Title: Toward Off-the-Shelf Vascularized Skin Grafts: Engineering Acellular Scaffolds that Preserve Microvascular ECM Architecture

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Background: Acellular dermal matrices are widely used in reconstructive surgery because they reduce immunogenicity and can be stored for off-the-shelf clinical use. However, most existing acellular scaffolds lack preserved microvascular extracellular matrix (ECM) architecture, requiring host vessels to invade and form new vasculature *de novo*. This process is slow and can limit graft integration, particularly in large or compromised and chronic wounds. We hypothesize that preserving microvascular ECM architecture generated during vascular self-assembly can create instructive templates that guide host-driven vascular integration after implantation.

Methods: Engineered human skin constructs containing pre-assembled microvascular networks were generated using endothelial cells, fibroblasts, and dental pulp stem cells embedded within collagen–fibrin matrices. Constructs were then decellularized using supercritical carbon dioxide ($ScCO_2$), a solvent-free approach designed to remove cellular components while preserving extracellular matrix organization and mechanical properties. Decellularization efficiency was evaluated using histological staining. Preservation of ECM architecture was assessed using scanning electron microscopy (SEM) to evaluate collagen organization. Decellularized scaffolds were subsequently implanted into full-thickness dorsal wounds in mice to evaluate host-driven vascular invasion and scaffold integration.

Results: Preliminary data demonstrate that $ScCO_2$ processing effectively removes cellular material while preserving gross dermal ECM architecture and collagen fibrillar organization. Histological analysis shows maintenance of layered dermal structure after decellularization, and electron microscopy confirms preservation of collagen fiber continuity and organization. Early implantation studies demonstrate retention of scaffold structure and integration with host tissue, supporting the feasibility of using decellularized engineered skin constructs as vascular guidance templates.

Conclusions: These findings suggest that engineered skin constructs can be converted into acellular scaffolds while preserving instructive vascular ECM architecture. Such scaffolds may guide host-driven vascular invasion and improve integration of skin grafts without the need for donor endothelial cells. This strategy could enable development of next-generation off-the-shelf skin substitutes for improved wound reconstruction.