

Nahum Sonenberg- Lay Summary

Modulation of synaptic transmission by different forms of synaptic plasticity (i.e. synaptic strengthening and weakening) allows neurons to adapt to the stimuli encountered throughout their lifetime, thus modifying brain function. Synaptic plasticity is of particular importance during the development of neural circuits. For example, visual inputs refine the neural connections of the developing visual cortex via synaptic plasticity. Vision imbalance (amblyopia), due to the absence of visual inputs or genetic alterations, such as congenital cataract, unequal refractive power, strabismus, or Down syndrome, prevents the visual field from developing properly. If untreated by 8 years of age, amblyopia results in the most common cause of vision loss. Furthermore, one fourth of the recovered amblyopic children experience recurrence. Impairment of synaptic plasticity in the developing visual cortex also precludes children from learning aspects of social interaction that are impaired in autism spectrum disorders (ASD), which affect 1 in 66 children. It follows that up to ~50% of children with visual impairment exhibit ASD.

To devise treatments for these neurodevelopmental disorders, it is imperative to understand the molecular mechanisms underlying synaptic plasticity. Recent studies revealed that exposing the visual cortex to a common stimulus causes cell type-specific changes in gene expression, but opposite regulation of the synthesis of the protein Arc resulting in distinct forms of synaptic plasticity, respectively, at the same neuron. This renders it difficult to investigate the regulation of protein synthesis in synaptic strengthening and weakening *in vivo* on a wide scale, as it would be confounded by the presence of different cell types in addition to diverse forms of synaptic plasticity.

To overcome this major hindrance, we propose to employ monocular deprivation (i.e. suture of one eyelid) as an experimental strategy. Monocular deprivation during a 'critical period' (starting at postnatal day 28 in mouse) is well-established to induce ocular dominance through protein synthesis-dependent synaptic plasticity in the primary visual cortex. Most importantly, monocular deprivation provides a unique advantage of inducing homogenous synaptic weakening for the contralateral eye and homogenous synaptic strengthening for the ipsilateral eye. Combining monocular deprivation with a comprehensive analysis of the protein synthesis at single-cell-type resolution and biochemical isolation of pre- and post-synaptic compartments will allow to identify the *in vivo* local protein synthesis in synaptic weakening and strengthening. Furthermore, we will screen for the modulation of protein synthesis regulators known to engender ASD when dysregulated and we will investigate the proteins whose synthesis is selectively regulated in the

synaptic compartments of related ASD mouse models. Finally, we will validate the local synthesis of candidate proteins and examine their function.

The proposed project will enable for the first time to identify the protein synthesis regulators, their signatures and functions in the different forms of synaptic plasticity in an intact circuit of the developing primary visual cortex in control and ASD mouse models. These data will impart invaluable insight into the mechanisms underpinning neural circuit remodeling and unveil key targets for therapeutic intervention on amblyopia and ASD, setting the stage for developing translatable approaches.