

## Protein Kinase Inhibitors for Clinical Targeted Cancer Treatment

Xiao-Wu Chen<sup>1</sup>, Jiazhi Sun<sup>2</sup> and Shu-Feng Zhou<sup>2\*</sup>

<sup>1</sup>Department of General Surgery, Shunde First People's Hospital, Southern Medical University, Foshan, Guangdong, China

<sup>2</sup>Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida, Florida, USA

Protein kinases are defined by their ability to catalyse the transfer of the terminal phosphate of ATP to substrates that usually contain a serine, threonine or tyrosine residue. They typically share a conserved arrangement of secondary structure elements that are arranged into 12 sub domains that fold into a bi-lobed catalytic core structure with ATP binding in a deep cleft located between the lobes. ATP binds in the cleft with the adenine ring forming hydrogen bonds with the kinase 'hinge' - the segment that connects the amino- and carboxy-terminal kinase domains. The highly conserved DFG-motif position in A-loop along with catalytic Lys from  $\beta_3$  strand usually determines kinase activity. Deregulation of protein kinase activities, particularly dominant kinase mutations (such as BRAF V600E in A-loop, and JAK2 V617F in the auto-inhibitory pseudokinase domain), may result in a number of conditions such as cancer, inflammatory or infectious diseases, diabetes, degenerative nerve diseases, and cardiovascular disorders. There are 518 protein kinases and about 20 lipid-modifying kinases encoded by the human genome [1,2], and a much larger proportion of additional kinases are present in parasite, bacterial, fungal, and viral genomes that are susceptible to exploitation as drug targets. Cancer is global leading causes of death which is responsible for about 25% of all deaths and features with 0.5% annual diagnostic rate. The National Institutes of Health (NIH) estimates that the overall costs of cancer in 2007 were \$226.8 billion.

Currently, approximately one third of all protein targets under investigation in the pharmaceutical industry are very attractive protein tyrosine kinases (90 total in human kinome) or serine/threonine kinases [3,4]. The former tyrosine kinases have major oncogenic essential for tumor transformation, metabolism and metastasis, which is so-called oncogene addiction to render the cancer cell exceptionally susceptible to the kinase inhibitors [5]. When inhibition of the second class of protein serine/threonine kinases (such as MEK1/2 in MAP kinase pathway, mTOR in PI3K pathway and CDKs in cell cycle regulation) usually it results in a synthetic lethal phenotype [5]. The kinase inhibitors (KIs) are representing the best characterized targeted treatment to date. Most KIs discovered are ATP competitive analogues with A-loop in "DFG-out" configuration to share a similar pharmacophore and present one to three hydrogen bonds to the amino acids located in the hinge region of the target kinase, thereby mimicking the hydrogen bonds that are normally formed by the adenine ring of ATP [6]. So far at least 18 small molecule kinase inhibitors including axitinib, bosutinib, cabozantinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ponatinib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib, and vemurafenib have been approved by the FDA for cancer treatment and about 150 KIs such as danusertib, lestauritinib, bafetinib and selumetinib are under Phase I and Phase II clinical evaluations [3]. A much larger number of KIs are in stages of preclinical development. Among those KIs, tyrosine kinase inhibitors (TKIs) are most dominant against cancer, following by serine/threonine kinase inhibitors such as BRAF, MEK1/2, PI3K, mTOR, Aurora Kinase, JAKs/STATs, CDKs with much broad clinical applications. Recently discovery of first ever MET/ALK inhibitor, crizotinib, with anaplastic lymphoma kinase (ALK) and feasibility genetic pre-screen NSCLC leads a "crizotinib-personalized medicine

in NSCLC legend" with much higher response rate by targeting specific 5% ALK mutated NSCLC patients, which shines TKI-based targeted therapy.

The major challenge of those KIs in drug development and clinical setting are drug resistant and toxicity. They are usually closely associated with their pharmacokinetics and pharmacodynamics profiles. Almost all FDA registered KIs (except saracatinib, a dual-specific inhibitor of Src and Abl), are directed toward the ATP-site and show different selectivity towards kinase targets, potencies, and pharmacokinetic properties [7,8]. Those KIs are all orally active and share certain pharmacokinetic features, including great extent of tissue distribution with large apparent volume of distribution and long terminal half-lives, high degree of protein binding, cytochrome P450 (CYP)-dependent metabolism, and interaction with the ATP binding-cassette transporters, which render this class of drugs prone to drug-drug interactions [8,9]. In particular, some KIs have been shown to remarkably inhibit human CYP3A4 and other CYPs and drug transporters (all TKIs appear to be transported by the efflux ATP binding-cassette transports B1 and G2), raising the potential of KI-drug interactions. Furthermore, the active metabolites of imatinib and sunitinib contribute to their antitumour activity which reflects the important CYPs in TKIs metabolism. However, KIs toxicity, especially cardiovascular side effects are likely due to dysregulation of multiple kinase regulated pathways (mainly EGFR, JAK/STAT and PI3K/Akt/mTOR pathways in cardiomyocytes). The serious cardiovascular effects of TKIs include left ventricular dysfunction/heart failure, systemic and pulmonary hypertension, thromboembolism and arrhythmia, which results in unsolved prolonged clinical issues and the need for a translational cardio-oncological approach.

### References

1. Johnson SA, Hunter T (2005) Kinomics: methods for deciphering the kinome. *Nat Methods* 2: 17-25.
2. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S (2002) The protein kinase complement of the human genome. *Science* 298: 1912-1934.
3. Fabbro D, Cowan-Jacob SW, Mobitz H, Martiny-Baron G (2012) Targeting cancer with small-molecular-weight kinase inhibitors. *Methods Mol Biol* 795: 1-34.
4. Cohen P (2002) Protein kinases--the major drug targets of the twenty-first century? *Nat Rev Drug Discov* 1: 309-315.

**\*Corresponding author:** Shu-Feng Zhou, MD, PhD, Associate Vice President for Global Medical Development, Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida, 12901 Bruce B Downs Blvd., Tampa, FL 33612, USA, Tel: 813 974-6276; Fax: 813 905-9885; E-mail: [szhou@health.usf.edu](mailto:szhou@health.usf.edu)

Received March 02, 2013; Accepted March 05, 2013; Published March 11, 2013

**Citation:** Chen XW, Sun J, Zhou SF (2013) Protein Kinase Inhibitors for Clinical Targeted Cancer Treatment. *Clinic Pharmacol Biopharmaceut* 2: e112. doi:10.4172/2167-065X.1000e112

**Copyright:** © 2013 Chen XW, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

5. Weinstein IB, Joe AK (2006) Mechanisms of disease: Oncogene addiction--a rationale for molecular targeting in cancer therapy. *Nat Clin Pract Oncol* 3: 448-457.
6. Zhang J, Yang PL, Gray NS (2009) Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer* 9: 28-39.
7. Fabian MA, Biggs WH 3rd, Treiber DK, Atteridge CE, Azimioara MD, et al. (2005) A small molecule-kinase interaction map for clinical kinase inhibitors. *Nat Biotechnol* 23: 329-336.
8. Di Gion P, Kanefendt F, Lindauer A, Scheffler M, Doroshenko O, et al. (2011) Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on pyrimidines, pyridines and pyrroles. *Clin Pharmacokinet* 50: 551-603.
9. van Erp NP, Gelderblom H, Guchelaar HJ (2009) Clinical pharmacokinetics of tyrosine kinase inhibitors. *Cancer Treat Rev* 35: 692-706.