

Meeting report  
**Of rats and men**  
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A report on the third biannual 'Rat Genomics and Models' meeting, Cold Spring Harbor, USA, 11-14 December 2003.

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The rat has been studied as a model for human physiology and disease for many years. The advent of modern molecular genetics in the 1980s subsequently made the rat one of the pre-eminent models for the study of the genetics of complex human disease. The series of Cold Spring Harbor meetings on rat genomics was initiated in 1999 to bring rat researchers using genetic and genomic techniques together with the scientists developing genomic resources (data and tools), along with experts from other emerging fields. It was serendipitous that the most recent meeting fell at the end of 2003, a spectacular year that has seen the release of the rat genome sequence, the development of knockout technologies and many other developments in rat genomics that were presented at the meeting.

### **The rat genome and comparative genomics**

The highlight of the meeting was the presentation by George Weinstock (Baylor College of Medicine, Houston, USA) describing the sequencing of the genome of *Rattus norvegicus* through the combined efforts of the Rat Genome Sequencing Consortium. Although it has been sequenced to only a draft level, Weinstock reported that over 90% of the genome has been sampled, with over 36 million sequence reads being used to assemble the latest build (version 3.1). The assembly shows that the rat genome is around 2.7 gigabases (Gb) long, intermediate between the mouse (2.5 Gb) and human (3 Gb). Weinstock summarized the extensive comparative analyses undertaken by numerous groups since the genome was released; these include measuring the extent of shared sequence similarity between the rat, mouse and human genomes, analyzing segmental duplications and the genes found within duplicated regions, and the conservation of genes between the rat, mouse and human. The

primary sequencing paper and the results of the initial studies will be published early in 2004.

Shaying Zhao (The Institute for Genomic Research, Rockville, USA) discussed the large-scale genome rearrangements that her group has uncovered between the rat, mouse and human genomes. The rat has more intrachromosomal duplications than the human genome, whereas the mouse has more interchromosomal duplications. When trying to reconstruct ancestral mammalian genomes and identifying the rearrangement paths between species, it is important to remember that rearrangements have kept the balance between beneficial variation and deleterious genome instability during evolution. At a higher resolution, Leo Goodstadt (University of Oxford, UK) examined specific genes from rat and mouse in order to determine the selective pressures exerted on them in the different genomes. Goodstadt also described an interesting study of gene duplications between rat and mouse, which may provide clues to the origins of the physiological and behavioral differences between the two rodents.

Although comparative-genomics studies concentrate on genes and coding regions, there has been much research directed at so-called noncoding conserved sequences, believed to represent regulatory regions. Eric Green (National Institutes of Health, Bethesda, USA) presented his group's work sequencing the region around the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) in multiple organisms, which illustrated the power of multiple genome alignments to identify such conserved elements. Coding regions have a known structure that enables their detection so that one can then measure conservation between species. Noncoding regions, on the other hand, typically have no known structure, and so the reverse process is used to identify them: if an otherwise unknown sequence motif is conserved across multiple organisms, it is likely to be serving some role in those organisms. This approach allows the structure of the noncoding conserved sequence to be defined by the region of conservation.

Following on from Green's work, Ross Hardison (Penn State University, University Park, USA) and his colleagues showed that rat, mouse and human share a core of approximately one third of the genome, including the majority of coding regions but also a significant amount of noncoding DNA under neutral selection, potentially containing regulatory regions. Marcello Nobrega (Lawrence Berkeley National Laboratory, Berkeley, USA) elegantly illustrated the concept of noncoding conservation using alignments of a variety of vertebrate genomes - from human to *Fugu* - to detect conserved elements in 'gene deserts', gene-poor regions longer than 500 kb. Testing these elements in transgenic mice showed that the majority were able to direct expression of a reporter in a tissue-specific manner, further highlighting that there is a great deal more to the genome than the coding elements on which we traditionally concentrate.

### Rat models of human disease

One of the primary rationales for using the rat as a model system is the availability of inbred strains that recapitulate many aspects of human complex diseases. Traditional genetic mapping techniques have crossed strains displaying the disease trait and the normal trait and identified genomic regions associated with the disease trait using a variety of statistical techniques correlating genotype and phenotype. These genomic regions - also known as quantitative trait loci - are then further examined for the genes responsible for the trait of interest. Four sessions of the meeting were devoted to the presentation of results using the rat as a model in areas such as neuroscience, renal disease, cancer, diabetes, lipid metabolism, cardiovascular disease, arthritis and immunity. The work described by Bina Joe (Medical College of Ohio, Toledo, USA) and her colleagues illustrated the wide variety of techniques now being used in these kinds of positional-cloning experiments. Their original work identified 16 genomic regions related to blood pressure. One region of rat chromosome 1 was found to be associated with blood-pressure regulation by a number of other rat studies, and comparative analysis showed blood-pressure relationships in the syntenic regions in humans and mice. Expression profiling was then used to survey genes in the region, leading to the identification of a single candidate gene, which is now being further examined in Joe's laboratory. The use of multiple lines of evidence - rat genetics, comparative data and expression analysis - is becoming ever more prevalent as researchers endeavor to identify a candidate gene for traits of interest.

As more and more data connecting diseases to genes become available, manipulating genes *in vivo* is an obvious next step. Traditionally this has been a technical challenge in the rat, but the ethylnitrosourea (ENU) mutagenesis protocols described by Michael Gould (University of Wisconsin, Madison, USA) and Edwin Cuppen (Netherlands Institute for Developmental Biology, Utrecht, The Netherlands) illustrated powerful knockout technologies that are now viable in the

rat. Techniques like these, along with progress in rat embryonic stem-cell manipulation and the potential power of RNA interference, are set to provide researchers with the tools to take these next steps. The focus of this conference was the release of the rat genome sequence and the many ways in which this new dataset can be used. From the enthusiasm of the community and the quality of the research presented, one can expect great things from the rat in the coming years.