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EDITORIAL

A New Look at Animal Models of Neurological Disorders

Marie-Françoise Chesselet[1]

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The impact of animal models of neurological disorders remains hotly debated, the main point of contention being the frequent clinical failure of therapies successfully tested in animal models. This lack of predictability has plagued models of a wide range of neurological disorders and raised concerns about their usefulness. In fact, translational limitations of animal models are to be expected. Animals usually used for preclinical studies such as rats, mice, and even non-human primates not only differ from humans in many respects, but the conditions under which they are bred and housed are fundamentally different from the conditions in which humans develop and live.

These limitations, however, do not necessarily negate the usefulness of all animal models of neurological disorders when those are well conceived and thoughtfully used with their limitations in mind. Furthermore, preclinical drug testing with the goal of providing evidence that a potential therapy should provide benefits to patients is not the only use of animal models. A wide range of models have and will continue to provide critical information on mechanisms of disease that are often impossible to study in humans or even in human material such as stem cells or postmortem brains, for example. Animals can be genetically modified, exposed to specific environments, and analyzed at different stages of a pathological process, which is generally not possible in humans. They also represent a level of complexity usually missing in simplified systems that can be required to understand certain aspects of diseases, for example, how neuronal circuits or a cross-talk between the immune system and neurons critically determine the pathological process. With this in mind, it is futile to search for the "perfect" or even"the best" animal model of neurological disorders. A model needs to suit the scientific question asked and the results interpreted mindfully.

✉ Marie-Françoise Chesselet
mchesselet@yahoo.com

[1] Departments of Neurology and of Neurobiology, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

In this issue of *Neurotherapeutics*, authors illustrate how critical novel information can be provided by well-chosen animal models of a variety of neurological disorders. These insights range from a better understanding the impact of environmental factors, primarily heavy metals, on the developing brain as reviewed by Smith and Strupp [1], to novel information on multiple sclerosis provided by state-of-the-art imaging techniques when used in animal models of the disorder as described by Buttigieg et al. [2].

A major recent contribution of animal models to the understanding of stroke (Carmichael and Llorente [3]) and Huntington's disease (Cvetanovic and Gray [4]) comes from the ability to model the complex role of glial cells, long neglected contributors to pathology.

Synucleopathies form a diverse group of disorders that encompass Parkinson's disease, Lewy Body Dementia, and Multiple Systems atrophy among others. Since the discovery of the role of alpha-synuclein in these disorders through human genetics and pathology, animal models based on the expression of the protein have supplanted previous toxin-based models which only reproduced the end point of the pathological process, the death of dopaminergic neurons, rather than the pathological process. Extensive animal studies are beginning to clarify the contribution of various forms of alpha-synuclein to the pathology (Peelaerts and Baekelandt [5]), to elucidate the mechanisms of disease spread first suspected on the basis of human postmortem pathological studies (Pinto-Costa et al. [6]), and to model previously neglected non-motor aspects of Parkinson's disease (as reviewed by Richter et al. [7]). Furthermore, Stefanova [8] shows how genetic manipulations in mice led to the generation of a model of Multiple Systems Atrophy, a rare disease in which alpha-synuclein surprisingly accumulates in glial cells rather than in neurons. Each of these models contributes to a better understanding of synucleopathies, and some provide meaningful tools for the preclinical testing of novel therapies [7, 8]. In the absence of a neuroprotective treatment that has been validated in the clinic, their predictability remains uncertain. However, the mechanistic insights that underlie their respective design bring some confidence that this new generation of models will

not suffer from the same limitations of previous models that were based on *face validity* (i.e., that reproduce the phenotype of a disease) rather than *construct validity* (i.e., that reproduce the pathophysiological mechanism of the disease).

Besides alpha-synuclein, other proteins became a focus of intense interest in the animal model field because of their association, through human genetic studies, with neurological disorders that are rarely familial and much more often sporadic, such as Parkinson's disease [9] and frontotemporal dementia [10]. In both cases, genetic manipulations in mice attempt to provide insights into the human disease by reproducing the mutation to study its effects on the mammalian brain, in order to hopefully identify novel therapeutic targets, as explained by Volta [9] and by Kashyap et al. [10], respectively, in their contributions. Similarly, new mechanistic data on the frequent neurological disorder Restless Leg Syndrome have led to efforts to generate and evaluate novel models of the disorder as reviewed by Silvani and colleagues [11]. As researchers who strive to model neurological disorders grapple with the respective value of face versus construct validity of their model, one is reminded that this debate continues and that a large diversity of models, rather than "a perfect" model, is necessary to gain insights into the complexity of human neurological disorders. Many models can contribute to partial insight, and when used with rigor, they advance the field and bring us closer to the ultimate goal of curing neurological disorders, as illustrated by the articles in this issue of *Neurotherapeutics*.

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