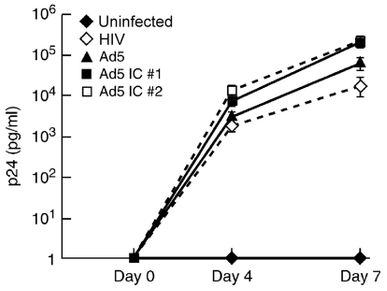


AD5-antibody complexes (Ad5 IC) augment HIV replication in human cells.

Adenovirus antibodies assist HIV

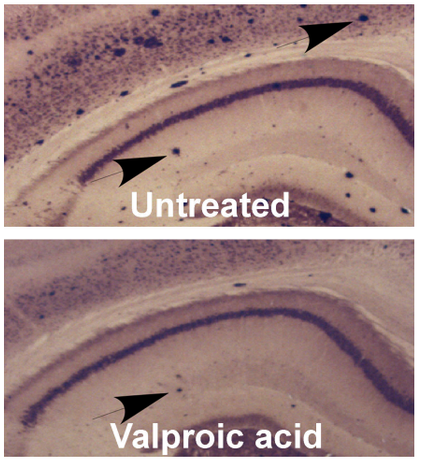
Antibodies against a vaccine vector render T cells more susceptible to HIV-1 infection, say Perreau et al. on page 2717. Their results may help explain the failure of a recent HIV vaccine trial.

The HIV-1 vaccine used in Merck's STEP trial relied on a weakened form of a common cold virus, Adenovirus 5 (Ad5), to carry bits of HIV into the body. One worry about the Ad5 vector was that widespread immunity to adenoviruses might cause the vaccine to be ousted before an anti-HIV response could develop. Instead, there was a chance that vaccine recipients who had circulating antibodies against Ad5 were contracting the virus more often, one factor that forced termination of the trial.

Perreau et al. now show that HIV spread through T cell–dendritic cell (DC) co-cultures three times as fast when Ad5 and neutralizing antiserum—present in people with prior immunity—was added to the cultures. Ad5-antibody complexes triggered DC maturation in the presence of Fcγ receptors (FcγR) and Toll-like receptor (TLR)–9. The authors suspect that FcγR facilitated the uptake of Ad5-antibody complexes into the cell, where viral components could then activate TLR9 to trigger DC maturation and activation.

The mature DCs activated both $CD4^+$ and $CD8^+$ T cells, which may have assisted HIV infection in two ways. Activated $CD4^+$ cells could provide HIV with more cells to infect. And activated Ad5-specific $CD8^+$ T cells could attack infected DCs, thereby reducing the pool of DCs presenting HIV antigens. Indeed, weaker HIV-specific CD8 responses were seen in Ad5-seropositive individuals in response to vaccination.

Merck's vaccine may have made it to phase 2 trials because nonhuman primates don't naturally come in contact with human adenoviruses, and therefore the potential problem went unrecognized. **AM**



Valproic acid treatment reduced Aβ plaques (arrows) in the brains of mice with Alzheimer's-like disease.

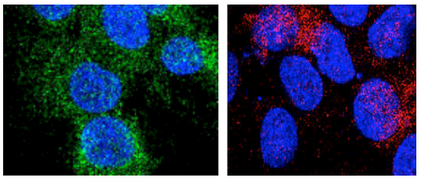
Acid to remember

A popular epilepsy drug may also be beneficial in patients with Alzheimer's disease (AD), if the findings on page 2781 hold true in clinical trials. Qing et al. improved memory and ameliorated brain plaques in mice with an AD-like disease by injecting them with the anti-seizure drug valproic acid.

Mice with the AD-like disease typically develop amyloid-rich brain plaques after six months. When Qing et al. treated the mice with valproic acid soon after plaque formation, the plaques shrank and some of the damaged axons in their brains resumed growth. The drug also improved performance in memory tests.

The acid worked by inhibiting the activity of glycogen synthase kinase-3β (GSK-3β), which normally turns on γ-secretase—the enzyme that cleaves β-amyloid precursor proteins. Lithium chloride, another drug used in patients with AD, also curbs amyloid-β production by inhibiting GSK-3α and GSK-3β, and has recently been shown to ameliorate axonal damage.

Valproic acid helped mice less as their disease progressed. The authors thus suggest that clinical trials should focus on people with early signs of AD. Valproic acid has been given to people with AD in the past but, unfortunately, memory improvement was never assessed in those studies. **AM**



Estrogen loss triggers the production of IL-18 (green) and IFN-γ (red) by epithelial cells in human salivary glands.

Epithelial cells as APCs

Epithelial cells masquerading as antigen-presenting cells (APCs) may lead to autoimmune disease, as shown by Ishimaru et al. on page 2915. The findings suggest that Sjögren's syndrome stems from salivary gland epithelial cells that make interferon (IFN)-γ and then present self-antigens.

During Sjögren's syndrome, the body's immune cells attack moisture-producing cells in salivary glands and tear ducts. The destruction of these cells is initiated by estrogen loss during menopause via the induction of a chromatin-modifying protein called RbAp48, which triggers p53-dependent cell death.

The timing of mouse menopause is difficult to pin down, so to better understand RbAp48's role, the group created mice that overexpress RbAp48 in gland cells. They now find that these mice develop symptoms resembling Sjögren's syndrome.

Epithelial cells from transgenic salivary glands produced IL-18 and IFN-γ, which then induced the expression of MHC class II molecules. These cytokines also stimulated the proliferation of

Text by Amy Maxmen: amaxmen@rockefeller.edu
and Nicole LeBrasseur: lebrasseur@gmail.com

local autoreactive T cells that had previously ignored epithelial self-antigens. IFN-γ and RbAp48 were also found in epithelial cells of patients with Sjögren's syndrome.

Professional APCs seem to be required to start or maintain autoimmunity when estrogen levels are normal, as transferring T cells from transgenic lymph nodes into nontransgenic mice initiated gland cell destruction only if APCs were included. But epithelial cells may be self-sufficient APCs in the absence of estrogen; T cells from the transgenic mice were enough to cause disease in mice whose ovaries had been removed. **NL**

Beekeepers show way to allergen tolerance

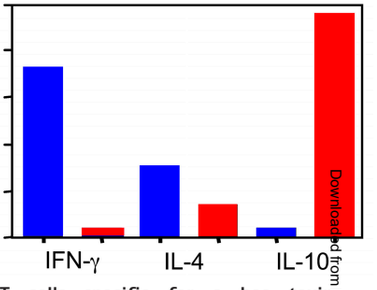
Beekeepers are the new, improved mouse model for immune responses to allergens, according to a study from Meiler et al. (page 2887). The fleeting tolerance of these intrepid honey lovers to bee antigens is now revealed to require a Jekyll-and-Hyde set of T cells that go from attack to suppressive mode and back again.

It's an immunologist's dream. By the very nature of their jobs, unprotected beekeepers are voluntarily and repeatedly injected with high doses of bee antigen—an average of 13 antigen-loaded stings in the first week of honey-harvesting season alone, according to the study. And in just these seven days, the beekeepers developed an immune tolerance that was noticeable in both skin reactions and T cell responses.

T cells that started out proliferation-happy in response to bee antigen became much more subdued soon after the season began. The authors traced this change to cytokine alterations: within a week, T cells that had made mostly IFN-γ started making more IL-10, which tempers immune reactions. IL-10–producing cells curbed the in vitro proliferation of other T cells in response to bee antigen.

The cytokine switch, the authors found, was initiated through the histamine pathway. As with many allergens, bee venom induces mast cells to unload histamine. In vitro experiments with the beekeepers' T cells revealed that histamine induced IL-10 production and T cell lethargy, both of which required the H2 histamine receptor.

The beekeepers' tolerance was lost within two months of season's end, unveiling a relatively short lifespan of T cell suppression. The cycle repeated at the onset of the next season, so beekeepers have little to worry about. But allergy sufferers, who may be defective in this IL-10 response, might be less enthused, because the findings suggest that successful therapies involving allergen-specific immunotherapy probably require considerable perseverance. **NL**



T cells specific for a bee toxin make mostly IFN-γ and IL-4 before beekeeping season (blue) but mostly IL-10 after the season begins (red).

Reviving the attack against HIV

Researchers breathe life into exhausted T cells in a study on page 2763.

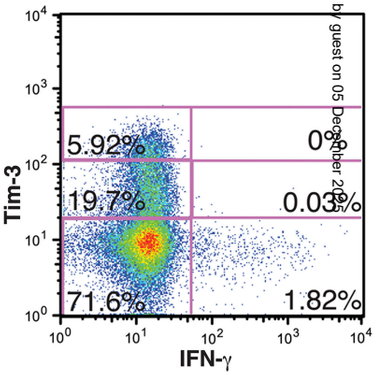
HIV beats the immune system in part because killer T cells stop fighting the virus. PD-1, a T cell inhibitory protein that normally prevents over-inflammation, was recently associated with chronic HIV. Now Jones et al. identify another manipulated manager, TIM-3.

When $CD4^+$ T cells express the glycoprotein TIM-3, proliferation and cytokine production are suppressed. Because disruption of TIM-3 is known to induce hyperactive inflammatory responses, as seen in autoimmune diseases like multiple sclerosis, Jones et al. predicted that the opposite might be true in HIV infection. The team assessed T cells from HIV patients and found that high levels of the protein indeed corresponded to a heavy viral load.

TIM-3–expressing $CD4^+$ and $CD8^+$ T cells from HIV-infected patients secreted far less interferon (IFN)-γ and TNF than did cells without TIM-3. And blocking TIM-3's ligand reversed this effect. Although the effect of blocking TIM-3 and PD-1 is similar, these molecules were found on distinct populations of $CD8^+$ T cells.

Half of the participants undergoing antiretroviral therapy maintained high TIM-3 expression, even after their viral loads diminished, suggesting to the authors that TIM-3 upregulation may be irreversible in some individuals. And obstructing its signals could be an important means of controlling the underlying virus that persists despite therapy.

Many of the steps between the virus and TIM-3 manipulation aren't yet known, and it appears that HIV isn't the only T cell exhauster. Learning how to revive tired cells might therefore help patients with other chronic infections as well. **AM**



HIV-specific T cells that express TIM-3 produce less IFN-γ.