

CHARLES GERSBACH

"Genome and Epigenome Editing for Gene Therapy and Cell Programming"

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3:30 PM

Wu and Chen Auditorium

Levine Hall



John W. Strohbahn Distinguished
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ABSTRACT

The advent of genome engineering technologies, including the RNA-guided CRISPR/Cas9 system, has enabled the precise targeting and manipulation of genomic locations with molecular machinery. For example, we engineered various DNA editing systems to correct the mutated human dystrophin gene in cells isolated from Duchenne muscular dystrophy (DMD) patients. When delivered directly to a mouse model of this disease, gene editing by the CRISPR/Cas9 system led to gene restoration and improvement of biochemical and mechanical muscle function. We have observed gene editing in muscle satellite cells following AAV-CRISPR delivery in vivo, supporting the possibility of long-term gene correction despite muscle cell turnover. More recently, we have developed novel humanized models of this disease for the preclinical development of therapies that will correct human disease-causing mutations. New constructs have been developed and validated for significant levels of gene correction and dystrophin restoration in this model. Moreover, we have demonstrated in vivo gene editing that restores a full-length dystrophin gene, in contrast to previous approaches that restore a truncated, partially functional protein. These studies demonstrate the potential for genome editing to be used to treat DMD and other neuromuscular disorders, and also highlight issues for further study and development.

While most widely used for editing DNA sequences, these technologies may have even greater and broader impact by programming other functions at specific genomic locations. For example, CRISPR technologies have been adapted and applied to robustly and precisely manipulate gene expression, program the epigenome, annotate the function of the non-coding genome, and control cell fate decisions. Genome-wide analysis of the DNA-binding, gene regulation, and chromatin remodeling by these targeted epigenome modifiers has demonstrated their exceptional specificity. We have continued to expand the CRISPR epigenome editing toolbox via the characterization of novel CRISPR-Cas systems and the discovery of new effectors that coordinate gene expression changes at targeted loci. We have applied these technologies to control the decisions of stem cells to become specific cell fates and reprogram cell types into other lineages for drug screening, disease modeling, and in vivo tissue regeneration. High-throughput pooled CRISPR screening with epigenome editors has enabled the discovery of master regulators of complex cell fate decisions. We have also used epigenome editing to reprogram complex epigenetic states, such as imprinting, at disease-relevant loci. Collectively, these studies demonstrate the potential of modern genome engineering technologies to capitalize on the products of the Genomic Revolution and transform medicine, science, and biotechnology.

BIO

Dr. Charles A. Gersbach is the John W. Strohbahn Distinguished Professor of Biomedical Engineering at Duke University, the Director of the Duke Center for Biomolecular and Tissue Engineering, and the Director of the Duke Center for Advanced Genomic Technologies. His research interests are in genome and epigenome editing, gene therapy, regenerative medicine, biomolecular and cellular engineering, synthetic biology, and genomics. His work has led to new approaches to study genome structure and function, program cell biology, and treat genetic disease. Dr. Gersbach's work has been recognized through awards including the NIH Director's New Innovator Award, the NSF CAREER Award, the Outstanding New Investigator Award from the American Society of Gene and Cell Therapy, and induction as a Fellow of the American Institute for Medical and Biological Engineering. He currently serves as co-chair of the Steering Committee for the NIH Somatic Cell Genome Editing Consortium. He is also the co-founder of three biotechnology companies, an advisor to several others, and currently serves as the Acting Chief Scientific Officer of Tune Therapeutics.