pheres could serve as an active adjuvant in other antigen-specific immunotherapy.

Delivery of agents via microspheres can offer other advantages. They can ameliorate the toxic or adverse effects associated with drugs like interferon (IFN)-α, for instance. Yasuhiko Tabata and coworkers at the Kyoto University Research Center for Biomedicine found that administration of IFN-α conjugated to pullulan, a water-soluble polysaccharide with a high affinity for liver cells, induces the production of 2-5A synthetase in mouse livers, a defense against hepatitis C virus infection. According to Tabata, the IFN–pullulan system induces antiviral activity at much lower doses of interferon than are used in current intravenous administrations. This could reduce some of the side effects of IFN.

Similar ameliorative effects were seen by Blanka Rihova and colleagues at the Institutes of Microbiology and Macromolecular Chemistry (Prague, Czech Republic), who coupled a hydroxypropyl methacrylamide (HPMA) copolymer carrier to the anticancer agent doxorubicin. According to Rihova, conjugating the doxorubicin to the copolymer not only did not diminish the drug's activity, it enhanced its therapeutic action in mice by targeting it to the tumors. Ruth Duncan and colleagues at the Center for Polymer Therapeutics, the School of Pharmacy (University of London) explored the targeting potential of carrier polymers further. They have developed "dendrimers," a class of methylacrylate-based polymers with surface chemistries that the researchers believe can be targeted to specific types of cancer cells. The effects of one of the dendrimers, *N*-(2-hydroxypropyl) methacrylamide, combined with doxorubicin, are now being evaluated in a phase I clinical trial.

Mary Jean Pramik

Companies aim at new HIV targets

All AIDS drugs now in use or in late-stage trials are narrowly focused on only two targets in the AIDS virus life cycle—HIV protease and reverse transcriptase, according to Didier Trono from the Salk Institute for Biological Studies (San Diego, CA), speaking to the XIth International Conference on AIDS in Vancouver, BC (Canada) in July. "While these two enzymes govern the processes of RNA transcription into DNA and cleavages during virion maturation, there are 12 other proteins unique to HIV which are not found in host cells which should also be considered as targets," he said.

One of these other 12 HIV proteins is the particle assembly protein, Gag. Hybridon (Worcester, MA) has targeted Gag with its 25-mer phosphorthioate antisense oligonucleotide, GEM-91, currently in phase 1b/2 trials with 170 patients in the United States and Europe. Early results indicate that GEM-91 produces potent inhibition of acute HIV-1 infection in cells, blocking attachment of viral particles in a dose-dependent manner and inhibiting production of viral DNA. In vitro data presented by Hybridon in Vancouver showed that GEM-91 caused a 60–70%, sequence-specific, reduction in *gag* messenger RNA levels in chronically infected cells.

Alternative approaches to target the Gag protein have included cyclosporin, which disrupts the interaction between Gag and the host cell protein, cyclophilin (see *Nature Biotechnology* 14:428, April 1996). Theratechnologies (Montreal, Canada) reported data showing that they could block synthesis of the Gag-Pol protein using an antisense oligonucleotide, TH-9407, which targets sites on the host ribosome in order to interfere with the ribosomal frameshift, thereby inhibiting viral replication. Lea Brakier-Gingras of Theratechnologies said this treatment has the advantage of reduced likelihood of resistance because the target is host ribosomes rather than the virus.

Another approach is to induce cells to resist infection by inhibiting binding of another of the 12 HIV proteins, the HIV transactivation protein, Tat. Allelix Biopharmaceuticals (Mississauga, Canada) used a nine amino-acid synthetic oligocationic peptide, ALX40-4C, to mimic the basic domain of the HIV-1 Tat protein, thus inhibiting Tat binding to its specific RNA hairpin target, TAR. This reduces HIV-1 gene expression and replication in a range of cell types by as much as tenfold. ALX40-4C is now being tested in two phase I/II trials that are expected to be completed shortly.

Trono likened the challenge of HIV infection to that of tuberculosis: In both diseases, grave problems of drug resistance arise and patients may find it difficult to comply with long and complex regimes of multiple drugs with unpleasant side effects.

Another approach involves modifying in vivo virulence factors like the Vif, Vpr, Vpu, and Nef proteins to inactivate HIV virions. Theratechnologies showed that CD4 cells transformed with one or more chimeric Vpr proteins were more resistant to infection, and the virions these cells produced were 10-fold less infectious than the untransformed virus.

Trono also pointed out that the recently discovered cofactor for HIV-1 entry into the cell, fusin, could be targeted, possibly via antibodies that can block entry into host cells. This approach has been taken by Progenics (Tarrytown, NY), the Aaron Diamond AIDS Research Center (New York), and Scripps Research Institute (La Jolla, CA), who jointly published in June (*Nature* 381:667–673, 1996) the discovery of a second HIV receptor, CC-CKR-5. More recently still, researchers have shown that white blood cells from an individual who is homozygous for a CCR-5 null allele are highly resistant to HIV-1 infection. As Trono noted, CC-CKR-5 is related to fusin and serves as the receptor for the β-chemokines, RANTES, MIP-1α, and MIP-1β. Progenics has developed a fusion protein, PRO-542, that incorporates the CC-CKR-5 receptor into a human monoclonal antibody-like protein that can attach with high affinity to any strain of HIV or to infected cells, and neutralizes HIV by stripping off the envelope glycoprotein. The company plans to begin phase I trials by the end of the year.

Trono likened the challenge of HIV infection to that of tuberculosis: In both diseases, grave problems of drug resistance arise and patients may find it difficult to comply with long and complex regimes of multiple drugs with unpleasant side effects. Although new therapies for HIV infection are at an early stage compared with protease inhibitor/RT inhibitor combination therapies, Trono believes they are needed in order to avoid or minimize the problem of drug resistance. He also believes that although gene therapies or antisense treatments are expensive at the moment, they are likely to be cheaper soon. And because they may have to be administered only once or twice, this may render them "ultimately more cost effective."

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