The Ethics involved in the Role of Tissue Engineering in the Management of Ligament and Tendon Injuries

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INTRODUCTION

Two years ago, the Tissue Engineering International and Regenerative Medicine Society (TERMIS) awarded my research group a large grant to design and develop stem cell derived replacement tissue for ligaments and tendons in the body. According to an article I recently read, “What We Should Know Before Using Tissue Engineering Techniques to Repair Injured Tendons: A Developmental Biology Perspective”, “In the United States, about 45% of the 32.8 million musculoskeletal injuries each year involve tendons and ligaments” [1]. This means that 14.76 million people each year in the United States need treatment for these types of injuries. The limitations of current treatments have led to an increased urgency for better treatment options for tendon and ligament injuries. Knowing these facts, my research team was excited to begin our research to engineer replacement tissues for ligament and tendon reconstructions. This was an opportunity for our team to really impact millions of people’s lives. If our research is successful, it could lead to many new advancements in the field of tissue engineering. The possibilities in this field hold “tremendous promise of curing disease or accidental body damage” [2]. Advancements made in tissue engineering of ligaments and tendons could lead to breakthroughs in tissue engineering of other parts of the body, ultimately altering modern medical practices. My team’s research could advance the concept of applying the principles of engineering to medical science to generate living tissue and organ replacements.

THE RESEARCH

The new technology involved the development of biological substitutes to restore or replace lost ligament and tendon function. The substitutes combined stem cells and biomaterials into functional tissues. Stem cells can be engineered into specialized cells that can replace the damaged ligament and tendon tissue. To engineer the stem cells, we first had to understand the natural mechanisms involved in the cell differentiation of tendons and ligaments in early stages of development as well as the maintenance of the cells [3]. Tendon and ligament differentiation is dependent on several protein and growth factors, which aid in the organization of the collagen type 1 and type 3 fibers [1]. In addition, the differentiation of tendon and ligament cells depends on surrounding muscle and bone development [3]. Much of our early research was to understand how the different tissue components; muscle, tendons, ligaments, and bones, function together. Some of the first clinical practices aimed at tendon and ligament healing utilized “biological cocktails with growth factors” [3] including platelet-rich plasma (PRP) and autologous conditioned serum (ACS) to promote regeneration of the damaged tissue. We can use these “biological cocktails” to help develop the undifferentiated stem cells and as an aid in the integration of these stem cells into the existing tissue. The next step in my research group’s process was to understand the “gene expression patterns during tendon development” to ensure proper cell differentiation occurs [1]. At this point in our research, we were able to grow stem cell derived scaffolds in culture from undifferentiated embryonic stem cells. The problem with these cells is that there will be problems with immunogenicity [4]. Therefore, utilizing this type of stem cell required a strategy to combat this immune system response and promote biological acceptance. In addition to the use of embryonic stem cells, we tried several other sources of stem cells to develop scaffolds to replace damaged ligament or tendon tissue. These other sources of cells include autologous differentiated cells, allogeneic differentiated cells, and adult stem cells [4]. The autologous differentiated cells have “no issue of immunogenicity” since these types of cells are taken from the patient with the ligament or tendon injury. Allogeneic differentiated cells are taken from another person and will require a strategy for immune system acceptance [4]. The final source of stem cells were taken from adult stem cells located in the bone marrow of the host and will be biocompatible because these cells were taken from the patient. All of these sources are viable. The choice of stem cell source is based on the situation. Depending on how quickly the patient needs the surgery, some of the sources, specifically embryonic stem cells and adult stem cells, require growth in culture before the cells can be implanted. In contrast, the autologous differentiated and allogeneic differentiated cells have off-the-shelf potential, allowing for immediate implantation [4]. Each of the sources of stem cells used to develop replacement tissue for damaged ligaments and tendons have advantages and disadvantages, which will need to be factored into deciding which source is best for a patient. The final step in our research process was to begin clinical trials and with a deadline established by the funding group quickly approaching, my team had tough decisions to make.

INTRODUCTION TO THE ETHICAL DILEMMA

With time running out on the grant, my research team is not going to be able to perform all of the clinical trials in the
Ryan Black

order as planned. Failure to meet this grant’s deadline to design and develop stem cell derived replacement tissue for ligaments and tendons in the body would reflect poorly on my research team’s professional reputation. Consequently, future funding and grants would be significantly harder to secure. With all of this pressure on my research team to finish the project on time and on budget, several members of the team suggested to take “shortcuts” in the final phase of our research. These members suggested that clinical trials on humans and animals begin at the same time. Additionally, it was suggested that our standards for defining a successful implantation be relaxed without reporting these changes to the funding agency. Being the last person to vote on the suggestions, I become the person who makes the final decision regarding the direction the research takes. At this point, I am unable to make a decision and ask for additional time to consider all of the consequences involved with the decision. I want to make sure that I understand the possible outcomes of each choice prior to making a decision. Before I begin thinking about their suggestions, I consider other ethical issues involved in our research. When implanting engineered products in the body of a test subject, there are risks of bio-incompatibility and many other unknown side-effects are possible. Will the stem cells properly differentiate into the desired tendon or ligament tissue? What strategy or drug therapy can we utilize to combat immune system rejection? We need to be prepared to treat any type of reaction in our test subject to the implant. Also, the criteria used to choose the test subjects must be carefully developed making sure patients are not put at risk. As with any clinical trial, we must consider the rights of the subjects we are implanting with these engineered stem cells, according to the Biomedical Engineering Society Code of Ethics [5]. The subjects need to be informed about our research and what we are implanting in their bodies along with all of the possible side-effects. Prior to human testing, animals can be used in initial in vivo trials. By choosing an animal model with tissue close to a human tendon or ligament, we can gain “much more information before proceeding with human trials” [6]. Animal trials would give us in vivo experimental data and allow us to better understand how the stem cells will interact with existing tissue in a biological system [7]. During the animal trials, we have more freedom to do more extensive invasive monitoring of the animals that we cannot do with humans. A more intensive drug therapy aimed at accelerating the growth and acceptance of the scaffold can be employed in animals because of this close monitoring allowing for quick reaction to adverse response. Furthermore, we can regularly check how the replacement tissue is interacting with the existing tissue. Also, we can test the stem cell derived scaffolds from the four different sources of stem cells, previously discussed, within one animal. Each test site can be closely monitored giving data to determine which stem cells and growth mechanisms improve the overall joint function. In humans, only one stem cell derived scaffold from a single source can be used since ethical questions arise with respect to experimentation leading to permanent damage. Collecting data first in animals can lead to a better design and clearer understanding of what will happen when we place these stem cell derived scaffolds in a human [7].

THINKING THROUGH THE ETHICAL DILEMMA

Many ethical questions are prevalent in tissue engineering research involving human and animal test trials. The additional suggestions given by members of the research team create several new ethical issues. Choosing to proceed with animal and human testing at the same time while lowering the criteria for successful implantation without reporting these changes to the funding agency puts at risk the value and integrity of our experimental results. If we do not report these changes to our clinical trial process we would be violating several codes of ethics created by engineering societies, including the Biomedical Engineering Society (BMES) and the National Society of Professional Engineers (NSPE), that as engineers we are bound to adhere by. The first rule we would violate is that “engineers shall hold paramount the safety, health, and welfare of the public”, according to the NSPE’s code of ethics [8]. We would be placing stem cells into a patient without certainty that the cells will properly differentiate into the desired ligament or tendon tissue. These introduced stem cells could also trigger some unforeseen side-effect that we could have discovered in the animal testing phase of the trial process if properly executed to plan. There are too many unknowns involved if we were to test in this manner putting the subjects at risk. Another rule we would violate is to “publish and/or present properly credited results of research accurately and clearly”, according to the BMES’ code of ethics [5]. The data reported from the trials would not be entirely truthful since the changes made to our initial clinical trial process would not be reported. This could lead to a design and method put out on the market that could cause further complications to patients who choose this treatment. Another rule we would be violating is “engineers shall not complete, sign, or seal plans and/or specifications that are not in conformity with applicable standards”, according to the NSPE’s code of ethics [8]. By lowering the standards for a successful implant, we would be reducing the time to perform the trials at the cost of quality results. We would not be placing our best method and design for stem cell derived scaffolds on the market. In addition, if we decide to perform trials in animals and humans at the same time, then why test the implantation on animals at all? Testing on animals would accomplish nothing and put these animals at risk for further injury if we performed these tests at the same time as human testing. By performing trials on animals and humans at the same time, we lose the extremely important initial in vivo data collected through animal testing [7]. We lose the
possibility of perfecting our design before testing it in humans, putting the patients at risk [6]. Thinking through this dilemma, I want to find out what happens to researchers who commit ethics violations. I consulted several websites for guidance and learned that most of these people lose their professional license, end up in lawsuits, and have to recall their innovation from the market. These are all possible outcomes if I choose to go with the other team member’s suggestion. The final two sources I would utilize when dealing with this ethical dilemma would be my parents and the bible. All my life my parents helped me make tough decisions. In this situation, my parents would be useful since my Mom is a clinical immunologist and my Dad is an advisor engineer. Being in the field related to my research, my parents understand the ethics involved in medicine and engineering and would be able to advise me properly. The bible would play a key role in my decision process since it is a part of the religion I believe in. The book would give me an answer to the question, if the research is properly aligned with my beliefs. Having gone through all these resources addressing this ethical issue, I am ready to make a decision.

**MY DECISION**

My decision, after considering all possible outcomes and the other ethical issues involved in our research, is to not proceed with animal and human testing at the same time while lowering criteria for the successful implantation without reporting these changes. The benefit from testing animals is essential for perfecting our design and method of implantation of stem cells. Initial animal testing significantly reduces the risk taken by human subjects choosing to participate in the study. In addition, by lowering the standards for a successful implant we would be reducing the time to perform the trials at the cost of quality results. Therefore, we would not be giving TERMIS the best stem cell derived implant for tendon or ligament tissue damage that we could possibly provide. Also, we would be violating several codes of ethics by not reporting changes to our clinical trial process to the funding agency. The data reported by the team, if we were to go with the suggestions, would be false and deceitful. In addition, we would put patients at risk because of the uncertainty of whether the stem cells will integrate with the existing tissue properly. Deciding to go with the team members' suggestions would go against my personal religious beliefs, as well as the advice from my parents. As an engineer, I would be required to “notify the proper authorities and withdraw from further service on the project” if the team decided to go with the suggestions, according to the NSPE’s code of ethics [NSPE]. Knowing I thought through all outcomes and ethical issues, I am confident in my decision.

**ADVICE FOR OTHER ENGINEERS**

My advice to engineers facing an ethical dilemma would be to carefully consider the consequences and ethics involved when making a decision. From my experience going through the ethical scenario described above, understanding the outcomes of a decision and being able to support your decision is key to being confident with your choice. Using the engineering process and principles helps in giving supporting evidence for the outcomes of each decision. Knowing that you can back up your choice with technical support is enough to assure yourself the right decision was made.

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ADDITIONAL SOURCES


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