'Molecular grenade': Drug from Mediterranean weed kills tumor cells in mice

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Scientists at the Johns Hopkins Kimmel Cancer Center, working with Danish researchers, have developed a novel anticancer drug designed to travel -- undetected by normal cells -- through the bloodstream until activated by specific cancer proteins. The drug, made from a weedlike plant, has been shown to destroy cancers and their direct blood supplies, acting like a "molecular grenade," and sparing healthy blood vessels and tissues.

In laboratory studies, researchers said they found that a three-day course of the drug, called G202, reduced the size of human prostate tumors grown in mice by an average of 50 percent within 30 days. In a direct comparison, G202 outperformed the chemotherapy drug docetaxel, reducing seven of nine human prostate tumors in mice by more than 50 percent in 21 days. Docetaxel reduced one of eight human prostate tumors in mice by more than 50 percent in the same time period.

In a report June 27 in the journal *Science Translational Medicine*, the researchers also reported that G202 produced at least 50 percent regression in models of human breast cancer, kidney cancer and bladder cancer.

Based on these results, Johns Hopkins physicians have performed a phase I clinical trial to assess safety of the drug and have thus far treated 29 patients with advanced cancer. In addition to Johns Hopkins, the University of Wisconsin and the University of Texas-San Antonio are participating in the trial. A phase II trial to test the drug in patients with

prostate cancer and liver cancer is planned.

The drug G202 is chemically derived from a weed called Thapsia garganica that grows naturally in the Mediterranean region. The plant makes a product, dubbed thapsigargin, that since the time of ancient Greece has been known to be toxic to animals. In Arab caravans, the plant was known as the "death carrot" because it would kill camels if they ate it, the researchers noted.

"Our goal was to try to re-engineer this very toxic natural plant product into a drug we might use to treat human cancer," says lead study author Samuel Denmeade, M.D., professor of oncology, urology, pharmacology and molecular sciences. "We achieved this by creating a format that requires modification by cells to release the active drug."

By disassembling thapsigargin and chemically modifying it, the researchers created a form that Denmeade likens to a hand grenade with an intact pin. The drug can be injected and can travel through the bloodstream until it finds the site of cancer cells and hits a protein called prostate-specific membrane antigen (PSMA). PSMA is released by cells lining tumors of the prostate and other areas, and in effect "pulls the pin" on G202, releasing cell-killing agents into the tumor and the blood vessels that feed it, as well as to other cells in the vicinity. Specifically, G202 blocks the function of a protein called the SERCA pump, a housekeeping protein necessary for cell survival that keeps the level of calcium in the cell at the correct level, the researchers report.

"The exciting thing is that the cancer itself is activating its own demise," says senior study author John Isaacs, Ph.D., professor of oncology, urology, chemical and biomedical engineering at Johns Hopkins.

Because the drug is targeted to the SERCA pump, which all cells need to stay alive, researchers say it will be difficult for tumor cells to become

resistant to the drug, because they cannot stop making the protein.

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