

The official EFMC e-newsletter

# MedChem Watch

# 12

May 2011

49 EDITORIAL

50 PERSPECTIVE

Chemistry at the Biology  
Disease Interface

55 LAB PRESENTATION

The Computer-Assisted  
Drug Design Group at ETH Zurich

58 YOUNG RESEARCHER

Gerd Wagner

63 EFMC NEWS

65 EFMC EVENTS

66 REPORT

18th European Symposium on  
Quantitative Structure – Activity  
Relationships, Rhodes, Greece.  
Third EFMC Short Course



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# MedChemWatch

## MedChemWatch no.12

May 2011

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The European Federation for Medicinal Chemistry (EFMC) is an independent association founded in 1970. Free from any political convictions, it represents 24 scientific organisations from 21 European countries and covers a geographical area the size of the USA with a similar scientific population. Its objective is to advance the science of medicinal chemistry by promoting cooperation and encouraging strong links between the national adhering organisations in order to promote contacts and exchanges between medicinal chemists in Europe and around the World.



*Dear colleagues,*

As medicinal chemists, either from the industry or from the academia, we are still experiencing the impact of the global crisis and we are still facing the problems posed by industrial reorganization and by the budget cuts that many European Universities are suffering of. Difficulties can also be opportunities, and we should take these times as an occasion for a reappraisal of the position of medicinal chemistry in the rapidly changing world of medicines and diseases. We have the ambition to promote MedChemWatch as an instrument to convey different opinions among our community, and the Perspective articles are the preferred means to this aim. In this issue, Graeme Robertson comments on the role of chemistry (and medicinal chemists) at the biology/disease interface. Besides the Perspectives, this issue continues the presentation of leading European labs, and this is the turn of Gisbert Schneider, who recently moved to ETH Zurich, and emerging labs, and we are now presenting Gerd Wagner, King's College (UK). Furthermore, Anna Tsantili reports on the 18th EuroQSAR meeting, held in Rhodes (Greece) last September. As usual, you will find the columns on news from member societies and from the EC of the EFMC. Among the other news, we report the names of the winners and of the most meritorious runners up of the EFMC prizes for a young medicinal chemist in Industry and Academia. The winners will be awarded during the 4th International Symposium on Advances in Medicinal Chemistry (ASMC). Indeed, among the various and interesting events that will take place this year (and you will find the updated list in the 'EFMC events' section, as well as in the Meeting Calendar section of [www.efmc.info](http://www.efmc.info)), the 4th edition of ASMC, which will be held in St. Petersburg, August 21-25, 2011, and the 3rd edition of the Frontiers in Medicinal Chemistry Meeting, which will be held in Stockholm on June 19-21, 2011.

**Gabriele Costantino**, *Editor of MedChem Watch*



# Chemistry at the Biology/Disease Interface

BY GRAEME ROBERTSON

## Scientific Advances

The science of medicinal chemistry is advancing rapidly and the availability of data at the chemistry biology interface allows medicinal chemist to design new compounds with ever more data. The overall process of drug discovery however requires significant change to become a more sustainable endeavour. There are many aspects amongst the evolving role of medicinal chemistry to consider from potentially encompassing different molecule types to moving closer to biology and better integrating chemistry and biological data in order to chemically navigate efficiently in biological space to better design effective molecules.

Drug discovery is however still and will most likely remain a largely discipline based, i.e. bio-centric or chemo-centric. An arena in which, chemists and biologists “see” the challenges and problems of understanding biology, its connection to cellular function, and how to modulate these effects from very different perspectives. Key to the medicinal chemist’s role is the need to understand the chemical basis for changes in biological systems and disease pathobiology to thus design mol-

ecules with the properties needed to probe target modulation in a disease context. To best achieve this, a more open or less discipline-bounded, approach is required potentially also broadening the chemical space considered of interest to medicinal chemistry.<sup>1</sup>

The progress in the field of GPCRs, for example, illustrates very well the recent scientific progress and the better availability of data for medicinal chemists. GPCRs are the largest protein family targeted by small molecules and remain a mainstay of drug discovery. Many of the ligands developed such as, the antipsychotic agents dopamine D<sub>3</sub> receptor antagonists evolved from an initial knowledge of the binding (and kinetics) of the “original” natural ligand and the use of phenotypic assays. Most chemists who have worked in the past on dopamine receptors would marvel at the recent availability of a co-crystal structure of the D<sub>3</sub> receptor with eticlopride and the possibilities for structure-based design.<sup>2</sup>

How general this will become remains to be seen but GPCRs are benefiting from a range of scientific advances that is promoting the investigation of

their effects not only at a target class level but also to now drive this from a structural perspective. Site-directed mutagenesis and modelling of GPCRs has long played a role in ligand design, but the increasing availability of structural data is allowing better analysis of ligand-protein interactions and the investigation of state-dependant protein conformations (agonist, antagonist, etc.). A range of different receptor templates (X-ray structures) are now available for GPCR homology modelling in addition the thermal stabilisation of GPCRs allows the isolation of specific receptor conformations to elucidate physiologically relevant receptor conformations. For example, both adenosine A<sub>2A</sub> and muscarinic M<sub>1</sub> receptors have been stabilised receptors (StaRs) in the inverse agonist conformations and used to profile association and dissociation rates of antagonists.<sup>3</sup>

Recent results on high-resolution NMR study of rhodopsin II suggest that aminergic GPCRs could also be accessible using solution NMR techniques, potentially allowing a more dynamic analysis of receptor conformational variation and the impact of ligand-receptor interactions.<sup>4</sup>

## Chemistry at the Biology Disease Interface

Notwithstanding these great scientific advances and the contextual richness of data available to medicinal chemists at a target level, the overall drug discovery process in which they work needs serious revision.

Chemistry (medicinal chemists) needs to play a major role in the process of target validation (target modulation) and in the development of more predictive animal models (data sharing). Both these areas are compounded by the relatively poor understanding of the underlying pathophysiology and disease mechanisms, particularly in humans coupled with a need to navigate biological space from a chemistry (modulator) perspective or viewpoint. Bringing the data together necessary to find new targets across disciplines, i.e. Medicinal Chemistry to Chemical Biology and back again, allows an emphasis on target modulation from project inception to clinical studies in a more complete biological/disease context. Progressing compounds by compound effect relationships, phenotypic profiling, imparts a need for chemists to develop new ways of visualising and using more complex multi-dimensional data to design novel therapeutic agents.

In order to achieve this high quality proof-of-concept compounds (probes) are required that facilitate target validation.<sup>5</sup> Target validation requires modulation of protein signalling, preferably with temporal control, in a disease context. This may well require medicinal chemists to apply their skill sets to non-small molecules that best allow investigation of target modulation in the appropriate setting (biological system) and to help drive novel drug discovery away from single

compound – single target analyses and perhaps also finally into more novel target space.<sup>6</sup>

Taking neurodegeneration as an example of target modulation in a disease framework illustrates many of the challenges in being able to monitor the effects of compounds in complex systems and use data to design new ligands. Neurodegeneration features a complex interaction of challenges to the proteostasis network in the brain leading to; protein misfolding, inflammation, mitochondrial dysfunction, and oxidative damage. This proteostasis landscape deteriorates with time and many neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's disease are characterized by the appearance of protein deposits, aggregates, plaques that constitute key elements in the disease pathobiology.<sup>7</sup> Confronting unbalance in the proteostasis network with small molecules and interpreting changes in this network at a molecular level is a tough challenge for medicinal chemists. It can't be expected that a single compound/target approach could improve all aspects of proteotoxicity, and monitoring of the influence of compound treatment across cellular functions is needed rather than focus on say only metabolism or neuroinflammation. Ligand-target effects need to consider ligand-network perturbations, rather than ligand-target or pathway effects.

We're accustomed to see links in biology at the signalling or disease level, but compound trends are usually displayed within a target or target-class environment rather than a Compound Effect Relationship.<sup>8</sup> For example, typical kinase inhibitors are ATP-binding site ligands and kinases are designated as a "family" based on their ligands

greatly facilitating a systematic exploration of kinase-space.<sup>9</sup> Classification of kinases via the ATP-binding site had been one of the best examples of systems-based research<sup>10</sup> but consideration of kinase effector domains would provide a very different route to analysing and exploiting this family. The protein-protein interactions of kinases and their effector proteins remains perhaps a future challenge of chemical biology and the use of both chemistry to advance a molecular understanding of biology.<sup>11</sup>

The perturbation of biological systems to gain a more holistic understanding of ligand-target interactions with complex biological systems via linking chemogenomics with systems chemical biology could be one of the answers.<sup>12</sup> The modelling of signalling specificity or redundancy is difficult and transferring the information to drug design data can be even more problematic. Here perhaps a good example is the recent demonstration of the chemical dissection of mitochondrial oxidative phosphorylation (OXPHOS) and its application to screening/profiling compound collections across signalling processes to better understand (mitochondrial) biology and toxicity. Screening across 4 cell-based assays of OXPHOS physiology with multiplexed measurements of nuclear and mitochondrial DNA gene expression revealed several complexities of mitochondrial modulation, including that (i) protein synthesis inhibitors can decouple coordination of nuDNA and mtDNA transcription and that (ii) a subset of HMG-CoA reductase inhibitors, combined with propranolol, can cause mitochondrial toxicity, yielding potential clues about the aetiology of statin myopathy.<sup>13</sup> A recent example of a network approach to target identifi-

cation and new applications for known compounds or mechanisms has been reported via the integration of phenotypic and chemical indexes in pharmacological space and protein-protein interactions in genomic space.<sup>14</sup> The use by medicinal chemists of such compound (drug) biological profiles or fingerprints calls for a move away from single target SAR but also calls for innovative ways by which to portray the information and visualise the factors influencing these “compound effect relationships”. In other words how best to translate knowledge into innovation-based drug discovery.

Animal models play a central role in translating basic biology into a disease understanding; an excellent recent example was the use xenograft models to offer an explanation of the development of resistance to the glioblastoma chemotherapy, Temozolomide (TMZ). Data from this model and in vitro experiments demonstrated that long-term treatment of astrogloma with TMZ induces increased expression of GLUT/SLC2A transporters, mainly GLUT-3, and the pro-proliferative AKR1C phase 1 drug-metabolizing enzymes that lead to increased resistance. Targeting of GLUT-3 in GBM and/or AKR1C proteins could thus delay the acquisition of TMZ resistance.<sup>15</sup> Experimental animal models should however connect screening environments and data, to readouts used in the clinical setting and critically evolve using results from downstream activities so that compound design and modification can become more predictable and based on knowledge better connect to the human disease context. The depth of knowledge (use) of a given model can however be restricted simply by the limited number of compounds and compound types screened in a given organisation. Much could be

gained via the collation of animal model data from larger compound (data) sets across organisations to give statistically more relevant data and hopefully models that are more predictive of clinical effects. Such a move would require a more open approach to data sharing although there are some initiatives underway many within the Innovative Medicines Initiative (IMI) to address at least some of the issues such as creating knowledge infrastructures that enable integration of chemical and biological data (Open Pharmacological Space) and drug safety databases (eTOX).<sup>16</sup> Sharing drug safety and toxicology data or being able to search safety/toxicology papers by similarity searching even would provide great reinvestment and help drive the flow of data from later stage development and the clinic back to early research. For example the eTOX initiative aims to develop just such a database from legacy toxicology reports and public toxicology data; combining this with in silico strategies and tools aimed at

better predicting the toxicological profiles of small molecules in earlier stages of research.

### The Need for Change

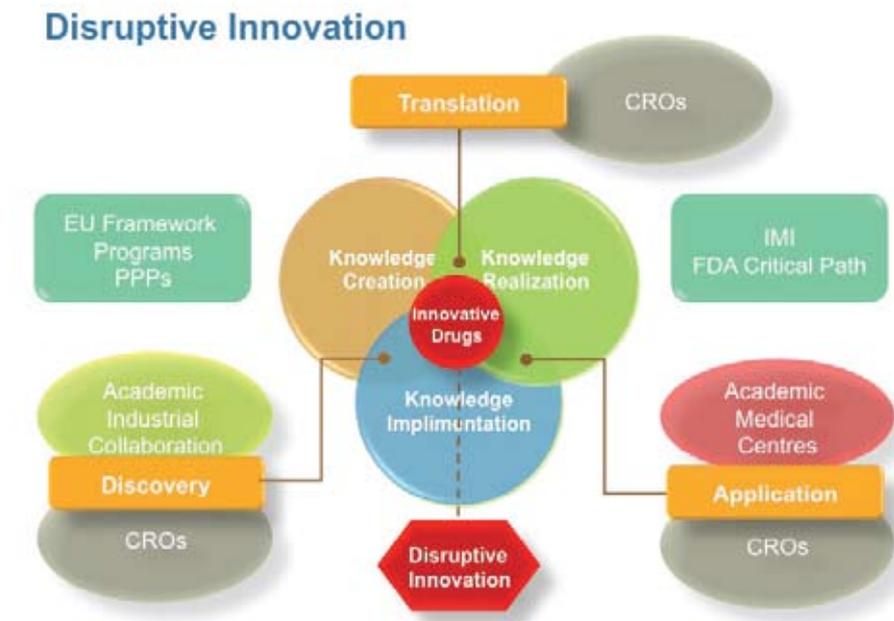
Obviously a chemical perspective at the whole animal level also needs to be reflected at an efficacy or mechanistic level. Thus in order to realise an approach based on a chemical perspective on disease biology a greater understanding of the basic biology that underpins the disease pathophysiology is necessary. The reductionist nature of the target-based approach and over focussing on subsets of information doesn't effectively consider the complexity of the chemistry-biology-disease interface which is thus not considered in a holistic manner. As a result a considerable “knowledge gap” has developed between an understanding of the dynamics of target signalling at a cellular, phenotype, and disease levels with many compounds failing



because of an insufficient knowledge of the basic biology driving the disease phenotype.

There are many options/alternatives for approaching this knowledge gap and if R&D is to progress to become more sustainable then a more collaborative approach to addressing these gaps and to drive innovation via academic-industrial, public private partnerships, or other collaborations where more of the basic underlying biology is utilized for compound effect relationship and their use in compound design are needed. How to translate this knowledge (basic research) into better approaches to drug discovery is therefore a key current consideration, critically a substantial improvement in validation of new therapeutic targets is required, via ligands that modulate target functions in a temporal and dose-dependent manner. This integration of medicinal chemistry with basic biology may well come about by building a more collaborative environment particularly between academia and industry. Bringing together centres of excellence and promoting basic research could significantly help in gaining sufficient in-depth understanding of disease pathophysiology.

Historically, academia has had three equally important missions: **teaching**, i.e. transfer of knowledge, **research**, i.e. discovery of new knowledge, and the **translation** of academic innovation into industry as a contribution to “knowledge-based economy”. Academia has typically performed the basic research that elucidated the underlying mechanisms of disease and identified promising points of intervention, whereas corporate researchers have focussed on applied research toward the discovery and commercialisation of novel drug treatments.<sup>17</sup> This need for re-



search centres to develop expertise in depth and collaborate most likely goes well beyond current concepts of open innovation and requires a more substantial revamp of the process to and indeed beyond clinical studies.<sup>19</sup>

Chemical modulation of signalling networks and cellular events offers opportunities often not accessible with genetic methods, in particular the option for temporal control of cellular events and the development of small-molecule modulators of protein function is at the heart of chemical biology research. It is here that the need to link chemical and biological space and really impact on defining suitable starting points that guide compound design by the recognition of complex structural relationships associated with biological activity. In other words, to use chemical biology to put the “medicinal” back into medicinal chemistry.

To facilitate this and help drive disruptive innovation it also serves to “simply” bring data together better to permit this chemical navigation of biological and disease space or mapping of the chemistry interfaces. This integration of in-depth basic biology (pharmacology) with cheminformatics and chemogenomic approaches is not however necessarily a “simple” task.<sup>20</sup> Good navigation tools are also required that allow chemists to emerge from rule-based and reductionist approaches to develop a more holistic and knowledge (data) driven approaches.<sup>21</sup> The tools that allow chemical interrogation of biological and disease data should also facilitate the sharing of this across disciplines and organisations. Ultimately, there will be a redefining of the definition of Medicinal Chemistry and a great opportunity for chemists to help drive the next generation of drug discovery.

However, chemists need to **remain experts at chemistry** but diversify to play a wider role in innovative “disruptive” drug discovery, just as centres of excellence need to focus on just that “experts in a particular field collaborating with other experts or centres.”<sup>22</sup> This bringing people together to share both contextual and tacit knowledge is often underestimated and more energy needs to be given to the currency or language of collaboration, that is “information sharing”. The direct route to knowledge is not always know or

even desired – efficient navigation and interaction is! As stated in the introduction research is still (will remain?) discipline based i.e. bio- or chemocentric, but the overall drug discovery requires a more open (less bounded) approach. Moreover, generally the more innovative the target the greater the need for collaboration between experts. Such collaboration within networks between centres of excellence (small/large companies and/or academic groups) provides an alternative highly flexible and potentially highly

adaptable environment that capitalizes on the collective expertise within the collaborative network. One in which chemists can refine and evolve the role of Medicinal Chemistry.

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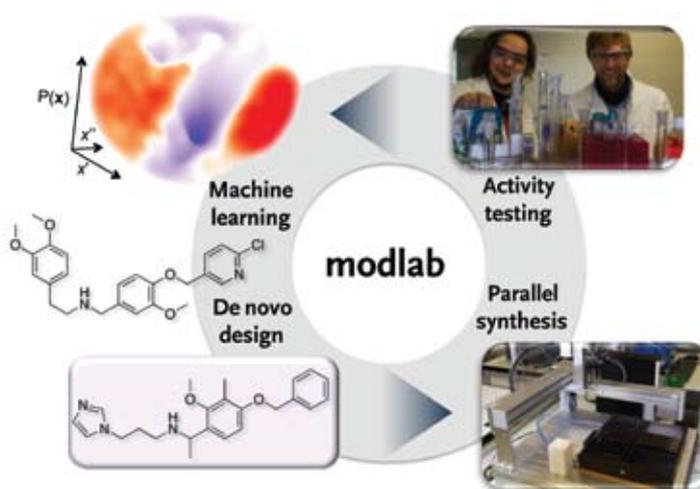
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# The Computer-Assisted Drug Design Group at ETH Zurich

BY GISBERT SCHNEIDER



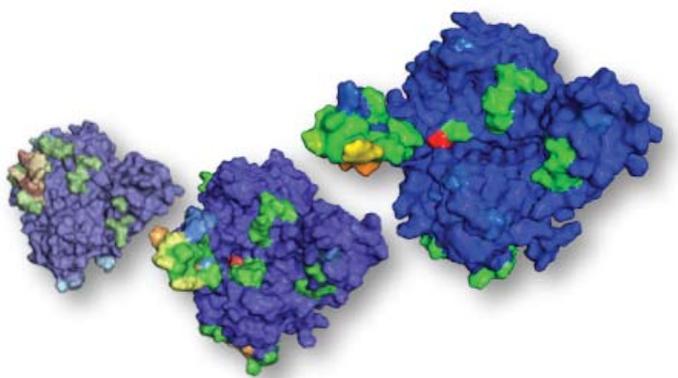
## MODLAB – The Molecular Design Laboratory

Research activities of the *Computer-Assisted Drug Design Group*, which was installed in the *Department of Chemistry and Applied Biosciences* at ETH Zurich in 2010, concentrate on method development for virtual screening, molecular *de novo* design, and adaptive autonomous systems in drug discovery. In a *trans*-disciplinary approach the international team amalgamates computer-based pattern recognition and machine learning with compound synthesis and biochemical activity determination. Prior to joining ETH, Prof. Gisbert Schneider was a full professor (*Beilstein Endowed Chair for Chem- and Bioinformatics*) at Goethe-University in Frankfurt, Germany (2002-2009), where he currently holds a distinguished adjunct professorship, and a researcher with F. Hoffmann-La Roche Pharmaceuticals in Basel, Switzerland (1996-2001).

The “modlab team” at ETH conceives, develops and implements new concepts, algorithms and software for rapid identification of bioactive tool compounds and pharmaceutical lead structures. We employ a broad repertoire of computational techniques for automated hypothesis generation, activity prediction and simulation. At the heart of our studies lies the machine-driven *de novo* design of both individual candidate molecules and small focused compound libraries that exhibit a desired pharmacological activity profile. Research studies also include drug re-purposing, target and off-target prediction, *in silico* polypharmacology and chemogenomics projects, analysis of protein structure and modulation of protein-protein interaction, as well as the de-orphanization of drugs and their macromolecular receptors. We run own synthesis and testing facilities and a service point for virtual screening (SerViS). In collaborative

projects we investigate RNA-protein interactions, and design innovative immunomodulatory agents and anti-inflammatory lead structure candidates. More recently, the scope has been extended to antigen prediction and design, bacterial genome mining for new antimicrobial drug targets, the rational design of host-defense peptides, and the application of computational tools to natural product simulation and the design of natural-product mimicking compounds.

The group has a long-standing track record in molecular *de novo* design. Since 20 years, we have consequently optimized adaptive algorithms for computer-assisted compound generation by “simulated molecular evolution”. Ten years ago, our ligand-based *de novo* design software TOPAS (TOPology Assigning System) provided the basis for a fully automated evolutionary molecular design tool. Its youngest descendant, the software DOGS (Design Of Genuine Structures), employs validated chemical reactions and fragment-based building-block assembly for “scaffold-hopping”. *De novo* designed compounds are analyzed using own software for “fuzzy pharmacophore” matching, chemical landscape analysis, and automated ligand docking. DOGS has recently been applied to generating a novel selective inhibitor of polo-like kinase 1 (Plk1), a target for the development of cancer therapeutics. This pioneering study demonstrates that by coupling of virtual screening, fragment-based chemical synthesis and activity testing, new bioactive agents with a desired target profile can be obtained.



### **“Leads on demand”**

On the way from models to molecules our algorithms guide an evolutionary design process that constantly adapts to a dynamic fitness landscape (structure-activity function) by integrating new test results that are fed back in iterative synthesis-and-test cycles (active learning concept). Compounds are generated from readily available building blocks by straightforward chemical synthesis in analytical or semi-preparative amounts, and subsequently tested for target binding *in vitro*. The ultimate goal is to construct an unsupervised molecular design automaton generating “leads on demand”. While the actual realization of this idea might appear futuristic, the overall concept is well motivated and meant to support drug discovery projects by providing innovative technology for the identification of pharmaceutically active agents in a cost- and time-efficient manner. We couple machine-learning with miniaturized synthesis technology and microfluidic lab-on-a-chip devices to prospectively enable broad application of *de novo* molecular design in medicinal chemistry and explore the full potential of computer-assisted compound optimization.

In tight cooperation with leading groups from academia and pharmaceutical industry, our innovative design concepts are applied and tested for their applicability and usefulness in drug discovery projects. As the molecular design cycle involves multiple scientific disciplines and requires rigorous inter-disciplinary thinking, our team consists of students and researchers with different scientific skills and background. Excellent equipment is available to support computer scientists, bio/cheminformaticians, pharmaceutical chemists, biochemists, and engineers alike. The aim is to provide an ideal research environment for the complete spectrum of computer-assisted drug discovery and break down potential barriers between individual scientific disciplines.

### **Lead finding in a nutshell – A case study**

Increasing bacterial resistance against current therapeutic drugs is observed, and novel intervention strategies are urgently sought for. This is also true for the human pathogen *Helicobacter pylori* (*H. pylori*), which is responsible for the development of severe gastric inflammation and cancer diseases. In tight cooperation with an expert microbiology team (Prof. S. Wessler, Paris-Lodron University Salzburg, Austria), we analyzed the *H. pylori* genome by bioinformatics

methods and identified the protease HtrA as a novel virulence factor and potential drug target for treatment of bacterial infection. We developed a structure-based virtual screening protocol that starts from the prediction of “hot-spot” surface residues and the automated extraction of a ligand-binding pocket from the protein model. Then, an idealized “virtual ligand” was computed inside this pocket volume, so that pharmacophoric interaction sites between the protein and potential ligand compounds are satisfied. The virtual ligand model finally served as template for rapid virtual screening of compound databases. By using comparative protein modeling and multiple virtual screening techniques, we rapidly identified first-in-class inhibitors of HtrA that efficiently block *H. pylori* invasion of gastric epithelia. This study nicely demonstrates how computational genome mining can lead to novel antibacterial drug target candidates, for which receptor-based virtual screening with a “fuzzy” structure-based pharmacophore model retrieved druglike bioactive agents that combat pathogens.

This outcome and others alike corroborate our *trans-disciplinary* approach at the interface between theory and laboratory experiment, which proves to be both appropriate and essential for finding inventive solutions to pressing issues in medicinal chemistry.

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**Selected Recent Publications:**

- Hartenfeller, M. & Schneider, G. (2011) *De novo* drug design. *Methods Mol. Biol.* 672, 299-323.
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## Gerd Wagner

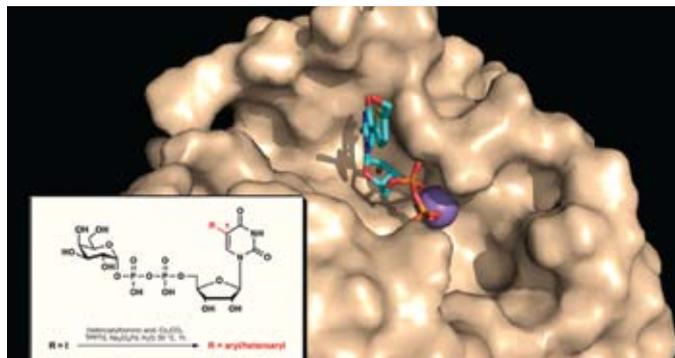
Gerd Wagner is currently a Senior Lecturer in Medicinal Chemistry at King's College London. Originally from beautiful South Germany, Gerd holds a degree in Pharmacy from the University of Freiburg and a PhD in Medicinal Chemistry (mentor: Professor Stefan Laufer) from the University of Tuebingen – two of Germany's oldest and most prestigious academic institutions. In 2002, he joined the group of Professor Barry Potter at the University of Bath (UK) for postdoctoral studies on the role of cADPR and related dinucleotides in calcium signalling. He stayed in the UK to start his independent academic career, taking up a lectureship in Medicinal Chemistry at the University of East Anglia in 2004. In 2010, he moved to his current position at King's College, where he is based in the Institute of Pharmaceutical Science. He is also the Head of the Institute's Chemical Biology Unit and is chairing the steering group for the development of a new undergraduate programme "Chemistry with Biomedicine", which is scheduled to launch at King's in 2012.

Gerd's main research interests are in medicinal chemistry and chemical biology. Research in the Wagner laboratory is concerned with the design, development and application of chemical tools to address important biological and biomedical questions, particularly in the area of glycobiology. The Wagner group currently occupies a large laboratory overlooking London's South Bank, which is well equipped for synthetic and bioanalytical chemistry as well as protein biochemistry. Gerd's research has been funded by the EPSRC, the MRC, the BBSRC, the Royal Society and the Leverhulme Trust, and he collaborates successfully with research groups in the UK, Denmark and Germany.

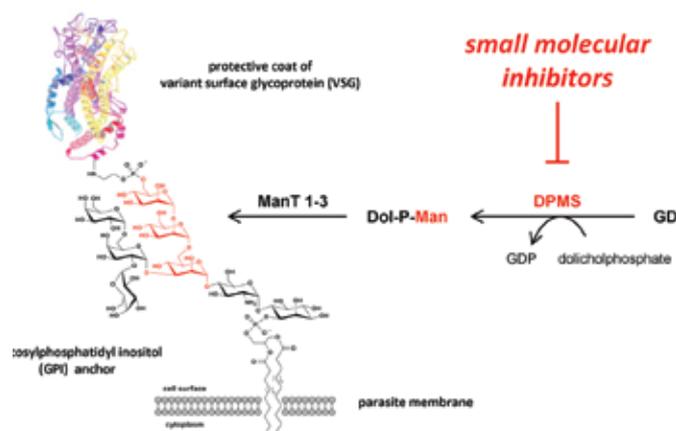


**Glycosyltransferases as drug targets.** Glycosyltransferases (GTs) are a large family of carbohydrate-active enzymes which transfer a sugar from a glycosyl donor to a suitable acceptor. GTs play a key role in many biological processes underpinning human health and disease, including glycoprotein and cell wall biosynthesis in human pathogens, carcinogenesis, and cellular adhesion. The considerable potential of GTs for drug discovery is undisputed, especially in therapeutic areas such as infection, inflammation and cancer. However, realising this potential has been

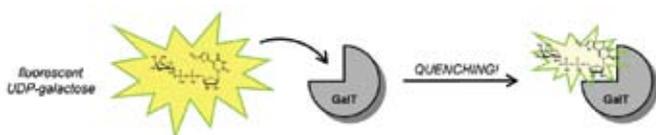
hampered by a lack of potent, drug-like GT inhibitors. The Wagner group has recently discovered, in collaboration with Monica Palcic (Copenhagen) a novel type of GT inhibitor which exploits the conformational plasticity of these enzymes (*Nat Chem Biol* 2010, 6, 321-323). The structural and enzymological information gleaned from these studies is currently being used for the rational development of 2<sup>nd</sup> generation inhibitor chemotypes with suitable properties for cellular studies and, potentially, drug development.



**African Sleeping Sickness.** African Sleeping Sickness is a devastating parasitic disease which threatens millions of people in sub-Saharan Africa. Current treatment options are limited, outdated and increasingly ineffective. The Wagner group is pursuing a variety of approaches to identify new therapeutic strategies for combating African Sleeping Sickness. We have a longstanding interest in the development of drug-like inhibitors for parasitic glycosyltransferases involved in the biosynthesis of glycosylphosphatidyl inositol (GPI) anchors, which are essential for parasite viability. In collaboration with Terry Smith (St Andrews), we have recently identified the first small molecular inhibitors of GPI anchor biosynthesis (*Bioorg Med Chem Lett* **2009**, *19*, 1749-1752). More recently, we have also started to explore the potential of iron chelators as novel anti-parasitic agents (with Bob Hider, King's College).



**Synthetically modified biomolecules.** The Wagner group has a proven track record in developing synthetic methodology for the direct structural modification, by cross-coupling chemistry, of sensitive biomolecules such as nucleotides, sugar-nucleotides and amino acids. Obviating the need for protecting groups and lengthy synthetic sequences, this synthetic approach has provided rapid access to structural analogues of naturally occurring biomolecules with interesting biological and biophysical properties. Cross-coupled derivatives of UDP-galactose, for example, are useful as broadly applicable fluorescent probes for glycosyltransferase ligand-displace-



ment assays (*ChemBioChem* **2010**, *11*, 1392-1398). A similar synthetic strategy has led to the discovery of base-modified NAD derivatives which act as isoform-selective inhibitors of human sirtuins, NAD-dependent histone deacetylases that are emerging as promising anti-cancer targets (*J. Med. Chem.* **2011**, in print).

### Information and Contact

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### Key references

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International Symposium

# Advances in Synthetic and Medicinal Chemistry

August 21-25, 2011  
St. Petersburg, Russia

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(The Scripps Research Institute & University of California, San Diego, United States)

Dr Anthony WOOD

(Pfizer, Sandwich, United Kingdom)

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## Confirmed Speakers

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 Dr Mark BUNNAGE (*Pfizer, United Kingdom*)  
 Dr Sylvain CELANIRE (*Addex Pharmaceuticals, Switzerland*)  
 Prof. Vy M. DONG (*University of Toronto, Canada*)  
 Dr Mark FLANAGAN (*Pfizer, United States*)  
 Prof. Athanassios GIANNIS (*University of Leipzig, Germany*)  
 Prof. Henri KAGAN (*University Paris-Sud 11, France*)  
 Dr Rodney KIP GUY (*St. Jude Children's Research Hospital, United States*)  
 Prof. Dawei MA (*Shanghai Institute of Organic Chemistry, China*)  
 Prof. Christina MOBERG (*KTH School of Chemical Science and Engineering, Sweden*)  
 Prof. Ei-ichi NEGISHI (*Purdue University, United States*)  
 Prof. K.C. NICOLAOU (*The Scripps Research Institute & University of California, United States*)  
 Dr Alessandro PADOVA (*Siena Biotech, Italy*)  
 Prof. Seung Bum PARK (*Seoul National University, South Korea*)  
 Prof. Ian PATERSON (*University of Cambridge, United Kingdom*)  
 Dr Sherrie L. PIETRANICO-COLE (*Roche, United States*)  
 Dr Pierre RABOISSON (*Tibotec, Belgium*)  
 Dr Jeff REAGAN (*Amgen, United States*)  
 Dr Jean-Paul RENAUD (*NovAliX, France*)  
 Dr Juswinder SINGH (*Avila Therapeutics, United States*)  
 Prof. Scott SNYDER (*Columbia University, United States*)  
 Prof. Mikiko SODEOKA (*RIKEN (The Institute of Physical and Chemical Research), Japan*)  
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# Frontiers in Medicinal Chemistry



# FMC2011

STOCKHOLM SWEDEN  
JUNE 19-21 2011

Welcome to the 3<sup>rd</sup>  
**Frontiers in Medicinal Chemistry Meeting:**  
**Emerging Targets, Novel Candidates and Innovative Strategies**  
Stockholm, Sweden, June 19-21, 2011

The meeting is co-organized by the ACS, Division of Medicinal Chemistry,  
the European Federation for Medicinal Chemistry and the Swedish Academy of Pharmaceutical Sciences.  
It will bring together speakers from Scandinavia/Europe and USA that will share exciting new results  
and first time disclosures in several areas of drug discovery.  
Visit the website for more information.

[www.fmc2011.org](http://www.fmc2011.org)





## 31ST EDITION OF THE EUROPEAN SCHOOL OF MEDICINAL CHEMISTRY (ESMEC)

July 3-8, 2011  
Urbino, Italy  
[www.esmec.eu](http://www.esmec.eu)

The Division of Medicinal Chemistry of the Italian Chemical Society and the European Federation for Medicinal Chemistry organize in Urbino (Italy) the 31st edition of the European School of Medicinal Chemistry (ESMEC).

The mission of the ESMEC is to provide participants, PhD students and junior researchers from both academia and industry, with the most recent advances in the field of medicinal and organic chemistry, pharmacology, molecular biology and analytical/ structural chemistry. The School is directed to par-

ticipants at a graduated and post-graduated level, in chemistry but also in pharmacology or biology, who are keen to explore the interdisciplinary context of current cutting-edge research in medicinal chemistry.

This year the scientific program includes the following topics: Infectious Diseases; Bacterial and Mycobacterial Infections; The Problem of Bacterial Resistance; Protein-Protein Interactions in Drug Discovery; Organo- and Bio-catalysis in the Synthesis of Bioactive Compounds; Hot Topics.

EFMC is offering 3 free registrations to students from outside Italy. Applications should consist of a CV and a motivation letter, and should reach the Administrative Secretariat by May 20, 2011.

Please contact: [administration@efmc.info](mailto:administration@efmc.info).



## SECOND SUMMER SCHOOL ON "MEDICINAL CHEMISTRY IN DRUG DISCOVERY: THE PHARMA PERSPECTIVE"

### 2ND SUMMER SCHOOL ON "MEDICINAL CHEMISTRY IN DRUG DISCOVERY: THE PHARMA PERSPECTIVE"

June 26-29, 2011  
San Lorenzo de El Escorial, Madrid  
[www.seqt.org](http://www.seqt.org)

The second edition of the Summer School on "Medicinal Chemistry in Drug Discovery: The Pharma Perspective" is organized by the Spanish Society of Medicinal Chemistry (SEQT) and Janssen with the aim of approaching the pharma industry to young researchers, both graduate students and post-doctoral associates working in the chemistry and health sciences related fields. Fellowship applications for national and international attendants will be open soon. In the firstclass facilities of Euroforum (San Lorenzo de El Escorial, Madrid) and during three days, the participants will have the opportunity to learn about the latest research trends in pharmaceutical drug discovery and development illustrated through real case studies led by an exceptional panel of industry experts currently working at Almirall, Esteve, GlaxoSmithKline, Faes Farma, Janssen, Novartis and Pfizer.

#### Speakers

Dr. Mark Bunnage (Pfizer)  
Dr. José Cid (Janssen)  
Dr. Kristof van Emelen (Janssen)  
Dr. Jordi Gràcia (Almirall)  
Dr. Víctor Rubio (Faes Farma)  
Dr. Rob Young (GlaxoSmithKline)

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The **XXII<sup>nd</sup> International Symposium on Medicinal Chemistry** (EFMC-ISMC) will take place in Berlin, Germany on September 2-6, 2012 at the ESTREL Convention Centre. Please note that the date and location have changed since the original communication. This change was necessary due to time conflicts with other overlapping major activities in Berlin. EFMC – ISMC, which is internationally recognized as one of the leading Medicinal Chemistry meetings, will provide an international forum for presentations and discussions for leaders in Medicinal Chemistry. To find out more on the previous editions of ISMC and to follow the preparations of ISMC 2012, we invite you to visit the symposium website [www.ismc2012.org](http://www.ismc2012.org)

A large entry of young medicinal chemists answered the call for nominations for the second edition of the “EFMC Prize for a Young Medicinal Chemist in Industry” and the “EFMC Prize for a Young Medicinal Chemist in Academia”. The Selection Committees are very pleased to announce the names of the winners and the most meritorious runners-up.

#### **EFMC Prize for a Young Medicinal Chemist in Industry**

Alexander V. Mayweg, Roche, Switzerland  
Charlotte Mitchell, GSK, UK  
Sarah Skerratt, Pfizer, UK

#### **EFMC Prize for a Young Medicinal Chemist in Academia**

Christian Heinis, EPFL, Switzerland  
Constance Chollet, University of Leipzig, Germany  
Silvia Ortega-Gutiérrez, Universidad Complutense de Madrid, Spain  
The prizes are established to acknowledge and recognize an outstanding

young medicinal chemist ( $\leq 35$  years old) working in industry or in academia within Europe. The winners will be awarded at the 4<sup>th</sup> International Symposium on Advances in Medicinal Chemistry (ASMC) (St. Petersburg, August 21-25, 2011), where they will give a short presentation.

The third edition of the **EFMC Short Course** took place in April in The Netherlands and focused on “Principles and Applications of in vitro Pharmacology in Drug Discovery for Medicinal Chemists”. The Course was again fully booked, and both organisers and participants look back on a successful Course. The next Short Course, scheduled for December 7-9, 2011 will focus on Safety and Attrition. More information will soon be available on the website [www.efmc.info](http://www.efmc.info)

EFMC is offering 3 free registrations for the **European School of Chemistry (ESMEC)** to students from outside Italy. The School, accredited by EFMC, will take place on July 3-8, 2011 in Urbino, Italy. Applications should consist of a CV, a motivation letter and an abstract summarizing the research carried out during the doctorate (for abstract instructions, please visit the ESMEC website [www.esmec.eu](http://www.esmec.eu)). The abstract is a prerequisite for the poster that the students will present during the School. Applications should reach the Administrative Secretariat ([administration@efmc.info](mailto:administration@efmc.info)) by May 15, 2011.

EFMC is **funding grants** for EFMC organised events with the aim to support the participation of young academic scientists. Upon application, up to 50% of the registration fee for EFMC-ISMC, EFMC-

ASMC, Frontiers in Medicinal Chemistry, EFMC Short Courses or the EFMC Accredited School will be covered by EFMC. Applications should reach the Administrative Secretariat ([administration@efmc.info](mailto:administration@efmc.info)) at least six weeks prior to the event and should consist of a CV and a short motivation letter.

The session on “**Drug-Target Residence Time**” organised by EFMC at the ACS symposium in Anaheim on March 25, 2011 was a big success. About 500 participants attended the session with contributions from Robert Copeland, Koen Augustyns, Peter J. Tonge, Juswinder Singh, David Millan and Daniel Rauh.



## 4th Short Course on Medicinal Chemistry

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### SAFETY AND ATTRITION WORKSHOP

December 7-9, 2011

#### Organisers

Alan Stobie, *Pfizer*  
Henk Timmerman, *VU Amsterdam*

#### Deadline for registration

October 24, 2011

#### Venue

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

#### Fee

€ 1275,00  
Including 3 nights accommodation,  
breakfast, coffee breaks, lunches and  
dinners during the  
3 days of the conference.

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

#### Course Outline

The 4th EFMC Short Course on "Safety and Attrition" will be a repetition of the 2nd Short Course, organised in April 2010.

#### Contact

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EUROPEAN FEDERATION  
FOR MEDICINAL CHEMISTRY

# EFMC EVENTS

BY NELE COULIER AND KOEN AUGUSTYNS

## EFMC ORGANISED EVENTS

### FRONTIERS IN MEDICINAL CHEMISTRY MEETING: EMERGING TARGETS, NOVEL CANDIDATES AND INNOVATIVE STRATEGIES

June 19-21, 2011  
Stockholm, Sweden  
<http://www.fmc2011.org>

### 4TH INTERNATIONAL SYMPOSIUM ON ADVANCES IN SYNTHETIC AND MEDICINAL CHEMISTRY

August 21-25, 2011  
St-Petersburg, Russia  
<http://www.asmc11.org>

## EFMC SPONSORED EVENTS

### 12TH CONFERENCE ON ADVANCED MEDICINAL CHEMISTRY: "RATIONAL DRUG DESIGN AND DEVELOPMENT"

May 20-21, 2011  
Thessaloniki, Greece  
<http://camc2011.web.auth.gr>

### EFMC SPONSORED SESSION AT PHARMSCIFAIR 2011: "INNOVATIVE STRATEGIES TO COMBAT NEGLECTED DISEASES"

June 13-17, 2011  
Prague, Czech Republic  
<http://www.pharmscifair.org/>

### SEQT SECOND SUMMER SCHOOL ON MEDICINAL CHEMISTRY: "THE PHARMA PERSPECTIVE"

June 26-29, 2011  
Madrid, Spain  
<http://www.seqt.org/englinf/summer.asp>

### 4TH BBBB INTERNATIONAL CONFERENCE ON PHARMACEUTICAL SCIENCES

September 29-October 1, 2011  
Bled, Slovenia  
<http://www.bbbb-eufeps.org/>

### 29TH CYPRUS-NOORDWIJKERHOUT-CAMERINO SYMPOSIUM

October 2-7, 2011  
Limassol, Cyprus  
<http://www.quintessence.com.cy/index.php?link=trendsindrugs.php>

### ANNUAL ONE DAY MEETING ON MEDICINAL CHEMISTRY AT SRC & KVCV: "DRUG DESIGN AGAINST EMERGING TARGETS: OPPORTUNITIES AND CHALLENGES"

November 25, 2011  
Ghent, Belgium  
<http://www.ldorganisation.com>

### EFMC SPONSORED SESSION ON ONCOLOGY AT THE AFMC MEETING 2011

November 29-December 2, 2011  
Tokyo, Japan  
<http://www.aimecs11.org/>

### 19TH EUROQSAR KNOWLEDGE ENABLED LIGAND DESIGN

August 26-31, 2011  
Vienna, Austria  
[http://www.ldorganisation.com/produits.php?langue=english&cle\\_menu=1238915416](http://www.ldorganisation.com/produits.php?langue=english&cle_menu=1238915416)

## EFMC ACCREDITED SCHOOLS

### 31TH EDITION OF THE EUROPEAN SCHOOL OF MEDICINAL CHEMISTRY (ESMEC)

July 3-8, 2011  
Urbino, Italy  
<http://www.esmec.eu>

## EFMC SPONSORED SCHOOLS

### RESIDENTIAL SCHOOL: MEDICINAL CHEMISTRY 2011

July 4-8, 2011  
Loughborough, UK  
<http://www.rsc.org/ConferencesAndEvents/RSCEvents/MedChemTrainingSchool/index.asp>

### 6TH SUMMER SCHOOL ON DRUG DESIGN

September 11-16, 2011  
Vienna, Austria  
<http://summerschool.europin.at>

### SUMMER SCHOOL ON PHARMACEUTICAL ANALYSIS (SSPA)

September 19-21, 2011  
Pavia, Italy  
<http://chifar.unipv.it/sspa2011/>

### 20TH LACDR SCHOOL ON MEDICINAL CHEMISTRY

October 25-28, 2011  
Oegstgeest (near Leiden), The Netherlands  
<http://medchem.lacdr.gorlaeus.net/node/3039>

## 18th European Symposium on Quantitative Structure–Activity Relationships, Rhodes- Greece

BY ANNA TSANTILI-KAKOULIDOU

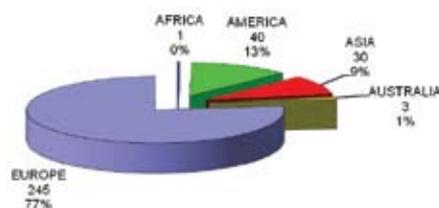
### REPORT

The 18th European Symposium on Quantitative Structure Activity Relationships took place in Rhodes, Greece, on 19-24 September, 2010. The venue was in RODOS PALACE INTERNATIONAL CONVENTION CENTRE. The Symposium was co-organized by the Hellenic Society of Medicinal Chemistry and the Cheminformatics and QSAR Society. The 18th EuroQSAR continued the uninterrupted tradition of holding bi-annual meetings in different European countries since 1973. For the first time the EuroQSAR Symposium was an EFMC sponsored event, in the intent to strengthen its relations with the medicinal chemistry community. In fact, throughout the years, the EuroQSAR meetings always took place in tight connection to the ISMC, usually with one week interval before or after it.

The Symposium has been a very successful event with outstanding speakers and high quality program, embracing the current challenges in the field of QSAR. 320 participants coming from 44 countries around the world (Figure 1) gathered together for 5 days under the sun and brightness of the island of Rhodes and created a vivid and motivating scientific environment and congenial atmosphere inside and outside the sessions and during the social events. Among the participants, 44% were from academia, 34% from Industry, and 22% were students (Figure 2). Moreover, the generosity of sponsors and exhibitors

was an important component for the success of the 18th EuroQSAR.

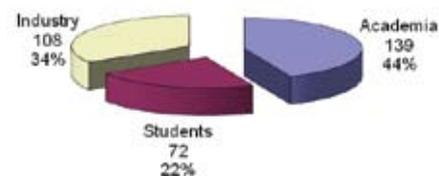
Since its early years (in the midst of '60s) the evolution of the QSAR field has seen remarkable growth, bringing together the latest ideas in chemistry, biology, mathematics, and computer science, in the aim to predict the biological behavior of compounds directly from their chemical structure and thereupon to support the efforts of the medicinal chemists to synthesize efficient drug candidates. The increasing appreciation and understanding of biological complexity and disease underlying causation, delineates the impact of informatics in all its aspects (cheminformatics, bio-informatics, pharmacoinformatics) in the achievement of this goal and this was reflected in the title of the Sympo-



sium "Discovery Informatics and Drug Design".

The Symposium started on Sunday afternoon, 19th September 2010, with the opening ceremony, led by the Chair, Prof. Anna Tsantili-Kakoulidou (University of Athens), the Co-Chair, Dr. Dimitris Agrafiotis (Johnson@Johnson) and the Chair of the Cheminformatics and QSAR Society, Prof. Tudor Oprea (University of New Mexico). Prof. Hugo Kubinyi followed with his inaugural lecture on 'The long road from QSAR to virtual screening.... to drugs', underlining the accomplishments of QSAR but also expressing a strong criticism in regard to its limitations and misuse. This starting point motivated fruitful discussions

during the next five days of the Symposium and stimulated the speakers to address the challenges, to defend the achievements and demonstrate the new avenues and perspectives in QSAR. The best practices for model selection and validation as well as the development of more accurate and representative molecular descriptors were among the topics addressed during the Symposium. Chemical space navigation, virtual screening, activity cliffs and scaffold effect exploitation in biological oriented synthesis were core highlights and were discussed as tools for ligand design and lead generation. Emphasis was further extended to multi-parameter drug optimization in order to balance potency, ADME, physico-chemical properties, and safety endpoints. In this aspect, the



key role of metabolism in drug efficacy and safety, *in silico* evaluation of protein binding and permeability, as well as modeling drug-transporter interactions were discussed in relevant sessions. The multi-target concept (expressed also by the term 'poly-pharmacology') was another dominant high spot, guiding the shift of the QSAR dream from the study of a single target to the consideration of a series of targets and anti-targets and from modeling of biological activity to multi-level modeling of complex relationships for the prediction of clinical outcomes. Observational data obtained through text mining of patient records and public sources may support the assessment of the *in silico* target profiling

and drug repurposing as suggested by some speakers. Predictive toxicology has its own position in addressing pre-competitive bottlenecks in pharmaceutical R&D and a number of lectures were devoted to this topic, emphasizing the challenge to translate from *in silico* predictions to *in vitro* to *in vivo* data. Next to drugs, the design of potent crop protection compounds constitutes an important issue, strongly related to the first steps of QSAR history. Computational Strategies in agrochemical research were discussed in a relevant session.

Summarizing the Symposium scientific program, there were 14 plenary lectures (+ the inaugural lecture), 6 keynote lectures and 36 oral presentations as well as 225 posters, divided in two poster sessions. Among the posters, four were selected as short oral communications and were presented in a young researchers forum. The authors received poster prizes, one sponsored by *Sunset Molecular*-1st prize, awarded to Dr. Juliana Cheliski from Brazil- and two by *Molecular Informatics/Wiley, Ltd* - one awarded to Dr. Andrea Volkamer from Germany and one shared between Dr. Sun Choi, Korea and Dr. George Lamprinidis, Greece.

In the frame of the Symposium, the Cheminformatics and QSAR Society meeting took place and the status of the Society and its future perspectives were discussed. In this meeting, chaired by Tudor Oprea, Dr Ismael Zamora was announced as the 2010 Hansch award recipient.

Selected papers presented in the Symposium appear in a EuroQSAR 2010 special issue of *Molecular Informatics* (Vol. 30, issue 2-3, 2011).

The *in silico* approaches have become more important than ever in reducing attrition rate and accelerating drug discovery and development and are currently implemented in many recent

calls for proposals by healthcare funding agencies. In this aspect, the 18<sup>th</sup> EuroQSAR Symposium made a significant contribution to the medicinal chemistry community, providing new ideas, new methodologies, and new ways of thinking by integrating a holistic multi-level view in ligand design, exploiting and rationalizing the maximum of the available vast information. Further to the impact of informatics in shaping the future avenues of QSAR, knowledge management is now emerging as particular critical to tackle this enormous increase in the size, complexity and noise level of the data sets. This issue was clearly outlined during the Symposium and in the closing round table discussion, thus, creating the bridge to the 19<sup>th</sup> EuroQSAR Symposium, entitled **Knowledge Enabled Ligand Design**, which will take place in **Vienna, August 26-31, 2012**.

Anna Tsantili-Kakoulidou  
Department of Pharmaceutical Chemistry  
School of Pharmacy, University of Athens  
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## Third EFMC Short Course

BY HENK TIMMERMAN



### REPORT

The third EFMC Short Course *Principles and Applications of in vitro pharmacology in Drug Discovery for Medicinal Chemists* has become a major success. From 10 to 13 April 45 participants came to the small castle Oud Poelgeest near Leiden in the Netherlands, which has become the venue for these courses.

Many aspects of modern *in vitro* pharmacology were handled by an enthusiastic teaching team of six, headed by Michael Trevethick. The participants rated both the teachers and the information they provided very high. The open interactive atmosphere was appreciated much. The including of break out sessions - tutorials with questions, problems from the preceding talks - was extremely successful. The availability of the teachers throughout the complete course was applauded by the participants.

The venue was at its best in a sunny period in this spring. Lots of flowers, pleasant temperatures. On one of the evenings all participants joined a guided walk through historical parts of Leiden, the birthplace of Rembrandt, the university "of" Van der Waals, the city from which the Pilgrim fathers departed towards the United States.

The EFMC thanks all teachers who contributed without asking for a fee; great!

The EFMC has decided to organize from 2011 on two short courses each year. The next course is scheduled for 7-9 December 2011