THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

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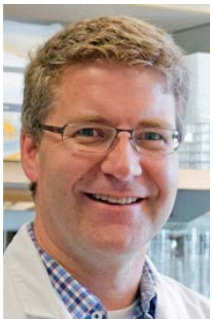

Enzyme Replacement Therapy for Inborn Errors of Metabolism

Inborn errors of metabolism (IEM) are rare single gene defects involving mutations of enzymes in key metabolic pathways. While many have an incidence of less than 1 in 100,000 births, collectively they have an incidence of about 1:800 to 1:2,500 births. Many IEM are lethal to children at birth or in early childhood; and are often associated with profound developmental abnormalities, cognitive impairments, seizures, and blindness. Enzyme replacement therapy should compensate functionally for a missing or defective enzyme, but an effective therapy has only been demonstrated for the treatment of one subset of IEM called lysosomal storage disorders. Enzyme replacement therapy has been of limited utility because most defective enzymes are located in the cytoplasm, mitochondria, nucleus, or other organelles within a cell and delivery of replacement enzymes to these cellular regions is blocked by degradation of the enzymes within lysosomes before they can reach the part of the cell where they are needed most. By contrast, in lysosomal storage disorders the defective enzymes are localized to the lysosome; therefore replacement proteins are not degraded and can provide a therapeutic benefit. To address this unmet need for an improved therapy that will overcome the barriers to intracellular protein and RNA delivery, John developed a strategic lentivirus-based nanoscale protein delivery platform (that he named *nanoPOD*) that is highly efficient at moving enzymes across biological membranes and into the cytoplasm, mitochondria or nucleus of a cell. John's strategy is to co-opt the natural biology of a lentivirus to spread and infect tissues within the host, but for therapeutic benefit. He proposes to use two mouse models of IEM where the defective enzymes are not in lysosomes: glucose-6-phosphatase (associated with the endoplasmic reticulum) or pyruvate dehydrogenase (in mitochondria). The nanoPOD virus-like particles will package the replacement enzymes or RNAs encdoing them and will be optimized for targeted delivery to specific subcellular regions. He will monitor and optimize biodistribution using cryo-fluorescence whole-mouse imaging for precise visualization and 3D reconstruction of on-target and off-target delivery. To assess the immunogenicity of the modified particles, he will monitor immune responses in the mice against the specific nanoPOD. If John is successful in demonstrating the introduction of these two enzymes directly into their cell location, the outcome will lead to clinical translation of the nanoPOD platform for many other intractable metabolic disorders, providing hope for the those patients and their families who suffer from the limited therapeutic options and devastating effects of IEM.