Study Shows Liver an Excellent Target For Cancer Gene Therapy Using Viral Vectors

February 13, 2007 |

A featured paper in the February issue of the research journal *Cancer Gene Therapy* demonstrates that cancer cells in the liver are excellent targets for gene therapy using adenoviral vectors, based upon a fundamental new understanding of the differences between cancerous and normal liver cells. The findings signal a new way to treat cancers that have spread to the liver, such as metastatic cancers of the colon and breast.

The research team, led by Tony Reid, M.D., Ph.D., of the Moores Cancer Center at University of California, San Diego (UCSD), reports that in normal liver cells there is only one receptor – or doorway the vector uses to enter the cell. This doorway is located at the base of normal liver cells, hidden from the blood vessels. The research also demonstrates that in cancerous cells the receptor for adenovirus, called the coxsackie-adenoviral receptor or CAR, is expressed randomly over the surface of the cell and is exposed to the blood vessels.

"Since the receptor is distributed randomly on the surface of tumor cells, the doorway is open for the adenoviral vectors circulating in the blood stream to infect and kill these cells," said Reid, who was at Stanford University when this work was conducted. "At the same time, normal liver cells are protected. These findings may signal a new way to treat any cancer that has spread to the liver."

Reid explained: "We are taking advantage of a fundamental characteristic of cancer cells – structural disorganization. The disorganized structure of the cancer cells exposes the receptors so that Onyx-015, the adenoviral vectors used in this study, can readily enter tumor cells. This may be the first time a therapy has been directed against the disorganized nature of cancer cells."

Reid and his colleagues undertook this study following the death of Jesse Gelsinger, a participant in a gene therapy clinical trial at University of Pennsylvania for ornithine transcarbanoylase (OTC) deficiency, a metabolic liver disorder. That case virtually stopped gene therapy research and spawned widespread safety concerns about gene therapy involving the liver.

"At that time, I was treating patients with colon cancer that had spread to the liver using a very similar adenoviral vector administered in exactly the same way – direct infusion into the main

artery feeding the liver," said Reid, who is now an associate professor of clinical medicine in the UCSD School of Medicine. "We saw virtually no problems with toxicity in 35 study participants who received a total of nearly 200 infusions across several study sites."

So Reid and colleagues carefully re-analyzed the data from the 17 participants from the Stanford site to determine the impact of repeated adenoviral exposure on liver function, and documented that there were no significant problems. While the analysis was not designed to demonstrate impact on disease, it showed that seven of the 17 patients had stable-to-improving disease at the completion of four viral infusions. The researchers then demonstrated that normal liver cells could not be infected with an adenovirus, which led them to investigate where the receptor was located. They found it hiding at the junction between liver cells and proved that it was inaccessible from the blood flow in the liver. From there they showed that cancer cells had lost structural polarity, resulting in random distribution of CAR receptors on their surface, thereby allowing the virus to attach to and infect the tumor cells.

"In the process of proving that liver toxicity is not an issue in gene therapy, we have also shown that cancer cells metastatic to the liver are a perfect target for gene therapy because the cancer cells, but not the normal liver cells, are infected by the adenoviral vector," said Reid. "We also found that other cancer cells, including those from the breast, pancreas and prostate, are readily infected by adenoviral vectors indicating disorganized expression of the CAR receptor in these tumor cells. We believe these findings may have important implications across several types of cancer."

The researchers emphasized that while this study demonstrates that adenoviral vectors can be used to deliver targeted therapies and can be a useful tool for the treatment of cancer, further clinical trials are needed.

Co-authors besides Reid are Tina Au, Steve Thorne and Daniel Sze of Palo Alto Veteran's Administration Health Care System and Stanford University; W. Michael Korn of the University of California, San Francisco; and David Kirn of Oxford University, Jennerex Biotherapeutics, San Francisco.

To download a copy of the paper, **click here.** (Adobe Acrobat required)

Media Contact: Nancy Stringer, 619-543-6163, nstringer@ucsd.edu

---

Related Specialties

Gastrointestinal Cancer Unit

UCSD Moores Cancer Center

Share This Article

Related News

UC San Diego Health Begins Treating Multiple Myeloma with CAR T-cell Therapy
6/3/2021

Social Justice as Part of the Remedy for What Ails Us
6/3/2021

Diet Plays Critical Role in NASH Progressing to Liver Cancer in Mouse Model
6/1/2021

Noted Researcher and Scientific Leader Jack E. Dixon Retires
5/27/2021

View All News >

Follow Us

Follow @ucsdhealth