

Of Mice and Men: The Murine Intrigues in Drug Discovery

Medicine is a science of uncertainty and an art of probability. — William Osler

Animal models occupy a central position in drug discovery. *In vivo* experiments are the *sine qua non* for identifying basic pathophysiological mechanisms, evaluating therapeutic approaches, and in deciding whether clinical trials are worthwhile. And yet, it would be imprudent to ignore the many arguments that challenge the validity of extrapolating the results of animal experiments to human conditions.

The drying pipelines of drug discovery famously quote two reasons for the ongoing innovation deficit in drug research: unprecedented escalation of costs and the popular notion that “all the simple problems are solved.” On the other hand, an insightful review by Shanks *et al.*^[1] faults the “axiomatic” assumption that rationalizes the predictive value of animal models in drug discovery. The congruence between *in vitro* screening, animal models, and the human condition suffers from multiple flaws. Neither cell culture nor animal models simulate the living reality. Older animal models (such as those for hypertension etc.) as well as the newer ones involving genetically modified mice, fail to replicate human pathology. Despite astounding breakthroughs in molecular biology, cell culture systems present static approximations frozen in time. Cell cultures neither incorporate the dynamism of circulation, account for checks on cell division nor account for the rates of supply/removal of nutrients and oxygen/carbon di oxide, or the endocrine environment. The phospholipid environment being different protein structure is altered. Even when the components are appropriate, the concentration of each component could be grossly different.

Animal models are considered inappropriate *per se* because our understanding of the model is inadequate. So is our understanding of the human diseases that such models propose to mimic.^[2] While some pathological conditions such as endocrine deficiencies can be replicated more easily, animal models of inflammation, vascular diseases, etc., “represent nothing more than a leap of faith.”^[1] Modern genomics and molecular biology, they argue, are entirely kinetic free zones. The models only trace the anatomical pathways frozen in time. While the understanding of anatomy has grown from organ to genome, cell cultures fail to replicate the dynamism of the functional milieu.

Animals bred and maintained in the laboratory environment are stressed by a life in perpetual, fretful captivity, frequent “man”-handling, restricted movement in cramped spaces, transportation into novel environments, experimental restraints, etc. These can alter their normal physiology and response to experimentation. Experimental stress also generates confounders in different ways, altering outcomes. Psychological and

physiological stress activate neuroendocrine networks with pervasive aftereffects. Psychological stress has been shown to induce stereotypical behaviors such as repetitive pacing and circling, even self-harm. Compromised immune and metabolic function, inappropriate inflammatory responses, and susceptibility to diseases can create a situation different from the ideal. Epigenetic changes, which accrue over a period of time, are potentially heritable and would change the physiology of laboratory-bred animals in unpredictable ways. All these could adversely impact the reliability and reproducibility of experimental results that form the foundation of pharmacological innovation.

In the absence of systematic studies evaluating the applicability of mouse models in human inflammatory diseases, Seok *et al.*^[2] of the Stanford Genome Technology Center conducted a systematic comparison between the gene expression patterns in humans and mice in three different conditions of systemic inflammatory conditions, namely trauma, burns, and exposure to endotoxin. Surprisingly, gene expression in white blood cells of humans and mice showed negligible correlation. Even more surprisingly, gene expression patterns differed between different mouse models too.

Murine models, though widely used to identify drug candidates, seldom yield molecules that pass human trials. In the field of inflammation, nearly all of 150 clinical trials to block inflammatory responses in critically ill patients failed.^[3] Despite paucity of evidence on the validity of animal models mimicking human immunology, investigators and public regulators assume animal models mirror human afflictions.

Animal models have also been dubbed as superfluous and sometimes distracting, when human data already exist. For instance, data on how aspirin can be useful in Alzheimer’s disease become unnecessary because clinical data already exist on the above question.

Drug discovery research has always been wary of extrapolating animal toxicity data to humans. For instance, corticosteroids are teratogenic in many animals but not in humans. The converse is true for thalidomide. Predicting toxicity from animal data is problematic. Studies have shown that only 4 of 24 toxicities were detected first in animal studies. Toxicity in humans had animal correlates in only 6 of 114 cases, which could also mean that many leads potentially useful to humans could have been eliminated on account of adverse animal data. In a frequently quoted tragedy that won widespread media attention, the phase 1 trial (first in man) of Theralizumab (TGN1412), an immunomodulatory monoclonal antibody, sent six healthy volunteers to the intensive care unit with a life-threatening cytokine storm.^[4] Victims were reported to suffer from many serious problems,

including multiple organ failure. Even more surprisingly, TGN1412 was administered at a dose 500 times lower than what was found safe in animals, including nonhuman primates. The TGN1412 episode has since become a stick to beat the protagonists of animal experimentation with.

Yet, another phenomenon that rarely meets the eye is publication bias. Positive results have a much higher probability of getting published. In a study covering 16 systematic reviews on animal models of acute ischemic stroke, only 10 (2%) of a total of 525 unique publications reported negative results on infarct volume.^[5] Only six publications (1.2%) failed to report at least one significant result. Statistical analysis suggested that publication bias might account for a third of the efficacy reported in systematic reviews. Further reviews identified 214 experiments that were conducted but not reported. Although the above study was specific to stroke, authors conclude that publication bias is likely to be pervasive across animal models in drug discovery, even life sciences in general.

Therapeutic options are shaped by standard text books that comprise of the filtered essence of a large volume of primary sources and scholarly reviews published by prestigious, highly cited journals. When negative data do not get published, a great deal of evidence goes missing from literature, generating an unjustifiable bias toward positive outcomes in animal experiments. Publication bias may contribute substantially to generating false premises and prejudiced guarantees in preclinical evaluation, potentially aggravating the steadily mounting innovation deficit in drug discovery and pharmacotherapy.

The above difficulties are all related to the scientific validity of animal models. However, problems do not end with science. There is a sociopolitical dimension to how we treat animals. Modernity is all about inclusivity. Over the course of many decades, we have expanded the sociopolitical space to embrace all humankind. Women (who did not even have voting rights), minorities, the marginalized communities, disabled citizens, and the lesbian, gay, bisexual and transgender (LGBT) enjoy state protection in modern democracies. More recently, the world has been witnessing a shift from an “anthropocentric” to “biocentric” perspective. Man does not “own” the planet; the biocentric world holds all life sacred. When technology would fashion the large-scale production of synthetic meat into a profitable industry, one should not be surprised if capitalist democracies legislate against killing animals for food. Future generations, potentially “reformed” by a possible “vegan legislation,” might even look on our relish for “tandoori chicken” with brazen disgust, much like the moral revulsion that cannibals arouse today!

The steady rise in animal rights activism, fuelled by the fashionable legitimacy of a biocentric outlook, together with the emerging skepticism in animal models, might alter the course and approaches in pharmacological research. The European Union (EU) has already banned animal testing for finished cosmetic products and their ingredients. EU has

also banned the marketing of cosmetics tested on animals elsewhere. Many activist groups are already working toward the liberation of animals from the horrors of laboratory testing. The Fund for the Replacement of Animals in Medical Experiments (FRAME), an organization that started with a meager fund of 100 pounds, will be soon conducting a symposium to mark its 50th year of existence. FRAME also runs a journal, *Alternatives to Laboratory Animals*, focusing on how animal experiments can be “reduced, replaced and refined.” The clock is ticking!

While animal models are statutory requirements for obtaining regulatory approvals, the unchallenged faith in the fidelity of animal experiments would continue to direct the course and pattern of the current drug discovery paradigm. In this context, knowing the limitations of animal models is itself a step closer toward improving scrutiny and the search for alternatives. To quote Thomas Kuhn, “...novelty ordinarily emerges only for the man who, knowing with precision what he should expect, is able to recognize that something has gone wrong.”

M. K. Unnikrishnan

National College of Pharmacy, Kozhikode, Kerala, India

Address for correspondence: M. K. Unnikrishnan,
National College of Pharmacy, Kozhikode - 673 602, Kerala, India.
E-mail: unnikrishnanmazhuvancherry@gmail.com

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