Vital-Dent, A Revitalizing Root Canal Implant

CLINICAL NEED

Over 15 million root canal therapy (RCT) procedures are performed each year to treat carious infected teeth. Conventional RCT removes infected pulp tissue and fills the void with inert materials. The long-term survival of treated teeth is limited because the tooth is dead; it cannot mount an immune response to fight reinfection. On average, periapical infection is evident by 10 years, and the tooth is lost by 20 years.

SOLUTION

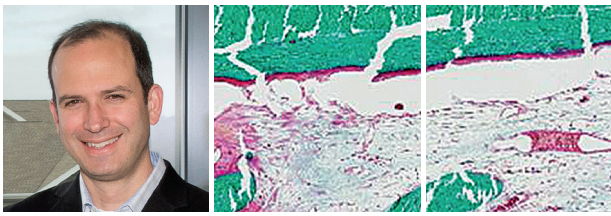
A team of researchers at the University of Pittsburgh, led by Drs. Juan Taboas and Herbert Ray, is developing a device to regenerate vital tissue within RCT-treated teeth. The two-part drug-free material system, termed Vital-Dent, is designed to be an off-the-shelf implantable device that replaces conventional sealers with a hydrogel and conventional obturating points with a sponge.

COMPETITIVE ADVANTAGE

Vital-Dent is anticipated to increase the long-term survival of the tooth by guiding ingrowth of cells and generating vascularized tissue capable of mounting an immune response. In a preliminary canine study, Vital-Dent showed regeneration of vital tissue within the RCT-treated roots, with mineralized tissue along the dentin walls, and vascularized fibrous tissue in the root canal proper, up to the crown sealer.

ITP SUPPORT

The ITP program will support the evaluation of Vital-Dent towards a design freeze of the device composition and delivery process, analyzing regenerated tissue composition and outcomes, as compared to revascularization procedure and conventional treatment with resin sealer and gutta-percha points.



JUAN TABOAS, PHD

University of Pittsburgh

"Vital-Dent is an off-the-shelf device that regenerates living tissue in root canal therapy treated teeth and prolongs tooth survival."

www.dental.pitt.edu/person/juan-m-taboas-1

CLINICAL TRANSLATION PATHWAY

Publications:
Acellular hydrogel regenerates a vascularized tissue producing organized mineral along the instrumented canal wall. Pulp Biology and Regeneration Group Satellite Meeting: Basic and Translational Research in Pulp Biology – Developing Technologies for Regenerating Vital Dental Tissues, 2019.

Intellectual Property:
PCT/US2019/023132
Regeneration of Vital Tooth Pulp

Regulatory Pathway:
Anticipated: Device, IDE

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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Vital-Dent, a Revitalizing Root Canal Solution

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DOCTRC DENTAL, ORAL, & CRANIOFACIAL TISSUE REGENERATION CONSORTIUM

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UNMET CLINICAL NEED

Traumatic injury and bacterial insult cause pulpitis in the pediatric population (6-14 years-old). Inflammation and necrosis often occurs only in the coronal pulp leaving the radicular pulp viable. The AAPD and AAE recommend vital pulp therapy (VPT) for immature permanent teeth with reversible pulpitis because the roots need to develop to establish full strength. VPT encompasses several procedures that aim to preserve compromised but vital pulp and thereby conserve tooth vitality, structure, and immune response, ultimately reducing long-term treatment costs.

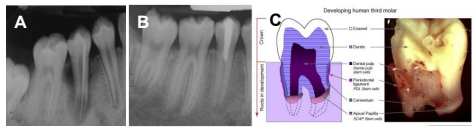

Figure 1. (A) Periradicular radiolucency in an infected permanent tooth in a juvenile. (B) Successful treatment with revascularization therapy. (C) Tooth anatomy and stem cell pools in growing teeth. (See references 4 and 5)

VPT procedures such as pulpotomy, apexogenesis, and revascularization have high success but several disadvantages including discoloration of teeth, loss of tooth structure, and deposition of dentin only along the root apex. Moreover, the AAPD and AAE recommend VPT only on a healthy or traumatically exposed pulp of permanent young teeth, not for reversible pulpitis from carries and not for irreversible pulpitis.

MARKET ANALYSIS

Pediatric pulpal procedures comprise approximately 20% of all pediatric cases in dental clinics. We estimate capturing 5% of the pediatric pulpal procedures in the first two years in market. ADA reporting does not capture the specific procedure types to precisely estimate the market. We are continuing our market analysis through practitioner interviews and extrapolation from ADA, AAE, and AAPD historical reports.

In the long-term, we expect Vital-Dent expand in market to root canal treatment (RCT) in the adult population. RCT is used to treat carious infected teeth, with over 15 million procedures performed annually in the US (1). Conventional RCT therapy removes infected pulp tissue and obturates with inert materials to eliminate space for bacterial ingrowth and to preserve tooth structure and mechanical function. However, the dead tooth is incapable of mounting an immune response to fight potential reinfection. 10% - 30% of conventional RCTs fail in the short-term due to inadequate disinfection and practitioner error (2). In successfully treated teeth, the long-term survival is approximately 20 years, but diagnosis of post-treatment disease occurs earlier, at an average 10 years (3). Unfortunately revascularization therapy proves inconsistent in adults because mature teeth have a narrow apex and lack progenitor cells.

INTELLECTUAL PROPERTY

Vital-Dent is an acellular, drug-free, off the shelf implantable device to regenerate vital tissue after pulpotomy and pulpectomy procedures. It consists of a colorless hydrogel in syringe and radiopaque porous sponge point. The hydrogel is inserted into the resected pulp space. The sponge is inserted if performing pulpectomy and if support for capping material or radiographic evidence of treatment are needed. The hydrogel supports migration of progenitor cells from the periapical space, through the opened apex, and into the tooth root. The implant is resorbed within half a year and completely replaced with living tissue, permitting continued root / tooth development. In contrast to the conventional VPT, Vital-Dent can be used in teeth diagnosed with both reversible and irreversible pulpitis with / without apical periodontitis. We have patents pending on this technology in the USA (PCT/US2019/023132), the European Union (# 19771745.7), and Japan (# 2020-550177).

RESULTS

To date, 192 roots in 12 adult beagle dogs (the premolars P2-P4 and first molar M1) have been treated with RCT comparing Vital-Dent formulations to revascularization therapy (Clot) and to conventional obturation with gutta-percha. Vital-Dent and revascularization therapies include drilling through apex. 32 roots were allocated to compare the efficacy of adding chemotactic and angiogenic drugs to the Vital-Dent formulation; these have been fully analyzed. The remaining roots were allocated to compare the material formulation of the hydrogel (gelatin + heparin versus gelatin + chondroitin sulfate) to revascularization and gutta percha; These have been µCT scanned and are in histological processing with the first 15 currently in sectioning.

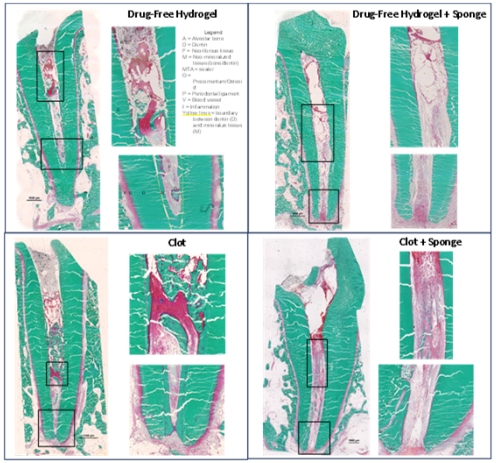

Figure 1. Regenerate tissue after three months growth. Stain = Goldner's trichrome.

Treatment with Clot and the drug free Vital-Dent hydrogel induced formation of mineralized tissue along the canal walls (over 50% of canal wall for Clot and drug-free hydrogel) and in the canal proper (12-20% of canal area, Figures 1 and 2). Based on FTIR imaging, the mineral tissue was similar to dentin (though less mature) and not to bone (Figures 3 and 4). The sponge appeared to reduce formation of mineralized tissue in the canal across all groups (Figures 1 and 2). No dystrophic calcification of the canal space occurred in the drug-free hydrogel, but large volumes of mineralized tissue were evident at the MTA interface and/or apex in the Clot group. No infections occurred in treated teeth. The drug containing formulations did not afford an advantage over the drug-free.

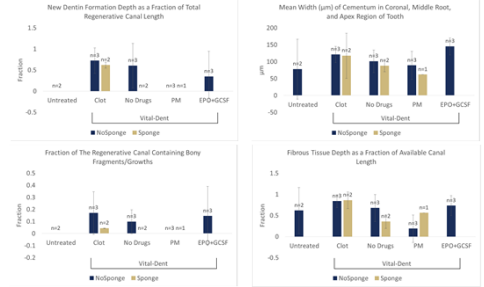

Figure 2. Quantification of regenerate tissue composition after 3 months growth.

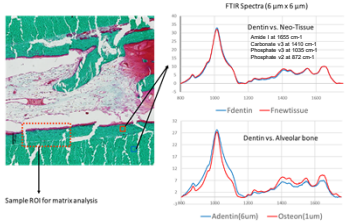

Figure 3. FTIR signal of neo-mineralized tissue along dentin wall versus of dentin proper and of alveolar bone.

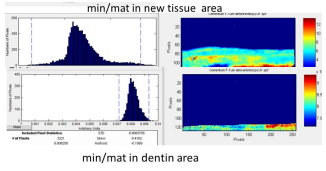

Figure 4. FTIR signal mapping of mineral to matrix. Ratio of min/matrix varies along length of the root, with highest ratio at apex (possibly oldest neotissue).

MANUFACTURING

We manufacture all components of the implant device in-house. For the hydrogel, we methacrylated porcine gelatin (Type B, Mr = 40,000- 50,000) and sodium heparin (intestinal mucosa, Mr = 15,000) per the methods of Nichol et al. 2010 and Schuurman et al. 2013. We synthesized LAP (the photoinitiator) via the method of Majima et al. 1991. For the sponge, dip coat fine needles in a gelatin solution followed by drying and thermal denaturation to create hollow tubular points similar in geometry to gutta percha points. The hydrogel and sponge scaffolds are physically characterized for chemical and mechanical properties, and for cytotoxicity on stem cells. The hydrogel polymers were methacrylated to high degree, with the gelatin showing 100% modification of lysine residues (Figure 5) and heparin 10% of saccharide units. The hydrogel and sponge were not cytotoxic as determined by Live/Dead assay (Figure 6). Neither the hydrogel or its components (LAP, methacrylated heparin and gelatin) showed lower viability compared to untreated cells (n=3).

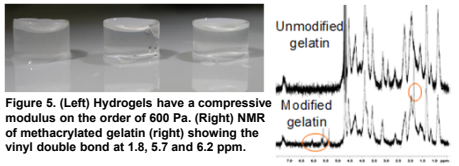

Figure 5. (Left) Hydrogels have a compressive modulus on the order of 600 Pa. (Right) NMR of methacrylated gelatin (right) showing the vinyl double bond at 1.8, 5.7 and 6.2 ppm.

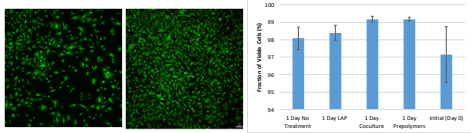

Figure 6. (Left) Goat primary bone marrow stem cells subjected to co-culture with the drug-free Vital-Dent hydrogel. (Right) Quantification of cell viability subject to co-culture with the hydrogel or to medium supplementation with precursor components of the hydrogel (i.e., LAP, uncrosslinked prepolymers).

REGULATORY PATHWAY

Our regulatory strategy is to seek 510(k) designation given predicate tooth and bone-filler devices, with an IDE designation as acceptable. We are currently seeking designation through the pre-RFD process in which additional studies to further define the device's MOA were deemed necessary. In addition, the histological results of the material formulation study will determine whether the heparin component is essential for function. Though made from animal products, Vital-Dent contains no biologic or drug components beyond the animal products that compose the scaffold device.

TIMELINE & FUTURE DIRECTIONS

We are working towards evaluation of Vital-Dent for the pediatric indications and furthering commercialization. We anticipate initiating our pre-clinical study in two years and our first clinical study in the USA in four years.

1. Determine PMOA of hydrogel components on cell infiltration using in vitro assays
2. Comparative effectiveness study in juvenile beagle dogs to direct pulp capping, pulpotomy, revascularization and apexogenesis
3. Analyze immune responsiveness of treated teeth in dogs with periodontal infection
4. Build IP portfolio with disclosure of PMOA and pediatric applications
5. Pre-RFD from FDA using PMOA data
6. Market analysis for pediatric population
7. Business development with biotech accelerators and investment firms

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