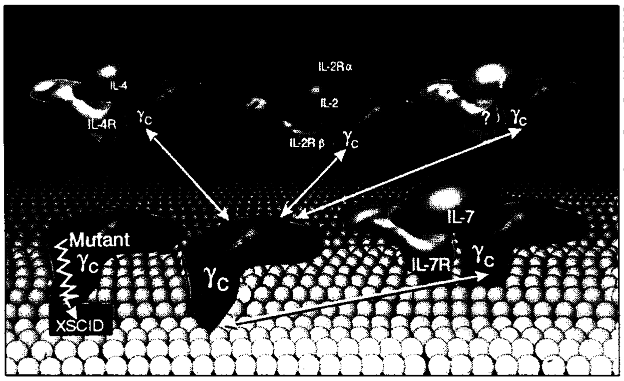
IMMUNOLOGY

'Bubble Boy' Paradox Resolved

Earlier this year, a team of researchers at the National Institutes of Health (NIH) solved a biological mystery when they identified the gene that is at fault in the hereditary disease known scientifically as X-linked severe combined immunodeficiency (XSCID)—and colloquially as "bubble boy disease." By so doing, however, they created another mystery. The defect they identified was in the gene for one of the proteins that make up the receptor for interleukin 2 (IL-2), a cytokine, or intracellular signaling protein, that helps regulate the immune system. And although the defect presumably blocks all of IL-2's effects, it did not seem capable of causing the devastating immune system failure that afflicts XSCID patients. Humans and mice that lack IL-2 entirely, for example, suffer far milder symptoms.



W.J. LEONARD AND J.M. AARONS

Common bond. The normal γ chain is part of the active forms of at least three interleukin receptors.

Now, two teams, one led by Warren Leonard of the National Heart, Lung, and Blood Institute (NHLBI), the other by Kazuo Sugamura of Tohoku University School of Medicine in Sendai, Japan, have solved this mystery (also see pages 1874, 1877, and 1880). And while their work doesn't promise an immediate cure for XSCID, it does add an important piece to an emerging picture of the structure and function of cytokine receptors.

What the two teams have shown is that the IL-2 receptor protein defective in XSCID (the γ chain) may form part of two other cytokine receptors as well: those for IL-4 and IL-7. Each of the three cytokines IL-2, IL-4, and IL-7 boosts a different stage in the growth and development of T and B cells. These cells provide both the commanders and weapons of the two major arms of the immune system —the arm based on cells that kill infected, cancerous, or damaged cells and the one based on antibodies. A defect in the three receptors should thus explain the severity of XSCID, says Leonard: "When you simultaneously inactivate multiple cytokine systems, the defect is going to be greater than when you inactivate any one alone."

The investigation that led to the new finding began in January, when Leonard, working with NHLBI colleague Masayuki Noguchi and O. Wesley McBride of the National Cancer Institute, discovered the XSCID IL-2 receptor defect. Because of the devastating nature of the XSCID immunodeficiency compared to that of IL-2 deficiency, the Leonard team immediately suspected the γ chain would turn up in receptors for other cytokines that regulate T and B cells, most of which comprise two or three protein chains. To the NHLBI team, the IL-4 and IL-7 receptors were obvious suspects. "Only a single chain for the IL-4 and IL-7 receptors had been identified," says Leonard, "so we postulated that, analogous to many other cytokine systems, a second chain would also exist."

Something else piqued the Japanese team's interest in the IL-4 receptor: The strength with which the receptors bound IL-4 appeared to vary from lab to lab. "We guessed that there must be another component to the receptor to account for this [difference]," says Tohoku University's Masataka Nakamura. Spurred on by these observations, the Sugamura team went on to demonstrate that the mouse IL-4 receptor can contain a γ chain, and the Leonard team showed that both the human IL-4 and IL-7 receptors can contain it.

According to the researchers, one chain in the multichain IL-2, IL-4, and IL-7 receptor complexes is unique to the receptor and binds its specific cytokine, while the addition of the common γ chain increases the strength of the binding between the cytokine and the receptor. The γ chain also enables the receptor to pass its signal to the cell interior.

The Leonard and Sugamura teams are now hot on the trail of other interleukin receptors that might share the common γ chain. A report in the July *EMBO Journal* from Gerard Zurawski and his colleagues at the DNAX Research Institute in Palo Alto, California, suggests one likely possibility. They found that the IL-13 and IL-4 receptors share a second chain, which they hadn't yet identified. Both Sugamura and Leonard predict this will prove to be the widespread γ. "It's very exciting, this shared receptor subunit business," says Maureen Howard, director of immunology at DNAX and a codiscoverer of IL-4. "In the last couple of years it's become a theme: Cytokines with overlapping biological properties share common receptor chains."

It now appears that cells may mix and match a limited number of receptor subunits to create a larger array of cytokine receptors. This, the researchers say, may be nature's way of upgrading the signaling systems to handle the increasingly complex interactions of the cells of higher organisms.

–Rachel Nowak

PALEOCLIMATES

Ancient Climate Coolings Are on Thin Ice

SAN FRANCISCO—Like readers nearing the end of a fascinating tale, only to find that the last chapter may have been garbled by a careless printer, climate researchers today are a frustrated bunch. For the past year, the climate community has been transfixed by the history of ancient climates gleaned from two ice cores drilled out of the thickest part of the Greenland ice sheet. First the two cores—the European Greenland Ice-Core Project (GRIP) and the U.S. Greenland Ice Sheet Program II (GISP2)—revealed that the last ice age, from about 12,000 to 110,000 years ago, was punctuated by bursts of warming that took hold in as little as 10 years. Then, in July, a preliminary analysis of the GRIP core suggested that just before the ice age, the warm interglacial period was shattered by sudden cooling pulses (*Science*, 16 July, p. 292). That, researchers thought, implied that our own warm climate—analogous to the last interglacial—may be less stable than it seems. If they obtained similar data from GISP2, it would bolster that conclusion.

Instead the two-core comparison, reported last week, has undermined it. As GRIP and GISP2 investigators announced at the fall meeting of the American Geophysical Union in San Francisco, and in papers in *Nature*, they tried to match the cores' records of two climate signals. One signal is electrical conductivity, which decreases in ice formed during cold periods because it contains more windblown dust. The second is the oxygen-isotope ratio in the water molecules, a measure of temperature. For 90% of their length, down to a depth of about 2700 meters and an age of more than 100,000 years, the records dovetail almost exactly, adding to the groups' confidence in their ice-age findings. Below that depth, however, where some of the ice probably dates from the interglacial period between about 110,000 and 130,000 years ago, the correlation between the two cores falls apart. Notes GRIP investigator Willi Dansgaard of the

University of Copenhagen, "Both records cannot be correct." In fact, Dansgaard concludes gloomily, "maybe neither is."

Though the news is disappointing, the problems aren't all that surprising, the ice corers note. At depths corresponding to the interglacial period, just a few hundred meters above the bedrock, the record is vulnerable to distortion by ice flow. At those depths, "there are much higher stress levels," says Ken Taylor of the Desert Research Institute, who works on GISP2. "If you're going to run into problems, you'd expect it to be there."

The crushing pressures can thin softer ice layers or even squeeze them out of the layer-cake climate record altogether, like ripping random pages out of a novel. And the flow of ice across the bedrock generates shear stresses that can fold the layers, sandwiching older ice between younger or vice versa. That process could create the appearance of an abrupt climate shift where none had occurred, says Taylor—as if a key scene had been inserted in the wrong chapter.

Ice from the lowermost 200 to 300 meters of the GISP2 core shows ample signs of trouble. The millimeters-thick annual layers of ice are tilted and contorted, in places vanishing entirely. And those small-scale disturbances probably signal bigger trouble, says Taylor, including folding that could seriously scramble the chronology.

Some GRIP investigators, however, aren't ready to abandon their conclusions about interglacial climate just yet. They are pinning their hopes on the fact that the first tilted layers found so far in their core are more than 100 meters lower than they are in the GISP2 core. That raises the possibility that the GRIP core's record of the last interglacial has escaped distortion, says Dansgaard. On the other hand, Taylor reported that he could correlate some features in the two electrical conductivity records only if he assumed that squeezing and folding began at the same place in both cores, casting doubt on the idea that GRIP has an extra 100 meters of clean ice.

Until investigators know for sure whether or not the GRIP record can stand on its own, their conclusions about the last interglacial are as unstable as they recently assumed the interglacial climate was. Researchers are now discussing one way to get a firmer answer: measuring an isotopic signal in ancient air trapped within the GRIP ice to see whether it matches readings from Antarctic ice dating from the last interglacial period. A good match might bear out the GRIP investigators' hopes that they have an accurate record of the last interglacial. But if not, disappointed investigators will be left scrutinizing the crystal fabric and chemical makeup of the ice cores for ways to write the true version of this climatic mystery story.

–Tim Appenzeller

MATERIALS SCIENCE

Is the Future Here for Gallium Arsenide?

In the world of semiconductors, where silicon is king, a cynical jest has circulated for years among materials scientists. Gallium arsenide, they say, is the material of the future—and it always will be. Over the years this promising material—which can be six times as fast as silicon in microelectronic circuits—has proven less reliable and more difficult to exploit than silicon. Now, Gallia Inc., a small startup company in Weston, Massachusetts, hopes to change that by eliminating a key barrier to the compound's application in semiconductor manufacture.

Specifically, the obstacle is an inability to easily coat the compound with a stable, protective layer of insulation, a process known as passivation. Without such a layer, it is impossible to take full advantage of gallium arsenide's electrical properties and create, for instance, a counterpart to the most popular type of silicon transistor. But at a recent materials meeting,* Gallia scientist Andrew MacInnes reported that his company can for the first time permanently passivate gallium arsenide with a novel form of gallium sulfide.

If Gallia's new passivation method meets industry approval, it could boost the material's fortunes and may one day lead to more robust and powerful lasers, better solar cells, and faster microcircuits. "It's very interesting work. They've done a good job," says passivation expert Jerry Woodall of Purdue University. He adds, however, that industry's proficiency with silicon is now so great that even passivating gallium arsenide may not be enough to dethrone silicon.

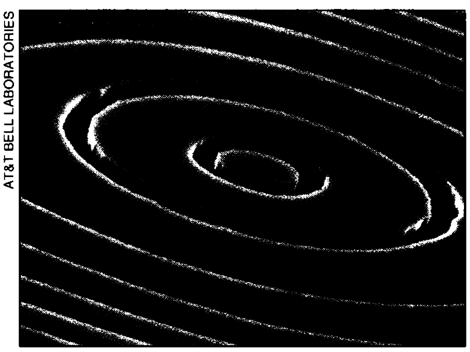
Gallium arsenide's promise has intrigued researchers for years, not only for its speed, but because gallium arsenide is a direct-band gap material. That means that it can easily absorb and emit light, making it a natural choice for photonics applications and solar cells and lasers. Yet gallium arsenide has always lagged behind silicon, in large part because silicon can be easily passivated by a simple thermal oxidation procedure that creates a shell of silicon dioxide.

But because gallium arsenide doesn't form a passivating oxide layer, researchers were forced to take another tack. Six years ago, for example, Claude Sandroff and his colleagues at Bell Communications Research discovered they could passivate gallium arsenide by immersing it in solutions of inorganic sulfides, a process that formed a few monolayers of gallium sulfide on the surface (*Science*, 2 October 1987, p. 27). But this approach does not lend itself to large-scale commercial application, especially since the coatings quickly decay when exposed to air.

MacInnes and his colleagues at Gallia have now improved on Sandroff's approach. In their work, spun off from research at Harvard University and the National Aeronautics and Space Administration, they use chemical vapor deposition (CVD) to lay down stable layers of a novel cube-shaped gallium sulfide crystal onto gallium arsenide. In this process, an organic gallium sulfide precursor molecule is vaporized, releasing gallium and sulfur atoms that combine to form gallium sulfide molecules that are deposited onto a substrate. The CVD method should be easy to integrate into current semiconducting manufacturing, MacInnes says.

Gallia is exploring several immediate applications for its new technique. The company has shown, for instance, that their passivated gallium arsenide lasers operate at much higher powers than conventional gallium arsenide lasers without blowing up. Another company goal is to find out more about the properties of their gallium sulfide: It, too, is a direct band-gap semiconductor, one that might be used to make an ultraviolet laser.

AT&T BELL LABORATORIES



Coming on target. Passivation may improve gallium arsenide lasers like this one.

There is another, more far-reaching hope as well. Silicon has so dominated the semiconductor industry partly because its silicon dioxide coating allows the creation of a switch called a MOSFET (metal oxide semiconductor field effect transistor), which is used in almost every digital circuit. At the meeting, MacInnes asserted that, thanks to their new passivation technique, they can now make a MOSFET-like switch with gallium arsenide. There have, however, been false claims of gallium arsenide MOSFETs in the past, so Gallia's claim will certainly meet skepticism for some time. As Sandroff, who now consults on surface passivation, points out, "So far no one has been able to do it." Gun-shy after all these years, it seems that no one is about to predict the gallium arsenide revolution until it happens.

–John Travis

* *The Materials Research Society meeting was held from 29 November to 3 December in Boston.*