By weight, the brain is the body’s most energetically expensive organ – accounting for nearly a quarter of all oxygen and glucose consumption. This demand for fuel renders the brain particularly vulnerable to even a modest decline in its bioenergetic capacity. New research is now suggesting that changes in energy metabolism may be a common initiating factor in the emergence of age-associated neurodegenerative disorders.

Mitochondria, the cellular power generators, are unique in that they harbor their own genome, which encodes the most essential components to perform bioenergetic transduction – making them a natural target for intervention. Through deep mitochondrial genotyping and phenotyping of aged and Alzheimer’s disease models, bioenergetic dysregulation often occurs in parallel with widespread neuroinflammation; how these processes interact is unclear. We are delineating the cross-talk between brain energy metabolism and chronic neuroinflammation, focusing on cellular redox dysregulation and lipid dyshomeostasis as candidate bridging factors and potential therapeutic targets for age-associated neurodegenerative disorders.

We are leveraging these fundamental insights into the pathophysiology of disease to develop rodent and cellular models that combine targeted disruption of the mitochondrial genome with genetic risk factors for Alzheimer’s, Parkinson’s, ALS, and MS. By more closely mirroring human disease we are able to improve the predictive translational validity of drug development assays based on these models.