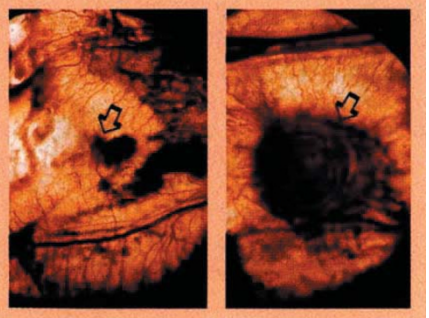
Tied up tumors



Using a soluble form of a signaling receptor, researchers at Duke University Medical Center have substantially reversed the process of angiogenesis in tumors. While the angiogenic signaling pathway has not been fully elucidated, it is known that the Tie2 receptor tyrosine kinase stabilizes newly formed blood vessels during development or tumorigenesis. Previous work had shown that mice lacking Tie2 die early in development from an inability to form blood vessels. The team at Duke, whose findings were reported in a recent issue of *Journal of Clinical Investigation* (100:2072–2078, 1997), grafted human mammary tumors to the backs of rats and bathed the tumors in a solution of truncated Tie2, which acted as a competitive inhibitor of the signaling pathway. Rats that received the treatment showed a 75% reduction in tumor size (left panel) compared with untreated controls (right panel). "[These are] the first data that demonstrate that the Tie2 family is involved in pathogenic states as well as normal angiogenic processes," says Kevin Peters, the study's principal investigator. Peters suggests that this approach could be used to drive a tumor into a dormant state while other therapies are applied to kill the tumor cells. Because angiogenesis is also involved in such disorders as arthritis and atherosclerosis, the technique could be broadly applicable.

Redux receptor subtype

Scientists have identified a receptor subtype localized solely in the brain through which the antiobesity drug Redux mediates appetite suppression. Redux (or *d*-fenfluramine) has recently been reported to have severe cardiac side effects and has been withdrawn from the US and European markets. An international team of researchers collaborating with a UK-based company Cerebrus (Wokingham, UK), presented evidence at the Annual Meeting of the Society for Neuroscience conference in New Orleans that mice lacking the 5-hydroxytryptamine (serotonin) receptor subtype 5-HT_{2C} are less sensitive to the effects of *d*-fenfluramine. By generating a mouse model with a targeted deletion of the 5-HT_{2C} receptor, they were able to study the effects of *d*-fenfluramine on food consumption and the stereotypical behaviors that accompany satiety. At a dose of 3 mg/kg *d*-fenfluramine, wild-type mice showed enhanced satiety and reduced food intake. In contrast, mice lacking the 5-HT_{2C} receptor were less sensitive to the satiety-inducing effects of the drug. According to Colin Dourish, Cerebrus's chief scientific officer, these results indicate that "the mechanism of action of *d*-fenfluramine is through the 5-HT_{2C} receptor, and because this receptor subtype is found only in the brain, future drugs can be developed to target specifically the 5-HT_{2C} receptor". Cerebrus is currently identifying potential drug candidates that are unlikely to exhibit Redux's adverse effects.

Research News Briefs written by Alan Dove and Margret Einarson.

Salmonella infusions

In an approach that seems counterintuitive, researchers at Yale University School of Medicine and Vion Pharmaceuticals (New Haven, CT) are developing an anticancer therapy that entails injecting live *Salmonella* bacteria into cancer patients. It has been known for some time that these bacteria will invade and destroy tumor cells, but the new study, employing attenuated strains, is the first to show tumor suppression by *Salmonella* without the danger of septic shock. The work, reported in *Cancer Research* (57:4537–4544, 1997), tested the effectiveness of bacteria in a mouse melanoma system. The researchers transformed the mutant bacteria with the herpes simplex virus thymidine kinase gene, resulting in specific expression of the enzyme inside the tumor, which could then be targeted with the antiviral compound ganciclovir. Nondividing healthy cells were unaffected. "Mice tolerate [the therapy] extremely well. . .they cure themselves of the bacteria [in] roughly a month." says David Bermudes, a researcher at Vion and an author on the paper. Not suprisingly, the idea of infecting a cancer patient with *Salmonella* has encountered some skepticism, but Bermudes is optimistic: "We really got some resistance early on, but we don't see resistance anymore. I would say it's changed into enthusiasm. . .there are no other cancer agents that have this therapeutic ratio of a thousand to one." Further work is needed to elucidate the mechanism by which *Salmonella* targets tumor cells. Vion hopes to begin clinical trials with the new therapy by the end of 1998.

Dystrophin gets stuffed

Duchenne muscular dystrophy, which affects one in 3,500 males in the US, is a tantalizing target for gene therapy. Unfortunately, the disease gene, dystrophin, is the largest human gene ever identified and does not fit into ordinary gene therapy vectors. To get around this difficulty, researchers at the University of Michigan have engineered a "gutted" adenovirus by deleting all but a few small segments of the viral genome, then inserting a dystrophin cDNA sequence driven by a muscle-specific promoter. In immunodeficient dystrophic mice, the recombinant virus carries the replacement gene to its target very efficiently. "We can perform a single injection into a mouse muscle and infect up to 90% of the muscles in that group," says Jeffrey Chamberlain, Associate Professor of Human Genetics at University of Michigan, who presented the results at the meeting of the American Society for Human Genetics in Baltimore on October 29th. The gene is expressed at high levels in the mice for at least three months after the initial infection. "The next step," he says, "is to test the virus in mice with a normal immune response."

Ex vivo gene therapy in the bag

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID; Bethesda, MD), the National Institutes of Health (NIH; Bethesda, MD), Baxter Healthcare (Deerfield, IL), and Cell Genesys (Foster City, CA) report the use of retroviral transduction into peripheral blood stem cells (PBSCs) for the treatment of chronic granulomatous disease (CGD), an immune deficiency caused by defects in the phagocyte NADPH oxidase (*PNAS* 94:12133–12138, 1997). Researchers delivered a gene encoding one of the NADPH oxidase subunits, $p47^{phox}$, into PBSCs from CGD patients, then injected the modified cells back into the patients. The corrected cells were detectable in the bloodstream up to six months after treatment, and the patients appeared more resistant to infection. The team used a new process for manipulating the cells in culture, utilizing sealed gas-permeable bags developed by Baxter Healthcare to reduce the chance of contamination and serum-free medium to avoid introducing foreign animal proteins into the patients. "I'm not aware of anyone who's used serum-free media in the application of gene therapy in the clinic for targeting stem cells. I think it's an important safety feature," says Harry Malech, deputy chief of the Laboratory of Host Defenses at NIAID.