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MEETING REPORT

5th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone Disease: Oxford Workshop 2012

T John Martin[1] and James R Edwards[2]

[1]St Vincent's Institute of Medical Research, University of Melbourne, Melbourne, Victoria, Australia.
[2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK.

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Meeting Report from the 5th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone Disease, Oxford, UK, 27–30 June 2012

This fifth meeting in a series organized in the last decade by Professor Graham Russell, Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford, was aimed at bringing academic and industry scientists together to discuss disease mechanisms and current and prospective molecular targets for development of drugs for metabolic bone diseases. As in the previous meetings, this benefited by having strong representation from industry as well as academic scientists, with the sessions held in an atmosphere of very open discussion. The topic was covered broadly and in depth, with 200 participants in the 4-day meeting. It was preceded by a 2-day instructional course for PhD students, organized by the European Calcified Tissue Society, and with more than 60 graduate student participants. This report outlines only some aspects of a most successful meeting, made possible, as with the previous meetings, by the excellent help provided by Janet Crompton as Conference Organiser. Further details about the program and speakers, sponsors and other information can be found on the website www.oxfordbonepharm.org/.

Genetics

Several views of genetics were discussed, reflecting the many advances in skeletal biology provided by both human and mouse genetics, and beginning with a review by Stuart Ralston (Edinburgh). He pointed out that collagen gene mutations accounted for most cases of osteogenesis imperfecta, but the relatively recent discovery of osteogenesis imperfecta caused by abnormal hydroxylation of collagen despite normal collagen secretion[1] shows that primary structure alone is not the only determinant. For osteoporosis, twin studies show us that the heritability of bone mineral density (BMD) is 50–80%, of bone turnover is 40–70%, but total fractures only 0–68%. Despite the heterogeneity of fractures indicated by the latter figures, early-age fractures show a stronger inheritance. Improved appreciation of the genetic basis of low BMD and osteoporosis has come from several genome-wide association studies and next gene sequencing (predominantly exome sequencing) in the past several years. From the beginning of these studies, genes in the RANKL/RANK and Wnt pathways featured, and were repeated in later studies.[2] A 2012 study revealed 56 new gene loci linked to BMD, which include the RANK, Wnt and NOTCH pathways.[3] Outcomes of the genome-wide association studies approach loci have been in proportion to sample size, with most key regulatory genes in the bone pathways having been identified. This approach has a potential role in target identification and validation, but alleles of large effect have yet to be discovered, a hope that remains with exome sequencing.

Genetics provided other sources of great interest. Sir Archibald Garrod coined the term, 'Inborn Errors of Metabolism' in the 18th century when he described the syndrome of alkaptonuria, shown later to result from mutations in the enzyme homogentisate 1,2-dioxygenase, a crucial component of tyrosine degradation. This defect leads to accumulation of homogentisic acid, then converted to ochronotic acid, with affected individuals' urine turning black, and severe osteoarthritis (OA) developing as a result of bone and cartilage lesions that occur in response to relatively minor damage.[4] This was presented by James Gallagher (Liverpool) and Alan Boyde (London), as a model of severe OA and demonstrated using novel *in vitro* models,[5] *ex vivo* organotypic cultures[6] and a mouse model of the disease.[7] The formation of homogentisic acid can be blocked with Nitisonone, and studies are ongoing examining this mechanism in the pathogenesis of disease and as a potential treatment.

Another particularly exciting treatment for an inborn error of metabolism came from Michael Whyte (St Louis).

Hypophosphatasia, due to mutations in the alkaline phosphatase gene, manifests itself from very severely affected infants to mildly affected adults. The human syndrome was recapitulated in genetically manipulated mice, and led to the development of an engineered form of alkaline phosphatase, in which the TNSALP dimer is linked to IgG1-Fc and targeted to bone with aspartic residues added (Enobia, Montreal, Quebec, Canada). This reagent was successful in treating skeletal and dental defects in alkaline phosphatase-deficient mice,[8–10] but most importantly, in the treatment of some very severely affected children, both with severe neonatal hypophosphatasia, and in less severely affected older children.[11] This exciting advance clearly has implications for bone-targeted therapy in other disorders as well.

Cell Biology

Cell biology of bone, cartilage, muscle and even tendon featured in many of the talks, reflecting the scope of biological interest broadened to be genuinely musculoskeletal. For example, Philippa Hulley (Oxford) highlighted drugable approaches to tendon therapy including growth factors, ion channel targets and oxidative stress, and strategies to combat the damaging effects of glucocorticoids, highly overused in the management of tendon disease. Joanna Price (Bristol) took the mechanostat as her theme, pointing out that increased bone mass is a continuous variable determined by functional loading. Application of strain decreased sclerostin in osteocytes within 30 min and increased periosteal cell number within 24 h *in vivo* through inhibition of Wnt signaling. Loading was linked to sites of bone formation, and was seen at secondary rather than primary spongiosa.[12] Furthermore, *in vitro* osteoblast proliferation induced by strain was blocked by treatment with sclerostin. A key question is—how is production of sclerostin so rapidly regulated by strain? Prostaglandin E2 is a candidate, but so too are other local products such as PTHrP, and gp130 cytokines. Michaela Kneissel (Basle) comprehensively reviewed sclerostin regulation and action, with several aspects of interest. The increased bone formation of *sost* deficiency relies in part on LRP5, and notably, LRP4 was shown to be an osteoblast- and osteocyte-specific facilitator of sclerostin action, with the latter largely prevented in *LRP4* –/– mice. The parathyroid hormone (PTH) effect on periosteal bone formation was lost in sclerostin-overexpressing mice, and the increased bone resorption appearing over time with PTH treatment in the mouse was not evident with co-treatment with antisclerostin.

The role of fat mass in skeletal biology was highlighted by Cliff Rosen (Maine) who drew attention to the high uptake of lipids in the bone marrow, the distinct differences between white- and brown adipose tissue and how each may determine skeletal remodeling rates. Specifically how the volume of preformed brown adipose tissue directly related to BMD.[13] Brown adipose tissue influences thermogenesis in humans and can be altered by overall body mass index and temperature. The hypothesis that the thermoregulatory system may impact skeletal homeostasis is supported by Dock 7 loss of function mice (Misty mice), which lack brown adipose tissue and develop accelerated age-related trabecular bone loss. Interestingly, similar to bone mass, brown adipose tissue is lost with increasing age, suggesting a link between ageing, diet and skeletal remodeling. This concept was explored by James Edwards (Oxford) who highlighted confounding data relating to obesity and bone mass, how caloric restriction can protect against age-related bone loss in addition to prolonging lifespan, and suggested potential mediators of this effect such as SIRT1 and the adipokine, adiponectin. The convergence of dietary- and ageing-related mechanisms were further examined by Katja Simon (Oxford) with a focus on autophagy, a lysosomal degradation pathway that prevents cellular damage. The autophagic process is retarded in ageing cells, can be increased by caloric restriction and deletion of key autophagy-related genes such as Atg7 display an accumulation of mitochondria and reactive oxygen species, as well as increased proliferation and DNA damage within the hematopoietic stem and progenitor cell compartment.[14] These findings are particularly relevant for how age-related DNA damage may be resolved within the cells of the ageing skeleton, and suggest further mechanisms through which diet may impact bone homeostasis over time. Alison Gartland (Sheffield) reviewed purinergic signaling, whereby energy metabolism, specifically ATP and adenosine release, have the potential to impact bone biology through numerous subtypes of receptors expressed on osteoblasts and osteoclasts. Osteoblasts release ATP into the bone microenvironment, a feature enhanced by mechanical loading, and mice deficient in the P2Y13 receptor have decreased bone volume brought about by a shift in the RANKL/osteoprotegerin ratio,[15] whereas polymorphisms in the P2X7 receptor are associated with decreased BMD and increased fracture.[16,17]

Paolo Bianco (Rome) delivered a thought-provoking summary of current attitudes and applications in stem cell biology, and emphasized the role of Gsα signaling in this system. This included the deletion of GsaR201C in cells of an osteoblast lineage and a resulting increase in overall bone mass.

Therapeutics: Those on the Way, Those in Current Use, and Those That May Not Get There

Some new aspects of the anabolic action of PTH were broached. Serge Ferrari (Geneva) had noted that even when bone remodeling is virtually entirely blocked by anti-RANKL, PTH was still able to increase bone formation to some extent. That was perhaps not surprising, given the known direct effects of PTH on the osteoblast lineage. One such effect was to increase proliferation of periosteal osteoblasts.[18] Ferrari reported that these cells selectively express periostin,[19] a known PTH-regulated gene.[20] Both PTH and periostin treatment of UMR106 cells decreased sclerostin expression, and PTH treatment increased periostin *in vivo*, revealing a correlation of serum periostin with periosteal bone formation in mice treated with PTH(1–34). The question is asked whether the periosteal effect of PTH could be due to sclerostin suppression? Another interesting aspect of PTH action was presented by Natalie Sims (Melbourne), who showed that when mice were treated daily with PTH (1–34), concomitant treatment with blockade of ephrinB2 interaction with its receptor, EphB4, resulted in a resorptive phenotype and loss of the anabolic effect of PTH. This was due to ephrinB2/EphB4 receptor blockade leading to increased osteoclast formation, shown *in vitro* in co-cultures in response to several stimuli, and *in vivo* with PTH treatment.

Lorraine Fitzpatrick (Philadelphia), in discussing the search for a 'perfect anabolic agent', focussed on PTH, aiming to extend the gap between the increase in bone formation markers and the onset of increased resorption markers—what some call

'the anabolic window'. A calcium-sensing receptor antagonist, Ronacaleret, used to promote PTH secretion, produced plasma levels of PTH with a profile broader than that with PTH (1–34), but with a lower peak. The drug's effects on formation and resorption markers were similar to those of PTH injections, but unlike the latter, lacked increase in vertebral BMD. Importantly, all doses were hypercalcemic, thus it induces a state of mild hyperparathyroidism.

Henry Bryant (Indianapolis) outlined the searches made over several years for selective modulators of the vitamin D and glucocorticoid receptors. The tantalizing evidence that active vitamin D analogs could stimulate periosteal bone formation kept this goal alive, with the aim of dissociating a beneficial bone effect from the undesirable consequences of hypercalciuria and hypercalcemia. Targeting a non-secosteroid molecule, and using activation of the osteocalcin promoter as an osteoblast response and intestinal calcium transport through TRPV6 activation as assays, it was possible to find compounds that dissociated these two effects by as much as 70-fold. Although these encouraging differences were consistent in mouse and rat preclinical models, they failed to transfer to normal human subjects. Again, in searching for a selective glucocorticoid receptor modulator, aiming at preservation of the anti-inflammatory but loss of the bone effect, preclinically promising candidates did not translate to human subjects either as anti-inflammatory agents, or in respect of safety margins. This experience with these two nuclear receptor targets seems to be reflected by outcomes of the searches of other groups. There is little at present to suggest that in these cases there will be outcomes similar to those with Tamoxifen, and particularly Raloxifene, where tissue-selective activation of the estrogen receptor could clearly be shown.

It was valuable to have these frank appraisals of some negative outcomes of the drug discovery process, and interesting that efforts continue with other nuclear receptors.

Gary Krishnan (Indianapolis) outlined early attempts to develop a selective androgen receptor modulator (SARM) for age-related decline, one that would build muscle, and perhaps bone also, while not activating the prostate. He described the development of an immortalized cell line from Pax7-positive satellite cells derived from rat muscle that were androgen-responsive, and could assimilate into C2C12 myotubules. The satellite cells themselves were distinct from C2C12 cells, did not express either myogenin or MyoD, and responded to androgen with increased IGF-1. Evidence was presented that the androgen responsiveness *in vivo* was limited to a subset of cells that functioned as a local source of the hypertophy-inducing agent, IGF-1. Screening in the satellite cell line identified three SARM candidates in which the rank-order effect on the satellite cells correlated closely with rank order of effect on muscle anabolism *in vivo*. Importantly, these completely avoided any prostate stimulation, and one candidate SARM increased vertebral bone in a delayed rat orchidectomy treatment model. The approach being used here is novel, and the early outcomes interesting and encouraging.

This meeting had quite a focus on bisphosphonates, from the very clinical to the search for new analogs that might have other applications. At the clinical level, Ian Reid (Auckland) reported the dose-dependence between 1 and 5 mg, of single-dose treatment with zoledronate and measurement of bone density and biochemical markers.[21] Strikingly though, a single dose of 5 mg kept BMD up and bone resorption markers down for 5 years. Although the bone resorption markers rose slightly after 2 years, their levels then flattened well below controls.[22] He reported that single-dose treatment of Paget's Disease with zoledronate has revolutionized the treatment of that condition, with remissions lasting longer than 6 years, and confirmed in an excellent review of the biology and management of Paget's disease by David Roodman (Indianapolis).

The cathepsin K enzyme in osteoclasts has proven to be an interesting target for antiresorptive drug development, with Merck's Odanacatib reported by Le Duong (Philadelphia). In preclinical studies in rabbits and monkeys Odanacatib is an effective inhibitor of resorption without inhibiting bone formation. Osteoclast numbers on bone increase, but their resorption capacity is disabled, with shallow resorption pits evident, the result of lack of the crucial protease. The monkey treatment studies show that Odanacatib is an effective resorption inhibitor, with a dose-dependent inhibition of trabecular bone formation but endocortical and intracortical bone formation are maintained, and most strikingly, periosteal bone formation is increased.[23,24] The latter is a most intriguing outcome, with no obvious explanation—perhaps the periosteum or the osteocyte population might contain target cells for the enzyme inhibitor. The human Phase II study showed decreased bone resorption markers, with no decrease in bone formation markers. The large Phase III fracture study is awaited with much interest and expected to be completed late 2012, with the possible emergence of a new class of 'dual action' resorption inhibitor.

Arthritis

Cyrus Cooper (Oxford/Southampton) posed an interesting challenge, to re-define OA with regard to recent data describing stark variation in disease progression and pain.[25,26] The potential for strontium ranelate as a therapy in this setting was also explored based on emerging evidence from phase III trials, suggesting a decreased progression of vertebral OA and up to 30% decrease in knee joint space narrowing following treatment with strontium ranelate. The continuing search for better therapies to treat inflammatory arthritic disease was discussed by Peter Taylor (Oxford) who clearly illustrated this need by emphasizing how only 20% of patients on current anti-inflammatory drugs (for example, golimumab) show a good response. Small molecules targeting receptor kinase proteins are considered mainly after anti-tumor necrosis factor therapy fails and include those in the Syk pathway such as Fostanatinib, which has shown good results in phase II trials though is largely cell non-specific, Jak inhibition by for example Tofacitinib, which improves joint function and inhibits structural joint damage in Phase III trials, and drugs targeting the MAPK pathway (for example, BMS582949).

Cancer

Multiple myeloma illustrates very well how the bone microenvironment can influence cancer progression. Claire Edwards (Oxford) described how identifying changes in the bone marrow microenvironment that contribute to myeloma pathogenesis can lead to the identification of new therapeutic approaches for the treatment of myeloma and the associated bone disease. In a series of elegant experiments, utilizing adiponectin-deficient mice and serum from patients with the pre-malignant condition

monoclonal gammopathy of undetermined significance, she demonstrated that a decrease in host-derived adiponectin can promote myeloma pathogenesis. Furthermore, she used an apoplipoprotein A1 peptide mimetic, L-4F, to increase circulating adiponectin and subsequently reduce tumor burden and bone disease in a murine model of myeloma, and increase bone in non-tumor bearing mice.[27] The anti-tumor and bone anabolic effects were dependent upon host-derived adiponectin, highlighting the potential for targeting adiponectin in bone disease. Andrew Chantry (Sheffield) addressed the use of skeletal anabolic therapies in myeloma. A transcriptional array study of 15 human myeloma samples featured a number of osteoblast activity inhibitors, particularly Wnt signaling inhibitors, including Dkk-1. Anti-Dkk-1 treatment prevented the 5T2 MM-induced decrease in osteoblast number *in vivo*, but did not prevent the increase in osteoclast number and resorption. He presented other examples of promoting bone formation in experimental multiple myeloma that prevent lytic lesions, reduce tumor burden and promote survival, while not slowing the osteoclast and resorption increases.

Robert Coleman (Sheffield) addressed the clinical management of metastasis to bone of solid cancers, breast and prostate. From the time of the first adjuvant trials,[28] treatment of breast cancer with bisphosphonates has consistently improved metastasis-free survival, without affecting mortality. The benefit in some more recent studies has not necessarily been entirely driven by recurrence in bone. For example, in the adjuvant zoledronic acid to reduce recurrence (AZURE) study[29] there was a slightly reduced (not significant) decrease in bone recurrence found in those participants with established menopause, but a very large reduction in first recurrence outside bone. This is clearly something that needs to be pursued, perhaps relevant to the vexed question of whether bisphosphonates can have a killing effect directly on cancer cells. The newer resorption inhibitor, Denosumab, the anti-RANKL antibody, increased the time to bone metastases in prostate cancer.[30] In a head-to-head comparison in preventing skeleton-related events, Denosumab was shown to be significantly more effective than zoledronate.[31] Approximately, the same incidence of osteonecrosis of the jaw was observed with both agents. Coleman reported early results of very great interest with two further treatments. Radium 233 acts as a calcium mimic in targeting new bone growth in and around metastases. It is a very safe isotope, an alpha emitter with a two to three-cell penetration and claimed to be the only bone-targeted drug to have improved overall patient survival in prostate cancer.[32–34] Also, a MET and vascular endothelial growth factor receptor kinase inhibitor, Cabozantinib (XL184) has been reported to bring about massive, rapid reduction in prostate cancer bone metastases on bone scanning, a response that has not previously been seen.[35]

The Structural Genomics Consortium (www.thesgc.org)

Five years ago at this meeting, the early years of this Consortium between Oxford and Toronto were presented as an exciting prospect. The realization of this was outlined in an enthusiastic summary by its Director, Chas Bountra (Oxford). The Structural Genomics Consortium (SGC) is an academic enterprise devoted to structural biology, epigenetics and drug discovery, with its participants agreeing to undertake all aspects of the work without regard to intellectual property rights. This has been done with remarkable success, the Consortium having solved 1400 protein structures since 2003, with a number taken though to patients with pharmaceutical industry help, and without intellectual property restrictions—what amounts to a knowledge bank. What seemed an idealistic dream is now a fact, it was inspiring for the academics at the meeting to see what could be done, but many wondered (particularly the US-based researchers) how their institutions would cope without their insistence on intellectual property protection. Bountra pointed to the immense failure rate inherent in drug development (>90% of drugs fail at phase 2 trials) and the wasted time, effort, money and careers spent chasing targets in parallel and in secret through the massive duplication of research that constitutes the 'lottery of drug discovery'. The willingness of Industry to co-operate openly in the very liberal approach to early-stage research championed by the SGC is very apparent, and has led to successful studies aimed at unraveling the human kinome with potential to target disorders such as myelofibrosis, pancreatic cancer and arthritis, as summarized by Stefan Knapp (Oxford). A pleasing number of the SGC projects are focussed on bone, through the strong musculoskeletal biology and research facilities available locally and highlighted by Andrew Carr (Oxford). Udo Oppermann (Oxford) summarized work with GlaxoSmithKline on a compound arising from SGC investigating epigenetic regulation by UTX and JMJD3 histone demethylases, and the beneficial effects of inhibiting these targets in cells of the musculoskeletal system. This selective demethylase inhibitor reduces osteoclast formation and has an antiproliferative effect in Ewing's sarcoma cells. Further epigenetic targets mediating stem cell differentiation to osteoblasts are under investigation with European Union partners.

Alex Bullock (Oxford) in the SGC described the role of bone morphogenetic protein (BMP) signaling in fibrodysplasia ossificans progressiva (FOP), a condition worked on for years in the Oxford laboratories by James Triffitt (Oxford), who contributed to the recent identification of the responsible gene, *ACRV1* (ALK2), where the commonest mutation associated with FOP is identified as R206H. They found that mutants show gain of function, with activity in the absence of BMP6 ligand. This provided the basis of a screen for a BMP6 inhibitor in zebrafish, and the first lead compound that could be tested in a mouse genetic model of FOP.[36]

Science, Medicine and Society

In this session that reflected the eclectic nature of the Conference's coverage, the topics ranged from research funding through to litigation. Alan Silman as Medical Director of Arthritis Research UK (ARUK) described the role of the charity sector and specific initiatives from ARUK (www.arthritisresearchuk.org), including recent funding of academic Centres of Excellence in key areas, some in partnership with the Medical Research Council, with ARUK providing outstanding support for research into bone diseases as well as arthritis. Joan McGowan (Bethesda), who is Director of the Division of Musculoskeletal Diseases at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, described the changing scene and new initiatives in the USA from the perspective of National Institute of Health funding. Ranjit Dhindsa (Washington) described the interface between law and medical science, with salutary tales of the costs incurred by industry if law suits were

lost. His account contained mature advice for scientists involved in litigation procedures.

The costs and adverse medical consequences associated with hip fractures are well known, and Keith Willett (Oxford) gave an inspirational account of efforts to reduce the impact of hip fractures in real life through his role as National Clinical Director of Trauma Care for the UK. The aims of the program were simple, if daunting—first, to have all UK local health systems establish an integrated service for the prevention of falls and fractures, and second, to reduce the number of falls resulting in serious injury. In a short period of time, by providing encouragement and incentives to health-care groups, the implementation of better standards of care for patients after hip fracture has resulted in better outcomes, reduced costs and improved survival. These remarkable results offer a model for adoption on an international scale.

Bisphosphonates

The meeting concluded with a day of discussion focused upon bisphosphonate drugs, including a detailed clinical summary of their ongoing use, novel analogs and exciting new applications and future prospects. Paul Miller (Colorado) outlined current treatment approaches from a US perspective, which included the possible use of a 'Drug Holiday' after 3–5 years of bisphosphonate therapy for osteoporosis, and Kenneth Lyles (Durham) explored the intriguing possibility that in addition to well-established beneficial effects in bone, bisphosphonates may also impact overall lifespan through mechanisms unrelated to improved bone mass. This theory is fuelled by studies documenting a partial rescue of the accelerated ageing phenotype observed in a mouse model of progeria following bisphosphonate treatment (in combination with statins).[37] Clinical data suggest a significant and substantial improvement in survival in women receiving bisphosphonates before or after their hip fracture and that only 2% of mortality can be explained by prevention of subsequent fractures in patients on bisphosphonates.[38,39] The underlying suggestion of these studies is that bisphosphonates confer an enhanced ability to survive acute illnesses associated with older age (such as myocardial infarction), though we are a long way from proving this appealing notion. One potential mechanism mediating the effects of bisphosphonates on bone may occur via Erk signaling. Lilian Plotkin (Indianapolis) highlighted the antiapoptotic effect of bisphosphonates following glucocorticoid treatment in osteoblasts and osteocytes, an effect demonstrated even with bisphosphonate-analogs that lack antiresorptive activity, which can be abrogated with Erk inhibitors.[40] Downstream mediators of this bisphosphonate-induced protection likely involve the regulation of connexin (Cx43) hemi-channels and Erk activation within the cytoplasm, where alendronate failed to prevent prednisolone-induced apoptosis in osteoblast- and osteocyte-specific Cx43 knockout mice.[40]

The interesting role of nitrogen-containing bisphosphonates as immunomodulatory agents was explored by Keith Thompson (Aberdeen), with a specific focus on the activation of a subgroup of T cells known as gamma delta T lymphocytes. These non-conventional T cells recognize non-peptide antigens in an major histocompatibility complex-independent manner and can identify and kill target cells similar to natural killer and cytotoxic T cells. Intermittent treatment of human mononuclear cells with physiologically relevant doses of zoledronic acid triggered the activation of gamma delta T cells in a cell contact-dependent manner.[41,42]

The use of fluorescently conjugated bisphosphonates to study their skeletal distribution and use as bone targeting agents was illustrated by Charles McKenna (Los Angeles) where carboxyfluorescein-labeled zoledronate was shown in all types of bone, including jaw and the cochlear and where progression of otosclerosis could be visualized, and by Fraser Coxon (Aberdeen) demonstrating increased binding affinity at bone-forming rather than resorbing surfaces, distribution into the osteocyte network, and internalization of carboxyfluorescein-labeled risedronate by monocytes/macrophages *in vivo*.[43,44] Crucial differences in binding affinity and activity between bisphosphonates and novel analogs were described by Aimee Duan (Oxford) and James Dunford (Oxford), and their impact upon normal osteoclastogenesis explored by Guillaume Mabilleau (Angers), while Gordon Klein (Galveston) and Michael Pazianas (Oxford) discussed future applications of bisphosphonate drugs as preventative agents against burn-induced bone loss and colon cancer, respectively.

Summary

This conference benefited greatly from the breadth of its coverage of topics in musculoskeletal biology at large, the insights it provided into the science of the pharmaceutical industry in these areas, and its highlighting of several recent important advances in therapeutics. Above all, informal, productive discussion among all attendees was more readily achieved than is usually possible. This was facilitated by the relatively small number of participants and the location at an Oxford college campus that was so conducive to interaction.

Conflict of Interest

The authors declare no conflict of interest.

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