

Associate Professor of Computational Genomics, Cold Spring Harbor Laboratory

ABSTRACT

The Transcriptional Legacy of Developmental Stochasticity

X-chromosome inactivation is an epigenetic process that regulates gene dosage in females. Occurring as a random coin-flip early in development, the status of inactivation is then stably inherited down cell lineages via DNA methylation. The degree of "skewing" toward one chromosome over the other has been researched intensively, and importantly it has been linked to disease, where female carriers of X-linked disorders can have differential disease penetrance as a function of skewing.

But what about the autosomes? Is the allelic expression of autosomal genes epigenetically regulated? And if so, could it have an impact on disease risk?

In this work, we uncover one major axis of random variation with a large and permanent regulatory influence on the allelic expression on autosomes: developmental stochasticity. By assaying the transcriptome of wild monozygotic quadruplets of the nine-banded armadillo, we find that persistent changes occur early in development, and these give rise to clear transcriptional signatures, which uniquely characterize individuals relative to siblings. Our central experimental strategy is to measure gene expression over time and look for signatures permanently distinguishing siblings from one another. As an aggregate readout of gene regulation between the genetically identical individuals, gene expression serves as a likely intermediate to capture purely non-genetic regulatory variability with an influence on phenotype.

We find that purely stochastic variation in development has a large and permanent impact on gene expression. Using allelic imbalances, we timed the contribution of developmental stochasticity within our data to the assignment of tissue-specific epigenetic marks. Using expression profiles, including co-expression and human twin data, we determined conserved functions affected by developmental stochasticity. Comparing these results to human twins, we find the transcriptional signatures, which define individuals exhibit, conserved co-expression, suggesting a substantial fraction of phenotypic and disease discordance within mammals arises from regulatory stochasticity occurring early in development. We examine regulatory basis of the largest effect size changes in single cell data.

Genetic variation, epigenetic regulation and major environmental stimuli are key contributors to phenotypic variation, but the influence of minor perturbations or "noise" has previously been difficult to assess in mammals. By using armadillos as a model, we control for genetic and environmental factors and reveal early developmental stochasticity as a major source of variability between individuals.

BIOGRAPHY

Dr. Gillis is an Associate Professor of Computational Genetics at Cold Spring Harbor Laboratory. Since starting his own lab at Cold Spring Harbor Laboratory in 2012, his research has aimed to understand the flow of information from the genome to whole organism biology through modeling and analysis of functional genomics data. This research is broadly integrative across modalities, systems, and even species, but also integrative across levels of organization, using molecular processes within cells to understand how and why cells diversify and how that diversity, in turn, affects organism phenotype.

As functional genomics data has continued to increase in abundance and specificity, Dr. Gillis' lab has benefited from the opportunities to provide organizing frameworks, grounded in both biology and statistical insight. They have been particularly interested in determining base vocabularies to compare quite disparate data with the goal of better exploiting conservation as a central principle to understand function in physiological systems.

A particular focus within his lab is the analysis of gene co-expression, or the shared expression profile of genes across conditions. Genes which express under similar conditions will tend to share functions, and by tailoring data and methods, this can usefully model biological systems from cells to organisms to species. In addition to research on cell identity and co-expression, Dr. Gillis has experience in the development of methods and bioinformatics pipelines for external use, including stand-alone packages and web-based user-friendly analysis tools.

He is strongly dedicated to assessments of robustness and replicability, particularly in novel data. His lab's research focuses on making not only their own methods available, but also improving the utility of related data from other researchers. Dr. Gillis' graduate training was in Computational Neuroscience. He obtained a Ph.D. with Frances Skinner from the University of Toronto. His post-doc, with Paul Pavlidis, at the University of Toronto focused on largescale integration of expression data to improve our understanding of gene function.

MOLLY BURHANS

Founder and Executive Director, GoodLands

ABSTRACT

It's the End of the World as We Know It (and I feel fine)

Despite dire warnings about human-driven global ecosystems collapse, our efforts to curb environmental destruction continue to fall short. What we do over the next decade will determine the fate of life on earth. Humans unique physical and cognitive capacities have enabled our increasingly efficient exploitation of the environment through technology. Civilization's advancement relies on the concomitant development of technology and science. These advances have improved the quality and duration of life for an increasing percentage of the human population. They have also led to our current planetary predicament. Technology and science today allow us to measure and track the state of our environment. We now understand the extent of damage caused by human activity and the critical situation we find ourselves in. The continuation of civilization will be enabled not by our collective regression, but by using our best technology, most advanced science, novel collaborations, and creativity to reframe our relationship with nature. GoodLands is one of the most internationally recognized emerging efforts among an increasing number of institutions, organizations, and individuals whose work embraces this integrative approach.

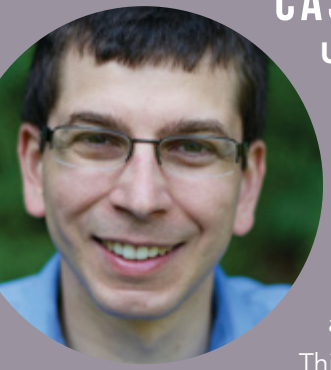
GoodLands is a social enterprise that helps organizations use and manage their properties to restore ecosystems and increase the well-being of people in their communities. GoodLands' model has been recognized by the United Nations as one the most innovative, feasible, and scalable approaches to ecosystem restoration. It uses cutting edge technology to integrate a community's needs and ideas with a foundational understanding of their property portfolio's current and potential impacts. Our solutions incorporate emerging research from public health, environmental sciences, and economics.

GoodLands services were initially developed for the largest nongovernmental landholder in the world; the Catholic Church. Molly quickly learned that The Church also had not updated their record keeping systems in a long time. It turned out that the Vatican's last map update was during the Holy Roman Empire. Before the age of thirty Molly led the development of the first digital map of the Catholic Church in history. She has since received Papal approval to trial-run a geographic institution in the Vatican. GoodLands created a climate solution that can be used to transform any organization's real estate portfolios into positive forces for planetary change. The story behind how this all came to be is a wild adventure that has led Molly through the halls of Vatican palaces, slums in Nairobi, forested mountains owned by monasteries, and beyond. Like most of life's great stories, this one begins with DNA replication stress.

BIOGRAPHY

Molly Burhans combines her passion for people and the planet with her experience in design thinking, business development, and scientific research to understand and transform complex systems and make land work for good. As the Founder and Executive Director of GoodLands, Burhans brings her unique combination of skills and networks together to help communities manage their property for environmental, social, and financial impact. She was the Chief Cartographer for the first global data-based maps of the Catholic Church, and her trailblazing environmental and cartographic work with the Vatican has received international coverage and acclaim. Burhans is an Ashoka Fellow (2018), the 2019 UN Young Champion of the Earth for North America, and a Henry Arnhold Fellow (2020). She has been involved with the Vatican Youth Symposium, Vatican Arts and Technology Council, United Nations Youth Assembly, the Buckminster Fuller Catalyst program, and was an Echoing Green Fellowship finalist. She has also been an invited speaker at numerous conferences and institutions, including but not limited to Harvard University, Yale University, Esri, the Pontifical Academy of Sciences, and ICT4D. She holds degrees in Philosophy (Canisius '14) and Ecological Design (Conway School '15).

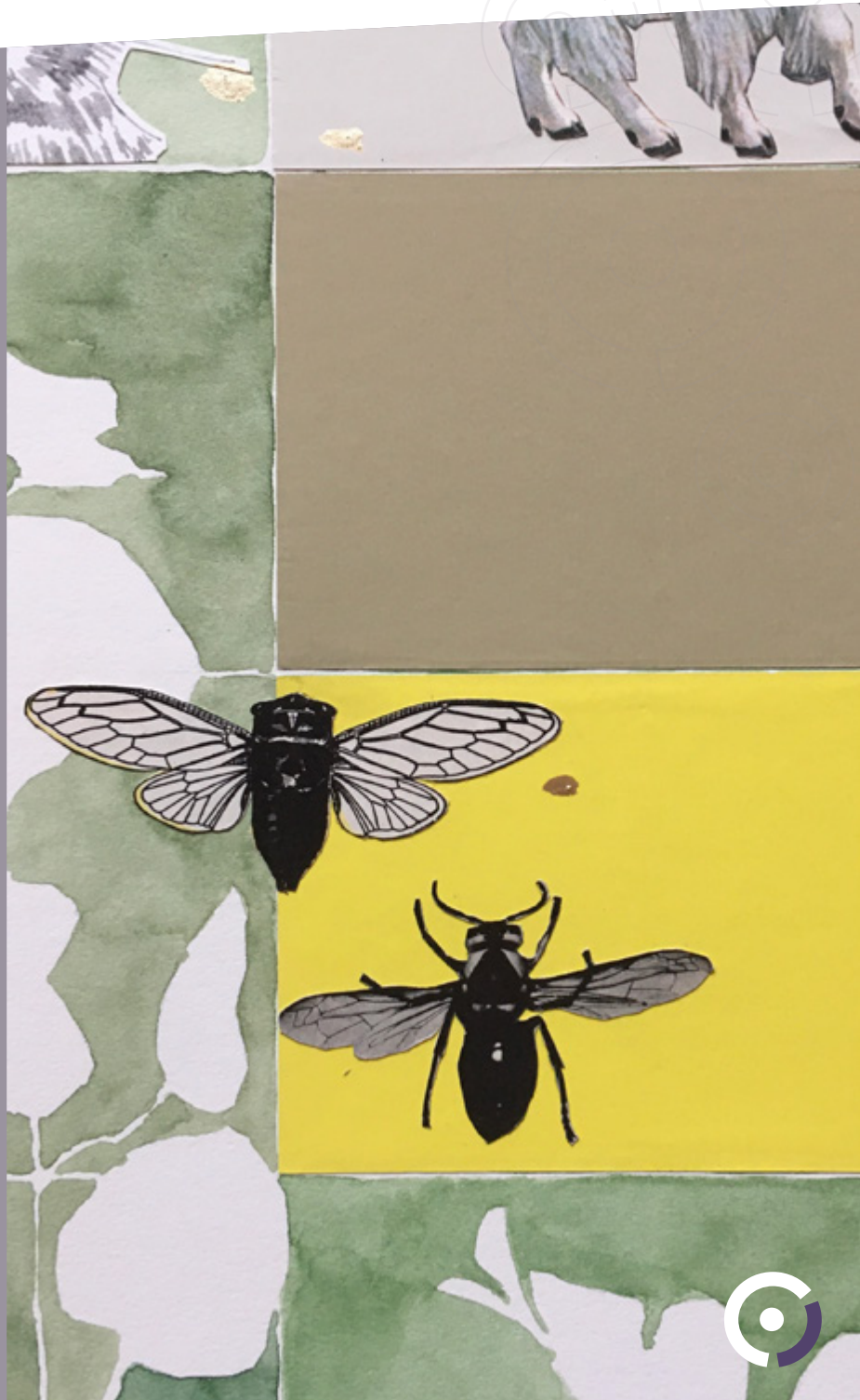
MODERATOR DAY 2



CASEY GREENE, PH.D.

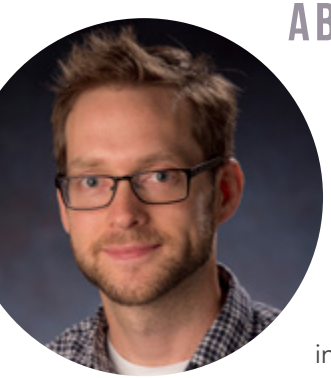
University of Colorado School of Medicine

Casey is a Professor in the Department of Biochemistry and Molecular Genetics and the founding Director of the Center for Health AI in the University of Colorado School of Medicine. His lab develops machine learning methods that integrate distinct large-scale datasets to extract the rich and intrinsic information embedded in such integrated data. This approach reveals underlying principles of an organism's genetics, its environment, and its response to that environment. Extracting this key contextual information reveals where the data's context doesn't fit existing models and raises the questions that a complete collection of publicly available data indicates researchers should be asking. In addition to developing deep learning methods for extracting context, a core mission of his lab is bringing these capabilities into every molecular biology lab through open, transparent science conducted by a diverse team of researchers. Before starting the Integrative Genomics Lab in 2012, Casey earned his Ph.D. for his study of gene-gene interactions in the field of computational genetics from Dartmouth College in 2009 and moved to the Lewis-Sigler Institute for Integrative Genomics at Princeton University where he worked as a postdoctoral fellow from 2009-2012. The overarching theme of his work has been the development and evaluation of methods that acknowledge the emergent complexity of biological systems.



AARON CLAUSET, PH.D.

Associate Professor Department Of Computer Science and Biofrontiers Institute University Of Colorado;
External Faculty Santa Fe Institute



ABSTRACT

Prediction and Its Limits in Scientific Discovery

The desire to predict discoveries, to have some idea, in advance, of what will be discovered, by whom, when, and where, pervades nearly all aspects of modern science, from individual scientists to publishers, from funding agencies to hiring committees. The successes and failures of predicting scientific discoveries -- the creation of new knowledge -- have broad implications for understanding the nature of knowledge itself, and the likely future role that computers and artificial intelligence can play in its creation. In this talk, I'll begin with a simple conceptual framework for thinking broadly about prediction and its limits for scientific discovery. I'll then do a dive deep into two areas where accurate predictions would be highly useful for science policy: the predictability of researcher productivity over an entire career, and the predictability of when in a career scientist make their most important discoveries. To close, I will draw some broader conclusions from these results about the future of science, and I'll describe strategies and dangers for scientific discovery in the age of big data.

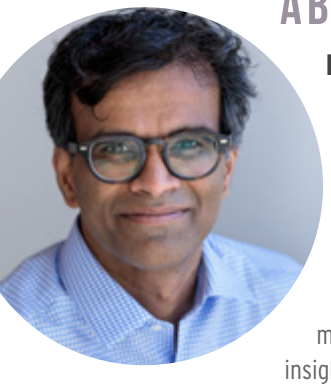
BIOGRAPHY

Dr. Clauset is an Associate Professor in the Department of Computer Science and the BioFrontiers Institute at the University of Colorado Boulder, and is External Faculty at the Santa Fe Institute. He received a Ph.D. in Computer Science, with distinction, from the University of New Mexico, a BS in Physics, with honors, from Haverford College, and was an Omidyar Fellow at the prestigious Santa Fe Institute. In 2016, he was awarded the Erdos-Renyi Prize in Network Science, and since 2017, he has been a Deputy Editor at *Science Advances*, responsible for the Social, Computing, and Interdisciplinary Sciences.

Clauset is an internationally recognized expert on network science, data science, and machine learning for complex systems. He is best known for his seminal work on developing statistical and computational methods for clustering networks, predicting missing links, and modeling highly-variable quantities in complex systems. His research program aims to advance computation as a third pillar of science, co-equal with experiment and mathematical theory as a method for generating new scientific knowledge. This program spans both methods development and applications, and includes work on evolutionary biology, cancer, the statistics of global terrorism, and the "science" of science itself. His work has appeared in many prestigious scientific venues, including *Nature*, *Science*, *PNAS*, *SIAM Review*, *Science Advances*, *Nature Communications*, *AAAI*, and *ICDM*. His work has also been covered in the popular press by *Quanta Magazine*, the *Wall Street Journal*, *The Economist*, *Discover Magazine*, *Wired*, the *Boston Globe* and *The Guardian*.

SENDHIL MULLAINATHAN, PH.D.

Roman Family University Professor of Computation and Behavioral Science,
University of Chicago, Booth



ABSTRACT

Machine and Human Intelligence: Algorithms as a Source of Bias or Insight

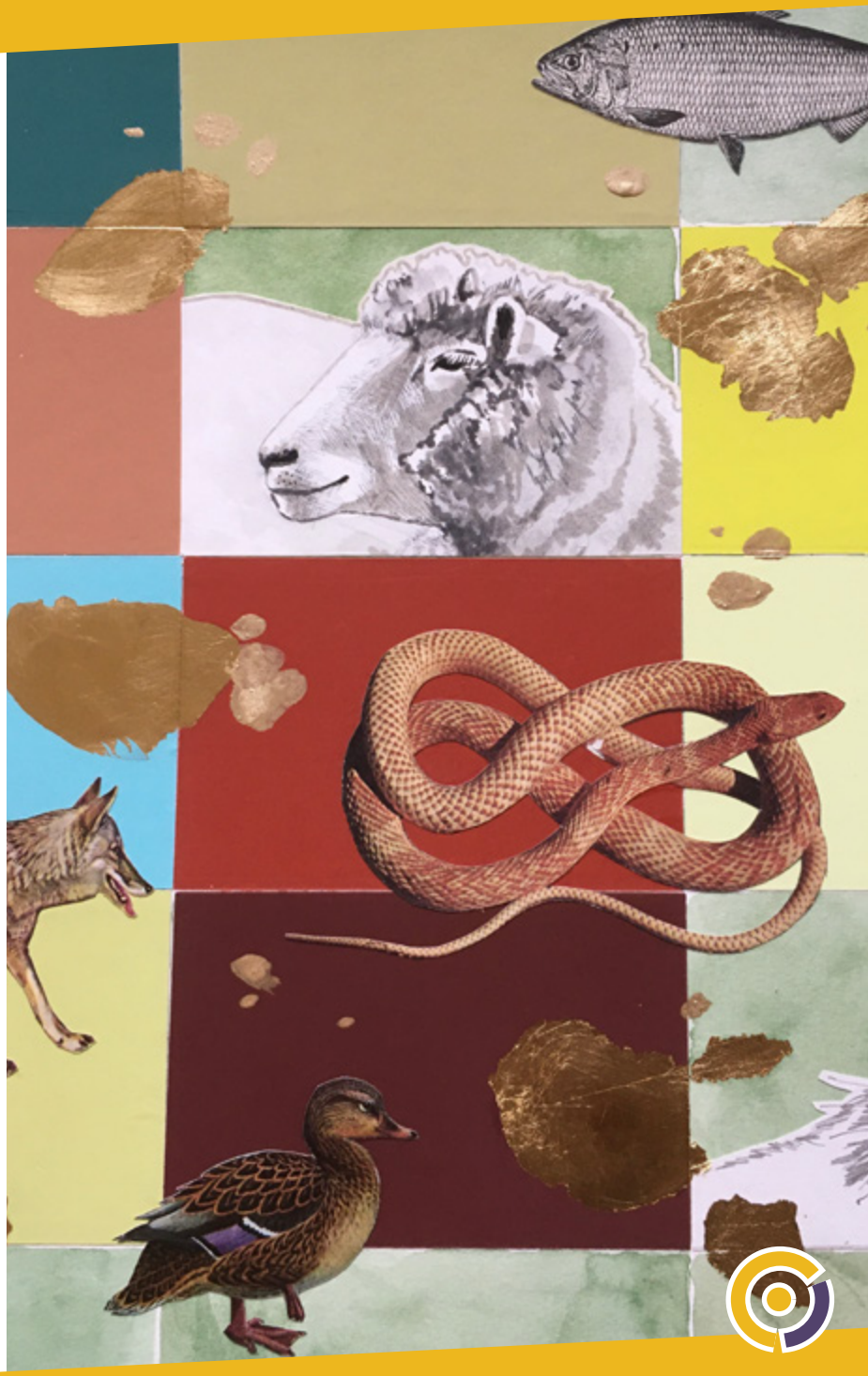
BIOGRAPHY

Dr. Mullainathan is the Roman Family University Professor of Computation and Behavioral Science at Chicago Booth. His current research uses machine learning to understand complex problems in human behavior, social policy, and especially medicine, where computational techniques have the potential to uncover biomedical insights from large-scale health data.
He currently teaches a course on Artificial Intelligence.

In past work he has combined insights from economics and behavioral science with causal inference tools–lab, field, and natural experiments–to study social problems such as discrimination and poverty. He recently co-authored *Scarcity: Why Having too Little Means so Much* and writes regularly for the *New York Times*. Additionally, his research has appeared in a variety of publications including the *Quarterly Journal of Economics, Science, American Economic Review, Psychological Science*, the *British Medical Journal*, and *Management Science*.

Dr. Mullainathan helped co-found a non-profit to apply behavioral science (ideas42), co-founded a center to promote the use of randomized control trials in development (the Abdul Latif Jameel Poverty Action Lab), serves on the board of the MacArthur Foundation, has worked in government in various roles, is affiliated with the NBER and BREAD, and is a member of the American Academy of Arts and Sciences.

Dr. Mullainathan is a recipient of the MacArthur "Genius Grant," has been designated a "Young Global Leader" by the World Economic Forum, was labeled a "Top 100 Thinker" by *Foreign Policy Magazine*, and was named to the "Smart List: 50 people who will change the world" by *Wired Magazine* (UK). His hobbies include basketball, board games, googling, and fixing up classic espresso machines.



ROBIN DOWELL, D.S.C.

Associate Professor in Molecular, Cellular and Developmental Biology and Computer Science at University of Colorado Boulder;
Co-Founder Arpeggio Biosciences

ABSTRACT

Cracking the Regulation Code

Dr. Francis Collins, director of the National Institutes of Health (NIH), describes DNA as the "language of life". It's a language written in a cryptic, simple four-letter biochemical alphabet. The NIH has spent millions to record, or write down the code in books, a.k.a. genomes. Volumes with titles as exciting as "Human", "Mouse", and more recently "Owl monkey" have been release over the last 20 years. Reading those books is the next major challenge of biology.

In December of 2020, code breakers announced they had finally deciphered a message left 51 years earlier by the Zodiac Killer. Some find it astonishing that it took years to decode this one message. The time commitment necessary to crack the Zodiac's cipher is just a fraction of what it will take to crack the code of life.

Deciphering the human genome, with all its complexity, is a far more challenging task than breaking the Zodiac's code. Each human genome encodes massive amounts of information in billions of bases. Readout of the genome results in not only a startling diversity of cell types, tissues, and systems, but also how each cell responds to its environment. Our challenge is to decode the genome and understand how it is regulated. This challenge requires some patience and dedication devoted to the Zodiac's message. While it is not a fast process, it is a necessary and thrilling ride. Ultimately, decoding the genome has vast implications for agriculture, ecology, and medicine.

BIOGRAPHY

Dr. Dowell is an Associate Professor in Molecular, Cellular and Developmental Biology and Computer Science at University of Colorado Boulder. Dr Dowell is also co-founder of the Boulder biotech startup Arpeggio Biosciences and holds a patent for the assessment of transcription factor activity.

In the human genome, the majority of disease associated mutations reside within regulatory regions, but how these mutations lead to disease is not well understood. To tackle this problem, Dr. Dowell uses computational biology and molecular genetics to decipher transcription regulation and the activity of transcription factors, the major drivers of regulation. In addition to pursuing translational research activities, Dr. Dowell is a dedicated educator focused on bringing bioinformatics and data science initiatives to the University of Colorado Boulder campus.

Dr. Dowell earned two bachelor's degrees (Computer Engineering and Genetics) from Texas A&M University, a D.Sc. in Biomedical Engineering from Washington University in St Louis, and did postdoctoral research at MIT. She is a member of the Linda Crnic Institute and a Boettcher Investigator.

PANEL DISCUSSION The Evolution of Machine Intelligence

CRAIG J. MUNDIE

President, Mundie & Associates

Craig J. Mundie is President of Mundie & Associates. He joined Microsoft in 1992. In 2014 he retired from Microsoft as Chief Research and Strategy Officer (since 2007) and was the Principal Technology-Policy Executive (since 1998). Previously he was CEO and co-Founder of Alliant Computer Systems.

He was co-Executive Chairman of Bridgewater Associates (2015-2016). He is a Director of the Institute for Systems Biology. He advises Microsoft, Bridgewater, Exicure, SomaLogic, the CFR, and the Cleveland Clinic. Mundie served Presidents Clinton, Bush, and Obama on the NSTAC and Obama on PCAST.

MIRA MURATI

SVP of Research, Product & Partnerships, OpenAI

Mira Murati has been working on practical applications of technology and their impact on society. She currently is SVP of Research, Product & Partnerships at OpenAI. The goal of OpenAI is to advance digital intelligence in the way that is most likely to benefit humanity as a whole.

Murati previously has led the product and engineering teams at Leap Motion building spatial human-machine interfaces. She also led the design, development, and launch of vehicle products at Tesla Motors including the Model X, as well as innovative programs in aerospace.

She holds a Bachelor of Engineering from Thayer School of Engineering at Dartmouth.

LARRY HUNTER, PH.D.

Director of the University of Colorado's Computational Bioscience Program Professor of Pharmacology (School of Medicine) and Computer Science (Boulder)

Larry Hunter is the Director of the University of Colorado's Computational Bioscience Program and a Professor of Pharmacology (School of Medicine) and Computer Science (Boulder). He is widely recognized as one of the founders of bioinformatics; he served as the first President of the International Society for Computational Biology (ISCB), and created several of the most important conferences in the field, including ISMB, PSB, and VizBi. Dr. Hunter's research interests span a wide range of areas, from cognitive science to rational drug design. He has published more than 100 scientific papers, holds two patents, and has been elected a fellow of both the ISCB and the American College of Medical Informatics. His primary focus recently has been the integration of natural language processing, knowledge representation, machine learning, and advanced visualization techniques to address challenges in interpreting data generated by high throughput molecular biology.

He received a Ph.D. in computer science from Yale University in 1989, and then joined the NIH as a staff scientist, first at the National Library of Medicine and then at the National Cancer Institute, before coming to Colorado in 2000.

DAN SHEFET

Advisor to UNESCO/Mahatma Gandhi Institute of Education for Peace and Sustainable Development (MGIEP)

ABSTRACT

Regulating AI

Since the Symposium in 2019, we have witnessed a clear trend towards stronger privacy protection both in the US (especially California) and in Europe. In addition, the influence of platforms on behavior and ultimately democracy has been recognized.

The European Commission's Digital Services Act was published on the 15th of December 2020 and creates a new liability standard for such platforms. The latest development in tech regulation is the Commission's draft Regulation on Artificial Intelligence (published on 21 April).

This presentation will focus on this recent initiative, which may be seen as the logical sequel to privacy and accountability regulation.

BIOGRAPHY

Advisor to UNESCO/Mahatma Gandhi Institute of Education for Peace and Sustainable Development (MGIEP)

Expert with the Parliamentary Assembly of the Council of Europe's Committee on Culture, Science, Education and Media

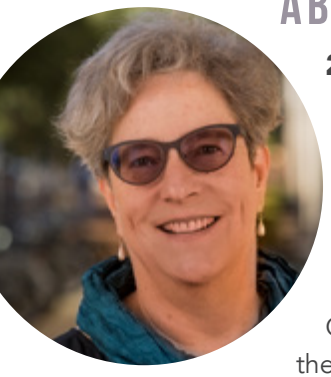
Expert with UNESCO and UN's Office on Genocide Prevention and Hate Speech

Member of the American Law Institute

Dan Shefet is a French lawyer, born in Denmark, and the author of the individual specialist report to UNESCO on 'Online Radicalization'. Expert with the Council of Europe on the Internet Ombudsman and President of AAID. Shefet holds a philosophy degree and a law degree from the University of Copenhagen in addition to law studies in France. He specializes in European law as well as Human Rights, in general, and in the IT environment, in particular.

Shefet is a frequent speaker at international conferences on IT law, data privacy, and content regulation. In 2014, he founded the Association for Accountability and Internet Democracy (AAID). The main objective of this association is to introduce a general principle of accountability on the internet in order to secure the protection of human integrity.

REBECCA TRUMBULL & ERIC TRUMBULL, PH.D.



ABSTRACT

23 & Us - Family Ties, Family Lies

What's in a [family] name? That which we call a Trumbull by any other surname would feel as sweet. Or would it?

Or how about Murphy?

Or how about going from thinking your family's heritage is Spanish to learning that the heritage is Pakistani? And how reliable is that information, anyway?

The two youngest Trumbull siblings take us through the journey of their lives as the "mistakes" of the family–though mistakes of a different kind than what they had thought all their lives. What they discover late in their lives is that lifelong family friends were intertwined in ways they had never anticipated. They will explore the nature of "family," of genetics, of identity, in a world that changed for them a few years ago from the results of DNA testing.

What is the significance of our family name? And why does it seem important to us? What influence does it have on our identity? What's in your name? What difference does biology make?

And who, by the way, owns the truth about one's own self?

And what do so many people with "genetic identity issues" mean for the society at large? For the social work community? For the scientific community? For politics and education, finance and social services, etc.?

BIOGRAPHY

Rebecca Trumbull

Trumbull is trained as an architectural historian and never veers far from her chosen path, maintaining a love of architecture and, in particular, planned communities such as Sunnyside Gardens in Queens, NY. While living in Chicago she became a docent extraordinaire for the Chicago Architecture Center's Architectural River Cruise. Nurturing a love of her interest in medicine, she enjoyed a career in academic medicine for twenty years of her life in the role of Strategic Planner in a plethora of top notch schools of medicine throughout the US, including UPenn, Stanford, UCSF, UChicago, and Northwestern. She recently retired from Stanford University, her most beloved academic institution, where she worked in the Distinguished Careers Institute, a program for people in later life returning to campus for a year or more to reflect upon their lives and reassess their purpose, wellness, and community. She and her husband live in Berkeley, California, in the ninth of nine houses they have renovated throughout their lives together. Her children, Daniel and Bettina, have brought tremendous joy to their lives.

Eric Trumbull, Ph.D.

Trumbull is a retired professor of Theatre and Communications who made a living of sorts doing theatre of one kind or another - teaching theatre and directing productions in an educational setting and performing in local non-professional theatres. His interests lie primarily in the intersection of art and information/propaganda, specifically the relationship between public performance and social/political change. Since retirement, he has enjoyed performing in community theatre and working on a history of his family.

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May 19 & 20, 2022

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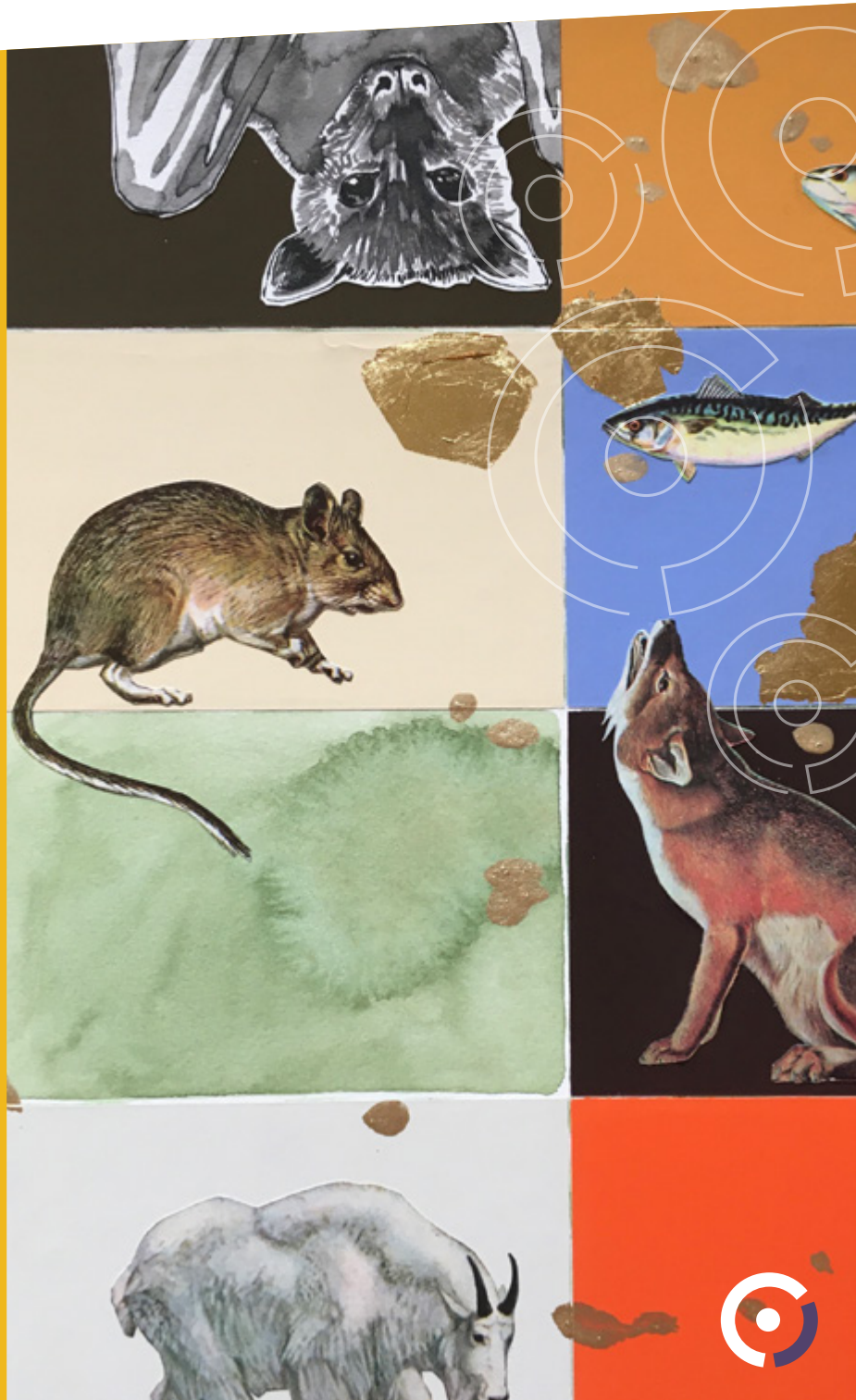

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