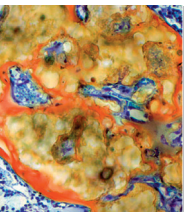
Optimization of a Novel Organic-Mineral Bone Adhesive



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LaunchPad Medical

"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

CLINICAL NEED

Although over 50% of adults over the age of 45 in the US have one or more missing teeth, only 2% of the eligible population receives a prosthetic tooth due to factors including time involved in multi-stage bone grafting procedures and associated costs. While most bones grafting materials demonstrate osteoconductivity to regenerate bone, many suffer from poor mechanical properties, necessitating 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 which can create a strong load-bearing bond between 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. Given these unique properties, the material is predicted to eliminate the need for ancillary or graft containment devices currently required to support the existing bone graft. In addition, Tetranite enables immediate placement of implants simultaneous to the bone augmentation procedure, simplifying the bone grafting procedure. The reduction in surgical intervention and costs are expected to enable prosthetics to more widely benefit patients.

ITP SUPPORT

The work supported by the ITP program will prepare for 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:
Optimization of a Novel Organic-mineral Bone Adhesive for Dental Bone Grafting. Presented at IADR General Session 2019, Academy of Osseointegration Annual Meeting 2019

Intellectual Property:
US 8,232,327, US 8,273,803 Tetra calcium phosphate based organophosphorus compositions and methods

US 8,765,189 Organophosphorous and multivalent metal compound compositions and methods

Regulatory Pathway:
Anticipated: Device, 510(k)/de novo (clinical trial underway for dental implant stabilization)

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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Optimization of a Novel Organic-Mineral Bone Adhesive for Dental Bone Grafting

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Annual Retreat 2020 | December 8, 2020

UNMET CLINICAL NEED

Based on market research conducted by RevBio, almost half the patients that seek a dental implant supported crown suffer from chronic edentulism and require extensive bone grafting to rebuild their alveolar ridge (Figure 1), and over 30% of the time, these grafting procedures achieve less than desired results and require some form of re-grafting (Figure 2) adding to the overall cost, treatment time, and morbidity for these patients.

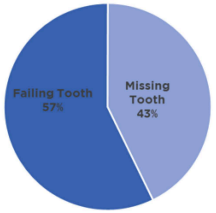

Figure 1. Patient Presentation at Initiation of Implant Treatment[1]

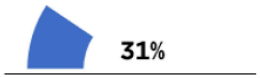

Figure 2. Percentage of Grafting Cases Requiring Subsequent Augmentation

The goal of this project was to optimize a synthetic, injectable, cohesive organic-mineral bone graft biomaterial with adhesive properties called Tetranite® (TN) so that this material resorbs and is replaced by bone on a timescale commensurate with existing graft materials but does not require ancillary fixation (screws, tacks) or containment devices (membranes, mesh).

MARKET ANALYSIS

A marketing survey was conducted with significant support from The Avenues to verify the need for a grafting product with the unique attributes of TN. Twelve key opinion leaders in the field of dentistry were interviewed using a scripted set of questions to guide the discussions. A follow-up online survey was also conducted to generate quantitative data to support the qualitative data collected in the interviews.

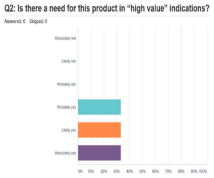

Figure 3. Survey Results for Product Use

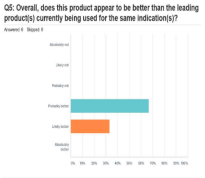

Figure 4. Survey Results for Product Superiority

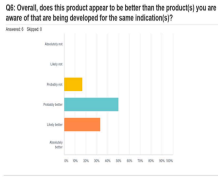

Figure 5. Survey Results for Known Better Solutions Under Development

Results of the marketing study conclusively evidence that a strong value proposition exists for TN as a bone graft material for complex procedures such as ridge augmentation and sinus floor lifts (Figure 3), and that its unique handling properties and product attributes would clearly differentiate TN from other existing grafting solutions (Figure 4). Most of these key opinion leaders also indicated a strong interest in adopting this product into their own clinical practice, which provides a strong rationale and incentive for continuing to invest in the development of this product. Furthermore, perhaps most importantly, none of the key opinion leaders or industry representatives knew of a better solution currently under development (Figure 5). This analysis confirmed that continued efforts for the commercialization of this project are justified.

INTELLECTUAL PROPERTY

RevBio has an exclusive, worldwide license from Stryker to several patent families covering both the composition of Tetranite, and derivations to it, as well as specific methods for its use. The most relevant patent families that cover the technology and specific uses related to this project are issued in the U.S.: #8,232,327, #8,273,803, #9,265,857 and #8,765,189. These patent families expire between 2029 and 2033, providing a lengthy period of protection enabling RevBio to develop and sell TN without the threat of direct competition. Within the terms of the license agreement, RevBio also has the right to manage the ongoing prosecution of both domestic and international patent filings, as well as the right to secure patents for derivative formulations and inventions associated with the base patented technology. As a result, RevBio filed eight PCT patent applications, five of which have since published, all of which will expand the patent estate.

RESULTS

A pilot animal study in a relevant large animal model (mixed breed hounds) was conducted using the criteria specified by the FDA to support the translation to humans as part of an IDE application.[2,3] The mandibular premolars and first molars were extracted bilaterally in 5 adult canines (Marshall BioResources, New Rose, NY) using the same bone grafting defect model published by Nakajima, et. al.[4] Three months after the extractions, eight rectangular defects (7mm apicocoronally, 7mm mesiodistally, and the entire width of the ridge buccolingually) were surgically created in the alveolar processes to ensure critical-size defects (Figure 6).

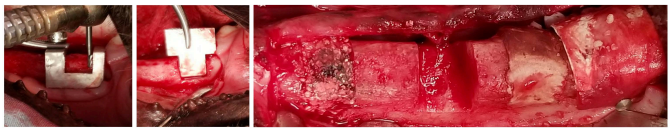

Figure 6. Surgical Defect Creation and Deposit of TN Bone Graft Formulation, consisting of TN3 (left), empty defect (center 1), TN1 (center 2), Allograft with membrane-MC2 (right)

The bone graft biomaterials used in this study consist of four TN test groups, two market controls (a cartridge-based injectable putty form of bioactive glass (NovaBone, Osteogenics Biomedical, Inc., Lubbock, TX), MC1, and demineralized freeze dried bone allograft (OraGRAFT®, LifeNet Health, Virginia Beach, VA) used in conjunction with a resorbable membrane and fixation screws, MC2, and two negative controls (empty defect sites filled with a blood clot with and without membranes), BCM and BCO, respectively, which were randomly assigned for placement into each of the 40 rectangular defects. Overall, each graft material was placed in 5 defect sites as per the original pilot study design.

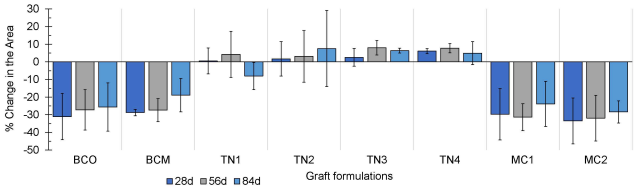

Figure 7. Ridge Area Maintenance of the Graft Materials relative to Time 0d
(Time 0d is when the graft materials were implanted immediately following the defect creation)

In Figure 7, CT analysis shows that the blood clot with membrane (BCM) performed only marginally better than the blood clot without a membrane (BCO). Furthermore, the performance of the market controls was similar to the negative control with an average reduction in ridge height of approximately 20% over the course of the period of examination. Only NovaBone (MC1) showed an initially reduced level of ridge height resorption at the 28-day and 84-day time points. In comparison, TN2, TN3, and TN4 all showed no reduction in the ridge height. Only TN1 showed an approximate 10% reduction in volume.

While all TN formulations (TN1-4) demonstrated their ability to maintain ridge height, TN3 showed the most rapid turnover. Building on those findings, new formulation (TN5) was developed with enhanced porosity to further optimize the rate of turnover. In a subsequent canine *in vivo* study, TN5 was implanted into a fresh alveolus and was allowed to heal for 10 weeks. Following necropsy the sites were prepared for histological evaluation of ground section samples (Figure 8).

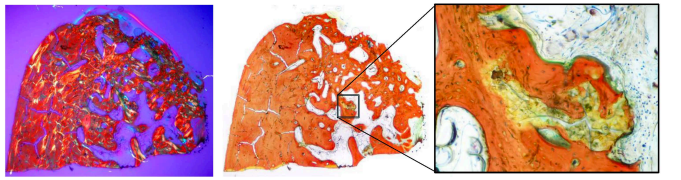

Figure 8. Coronal Plane through site of deposit of TN5 material into fresh alveolus. 10 weeks post implantation. 1. Polarized low magnification (left), 2. Bright field low magnification (center), 3. Bright field high magnification (right)

The architecture shown in the bright field image (center) and the orientation of collagen fibers in the polarized light image (left) indicate new bone that has been deposited as a replacement for the TN5 material in the area of deposition. The highlighted detail shows the only remaining TN5 material in the high magnification image (right), the remaining material having turned over to newly deposited bundle bone. No significant volumetric change occurred throughout the process.

MANUFACTURING

RevBio has developed a product kit representative of the anticipated commercial system which contains a sealed mixing bowl containing TN, a pre-filled syringe containing water to mix the adhesive graft, a mixing spatula, and an open bore delivery syringe, all assembled, sealed and sterilized within a blister tray assembly (Figure 9). The delivery syringe is an off-the-shelf commercial system, which allows the TN material to be dispensed with control to the defect site.

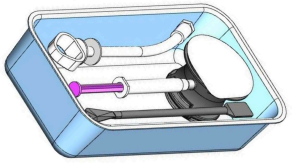

Figure 9. Final Product Kit and Packaging

RevBio has developed a pilot manufacturing process that is capable of producing 4,000 units of product during a 5-day production cycle. In the next phase of development the manufacturing process will be validated. Based on an internal production capacity analysis, the existing manufacturing process can be easily scaled by duplicating the existing pilot production line.

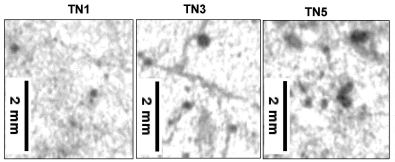

Figure 10. Qualitative analysis of pore size/ porosity using µCT

The company has developed a lot release protocol which is conducted to characterize the physicochemical and mechanical properties of TN bone graft. A key parameters include compression strength, phase composition, exotherm, pH and pore size/porosity as exhibited in Figure 10 using uCT.

REGULATORY PATHWAY

FDA previously designated TN to be a device when used in conjunction with dental and orthopedic fixation devices. In January, 2020, the Company filed a Pre-Request for Designation (Pre-RFD) with the FDA Office for Combination Products (OCP) to address the stand-alone use of TN as a bone grafting material. To date, the review has taken more than 230 days with the FDA reviewers citing delays due to the COVID-19 crisis.

TIMELINE & FUTURE DIRECTIONS

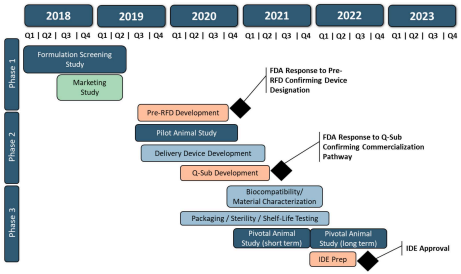

Figure 11. Product Development Plan & Milestones

Since the initiation of this product development effort significant progress has been made. In December, 2020, RevBio will initiate its pivotal animal study. (Figure 11) The results of this study will be used to prepare an Investigational Device Exemption (IDE) application for the FDA. Based on the Pre-RFD review, either a 510(k) clearance or a De Novo approval will likely result in the commercialization of this product

REFERENCES

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