EFMC Short Course

5th Short Course on Medicinal Chemistry

TARGET SELECTION THROUGH APPLICATION OF CHEMICAL AND SYSTEMS BIOLOGY

April 1-4, 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 recent years drug discovery shifted from a traditional target-based approach towards phenotype and patient-based approaches. This course will discuss how systems biology contributes to a better understanding of human physiology and diseases (session I) and of the cellular biological systems behind (session II). This understanding is key for the discovery of novel drugs in order to address the right targets and biological mechanism. In addition experimental (and computational) approaches to target identification will be a topic (session III), which are key for de-convolution of the molecular target(s) of known drugs or of hits from phenotypic screens (e.g. chemical proteomics). The last session will then describe how 'omics data can be used to identify signatures of diseases (e.g. gene expression signature) and how these signatures can foster the understanding of a disease-phenotype. These disease signatures can be mapped to signatures of drugs for modern drug discovery. Each of the four sessions of the course will be introduced by an overview, followed by several case studies and some hands-on exercises using various modelling tools.

Course Organisers
Thomas Klabunde, *Sanofi-Aventis, DE*
Birgit Schoeberl, *Merrimack Pharma, USA*
Local Organiser
Henk Timmerman, *VU University Amsterdam, NL*

Deadline for preregistration
February 28, 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.

Contact
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EUROPEAN FEDERATION FOR MEDICINAL CHEMISTRY

Target Selection through Application of Chemical and Systems Biology

April 1-4, 2012
Oegstgeest (near Leiden), The Netherlands

Course Organisers
Birgit SCHOEBERL (Merrimack Pharmaceuticals, USA)
Thomas KLABUNDE (Sanofi-Aventis, Germany)

Additional Speakers:
Christina Friedrich (Rosa & Co, USA)
Julio Saez-Rodriguez (EBI, UK)
Uwe Rix
(H. LEE MOFFITT CANCER & RESEARCH INSTITUTE, USA)
Francesco Iorio
(EMBL-EBI & WELCOME TRUST SANGER INSTITUTE, UK)

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Session I: How can modelling & simulation help to understand disease physiology? The first session will cover what physiological and disease modelling is and how it can help to understand (disease) physiology. Case studies will be given how disease and physiological modelling can support the understanding of human (patho)physiology and can be used to foster the discovery of novel therapeutic approaches. The first session of the course will end with a work-shop on mechanistic physiological models for use in pharmaceutical discovery and development to provide some hands-on experiences with modelling software (e.g. JDesigner).

Session II: How can molecular mechanistic modelling help to find new targets? Whereas the first session is focussing on modelling of physiological processes (e.g. the interplay of the organs), molecular mechanistic modelling – the topic of this session – captures the processes occurring on the (intra)cellular level. After having looked into (disease) physiology in the first session of the course, in this session we will take a magnification glass to see what is happening within the cell. Case studies will be given of how these models can be used to identify or validate molecular targets. At the end of the session some more detailed technical insights will be provided into various modelling approaches of cellular

systems (e.g. biochemical modelling based on differential equations and logic-based modelling). We will discuss advantages and disadvantages of the different formalisms, and finally some practical exercises introducing to tools like Copasi, Matlab and/or CellNOpt will be given.

Session III: Within recent years drug discovery is moving from target-based approaches using single enzyme or cell-based screenings towards phenotypic screening of (patho) physiologically relevant (primary) cells. This can be explained by the limited success of target-based approaches and by the discovery that several successful drugs often modulate an orchestra of different targets. Within this session experimental (and computational) approaches to target identification will be discussed, which are key for de-convolution of the molecular target(s) of known drugs or for finding the molecular basis for the activity of hits from phenotypic screens (e.g. chemical proteomics). At the end of the session some approaches and tools will be presented that allow predictions of putative molecular targets of compounds based on the information of their chemical structure (e.g. SEA approach).

Session IV: A significant number of recent studies wink at the idea that every biological state can be described by a proper gene expression signature: a well defined set of genes together with a pattern of expression that is exclusively linked to it. In this scenario DNA-microarray technology can be deemed as the natural language through which these "biological-state-summaries" can be generated. By making use of novel non-parametric genome-wide metrics it has been possible to "connect" drugs, genes and diseases by simply comparing the corresponding gene-expression signatures. As a consequence, several approaches have been proposed to exploit the massive amount of publicly available gene-expression data for computational "drug re-purposing" by using a "guilt-by-association" approach (i.e. if two drugs elicit a "similar" transcriptional response then they could share a therapeutic application) or by measuring the extent of "anti-similarity" between drug- and disease-signature (i.e. if a drug is able to revert a phenotype signature then it could be able to "revert the phenotype" as well). On the same time more rationale approaches have been recently designed to extract important features from expression signatures, to "finger-print" patients in order to detect the activity of crucial biological pathways and to correlate these measurements with clinico-patological features. In this session we will review some of the introduced methods by discussing successful study cases and tutoring the use of publicly available tools.