PERIPHERAL DETERMINANTS OF VIRAL ENCEPHALITIS: TOWARDS PREDICTIVE BIOMARKERS AND LIMITED NEUROVIRULENCE

The Covid-19 pandemic was a reminder of the threat posed to human health by the burden of RNA viruses. RNA viruses include both emerging viruses such as Nipah virus (NiV) and West Nile virus (WNV), and long-established viruses for which the number of cases is rising again today, such as dengue virus (DENV) or measles virus (MeV). Measles virus (MeV) and Nipah virus (NiV) are enveloped negative-strand RNA viruses of the Paramyxoviridae family, both of which infect the respiratory system early in the course of infection. NiV usually reaches the central nervous system (CNS) and induces an acute, fatal neurological disease, and relapses can occur in patients who have survived. In rare cases, MeV virus also infects the CNS, causing fatal neurological disease, sometimes even years after primary infection: the high mutation rate of RNA viruses allows neuroinvasive variants to emerge, even if CNS cells do not express any MeV receptors. Dengue virus (DENV) and West Nile Virus (WNV) are two enveloped positive-strand RNA viruses within the Flaviviridae family. DENV causes different neurologic complications, such as viral encephalitis when the virus reaches the CNS or encephalopathy that involves acute liver failure. WNV is notably responsible for encephalitis manifested by extrapyramidal disorders, tremor, parkinsonism, and a case fatality rate between 10% and 30%.

In the first task of this PhD project we will focus on the early peripheral events determining the neurovirulence of viral infections. In subtask 1.1 we will take advantage of hamster and human organotypic lung and liver cultures well mastered in the laboratory, to **identify predictive biomarkers of neurovirulence** by RNA sequencing and RT-qPCR of infected tissue, and assay of several molecules in culture media, by comparing the pathogenesis of neurovirulent and non-neurovirulent viral strains. As neuroinvasive leukotropic viruses can use white-blood cells to disseminate in the body through the blood flow, we want to figure out in subtask 1.2 what the **differences of peripheral resident macrophages susceptibility and cell-mediated transport are**, when infected by neurovirulent or non-neurovirulent viral strains. In subtask 1.3 we will focus on the **infection of the liver that can induce major changes in the organism homeostasis**. **We wonder to what extent it consequently participates in the associated neurological injuries**, by altering the BBB integrity or over-activating microglia for instance, or in the enlargement of the virus tropism through the acquisition of a new molecular phenotype of the viral envelope including molecule involved in liver-brain exchanges after budding.

The second task of this PhD project will focus on the CNS response upon infection and in subtask 2.1 we will investigate the cellular tropism of different viral strains, neurovirulent or not, using IF and FACS methods developed and mastered by the team. As several neurovirulent viruses target immune cells, we will compare the antiviral and proviral roles of microglia, as well as the consequences of microglia infection/activation on the brain parenchyma in subtask 2.2. Our final question will be to decipher the functional consequences of different CNS viral infections in subtask 2.3, and how the use of neuromodulatory therapies could restore a physiological phenotype. We will adapt **GCaMP** protocols for brain slices from the literature to hamster organotypic cerebral cultures, whether whole sagittal brain cultures or cerebellum cultures. We will then use them to assess the **functional consequences of infection on neuronal electrical activity**, comparing neurovirulent to non-neurovirulent strains. We will then be able to study the spatial correlation between infected foci and local or global electrical activity disturbances. As epileptic seizures are common complications of viral encephalitis, this tool could help us to model and study its pathogenesis, and we could use it as a **platform to assess the therapeutic potential of anti-epileptic drugs or other neuromodulators to correct the electrophysiological phenotype** of infected brains.

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Main ArchiFun theme involved:

- ☐ Host-pathogen interactions;
- ☐ Mechanisms of bacterial resistance and cancer onsets;
- ☑ Neurodegenerative and autoimmune diseases;
- ☐ Translational research in prevalent diseases;
- ☐ Physiology and ecology;
- ☐ Neurosciences and cognition.