

New Cancer Treatment Shows Promise in Testing, The New York Times, June 29, 2009

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A new method of attacking cancer cells, developed by researchers in Australia, has proved surprisingly effective in animal tests.

The method is intended to sidestep two major drawbacks of standard chemotherapy: the treatment's lack of specificity and the fact that cancer cells often develop resistance.

In one striking use of the method, reported online Sunday in *Nature Biotechnology*, mice were implanted with a human uterine tumor that was highly aggressive and resistant to many drugs. All of the treated animals were free of tumor cells after 70 days of treatment; the untreated mice were dead after a month.

The lead researchers, Jennifer A. MacDiarmid and Himanshu Brahmhatt, say their company, EnGeneIC of suburban Sydney, has achieved a similar outcome in dogs with advanced brain cancer. "We have been treating more than 20 dogs and have spectacular results," Dr. Brahmhatt said. "Pretty much every dog has responded and some are in remission." These experiments have not yet been published.

Cancer experts who were not involved with the research say that the new method is of great interest, but that many treatments that work well in laboratory mice turn out to be ineffective in patients.

Bert Vogelstein, a leading cancer researcher at Johns Hopkins University, called the method "a creative and promising line of research," but noted the general odds against success.

"Unfortunately our track record shows that far less than 1 percent of our promising approaches actually make the grade in patients," he said.

The EnGeneIC researchers said they had conducted successful safety tests in a large number of monkeys and will start safety trials in patients with all kinds of solid tumors in three Melbourne hospitals next month. They said they had discussed licensing their technology with large pharmaceutical companies and others.

Stephen H. Friend, head of cancer research at Merck until early this year, said he had been following EnGeneIC's work for more than a year, and praised the company for trying a method that others had written off without trying.

"I consider the approach is remarkable and more than intriguing," said Dr. Friend, who is now at Sage Bionetworks in Seattle. But he warned that cancer cells are very versatile and can "evolve around any pressure you put on them," so that no single approach is likely to afford a cure.

The EnGeneIC method uses minicells to deliver a variety of agents to tumor cells, including both anticancer toxins and mechanisms for suppressing the genes that make tumors resistant to toxins.

The minicells are generated from mutant bacteria which, each time they divide, pinch off small bubbles of cell membrane. The minicells can be loaded with chemicals and coated with antibodies that direct

them toward tumor cells.

No tumor cell, so far as is known, produces a specific surface molecule for toxins to act on. But 80 percent of solid tumors have their cell surfaces studded with extra-large amounts of the receptor for a particular hormone, known as epidermal growth factor.

The minicells can be coated with an antibody that recognizes this receptor, so they are more likely to attach themselves to tumors than to the normal cells of the body. The tumor cells engulf and destroy the minicells, a standard defense against bacteria, and in doing so are exposed to whatever cargo the minicells carry.

What also helps direct the minicells toward tumors, the EnGeneIC researchers say, is that the blood vessels around tumors tend to be leaky, and the minicells are small enough to leave the circulation at the leak sites.

The minicells do not seem to be highly provocative to the immune system, even though they are made of bacterial cell membrane. The reason may be that the provocative parts of the membrane are masked by antibodies with which the minicells are coated, Dr. Brahm bhatt said.

In the experiments reported Sunday, EnGeneIC treated cancer-ridden mice with two waves of minicells. The first wave contained an agent that suppressed an important gene for toxin resistance. The gene makes a protein that pumps toxin out of cells, and is a major cause of the resistance that tumors often develop toward chemotherapeutic agents.

After the toxin-expelling gene had been knocked down in the tumor cells, the EnGeneIC researchers injected a second wave of minicells, each loaded with half a million molecules of doxorubicin, a toxin used in chemotherapy.

The two-wave treatment arrested tumor growth in mice implanted with either human colon or human breast tumors, and enabled mice with drug-resistant human uterine tumors to eliminate the tumors altogether.

"The technology looks very good," said Bruce Stillman, president of the Cold Spring Harbor Laboratory on Long Island. It provides a general method of delivering chemicals to tumors, he said, especially those that are usually degraded in the bloodstream.

Dr. Stillman, who has advised EnGeneIC and is a co-author of its report, said the minicells could be particularly helpful for delivering silencing RNAs, a promising new class of drug that is rapidly destroyed in the body unless protected.

Though the minicells can be varied to attack different receptors and to import any gene of interest on elements called plasmids, the method still has several hurdles to jump.

Robert M. Hoffman, of the University of California, San Diego, said that the minicells were "good strategy and good science" but that the researchers had implanted the human tumors under the mice's skin, a position from which they do not usually spread through the body. So the experiments do not answer the question of whether minicells can attack metastasized cancer, he said.

Dr. Hoffman, who is president of AntiCancer Inc., has obtained striking remissions with metastasized cancers in mice by treating them with salmonella bacteria. The bacteria have been engineered to lack

two kinds of amino acid, which makes them unable to grow in normal tissues. In cancer cells, however, where the missing amino acids are in more plentiful supply, the bacteria are highly virulent and kill the cells.

The idea of treating cancer with bacteria goes back to the 19th century, when physicians noticed that cancer patients who became infected sometimes enjoyed a remission. Both Dr. Hoffman's method and the minicells, in different ways, revisit these old observations. Both may face special scrutiny from regulators concerned at the prospect of putting bacteria into people.

Dr. Hoffman said his studies with the defective bacteria were going well and that his company might be ready to start a safety test in patients in two years if it can find a good partner. Use of bacteria in cancer "is an old story but there is definitely a lot of promise there," he said.

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