Bone Regulation Group

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BACKGROUND

Osteoporosis is the most common degenerative condition in developed countries. It is a disease resulting in low trauma fractures in over one third of women and one fifth of all men over 60 and results in widespread increases in chronic pain, morbidity and mortality. Current treatment focuses upon reducing bone loss through inhibition of osteoclast action; however, these can not restore bone tissue already lost in osteoporotic patients. Our laboratory is investigating ways to stimulate the production of bone by osteoblasts, in effect, reversing the aging process in these people. Excitingly, we have identified several powerful and unique anabolic pathways to bone associated with modulation of a neuropeptide pathway within the brain. This neuropeptide, called neuropeptide Y, is being studied in a long-standing collaboration with the Neuroscience Program, in which unique genetic models, developed here at the Garvan, are helping dissect the mechanism of these bone stimulatory signals in the brain and in bone. Recent findings from our group have identified an important role of direct neuropeptide signalling in osteoblasts and have revealed a pathway from the hypothalamus to bone. We are currently world leaders in this promising and emergent field of research. Cutting-edge geneticand viral techniques enable us to alter gene expression with temporal, spatial and cellular precision, whether within specific brain loci or individual cell lineages and assess the resultant skeletal response. These *in vivo* findings can be further dissected *in vitro* to enable system wide analysis of these powerful anabolic pathways.

PROJECT 1

Interaction of novel hypothalamic pathways and classic endocrine pathways in the regulation of bone mass

Our laboratory has identified several novel and powerful anabolic pathways that increase bone mass and strength through actions of the neuropeptide Y system. Recent findings have located a receptor for these neural signals on the bone forming cell, the osteoblast, thereby identifying the putative mechanism of action. This peripheral component of the pathway is by its position, more likely to interact with other skeletal regulators. Moreover, preliminary data indicate that this neural pathway interacts with the classic sex steroid pathways so integral to the loss of bone mass in osteoporosis and suggests potentially novel regulatory influences on these well known responses by neural factors. Given that sex steroids alter central neuropeptide action, is highly likely to represent a feedback mechanism between the peripheral skeletal and central neuropeptide signalling, thereby integrating these pivotal two regulatory systems. Using state of the art genetic models of conditional gene deletion in tandem with surgical and hormonal interventions, the interaction between the sex steroid and neuropeptide Y systems will be investigated. The project, covering both hypothalamic and skeletal sites, will see the successful applicant receive a broad range of *in vivo* experience, modulating gene expression using genetic, viral and pharmacological methods in both germline and conditional, inducible models. These models will be combined with surgical and chemical interventions, to provide a comprehensive in vivo skill base. In addition, cell culture involving chemical and genetic manipulations ex vivo and molecular dissection of critical cellular pathways will complete a broad-based range of techniques, combined with a focussed approach within an emerging and highly topical area of research.

Bone Regulation Group Selected Publications

Baldock PA, Sainsbury A, Couzens M, Enriquez RF, Thomas GP, Gardiner EM, Herzog H. (2002) Hypothalamic Y2 receptors regulate bone formation. *J Clin Invest* 109:915-921.

Baldock PA, Sainsbury A, Allison S, Lin D, Couzens M, Boey D, Enriquez, RF, Lin S, During M, Herzog H, Gardiner, EM. (2005) Hypothalamic control of bone formation: Distinct actions of leptin and Y2 receptor pathways. *J Bone Miner Res* 20:1851-1857.

Baldock PA, Allison S, Mc Donald MM, Sainsbury A, Enriquez RF, Little DG, Eisman JA, Gardiner EM, Herzog H. (2006) Hypothalamic Regulation of Cortical Bone Mass: Opposing Activity of Y2 Receptor and Leptin Pathways. *J Bone Miner Res* . 21:1600-1607.

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Baldock PA, Allison SJ, Lundberg P, Lee NJ, Slack K, Lin EJD, Enriquez RF, McDonald MM, Zhang L, During MJ, Little DG, Eisman JA, Gardiner EM, Yulyaningsih E, Lin S, Sainsbury A, Herzog H. (2007) Novel role of Y1 Receptors in the Coordinated Regulation of Bone and Energy Homeostasis. *J Biol Chem* 282:19092-19102.

Lundberg P, Allison SJ, Lee N, Baldock PA, Brouard N, Rost S, Enriquez R, Sainsbury A, Lamghari M, Simmons P, Eisman JA, Gardiner EM, Herzog H. (2007) Greater bone formation of Y2 knockout mice is associated with increased osteoprogenitor numbers and altered Y1-receptor expression. *J Biol Chem* 282:19082-19091.

Epidemiology and Genetics Group

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BACKGROUND

Fracture due to osteoporosis is a consequence of accumulated disturbances in skeletal homeostasis, resulting in reduced bone strength and deteriorated bone architecture. Identification of modifiable risk factors and development of prognostic model of fracture should lead to prevention, or reduction of fracture among postmenopausal women and older men in the community. At the Bone and Mineral Research Program, our research interests are centred around the epidemiology and genetics of fracture. In the epidemiology of fracture, we are interested in studying the natural history of osteoporosis through modelling of bone loss and their hormonal and genetic effects. As part of this project, we actively work on the development of prognostic models for individualizing the risk of fracture for a man or woman. Another active line of research is the application of Bayesian paradigm in the examination of fracture outcomes, treatment efficacy, and cost-effectiveness. We are interested in a wide variety of risk factors for good and bad outcomes following fracture including lifestyle, genetic, hormonal, fall-related, bone parameters, concurrent illness and medications for which we have over 15 years of longitudinal data. These projects require expertise in clinical medicine, epidemiology, advanced biostatistics, and computer simulation. Specific projects included:

☐ Application of mixed-effects and Bayesian methodology for the study of longitudinal progression to osteoporosis.

☐ Development of prognostic models, especially the Bayesian Belief Network model, for predicting fracture risk and adverse outcomes.

☐ Development of multivariable nomograms for individualizing the risk of fracture and adverse outcomes in a man and woman.

☐ Indirect comparison of anti-fracture efficacy among current therapies by using Bayesian models.

☐ Bayesian determination of treatment threshold to achieve optimal cost-effectiveness in the general community.

☐ Identification of risk factors for adverse (or good) outcomes following fracture including mortality, subsequent fracture and quality of life.

☐ Examination of the interrelationship between subsequent fractures and mortality.

Another aspect of the epidemiology of fracture relates to prediction of outcomes following a fracture such as risk of a subsequent fracture, mortality or adverse quality of life. These questions result from unknown and difficult clinical decisions faced when treating a patient. In the genetics of osteoporosis, we are interested in searching for novel genes that are involved in the regulation of bone phenotypes and fracture risk. We use both genome-wide linkage and population-based genetic association analyses. We are conducting a familial study into the genetics of bone phenotypes using extended pedigree design. The study involved some 95 families, among whom, there are 5 large families with more than 400 individuals. This line of research requires expertise in medical science, genetics, biostatistics, and bioinformatics. Specific projects included:

☐ Study the pleiotropic (genetic) effects on bone phenotypes using extended pedigrees.

☐ Haplotype analyses of candidate genes.

☐ Genome-wide linkage analysis of bone phenotypes.

☐ Gene-environmental interaction studies.

☐ Meta-analysis of genetic association studies using Bayesian models.

Epidemiology and Genetics Group Selected Publications

Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. *Osteoporosis Int*. 2007 Mar 17.

Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV. Residual lifetime risk of fractures in women and men. *J Bone Miner Res*. 2007 Jun;22(6):781-8.

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Nguyen ND, Eisman JA, Nguyen TV. Anti-hip fracture efficacy of biophosphonates: a Bayesian analysis of clinical trials. *J Bone Miner Res*. 2006 Feb;21(2):340-9.

Nguyen TV, Esteban LM, White CP, Grant SF, Center JR, Gardiner EM, Eisman JA.. Contribution of the collagen I alpha1 and vitamin D receptor genes to the risk of hip fracture in elderly women. *J Clin Endocrinol Metab*. 2005 Dec;90(12):6575-9.