Tiny microspheres release drugs slowly

The efficacy of many drugs hinges on their carefully timed delivery into the body. Some work best when administered continuously, while others prove most effective in repeated small doses.

Jeffrey L. Cleland, a chemist at Genentech in South San Francisco, and his colleagues have developed tiny capsules that slowly release compounds for specific periods of time. The scientists can design the beadlike microspheres to deliver a drug continuously or in pulses over a span ranging from a few hours to 6 months, Cleland said last week in San Francisco at a meeting of the Materials Research Society.

Made from poly(lactic-coglycolic) acid, already used safely in sutures that dissolve in the body, the microspheres carry delicate proteins and hormones for long periods without reducing their effectiveness — a problem that plagues other slow-release drug delivery systems, Cleland said. Measuring 10 to 40 micrometers, the tiny beads can be injected with an ordinary syringe.

The team sees the microspheres as most useful for drugs that patients need continuously and must inject frequently, such as insulin for diabetes or human growth hormone for dwarfism. Certain vaccines requiring sequential injections or boosters also make good candidates for microencapsulation, as do drugs to treat cancer or chronic illnesses — especially if the compounds cause toxicity in large doses or single injections.

To measure the release rate, the scientists entrapped a variety of agents in the microspheres and injected them into animals, ranging from mice to monkeys. Vaccines under investigation include ones for cholera, diphtheria, tetanus, hepatitis B, and rabies. The researchers are also testing human growth hormone, ordinarily injected daily or three times per week. In rhesus monkeys, the scientists find that injected microspheres release the hormone continuously for up to 1 month.

To use microspheres as potential immunity boosters against AIDS, Cleland's team has implanted in the capsules protein fragments from HIV-1 combined with an immunity-stimulating agent, QS-21. When injected into baboons, the two formulations together "exhibited the highest neutralizing antibody response to date," they report.

"For some formulations, the biological response was greater for the [microsphere-encapsulated] proteins than for the water soluble forms," says Cleland. "In the future, these protein formulations will be tested in human clinical trials and, if successful, will reach commercial use within the next 5 to 7 years." — *R. Lipkin*

Protein nips mouse tumors in the bud

Interleukin-12, the immune system messenger already showing great promise as a treatment for cancer, now appears to pack a double punch against tumors.

Judah Folkman, Emile E. Voest, and their colleagues at Children's Hospital in Boston, who already knew that IL-12 combats cancer by switching on the immune system's T cells, have found in tests with mice that "[IL-12] has another function. It inhibits or turns off new blood vessel growth," says Folkman. If tumors cannot grow new blood vessels, they can only reach a few millimeters in diameter.

Made by certain immune system cells, IL-12, a protein, normally circulates in the blood in low concentrations. Recently, it has sparked excitement among researchers by its ability to fight AIDS and parasitic infections, as well as cancer (SN: 8/20/94, p.120). Researchers have begun testing IL-12 as a cancer drug in humans.

But researchers have been puzzled by one finding, Folkman says. While IL-12 inhibits more than 20 kinds of tumors in mice, it doesn't kill tumor cells in laboratory dishes. This led his group to suspect that IL-12 curbs tumors indirectly, by slowing blood vessel growth, known as angiogenesis. They tested their idea by implanting a pellet containing a molecular growth factor in the corneas of mice.

This growth factor normally causes new blood vessels to creep across the cornea within days. Folkman's team found, however, that injections of IL-12 stopped new vessel growth almost completely — even in two mouse strains that have deficient immune systems and therefore lack T cells. "This is a very potent angiogenesis inhibitor," Folkman says.

His team then gave IL-12 to mice bred to develop lung tumors and found that "the tumors stopped at less than BB size." The group reports its results in the April 19 JOURNAL OF THE NATIONAL CANCER INSTITUTE.

Other tests showed that IL-12 doesn't shut off vessel growth directly. Rather, it switches on another immune system protein, interferon gamma, that may in turn activate a protein that stops endothelial cells from growing. Giving mice interferon gamma rather than IL-12 proved less effective, apparently because IL-12 triggers a continuous supply of the interferon.

Finally, IL-12 worked even better combined with a second antiangiogenic drug, suggesting that more than one inhibitor should be used in cancer therapy.

In an accompanying comment, Robert S. Kerbel of the Toronto-Sunnybrook Regional Cancer Centre notes that researchers are finding evidence that many conventional antitumor drugs may work in part by inhibiting angiogenesis. These results give "a whole new meaning to the term 'magic bullet' in cancer," Kerbel writes, because they could lead to a new way to target tumors while sparing normal cells. "It's becoming an extremely hot topic," he says.

— *J. Kaiser*

Fetal cells thrive in a Parkinsonian brain

Researchers have long suspected that transplanting fetal nerve cells could help people with Parkinson's disease, a neurological disorder characterized by a shuffling, unsteady walk. But they lacked direct proof.

A report in the April 27 NEW ENGLAND JOURNAL OF MEDICINE confirms that fetal nerve cells can beneficially set up shop in the adult brain. "It's really the first case of its kind," says lead author Jeffrey H. Kordower of Rush-Presbyterian-St. Luke's Medical Center in Chicago.

Kordower and his colleagues studied a 59-year-old man who suffered from advanced Parkinson's disease, a disorder that results from the destruction of cells originating in the brain's substantia nigra region. These nerve cells release the neurotransmitter dopamine, which is involved in regulating movement and emotional responses.

Kordower's team transplanted dopamine-producing nerve cells from donated tissue from aborted fetuses into the man's brain. The patient's motor function improved significantly, Kordower says. "He still had Parkinson's disease, but many of his problems had completely dissipated."

For reasons unrelated to the transplant, the man died 18 months later.

The researchers performed an autopsy and found that "the fetal cells survived in large numbers," Kordower says. The transplanted neurons had sent out long, fiberlike extensions that released dopamine, he adds.

"It is of paramount importance to determine whether the survival of implanted cells and the clinical improvement will be even longer-lasting in other patients," add Barry J. Hoffer and Craig van Horne of the University of Colorado Health Sciences Center in Denver. Hoffer and Horne wrote an editorial that appeared in the same issue of the journal. — *K. Fackelmann*