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Mini Review

Personalized medicine in hematology — A landmark from bench to bed

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ABSTRACT

Personalized medicine is the cornerstone of medical practice. It tailors treatments for specific conditions of an affected individual. The borders of personalized medicine are defined by limitations in technology and our understanding of biology, physiology and pathology of various conditions. Current advances in technology have provided physicians with the tools to investigate the molecular makeup of the disease. Translating these molecular make-ups to actionable targets has led to the development of small molecular inhibitors. Also, detailed understanding of genetic makeup has allowed us to develop prognostic markers, better known as companion diagnostics. Current attempts in the development of drug delivery systems offer the opportunity of delivering specific inhibitors to affected cells in an attempt to reduce the unwanted side effects of drugs.

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1. Introduction

Personalized medicine attempts to identify individual tailored treatments based on the susceptibility profile of each individual. Precision medicine utilizes both conventional medicine and cutting edge technology to concur the disease proven to be resistant to conventional medical techniques. The borders of personalized medicine are defined by limitations in technology and our understanding of biology, and pathology of various conditions. Current advances in technology have enabled us to uncover the molecular makeup of diseases and translating these findings to actionable targets has led to the development of small molecular inhibitors. Monitoring disease outcome utilizing companion diagnostics has also assisted physicians in routine patient care. To date serious efforts are directed in increasing the efficacy of drug delivery to reduce the undesired side effects of medications (Fig. 1). Despite the current advances there are fundamental limitations on implementing personalized medicine into daily practice. Here we lay out the steps from bench to bedside for personalized therapeutics in hematology and explore the complex problems at each steps. We will first discuss the discovery platforms, and compare the existing technologies. Major discoveries utilizing these platforms will be discussed followed by summarizing the targeted inhibitors developed which are currently in clinical practice. Next we will briefly discuss the advantages of small molecular inhibitors over existing chemotherapeutic regimens and explore conditions that affect the drug

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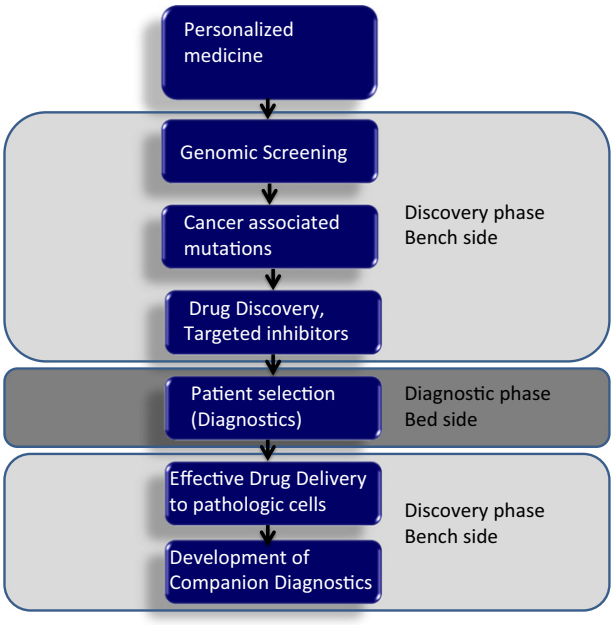

Fig. 1. Implementation of personalized medicine requires combining discovery platforms and clinical practice. Early stage of discovery requires interrogation of large numbers of samples to uncover the somatic genomic alterations of tumor cells. Further studies on genomic mutations are conducted to demonstrate that the aberrations are driver mutations and therefore actionable. Small molecular inhibitors are developed to target proteins intercepting these alterations. Patients are screened in clinics to ensure that they carry the desired mutation targeted by small molecular inhibitors. Intermediate end-point biomarkers are identified and studied in the audit trail as early predictors of anti-tumor activity.

response to these inhibitors (pharmacogenomics and pharmacovigilance). Finally we will discuss the drug delivery systems that could potentially enhance the outcome and limit the undesired effects of these medications.

Advances in human genetics have clearly demonstrated the contribution of specific genes to certain malignancies [1–3]. Such genomic alterations are functionally manifested as dysfunctional proteins leading to aberrant signal transduction [4–7]. Consequently, discovering genomic alterations underlying various conditions is a fundamental step in implementing precision medicine. Selecting an appropriate screening technology is crucial for both discovery and diagnostics. In the era of genomic innovation, several platforms are available [8–11]. Mass spectrometric genotyping, allele-specific PCR-based technologies, hybrid-capture massively parallel sequencing technologies, and whole-genome sequencing are among the available platforms [12,13]. For discovery purposes, sequencing of the entire genome would be the preferred option, but, for diagnostic purposes, one must presently focus on cost-effective platforms that cover actionable cancer-associated mutations (MassArrays) [14] (Fig. 2).

Though personalized medicine appears to bring us ever closer to a step away from the cure for cancer, the reality is far more complicated. Despite current advances in genomics, there is still a long path to decoding all cancer-associated mutations, let alone the signaling pathway of new and novel mutations which would be an additional area to explore [15]. In both hematologic and solid tumors, a large fraction of affected proteins is represented by kinases, which are essential for physiological functions of cells, such as cellular growth and development [16–18]. Blocking these molecules usually drives the cells into developing compensatory mechanisms, and cancer cells eventually escape the inhibition, developing tumor resistance [19,20]. Another obvious challenge is excessive toxicity by nonselective inhibition of both mutant and wild-type proteins by some inhibitors [21–24]. Additional factors can affect efficacy of treatment. In particular, some genetic variations can alter the drug response of individuals, and this should be taken into consideration with drug dosing [25,26]. Therefore it is crucial to develop companion diagnostics by combining genomic information with proteomics as well as personal medical history and family history data to tailor the desired agent for targeting the neoplastic cells [26–29]. Consequently, it is essential to develop prognostic biomarkers to both screen the outcome of the treatment and screen for residual disease [30–33].

Another limited challenge in personalizing cancer therapy is the limited technologies in drug delivery [34]. It is essential to deliver the appropriate inhibitors to the affected cells; however, advancement in the development of nanoparticles that can achieve selective cellular

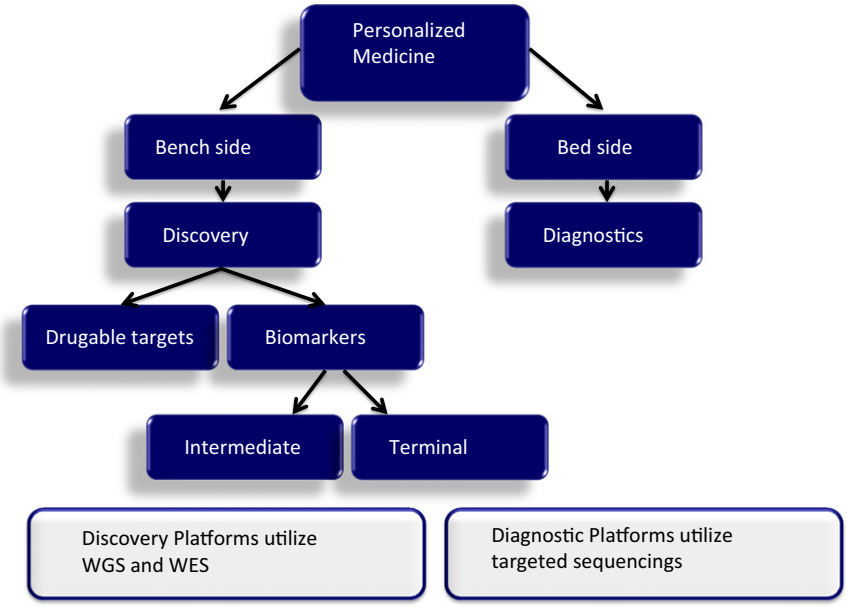

Fig. 2. Steps from bench to bedside for personalized medicine: Discovery of drugable targets lay out the path for development of targeted inhibitors. Usually more comprehensive platforms, such as whole genome sequencing (WGS) and whole exome sequencing (WES) are used at this step. It is well established today that the sole presence of a target in tumor cells does not guarantee the drug response. To determine the best group of patients who would benefit from targeted inhibitors, both intermediate and terminal genomic biomarkers are in need. Again, comprehensive platforms (WGS and WES) are used for discovery purpose. Patient selection for targeted inhibitors (diagnostics) could be run using less expensive techniques, i.e. targeted sequencing.