



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUL 28 2006

Scott J. Bloch
Special Counsel
U.S. Office of Special Counsel
1730 M. Street, NW.
Washington, DC 20036-4505

Dear Mr. Bloch:

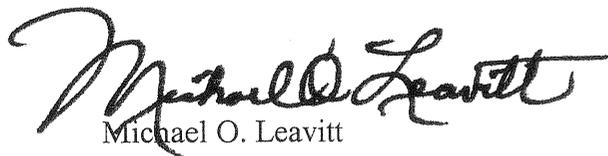
The purpose of this letter is to formally respond to your March 16, 2006, referral of a whistleblower disclosure that living cell lines were created from the DNA of study participants during a contract study at the National Institutes of Health, in violation of Federal guidelines requiring informed consent for such procedures (OSC File No. DI-06-0767).

In response to your referral, the Office of Inspector General conducted a formal investigation. Enclosed with this letter is the Office of Inspector General's Report of Investigation. This report details the efforts made by the Office of Inspector General during the investigation and fulfills the report requirements under 5 U.S.C. section 1213(d) that were outlined in your referral letter to me.

The facts surrounding this investigation were presented to the United States Attorney's Office and they determined no criminal or civil statutes had been violated.

Thank you for referring this matter of mutual interest. If you have any questions, please contact Daniel R. Levinson, Inspector General, at (202) 619-3148.

Sincerely,


Michael O. Leavitt

Enclosure

**OFFICE OF INSPECTOR GENERAL
 OFFICE OF INVESTIGATIONS
 REPORT OF INVESTIGATION**

Case Title Dr. Russell Ware	Date of Report June 13, 2006
	Type of Report Investigative
	Report of SA Chris Covington
	Signature
	Cross Reference Number

Notice

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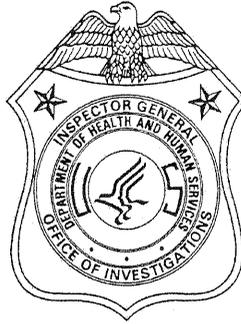
Approved: Acting Special Agent-in-Charge Carl Bocchicchio	File Number: 4-06-00243-4
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Copies:

DISSEMINATION RECORD OF ATTACHED REPORT

Agency	Req. Recd.	Date Fwd.	How Fwd.	By

United States
Department of Health
And Human Services



OFFICE OF INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS
REPORT OF INVESTIGATION CONCERNING

Dr. Russell Ware

OI File No. 4-06-00243-4

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*Section not applicable in this report.

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Office of Inspector General
DEPARTMENT OF HEALTH AND HUMAN SERVICES

File No.: 4-06-00243-4

Date: June 13, 2006

Report of: SA Chris Covington

Office: Nashville Field Office
Atlanta Regional Office

Section A - Narrative

Background

This investigation was predicated on a referral from the U.S. Office of Special Counsel (OSC). A complainant (not further identified in this report) contacted OSC with allegations about their employer – the National Institutes of Health (NIH). The OSC subsequently conferred “whistle-blower” status on the complainant, and referred the matter to HHS-OIG-OI for further investigation.

The complainant alleged that Dr. Russell Ware, a physician associated with St. Jude Children’s Research Hospital (St. Jude) in Memphis, Tennessee, had taken genetic material properly collected as part of a clinical trial funded by NIH and had established a cell line using this material without the patients’ consent.

The clinical trial was known as BABY HUG and involved the study of the drug Hydroxyurea and its effects on children with Sickle Cell Disease.

The complainant believed that Dr. Ware’s conduct represented a violation of 45 C.F.R. Part 46. This section regulates research involving human subjects.

Relevant Citations

45 C.F.R. Section 46 is entitled, “Protection of Human Subjects”. Section 46.116 reads in pertinent part:

“...no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or of the subject’s legally authorized representative.”

Section 46.122 states that:

“Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.”

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Since BABY HUG was an NIH-funded study, the investigators were required to obtain the informed consent of the participants.

Consent Form

A consent form was obtained from the parents of the participants of the BABY HUG clinical trials. The consent form read in pertinent part:

“We would like to have a small amount of left-over blood samples stored at the BABY HUG Central laboratory for possible future research. The blood samples would be kept for a long time or until the samples are used up. If your child’s blood or DNA sample is shared with other researchers, your child’s identify will be kept confidential. No facts that could identify your child will be given with the blood sample or its DNA.

You may choose whether or not to allow your child’s sample to be used for research. No matter what you decide to do about the use of your child’s samples, your child can still take part in the BABY HUG study. If you agree to allow your child’s blood to be kept for research, you are free to change your mind at any time. If this happens, we ask that you contact Dr. Wang by phone or in writing and let him know that you are withdrawing your permission for your child’s blood to be used for research. Any unused blood will be destroyed.”

The central question was whether this consent was sufficiently broad to include the actions of Ware in creating the cell line from material collected as part of the study, or whether another more specific consent form should have been obtained.

Witness Interviews

Interviews were conducted with nine individuals, including the complainant. A summary of these interviews follows:

Complainant

The complainant is a Medical Doctor and the former Project Officer for BABY HUG.

The complainant learned that Ware was considering establishing a cell line from genetic material obtained through the clinical trial in January or February 2005. Ware proposed the idea to the complainant, who agreed it was a “good” and “interesting” idea; however, the complainant did not authorize Ware to proceed.

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At the time Ware discussed his idea with the complainant, BABY HUG was over-budget and no ancillary studies could be funded. Additionally, the complainant believes Ware knew that such a study would have to be proposed to the BABY HUG Steering Committee, voted upon, and approved before he could continue. Ware's proposal was not a part of the BABY HUG Statement of Work nor was it part of the BABY HUG Protocol.

In September 2005, Ware made a presentation before the BABY HUG Steering Committee that included the announcement that he had created a cell line from genetic material obtained through BABY HUG. The complainant and others present at the meeting were shocked by the announcement.

The complainant had discussions with several individuals about Ware's conduct. These individuals agreed with the complainant that Ware had exceeded the scope of his authority by not obtaining the proper informed consent of the patients before proceeding with his research.

The complainant confronted Ware about his failure to obtain the proper authorizations for his work, and ordered the cell lines destroyed. Ware indicated that he thought the complainant had previously authorized his research and he objected to the destruction of the cell lines.

The complainant participated in a telephone conference call with Ware and Dr. Blaine Moore of NIH. In this conference call, Ware argued against the destruction of the cell lines. Ware indicated he hoped to obtain grants to study the cells, and that there was a shortage of material for such studies.

The complainant met with NIH officials, including Dr. Elizabeth Nabel, Dr. Carl Roth, and Dr. Henry Chang. Initially, these officials supported the complainant's position, and a decision was made to support the destruction of the cell line Ware had created.

The complainant later learned that NIH would not order the destruction of the cell line. Ware asked that the complainant be removed as the Project Officer for BABY HUG, and subsequently the complainant did lose this position.

Dr. Elizabeth Nabel

Dr. Elizabeth Nabel is the Director of the National Heart, Lung, and Blood Institute (NHLBI) at NIH. Nabel learned of an ethical problem with the BABY HUG clinical trial while reading the minutes of the Data Safety and Monitoring Board (DSMB).

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Nabel spoke to Dr. Susan Shurin, the Chair of the DSMB, and Dr. Henry Chang, the Executive Secretary of the DSMB, regarding the matter. Chang later informed Nabel the DSMB had decided to destroy the immortalized cell lines or obtain new patient consent forms.

The complainant asked for a meeting with Nabel to advocate for the destruction of the cell lines. Nabel listened to the complainant and agreed with her position. Nabel subsequently sent a letter to Ware asking that he destroy the immortalized cell lines.

Nabel was contacted by Dr. John Cunningham, the Chair of the Institutional Review Board (IRB) at St. Jude. Cunningham advised Nabel that the individual IRB's at the BABY HUG clinical sites had jurisdiction over the immortalized cells.

Nabel determined that although NHLBI could not order the destruction of the cell lines, they could "strongly encourage" it. Nabel sent letters to the IRB's recommending that they either "re-consent" the patients (i.e., obtain specific consent from patients for the retention of the immortalized cells) or destroy the cell lines.

Nabel later learned that the complainant may have been aware of the cell immortalization all along. Nabel was shown emails between the complainant and Ware that seemed to support this position. Regardless of who was to blame, Nabel thought NHLBI needed to take responsibility for and ownership of the problem.

Nabel was not aware of the outcome of the matter, since she left that to Dr. Charles Peterson. Peterson assumed the Project Officer position for BABY HUG after the complainant was removed from that position.

Dr. Henry Chang

Dr. Henry Chang is the Executive Secretary of the DSMB for the BABY HUG clinical trial and the Special Assistant to Dr. Chuck Peterson, the Director of the Division of Blood Diseases and Resources (DBDR) at NHLBI.

Chang became aware of an ethical problem with BABY HUG after receiving an email from the complainant. Chang advised the individual members of the DSMB of the problem, and later hosted a conference call meeting to discuss the matter.

Nine of the ten members of the DSMB were present for the conference call. The only member who did not participate was the patient advocate. The DSMB discussed destroying the cell lines or re-consenting the patients. Chang favored re-consenting because he felt the consent forms were "vague" and could be interpreted to allow cell immortalization

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Chang provided the rationale for both arguments as follows:

- One reason to destroy the immortalized cell lines would be to send a strong message to researchers that they must obtain proper consent before they proceed with experiments. Otherwise, researchers might begin to rationalize that they can do their research and re-consent at a later date. The NHLBI did not want to set this type of precedent.
- Another reason to destroy the cell lines was to avoid creating mistrust among the African American population who were primarily afflicted by Sickle Cell Disease. Historically, research has been conducted on African Americans without their consent. Chang cited the Tuskegee syphilis experiments and the HeLa cell line. NHLBI wanted to foster trust in the African American community for future research studies.
- The re-consenting argument was that some patients might like to have the opportunity to decide what to do with their immortalized cells. They might wish to allow them to be kept for future research. Destroying the cells without consulting the patients might send a paternalistic message that NHLBI did not think the patients were smart enough to make the decision themselves; therefore, the researchers were going to do it for them.

The DSMB decided that patients needed to re-consent or the cell lines needed to be destroyed.

The complainant was not satisfied with the DSMB's recommendation. The complainant wanted the cell lines destroyed, and asked for a meeting with Nabel. Chang attended the meeting and remembers the complainant felt strongly that keeping the cell lines would be the wrong message to send to the African American community given previous abuses by researchers.

Chang later learned that Ware may have thought he had approval to perform the cell immortalization from the complainant. Chang believed there had been some form of "miscommunication" between the complainant and Ware.

Dr. Carl Roth

Dr. Carl Roth was formerly the Acting Deputy Director of NHLBI, and has a background in the law. Roth holds a Juris Doctor and Master of Law (i.e., LL.M.).

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Nabel asked Roth to assist her in handling the controversy involving the immortalization of cells from BABY HUG. Some people believed the consent forms covered the cell immortalization while others did not. As Roth put it, "reasonable people disagree".

Roth reviewed the consent forms and determined that virtually all of the forms contained language that suggested the cells would be retained until they were destroyed or used up.

Since immortalized cells can be used indefinitely, Roth concluded the language suggesting they would be "used up" was not sufficient. Roth believed the patients had not given their consent for cell immortalization.

Roth remembers attending a meeting with the complainant, Nabel, Peterson, and others. Roth believes the "discussion gravitated towards destruction" of the cell lines. Roth believed the destruction order would:

- Send a strong statement to the scientific community that this is what NIH believed.
- Warn researchers that informed consent sets the boundaries of the research they could conduct.
- Catch the attention of the IRB's at the various clinical sites.

After the meeting, Nabel sent a letter to the researchers ordering the cell lines to be destroyed. Some time later, Roth received a call from Ware. Ware told Roth that Dr. John Cunningham, the Chair of St. Jude's IRB, believed the NHLBI did not have the authority to order the cell lines to be destroyed.

Roth spoke to Cunningham and then recommended Cunningham call Nabel. After Cunningham and Nabel spoke, Roth's planned trip to Memphis to supervise the destruction of the cell lines was cancelled.

According to Roth, the matter was complicated by evidence in the file that the researchers at St. Jude had been given "mixed signals" and "clearly conflicting information" from the complainant, the BABY HUG Project Officer.

Roth helped Nabel draft a letter to the IRB's recommending that they either destroy the cell lines or re-consent the patients.

Roth was not aware of the current status of the situation involving the cell lines.

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Dr. Charles Peterson

Dr. Charles "Chuck" Peterson is the Director of the DBDR at NHLBI. In September 2005, Peterson learned of a conference call by the Steering Committee for BABY HUG and the controversy over the cell immortalization.

Peterson did not think the investigators had done anything wrong: there was "no indication of collusion, deception or malfeasance". However, the NHLBI needed to take responsibility since it "happened on our watch".

Peterson was present at a meeting with Nabel that included the following participants:

- Complainant
- Chang
- Roth
- Moore
- Dr. Liana Harvath

According to Peterson, Harvath, the Deputy Director of DBDR, had to leave the meeting early.

Peterson and Chang felt it would be possible to re-consent the subjects and keep the cells; however, they did not say much during the meeting because they felt the decision had already been made to destroy the cells.

Peterson spoke privately to Roth to express his concerns over the destruction of the cell line; however, a letter was still produced ordering the cells be destroyed.

The IRB's took "exception" to NHLBI's order to destroy the cell lines. Dr. John Cunningham, the Chair of St. Jude's IRB, contacted Nabel.

Cunningham's argument focused on patient autonomy: If you do not give patients the right to decide what to do with the cells you are assuming a "loco parentus" position and violating patients' right to choose.

Ultimately, after conferring with NIH's legal counsel, NHLBI decided to allow the IRB's to make the final decision on the immortalized cells.

The IRB's at the BABY HUG clinical sites made patients aware of the cell immortalization. Three of the ten sites decided to give patients a choice on whether or not to destroy the cell lines.

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These institutions that opted to re-consent were:

- University of Mississippi Medical Center (UMMC)
- Duke University
- St. Jude

The other seven institutions decided to destroy the cell lines.

The entire process is being delayed because some institutions have not been able to make contact with their patients to get new consent forms signed. In some cases, the patients have “graduated” out of the study and are difficult to find. In other cases, specifically at UMMC, patients have dispersed as a result of Hurricane Katrina.

Patients have generally responded favorably to the re-consenting process. Some individuals are “proud” their cells will be used for future research. The cells are very valuable to researchers because they are rare.

If the patients cannot be found and consent cannot be obtained, their cell lines will probably be destroyed by default. When the destruction is conducted, someone will go down to supervise the destruction and conduct quality control. The cell lines are currently maintained at St. Jude.

The cell lines that will be retained, because patients have signed new consent forms, will be transferred to the NHLBI Depository and will be made available to the “wider community” for future research.

NHLBI has notified various parties of the lack of patient consent, including the:

- Office of Human Research Protection
- Food & Drug Administration (FDA)

The BABY HUG Protocol has also been redrafted so it is consistent with what they are now doing.

In November 2005, Peterson was approached by Moore regarding the possibility of removing the complainant as Project Officer for BABY HUG. Moore asked if Peterson would assume the complainant’s responsibilities.

Peterson felt the complainant was overwhelmed with managing two clinical trials that were “in crisis”. There was a lot of heat between the complainant, the investigators, and the coordinating centers. The “best solution was time and distance”.

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Dr. Blaine Moore

Dr. Blaine Moore is the Program Director in the DBDR at NHLBI. Moore was also the complainant's immediate supervisor.

In late August or September 2005, Moore learned that Ware had immortalized cell lines and that there was a question regarding whether he had obtained the patients' consent.

Ware's work was particularly important because the repositories of genetic material from previous Sickle Cell Disease studies conducted in the 1990's were depleted. Ware had the vision of creating cell lines that would serve as an "unlimited resource".

Ware thought he was doing NHLBI a favor through his research. The problem was "not all patients might have realized this was going to be done".

One person that was particularly concerned about the cell immortalization was Dr. Zora Rogers of Dallas, Texas. Rogers' IRB was "very sensitive". They wanted to know "any little thing out of the ordinary". Rogers was afraid she was going to be in trouble when her IRB found out about Ware's research and the lack of patient consent.

The complainant sent Ware an email ordering him to destroy the cells. Afterwards, Ware called Moore and made a number of different arguments as to why the cells should not be destroyed. Ware said he had put effort into the research, and it did not cost NIH anything. Ware wanted to discuss the destruction with other researchers.

There were several emails back and forth between Moore, Ware, and Ware's colleague – Dr. Winifred Wang. Ware and Wang wanted NIH to reconsider the destruction order.

Moore arranged a conference call between the complainant, Ware, and a NIH contracting officer named Lynda Bindseil. Moore moderated the call; the decision was made to allow the BABY HUG Steering Committee to consider destruction or obtaining a consent from patients to keep the immortalized cells (i.e., re-consenting). The issue was placed on the Steering Committee's agenda.

During the subsequent Steering Committee meeting, held via teleconference, some of the BABY HUG sites wanted the cells destroyed while others wanted to re-consent.

The conference call happened on a Thursday in October 2005. Moore learned over the weekend that the complainant had requested a meeting with NHLBI's Director – Dr. Elizabeth Nabel.

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The meeting was requested on a Saturday, and was scheduled for the following Monday. Neither Moore nor his supervisor – Dr. Charles Peterson – had been notified of the meeting by the complainant.

Moore was unable to attend the meeting because he was on vacation; however, Moore believes only one side of the argument was presented at the meeting. As a result, the decision was made to destroy the cell line.

NHLBI's order to destroy the cell line was rejected by the IRB's, who thought it was not transparent. The IRB's wanted to notify patients of the cell immortalization.

Of the ten original BABY HUG centers, most ordered the cell lines destroyed; however, three or four are considering re-consenting.

Moore removed the complainant as the Project Officer for BABY HUG for a number of reasons unrelated to the issues involving the cell immortalization. Reasons included difficulty interacting with contracting officers, researchers, and the DSMB as well as budget problems.

Dr. Winifred Wang

Dr. Winifred Wang is the Director of the Comprehensive Sickle Cell Disease Center at St. Jude. He was formerly the Principal Investigator for BABY HUG at St. Jude and the Chair of the BABY HUG Steering Committee, which represented the ten clinical sites involved in the BABY HUG trial.

Wang understands that his colleague at St. Jude – Ware – and the complainant attended a conference together in November 2003. The conference was sponsored by NHLBI, and discussed DNA research as it applies to Sickle Cell Disease. An idea that was promoted at the conference was to immortalize cells for future Sickle Cell research.

Ware discussed this idea with the complainant, and suggested material from BABY HUG be used to create an Epstein-Barr Virus (EBV) cell line. According to Wang, the complainant “agreed this was a good thing to do.”

In 2005, a controversy erupted when some researchers suggested the BABY HUG consent form was not sufficient to allow for the EBV cell line. The key problem was that the consent form indicated genetic material could be used for future research until it was “used up”. However, since the EBV cell line created a “renewable supply of DNA”, it would never be “used up”.

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In September or October 2005, the complainant sent Ware an email ordering that the cell lines be destroyed. Ware was "somewhat distraught" over the email. Ware responded to the complainant that there was no intent to perform studies without NHLBI's knowledge. Ware provided "full evidence" that the EBV cell lines had previously been discussed.

In fact, at one point in 2004 Ware had even sought reimbursement from NHLBI for carrying out the cell immortalization. Because of concerns over the BABY HUG budget, the decision was made that St. Jude would assume most of the costs.

After Ware and the complainant traded emails, Dr. Elizabeth Nabel, the Director of NHLBI, got involved. Nabel ordered that all of the EBV samples were to be destroyed. Nabel was going to send a representative to St. Jude on a particular date to observe the destruction.

Dr. John Cunningham, the Chair of St. Jude's IRB, expressed concern over what he believed was an inappropriate process. Cunningham did not think the samples could be destroyed without the express consent of the families.

Cunningham had lengthy conversations with Nabel, and ultimately, she "acquiesced" to his wishes.

In January 2006, a conference call was held that included a number of participants, including:

- The Chairs of the IRB's at the BABY HUG centers
- The principal investigators
- Dr. Charles Peterson from NHLBI, who had taken leadership of BABY HUG from Bonds
- Dr. Susan Shurin, the Chair of the BABY HUG Data Safety and Monitoring Board

The call "went on for a couple of hours". There was "a lot of disagreement" and a "lot of different opinions expressed". There were basically two positions:

- Destroy the cell lines.
- Give the families a choice: destroy the cell lines or keep them for future research.

The majority believed destruction was the best option because it was the "simplest resolution to a controversial, gray area".

Ultimately, each BABY HUG center was allowed to follow the lead of their IRB. Three centers chose to inform subjects; six centers wanted the cell lines destroyed; one center was "on the fence".

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So far, eight of the nine subjects at St. Jude have signed consent forms authorizing retention. The ninth subject was only contacted by phone, and has not been able to sign the consent form.

All of the samples that are "saved" will be sent to a storage facility at the NIH. Destruction of the cells will also take place at that location.

The cells are still retained at St. Jude. They were transferred from Ware's lab in 2005 and are currently held by Dr. Jim Downing, the Scientific Director at St. Jude.

Dr. Russell Ware

Ware is the Director of the Division of Hematology at St. Jude. He previously worked for Duke University for 18 years.

Ware has served as the Principal Investigator for BABY HUG at both Duke and St. Jude. He has also served as the Deputy Chair of the BABY HUG Steering Committee.

In November 2003, Ware attended a conference sponsored by the NHLBI and the Human Genome Project. One topic at the conference involved the importance of DNA for research and the possibility of immortalizing cell lines so you could get more DNA.

Ware attended the conference with the complainant. He discussed the possibility of immortalizing cells from participants in the BABY HUG clinical trial. The complainant "readily agreed" to Ware's proposal. This would create a "renewable source" of material for Sickle Cell Disease research.

Ware initially took leftover blood for the cell immortalization project. He then began to ask study centers to send him an extra ½ teaspoon of blood because the process was taking more blood than he initially expected.

In January 2004, in an Operations Call relating to BABY HUG, Ware explained to the principal investigators at the BABY HUG clinical sites why he was requesting extra blood from them (i.e., in order to create an EBV cell line). Ware claims the discussion is well documented in the minutes of the call, which the complainant edited and approved.

In August or September 2004, Ware began contract negotiations with NHLBI. In addition to being reimbursed for certain DNA analyses he was performing as part of BABY HUG, Ware wanted to be reimbursed for the EBV cell lines he was creating.

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Although NHLBI never agreed to fund Ware's work, there was never a question about what he was doing. NHLBI only questioned their ability to fund his research, not the ethics of it. Ware believes he has always been "completely transparent" with his work into immortalized cells.

In April 2005, Ware made a PowerPoint presentation at the Sickle Cell Disease meeting in Cincinnati, Ohio. One slide from Ware's presentation specifically talks about the cell immortalization. Ware reported to the assembled group that:

- 35-40 cell lines were successful
- 10 were growing
- 10 had failed

NHLBI staff were present for this conference and were briefed on Ware's work.

In September 2005, at a second Sickle Cell Disease gathering in Bethesda, Maryland, Ware made another presentation about the cell immortalization. At that point:

- 70 cell lines were successful
- 10 were growing
- 10 had failed

One week after the September 2005 meeting, Ware received an email from the complainant. Ware was told that his study was being suspended for financial reasons and that the immortalized cell lines should be destroyed. The complainant told Ware they were "dismayed" that he had been making cell lines without knowledge or approval.

Within an hour, Ware responded to the complainant's email. He was "shocked" that the complainant was claiming ignorance about his work on cell immortalization. He was also angry that his DNA research was being suspended since he believed it was a "safety endpoint" in the BABY HUG study.

Shortly after the complaint's email, and at the complainant's request, Ware provided a 3-4 page document outlining his cell immortalization work and the ways that he had communicated this work to NHLBI.

Three weeks after the complainant's email, Ware received a letter from Dr. Elizabeth Nabel, the Director of NHLBI, ordering the cell lines to be destroyed. Ware took this letter to Dr. John Cunningham, the Chair of St. Jude's IRB.

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Cunningham did not believe that NHLBI had any jurisdiction over the matter. Cunningham felt that once the cell lines were created, they belonged to the patient and the patient had to be involved in the decision on whether to destroy them.

Cunningham and Nabel engaged in a series of conversations about the matter. Ultimately, it was determined that the IRB's would decide how to proceed. Most IRB's decided to destroy the cell lines; however, other IRB's – including St. Jude's – decided to go to patients and seek their consent to keep the cell lines.

Ware immortalized the cell lines for the “betterment of future research”. He always knew the cell lines would have to be transferred to NHLBI. He never thought it was going to help his laboratory.

Ware had no intention of doing anything wrong. The cells remain under “lock and key”. They have “never been studied.”

Ware was surprised when the complainant was removed as the BABY HUG Project Officer. He had asked that the complainant be removed as the Project Officer for another study (i.e., SWITCH), but that was a different matter. The SWITCH study was investigator-sponsored while BABY HUG was NHLBI-sponsored. As such, Ware had the right to choose his Project Officer for SWITCH. He felt he could no longer work with the complainant on SWITCH since the complainant had questioned his ethics.

Dr. John Cunningham

Dr. John Cunningham is the Chair of the IRB at St. Jude. He has served in this capacity for two years. Previously, he was Deputy Chair of the IRB for two years.

In 2005, Ware brought a letter to Cunningham from Dr. Elizabeth Nabel, the Director of the NHLBI. It was Ware's responsibility to notify the IRB of the concerns raised in the letter regarding Ware's immortalization of cells without proper patient consent.

Nabel indicated in her letter that NHLBI wanted the cell lines destroyed. Cunningham brought the matter before the IRB. According to Cunningham, it was one of the “longest things we've deliberated over”.

The IRB determined there was “no malfeasance” on the part of the researchers; they were not “misleading subjects”. The IRB suggested Cunningham contact Nabel to discuss the matter.

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The question was whether the consent form that Ware had obtained implicitly authorized the cell immortalization. St. Jude's IRB was relatively conservative; they decided the participants:

- should be informed about what happened.
- should be given the opportunity to decide what to do with the cells (i.e., destroy them or keep them for future research).

There was an inherent conflict in Nabel's letter and the basis for 45 C.F.R. Part 46, the regulation governing human subject research. According to the Belmont Report, upon which the regulation is based, researchers must consider three issues in regards to participants in clinical studies:

- Respect for patients
- Beneficence (i.e., justice) towards patients
- Patient autonomy

The IRB felt that in light of these three elements, they had to inform the patients about the cell immortalization and had to let the patients decide whether they wanted them destroyed.

Review of Relevant Documents

Documents were obtained from the complainant through the OSC. The documents included emails, memorandum, and letters pertaining to the consent issue. The following chronology of events was evident from the documents:

- September 2, 2005 – Summary Notes of the BABY HUG Steering Committee meeting: A vote was held on whether to continue the "EBV cell lines". Seven votes were in favor; three votes were opposed; and three abstained. The notes read in part, "It was noted that DNA needs to be added into the current BABY HUG consent form."
- September 6, 2005 – Email from complainant to Dr. Russell Ware: "I was very dismayed to learn at last week's BABY HUG Steering Committee meeting that cell lines had been set up to immortalize DNA from BABY HUG subjects. NHLBI did not authorize this work, it is not in the protocol, and this work is not specifically mentioned in the consent forms. Please destroy these cell lines immediately."

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- September 6, 2005 – Email from Ware to complainant: “I am shocked to receive this email from you.” Ware indicates he and the complainant have previously discussed the subject. He goes on to say he sent an email with a copy to the complainant on November 4, 2004, referencing “DNA isolation and storage”.
- September 7, 2005 – Email from complainant to Ware: Complainant explains BABY HUG did not have the funding for cell immortalization nor was it reviewed by the protocol review committee and Data Safety and Monitoring Board (DSMB). Complainant closes with, “I am sorry that you and I misunderstood each other about this issue.”
- September 8, 2005 – Email from complainant to Ware: Complainant asks Ware for a report on his cell immortalization activities and indicates the DSMB has asked that an independent body witness the destruction of the cell line.
- September 23, 2005 – Email from Ware to Moore and Peterson (the complainant’s superiors): “I strongly protest any insinuation that my laboratory efforts in BABY HUG have been inappropriate ...” Ware provides a timeline saying he made a PowerPoint presentation about the cell immortalization at the April 2005 Steering Committee meeting about “developing EBV cell lines”. Ware says St. Jude’s IRB Chair thinks the existing consent form is acceptable, but that Duke’s IRB Chair recommended “re-consenting”. Ware concludes, “each local IRB will have an independent opinion on this issue”. Ware proposes a new consent form so “this invaluable DNA resource for BABY HUG will not be lost.”
- September 26, 2005 – Memo from complainant to BABY HUG DSMB indicates that Ware performed the cell immortalization without verbal or written approval. It includes Ware’s report of events, copies of emails, etc.
- October 3, 2005 – Minutes from the BABY HUG DSMB. Dr. Susan Shurin, Chair of the DSMB, to the complainant and others: “The existing cell lines must either be destroyed, or must have the explicit consent of the parents of the subjects if they are to be retained.”
- October 5, 2005 – Memo from Chang, the Executive Secretary of the BABY HUG DSMB, to Nabel, the Director of NHLBI: The Division of Blood Diseases and Resources “has taken prompt action...to re-consent patients or destroy the cell lines if that is not possible.”

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- October 11, 2005 – Email from Ware to Moore asking that the complainant be removed as SWITCH Project Officer due to “ongoing negative experiences.” SWITCH was another clinical trial associated with the drug Hydroxyurea and Sickle Cell Disease.
- October 17, 2005 – Memo from Chang to Nabel with a timeline of events. The memo mentions that the complainant requested a meeting with Nabel on October 15, 2006.
- October 18, 2005 – Memo from the complainant to Nabel: Ware announced the immortalization of cell lines on September 1, 2005; the complainant instructed Ware to destroy the cell lines on September 7, 2005. The complainant concludes that it is “incumbent upon NHLBI to quickly enforce the destruction”.
- November 15, 2005 – Memo from Ware to Cunningham, the Chair of St. Jude’s IRB: Ware says cells will not be produced or maintained in his lab. Cell lines will be destroyed or transferred to the NHLBI’s DNA Repository.
- November 15, 2005 – Memo from Cunningham to Wang: A letter has been prepared for participants along with a re-consent form. The memo also indicates they have discontinued creating cell lines.
- November 15, 2005 – Memo from Moore removing the complainant as Project Officer for BABY HUG.

Investigative Summary

Based on the interviews conducted and documents reviewed, the following information was discovered:

- Genetic material was collected from participants in an NIH-funded clinical study called BABY HUG. The material was collected at multiple sites, then forwarded to St. Jude where a researcher created immortalized cell lines.
- The cell immortalization was not funded by NIH nor was it listed in the BABY HUG Statement of Work or Protocol. The cell immortalization was not approved by the Data Safety and Monitoring Board (DSMB) or the Institutional Review Boards (IRB’s) that exist at each BABY HUG clinical site.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

- The researcher who created the immortalized cell lines contends that he discussed the experiment with the complainant, who was the BABY HUG Project Officer. The researcher further stated that he openly discussed his findings with the BABY HUG Steering Committee in both April 2005 and September 2005.
- At the September 2005 Steering Committee meeting, the decision was made to continue the cell immortalization with a vote of seven to three, with three abstentions. The decision was also made to enhance the consent form with language regarding the DNA research.
- The complainant brought this matter to the attention of the BABY HUG DSMB. The DSMB was in a position to take any appropriate action, including stopping the BABY HUG clinical trial. The DSMB recommended destruction of the cell lines or obtaining new consent forms (i.e., re-consenting).
- The complainant argued for the destruction of the cell lines, and brought this argument to the Director of the NHLBI. The Director forwarded a letter to the researcher at St. Jude asking that the cell lines be destroyed.
- The Chair of the IRB at St. Jude advised the Director of the NHLBI that the local IRB's had jurisdiction over this issue. The Director subsequently wrote the IRB's at the various BABY HUG clinical sites and suggested they either destroy the immortalized cell lines or re-consent the patients.
- The NHLBI remains actively engaged with the IRB's in resolving this issue. Thus far, seven of the ten IRB's have decided to destroy the cell lines while three of the ten have decided to re-consent.
- The destruction of the cell lines has been delayed because the three IRB's that are seeking to re-consent have not yet located all of the patients and obtained their consent or refusal. Once this process is complete, the current Project Officer for BABY HUG has indicated he will order the destruction of the remaining cell lines and provide supervision to ensure the destruction occurs.
- This matter has been discussed with the Health Care Fraud Coordinator at the United States Attorney's Office in Memphis, Tennessee where St. Jude is located. This matter was declined for criminal prosecution.

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Office of Inspector General
DEPARTMENT OF HEALTH AND HUMAN SERVICES

- There is no allegation that the cell immortalization was funded by NIH; therefore, the matter was not presented for civil prosecution. However, a civil Assistant US Attorney was advised of the investigation and the allegations of the complainant.
- This matter is being resolved administratively by the NIH through the NHLBI and the local IRB's. No further action will be taken by HHS-OIG-OI.

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FORM OI-4 (12-84)

OFFICE OF INVESTIGATIONS
Office of Inspector General
DEPARTMENT OF HEALTH AND HUMAN SERVICES

File No.: 4-06-00243-4

Date: June 13, 2006

Report of: SA Chris Covington

Office: Nashville Field Office
Atlanta Regional Office

Section B - ENTITIES AND INDIVIDUALS

A. SUBJECT

- | | |
|---------------------------------|---|
| 1. Name: | Dr. Russell Ware |
| 2. Address: | St. Jude Children's Research Hospital
332 North Lauderdale
Memphis, Tennessee 38105 |
| 3. Telephone: | (901) 495-3300 |
| 4. General Counsel: | Wendy Shea, Esq.
St. Jude Children's Research Hospital |
| 5. General Counsel's Address: | Same As Above |
| 6. General Counsel's Telephone: | (901) 495-2341 |

B. OTHER INDIVIDUALS

None

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Section C - GOVERNMENT PROGRAM INVOLVED

The National Institutes of Health (NIH) is a component part of the U.S. Department of Health and Human Services. NIH consists of 27 Institutes and Centers, including the:

- National Cancer Institute
- National Eye Institute
- National Heart, Lung, and Blood Institute
- National Human Genome Research Institute
- National Institute on Aging
- National Institute on Alcohol Abuse and Alcoholism
- National Institute of Allergy and Infectious Diseases
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Biomedical Imaging and Bioengineering
- National Institute of Child Health and Human Development
- National Institute on Deafness and Other Communication Disorders
- National Institute of Dental and Craniofacial Research
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute on Drug Abuse
- National Institute of Environmental Health Sciences
- National Institute of General Medicine Sciences
- National Institute of Mental Health
- National Institute of Neurological Disorders and Stroke
- National Institute of Nursing Research
- National Library of Medicine
- Center for Information Technology
- Center for Scientific Review
- John E. Fogarty International Center
- National Center for Complementary and Alternative Medicine
- National Center on Minority Health and Health Disparities
- National Center for Research Resources
- NIH Clinical Center

The funding for the BABY HUG clinical study was provided by the National Heart, Lung, and Blood Institute.

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Office of Inspector General
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Section D - PROSECUTIVE STATUS

This matter was discussed with the Health Care Fraud Coordinator and a civil Assistant US Attorney at the United States Attorney's Office in the Western District of Tennessee at Memphis. Based on a review of the evidence in the case, there was no indication that any criminal or civil statutes had been violated. As such, no criminal or civil prosecution was pursued.

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FORM OI-4 (12-84)

OFFICE OF INVESTIGATIONS
Office of Inspector General
DEPARTMENT OF HEALTH AND HUMAN SERVICES

File No.: 4-06-00243-4

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Office: Nashville Field Office
Atlanta Regional Office

Section E - WITNESSES AND EVIDENCE

The following individuals can attest to the facts of this investigation and to relevant evidence concerning violations committed by the subject:

1. Complainant

2. Dr. Elizabeth Nabel
Director, National Heart, Lung, and Blood Institute
31 Center Drive, Bldg 31, 5A52
Bethesda, Maryland 20892
(301) 496-5166

3. Dr. Henry Chang
Special Assistant to the Director
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
6700A Rockledge Drive, Room 349
Bethesda, Maryland 20817
(301) 435-0067

4. Dr. Carl Roth
Associate Director for Scientific Program Operation
National Heart, Lung, and Blood Institute
31 Center Drive, Bldg 31, 5A03
Bethesda, Maryland 20892
(301) 496-6331

5. Dr. Charles "Chuck" Peterson
Director, Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
6700A Rockledge Drive
Bethesda, Maryland 20817
(301) 435-0080

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Office of Inspector General
DEPARTMENT OF HEALTH AND HUMAN SERVICES

6. Dr. R. Blaine Moore
Program Director, Blood Diseases Program
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
6700A Rockledge Drive
Bethesda, Maryland 20892
(301) 435-0080

7. Dr. Winifred Wang
Director, Comprehensive Sickle Cell Center
St. Jude Children's Research Hospital
332 North Lauderdale
Memphis, Tennessee 38105
(901) 495-3300

8. Dr. Russell Ware
Director, Division of Hematology
St. Jude Children's Research Hospital
332 North Lauderdale
Memphis, Tennessee 38105
(901) 495-3300

9. Dr. John Cunningham
Chair, Institutional Review Board
St. Jude Children's Research Hospital
332 North Lauderdale
Memphis, Tennessee 38105
(901) 495-3300

OFFICE OF INVESTIGATIONS
Office of Inspector General
DEPARTMENT OF HEALTH AND HUMAN SERVICES

File No.: 4-06-00243-4

Date: June 13, 2006

Report of: SA Chris Covington

Office: Nashville Field Office
Atlanta Regional Office

Section G - INTERVIEWS AND INVESTIGATIVE ACTIVITIES

Note: These items are available for review by the representatives of the U.S. Office of Special Counsel at their request, but are not being made part of this Report of Investigation. These documents are the property of HHS-OIG-OI. Their public availability to be determined by applicable law.

CONTENTS

<u>Exhibit</u>	<u>Description</u>
1	Referral from the U.S. Office of Special Counsel
2	Memorandum of Interview (Form OI-3) – Complainant
3	Form OI-3 – Dr. Elizabeth Nabel
4	Form OI-3 – Dr. Henry Chang
5	Form OI-3 – Dr. Carl Roth
6	Form OI-3 – Dr. Charles “Chuck” Peterson
7	Form OI-3 – Dr. Blain Moore
8	Form OI-3 – Dr. Winifred Wang
9	Form OI-3 – Dr. Russell Ware
10	Form OI-3 – Dr. John Cunningham



DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C.

Office of Inspector General

2007 FEB -8 AM 9: 34

Office of Investigations
330 Independence Avenue, S.W.
Washington, DC 20201

FEB 07 2007

Karen Gorman, Esq.
U.S. Office of Special Counsel
1730 M Street N.W., Suite 300
Washington, D.C. 20036

RE: Dr. Russell Ware
OI File No. 4-06-00243-4

Dear Ms. Gorman:

Thank you for giving us the opportunity to respond to your questions about our Report of Investigation (ROI) in the above captioned case. In response to your inquiry, this letter provides additional information.

On January 9-10, 2007, Special Agent Chris Covington of our Nashville Field Office re-interviewed several witnesses at the National Heart, Lung, and Blood Institute (NHLBI), a component part of the National Institutes of Health (NIH). He questioned the witnesses about three broad topics, as described below.

Was the work that Ware did outside the Statement of Work (SOW) and/or Protocol? If so, was this a violation of 45 C.F.R. 46, or any other NIH policy? If so, what process was used to determine that no penalty would be imposed on Ware?

One witness agreed that Ware's work was done outside the BABY HUG SOW and Protocol. He suggested the correct thing for Ware to have done was to ask for the SOW to be amended. This same witness said, "No Protocol goes without being violated". The Protocol may require patients to come in within a week, and the patient does not come in for 10 days. This type of thing is common, and does not result in disciplinary action.

Another witness said the SOW and Protocol of BABY HUG did not specifically address the cell immortalization issue; however, he added, it was not prohibited either. This same witness said it was "very hard to anticipate all contingencies" in the SOW and Protocol.

Following this line of reasoning, several witnesses discussed the evolving technology and its role in this case. One witness discussed the fact that the BABY HUG clinical study was discussed as early as 1994, and the cell immortalization technology had only become available in the past several years, after BABY HUG was underway.

Another witness commented on the changing regulatory standards in the industry. She said standards were "looser" several years ago but are more "transparent" today.

There was considerable discussion among all parties about whether Ware had done something improper. This matter was researched by the Data Safety and Monitoring Board (DSMB) that was responsible for oversight of the BABY HUG clinical trial. The matter was discussed by the BABY HUG Steering Committee, and at the highest levels of the NHLBI (i.e., at the Director's office).

The unanimous opinion of all witnesses was that Ware had not intentionally done anything wrong. One witness commented on the "implicit understanding" or "verbal understanding" between Ware and the BABY HUG Project Officer. This witness believed that the Project Officer had approved the immortalization of cell lines.

Three separate witnesses used the words "mal intent", and explained that there was no evidence that Ware had acted in that fashion. The Executive Secretary of the DSMB focused on the fact that Ware had never concealed his work, and that this lack of concealment suggested he did not intend to do anything wrong. As he put it, the DSMB felt this was "misunderstanding, not malfeasance."

One witness said that Ware's work was a "logical extension of current technology" and "a benefit to the scientific community." This witness commented on how Ware did what he did out of "beneficence" to the study and because of his "ambitious nature to do good."

One witness believed the technology "became available" and Ware "saw this as a service" to the scientific community. The same witness went on to say that in her discussions with various parties, she heard that Ware was an "honorable person" with "high integrity" who was "well respected in the scientific community." This witness was told that Ware would never have immortalized the cell lines if he had not believed he had been authorized to do so.

When asked whether he thought Ware had violated 45 C.F.R. 46, one witness responded, "You would have to show me where you think he violated it." This witness described the technology as an "evolving area" where "issues are squishy."

Another witness said she had recently reviewed the C.F.R. in question, and that it had "shades of gray". Another witness also used the phrase "gray area", when describing the controversy. One witness said the C.F.R. in question was "not sufficiently detailed to cover all contingencies."

One witness expressed the opinion that Ware did not intend to misuse public funds, misuse the samples, or misuse the patients. This witness said, "Everyone shares in the culpability"; even NHLBI was "complicit". A second witness echoed the same sentiment when he said, "We have found the enemy and he is us."

The Director of NHLBI said that she looked to the DSMB's to recommend any adverse action against a researcher. NHLBI could withdraw grant funding from anyone who was acting in an unethical matter. The Director referenced the case of Dr. Jim Wilson, a researcher at the University of Pennsylvania who failed to inform patients of the risks of his gene therapy research. Wilson has been banned from receiving future grants.

Was it appropriate for Ware to use samples from grant-funded research to conduct his own research outside the scope of the SOW and/or Protocol? Was this a misuse of Federal funds?

One witness said the cells were available to Ware for a "legitimate purpose". This witness argued that it was "inherent to the nature of scientists to tinker" and explore new technologies. In this witness' opinion, it did not cost NIH anything, and in the end NIH would benefit from any scientific developments that arose from the research.

The witness said that Ware's work was openly discussed at the BABY HUG Steering Committee meetings. The principal investigators had to approve particular projects with a given "pot of money". The matter only became controversial when someone pointed out that the BABY HUG consent forms did not cover the cell immortalization.

One witness said that the contract allowed for blood to be taken, and cells to be extracted and stored. In other words, the cells were available and any additional research was not impacting NIH.

Another witness thought Ware believed he was "providing a service to the Government" by immortalizing the cell lines. This same witness said he did not know whether Federal funds were used on the immortalization of cell lines, but commented that the process is "not expensive".

Why was it appropriate for the local Institutional Review Boards (IRB's) to decide whether to destroy the immortalized cells, or re-consent the patients? Is there a legal or policy basis for this decision? If the material never should have been collected, why should it not have been destroyed?

The Director of the NHLBI said she received guidance from multiple sources that the local IRB's had jurisdiction over this matter. Her sources included the HHS Office for Human Research Protection, and Dr. Carl Roth, an attorney who works for NHLBI.

One witness explained that the C.F.R. had codified certain principles that are held in the Nuremberg Code and Helsinki Agreement. These principles are based on the notion that abuses of individuals based on background, locality, or group would be less likely to occur if decisions were made at the local level by the affected individuals. This same witness said the idea of patient autonomy was then expanded out to include the local community, and the local community was best suited to make decisions about its citizens.

One witness said cell lines were essentially "owned" by the participants; therefore, they could not be destroyed without their consent. In other words, even if the cell lines were created improperly, once they existed, making an arbitrary decision to destroy them would violate patient autonomy.

One witness said a "simple back step is not the solution" to every problem. This witness explained that, "reversing everything is not the right way to handle it." Destroying the cells "like nothing ever happened" would not make all the problems "go away." It seemed

Dr. Russell Ware

appropriate to involve all parties in order to solve the problem. This witness went on to say that in the end patients were made aware that the scientists had done something wrong. He felt this strengthened the clinical study rather than "making it look like we were trying to cover something up."

One witness said if he were the patient, he would like to participate in the decision on whether his cells were going to be kept or destroyed.

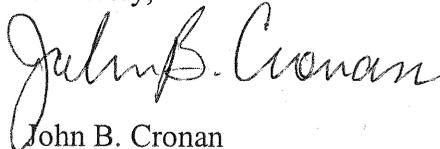
One witness commented on importance of re-consenting because of the evolving technology in the area of genetic research. He said there were samples in the NHLBI Repository that were put away and stored before anyone "dreamed what we could do with them." In essence, patients "had no idea what they were signing up for." These samples are "beyond the original assay of intent." Since the original informed consent forms likely do not cover future research projects, patients must be re-consented before this genetic material can be used.

Status of Cell Line

During the course of the recent interviews, Special Agent Covington learned that the majority of the cell lines that Ware created were destroyed on August 14, 2006; the remaining cell lines are stored at the NHLBI repository. Cell lines were only retained for patients who re-consented.

I hope that this additional information answers any questions that were not addressed in our ROI. If you have any other questions, please feel free to contact me at (202) 619-0530, or Special Agent Covington at (615) 736-5206.

Sincerely,



John B. Cronan
Director
Investigative Branch