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International meeting "Purines 2010: adenosine nucleosides and nucleotides in biomedicine"

Maria P. Abbracchio · Renata Ciccarelli

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The Purines 2010 International Meeting belonging to the well-known series of meetings started back in the 1980s of the last century took place between May 30 and June 2, 2010, in Tarragona (Spain), a pleasant and ancient town, located on the eastern Spanish Golden Coast (Costa Dorada), less than 100 km south of Barcelona. Throughout the meeting, the climate was pleasant and ideal, with the moderately warm temperatures that characterize the spring and summer seasons in this town. Participants (more than 400 scientists coming from many European and overseas countries like Australia, Brazil, Canada, Japan, and USA) enjoyed both Tarragona's picturesque scenery of the Roman ruins and monuments and the tasty food offered at the Congress site or at local restaurants.

The scientific program, arranged with the support of an International Board formed by the most eminent scientists in the field of Purines, was very efficiently managed by the local Organizing Committee, that included, for the most part, Spanish researchers, but also scientists from UK (Geoffrey Burnstock), Portugal (Rodrigo Cunha, Alex Ribeiro, and Ana Sebastiao), and Italy (Maria Abbracchio and Piero Borea). The program was very busy and included six plenary lectures and 18 symposia. The organizers left a wide space to the presentation of posters (more than 260 on 21 different topics) that were exhibited throughout the meeting. The presence of poster presenters was required every day in the first part of the morning, a notable change in this series of meetings that was appreciated and considered highly valuable by all participants. Noteworthy, the Organizing Committee selected 45 posters for brief oral communications to be given in three parallel sessions in the afternoon of each day at the end of the symposia sessions.

As a tradition, the opening lecture was delivered by Geoffrey Burnstock (University College, London, UK), recognized all over the world as the pioneer who, more than four decades ago, proposed the existence of purinergic transmission and whose illuminated vision and passionate dedication have guided hundreds of scientists over the years. Geoff gave a very detailed and updated overview of the localization and activity of purinergic receptors in different cells and tissues, with particular emphasis on the role played by purinergic signaling in central nervous system (CNS) disorders, pain, and cancer. In the following days, plenary lectures were given by several outstanding scientists. Holger Eltzschig (University of Colorado, USA) highlighted a novel protective role played by adenosine in cardiac adaptation during ischemia, based on the stabilization of the circadian gene period2 (Per2). Francesco Di Virgilio (University of Ferrara, Italy) superbly reviewed the history of $P2X_7$ receptors that do not only act as mediators of cytotoxic effects but may also promote the growth of both normal and tumoral cells, an effect that could be exploited for innovative antitumor therapies. Pnina Fishman (Can-Fite BioPharma, Israel) presented very exciting findings on the efficacy and safety of CF101 (IB-MECA), a selective A_3 receptor agonist, in patients bearing severe

M. P. Abbracchio
Laboratory of Molecular and Cellular Pharmacology of Purinergic Transmission, Department of Pharmacological Sciences,
University of Milan,
Milan, Italy

R. Ciccarelli
Department of Biomedical Sciences, "Gabriele D'Annunzio"
University of Chieti-Pescara,
Chieti, Italy

M. P. Abbracchio (✉)
Department of Pharmacological Sciences, University of Milan,
Via G. Balzaretti 9,
20133 Milan, Italy
e-mail: mariapia.abbracchio@unimi.it

autoimmune inflammatory diseases such as rheumatoid arthritis, psoriasis, and dry eye syndrome. Results from human phase II clinical trials are very promising and support the candidature of CF101 as a new therapeutic agent in the management of these diseases. Other preliminary results presented by P. Fishman also solicit further studies on the effects of A_3 agonists in additional human hematological diseases and malignancies. The last two plenary lectures were given by Marçal Pastor-Anglada (University of Barcelona, Spain) and George Gorodeski (University of Cleveland, USA). Marçal presented data on the role played by different nucleotide transporters belonging to the concentrative and equilibrative families, which are present in the plasma membrane of every type of cells, to assure not only purine salvage and metabolic turnover but also a balanced amount of extracellular purines for cell signaling and interactions. George Gorodeski focused on the apoptotic/cytotoxic role played by $P2X_7$ receptors in epithelial cells, emphasizing the possibility of exploiting these receptors as either potential biomarkers or as targets for innovative pharmacological treatment of epithelial cancers.

The 18 symposia were distributed in parallel sessions, three in the morning and three in the afternoon of each day. Each symposium accommodated three to four speakers, leaving ample time for discussion. In the following pages, we summarize some of the issues and novel findings. It is likely that our report is biased by our personal research interests and, therefore, we apologize for not mentioning all the important contributions presented during the symposia because we were unable to attend all the different sessions.

In the first symposium (S1) dedicated to Medicinal Chemistry, the synthesis and biological activity of new ligands for purinergic receptors were reported. In detail, Christa Muller (University of Bonn, Germany) showed a number of derivatives from Reactive Blue 2, some of which behave as potent antagonists of $P2Y_{12}$ receptors, whereas some others act as selective antagonists of $P2X_2$ receptors or of ecto-5′-nucleotidase. Sergio Castillon (University Rovira i Virgili, Spain) analyzed the most significant modifications introduced in the ribose or purine moieties of the nucleoside structure that enable new compounds to exhibit different (antiviral, antibacterial, or antimetabolic) properties. Gloria Cristalli (University of Camerino, Italy) showed recent findings on new $P2X_3$ receptor ligands, some of which behave as partial agonists and some other as full antagonists at these receptors, thus offering novel tools to counteract sense painful stimuli, whereas Ad IJzerman (Leiden University, The Netherlands) described in detail the $A_{2A}R$ crystal structure, which represents an indispensable basis for new drug design.

Three symposia (S5-13-18) were devoted to purine metabolism and turnover. One of these, chaired by Stephen Baldwin (University of Leeds, UK), analyzed the structure and activity of different nucleoside transporters in parasites or bacteria, as useful models to better understand the function of these molecules in eukaryotic cells. The second one dealt with the activity and the significance of enzymes hydrolyzing adenosine triphosphate (ATP) in normal (Jean Sevigny, University of Laval, Canada) and pathological conditions (Maria Schetinger, University of Santa Maria, Brazil), including vascular injury and systemic inflammation (Karen Dwyer, University of Harvard, USA), as well as urologic disorders (Paulo Correia-de-Sà, University of Porto, Portugal). The third symposium, chaired by Carles Solsona (University of Barcelona, Spain), focused on the release of purines from nervous cells through specific proteins acting as channels (connexin 32 and pannexin 1) and highlighted the importance of adopting sophisticated techniques to monitor extracellular nucleotide and nucleoside concentrations in situ. In this respect, Beata Sperlagh and colleagues (Hungarian Academy of Sciences, Hungary) presented data obtained with the microelectrode biosensor technique, which allows quantification of the efflux of neurotransmitters, including purines, with a resolution better than conventional methods.

Symposium S6 dealt with purinergic signaling in development and stem cell regulation. Maria Abbracchio (University of Milan, Italy) highlighted the pivotal role of the P2Y-like receptor GPR17 (whose ability to respond to uracil nucleotides has been recently confirmed by another independent group) in oligodendrocyte differentiation and myelin formation, and proposed this receptor as a new pharmacological target for demyelinating diseases. Doug Fields (NIH, USA) presented new exciting evidence in favor of non-vesicular release of ATP by axons through specific ion channels in response to action potentials. Due to the close anatomical and functional relationship between neurites and oligodendrocyte precursor cells (in the (CNS)) or Schwann cells (in the peripheral nervous system), this form of ATP release may play a key role in regulating neuronal myelination during development or after injury. Herb Zimmermann (University of Frankfurt, Germany) overviewed the role played by adenine nucleotides as paracrine or autocrine signaling molecules in promoting the proliferation, migration, and differentiation of neural progenitors in adult brain, whereas Katya Ravid (Boston University, USA) showed a fundamental role played by adenosine $A_{2B}R$ on mesenchymal stem cell differentiation into bone cells. Such an effect, coupled to the ability of these receptors to suppress osteoclast-mediated bone resorption, potentially favors fracture healing. Other two symposia concerning the involvement of purine receptors in sensory systems also attracted great interest. Of these, symposium S2 was devoted to different aspects of pain sensation. Kazu Inoue (Kyushu University,

Japan) focused on the upregulation of $P2X_4$ receptors in spinal microglia after nerve injury as a consequence of interferon-γ signaling and on its contribution to neuropathic pain. Elsa Fabbretti (University of Nova Gorica, Slovenia) described the involvement of $P2X_3$ receptors, which are upregulated via calcitonin gene-related peptide in an animal model of migraine, in inducing nerve sensitization, which, in turn, plays a key role in chronic pain. Stefan Lechner (Max Delbrueck Center, Germany) focused on the peripheral sensitization of C-fiber nociceptors induced by UTP via P2Y2 receptors, whereas Michael Salter (Hospital for Sick Children, Toronto, Canada) showed disinhibition of nociceptive neurons caused by brain-derived neurotrophic factor, that is, in turn, released by microglia upon $P2X_4$ receptor stimulation. In the second symposium, contributions focused on the involvement of purine nucleotides in the regulation of intraocular pressure via $P2Y_2$ receptors (Jesus Pintor, University of Madrid, Spain), hearing sensitivity via $P2X_2$ receptors (Gary Housley, University of New South Wales, Australia), olfactory system via both ionotropic and metabotropic P2 receptors (Colleen Hegg, Michigan State University, USA), and taste, mainly via $P2X_2$ and $P2X_3$ receptors (Thomas Finger, University of Colorado, USA).

Several symposia highlighted the role played by $A_{2A}R$ in brain function. One of these (S9) was dedicated to the interactions of $A_{2A}R$ with other receptors activated by neurotransmitters or purines themselves. Serge Schiffmann (University of Bruxelles, Belgium) and Francisco Ciruela (University of Barcelona, Spain) emphasized the relevance of striatal post-synaptic A_{2A}/dopaminergic D2 and of presynaptic A_{2A}/A_1 receptor heteromerization in modulating, respectively, striatopallidal neuronal depolarization and corticostriatal glutamatergic afferents. It was concluded that compounds with a preferential in vivo profile as striatal pre- or post-synaptic A_{2A} antagonists may be of potential utility for the therapy of dyskinetic/obsessive-compulsive disorders and drug addiction or Parkinson's disease, respectively (Sergi Ferrè, NIH, USA). Patrizia Popoli (ISS, Rome, Italy) highlighted the ability of A_{2A} receptors to heterodimerize and functionally interact with further receptors, such as cannabinoid CB1 receptors in striatum. Symposium S15 was devoted to the interactions between A_{2A} and growth factor receptors, which may play a significant role in neurodegenerative diseases (Alex Ribeiro, University of Lisbon, Portugal and Rod Cunha, University of Coimbra, Portugal). In this context, Cinzia Volonté (S. Lucia Foundation, Rome, Italy) dealt with the great heterogeneity of purinoceptors in the cell membrane and proposed the construction of a database to group all the known types of receptors as homo- or heteromers and develop a mathematical model for the prediction of oligomer formation. Similar aspects were discussed in symposium S10 on "Purinergic signaling and brain disorders," in which Ana Sebastiao (University of Lisbon, Portugal), Felicita Pedata (University of Florence, Italy), and Michael Schwarzschild (Harvard University, USA) confirmed the crucial role played by A_{2A} receptors in acute or chronic brain diseases, while Alexej Verkhratsky (University of Manchester, UK) gave an excellent account of purinergic signaling in neuroglia, underlying its involvement in both the physiological regulation of glial cells and in virtually every form of neuropathology. The widespread effects induced by caffeine, a well-known adenosine receptor antagonist, were reviewed in another symposium (S3) chaired by Piero Borea and William Lovallo. It was underlined how patients with hypertension, showing increased CNS reactivity due to enhanced cortisol, may have exaggerated responses to caffeine in combination with behavioral stress. On the other hand, new data on the consolidation and retrieval of memory by caffeine were presented, confirming its potent positive effects on cognitive performance.

Symposium S4 was entirely devoted to show the functional role of $P2X_7$ receptors, either in neurons (Maria Teresa Miras-Portugal, University of Madrid, Spain) or astrocytes (Peter Illes, University of Leipzig, Germany) under physiological conditions and in neuroblastoma cells, where $P2X_7$ stimulation affects cell differentiation (Antonio Artalejo, University of Madrid, Spain).

The therapeutic potential of purine drugs was discussed in symposium S7. Ken Jacobson (NIH, USA) recalled the therapeutic effects of some A_3R agonists already discussed by Pnina Fishman in her lecture, reporting that he is currently working on some further molecules belonging to the same class. He also mentioned molecules acting as agonists or antagonists of various P2 receptors, focusing on $P2Y_6$ receptors, whose activation may play a protective role in peripheral (pancreatic cells) or nervous cells. Ken also showed data obtained with a new technique able to incorporate fluorescent or reporter groups into ligands, thus providing new tools for receptor assay or imaging; finally, he provided interesting examples of multivalent G protein-coupled receptor ligand-dendrimer (GLiDe) conjugates, which have increased potency or selectivity in comparison to monomeric ligands. In the same symposium, Jiang-Fan Chen (Boston University, USA) summarized the role played by $A_{2A}R$ and its ligands in the cognitive impairment and behavioral rigidity found in acute traumatic brain injury as well as in neurodegenerative diseases; Joel Linden (University of Virginia, USA) emphasized how $A_{2A}R$ stimulation is able to reduce pulmonary dysfunction in mice with sickle cell disease, thus representing an alternative potential therapy to block the activation of CD1d-restricted iNKT cells which are recognized to act as trigger of an inflammatory cascade. Josè Boyer (Inspire Pharmaceuticals, USA) reported encouraging new data on the therapeutic potential of Denufosol, a

$P2Y_2$ receptor agonist, administered for 24 weeks to patients with cystic fibrosis in comparison to a placebo within a double-blind clinical trial. Another important symposium for therapeutic implications was that on "Purines and Cancer" (S17), in which Jashvant Unadkat (University of Washington, USA) showed the important role played by nucleoside transporters in mediating the efficacy and toxicity of nucleoside antineoplastic drugs (such as gemcitabine or ribavirin). In the same symposium, Igor Feoktistov (Vanderbilt University, USA) demonstrated that the overexpression of adenosine A_{2B} receptors in primary human tumors seems to promote tumor neovascularization, thus representing an important therapeutic target in cancer biology. Sally Coulthard (Newcastle University, UK) reported that the deletion of methyl-thioadenosine phosphorylase in cancer cells favors the antitumoral activity of thiopurines. Finally, Misha Sitkovsky (Northeastern University, Boston, MA, USA) provided data obtained with Kengo Moriyama on the role of A_{2A} and A_{2B} receptor interactions in generating an immunosuppressive response in vivo. Misha's original findings on the critical involvement of adenosine in the protection of normal and cancerous tissues have been recently corroborated by independent observations that even bacteria produce adenosine to evade immune responses. Another symposium that dealt with the purinergic regulation of immune cells and inflammation was symposium S11. Carmen Montesinos (University of Valencia, Spain) showed how promotion of wound healing by topical application of a selective adenosine A_{2A} agonist requires the expression of tissue plasminogen activator, via a complex mechanism involving its main inhibitor PAI-1 and its cell receptor annexin II. Bruce Cronstein (New York University School of Medicine, USA) reported evidence that both A_1 and A_{2A} receptors play a critical role in osteoclast formation and function. In detail, he showed that an adenosine A_{2A} agonist inhibits wear particle-induced bone loss, suggesting this receptor as a novel target for therapies designed to treat osteoporosis and to diminish prosthesis failure. In the same symposium, James Wiley (University of Melbourne, Australia) showed a novel role for the $P2X_7$ receptor in phagocytosis. Overexpression of $P2X_7$ in cells greatly augmented phagocytosis of beads and bacteria in the absence of serum. This novel phagocytic pathway also operates in vivo, as evidenced by inhibition of the uptake of latex beads and bacteria by peritoneal macrophages of mice by prior injection of ATP. Finally, Didier Communi (IRIBHM, ULB, Belgium) reported that lipopolysaccharide and ATPγS stimulated bone marrow-derived dendritic cells (BMDCs) to secrete estimated Epidermal Growth Factor Receptor (EGRF) ligand that, in turn, stimulated proliferation of Lewis lung carcinoma cell growth in vitro. Interestingly, also in vivo, tumor weights were significantly increased after co-injections of Lewis lung carcinoma cells with lipopolysaccharide and ATPγS-treated BMDCs or their supernatants, suggesting that ATPγS confers tumorigenic properties to human and murine dendritic cells.

At the end of the meeting, the Springer Prizes for the best poster and oral presentations were awarded by Geoff Burnstock (Editor-in-Chief of *Purinergic Signalling*) and Thijs van Vlijmen (Publishing Editor of Springer Publications) to

Filipa F. Ribeiro (Portugal)—First Poster Prize
Younis Baqi (Germany)—Second Poster Prize
Miriam Peeters (Netherlands)—First Presentation Prize
Miriam León-Otegui (Spain)—Second Presentation Prize

In conclusion, we believe that the Tarragona meeting has represented a good example of the vitality of research and of the recent progresses made in the field of purinergic signaling, where some innovative therapeutic applications are finally coming true. The time spent in Tarragona discussing and exchanging ideas with many colleagues was really exciting. Due to its friendly, informal, and open atmosphere, this type of meeting is ideal to meet old friends and welcome new scientists entering the field. For these reasons, it is our honor and pleasure to announce to all readers, on behalf of corresponding organizers, several future meetings in the field:

1. First Brazilian Purine Club Meeting on *Purinergic Signaling: Biological and Therapeutic Implications*, August 23–25, 2010 Águas de Lindoia, Brazil (Organizing Committee: Henning Ulrich, Robson Coutinho-Silva, and Ana Maria Oliveira Battastini)
2. The UK Purine Club Meeting in Nottingham, Sept 17, 2010 (Organizers: Vera Ralevic and Steve Alexander)
3. ASN (American Society of Nephrology) 2010 Symposium, Denver, CO, USA, November 16–21, 2010. Scheduled date: November 18, 2010; title: *Regulation of Renal Function by Extracellular Nucleotides*
4. Auxiliary Meeting at the ASN 2010 Venue in Denver. Scheduled date: November 17, 2010; title: *Purinergic Signaling in the Kidney: The Present and the Future*. Both meetings N.3 and N.4 have been promoted by the US Renal Purinergic Club
5. The Fourth German–Italian Joint Meeting belonging to the highly successful series of the Italian–German Purine Club meetings will be organized by Christa Muller in Bonn, in July 2011, and will be also open to scientists coming from all countries
6. The next international meeting of the "Purines" series (*Purines 2012*) will be organized by Kazu Inoue in 2012, in Japan

More details on these exciting meetings are available on the web.