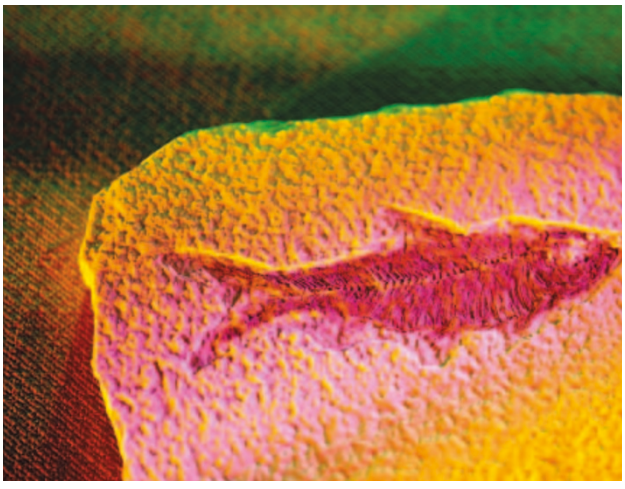
Online links

VIROLOGY

Resurrecting the past

In the 1918–1919 influenza pandemic, one-third of the world's population is believed to have been infected with the virus, and up to 50 million people died. Now, almost 90 years later, the genome sequence of the causative virus has been completed, not only facilitating comparative genomic and phylogenetic analysis, but also allowing researchers to reconstruct this deadly pathogen in the laboratory.

The 1918 genome-sequencing project started in 1995, when Jeffrey Taubenberger's group began analysing archived autopsy samples. Using these samples in conjunction with lung tissue from an influenza victim buried in a gravesite in Alaska that was covered with permafrost, Taubenberger and his collaborators have now been able to determine the complete genome sequence of the 1918 virus. The genomes of influenza A viruses comprise eight separate genome segments. The sequences of five of these segments have been published previously, and it is the sequences of the trimeric polymerase complex, comprising the PA, PB1 and PB2 proteins, that are now reported by Taubenberger *et al.* in *Nature*.



Analysis of the polymerase-complex genes confirms the conclusion drawn about the origin of the 1918 virus from analysis of the other genome segments. In contrast to the 1957 and 1968 pandemic viruses, which are thought to be reassortants between a Eurasian waterfowl strain and a human-adapted strain, the 1918 strain is not a reassortant but is an entirely avian virus that adapted to humans. The precise source of the virus remains unknown, however, as the sequence differs from that of all avian sequences available for analysis and so might have come from an evolutionarily isolated source. Interestingly, several of the amino-acid changes from the avian consensus sequence seen in the polymerase-complex genes have been observed in the highly pathogenic H5N1 viruses currently in circulation.

In a separate study published in *Science*, Terrence Tumpey *et al.* used reverse genetics to generate a virus with the same coding sequence as the 1918 virus. The reconstructed virus proved highly virulent in mice, with a virus titre 4 days after inoculation that was 39,000 times greater than after infection with a modern influenza strain. In addition, mice infected with the reconstructed virus lost up to 13% of their body weight 2 days after infection, and the virus could be lethal in as little as 3 days. As well as recreating the 1918 strain, Tumpey *et al.* also created viruses containing different combinations of 1918 genes, and determined that the polymerase complex and haemagglutinin are required for maximal replication in human cells.

Recreating the 1918 virus has raised safety concerns in some quarters, but all work with the virus was carried out under strict Biosafety Level 3 enhanced conditions, and the reconstructed virus was handled by a single individual. As fears of a new influenza pandemic continue to grow, such work is vital to understand the highly pathogenic influenza viruses.

Sheilagh Molloy

References and links

ORIGINAL RESEARCH PAPERS Taubenberger, J. T. *et al*. Characterization of the 1918 influenza virus polymerase genes. *Nature* **437**, 889–893 (2005) | Tumpey, T. M. *et al*. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. *Science* **310**, 77–80 (2005)
FURTHER READING Reid, A. H., Taubenberger, J. K. & Fanning, T. G. Evidence of an absence: the genetic origins of the 1918 pandemic influenza virus. *Nature Rev. Microbiol*. **2**, 909–914 (2004)