THE CANCER LETTER

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Five NIH Study Section Members Resign Over Peer Review Of Their Grant Proposals

By Kirsten Boyd Goldberg

Over the past three months, members of NIH oncology study sections complained about the quality of review of their own grant applications.

The scientists argued that a review process recently instituted by the NIH Center for Scientific Review in effect penalized them for serving on the panels that assess the merits of projects submitted by extramural scientists.

After receiving no assurances that the problem would be fixed, five scientists who served on two study sections chose to quit.

"I certainly did not want to resign, and I enjoyed my time on the study section, but I have some grants coming up [for review] and have concerns about how they will be adjudicated," said William Drobyski, professor of medicine and pediatrics, Medical College of Wisconsin, who resigned from the Cancer Immunopathology and Immunotherapy study section.

"I'm not convinced that there is a policy in place that will assure study

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Iressa Becomes First Accelerated Approval Drug To Be Placed In Limited Distribution By FDA

By Paul Goldberg

For years, FDA-watchers have been eager to see the agency decide the fate of a cancer drug that received an accelerated approval, but hadn't demonstrated efficacy.

Last week, the agency took action against an accelerated approval drug, restricting patients' access to the AstraZeneca drug Iressa (gefitinib).

On June 17, the agency announced that Iressa would be distributed under a limited access program, and made available only to patients who are responding to the therapy or had responded to it in the past.

The limited access mechanism has been used sparingly by the agency, and previously, access to therapies has been blocked due to toxicity.

Iressa is the first agent to be restricted based on the inability to demonstrate efficacy. The drug was approved two years ago, based on a single-arm trial that demonstrated tumor shrinkage in about 10 percent of second-line lung cancer patients. However, large randomized trials failed to show Iressa's impact on survival.

Meanwhile, another targeted drug, Genentech's Tarceva (erlotinib), received regular FDA approval after demonstrating a survival advantage. Both Iressa and Tarceva are orally administered epidermal growth factor receptor tyrosine kinase inhibitors.

"One would have to ask himself why would a rational physician be

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Reviewers Say Their Proposals Weren't Given Equal Review

(Continued from page 1)

section members an equitable review, commensurate with that given to investigators not on study sections," Drobyski said.

Under normal circumstances, scientists who apply for NIH grants send their applications to the study sections best qualified to evaluate their work. However, scientists who serve on study sections are precluded from submitting applications to their own panels. Such applications are referred to "Special Emphasis Panels" formed by CSR.

According to Drobyski and other reviewers, a new panel formed to evaluate their grant applications last April didn't have as high a level of expertise or peer review experience as the established study sections. The resulting scores deviated significantly from those given by regular study sections.

Fewer than one in six proposals submitted by the study section members met the payline, a percentage that is below the current NIH payline of 16 percent, the researchers said. Drobyski and other reviewers from CII and the Developmental Therapeutics study sections protested (The Cancer Letter, May 6).

"My reason for resigning is that CSR does not have a policy in place to ascertain that study section member applications are treated with the same standards as offered to the general applicant pool," said Jessie Au, Distinguished University Professor, Ohio State University, who resigned from the Developmental Therapeutics study section last month.

"I did resign since my priority has to be my own research program," said M. Rita Young, associate chief of staff for research at the Ralph H. Johnson VA Medical Center in Charleston, S.C., who left the CII study section.

"CSR will have a difficult time getting reviewers if they cannot give the reviewer's applications the same quality of review that the reviewers themselves give out," said William Murphy, professor in the Department of Microbiology and Immunology, University of Nevada School of Medicine, who resigned from the CII study section. "I was very reluctant to resign, but when research budgets are declining, such altruism is difficult."

David Cole, professor of surgery, Medical University of South Carolina, confirmed that he also resigned from the CII study section out of concern for his research program.

"All we have ever asked for is access to scientific peer review that is equivalent to that of the general applicant pool," said James Young, professor of medicine and head of the Laboratory of Cellular Immunobiology, Memorial Sloan-Kettering Cancer Center, and a member of the CII study section who had protested the review of his R01 grant application.

Young considered resigning from the study section, but decided to serve out the final months of his term. "My term ends anyway after the June meeting, and whether I stayed or resigned wouldn't have affected another R01 [grant application] I had submitted," Young said. "But if this continues, it's not going to be just a few people resigning. NIH isn't going to get enough people to agree to serve as standing study section members."

Murphy and Au said they offered to serve as ad hoc reviewers, since that status will allow them to submit grant applications to the study section on which they serve, providing they don't attend the meeting in which their application is being reviewed.

"My offering to serve on an ad hoc basis is because I believe in the peer review system and its importance," Au said. "As an ad hoc member, I can choose not to go when I have a grant in, so that my grants can be reviewed by the study section with the appropriate expertise, and percentiled against other grants in my field, as opposed to being percentiled against all CSR scores, which are typically much more favorable compared to the scores in my field."

While ad hoc membership will solve the problem

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for individual reviewers, it's not a solution for the peer review system, Murphy said. Study sections need a certain number of full members at each meeting to have a quorum. "You also want the continuity in scoring that members provide over several years," he said.

Before the resignations, 32 scientists served on the DT study section and 28 served on the CII study section.

CSR officials declined to comment on the resignations.

"I wouldn't be surprised if more reviewers decide to resign," said Henry Friedman, the James B. Powell Jr. Professor of Neuro-Oncology at Duke University, who served for 10 years on the Experimental Therapeutics 2 study section. "CSR is perpetuating the problem by allowing reviewers without study section experience to be brought into the peer review process without the appropriate apprenticeship that is done when a scientist first joins a study section. As a result, study section members are recognizing the extraordinary damage that can be done to their grants when they are reviewed by scientists with no study section experience.

"This is a colossal blunder whose ramifications are going to damage the peer review process," said Friedman, who no longer serves on a study section. "How many members are going to quit before CSR gets it?"

Beverly Torok-Storb, a member of the NIH Peer Review Advisory Committee and associate program head of transplantation biology at Fred Hutchinson Cancer Research Center, said peer reviewers have been aware of this problem for years.

"The review of applications submitted by study section members is a longstanding problem," said Torok-Storb. "Before, they gave the applications to another study section, and they didn't fare as well. The SEPs, I thought, would resolve that issue, and for a while, the general feeling was the SEPs erred on the other side, giving more favorable reviews. Getting assigned to an SEP was a benefit.

"One could ask facetiously, did anyone complain when they made the payline and shouldn't have?" Torok-Storb said. "Nobody likes it when their grant doesn't make it. Now, with the current funding level, many grants aren't making it. Many of us have to go and stand in line more than once.

"I was a reviewer for one committee or another for 20 years straight, and it did a couple of times cost me," Torok-Storb said. "But, who knows? The grant might not have made it anyway."

Question of Appropriate Expertise, Experience

The latest controversy began last April, when 18 grant applications submitted by CII and DT study section members were reviewed by a Special Emphasis Panel.

Usually, SEPs are comprised of experienced reviewers, such as former study section members, current members of different study sections, and a few members of the applicant's study section.

This time, CSR experimented with a new format, the researchers said. Only one member of the SEP was a full member of the CII study section, and one or two other SEP members had previously served or were ad hoc members of CII. No one on the SEP had served on the DT study section, the researchers said.

"This raises the issue of whether the SEP has the appropriate expertise or review experience," wrote 10 of the study section members whose applications were reviewed by the SEP, in a letter dated May 2 and addressed to CSR Acting Director Brent Stanfield.

The letter was signed by several of the reviewers who resigned or are leaving the study sections: Au, Drobyski, Murphy, M. Rita Young, and James Young. Others who signed were James Finke, of Cleveland Clinic; Manuel Hidalgo, of Johns Hopkins University; Scott Kaufmann, of Mayo Clinic; Bijay Mukherji, of University of Connecticut Health Sciences Center; and Edward Schwartz, of Albert Einstein College of Medicine.

Several other actions put the applications in jeopardy, the study section members wrote:

"It appears that the [Scientific Review Administrator] of the SEP was not allowed to, or did not, consult with the SRAs of DT or CII to obtain names of qualified or experienced reviewers with appropriate expertise.

"The roster of this SEP was listed incorrectly on the CSR website and was not provided on the CSR website 30 days prior to the meeting. Hence, many of us were not able to judge or voice our concerns on the level of expertise or review experience on the SEP.

"Most of the [NIH] program administrators were not informed in time to make arrangements to attend the SEP meeting and, therefore, could not obtain first-hand information on why the scoring distribution of the SEP deviated greatly from the norm and why the percentiles did not match the level of enthusiasm.

"The composition of the SEP (more than 60 percent of non-study section members) was such that the priority scores were percentiled against all CSR applications."

In their letter, the researchers asked CSR to

recalculate their priority scores against those of the DT and CII study sections. "The payline of grants in DT and CII typically fall in the excellent range (1.8-2.0), which is a much higher number compared to the payline of all CSR scores," the researchers wrote. "The overwhelming majority of the SEP members are not experienced DT and CII reviewers and hence would not have the reference point to judge what types of applications should rank in the top 16% or the bottom 84%.

"The scoring pattern of the SEP appears to be such that much fewer than one of six grants met the payline (i.e., much lower than the 16% payline)," the letter said. "This deviation from the norm is even more significant when one takes into account the fact that study section members typically have a much higher success rate (~50%)."

The SEP's summary statements indicated that the "relatively unfavorable percentiles" provided to some of the applications were "not in line with the high level of enthusiasm expressed by the reviewers in their critiques and in the summary of the discussion," the letter said.

"We would suggest that two of the guiding principles for CSR in dealing with member applications should be to provide members with a fair and high quality review comparable to that offered to the general applicant pool and to ascertain that the applications are ranked among their peers within their own scientific fields," the letter said.

"Study section membership automatically precludes review in the member applicant's study section, which is also the one with the most appropriate expertise. Hence, we propose the following:

—"Offer the member a choice to be reviewed in an alternate study section with overlapping expertise or in a SEP.

—"For SEP, the responsible SRA is encouraged to consult with the SRA of the applicant member's study section for suggested reviewers.

—"SEP should consist of current members of the same study section as the applicant member, constituting at least 40% of the SEP membership, with the remaining members selected from knowledgeable scientists and seasoned researchers, preferably those who have received funding from NIH or other federal peer-reviewed sources.

—"A SEP panel should be instructed to consider applications in the context of the larger body of proposals in their respective scientific fields, and are not solely ranked against each other. This reinforces the importance of including current study section members.

—"CSR guidelines state that a SEP must consist of a minimum of five reviewers. Hence, if a single application is reviewed in a SEP, the unintended consequences are (a) possibility for greater scrutiny by five reviewers compared to applications reviewed in a standing study section (usually reviewed by three reviewers), and (b) greater burden during revision due to the more extensive review. Hence, we propose that each SEP should review at least two member applications, usually with no more than three reviewers (primary, secondary and discussant) assigned to a single application.

—"Revised applications from nonmembers are customarily returned to the study section that has reviewed the original application, and are typically assigned to some or all of the previous reviewers. This practice provides continuity in review and lowers the risks of new reviewers asking for additional changes. To afford the same continuity in review to member applicants, we propose that for a revised application from members that is reviewed by a SEP, the SRA should make every attempt to include at least one, and preferably more, reviewers of the original application.

—"SEPs are customarily conducted several weeks after standing study sections. This creates a potential delay of providing summary statements to member applicants and, consequently, delays for applicants to prepare and submit revised applications. We propose that CSR considers extending the deadline for submission of revised applications where the summary statements are delayed."

CSR Response: Review "Properly Conducted"

In a letter emailed to the study section members on May 10, CSR Acting Director Stanfield said he and other CSR officials reviewed the situation with the SEP in question, called ZRG1 ONC-U (03).

"CSR has concluded that ZRG1 ONC-U (03) was properly composed and the reviews were properly conducted," Stanfield wrote. "CSR believes that the applications reviewed in ZRG1 ONC-U (03) were reviewed competently and fairly and the reviews and scores should stand. As you are aware, it is the right of applicants to request an appeal of the review with their program officials if the applicant feels that the review of their application was seriously flawed. This course is open to you if you feel the review of your application was substantially flawed in any way.

"In his discussions with some of the Principal Investigators whose applications were reviewed in ZRG1 ONC-U (03) it is my understanding that as a measure of good faith Dr. [Syed] Quadri [chief of the

Oncological Sciences Integrated Review Groups, who supervised the SEP] agreed to look into the possibility of grounds for percentiling applications reviewed in ZRG1 ONC-U (03) against another base—either that of DT or CII—instead of the base of all applications reviewed in CSR study sections that are percentiled (i.e., the CSR All base)," Stanfield wrote.

"However, Dr. Quadri found no basis in rule or principle for recalculating the percentile ranking," Stanfield wrote. "Indeed, doing so would violate the CSR rule that percentile ranking by Special Emphasis Panels composed of fewer than 40% chartered review group members will be against the CSR All base. Therefore, CSR cannot accommodate the first request of this current letter to recalculate percentile rankings of the grant applications reviewed in ZRG1 ONC-U (03)."

As for the study section members' request that CSR provide an equitable review process for member applications, Stanfield wrote:

"I take this request seriously. CSR strives to ensure competent and fair review of all applications. A hallmark of fair review is that no group of applications is either advantaged or disadvantaged in the review process. As you cite in your letter, applications from standing study section members generally do well in review. One would expect this because CSR and NIH seek high quality researchers to participate on its peer review panels and this has been an indication that that the practices that CSR has in place for review of applications from members of standing study sections are generally appropriate. However, I realize that the system that is in place may not be perfect or even the best possible given the constraints of the circumstances. All of our practices and policies constantly need to be assessed and opportunities for improvement need to be investigated."

Stanfield proposed that the topic be discussed at the September meeting of the NIH Peer Review Advisory Committee.

"Inflexibility At CSR"

The study section members who resigned said CSR's response was inadequate.

"CSR has not admitted that there were any substantive problems with that review," Drobyski said. "The other important issue is, what will happen in the future? We haven't gotten a concrete answer to that question. If people feel that by serving on a study section, their grants are not going to be reviewed in an equitable fashion, they are going to be reluctant to join, since they do this as a service to NIH and will not want to potentially compromise their own research."

Murphy said CSR mishandled the controversy. "The lack of real empathy and acknowledgment of the concern—or, importantly, the lack of timely, substantive action—reveals an inflexibility at CSR that compounds the problem," he said.

"Typically, people are put on study sections because they have a demonstrated ability to get grants," Murphy said. "Is it conceivable that we all had terrible grants? I don't think so. If you are on a study section, you're not doing wacky research."

However, James Young said CSR made two changes that Stanfield's letter didn't mention.

First, CSR backtracked from what appeared to have been a policy change that barred study section members from serving on SEPs reviewing applications from their own committees. "CSR conceded that while it's frowned upon to use members of study sections on a SEP reviewing another member's application, there is no written policy," Young said.

Second, CSR has stated that immediately after leaving a study section, members are no longer in conflict, which means they can submit grant applications to their former committee.

"There had been rumors that members remained in conflict for a full year [after their service ended]," Young said. "It turns out that's not the case. None of this is written down, but we have two emails from senior management saying you are no longer in conflict with the very first meeting after your term ends. For my immediate needs, that satisfied my concerns."

Young said the larger, long-term problem remains. "They still haven't addressed adequately how to guarantee a study section member the quality of review that is the same caliber as provided to a general applicant," Young said. "You can't penalize us by putting us out to less experienced reviewers. The devil is always in the details. On paper, the SEP was minimally acceptable by the rules, but that's not the way you treat volunteers who put in hundreds of hours of time."

Torok-Storb said the PRAC discussion in September may begin to address the problem. "The peer review system in this country is so strong, but it's a lot of work to be a reviewer," she said. "We'd like service on a study section not to come with a penalty. If anything, you would like to make it a benefit. But that's difficult to address fairly. There's no easy solution, but it's a serious problem.

"I don't know what we're going to recommend, but the meeting is open to the public and recommendations are welcome," Torok-Storb said.

"Limited Distribution" Ordered For Lung Cancer Drug Iressa

(Continued from page 1)

prescribing Iressa, with Tarceva on the market?" said Richard Pazdur, director of the FDA Office of Oncology Products.

Altogether, about 4,000 patients take Iressa in the U.S., the company estimates. These patients would continue to receive the drug through a central pharmacy that will be set up by the company.

"We are putting in place a distribution program which will pull Iressa back from pharmacies and centrally locate its access to one mail-order pharmacy," said Mary Lynn Carver, a spokesman for AstraZeneca. "That way, we can implement the signoff from patients and from doctors that enforces the label."

Studies approved by Institutional Review Boards would be allowed to proceed without the need for Investigational New Drug licenses from FDA. However, new studies would require INDs, as is the case with any unapproved, experimental drug. Meanwhile, the New Drug Application file for Iressa would remain open, and the drug wouldn't be formally withdrawn from the market.

Iressa is also approved in Japan.

Ultimately, the group of patients eligible to take Iressa will dwindle, and barring a new finding of efficacy, the market for the drug would wither away, observers say. Recently, AstraZeneca sent out a letter informing physicians about Iressa's failure to demonstrate a survival advantage, and urging that new patients be prescribed Tarceva.

Though no drug that went on the market under the accelerated approval mechanism has been withdrawn, FDA in recent years exerted pressure on drug companies to follow through on their post-approval commitments.

Two years ago, the agency held a meeting of the Oncologic Drugs Advisory Committee where sponsors of accelerated approval drugs were asked to update the agency on the progress of their studies.

"We will be looking at accelerated approval commitments at future ODAC meetings, much as we did at a 2003 meeting," Pazdur said. "We will revisit phase IV commitments."

Access to Iressa could be limited because the drug received accelerated approval for only one indication. Had multiple indications been granted by the agency, access would have had to be restricted for all indications.

AstraZeneca has been diligent in sponsoring trials, both before and after receiving accelerated approval, Pazdur said. "They did an admirable job developing the drug," he said. "This company did more than enough. The drug simply didn't meet its objectives in multiple trials. It's a different picture than some of the people who aren't doing the trials."

Iressa appears to work in Asians and women who had never smoked. However, studies in these populations are inconclusive.

The company's efforts to analyze tissues obtained from the pivotal trial concluded last December were insufficient to forestall FDA action. Carver said tissue was obtained from 22 percent of the1,692 patients who were randomized to receive Iressa or placebo. Only 6 percent of these patients could be described as Asians, and 13 percent were classified as never-smokers.

Now, the drug's future would likely be determined by scientists' ability to find a method for prospective selection of patients who stand to benefit from it.

"We are not going to be moving forward with another trial until we are sure that there is some way to look at the patient population in a different way than what we've done to date," Carver said.

Capitol Hill:

House Approves $210 Million For DOD Cancer Research

By Eric Lai

The House passed an appropriations bill June 20 providing $210 million for the Department of Defense Peer Reviewed Cancer Research Programs for fiscal 2006.

The bill allocates $115 million to the Breast Cancer Research Program, $80 million to the Prostate Cancer Research Program, and $15 million to the Ovarian Cancer Research Program for 2006.

Compared to fiscal 2005, the allocation represents a $35 million cut for the breast cancer program and a $5 million cut for the prostate cancer program. The ovarian cancer program would receive a $5 million increase.

* * *

HOUSE COMMITTEE on Appropriations June 17 approved a $142.29 million (0.5 percent) increase for NIH. This funding level is $3 million below the President's budget proposal.

After the increase, the NIH budget would be $28.5 billion. The committee bill includes $97 million for research activities to develop radiological, nuclear and chemical threat countermeasures. NCI would receive a $16.5 million (0.3 percent) increase, which would boost its budget to $4,841,774,000.

House Panel Investigating NIH Handling Of Tissue Specimens

By Paul Goldberg

The House Committee on Energy and Commerce began an investigation of handling of human tissue samples at NIH.

The committee appears to continue to pursue the investigations of conflict of interest on the part of NIH scientists, as well as an investigation of former NCI Director Richard Klausner.

Announcing the new investigation, Committee Chairman Joe Barton (R-Tex.) noted that he would press for reauthorization of NIH. The most recent reauthorization of the institutes occurred in 1993.

The letter notifying NIH Director Elias Zerhouni about the latest investigation states that NIH lacks uniform procedures for handling human biospecimens and asking for extensive documentation on handling of tissues by intramural researchers.

NIH insiders said much of the information requested by the committee simply doesn't exist.

"There are complex rules that govern obtaining, storing, using, and destroying human tissue samples," an NIH spokesman said to The Cancer Letter. "These involve important considerations of safety, protection of human subjects, research integrity, and clinical use. NIH will be responding to the committee's request for information."

The letter, dated June 20, was signed by Barton, ranking member John Dingell (D-Mich.), Oversight and Investigations Subcommittee Chairman Ed Whitfield, (R-Ky.), and subcommittee ranking member Bart Stupak, (D-Mich.).

The text of the letter follows:

The Committee on Energy and Commerce is investigating the adequacy of the National Institutes of Health (NIH) policies for maintaining research samples of human tissue.

Our interest in the NIH's maintaining of human tissue samples arises from concerns raised by a scientist at NIH ("NIH scientist"). She contacted the committee staff about the problems she encountered in locating spinal fluid samples she and her colleagues had collected from over 30 patients with Alzheimer's disease.

The NIH scientist had previously worked at the National Institute of Mental Health (NIMH) with the Geriatric Psychiatry Group. She left the NIMH in 1997, and returned to NIH at another institute/center in August 2001. Prior to leaving the NIMH in 1997, she was the principal investigator on drug studies in which she and other colleagues collected spinal fluid from over 30 Alzheimer's patients. Approximately 20 ccs of spinal fluid were collected with each spinal tap. The NIH scientist left the NIMH before conducting these studies and did not use the spinal fluid samples. According to the NIH scientist, these spinal fluid samples were stored in appropriately backed-up freezers when she left NIMH in 1997.

Sometime in mid-2004, the NIH scientist, now at another NIH institute/center, asked her former supervisor at NIMH for these patient samples for a study she wanted to conduct. After several months, the former supervisor in January 2005 reported to the NIH scientist that his group would be able to produce 10 subjects total (before and after taps) with only 0.5 cc available for most of the subjects. The former supervisor and the NIMH have been unable to account for what happened to the rest of the spinal fluid samples.

The committee staff has learned from NIH officials that the NIH has no uniform, centralized, and mandatory authority regulating the handling of human tissue samples. Some NIH laboratories keep a written record on the maintenance of these samples, but other NIH laboratories do not. Although there are explicit regulations defined in 42 C.F.R. 72.6 detailing the handling for hazardous biological materials and select agents, there is no explicit policy for the handling and accounting of human tissue samples. In addition, there is no formal inventory control or tracking system at NIH. If a freezer or other storage facility malfunctions and the human tissue samples become unusable, NIH laboratories are not required to account for the disposition of these samples. There is reason to believe that there are cases where NIH loses human tissue samples but has no record of what has been lost. Moreover, the lack of accountability leaves NIH wholly vulnerable to theft and diversion of valuable human tissue samples.

We are extremely concerned over what was described to committee staff by NIH officials of a fairly loose, ad-hoc approach to controlling human tissue samples. These samples were collected under informed consent from human subjects who agreed to provide their tissue because they were told that the sample would be used for a particular purpose in the study, perhaps even used to look at the effects from a particular drug. Some of these samples are extraordinarily precious from a research standpoint because some patients who donated samples had a rare disease. For example, we note that the National Institute of Allergy and Infectious Diseases obtained blood samples from SARS patients as part of its immunological research of SARS and coronaviruses. In addition, NIH intramural researchers sometimes rely on obtaining human tissue samples from sources outside NIH for their laboratory work, or even in their work for Cooperative Research and Development Agreements with third parties.

NIH has an obligation to the human subjects and the outside scientific community to require an appropriate tracking system or protocol for all laboratories involved with collection and maintenance of human tissue samples. NIH officials acknowledged to committee staff the importance of maintaining human research samples because for all published work, scientists are expected to provide access to other researchers to the human tissue samples for the purpose

of reproducing the results reached in the scientist's reported study.

In light of the concerns about the current handling by NIH of human tissue samples, pursuant to Rules X and XI of the U.S. House of Representatives, please provide the following by no later than Tuesday, July 5, 2005:

1. The current total number of human tissue samples maintained at NIH, with a breakdown for each institute or center. The current total number of laboratories at NIH that maintain human tissue samples and the current total number of laboratories that have a tracking system accounting in place for the human tissue samples.

2. All records dated on or since January 1, 2002, in possession of NIH, including communications within each institute/center and each laboratory, relating to any distinct direction, instruction, or policy relating to the handling of human tissue samples.

3. All records dated on or since January 1, 2002, in possession of the NIH Office of Intramural Research or the NIH Office of Management Assessment relating to any closed investigation of an allegation relating to the handling or accounting of human tissue samples. Please also state whether there are any open investigations and, if so, which institutes or centers are under investigation.

4. The current total amount of expenditures for FY2005 by NIH for maintaining and repairing freezers or other storage facilities containing human tissue samples.

5. An estimate of the total number of human tissue samples lost each year at NIH laboratories, and an estimate of the number of human tissue samples lost each year at NIH laboratories because of freezer or storage facility malfunctions.

6. A description of any measures NIH is taking to reduce the number of research freezer or other storage facility malfunctions or breakdowns.

7. List the names of the ten rarest diseases for which NIH has human tissue samples, the name of the institute and laboratory that has possession of these samples, and the specific measures currently being taken to track these samples.

8. All records relating to the CSF samples collected by the NIH scientist and others in a NIMH study on lithium in early Alzheimer's disease patients. Patient identifiers may be redacted.

Additionally, please provide the following:

9. Since January 1, 1995, has any official at NIH authorized the use of human tissue samples in possession of NIH to be used by any NIH employee in support of an outside activity?

10. Since January 1, 1995, has any official at NIH ever used human tissue samples that were in possession of NIH in connection with any of his or her outside activities?

A Notch-Signaling Pathway Inhibitor in Patients with T-cell Acute Lymphoblastic Leukemia/Lymphoma (T-ALL)

An investigational study for children, adolescents and adults with relapsed and refractory T-cell acute lymphoblastic leukemia/lymphoma is now accruing patients at various centers around the country.

This study's goal is to evaluate the safety and tolerability of a Notch inhibitor as a rational molecular therapeutic target in T-ALL, potentially uncovering a novel treatment for these cancer patients.

Eligibility criteria and treatment schema for the study include:

Notch-Signaling Pathway Inhibitor in Patients with T-ALL	
Eligibility Criteria	Patient must be = 12 months with a diagnosis of T-cell acute lymphoblastic leukemia/lymphoma AND must also have: • Relapsed T-ALL • T-ALL refractory to standard therapy • Not be a candidate for myelosuppressive chemotherapy due to age or comorbid disease ECOG performance status =2 for patients >16 years of age OR Lanksy performance level >50 for patients 12 months to =16 years of age Fully recovered from any chemotherapy and >2 weeks from radiotherapy, immunotherapy, or systemic steroid therapy with the exception of hydroxyurea or intrathecal therapy Patient must be >2 months following bone marrow or peripheral blood stem cell transplantation No treatment with any investigational therapy during the preceding 30 days No active or uncontrolled infection
Treatment Plan	Open label and non-randomized, this study is conducted in two parts. Part I is an accelerated dose escalation to determine the maximum tolerated dose (MTD), and Part II is a cohort expansion at or below the MTD. MK-0752 will be administered orally. Plasma concentrations will be measured at defined time intervals.

For information regarding centers currently open for enrollment, please contact 1-888-577-8839.

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