Cell Therapy: Exploring New Approaches to Identify Potential Stroke Treatments

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In this special issue, articles have been solicited to cover key topics in the field of cell therapy for stroke. An ever increasing number of cell types have been shown to improve neurological outcome in animal stroke models. Many of these cellular preparations are attractive because they are derived from readily available tissues such as bone marrow, blood, placenta, umbilical cord, and fat. Even dental pulp, menstrual blood, and amniotic fluid harbor cells that can be purified and possibly manufactured to develop potential cellular therapies. Pivotal translational questions that will advance this field are being tackled by various leaders in stem cell biology and neuroscience. We are honored to have contributions by many of these leaders in this special issue.

A major question, for example, is the optimal delivery routes for the administration of cells. Intra-arterial delivery is a popular approach in the cardiology literature given that endovascular therapy is the main treatment approach for acute coronary syndromes. However, in stroke, we are concerned that intra-arterial administration of cells can lead to embolization and microvascular plugging. How do we study and design approaches to reduce this potential risk in animal models? Raphael Guzman has been tackling this issue in his laboratory and reviews intra-arterial delivery of cell therapies in stroke. Another more direct route of cell administration is stereotactic delivery into the brain parenchyma. Keith Muir is the principal investigator of the ReNeuron Trial, a phase I study on the safety of intracranial injection of neural stem cells. Dr. Muir

discusses important variables that impact the safety of this approach in patients with chronic stroke.

The use of neural stem cells has undergone a rollercoaster in popularity among studied cell types for stroke. Initially, there was much interest to use neural cells for stroke in the 1990s, but the availability of fetal tissue limited their clinical applications. With the rise in the use of “alterative” cell types from adult tissues such as bone marrow, the study of NSCs declined in the first decade of this century. But, improvements in technology and increased availability of tissue including embryonic tissue have brought NSCs back to center stage. How NSCs promote recovery from stroke remains an elusive question. Investigators first used NSCs in the hopes of reconstituting lost brain circuitries, but some studies suggest that NSCs promote recovery much the same way other cell types exert an effect in the brain through the release of cytokines and trophic factors. Zaal Kokaia and his colleagues have been leaders in NSC research for more than 10 years. Dr. Kokaia discusses the most recent advances and current thinking in the use of NSCs for stroke.

While NSCs and other stem cells remain at the forefront, the field of cell therapy also involves the use of heterogeneous bone marrow or umbilical cord cell preparations, which contain many different types of cells in addition to stem cells. Bone marrow mononuclear cells (MNCs), for example, are a mixture of different populations of cells, and MNCs have been shown in multiple labs to improve outcome in rodent stroke models. Now, Johannes Boltze and his team at the Fraunhofer Institute have developed a sheep model of stroke that permits long-range neurological testing in a large animal with a gyrencephalic brain. Dr. Boltze reports that autologous bone marrow-derived MNCs reduce injury both in the grey and white matter after stroke. Based upon collective data

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from preclinical studies in stroke animal models, our center has brought forward MNCs to clinical trial and is conducting one of the first intravenous studies of bone marrow MNCs in patients with acute ischemic stroke.

Lastly, we end this special issue by focusing on the important topic of cell manufacturing. Dr. Santoshi Kuroda and his team in Japan provide original data on the challenges of manufacturing a more purified population of cells from the bone marrow, called marrow stromal cells (MSCs). MSCs have been extensively studied in the laboratory of Dr. Michael Chopp, who has written a guest editorial for this issue. The pioneering work of Dr. Chopp has led to the initiation of studies worldwide on the use of

MSCs for stroke. One of the essential issues to translate MSCs to the clinic is optimizing their manufacture without animal serum. Dr. Kuroda's group addresses key points in growing and expanding MSCs in animal serum-free medium for clinical testing. These studies will hopefully be helpful to other research teams working to create clinical-grade cells for testing in patients.

There is much interest and excitement to develop a cellular therapy to enhance recovery from stroke. Many different cell types have now entered initial safety testing in patients. We hope that the translational barriers discussed in this issue will stimulate active discussion and new research in the field.