

Research Interests

The embryonic neural tube differentiates into diverse structures depending upon their spatial coordinates. The forebrain, which is at the rostral end of the neural tube, differentiates into the cerebral cortex, the basal ganglia and other components, each with distinct histologies and functions. Our laboratory is interested in studying the genes that regulate regional specification and differentiation of the mammalian forebrain. In addition, we have a long-standing interest in integrating these findings to better understand the development and evolution of forebrain neural systems and to help elucidate mechanisms underlying human neurodevelopmental disorders such as Autism. Our laboratory has several types of projects.

Organization of the embryonic forebrain:

The discovery of regulatory genes with regionally restricted patterns of expression in the forebrain opened the door to the recognition of its embryonic subdivisions. With Luis Puelles, we investigate topological organization of distinct progenitor zones and their neuronal derivatives.

Forebrain patterning centers:

We investigate regions of the neural plate and neural tube that produce secreted factors that control regionalization and growth of the forebrain. Foremost in this arena have been our studies on Fgf8 and Fgf17 function in regionalization of the neural plate and cerebral cortex. This work has opened the door to elucidating the genetic circuitry of prefrontal cortex development, as Fgf17 mutant mice have hypoplasia of their anterior cingulate gyrus, and circumscribed behavioral deficits particularly in social interactions, providing insights into human neuropsychiatric disorders.

Transcription factors that control regional specification of brain subdivisions:

Ongoing studies focus on defining the transcription factors that control CNS development. These include the roles of the Nkx genes in specifying ventral neural progenitors (e.g. Nkx2.1 for globus pallidus principal neurons and cortical interneurons). These results are contributing towards elucidating the transcription factor code that defines the development programs of forebrain progenitor zones. This information shows linkage of regional and cell-type specification in the telencephalon; i.e. distinct telencephalic progenitor zones generally produce neurons that utilize different types of neurotransmitters. Ventral regions produce cholinergic, intermediate regions produce GABAergic and dorsal regions produce glutamatergic neurons.

Transcription factors that control and cell-type differentiation:

In this regard, we currently focus on the differentiation of forebrain GABAergic neurons, and the functions of the Dlx1, 2, 5 & 6, and Lhx6 & 8 transcription factors. Mutation of Dlx1&2 blocks differentiation of GABAergic neurons; see below.

Cortical inhibitory neurons are generated in the basal ganglia and tangentially migrate to the cortex

:

There is migration of GABAergic neurons from the subcortical telencephalon into the cerebral cortex, where these cells become the major class of inhibitory neurons in the mouse. There is a similar tangential migration for cholinergic striatal interneurons. We are currently defining the molecular mechanisms that control the movement and integration of the migratory cells to their destinations.

Control of mature GABAergic cortical interneuron function:

Mutation of *Dlx1* leads to an age-dependent death of a subset of dendrite innervating cortical interneurons. As these interneurons die, the mutant mice develop epilepsy. We are currently learning how *Dlx* function in neurons controls their function and survival. These insights could be pertinent for neuropsychiatric disorders, such as autism and schizophrenia, in which patients show largely normal development prior to the onset of symptoms. With Arturo Alvarez-Buylla, Scott Baraban and Arnold Kriegstein, we are developing methods for interneuron transplantation to treat forebrain disorders, such as epilepsies.

Neuropsychiatric Disorders (Autism):

The lab has a longstanding clinical interest in Autism. Ongoing studies involve sequencing of candidate genes, and functional analyses of mutant alleles.

Dlx Transcription factors that control craniofacial patterning:

Often neuropsychiatric disorders are associated with craniofacial dysmorphologies. Studies of *Dlx* function in craniofacial neural crest have illuminated the role of these genes in patterning the jaw and middle ear skeleton, findings that have important evolutionary and medical ramifications.

Contact Us
UCSF Main Site

© 2013 The Regents of the University of California

Source URL: <https://rubensteinlab.ucsf.edu/research-interests>