

## Of mice and men: COVID-19 challenges translational neuroscience

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“Mouse is not man and blood is not brain” is a frequent response when neurologists are confronted with findings from translational medicine. The article was written on behalf of the European Academy of Neurology Neuroscience/Translational Neurology Section and impressively reinforces the significance of pre-clinical research in understanding complex pathophysiological processes and in setting priorities for clinical research. Indeed, translational medicine is an emerging field that aims to promote pre-clinical insights for the advancement of prevention, diagnosis and therapies. Some may not be aware that translational research does not exclusively focus on animal models and *ex-vivo* experiments but also concerns bench-to-bedside transfer and public health.

Severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 is the seventh member of the CoV family that can infect humans [1]. Speculation about the neuroinvasive potential of SARS-CoV-2 is sustained by reports about neurological signs and symptoms in some COVID-19-infected patients [2]. It remains speculative as to whether these clinical observations are related to infectious or parainfectious nervous system complications as cases with confirmation of SARS-CoV-2 and markers of inflammation in cerebrospinal fluid are scarce. The medical efforts during the initial outbreak of the novel CoV-2 disease (COVID)-19 were certainly dictated by severe respiratory symptoms and the limited hospital capacities for critically ill patients [3]. Moreover, the challenges for preventive and protective measures in the healthcare system were multifaceted and tied up resources.

To fill this knowledge gap about the potential neuroinvasiveness and route of central nervous system (CNS) entry, Silvia Natoli and collaborators went back to the scientific literature on animal models of SARS-CoV and Middle East respiratory syndrome virus [4]. They studied whether there is evidence for neuropathogenesis in experimental studies of these structurally similar CoVs, which were responsible for the epidemics with severe respiratory disease in 2002 and 2012, respectively. SARS-CoV and SARS-CoV-2 share 79.6% sequence homology [5]. CoVs utilize distinct receptors for cell invasion and there are structural differences in human vs. murine receptors. SARS-CoV and SARS-CoV-2 utilize the human

angiotensin-converting enzyme (ACE) receptor, whereas the receptor of Middle East respiratory syndrome-CoV is dipeptidylpeptidase-4 (CD26) [1]. There are also differences in the binding site of ACE2 receptor for CoV and CoV-2 [6]. ACE2 is not only expressed in the lung and small intestine, but also in the vasculature and in the cytoplasm of neurons. Animal studies in human ACE2 transgenic mice confirmed neuronal vulnerability for infection by CoV and tropism for the brainstem [7]. The animal studies also provided hints for the potential routes of CNS entry, i.e. olfactory bulbs, peripheral nerves, synapse-connected route from the lungs to the medullary cardiorespiratory center and hematogenic spread [4]. The animal experiments furthermore identified that features of CoV CNS infection include a key role for the innate immune system, impact of aging and an earlier viral clearance in animal models. The experimental work on CoVs was not only conducted in mice but also non-human primates, hamsters and ferrets; the most suitable animal model has not been found so far.

Neurologists therefore need to be involved in the care of patients with COVID-19 and provide a more comprehensive picture of the spectrum of nervous system manifestations [8]. Then, the bed-to-benchside approach with development of animal models for CoV-2, which resemble human CNS infection, should have high priority. Such a model would not only enable the development of preventive strategies (e.g. blocking viral entry to the CNS) but also provide a mode to study therapies aimed at limiting brain injury and subsequent neurological sequelae. Some of the pre-clinical preparatory work for this step has been done.

## Disclosure of conflicts of interest

J.S. is the Co-Chair of the Scientific Panel for Infectious Diseases and member of the Education Committee of the European Academy of Neurology.

**J. Sellner**<sup>a,b,c</sup> 

<sup>a</sup>Department of Neurology, Landeskrankenhaus Mistelbach-Gänserndorf, Mistelbach; <sup>b</sup>Department of Neurology, Christian Doppler Medical Center, Paracelsus Medical University,

Salzburg, Austria and <sup>c</sup>Department of Neurology, Klinikum rechts der Isar, Technische Universität München, München, Germany (e-mail: j.sellner@salk.at)

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