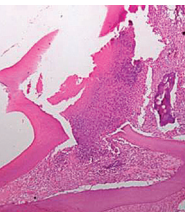
RegendoGEL: A Bioinspired Hydrogel System for Endodontic Therapy



PAMELA YELICK, PHD
Tufts University

LUIZ BERTASSONI, DDS, PHD
Oregon Health & Science 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."

www.bertassonilab.com

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

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 team led by Luiz Bertassoni, DDS, PhD and Pamela Yelick, PhD has developed a novel material for regenerative pulp treatment, intended to be the first-of-its-kind clinical product to promote vital pulp regeneration. RegendoGEL contains key stimulatory molecules found in healthy teeth that naturally promote pulp repair and regeneration, and may be used for direct pulp capping and pulpotomy.

COMPETITIVE ADVANTAGE

As compared to the existing synthetic rigid silicate or calcium hydroxide-based products currently used for endodontic treatments, RegendoGEL is a soft hydrogel system that more closely resembles the natural pulp tissue. Unlike traditional non-degradable cements, RegendoGEL stimulates cells to migrate into the defect site and regenerate living dental pulp tissue and dentin, thus revitalizing the tooth and regenerating tooth tissues in the target location. In addition, RegendoGEL is designed as a ready-to-use system that can be integrated into routine dental procedures in the clinic.

ITP SUPPORT

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. Sci Rep 2017.

Photopolymerization of cell-laden gelatin methacryloyl hydrogels using a dental curing light for regenerative dentistry. Dent Mater 2018.

Intellectual Property:
US 16/618,329 Dental pulp construct

US 15/777,304 Pulp regeneration compositions and methods of forming and using the same

Regulatory Pathway:
Anticipated: Device, IDE to enable 510(k)

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

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Contact Information:
Mutsumi Yoshida, PhD | Managing Director, U-M site | yoshidam@umich.edu | **www.doctrc.com**

RegendoGEL – a bioinspired hydrogel for endodontic therapy

Luiz Eduardo Bertassoni[1], Pamela Yelick[2]

[1] Oregon Health & Science University, [2] Tufts University

DOCTRC

DENTAL, ORAL, & CRANIOFACIAL TISSUE REGENERATION CONSORTIUM

Michigan · Pittsburgh · Wyss Regenerative Medicine Resource Center

Annual Retreat 2020 | December 8, 2020

UNMET CLINICAL NEED

Dental caries is the most prevalent chronic infectious disease in humans. It has an estimated prevalence of over 90% of adults and 20% of children in western countries. If not treated, virtually all caries lesions will progress to affect the dental pulp, eventually requiring some form of endodontic treatment. The current gold standard of care for teeth with extensive caries or non-carious injury is direct pulp capping, or pulpotomy, which propose a partial amputation of dental pulp and replacement with either with a silicate cement (i.e. MTA) or the fixation of remaining pulp tissue using formocresol (Fig 1). Silicate cements are non-resorbable, and result in complete loss of pulp tissue responses. Formocresol contains 20% formaldehyde, and is officially classified as a potent carcinogenic as defined by the Center for Disease Control. ***There is an important need to develop improved materials for pulpotomy treatment that allow for regeneration (rather than amputation) of dental pulp and the lost dentin tissue.***

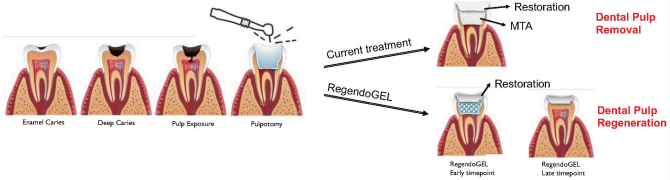


Fig. 1. Comparison of outcomes from current treatment for pulpotomy with MTA or RegendoGEL

MARKET ANALYSIS

Avenues

Interviews with clinical experts in Endodontics

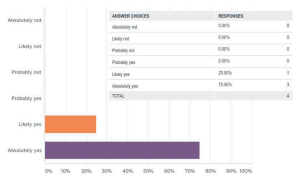


Fig. 2. Answers to the question: 'Is there an unmet clinical need for this product in your practice?'

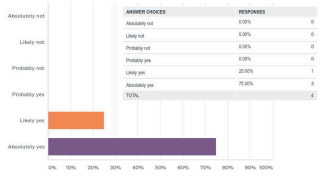


Fig. 3. Answers to the question: Is there a need for this product in 'high value' indications in your practice?

- Most respondents agreed that there is an unmet clinical need for root canal therapy because MTA and Biodentine are not permanent and will need to be replaced a few years down the line.
- For most endodontists, it was agreed that RegendoGEL would be a "high value" indication. They would not need it very often, but when they do this material would make their lives a lot easier
- Very positive feedback: ***RegendoGEL is the first product that will regenerate the dentin and keep the structure of the tooth intact. RegendoGEL is the ideal material for pulpotomy cases; if it is long lasting and has the ability to regenerate the original tooth dentin, tooth structure is never lost.***

INTELLECTUAL PROPERTY

- OHSU/Tufts Tech Transfer office have been supporting our work since the beginning of this grant resulting in the submission of **3 IP patents/disclosures** (pending or issued).
- Additionally, our group have the support from the Oregon Clinical and Translational Research Institute (OCTRI), via its biomedical innovation program (BIP) in developing and implementing commercialization strategies for RegendoGEL.
- We have partnered up with Research Bridge Partners, a business development firm, that is advising on all issues related to IP and commercial development in the PI's laboratory and particularly on RegenedoGEL commercial development.

RESULTS

1. RegendoGEL Synthesis

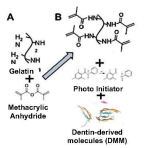


Fig. 4. Composition of RegendoGEL

2. Microgels

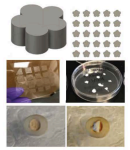


Fig. 5. RegendoGEL fabrication

3. Cytotoxicity microgel size effect

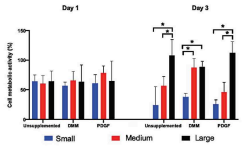


Fig. 6. Larger microgels promote higher cell metabolic activity (MTT assay).

4. Cell migration Microgel size effect

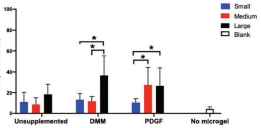


Fig. 7. Larger microgels promote higher cell migration (Transwell assay). ANOVA, Tukey post-hoc

5. Effect of sterilization on cell migration and metabolic activity

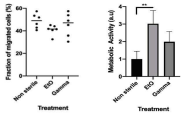


Fig. 8. Sterilization does not interfere with RegendoGEL biological function (MTT and Transwell assays). ANOVA, Tukey post-hoc.

6. Scalability

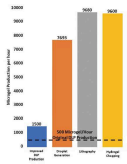


Fig. 9. Hydrogel chopping is the best method to scale up the fabrication of RegendoGEL.

7. Orthotopic study in rats

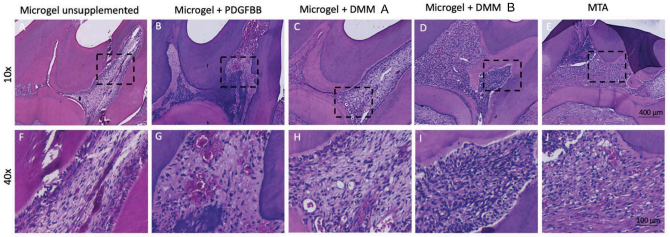
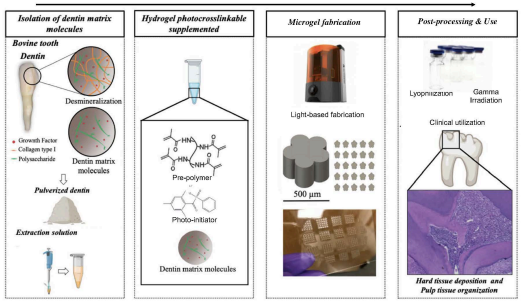


Fig. 10. Microgel unsupplemented, supplemented with PDGFBB (positive control) and supplemented with DMM formulation A presented more vessels and less inflammatory infiltrate compared to microgel + DMM formulation B and MTA group (gold standard).

MANUFACTURING



- Consulted with Mayo Clinic GMP facility to begin manufacturing in 2021 if approved by advisory team and consortium leadership

REGULATORY PATHWAY

- MDRS LLC. determined RegendoGEL to be regulated by the FDA as a class II medical device
- It will require a pending premarket notification (PMN) or 510k submission for clearance by the FDA
- MDRS anticipates a substantial equivalence to known predicate devices via a stacked predicate approach

- RegendoGEL is currently completing milestones to freeze formulation:
  - A. Determination of size variation of microgels (completed)
  - B. Ensuring ability to scale up manufacturing per GMP requirements (completed)
  - C. Determination of reproducibility of active compound isolation from tooth matrix (experiments ongoing)
- Next GMP plans will be discussed and reviewed with Regulatory & QAQC Core to ensure that the CRO is pre-qualified to do the proposed work.

TIMELINE & FUTURE DIRECTIONS

	1st Funded project 2019/ 2020	2nd Funded project 2020/2022 Milestone 1	Milestone 2	Milestone 3	Milestone 4
Research/ Technical	USDA Sourcing Isolation of active ingredient Hydrogel Optimization Microgel development In-vitro validation of active ingredient Determination of: > 50% more cell metabolic activity than MTA > 50% more cell migration than MTA > 50% more cell invasion than MTA In-vivo validation – subcutaneous model - rats In-vivo validation – orthotopic model- rats	In-vitro test of the size effect of microgels Larger microgels promote more DMM release, cell migration and metabolic activity	In-vivo dogs – Pittsburgh - Inflammation - dentin formation Batch-to-batch variation of DMM components - Proteomics - In-vitro migration - In-vitro metabolic activity	Fabrication of RegendoGEL in a GMP facility	Prototyping Sterilization, packaging
Regulatory	Regulatory Pathway 510k Finalized Regulatory Basis Letter to be sent to the FDA is complete – Kay Fuller		Freeze formulation Letter to FDA	QA/QC	FDA discussions
Business ITP	3 patents – pending or issued Market assessment – Avenues (Francine) – very positive feedback	Map out production chain	Strategize business model with SciVelo	1. Business Partner (license agreement) OR 2. PI's start up – assistance of Research Bridge Partners	

- GMP manufacturing (Mayo Clinic) and GLP testing (Charles River) planned for completion by early/mid 2022

REFERENCES

- Horsophonphong S, Sercia A, Franca CM,et al. Equivalence of human and bovine dentin matrix molecules for dental pulp regeneration: proteomics analysis and biological function. *Archives of Oral Biology*
- Subbiah R, Hipfinger C, Tahayeri A, Athirasala A, Horsophongphong S, Thrivikraman G, Franca CM, Cunha DA, Manssorifar A, Zahariev A, Jones JM, Coelho PG, Witek L, Xie H, Guldberg RE, Bertassoni LE. 3D printing of microgel-loaded modular mirocages as instructive scaffolds for tissue engineering. *Adv Materials*. 2020