In order to understand disease and disease susceptibility and to be able to interpret personal genomic information, a systematic understanding of the functional elements in a genome and the effects of genetic variation on these elements is required. The goal of EURATRANS is to enable comparative approaches that will allow investigators to understand physiological function based on conserved genetic pathways among rat models and humans in health and disease. The rat is a pivotal resource for these studies as it has been studied across the biomedical sciences and has been used for research into a broad array of human conditions

The primary motivation of this project is to leverage the deep biological history of the rat towards an in depth understanding of the pathogenesis of common human disease of high prevalence in the EU and worldwide.
Our project capitalizes on the resources and technologies developed by the EU FP6 Euratools consortium and our U.S. and Japanese partners and will apply those advances, coupled with further innovation across a spectrum of complimentary high throughput technologies, to the study of disease mechanism. Rather than focusing on individual genetic factors independently, we will study disease mechanisms at the level of gene networks in order to identify the pathways and networks that prominently influence common complex disorders. This provides a more complete mechanistic understanding rather than a snapshot view on individual factors contributing to disease. We undertake a multilevel approach to identify the major regulatory pathways in selected rat models of cardiovascular/metabolic, inflammatory, and behavioural phenotypes and translate our findings to progress the understanding of common human diseases.

Enabling technologies are overarching priorities of the programme which will focus on the application of novel technologies and the development of novel strategies for a large-scale multi-disciplinary functional genomics programme in the rat. Complementary technologies includes: 1) Next-generation sequencing technology and analysis of the generated data, 2) transcriptome analysis, 3) genomic variation analysis (SNP and CNV), 4) methylation-sequencing & ChIP-seq, 5) quantitative proteomics, 6) metabonomics, 7) advanced databases, 8) building regulatory networks, 9) germline manipulation of the rat genome and rat ES cell technology, 10) pathophysiology of cardiovascular/metabolic, inflammatory, and psychiatric/ behavioural phenotypes, 11) translation to humans and diagnosis & therapy, 12) consistent data processing and integration.
Biological concepts: We will use enabling technologies to generate large-scale multilevel datasets in recombinant inbred (RI) rat lines in which multiple phenotypes can be accumulated, combined with high resolution mapping in heterogeneous stock (HS) and congenic lines where appropriate. We will extend and complement the databases of gene expression and physiological phenotypes that were generated in the Euratools programme by generating transcriptome inventories, and develop new metabonomic, proteomic, and epigenomic datasets in RI and selected HS/congenic animals. Furthermore, we will map the genetic determinants of

these new phenotypes to the genome using existing high-resolution maps based on Euratools-generated SNP and structural variation databases, permitting identification of the cis and trans-regulatory control loci of these phenotypes. Using these multi-modality QTL datasets we will identify the most important pathways leading to clinically relevant phenotypes.

To maximise the general application of our multilevel network approaches we will focus our efforts on three disease research areas in which the rat model has traditionally played a major role and in which rat biology and physiology facilitates translation to humans. Those are: i) cardiovascular/metabolic disease, ii) inflammatory disorders, and iii) psychiatric disorders. We will prioritize key components in disease-related networks for functional validation by loss and gain of gene function in vivo and in vitro. To this end, we will utilize large existing and emerging resources to validate our findings: ENU-induced mutant archives, transgenesis, germline-manipulation of the rat genome by transposon-mediated mutagenesis, shRNA-mediated gene knockdown and nuclear-zinc-finger approaches and novel rat ES-cell technology.