SL05 **French/European Academic Compound Library and Screening Initiative: Scientific and Therapeutic Outcomes**

Marcel HIBERT
Laboratoire d'Innovation Thérapeutique, University of Strasbourg

Medicinal chemistry has entered a new era after the deciphering of the human genome. Several thousands of novel proteins have been identified that may represent important targets for drug discovery. The medicinal chemist is now challenged to rationalize and accelerate the discovery of potent and specific ligands acting at these targets to provide biologists with physiopathological research tools and pre-clinical candidates.

We had anticipated this evolution since we decided 13 years ago to develop several convergent medicinal chemistry strategies to produce novel ligands as efficiently as possible in the academic environment. High throughput screening represented clearly a mean to accelerate the discovery of original ligands for target molecules. We have set up in 1999 an open academic screening platform, gathered a collection of molecules and natural extracts produced by generations of scientists in academic laboratories (the Chimiothèque Nationale) and developed several generic assays to address issues such as target deorphanization, allosteric ligand discovery or ultra miniaturization. The Chimiothèque Nationale currently gathers 42 000 molecules and 14 000 extracts of natural substances provided by more than 40 French academic laboratories. It is extremely diverse and drug-like ranking in this respect among the best libraries in the world. In parallel several generic and original assays have been developed. For example, a FRET based assay has been set up and validated as an alternative to scintillation assays allowing the specific detection of ligands binding to target proteins in complex environment, such as G protein coupled receptors. For soluble purified proteins, fluorescence anisotropy has been used to detect ligand binding. For both types of targets, we designed and prepared libraries of fluorescent frequent hitters that can be directly screened to discover the very first ligands of orphan receptors (receptor deorphaning) or molecules binding to allosteric sites of functional relevance on known receptors. As we will illustrate, these original screening methods allowed to overcome important methodological blockades and opened the route to the functional study of classical and orphan targets.

The academic screening strategy proved to be extremely efficient both in terms of scientific and therapeutic output. For instance, we have discovered molecules binding to natural ligands such as chemokines, and not to their receptor, leading to the 'neutraligand' concept. We have also characterized the first 'functional switch', that is an allosteric ligand able to switch the function of a natural neurotransmitter from a signaling pathway to another. More classically, we have discovered novel anti-inflammatory molecules active on Alzheimer disease and currently in Phase 2 in the clinics.

This initiative is currently being extended at the European level via the EU-OPENSCREEN project (Coordinator: Ronald Frank; http://www.eu-openscreen.de/).