COLUMBIA PRECISION MEDICINE INITIATIVE

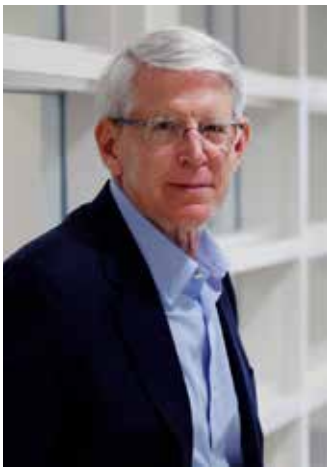
ADVANCES IN PRECISION MEDICINE

GENETICS OF NEURODEVELOPMENTAL DISEASE

VIRTUAL CONFERENCE: WEDNESDAY, APRIL 7, 2021

COLUMBIA | PRECISION MEDICINE

Welcome Letter



I am delighted to welcome you to the Fifth Annual Columbia Precision Medicine Initiative (CPMI) conference, Advances in Precision Medicine: Genetics of Neurodevelopmental Disease.

Due to the COVID-19 pandemic, this year's conference is taking place online.

The recent past has seen major advances in the understanding of the genetic and genomic architecture of neurodevelopmental disorders. We now have a deeper understanding of how genetic risk for many complex traits including neurodevelopmental disorders is driven by natural selection and distributed across the allelic spectrum.

While reliable results have emerged for conditions ranging from schizophrenia to bipolar disorder to autism, providing important insights into aspects of the neurobiology of these syndromes, a comprehensive understanding of their underlying biology is still out of reach.

In addition to the emerging genetic and molecular advances, there is the increasing realization that neurodevelopmental disorders target specific brain circuits. The interaction between genetic background, brain structure, and brain function is now the scientific background upon which specific neurodevelopmental conditions can be studied and understood.

Looking forward, systems integration of multiple levels of biological hierarchy—from genes, molecules, cells, and circuits to behavior and clinical outcomes—will illuminate causal models of disease and further establish this field as a component of precision medicine. We have been fortunate to assemble an extraordinary group of speakers to address this question.

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

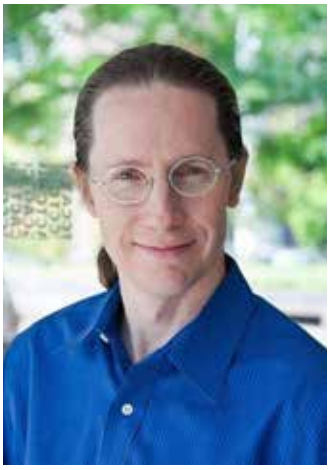
Conference Schedule

10:10 a.m.	**Tom Maniatis, PhD:** Welcome
10:13 a.m.	**Thomas Lehner, PhD, MPH,** Moderator
10:15 a.m.	**Mark Daly, PhD,** Harvard Medical School, University of Helsinki
10:55 a.m.	**Elise Robinson, ScD,** Harvard T.H. Chan School of Public Health
11:35 a.m.	**Matthew State, MD, PhD,** University of California, San Francisco
12:15 p.m.	**David Goldstein, PhD,** Columbia University
12:55 p.m.	Lunch break
2:00 p.m.	**Sergiu Pasca, MD,** Stanford University
2:40 p.m.	**Nenad Sestan, MD, PhD,** Yale School of Medicine
3:20 p.m.	**Kristen Brennand, PhD,** Yale School of Medicine
4:00 p.m.	**Huda Zoghbi, MD,** Baylor College of Medicine
4:40 p.m.	**Tom Maniatis, PhD:** Final Remarks

THOMAS LEHNER, PhD, MPH

Scientific Director, Neuropsychiatric Disease Genomics, New York Genome Center;
Professor of Clinical Neurobiology, Department of Psychiatry, Columbia University

Dr. Thomas Lehner is the scientific director, Neuropsychiatric Disease Genomics, at the New York Genome Center (NYGC) and a professor of clinical neurobiology in the Department of Psychiatry at Columbia University. Dr. Lehner leads the development of the neuropsychiatric disease genomics program at the NYGC including efforts to build an interinstitutional Precision Psychiatry Platform. Before joining the NYGC he served as the director of the Office of Genomics Research Coordination and senior advisor on genomics at the National Institute of Mental Health. During his career Dr. Lehner has transformed the field of psychiatric genomics, launching over 30 funding initiatives and fostering large national and international Team Science collaborations, resulting in breakthroughs in our understanding of the genetic architecture and pathophysiology of major neuropsychiatric disorders such as schizophrenia, autism, and depression.



MARK DALY, PhD

Chief, Analytic and Translational Genetics Unit, Massachusetts General Hospital; Associate Professor, Harvard Medical School; Co-Director, Medical Populations Genetics at the Broad Institute of MIT and Harvard; Director, Institute for Molecular Medicine Finland FIMM, HiLIFE, University of Helsinki

Mark Daly is the founding chief of the Analytic and Translational Genetics Unit (ATGU) at Massachusetts General Hospital and an assistant professor at Harvard Medical School. His research has historically focused on the development and application of statistical methods for the discovery and interpretation of genetic variation responsible for complex human disease; and, with the creation of the ATGU, he and other core faculty are focused on the interpretation of genome sequence and the use of genome information in clinical settings. Dr. Daly is also an institute member and co-director of the Program in Medical and Population Genetics at the Broad Institute, where he leads many large-scale genome sequencing studies in autism and inflammatory bowel disease.

While developing computational and statistical methods that can be broadly applied, his group has several primary medical genetics research foci. He has extensive research program experience in neuropsychiatric genetics—particularly in autism, schizophrenia, and ADHD—and has led large-scale GWAS and exome sequencing efforts in this area. His lab, along with Dr. Ben Neale's lab, serves as an analytic hub for the Psychiatric GWAS Consortium, an international consortium leading the largest collaborative GWAS studies in five major psychiatric disorders. He also has made a long-standing effort in the mapping of genes for Crohn's disease and ulcerative colitis, where he has helped found and lead an international effort that has identified more than 150 genetic risk factors and, in collaboration with Dr. Ramnik Xavier's group, pursues the functional interpretation and clinical ramifications of these continued gene discovery efforts. Along with Dr. Heidi Rehm, he is co-PI of the gnomAD project and committed to ensuring that the output of all ATGU genomic research is maximally accessible and useful to the clinical and research communities.

Dr. Daly was appointed director of the Institute of Molecular Medicine Finland (FIMM) at the University of Helsinki in February 2018 and now divides his time between Helsinki and Boston though he maintains his primary lab and affiliations in Boston. FIMM is a translational research institute with a focus on cancer, digital diagnostics, genetics, and epidemiology and is the home of landmark efforts such as the FinnGen Project.

Progress in Schizophrenia: From Genome to GWAS to Medicine

ABSTRACT:
Schizophrenia has a complex genetic architecture made up of both common and rare variation. Rare risk variants under strong negative selection are often *de novo* and may confer substantial risk—with both point mutations and CNVs often studied separately—while common variants at many sites drive the majority of high heritability in a polygenic fashion. I will review the progress in gene discovery over the past 15 years, how it fits with the clear natural selection acting against schizophrenia and other severe neuropsychiatric and neurodevelopmental phenotypes, and what prospects these data hold to revealing actionable biology and therapeutic hypotheses.

ELISE ROBINSON, ScD

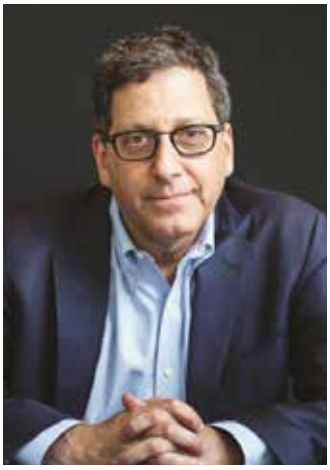
Assistant Professor, Harvard T.H. Chan School of Public Health; Member, Broad Institute of MIT and Harvard

Elise Robinson is an assistant professor of epidemiology at the Harvard T.H. Chan School of Public Health and an institute member of the Broad Institute of MIT and Harvard. She is also an affiliated faculty member with the Analytic and Translational Genetics Unit at Massachusetts General Hospital (MGH). Dr. Robinson's research focuses on the genetic epidemiology of behavior and cognition. She is interested in using genetic data to understand the biology of neurodevelopmental variation and to study differences within and between neuropsychiatric disorders. The Robinson lab uses techniques from statistical genetics and epidemiology to study how common and rare genetic risk factors for severe neuropsychiatric disorders may differ and develops approaches for examining these questions in large samples. Dr. Robinson received an ScD in psychiatric epidemiology from the Harvard School of Public Health, supervised by Karestan Koenen. She completed postdoctoral training in the lab of Mark Daly at MGH and the Broad Institute, using statistical genetic approaches to study neurodevelopmental disorders.

Genetic Clues to Autism Heterogeneity

ABSTRACT:

Recent studies have produced a wealth of genetic associations to autism spectrum disorders (ASDs) and related neuropsychiatric disorders. The Robinson lab focuses on interpretation of these results using detailed human behavioral, cognitive, and medical data. Dr. Robinson will discuss rare and common genetic risk factors for ASDs, and the association between those risk factors and ASD heterogeneity.



MATTHEW STATE, MD, PhD

Oberndorf Family Distinguished Professor, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco

Matthew State, MD, PhD, is the Oberndorf Family Distinguished Professor of Psychiatry and Behavioral Sciences, chair of the Department of Psychiatry and Behavioral Sciences, and member of the Weill Institute for Neurosciences at the University of California, San Francisco. He is a child and adolescent psychiatrist and human geneticist. Over the past 15 years, his laboratory has played a leading role in illuminating the genetics of childhood-onset neurodevelopmental disorders including autism spectrum and Tourette disorders. He has been the recipient of numerous awards, including the Tarjan Award from the American Academy of Child and Adolescent Psychiatry, the Ruane Prize from the Brain and Behavior Research Foundation, and the Rhoda and Bernard Sarnat International Prize in Mental Health from the US National Academy of Medicine. He was elected to membership in the National Academy of Medicine (NAM) in 2013.

Gene Discovery–Based Therapeutics Development in Autism Spectrum Disorder: Opportunities and Challenges

ABSTRACT:

The last decade has ushed in an era of highly successful gene discovery in autism spectrum disorders (ASD) and related neurodevelopmental syndromes. In contrast to most later-onset common psychiatric conditions, the findings have been dominated by the discovery of large-effect, heterozygous, often *de novo,* mutations in the germline that map to the coding portion of the genome. While this steadily growing resource, now totaling more than 100 genes, brings some distinct advantages at the bench compared with efforts to study multiple simultaneous common risk alleles of small effect, the challenges in elaborating pathophysiological mechanisms have been considerable. And efforts to leverage this new molecular understanding to develop novel treatment strategies are in their early stages. This presentation will review the specifics of progress in gene discovery, the status of efforts to address the notable heterogeneity and biological pleiotropy of the growing pool of high-confidence risk genes, and the key challenges that face efforts to develop novel somatic treatments targeting social disability and other core features of ASD.

DAVID GOLDSTEIN, PhD

John E. Borne Professor of Genetics and Development and Director, Institute for Genomic Medicine, Columbia University Irving Medical Center

David Goldstein, PhD, is the John E. Borne Professor of Genetics and Development and director of the Institute for Genomic Medicine at Columbia University Irving Medical Center (CUIMC). Dr. Goldstein leads a dedicated effort in precision medicine that includes active research programs advancing the study of the genetic bases of epilepsy and characterizing the mechanisms of disease-causing variants. He is responsible for establishing a group of Precision Medicine Initiatives in partnership with NewYork-Presbyterian Hospital and in collaboration with key faculty and physicians at CUIMC. These initiatives enroll thousands of patients annually in the areas of epilepsy, maternal fetal medicine, kidney and liver disease, ALS, and undiagnosed childhood disease. Dr. Goldstein serves on the Advisory Council at the National Institute of Mental Health (NIMH), and he is currently directing Epi25, the largest epilepsy genetics project in the world, and the Epilepsy Genetics Initiative (EGI) to develop an infrastructure to compile clinically generated exome sequences for diagnostic purposes to facilitate gene discovery. He also serves as a director of the New York Consortium of All of Us program that advances individualized prevention, treatment, and care for people of all backgrounds.

Toward Precision Medicine in Neurological Disease

ABSTRACT:

One primary challenge in the interpretation of large-scale sequencing studies is the huge number of candidate variants that emerge. This occurs primarily because there are many functional variants in every sequenced genome and because our ability to prioritize variants based on bioinformatic criteria remains limited. Integrating functional characterization of identified mutations with careful genome interpretation can often provide compelling evidence implicating new disease-causing mutations and genes in phenotypically well-characterized patients. Here I report progress in identifying pathogenic mutations in large-scale studies in epilepsy, in particular focusing on identifying *de novo* mutations as a cause of the epileptic encephalopathies. Next, I discuss how sequencing is being used to diagnose rare, serious, unresolved genetic conditions. Finally, I describe a number of examples in which a secure genetic diagnosis has led directly to a change in clinical management.

SERGIU PASCA, MD

Bonnie Uytengsu and Family Director of Stanford Brain Organogenesis,
Stanford University

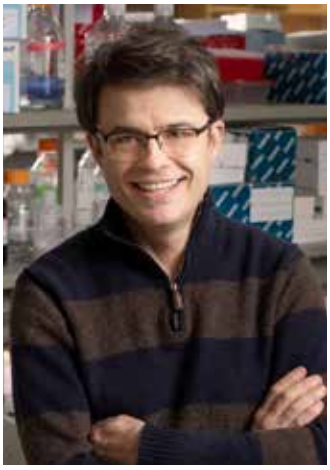
Dr. Sergiu Pasca is a tenured associate professor in the Department of Psychiatry and Behavioral Sciences and the Bonnie Uytengsu and Family Director of Stanford Brain Organogenesis at Stanford University. He is also a CZI Ben Barres Investigator and an NYSCF Robertson Investigator. A physician by training, Dr. Pasca is interested in understanding the rules governing brain assembly and the mechanisms of disease. Dr. Pasca developed some of the initial in-a-dish models of disease by deriving neurons from skin cells taken from patients with genetic neurodevelopmental disorders. His laboratory at Stanford introduced the use of instructive signals for reproducibly deriving from stem cells self-organizing 3D cellular structures named brain region–specific spheroids or organoids. Dr. Pasca also pioneered a modular system to integrate 3D brain region–specific organoids and study migration and neural circuit formation in functional preparations known as assembloids. His laboratory has applied these models to gain novel insights into human physiology, evolution, and disease mechanisms and supported researchers around the world in learning and implementing these techniques.

Dr. Pasca was named a Visionary in Medicine and Science by the *New York Times*. He is the recipient of the 2018 Vilcek Award for Creative Biomedical Promise (shared with Feng Zhang and Polina Anikeva), the NIMH's BRAINS Award (2015), the A.E. Bennett Award in Biological Psychiatry (2018), the Folch-Pi Neurochemistry Award (2017), the Günter Blobel Early Career Award for Cell Biology (2018), and the Daniel E. Efron Award from ACNP (2018) and was a winner of the 2020 Falling Walls Breakthrough in Life Sciences Award.

Brain Assembloid Models to Study Human Neurodevelopment and Disease

ABSTRACT:

A critical challenge in understanding the programs underlying development, assembly, and disease of the human brain is the lack of direct access to functioning human brain tissue for detailed investigation and manipulation. In this talk, I will describe work from my laboratory to develop 3D brain region–specific organoids from human pluripotent stem cells, establish reproducibility, and apply this preparation in long-term cultures to gain insights into neural development and evolution. I will also present efforts to combine organoids to generate assembloids and study neural circuit formation, cell migration, and model neuropsychiatric disease.



NENAD SESTAN, MD, PhD

Harvey and Kate Cushing Professor of Neuroscience; Professor of Comparative Medicine, of Genetics and of Psychiatry; Member, Kavli Institute for Neuroscience, Yale School of Medicine

Nenad Sestan, MD, PhD, is the Harvey and Kate Cushing Professor of Neuroscience; professor of comparative medicine, of genetics and of psychiatry; and a member of the Kavli Institute for Neuroscience at Yale School of Medicine. He obtained his MD from the University of Zagreb and his PhD in neurobiology from Yale University. Dr. Sestan's laboratory investigates how neural circuits are formed within the developing cerebral cortex—the outside part of the mammalian brain that processes our senses, commands motor activity, and helps us perform higher-order cognitive functions like language. He also studies how neural circuits were modified during human evolution and may become compromised in neuropsychiatric disorders. Most recently, his laboratory discovered that the large mammalian (porcine) brain is more resilient to a lack of oxygen than previously thought. It also described a first-in-class technology that can restore brain perfusion and reverse some of the effects of oxygen deprivation. Dr. Sestan is the recipient of several international honors and awards, including memberships in the National Academy of Medicine, Croatian Academy of Sciences and Arts, and Connecticut Academy of Science and Engineering; *Nature*'s 10 Who Mattered in Science, the Constance Lieber Prize, the Krieg Cortical Discoverer Prize, NARSAD Distinguished Investigator, McDonnell Scholar, and Krieg Cortical Scholar. He has been a member of the BrainSpan, BRAIN Initiative Cell Census Network, and PsychENCODE consortia.

Building the Human Neocortex: Molecular Logic of Neural Circuit Formation and Evolution

ABSTRACT:

The question of what makes human beings unique has fascinated humankind throughout modern history. Today, we view the brain as the core component of human identity, and an understanding of this organ is consequently essential for answering why we as a species are what we are. What distinguishes humans from other species is largely thought to reside in the unique features of brain development, especially in the wiring of the immensely complex neural circuits of the cerebral neocortex that underlie our cognitive and motor abilities.

In my presentation, I will describe some of our recent efforts to understand the molecular and cellular basis of how neurons acquire distinct identities and form proper connections in the cerebral neocortex—the outside part of the brain that processes our senses, commands motor activity, and helps us perform higher-order cognitive functions, including those that are most distinctly associated with the human mind. I will also present evidence on how these complex developmental processes were modified during human evolution and may become compromised in neuropsychiatric disorders.

KRISTEN BRENNAND, PhD

New Faculty Member, Yale School of Medicine

Kristen Brennand, PhD, is a professor of psychiatry at Yale School of Medicine, formerly the director of the Alper Neural Stem Cell Center, and an associate professor in the Pamela Sklar Division of Psychiatric Genomics at Mount Sinai. Her research integrates stem cell–based approaches, with CRISPR-mediated genomic engineering strategies, in order to study the impact of patient-specific variants across and between the cell types of the brain. The goal of her research is to uncover the convergence and synergy arising from the complex interplay of the many risk variants linked to brain disease. Dr. Brennand's work is funded by the National Institutes of Health, the New York Stem Cell Foundation, the Brain Research Foundation, and the Brain and Behavior Research Foundation.

Using Stem Cells to Explore the Genetics Underlying Brain Disease

ABSTRACT:

Schizophrenia (SZ) is a debilitating psychiatric disorder for which the complex genetic mechanisms underlying the disease state remain unclear. There is an urgent need for functional validation of risk variants in a cell-type-specific and context-dependent manner, in order to facilitate the clinical translation of genetic findings. Toward this, we employ a functional genomics approach that integrates stem cell models and genome engineering, resolving the combinatorial impact of patient-specific variants across cell types, donor genetic backgrounds, and environmental contexts. First, we evaluated the impact of patient-specific NRXN1+/- deletions in hiPSC-neurons, observing greater than two-fold reduction of half of the wildtype NRXN1αα isoforms and detecting dozens of novel isoforms expressed from the mutant allele; reduced neuronal activity in patient hiPSC-neurons was ameliorated by overexpression of individual control isoforms in a genotype-dependent manner, whereas individual mutant isoforms decreased neuronal activity levels in control hiPSC-neurons. Second, by integrating CRISPR-mediated gene editing, activation, and repression technologies to study one putative causal SZ SNP (FURIN rs4702) and four top-ranked SZ-eQTL genes (FURIN, SNAP91, TSNARE1, CLCN3), our hiPSC-based neuronal platform uncovered an unexpected synergistic effect between SZ-eQTL genes that converges on synaptic function and links the rare and common variant genes implicated in psychiatric disease risk, one which may represent a generalizable phenomenon occurring more widely in complex genetic disorders. We demonstrate a systematic and scalable strategy to interpret and evaluate the growing number of SZ-associated variants and genes across neural cell types and genetic backgrounds. Our overarching goal is to explore the impact of genetic variation, in order to improve diagnostics, predict clinical trajectories, and identify pathways that might serve as pre-symptomatic points of therapeutic intervention.

HUDA ZOGHBI, MD

Investigator, Howard Hughes Medical Institute; Ralph D. Feigin Professor, Baylor College of Medicine; and Director, Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital

Huda Y. Zoghbi, MD, is Professor of Pediatrics, Neurology, Neuroscience, and Molecular and Human Genetics at Baylor College of Medicine; an investigator with the Howard Hughes Medical Institute, and director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. Dr. Zoghbi was born in Beirut, Lebanon, where she earned a BS from the American University of Beirut. She completed her MD at Meharry Medical College and joined Baylor College of Medicine for training in pediatrics, neurology, and molecular genetics. Dr. Zoghbi's clinical encounters with young girls with Rett syndrome inspired her to go into basic research. Her laboratory ultimately discovered the genetic cause of Rett syndrome and provided insight into the function of the gene in various neurons. Her discovery (with Harry Orr) that Spinocerebellar Ataxia type 1 is caused by expansion of a polyglutamine tract and her studies that such expansion leads to accumulation of the mutant protein have informed studies of other neurodegenerative disorders. Dr. Zoghbi also discovered Math1/Atoh1 and showed that it governs the development of several components of the proprioceptive, balance, hearing, vestibular, and breathing pathways. Dr. Zoghbi has trained over 90 scientists and physician-scientists who have gone on to successful careers. She was elected to the National Academy of Medicine, the National Academy of Sciences, and the American Academy of Arts and Sciences. Among Dr. Zoghbi's recent honors are the Shaw Prize in Life Science and Medicine, the Breakthrough Prize in Life Sciences, the Canada Gairdner International Award, and the 2020 Brain Prize.

Epigenetics and Brain Plasticity: Lessons from Rett Syndrome and Other MECP2 Disorders

ABSTRACT:

Rett syndrome is a delayed-onset childhood disorder, typically found in girls, that causes a broad range of severe neurological disabilities, including loss of the ability to speak and socialize, and the development of tremors, ataxia, seizures, autonomic dysfunction, and stereotypic hand-wringing movements. We discovered that loss-of-function mutations in the MECP2 gene cause Rett syndrome, and before long it became clear that milder mutations in MECP2 can also cause other neuropsychiatric phenotypes ranging from autism to bipolar disorder. Using genetically engineered mice, we learned that the brain is acutely sensitive to MeCP2 protein levels; both decreases and increases in the amount of MeCP2 protein can lead to neurological problems that are also observed in humans. Nonetheless, normalizing MeCP2 protein levels reverses symptoms in a humanized mouse model of MECP2 duplication syndrome, a disorder that results from excess MeCP2 protein and typically affects boys. Most recently we have found an approach that could delay onset of Rett symptoms, suggesting that earlier diagnosis through screening may be worthwhile for these disorders.