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Barriers to the Clinical Translation of Orthopedic Tissue Engineering

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Tissue engineering and regenerative medicine have been the subject of increasingly intensive research for over 20 years, and there is concern in some quarters over the lack of clinically useful products despite the large sums of money invested. This review provides one perspective on orthopedic applications from a biologist working in academia. It is suggested that the delay in clinical application is not atypical of new, biologically based technologies. Some barriers to progress are acknowledged and discussed, but it is also noted that preclinical studies have identified several promising types of cells, scaffolds, and morphogenetic signals, which, although not optimal, are worth advancing toward human trials to establish a bridgehead in the clinic. Although this transitional technology will be replaced by more sophisticated, subsequent systems, it will perform valuable pioneering functions and facilitate the clinical development of the field. Some strategies for achieving this are suggested.

Introduction

According to most commentators, the overlapping fields of tissue engineering and regenerative medicine (TERM) date to the late 1980s and early 1990s, suggesting that the field is a little over 20 years old.[1,2] During this time, private and public sources have invested over $5 billion in the TERM enterprise. A recent PubMed search using the keywords "Tissue Engineering and Bone" registered nearly 10,000 hits, and "Tissue Engineering and Cartilage" over 4000 hits, so there is no shortage of activity in the orthopedic field. Yet, with the possible exceptions of autologous chondrocyte implantation (ACI), Infuse® and OP-1®, no orthopedic product related to TERM has reached the market, despite the remarkable regenerative powers of bone, one of the key target tissues. According to Nerem,[2] "in a very real sense [TERM] has underdelivered." This review examines some possible factors that constrain the clinical use of TERM in orthopedics, as seen subjectively through the eyes of one biologist based in academia. Because the scientific, technological, and financial constraints to progress have been reviewed comprehensively by previous authors,[3–11] this commentary focuses more on the sociological elements.

Perfect as the Enemy of Good

In its grandest sense, tissue engineering requires several intersecting components: cells, scaffolds, morphogenetic stimuli, and bioreactors.[12] There is a tendency among scientists to seek to optimize, such that the ultimate engineered product would combine the optimal cell population seeded onto the optimal scaffold, incubated in the optimal bioreactor under the optimal physicochemical conditions with the optimal morphogenetic factor(s). This is operationally unachievable.

Each of the individual components cited above is complex and, in some cases, rapidly changing. Take cells, for instance. Researchers started out using differentiated cells, but recent years have seen the increasing application of adult stem cells, then embryonic stem cells (ESCs), and, most recently, induced pluripotent stem (iPS) cells.[13,14] The technology for producing iPS cells is developing rapidly, eliminating the need for permanent genetic modification of the parent cells. Moreover, there is increasing interest in using allogeneic or even xenogeneic cells for certain applications. With such a constantly moving target, it is difficult to see how optimization can be achieved expeditiously.

Optimization of scaffolds presents a related, but slightly different problem. There are an enormous number of different scaffolds already described in the literature and each of these can be functionalized, derivatized, and otherwise modified in infinite ways.[15] At what point is it best to stop tweaking and move forward to the next phase of development? This decision is complicated by the likelihood that different cells will require different scaffolds, so optimization is not possible until the type of cell to be used has been settled. As noted above, this can be problematic.

So it is for morphogenetic stimuli. There are scores of candidate growth factors, as well as chemical, mechanical,

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and other physical stimuli to evaluate. Moreover, there is a tendency to investigate combinations of growth factors. With bone, for example, many consider it an advantage to combine an osteogenic factor, such as bone morphogenetic protein-2 (BMP-2), with an angiogenic factor, such as vascular endothelial growth factor.[16] The number of possible combinations of size k within n items is $n!/[k!\times(n-k)!]$. For example, if we want to examine the properties of combinations of $k=3$ growth factors from a pool of $n=20$ growth factors, the total number of combinations is 1140. This does not even take into account different doses, etc. Clearly, exploring them all is impossible.

Another temptation is to improve growth factors through biotechnology. This might take the form of site-directed mutagenesis that, for instance, will render BMP-2 resistant to the effects of noggin, chordin, and other inhibitors. Alternatively, fusion proteins could be engineered to produce a single protein that stimulates both osteogenesis and angiogenesis. While such artifacts can be quite sophisticated, patentable, intellectually satisfying, and powerful in animal models, their human application is likely to be problematic because these novel molecules will be foreign to nature and thus prompt the Food and Drug Administration (FDA) to require extensive testing of their safety, pharmacology, and toxicology. They may also create novel epitopes that provoke powerful, neutralizing immune responses.

A related temptation is to wait for the additional, complementary technologies that are just around the corner and which will facilitate the next big advance. For TERM, these include bioinformatics, advanced imaging techniques, robotics, and synthetic biology.

However, at some point, it is necessary to stop treadmilling. Instead, it is better to identify the best available components at the time, and move forward into the next phase of development, even if it will lead to transitional technology to be superseded by later generation products. The history of technology abounds with examples of such an approach, from the motor car to cell phones.

The Translational Environment

Research translation is one of those activities that everyone is talking about, but few are doing. In an orthopedic setting, it has been described as "PhDs going into the operating room and surgeons going into the laboratory." In practice, there are several major external constraints to this ideal.

Many PhDs in academia hold untenured positions and, to a greater or lesser degree, depend on soft money from short-term contracts and grants for their livelihood. Their success in gaining promotion and tenure, or even the next grant, is largely predicated on data and publications, especially publications as first or last author. A possible hindrance to the clinical development of TERM is the reality that the more translational the research, the slower the progress and the more it costs. Moreover, it involves more and more collaborators, thereby increasing the chances of being a middle author. This is clearly detrimental to career advancement. A safer route to articles, first authorship, grant funding, and hence job security is to go back and do more tweaking of the type described in the previous section. Tenured faculty are in a better position to undertake translational research, but the research still needs to be funded. In the absence of large endowments, there is still the need to demonstrate productivity in the form of a steady stream of peer-reviewed publications. Under these circumstances, certain privately funded research institutions are probably best placed to drive forward this type of research until it reaches a stage where a large commercial entity is willing to invest.

From the perspective of the orthopedic surgeon, the constraints are quite different. It is becoming increasingly difficult for surgeons in the United States to spend quality time in the laboratory. In many hospitals, even within an academic setting, orthopedic surgery is seen as a major source of revenue for the institution and there is thus pressure to perform as much surgery as possible. In many centers, the surgeon's income is directly related to volume of surgery, which thus places clinical activities in direct financial competition with research, translational or otherwise. A day spent each week in the laboratory instead of the operating room can have a large impact on the surgeon's salary and standing within the institution.

Implementing translational research is further complicated by its funding structure. National Institutes of Health (NIH) has a policy of tapering its research allocation the further removed the research is from the basic. The expectation is that industry, whose funding has a reverse taper, will take over the enterprise and move the project forward into a clinical product. As discussed in the next section, this will only happen if products, in addition to being clinically effective, are free from intellectual property (IP) issues, affordable, practical, and lacking in complicated regulatory issues. To date, investment in TERM from industry has been modest. The projected worldwide net revenues for regenerative medicine of all types for 2010 have been estimated at approximately $2 billion, rising to $12 billion by 2020.[17] The question is whether a slice of the orthopedic component of this market will provide a big enough return on investment to attract sufficient capital?

NIH is aware of the funding gap for translational research and, to help in this regard, has established a Rapid Access to Interventional Development (RAID) program as part of its roadmap (http://nihroadmap.nih.gov/raid/). NIH is also in the process of establishing a National Center for Advancing Translational Sciences, something that has provoked some controversy in these times of budgetary restrictions. The Department of Defense is becoming another major source of federal funding for translational activities in the orthopedic application of TERM. Of note, the Armed Forces Institute of Regenerative Medicine has established two large consortia each funded to the tune of $50 million.

Other centers for TERM are also emerging, in some countries at the national level. These seem well positioned for addressing fundamental issues in fostering a supportive translational research environment. Besides the advantages of pooled resources, such as core facilities, they bring together investigators from different disciplines to interact and apply for unique funding opportunities that any one investigator could not get on their own. Moreover, dedicated centers that include individuals with knowledge of regulatory issues and commercial reality in addition to the usual mix of engineers, scientists, and clinicians will be able to address the fact that many researchers within the TERM area are not actually aware of which regulations are relevant.

Complexity, Regulatory Approval, and Commercialization

A recent survey found that orienting research to market needs was the second-ranked hurdle to commercialization reported by academics[18] (predictably, obtaining sufficient funds for research ranked first). A project formulated from the beginning with approval regulations in mind has a greater chance of clinical application than those that attempt to fit within the rules after being developed. Attention to these matters before the project starts can avoid considerable downstream wastage.

TERM can quickly become very complex, which increases the probability of major regulatory issues once the FDA become involved. For instance, when using a product that combines two or more components, the FDA requires each component to be tested in experimental animals both individually and in combination. The approval process is complicated and evolving, and we lack a clear regulatory pathway. This matter is not dealt with in great detail in this review, but is mentioned because it represents a major hurdle to clinical application and laboratory researchers often do not appreciate its importance until it is too late, thereby running the risk of condemning years of beautiful research to oblivion. As noted, the regulatory issues need to be kept in mind from the very beginning.

Depending on the product in question, the FDA will treat it as a device, a biologic, or a drug. The route to approval is most straightforward for a device, such as a scaffold lacking cells, recombinant proteins, or other biological agents. Although there are literature reports of scaffolds that have intrinsic regenerative properties, particularly for bone,[19] many products to be implanted for the purposes of TERM are likely to include cells, proteins, or genes. Such combinatorial products are particularly difficult, time-consuming, and expensive to navigate through the regulatory system, especially as the rules seem to be ever tightening. In a recent survey, established companies ranked working with the FDA as one of the major problems hindering the development of a commercial product.[18] IP issues also need to be considered early. Although these are not a hindrance in the research laboratory, they can be a literal deal-breaker once commercialization is on the horizon.

There are huge political and economic pressures to keep down the costs of healthcare. Related to this is the desire for a straightforward delivery system. Although an oral or transdermal mode of delivery would be favored, most orthopedic constructs will probably require surgical implantation. An off-the-shelf product, such as Infuse and OP-1, which can be easily implanted, is favored in this regard. It is difficult to see how a product using living autologous cells can be off-the-shelf. However, there is the possibility to manipulate autologous cells intraoperatively. If the cells are minimally manipulated, there are few regulatory barriers to their use in this setting. As noted previously, the use of expanded autologous cells is problematic because it involves two invasive procedures to harvest the cells and then implant them, and because of the costs of growing the cells under Good Manufacturing Practice conditions.[12] The lack of clearly focused, well-designed prospective studies is hindering the acceptance of many methods by care providers and insurance companies. Until efficacy has been clearly demonstrated, healthcare companies will not pay for treatments. Tissue Engineering and Regenerative Medicine International Society–North America chapter recently established an Industry Committee to study the issue of commercialization.[20]

Realistic Expectations

In 2009, *Science* published a timely article by James Wilson,[21] a gene therapy pioneer, entitled "A History Lesson for Stem Cells." Although it was directed primarily at the ESC community, it is also relevant to the broader TERM field.

Wilson points out that the field of gene therapy began in the mid to late 1980s with a massive burst of enthusiasm and exaggerated claims of its potential to cure many diseases. This led to a steep rise in the number of publications on the topic. The first properly authorized clinical trials began in 1989, and by the year 2000 more than 400 clinical gene therapy trials had been initiated. Then, in 1999, Jesse Gelsinger died. This was the first recorded death of a subject in a gene therapy trial and it sent the field into a tailspin from which it is only now properly recovering.[22] After 2–3 decades of gene therapy research, there is still only one gene therapy product on the market, Gendicine™, which is available in China for head and neck cancer.

Research into ESCs also began in the 1980s but the first clinical trial did not start until 2010, a gap of over 20 years. The point of Wilson's article was to warn the ESC community not to get too carried away with its own propaganda and not to rush too rapidly into clinical trials without devoting resources to understanding fundamental information about the biology of ESCs.

It is interesting to extend this comparison to the broader TERM field, which is also a child of the 1980s. All three technologies have been accused of over promising and under delivering, which seems to be the way it is with novel, potentially breakthrough technologies. The reasons for the exaggerated expectations include the enthusiasm of the scientists, the hopes of the patients, the projections of the biotechnology industry, and the spin of publicity agents and the media. With the exceptions of ACI, Infuse and OP-1, which have rather different histories, there have been no clinical trials of orthopedic TERM beyond individual case reports. However, there have been a large number of publications. In this regard, the recent history of TERM resembles more ESCs than gene therapy, suggesting that TERM has resisted the temptation of a premature rush to the clinic. Having instead accumulated a large amount of preclinical data, is it time to start thinking seriously about human clinical trials?

One conclusion that emerges from all of this is that the translation of a complex new technology into a product takes time. Perhaps the TERM community is being a little hard on itself in lamenting the absence of a product just yet.

What Next?

It is possible to advance the argument that the progress of TERM for orthopedic applications is not limited by raw materials. We have various cells, matrices, morphogens, etc., which may not be ultimate, perfect, or ideal, but which are serviceable. Sooner or later it is necessary to take the plunge, implement a "design freeze" and proceed with cautious

expediency into advanced preclinical studies using large animal models. Judging from the peer-reviewed literature, the small animal–large animal transition seems to represent a check-point and barrier to progress toward the clinic. Although large animals are expensive, lack of funding is only partially responsible; the security and comfort of preclinical tweaking using *in vitro* systems or small animals, discussed earlier, also play a role. The logistics of large animal studies in the United States may also be a factor; in a recent review of gene therapy for bone healing,[23] it was noted that several of the large animal studies have been performed in China. Whatever the barriers, it is worth investing in the responsible development of safe protocols that can be taken into human trials. A successful product used in human clinical medicine, even of a transitional, first-generation Model-T type, would stimulate the field immensely, attracting industry, commercial funding, and other resources.

What might such a protocol look like? To diminish risk and facilitate FDA approval, it is best to start with simple constructs using components that have already seen human use and thus have already been scrutinized from the regulatory point of view. For cells, this means steering clear of ESCs, iPS cells etc. which need further characterization, instead using something more pedestrian. Mesenchymal stem cells (MSCs) derived from bone marrow might be a good place to start, because they have been used in a number of clinical trials and should not raise too many red flags.[24] Moreover, there have been several clinical trials using allografted MSCs. Alternatively, freshly isolated marrow, possibly enriched intraoperatively for stromal cells, could be considered. A variety of scaffolds, ranging from simple collagen sponges, fibrin, and hyaluronate, to alginate, synthetic polymers, and beyond, have already been used safely in humans. In addition, numerous growth factors, including BMP-2, BMP-7, insulin-like growth factor-1, fibroblast growth factor-2, platelet-derived growth factor, parathyroid hormone, insulin, and growth hormone, have been used in the clinic for various reasons. There is thus a selection of component parts with which to establish a bridgehead in the clinic.

Clinical trials can be further facilitated by selecting, as the initial clinical target, an orphan indication, defined by the FDA as one affecting less than 200,000 individuals in the Unites States. The FDA has an Office of Orphan Products Development (www.fda.gov/ForIndustry/Developing ProductsforRareDiseasesConditions/default.htm) whose mission is "to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions." This office also administers an Orphan Products Grant Program to fund clinical research that tests safety and efficacy. In addition, it administers a Humanitarian Use Device Program for devices intended to treat less than 4000 patients per year in the United States.

Veterinary applications provide another expeditious route into clinical use. Many animals, including horses, dogs, and cats, suffer orthopedic conditions with human counterparts, and the pathway to regulatory approval is simpler. Moreover, the FDA has a designation called Minor Use/Minor Species that is very similar to the Orphan Drugs track for human medicines. Applications in veterinary medicine are commercially viable and the data can be used to support subsequent human trials.

Summary and Conclusions

Although research can always do with more money, this article has focused more on how the money is spent than on how much we have. From this perspective, it is possible to argue that, although we have imperfect knowledge of the individual components of TERM, we have identified promising approaches that merit further preclinical development in large animal models as a prelude to contemplating possible human trials. This is more likely to provide tangible returns than additional research aimed at further refining the fundamental components of TERM—matrices, cells, morphogenetic stimuli, etc. Although there are certain cultural, operational, and psychological barriers to pressing forward into the clinic, these can be overcome. It is better to advance expeditiously into clinical development with serviceable products that can be progressively improved, than to try first to optimize each individual component and then combine them into a final, merged, optimized product—a massive, expensive, and operationally endless task.

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