2016 Webb-Waring Biomedical Research Awards
Investigator Research Profile

Schuyler B. van Engelenburg, Ph.D.

University of Denver

Dr. van Engelenburg is currently an assistant professor at the University of Denver, natural sciences and mathematics, department of biological sciences. He completed postdoctoral training in cell biology and virology at the National Institute of Child Health and human development (NIH, Bethesda, MD) and earned his Ph.D. in biochemistry at the University of Colorado, Boulder.

Select Honors

Dr. van Engelenburg has been the recipient of a Creative Training in Molecular Biology Grant from the National Institutes of Health, a Mentor of the Year Award from the National Institutes of Child Health and Human Development and a Publication Recommendation F1000Prime in Structural Biology from the Faculty of 1000.

Medical Focus

Genetic diseases, which are typically present at birth and last for the patient's lifetime, are often medically intractable and associated with high mortality rates and poor quality of life. One such genetic disorder of the blood is X-linked Severe Combined Immune Deficiency Syndrome (SCIDS), which is caused by mutations in the interleukin-2 receptor (IL2Rγ) and causes affected children to be chronically immunocompromised. There has been much interest in attempting to cure SCIDS through the use of gene therapy, which involves a medical attempt to replace a patient's defective gene with a corrected one and which holds high promise to eradicate genetic diseases by restoring normal biological function to an otherwise diseased patient. Unfortunately, the success of gene therapy has been hindered by technological barriers that have led to catastrophic outcomes for patients. For example, current use of retrovirus-based vectors for delivering gene therapy to SCIDS patients has unfortunately been met with difficulties. Following human gene therapy trials for X-linked SCIDS, occurrences of leukemia and death have been reported due to the integration of retrovirus-delivered transgenes at random sites within the recipient genome. Therefore, there is a critical need to develop safe technologies that can transmit corrective transgenes to these immunodeficient children.

Research Proposal

Dr. van Engelenburg's research will focus on devising new technology for the selective, site-specific and safe delivery of corrective genes to children suffering from genetic blood disorders, starting with SCIDS and the IL2Rγlocus. His team will achieve this by combining the specificity of novel genome-editing technologies with next-generation virus particles. Dr. van Engelenburg's central hypothesis is that an engineered, chimeric construct consisting of the Cas9 gene editing enzyme and the LEDGF protein, which directs retroviral integration into the genome, can safely direct corrective gene integration at the IL2Rγloci when directed by a site-targeted guide RNA. The first aim of his research will be to construct a Cas9-LEDGF hybrid protein and demonstrate site-specific retroviral integration of a control gene into cells expressing the construct, using human immunological cell lines as a model system. This will serve as a proof-of- concept demonstration that site-specific virus integration will translate to safer retroviral vectors for correcting defective IL2Rγin SCIDS afflicted children. The second aim will be to engineer highly effective retroviral vectors incorporating chimeric constructs for transduction into human hematopoietic ($CD34^+$) stem cells. The results of his work would provide the proof of principle pilot data for creating safer retroviral vectors for use in human gene therapy trials. Extension of this site-selective targeting system will undoubtedly enable correction of other genetic disorders and pave the way for commonplace gene therapy medical procedures.