

Screening Section



Jim R. Bischoff

Section Head

Jim Bischoff obtained his Ph.D. in Biochemistry and Molecular Biology from the University of California. He then moved to the Cold Spring Harbor Laboratory, Cold Spring Harbor (USA), as a Leukemia Society of America Postdoctoral Fellow in the laboratory of D. Beach.

In 1992 he joined ONYX Pharmaceuticals as a Staff Scientist. His group was the first to demonstrate the potential therapeutic benefit of tumour dependent oncolytic viruses and proposed ONYX-015 for clinical development. In 1996 he moved to SUGEN Inc. as a Senior Group Leader. His work at SUGEN led to the discovery of the oncogene, Aurora A, that provided the first genetic link between the centrosome and human cancer. In 1998 he became Director of Biochemistry.

From 2000-2005 Bischoff was the Director of Pharmacology for the oncology research divisions of Pharmacia, Pfizer, and Aventis. Currently there are four novel therapeutics in clinical development for the treatment of cancer that were developed by Bischoff and his teams. Bischoff joined the CNIO in August 2005.

Summary

The screening process in drug discovery is the systemic evaluation of compounds (natural products and/or synthetic) for binding activity or biological activity against target molecules or pathways. Test compounds can act as inhibitors of target enzymes, as competitors for binding of a natural ligand to its receptor, as agonists or antagonists for receptor-mediated intracellular processes, and so forth. The results of these experiments provide starting points for drug design as well as for understanding the interaction or role of a particular biochemical process in biology.

Main Objectives

- Identify active compounds that target pathways and/or proteins that are genetically altered in human cancer
- Develop innovative methods to chemically interrogate signalling pathways involved in cancer
- Develop robust biochemical and cell-based assays suitable for medium throughput screens
- Enlarge our antiproliferation database to facilitate the determination of the combination index of the CNIO Experimental Therapeutics Programme (ETP) derived therapeutics with current clinical therapies





Technicians: M. Isabel Albarrán, Antonio Cebriá, Genoveva Mateos, Irene Palacios and María I. Reymundo.

Highlights

The High Throughput Screening Section uses automated technologies whenever possible to rapidly identify promising compounds with the desired biochemical and/or cellular activity. In general, compounds with potencies <200 nanomolar against the primary target are also tested in various cellular-based assays to determine if the compounds elicit the expected mechanism of action. Once the mechanism is confirmed the positive compounds are tested for antiproliferative activity against several human tumour cell lines. These data are used by the Programme's medicinal chemists to develop a Structure Activity Relationship (SAR) for our inhibitors. Our assays are performed using an integrated workstation. Our workstation includes a Biomek FX Dual Arm Liquid Handling System with Span-8 Pipettor and Multi-Channel Pipettor linked to a Cytomat Microplate Washer and a Cytomat 2 CO₂ incubator.

This year we continued our work focusing on the identification of compounds that inhibit the catalytic activity of PI3K α , a target frequently mutated in a variety of human cancers, as well as for inhibitors of Pim-1 and Pim-2, two protein kinases that are thought to mediate inappropriate survival signals in several human tumours. New chemical series were identified with IC₅₀'s less than 1 nM. These series of compounds have demonstrated an appropriate mechanism of action as well as potent anti-proliferative activity in a variety of tumour cell lines derived from multiple tumour types.

This year we have added several new biochemical and cell-based assays to enhance our characterisation of novel cancer therapeutics. In addition, we have increased our tumour cell line panel

to more than 60 cell lines representing different tumour types and genetic backgrounds. These tools will allow us to propose effective combinations of ETP compounds with established therapeutics for *in vivo* studies.

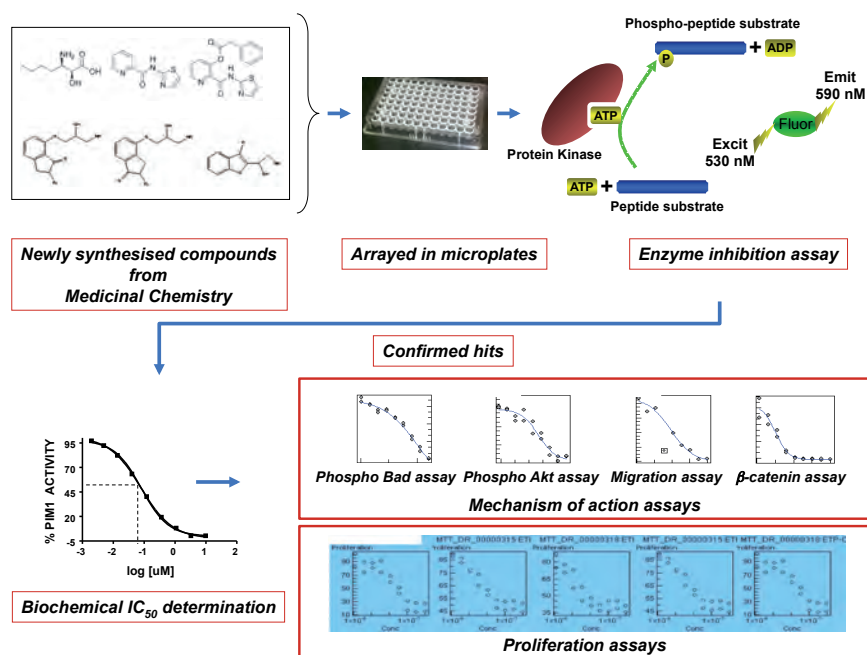


Figure: Workflow of the High Throughput Screening Section. Compounds synthesised in the Medical Chemistry Sections or acquired from outside sources are arrayed in 96 well microplates to be archived into our chemical compound collection as well as formatted for different assay platforms – we perform single point biochemical assays, biochemical IC₅₀ determinations, cellular mechanism of action and proliferation assays.

Publications

Wozniak MB, Villuendas R, Bischoff JR, Aparicio CB, Martínez Leal JF, de La Cueva P, Rodriguez ME, Herreros B, Martin-Perez D, Longo MI, Herrera M, Piris MA, Ortiz-Romero PL (2010). Vorinostat interferes with the signaling transduction pathway of T-cell receptor and synergizes with phosphoinositide-3 kinase inhibitors in cutaneous T-cell lymphoma. *Haematologica* 95, 613-621.

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.

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.

Brasca MG, Albanese C, Alzani R, Amici R, Avanzi N, Ballinari D, Bischoff J, Borghi D, Casale E, Croci V, Fiorentini F, Isacchi A, Mercurio C, Nesi M, Orsini P, Pastori W, Pesenti E, Pevarello P, Roussel P, Varasi M, Volpi D, Vulpetti A, Ciomei M (2010). Optimization of 6,6-dimethyl pyrrolo[3,4-c] pyrazoles: identification of PHA-793887, a potent CDK inhibitor suitable for intravenous dosing. *Bioorgan Med Chem* 18, 1844-1853.