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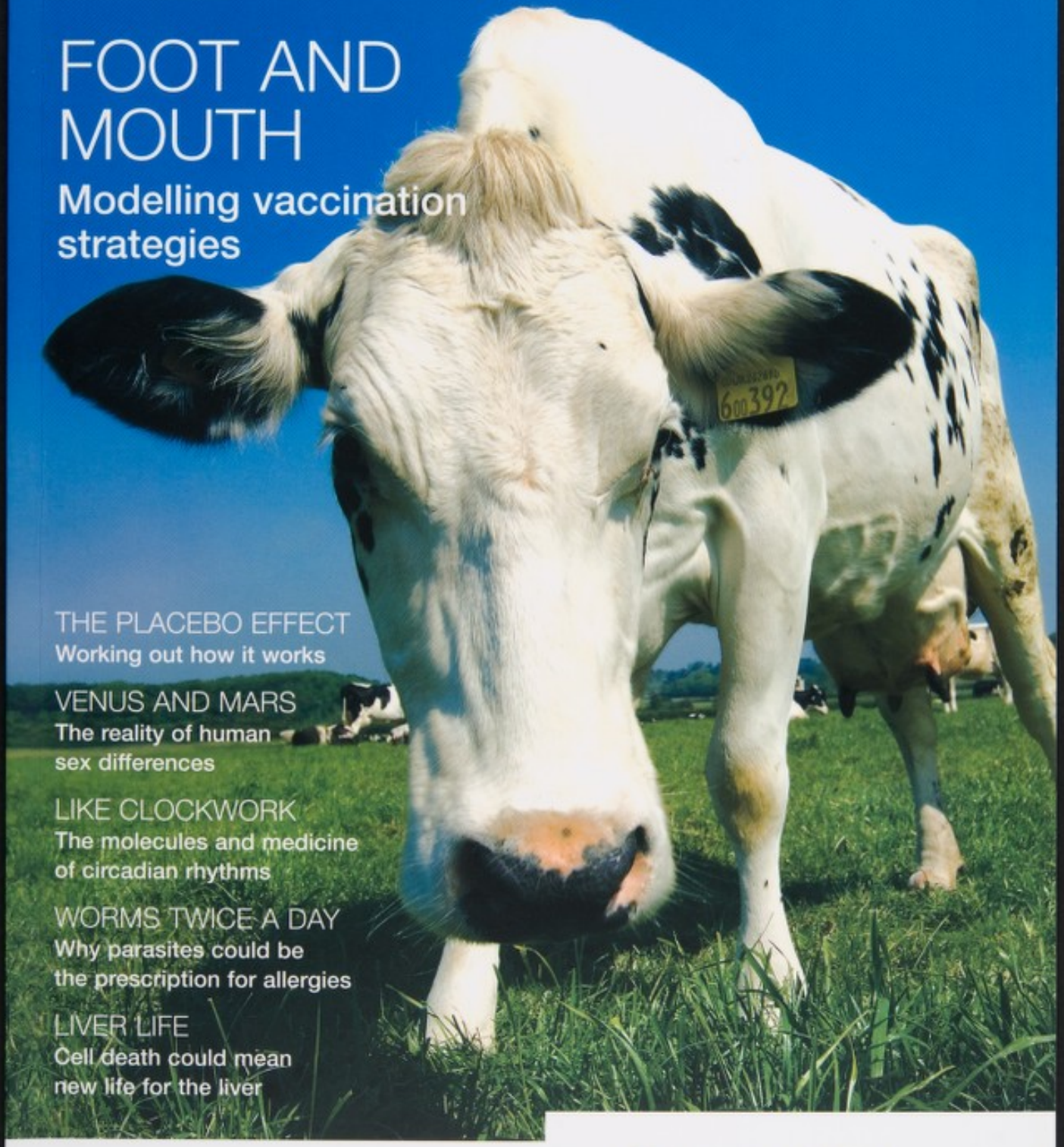
ISSUE 3 **SEPTEMBER 2006**



FOOT AND MOUTH
Modelling vaccination strategies

THE PLACEBO EFFECT
Working out how it works

VENUS AND MARS
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LIKE CLOCKWORK
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WORMS TWICE A DAY
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LIVER LIFE
Cell death could mean new life for the liver

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Forms most wonderful

Charles Darwin spoke of the grandeur of life's diversity, "the endless forms most wonderful". We now know that information coded in DNA is responsible for this diversity. Malcolm Ferguson-Smith, seen here in the Zoological Museum in Cambridge, certainly works with endless forms of animal, managing a genome resource providing access to DNA from scores of obscure animals. He also studies that evolutionary quirk *par excellence*, the duck-billed platypus.

IN A NUTSHELL

- Chromosomes evolve over time, swapping chunks of DNA, fusing or fragmenting.
- Similar genes, or blocks of DNA, may be on different chromosomes in different species.
- DNA probes can highlight particular chromosomal sections in different species.
- By looking at chromosome arrangements in different species, researchers can deduce their evolutionary history.

PAINTING BY NUMBERS:

Mapping the evolutionary history of mammalian genomes

Homo sapiens is connected, through its DNA inheritance, to every other living creature on the planet. Our genome is a living record of the journey our species has made from long-dead ancestors that we share with these animals. By comparing genomes, researchers can trace the rearrangements of chromosomes as each species has travelled along its own individual evolutionary path. Professor Malcolm Ferguson-Smith, a medical geneticist from Cambridge Veterinary School, is analysing chromosomes from a rich variety of animals to uncover secrets about our own DNA.

If you ever need a DNA probe for the red-eared slider, aardvark, manatee, common wombat, yellow-footed rock wallaby or long-nosed potoroo, there is only place to go: the Cambridge Resource Centre for Comparative Genomics.

The Resource Centre, headed by Professor Ferguson-Smith, is building the world's most comprehensive database of cross-species genomics. With so much energy, investment and scientific research focused on the human genome, he believes that the study of human genomics often overlooks the wealth of human-related knowledge that can be gained from other animals. To understand how the human genome is managed, and influences health, it is useful to know how it has evolved.

After 14 years as Professor of Medical Genetics in Glasgow, he moved to Cambridge to take up the posts of Head of Pathology and Director of the East Anglian Regional Genetics Service. But Professor Ferguson-Smith left these roles, admitting that he was drawn to the laboratory bench.

Now, together with his team of nine geneticists and a £950 000 grant from the Wellcome Trust, he is developing an extensive bank of chromosome-specific DNA from across the animal kingdom, ranging from our close relatives the great apes to such weird and wonderful creatures as the yak, the long-eared hedgehog and the duck-billed platypus.

"The Centre is designed to be a source of chromosome-specific DNA from various animals to scientists worldwide so that cross-species comparisons can be made," explains Professor Ferguson-Smith. "The whole project has grown enormously over the past two years and all the information generated now needs to be incorporated into a genome database."

To gain maximum benefit from this extensive resource in research terms, and in line with trends for open access to data, the information generated by the cross-species mapping is being made available on a website. "Part of the project is a website that

By Becky McCall, a freelance science writer.

Left:
(Clockwise from left) Two of the species studied – water buffalo and bush baby (NHPA/Photoshot); chromosome painting technique (Cambridge Resource Centre for Comparative Genomics).

we are developing called Chromhome, which as the name suggests, is where we record the homologies between the chromosomes of different species, so we construct maps of unmapped species mainly that show homology to known genomes such as that of humans and mice."

One big family

Underpinning these maps is the concept that the genomes of all species are remarkably conserved, so large chunks of genes grouped together in one animal may be found grouped in the same way in the genomes of other animals. These chunks of genes result from structural rearrangements in the chromosomes, which end up reassembled in different ways in different organisms.

So although different species have differing numbers of chromosomes, species differences probably reflect a relatively small number of rearrangements. For example, the diversity of chromosomes seen in mammals seems to be due to about 20–40 rearrangements. This makes it much easier to track the location of identical gene groupings, or homologies, across species.

The value in mapping homologies between species lies in its use to identify the relationship between one species and another. When this information is combined with other avenues of research, such as fossil records, it builds a more complete picture of evolutionary history. The greater the number of homologies shared by two species, the more likely that they are closely linked in ancestry.

This growing bank forms the backbone of international research into comparative genomics. In essence, this involves tagging DNA specific for particular chromosomes (or parts of chromosomes) from one species and seeing where the tag binds in other species (see box). As well as the evolutionary interest, this also has implications for medical genetics.

Highly conserved gene sequences have been found between human and over 120 different species, including domesticated animals. "Indeed, much work has centred on the genetics of dogs, and many of the genes involved in the 400 known genetic diseases in these animals are similar to disease genes in humans," says Professor Ferguson-Smith. "The idea was that in animal models, we might be able to find genes that play a part in cancer, for example, in humans."

The research also has veterinary impact, as befits a group based at the Cambridge Veterinary School. For example, the group has published a chromosome-painting technique (see box) that can detect specific rearrangements in canine sarcomas (bone cancers). They hope that this technique will lead to the discovery of new cancer genes in dogs.

A question of sex

Professor Ferguson-Smith's own research illustrates a further use of such resources. He has long had a fascination with the sex-determining genes. The important determinants of sex are found in the sex chromosomes (X or Y in mammals; Z or W in birds). In mammals, the key male-determining gene – *SRY* – is carried on the Y chromosome.

Recently, alongside colleagues in Australia, Professor Ferguson-Smith has been studying the mechanisms of sex determination in the duck-billed platypus and echidna. The platypus has been a source of intrigue to biologists for decades. It has a host of unusual characteristics: it lays eggs, contains snake-like poison in its hind legs, and has a leathery bill like a duck (see *Wellcome Science* 1, page 48). Moreover, little is known about its evolution because fossil records for monotremes (egg-laying mammals) are poor.

But from a geneticist's perspective, the fascination lay in trying to understand a strange anomaly in its chromosome arrangement. During meiosis – the cell division that creates sex cells – chromosomes in most mammals arrange themselves in pairs. But the platypus shows a quite different pattern.

In late 2004, Professor Ferguson-Smith and his colleagues published a paper showing that the duck-billed platypus possessed ten sex chromosomes – five Xs and five Ys in the male, and five pairs of Xs in the female – in addition to 42 non-sex chromosomes. But most strikingly, they discovered a highly unusual orientation of chromosomes during meiosis. Instead of being paired, the end of one X chromosome was complementary to the end of another, linking Xs and Ys in a chain formation.

As well as this intriguing arrangement, the team also made another exciting discovery. "We found evidence of an X chromosome on one end of the chain that contains genes homologous to the human X chromosome, whilst at the other end a chromosome known as X5 showed homology to the sex-determining Z chromosome found in chicken," explains Professor Ferguson-Smith. The platypus therefore seems to combine aspects of mammalian and bird sex determination systems.

Professor Ferguson-Smith also has a long-standing interest in 'dosage compensation' – the way that cells make allowance for the differing number of X chromosomes in male and females. In humans, one X chromosome in each cell is shut down almost completely (but not quite – see *Wellcome Science* 2, pages 24–27).

The female platypus, with ten X chromosomes, has substantially more X-linked genes than the male, which has half the number of Xs. But it does not seem to use the human X-inactivation system to even things up. Instead, platypus dosage compensation of X-linked genes is likely to be achieved by widespread down-regulation of gene expression.

Despite such revelations, much remains to be understood about the platypus and its unusual arrangement of chromosomes. If sexual reproduction relies on the production of equal numbers of X-bearing and Y-bearing sperm, how then can a single chain of sex chromosomes segregate into two different types of sperm? This remains an enigma, and one that currently challenges Professor Ferguson-Smith and his colleagues.

While a large part of the work of the Cambridge Centre consists of preparing and distributing chromosome-specific DNA for the comparative genomics community, there is still time for productive research. Genetic mapping of the platypus and echidna continues apace, with the aim of discovering their elusive sex-determining system and more about the mechanism of X-chromosome dosage compensation. The group members clearly enjoy their joint role in service and research, and regard it as a privilege as well as a responsibility to work on very diverse projects with scientists from all over the world.

FISHING EXPEDITIONS

The tool for deciphering homologies between the chromosomes of different species is a technique called chromosome painting.

To describe in more detail how his method of chromosome painting works, Professor Ferguson-Smith turns to the colourful array of chromosome karyotype charts plastering the walls of his office. He pulls out one of many maps comparing the great apes.

Initially, he explains, suspensions of chromosomes from dividing cells are sorted by a method known as flow cytometry. DNA from one chromosome is then labelled with a fluorescent dye using a technique called fluorescence *in situ* hybridisation (FISH). Effectively, this labelled DNA 'paints' the chromosome region and allows homologous regions of DNA of other species, from great apes to mice, to be identified. Homologous regions show up as the same colour on the chromosome charts.

"If you take a paint made from human chromosome 2 and hybridise it onto the chromosomes of another species then you'll see segments of paint on different chromosomes, each being homologous to part of human chromosome 2," says Professor Ferguson-Smith. "So with the gibbon karyotype, regions on chromosome 2 in human can be tracked to 5 different chromosomes in gibbon. This tells us that the lineage that produced gibbon and the lineage that produced human have diverged over several million years and during this time rearrangements have occurred between the two species which can be tracked using the painting technique."

When human chromosome probes are hybridised to chromosomes from other species, the same set of blocks dispersed across multiple human chromosomes are often located together on one chromosome in other species. For example, parts of human chromosome 3 and 21, or 14 and 15, or 12 and 22, tend to be located together on one chromosome in other animals. This is evidence that an ancestral block of genes has been split apart and moved to different chromosomes during human evolution.

Collating all these patterns of linked regions of chromosome across various mammalian species has enabled Professor Ferguson-Smith and colleagues to assemble a picture of genomic commonalities across multiple species. By extrapolating from these patterns, it is possible to re-create the probable karyotype of the common ancestor of all mammalian species – an animal that existed roughly 200 million years ago.

Further reading

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