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Researcher creates patented personalized therapy that causes cancer cells to kill themselves

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A Wayne State University School of Medicine physician-researcher has developed a personalized therapy to treat a wide range of cancers. The treatment is based on a naturally occurring human enzyme that has been genetically modified to fool cancer cells into killing themselves.

The unique concept, patented by Wayne State University, was successfully demonstrated on melanoma cells that are resistant to routine treatments such as chemotherapy or radiotherapy. Melanoma is a perfect model for testing this new therapy because it is considered the most aggressive form of human cancer due to its many defense mechanisms against available treatments. The success of the therapy in killing melanoma suggests a similar outcome in treating other cancers.

Developed by Karli Rosner, M.D., Ph.D., assistant professor and director of Research in the Department of Dermatology, the method uses genetic constructs that contain a genetically modified enzyme -- DNase1 protein -- to seek out and destroy cancer cells. The novel technology was published in the article "Engineering a waste management enzyme to overcome cancer resistance to apoptosis: adding DNase1 to the anti-cancer toolbox" in the Jan. 14 online edition of Cancer Gene Therapy, a Nature Publishing Group journal.

Dr. Rosner modified the genetic code for DNase1, a highly potent DNA-degrading enzyme, and altered its genetic composition by deleting a part

of the code, mutating another part and adding an artificial piece of code. Through these changes, the altered DNA program is translated into a modified protein. In contrast to the natural protein, the modified protein will not be eliminated from the cancer cell, will resist deactivation by cell inhibitors and will gain access to the cell's nucleus. "If you imagine the cell's nucleus as a computer and DNA in the nucleus as computer software," Dr. Rosner explained, "then the altered, hacked DNA program corresponds to a computer virus."

"To further understand this anti-cancer technology," he continued, "recollect the plot from the movie, Independence Day. In this movie, a computer virus is introduced into an alien ship to neutralize its defenses and make it vulnerable to external weapons. We do something similar but much better by introducing the altered genetic code of DNase1 into the DNA of cancer cells alien to the healthy body." The cancer cell, unaware of the destructive potential of the modified code, translates it into a protein that evades the cell's defense mechanisms and enters the nucleus. In the nucleus, the protein damages DNA by chopping it into fragments without the need for external weaponry, i.e., other medications. Following damage to DNA, the cell's organelles disintegrate and the cancer cell dies. In this way, Dr. Rosner's technology leads cancer cells into committing suicide because he fools them into generating the protein that will cause their own death.

The beauty of this therapy is that specifically-targeted cancer cells destroy themselves through the physiological mechanism of apoptosis, leaving surrounding healthy cells intact. This mode of cancer cell elimination leaves no residual debris to alert the immune system to kick in, essentially committing "the perfect crime," Dr. Rosner said. This is important because the many side effects of current anti-cancer treatments are attributed to activation of the immune system. The fact that this therapy does not require participation of the patient's immune system to kill cancer cells is a big advantage over other newly developed

technologies, such as the cancer vaccine. Those technologies depend on the patient's immune system to destroy cancer. Unfortunately, they are not effective in the presence of a compromised immune system, which is true for many cancer patients. In contrast, Dr. Rosner's therapy will be able to treat even the most severely immuno-compromised patients with the same degree of success as in treating patients with a fully functional immune system.

Patients with the same cancer type vary in their response to identical treatment because the biological characteristics of the same cancer type usually differ between patients. As a result, the medical field strives to develop treatments that can be adjusted to each patient. The structure of Dr. Rosner's technology is flexible in that it contains Lego-like pieces that together form a genetic construct. Each piece can be replaced by one of several other genetic pieces that perform the same task, but differ slightly in their genetics. The multiple options available for each genetic piece will allow the physician to tailor the finalized treatment to each patient based on the unique characteristics of his or her cancer. In this way, the new technology is a "true personalized therapy" he said. The physician will expose a patient's cancer cells obtained by biopsy, to various genetic constructs to identify the version of therapy that kills the patient's cancer with the utmost efficiency.

Of particular importance is the potential for this technology to treat a large variety of tumors, such as prostate, lung and breast cancers. Dr. Rosner likened the therapy to the military's Tomahawk missile platform. The Tomahawk is directed to its target by programming the missile's homing device. Likewise, the destructive genetic construct can be targeted to a particular cancer type by incorporating a genetic piece that specifically identifies the cancer. Multiple genetic homing devices will be at the physician's disposal. The ability to target the therapy specifically to cancer cells will reduce side effects common with today's anti-cancer therapies. Moreover, the ability to target multiple cancers

will immensely increase the number of cancer patients who will benefit from the new technology.

The one side effect that Dr. Rosner foresees is the potential for lightening of skin hue at a level that he cannot predict, but that's a tradeoff someone suffering from metastatic cancer and given a limited prognosis may accept in exchange for becoming cancer-free.

To date, Dr. Rosner has demonstrated cancer cell kill rates of 70 to 100 percent with his first generation of "gene suicide therapy." To further increase the killing efficiency, he has recently designed a second generation of constructs. In the near future he intends to test the therapy in an animal model, an intermediate step required before moving the treatment into clinical trial.

"Although this has been tested on melanoma cell lines, Dr. Rosner's approach can be tailored to other types of tumors," said Darius Mehregan, M.D., the Hermann Pinkus Chair of the Department of Dermatology. "I think it is important for other researchers in the Wayne State University system to be aware of possibilities to collaborate, and for the pharmaceutical industry to be aware of the economic potential of this novel technology."

More information: To read the complete study, visit www.nature.com/cgt/journal/vao … full/cgt201084a.html

Provided by Wayne State University