

Nachum Sonenberg- Scientific Summary

Project Title: Single-cell mRNA translational control mechanisms in diverse forms of synaptic plasticity in an intact circuit of the developing primary visual cortex and in Autism Spectrum Disorder

Statement of Purpose: Identification of translational regulators, signatures and functions in synaptic plasticity in the developing primary visual cortex to uncover the mechanisms underpinning neural circuit remodeling and their dysregulation in neurodevelopmental disorders.

Project Summary:

Modulation of synaptic transmission by different forms of synaptic plasticity 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 such 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 undergo recurrence. Impairment of synaptic plasticity in the developing visual cortex also precludes children from learning aspects of social interaction that are well documented to be 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 transcriptional changes, but opposite translational regulation of the mRNA Arc resulting in synaptic potentiation and depression, respectively, at the same neuron. This renders it difficult to investigate mRNA translational regulation in synaptic strengthening and weakening in vivo on a genome-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 as an experimental strategy. Suture of one eyelid 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 the unique advantage of inducing homogenous synaptic weakening for the contralateral eye and homogenous synaptic strengthening for the ipsilateral eye. Combining monocular deprivation with Cre-Lox-mediated RiboTag at single-cell-type resolution and biochemical isolation of pre- and post-synaptic compartments will allow to identify the in vivo local translome in synaptic weakening and strengthening. Furthermore, we will screen for the modulation of translational regulators known to engender ASD when dysregulated, such as 4E-BP2 and FMRP, and investigate the mRNAs which are selectively translationally regulated in the synaptic

compartments of related ASD mouse models. Finally, we will validate the local translation of candidate mRNAs and examine their function by live imaging and measuring synaptic density, spatial organization and volume.

The proposed project will enable for the first time to identify the translational regulators, their translational 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 throughout and beyond the critical period and on ASD, setting the stage for developing translatable approaches.