Five years ago, we stated in this Controversies section that it was quite implausible to us that efficacy of neuroprotection in animal models could not be translated into human stroke, given a potent agent that penetrates into the ischemic region, a short time window, lack of toxicity, and well-designed clinical trials. Where are we, in 2007? Despite application of at least some of these principles in large neuroprotection trials, that have largely followed the STAIR criteria, success remains elusive. For both academic investigators and the pharmaceutical industry, the most recent failures have created an atmosphere of negativity.

Rother has argued that tissue salvage in ischemic stroke is only achieved with reperfusion. Even those who had argued that successful neuroprotection necessitated concurrent reperfusion must note the lack of suggestion of benefit in large subsets of patients in trial receiving the combination of tPA and trial therapy. Indeed, many investigators have suggested that the litany of failures of neuroprotection as an acute stroke strategy signals the death knell of this area of research.

Our position remains unchanged! There is considerable indirect evidence of a similar neurotoxic cascade in humans to that in animals, based on brain and serum levels of excitatory and other compounds. We think it most unlikely that the 30 years of research into the ischemic cascade in animal models has no validity in human stroke.

We would agree with Hussain and Shuaib that the initial goal must be to establish proof of concept in humans as a prelude to pivotal clinical trials. There are a number of different in vivo models in which this could be tested, but we would favor a stepwise approach including an initial demonstration of an effect in human cell cultures. This could be easily achieved using the oxygen-glucose deprivation model. Subsequent steps should involve demonstration of penetration of drug into the ischemic region using positron emission tomography (PET) and selection of patients for surrogate outcome clinical trials with penumbral selection on MRI or CT. In such trials, the primary outcome would be the attenuation of infarct growth or penumbral salvage. Innovative clinical strategies, such as hypersonic prehospital treatment being used in the FAST-Mag trial, should be encouraged.

Stroke research is difficult! Although we do need to go back to the neuroprotection drawing board, we should not abandon such an important research direction, where the potential applications are so great.

Disclosures
None.

References

Key Word: neuroprotection
Neuroprotection: Still Achievable in Humans
Geoffrey A. Donnan and Stephen M. Davis

Stroke. 2008;39:525; originally published online January 17, 2008;
doi: 10.1161/STRKEAHA.107.494807
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/39/2/525

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/