Journal of Developing Drugs
ISSN: 2329-6631

Kanwar et al., J Develop Drugs 2013, 2:3
DOI: 10.4172/2329-6631.1000e128

Editorial Open Access

Personalized Medicine through Circulating Tumor Cells: The New Dimension in Cancer Research

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Outcomes in some of the current clinical trials could be misleading as they fail to represent the high genetic variability seen among cancer patients, leading to averaged responses taken from broader patient groups. In fact, clinicians and drug makers both agree that no group of trial volunteers could ever match the extraordinary biological diversity of the drug's eventual consumers i.e., patients [1]. With such challenges the American Cancer Society anticipates that 580,350 Americans will die of cancer this year, resulting in nearly 1,600 people per day [2]. Since metastasis is a major cause of such high mortality rate, elucidating this enigmatic process can potentially help to change the current paradigm of cancer diagnosis, treatment and monitor efficacy of therapies. Emerging evidence indicates the important roles of Circulating Tumor Cells (CTCs) in the spread of cancers and metastasis [3,4]. CTCs are the cells shed by primary tumor into circulation and known to be key players in metastasis [5,6]. Recent reports also show that these cells could be a good surrogate biomarker for not only prognosis, but also for cancer detection and development of personalized treatment [7-9]. This editorial briefly examines the current perspectives in using CTCs as a liquid biopsy to develop personalized targeted therapies for advancing the field of cancer research.

The first critical step in using CTCs as biomarker is the optimal isolation of these cells. This step represents a major technological challenge, since CTCs make up a minute fraction of the total number of cells circulating in blood, 1-10 CTCs per mL of whole blood compared to a few million white blood cells and a billion red blood cells. In consequence, a plethora of novel technologies have emerged in the past years for detecting and isolating CTCs [5,10,11]. These techniques are classified based on properties that distinguish CTCs from surrounding hematopoietic cells, such as physical properties and biological properties. Physical properties include size, density, electric charges, and deformability; while biological properties mainly focus on cell surface protein expression and viability [12-15]. For either of these strategies, it is imperative that developing an optimal CTC isolation method needs to meet following criteria: (1) high recovery, (2) high purity of CTCs by removal of all other blood components, and (3) high system throughput to assure practical application of large sample volume [16].

Currently, Cell Search® Method is the only FDA approved system and the "gold standard" for emerging CTC isolation methods, however, many questions remained unanswered regarding the general clinical acceptance, validation and optimal characterization assay for CTCs [17,18]. Cell Search® Method is a surface expression based method, using antibodies against epithelial cell adhesion marker (EpCAM) [19]. As in any other biological based method, its major limitation is potential loss of any subpopulation of CTCs that do not express the EpCAM-antigens used in the capture protocol. Recognizing this limitation, ongoing efforts are directed towards methods that are independent of EpCAM expression exploiting CTC's biological and physical properties as previously mentioned [20-22].

Once optimal enrichment of CTCs is achieved, the second critical step involves the practical use of CTCs for advancing research from the bench-to-bedside. CTCs isolated from newly diagnosed cancer patients as well as those undergoing treatments, can be used to unravel the mysteries behind disease progression by elucidating key-cellular interactions of metastasis through functional assays [8,12]. Understanding the science of CTCs therefore leads the way to personalized medicine. Despite of technological advancements made in this field, a standardized clinical approach to identify CTCs and its characterization is yet to be found. The challenge arises because of the extremely low number CTCs present in blood (limiting their availability for downstream assays) and therein the erogeneity [9,23].

Researchers have identified new methods to characterize CTCs based on quantifying the levels of protein expression, mRNA expression and chromosomal abnormalities. For examples, it has shown that protein expression of HER2 correlate well with gene amplification when assessed in parallel by Fluorescence In Situ Hybridization (FISH) on cytospun CTCs obtained from cell lines and patient samples [24,25]. Additionally, other clinical studies have utilized mRNA expression profile of CTCs using Reverse Transcription Polymerase Chain Reaction (RT-PCR) mainly using commercially available Adna Test® (AdnaGen AG, langenhagen) [26,27]. However, as mentioned earlier, most of these assays are yet to be validated.

Other characterization assays include performing FISH at RNA and DNA level to analyze tumor-specific markers and chromosomal aberrations to identify gene amplifications and translocations [23]. Considering the genomic characterization, single cell isolation of CTCs employing microfluidic approaches have demonstrated to have major clinical importance [5]. Ongoing research is currently focused on gaining extensive data-characteristics of few CTCs through combining immunofluorescence-based assays using different fluorophores, image cytometry and FISH as well as PCR-based multiplex assays [8,28-30].

Current beliefs in oncology are shifting to personalized medicine. Therefore, an approach of personalized medicine for developing drugs in cancer therapy seems imperative than ever

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Received August 27, 2013; **Accepted** August 29, 2013; **Published** September 04, 2013

Citation: Kanwar SS, Rivera L, Nagrath S (2013) Personalized Medicine through Circulating Tumor Cells: The New Dimension in Cancer Research. J Develop Drugs 2: e128. doi:10.4172/2329-6631.1000e128

before. CTCs analysis, often described as a "liquid biopsy", could serve as a companion diagnostic for the pharmaceutical industry by incorporating CTCs based biomarkers as endpoints in future clinical trial design [31]. Accordingly, CTCs are currently implemented into more than 400 clinical trials at which the integration of CTCs into immunotherapeutic approaches seems to be very promising [32].

In the pharmaceutical industries, which are associated with a high failure rate, significant savings are possible if companies can assess efficacy at an early stage in clinical trials [33] through the easily accessible CTCs, which can represent better the dynamic changes of tumor progression. The dynamic changes in CTC counts before initiation of therapy and during (neo) adjuvant therapy provide strong prognostic value in evaluating real-time information on the efficacy of therapy. CTCs as surrogate endpoints could provide new insights into the complex mechanism of drug resistance, allowing clinicians to take individual therapy decision when change in the treatment course is needed. New ongoing trials investigating the use of CTCs as predictive markers are expected to provide great insights about its measurable benefits for the individual patients [34,35]. Conjoining the approaches of single CTC isolation with genomic profiling, it has become possible to accurately identify the disruptive molecular pathway(s) at any given time, thereby, leading to individualized clinical decisions. Hence, a genuine personalized treatment approach in cancer patients utilizing CTCs seems to be feasible in near future.

Although, the presence of CTCs is known for a long time they became the subject of active research only in last two decades [36]. Significantly, the research in past decade has been instrumental in bringing forth CTCs to clinic. However, CTCs are far from being a mainstream clinical assay. We acknowledge a strong need of benchmarks for CTCs isolation and characterization in order to realize their full potential in clinical setting and for tailoring the individual therapies. Nonetheless, the study of CTCs poses a direct impact upon society by presenting novel ways to address some of the major hurdles in cancer research such as early detection, real-time monitoring for drug efficacy, and patient screening for enabling better clinical trials. CTCs will potentially foster the further understanding of the pharmacodynamics, thereby, facilitating testing of novel therapeutic targets for the advancement of personalized medicine.

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