WEB WATCH

Dispatches from the HIV frontline

- HIV Vaccines Trial Network: http://www.hvtn.org
- International AIDS Vaccine Initiative: http://www.iavi.org

With clinical trials of HIV vaccines now underway, how can you keep up to date with the progress and inevitable setbacks? We found two websites that provide the latest news, together with essential background information on HIV-vaccine development.

The HIV Vaccines Trial Network (HVTN), which was established in 1999 by the Division of AIDS at the National Institute of Allergy and Infectious Diseases, is a worldwide network of research institutes and clinical-trial centres that aims to develop and test preventive HIV vaccines. The HVTN website contains links to the latest news stories and clear information on the challenges of HIV-vaccine development. HVTN vaccine trials that are underway and in the pipeline are also listed, although there are no progress reports posted yet.

The website of the International AIDS Vaccine Initiative (IAVI) — a global organization that works to promote the development and distribution of preventive AIDS vaccines — offers a broader perspective. For example, it covers issues such as education and advocacy; accelerating scientific progress; encouraging industrial participation in AIDS-vaccine development; and assuring global access. On this website, you can find up-to-date HIV news, and current statistics on the scale of the problem. The site contains an easily searchable database of preventive vaccines that are currently under trial. Basic vaccine science and current vaccine strategies are clearly explained, and articles on social, economic, political and ethical issues make for a well-rounded site.

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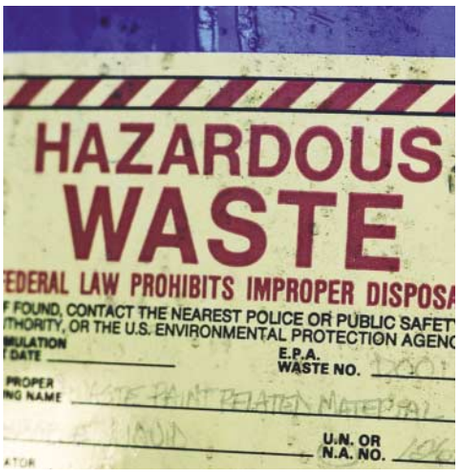
T-CELL DEVELOPMENT

Hazardous waste disposal



During T-cell development, autoreactive thymocytes that recognize self-antigens and, therefore, are potentially destructive to the organism are negatively selected and undergo apoptosis. Negative selection is a crucial step in the prevention of autoimmunity, but the mechanisms underlying this process are not well understood. Bouillet and colleagues now report in *Nature* an essential role for the pro-apoptotic BH3-only Bcl-2 family member Bim in the negative selection of autoreactive thymocytes.

Mice deficient for Bim had been generated previously by this group, identifying Bim as a crucial regulator of lymphocyte homeostasis, autoimmunity and apoptosis. However, the role of this protein in negative selection had not been investigated. Here, the authors used several models of negative selection, and in all cases, Bim deficiency provided protection against these processes. For example, the injection of anti-CD3 antibodies into wild-type mice (which mimics T-cell receptor (TCR) ligation) resulted in the death of 80–90% of $CD4^+CD8^+$ double-positive (DP) thymocytes. By contrast, nearly all of the thymocytes in *Bim*$^{-/-}$ mice survived, showing that Bim is required for the apoptosis of immature thymocytes induced by TCR ligation.

Next, Bouillet and co-workers used OT-II-transgenic mice — in which T cells express a Vα2/Vβ5 TCR that is specific for an ovalbumin (Ova) peptide presented by $I\text{-}A^b$ MHC class II molecules — to examine the role of Bim in the negative selection of thymocytes mediated by endogenous superantigen or exogenous peptide. Wild-type C57BL/6 mice have ~1×10^8 DP thymocytes, but OT-II-transgenic mice have only ~1.5×10^7 of these cells, because their transgenic $TCRV\beta5^+$ T cells are deleted by the endogenous superantigen Mtv-9. OT-II-transgenic mice that lack expression of Bim had nearly normal numbers of DP thymocytes. In addition, the injection of Ova peptide further reduced the number of DP thymocytes in *Bim*$^{+/+}$ OT-II transgenics by 60%, whereas only ~30% of T cells were deleted in *Bim*$^{-/-}$ OT-II-transgenic mice. These results show that Bim is essential for the deletion of autoreactive thymocytes promoted by superantigen or a specific peptide.

To investigate the role of Bim in the negative selection of thymocytes responding to a conventional endogenous antigen, the *Bim*$^{-/-}$ mice were crossed with HY-TCR-transgenic mice (which express an αβ TCR that recognizes a peptide from the male antigen HY, presented by $H\text{-}2D^b$ MHC class I molecules). In transgenic male mice, most DP thymocytes are autoreactive and are deleted, whereas female mice have normal thymocyte cellularity. The number of autoreactive thymocytes surviving in *Bim*$^{-/-}$ HY-TCR-transgenic male mice was sevenfold the number seen in

VACCINES

Advantageous AdC68?

Replication-defective adenoviruses — in particular, human serotype 5 (Adhu5) — have been tested extensively as vaccine vectors in several model systems. These viruses induce good B-cell and T-cell responses in experimental animals. However, Adhu5 is a ubiquitous common-cold virus that infects most humans early in life. Therefore, pre-exisiting immunity to Adhu5 is likely to reduce the efficacy of vaccines that are based on this adenovirus serotype. Now, Hildegund Ertl and colleagues have developed a replication-defective chimpanzee serotype 68 virus (AdC68) and have shown that the efficacy of this vaccine vector is virtually unaffected by pre-existing immunity to common human adenoviruses.

The AdC68 vector was tested using the well-defined rabies glycoprotein (rab.gp) model antigen. Immunization with AdC68–rab.gp and Adhu5–rab.gp induced neutralizing serum antibody responses of comparable titre, but different isotype profile. Protection against rabies is dependent on neutralizing antibodies, and both vaccines protected mice against challenge with a lethal dose of rabies virus.

Next, the authors tested the effect of pre-exposure to other adenoviruses on the efficacy of the AdC68–rab.gp vaccine. Mice were exposed to replication-competent human adenoviruses of various serotypes before immunization with the chimpanzee vaccine. Importantly, the ability of the AdC68–rab.gp vaccine to induce antibody responses was only marginally affected by pre-existing immunity to human adenoviruses, which can severely reduce the efficacy of homologous human adenoviral vaccines. The antibody response to AdC68–rab.gp was inhibited in mice that were pre-exposed to the AdC68 virus, but this is not of major concern, because AdC68 is not present in the human population and human serotypes do not share any neutralizing epitopes with AdC68.

Therefore, the AdC68 vaccine has an advantage over human adenovirus vaccines, and it is an important addition to the current arsenal of virus vectors.

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References and links

ORIGINAL RESEARCH PAPER Xiang, Z. *et al.* Novel, chimpanzee serotype 68-based adenoviral vaccine carrier for induction of antibodies to a transgene product. *J. Virol.* **76**, 12667–12675 (2002)