ELU42, a small molecule WNT signaling inhibitor, significantly accelerates wound closure and promotes regenerative repair following cutaneous and third-degree burn injury in Yorkshire pig

ELUCIDERM
CHANGING THE WORLD OF WOUND HEALING

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ABSTRACT

BACKGROUND: The canonical WNT signaling pathway is quiescent in many mammalian organs and becomes activated in response to injury. WNT signaling promotes fibrotic wound healing (including scarring) following acute cutaneous injury. Topical "spray-on" application of a proprietary WNT signaling inhibitor accelerated wound closure and promoted regenerative cutaneous repair in acute and third-degree burn wounds.

METHODS: In this study, we utilized two porcine models to analyze wound repair. Six full-thickness 3 x 3 cm^2 acute and ten third-degree burn excisional wounds were created on the backs of Yorkshire pigs. ELU42, a novel, potent, aqueously soluble, topical "spray-on" small molecule WNT signaling inhibitor, was applied three days a week up to Day 30. The animals were allowed to heal for another 30 days before being sacrificed at Day 60. Histopathological analyses were performed on excised tissues.

RESULTS: In full-thickness acute and third-degree excisional wounds, topical application of the novel small molecule WNT signaling inhibitor, ELU42, significantly promoted wound closure, and also promoted regeneration of tissue, as evidenced by the presence of restored skin architecture with adnexal structures and restoration of well-organized granulation tissue. A statistically significant increase in rete peg formation at the dermal–epidermal junction was also identified. Significance calculations were performed using a two-way Analysis of Variances (ANOVA) using the Prism10 software (Graph-pad prism). $P \leq 0.05$ was considered significant.

CONCLUSIONS: Until now, studies using small molecule WNT signaling inhibitors were limited for therapeutic usage due to their poor aqueous solubility. We have created ELU42, a water-soluble small molecule WNT signaling inhibitor, in spray-on form. It is a non-toxic potential drug and does not require a sterile environment when applying to traumatic soft tissue (acute) wounds and third-degree burns. Our study presents a stable, potent, bioavailable, small molecule WNT signaling inhibitor that has strong pharmacological potential for use as a therapeutic for the regenerative repair of chronic cutaneous wounds.

ELU42: First in a generation of novel, potent, aqueously soluble, topical "spray-on" small molecule WNT signaling inhibitors

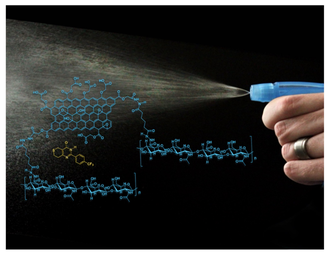


Figure 1. ELU42: Eluciderm Inc. has developed a patented, portable, safe and topical Wnt signaling inhibitor for acute, chronic, and third degree burn wounds.

Wnt signaling pathway: An attractive target for chronic wounds

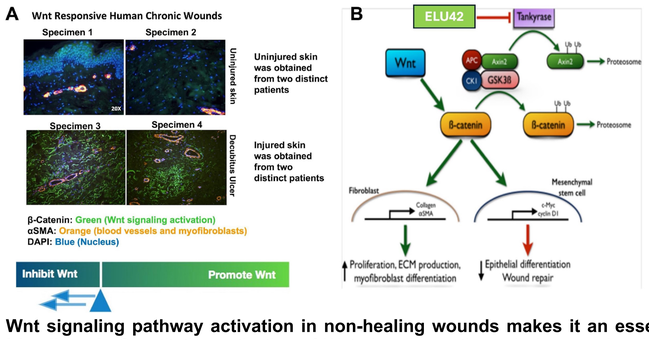


Figure 2. **Wnt signaling pathway activation in non-healing wounds makes it an essential target for wound healing. A.** Constitutive activation of Wnt signaling pathway in human chronic wounds. A representative image of uninjured skin (specimen 1 and 2) and decubitus ulcer (specimen 3 and 4) stained with β-catenin (green), α-SMA (orange) and DAPI (blue). Strong expression of β-catenin was identified in the chronic wounds represented by decubitus ulcer whereas no β-catenin expression was identified in uninjured human tissue. α-SMA stained the blood vessels and DAPI was used for nuclear staining. **B.** ELU42 is a Wnt signaling inhibitor that targets Tankyrase 1 and 2. Wnt signaling inhibition promotes repair by increasing epithelial cell differentiation and suppressing myofibroblast activation.

ELU42 promotes regenerative healing following full thickness excisional wounds in Yorkshire porcine model

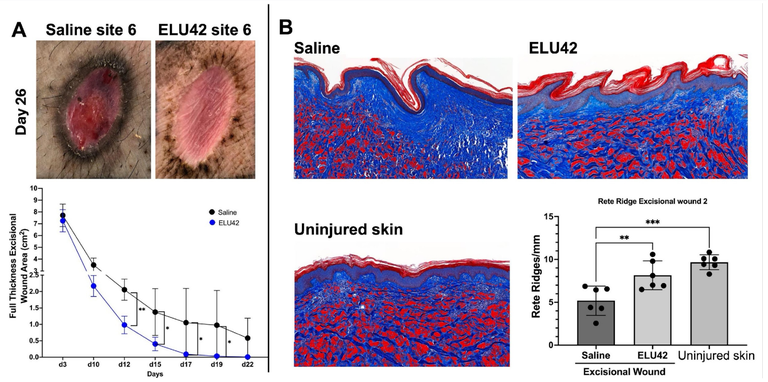


Figure 3. **ELU42 promotes regenerative healing, reduces scarring, and promotes rete ridge formation in full thickness porcine wounds. A.** 3 cm x 3 cm open wounds were created on the back of Yorkshire pigs and treated with either saline or ELU42 three times per week for up to 30 days. Representative wound pictures of saline treated and ELU42 treated open wounds at day 26 following injury **(Top)**. ELU42 significantly increases rate of healing in soft tissue open wounds **(Bottom)**. **B.** Pigs were sacrificed at day 60 for histological analysis. Paraffin embedded tissue sections were stained with Trichrome Blue to assess wound architecture, collagen organization, and rete ridge formation. ELU42 treatment regenerates healthy tissue within the center of the wound with organized reticular collagen and increased rete ridge formation (quantification shown in bottom right). Statistical significance: * indicates $p \leq 0.05$; ** indicates $p \leq 0.01$; *** indicates $p \leq 0.001$.

ELU42 promotes regenerative healing following third degree burn wounds in Yorkshire porcine model

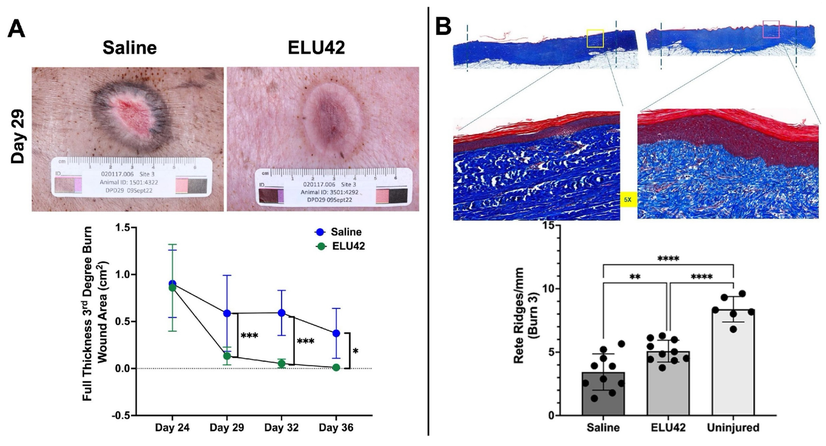
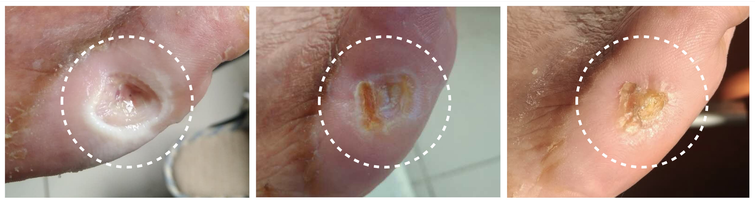


Figure 4. **ELU42 promotes regenerative healing, reduces scarring, and promotes rete ridge formation in full thickness third degree burn wounds. A.** 3 cm x 3 cm burn wounds were created on the back of Yorkshire pigs and treated with either saline or ELU42 three times per week for up to 30 days. Representative wound pictures of saline treated and ELU42 treated open wounds at day 29 following injury. ELU42 treated wounds exhibit less pigmentation, inflammation while achieving superior wound closure. **(Top)**. ELU42 significantly increases rate of healing following full thickness third degree burn wounds **(Bottom). B.** Pigs were sacrificed at day 60 for histological analysis. Paraffin embedded tissue sections were stained with Trichrome Blue to assess wound architecture, collagen organization, and rete ridge formation. The tissue next to the wound margin is enlarged with higher magnification. ELU42 treatment promotes regeneration in burn wounds with organized reticular collagen and increased rete ridge formation (quantification shown in the bottom). Statistical significance: ** indicates $p \leq 0.01$; *** indicates $p \leq 0.001$; and **** indicates $p \leq 0.0001$.

CASE STUDY: ELU42 Treatment of a Diabetic Foot Ulcer (Dramatic Results: With 5 Drops)



Day 0, Before First Drop of ELU42 (50 ul)

Day 5, After Second Drop

Day 15, After Fifth Drop

Figure 5.**CASE STUDY: ELU42 treatment of a diabetic foot ulcer.** A 75 year old patient, Type II diabetic was suffering from chronic non-healing wound that would not heal for over 1 year. She was dosed with 1 drop of ELU42 every 2-3 days for 15 days. The wound was completely healed within two months and never opened again. The patient was followed up regularly for over two years.

CONCLUSIONS

- Wnt signaling pathway is upregulated in chronic wounds.
- Eluciderm Inc. has generated ELU42, first in a generation of novel, potent, aqueously soluble, topical "spray-on" small molecule WNT signaling inhibitors.
- ELU42 promotes regenerative healing, reduces scarring, and promotes rete ridge formation in full thickness porcine wounds and full thickness 3rd degree burn wounds.
- ELU42 shows promise in treating Diabetic Foot Ulcers.
- ELU42 is a promising, patented, portable, safe and topical Wnt signaling inhibitor for treatment of acute, chronic, and 3rd degree burn wounds.

ACKNOWLEDGEMENTS

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