

FULL SPEAKER BIOGRAPHY and ABSTRACT

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Jeffrey D. Macklis' laboratory is directed toward both 1) understanding the molecular controls over neuron sub-type specification and development in the cerebral cortex, and 2) applying developmental controls toward brain and spinal cord repair and therapy—specifically, of complex cerebral cortex and cortical output circuitry (in particular, cortico-spinal motor neuron (CSMN) circuitry that degenerates in ALS and other “upper motor neuron” degenerative diseases, and whose injury is centrally involved in loss of motor function in spinal cord injury). He is Professor of Neuroscience, Neurology and Neurosurgery at Harvard Medical School (HMS), and Professor, Department of Stem Cell and Regenerative Biology, Harvard University; Director of the MGH-HMS Center for Nervous System Repair; and Program Head, Neuroscience / Nervous System Diseases, Harvard Stem Cell Institute, Harvard University. He attended M.I.T., Harvard Medical School, and graduate school at M.I.T. within the Harvard-M.I.T. Division of Health Sciences and Technology. He was a postdoctoral fellow in developmental neuroscience with Richard Sidman at HMS, where he also trained clinically in neurology. He is the recipient of a number of awards and honors, including a Rita Allen Foundation Scholar Award, a Schepp Foundation Scholar award, an Innovation Award from the NIH Director's Office, a Soderberg Prize Symposium Lectureship at the Swedish Society for Medicine, The CNS Foundation Award, Pearlstein Scholar Award, Seidman Award in CNS Research, and a Senator Jacob Javits Award in the Neurosciences from the NINDS/NIH.

Building or Repairing a Brain is Complex; Assembly Instructions Required: Molecular Development of Corticospinal Motor Neurons

Given the heterogeneity of CNS neuronal subtypes, and the complexity of their connections, detailed understanding of molecular controls over differentiation, connectivity, and survival of specific neuronal lineages will contribute not only to 1) understanding of the development, evolution, organization, and function of CNS circuitry, but also to 2) support or regeneration of vulnerable populations in neurodegenerative (e.g. ALS, HSP/PLS, HD, PD) or acquired disease (e.g. SCI), to 3) enabling accurate models of neuron type-specific disease, to 4) identification of disease genes, and to 5) attempts to functionally repair CNS circuitry. For example, data from our lab demonstrate that new neurons can be added to adult neocortical circuitry via manipulation of transplanted or endogenous precursors in situ (including induction of limited neurogenesis of clinically important corticospinal motor neurons- CSMN- in adult mice), indicating that cellular repair of cortical and cortical output circuitry is possible, if controls over specific lineage differentiation are understood. Using FACS-purified CSMN and other projection neuron populations at critical stages of development in vivo, we have identified both developmentally regulated transcriptional programs of novel and largely uncharacterized genes, and cell-extrinsic controls, that are instructive for development of specific neuron lineages as they develop in vivo (in particular, for CSMN, corticothalamic, callosal, and other projection neuron populations); these control key developmental processes from progenitor parcellation and progenitor subtype restriction to subtype-specific differentiation to acquisition of precise areal identity to axonal outgrowth. Loss-of-function and gain-of-function analyses for multiple identified genes and molecules reveal combinatorial molecular-genetic controls over the precise development of key forebrain projection neuron populations that may allow directed control of neural precursors / progenitors / “stem cells” (or ES / iPS cells) toward accurate disease models, neuronal support or regeneration, or functional CNS repair.

What is the central hypothesis of your presentation?

Molecular-genetic controls over development of specific neuronal circuitry that degenerates or is injured in human disease can enable at least partial reconstruction of the affected circuitry.

What is the most important observation you will discuss?

A logical, combinatorial set of intersectional molecular-genetic controls regulate the specification, development, and connectivity of corticospinal motor neurons (central to ALS/motor neuron diseases and spinal cord injury), affecting a series of developmental steps from progenitor partial fate restriction to post-mitotic regulation of precision of development and acquisition of identity.

What is the translational significance?

Manipulation of molecular-genetic controls over initial neuronal circuit development can enable re-building of human diseased circuitry and degenerated / injured neurons.