of celestial objects due to the gravitational pull of Earth, the moon, other planets, and our sun, "SIM will be able to verify Einstein's general theory of relativity to a few parts per million, 300 to 500 times better than today," says Shao.

Although SIM will avoid the technical challenges of formation flying, it still has many hurdles to overcome. One of the toughest will be vibration. The kind of vibration that the Hubble Space Telescope has had to endure from the wheels of its tape recorders would spell disaster for a space interferometer. SIM will dispense with tape recorders, but it will have to rely on spinning wheels, known as reaction wheels, to control its spin and rotate it toward its targets. Even the best possible bearings transmit vibration to the optics. Vibration caused by thermal "snaps," when solar panels move between light and shade, also poses a threat to the interferometric signal. The JPL team hopes that a combination of vibration decoupling—"basically just a very soft spring," says Shao—and yet more active optics should overcome this problem.

World view

The effort to actually image extrasolar planetary systems will begin in earnest with ESA's Infrared Space Interferometer (IRSI) and NASA's Terrestrial Planet Finder (TPF). These two projects, still at a much earlier stage of planning than DS-3 and SIM, are both designed to snap more detailed family portraits of other systems and probe the atmospheres of the planets for elements and compounds that are hallmarks of life. Both will operate at infrared wavelengths, where the signatures of these substances are strongest. The infrared has other advantages, too: Planets are brighter in the infrared relative to their suns, and at these slightly longer wavelengths the demands for optical accuracy in the interferometer are loosened.

Top of the list of telltale substances is ozone, which can be formed when ultraviolet light strikes oxygen produced by plant life. "The presence of ozone would tell us that some form of life already exists on the planet, which would be fascinating indeed," says Fridlund. The other two key signatures of a life-bearing planet are water and carbon dioxide.

With a tentative launch date of 2009, IRSI is still very much on the drawing board. "Currently we are studying concepts, feasibility, eventual cost," says Fridlund. The current vision is for six 1.5-meter telescopes flying in a formation up to 50 meters across. The array will orbit the sun at L2, a point on the Earth-sun axis where the gravitational gradient is flat. There, says Fridlund, "the biggest force acting on the array is solar photon pressure."

Fridlund sees a mountain of technical challenges before IRSI takes its first pictures. "What is going to be extra challenging is the optical arrangement," he says. It would take the array about 10 hours to detect an Earth-like planet and perhaps 14 days to obtain a reasonable spectroscopic signal; holding the array steady over such long periods is a major issue, he notes.

Like IRSI, the TPF is still at a formative stage. Current plans envisage four to six mirrors, each up to 5 meters in diameter, spanning a total distance of between 75 and 100 meters, with a tentative launch date of 2010. The mirrors might be mounted on a single structure, but "formation flight is a very serious option," says JPL's Beichman, the TPF project manager. The big challenge facing TPF is the need for large, lightweight telescopes. "This relies on developments for the Next Generation Space Telescope project [the successor to Hubble]," says Beichman. "We also need interferometry techniques being developed for SIM. With these projects under our belt, TPF can be done with acceptable risk."

But of all the planned missions, the grandest, most speculative, and furthest over the horizon is NASA's Planet Imager (PI). The PI is a "dream mission," says Fridlund, and "a gleam in Mr. Dan Goldin's eye," according to Alan Penny of Britain's Rutherford Appleton Laboratory, a member of the IRSI project team. The PI, with a tentative launch date of 2020, is likely to comprise a squadron of TPF-type spacecraft, each one carrying four 8-meter telescopes. They would be dispersed over distances comparable to the width of the United States and would produce images of alien Earths which, although fuzzy, would have discernible details. In NASA's words, the PI will offer "humanity's first image of another world."

Whether or not it is NASA's PI that will give us our first glimpse of distant life, astronomers are convinced that some kind of space interferometer capable of seeing life-bearing planets is just a matter of time. The urge to learn about habitable new worlds is too basic to ignore for long, says Antoine Labeyrie, director of the Observatory of Haute-Provence near Marseilles, France. "It is perhaps the same curiosity which may have stimulated the prehistoric dwellers of the Greek coastline into observing and exploring the islands they could see in the distance," he says. Now that we have spotted clues to other worlds, he adds, "we are in a similar situation." **–ANDREW WATSON**

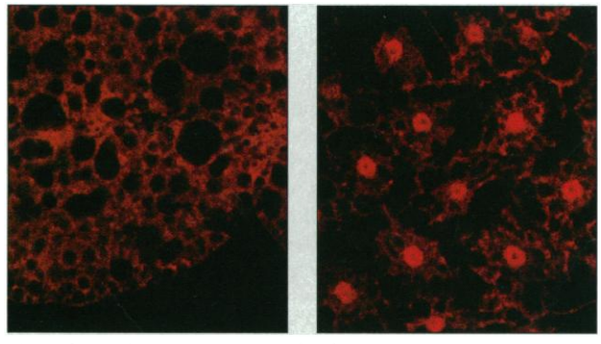
IMMUNOLOGY

Fly Development Genes Lead to Immune Find

Guided by fruit fly genetics, scientists are finding that the human innate immune system may be more specialized than they had thought

Like a lowly foot soldier toiling in the shadow of better equipped and better trained cavalry units, the innate immune system, the body's first line of defense against invading pathogens, has long been eclipsed by its partner, the adaptive immune system. In part, this relative lack of interest can be traced to immunologists' view of innate immunity as a sort of brute-force system that unleashes blunt, nonspecific weapons at any and every invader, keeping the foe at bay until the adaptive system with its highly specific weapons—antibodies and T cells—can take over. But now, aided by results from an unlikely source—the developmental control genes of the fruit fly—researchers are developing a new and more intriguing picture of the innate immune system.

Over the past few years, researchers have found that a family of proteins related to the Toll protein of fruit flies, which was first identified as a developmental protein, plays a key role in triggering innate defenses against bacterial and fungal invaders—not only in flies, but in organisms as divergent as tobacco plants and humans. Scientists are still sorting out the roles of the newly discovered proteins, but a few trends are emerging. There is strong evidence



K. ANDERSON

First alert. The Dorsal protein (red) moves from the cytoplasm *(left)* to the nucleus *(right)* after infection in these larval fly cells.

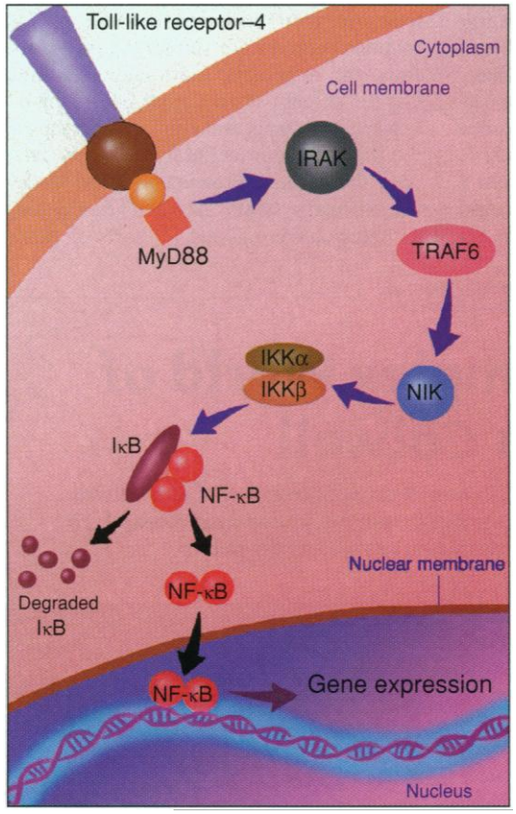
that the innate system not only provides a first line of defense, but also alerts the more specialized adaptive immune system to the presence of a dangerous microbe. And there are tantalizing clues that the innate system itself, instead of mounting a single generalized response as long thought, may have specific pathways to target particular pathogens.

Drug companies are especially interested in these findings, as they could eventually help scientists design more effective and safer vaccines and provide better treatments for chronic inflammatory and autoimmune diseases and severe microbial infections. Indeed, more than half a dozen pharmaceutical and biotechnology firms, plus dozens of academic labs, are doing research on the Toll pathway, and results are coming thick and fast. Five human Toll-like proteins have been published to date, molecular biologist Fernando Bazan of DNAX in Palo Alto has described at least five more at meetings, and there are likely more waiting in the wings. The field "is going to be dynamite" for the next few years, says molecular biologist Paul Godowski at Genentech Inc. in South San Francisco.

Thirteen years ago, when the first *toll* gene was identified, no one would have anticipated that the proteins would be playing such a "dynamite" role in immunology. The gene was discovered in a screen for mutations that interrupt the early stages of embryonic development in the fruit fly *Drosophila melanogaster*; the *toll* mutation disrupts proper formation of the insect's front and back. Developmental biologist Kathryn Anderson of the Sloan Kettering Institute in New York and her colleagues eventually showed that the *toll* gene makes a receptor protein that picks up developmental signals at the cell membrane and sends them to the nucleus. But as Anderson and other developmental biologists began identifying the various intracellular molecules that relay those signals, they found their work taking an unexpected direction—merging with work on the innate immune system.

In the late 1980s, researchers studying inflammation—one of the main weapons of innate immunity—began uncovering signaling pathways that converge on a protein called NF-κB, which turns on genes that make proteins that trigger inflammatory responses in other cells. They found that one of the cell surface receptors that passes its signal to NF-κB is the receptor for the protein interleukin-1 (IL-1), which among other things helps to induce fever.

As it happened, the developmental biologists found that one of the proteins they had identified in their signaling path, which goes by the name Dorsal, is structurally similar to NF-κB. Soon they also realized that the upstream proteins Toll and the IL-1 receptor had similarities, too. A few years later, researchers linked the Toll pathway to the immune system of insects when they found that Dorsal and a related protein, Dif, travel to the nucleus in response to infection. Even more remarkably, plant scientists found that proteins resembling Toll help plants fend off attacks from bacteria and fungi. And last summer, immunologist Charles Janeway of Yale University and his colleagues made the first link to human immunity. They identified the first human Toll protein, now called Toll-like receptor–4 (TLR4), and showed that it activates NF-κB, an indication that it may play a role in the innate immune system.



Toll road. The human Toll pathway conveys signals to the nucleus, turning on immune-system genes.

Indeed, just last week researchers reported the first direct evidence for such a role. Godowski, Austin Gurney, and their colleagues at Genentech reported in *Nature* that one of the human Toll-like receptors helps to alert immune cells to the presence of lipopolysaccharide, a component of certain bacterial cell walls, including *Escherichia coli* and *Salmonella*. Although scientists knew that lipopolysaccharide triggers an innate immune response that involves NF-κB, exactly how the cell detects its presence was a mystery. Toll had already become a leading suspect in the lipopolysaccharide reaction, however, because previous work in flies had shown that Toll activates Dorsal—the NF-κB relative—in response to fungal invasion.

To test if any of the human Toll-related receptors really do respond to lipopolysaccharide, the Genentech scientists exposed immune cells to purified lipopolysaccharide. In response, the RNA instructions for making Toll-like receptor–2 (TLR2) increased, indicating that more of the receptor was being made. What's more, the researchers found that the receptor could respond to lipopolysaccharide by increasing NF-κB activity. Molecular biologists Mike Rothe and Carsten Kirsching of Tularik, a biotech firm in South San Francisco, have reported very similar results at several meetings.

Other experiments, chiefly in the fruit fly, suggest that there are specialized Toll receptors that respond to different pathogens. For example, Toll is known to trigger the production of an antifungal peptide, drosomycin, in the fly. But molecular biologist Jules Hoffmann, of the Institute for Cellular and Molecular Biology in Strasbourg, France, has reported that *Drosophila* larvae lacking Toll could still turn on an antibacterial peptide called diptericin. Hoffmann and his colleagues suspect that a parallel path—perhaps through one of the four Toll-related proteins reported so far in flies—responds to bacteria, while the original Toll responds to fungal infections. They have shown that different proteins in the Toll pathway respond to fungal and bacterial infections, as do Anderson's recent unpublished experiments.

The human innate immune system may have similar specificity. Godowski found that TLR2 has varying sensitivity to lipopolysaccharide molecules from different kinds of bacteria—two strains of *E. coli* and one of *Salmonella*. Although that may be due to different preparation techniques, Godowski says it "raises an intriguing possibility that different Toll receptors may have the ability to recognize different pathogens." What's more, in unpublished work Rothe and his colleagues have tested several other members of the human TLR family, and only TLR2 responded to lipopolysaccharide, Rothe says. Says Godowski: "There's going to be an incredible amount of interesting work that will come out of looking at these Toll receptors individually and perhaps in combination."

Because so far the handful of Toll proteins with known functions seem to respond

ILLUSTRATION: TAINA LITWAK

to one kind of pathogen, Anderson speculates that both humans and flies may have specific protein pathways for different invaders, although this isn't proven yet. Scientists hope that with a better understanding of how specific pathogens trigger the immune system, they might be able to selectively shut down certain proteins to treat inflammatory diseases.

Although researchers are still teasing out all the action of the various Toll proteins, they do know that Toll provides a link between the adaptive and innate immune systems. Naïve T cells—members of the adaptive immune system—that have not been exposed to antigens need two signals to become active. The first comes from the binding of an unfamiliar protein, or antigen, and the second comes from a protein called B7.1 and its relatives. And Janeway's work now links B7.1 to the innate immune system via the Toll pathway.

Janeway reported last summer that the active form of TLR4 increases production of B7.1. Immunologist Douglas Fearon of the Wellcome Trust in Cambridge, U.K., says that B7.1 may be a sort of red alert, released if the innate immune system, through its Toll-like receptors, has recognized an infectious invader.

While researchers pursue Toll proteins in hopes of medical applications, they are also thinking about what these new findings are telling us about evolution. Because the Toll immune proteins are similar across plants, flies, and mammals, most scientists think that the defense system arose before the divergence of plants and animals—perhaps at the dawn of multicellular life. Only later were the immune proteins co-opted by developmental systems. "You can't do anything as luxurious as making all sorts of fancy body parts without an immune response," says molecular biologist Michael Levine of the University of California, Berkeley.

It may be that only flies have used Toll in developmental roles, however—to date, there is very little evidence that Toll relatives are important for mammal or plant development. "In all of our experiments doing knockouts in mice, we've never seen a developmental phenotype," says David Baltimore of the California Institute of Technology in Pasadena, who helped characterize the NF-κB pathway.

Meanwhile, even as researchers continue to probe the functions of the Toll proteins, more of them continue to be uncovered. "We're not sure where this family ends," says molecular biologist Michael Karin of the University of California, San Francisco. "It's a very exciting field."

–GRETCHEN VOGEL

NATIONAL SCIENCE FOUNDATION

The Biocomplex World of Rita Colwell

In a discussion with *Science*, NSF's new director, microbiologist Rita Colwell, outlines her views on topics ranging from environmental research to computer science and educating students as well as the public

Biocomplexity. The word evokes images of the incredibly rich variety of the living planet, and it hints at the formidable scientific challenge of trying to understand such an intricate system. That twin message appeals to Rita Colwell, the new director of the National Science Foundation (NSF), who plans to make the study of biocomplexity a major new thrust for the $3.5 billion agency.

Last month Colwell, a microbiologist from the University of Maryland, was sworn in as the first woman to head the 48-year-old foundation, the government's flagship agency for the support of nonbiomedical academic research. She's no stranger to NSF, having served on its presidentially appointed oversight board under Reagan appointee Erich Bloch and as a longtime reviewer and grantee (*Science*, 13 March, p. 1622). "It's sort of like becoming president of your alma mater," she says. Her "campus" consists of a 5-year-old, 12-story building in Arlington, Virginia, that houses NSF's administrative staff of 1250, and the job comes with a 6-year term, sub-Cabinet rank, and an annual salary of $136,700. Earlier this month, Colwell, 63, met for 90 minutes with a group of reporters and editors at *Science* to discuss her plans for the agency.

Colwell takes the reins from physicist Neal Lane, now the president's science adviser and head of the Office of Science and Technology Policy (OSTP). Lane managed to win steady annual budget increases for both core programs and new facilities during nearly 5 years as director by emphasizing the agency's role as the government's major funder of basic academic research. With a deft wordsmith's touch, Lane successfully deflected congressional pressure to fund more applied research by redefining NSF's mission as "conducting basic research for strategic purposes" (*Science*, 20 December 1996, p. 2000). Similarly, by defining biocomplexity as "the interaction of biological, chemical, social, and economic systems," Colwell hopes to avoid the "baggage" attached to such related terms as biodiversity, which some conservative politicians see as a refuge for tree-hugging environmentalists, and sustainability, which some industrial leaders say smacks of bureaucratic meddling in the free market. She sees biocomplexity as a unifying theme for several NSF initiatives, some ongoing and others still in the planning stage (see the related News of the Week story, p. 1935).

PHOTOS BY: SAM KITTNER

Lane also championed the importance of undergraduate teaching and the need to explain to the public how long-term investment in research translates into a stronger economy, two issues that Colwell says are high on her agenda, too. "Seventy-five percent of the public is in favor of basic research," she says, citing a recent study. But "they don't understand it." And compared to what many companies spend on R&D to improve their products, she says the federal investment in science "is marginal."

Colwell's interest in science education also extends to the nation's elementary and secondary schools. And she believes that scientists must play a major role. "No group bears more responsibility for improving K-12 math and science education than the scientific community itself," she told a recent gathering of science writers. Using a variation on Clinton's 1992 campaign slogan to play on the current preoccupation with the millennium computer bug, Colwell punned, "It's not Y2K, stupid, it's K-12."

Information technology is another priority area, says Colwell, and her vision of the field extends far beyond computer science. "IT pervades the country's business," she says. "For instance, I think that the behavioral and social sciences are one