Michigan • Pittsburgh • Wyss

Regenerative Medicine Resource Center

2018 Annual Report

Michigan • Pittsburgh • Wyss
Regenerative Medicine Resource Center

In March 2017, the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center was formally launched with the start of the U24 grant from the National Institute of Dental Craniofacial Research (NIDCR), awarded to the consortium led by the University of Michigan, the University of Pittsburgh, and the Wyss Institute at Harvard University, to support the development of technologies for the regeneration of dental, oral, and craniofacial tissues.

The success of the Resource Center is built on the foundation of collaboration and partnership. With the collaboration amongst the member institutions and individuals, and in partnership with NIDCR and the Center for Dental, Oral, & Craniofacial Tissue & Organ Regeneration, our sister consortium comprised of several California institutions, we have initiated two cycles of translational research funding in 2018, providing support for 16 teams from academic institutions and for-profit entities across the country, addressing clinical needs that span across the spectrum of dental, oral, and craniofacial tissues.

On behalf of the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center, we are proud to present this booklet describing the projects we are supporting, and the impact of the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center. We look forward to making continued progress as we strive to become a hub for accelerating the clinical translation of dental, oral, and craniofacial regenerative therapies.

Sincerely yours,

David J. Mooney, PhD
Wyss Institute

David H. Kohn, PhD
University of Michigan

William V. Giannobile, DDS, DMSc
University of Michigan

Charles S. Sfeir, DDS, PhD
University of Pittsburgh

William R. Wagner, PhD
University of Pittsburgh

About Us

The translation of innovative tissue engineering/regenerative medicine (TE/RM) technologies requires a new approach to bring these technologies to clinical practice in the dental, oral, and craniofacial (DOC) space. To meet this need, an integrated, multidisciplinary Resource Center (RC) has been established as a partnership amongst the University of Michigan, the University of Pittsburgh/McGowan Institute, Harvard University/Wyss Institute for Biologically Inspired Engineering, and clinical and industrial experts. This RC, named the Michigan-Pittsburgh-Wyss Resource Center: Supporting Regenerative Medicine in Dental, Oral and Craniofacial Technologies, consists of leaders with clinical, basic science, engineering and business expertise, and an infrastructure to support navigation through the regulatory process and clinical trials. The goal of this RC is to translate TE/RM innovations that address the ongoing clinical need to restore or create healthy, functional DOC tissues.

The MPWRM Resource Center is a partnership with NIH's National Institute of Dental and Craniofacial Research (NIDCR) and supports NIDCR's mission to improve dental, oral, and craniofacial health through research, research training, and the dissemination of health information.

>70 MEMBERS

with expertise that span the spectrum of translational research and commercialization

$11.7M

Award from the National Institute of Dental & Craniofacial Research of the National Institutes of Health, aimed to shepherd new regenerative medicine therapies towards first-in-human clinical trials and commercialization

Corporate Partners Program

The Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center is in pursuit of new research directions and therapeutic solutions for the regeneration and restoration of the dental, oral, and craniofacial tissues. With these come new opportunities for collaboration towards technology translation. The Corporate Partners Program aims to support the mutual needs of industry and the innovation ecosystem of the Resource Center and to catalyze fruitful partnerships to facilitate the commercialization and clinical adoption of tissue engineering/ regenerative medicine technologies in the dental, oral, and craniofacial market place.

Disclaimer: The MPWRM Resource Center is supported in part by the National Institute of Dental & Craniofacial Research of the National Institutes of Health under Award Number U24DE026915. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

About the Interdisciplinary Translational Project Program

The Michigan-Pittsburgh-Wyss Regenerative Medicine (MPWRM) Resource Center is one of the two national Resource Centers established by the National Institute of Dental and Craniofacial Research (NIDCR)'s Dental Oral and Craniofacial Tissue Regeneration Consortium (DOCTRC) initiative. With the overarching goal of developing clinical trial-ready tissue engineering/ regenerative medicine products and protocols, the DOCTRC initiative is providing funding and resources through the Interdisciplinary Translational Project (ITP) program administered by the two national Resource Centers. For more information about the DOCTRC initiative, please visit ***https://www.nidcr.nih.gov/news-events/nidcr-news/2017/nidcr-funds-consortium***.

The ITP program seeks to identify promising technologies that address clear unmet clinical need with market potential in the dental, oral, and craniofacial (DOC) space, and to catalyze clinical translation of these technologies towards FDA submissions to achieve high impact outcomes in clinical practice.

16 ITPs Supported

$1.6M Funding committed to ITPs

9 Tissue Types Addressed

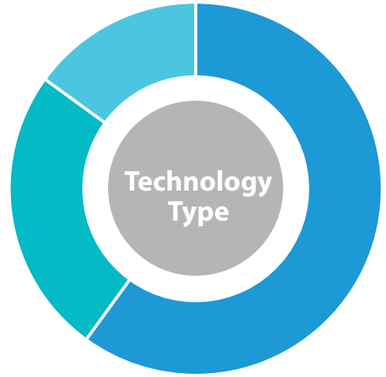
Interdisciplinary Translational Project Program: 2018 At a Glance

Cycle 1 ITPs

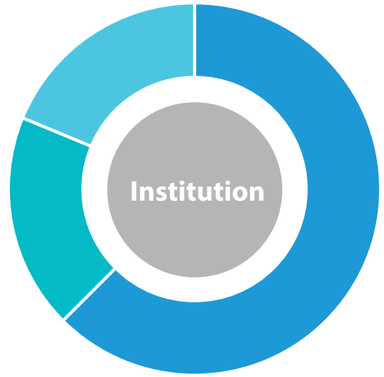
- Extracellular Matrix Scaffold for TMJ Disc Repair
- Hylafix: A Technology that Accelerates Bone Healing
- Tissue Engineering Functional Human Lips
- Sclerostin mAntibody to Treat Periodontal Disease
- Optimization of a Novel Organic-Mineral Bone Adhesion
- Controlled Release System for Immunoregulation and Treatment of Periodontal Disease
- Pulsatile Parathyroid Hormone Delivery for Local Bone Regeneration
- Gel-Factor Delivery for Reinnervation
- Bioabsorbable Magnesium/PLGA Barrier Membranes
- Cryopreserving Adipose Tissue Grafts

Cycle 2 ITPs

- Non-viral Aquaporin-1 Gene Therapy to Restore Salivary Flow in Patients Suffering from Radiation-induced Xerostomia
- Stem Cell-Based Regenerative Endodontics
- AxoMax®: A Novel Conduit for Long-Gap Nerve Repair
- Targeted Remineralization Treatment Using Mineral Loaded Starch Nanoparticles
- REGEndogel: a Bioinspired Hydrogel System for Endodontic Therapy
- Reversing Tooth Decay with Biomimetic Peptide Gel



- Devices | **60%**
- Biologic | **25%**
- Cellular | **15%**



- Internal | **62%**
- External | **19%**
- External: for-profit | **19%**

- Bone | **23%**
- Tooth | **23%**
- Dental implant | **15%**
- Nerve | **9%**
- Periodontal | **9%**
- Skin | **9%**
- Muscle | **4%**
- Salivary gland | **4%**
- TMJ | **4%**

Extracellular Matrix Scaffold for TMJ Disc Repair

Clinical Need

Individuals suffering from severe Temporomandibular Joint (TMJ) disc disease experience painful clicking or locking that can dramatically affect quality of life. Total TMJ reconstruction is often the last-resort surgical intervention for the irreparably damaged joint. Current therapies include joint replacement using alloplastic implants or autogenous grafts; however, long term outcomes with alloplastic implants are unclear, while autogenous grafts are associated with donor site morbidity.

Solution

University of Pittsburgh team of Alex Almarza, PhD, Stephen Badylak, DVM, PhD, MD, William Chung, DDS, MD, and Bryan Brown PhD is developing an extracellular matrix (ECM)- based scaffold device for the reconstruction of the TMJ. In particular, the device is designed to replace the meniscus of the temporomandibular joint (TMJ) by inducing the formation of new, patient-specific, functional tissue formation.

Competitive Advantage

Unlike currently available alloplastic implants, ECM-based device is biodegradable, and mimics the shape and size of native TMJ meniscus, without the need for autologous tissue harvesting. The device has been validated in canine and porcine models, where the scaffold demonstrated rapid transformation into a fibrocartilagenous tissue with biomechanical and biochemical properties similar to the native TMJ disc, as well as elicited formation of near-normal tissues in only one month following implantation.

Alejandro Almarza, PhD
University of Pittsburgh

"This technology will provide an off-the-shelf solution for the repair of the TMJ disc."

www.dental.pitt.edu/person/alejandro-j-almarza

How the ITP Program Supports this Project

The long-term objective of this program is the development of a safe and effective therapeutic option for reconstruction of the TMJ disc. In preparation for submission to the FDA, the ITP program will support the validation of devices made in a GMP facility, and for the submission of a pre-IDE application to the FDA.

Clinical Translation Pathway

Publications:

Brown BN, Chung WL, Pavlick M, Reppas S, Ochs MW, Russell AJ, Badylak SF. "Extracellular matrix as an inductive template for temporomandibular joint meniscus reconstruction: a pilot study." J Oral Maxillofac Surg. 2011 Dec;69(12):e488-505. (https://www.ncbi.nlm.nih.gov/pubmed/21684655)

Brown BN, Chung WL, Almarza AJ, Pavlick MD, Reppas SN, Ochs MW, Russell AJ, Badylak SF. "Inductive, scaffold-based, regenerative medicine approach to reconstruction of the temporomandibular joint disk." J Oral Maxillofac Surg. 2012 Nov;70(11):2656-68. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3368066/)

Intellectual Property:

US 9,314,340 Joint bioscaffolds (https://patents.google.com/patent/US9314340B2/en)

Commercialization Strategy:

In development with the MPWRM Commercialization/Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/Market Needs Core

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Hylafix: A Technology that Accelerates Bone Healing

Clinical Need

An exigent problem confronting head and neck cancer reconstruction is overcoming the impediments of damage imposed by radiation therapy (XRT) on surrounding tissue, resulting in the need for autologous free tissue transplantation. While these operations provide solutions for delivering sizable vascularized tissues to the irradiated area of reconstruction, they are complex and introduce significant donor site morbidity. In the case of dental concerns for patients with osteoradionecrosis and other post-radiation bony sequelae, there are currently no good clinical solutions, demonstrating a significant limitation in the current standard of care.

Solution

A team of University of Michigan researchers led by Steven Buchman, MD, has developed an implantable, sustained-release formulation of a known angiogenic small molecule, deferoxamine (DFO), conjugated to hyaluronic acid (HA) backbone for reconstruction of craniofacial bone. Through this approach, the team has shown accelerated bone regeneration in preclinical murine models of mandibular fracture repair. Moreover, in a patient with previously irradiated maxilla, enhanced bone formation following deferoxamine application was observed.

Competitive Advantage

Using a molecule previously approved for medical use in a new formulation, this HA-DFO product presents a non-cellular approach to bone defect repair. This approach may enable once-precluded reconstructive strategies, such as distraction osteogenesis and non-vascularized bone grafting to be viable reconstructive options for patients with XRT-induced bone degradation.

Steven Buchman, MD, FACS
University of Michigan

"We are on the cusp of translating the exciting results that we have seen at the bench to the bedside, with the ultimate potential to impact millions of patients who undergo fracture repair each year."

How the ITP Program Supports this Project

The work supported by the ITP program is focused on the completion of non-GLP pre-IND studies including pharmacokinetics and toxicology studies, as well as efficacy studies in irradiated bone fracture model.

Clinical Translation Pathway

Publications:

Momeni, A., Rapp, S., Donneys, A., Buchman, S. R., & Wan, D. C. (2016). Clinical Use of Deferoxamine in Distraction Osteogenesis of Irradiated Bone. The Journal of craniofacial surgery, 27(4), 880. *(https://www.ncbi.nlm.nih.gov/pubmed/27171947)*

Donneys, A., Weiss, D. M., Deshpande, S. S., Ahsan, S., Tchanque-Fossuo, C. N., Sarhaddi, D., Levi, B., Goldstein, S.A. & Buchman, S. R. (2013). Localized deferoxamine injection augments vascularity and improves bony union in pathologic fracture healing after radiotherapy. Bone, 52(1), 318-325. *(https://www.ncbi.nlm.nih.gov/pubmed/23085084)*

Intellectual Property:

PCT/US2016/067320 Devices, Compositions, and Related Methods for Accelerating and Enhancing Bone Repair. *(https://patents.google.com/patent/WO2017106744A1/)*

For more information about this technology, please visit: http://bit.ly/MPWRM_bonehealing

Commercialization Strategy:

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Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

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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.

Stephen E. Feinberg, DDS, MS, PhD
University of Michigan

"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."

How the ITP Program Supports this Project

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.

Clinical Translation Pathway

Publications:

Bayar GR, Kuo S, Marcelo CL, Feinberg SE. In Vitro Development of a Mucocutaneous Junction for Lip Reconstruction. J Oral Maxillofac Surg. 2016 Nov;74(11):2317-2326. *(https://www.ncbi.nlm.nih.gov/pubmed/27160362)*

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 Eng Part C. 2012;18(4):273. *(https://www.ncbi.nlm.nih.gov/pubmed/22067042)*

Intellectual Property:

US 7,887,829: Mucosal cell composites and methods *(https://patents.google.com/patent/US7887829B1)*

US 8,835,169: Compositions, methods and systems for preparation of a stem cell-enriched cell population *(https://patents.google.com/patent/US8835169B2/)*

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Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

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Sclerostin mAntibody to Treat Periodontal Disease

Clinical Need

Periodontitis is known to affect approximately 50% of the U.S. adult population, with approximately 10% of patients afflicted with severe form of the disease leading to tooth loss. Although various procedures have been explored for the regeneration of the periodontium and bone, predictable treatments to arrest and rebuild lost tissues around teeth and/or tooth-replacing dental implants are limited, and to date, there are no FDA-approved bone anabolic agents available to treat periodontal or peri-implant bone loss.

Solution

A team of researchers led by Dr. William Giannobile at the University of Michigan, is developing a systemic and local delivery of sclerostin monoclonal antibody to restore lost periodontium or implant-supporting alveolar bone. The approach offers the potential for easy dosing of sclerostin antibody to regenerate lost periodontium or improve peri-implant bone density.

Competitive Advantage

By taking advantage of easy delivery of sclerostin monoclonal antibody, which is already being clinically explored for improvement of bone density in other indications such as osteoporosis, this approach may represent an improved access to drug therapies for periodontal and dental implant-related diseases that might otherwise not be as available due to limited reimbursement through typical dental insurance.

William Giannobile, DDS, DMedSc
University of Michigan

"This novel technology offers both local or systemic bone anabolic drug delivery to promote the regeneration of bone defects around teeth affected by periodontal disease or dental implants needing bone reconstruction."

media.dent.umich.edu/labs/giannobile/

How the ITP Program Supports this Project

The work supported by the ITP program is focused on the IND submission for the design of a phase I/II human clinical trial to use systemic sclerostin antibody delivery to treat periodontal disease.

Clinical Translation Pathway

Publications:

Yu SH, et al. Sclerostin neutralizing antibody enhance bone regeneration around oral implants. Tissue Eng Part A. 2018 Jun 19. *(https://www.ncbi.nlm.nih.gov/pubmed/29921173)*

Taut AD, et al. Sclerostin antibody stimulates bone regeneration after experimental periodontitis. J Bone Miner Res. 2013 Nov;28(11):2347-56. *(https://www.ncbi.nlm.nih.gov/pubmed/23712325)*

Intellectual Property:

US 9,657,090 Method of treating alveolar bone loss through the use of anti-sclerostin antibodies. *(https://patents.google.com/patent/US9657090B2/)*

Commercialization Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

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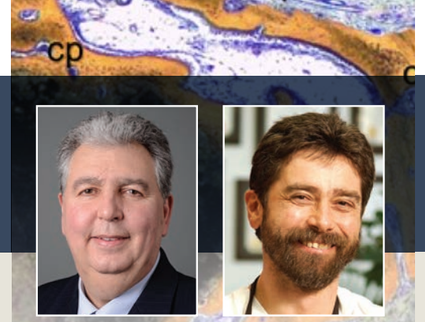
Optimization of a Novel Organic-Mineral Bone Adhesive



Joseph Fiorellini, DMD, DMSc
Penn Dental Medicine

George Kay, DMD, MMSc
Harvard School of Dental Medicine

LaunchPad Medical LLC

Clinical Need

In the United States (US), more than 50% of adults over the age of 45 have one or more missing teeth. While dental implant devices have become the standard of care, only 2% of the eligible population receives a prosthetic tooth due to the cost factors, amount of available bone, and the length of time involved in these multi-stage procedures. While most of the bones grafting materials demonstrate osteoconductivity to regenerate bone, many suffer from poor mechanical properties. Due to the lack of structural integrity, these materials typically require the use of ancillary fixation or containment devices to prevent graft migration and ingrowth of fibrous tissue that impedes bone regeneration and remodeling.

Solution

Researchers at LaunchPad Medical are exploring a novel technology, Tetranite®, for bone grafting applications. Tetranite is an injectable, synthetic, wet-field bioresorbable biomaterial. Characterized as a strong, functional adhesive, Tetranite is able to create a load-bearing bond to wet bone tissue and metals. The material is chemically and structurally stable in a neutral pH aqueous environment and is degraded and resorbed in vivo without the loss of bond to bone resulting in continuous bone deposition to exposed surfaces.

Competitive Advantage

The unique hard-setting and adhesive properties of Tetranite enable it to conform and fixate to complex, open-walled, horizontal, and vertical defect sites. These properties of Tetranite are predicted to eliminate the cost and time associated with the use of ancillary or graft containment devices that are required to support the existing bone graft. In addition, the adhesive material enables immediate placement of implants simultaneous to the bone augmentation procedure. Overall, with the reduction in surgical intervention and costs, fewer patients may decline the invasive dental implant procedures.

"The ITP program has been an innovative partnership between NIDCR, academia and a corporate entity. This partnership is ideally suited for a product such as Tetranite. With multiple resources available to all parties, the development process has been streamlined and made more efficient."

www.launchpadmedical.com/applications.html

How the ITP Program Supports this Project

The work supported by the ITP program is designed in preparation of the pivotal animal studies to assess the optimal Tetranite formulation for bone regeneration. The data from this investigation will better characterize the temporal formation of bone and resorption of the Tetranite graft material.

Clinical Translation Pathway

Publications:

Manuscripts pending

Intellectual Property:

US 8,232,327: Tetra calcium phosphate based organophosphorus compositions and methods (https://patents.google.com/patent/US8232327)

US 8,273,803: Tetra calcium phosphate based organophosphorus compositions and methods (https://patents.google.com/patent/US8273803B2)

US 8,765,189: Organophosphorous and multivalent metal compound compositions and methods (https://patents.google.com/patent/US8765189B2)

Commercialization Strategy:

In development with the MPWRM Commercialization/Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

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Controlled Released System for Immunoregulation and Treatment of Periodontal Disease

Steven Little, PhD
University of Pittsburgh

Clinical Need

Periodontitis is one of the most pressing oral health concerns today. While about 65 million adults in the U.S. are diagnosed with periodontitis, there are approximately 12 million patients who suffer from the most severe form of the disease. Antibiotics (killing of bacteria) are currently used as an adjunct therapy to scaling and root planing (removal of bacteria), which remains the current gold standard of care for periodontitis. However, with all medical practice shifting away from the overuse of antibiotics, new treatment modalities are needed.

Solution

A team at the University of Pittsburgh led by Dr. Steven Little has developed a non-antibiotic, controlled release system that repairs the underlying immunomodulation dysfunction responsible for tissue degeneration in periodontitis. Studies in canine and murine models suggest that this system reduces bone resorption and results in the expression of factors indicative of tissue regeneration.

Competitive Advantage

Current clinical therapies for periodontitis focus on removal of bacterial species by scaling and root planing or debridement, often in conjunction with local or systemic antibiotics. While this approach has shown clinical benefit, it does not directly address the host's chronic inflammatory response, which has ultimately been found to be responsible for tissue destruction in periodontal disease. By targeting the underlying immunoregulatory discourse in periodontitis, this controlled release system is thought to overcome the current limitation in the treatment of periodontal diseases.

"This new class of treatments is extremely exciting in that organizing extraordinarily tiny amounts of proteins that are already found in the body seem to be capable of influencing the body's own cells to repair the destructive inflammation that produces periodontal disease. To give perspective, it is possible to deliver millions of times less drug and achieve a better effect than the current gold standard."

www.littlelab.pitt.edu

How the ITP Program Supports this Project

The team has demonstrated the effectiveness of this approach in preclinical canine model of periodontitis. The goal of the work under the ITP program is to develop GMP-grade manufacturing and sterilization protocols to produce quality-controlled product for pharmacokinetic testing and toxicology studies in support of an FDA submission.

Clinical Translation Pathway

Publications:

Glowacki, A.J., Yoshizawa, S.A., Jhunjhunwala, S., Vieira, A.E., Garlet, G.P., Sfeir, C.S., Little S.R. (2014) Prevention of Inflammation-Mediated Bone Loss in Murine and Canine Periodontal Disease via Recruitment of Regulatory Lymphocytes. Proceedings of the National Academy of Science, 110(46):18525-30). *(https://www.ncbi.nlm.nih.gov/pubmed/24167272)*

Garlet, G.P., Sfeir, C.S., Little, S.R. (2014) Restoring Host-Microbe Homeostasis via Selective Chemoattraction of Tregs. Journal of Dental Research, invited review, 93(9):834-839). *(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213252/)*

Intellectual Property:

US 8,846,098 Artificial cell constructs for cellular manipulation *(https://patents.google.com/patent/US884609B2)*

Commercialization Strategy:

In development with the MPWRM Commercialization/Market Needs Core

Regulatory Pathway:

IND

Product Launch Strategy:

In development with the MPWRM Commercialization/Market Needs Core

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Pulsatile Parathyroid Hormone Delivery for Local Bone Regeneration

Clinical Need

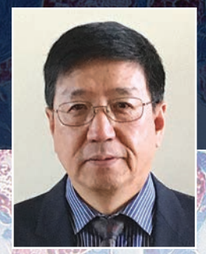
Reconstruction of cranial and maxillofacial bone loss resulting from trauma, disease, or tumor remains a significant clinical challenge. While parathyroid hormone (PTH) is well known to stimulate bone remodeling, and its application in the treatment for osteoporosis has been widely-explored, its utility in bone regeneration via a localized delivery has not yet been established.

Solution

A team of researchers at the University of Michigan led by Dr. Peter Ma and Dr. Laurie McCauley has developed a polymeric controlled release device to locally deliver PTH in a pre-programmed pulsatile manner. Using this approach, the local pulsatile delivery of PTH not only showed the regeneration of a critical-sized bone defect with negligible systemic side effects in a murine model, but also achieved higher quality regenerated bone than the standard systemic PTH injection.

Competitive Advantage

Although intermittent administration of PTH is associated with net bone formation, continuous exposure to PTH has been associated with bone resorption. This controlled release system enables localized, pulsatile delivery of PTH to achieve bone formation, and is intended to avoid systemic side effects, enhance patient compliance, while preserving PTH bioactivity to promote bone regeneration via enhanced bone remodeling.



Peter Ma, PhD
University of Michigan

"This technology enables the regeneration of a critical sized bone defect without using transplanted cells, significantly simplifying the clinical translation"

www.media.dent.umich.edu/labs/ma/

How the ITP Program Supports this Project

The overall goal of this project is to develop a cell-free system to deliver PTH to regenerate bone. To build upon the proof-of-concept work completed in a murine model, the ITP program will support further studies to demonstrate efficacy in a larger animal model, while developing marketing and regulatory strategies.

Clinical Translation Pathway

Publications:

Local pulsatile PTH delivery regenerates bone defects via enhanced bone remodeling in a cell-free scaffold. Biomaterials, 2017. 114:1-9. *(https://www.ncbi.nlm.nih.gov/pubmed/27835763)*

Intellectual Property:

PCT/US2017/052670 Delivery devices and methods for making the same. *(https://patents.google.com/patent/WO2018057709A1)*

US 8,623,397 Delivery device and method for forming the same. *(https://patents.google.com/patent/US8623397B2)*

Commercialization Strategy:

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Regulatory Pathway:

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Product Launch Strategy:

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Gel-Factor Delivery for Reinnervation

Clinical Need

Craniofacial skeletal muscle plays a number of crucial roles, including control over facial expression, mastication, and respiration. There is a significant need for functional skeletal muscle tissue in reconstructive craniofacial surgery, where the current standard treatment for facial paralysis is the microvascular transfer of an innervated gracilis muscle to the affected side. However, this approach is limited by the unpredictable recovery and reinnervation of the muscle after transfer, leaving some patients with less than desirable functionality post-treatment.

Solution

A team of researchers at the Wyss Institute led by Dr. David Mooney has developed a degradable hydrogel that provides sustained release of growth factors when injected into transferred muscle. These hydrogels provide a direct neuroprotective role to the transplanted tissue, enhance reestablishment of neuromuscular junctions, and promote muscle engraftment. With these added functionalities, this approach is expected to enhance the success of the current clinical standard for skeletal muscle replacement in the craniofacial complex.

Competitive Advantage

There is currently no approach utilized in the clinic to enhance the function of these grafts. This new strategy is envisioned to be used with the current standard of care and is anticipated to provide a practical and clinically relevant approach that could be readily translated to the clinic. Furthermore, this product is expected to find utility in other clinical applications once it is established in the craniofacial complex.

David Mooney, PhD
Harvard University

"With minimally invasive injections we can deliver a combination of these active molecules while controlling degradation rates, and our tests in different ischemia animal models are very promising."

mooneylab.seas.harvard.edu

How the ITP Program Supports this Project

The goal of the work under the ITP program is to develop and validate a process to terminally sterilize the final hydrogel/ growth factor product. Demonstrating an effective terminal sterilization process that can provide sterility assurance without compromising the effectiveness of factor delivery, biocompatibility, and mechanical properties would be a major advancement towards clinical trials and potential commercial launch.

Clinical Translation Pathway

Publications:

VEGF and IGF Delivered from Alginate Hydrogels Promote Stable Perfusion Recovery in Ischemic Hind Limbs of Aged Mice and Young Rabbits. J. Vasc. Res. 2017. *(https://www.ncbi.nlm.nih.gov/pubmed/28930755)*

Intellectual Property:

US 9,610,328 Enhancement of skeletal muscle stem cell engraftment by dual delivery of VEGF and IGF-1. *(https://patents.google.com/patent/US9610328B2/)*

PCT/US2016/058866 Reduce and Oxidized Polysaccharides and Methods of Use Thereof. *(https://patents.google.com/patent/WO2017075055A1)*

Commercialization Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center is supported in part by the National Institute of Dental & Craniofacial Research of the National Institutes of Health under Award Number U24DE026915. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Bioabsorbable Magnesium/ PLGA Barrier Membranes

Clinical Need

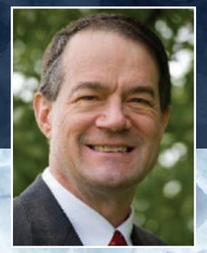
Over one million dental bone grafting procedures are performed annually in the U.S., most frequently in the preparation of dental implant placement. While alveolar ridge preservation and augmentation procedures are mostly associated with positive outcomes, results for defects with a significant vertical component are unpredictable and unreliable. Maximization of the alveolar ridge augmentation is frequently attempted through guided bone regeneration using a form-stable barrier membrane that can protect the healing site from mechanical insults. Unfortunately, existing membranes require an invasive removal procedure, which decreases the likelihood of achieving optimal grafting outcomes, and currently available resorbable membranes lack the form-stability needed to maximize alveolar ridge augmentation.

Solution

An interdisciplinary team at nanoMAG and the University of Pittsburgh is developing a barrier membrane with handling characteristics that enable customization to the defect site while providing mechanical strength and controlled degradation to enable unimpaired implant placement post-bone grafting. Proof-of-concept studies in a canine model of vertical ridge preservation showed safety and effectiveness of the membrane in regenerating bone.

Competitive Advantage

The barrier membrane in development is designed to meet critical clinical design requirements of mechanical properties to provide form stability and resorbability. Taken together, these characteristics enable maximization of alveolar ridge augmentation while obviating the need for device removal.



Stephen LeBeau, PhD
nanoMAG, LLC

"nanoMAG is an advanced materials and medical device manufacturing company that has developed a patented magnesium-based alloy that provides the strength of metal but is biocompatible and bioabsorbable. We are very excited about our collaboration with the University of Pittsburgh under the ITP program to provide us access to pre-clinical expertise and market knowledge in dental reconstruction as well as FDA regulatory assistance via the ITP core services team that will assist us in our commercialization efforts."

www.nanomag.us

How the ITP Program Supports this Project

The objective of the work to be completed under the ITP program is to establish design freeze and manufacturing methods in support of an FDA submission. Towards this end, longer term studies will also be conducted in a canine vertical ridge augmentation model.

Clinical Translation Pathway

Publications:

A Brown et.al. "Porous magnesium/PLGA composite scaffolds for enhanced bone regeneration following tooth extraction" Acta Biomaterialia, Vol 11, Jan 2015, p 543-553. *(https://www.ncbi.nlm.nih.gov/pubmed/25234156)*

S LeBeau, et.al. "Controlling the Degradation Profile of Mg Biomedical Devices by Alloy Design and Thermomechanical Processing" National Association of Corrosion Engineers, 2017. *(https://www.onepetro.org/conference-paper/NACE-2017-9395)*

Intellectual Property:

US 9,017,602 Method and Apparatus of Forming a Wrought Material Having a Refined Structure. *(https://patents.google.com/patent/US9017602B2/en)*

WO02014145672 High Strength and Bio-absorbable magnesium alloys. *(https://patents.google.com/patent/WO2014145672A1)*

WO20188076003 Degradable bulk metallic magnesium/ polymer composite barrier membranes for dental, craniomaxillofacial and orthopedic application s and manufacturing methods. *(https://patents.google.com/patent/WO2018076003A1/)*

Commercialization Strategy:

Via collaboration between NanoMAG, University of Pittsburgh, and strategic dental device OEM manufacturers

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/Market Needs Core

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Cryopreserving Adipose Tissue Grafts

Clinical Need

Soft tissue deformities and volume/ contour deformities from craniofacial trauma, congenital anomalies, and cancer treatment are difficult to correct. Current standard of care includes injectable fillers, implants, and soft tissue flap procedures, which have limitations and often involve operations with significant risk. As such, autologous fat transfer is being explored as a lower risk alternative. However, as optimal results with fat transfer often require at least two treatments, there is a need for an on-site preservation of harvested tissue for subsequent procedures to minimize donor site morbidity and encourage fast recovery.

Solution

A team of researchers at the University of Pittsburgh let by Dr. Peter Rubin has previously validated the use of autologous fat transfer as a minimally invasive therapy for the restoration of craniofacial form. In order to facilitate fat transfer with minimal donor site morbidity, the team has developed a novel device to cryopreserve adipose for storage at the treatment facility, which can directly be used for the subsequent fat transfer(s).

Competitive Advantage

With the on-site cryopreservation and storage of the fat tissue, the device is envisioned to reduce patient and clinician burden for tissue harvest. The utilization of the device obviates the need for repeat tissue grafting procedures, and is anticipated to lead to reduction in treatment costs as the fat transfer injections may be performed outside of an operating room in a less acute setting.

J. Peter Rubin, MD, FACS
University of Pittsburgh

"The ability to easily and inexpensively store tissue onsite will result in significant decrease in patient discomfort and risk, as well as significant decrease in surgeon time spent on the repeat procedure."

plasticsurgery.pitt.edu/portfolio-items/j-peter-rubin-md/

How the ITP Program Supports this Project

The work supported by the ITP program is focused on the generation of a prototype cryopreservation/ storage device that can be used for clinical trials. Towards that end, project plans include prototype development and validation, as well as the development of a regulatory strategy and commercialization plan.

Clinical Translation Pathway

Intellectual Property:

Provisional patent application filed, Sept 2017

Commercialization Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

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RegendoGEL: A Bioinspired Hydrogel System for Endodontic Therapy

Clinical Need

Dental caries is the most prevalent chronic infectious disease in humans. If not treated, virtually all caries lesions will progress to affect the dental pulp, eventually requiring some form of root canal therapy. The current standard of care using polymeric/ceramic-like materials can elicit tertiary dentin formation in vital young teeth, but fail to mimic the composition, physical properties, and regenerative/ biological capacity of the native pulp.

Solution

A research team led by Luiz Bertassoni, DDS, PhD, of Oregon Health and Science University and Pamela C. Yelick, PhD of Tufts University has developed a photocurable biodegradable hydrogel system for endodontic regeneration that can be injected into the root canal. The hydrogel alone exhibits strong regenerative capacity, which is enhanced with combination with dental pulp cells and/ or natural dentin matrix molecules. The product can be used for direct pulp capping and pulpotomy.

Competitive Advantage

As compared to the existing synthetic rigid silicate or calcium hydroxide-based products, RegendoGEL is a soft hydrogel system that more closely resembles the natural pulp tissue. With the ability for photo-crosslinking and incorporation of cell-adhesive ligands, the product can be stiffened to instruct cell response via mechanotransduction and durotaxis. In addition, RegendoGEL is designed as a ready-to-use system with the dental light curing, for integration into routine dental procedures in the clinic.

Luiz Bertassoni, DDS, PhD
Oregon Health & Science University

Pamela Yelick, PhD
Tufts University

"This technology will allow for much more predictable and successful outcomes in regenerative endodontics, and can be integrated into routine dental procedures with ease."

http://www.bertassonilab.com

https://dental.tufts.edu/people/faculty/pamela-yelick

How the ITP Program Supports this Project

With a focus on direct pulp capping and pulpotomy, the support from the ITP program will be used to complete *in-vivo* validation and optimization of the RegendoGEL system to enable FDA submission.

Clinical Translation Pathway

Publications:

A Novel Strategy to Engineer Pre-Vascularized Full-Length Dental Pulp-like Tissue Constructs. Bertassoni LE et al. Sci Rep. 2017 Jun 12;7(1):3323. *(https://www.ncbi.nlm.nih.gov/pubmed/28607361)*

Photopolymerization of cell-laden gelatin methacryloyl hydrogels using a dental curing light for regenerative dentistry. Bertassoni LE et al. Dent Mater. 2018 Mar;34(3):389-399. *(https://www.ncbi.nlm.nih.gov/pubmed/29199008)*

Engineering Microvascular Networks in LED Light-Cured Cell-Laden Hydrogels. Bertassoni LE et al. ACS Biomater. Sci. Eng., 2018, 4 (7), pp 2563–2570 *(https://pubs.acs.org/doi/full/10.1021/acsbiomaterials.8b00502)*

GelMA-Encapsulated hDPSCs and HUVECs for Dental Pulp Regeneration. Yelick PC et al. J Dent Res 2017 96(2), pp192-199 *(https://www.ncbi.nlm.nih.gov/pubmed/28106508)*

Intellectual Property:

US 62/512,675
Dental pulp construct

US 15/777,304
Pulp regeneration compositions and methods of forming and using the same *(https://patents.google.com/patent/WO2018102750A1)*

Commercialization Strategy:

In development with commercialization partner

Regulatory Pathway:

In development with commercialization partner

Product Launch Strategy:

In development with commercialization partner

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Targeted Remineralization Treatment Using Mineral Loaded Starch Nanoparticles

Clinical Need

Dental caries, caused by the demineralization of enamel, is the most common chronic disease worldwide. While caries is often treated surgically, recent treatment methods include the non-invasive approach of mineral ions and fluoride delivery using professionally applied fluoride varnishes, prescription and over-the-counter fluoride toothpastes, and calcium phosphate-based remineralization agents. However, these treatments are unable to regenerate enamel within the depth of subsurface carious lesions.

Solution

GreenMark Biomedical Inc. has developed targeted biodegradable nanoparticles capable of delivering minerals and fluoride specifically to enamel, for in-office treatment of non-cavitated carious lesions ("pre-cavities"). The same technology platform is also being used in the development of a diagnostic product which illuminates carious lesions using a standard dental curing lamp to allow earlier detection of pre-cavities. The nanoparticles consist of starch, readily degraded by natural amylase enzymes in saliva, and their specific adhesion defines the interior lesion sub-surface morphology. While traditional fluoride treatments impact the surface of enamel lesions, this targeted delivery of minerals and fluoride to the dominant subsurface lesion is expected to enable a superior non-surgical dental treatment.

Competitive Advantage

High localized concentration of these minerals and fluoride is expected to facilitate tooth structure regeneration through nucleation and targeted formation of hydroxyapatite-like crystals to improve efficacy, lower the required therapeutic dose, and minimize reliance on patient compliance, yielding superior remineralization of lesions compared to other available treatments.

Steven Bloembergen, PhD
GreenMark Biomedical Inc.

"Targeted nanoparticle based regeneration of enamel will allow for more natural repair of dental caries using painless and non-invasive treatment, reducing discomfort during dental procedures, preserving dental tissue and improving long term oral health of patients."

http://greenmark.bio/

How the ITP Program Supports this Project

The support from the ITP program is expected to advance the technology with continued technical validation and development of regulatory and marketing strategies.

Clinical Translation Pathway

Publications:

Nanoparticle-Based Targeting and Detection of Microcavities. Jones NA, Chang SR, Troske WJ, Clarkson BH, Lahann J. Advanced Healthcare Materials. 2017, 6(1). *(https://www.ncbi.nlm.nih.gov/pubmed/27863155)*

Intellectual Property:

US15/331,408 Detection and treatment of caries and microcavities with nanoparticles *(https://patents.google.com/patent/US20170112949A1/en)*

Commercialization Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/Market Needs Core

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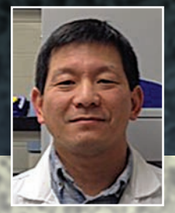
Reversing Tooth Decay with Biomimetic Peptide Gel



Hanson Fong, PhD
University of Washington

Mehmet Sarikaya, PhD
University of Washington

Clinical Need

Demineralization in tooth is often the cause of various dental concerns including dental cavities and hypersensitivity. The currently available commercial products with claims for remineralization properties aim to stabilize calcium and phosphate to deliver a high dosage of the ions to the oral cavity. Because this process is an indirect approach to mineralization, it cannot direct and catalyze mineral formation on the tooth surface, thereby limiting their clinical and long-term effectiveness.

Solution

To address this need, a team of researchers at the University of Washington, led by Prof. Mehmet Sarikaya and Dr. Hanson Fong, has developed a peptide - containing gel to direct primary biomineralization of the lost dental tissues to treat tooth decay and other dental ailments caused by demineralization. The peptides have been demonstrated to form calcium phosphate minerals of controlled structural characteristics, forming stable layers of deposited mineral on extracted human and rat teeth, both on dentin and on enamel.

Competitive Advantage

This gel formulation is expected to be topically applied on the carious teeth with early stage tooth decay to restore mineral on the affected surface. As with the currently used fluoride varnish, this gel would also be applied in dentist's office. While the fluoride varnish does not actively add new mineral to the tooth surface, the active, generalizing gel will serve as an effective procedure to reverse cavity progression.

"Novel remineralization therapies guided by naturally derived peptides will transform current dental health providing preventative and restorative oral care."

www.uwgemsec.com/principal-investigator

How the ITP Program Supports this Project

With the overall objective to develop a user-friendly prototype product for the permanent treatment of demineralization-driven conditions including dental caries and hypersensitivities, the ITP program will be supporting the continued validation of the peptide-containing gel formulation for guided remineralization and exploration of FDA regulatory and OTC and clinical marketing strategies.

Clinical Translation Pathway

Publication:

Biomimetic Tooth Repair: Amelogenin-Derived Peptide Enables in Vitro Remineralization of Human Enamel. Dogan S, Fong H, Yucesoy DT, Cousin T, Gresswell C, Dag S, Huang G, Sarikaya M. ACS Biomater. Sci. Eng., 2018, 4 (5), pp 1788–1796. (https://pubs.acs.org/doi/10.1021/acsbiomaterials.7b00959)

Early caries in an in vivo Model: Structural and nanomechanical characterization, Yucesoy DT, Fong H, Gresswell C, Saadat S, Chung WO, Dogan S, Sarikaya M., J Dent Res, Aug 1, 2018. (https://www.ncbi.nlm.nih.gov/pubmed/30067915)

Intellectual Property:

PCT/US2016/039650 Reagents and Methods for Treating Dental Disease (https://patents.google.com/patent/WO2012166626A1/)

PCT/US2016/013301 Reagents and methods for whitening teeth (https://patents.google.com/patent/WO2016115283A2)

PCT/US2017/013492 Reagents and methods for mineralization of tooth enamel (https://patents.google.com/patent/WO2017123986A1)

Commercialization Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

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AxoMax®: A Novel Conduit for Long-Gap Nerve Repair

Kacey Marra, PhD
University of Pittsburgh

Clinical Need

Injuries resulting in facial paralysis significantly affect a patient both physiologically and psychosocially. The standard of care for nerve injury requiring surgical repair is nerve autograft, which is suboptimal for various reasons. While several nerve guides are commercially available for regeneration of nerve gaps <3cm, those for use in large nerve gaps (>3cm) are not. Furthermore, despite the available interventions, current cases of nerve autografting or allografting result in insufficient functional recovery, where ~50% of patients are unable to return to pre-injury employment one year post-operation.

Solution

Kacey Marra, PhD, and her team at the University of Pittsburgh have developed a novel conduit for long-gap nerve repair, named AxoMax®. AxoMax® consists of a degradable poly(caprolactone) nerve guide capable of controlled local delivery of drugs for nerve regeneration. Evaluation of the AxoMax® in a 5cm median nerve defect model showed ~80% return to function after 1 year as compared to ~70% for an autograft, the standard of care.

Competitive Advantage

Unlike decellularized technologies, AxoMax® elutes factors essential to nerve growth for several months, rendering it biologically similar to an autograft, the standard of care, without the need for a surgery to harvest the graft, thereby avoiding comorbidities associated with such procedures. The elimination of the harvesting procedure spares the patient from lifelong loss of sensation, as well as in an operating room time saving in excess of 60 minutes per case.

"This technology has the potential to revolutionize treatment of long gap nerve repair."

http://www.mirm.pitt.edu/our-people/faculty-staff-bios/kacey-g-marra-phd/

How the ITP Program Supports this Project

With the ultimate goal of commercialization of AxoMax® for bridging craniofacial nerve defects, the work to be supported by the ITP program includes continued market validation and biocompatibility testing in support of a Q-submission to the FDA.

Clinical Translation Pathway

Publication:

Incorporation of double-walled microspheres into polymer nerve guides for the sustained delivery of glial cell line-derived neurotrophic factor. Biomaterials, 2010. 31 (8): p. 2313-22. *(https://www.ncbi.nlm.nih.gov/pubmed/19969346)*

Sustained Growth Factor Delivery Promotes Axonal Regeneration in Long Gap Peripheral Nerve Repair. Tissue Engineering, Part A, 2011, 17(9-10):1263-75. *(https://www.ncbi.nlm.nih.gov/pubmed/21189072)*

Intellectual Property:

US 9,498,221 Implantable medical devices having double walled microspheres. *(https://patents.google.com/patent/US9498221B2/en11)*

For more information about this technology, please visit: *http://bit.ly/MPWRM_AxoMax*

Commercialization Strategy:

New company formation in development

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

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Stem Cell-Based Regenerative Endodontics

Clinical Need

Dental trauma and caries are leading causes of pulp tissue necrosis and premature loss of immature permanent teeth. Indeed, approximately 5.4 million children and young adults suffer pulp necrosis associated to caries and/or dental trauma yearly in USA. The current standard of care for these patients is calcium hydroxide treatment with mineral trioxide aggregate (MTA) apical plug and root canal filling with gutta-percha. This approach does not allow for completion of vertical and lateral root formation in necrotic immature permanent teeth, and as a result, these teeth are structurally weak and highly susceptible to root fracture and premature tooth loss.

Solution

To revitalize necrotic immature teeth, enabling completion of root formation in these pediatric population, a team of researchers led by Jacques Nör, DDS, MS, PhD, at the University of Michigan is developing a stem cell-based strategy for regenerative endodontics.

Competitive Advantage

The current standard of care is conceptually based on tooth restoration, where a vital tissue (dental pulp) is replaced by an inert plastic (gutta-percha) which does not enable protective responses. The stem cell-based strategy proposed here is fundamentally based on tissue regeneration, to enable the engineering of functional dental pulp and strengthening of tooth structure through new tubular dentin deposition. With completion of root formation, the long-term outcome of the tooth is expected to be significantly improved.

Jacques Nör, DDS, MS, PhD
University of Michigan

"Here, we propose autologous transplantation of stem cells from the dental pulps of permanent (or primary) teeth as a strategy to engineer a new, functional, pulp for the treatment of young immature necrotic permanent teeth."

http://www.dent.umich.edu/about-school/department/crse/nor-lab

How the ITP Program Supports this Project

With the eventual goal of conducting a first-in-human clinical trial on dental pulp stem cell transplantation for the regeneration of dental pulp tissue, the ITP program support is focused on exploring potential strategies for the clinical adoption and commercialization of this stem cell-based regenerative endodontics therapy.

Clinical Translation Pathway

Publications:

Dental pulp tissue engineering in full-length human root canals. Rosa V, Zhang Z, Grande RH, Nör JE. J Dent Res 92(11):970-975, 2013. *(https://www.ncbi.nlm.nih.gov/pubmed/24056227)*

A hydrogel scaffold maintains viability and supports differentiation of dental pulp stem cells. Cavalcanti BN, Zeitlin BD, Nör JE. Dent Mat 29(1):97-102, 2013. *(https://www.ncbi.nlm.nih.gov/pubmed/22901827)*

Intellectual Property:

In development

Commercialization Strategy:

In development with the MPWRM Commercialization/ Market Needs Core

Regulatory Pathway:

In development with the MPWRM Regulatory Core

Product Launch Strategy:

In development with the MPWRM Commercialization/Market Needs Core

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Non-viral Aquaporin-1 Gene Therapy to Restore Salivary Flow in Patients Suffering from Radiation-induced Xerostomia

Clinical Need

In the treatment of head and neck cancers, radiotherapy is commonly prescribed in conjunction with other modalities such as surgery and/or chemotherapy. Because of the anatomical proximity, salivary glands receive secondary damage, where xerostomia is one of the common effects of this damage. While intensity-modulated radiotherapy (IMRT) has significantly reduced the incidence of radiation-induced xerostomia, a pressing need exists for the remaining patients, especially for those in whom amifostine leads to significant side effects.

Solution

A team of researchers at the Allegheny Health Network led by Michael Passineau, PhD, has developed an ultrasound-assisted gene transfer technique (UAGT), to deliver AQP1 gene for the amelioration of radiation-induced xerostomia. This non-viral gene delivery is based on sonoporation generated by the ultrasound, enabling gene transfer as cell membrane permeability is altered. The delivery of AQP1 to the parotid glands in a mini-swine model has restored salivary flow to pre-treatment levels, demonstrating the efficacy of non-viral AQP1 gene transfer.

Competitive Advantage

While a recent clinical trial using AQP1 gene delivery demonstrated increase in saliva production, this approach has not advanced beyond a successful Phase I/II trial to regulatory approval due to the utilization of the adenovirus vector for gene delivery. With the preclusion of a virus for gene transfer, this approach is anticipated to provide enhanced safety and enable serial dosing to provide patients with the benefit of the AQP1 gene transfer throughout their lifetime.

Michael Passineau, PhD
Allegheny Health Network

Isabelle Lombaert, PhD
University of Michigan

"We are working to develop a safe gene therapy to provide lifelong relief from dry mouth in patients whose salivary function has been damaged by radiotherapy for head and neck cancers."

http://media.dent.umich.edu/labs/lombaert/

How the ITP Program Supports this Project

The long-term objective of this research program is to improve the quality of life in patients who have suffered from radiation-induced xerostomia. In collaboration with Dr. Isabelle Lombaert at the University of Michigan, the ITP program will support the continued validation and characterization of UAGT for the delivery of AQP1 gene towards enabling FDA submission.

Clinical Translation Pathway

Publication:

Ultrasound-assisted nonviral gene transfer of AQP1 to the irradiated minipig parotid gland restores fluid secretion. Wang Z, Zourelias L, Wu C, Edwards PC, Trombetta M, Passineau MJ. Gene Ther. 2015 Sep;22(9): 739-49. (https://www.ncbi.nlm.nih.gov/pubmed/25871828)

Intellectual Property:

US 15/144,683 Ultrasound-Assisted Gene Transfer for Treatment of Xerostomia. (https://patents.google.com/patent/US20160317613A1/en)

Commercialization Strategy:

In development with the MPWRM Commercialization/Market Needs Core

Regulatory Pathway:

IND application in preparation to pursue a Phase I/II human clinical trial

Product Launch Strategy:

Clinic-ready device to deliver our ultrasound-assisted gene therapy/Seeking regulatory approval to begin human studies.

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Leadership

Operating Committee

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Albert Donnenberg, PhD (University of Pittsburgh)
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Don Taylor, PhD, MBA (sciVelo/ University of Pittsburgh)
William Wagner, PhD (University of Pittsburgh)

Core Services & Resources

In Vitro & In Vivo Validation

- Microcomputed Tomography
- Histology/Histomorphometry
- Microscopy/Image Analysis
- Biomechanics
- Materials Fabrication & Characterization
- Mechanical & Functional Assessment
- Pre-Clinical Animal Models and Testing

Prototyping/Manufacturing

- Cell/Materials Manufacturing
- Method and Process Development
- Pre-clinical Testing
- Drug Release Profiling
- Material Characterization

Regulatory Support

MPWRM Resource Center's experts advise on navigating the regulatory pathways in support of new DOC therapies.

Commercialization

MPWRM Resource Center's commercialization planning services are designed to assist investigators to achieve successful business milestones, and provide guidance and education regarding technology commercialization process.

Intellectual Property Strategy

MPWRM Resource Center's Intellectual Property experts use their experience and expertise to unearth, evaluate, analyze, and broadly identify IP opportunities related to DOC technologies. Our process will assist innovators in thoroughly understanding their technology and patent novelty, resulting in stronger protection of their assets.

Market Research and Analysis

MPWRM Resource Center's market assessment services are designed to support the strategic decision making processes for new technology development by exploring market opportunities in the current dental, oral and craniofacial landscape.

Translational Training Resources

MPWRM Resource Center offers training resources through various medium to assist in the translation of DOC-related scientific discoveries into clinical practice. In addition, the Resource Center has partnered with the Clinical and Translational Science Award sites to foster research development, cultivate multidisciplinary collaborations, and train the next generation of researchers to improve health outcomes for patients in need.

For more information, please visit the Core Services & Resources tab at ***www.doctrc.com***.

About the Institutions

University of Michigan, School of Dentistry

The University of Michigan School of Dentistry is one of the nation's leading dental schools engaged in oral health care education, research, patient care, and community service. The research mission promotes an integration of basic, translational, clinical and health services research along with associated educational programs to stimulate discoveries and their diffusion into practice. The school has an extensive history in the merger of engineering and life science technologies to solve problems in the dental, oral, and craniofacial space. Through partnership and collaborations with the School of Medicine and College of Engineering at Michigan, investigators and research cores have expertise in many technologies central to advancing tissue engineering/ regenerative medicine, including: biomaterials and drug delivery; biomechanics, imaging, and functional analyses; stem cells and cell sourcing, and gene therapy. Michigan also has significant expertise in the clinical trials arena and from bench to proof-of-concept (bed-side or chair-side), and bench to start-up for clinical application. Furthermore, the School of Dentistry has been a leading center for early stage (Phase1) clinical trials as well as pivotal clinical trials that have led to the Food and Drug Administration (FDA) approval of new dental drugs and regenerative devices. For more information about the School of Dentistry, please visit ***www.dent.umich.edu.***

University of Pittsburgh McGowan Institute for Regenerative Medicine

The McGowan Institute for Regenerative Medicine is a translational research enterprise focused on the development and delivery of technology to address tissue and organ insufficiency. McGowan Institute serves as a single base of operations for the University of Pittsburgh's leading scientists and clinical faculty working to develop tissue engineering, cellular therapies, and artificial and biohybrid organ devices. McGowan Institute integrates an ambitious regenerative medicine technology portfolio, coupling biology, clinical science and engineering. Success in our mission will impact patients' lives, bring economic benefit, serve to train the next generation of researchers, and advance the expertise of our faculty in the basic sciences, engineering and clinical sciences. For more information about the McGowan Institute, please visit ***www.mcgowan.pitt.edu***.

University of Pittsburgh Center for Craniofacial Regeneration

Rooted in ground-breaking tissue regeneration and biomaterial advances made at the University of Pittsburgh, the Center for Craniofacial Regeneration (CCR) develops treatments for wounds and defects of the face and skull that restore function and appearance. Representing many scientific disciplines and interests, our team is dedicated to exploring all aspects of the varied and complex craniofacial region. The CCR's dynamic approach draws upon the expertise of scientists, from cell and molecular biologists, polymer chemists and material scientists to bioengineers, imaging experts and clinicians. The CCR encourages the transfer of developed technologies and treatments to enable new biotechnology ventures. Recently awarded funding from the National Institutes of Health (NIH) to support a translational resource center bears this out, demonstrating how the work of centers, such as the CCR, ultimately can improve the lives of patients by bridging the gap between basic science and clinical treatments. For more information about CCR, please visit ***www.dental.pitt.edu/center-craniofacial-regeneration***.

Wyss Institute for Biologically Inspired Engineering

The Wyss Institute for Biologically Inspired Engineering uses biological design principles to develop new engineering innovations that will transform medicine and create a more sustainable world. They leverage recent insights into how Nature builds, controls and manufactures to develop new engineering innovations - a new field of research we call Biologically Inspired Engineering. Biologically Inspired Engineering combines synthetic biology, nanobiotechnology and other approaches that leverage biological design principles to develop new engineering solutions for medicine and non-medical fields never before touched by the biology revolution. By emulating biological principles of self-assembly, organization and regulation, we are developing disruptive technology solutions for healthcare, energy, architecture, robotics, and manufacturing, which are translated into commercial products and therapies through formation of new startups and corporate alliances. For more information about the Wyss Institute, please visit ***www.wyss.harvard.edu***.

National Institute of Dental and Craniofacial Research

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to improve dental, oral, and craniofacial health.

We accomplish our mission by:

- Performing and supporting basic, translational, and clinical research;
- Conducting and funding research training and career development programs to ensure an adequate number of talented, well-prepared, and diverse investigators;
- Coordinating and assisting relevant research and research-related activities among all sectors of the research community;
- Promoting the timely transfer of knowledge gained from research and its implications for health to the public, health professionals, researchers, and policy-makers.

For more information about NIDCR, please visit ***www.nidcr.nih.gov***.

Michigan • Pittsburgh • Wyss
Regenerative Medicine Resource Center

Mission

Michigan-Pittsburgh Regenerative Medicine Resource Center's mission is to strategically partner with scientists, engineers and clinicians to translate dental, oral and craniofacial tissue engineering and regenerative medicine technologies to clinical practice market place. We assist by building a customized approach for success utilizing an innovative toolkit, access to an exclusive mentorship and an expansive community of translational resources.

Contacts

Program Administration

Patrick Cantini
University of Pittsburgh/McGowan Institute
450 Technology Drive, Suite 300
Pittsburgh, Pennsylvania 15219
(412) 624-5209
cantinip@upmc.edu

Interdisciplinary Translational Project (ITP) Program

Mutsumi Yoshida, PhD
University of Michigan
School of Dentistry
1011 North University Avenue, Room 3228C
Ann Arbor, Michigan 48109
(734) 764-4622
yoshidam@umich.edu