THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

Jennifer Adair, Ph.D.

Assistant Member
Clinical Research Division

Fred Hutchinson Cancer Research Center

Engineering a Simplified Universal Delivery Method for Gene Therapy

Gene therapy is the introduction of genetic material into cells to compensate for abnormal genes or to restore the function of a protein. The delivery of gene therapy to blood cells has great potential to treat common genetic diseases and if readily available would benefit hundreds of thousands of children in the US. Delivery of a corrected gene into blood stem cells has already been shown to dramatically improve the outcome and quality of life for a variety of disorders, such as primary immunodeficiencies, hemoglobinopathies like sickle-cell, and even rare forms of blindness. However, availability of such gene therapy is severely limited by the complexity of the technology. To integrate therapeutic genes into cellular DNA, the current state-of-the-art requires that cells be treated with engineered retroviruses ex vivo, *outside* the body. Because there is no concrete way to distinguish blood stem cells from the presence of a myriad of other cells in vivo, *inside* the body, the cells must be isolated and purified first. Depending upon the stem cell markers used for identification however, the composition of isolates may be variable and therefore influence gene therapy outcomes. Moreover, while retroviruses can easily be modified to deliver any therapeutic gene, they cannot be produced in high enough quantities to treat even hundreds of patients. Furthermore, there is a genotoxic risk associated with retroviruses due to their potential for semi-random insertions that can lead to cancer. To expand the availability of gene therapy, there is an urgent need for a safe and effective method of delivering therapeutic genes into blood cells inside the patient's body. Jennifer's working hypothesis is to adapt the best and most distinctive features of existing technologies, including programmable nuclease-based genome-editing technology; identification of genomic safe harbor sites for gene insertion ; and leveraging the unique properties of a cell targeting system. Her approach will eliminate the need for cells to be purified and treated outside the body. Based upon her recent identification of a safe site within recipient DNA in which to insert therapeutic genes, Jennifer proposes a new non-viral delivery system for in vivo therapy. In effect, she will add a therapeutic gene and an engineered CRISPR/Cpfl nuclease to gold carrier nanoparticles, formulated to contain a small synthetic single-strand of nucleic acids (aptamer) that will enable high affinity binding with a particular molecule expressed on the blood cells of interest, without toxic side effects. To advance clinical translation of this genome-editing approach, she will optimize delivery effectiveness and safety in non-human primates. If Jennifer is successful, her delivery system will enable gene therapy to be more readily available to those children in desperate need of this remarkable intervention, reducing morbidity and mortality as a side-effect while dramatically increasing their quality of life.