

BIOMEDICAL ENGINEERING
COLLEGE OF ENGINEERING AND APPLIED SCIENCE

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PROJECT TITLE: 3D Bio-Printing of a Human Blood Brain Barrier-Chip for Modelling of COVID-19-induced Cerebrovascular Diseases

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Project Description

Coronavirus disease 2019 (COVID-19) is primarily a respiratory disease but several aspects of severe acute respiratory syndrome (SARS) infection are likely to impact on cognition. Indeed, up to two-thirds of hospitalized patients show evidence of brain damage including ischemic and hemorrhagic stroke [1]. It is still not clear whether cerebrovascular dysfunctions are caused by direct viral action or indirect inflammatory response of the infected patient [2]. A growing body of evidence indicates that the spike protein, one of the most studied portions of the SARS-COVID-19 owing to its strong immunogenic profile, may cause brain injury with mechanisms still poorly understood. The spike protein is known to bind to brain endothelial cells when exposed to physiological fluid-flow (shear stress) [3,4]. Moreover, results published in multiple research papers support a potential pro-thrombotic effect of the protein [5]. Traditional cell culture systems do not allow for recapitulating the complex tissue architecture of the human blood-brain barrier (BBB) nor the vascular blood-fluid dynamics. At the same time, animal models are rarely predictive of human response to pathogenic infections. An in vitro system designed to reflect the multicellular 3D architecture of the BBB could help gain a better understanding of molecular mechanisms underpinning COVID-19-induced cerebrovascular dysfunction and may represent a valuable tool for identifying novel therapeutic targets in the future. The Organ-on-Chip technology is conceived to include multicellular co-culture on tissue-specific substrates (extracellular matrix) and physiologically relevant 3D geometries. Cells growing within these chips are also exposed to physiologically relevant biomechanical forces. In this project, we will leverage our expertise in bioprinting of vascularized 3D models to engineer a microfluidic system designed to capture the full tridimensional architecture of the human BBB and to recapitulate early cellular and molecular events leading to BBB dysfunction caused by the

recombinant spike protein. We plan of using a combination of tissue engineering and 3D bioprinting methodologies [6] in order to recreate a hollow vessel-like structure (or vascular compartment) entirely surrounded by human astrocytes and pericytes (or glial cells) . Finally, pro-inflammatory and pro-coagulant factors will be used alone or in combination with the (commercially available) recombinant spike protein to determine whether our 3D Bio-printed model of BBB (3D BBB-Chip) can recapitulate spike-protein mediated injury of the cerebrovascular tissue as observed in patients, including increasing vascular expression of inflammatory markers, and altered barrier properties.

References.

1. Aggarwal, C.S.; Walser, S.; Bhandari, A.; Garg, N.; McClafferty, B.; Ramgobin, D.; Golamari, R.; Sahu, N.; Kumar, A.; Jain, R. A Comprehensive Review of COVID-19 Associated Neurological Manifestations. *S D Med* 2020, 73, 569–571.
2. Buzhdygan, T.P.; DeOre, B.J.; Baldwin-Leclair, A.; Bullock, T.A.; McGary, H.M.; Khan, J.A.; Razmpour, R.; Hale, J.F.; Galie, P.A.; Potula, R.; et al. The SARS-CoV-2 Spike Protein Alters Barrier Function in 2D Static and 3D Microfluidic in-Vitro Models of the Human Blood-Brain Barrier. *Neurobiology of Disease* 2020, 146, 105131, doi:10.1016/j.nbd.2020.105131.
3. Kaneko, N.; Satta, S.; Komuro, Y.; Muthukrishnan, S.D.; Kakarla, V.; Guo, L.; An, J.; Elahi, F.; Kornblum, H.I.; Liebeskind, D.S.; et al. Flow-Mediated Susceptibility and Molecular Response of Cerebral Endothelia to SARS-CoV-2 Infection. *Stroke* 2021, 52, 260–270, doi:10.1161/STROKEAHA.120.032764.
4. Lei, Y.; Zhang, J.; Schiavon, C.R.; He, M.; Chen, L.; Shen, H.; Zhang, Y.; Yin, Q.; Cho, Y.; Andrade, L.; et al. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. *Circ Res* 2021, 128, 1323–1326, doi:10.1161/CIRCRESAHA.121.318902.
5. Grobbelaar, L.M.; Venter, C.; Vlok, M.; Ngoepe, M.; Laubscher, G.J.; Lourens, P.J.; Steenkamp, J.; Kell, D.B.; Pretorius, E. SARS-CoV-2 Spike Protein S1 Induces Fibrin(Ogen) Resistant to Fibrinolysis: Implications for Microclot Formation in COVID-19; *Infectious Diseases (except HIV/AIDS)*, 2021;
6. Galpayage Dona, K.N.U.; Hale, J.F.; Salako, T.; Anandanatarajan, A.; Tran, K.A.; DeOre, B.J.; Galie, P.A.; Ramirez, S.H.; Andrews, A.M. The Use of Tissue Engineering to Fabricate Perfusable 3D Brain Microvessels in Vitro. *Front. Physiol.* 2021, 12, 715431, doi:10.3389/fphys.2021.715431.