

## Towards Improved Translational Stroke Research Progress and Perspectives of the Recent National Institute of Neurological Disorders and Stroke Consensus Group Meeting

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Preclinical stroke research faces a substantial transition. Past classical rodent stroke models and study designs revealed numerous potential targets for novel stroke therapies; yet, subsequent clinical stroke trials failed to confirm promising preclinical findings. Pharmacological and mechanical recanalization therapies, representing the only strategies that have substantially improved acute ischemic stroke outcomes, were largely developed omitting conventional preclinical methods.<sup>1-3</sup> In this issue of *Stroke*, a National Institute of Neurological Disorders and Stroke consensus group comprising leading academic, industry, and Food and Drug Administration (FDA) experts working at the forefront of stroke research has recently published guidelines for improved translational studies.<sup>4</sup>

Distinguishing between explorative (basic) versus confirmative (translational) studies has been suggested. Exploratory research uses simpler rodent models but a broad spectrum of basic science methods to gain comprehensive information on a putative treatment target. Subsequent confirmative research adopts study designs similar to those used in clinical stroke trials and puts more emphasis on predictive stroke models and study end points using larger and adequate sample sizes for necessary statistical power.<sup>5</sup> The group's recommendations reflect latest developments and concepts in the field, aiming to ultimately enhance the predictive value of preclinical stroke research.

### Current Challenges

Key challenges include the choice of end points, homogeneity, utilization of imaging, assessment of important comorbid conditions, and conceptually disentangling the components of neurorecovery. End points in confirmative stroke research need to reflect central clinical safety and efficacy readout parameters

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Guest Editor for this article was Eric Smith, MD, MPH.

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rather than intermediate outcomes that are designed to confirm the impact of the therapeutic approach. Because the accepted outcomes after stroke in the clinic are assessed at 90 days, this means including a surveillance period of at least a month after intervention.<sup>6</sup> This is important because transient functional improvements after experimental therapy lasting  $\leq 9$  weeks have been observed preclinically.<sup>7</sup> Shorter observation periods might lead to false-positive or simply incorrect results. Homogeneity of preclinical stroke models, at best marginally representing the broad spectrum of cortical, subcortical, and combined ischemic lesions exhibited by stroke patients, is a key challenge. In acute stroke, the highly dynamic changes in the infarct core and particularly in the penumbra should be understood by preclinical stroke models because the existence and size of the latter became an important criterion to select individuals who might benefit from acute intervention both preclinically and clinically.<sup>8,9</sup> Influence of age, sex, and common stroke comorbidities, such as hypertension, diabetes mellitus, or hypocholesterolemia, should also be modeled. Potential interactions between a novel stroke treatment and medications required to treat those comorbidities need to be identified to increase safety and efficacy during the translation process.<sup>10</sup> Finally, reliable discrimination between functional compensation and recovery is important because rodents have a higher ability to compensate functional benefits while economic and simple; hence, frequently performed behavioral tests are often insensitive to such masking behavior.<sup>11</sup>

### Recent Milestones and Moving Forward

The evolution of endovascular therapy has produced a consistent true ischemia–reperfusion model in human acute ischemic stroke.<sup>12</sup> Failure of translation of over a thousand molecules that were proven to be effective in rodent or small mammal ischemia–reperfusion models may in large part be because of the fact that, in the recent past, human ischemic stroke was a permanent focal ischemia model and not a transient focal ischemic model as believed.<sup>2</sup> A fundamental principle of the human endovascular ischemic stroke trials was the identification of a target vessel occlusion and a tissue window for patient selection. The same principle may be used in preclinical stroke research while recognizing possible measurement error of imaging techniques and their matching with actual pathology to an intermediate extent. Future therapies must select subjects in both preclinical and clinical stroke trials on the basis of the tissue window to target the population of interest.

We do not have strong clinical examples of medical or device interventions for neurorecovery yet. However, the components of neurorecovery must be elucidated, and an implied focus on specific types of recovery is needed. Focus on the

upper limb, lower limb, kinesthesia, language, and other specific neurological functions will be necessary to understand how the brain and the patient recover. While function is the principle pragmatic outcome, some combination of adaptation, rehabilitation, and true recovery of function will likely occur; each component may respond to specific intervention(s). This can and should be modeled.

Similarly, stroke prevention models are lacking for many types of ischemic stroke. Stroke suffers from causal multiplicity. While much has been learned about atherosclerosis spurred by research on the coronary circulation, the causes of cervical artery dissection, some types of cardioembolism, and lacunar stroke are poorly understood. Modeling stroke prevention by specific cause of stroke is needed.

Finally, in all types of models, and particularly in the confirmative concept of translational research, there is a growing awareness of the need to emulate strong clinical data methods. Double-blind, randomized trials in animal models must be used and powered appropriately to detect key clinical outcomes. Such trials can be multicenter. The impact of big data and open science can help stroke research if we embrace the concepts of widely sharing data and techniques, using public data deposit with standardized data definitions.

### Future Solutions and Conclusions

Success of future translational stroke research will not only critically depend on focusing on the most appropriate end points but also on addressing the right patient population. There is a need to think circularly not only from bench to bedside but also from bedside to bench. Confirmative preclinical stroke trials should be designed toward the patient population most likely to be seen in the subsequent clinical trial. Clinical stroke trials must recruit patients who match the characteristics of experimental subjects in the preclinical stroke trial it is based on and only later expand to broader population. When the preclinical and clinical stroke research is consistent, translational success will follow.

### Disclosures

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