COLUMBIA PRECISION MEDICINE INITIATIVE

ADVANCES IN PRECISION MEDICINE

GENOMIC INNOVATION AND PRECISION MEDICINE: READING, IMAGING, EDITING, AND WRITING THE GENOME

TUESDAY, APRIL 5, 2022

COLUMBIA | PRECISION MEDICINE

GENOMIC INNOVATION AND PRECISION MEDICINE: READING, IMAGING, EDITING, AND WRITING THE GENOME

Conference Schedule

9:00 a.m.	**Tom Maniatis, PhD:** Welcome
READING	
9:15 a.m.	**Jay Shendure, MD, PhD,** University of Washington
9:55 a.m.	**Rahul Satija, PhD,** New York Genome Center (NYGC); New York University (NYU
IMAGING	
10:35 a.m.	**Joakim Lundeberg, PhD,** KTH Royal Institute of Technology
11:15 a.m.	**Xiaowei Zhuang, PhD,** Harvard University
11:55 a.m.	**Ed Boyden, PhD,** MIT
12:35 p.m.	**Lunch**
EDITING	
1:30 p.m.	**Feng Zhang, PhD,** MIT
WRITING	
2:10 p.m.	**Jef D. Boeke, PhD, DSc,** NYU Grossman School of Medicine
FUNCTION	
2:50 p.m.	**Tuuli Lappalainen, PhD,** KTH Royal Institute of Technology; SciLifeLab, Sweden; New York Genome Center
3:30 p.m.	**Olga Troyanskaya, PhD,** Lewis-Sigler Institute for Integrative Genomics; Flatiron Institute, Simons Foundation
FUTURE	
4:10 p.m.	**George Church,** PhD, Harvard Medical School; PersonalGenomes.org
4:50 p.m.	**Final Remarks**
5:00 p.m.	**Networking Social**

Welcome Letter

I am delighted to welcome you to the Sixth Annual Columbia Precision Medicine Initiative (CPMI) conference, Advances in Precision Medicine: Genomic Innovation and Precision Medicine.

We are thrilled to be gathering in person again, but we understand that some attendees need to attend virtually, so this year's conference is in a hybrid format. We are grateful for the technology innovations that enable us to connect in this way.

Our topic this year is Genomic Innovation and Precision Medicine, and our objective is to provide an up-to-date perspective on the impact of genomic technologies on understanding the functional consequences of disease-associated DNA sequence variation on cellular and organismic function. For example, technologies such as multi-omics can simultaneously interrogate RNA transcription, chromatin modification, and chromosome structure in individual cells. These technologies are making it possible to probe deeply into the functional consequences of DNA sequence variation that associates with disease, at single cell, single molecule, and atomic resolution.

We have been fortunate to assemble an extraordinary group of international leaders in the development and application of these technologies to discuss progress and challenges.

I sincerely hope that you enjoy, and are informed by, the conference.

Tom Maniatis, PhD
Director, Columbia University Precision Medicine Initiative
Isidore S. Edelman Professor of Biochemistry and Molecular Biophysics

Jay Shendure, MD, PhD

Investigator, Howard Hughes Medical Institute; Professor of Genome Sciences, University of Washington; Director, Allen Discovery Center for Cell Lineage Tracing; Scientific Director, Brotman Baty Institute for Precision Medicine

Jay Shendure is an investigator of the Howard Hughes Medical Institute, professor of genome sciences at the University of Washington, director of the Allen Discovery Center for Cell Lineage Tracing, and scientific director of the Brotman Baty Institute for Precision Medicine. His 2005 doctoral thesis with George Church included one of the first successful reductions to practice of next-generation DNA sequencing. Dr. Shendure's research group in Seattle pioneered exome sequencing and its earliest applications to gene discovery for Mendelian disorders and autism; cell-free DNA diagnostics for cancer and reproductive medicine; massively parallel reporter assays, saturation genome editing; whole organism lineage tracing; and massively parallel molecular profiling of single cells. Dr. Shendure is the recipient of the 2012 Curt Stern Award from the American Society of Human Genetics, the 2013 FEDERAprijs, a 2013 NIH Director's Pioneer Award, the 2014 HudsonAlpha Life Sciences Prize, the 2018 Richard and Carol Hertzberg Prize for Technology Innovation, and the 2019 Richard Lounsbery Award from the National Academy of Sciences. He serves or has served as an advisor to the NIH Director, the US Precision Medicine Initiative, the National Human Genome Research Institute, the Chan-Zuckerberg Initiative, and the Allen Institutes for Cell Science and Immunology. He received his MD and PhD degrees from Harvard Medical School in 2007.

Systematic Reconstruction of Developmental Trees

ABSTRACT

Mammalian embryogenesis is a remarkable process wherein, within a few weeks, a single cell zygote gives rise to millions to billions of cells expressing a panoply of molecular programs, including much of the diversity that will subsequently be present in adult tissues. Although intensively studied, a comprehensive delineation of the cellular trajectories and lineages that comprise in vivo mammalian development remains elusive. In a first line of work, we are developing and applying methods to profile single cell gene expression and chromatin accessibility throughout mouse development, from zygote to pup, as well as to integrate these data across time, compare such maps across species, etc. In a second line of work, we are developing a new generation of in vivo molecular recorders that are temporally resolved ("DNA Ticker Tape"), with the long-term goal of reconstructing high-density cell lineages of large model organisms, both to understand normal development and to shed light on myriad genetic disorders of development.

Rahul Satija, PhD

Core Faculty Member, New York Genome Center (NYGC); Associate Professor, Center for Genomics and Systems Biology, New York University (NYU)

Rahul Satija, PhD, is a core faculty member at the New York Genome Center (NYGC), with a joint appointment as associate professor at the Center for Genomics and Systems Biology at New York University (NYU). Prior to joining the NYGC, Dr. Satija was a postdoctoral researcher at the Broad Institute of Harvard and MIT, where he developed new methods for single cell analysis. The Satija Lab focuses on developing computational and experimental methods to sequence and interpret the molecular contents of a single cell. His lab applies single cell genomics to understand the causes and consequences of cell-to-cell variation, with a particular focus on immune regulation and early development. Dr. Satija is a recipient of the NIH New Innovator Award and, in 2020, was selected to direct an NIH Center for Excellence in Genomic Science. Dr. Satija holds a BS degree in biology and music from Duke University and obtained his PhD in statistics from Oxford University as a Rhodes Scholar.

Integrated Analysis of Single-Cell Data across Technologies and Modalities

ABSTRACT

Single-cell RNA-seq has transformed our ability to characterize cell states, but in order to understand cellular identity and function, new methods are needed to integrate these measurements with additional molecular modalities. Here, I will present a suite of experimental technologies and computational methods designed for this purpose. Multimodal technologies (CITE-seq, ASAP-seq, and scCUT&Tag-pro) pair simultaneous measurements of gene expression, chromatin accessibility, and histone modifications with a shared panel of cell surface proteins to facilitate harmonization. Alongside these technologies, tailored computational methods (scChromHMM) leverage these rich datasets to characterize genome-wide heterogeneity in chromatin state at single-cell resolution. Finally, techniques from the field of representation and dictionary learning ("bridge integration") enable the robust integration of a wide diversity of single-cell technologies, even when they measure different sets of features.

Joakim Lundeberg, PhD

Professor in Molecular Biotechnology, KTH Royal Institute of Technology

Joakim Lundeberg, PhD, is a professor in molecular biotechnology at the KTH Royal Institute of Technology since 2000. Dr. Lundeberg was one of the co-founders of SciLifeLab, in 2010, a national and multiuniversity effort in large-scale life sciences providing access to infrastructures such as genomics, proteomics, imaging, metabolomics, and drug development. He has, during the most recent years, focused on spatial transcriptomics technology that enables a detailed description of gene expression patterns in tissue sections (https://www.spatialresearch.org/). Dr. Lundeberg has several publications demonstrating the development of technology and examples of the impact of technology in biology. The spatially resolved transcriptomics was announced as the Method of the Year 2020 by *Nature Methods,* and spatial transcriptomics is commercially available from 10X Genomics Inc as Visium. The technology is now also part of the infrastructure offered at SciLifeLab.

Exploring the Spatial and Multimodal Landscape in Tumors

ABSTRACT

The proximal environment of tumors forms an intricate network of various cell-cell interactions, and spatially resolved transcriptomics carries great potential to unravel signaling pathways, which can be screened for new therapeutic targets and provide a fundamental understanding of tumor biology. We have previously reported using spatial transcriptomics methodology in prostate, breast, and squamous cell cancer. Here, a computational deconvolution approach was used to define and characterize tumor-specific expression profiles of multifocal cancer sites together with stromal and immune compartments. This unbiased analysis of the tumor revealed that cancer-associated expression patterns appeared in regions where histological evidence was missing, thus highlighting the potential of unbiased gene expression approaches to capture signals otherwise missed by conventional histopathology. Indeed, defining the transition from benign to malignant tissue by molecular strategies will be fundamental to improving cancer's early diagnosis. In this presentation, we describe an approach for an unsupervised analysis to study spatial genome integrity in situ to gain molecular insight into clonal relationships. We demonstrate that genome-wide copy number variation reveals distinct clonal patterns within tumors and in nearby benign tissue. Our results suggest a model for genomic instability in histologically benign tissue that may represent early events in cancer evolution. We highlight the power of an unsupervised approach to capture the molecular and spatial continuums in a tissue context and challenge the rationale for treatment paradigms.

Xiaowei Zhuang, PhD

David B. Arnold Professor of Science and Investigator, Howard Hughes Medical Institute, Harvard University

Xiaowei Zhuang is the David B. Arnold Professor of Science and an investigator of Howard Hughes Medical Institute. She pioneered the development of super-resolution imaging and genome-scale imaging methods. She invented STORM, a super-resolution imaging method, and discovered novel cellular structures using STORM. She invented a single-cell transcriptome and genome imaging method, MERFISH, and made discoveries in the areas ranging from 3D genome organization and gene regulation in cells to cellular organization in tissues, using MERFISH.

Zhuang received her B.Sc. degree in physics from the University of Science and Technology of China, her Ph.D. in physics under the supervision of Prof. Y. R. Shen from University of California at Berkeley, and her postdoctoral training in biophysics in the lab of Prof. Steven Chu at Stanford University. She joined the faculty of Harvard University in 2001 and became a Howard Hughes Medical Institute investigator in 2005.

Zhuang is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, and the American Philosophical Society; and a foreign associate of the Chinese Academy of Sciences and the European Molecular Biology Organization. She received honorary doctorate degrees from Stockholm University and Delft University of Technology. She has received many awards, including the FNIH Lurie Prize in Biomedical Sciences, the Vilcek Prize in Biomedical Science, the Breakthrough Prize in Life Sciences, the Pearl Meister Greengard Prize, the National Academy of Sciences Award for Scientific Discovery, the Heineken Prize for Biochemistry and Biophysics, the National Academy of Sciences Award in Molecular Biology, the Raymond and Beverly Sackler International Prize in Biophysics, the Max Delbruck Prize in Biological Physics, and the MacArthur Fellowship.

Spatially Resolved Single-Cell Genomics and Cell Atlases of Complex Tissues

ABSTRACT

Inside living organisms, thousands of different genes function collectively to give rise to cellular behavior and tissue function. Understanding the behaviors and functions of cells and tissues thus require imaging at the genome scale, which will advance our understanding in many areas of biology, ranging from gene regulation in cells to the development of cell fate and organization of cell types in complex tissues. We developed a single-cell transcriptome and genome imaging method, multiplexed error-robust fluorescence in situ hybridization (MERFISH), which allows RNA, DNA, and epigenomic mark imaging at the genome scale. Using this method, we

demonstrated simultaneous imaging, localization, and quantification of thousands of genes and genomic loci in individual cells. This approach enabled in situ, spatially resolved transcriptomic profiling, epigenomic profiling, and 3D genome organization mapping in single cells. The ability to perform single-cell gene expression profiling in intact tissues further enabled the identification, spatial mapping, and functional annotation of distinct cell types in intact tissues. In this talk, I will describe the MERFISH technology and its applications, with a focus on mapping the molecular, spatial, and functional organizations of cell types in the brain.

Ed Boyden, PhD

Y. Eva Tan Professor in Neurotechnology, MIT; Investigator, Howard Hughes Medical Institute and MIT McGovern Institute; Professor of Brain and Cognitive Sciences, Media Arts and Sciences, and Biological Engineering, MIT

Ed Boyden is Y. Eva Tan Professor in Neurotechnology at MIT, an investigator of the Howard Hughes Medical Institute and the MIT McGovern Institute, and professor of Brain and Cognitive Sciences, Media Arts and Sciences, and Biological Engineering at MIT. He leads the Synthetic Neurobiology Group, which develops tools for analyzing and repairing complex biological systems, such as the brain, and applies them systematically to reveal ground truth principles of biological function and to repair these systems. These inventions include optogenetic tools, which enable control of neural activity with light; expansion microscopy, which enables ordinary microscopes to do nanoimaging; new tools for high-speed imaging of living biological signals and networks; noninvasive brain stimulation strategies that may help with conditions ranging from Alzheimer's to blindness; and new strategies for inexpensively creating 3-D nanotechnology. He co-directs the MIT Center for Neurobiological Engineering, which aims to develop new tools to accelerate neuroscience progress, and is a faculty member of the MIT Center for Environmental Health Sciences, Computational & Systems Biology Initiative, and Koch Institute.

Among other recognitions, Dr. Boyden has received the Wilhelm Exner Medal (2020), the Croonian Medal (2019), the Lennart Nilsson Award (2019), the Warren Alpert Foundation Prize (2019), the Rumford Prize (2019), the Canada Gairdner International Award (2018), the Breakthrough Prize in Life Sciences (2016), the BBVA Foundation Frontiers of Knowledge Award (2015), the Carnegie Prize in Mind and Brain Sciences (2015), the Jacob Heskel Gabbay Award (2013), the Grete Lundbeck Brain Prize (2013), the NIH Director's Pioneer Award (2013), and the Perl/UNC Neuroscience Prize (2011). He was named to the World Economic Forum Young Scientist list (2013) and the Technology Review World's "Top 35 Innovators under Age 35" list (2006) and is an elected member of the National Academy of Sciences (2019), the American Academy of Arts and Sciences (2017), the National Academy of Inventors (2017), and the American Institute for Medical and Biological Engineering (2018). His group has hosted hundreds of visitors to learn how to use new biotechnologies; and he also regularly teaches at summer courses and workshops in neuroscience and delivers lectures to the broader public, e.g., TED (2011), TED Summit (2016), and World Economic Forum (2012, 2013, 2016).

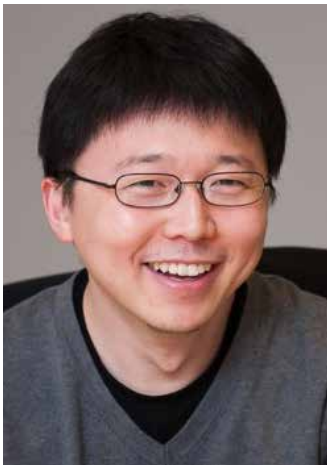
Dr. Boyden received his PhD in neurosciences from Stanford University as a Hertz Fellow, working in the labs of Jennifer Raymond and Richard Tsien, where he discovered that the molecular mechanisms used to store a memory are determined by the content to be learned. In parallel to his PhD, as an independent side project, he co-invented optogenetic control of neurons, which is now used throughout neuroscience. Previously, he studied chemistry at the Texas Academy of Math and Science at the University of North Texas, starting college at age 14, where he worked in Paul Braterman's group on origins of life chemistry. He went on to earn three degrees in electrical engineering and computer science, and physics, from MIT, graduating at age 19, while

working on quantum computing in Neil Gershenfeld's group. In the long term, he hopes that understanding how the brain generates the mind will help provide a deeper understanding of the human condition and help humanity achieve a more enlightened state.

Optical Tools for Analyzing and Controlling Biological Systems

ABSTRACT

Understanding and repairing complex biological systems, such as the brain, requires technologies for systematically observing and controlling these systems. We are discovering new molecular principles that enable such technologies. For example, we discovered that one can physically magnify biological specimens by synthesizing dense networks of swellable polymer throughout them, and then chemically processing the specimens to isotropically swell them. This method, which we call expansion microscopy, enables ordinary microscopes to do nanoimaging—important for mapping the brain across scales. Expansion of biomolecules away from each other also decrowds them, enabling previously invisible nanostructures to be labeled and seen. As a second example, we discovered that microbial opsins, genetically expressed in neurons, could enable their electrical activities to be precisely controlled in response to light. These molecules, now called optogenetic tools, enable causal assessment of how neurons contribute to behaviors and pathological states, and are yielding insights into new treatment strategies for brain diseases. Finally, we are developing, using new strategies such as robotic directed evolution, fluorescent reporters that enable the precision measurement of signals such as voltage and calcium. By fusing such reporters to self-assembling peptides, they can be stably clustered within cells at random points, distant enough to be resolved by a microscope but close enough to spatially sample the relevant biology. Such clusters, which we call signaling reporter islands (SiRIs), permit many fluorescent reporters to be used within a single cell, to simultaneously reveal relationships between different signals. We share all these tools freely and aim to integrate the use of these tools so as to enable comprehensive understandings of neural circuits.



Feng Zhang, PhD

Broad Institute; Investigator, McGovern Institute for Brain Research; James and Patricia Poitras Professor of Neuroscience, MIT; Howard Hughes Medical Investigator

Feng Zhang is a molecular biologist focused on improving human health. He played an integral role in the development of two revolutionary technologies, optogenetics and CRISPR-Cas systems, including pioneering the use of Cas9 for genome editing and discovering CRISPR-Cas12 and Cas13 systems and developing them for therapeutic and diagnostics applications.

Dr. Zhang's seminal work provided the foundation for CRISPR-based medicines, and his discoveries continue to fuel the clinical translation of CRISPR technologies. Additionally, he developed the diagnostic platform SHERLOCK, which is being leveraged to help monitor infectious diseases, including the coronavirus outbreak.

Zhang is a core member of the Broad Institute, an investigator at the McGovern Institute for Brain Research, the James and Patricia Poitras Professor of Neuroscience at MIT, and a Howard Hughes Medical Investigator. He is also a member of both the National Academy of Sciences and the American Academy of Arts and Sciences.

Exploration of Biological Diversity

ABSTRACT

Many powerful molecular biology tools have their origin in nature, and, often, in microbial life. From restriction enzymes to CRISPR-Cas9, microbes utilize a diverse array of systems to get ahead evolutionarily. We are interested in exploring this natural diversity through bioinformatics, biochemical, and molecular work to better understand the fundamental ways in which living organisms sense and respond to their environment and ultimately to harness these systems to improve human health. Building on our demonstration that Cas9 can be repurposed for precision genome editing in mammalian cells, we began looking for novel CRISPR-Cas systems that may have other useful properties. This led to the discovery of several new CRISPR systems, including the CRISPR-Cas13 family that target RNA, rather than DNA. We developed a toolbox for RNA modulation based on Cas13, including methods for precision base editing. We are expanding our biodiscovery efforts to search for new microbial proteins that may be adapted for applications beyond genome and transcriptome modulation, capitalizing on the growing volume of microbial genomic sequences and building on our bioengineering expertise. We are particularly interested in identifying new therapeutic modalities and vehicles for delivering cellular and molecular cargo. We hope that this combination of tools and delivery modes will accelerate basic research into human disease and open up new therapeutic possibilities.

Jef D. Boeke, PhD, DSc

Professor, Department of Biochemistry and Molecular Pharmacology, NYU Grossman School of Medicine; Sol and Judith Bergstein Director, Institute of System Genetics

Jef D. Boeke, PhD, DSc, founded and directs the Institute for Systems Genetics at NYU Langone Health. From 1985 to 2014, Dr. Boeke was on the faculty at Johns Hopkins University School of Medicine. He is known for foundational work on mechanistic and genomic aspects of retrotransposition. His lab develops new technologies in genetics, genomics, and synthetic biology. He elucidated a major form of mobile DNA, based on reverse transcription of RNA. He coined the term "retrotransposition" to describe this process, common to virtually all eukaryotic genomes and now studied by a worldwide scientific community. His systems-level studies helped elucidate intricate molecular mechanisms involved in retrotransposition in yeasts, mice, and humans.

In the area of synthetic genomics, Dr. Boeke's research group uses yeast as a platform for exploring the construction of fully synthetic chromosomes for practical and theoretical studies. He leads the international team synthesizing an engineered version of the yeast genome, Sc2.0, the first synthetic eukaryotic genome, and a consortium to explore the design and synthesis of even larger genomes. In 2018, he launched the "Dark Matter Project" (www.thedarkmatterproject.org), designed to better understand the "instruction manuals" that specify how human genes are expressed, using big DNA technology to build mammalian gene loci in yeast and then deliver those loci and their variants to stem cells. This has among other things led to a technology to very rapidly design and deploy humanized mouse models. During the SARS-CoV2 pandemic, he led a team of volunteers to develop ultra-high throughput coronavirus PCR testing, which led to the formation of the Pandemic Response Lab, the largest COVID-19 testing operation in New York City. Dr. Boeke has founded several biotechnology companies, including Avigen Inc., CDI Labs, Neochromosome, Inc., and the Pandemic Response Laboratory (Reopen Diagnostics, LLC) and serves on a number of scientific advisory boards.

Tormenting Genes and Genomes

ABSTRACT

Rapid advances in DNA synthesis techniques have made it possible to engineer diverse genomic elements, pathways, and whole genomes, providing new insights into design and analysis of systems. The synthetic yeast genome project, Sc2.0, is well on its way with the 16 synthetic *Saccharomyces cerevisiae* chromosomes now completed by a global team. The synthetic genome features several systemic modifications, including TAG/TAA stop-codon swaps, deletion of subtelomeric regions, introns, tRNA genes, transposons, and silent mating loci. Strategically placed loxPsym sites enable genome restructuring using an inducible evolution system termed SCRaMbLE, which can generate millions of derived variant genomes with predictable structures leading to complex genotypes and phenotypes. The fully synthetic yeast genome provides

a new kind of combinatorial genetics based on variations in gene content and copy number. Synthetic chromosome IV is the largest in the genome in terms of bp synthesized at over 1.4Mb. We have created an "inside out" version of this chromosome. Remarkably, the 3D structures of synthetic and native chromosomes are very similar despite the substantial number of changes introduced.

Chromosome I is the smallest *S. cerevisiae* chromosome, and anticipating issues of instability related to its small size, we decided to fuse it to other chromosomes–and were surprised by how easy it was to do this. This led to larger questions about whether it would be possibly to radically reduce chromosome number by continuing to fuse chromosomes. We completely reengineered the yeast karyotype, by systematically fusing pairs of telomeres and deleting single centromeres, generating an isogenic series of yeast ranging from n=16 to n=2. These strains show reproductive isolation and a massively altered 3D genome structure but are surprisingly "normal" and show high fitness. We have also developed a method that allows us to move megabase segments to distant locations in the genome in a single step, again, with surprisingly little impact on fitness.

Yet another form of genome torment is switching up the protein packaging of DNA. The substitution of human for yeast nucleosomes leads to a number of unexpected transcriptional and other phenotypes.

Last but not least, we reconfigured yeast as an efficient platform for the assembly of 100kb to megabase native mammalian genes or gene clusters. We are now enabled to rapidly deliver these genes and their many variants to embryonic stem cells and mice. This opens many avenues for tormenting human genes . . .

Tuuli Lappalainen, PhD

Professor, KTH Royal Institute of Technology; Director, Genomics Platform and the National Genomics Infrastructure, SciLifeLab, Sweden; Associate Faculty Member, New York Genome Center

Tuuli Lappalainen, PhD, is a professor at KTH Royal Institute of Technology; the director of the Genomics Platform and the National Genomics Infrastructure of SciLifeLab, Sweden; and an associate faculty member at the New York Genome Center. Dr. Lappalainen received her PhD in genetics from the University of Helsinki, followed by postdoctoral research at the University of Geneva and Stanford University. Her research focuses on functional genetic variation in human populations and its contribution to human traits and diseases, which her lab studies using both computational and experimental approaches. She has pioneered in integrating large-scale genome and transcriptome sequencing data to understand how genetic variation affects gene expression, which gives insight to biological mechanisms underlying genetic disease risk. She has contributed to many of the most important international research consortia in human genetics, including the 1000 Genomes Project, the Geuvadis Consortium, the GTEx Project, MoTrPAC, and TOPMed. She is a principal investigator of numerous NIH grants and a recipient of the Leena Peltonen Prize for Excellence in Human Genetics and the Harold and Golden Lamport Award in Excellence in Basic Research.

Functional Variation in the Human Genome: Lessons from the Transcriptome

ABSTRACT

Detailed characterization of molecular and cellular effects of genetic variants is essential for understanding biological processes that underlie genetic associations to disease. A particularly scalable approach has been linking genetic variants to effects in the transcriptome that is amenable for scalable measurements in human populations and in experimental settings, including at the single cell level. Our multi-omic analysis in human cohorts in the TOPMed project has identified genetic and environmental effects on molecular variation together with their complex interplay with clinical phenotypes. Furthermore, in this talk I will discuss how CRISPRi silencing of regulatory elements followed by single-cell analysis provides novel insights of mechanisms of genetic associations to complex traits. Altogether, these diverse approaches for integration genome and transcriptome data uncover functional genetic architecture of human traits, and they enhance our understanding of both basic biology and precision medicine applications.

Olga Troyanskaya, PhD

Professor, Lewis-Sigler Institute for Integrative Genomics and the Department of Computer Science, Princeton University; Deputy Director for Genomics, Flatiron Institute, Simons Foundation

Olga Troyanskaya is a professor in the Lewis-Sigler Institute for Integrative Genomics and the Department of Computer Science at Princeton University and deputy director for genomics at the Flatiron Institute of the Simons Foundation. Her group is focused on developing machine learning methods in genomics and precision medicine. Dr. Troyanskaya received her PhD from Stanford University. She is a fellow of the International Society for Computational Biology and of the ACM and has been honored as one of the top young technology innovators by the MIT Technology Review; she is a recipient of the Sloan Research Fellowship, the NSF CAREER Award, the Howard Wentz Faculty Award, and the Blavatnik Finalist Award. She is also the 2011 recipient of the Overton Prize from the International Society for Computational Biology and the 2014 recipient of the Ira Herskowitz Award from the Genetic Society of America.

Enabling Precision Medicine: Decoding the Human Genome with Deep Learning Models

ABSTRACT

A key challenge in medicine and biology is to develop a complete understanding of the genomic architecture of disease. Yet the increasingly wide availability of "omics" and clinical data, including whole genome sequencing, has far outpaced our ability to interpret these sequences. Challenges include interpreting the 98 percent of the genome that is noncoding to identify variants that are functional and may lead to disease, detangling genomic signals regulating cell-lineage-specific gene expression, and mapping the resulting genetic circuits and networks in disease-relevant cell-types to specific phenotypes and clinical outcomes. I will discuss methods that address these challenges and highlight their applications to cancer and mental health disorders.

George Church, PhD

Professor of Genetics, Harvard Medical School; Director, PersonalGenomes.org

George M. Church, PhD '84, is professor of genetics at Harvard Medical School; a founding member of the Wyss Institute; and director of PersonalGenomes.org, the world's only open-access information on human genomic, environmental, and trait data. Church is known for pioneering the fields of personal genomics and synthetic biology. He developed the first methods for the first genome sequence and dramatic cost reductions since then (down from $3 billion to $600), contributing to nearly all "next-generation sequencing" methods and companies. His team invented CRISPR for human stem cell genome editing and other synthetic biology technologies and applications—including new ways to create organs for transplantation, gene therapies for aging reversal, and gene drives to eliminate Lyme disease and malaria. Church is director of IARPA and NIH BRAIN Projects and National Institutes of Health Center for Excellence in Genomic Science. He has co-authored more than 590 papers and 155 patent publications, and one book, Regenesis. His honors include Franklin Bower Laureate for Achievement in Science, the Time 100, and election to the National Academies of Sciences and Engineering.

Affordable Precision Medicine via Somatic and Germline Genome Editing

ABSTRACT

The cost of reading and writing DNA has dropped over 30 million-fold recently. The cost of therapies and prevention has, in contrast, generally gone up. The exceptions are in categories with large markets, like vaccines and age-related diseases, which affect nearly all of us ($2 rather than $2M/dose). For rare diseases, well-tested precision diagnostics can be applied preventatively, at low expense, with essentially zero consequences of false positives (but adoption has been slow). Multiplex germline editing seems the best route for organ transplants, and preclinical trials in primates and patients have already begun. Multi-virus resistant cell therapies (or bioproduction) might play a role in improving the cost-effectiveness and safety on this last category.