Abstract of ECTS Exchange-Grant award, 2003 **2007-07-06**

Linkage Disequilibrium Mapping Of Loci Syntenic To Mouse BMD QTL's By DNA Pooling

Host Laboratory: Professor Robert J Shmookler Reis, University of Arkansas for Medical Sciences, Little Rock, USA.

Aim of Exchange: To gain experience in techniques for genetic association mapping of regions of conserved synteny between the human and mouse genomes in order to exploit the innovative technique of DNA pooling and linkage disequilibrium mapping, enabling the identification of novel genes regulating bone mineral density (BMD).

Background: The regulation of bone mass and other determinants of osteoporotic fracture risk is determined by a complex interaction of genetic and environmental factors. Recently, attention has turned to the identification of BMD quantitative trait loci (QTL) by genetic mapping studies in mice as a means to dissect out the genetic contribution to this complex disease. Previous studies have identified QTLs showing linkage to BMD which are conserved between strains, implying that the alleles responsible have also been conserved throughout evolution. This indicates that mouse QTL's for BMD are an attractive area in which to look for QTL's that regulate BMD in man.

Professor Robert J S Reis previously identified in mice, QTL's for post-maturity change in spine BMD using interval mapping in an interstrain-cross F2 population of SAMP6 with AKR/J. In particular, significant peaks on chromosome X and chromosome 11 were identified. The next stage of this study will focus on fine mapping the QTL and identification of novel BMD regulatory genes.

Experimental approach: Linkage Disequilibrium (LD) mapping is based on the assumption that alleles which confer susceptibility to a disease will be over-represented in patients with that disease as compared with controls because of LD between alleles at marker loci and the putative disease locus. After identification of syntenic loci in humans we will identify SNP markers (at ~50Kb intervals) across candidate loci and determine differences in allele frequencies in DNA pools derived from individuals in the top 16% and bottom 16% of the BMD distribution. Further investigation of informative SNPs will be ?????

Training and Techniques: (i) Advanced training in navigating NCBI mouse and human genome resource databases (ii) Candidate SNP selection across candidate regions and advanced primer design for downstream techniques (iii) Single base extension SNP assay (iv) Quantitative analysis of target SNP allele ratios in DNA pools.

Publications resulting from this work: Interspecies synteny mapping identifies a quantitative trait locus for bone mineral density on human chromosome Xp22. Parsons C[#], Mroczkowski H[#], McGuigan F[#], Albagha O, Manolagas S, Reid D, Ralston S, Shmookler Reis R Human Molecular Genetics 2005 14 (21) 3141-3148 [#]Joint first author