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Bioprinted Human Lymphatic Microvessels to Restore Salivary Gland Function in Sjögren's Disease

Abstract: Sjögren's disease (SjD) is featured by chronic lymphoepithelial inflammation, aberrant cytokine signaling, and progressive loss of salivary gland function leading to xerostomia. While T cell- and cytokine-driven epithelial injury is well described, the contribution of lymphatic dysfunction, a key regulator of interstitial fluid balance, antigen trafficking, and inflammatory resolution, remains poorly understood. Emerging evidence suggests that type I interferons, IFN-gamma, IL-17, and T-cell infiltration may directly impair human lymphatic endothelial cell (hLEC) integrity and drainage, potentially amplifying glandular injury. However, no current ex vivo, lab-built hydrogel model allows mechanistic study of LEC-epithelium-immune interactions in a human, tissue-level context.

We propose to engineer a bioprinted human lymphatic–salivary construct using primary human LECs, salivary fibroblastic cells (hSFs), microvascular endothelial cells (hMVECs), and salivary epithelial stem/progenitor cells (hS/PCs) that we call L3D-ST (lymphatic 3D-salivary tissue). Using an Aspect microfluidic bioprinter, we will fabricate perfusable hLEC-lined lymphatic vessels (LVs) embedded in a salivary-like customized hydrogel with a mixture of stromal cells in co-culture. Aim 1 will optimize bioprinting, validate hLEC identity (PROX1, LYVE1, podoplanin, VEGFR3), and assess lymphatic barrier function and solute clearance while assessing effects on adjacent engineered salivary tissue. Aim 2 will introduce SjD-relevant cytokine milieu and introduce activated CD4+ T cells to model lymphatic dysfunction, quantify transcriptional and functional impairment, and test pro-lymphatic rescue strategies. This platform will provide the first human biomimetic system to dissect lymphatic contributions to SjD pathogenesis and identify potential new therapeutic approaches to restore lymphatic and epithelial function, addressing a critical unmet need in the treatment of autoimmune xerostomia.

For more information, please contact the Sjögren's Foundation at research@sjogrens.org.