Confidence in preclinical research

For decades, model organisms have provided an important reductionist approach for understanding the mechanistic basis of human diseases. With developments in methods like CRISPR/Cas9, optogenetics and next generation sequencing, researchers can now measure and manipulate whole organisms as never before, opening up new avenues for human disease modeling in animals. But in pursuing these avenues, we must confront a stubborn fact: translational success of biomedical research using disease models in key therapeutic areas, like cancer and psychiatric disease, is abysmally low.

While there are several potential reasons why positive results from an animal model might not hold up in humans—models will always have their limitations—there's growing evidence that our troubles with translation start early on in the research pipeline. Too often, investigators are unable to reproduce key findings from previous basic or preclinical studies, a prerequisite step on the long road to clinical translation. Although not guaranteeing clinical success, getting out of what some are calling a 'reproducibility crisis' in biomedical research is a logical first step towards improving the rate of therapeutic translation.

In this special Focus, *Lab Animal* presents several reviews, perspectives and commentaries addressing topics that affect the reproducibility and translation of results from disease models. The articles are connected by a common message: some of our current practices using animal models are flawed and can lead not only to irreproducible results, but failures to validate models and translate findings from the lab to the clinic (see page 103).

The rodent microbiome provides a great example of the complexity researchers encounter—whether they know it or not—when modeling human disease and trying to reproduce results obtained in another lab or institution (see page 114). Our increasing knowledge of the consortia of microorganisms living in man and mouse, and how those consortia impact biological function, provides exciting opportunities to develop better and more relevant models of complex human disease states. But as we delve deeper into the microbiome, we are still finding more questions than answers. Fortunately, researchers are making strides in their efforts to understand and control for the complexity of the microbiome in rodent models (see page 114)

Similar to the microbiome, other 'hidden' variables can affect the robustness of results with mice or rats. Rodent models are susceptible to stress, and vivariums and labs can be stressful environments (see pages 136 and 142). Regardless of what disease is being modeled, significant amounts of uncontrolled stress are likely to influence study outcomes. Rodent pain models can be affected by stress, causing significant changes in measured pain sensitivity (see page 136). Specific sources of stress, like thermal stress in the vivarium, can be detrimental to cancer modeling in mice (see page 142).

While identifying these sources of stress is important, developing useful methods to reduce stress is also critical. Providing mice with more behavioral control over their environment, for instance with nesting material for self-regulation of body temperature according to the changing needs of the animal, is a good example of a relatively simple and 'low-tech' solution that not only improves model validity, but also improves welfare (see page 142).

More researchers should also consider that rodents are social creatures and form complex social hierarchies in their homecages. Although aggression is a natural by-product of these hierarchies, when groups of rodents are confined to a typical vivarium homecage, aggression can lead to injury and unpredictable variation in stress levels between animals (see page 157). Methods and research to monitor and understand factors influencing rodent homecage aggression (see *Lab Anim (NY)* **46**, 176–184; 2017) could help scientists incorporate aggression as a variable into their analysis and potentially improve the reproducibility of their findings.

Problems with reproducibility and translation also extend beyond the lab and vivarium. Regulatory and policy factors, such as the weights given to harm *vs.* benefit during ethical review of a study (see page 164), or the responsibilities of an IACUC beyond protocol review (see page 129), can also play an important role in shaping the reproducibility of basic and preclinical research with animal models. And once a new model is developed, our

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current business practices of sharing those models can hinder access for scientists in academia and biotech, limiting their ability to validate and push forward those models in pursuit of drug development (see page 162)

Lab Animal hopes readers will take away some important new knowledge from this Focus, but most of all, a renewed sense that basic and preclinical research with animal models has been and will always be complex, and to improve our confidence in results, we must tackle these complexities head on, no matter wherein they lie.

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