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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 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.

Contents

Abbreviations: 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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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

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