Thomas Willis Lecture

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The research of Ulrich Dirnagl is focused on stroke, cerebral blood flow regulation, and brain imaging. In preclinical models as well as clinical trials he and his coworkers and collaborators explore mechanisms by which brain ischemia leads to cell death, and develops novel methods to intercept mechanisms of damage in acute brain damage, as well as to foster regeneration and repair of the lesions. He is particularly interested in how the brain protects itself (‘endogenous neuroprotection’), and how the brain interacts with other systems of the body after it has been injured. Closely linked to his interest in stroke pathophysiology is his interest in the coupling of regional blood flow to neuronal activity, the mechanism underlying functional brain imaging with MR and PET. Beyond imaging structure and function of the CNS he and his team are developing, validating and using techniques that allow the non-invasive imaging of brain biochemistry and molecular signaling. To this end they use optical, MR, and nuclear medicine approaches in mouse and man. To improve the predictiveness of preclinical translational research he is actively promoting the introduction of quality standards for experimental design and reporting, as well as international collaboration in large, phase III-type preclinical trials. At the Charité Universitätsmedizin Berlin Ulrich Dirnagl serves as Director of the Department of Experimental Neurology, Chief Executive Director of the Center for Stroke Research Berlin, Clinical program coordinator of the Excellence Cluter NeuroCure and the Berlin partner site of the German Center for Stroke Research Berlin, Clinical program coordinator of the Department of Experimental Neurology, Chief Executive Director of the Excellence Cluter NeuroCure and the Berlin partner site of the German Center for Neurodegenerative Diseases (DZNE), as well as Program Director of the International Graduate Program Medical Neuroscience.

WHY TRANSLATIONAL STROKE RESEARCH CANNOT SUCCEED WITHOUT FAILURE

Based on research mostly in rodents, tremendous progress has been made over the last decades in our basic understanding of pathophysiological events following focal cerebral ischemia. This has led to the unravelling of numerous cellular and molecular targets for brain protective and restorative therapies. According to published results, almost any drug tested in rodent models of stroke which intercepts deleterious or boosts protective signaling is capable of improving outcomes compared to controls. Yet, after numerous subsequent failed phase II and phase III trials, none of those therapeutics has made it into the guidelines for stroke therapy. There are a number of potential reasons for this ‘translational roadblock’, which apparently afflicts other medical fields as well: 1) Animal models may not be predictive for human pathophysiology. However, there is good evidence that preclinical modeling of stroke can predict human pathophysiology, clinical phenotypes, and therapeutic outcomes (Dirnagl, Endres. Stroke 2014;45:1510–8); 2) Internal and external validity of stroke modeling in rodents may have been low, producing false positives and inflating effect sizes. Indeed, recent meta-research has exposed the substantial prevalence and impact of bias (such as selection, performance, attrition, and reporting bias) in preclinical research (Howells, Sena, Macleod MR. Nat Rev Neurol. 2014;10:37–43); 3) Inappropriate clinical trial designs and lack of statistical power may have produced false negatives; and paradoxically 4) Failures may be a necessary element of the translational research enterprise, and may actually promote our understanding of pathophysiology and successful translation in the long run. Argument 1, 2, and 3 have recently been covered extensively. Through the combined efforts of researchers, journals, and funding agencies this may have already led to improvements in experimental design and reporting. Argument 4, ‘attrition as promoter of translation’ (London and Kimmelman, Elife. 2015;4. pii: e12844) may sound counterintuitive or even preposterous, but may provide an overarching framework to improve the efficiency of the translational enterprise. In my talk I will forward the argument that we need to reduce preventable (‘detrimental’) attrition in stroke research by improving preclinical design and reporting (i.e. reduce bias, improve external validity, statistical power, and reporting). In the ensuing high quality studies, however, we need to embrace inevitable ‘negative results’ as a means to improve our pathobiological understanding and refine the interventions based on this knowledge. Negative results (‘failures’) in well designed studies providing good quality evidence result in information which can, among other benefits, correct mechanistic concepts, define dosing and timing of treatments, and free up resources for other avenues of investigation. I will argue that to harness the power of such ‘failures’ we need to distinguish between exploratory and confirmatory preclinical research (Kimmelman, Mogil, Dirnagl. PLoS Biol. 2014;12:e1001863), consider publication of study protocols at least of confirmatory studies, facilitate and incentivize the reporting of neutral or negative results as well as the publication of full data sets, and collaborate in preclinical randomized controled multicenter trials.