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

Reconstitution Of Human Hematopoietic Niche On-chip For Real-time Analysis Of Leukocyte Mobilization And Mcm Development

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Background:Traditional bone marrow (BM) models typically employ static cell cultures that do not accurately emulate the dynamic biochemical and biomechanical properties of the human hematopoietic niche. These limitations hinder the ability of researchers to study complex immune responses and hematopoietic processes under physiologically relevant conditions, thereby impacting the translational value of such studies. Purpose: This project aimed to harness advanced Organ-on-a-Chip technology to construct a human-derived bone marrow model that effectively simulates the hematopoietic environment. This model can enable detailed investigations into the behavior and regulation of myeloid innate immune cells and the dynamics of leukocyte mobilization, which are critical for understanding immune system function and disorders. Objective: To engineer a 3D matrix-embedded human myeloid bone marrow niche (hBM-Chip) that supports the growth, differentiation, and functional analysis of hematopoietic stem and progenitor cells (HSPCs) in a controlled in vitro setting. The objective extends to using this platform to assess the immune responses elicited by these cells when exposed to various stimuli. Rationale of the Research: The development of the hBM-Chip addresses a critical gap in immunology and hematology research by providing a more dynamic and physiologically relevant model system. The traditional limitations of bone marrow models—such as the lack of real-time data and the inability to monitor cellular responses accurately—are overcome by integrating microfluidic technologies with live-cell imaging capabilities. Relationship to Other Areas of Study: This research is interdisciplinary at its core, intersecting with fields such as tissue engineering, immunology, and drug development. By providing a more accurate model of the bone marrow, the hBM-Chip facilitates the translation of basic biological findings into therapeutic strategies for diseases like leukemia, anemia, and immune disorders, thereby influencing multiple fields of biomedical research. Methods: The hBM-Chip incorporates a novel design featuring a 3D matrix that mimics the extracellular matrix of the bone marrow, embedded within a microfluidic device. This setup is linked with Inline Cyto-Descriptor (ICD), an optical system that we designed and developed for real-time, high-resolution imaging and analysis of cell behavior within the chip. The system specifically tracks the migration of leukocytes in response to chemotactic signals such as leukotriene B_4, mimicking inflammatory responses. Results: Initial experiments have demonstrated that the hBM-Chip supports the effective differentiation of hematopoietic stem cells into lineage-committed neutrophils and monocytes, with significantly improved viability and functionality compared to static cultures. Furthermore, the real-time analysis capability of the ICD has allowed for unprecedented observations of leukocyte egress and mobilization, providing insights into the cellular dynamics at play during immune responses. Conclusions: The hBM-Chip, along with its companion technology ICD, are a valuable tool for hematological and immunological research, offering deeper insights into cell interactions and responses within the bone marrow niche. Impact to the JSTO Mission and the Joint Force: The hBM-Chip enhances the Joint Science and Technology Office's mission by enabling rapid assessment of immune cell behaviors and responses, accelerating the development of MCMs, and improving military readiness. Its relevance extends to personalized medicine and targeted treatments in both military and civilian healthcare.

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