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COMMENTARY

The American Society for Neural Transplantation and Repair Considerations and Guidelines for Studies of Human Subjects The Practice Committee of the Society Approved by Council

D. E. Redmond, Jr., Chairperson; Thomas Freeman, Co-Chairperson;
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Goal: An important goal of the American Society for Neural Transplantation and Repair is to facilitate the discovery of novel cellular and molecular treatments for nervous system (neural) diseases and disorders. *The ASNTR recommends* that investigators and members of the Society consider the following in planning and carrying out studies of possible new treatments for nervous system diseases and disorders in human research subjects.

I. GENERAL CONSIDERATIONS

The research plan should proceed according to established clinical trial principles and federal guidelines. Any special issues related to the disease or condition being studied should be addressed, including problems with informed consent, the adequacy and limitations of present treatments, the considerations regarding the appropriate stage of the disease for intervention, and the expected course of the disease left untreated or utilizing the best available treatments. There should be enough known about the mechanisms of the disease and the proposed intervention to suggest that the risks to the subjects are reasonable in light of a possible benefit to the subjects or society from the knowledge acquired.

II. PRECLINICAL STUDIES

Appropriate data should be acquired in animals prior to human studies. The types of animal studies required might differ depending upon the target condition and the therapeutic modality that is the subject of the investigation. The status of animal models for each target disorder should be considered in determining what studies are most likely to offer the ability to predict any benefits. In general, the proposed treatment should be tested in the best animal models of the target condition, and the results should be clearly beneficial in these models and should be peer reviewed by independent experts. Preferably, the principal preclinical findings should be published in peer-reviewed journals. Safety issues should also be evaluated in the best and most appropriate animal model for potential toxicities including nonhuman primates if appropriate. These considerations may lead to the need to conduct the preclinical benefit studies and the safety studies separately in different models, so as to obtain the best information regarding both aspects.

A. Safety Issues for Consideration Related to Novel Treatments

1. **Any treatment:** Toxicity of treatments and interventions, including biological products, should be determined and should be within limits that are acceptable assuming that the treatments are successful. Any toxicity should be in reasonable balance with evidence for possible benefits.
2. **Cell-based treatments:** Fetal tissue, stem cells, other cell lines, cross-species tissue, or cell sources should be specifically tested to minimize the possibility of biological contamination. For cell lines and sources which may have continued potential for growth, the tissue sources should be tested to minimize the possibility of uncontrolled growth, tumor formation, or undesirable migration. Cellular products which have the potential for differentiation into varied phenotypes or undesirable migration should be assessed for those possibilities in the neural location intended for use.
3. **Molecular and gene therapy interventions:** There should be a justification and supporting preclinical data for the proposed choice of delivery system or vector compared with other possibilities. Toxicity of vector constructs and any gene products on cells, tissue, and animals should be balanced against the possible benefits. The absence of effects on the germ

line and progeny should be demonstrated, as well as the absence of vector/viral replication or reversion to wild-type virus. The spread of the vector in the host which depends on host mechanisms, such as retrograde transport, should be determined specifically in the most appropriate animal species, and possible adverse consequences considered.

The spatial, temporal, and quantitative analyses of transgene expression should be determined and should be adequate to expect a useful therapeutic effect in the target condition and one that can likely be measured during a reasonable time period for study. The consequences of extended, unregulated, and supraphysiologic transgene expression from vectors should be considered and justified if there is no means for regulating transgene expression or activity.

4. **Ex vivo gene therapy:** For the combination of gene and cell-based interventions, such as "ex vivo gene therapy," the rationale should be explained for using autologous vs. nonautologous cells, isotopic vs. nonisotopic cell grafts, or the use of xenografts. Any special risks of using the sources should be determined empirically if possible. All of the safety issues raised for cell-based treatments should also be considered for cells used for ex vivo gene therapy.

B. Evidence of Beneficial Effects

The cellular, metabolic, hormonal, behavioral responses, and physiological responses in the host animal that are evoked by the intervention should be consistent with the intent of the intervention. Any significant systemic effects or other undesirable effects should be considered. Recognition should be given that the relative balance of desired and undesired effects may differ between animal models and human subjects. Persistent effects of treatments should be demonstrated in appropriate animal models for a period that, at the minimum, would be sufficient to demonstrate and measure a safety issue or a beneficial effect, considering the known variability of the disorder or condition and the precision of the best measurement instruments. Studies should be carried out in the best available model of the disorder.

III. CLINICAL STUDIES

The design and conduct of the study, with regard to the risks and possible benefits, patient consent, risk, conflict of interest disclosures, clinical competency of the investigators and clinicians should be in full compliance with the regulations of the local jurisdictions in which any portion of the study takes place. Regulations of the U.S. Food and Drug Administration, Institutional Review Boards, and specific regulations related to the procurement and use of fetal tissue, transplanted tissue, recombinant DNA, propagated cells, etc., should be consulted and met if appropriate. The following study design issues should be considered.

A. Study Phases

Studies should follow the model of initial safety assessment (Phase I), followed by establishing early indications of activity and dose/regimen selection (Phase II), and Phase III for the establishment of the definitive assessment of safety and efficacy. In initial safety and toxicity studies, functional outcome measures should be as objective as possible to avoid participant or experimenter bias. As much information about physiologic or functional activity as possible should be obtained in "safety studies" without compromising the primary aims. In later studies, the best generally accepted rating scales in the field should be used to determine clinical effects, providing data that are understandable to others and which will allow comparison among various established and novel treatments.

B. Study Duration

Improvement should be judged significant at a time point which will be conclusive, consistent with the known variability of the condition during the best treatments.

C. Study Size

Studies should be large enough to meet the study objectives. Later studies to assess efficacy should be sized with consideration of existing data in the field, the size of likely effects, variability of the disease, and effects predicted from animal studies.

D. Existing Treatments for the Target Condition Should be Considered in the Study Protocol in the Following Ways

1. The existence or absence of an effective treatment may influence the risk/benefit ratio for proceeding with the experiment. For example, a gene therapy study for a fatal disease with no treatments might be ethically acceptable with more unknowns and possible toxicity than a similar study for a nonfatal condition with treatments already available.
2. Can patients be studied without medication for adequate periods of time? If this would not work for the entire study, could it be done for fixed evaluation periods to eliminate some of the influence of medications on outcome—"drug holidays?"
3. Can patients be studied with "fixed doses" of optimized medication, if medications are required? Can these reasonably be maintained over sufficient periods of time?

4. Can patients be studied with "optimized" medication management in addition to the proposed new treatment?
5. Other medications and treatments which are administered during the study period should be minimized (consistent with patient safety), recorded, reported, and their impact on study outcome considered.

E. Participant/Subject Selection, Assignment to Study Groups, and Statistical Analyses

The criteria for participant selection should be defined to give the appropriate population for each phase of investigation. Highly homogeneous groups may be more readily interpretable, but less generalizable to the full diversity of the patient population. Narrowly defined groups may be safer in initial studies, but may not adequately assess safety in the broad patient population. Consideration should be given in each phase to exclude conditions which would confound interpretation or be likely to suffer excessive adverse events during the study. Subjects should be randomly assigned to active or control groups. Plans for data collection and statistical analyses should be included in the study design, and data management resources should be adequate for all aspects of the studies.

F. Control or Comparison Groups

The clinical study should include controls or comparison groups and unbiased procedures, depending upon the stage of the study. Control groups that would be ideal for animal studies might be inappropriate for human studies and vice versa. Possible experimental controls might include the use of sham surgery or "imitation operation" as a means to control bias. Studies should minimize harm to participants whenever possible, consistent with achieving an unbiased assessment of outcome.

G. Immune Problems and Rejection

Since many currently considered treatment strategies carry the risk of producing an immune response in the recipient, the research plan should consider how an immune response would be measured and prevented and how it would impact on study outcome.

H. Assessment Methods Should Be Comparable to Other Studies in the Field

New studies should use comparable assessment methods to those of other investigators and to standard studies of the target condition. Additional, perhaps improved, methods are not precluded, but there are significant disadvantages for significant progress if the various studies cannot be meaningfully compared.

I. Independent Evidence of the Activity of the Studied Intervention Should Be Obtained as a Part of the Study Design

Ideally, a clinical study should include in vivo assessments of the treatment intervention which are independent of the clinical toxicity or functional outcome measures. These might include imaging studies such as PET, SPECT, MRI, fMRI, or cerebrospinal fluid metabolites or indicators, if they might provide independent evidence of the status of the studied intervention. Although these measures will not substitute for nor supplant clinical assessments, a clinical study lacking such measures may be more difficult to interpret. Every effort should be made, as a part of the study design and subject consent, to obtain autopsy material for evaluation in the event of the death of a research subject. A plan for how these samples will be obtained and studied, under the difficult conditions which are likely, should be included as a part of the research protocol.

J. Patient Informed Consent

Each subject involved in a clinical study should give appropriate consent for participation in the study, being fully informed as to whether the study aims to produce basic scientific knowledge, disease-specific knowledge, or potentially individual therapeutic benefit to the participant, as well as an idea of the possible negative outcomes. This written consent should meet the standards and be approved by the Institutional Review Board of the institution.

IV. CONSIDERATIONS RELATED TO CONFLICTS OF INTEREST

Commercial patentable interests should not operate to the detriment of the free sharing of scientific information and the adherence to these goals and considerations. The ASNTR believes that it is in the best interest of society and of patients that studies be carried out in the best manner possible, that results, both positive and negative, are communicated by publication after a reasonable limited period of notification to allow the protection of new intellectual property. Financial support for and potential conflicts of interest by ASNTR investigators should be fully disclosed during publication or presentation of data. Such support or potential conflicts include the ownership of patent interests, stock or stock options valued at more than $10,000, paid consultantships, or membership in Scientific Advisory Boards of companies which might benefit from the study. *The Society, in addition, supports the Ethical Guidelines of the Society for Neuroscience.*

V. PUBLICATION AND COMMUNICATION OF STUDY RESULTS

The ASNTR supports the free and open communication of study results to the scientific community and to the public. The Society notes, however, that communication of study outcomes to the general public through press releases, news conferences, and interviews with reporters, prior to publication of results in a peer-reviewed journal, deprives the public of the protection of the peer review process and may jeopardize appropriate publication in leading journals. This process may also confuse and mislead patients and reflect unfavorably on the scientists and the entire field. These consequences are particularly unfortunate for clinical studies in our field and should be avoided.

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OTHER USEFUL DOCUMENTS TO CONSULT

- Guidelines for the Use of Fetal Tissue. http://www.fda.gov/cber/genadmin/frtissue.pdf
- Uniform Anatomical Gift Act. http://www.law.upenn.edu/bll/ulc/fnact99/uaga87.htm
- Regulations on storage and transplantation of tissue. http://www.epa.gov/fedrgstr/EPA-IMPACT/2001/January/Day-19/i1126.htm; http://www.fda.gov/cber/rules gtp010801pr.htm
- FDA Part 1270—Human Tissue Intended for Transplantation. DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration 21 CFR Parts 210, 211, 820, and 1271 [Docket No. 97N-484S] Suitability Determination for Donors of Human Cellular and Tissue-Based Products. http://www.fda.gov/cber/genadmin/frtissue.pdf
- Gudelines for Gene Therapy by Federal Regulatory Agencies. http://www.fda.gov/cber/infosheets/genezn.htm; http://www.fda.gov/cber/rules/frgene011801.htm; http://www4.od.nih.gov/oba/rac/guidelines/guidelines.htm
- G. J. Boer et al. NECTAR: Ethical guidelines for the use of human embryonic or fetal tissue for experimental and clinical neurotransplantation and research. J. Neurol. 242:1–13; 1994.
- D. A. Kessler et al. Regulation of somatic-cell therapy and gene therapy by the Food and Drug Administration. N. Engl. J. Med. 329(16):1169–1173; 1993.
- Information on submitting an Investigational New Drug Application For a Biological Product IND Regulations (PDF)—Title 21 of the Code of Federal Regulations (CFR), Part 312 (21 CFR 312). www.fda.gov/cber/ind/21cfr312.pdf

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