

Correcting the Trajectory of Stroke Therapeutic Research

Keith R. Pennypacker¹ · Gregory Bix² · Justin F. Fraser³

Received: 16 December 2016 / Accepted: 20 December 2016 / Published online: 30 December 2016
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One of the most vital issues in stroke research is the paucity of animal studies that have translated into treatments for human stroke patients. The August and October issues of this journal were devoted to this topic and raise a number of points of concern to rectify this problem. In fact, NINDS is keenly aware and recently hosted the workshop “Translational Stroke research: Vision and Opportunities,” which raised similar concerns. The introductory article encompassed this theme of transition of stroke research to develop strategies for clinical relevance [4].

Unfortunately, there are a great number of problems and challenges to translating experimental stroke therapies, and there is likely no one or simple solution. One major problem is that the preclinical studies are using a homogeneous population with a similar age and being treated at a specific time point. Whereas, human patients are genetically diverse with different ages and many are consuming an assortment of pharmaceuticals. Other confounding variables include the timing of the stroke and type of stroke. With this diversity of the human patient, we may be overlooking potential treatments that were effective in a specific human population but not

clear because clinical studies were not designed specifically to analyze that subgroup.

Several papers in both issues address the shortcomings with animal models reflecting the human condition. There is a necessity to interject co-morbidities, age, and sex into existing animal models to better mirror the heterogeneity of the human population. Most studies are performed using young male rats. However, therapeutic testing in animal stroke models should include assessment in subjects with co-morbidities, such as diabetes and hypertension, which are common to most stroke patients [7]. Furthermore, there are clear gender differences in stroke severity and in response to treatment. These sex differences in stroke have not been well studied at both preclinical and clinical levels [1]. One study has shown that the administration of uric acid with tPA clearly benefits women but not men. However, the study had to investigate the independent effect of sex to dissect out this positive effect on women [15]. While the uric acid experience is reflective of excellent stroke animal model to human translation, it also shows the vulnerability of translation. By not designing the clinical trial specifically with preplanned gender-based outcome analysis, investigators nearly missed the potentially profound beneficial effect of uric acid on stroke outcomes in women.

Another vital avenue of research is the stroke immune response, which plays a critical role in the pathophysiology of stroke, and different rodent strains have disparities in their immune responses. These disparities affect translation between rodent species and between animal and human and have a critical impact on therapeutic translation of immunomodulatory therapies [2]. With that in mind, reverse-translational methodologies, which start at analyzing stroke in humans, may play a growing role. Should the neurointerventional suite become one of the

✉ Keith R. Pennypacker
keith.pennypacker@uky.edu

¹ Departments of Neurology and Anatomy & Neurobiology, University of Kentucky, 441 S. Limestone Street, Room B457, Lexington, KY 40536, USA

² Departments of Neurology and Anatomy & Neurobiology, Sanders-Brown Center of Aging, University of Kentucky, 800 S. Limestone Street, Room 430, Lexington, KY 40536, USA

³ Department of Neurological Surgery, University of Kentucky, 800 Rose Street, Room MS105a, Lexington, KY 40536, USA

routine ‘laboratories’ for the stroke researcher? To achieve this, stroke researchers must partner with their clinician colleagues to study stroke in humans and then bring those findings back to the lab for novel modeling.

One potential correction for failure of translation would be approaching preclinical studies in a similar fashion as clinical trials in design. One novel approach would be to report baseline factors in preclinical studies that were developed for clinical trials [12]. These objective methods would identify therapeutic approaches better suited for translation to clinical trials. Both preclinical and clinical studies have relied on behavioral studies, but there are problems that bias these recovery studies [11]. A possible solution is to use structural equation modeling that benefit both preclinical and clinical studies in assessing recovery [10]. Another method is to try to model monitoring stroke animal ‘patients’ like their human counterpart. Is there a utility to creating a rodent NIH Stroke Scale, which could be administered quickly and repetitively to monitor pre- and post-treatment status? Data support the role of using comorbidity analysis and improved reporting measures to further translation of stroke therapies, as exemplified by the analysis of IL-1RA as a stroke therapy [16].

A multicenter phase III preclinical trial concept, such as the Multi-PART, has been discussed as a solution to the lack of translation [6]. This approach is believed to enhance efforts to translate preclinical studies to the clinical realm. Many in the research community support this effort. This would change the basic research environment and culture as well as require funding. One potential source of funding could be through industrial-academic partnerships [5]. This partnership has proven effective in supporting randomized trials, such as MR CLEAN, in examining intra-arterial treatment for acute ischemic stroke [3].

Stem cell therapies have shown great promise in animal models but have not been translated to human patients. Reasons for failure could include problems with administration routes and lack of understanding the most efficacious components within cell therapies [17, 19]. Moreover, other potential therapeutic targets should be investigated, such as regulatory T cells which dampen immune-based neurodegeneration [13, 18]. Improvement in current reperfusion therapies could lead to an extended therapeutic time window allowing for more eligible patients to be treated [8, 14]. The use of anesthetics in stroke models can affect many physiological systems and is a confounding factor in determining efficacy of a treatment [9].

Stroke research is facing many impediments to attaining a treatment. A starting point would be better integration between the basic scientist and the clinician, in which both can learn from each other to develop better translational studies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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