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Review

# Pharmacogenomics and targeted therapy of cancer: Focusing on non-small cell lung cancer

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ABSTRACT

Recent studies have been established high degree of genetic diversity in solid organ tumors among individuals and even between individual tumor cells. This intratumor and intertumor genetic diversity results in a heterogeneous tumor with unique characteristics which potentially allows effective drug therapy. The goal of pharmacogenomics is to elucidate the genetic network(s) that underlie drug efficacy and drug resistance. Advances in targeted and personalized therapy play an increasingly important role in many common cancers, notably lung cancer, due to the high incidence, prevalence, mortality and the greater tendency towards drug resistance seen in these patients. Non-small cell lung cancer (NSCLC) is characterized by mutations in the epidermal growth factor receptor (EGFR) and or downstream kinase pathways. This has led to the development of highly selective monoclonal antibodies and EGFR tyrosine kinase inhibitors (EGFR-TKIs) to prevent cancer initiation, proliferation, differentiation, angiogenesis, survival, and invasion. However, resistance to many of these new treatments is induced and further pharmacogenomic analysis has revealed mutations associated with increased or reduced drug efficacy. Combinations of kinase inhibitors or potentially the targeting of cancer stem cells may further increase the success of pharmacogenomics in treating patients with lung cancer.



**Contents**



*Abbreviations:* ALDH, aldehyde dehydrogenase; ALK, anaplastic lymphoma kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; CSC, cancer stem cell; EGFR, epidermal growth factor receptor; EGFR-TKIs, EGFR tyrosine kinase inhibitors; EGFRvIII, EGFR variant III; EML4, echinoderm microtubule-associated protein-like 4; FISH, fluorescence in situ hybridization; FDA, America Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; HGFR, hepatocyte growth factor receptor; IACR, International Agency for Research on Cancer; IHC, immunohistochemistry; JAK/STAT, janus kinase/signal transducer and activator of transcription; K-RAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LOH, loss of heterozygosity; MAPKs, mitogen-activated protein kinases; NSCLC, non-small cell lung cancer; NTRK1, neurotrophic tyrosine kinase receptor type 1; PI3K/AKT, phosphatidylinositide 3-kinases/protein kinase B; RET, rearranged during transfection; ROS1, c-ros oncogene 1; RTK, receptor tyrosine kinase; RT-PCR, reverse transcription polymerase chain reaction; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SNPs, single nucleotide polymorphisms; VEGF, vascular endothelial growth factor

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## 1. Introduction

The term of *genetic* was first used by William Bateson in 1900 to describe his studies of human Mendelian inheritance (Charlab and Zhang, 2013; Meyer, 2004). Two years later, Archibald Grove and colleagues observed that diseases such as Pentosuria and Alkaptonuria were inherited in an autosomal recessive manner and introduced the concept of *chemical individuality* for the first time (Charlab and Zhang, 2013; Meyer, 2004). Nevertheless, the beginning of pharmacogenetics is attributed to Laurence Snyder's study on "Inheritance of phenylthiocarbamide taste recognition" (Meyer, 2004). He indicated that only some people were able to taste *phenylthiocarbamide* and that this ability was inherited in an autosomal recessive manner (Meyer, 2004). As such, Snyder demonstrated the relationship between inheritance and the response to an intervention.

The clinical importance of inheritance and the response to treatment was demonstrated in the 1950s with the appreciation of the relationship between a glucose-6-phosphate dehydrogenase (G6PD) defect and the occurrence of hemolysis during treatment with primaquine (an antimalarial drug) (Carson et al., 1956; Clayman et al., 1952; Meyer and Zanger, 1997). Simultaneously, a link between the response to isoniazid (an anti-tuberculosis drug) and an autosomal recessive defect in enzymatic acetylation was established (Blum et al., 1991; Evans et al., 1960; Hughes et al., 1954; Vatsis et al., 1991). Also, at this time, genetic defects in other drug metabolizing enzymes were realized as being important in the cause of death in affected individuals (Meyer, 2000, 2004; Wood et al., 2003). Friedrich Vogel and colleagues applied the term "pharmacogenetics" to such studies. The term "Pharmacogenomics" was introduced in 1989 to encompass the involvement of complex genetic networks behind drug resistance, efficacy, and side effects (Charlab and Zhang, 2013; Meyer, 2004; Nebert et al., 2008; Wang et al., 2011; Weinshilboum and Wang, 2006; Whirl-Carrillo et al., 2012).

In has become clear that cancers, particularly solid organ tumors, have a high degree of genetic diversity (Balmain et al., 2003; Morin et al., 2008). Indeed, solid tumors may have up to 100 mutated genes which vary between individual cells within the tumor and as a result it is often unclear what the driver mutations are. The realization that many driver mutations are linked to a smaller number of pathways which are critical for oncogenesis has highlighted the need for tumor analysis at the molecular level. This approach has increased our understanding of the basis for NSCLC pharmacogenomics.

Targeted therapy is a powerful strategy for cancer treatment and overcome drug resistance (Gerber, 2008). The accumulation of knowledge about the differences between normal and cancer cells and differences among cancer cells has allowed for the development of new anticancer agents which target key molecules involved in cancer initiation, proliferation, differentiation, angiogenesis, survival, and invasion. (Gerber, 2008; Hanahan and Weinberg, 2011; Luo et al., 2009). In this review we summarized the history of pharmacogenomics and its potential in personalized medicine. We also discuss the place of pharmacogenomics in cancer-targeted therapy with a focus on NSCLC.

## 2. Pharmacogenomics and cancer therapy

Cancer progression is related to the combined effects of functional changes in cell membrane receptors and intracellular signaling pathways which modulate cell proliferation, apoptosis, motility, adhesion, and angiogenesis (Hanahan and Weinberg, 2011). Human cancer genome sequencing has detected a series of genetic changes that occur in different cancers. Single nucleotide polymorphisms (SNPs), haplotypes, microsatellites, insertion or deletion of nucleotides (Ins/Del), copy number variations, aneuploidy, and loss of heterozygosity (LOH) are the most common genetic changes reported to be associated with uncontrolled growth and metastasis (Pleasance et al., 2010; Savonarola et al., 2012; Stratton et al., 2009). In addition, the resistance of cancer cells to various drugs has been associated with a number of processes including the increased expression of cell membrane transporter proteins, changes in the activity of cellular proteins involved in detoxification, DNA repairing, apoptosis and activation of oncogenes/inactivation of tumor suppressor proteins (Luo et al., 2009).

The high prevalence of drug resistance in NSCLC, especially in advanced stages of disease, has driven the increase in the number of pharmacogenomics studies (Gadgeel et al., 2010; Pao et al., 2005a; Stewart et al., 2004; Tsuruo, 2003). Indeed, the American Food and Drug Administration (FDA) strongly recommends pharmacogenomics testing before the prescription of several anticancer agents in order to avoid, or at least minimize, possible life-threatening side effects and to reduce the costs of ineffective treatment (Coleman, 2014; Meyer, 2000).

## 3. Non-small cell lung cancer

Lung cancer is the leading cause of cancer-related death worldwide (Jemal et al., 2011; McErlean and Ginsberg, 2011). The International Agency for Research on Cancer (IACR) has estimated that the number of deaths due to lung cancer will increase to ten million deaths per year by 2030 (Minna and Schiller, 2008). The main risk factor for lung cancer is smoking and 75–90% of patients have a history of smoking (McErlean and Ginsberg, 2011). The term lung cancer usually refers to tumors that originate from the lining cells of the respiratory tract (epithelial cells) (Minna and Schiller, 2008). Based on differences in biological characteristics, lung cancer is classified into two types, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of lung cancer cases (Minna and Schiller, 2008; Reck et al., 2013). Platinum-based chemotherapy is prescribed as the standard first-line therapy in patients with advanced NSCLC (Minna and Schiller, 2008). However, resistance to platinum-based drugs reduces the survival rate which, as a