SCIENTISTS SEND IN THE SMALL GUNS TO HELP BLOW AWAY BRAIN CANCER

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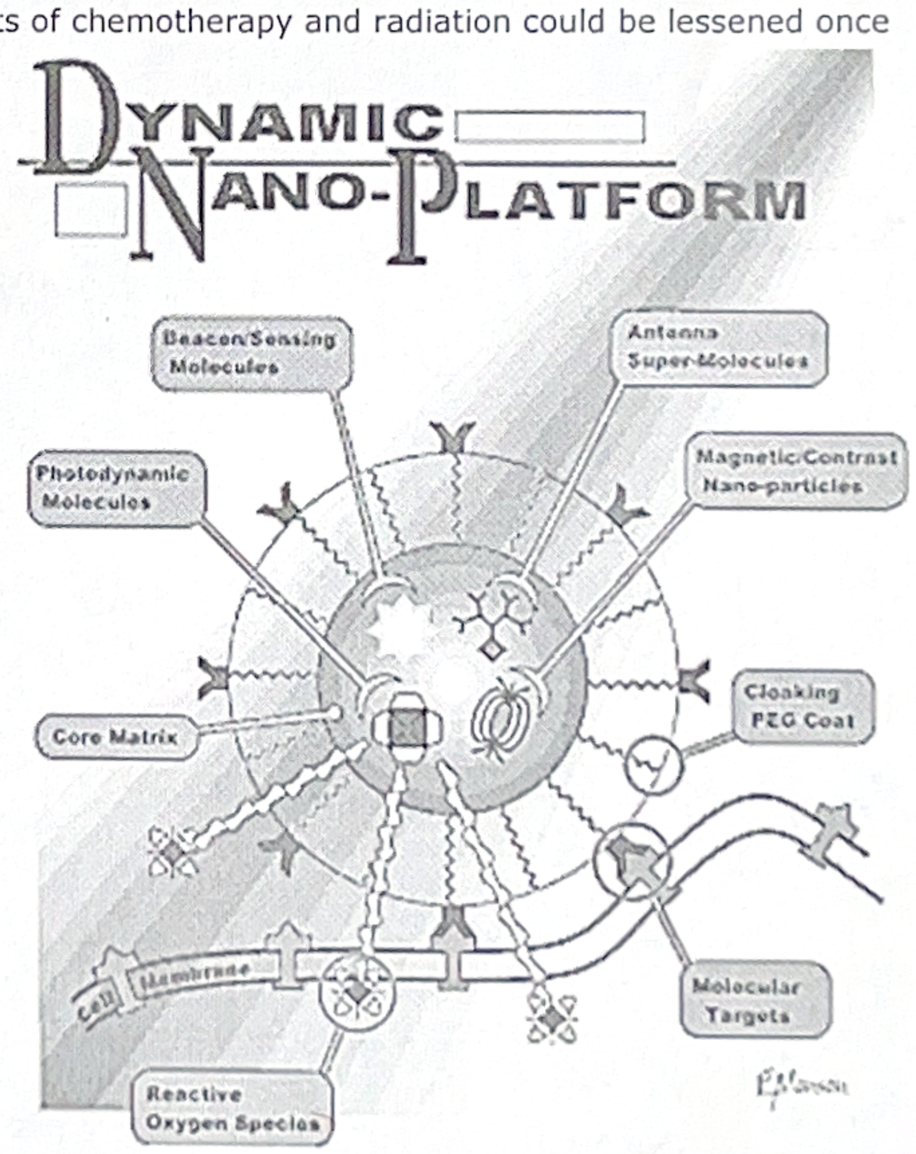
Sept. 28, 2001 – Two federally funded research efforts are developing ways to use nanotechnology in removing tumors and other cancerous cells in the brain.

Techniques like these could lessen risks associated with traditional brain surgery – such as loss of cognitive ability, hearing, speech and other functions.

The often-debilitating side effects of chemotherapy and radiation could be lessened once nanoparticles hunt down and destroy cancer cells too small to locate and remove surgically, predict scientists working under two grants funded by the National Cancer Institute's Unconventional Innovations Program.

At the University of Michigan, Raoul Kopelman, a chemistry and physics professor, and Martin A. Philbert, associate professor of toxicology, are developing nanoparticles with a magnetic core and a plastic outer coating. The particles are attached to a cancer antibody or another tracer molecule that attract cancer cells. The particles are also affixed with a nanopacket of a substance akin to dye that makes them highly visible on magnetic resonance imaging (MRI).



This illustration shows University of Michigan professors Raoul Kopelman's and Martin A. Philbert's proposed extensions of their technology. They eventually want to incorporate magnetic and optical control and contrast elements to enable a number of functions, from biological sensing to targeted photo dynamic cancer therapy.

The miniscule size of the particles – 20 to 200 nanometers – allows them to go into areas of the brain that would otherwise be severely damaged by invasive surgery. Normally, the blood-brain barrier would prevent the nanoparticles from entering the brain. But when cancer is present, the barrier is weakened and a bit diffuse. This allows the nanoparticles to seep into the areas of the brain affected by cancer.

"As long as we keep the nanoprobes down to 200 nanometers they can cross the compromised barrier into the tumor," said Philbert. "But they will not cross into healthy brain."

The contrast agents that are attached to the nanoparticles allow MRI to see a few small tumor cells in the brain, said Kopelman, who received a National Cancer Institute contract for $3.4 million. The goal is to use the nanoparticles with their affixed cancer antibodies to detect and latch onto cancer cells as small as 50 microns. Depending on the type of cancer, the cells can range from 5 to 50 microns each.

To prevent the body's immune system from destroying the particles, Kopelman cloaks them with polyethylene glycol, a biologically friendly plastic. Once the nanoparticles latch onto cancer cells and are detected by MRI, a laser zaps them. The nanoparticles enhance the killing effect of the laser.

The American Cancer Society estimates that by the end of 2001, there will be 17,200 new cases of cancers of the brain and other parts of the nervous system. Of those, about 13,000 cases are expected to result in death.

After tumors are surgically removed from patients with brain or any type of cancer, subsequent treatment often includes chemotherapy and radiation. Micron-sized cancer cells sometimes are not visible to surgeons because they grow in locations separate from the tumor site. Chemotherapy and radiation kill cancerous cells but they also destroy healthy cells. By using nanoparticles, the killing agents can be made to directly attack only the sick cells.

Kopelman said that his project is at least three years away from clinical trials. "We want to prove in two years that it works on rats."

The Unconventional Innovations Program funds high-risk, high-impact technology, said Carol Dahl director of the institute's Office of Technology and Industrial Relations. "We're stepping outside the box. The intent of the program is to create a platform technology that looks at the very early stages of cancer inside the living body and respond to get sufficient information for diagnosis and target for intervention."

In another broad-applications project that is roughly similar to Kopelman's, the NCI granted $2 million to Gregory Lanza, Sam Wickline and a team of nearly 30 researchers at Washington University in St. Louis, Mo.

The big difference with their research is that their nanoparticles are attracted not to the cancer cells, but to the newly forming capillaries that deliver blood to solid tumors. The capillaries emit a protein that becomes the target for the nanoparticles. The nanoparticles circulate through the bloodstream carrying an antibody for the protein and when they bump into the complementary protein, they attach to the wall of the blood vessel. Then they slowly effuse a payload of chemotherapy into the capillary membrane.

"It can be very effective," said Lanza, assistant professor of medicine and bioengineering. "When you target a site, you know it's there. It can be detected with MRI."

In addition to primary-site brain cancer, the technology will be important for cancers that metastasize, or spread to other parts of the body. In many patients, particularly those with breast cancer, the cancer can metastasize even after the original cancer tumor has been removed. The nanoparticles traveling in the bloodstream would be able to locate additional cancer sites.

"We're going after smaller tumors," Lanza said. "Our goal is to stop the blood vessels that are feeding the cancer. At that point, the tumor will either stop growing or become weakened and more vulnerable to more conventional therapy or systemic drugs. So now you could have therapy with an 80 percent to 90 percent lower dose – that's our goal."

Dahl said that both of the technologies are geared for "whole body applications."

"You're not extracting a piece of tissue or specimen. And you're doing it in real time. It would be less offensive to the patient," she said.

Lanza's research is in the early stages and has only been demonstrated in animals.

Lanza said the nanoparticles were initially developed to prevent stroke and heart attacks by locating loose plaque in blood vessels and detecting tiny blood clots in the cardiovascular system. The technology may also be used to prevent arteries from

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narrowing after they have been surgically opened. Re-narrowing negates the benefits of coronary angioplasty in about 30 percent of cases.

To take the technology out of the research lab and into the market, Lanza and colleague Wickline formed Kereos Inc. last year and received a seed-stage investment of $350,000 from RiverVest Venture Partners. Thomas C. Melzer, managing director of RiverVest, said that one of the short-term obstacles Kereos faces is identifying antibodies or other tracer molecules that would be used to target to disease sites in the body.

But, he said, "In terms of private equity investing, it's a good a time to be investing in technologies that have a lot of long-term promise as we think this one does." Melzer plans to lead a second round of investing within one year.