schulte says, those ACS journals will not publish papers that appear first on ChemWeb's preprint server. And that, says Ralph Nuzzo, a chemist at the University of Illinois, Urbana-Champaign, would convince him and most of his colleagues not to post their articles on ChemWeb. "If I couldn't publish my paper [in a conventional journal], I probably wouldn't do it," Nuzzo says.

In an effort to find a compromise, Weeks says ChemWeb will remove the full text of papers from the site when they are published in a print journal, keeping an abstract and a link to the journal article. But Bovenschulte says ACS journals would still not consider such papers, because the results would already be public knowledge.

Not all journals are playing hardball. Ginsparg points out that American Physical Society journals, including the prominent *Physical Review Letters*, not only publish articles already posted on the Los Alamos preprint server, but even provide the electronic connections for authors to submit to the journals at the click of a button.

Elsevier's own journals will publish articles that appear first on ChemWeb. Indeed, Elsevier—which is ACS's chief competitor in the chemistry journal publishing business—may be counting on ChemWeb to give its journals an edge among some chemists. Elsevier officials may be hoping that researchers interested in distributing results quickly will then send their articles to Elsevier journals, says Bovenschulte. For Elsevier, he says, "this could be considered a cost of attracting the best authors."

Whatever the motivation, chemistry preprints are long overdue, says R. Stephen Berry, a chemist at the University of Chicago. The culture among chemists—with their history of close ties to industry—is more conservative than that among physicists, says Berry. Still, Berry believes that chemistry preprints have a shot. "We just have to wait and see if it works," he says. "But this is the kind of experiment we should be doing."

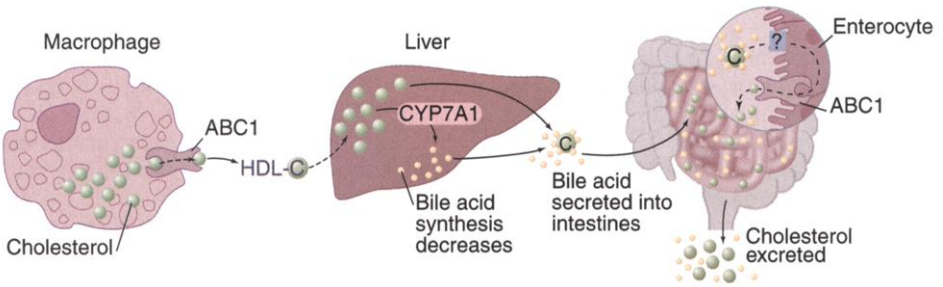
–ROBERT F. SERVICE

LIPID RESEARCH

Possible New Way to Lower Cholesterol

Clinicians may soon be able to mount a multipronged attack against cholesterol, the artery-clogging lipid whose buildup in the body is a major contributor to heart attacks and other cardiovascular diseases. Millions of people take drugs that lower cholesterol levels by blocking the body from making it. But we also consume the lipid in our diet, and today's drugs don't do much to keep our body from taking it in; nor do they take advantage of our body's ways of getting rid of excess cholesterol. New results could change that.

In work reported on page 1524, a team led by molecular pharmacologist David Mangelsdorf of the University of Texas Southwestern Medical Center in Dallas has pinpointed a biological master switch in mice that controls three pathways that work together to both rid the body of excess cholesterol and prevent its absorption from the intestine. "This is a real tour de force," says Steve Kliewer, senior research investigator at Glaxo Wellcome Inc. in Research Triangle Park, North Carolina. "It's exciting because it suggests an entirely new mechanism for reducing cholesterol." This might be done, for example, with drugs that turn up the activity of the master switch, a protein known as the retinoid X receptor (RXR).



Three ways to go. The drug LG268 fosters cholesterol elimination from the body by stimulating ABC1-mediated export of the lipid from macrophages and intestinal cells and also by inhibiting CYP7A1, a key enzyme needed for bile acid formation by liver cells.

The findings are a serendipitous outgrowth of previous test tube experiments by several groups showing that RXR teams up with any of several other proteins to turn on genes involved in cholesterol metabolism. For example, the Texas team found 3 years ago that RXR and a protein called the liver X receptor (LXR) work together to activate genes whose protein products are needed in the liver to break down cholesterol to bile acids, which are then excreted into the gut. This suggested that drugs that boost the activity of LXR might help the body rid itself of cholesterol.

To test this idea, postdoc Joyce Repa turned to a drug called LG268, which is a so-called rexinoid. These drugs bind to, and activate, RXR, which then teams up with its partner proteins, including LXR. Thus, the researchers expected that LG268 would boost LXR activity and stimulate bile acid formation.

To test that expectation in mice, Repa gave the drug to animals fed a high-cholesterol diet, which would ordinarily cause cholesterol accumulation in the liver. Sure enough, LG268 reduced these high liver cholesterol levels. But the researchers got a surprise when they conducted a second test. They redid the experiments on mice that cannot make LXR, expecting to see cholesterol pile up in the liver. Instead, the cholesterol content of the animals' livers plummeted. "We couldn't figure out why that was happening," Mangelsdorf says.

Further tests pointed to the explanation: Rather than speeding cholesterol breakdown to bile acids, LG268 exerts a powerful block on cholesterol absorption from the gut. At first, the researchers had no idea how the drug does this. They tested its effects on about 100 different genes involved in various aspects of lipid metabolism, but the experiments came up empty. Then, about a year ago, a clue appeared.

Other researchers discovered that people with Tangier disease, a rare hereditary condition that causes high blood cholesterol concentrations and severe atherosclerosis, have a defect in a protein called ABC1. They also have very low levels of high-density lipoprotein, which helps rid the body of cholesterol by carrying it back to the liver, the organ where most cholesterol breakdown occurs. "It was just like a light went on," Mangelsdorf recalls. "Bingo! Maybe [ABC1] was sitting in the intestinal cell and pumping [the cholesterol] back out" so that it wasn't absorbed into the blood, and LG268 was assisting in that process.

That's exactly what seems to be happening. The researchers found that LG268 ups production of ABC1 in cells of the intestinal wall, causing the lipid to pass right through the intestine without being absorbed. What's more, the drug turned out to activate cholesterol transport out of immune cells called macrophages. That's important, because cholesterol-laden macrophages help trigger the formation of artery-blocking atherosclerotic plaques. Activating ABC1 might thus help reverse the early steps of plaque formation, Mangelsdorf says.

The Texas group also found that LG268 stimulates ABC1 production by specifically boosting the activity of RXR-LXR pairs, and it has another surprising effect as well. The drug also boosts the activity of RXR paired with a protein called FXR, a partnership that reduces the production of bile acids by the liver. That should also help inhibit cholesterol absorption, because the bile acids dissolve

ILLUSTRATION: C. CAIN

cholesterol and other lipids in the gut, thus facilitating the absorption of these otherwise water-insoluble materials. Bile acids and cholesterol that fail to be absorbed or reabsorbed by the gut are excreted in the feces.

Despite the cholesterol-lowering potential of the rexinoids, drug researchers caution that the current drugs may not be usable because of their side effects. For example, a rexinoid derived from LG268 is approved for treating certain types of late-stage cancer and is being tested on others, but it raises levels of lipids called triglycerides in the blood, which could worsen obesity and cardiovascular disease. That may be acceptable for people with late-stage cancer who "have no other choice," says Vincent Giguère, a molecular biologist at McGill University Health Centre in Montreal. But "side effects become a big issue" for otherwise healthy people who may take cholesterol-lowering drugs for decades. Drugs that target LXR rather than RXR might be safer, because they would activate a smaller group of genes, Giguère suggests. Still, he adds, "these findings augur well for the future of cholesterol-controlling drugs."

–DAN FERBER

Dan Ferber is a writer in Urbana, Illinois.

INFORMATION THEORY

'Ultimate PC' Would Be A Hot Little Number

If gigahertz speeds on a personal computer are still too slow, cheer up. Seth Lloyd, a physicist at the Massachusetts Institute of Technology, has calculated how to make PCs almost unimaginably faster—if you don't mind working on a black hole.

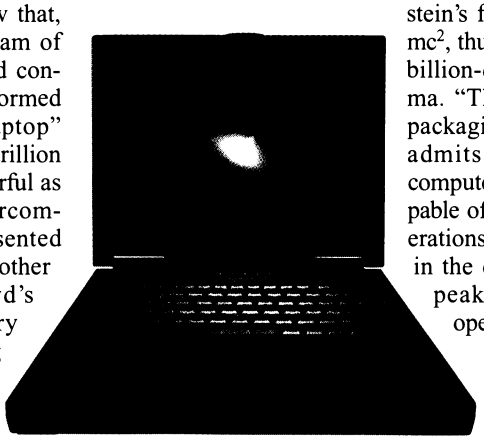
Lloyd has used the laws of thermodynamics, information, relativity, and quantum mechanics to figure out the ultimate physical limits on the speed of a computer. His calculations show that, in principle, a kilogram of matter in a liter-sized container could be transformed into an "ultimate laptop" more than a trillion trillion trillion times as powerful as today's fastest supercomputer. Although presented in whimsical terms, other scientists say Lloyd's work marks a victory for those striving to figure out the laws of physics by investigating how nature deals with information.

"It's incredibly interesting—bold," says Raymond Laflamme, a physicist at the Los Alamos National Laboratory in New Mexico. In addition to its theoretical importance, Laflamme says, the study shows what lies ahead. "Right now we are on roller skates. [Lloyd] says, 'Let's get on a rocket.'"

Lloyd's unconventional calculations are based on the links between information theory and the laws of thermodynamics, specifically entropy, a measure of the disorder of a system. Imagine dumping four balls into a box divided into four compartments. Roughly speaking, entropy is a measure of the probabilities of how the balls can land. "Ordered" outcomes (such as all four balls landing in a single compartment) are rare and have low entropy, while "disordered" outcomes (such as two balls in one compartment and a single ball in each of two others) are more common and have higher entropy.

In 1948, Bell Labs scientist Claude Shannon realized that the thermodynamic principle of entropy could also apply in the realm of computers and information. In a sense, a system such as a box with balls in it or a container full of gas molecules can act like a computer, and the entropy is related to the amount of information that the "computer" can store. For instance, if you take your box and label the four compartments "00," "01," "10," and "11," then each ball can store two bits' worth of information. The total amount of information that a physical system can store is related to entropy.

In the 31 August issue of *Nature*, Lloyd uses this principle to show that a 1-kilogram, 1-liter laptop could store and process 10^{31} bits of information. (A nice-sized hard drive holds about 10^{11} bits.) Then he figures out how quickly it could manipulate those bits, invoking Heisenberg's Uncertainty Principle, which implies that the more energy a system has available, the faster it can flip bits. Lloyd's ultimate laptop would convert all of its 1-kilogram mass into energy via Einstein's famous equation $E = mc^2$, thus turning itself into a billion-degree blob of plasma. "This would present a packaging problem," Lloyd admits with a laugh. The computer would then be capable of performing 10^{51} operations per second, leaving in the dust today's planned peak performer of 10^{13} operations per second.



All-powerful. At 10^{51} operations per second, Seth Lloyd's black-hole laptop would be the last word in computing.

CREDIT: PHOTODISC (LAPTOP); AFP/CORBIS/NASA (BLACK HOLE)

But processing speed is only half of the story. If you *really* want to speed up your computer, Lloyd says, you must also slash the time it takes to

ScienceScope

GMO Scientists Unite! Hoping to bring a voice of reason to the debate over transgenic crops, a group of scientists is launching the first society and journal to specifically address their risks.

The idea grew out of a series of international meetings, held biannually since 1988, that brought together an ad hoc group of scientists to discuss science-based regulatory policy for genetically modified organisms (GMOs). At its July meeting, organizers decided to form a permanent International Society for Biosafety Research. After years of getting hammered by "both the Greens and industry people," explains Mark Tepfer, who studies virus transfer at INRA, France's national agronomy research institute, "we need a clearer voice for scientists in the field." He and others hope to exercise "complete neutrality" in studying such hot-button issues as Bt corn's impact on butterflies.

The group's journal, *Environmental Biosafety Research*, will be launched early next year by Elsevier. Alan McHughen, a plant geneticist at the University of Saskatchewan, says it will feature research that other journals often turn down—including "negative results" studies showing that a transgenic crop appears no different from its traditionally bred counterpart.

Microbial Month Now that it is nearly finished sequencing its share of the human genome, the Department of Energy's Joint Genome Institute (JGI) has decided to tackle as many as 17 microbes—all in 1 month.

Microbial genomes typically are less than 10 million bases long, so decoding the bugs should be a snap compared with assembling the 3-billion-base human genome, says JGI's Trevor Hawkins. He predicts the Walnut Creek, California, facility will have no trouble sequencing about 2 million bases a day, enabling his team to take six or eight passes through each microbe's DNA. JGI doesn't plan to "finish" the genomes, however. Instead, it will post the data on its new "Genome Portal" Web site.

On JGI's sequencing hit list are two plant pathogens and several bacteria that fix nitrogen or sequester carbon. Two others are magnetotactic—which means they sense and move toward sources of magnetism. Stuart Levy, a geneticist at Tufts University School of Medicine in Boston, hopes his bug, a soil-dwelling *Pseudomonas* with potential for breaking down pollutants, will be among the first sequenced. That information, he says, "will move the research along much more quickly."

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