Project Proposal

Ultrasound Mediated Tissue Engineering Project
Team 21

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Project 40
for
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Executive Summary:

Tissue-engineered systems involve the use of cells, growth factors, and scaffolds to repair and restore tissue function. Ultrasound is used as a treatment for clinical fracture repair. Evaluating the mechanism behind the efficacy of low intensity pulsed ultrasound for fracture repair has revealed the existence of a small mechanical force that may be beneficial to repairing musculoskeletal tissues using tissue-engineered scaffolds. Using the elements of hydrogel scaffold synthesis, ultrasound, and principles of musculoskeletal tissue regeneration, a fracture repair device is designed.

The proposed device is designed to enhance current techniques of bone formation in a more efficient and a minimally invasive way. It will serve as an alternative solution to surgical methods of healing bone fractures, especially since the medical industry is shifting towards least invasive methods of treatment. This device will also serve as the answer to healing non-union fractures, or fractures that do not heal on their own for unknown reasons.

Compared to other systems in the medical industry, this project is low-cost and has research proving its future success. Recent data has proven that a low intensity ultrasound beam mimics the effect of mechanical loading on bone formation. ANSYS simulation of the mechanical forces on various viscoelastic ranges will serve as the preliminary sketch for designing parameters of the system. This proposed system holds the potential to revolutionize orthopaedics by becoming the new standard in non-union fracture treatment.

1 Introduction:

1.1 Background (client and disability)

In the field of biomaterials, researchers and clinicians are constantly looking to improve the efficiency and rate of healing of fracture repair. It is shown for non-union fractures that all periosteal and endosteal repair processes will stop if there is no surgical intervention. Therefore, it is convenient to both the clinician and primarily the patient, to have a less invasive, alternative means for treatment. Delayed healing can lead to various complications such as infection, malformations of the healing site and a multitude of secondary defects.

The most common method of bone repair consists of resetting the joint or bone to a position of function, immobilizing it there and simply waiting for the natural healing cycle to occur. Up to 10% of fractures can be categorized as delayed-union or nonunion, both of which require secondary intervention [1]. These interventions usually require the bone to be connected to itself using a plate and bone screws. In some cases, improperly applied primary treatments result in nonfunctional healing processes such as hypertrophic non-unions.

Dr. Khan is a professor of Biomaterials at the UConn Health Center. His work with biomaterials has focused on orthopaedic devices and how they can be improved. Through his research, Dr. Khan has proven that osteoblasts form mineralized bone tissue faster when subjected to Low-Intensity Ultrasound (LIPUS). He would like a system to be designed that includes the necessary parts for a clinician to seed a tissue scaffold with osteoblasts and then inject it at the desired wound site. This can then be activated with an ultrasound in a procedure that is minimally invasive.
1.2 Purpose of the project

The purpose of our project is to design a non-union fracture repair device that will minimize the negative effects of current fracture repair methods. Our biomaterial scaffold will be constructed to create a three-dimensional (3D) environment. When designing a tissue engineering system, the choice of biomaterials that will be chosen for the scaffold must also be considered.

As mentioned previously, there are many negative effects to current bone tissue healing methods. Existing methods consist of autografts, allografts, and xenografts. With regard to autografts, the negative consequences include donor site morbidity, limited tissue supply, invasive surgical approach and risk of infection. The shortcomings of allografts and xenografts are immunogenicity, disease transmission, length of lifetime variation, graft-vs.host-disease, and the potential need for immunosuppression. Because of these deficiencies, there is a great demand by clinicians to have a less-invasive means that will reduce the risk of infection during fracture repair.

1.3 Previous Work Done by Others

Dr. Julius Wolff developed Wolff’s Law which states that bone is formed and resorbed in response to the stress applied to it. Bone responds to mechanical stimulation where a load induces bone formation and lowered load induces bone resorption. This is an important concept to understand while considering fracture repair since bone formation is key to healing at the site.

It has recently been discovered that low-intensity pulsed ultrasound can be used to stimulate the osteoblasts of injured bone when mechanical loading is not possible.

Ultrasound has historically been used for therapeutic soft tissue treatment, imaging and tissue destruction. However, recent results have shown that decreasing the intensity in ultrasonic beams can initiate cell proliferation, particularly osteoblasts and osteocytes. These devices transmit sound pulses into the body using a probe and are composed of four main parts. An electrical signal is sent through a transducer, which converts the signal to low amplitude mechanical vibrations. Next, the generator uses its electrical energy to convert these vibrations to vibrational energy by a transducer that contains a piezoelectric element. A low-intensity ultrasound uses lower intensities to prevent damage to tissues, as well as to provide a stimulus for cell proliferation.

Researchers have also learned how cells react to the administration of low-intensity pulsed ultrasound throughout the four stages of fracture repair. These stages are inflammation, soft-callus formation, hard-callus formation, and remodeling. It has also been proven in in vitro cell studies that low-intensity pulsed ultrasound exposure triggers the activation of hypoxia-inducible factor-1a and an increase in nitric oxide production. This leads to the increased expression of growth factors in osteoblasts which stimulates angiogenesis. Angiogenesis is the development of new blood vessels and is a key component in not only early bone repair but also as a necessary precursor to endochondral ossification [1].

1.3.1 Products
Pins, plates, nails and screws are the currently used for fracture repair where bone union wouldn’t otherwise occur on its own. However, these products all must be placed during open surgery, and no minimally invasive system has been proposed such as an ultrasound-mediated scaffold device system.

DBX Bone Graft Substitute is a commercially available product that is that consists of demineralized bone matrix from human donors in a biocompatible carrier that is fully degradable in six months [4]. The bone matrix is made of collagen and bone morphogenic proteins (BMPs), a type of bone growth factor. The carrier is sodium hyaluronate formed by plasma membrane proteins. This is injected into the bone fracture site and can be used to fill bone voids or gaps to promote bone growth, but cannot be used where mechanical stability is important to the bone structure. DBX must be used in conjunction with bone fixation devices as described above in order to maintain mechanical integrity.

The CMF OL1000 Bone Growth Stimulator [5] is the closest product on the market to our proposed design system. This is a treatment system designed for use with non-union fractures, similar to the goal of our design. However, this product uses an electromagnetic waves as its stimulator as opposed to ultrasound. The CMF OL1000 Bone Growth Stimulator can be used with internal or external fixation or over a cast.

1.3.2 Patent Search Results

United States patent number 7510536 is similar to the proposed system device, but this concerns the use of high-intensity ultrasound for use with nerve damage repair. It is held by Foley et al. and was issued on July 3, 2012.

Additionally, patent number 8,057,408, issued to Cain et. al on November 15, 2011, identifies a procedure of using pulsed cavitation ultrasound as therapy for bone repair, but as the proposed device will not be using cavitation, this is not a concern.

Patent 8,226,582 outlines the process of using a modal converter assembly used to deliver acoustic energy to a tissue sample to induce a healing effect. Specifically, the transducer is described as being perpendicular to the tissue surface and delivered as both shear and longitudinal waves.

The NELL-1 patent (8,207,120) was issued on Jan 26, 2012 and refers to an osteogenic polypeptide (NELL-1) that is has very favorable bone mineralization properties, and can be used as components of bone grafts or as a “stand alone agent” for enhancement of fracture repair.

Patent number 8,123,707 refers to a procedure for therapeutically treating connective tissue or increasing vascularization in tissue using ultrasound. This patent was issued February 28, 2012 to Huckle, et. al. This product focuses on treating spinal discs only, and the proposed device will use a similar pulsed ultrasound procedure, but aims to target in conjunction with a stabilizing scaffold in the wound.

However, these models are all significantly different than the proposed device and thus patent infringement is not an issue.

2 Project Description
2.1 Objective

The system designed will be composed of multiple components that work synergistically to promote bone healing in a minimally invasive manner. The scaffold, once implanted, should be rigid enough to maintain its position, but elastic enough to deform when exposed to the applied acoustic energy. The ultrasound waves will be used in a technique called acoustophoresis to promote osteoblast activity without mechanically loading the bone. This process utilizes sound energy to modify the position or concentration of cells and other particles. There are numerous changes in cellular level activity which all follow the standard definition of healing. One metric of change is increased levels of alkaline phosphate - a strong indicator of osteoblast differentiation. The overall healing effect can be summarized by the formation of an external osseous cortex and an intramedullary canal. Low intensity pulsed ultrasound has been proven to have this substantial effect on cell proliferation as well as differentiation.

2.2 Methods
Ultimately, Dr. Khan, would like an all inclusive system to be developed capable of fulfilling the requirements of a clinical orthopaedic treatment. A schematic demonstrating the usage of ultrasound based matrix loading can be seen in Figure 1 below.
In order to develop a scaffold, we will be modeling the viscoelastic behavior using a design tool called ANSYS. Viscoelasticity is a property that combines both elastic and viscous characteristics and possesses time dependent strain. The construction of the scaffold itself will be next in the procedure.

There are multiple parameters that need to be manipulated and tested with the design project. The finished system will clarify amount of cell movement and proliferation based off of specific frequencies of the ultrasound as well as consistencies of the scaffold. It will necessary to optimize material ratios based upon key measurements, and to adapt to allow for optimal results of the requirements of the system.

3 Budget

Overall, this can be considered a low-budget project. According to the client, everything necessary for this non-union fracture repair device can be created for under $10,000 easily. This is especially important to note since similar medical devices are usually at a higher price range.

There are other systems similar to this proposed design currently on the market that are around the $10,000 cost level. For example, Symphony II Platelet Concentrate System has a list price of $9,995.00 and concentrates the body’s natural growth factors which are found in platelets. This is similar to the proposed device because Symphony II is a system that contains the syringe needed to extract blood, and then the centrifuge needed to separate out the growth factors, while our design is for a system that consists of the scaffold that is to be injected and then the ultrasound to stimulate osteoblast proliferation. Another device that is similar to ours is the CMF OL1000 Bone Growth Stimulator, which uses electromagnetic waves to promote fracture repair, but this device can be sold for around $3000.00. This, however, has no growth factors and must be used in conjunction with fixation devices which could cost upward of $10,000.00.

The exact cost of these supplies is not yet known, but the client is inquiring about these components at this point.
Access to the necessary laboratories will be available at no cost. The ultrasound used in the design is also available free of cost, as well as EHS Biological Health and Safety classes necessary for safety accreditation when handling biological samples.

4 Conclusion

The system being designed is meant to provide clinicians with a less-invasive means of non-union bone fracture repair. Healing fracture injuries with current methods require a surgical approach and leave the wound prone to infection. With our design, we attempt to minimize these negative consequences of standard bone tissue repair procedures (allografts, autografts, xenografts). The system will optimize qualities of current scaffolds and meet the requirements necessary for tissue repair.

When designing the system, we are faced with realistic limitations. Although our device can be manufactured under a low-budget, other pressing issues (health, manufacturing, ethical constraints) must be taken into serious consideration. With the proper awareness and caution taken towards these limitations, we aim to create a self-enclosed device.

Works Referenced


Alginate Hydrogel Scaffolds with High Cell Viability. *Tissue Engineering* 2011; 17, Number 2. 10.1089/ten.tec2009.0582