Preface

Circulating tumor cells (CTC) were first observed and described as epithelial tumor cells found in blood over a century ago [1]. But reliable methods have been developed only recently to interrogate this rare population in blood. These methods are developed either utilizing unique antigen expression on CTC, such as the only FDA-cleared technology CellSearch™ [2], or utilizing their unique physical properties including size [3], density [4], electrical properties [5], etc. After an overview of the current status of our knowledge about CTC in the introductory chapter (**Chap. 1**), **Datar and coauthors** present details of affinity-based and non-affinity-based CTC capture technologies in **Chaps. 2** and **3**, respectively.

As more and more in-depth molecular and functional characterization of CTC studies has been carried out, the validity of CTC capture based on EpCAM expression is being questioned. CTC population is discovered to be heterogeneous and the gene expression levels vary from cell to cell even within the same patient sample [6]. To address this heterogeneity, an increasing number of studies have begun to look beyond CTC enumeration to elucidate the subpopulations among CTC. Details on molecular characterization of CTC that can help resolve this heterogeneity are described by **Lianidou and her colleagues** in **Chap. 4**. A potential subpopulation that is worth studying in CTC is the cancer stem cell population. Cancer stem cell population in CTC is further discussed by **Wicha and his colleagues** in **Chap. 5**.

CTC in circulation may assume one or more of several optional states: they could undergo elimination (by anoikis, apoptosis, necrosis, or immune attacks), successfully invade into secondary site, only to stay dormant or locked in mesenchymal states, or invade into a secondary site and metastasize by rapid proliferation. CTC dormancy studies are discussed in more detail in **Chap. 6** (**Allan and Chambers**) and **Chap. 7** (**Barkan and Chambers**). An important process involved in tumor metastasis that brings EpCAM-based CTC capture in question is the Epithelial-Mesenchymal Transition (EMT). In this process, tumor cells can potentially down-regulate their expression of epithelial markers including EpCAM and E-Cadherin and gain a mesenchymal and more invasive phenotype. In **Chap. 8**, **Thiery and colleagues** discuss more about this EMT process as a mechanism through which CTC establish distant metastasis.

An ability to perform phenotypic and genotypic studies of CTC is expected to lead to the development of assays with clinical applications to benefit cancer management. **Chapter 9** (**Dandachi and colleagues**) and Chap. **10** (**Magbanua and Park**) provide detailed discussions on phenotypic and genotypic analysis of CTC. In addition to molecular characterization of CTC, another interesting direction is the functional characterization of CTC employing technologies that enable viable CTC capture and culture. **Cote and colleagues** present a detailed review of functional characterization of CTC in **Chap. 11.**

With the emerging technologies to enumerate CTC from cancer patients, the clinical utilities of CTC have been investigated extensively in the past decade. One well-validated clinical application of CTC is their prognostic value at baseline. A detailed review on prognostic implications of CTC in breast cancer can be found in **Chap. 12** (**Smerage**). Although CTC have been well validated as prognostic markers for various cancer types, clinical applications for CTC as a surrogate endpoint, their use as a predictive marker to guide therapy, or use as an early detection marker are areas that are still largely unexplored and require large-scale clinical trials for validation. Although it is perhaps still a little early, it is not hard to envision CTC as powerful biomarkers as "liquid biopsy" which can provide valuable information via a minimally invasive blood draw. **Chapter 13** (**Cristofanilli**) and **Chap. 14** (**Polzer and Klein**) discuss in more detail the clinical applications of CTC. **Chapter 15** (**Huang and Lackner**) tackles a crucial concept for pharmaceutical industry, that of developing CTC assay as a companion diagnostic for either a pre-approved or an under-development anticancer drug. This chapter thus emphasizes an early and close partnership between the drug development sponsors and the CTC diagnostic companies to successfully navigate the regulatory landscape through phase II and III clinical studies, which in turn would allow for synchronized regulatory review of the drug and CTC assay. Finally, **Chap. 16** (**Kulkarni and Jeffrey**) summarizes the clinical applicability of CTC, while providing considerations for the future clinical trials.

As will be clearly evident, this volume is a result of a highly scholastic activity, with all of the contributors being thought leaders in the field, with decades of extensive contributions to the study of molecular biology of metastasis and the clinical applications of these critical findings.

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