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EDITORIAL

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JMMC 2007

A Successful Joint Effort

Danijel Kikelj*[a]

In the years between the biennial International Symposia on Medicinal Chemistry (ISMC) the Joint Meetings on Medicinal Chemistry (JMMC), organized by several European national medicinal chemistry societies, are becoming increasingly important scientific events at which several hundreds of medicinal chemists gather, not only from Europe, but also from other parts of the world. As the role of medicinal chemistry in the drug-discovery process is undergoing major changes due to emerging new technologies and vast amounts of new biological information, these meetings provide opportunities for stable scientific interactions in the changing environment of medicinal chemistry.

The 2007 Austrian–German–Hungarian–Italian–Polish–Slovenian Joint Meeting on Medicinal Chemistry (JMMC 2007), held during June 17–21 in Portorož on the Slovenian Adriatic, was the fifth meeting in a series of joint meetings initiated in Taormina (Italy) in 1999 and successfully continued in Budapest (2001), Krakow (2003), and Vienna (2005). JMMC 2007 was organized by the Medicinal Chemistry Section of the Slovenian Pharmaceutical Society under the auspices of the European Federation for Medicinal Chemistry (EFMC) and assembled more than 300 medicinal chemists coming not only from the six co-organizing EU countries, but also from 20 other countries the world over. Importantly, many doctoral students and postdoctoral researchers participated in this meeting, affording young scientists the opportunity to meet established medicinal chemists for an exciting exchange of ideas.

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The meeting dealt with important new aspects of the drug-discovery and development process, with a focus on anti-infectives, drugs for cardiovascular and metabolic disorders, enzymes and receptors as targets for new drugs, computer-aided drug design and discovery, emerging strategies in drug discovery, and medicinal chemistry case studies. In addition to a rich scientific program including seven plenary lectures given by Robert Huber, Ian Chopra, Gerhard Klebe, Jean Martinez, Giuseppe Ronsisvalle, Giulio Superti-Furga and Csaba Szántay, and 20 keynote lectures given by scientists of the six co-organizing countries, JMMC 2007 also offered a round-table discussion on education and training in medicinal chemistry, organized by the Education and Training Committee of the EFMC (see the Report on page 561). This issue of *ChemMedChem* features eight articles contributed by participants at JMMC 2007. Seven of these deal with scientific topics of the conference spanning various therapeutic areas, and one is devoted to the transformational accomplishments and challenges in European medicinal chemistry education.

These studies exemplify the use of ESI-MS for the analysis of metalloenzymes of medicinal interest.

In recent years, a large amount of evidence has accumulated that drugs belonging to various pharmacological classes may block hERG channels, thus prolonging the duration of the action potential; this results in the so-called long-QT syndrome, which may result in a potentially lethal form of arrhythmia. The withdrawal of several marketed drugs that cause QT prolongation in humans as well as an increasing awareness of the urgent need to identify hERG-inactive and hERG-active drug candidates early in the drug-development process has initiated intense research of medicinal chemistry concepts and strategies to minimize hERG channel blockade. On page 523 Recanatini et al. review computational works on potassium channels and recent advances in modeling the hERG channel and its interactions with drugs. Some recent drug–hERG docking models show promise as useful tools for predicting hERG binding affinity and interpreting hERG blockade by small molecules.

They took a multidisciplinary approach involving synthesis, molecular docking, molecular dynamics, and biological studies.

Schofield and co-workers demonstrate the use of non-denaturing electrospray soft ionization mass spectrometry for the study of noncovalent interactions between enzymes, small organic molecules, and ions on page 569; this could potentially be adopted for screening. They report ESI-MS metal binding studies on the catalytic domain of prolyl hydroxylase domain 2, an iron(II) and 2-oxoglutarate oxygenase that acts as an oxygen sensor in humans. These studies revealed an anticipated second metal binding site and exemplify the use of ESI-MS for the analysis of metalloenzymes of medicinal interest.

In his review on the medicinal chemistry aspects of drug targets in sphingolipid metabolism on page 543, Nussbaumer deals with enzymes involved in the biosynthesis and metabolism of sphingolipids modulating endogenous levels of the signaling molecules. He focuses on the chemistry and biology of sphingolipids, available tool compounds, the function of sphingolipids in cell signaling, the role of sphingolipids in disease and their pharmacological modulation, target validation, and drugability. Sphingolipid research has become a very active field with a number of hypotheses for therapeutic opportunities. With the invention of FTY720, which is currently in Phase III clinical trials for multiple sclerosis, it has been proven that medicinal chemistry can successfully develop sphingolipid structures into drugs.

On page 536 Bielawski and Bielawska describe small-molecule-based delivery systems for alkylating anti-neoplastic compounds, which still remain components of combination chemotherapy regimens. They discuss the targeting of alkylating moieties to DNA by amidine analogues and by proline-containing prodrugs with lower hydrophobicity and cytotoxicity which are preferentially activated in cancer cells by prolidase, which is overexpressed in some neoplastic cells.

No matter how this debate unfolds, European medicinal chemistry education is headed into an exciting period.

In their paper on page 552, Radosevich and co-workers describe the effect of proton-pump inhibitors, which are commonly used to treat gastroesophageal reflux disease, on the acid-producing bacteria in both the oral cavity and esophagus. The normal balance of flora found in the oral cavity and gastrointestinal tract of patients taking proton-pump inhibitors can be disrupted, possibly leading to long-term complications in some cases. This action of proton-pump inhibitors supports the idea that proton pumps can be a target for antibacterial drugs.

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Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are essential components of first-line anti-HIV-1 therapy. Botta and co-workers report the identification of two (*S*)-3,4-dihydro-2-alkoxy-6-benzyl-4-oxypyrimidine cytosine analogues and 4-dimethylamino-6-vinylpyrimidines as two novel subclasses of HIV-1 NNRTIs (see page 573). They took a multidisciplinary approach involving synthesis, molecular docking, molecular dynamics, and biological studies.

The improper functioning of γ-secretase, an integral membrane protease, is critically involved in the pathogenesis of Alzheimer's disease. The structure of the enzyme as well as its proteolytic mechanism remain poorly understood. Filipek and co-workers present a molecular model on page 627 of the interaction between proteins APH-1 and presenilin forming γ-secretase and propose the interface motifs. The proposed model will aid further structural characterization of γ-secretase.

The paper on page 561 by de Souza and co-authors is based on a round-table discussion on training and education in medicinal chemistry, held at JMMC 2007 and chaired by Péter Mátyus (Semmelweis University, Budapest). The discussion highlighted current EFMC educational initiatives, progress in medicinal chemistry education at the university level, and industry–university collaboration. It defined undergraduate streams from which today's students opting for a career in medicinal chemistry originate, and tried to define the optimal philosophy of educating medicinal chemists. A question about the need for a new definition of medicinal chemistry was the subject of a keen discussion at the round table. As the authors conclude, no matter how this debate unfolds, European medicinal chemistry education is headed into an exciting period.

The growing need to develop new, better, and safer drugs is a big challenge to medicinal chemists. We hope and believe that scientific interactions at JMMC 2007 and in future joint meetings of this series will contribute to this exciting task.

[a] *Prof. Dr. D. Kikelj*
University of Ljubljana, Faculty of Pharmacy
Aškerčeva 7, 1000 Ljubljana (Slovenia)
Fax: (+386) 1-4258031
E-mail: danijel.kikelj@ffa.uni-lj.si

