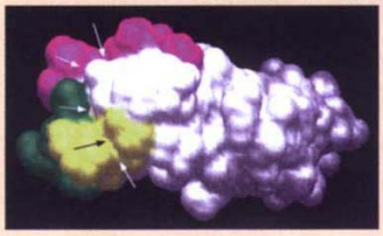
A new class of viral inhibitor

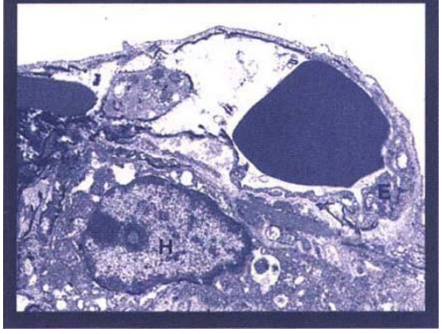
The inhibition of virus receptors on cell surfaces is an attractive target for antiviral therapeutics. The CD4 molecule on T cells serves as the coreceptor for HIV. Rather than creating a receptor decoy, which would directly bind to the virus to inhibit virus infection, Greene and collaborators have shown that small constrained forms of a defined region of the receptor associate with the holoreceptor, thus disabling it from mediating its biological activity (see p. 150). Synthetic complementary determining-like regions of CD4 inhibited binding of gp120, the HIV envelope protein that mediates infection, to both soluble CD4 and CD4⁺ Jurkat cells. Furthermore, syncytium formation, a hallmark of HIV infection, is inhibited by the small constrained peptidomimetic, thus demonstrating the pharmaceutical potential of this class of molecules.



Antifungal single-chain Fv

Antiidiotypic antibodies (antiantibodies) often mimic the structure and function of the protein to which the original antibody was directed. Those antiidiotypes raised against antibodies to the killer toxin of the yeast *Pichia anomala* have been shown to exhibit the killer toxin's antifungal activity. Magliani and colleagues show that engineered single-chain antiidiotypic antibodies, produced in bacteria, confer immunoprotection against *Candida albicans* (see pp. 123 and 155). The best candidate clone reduced up to 90% of suspended *Candida* cells and conferred a high degree of protection against *Candida* infection in an experimental rat vaginitis model. Polyclonal antibodies are not feasible as drugs, thus the single-chain antiidiotypic antibody format is therapeutically promising.

By reformulating cationic lipsosomes, higher transgene expression in mice has been achieved. The modified liposomes contain cholesterol instead of the commonly used lipid, dioleoylphosphatidylethanolamine (DOPE), and consist of large multilamellar, rather than unilamellar, vesicles (see p. 167).



Research briefs written by Emma Johnson and Philip Bernstein.

A phytoplasma, a cell wall-less mycoplasma-like plant pathogen, has been identified as the agent that induces the desirable free-branching phenotype found in commercial poinsetta cultivars (see p. 178).

Shocking astroglial cells

Nerve growth factor (NGF) production by astroglial cells has the ability to stimulate neuronal cell growth. NGF production can be induced by cytokines, though the therapeutic potential may be limited because of unwanted side effects. Koyama et al. have applied direct electrical stimulation to induce the production of NGF from resting astrocytes in cell culture (see p. 164). Electrically stimulated release of NGF is apparently mediated by a protein kinase C pathway, suggesting a possible in vivo application to promote neuron survival.

Single-chain antibodies with multiple specificity

Bispecific antibodies can simultaneously recognize two different antigens; however, the means to produce them can be difficult or inefficient. By specifically fusing one single-chain antibody to an antibody with a different specificity, Coloma and Morrison were able to generate a single molecule that recognizes two different epitopes while maintaining some of the effector functions associated with the constant region (see pp. 125 and 159).

Cytokine fusion increases bioactivity

Expansion of hematopoeitic progenitor cells requires the stimulation of the gp130 receptor subunit by both cytokine IL-6 and its soluble ligand-binding receptor, sIL-6R. High concentrations of both molecules are needed for ex vivo cell stimulation. By covalently linking IL-6 with sIL-6R, via a flexible peptide linker, Stefan Rose-John and his colleagues have designed a chimeric molecule that has synergistic effects on hematopoietic cell growth (see p. 142). The designer fusion molecule stimulates cell expansion at concentrations two to three orders lower than the separate proteins, thus exhibiting considerable therapeutic potential.

Plants to clean up after polluters

Vegetation is often introduced to sites contaminated with organic pollutants to create a colonizable rhizosphere for microbial populations that can degrade the contaminants. The role of the plants in directly mediating remediation has not been clear, but Gregory Payne and coworkers have shown that plant cells can contribute to metabolizing certain contaminants (see pp. 127 and 174). Sugar beet cells degraded the nitrate ester, glycerol trinitrate at rates comparable, and a mechanism similar, to *Bacillus*, a microorganism with demonstrated remediation potential.

Toward an anticoagulant thrombin

Thrombin, a key enzyme in the coagulation cascade, has a dual role: In the Na^+-bound form it acts as a procoagulant converting fibrinogen to fibrin, whereas in the Na^+-free form it acts as an anticoagulant by activating protein C. The procoagulant form is favored in the blood. Di Cera and colleagues have demonstrated that the anticoagulant activity can be favored by introducing a point mutation that suppresses Na^+ binding (see pp. 124 and 146). The engineered protein has a 50-fold enhanced anticoagulant activity. In vivo studies will determine if this approach can be used to create novel anticoagulant therapeutics.