McGill

Centre universitaire de santé McGill
McGill University Health Centre

DDTP Symposium

Molecular Recognition in Drug Discovery

Monday, April 18, 2011

8:30 AM to 12:30 PM

Faculty Club, McGill University

presented by

McGill-CIHR

Drug Development

Training Program

CIHR IRSC

Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Schedule

8:30 - 9:00 **Coffee/Registration**

9:00 -10:00 **Prof. James G. Omichinski**

Structure-Based Design of an Artificial Activation Domain

10:00 -10:15 **Coffee**

10:15 -11:15 **Dr. Christopher Bayly**

Current and Future Directions for Structure-Based Design in Lead Optimization

11:15 –12:15 **Prof. Dr. François Diederich**

Molecular Recognition Studies with Biological Receptors

Chair: **Dr. Youla Tsantrizos**

Prof. James G. Omichinski

Department of Biochemistry
Faculty of Medicine, Université de Montréal

Structure-Based Design of an Artificial Activation Domain

Over the last several years there has been considerable effort in creating artificial transcription activators (ATAs) that specifically target genes associated with human disease. ATAs must minimally contain a DNA-binding domain (DBD) and a transactivation domain (TAD) to function. Although several successful procedures have been developed to design artificial DBDs that target a specific DNA sequence, artificial TADs have proven much more difficult to develop in large part due to their intrinsically disordered nature in the unbound state. I will present a structure-based strategy for developing artificial TADs using all natural amino acids that is based on the structure of the TAD of tumour suppressor protein p53 bound to the general transcription factor IIH (TFIIH). Our protocol strategically introduces motifs to increase the helical character of the p53 TAD and using this protocol we have developed several potent activators. The most potent is a 13-mer peptide [E-Cap-(LL)] that preserves four key residues of p53 at the interface with TFIIH as well as a N-terminal capping motif and a di-leucine bridge. We have demonstrated that E-Cap-(LL) interacts with several known p53 target proteins in vitro with high affinity and it functions as an extremely potent in vivo activator in a yeast model system. Our results demonstrate that structure-based design represents a promising approach for developing artificial TADs that can be incorporated in the development of ATAs.

Dr. Christopher Bayly

Senior Scientist
OpenEye Scientific Software

Current and Future Directions for Structure-Based Design in Lead Optimization

In applying Structure-Based Design (SBD) in the context of lead optimization in drug discovery, the task is to maintain or improve potency (as mediated by protein-ligand binding interactions) together with other pharmaceutical properties. The simple picture of binding interactions between the ligand and the active site is complicated by protein and ligand flexibility and desolvation. This requires computational chemistry methods that go beyond the traditional static modelling based on Xray crystal structures. In the context of two case studies, several such SBD methods will be presented showing their utility for drug discovery.

Prof. Dr. François Diederich

Department of Chemistry and Applied Biosciences
ETH Zürich

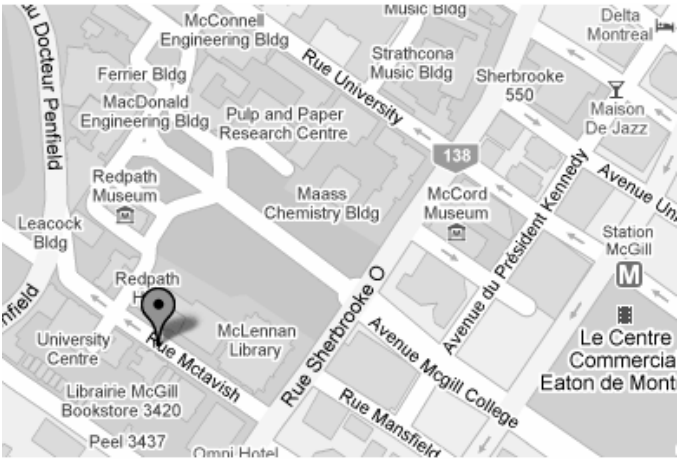
Molecular Recognition Studies with Biological Receptors

We pursue a multi-dimensional approach towards deciphering and quantifying weak intermolecular interactions in biological systems. Starting from the observation of an unfamiliar intermolecular contact seen in the X-ray crystal structures of protein-ligand complexes, we undertake data base mining in the Cambridge Crystallographic Database (CSD) and the Protein Data Bank (PDB) to explore its statistical relevance. If the contact is of a more general nature, we quantify it - depending on its energetic magnitude - by protein-ligand binding assays, molecular recognition studies with synthetic receptors or, if very weak, by studying intramolecular dynamic processes in designed model systems. This multidimensional approach is illustrated in examples taken from a variety of structure-based drug design projects pursued by our group. The lecture analyzes strategies for the optimal filling of differently sized sub-pockets at enzyme active sites. Opportunities for energetically favorable displacement of water molecules observed in enzyme-ligand co-crystal structures are discussed, and the quantification of a single water replacement at the active site of catechol *O*-methyltransferase, a target in Parkinson's disease, is presented. The quantification of weak intermolecular interactions, such as orthogonal dipolar interactions, cation-π interactions, and halogen bonding, in biological systems is reported. Halogen bonding is found to rival strong hydrogen bonding in terms of its contribution to the free enthalpy of protein-ligand complexation. However, it is not as easily established due to more rigorous geometric requirements.

Directions

The symposium will take place in the ballroom at the Faculty Club of McGill University located at 3450 McTavish Street, Montreal, QC, H3A 1X9.
(Tel.: 514.398.6660)

Faculty Club



Drug Development Training Program

514-934-1934 ext. 34460
trainingindrugdev@mcgill.ca
contact: Aube Mamias