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Bioactive inks as potential wound healing therapeutics: cellular responses in the presence of chronic wound exudates

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OBJECTIVES

Chronic wound exudates (cWEs) contain pathophysiological factors which maintain the non-healing environment. They have been demonstrated to inhibit fibroblast proliferation[1] and induce pro-inflammatory cytokine secretion in macrophages.

These *ex vivo* systems were used to investigate hyaluronic acid-based bioactive inks (BI) developed in the Horizon Europe FORCE REPAIR project.

The BIs were designed as smart, multifunctional, 3D-printed dressings to combat bacterial infection, inflammation and promote healing. They integrate an anti-inflammatory drug, antibiotics, and pro-regenerative active ingredients[2].

METHODS

- Patient material: cWE from 12 venous leg ulcer patients were collected from wound-individualized polyurethane foam and used bandages after obtaining patient informed consent.
- Wound exudates were titrated (0.5-8%) to identify a concentration causing 30–60% inhibition of cell proliferation, which was then used in subsequent experiments to assess the toxic or rescue effects of BIs.
- Hyaluronidase-digested BIs or their individual components were added to primary human dermal fibroblasts (72h) or macrophages (24h) in the presence of cWEs. Cell proliferation was determined upon fixation and staining, and cytokines were quantified by ELISA or multiplex analysis.
- All experiments were carried out in triplicate and means ± standard deviation were calculated, with significance being assessed by the Student T-Test. * indicates p values <0.05 compared to medium or cWE levels alone. Results were expressed as percentage of unstimulated control values.

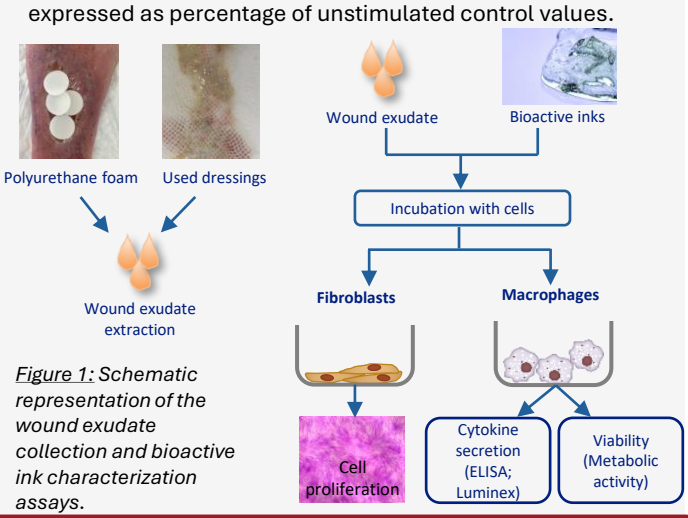

Figure 1: Schematic representation of the wound exudate collection and bioactive ink characterization assays.

RESULTS

Fibroblast proliferation was reduced in the presence of 10 out of 12 cWEs.

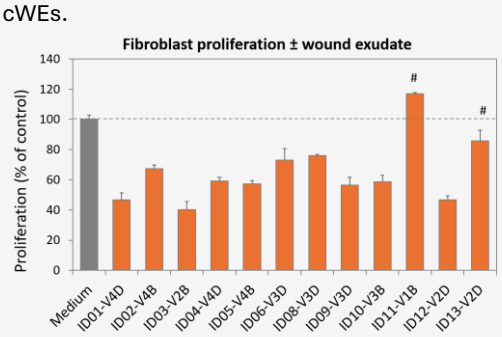

Figure 2: Proliferation is given as percentage relative to medium control (grey dotted line). # marks exudates considered ex vivo healing (≥80% of proliferation in control conditions). All others are ex vivo non-healing.

RESULTS

The efficacy of the anti-inflammatory, anti-bacterial, and pro-regenerative inks differed depending on the cWE sample. The bioinks showed a more pronounced effect to promote fibroblast proliferation (83% of the samples), while the anti-inflammatory effect on macrophages was moderate (33% of the samples).

Representative data from two patients highlight the variability in treatment responses. All BIs had a clearly positive dose-dependent rescue activity of fibroblast proliferation in the presence of cWE sample ID03-V2B and a modest positive effect for sample ID05-V4B (Fig. 3). Although fibroblast proliferation was improved in both WEs, a clear reduction in cytokine secretion was only observed for ID03-V4B (Fig. 4).

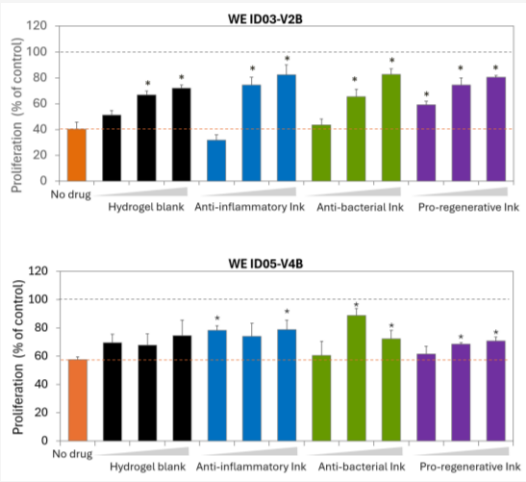

Figure 3: Quantitative evaluation of fibroblast proliferation in the presence of cWEs and the different bioactive inks.
: concentration gradient of bioactive ink (1:20 – 1:10 – 1:5).

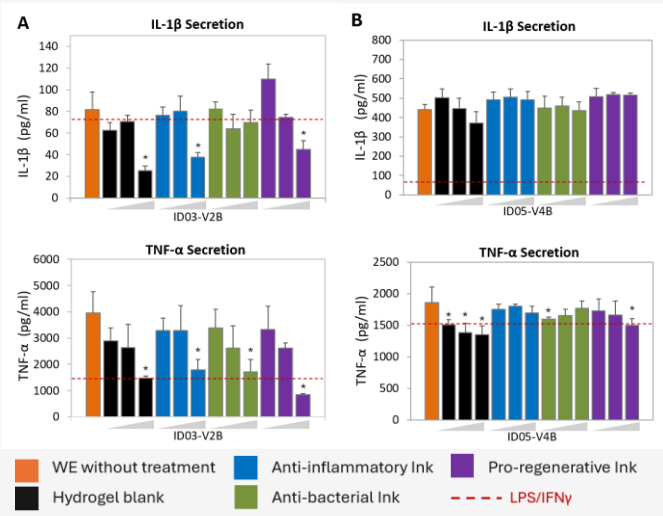

Figure 4: Effect of complete bioinks on IL-1ß and TNFα secretion in the presence of the chronic WEs ID03-V2B (A) and ID05-V4B (B).

CONCLUSION

- The rescue ability on fibroblast proliferation and reduction of pro-inflammatory cytokines in macrophages by the bioactive inks was highly dependent on the individual cWE sample. Similar results were reported for two drugs currently used in chronic wound management[1], leading to the assumption that patient-specific factors account for the differences.
- Thus, a personalized approach is recommended to pre-select patients for optimal benefits from BI treatment.

References:
1. Doerfler *et al.* JID (2024) doi.org/10.1016/j.jid.2024.05.029
2. FORCE REPAIR project website: www.forcerepair-wounds.eu