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**“Role of Tissue Engineering in Maxillofacial Reconstruction”**

**I. The *ex vivo* development of a human full-thickness oral mucosal tissue that is suitable for intraoral grafting procedures**

Our long-term goal is to produce a “smart” transduced oral mucosal graft that will be used for reconstruction of major oral defects secondary to oncologic resection, traumatic events or developmental disturbances. The graft would act both as a material for reconstruction and as a repository for *in situ* transmucosal delivery of recombinant growth factors or cytokines.

Several barriers presently exist that prevent this technology from moving into the clinical arena. First, is the ability to fabricate these “smart” grafts in a more efficient manner, i.e. develop a more highly proliferative and expanding cell population, second, the ability to isolate a stem/progenitor cell (this will make gene therapy more practical by achieving high-level gene expression in a significant percentage of cells), and lastly, if stem cells are to play a role in clinical therapies the cells must NEVER come into contact with foreign or undefined proteins (animal serum or feeder layer cells, or pituitary extract) in order to gain FDA acceptance. A more practical approach is to isolate and expand the progenitor/stem cell populations using only physical and pharmacological means.

At present, we use an unfractionated human adult single oral keratinocyte suspension to manufacture a “naive” non-transduced **Ex Vivo Produced Oral Mucosa Equivalent (EVPOME)**. Our EVPOME is suitable for intraoral reconstruction in a defined medium without bovine serum, nor pituitary extract or use of a xenogeneic feeder layer. This allows us to place it back into the original tissue donors/patients with FDA sanction. Clinical trials using the human EVPOME have been initiated under our investigator sponsored and approved IND from CBER/FDA.

We realize construction of EVPOMEs is limited by amount of tissue harvested and time necessary to proliferate, seed and mature keratinocytes on dermal equivalents. Our success with unfractionated/unsorted cultured adult human oral mucosal cells provides compelling empiric evidence that a subpopulation exists within our cell population that represents the “stem” cell compartment. In order for our technology/gene therapy to become a viable clinical alternative we need to isolate a progenitor/stem cell population. Our goal is to establish expanded cultures of an enriched population of oral mucosa progenitor/stem cells, using only physical and pharmacological means, under chemically defined conditions consistent with FDA guidelines that will be the foundation for our advances into cell replacement therapy.

**II. Development of 3-dimensional biomimetic scaffolds for tissue engineering of bone and/or cartilage for reconstruction of the temporomandibular joint.**

Our interdisciplinary bioengineering partnership plans to develop an image based approach for designing and manufacturing patient site-specific biomaterial scaffolds with specific internal architecture using an image based engineering design method combined with a solid free form fabrication manufacturing approach. Our focus is on the area of internal architecture of the scaffold, *i.e.* pore size, direction of interconnective channels and trabecular orientation, to optimize resistance to mechanical forces, encourage cell migration and nutrient diffusion and direct cell function through biologic cues or signals. We have a particular interest in development of biomimetic scaffolds

that assist in the development of a prosthesis to reconstruct the condyle-ramus unit for use in reconstruction of the temporomandibular joint.

We hypothesize that the fabrication of a designed and manufactured biomaterial scaffold, containing chondrocytes and bone marrow stromal cells, in different locations on the same scaffold, can successfully reconstruct a TMJ by forming a fibrocartilaginous cap or joint surface on top of a bony strut. This scaffold, a composite of cartilage and bone, similar in structure to a costochondral rib graft (a bony rib with a cartilaginous cap), can be fixated and eventually integrated into the underlying bony vertical ramus of the mandible.