Oral bacterial vaccine

Oral vaccination methods are desirable in that user compliance is higher than with other routes of administration, and that most microbial pathogens use mucosal surfaces as sites of infection. Although recombinant bacteria have been effectively used as vaccine delivery systems, they must be attenuated for safe use. Robinson et al. (see pp. 622 and 653) have used *Lactococcus lactis*—a nonpathogenic, noninvasive, noncolonizing Gram-positive bacterium (as a vector for the delivery of a tetanus toxin antigen to demonstrate that this vector can effectively be used to elicit a protective level immune response in a mouse model when given orally.

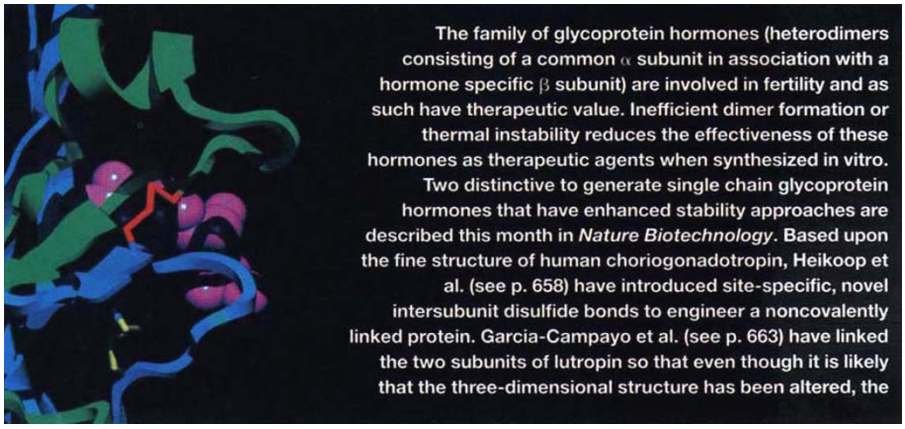
Making muscle into an APC

Professional antigen-presenting cells (APCs), such as dendritic cells, stimulate an immune response by presenting antigen in the context of MHC along with the proper constituency of costimulatory molecules. Immunization strategies have been designed so that target-specific antigens are presented via APC to generate immune surveillance. Although muscle cells can express antigen after inoculation with DNA, these cells do not possess the full complement of costimulatory molecules necessary for efficient antigen presentation. Kim et al. have found that by inoculating muscle cells with DNA encoding not only the antigen of choice but costimulatory molecules as well, T helper cell proliferation and a CTL could be generated (see pp. 619 and 641). Furthermore, they showed that CD86 was sufficient to turn muscle into an effective APC.

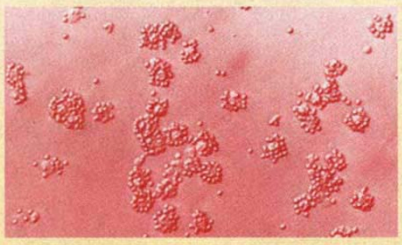
Long-life antibodies

Therapeutic antibodies, used for diagnosis and treatment of human disease, should not only bind specifically and with high affinity to the intended target, but should have a long enough serum half-life to facilitate in vivo targeting. Serum stability is mediated by the interaction of the antibody with the MHC-class I related receptor, FcRn. By randomly mutagenizing the known receptor interacting residues on IgG, Ghetie et al. were able to select mutants that not only had higher affinity for FcRn, but the desirable property of increased serum half-life as well (see pp. 617 and 637).

Research Briefs written by Philip Bernstein.



The family of glycoprotein hormones (heterodimers consisting of a common α subunit in association with a hormone specific β subunit) are involved in fertility and as such have therapeutic value. Inefficient dimer formation or thermal instability reduces the effectiveness of these hormones as therapeutic agents when synthesized in vitro. Two distinctive to generate single chain glycoprotein hormones that have enhanced stability approaches are described this month in *Nature Biotechnology*. Based upon the fine structure of human choriogonadotropin, Heikoop et al. (see p. 658) have introduced site-specific, novel intersubunit disulfide bonds to engineer a noncovalently linked protein. Garcia-Campayo et al. (see p. 663) have linked the two subunits of lutropin so that even though it is likely that the three-dimensional structure has been altered, the



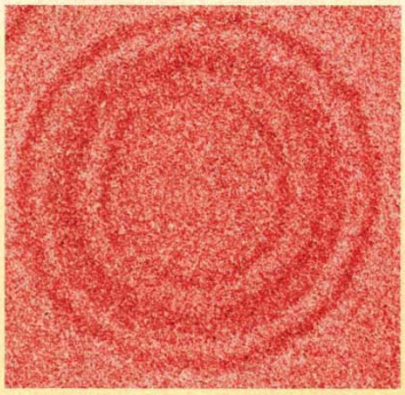
With the development of phage display technology came the advent of human monoclonal antibodies. These antibodies, unlike their natural counterparts, are produced as either single chain or Fab fragments. Although their small size gives them the potential therapeutic advantage of increased penetrability in vivo, the absence of an Fc portion makes them relatively unstable and prevents them from recruiting either cell- or complement-mediated effector functions, thus limiting their therapeutic potential. By engineering diabodies (see pp. 618, 620, and 632)—which are divalent antibody fragments—to target both an antigen of choice (with one arm) and either the first component of the complement cascade or serum Ig (with the other arm), a range of antibody effector functions can now be recruited by the fragments, offering new promise for immunotherapy.

Minimal NGF antagonist

By virtue of its interaction with a the tyrosine kinase receptor TrkA, nerve growth factor (NGF) has trophic effects on cells involved in neurodegenerative processes such as Alzheimer's disease and pain sensation. The design of small molecule mimetic agonists or antagonists have been dependent upon functional mapping of the NGF-TrkA interaction. By expressing the extracellular immunoglobulin-like domains of the TrkA receptor, Holden et al. have defined the functional epitope, showing that this domain is sufficient to bind to and inhibit that activity of NGF in vitro and in vivo (see pp. 623 and 668).

GLP-2: Between mice and rats

It is not always apparent why a pharmacoactive protein will be active in one species, but not another. The intestinotrophic peptide glucagon-like peptide 2 (GLP-2), isolated from rat, is active in mice, but has no trophic effects in rats. Its trophic activity makes GLP-2 an attractive therapeutic candidate for the treatment of Crohn's disease. Drucker et al. show that the enzyme DPP-IV cleaves GLP-2 at the aminoterminus, thus inactivating it (see p. 673). A synthetic GLP-2 analog, which is not cleavable by DPP-IV, retains the ability to increase small bowel mass in rats, suggesting that these analogs may be therapeutic candidates.



Non-viral DNA delivery vectors hold the promise of circumventing the immunogenicity inherent in viral-mediated gene delivery; however, these vectors cannot match the in vivo efficiency of their viral counterparts. A step toward that promise is described by Templeton et al. (see pp. 620 and 647) who, by altering the composition and formulation, show a novel liposome–DNA structure that is responsible for the 100-fold enhanced gene delivery. Furthermore, these lipids can be modified to allow them to target specific cells in vivo.