Topical Delivery of Fidgetin-Like 2 siRNA to Enhance Cell Migration for Burn Wound Healing in a Swine Model

Christine Kowalczewski, Logan Leatherman, Michelle Holik, David Larson, Lucy Shaffer, Robert Christy
US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX

Introduction

- Donor site skin is a precious commodity for burn wounds and graft-sparing procedures are critical for larger total body surface area burns (TBSA). Currently, large ratio skin grafts have been found to preserve donor skin but at the expense of delayed reepithelialization and increased scar formation at the recipient site [1].
- For patients with large burn TBSA, improving the functional and cosmetic outcomes of large mesh ratios would reduce the need for two-stage treatments.
- Investigation into alternative therapies include administration of small interfering RNA (siRNA) which are sequence-based and are therefore unique for the target mRNA, minimizing off-target effects.
- Local delivery of siRNA encapsulated nanopartciles (NPsi) can be used to suppress the expression of one microtubule regulatory protein, Fidgetin-Like 2 (FL2), which has been shown to increase cell migration rate both in vitro and in vivo [2, 3].
- In this study, we propose to utilize a topical gene therapy treatment as an adjunct to higher meshing ratio (3:1) split thickness skin grafts (mSTSG) to improve re-epithelialization and reduce donor skin requirements.

Hypothesis/Objectives

- We hypothesize that topical application of nanoparticle encapsulated FL2 siRNA (FL2 NPsi) will increase cell migration resulting in expedited reepithelialization in large mesh ratio mSTSG in a porcine burn model.
- A pilot study was conducted to down-select siRNA dose by measuring the rate of reepithelialization of grafted burns.

Methods

FL2 NPsi Fabrication: The NPsi are manufactured using a water-in-oil 118 emulsion whereby the aqueous FL2-targeting or scramble (control) siRNA solution is encapsulated by Zonyl ® FSO 119 and polyetheiene oxide-polypropylene oxide polymer. Doses tested: 5, 10, 20μM FL2 NPsi or 20μM scramble NPsi (n=2).

Porcine Burn Model:

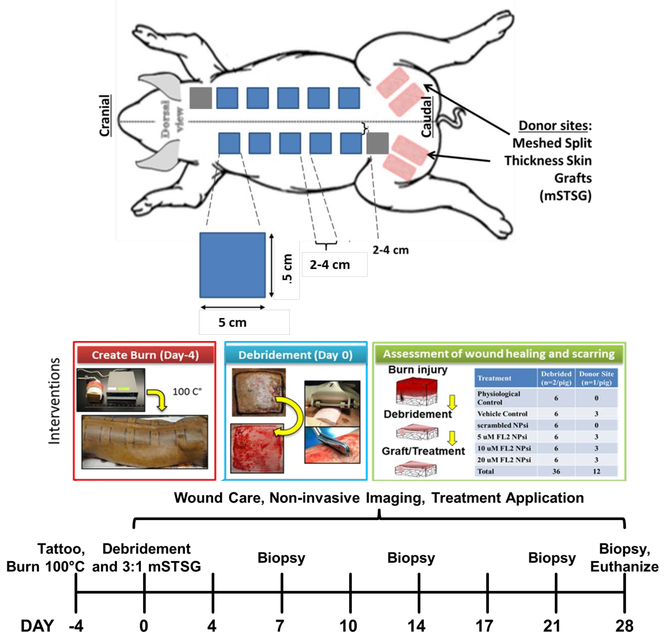

Figure 1: Pig schematic and timeline. Ten 5x5 cm burn wounds were created on the dorsum of anesthetized Yorkshire pig (N=1). The schematic indicates the timeline and methods utilized throughout the study. Non-invasive measurements to include digital, Silhouette, and laser speckle imaging.

Results

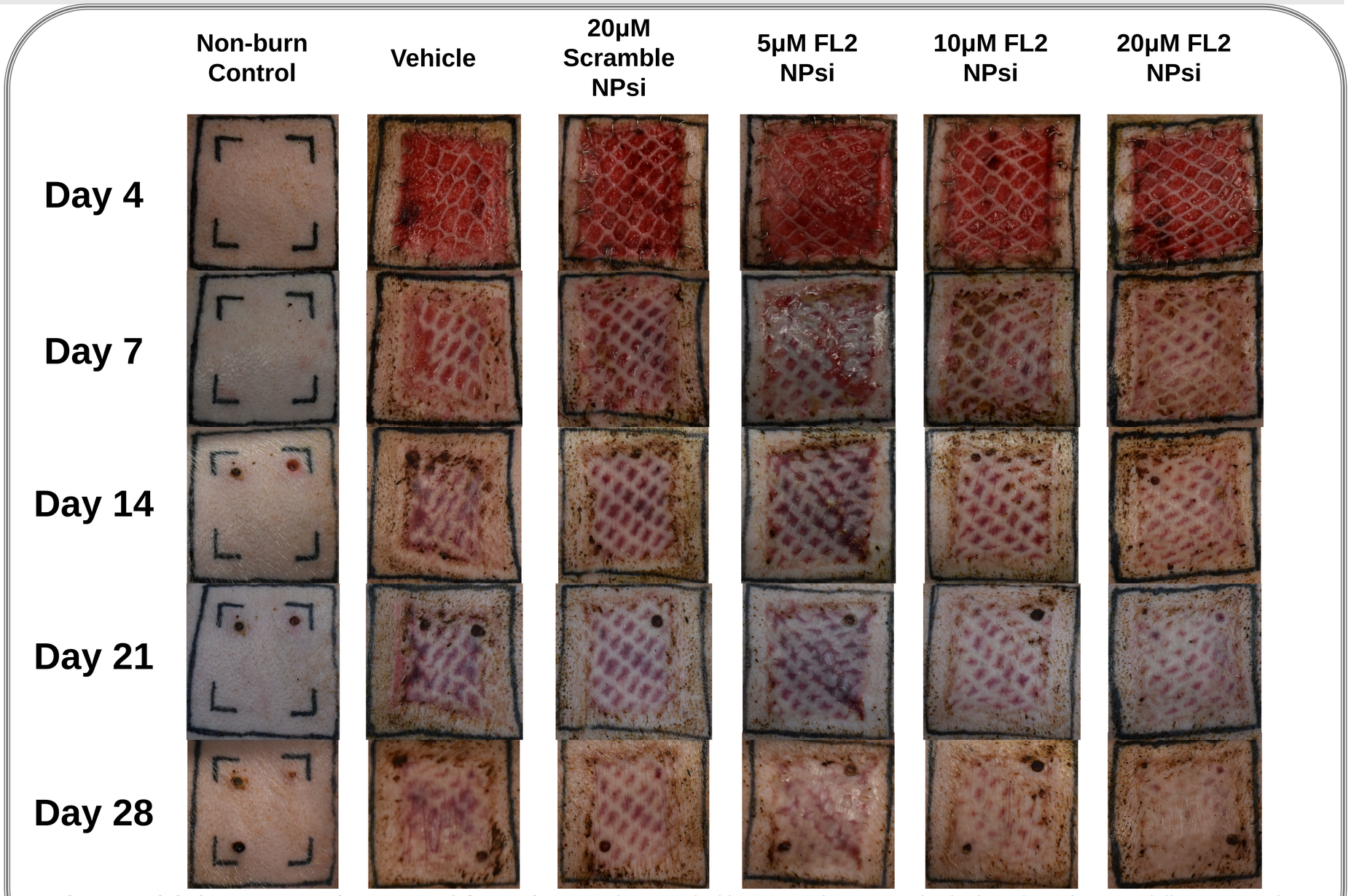

Figure 2. Digital Images over the course of the study. Wounds treated with FL2 NPsi appear to be further along the remodeling process by reduced redness and "waffle" patterning compared to vehicle and Scramble NPsi treated wounds. Currently, awaiting blinded pathologist evaluations to verify visual observation.

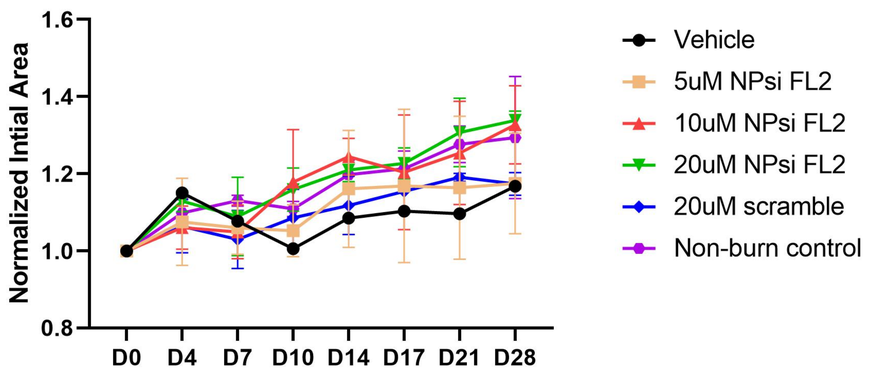

Figure 3. Silhouette analysis over the course of the study. Wound size was normalized to D0 preburn measurements.

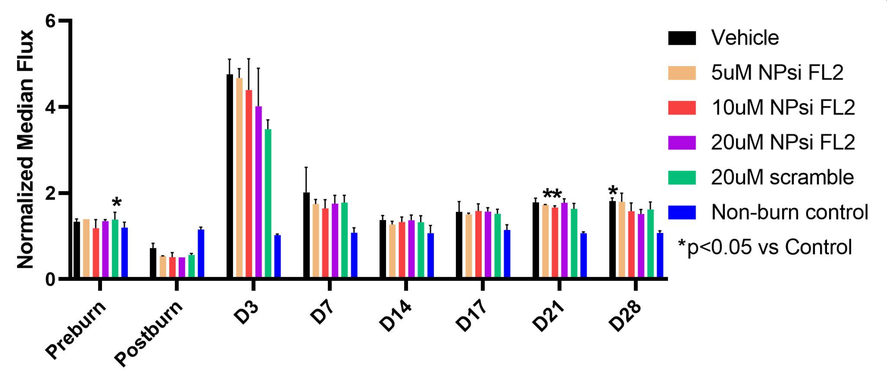

Figure 4. Laser Speckle Imaging analysis over the course of the study. Median wound flux was normalized to preburn flux measurements.

Conclusions

- Topical application of NP FL2 siRNA did increase the rate of reepithelialization of large ratio mSTSG treated injuries.
- LSI data showed no statistical differences to vehicle control.
- Additional pilot animals are currently ongoing to down-select siRNA dose for future studies comparing the experimental treatment to the current clinical gold standard 1:1.5 mesh ratio.

Acknowledgements

This research was supported in part by an appointment to the Postgraduate Research Participation Program at the U.S. Army Institute of Surgical Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and USAISR. This research was funded by the U.S. Army Medical Research and Materiel Command and Military Burn Research Program.

Statements

Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AAALAC International.

References

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