Potential of stem/progenitor cells in treating stroke: the missing steps in translating cell therapy from laboratory to clinic

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'...it is imperative for clinical translation that these cells be tested in multiple models of focal stroke, in two species, in both genders and in multiple laboratories.'

Accumulating laboratory evidence demonstrates the potential of transplanting stem/progenitor cells for treating CNS disorders. The realization of neuroprotection or neurorestoration in the CNS challenges the central dogma that the brain is not capable of regeneration during aging or after injury. However, despite the encouraging results that lend support to CNS regeneration, critical gating items remain that limit the translation of the laboratory findings into meaningful clinical applications of cell therapy for stroke. Foremost among the several important preclinical factors that will require additional laboratory tests and validations is the establishment of a consortium of stem cell and stroke experts who will be able to independently analyze the efficacy and safety of cell therapy in stroke.

The continued failure in drug clinical trials for treatment of acute stroke has been attributed to poor experimental designs of the drug development programs that do not adhere to the Stroke Therapy Academic Industry Round Table (STAIR) guidelines. However, the recent NXY-059 (Stroke-Acute Ischemic NXY Treatment [SAINT] II) trial still failed to achieve the expected efficacy despite including many of the STAIR criteria. Accordingly, there is an urgent call to revisit the stroke drug discovery pathway [1]. There is a clear and present need to develop a consortium approach including academia, government (US FDA/NIH) and pharmaceutical industry in drug-development programs. Equally important is recognizing the need for a translational medicine approach, in particular characterizing the drug candidate nature-target interaction, as well as determining the mechanisms underlying the phenotypic outcomes.

To this end, responding to the STAIR call, our group (Borlongan, Chopp, Steinberg, Hess and Kondziolka), together with other stroke and cell-based therapy experts, and FDA and NIH representatives, played a key role in the first Stem cell Therapeutics as an Emerging Paradigm in Stroke

(STEPS) Consortium meeting (October, 2007) whose main objective was to define several key areas that are deemed relevant to the development of cell-based, biologic and pharmacological restorative therapies (hereafter referred to as restorative therapies) for the treatment of stroke. Our guiding principle was to advocate science as the catalyst for designing preclinical studies so that we can most effectively and accurately translate this research to clinical practice. This preclinical STEPS workshop recommended the following translational criteria for designing laboratory studies on cell therapy for stroke:

- The use of appropriate species and clinically relevant type of stroke models
- The standardization of outcome measures and treatment protocols
- The need for imaging of cell tracking and host response
- The requirement for safety indices
- A call for demonstrating mechanisms of action underlying restorative therapies in ischemic stroke

To the best of our knowledge, no studies on cell therapy for stroke incorporating all these STEPS preclinical workshop recommendations exist. Despite many rodent studies showing that cell transplantation can improve recovery from stroke, the variables responsible for the success of these therapies are largely unknown. Researchers have used different cell types, rodent strains, stroke models, transplant brain target locations and time points after stroke, and behavior tests to assess the transplant's efficacy (reviewed in [2-4]). Any or all of these parameters could be critical to the outcome of functional recovery. This lack of consistency in the field makes it very difficult to compare studies and truly ascertain the optimal conditions for cell transplant therapy following stroke. For example, is good functional recovery reported in one laboratory due to the cell type used or perhaps the behavior tests employed? The realization of a collaborative effort among multiple preclinical stroke laboratories evaluating the efficacy and safety of a particular stem/progenitor cell using the same testing paradigm until now remains a challenge. In order to address this significant gap

in our knowledge, we have assembled a consortium of three established preclinical stroke laboratories, interfaced with a data coordination center and a clinical advisory board. We recognize that the establishment of such consortium between academics and industry, with close guidance from the NIH and FDA, is the first step towards realizing this laboratory-to-clinic translational goal, resonating the core principle of both STEPS and STAIR. Accordingly, our preclinical consortium incorporates all the STEPS criteria. The primary goal is to harness a collaboration across three established preclinical stroke laboratories (Borlongan, Chopp and Steinberg) that have extensive experience in conducting laboratory studies in multiple species (rat and mouse), strain, age and gender, characterizing a variety of focal stroke models using a standardized set of behavioral and histological outcome measures, and demonstrating mechanisms of action for testing the potential of restorative therapies in ischemic stroke.

The fact that all three laboratories will carry out identical studies will help confirm the results for each parameter, which lends an unprecedented degree of veracity that is essential to a translational study. Investigation of the effect of age and gender on cell transplantation therapy is another novel aspect of our proposal as such parameters are generally overlooked in current rodent studies but are of critical clinical significance.

Our individual laboratories have performed many of the studies proposed in the STEPS guidelines. Building on these extensive studies, we have elected to test the efficacy of two bone marrow stromal cell types (from SanBio, Inc., CA, USA, and Theradigm, Inc., MD, USA) administered at 1 month post-stroke. The 1-month time point was selected because it is clinically reasonable and desirable; neurological deficits are well defined, patients are stabilized and the extended therapeutic window permits nearly all ischemic patients to be enrolled. Two routes of cell administration, namely intracerebral (SanBio, Inc.) and intravenous (Theradigm, Inc.), will be employed. A dose-finding analysis will be performed for both cell

types. Our proposed studies are therefore designed to develop treatment paradigms that can be readily translated to clinical stroke. We also seriously considered performing imaging experiments along the line of our recently published reports [5,6], which will be pursued in parallel studies. In addition, the establishment of a Data Coordination Center (Lu) and a Clinical Consortium (Hess and Kondziolka) as part of our investigative team should allow us to efficiently manage and evaluate the data, and assess the clinical relevance and applicability of our preclinical studies. Lastly, our industry partnerships with SanBio, Inc. and Theradigm, Inc. facilitates an ample supply of transplantable cells produced under good manufacturing practice, quality assurance and quality control regimen, which should expedite our translational goal of delivering a clinical grade product to the clinic. In summary, our preclinical STEPS consortium is desirous to deliver missing critical steps in the translational testing and validation of efficacy and safety of cell therapy in ischemic stroke, which, to date, has not been realized in the field of neurorestoration. Although these cell treatments have demonstrated therapeutic efficacy in individual laboratories [2–8], it is imperative for clinical translation that these cells be tested in multiple models of focal stroke, in two species, in both genders and in multiple laboratories.

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