McGill

Centre universitaire de santé McGill
McGill University Health Centre

DDTP Symposium

The Drug Discovery and Development Process

Wednesday, October 12, 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 — **Dr. Wolfgang Jahnke**

Fragment-based approaches in drug discovery research

10:00 -10:15 — **Coffee**

10:15 -11:15 — **Dr. Patricia Schroeder**

The impact of drug-drug interactions and pharmacokinetic variability on PK/PD endpoints: ADME/PK tools to clarify the risk in drug discovery

11:15 –12:15 — **Dr. Ann Kwong**

Discovery of Telaprevir: A novel protease inhibitor for the treatment of Hepatitis C virus infection

Chair: **Dr. Youla Tsantrizos**

Dr. Wolfgang Jahnke

Leading Scientist
Novartis Institutes for Biomedical Research
Basel, Switzerland

Fragment-based approaches in drug discovery research

Drugs can be discovered in multiple ways. A common approach to lead finding is High-Throughput Screening (HTS) of large compound libraries, modification of existing (natural) ligands, or structure-based design. Fragment-based screening (FBS) is a relatively new approach that has been added to the arsenal of lead finding technologies[1]. It consists of the screening of very small molecules (fragments) using a robust assay system, and its subsequent optimization with the help of structural information.

NMR is a useful and highly versatile biophysical technique that can support the drug discovery process in a variety of ways[2]. On one hand, biomolecular NMR is a very robust and reliable method to detect and characterize protein-ligand interactions, and is therefore ideally suited for fragment-based screening, together with other methods such as X-ray crystallography. On the other hand, NMR itself can give structural information on proteins and protein-ligand complexes.

In my presentation, I will present two recent applications of FBS in drug discovery: Allosteric non-bisphosophonate inhibitors of FPPS[3], and allosteric inhibitors of Abl kinase[4]. The latter application involved the development of a conformational assay, where the position of a particular helix in Abl kinase was monitored in various ligand complexes, and it was shown that the helix position determines agonistic or antagonistic behaviour of the ligand[4].

[1] W. Jahnke, D. Erlanson (Eds.) "Fragment-based approaches in drug discovery" *Wiley-VCH* (2006)

[2] W. Jahnke "Perspectives of biomolecular NMR in drug discovery: The blessing and curse of versatility" *J. Biomol. NMR* **39**, 87-90 (2007)

[3] W. Jahnke, J.-M. Rondeau, S. Cotesta, A. Marzinzik, X. Pellé, M. Geiser, A. Strauss, M. Götte, F. Bitsch, R. Hemmig, C. Henry, S. Lehmann, J.F. Glickman, T.P. Roddy, S.J Stout, J. R. Green "Allosteric non-bisphosphonate FPPS inhibitors identified by fragment-based discovery" *Nature Chemical Biology* **6**, 660-666 (2010)

[4] W. Jahnke, R.M. Grotzfeld, X. Pellé, A. Strauss, G. Fendrich, S.W. Cowan-Jacob, S. Cotesta, D. Fabbro, P. Furet, J. Mestan, A. Marzinzik "Binding or bending: Distinction of allosteric Abl kinase agonists from antagonists by an NMR-based conformational assay" *J. Am. Chem. Soc.* **132**, 7043-7048 (2010)

Dr. Patricia Schroeder

Senior Scientist
AstraZeneca Pharmaceuticals
Boston, MA

The impact of drug-drug interactions and pharmacokinetic variability on PK/PD endpoints: ADME/PK tools to clarify the risk in drug discovery.

The poor translation of pre-clinical efficacy endpoints towards proof of concept in the clinic is a primary source of attrition. As such, there is an increasing effort to develop and apply mechanistic and quantitative means to describe the extent of target coverage required for efficacy. The optimization of new chemical entities with the desirable ADME/PK properties to compliment target coverage is now prioritized in the earliest stages of drug discovery. Within the framework of a case-study for a CNS-indicated compound, this discussion will describe the set translational ADME tools and methods used to predict clinical kinetics. Furthermore, the discussion will explore the impact of pharmacokinetic variability and drug-drug interaction liabilities on predicted pharmacodynamic endpoints with a description of how standard in vitro ADME tools combined with FDA-endorsed simulation software are used industry-wide to assess pharmacokinetic risk before a drug candidate progresses to clinical trials.

Dr. Ann Kwong

Vice President, HCV Franchise Lead
Vertex Pharmaceuticals Inc.
Boston, MA

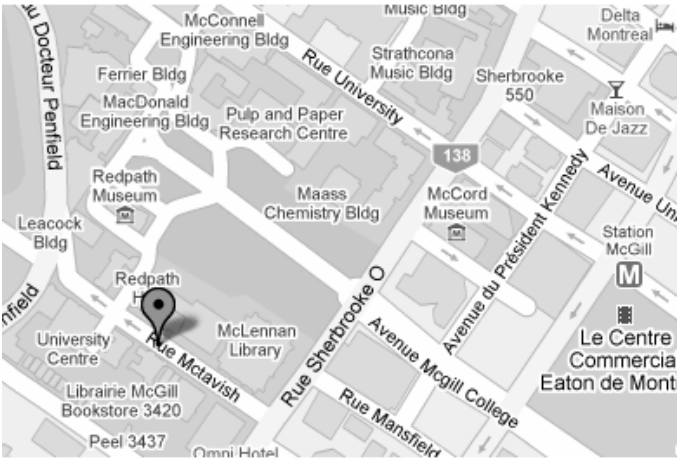
Discovery of Telaprevir: A novel protease inhibitor for the treatment of Hepatitis C virus infection.

Infection with hepatitis C virus (HCV) is a major medical problem with over 170 million people infected worldwide. Significant morbidity and mortality are associated with hepatic manifestations (cirrhosis and hepatocellular carcinoma), which develop with increasing frequency in people infected with HCV for more than 20 years. For patients infected with genotype 1 HCV, treatment with pegylated interferon (P) and ribavirin (R) is associated with a low (40-50%) success rate, significant treatment-limiting side effects and a long (48-week) duration of treatment for patients infected with genotype 1 HCV. The development of telaprevir, a HCV protease inhibitor, by Vertex faced substantial obstacles which required the development of tools to follow a rational drug design model and to demonstrate the preclinical proof of concept. Scientific experimentation beyond the minimum regulatory requirements, such as the decision to focus on shortening treatment duration and improving efficacy using response-guided therapy, provided insights so that physicians and patients have the opportunity to make the best treatment decisions on an individual basis. Telaprevir combination therapy was granted priority review and recently received FDA approval in the US (INCIVEK™) and EU (INCIVO™). INCIVEK™ represents a paradigm shift in HCV therapy by offering both patients improved SVR rates and the possibility of shortened treatment duration, albeit while increasing the rate of certain adverse events, compared to PR therapy alone.

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

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