

The potential and challenge of multicenter preclinical research[☆]

Francis S. Collins (2011)

A substantial problem in preclinical biomedical research has been the lack of reproducibility of animal studies (Jilka, 2016; Tortella, 2016; Pritt and Hammer, 2017; Harte-Hargrove et al., 2018). This takes on particular importance when animal data are used to design controlled clinical trials (CCTs) (Balduini et al., 2016). The literature is replete with positive findings in preclinical studies followed by failure of the CCTs of therapeutic intervention in traumatic brain injury (Xiong et al., 2013) and in many other areas of medical research (Hackam and Redelmeier, 2006; van der Worp et al., 2010). For this reason, nearly 20 years ago Treiman (2002) suggested that preclinical CCTs should be done before clinical CCTs. However, such preclinical CCTs represent a challenge because of the need for large numbers of animals in labor intensive studies. A solution to this challenge that has recently been initiated is the idea of NINDS Centers-Without-Walls. The intent is to support unique consortia of investigators to focus on major hurdles to the advancement of epilepsy research and treatment that are likely to only be overcome through large collaborative approaches. However, such collaborative approaches are not without their own set of risks. When the same experiment is conducted in multiple laboratories it is very possible that seemingly inconsequential variations in the experimental techniques used may result in substantial differences in outcomes.

Two small examples from my own laboratory illustrate the importance of small details in the harmonization of laboratory techniques. When attempting to replicate, in a new institution, the cobalt/homocysteine model of generalized convulsive status epilepticus that Nancy Walton and I developed a number of years ago (Walton and Treiman, 1988) it became apparent after several unsuccessful efforts that penetration of the dura was essential to allow the powdered cobalt placed in a small twist drill craniotomy hole to induce a seizure focus. More recently, using the controlled cortical impact (CCI) model (Dixon et al., 1991) to induce posttraumatic epilepsy, it became apparent that carefully drying the operative field to be sure that the CCI apparatus piston was in full contact with the dura is also essential. A small bubble of saline pooling in the craniotomy erroneously reduced the depth of piston excursion, which resulted in insufficient brain penetration so the animals did not develop seizures.

These examples from a single laboratory make clear the importance of harmonization of techniques across sites. To harmonize is to bring into consonance or accord. Harmonization of study design and execution has long been an essential feature of multicenter controlled clinical trials, but this concept has only recently begun to be adopted as a strategy in preclinical biomedical research in order to conduct randomized controlled clinical trials in the laboratory before translating results of such trials to the clinic. Laboratory research is labor intensive, and thus multicenter trials offer the potential of studying a large enough number of animals to achieve adequate statistical power.

Pitkanen et al. in this virtual special issue have shown that harmonization between laboratories is possible if properly planned and rigorously evaluated.

An overview of such an effort, the NINDS funded Center-Without-Walls: Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx) is provided by the study principal investigators (Pitkanen et al., 2019) and this is followed by six articles that provide a detailed description of the harmonization procedures being used in this multi-national collaboration. This virtual special issue may serve as a guideline for other investigators who wish to develop multicenter preclinical studies related to epilepsy and its treatment.

References

- Balduini, W., Carloni, S., Cimino, M., 2016. Preclinical randomized controlled multicenter trials (pRCT) in stroke research: a new and valid approach to improve translation? *Ann. Transl. Med.* 4, 549.
- Collins, F.S., 2011. Reengineering translational science: the time is right. *Sci. Transl. Med.* 3 90cm17.
- Dixon, C.E., Clifton, G.L., Lighthall, J.W., Yaghmai, A.A., Hayes, R.L., 1991. A controlled cortical impact model of traumatic brain injury in the rat. *J. Neurosci. Methods* 39, 253–262.
- Hackam, D.G., Redelmeier, D.A., 2006. Translation of research evidence from animals to humans. *JAMA* 296, 1731–1732.
- Harte-Hargrove, L.C., Galanopoulou, A.S., French, J.A., Pitkanen, A., Whittemore, V., Scharfman, H.E., 2018. Common data elements (CDEs) for preclinical epilepsy research: Introduction to CDEs and description of core CDEs. A TASK3 report of the ILAE/AES joint translational task force. *Epilepsia Open* 3, 13–23.
- Jilka, R.L., 2016. The road to reproducibility in animal research. *J. Bone Miner. Res.* 31, 1317–1319.
- Pitkanen, A., O'Brien, T.J., Staba, R., 2019. Preface – practical and theoretical considerations for performing a multi-center preclinical biomarker discovery study of post-traumatic epileptogenesis: lessons learned from the EpiBioS4Rx consortium. *Epilepsy Res.*
- Pritt, S.L., Hammer, R.E., 2017. The Interplay of ethics, animal welfare, and IACUC oversight on the reproducibility of animal studies. *Comp. Med.* 67, 101–105.
- Tortella, F.C., 2016. Challenging the paradigms of experimental TBI models: from preclinical to clinical practice. *Methods Mol. Biol. (Clifton, N.J.)* 1462, 735–740.
- Treiman, D.M., 2002. Will brain damage after status epilepticus be history in 2010? *Prog. Brain Res.* 135, 471–478.
- van der Worp, H.B., Howells, D.W., Sena, E.S., Porritt, M.J., Rewell, S., O'Collins, V., Macleod, M.R., 2010. Can animal models of disease reliably inform human studies? *PLoS Med.* 7 e1000245–e1000245.
- Walton, N.Y., Treiman, D.M., 1988. Experimental secondarily generalized convulsive status epilepticus induced by D,L-homocysteine thiolactone. *Epilepsy Res.* 2, 79–86.
- Xiong, Y., Mahmood, A., Chopp, M., 2013. Animal models of traumatic brain injury. *Nat. Rev. Neurosci.* 14, 128–142.

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