Real Life™

Larry Goldstein, PhD
Chair, CIRM Neuro Task Force

Neuro Task Force Meeting #3

April 24, 2023

CIRM
CALIFORNIA'S STEM CELL AGENCY

Elements Speakers to Address:

1. Which types of models do you think are generally best for modeling neuropsychiatric disorders (i.e animal/stem cell based…)? What are your views about Pros and Cons of each type?
2. Are there some models better suited for some diseases than others?
3. What are your thoughts about models based on multiple common variants versus single high penetrance rare variants?
4. What are your thoughts with regards to addressing power limitations in the design of stem cell based studies for complex genetic disorders such as neuropsych/neurodev? If CIRM were to propose a consortia approach, what would you prioritize in order to tackle this challenge?
5. There is some reason to think that some genetic variants cause more than one disease based on background. Is there any particular approach you would recommend in these situations?
6. Do you think that all neuron types are affected by genetic variants causing disease or is there significant specificity of affected cell types in the brain?
7. Are there any diseases that you think might be suitable for stem cell or gene therapy or are small molecules the most likely interventions?

Thomas C. Südhof, M.D.

Thomas Christian Südhof was born in Göttingen, Germany in 1955 and obtained his M.D. and doctoral degrees from the University of Göttingen in 1982. He performed his doctoral thesis work at the Max-Planck-Institut für biophysikalische Chemie in Göttingen with Prof. Victor P. Whittaker on the biophysical structure of secretory granules. From 1983-1986, Südhof trained as a postdoctoral fellow with Drs. Mike Brown and Joe Goldstein at UT Southwestern in Dallas, TX, and elucidated the structure, expression and cholesterol-dependent regulation of the LDL receptor gene. Südhof began his independent career in 1986 at UT Southwestern, where he stayed until 2008 and, among others, was the founding chair of the Department of Neuroscience. In 2008, Südhof moved to Stanford, and became the Avram Goldstein Professor in the School of Medicine at Stanford University. In addition, Südhof has been an Investigator of the Howard Hughes Medical Institute since 1986.

Prior to becoming a neuroscientist, Südhof was trained in the biophysics of subcellular organelles at the Max-Planck-Institut für biophysikalische Chemie and in cholesterol metabolism at UT Southwestern. When Südhof started his laboratory, he decided to switch to neuroscience to study synapses because of their central, as yet incompletely understood role in brain function. Südhof's work initially focused on the mechanism of neurotransmitter release, which is the first step in synaptic transmission that accounts for the speed and precision of information transfer in the brain. It was for this work that Südhof was awarded in 2013 the Albert Lasker Basic Medical Research Award (with Richard Scheller) and the Nobel Prize in Physiology or Medicine (with James Rothman and Randy Schekman). In the last decade, Südhof's research emphasis has switched to focus on a different unsolved problem in neuroscience that regards synapses, namely how synapses are established specifically between defined pre- and postsynaptic neurons, and how such connections are endowed with specific properties by these neurons. Addressing this fundamental question is essential for understanding how circuits are wired and how they process information, but the basic rules that govern synapse formation and specification are only now beginning to emerge. Elucidating these rules is the goal of Südhof's present work.

Source: https://med.stanford.edu/sudhoflab/about-thomas-sudhof.html

Kristen Brennand, Ph.D.

Kristen Brennand, PhD is the Elizabeth Mears and House Jameson Professor of Psychiatry and Professor of Genetics at Yale University School of Medicine. She first established her independent laboratory in the Pamela Sklar Division of Psychiatric Genomics at the Icahn School of Medicine at Mount Sinai in 2012, after having completed post-doctoral training at the Salk Institute for Biological Studies and PhD studies at Harvard University. Dr. Brennand's research combines expertise in genomic engineering, neuroscience, and stem cells, to identify the mechanisms that underlie brain disease. Her focus lies in resolving the convergence of, and complex interplay between, the many risk variants linked to disease, towards the goal of facilitating the clinical translation of genetic findings. 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.

Source: https://medicine.yale.edu/profile/kristen-brennand/

Reference

- Defining the Genetic, Genomic, Cellular, and Diagnostic Architectures of Psychiatric Disorders. Sullivan PF, Geschwind DH.Cell. 2019 Mar 21;177(1):162-183. doi: 10.1016/j.cell.2019.01.015.PMID: 30901538 **Free PMC article.** Review.