# Polylactic acid matrices directly promote neo-angiogenesis and immune balance in diabetic foot ulcers

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## Background

**Objective:**

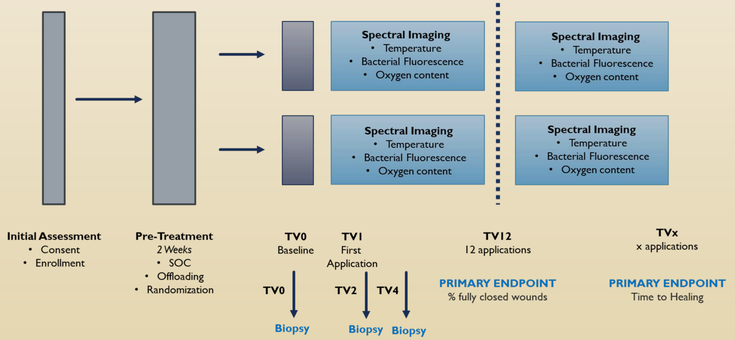
- Data from two randomized clinical trials (RCTs) demonstrated that **polylactic acid (PLA) guided closure matrices** are superior to standard of care in promoting diabetic foot ulcer (DFU) closure. Here, we describe the direct effects of PLA matrices on angiogenesis and inflammation with greater detail.

**Background:**

- A recent pilot RCT demonstrated a **44% reduction in time** for achieving DFU healing when using a novel PLA wound closure matrix compared to collagen dressings. [1]
- An interim analysis of **a larger RCT demonstrated similar results**, with 84% of DFUs treated with PLA matrices fully healed by 12 weeks, as compared to only 32% of those treated with collagen dressings (p <0.001). ***(Poster CR-051 - Effectiveness of a novel polylactic acid matrix for diabetic foot ulcer closure: results from a single center interim analysis)***
- PLA matrices exert their biological effect through the release of **lactate**, which acts as a paracrine agent (lactormone) with potent pleiotropic signaling effects.
- Here, we report our results on the gene and histological analysis of biopsy data of the RCT.

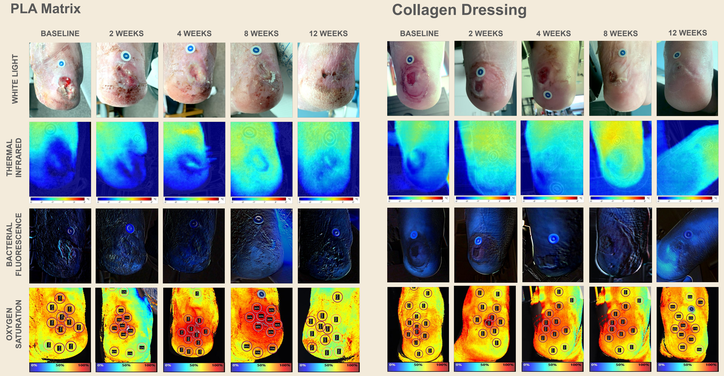
## Methods

- Patients with diabetes mellitus and a single foot ulcer of at least 3 months of evolution were **included** in the trial. **Exclusion criteria** were presence of active infection, uncontrolled diabetes mellitus or any other uncontrolled comorbidity, and use of drugs or medications that would affect wound healing.
- Patients were **randomized** to receive either the weekly applications of a PLA matrix or collagen dressings as adjuncts to the standard of care.
- Ten patients from each arm were randomized to receive **tissue biopsies at baseline, 2, and 4 weeks** of treatment. Biopsy data includes gene expression analysis and histology assessment.
- **Gene expression analysis:**
  - An RNA Profiler array aimed to compare the efficacy of PLA matrices or collagen dressings in managing non-healing DFUs by evaluating the expression of 84 biomarkers in response to treatment.
  - The markers included (1) ECM and cell adhesion molecules, (2) inflammatory cytokines and chemokines, (3) growth factors, and (4) signal transduction molecules.
- **Histological data analysis:**
  - Biopsies were fixed in 10% buffered formalin and paraffin embedded. 4 µm sections were prepared and stained using hematoxylin-eosin (H&E) and Masson's Trichrome. Immunohistochemistry was done against CD31 for vascular endothelium and CD68 for macrophages.




## Results

- No significant differences between patient or wound characteristics or were found at baseline.
- The **median time for achieving full closure** in the collagen group was 17 vs. 9 weeks (reduction of 61.5% in the PLA group, p< 0.001). 32% vs 84% of wounds healed by 12 weeks in the collagen and PLA groups, respectively (p< 0.001).
- **Spectral imaging data** showed significantly higher oxygen saturation and temperature in the peri-wound area and wound bed of the PLA-treated wounds after the second week of treatment.

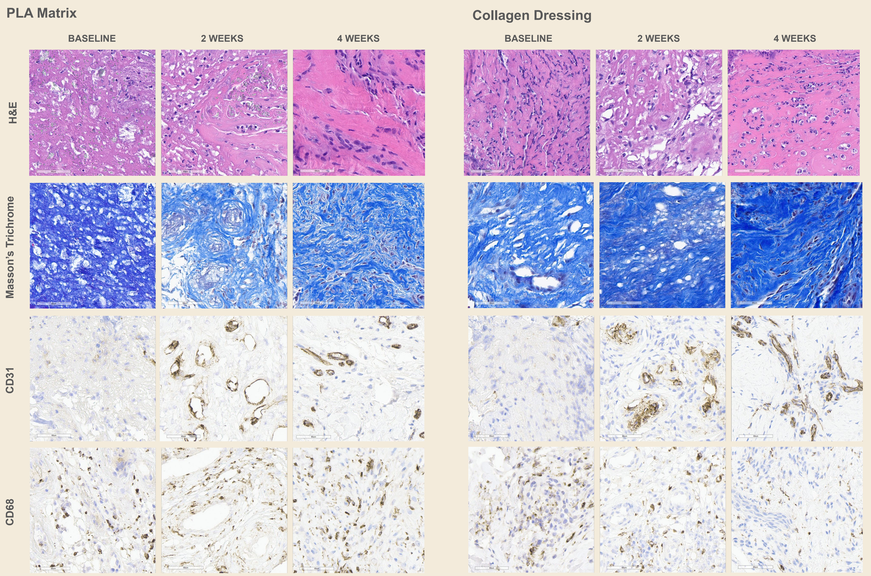



*White light, thermal, and fluorescence images were acquired with a Ray-1 imaging device (Swift Medical, Toronto, ON).*
*Oxygen content images were acquired with a Kent Snapshot device (Kent Imaging, Calgary, AB)*

- **Gene expression analysis:**

| COMPARISON | DOWNREGULATED GENES *(compared to collagen)* | UPREGULATED GENES *(compared to collagen)* |
|---|---|---|
| **Baseline** PLA vs. Collagen | FGF10 *(growth factor)* | CCN2 *(cell adhesion)* |
| **2 Weeks** PLA vs. Collagen | CCL7 *(Chemokine)*, CSF2 *(Colony Stimulating Factor)*, CSF3 *(Colony Stimulating Factor)*, FGF2 *(Growth Factor)*, IL6 *(Cytokine)*, MMP1 *(ECM)* | COL4A3 *(ECM - basal membrane)*, MMP7 *(ECM)*, CXCL5 *(Chemokine, pro-angiogenic factor)* |
| **3 Weeks** PLA vs. Collagen | None | COL5A1 *(ECM)*, COL5A3 *(ECM)*, FGF7 *(Growth Factor)*, GM-CSF *(growth factor)*, ITGA3 *(endothelial adhesion molecule)* |

- PLA-treated gene analysis results indicate that subjects who received the treatment had **increased angiogenesis and structural biomarkers expression** at week 2 and the **restoration of the immune balance** by week 4.
- **Type V collagen** is essential for fibrillation of types I and III collagen and consequently for maturation of collagen structures and tissue quality.




- The histology data showed better organized tissue, with higher blood vessel density and more macrophage content in the PLA group.
- This is highly suggestive of a more mature healing process with faster healing rates and better tissue quality.
- The histological findings demonstrate the basis for the faster healing rates observed in the clinical data and support the spectral imaging findings.

## Discussion

- **PLA matrices are more effective** than active collagen dressings in promoting diabetic wound closure.
- Spectral, histological, and gene data analysis demonstrate an increase in **cell migration, vascularization, and remodelling** of the tissue produced in response to the PLA matrices.

**In summary, compared to standard of care, the use of a PLA guided closure matrix was more effective to promote closure of diabetic foot ulcers. Specifically, its use led to significant increases in blood flow, vascularity, granulation tissue content, and a reduction in the time required to achieve full closure of the wound.**

### References

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