Turning Ideas Into Science

The Bone Biology group at the ANZAC Research Institute is still new but is changing understanding of complex bone diseases.

By Beth Quinlivan

Among the worst news for men with prostate cancer and women with breast cancer, is that the disease has metastasised to bone. In the case of both cancers, secondary tumours in the bone are common – 70% of the women who develop advanced breast cancer have bone metastases – with serious consequences. Not only does the spread of cancer reduce the prognosis, the tumours are likely to cause further pain and lead to fractures and immobility.

But if the consequences of cancer metastases are severe, the extraordinary complexity of bone biology and metabolism means that researchers looking to understand, and to limit or prevent their spread, face a difficult path.

In both prostate and breast cancer, as the tumour cells grow in the bone, they induce the normal bone-resorbing cells to destroy the surrounding bone. It is likely that destruction of bone releases factors that help the cancer cells grow faster, creating a vicious cycle that increases the dire consequences of bone metastases.

In looking at what it is about the bone environment that makes it a receptive site for secondary tumours, the Bone Biology group at the Faculty of Medicine’s ANZAC Research Institute has recently made two discoveries with the potential to improve the outlook for women with breast cancer.

In the first of these – reported in the journal Cancer Research in late 2007 - they found that in mice, breast cancer bone growth was strongly promoted by low serum calcium levels, and hence increased bone turnover. More recently, and again in mice, they found that vitamin D deficiency stimulated breast cancer growth in bone.

“Obviously, we would need to run clinical studies providing calcium and vitamin D supplements to determine conclusively whether these findings are clinically significant,” said Professor Markus Seibel, Director of the Bone Research Program at ANZAC.

“But given that older people in general are deficient in calcium, and that serum calcium levels are regulated by vitamin D, there is a sound argument for those with cancer to make sure that their calcium and vitamin D levels are not deficient.”

Original research

The Bone Biology group at the ANZAC Research Institute is still relatively new but increasingly making waves both for its original basic research and its clinical science.

Over the past couple of years, the research of Dr Hong Zhou on the actions of glucocorticoids in and on bone cells, is changing our understanding of steroid-induced osteoporosis. Glucocorticoids (often called ‘cortisone’) are widely used to treat cancer, inflammatory and auto-immune diseases but more than 50 per cent of people who are chronically treated with these agents later experience bone loss and fractures. Dr Zhou’s findings in the past 18 months have been published in a number of leading journals, including the ‘Journal of Biological Chemistry’ and ‘Development’.

Dr Colin Dunstan and Dr Yu Zheng have led the research on the potential preventative role of calcium and vitamin D in limiting the spread of cancer to bone.

Under the leadership Dr Anna Li, the group has also established a clinical research program at Concord Hospital, with the purpose of improving diagnosis and treatment of osteoporotic fractures. In general, patients with osteoporotic fractures are underdiagnosed and undertreated. As a result of the clinical program, rates for compliance with treatment regimes have increased from less than 7% to greater than 80%.

The Bone Research Program was begun in 2001 by Professor Seibel following his recruitment from the University of Heidelberg in Germany, where he had been Director of the Bone Research Laboratory for the previous 10 years. An internationally recognised researcher and author on bone biology and metabolism, his long term interests in bone cancer, vitamin D, and osteoporosis and the effect of steroid hormones on bones, are reflected in the ANZAC’s current bone research line-up.

In 2002, he was joined by Dr Colin Dunstan, a University alumnus who had spent a number of years working for biotech company Amgen in the US, where he co-discovered an important regulator of bone cell function, osteoprotegerin.

Dr Zhou, who now heads the Bone Biology group, joined the team in 2004 from the highly recognised bone research group at the St Vincent’s Hospital in Melbourne.

All up, the lab now has 10 permanent members plus students and numerous visitors. In keeping with the ANZAC theme, the Bone Research Programs focus on diseases or biology of ageing. Research is supported through funding from within Australia and from overseas. With collaborators, the group has current and future funding of over $6 million, including six NHMRC project grants.

Lead programs

Given the large number of people affected by common bone diseases - and with costs rising as populations in developed countries age – no surprise that bone research attracts a big research effort. Within the Faculty of Medicine, there are a number of highly respected specialist bone research groups or individuals, including Professor Philip Sambrook at Royal North Shore Hospital and Associate Professor David Little at The Children’s Hospital at Westmead.

The Australian Institute of Health and Welfare estimates that in this country, 600,000 mostly older people have osteoporosis. That is largely preventable through a balanced healthy diet, adequate calcium and vitamin D and regular exercise, underpins the growing public health efforts.

Dr Zhou at the ANZAC Research Institute has spent much of her time in recent years focusing on the precise details of the interaction of glucocorticoids within bone cells.

“Cortisone drug treatments have been of great benefit to countless patients suffering from rheumatoid arthritis, asthma, inflammatory bowel disease or who have undergone organ transplantation,” Dr Zhou said. “But it is well known that steroids have a detrimental effect on bone, causing osteoporosis.”

In her lead program, an initial significant discovery was that mature osteoblasts (bone building cells), under control of endogenous (as opposed to the synthetic) glucocorticoids, actually control the differentiation of mesenchymal progenitor cells (“stem cells”) into adipocytes (fat) or osteoblasts.
The signals used for this cross-talk between mature and immature cells are the so-called Wnt proteins, which have been shown to play an important role in many biological systems. Subsequently, Dr Zhou and her colleagues found that endogenous glucocorticoids, again via the osteoblast, control the formation of the mouse skull bones. This was an important new finding that again demonstrates that the role and effect of endogenous glucocorticoids has not only been underestimated but is also quite different from the effects of exogenous glucocorticoids given at pharmacological levels. In the long term, these novel findings may open new avenues to control and perhaps stimulate bone formation in patients with osteoporosis, or to prevent the development of the disease in patients treated with glucocorticoids for other disorders.

In another project, the group has been looking at the impact of endogenous glucocorticoids on the susceptibility and severity of rheumatoid arthritis.

“We use cortisone to treat inflammation but in our new experiments using transgenic mice where glucocorticoid signaling has been disrupted in the osteoblast only, we have found that at a tissue level, glucocorticoids promote inflammation,” said Professor Seibel. “That opens the door on a new approach to treatment of inflammatory diseases.”

CANCER STUDIES

In the work on bone cancer, Dr Dunstan, Dr Zheng and the team at the Bone Research Program have been trying to understand what makes bone marrow a receptive site.

“Our interpretation is that the dissemination of cancer cells into the body tissues is probably a random process. The cells settle down where they find the most receptive environment. For breast and prostate cancer, one of the more ideal environments is certainly bone,” said Professor Seibel.

“The next question is whether high bone turnover increases not only the rate of metastases, but also increases their growth in bone. As part of that, Colin and Yu took mice and made them calcium deficient. Calcium deficiency alone made the cancers grow bigger and faster in mice.”

“That was published in Cancer Research in 2007, and then Colin suggested we look seriously at the impact of vitamin D. Calcium is regulated by vitamin D, which is a steroid hormone that drives cells away from proliferation towards differentiation. What Yu and Colin have found so far is that vitamin D deficiency clearly promotes cancer growth.”

The processes are complex, though, and a lot more work is required to really understand what is happening, he said.

“The next step is to translate these findings into the clinical situation and see whether they hold true for our patients with breast and prostate cancer. That’s going to be a huge task as neither calcium nor vitamin D are expensive or patented agents, so to find the money for a large clinical trial will be a challenge. But given our results so far, it’s a task worthwhile” says Professor Seibel.

“The other theme we are increasingly interested in is the potential of bone, and specifically osteoblasts, to regulate energy metabolism. Just think of bone as a huge endocrine organ that fine-tunes glucose and fat metabolism. Perhaps a crazy idea but it’s probably the future of bone research.”

After eight years, he is delighted with the program they have been able to develop at ANZAC and excited at the prospects for the future.

“This is a wonderful team, what makes it so exciting is that we have really top level scientists who are open to new ideas. Turning what might sound like wild ideas into solid science that benefits our patients, what could be better?” —radius