

## Modeling Immunity and Inflammation in Stroke: Can Mice Be Trusted?

Ulrich Dirnagl

*Stroke*. published online July 24, 2014;

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2014 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/early/2014/07/24/STROKEAHA.114.005640.citation>

**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/>

## Modeling Immunity and Inflammation in Stroke Can Mice Be Trusted?

Ulrich Dirnagl, MD

Sixty-five million years have passed since mouse and man shared a common ancestor. The principles of evolution, as well as the scientific literature, suggest that there are many similarities between both mammal species but also significant differences. Humans are definitely no 75 kg mice,<sup>1</sup> but is it true that “the mouse model has been totally misleading for at least three major killers—sepsis, burns, and trauma,” as the New York Times concluded after the publication of a study by Seok et al?<sup>2</sup> By looking at transcriptional responses of blood cells, this study found “that, although acute inflammatory stresses from different etiologies result in highly similar genomic responses in humans, the responses in corresponding mouse models correlate poorly with the human conditions and also, one another.”

The results of the Seok et al<sup>2</sup> study are by no means surprising or new,<sup>3</sup> but they nevertheless carry an important message for experimental stroke research. The authors used male mice of the C57 BL/6J strain, which is exquisitely resistant to sepsis: more than one million-fold doses of endotoxin are required to cause shock in this mouse strain. The mice are inbred and raised under specific pathogen-free conditions, so at the time of the study, the 8-week-old mice had a naive and immature immune system.

In contrast, rodents are as sensitive to focal cerebral ischemia as humans. The evolution of the infarct and surrounding penumbra has similar temporal and histopathologic dynamics, and the time windows for thrombolysis after embolic stroke are practically identical.<sup>4</sup> I think that there are at least 4 separate lines of evidence indicating that rats and mice share a common pathophysiology of inflammation and immunity after focal cerebral ischemia and that this is true for brain tissue proper, as well as for the stroke-induced responses of peripheral organs.

1. Brain tissue damage after stroke results in the homing of blood leukocytes to the brain and their transmigration across brain endothelial barriers. Although the functional consequences of this complex inflammatory response, which involves cells of both the innate and the adaptive

immune systems, remain controversial and poorly understood, histopathologic investigation of rodent and human brains has revealed similar findings.<sup>5</sup>

2. Noninvasive brain imaging in patients with stroke, in particular with positron emission tomography and the microglial marker PK-11195, has demonstrated temporal and spatial activation patterns similar to those found with invasive, histological methods in rodent models of stroke.
3. The current quest for blood biomarkers in patients with stroke has revealed several inflammatory proteins, which appear to be robustly upregulated and to correlate with stroke severity, outcome, or subtype. These include, among many others, interleukin-6, matrix metalloproteinase-9, tumor necrosis factor- $\alpha$ , and monocyte chemoattractant protein-1. Because of the availability of more invasive and direct assays, blood biomarkers have been studied much less in rodents—and particularly much less in mice—than in humans. However, where parallel evidence is available (eg, for the 4 proteins mentioned above), upregulation of the same inflammatory proteins in the blood has been shown in mice and man.
4. Stroke leads to a rapid downregulation of the cellularity and functionality of the peripheral immune system (stroke injury–induced immunodepression, SIDS). This was first described in patients with stroke in the 1970 and then rediscovered in the mouse in 2003.<sup>6</sup> Several recent studies in patients and experimental models demonstrate that the characteristics and functional consequences of SIDS (eg, poststroke infection) are similar in mice and man.

Stroke research has a dismal record when it comes to translating its findings into novel and effective therapies. Several hundred clinical trials have been unable to replicate neuroprotection, which was highly effective in rodents. In line with Seok et al,<sup>2</sup> this may be a result of fundamental differences between rodent and human stroke pathophysiology. However, there are other possible reasons for translational failure in

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association. This article is Part 1 of a 3-part article. Parts 2 and 3 appear on pages x and x, respectively.

Received May 21, 2014; accepted June 3, 2014.

From the Departments of Neurology and Experimental Neurology Charité, Center for Stroke Research Berlin, Charité, ExcellenceCluster NeuroCure—Universitätsmedizin Berlin, Berlin, Germany; German Center for Neurodegenerative Diseases (DZNE), Partner Site, Berlin, Germany; and German Center for Cardiovascular Diseases (DZHK), Partner Site, Berlin, Germany.

Correspondence to Ulrich Dirnagl, MD, Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail [ulrich.dirnagl@charite.de](mailto:ulrich.dirnagl@charite.de)

(Stroke. 2014;45:00-00.)

© 2014 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.114.005640

stroke research, which include a lack of internal (eg, bias) and external (eg, lack of comorbidities, young age) validity in experimental stroke research but also weaknesses in clinical trial design (eg, wrong time window). In a recent article, we summarized potential reasons for the translational roadblock in stroke research and argued that despite the current nihilism, preclinical stroke research can successfully predict human pathophysiology, clinical phenotypes, and therapeutic outcomes.<sup>7</sup>

I would like to propose that when it comes to modeling immunity and inflammation in stroke, we trust mice more than we trust stroke researchers. Among many other relevant insights, immunologic research in mice by George Snell led to the discovery of the major histocompatibility complex and, ultimately, successful organ transplants. To me, the important (hypothetical) question here is should we expect identical transcriptomic profiles when we compare blood samples from a cohort of adolescent, identical, male human twins, raised in 6 m<sup>2</sup> isolator tents, fed with granola, and a cohort of elderly or senescent, multimorbid retired persons of both sexes on various drug regimens?

In summary, the physiology and pathophysiology of rodents is sufficiently similar to humans to make them a highly relevant model organism but also sufficiently different to mandate an awareness of potential resulting pitfalls. In any case, before hastily discarding highly relevant past, present, and future findings, experimental stroke research needs to improve

dramatically its internal and external validity to overcome its apparent translational failures.

## Disclosures

None.

## References

1. Leist M, Hartung T. Inflammatory findings on species extrapolations: humans are definitely no 70-kg mice. *Arch Toxicol*. 2013;87:563–567.
2. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, et al; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2013;110:3507–3512.
3. Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. *J Immunol*. 2004;172:2731–2738.
4. Sena ES, Briscoe CL, Howells DW, Donnan GA, Sandercock PA, Macleod MR. Factors affecting the apparent efficacy and safety of tissue plasminogen activator in thrombotic occlusion models of stroke: systematic review and meta-analysis. *J Cereb Blood Flow Metab*. 2010;30:1905–1913.
5. Enzmann G, Mysiorek C, Gorina R, Cheng YJ, Ghavampour S, Hannocks MJ, et al. The neurovascular unit as a selective barrier to polymorphonuclear granulocyte (PMN) infiltration into the brain after ischemic injury. *Acta Neuropathol*. 2013;125:395–412.
6. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci*. 2005;6:775–786.
7. Dirnagl U, Endres M. Found in translation: preclinical stroke research predicts human pathophysiology, clinical phenotypes, and therapeutic outcomes. *Stroke*. 2014;45:1510–1518.

KEY WORDS: immune system ■ inflammation ■ models, animal ■ stroke



# Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION