MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

A High-throughput Human Primary Cell-based Blood-brain Barrier Model For Evaluation Of Treatments And Prophylaxis For Nerve Agents

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Background information: Organophosphate nerve agents (OPNA) represent a highly toxic threat to warfighters and civilians, causing seizures and brain damage and leading rapidly to death unless treated immediately. One of the most challenging barriers to the development of efficacious protective agents for OPNA poisoning is a dearth of accurate and predictive preclinical models capable of evaluating the ability of candidate therapeutics to cross the blood-brain barrier. Animal models are costly and poorly predictive of human responses due to species differences, pointing to a need for in vitro human primary cell-based platforms that support the ability to interrogate transport mechanisms in a physiologically relevant microenvironment.
Purpose: The purpose is to establish a high-throughput human primary co-culture model of the blood-brain barrier with hemodynamic shear stress imparted to the endothelium, applied to evaluation of transport of candidate protective agents and drug delivery systems across the blood-brain barrier (BBB) in the platform.
Objective: The objective here is to establish a high-throughput in vitro model based on co-culture of human primary astrocytes, brain microvascular endothelial cells and pericytes, in an instrumented organ-on-chip platform capable of imparting physiologically relevant hemodynamic shear to recapitulate the microenvironment of the BBB.
Rationale for the research: Clinical evaluation of therapeutic agents for OPNA poisoning is precluded, necessitating the need for in vitro platforms to predict human responses and identify delivery techniques capable of crossing the BBB.
Relationship to other areas of study: In vitro systems have emerged as capable of augmenting and potentially replacing animal models for modeling the effect of chemical, biological, radiological and nuclear (CBRN) threat agents on human tissues and organs. Target organs and tissues include the lung, kidney, liver, vascular, and intestines, necessitating the development of practical, high-throughput platforms capable of supporting disease modeling and therapeutic screening across all of these applications.
Methods: We have established the PREDICT96 platform, an instrumented organ-on-chip system developed by Draper for evaluating safety and efficacy across a wide range of disease areas and applications, as the basis for the BBB model.
Preliminary results: We have established monoculture brain microvascular endothelial cells, co-culture with astrocytes, and tri-culture including pericytes, in the PREDICT96-BBB platform, demonstrating TransEpithelial Electrical Resistance (TEER) and molecular permeability as assays to confirm model functionality. We have applied this model to the evaluation of candidate delivery systems capable of ferrying OPNA therapeutics across the BBB.
Preliminary conclusions: Initial conclusions of this work are that the establishment of human primary endothelial cells, astrocytes and pericytes on a semi-permeable membrane across 96 devices on the PREDICT96 platform results in a physiologically relevant model of the BBB. Through the application of hemodynamic shear and the co-culture system, we demonstrate highly reproducible TEER and molecular permeability that recapitulate in vivo levels.
Impact to the JSTO mission and the Joint Force: Models capable of rapidly and accurately evaluating therapeutic and prophylactic candidates OPNA toxicity are critical to accelerating the discovery of more effective approaches to protecting warfighters from chemical warfare agents.