DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

July 7, 2008

TO: Elizabeth G. Nabel, M.D., Director, NHLBI
Through: Sandra Gault, Chief, FMB
Susan Shurin, M.D., Acting Director, DBDR
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FROM: Thomas Croxton, Ph.D., M.D., Chief, ABDB
Hannah Peavy, M.D., Program Director, LBDB
Elizabeth Wagner, M.P.H., NHLBI Repository Project Officer

SUBJECT: NHLBI Acceptance of DOE Beryllium Biorepository Specimens

This is to request approval for the NHLBI Biologic Specimen Repository to accept, for storage and distribution, the specimens and data that are currently being collected by the U.S. Department of Energy (DOE)-supported Beryllium Biorepository. This request stems from a planning process that has been going on for approximately seven years and has involved extensive discussions among staff of DOE, DLD, and DBDR. DOE has historically supported the majority of federally-funded research in this area, because the use of beryllium is common in the nuclear industry and many of the cases of chronic beryllium disease (CBD) have occurred in employees and contractors of that department. NHLBI funds approximately 3 grants in this area, with DLD's primary interest in this research deriving from its mechanistic relevance to other lung diseases. CBD is a granulomatous lung condition with many clinical, pathological, immunologic, and genetic similarities to sarcoidosis.

Several years ago, DOE allocated funding for a repository program to collect biospecimens and data from individuals at risk for and with chronic beryllium disease and to make these specimens available for use by the broader research community. DLD staff were supportive of this program and saw an opportunity for NHLBI to contribute needed expertise and infrastructure through the existing NHLBI Biologic Specimen Repository. Hence, we shared our experience with the LTRC, assisted in selection of a steering committee chair, and encouraged DOE to consider placement of these specimens in the NHLBI Biologic Specimen Repository. DOE proceeded to establish the Beryllium Biorepository (BBR) and began collecting and archiving biological specimens and associated clinical data from individuals with chronic beryllium disease, beryllium sensitization, or beryllium exposure without sensitization. Approximately 1500 former and current DOE workers, contractors and subcontractors are now being recruited over a 36 month period from five participating clinical centers. Study participants donate blood; complete questionnaires; allow review of their medical testing and DOE work history records; and, if appropriate, give permission for research use of residual bronchoalveolar lavage fluid, cells, and transbronchial biopsy lung tissues obtained for the purpose of a participant's clinical evaluation. The accumulating specimens are currently housed at one of the participating centers, but DOE wishes to avoid conflict of interest by divorcing these centers from the later distribution of samples.

Since the NHLBI/DOE discussions on planning for the BBR, NHLBI has re-examined the operation of the NHLBI Biologic Specimen Repository and has instituted new procedures for the acceptance of biospecimen collections. This has generated uncertainty regarding NHLBI's willingness to accept and distribute the beryllium-related specimens and data. This memo seeks to clarify NHLBI's commitment to accept this specimen collection when it eventually becomes available.

We enthusiastically support NHLBI accepting the BBR biospecimens and data for storage and distribution to qualified investigators through the NHLBI Biologic Specimen Repository. Our recommendation is based on the following:

1. CBD research is relevant to the mission of the NHLBI. Biospecimen-based studies of CBD are opportune and have great potential for identifying genes and individual immunological traits that predispose to beryllium sensitization and disease. Such findings may have great significance for other granulomatous conditions such as sarcoidosis. These data and biospecimens constitute a unique resource that could be collected only within the programs established by DOE.
2. Accepting and distributing these specimens will provide a valuable service to investigators, highly consistent with our Strategic Plan. NHLBI, through its experience with the Biologic Specimen Repository, is uniquely qualified to perform this function. SeraCare has estimated that the costs for housing a collection of this size in the NHLBI Biologic Specimen Repository will be approximately $1,097/year.
3. Acceptance of this specimen collection will not commit the NHLBI to fund research that utilizes the biospecimens nor will it usurp the role of DOE as the federal lead in CBD. DOE fully intends to remain actively involved in screening, diagnosis, and treatment of CBD through its established network of centers. This is an excellent example of inter-departmental cooperation, enhancing the public benefit by combining interests and strengths of the two departments.
4. There is likely to be excellent demand for these resources from investigators. Studies using these specimens are needed to extend and apply recent findings on the pathogenesis of CBD. The existing centers for beryllium research, established by DOE, include an active community of qualified and interested researchers. In addition, our survey of a few DLD-funded pulmonary researchers revealed considerable enthusiasm for this topic and significant interest in the availability of biospecimens. Because these biopsy and BAL specimens are small in volume, it is likely that they will be depleted within several years and will not require long-term storage. The negotiated agreement with DOE will include a provision for the transfer of any remaining specimens to an appropriate research center after a period of NHLBI custodianship not to exceed 7 years.
5. DOE is willing to partially support our management of this collection by providing approximately $15,000 toward costs of transfer and retrieval.
6. DOE will promote the use of these specimens by a variety of means, including interactions with relevant staff of NIOSH, posting of an informational web page, advertisements of the resources to investigators, and presentations at meetings of beryllium researchers that they convene.

7. DOE will provide employees with expertise in CBD to assist in the scientific review and prioritization of requests for BBR tissues at the request of the NHLBI Biologic Specimen Repository.
8. DLD staff will actively encourage the use of these specimens, informing lung researchers about the availability of these resources. We further intend to establish metrics for monitoring and documenting usage.
9. Because of previous discussions with several NHLBI staff members, DOE has committed substantial resources in establishing this program. Although no formal agreement was reached and no legally-binding obligations were made, we believe that this would be a productive partnership, consistent with the informed consent of the participants.

If approved, we will share this memo with staff of DOE as an indication of our intention to accept the BBR specimens. We will then proceed to negotiate a detailed agreement, consistent with this memo, for transferring custodianship of the specimens to NHLBI. NHLBI will assume responsibility for maintaining the specimen collection, managing inquiries and access, and distributing materials to investigators whose study proposals are approved. De-identified specimens and data will be transferred as a unit after collection has been completed in 2010. This transfer will not be made until an MOU detailing conditions of the transfer has been approved by NHLBI.

The following are the estimated maximum number of specimens to be transferred to NHLBI after the collection period is complete.

Blood Specimens: 1500 participants

Specimen	Aliquots/subject	Vial content	Storage	Number of specimens
Plasma	10	0.2-0.4 ml aliquots	-80°C	10,000-15,000 tubes
DNA	10	< 1 ml aliquots	-80°C	10,000-15,000 tubes
Cells	6	$5 X 10^6$ cells	LN_2	5,000-7,500 cryovials

Lavage Specimens: 500-700 participants maximum

Specimen	Aliquots/subject	Vial content	Storage	Number of specimens
BALF	5	3 ml BALF	-80°C	2,500-3,500 3mL tubes
Cells	5	$10X10^5$ cells	LN_2	2,500-3,500 cryovials

Tissue: 500-700 participants

Type of Specimen	# of aliquots/subject	Number of slides
Slides with pathology affixed	3 slides per participant	~1,500-2,000 slides

It is anticipated that the total number of vials (22,500-33,500 at -80°C; 7,500-11,000 in LN_2) will be stored in 2-3 -80°C freezers and 2-3 liquid nitrogen dewars by the BBR.

Page 4 – Elizabeth G. Nabel, M.D.

Approved ✓ Disapproved _____

Elizabeth Nabel 7.17.08
Elizabeth G. Nabel, M.D. Date

cc: Dr. Gail, Chief, LBDB
Dr. Glynn, Chief, TMCTB
Sean Coady, NHLBI Data Distribution