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# Is flu stronger, or are we weaker?

**Scott Ewan**, BMN News

What is it about the recent deadly flu infection, Fujian flu, which makes it so virulent and dangerous? 'We don't really know,' said Wendy Barclay, a lecturer in microbiology at the University of Reading (http://www.reading.ac.uk), 'but there are two possibilities.' If Fujian flu is truly more virulent, it could be that the virus has changed in some way.

### What is different, the virus or man?

However, many virologists do not believe that Fujian flu is unusually virulent. It is feasible that the patients' themselves are different somehow, and are more susceptible to the effects of the infection.

Barclay continued, 'The number of deaths with this strain so far is still small.' Every year there are unexplained deaths with whatever strain is prevalent, and this year is no different.

'We shouldn't be alarmed,' said John Oxford at Queen Mary's School of Medicine in London, UK (http://www.smd.qmul.ac.uk/), who is also Scientific Director of the virological research and clinical trials company, Retroscreen Virology (http://www.retroscreen.com/). We have 'background' immunity against flu, which was developed over years of living alongside the disease and provides some protection against infection or related complications.

'There's not been much flu over the past few years,' said Oxford. This unusual coincidence means that the very young may not have had the chance to develop their background immunity and could have resulted in the higher incidence of flu-related deaths this year in young children.

### Antigen mutations

Indeed, it is known that the Fujian flu currently emerging in the UK, northern Europe and North America, is essentially the same as the prevailing flu observed for the past 30 years. The flu virus undergoes antigenic drift – mutating slightly to ensure its survival against immunity. These mutations take the form of simple changes to the amino acid sequences of two antigens on the viral surface. These antigens – haemagglutinin and neuraminidase – control the virus' entry and exit from the host cell. The antigens are the points at which drug development has focused.

The two modern drugs currently on the market – GlaxoSmithKline's Relenza and Roche's Tamiflu – both inhibit neuraminidase's normal function of releasing the virus from the host cell.

Oxford remains concerned however. 'We've still not taken on board the WHO's [World Health Organization; http://www.who.org] recommendation that we should be prepared for a pandemic.' We have not coped well with Fujian 'flu, he says, which is essentially a 'normal' flu. What will happen, he wonders, when the next true pandemic occurs?

Vaccines and drugs are available to us to combat flu – but economics, logistics and lack of public knowledge are hindering their effective deployment. With an estimated 69 million workdays lost to flu in the USA each year, and at an estimated cost of over US$14 billion, it is almost inconceivable that the best use of these agents is not being made.

### New therapies

Research is still ongoing into developing new therapies. Oxford envisages a future where a single treatment might be effective against a range of respiratory tract infections – including flu. 'By identifying common responses to different viruses, it may be possible to block the pathway, preventing spread of a number of infections,' he predicted.

# Mouse transcripts inform on human splice sites

**Henry Nicholls**, BMN News

Comparison of data from the mouse and human genome projects predicts the existence of a multitude of splice sites that analysis of the human genome alone has failed to detect.

### Specific splice sites

Databases of human transcripts reveal evidence for hundreds of thousands of splice sites, specific places where RNA is edited following its transcription from



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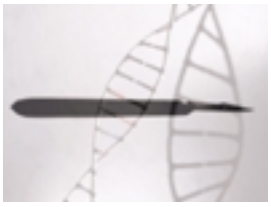


DNA. This insertion, deletion or substitution of whole strings of nucleotides helps explain how so few human genes can encode so many different proteins with so many different functions.

However, despite the intensity of work in this area, many alternative splice variants of human genes have been missed, says Zhengyan Kan, Senior Research Scientist at Rosetta Inpharmatics in Kirkland, Washington DC (http://www.rii.com). 'You'd expect not to see any surprises because we've really studied the human transcriptome quite well,' he said.

But when mouse transcripts rather than human transcripts are aligned against the human genome, there are a lot of novel splicing patterns that have not been observed in human transcripts, says Kan. Humans and mice share so much of their evolutionary past, some of these newly discovered arrangements could be present in humans, he suggests.

### Cross-species analysis

Comparing unedited DNA sequences with expressed sequence tags (ESTs) – 400–500-nucleotide fragments of cDNA – is the most common means of identifying splice sites. Aligning these edited DNA fragments alongside the complete DNA sequence reveals which chunks of DNA end up coding for protein and which do not. Importantly, such alignment also shows up the sites where the RNA was spliced before being translated.

'We have predicted novel splice forms for 42% of human genes and 51% of mouse genes through cross-species analysis,' note Kan and colleagues in a paper presented 6–10 January 2004 at the *Pacific Symposium on Biocomputing 2004* in Hawaii, USA (http://psb.stanford.edu/) [1]. Work is now underway to validate these predictions experimentally, say the researchers.

### Evolutionary divergence

One key point that the researchers have yet to address is the fact that the accurate identification of intron–exon boundaries relies on the accurate alignment of genomic sequences. By definition, the alignment between a transcript of one species and the genome of another is rarely perfect. This makes it difficult to be sure that what looks like a novel splice pattern is not simply a consequence of evolutionary divergence.

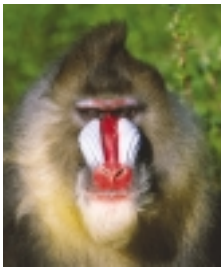
'We don't know whether these are real events in humans yet,' admitted Kan, 'A lot of that could be due to evolutionary divergence.' But this does not undermine his confidence in the approach. 'Mouse transcripts represent a potentially valuable resource for discovering alternative splice variants of human genes,' he concluded.

### Reference

1 Kan, Z. *et al.* (2003) Detection of novel splice forms in human and mouse using cross-species approach. (see http://www-smi.stanford.edu/projects/helix/psb04/kan.pdf)

# Monkey business over

**Branwen Morgan**, BMN News



Three years after applying for planning permission to build a new neuroscience center to house their non-human primates, Cambridge University's (http://www.cam.ac.uk) application has been finally accepted, generating an almost audible sigh of relief from many scientists across the UK.

### State-of-the-art facility

The 'state-of-the-art' facility at Cambridge University will benefit the animals housed there, say researchers in Cambridge and beyond. Animal rights activists who are trying to prevent the building of the new facilities should ask themselves who their actions are benefiting, they add.

David Morton, Professor of Biomedical Science & Ethics at the University of Birmingham (http://www.bham.ac.uk) notes that, 'the centre could also minimize the number of primates being used in research, for example, by sharing tissues and information on good practices.' Certainly, it would bring together researchers working in different areas of neuroscience who until now how been working in separate laboratories scattered around the campus.

Alistair Kent, Director of the Genetics Interest Group (http://www.gig.org.uk/), says, 'Of course, it would be nice if we didn't have to do them [experiments on non-human primates (NHPs)]. If there was an alternative that could likely lead to results as quickly, as safely and as effectively as doing primate-based research then I, and every scientist I know, would be happy to take it.'

### NHPs and practical issues

The complex physical and social requirements of NHPs and their relatedness to humans mean that they