New Hope in HIV Disease

Potent new drugs and new insight into how HIV infects cells mark a turning point in the battle against HIV; other fields saw breakthroughs ranging from new lasers to the mysteries of the origins of life

What a difference a year can make. Just 12 months ago, AIDS was considered a death sentence, and those seeking to treat it seldom uttered the words "AIDS" and "hope" in the same sentence. Today, those terms have become inextricably linked in the minds and hearts of researchers and patients alike. And while the new optimism must be tempered with numerous caveats, the past year has ushered in a series of stunning breakthroughs, both in AIDS treatment and in basic research on HIV, the virus that causes the disease.

On the therapeutic side, new drugs called protease inhibitors—the fruits of years of work by armies of pharmaceutical company scientists—can now dramatically reduce HIV levels in the blood when taken with other antiviral compounds. At the same time, natural weapons in the immune system's defenses, polypeptide molecules called chemokines, have been unveiled as potent foes of HIV. To enter cells, the virus must bind to cell surface proteins that normally serve as receptors for the chemokines—and people born with defective receptors are immune to HIV infection. This work offers new insight into the pathogenesis of the disease and may one day blossom into new treatments or even vaccines.

And so although AIDS remains a scourge of our era, especially in the developing world, 1996 marks a turning point in the frustrating 15-year battle against the disease, because both protease inhibitors and chemokines have a profound ability to block HIV replication. On the premise that any enemies of HIV are friends to humanity, we honor these twin discoveries as the 1996 Breakthrough of the Year.

These breakthroughs are the payoff of more than a decade of painstaking research into the life cycle of the AIDS virus. To wreak its deadly havoc, HIV must first attach to a target cell and inject its genetic material, in the form of RNA, into the cell cytoplasm. The viral RNA is transcribed into DNA via an enzyme called reverse transcriptase and then integrated into the cell's chromosomes, thus hijacking the cell's genetic machinery to make new viral RNA and proteins. But before these proteins can be assembled into new progeny viruses, they must first be clipped to their proper sizes by an enzyme called a protease.

Until this year, the only way to interrupt this process was to inhibit reverse transcriptase, as AZT and similar drugs do. But over time HIV learns to dodge this single bullet, developing resistance to the drugs. What was needed was a molecule that struck at another phase of the viral life cycle.

Enter the protease inhibitors, which jam the active site of the protease. But a number of hurdles had to be overcome to bring these drugs to market. Once the detailed three-dimensional structure of the protease was identified, scientists pored over drug-design computer programs for years before creating compounds which could be taken orally with few side effects and yet were still powerful enough to block the enzymatic site. Finally, in December 1995, the U.S. Food and Drug Administration (FDA) approved the first protease inhibitor for therapeutic use, saquinavir; two others, ritonavir and indinavir, quickly followed in March 1996. Studies have shown that in a majority of subjects, a protease inhibitor taken as a "triple therapy" cocktail with two inhibitors of reverse transcriptase can reduce blood concentrations of HIV to undetectable levels. This is indeed a major victory—one almost undreamt of a few years ago—because another study this year showed that patients with a lower "viral load" progress to AIDS much more slowly.

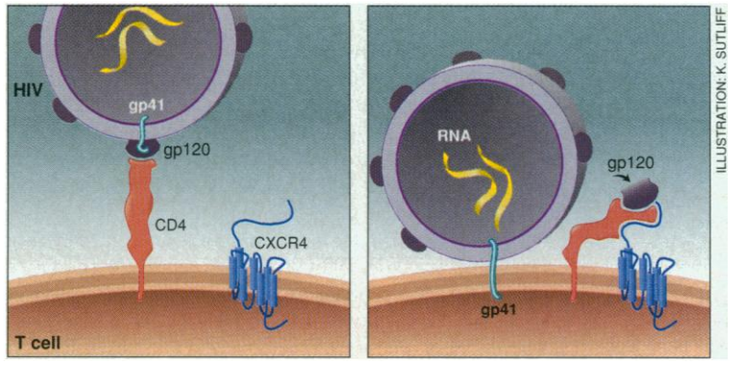


ILLUSTRATION: K. SUTLIFF

Open, sesame. HIV uses chemokine receptors like CXCR4 to enter T cells.

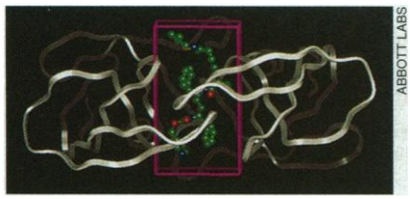
Just when the protease inhibitors were transforming the AIDS clinical world, the chemokines—small proteins involved in inflammatory responses—rocketed from relative obscurity to fame among basic researchers, as scientists grappling with two seemingly unrelated riddles of HIV infection converged on these molecules. The first line of research sought to explain how a small number of HIV-infected people could harbor the virus for years without getting sick. A team at the University of California, San Francisco, suggested that the so-called CD8 white blood cells in many of these patients produced a factor that could suppress HIV replication, but they couldn't isolate the substance.

The second mystery involved how HIV infects cells. Researchers had known for more than a decade that the virus must bind to a particular cell surface protein, called CD4, before it can enter target cells. But CD4 alone was not sufficient for entry, and dozens of labs had been engaged in a frustrating hunt for a second receptor.

On 15 December 1995, just 9 days after the FDA approved the first protease inhibitor, a paper by researchers from the U.S. National Cancer Institute and the San Raffaele Scientific Institute in Milan, Italy, claimed to identify the mysterious anti-HIV factor. The elusive molecule, the team said, was actually three related chemokines that worked in concert to suppress the virus. The news flashed across the AIDS research landscape like a flare lighting the night sky, because several chemokine receptors had recently been identified, although no one had connected them to HIV. Now it became clear that the two riddles might be linked: One of the chemokine receptors could be the long-sought second receptor for HIV, and the chemokines themselves might suppress the virus by blocking the binding site.

The results sent AIDS researchers chasing after chemokines and their receptors, and unleashed a flurry of new lab work. In a few months, this stampede turned into a roundup: During 2 weeks in June, five teams publishing in three journals branded a chemokine receptor called CCR5 as the co-receptor for HIV strains that predominate in early stages of infection, a finding that fits well with work by U.S. and Belgian teams showing that people with defective CCR5 receptors cannot be infected with HIV. What's more, just a few weeks earlier, researchers at the

U.S. National Institutes of Health identified another protein they named fusin (now called CXCR4) as the co-receptor for HIV strains that appear to dominate during later stages of infection. And the molecule that naturally binds to CXCR4 also turned out to be a chemokine.


ABBOTT LABS

Out of action. Protease inhibitors jam the active site of a key HIV enzyme.

With these new insights, drug designers have once again shifted into high gear, and a number of laboratories and companies are scrambling to develop modified versions of chemokines that might block the receptors from viral attack—without triggering the panoply of inflammatory reactions that natural chemokines normally activate. Other options are therapies, including vaccines, that might spur chemokine-producing cells to pump out enough of these molecules to keep HIV at bay.

Despite the promise of the chemokines and the dramatic effects of the protease inhibitors, neither one can be considered the "magic bullet" that could vanquish HIV entirely. Indeed, it's an open question as to whether any drug could actually roust the virus from its many hiding places in the body. For example, the currently approved protease inhibitors cause mild to severe side effects and don't easily cross the blood-brain barrier, although that flaw could be corrected in new versions of these drugs.

But one problem that scientists alone cannot solve is the issue of access to the new therapies. The World Health Organization's statistics indicate that more than 90% of the 22.6 million HIV-infected people live in developing countries, and most of them lack access even to AZT, let alone the expensive triple therapy. Even in the United States, where the new therapies cost an estimated $12,000-plus per year, only a small minority of HIV-infected individuals currently receive them. So although researchers have added promising new weapons to the fight against AIDS, it's up to policy-makers to see that the fruits of these scientific labors are available to all.

–Michael Balter

And the runners-up are ...

From the depths of the Earth to the outer reaches of the galaxy, scientists uncovered new marvels in the natural world in 1996. We highlight nine dramatic discoveries that also may have great potential impact on society.

Original mysteries. How—and where—did life begin? That's one of humanity's oldest questions, and this year scientists in several fields suggested startling new answers, firing the public imagination with possible traces of ancient life on Mars and supporting one view of life's basic family tree with the genetic sequence of a bizarre microbe.

In August, a NASA-led team announced evidence of past life in an ancient martian meteorite, prompting a presidential pronouncement, grabbing front-page headlines, and refocusing NASA's space-exploration plans overnight. Each of the team's four lines of evidence—certain minerals, organic matter, chemical imbalances, and bacterialike structures—could be due to abiotic causes, but the group argued that taken together, the most likely explanation was life. Then in November, a British team suggested that another martian meteorite also held organic compounds indicative of ancient organisms.

But many scientists remain skeptical, noting that the organic matter could be the leftovers of abiotic chemical reactions or earthly contamination (see Technical Comments). More study could boost the case, if new life signs such as key amino acids or tiny structures turn up. But final answers may have to wait for rock samples from the Red Planet—which aren't due until after the turn of the century.

Back on Earth, isotopic clues in Greenland rocks suggested that life had appeared here by 3.8 billion years ago. And also this year, scientists presented genetic data showing that life falls into just three major domains, rather than the five kingdoms of classical textbooks. This trinitarian view was proposed in the 1970s, but this year's work all but clinched the case. The genetic sequence of a heat-loving microbe, *Methanococcus jannaschii*—a member of one of the big three, the Archaea—was strikingly different from sequences from the other two groups, bacteria and eukaryotes (which include all plants and animals). The data suggest that the Archaea can no longer be lumped with bacteria, and indeed are probably closer kin to eukaryotes. Researchers are now unraveling more genomes from primitive organisms, hoping to work backward to the very root of life on Earth.


NASA

Ancient Martians? To some, tiny tubes in a martian meteorite suggested life.

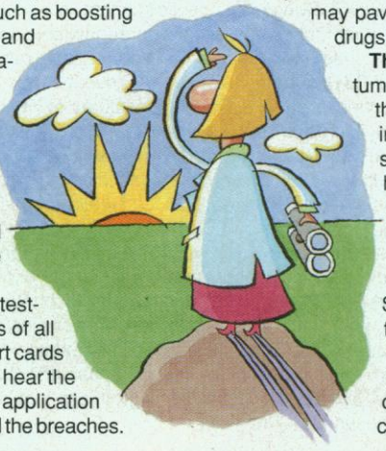
Scanning the Research Horizon

What's hot for 1997? *Science* offers its picks.

Closing in on cancer. Will there ever be a simple, globally effective cure for cancer? In 1997, the standard answer—"No"—may be up for revision. Already, researchers working in experimental systems have foiled many cancers with broadly targeted strategies such as boosting killer T cells, designing a virus to kill cancer cells, and thwarting the growth of blood vessels that feed metastatic tumors.

Just the place for a squark! As the Large Electron-Positron Collider at CERN gradually ramps up in energy, many particle theorists are echoing the Bellman in Lewis Carroll's *The Hunting of the Snark*: They believe that elusive supersymmetric particles—which would complete the Standard Model of the universe and which have names like squarks and selectrons—are sure to turn up at CERN.

Breaking the code(s). This year, cryptographers testing their handiwork breached computer security codes of all descriptions, from public-key systems that protect smart cards to a secret-key code banks use to swap data. Expect to hear the sound of more codes cracking in 1997, thanks to wider application of the powerful strategy, called a systemic attack, behind the breaches.



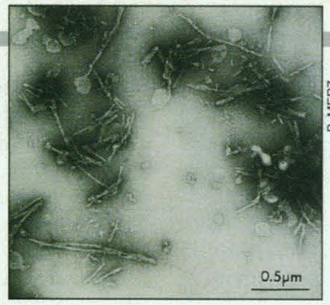
Carbo loading. Carbohydrates, seemingly simple molecules made from collections of sugars, somehow help cells recognize each other and stick together, but the details have been a mystery. Advances in artificial synthesis and in probing carbo's role in cell-cell interactions may pave the way for synthetic carbohydrates tailored as drugs fighting everything from infection to inflammation.

The smallest mistakes. Computers based on quantum mechanics promise undreamt-of speed, but it was thought that correcting the inevitable errors required invoking the blundering, macroscopic world, destroying the quantum advantage. Such worries may have been unfounded: If 1996's theoretical progress in quantum error correction continues, the field may leap ahead in 1997.

X-ray visions. After 15 years and nearly $1 billion in the making, the Advanced Photon Source is finally online at Illinois's Argonne National Laboratory. Expect the 70 beamlines using the world's most brilliant source of high-energy x-rays to reveal the dynamics of chemical reactions as they happen, the structure of complex proteins, and more.

ILLUSTRATIONS BY TERRY E. SMITH

Prions hit the press. In 1996, "prion," short for "proteinaceous infectious particle," became a household word that commanded respect and fear from Blackpool to Bavaria. Earlier blamed for 160,000 cases of bovine spongiform encephalopathy (BSE) in British cows, prions this year were suspected of jumping the species barrier to cause a new variant of Creutzfeldt-Jakob disease (CJD), a crippling neurodegenerative disease of humans.



P. MERZ

Prion power. Scrapie-infected mouse brains show clumps of protein.

As a result, despite a continuing ban on infected animals entering the food chain, public confidence in British beef crashed. Other nations banned British beef imports and refused to reconsider, especially when scientists in November revealed chemical similarities between prions from BSE-infected cows and people with the new CJD variant. The European Union finally launched a $63.5 million research program in these diseases.

Meanwhile, debate continues on whether proteins alone, without any nucleic acids, can exist in different strains, as argued on page 2079, and whether they can really transmit disease. This year's results showing that a protein can pass a trait between mother and daughter yeast cells may help. But there is plenty of work to be done before reaching final answers about the hazards of these sturdy bits of protein.

Cyber crush. In 1996, almost every scientific publisher sought an identity in cyberspace, joining the ever-expanding circle of online databases, usenet groups, and Web pages. Although some merely showed images of their pages online, others—spurred by competition from independent journals and tempted by the chance to go beyond the printed page—experimented with new ways to exchange information.

No one knows yet just how often researchers will reach into cyberspace rather than to their shelves, and growing pains still sometimes turn the Web into the World Wide Wait. But the experiments serve scientists in new ways. Physicists can download data sets too large to publish, thanks to a service of the American Institute of Physics. Medical scientists can watch three-dimensional (3D) videos on the electronic *Journal of Image Guided Surgery*, and GeneCOMBIS readers, like users of *Science*'s Next Wave, can debate each other in forums.

Behind the scenes, library and database experts are designing searchable electronic repositories, bringing several fields closer to "online maturity," which is defined by one journal editor as the point at which a researcher can write a credible review article—without leaving the office.

Lasers in the limelight. Lasers long ago went from wunderkinds to workhorses of the modern world, useful in everything from surgery to surveying. In 1996, new materials and designs lit up the field on several fronts, and could make lasers even more versatile in applications ranging from home electronics to ultraprecise research measurements.

Early this year, lasermakers reached one long-sought milestone, developing blue-light lasers from semiconductor chips made from gallium-nitride; these devices are rapidly improving in longevity and may prove more durable than previous blue-light emitters. The shorter wavelength of these lasers may one day help audio compact discs and computer CD-ROMs store up to four times as much data as do current devices.

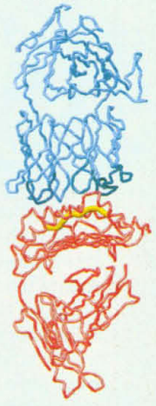

NICHIA CHEMICALS

True blue. New blue lasers shone in 1996.

Also this year, researchers developed the first arrays of semiconductor "quantum dot" lasers, in which light is emitted by a multitude of tiny semiconductor grains. Others managed to coax the first laserlike light emission from plastics. And 1996 also saw the first critical steps toward a brand-new kind of laser, as researchers began to transform last year's breakthrough winner—a cloud of supercooled atoms called a Bose-Einstein condensate—into a laser that fires beams of coherent atoms instead of light. For lasers, 1996 was a bright year indeed.

T-cell tales. T lymphocytes are one of the immune system's most potent weapons, directly triggering attacks on virus-infected cells. This year, a Nobel Prize went to the researchers who first began to describe how T cells recognize foreign antigens, and in a fitting complement, T cells also gave up their last great structural secret. In 1996, two independent groups managed to coax recalcitrant T cell receptor molecules to form crystals, allowing the first x-ray analysis of their 3D structure. And the teams captured the receptors in action—bound to their target molecules—offering new insight into how T cells learn to recognize their prey.

T cells depend on other cells to process foreign antigens into small peptides, which are then returned to the cell surface and displayed by proteins encoded by the major histocompatibility


GARCIA *ET AL.*

The T cells that bind. A T cell receptor *(blue)* binds to MHC protein *(red)* and foreign peptide *(yellow)*.

Haves and Have-Nots

It was a mixed year for research funding around the world, as Japanese scientists enjoyed heady growth in their budgets, and many U.S. programs dodged the worst of promised cuts. But in Europe, scientists tightened their belts and prepared for what may be leaner times ahead.

Indeed, all year three little words hovered like a specter over European spending: single European currency. The European Union plans to introduce the new "Euro" in 1999, but qualifying countries must meet certain economic criteria by 1997—and that means budget cuts for many programs, including science. For example, last month the Bundestag approved a 3.7% reduction in research and education and slashed Germany's space program by 13%; Germany also plans to cut contributions to several international laboratories, including CERN in Geneva.

Elsewhere in Europe, the trend was toward moderation. French research was largely spared the ax, while some ministries suffered cuts as deep as 17%. The United Kingdom—which is still dithering about joining the single currency and which faces a general election in '97—held research funding level to pay for tax cuts and other vote winners. In Russia, however, the chaotic economy continued to drag down science, provoking scientists into hunger strikes and even, apparently, suicides.

Meanwhile, in the United States, a somewhat chastened Congress failed to carry out a budget plan that would have cut deeply into federal R&D as part of a drive to reduce the federal deficit. The final results for the 1997 budget were checkered: The National Institutes of Health emerged with a hefty increase for the second year in a row—7% for '97—and the National Science Foundation rebounded somewhat from a flat budget in 1996. But programs such as magnetic fusion and space science suffered real cuts, and their prospects for '97 are no brighter.

In Japan, however, the funding outlook was rosy, as the national government continued to dramatically boost public spending. For the fiscal year beginning next April, the national science and technology budget could jump as much as 10.1%, to $28.14 billion. That comes on the heels of a 7% increase in this fiscal year. Also, companies rebounded from a recession, and private sector spending rose last year for the first time in 3 years. In matters of R&D funding, at least, Japan may invoke the envy of the world.

Scorecard '96

Last December, *Science* picked seven areas of research to watch in 1996. Here's how our favorites fared in the last 12 months, showing whether our crystal ball was cloudy or clear.

Genetic testing: Debates raged over insurance as well as ethics; a new U.S. law blocks insurance firms from using genetic data to deny coverage.

Neutrino news: Neutrino hunters circled their quarry, but no hard news yet on if this elusive particle has mass.

Bacterial warfare: Some of the molecular missiles of the type III secretion system—which deliver toxic proteins into target cells—were identified.

Animal-to-human transplants: Transplantation got the go-ahead from the U.S. Food and Drug Administration, but a British panel cautioned against it, and most such research stalled in '96.

Schizophrenia marker: The elusive disease has yet to be tied to specific genes, although new data boost linkages on chromosomes 6 and 8.

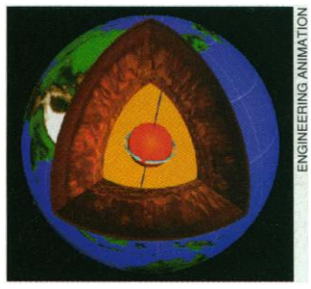
Extremophiles: The first genetic sequence of a heat-loving microbe showed that life is divided into just three major domains.

G proteins: New players were identified in the signaling cascade involving G proteins Rac and Rho.

complex genes; the T cell then binds to the MHC protein complex. The new x-ray data clinch many previous predictions about this complex interaction and shed new light on exactly how the receptor aligns with the MHC molecule. Two rival orientations—orthogonal and congruent—had been predicted, but it turns out that neither is quite right: The receptor molecule finds a halfway house between them. This detailed knowledge helps pave the way to designing molecular therapies to jump-start the binding process in the many diseases where natural responses fail.

Earthly revolutions. If you think your day goes by too fast, consider that although the Earth spins once on its axis every 24 hours, it harbors at its center what is in essence a second planet: the inner core. In 1996, direct measurements of this mysterious crystalline-iron realm revealed that it rotates faster than the bulk of the planet, perhaps hastened by the magnetic effects of the molten outer core.

Clocking this swift rotation took patience, because the inner core gains a full turn on the rest of the planet only every 400 years. Seismologists depended on the woodlike grain of the inner core, which alters the speed of seismic waves passing through it, and compiled 30 years of data to pin down a change of a few tenths of a second in wave travel times.

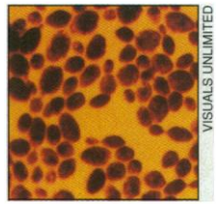


ENGINEERING ANIMATION

Quick spin. Earth's inner core rotates faster than the rest of the planet.

The inner core's declaration of independence also accelerated theoretical studies. Computer models suggested that the magnetic field at the inner core is perhaps 200 times stronger than at the surface and may be the force hastening its rotation. Expect more revelations about Earth's final frontier as monitoring and modeling continue.

Yeast on the rise. The short history of the booming field of gene sequencing is already scattered with milestones, but 1996 marks a major landmark: the first full sequence of a eukaryote, the baker's yeast *Saccharomyces cerevisiae*. Researchers now have sequence data for all the genes needed to run a yeast cell, data that will help unravel the basic genetic tool kit for eukaryotic processes such as cell division and chromosome organization. And the sequence of 12 million bases, containing 6000 genes arranged in 16 chromosomes, is freely available.



VISUALS UNLIMITED

Mission accomplished. The entire yeast genome was sequenced.

The 7-year, $30 million project began as something of a European cottage industry among 37 laboratories but mushroomed into a global collaboration of more than 100 groups, who completed the task last April—much sooner than anticipated. As predicted, the team found one gene in every 2000 bases, but the sequence reveals a surprising degree of redundancy: Often several genes appear to have similar sequences. Also, about 25% of the gene sequences were of unknown function—although genomic analysis has already begun (see p. 2069). Indeed, European Union scientists are now coordinating a systematic exploration of each gene's function and hope to finish in 2000.

Early orientation. The satellite-based Global Positioning System may be a big boon to today's navigators, but it's far outstripped by the sophisticated "biological positioning system" in every developing animal embryo, where each cell learns its exact location relative to other cells in order to give rise to the appropriate organ, tissue, or nerve. This year, researchers gained insight into how cells exchange this information by identifying additional molecules that carry and detect positional signals.

For example, researchers had known for years that members of the "Wnt" and "Hedgehog" families of signaling proteins help developing limbs and organs tell up from down and build repeating body segments in fly embryos. In 1996, experiments in several labs identified the receptor for the fruit fly Wnt family member Wingless as a protein called Drosophila frizzled 2; the receptor for the vertebrate protein Sonic hedgehog was unveiled as a complex including both Patched and Smoothened proteins. These findings will help unmask other molecular parties to these orientation feats. And because signaling pathways are often conserved across a wide range of organisms, including humans, the work could even help lead to treatment for the cancers, such as basal cell carcinoma, that arise when the signals go haywire.

Divining the death wish. Every cell contains a suicide program, activated when the good of the organism demands the sacrifice of individual cells. This year, researchers made new leaps in decoding this genetic self-destruct program, helping to clarify the normal process of programmed cell death, or apoptosis, and offering new understanding of diseases in which it goes awry.

Some of the executioner molecules inside cells were already known to belong to a family of protein-degrading enzymes known as ICE-like proteases. Turning on one ICE allows it to awaken others, unleashing an army of proteases that chop up proteins and kill the cell. But what signal turns on that first ICE? This year, researchers found that in at least some cases, the pathway is surprisingly short: When a cell surface receptor called Fas receives an extracellular death signal, it bypasses the usual long chain of signaling enzymes and immediately grabs and apparently activates an ICE enzyme.

Another death inducer, tumor necrosis factor, deals a weaker blow, and this year researchers found out why: TNF triggers a less direct suicide pathway and at the same time activates a competing pathway that prevents death. The fate of the cell depends on which signaling cascade wins the race. All this has practical import: It may one day help researchers learn to sabotage the anti-death pathway in cancer cells, or block the suicide pathway in brains after stroke.

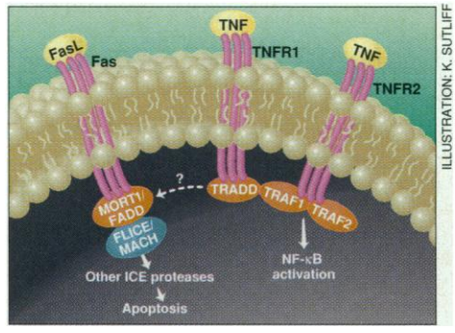


ILLUSTRATION: K. SUTLIFF

Suicide mission. An ICE protease triggers cells' self-destruct program.

–The News and Editorial Staffs

For an expanded version, with references and links, see Science Online *at* http://www.sciencemag.org/science/content/vol274/issue5295/#special