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SYMPOSIA ABSTRACTS

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S1.1

Abstract not available

S1.2

Why Do We Need Clinical Trials?
Ian Reid
Auckland, New Zealand

Clinical trials have a number of characteristics that make them the most reliable way of assessing the efficacy and safety of medical interventions. Clinical trials use randomisation to produce groups which are comparable for both known and unknown factors influencing outcome

- Studies are blinded so that biases of participants or investigators cannot influence assessments of efficacy or safety
- Endpoints are pre-specified and consistently defined
- Analyses are planned a priori to prevent data dredging with a view to generating specific outcomes
- Studies are powered to be able to detect a clinically meaningful difference in endpoints

These safeguards allow a high level of confidence in the reliability of any statistically significant difference found between the treatment groups. No other form of clinical investigation has comparable rigour. Observational studies have a role to play in hypothesis generation and in monitoring events too rare to be assessed in trials. The repeated instances of major discrepancies between trial outcomes and analyses of observational data reinforce the belief that all major treatment policies in medicine should be based on clinical trial results.

S2.1

New Directions in Cancer and Bone - New Treatments
Robert Coleman
University of Sheffield, UK

Over recent years the introduction of bone-targeted treatments has transformed the clinical care of patients with metastatic bone disease. Both bisphosphonates (BP) and denosumab have a major beneficial impact on skeletal morbidity, leading to improved quality of life and physical functioning and reduced demands on expensive interventions and hospital care. Improvements have also been seen in radiation based therapies with the widespread use of single large (8Gy) treatment fractions for bone pain, improved delivery of high dose radical radiation treatment to oligo-metastatic disease through the use of stereotactic ablative radiation (SABR) and the introduction of highly effective and safe, novel radiopharmaceuticals such as radium-223. Coupled with these improvements in bone-targeted treatments, are rapid developments in both cytotoxic therapy and molecularly targeted treatments for cancer. These can now provide disease control, albeit only temporary at present, to most patients and are resulting in steadily improved survival and ever increasing treatment options such that, for many, advanced cancer is becoming a chronic disease and no longer the rapid death sentence of yesteryear. Some of these targeted cancer treatments also have important effects on bone metabolism that are of importance to bone specialists. Finally, improved surgical and interventional radiologic options are contributing to the multidisciplinary care of >1 million patients with metastatic disease worldwide. Through their profound effects on bone physiology, bone targeted treatments can potentially modify the process of metastasis and have important effects on disease outcomes as well as bone health. Metastasis prevention trials have reported variable outcomes in terms of disease recurrence with efficacy apparently influenced by tumour type and, at least in breast cancer, by levels of reproductive hormones. At least in breast cancer we now understand better the potential of BP to influence relapse and survival rates. In a recent initiative with the Early Breast Cancer Clinical Trials Group, we sought individual patient data for meta-analysis from 36 randomised trials that compared BP to no BP (placebo or open control) and evaluated the effect of adjuvant BP on disease outcomes. Data on 18,766 women were received, with 3,453 and 2.106 breast cancer recurrences and deaths respectively. BPs reduced first distant recurrence in bone (RR=0.83; 95%CI 0.73-0.94, 2p=0.004) but not recurrence at other distant sites, or local or contralateral breast cancer recurrence. Importantly, there was a significant interaction between treatment efficacy and menopausal status with no apparent benefit for premenopausal women but highly significant reductions for postmenopausal women in bone recurrence (RR=0.72; 95%CI 0.60-0.86, 2p=0.0002) and breast cancer mortality (0.82; 95%CI 0.73-0.93, 2p=0.002). These findings are changing clinical practice and are being followed by adjuvant trials of other agents such as denosumab and in other disease settings such as prostate and lung cancers to see if we can build further on these exciting clinical observations and fulfill the preclinical promise of the past 25 years.

S2.2

Lysyl-oxidase and the Pre-metastatic Bone Niche

Alison Gartland, Thomas R. Cox, Robin M.H. Rumney, Erwin M. Schoof, Lara Perryman, Anette M. Høye, Ankita Agrawal, Demelza Bird, Norain Ab Latif, Hamish Forrest, Holly R. Evans, Iain D Huggins, Georgina Lang, Rune Linding and Janine T. Erler
Sheffield, UK

Lysyl oxidase (LOX) is an exciting new potential therapeutic target for the treatment and prevention of metastatic disease. We and others have shown that LOX is highly expressed by invasive/metastatic cancer cells, enhances tumour progression and that patients with high LOX expression had lower metastasis-free survival. We have also shown that LOX is critical for pre-metastatic niche formation in soft-tissue (lungs, liver and brain) enhancing bone marrow-derived cell invasion and thereby enabling colonisation of metastasising tumour cells. More recently we have begun to unravel the role of LOX in the bone pre-metastatic niche, in particular the early events governing osteolytic lesion formation. Using multiple *in vitro* and *in vivo* models, and a large clinical cohort, we show that LOX gene expression is significantly correlated with osteotropism and bone relapse. We show that high expression of LOX in primary breast tumours or systemic delivery of LOX *in vivo* leads to osteolytic lesion formation, and that silencing or inhibition of LOX activity abrogates this. The enzymatic activity of tumour-secreted LOX affects both osteoclasts and osteoblasts, disrupting normal bone homeostasis leading to bone lesion formation. These changes and lesions occur prior to tumour cell arrival in the bone and act to provide the initial foothold for circulating tumour cells to colonise the niche and form bone metastases. Mechanistically, we identify tumour-secreted LOX as a novel regulator of osteoclastogenesis through NFATc1 transcription factor translocation. In summary, we have uncovered a novel step in bone metastasis and mechanism of bone homeostatic regulation, opening up new opportunities for therapeutic intervention with important clinical implications.

S3.1

Organoid Cultures for *In-vitro* Disease Modeling

Marc van de Wetering
The Netherlands

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined Lgr5 as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. Using lineage tracing experiments in adult mice, we found that these Lgr5+ve crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific and almost 'generic' marker for stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear, tongue and stomach epithelium. Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of stomach, liver, pancreas and kidney. Using CRISPR/Cas9 technology, the CFTR locus has been corrected in intestinal organoids of cystic fibrosis patients.

S3.2

New Strategies for Bone Repair – Harnessing Skeletal Stem Cells From Bench to Clinic

Richard OC Oreffo
Bone and Joint Research Group, Centre for Human Development, Stem Cells and Regeneration, Institute of Developmental Sciences, University of Southampton, Southampton, UK

Skeletal stem cells confer to bone its innate capacity for regeneration and repair. Bone regeneration strategies seek to harness and enhance this regenerative capacity to repair skeletal defects resulting from trauma and disease with the application of cells, typically isolated from the patients themselves, in combination with porous biomaterials or scaffolds. Skeletal stem cells, commonly referred to as Mesenchymal stem cells, or human bone marrow stromal stem cells are defined as multipotent progenitor cells with the ability to generate cartilage, bone, muscle, tendon, ligament and fat. To date, technologies to facilitate the identification and isolation of specific skeletal stem cells and development of scaffolds that address issues of growth factor delivery and angiogenic support to aid de novo tissue formation remains a significant unmet clinical need. We have developed protocols for the isolation, expansion and translational application of skeletal stem cell populations with cues from developmental biology, nanotopography and nanoscale architecture as well as biomimetic niche development informing our skeletal tissue engineering approaches. We have developed ex vivo approaches to bone formation evaluation and analysis and central are large animal in vivo translational studies to examine the efficacy of skeletal stem and cell populations in innovative scaffold compositions for orthopaedics. This talk will also highlight current clinical translational studies to examine the efficacy of skeletal populations for orthopaedic application. Advances in our understanding of skeletal stem cells and their role in bone development and repair, offer the potential to open new frontiers in bone regeneration and offer exciting opportunities to improve the quality of life of many.

S4.1

Modelling and Remodelling of the Corticol Bone

David W. Dempster
New York, USA

Cortical bone comprises 80% of the adult skeleton. Yet in recent years it has received less attention from bone researchers than cancellous bone. Cortical bone undergoes both modeling (resorption and formation occurring independently of each other at different sites) and remodeling (coupled and sequential resorption and formation occurring at the same site). Modeling and remodeling occur on both the endocortical and periosteal surfaces of the cortex, whereas within the cortex only remodeling – referred to as Haversian remodeling - takes

place. Bone modeling plays a key role during growth and determines the size and shape of the adult bone. This process is largely under genetic control. Disruptions in the modeling process during growth results in deformed bones, the classic case of which is the Erlenmeyer flask deformity. Modeling also occurs in adults, primarily in response to changes in mechanical loading. For example, modeling is responsible for the increase in mass and strength of the forearm bones in the dominant arm of experienced tennis players. Remodeling of the cortex, occurs, throughout life and is influenced by a variety of endocrine, mechanical and local factors. After skeletal maturity, remodeling increases with age and particularly after menopause. On the endocortical surface net resorption exceeds formation leading to expansion of the medullary cavity, thinning and trabecularization of the cortex. On the periosteum, net formation exceeds resorption leading to a gradual increase in the diameter of the bone, but the rate of periosteal expansion is less than that of the endocortex and so cortical thickness declines. Resorption also exceeds formation in the intracortical envelope leading to an increase in the diameter of the Haversian canals and evolving Haversian systems can fuse to form "giant" canals. The net result of these age- and menopause- related changes is loss of cortical, mass, structure and strength leading to skeletal fragility.

S4.2

The Effect of Osteoporosis Treatments on Cortical Bone: Insights from Clinical Trials

Juliet Compston
Cambridge, UK

In clinical trials conducted in postmenopausal women with osteoporosis, reductions in fracture risk of up to 70% in the spine, 40% in the hip and 15-20% at non-hip non-vertebral sites have been demonstrated. The limited efficacy at non-vertebral sites is a concern, given the high burden and cost of these fractures. Whilst poor adherence to therapy and continuing falls risk are likely to contribute to the small effect on non-vertebral fractures, drug-specific factors may also operate. Investigation of approved and investigational drugs with differing mechanisms of action, together with improved methods for studying cortical bone structure has provided some new insights into mechanisms by which drugs may influence cortical bone strength. A number of limitations in the assessment of cortical bone structure and strength should be recognised. First, effects of drugs on cortical bone may vary according to skeletal location. Secondly, even at a particular site, for example the femoral head and neck, there is marked heterogeneity of structure and strength and effects of drugs may be focal. Thirdly, many of the current methods for in vivo assessment of cortical bone are limited by inadequate resolution leading to difficulties in accurately assessing cortical porosity. Finally, other characteristics of cortical bone, for example the degree of mineralization and its homogeneity, and the structure of the mineral/matrix composite may affect estimates of cortical bone structure and strength. Notwithstanding these limitations, clinical trials of approved and investigational drugs have indicated interesting differences in effects on cortical bone. Whilst bisphosphonates reduce or prevent age-related deterioration of cortical bone structure and strength, denosumab appears to increase cortical thickness, perhaps as a result of its greater accessibility to intracortical bone. The effect of parathyroid hormone peptides is variable and influenced by mechanical loading. Cathepsin K inhibitors and sclerostin inhibitors, which uncouple bone remodeling by distinct mechanisms may have greater osteoanabolic effects on cortical bone although whether this translates into greater efficacy in reducing non-vertebral fractures remains to be established.

S5.1

Abstract not available

S5.2

Subchondral Bone as a Source of Arthritis Pain

David A Walsh
UK

Arthritis is a major source of chronic pain, distress and disability, although mechanisms of arthritis pain are incompletely understood, and current treatments often have limited efficacy. In osteoarthritis (OA), subchondral bone marrow lesions (BMLs) seen by magnetic resonance imaging are associated with current pain, and change in parallel with changing pain. Bone marrow lesions reflect diverse histological characteristics, with increases in bone turnover, as well as fibrovascular and inflammatory cell infiltration of bone marrow spaces. These changes are associated with increased osteoclast activity. Interventions that reduce osteoclast activity display analgesic efficacy in OA, both in animal models and in clinical trials. Bisphosphonates reduced pain in people with BMLs in a randomized clinical trial. Osteoprotegerin-Fc reduced pain behaviour in rodent models of OA. Osteoclasts, by reducing pH within the subchondral bone, might facilitate nociceptor activation through pH sensitive ion channels such as TRPV1. Furthermore, osteoclasts express factors that might sensitise nociceptors, and release other pain mediators during matrix degradation. In the medium to long term, structural changes at the osteochondral junction might further contribute to OA pain. The tidemark (junction between calcified and non-calcified articular cartilage) forms a barrier to diffusion and mass transport of molecules from within the synovial cavity into subchondral bone. In OA, this barrier is disrupted, initially by the penetration of vascular channels from subchondral bone spaces into the non-calcified cartilage, and later through fissuring or cleavage of the articular surface leading to microscopic or macroscopic chondral defects. Osteochondral defects are further associated with bone marrow lesions and articular pain. Far from being a passive, degenerative disease, OA is associated with increased metabolic activity and growth in subchondral bone. Sensory nerve growth from subchondral bone leads to innervation of vascular channels within the non-calcified cartilage, and so a tissue that is normally not innervated might become a source of OA pain. BMLs and increased osteoclast activity are also observed in rheumatoid arthritis, especially in late stage disease. Novel pharmacological interventions might complement joint replacement surgery as a means of reducing arthritis pain originating in subchondral bone.

S6.1

Abstract not available

S6.2

Treatment of Osteoarthritis: Present and Future

João Eurico Fonseca
Lisbon Academic Medical Centre, Lisbon, Portugal

During this presentation the cornerstone of current osteoarthritis treatment will be reviewed, including critical appraisal of the evidence of presently used drugs, integrating them with available guidelines. In addition, new concepts of osteoarthritis treatment interventions, interfering with metabolic and inflammatory pathways and with structure and biomechanics will be discussed.