DOE's Genome Project Comes of Age

Long in NIH's shadow, DOE's genome project has taken on new vigor and direction under the leadership of molecular biologist David Galas

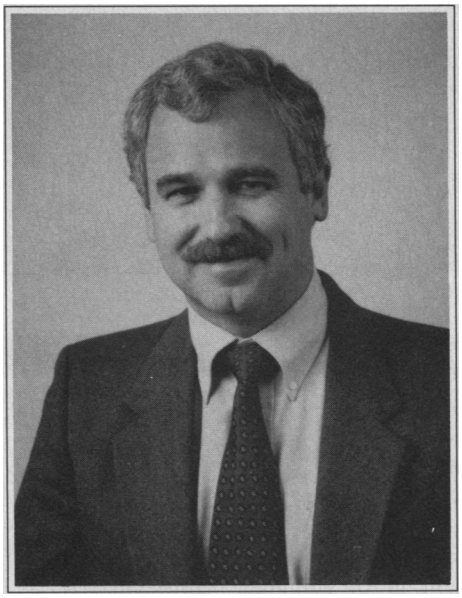
WHEN THE HUMAN GENOME PROJECT WAS getting under way in the late 1980s, it was the Department of Energy (DOE) that did most of the early running, championing the $3-billion venture within the federal bureaucracy and pushing to lead the effort. But DOE was soon eclipsed by the National Institutes of Health (NIH), which has $87 million of the project's 1991 budget of $135 million—and the visible and highly quotable Nobel laureate James Watson as its leader and chief lobbyist. DOE's genome effort, in contrast, has not had anybody at the helm since Charles DeLisi left his job as director of health and environmental research in 1987. And although DOE is generally perceived as sponsoring good, solid work, it has never achieved the level and status its champions originally hoped for.

So when David Galas, a respected molecular biologist from the University of Southern California, signed on as DOE's new associate director of health and environmental research last spring, he set himself quite a challenge: to infuse new life into DOE's genome effort. While the genome project, budgeted at $47 million this year and $59 million next, represents just a small chunk of the $310-million research enterprise Galas presides over (see box on p. 499), it is a very visible one—and one to which he has devoted a considerable amount of his energies.

In just 1 year on the job Galas has made substantial progress. He has reoriented the program, shored up the work of the three genome centers at the national labs, built up the biological component of the program, expanded into several areas previously considered off limits, and forged new ties with NIH and the outside world. And in the process, the distinctions between the NIH and DOE projects, so carefully delineated during the early turf battles, are disappearing.

All of which has been met with rave reviews from biologists both inside and outside the national labs—and from NIH officials as well—who call Galas everything from a visionary to a breath of fresh air. "What David has brought to DOE is a very good sense of biology and a broad view of science as a whole," says Caltech biologist Leroy Hood, who also serves on the DOE project's coordinating committee. "He will play a key role in trying to fit DOE's expertise with the role it can play in biology."

"It makes a tremendous difference to have someone in that job. And to have a molecular biologist is especially wonderful," says Charles Cantor, DOE's principal scientist for the project. Galas has also won what



Breaking new ground. *David Galas is winning high marks for reorienting DOE's genome effort.*

counts as high praise from James Watson, who says: "I like him a lot."

Not everyone credits Galas with turning the program around; in fact, some scientists within the national labs point out that the three genome centers have done quite well, thank you, under local direction and with guidance from geneticist Ben Barnhardt, the project's manager at DOE headquarters in Washington. But they, too, are enthusiastic about what they see as a new attitude in Washington. Says Elbert Branscomb of Lawrence Livermore Laboratory, who is a member of DOE's coordinating committee for the genome project: "Galas did not grab the bridle and jerk the project around before it fell off a cliff. Efforts have gone on more or less as they have before, but with strong support and sympathy and true understanding from Washington. It is a qualitative improvement in things."

What has Galas done to win all this praise? One of the first things was his decisive actions about the human genome center at Lawrence Berkeley Laboratory, where productivity was low and tensions high under Cantor's direction. Galas will not discuss the matter, but others say he was behind the decision to offer Cantor a new post as principal scientist for DOE and then bring in another director. And when negotiations with Hood and other candidates for that position fell through, Galas gave his full support to a bold and risky new plan to run the center without a director (see box on page 500)—an idea that never would have flown without his active encouragement. Says Hood: "He knows when to take a gamble."

Since then, Galas has set out in a number of ways to broaden the vision of the genome project, which DOE had defined somewhat narrowly, partly to set itself off from NIH but also to ward off critics who worried about DOE's lack of expertise in molecular biology. Much of the DOE effort has been devoted to its two big physical mapping efforts at Livermore and Los Alamos, where teams are mapping chromosomes 19 and 16—and by all accounts, "going like gangbusters," as Livermore center director Anthony Carrano puts it. But other than that, DOE carved out its niche largely on the technological and computational side of the project, leaving the more exciting biological questions, related to human disease and gene function, mostly to NIH-funded researchers.

That is beginning to change under Galas. "He sees this project, in its DOE embodiment, as having a more legitimate role in the progress of medical science—and in understanding life at a genetic level—than was articulated before," says Branscomb.

DOE is embarking, for example, on an aggressive new program to map and partially sequence all the expressed genes, or complementary DNAs, in the human genome (see *Science*, 16 November 1990, p. 913), a strategy also endorsed by Sydney Brenner at the Medical Research Council in England but earlier rejected by NIH, in part because it will be difficult. Galas is pushing the plan because it promises a biological payoff earlier in the game. Says Galas: "It skews the mapping toward the biologically interesting stuff."

As Galas explains it, DOE mappers are already devoting a considerable amount of their effort to finding and making special markers, or landmarks, to put on their maps. So, he reasoned, instead of fashioning these markers out of short, anonymous pieces of DNA, as is the norm, why not make them out of expressed genes instead? That way, when the map was complete, it would show the location of all the genes. Even though the function of most of the genes would still be unknown, such a map would be immensely useful: If a disease gene hunter was looking for the culprit, say, on the tip of the short arm of chromosome 4, he would instantly have some candidates to investigate.

DOE is starting out with a plan to map 3000 expressed genes, out of the 100,000 or so thought to exist, within a few years. That should be enough to see whether this approach is really feasible. And NIH is now following suit; it has just issued a request for proposals for new techniques for finding all the expressed genes—though so far NIH has stopped short of endorsing the idea of mapping them all.

Galas is also bucking DOE's longstanding bias against investigating any genome other than the human. Early in the debate over the genome project, when NIH and DOE were vying for turf, they struck an agreement that DOE would focus on the human genome, while the NIH effort would include the mapping and sequencing of the genomes of model organisms, ranging from yeast to the mouse. The reason for studying model organisms is simple: many genes are conserved among species, and it is far easier to study and eventually understand them in yeast than in man.

But that logic had not penetrated very far at DOE, says Livermore's Branscomb, or at least not far enough for anyone to challenge the informal agreement with NIH—until Galas arrived. When he visited Oak Ridge National Laboratory last June, Galas realized DOE was sitting on a goldmine: a wealth of knowledge about mouse genetics from a decades-long study of radiation effects, and the second largest collection, outside of Jackson Laboratories, of mutant mice in the country. He also realized this expertise could speed the human mapping effort. Since then, Galas has been trying to set up new collaborations, not only between the Oak Ridge mouse experts and the DOE genome centers but also with NIH-funded researchers. Galas has encountered no opposition from NIH—indeed, the two agencies are setting up a joint committee on the mouse genome. But many of Galas' colleagues within DOE have been less than thrilled. "Everyone at DOE has been very rigid about what that agreement [with NIH] meant," says Galas, who calls such rigidity "foolish."

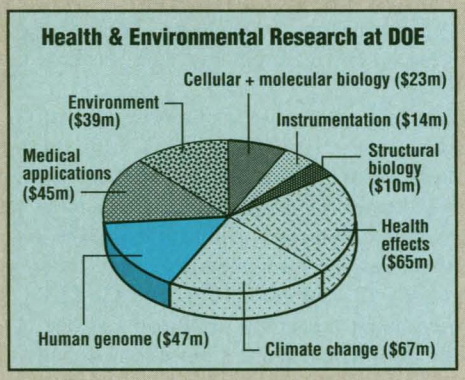
"Our principal goal is still physical mapping of human chromosomes, but we are not going to do it stupidly. We are going to use everything we can lay our hands on, and cooperate with everyone we can."

That effort ties in directly with what Galas sees as perhaps his overriding mission at DOE—increasing interactions both among the biologists and the technological types and among the national labs and the outside academic community. He considers such interactions vital to strengthening science within the labs. "The labs have probably been more isolated in scientific terms than they should have been, but that is changing rapidly," says Galas, who attributes the change in large part to the genome project, which he calls "really catalytic." As the genome centers set up a growing number of collaborations, "the external scientific community has realized that the labs, though not like universities, have a tremendous amount to offer," Galas says, such as flexibility, resources, and an interdisciplinary approach to research that

Refocusing Biology at DOE

When David Galas took on his new job at DOE a year ago, he inherited a vast enterprise: Eight programs, with a budget of $310 million for 1991, encompassing all health and environmental research conducted by the agency. Galas came in with strong ideas about changing most of those programs, except for DOE's big climate change effort, and has set out to do so, winning praise from his fellow biologists in the genome project (see story) but incurring the wrath of others in the process.

Health Effects. The $65-million health effects program has not held up well to Galas' scrutiny. This program, which focuses on the effects of radiation and chemicals on human health, has a "long and distinguished history," says Galas, but it needs to be revitalized and refocused to bring it into the modern biological age. The problem, he says, is that the extensive animal studies looking at tumor responses to low-level radiation have been "too phenomenological. Without a mechanistic interpretation, I frankly consider them to be of very little use." Galas is bringing in a new emphasis on the fundamental processes of carcinogenesis. As a first step, Galas scaled back funding for the animal radiobiology studies in 1991 and consolidated the effort in the national labs, with the intent of finishing the work quickly. That drew an outraged letter from the radiation biologists inside and outside the national labs.



Environment. DOE's $39-million environment program, which includes both a marine biology and a terrestrial ecology effort, also needs an infusion of modern molecular biology, Galas contends. "I am struck by how little is known," he says. Part of the problem, he suspects, is that ecologists "attack problems that are too big for the resources available. As a result, they get only partial answers." He organized a workshop last January in Asilomar, California, to which he invited ecologists, biogeographers, molecular biologists, and microbiologists. The idea, he says, was for the ecologists to explain which questions are important to their field, and for the others to speak on what techniques are available to address them. He calls the workshop "an experiment, but one I think needs to be done." From it, he hopes to frame a new direction for the program.

Structural biology. Galas is also committed to building up DOE's modest, $10-million structural biology program into a major initiative, perhaps along the lines of the genome project, to tackle some of the fundamental questions in biology, such as what makes proteins fold the way they do. As Galas explains, DOE has under its aegis a handful of synchrotron light sources that are essential for structural biology. As two new synchrotrons are coming on line at the national labs at Argonne and Berkeley, Galas is working to ensure that there will a dedicated beamline available for the life sciences, both for DOE's in-house research and for the larger user community at universities. He views this initiative as a way to increase the interactions among the national labs and academia, one of his goals for the genome project as well. ■ L.R.

LBL Genome Center to Try Leadership by Committee

First Caltech superstar Leroy Hood turned them down. Then their negotiations with Glen Evans of the Salk Institute fell through. Next they called David Cox, Maynard Olson, Raymond White, and 15 or so other big names in the human genome project, but to no avail. The search committee couldn't find a taker for the job of director of the Human Genome Center at the Lawrence Berkeley Laboratory (LBL), a slot that has been vacant since Charles Cantor stepped down last summer to become the principal scientist for the DOE's human genome initiative.

Now the committee has come up with an audacious new gameplan: to bring in a crew of hot young scientists and set up a committee to run the center without a director, at least for a few years. LBL officials and their advisers admit the idea was born of desperation. "We had nobody else to go to," says University of California geneticist Gerald Rubin, a member of the search committee. As word of the new plan trickles out, some researchers inside the national labs have dismissed the leadership-by-committee notion as manifest folly. But most people *Science* spoke with give the strategy a good chance of success. At any rate, they say, LBL has little to lose.

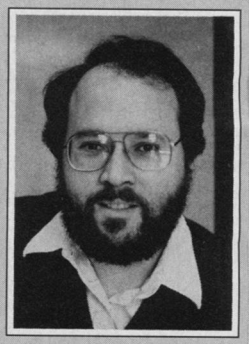
The LBL genome center was created with great optimism in 1987. Along with the center at Los Alamos National Laboratory and another created at Livermore soon afterward, it was to be the main thrust of DOE's new human genome initiative, now budgeted at $47 million for 1991. But the LBL center ran into trouble almost from day one. The scientific program Cantor envisioned never took off, for a number of complicated reasons (*Science*, 14 September, p. 1238), and his ambitious plan for a staff of 100 or more stalled at about 30. Now the two dozen or so scientists who have remained at the center since Cantor's departure are struggling as best they can to continue their work. For example, a handful of biologists are still mapping chromosome 21, a major interest of Cantor's, though it is unclear whether that focus will continue. Meanwhile, two other groups are developing new technologies for DNA sequencing and mapping and new approaches for handling the mass of data already emerging from the genome project.

But all the researchers are handicapped by having no clear direction from above. "It is an extremely difficult work environment. It is quite demoralizing and painful," says Elbert Branscomb of the genome center at nearby Lawrence Livermore Laboratory.

Recruiting a new director in that situation would have been tough anyway. But probably the biggest impediment, says Rubin, is simply that the two dozen or so people qualified to run a center are happily employed—and well funded—elsewhere. Indeed, many of the big names have already been tapped to run or participate in the six new genome centers that the National Institutes of Health is funding at major universities to the tune of about $1.5 million a year each.

No director would be better than a second-rate one, reasoned Rubin, who cooked up the new scheme and then sold it to LBL director Charles Shank and, in turn, to David Galas, head of the Office of Health and Environmental Research at DOE, who oversees that agency's entire genome effort (also see p. 498). The idea is to bring in four or five of the hottest young researchers in the field, says Rubin—the best postdocs coming out of the genome labs in, for example, St. Louis or Salt Lake City. Says DOE's Galas: "What I hope will happen is we'll build a constellation of young, exciting, and extremely high-quality researchers, working on similar things that are interlinked but not focused the same way as Livermore or Los Alamos. In a way, the situation at LBL is so unique, because of its proximity to the terrific biological community [at UC], that I think we should try something different."

Both the Livermore and Los Alamos centers have taken on the task of mapping a complete human chromosome—chromosome 19 at Livermore, 16 at Los Alamos—and are pursuing them doggedly. For LBL, Galas envisions a center with a more academic bent, in which each investigator is reviewed and funded independently. The hope is that within the next 5 years or so, a leader will emerge from the group of new recruits who can take over as lab director.



Plan architect. *Gerald Rubin*

But that depends on getting first-rate young scientists to sign on with the troubled center. The sweetener to lure them will be a joint appointment at LBL and the Berkeley campus of the University of California, probably as an adjunct professor—a position that Rubin says is not given out lightly. This arrangement offers the best of both worlds, he maintains: the resources and space at LBL, plus participation in campus life and access to graduate students—all with one-third the teaching and administrative load of a regular professor. Rubin thinks the offer will prove irresistible: "It will be highly competitive with a job at any medical school."

Overall scientific direction for the genome center will come from a new committee, with impeccable credentials, that LBL director Shank has just assembled. It includes Lee Hood, who will chair the committee along with Rubin, as well as geneticist Jasper Rine from UC, and noted genome experts David Botstein of Stanford and David Cox of UC San Francisco. The UC members will work more closely with LBL administrators to keep an eye on the budget and the day-to-day operations of the center.

The scientific plan will depend, in large part, on whom they recruit. "We are looking

is hard to muster in a university.

"A lot of the major gains to be made in biotech research in the future are at the interface of biology, engineering, physics, chemistry, and computer science—and those are areas that can be most easily focused on by the national labs." He cites, for example, the new collaborations gearing up between Hood's Caltech team and researchers at both Lawrence Berkeley Laboratory and Los Alamos, which he believes will be critical to both sides. Says Galas: "The genome is really an important example of how things might happen in the future."

In case Galas did not already have enough on his plate, he is also committed to shoring up DOE's in-house peer review, which has always been somewhat suspect to the outside biological community. "That is one area in which Galas had made an important impact already and is promising to do more," says Branscomb. And Galas has also tackled head on the question of the proper split of funds between the national labs and extramural research—a question that exercises people on both sides. Seventy percent of DOE's genome research budget is now devoted to the three centers at the national labs, a division that galls people like MIT's Eric Lander, who calls it "inimical to peer review." He adds: "The labs do a good job, but I don't know if they are doing a $40-million job." Galas insists, however, that the split is not rigid and that from now on decisions will be made on scientific merit alone. "If a lab is faring well, OK. If not, it

for the best people doing relevant work, and then we'll see if we can mold something coherent out of that," says Rubin. "This is not a radical departure from how some of the best academic departments have been built—but it is radically different for a government lab." The new gameplan doesn't preclude the possibility of hiring a director from the outside. Shank emphasizes that this is a temporary arrangement, though he says it will continue "until we find exactly the right person."

In the hallways at the genome center at Livermore, where word of the new plan has been leaking out, some people at least are openly skeptical. As Anthony Carrano, who runs the genome center there, puts it: "It is a concept I would never ascribe to. Rule by committee is always difficult. But I wish them luck." Indeed, several others, who asked not to be named, say that LBL has a number of administrative problems that could tie the hands of anyone but a seasoned pro. "You really need a Lee Hood," says one.

But *Science* spoke with numerous others, including James Watson, who heads the genome effort at NIH, and Eric Lander, who directs a new NIH-funded genome center at MIT, who are optimistic about the new plan. Says Lander: "It sounds like the instincts are right. A committee to run it may be unwieldy, but if that is what it takes to bring in good people, OK." Adds Branscomb, another fan: "It should make the job of director more attractive." And at LBL, where opinion perhaps matters most, "We are hopeful about the future in a way we weren't before," reports Nina Bissell, director of the lab's cell and molecular biology division.

The new steering committee, which meets for the first time on 17 May, is just now placing ads and hopes to hire several investigators this summer, if not sooner. "I think that in 2 years LBL and Berkeley could be recognized as far and away the best government lab working on the genome project and could be the equal of the NIH genome centers, even starting from this dismal state," predicts Rubin. But, he admits, LBL had few options. "It was this or give up." ■ L.R.

will lose its money. I think the labs understand that now."

As Galas ventures into these and other areas, the question many people are asking is simply, Will he stay? He went to DOE on loan from USC with the announced intention of returning. Speculation to the contrary, Galas is emphatic: "I am returning to science." But, he adds, "if sufficient progress is made, DOE won't have any trouble attracting someone to do the job well."

■ LESLIE ROBERTS

Deaths In Vaccine Trials Trigger French Inquiry

Two AIDS patients treated with an experimental vaccine may have died from vaccine-related complications

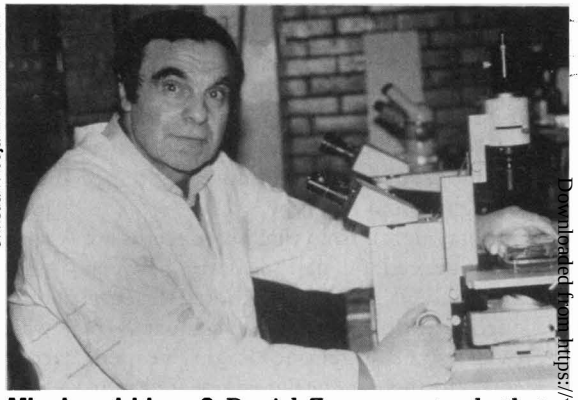
THE FRENCH MINISTER OF HEALTH, BRUNO Durieux, announced last week that he will order a new investigation of experiments conducted by AIDS researcher Daniel Zagury. Durieux's announcement, which came just days after a Paris hospital inquiry cleared Zagury of violating French research ethics regulations (*Science*, 12 April, p. 203), was prompted by articles in both the *Chicago Tribune* and the French newspaper *Le Monde* reporting that trials of Zagury's controversial AIDS immunotherapy treatment may have caused the deaths of two patients at the Saint-Antoine Hospital in Paris. Zagury's work was conducted in collaboration with researchers at the U.S. National Institutes of Health, including Robert C. Gallo.

Behind the accusations is evidence gathered by a French dermatologist, Jean-Claude Guillaume, that suggests that two of Zagury's AIDS patients developed a fatal vaccinia infection after being treated with a vaccinia virus preparation. The virus, which had been inactivated and should not have been capable of producing an infection, had been genetically engineered to express AIDS virus proteins. The researchers hoped these proteins would help stimulate the immune system to fight AIDS. Neither of the deaths was mentioned in an account of the experiment published by Zagury last July in the British medical journal *The Lancet*.

Although Guillaume's work has not yet been published—it too has been sent to *The Lancet* and may appear as early as next week—Zagury has already counterattacked with an article in the French medical weekly *Impact Médecine* disputing the scientific basis of Guillaume's diagnosis.

According to Guillaume, a remarkable series of coincidences led him to conclude that the two patients died from vaccinia necrosis. Guillaume works at the Henri-Mondor Hospital in Créteil and the Gustave-Roussy Institute in Villejuif, both large hospital and research centers in the suburbs of Paris. Last September, he was asked to see an AIDS patient, referred from the Saint-Antoine Hospital, who had developed unusual skin lesions. Guillaume had seen nothing like it before and could make no diagnosis. But he made sure that photographs and samples of tissue were taken; soon after, the patient died.

The mystery deepened the following month when Guillaume ran into a colleague who told him that in June he had seen an almost identical case: a patient referred from Saint-Antoine with unusual skin necroses that soon proved fatal. Neither physician could pinpoint the origin of the lesions. A few weeks later, fate intervened again when Guillaume picked up a copy of *The Lancet* in which Zagury described treating his patients at Saint-Antoine with inactivated vaccinia virus. "I dashed for a dermatology textbook and immediately realized that the lesions were typical of gangrenous vaccinia," says Guillaume.



Christian Vioujard/Gamma-Liaison

Misplaced blame? *Daniel Zagury contends that herpes, not vaccinia, caused the deaths.*

Guillaume then telephoned Odile Picard, the Saint-Antoine physician in charge of administering the experimental vaccine, to warn her that two of her patients had probably contracted gangrenous vaccinia. A few minutes later, Guillaume recalls, he received a telephone call from Zagury who argued that vaccinia infection could not be the cause of the skin lesions because viruses used in the experiments had been inactivated.

But Guillaume did not let matters rest there. He obtained antivaccinia monoclonal antibody to test the skin samples that he and his colleague had taken from the now dead patients. The results, he says, show the presence of vaccinia virus in the skin cells of the patients.

Zagury disputes the significance of this

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Leslie Roberts

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