Columbia research lifts major hurdle to gene therapy for cancer

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Researchers at Columbia University Medical Center have discovered a way to overcome one of the major hurdles in gene therapy for cancer: its tendency to kill normal cells in the process of eradicating cancer cells. In a new study published in the Jan. 25 issue of the Proceedings of the National Academy of Sciences (PNAS), the researchers demonstrated that the technique works by incorporating it into a specially designed virus. The virus eradicated prostate cancer cells in the lab and in animals while leaving normal cells unscathed.

Gene therapy based on the new technique should also be effective for a wide range of tumors - such as ovarian, breast, brain (glioma), skin (melanoma) and colon cancer - because the virus is constructed to exploit a characteristic of all solid cancers.

"What's exciting is we may now be able to design a therapy that will seek out and destroy only cancer cells," said the study's senior author, Paul B. Fisher, Ph.D., professor of clinical pathology and Michael and Stella Chernow Urological Cancer Research Scientist at Columbia University Medical Center. "We hope it will be particularly powerful in eradicating metastases that we can't see and that can't be eliminated by surgery or radiation. Gene therapy, especially for cancer, is really starting to make a comeback."

The virus's selectivity for cancer cells is based on two molecules called PEA-3 and AP-1 that, the researchers found, are usually abundant inside cancer cells. Both of the molecules flip a switch (called PEG) that turns

on the production of a cancer-inhibiting protein uniquely in tumor cells.

The researchers say the PEG switch can be exploited to produce gene therapies that will only kill cancer cells even if the therapy enters normal cells.

As an example, the researchers constructed an adenovirus that carries the PEG switch and a toxic protein. The switch and the protein were connected to each other so that the deadly protein is only unleashed inside cancer cells when the switch is flipped on by PEA-3 or AP-1.

When added to a mix of normal and prostrate cancer cells, the virus entered both but only produced the toxic protein inside the cancer cells. All the prostrate cancer cells died while the normal cells were unaffected.

The same virus also selectively killed human cancer cells from melanoma and ovarian, breast, and glioma (brain) tumors.

Dr. Fisher's team is now altering the virus and developing additional viruses based on the PEG switch for use in clinical trials with patients. Other investigators associated with the PNAS study include Drs. Zao-zhong Su (research scientist), Devanand Sarkar (associate research scientist) and Luni Emdad (postdoctoral research scientist) in Dr. Fisher's group; Drs. Gregory J. Duigou (associate research scientist) and C. S. Hamish Young (professor) in the Department of Microbiology (Columbia University Medical Center); and Dr. Joy Ware (professor), Mr. Aaron Randolph (graduate student) and Dr. Kristoffer Valerie (professor) at Virginia Commonwealth University, Richmond, VA.

Source: Columbia University College of Physicians and Surgeons