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PERSPECTIVES IN CELL THERAPY

Cellular Therapies Clinical Research Roadmap: lessons learned on how to move a cellular therapy into a clinical trial

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Abstract

Background aims. A clinical research roadmap has been developed as a resource for researchers to identify critical areas and potential pitfalls when transitioning a cellular therapy product from the research laboratory, by means of an Investigational New Drug (IND) application, into early-phase clinical trials. The roadmap describes four key areas: basic and preclinical research, resource development, translational research and Good Manufacturing Practice (GMP) and IND assembly and submission. *Methods.* Basic and preclinical research identifies a new therapeutic concept and demonstrates its potential value with the use of a model of the relevant disease. During resource development, the appropriate specialists and the required expertise to bring this product into the clinic are identified (eg, researchers, regulatory specialists, GMP manufacturing staff, clinicians and clinical trials staff, etc). Additionally, the funds required to achieve this goal (or a plan to procure them) are identified. In the next phase, the plan to translate the research product into a clinical-grade therapeutic is developed. Finally regulatory approval to start the trial must be obtained. In the United States, this is done by filing an IND application with the Food and Drug Administration. *Results.* The National Heart, Lung and Blood Institute–funded Production Assistance for Cellular Therapies program has facilitated the transition of a variety of cellular therapy products from the laboratory into Phase1/2 trials. *Conclusions.* The five Production Assistance for Cellular Therapies facilities have assisted investigators by performing translational studies and GMP manufacturing to ensure that cellular products met release specifications and were manufactured safely, reproducibly and at the appropriate scale. The roadmap resulting from this experience is the focus of this article.

Key Words: *cellular therapy, FDA, GMP, IND filing, NHLBI, PACT*

Introduction

The National Heart, Lung, and Blood Institute's (NHLBI) Production Assistance for Cellular Therapies (PACT) program was developed to assist investigators to transition promising new cellular therapies into early-phase clinical trials. The program provided successful applicants with assistance by developing product manufacturing and testing procedures to support the clinical trial, regulatory assistance for filing the Investigational New Drug (IND) application with the US Food and Drug Administration (FDA), production of the cellular product for patient administration and collection of follow-up data for use in IND annual reports.

Experience from this program suggested that many investigators were unfamiliar with the various phases of this process, and, as a result, the transition took longer than expected. To address this issue, a clinical research roadmap was developed by the five PACT cell processing facilities, the NHLBI, and the Coordinating Center as a resource for researchers new to the cellular therapy field. This was intended to assist them to identify critical areas that must be addressed when transitioning a new cellular therapy

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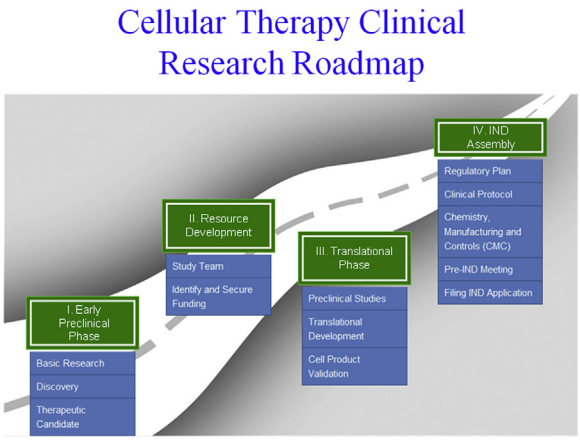

Figure 1. The roadmap identifies the critical areas that must be considered when developing a cellular therapy intended for evaluation in human clinical studies under an IND application.

into human clinical studies under an IND application (see Figure 1).

Critical areas of the clinical research roadmap: basic and preclinical research phase

Basic laboratory research may result in the discovery or identification of a cellular system with therapeutic potential. Many times the researcher is unaware of the steps required to demonstrate this potential in a disease-related model and of the procedure to transition their discovery into a clinical trial. This can be facilitated by input and advice from other investigators familiar with the design and performance of preclinical studies to demonstrate therapeutic promise. Assistance may take the form of evaluating the cells in animal models of the disease and/or *in vitro* experiments to show that the therapeutic candidate can achieve the desired effects in the laboratory [1]. Even at this early stage, a team approach is encouraged, involving individuals with an understanding of experimental models, statistical design, pharmacology/toxicology studies, generation of a preclinical data package and of potential barriers to manufacturing the therapeutic candidate for therapeutic use. These studies should result in the identification of a cellular product in a form that is ready for (or can easily be adapted to) evaluation in clinical trials.

Resource development: study team

Once a promising therapeutic candidate has been identified, and preclinical studies have confirmed its potential value, a team must be assembled to determine the resources required to move the candidate through to a clinical study. The resources are not only financial but must include individuals with the appropriate expertise. These should include the Principal Investigator (PI): the individual who has ultimate responsibility for the clinical study and is familiar with the therapeutic potential of the product and the IND process; the Project Manager: the individual who coordinates the efforts of the study team and ensuring milestones and timelines are met within the project budget. The project manager flags issues and works with the team to develop strategies to mitigate risks and serves a key role in facilitating technology transfer and process development through effective management of people and resources; the Clinical Research Team: composed of physicians, research nurses, clinical research associates and other staff who conduct subject enrollment, treatment and follow-up care. Technology Transfer, Product Development and Good Manufacturing Practice (GMP) manufacturing experts work closely together and interface directly with the basic researchers, the PI, study team, quality assurance and regulatory experts to transition processes from the discovery or translational phases to larger-scale GMP-compliant manufacturing procedures to produce cells for the clinical trials. The manufacturing technologists must be trained in both GMP compliance and also on the standard operating procedures (SOPs) for making and testing the new product (see "Translational phase" section). Biostatisticians assist the PI and study team with formulation of aims/hypotheses, study design and identification of appropriate sample sizes. The biostatistician performs interim and final statistical analysis. Regulatory experts provide regulatory oversight of the project from research development through clinical trials. They are involved in preparing and submitting data to the regulatory groups overseeing the clinical trial, such as the FDA, institutional review board (IRB) and data and safety monitoring board. Quality Assurance experts ensure compliance with GMP regulations throughout product development and manufacturing and verify that the clinical product meets predefined lot release criteria. They conduct compliance audits and advise on product manufacturing issues. Quality control experts perform release testing on the clinical products under SOPs and provide data to demonstrate ongoing GMP compliance.

Translational phase

It is not uncommon for a PI to underestimate time, costs, and the regulatory/quality challenges associated with bridging the gap between discovery and clinical trials. In the academic setting, the primary measure of success is a strong publication record, which may be important for product development but is not predictive for determining product efficacy. Investigators are also motivated, out of necessity, to write grant applications, which, to be competitive, require innovative technologies and ideas that identify underlying mechanisms and continue to build on the core scientific