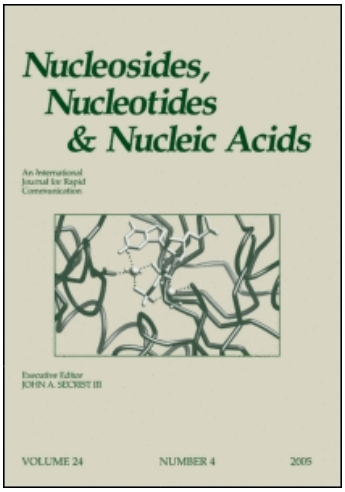

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PP07: New Approaches, New Knowledge, New Challenges in Human Purine and Pyrimidine Metabolism

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PP07: NEW APPROACHES, NEW KNOWLEDGE, NEW CHALLENGES IN HUMAN PURINE AND PYRIMIDINE METABOLISM

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The 12th International Symposium on Purine and Pyrimidine Metabolism in Man (PP07) was held in Chicago, Illinois, USA from June 24 to June 28, 2007. Beginning with the Purine Symposium in Tel Aviv in 1973, organized by Professors Sperling and deVries, international meetings have been held at least every three years at venues worldwide. These meetings have aimed at promoting and disseminating new knowledge in purine and pyrimidine science and medicine and at fostering collegiality. We were pleased to host PP07, the first symposium held under the auspices of the Purine and Pyrimidine Society (PPS), an organization formally created in 2005 by agreement between the European Society for the Study of Purine and Pyrimidine Metabolism in Man (ESSPPMM) and representatives of the International Symposium movement. The articles published in this volume represent the peer-reviewed Proceedings of PP07.

Symposia on human purine metabolism were initiated in response to accelerated investigative interest in this field, prompted by major advances in the preceding decades that had provided increased understanding of many of the biochemical, genetic, physiological, and clinical aspects of this class of compounds. During the 1950s and early 1960s, classical methods of protein purification, enzymology, and intermediary metabolite analysis were successfully employed in a wide range of species to identify and characterize virtually all of the steps in purine (and pyrimidine) biosynthetic and degradative pathways. Contemporaneously, increasing attention was directed to purine metabolism in humans, largely as a result of the identification of urate crystal deposition as the basis of gout and the application of

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stable and radioactive isotopic labeling methods for analyzing normal and aberrant purine metabolic balance. By the mid-1960s, when the xanthine oxidase inhibitor, allopurinol, was introduced into clinical practice for the treatment of the hyperuricemia of gout, impaired renal uric acid clearance and purine nucleotide overproduction had already been established as the distinctive major mechanisms underlying primary hyperuricemia. Then, in 1968, inherited severe deficiency of HPRT was identified as the enzymatic defect in Lesch-Nyhan syndrome, an X chromosome-linked neurobehavioral disorder accompanied by defective regulation of purine nucleotide and urate synthesis.

Much of the work presented at international purine symposia during the 1970s and early 1980s appropriately focused on the molecular and pathogenetic understanding of an increasing number of inborn errors of purine metabolism (Lesch-Nyhan syndrome and variant forms of HPRT deficiency; PRPP synthetase overactivity; deficiencies of myoadenylate deaminase and adenylosuccinate synthase; and, later, inherited forms of immunodeficiency associated with adenosine deaminase and purine nucleoside phosphorylase deficiencies). Nevertheless, these meetings also featured increasingly sophisticated delineation of renal uric acid handling, the regulation of purine nucleotide synthesis, enzymes involved in cellular uptake and metabolism of purine bases and nucleosides, and the effects of pharmacological, genetic, and physiological manipulation of normal and cancer cells in culture and in patients.

In the mid-1980s, two changes in format broadened the outlook of the international symposium program. First, in recognition of the considerable overlap in investigative interest, scientific commonality, and clinical and therapeutic importance, the study of pyrimidines was added to the agenda of the international meetings. Second, a need was recognized by our European colleagues for more frequent and geographically proximate meetings. This resulted in the creation of the ESSPPMM, and a series of 10 biennial meetings were held in Europe, some in conjunction with an International Symposium on Purine and Pyrimidine Metabolism in Man. These initiatives have led to increasing inclusion and interaction among investigators and trainees in our allied fields and have had practical and conceptual benefits that have been exploited over the past two decades. Among these benefits have been: (1) a broadened range of interest and collaboration among investigators; (2) an increased appreciation of how knowledge gained about one of these classes of compounds can be readily applied to the study of the other; (3) provision of a single venue for relating experimental findings in fields of molecular as well as conceptual overlap, especially in research areas, such as in membrane transport and in purine and pyrimidine antimetabolite chemotherapy; and (4) translation of innovative findings to fields of clinical interest, such as rheumatology, cardiology, virology, inflammation, inborn errors, cancer, etc.

The arrival of the era of genomics, proteomics, and metabolomics offers for the first time the opportunity to put many of the concepts in human purine and pyrimidine science to the molecular structural and functional test. These concepts have evolved over the past half century, through the ongoing efforts of both former and current colleagues. Among the outcomes likely to arise from these activities are translational initiatives that will favorably influence many areas of biomedical decision making. There are several examples of clinical areas likely to be impacted. First, cardiovascular diseases, where it is a critical issue to determine whether the risk imparted by high levels of soluble urate reflects a causal role for this purine catabolite in coronary heart disease, peripheral vascular disease, hypertension, congestive heart failure, or chronic kidney disease. Second, cancer and autoimmune disease chemotherapy, where purine and pyrimidine analogues and derivatives continue to be in wide use and the identification of genetic polymorphisms associated with responsiveness/resistance or enhanced toxicity to specific agents may lead to individualized therapeutic protocols that are safer and more efficacious. Third, gout, a disease in which newer urate-lowering agents, such as several currently under study, are needed to improve patient outcomes. And, finally, infectious diseases, particularly viral, retroviral, and parasitic disorders, for which purine and pyrimidine analogues/derivatives are either already providing, or may potentially provide, benefit in some of the world's most prevalent disorders. In light of these exciting prospects for continued productive basic purine and pyrimidine research and translational therapeutics, the commitment of the PPS to hold International Symposia as biennial events, an initiative reflecting the spirit of ESSPPMM, seems entirely appropriate.

In its role as the first symposium under the PPS, the PP07 schedule and venue was planned to maximize opportunities for information exchange and intellectual collaboration. Toward achieving these aims, the scientific program of PP07 retained the format of recent purine/pyrimidine symposia, combining oral and poster presentations covering a broad range of topics of contemporary scientific and medical relevance to which the study of purines and pyrimidines continues to advance knowledge. Each plenary session of PP07 (Table 1) was composed of short oral presentations, selected by peer review from among submitted abstracts, and lengthier invited state-of-the-art presentations by leaders in the respective fields of study. Poster presentations, displayed in conjunction with these topics, were available for viewing throughout the meeting in order to promote careful review, and selected abstract data were briefly presented in oral "poster mini-sessions" immediately preceding dedicated sessions during which attendees and poster presenters interacted at the posters.

Several novel aspects of PP07 program content warrant comment. First, PP07 sponsored, together with the Lesch-Nyhan Syndrome Children's Research Foundation, a pre-symposium session that provided an in depth

TABLE 1 PP07: Plenary sessions

Session 1:	Lesch-Nyhan Syndrome Children's Research Foundation Symposium
Session 2:	Mechanistic Advances in Gout and Hyperuricemia
Session 3:	Hyperuricemia, Metabolic, and Cardiovascular Disease: Associations and Mechanisms
Session 4:	Inborn Errors of Metabolism: Strategies and Analytical Methods
Session 5:	Purines/Pyrimidines in the Brain
Session 6:	Purines/Pyrimidines and Cancer
Session 7:	Extracellular Metabolism and Receptors
Session 8:	Purine/Pyrimidine Transport
Session 9:	Purine/Pyrimidine Metabolism in Protozoans, Viruses, and Other Species
Session 10:	Molecular Mechanisms of Disease
Session 11:	Recent Advances in Purine/Pyrimidine Enzyme Regulation
Session 12:	Protein Structure and Catalytic Mechanisms

update by world-renowned investigators on scientific and clinical advances in the study of this disorder. Historically, the biochemical, molecular genetic, cell physiological, and clinical consequences of HPRT deficiencies have been of considerable interest at all preceding purine/pyrimidine symposia. Therefore, inclusion of this session at PP07 emphasized both the continuity and incremental nature of knowledge in our fields of common interest and the bidirectionality of translational scientific investigation. Second, the accelerating evolution of knowledge in our discipline dictated addition to the program of sessions dedicated to several especially dynamic areas in the field. These included: the relationships between hyperuricemia and metabolic and cardiovascular disease; cell membrane transport of purines and pyrimidines; and the protein structural bases of the catalytic mechanisms of purine/pyrimidine metabolic enzymes. Finally, a session was organized entitled "Purine/Pyrimidine Metabolism in Protozoans, Viruses, and other Non-Mammalian Species." This session reflected the current international attention focusing on major viral and parasitic diseases, for which the study of purine and pyrimidine metabolism is critical in the ultimate development of effective therapies for these disorders.

The sequence of the papers in these Proceedings follows the organization of the PP07 program, and each section contains papers based on material presented at PP07 either as an invited State of the Art lecture, an oral podium presentation, or a poster presentation.

In recent years, many of the key participants in earlier Purine and Pyrimidine Metabolism Symposia have retired or were unable to attend PP07. Here, we wish to acknowledge these outstanding scientists and physicians (Table 2) for the many contributions they have made to the development of our field. In addition, memoria for two of our most esteemed colleagues who have recently passed away are included in these Proceedings (Chapters 2 and 3). Happily, the quality of the research presented at PP07 reassures us that the study of purine and pyrimidine science has passed to a new

TABLE 2 The Purine and Pyrimidine Society wishes to acknowledge and honor the following medical scientists and retiring members of the PPS Scientific Committee for their consistent and long-standing support for International and ESSPPMM Symposia and their contributions to purine and pyrimidine science

Elizabeth Carrey	London, UK
Ronney De Abreu	Nijmegen,The Netherlands
Alessandro Giacomello	Rome, Italy
Wieslaw Makarewicz	Gdansk, Poland
Mathias Muller	Vienna, Austria
H. Anne Simmonds	London, UK
Oded Sperling*	Tel Aviv, Israel
Maria Staub	Budapest, Hungary
Georges van den Berghe	Brussels, Belgium
Nepomuk Zollner	Munich, Germany

*PP07 attendee.

and equally able generation of superb investigators and clinicians who have taken up the challenge to advance our fields of study and to continue to share their contributions at forthcoming Symposia.

We would like to express our appreciation to the many individuals and organizations without whose support PP07 and these Proceedings would not have been possible. Among these are the corporate, private, academic, and foundation supporters, listed individually in Table 3. In addition, we are indebted to: the members of the PP07 Organizing and Program Planning Committee; the invited expert consultants (Table 4) who assisted in abstract and manuscript peer review and provided critical advice in organizing the meeting; and the retiring Secretary and Treasurer of the PPS, Drs. Elizabeth

TABLE 3 Supporters of the 12th International Symposium on Purine and Pyrimidine Metabolism in Man

The Purine and Pyrimidine Society and the organizers of PP07 wish to offer our appreciation to the following individuals and institutions for their generous support for the Symposium:

Academic and Private Sponsors

- Rheumatology Section, Department of Medicine, The University of Chicago
- Department of Medicine, The University of Chicago (Dr. Joe G. N. Garcia, Chairman)
- Styliades Hellenic Orthodox Foundation (Mr. James and Mrs. Lillian Thomas)
- Mr. Daniel Epstein and Ms. Sunni Reed
- Lesch-Nyhan Syndrome Children's Research Foundation (Mrs. Elaine and Mr. Stephen Timbers)
- Purine Metabolic Patients' Association — PUMPA (Travel Grants)

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TABLE 4 PP07 abstract and proceedings reviewers

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Andre van Kuilenburg	Amsterdam, The Netherlands

Carrey and Andrea Griesmacher, respectively. We wish also to acknowledge the groups/persons who were instrumental in accomplishing the many tasks necessary for accomplishing the aim of a successful meeting: Edina Lessack of Meetings and Events, USA; Matt Volk and Kathy Syversen of Uni-

versity Outreach, Northern Illinois University; Marquetta A. Lewis, Director of the Continuing Medical Education Center at the University of Chicago; Elaine Timbers of the Lesch-Nyhan Syndrome Childrens' Research Foundation; Anne Morgan, the PPS webmaster, and the volunteers whose efforts to assist PP07 participants during the meeting optimized the experience. We especially thank our two featured symposium speakers: Dr. Edward W. Holmes delivered a timely keynote speech centered on the importance of translational research at the PP07 opening reception; and James D. Montgomery, JD, eloquently detailed his recollections of nearly 50 years in legal affairs and the civil rights movement in America at the PP07 reception at the McCormick-Tribune Freedom Museum and in doing so reinforced the necessity of free speech as a prerequisite for the intellectual and scientific advancement of society. We owe a great debt to Professor Godefridus J. Peters, our coeditor of these Proceedings, whose constant availability and sound advice were indispensible in organizing PP07. Finally, we greatly appreciate and wish to recognize our spouses, Mary Baim and Mary Sabina, for tolerating our ups and downs and encouraging our efforts in organizing PP07 and editing the PP07 Proceedings.