Platelet-derived Extracellular Vesicles for Rapid Treatment and Regeneration of Severe Burns and Wounds

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Introduction

Severe burns and wounds are among the most common injuries suffered by active-duty military personnel and present a significant unmet military medicine need. These injuries often occur in the battlefield environment and require rapid intervention[1,2]. Under these conditions, traditional wound management strategies are therapeutically ineffective or logistically unfeasible. To address this limitation, RION has developed a regenerative clinical-grade human platelet-derived extracellular vesicle (EV) product, designed for broad application to damaged soft tissues in austere therapeutic environments. The final product is a lyophilized powder that is stable at ambient temperature and can be utilized as an allogeneic, regenerative therapeutic[3,4]. It is rapidly prepared at the point of use for topical administration as a flowable gel or broad-coverage self-gelling spray.

Background

EVs are lipid bilayer delimited vesicles which transport biomolecules between cells. Regenerative platelet derived EVs deliver a unique subset of growth factors, cytokines, and enzymes tailored to promote regeneration. Regeneration is supported via four key modes of action: cytoprotection, pro-regenerative immune modulation, recruitment of local progenitor cells, and neo-angiogenesis (**Figure 1**).

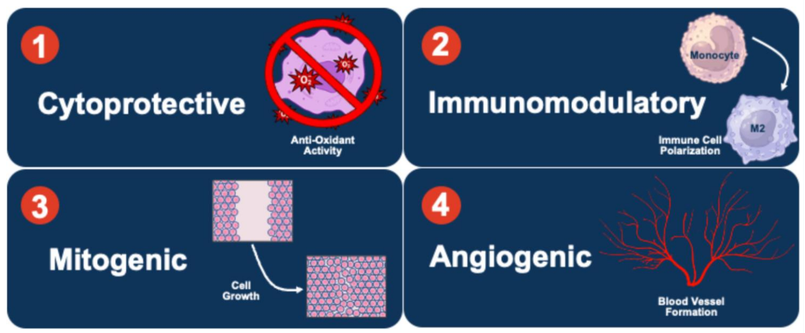


Figure 1. Summary of RION's PEP Drug Product Mechanism of Action.

References

1. Khorram-Manesh, Amir, Krzysztof Goniewicz, Frederick M Burkle, and Yohan Robinson. "Review of Military Casualties in Modern Conflicts—The Re-emergence of Casualties From Armored Warfare." Military Medicine 187.3-4 (2022): e313-e321.
2. Breederveld, Roelf, and Wim Tuinebreijer. "Incidence, Cause and Treatment of Burn Casualties Under War Circumstances." European Journal of Trauma and Emergency Surgery 35.3 (2009): 240-243.
3. Shi, Ao, et al. "TGF-β loaded exosome enhances ischemic wound healing *in vitro* and *in vivo*." *Theranostics*, vol. 11, no. 13, 2021, pp. 6616–6631, https://doi.org/10.7150/thno.57701.
4. Pumford, Andrew D., et al. "Exosome therapy for a nonhealing scalp wound following chemoradiation and surgical therapy." *Mayo Clinic Proceedings*, vol. 99, no. 6, June 2024, pp. 1006–1012, https://doi.org/10.1016/j.mayocp.2024.04.011.

Materials/Methods

Our application approach leverages the inherent hemostatic potential of our drug product and its stability at ambient temperature to produce a robust, biopotentiated gel amenable to rapid field preparation. A dual chamber syringe and applicator tip ensure proper product mixing and ease of use. The final product is sprayed directly onto the target site as a thin, robust gel which adheres on contact and promotes wound healing (**Figure 2**).

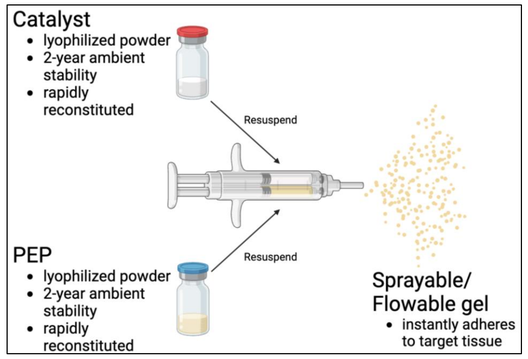


Figure 2. Dual chamber gel application device and components.

Results

Release of bio-active molecules from the gel was assessed over the course of 7 days. The concentrations of four pro-regenerative cytokines (ANG-1, EGF, PDGF-BB, and VEGF-A) eluted from the gel increased in the first 1-3 days of the study (**Figure 3**), indicating sustained release in the initial days after application. These data are indicative of the preservation of our angiogenic mechanism of action in this formulation, indicating suitability for use in wound management.

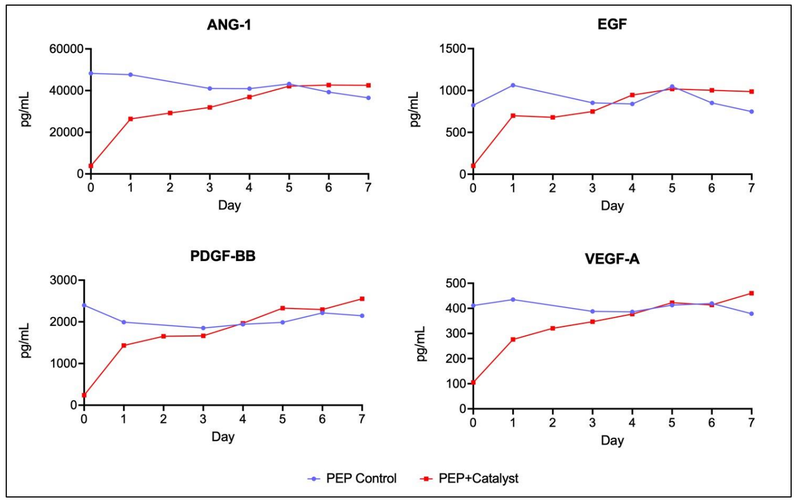


Figure 3. Release of pro-regenerative cytokines (ANG-1, EGF, PDGF-BB, and VEGF-A) over 7 days. Gel was dispensed into 15mL falcon tubes and suspended in PBS. Tubes were rotated at ambient conditions for 7 days, with supernatants being collected each day. Multi-plex ELISA was used to measure cytokine concentrations.

Results

Release of bio-active molecules from the gel was assessed for the capacity to support cell growth over the course of 7 days. Normal human dermal fibroblast proliferation was supported to a similar degree as the standard growth media control (FBS). These data are indicative of the preservation of our product's capacity to support cell growth in this formulation, indicating suitability for use in wound management (**Figure 4**).

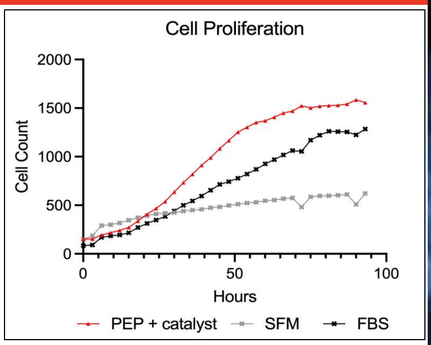


Figure 4. Release of biomolecules supportive of cell growth over 7 days. Gel was dispensed into 15mL falcon tubes and suspended in PBS. Tubes were rotated at ambient conditions for 7 days, with supernatants being collected each day. Supernatants were applied to cells in culture, and cell counts were collected every 6 hours through automated imaging and counting of nuclear stain. Serum Free Media (SFM) was used as a negative control.

Results

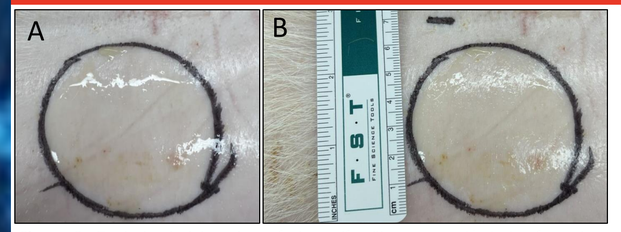


Figure 5. Topical administration of the self-gelling spray. A) 1mL of product administered to intact skin in 6cm diameter area. Photo taken immediately after application. B) 20 minutes post-application.

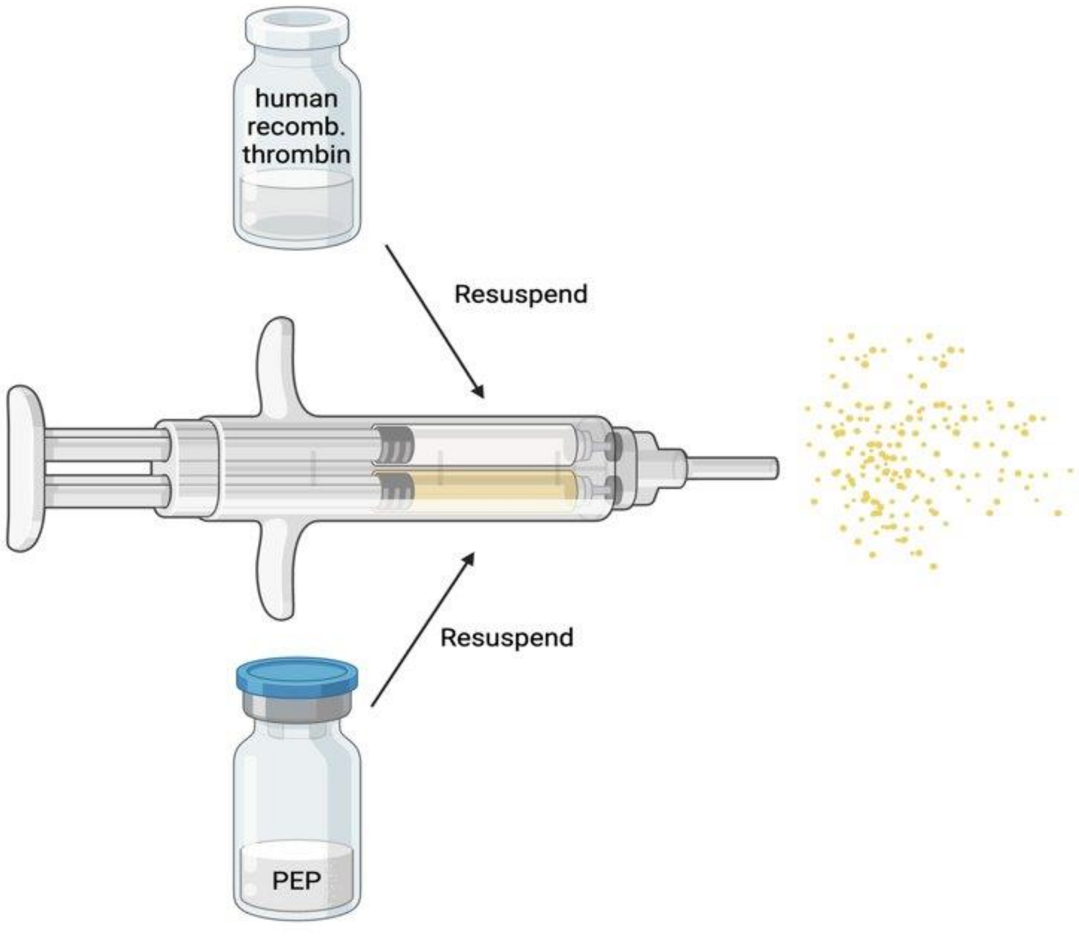
The self-gelling spray is suitable for topical application onto intact skin (**Figure 5**). Product adheres instantly.

Conclusions

Here, we have presented *in vitro* and *in vivo* proof of concept data to support broadening the use of RION's platelet-derived EVs for the treatment of severe burn or blast injuries in austere environments.

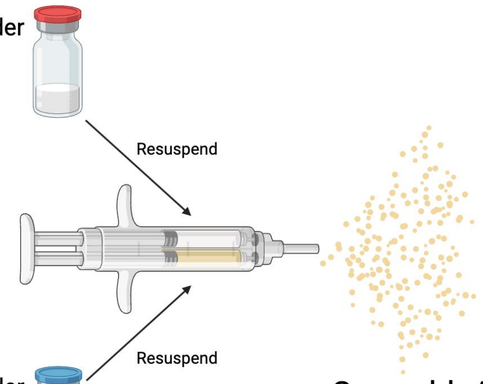
About RION

RION is a clinical-stage biotechnology company that has established a cGMP-compliant, clinical-grade manufacturing process that yields a sterile, reproducible product appropriate for human use. This manufacturing process, quality control strategy, and final Drug Product have received US FDA approval to conduct a Phase 2 clinical study in wound healing. Additional case-specific applications have also received approval under FDA's Expanded Access Program for the treatment of non-healing wounds resulting from ionizing radiation.



Catalyst

- lyophilized powder
- 2-year ambient stability
- rapidly reconstituted

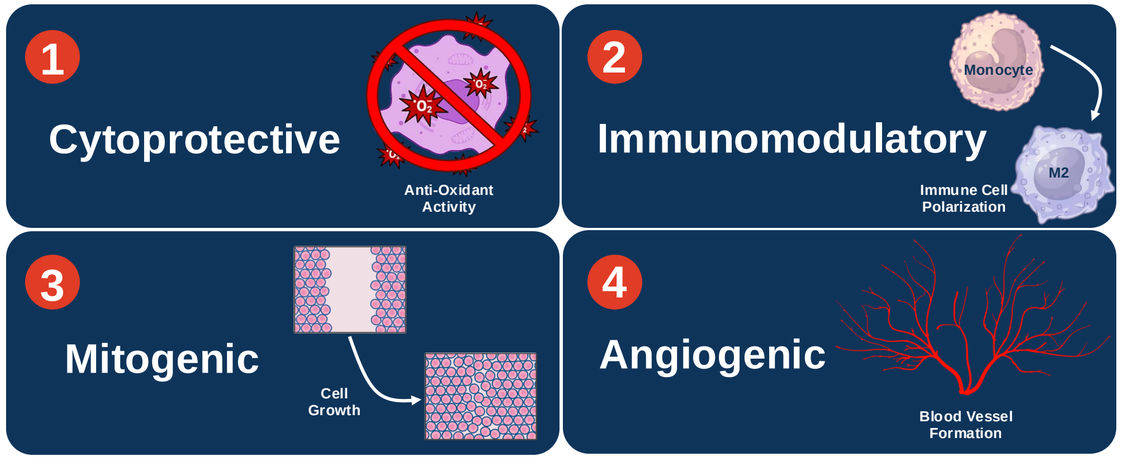


PEP

- lyophilized powder
- 2-year ambient stability
- rapidly reconstituted

Sprayable/
Flowable gel

- instantly adheres to target tissue


1
Cytoprotective
Anti-Oxidant
Activity
2
Immunomodulatory
Monocyte
M2
Immune Cell
Polarization
3
Mitogenic
Cell
Growth
4
Angiogenic
Blood Vessel
Formation