



EUROPEAN  
COMMISSION

Community research

# EuroNanoForum 2005 Nanotechnology and the Health of the EU Citizen in 2020

European and International Forum on Nanotechnology  
Edinburgh (Scotland), 5-9 September 2005  
Edinburgh International Conference Centre

# CATALOGUE *of* POSTERS

CATALOGUE OF POSTERS



NANOTECHNOLOGIES AND NANOSCIENCES,  
KNOWLEDGE-BASED MULTIFUNCTIONAL MATERIALS,  
AND NEW PRODUCTION PROCESSES AND DEVICES



### 3.8 Fighting Cancer at the Nanoscale: Computational Structural Biology and the Bcr-Abl/Imatinib Paradigm

Marco Ferrone<sup>1</sup>, Maria Silvia Paneni<sup>1</sup>, Paolo Cosoli<sup>1</sup>, Maurizio Fermeaglia<sup>1</sup>, Elena Tamborini<sup>2</sup>, Marco A. Pierotti<sup>3</sup>, Silvana Pilotti<sup>2</sup>, Sabrina Pricl<sup>1</sup>

<sup>1</sup>Molecular Simulation Engineering (MOSE) Laboratory, Department of Chemical Engineering, University of Trieste, Trieste

<sup>2</sup>Experimental Molecular Pathology, Department of Pathology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Italy

<sup>3</sup>Department of Experimental Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

Chronic myeloid leukemia (CML) is a clonal disease involving the pluripotent hematopoietic stem cell compartment, and is associated with the Philadelphia chromosome, a reciprocal translocation between chromosome 9 and 22. This translocation links the c-Abl tyrosine kinase oncogene on chromosome 9 to the 5' half of the BCR gene on chromosome 22, and originates the fusion gene BCR-ABL. The fusion gene produces a chimeric 8.5-kb transcript that codes for the p210BCR-ABL protein, which possesses constitutive tyrosine kinase activity and is the pathogenic agent of CML.

From the therapeutic perspective, as CML arises from a single genetic lesion, a research goal has been to develop kinase specific inhibitors. The development of Imatinib is a landmark achievement in this respect, as it has shown great promise in the chronic phase, and some expectations in the accelerated and blastic phase of CML, as well as in BCR-ABL-expressing acute lymphoblastic leukemias. Unfortunately, however, most responding blast phase patients relapse despite continued chemotherapy, and resistance to imatinib has been reported in both Bcr-Abl expressing cell-lines and in patients with CML.

Several Bcr-Abl kinase domain (KD) mutations have been shown to decrease the sensitivity of the Abl kinase to Imatinib, thus accounting for resistance to this inhibitor. Here we present the results obtained from a detailed computational structural biology study of the wild type and several mutant Abl KDs, aimed at offering a comprehensive picture of the molecular mechanism of failure of the tyrosine kinase inhibitor binding to the mutated protein.

Coupling the observations from the molecular dynamics trajectories to the relevant energetic data, obtained in the framework of the MM/PBSA methodology, led to the conclusion that all analyzed mutations can be classified into two major groups:

- Group A, that is mutations that play a major role in imatinib binding;
- Group B, or mutations that play a modest role in imatinib binding.

Mutations belonging to group A greatly decreases sensitivity of Abl toward Imatinib, and can be claimed to be the cause of resistance when identified in patients. Mutations found in group B can be further subdivided into two categories. The former includes those mutations for which the relevance in causing the resistant phenotype is questionable, and for which a dose escalation of the inhibitor would be expected to recapture a response. The latter category groups all those mutations which will indeed be unresponsive to dose escalation, as no significant interaction is involved with the inhibitor. For these substitutions, we propose that they confer drug resistance through alternative mechanisms as, for instance, by interfering in the intramolecular regulation of c-Abl by the SRC Homology Domains 3 (SH3) and 2 (SH2) via a structural alteration of the contact point environment.

Having tested a number of Abl-kinase domain mutations, differing by position and affinity towards the inhibitor, and verified the correspondence between experimental and computational evidences, we claim that this technique can be adopted as a routine analysis, and flanked to all other techniques already employed in cancer research to define a better therapeutic strategy.