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**Analysis of Disclosures, Agency Investigation and Reports,
and Comments of the Special Counsel**

OSC File No. DI-06-0767

Summary

The whistleblower, Duane R. Bonds, M.D., disclosed that in September 2005, she became aware that an investigator from St. Jude Children's Research Hospital, working under a study funded by the National Institutes of Health (NIH) used genetic material collected as a part of the study to establish immortalized DNA cell lines, known as Epstein-Barr Virus (EBV) transformed cell lines. Dr. Bonds alleged that the establishment of the cell lines constituted a violation of law, rule, or regulation, gross mismanagement, an abuse of authority, and a substantial and specific danger to public health and safety.

The Secretary of the Department of Health and Human Services (HHS) asked the Office of the Inspector General (OIG), HHS, to investigate Dr. Bonds' allegations. OSC received an initial report dated July 28, 2006, signed by DHS Secretary Michael O. Leavitt. The agency produced a supplemental report dated February 7, 2007, signed by John B. Cronan, Director, Investigative Branch, OIG. The whistleblower provided extensive comments on the reports.

As discussed more fully below, the agency investigation did substantiate the allegation that genetic material was collected from participants in an NIH-funded clinical study, and that it was used to create immortalized cell lines. The investigation revealed that the cell immortalization was neither funded by NIH, nor contemplated formally as a part of the study. The investigation did not substantiate that the investigator knowingly and willingly obtained and used genetic material without informed consent, but rather obtained the genetic material with the mistaken understanding that subjects had consented and that the procedure had been approved. The reports stated that the NIH's National Heart, Lung, and Blood Institute (NHLBI) was working with the local study sites to resolve concerns regarding the collection of this material, either through destruction of the samples collected, or by obtaining additional consent from participants.

The Special Counsel (OSC) finds that the agency's reports contain all of the information required by statute. The statute also requires that I make a determination whether or not the findings of the agency head appear reasonable. In this case, I cannot conclude that all of the findings set forth in the reports appear reasonable, primarily with respect to the conclusion that the contract investigator's actions did not constitute an ethics breach or a violation of federal regulations.

The Whistleblower's Disclosures

The whistleblower, Duane R. Bonds, M.D., is the Sickle Cell Disease Coordinator, Division of Blood Diseases & Resources (DBDR), NHLBI, NIH, Department of Health and Human Services (HHS), Bethesda, Maryland. She is a recognized leader in the research and understanding of Sickle Cell Disease, the most frequently inherited blood disorder in the United States. Dr. Bonds was, until her report of the allegations discussed herein, the Project Officer (PO) for a comprehensive study examining the use of the drug hydroxyurea in infants with Sickle Cell Disease, the Pediatric Hydroxyurea Phase III Clinical Trial, a project known as BABY HUG. Dr. Bonds disclosed concerns about the use of genetic material taken from subjects as a part of the BABY HUG study, for the creation of immortalized cell lines for future research, without proper informed consent of the study participants.

The study involved the recruitment of subjects from sites around the country. One such site is St. Jude Children's Research Hospital in Memphis, Tennessee. The BABY HUG trial is a contract-funded study, meaning that NIH funds the costs of the study, but outside investigators (doctors and researchers) perform the recruitment, collection and analysis. The principal outside investigator for the BABY HUG trial at St. Jude is Winifred Wang, M.D. The investigator responsible for processing specimens collected as a part of the trial is Russell Ware, M.D., Ph.D.

Dr. Bonds alleged that on September 1, 2005, at a monthly steering committee meeting, Dr. Ware presented a report on blood samples collected between October 2003 and August 2005. In that report, he stated that he had established cell lines from the DNA samples collected from study participants, in a process known as Epstein-Barr virus (EBV) cell line transformation. A cell line is a "living" tissue sample that can provide an unlimited supply of DNA, which otherwise could be used up in future research studies. Dr. Bonds alleged that the production of these EBV-transformed cell lines was not authorized by the trial protocol (the approved research plan), nor was it included in the consent forms signed by parents on behalf of their minor children.

On October 3, 2005, the Data Safety and Monitoring Board at NIH (DSMB) convened to discuss the immortalization of cell lines. It was determined at that meeting that neither the trial protocol nor the consent forms mentioned the creation of a human tissue repository (the immortalized cell lines). The minutes of this meeting report that HHS guidelines specifically address the creation of such a repository, and require the oversight of the Institutional Review Board (IRB). The IRB reviews and approves the conditions under which data and specimens may be accepted and shared, and ensures adequate protections of subject privacy and data confidentiality. The DSMB recommended that, "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. If these are to be created in the future, the protocol requires amendment to include the repository as an ancillary study." *Minutes of BABY HUG DSMB teleconference*, October 3, 2005.

Thereafter, Dr. Bonds was removed as Project Officer. As of the date of her filing with OSC, Dr. Bonds was not aware that either the proper informed consent of the study participants, or the destruction of the cell lines, had occurred. Nor was she aware that the study protocol had been properly amended, or that the creation of new cell lines has ceased. She believed that Dr. Ware's conduct violated 45 C.F.R. Part 46, which requires the legally effective informed consent of human research subjects.

The Report of the Department of Health and Human Services

The OIG conducted the investigation of the whistleblower's allegations. The agency investigation considered the allegation of a violation of 45 C.F.R. Part 46. In addition, the investigation considered whether or not federal funds were expended for research involving human subjects without their informed consent, in violation of 45 C.F.R. § 46.122. The report identified the central question as, whether or not the consent form obtained was sufficiently broad to include the creation of the cell lines from the genetic material collected as part of the study, or whether another more specific consent form should have been obtained.

The OIG interviewed nine individuals, including Dr. Bonds and Dr. Ware. The OIG also reviewed documents obtained from Dr. Bonds. Based on the interviews and document review, the OIG prepared a summary of the information discovered.

The OIG found that 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 Dr. Ware 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 DSMB or the IRBs that exist at each BABY HUG clinical site.

According to the agency report, the researcher who created the immortalized cell lines, Dr. Ware, contended that he discussed the experiment with Dr. Bonds, who was the BABY HUG Project Officer. Dr. Ware also maintained that he openly discussed his findings with the BABY HUG Steering Committee in both April 2005, and September 2005. At the September 2005, meeting, the Committee decided to continue the cell immortalization, and to enhance the consent form with language regarding the DNA research.

The agency report found that after this September 2005, meeting, Dr. Bonds brought the matter to the attention of the BABY HUG DSMB. The DSMB recommended either that the cell lines be destroyed, or that new consent forms be obtained from the study participants. Dr. Bonds argued for the destruction of the cell lines, and brought the argument to the Director, NHLBI. The Director forwarded a letter to Dr. Ware requesting the destruction of the cell lines. Thereafter, the Chair of the St. Jude IRB informed the Director, NHLBI, that the local IRBs at each site had jurisdiction to decide whether the cell lines should be destroyed or whether to obtain the enhanced consent of study participants. The Director subsequently contacted the IRB at each clinical site to suggest destruction or re-consenting.

The NHLBI remains actively engaged with the IRBs in resolving the issue by ensuring the re-consent of study participants or the destruction of the cell lines. According to the initial report, seven of the ten IRBs have decided to destroy the cell lines, and three have decided to obtain enhanced consents. The destruction of the cell lines has been delayed because the three IRBs that are seeking to re-consent have not yet located all of the patients to obtain consent or refusal. Once the process is complete, the current Project Officer for BABY HUG has indicated that he will order the destruction of the remaining cell lines, and provide supervision to ensure that the destruction occurs.¹

The agency report reflects that the OIG considered whether or not criminal or civil violations of law occurred in the creation of the cell lines and/or the use of federal funds in their creation. Because the agency report did not substantiate the allegation that Dr. Ware was using federal funds for the creation of the lines, and that NIH declined his request for funding, the report concluded that there was no evidence that would warrant consideration of the matter as a violation of ethical standards or a violation of criminal law.

The interviews conducted revealed significant disagreements among the principals involved, (members of the DSMB and IRB at NIH, as well as the IRBs at the local study sites) regarding whether the language of the consent form that was originally used was sufficient to permit the creation of living cell lines. There was also significant professional disagreement regarding whether or not the destruction of the established cell lines, without the consent of the study participants whose genetic material had been used, would be improper. The agency concluded that the decision to seek the re-consent of study participants, or to destroy the cell lines, rested with the local IRB at each study site. NIH has committed to overseeing the destruction of cell lines, and ensuring that those sites electing to re-consent have completed the process or destroyed any remaining cell lines.

Supplemental Report of the Department of Health and Human Services

The agency's supplemental report addressed specific questions posed by OSC. HHS, OIG officials re-interviewed several key witnesses at NHLBI, including the Director, NHLBI. The supplemental report concluded that most witnesses believed that Dr. Ware's work was done outside of the Statement of Work and Protocol. None of the witnesses found this unusual or improper. According to one witness, in all cases, the protocol is violated in some manner, and that this does not result in disciplinary action. In this case, the Statement of Work and Protocol of BABY HUG did not specifically address the cell immortalization issue, but it was not specifically prohibited. The supplemental report stated that it is very hard to anticipate all contingencies in the statement of work and protocol. In addition, the technology allowing cell immortalization became available after the BABY HUG trial was already underway, and so would not have been contemplated.

¹ The agency's supplemental report, discussed below, states that the majority of cell lines were destroyed, and that the remaining cell lines, for which re-consent was obtained, are stored at NHLBI.

In support of Dr. Ware's actions, the supplemental report cites the Director and other witnesses as unanimous in their opinion that Dr. Ware had done nothing improper. They believe that he acted openly, in good faith, in the public interest, and with what he believed was the approval of the Project Officer, Dr. Bonds. The DSMB researched the matter and concluded that this was a misunderstanding, not malfeasance, and that the work Dr. Ware did was a logical extension of current technology and of benefit to the scientific community. All of the witnesses stated their belief that the federal regulations are less than entirely clear on whether the immortalization of cell lines without obtaining a specific consent, or seeking an amendment to the statement of work and protocol, would constitute a violation of law. Most believed that this is a gray area, and that it is within the jurisdiction of the DSMB to determine if there was unethical conduct and to recommend adverse action. In this case, the DSMB found no misconduct.

Dr. Ware used samples from grant-funded research to establish the cell lines. The supplemental report addressed whether this would be viewed as a misuse of federal funds. The witnesses interviewed believed that the cells obtained through the grant-funded research would be available to Dr. Ware for a legitimate purpose, and that it is inherent to the nature of scientists to explore new technologies. The contract between NIH and Dr. Ware allowed for blood to be taken, and for cells to be extracted and stored. The cell immortalization was potentially of great benefit to the federal government, and there was no cost to the agency.

Finally, the supplemental report addresses whether or not it was appropriate for the local IRBs to decide whether to destroy the immortalized cells, or obtain the re-consent of the patients. The Director, NHLBI stated that she received guidance from the HHS Office for Human Research Protection, and Dr. Carl Roth, an attorney with NHLBI. Both concluded that the local IRBs had jurisdiction over this matter. According to one witness, the cell lines, once established, are "owned" by the study participants, and they would have to consent to their destruction. Because the IRBs are the closest link to the patient community, it made sense to have each IRB seek re-consent of their own study participants.

The supplemental report stated that the majority of the cell lines that Dr. Ware created were destroyed on August 14, 2006. The remaining cell lines are stored at the NHLBI repository. Cell lines were retained only for patients who re-consented.

The Whistleblower's Comments

Dr. Bonds strongly disagrees with the conclusions set out in the agency report. She believes that the individuals interviewed misrepresented facts in order to avoid liability. She explains that the NHLBI contracts with medical scientists around the country to purchase their expertise in the accomplishment of certain requirements outlined in the BABYHUG statement of work, protocol, and consent forms. Absent specific written authorization from NHLBI, no modifications, deviations, or enlargements of the statement of work, the scientific studies and testing involved, or the use of data and specimens acquired would be permitted.

Dr. Bonds stated that although she recognized the scientific importance of the proposed ancillary study by Dr. Ware, she never authorized him in writing to either perform or continue his proposed ancillary study. She could not have done so, and did not bring the matter to NHLBI staff for review and approval to add to the statement of work, protocol, and consent form, for the following reasons: 1) Dr. Peterson, Director of DBDR, was not in favor of Dr. Ware's ancillary study of VDJ mutations, so Dr. Bonds knew he would not look favorably on the addition of another ancillary study; and 2) BABY HUG was already running a deficit of \$7 million, and there was no additional money for ancillary studies; in fact, as of June 2005, Dr. Peterson said that BABYHUG would be shut down.

Dr. Bonds asserts that Dr. Ware was aware that the NHLBI staff had to approve any proposed addition to the protocol before it could be implemented and funded in the contract line. Dr. Bonds never provided Dr. Ware with the go-ahead to obtain samples for immortalization – he did so without the consent of the parents of children in the study. The BABYHUG consent forms had never been modified to incorporate his proposed ancillary study. Dr. Bonds is convinced that Dr. Ware fully understood that even if she agreed with the scientific merit of his desire to obtain and use genetic material, and used language indicating this agreement, those words would not constitute consent to perform the work.

Dr. Bonds also points out that her colleagues, but not her immediate supervisors, agreed with her and understood her position on the matter. They uniformly condemned immortalization. Dr. Bonds does not regret that her attempts to defend and protect children and families from abuse and misuse of their genetic material have caused her such personal and professional turmoil. She does regret that the legal community could not see the serious breaches of bioethics and regulations in Dr. Ware's behavior, but chose to hide behind his words – words of the individual who stood most to lose professionally and personally.

Dr. Bonds cites compelling examples of past unethical treatment of individuals, primarily minority individuals, and states that these are examples of the kind of unethical behavior 45 C.F.R. 46 is intended to protect. She states that 45 C.F.R. 46 needs to be amended so that these sorts of incidents will be punishable by criminal or civil penalties. She believes that fines must be imposed to compensate victims whose tissue samples are obtained without consent or financial compensation. Amendments must be passed swiftly so that these incidents can be deterred, especially due to the potential for harm to minority individuals.

Dr. Bonds also responded to the supplemental report. She stated that she reviewed the supplemental report with great sadness. She believes that the agency's attempts to defend the indefensible are unconscionable and immoral. She believes, centrally, that the agency reports omit what she contends is a critical point; that although Dr. Ware's project may have been scientifically worthwhile, it was not in the original BABYHUG contract statement of work, the protocol, or the informed consent. The project would have required presentation to the DSMB by Dr. Bonds as Project Officer. She did not present the project, because Dr. Peterson opposed Dr. Ware's other projects in the protocol, and the BABYHUG contract had an approximately \$7 million deficit.

Dr. Bonds feels vindicated that the Institutional Review Boards of most of the BABYHUG clinical sites agreed with her original decision to order the destruction of the genetic material that had been collected without informed consent. Overall, she believes that had the project not been mishandled by Dr. Peterson, it would have been completed in a timely fashion and not held up for more than two years without allowing subjects to be recruited. She believes that the sabotage of science and human subject protection by Dr. Peterson, and the institution's failure to prevent it, represent a waste of taxpayer funds and a failure of scientific stewardship.

Conclusion and Comments of the Special Counsel

Based on my review of the original disclosures and the agency's reports, I have determined that the agency's reports contain all of the information required by statute. The statute also requires that I make a determination whether or not the findings of the agency head appear reasonable. In this case, I cannot conclude that all of the reports' findings appear reasonable.

The essential facts are undisputed. A contract researcher used surplus samples of blood obtained through his NIH-funded research to expand the research beyond what was originally intended or approved. It is undisputed that, in so doing, this researcher employed a technology, EBV-transformed living cell lines, that had not been fully developed at the time the contract documents, including the patient consent form, were written. It is clear, therefore, that the consent form could not have been written to include such a procedure. Thus, it is against all logic to conclude that the samples were obtained with the fully informed consent of the patients.

The testimony of numerous high-level officials at NIH that Dr. Ware's research expansion was scientifically meritorious, that it was not undertaken maliciously or with "mal intent," and that no penalty or debarment from further contract work is warranted, is, frankly, outrageous. 45 C.F.R. Part 46 mandates protection of human research subjects. Protection is guaranteed through the use of contract documents such as the Statement of Work, Protocol, and Informed Consent Form. If NIH chooses to ignore the contract documents by permitting experimentation on human genetic material beyond what is set forth in the documents, without amendment, all human research protections are diluted, and will eventually be eroded. Moreover, NIH officials have participated in the violation of federal law.

History has demonstrated that the desire for scientific advancement has, at times, run roughshod over the rights of the most vulnerable members of our human population – those who are economically or physically disadvantaged, minorities, and children. Institutions from all over the world have reached the same conclusions about how to balance these interests. The informed consent of human research subjects is paramount to protection against scientific overreaching. Any number of arguments could be made to justify the need for a renewable source of genetic material on which to conduct scientific experimentation.

None outweighs the right of an individual, submitting himself or his child to such research, to be fully informed of the nature and risks of such research.

At a minimum, I am satisfied that no collected genetic material ultimately will be used without the informed consent of study participants, and that in cases where such consent cannot be obtained, the material will be destroyed. I am, nevertheless, disappointed that NIH officials have taken the position that established scientific safeguards apply at their discretion, and that they countenance experimentation outside the established protocol of a federally funded study. This rationale and practice could be used to justify the most horrendous bioethics practices imaginable. In these times of increasing uses of genetic materials for good causes as well as for commercial exploitation, we have to uphold higher standards for federal funding of research of human blood and DNA. Thus, in this case, I cannot conclude that the findings of the agency head appear reasonable.