Are Stem Cells the Next Generation of Stroke Therapeutics?

Sean I. Savitz, MD

Downloaded from http://stroke.ahajournals.org/ by guest on May 27, 2018

In this exciting atmosphere of having new endovascular treatment options for our acute stroke patients, the *Stroke* journal commissioned a focused update on the application of stem cells and cell-based therapies given new advancements in our mechanistic understanding of stem cells and given the launch of phase 2B and 3 efficacy trials. After initial attempts in cell transplantation approaches for patients with chronic subcortical strokes in the 1990s, the field of stem cells in stroke shifted focus over the past 20 years, resulting in new therapeutic strategies using easily accessible cell types that modulate immune responses to injury and amplify endogenous repair processes. We have learned that the secretomes and microparticles that cell therapies release may be the principal mediators of their therapeutic effects.

Partnerships between industry and academia have been instrumental in advancing this field. Only a select few companies have sustained investments to carry out studies from preclinical development all the way to efficacy trials. Notably, Athersys has initiated two phase 3 efficacy trials on its cell-based platform, MultiStem, for patients with acute ischemic stroke, whereas ReNeuron and SanBio are now in phase 2B stages for patients with chronic stroke.

In this focused update, we begin with a review by Mays and Savitz[1] on cellular therapies for acute ischemic stroke as exemplified by the intravenous application of Multipotent Adult Progenitor Cells (trademarked as MultiStem by Athersys). We now understand that these cells very likely exert beneficial changes within the brain by their profound effects on the peripheral immune responses after stroke. A model hypothesis describing the interactions between the peripheral immune response involving the spleen and the brain suggests that we may have another therapeutic, time-dependent window that opens up during the inflammatory response to ischemic injury and closes within 1 to 2 days of symptom onset. A new therapeutic window may open a whole new area for cell-based immunomodulatory therapies in the future.

Wechsler et al[2] along with scientific leaders from SanBio and ReNeuron then present an update on the intracranial injection of cell-based therapies for chronic stroke. Studies from SanBio show intriguing results how their gene-modified mesenchymal stem cells reduce glial scar formation and produce extracellular matrix allowing for enhanced intrinsic repair. ReNeuron has developed a neural stem cell product that may engage and reprogram the myeloid cell populations within the brain to amplify repair mechanisms such as neurogenesis. Both cell therapy platforms have shown safety and signals of treatment effects in early-phase clinical trials.

Our third review by Guzman et al[3] addresses the latest updates and challenges of intra-arterial, endovascular-based delivery of cell-based therapies, an exciting area given the era of highly effective endovascular thrombectomy in patients with large artery occlusions. These pioneers in the development of intra-arterial delivery review the latest data in clinical studies, factors associated with safety, and then present their advanced novel imaging methods to visualize and monitor the process and biodistribution of cell delivery into the brain parenchyma.

The last 3 reviews of this focused update discuss the future for the field. Chen and Chopp,[4] 2 wonderful colleagues who have made fundamental advancements in this field for over 15 years, discovered that exosomes are a principal mediator of the therapeutic effects of mesenchymal stem cells for stroke. They review their seminal studies on the application of exosomes by themselves as a novel treatment for stroke.[4] The question will arise in the future whether the daughter exosomes will become an alternative or better therapy compared with the parent cell therapy. Kokaia et al[5] then present the future for creating customized cellular therapies for stroke patients. They review animal studies and how different types of brain cells or neural stem cells generated from embryonic stem cells and induced pluripotent stem cells could be used as personalized, patient-specific sources for direct cell transplantation into the brain. The mechanisms underlying functional improvement include activation of distinct tissue responses through paracrine signaling and differentiation into functional mature brain cell types in the poststroke-injured brain. The authors paint an exciting future in which a patient's own skin cells could be converted into a range of different brain cell types for autologous restorative treatments versus the creation of a universal iPSC bank for allografting.

Last, Modo et al[6] review the future for animal modeling and specifically focus on the factors that need to be addressed to develop true cell and tissue replacement strategies in stroke. They also discuss how animal modeling can be optimized for preclinical testing and point out the need to address concurrent treatments such as rehabilitation and pharmacological agents.

The future of this field will hinge, to some extent, on the outcomes of the current phase 3 trials. As discussed in

Received February 6, 2018; final revision received February 20, 2018; accepted February 23, 2018.
From the Institute for Stroke and Cerebrovascular Disease, UTHealth-Houston, TX.
Correspondence to Sean I. Savitz, MD, Institute for Stroke and Cerebrovascular Disease, UTHealth-Houston, Houston, TX 77030. E-mail Sean.I.Savitz@uth.tmc.edu
(*Stroke*. 2018;49:1056-1057. DOI: 10.1161/STROKEAHA.118.019561.)
© 2018 American Heart Association, Inc.

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.118.019561**

the first review, the phase 2 MASTERS trial (MutliStem® Administration for Stroke Treatment and Enhanced Recovery Study) conducted by Athersys found signals that MultiStem exerted treatment effects that were consistent across a range of different outcomes, both in favor of better recovery and reduced stroke-related complications in the cell-treated group. Positive results in phase 3 would initiate an unprecedented new era of therapeutics for stroke patients.

Disclosures

As an employee of the institution (UTHealth), Dr Savitz has served in the following roles: as a site investigator in clinical trials sponsored by industry companies—Athersys, Genentech, Pfizer, Dart Neuroscience, and SanBio, for which UTHealth receives payments on the basis of clinical trial contracts; as an investigator on clinical trials supported by National Institutes of Health (NIH) grants, Department of Defense, Let's Cure CP, the Texas Institute for Rehabilitation and Research Foundation, and the Cord Blood Registry Systems; as a principal investigator on NIH-funded grants in basic science research; as principal investigator for an imaging analysis center for clinical trials sponsored by SanBio. Whereas UTHealth uses Dr Savitz with expertise in stroke, UTHealth has served as a consultant to Neuralstem, SanBio, Mesoblast, ReNeuron, Lumosa, Celgene, Dart Neuroscience, and Aldagen. All funding goes to the institution.

References

1. Mays RW, Savitz SI. Intravenous cell therapies for acute ischemic stroke. *Stroke*. 2018;49:1058–1065. doi: 10.1161/STROKEAHA.118.018287.
2. Wechsler LR, Bates D, Stroemer P, Andrews-Zwilling YS, Aizman I. Cell therapy for chronic stroke. *Stroke*. 2018;49:1066–1074. doi: 10.1161/STROKEAHA.117.018290.
3. Guzman R, Janowski M, Walczak P. Intra-arterial delivery of cell therapies for stroke. *Stroke*. 2018;49:1075–1082. doi: 10.1161/STROKEAHA.117.018288.
4. Chen J, Chopp M. Exosome therapy for stroke. *Stroke*. 2018;49:1083–1090. doi: 10.1161/STROKEAHA.117.018292.
5. Kokaia Z, Llorente IL, Carmichael ST. Customized brain cells for stroke patients using pluripotent stem cells. *Stroke*. 2018;49:1091–1098. doi: 10.1161/STROKEAHA.117.018291.
6. Modo MM, Jolkkonen J, Zille M, Boltze J. Future of animal modeling for poststroke tissue repair. *Stroke*. 2018;49:1099–1106. doi: 10.1161/STROKEAHA.117.018293.

KEY WORDS: adult ■ atmosphere ■ brain ■ spleen ■ stem cells

Downloaded from http://stroke.ahajournals.org/ by guest on May 27, 2018

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

Are Stem Cells the Next Generation of Stroke Therapeutics?

Sean I. Savitz

Stroke. 2018;49:1056-1057; originally published online April 18, 2018;
doi: 10.1161/STROKEAHA.118.019561
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2018 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/49/5/1056

Downloaded from http://stroke.ahajournals.org/ by guest on May 27, 2018

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/