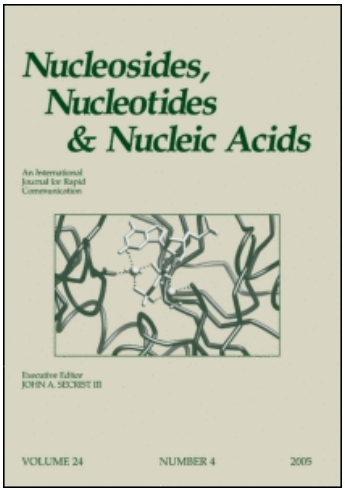

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Purine and Pyrimidine Metabolism: New Challenges

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Purine and Pyrimidine Metabolism: New Challenges

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In 2003 a joint International and European symposium on Purines and Pyrimidines was held in the Netherlands. The international series of symposia dates back to 1974 and was inspired by several exciting observations in the field of inborn errors. First an association was described between gout and a partial deficiency of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and between the Lesch-Nyhan syndrome and a complete HGPRT deficiency. Subsequently in 1973 an association between adenosine deaminase and Severe Combined Immunodeficiency was described, followed in 1977 by a similar finding between purine nucleoside phosphorylase and severe T-cell specific dysfunction. These formed the basis for an international series of meetings held every 3 years all over the world. In order to have a more frequent opportunity for European investigators to meet each other in 1987 the European Society for the Study on Purine and Pyrimidine Metabolism in Man was founded, which held their meetings every 2 years. The meeting was held together with the international meeting every 6 years. The initiative for the European meetings was taken by Dr. Anne Simmonds in London, Prof. Nepomuk Zöllner in Munich and Dr. Francoise Roch-Ramel from Switzerland. Dr. Roch-Ramel did pioneering work in the field on uric

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acid transport, another major aspect in the pathophysiology of gout. Her achievements are being described in a separate paper dedicated to her.

The field of purine and pyrimidine metabolism boosted enormously after the above-described discoveries and formed the basis to investigate the pathophysiology of many other inborn errors, while the association between an enzyme deficiency and an immunodeficiency formed the basis to develop nucleoside analogs which would create a similar condition in cancer cells, or other types of diseased cells, such as inflammatory cells. Purine and pyrimidine analogs now form the mainstay for the treatment of a variety of diseases such as various forms of cancer (both haematological and solid tumours), viral infections, other haematological disorders, rheumatoid arthritis and cardiovascular diseases. This series of symposia always focused on these and related aspects, with an emphasis on metabolism. The required synthesis of novel compounds to be used for treatment of diseases was usually a major aspect at the Round Table conferences, held every two years. Although there is some overlap the meetings seem very complimentary. In order to get a better interaction between these fields the organisers of the Purine and Pyrimidine meeting reasoned that it might be useful to publish the proceedings of the Joint Purine and Pyrimidine symposium in Nucleosides, Nucleotides and Nucleic Acids. The current proceedings give a very good impression of the subjects being discussed at this meeting.

This volume covers both traditional and novel aspects. Although allopurinol was the standard drug of choice for treatment of gout, several novel developments led to the evaluation of new drugs and approaches to control uric acid overproduction. Various novel purine and pyrimidine analogs are also being used in the treatment of inflammatory diseases. Although significant progress has been made in the characterization of the genetic defects of the Lesch-Nyhan syndrome with several variants of HGPRT, the neurological basis of the disease is still poorly understood, but can be dealt with better than several years ago. The use of novel molecular biological techniques has enabled to characterize the molecular basis of a number of inborn errors, most recently that of the association of enzyme defects with two mitochondrial disorders. The genomics era will certainly lead to the better characterization of more disorders, while the application of pharmacogenomics will enable to characterize patients, either cancer patients or other diseases, which are at risk for toxicity when receiving chemotherapy. Proper intervention will prevent that these patients will get potentially toxic therapy. Ideally application of pharmacogenomics should lead to tailored therapy of the disease, which is becoming a real possibility since for many diseases including cancer, more choices are available.

Both pharmaceutical companies and university laboratories have contributed significantly to this increase of our pool of potent chemotherapeutic agents. However, the process of development from the bench to the clinic has become more complicated, both from a registrational point of view, and from the increased complexity of the processes underlying the various diseases. This has made the field even more challenging. Application of new technologies has given more insight in enzyme regulation, not only at the protein level but also at the genome. Regulation of gene expression at the promotor site, by methylation, by alternative splicing, or by single nucleotide polymorphisms (SNPs) has yielded various forms of enzymes in different populations. Knowledge of these variants is important to characterize resistance to existing therapies, but also offers the possibility of tailored therapy especially when these variants can be characterized at the somatic level.

The meeting formed an excellent environment to translate research not only from the bench to the clinic, but also from one discipline to another. Traditionally the international and the European meetings have been attended by scientists from various fields, such as chemistry, biochemistry, genetics, clinical chemistry and by physicians with different backgrounds such as paediatrics, haematology, cardiology, and oncology. This enabled to gain knowledge from each other, both in terms of insight in treatment of own patients as well as patients with other diseases. This volume is a reflection of all the various fields and proves that the study on purines and pyrimidines is still challenging and will also provide the background for novel target directed therapy, not only in cancer but also in other diseases.