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PRECLINICAL STROKE RESEARCH: GAINS AND GAPS

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The Stroke Progress Review Group (SPRG), commissioned by NINDS 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 [1]. 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 more than 50 years [2], few advances in the treatment of acute stroke have occurred. Numerous authors have addressed possible explanations for this paradox and recommended new approaches [3–6], and the SPRG 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 1,026 “neuroprotective” agents deemed successful in animals, reinforcing the perception that “everything works in animals but nothing works in people” [7]. But the authors also noted that the animal studies in question employed a variety of models and endpoints, 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 experimentally successful drugs were advanced for clinical use. It is reasonable to wonder if 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 might be 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 [8], even if ineffective when given alone. Youth and lack of comorbid conditions in experimental animals could make them

DISCLOSURE
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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 [9–11].

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. Asked to identify recent advances in the field, SPRG working groups pointed to new insights regarding interactions among neurons, glia, and vascular cells; systemic, including immune-mediated influences in stroke pathophysiology; and mechanisms of brain plasticity, repair and recovery following stroke [1]. 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.

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