

## **Kinases as therapeutics targets: Control of selectivity in drug design**

*Laurent Schio<sup>1</sup>, Cécile Combeau<sup>2</sup>, Anke Steinmetz<sup>3</sup>, Nicolas Baurin<sup>3</sup>*

*<sup>1</sup>sanofi-aventis, Oncology Medicinal Chemistry, 94400 Vitry-sur-Seine – France*

*<sup>2</sup>sanofi-aventis, Oncology Molecular Exploratory Research, 94400 Vitry-sur-Seine – France*

*<sup>3</sup>sanofi-aventis, In Silico Sciences, 94400 Vitry-sur-Seine – France*

The current decade has been the advent of kinase inhibitors as therapeutics drugs for the treatment of cancer. Recently, Sutent<sup>®</sup> (sunitinib) in gastrointestinal stromal tumors (GIST) and Sprycel<sup>™</sup> (dasatinib) in chronic myeloid leukemia (CML), have followed the breach opened by Gleevec<sup>®</sup> (imatinib) launched in 2001 for the treatment of patients with Philadelphia chromosome-positive (Ph+) CML and in 2002 for the treatment of patients with Kit-positive unresectable and/or metastatic malignant GIST. Overall, a dozen of anticancer kinase inhibitors have received FDA approval during the last five years and the market for this class of drugs is expected to reach \$58.6 billions in 2010.

The development of the targeted therapy concept in Oncology as well as the clinical demand for much better tolerated treatments have conducted research programs in pharmaceutical companies towards the discovery of selective kinase inhibitors. On the other hand, the search for potent enough inhibitors in pharmacological models as well as the economical benefit for multi-indication drugs has led pharmaceuticals companies to develop tools and strategies to control and modulate kinase selectivity of inhibitors in drug discovery programs. We will review some of the tools and approaches that are used in our group for selectivity monitoring and fine-tuning in the kinase target field. Light will be shed on innovative chemo-informatics predictions, 3D-structure based visualizations and fingerprint analysis which open new areas for efficient rational drug discovery.