

# Custom-made vaccines at speed

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A concept called reverse genetics has recently enabled researchers at the St Jude Children's Research Hospital (<http://www.stjude.org>) to construct an experimental vaccine against H5N1, a potential pandemic influenza strain, in less than a month. A similar approach could be used to develop vaccines for severe acute respiratory syndrome (SARS).

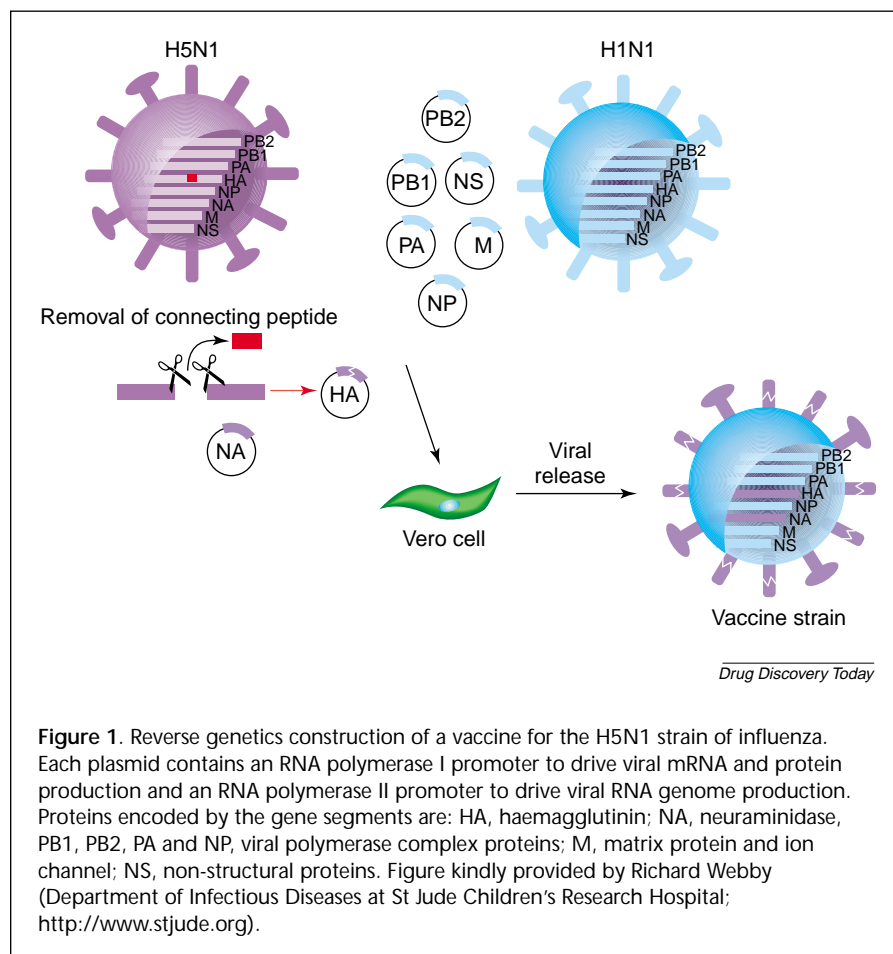
Vaccines against new strains of well-known viruses or emerging infectious diseases used to take many months to develop. However, the increasing availability of genome sequences for pathogens is now expediting the development of safer, more effective vaccines.

## Reverse genetics of flu

'To virologists,' explains Richard Webby, a postdoctoral fellow in the Department of Infectious Diseases at St Jude, 'reverse genetics means the production of a virus from cloned DNA'. A team led by Yoshihiro Kawaoka, Professor of Virology at the University of Wisconsin-Madison (<http://www.vetmed.wisc.edu>) was the first to achieve this feat for influenza, a segmented negative-sense RNA virus, in 1999 [1].

The classic method of making a vaccine to a new flu variant, explains Webby, is to co-infect hens eggs with the field isolate and a vaccine strain and then to genetically select for reassorted viruses containing the desired mix of genome fragments, a process that can take many weeks.

'Because of its pathogenicity, traditional reassortment was never an option for H5N1,' Webby continues. Instead, to develop a vaccine against H5N1, the St Jude team isolated the



H5N1 genome segments encoding haemagglutinin and neuraminidase – the surface glycoproteins against which neutralizing antibodies are raised. They then engineered haemagglutinin so that it was less pathogenic and mixed plasmids carrying these two fragments with six plasmids carrying the remaining flu genome fragments from H1N1, a standard vaccine strain (Fig. 1).

'In four weeks, we went from a newly isolated, potentially pandemic flu strain to an experimental vaccine,' says Webby. This flu vaccine will be the first produced by reverse genetics to go

into clinical trial, and the speed with which it was produced, comments Rino Rappuoli, Vice President of Vaccine Research at Chiron Corporation (<http://www.chiron.com>) 'could be critical if H5N1 turns out to be the next, long-overdue pandemic strain to emerge from the Far East'.

## A powerful tool for vaccine development

Reverse genetics is being used to develop vaccines for many other viruses, including respiratory syncytial viruses and parainfluenza viruses [2]. And if the

definition of the technology is broadened to include expression of proteins from engineered genes, then its future applications are virtually boundless. 'Even 10 years ago,' says Rappuoli, 'genetics was used minimally in vaccine development. Nowadays, we would not even try to develop a vaccine without using all the genetics tools available.'

Speed is only one aspect of this revolution. Even more important is the flexibility that is now available for vaccine design [3]. For example, says Kawaoka, 'many companies are planning to use reverse genetics to produce attenuated flu strains to be used as live vaccines that should give more protection than current inactivated vaccines'. In other cases, says Rappuoli, 'this technology has facilitated the development of previously elusive vaccines. For example, for 50 years we failed to develop an effective vaccine for meningococcus B. With reverse genetics we went from getting its genome sequence through identifying new antigens to starting clinical vaccine trials in less than four years.'

### A speedy vaccine against SARS?

The earliest known cases of SARS were reported in mid November 2002. By 10 May 2003, 7296 probable cases and

526 deaths had occurred in more than 30 countries. In response to this threat to global health, researchers have moved fast. 'In early March, no-one knew what this disease was caused by,' explains Rappuoli. 'In late March somebody suggested it could be a coronavirus. By mid April we knew its genetic code. At Chiron, we are already expressing SARS envelope proteins to try to develop a vaccine,' he continues. 'We will also be using the information available on animal coronavirus to introduce attenuating mutations into the SARS virus to make a live vaccine.'

For the latter approach, recombinant virus will have to be generated, not an easy task given the size of the coronavirus RNA genome. But, says Luis Enjuanes, Research Professor at the Centro Nacional de Biotecnología (<http://www.cnb.uam.es>), since 2000, systems have been available to do this [4]. Several laboratories are engineering coronavirus genomes as vectors for vaccine development and gene therapy, says Enjuanes, so it should be possible to make vaccines for SARS by adapting the available infectious cDNA clones.

However, Enjuanes warns that these will be the vaccines of the future. For now, other types of vaccine – based on single viral components, for example –

can be made more quickly, he says.

Other experts agree – the use of reverse genetics to make recombinant SARS vaccine could ultimately be the most effective and adaptable system for vaccine development, but will require considerable research set-up time.

For now, most emphasis is on using inactivated SARS virus as a vaccine. This is the approach that the US National Institute for Allergy and Infectious Diseases (<http://www.niaid.nih.gov>) will initially focus on although NIAID Director Anthony Fauci says that 'other approaches will soon follow... as more knowledge about the cause of SARS and its etiology becomes available'. This classic approach will not be fast – Fauci estimates that it will be least a year before a vaccine is ready for human testing – but 'it is probably the fastest way to go,' concludes Kawaoka.

### References

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- 4 Enjuanes, L. *et al.* (2001) Coronavirus derived expression systems. *J. Biotechnol.* 12, 183–204

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