

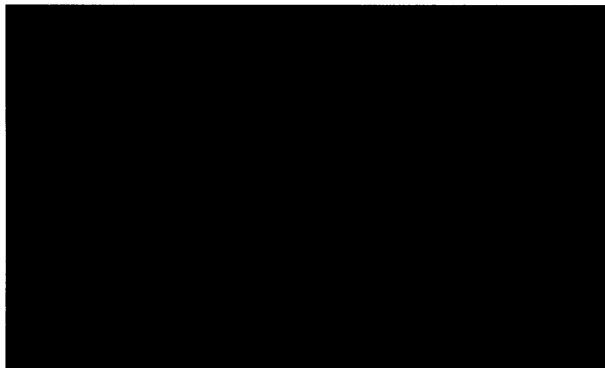
fault in other neurological diseases as well. Alzheimer's disease is defined in part by protein tangles inside the cell similar to those modeled in the current study. But other protein clumps, amyloid plaques outside neurons, have received more attention lately (see following story). Kopito says it's possible an overloaded UPS or similar mechanism could allow plaques to form. He also suspects UPS overload in bovine spongiform encephalopathy, or "mad cow disease," and its human cousin, Creutzfeldt-Jakob disease, which are both characterized by clumps of abnormal protein fragments. If so, says Kopito, "this could be an explanation" for how these mysterious diseases kill neurons.

—LAURA HELMUTH

NEUROBIOLOGY

New Clue to the Cause of Alzheimer's

Alzheimer's disease sneaks up on its victims, robbing them first of short-term memory and then ultimately of all ability to think and reason. Like several other neurological diseases, Alzheimer's seems to be caused by abnormal protein deposits accumulating in the brain (see previous story). In Alzheimer's



Alzheimer's suspect. The red staining shows the distribution of neprilysin in the normal mouse brain.

er's, the prime suspect is a small protein called amyloid beta ($A\beta$), which is a major component of the pathological plaques that stud the patients' brains. But what causes that protein to accumulate?

Most Alzheimer's researchers have focused on the enzymes that free $A\beta$ from its precursor protein (*Science*, 29 September 2000, p. 2296). By releasing too much $A\beta$, overactive enzymes could lead to abnormal $A\beta$ deposition in the brain. Recently, however, researchers have been approaching the problem from a different direction: looking for enzymes that degrade the peptide. If the enzymes are underactive, the result could also be $A\beta$ buildup. "It's just as important to find the [$A\beta$] degradation pathway as the synthesis pathway," says Rudolph Tanzi, an

Alzheimer's researcher at Massachusetts General Hospital in Boston.

On page 1550, a team led by Takaomi Saido of the RIKEN Brain Science Institute in Saitama, Japan, now provides direct evidence in mice that a protease called neprilysin could be a natural $A\beta$ -degrading enzyme. "It might play an important role in clearing $A\beta$ in the brain," says Alzheimer's researcher Sangram Sisodia of the University of Chicago Pritzker School of Medicine. But he and others caution that more work will be needed to confirm that neprilysin does indeed break down $A\beta$. Neprilysin is not the only candidate for that job, however.

Last year, Dennis Selkoe's team at Harvard Medical School in Boston showed that a neuronal protein called insulin-degrading enzyme can break down the peptide in lab cultures. If a deficiency of either—or both—of these enzymes turns out to contribute to Alzheimer's, the enzymes could provide new targets for drugs to prevent or treat the disease, which afflicts 4 million people in the United States alone.

Saido's team identified neprilysin as a possible $A\beta$ -degrading enzyme about a year ago. In that work, the team injected mouse brains with $A\beta$ and also with a series of specific protease inhibitors to see which would reduce the breakdown of the peptide. This led the researchers to neprilysin and three related protein-destroying enzymes. Because neprilysin had the greatest activity against $A\beta$ in test tube studies, the scientists collaborated with Craig Gerard's team at Harvard Medical School, which had knocked out the neprilysin gene in mice, to see how that affected the animals' ability to degrade the peptide.

When injected into the brains of normal animals, $A\beta$ is broken down within about 30 minutes. But in the knockout mice, the researchers found, almost all of the peptide persisted. By crossing knockout mice with normal animals, the team produced mice that have just one active copy of the neprilysin gene. These animals yielded intermediate results: More of the injected $A\beta$ persisted than in normal animals, but less than in the complete knockouts. That's important, Saido says, because it "indicates that even partial reduction of neprilysin activity, which could be caused by aging, will elevate $A\beta$ and thus cause Alzheimer's."

The Saido team also found that natural $A\beta$ levels in the knockout mice were highest in brain regions, such as the hippocampus and cortex, where Alzheimer's plaques are most prominent. This and recent findings from

Patrick McGeer and his colleagues at the University of British Columbia in Vancouver are consistent with the possibility that neprilysin deficiency could contribute to Alzheimer's, says Saido. When McGeer's group analyzed neprilysin levels in the brains of patients who had died of the disease, they found the lowest levels in the high-plaque regions. "If you have adequate amounts of neprilysin, you never accumulate $A\beta$," McGeer concludes.

Despite the biochemical evidence suggesting that neprilysin deficiency could lead to Alzheimer's, to clinch the case researchers are waiting for two additional findings. One would be the demonstration that neprilysin deficiency increases plaque formation in an Alzheimer's mouse model—an experiment that Saido describes as the "top priority." The other is genetic evidence linking the neprilysin gene to human Alzheimer's.

Tanzi's group at Harvard has found hints of such a genetic linkage between human Alzheimer's and the region on chromosome 3 where the neprilysin gene is located. It was just short of statistical significance, however, and he hasn't published the work. But a neprilysin deficiency could be caused by a defect in the machinery needed for expressing the gene, as well as in the gene itself, Saido speculates.

Meanwhile, Selkoe and his colleagues are following up on the insulin-degrading enzyme. Among other experiments, they are knocking out the gene in mice to see whether that alters $A\beta$ handling in the brain. If at least one of these enzymes proves to be a bona fide $A\beta$ -degrading enzyme in the brain, Alzheimer's researchers will have an important new line of investigation to pursue in their efforts to tame this devastating disease.

—JEAN MARX

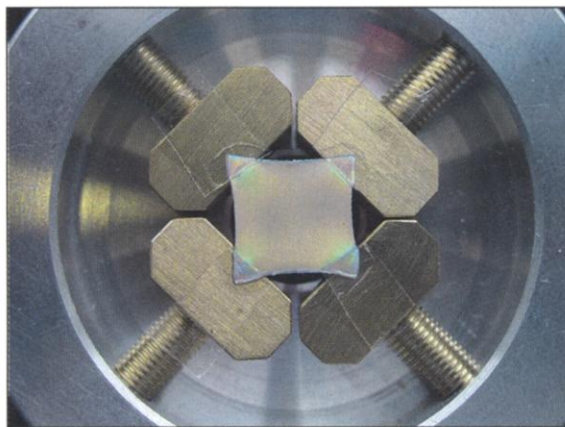
SOLID STATE PHYSICS

Rubbery Liquid Crystal Gives Lasers a Stretch

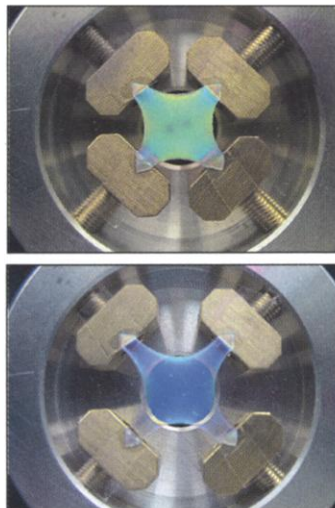
You won't find it in gumball machines, but Heino Finkelmann's stretchable laser may be the cutest example of elasticity since Silly Putty. Finkelmann, a physical chemist at the University of Freiburg, Germany, created a new type of artificial rubber with the light-altering properties of a liquid crystal display. Then, colleagues at Kent State University in Kent, Ohio, showed that it could be used as a new type of laser—one that emits light without mirrors or a cavity and that changes its wavelength when pulled like taffy.

Behind the fun lies serious physics. Finkelmann's rubber is a photonic bandgap material, one that can block light in a controlled way. Such materials are important as tiny light guides in the world of optical communications, but they are expensive and tricky to en-

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Stress test. Stretching a 1-cm square of liquid crystal rubber changes its molecular structure, causing captured light to shift toward the blue.



gineer. "Here's a hope that one can make naturally occurring bandgap materials that therefore are very inexpensive, and here they're also tunable," says Azriel Genack, a physicist at the Queens College of City University of New York in Flushing. "It's just a question of mixing the chemicals together."

The transparent rubber is about as stretchy as an office rubber band. It is also a liquid crystal, a member of a class of twilight materials whose structures lie partway between the neat ordering of a true crystal and the haphazard disorder of a liquid. In a typical liquid crystal, long, rodlike molecules spontaneously line up with one another. Finkelmann's material varies the theme: The rodlike molecules twist like the steps of a spiral staircase, a structure first observed in derivatives of the cholesterol molecule. In such so-called cholesteric liquid crystals, the helical structure is described by its pitch, the distance needed to make one complete twist.

What makes cholesteric crystals useful, Finkelmann explains, is their ability to capture light. "If light is coming in the direction of the pitch axis, light of a given wavelength is reflected," he says. That means that if light of just the right wavelength enters the liquid crystal material, the twisted molecules can trap it just as mirrors do in a regular laser. Where to get such fine-tuned light? The trick, Finkelmann says, is to impregnate the material with a fluorescent dye that, when excited by an external laser, gives off light of just the right wavelength to be trapped. If the exciting laser is powerful enough, the light emitted by the dye escapes as laser light at wavelengths both just above and just below the forbidden, trapped wavelength band.

Last year, Genack demonstrated such a fluorescent-lasing mechanism in a liquid. Finkelmann saw similar results presented at a conference by Peter Palffy-Muhoray of Kent State. Finkelmann's lab had just succeeded in creating cholesteric ordering in a rubber. "It was straightforward to transfer

this concept to our rubbers," he says.

The result, as Finkelmann, Palffy-Muhoray, and three colleagues will report in an upcoming issue of the journal *Advanced Materials*, is a material with its spiral axis oriented through its thickness. Shine a laser beam on one side, and laser light of a different frequency comes out the other. Stretch the rubber in two directions at once (see figure), and the molecular spirals shorten, causing the emitted light to shift toward the blue end of the spectrum. The color of the light leaving the rubber changes before your eyes, Finkelmann says.

The new work is a "significant step" in the progress of liquid crystal lasing, says physicist Cliff Jones of ZBD Displays in Malvern, United Kingdom. Applications may be in the offing. "I can imagine that this may lead to a low-cost, tunable laser," Jones says. Genack says he is interested in using the rubber to develop practical devices for display technology.

—ANDREW WATSON

Andrew Watson writes from Norwich, U.K.

GENE SILENCING

A Faster Way to Shut Down Genes

When scientists say a new technique ranks up there with the polymerase chain reaction (PCR), you know it's big. That's how at least one researcher is viewing a report this week of a new method for shutting off specific genes in mammalian cells. Although still in its infancy, the approach, known as RNA interference (RNAi), makes a currently arduous process much faster, much as PCR did for copying segments of DNA.

"It's going to totally

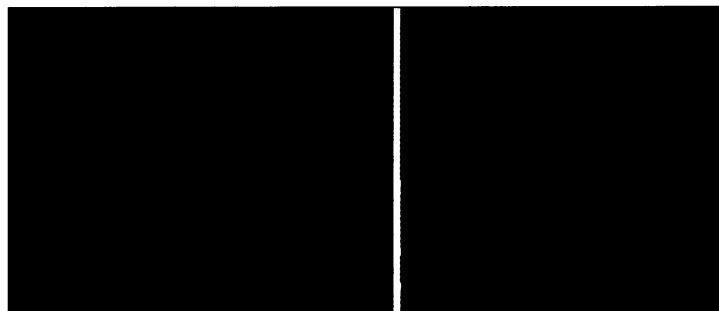
revolutionize somatic cell genetics in mammals," predicts Phillip Zamore of the University of Massachusetts Medical Center in Worcester. "Instead of devoting 6 months to a year figuring out how to turn off expression [of a mammalian gene], people will be able to go in and in a week turn off the expression of 10 genes."

RNAi is a process in which double-stranded RNA (dsRNA) molecules turn off, or silence, the expression of a gene with a corresponding sequence (*Science*, 26 May 2000, p. 1370). A variety of organisms, including plants, fruit flies, the roundworm *Caenorhabditis elegans*, and likely mammals, seem to enlist RNAi to fight off viruses and restrain the movement of transposons, pieces of DNA that can hop around and disrupt a genome.

Recently scientists have also harnessed this process as a research tool, injecting dsRNA into cells to turn off specific genes, thereby garnering clues about their function. That work has yielded some stunning results; last year, for instance, scientists used the technique to systematically block expression of nearly all the genes on two *C. elegans* chromosomes. But so far, silencing genes using RNAi has not worked well in mammalian cells; although successful in mouse embryos, dsRNA triggers a global shutdown of protein synthesis in other mammalian cells.

Now scientists at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, report in the 24 May issue of *Nature* that they have finally overcome this barrier: By using specially constructed dsRNA molecules that are shorter than those tried to date, they have shut down target genes in several different cultured mammalian cells lines. The technique won't replace gene knockout strategies, but RNAi does offer some advantages. It is faster and less labor intensive than making a knockout, and genes that are lethal when knocked out in embryos can be analyzed with RNAi in cell culture.

The new work grew out of studies of RNAi in *Drosophila*. Although much of the RNAi mechanism is mysterious, researchers know that dsRNA triggers the degradation of the messenger RNA (mRNA), blocking



Running interference. An siRNA stops its target from making protein (left); siRNAs to other genes have no effect (right).