The Stroke Progress Review Group, commissioned by National Institute of Neurological Disorders and Stroke to review the status of stroke research in 2011, addressed a variety of clinical and preclinical areas, including progress and unmet needs in preclinical investigation. Identified among the latter were the need to develop better molecular, cellular, and animal models of stroke. This finding reflects understandable disappointment that, although such models have been available for >50 years, few advances in the treatment of acute stroke have occurred. Numerous authors have addressed possible explanations for this paradox and recommended new approaches, and the Stroke Progress Review Group produced no new conceptual breakthroughs in this respect. However, there may be value in reflecting again on some of the extant issues.

What should be expected of a disease model? Should it resemble the disease outwardly, reproduce known pathophysiologic features of the disease (which have often been inferred from other models), predict effective treatments, or all of these? Considering that predicting treatment is of most practical benefit, how effective must the treatment be to validate the model? For example, if thrombolytics end up helping only a tiny fraction of all patients with stroke, does their efficacy in rodents help to validate or to refute the rodent model?

How bad are the existing (primarily rodent) models of stroke? A frequently cited review noted that no clinical treatment had emerged from 1026 “neuroprotective” agents deemed successful in animals, reinforcing the perception that “everything works in animals but nothing works in people.”

But the authors also noted that the animal studies in question “exploit” one or more mechanisms for this paradox and recommended new approaches, and the Stroke Progress Review Group produced no new conceptual breakthroughs in this respect. However, there may be value in reflecting again on some of the extant issues.

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But the authors also noted that the animal studies in question used a variety of models and end points, that the extent of protection in some cases was quite small, and that only a small percentage of the preclinical successes were actually tested in patients. Moreover, there was no evident logic in which experimental successful drugs were advanced for clinical use. It is reasonable to wonder whether the record might be better if commercial considerations were less dominant in the clinical phase of testing, and whether potentially effective drugs have been abandoned because of side effects that make it tolerable in exchange for a better neurological outcome.

If preclinical studies of stroke may have been overinterpreted and misapplied clinically, this does not imply that the studies themselves could not be improved, and most investigators in the field are well aware of some obvious candidate defects. Stroke is a heterogeneous disorder, and mismatches in pathophysiology may occur between a given preclinical model and the clinical setting. Preclinical studies are still often conducted with treatment administered either before the onset of stroke or too soon after (at least in rat hours) for wide clinical application. Anesthetics required for surgically induced stroke models might enhance the beneficial effects of experimental treatments, even if ineffective when given alone. Youth and lack of comorbid conditions in experimental animals could make them more responsive to treatment than the typical stroke patient, although these factors are not always associated with worse outcome or treatment resistance in preclinical models.

Experimental models of disease can be useful not only for discovering treatments but also for elucidating pathophysiology. In this respect, the recent record of preclinical stroke research seems much better. When asked to identify recent advances in the field, Stroke Progress Review Group working groups pointed to new insights on interactions among neurons, glia, and vascular cells; systemic, including immune-mediated influences in stroke pathophysiology; and mechanisms of brain plasticity, repair, and recovery after stroke. Even if existing models have not produced clinically validated acute neuroprotective treatments, they may still spur efforts to exploit one or more of these other targets.

Sources of Funding
This work was supported by National Institutes of Health grants NS44921 and NS62414.

Disclosures
None.

References


**Key Words:** ischemia ■ neuroprotection ■ stroke
Preclinical Stroke Research: Gains and Gaps
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Stroke. 2013;44:S114-S115
doi: 10.1161/STROKEAHA.113.002088

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