FOREWORD

Primary tumor and/or metastasized sites release a small number of tumor cells into the blood circulation. As a result, the detection of circulating tumor cells (CTCs) requires specialized technologies for the enrichment and detection of single tumor cells [1]. Since most CTC assays rely on epithelial biomarkers, they have a tendency to miss CTCs undergoing an epithelial-to-mesenchymal transition (EMT). Newly discovered biomarkers such as the actin-bundling protein plastin-3 [2] could address this concern because they are not downregulated during EMT and they are not expressed in normal blood cells. As demonstrated by several research groups, CTC isolation, enumeration, and analysis offer reliable information for cancer prognosis, potentially serving as a method of liquid biopsy [3]. Functional characterization using specialized in vitro and in vivo test systems has started [4–6]. Furthermore, monitoring the change in the CTC number before, during, and after anticancer therapy (e.g., chemotherapy or hormonal therapy in breast cancer [7]) and determination of therapeutic targets (e.g., HER2 [8] or PD-L1 [9]) might serve as a surrogate marker for response to therapy. These individualized therapy responses can be employed as a tool of companion diagnostics to help the stratificatio of anticancer therapies and to gain insights into therapy-induced selection of tumor cells [10–12].

This book is the first one to focus on the current platforms of CTC isolation. CTCs can be enriched positively or negatively based on biological properties (e.g., expression of protein markers). For example, the positive enrichment involves using antiepithelial antibody (Ab), antimesenchymal Ab, or a combination of antiepithelial and antimesenchymal Ab, whereas the negative depletion employs anti-CD45 Ab to remove the unwanted leukocytes (see Chapter 14 for the details). Moreover, physical properties (e.g., size, density, deformability, electric charges) can be applied to

capture CTCs. For example, CTCs can be isolated by using a membrane filte system based on the CTC size, microposts in a microchip based on the CTC size plus deformability, centrifugation on a Ficoll density gradient based on the CTC density, dielectrophoresis (DEP) based on CTC dipole moment, or spiral CTC chips based on the CTC size. Some of them may combine with protein-expression-based CTC strategies (e.g., CTCs are first selected based on their presumably larger size, while the smaller leukocytes are removed; then, CTCs are conjugated with beads-tagged antiepithelial Abs and captured in a magnetic fiel [13]). This book gives an excellent overview of current technologies and discusses the potential and challenges for their future development as diagnostic tools in oncology.

Better understanding of CTC biology will help CTC assay development. As a result, tumor-specifi CTC assays could be advantageous than a CTC technology developed for all cancer types [1]. Most importantly, clinical validity must be achieved for newly developed CTC assays through clinical trials, and clinical utility must be identifie in the appropriate context of use [14]. This may take considerable efforts, time, and budget, which might be one important reason why after 10 years of intense development work in the CTC fiel only one assay (CellSearch®, see Chapter 19 for the details) has received FDA clearance. One of the future goals of CTC characterization is to identify metastasis-initiation cells and drug-resistant clones. The genetic analysis of mutations relevant to cancer therapies in these subpopulations by concurrent monitoring of CTCs might lead to the development of new companion diagnostics in cancer therapy. The validation of liquid biopsy assays is an important task of the new European consortium CANCER-ID that comprises more than 30 institutions from academia and industry (www.cancer-id.eu). This important book will stimulate further developments in new technologies for the detection and characterization of CTCs as liquid biopsy.

Klaus Pantel, M.D., Ph.D.
University Medical Centre Hamburg-Eppendorf, Germany

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