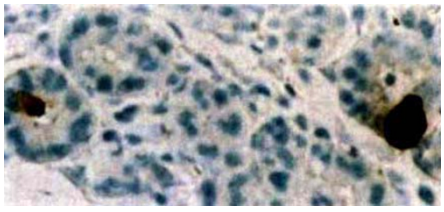
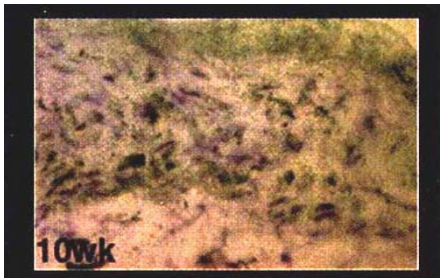
Tethering chemotherapy

Converting an inactive prodrug to a toxic compound specifically at a tumor is an attractive chemotherapeutic strategy. The scheme requires that the systematically delivered prodrug be taken up by cells that have been transformed with an enzyme not normally found in the patient. Thus bacterial enzymes that can convert the inactive prodrug CMDA to its toxic form have been targeted to tumors by newly developed delivery systems. In order to alleviate the necessity of prodrug cell permeability, Marais et al (see p. 1373) have shown that the converting activity can be targeted to the cell surface, rather than the interior. Cells with the enzyme on their surface are substantially more sensitive than those expressing the cytosolic form of the enzyme and were furthermore able to effectively kill their non-transformed neighbor cells—the so-called bystander effect. In a model mouse system, this strategy resulted in tumor regression and cure.



The use of gene therapy approaches for the systemic delivery of protein pharmaceuticals depends on the ability to manufacture the protein in vivo and deliver it to the circulatory system. Goldfine and colleagues (see p. 1378) show that, the pancreas, liver, and salivary glands—which are well suited towards the manufacture and secretion of proteins—can be coopted to this end. These authors demonstrate that DNA vectors can be delivered to these glands, in a relatively noninvasive manner by retrograde transport, such that either insulin or human growth hormone could be expressed in the relevant rat tissue and secreted into the blood with demonstrated therapeutic results.

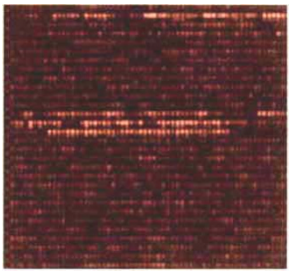


The rapid loss of potentially therapeutic genes delivered to the cutaneous epithelium has been a major obstacle in gene therapy protocols in human skin. By engineering self-inactivating retroviral vectors, in which the 5′ LTR is ultimately deleted allowing transcription to proceed via an internal promoter, Deng et al have been demonstrated durable cutaneous gene delivery in a mouse model (see p. 1388).

Research Briefs written by Philip Bernstein.

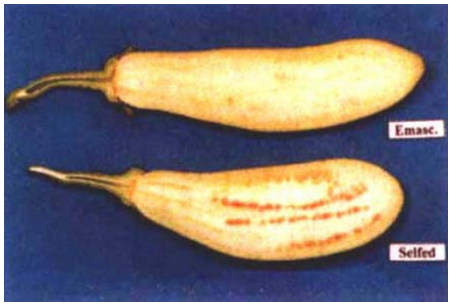
Measuring differential expression on a square inch

The use of genetic tools for the development of therapeutic strategies—functional genomics—requires genomic sequencing and expression profile analysis. With the sequencing of the entire genome of the model eukaryotic organism *Saccharomyces cerevisiae*, the first step was shown to be possible. Wodicka et al. (see pp. 1343 and 1359), have used the oligonucleotide DNA chip technology to accomplish the second step—massive differential analysis. Subsets of all genes, which were preferentially expressed when yeast were grown in either minimal or enriched media, were identified. While the functions for some of the identified genes are already known, the identity of many of the differentially expressed genes remains to be determined.



Persistent little genomes

Deletion of the genes encoding the immunogenic proteins of adenovirus should enhance its gene therapy potential. The creation of a minimized vector has allowed the efficient transduction of cells without associated toxicity, however the resultant vector was lost from the nucleus of the transduced cells negating one of the chief advantages of adenoviral vectors—genome stability. By coexpressing the E2-preterminal protein from the vector, or in trans, the episomal vector was stabilized while maintaining its lack of toxicity.



While seedless fruits and vegetables may be appealing to a subset of discriminating consumers, parthenocarpic plants have the potential to offer consistent quality fruit under a variety of environmental conditions in the absence of fertilization. Auxins (plant hormones) can be added, in place of their production in fertilized ovules, to support fruit growth. Rotina et al. (see pp. 1344 and 1396) have shown that by creating transgenic eggplant and tobacco that express an enzyme that leads to the production of auxin during early phases of fruit development, fruit setting and growth can be established in the absence of pollination.

Mimicking genotype analysis

Detecting single nucleotide polymorphisms is of more than just academic interest. The ability to detect single base changes in a high-throughput manner might allow disease detection prior to the appearance of a detrimental symptom. Peptide nucleic acid (PNA) mimics of DNA have higher affinity and better single nucleotide discriminating power than their DNA counterparts and do not require high salt for DNA binding. Griffin et al. (see pp. 1346 and 1368) have shown that these properties make PNA ideally suited as probes for mass spectrometry analysis by MALDI-TOF. By developing probes with different masses, single base pair differences can be easily determined in the rapid mass analysis afforded by this technology.

The latest in toxicological bioassays. A transgenic relative has been developed that expresses the human growth hormone (hGH) gene under the transcriptional control of the heat shock 70 promoter, which has been shown to respond to chemical stressors. Exposure to a toxic chemical results in the production and secretion of hGH into the bloodstream where it can easily be detected. hGH levels thus indicated the presence of a toxic compound. This assay does not require that the mouse be sacrificed.