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CRISPR Platform & Portfolio

While genomic research has identified many genetic targets that have the potential to modify the course of a disease, there has been little translation of that into genetic therapies. However, the discovery of clustered regularly interspaced short palindromic repeat (CRISPR) segments and the subsequent development of CRISPR systems in 2011 revolutionized the field of genome editing. CRISPR, with its unprecedented ability to control gene expression and precisely delete and add in genes, is paving the way to genetic and epigenetic therapies and investigational gene editing and modulation. CRISPR isn't perfect, though, and has been shown to delete and rearrange large sections of DNA and might result in increased cancer risk in altered cells. CRISPR systems need further work to minimize genomic off target effects and maximize in vivo gene editing efficiency, cellular delivery and spatial-temporal regulation.

Researchers at Arizona State University have developed a platform and robust portfolio of CRISPR related technologies that enable more efficient, safer and controllable gene editing/modulation. In one embodiment, they combined logic-based design principles of synthetic biology with the function of the CRISPR/Cas9 system to carry a multilayered regulatory control element which provides spatial and temporal control over the synthetic circuit in vivo. The control elements in the synthetic CRISPR-based genetic circuits enable safe regulation of gene expression. Safety switches were also designed to spatiotemporally inactive CRISPR in the event that an adverse reaction is observed or reproductive organs are inadvertently targeted. In another embodiment, truncated gRNAs are used to repress key enzymes of the non-homologous end joining (NHEJ) DNA repair pathway to increase the efficiency of the homology directed repair (HDR) pathway and subsequently the efficiency of CRISPR-based gene editing. Improved Cas9 repressors were also developed to perform multilayered silencing of genes. Methods have also been developed to identify potential patients with pre-existing immunity to Cas9 prior to initiation of therapy. These methods screen for B and T cell responses to Cas9 and create personalized treatments to overcome immunogenicity by modifying the Cas9 protein to remove epitopes that can cause a disruptive immune response. Therapeutics utilizing components of this portfolio have also been developed. One particular synthetic CRISPR gene circuit composition can be used to prevent noise-induced hearing loss. In this composition, the gene circuits are delivered via a viral vector and target hair cells of the inner ear to activate endogenous genes. Another method uses CRISPR based silencing to program host defense against pathogens. To enable superior detection and measurement of gene editing by CRISPR gRNA, a construct was created that incorporates a fluorophore-binding RNA aptamer sequence into the gRNA that is activated by a small molecule inducer to fluoresce.

This portfolio of technologies, which is continually expanding, may prove to be the best path forward for more effective and safer CRISPR-based gene and cell therapies.

Potential Applications

- Gene editing/modulation
  - Treating cancer, HIV, blindness, genetic disorders, etc.
  - Preventing hearing loss
- Infectious disease prevention or elimination in humans and insects
- Creating enhanced crops/plants/livestock
- Genomic research

Benefits and Advantages

- Can activate genes, repress genes or do both
- Modulates cellular function in a predictable and user-defined manner with minimal off-target effects
- Cell/tissue type-specific CRISPRs
- Low-cost & efficient
- Provides a means for direct, non-invasive measurement of gene editing
- Decreases undesirable immune response in patients undergoing CRISPR-based gene therapy
- Built in kill switch turns off gene expression in response to small molecules already in use
- Improved results of single and dual guide RNA library screens

For more information about this opportunity, please see

Ferdosi et al - Nat Commun - 2019

Yeo et al - Nat Methods - 2018

Menn et al - ACS Synth. Biol - 2018

Pinenda et al - ACS Synth. Biol - 2017