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Preface



This special issue of the *Vaccine* journal entitled 'Rabies Vaccines and Therapeutics' provides an up-to-date review of the rabies situation worldwide from a 'One Health' perspective for scientists, clinicians, veterinarians, policy-makers and stakeholders involved in human rabies treatment and control in animals. The research efforts for identifying therapeutic molecules that are efficacious in treating clinical rabies in humans will be discussed. A therapeutic molecule capable of clearing replicating rabies virus from the brain of an infected patient remains the 'Holy Grail' of research in the 21st century. Additionally, global intervention strategies used for the elimination of (terrestrial) rabies from reservoir populations using vaccination are also discussed.

The majority of manuscripts published in this special issue were funded by the European Union as part of the Network of Excellence ASKLEPIOS (Advanced Studies towards Knowledge on Lyssavirus Encephalitis Pathogenesis Improving Options for Survival) consortium project. The ultimate goal of projects under this call was to deliver knowledge that can contribute to the future prevention, treatment or diagnosis of neglected diseases that are disproportionately affecting countries with poor health infrastructures. This knowledge should focus on biological mechanisms and pathology of the diseases in question.

Rabies remains one of the deadliest neglected infectious diseases known to humankind, with a case fatality rate approaching 100% following the onset of clinical disease. The domestic dog represents the principal reservoir of the rabies virus globally and 99% of human cases involve the transmission of the virus to a human following a bite from an infected dog. The disease remains neglected due to numerous societal and anthropogenic factors, including poor reporting and surveillance, misinformation in dealing with animal bites, resource limitations, inadequate advice concerning pre- or post-exposure prophylaxis and a lack of knowledge regarding the disease's symptoms and possible post-exposure treatments (PETs). The most cost-effective strategy to reduce the global burden of human rabies is to combine different approaches to control dog-mediated rabies, including the vaccination of dogs and restriction of free-roaming dog populations using animal birth control methods, along with the expansion of the availability of low-cost human vaccines and PET.

Rabies has a strong impact at the scientific, clinical, and cultural levels. It is one of the most ancient known diseases that can be effectively prevented by means of vaccination, yet is still one of the most devastating diseases to date. Morbidity and mortality caused by RABV outcompetes that of Ebola and Marburg virus infections, being the only virus known to kill approximately 100% of the affected persons once clinical symptoms develop. A handful of patients with rabies have recovered from the disease, albeit with severe neurolog-

ical sequel. All approaches to treat rabies have been based on the "trial-and-error" approach and therefore the reasons for these few successful treatments are poorly understood and have not been reproduced. One of the main bottle-necks in progressing with identification of successful treatment strategies is the fact that the pathogenesis of the disease is poorly understood which limits the possibilities of rationally designing intervention strategies. The aim of ASKLEPIOS was to address this point by bringing together existing knowledge in order to understand the mechanisms that govern pathogenesis of rabies and subsequently design novel intervention strategies. These novel intervention strategies are based on rational choices of compounds with high likelihood for success, rather than desperate bed-side, trial-and-error approaches.

Three issues remain of paramount importance and were addressed within ASKLEPIOS:

1. Rabies pathogenesis is a multifactorial process. As a result, successfully treating rabies most likely will require a combination of compounds that will hit different determinants of pathogenesis;
2. Previous studies (including studies from the partners involved in ASKLEPIOS) have identified that both the virus and the host response play an equally important and detrimental role during rabies encephalitis. As a result, a successful combination therapy against rabies most likely will require compounds that inhibit both virus replication and detrimental host responses;
3. Rabies virus is exclusively neurotropic and the disease caused by this virus is restricted to the central nervous system. As a result, a successful treatment should be able to reach the target organ even if given peripherally. ASKLEPIOS is using an innovative approach to address this issue by using blood-brain-barrier openers to enable combination therapy to enter the CNS and with the aim to effectively eliminate both the virus and the host responses that can have a detrimental effect on the brain;

Within ASKLEPIOS a number of compounds that can significantly increase survivorship of experimentally infected mice were identified and have therefore taken a notable step forward in the identification of rationally designed treatment strategies for treating clinical rabies in humans.

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