Topical treatment with a novel quaternary polyethyleneimine (QPEI) significantly accelerates wound healing in healthy and diabetic animal models

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Introduction

Globally, 1-2% of the population suffers from chronic wounds each year. The prevalence of chronic and complex wounds are a major clinical and economic burden, with high infection rates.

Quaternary ammonium polyethyleneimines (QPEIs) are a family of broad-spectrum antimicrobial polymers that disrupt bacterial cell walls and membranes via electrostatic interactions, leading to cell lysis.

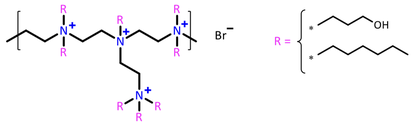

Figure 1. Quaternary ammonium polyethyleneimines (QPEIs) are alkyl-derivatives of a branched polyethyleneimine (a synthetic polymer). A representative QPEI structure is shown.

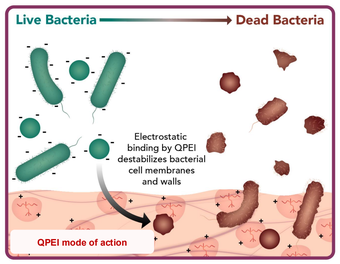

Figure 2. A pictorial depiction of the electrostatic interactions that take place between a positively charged QPEI and the negatively charged bacterial components, leading to anti-microbial activity.

While evaluating the safety of a QPEI in an uninfected *in vivo* mouse wound model, we discovered that **accelerated wound healing** was taking place. Wound healing is a complex and coordinated process which can become dysregulated, particularly in individuals with complicating conditions such as diabetes, leading to poor patient outcomes.

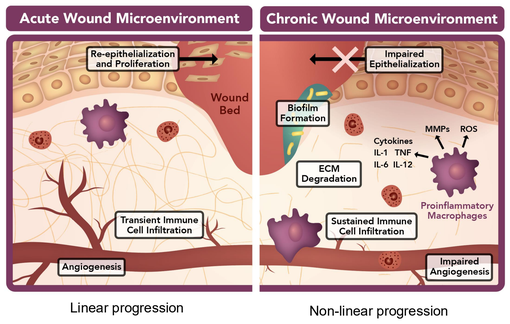

Figure 3. Wound healing is stalled in chronic wounds and treatment with QPEI C24J could remove or modulate the pathways which are blocked

This study investigated the activity of a specific research grade QPEI (C24J) in promoting wound closure in mouse models of healthy and compromised wound healing.

Results

Aqueous emulsion

C24J accelerates wound closure in healthy mice

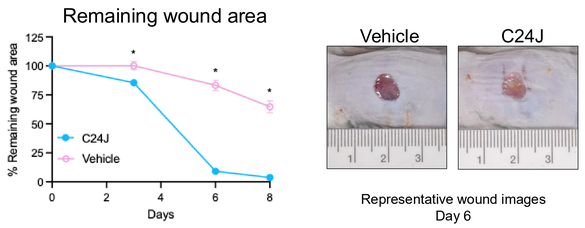

Figure 4. Wound healing study in Balb/c mice with full-thickness wounds with single application of C24J at day 0. Six-millimeter punch biopsy wounds were created on the dorsal flank of male Balb/c mice (9-10 mice per group). 20 µL of C24J QPEI (2 mg/mL in 0.5% DMSO-H_2O) or vehicle was applied topically at Day 0. Wounds were covered by Tegaderm™ (replaced on Days 3 and 6). Wounds were examined visually, and closure was determined using the image analysis software Image Pro. Closure is defined as the presence of an epithelial layer on the wound. * p ≤ 0.05 compared to vehicle

Re-epithelialization in healthy mice is significantly improved with C24J treatment

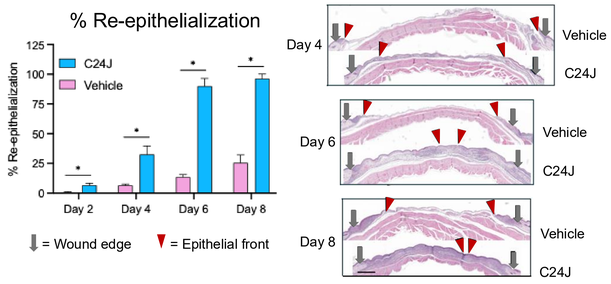

Figure 5. Balb/c mice with full-thickness wounds were sacrificed at the time points indicated (9-10 mice per group), and wound sections analyzed histologically. The epithelial front (red arrowheads) comes together rapidly with single C24J application (2 mg/mL in 0.5% DMSO-H_2O) at day 0 as compared to vehicle control. This is quantified in the graph over time. * p ≤ 0.05 compared to vehicle.

C24J enhances granulation tissue formation in healthy mice

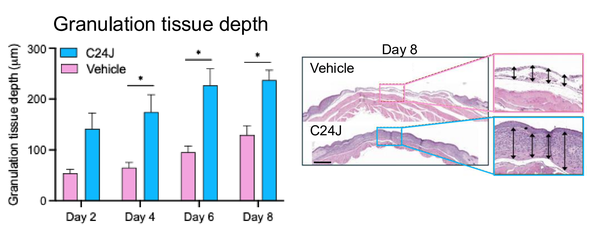

Figure 6. Upon single C24J application (2 mg/mL in 0.5% DMSO-H_2O), granulation tissue depth in healthy Balb/c mice with full-thickness wounds is increased compared to vehicle, potentially providing more ideal conditions to promote wound healing. This is quantified in the graph over time. * p ≤ 0.05 compared to vehicle; n= 9-10 animals per time point.

Hydrogel prototype

Application of a C24J hydrogel accelerates wound closure in healthy mice

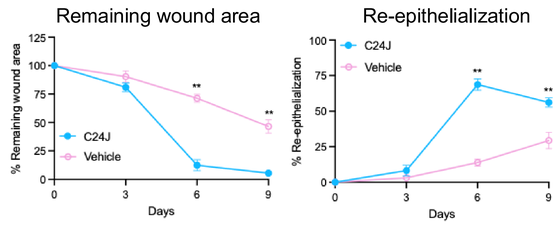

Figure 7. Wound healing study in Balb/c mice with full-thickness wounds with single application of 0.1% C24J hydrogel at day 0. A C24J hydrogel or vehicle was applied topically at Day 0 to 6 mm full thickness punch biopsy wounds on the dorsal flank of male Balb/c mice (6 mice per group). Wounds were covered by Tegaderm™ (replaced on Days 3 and 6). Wounds were examined visually, and closure was determined using the image analysis software Image Pro and defined as the presence of an epithelial layer on the wound. ** p ≤ 0.01 compared to vehicle

A mouse strain to model diabetes and delayed wound healing was selected

db/db: BKS.Cg-*Dock7*^{m}+/+*Lepr*^{db}*J*

Characteristics include:

- Depletion of insulin-producing beta cells of the pancreatic islets
- Uncontrolled blood glucose levels
- Obesity, peripheral neuropathy
- **Delayed wound healing**

Wound closure in diabetic mice is significantly improved with single and repeated application of C24J hydrogel

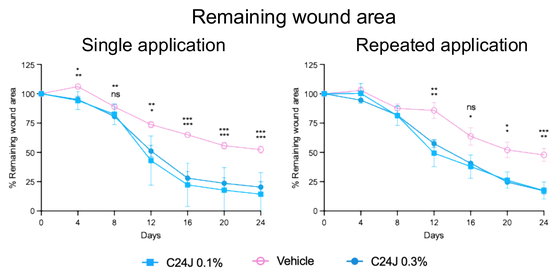

Figure 8. Wound healing study in db/db mice. A single full-thickness punch biopsy wound (10 mm) was created on the dorsal flank of each male db/db mouse. Treatment groups received topical applications of C24J hydrogel (0.1% or 0.3%) as a single dose on Day 0 or as repeated applications on Days 0, 4, and 8. Control groups received gel vehicle treatment following similar schedules. Each wound received 30–40 µL of the designated treatment immediately post-injury. Wounds were digitally photographed on Days 0, 4, 8, 12, 16, 20, and 24 to measure closure rates. To facilitate assessments, dressings (Tegaderm™) were applied post-treatment and replaced on Days 4, 8, and 12. Wounds were examined visually, and closure was determined using the image analysis software Image Pro. * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 compared to vehicle, ns non-significant; n=7 per group

Re-epithelialization occurs with C24J hydrogel single and repeated application in diabetic mice

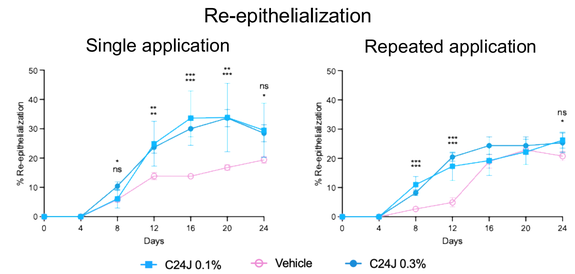

Figure 9. Wound healing study in db/db mice as described in Figure 8. Wounds were examined visually, and extent of re-epithelialization was determined using the image analysis software Image Pro. * p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 compared to vehicle, ns non-significant; n=7 per group

C24J hydrogel enhances granulation tissue formation in diabetic mice

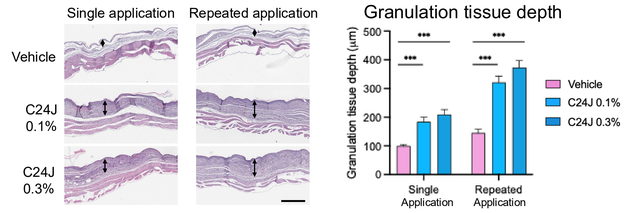

Figure 10. Wound healing study in db/db mice as described in Figure 8. Granulation tissue deposition was examined using histology at the end of the study. *** p ≤ 0.001 compared to vehicle; n=7 per group

Conclusions

In both healthy and diabetic mice using topical C24J application, we observe:

- Accelerated wound closure
- Enhanced re-epithelialization
- Improved deposition of granulation tissue

Improved wound closure and re-epithelialization are observed at several C24J dose levels.

A C24J hydrogel is amenable to both single and repeated application.

Innovation and pipeline

We are actively exploring the use of QPEIs in medical devices within the wound care space.

Various innovative and disruptive solutions may be achievable depending on the functions of the QPEI and how it is incorporated into the medical device.

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