School of Molecular Sciences
Arizona State University

SMS Fall 2021 Eyring Seminar

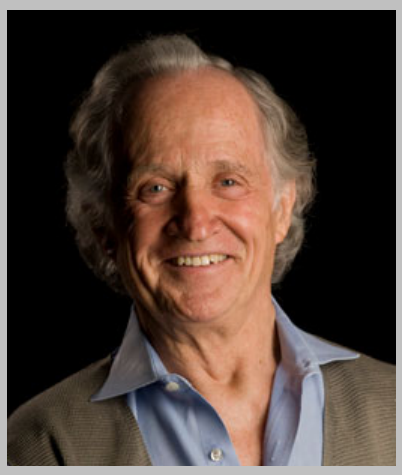
Friday Nov 5 | 2:30pm | Biodesign Auditorium*

Mutant *Hoxb8* Microglia Are Causative for Chronic Anxiety and OCD-Spectrum Disorders in Mice

Hoxb8-mutant mice show chronic-hyperanxiety, as well as aberrant behavior very similar to the Obsessive-Compulsive-Spectrum Disorder, Trichotillomania. The only *Hoxb8*-lineage labeled cells in the brain are a subpopulation of parenchymal microglia, suggesting that defective *Hoxb8*-microglia cause the behavioral disorders. What is the source of this subpopulation of microglia? It has been posited that all microglia progenitors arise at E7.5 during yolk sac hematopoiesis, which colonize the brain at E9.5. In contrast, we demonstrate through cell lineage analysis the presence of at least two microglia subpopulations: canonical, non-*Hoxb8*-microglia, and *Hoxb8*-microglia. Unlike non-*Hoxb8*-microglia, *Hoxb8*-microglia appear to be generated during the second wave of yolk sac hematopoiesis (E8.5), are then detected in the AGM and fetal liver, where they are extensively expanded, prior to infiltrating the brain at E12.5 and thereafter. Further, we demonstrate by cell transplantation experiments, that cell sorted *Hoxb8*-hematopoietic progenitor cells taken from fetal liver are competent to give rise to mature microglia *in vivo* that express markers specific to mature parenchymal microglia. Following the specific *in vivo* cell ablation of the *Hoxb8*-microglia subpopulation, wild type mice recapitulate the behavioral disorders common to mice with the *Hoxb8* mutation, both with respect to hyper anxiety as well as pathological over grooming. These experiments demonstrate that defective *Hoxb8* microglia are causative for both hyper anxiety and the OCD spectrum disorder, Trichotillomania. The two subpopulations of microglia are very similar molecularly and in their responses to injury and participation in synaptic pruning, but only *Hoxb8* microglia show distinct distributions in the brain that coincide with the “OCD circuit” as well as their unique role in the maintenance of normal levels of anxiety.

Mario Capecchi, PhD

Professor, University of Utah



Dr. Capecchi is known for his pioneering work on the development of gene targeting in mice. This technology allows creation of mutations in any desired gene, giving virtually complete freedom to manipulate the genome of living mice. His work in this area revolutionized the study of mammalian biology and is used to understand countless diseases by scientists worldwide. In 2007, he was recognized for this achievement with the Nobel Prize in physiology or medicine.

His current research interests include the molecular genetic analysis of early mouse development, neural development, neuropsychiatric disorders, production of mouse models of human genetic diseases including cancers and neuropsychiatric disorders.

**ZOOM option available: https://asu.zoom.us/j/87081218152*