Millions of years old but how does this Peptide work?

A grant over three years from the National Health and Medical Research Council will enable Professor Markus Seibel to lead a significant project investigating a bone-specific peptide known as osteocalcin, with the possibility of unlocking the secrets of how and why glucocorticoids have side-effects including obesity and diabetes.

Prof. Seibel’s research has already shown that steroid (glucocorticoid) induced diabetes is actually a disorder arising from bone, and he now suspects osteocalcin, a peptide produced by osteoblast, the main bone forming cells, can play a major role in its pathogenesis.

“Osteocalcin has been used for many years as a bone formation marker but we never knew what its function was. It’s been found in dinosaur bones, so it’s been around for millions of years, pretty much unchanged. So it must have a function,” he argues.

“We knew it was made by osteoblast and we knew that in patients treated with glucocorticoids the serum osteocalcin levels drop within hours of commencement of therapy. It’s not very often that you have a single cell type, osteoblast in this case, making a specific peptide that no other cell in the body makes. So it’s a very bone-specific molecule. But here is the strange thing. Osteocalcin is not essential to maintaining bone. It has no obvious role in bone itself.”

When humans or mice are being treated with glucocorticoids (synthetic form of the natural steroid hormone cortisol), they usually gain a lot of weight and develop glucose intolerance or even diabetes. Prof. Seibel and his team found that mice treated with glucocorticoids maintained normal body weight and glucose tolerance if certain bone cells were protected from the actions of glucocorticoids. This was a very surprising finding for the team.

“Why would a bone cell have any effect on body weight, body fat mass, body composition or glucose metabolism? That was strange,” he says.

“If you inhibit glucocorticoid signalling in the bone forming cell, the osteoblast, you can prevent glucocorticoid induced diabetes. That means the osteoblast has a role in mediating the actions of glucocorticoids on fuel metabolism. But how does it do it? Our results suggest that osteocalcin is involved in some or other way.”

Based on results from a group at Columbia University, New York, the researchers think that osteocalcin leaves the bone and regulates systemic glucose and fat metabolism. When the production of osteocalcin is suppressed through the action of glucocorticoids, osteocalcin concentrations drop and systemic fuel metabolism derails. In order to prove this theory, Prof Seibel’s team has found ways to artificially elevate levels of osteocalcin in mice, eventually inducing the liver to make osteocalcin.

“If you treat a normal mouse with glucocorticoids it develops fatty liver and diabetes. If you take the mice that make osteocalcin in the liver and treat them with the same dose of glucocorticoids, their livers deposit much less fat. Even in mice that you don’t treat with glucocorticoids, as soon as you make the liver produce the osteocalcin, the liver gets rid of all fat. It’s quite an effect.”

So how does osteocalcin do it? Prof. Seibel says the team will look at two possible pathways: adipose tissue and liver metabolism. The answers may be several years away but already there is a much greater understanding of osteocalcin – the bone-related molecule that’s older than the dinosaurs.
Could Cartilage hold the key?

Glucocorticoids – a class of steroid drugs – have been used widely for more than 60 years to control inflammatory and autoimmune diseases, rheumatoid arthritis in particular. However, long-term use of glucocorticoids can result in severe side effects, including osteoporosis, hypertension, and type 2 diabetes.

Associate Professor Hong Zhou has received a grant from the National Health and Medical Research Council to explore the possibility that it is specifically the cartilage cells in our joints that are targeted by glucocorticoids, and if so, to investigate other potential drugs which could replace glucocorticoids.

Chondrocytes are the only cells found in healthy cartilage, and A/Prof. Zhou has already discovered that mice with arthritis are completely resistant to glucocorticoid treatment if the relevant receptor in their chondrocytes is suppressed.

“We were just thinking the cartilage is such a big area in joints, so what are those cells doing during inflammation, just to be degraded?” she says.

“So we created a mouse model to block the glucocorticoid receptor specifically in the cartilage, and then we induced arthritis and treated it with glucocorticoid, just to see what happens if we block this particular cell population.

“We were surprised to see that when we treated these mice already induced with arthritis they were resistant to the glucocorticoid completely. That means that the cartilage must initiate the inflammation and that inflammation may attract all the immune cells.

“So glucocorticoid must target chondrocytes in the cartilage – we’re not saying it doesn’t affect other cells but what we found is that cartilage cells are not just being degraded and must play a big role in initiating the inflammation.”

The NHMRC grant extends over three years and if the research proves that cartilage cells play a role in the inflammation, then the therapeutic target can be changed and other medicines could be developed to replace glucocorticoid.

Isolating Mutant Genes with the help of a Worm

A transparent worm, only a millimetre in length, no bigger than the width of a fingernail, may be instrumental in identifying specific genetic mutations that cause the degeneration of the nerves in disorders such as Charcot-Marie-Tooth (CMT) neuropathy.

Dr Megan Brewer, Senior Hospital Scientist and Postdoctoral Fellow at the ANZAC Research Institute and an affiliated Research Fellow with the University of Sydney Medical School, is using the worm species known as C. elegans to assist in detecting the true neurotoxic mutations in patients.

“We’re trying to identify the actual mutations causing CMT,” explains Dr Brewer, whose earlier work in this field at the Institute was furthered by an appointment at the University of Michigan.

“The idea is to model these mutations in vivo or in the context of a whole organism. We can take these candidate mutations and express them in the worm and then see if that worm’s neurons degenerate.

CMT is an incurable disorder which affects both sensory and motor nerves, leading to weakness of muscles in the arms and legs, foot deformities and impaired sensation in the hands and feet. Other similar disorders may affect only the motor neurons or only the sensory neurons.

Reducing the risk of Heart Attacks

A significant and frequently fatal complication of many diseases, including cardiovascular disease, is the formation of pathological blood clots. Blood clots that form in the heart, for example, are the major cause of stroke in people with atrial fibrillation, while a blood clot in an artery can stop the flow to the heart and lead to a heart attack.

Dr Caroline Reddel is investigating ways of measuring the likelihood of a patient developing blood clots so preventive treatment can be started, and has received a University of Sydney Early Career Research grant to fund the initial year of her project.
Reducing the risk of Heart Attacks continued

Central to her research is the role of microparticles in the blood — small particles released by the various cell types including platelets. Working in the Vascular Biology group alongside Dr Gabrielle Pennings she noticed that under certain conditions, the use of the anti-inflammatory medication colchicine increased the production of these microparticles.

“Having been looking at ways to measure the potential of the blood to clot by looking at plasma and stimulating that outside the human body to form a blood clot,” says Dr Reddel.

“We can measure the way that happens and the amount of time it takes, and measure the potential of the blood to clot in that way and also its potential then to break down after it’s clotted, which is the other important part of it.

“Now I’m looking at the role of microparticles in that, looking at it from a couple of different points of view. One is by removing all the microparticles from plasma and looking at the potential for the blood to clot once you remove the microparticles. And the second is where we’ll be looking at specific microparticles produced in response to colchicine is by adding microparticles into plasma and comparing results under various conditions.”

Dr Reddel hopes her research will lead to novel treatments and a better understanding of the two-way relationship between blood clotting and disease.

Making Coronary Physiology measurements cheaper and safer

A patient admitted to hospital with chest pains and suspected of suffering from coronary stenosis — the build-up of plaque within an artery leading to the heart — will normally undergo an angiography. A large proportion of these patients undergo coronary physiology assessment. This involves the insertion into the artery of a wire with a pressure sensor near its tip.

It’s a procedure which helps doctors determine how narrow the artery has become and what treatment is necessary, but it is also expensive and carries a degree of risk.

Dr Andy Yong, a member of the ANZAC Research Institute laboratory and a member of the cardiology staff, believes he has the answer to reducing both expense and risk. To assist him in his research, Dr Yong has received a Heart Foundation Future Leadership Fellowship and a Sir Roy McCAughney Fellowship from the Royal Australasian College of Physicians.

Dr Yong also acknowledges the generous support of Mr Ian Palmer, of Ashfield in Sydney, who donated $10,000 to the Vascular Biology Group.

“My idea is to develop a system where we can take multiple images of the affected artery and then blend them to make a 3-D image. Using computer modelling, we will be able to simulate coronary physiology measurements which will give doctors a much more complete view of the artery.” Dr Yong says.

“This way, without having to insert a wire, we will be able to measure what we call fractional flow reserve, to estimate how the flow of blood is being affected.”

Dr Yong estimates that the current procedure, using the wire and pressure sensor, costs about $1000 for each patient, and at Concord Hospital alone, it is required for about 100 patients each year.

“This system could save hospitals a small fortune, and make it safer for patients as it may obviate the need for extra wire instrumentation of their arteries.

“We’ll start by testing it at Concord and then roll it out to another four hospitals in Sydney for them to evaluate and validate the system,” he says.

Used for thousands of years but how does this drug work?

For more than 2000 years — from the time of ancient civilisations in Greece, Persia and Egypt — physicians have been prescribing a medication known as colchicine, which is derived from a plant known as the autumn crocus. It is still being used extensively today, yet no one is quite certain how colchicine works.

Dr Gabrielle Pennings, a scientist in the Vascular Biology group, has set herself the task of finding the answer, and has been awarded an early career research grant by the University of Sydney to support the initial stages of her project.

“It’s known that colchicine is an anti-inflammatory drug and it’s used in conditions like gouty arthritis, familial Mediterranean fever, Behçet’s disease, and they’ve more recently used it in pericarditis, atrial fibrillation — so heart-related things,” says Dr Pennings.

“They’ve found in the past year or so that it’s good for secondary prevention of cardiac events after someone’s had a heart attack or surgery for coronary disease. But they still don’t understand how it’s working and what role the platelet is having in this.”

Platelets are the smallest of our blood cells and bind together when blood vessels are damaged to stop the bleeding.

“I’ve been looking at how colchicine in vitro affects platelet functions and aggregation, so how the platelets come together, the platelet activation in general, and what happens to the surface of the platelet,” Dr Pennings explains.

“The platelet is made up of granules, it’s very small and when it becomes activated it releases those granules. So I’m looking at can colchicine affect what gets released and what is being affected overall.”

Her theory is that while it’s been known for some time that platelets are involved in inflammation, colchicine may be affecting the release of inflammatory mediators not only in the white blood cells but also the inflammatory complex within the platelet.

“If it’s working for cardiovascular disease but they don’t know how, could it be something to do with the platelets, because platelets play a large role in cardiovascular disease.”
Honour for Vascular Biology Team

The Australian Vascular Biology Society has recognised the outstanding work of the ANZAC Research Institute’s Atherosclerosis group by awarding its Distinguished Achievement Award jointly to the team’s leaders, Professors Len Kritharides and Wendy Jessup. The former delivered a lecture and accepted the award, as Professor Jessup was overseas.

“Len and I have been collaborating for many years,” said Prof. Jessup, “so this was really special, coming just two years after we moved here from the University of NSW.”

“We have been collaborating since he started doing research. When Len was a PhD student at the Heart Research Institute in the early 1990s I was his co-supervisor, so we’ve been working together for a long time now.”

Professor Kritharides trained in Medicine, specialising in Cardiology, at the University of Melbourne, before moving to Sydney to undertake his Ph.D. Professor Jessup completed her scientific training at the Universities of Manchester and Sheffield in the UK. She moved to Australia in 1989 to join the Heart Research Institute. Together with Prof. Kritharides, she was co-leader of the Macrophage Biology Group in the Centre for Vascular Research at the University of NSW before transferring that team to the ANZAC Research Institute on the Concord campus.

“I am certainly enjoying being here at ANZAC,” said Prof. Jessup. “The group’s going well and we recently had some new PhD students join us at ANZAC from the cardiology department so it’s good to have that cross-fertilisation from the clinical department to the basic laboratory.”

The Distinguished Achievement Award is only the fourth to be presented in the 22 year history of the Vascular Biology Society.

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