Protein synthesis is an important control step in the gene expression pathway, but one often neglected. Translation initiation is a complex multistep process that is subject to both general and gene-specific controls and is highly conserved from yeast to man. Translational controls have been found to be particularly important in stress responses, early development and in learning and memory and are now implicated in disease. Studies have highlighted common themes between all these processes. We are interested in protein synthesis mechanism and translational controls in general and have been studying aspects of the genetically inherited and fatal leukodystrophy called both CACH (Childhood Ataxia with CNS hypomyelination) and VWM (Vanishing White Matter disease). This disorder, which is highly variable in its onset, primarily affects astrocytes and oligodendritic cells and is caused by partial loss of function mutations in the general translation factor eIF2B, which is necessary in all cells. eIF2B is a key regulator of protein synthesis in response to diverse stresses and functions as a guanine nucleotide exchange protein for its G protein partner eIF2. I will discuss our current understanding of the role and regulation of eIF2B and our development of both genetic and chemical library screens in yeast (S. cerevisiae) to identify modifiers of eIF2B function that may provide novel insight into eIF2B biology or help identify potential therapeutics for this fatal disease.