Origins of Bone and Cartilage Disease
Wellcome Trust Strategic Award
Information for Applicants

The aim of this work is to perform high-throughput skeletal phenotype analysis of knockout mice generated by the Wellcome Trust Sanger Institute Mouse Genetics Project in order to (i) identify new genes that determine bone and joint development and function and (ii) provide new disease models.

The successful applicants will work on a large program funded by a new Wellcome Trust Strategic Award entitled *Origins of Bone and Cartilage Disease*. Substantial funding for five years has been awarded to an international collaboration led by Imperial College London with partners the Garvan Institute of Medical Research, Sydney, Australia; the Wellcome Trust Sanger Institute, Hinxton; and Queen Mary University of London.

Three Post-Doctoral Research Associates and two Research Technicians will be appointed at Imperial College London. A further Post-Doctoral Research Associate and one Research Technician will be appointed at the Garvan Institute.

**Scientific background**
Half of all adults are affected by bone and cartilage disorders. There are over 11 million people with osteoporosis or osteoarthritis in the UK, suffering pain and disability at enormous personal and economic cost. Osteoporosis is the commonest skeletal disorder resulting in NHS expenditure of more than £1.7 billion per annum, whilst osteoarthritis costs over 1% of Gross National Product. This expenditure is increasing markedly as the population ages.

Available treatments for osteoporosis reduce fracture risk by only 50%, there are few approaches to restore bone mass and the effectiveness of current drugs is limited by side effects and patient acceptability. The pathogenesis of osteoarthritis is poorly defined, no drugs are available that prevent or delay disease progression and biomarkers have not been defined. Thus, there is an urgent need to (i) improve understanding of the mechanisms that cause bone and joint disease, and (ii) develop better treatments.

An international effort is underway to delete all protein coding genes in order to provide disease models that will facilitate studies of disease susceptibility, gene function and new treatments. This program is being carried out by the International Knockout Mouse Consortium (IKMC), with characterisation of mutant strains undertaken by the International Mouse Phenotyping Consortium (IMPC). The Wellcome Trust Sanger Institute (WTSI) Mouse Genetics Project (MGP) is a major contributor, generating approximately 160 new knockout mouse lines per year and performing broad-based primary phenotype analysis ([https://www.mousephenotype.org](https://www.mousephenotype.org)).

**The program**
We will adopt a multi-disciplinary approach, exploiting the power of the MGP to identify genes and regulatory networks that underpin (i) normal bone formation, maintenance and strength, and (ii) joint morphology, integrity and function.

We will screen over 1500 knockout lines for abnormalities of (i) bone structure and strength, and (ii) joint shape, structure and articular cartilage integrity. Transcriptome analyses will
define key gene networks that control bone and joint development, maintenance and function, and which may be disrupted in skeletal disease. Data will be disseminated publically and rapidly, and collaborations with international consortia studying bone and joint disease in human populations will translate gene discovery in the mouse to human disease and link gene discovery in humans to new knockout mouse disease models.

Fifteen selected knockout lines will be investigated in detail to determine the molecular basis of specific skeletal abnormalities and identify new possibilities for drug development. This work builds on our prior experience of high throughput analysis, in which we developed a rapid-throughput phenotyping platform and identified nine new genes with diverse and unpredictable functions that determine bone mass and strength (http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1002858).

The model systems, reagents, techniques and all equipment required to perform the proposed studies are already established, and training will be available as necessary.

Positions available

**Imperial College London, UK**

*a) Scientific coordination and program management*  
Post-doctoral research associate

*b) Bone high-throughput and detailed phenotype analysis*  
Post-doctoral research associate  
Research technician

*c) Articular cartilage and joint high-throughput and detailed phenotype analysis*  
Post-doctoral research associate  
Research technician

**Department of Medicine**

The Department of Medicine at Imperial College is one of the largest teaching and research departments in the UK (http://www1.imperial.ac.uk/departmentofmedicine/). It has an annual research spend of £60M, approximately 900 staff, including 200 academic staff, and around 400 PhD students. The Department is also responsible for delivering the majority of the undergraduate medical curriculum and has an extensive program of postgraduate teaching, including Masters Courses and higher research degrees. The Department is led by Professor Gavin Screaton and comprises five Divisions: Experimental Medicine; Immunology & Inflammation; Infectious Diseases; Diabetes, Endocrinology & Metabolism; and Brain Sciences. There is a diverse range of basic and clinical research that applies cutting edge technology and methods to elucidate disease pathogenesis and develop novel treatment approaches.

**Molecular Endocrinology Group**

The Molecular Endocrinology Group is located in newly refurbished laboratories in the Commonwealth Building at the Hammersmith Campus of Imperial College. Professors Graham Williams and Duncan Bassett have international reputations for integrated research in hormone action and skeletal biology with established expertise in phenotype analysis of *in vivo* models of bone and cartilage disease. International cross-disciplinary collaborations with geneticists, bioengineers and imaging specialists ensure that state-of-the-art techniques
are developed and applied. These include digital x-ray microradiography, micro-CT, BSE-SEM, confocal laser scanning microscopy, biomechanical testing and materials analysis, synthetic chemistry capability, and comprehensive facilities for molecular and cellular biology. Additional core equipment and expertise includes: a Leica SP5 confocal microscope; FACS cell sorting; a gene targeting, transgenic and re-derivation suite; and proteomics and automated fluorescent sequencing facilities with genome and transcriptome analysis and bioinformatics capabilities.

Molecular Endocrinology Group
http://www1.imperial.ac.uk/departmentofmedicine/divisions/diabetesendocrinologymetabolism/meta/molecular_endocrinology_group/

Professor Graham Williams
http://www.imperial.ac.uk/AP/faces/pages/read/Home.jsp?person=graham.williams

Professor Duncan Bassett
http://www.imperial.ac.uk/AP/faces/pages/read/Home.jsp?person=d.bassett

Garvan Institute of Medical Research, Sydney, Australia
a) Transcriptomics and bioinformatics
Post-doctoral research associate

b) Micro-CT, histomorphometry
Research technician

The Garvan Institute of Medical Research
The Garvan Institute of Medical Research is led by Professor John Mattick and is one of Australia’s premier medical research institutions, with approximately 500 staff. Research is focused upon understanding the role of genes in human health and disease as the basis for developing future cures. The Garvan Institute is a world leader in its field, pioneering study into some of the most widespread diseases affecting our community today, including cancer, diabetes, and immunological and neurological disorders. Professor Mattick has made a significant contribution to understanding genetics and genomics through his far-sighted insights and work showing that the large sections of the genome that do not code for protein express a previously hidden layer of regulatory RNAs that guide the epigenetic trajectories of human development. With a particular emphasis on understanding the transcriptome and the epigenomic environment responsible for regulating gene transcription, the Institute has highly developed sequence analysis, informatic expertise and computational facilities.

Division of Osteoporosis and Bone Biology
The Division of Osteoporosis and Bone Biology is one of the five Divisions of the Garvan Institute. Members of the Division have made many seminal discoveries, including: identification of the first genetic variant associated with bone mass; definition of the scope of osteoporosis and increased mortality following fracture in men; and identification of critical signalling pathways between bone and the brain. As part of a strategic development in 2011 to increase capacity and expand research in bone and joint disorders, the Institute recruited Professors Peter Croucher and Mike Rogers, with interests in physiological and pathological regulation of the skeleton, tumours that grow in or metastasise to bone, osteoclast biology and the molecular therapeutics of bone disease. The laboratories benefit from the latest ex vivo and in vivo high-resolution micro-CT instrumentation,
histomorphometry equipment and contemporary optical imaging and two-photon, intra-vital microscopy, along with comprehensive facilities for all aspects of molecular and cellular biology.

**Division of Osteoporosis and Bone Biology**
http://www.garvan.org.au

**Professor Peter Croucher**

**Professor John Mattick**

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**Information about Wellcome Trust Sanger Institute, Hinxton, UK**

*a) Sample collection and logistics*
Research technician

**Mouse Genetics Program**
The Wellcome Trust Sanger Institute Mouse Genetics Project, led by Dr. David Adams, aims to advance understanding of mammalian gene function by extending functional annotation of the mammalian genome via large-scale production and characterisation of knockout mouse lines. Phenotype data are imported into a bespoke mouse-tracking database where detailed quality control strategies are applied. Once quality assured, data from the MGP and all other IMPC contributors are exported to a centralised web-based interface; a one-stop-shop freely available to the scientific community for data mining, hypothesis generation, and disease model identification and utilisation (https://www.mousephenotype.org). Structural and functional analyses performed by the Origins of Bone and Cartilage Disease program will generate both imaging and numerical data that will be freely available on the IMPC website. The program will also establish a web resource to facilitate dissemination of information to the bone and cartilage research community and communicate with parallel research programs focused on other physiological systems.

**Systems Biology of Bone**
The Systems Biology of Bone team, led by Dr Vijay Yadav uses the mouse as a model organism to identify genetic determinants of bone mass and investigates the gene networks involved. The goal is to develop new mouse models for bone diseases that will facilitate identification of key signalling pathways to allow a systematic analysis of the process of bone remodelling. These studies will further understanding of bone biology and ultimately identify novel therapeutic targets for skeletal disease.

**Wellcome Trust Sanger Institute Mouse Genetics Project**
http://www.sanger.ac.uk/resources/mouse/

**Dr. Vijay Yadav**
http://www.sanger.ac.uk/research/faculty/vyadav/