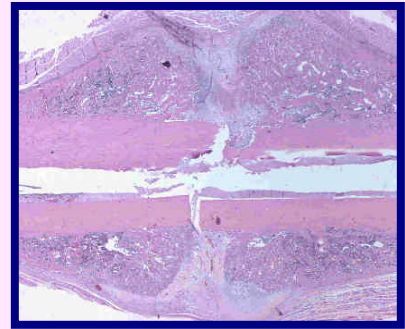
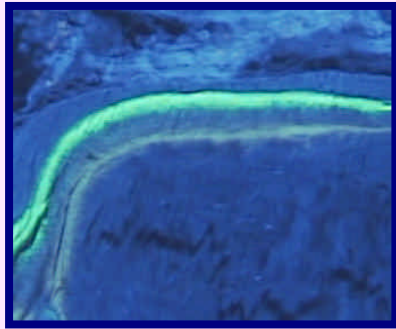


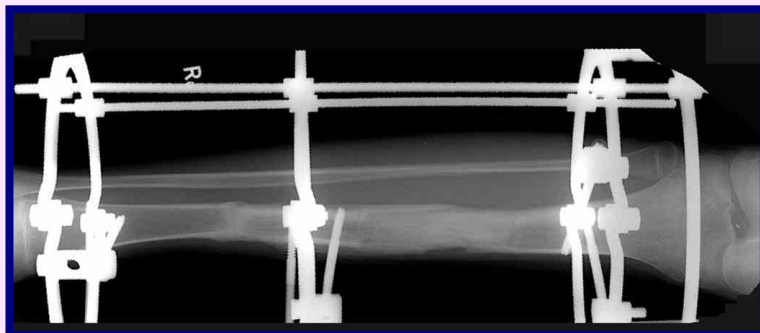


orthopaedic **rese^arch**
and biotechnology



orthopaedic **rese^arch** and biotechnology

2008 Research report



Early Beginnings

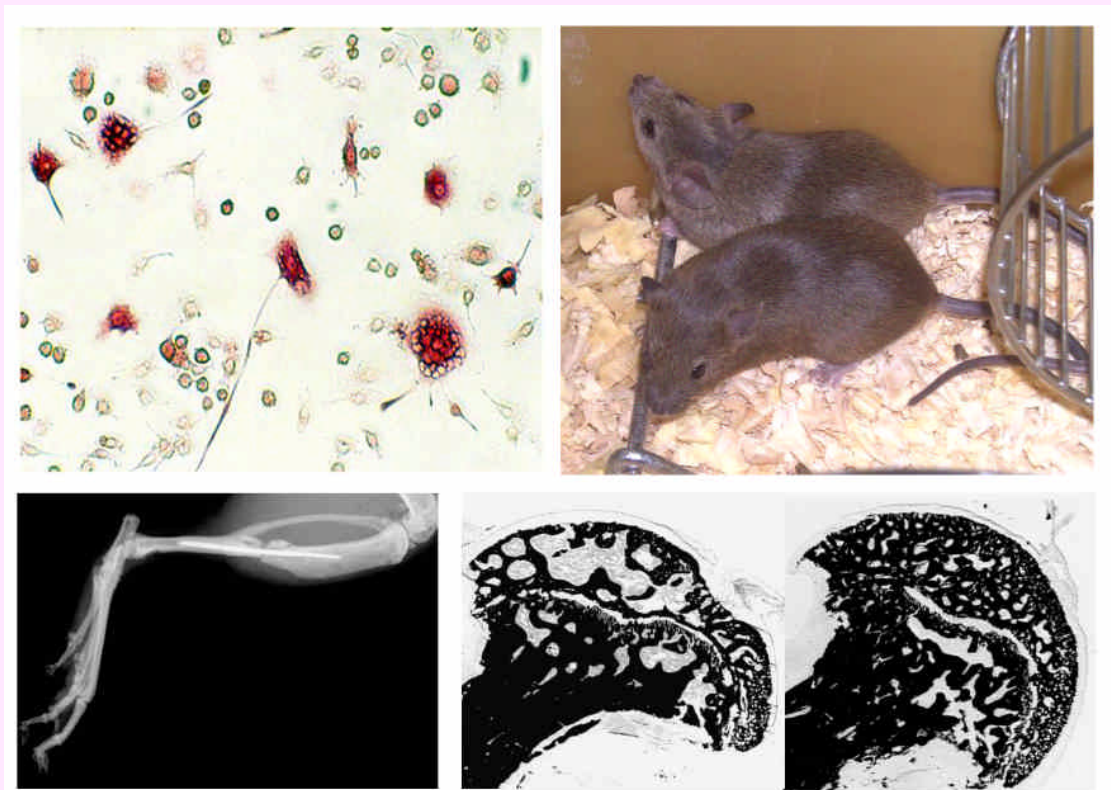
The Orthopaedic Research and Biotechnology Unit was founded in 1998 primarily to investigate possibilities of advancing bone healing in limb lengthening procedures.

Collaborations with the Garvan Institute (Bone and Mineral Program), the University of Sydney (Department of Biomedical Engineering), the Prince of Wales Medical Research Institute, the University of Queensland (School of Biomedical Sciences), and the Children's Medical Research Institute (Embryology Unit) have broadened the base, scope and technical proficiency of the Unit.

The Unit has grown such that in 2008 an active group of researchers comprising Orthopaedic Surgeons, Orthopaedic Surgical Fellows and Research Scientists make up a thriving laboratory.

Our Mission

Advancing orthopaedic care through improved understanding of bone diseases, bone healing and pharmaceutical therapies.



Research theme

An emerging theme of our research is that bone healing outcomes are determined by the levels of **anabolism** (bone formation) and **catabolism** (bone resorption)

In many clinical situations, our research has demonstrated that the underlying defect is excessive catabolism. This can be treated using anti-resorptive drugs, such as bisphosphonates, which are commonly used to treat osteoporosis in the aged.

In other clinical situations, we have found anabolic deficiencies that cannot be overcome by anti-resorptive drugs. In these situations, we can apply anabolic drugs, such as bone morphogenetic proteins (TGA-approved bone forming agents). However, we are increasingly finding that the effect of anabolic drugs can be maximised with co-treatment with an anti-catabolic drug.

Finally, these anabolic and anti-catabolic drugs act upon **stem cells** found within bone and adjacent tissues. We are looking at these cells to determine their origin and whether we can increase their recruitment to enhance bone healing.

Roles within the unit

The Orthopaedic Research and Biotechnology Unit designs and executes studies aimed at investigating the etiology of childhood orthopaedic problems. Our unit is particularly focused on developing *clinically relevant* model systems of bone diseases. These systems enable the critical evaluation of both surgical and drug-based therapies.

Experimental work is carried by the many experienced researchers within the unit. They include:

- ❖ **Orthopaedic surgeons**
- ❖ **Veterinary surgeons**
- ❖ **Research scientists**
- ❖ **Biomechanical and biomedical engineers**
- ❖ **Technical support staff**



Established research projects

➤ Bisphosphonates as therapeutics for paediatric orthopaedics

Bisphosphonates (BPs) are a class of anti-resorptive drugs that were originally developed for the treatment of osteoporosis. We speculated that the fundamental source of the pathology in some orthopaedic conditions may be due to excessive bone resorption. In these cases, BP therapies may be advantageous. Our work in pre-clinical models now forms a key portion of the literature. Bisphosphonates are increasingly used in orthopaedics for the treatment of genetic and metabolic bone diseases. There are orthopaedic indications for the use of BPs that we are continuing to investigate through our translational and clinical research programs.

Our work in bisphosphonates has led to the development of one of our main research themes– optimisation of the anabolic (bone-forming) and catabolic (bone-resorbing) responses. By combining local anabolic treatment (bone morphogenetic proteins) with systemic BP therapy, we achieved synergistic (more than additive) effects. We are continuing to explore this drug combination experimentally as well as applying it to clinical situations.

➤ Bone defects in Neurofibromatosis type 1 (NF1)

NF1 is a common genetic disease (affecting 1 in 3000 children) that can manifest as a variety of characteristic symptoms including prevalent tumour formation. These children can also develop severe orthopaedic problems, including scoliosis (curvature of the spine) and a congenital tibial dysplasia. Orthopaedic surgery on NF1 children has a poor prognosis due to underlying problems with bone healing.

We have been using genetic mouse models of NF1 deficiency, as well as studies with NF1 patients treated at the Children's Hospital at Westmead to explore the mechanism of these bone defects. Our ongoing research is funded by both the National Health & Medical Research Council (www.nhmrc.gov.au) and the Children's Tumor Foundation (www.ctf.org). We have published studies that indicate that dual problems in bone anabolism and bone catabolism may both contribute to the NF1 bone phenotype.

➤ The role of muscle in bone repair

It is not uncommon for bone to form in abnormal locations, and muscle is the most common site for this to occur. Our research has shown that muscle stem cells have a strong innate capacity to form bone, and we hypothesize that muscle cells may be actively recruited for bone healing.

In this NH&MRC-funded project, we are investigating the contribution of muscle cells to fracture repair using a combination of cell culture and genetic mouse models. As well as revealing key insights into the cellular contributions to bone formation and repair, this project may result in new cell-based therapies for bone repair that utilise muscle cells.

➤ The role of osteoclasts in fracture repair

The majority of fractures heal via the process of *endochondral ossification*, where cartilage acts as a precursor to the primary ossification event. The conventional dogma purports that osteoclasts are the cells responsible for the removal of cartilage prior to bone formation. However, we have found in models of osteoclast inhibition or dysfunction, the early stages of fracture repair progress normally.

We are currently investigating the effects of anti-osteoclastic agents on the early stages of fracture repair. We are also testing the effects of agents that disrupt the action of matrix metalloproteases (MMPs), enzymes secreted by a range of cell types that may also contribute to matrix degradation and cartilage resorption.

Emerging research directions

➤ Stem cell therapies for *Osteogenesis Imperfecta*

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a severe genetic disease affecting children. Currently, children with OI receive bisphosphonates to strengthen their bones, but such treatments do not address the underlying genetic deficiency and offer only lesser benefits to those with severe deforming OI.

In collaboration with the Oncology and Gene Therapy Units and the Department of Endocrinology, we are undertaking a joint project to explore emerging stem cell-based therapies for treating children with severe OI. Initial pre-clinical studies will commence in late 2008.

➤ Human orthopaedic cell & tissue bank

Following review by our institutional ethics committee, in 2007 we commenced collection of samples from patients with and without genetic bone disease who are undergoing surgery. Bone cells can be isolated, grown, and cryo-stored in the laboratory for future research efforts. These specimens will be an invaluable aid for the future translation of our pre-clinical studies.

➤ Sclerostin and fracture healing

Sclerostin is a recently discovered molecule secreted by osteocytes. Osteocytes are cells within bone that are critical for the regulation of bone mass, and genetic defects in Sclerostin have been linked to high-bone mass diseases. Sclerostin-based therapies are currently being developed for osteoporosis, however the normal and potential therapeutic role for Sclerostin in orthopaedics remains unclear.

In an emerging collaborative effort with scientists the Children's Medical Research Institute, as well as commercial biotech interests, we are examining the orthopaedic actions of Sclerostin as well as its associated signalling molecules.

Director

A/Prof David Little MBBS, FRACS(Orth), FAOrthA, PhD

A/Prof Little is the Head of the Orthopaedic Research and Biotechnology Unit at the Children's Hospital at Westmead (CHW), Senior Staff Specialist in Paediatric Orthopaedics and a Senior Lecturer in Paediatrics and Child Health at the University of Sydney. As a clinician-scientist with a PhD, A/Prof Little is in an ideal position to answer research questions in areas of clinical need.

In 2003 A/Prof Little published the first paper to suggest bisphosphonates may be a useful therapy for osteonecrosis. These studies have led to patent applications for CHW, which were successfully licensed to Novartis Pharma AG in 2003. He has pioneered the investigation of bisphosphonate modulation of bone repair, and has 11 recent peer reviewed publications on the topic. Five of these have been in the high ranking Journal of Bone Mineral Research.

Besides having multiple peer-reviewed publications, A/Prof Little won the Hibbs Award for best scientific presentation for 'Prediction of the Crankshaft Phenomenon by Peak Height Velocity' at the Annual Scientific Meeting of the Scoliosis Research Society, North Carolina, 1996. A/Prof Little was selected as the 2002 ABC Travelling Fellow, the most prestigious academic award for Orthopaedic Surgeons under 40. This involved a six-week USA/Canada tour with other international recipients, visiting major centres, giving invited talks and interacting with research units.

His group consists of a diverse multidisciplinary team, including scientists, surgical registrars, biomedical and biomechanical engineers, histologists, veterinary support, and technicians. A/Prof Little currently supervises or co-supervises five postgraduate students. He has developed a large program investigating therapeutics approaches for the treatment of orthopaedic complications and he has established a number of small and large animal surgical models.

A/Prof Little is now a leading figure in Australian Orthopaedic Research. In 2004-5 A/Prof Little was an invited speaker at the ANZBMS annual scientific meeting, the Paediatric Bone Symposium, The Australian Health and Medical Research Congress, The Australia and New Zealand Orthopaedic Research Society, The North American Limb Lengthening and Reconstruction Society and the American Academy of Orthopaedic Surgeons. In 2006 he was invited to speak at the European Calcified Tissue Society in Prague, a satellite symposium on novel therapies for Perthes disease in Baltimore and the International Paediatric Orthopaedic Society in Orlando FL, USA. Prior to this A/Prof Little has given 5 other invited talks on this topic at national and international meetings. A/Prof Little's expertise has also been recognized by an invited chapter on Enhancements in Regenerate Bone Healing in the text "Limb Lengthening and Reconstruction Surgery".

A/Prof Little is an Australian Orthopaedic Research Foundation Board Member and is also on the Australian Orthopaedic Association Scientific Committee.



Research Staff & Students

Current Members

Dr Aaron Schindeler, BSc(Hons), PhD	Research Scientist
Dr Michelle McDonald, BMedSc, PhD	Research Officer
Dr Paul Bokko, DVM, MVSc, PhD	Research Officer
Dr Craig Godfrey, BVSc	Veterinary Surgeon/PhD Student
Ms Alyson Seymour, BBiotech(Hons)	Research Assistant
Mr Jad El-Hoss, BSc, MSc	Research Assistant
Ms Renjing Liu, BSc(Hons)	PhD Student
Ms Nicole Yu, BE	PhD Student
Ms Haoi-Lan Mai, BSc	Technical Assistant
Ms Kathy Mikulec	Technical Assistant
Ms Lauren Stanmore	Technical Assistant
Ms Tajana Lah, BMedSc	Honours Student

Former Members

Dr Negin Amanat, BE, PhD
 Ms Rachael Bugler, BMedSc
 Ms Rachel Peat, BSc(Hons)
 Ms Belinda Hamilton, BSc
 Ms Elisabeth Smith BSc, MSc(Hons)

Visiting International Researchers

Dr Magnus Tägil (2005, 2006)
 Dr Lorainne Harry (2005)

Research Fellows in Orthopaedic Surgery

Dr Mark Latimer (2007-8)
 Dr Piers Mitchell (2007)
 Dr Tim O'Mara (2006-7)
 Dr Michalis Zenios (2006)
 Dr Manoj Ramachandran (2005-6)
 Dr Menahem Singer (2005)
 Dr Patrick Kiely (2004-5)
 Dr David Nelson (2004)
 Dr Sukdeep Dulai (2003-4)
 Dr Richard Brown (2003)
 Dr Rick Bransford (2002-3)
 Dr Elisabeth Goergens (2002)
 Dr Ian Sharpe (2001-2)
 Dr Anthony McEvoy (2001)
 Dr Paul Williams (2000-1)
 Dr Nick Smith (2000)



Acknowledgement of Funding Sources

Current support

Our research into treating the “bone defects in Neurofibromatosis type 1 (NF1)” is currently supported by an **NH&MRC Project Grant**. We are also receiving funding from the **Children’s Tumor Foundation (CTF)**. This work has been previously supported by the **Australian Orthopaedic Association (AOA)** as well as the **NF1 Association of Australia (NFAA)**.

Our projects investigating “the role of osteoclasts in fracture repair,” and “the role of muscle in bone repair,” are also currently supported by **NH&MRC Project Grants**.

Support for a pilot project to examine the feasibility of selective cell-based therapy for *osteogenesis imperfecta* is currently being granted from the **Bone Growth Foundation (BFG)**.

The Orthopaedic Department receives ongoing funding support for Orthopaedic Research Fellows from **Ingham Enterprises**.

Prior support

Our past research examining “bisphosphonates as therapeutics for fracture healing, distraction osteogenesis, and osteonecrosis”, and “anabolic and anti-catabolic combination therapies” were supported by **NH&MRC Project Grants**. Our work with bisphosphonates has also been supported by **Novartis Pharma AG**. Our research into bone morphogenetic proteins and combination therapies receives in-kind support from **Stryker Biotech**.

Start up funding for the “the role of muscle in bone repair” project and for work on “bone tissue engineering” was granted by the **AOA**.

The Orthopaedic Department has received past funding support for Orthopaedic Research Fellows from **Smith & Nephew**