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Comment on: Rodent stroke model guidelines for preclinical stroke trials (1st edition)

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Abstract

Over the past years, severe difficulties in translating experimental stroke research from bench-to-bedside have become apparent, and call for fresh ideas on why bench results get "lost in translation". In an attempt to close this gap, we suggest to perform experimental stroke studies in an *intraindividual, longitudinal and translational way* using multi-modal *in vivo* imaging protocols. Besides allowing us to stratify experimental animals *in vivo*, non-invasive imaging can also generate specific read-outs that allow monitoring the efficiency of individual treatments. Such an experimental design may specifically overcome the disadvantageous effects of increased variability in embolic stroke models. The quite novel "macrosphere model" of embolic stroke comprises a number of advantages, both regarding its particular usefulness for longitudinal imaging as well as its interesting pathophysiological aspects linking it to human stroke.

Keywords: Stroke; animal model; guideline.

With great interest we have read the first edition of stroke model guidelines by Liu et al (Liu et al, 2009). "Translational stroke research is a challenging task that needs long term team work of the stroke research community". We fully agree that stroke models "must be performed under conditions to avoid confounding factors influencing outcomes and widely available to most investigators". In a translational approach from bench to bedside we use highly standardized animal stroke models with the aim of translating the results to human stroke. Nevertheless, hundreds of neuroprotective agents with promising results in transient and permanent MCAO models have failed to be efficacious in human stroke, despite a 50% reduction of infarct volume that had previously been reported for all of those substances in experimental stroke models. In the end, not one of these neuroprotective agents succeeded in the clinical setting, highlighting the difficulties in translating experimental stroke research from bench-to-bedside (Dirnagl, 2006).

Thus, we argue that transient MCAO, while "highly consistent in performing injury", does not sufficiently produce relevant results from a translational point of view. This will likely be due to interindividual differences of subjects, especially when translating experimental results to the clinic, but also due to the heterogeneity of individual infarcts. In fact, human stroke is quite heterogeneous, so that individual stratification is indispensable in clinical studies. Back from bedside to bench, we should use similar strategies when designing preclinical studies, so the experimental model should rather be chosen according to the experimental objective, and not to the prevalent technical expertise. Thus, the stroke model should mimic the pathophysiological aspect that is modified by the therapeutic agent under investigation as accurately as possible (Schroeter et al, 2009). Moreover, as an alternative to studies with uniform groups of numerous animals, we suggest performing studies in an *intraindividual, longitudinal and translational way*. The general concept of this is the establishment of multi-modal *in vivo* imaging protocols that allow for a non-invasive and repetitive characterization of stroke-specific changes (e.g. cerebral blood flow (Heiss et al, 1997), blood-brain-barrier (Durukan et al, 2009), inflammatory responses (Schroeter et al 2009)). These parameters can then be used not only to stratify experimental animals, but also as specific read-outs that allow to monitor the

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efficiency of individual treatments targeting specific pathophysiological processes (reviewed by Rueger et al, 2007). Intraindividual and longitudinal multi-modal imaging thus enables us to study the specific fate of brain subareas that may succumb to ischemia, to secondary damage, or be rescued by therapeutic interventions. In principal, *in vivo* imaging studies can be performed using any type of experimental stroke model. However, only models that allow for direct monitoring of the actual evolution of cerebral ischemia can be used to characterize the hyperacute phase of stroke. This in turn calls for experimental stroke models that allows for a remote occlusion in an imaging scanner for e.g. Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) or Computer Tomography (CT). This permits for an immediate stratification of experimental animals, controlling e.g. the high variability of embolic stroke models. In turn, emboligenic stroke models add substantially to our methodological repertoire, since they closely resemble cardiogenic and arterio-arterial embolism as the main etiology of human stroke. Recently, the "macrosphere model" of embolic stroke has been added to the panel of available stroke models. In the "macrosphere model", the intra-arterial injection of TiO_2 spheres leads to permanent occlusion of the MCA, resulting in large focal ischemia (Gerriets et al, 2003; Schroeter et al, 2009). In contrast to the "autologous blood clot" model, in which a soft thromboembolic clot is used, the macrosphere model mimics arterio-arterial embolism of "hard" atherosclerotic plaque material (Schroeter et al, 2009) as the most frequent cause of human stroke (Grau et al, 2001; STAIR, 1999). Moreover, using standardized spheres, emboli size is tightly controlled. Most importantly, the "macrosphere model" easily allows for a remote vessel occlusion within the imaging scanner (Gerriets et al, 2004b; Gerriets et al, 2009), similar to other embolic stroke models. Moreover, in contrast to the well-established suture model of permanent ischemia, the macrosphere model avoids hypothalamic injury and subsequent hyperthermia (Gerriets et al 2003a; Gerriets et al 2003b; Gerriets et al, 2004a), which may be a confounding factor in therapeutic studies and may influence CNS inflammatory responses as well. Furthermore, the temporo-spatial dynamics of neuroinflammatory responses in the "macrosphere model" seem to mimic those observed in human stroke quite accurately (Dennin et al 2009). Satisfying the demands of (i) being a clinically relevant (embolic) stroke model, (ii) allowing for remote vessel occlusion required for imaging studies, and (iii) featuring interesting pathophysiological aspects linking it to human stroke, we argue that the "macrosphere model" is one step closer to human stroke and should be incorporated into the "Rodent stroke model guidelines for preclinical stroke trials".

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