Tobacco plants enlisted in war on cancer

In an ironic twist on its infamous role as a cause of deadly tumors, tobacco might soon offer physicians a way to rapidly make vaccines tailored to fight a patient's specific cancer.

This role reversal stems from the ability of a well-studied pathogen, the tobacco mosaic virus, to force an infected plant to mass-produce the proteins of the virus. A biotech firm has exploited this capability by slipping selected genes into the viruses and using them to turn tobacco into a protein factory.

"Literally every cell becomes infected," says Daniel Tusé of Biosource Technologies in Vacaville, Calif. "The yield is phenomenal, and the [time] that it takes from inoculation to harvest is 2 to 3 weeks."

Biosource has used this technique for a decade, generating commercial enzymes as well as proteins for a potential malaria vaccine. Hoping to showcase the technology further, the company recently approached Ronald Levy of the Stanford University School of Medicine, who has studied vaccines for treating non-Hodgkin's lymphoma.

In this cancer, a single antibody-producing B lymphocyte, or B cell, breaks free of normal growth controls and copies itself endlessly. The cancer has a weak spot, however. All the lymphoma cells in a patient sport the same protein, the unique antibody made by the original B cell, on their surface. Researchers have shown that inoculations with this shared protein can stimulate the immune system to attack the lymphoma cells of that patient.

"We have a surface molecule unique to each lymphoma," says Levy. "It's really a problem of how you can make these [vaccines] fast and cheap."

"Our goal is to produce customized vaccines to treat non-Hodgkin's lymphoma in a matter of weeks after receiving the biopsy," adds Tusé.

To test that possibility, Tusé, Levy, and their colleagues used tobacco plants to make a fragment of an antibody from a mouse B cell lymphoma. Although physicians have had promising results with cancer vaccines made of complete antibodies, researchers are just beginning to test antibody fragments in people.

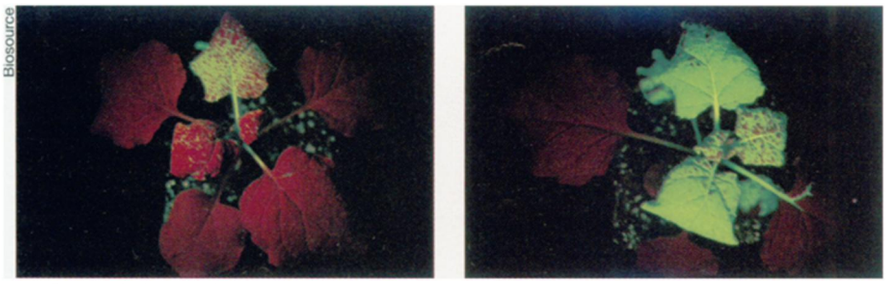
It can take months to a year to genetically engineer plants to make antibodies (SN: 12/5/98, p. 359). In just a month, however, Biosource used an engineered tobacco mosaic virus to make tobacco plants churn out large quantities of the antibody fragment. When this fragment was injected into healthy mice as a cancer vaccine, the animals produced antibodies targeting the protein, the scientists report in Jan. 19 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

More important, the vaccine protected the mice against injections of the lymphoma cells from which the researchers had isolated the antibody fragment.

Biosource and Levy's group has already infected tobacco plants with antibody-fragment genes from people with non-Hodgkin's lymphoma. Tusé predicts that customized vaccines could help thousands of patients. "We're not there yet. We have to show that these things work in people," he cautions.

If researchers can identify appropriate target molecules on tumors of solid tissues, Biosource also hopes to use their tobacco technology to make patient-specific vaccines for diseases such as breast and prostate cancer.

"The creation of unique vaccines for individuals or groups of individuals is clearly the way people are thinking about treatment for the future," says Charles J. Arntzen of the Boyce Thompson Institute for Plant Research in Ithaca, N.Y. —*J. Travis*



At 5 days (left) and 8 days (right) after being infected by a virus carrying the gene for a fluorescent protein, this plant has a greenish glow that shows how quickly the virus spreads.

Do reshuffled genes cause autoimmunity?

Deep in the bone marrow of mammals, immune cells called B lymphocytes, or B cells, gear up to distinguish enemies from friends. The lymphocytes shuffle their genes to produce a diverse population of cells that makes millions of distinct antibodies, ready to battle whatever microorganism may come along (SN: 11/7/98, p. 302).

Once the immune system devises an antibody that can recognize and latch onto an enemy organism, it mass-produces the particular type of B cell that made the antibody. These and the antibodies they make are then sent out into the fray. Poorly programmed B cells that might attack healthy tissues are typically weeded out in the bone marrow.

The gene shuffling that produces B cell variations is guided by proteins encoded by recombinase activating genes, *RAG1* and *RAG2*. Researchers have believed that the shuffling ceases once the mature B cells leave the marrow. Recent studies, however, have shown that some B cells continue to rearrange their genes in the spleen or lymph tissue.

Researchers report in the Jan. 28 NATURE that one class of B cells, B-1, continues to reshuffle its genes in the peritoneal cavity of the abdomen. The findings in mice suggest a possible mechanism behind autoimmune diseases, in which immune cells attack the body's own tissues. The mouse breed used in the study shows an autoimmune disease similar to human lupus.

Researchers found 10 to 20 times more *RAG* gene activity in B-1 cells in the animals' peritoneal cavity than in normal mice, says study coauthor and immunologist Michel C. Nussenzweig of the Howard Hughes Medical Institute at Rockefeller University in New York City. The reason for this gene rearrangement outside the bone marrow remains elusive, as does any hard link to the chronic autoimmune problems these mice face.

Antibodies produced by B-1 cells are less specialized than those made by other B cells. Nussenzweig suggests that because many foreign microorganisms leak into the peritoneal cavity from the adjacent digestive tract, one role for B-1 cells there might be to generate a population of antibodies able to deal with whatever comes along. The gene rearrangements he and his colleagues detected may maintain the diversity of these B-1 cells, Nussenzweig says.

That strategy could have repercussions, however. These shoot-first-and-ask-questions-later antibodies constantly flow out of the peritoneal cavity into the blood and lymph systems, where they contact healthy tissues. This leakage might represent the still-theoretical autoimmune connection. The picture is incomplete, Nussenzweig says, because autoimmune reactions probably require other genetic factors.

"This study shows a low but measurable frequency of these cells having gene rearrangement" in the peritoneal cavity, says immunologist Mark S. Schlissel of Johns Hopkins Medical Institutions in Baltimore. "That's unusual for mature B cells."

Nussenzweig is studying fluid from arthritic joints in people—common sites of inflammatory autoimmune reactions—to see if the *RAG* genes there are stimulating gene shuffling in B cells. —*N. Seppa*