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FDA Commissioner Says Science Is Far From Eliminating Cancer As A Threat

Science is far from producing strategies for curing cancer or making it into a manageable chronic disease, FDA Commissioner Mark McClellan said in a lecture at NCI earlier this week.

"A lot of new technologies that we have developed over the last five years—proteomics, genomics, microarrays, information technology—so far have primarily just added to the cost of discovery and development, without making the process faster or more certain," said McClellan, delivering the first lecture of the NCI Director's series Feb. 2.

At any other venue, these remarks would have been regarded as non-controversial. However, at Andrew von Eschenbach's NCI, an institution

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In Congress:

NIH Institute Directors Earn Higher Salaries Than The Vice President, House Member Says

NIH has improperly used a hiring program designed to attract scientists and other "special experts" as a way of boosting the pay for institute directors and other senior officials up to $225,000 annually, more than the salary of Vice President Dick Cheney, a member of Congress said this week.

Expanding an investigation into management and ethics at NIH, James Greenwood (R-PA), chairman of the Oversight and Investigations Subcommittee of the House Committee on Energy and Commerce, sent a letter Feb. 4 to HHS Secretary Tommy Thompson, requesting information about the NIH use of the program known as Title 42.

The hiring program, established under a provision in Title 42 of the U.S. Code, was intended to allow the Public Health Service to employ "special consultants," on a temporary basis, bypassing civil service laws.

Most of the institute directors at NIH have Title 42 status, and could be earning as much as $225,000, the letter said. Cheney's salary is $198,600, while Thompson's is reportedly $172,000. President Bush's salary is $400,000 annually.

Greenwood wrote that if the Title 42 program is intended only for hiring consultants, then the institute directors and other high-level NIH officials who receive Title 42 pay don't have legal authority to do their jobs.

"My fundamental concern is that 42 U.S.C. 209(f) on its face appears to be a provision for hiring special consultants who have limited responsibilities, not as authority for employing NIH institute directors and other high-level NIH officials, who occupy continuing, full-time positions and exercise broad-based levels of decision-making responsibility (such

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McClellan Provides Sober Counterpoint To NCI Goal

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driven by the goal to "eliminate suffering and death due to cancer" by the year 2015, sober discussion of the state of science contradicts the doctrine.

For nearly an hour, McClellan spoke about the slowing progress of drug discovery, the risks of investing in biotechnology, the rising medical costs, and the difficulty inherent in development of targeted therapies.

"If recent history is any guide, the vast majority of new treatments that show promise in the lab and lead to these investments to promote further development will not ever make it into testing in people," McClellan said. "And of those that are tested, fewer than one in five will result in new product applications to FDA. And those applications will typically come in more than a decade after the initial development of a drug, a biologic, or other products."

These oft-cited industry figures have devastating implications for von Eschenbach's vision. If it takes over a decade to move a drug from discovery to FDA's doorstep, then scientists need to have found all the agents needed to combat all cancers if they are to have a prayer of achieving the 2015 goal.

The content of McClellan's speech clashed with the buildup for the lecture series, called Progress with a Purpose.

"This series is designed to bring the nation's leaders to the National Institutes of Health to discuss extraordinary advances in their fields as we work towards eliminating the suffering and death due to cancer by 2015," the NCI press office said in an announcement dated Jan. 22.

This language implies that NIH and FDA have joined NCI in its 2015 goal. In fact, insiders are unable to point to any expression of support for von Eschenbach's goal on the part of NIH.

Since von Eschenbach's vision is not accompanied by a written plan, it has evaded review. The director's "challenge goal" is often mentioned at the NCI presentations, on the Institute's website, and in the Bypass Budget, a document that bypasses NIH review and is presented by the Institute director to the President. The goal drives the Institute's programs and appears in concepts, Requests for Applications, and Program Announcements.

Drug Discovery Remains an Art

Making no reference to the 2015 goal, McClellan, in effect, critiqued its underpinnings.

Biomedical research is not an engineering problem, he said. "For all that modern science has to offer, [drug discovery] today is still very much an art in which hunches, and intuition, and luck all play critical roles, and in which the odds are way too long," McClellan said. "For medicine that is both affordable and innovative, we need more science to improve the odds to make it less of an art and more of a technically predictable process."

Producing a targeted drug is no easy matter, he continued.

"When it comes to developing targeted cancer drugs that can inhibit … complex signaling pathways, it seems that understanding the practical consequences of the biology around the drug's target is still a challenge today," McClellan said.

It's unlikely that single markers would be sufficient to stratify patients by disease site. "Rather, we'll have to look for patterns of genes and protein expression," McClellan said. "And a lot of research on this is going on right here at NCI. We are collaborating on some of that at FDA. And the technology to take these measurements and connect them to their clinical implications is making its way from the academic research labs to product development. But the process is slow, and it needs encouragement."

Consider what is known about EGF receptors, the much-explored target in development of cancer drugs:

"The intricacy of the EGF signaling pathway

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demonstrates some of the important gaps in our development science, and highlights the need and the complexities inherent in developing validated biomarkers that can be used to assess pharmacodynamics in order to set dosages in selected patients who are most likely to respond," McClellan said. "And I know that some important work to address these questions is going on right now at NCI. Such markers and marker combinations… have yet to be identified and validated for use in clinical trials of EGF products."

Science doesn't justify testing cancer prevention compounds based on surrogate markers, McClellan said, striking at one of NCI's apparent strategies for reaching the 2015 goal.

"We need to find better ways to integrate this information with good epidemiologic data, along with better clinical endpoints and trial designs that maintain a high degree of scientific rigor required to demonstrate a prevention benefit," McClellan said. "We need to have a clear way to more easily determine whether the benefits of these new preventive treatments outweigh the risks. And this is another example of where much work needs to be done on the critical path to evaluating preventive treatments and making these determinations."

Altogether, U.S. investment in biotechnology research is estimated at $100 billion a year, McClellan said. "These investments face a very uncertain future, which means that the payoff from them may not be that high," he said.

The cost of developing a new drug has doubled over the past decade, requiring a private investment of over $1 billion above NIH contributions to laying the scientific foundations and helping provide the guidance to develop a new drug, McClellan said.

As the costs increased, the number of products in the pipeline has dropped. "Rising costs of discovering and developing new treatments combines with increasing pressure to contain rising healthcare costs is not a good combination for medical innovation," he said.

McClellan said NCI, FDA, and others have been working to simplify the process of approval of cancer therapies. FDA recently streamlined its review procedures, decided to start accepting the Investigational New Drug applications in electronic form, and launched a reexamination of standards for approval of cancer drugs, he said.

McClellan concluded the lecture by reiterating that advances in science that have generated so much excitement at NCI have not demonstrated relevance to drug development:

"There is an awful lot going on in a way of microarray results. We know a lot about how different types of compounds can have effect on up- or down-regulation of genes and proteins.

"The problem is today that much of that data is really in the informational stage. I have talked to a lot of product developers who have run all these microarrays on their compounds.

"They cost thousands of dollars, and in principle, if we knew what those microarray results meant, it could really shorten and improve the efficiency of the development process, and of targeting treatments to individual patients.

"The problem is, we haven't done as much work on the validation of what these combinations of biomarkers mean for actual toxicity and clinical benefits in patients. Until we make a strong link between these kinds of relatively easy and less costly test results, and important clinical benefits or harm for patients, then you can really influence the development process and help develop more targeted clinical trials that are more likely to show payouts at a much lower cost.

"Then it would be much easier for payers to go along with paying for some of these treatments if they knew that there was a strong predictor of effectiveness. We haven't done the validation science. That's a great example of what I mean by needing to do more in the applied science of development. Not just discovery of a new treatment, but finding paving steps that help product developers get more out of the process.

"If a product developer knew that certain kinds of up or down gene regulation or microarray result really was a strong predictor of clinical benefit or risk, that would be of big help in making the development process less uncertain.

"We haven't done that validation yet, and that's something that an individual company can't do by itself. They don't see the whole universe. They see their own product. This is a public good. There is benefit for everyone who is developing products in understanding the relationship between microarray results and actual clinical consequences in patients. It is a good example of our hope that we can work together closely to improve the development process."

A webcast of the lecture is available at http://videocast.nih.gov/PastEvents.asp?c=52

A Glass "Ovation"

Von Eschenbach didn't dispute McClellan's view of the state of drug development. Taking a turn at the microphone, he returned to the purpose of the lecture: the 2015 goal.

"Mark, I want to express on behalf of the entire National Cancer Institute our deep gratitude for your presentation today," he said. "The NCI has set a very ambitious goal, and has a vision of creating a world in which no one suffers and dies from cancer. We know that to achieve that lofty vision requires us to work collaboratively and cooperatively. No one could exemplify better the openness to working together to achieve a better world than you did this morning."

As the two men stood over the lectern, von Eschenbach carefully handed a large glass trophy to McClellan.

"We would like you to take this token of our appreciation and respect, and, hopefully, it will remind you, as you place it in your office, of our enduring friendship relationship, and commitment to change the world," the NCI director continued.

"Absolutely," said McClellan. "I'll treasure it. Thank you all very much."

Ushering the Commissioner into a grip-and-grin photo with the trophy may not have been a politic move on von Eschenbach's part, some observers say.

Gift-giving is unusual among government officials. Had McClellan spoken at the NIH director's lecture series, he would have received nothing but an inexpensively framed copy of the poster announcing his appearance.

More importantly, FDA regulates NCI. The Institute submits Investigational New Drug applications for agents tested at the NIH Clinical Center, cooperative groups, and cancer centers. Also, NCI helps companies prepare New Drug Applications. Often, Institute employees take part in negotiations with the regulatory agency and present data to its advisory committees.

Von Eschenbach is more than the NCI director. He serves as vice chairman of the board of C-Change (formerly the National Dialogue on Cancer), a coalition heavily funded by pharmaceutical companies. C-Change has indicated that it would like to play a pivotal role in drug discovery and development. AstraZeneca, Aventis Oncology, Bristol-Myers Squibb, GlaxoSmithKline, Pharmacia, and Novartis pledged between $1 million and $1.5 million each to that organization (**The Cancer Letter**, Dec. 12, 2003).

"Given that the FDA apparently performs some regulatory oversight of some of NCI's activities, NCI may be considered a 'prohibited source' of gifts under federal ethics laws," said Jeffrey Lubbers, an expert in administrative law at American University's Washington College of Law. "In that case, the FDA Commissioner would be well advised to return any gift valued at over $20, or to reimburse the NCI for its market value."

A federal law that regulates acceptance of gifts states that "an employee may not accept an award from an organization which the employee knows, or should know, has a contractual or other business arrangement with, or is regulated by, the principal operating component, or a sub-unit, in which he or she is employed or with respect to which the employee has official duties, unless acceptance is approved by the head of the employee's principal operating component. The head of the component may not approve acceptance unless he or she is satisfied that no actual conflict of interest would result."

The Cancer Letter identified the award as "Ovation." Nearly a foot tall, it consists of a glass block topped with an antler-like form and a small cobalt-blue sphere. With an inscription, an Ovation usually costs $287. A photo of the trophy is available at http://www.corporategiftshowcase.com/jcovationaward.asp.

An NCI spokesman said $184 in private money from the NCI Gift Fund was used to purchase and engrave the Ovation.

An NIH spokesman added that no ethical issues were involved in giving the item to McClellan. "NCI gave FDA the memento," said NIH spokesman John Burklow. "This doesn't involve ethics, because it's a transfer of property from one government agency to another, and they are both within HHS. NCI gave it to FDA for display purposes."

The memento's stay at FDA will be short, officials said.

"Dr. McClellan was honored to be asked to speak at this forum, and he values the close working relationship that FDA has with NCI," said the agency spokesman Lawrence Bachorik, adding that "FDA is returning this item to NCI, because we think it's the appropriate thing to do."

NIH Pay To Top Officials Under House Investigation

(Continued from page 1)

as making final decisions on substantive policies or functions in the NIH chain of command) considered to be inherently governmental," Greenwood wrote in the letter to Thompson.

"If this concern is correct, it would mean that high-level NIH officials compensated under 42 U.S.C. 209(f) lack the legal authority to exercise their inherently government functions and are improperly holding themselves out as NIH institute directors or other high-

level titles, when by law they are only special-consultant employees," the letter continued.

In 2001, HHS said NIH appeared to be using the program indiscriminately and asked the Institutes to review the status of about 70 employees. In previous years, NIH officials were actively promoting the program as a way to attract and retain not only scientists, but also administrators and managers. Many career civil service employees were "converted" from GS14 and 15 to Title 42 (**The Cancer Letter**, July 13, 2001).

Former NCI Director Richard Klausner became a Title 42 employee in March 2000, and began receiving an annual salary of $200,000, the subcommittee said last year in its investigation of Klausner's lecture awards (**The Cancer Letter**, July 4, 2003).

The letter doesn't specify whether the current NCI Director Andrew von Eschenbach receives Title 42 pay. However, Greenwood requested this information.

HHS does not appear to have any written legal opinion supporting the use of Title 42 for hiring and compensating high-level NIH officials, Greenwood wrote. A review by the Congressional Research Service determined that the program should not be used for positions that require activities that are "inherently governmental," including hiring and firing of personnel, or decision-making authority about agency operations.

Also, Title 42 employees at NIH are not required to file financial disclosure reports, a practice that Greenwood said is an incorrect interpretation of federal ethics rules. At a Senate hearing Jan 22 on conflicts of interest at the Institutes, NIH Director Elias Zerhouni said he would review the disclosure rules (**The Cancer Letter**, Jan. 23, 2004).

The excerpted text of Greenwood's letter follows:

As part of its oversight of the ethics programs at the National Institutes of Health, the Committee has identified a serious concern about the NIH's use of special authority under Title 42 of the Public Health Service Act. The special authority, 42 U.S.C. 209(f) "Special Consultants," provides that under certain circumstances, special consultants may be employed "to assist and advise in the operations of the [Public Health] Service" without regard to civil service laws.

It appears that since 2000 the NIH has been using 42 U.S.C. 209(f) as a mechanism to compensate some NIH Institute Directors and other senior NIH officials at annual salary rates of up to $225,000. One result from using this mechanism is that these NIH officials employed under 42 U.S.C. 209(f) are not required under the Ethics in Government Act to file Public Financial Disclosure Reports (SF 278s), as the Congress and the public have recently learned. I note that on January 12, 2004, the HHS Associate General Counsel for Ethics requested a determination from the Office of Ethics to require these certain employees to file Public Financial Disclosure Reports. In support of this request, the HHS Associate General Counsel for Ethics stated that the roles of these NIH officials "carry particularly high levels of responsibility."

However, closer scrutiny of 42 U.S.C. 209(f) yields an additional concern, beyond the lack of public financial disclosure. My fundamental concern is that 42 U.S.C. 209(f) on its face appears to be a provision for hiring special consultants who have limited responsibilities, not as authority for employing NIH Institute Directors and other high-level NIH officials, who occupy continuing, full-time positions and exercise broad-based levels of decision-making responsibility (such as making final decisions on substantive policies or functions in the NIH chain of command) considered to be inherently governmental. If this concern is correct, it would mean that high-level NIH officials compensated under 42 U.S.C. 209(f) lack the legal authority to exercise their inherently government functions and are improperly holding themselves out as NIH Institute Directors or other high-level titles when by law they are only special-consultant employees.

Almost two months ago, the Committee staff contacted the HHS Office of General Counsel (OGC) raising this concern and asked for background information that would support the use of 42 U.S.C. 209(f) to compensate high-level NIH officials. Last week, HHS OGC staff advised the Committee staff of the following:

1. HHS had not yet found any written, legal opinion supporting the use of 42 U.S.C. 209(f) as a mechanism to hire and compensate NIH Institute Directors, and other high-level NIH officials.

2. HHS is continuing its search for historical evidence supporting the use of 42 U.S.C. 209(f) as a mechanism to hire and compensate NIH Institute Directors, and other high-level NIH officials. At this time, HHS did not report any such historical evidence to the Committee staff.

3. There is no current employee at HHS OGC who has first-hand knowledge about any oral advice given to NIH that led to the use of 42 U.S.C. 209(f) to compensate high-level NIH officials. NIH was verbally advised by an HHS attorney, who has since retired from government service.

4. Even though it lacks a written legal opinion, HHS OGC believes that 42 U.S.C. 209(f) can be permissibly interpreted as an appropriate authority for hiring and compensating NIH Institute Directors, and other high-level NIH officials because such authority can be ascertained through inference. HHS OGC stated that it is a permissible interpretation of "assist" and "advice" that such consultants have authority beyond mere advice, but also managerial authority. The statutory provision in some form appeared in the 1930's and was originally intended to assist the National Cancer Institute, giving power to NCI to retain the services of employees outside 5 U.S.C. 3109, which

relates to the appointment of special experts and includes a limitation that experts hired under this authority cannot perform administrative and supervisory work. Because 42 U.S.C. 209(f) lacks such a limitation, it can be inferred that consultants hired under this provision can perform such administrative and supervisory work. In addition, the use of the word "appointed" indicates that these consultants are not contractors since contractors receive awards not appointments.

Notwithstanding the views expressed by HHS OGC to Committee staff, my concerns about the proper use of 42 U.S.C. 209(f) remain. First, HHS documents seem to support the understanding that 42 U.S.C. 209(f) is for limited scientific appointments, not an alternative compensation scheme that permits high-level NIH officials to continue exercising broad-based, inherently governmental functions while being paid significantly higher salaries than if they had remained in the federal civil service system. For example, I note that HHS Personnel Instruction 304-1 (transmitted May 3, 1996), "Appointment of Experts and Consultants," references 42 U.S.C. 209(f) as a specific statutory authority for the Public Health Service under the section 304-1-20, Legal and Regulatory Authorities. Section 304-1-30, "Policies for Employment of Experts and Consultants," states:

"When expert and consultant appointments are made under one of the authorities listed in 304-1-20, the services to be performed must be ones that are properly covered by those authorities; the persons employed must be experts or consultants by definition; the needed services must be of such a nature that they can be met by an appointment of one year or less--unless the appointment is made under a statutory authority permitting a longer term.

Experts and consultants will not be employed in HHS to fill positions that are subject to competitive civil service examinations, position classification, and the General Schedule pay rates, or in cases where regular employees are available and have the skills and knowledge to perform the work. Nor will consulting services be obtained to bypass or undermine personnel ceilings, pay limitations, or civil service appointment procedures."

The section further states:

"Neither a consultant nor an expert may be assigned to perform the duties of a continuing, full-time position. While experts may serve as team leaders or directors of projects for which they were hired, neither experts nor consultants may make final decisions on substantive policies or functions in the agency chain of command."

On its face, it would appear that past written HHS policy and practice prohibited the application of 42 U.S.C. 209(f) to high-level NIH employees who "make final decisions on substantive policies or functions in the agency chain of command." I note that on November 1, 1999 the NIH Policy Manual providing guidance on Instruction 304-1 released new instructions about the employment of NIH, NCI and NHLBI Special Experts. This document discusses Title 42 special-expert appointment authorities, but does not mention 42 U.S.C. 209(f) as a specific statutory authority.

Second, the preliminary view of a specialist in American National Government, Government and Finance Division, Congressional Research Service substantiates my concern. The CRS specialist examined the text of 42 U.S.C. 209(f) and noted that the use of consultants is generally limited to activities that are not inherently governmental. The CRS specialist stated: "If one were actually administering a program in which there was authority for such things as hiring and firing of personnel, having decision-making authority related to the operation of the agencies and other such activities, that would be considered to be inherently governmental." In addition, the CRS specialist looked at the 1996 and 2000 Plum Books published by the House Committee on Government Reform and Oversight and the Senate Committee on Governmental Affairs, respectively. The Plum Book lists over 7,000 Federal civil service leadership and support positions in the legislative and executive branches of the Federal government that may be subject to noncompetitive appointment, nationwide. In the 1996 volumes most of the directors of the institutes are listed as career incumbents paid under Senior Executive Service schedules, with the primary exception of the NCI director, who is appointed under a special authority. In the 2000 edition, with the exception of the NCI director and one vacant position, there are no listings for directors of the institutes. They apparently were taken off the rolls of positions available to fill in the federal system. The CRS specialist concluded that on the face of it, it would support my concern that the positions are being filled by persons other than federal staff.

Finally, the application of Title 42 to high-level NIH decisionmakers has led to the anomalous result under current ethics law and regulation that these officials--some who earn more than the Vice-President of the United States and exercise power over the direction of millions and perhaps even billions of dollars of biomedical research funding--are not required to file public financial disclosure reports. The available information indicates that the practice of compensating high-level NIH officials appears to have started in 2000, well after the enactment of the Ethics in Government Act and the promulgation of federal ethics rules. According to HHS OGC, the statutory provision, 42 U.S.C. 209(f), has been in existence since the 1930's in one form or another, well before the Ethics in Government Act. There is no available information that the Ethics in Government Act was intended to provide a Title 42 loophole. There is reason to be dubious about the interpretation of Title 42 applicability to high-level NIH officials existing at the time of the passage of the Ethics in Government Act and that the anomalous result was intended. In fact, the anomalous result of applying Title 42 to high-level NIH officials suggests that current Title 42 interpretation may not be correct since it is an uneasy fit with the legal structure of federal ethics laws and regulations.

I note that it appears the OGC interpretation of Title 42 and NIH practice of using Title 42 U.S.C. 209(f) for high-level NIH employees predated your leadership of the Department. Under your leadership, I am aware that the Department

found and took action with regard to about 70 non-scientific employees at NIH who were improperly converted from the civil service to higher-payment appointments under Title 42 (but not under 42 U.S.C. 209(f)). I am appreciative of your concern to these issues and look forward to working with you to resolve my concern.

Given our concerns, pursuant to Rules X and XI of the U.S. House of Representatives, please provide the following by February 20, 2004:

1. Does HHS believe that 42 U.S.C. 209(f) can be permissibly interpreted as an appropriate authority for hiring and compensating NIH Institute Directors, and other high-level NIH officials?

2. When did the practice of applying 42 U.S.C. 209(f) to NIH Institute Directors start? Who authorized it? What was the rationale for the authorization?

3. Are all appointments made under 42 U.S.C. 209(f) affected in any way by 5 U.S.C. 3109? If so, are these appointments in compliance with 5 U.S.C. 3109?

4. All records since January 1, 1999 relating to the use of 42 U.S.C. 209 (f).

5. All records relating to the use of 42 U.S.C. 209(f) as a mechanism to hire and compensate NIH Institute Directors, and other high-level NIH officials.

6. Identify all HHS OGC employees who provided any advice given to NIH that led to the use of 42 U.S.C. 209(f) to compensate high-level NIH officials.

7. Please provide the number of Title 42 hires at NIH (with a breakdown for each Institute or Center) for each fiscal year starting with FY 2000.

White House:

Bush Proposes 2.7% Increase For NIH In Fiscal Year 2005

The Bush Administration this week proposed a $28.8 billion budget for NIH in fiscal 2005, an increase of $764 million, or 2.7 percent, over the current level.

NCI, the largest of the 27 Institutes and Centers in NIH, would receive $4.87 billion, an increase of $134 million, or 2.8 percent, over the fiscal 2004 appropriation of $4.736 billion.

Administration officials said the small percentage increase for NIH was justified because President George W. Bush had fulfilled his promise to complete the five-year doubling of the NIH budget.

"This budget builds on the five-year doubling of the NIH budget by increasing our commitment to medical research to $28.8 billion," HHS Secretary Tommy Thompson said in a prepared statement on the budget proposal, released Feb. 2. "That is a 41 percent increase over 2001 and will support nearly 40,000 research project grants--a record total for NIH."

Under the proposed budget, NIH would support 10,393 new and competing awards, an increase of 258 over the number funded this year. However, annual cost-of-living increases on non-competing continuation grants will be trimmed. Cost increases for new and recompeting grants will be limited to 1 percent.

According to budget documents, NIH will provide a 1.9 percent increase for direct costs on continuing grants, and will hold the average cost increase for all grants to 1.3 percent.

Also affecting the NIH budget is a proposal by President Bush for a 1.5 percent pay increase for civilian federal employees.

In a related development, a coalition of health advocacy organizations sent a letter last week to President Bush and members of Congress urging an increase in spending on public health. The letter was signed by more than 370 groups, including the American Cancer Society, American Association for Cancer Research, American Society of Clinical Oncology, American Society for Therapeutic Radiology and Oncology, American Society of Hematology, Association of American Cancer Institutes, Coalition of National Cancer Cooperative Groups, Oncology Nursing Society, Association of American Medical Colleges, and Trust for America's Health.

The coalition called for a 12 percent increase for discretionary funding for Function 550, the budget account that finances feeral agencies dedicated to disease prevention, medical research, health care delivery, food safety, and training the public health workforce. A copy of the letter with signatories is available at www.cancer.org/takeaction or www.healthyamericans.org.

The Administration's budget request included:

--For FDA, $1.8 billion, an increase of $149 million, including $350 million derived from industry-specific user fees. Increases are included for food safety, accelerating the availability of drugs and devices. The budget also supports FDA's administrative consolidation efforts, including moving 1,700 staff into their consolidated headquarters under construction at White Oak, Md. FDA will also direct an added $5 million to finance its role in the government-wide biosurveillance effort designed to provide the earliest possible detection of the international release of deadly pathogens into food, water, or the environment.

--The Centers for Disease Control and Prevention would receive $6.9 billion, a net decrease of $58 million below FY 2004. The National Breast and Cervical Cancer Early Detection Program would receive $220 million, an increase of $10 million to increase support

to states to pay for additional outreach and services.

--The CDC budget also requests $150 million for health statistics, an increase of $22 million over FY 2004. The increase would enable the National Center for Health Statistics modernize its system, expand contracts with states to purchase birth and death data, and update the content of birth and death records. The increase will also provide the robust sample sizes necessary for the National Health and Nutrition Examination Survey and the National Health Interview Survey to provide information on a wide range of conditions, diseases, and population subgroups.

Following is the excerpted text of the HHS "Budget in Brief" document for NIH. The document is available at: www.hhs.gov/budget/docbudget.htm.

Research Priorities in FY 2005: The FY 2005 budget request will allow NIH to address imperative requirements in biodefense; implement the NIH Roadmap for Medical Research; pursue an obesity research initiative; and manage a research initiative on developing nuclear and radiological threat countermeasures. Additional support will be provided to continue progress in promising arenas of science related to specific diseases such as cancer, HIV/AIDS, diabetes, Parkinson's disease, and Alzheimer's disease; while also pursuing whole new avenues of post-genomics research.

Biodefense: For FY 2005, the President's budget proposes a total of $1.7 billion for NIH biodefense efforts, an increase of $121 million, or 7.5 percent, over FY 2004. Our nation's ability to detect and counter bioterrorism ultimately depends heavily on the state of biomedical science. Guided by its long-range strategic plan that includes short-, intermediate-, and long-term goals, NIH's biodefense research stresses two overarching, complementary, and urgent components: a) basic research on the biology of microbial agents with bioterrorism potential and the properties of the host's response to infection and defense mechanisms; and b) applied research with predetermined milestones for the development of new or improved diagnostics, vaccines, and therapies. NIH will continue to ensure full coordination of these research activities with other Federal agencies in the war against terrorism.

In just the past two years, NIH has made tremendous strides towards developing countermeasures to protect all Americans from bioterrorism. For example, researchers supported by NIH have sequenced genomes representative of all bacteria considered bioterrorism threats, and are sequencing genomes for at least one strain of every potential viral and protozoal bioterrorism pathogen. NIH has also developed and expanded contracts to screen new drugs; develop new animal models; establish a reagent and specimen repository; and provide researchers with genomic, proteomic and bioinformatic resources related to potential bioterrorism agents. NIH is funding more than 100 grants and contracts with pharmaceutical and biotechnology companies in collaborative projects to develop high-priority biodefense products. Work on a second-generation anthrax vaccine has rapidly progressed to the point that a vaccine product is expected to be ready for procurement later this year through the new DHS BioShield program.

In FY 2005, NIH will complete the national network of extramural Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, including awarding the last two of the planned 10 regional centers. Also in FY 2005, NIH will continue testing a range of candidate vaccines in clinical and pre-clinical studies, including third-generation vaccines against smallpox; a DNA vaccine to prevent Ebola virus; and new vaccines for plague, tularemia, Rift Valley Fever, and other viral hemorrhagic fevers, such as Marburg and Lassa viruses.

The FY 2005 budget requests $150 million to continue support for construction of specialized biosafety laboratories at universities and research institutions across the country. Prior to FY 2002, only a few of these specialized laboratories existed in the United States that were capable of conducting research on potential bioterrorism agents. The $150 million investment in FY 2005 will fund an additional 20 Level 3 laboratories in metropolitan areas throughout the country. Once these facilities are completed, we will be able to support over 200 research projects at the same time aimed at developing medical protection from bioterrorism. These facilities will also back up State and Federal public health laboratories if there is an actual or suspected bioterrorism attack. This increase in FY 2005 will be funded as a result of the completion of NIH's applied research on new anthrax and smallpox vaccines.

The ability to mitigate the health effects of radiation exposure in the potential event of the use of a limited nuclear or radiological device in a terrorist attack presents a critical challenge for which little progress has been made in the last 40 years. The FY 2005 biodefense request for NIH includes $47 million for the Public Health and Social Services Emergency Fund to support specific targeted research activities needed to develop medical countermeasures to more rapidly and effectively treat nuclear or radiological injuries. This research initiative will focus on a) developing drugs that can be used to prevent injury from radiological exposure; b) improving methods for measuring radiological exposure and contamination; and c) developing methods or drugs to restore injured tissues and eliminate radioactive materials from contaminated tissues.

NIH Roadmap for Medical Research: In an effort to target major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone, the FY 2005 budget allocates a total of $237 million for the "Roadmap" initiative, an increase of $109 million over FY 2004. The request includes $60 million in the Office of the Director, an increase of $25 million, and $177 million, an increase of $84 million, in the budgets of the Institutes and Centers and used in a coordinated effort to support the Roadmap.

The Roadmap will help transform new scientific knowledge that will result in tangible benefits for the

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National Institutes of Health
President's Budget Proposal FY 2005

	2003	2004	2005	2005 +/- 2004
Institutes:				
National Cancer Institute	$4,584	$4,736	$4,870	+$134
National Heart, Lung, & Blood Institute	2,792	2,878	2,964	+86
National Institute of Dental & Craniofacial Research	371	383	394	+11
Natl Inst. of Diabetes & Digestive & Kidney Disease	1,721	1,821	1,876	+55
National Institute of Neurological Disorders & Stroke	1,455	1,501	1,546	+45
National Institute of Allergy & Infectious Diseases	3,703	4,303	4,426	+123
National Institute of General Medical Sciences	1,847	1,905	1,960	+55
Natl Inst. of Child Health and Human Development	1,204	1,242	1,281	+39
National Eye Institute	632	653	672	+19
National Institute of Environmental Health Sciences:				
Labor/HHS Appropriation	612	631	650	+19
VA/HUD Appropriation	84	78	80	+2
National Institute on Aging	993	1,025	1,056	+31
Natl Inst. of Arthritis & Musculoskeletal & Skin Dis	486	501	515	+14
Natl Inst. on Deafness & Communication Disorders	370	382	394	+12
National Institute of Mental Health	1,339	1,382	1,421	+39
National Institute on Drug Abuse	961	991	1,019	+28
National Institute on Alcohol Abuse & Alcoholism	416	429	442	+13
National Institute for Nursing Research	130	135	139	+4
National Human Genome Research Institute	464	479	493	+14
Natl Inst. for Biomedical Imaging & Bioengineering	280	289	298	+9
National Center for Research Resources	1,139	1,179	1,094	-85
Natl Center for Complementary & Alternative Med	113	117	121	+4
Natl Center for Minority Health & Health Disparities	186	192	197	+5
Fogarty International Center	62	65	67	+2
National Library of Medicine	306	317	325	+8
Office of the Director	286	327	360	+33
Buildings & Facilities	639	99	100	+1
Nuclear/Radiological Countermeasures Research	0	0	47	+47
ONDCP Drug Forfeiture Fund Transfer (NIDA)	4	5	0	-5
Type 1 Diabetes Research 1/	0	0	0	0
Total, Program Level	**$27,178**	**$28,041**	**$28,805**	**+$764**
Less Funds Allocated from Other Sources:				
Nuclear/Radiological Countermeasures Res. (PHSSEF)	$0	$0	-$47	-$47
ONDCP Drug Forfeiture Fund Transfer (NIDA)	-4	-5	0	+5
PHS Evaluation Funds (NLM)	-8	-8	0	+8
Type 1 Diabetes Research 1/	-100	-150	-150	0
Total, Budget Authority	**$27,066**	**$27,878**	**$28,607**	**+$729**
Labor/HHS Appropriation	**$26,983**	**$27,800**	**$28,527**	**+$727**
VA/HUD Appropriation	**$84**	**$78**	**$80**	**+$2**
FTE	17,596	17,522	17,522	0

1/ These funds were pre-appropriated in the Benefits Improvement and Protection Act of 2000 and P.L. 107-360.

(Continued from page 8)
American public of new treatments, prevention strategies, and diagnostics through overcoming barriers to rapid progress in biomedical research. The Roadmap is organized into three core themes: New Pathways to Discovery; Research Teams of the Future; and Re-engineering the Clinical Research Enterprise.

HIV/AIDS Research: The FY 2005 budget includes a total of $2.9 billion for HIV/AIDS-related research. This is an increase of $80 million, or 2.8 percent over the FY 2004 level. In addition to these funds, the FY 2005 budget includes $100 million in NIAID to continue HHS contributions provided since FY 2002 to the Global Fund to Fight HIV/AIDS, Tuberculosis, and Malaria. The FY 2005 NIH HIV/AIDS research agenda continues the following overarching themes: HIV prevention research, including development of vaccines, microbicides, behavioral interventions, and strategies to prevent perinatal transmissions; therapeutics research to develop simpler, less toxic, and cheaper drugs and regimens to treat HIV infection and its complications; international research, particularly to address the critical research and training needs in developing countries; and research targeting the disproportionate impact of the AIDS epidemic on racial and ethnic minority populations in the U.S. All of these efforts require a strong foundation in basic science.

Obesity: The epidemic of obesity threatens the Nation's health by sharply increasing the incidence of type 2 diabetes, fatty liver disease, kidney failure, and cardiovascular and other diseases. However, dramatic advances in our understanding of how appetite and weight are regulated offer new opportunities to develop methods to treat obesity and to prevent type 2 diabetes and other obesity-related diseases. In FY 2005, NIH plans to expand its obesity research portfolio by $40 million, for a total of $440 million. This includes a targeted, $22 million, trans-NIH initiative that will seek to better understand the neurobiological, genetic, behavioral, and environmental basis of obesity and its co-morbid conditions; improve strategies for maintaining healthy weight in adults and children, particularly in primary care, school, and workplace settings; and develop new therapeutic anti-obesity modalities to complement lifestyle interventions.

This obesity initiative will complement the ongoing work of NIH on diabetes, including, for example, efforts to build upon the Secretary's Diabetes Detection Initiative by discovering new approaches to accurately and effectively diagnose type 2 diabetes; and moving forward with a full-scale, landmark, clinical trial to test the best approaches to lowering the risk of heart disease and stroke in adults with type 2 diabetes.

Research Project Grants: The support of basic medical research through competitive, peer-reviewed, and investigator-initiated research project grants represents 54 percent of NIH's total budget request for FY 2005. In FY 2005, the NIH budget provides $15.5 billion, a 2.7 percent increase over FY 2004, to fund 39,986 total projects, the highest level in the agency's history. This is 558 more grants in total than are expected to be funded in FY 2004. Within this total, NIH estimates it will support 10,393 competing RPGs in FY 2005, an increase of 258 over FY 2004. The average cost of research project grants will increase in the aggregate by 1.3 percent.

Facilities Construction: During FY 2004, both the Mark O. Hatfield Clinical Research Center and part of the John E. Porter National Neurosciences Research Center are scheduled to open, which together will provide an additional 1,115 gross square feet of laboratory and patient research space to NIH's main campus in Bethesda. In addition, over the past two years, approximately $800 million has been appropriated for both intramural and extramural biosafety laboratory construction which are currently in design stages. In FY 2005, another $150 million is requested to further expand laboratory space in universities and research institutions around the country critical to biodefense research activities. The budget also includes a total of $108 million for other non-biodefense intramural facilities projects, such as general repairs and improvements across NIH's nearly 200 total buildings. No funds are requested for non-biodefense extramural research facilities construction grants. Over the past 10 years, $633 million have been appropriated for non-biodefense extramural construction projects. In FY 2005, NIH's budget places a higher priority on the support of additional research project grants.

Tobacco Control:

HHS Plans National Network Of Toll-Free Smoking Quitlines

The Department of Health and Human Services said it plans to support a network of smoking cessation quitlines nationwide to help smokers kick the habit.

HHS will establish a single, toll-free phone number that smokers in every state can call for information on quitting smoking. Currently, telephone quitlines deliver information, advice, support, and referrals to smokers in 38 states.

"The combination of lives lost and the cost of treating smoking-related diseases makes our investment in smoking cessation services imperative," HHS Secretary Tommy Thompson said. "By providing smoking cessation resources to the 46 million adults in this country who smoke, we can make an enormous improvement in public health."

States with existing quitlines will receive increased funding to enhance existing services, such as expanding hours of operation, hiring bilingual counselors, linking with local health care systems, or outreach, HHS said. States that do not have quitlines will receive grants to establish them.

The NCI Cancer Information Service telephone counselors will provide assistance to individuals in states without quitlines, HHS said.

Funding Opportunities:

RFAs Available

RFA-GM-04-002: Pharmacogenetics Research Network and Knowledge Base

Letter of Intent Receipt Date: July 19, 2004

Application Receipt Date: Aug. 19, 2004

The RFA solicits applications for a network of multidisciplinary, collaborative groups of investigators to contribute data to the publicly available knowledge base PharmGKB. The research groups in the network have interests across a range of biological processes: drug metabolism, small molecule transport, target receptors, and biological pathways involved in the drug treatment of cardiovascular diseases, asthma, cancer, and depression; other areas are welcome consistent with the interests of the funding institutes.

NCI is interested in projects that can lead to improvements in clinical and survival endpoints, and in studies of genetic variability in human populations that may influence risk of preneoplastic conditions or primary and secondary malignancies after exposure to medications, including cancer therapies. The RFA will use the NIH U01 award mechanism. The RFA is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-04-002.html.

Inquiries: Ken Kobayashi, Cancer Therapy Evaluation Program, phone 301-496-1196; fax 301-402-0428; e-mail kobayashik@ctep.nci.nih.gov; J. Fernando Arena, Division of Cancer Control and Population Sciences, phone 301-594-5868; fax 301-402-4279; e-mail arenaj@mail.nih.gov.

RFA-CA-04-015: Strategic Partnering to Evaluate Cancer Signatures

Letter of Intent Receipt Date: June 22, 2004

Application Receipt Date: July 22, 2004

NCI invites investigators to form partnerships of multi-disciplinary expertise and resources to determine how the information derived from comprehensive molecular analyses can be used to improve patient care and ultimately, patient outcomes. Applicants are asked evaluate clinical usefulness of molecular signatures already developed using molecular analysis technologies including DNA, RNA or protein-based technologies. The initiative will help ensure that the NCI goal of eliminating the suffering and death from cancer by 2015 is met. This RFA will use the NIH cooperative agreement (U01) award mechanism. The RFA is available at http://grants2.nih.gov/grants/guide/rfa-files/rfa-ca-04-015.html.

Inquiries: James Jacobson, Division of Cancer Treatment and Diagnosis, phone 301-402-4185; fax 301-402-7819; e-mail jacobsoj@mail.nih.gov. or Tracy Lugo, phone 301-96-1591; fax 402-7819; e-mail lugot@mail.nih.gov.

Program Announcements

PA-04-053: Developmental Projects in Complementary Approaches to Cancer Care

The NCI Office of Cancer Complementary and Alternative Medicine, National Center for Complementary and Alternative Medicine, National Institute of Nursing Research, and the National Institute of Dental and Craniofacial Research invite research grant applications for basic and clinical complementary cancer research and for more extended research projects by establishing the methodological feasibility, strengthening the scientific rationale for the projects, and collecting preliminary data.

Applicants may consider complementary approaches as they relate to the prevention, diagnosis, and treatment of cancer, cancer-related symptoms, and side effects of conventional treatment. In addition, applicants may consider research on interactions of complementary approaches with conventional cancer therapies. The PA will use the NIH Exploratory/Developmental R21 award mechanism. The PA is available at http://grants2.nih.gov/grants/guide/pa-files/PA-04-053.html.

Inquiries: Wendy Smith, NCI OCCAM, phone 301-435-7980; fax 301-480-0075; e-mail smithwe@mail.nih.gov; OCCAM website: www.cancer.gov/cam. Yali Hallock, Developmental Therapeutics Program, NCI Division of Cancer Treatment and Diagnosis, phone 301-496-8783; fax 301-402-5200; e-mail hollocky@mail.nih.gov. or Roy Wu, Clinical Grants and Contracts Branch, Cancer Therapy Evaluation Program, phone 301-496-8866; fax 301-480-4663; e-mail wur@mail.nih.gov.

PAR-04-055: Cancer Prevention, Control, Behavioral and Population Sciences Career Development Award

The award provides protected time through salary and research support for up to 5 years to individuals with a health professional or science doctoral degree who are 1) already proficient in general epidemiology, behavioral sciences, or other relevant disciplines, and now want to make use of these proficiencies in cancer-focused research careers in prevention, control, population and/or the behavioral sciences, or 2) already trained in cancer epidemiology, etiology, prevention, control and the behavioral and population sciences but are not yet fully independent investigators. Examples of relevant disciplines include any aspect of human cancer prevention (modifiable risk factors, new animal models and extrapolation of these models to human cancer, genetic predisposition to cancer and detection of precursor lesions, patient-oriented research focused on cancer prevention, and behavioral research and behavioral intervention trials in cancer prevention), epidemiology (biochemical, genetic, molecular), biostatistics, human cancer genetics, clinical oncology, human nutrition, behavioral and social sciences, health promotion, health services and health policy research; and medical decision analysis, survivorship and quality of life as they relate to cancer. The PA will use the NIH Cancer Prevention, and Control Career Development K07 Award mechanism. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PAR-04-055.html.

Inquiries: Lester Gorelic, Cancer Training Branch, NCI, phone 301-496-8580; fax 301-402-0181; e-mail gorelicl@mail.nih.gov.

American Cancer Society Request for Applications

Pathogenesis and Treatment of Lymphedema Secondary to the Management of Breast Cancer
RFA-01-2004
Applications due April 1, 2004

Purpose: The American Cancer Society, supported by the Longaberger Company, is announcing this RFA to investigate the incidence, etiology and new treatments for secondary lymphedema in human subjects. The purpose of this RFA is to stimulate research on the modification of morbidity from lymphedema secondary to treatment for breast cancer and to gain some understanding the natural history and effective interventions aimed at minimizing that morbidity. The scope of this research includes attempts to improve early diagnosis of affected individuals, the choice and timing of treatment, the pathophysiology of the disorders of skin and subcutaneous tissue secondary to chronic lymphedema resulting from breast cancer treatment.

Eligibility Requirements: Applications may be submitted by not for profit institutions located within the United States, its territories and the Commonwealth of Puerto Rico. Independent investigators at all stages of their career are eligible to apply. Thus, the usual ACS restriction to investigators within the first eight years of their initial independent research appointment does not apply to this RFA.

Mechanism of Support: This RFA will use the American Cancer Society targeted research scholar grant award mechanism. The applicant will be solely responsible for the planning, direction, and execution of the proposed project, which is not to exceed a period of 3 years. Complete and detailed instructions and information on grant applications can be found at http://cancer.org.

Research Objectives: Lymphedema is an important health problem for many women who have been treated for breast cancer. About 15% to 20% of breast cancer patients have developed lymphedema after breast cancer treatment; thus, among more than 2 million breast cancer survivors, approximately 400,000 cope daily with the disfigurement, discomfort, and disability of arm and hand swelling. Those survivors without lymphedema who have had surgical or radiation treatment of the axilla remain at risk indefinitely. Aside from breast cancer recurrence, lymphedema is one of the most serious sequelae of breast cancer treatment. Daily swelling of the hand, wrist and arm create both psychological and physical reminders of the cancer. Appropriate areas of investigation for this RFA include:

1. Comparative studies of breast cancer treatment interventions and their sequelae for both incidence and severity of the edema should be considered.
    a. Particular emphasis on the relative contributions of the breast cancer, lymph node removal (sentinel lymph node examinations) and radiation therapy to include the time of onset and natural progression of the lymphedema should be considered.
    b. Methods to prevent radiation-induced or surgery-related lymphedema
2. Innovative and practical methods of detecting and measuring lymphedema to assess its natural history, exacerbations and normal amelioration should be considered.
    a. Investigation of the importance of early detection and aggressive intervention for reducing severity and progression of lymphedema;
    b. Research to determine the relative efficacy of each component of a comprehensive treatment program, including optimal timing for application.
    c. The development of methods to image and quantitate lymph flow to provide useful endpoints for clinical evaluations.
3. Development of cost/economic analysis on the burden and treatment of lymphedema.
4. The incidence of infectious complications, tracking their sequelae and the development of appropriate infection management guidelines should be considered.
5. Rigorous comparative evaluations of therapeutic interventions using secular and crossover designs to dissect the efficacy of the methods in subgroups of patients.

Budget Implications: It is anticipated that a total of $1,500,000 will be available for 4 to 6 applications selected through the Society's peer review system.

For additional information, contact Dr. Ronit Elk at 404 417 5957 or by email: ronit.elk@cancer.org or Dr. Ralph Vogler at 404 329 7542 or by email: ralph.vogler@cancer.org. For specific questions about the research objectives for this RFA, contact Dr. Robert Smith at 404-329-7610, or by email at robert.smith@cancer.org.

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