European meeting “P2 receptors: new targets for the treatment of osteoporosis”

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Over the past decade, evidence has accumulated that the purinergic system plays a central role in bone physiology, and a number of research groups have focused on the investigation of this [1–3]. However, no formal collaboration had been established before the first call in the 7th Framework Programme under the European Union was announced during winter 2006. One of the topics in the HEALTH program was “Osteoporosis: signalling pathways in bone formation and homeostasis”. With the aim of submitting a proposal for this topic, the ATPBone consortium was created consisting of seven partner institutions from five European countries. The participants were: University College London, University of Sheffield and University of Liverpool from the UK, University of Ferrara, Italy, Université Libre de Bruxelles, Belgium, University of Maastricht, The Netherlands, and University of Copenhagen, Denmark. They had all extensive research experience in the fields of purinergic signaling, bone biology, inflammation,

and related areas. In addition, the project was kindly supported by Geoffrey Burnstock, who as senior advisor gave important input to the design and objectives of the project. The project, “Fighting osteoporosis by blocking nucleotides: purinergic signaling in bone formation and homeostasis”, was funded with 3,000,000 € for a 3-year period, and in January 2008 the first meeting was held at London.

The overall aim of the project was to provide mechanistic basis for nucleotide-based therapeutics in osteoporosis, effective through modulation of bone formation and homeostasis. The project was therefore focused on (a) the role of P2 receptors in bone physiology and in skeletal mechanotransduction, (b) the role of single nucleotide polymorphisms of P2 genes in osteoporosis etiology and their possible use for osteoporosis diagnosis and prognosis, and (c) the effect of intervention using P2 receptor agonists and antagonists on osteoporosis. Thus, the project was designed as a multidisciplinary project, ranging from the basic understanding of the role of P2 purinergic signaling in bone cells over translational studies on the in vivo pharmacological effects of P2 receptor modulation on bone to early clinical studies of the effects of nucleotides in humans.

The initiation of the project has led to an extensive collaboration across the participating centers with frequent exchange visits of scientific personnel among groups. Furthermore, during the course of the project, there have been semi-annual ATPBone mini-symposia with the presentation of scientific achievements from the researchers involved in the project in addition to presentations from invited speakers relevant to the field. The first mini-symposium was held in conjunction with the Purines 2008 meeting in Copenhagen, and the latest took place in Brussels on November 19, 2010.

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The opening lecture was delivered by Jean-Jacques Body (Université Libre de Bruxelles), chairman of the Belgian Bone Club. He presented an overview of osteoporosis, its current therapies, and unmet needs. Alistair Bond (University of Liverpool) presented his last results on the control of nucleotide release by osteoblasts and showed that fluid shear stress, but not compressive forces, induces ATP release. Patrizia Pellegatti (University of Ferrara) showed that the P2X₇ receptor drives osteoclast fusion by increasing the extracellular adenosine concentration, demonstrating a yet undescribed cooperation between P2 and adenosine receptors. Isabel Orriss (University College London) showed that the P2Y₆ receptor is the most highly expressed of the P2 receptors present on mature osteoclasts and that the bone resorptive activity is strongly reduced in osteoclasts obtained from P2Y₆^{-/-} mice, resulting in increased cortical bone mass. Ning Wang (University of Sheffield) described the bone phenotype of P2Y₁₃^{-/-} mice, which is characterized by a reduced bone turnover, with a decrease in both osteoblasts and osteoclasts, resulting in less trabecular bone but thicker cortical bone.

In the afternoon, Valérie Gangji (Université Libre de Bruxelles) summarized the current status of cell therapy for bone disease. Galadrielle Biver showed that the decreased bone formation in P2Y₁₃-deficient mice might be explained by a reduced differentiation of bone marrow mesenchymal stem cells/osteoprogenitors into osteoblasts. Susanne Syberg (University of Copenhagen) showed that P2 receptor modulation in vivo has an impact on bone. Anke Wesselius (University of Maastricht) presented preliminary results on the association between single nucleotide polymorphisms of P2 receptors and bone density.

Francesco Di Virgilio (University of Ferrara) presented the concluding remarks. He emphasized that ATPBone has given a big boost to our understanding of the role of P2 receptors in bone, placing the purinergic axis at the heart of bone metabolism. The participating units have shown that extracellular nucleotides play a major role in bone deposition, acting at P2Y₂ and P2Y₁₃ osteoblast receptors, and in bone resorption, acting at P2Y₆ and P2X₇ osteoclast receptors. Strong evidence has been gathered that, by modulating cytokine release by immune cells in the bone

marrow, nucleotides have a strong indirect effect on osteoblast and osteoclast functions, not to mention the crucial participation of extracellular ATP in all inflammatory processes involving bone (infections, aseptic necrosis, cancer metastasis). Thanks to the tight collaboration among the different partners, bone metabolism in different transgenic animals (P2Y₆^{-/-}, P2Y₁₃^{-/-}, P2X₇^{-/-}) has been investigated, thus highlighting the effect of selected P2 receptor gene deletions on bone homeostasis [4]. Initial attempts to monitor in vivo ATP release in response to mechanical stress have also been made, thanks to the use of pmeLUC transgenic mice expressing luciferase on the cell membrane [5]. Furthermore, the effect on bone homeostasis of several P2-targeted drugs has been investigated in vivo, providing additional strong proof for the important function of P2 receptors in the pathophysiology of bone. Emphasis has also been placed on the translational aspect, which involved recruitment of a large cohort of patients for the investigation of the association with osteoporosis of selected mutations in the P2X₇ receptor. A wealth of genetic and biochemical data have been collected that are now being processed.

In conclusion, the Brussels meeting has shown without doubt that the ATPBone project has generated more knowledge than was anticipated at the beginning and will be a landmark in ATP and bone studies.

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