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Elroy-Stein's lab is meticulously utilizing 'Marisol mice' (which are homozygous to Marisol's mutation in the eIF2B5 gene) to unravel the intricate molecular mechanisms underlying VWM disease's pathophysiology. Experiments are designed to identify, at molecular resolution, the functional defects of various cell types isolated from Marisol mice strain compared to a control strain.

Experiments over the last decade involved isolating glial cells responsible for brain homeostasis and myelination (i.e., astrocytes and oligodendrocytes, respectively) and cells found in connective tissues (i.e., fibroblasts) for comparison. One of the most significant findings was the detrimental impact of the hypo-active enzymatic activity of eIF2B due to the mutation on mitochondrial function. Biochemical analyses revealed defective mitochondrial oxidative respiration and energy metabolism in all the eIF2B-mutated cell types. However, while mutant fibroblasts manage to fully compensate for their faulty mitochondrial function by increasing their mitochondria biogenesis, mutant brain glial cells fail to achieve complete restoration of mitochondrial respiration despite massive adaptation efforts. This finding aligns with the confinement of the clinical symptoms to the brain's white matter. The difference in energy requirements between fibroblasts and brain glial cells could partly explain the asymptomatic phenotype of fibroblasts along with the defective function of brain glial cells of VWM patients. In addition to the poor energy status of eIF2B-mutant astrocytes, Elroy-Stein's lab has demonstrated their high vulnerability to reactive oxygen species (ROS) and their inferior ability to stimulate the (ROS)-mediated biochemical axis, which plays a crucial role in redox homeostasis. These defects earned the title ‘Achilles heel of VWM disease’.

In another study, the functional defect of the mitochondria was chosen as a readout for a cell-based fluorescent assay to screen the effect of drug-like molecules using a library of 50,000 compounds. Three promising candidates were found on this screen. One of them was identified as a sigma-1-receptor (S1R) agonist which offers hope for potential treatment.

Elroy-Stein's research currently combines a multidisciplinary integrative approach with an emphasis on quantitative analyses related to the regulation of gene expression in response to a changing physiological environment. The

genome-wide angle includes the generation of datasets of the transcriptome, translatome, and proteome. Importantly, these unbiased 'omics '-related experiments, followed by extensive bioinformatic analyses, confirmed the connection between eIF2B mutation and mitochondrial malfunction. Furthermore, it currently enables ongoing discoveries of additional cellular pathways that are negatively affected by eIF2B mutations and thus can be targeted in the future for the development of new therapeutic modalities. Discoveries related to the malfunction of specific biochemical circuits are similarly instrumental for diagnostic purposes related to the progression of the disease on the molecular level, which usually appears in the pre-symptomatic stage, and for assessment of drug treatments used in clinical trials.