

# Computational Chemistry and Chemoinformatics Section



Julen Oyarzabal

Section Head (until August)

Julen Oyarzabal, born in Bilbao (Spain) in 1970, began his scientific career at the Pharmaceutical and Organic Chemistry Department, School of Pharmacy, the *Universidad del País Vasco*, Spain, where he carried out his PhD studies focusing on the synthesis of aminophosphonates and aminofluorinated compounds. For his PhD work he received the Extraordinary Award from the *Universidad del País Vasco*.

After finishing his PhD in 1998, he moved to the Pharmaceutical Chemistry department at the University of California San Francisco (UCSF, USA) where he spent one year working on the design, synthesis and biological evaluation of compounds to study the substrate specificity of *M. tuberculosis* alkylhydroperoxidases. He then received a Marie Curie individual Postdoctoral Fellowship and joined the Chemistry department at the University of Southampton (UK), where he worked in computational chemistry to develop free energy based methods of scoring docked complexes and lead optimisation.

In November 2001, Julen joined Johnson and Johnson Pharmaceutical R&D in Toledo (Spain) where he was responsible for setting up the Molecular Design and Chemoinformatics Unit. During this period, he led several projects in molecular informatics in the CNS therapeutic area. His work involved initial phases in the drug discovery process to late lead optimisation. He was promoted to Senior Scientist in 2004.

He left Johnson and Johnson Pharmaceutical R&D in October 2006 to join the CNIO's Experimental Therapeutics Programme. He is co-inventor of 11 published patents.

## Summary

The Computational Chemistry and Chemoinformatics Section is involved in nearly every aspect of the drug discovery process as part of an integrated team with medicinal chemists and biologists.

Our Section assumes several roles in the drug discovery process, from the earliest phases (including target ID, library enrichment, HTS/HCS hit analyses and assessment, *de novo* design) to late lead multifactorial optimisation (primary activity, off-target selectivity, ADME), as well as more general processes such as compound logistics, chemical and biological data management and integration.

## Main Objectives

To speed up the drug discovery process from two perspectives:

*Drug discovery information platform:*

- Centralising all the information, from logistics to knowledge including data management, decision-making and project management tools
- Chemoinformatic tools for patents intelligence

*Computational medicinal chemistry:*

- Identify and design new chemical space, providing Intellectual Property (IP): i) within the biological space defined by our therapeutic area, including known and potential new targets, ii) around proprietary chemical series
- Multifactorial optimisations overcoming ADME and selectivity issues

## Highlights

During 2010 our Section focused on two key areas in drug discovery informatics:

### Refinement of drug discovery information platform

Continuation of the work completed in 2009: a platform centralising discovery informatics for planning, linking and analysing heterogeneous data sources was completed and is fully operative. Thus, the common chemical and biological repository (CCBR) constitutes the central core for all the information generated in our drug discovery process. All the implemented visualisation tools for strategic decisions operate on data retrieved from the CCBR. This knowledge base is built on a federation of operational LIMS systems that point to the CCBR (Figure) when quality control criteria are fulfilled; automatic data curation processes have also been enforced. Finally, to provide an efficient executive workflow, project management tools (e.g. assay planning and request) are implemented within the same web interface including decision-making tools.

In addition, a set of chemoinformatic tools for patent intelligence has been implemented to extract and articulate the most value of information deposited in patents from chemical and biological perspectives.



**Figure:** Four key domains support and feed our discovery platform, the CCBR: a) chemistry, including *in silico* profiling – phys-chem properties and chemogenomics; b) logistics; c) *in vitro*, considering biochemical, cellular and ADME data; together with d) *in vivo* pharmacology. Currently, CCBR contains more than 43,000 unique structures and 350 different biological assays.



Staff scientists: M. Obdulia Rabal and Manuel Urbano.

### Computational medicinal chemistry

Projects:

- Participate collectively with the Medicinal Chemistry Department in the selection of compounds for High Throughput Screening of CDK8, including the follow-up of preliminary results obtained from searching initial hits for analogues based on parameters of similarity.
- Collaborate with the Medicinal Chemistry Department in the selection of compounds already prepared for the PI3K project as potential inhibitors of ATR kinase. The exploration of initial hits led to the identification of potent and selective ATR inhibitors.

## Publications

Rabal O, Link W, G Serelde B, Bischoff JR, Oyarzabal J (2010). An integrated one-step system to extract, analyze and annotate all relevant information from image-based cell screening of chemical libraries. *Molecular Biosystems* 6, 711-720.

Oyarzabal J, Zarich N, Albarran MI, Palacios I, Urbano-Cuadrado M, Mateos G, Reymundo I, Rabal O, Salgado A, Corrionero A, Fominaya J, Pastor J, Bischoff JR (2010). Discovery of mitogen-activated protein kinase-interacting kinase 1 inhibitors by a comprehensive fragment-oriented virtual screening approach. *J Med Chem* 53, 6618-6628.

## Patent

Pastor Fernandez J, Martínez González S, Oyarzabal Santamaría J (2010). Preparation of imidazopyrazines as PI3-K and/or mTOR kinase inhibitors. PCT Int Appl WO 2010119264 A1 20101021.