EFMC Short Course

6th Short Course on Medicinal Chemistry

IMPROVING COMPOUND QUALITY: PHYSICAL CHEMISTRY AND DMPK PROPERTIES IN DRUG DISCOVERY. PRINCIPLES, ASSAYS AND PREDICTIONS

October 21-24, 2012

This intensive course is intended for scientists working in the field, and the presentations will be given by senior scientists from industry. The number of participants will be limited to 35, to favour in depth discussion.

Course Outline

In modern drug discovery, it is important that the Medicinal Chemist understands how to balance potency and ADME properties in order to provide high quality compounds for progression to clinical studies.
This short course will be a mixture of talks and worked exercises designed to further the understanding of DMPK.

The course will include: Outlines of the key DMPK in vitro assays: physico-chemistry for ADME; Oral drug absorption; Fundamentals of drug distribution; drug metabolizing enzymes; drug transport proteins; basic PK principles and human PK prediction; PKPD relationships.

Course Organisers
Kevin Beaumont, *Pfizer, USA*
Local Organiser
Henk Timmerman, *VU University Amsterdam, NL*

Deadline for preregistration
September 15, 2012

Venue
Castle "Oud Poelgeest", Oegstgeest
(near Leiden), The Netherlands
Airport: Schiphol, Amsterdam

Fee
€ 1375,00
Including accommodation, breakfast, coffee breaks, lunches and dinners during the days of the conference.

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EUROPEAN FEDERATION FOR MEDICINAL CHEMISTRY

October 21-24, 2012
Oegstgeest (near Leiden), The Netherlands

Course Organiser
Kevin Beaumont (Pfizer, US)

Improving Compound Quality: Physical Chemistry and DMPK Properties in Drug Discovery. Principles, Assays and Predictions

The vast majority of drugs are delivered by routes that are remote from their sites of action. Thus, in order to be effective, compounds must move from the site of administration to the site of their target, avoiding a number of barriers to drug passage. Once at the target, it is also important that a drug remains there long enough to exert its pharmacological effect. This defines the dose regimen of the drug. The physicochemical and DMPK properties of a compound will often define how it will overcome barriers to drug delivery as well as the duration of action of the drug.

An early review of drug development compound attrition highlighted inappropriate human pharmacokinetics as a key attrition risk. Up to 40% of compounds selected for clinical development were not passing the human pharmacokinetics set out in the project objectives. This included limited drug exposure due to poor oral absorption and bioavailability as well as short elimination phase half-life values leading to unacceptable dose regimens. Analysis showed that the majority of these compounds were optimized based on potency, leading to molecules with significant size and lipophilicity. It was reasoned that consideration of ADME properties into compound optimization would reduce human pharmacokinetic attrition. Subsequently, DMPK expertise has become a crucial component of the compound optimization and selection process, and compound loss due to inappropriate human pharmacokinetics has fallen.

In modern drug discovery, it is important that the Medicinal Chemist understands how to balance potency and ADME properties in order to provide high quality compounds for progression to clinical studies.

The application of DMPK expertise into compound optimization and selection is based on the following key aspects and assays:

1) A thorough understanding of the effect of physicochemistry on drug disposition as it relates to oral absorption, drug distribution and clearance.

2) A strong background understanding of the enzymes and transporters that determine drug disposition. I addition, a feel for the SAR of such drug metabolizing enzymes and transporters.

3) An array of *in silico*, *in vitro* and *in vivo* assays that aim to understand pharmacokinetic behavior in animals and humans.

4) Methodologies to predict the pharmacokinetics and pharmacodynamics of a compound in humans from preclinically available information.

This course will cover the fundamentals of DMPK that a Medicinal Chemist needs to understand in order to efficiently incorporate ADME properties into compound optimization and selection. The course will include in presentations and tutorials on key aspects of the use of DMPK including:

1) Outlines of the key *in vitro* assays available to optimize compounds in terms of oral absorption, drug distribution and rate of metabolism. Additionally, an understanding of assays to address key safety issues such as drug-drug interactions will be provided.

2) An in depth examination of the influence of physicochemistry (Log P, Log $D_{(7.4)}$, MW, TPSA etc) on drug disposition, including optimal properties for oral drug absorption, membrane permeation and drug metabolism.

3) Description of the physiology of the human body to understand the barriers to oral drug delivery, including dissolution in the gastrointestinal tract fluid, crossing the gastrointestinal tract wall and avoiding hepatic first-pass extraction.

4) Fundamentals of drug distribution, including plasma protein binding, the 'free drug' hypothesis and CNS penetration.

5) Overview of the array of drug metabolizing enzymes and their role in drug elimination and excretion.

6) A review of the emerging science of drug transport proteins and their effects on drug disposition, including absorption, distribution and clearance.

7) Basic pharmacokinetic principles (half-life, clearance, volume of distribution, oral bioavailability) and prediction to human from *in vitro* and *in vivo* preclinical information.

8) How to relate pharmacology at the drug target to the time course of effect and prediction of clinical dose (Pharmacokinetic/Pharmacodynamic relationships).

At the end of this intensive 2.5 day course, the attending medicinal chemists should have gained an understanding of the key aspects of DMPK required to work effectively in compound optimization and selection. They will leave with a common drug metabolism language that should enhance their partnerships with DMPK colleagues in the drug discovery process.