# Kaposi's Sarcoma Gives on Key Fronts

*Two groups have identified a compound that makes Kaposi's cells grow, a third is hot on the trail of the receptor, and a fourth is testing a promising drug*

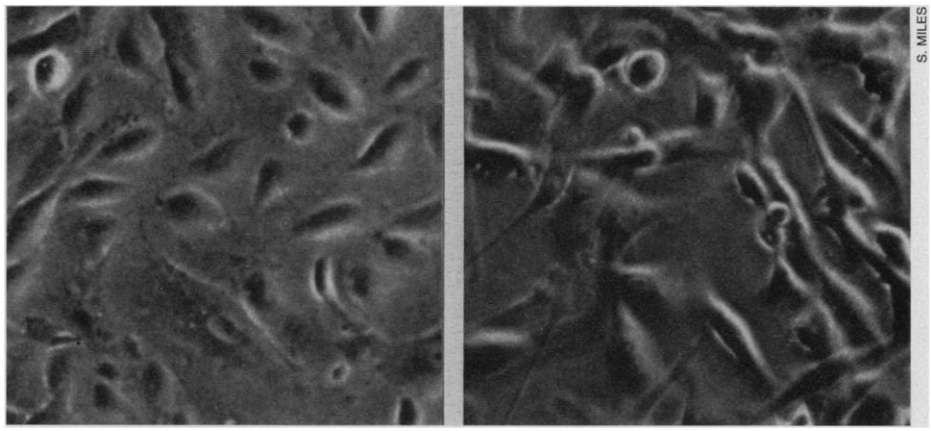
A DECADE AGO, DERMATOLOGISTS IN NEW York and California began seeing a startling increase in the number of patients showing up in their offices with a rare skin lesion that had previously been seen only in older men of Mediterranean origin. This baffling development was quickly explained at one level: The surge in cases of the disease, Kaposi's sarcoma (KS), turned out to be among the first signs that AIDS had arrived in the United States. Patients with ravaged immune systems are apparently susceptible to this skin cancer, which in severe cases can be fatal. But while researchers were quick to identify its cause, they have been slow to comprehend its mechanism. Now, after a decade of feverish research, some of the mysteries of Kaposi's sarcoma are finally beginning to yield.

While several pieces of the jigsaw are yet to be found, six papers published within the past 2 weeks (four in this issue of *Science*, beginning on p. 1430) should go a long way toward showing researchers where to look for them. The new results push the understanding of Kaposi's sarcoma ahead on several fronts. Two labs have independently identified a growth factor that prompts cells that have become cancerous to grow into the Kaposi's sarcoma lesions, and a third lab has begun to piece together a picture of a receptor molecule that may mediate the action of this protein. Yet another group has found a nontoxic compound that appears to be more effective than currently available compounds in stopping the growth of Kaposi's sarcoma cells in the laboratory. And finally, there is evidence that another infectious agent—in addition to HIV—appears to play a crucial role in the development and transmission of Kaposi's sarcoma (see sidebar). As Sherlock Holmes might say, the game's afoot, and Kaposi's sarcoma researchers are in hot pursuit.

The growth factor story began to unfold about 4 years ago when Robert Gallo and his colleagues in the laboratory for tumor cell biology at the National Cancer Institute (NCI) were trying to coax Kaposi's sarcoma cells to grow in culture. In the course of testing various growth media, they hit upon a curious discovery: The cells grew best in the presence of a protein produced by T cells that had been immortalized with human retroviruses. They determined that this protein had a molecular weight of about 30,000, but beyond that the NCI researchers had no idea what it was. So over the past few years they have been slowly amassing enough of this mysterious protein to determine at least part of its amino acid sequence. Now, they have done that, and after searching a protein sequence database they report on page 1430 that they were looking at a compound called Oncostatin M.

While Gallo's group was sequencing the protein, molecular virologist Steven A. Miles at the University of California, Los Angeles (UCLA), was taking a different route to establishing its identity. Miles was convinced that the growth factor was a cytokine called interleukin-6. His reasoning seemed impeccable: IL-6 levels are elevated in AIDS patients and its molecular weight was around 30,000, the same as Gallo's mystery protein. But the Miles and Gallo groups independently found that, while IL-6 does induce Kaposi's sarcoma cells to grow, this effect is not consistent. This suggested that IL-6 couldn't be the major growth factor. So Miles reasoned that, since IL-6 levels were elevated in Kaposi's sarcoma cell cultures, perhaps some other agent was stimulating the Kaposi's sarcoma cells not only to grow but also to produce IL-6. "Peter Linsley at Bristol-Myers Squibb had shown that Oncostatin M could induce IL-6 in normal endothelial cells," recalls Miles. So Miles' group decided to test Oncostatin M on Kaposi's sarcoma cells. They grew like topsy. Moreover, as Miles reports on page 1432, they adopted the spindle-like shape of Kaposi's sarcoma cells taken from patient's lesions.

Now that they have the growth factor in hand, researchers are trying to figure out how it works—and ultimately how to block it. But they're starting almost from scratch. Oncostatin M was discovered only in 1986 by Joyce Zarling and her colleagues at Oncogen in Seattle. They came upon Oncostatin M while searching for proteins that would inhibit tumor cell growth; now Miles and Gallo have shown that it has the opposite effect on Kaposi's sarcoma cells.




**Before and after.** *Cultured Kaposi's sarcoma cells* (left) *treated with Oncostatin M proliferate and assume characteristic spindle shape* (right) *of cells in KS lesions.*

This apparently contradictory behavior isn't really so unusual: Many cytokines have utterly different affects depending on the type of cell they interact with. The key to how Oncostatin M effects Kaposi's sarcoma cells probably lies in the nature of the cell surface receptor to which the compound binds. David Gearing, a molecular immunologist at Immunex in Seattle, and his colleagues think they have made a critical discovery in this regard. Gearing's group reports on page 1434 that it is close to pinning down the precise nature of the receptor. In particular, they show that there are similarities between the receptor for Oncostatin M as well as two other cytokines, one called leukemia inhibitory factor (LIF), and IL-6, the same protein Miles thought played a key role in the growth of Kaposi's sarcoma. If Gearing's

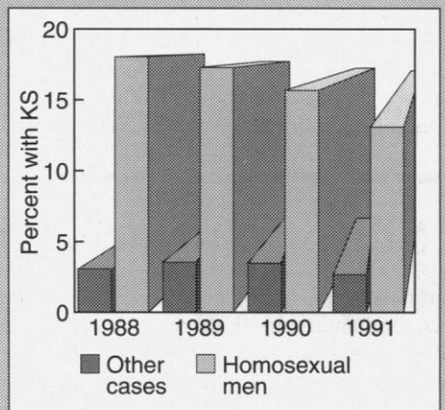
# On the Track of a Second Infectious Agent

While molecular biologists have been puzzling over the mechanisms that cause Kaposi's sarcoma (KS) cells to proliferate, epidemiologists have been trying to figure out another mysterious aspect of the disease: Why did this once-rare cancer suddenly become so common among AIDS patients? The answer, most epidemiologists have come to believe, is that it is caused by an infectious agent entirely separate from HIV, but one that becomes highly pathogenic in patients whose immune systems are depressed. There's even a candidate, albeit a highly controversial one: Two weeks ago, in a paper published in *The Lancet*, a papillomavirus—the virus that has been associated with genital warts and cervical cancer—was named as the possible culprit, but so far the disbelievers probably outnumber the believers.

Evidence for some sort of second infectious agent began to gel a couple of years ago. Studies by Valerie Beral at the Imperial Cancer Research Fund (ICRF) in Oxford and Harold W. Jaffe and his colleagues at the Centers for Disease Control in Atlanta showed that Kaposi's sarcoma is far more prevalent among male homosexual AIDS patients than among AIDS patients from other risk groups—IV drug users, for example, and those who received tainted blood transfusions. This suggested that an infectious agent was being transmitted preferentially within that group. Beral and Jaffe also showed that among women with AIDS, those who had slept with bisexual men had the highest risk of getting Kaposi's sarcoma.

Alvin Friedman-Kien, a dermatologist and virologist at New York University, thinks he knows what that infectious agent is. In a paper published 2 weeks ago in *The Lancet* (29 February, p. 515), Friedman-Kien announced that he and his colleagues had used the polymerase chain reaction to show that DNA resembling human papillomavirus-16 (HPV-16) DNA was present in cells taken directly from Kaposi's sarcoma lesions and in Kaposi's sarcoma cells grown in the lab. Although the percentage of Kaposi's sarcoma cells apparently infected with HPV-16 was not very high in the data presented in the paper (only 15% of cells from 69 AIDS patients with Kaposi's sarcoma), Friedman-Kien says he has revised his detection methods and is now detecting the viral DNA in about 95% of cells he has tested. He has also found HPV-16-like sequences in 5 of 17 HIV-negative Kaposi's sarcoma patients.

Friedman-Kien has yet to convince many of his peers that papillomavirus is the cause of Kaposi's sarcoma, however. Joel Palefsky, who studies the virus at the University of California, San Francisco, says he has been testing Kaposi's sarcoma lesions for the presence of papillomavirus and has failed to find it. And William Blattner, a cancer epidemiologist at the National Cancer Institute, says he thinks the Kaposi's sarcoma agent will turn out to be a retrovirus. He says a research group at the University of Vienna that he collaborated with found retroviral-like particles in electron micrographs of Kaposi's sarcoma lesions.




**Different risks.** *Male homosexual AIDS patients are most likely to get Kaposi's sarcoma. The proportion is declining, perhaps because of safe-sex practices.*

SOURCE: CDC ILLUSTRATION: J. CHERRY

ICRF's Beral also has her doubts about the papillomavirus connection because, she argues, these viruses are too ubiquitous to be implicated in a disease that is rare in Western countries, primarily afflicting homosexual males. In fact, she now has evidence that even within the homosexual male population, only a subset is at high risk for Kaposi's sarcoma. In an article that will appear in the 14 March issue of *The Lancet*, Beral presents data showing that Kaposi's sarcoma is most common among HIV-infected homosexual men who engage in oral-fecal contact. That challenges Friedman-Kien's theory because papillomaviruses are more frequently transmitted through genital to genital sexual contact. Finally, Beral says her data may help explain the fact that Kaposi's sarcoma is endemic in Africa, where hygienic factors rather than sexual practices may be responsible for fecal contact.

To Steven Miles, a molecular virologist at the University of California, Los Angeles, who has been studying the molecular basis of Kaposi's sarcoma, the evidence pointing toward a second infectious agent may explain some of the molecular changes seen in Kaposi's sarcoma cells (see main text). The agent—whatever it is—"could be altering the expression of one of the receptors, or allowing for response to something it wouldn't ordinarily respond to," he says. ■ J.P.

work on the similarities of the receptors for these three cytokines holds up, it could go a long way toward sorting out some puzzles in cytokine research, especially why different cytokines can have the same effect on different cell types.

For the present, however, the question is just what kind of receptor is on the Kaposi's sarcoma cells. The answer will have important implications for potential therapies. "It's obvious that an agent that inhibited the proliferative effects of Oncostatin M on Kaposi's sarcoma cells might be a way to approach treatment of the disease," says Gearing. Immunex is hoping to make its mark with soluble receptor molecules that could be used as therapeutic agents. "Right now we're involved in testing the interleukin-1 receptor and [tumor necrosis factor] receptor as possible therapeutics, so we're obviously interested in applying this approach to Kaposi's sarcoma," he says.

Although it is likely to be several years before work on the Oncostatin M receptor will lead even to a candidate Kaposi's sarcoma therapy, two new drugs derived from naturally occurring compounds are already showing some promise—though their mechanism at this point is unclear. A little more than a year ago, AIDS researcher Judah Folkman and his colleagues at Harvard Medical School showed that fumagillin, a synthetic form of an antibiotic secreted by the fungus *Aspergillus fumigatus* could suppress tumor growth and inhibit angiogenesis, the process by which new blood vessels infiltrate cancerous tumors. Since angiogenesis is crucial to the growth of Kaposi's sarcomas, some researchers expect fumagillin to be effective against the cancer. Now Shuji Nakamura, formerly an associate of Gallo's at NCI who is currently at the University of Southern California (USC) medical school, reports on page 1437 that a sulfated polysaccharide-peptidoglycan (SP-PG for short) produced by the

bacterium *Arthobacter* inhibits angiogenesis and suppresses the growth of Kaposi's sarcoma cells in culture.

SP-PG has an important difference from traditional anticancer therapies: It doesn't devastate normal cells. "Shuji and I share a dream," says S. Zaki Salahuddin, another former Gallo associate now working with Nakamura at USC, and one of the authors of the paper. "The dream is to bring into tumor biology nontoxic drugs." SP-PG's manufacturer Daiichi Pharmaceutical Co. Ltd. of Tokyo has now purified SP-PG and is producing enough of it to complete preclinical trials of the drug by this summer.

UCLA's Miles is excited about what all these findings mean for the future of Kaposi's sarcoma research. "I think the whole thing is really coming together in terms of the LIF receptors and the IL-6 receptors being the receptors for Oncostatin M," he says. "This is really big, and it gives us a lot of different directions to go in." Taken with the potential advances in therapy and the narrowing search for another infectious agent, there is room for cautious optimism about getting a clear picture of the KS puzzle. ■ JOSEPH PALCA

# Building a Silicon Surface, Atom by Atom

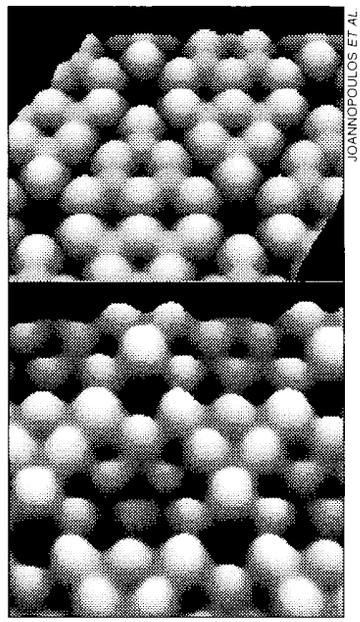
Almost all of us, mostly in childhood, have played with building blocks, carefully arranging them to create model houses, skyscrapers, or bridges. A more sophisticated version of that playful behavior is now taking place in the field of materials science, where researchers are using the principles of quantum mechanics to assemble imaginary atoms into models of the microscopic structure of real materials. Just last week, this high-tech Lego game reached a turning point.

In a photo finish, two groups of physicists reported that by harnessing the power of new parallel computers, they had independently succeeded in modeling the arrangement of atoms known as the 7×7 Takayanagi reconstruction of silicon. This extremely complicated structure, which draws its name from the Japanese scientist who first described it, is the configuration of atoms found on one of the faces of a silicon crystal. The results, published in back-to-back papers in the 2 March *Physical Review Letters*, don't hold any surprises about this well-studied atomic arrangement—except for the unprecedented scale of the models. While comparable earlier efforts at assembling silicon atomic Lego had peaked at about 100 atoms, the two groups in this case, led by physicists John Joannopoulos of the Massachusetts Institute of Technology and Michael Payne of the University of Cambridge, upped the figure to about 700 atoms—enough to reproduce the full complexity of the silicon surface.

Modeling on this scale could eventually offer new insights into how defects and changes in composition alter the atomic structure of materials, and hence their properties. "The excitement here is that you can do ab initio calculations on real material problems now," says Joannopoulos.

The term ab initio—meaning "from first principles"—sums up the challenge both groups faced: They had to calculate the most energetically favorable position for each atom using only the quantum mechanical equations that describe the total energy of a system of atoms. In theory it should be possible to calculate the most stable arrangement of any number of atoms; after all, nature does it every time a solid takes shape. In practice, the calculations are enormously time-consuming. The process starts with a collection of atoms arranged in a ballpark estimate of the structure based on theory or experiment. Next, the computer "jiggles" the atoms around in search of the equilibrium state—the one in which the structure has the lowest total energy. To do this jiggling, the computer calculates the forces on each atom, shifts the atoms slightly in response to these forces, allows the electrons to relax back to their ground state, and finally recomputes the total energy of the structure.

By repeating this procedure over and over again, the computer ultimately arrives at the lowest-energy, most stable structure. Doing this for 700 atoms takes hundreds of hours of computer time—even on parallel computers, which are well suited to such simple, repetitive calculations.



JOANNOPOULOS *ET AL.*

**Fair likeness.** *A hypothetical STM image of a computer-modeled silicon surface* (top) *resembles an image of the real thing.*

In a task of this magnitude, errors can easily creep in. But because they worked independently and followed different procedures, the Cambridge and MIT groups inadvertently acted as a check on each other's results. Joannopoulos' team ran the calculations on a Connection Machine, which has more than 16,000 simple processors; Payne's group used a different algorithm and ran it on a Meiko i860 Computing Surface, which has only 64 processors, albeit more powerful ones. In spite of the differences, the two groups arrived at virtually the same result for a key parameter: the energy per surface atom. Right before simultaneously submitting their manuscripts, the groups compared their figures and found less than a 3% difference. "We all burst out laughing in relief," remembers Payne.

The surface energy figure, both groups note, is well below the energy per atom calculated for other conceivable arrangements, which explains why the 7×7 reconstruction is the stable arrangement of surface atoms. And, as a graphic demonstration that they have reproduced the surface arrangement that forms in nature, the MIT group produced computer images that show how their theoretical surface would look through a scanning tunneling microscope (STM). In a comparison with an actual STM image of a silicon surface, the computer image holds up quite well.

Reproducing known structures isn't the ultimate goal of such supercomputer calculations, of course. As a first step toward using simulation to open a new, atomic-scale window on materials, Joannopoulos would like to see the calculations extended to larger systems of atoms. Modeling structures of 1000 atoms should be feasible with the same techniques that recreated the silicon surface, he says. And "as you go bigger," Payne says, "you can begin to study more problems." For example, it usually takes systems of more than 100 atoms to model cracks or defects. Once you get into the thousands of atoms, a range of other processes that can affect the physical and chemical character of a material can be examined. Beyond that, some researchers think, lies the possibility that supercomputers could be used to discover completely new materials.

Such feats could make the parallel supercomputer a standard tool of materials research. And when that day comes, predicts Oscar Alehand, a physicist at Bellcore, "These papers will [be seen as] a milestone." ■ JOHN TRAVIS