



## The Future of Precision Medicine in Oncology: Targeting Cancer Stem Cells

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### Editorial

Precision medicine in oncology has been a popular topic of discussion in the health-care field since US President Barack Obama announced the Precision Medicine Initiative at his 2015 State of the Union address. Precision medicine is focused on identifying which therapies are most effective for individual patients based on the genetic characterization of their cancer [1-3]. Since the late 1990s, the basis of precision medicine has been to develop targeted therapies to inhibit specific molecular pathways involved in tumor growth and dissemination of cancer cells [2].

Cancer, as we know it, is a heterogeneous and progressive genetic disease caused by genetic instability. Genetic instability is an inherent and normal process that transforms a normal cell into a cancer cell. Normal DNA replication, cell division, and repair are not infallible and are influenced by a variety of inherited and environmental factors. Ultimately, cancer growth and progression is the end result of a wide variety of genetic changes that accumulate in the cancer cells over time. Mutations may happen anywhere in genomic DNA of cancer cells; however, only a subset of mutations found within the genomic landscape of cancer is likely to provide a fitness advantage to the cell. These mutations that provide a growth advantage to cancer cells are called driver mutations. The detection of specific gene driver mutations in certain cancers that either stimulate or interrupt important growthregulatory gene pathways has led to a series of studies aimed at identifying treatments against these genetic changes and the discovery of targeted therapies. However, the fact that targeted treatment is most successful in a subset of tumors indicates the need for better classification of clinically related molecular tumor phenotypes based on improved understanding of the mutations in relevant genes, especially in those oncogenic driver mutations.

There are two fundamental aspects that we need to consider when we think about targeted anticancer treatments. The first is that targeted therapy, as well as also conventional chemo- and radiation-therapy, are all known to cause additional accumulation of genetic changes in cancer cells due to their genomic instability. The second is that, intrinsically genetic instability and the accumulation of additional mutations in cancer cells is a way that cancer cells use to adapt to and survive in a hostile environment such as the one created by these treatment modalities. Collectively, all these post therapy-induced additional genetic changes, may happen in a gene or in a group of genes that are located upstream or downstream to the “driver” mutated gene in a gene pathway, thus causing the targeted treatment to be unfortunately unsuccessful.

Besides the introduction of targeted therapies for cancer, traditional chemotherapy has been largely established on cytotoxic drugs that destroy rapidly dividing cells which are chosen empirically by the treating physicians, and this approach has been used for the past eight decades. Several studies have been performed to develop diagnostic tools to predict effectiveness of chemotherapy [4]. Chemo-Sensitivity and Resistance Assays (CSRA), which measure cell death or lack of cell death by drug-induced apoptosis, are one of such diagnostic tools. Several studies on CSRA focused on ovarian cancer [5-7], gastric cancer [8], colorectal adenocarcinoma [9], breast cancer [10, 11], non-

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small cell lung cancer [12] and small-cell lung cancer [12, 13], have followed similar protocols with minor variations in their assay setup. All of these assays, which have been developed in the past 20-30 years, used cultures of bulk tumor cells to determine cytotoxicity and to predict anticancer response. A major breakthrough in the 1990s in the understanding of cancer initiation and progression has been the discovery of a cellular subpopulation with stem cell-like features, commonly referred to as cancer stem cells (CSCs), which is critical for tumorigenesis, treatment resistance and cancer recurrence [14, 15]. CSCs share many properties with normal adult stem cells, have been shown to propagate the parental tumor in animal models, and to be the cause of metastasis [14-17]. Importantly, cancer lethality is mainly due to the onset of distant metastases and their resistance to chemotherapy. Several evidences demonstrated that CSCs are widely protected against commonly used chemotherapeutic agents by means of different mechanisms, including increased expression of ATP-binding cassette drug transporters, augmented ability in DNA damage repair, and activation of PI3K/AKT and Wnt pathways [18]. Because of the presence of therapy resistant CSCs, each time patients are treated they always have a chance to relapse, and their cancer will likely become more resistant to therapy [19].

Of note is that selection of effective chemotherapy is extremely important not only when therapy is first initiated, but for recurrent disease as well. In fact, administration of ineffective anticancer therapy is often associated with unnecessary toxicity and the development of more aggressive cancer cell clones that are resistant to subsequent therapies [20].

Unfortunately, research on CSCs has failed thus far to discover universally clear and informative biomarkers, mutations, or gene-expression patterns [21]. Recently, a new drug response assay has been developed, which is called ChemoID that tests separately CSCs and bulk of tumor cells. This test has been used effectively to predict the most active chemotherapy agents' combination to treat individual cancers [22-27]. Targeting CSCs along with the bulk of other cancer cells is a new paradigm in cancer treatment, which is fulfilling the Precision Medicine Initiative that was launched by President Barack Obama in 2015. The ChemoID® drug response assay in a recent prospective study of 41 glioblastoma patients, showed a statistically significant improved response rate (2.2-fold increase) in patients who were given assay-indicated chemotherapy [28] demonstrating that the ability to personalize therapy by providing the treating physician with drug response information on a panel of standard-of-care first and second choice drugs should aid in the selection of most effective chemotherapy for individual patients, thus resulting in improved clinical outcomes. A drug response assay like ChemoID® that targets CSCs may become a very useful tool for optimizing treatment selection especially when first-line therapy fails, and when there are multiple clinically -acceptable and -equivalent treatments available.

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