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Current Fields of Research

The Musculoskeletal Research Collaboration encompasses a diverse group of related research areas, including bone cell biology, pharmacology, molecular exercise physiology, genetics of musculoskeletal disease, regenerative medicine, skeletal imaging and musculoskeletal epidemiology.

We are world leaders in characterising the **pharmacology of bisphosphonate drugs**, which are the front-line treatment for diseases of excessive bone resorption such as post-menopausal osteoporosis and Paget's disease. We discovered that these agents act on osteoclasts by inhibiting an enzyme of the mevalonate-cholesterol biosynthetic pathway, thereby indirectly preventing the post-translational lipid modification (prenylation) of small GTPase signalling proteins that are fundamental for osteoclast function and survival. Understanding the role of these proteins in bone cells, and how bisphosphonates affect their downstream signalling pathways, has since become a major focus of our research. Our studies have also identified new classes of pharmacological agents that inhibit other enzymes of the mevalonate pathway, and have helped to clarify the molecular basis for some of the adverse effects of bisphosphonates, such as the acute phase reaction (caused via the accumulation of intermediates of the mevalonate pathway and activation of γ,δ -T cells). Our ongoing research seeks to understand the skeletal distribution of these agents and their potential effect on cells other than osteoclasts, and to clarify the mechanism underlying the in vivo anti-tumour activity of these agents.

Our studies on **bone biology** are largely focused on understanding the molecular processes (particularly vesicular trafficking and membrane reorganisation) involved in regulating the function and survival of bone-destroying osteoclasts. Several diseases of the skeleton involve the overactivation of osteoclasts (Paget's disease) or underactivation/lack of formation of osteoclasts (osteopetrosis) and our studies have highlighted how these diseases are caused by mutations in genes encoding the proteins Sequestosome-1, Plekhm 1, RANK and RANKL. Ongoing work seeks to clarify the exact role of these proteins in osteoclast biology.

Molecular exercise physiology is the study of genetics and signal transduction in relation to exercise. Our group conducts both genetic and signal transduction research and we use models ranging from cultured cells to humans. In our genetic research we use inbred mouse strains with variations in muscle mass, fibre type percentages and metabolic differences to search for the underlying genetic variants. In our human genetic research we search for associations between gene variants, muscle mass and strength and health related variables such as falls. One focus of our signal transduction research is the Hippo pathway, where we have identified Yap, a key member of this pathway, as a novel regulator of myogenesis. We are currently studying the function of Yap in skeletal muscle in transgenic animal models. We are also studying signal transduction in relation to sarcopenia, the loss of muscle mass and function during normal ageing. In this context we study the response of aged muscle to anabolic stimuli, the function of myostatin-related signalling in old muscle and the use of polyunsaturated fatty acids to potentially treat sarcopenia.

Genetics plays an important role in many musculoskeletal diseases, including osteoporosis, osteoarthritis, falls, Paget's disease, rheumatoid arthritis, chronic pain, osteopetrosis and congenital talipes equinovarus (idiopathic clubfoot). We are part of a number of international collaborative population-based and disease-based studies that aim to determine the genetic variants responsible for these conditions. We have also identified a number of mutations in the genes encoding Sequestosome-1, RANK and RANKL that cause disorders with overactive osteoclasts (Paget's disease of bone and osteopetrosis). As well as functional assessment of these mutations, we are examining common (and novel rare) variation in these genes and their signalling partners. This will shed light on the role these play in determining normal bone density and postmenopausal bone loss (leading to osteoporosis); and allow us to examine how these interact with genetic risk factors for falls to produce an osteoporotic fracture. The results of all this work will be used in the future to target specific treatment and lifestyle advice to the individuals who will benefit most from it.

The ultimate goal of the **Regenerative Medicine** Team is the development of novel stem cell-based therapies for the repair of skeletal tissues by delivery of quality controlled stem cell preparations or by activation and recruitment of endogenous stem cells.

The capacity of stem cells to replace lost cells and tissue components, together with their unexpected immunomodulatory properties, is promoting stem cell therapies for treatment of autoimmune diseases and traumatic, inflammatory and degenerative joint disorders. The variability in the biological properties of mesenchymal stem cell (MSC) preparations is likely to affect the outcome of clinical applications. There is therefore a pressing clinical need to establish MSC preparations with consistent and reproducible biological behaviours, quality-controlled for specific therapeutic applications. To this end, we are developing and validating potency assays and related surrogate measures of MSC preparations to be proposed as quality controls for clinical applications. Such strategy will enhance consistency of stem cell products and lead to standardization of stem cell-based therapeutic protocols.

Activation and recruitment of endogenous stem cells and delivery of stem cell preparations are potential therapeutic interventions to achieve joint tissue repair, while modulation of stem cell niches and remodelling signals is the goal for prevention of the excessive cartilage and bone formation that occurs in spondyloarthropathies and osteoarthritis. However, the current knowledge of the location and functional modulation of endogenous joint stem cells is limited.

We recently reported the identification and characterization of stem cell niches in the joint in vivo and are currently investigating their role(s) in joint homeostasis, remodelling and disease (inflammatory and degenerative). This knowledge will be instrumental for the development of novel therapies by targeting stem cell niches to achieve tissue repair and modulate disease outcome, with the ultimate goal of restoring a functional joint homeostasis.

Our extensive work in **skeletal imaging** is focused on applications of active shape modelling of hips and knees from radiographs or DXA images to develop diagnostic and prognostic markers for OA incidence and progression and for femoral neck fractures. Aberdeen is home to the only positional MRI research scanner in the UK and has enabled unique imaging studies with subjects in upright and weight-bearing positions. Using this we have shown that the spine has an intrinsic shape and are currently investigating whether this may predispose to back pain. We have identified significant changes in the subchondral bone of patients with osteoarthritis of the hip and are investigating the nature of these changes in more detail using a variety of physical methods. We have hypothesised that generalised osteoarthritis is a systemic, metabolic disorder in an attempt to explain the involvement of multiple joints, all musculoskeletal tissues and the strong link with obesity.

We have built a number of devices for applying mechanical stimuli to cells in vitro and are using these to study the responses of osteoblasts and chondrocytes. Stimuli include cyclical or impact loading and fluid flow. We found that chondrocytes from elderly human cartilage do not behave in the same way as those from young bovine tissues, commonly used as a model and that mechanical loads could cancel the stimulatory effects of IGF-1. Following an impact load we have shown that apoptosis and matrix degradation are separately regulated and, therefore, a two-pronged approach will likely be needed for any intervention designed to rescue cartilage after trauma.

The **Epidemiology** Programme in Musculoskeletal Research focuses on: Life course influences on the development of chronic pain in adulthood; Biological pathways linking the psychosocial environment and pain reporting; Musculoskeletal health (incorporating predictors of musculoskeletal health and randomised controlled trials of pain management).

We were the first group to demonstrate, using birth cohort studies, that factors early in childhood (social, psychosocial, injury) were predictive of reporting chronic widespread pain in adulthood. We were also first to demonstrate that the reporting of chronic widespread pain is predictive of early mortality, in particular early death from cancer and cardiovascular disease. We are currently:

- Investigating the aetiology and management of pain amongst older people
- Investigating the aetiology and management of fatigue amongst persons with rheumatic disease.
- Establishing and running the British Society for Rheumatology Ankylosing Spondylitis register
- Determining the mechanisms by which pain reporting is linked to premature mortality.
- Running randomised controlled trials to determine optimal management of regional and widespread pain conditions.
- Undertaking reviews of the effectiveness of complementary medicines and therapies in the management of rheumatic disease.
- Undertaking methodological work related to population health surveys.

Clinical studies:

Our clinical focus is on osteoporosis, osteoarthritis, rheumatoid arthritis in addition to regional and widespread pain syndromes. We are involved in a number of current population-based studies which are examining how bone health is affected by different factors in normal populations, both genetic and environmental. Imaging is a major focus, exploring new techniques and how these can be used to diagnose fracture risk. The effects of diet on bone health are another a strong interest of the group with findings from our epidemiological work leading to an 2-year randomised controlled trial (RCT) to determine the mechanism behind the benefits of fruit and vegetables on bone health. Being located at northerly latitude (57°N) our work has shown that the Scots are particularly at risk of vitamin D deficiency. Our cross-sectional findings were confirmed by a longitudinal study to assess sunlight and diet contributions to vitamin D status with our study design being followed by group in Surrey to enable direct North-South UK comparisons. Current work includes an RCT to assess whether vitamin D affects markers of cardiovascular risk as well as bone health. In addition to the conventional nutrient approach we use dietary patterns to determine future risk of bone disease. Our group has contributed one of the largest studies world-wide for gene-nutrient interaction.

Selected Publications (in alphabetical order)

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