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Ethical Considerations in Tissue Engineering Research: Case Studies in Translation

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Abstract

Tissue engineering research is a complex process that requires investigators to focus on the relationship between their research and anticipated gains in both knowledge and treatment improvements. The ethical considerations arising from tissue engineering research are similarly complex when addressing the translational progression from bench to bedside, and investigators in the field of tissue engineering act as moral agents at each step of their research along the translational pathway, from early benchwork and preclinical studies to clinical research. This review highlights the ethical considerations and challenges at each stage of research, by comparing issues surrounding two translational tissue engineering technologies: the bioartificial pancreas and a tissue engineered skeletal muscle construct. We present relevant ethical issues and questions to consider at each step along the translational pathway, from the basic science bench to preclinical research to first-in-human clinical trials. Topics at the bench level include maintaining data integrity, appropriate reporting and dissemination of results, and ensuring that studies are designed to yield results suitable for advancing research. Topics in preclinical research include the principle of “modest translational distance” and appropriate animal models. Topics in clinical research include key issues that arise in early-stage clinical trials, including selection of patient-subjects, disclosure of uncertainty, and defining success. The comparison of these two technologies and

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their ethical issues brings to light many challenges for translational tissue engineering research and provides guidance for investigators engaged in development of any tissue engineering technology.

Keywords

human research ethics; animal research ethics; translational research ethics; tissue-engineered skeletal muscle; bioartificial pancreas

1. Introduction

Tissue engineering research is regenerative medicine research that emphasizes combining cells, tissues, and various enabling technologies, from scaffolds and capsules to bioreactors, to develop tissues and other biomaterials capable of replacing or augmenting physiological and biochemical functions impaired by illness or injury [1, pp. 215–216; 2, p. 11]. Research to develop so-called “combination products” is complex, both scientifically and from a regulatory standpoint. The ethical issues that arise in tissue engineering research are likewise complex and worthy of careful examination [3–5]. It is often helpful to address research ethics issues in the context of specific research case studies [6]. This essay enumerates some basic ethical considerations for tissue engineering research, and examines in detail their application to two representative research case studies: tissue-engineered skeletal muscle (TESM) constructs and the bioartificial pancreas (BAP).

It is currently popular, even necessary, to describe research—especially research involving novel biotechnologies—as “translational.” In addition to being trendy, however, the term is important, because it helps to illustrate the need for and value of viewing all health-related research comprehensively relating each line of research to anticipated knowledge gains and health improvements. Translation should not imply certainty that a line of research will lead neatly to safe and effective products or treatments. Rather, it should signal the responsibility of investigators to think ahead along the line of research, to anticipate the relationship between study design and research ethics, and to consider and periodically reconsider how to do research that has scientific and societal value, regardless of the direction taken along the translational pathway from one experiment to the next [7].

Investigators at all stages of translational research are moral agents, with profession-specific moral duties that apply to the design and conduct of their research. These duties can be described generally, but must also be articulated and applied to the specific context of a given study. This essay therefore first addresses common ethical considerations in tissue engineering research at the laboratory, preclinical, and human research stages. There are important ethical considerations common to all research, and additional considerations that particular research stages have in common. Next, we consider these ethical issues as they arise in our two case studies, which were chosen for their differences, with the goal of comparison and contrast. It is our hope that examining the application and relative importance of the ethical considerations affecting the design and conduct of studies of TESM and BAP along the translational pathway will help to model similar thinking for tissue engineering researchers working with different tissue constructs, and thus make it easier to engage in thoughtful research at all stages from the bench to the bedside.

1.1. In the laboratory (in vitro and pre-clinical animal research)

Much tissue engineering research is still in preclinical stages. Although ethical issues are often underaddressed in research until human trials have begun [8], there are many issues worthy of consideration at the bench. These include: data integrity, responsible reporting and dissemination of results, and ensuring that every study is designed and conducted so that it can yield results suitable to decide on the next research steps [9]. It is important to recognize that, at any stage, the results of well-designed and properly conducted research might lead not forward, but back or in a different direction entirely, to refine and expand knowledge at an earlier stage or to explore and develop newly identified possibilities [7].

The use of animal models at preclinical stages remains vital to the success of tissue engineering research. Efforts are underway to minimize the use of animals, but potential alternatives like computer modeling and body-on-a-chip organoid arrays have significant limitations and require considerable further development [10]. Researchers therefore must consider the three Rs of animal research -- Reduce, Refine, and Replace [11]. The choice of animal models, and their humane and appropriate use, helps to ensure that the research transition from animals to humans adheres to the principle of “modest translational distance” described by Jonathan Kimmelman. Translational distance (TD) refers to the number and size of inferential leaps from animals to humans [7], pp. 117–122 – in other words, it is a measure of uncertainty. In first-in-human (FIH) and other early-stage research, modest TD may provide an analytical model for considering the relationship of research design and ethics – a role that cannot be filled by the concept of clinical equipoise, which applies only to later-stage research such as trials comparing experimental interventions to standard treatment. Clinical equipoise justifies asking patient-subjects to risk receiving an unproven intervention in a clinical trial when there is sufficient evidence that reasonable clinicians consider both the unproven intervention and currently available standard treatment to be a reasonable *treatment* choice under the circumstances [12]. Early-stage research cannot offer the potential for direct benefit to patient-subjects that may be available in later-stage research. Instead, modest TD justifies asking patient-subjects in early-stage research to risk receiving an unproven intervention only when the “inference gap” is small enough to predict both that the clinical trial can yield useful results and that it can adequately protect their safety – *not* because it is reasonable to anticipate direct benefit.

1.2. Clinical research with patients as subjects

Much has been written about ethical issues in clinical trials [13–15]; this body of scholarly literature, and the issues it addresses, continues to grow. For tissue engineering, like other regenerative medicine research, it is most important to address key issues arising in early-stage clinical trials [16–18]. Those issues include: moving into human subjects; designing FIH trials; selecting patient-subjects; and informed consent.

In order to move from preclinical to FIH and other early-stage trials, several questions must be answered in the affirmative:

- Has enough preclinical information been collected so that the only reasonable way to learn more is to move to humans? This is another way of asking whether modest TD has been achieved.

- Has enough been done to reduce the risks of harm to humans, and to maximize the likelihood that the intervention will ultimately show benefit in humans? This question about the appropriate balancing of the risks of harm and potential benefits applies at all stages of clinical research, but is particularly important in early-stage research, because what counts as potential direct benefit to patient-subjects in these trials is limited and uncertain at best [19].
- Has the point of irreducible uncertainty been reached? In early-stage research, this question is more applicable than the question “Have the risks of harm been minimized as far as possible?” because it acknowledges that some risks of harm are still unknown, and that it is never truly possible to eliminate all uncertainty.
- Is the amount of irreducible uncertainty small enough that it is fair to subjects to ask them to become involved in the research? Addressing this evaluative question is a key component of the researcher’s ethical inquiry. The answer is less important than the reasons that can be given to support an affirmative answer. Like the more familiar requirement that risks of harm and potential benefits “must be balanced and shown to be in a favorable ratio” [15], this reasoning forms the basis of productive discussions between researchers, their colleagues, and oversight bodies like funders, study sections, and institutional review boards (IRBs).

Two key considerations that relate the design of clinical trials to research ethics considerations are scientific validity and social value. A valid study is methodologically rigorous, designed and powered to provide useful answers to the questions it asks – including negative answers. A valuable study asks a socially meaningful and/or scientifically useful question [14]. Value in research is usually defined as progressive value—that is, whether a study’s results are able to move the line of research directly forward to the next phase. However, FIH and other early-stage research is also highly likely to have translational value that is not progressive, but may be reciprocal, iterative, or collateral [7], pp. 92–94]. *Reciprocal* value highlights the necessity of and informs new preclinical work. *Iterative* value helps to inform the clinical trial itself by providing new information that can be productively used for in-trial modifications as the trial goes forward. *Collateral* value helps one or more different trials, by making new information, experience, and techniques more broadly available to researchers in related research or related fields. Researchers who recognize the broad applicability of study data and design translational research to take advantage of many different types of value can readily plan both to address what would otherwise simply be regarded as failures of research progress and to enhance the value of successful research.

Selecting patient-subjects from whom scientifically useful data can be collected and who are also able to make well-informed choices about research participation is especially important in early-stage research. Choosing the population from whom the most may be learned and who also can most readily be helped to make autonomous choices about participation may be challenging, as sometimes those are two different populations of potential patient-subjects [16,20]. Researchers must take care to provide good information, not only to potential subjects in the consent form and process, but also to the media and in publications discussing study results. Good information reduces the likelihood that the therapeutic

misconception (TM) will cause potential subjects, their families, oversight bodies, the media and the public, and even fellow researchers to overestimate the potential benefits of the research or to underestimate its risks of harm [21,22]. The need for long-term follow-up, both to monitor the health and function of patient-subjects after the intervention and to determine the intervention's success or failure, is often overlooked, not only in study design and budgeting, but also in disclosure to potential subjects.

2. Case study 1: Ethical considerations in translation of TESM technologies

2.1. Introduction to the technology

In this case study, the TESM consists of a cell-seeded biomaterial construct used to enable repair and/or remodeling in a muscle loss injury or pathology. Such a technology aims to replace the current standard of care, which is the use of host or cadaveric muscle flaps for repair and reconstruction. Using host muscle flaps means creating a new, ideally less consequential region of muscle loss in order to repair the initial injury. Using cadaveric muscle flaps requires an immunosuppressive regimen. In contrast, using TESM, if perfected, would also require surgical implantation, but would not create an additional injury or the need for immunosuppression.

In future human studies, the generation of a TESM construct would begin weeks prior to implant with isolation of muscle cells from a biopsy taken from a patient-subject. Those cells would then be expanded in culture and eventually seeded onto a biocompatible scaffold. Next, depending on the particular TESM technology employed, the cellularized scaffold may be subjected to additional physiological cues to guide further maturation of the cells on the construct [23,24] Finally, the construct would be sutured into the tissue void.

Initial proof of concept for a TESM technology must be established *in vitro* prior to any animal studies; this alone can take years. This initial effort would be followed by *in vivo* studies, which seek to first develop a working animal model of a muscle injury that the investigator is interested in treating. This *in vivo* work can be inherently lengthy, as each study will need to carry on long enough to capture the full potential recovery for the muscle pathology of interest, which can vary from days for minor injuries, such as sports-related muscle damage, to months for volumetric muscle loss injuries [23,25]. The complexity of this research suggests unique ethical considerations at each stage leading up to clinical translation. This case study explores those issues at both early and pre-clinical stages and in clinical trials.

2.2. Research ethics in the lab

As noted previously, for preclinical research early on in a translational project, the primary ethical considerations should focus on data integrity, both for the value of the science and for the sake of future beneficiaries of the research. Every trial should produce results that are able to guide researchers in designing the next study. In animal studies, in addition, researchers should apply the three Rs to the maximum extent possible.

2.2.1. In vitro—Ethical considerations at the bench include: keeping good records, practicing good data collection and management, transparency of data-sharing and realistic representation of study results, and preparing for transition to animal studies.

When conducting translational research on TESM, even early stage investigators must consider the potential beneficiaries of the technology. Work at the bench and in the culture hood may someday help treat a wounded warrior, a cancer patient, or someone born with a congenital birth defect. Therefore, ethical considerations are vital at all times. This means that the quirk identified in the protocol but left undocumented might be the difference between successful translation of work into the clinic and loss of progress. Details—in cell culture, making up reagents, and handling of constructs—are all very important, and good documentation is a key requirement. Staying aware of the potential benefits of responsible laboratory practices and the potential harms of failure to attend to detail is important in day-to-day research even in its earliest stages [9].

In complex research like TESM, it may be necessary to involve an unbiased third party research group such as a contract research organization (CRO) to repeat some of the research. Doing so at an early stage may make it easier to reduce TD, show proof of concept for animal studies, and prepare to move toward clinical trials.

In addition to facilitating direct translational progress, *in vitro* research can also have knowledge-generating results with broader applications. In TESM research, culture of muscle cells on scaffolds can help to inform both the use and development of enabling technologies such as specialized imaging modalities and the use of muscle cells in other applications [26,27] – important examples of reciprocal and collateral value.

2.2.2. In vivo—Meeting the goals of the three Rs is challenging in TESM research. With respect to the first R, “Replace,” there exists no potential alternative, such as a computer model or a cell line, that can completely replace the use of animals to study TESM technology in a physiologically meaningful manner. Studying muscle cells seeded onto biomaterial scaffolds can provide useful information about the interaction between the cells and the construct, but cell-seeded scaffolds alone cannot recapitulate the necessary physiologic environment. Thus, for *in vivo* work, the other two Rs, “Reduce” and “Refine”, inform the planning of humane animal studies. These two Rs help to ensure that the number of animals used is minimized, and that animals experience the least amount of pain possible in a study and are housed and cared for according to established guidelines [28].

Reduction entails both making use of only the best animal model and determining the optimum number of animals needed to achieve significance in results. For example, in a muscle injury model it would be unwise to test a large number of TESM interventions in small groups of animals, as this could create additional “noise” in an experiment, impeding determination of efficacy for any particular intervention. Refinement entails not only ensuring adequate analgesia for all animals used, but also ensuring that the use of animals is parsimonious and targeted. This might include conducting *in vitro* studies and studies with smaller animals (e.g., rodents) to develop techniques for injury production and application of TESM prior to use in a large animal model (e.g., sheep or pigs).

Because TESM is a complex technology with cellular, biomaterial, and bioreactor components, all of which must be fully functional for success, the risk profile may be heightened, as there are several risks of harm associated with each component. Ensuring modest TD requires demonstrating through pre-clinical evidence that these risks are manageable. Species to species differences must be ruled out as much as possible when moving from animals to humans. Ensuring modest TD is particularly difficult in this context. Although volumetric muscle loss in human patients is not standardizable, creating a “spontaneous” and unique injury in animal models through surgically induced irregular trauma or blasts is difficult to justify in both regulatory and ethical terms. Thus, it is reasonable to create more uniform and less traumatic defects in animal models, especially in non-human primates, both for ethical reasons and to establish proof of concept. Even so, it will be challenging to gather generalizable data because there will always be irreducible differences in injuries, both across animals and between animals and human patient-subjects.

Additional considerations when matching animal models of muscle pathologies to humans include (1) developing a model in which the untreated animals will recover (or not recover) in the same manner/timeline as the clinical presentation of the particular injury and (2) matching the muscle fiber type and anatomy in the animal model site to the fiber type or fiber orientation planned for the clinical application. Studies should also include both male and female animals of varying ages. Finally, if cells are used, the same cell source or an equivalent source should be appropriate and planned for human trials.

For maximal knowledge generation, animal studies of TESM using an injury model require proper controls. A negative control for TESM animal studies entails use of a no-repair group in which an injury is created and allowed to heal without surgical intervention. This is necessary for muscle injury models in order to study the extent to which the intervention enables repair and regeneration within the injury site. Positive controls -- the use of an uninjured control group or treatment with autologous and allogeneic flap transfers -- are also necessary in order to begin determining the effectiveness of the TESM strategy under study relative to the current standard of care. The ultimate goal of this line of research is to determine whether TESM can replace flap transfer. In order to show whether TESM can overcome the problems of graft failure associated with cadaveric transplant and the cosmetic impairment caused by resection of the patient’s own tissue, clinically relevant animal studies involving TESM need appropriate controls.

Finally, reducing TD also means ensuring data transparency and both internal and external validity [29,30]. Internal validity [7, p.119] is a measure of the strength of causal inferences arising from trial data, and thus of the predictive power of a trial. Ways to improve internal validity include randomization and limiting variability within and across arms (even when blinding is not possible). For TESM studies, one option is ensuring the ability to repeat the work done previously within the same lab group, by maintaining good lab notes. Turnover of students, post-doctoral fellows, and lab technicians can hinder this process. External validity is most fundamentally challenged by the inherent divergence between animal models and human subjects, and can best be addressed through close correspondence in study designs and goals, increased use of pilot and feasibility studies in FIH settings, transparency, and minimization of bias [7, pp. 120–121]. This may be accomplished by making use of a third

party research group such as a CRO to repeat some of the research in order to prove efficacy in animal studies. Finally, pre-clinical data should be published, so that scientists can learn from one another and further the field of their research in general. Failures of transparency increase the likelihood that a technology with low odds of ultimate success will make it to clinical trials.

2.3. Research ethics in early-stage human trials

Every clinical trial should produce results that are able to guide researchers in designing the next study. Because the ultimate goal of medical research is to improve clinical practice, all trials should be designed for both validity and value. Trial design and conduct must also address protections for research subjects: Risks of harm to subjects should be clearly identified and minimized, and the potential, or lack thereof, for direct benefit must be addressed; this includes defining success and failure, and examining what can be done for patient-subjects if/when the experimental intervention fails. Addressing these considerations in first-in-human and early-stage TESM research may pose special challenges.

2.3.1 Patient-subject selection and informed consent—Fair and appropriate subject selection is a key component of scientifically and ethically sound clinical trial design. Should the first subjects in a TESM construct study be patients with extensive injuries, or with small defects? What control groups are most appropriate? Early-stage TESM research in humans will necessarily focus only on repair of injuries and defects of relatively small volumes, primarily because of the need to develop or provide a vascular supply. Vascularization is an essential aspect of TE research that requires further development [31]. Consideration might also be given, however, to enrolling patients with more extensive injuries, if proof of concept data could be gathered prior to standard repair or amputation. Thus, early-stage TESM research might also be undertaken in patient-subjects with more extensive injuries if there is sufficient time to do so before standard treatment with cadaveric muscle or flap transfer is attempted. It would be critical to design and conduct such studies so that (1) standard treatment would remain available, (2) delaying standard treatment would be minimally disadvantageous to patient-subjects, and (3) a clear and robust consent process can be undertaken so that patient-subjects understand the study design and the harm-benefit balance and can make free and informed decisions about participation. In addition, it might be useful to collect data from patient-subjects who choose not to have any repair. In early-stage TESM trials where vascular supply does not pose a barrier, randomization of patient-subjects who would otherwise choose standard treatment to no-treatment or sham surgery is not ethically justifiable when the design requires withholding reasonably effective standard treatment [14,32,33].

A patient who volunteers to take part in a clinical trial should know first and foremost that he or she is a research partner who, by joining the study, will further scientific research aimed at advancing the field regardless of the outcome. Potential patient-subjects must be told that the goal of the study is to find out if TESM technology can restore function and improve appearance in the area of muscle injury. Outcomes for patient-subjects are unknown and will vary. Research is not treatment, but rather an investigation into a possible solution. In TESM research, the need to seek consent to participation from patients with recent

traumatic injuries may make it more difficult to convey essential information effectively. And even well-informed potential subjects may still believe strongly that in spite of the risk of failure, TESM is sure to work for them. Such patient-subjects may be expressing acceptable optimism, or may be significantly underestimating the risks of harm, overestimating potential benefits, and mistakenly viewing research as treatment – that is, some may be affected by the therapeutic misconception (TM) [21,34–38]. TM can often be minimized by careful discussion and expectation management with patients who are potential subjects during screening and interviews prior to enrollment, as well as continuing discussion during trial participation. A high degree of attention to informed consent for patient-subjects with recent injuries will be essential in TESM research [39].

In FIH trials of TESM interventions, there are several important “unknowns.” Injuries created in animals will not be the same as the injuries in patients: anatomical differences will be present, and the injuries will be of different geometries and complexities. In general, every injury is uniquely complex. Thus, researchers in FIH TESM trials must identify (and then explain to potential subjects) what is unpredictable and unknown. This is true regardless of study design, as it applies to pilot and feasibility studies as much as it does to trials with more than one arm.

In translating tissue engineering research like TESM to human patient-subjects, the risks include not only the risks of harm associated with all surgical procedures, such as infection at the implant site, but also the risk of failure to meet patient expectations. TESM is a permanent alteration to the patient-subject’s body, which is only reversible by additional surgery [5]. Potential subjects must be told that if the experimental intervention were to fail, an additional surgery would be needed to correct the defect, possibly entailing replacement of the experimental implant with a standard flap transfer, which poses all the risks of additional surgery and potentially adds the risk of rejection of the flap. Moreover, a TESM graft might not be physically rejected but might nonetheless fail to meet the patient-subject’s expectations about appearance or functional recovery. To mitigate dissatisfaction with a TESM repair outcome, the patient-subject’s expectations should be addressed and discussed before enrollment – a process similar to standard consent practice in plastic and reconstructive surgery.

2.3.2. Success and failure in TESM—Several metrics could be used to assess the degree of success achieved in a TESM study. For repairs involving load-bearing muscles such as those in the extremities, function could be analyzed through electromyography or more simply through physical strength tests administered by a physical therapist. Another important metric is the appearance of the treated muscle after surgery. Improving the aesthetic quality of muscles in the face and neck or the extremities can greatly improve self-confidence and quality of life, even if the muscles are not fully functional. Assessment of personal qualitative metrics should be conducted through careful interviews with patient-subjects before and after surgery. These measurements are likely to vary in importance from person to person, and for each person, some bodily characteristics may be more important than others. Before beginning a clinical trial, these metrics must be clearly defined and perhaps ranked by patient-subjects before, during, and after the process of surgery and recovery. For some patient-subjects who may have experienced trauma associated with their

muscle loss injuries, mental health and wellbeing should be especially carefully evaluated to help determine the impact of TESM on overall quality of life.

The above considerations suggest that human clinical trials of a TESM construct should explicitly interrogate the meaning of success. What counts as success is likely to depend in large part on the preferences and values of patient-subjects, and thus may vary considerably between individuals. Success, as defined by the goals and expectations of patient-subjects, could focus on restoring appearance associated with damaged muscle, or on recovering muscle function to varying degrees, from simple weight-bearing to returning to competitive athletics. In this respect, research outcomes in TESM clinical trials may have a more significant subjective component than is typical in many trials. Researchers should discuss realistic expectations with potential subjects, learn what patient-subjects seek, and consult with them both immediately after the intervention and as a matter of long-term follow-up to evaluate quality of life and assess success. Functional outcomes can be identified and physiologically relevant outcome measures can be applied, but if, ultimately, patients are not satisfied with their outcomes, TESM was not successful. Similarly, patients who are satisfied with a non-functional repair, perhaps due to the restoration of desired appearance, will deem TESM successful. As success is ultimately crucial in all translational research, investigators and subjects must talk together about what success means in TESM research on an individual basis.

Of course, well-designed translational research has value even when ultimately unsuccessful. Failure in a well-designed FIH TESM study supports investigating potential reciprocal, iterative, or collateral value. Reciprocal value could be finding out that patient-subjects with a pre-existing condition react differently from other patient-subjects, leading to a preclinical TESM study done in animals with that condition. Procedural nuances necessary for success may present iterative value in FIH trials. Surgical techniques may be refined extensively from one patient-subject to the next in a single protocol [40], and many other in-trial procedural modifications (e.g., special postoperative treatment, a specific exercise, bed rest protocol, or specialized physical therapy) may also be developed. Finally, exposing more surgeons and specialists to TESM is by itself a major foreseeable collateral value. For instance, muscle scaffolds may be discovered to have new, unanticipated surgical applications. Thus, research that can identify potential reciprocal, iterative, and collateral value can respond productively to apparent failure, providing hope that the research may continue and return to additional clinical trials.

3. Case Study 2: Ethical considerations in the bioartificial pancreas (BAP)

3.1. Introduction to the technology

The BAP is in development as an alternative to standard treatments for Type 1 diabetes. Standard treatments include daily insulin injections, continuous infusion insulin pumps, pancreas transplantation, and clinical islet transplantation. Research into islet cell microencapsulation technologies began as early as 1980, in order to overcome the need for immunosuppression that accompanies transplantation of allogeneic cells, tissues, and organs. The BAP utilizes either insulin-producing β -cells or aggregates of these cells, which are known as islets. These cells are incorporated into either a macro- or microencapsulating

device, and then implanted into the body for the regulation of blood glucose levels. Several BAP models have been studied; one key feature of current BAP research addresses optimal implantation sites, which include the peritoneal cavity and the omentum [41,42]. There are many similarities between the ethical considerations arising in TESM and the BAP during pre-clinical research and human trials, but the BAP also poses several ethical considerations that are meaningfully different from those in TESM. Type 1 diabetes is a chronic condition, with several alternative treatment options. Because of the multiple treatment options available for Type 1 diabetes, the performance of the BAP comes under additional scrutiny—the BAP needs to alleviate the long-term comorbidities of Type 1 diabetes and avoid both hypoglycemic and hyperglycemic events. If the BAP is unable to improve upon the treatment provided through exogenous insulin injection or the use of an insulin pump, it will not be a viable treatment alternative. The BAP must also ultimately prove functional over the long term. Thus, questions arise about the acceptable balance of harms and benefits and the meaning of success and failure for this tissue engineering technology, as they do for TESM, but the answers are likely to be different.

3.2. Research ethics in the lab

The same general concerns about data integrity, transparency, and anticipation of translation to animal and human studies discussed in Case 1 apply to BAP research. Animal study of the BAP is farther advanced than is TESM research, but different aspects of BAP research are at very different stages. As always, it is important to follow good laboratory practices and maintain a clear and transparent record of all data in order to identify risks of harm that may be associated with a potential future therapy and to avoid redundant or repetitive studies. Several additional issues unique to the BAP also arise at the earliest stages of bench research.

3.2.1. In vitro—Most BAPs utilize whole islets; thus, the technology requires researchers to work with primary cell lines, which are in limited supply and can only be cultured or stored for a finite amount of time. This feature has led to an important ethical consideration in the laboratory: Islets can be maintained *in vitro* for only a limited time before transplantation, and there can be significant batch to batch variation between islet isolations. It is thus essential that the tissue be evaluated as thoroughly as possible *in vitro* prior to transplantation, and it is problematic when *in vitro* evaluation is not sufficient. Some of the techniques commonly used are insufficient to evaluate both the functionality and the viability of the islet cells in culture [43]. Utilizing the most appropriate *in vitro* tests includes identifying those that are as close to clinical tests as possible, to minimize TD. For the BAP, this means using *in vitro* tests that have been shown to strongly correlate with transplant outcomes, such as tests that measure the metabolic activity or insulin secretion rates of islets as opposed to more traditional live-dead viability stains [43,44].

The use of more predictive *in vitro* tests is especially important when considering the three “R’s” of animal research when moving to animal models: reduction, refinement and replacement. Ideally, the use of more accurate *in vitro* tests should reduce the number of animals or groups needed when research progresses to *in vivo* studies.

A second issue specific to the BAP also relates to the limited availability of human cadaveric pancreases. The urgent need for alternative tissue sources affects BAP research from the earliest stages, because it gives rise to an important ethical issue surrounding BAPs: the use of non-human tissue in humans. Using xenografts, most often from porcine tissue, requires a very high level of awareness and vigilance with regard to the risks and safeguards associated with non-human tissues [45–47]. Of chief concern with porcine cells is the transfer of zoonotic disease like porcine endogenous retrovirus (PERV) [48]. As a result of these differences, the risks of harm and potential benefits for the BAP, at every stage of research and ultimately in the clinic, are significantly different from those for TSM.

3.2.2. In vivo—Identification of the appropriate small animal model and the use of proper controls for the chosen animal model are important considerations in BAP research, in order both to conform to the three Rs and to reduce TD. As with TSM, it is especially important to use a small animal model that best represents the clinical disease. In the case of a BAP, it is important to consider whether it is preferable to utilize a knockout model (where the disease develops spontaneously) or an induced model for diabetes (where the animal is given a chemical such as streptozotocin to cause disease). It is also important to consider the appropriateness of using an immunocompromised or an immunocompetent animal model. Using the former concentrates attention on factors other than the immunoprotection afforded by the BAP, thus, for example, facilitating research on vascularization, which is as essential for success of the BAP as for TSM. However, using immunocompromised animals may increase the number of animal studies necessary before moving into humans to test a BAP with an immunoprotective coating.

The most appropriate animal models in BAP research will always include large animals. Although large animal models are not necessarily required for all TSM, large animal models are required for islet cell transplantation because diabetic conditions in rodents are significantly different from those in humans [49]. When using large diabetic animal models for BAP studies, the reproducibility of the model is a critical factor. It is also important to consider the clinical relevance of the insulin therapy given to controls. In the case of the BAP, this means identifying the most appropriate and accurate protocol for insulin therapy, in order to maintain maximal translational relevance to the clinic.

Like TSM research, animal studies of the BAP are complex, often involving multiple surgical procedures, to induce diabetes and to implant the BAP. Especially in research involving creation of an omentum pouch to improve vascularization of the BAP it is essential to determine how best to maintain study protocol integrity while allowing for the flexibility needed to improve surgical techniques over the course of the study.

Several considerations unique to the BAP also apply to design of animal studies. Studies of a BAP that utilizes immunoprotective coatings to prevent immune rejection, must be able to demonstrate that these coatings remain intact over the course of the study. It is also important to adhere to clinically relevant islet acceptance criteria [50,51] in constructing and using the BAP *in vivo*.

Determining the point at which the research is ready for human trials raises several provocative considerations in BAP research that differ from TESH research. First, determining the outer limits of the harm-benefit balance in BAP requires special attention to ethical and design questions in animal studies before translation to human studies. One issue is the role of immunosuppressants in BAP research. Ideally, the BAP would not require the use of immunosuppressants, because long-term immunosuppressant use poses risks that could outweigh the BAP's benefits. Thus, the most desired endpoint of BAP research is an encapsulated device that can restore a sufficient degree of pancreatic function and that has an immunoprotective coating that is effective over the long term. However, studying the use of immunosuppressants with the BAP could ultimately facilitate the earlier clinical availability of devices that could benefit seriously ill patients, for whom the increased risk might be a reasonable choice under the circumstances. Thus, two very different clinical applications may follow from research designed for different patient populations with different options and needs.

Along the same lines, because there are different BAPs, there are different harm-benefit assessments that can lead to different conclusions. Some BAPs carry higher risks but are viewed as acceptably risky for broad clinical use. BAPs that make use of xenografts are risk-bearing due to the concerns associated with the use of porcine or other non-human tissues, in particular zoonotic disease, but the limited availability of human tissue makes research focused on the use of porcine tissues reasonable under current circumstances. Thus, research has proceeded using both allografts and xenografts in non-immunosuppressed animals [42]. In contrast, however, some types of BAP constructs are now considered unacceptably risky. BAP constructs that connect directly to the circulatory system are riskier because there is a higher chance of clot formation and rejection. Additionally, these devices cannot be retrieved or removed as easily as devices that are simply implanted. These lines of research have been supplanted as more has been learned about the inherent risks associated with these approaches [42].

Additional factors to consider when determining the point at which a BAP is ready for human trials include study duration, size, and reproducibility. As with TESH studies, one method to externally verify results is the use of a CRO. Challenges here include establishment of the diabetic animals, technology transfer, and the training of CRO staff [48,52,53].

Finally, when planning *in vivo* studies it is necessary to consider how they can be designed to better identify the causes of failure if they are unsuccessful at achieving insulin independence. The long history of BAP research includes many examples of research that has provided important iterative value (e.g., in-trial surgical modifications), reciprocal value (e.g., research focusing on better vascularization to improve the longevity of the BAP and research utilizing different islet cell sources), or collateral value (e.g., development of BAPs intended only for limited patient populations, such as those for whom long-term immunosuppression does not pose a significant risk), even though the ultimate goal of BAP research has not yet been reached.

3.3. Research ethics in early-stage clinical trials

As compared to TISM, the BAP has one distinct advantage when moving into clinical trials, and this is the historical precedent for the use of islet cell transplantation. For BAP, unlike TISM, there is both a network of islet transplant centers and a set of published donor selection criteria, as well as established guidelines for involvement in an islet transplant study [50,51]. In this respect, BAP research benefits from the collateral value generated by prior research. BAP researchers can also make use of existing infrastructure and guidance to help design and conduct trials that minimize risks of harm, maximize the production of generalizable knowledge, and fully inform potential subjects.

3.3.1 Patient-subject selection and informed consent—Another difference from TISM appears in the selection of patients as research subjects. Several populations of diabetic patients who are potential subjects for BAP research have characteristics that put them at greater risk but also may make them better candidates for some early-phase designs. One group, mentioned previously, is seriously ill patients, whose disease course and anticipated longevity might in some circumstances make them suitable candidates for BAP designs requiring immunosuppression. Another such population is patients who have reduced awareness of hypoglycemia. This is a dangerous condition [54]; consequently, these individuals may be candidates for early clinical trials involving either islet transplantation or the BAP, since current insulin therapies are inadequate for them. For populations like these, early-stage research involving patient-subjects with diabetes most resembles Phase I oncology research, where patients are chosen as subjects because there are no adequate standard treatments currently available to them. Unfortunately, TM can be exacerbated in such trials, as it is tempting to move from “nothing else works well for you” to “this research is your best hope” even though direct benefit is very unlikely. As always, a clear and complete consent process is the best way to avoid TM when patients are enrolled as research subjects under such circumstances.

As trial designs change and scientific thinking about best subject populations also changes, it may be worth speculating about how BAP research might be regarded if it were thought that better data could be gathered from young, treatment-naïve patient-subjects than from patient-subjects for whom nothing else has proven effective. A contemporary parallel might be found in current research using a new smartphone-based application to regulate insulin pump delivery based on continuous data readouts [55]. In this Type 1 diabetes intervention, a sensor is used to monitor blood sugar in the patient-subject, and blood sugar levels are managed through a dual pump to supply insulin (to lower blood sugar levels) and glucagon (to prevent blood sugar level drops) to achieve normoglycemia. Some patient-subjects in ongoing trials are teenagers, which is a departure from the traditional adults-first model. This choice of subject population more closely resembles the most likely patient-subjects in FIH trials of TISM constructs: younger patients with smaller injuries or defects. Determining which patients are the best subjects in FIH trials, especially when the potential subject populations are as different as very young, treatment-naïve patient subjects and adult patient-subjects for whom no adequate alternatives exist, represents an extremely important ethical and design challenge. Which patient-subjects should be first is an ongoing issue in gene transfer research and many other novel biotechnologies as well [2,28].

3.3.2. Xenografting and risk in the BAP—One of the most discussed issues involving the BAP, which does not arise in TESM research, is the use of xenografts. As previously mentioned, the use of porcine islets is one solution to the shortage of available human donor islets. However, the use of xenografts dramatically increases the risks associated with the BAP. Of particular concern is the risk of spreading zoonotic diseases. As a result of this increased risk, there has been a significant amount of research focused on creating disease-free pigs, with a particular focus on pigs free of PERV. In response to the increased research into xenografts, the International Xenotransplantation Association has published a consensus statement [56], which reviews the key ethical requirements of an international regulatory framework for clinical trials of xenotransplantation, the recommendations on source pigs, release criteria, and necessary preclinical data required to justify a clinical trial, strategies to prevent the transmission of PERV, patient selection, and an outline for informed consent [57–60]. Risk reduction in this area may in the future change what is regarded as an acceptable risk-benefit balance in BAP human studies and related trials.

3.3.3. Success, failure, and the BAP—For the BAP to become a successful treatment, it has to function better than insulin therapy with its attendant complications. Yet what that means in terms of defining success in BAP research may not be as clear-cut as it seems. On the one hand, it could be reasonable to expect that the BAP should ultimately prove a genuine cure. On the other hand, what if the BAP transforms what can be described as a progressively fatal disease into a chronic disease? If partial functional correction is an acceptable goal, then a BAP might be introduced into the treatment armamentarium as another useful “halfway technology” that is not a cure. BAPs that meet this goal of partial functional correction could reduce the need for insulin therapy and thus reduce the occurrence of hypoglycemic unawareness and stabilize or reduce the comorbidities of Type 1 diabetes.

If the BAP is likely to reduce but not eliminate the need for exogenous insulin, then the preferences and perspectives of patient-subjects may be highly relevant in determining what counts as success for the BAP, even though there is no aesthetic component as in TESM. Because Type 1 diabetes is a chronic and progressive condition that begins to change most patients’ lives at a relatively young age, potential subjects may be more knowledgeable and under less decision-making pressure than in TESM research, where most potential subjects will have recently experienced a wide variety of muscle injuries and loss. Thus, potential subjects for BAP research may consider the impact of different research outcomes on their decisions to participate and their ultimate satisfaction from a very different emotional and psychological vantage point. Moreover, the consequences of partial success—reducing but not eliminating the need for exogenous insulin and the effects of the many comorbidities of Type 1 diabetes – are quite different from those potentially faced by TESM subjects.

4. Discussion and conclusions

4.1. Strengths and limitations

By examining in some detail two very different examples of tissue engineering research, we have been able to focus in-depth on some key issues that are not as carefully reviewed

elsewhere. However, a case-based review cannot address all of the many relevant ethical issues arising in tissue engineering research.

The use of cells and cell lines has been thoroughly examined elsewhere [1,5,16]. So has the problem of access and cost, which is of considerable concern for all novel biotechnologies [1,2,16]. The overall goals of tissue engineering include not only developing treatments that are more effective than currently available alternatives, but also keeping costs low and improving access. The complexity of tissue engineering interventions represents a challenge to achievement of this goal, but it is nonetheless one toward which the field strives [61].

4.2. Key lessons learned

Several key ethical issues emerge from these case studies. First, it is essential to look for iterative value in tissue engineering research. Because tissue engineering research methods are complex and mixed, including surgery, cells, and a wide range of enabling technologies in animal and human trials, innovations are almost inevitable. Researchers should anticipate the likelihood of innovation, and should design and describe protocols that can not only accommodate innovations but also convert them into study features when warranted [15,62]. Clear and close communication with research oversight bodies is therefore essential, both to ensure the proper balance of flexibility and reproducibility in tissue engineering protocols and to amend protocols when amendment is necessary to capture methodological innovations.

Second, data transparency is critical, even though it is increasingly difficult to achieve in the current highly competitive funding environment. For tissue engineering research, it is particularly vital that researchers (1) register clinical trials and (2) publish clear and complete data from well-designed research at all stages, especially data from early clinical trials, regardless of success or failure. Being transparent about the research strategy and results of the trial enables scientists at earlier stages of development to see what is and is not working with the model being used. This will fuel and inspire future work and advance the field as a whole [63,64]. In addition, making the results of these trials publicly available and understandable to the lay public will inform those considering participation in such trials and help to set the stage for understanding the benefits and limitations not only of trial participation but also of any future treatments and new research directions that may later emerge from the research.

Third, much work is needed to increase parsimony in animal research while identifying best animal models and designing effective adjuncts and alternatives to use of animals. As noted earlier, body-on-a-chip and organ-on-a-chip research shows great promise in this regard.

Fourth, it is becoming apparent that FDA's traditional phase designations are not always a good fit with novel trial designs and the increasingly nuanced considerations influencing subject selection. Like Phase I oncology trials and most if not all FIH and early-stage clinical trials of novel biotechnologies, early TESM and BAP clinical trials necessarily enroll patients as subjects, instead of the "healthy volunteers" traditionally enrolled in Phase I drug trials. The first patient-subjects in these trials may be older or younger, and experienced or treatment-naïve. The ethical considerations that arise in early clinical trials of

novel biotechnologies like tissue engineering match up more closely with design and subject selection than they do with phase designation. Thus, clear justification for a clinical trial's design and goals is paramount regardless of phase designation, and thorough consideration of the implications of enrolling patients as subjects, including but not limited to the consent form and process, is essential. A related challenge arises when complex tissue engineering intervention trials cannot effectively or ethically be randomized and blinded. Patients who are potential subjects may have strong and reasonable preferences for one arm over another, as their goals and quality of life assessments may differ in ways that significantly affect their choices about participation. It may be prudent to consider whether there might be new ways to gather important information in research in addition to "gold standard" randomized controlled trials. Much attention is now being given to "patient-centered outcomes" in clinical research [65]. Incorporating patients' perspectives into research could be well-suited to some tissue engineering trials, and could increase enrollment.

Methodological challenges will inevitably arise in new trial designs, including not only statistical design and data credibility but also a potential increase in the likelihood of TM in investigators, the media, the public, and patient-subjects. These challenges can be effectively addressed with clear and transparent justification for each step along the research pathway, strong preclinical data, exemplary communication, and the creativity that arises from collaborative scholarship along the translational pathway. The result could yield intervention profiles that are more predictive of outcomes in clinical practice.

Finally, not only is long-term follow-up essential, but in addition, researchers can play a critical role in facilitating translation to clinical care for these complex tissue engineering interventions. Clinical use of cell-seeded scaffolds and capsules in TESM and BAP will continue to pose challenges even after successful research. One often overlooked issue is the infrastructure needed for feasible and efficient tissue engineering treatments. For instance, hospital personnel would need to be trained in handling cell-scaffold products, and hospitals would need to affiliate with a Good Manufacturing Process facility for generation of the constructs [66]. Several biomaterial scaffolds have been approved by the FDA for a variety of applications, including rotator cuff repair, hernia repair, and heart valve patches [67]. Familiarity with these devices may facilitate acceptance and use of tissue engineering technologies in the future, as long as researchers and sponsors plan well in advance for effective clinical translation.

We encourage detailed examination of additional case examples of research using tissue engineering and other cell-based interventions. Case-based discussion of ethics and design questions throughout the translational trajectory is the best way we know of to promote transparency, encourage discussion, and maximize the knowledge gained from this important research.

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Abbreviations (nonstandard)

TESM	tissue engineered skeletal muscle
BAP	bioartificial pancreas
TM	therapeutic misconception
TD	translational distance
FIH	first-in-human
CRO	contract research organization

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Highlights

- Investigators at all stages of translational research are moral agents
- Every trial should produce results that are able to guide researchers in designing the next study
- Well-designed translational research has value even when ultimately unsuccessful
- Increased discussion of ethics promotes transparency and knowledge-sharing in research