Preface to Special Topic: Microfluidics in Cancer Research

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Preface to Special Topic: Microfluidics in Cancer Research

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In 2012, more than half a million people have been projected to die of cancer in the United States of America alone. In spite of the best efforts by the research community, following the declaration of the war on cancer 40 years back, cancer incidents and death rates have declined marginally. These facts vividly show that cancer research needs a shift in the paradigm, and in this respect, microfluidics is expected to provide the next generation tools for the oncologists. In recent years, a significant volume of literature has appeared to demonstrate that microfluidic strategies could be used to throw new light on cancer development, detection, diagnosis, and treatment. These developments take advantage of the fact that at the operational scale of a typical microfluidic system, researchers are able to address a single biological cell, even a portion of it; generate complex and stable gradient of chemical compounds; assay the activities of several therapeutic agents simultaneously, using a very small volume of the reagents and biological samples; separate a specific single cell from a population with a million others; and above all, create a confined microenvironment that mimics the physiological milieu. The sheer diversity in design and functionalities of these microfluidic systems further illustrates the enormous scope for researchers, who are willing to apply microfluidics in cancer research. Nevertheless, many corners of cancer remain unexplored, and new research developments are always in progress. I feel extremely honored to edit this special topics section entitled Microfluidics in Cancer Research, and I am thankful to Dr. Leslie Yeo (Editor of Biomicrofluidics) for giving me the opportunity to do so. In this section, we have an assortment of 11 papers, which cover both the fundamental and applied aspects of this stimulating research domain.

To gain a comprehensive understanding of the research field, one must know what has already happened in the field and what lies ahead. In addition, since a topic like this is essentially interdisciplinary, involving physics or engineering and biology, there should be proper integration of core proficiencies. Here, I believe it is important that the microfluidic research community should be aware of the most important problems that bother the cancer biologists. With this view in mind, we include in the section a perspective article, authored by Das and me.[1] In this article, we have first reviewed the advancement of microfluidics in cancer biology, especially in the last five years. We have then outlined different biophysical aspects of cancer and the effects of the confined microenvironment on cell behavior and cellular dynamics. Lastly, we have tried to compile some of the most important problems in cancer biology to encourage future microfluidic applications in cancer research. As it has been illustrated in the perspective article, many physical properties of cancer cells, such as stiffness, motility, and electrical properties, are emerging to be key targets for anti-cancer therapy. Relevantly, Khan and Vanapalli[2] have reported the development of a novel microfluidic device, which is capable of rapidly characterizing the deformability of brain cancer cells, as cells are hydrodynamically transported through a narrow channel. While it is conventionally believed that cancer cells are softer than the normal cells of same tissue origin, this report presents substantial evidence that the brain tumor cells are stiffer than the benign cells. In another article, Salmanzadeh *et al.*[3] have investigated the dielectric properties of different stages of syngeneic murine ovarian cancer cells in a microfluidic system. They have reported that specific membrane capacitance increases as the

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stage of malignancy advances from very benign to the most aggressive stage. According to the authors, such change in dielectric property could be attributed to the changes in the internal cytoskeletal structures of the cell during cancer progression.

One key step in oncogenesis is the metastatic transport and propagation of cancer cells in the human body. The disease could be diagnosed at a relatively early stage if we could isolate and characterize the circulating tumor cells (CTCs) from the blood samples. Since CTCs are rare among other blood-borne cells, microfluidic devices with embedded antibody-arrays have been used to capture and enrich the CTC population. To implement this strategy, however, one requires knowing the expression profile of marker proteins on the surface of cancer cells. An alternative and upcoming strategy is to isolate the CTCs on the basis of physical— especially hydrodynamic and electrical— properties. Along this line, Shim *et al.*[4] present a microfluidic system, capable of isolating CTCs from 10 ml clinical blood specimens in 40 min, using continuous-flow dielectrophoresis. They have further verified that the CTCs isolated by this device possess the same genetic characteristics as the primary tumor from the patient, and it confirms the correctness of their approach. In the following article,[5] researchers belonging to the same group (of Peter Gascoyne, University of Texas, USA) have measured the dielectric and density properties of the NCI-60 panel of tumor cell types by a dielectrophoretic field-flow fractionation method, against the properties of other blood cell types. Here, they show that all of the NCI-60 cell types, irrespective of their tissue origin, exhibit dielectric properties significantly different from normal peripheral blood cells, and this signature could be used to isolate the cancer cells by dielectrophoretic method. Taking the matter further up-front, Alshareef *et al.*[6] have reported a method for distinguishing between two types of cancer, of different tissue origin, based on their dielectrophoretic properties. Using a microfluidic dielectrophoretic sorter with optically transparent electrodes, they have studied the effect on different input parameters, such as AC frequency, voltage, and flow rate, on the separation efficiency. Beyond dielectrophoresis, in an alternative approach, Sun *et al.*[7] have proposed a size-based mechanism for separating the tumor cells from the normal blood cells, using a double spiral microfluidic channel. In this device, the competition between the inertial lift force and Dean force mediates the size-based cell separation of the large tumor cells from the small blood cells. Similarly, Liu *et al.*[8] have reported another interesting mechanical means to separate the tumor cells, by using microfluidic deterministic lateral displacement (DLD) structure. They have evaluated the separation efficiency for different cancer cell types, using both circular and triangular post arrays. For their operational simplicity, microfluidic DLD devices should have many future applications in the clinical studies of circulating tumor cells. Finally, Cima *et al.*[9] have reviewed the recent advances in label-free approaches to enrich, isolate, and manipulate CTCs. They provide a list of the technologies that are used in label-free isolation of CTCs and highlight the advantages and drawbacks of these technologies.

In cancer therapy, before commencing the actual treatment course, clinicians need to determine the type and the dose of the chemotherapy that are the most likely to be successful, by testing the chemoresponse of biopsied tumor samples *in vitro*. For this purpose, they need to analyze the response of a small volume of the sample to different drugs and to different concentrations of each drug, which is technologically challenging. At the level of cancer treatment, microfluidic devices offer high-throughput operational capability and massive parallelization. In this issue, Das *et al.*[10] report a microfluidics-based multiplex platform for empirical chemosensitivity assays. In this device, they are able to trap three-dimensional (3D) spheroids of ovarian cancer cells and assay their response to two common anti-cancer agents, namely carboplatin and paclitaxel. Importantly, in spheroid culture, the chemoresistance of cancer cells increased by almost an order of magnitude, as compared to the value measured in two-dimensional (2D) culture. Microfluidic systems like this are predicted to play important roles in the emerging field of personalized medicine. Finally, in an article by Park *et al.*,[11] the authors have implemented a sequentially pulsed fluid delivery (SPFD) scheme, which has allowed them to maintain almost zero shear stress in the chamber, while establishing the chemical concentration gradient. The device is expected to accelerate the study of cellular responses to the gradients of soluble signals and chemotherapeutic agents.

Taken together, these articles show the glimpse of the true potential of microfluidics in cancer research, at every level, starting from fundamental cancer cell biology to cancer treatment. I hope that the readers of *Biomicrofluidics* will be excited after going through this collection of papers, and it will offer new stimuli and perspectives for the researchers in this exciting and emerging field. Finally, I sincerely acknowledge the generous assistance of Christine Urso and other editorial and production staffs of *Biomicrofluidics* for making this special topics section a reality.

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