Targeting pathogenic Lafora bodies in Lafora disease using an antibody-enzyme fusion

Grant Austin, MS [1] • M. Kathryn Brewer [1] • Annette Uittenbogaard [1] • John J. McCarthy, PhD [2] • Dyann M. Segvich [3] • Anna DePaoli-Roach, PhD [3] • Peter J. Roach, PhD [3] • Bradley L. Hodges, PhD [4] • Jill Zeller, PhD [5] • James R. Pauly, PhD [6] • Tracy McKnight, PhD [4] • Dustin Armstrong, PhD [4] • Matthew S. Gentry, PhD [1]

[1]Molecular and Cellular Biochemistry, University of Kentucky • [2]Physiology, University of Kentucky • [3]Biochemistry and Molecular Biology, Indiana University School of Medicine • [4]Valerion Therapeutics • [5]Northern Biomedical Research • [6]Pharmaceutical Sciences, University of Kentucky

Abstracts will be considered for both poster and platform presentations

Epilepsy/Brain metabolism

Lafora disease (LD) is a fatal childhood epilepsy and a non-classical glycogen storage disorder with no effective therapy or cure. LD is caused by recessive mutations in the EPM2A or EPM2B genes that encode the glycogen phosphatase laforin and an E3 ubiquitin ligase malin, respectively. A hallmark of LD is the intracellular accumulation of abnormal and insoluble α-linked polysaccharide deposits known as Lafora bodies (LBs) in several tissues, including most regions of the brain. In mouse models of LD, genetic reduction of glycogen synthesis eliminates LB formation and rescues the neurological phenotype. Since multiple groups have confirmed that neurodegeneration and epilepsy result from LB accumulation, a major focus in the field has shifted toward the development of therapies that reduce glycogen synthesis or target LBs for degradation with the goal of treating LD. Herein, we identify the optimal enzymes for degrading LBs, and we develop a novel therapeutic agent by fusing human pancreatic α-amylase to a cell-penetrating antibody fragment. This antibody-enzyme fusion (VAL-0417) degrades LBs in vitro, shows robust cellular uptake, and significantly reduces the LB load in vivo in Epm2a-/- mice. VAL-0417 is a promising therapeutic for the treatment of LD and a putative precision therapy for an intractable epilepsy. Antibody-enzyme fusions represent a new class of antibody-based drugs that could be utilized to treat glycogen storage disorders and other diseases.