Docket #: S22-191

Use of complement inhibition to improve wound healing

Wound healing is a huge clinical problem. Problematic outcomes of skin wounds can range from under-healing (e.g., chronic/non-healing wounds) to over-healing (e.g., scarring). Healing via scarring has major consequences for human health: scarring can cause disfigurement, functional loss, and reduced quality of life. Despite the substantial clinical burden scars impose, there are no current therapies that induce scar-free healing in humans. Existing methods for reducing scarring are limited to tension-offloading dressings, which can be unwieldy, may be difficult to apply depending on the location of the injury, and have no potential for translation to non-skin fibroses. Existing methods for improving healing of chronic wounds are limited to conservative treatment or hyperbaric oxygen therapy, which is expensive, inconvenient, resource-intensive, and not available to most patients.

Stanford inventors have identified complement pathway inhibition as an approach for improving wound healing outcomes, including accelerating wound repair, decreased scarring/fibrosis, and increased wound regeneration. They investigated the genetic profile of MRL mice, a strain of laboratory mice with known super-healing properties, including the ability to fully regeneratively heal through-and-through ear punch wounds. Regenerative ear healing in this strain includes features such as regeneration of key tissue types (including cartilage and normal/unwounded-like skin) as well as accelerated/enhanced wound closure and re-epithelialization. They identified genes with patterns of cis-regulation that were unique to MRL ear wounds, which are candidate drivers of regenerative/enhanced healing. Complement factor H (CFH) - a natural inhibitor of the complement pathway – was identified as the gene specifically upregulated in MRL ear wounds, suggesting that complement inhibitory activity may play a role in wound regeneration/enhanced wound healing. Inventors found that CFH treatment improved wound healing, leading to: accelerated wound closure and accelerated/more complete re-epithelialization; less-fibrotic tissue ultrastructure; evidence of hair follicle regeneration on histology, and decreased scar thickness indicating decreased scarring/fibrosis. The method of complement

inhibition could improve wound healing by reducing scarring/promoting regeneration or accelerating/enhancing wound repair.

Applications

- Topical/local wound treatments involving CFH or other complement inhibitors

Advantages

- Can reduce scarring. Existing methods for reducing scarring are limited to tension-offloading dressings (embrace device, Neodyne Biosciences) which can be unwieldy, may be difficult to apply depending on the location of the injury, and have no potential for translation to non-skin fibroses (e.g., internal organ fibroses) which may be driven by similar mechanisms to scarring and thus benefit from similar anti-fibrotic approaches (such as complement inhibition). No targeted molecular therapies exist to prevent or reverse scarring.
- Can treat chronic wounds. Existing methods for improving healing of chronic wounds are limited to conservative treatment (e.g., wound dressings to keep the wound protected/moist, antibiotics to prevent or treat infection) or hyperbaric oxygen therapy, which is expensive, inconvenient, resource-intensive, and not available to the vast majority of patients. No targeted therapies exist that have been shown to improve/accelerate healing of chronic wounds.

Publications

- Talbott, H. E., Mack, K. L., Griffin, M., Guardino, N. J., Parker, J. B., Spielman, A. F., ... & Longaker, M. T. (2022). " Allele-specific expression reveals genetic drivers of tissue regeneration in mice". bioRxiv, 2022-09.

Patents

- Published Application: WO2023215294

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