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

Bioinspired Microfluidic Design Of Coagulation-free Blood Perfusion Systems

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Background information
Recent reports of microfluidic systems ranging from immune-integrated in vitro models and coagulation-on-a-chip platforms to organ support systems are prone to complications such as coagulopathy and immune cell activation due to the non-physiological design approaches. Materials and formats which prevent the inappropriate activation of immune cells are critical for the future development of these systems.
Purpose
Here we report on the development of bioinspired branching microchannel networks that are designed to precisely control fluid shear stress acting on circulating cells, minimizing clotting and activation and supporting blood perfusion and immune cell transport in a microfluidic architecture.
Objective
The objective of this work is to generate a microfluidic design paradigm that mimics key properties of healthy microvascular flow, enabling the application of these platforms to modeling immune cell transport and blood perfusion, as well as the construction of large-scale systems suitable for therapeutic intervention in the ICU and in prolonged field care settings.
Rationale for the research
Microfluidic devices and systems are inherently suitable for application to supporting immune cell circulation and whole blood perfusion, but if designed incorrectly, can be of limited utility stemming from non-physiological designs. Microfluidic architectures that precisely control wall shear stress and avoid sudden diameter changes, sharp corners and dead zones are needed to realize the full potential of microfluidics in these contexts.
Relationship to other areas of study
The design of microfluidic systems that support immune cell circulation and blood perfusion can have wide applicability as a platform for immune-integrated organs on chips, devices for the evaluation of coagulation and hemorrhage resulting from viral hemorrhagic fevers and other severe infections, and ultimately critical care systems for treatment of sepsis, lung and kidney failure.
Methods
We have developed computational modeling tools and microfluidic device designs and fabrication techniques that faithfully reproduce the properties of physiologic immune cell circulation and blood flow. Devices are evaluated computationally and tested in vitro and in vivo in large animal studies to assess levels of clotting, bleeding and activation.
Preliminary results
Computational analysis shows wall shear stress tightly controlled in a physiological range of 1 – 5 dyn/cm2, and microfluidic devices constructed using precision micromachining and replica molding techniques show accurate dimensional control with SEM analysis. In vitro testing shows very low levels of clotting, hemolysis and activation over 6 hours of testing, while animal studies over 48 hours show stable, physiological performance.
Preliminary conclusions
Precise control of fluid shear stress results in microfluidic blood perfusion systems with minimal clotting and bleeding, a major advance over previously reported platform technologies. These systems serve as a foundational element of immune-integrated organ on chip models and organ support systems.
Impact to the JSTO mission and the Joint Force
Model systems for integrating immune cells and whole blood in organs-on-chips are required to test therapeutics for chemical and biological threat agents. Large-scale blood perfusion systems that minimize clotting and bleeding are key to next-generation prolonged field care systems for combat casualty care applications.