Preface to Special Topic: Microsystems for manipulation and analysis of living cells

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This Preface describes exciting papers contributed to the Special Topic section on manipulation and analysis of cells using microsystems. Brief summaries of each paper are provided and general trends are discussed. © *2011 American Institute of Physics*. [doi:10.1063/1.3641860]

INTRODUCTION

Microfabrication and microfluidic approaches are finding an increasing number of biological applications. One of the more exciting applications is interfacing living cells with microdevices. Recent years have seen an explosion in use of microtechnologies for sorting, sensing, and cultivation of cells.[1,2] This special topics section provides a sample of the types of microsystems being developed for cell analysis and manipulation. The research directions covered in this thematic section include sorting of mammalian cells,[3,4] pairing of mammalian cells,[5] sorting of viral particles,[6] concentration of bacteria,[7] cultivation of cells in microfluidic devices,[8,9] on-chip monitoring of cell function,[10] and on-chip flow cytometry.[11]

MANIPULATION OF MAMMALIAN CELLS IN MICRODEVICES

On the cell sorting side, Koh and co-workers describe shape-encoded microboards that can be used for cell cultivation and high-throughput analysis.[3] Instead of positioning cells on culture substrates, authors describe placing cells on microboards – flat and thin objects of defined shapes that are not anchored to the substrate. Authors demonstrate that different cell types can be attached to different microboards and then co-cultured in the same petri dish. Importantly, cell type is encoded in the shape of the microboard so that the cells of interest may be easily identified and analysed.

In their paper, Albritton and co-workers provide a different approach to cell sorting.[4] This approach entails fabricating arrays of polymer microrafts on top of a silicone rubber (PDMS) membrane. The microrafts are impregnated with magnetic nanoparticles and are made large enough to house individual cells. Single cells/rafts may be dislodged by puncturing PDMS surface from below and, once dislodged, cells/rafts may be preconcentrated using a magnet. The approach developed by Albritton and co-workers addresses the need for retrieval of live single cells from culture surfaces for clonal expansion or downstream analysis.

Cui *et al*. describe yet another variant of a microdevice for cell manipulation.[5] In cell biology in general and in immunology in particular, it is imported to create heterogeneous cell pairs where two cells belonging to different types interact with each other. Such heterotypic pairing occurs during formation of immune synapse between an antigen presenting cell and a T-cell. Pairing is also important in creation of antibody producing hybridoma cells where B-cells and stromal cells are fused together. Cui *et al*. developed a microfluidic device that enables high efficiency formation of heterotypic cell pairs. This device employs hydrodynamics to assemble and hold two different cell types in proximity to each other.

SEPARATION OF MICROBES FROM BIOLOGICAL FLUIDS USING MICROFLUIDICS

Analysis of biological fluids such as blood frequently necessitates separation and preconcentration of disease-causing organisms such as bacteria or viri. The efforts of bioMEMS

community to develop devices for sample processing and microbe preconcentration are represented by papers from Cheng and Chang labs.

Cheng and co-workers from Lehigh University describe a simple and elegant approach for separating viral nanoparticles from blood cells.[6] In this approach, blood carrying viral nanoparticles is layered on top of a buffer stream inside a microfluidic channel. Because the flow is laminar, diffusion is the main driving force in the transport of nanoparticles through the fluid stream. Authors demonstrate numerically and experimentally that viral nanoparticles diffuse slower than blood cells through the fluid column and that investigators are able to collect fluid stream enriched with viral particles. This paper is significant as it points to a way for separating viral particles (e.g., human immunodeficiency virus (HIV)) from whole blood without the need for sophisticated equipment.

In another study under the rubric of cell separation, Chang and co-workers describe microfluidic devices relying on dielectrophoresis (DEP) for separation of bacteria from blood.[7] Presence of bacterial species in blood signifies a serious pathology that may lead to sepsis or multiple organ failure. It is therefore important to develop technologies for early and sensitive determination of bacteria in blood. The paper by Chang and co-workers demonstrates the use of DEP and microfluidics to separate smaller bacterial cells from larger blood cells, achieving several fold enrichment of *E.coli*.

MICRODEVICES FOR CELL CULTIVATION AND ANALYSIS

Another important research thrust in the bioMEMS community is the development of microdevices for culturing and analysis of cells.

Sethu and co-workers from University of Louisville created a microdevice for mimicking mechanical stimulation experienced by endothelial cells.[8] Endothelial cells form an inside lining of blood vessels and are important participants in plaque formation. Function of these cells may be affected by the disturbed flow patterns associated with partially occluded blood vessels. The team from Louisville employed microfluidics to recreate and superimpose varying mechanical stimuli experienced by endothelium in vivo. These stimuli included cyclical stress, pressure, and shear stress. It is envisioned that this microfluidic model of endothelium will replicate in vivo injury more faithfully and will be more informative when determining molecular mechanisms of plaque formation and when screening for therapeutic agents.

Another demonstration of microsystems for cell cultivation was provided by Qin laboratory from Dalian Institute of Chemical Physics, Chinese Academy of Sciences.[9] This group describes a simple method for creating PDMS substrates with nanometer-scale patterns. Such substrates seek to mimic native tissue where ECM proteins are typically assembled into fibers nanometers in width and tens of micrometers in length. Qin and co-workers demonstrate that cell shape, orientation, and migration are affected by the topology of the nanostructured substrate.

In addition to culturing cells in microfluidic devices, it is frequently important to analyze their function *in situ* without having to disturb culture conditions. Revzin laboratory from UC Davis demonstrated integration of a biosensor for detection of hydrogen peroxide with macrophages cultured inside a microfluidic device.[10] Hydrogen peroxide is an important inflammatory marker that is released by activated immune cells in response to pathogens. UC Davis team demonstrated that enzyme-based electorchemical biosensor for peroxide monitoring could be miniaturized, positioned at the site of the cells and used to continuously monitor peroxide release by macrophages. Such sensors could be used in the future for disease diagnostics or for investigation of cellular responses to pathophysiological conditions.

Yet another illustration of microdevices for cell analysis was provided by Ligler group from the Naval Research Laboratory (NRL).[11] In this paper, a team of scientists from NRL was concerned with developing a miniature flow cytometer for analyzing plankton and was addressing a need for 3D hydrodynamic focusing. While laminar flow is well suited for 2-dimensional focusing, cells are normally not focused in the vertical direction which leads to cell stacking and compromises sensitivity of flow cytometry analysis. To remedy this, NRL investigators

fabricated chevron patterns in the roof and the floor of the microfluidic device such that hydrodynamic focusing was achieved in the vertical as well as lateral directions.

CONCLUSION

This thematic issue demonstrates diversity of approaches and problems being tackled by scientists and engineers developing microsystems for cell analysis and manipulation. Contributing authors range from leaders in the field to up-and-coming young investigators and hail from the United States as well as from abroad. It is my hope that the reader finds the diversity of topics and approaches presented in this thematic section, interesting and stimulating.

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