BRMAC Meeting #27
Human Stem Cells as Cellular Replacement Therapies for Neurological Disorders
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BRIEFING DOCUMENT

INTRODUCTION

FDA recognizes that therapies based on stem cell technology may hold unprecedented potential. Among many conditions for which this class of products might be considered, serious disorders of the nervous system are prominent. Conventional treatment for these diseases is often nonexistent or unsatisfactory. Available preclinical data appear to provide rationale for the use of cellular replacement therapies in several CNS indications. Existing evidence suggests that certain types of pluripotential cells delivered to the CNS may be unusually responsive to signals from the local environment, and so adopt characteristics appropriate to the desired clinical effect. In other cases, it may be possible to supply signals *ex vivo* that will instruct cells to assume desired characteristics following administration. Accordingly, initial human safety studies involving stem cells in patients with serious diseases of the central nervous system are likely to be proposed in the near future.

MEETING SCOPE

The purpose of the workshop is to provide FDA with the best scientific and medical guidance available to facilitate appropriate regulatory decisions relating to cellular replacement therapies in neurological disorders. Though there may be important technical considerations specific to different types of stem cells, FDA believes that many aspects of the regulatory framework for these cells will not depend on their source, and that the appropriateness or inappropriateness of certain sources of cells is beyond the scope of FDA's authority. Therefore, questions related to this issue are explicitly excluded from this discussion.

All cellular products present many complex issues not encountered with other classes of biologicals. These products can easily support the growth of many pathogenic microorganisms and cannot be sterilized. Moreover, they quite likely will be administered to very sensitive sites, such as the central nervous system. Thus, efforts to minimize risks (e.g., stringent microbiological controls) and to justify these risks (e.g., a rationale for human use supported by appropriate animal studies) are of special importance. Since these issues are generic to other types of cellular therapies, they have been considered previously (see relevant guidance at http://www.fda.gov/cber/gdlns/somgene.pdf). These issues will therefore also be outside the scope of this workshop.

Production of some pluripotential cells is done with feeder cells of murine origin. Any such product will need to address special requirements FDA has implemented to minimize the risks of xenogeneic source materials, as described in existing guidance

(http://www.fda.cber/guidelines.htm). Issues specific to xenotransplantation will thus be excluded from discussion at this meeting.

FDA therefore needs to identify the novel and significant issues that must be considered in order to evaluate the risks and benefits of these novel approaches intelligently. These types of questions generally fall into three main categories: Product, Preclinical Pharmacology and Toxicology, and Clinical Trial Design and Analysis. The issues we wish to focus on are described more fully below and in the accompanying lists of questions to be posed.

PRODUCT CONSIDERATIONS

Rationale

A new investigation begins with a solid rationale for the production and use of the experimental product. An understanding of the concepts on which both the production and the rationale for clinical use are based is essential to guide oversight of experiments.

- What is the basic biology and technology involved in the manufacture, formulation, and administration of the therapeutic material?

- Do pluripotential cells of various origins have different properties? What are they? Can they be analyzed?

Source Controls

"Source controls" refer to formal criteria for accepting or rejecting starting materials used in the production of a biologic product, and for ensuring the ability of a manufacturer to trace a final product to its source unambiguously. Experience has taught the importance of such controls repeatedly. They are considered a cornerstone of our regulatory policy for all biologics.

- What controls over the source of donor tissue are appropriate?

    - Will donor screening according to existing blood banking criteria be sufficient to address risks from transmissible diseases? Should re-testing of donors for HIV following the 'window' period be done routinely if the constraints of product manufacture allow this?

    - Should donors be screened for known heritable neurologic disorders (e.g., Huntington's Disease, familial forms of ALS, Parkinson's Disease, etc.)? Should positive test results exclude donors? If so, under what circum-stances? For example, should the exclusion be for all uses of the cells, or only for those presently known to be relevant to the proposed use (e.g., Huntingtin gene defect for use in the potential treatment of Huntington's Disease)? What should be done with the information?

    - If the donor can not be identified, will it be appropriate to so indicate on the consent form?

Process Controls

It is usually the case that available scientific knowledge is insufficient to allow definitive characterization of a product by analytical means alone. Careful control over the manufacturing processes is therefore essential to produce a safe, effective product consistently. As scientific understanding and manufacturing experience accumulate, understanding of the critical process elements improves. Because stem cell technology is quite new, it is especially important for FDA to assess the current level of knowledge in this area.

- What elements of product manufacture are critical to ensure a safe, effective, consistent product? Examples of parameters to be evaluated might include media and media components, cell density, feeder layers, oxygen tension, and so forth.

- What process parameters remain to be evaluated carefully before initiation of human trials?

- Are tests available to assess the integrity of the manufacturing process at intermediate steps? What are they?

Characterization and Specifications

All biological products need to be characterized as fully as current technology allows. In the area of cellular therapies, this is a special challenge for two primary reasons. The obvious one is that living cells are far more complex than most other biological products. This suggests that evaluation may need to be more involved than for other types of products. The other concern is that in most-if not all-cases, current understanding of cellular and developmental biology does not allow definitive conclusions regarding a cell-based product to be based on analytical procedures alone. This is made especially challenging by the fact that the therapeutic material will quite likely assume final characteristics following administration that will be impossible to assess in the biological product itself. Nevertheless, serious effort should be directed toward identification of measurable product characteristics that may be related to product efficacy and safety. Based on comprehensive characterization studies, a subset of the tests evaluated can be proposed as product specifications. These may be modified as experience provides additional insights. As for process controls, available knowledge in this area must be evaluated.

- What characteristics of stem cells are related to optimal, mediocre, or unacceptable performance?

- Has evaluation been sufficiently detailed to allow a set of tests to be developed that will ensure that the product has consistent properties and acceptable performance?

- What specifications will be useful to establish identity?

- What specifications will be useful to establish purity? Impurities?

- What assays can be used to predict desirable performance (potency)?

- How will the answers to these questions depend on the nature (e.g., autologous, allogeneic germ cell, allogeneic stem cell) and manufacture (ex vivo modifications-genetic, via exogenous growth factors, etc.) of the stem cell product?

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Generic Questions

Certain questions apply to all products based on stem cells. Given the current level of understanding of these products, it is not clear which of these concerns represent real safety issues. FDA therefore needs guidance on several questions:

- What is the potential of stem cells to form tumors? If some types of products can form tumors, how frequently does this occur? Should potentially tumorigenic cells be engineered to express 'suicide genes'?

- Implanted cells may migrate to sites quite distant from that of original implantation. Is this *ipso facto* a safety issue? How may this question best be resolved?

Cell Fate, Determination, and Specification

The ultimate fate of exogenous cells may depend on both cell autonomous and cell non-autonomous factors. The balance between these factors may depend on both the site of administration and the influence of manufacturing procedures on the competence of the cells to respond to instruction by local signals from the host tissue. The fate of the cells following administration is of course the essential factor in determining the safety and clinical effectiveness of the therapy. Several questions are germane:

- What methods or combinations of methods are best (sensitive, specific, comprehensive) to assess cell fate? Biochemical studies? Immunohistochemistry? Hybridization in situ? Cell marking experiments? Others?

- How long should animals be followed? How long should exogenous cells survive in preclinical models to justify the risks of initial human experiments?

- What are the risks of inappropriate fate specification? How serious are these risks?

Proliferation: Non-Neoplastic

- Is the possibility of inappropriate proliferation of implanted cells-without malignant transformation-a safety concern?

- How shall this be evaluated?

- Should such studies be routine in developing a rationale to support initial doses in humans?

It is likely that many of the products under consideration will consist of more than one cell type. The possibility that each type might behave differently following administration therefore needs to be considered.

- How should the issue of product heterogeneity be assessed preclinically?

Models-General Considerations

Given the indications being considered, the likely routes of administration present special concerns. Certain models (e.g., rodents) may be appropriate for initial preclinical studies, but may not reflect adequately the anatomical characteristics of humans.

- Is this the case?

- Does this represent a consensus in the field?

- As before, if not, enumerate the salient viewpoints.

Specific Models

It is often the case that the comparison of perceived risk to potential benefit depends on the adequacy of existing preclinical evidence in the context of the specific clinical situation under consideration. FDA does not wish to judge prospectively whether particular indications are appropriate or inappropriate for initial trials. Nevertheless, it may be feasible to identify particular clinical indications and eligibility criteria for which preclinical experimentation has provided especially favorable prospects. In some of these cases, conventional therapeutic alternatives may be unsatisfactory. Enumeration of such clinical/preclinical correlates would be useful.

Moreover, substantial consensus may exist regarding appropriate preclinical models and experimental paradigms relevant to these clinical indications. Enumeration of broad areas of consensus could accelerate product development by facilitating comparisons of different approaches and by reducing duplication of effort. In these cases, a concise summary of areas of consensus would be quite valuable. Conversely, identification of controversial areas, and concise summaries of the arguments and evidence supporting alternative viewpoints, would be very useful. Finally, for situations where additional pre-clinical studies prior to initial clinical trials are needed, there may be agreement on the nature of these preclinical studies. Enumeration of the appropriate experiments would also advance the field.

Key questions to be discussed are thus:

- Can clinical situations be identified for which *existing* preclinical and manufacturing information provide strong rationale in support of human trials?

- Does available proof-of-concept data justify initial human trials? If not, what further studies are needed?

- Is the preclinical safety database adequate to justify initial human trials? If not, what further studies should be done?

- Does existing preclinical data support appropriate dosing for initial human studies?

- Conversely, are there disorders or classes of patients for which the above information clearly is inadequate?

- Where information is inadequate to support human trials, what additional studies remain to be performed?

- With respect to these questions, is there consensus in the field or not? If not, enumerate the salient viewpoints.

In certain types of disorders, there may be sufficient information at present to recommend particular preclinical models or combinations of models and perhaps even experimental paradigms.

ATTACHMENTS

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