Executive summary

Osteoarthritis (OA) is the most common cause of disability in Europe and currently there are no drugs that can cure, reverse or halt the disease. TREAT-OA was a large-scale trans-disciplinary project using extensive collections of OA phenotyped subjects with available genome-wide association scan data and *in vitro* and *in vivo* state of the art technologies to further our understanding of OA. The study was highly integrated and included epidemiologic, biochemical and genetic approaches. TREAT-OA translated genetic findings into drug discovery and diagnostic development. The project was subdivided into 9 scientific and technological workpackages, a management WP and a dissemination WP.

WP 1: Novel Genes involved in OA risk and progression Genomewide scans (GWAS) for hip, hand, and knee OA were performed. Focused analysis on candidate pathways was also performed.

WP 2: Generalisability of genes and biochemical markers. Candidate variants were tested and several large scale meta-analyses showing the generalisability of candidate genes (e.g. *TRPV1, SMAD3, GDF-5*) and the lack of it from GWAS (*BTLN2*) or previous candidate gene reports (Il6, IL1). Meta-analyses of the top knee OA signals were also performed in Asian populations, showing the signal to be specific to European populations. A GWAS meta-analysis for OA biochemical markers CTX-II and COMP was carried out.

WP 3: Meta-analysis and Bioinformatics: A standardized meta-analysis protocol was developed. The first large scale meta-analyses for knee OA and hip OA were generated by TREAT-OA and have published/ accepted for publication in the highest ranking rheumatology journal.

WP 4: Biochemical markers Measurements of CTX-II & COMP levels were performed on 3500 subjects from the TREAT-OA study cohorts part of TREAT-OA. The novel markers, S-CIIM was also measured in all cohorts. Two novel markers have been measured in the cohort with MRI and synovitis data, namely, S-C3M & S-CRPM. The diagnostic value of these markers was assessed in WP8.

WP 5: Functional genetics using in vitro models Systematic expression screens *in vitro* primary cells and tissues of relevance to the joint and joint associated tissues such as chondrocytes/cartilage, osteoblasts/bone, meniscal cells, and mesenchymal stem cells/synovium were carried out for all genes of interest to facilitate the investigation of their mode of action on disease aetiology.

WP 6: Functional genomics using zebrafish and chick disease models of OA Developed zebrafish and chick gain of function and loss of function models to study the mechanisms of action of discovered genes. The role of *GPR22* and *PRKAR2B* in early development was identified.

WP 7: Functional genomics using mouse models of OA A systematic screen of the large-scale N-ethylnitrosourea (ENU) mutagenesis in mouse was performed. The roles of selected genes identified from human genetic studies were investigated using murine OA postnatal models. Mutations were found in all of the genes studied. ENU-induced polymorphism in the 5' UTR/promoter of *Gdf5* results in increased Gdf5 expression $Gdf5^{bp/+}$ mice show increased incidence and severity of OA.

WP 8: Translation into diagnostics the diagnostic value of genetic variants and biomarkers involved in risk in OA in severity and progression of OA was assessed using ROC analysis. The paper reporting the diagnostic value for predicting incidence of knee OA is in press. Sequencing projects were completed and the role of functional variants in the genes of interest has been described.

WP 9: Drug Target Screening. A reporter based BMP assay was successfully optimised for compatibility with high throughput screening (HTS). A pilot screen was performed with a chemically diverse test set of 1000 compounds. The estimated hit rate is around 0.5-1%. The second HT assay focused on the Wnt pathway, the estimated hit rate was somewhat lower 0.1-0.5%, but still sufficient to end up with a reasonable number of high quality hits. The effect of pharmacological inhibition of DOT1L was tested on human primary chondrocytes, but no effect on ECM synthesis or chondrocyte metabolism was observed.

WP11: Dissemination. Having generated over 55 peer-reviewed high quality scientific publications, and several more in preparation, TREAT-OA has also contributed to lectures and presentations and organized two summer schools (Oxford 2010 and 2011), a symposium on the molecular pathogenesis of OA in London in 2010 and a workshop on phenotyping for OA studies in Mallorca in 2010, a symposium on the role of OMICs studies in OA in London 2012 and a final conference in Mallorca in 2012. The project website has been running since 2008 and continues to be updated. www.treatoa.eu