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

Immunity Twin: Utilizing Mechanistic Modeling And MI-informed Image Analysis To Develop Actionable Medical Interventions For Challenges To Human Lung

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Our bodies represent a collection of highly regulated and exquisitely tuned chemical reactions compartmentalized in a diverse array of cell types. Unfortunately, this system is also vulnerable to exploitation by a wide array of biological threats, including bacteria, viruses, and fungi. The human immune system is an incredible defense force that counters these biological adversaries; however, it is complex and varies greatly from individual to individual. Project Immunity Twin ("iTwin") aims to combine the power of AI/ML with advanced organotypic tissue culture systems to understand what underlying individual-specific traits most affect the response to viral infection. The foundation of this work is built upon two interdependent approaches: (i) an in vitro wet-lab effort using a 3D model of the human lung, and (ii) an in silico pipeline that uses both ML-based image analysis and mechanistic modeling. By infecting these "mini lungs" with closely related strains of influenza A (IAV), we can collect a variety of molecular data over the course of viral replication. These data are then used to refine the parameter space of a mechanistic model that allows us to predict how differences in a given individual's baseline biological status alters their response to IAV. These cell cultures are simultaneously sent through a live-cell confocal imaging protocol, termed "cell painting," which collects thousands of pictures that can be analyzed for subtle morphological changes that correlate with progression of infection. Together, these efforts standardize a pipeline that can (i) identify, and (ii) predict the effects of, an individual's biology on their response to a biological threat. These computational models, which are iteratively refined and validated in the laboratory, represent an important step forward in the generation of immunological "digital twins"- a Holy Grail in the field of personalized medicine.

In its initial funding cycling, Project iTwin has successfully shown the difference in responses to H1N1 and H3N2 strains of IAV using both monoculture and "mini lung" cultures from a representative donor. Viral replication varies by strain, and differences in cytokine responses both replicate expected results from the literature and additionally highlighting heretofore unknown phenotypes. These molecular data points have informed a pilot mechanistic model that has shown reproducibility across multiple trials. A novel cell painting protocol has also been implemented with these 3D cultures, with features extracted from image data showing strong clustering in PCA analyses across (i) virus strain, (ii) infection status, and (iii) time point post-infection. Similar work using cultures derived from different donors is on-going.

With the protocols developed during Project iTwin in place, we have the proof-of-concept for a tool that could be utilized to keep our warfighters safe. This pipeline could inform the educated deployment of troops to regions where certain diseases are/are not endemic, tailored treatments following an exposure, or even provide person-specific prophylaxis. While the field of personalized medicine continued to evolve, efforts like iTwin can potentially play a role in the generation of a truly individual-centered health care system.

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