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EDITORIAL

First joint Italian-German Purine Club meeting "Progress in Purinergic Receptor Pharmacology and Function"

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This special issue of *Purinergic Signalling* brings together 12 peer-reviewed reviews and original research papers presented at the first joint Italian-German Purine Club meeting "Progress in Purinergic Receptor Pharmacology and Function" held in Chieti (Italy), 18–20 September 2005. These contributions were selected among those focusing on four topics that the Scientific Committee of the Boards of the Italian and German Purine Club Chapters recognized to be most representative of status of the art: (1) advances in purinergic receptor structure and function, (2) new agonists and antagonists of P1 and P2 receptors, (3) non-adenine-based nucleotide and nucleoside signalling, and (4) 5′-nucleotidase activity. As guest editors we deeply appreciated the effort of all the authors who agreed to contribute to this special issue in the hope that also non-specialist readers can share our enthusiasm for this field of research.

The paper by D'Ambrosi and colleagues, well representative of the topic "advances in purinergic receptor structure and functions", provides evidence for the formation of $P2Y_4$ dimers and oligomers in neuronal cells. Although it is well established that P2X receptors as well as G protein-coupled receptors (GPCRs) can directly associate, little is known about P2Y receptor assembly. The results presented in this article are of particular interest in that they may help to explain the different biological responses often triggered by the activation of P2Y receptors and may help to better define the "combinatorial P2 receptor web" as recently defined by Volontè and colleagues (2006). The articles by Gessi and colleagues and by Dal Ben and colleagues, epitomizing the topic "new agents and antagonists of P1 and P2 receptors", describe novel receptor ligands for P1 receptors, with particular emphasis on A_{2B} and A_3 receptors, respectively. The former describes the effects of novel selective ligands for A_{2B} receptors by testing their antagonist or inverse agonist properties on the modulation of stimulated cAMP accumulation in HEK293 cells transfected with the recombinant human A_{2B} receptor and cells expressing the native A_{2B} receptor. Binding experiments were also performed to measure the affinity of these new ligands. These molecules might help to develop new potent and selective tools to modulate A_{2B} receptor function with several important clinical applications, including type II diabetes, Alzheimer's disease, cystic fibrosis and asthma. Growing interest focuses on the synthesis of selective A_3 receptor ligands, given the role played by this adenosine receptor in cell growth. The paper by Dal Ben and colleagues shows that newly synthesised 2-phenylethynyladenosine derivatives exhibited very high potency and selectivity for the human A_3 receptor subtype. In particular the N^6-methoxy-2-phenylethynyl-5′-*N*-methylcarboxamidoadenosine turned out to be the most potent and selective agonist for this site. Binding and functional data were confirmed by molecular modelling studies.

The article by Abbracchio and Ceruti provides a comprehensive review on P2 receptor functions in glial

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cells with particular attention on astrocytes. These cells, which represent a major brain cell type, release adenosine triphosphate (ATP) and trigger, following ATP exposure, a calcium wave that establishes a key pathway for glia-glia and glia-neuron interaction. The important role of P2 astrocyte receptors in CNS diseases, including neuroinflammation and neurodegeneration, is also discussed. The papers by Visentin and colleagues and by Tebano and colleagues, along with that by Merighi and colleagues, cover the topic "adenine-based nucleotide and nucleoside signalling". In the first paper the authors investigate the role of purine nucleotides in the modulation of calcium signalling. Calcium imaging and mRNA expression studies indicate the adenosine diphosphate (ADP)-selective $P2Y_{12}$ as a key calcium-mobilizing receptor in microglial cells. In the second study the authors followed up their previous results obtained in the striatum to provide evidence of the occurrence of A_{2A}/mGlu5R functional interaction also in the hippocampus. Besides the relevant role of this interaction in the modulation of *N*-methyl-D-aspartate (NMDA)-mediated neurotoxicity, which makes A_{2A} receptors additional important targets for the development of new therapies for neurodegenerative diseases, the individuation of A_{2A}/mGluR interplay in the hippocampus may help elucidate the neurophysiological basis of learning and memory. The paper by Merighi and colleagues provides novel information on A_3 adenosine receptor signalling. These authors show that in A375 human melanoma cells the A_3-mediated inhibition of cell proliferation is linked to a complex inhibitory link involving the PLC-PI3K-Akt system and the ERK pathway. A better understanding of adenosine signalling in tumor cells is of great interest for the development of new therapeutic approaches to neoplasias.

Within the topic "non-adenine-based nucleotide and nucleoside signalling" the papers by Pietrangelo and colleagues, Ballerini and colleagues and Jiang and colleagues report intriguing observations on cell responses to guanine-based purines. In the first article the authors report on the role of guanosine triphosphate (GTP) in the differentiation of rat pheochromocytoma PC12 cells and mouse skeletal muscle C2C12 cells. In both the cell lines extracellular GTP appears to bind to specific P2Y-like receptor(s) and to increase intracellular Ca^{2+}. The Ca^{2+} rise in turn is responsible for ERK activation and for increased expression of myosin heavy chain (MyHC) in PC12 and C2C12 cells, respectively, thus leading to cell differentiation. The paper by Ballerini and colleagues shows that guanosine increases cholesterol efflux and ApoE expression in glial cells, thus providing evidence for a further mechanism by which this nucleoside, by regulating astrocyte activity, may exert its neuroprotective effects. Jiang and colleagues present data showing that in the mouse topical application of guanosine and inosine accelerates wound healing in excisional dermal wounds. The mechanism seems to be distinct from those mediated by adenosine-based purines. Similar effects were found in genetically diabetic (BKS.Cg-m+/+leprdb) mice which, like humans with adult-onset diabetes, have significantly delayed wound healing. This suggests a potential alternative approach for the treatment of wounds in several clinical settings. The paper by Deussen and colleagues presents data on adenosine metabolism in mouse heart. Even though mouse heart is a pretty well-known model system in experimental cardiology, little is known on adenosine metabolism and transport in the heart so far. The results by Deussen and co-workers indicate an active extracellular adenosine production by ecto-enzymes and the presence of membrane adenosine transporters relatively insensitive to nitrobenzylthioinosine (NBTI). The final article by Ipata and Tozzi shows recent studies on the structure, function and regulation of cytosolic IMP-GMP specific 5′-nucleotidase II (cN-II), a key enzyme involved in the modulation of uric acid production, in the control of AMP and GMP concentration, and in the purine "de novo" synthesis. These data suggest that cN-II might also be involved in the regulation of 5-phosphoribosyl-1-pyrophosphate (PRPP) and in xanthosine salvage. This paper is of particular interest as a growing number of neurological impairments seem to be associated to misfunction of 5′-nucleotidase and related enzyme systems.

Finally, we are grateful to the Editor in Chief of *Purinergic Signalling* Prof. G. Burnstock and to Springer for their support and advice in the organization of this special issue. A special thanks also to the Congress Co-chairman, Prof. Peter Illes for his precious and continuous collaboration. Sincere thanks to all the contributors and a warm invitation to reconvene in the fall of 2007 in Leipzig for the second joint Italian-German Purine Club meeting.