THE HARTWELL FOUNDATION

2009 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Charles A. Gersbach, Ph.D.**
Assistant Professor
Department of Biomedical Engineering

Institution: **Duke University**

Proposal: **Engineering Synthetic Enzymes for the Genetic Correction of Duchenne Muscular Dystrophy**

Dr. Gersbach proposes to edit the human genome to correct the hereditary mutations responsible for Duchenne Muscular Dystrophy (DMD) by means of targeted repair of the abnormal gene responsible for the disease. DMD is a degenerative disease that results from mutation of the gene encoding the dystrophin protein. The genetic nature of the disease has led to substantial interest in gene therapy, including several clinical trials involving the integration of exogenous DNA into the genome, or the lifelong administration of transient gene therapy using viruses to deliver genetic material into cells. However, both approaches are known to have substantial safety and practical concerns. The major stumbling block to these strategies has been an inability to effectively deliver the large and complex dystrophin gene. There are also several promising therapies being developed to prevent the muscle degeneration associated with DMD, including transplantation of skeletal muscle cells, stem cell transfer, and various pharmacologic approaches; each with their own significant safety concerns. For example, cell transplantation is limited by the ability to produce, administer, and engraft sufficient amounts of dystrophin-positive muscle progenitor cells, as well as the requirement to overcome the immune response against foreign tissue. By contrast, Dr. Gersbach proposes to deploy cutting-edge zinc finger enzymes (artificial enzymes whose structure is based upon the native protein structure of DNA-binding proteins in a human cell) to correct the faulty DNA sequence in the dystrophin gene in a standard mouse model of DMD. His working hypothesis is that dystrophin gene repair by engineered zinc finger enzymes can be used to increase the number of dystrophin-positive muscle fibers and reduce muscle degeneration. The effects of dystrophin restoration on muscle degeneration will be analyzed both through gene modification via implantation of dystrophin-repaired muscle cells in culture, as well as gene repair in the living animal. The approach offered by Dr. Gersbach represents an innovative approach to induce permanent dystrophin expression in mutant cells — a potential cure for DMD without the need for permanent integration of, or repeated exposure to, foreign biological material. If the technology is successfully validated, the long-term goal will be translation into a clinical therapeutic for reversing muscle degeneration and premature death in DMD patients. The technology also would have the potential for gene repair in other single gene disorders.