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Xerostomia, a condition characterized by decreased saliva production and flow reduces the quality of life for approximately half a million people worldwide and leads to difficulty in eating, swallowing, and speaking. Additionally, patients with xerostomia can suffer increased rates of dental caries if the condition persists. In the absence of autoimmune salivary destruction such as occurs with Sjögren's Syndrome, xerostomia also occurs as one of the consequences of radiation therapy subsequent to treatment of head and neck cancers. Despite advances in the use of techniques designed to protect the normal tissue of the salivary glands during radiation treatment, compromised salivary secretion of both protein and water components still occurs. Thus, current strategies to prevent or reduce xerostomia have been ineffective. To mitigate the difficulties associated with the loss of salivary cells post-radiation, our team is working to develop a biologically based, surgically implantable salivary gland replacement tissue. Recently developed procedures have allowed us to culture intact pieces of resected major salivary glands in 3D hydrogels, with high viability and persisting several months. Based on this promising preliminary data, this project aims to identify and optimize methods for long-term culture and expansion of minor salivary gland tissue in 3D hydrogels for future surgical transplantation into oral tissues of patients with xerostomia. The use of minor salivary glands from the lip would make an ideal tissue source to utilize in these salivary gland engineering approaches, since they can be obtained with minimal morbidity. This is an approach that has previously not been possible and provides a translational pathway for a technology that could provide significant benefit to those with compromised salivary function. The goal of this project is to develop a novel and effective therapeutic approach for radiation-related xerostomia. Accordingly, we envision a new strategy involving harvested minor salivary glands, a novel and largely untested tissue source utilizing ex vivo culture of intact non-dissociated structures from minor glands. We propose the following two aims: Aim 1 will perform baseline functional and phenotypic analysis of harvested minor salivary glands and their component cells. Aim 2 will evaluate the ability of 3D hydrogel long-term cell culture methods to assess retention of target phenotypes established in Aim 1. The impact of the knowledge gained from this proposal is two-fold. In the short-term, it will help establish a standard protocol for minor salivary gland collection and glandular culture in hydrogels. In the longer-term, the data will provide the basis of interdisciplinary extramural applications to pursue projects focused on providing novel salivary gland tissue-engineered therapies for patients who suffer from xerostomia as a result of radiation therapy for cancer or autoimmune disease.