

Lecture series: "Model Organisms and Human Genetic Disease"

Many experiments cannot be performed in humans and must be done in model organisms. Even without experiments, the knowledge and data in other organisms are relevant for the understanding of human disease. The lecture series will have its own home page at <http://www.stats.ox.ac.uk/~hein/ModelOrganisms/> closer to the term. If the individual lecturers agree, their slides will be made available at this www-site before the lecture. This lecture series is inspired by the success of previous lecture series – "The Human Genome" – "Beyond the Human Genome" – "Bioinformatics, Systems Biology and the Omics", "All about Drosophila" and is a natural follow up to these. The lecture series will be in Michaelmas Term 2008 and take place 2-4 pm Tuesdays in Seminar Room, Oxford Centre for Gene Function 3rd floor, Oxford. Each lecture is 90 minutes. If you plan to attend the lectures, please email Maddy at mitchell@stats.ox.ac.uk. The lecture series is supported by the John Fell Fund.

14/10 Yeast as a Model Organism Kim Nasmyth (Oxford)

Yeast is one of the 5-10 most studied organism in the biosciences and has contributed uniquely to the understanding of eukaryotic biology. Besides basic phenomena like the cell cycle, yeast has been used as model for a series of biological networks (metabolic, signal transduction, protein interactions, regulatory networks) and motors. Several of these have helped interpret genetic disease in humans. After a general survey, I will present some of the key topics coming from my own lab.

21/10 MOUSE GENETICS: DETERMINING GENE FUNCTION AND IDENTIFYING DISEASE MODELS Steve D.M. Brown MRC, Harwell, Oxford

With the completion of the mouse genome sequence, a key goal for functional genomics is the creation of a series of mutant alleles for every mammalian gene. The most versatile organism to study mammalian gene function is the mouse as there is an extensive toolkit for modifying the genome and specific genes encompassing gene-driven and phenotype-driven approaches. For example, as part of an International Mouse Mutagenesis Consortium, programmes are underway in both Europe (EUCOMM, European Conditional Mouse Mutagenesis Programme) and North America (KOMP, the US Knock-Out Mouse Project, and NORCOMM, the Canadian Conditional Mouse Mutagenesis Project) to generate conditional mutants for all mouse genes, a vital resource in exploring gene function in any body system. An even greater challenge will be the determination of phenotypic outcomes for each mutation and the identification of disease models. A vital element of this endeavour will be to develop standardised phenotyping platforms that allow for reproducibility of test outcome over both time and place. The availability of standardised screens and associated informatics structures and tools will be a vital underpinning for a systematic and rational functional annotation of the mouse genome. Representing phenotypic information in a standardised way presents further challenges. Development of phenotype ontological structures that take into account assay protocol, genetic background and environment will be crucial. In addition, the mining of phenotypic characters for correlations indicative of underlying processes will require the availability of databases of raw phenotype data. Large-scale programmes in mutagenesis and phenotyping will be critical to the wider identification and development of pre-clinical disease models.

BROWN, S.D.M. et al. (2005) EMPRESS: standardised phenotype screens for functional annotation of the mouse genome. *Nature Genetics* 37: 1155.

BROWN, S.D.M., HANCOCK, J.M. AND GATES, H. (2006) Understanding mammalian genetic systems: the challenge of phenotyping in the mouse. *PLoS Genetics* 2: e118.

ROSENTHAL, N. AND BROWN, S.D.M. (2007) The mouse ascending: perspectives for human disease models. *Nature Cell Biol.* 9: 993-999.

28/10 C. elegans as a Model Organism Jonathan Hodgkin (Oxford)

The small nematode worm *Caenorhabditis elegans* provides a powerful system for the examination of many fundamental problems in animal biology. Its usefulness has been amply demonstrated by major discoveries made using the worm, in areas such as developmental biology, neurobiology, apoptosis, ageing, RNA interference and microRNAs. Its experimental advantages include rapid growth (3 day generation time), ease of culture, facile forward and reverse genetics, compact genome, simple anatomy and completely described cellular development and neuronanatomy. Properties and advantages of the system will be discussed, along with applications for the study of human disease.

04/11 The pig as a model organism Heiner Niemann, Neustadt, Germany

The domesticated pig shares several similarities with human, in particular as it relates to the size of organs and various aspects of anatomy and physiology. Pigs and also other farm animals have been proposed as models to study human diseases, including non-insulin dependent diabetes, cancer and neurodegenerative disorders, because these require longer observation periods than those possible in mice. An important pig model has already been developed for the rare human eye disease Retinitis pigmentosa. The development of somatic cloning technology and the merger with techniques of targeted genetic modification and conditional gene expression will enhance the possibilities for creating useful models for human diseases in pigs. Numerous models for various diseases may become possible, for example for studying Alzheimer disease, arteriosclerosis, arthritis, and others. An important aspect of large animal models for human diseases is the finding that somatic cloning *per se* does not result in shortening of telomeres and thus does not reduce the natural lifespan of cloned animals. The pig has also evolved as the major target species for producing xenografts to overcome the growing gap between demand and availability of appropriate human organs. The porcine genome has not yet been completely sequenced, it is expected that the first draft with the complete sequence will be available within the near future. Detailed information on the porcine genome together with emerging transgenic technologies, such as siRNA, or conditional knock outs, etc. will enhance our possibilities to create useful pig models. A current caveat is the lack of true embryonic stem cells. However, the recent availability of iPS (induced pluripotent stem cells) may overcome this bottleneck and will enhance the creation of useful porcine models.

11/11 Do we still need models of human disease? Colin Blakemore (UK)

The logic is simple. Ethical, scientific and legal arguments justify the use of procedures on other organisms in order to understand both normal and abnormal functions, and to improve the quality and duration of life of people (and other animals). But such approaches make sense only to the extent that the processes under investigation are tightly conserved across species (as a result of common genetic or epigenetic mechanisms). Non-human models have been spectacularly successful in revealing fundamental mechanisms - from the development of the eye to the origin of biological clocks - and in illuminating the basis of familial patterns of disease. But in many areas of bioscience, non-human models have been either insufficiently sophisticated (e.g. polygenic disorders; stroke) or perhaps inherently inappropriate (e.g. language; psychosis; cognition). Against this background it is important to remember that the best models of human function and human disease are normal and diseased humans. The advance of ethically acceptable experimental approaches for the study of human function, closely integrated with the parallel development of more sophisticated non-human models might offer a way forward. A crucial step in such studies of 'integrated models' is the recognition of appropriate (not necessarily identical) phenotypes to study in each model species.

18/11 The Mouse as a Model Organism II Jonathan Flint (Oxford)

"Behaviour genetics in the mouse is at a turning point. In the next few years resources will become available to test the behavioural function of any gene in the genome, placing it within genetic, transcript and protein networks. Interpreting the new data will require a modification of the causal model in which genes are arranged in linear pathways. Instead, a systems biology approach will be necessary".

25/11 Using Drosophila to Solve Explicit Problems in Human Genetics Ethan Bier, UCSD, CA, USA

Drosophila is a pioneer model organism which has played a central role in defining important biological concepts such as establishing the linear arrangement of genes on independently segregating chromosomes during meiosis, the discovery of heritable induced mutations by X-rays and chemical mutagens and chromosomal rearrangements, the first identification of behavioural mutants, and the elucidation of gene regulatory networks controlling cell-cell communication and development of the body plan and organ systems. The genetic control of all of these processes has been remarkably conserved during the course of evolution. In addition, an important revelation resulting from genome sequencing projects is that many of the genes causing genetic disease in humans have highly conserved orthologues in *Drosophila*. Based on this firm groundwork, rapid progress has been made in the past decade in using *Drosophila* to understand the mechanisms by which mutations in human genes cause a broad range of diseases including developmental disorders, cancer, neurological diseases, metabolic disorders, as well as analyzing how pathogens interact with target proteins in multicellular hosts.

02/12 Arabidopsis (and other plants) impact on human health Alan Jones, UNC, NC, USA

Over the last three centuries, fundamental discoveries made first in plants have turned out to be crucial in our understanding of human biology: cells, nuclei, genes, molecular chaperones, viruses, transposable elements, programmed cell death, and gaseous hormones. In recent decades, focus on *Arabidopsis thaliana*, the reference species for plant biology and a key model system for all of biology, enabled great impact on human health research. I will highlight examples, where research using Arabidopsis was informative for the identification of a prototype protein or domain involved in a human disease, human development, or other important aspects of human biology. These examples do not include the enormous impact that Arabidopsis and plant research has had toward understanding plant biology in general, improving food security, and alleviating malnutrition, major threats to human health and the basis of 50% of human disease worldwide. Plants now serve as the vehicles of edible vaccines to serve citizens of developing nations. Recently, plant-based bioreactors provide idiotypic chemo-therapeutics.