Cell therapy represents a new frontier in the development of therapeutics for stroke. Aside from physical rehabilitation, few options exist to enhance recovery from stroke. Prior studies in the 1990s provided precedence for considering a cellular approach to treat neurological disorders with the pioneering work on transplantation in Parkinson disease. These trials furnished preliminary evidence for a modest benefit in young patients with a neurodegenerative disorder who underwent neural transplantation. From those initial studies, pilot work emerged on the application of cellular replacement in Huntington disease and other neurological disorders. In an entirely different area of medicine, stem cell transplantation in oncology provided support for the idea that stem cells could be administered intravenously for a range of disorders including stroke. Over the past decade, investigators accordingly began showing that intravenously injected stem cells from the bone marrow and umbilical cord could promote recovery in animal stroke models. Thus began a new area of investigation in which adult stem cells from other sources, rather than the brain, could be tested for therapeutic applications in stroke.

As transplantation studies have been growing, it has also now clearly been established that the adult brain undergoes neurogenesis. Elegant work from Lindvall and Parent and others have shown that the periventricular regenerative zones of the brain upregulate neural stem cell proliferation in response to ischemic stroke. Newly generated progenitor cells migrate to the site of injury and differentiate, but most die before they are able to integrate and function as mature neurons. The brain, therefore, has the capacity for self-repair. Thus began a new area of investigation in which adult stem cells from other sources, rather than the brain, could be tested for therapeutic applications in stroke.

Goals of Cell Therapy
How would the administration of cells enhance repair? At first, the goal over a decade ago was to promote tissue grafting to repair lost neuronal connections and conductivity. Over time, the field has changed with alternative or additional aims. An increasing number of studies suggest that exogenous cells serve as a source of trophic support, promoting endogenous repair such as neurogenesis, angiogenesis, and synaptogenesis. Still yet, a third goal is to prevent ongoing cell death, dampen the inflammatory response, and potentially reduce scar formation. It is therefore not necessary that cells exhibit the properties of stem cells to exert these mechanisms of action.

Complexity of Cell Transplantation for Stroke
Although the goals of cellular therapy have changed over time, ischemic stroke as a clinical entity poses special conditions that need to be considered in designing cell therapy studies. First, there are anatomical issues: which infarcts should be considered, including location and size. Multiple types of neurons and neurotransmitter systems can be damaged in a stroke. Nonneuronal cells such as glia, endothelia that form the neurovascular unit, are also affected. Should posterior circulation strokes be included in clinical studies because animal modeling is mainly based on middle cerebral artery occlusion? Should gray matter versus white matter strokes be considered separately? Second, when should cellular injection be contemplated after stroke? In the acute stage, excitotoxicity, oxidative stress, and inflammation may threaten any new cells introduced into the freshly ischemic area. Waiting until the chronic phase allows for natural recovery, but fewer studies have shown an effect in animals when cells are administered at later time points after stroke. Third, the route of delivery is very much under debate. A direct injection might be the most reliable to ensure cells are in the brain. A less invasive route may be an intracarotid injection and an intravenous route is the least invasive; in some laboratories, intravenous administration leads to selective migration of cells to the injured brain. However, the pulmonary barrier may preclude many types of intravenously injected stem cells from entering the injured brain. But is it unclear at this point whether exogenous cells even need to enter the brain to exert a therapeutic effect. The cerebrovascular may play an important role if exogenous cells need to penetrate the injured areas of the brain parenchyma. A large vessel occlusion may obstruct cells intra-arterially injected depending on the release site, for example, while an intravenous route may direct cells through collateral vessels.

Complexity of Different Cell Types
Although stroke is a complex condition to consider for cell therapy, we also face the complexity of different cell types.
A range of cells are under investigation from embryonic stem cells to neural stem cells to adult stem cells from the umbilical cord, blood, fat, and bone marrow. Various heterogeneous cellular preparations containing different populations of cells such as bone marrow or umbilical cord mononuclear cells are also being tested. Which types of cells may prove to be safer or better remain purely speculative and await comparison studies. The same questions also apply to allogeneic versus autologous administration.

Speakers
In this section, we are fortunate to have 4 leaders in stroke cell therapy who address key areas of research in this field. First, Michael Chopp discusses his experience on what are the real mechanisms of cell therapy. His laboratory has generated a wealth of data showing that the underlying biochemical mechanisms of cell therapy are multifactorial. Cesar Borlongan shares his experience on what are the remaining preclinical issues that still need to be explored before advancing cellular products to clinical trials. Larry Wechsler has already conducted one of the first clinical trials in neural cell therapy for stroke and discusses what we have learned from pilot safety studies. Finally, Alison Willing, who has been investigating umbilical cord cells, addresses the question of how do our experimental models influence our progress in the development of cell therapy for stroke.

Future
The future for cell therapy is exciting. The field is still in its infancy as it enters the clinical arena for certain cell types. Which cells should be tested in clinical trials? Do we need comparison studies? How long should patients be followed in initial safety studies? What are the real risks after cell administration, including the potential for acute toxicity, tumors, and seizures? Are large animals needed and for what purpose? What sorts of surrogates of activity from the cells can be embedded in our clinical trials? We look forward to a plethora of fruitful studies ahead to answer these and other questions in the future.

Key Words: cell therapy / stroke care / stroke therapeutics
Introduction to Cellular Therapy: The Next Frontier for Stroke Therapeutics

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