METHOD TO CREATE DESIGNER STEM CELLS FOR SAFER, MORE EFFECTIVE THERAPEUTICS

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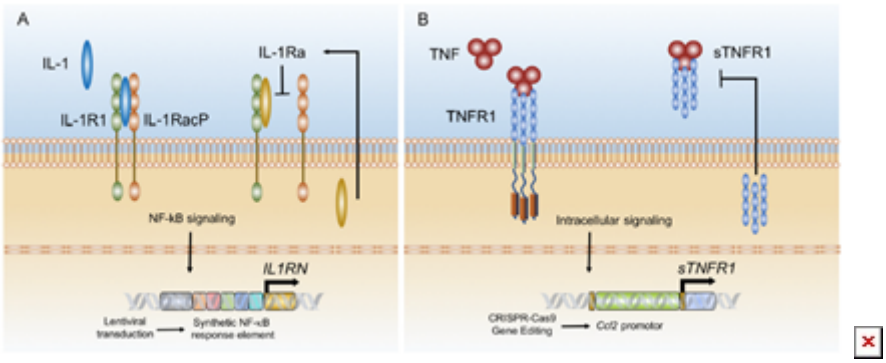
T-018758

Technology Description

Researchers at Washington University in St. Louis have developed a method to create designer stem cells which provide a safer, more effective cell therapy approach to treating disease. Cell-based regenerative therapies could potentially be used to treat many diseases and restore damaged tissues. However, clinical use has been limited by the inability to precisely control cell function. To overcome this limitation, the inventors have developed a strategy to create designer stem cells– cells that are engineered to execute controlled, real-time, programmed responses to environmental cues, such as pro-inflammatory cytokines. To generate such cells, the inventors used CRISPR-Cas9 gene editing to reprogram the normal inflammatory signaling pathway to allow transient, auto-regulated production of cytokine antagonists in direct response to cytokine stimulation. This approach can be adapted for other signaling pathways as well. This technology enables the customization of intrinsic cellular signaling pathways to provide safer, more effective cell therapy-based disease treatments. More complex synthetic gene circuits have also been developed to deliver more than one biological drug at a time in an autoregulated manner.



Synthetic gene circuits used to develop self-regulating biologic drug delivery systems. (A) Synthetic promoter containing multiple NF-kB recognition motifs upstream of *IL1RN* (gene for IL-1Ra) to create an inducible promoter that is activated by inflammation. In response to IL-1, the synthetic promoter is activated and produces IL-1Ra, which then inhibits IL-1 in an autoregulated manner. (B) CRISPR-Cas9 targeted gene editing was used to insert a therapeutic transgene (*sTNRF1*) in the *Ccl2* locus. Activation of the endogenous *Ccl2* promoter by TNF results in dynamic expression of *sTNFR1*, which then inhibits TNF, creating a self-regulating system. (From Guilak et al., see publications.)

Stage of Research

The inventors performed targeted addition of TNF-alpha or IL-1 antagonists to the cytokine-responsive

Ccl2 locus. Transgene expression from the engineered cells was feedback-controlled with rapid on/off dynamics and it mitigated the inflammatory effects of physiological concentrations of TNF-alpha/IL-1 in engineered tissues such as cartilage. These studies have shown excellent efficacy and safety in a preclinical animal model of rheumatoid arthritis, showing significant inhibition of pain, swelling, and disease progression.

Publications

- Brunger, J. M., Zutshi, A., Willard, V. P., Gersbach, C. A., & Guilak, F. (2017). Genome Engineering of Stem Cells for Autonomously Regulated, Closed-Loop Delivery of Biologic Drugs. *Stem cell reports*, *8*(5), 1202–1213.
- Dryden, J. Stem cells edited to fight arthritis. *The Source from Washington University in St. Louis*. April 27, 2017.
- Guilak, F., Pferdehirt, L., Ross, A.K., Choi, Y.R., Collins, K.H., Nims, R.J., Katz, D.B., Klimak, M., Tabbaa, S., and Pham, C.T.N. (2019). Designer stem cells: Genome engineering and the next generation of cell-based therapies. Journal of Orthopaedic Research, 37(6):1287-1293.
- Choi, Y.R., Collins, K.H., Springer, L.E., Pferdehirt, L., Ross, A.K., Wu, C.L., Moutos, F.T., Harasymowicz, H.S., Brunger, J.M., Pham, C.T., and Guilak, F. A genome-engineered bioartificial implant for autoregulated anti-cytokine drug delivery, bioRxiv 535609.

Applications

- Regenerative medicine
- Inflammatory arthritis
- Autoimmune diseases
- Joint injury
- Diabetes

Key Advantages

- Adaptable to additional signaling pathways
- Enables safer, more effective therapeutics
    - Cells sense level of inflammation and respond according to the degree of pathology
    - Overcomes limitations associated with delivery of large drug doses or constitutive overexpression of biologic therapies
- Targeted integration
- Uses iPSCs- base cell population can be precisely defined and potentially undergo additional genome modifications if needed
- Attractive for regenerative medicine- clones may be screened for function and then expanded and differentiated toward a variety of terminal cell types to treat multiple tissues from the same engineered cell population
- This approach may enable therapeutic delivery during the early stages of the disease

Patents

- Non-Provisional Patent Application- Compositions, systems and methods for cell therapy. Publication number US20180201951

Related Web Links

- Dr. Guilak profile