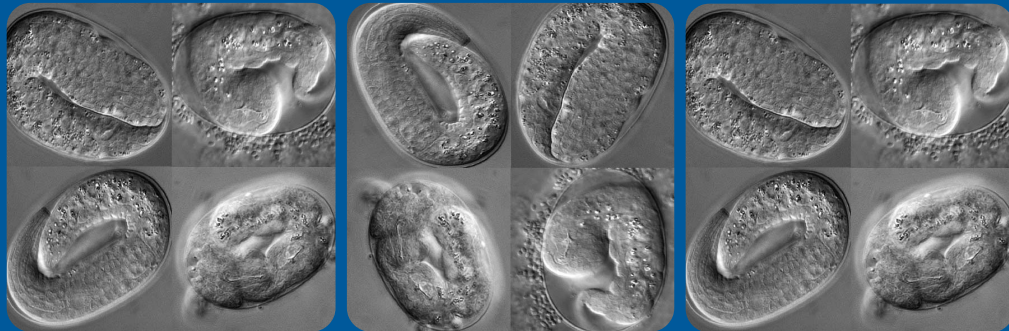


The
Royal Society
of Edinburgh



Beyond the Human Genome: Deciphering Biology and Disease



Report of a Conference
organised by
The Royal Society of Edinburgh and
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Thursday 27 & Friday 28 April 2006

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INTRODUCTION

In his book '*What Mad Pursuit*', Francis Crick says '...for at least several billion years...the double helix has been there, and active, and yet we are the first creatures on Earth to become aware of its existence.' Fifty years after becoming aware of its existence, we have determined its sequence, thereby opening a completely new chapter in biomedical research. The goal now is to understand how the DNA sequence programmes the complex functions that are needed for the development of cells, tissues and organisms. During this meeting 17 internationally-renowned scientists spoke about recent progress and future directions in the post-genomic era.

Key messages

- The way the genome sequence is modified and packaged has a direct effect on gene function.
- Activation of gene expression involves complex and dynamic interactions between DNA and proteins.
- Changes in gene dosage and gene expression levels are emerging as important disease mechanisms.
- Repeated sequences, often dismissed as junk DNA, have important consequences for genome stability and gene function.
- High throughput screens for gene and protein function are identifying new cellular pathways and new targets for cancer therapies.
- Proteins that appear to have a general role in the cell may have additional specific functions which might be relevant to disease.
- Population-based screens are highly effective in teasing out the genetic factors in complex diseases. DNA sequence comparisons between species and populations can give new insights into the way genes evolve.
- Model systems such as yeast and mice have direct relevance to the understanding of human development and disease.

THURSDAY 27 APRIL 2006

Professor Phillip Sharp HonFRSE

*Centre for Cancer Research,
Massachusetts Institute of Technology,
Cambridge, USA*

The Surprising Biology of Short RNAs

Fifty years ago it was discovered that genetic information is conveyed from genomic DNA to protein by an RNA intermediate called messenger RNA (mRNA). Later two other RNAs, transfer RNA and ribosomal RNA, were found to have an important role in protein synthesis. Professor Sharp spoke about an unexpected new regulatory role RNA – as a regulator of gene expression.

Very short RNA molecules called microRNAs (miRNA) can reduce gene expression by a variety of mechanisms and are thought to regulate between 25-50% of all genes in vertebrates. A feature of miRNAs that distinguishes them from other RNAs is that they have a double-stranded hairpin RNA precursor stage. This is processed by enzymes to release the mature miRNA, which is typically just 21-22 bases long.

miRNAs act by binding to complementary sequences in the 3' untranslated region of their target mRNAs. This can lead to mRNA degradation, but the major effect is on protein synthesis (translation). The vast majority of

miRNA/mRNA complexes are associated with the protein synthesising machinery in the cytoplasm, but translation is not completed efficiently. A small proportion of miRNA/mRNA is found in cytoplasmic granules, some of which are sites of mRNA degradation.

As T-lymphocytes develop they pass through a number of distinct precursor cell stages, each of which has its own highly characteristic pattern of miRNAs. Each miRNA reduces the expression of numerous target genes. Therefore the miRNA profile helps create a pattern of gene expression which is specific to each cell type.

Q&A: When asked if miRNA levels had been quantitatively examined in other mature cell types, Professor Sharp said that this had not yet been done, but he predicted that in any cell a certain concentration of miRNAs was needed to affect translation. Professor Bickmore queried whether the widely used approach of looking at mRNA levels to predict protein expression in developing embryos might be misleading. Professor Sharp replied that the role of miRNAs in embryos was unclear, but that caution should always be exercised in predicting protein levels from mRNA levels. Professor Lupski asked if it was possible to use inhibitors to prevent the proteins made from miRNA-targeted mRNAs being degraded. Professor Sharp said that proteasome inhibitors had been tested but had no effect.

SESSION 1: GENOME ORGANISATION

Professor Kim Nasmyth FRS

*Department of Biochemistry,
University of Oxford*

Genome Propagation: the Chemistry of Sister Chromatid Cohesion and its Dissolution at Anaphase

Cell division is a highly complex process. The entire genome must be copied and the two new sets of chromosomes must be organised in such a way that one set ends up in each of the two daughter cells.

Professor Nasmyth's talk focussed on the mechanism that helps ensure that the chromosomes are distributed correctly. When the chromosomes are copied they give rise to a pair of identical sister DNAs. The sisters stay together while they are attached to protein fibres, which eventually pull the sisters to opposite poles of

the cell before it divides. One factor essential for this process is cohesin, a highly conserved multi-subunit protein complex, which forms a large ring structure. Experiments with circular mini-chromosomes in yeast gave evidence that the two sister DNAs are physically trapped inside the cohesin ring.

How does the chromosomal DNA get inside the ring? To test the idea that the interaction between the cohesin subunits is temporarily disrupted, the subunits were modified to lock them together. When the 'hinge' region was locked, cohesin was unable to clamp on to the DNA and the cells died. The current model is that cohesin shackles the sister DNAs together until another protein, separase, opens the ring, allowing the two chromosomes to be pulled apart.

It was recently discovered that cohesin hinge mutations cause a mild form of Cornelia de Lange syndrome in humans. Cohesin is involved in a process common to

every cell, yet highly specific developmental defects occur if the protein is abnormal. Understanding why will shed further light on the function of cohesin.

Q&A: Professor Blackburn asked whether the structure of cohesin gave any clues as to how it might work. Professor Nasmyth said that the hole in the hinge was not big enough for DNA to pass through, so it might work by binding to the DNA and then sliding round it. When asked whether cohesin was a molecular motor, Professor Nasmyth replied that this was unlikely because the energy-releasing ATPase activity of cohesin was extremely low. He thought that ATPase activity might be required only for cohesin to lock on to the DNA. In response to a query from Professor Sharp, Professor Nasmyth said that cohesin was present in the nuclei of all cells at all stages of the cell cycle.

Professor Wendy Bickmore FRSE

*Chromosome and Gene Expression Section,
MRC Human Genetics Unit, Edinburgh*

Mapping the Chromatin Structure of the Mammalian Genome

The nucleus of a typical human cell is just 0.0000005 metres in diameter, yet contains nearly 2 metres of genomic DNA divided between 46 chromosomes. The genome must be packed into a tiny volume, yet organised in such a way that individual genes can be activated at the right time.

Professor Bickmore spoke about new approaches to investigate the structure of chromatin – nuclear DNA complexed with packaging and regulatory proteins. The availability of whole genome sequences has made it possible to study large gene clusters and ultimately to understand how chromatin structure relates to gene function.

Professor Bickmore described techniques to separate ‘open’ and ‘compact’ chromatin. The purified chromatin types could then be used as probes to highlight the corresponding regions of the genome. In general, compact chromatin corresponded to gene-poor genomic regions, while open chromatin correlated with the regions of highest gene density. Open chromatin did not automatically signify gene activity as previously assumed, because some inactive genes are found in open domains; however most of the genes in open chromatin regions are expressed in most cell types. Open regions apparently create an environment in which genes can easily be switched on. Under the microscope these domains appear to be

looped out from the rest of the chromosome, making them accessible to regulatory proteins. The genes in these domains may be clustered together because it is advantageous for them to stay in a region that is favourable for gene expression.

Q&A: Dr. Lahn asked whether different patterns of chromatin organisation were seen in different cell types. Professor Bickmore said that the chromatin around gene clusters that were needed at specific stages of development, such as the Hox genes, opened up when the genes were activated. However, domains containing genes expressed in most tissues were consistently open in different cell types. Professor Lamond asked how chromatin structure correlated with the timing of DNA replication. Professor Bickmore replied that in general open chromatin was copied earlier while closed chromatin was copied later. However, there were exceptions to this which meant that there must be additional mechanisms controlling the precise timing of replication.

Professor Doug Higgs FRS

*Weatherall Institute of Molecular Medicine,
University of Oxford*

Regulating Gene Expression from a Natural Chromosome Locus

Our red blood cells (erythrocytes) are packed with millions of molecules of the oxygen-carrying protein haemoglobin, which is made of alpha-globin and beta-globin subunits. As red blood cells develop they progress through a number of distinct precursor cell states, each of which is more committed to becoming a mature erythrocyte. Only towards the end of their development do the cells switch on the alpha and beta globin genes at high levels.

Professor Higgs described the dynamic processes which prepare the human alpha-globin gene cluster for activation. Although the genes themselves are quite small, hundreds of thousands of base pairs of flanking DNA are required for proper control of their expression. By comparing the sequence of the gene cluster in many different species it is possible to pick out the stretches of DNA that are critical for alpha-globin regulation, because these are virtually identical in the different species examined. These conserved motifs act as recruiting stations for regulatory proteins that are needed to activate the globin genes. Prior to gene activation, changes in chromatin structure cause looping of the DNA which allows the genes to reel in regulatory proteins from the recruiting sites.

A reduction in the level of alpha-globin protein causes the disease alpha-thalassaemia. By studying the genetic defects in alpha-thalassaemia patients it has been possible to identify many of the mechanisms important for normal regulation of the alpha-globin genes. Professor Higgs reported a new alpha-thalassaemia variant, caused by a single base change in the alpha-globin region. This mutation created a DNA sequence that was able to bind the regulatory proteins and divert them away from activating the alpha-globin genes.

Q&A: Professor Blackburn asked whether the creation of new protein binding sites by DNA sequence changes might be an evolutionary mechanism to alter gene expression patterns. Professor Higgs agreed, but he said that it was often difficult to prove that a sequence change had a functional consequence. Professor Sharp queried whether transcription occurred at the sites where the polymerases and regulatory factors were recruited. Professor Higgs said this was difficult to address because of the presence of other genes nearby. Professor Tjian asked if transcription occurred around the mutant alpha-thalassaemia binding site. Professor Higgs confirmed that it did, and that it was in the same direction as the alpha-globin genes.

Professor Neil Brockdorff

*Epigenetics and Development Section,
MRC Clinical Sciences Centre, London*

Epigenetic Regulation in Development

In evolutionary terms, X-inactivation is a very recent phenomenon. Professor Brockdorff's talk addressed the way the genome develops new mechanisms for long-range control of gene expression.

X-inactivation occurs early in the development of female mammalian embryos and results in the shutting down of one of the two X chromosomes. This leaves each female cell with a single dose of X-linked genes, making them equivalent to male cells, which carry a single X. X-inactivation begins when the activity of the Xist gene is increased on one copy of the X, producing large quantities of Xist RNA, which coats that copy of the X and leads to gene silencing by triggering a series of epigenetic changes (heritable alterations that affect gene activity without changing the sequence of the underlying DNA).

Xist can be experimentally inserted into other chromosomes, inducing silencing in the neighbouring regions. However, this process is less efficient than on

the X chromosome. What features of the X ensure stable epigenetic modification? 30% of the DNA on the X chromosome is made of L1 repeats, which are remnants of retrotransposons (parasitic DNA sequences). A novel computer program, designed to scan the mouse and human genomes for L1 sequences, showed that the X chromosome has an unusual L1 distribution. Whereas most chromosomes have very few L1 repeats in gene-rich regions, the X has a very high density. When Xist is transferred to other chromosomes, gene-rich/L1-poor regions block silencing. The X appears to use L1 elements as way-stations to spread the silencing signal.

Inspection of the whole genome sequence revealed that some non-X gene clusters have very high L1 density. In general the L1 density was higher near tissue-specific genes and lower near widely expressed genes. The significance of this is not yet known but it seems that the mammalian genome has adapted junk DNA (in this case L1 sequences) for long-range gene silencing and chromatin organisation.

Q&A: Dr. Lahn asked if Xist RNA left the nucleus. Professor Brockdorff said that Xist RNA immediately coated the adjacent chromosomal DNA and did not leave the nucleus. When asked if the density of L1 repeats was lower in the region of the X chromosome that escapes inactivation, Professor Brockdorff replied that it was. Professor Bickmore asked if it was possible to determine the evolutionary age of L1 elements as a way of investigating whether they had been positively selected in tissue-specific gene clusters or negatively selected in clusters of widely expressed genes. Professor Brockdorff replied that this was feasible but had not yet been done.

SESSION 2: GENOME FUNCTION

Professor Rene Bernards

*Division of Molecular Carcinogenesis,
The Netherlands Cancer Institute, Amsterdam*

Cancer Networks Revealed by RNAi

Cancer occurs when cells undergo genetic changes that allow them to escape from normal growth control. Professor Bernards described new high-throughput techniques for putting cancer genes in pathways. Working out how genes are functionally linked to each other makes it possible to improve the effectiveness of existing treatments and design new ones.

Histone deacetylase (HDAC) inhibitors stop the growth of cancer cells, but little is known about how these drugs work. A large collection (library) of genes was introduced into cancer cells, which were then treated with an HDAC inhibitor. A small number of cells were resistant to the inhibitor because they had taken up the RAR or PRAME genes. Further experiments showed that the HDAC, RAR and PRAME proteins all interact in the retinoic acid signalling pathway. PRAME makes cells resistant to HDAC inhibitors, so these drugs might be relatively ineffective in PRAME-positive tumours. Activators of retinoic acid signalling on the other hand are highly effective at inhibiting cancer cell growth and retinoic acid is now being tested in conjunction with HDAC inhibitors as a new therapy.

Professor Bernards also described the way that small interfering RNAs (siRNAs) can be used to reduce gene activity. The availability of new tagged vector systems to deliver siRNAs to cells made it possible to target every gene in the genome. This approach had successfully linked the functions of genes involved in different stress responses. Synthetic siRNAs designed to target specific genes were helping to identify genes that might lead to the development of the ultimate anti-cancer drug – one that is only toxic in the presence of a second, tumour-specific mutation and therefore has no effect on normal cells.

Q&A: When questioned about the possible role of other PRAME-like proteins in tumours, Professor Bernards said that humans had about 20 PRAME-like genes, all of which appeared to encode proteins that repressed nuclear receptors. However, it was not yet known which PRAME-like protein interacted with which receptor. Professor Sharp asked if the synthetic

siRNAs had been tested to confirm that they suppressed the intended target gene. Professor Bernards said that on average, each pool of four siRNAs contained two that acted specifically on the target gene.

Professor Robert Tjian

*Howard Hughes Medical Institute,
Department of Molecular and Cell Biology,
University of California, Berkeley, USA*

Transcriptional Control Mechanisms and Disease

Professor Tjian's talk focussed on the way that protein complexes interpret DNA sequences to control gene activity. Genes have control regions, called promoters, containing short DNA motifs that are recognised by regulatory proteins. These proteins bind to other proteins, forming large multi-subunit assemblies called co-activator complexes, which together determine the level of transcription. Expression of a human gene requires around 100 different proteins.

Some co-activator complexes have been frozen and viewed by electron microscopy, revealing that they are able to adopt different shapes depending on which other protein co-factors are present. This suggests that there are dynamic interactions between the complexes that can be modified by other regulatory signals.

Work in the fruitfly showed that different genes are dependent on different combinations of activator proteins. For example the metallothionien gene relies on the TFIID and CRSP/MED co-activator complexes. When the levels of the individual subunits were reduced one by one it became clear that are interactions between the two complexes that determine the exact level of expression from the gene.

Huntington's Disease is a severe neurodegenerative disorder caused by a mutation in the HTT gene. Part of the gene becomes abnormally expanded, creating a protein with a long stretch of glutamine amino acids. Little was known about how this mutation leads to degeneration of brain cells, but recently it was found that the extended glutamine region of the mutant protein binds to a number of different regulatory proteins, impairing their function. This could cause

uncoordinated gene expression which might eventually lead to cell death.

Q&A: Professor Bickmore asked about the steps involved in activating the metallothionein gene. Professor Tjian said that when metal ions were present they induced a conformational change in transcription factors already bound to the gene's promoter, allowing them to recruit co-factor complexes and initiate transcription. Professor Lupski asked whether a synthetic poly-glutamine peptide had the same effect as the mutant HTT protein. Professor Tjian replied that poly-glutamine peptides alone had very little effect and that other amino acids around the expanded glutamine region were necessary for protein binding.

Professor Angus Lamond FRSE

*Division of Gene Regulation and Expression,
Wellcome Trust Biocentre, University of Dundee*

New Approaches to Studying Protein Dynamics in the Cell Nucleus

Professor Lamond spoke about the nucleolus, a highly specialised area of the nucleus that is responsible for assembling the subunits of ribosomes, the cell's protein-making machines. Using advanced mass spectrometry techniques, 700 nucleolar proteins have been identified to date. What methods can be used to investigate how these proteins behave as the function of the nucleolus changes during the cell cycle?

One approach is to add fluorescent tags to proteins, allowing them to be viewed in living cells under the microscope. This shows that some proteins are permanently located in the nucleolus, some are exported to other cell compartments and some shuttle rapidly in and out. In a variant of this method, the cell is photo-bleached so that the tagged protein becomes invisible. Recovery of the fluorescent signal occurs only if new protein is made, so this method can be used to see how rapidly a protein is synthesised.

Another extremely powerful technique is SILAC (stable isotope labelling of amino acids in cell culture), which allows the levels of hundreds of proteins to be investigated at once. After the proteins are labelled, cells can be harvested at different time-points and changes in multiple protein levels can be deduced by mass spectrometry.

These methods showed that ribosomal proteins are made and degraded extremely quickly, raising the possibility that their turnover is part of a balancing mechanism that helps determine the level of mature

ribosomes in the cell. Professor Lamond stressed that although these new techniques had been used to study the dynamics of nucleolar proteins, they were equally applicable to other regions of the cell.

Q&A: When asked by Professor Blackburn for more information about p68, one of the proteins that shuttles in and out of the nucleolus, Professor Lamond said that p68 is a component of the splicing complex and is usually associated with nuclear mRNAs. He proposed that if fewer mRNAs were synthesised, p68 was free to move into the nucleolus, thereby signalling that transcription of nuclear genes had decreased. Professor Sharp commented that other proteins involved in mRNA processing could play a similar signalling role and Professor Lamond agreed. Professor Sharp said that colleagues at MIT had shown that mutations in ribosomal protein genes cause tumours in zebrafish. Professor Lamond responded that changes in nuclear and nucleolar organisation had been seen in human tumour biopsies.

Professor Adrian Bird FRS FRSE

*Wellcome Trust Centre for Cell Biology,
University of Edinburgh*

Reading the DNA Methylation Signal

Methylation of cytosine in CpG dinucleotides is the best known and most extensively studied epigenetic modification of the human genome. Methylated CpGs are recognised by a family of methyl-binding proteins (MBPs), which switch off nearby genes by recruiting complexes of repressor proteins.

Professor Bird talked about two MBPs, MBD2 and MeCP2. Since CpG methylation is widespread in the mammalian genome, it might be expected that inactivating these proteins would have a very general effect. In fact, evidence has emerged for specific and unexpected functions of these proteins.

In mice that are genetically prone to intestinal cancer, loss of MBD2 activity greatly reduces tumour frequency. MBD2 is present at high levels in the normal colon, where it switches off a number of digestive enzyme genes. In colon tumours, it seems that MBD2 also switches off genes that are important for normal growth control. When MBD2 is removed, these growth control genes are reactivated, making it harder for tumour cells to grow.

The gene encoding MeCP2 is mutated in Rett Syndrome, a severely debilitating condition that involves regression of mental and motor skills in infant

girls. A mouse model of Rett-Syndrome has been created to explore the hypothesis that the disease is caused by failure of MeCP2-induced gene silencing. Preliminary results show that stress-related genes are slightly up-regulated but the significance of this is not yet known.

Why do MBD1 and MeCP2 have these specific effects? When the binding sites of the different MBPs were studied in more detail it was found that the DNA sequence around the methylated CpG is critical for determining which protein binds where. This helps to explain why different MBPs act on different target genes.

Q&A: Professor David Tollervey asked about the modest increase in mRNA levels from stress-related genes in MeCP2 mutant mice. He wanted to know if

miRNAs were involved in the regulation of these genes, in which case there might be a significant increase in protein levels. Professor Bird said that the role of miRNAs was unknown. Dr. David FitzPatrick asked about Mbd2 mutant mice, which have a maternal nurturing defect. He said that children with Prader-Willi syndrome (PWS) have difficulty bonding with their mothers and he wondered whether the PWS locus was an MBD2 target, in which case it might be misregulated in Mbd2 mutant mice. Dr. Brian Hendrich, a former member of Professor Bird's group, said that there were no differences in PWS gene expression in Mbd2 mutant mice.

FRIDAY 28 APRIL 2006

SESSION 3: FROM GENOME TO BIOLOGY

Professor Elizabeth Blackburn FRS
*Department of Biochemistry and Biophysics,
University of California, San Francisco, USA*

Telomeres – The Means to an End

The tips of eukaryotic chromosomes – the telomeres – are specialized protective structures consisting of short repeated DNA sequences complexed with proteins. Because of the way DNA is copied when cells divide, the extreme ends of telomeres are not replicated. Most normal human cells have a finite lifespan because after many divisions their telomeres eventually dwindle away and the cells die.

Telomerase is a ribonucleoprotein (RNA/protein complex) that stabilises telomere length by adding DNA to the chromosome ends. Cells that need to divide infinitely, such as germ cells and stem cells, have high telomerase activity, while other cells have low activity. Professor Blackburn spoke about new aspects of telomerase biology.

Most human tumour cells have abnormally high levels of telomerase activity, allowing them to keep dividing. Experiments with cultured cancer cells showed that if telomerase RNA is inactivated, cell growth is inhibited

surprisingly quickly and the telomeres are not shortened. Inactivation of telomerase RNA appears to trigger a novel cellular pathway, suggesting that telomerase promotes tumour growth in a way that is independent of telomere maintenance. Although the mechanism of this phenomenon is not yet understood, it opens up the possibility of new anticancer therapies.

The second unexpected discovery is that there appears to be a direct link between chronic psychological stress and telomere length. Long-term care-givers were found to have lower levels of telomerase, and shorter telomere length, than non-care-givers of a similar age. The reasons why stress reduces telomerase activity are not yet known, but this observation helps to explain why long-term stress causes premature ageing. Low telomerase activity was also associated with risk factors for cardiovascular disease, such as smoking.

Q&A: Dr. FitzPatrick asked whether stopping smoking would reverse the decrease in telomerase activity. Professor Blackburn said that a large prospective study was underway to investigate the effects of smoking, stress and other heart disease risk factors on telomerase activity and telomere length. Professor Lupski asked about the life expectancy of mice with mutations in the telomerase gene. Professor Blackburn replied that mice with a single mutant copy of

telomerase seemed normal, but the fact that mice had a short lifespan and long telomeres meant that it was difficult to draw comparisons with humans.

Professor Jeff Boeke

*Department of Molecular Biology and Genetics,
The Johns Hopkins University School of Medicine,
Baltimore, USA*

Recycling Junk

Professor Boeke spoke about the impact of retrotransposons on the yeast and mammalian genomes. Most genomes are littered with transposons – parasitic DNA elements that are capable of jumping to new sites. About 45% of the human genome is composed of transposons, mostly retrotransposons, including both active sequences and their defunct remnants. When retrotransposons move, there is a chance that they will disrupt a functional gene, and so they are potentially an important source of new mutations in the human genome.

In yeast, just 1% of the genome is composed of retrotransposons, called Ty elements. To investigate how a heavy retrotransposon burden affects the genome, ultra-high copy number (UHC) strains were created, containing up to 300 new Ty1 elements. The UHC strains were generally normal, but they showed increased sensitivity to DNA-damaging agents and a greater frequency of chromosomal rearrangements because of recombination events between Ty1 sequences. When individual yeast genes were mutated it was found that genes that help copy and repair DNA but are not essential in normal yeast cells are crucial for genome stability in UHC strains. The UHC cells constantly strain their genome integrity maintenance resources to the limit to maintain their retrotransposon-dense genomes.

Mammalian genomes tolerate a huge number of retrotransposons, the most common of which are L1 elements. Professor Boeke described the creation of an artificial, trackable L1 retrotransposon with greatly improved mobility in mice. This made it possible to see how frequently L1 elements move and where they move to. L1 insertions occurred throughout the genome, with a slight preference for genes, meaning that synthetic L1 elements could potentially be used as a tool to randomly mutate mouse genes and help work out their function.

Q&A: Professor Bradley asked if there was any evidence that the synthetic L1 element was mutagenic in mice. Professor Boeke replied that the original element had not been designed to be mutagenic but

new versions were being developed to carry out this function. Professor Bird pointed out that the synthetic L1 element appeared to have overcome any mechanisms that defended the genome against transposition. By looking for variations in transposition efficiency in different mouse strains, it might be possible to learn more about the factors that affect transposon movement.

Professor Allan Bradley FRS

*The Wellcome Trust Sanger Institute,
University of Cambridge*

Extracting Function from the Mouse Genome

A powerful method for working out the function of a gene is to mutate it in a living animal. This approach has been used extensively in mice but it is laborious and slow. Professor Bradley presented new methods that can be used on a large scale to mutate and analyse the function of all mouse genes.

To create mice with mutations in a specific gene of choice, it is necessary to target that gene by inserting inactivating sequences into it. New vectors have been developed to help make this process more efficient. Now that the mouse genome sequence is complete, computer programs can select the best sequences for targeting a particular gene.

In another approach, large vector libraries have been created that contain tens of thousands of different DNA fragments so that any part of the genome can be targeted. By using different combinations of vectors and performing genetic manipulations once targeting is complete, it is possible to engineer chromosomal rearrangements as well as knocking out individual genes.

Despite these advances, creating mutant mice is still relatively slow. Professor Bradley described the use of cultured embryonic stem (ES) cells for rapid analysis of gene function. Using targeting libraries, it is possible to create populations of ES cells with mutations across the whole genome. The mutant cells can then be exposed to various stresses and stimuli to see how they respond. Cells with unusual responses can be rapidly analysed to identify which gene has been mutated.

Q&A: When asked whether other mutations might arise in ES cells in addition to the desired mutation, Professor Bradley replied that this had not been seen in practice, but in any case five independent ES cell clones were created so there were back-ups for each targeting event. Professor Boeke asked about the

genetic screens in ES cells. He wanted to know what methods were available to analyse the 40% of genes that are not expressed in ES cells. Professor Bradley replied that these genes would be targeted in the conventional way. Professor van Heyningen commented that in humans, diseases are often caused by mutations in one copy of a gene, and therefore it would be worth looking at heterozygous as well as homozygous mutant mice.

Dr. Bruce Lahn

*Department of Human Genetics,
The University of Chicago*

Probing the Genetic Evolution of the Human Brain

The human brain is significantly bigger relative to body size than in any other species. In the last 30-40 million years it has enlarged tenfold, resulting in increased behavioural and cognitive complexity. Dr. Lahn spoke about the genetic changes that might underlie this phenomenon.

Using DNA and protein sequence comparisons between species, the mutation rate of over 200 brain-expressed genes was found to be significantly higher in primates than in rodents. When the genes were split into groups according to their function, the fastest evolving genes were those involved in brain and nervous system development. With the availability of additional genome sequences from other primates it was possible to show that these genes evolved fastest in the evolutionary lineage leading to humans.

Among the fastest evolving genes were MCPH1 and ASPM. This is a striking finding because both are known to cause reduction in brain size when mutated in humans. By examining the pattern of genetic variants (haplotypes) around these genes in the human population, it was possible to show that the current versions of these genes arose relatively recently and became fixed in the population extremely rapidly. MCPH1 and ASPM both show strong evidence of positive selection, which occurs when a genetic change increases an organism's ability to survive. Such a change is more likely to be passed on to the next generation and therefore becomes fixed in the population far more quickly than a neutral change.

This work provides an intriguing link between specific genes and the anatomical and behavioural evolution of modern humans. However studies of this type are necessarily retrospective and Dr. Lahn pointed out that it is important to keep an open mind about the results.

Q&A: Professor Goodfellow asked which genes were the fastest evolving when the whole genome was compared with different species. Dr. Lahn replied that when all genes were compared, brain-expressed genes appeared to show the greatest increase in the rate of change for brain genes is lower than most other genes. However there were other genes showing increased rate of change in primates than rodents that were not predominantly expressed in the brain.

Professor Goodfellow commented that there may be other factors underlying rapid sequence change. When asked whether it was possible to examine genes that control other changes accompanying increased brain size, such as delayed physical and sexual maturity, Dr. Lahn replied that this was difficult because these genes were largely unknown.

SESSION 4: GENOMES AND DISEASE

Professor Kári Stefánsson

DeCode Genetics, Reykjavik, Iceland

Deciphering Complex Disease

DeCode Genetics was founded in Iceland ten years ago. It was the first biopharmaceutical company to embrace the idea that studying large populations is essential for uncovering the genetic factors that contribute to complex diseases. Professor Stefánsson spoke about recent progress made by DeCode.

In diseases with clear inheritance patterns, there is usually a direct link between the mutated gene and

development of the disease. On the other hand, diseases with less obvious inheritance patterns, such as stroke, heart attack and mental illness, result from an interaction between genes and the environment. Although it is difficult to identify the genes involved in complex diseases, it is important to do so because these conditions are common and contribute significantly to the burden of ill-health in developed countries.

By scanning the genomes of many people with and without a disease, it is possible to identify genetic variants that correlate with increased risk of that disease. The availability of huge numbers of volunteers from the Icelandic population and excellent

genealogical records makes it relatively straightforward to sort out the key variants from the many other genetic changes that are naturally present in the genome but have no effect on gene function.

DeCode has succeeded in identifying genetic variants that increase the risk of stroke, schizophrenia, heart attack, diabetes and prostate cancer. These variants usually change the level of gene expression. Some of the results have been duplicated in non-Icelandic populations, but the associated risk may be higher or lower in different racial groups depending on what other genetic variants and environmental factors are present. Ultimately, understanding the function of the genes in which these variants lie could lead to new treatments.

Q&A: When questioned about a variant of the FLAP gene that confers moderately elevated risk of heart attack in Caucasians but greatly elevated risk in African Americans, Professor Stefánsson said that further studies were underway to investigate what might underlie this difference. Following on from this, Dr. Lahn asked if another protective variant of FLAP might be under positive selection. Professor Stefánsson said that the different variants were probably under balancing selection, so that both were maintained in the population. Although the protective variant decreased the risk of heart attack it might increase the risk of other diseases and this was under investigation.

Dr. James Lupski

*Department of Molecular and Human Genetics,
Baylor College of Medicine, Houston, USA*

Molecular Mechanisms for Rearrangements and their Conveyed Phenotypes in Genomic Disorders

Dr. Lupski spoke about the role of genome rearrangements in genetic disease. Most studies of inherited disease tend to focus on searching for DNA sequence changes, usually single base changes, which impair the function of a gene. However large-scale genome rearrangements may be a more frequent cause of genetic disease than previously suspected.

Genome rearrangements occur when part of a chromosome is duplicated, deleted or inverted. Some human disease syndromes are caused by chromosome rearrangements. In recurrent syndromes the chromosome breaks always occur at the same place in different patients, while in non-recurrent syndromes the breakpoints are different in each patient. By examining the DNA sequences at the breakpoints in various syndromes it was shown that different kinds of

repeated sequences in the genome increased the chances of abnormal genetic shuffling. In particular, low copy repeats are hotspots for duplications or deletions in recurrent syndromes. Since repeats are common in the genome, there may be many previously undetected rearrangements, and new techniques are being developed to look for these.

Genome rearrangements can affect genes in many ways: by interrupting them, fusing them, separating them from their regulatory elements, or changing their copy number. If a chromosome segment is deleted, the genome is left with one copy of any gene in that segment; conversely, duplication leaves the genome with three copies of any gene in that segment. Although the genes themselves are normal, they are now present in the wrong dose. It may be that long-term exposure to abnormal levels of gene expression in non-regenerating cells, such as neural cells, is highly damaging over time.

Q&A: Professor van Heyningen and Professor Goodfellow wanted to know if environmental factors made genomic rearrangements more likely and whether it would be possible to prevent them. Professor Lupski said that rearrangements occurred with equal frequency in different parts of the world and appeared to depend only on genome architecture. However, the fact that they changed gene copy number meant that their effects were potentially treatable if a way could be found to normalise gene expression. When asked about the effects of duplication on RNA and protein levels, Professor Lupski responded that in Charcot-Marie-Tooth syndrome there was only a 1.5-fold increase in RNA and protein from the duplicated PMP22 gene, yet this small elevation was enough to cause neuropathy.

Professor Stephen O'Rahilly FRS

*Department of Clinical Biochemistry,
University of Cambridge*

Fat is a Wide Issue

Professor O'Rahilly spoke about recent advances in understanding the genetic basis of obesity. Obesity is on the increase in the UK, particularly amongst children, and is a major cause for concern because it causes medical, psychological, social and economic problems.

The causes of obesity are complex and include individual lifestyle choices (diet, level of exercise) and environmental influences (ready availability of cheap high-energy foods). Almost nothing was known about the role of genetics in obesity until relatively recently,

when studies in laboratory mice identified some of the genes that control energy balance.

Fat-storing adipose cells release a hormone called leptin that triggers complex signalling pathways in the brain and leads to decreased appetite and increased energy expenditure. It is now clear that many obese humans have mutations in genes involved in leptin signalling. For example children with mutations in both leptin genes are constantly hungry and become extremely obese. If they are given leptin injections their appetite and weight decrease rapidly, a dramatic illustration of how behaviour can be controlled by a single protein. Most of these mutations are rare, however, and work is now being done to identify more common genetic variants that have subtler effects on gene function and increase the risk of obesity in conjunction with other factors.

Excessive body fat often causes metabolic problems such as insulin resistance, type 2 diabetes, raised blood pressure and abnormal blood lipid levels. Paradoxically this spectrum is also seen in individuals with a disease that prevents them laying down body fat. It may be that only when the body exceeds its natural capacity to store excess energy as fat that metabolic dysfunction begins, bringing with it chronic health problems.

Q&A: When asked if it was possible to measure the number of fat cells in humans or mice, Professor O’Rahilly said that it was relatively easy to measure the size of the cells but not the number. Professor van Heyningen asked if any of the genes mentioned fitted with the ‘thrifty gene’ hypothesis. This proposes that humans have evolved to build up fat deposits when food is abundant so that they have energy reserves when food is scarce; however with modern high-calorie diets the result is obesity and metabolic dysfunction. Professor O’Rahilly replied that any gene involved in energy storage and release could be considered in terms of the thrifty gene model.

Professor Peter Goodfellow FRS
GlaxoSmithKline plc, Middlesex

The Art of the Soluble

Professor Goodfellow introduced his talk with a quote from the Nobel Prize-winning British immunologist Sir Peter Medawar:

“If politics is the art of the possible, research is surely the art of the soluble. Both are immensely practical-minded affairs.”

Biomedical research has proved itself to be very much

‘the art of the soluble’ over the last century, delivering major advances in health care such as vaccinations, control of infectious diseases, birth control and therapeutic interventions such as AIDS medicines.

However the rate of progress appears to be slowing down, at least as judged by the number of new medicines that are licensed each year. Although the Human Genome Project captured the public imagination with its promise of providing new treatments for human genetic disease, it takes between 15 and 20 years to go from scientific discovery to a prescription medicine. Therefore a major challenge facing biological scientists in the immediate future lies outside the laboratory: how can the tax-paying public be persuaded that the millions of pounds spent on biomedical research continue to be justified?

The way forward is for scientists to keep communicating their creative and imaginative ideas to the public. Professor Goodfellow concluded his talk with another quote from Peter Medawar, who knew the value of conveying the purpose of science to a general audience:

“...scientific research is a passionate undertaking and the promotion of natural knowledge depends above all on...what can be imagined but is not yet known.”

Q&A: Professor Stefánsson expressed the view that one reason for the alarming decline in new medicines was that it was becoming more difficult to fulfil the Food and Drug Administration’s stringent safety requirements. Professor Goodfellow agreed, adding that the slightest adverse effect in clinical trials could stop a drug being licensed. Professor Stefánsson said that risks were accepted in every area of society except the development of new drugs and the reason for this was a lack of proper communication between the pharmaceutical industry and the public. Professor Goodfellow responded that pharmaceutical companies needed to develop a better partnership with the public, but ultimately the responsibility for communication lay with biomedical researchers.

APPENDIX ONE

PROGRAMME

Thursday 27 April 2006

9.00:	Registration / Tea & Coffee	12.05:	Epigenetic Regulation in Development <i>Professor Neil Brockdorff</i> <i>Epigenetics and Development Section,</i> <i>MRC Clinical Sciences Centre, London</i>
9.25:	Caledonian Research Foundation Welcome <i>Professor David Baird CBE FRSE</i> <i>Chairman, The Caledonian Research Foundation</i>	12.30:	Q & A
	Chairman's Welcome <i>Professor Adrian Bird FRS FRSE</i> <i>Wellcome Trust Centre for Cell Biology,</i> <i>University of Edinburgh</i>	12.35:	Lunch
9.35:	The Surprising Biology of Short RNAs <i>Professor Phillip A Sharp Hon FRSE</i> <i>Centre for Cancer Research,</i> <i>Massachusetts Institute of Technology,</i> <i>USA</i>		Session 2: Genome Function Chair <i>Professor David Tollervey FRS FRSE</i> <i>Wellcome Trust Principal Research Fellow,</i> <i>Wellcome Trust Centre for Cell Biology,</i> <i>University of Edinburgh</i>
10.00:	Q & A	13.35:	Cancer Networks Revealed by RNAi <i>Professor Rene Bernards</i> <i>Division of Molecular Carcinogenesis,</i> <i>The Netherlands Cancer Institute,</i> <i>Amsterdam</i>
	Session 1: Genome Organisation Chair <i>Professor Nick Hastie CBE FRS FRSE</i> <i>Director, MRC Human Genetics Unit,</i> <i>Edinburgh</i>	14.00:	Q & A
10.05:	Genome Propagation: the Chemistry of Sister Chromatid Cohesion and its Dissolution at Anaphase <i>Professor Kim Nasmyth FRS</i> <i>Department of Biochemistry,</i> <i>University of Oxford</i>	14.05:	Transcriptional Control Mechanisms and Disease <i>Dr Robert Tjian</i> <i>Howard Hughes Medical Institute,</i> <i>Department of Molecular and Cell</i> <i>Biology, University of California,</i> <i>Berkeley, USA</i>
10.30:	Q & A	14.30:	Q & A
10.35:	Mapping the Chromatin Structures of the Mammalian Genome <i>Professor Wendy Bickmore FRSE</i> <i>Chromosome and Gene Expression</i> <i>Section, MRC Human Genetics Unit,</i> <i>Edinburgh</i>	14.35:	New Approaches to Studying Protein Dynamics in the Cell Nucleus <i>Professor Angus Lamond FRSE</i> <i>Division of Gene Regulation and</i> <i>Expression, Wellcome Trust Biocentre,</i> <i>University of Dundee</i>
11.00:	Q & A	15.00:	Q & A
11.05:	Tea / Coffee Break	15.05:	Tea / Coffee Break
11.35:	Regulating Gene Expression From a Natural Chromosomal Locus <i>Professor Doug Higgs FRS</i> <i>Weatherall Institute of Molecular</i> <i>Medicine, University of Oxford</i>	15.35:	Reading the DNA Methylation Signal <i>Professor Adrian Bird FRS FRSE</i> <i>Wellcome Trust Centre for Cell Biology,</i> <i>University of Edinburgh</i>
12.00:	Q & A	16.00:	Q & A
		16.05:	Closing Remarks
		16.30:	Close

Friday 28 April 2006

		12.00:	Lunch
	Session 3: From Genome to Biology Chair <i>Professor Jean Beggs FRS FRSE</i> <i>Wellcome Trust Centre for Cell Biology,</i> <i>University of Edinburgh</i>	13.00:	Molecular Mechanisms for Rearrangements and their Conveyed Phenotypes in Genomic Disorders <i>Dr James Lupski</i> <i>Department of Molecular and Human Genetics, Baylor College of Medicine,</i> <i>Houston, USA</i>
9.00:	Telomeres: The Means to an End <i>Professor Elizabeth Blackburn FRS</i> <i>Department of Biochemistry and Biophysics, University of California,</i> <i>San Francisco, USA</i>	13.25:	Q & A
9.25:	Q & A	13.30:	Fat is a Wide Issue <i>Professor Stephen O'Rahilly FRS</i> <i>Department of Clinical Biochemistry,</i> <i>University of Cambridge</i>
9.30:	Recycling Junk <i>Professor Jeff Boeke</i> <i>Department of Molecular Biology and Genetics, The Johns Hopkins University</i> <i>School of Medicine, Baltimore, USA</i>	13.55:	Q & A
9.55:	Q & A	14.00:	Progress: The Art of the Soluble <i>Professor Peter Goodfellow FRS</i> <i>GlaxoSmithKline plc, Middlesex</i>
10.00:	Tea / Coffee Break	14.25:	Q & A
10.30:	Extracting Function from the Mouse Genome <i>Professor Allan Bradley FRS</i> <i>The Wellcome Trust Sanger Institute,</i> <i>University of Cambridge</i>	14.30:	Closing Remarks / Conference Summary
10.55:	Q & A	15.00:	Drinks Reception
11.00:	Probing the Genetic Evolution of the Human Brain <i>Dr Bruce Lahn</i> <i>Department of Human Genetics,</i> <i>The University of Chicago, USA</i>	16.00:	Close
11.25:	Q & A		
	Session 4: Genomes and Disease Chair <i>Professor Veronica Van Heyningen FRSE</i> <i>Head, Cell Genetics Section, MRC Human</i> <i>Genetics Unit, Edinburgh</i>		
11.30:	Deciphering Complex Disease <i>Professor Kari Stefansson</i> <i>decode Genetics, Reykjavik, Iceland</i>		
11.55:	Q & A		

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The Caledonian Research Foundation (CRF)

The Caledonian Research Foundation is a Scottish charitable company limited by guarantee and has supported independent research in Scotland since 1990. Originally established in 1977 as a spinout from a scientific research organisation and as a charity, the emphasis of its activities changed in 1990 and its interest now lies mainly in sponsoring and encouraging research in Scotland. The Governors of the Foundation include senior figures active in the Scottish academic and business communities. In seeking to achieve its aim of promoting research of international standard in Scotland, it supports a number of Research Fellowships in the Biomedical Sciences, European Visiting Research Fellowships in the Humanities, Postgraduate Scholarships, an International Conference of the Royal Society of Edinburgh and awards an annual Prize Lectureship.



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