HHS Public Access

Author manuscript

*Transl Stroke Res*. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

*Transl Stroke Res*. 2017 February ; 8(1): 65–66. doi:10.1007/s12975-016-0517-z.

# Correcting the Trajectory of Stroke Therapeutic Research

**Keith R. Pennypacker**, **Gregory Bix**, and **Justin Fraser**

University of Kentucky, UNITED STATES

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 timepoint. 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 pre-planned gender-based outcome analysis, investigators nearly missed the potentially profound beneficial effect of uric acid on stroke outcomes in women.

All authors declare no conflict of interest.

Another vital avenue of research is the stroke immune response, which plays a critical role in the pathophysiology of stroke, and different rodent stains 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 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 have proven effective in supporting randomized trials, such as MR CLEAN, in examining intraarterial 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 anesthestics 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.

## References


1. Ahnstedt H, Mccullough LD, Cipolla MJ. The Importance of Considering Sex Differences in Translational Stroke Research. Transl Stroke Res. 2016; 7:261–273. [PubMed: 26830778]
2. Becker KJ. Strain-Related Differences in the Immune Response: Relevance to Human Stroke. Transl Stroke Res. 2016; 7:303–312. [PubMed: 26860504]
3. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015; 372:11–20. [PubMed: 25517348]
4. Boltze J, Ayata C. Challenges and Controversies in Translational Stroke Research - an Introduction. Transl Stroke Res. 2016; 7:355–357. [PubMed: 27581304]
5. Boltze J, Wagner DC, Barthel H, et al. Academic-industry Collaborations in Translational Stroke Research. Transl Stroke Res. 2016; 7:343–353. [PubMed: 27301976]
6. Boltze J, Wagner DC, Henninger N, et al. Phase III Preclinical Trials in Translational Stroke Research: Community Response on Framework and Guidelines. Transl Stroke Res. 2016; 7:241–247. [PubMed: 27297402]
7. Ergul A, Hafez S, Fouda A, et al. Impact of Comorbidities on Acute Injury and Recovery in Preclinical Stroke Research: Focus on Hypertension and Diabetes. Transl Stroke Res. 2016; 7:248–260. [PubMed: 27026092]
8. Henninger N, Fisher M. Extending the Time Window for Endovascular and Pharmacological Reperfusion. Transl Stroke Res. 2016; 7:284–293. [PubMed: 26739964]
9. Hoffmann U, Sheng H, Ayata C, et al. Anesthesia in Experimental Stroke Research. Transl Stroke Res. 2016; 7:358–367. [PubMed: 27534542]
10. Hommel M, Detante O, Favre I, et al. How to Measure Recovery? Revisiting Concepts and Methods for Stroke Studies. Transl Stroke Res. 2016; 7:388–394. [PubMed: 27498680]
11. Jolkkonen J, Kwakkel G. Translational Hurdles in Stroke Recovery Studies. Transl Stroke Res. 2016; 7:331–342. [PubMed: 27000881]
12. Kent TA, Mandava P. Embracing Biological and Methodological Variance in a New Approach to Pre-Clinical Stroke Testing. Transl Stroke Res. 2016; 7:274–283. [PubMed: 27018014]
13. Liesz A, Kleinschnitz C. Regulatory T Cells in Post-stroke Immune Homeostasis. Transl Stroke Res. 2016; 7:313–321. [PubMed: 27030356]
14. Linfante I, Cipolla MJ. Improving Reperfusion Therapies in the Era of Mechanical Thrombectomy. Transl Stroke Res. 2016; 7:294–302. [PubMed: 27221511]
15. Llull L, Laredo C, Renu A, et al. Uric Acid Therapy Improves Clinical Outcome in Women With Acute Ischemic Stroke. Stroke. 2015; 46:2162–2167. [PubMed: 26159792]
16. Mccann SK, Cramond F, Macleod MR, et al. Systematic Review and Meta-Analysis of the Efficacy of Interleukin-1 Receptor Antagonist in Animal Models of Stroke: an Update. Transl Stroke Res. 2016; 7:395–406. [PubMed: 27526101]
17. Rodriguez-Frutos B, Otero-Ortega L, Gutierrez-Fernandez M, et al. Stem Cell Therapy and Administration Routes After Stroke. Transl Stroke Res. 2016; 7:378–387. [PubMed: 27384771]
18. Xia Y, Cai W, Thomson AW, et al. Regulatory T Cell Therapy for Ischemic Stroke: how far from Clinical Translation? Transl Stroke Res. 2016; 7:415–419. [PubMed: 27307291]
19. Yang B, Parsha K, Schaar K, et al. Various Cell Populations Within the Mononuclear Fraction of Bone Marrow Contribute to the Beneficial Effects of Autologous Bone Marrow Cell Therapy in a Rodent Stroke Model. Transl Stroke Res. 2016; 7:322–330. [PubMed: 26997513]