Oncolytic Viruses Take Step Forward

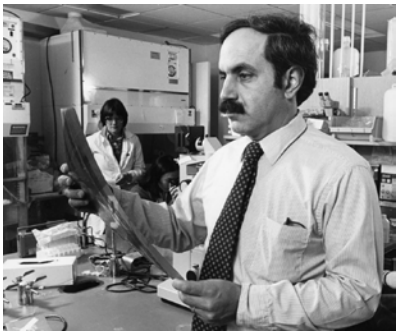
In current clinical trials, viruses engineered to target cancer cells must be delivered directly into tumors. But David Kirn, CEO of Jennerex, Inc., says that to become broadly useful as cancer treatments, they must be given systemically with an IV—allowing them to reach even metastatic tumors. Jennerex recently announced a major step toward that goal, demonstrating that an oncolytic virus delivered intravenously can selectively target and replicate in metastatic solid tumors in humans, and deliver multiple transgenes to the tumor tissue (Nature 2011;477:99–102).

The therapy, called JX-594, is an oncolytic poxvirus derived from a vaccinia vaccine. The treatment is designed to seek and destroy cancer cells, as well as stimulate an immune response against them. It has been altered to replicate selectively in cancer cells and carries two transgenes: one encoding a protein that stimulates the immune system, and another that serves as a marker for detecting viral activity.

In a phase I dose-escalation trial in 23 patients with advanced metastatic solid tumors that had failed other treatments, biopsies taken several days after treatment demonstrated that 87% of patients were positive for JX-594 when given at higher doses. The results add to previous trials demonstrating the efficacy of the therapy when injected directly into tumors.

The company is now involved in a phase II trial in patients with end-stage liver cancer. The next big question is whether the drug will remain effective over time when given systemically. ■

BATTLES IN THE WAR ON CANCER: ON/OFF SWITCHES



Whitehead Institute for Biomedical Research

Robert A. Weinberg, shown here circa 1985, is one of several investigators who played key roles in the discoveries of *RAS* and *RB1*.

In the mid-1970s, retrovirus experiments by Harold E. Varmus and J. Michael Bishop demonstrated that cancer-causing virus genes are normal genes that are manipulated by the virus. Inspired by that finding, several researchers—including Mariano Barbacid, Geoffrey M. Cooper, Robert A. Weinberg, and Michael H. Wigler—combed through cancer-causing genes in the genome of cancer cells.

"We were looking for any activity that might transform a normal cell into a cancer cell," recalls Channing J. Der, PhD, then a post-doc in Cooper's lab and now a pharmacology professor at University of North Carolina, Chapel Hill. Der was tasked with teasing out 30 possible oncogenes from retroviruses. "No one really thought that these genes were the very same genes identified a decade earlier in oncogenic retroviruses," he says. But in 1982, after performing dozens of experiments, Der and Cooper realized they had uncovered *RAS*, the first human oncogene. The same discovery happened almost simultaneously in the other researchers' labs.

"It was a revolutionary discovery," says Allan Balmain, PhD, who heads the cancer genetics program at UCSF and has studied *RAS* for nearly 3 decades.

Although biologists generally expected to find the opposites of oncogenes, or tumor suppressors, locating one proved tricky because such genes are mutated or lost in tumor cells. "How can you see something that's not there?" asks Philip W. Hinds, PhD, deputy director of Tufts Medical Center's cancer center. But by comparing the DNA of rare eye tumors called retinoblastomas with normal cells, Weinberg's lab, in conjunction with other Boston-area researchers, discovered *RB1* in 1986.

These seminal discoveries have yet to lead to the development of *RAS*- or RB1-targeted therapies. But they have fueled the search for more oncogenes and tumor suppressors—laying the foundation for today's rapid progress in cancer therapeutics.

This article is the third in a 5-part series commemorating the passage of the National Cancer Act in 1971.

NOTED

- The **AACR Cancer Progress Report 2011** makes the case for boosting funding for the National Institutes of Health and the National Cancer Institute with annual budget increases at least 5% above the biomedical research inflation rate. The report can be downloaded at http://cancerprogressreport.org.
- Worldwide, **the number of reported breast cancer cases has risen by 3.1% annually** since 1980, while the incidence of cervical cancer has edged up by 0.6% a year, says a study from the Institute for Health Metrics and Evaluation. Developing countries are experiencing the majority of breast and cervical cancer occurrences, and higher mortality rates than developed countries.
- **Donations are targeting tailored cancer treatments**. The Johns Hopkins Kimmel Cancer Center received a $30 million donation from the Commonwealth Foundation for Cancer Research to establish a center for personalized cancer care. Former Genzyme chief executive Henri A. Termeer contributed a $10 million gift to Massachusetts General Hospital for the creation of a targeted cancer therapies center.
- The **Food and Drug Administration has restructured its oncology division** to allow for a more disease-specific approach. The new Office of Hematology and Oncology Products aims to provide greater clarity about where applications for specific therapies will be handled.
- **The U.S. allotted 5.5% of its health care funds to research** in 2010, for a total of $140.5 billion, according to Research!America's latest report. This percentage has remained unchanged over the last 6 years.
- The **2011 Lasker-Bloomberg Public Service Award went to the NIH Clinical Center**, the world's largest clinical research hospital. About 1,500 clinical research studies are currently in progress at the Center.
- As of 2009, **26 states have accumulated $4.1 million for breast cancer research from specialty license plates.** Illinois generated more than $7.4 million through its one-of-a-kind breast cancer lottery ticket.

Noted

Cancer Discovery 2011;1:369.