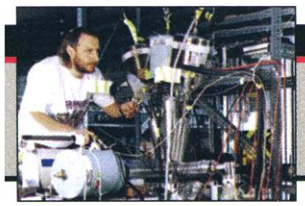
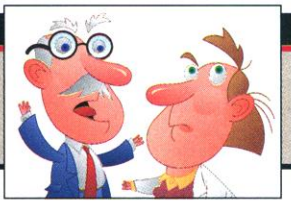


1184
Packing the nickel nucleus

LEAD STORY 1188
The blurry line between ecology and politics



1196
Gene patents: The debate heats up

they will continue using ASCA and seek observing time on the U.S. and European x-ray observatories.

The failure of the M5 rocket, in its third launch after two successes, puts a cloud over future ISAS missions. The M5 is intended to be ISAS's primary launch vehicle for the next decade. Its next scheduled mission is not until the summer of 2002, giving some breathing room to fix whatever went wrong.

ISAS officials are focusing on the first stage of the rocket, in particular the possibility of damage to the graphite rocket nozzle. Onboard cameras transmitted images of sparks coming from the rocket nozzle just before altitude control problems developed about 40 seconds after lift-off. The rocket did not achieve the desired trajectory by the time the first stage separated, and the second and third stages failed to lift the satellite into orbit, causing it to burn up in the atmosphere.

–DENNIS NORMILE

With reporting by Govert Schilling in the Netherlands.

GENOMICS

Mouse Sequencers Take Up the Shotgun

MARCO ISLAND, FLORIDA—In a dramatic departure, the genome community will be using a controversial sequencing strategy—one that many scientists have publicly trounced—to tackle its next big target: the mouse. Discussions at a meeting* held here last week made clear that a good part of the mouse will be sequenced using the whole-genome shotgun method pioneered by J. Craig Venter of Celera Genomics in Rockville, Maryland. But it will be used in combination with the more incremental strategy used by the Human Genome Project, the publicly funded consortium sequencing the human genome and the genomes of other organisms. "Both approaches have something to offer for getting large, complex genomes sorted out," says Robert Waterston, who heads Washington University's sequencing center in St. Louis.

Less than 2 years ago, the sequencing community sharply criticized the shotgun approach when Venter announced that he planned to tackle the human genome this way (*Science*, 22 May 1998, p. 1185). In the shotgun approach, the entire genome is cut into tiny pieces and then sequenced and reassembled all at once. Many genome scientists thought Venter would never be able to put his millions of pieces of DNA back together in the right order—a process akin to assembling a jigsaw puzzle consisting almost entirely of blue sky. "Over 100,000 serious gaps" would remain, predicted Maynard Olson, a sequencing authority at the University of Washington, Seattle, in 1998.

But a collaboration between Celera and academic partners to sequence the 160-million-base genome of the fruit fly *Drosophila melanogaster* (*Science*, 5 February 1999, p. 767) is showing that a hybrid strategy—combining whole-genome shotgun data with sequence generated the more traditional way, one bit at a time—can work. Because the chromosomal locations of those bits, which are represented in bacterial artificial chromosomes (BACs), are known, they can help sequencers assemble data from the whole-genome shotgun approach more accurately. "*Drosophila* taught us a compelling lesson. The hybrid approach has a lot of validity," says Eric Green, a geneticist at the National Human Genome Research Institute (NHGRI) in Bethesda, Maryland. Venter seems to agree: He announced last month that Celera is relying on public data to speed its human genome effort.

Even so, the decision to sequence the 3-billion-base mouse genome this way is not being made lightly, and many details "are still being thrashed out," says Green. For Green and others, the mouse genome is pivotal because it can help them decipher the human genome. The mouse will be only the second mammal sequenced in its entirety, after the human, making possible all sorts of comparative analyses. Humans and mice share many of the same genes; indeed, many mouse aficionados assert that the best way to figure out how human genes work is to study them in the mouse.

Understandably, the consortium of 10 labs tackling the mouse wants to be sure to do it right. To sequence a genome to the desired standard of accuracy—99.99%—each small stretch must be represented perhaps five to 10 times in the various pieces of sequenced DNA, whatever method is used to produce them. As recently as last October, when the 10 labs received $21 million from NHGRI to begin on the mouse, no one had seriously considered tackling the mouse genome with anything but the tried-and-true approach (*Science*, 8 October 1999, p. 210). But that changed at the first meeting of the mouse network, when Richard Gibbs of Baylor College of Medicine in Houston proposed doing some "shotgunning" of the mouse. Not only might the shotgun approach be faster, suggested Gibbs, but it would ensure that the laborious front-end work needed to characterize the BACs wouldn't delay the project.

Most of the group was receptive, recalls Bruce Roe, who will sequence some of the mouse genome at the University of Oklahoma, Norman. But some were worried that a combined approach might diminish a key

MOUSE GENOME GRANTS

Principal investigator	Institution	Millions
Kucherlapati, Raju S.	Albert Einstein College of Medicine, Bronx, NY	$6.127
Nierman, William C.	Genomic Research, Rockville, Maryland	$1.60 (1 yr)
Gibbs, Richard A.	Baylor College of Medicine, Houston, Texas	$22.344
Roe, Bruce A.	University of Oklahoma, Norman	$12.192
Lander, Eric S.	Whitehead Institute for Biomedical Research	$21.507
Weiss, Robert B.	University of Utah, Salt Lake City	$6.067
McCombie, W. Richard	Cold Spring Harbor Laboratory, New York	$6.874
Smith, Douglas R.	Genome Therapeutics Corp., Waltham, Massachusetts	$12.874
McPherson, John D.	Washington University School of Medicine, St. Louis, Missouri	$24.642
Green, Eric	National Human Genome Research Institute, Bethesda, Maryland	$16.060

PHOTO CREDIT: THE JACKSON LABORATORY

* "Advances in Genome Biology and Technology I" was held 5 to 8 February.

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

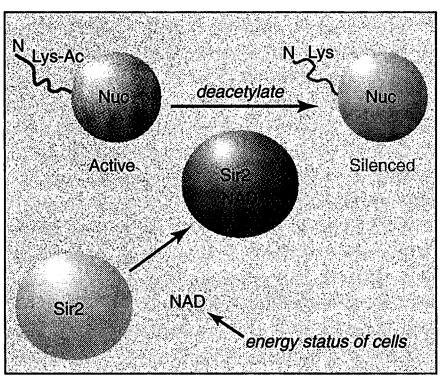
CELL BIOLOGY

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).

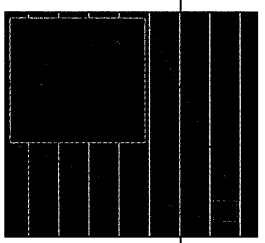
That discovery also provides a link to calorie restriction, because NAD normally helps the cell capture energy from food. When food is restricted, concentrations of available NAD could rise, Guarente proposes. This rise, in turn, could boost Sir2's silencing activities to help cells live longer. "If 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.