DEVELOPMENT OF IMMUNE MICROPHYSIOLOGICAL SYSTEMS (IMMUNE SYSTEMS ON A CHIP) FOR MCM TESTING

Multi-organ Models Of The Neuro-immune Response To Vaccination

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Although the past decade of advances in animal studies and human multi-omics platforms yielded dramatic advances in understanding of immune processes, effective vaccines and countermeasures remain challenging to develop, especially for acute infections of the central nervous system (CNS). Several acutely infectious viruses that fall within the Chemical Biological Radiological Nuclear (CBRN) defense mission, including the encephalitic alphaviruses, exhibit neurotropism and cause significant long term damage in the CNS due to blood-brain-barrier damage and dysregulated immunity. Neuronal damage from alphaviruses in particular is significantly immune-mediated and is modulated by sex, diet, and obesity leading to difficulties in predict or control outcomes. In this context, a lack of accurate models that recapitulate immune responses in relation to human disease has become a critical hurdle to development and regulatory approval of countermeasures. Microphysiological system (MPS) offer the potential to fill this gap, but integration of adaptive immune function into MPS is still in early stages. In addition, factors such sex and metabolic state (adipose tissue) are rarely considered in MPS models, but significantly impact immune responses to infection and vaccination.

Our current efforts are geared towards the optimization of an MPS platform that models neuro-immune and endocrine interactions across diverse populations, for ultimate use to test vaccines and to elucidate immune mechanisms in response to neurological threat agents. Currently, our laboratories have developed separate 3D cultured organ modules of the human brain, meningeal lymphatics, lymph node stroma, and adipose tissue. Each of these modules is cultured separately atop a membrane until maturation, providing flexibility in the timeline. We have also developed a 3D printed microfluidic platform that easily accepts the membranes and connects them into a fluidic media loop, with recirculating flow of media driven by a tubing-free magnetic impeller pump. To address the incompatibility of brain media and peripheral media, we developed a unique dual-medial design separated by a lymphatic barrier.

Our future efforts will be focused on combining the validated models of brain, lymph node, and adipose tissue, as well as the lymphatic barrier, for long-term co-culture. We eventually plan to incorporate a well established blood brain barrier module as well. This combined MPS will be the first to co-culture a brain with either a LN or adipose tissue, and will enable predictions of neuro-immune interactions including lymphocyte trafficking and drainage of brain-derived factors to the lymph node. This model will be applied to assess the ability of the MPS to replicate key features of neurotropic infection using Venezuelan Equine Encephalitis Virus (VEEV) as a model organism and corresponding vaccination. The tubing-free perfusion is a significant advantage because of its compatibility with federal regulations for high containment (BSL3) work for CBRN-mission-relevant pathogens. Our long term goals include establishment of scalable fabrication methods and expanding application to other (re)emerging viral pathogens that target the CNS, to enable efficient testing of neurotropic threat agents.