The Challenges of Translational Animal Research

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Regulatory authorities in the western world request performance of efficacy and safety testing in animal models. But how predictive are animal models for human outcome and what are the circumstances leading to maximum predictability?

A recent literature analysis in the field of acute stroke research has revealed that almost five hundred interventions tested in animal models showed positive outcome, whereas only three have a positive effect on human stroke patients in the clinic.1 Reasons for this tremendous discrepancy are only partially specific for stroke research. It was found that application schedules of drugs or time until treatment varied compared with the situation in the clinic. Furthermore, animals often did not reflect the situation of the majority of stroke patients by lacking appropriate comorbidities like hypertension or diabetes.1 Besides such disease specific mismatches, it was revealed that study design in preclinical animal research mostly does not fulfill standards as they are mandatory for the performance of clinical trials. Animal studies often lack sample size estimation prior to study performance, animals are rarely allocated in a random way to treatment and control groups and data is often not analyzed in a blinded fashion. It has been proven that non-performance of for example blinded assessment of outcome leads to overestimation of effect size.2,3 These observations are not specific for stroke research, but also occur in other fields.4,5,6 In addition, experiments and data sets are often poorly documented in research papers and sometimes, presented data doesn't even reflect major outcome over all performed experiments within a research team.5 One of the reasons for this unacceptable practice might be the fact that many journal editors ask for positive, striking effects. The therefore arising bias in literature towards positive outcome is well known as publication bias and has been well investigated especially for clinical trials. For acute stroke research in animal models, it has been estimated that approximately 30% of an intervention effect determined via a meta-analytic approach is due to publication bias.7

How does the situation in the field of molecular imaging and specifically in preclinical research of nuclear medicine look like? It is most probably fair to assume that general study design is not better there than it is in other fields of research. For the field specific aspects of work with animal models, George Box' statement "all models are wrong, but some are useful" hits the bull's eye: humans are not 70kg mice, but findings in animal models can help predict human outcome if models are chosen carefully and studies are performed in the best possible way regarding study design and data reporting.

References:

1. Sena E et al. TRENDS in Neurosciences. 2007; 30:433-469.
2. Perel P et al. BMJ 2006;334:197.
3. Bebarta V et al. Academic Emergency Medicine. 2003;10:684-687.
4. Martic-Kehl MI et al. Unpublished results.
5. Prinz F., Schlange T., Asadullah K. Nature Reviews. 2011;10:712.
6. Begley GC et al. Nature. 2012;483:531.
7. Sena E et al. PLoS Biology. 2010;8:e1000344.