

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

Hypothetical Case Description: Clinical Trials of Human Neurostem Cells for Neonatal Hypoxic-Ischemic Injury

Hypoxic-ischemic injury is a common cause of neonatal brain injury in preterm and term infants, leading to significant neurological deficits such as learning disabilities, cerebral palsy or mental retardation. Injury to oligodendrocyte precursor cells may contribute to the pathogenesis of hypoxic-ischemic injury by disrupting the maturation of myelin-forming oligodendrocytes. As documented in the literature, human neurostem cells (HNSC) have demonstrated the capacity to engraft, proliferate, migrate and differentiate into different neural phenotypes in vitro and in vivo, using neonatal mouse models. These (and other) observations have led to the hypothesis that inserted HNSCs may reduce or reverse the neurological deficit secondary to neonatal brain injury after a hypoxic-ischemic event.

There are several experimental animal models of neonatal hypoxic-ischemic injury that are discussed in the literature. Perinatal rodent models have been developed as an experimental platform of hypoxic-ischemic injury for preclinical testing of potential therapeutic interventions. However, they do not reproduce the many distinct physiologic features unique to the premature human infant. Other models are thus being developed such as the preterm fetal sheep and non-human primate models (e.g., the preterm baboon and rhesus monkey). Several investigators are currently exploring the role of HNSCs in reducing or reversing hypoxic-ischemic injury in these different models in anticipation of pediatric clinical trials. Of necessity, the HNSCs would need to be surgically inserted while a child was under general anesthesia – rendering the experimental intervention greater than minimal risk regardless of the risks of stem cell insertion. In addition, the child may need immunosuppressive medication to assure engraftment.

Questions:

- (1) Please discuss the ethical issues in selecting an appropriate subject population for the initial clinical development plan of these HNSC products. Issues you may want to consider include: (a) differences in the natural history of the disease between adults and pediatric subjects which may influence the timing of HNSC insertion; (b) whether dosing, safety and/or efficacy should first be established in suitable adult subjects prior to enrolling children; and (c) differences between pediatric and adult subjects with hypoxic-ischemic brain injury (e.g., possibility of direct benefit, usefulness of safety information, assessment of physiologic response, long-term effects).
- (2) Please discuss the ethical issues in designing a “first-in-children” clinical trial of these HNSC products. Issues you may want to consider include: (a) the need to establish a sufficient prospect of direct benefit to justify the risk of the experimental intervention; (b) the range of animal models available for pre-clinical studies; (c) the different types of physiologic changes in response to the experimental product (e.g., structural, functional, disease reversal); (d) the severity of the disease; and (e) the availability of alternative treatments.

Hypothetical Case Description: Clinical Trials of Human Neurostem Cells for Neonatal Hypoxic-Ischemic Injury

Background Literature:

Back, S. A. and S. A. Rivkees (2004). "Emerging concepts in periventricular white matter injury." *Seminars in Perinatology* 28(6): 405-14.

Back, S. A., A. Riddle, et al. (2006). "Role of instrumented fetal sheep preparations in defining the pathogenesis of human periventricular white-matter injury." *Journal of Child Neurology* 21(7): 582-9.

Belicchi, M., F. Pisati, et al. (2004). "Human skin-derived stem cells migrate throughout forebrain and differentiate into astrocytes after injection into adult mouse brain." *Journal of Neuroscience Research* 77(4): 475-86.

Ferriero, D. M. (2006). "Can we define the pathogenesis of human periventricular white-matter injury using animal models?" *J Child Neurol* 21(7): 580-1.

Inder, T., J. Neil, et al. (2004). "Non-human primate models of neonatal brain injury." *Semin Perinatol* 28(6): 396-404.

McKenzie, I. A., J. Biernaskie, et al. (2006). "Skin-derived precursors generate myelinating Schwann cells for the injured and dysmyelinated nervous system." *Journal of Neuroscience* 26(24): 6651-60.

Vannucci, R. C. and S. J. Vannucci (2005). "Perinatal hypoxic-ischemic brain damage: evolution of an animal model." *Developmental Neuroscience* 27(2-4): 81-6.