

Institut Pasteur's Euroconference on Protein Kinase Inhibitors

Paris, France, October 12-13, 2006

Tomi K. Sawyer, Ph.D.

Senior Director and Head, Chemical Sciences
Pfizer Research Technology Center
620 Memorial Drive
Cambridge, Massachusetts, 02139 U.S.A.

TITLE OF PRESENTATION:

“Structural and mechanistic properties of oncogenic protein kinases that manifest resistance: Chemical biology and drug design”

FULL ABSTRACT OF MY PRESENTATION:

Oncogenic protein kinases are key therapeutic targets for drug discovery. X-ray crystallographic, biochemical and cellular studies have revealed both structural and mechanistic properties of several oncogenic protein kinases. A case example is Src kinase, and its roles in cancer biology from the perspective of its structural and mechanistic properties. Src kinase activity is controlled, in part, by protein-protein interactions and C-terminal regulatory tail mutation or truncation. Approaches to advance Src kinase inhibitors illustrate an extraordinary wide scope of molecular diversity and drug design. Examples of ATP-competitive inhibitors, peptide substrate inhibitors, and SH2 inhibitors will be highlighted. Noteworthy, an emerging number of dual Src/Abl kinase inhibitors have been advanced, including the most recent FDA-approval for BMS-354825 (Dasatinib, SprycelTM).

In an increasing number of cases, resistance to inhibition has shown to involve critical amino acid mutations in the ATP or proximate binding sites for small-molecule inhibitors. These challenges are being addressed by both chemical biology and drug design strategies. A case example is T315I mutation of Bcr-Abl kinase. In retrospect, the significant breakthrough of STI-571 (Imatinib, GlivecTM/GleevecTM) for the treatment of chronic myelogenous leukemia and other cancers has provided tremendous insight into the field of protein kinase inhibitor drug discovery. Unfortunately, for many patients the issue of Imatinib-resistance has provided impetus for the development of second-generation Bcr-Abl kinase inhibitors capable of overcoming known Bcr-Abl mutations underlying Imatinib resistance (e.g., T315I mutation). Examples of such mutant Bcr-Abl kinase inhibitors will be highlighted. From a structural and mechanistic property standpoint, such mutant Bcr-Abl kinase inhibitors illustrate both so-called DFG-in and DFG-out classes of small-molecule kinase inhibitors. Also noteworthy, alternative strategies in signal transduction pathways blockade may be promising to address resistance to such mutant Bcr-Abl kinases.