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SCS Division of Medicinal Chemistry

Conference Report

Frontiers in Medicinal Chemistry – Joint German-Swiss Meeting on Medicinal Chemistry

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Abstract: 'Frontiers in Medicinal Chemistry 2009' was organized as a joint German-Swiss meeting at the University of Heidelberg. It covered the areas of kinases and nuclear hormone receptors, inflammatory diseases, atherosclerosis and neuropsychiatry. Special sessions were dedicated to new technologies in nanomedicine, proteomics and drug targeting. A session on highlights in medicinal chemistry completed the program. The lectures covered a broad range of interdisciplinary topics including molecular design and lead optimization programs, development and application of new technologies in proteomics, drug delivery & chemical synthesis.

Keywords: Atherosclerosis · Drug targeting · Highlights in medicinal chemistry · Inflammatory diseases · Kinases · Nanomedicine · Neuropsychiatry · New technologies · Nuclear hormone receptors · Proteomics

The Event

This congress was the fourth joint German-Swiss Medicinal Chemistry Meeting following those in Berlin (2007), Basel (1999) and Freiburg i. Br. (1987). It was organized jointly by the Medicinal Chemistry Division of the Gesellschaft Deutscher Chemiker (GDCh), chaired by Dr. *H. U. Stilz*, the Division of Pharmaceutical/Medicinal Chemistry of the Deutsche Pharmazeutische Gesellschaft (DPhG), chaired by Prof. *P. Gmeiner*, and the Division of Medicinal Chemistry of the Swiss Chemical Society, chaired by Dr. *H. P. Märki*. It took place at the University of Heidelberg and was hosted by Prof. *C. Klein* who chaired the scientific committee. About 200 participants gathered in Heidelberg. The scientific program included over 30 lectures and about 60 posters spanning a range of recent developments and trends in the fields of target families, kinases and nuclear hormone receptors, inflammatory diseases and atherosclerosis, neuropsychiatry, new technologies, drug proteomics and other highlights in medicinal chemistry. The welcome addresses were given by Prof. *A. Jäschke* (Vice President, Univ. of Heidelberg), Prof. *C. Klein,* and Dr. *H. P. Märki*.

Dr. Märki and Dr. Stilz

Opening Lecture

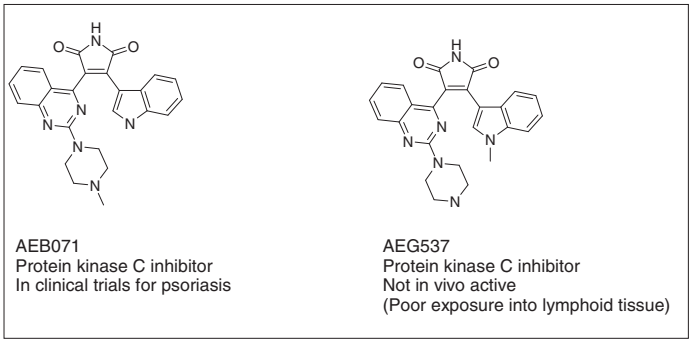
The opening lecture on 'Personalized Health Care: Opportunities and Challenges' was given by Prof. ***K. Lindpaintner*** (Roche, Basel). Prof. Lindpaintner presented an overview on the concept of individualized healthcare and its historical development. He pointed out that finding the optimal treatment for every patient through differential diagnosis is as old as medicine itself, dating back to Pythagoras (530 BC) who had observed that while some people tolerate the ingestion of fava beans, others do not. In 1980 (AD) only, the reason for this observation could be attributed to a deficiency in glucose-6-phosphate-dehydrogenase. In 1990, SNPs in the G6PD gene were characterized and found to be responsible for the disease. He then outlined the concepts of pharmacogenetics and -genomics, two fundamentally different concepts of which the former has 'nothing to do' with a disease but relates to individual variations on the germ-line level, whereas the molecular concept (genomics) has 'everything to do' with a disease, refers to individual variations on the disease level, is cause-effect driven and generally affects pharmcodynamics. As a personalized approach to patients he gave the treatment of breast cancer with Herceptin as an example which requires prior screening of the patients for overactive hHER2 receptors to make treatment successful. As an additional example he outlined that screening patients with the Roche CYP450 Amplichip for CYP450 drug metabolizing enzymes allows broad allelic coverage of known variants for many ethnic groups (CYP2D6 and CYP2C19); this was the first microarray technology introduced to diagnostics, certified as a first-in-class device by the CE and FDA. In the final part of his talk Prof. Lindpaintner focused on biomarker strategies for clinical Phase 0/2 and Phase 2–4 trials.

Prof. Lindpaintner

Target-Families: Kinases and Nuclear Hormone Receptors

This session focused on protein kinases as an eminent target class and gave an overview on the efforts to design & develop selective inhibitors for treatment of cancer, inflammation, neurodegenerative diseases and diabetes, respectively. Lectures were given on 'AEB071, an Immune-modulating Kinase Inhibitor' (Dr. ***J. Wagner***, Novartis, Basel), 'Protein Kinase Inhibitors: The Contribution of Structural Information for Design and Mechanism' (Prof. ***L. N. Johnson***, Univ. of Oxford), and 'Targeting Protein Kinases' (Prof. ***S. Laufer***, Univ. of Tübingen). In addition, an overview was presented on nuclear receptors, their regulation, structure, and function, by Dr. ***D. Moras*** (IGBMC, Illkirch, France) with a lecture entitled 'Allosteric Control of Nuclear Receptors'.

The session was opened by the lecture of Dr. Wagner on 'AEB071, an Immune-modulating Kinase Inhibitor', a case study on the identification of AEB071 (sotrastaurin), the first small molecule inhibitor preventing T-cell activation *via* a calcineurin-independent pathway: AEB071 inhibits all protein kinase C (PKC) isotypes and is the first arylindolylmaleimide derivative in clinical trials for psoriasis. The results of a multiple dose study



AEB071
Protein kinase C inhibitor
In clinical trials for psoriasis

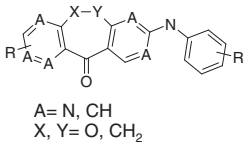
AEG537
Protein kinase C inhibitor
Not in vivo active
(Poor exposure into lymphoid tissue)

Fig. 1.

(25 to 300 mg b.i.d. for 14 days) in psoriatic patients showed a significant, dose-dependent reduction in lesions at 2 weeks post-dosing for the 200- and 300-mg groups as determined using the psoriasis area severity index.[1] These data suggest the use of AEB071 as an effective novel treatment regimen for psoriasis and other autoimmune diseases. In the process of identification of AEB071, the physicochemical properties of analogues were extensively optimized through fine-tuning of the pKa value of the distal piperazine nitrogen, since it was found that a pKa >7 is required to achieve sufficient potency at the enzyme, but that at too high pKa values (>8) oral absorption of the compound is dramatically reduced (Fig. 1). As Dr. Wagner pointed out, key to success was the observation that small structural modifications can result in profound effects on tissue distribution profiles as exemplified by AEG537 which shows very low distribution into lymphoid tissue and therefore no *in vivo* activity, whereas AEB071, the methyl regioisomer, which has 15× higher exposure in this tissue exhibits high *in vivo* activity (Fig. 1).

Prof. Johnson

Prof. Johnson gave an overview on protein kinases and the status of development of their inhibitors as anticancer and anti-inflammatory drugs: About 22% of the 'druggable' genome encodes protein kinases, controlling key phosphorylation reactions in signaling cascades and affecting every aspect of cell growth, differentiation, inflammatory response and metabolism. They have become privileged targets for drug intervention in many diseases, especially in cancer, and by now ten protein kinase inhibitors have been approved for clinical use. She further outlined mechanistic and structural knowledge to design selective inhibitors and discussed the mode of action for some of the approved drugs:[2] All but one target the ATP binding site of the kinase. Both the active and inactive conformations of protein kinases have been used in strategies to design potent and selective compounds. Targeting the inactive conformation can lead to high specificity; targeting the active conformation, on the other hand, is favourable if the diseased state has arisen from mutations, (over)activating a given kinase; however, since almost the same active conformation is common to all protein kinases, such inhibitors tend to be generally less specific. Compounds binding to both conformational states bear the potential risk for drug resistant mutations, since drug-binding regions are not directly involved in the catalytic process. Prof. Johnson then presented several examples: Imatinib (Glivec), the most successful of the protein kinase inhibitors, targets the inactive conformation of ABL tyrosine kinase, whereas newer compounds, *e.g.* dasatinib (Sprycel), targeting the ABL active state, proved to be efficacious against some drug resistant mutations.



A= N, CH
X, Y= O, CH_2

Novel dibenzosuberone scaffold:

Selective p38 mitogen activated protein kinase (MABK) inhibitors

Fig. 2.

The first EGFR inhibitors in clinical use, gefitinib (Iressa) and erlotinib (Tarceva), target the active form of the kinase and this turned out to be advantageous for patients whose cancer was caused by mutations resulting in a constitutively active EGFR kinase domain.

The challenges to achieve selectivity was further addressed in the lecture of Prof. Laufer who outlined strategies to tackle the selectivity problem on the molecular level. He pointed out that due to the conservation of key structural features within the ATP binding cleft, high specificity with ATP-site directed inhibitors is difficult to achieve. However, regions close to the ATP binding site showing structural diversity between different kinases can be exploited. Another strategy that he outlined tries to capitalize on a peptide flip within the hinge region, induced by a carbonyl-interaction of an inhibitor with two backbone NH-groups. Both approaches were successfully combined in the case of p38 mitogen activated protein kinase (MAPK) inhibitors with a dibenzosuberone scaffold (Fig. 2): These structures with reduced conformational flexibility revealed very good selectivity, affecting in the full Ambit KINOME scan no other kinase except p38α and p38β.[3]

Dr. Moras gave an overview on nuclear hormone receptors, their different classes and how they communicate: Nuclear receptors constitute a large family of ligand-dependent signaling proteins that regulate gene expression in metazoan cells. The basic mechanism underlying transcriptional activation by nuclear receptors involves their binding to specific response elements on promoters and their interaction with coactivators, the assembly of which triggers the recruitment and activation of the transcriptional machinery. They function as homo or heterodimers (class I or II) with specific signature motifs, respectively. He presented his work on retinoid nuclear receptors, on the role of ligands, cofactors and post-translational modifications, such as phosphorylation, in relation to the activity of the functional heterodimers. His results point to an allosteric control of the dimerization through ligands and cofactor binding.

Inflammatory Diseases/Atherosclerosis

Dr. ***M. Hinder*** (Nycomed, Konstanz) opened the session with an overview lecture entitled 'Pathophysiology and Treatment of Cardiovacular Disease: From Hemodynamics over Metabolism to Inflammation'. His presentation was followed by three medicinal chemistry drug development programs on 'CCR2/CCR5 Antagonists: A New Approach for the Treatment of Atherosclerosis and Auto-immune Diseases' (Dr. ***W. Milz***, Novartis, Basel), 'Compounds Targeting the Glucocorticoid Receptor for Anti-inflammatory Therapies' (Dr. ***H. Rehwinkel***, Bayer, Berlin) and 'Advances on LFA-1 Antagonism for the Treatment of Inflammatory Conditions' (Dr. ***T. Kelly***, Boehringer, Ridgefield, USA).

Dr. Hinder outlined from an historical perspective how the perception of cardiovascular diseases has progressed from merely symptomatic aspects to deeper pathophysiological understanding, and how genetic and lifestyle related predisposing factors affect the disease state. He pointed out that treatment of CVD has transformed from symptom control to prevention, and that

recent findings suggest a cross-talk between cardiovascular diseases and other diseases such as rheumatoid arthritis.

Dr. Milz gave an account on a drug discovery program to develop potent dual CCR2/CCR5 antagonists. He emphasized the importance of chemokine receptor signaling in various diseases: CCR2 and to some extent CCR5 play a crucial role since they are expressed on most inflammatory cells, in particular monocytes. CCR2/5 positive monocytes and macrophages are key drivers of inflammation in metabolic disease, *e.g.* mediating monocyte migration into atherosclerotic plaques which can trigger plaque rupture, causing myocardial, cerebral and other peripheral infarctions. As a consequence, CCR2/5 antagonists should reduce monocyte migration and stabilize vulnerable plaques. He pointed out that several inhibitors are in development by different companies for treatment of various inflammatory diseases. He further underlined the importance to achieve dual CCR2/CCR5 antagonism because selective antagonists might not be efficacious due to the high redundancy of chemokine receptors.[4] He then summarized the lead optimization program starting from a benzothiazole screening hit towards a third generation advanced key compound, compound **9**, for which he showed *in vitro* and *in vivo* activity data (active at 3 mg/kg in a monocyte migration assay) and the PK profile (Fig. 3).[5] He also referred to the multiple challenges in developing CCR2/CCR5 antagonists: the low cross-reactivity with rodent receptors (10–20× less active in rat/mouse binding assays) rendering *in vivo* experiments more demanding, high redundancy of the chemokine receptors (CCR1-5), a liability towards activity on hERG channels due to a similar pharmacophore (basic nitrogen, aromatic system), and a liability for phospholipidosis.

Dr. Rehwinkel illustrated an approach to find glucocorticoid (GC) receptor agonists with high anti-inflammatory activity and largely suppressed (undesired) metabolism/catabolism related properties: The approach takes advantage of new insights in the molecular mechanism of glucocorticoid receptor activation pathway. Glucocorticoids function by binding to and activating the GR receptor that positively or negatively regulates the expression of specific genes. Experiments suggest that the negative regulation of gene expression (transrepression path) accounts for anti-inflammatory action. This occurs through direct or indirect binding of the receptor-ligand complex, after translocation to the nucleus, to transcription factors such as activator protein-1, nuclear factor-kappa-B, or interferon regulatory factor-3 that are already bound to their regulatory sites. In contrast, the transactivation path, the positive regulation of the GR receptor, is triggered through ligand binding followed by formation of a homodimer-ligand complex. This translocates then to the nucleus and binds there to discrete nucleotide sequences. This pathway controls those properties of the glucocorticoids that are related to metabolism such as fat mobilization and trans-location, gluconeogenesis, and catabolism.

He discussed data of a new class of selective GR ligands (SEGRA) which have high anti-inflammatory activity and much reduced risk to elicit metabolic side effects; ZK 245186 is currently in clinical development. Its profile is explained by the specific binding features of the molecule giving rise to selective activation of the transrepression pathway. ZK 245186 has good selectivity over the other nuclear receptors (PR, AR, MR), and is currently in development for inflammatory skin diseases and ophthalmic indications (Fig. 4).

Dr. Kelly gave in his lecture an account on how they found and developed a class of small molecule antagonists of the protein-protein interaction of lymphocyte function-associated antigen 1 (LFA-1, CD18, CD11a), a cell-adhesion molecule mediating critical immunological processes. The lymphocyte function-associated antigen 1 (LFA-1) is an alpha integrin required for the migration and activation of immunomodulatory cells. The benefit of antagonizing the interaction of LFA-1 to its ligands, the intercellular adhesion molecules (ICAMs), has been demonstrated clinically, as he pointed out, with the positive data of the anti-LFA-1 antibody Raptiva, approved for the treatment of psoriasis.

The program towards small molecule antagonists started with a HTS from which BIRT 377 was identified as early lead compound. Its binding mode has been elucidated from X-ray structural data: It interacts specifically with LFA-1 *via* non-covalent binding to the CD11a chain and prevents LFA-1 from binding to its ligand ICAM-1 (allosteric binding). BIRT 377 is orally bioavailable and inhibits lymphocyte activity both *in vitro* and *in vivo* in functional assays. However, the molecule was found to be not potent enough for development due to high protein binding.

A subsequent LO program produced BIRT 2548 as improved compound with higher potency and *in vivo* efficacy due to increased fu values (free fraction) which made it to Phase I clinical trials and reached similar biomarker end points as Raptiva in a POC study (lympocytosis) (Fig. 5). Its development, however,

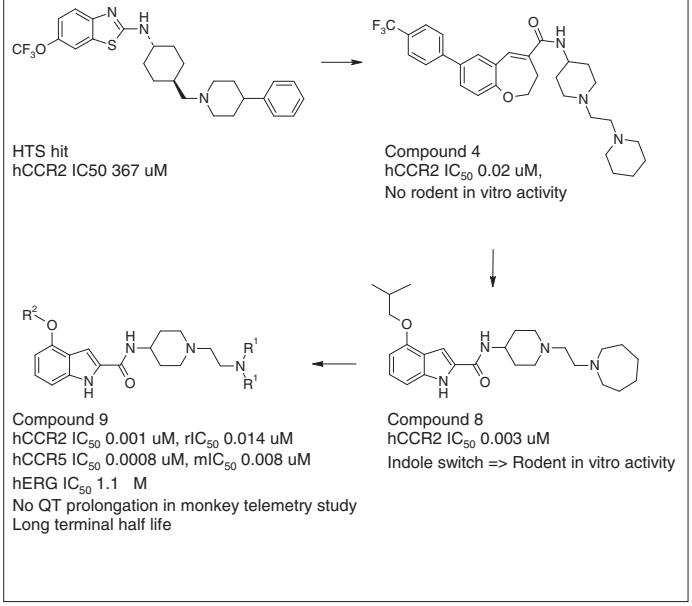


Fig. 3.

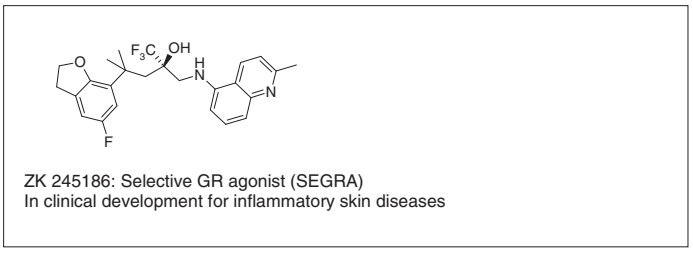


Fig. 4.

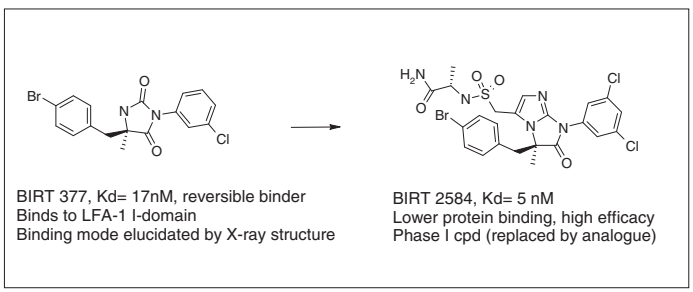


Fig. 5.

was stopped in favour of a further improved analogue (structure not disclosed).

Dr. Kelly pointed out that the whole approach targeting this class of integrins has 'become complicated' due to rare but fatal cases of brain infections that occurred recently with the two antibodies anti-VLA-4 (Tysabri) and anti-LFA-1 (Raptiva).

Neuropsychiatry

Highlights of this session included the talks of Dr. ***C. Boss***, Actelion, Allschwil, on 'Orexin Receptor Antagonists – Medicinal Chemistry and Therapeutic Opportunities' and Dr. ***J.-P. Rocher*** (Addex, Geneva) on 'Allosteric Modulation of GPCRs: From Concept to Application on mGluR5 Receptors'. Both covered drug development programs with frontrunner compounds currently in advanced clinical trials.

In his lecture Dr. Rocher started with an overview on glutamate as a major brain excitatory neurotransmitter and its receptors: Glutamate mediates its actions *via* activation of both ligand gated ion channels (iGluRs) and a family of class C G-Protein coupled receptors, the metabotropic glutamate receptors (mGluRs).

mGluRs play important roles in various neurological disorders. The receptors consist of eight subtypes, all of which have allosteric binding sites which are topologically distinct and less conserved within the subtypes in comparison to the glutamate (orthosteric) binding sites. Therefore, targeting the allosteric binding site has clear advantages over the orthosteric one, because it offers higher pharmacophore diversity and room for gaining selectivity. Allosteric modulation of mGluR1-8 has been shown to be a valid strategy to develop non amino-acid like therapeutics that can be administered orally and that readily cross the blood-brain barrier. The allosteric modulators bind in the cell membrane *via* a non-competitive mechanism, influencing signal transduction caused by gluatamate, the endogenous active ligand. mGluR5 receptors are located mainly on post-synaptic elements in the brain (cortex, thalamus, hippocampus and cerebellum), from where they regulate the activity of NMDA & AMPA, as well as the excitability of the post-synaptic neurons. mGluR5 negative allosteric modulators (NAM) are thus potential drugs to treat CNS disorders such as depression, movement disorders (*e.g.* Parkinson's disease), neuroprotection (stroke and head injury), and addiction. Proof of concept in man for mGluR5 NAM has been demonstrated for anxiety, gastroesophageal reflux disease and migraine. He further mentioned that preclinical findings support the concept to study mGluR5 positive allosteric modulators (PAM) as potential therapeutics for CNS disorders such as schizophrenia and cognitive disorders.

Dr. Rocher described then a program towards highly selective mGluR5 receptor NAM, ADX50817 and ADX50818, of which a new analogue ADX48621 (structure not disclosed) has completed Phase I clinical development and is expected to start Phase IIa proof of concept studies (POC) in Parkinson's disease. The LO program started from screening hits and literature data and allowed to identify and develop ADX48621as clinical compound which is soluble, has good potency, oral bioavailability and favorable BBB properties (IC50 = 20 nM, CSF/plasma= 5, o-F 45 %, rat) (Fig. 6).

In the second part of his talk he described the discovery of ADX47273, a novel mGluR5 positive allosteric modulator (PAM) for schizophrenia and cognitive dysfunction. He presented the results of *in vivo* efficacy studies in rodent behavioral models demonstrating that ADX47273 can reverse d-amphetamine induced locomotor activity, apomorphine disruption of prepulse inhibition (PPI) and improve performance in novel object recognition tests (Fig 7).

The talk of Dr. Boss centred around a drug identification & development case study resulting in the discovery of Almorexant,

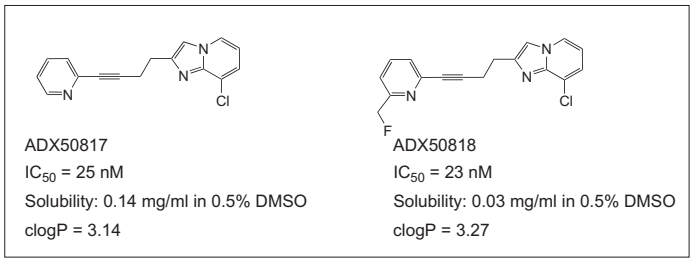


Fig. 6.

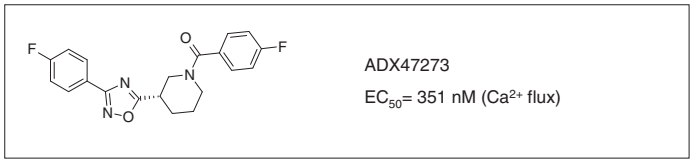


Fig. 7.

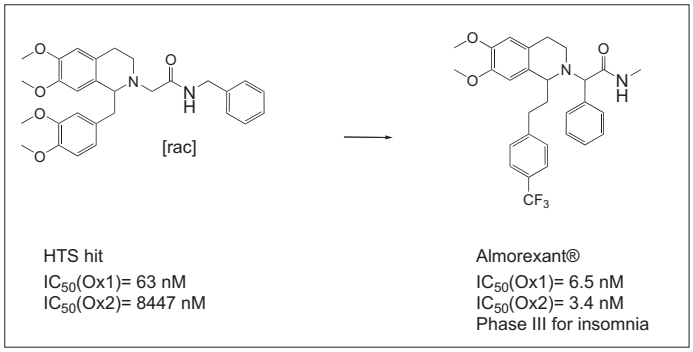


Fig. 8.

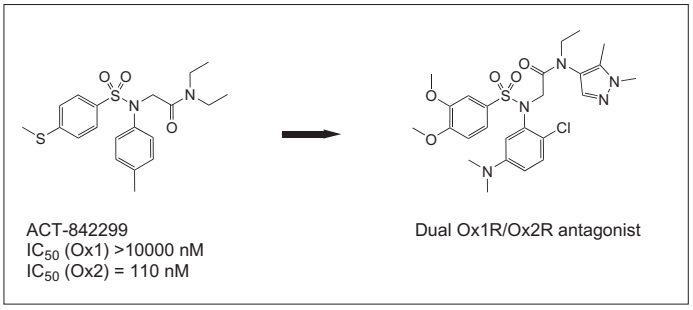


Fig. 9.

a dual orexin-1,2 receptor antagonist currently in advanced Phase III clinical trials for insomnia.[6] He started with an overview on the biological background: Orexins are neuropeptides produced in the brain, in a small area of specialized neurons located in the hypothalamus. They play an important role in maintaining wakefulness and regulate the sleep-wake-cycle. Almorexant was developed from a tetrahydropapavarine screening hit which was OxR1 selective (Fig. 8).

Another lead series of dual inhibitors with an N-glycine sulphonamide scaffold was developed from an OxR2 selective antagonist ACT-842299 (Fig. 9).

New Technologies: Nanomedicine, Proteomics and Drug Targeting

This session highlighted new developments in discovery technologies comprising lectures on 'Fragment-based Lead Discov-

ery in Drug Research' (Prof. ***R. E. Hubbard***, Univ. of York, UK), 'Drug Proteomics' (Prof. ***G. Superti-Furga,*** Austrian Academy of Science, Vienna), 'Quantitative and Functional Proteomics' (Prof. ***M. Mann***, Max Plank Institute for Biochemistry, Martinsried, Germany), 'Ligand-mediated Targeting of Therapeutic Agents to Cancer Tissues and Sites of Inflammation' (***P. S. Low***, Purdue Univ., USA), as well as on 'Pores and Sensors' (Prof. ***S. Matile***, Univ. of Geneva), 'Anti-angiogenic Marine Natural Products' (Prof. ***N. Kotoku,*** Univ. of Osaka, Japan), and 'Conformational Transitions and Ligand Binding Studies in CDks' (Dr. ***F. L. Gervasio***, ETH Zürich).

To highlight some of the contributions: Dr. Low outlined his approach to identify molecules targeting certain cancer cells by making use of the fact that many cancer cells (including those of breast, ovary, endometrium, lung, kidney, colon, brain, and myeloid cells of hematopoietic origin) have folate receptors (FR) upregulated on the outer surface. He described synthesis and use of folate drug conjugates that specifically bind to cancer cells through the folate receptor and enter the cell through endocytosis. He developed this technology for selective delivery of imaging agents as well as for therapeutic drugs. He pointed out that several folate-targeted therapeutic drugs are currently undergoing clinical trials or are in late stage preclinical development. Also, folate receptor targeted imaging agents are important tools to screen for patients who have FR-expressing tumors and therefore are likely to respond to folate targeted therapies.

Since the FR is also overexpressed on activated macrophages which either cause or contribute to inflammatory and autoimmune diseases, folate-conjugated imaging and therapeutic agents offer also the potential for diagnosis and treatment of such diseases.[7]

Prof. Mann gave an overview on scope and application of the SILAC technology for quantitative and functional proteomics. This cutting edge methodology is very powerful and he showed the quantitative assessment of yeast proeteome comprising about 2000 proteins as an example. The SILAC approach (stable isotope labeling with amino acids in cell culture) is a mass spectrometry-based technique: The proteome is labeled by metabolic incorporation of either a normal or a heavy isotope-substituted amino acid, such as ^{13}C-labeled lysine. Peptides derived from the two samples are then differentiated in a mass spectrometer owing to their mass difference. The ratio of signal intensities for such peptide pairs reflects the abundance ratio for the corresponding proteins analyzed in form of a 'contour plot' of LC–MS/MS runs.[8]

The technology has also been developed to screen cells for protein-protein interactions by combining it with RNA interference (RNAi) and quantitative co-immunoprecipitation techniques (QUICK).[9]

Highlights in Medicinal Chemistry

There were two highlight session scheduled, the first one comprising lectures from Dr. ***P. Mohr*** (Roche, Basel) on 'Aleglitazar, A Potent and Balanced Dual PPARα/γ Agonist for the Treatment of Type II Diabetes and Dyslipidemia' and *Prof.* ***B. Clement*** (Univ. of Kiel) on 'The Fourth Molybdenum-containing Human Enzyme mARC: Involvement in Drug Metabolism and in the Activation of N-hydroxylated Prodrugs'. Dr. Mohr outlined the clinical symptoms and underlying causes of type 2 diabetes from an historical perspective, as it was described in the 17th century as 'the pissing evil': The role of insulin in maintaining glucose homeostasis, the more recent discoveries of the PPARs (peroxisome proliferator-activated receptors, ligand-dependent transcription factors) which are nuclear hormone receptors and control the expression of genes involved in transport and metabolism of lipids and glucose, role, function and expression

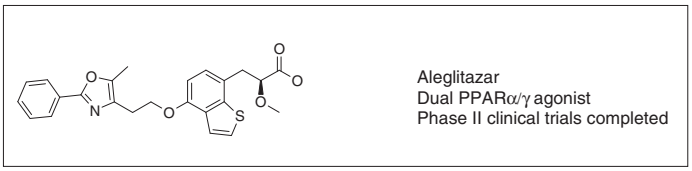


Fig. 10.

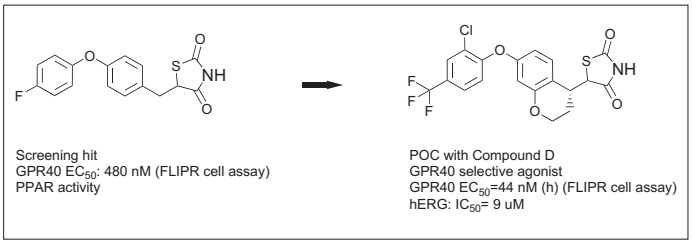


Fig. 11.

pattern of the α- and γ-subtypes (PPARα: lipid catabolism and homeostasis, liver, skeletal muscle; PPARγ: glucose homeostasis, lipid storage, adipose tissue). He then gave an account on a drug discovery program aimed to design and develop dual PPARα,γ coagonists that are expected to have beneficial effects on both glucose control and dyslipidemia, including atherosclerotic progression and β-cell function in type 2 diabetic patients. The strategy that he outlined to get to these dual agonists was a molecular design approach based on X-ray structural data of the PPARα/γ coagonist Tesaglitazar and the PPARγ agonists Farglitazar and Edaglitazone, co-crystallized with the respective receptor. This resulted in the discovery of Aleglitazar, a potent and balanced PPARα,γ agonist.[10] Aleglitazar has successfully completed Phase II clinical trials showing a favorable safety and efficacy profile (Fig. 10).

Prof. Clement described in his talk a new class of mitochondrial enzymes involved in the transformation of N-hydroxylated amidine pro-drugs back to the active amidines, the mitochondrial amidoxime reducing component (mARC) molybdoproteins. He found that mARCs are involved in the reduction of a broader array of *N*-hydroxylated molecules and xenobiotics.[11]

The second highlight session comprised lectures from Prof. ***S. V. Ley*** (Univ. of Cambridge) on 'Adventures in the Synthesis of Biologically Active Natural Products' and Dr. ***L. Yang*** (MSD, Rayway, USA) on the 'Discovery of GPR40 Agonists for the Treatment of Diabetes'.

Dr. Yang summarized the program to develop potent GPR40 receptor agonists for the treatment of type 2 diabetes. He first gave an overview of the biological background: GPR40 is a G-protein coupled receptor, highly expressed in brain and pancreatic β-cells and was first cloned in 1997. It potentiates GDIS (glucose-dependent insulin secretion) on activation either by its natural ligands which are long-chain fatty acids or by certain synthetic PPARγ thiazolidinedione agonists which can also bind to and activate the receptor.[12] In the second part he described the drug discovery program towards selective agonists starting from a thiazolidinone screening hit that was also active on PPAR receptors (Fig. 11). The challenges that had to be overcome were to get rid of PPAR activity, achieve patentability and find compounds with low activity on hERG channels. *In vitro* and *in vivo* profiling data were then presented with a POC compound (compound D). PPAR activity in this lead series was eliminated through introduction of conformational constrains (additional ring). hERG activity was reduced through implementation of heteroatoms in the scaffold. No advancement of the molecule towards clinical development was reported.

Prof. Ley gave first an overview on the synthesis of biologically active natural products that have been achieved by his group. He then outlined scope and power of 'flow chemistry' his group is right now developing by setting up micro-fluidic reactor systems in combination with immobilized reagents and scavengers (the Uniqsis FlowSyn reactor units). He showed that multistep reaction sequences can be performed with these systems and that a broad range of transformations is possible (*e.g.* Curtius rearrangement, Seyferth-Gilbert reaction, selective fluorination), including purification under continuous flow conditions and all this much faster than with batch-type chemistry.

Short Lectures

The meeting also offered a forum for young scientists to present their work; three short lecture sessions were organized with seven contributions that covered topics of natural product synthesis (***A. Blum***, Imperial College, London, 'Towards the Total Synthesis of Lactonamycin'), work on kinases to overcome drug resistance (***D. Rauh***, Chemical Genomics Centre of the Max-Planck-Society, Dortmund, 'New Methods for Tackling an Emerging Problem'), and molecular design programs (***F. Boeckler***, Ludwig-Maximilians-University, Munich, 'Targeted Rescue of a Destabilized p53 Mutant by *in silico* and Biophysical Screening – A Novel Approach for Anti-tumor Therapy').

Posters and Prizes

About 60 posters were presented three of which were recognized by the scientific committee with a prize. ***A. Kaiser*** (Univ. of Mainz) received an award for his work on immunological evaluation of a toll-like-receptor-2 (TLR2) agonist, ***C. Steuer*** (Univ. of Heidelberg) for his work on finding lead structures for Dengue NS3 protease inhibitors, and ***M. Kühnle*** (Univ. of Regensburg) for investigations towards the potential of ABCG2 modulators for the chemotherapy of glioblastoma by use of optical imaging of orthotopic human brain tumors in nude mice.

Conclusions

The meeting was well received by all attendants, impeccably organized, with an excellent scientific program, offering a truly international platform that allowed many stimulating discussions and exchange of ideas. It brought together scientists with diverse backgrounds from biology, medicinal chemistry, molecular design and molecular medicine, from academia and industry, which was highly rewarding. It is planned to organize a 5th Joint German-Swiss Medicinal Chemistry meeting in 2011. Participation in future conferences of this series is highly recommended.

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