Tissue Engineering Functional Human Lips

CLINICAL NEED

Tissue engineering and regenerative medicine face several barriers preventing translation of *in vitro* technology to the clinical arena: (1) the inability to create composite soft tissue structures that contain striated muscle, skin, and mucosa with a mucocutaneous junction (lip) and (2) difficulty in developing an *in vivo* perfusion system (blood vessels) to supply nutrition for large segments of tissue created in vitro. Lack of tissue perfusion is a major limitation of survival of implanted *in vitro* produced complex composite soft tissue implants.

SOLUTION

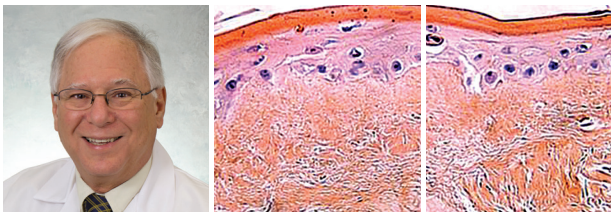
A team of researchers at the University of Michigan led by Dr. Stephen E. Feinberg has developed a tissue engineering approach in conjunction with the surgical technique of prelamination, to create an innervated pre-vascularized prelaminated composite soft tissue microvascular free flap based on the latissimus dorsi muscle for use in functional reconstruction of human lips.

COMPETITIVE ADVANTAGE

This approach addresses the issues of creating autogenous complex composite soft tissue structures with an adequate perfusion system. In addition, this approach provides a platform technology for fabrication of autogenous mucocutaneous junctions in the body such as the anus, vagina, and eyelid that circumvents the need for immunosuppression required from allotransplants.

ITP SUPPORT

With the overall objective of using mucocutaneous constructs to restore soft tissue, support from the ITP program will be used for preparatory and follow-through events surrounding IND discussions with the FDA for initiation of a first-in-human clinical trial.



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"The success gained from the proposed first-in-human Phase I multicenter clinical trial to tissue engineer functional human lips will establish a platform technology that will create a paradigm shift on how the surgeon may reconstruct composite soft tissues that have a mucocutaneous junction, i.e., lips, vagina, eyelids, and anal sphincter. It will also validate a method to fabricate autogenous composite soft tissue grafts that will supplant procedures requiring lifetime immunosuppression."

CLINICAL TRANSLATION PATHWAY

Publications:
In Vitro Development of a Mucocutaneous Junction for Lip Reconstruction. J Oral Maxillofac Surg. 2016.

Tissue engineering of lips and muco-cutaneous junctions: *in vitro* development of tissue engineered constructs of oral mucosa and skin for lip reconstruction. Tissue Eng Part C. 2012.

Intellectual Property:
US 7,887,829 Mucosal cell composites and methods

US 8,835,169 Compositions, methods and systems for preparation of a stem cell-enriched cell population

Regulatory Pathway:
Anticipated: Biologic, IND to enable BLA

Commercialization Strategy:
In development with the MPWRM Commercialization/ Market Needs Core

Product Launch Strategy:
In development with the MPWRM Commercialization/ Market Needs Core

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UNMET CLINICAL NEED

Lips form a structure of the face that is difficult to reconstruct after a traumatic avulsion injury secondary to loss of volumetric muscle mass because it represents a dynamic composite tissue of sensate mucosa, skin and motor innervation of skeletal muscles. Significant loss of lips is a functional and esthetic concern because the neuromuscular control of normal lip structures is required for eating, drinking, talking and social gesturing. Traumatic avulsion of the lips is a survivable injury; however, without functional lip reconstruction (restoration of muscle volume and reinnervation of the end organ; lips) life for injured individuals is burdened by drooling, food spillage while eating, unintelligible speech and social rejection which is emotionally devastating. Functional reconstruction of lips is critical when >50% of the lips are avulsed, because the alternative treatments are either non-innervated autogenous tissue flap reconstruction or allogeneic face transplantation, which requires lifetime immunosuppression.

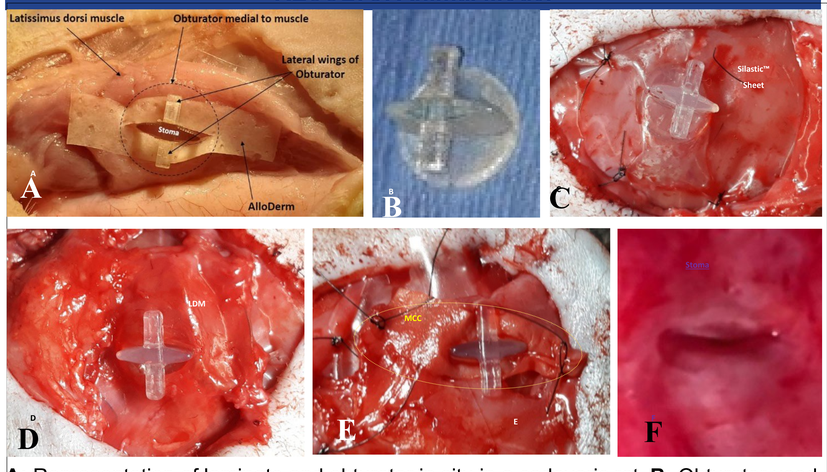
MARKET ANALYSIS

Preliminary market research initially conducted by SciVelo and by personal interviews with end users (surgeons) completed by The Avenues showed that there was sufficient evidence of market size to support orphan drug designation (ODD).

INTELLECTUAL PROPERTY

Provisional patent submitted for our technology platform to tissue engineer complex soft tissue grafts with the assistance of Kristen Wolff, UM TechTransfer and Jennifer Turchyn, patent attorney, Harness and Dickey company.

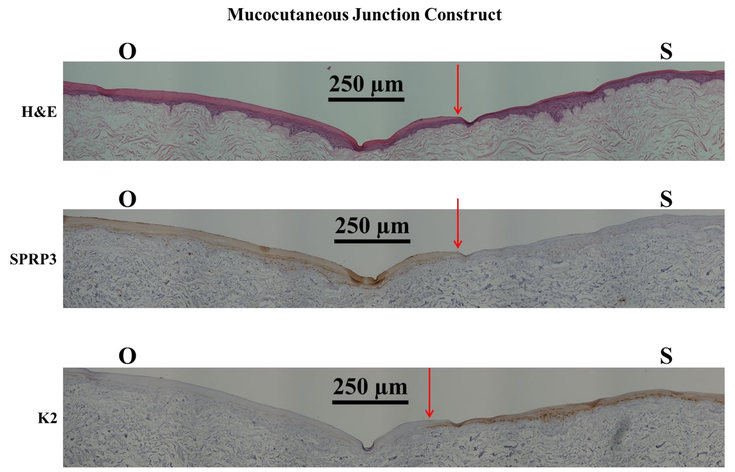
RESULTS: Animal Model



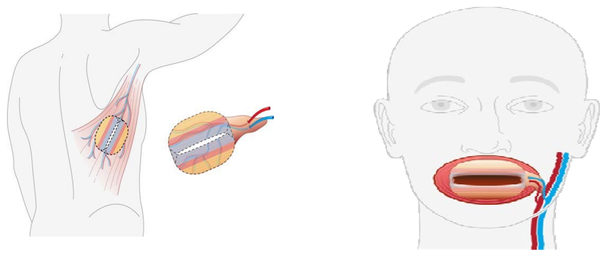
A: Representation of laminate and obturator in situ in a cadaveric rat, **B:** Obturator used in rat studies, **C:** Obturator in place. Silastic™ sheet and obturator sutured in place to underlying SQ tissue, **D:** LDM placed over obturator through the surgically created stoma in the muscle, **E:** MCC placed over the obturator on the LDM and sutured in place, **F:** Stoma maintained, healed and functional 2 weeks s/p surgery.

MANUFACTURING

- Take biopsies of skin behind ear and buccal mucosa; Dissociate cells from skin and oral mucosa.
- Establish primary cell cultures and expand cells to enough numbers.
- Seed oral keratinocytes flanked by skin keratinocytes with barriers to create cell-free zones between skin and oral keratinocytes.
- Remove barriers to allow cells to merge to each other in liquid phase for 5 days followed by at least additional 10 days of air-liquid phase to allow cells to mature and stratify.
- Implant the construct under the latissimus dorsi muscle (LDM) for 2 weeks to create a prefabricated innervated prevascularized prelaminated (PIPP) muscular flap.



O: oral keratinocytes culture side; S: skin keratinocytes culture side.



Mucocutaneous construct (MCC) integrated onto LDM with a surgically created stoma (opening). The LDM with integrated MCC surgically removed to create a PIPP Flap.

REGULATORY PATHWAY

Kay Fuller, MDRS, did an ICDM and CPT code assessment which verified that our technology qualified for orphan drug designation (ODD). A Request for Designation has been submitted to the FDA.

TIMELINE & FUTURE DIRECTIONS

Animal Studies Next Year

a) Assessment of patency of stoma at time of harvest
b) Nerve stimulation immediately post implantation and at the time of harvest
c) Prototype design confirmation
d) Finalize surgical procedures prior to placement of mini lip constructs.

Regulatory Work Next Year

a) Preliminary Hazard analysis and risk management plan for obturator
b) Develop biocompatibility matrix of obturator
c) Qualify manufacture of silicone and industry partner for manufacture of obturator
d) Record specifications of obturator: Biocompatibility, sterilization, shelf life, durometer

We plan to pursue (1) preclinical GLP animal studies, and (2) submission of IND to FDA for a first-in-humans clinical trial for our technology. Through conversations with experts in the field we were advised that it is important to have human clinical data **prior to** engaging for-profit companies to consider a collaboration to explore commercialization and a business plan.

REFERENCES

1. Peramo A, Marcelo CL, Feinberg SE: Tissue Engineering of Lips and Muco-Cutaneous Junctions: In Vitro Development of Tissue Engineered Constructs of Oral Mucosa and Skin for Lip Reconstruction, Tissue Engineering, 18:273-282, 2012.

2. Kuo S, Miyazawa A, Feinberg SE: Chapter 7: “Principles of Soft Tissue Engineering for Craniomaxillofacial Reconstruction”, J.C. Melville, Mark E Wong, Jonathan Shum, Simon Young (editors) Regenerative Strategies for Maxillary and Mandibular Reconstruction: A Practical Guide, Springer, 2019.

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