

Editorial

International, multicenter randomized preclinical trials in translational stroke research: It's time to act

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Over the last decades, tremendous progress has been made in our understanding of the vascular, cellular, and molecular mechanisms leading to brain tissue injury after ischemic stroke. This research has exposed numerous potential targets to intercept the cascades of ischemic damage (Vosler and Chen, 2009). This promise of 'neuroprotection' has been an important potential therapeutic consideration in the cerebral ischemia field ever since the discovery of 'excitotoxic' mechanisms of cell death in experimental models of stroke in the 1980s. Experiments in rodents demonstrated that the focally ischemic brain can indeed be protected pharmacologically, reducing infarction and improving functional outcome. However, so far every attempt to translate this preclinical success into clinically effective therapies has failed (Endres *et al*, 2008). The very recent failure of the AXIS-2 trial investigating treatment with the hematopoietic cytokine G-colony stimulating factor (G-CSF) in acute ischemic stroke (Sygnis, 2011) has further reinforced the apparent translational roadblock. Translational stroke research is in a crisis, and pharmaceutical companies continue to exit the field.

Many reasons for the apparently insurmountable barrier between the bench and bedside in stroke drug development have been identified. These include quality problems in preclinical research, bias towards the inclusion of young, healthy animals, small studies and hence low predictive value, a strong negative publication bias, among many others (Dirnagl, 2006). For many of these issues, a substantial contribution to the attrition rate was demonstrated with quantitative indicators, for example by systematic reviews (Dirnagl and Macleod, 2009). In addition, design flaws of clinical trials may also be incriminated as possible causes of these overall failures to predict and then develop effective acute stroke therapies beyond thrombolysis. In principle, most experts agree on the key elements of the problem related to translating beneficial effects in preclinical studies into proven acute ischemic stroke therapies. Various remedies have been suggested. It is time to act now to bridge the gap between preclinical and clinical studies of purported new therapies.

A central question in drug development is whether and when the researcher, investor, or pharmaceutical company should venture from preclinical testing into clinical development. Clinical development programs are exceedingly expensive, take a long time, and carry the risk of potential harm for both volunteers and patients. At present, no firm criteria exist for such go/no go decisions. In many prior translational stroke research programs, the decision to proceed was based on limited experimental evidence and personal opinions of stakeholders in the process. In a few cases, such as the AXIS-2 trial and ongoing hypothermia trials, the decision was informed by systematic reviews of experimental studies that suggested benefit from multiple laboratories that performed reasonably high-quality studies (England *et al*, 2009, van der Worp *et al*, 2007). However, data and study design extraction from experimental stroke studies is difficult, as only recently have standards for reporting animal research been introduced that have been increasingly adhered to (Kilkenny *et al*, 2010). In addition, systematic reviews of experimental stroke research have consistently reported low-quality scores, negative publication bias, and a paucity of data from aged animals or those with comorbidities, questioning the robustness and predictive value of such reviews (Lemon and Dunnet, 2005).

The decision to move from animal experiments to patients should be based on robust, high-quality data. We propose that preclinical translational stroke research should learn from the experience of clinical stroke research. Over the last decades, the quality of clinical trials and hence the robustness of their results, not only in the stroke field but in many other therapeutic areas, has tremendously improved. This was the result of a plethora of measures, such as strategies to minimize bias (randomization, blinding, allocation concealment), *a priori* Power analysis and other biostatistical advances, careful definition of the primary and secondary end points, data monitoring and auditing, internationalization and inclusion of many centers, external steering committees and safety monitoring, rigid publication standards (CONSORT), trial registries, among others.

Following the suggestion by Bath *et al* (2009), we are calling for international, multicenter preclinical 'phase III'-type studies of promising, novel ischemic stroke therapies before moving from animal modeling to clinical trial. Such a trial would not replace basic research targeted at discovering or investigating pathophysiological mechanisms of drugs (preclinical phase I), or initial preclinical trials by individual scientists (preclinical phase II). Rather, 'phase III' preclinical trials would be based on such prior studies, and only those compounds or treatment modalities would enter phase III that were highly promising in phases I and II.

Ideally, such phase III preclinical trials would be international, randomized, blinded, and multicenter. They should be performed in rodent stroke models. A steering committee (including both preclinical and clinical researchers) would develop the design, select participating laboratories, oversee the progress of the study, and analyze the combined data sets. The study would use robust, clinically relevant short- and long-term end points (outcomes), such as mortality, infarct size, and behavioral/functional deficit. Biomarkers, including imaging, may be included to inform subsequent clinical trials. The necessary number of experiments should be calculated by an *a priori* power analysis and include studies in young healthy animals and then subsequent studies with agents showing initial promise in animals with clinically relevant comorbidities and advanced age. A primary end point would be defined *a priori* to assess efficacy, and secondary end points used for hypothesis generation. Prospectively planned subgroup analyses could also be prespecified. Depending on the end points (infarct volume, sensory-motor function, etc.), raters could be trained via on-line tutorials. Data monitoring and analysis would be done by an independent group of researchers who did not perform the actual experiments. Such studies would be publicly registered (similar to clinicaltrials.gov). Registration will be mandatory for publication.

Such an approach could utilize the complexities of a multicenter multimodel paradigm. One might include centers with various middle cerebral artery occlusion models to recreate the heterogeneity of stroke types and severities. Various strains (or even species) may mimic patient heterogeneity (Howells *et al*, 2010). By including various laboratories and their animal husbandry, treatment heterogeneity in stroke units is modeled. Studies can be designed in such a way that they are informative even when 'negative.' With molecules showing promise in rigorous rodent studies, at least one additional study should be strongly considered in a high-quality, gyrencephalic stroke model, potentially concurrent with early phase clinical studies.

Our proposition is ambitious, but not unrealistic. At present, several international consortia are gearing up for various types of multicenter preclinical stroke studies. Multiple challenges exist. As no

blueprint for this type of collaborative assessment exists, it needs to be generated. Funding agencies, as well as the pharmaceutical industry need to be persuaded to support the development of such a preclinical stroke treatment consortium. A common objection against the feasibility of this approach is the apparent lack of incentive for the individual laboratory or researcher to participate. This need not be so. The publication of large multicenter preclinical trials will follow the example of clinical trials, and give credit to participating authors. Even the recent clinical failures of acute stroke trials were published in high-ranking journals such as the *New England Journal of Medicine*, *Lancet*, *Stroke*, etc. Why should well-conducted, relevant preclinical trials not find their way into the top journals?

We strongly believe that it is too early to abandon translational stroke research. Key elements of the roadblock have been identified, but not overcome. Preclinical, randomized, multicenter trials may expeditiously eliminate major hurdles of bench-to bedside translation and provide a robust basis for decisions to enter clinical development of novel treatments.

Ulrich Dirnagl¹ and Marc Fisher²

¹Center for Stroke Research, Charité
Universitätsmedizin, Berlin, Germany;

²Department of Neurology, University of
Massachusetts Medical School, Worcester,
Massachusetts, USA

E-mail: ulrich.dirnagl@charite.de

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