The IPCC panel also tackled head on the good news message in a report last year by the George C. Marshall Institute that was well received at the Bush White House (*Science*, 24 November 1989, p. 992). The institute concluded that the enhanced greenhouse effect may well be a modest one and that it will possibly be counteracted in the next century by another Little Ice Age induced by a fading of the sun.

The IPCC's conclusion is that a varying sun cannot be a major player in the climate of the next century. Even another Little Ice Age cannot offset the greenhouse warming. The report says that "even if such a change occurred over the next few decades, it would be swamped by the enhanced greenhouse effect."

The Marshall report attracted attention in part because it was written by three prominent scientists: William Nierenberg, director emeritus of Scripps Institution of Oceanography; Robert Jastrow, founder and former director of NASA's Goddard Institute for Space Studies; and Frederick Seitz, president emeritus of Rockefeller University. "The problem is that these three well-known scientists are not experts in climate change," says Donald Wuebbles of the Lawrence Livermore National Laboratory and a lead author of the section on radiative forcing of climate. "The White House took [the report] overly seriously. A report done by famous scientists seems to have a lot of credence; whether it is inside or outside of their area of expertise doesn't seem to matter. We just couldn't let these misinterpretations go on any longer."

As for Lindzen's claim that a greenhouse-induced drying of the upper atmosphere would largely counteract the warming (*Science*, 1 December 1989, p. 1118), it garnered nary a mention. The process occurs in the models, IPCC researchers concede, but it has a small effect that is overwhelmed by other changes induced by greenhouse warming. But the report did consider at length the contention, based on studies of warm climates in the geologic past, that the future greenhouse world would largely be a mild, moist paradise. No such luck, say IPCC's climatologists. Weather patterns induced by greenhouse warming will be unlike those of previous periods of global warmth, so strict comparisons are meaningless.

Scientific outcasts have never fared well in consensus-building, but some have still triumphed. For now, the greenhouse skeptics are out in the cold. They will likely remain there for at least another decade while computer models are cranked up, the climate gives more clues of its ultimate direction, and the politicians draft international agreements. ■ RICHARD A. KERR

# New Clue to Cancer Metastasis Found

*A defect in one of the cell's major signaling pathways may contribute to the tendency of some cancer cells to spread*

A REMARKABLE CONFLUENCE OF RESULTS from laboratories on three continents, working independently and on totally different organisms, set researchers hot on the trail of a major mystery in cancer biology: What causes tumor cells to metastasize to new sites in the body? Although numerous genes have been found that contribute to cancer development, the biological changes that allow some tumor cells, but not others, to spread are poorly understood. And since metastasis is what ultimately kills the great majority of cancer patients who succumb to their disease, the new findings have opened a window on a cellular process that researchers would dearly love to understand.


**Unexpected result.** *A gene found by Patricia Steeg encodes a key regulatory enzyme.*

The story began 3 years ago when a team of researchers at the National Cancer Institute discovered a novel gene with an intriguing activity; it apparently suppresses the ability of cancer cells to metastasize. But the group that found the gene, which was led by Patricia Steeg and Lance Liotta, had no clue about how it might work and they have been trying to puzzle it out ever since.

Now, thanks to an extraordinary piece of scientific serendipity, their puzzle may be solved. The metastasis suppressor gene, it turns out, closely resembles genes that control development in organisms as diverse as bacteria, slime molds, and fruit flies. Moreover, the new evidence indicates that the gene encodes a key enzyme in one of the cell's major pathways for responding to external stimuli. Since these stimuli include hormones and growth factors, alterations in the enzyme might derail a cell's growth control, pushing it into malignancy.

The connection between the metastasis suppressor gene and the signal transmission pathway took a lot of people by surprise, including the NCI workers who discovered the gene. Steeg says: "We never expected the relationship, but it makes for all sorts of exciting new prospects for understanding the mechanisms of metastasis."

Other genes are known to affect metastasis. Some make cancer cells more or less susceptible to killing by the immune system. Others affect the activity of the secreted protein-dissolving enzymes that cancer cells need to escape from a tumor and migrate to new sites. But this one is the first to work inside the cell in a regulatory pathway.

And that raises an intriguing possibility for therapy: It might be possible to find drugs that buttress the activity of the metastasis suppressor gene. "You can visualize inhibitors of metastasis that work inside the cell," Liotta remarks. Such inhibitors might be combined with agents that work externally, inhibitors of the protein-dissolving enzymes, for example. Moreover, by measuring the activity of the suppressor gene in cancer cells, physicians might be able to predict which tumors are likely to metastasize and require aggressive therapy.

Steeg, Liotta, and their colleagues originally detected the gene in mouse melanoma cells in 1987. These cells, like other cancer cells, differ widely in their metastatic potential. The NCI workers were comparing patterns of gene expression in melanoma cells that have little tendency to metastasize with the patterns in cells that metastasize readily. When they found one gene that was consistently expressed at higher levels in the poorly metastatic cells, they thought they might be on to a metastasis suppressor.

Steeg and her colleagues went to work and subsequently determined the nucleotide sequence of the gene, which they designated NM23 (because it was nonmetastatic and the 23rd gene clone they examined). Once they verified that the sequence didn't resemble that of any other gene recorded in the data banks at the time, they knew they had come up with a new gene. But because they had nothing to compare the new gene with, the NCI workers could make no predictions about how it might work. And that's where

matters stood for nearly 3 years.

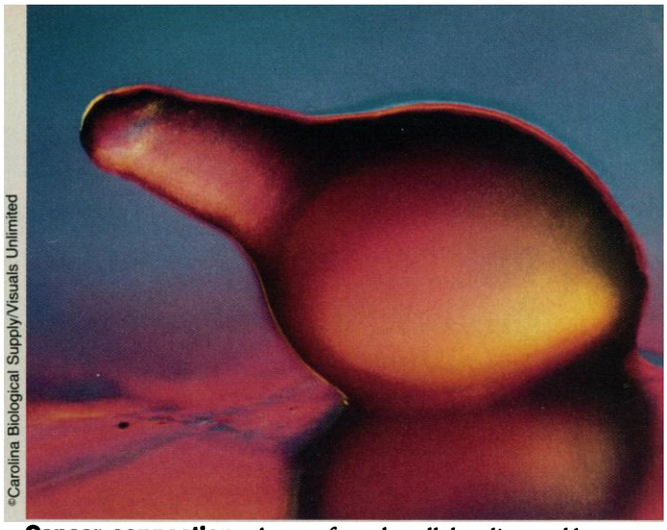
Meanwhile, Allen Shearn's group was pursuing an apparently unrelated line of work at Johns Hopkins University in Baltimore. Shearn and his colleagues had identified a gene mutation that causes a variety of developmental defects in fruit flies, resulting in the death of the larvae. By the fall of 1988, the researchers had isolated the gene, which is called *awd* (because its developmental defects include abnormal wing disks) and determined its sequence. They also deposited the sequence in a gene data bank.

Then in May 1989, when Liotta was making a periodic update of the comparison of the NM23 sequence, lightning struck. Liotta plugged the NM23 sequence into the computer—and out popped *awd*. The human and *Drosophila* proteins proved to be 78% identical, a tremendous degree of sequence conservation for two species so far apart on the evolutionary scale. Although that strongly suggests that the gene has an important function, it still provides no information about what that function is.

The key connection was finally made by researchers from the Centre National de la Recherche Scientifique at the Pasteur Institute in Paris and the University of Konstanz in Germany. The CNRS group, led by Michel Veron, was looking for genes that control the development of the slime mold *Dictyostelium discoidium*. When food is plentiful, the amoeba-like cells of this organism live independently. But when starvation threatens, the cells stream together, producing an aggregate resembling a small slug. After migrating for a time, the slug settles down and differentiates, forming a stalk topped by a "fruiting body" that produces spores.

The French workers were particularly interested in finding genes encoding proteins that bind the compound GTP (guanosine triphosphate). Work from several labs had indicated that these proteins play important roles in transmitting the signals that tell slime mold cells to aggregate and differentiate. With the aid of a screening technique devised by Marie-Lise Lacombe, the Veron group found a gene. When the researchers determined its nucleotide sequence, however, they realized that its product could not be a classical GTP-binding protein. But a conversation with Octavian Barzu, a Pasteur colleague, led to another idea, Veron says—that the gene might encode a nucleoside diphosphate (NDP) kinase, an enzyme that synthesizes GTP and other nucleoside triphosphates by tacking a phosphate group onto the corresponding diphosphates. And that proved to be the case.

The paper describing these results was in press at the *Journal of Biological Chemistry* when Shearn, Liotta, and Steeg's report on the *awd*-NM23 link came out in *Nature* on 9 November 1989. Rupert Mutzel at Konstanz, a former postdoc in the Veron lab who still collaborates with his old group, noted that the sequence of the slime mold enzyme also closely resembled that of the human NM23 protein; they are 62% identical. "At that moment we were very excited, as you might expect," Veron says, "and we modified the *JBC* paper [to include the new finding]." So now at last, there was a clear indication of a possible function for NM23. It might be an NDP kinase, and that would put the protein smack in the middle of a major signal transmission pathway.




**Cancer connection.** *A gene from the cellular slime mold provided a function for Steeg's metastasis suppressor gene.*

The NDP kinases were originally discovered some 40 years ago and have mostly been considered to be "housekeeping" enzymes, made in all cells where they perform such activities as synthesizing the building blocks for nucleic acids. But some researchers, including Narimichi Kimura and Nobuko Shimada of the Tokyo Metropolitan Institute of Gerontology, have evidence suggesting that the kinases might also have a regulatory role in the cell. The enzymes, they found, associate with G proteins, which are so called because they bind GTP.

The G proteins are located in cell membranes in close conjunction with the receptors for many hormones and growth factors. When one of these agents binds to its receptor, the associated G protein serves as a relay, transmitting the hormone's signal to the cell interior where it will be converted into a response. This requires energy, which the G protein generates by breaking the GTP it has bound down to GDP (guanosine diphosphate). The NDP kinase might regenerate the GTP, Kimura and Shimada postulated, allowing the G proteins to keep working. . . . And so might the NM23 protein, as Lacombe, Veron, and their colleagues pointed out in their *JBC* paper, published in the issue of 15 June.

But that may not be the NM23 protein's only function. NDP kinases have also been found associated with the microtubules, a set of protein filaments that help to maintain cell shape and also form the mitotic spindle, which is needed for orderly cell division. Microtubule formation requires GTP, too, and the NDP kinase might provide it. Anything that alters the NM23 protein or affects its synthesis might therefore contribute to the microtubular and chromosomal abnormalities found in cancer cells, Liotta points out.

There is one possible hitch to this emerging picture of NM23's action, however. So far the evidence that the gene's product is an NDP kinase rests solely on the similarity between its sequence and those of the known enzymes. But no one expects any problems because that evidence is strengthening by the minute.

Shearn's group has already shown that the *awd* protein is an NDP kinase. In addition, Veron says that Anne-Marie Gilles, a Pasteur colleague, and Ioan Lascu of the University of Cluj in Romania, sequenced an NDP kinase from human red blood cells and have found it to be identical to that of NM23. In addition, Kimura and Shimada have gotten the sequence of the rat liver enzyme, and that one, Steeg and Liotta say, is about 90% identical to the human NM23 sequence. "That's encouraging," Steeg says, "because you can get rid of those long evolutionary leaps." Steeg's group is nonetheless working hard trying to show directly that the NM23 protein is an NDP kinase.

All the researchers are hard at work trying to pin down the role of NM23 in cancer metastasis and cell proliferation. Veron's group, for example, has joined forces with Xavier Fasstre of the Curie Institute in Paris to look at NDP kinase activity in human cancers, including breast and colon cancer. They have preliminary evidence suggesting that the activity might first go up in cancer cells and then decrease as tumors become metastatic.

And Shearn now has the powerful *Drosophila* genetic system for exploring NDP kinase activity. In fact, before the link between *awd* and NM23 was discovered, he was on the verge of taking a year's leave of absence to serve as a program director at the National Science Foundation. But he canceled those plans. "Now is no time to leave the lab for a year," he declares.

■ JEAN MARX