LA JOLLA, CALIFORNIA Dec. 11, 1992 -- Scientists at The Scripps Research Institute (TSRI) have reported in this week's issue of the journal Science, the first successful use of injected antisense for treatment of tumors in mice.

The studies were carried out on Human T-cell leukemia virus type 1 (HTLV-1), a virus that is prevalent in Southern Japan, the Caribbean, Africa and the Southeastern portion of the United States. HTLV-1 has been associated with a highly malignant form of adult T-cell leukemia which is almost always fatal and does not respond well to chemotherapy. The virus may be transmitted by breast milk, by sexual contact, by blood transfusion, or among intravenous drug users where it has been found frequently associated with HIV. Like its distantly related cousin HIV (the virus that causes AIDS), the incidence of HTLV-1 appears to be increasing in the United States, though it appears less of a health risk than HIV.

A viral gene called tax (transcriptional activator of expression), is thought to be an important factor in HTLV-1
associated leukemia, said Michael Nerenberg, M.D., the lead author of the *Science* article and a member of TSRI's Department of Neuropharmacology.

"To evaluate the importance of tax, we created genetically engineered mice which express the tax gene in many organs," he said. "Though these mice do not develop leukemia, they do develop another form of cancer which has biochemical similarities to leukemia. In these tumors, tax causes enhanced expression of a cellular gene called Nuclear Factor Kappa B (NF-\(\kappa\)B), which regulates growth and activation of many cells. Because NF-\(\kappa\)B controls growth of cells, Isao Kitajima, a postdoctoral fellow in the lab, decided to look at the effects of inhibiting expression of this gene."

The researchers synthesized a short piece of DNA (an antisense oligonucleotide), which would specifically recognize the NF-\(\kappa\)B gene product and inactivate it. This is a technique which has been widely used in the test tube and in cultured mammalian cells, but which has had limited use in whole animals.

Nerenberg explained that antisense refers to a nucleic acid sequence. "DNA from normal cells produces messenger RNA (mRNA), a nucleic acid molecule which directs the synthesis of proteins that are the building blocks of cells. When read from left to right, this mRNA contains the direct code for protein synthesis and hence is in the 'sense' direction. A nucleic acid sequence which encodes the complement of this sequence from right to left is called antisense."

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The TSRI researchers gave injections of the antisense oligonucleotide to mice bearing transplanted tax induced tumors; this resulted in complete regression of the tumors. The researchers also demonstrated in the test tube that the growth of human HTLV-1 infected leukemia cells could be inhibited by these oligonucleotides.

"This study is among the first to demonstrate successful use of antisense oligonucleotides to ablate tumor growth in animals and suggests that NF-kB may represent a good target for intervention in HTLV-1 associated leukemias," Nerenberg said. He added that additional studies and pilot clinical trials in humans will be needed to assess the role of antisense therapeutics in adult T-cell leukemias.

Additional authors of the Science article, which is titled "Ablation of transplanted HTLV-1 tax mediated tumors in mice by antisense inhibition of NF-kB," are TSRI researchers Isao Kitajima, M.D., Ph.D.; James Bilakovics, B.S.; David A. Brown, Ph.D.; and Xiao Xu, M.D. An additional author is former TSRI researcher Toshiya Shinohara, M.D., Ph.D., who is currently a member of the Department of Pathology, Hokkaido University School of Medicine, Japan.

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