Published in final edited form as:

Transl Res. 2011 May ; 157(5): 320–321. doi:10.1016/j.trsl.2010.12.010.

Role of academic medical centers in cell-based therapeutic clinical trials

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Introduction

Allogenic cell-based therapies derived from pluripotent or multipotent stem cells are being developed for a range of human disorders, including degenerative neurological disorders, spinal cord injury, diabetes, myocardial infarction, and acute lung injury (1). Because the biology and regulation of stem cell development is just becoming established, academic medical centers encompassing basic science, clinical expertise and research infrastructure seem to be the ideal environment for initial clinical trials of such cell-based therapies. Here, we examine the benefits and potential challenges to academic-industry collaboration on clinical trials involving cell-based therapies.

Advantages of industry-academic collaboration for cell-based clinical trials

There are several advantages to academic-industry collaboration on clinical research trials of cell-based therapeutics, including:

1. Multi-disciplinary expertise. The expertise at academic medical centers could be critical for understanding the potential benefits and risks of a cellular therapy and designing a clinical trial. Clinical-translational training programs aim to produce investigators with the ability to evaluate innovative therapies using cutting edge scientific principles as well as clinical acumen. For example, academic researchers might suggest novel methods to identify transplanted cells through imaging techniques and cytopathology as well as surrogate markers for the effects of transplanted cells. Experts might also identify potential risks, concerns, and fatal flaws that might not have been anticipated by the sponsor or the FDA.
2. Sophisticated Research Infrastructure. At academic medical centers, many sub-specialists are available to join the research team. NIH-supported Clinical Translational Science Awards (CTSAs) to academic medical centers provide in-house research nurses and coordinators, biostatisticians, data management services, and clinical research centers. If complications occur, academic centers provide 24-hour access to critical care units and

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The authors declare no conflicts of interest, and they thank Lindsay Parham for helpful editing of the text.

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subspecialists, which might not be available at a community hospital or contract research organization.

3. Enhanced Credibility. A sponsor may find that the results of a clinical trial are more credible if it is carried out at a prestigious academic center by investigators with no financial interest in the product other than the contract or grant to carry out the trial.

Potential concerns of industry sponsors

From the point of view of the industry sponsor, an academic medical center might present challenges to the timely implementation of a trial of stem cell based therapies in the following ways:

1. Time-consuming and overly demanding institutional reviews. IRBs need to carry out combined ethical and scientific review of protocols to assess the risks and benefits of a trial. However, academic reviewers may request additional data on mechanisms of action, proof of principle, or safety that were not required by FDA reviewers and are not, strictly speaking, essential to complete before a Phase 1 trial. Many interesting questions regarding scientific mechanisms may emerge during review of cell-based therapies that do not need to be resolved before IRB approval of the trial. Indeed, in another innovative field, gene transfer, review by the NIH Recombinant DNA Advisory Committee has been criticized for suggesting additional pre-clinical studies of academic interest which were not deemed necessary by the FDA (2).

Academic IRBs commonly require longer reviewing protocols than independent IRBs. Furthermore, coordination among multiple review committees -- the IRB, stem cell research oversight committee (SCRO), and biosafety committees -- may be poor. Finally, in a multicenter trial, academic centers may be unwilling to accept central IRB review.

2. Concerns regarding intellectual property. Concerns about trade secrets may make sponsors reluctant to have reviewers see detailed information about the product formulation and preclinical data, particularly since academic experts may have ties to competitors and potential competitors. However, reviewers should be independent, with no ties to the sponsor or competitors

3. Concerns regarding publication of “negative” results. After the trial is completed, the sponsor and the academic investigator may have different views on the appropriate data analysis and interpretation, as well as the level of detail disclosed about the study intervention. Academic investigators and institutions should insist on having control over the data and publication of articles, while giving the sponsor an opportunity to review draft manuscripts and make suggestions (3).

The way forward

Academic medical centers should reaffirm their commitment to translational research, including first-in-human trials of innovative stem cell therapies.

1. Streamline the review process. IRBs and academic medical centers need to identify and eliminate unnecessary delays. Different institutional review committees should be coordinated. Truly expedited review should be available for minor protocol changes. The goal is to carry out careful review in as timely a manner as independent IRBs. This may require more frequent meetings than is customary at academic IRBs. Furthermore, IRBs should develop expertise in innovative stem cell clinical trials by identifying members or *ad hoc* reviewers with expertise in stem cell biology. Academic PIs and small companies may

need enhanced pre-review screening of applications and additional staffing/training on regulatory procedures and requirements. These services may require additional charges to the sponsor. Academic medical centers should also facilitate coordinated or central review in multi-site trials, similar to the National Cancer Institute Central IRB (4).

2. Distinguish between studies that are necessary before a trial can be approved and add-on studies of scientific interest that need not be completed before the trial is initiated. Examples of the latter are the development of better ways of detecting cells of donor origin in transplant recipients and understanding the mechanisms by which transplanted cells engraft, integrate, and function; such studies might be excellent projects for Ph.D. students or post-doctoral fellows.

3. Facilitate scientific consultation to companies by faculty experts at the front end of basic science, development of therapies, and design of clinical trials. Open scientific exchange, within the parameters of thoughtful conflict of interest policies, can benefit sponsors, faculty, academic institutions, and ultimately patients through timelier and better-designed trials (5). Such coordinated consultation can be carried out, for example, through Clinical and Translational Science Awards.

In summary, academic-industry partnerships hold promise for carrying out clinical trials of innovative stem cell therapies. Academic institutions need to carry out rigorous review without imposing undue delays on investigators and industry sponsors.

Acknowledgments

D.H.R. is a Howard Hughes Medical Institute Investigator. B.L. acknowledges support by National Institutes of Health (NIH) Grant Number 1 UL1 RR024131-01 from the National Center for Research Resources (NCRR), by National Institutes of Health Grant MH062246, and NIH Roadmap for Medical Research and by the Greenwall Foundation. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR of NIH.

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