BRMAC Meeting: July 13-14, 2000
Human Stem Cells as Cellular Replacement Therapies for Neurological Disorders
July 13-14, 2000
Hilton Hotel, Gaithersburg, MD

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY: Discussion Questions

One of the many unique challenges created by the use of stem cell therapy for neurological disorders is the determination of safety and efficacy in the preclinical arena prior to initiation of these therapies in humans. The primary intent of preclinical safety studies is to acquire information that enables clinical trials to be conducted. Moreover, experimental results obtained by preclinical testing aid in avoiding additional injury which could result in a decreased life-span or diminished quality of life (i.e., increased disease progression or enhanced degree of disability, possible morbidity incurred from the cell implantation, etc…). There are numerous questions/considerations that need to be addressed in the extrapolation of safety/efficacy data from animal models to human physiology. Ideally, preclinical studies should provide information about potential toxicities as well as establish a basis for dose selection in the proposed clinical trial.

Listed below is a series of concerns that have evolved and which pertain to effective safety assessment of stem cell therapies for human neurological disorders using data derived from well designed preclinical animal studies.

1. Animal Models

What considerations should be used to select the most appropriate animal model for the assessment of the safety and/or to determine the potential for efficacy of the intended cellular therapy?

a. How predictive are existent animal models for safety evaluation in humans?

b. How accurately does the animal model(s) mimic the target human population and disease process?

2. Tumorigenicity

Please discuss the need for assessment of each stem cell source for the potential to elicit tumor formation:

a. How does one assess the tumorigenic potential of a particular cellular therapy?

b. What are the most appropriate animal species to use and what should the study duration be?

3. Post-Implantation Cellular Fate

- **Relevance of Migration**
- **Cellular Differentiation (cell autonomy vs. competence to respond to instructive signals from the host)**
- **Analysis of Cell Phenotype (molecular markers, morphology, etc.)**
- **Anatomic and Functional Integration**
- **Survival of Implanted Cells**

Issues

a. What species should be used (i.e., rodent/non-rodent) for the preclinical studies?

b. What should the duration of the preclinical studies be in order to assess the above parameters adequately?

c. Please discuss the parameters that should be incorporated into preclinical studies (e.g., observational, detailed behavioral, electrophysiological, biochemical, etc…) in order to evaluate the potential for adverse effects to occur due to the following:

- Existing evidence of cell migration
- Existing evidence, anatomical, biochemical, or functional, for various fates (desired vs. undesired) of the implanted cells
- Excessive activity of the differentiated, post-implantation stem cells, due, for example, to unanticipated hyperplasia or unusually high pharmacologic, electrical, or metabolic activity of the cells
- Appropriate vs. inappropriate integration of the cells over time
- Death of some/all of the implanted cells

d. Please discuss the types of data (i.e., general histopathological, immunohistochemical, etc.) that should be generated in the animal studies following implantation to adequately evaluate the above parameters.

e. If behavioral data are needed in order to address the safety of stem cell therapy adequately, what assessment measures should be used in order to assure a reasonable level of safety?

f. Please discuss how these data should be used in the overall interpretation of safety assessment.

g. Please discuss how best to determine whether implanted stem cells will behave in a manner that is different from their host-derived counterparts as a function of age or trauma. Will "young" (embryonic/fetal) or "old" (adult) stem cells function in a manner that is reflective of their "age"?

h. Please discuss the various rationales used for determining the administered clinical dose, such as: 1) based on total cell number; 2) based on the number of cells possessing a desired neuronal phenotype(s); or 3) based on the estimated amount/level of a specific neurotransmitter or biochemical marker.

i. Please discuss any additional safety concerns not yet identified.