near-term benefit of the mouse sequence: Geneticists want to use the mouse genome to find and characterize new genes in the human sequence, but that would require identifying genes in the mouse at very early stages in the project and also discerning areas where the mouse and human genomes are nearly the same. Roe had broader concerns as well: "I was afraid that there would be momentum to do something that was not well thought out."

So instead of settling on a sequencing strategy right away, the group decided to test the validity of the hybrid approach, and especially whether shotgun data could aid gene discovery. "The answer came back a resounding 'Yes,' " says Green. Working with three other network members, Genome Therapeutics Corp. in Waltham, Massachusetts, simulated shotgun data by stripping down known sequences to a bare minimum. The group then evaluated how useful these new data would be for finding conserved sequence in both human and mouse genomes—sequence that would likely represent undiscovered genes. At last week's meeting, Lynn Doucette-Stamm of Genome Therapeutics reported that gene-finding programs could still pick up almost all the coding regions in shotgun data. What's more, those conserved regions helped the researchers pinpoint regulatory regions in both genomes.

Although the network has agreed to tackle "most" of the mouse genome with the shotgun approach, the researchers are still debating exactly what "most" means. Last week, Washington University's John McPherson suggested at least three-quarters. But another network member, W. Richard McCombie of Cold Spring Harbor Laboratory in New York, is not comfortable with such a high proportion. Even Gibbs has reservations. "The real scientific issues [about the optimum ratio] remain unsettled," he concedes. But the network expects to settle them soon, adds Francis Collins of NHGRI, who heads the network. Already, some mouse DNA is in the sequencing pipeline, with much more expected in the coming months. Boasts McPherson: "You should start seeing some mouse sequence hitting GenBank" soon.

–ELIZABETH PENNISI

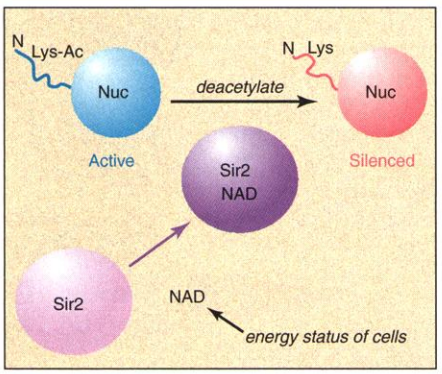
CELL BIOLOGY

New Clue to Age Control in Yeast

In fairy tales, you drink a magic potion to live longer. In real life, just eating less might do the trick. For years, researchers who work on aging have known that they could extend the lives of species from yeast to rodents by restricting their food intake. The mechanism, however, has remained mysterious. Now, a team led by molecular biologist Leonard Guarente of the Massachusetts Institute of Technology may have turned up part of the answer. The group has identified what may be a biochemical link between calorie restriction and increased life-span, at least in yeast.

The link appeared fortuitously during studies of a phenomenon called silencing that both turns genes off at particular chromosomal regions and also helps maintain the structural integrity of the DNA. In previous work, Guarente's group showed that Sir2, a protein needed for silencing in yeast and possibly other organisms, controls yeast life-span. This was likely due to its silencing activities, but no one knew exactly how the protein performed this silencing feat—much less how it might be related to aging.

As the researchers report in the 17 February issue of *Nature*, Sir2 might work by removing acetyl chemical groups from the histone proteins that bind DNA in the chromatin, a chemical change that ultimately ties up the DNA so that the proteins needed for gene activity can't gain access. Geneticists had suspected for many years that such an activity was behind Sir2's silencing action, but had never been able to catch the protein in the act of removing the acetyl groups. The Guarente team succeeded while actually studying a different type of reaction that is also catalyzed by Sir2. In the course of that work, they added a chemical called NAD to the reaction mixture. They found that when—and only when—NAD is present, Sir2 removes acetyl groups from a synthetic portion of a histone.



Silencer. With NAD, Sir2 can remove acetyls (Ac) from certain lysines (Lys) in the histones bound to DNA in the nucleosomes (Nuc).

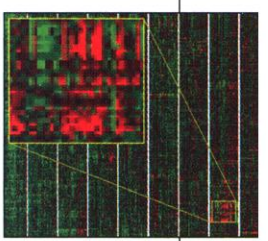
That discovery also provides a link to calorie restriction, because NAD normally helps the cell capture energy from food. When food is restricted, concentrations of available NAD could rise, Guarente proposes. This rise, in turn, could boost Sir2's silencing activities to help cells live longer. "If you lose silencing over time, you could get inappropriate gene expression, and these changes could be responsible for some of what we see in aging."

George Roth, who studies caloric restric-

CREDITS: (LEFT TO RIGHT) L. GUARENTE; J. TRENT

ScienceScope

Next-Generation Genomics Worried that the upcoming human genome sequence "won't be very useful" by itself, Francis Collins, director of the National Human Genome Research Institute (NHGRI), wants to start a new network of interdisciplinary centers that will take the next step in genome studies. Later this month, Collins hopes his Advisory Council will approve plans to solicit proposals for new Centers of Excellence in Genomics.



Over the next 3 years, Collins wants to jump-start about a dozen of the new centers. Each could have an annual budget of up to $4 million, he says, enough to combine training and research in hot areas, such as DNA chips (above). "Many centers have raw talent but no mechanism for pulling it together," he says, adding that the effort could become "a large part of [NHGRI's] portfolio."

The potential cash infusion could come at a good time for the many universities—from Caltech to Harvard—that are spending heavily on new genomics operations. "There are clear benefits to getting multiple investigators together," says Robert Waterston, who heads sequencing efforts at Washington University in St. Louis, Missouri.

Still Connected Luther Williams, who last summer was replaced as head of the education directorate at the National Science Foundation (NSF) (*Science*, 13 August 1999, p. 997), is still on the agency's payroll despite taking a job across the street with Tulane University's Payson Center for International Development and Technology Transfer. Williams is one of 119 science administrators at NSF employed under the 1970 Intergovernmental Personnel Act, which allows the government to pay above-scale salaries to attract scarce talent. But most of NSF's so-called IPAs have been recruited temporarily into the agency from universities or industry. Williams, in contrast, is one of just nine officials who have been "lent out" to another institution.

NSF deputy director Joseph Bordogna, himself a former longtime IPA, says that Williams is working on issues relating to his 10-year NSF tenure, including education reform and increasing minority participation in science. Williams declined to comment on his duties at the center, a pet project of Tulane's president emeritus, Eamon Kelly, currently head of the National Science Board.

tion in primates at the National Institute on Aging in Baltimore, says Guarente's idea is "consistent with what one might expect." Still, he cautions, "it's a big stretch to go from that observation in yeast to mammals."

When the Guarente team began its work, the researchers were investigating another theory about how Sir2 might silence DNA. Results from bacterial and mammalian proteins that resemble yeast Sir2 suggested that it might transfer part of NAD, containing the sugar ribose attached to the nucleotide adenosine diphosphate (ADP), to other proteins. They wanted to see if Sir2 would add the ADP-ribose to a synthetic histone segment, and it did. But when they further analyzed the reaction mixture, they got a surprise. Addition of ADP-ribose should increase the histone peptide's weight by 541 daltons. Instead, the researchers found a major product that weighed 42 daltons *less* than the original peptide. "That was an astounding thing," says Guarente. "It was getting smaller, not bigger."

Fortunately, Guarente knew his numbers: 42 is exactly the size of an acetyl group. "So we thought, 'Oh my goodness, it's deacetylating the peptide,' " he recalls. Other researchers hadn't been able to detect that reaction with Sir2 before, he postulated, because they hadn't added NAD. When he and his colleagues then repeated the experiments with and without NAD, they found that indeed, it is required for deacetylation by Sir2. They also showed that a related protein in the mouse performs a similar function, suggesting that Sir2 carries out the same reaction in mammals.

Although the work provides the first direct evidence that Sir2 can deacetylate, it does not prove that deacetylation is responsible for the protein's silencing activity. The problem is Sir2's ADP-ribosyl transferase activity. Last year, Danesh Moazed, a molecular biologist at Harvard University, and his colleagues showed that a particular mutation could obliterate both it and Sir2-mediated silencing. This raises the possibility that the transferase, rather than the deacetylase, is what's necessary for silencing. Guarente has shown, however, that the same mutation also curbs Sir2's ability to deacetylate histones, so it's not clear which activity is more important for silencing.

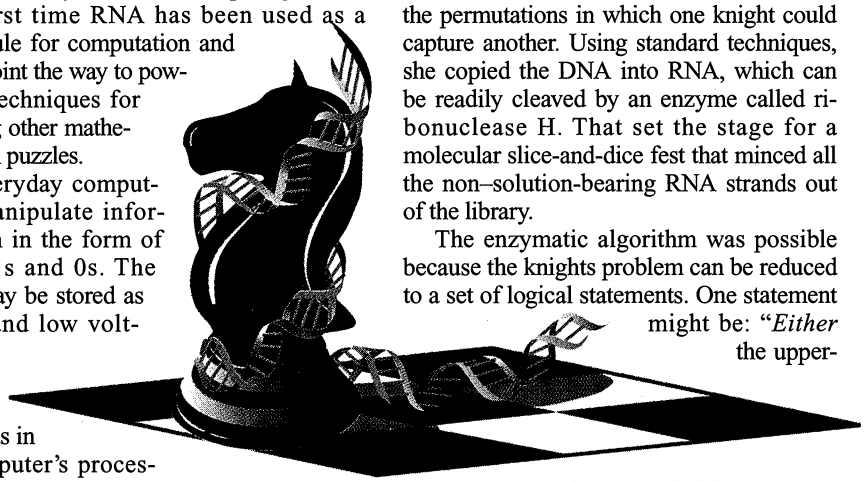
He and his colleagues tried to find out by creating a modified version of Sir2 that lacks most of its ADP-ribose transferase activity, but retains deacetylase activity. This protein performed many of the usual silencing feats, but the experiment wasn't conclusive because the protein was still a weak transferase. "I'm very excited about the new result," Moazed says. "But until we get mutations that cleanly separate the activities, the issue won't be settled." Either way, NAD seems to be involved and could thus serve as a biochemical link between Sir2-mediated silencing, caloric restriction, and aging. If so, Guarente's hypothesis may help us take a step toward living, well, happily ever after.

–EVELYN STRAUSS

MOLECULAR COMPUTING

RNA Works Out Knight Moves

Silicon upstarts aside, the best chess computers are biological—the brain of grand master Gary Kasparov, for example. Now a team of scientists at Princeton University has used a different sort of biological computer—beakers full of organic glop—to solve a chess problem. The feat, the most difficult problem ever solved by molecular computing, marks the first time RNA has been used as a molecule for computation and may point the way to powerful techniques for solving other mathematical puzzles.



Everyday computers manipulate information in the form of bits: 1s and 0s. The bits may be stored as high and low voltages (as in a computer's processor) or as north- or south-pointing magnetic fields (as in a hard drive). But they may also take more exotic forms. For example, the chemical bases that make up molecules of DNA and its cousin RNA are ideal for storing digital information. In 1994, computer scientist Leonard Adleman of the University of Southern California in Los Angeles showed that jugs of DNA could be turned into computers (*Science*, 11 November 1994, p. 1021). Since then, scientists have been using DNA to solve small mathematical problems such as adding two numbers together. Now, in the 15 February *Proceedings of the National Academy of Sciences*, evolutionary biologist Laura Landweber and her colleagues at Princeton University describe how they used RNA to solve the "knights problem" on a 3 × 3 chessboard: finding all the ways to place a collection of knight pieces (which move in an L-shaped pattern) so that no knight can attack another.

To solve this problem with a regular computer, you could start by assigning one bit to each of the nine squares on the board. Each bit represents whether a knight is sitting in that position (1) or if that position is empty (0). Then you could simply crank through all the possible combinations of 1s and 0s for the nine positions and eliminate the ones where knights are able to attack each other.

Landweber took a similar "brute force" approach. First, she synthesized 18 different stretches of DNA, each consisting of 15 base pairs. Each stretch represented a bit for a particular space—a "knight" or a "blank" for each of the nine positions on the board. (For instance, CTCTTACTCAATTCT meant that the upper left-hand corner is blank, while ACCTTACTTTCCATA meant there's a knight in the center square.) She then created a "library" of millions of DNA strands representing all possible configurations of the board—that is, every possible permutation of knights and blanks.

Landweber then methodically eliminated the permutations in which one knight could capture another. Using standard techniques, she copied the DNA into RNA, which can be readily cleaved by an enzyme called ribonuclease H. That set the stage for a molecular slice-and-dice fest that minced all the non–solution-bearing RNA strands out of the library.

The enzymatic algorithm was possible because the knights problem can be reduced to a set of logical statements. One statement might be: "*Either* the upper-left corner is blank, *or* the two squares that a knight threatens from that position must be blank." To satisfy that statement, Landweber split the library into two. Into one jug, she poured an enzyme that targeted the sequence that meant "there is a knight in the upper-left corner." To the other jug she added two enzymes that targeted the sequence that signaled the presence of a knight in the two threatened positions. After the broken fragments were all weeded out, neither jug contained an RNA strand that included sequences that had both a knight in the upper-left corner and a knight in one of the two squares threatened from that position.

Landweber then mixed the jugs together, converted the RNA back to DNA, amplified the DNA, and started all over again with another logical statement. After repeating the process for each logical statement that describes the knights process, she was left with a flask full of strands corresponding to every valid solution to the knights problem—plus a few rogues that escaped the cleaving enzymes by a fortuitous mutation. "We pulled out 42 correct solutions and one incorrect solution out of 43 clones that we tested,"

ILLUSTRATION BY C. CAIN