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New probe of brain function

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Battle over a second coelacanth

MEDICAL PHILANTHROPY

Colorado Nobelist Chosen To Lead Howard Hughes

Joining a list of world-class life scientists who have taken on major management positions without abandoning their research, chemist Thomas Cech has been named as the next president of the $11 billion Howard Hughes Medical Institute (HHMI). The 51-year-old Cech, who won the 1989 Nobel Prize for his work on the enzymatic activity of RNA—which influences everything from the origin of life to treating diseases—will keep his lab at the University of Colorado, Boulder, where he is an HHMI investigator. In doing so, he is following in the steps of fellow Nobelists Harold Varmus, who leads the National Institutes of Health, and David Baltimore, president of the California Institute of Technology, as well as Bruce Alberts, president of the National Academy of Sciences.

Long reach. Thomas Cech will keep his Colorado lab when he becomes president of HHMI.

Cech replaces current HHMI president Purnell Choppin, who is retiring in December after 12 years. With the help of chief scientific officer Maxwell Cowan, who is staying on—and an endowment that has more than doubled to $11.4 billion during his tenure—Choppin established HHMI as a leading supporter of basic biology research through its network of more than 300 university-based investigators.

Cech's colleagues think he's just the person to continue building HHMI. "It's a great call," says Nobel laureate J. Michael Bishop, chancellor of the University of California, San Francisco. "I couldn't think of anyone better."

In taking the new job, Cech resisted the HHMI board's initial request that he shut down his HHMI-funded lab. "Things are going so well in the research lab, I hate to interrupt it," he says about recent work on x-ray crystallography of RNA and the study of telomerase, an enzyme that helps dividing cells protect their chromosomes. The board eventually agreed to let Cech spend 1 week a month in Colorado.

Heading the Chevy Chase, Maryland–based organization, however, means reducing his HHMI funding and downscaling his lab. Cech says he'll give up many outside activities, too, including his work with biotechnology companies. Cech also is a deputy editor of *Science*, a job he says he may keep without compensation. Cech's salary has not yet been made public; Choppin earned $600,000 last year.

Cech declined to discuss his plans for HHMI but says he is particularly interested in merging biology with other disciplines, bioinformatics, and science education. He'd also like to explore ways to mesh HHMI's research program, which last year gave its investigators $424 million, with the grants program that spent another $99 million on science education, postdoctoral training of physicians, and an international scholarship program for researchers.

One perennial management issue is resource allocation. Yale University's Sidney Altman, who shared the 1989 Nobel with Cech, says HHMI is "open to a lot of criticism" about who and what it funds. "They can't help but fund people who would be funded otherwise," says Altman about its ongoing support for genetics, immunology, and neuroscience. He says HHMI is at its best when it exercises leadership in a field, like it did 20 years ago in helping to build up structural biology.

Cech concedes that there might be questions about his abilities to manage an organization as big as HHMI, with more than 2500 employees and an annual budget that exceeds half a billion dollars. "I've never run anything larger than my research group," he says. But he says he's learned a lot in the past decade from sitting on the boards of several large research institutions. A former researcher in his lab, Michael Been of Duke University, says Cech is an excellent manager who "handles a lot at once, and very efficiently."

Running HHMI does have its downside, however. For his wife, Carol, vice president at Baxter Hemoglobin Therapeutics, it means leaving her job and moving to the Washington, D.C., area. "I'm really grateful that she's seen it possible to allow us to do this as a family, even though it's not a good career move for her," he says.

To Cech, the Hughes presidency is "a bit of a dream job," allowing him to have a "high impact" on the direction of science without having to raise money. Columbia University neuroscientist and fellow HHMI investigator Eric Kandel says Cech's task will be made easier by HHMI's wealth and the absence of any looming crises. "Cech can do visionary things," says Kandel. "It's not like walking into your typical academic situation, where you have enormous debts and the faculty is demoralized and worried about health care. The faculty does not bitch at Hughes."

Although Hughes's financial stability is part of what attracted Cech, the diversity it fosters may also present him with his biggest challenge. "Tom has to find his way through the forest," says Altman. "But he's a very creative scientist, and I'm sure he'll do fine."

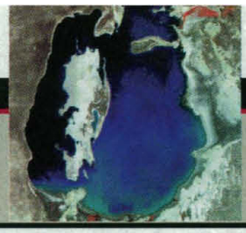
—JON COHEN

SCIENTIFIC COMMUNITY

Research Shutdown Roils Los Angeles VA

In a stunning one-two punch from the federal government, all research projects affiliated with the Veterans Administration (VA) in Los Angeles, California, were put on indefinite hold last week. On 22 March, the National Institutes of Health (NIH) announced that the VA Greater Los Angeles Healthcare System could no longer conduct human studies supported by NIH's parent, the De-

CREDIT: PAUL FETTERS/HHMI



partment of Health and Human Services, because of lax procedures for approving and overseeing these trials. Hours later, the VA's home office extended the suspension to all test tube and animal research, citing additional administrative problems. With more than 1000 research projects shut down, investigators are confused, frustrated, and worried about losing the confidence of their patients and funders like the NIH.

"This is a devastating situation," says Matthew Goetz, who heads the infectious disease department at the VA Medical Center–West Los Angeles (VAMC-WLA). Hospital management is working overtime to address the government's concerns, and investigators are hoping to win exemptions for many projects. "How grave the impact is will be determined by how the process is handled from here on out," says Goetz. The federal actions were first reported in the 24 March *Los Angeles Times*.

COLUMN ONE

VA Hospital's Ethical Nightmare

■ Morality and medicine collide at West L.A. facility, where probe about informed consent clouds research.

he was hiding bullets in his hospital room, also had his heart catheterization treatment prolonged for research purposes, though he did not give his legally req either.

formed consent problems documented in recent years. Even now, nearly four years later, this conflict of morality and medicine continues to plague

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U.S. Suspends Research at VA Hospital in L.A.

By TERENCE MONMANEY
TIMES MEDICAL WRITER

To protect patients in clinical studies, the Department of Veterans Affairs is taking the unprecedented step of suspending research activities at the West Los

VETS: Consent by Patients Under Scrutiny

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it not consent at all," said Gary Ellis, director of the federal risk office.

Probe Started in 1995

Unwelcome spotlight for researchers. Recent stories from the *Los Angeles Times* have highlighted problems at the Los Angeles VA.

The VAMC-WLA, the largest hospital of the VA's 173 hospitals and an affiliate of the University of California, Los Angeles, had long been scrutinized by the NIH's Office for Protection from Research Risks (OPRR), which oversees experiments that involve humans. Gary Ellis, OPRR's director, explains that several factors led to the decision to suspend ongoing clinical studies and prohibit enrollment of patients into new ones. "It's a very serious step in response to unusual circumstances," Ellis says. "There are serious, systemic deficiencies. It's a pattern of nonresponsiveness to our concerns over 5 years."

A 22 March memo from OPRR faults the VAMC-WLA primarily for the way its Institutional Review Boards (IRBs)—the groups within each VA that approve and monitor clinical trials—conducted meetings. Specifically, OPRR found that these IRBs repeatedly violated procedures by holding meetings without including community representatives, convening a quorum, or adequately briefing members about trial protocols and the like. OPRR further charged that the VAMC-WLA had failed to establish independent Data Safety and Monitoring Boards to review results from ongoing psychiatric research in which the investigators also served as primary care physicians for the patients under study.

In a memo broadening the suspension to other research, the VA's undersecretary of health, Kenneth Kizer, stressed that "there currently is no evidence to suggest any actual harm to either human or animal research subjects." He described the suspension, which went into effect on 26 March, as "a preemptive measure." Kizer offered no clear explanation for the scope of the suspension but said that administrators in Los Angeles had failed "to correct deficiencies in fiscal and personnel management" and had been "unresponsive" to probes by the VA's own investigators. Ultimately, he said, their mismanagement "adversely affects individual investigators" and "jeopardizes the public's perceptions of VA's entire research enterprise."

When asked why the restrictions had such a broad scope, John Feussner, chief of research and development at VA headquarters, explained that officials assume human studies are carried out more carefully than any others. "We inferred that since there were difficulties with the human components, we need to verify for ourselves that this was not the case with other studies." As for the financial problems, he said, "it's a simple matter of poor accounting, poor record keeping, and not being able to follow the dollars as easily as we'd like to." His office now has teams in Los Angeles investigating the research and financial issues.

Investigators can ask for exemptions to the suspension if interrupting a research project poses a threat to animals or humans, and they immediately began flooding administrators with requests to spare their studies. "We all have put in exemptions," says Alan Lichtenstein, a hematologist-oncologist who has worked at the VAMC-WLA for 20 years. But Lichtenstein said none of his colleagues has a clue about the timeline. "We're working with bureaucracies," he says. "Who knows?"

A personnel switch has further confused the situation. On 24 March, VAMC-WLA's head of research, Stephen Pandol, was "reassigned to other duties," according to a spokesperson, and replaced by Peter Eggena, who came from the VA's Sepulveda campus across town. Eggena was scrambling to determine how many research projects were under way and fielding exemption requests.

Approval for any of the 400 or so human trials to resume would have to come from OPRR, and Ellis says he does not anticipate granting many exemptions. "It would be very rare," says Ellis. "Patients need treatment. But people don't ordinarily need to be research subjects." Ellis says that OPRR will evaluate research requests on a project-by-project basis as soon as the VA repairs the IRBs.

The VAMC-WLA suffered another blow on 25 March, when reporter Terence Monmaney of the *Los Angeles Times* followed up his original article with a detailed account saying that some VAMC-WLA patients were put at risk in trials to which they had not consented. The VAMC-WLA had documented the alleged infractions in an internal report, but officials at both VA headquarters and OPRR said they had no knowledge of them.

The article further damaged morale at the VAMC-WLA. "If only part of this is true, it's a terrible blow to the institution," says Lichtenstein. "One patient brought in the article to the rheumatology clinic asking, 'Are you guys going to do this to me?' " Lichtenstein says he and many of his colleagues hope that some good may ultimately come from the added scrutiny, "but we're going to have to go through a very, very difficult time."

Feussner said he hopes that with site visits

now under way, processes will be in place to correct any problems by 23 April. "I suspect the total suspension may not be lifted at that time," predicted Feussner, but he said that by then it may be limited to human studies.

–JON COHEN

EXPERT WITNESSES

Court Views Engineers As Scientists

When engineers seek to testify in court as expert witnesses, judges should hold them to the same standards as scientists, the U.S. Supreme Court ruled last week. The 23 March decision, in a case called *Kumho* v. *Carmichael*, says judges may disallow testimony from engineers that doesn't meet broad scientific standards for reliability. The ruling was applauded by the National Academy of Engineering (NAE) and other organizations that had submitted briefs urging the high court to recognize the scientific basis of engineering. However, legal experts say that it leaves plenty of leeway—and uncertainty—in judging the validity of expert testimony in fields, including clinical medicine and forensics, that often rely on experience rather than scientific practices such as publication and peer review.

> **"[The ruling] should reinforce the obligation of trial judges to serve as gatekeepers."**
>
> **—Richard Meserve**

"I feel good about this decision," says William Wulf, president of NAE, which had argued that although engineering differs from science in trying to modify rather than understand nature, its methods are no less scientific. Adds attorney Richard Meserve, a former physicist who prepared the NAE brief, "It should reinforce the obligation of trial judges to serve as gatekeepers, to look at the background of the expert witnesses and examine how they arrived at their conclusions."

The gatekeeper role was spelled out in a 1993 case, *Daubert* v. *Merrell Dow Pharmaceuticals*, in which the Supreme Court proposed four factors that judges could weigh in deciding whether expert-witness testimony from scientists was relevant and reliable. The court suggested that judges should consider the testability, error rate, and degree of acceptance in the community of the analysis, including whether results had been peer reviewed and published (*Science*, 2 July 1993, p. 22).

The current case (97-1709) began with a suit filed by the Carmichael family of Alabama against Kumho Tire Co. after a blowout in 1993 caused an accident that killed one of their children. The plaintiff's case rested on testimony from a mechanical engineer and tire analyst, Dennis Carlson Jr., who said the blowout resulted from a defect in the tire's design or manufacture rather than from wear or improper care and use. The lower court excluded his testimony, submitted in a deposition, saying the analysis was scientifically flawed. An appellate court reversed the decision, ruling that Carlson's testimony was based on his experience rather than scientific analyses and was therefore not covered under *Daubert*. The company appealed to the high court, which heard the case in December.

Last week's decision, written by Justice Stephen Breyer, reverses the appellate court and extends *Daubert* to engineering. But legal experts say that it still gives judges great discretion to accept or reject expert testimony. "It does not knock out experience [as a basis for expert knowledge], but it emphasizes reliability and relevance," says Margaret Berger of the Brooklyn (NY) Law School. "I suspect that the way it's applied will vary from circuit to circuit."

That variability worries some scholars. "When Justice [Harry] Blackmun wrote the *Daubert* decision, he was clearly thinking of what it is that scientists do," says law professor Michael Green of the University of Iowa, Iowa City. "But what about accident reconstructionists? They wouldn't think of publishing their work in a journal or having it peer reviewed. What Breyer did is invite trial judges to look carefully at an expert's methods and reasoning and to throw it out if it's flawed. But what's acceptable to one judge may be unacceptable to another judge. And uncertainty means more litigation."

Meserve and others disagree. "I think the ruling sends a message to judges that [weighing expert witnesses] is an important job that they must take seriously," he says. Berger says she's "amazed" at the detailed discussion of tire composition and tread wear in Breyer's decision and speculates that he may have wanted to show trial judges how to approach such questions. Meserve also hopes the decision may weed out frivolous suits by raising the stakes for plaintiffs' lawyers and experts themselves. "After *Kumho*," he says, "they ought to be embarrassed if a judge finds their testimony not acceptable."

–JEFFREY MERVIS

ScienceScope

Delayed ... or Dead? A federal judge has ruled that the National Park Service must complete an environmental review before it can move ahead with a controversial bioprospecting contract. Government analysts say the ruling is a temporary setback for the precedent-setting deal, which allows Diversa, a San Diego biotechnology firm, to harvest plants and microbes from the park's hot springs in exchange for a $175,000 payment and royalties on any products it develops (*Science*, 13 March 1998, p. 1624). But one plaintiff's attorney believes the decision—handed down last week by Judge Royce Lamberth of the U.S. District Court in Washington, D.C.—is a death knell for any arrangement of this kind because Lamberth cast doubt on the government's claim that parks are "outdoor laboratories" available for commercial research. A coalition of nonprofits will soon be back in court seeking to ban such deals outright, promises Andrew Kimbrell of the Washington-based International Center for Technology Assessment. Unless Congress changes the law, he asserts, federal parks should remain off limits to profit-driven bioprospectors.

All Too Human Indian scientists hope emerging guidelines for research on human subjects will help reduce the risk of ethical problems. Jarred by the realization that the government regulates studies using animals more heavily than those involving people, the Indian Council of Medical Research (ICMR) last year began a review of 20-year-old human research guidelines that women's groups and others say need to be updated.

Last week in New Delhi, the council completed a quartet of public meetings on a 100-page draft of the new guidelines, which tackle everything from transplant rules to the thorny problem of obtaining informed consent from subjects in a country where illiteracy is widespread. Finalizing new "clear-cut and mandatory guidelines" would help researchers avoid trouble, says Kamal Hazari of Mumbai's Institute of Research in Reproduction. But guidance alone may not be enough, some researchers say. New national legislation that imposes penalties on violators may be needed to put some teeth into the guidelines, which the ICMR hopes to finalize this summer.

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