WEB WATCH

Who was Edward Jenner?

- http://www.jennermuseum.com

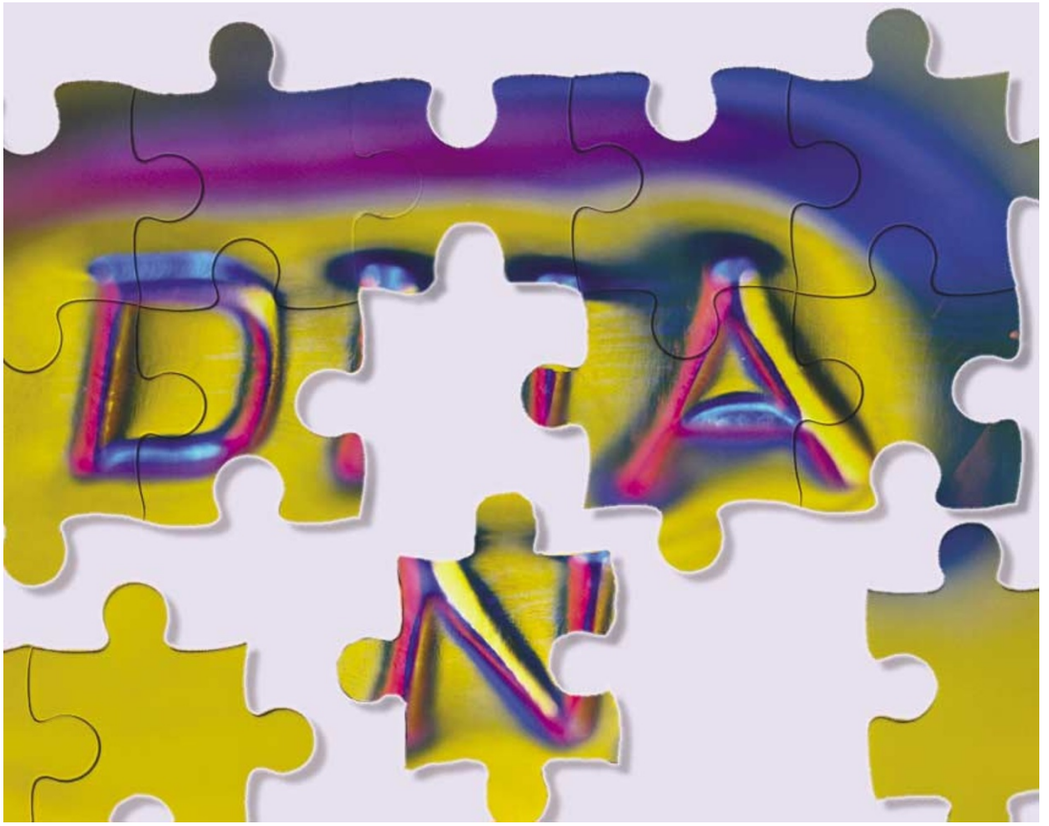
In 1980, the World Health Organisation declared that smallpox had been eradicated, but two stocks of the virus remain and smallpox is still of concern owing to potential use of the causative agent variola virus in bioterrorism. It was the work of the English physician Edward Jenner (1749–1823) that led to the development of a vaccine and the subsequent eradication of smallpox.

If you want to find out more about Edward Jenner, a good place to start might be the web site of The Jenner Museum in Gloucestershire, which was opened to the public in 1985.

This web site details the life and work of Edward Jenner, from his early life in Gloucestershire to his famous work on smallpox — or as Jenner called it 'the speckled monster' — and vaccination. Jenner's work on cowpox as a vaccine for smallpox led to the introduction of compulsory vaccination in 1853. There are some intriguing additional titbits about some of Jenner's other interests, including fossils, hibernation of hedgehogs and the nesting habits of cuckoos. You can also take a look at his family tree and find out what the museum facilities have to offer for visiting student groups.

The site is a useful educational resource for all ages — one section provides basic background information on the human immune system, vaccination, transplantation and defects in immunity, and a glossary of terms. This section also includes a topical opinion poll with questions about vaccination that should be useful for stimulating discussion. By answering the questions, you can access the poll results so far. Check the web site for further information!

Elaine Bell



LYMPHOCYTE DEVELOPMENT

The art of joining

During lymphocyte development, variable (V), diversity (D) and joining (J) gene segments recombine to form the variable regions of antigen receptors. Recently, Artemis — a member of the metallo-β-lactamase superfamily — was implicated in this process when it was found to be mutated in a subset of patients with severe combined immunodeficiency who have a complete block in V(D)J recombination (patients with RS-SCID). Now, a new study by Rooney and colleagues has clarified the *in vivo* functions of Artemis.

An early step in V(D)J recombination is the generation of double-strand breaks between the coding gene segments and the conserved recombination signal sequences that flank them, leading to the generation of two intermediates — a blunt recombination signal (RS) end and a hairpin coding end. Two coding ends can then be ligated through non-homologous end-joining (NHEJ) — a generic mechanism of double-strand break repair for which DNA-dependent protein kinase (DNA-PK) is an essential component.

Opening of the coding-end hairpins is a prerequisite for joining, but the identity of the molecule(s) that mediate this crucial step has been an important unresolved issue. *In vitro* studies have shown that Artemis can associate with the catalytic subunit of DNA-PK (DNA-PKcs) to form a complex that has hairpin-opening activity. But, whether this occurs *in vivo* has been a subject of debate.

To determine the physiological role of Artemis in V(D)J recombination and DNA repair, Artemis-deficient mice were generated by introducing mutations that mimic those in humans with RS-SCID (referred to as $Art^{N/N}$ mice). Overall, the phenotype of these mice was similar to that of patients with RS-SCID and of DNA-PKcs-deficient mice — B-cell and T-cell development were blocked and sensitivity to ionising radiation was increased.

Similar to DNA-PKcs-deficient mice, $Art^{N/N}$ mice had normal RS end joining but no V(D)J recombination, and unresolved hairpin intermediates accumulated in $Art^{N/N}$ thymocytes. Together, these data support previous proposals that Artemis co-operates with DNA-PKcs in the processing of hairpin coding ends.

Surprisingly, however, the fidelity of RS joining was reduced in DNA-PKcs-deficient, but not $Art^{N/N}$, mice, which indicates that DNA-PKcs has a broader role in V(D)J recombination. Moreover, unlike DNA-PKcs-deficient mice, a proportion of $Art^{N/N}$ mice do develop some T cells, which shows that a low level of V(D)J recombination can occur independently of Artemis. These are the first functional differences to be uncovered between Artemis and DNA-PKcs.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPER Rooney, S. *et al*. Leaky Scid phenotype associated with defective V(D)J coding end processing in Artemis-deficient mice. *Mol. Cell* **10**, 1379–1390 (2002)

FURTHER READING Ma, Y. *et al*. Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in non-homologous end joining and V(D)J recombination. *Cell* **108**, 781–794 (2002)

WEB SITE

Frederick Alt's lab: http://www.hhmi.org/research/investigators/alt.html