

Hardened cells

Professor Gerald Atkins explains the work he oversees which makes use of pioneering techniques to investigate bone at the cellular level, helping to shed light on numerous diseases



What are your responsibilities as Head of the Bone Cell Biology Group at the University of Adelaide?

As Head of the Bone Cell Biology Group, I conceive and drive our research programme on bone remodelling and metabolism. This seeks understanding of, and treatment approaches to, bone diseases, including osteoporosis, osteoarthritis, rheumatoid arthritis, cancer of bone and orthopaedic disease and peri-prosthetic osteolysis (also known as aseptic loosening). My group consists of five full-time PhD students and two postdoctoral fellows. In addition to developing these research aims, it is my responsibility to find research funding, my major source being the Australian National Health and Medical Research Council. I am in constant contact with my staff and students, and am centrally involved in data interpretation and planning experiments. I am chiefly responsible for publishing our findings in peer-reviewed scientific journals, and liaise with my collaborators, locally and internationally.

Could you sum up questions you seek to answer through your current research?

The overarching question my research addresses is: what are the cellular and biological mechanisms that regulate human bone remodelling and metabolism, and how does this relate to bone disease? Bone remodelling is the fundamental mechanism by which the integrity of the skeleton is maintained. Bone is continually replaced throughout our lifetime. Because humans are long-lived, maintaining skeletal integrity becomes a major health issue in our post-reproductive years. The diseases osteoarthritis and osteoporosis are both remodelling issues, and together affect more human beings than any other group of diseases. In order to develop effective therapies to address these and other conditions, such as rheumatoid arthritis and cancer of bone, it is essential to understand the underlying human cell and molecular biology. The fact is, we are only just beginning to understand these processes.

How have you focused your current work?

A primary focus of my recent studies centres around the osteocyte. There is much literature to suggest that these cells are vital to skeletal health and yet they are the least studied bone cell type, because of their relative inaccessibility and the lack of good cell models. My current questions include those of how osteocytes control bone remodelling, how they control the mineralisation of bone and how they influence systemic phosphate and calcium homeostasis. A related question is: how does bone cell metabolism of vitamin D influence bone health and biology? The osteocyte product sclerostin attracted my attention a number of years ago, and much of my research centres on this molecule.

What progress have you made to understand the role of vitamin D metabolism in bone?

My group and that of my local collaborators Dr Paul Anderson and Professor Howard Morris have published a number of papers describing the ability of bone and its constituent cells to synthesise their own 'hormonal' vitamin D. There is wide discussion about vitamin D and the amount needed for a healthy skeleton, but most is focused on its effects on intestinal absorption of calcium. We have demonstrated that vitamin D made within the bone has direct and important effects on the functions of osteoclasts, osteoblasts and osteocytes. Our current research is using genetically modified mice to fully elucidate the role of this important hormone. This work also serves to reinforce the notion that the skeleton is not simply an inert structure for mechanical support and protection of our 'vital organs', but is an important metabolic and vital organ in its own right.

Are there any difficulties in conducting research into the molecular mechanisms of bone disease?

The natural functions of osteocytes present their own challenges and recreating physiological mechanical loading, mineral metabolism and influence of both osteoblast and osteoclast behaviour, all require creative solutions. The first challenge is the fundamental characterisation of the biology of human osteocytes, and our work using patient bone-derived cells is seeking to address this. They are also a highly differentiated cell type so that it may take five to six weeks of culture under differentiating conditions before an experimental question can be asked. An approach we are using for validation purposes is comparing cell culture activity with that seen in actual bone cultured *ex vivo*, and we have adapted a bioreactor for this.

Skeletal sickness

Work is underway at the **University of Adelaide** to investigate bone physiology, bringing to light mechanisms which could help treat a range of bone diseases, from osteoporosis to arthritis

THE PREVALENCE OF osteoporosis and other bone diseases means that research being conducted on the biological mechanisms by which bones renew themselves is incredibly important. A team at Australia's University of Adelaide has been investigating regulation of cells within bones. Central to this work is their study of osteocytes, cells which lie buried throughout the hard bone tissue in an extensive interconnecting network called the lacunar-canalicular system, with communication between each other and alternative cells through long narrow extensions. With a life span of 25 years, these cells are among the longest lived of any in the body, and research has begun to reveal that they play a key role in the maintenance of the bone as a whole. One of the ways in which they do this is through secreting sclerostin, an important protein in regulating bone mass. The protein has recently received attention because of its possibility as a therapeutic target for treating low bone mass diseases, yet sclerostin and its effects have not been fully elucidated. Consequently, one of the team's major tasks has been looking at the specific cells that sclerostin targets, and the ways in which this impacts bone health.

The third element of the scheme which the team has been researching is pre-osteocytes, juvenile cells that occur near the surface of the bone and are affected strongly by sclerostin. Pre-osteocytes are connected to surface osteoblasts, and have the critical role of incorporating inorganic mineral into the bone matrix in order to form bone of the appropriate strength and stiffness. Thus osteocytes, buried deep within the bone matrix are able to affect pre-osteocytes



FIGURE 1. Electron microscopic image of resin-embedded and acid-etched rat bone, showing the highly-interconnected 'caves and tunnels' inhabited by osteocytes.

neither to the surface. The Adelaide group has identified the way they do this is through sclerostin, and therefore the way osteocytes regulate the formation of bone. Furthermore, pre-osteocytes are able to respond by secreting another protein, MEPE, which is processed outside the cell into a powerful inhibitor of mineralisation. Sclerostin also blocks the expression of the enzyme PHEX which promotes mineralisation, augmenting sclerostin's core role in mineralisation. Since osteocytes secrete sclerostin in response to inflammatory stimuli or the mechanical unloading of the skeleton, the implication of the team's work is that osteocytes are key to controlling bone mineralisation, which they hope will be able to be utilised for therapeutic effects. This work has been conducted in partnership with Professor Peter Rowe, at the University of Kansas Medical Center, and the group hopes that it will have a long-term impact on understanding of bone renewal.

IMPROVING TREATMENTS

Ultimately, it is hoped that these studies into the fundamental physiology of bone formation will lead to new understanding at the heart of bone treatment. Current disease response is sub-optimal because we lack critical knowledge of bone biology. Associate Professor Gerald Atkins has been leading the project in Adelaide, and is frustrated by the lack of knowledge on bone renewal in humans: "Because of this knowledge gap, we don't appreciate the implications of the various available treatments and the unwitting 'bystander effects' that a particular drug or therapy may have".

Furthermore, intervention in conditions such as osteoporosis invariably occurs too late, after significant amounts of bone mass have been lost, leading to treatment providing damage limitation rather than improvement. Recent anabolic therapies for building new bone are extremely expensive, and may suffer from patient compliance issues. In the case of osteoarthritis there is currently almost no understanding of the cause of this condition so that it is currently untreatable other than through surgery. Through advancing knowledge about the cells in bone, Atkins and his colleagues hope to have an impact on bone conditions broadly, which continue to cause severe problems for patients globally.

BONE NUTRITION

One of the ways in which individuals may be able to work to prevent bone problems is through a healthy lifestyle. Despite medical disputes about this, Atkins is confident that general rules can be adhered to: "I think that it's fair to say that a balanced diet, regular exercise and exposure to sunlight for the purpose of generating adequate vitamin D in our skin, allow us to attain our potential peak bone mass in our twenties". From this peak, different factors mean that bone mass is lost as we age; every bone remodelling event means that a little more bone is lost. The level of bone mass at peak is an important factor for determining how much bone an individual will have as they age, but changes in the digestive system, leading to less calcium and phosphate being absorbed, and a reduction in exercise, are also important factors. Given that treatments for bone disease frequently happen once these processes have already progressed too far to have a significant effect upon them, it is important for researchers to uncover these processes to assist people in having good bone health, giving them the best chance of avoiding the issues surrounding age related problems.

JOINT PROBLEMS

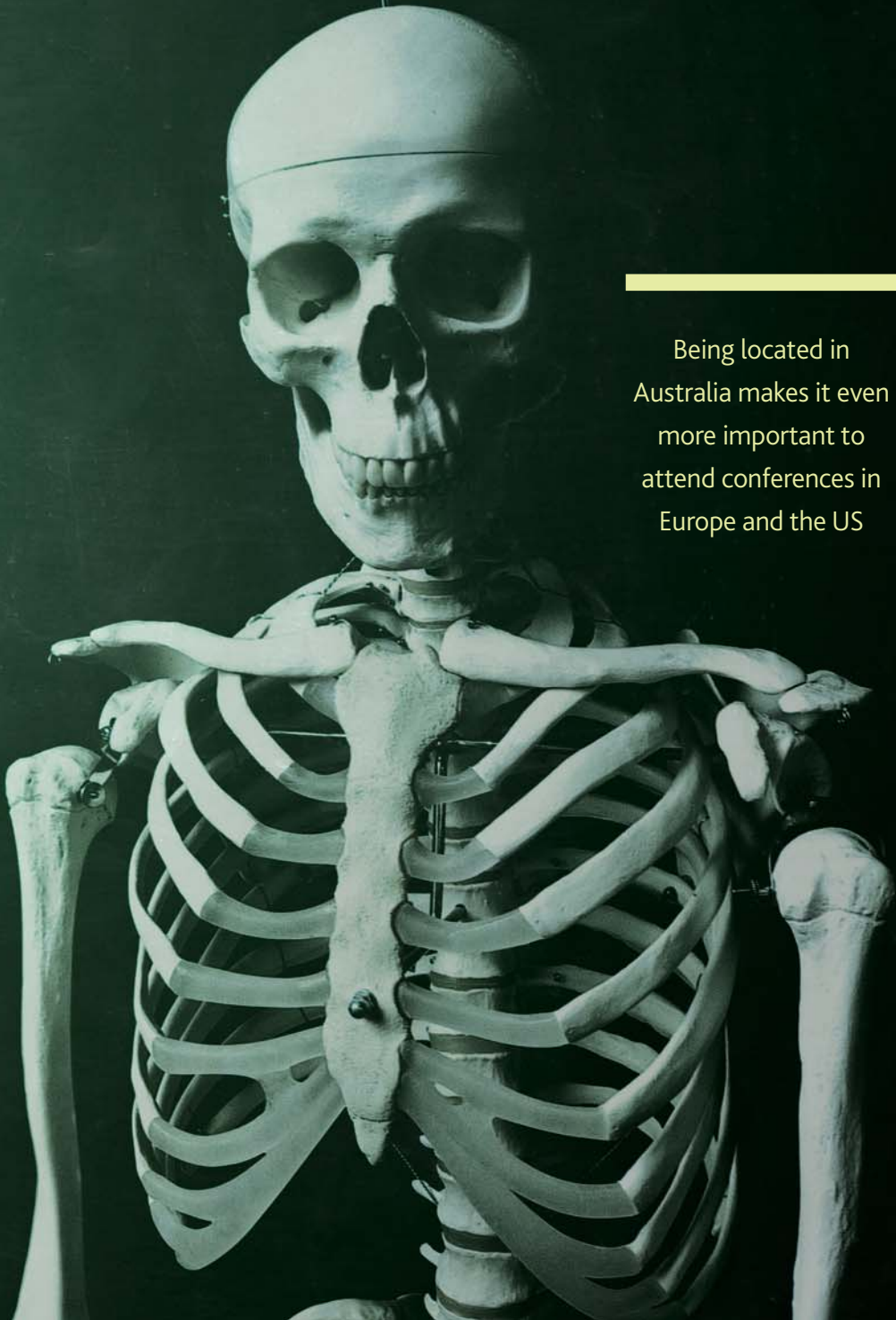
The team's work has also been able to point to an osteocyte role in aseptic loosening, the localised loss of bone around an implanted prosthesis. This problem is currently only treatable by a second surgery, which is both expensive and difficult, given that there is less bone stock available on which to affix the new prosthetic joint. The role of bone resorbing osteoclasts is well established in the condition, but the team's research is revealing that osteocytes are at the centre of this problem which may point towards potential new therapies, as Atkins realises: "The osteocyte-derived signalling molecules that influence osteoclastic resorbing activity may provide future therapeutic targets, and we hope that our work will eventually make possible therapeutic intervention before surgery becomes necessary". This again shows that by increasing understanding of the fundamental bone biology it is possible to bring forward ideas for new and better treatments for bone disease. Through focused research, it is expected

that these issues surrounding orthopaedic prosthetics will be able to be resolved.

COLLABORATIVE SOLUTIONS

Interdepartmental work has been an important part of the investigations completed by the team at Adelaide, and Atkins is at the centre of this collaboration: "On a personal note, one of the great privileges of being a scientist is the opportunity to interact with some of the elite thinkers in the field, and being located in Australia makes it even more important to attend conferences in Europe and the US".

Projects have grown from these interactions, including the original osteocyte programme which began with Dr Timothy Zheng of Biogen Idec in Boston. This initial work focused attention on SOST, the sclerostin gene, which has been at the centre of the work being conducted by the team since then. Important collaborators have also included Professor Lynda Bonewald from the University of Missouri and Rowe, from the University of Kansas. Furthermore, Professor David Findlay at the University of Adelaide has been formative in Atkins's career, and as skeletal research in Australia continues to strengthen, such collaborations will increase in importance.



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INTELLIGENCE

STRATEGIES FOR HEALTHY OSTEOCYTES

OBJECTIVE

This research seeks to elucidate a number of highly novel mechanisms of the regulation of bone mass with direct relevance to human biology and disease.

KEY COLLABORATORS

Professor Lynda Bonewald, USA • Professor Peter Rowe, USA • Dr Timothy Zheng, USA • Dr Kenneth Poole, UK • Dr Rachel Davey, Austin Health, Australia • Professor David Findlay; Professor Donald Howie; Associate Professor Bogdan Solomon; Professor Andreas Evdokiou; Associate Professor David Haynes; Associate Professor Dusan Losic, University of Adelaide • Professor Howard Morris and Dr Paul Anderson, University of South Australia and SA Pathology

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PROFESSOR GERALD ATKINS is Head of the Bone Cell Biology Group, Discipline of Orthopaedics & Trauma, University of Adelaide, and Honorary Secretary of the Australian and New Zealand Bone and Mineral Society (ANZBMS). Since obtaining a PhD (U. Adelaide) in 1998, he has attracted funding of more than AUD \$7 million and published more than 70 peer-reviewed publications in bone biology and disease. His editorial board memberships include the *Journal of Bone & Mineral Research*, the *World Journal of Orthopaedic and Frontiers in Bone Research* and professional memberships include the American Society for Bone & Mineral Research (ASBMR) and ANZBMS.



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