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The Role of Non-Vesicular Lipid Transport at ER-PM Contact Sites in Phosphoinositide Signaling in Early Dendrite Development

A. Proposal Description – Cover Page

Phosphoinositide lipid signaling is implicated in many cellular functions and is crucial in brain development. $PI(4,5)P_2$ is a key lipid at the plasma-membrane, mediating many signaling pathways downstream of secreted cues, directly from $PI(4,5)P_2$ or upon its phosphorylation to PIP_3. PIP_3 signaling is critical in dendrite development during embryonic brain development. The dendritic arbors of pyramidal neurons underlie synaptic connectivity. Disruption in dendrite development plays causative role in neurodevelopmental/psychiatric pathologies, epilepsy, Schizophrenia, autism, underlaid by abnormal $PI(4,5)P_2/PIP_3$ signaling. Using state-of-the-art genetic probes to track $PI(4,5)P_2/PIP_3$, cutting-edge genetic approaches including gene overexpression/knockdown *in utero*, CRISPR-mediated genome editing, and localized signaling manipulations, this RO1 application proposes a set of innovative specific goals to determine the mechanistic basis of Phosphoinositide signaling in dendrite development in mouse developing cortical neurons focusing on non-vesicular plasma-membrane lipid transport via the lipid transport protein, Nir2.

Our NIH-RO1 application scored 23% upon first submission (Neuronal Communications, NC Study Section). We identify ***five*** main concerns and gaps noted by the Reviewers. If awarded, these goals will be the focus of the work conducted under the *OVPR Revise and Resubmit Seed award*, with emphasis on specifically accomplishing *Goal 1* and *Goal 2*, as detailed in Section (C).