Wayne Sossin- Lay Summary

The wiring of the nervous system involves making connections between neurons that extend their projections far away from their main cell body. Correct wiring requires transporting messenger RNA (mRNA) that carries the code for making new proteins to these distal sites, and then synthesizing the proteins locally using the cellular decoding machine called the ribosome. The genetic cause of many neurodevelopmental disorders is due to mutations in proteins required for protein synthesis in these distal sites. We are looking deeply into how this process works to understand how it's disrupted in neurodevelopmental disorders. We think that specific mRNAs encoding proteins important for neuronal circuit formation begin decoding in the cell body and are then stalled, and these stalled ribosomes together with the mRNA being decoded are packaged into specialized cargo particles called neuronal RNA granules to be transported to the distal sites. This allows selective and fast synthesis of these proteins when they are needed at these distal sites simply by removing the stall. To understand how this works, we are purifying the neuronal RNA granules and using sophisticated electron microscopy techniques to solve the ribosome structure at the atomic level to elucidate their mechanism of stalling. We are also finding the specific codes on the mRNA where the stalling occurs and identifying the key regulators that interact with these codes in the stalling process. Finally, we are also examining all of these using RNA granules isolated from genetic models of neurodevelopmental disorders to see which step has been disrupted. Overall, these studies will piece together a complete picture of how RNA granules are generated and how they are dysfunctional in neurodevelopmental disorders suggesting new therapies for intervention.