

MedChemWatch

The official EFMC e-newsletter

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EFMC

MedChemWatch

The official EFMC e-newsletter

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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,

this year 2012 is finishing and it is likely that most of the problem associated with the global economical crisis will be bequeath to the incoming 2013. The crisis is impacting many countries and many productive sectors. Big pharma and SME biotech are not an exception, and they are still finding new organisational set-ups and new market opportunities. Scientific excellence, risk propensity and open innovation will be among the keys to the success of the recovery. In this issue's Perspective, Sarah Skerratt and Ian Storer discuss on this topic, bringing up many thoughtful cues. Please remember that Perspective articles, as well as any other topic, is open to public discussion through the EFMC Linked In page. As one of the major stakeholder in the area, EFMC is also reacting to the changing scenario by finding new set-ups, in order to more efficiently cope with the needs of the member societies and of the community of medicinal chemists. Year 2012 has seen the 22nd ISMC, in Berlin, as the main event, which has witnessed a high scientific vivacity, but also the quest for an active participation especially from the younger colleagues. Next February, the EC of the EFMC will organize a workshop on the future of EFMC in the changing field of medicinal chemistry, gathering together EC and Committee and Council members, as well as young researchers who attended the dedicated events in Berlin. Our hope is that a new organisational set-up will come up from the workshop, with the aim of linking more and more the EFMC activity to the community needs. MedChemWatch and the EFMC web site (www.efmc.info) will be the channels where the news will be communicated.

By now, I have the pleasure, also on behalf of the Executive Committee and of its President, to wish you a happy, healthy and productive New Year!

Gabriele Costantino, *Editor of MedChem Watch*



The Changing Faces of MedChem

BY SARAH SKERRATT AND R. IAN STORER

Introduction to the modern and changing role of the medicinal chemist

The pharmaceutical industry has changed dramatically over the past years and with it the role of the Medicinal Chemist. The traditional “under one roof” approach to drug discovery has been replaced by the outsourcing of compound synthesis and biological screening to vendors worldwide in an effort to reduce costs, with the recent annual R&D expenditure across nine large companies being estimated to be a staggering \$60 billion, yet per year this investment has resulted in the approval of only 7 NMEs in total on average.¹

Numerous expensive Phase II failures have brought into ever sharper focus the need to pick the right, disease-relevant, targets. Indeed, a re-emphasis on assessing which targets/pathways deliver clinical efficacy has spurred numerous scientific advances from the Medicinal chemistry community. The traditional remit of the Medicinal Chemist solely delivering small drug-like molecules that are active against a target preselected by a Biologist is changing. Chemical biology and chemical genetics are coming to the fore as examples of Medicinal

Chemistry more proactively engaging in the exploratory stage of target validation. Recent advances in structural biology, computational chemistry and bioinformatics have also enabled advances in areas such as the design of safer molecules.

The diversity of compounds that medicinal chemists deliver is changing too. Target space is not always “rule-of-5 compatible” and a recent focus on the delivery of ligands that modulate a greater array of targets has fuelled an expansion of the chemical tool-box to include aptamers, chemically stabilized proteins, oligonucleotides, carbohydrates and macrocycles to name but a few. The desire to further deliver drugs in biologics space will almost certainly continue to drive innovation in “Beyond Rule of 5” chemical space.

Finally, the days when all of the science related to drug discovery was conducted behind closed doors are over. More than ever Pharma companies are partnering with external organizations (both academic and other Pharma/Bio-tech) to share knowledge and tap into specific expertise and technology lacking within in their portfolios. Working in these consortia, pre-competitive

or otherwise, provides an additional avenue of opportunity for Medicinal Chemistry to exert a greater influence on scientific agenda.

Recent advances and impact from chemical biology and structural biology

In the past decade there have been numerous scientific advances in the fields of computational science, protein crystallisation, structural biology and biophysics, particularly in the arena of membrane associated targets, driven by close association of Pharma and academia. This is now making binding site analysis and structure based drug design (SBDD) a realistic future goal across a wider range of target classes. With a more accurate assessment of binding site morphologies these advances could further broaden our concept of druggable target space. Parallels can conceivably be drawn with the field of kinases, which have transitioned from being regarded as largely undruggable to being relatively attractive targets in the space of a decade, largely educated by SBDD. Pharma companies and academic-industrial collaborations have already begun to harness the structural breakthroughs of the

last 5-years on G-protein coupled receptors (GPCRs) to not only access proteins X-ray, but to also generate protein-ligand co-crystals to guide the medicinal chemists as to binding site, binding mode and ultimately towards a better understanding of the protein dynamics of GPCR coupling.²

However, many therapeutically attractive protein targets and complexes remain beyond small molecule drug space. In fact, of the ~30,000 human genes identified it has been estimated that only around 10% of these encode proteins that are anticipated to be applicable for modulation using classical small molecule drugs.³ Accordingly, there has been increased attention on how we might disrupt these and the estimated 130k-650k distinct protein-protein interactions (PPIs) in the human body.⁴ Currently this area still presents a major challenge to medicinal chemistry, having traditionally been the domain of natural products, peptides, toxins and antibodies. As a result, there has been increased momentum to harness understanding of these molecular classes into a designing a greater diversity of smaller-molecule drug-like products.⁵ Medicinal chemistry has seen clear progress in this area in recent years via small molecules that leverage small molecule binding sites that either overlap with or allosterically disrupt PPIs, with examples including BRD4, LEDGF/p75 inhibitors.¹ An alternative approach has been to design scaffolds that mimic protein secondary structural elements but retain drug-like properties, including β -turn mimetics, α -helix mimetics such as stapled peptides, and macrocycles influenced by natural products. Furthermore, new phage display methods have also been developed to express very large arrays of novel small peptides and oligonu-

cleotides based around an approximate design template, thereby permitting rapid optimisation via phage display panning.⁶

Despite these ongoing improvements in the chemistry repertoire for more effectively tackling difficult targets, there is increased shared responsibility for medicinal chemists and biologists to work together to ensure that the correct targets are selected in the first instance, prior to initiating the full drug delivery process. Although there has been a drive to harness the advances in genetic and proteomic profiling of individuals who exhibit therapeutically relevant phenotypes, this approach is only likely to provide target evidence in a limited number of cases that proves compelling enough on its own to warrant a full program (eg CCR5 or NaV1.7). As a result, there is clearly a need to develop and apply other methods for target identification and validation. Traditionally this gap was bridged by chemistry delivering a small molecule tool to biologists to generate in vitro or in vivo rationale in preclinical species, operating in isolation. However, this approach can prove unsuccessful owing to either an incomplete understanding of a relatively poorly characterised tool or poorly understood relevance of many preclinical disease models. In response, medicinal chemists have started to make a much broader contribution to biology studies at the chemical biology interface, harnessing a variety of techniques to answer important biology questions. These include the application of chemogenomic compounds sets to deconvolute disease relevant phenotypic screening data and the application of chemical-based proteomics methods such as activity-based proteomic profiling (ABPP) or affinity based techniques to elucidate proteins and signalling

pathways in cell lysates or in a whole cell environment.⁷ Increasingly these are being used in conjunction with state-of-the-art quantitative mass spectrometry to enable the identification of members of multi-protein complexes, further enabling an understanding of the distinct protein complexes associated with diseased relative to healthy cells. This offers the opportunity to gain clarity around the behaviour of the initial target but to also potentially identify new targets relevant to the disease. Beyond the target identification, other chemical biology methods such as molecular imaging tools can be generated to highlight the location and expression levels of the target within specific tissues, further educating the program as to the necessary target compound profile. Furthermore, the tools from this phase of the exploratory decision-making process can also sometimes be reused or adapted to enable the drug discovery process in other ways such as markers of drug distribution or the development of preclinical occupancy biomarkers of target engagement.

Changes to the industry-academia interface

The majority of breakthroughs in target biology research have occurred in the academic environment and this has driven a change in the way that industry and academia have operated over recent years. However, the days of drug discovery companies providing significant funding to areas of research outside of their scientific focus have largely passed. Commensurate with this, there is increased incentive for genuine collaboration between academia and industry to find common scientific ground and work together to find solutions that benefit both parties. Through such partnerships a broader

array of research can be explored than if companies and academia work in isolation with co-proposals for external funding as well as in-kind sharing of ideas, infrastructure and materials becoming more commonplace. Although this in theory sounds, and is, a sensible goal, it is one that will likely to take time to fully deliver and will not be without pitfalls. The union of two historically quite different scientific groups driven by different goals and ideals will likely take time and require effort from both parties to build an open and trusting relationship. It will also be critical to identify and openly communicate areas of scientific need such that pre-competitive opportunities can be found and the results openly shared and published.

So where does MedChem fit into all of this? Well, in addition to requiring new compounds and technologies to tackle Protein-Protein interactions (PPIs) and other difficult targets, there is also an increased need to provide state-of-the-art tools to aid target identification and probe protein structure and function. Generally this work is early enough to be precompetitive making it an ideal area for collaboration with academia and consortia.

To date, a number of network groups have been established with the aim of fostering communication and driving innovative solutions to scientific problems facing the drug discovery industry. One such collaboration between academia and over 20 organizations has received joint investment from several research councils (EPSRC, BBSRC and MRC) to aid research and knowledge-sharing at the chemical biology interface. The drive of Pharma companies to become part of a fully integrated pharmaceutical network and to explore opportunities in Open Innovation is also becoming more evident. Lilly's Drug

Discovery (TargetD2) and Phenotypic Drug Discovery (PD2) programmes provide an array of primary assays and secondary assays to characterise the biological activity of compounds from external investigators. Roche have set up a collaborative scheme in which they provide a 100K library of diverse compounds for use at academic centres involved in new target research. Pfizer have set up a "Centers for Therapeutic Innovation" initiative which is dedicated to establishing global partnerships between itself and Academic Medical Centres to transform research and development through translational medicine. GlaxoSmithKline have recently opened the door to clinical data sharing with the release of more data from its clinical trials that could provide unprecedented opportunities to understand disease biology and drug effects. These examples are by no means comprehensive but go some way to illustrating some of the approaches to build productive links between industry and academia.

In addition, a number of precompetitive consortia have been formed to bridge between industry and academia with the aim of tackling some of the larger scientific themes. An example is the Structural Genomics Consortium based in both Toronto and Oxford in which academic groups and pharmaceutical companies are working together to develop genuinely useful probes for novel epigenetic targets that will be made openly accessible to the academic and industrial community. The aim is to help define the role of protein targets in disease systems and thus elucidate which of the targets in the epigenome have the most therapeutic potential. The first example probe to emerge from this consortium was the JQ-1 probe that supported the validation of bromo-

domain-containing protein 4 (BRD4) as a potential target for NUT midline carcinoma. Since then an array of new chemical probes and X-ray structures of additional epigenetic targets have been delivered and confirm the potential for this type of open innovation model. It is likely that other precompetitive consortia of this type will continue to emerge to cover additional areas of potential target space and it will be fascinating to see how such collaborative endeavours develop over the coming years.

Future perspectives

The pharmaceutical industry has changed dramatically over the past years and so with it the role of the Medicinal Chemist. No longer is our remit restricted to SAR generation and it is incumbent upon us to use our curiosity and innovation to deliver broader solutions across the drug discovery portfolio. Two things need happen to deliver a positive Phase III result; a compound must be safe and must be efficacious. The role of Medchem to drive and champion new technologies that predict and assess safety in the pre-clinical setting will become more and more essential in years to come as clinical failures due to safety are just not a business-viable option. The compound must also be efficacious requiring the target to be correct and the mechanistic horsepower sufficient to drive the desired biological response. Medicinal chemistry need to be part of the decision-making process when a biological target is selected and the data generated utilising chemical genetics or chemical biology probes should drive increased confidence in the target choices made. Scientific collaborations will become more commonplace between Pharma partners and academia and the role of consortia more prominent. The most

fruitful collaborations will be built on a shared vision, great science and the recognition that building partnerships can take a certain amount of time and patience. The role and extent of pre-competitive research will also become key as Pharma and academia alike work together up to and potentially including clinical Proof of Concept. This would mean both our scientific breakthroughs and disappointments could be shared communally and the same mistakes not made twice. It will be interesting to see the level of uptake of this new method of working and the solutions that are found to keep it profitable for all parties concerned.

It is both a challenging and exciting time for MedChem. New areas of science are opening up and we need to be at the forefront, alongside our Biology colleagues, to harness these opportunities and maximise our impact in the Drug Discovery world.

The opinions expressed in this article are entirely personal and do not reflect those of Pfizer.

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Pharma Plexus Holland a unique CRO

BY CHRIS KRUSE*



Big Pharma is in big trouble: over 200.000 jobs were already lost in the past decade.

When you are reading these numbers it does not really touch you, unless you are one of them. This is what happened to the researchers working in Weesp, the Netherlands in the former Solvay Pharmaceuticals laboratories. After the takeover by Abbott they heard the message in September 2010: all Research in Weesp will be stopped per April 1st 2011.

The management of the medicinal chemistry department (Chris Kruse and Bart van Steen) decided to start initiatives to safeguard the unique scientific know-how that belonged to the members of their research unit. Their collaborators have worked with great passion in the area of industrial drug discovery research for a large number years and it would be most regretful if this experience would get lost.

In shaping our new future we considered that the changing environment forces big Pharma companies to find other ways to reach their goals. Collaboration with academia as well as with small Biotech companies and with CRO's has become the new philosophy. Clearly this state of affairs should give us new opportunities. After comprehensive studies and nu-

merous discussions, also with Abbott Healthcare Products, we decided that our chance of success would be highest if we would establish a novel CRO in the area of multidisciplinary lead optimization. This focus was clearly seen as relevant for both big Pharma and for Biotech companies and represented a relatively unexplored niche amongst the present CRO's.

Next we looked for professional help, because setting-up and running a company was not our speciality. We were fortunate to find two new colleagues (Herman Helder and Melchior van Voorden) having experience in setting up new businesses in the Pharma field. The NIBC supported us by conducting all financial assessments.

The result was that we started our new company Pharma Plexus Holland in August 2011.

We would present ourselves as "your experienced partner in lead optimization being able to accelerate your preclinical research projects". This claim may sound somewhat bold, but we were convinced that it was justified based upon the long-standing experience of Pharma Plexus Holland staff with on average over 20 years in multidisciplinary lead optimization. This includes the central nervous system, recognized as the most difficult area in lead optimization. Our team has accomplished the completion of many drug discovery projects, leading to 15 clinical candidates in less than 10 years!

Quickly we could start with our first projects and we were able to offer a job to ca 20 people. They were delighted to be able to continue with their passion: turning hits and leads into molecules with optimized properties to advance into clinical trials. We started working in our former laboratories, but quickly



it became clear that moving to a Science Park environment was business-wise more beneficial for Pharma Plexus Holland. With the help of Abbott we settled our company in the Utrecht Science Park, where we could move into the former organic chemistry laboratories of Utrecht University.

After one year our dreams have become reality. A customer recently evaluated our activities with the following statements:

– “The Pharma Plexus team is composed of and led by true medicinal chemists and differentiates itself from other chemistry specific teams in their ability to contribute to design of targets. Moreover, PPH may be characterized by high level of synthetic chemistry skill, genuine scientific curiosity and passion for drug discovery.”

– “Expectations were high with this team and yet they exceeded in this area. The team possesses a high level of professionalism and made excellent use of the combined years of experience to deliver high impact novel molecules. Open communication and commitment to tasks made for a highly successful collaboration.”

– “This was not a routine project and Pharma Plexus succeeded where multiple other pharmaceutical teams have failed. This was in part due to the willingness of the team to focus on expanding our SAR understanding through preparation of impactful molecules rather than focusing on libraries of a single functional handle.”

Our customer honoured Pharma Plexus Holland with their award of “best external company”. During the awarding ceremony the client summarized the performance by the words: “Pharma Plexus succeeded to design the right compounds and to synthesize these novel complex molecules with an unprecedented high speed!”

What are the ingredients of innovative lead optimization and what is the basis of our success?

In our experience, the exchange of information between molecular biologists, medicinal chemists and pharmacologists is a key feature to run a drug discovery process efficiently and to meet all requirements of a drug candidate. Close interaction between experts will result in the ability to tackle the right problems at the right point in time.

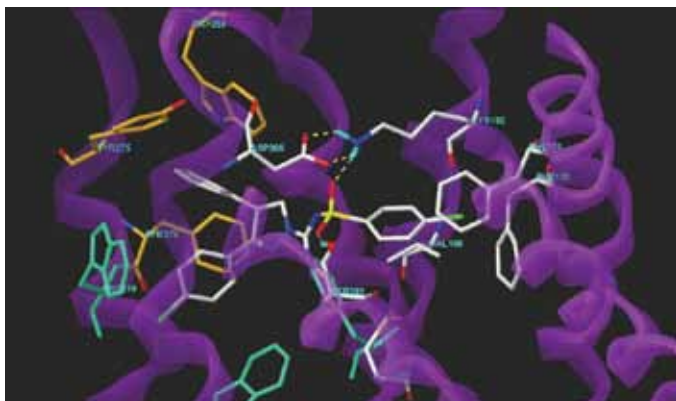
An integrated and multidisciplinary approach requires mobilizing a professional team of medicinal chemists, including designers and synthetically as well as analytically skilled experts, and stimulating strong cooperation between these disciplines. Each expert has his/her own specialism, but they all understand each other; they all speak the language of potential drug-like molecules. In practice we follow a fully integrated approach where all aspects of medicinal chemistry and drug optimization perfectly link up with each other: studying existing knowledge, interpreting produced data, determining relevant parameters, drawing up optimization schemes, designing molecular structures, synthesizing compounds and evaluating their pharmacodynamic as well as their pharmacokinetic potential.

Each optimization project requires a tailored approach with its own dynamic flow chart, comprising an optimizing schedule that may consist of several different parameters to be optimized based on the available information. Our experienced medicinal chemists know what pitfalls can be expected during the optimizing project. They are able to adjust their strategy and to avoid the wrong choices.

Except of the well-known pharmacodynamic parameters such as target affinity, target activity and target selectivity,

which often are given high priority, there are numerous other parameters that are at least as important. For instance intrinsic physicochemical properties such as solubility or lipophilicity and pharmacokinetic issues like metabolic stability, membrane permeability and the presence of free fractions in plasma and brain. In practice, however, optimization of these many different parameters may lead to contradictory demands to the molecular structure.

An essential element for any candidate drug is to secure the intellectual property through patenting. It plays a vital role already at the start of lead optimization. Our scientists with extensive experience in the pharmaceutical industry are well skilled in this field to understand the importance of patentability and to advise about optimal timing of patent applications. Moreover we as a CRO do not claim any intellectual property: all the results belong to the client.



Box/kader

Significantly better lead compound

The question: Optimizing an enzyme inhibitor lead compound that owes its high target affinity to two carboxylic groups

The facts: Affinity screening tests obviously showed the necessity of two carboxylic groups. By deleting one of these functional groups results affinity was lowered dramatically. Unfortunately, however, the presence of two carboxyl groups leads to poor membrane penetration and consequently to low bioavailability.

Usual approach: All initial efforts focused on chemical modification to improve membrane permeability without any concession to the carboxylic groups; they both should be preserved. Such chemical modification may include: temporary masking one of the carboxylic groups or replacing one carboxylic group by a bioisosteric group. These proposed chemi-

cal modifications typically result from a one dimensional optimisation approach: only optimising in the direction of target affinity. The result of this approach proved to be highly potent molecules with a bioavailability of less than 1%.

Our solution: We envisaged that a multidimensional optimisation approach taking into account both affinity and bioavailability would be the preferred way to go. We started by thoroughly studying the receptor, in this case the active site of the enzyme. This approach led to the insight we found an additional point of interaction in the active enzyme site. Then we replaced one of the two carboxylic groups by a functional group that exactly fits the third active site. It resulted in a significantly better compound with a somewhat lower affinity but with a bioavailability of at least 80%!

Box/kader

GPCR ligand without a basic N: alternative binding mode

The question: Finding a highly selective GPCR lead compound

The facts: In recent decades the G-Protein Coupled Receptors (GPCRs) have extensively been investigated. For decades ligands for these targets have been a rich source of new drugs for the pharmaceutical industry. The existing paradigm was that a vital molecular request for these drugs is the presence of a basic nitrogen atom in the molecular structure.

Our solution: We performed a high throughput screening and discovered a number of weak hits that did not contain the basic nitrogen atom. Despite the existing paradigm we decided to look for opportunities to optimize these hits and discovered an alternative binding motive that resulted in equipotent molecules. These compounds showed an unprecedented selectivity for other GPCR's and for a number of safety-related targets. The resulting optimized molecule is currently in phase II clinical studies!

*Director Business Development / Scientific Advisor

WINNER OF THE EFMC PRIZE FOR A YOUNG MEDICINAL CHEMIST IN INDUSTRY

Sharan K. Bagal



Dr. Sharan K. Bagal (1978) graduated with first class honours in MChem in 2001 from the University of Oxford, U.K. where she subsequently completed her DPhil in chemistry in 2004 under the supervision of Professor Sir Jack Baldwin and Dr. Robert Adlington. Her doctorate was based on biomimetic natural product synthesis, in particular, the first total synthesis of two natural products biatractylolide and biepiasterolide via a biomimetic radical dimerisation. Sharan then moved to Professor Samir Zard's group at the École Polytechnique in France as a postdoctoral researcher studying xanthate-based radical chemistry. This work led to the development of a novel acyl radical equivalent, along with a facile method for the generation of radicals from aldehydes.

In 2006 Sharan joined Pfizer Global Research and Development, Sandwich, UK as a medicinal chemist (www.pfizer.com), and is now a Senior Principal Medicinal Chemist at Pfizer Neusentis in Cambridge, UK (www.neusentis.com) with a focus on drug discovery targets for the treatment of pain. Sharan's research interests encompass all aspects of medicinal chemistry and she has worked on several drug discovery targets including voltage-gated ion channels, GPCRs and protein kinases e.g. NaV1.8 and CXCR1/2. This work has used ligand-based medicinal chemistry design methods to identify potent and selective ion channel modulators within highly challenging medicinal chemistry space, and highly potent chemokine receptor antagonists with a balanced subtype selectivity profile. More recently, Sharan has used structure-based design methodology to successfully design highly potent receptor tyrosine kinase inhibitors

with excellent selectivity and a favourable tissue distribution profile. Her focus has ranged from hit identification, hit to lead optimisation and candidate selection and Sharan has been directly involved in the invention of two compounds currently undergoing clinical trials.

So far over her career, Sharan has co-authored more than 20 papers and patents. She has a particular interest in aldehyde oxidase (AO) catalysed metabolism, in particular the structural aspects that underpin substrate recognition by AO and the role played by both steric and electronic effects of susceptible ring systems. She has developed several datasets that inform how structural features relate to species-specific metabolism by AO, and hypotheses of how this metabolism can be switched off by design. Sharan has also developed an interest in the design of compounds that penetrate, or are restricted from, the central nervous system (CNS) based on an understanding of CNS-located transporters and compound physicochemistry and the implications of CNS distribution on drug safety. She has delivered several reviews and presentations in this area.

WINNER OF THE EFMC PRIZE FOR A YOUNG RESEARCHER IN ACADEMIA

Stuart Conway



The interface of chemistry and biology, whether it be medicinal chemistry or chemical biology

My interest in biological and medicinal chemistry stems from undergraduate studies at the University of Warwick, where I read for a degree in Chemistry with Medicinal Chemistry (1994-1997). Summer placements at SmithKline Beecham (Worthing) and Unilever (Sharnbrook) were my first experience of a research environment and provided an early indica-

tion that this was a path I wished to pursue. During this time, a medicinal chemistry course, taught by visiting professor Roger Newton (Glaxo Wellcome), caught my imagination and I became interested in the idea of designing small molecules that have a certain effect on a biological system. This interest, coupled with the enjoyment of my final year project in the lab of Dr Andrew Clarke, led me to undertake a PhD. I moved to the University of Bristol to work in the lab of Prof. Jeff Watkins FRS and Prof. David Jane (1997-2000). Although my role was predominantly that of a synthetic chemist, the group was in the Department of Pharmacology and consequently research was carried out in an inherently multidisciplinary environment. My project was funded by Eli Lilly (Windlesham) and focused on the development of selective antagonists for the G-protein-coupled group III metabotropic glutamate receptors (mGluRs). From a scientific perspective, this work resulted in the most selective group III mGluR antagonists at the time.¹ I enjoyed working in an environment where the compounds that I had synthesised were rapidly evaluated and iterative cycles of synthesis and design were possible. Following my PhD, I moved back to a chemistry department to work in the group of Prof. Andrew Holmes FRS at the University of Cambridge (2001-2003). My research now focused on intracellular, rather than extracellular, signalling molecules with the aim being to make derivatives of the second messenger d-myo-inositol 1,4,5-trisphosphate (InsP₃) and the variously phosphorylated phosphatidylinositol phosphates (PIPs). This work was again, collaborative and multidisciplinary, working with the groups of Dr Martin Bootman and Drs Len Stephens and Phil Hawkins at the Babraham Institute. My time at Cambridge in the Holmes group reinforced my interest in not just making molecules, but employing synthetic organic chemistry as a powerful tool to study biology. In 2003 I began my independent research career as a Lecturer in Bioorganic Chemistry at the University of St Andrews. Since this time my research has focused on harnessing organic chemistry to develop probes for biological systems.

Chemistry illuminating biology – developing small molecule probes for biological systems

Although it is comparatively recently that a more collaborative approach between the pharmaceutical industry and academia has become common, I have long held the view that academia has a key role to play in therapeutic target identification and validation, and in the development of molecular tools to study biological systems. Most of the work conducted in my group is aimed at employing synthetic chemistry to enable biological

experiments or solve biological problems. I have retained an interest in inositol-based signalling molecules with a key aim being the development of antagonists for the InsP₃ receptors (InsP₃Rs). Despite significant advances in InsP₃-related biology, the pharmacology of these key receptors is relatively under-developed. We have systematically evaluated the effect of substituting the 4- and 5-position phosphate groups of InsP₃ with phosphate bioisosteres.^{2,3} This approach led to successful development of some inositol-based antagonists of InsP₃Rs,³ but there is still a lack of membrane permeant tool compounds for these fundamental receptors. Another project that I started early in my independent career is the development of light-activated (caged) molecular tools. Although unlikely ever to be a delivery tool *in vivo*, these compounds allow exquisite temporal and spatial control over the release of biologically active compounds *in vitro*. In particular our development of a wavelength-orthogonal system, in collaboration with Prof. Nigel Emptage, in which the release of the neurotransmitters GABA and glutamate was placed under the control of different colours of light, has many exciting applications.⁴ A collaboration with Prof. Ian Booth at the University of Aberdeen has led to an interest in the bacterial potassium efflux system, Kef. With Ian and Prof. Tarmo Roosild, we have been involved in elucidating the molecular mechanism of Kef gating by glutathione and its derivatives.⁵ This knowledge will allow us to design small molecules that are able to activate and inhibit the Kef system, a project that is on going within the group.

In 2008 my research group and I moved to the Department of Chemistry at the University of Oxford. The strong biological and medical science departments at Oxford have allowed me to develop a number of very exciting and productive collaborations. These projects include work on hypoxia-activated compounds with Dr Ester Hammond, work on Ca²⁺ signalling with Prof. Antony Galione and research on tumour imaging with Dr Ahmed Ahmed. Our interaction with the Structural Genomics Consortium (SGC, <http://www.thesgc.org>) was initiated by Dr Tom Heightman and Prof. Stefan Knapp and continues with Dr Paul Brennan. This collaboration has focused on the general area of epigenetics,⁶ and in particular on the development of small molecule probes for the acetyllysine-binding bromodomains.^{7,8} Epigenetics deals with heritable changes in gene expression or phenotype that are stable between cell divisions (and sometimes generations) but do not involve changes in the underlying DNA sequence of the organism.⁹ Epigenetic modifications include both methylation of DNA and post-translational modification (PTM) of pro-

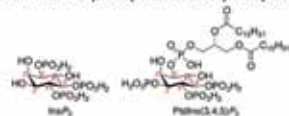
teins, including histones. Lysine acetylation is an important protein PTM, which is effected by histone acetyltransferases (HATs), removed by histone deacetylases (HDACs) and is recognised or “read” by bromodomains. In collaboration with the SGC, we have developed a range of compounds that bind to bromodomains and inhibit their interaction with acetylated lysine (KAc).^{9,10} This project started with work towards assay development identifying N-methyl-2-pyrrolidone (NMP) as a small and ligand-efficient fragment that binds to the CREB binding protein (CREBBP) bromodomain.¹¹ The ultimately led to the identification of the 3,5-dimethylisoxazole moiety as an effective KAc mimic and the development a range of bromodomain inhibitors based on this group. This work has mainly employed the structure-based design approach and, in addition to developing compounds that are potentially useful tools to study the bromodomains, we have learnt some fundamental information about the structure of the bromodomains, particularly about the role of some crystallographically-observed water molecules. We aim to employ this knowledge to further develop small molecules that are able to selectively prevent the interaction of a given bromodomain with its KAc-containing binding partner. By developing small molecule probes for these exciting targets we hope to further stimulate interest and research in this area.

The projects described above exemplify the approaches taken in the group and our core interests. I am excited about continuing to work on the chemistry-biology interface and I hope to further engage with the pharmaceutical sector in collaborative projects. I would like to thank all of my collaborators for making our interdisciplinary projects great fun to work on. I am deeply grateful to members of my research group, both past and present, who have successfully converted ideas that are formulated on a whiteboard in my office into physical reality in the lab.

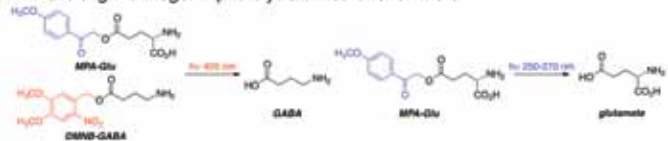
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A. Inositol phosphates and phosphatidylinositol phosphates



B. Wavelength orthogonal photolysis of neurotransmitters



C. Development of bromodomain inhibitors

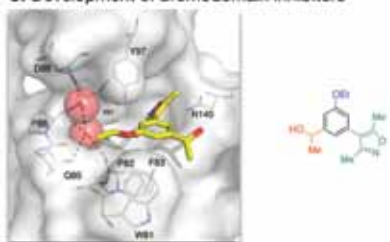


Figure 1. Examples of the molecules under investigation in the Conway group.

News from the Societies

BY ERDEN BANOGLU

THE BIOLOGICAL AND MEDICINAL CHEMISTRY SECTOR (BMCS) OF THE ROYAL SOCIETY OF CHEMISTRY (RSC)

1st AGRI-science Chemical Biology Postgraduate Symposium
8 November 2012, Imperial College, London

The 1st Agri-science Chemical Biology Postgraduate Symposium was hosted by The Biological and Medicinal Chemistry Sector of the RSC and The Chemical Biology Interface Division of the RSC in partnership with AGRI-net, BAYER Crop Science, Syngenta and the Biochemical Society.

The theme of the meeting was Agri-science Chemical Biology. Chemical Biology in this context was referring to physical sciences tools and technologies (in Chemistry, Physics, Mathematics, Engineering) which were applied to tackle biological problems in the agri-sciences, on a molecular level. This conference brought together PhD and postdoctoral students from these different research communities to showcase the current state of fungal, insect and plant chemical biology achievements within a spirit of multidisciplinary interaction and engagement.

For more information and photos of the prize-winners, please go to <http://www.agri-net.net/news/agri-science-chemical-biology-postgraduate-symposium>

Join AGRI-net today! AGRI-net welcomes all interested scientists working in either

academia or industry along with policy makers from government agencies. Membership is free and gives access to our networking area, where you can meet and interact with other members. It will also enable you to take part in our meetings, conferences and creativity events and apply for seed funding to support collaborative ideas

SOCIÉTÉ ROYALE DE CHIMIE (SRC), MEDICINAL CHEMISTRY DIVISION

MedChem 2012
Annual SRC & KVCV Symposium on Medicinal Chemistry

The annual Belgian Medicinal Chemistry Symposium, co-organized by SRC and KVCV, took place at Château de Colonster, University of Liège, on November 30. It attracted about 170 participants, half from Belgium and half from abroad, half from academia and half from industry – a well-balanced attendance, and a witness of the timeliness of the symposium theme “From Rapid Dissociation to Irreversible Inhibition - Optimisation of Drug-Target Residence Time”.

Indeed, earlier this year the European Union selected a consortium, called “K4DD” and led by Bayer and Leiden University to pave the way for ‘optimizing binding kinetics’. It is a major strategic project and part of IMI, the Innovative Medicines Initiative, a joint undertaking between the European Union and the pharmaceutical industry association EFPIA, and Europe’s largest

public-private initiative aiming to speed up the development of better and safer medicines for patients (see also <http://www.imi.europa.eu/content/ongoing-projects>).

Prof Ad IJzerman, from Leiden University, one of the coordinators of this consortium, chaired the meeting, which covered the entire range of interactions between a ligand and its target, from rapid dissociation to irreversible inhibition, and included six invited lectures, three oral communications and a poster session. A variety of targets were discussed and addressed, from G protein-coupled receptors to proteases, from kinases to phosphorylases. Further emphasis was on the development of suitable screening assays, also with the aim to move towards higher-throughput screening formats.

The presentations were followed by lively Q&A sessions, highlighting again the interest of the participants in an area which has so far been underestimated in drug discovery.

For more information on the programme, see www.medchem.be.

EFMC NEWS & EVENTS

BY NELE COULIER AND KOEN AUGUSTYNS



EFMC | ISMC
2012

With more than 1.270 scientists coming from 52 nations, the XXIInd International Symposium on Medicinal Chemistry (EFMC-ISM 2012), held at the Berlin Estrel Hotel & Convention Center from September 2-6, 2012, has been a very successful symposium with a diverse and high quality programme.

ISM 2012 was jointly organised by the German Chemical Society (GDCh) Division of Medicinal Chemistry and the German Pharmaceutical Society (DPhG) Section of Pharmaceutical/Medicinal Chemistry, on behalf of the European Federation for Medicinal Chemistry (EFMC).

The Opening Ceremony, led by Bernd Clement (Kiel University) and Eckhard Ottow (Bayer Healthcare), symposium chairmen, and Hans Ulrich Stilz (Sanoﬁ), EFMC President, was the start of a five day symposium with many scientific highlights. The organisers are very pleased to have reached the main objective of creating a major scientific event for Medicinal Chemistry in Europe, with about 100 expert speakers, 500 poster presentations, 50 exhibitors and 30 sponsors.

The next edition of this biennial symposium will take place on September 7-11, 2014 in Lisbon, Portugal and will

be organised by the Group of Medicinal Chemistry of the Portuguese Chemical Society. ISM 2014 will continue the tradition of the ISM symposia to create an international platform where scientists from all over the world meet and exchange their view and ideas. The first details can be found on the regularly updated website www.ismc2014.org

At the annual EFMC Council meeting held in Berlin on occasion of ISM 2012, it has been decided that ISM 2016 will take place in Manchester, UK, organised by the Biological and Medicinal Chemistry Sector (BMCS) of the Royal Society of Chemistry (RSC), on behalf of EFMC.

At the Council meeting, the EFMC Council elected Jordi Gracia (Almirall, Spain) as new member of the Executive Committee. Hein Coolen, EC member since January 2011, has been elected as successor of Rasmus Clausen, who served as EFMC Treasurer during the past 6 years. Koen Augustyns and Gabriele Costantino have been reelected respectively as Secretary and as EC member.

THE EFMC PRIZE

To acknowledge and recognize an outstanding young medicinal chemist (<35 years old) working in industry or in academia within Europe, EFMC established the EFMC Prize for a Young Medicinal Chemist in Industry and the EFMC Prize for a Young Medicinal Chemist in Academia. The Prizes consist of a diploma,

€ 1.000 and an invitation for a short presentation at the upcoming 5th EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry (ASMC13), May 5-8, 2013, Moscow, Russia. Deadline for nominations/applications is January 31, 2013. More information is available on www.efmc.info



The publication of the 11th edition of the EFMC Yearbook is scheduled for January 2013. The Yearbook will be distributed electronically to all members of the EFMC database, as well as to the members of the National Adhering Organisations (25 scientific organisations from 23 European countries). In addition, hard copies of the EFMC Yearbook will be distributed at all scientific meetings organised or sponsored by EFMC. If you would like to receive the electronic version of the EFMC Yearbook 2013, we invite you to register via the EFMC website www.efmc.info

In the upcoming year, EFMC will co-organize two international meetings to encourage contacts and exchanges between medicinal chemists in Europe and around the world. The 5th International

Symposium on Advances in Synthetic and Medicinal Chemistry (ASMC13) is scheduled to be held on May 5-8, 2013 in Moscow, Russia. The program, put together by Peter Seeberger (Max Planck Institute) and Alan Palkowitz (Eli Lilly), will cover topics including New Synthetic Methodologies, Total Synthesis of Natural Products, Heterocyclic Chemistry, as well as Medicinal Chemistry and Drug Discovery & Development. The list of confirmed speakers to date is available on the website www.asmc2013.org and registration already opened!

In 2013 EFMC and the ACS MediDivision will also be jointly organizing the fourth edition of the Frontiers in Medicinal Chemistry Meeting, to be held in San Francisco from Sunday, June 23 to Wednesday, 26, 2013. This symposium is the fourth in the series initiated in Siena in 2007 and continued in Barcelona in 2009 and Stockholm in 2011. The theme of this year's meeting is Emerging Targets, Novel Candidates and Innovative Strategies. More information will soon be available on www.efmc.info

With the aim to support training and networking within the medicinal chemistry community, EFMC is organising twice a year EFMC Short Courses on Medicinal Chemistry. In October 2012, Kevin Beaumont organized an interesting Course on "Improving Compound Quality: Physical Chemistry and DMPK Properties in Drug Discovery. Principles, Assays and Predictions". The Spring

2013 Short Course is planned for April 21-24, 2013. Topic will be «Principles of Molecular Recognition» and the programme will be put together by Andrew Leach (University of Liverpool) and George Keseru (Gedeon Richter).

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 (Urbino) will be covered by EFMC. Furthermore, in collaboration with Roche, EFMC is also funding the EFMC-Roche Studentships. More information is available on the website www.efmc.info

EFMC ORGANISED EVENTS

EFMC Short Course on Medicinal Chemistry: "Principles of Molecular Recognition"

April 21-24, 2013
Oegstgeest (near Leiden),
The Netherlands
www.efmc.info

5th International Symposium on Advances in Synthetic and Medicinal Chemistry (ASMC 2013)

May 5-8, 2013
Moscow, Russia
www.asmc2013.org

Frontiers in Medicinal Chemistry: Emerging Targets, Novel Candidates and Innovative Strategies

June 23-26, 2013
San Francisco, USA
www.efmc.info

EFMC SPONSORED EVENTS

EFMC Sponsored Session on "Global Health Challenges: The Need for New Anti-infectives and Antivirals" at ACS Spring Meeting 2013

April 7, 2013, New Orleans, US

31th Camerino-Cyprus-Noordwijkerhout Symposium

May 19-23, 2013, Camerino, Italy
<http://www.unicam.it/farmacia/symposium/Welcome.htm>

6th Anglo-Swedish Medicinal Chemistry Symposium

June 16-19, 2013
Stockholm, Sweden <http://www.lakemedelsakademin.se/templates/kurs/kurstillfalle.aspx?kld=5061&id=5062>

VIIIth Joint Meeting on Medicinal Chemistry (JMMC)

June 30 - July 4, 2013
Lublin, Poland

XXIInd National Meeting on Medicinal Chemistry

July 2013
Roma, Italy
<http://w3.uniroma1.it/nmmc2013/#>

ASMC MOSCOW 13

www.asmc2013.org

International Symposium on
Advances in Synthetic
and Medicinal Chemistry

May 5-8, 2013
Moscow, Russia

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Dr Alan PALKOWITZ (Eli Lilly & Co., USA)

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Simona COTESTA (Novartis, Switzerland)
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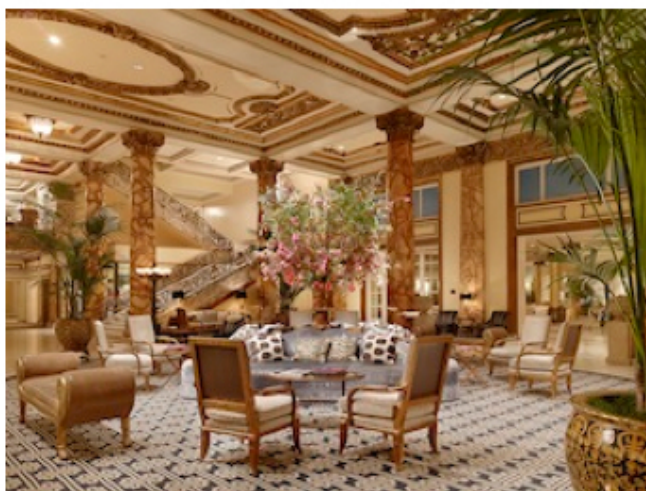
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Dear Colleagues,

On behalf of the organizing and scientific committees, we would like to invite you to participate in the Frontiers in Medicinal Chemistry Symposium, to be held in San Francisco, CA, USA from Sunday, June 23 to Wednesday, 26, 2013. This symposium is the fourth in the series initiated in Siena, Italy in 2007 and continued in Barcelona, Spain in 2009 and Stockholm, Sweden in 2011. The theme of this year's meeting is Emerging Targets, Novel Candidates and Innovative Strategies. The meeting is co-organized by the European Federation of Medicinal Chemistry and the American Chemical Society Division of Medicinal Chemistry. It is intended to bring scientists working in the medicinal chemistry field together in order to share new and exciting results and we encourage attendees to bring poster presentations. San Francisco provides a picturesque backdrop for this exciting conference, and we know you will have a scientifically rewarding and enjoyable stay.



Frontiers 2013 will take place in the historic Fairmont Hotel, located at 950 Mason St. on Nob Hill, in the heart of San Francisco. Central to the Financial District, Union Square, the Embarcadero and Fisherman's Wharf, the Fairmont Hotel is located at the only spot in San Francisco where each of the City's cable car lines meet.

The scientific program for Frontiers 2013 will feature a plenary session, followed by sessions covering the latest advances in medicinal chemistry. Session topic areas include:

Antiviral Drug Design
Advances in the Treatment of Inflammation
Molecular Imaging, Biomarkers & Translational Research
Oncology
Antibody/Drug Conjugates
Molecular Modeling and Structure-Based Design
Emerging Topics

Registration site opens December 17, 2012: <http://wizard.musc.edu/frontiers2013.html>

Frontiers in Medicinal Chemistry is jointly sponsored by the ACS Division of Medicinal Chemistry and the European Federation of Medicinal Chemistry



7th EFMC Short Course on Medicinal Chemistry – Spring 2013

PRINCIPLES OF MOLECULAR RECOGNITION

Course Organisers

George Keseru, *Gedeon Richter, HU*
Andrew Leach, *John Moores University, UK*

Local Organiser

Henk Timmerman, *VU University Amsterdam, NL*

Deadline for preregistration

March 22, 2013

Venue

Castle "Oud Poelgeest", Oegstgeest
(near Leiden), The Netherlands

Airport: Schiphol, Amsterdam

Fee

€ 1475,00 – Including accommodation,
breakfast, coffee breaks, lunches and dinners
during the 3 days of the conference.

Contact

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1348 Louvain-la-Neuve, Belgium
Tel: +32 10 45 47 74 Fax: +32 10 45 97 19
Mail: administration@efmc.info
Web: www.efmcshortcourses.org

April 21-24, 2013

Oegstgeest, near Leiden, The Netherlands

This intensive course is intended for scientists working in the field, and the number of participants will be limited to 35 to favour in depth discussion. The various presentations and tutorials will be taken by experts in the field who will present a broad historical perspective as well as cutting edge research from both academia and industrial settings. The course will take an informal approach and ought to prompt plenty of discussion among participants.

Course Outline

The interactions between molecules govern all of the properties that determine whether a compound will be an effective drug or not. This course will present the fundamental considerations determining the thermodynamic and kinetic properties of interactions between molecules. The first part of the course will begin with an introduction to the types of interactions that are usually considered important for drug-like compounds, including some of the less commonly considered weaker interaction types. The second part of the course will focus on applied aspects. This will take two forms: detailed presentations considering most key molecular properties and some hands on tutorial exercises. Both will be structured around real life case studies taken from the literature and the presenters' own experience.



EUROPEAN FEDERATION
FOR MEDICINAL CHEMISTRY

THE EFMC PRIZE

FOR A YOUNG MEDICINAL CHEMIST IN ACADEMIA

To acknowledge and recognize an outstanding young medicinal chemist (≤ 35 years old) working in Academia within Europe.

The **Prize** is given annually and consists of a diploma, €1.000 and an invitation to give a short presentation at the 5th EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry (ASMC13), May 5-8, 2013, Moscow, Russia.

Two additional nominees will also be identified and acknowledged.

Applications should be done via the application form on www.efmc.info and should consist of:

- a one-page letter by the candidate including a short rationale for their application
- one page with his/her 5 most important publications
- a brief cv of the candidate
- abstract of potential oral presentation

THE EFMC PRIZE

FOR A YOUNG MEDICINAL CHEMIST IN INDUSTRY

To acknowledge and recognize an outstanding young medicinal chemist (≤ 35 years old) working in industry within Europe.

The **Prize** is given annually and consists of a diploma, €1.000 and an invitation to give a short presentation at the 5th EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry (ASMC13), May 5-8, 2013, Moscow, Russia.

Two additional nominees will also be identified and acknowledged.

Nominations should be submitted by the candidate's supervisor via the submission form on www.efmc.info and should consist of:

- a letter by the supervisor
- a brief cv of the candidate
- abstract of potential oral presentation

Deadline for Nominations is January 31, 2013



EFMC
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for Medicinal Chemistry

See www.efmc.info for full details.