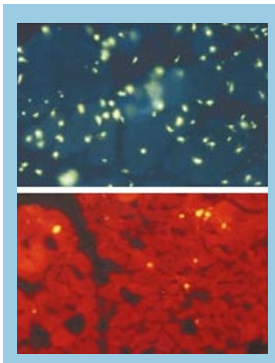
Engineering heparin-independent FGF

Fibroblast growth factor (FGF) family members play key roles in diverse cellular processes including differentiation, growth, and development. Fibroblast growth factor forms a complex with heparin and FGF receptors; however, without heparin, FGF is inactive and easily damaged by proteolysis, limiting its use in therapeutic applications such as wound treatment, gastric ulcers, and other injuries. In this issue, Yoneda et al. (see p. 641) describe an FGF analog engineered to circumvent the requirement for heparin. By fusing FGF-1 with the heparan sulfate proteoglycan (PG) core protein, they created a variant that could exert heparin-independent mitogenic activity, and that was protected from proteolytic degradation. Such an engineering approach may prove useful for other members of the FGF family and other heparin-binding molecules. *MS*



Gene therapy for Duchenne muscular dystrophy has failed to produce long-term stable expression of the dystrophin gene product because of difficulties in gene transfer and adverse immune responses. The recent successful use of chimeric oligonucleotides to repair sickle cell mutations in vivo prompted Bartlett and colleagues to test whether they could efficiently correct a frameshift mutation of the dystrophin gene in the skeletal muscle cells of affected dogs. The researchers designed a chimeric oligonucleotide that would revert a mutation in the splice acceptor site of an intron to the wild-type sequence in vivo, restoring the proper reading frame and production of the full-length gene product. They injected the chimeric oligonucleotide into skeletal muscle of a young affected male dog, and found that sustained repair of the chromosomal mutation could be detected for up to 48 weeks after treatment, along with synthesis of normal-sized dystrophin correctly localized to the sarcoplasmic reticulum. (See pp. 615 and 597). ***JJ***

This Month in Nature Biotechnology written by Natalie DeWitt, Judy Jamison, Andrew Marshall, and Meeghan Sinclair.

On page 630, Brenner et al. present a clever technology for sequencing 20-nucleotide-long stretches of genes—hundreds of thousands at a time. As a tool for global analysis of gene expression, the technique, called massively parallel signature sequencing (MPSS), may give DNA microarrays and "clone and count" methods like SAGE a run for their money. They started by constructing a cDNA library on the surface of a million microbeads, which they then immobilized in a flow chamber, where a series of solutions could wash over them, taking them through a series of cycles that make up the novel sequencing reaction. First an adapter sequence is ligated to the cDNA. It contains the binding site for *Bbv*I, a restriction enzyme that can reach over to the cDNA some distance from its binding site, and cleave it to expose a short bit of single-stranded sequence. Next, a single-stranded adapter binds to its complementary exposed sequence, followed by a set of fluorescent decoder oligonucleotides that reveal the identity of the bit of the cDNA sequence as the microbead flies past a detector. This is repeated for five cycles, providing enough sequence to identify the cDNA on each bead in the collection. The more a cDNA is represented, the more abundant is its expression in the cells from which the library was made. In addition to its impressively high throughput, MPSS has the advantages of detecting extremely rare genes, not requiring prior knowledge of gene sequences, and providing a statistically robust digital output. (See also p. 597) ***ND***

Metallothionein biomediator

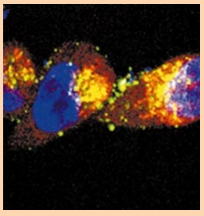
Soil remediation after heavy-metal contamination remains a serious challenge, and the promise of cheaper, more efficient, environmentally friendly methods is driving research into the use of microbes to immobilize these otherwise soluble pollutants. Valls et al. (p. 661) describe the engineering of the heavy metal-tolerant bacterium *Ralstonia eutropha* to display a mouse metal-binding metallothionein (MT) on its cell surface. Not only did the engineered bacterium efficiently gather cadmium ions from the soil, but it also protected tobacco plants from cadmium toxicity. *JJ*

A beetle biopesticide

In this issue, Kramer and colleagues show that transgenic maize expressing the egg white protein avidin is highly resistant toward many species of stored-product insect pests. This toxicity is mediated by avidin's ability to tightly bind to and sequester the essential coenzyme biotin, causing stunted growth and mortality in the insects. In anticipation of the potential use of transgenic avidin plants in food or feed production, Kramer et al. fed it to mice as their sole diet for three weeks but observed no ill effects (see p. 670). *JJ*

Surface vaccine combo

Live recombinant vaccines are capable of eliciting strong immune responses by colonizing host tissues and presenting antigens in this context. Until now, however, most surface display systems have been unable to present either large-sized antigens or multisubunit antigens. On page 645, Lee et al. use the bacterial ice nucleation protein (Inp) to display two different viral antigens, the hepatitis B surface antigen (HBsAg) and the core protein of hepatitis C virus (HCV), on the surface of *Salmonella typhi*. This was achieved by replacing the central repeating domain (CRD) of the Inp protein with the foreign antigens. Both intranasal and intraperitoneal vaccination of mice with the live bacteria elicited a strong immune response against these antigens. Significant increases in serum IgG antibodies to HBsAg and HCV core antigens were seen compared with *E. coli* expressing the antigen intracellularly. *MS*



Gene therapy approaches for treating cystic fibrosis have been stymied by the low efficiency of gene transfer to the airway epithelia. On page 635, Kreda et al. overcome this problem by retargeting a viral vector to a G protein-coupled receptor (GPCR) that is abundantly expressed in airway epithelial cells. They show that conjugation of a receptor's natural small-molecule agonist UTP will direct an adenovirus vector to a specific GPCR. Binding of the agonist to the receptor mediates internalization of the vector and gene transfer to the human airway epithelial cells. This approach potentially could be extended to other tissues by designing ligand–viral vector conjugates directed toward other tissue-specific GPCRs. ***MS***