Immunomodulatory Strategies to Treat Periodontal Disease

CLINICAL NEED

Periodontitis affects nearly half of adults over of 30 in the U.S. If left untreated, dental implants and bone grafting procedures may be required. Antibiotics are currently used as an adjunct therapy to scaling and root planing, which remains the standard of care. With a shift away from antibiotics overuse, new treatment modalities that address the host immune response are needed.

SOLUTION

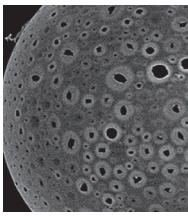
A team at the University of Pittsburgh led by Drs. Steven Little and Charles Sfeir has developed controlled release systems that repair the underlying immunomodulation dysfunction responsible for tissue degeneration in periodontitis. Both systems induce homeostasis and thereby reduce inflammation and destruction to promote tissue regeneration, either through recruiting regulatory T cells or polarizing M0-M1 to M2 macrophages.

COMPETITIVE ADVANTAGE

While bacterial removal has shown clinical benefit, it does not directly address the chronic inflammatory response. By targeting the underlying immunoregulatory discourse, these controlled release systems are thought to overcome the current limitation in the treatment of periodontal diseases.

ITP SUPPORT

With the goal of FDA submissions, the ITP program is supporting the GMP-grade manufacturing and development of sterilization protocols, and establishing the effectiveness in a larger animal model for the regulatory T cell recruitment and macrophage polarization systems, respectively.



STEVEN LITTLE, PHD
University of Pittsburgh

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University of Pittsburgh

"This new class of treatments is extremely exciting in that organizing extraordinarily tiny amounts of proteins that are already found in the body seems 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
www.dental.pitt.edu/person/charles-s-sfeir-0

CLINICAL TRANSLATION PATHWAY

Publications:
Prevention of Inflammation-Mediated Bone Loss in Murine and Canine Periodontal Disease via Recruitment of Regulatory Lymphocytes. PNAS 2014.

Restoring Host-Microbe Homeostasis via Selective Chemoattraction of Tregs. J Dent Res 2014.

Induction of M2 Macrophages Prevents Bone Loss in Murine Periodontitis Models. J Dent Res 2019.

Intellectual Property:
US 8,846,098 Artificial cell constructs for cellular manipulation

Provisional patent application filed

Regulatory Pathway:
Anticipated: Biologic, IND to enable BLA or NDA

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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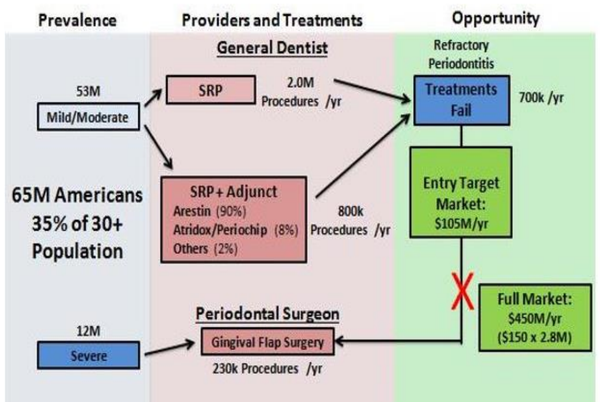
UNMET CLINICAL NEED

- Periodontitis one of the most pressing oral health care concerns. In 2010 ~65 million Americans were found to have periodontitis[1]
- Current treatment options focus on physical removal in combination with systemic administration of antibiotics
- WHO has noted the need to switch away from the use of antibiotics in general because of antibiotic resistance[2]
- **Current treatment approaches fail to address the uncontrolled host immune response that is responsible for most of periodontal damage and disease progression.**

MARKET ANALYSIS

- ~15 to 20% of patients do not respond to traditional antibiotics or physical removal
- 25% of 2.8M procedures done on mild/moderate patients fail (refractory periodontitis). With a treatment cost of $150 per use, we could reach an entry target market size of $105M
- Potential to reach an estimated full market of $450 M/year



- Recent data shows that the developed therapy is not only effective to prevent periodontal disease but to also treat active periodontitis

INTELLECTUAL PROPERTY

Patent/ IP information (appl/ serial #)	Date filed	Title	Assignee	Status (pending/ issued)	Licensing status (licensed/ optioned/ 3rd party obligations?)
US 13/383,122 PCT/US2010/041463	7/9/2010	Artificial Cell Constructs for Cellular Manipulation	University of Pittsburgh	Issued 9/30/2014	n/a
provisional 62/963,632		Treatment of Periodontitis via induction of m2 macrophages	University of Pittsburgh	Submitted 1/2020 PCT will be submitted January 2021	n/a

RESULTS

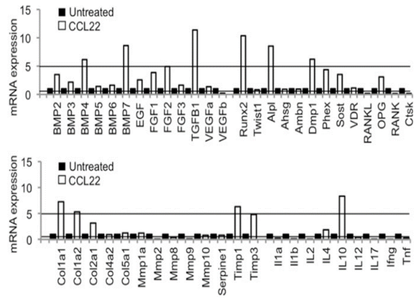


Figure 1 : Treg recruiting microspheres lead to an increase in expression of osteogenic, regenerative, and anti-inflammatory markers in periodontium

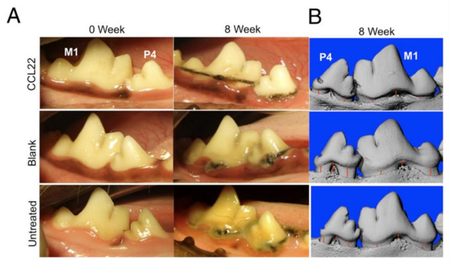


Figure 2: Treg recruiting CCL22 formulation diminished clinical severity of inflammation in preclinical canine model of periodontitis **(A)** Pictures of ligature after 0 wk. and after the 8 wk. of treatment **(B)** 3D images taken postmortem via microCT scan

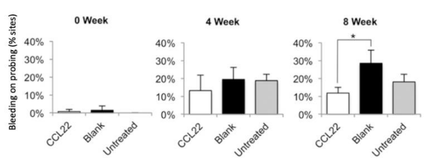


Figure 3: The percentage of bleeding sites on probing of all the probed sites at 0, 4, and 8 wk.

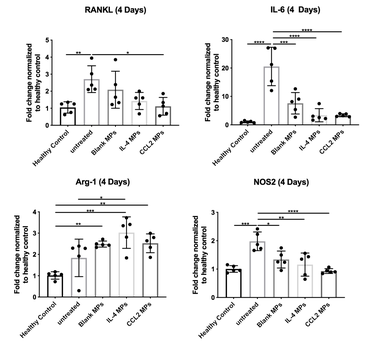


Figure 4: QPCR analysis of Macs polarization and bone resorption markers

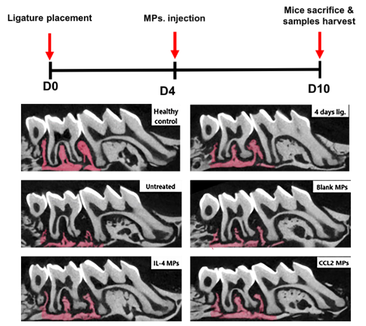


Figure 5: M2 Macs local induction as an **interventional therapeutic approach** for **murine periodontitis**

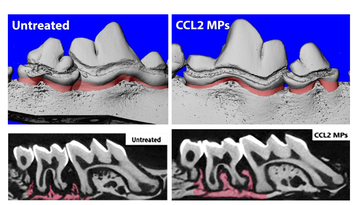


Figure 6: CCL2 formulation prevented the establishment of periodontal disease in canine model compared to sites receiving ligatures, but no CCL2.

MANUFACTURING

- cGMP grade manufacturing of CCL22 PLGA microspheres by CRO (University of Tennessee Plough Center)
  - Aseptic manufacturing to avoid loss due to terminal sterilization
- Production of rCCL2 by CRO (ProteinOne)

REGULATORY PATHWAY

- CCL22/CCL2 microspheres as an adjunct therapy to scaling and root planning
- Considered by FDA to be a biologic therapeutic (if recombinant version of API selected vs. considered as drug if solid state version of API selected).
- Division of Dermatology and Dental Products (DDDP) would hold oversight for Biologics License Application (BLA) or New Drug Application (NDA)

TIMELINE & FUTURE DIRECTIONS

ITP Cycle 4 Goals

Months 1-3	Months 4-6	Months 7-9	Months 10-12
Assessment of CCL22/CCL2 clinical applications	Selection of CCL22 API	cGMP manufacturing of pre-clinical grade CCL22 microspheres	Evaluation of cGMP manufacturing of pre-clinical grade CCL22 microspheres
Post API encapsulation activity evaluation via standardized R&D system assay	API Stability testing in accelerated conditions	Production of rCCL2	Analytical testing of rCCL2

Upcoming Years:

- Preparing for Pharmacokinetic and IND-directed toxicology studies for API - CCL22/ CCL2
- cGMP Manufacturing of CCL2 Microspheres

REFERENCES

1. Eke, P. I., Dye, B. A., Wei, L., Thornton-Evans, G. O. & Genco, R. J. Prevalence of Periodontitis in Adults in the United States: 2009 and 2010. *J. Dent. Res.* **91,** 914–920 (2012)
2. World Health Organization. Antimicrobial Resistance Global Report on Surveillance. *WHO* (2014).

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