DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

DEC 10 1999

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Dear Mr. Kimbrell:

This is in response to your "Petition Requesting the National Institutes of Health to Prohibit the Routine Use of Animals and Promote Non-Animal Alternatives in the Production and Use of Monoclonal Antibodies," dated March 26, 1998, to Dr. Harold Varmus, Director of the National Institutes of Health (NIH), pursuant to the Administrative Procedure Act, 5 U.S.C. §553(e).

The petition, filed on behalf of the American Anti-Vivisection Society (AAVS) and the Alternatives Research & Development Foundation (ARDF), requests that the NIH take the following actions:

(1) Prohibit the use of the ascites method for the production of monoclonal antibodies (MAb). This prohibition would include, *inter alia*:

   (a) a ban on the routine use of ascites methods for the production of MAbs in any NIH funded research;
   (b) a ban on NIH funded researchers using MAbs created by the ascites method produced in countries other than the United States and;
   (c) the establishment of an appeals procedure through local Institutional Animal Care and Use Committees (IACUC) for researchers requesting exceptions to the prohibition. This appeal procedure would include, *inter alia*:

      (i) a requirement that all requests for an exception are based on rigorous and well documented justification; and
      (ii) a requirement that no exception be granted for reasons of cost or convenience; and
      (iii) a requirement that all records be maintained in a central data repository and that such records be available for public inspection.

(2) Immediately instruct all grant review panels to give higher ratings and preference in funding to proposals and renewal grant applications based on the use of in vitro MAb

production techniques. This action would include:

(a) prominently displaying this change in policy in all relevant literature and Web sites available to researchers preparing NIH grants.

(3) Include funding in the next budget to establish significantly more Core In Vitro MAb Production Facilities and educational programs on using in vitro methods.

(4) Immediately provide regularly scheduled training courses where both intramural and extramural investigators are taught the latest methods for producing MAbs.

Procedure for Responding to a Petition

Under 5 U.S.C. §553(e), each agency must give an interested person the right to petition for the issuance, amendment, or repeal of a rule. The Department of Health and Human Services does not have regulations or guidelines establishing procedures for the filing and disposition of such petitions, but, consistent with the legislative history of 5 U.S.C. §553(e), it fully and promptly considers each such petition and takes such action as may be required, or notifies the petitioners of the denial of the petition. H.R. Rep. No. 280, 79th Cong., 2d Sess. (1946) at 26.

Background/ Procedural History

On April 23, 1997, the AAVS submitted a prior "Petition Requesting the National Institutes of Health to Prohibit the Use of Animals and Implement non-Animal Alternatives in the Production and Use of Monoclonal Antibodies" by: (1) prohibiting the use of animals in the production and use of MAbs resulting from the ascites method; (2) confirming the validity and reliability of alternative methods of MAb production; (3) encouraging the acceptance of the alternative methods by the scientific community by initiating an education and outreach program on them and by proposing a regulation requiring all NIH scientists and grantees to utilize the alternatives; and (4) initiating a training program at NIH to train scientists in the use of the alternatives. The NIH carefully considered this petition and replied by letter on September 18, 1997, that it had determined that it was not appropriate to prohibit the use of animals in the production of MAbs resulting from the ascites method because available scientific evidence indicated that there are circumstances in which this method is scientifically justified. This determination was consistent with Federal law

and policies governing care and treatment of laboratory animals and the use of alternative methods, and was a reasonable exercise of the NIH's discretionary authority. Regarding the AAVS's remaining requests, the NIH stated in that response that it was already engaged in activities to confirm the validity and reliability of alternative methods of MAb production, encourage acceptance of alternative methods by the scientific community, and train scientists in the use of alternatives.

On March 26, 1998, AAVS and ARDF filed the instant petition, requesting, among other things, a ban on the routine use of ascites methods for the production of MAbs. The NIH considers this petition to be a supplement to the AAVS initial petition. The arguments put forth by the petitioners include, among other assertions, that the NIH failed in its prior response to provide valid scientific reasons for not supporting a proposed ban on the use of the mouse ascites method.

Before responding to the supplemental petition, the NIH decided to seek the advice of nationally recognized experts in the field and promptly negotiated a contract with the Institute for Laboratory Animal Research (ILAR) National Research Council, National Academy of Sciences, to conduct an independent study and prepare a report on whether there is a continuing need to produce monoclonal antibodies by the mouse ascites method. (Letter from Dr. Lou Sibal to Ms. Letterman dated September 22, 1998.)

The Statement of Work in the NIH request to ILAR reads as follows:

> The NIH requests that the ILAR, NAS convene a panel of experts from relevant scientific disciplines and prepare a report that will answer the following basic question: Is there a continuing need to produce monoclonal antibodies (MAb) by the ascites method? The report will be used by the NIH in formulating an appropriate response to the petition submitted by the AAVS/ARDF and as a Guide for researchers and members of IACUCs in determining whether the use of the ascites method is justified for a particular research project. The NIH wishes to address that stage of the procedure that involves: (a) the propagation of selected hybridoma cells producing MAbs of desired specificity by growing the cells in the peritoneal cavity of an animal (generally, a mouse or a rat); and (b) the newer methods of growing the cells in vitro using various production systems and collecting supernatant culture fluids as a source of antibody.

The ILAR was specifically asked to assess the state-of-the-art of these technologies and address the following:

(1) Cite examples, if any, where the scientific objectives of a research project cannot be achieved using in vitro methods.

(2) If it is justifiable to continue using the ascites method under certain circumstances:

(a) What are the scientific reasons that would require the in vivo production of MAbs?
(b) What "refinements" to the in vivo method may be implemented to avoid or minimize discomfort, distress, and/or pain to the animals?
(c) Describe "best practices" to be employed under these circumstances.

(3) What evidence of scientific necessity should IACUCs accept from the principal investigator?

(4) Is it possible to predict the circumstances under which currently available in vitro methods will fail?

(a) If yes, describe them.
(b) If no, what constitutes a reasonable effort on the part of the investigator to identify suitable in vitro methods prior to rejecting them in favor of the ascites method?

(5) Are there regulatory requirements (e.g., FDA approval of validated test methods) that require the continued availability of the mouse ascites production method?

The ILAR Report (National Research Council, *Monoclonal Antibody Production*, National Academy Press, 1999) was released on April 9, 1999. A copy of the Report is enclosed as Appendix A. Additional copies of the Report may be obtained from the NRC or downloaded from the NIH home page on the Web at http://www.nih.gov. The ILAR report concluded that:

(1) There is a continuing need for the scientific community to avoid or minimize pain and suffering by animals. Therefore, over the next several years, as tissue-culture systems are further developed, tissue-culture methods for the production of monoclonal antibodies should be adopted as the routine method unless there is a clear reason why they cannot be used or why their use would represent an

unreasonable barrier to obtaining the product at a cost consistent with the realities of funding of biomedical research programs in government, academe, and industry. This could be accomplished by establishing tissue culture production facilities in institutions.

(2) The mouse ascites method of producing monoclonal antibodies should not be banned, because there is and will continue to be scientific necessity for this method.

(3) When the mouse ascites method for producing MAbs is used, every reasonable effort should be made to minimize pain or distress, including frequent observation, limiting the number of taps, and prompt euthanasia if signs of distress appear.

(4) MAbs now being commercially produced by the mouse ascites method should continue to be so produced, but industry should continue to move toward the use of tissue-culture methods.

These recommendations, together with the scientifically-based reasons for supporting them, are stated on pages 45-47 of the ILAR Report. The NIH posted the ILAR Report on its Web site and sought public comment for 60 days; however, no comments were received.

Summary of Response

Consistent with current scientific evidence and Federal laws and policies governing care and treatment of laboratory animals, the NIH concurs with the findings and recommendations of the ILAR Report. The NIH has determined that there is a continuing scientific need to produce monoclonal antibodies by the mouse ascites method. Therefore, this procedure should not be banned. However, the mouse ascites method cannot be considered "routine," because Federal laws, regulations, and policies governing treatment of laboratory animals require investigators to provide scientific justification for the use of animals, consider alternative methods to the procedures that may cause more than momentary pain or distress, and obtain approval from the appropriate IACUC before using the method. The NIH strongly supports the adoption of tissue-culture methods for MAb production as the default method unless there are clear scientific reasons why they cannot be used. The NIH declines to instruct grant review panels to give higher ratings to proposals using in vitro methods of MAb production, as this step would be inconsistent with Federal statutes and policies governing peer review procedures. The NIH will continue to support core

facilities for the in vitro production of MAbs and the training of investigators.

Responses to Petitioners' Requests for Agency Action

1) Immediately prohibit the use of the ascites method for the production of MAB.

The NIH accepts the recommendations of the ILAR Report and has determined that there is a continuing need to produce MAbs by the mouse ascites method. Since there are valid reasons not to ban this procedure, no action will be taken on this request. However, the use of the mouse ascites method cannot be considered "routine" because Federal laws, regulations, and policies governing treatment of laboratory animals require that the principal investigator of a project: (1) justify the need to propagate selected hybridoma cells in the peritoneal cavity of mice; (2) provide assurance that alternatives to procedures that may cause more than momentary pain and distress have been considered, and (3) obtain the approval of the appropriate IACUC. Because the method will not be banned but is subject to scrutiny, there is no need to establish an appeals procedure to use the MAb method. Acceptance by an IACUC to use the mouse ascites method is based on a rigorous review of the project; thus, any actions taken are documented in the minutes of the IACUC. *See* http://grants.nih.gov/grants/oprr/pubartindex.htm, OPRR Reports: November 17, 1997. The Office for Protection from Research Risks, "Dear Colleague" letter provides guidance to PHS awardee institutions and IACUCs regarding the use of the mouse ascites method.

The NIH strongly supports the use of tissue culture methods for MAb production as the default method unless there are clear scientific reasons why they cannot be used. The NIH concurs with the need to provide rapid exchange of information on in vitro MAb production to investigators and IACUC members and encourages them to consult existing references and resources contained in the ILAR Report (Appendix A), and on the Web sites of the following organizations: The Center for Alternatives to Animal Testing, Johns Hopkins University, http://www.altweb.jhsph.edu; the Animal Welfare Information Center, U.S. Department of Agriculture, Agriculture Research Service, National Agricultural Library, http://www.nal.usda.gov/awic/; and the University of California, Center for Animal Alternatives at http://www.vetmed.ucdavis.edu for this purpose. The NIH will post this information on its Web site at http:www.nih.gov/.

Governing Federal Law and Policy

The determination not to ban use of the mouse ascites method for MAb production when it is scientifically justified and approved by the appropriate IACUC is consistent with Federal laws and policies governing treatment of laboratory animals and the use of alternative methods. The determination is also rationally based on available scientific evidence regarding scientific necessity for continued use of the method and is thus a reasonable exercise of discretionary authority.

As stated in the NIH's response to the AAVS's April 23, 1997, petition, under section 495 of the Public Health Service (PHS) Act, the NIH is required to establish guidelines for animal care and treatment, but these guidelines cannot be construed to prescribe methods of research.[1] 42 U.S.C. §289d(a). The guidelines address the care and treatment of animals, and the organization and operation of IACUCs; they do not mandate research methods. Id.; *See also PHS Policy for Humane Care and Use of Laboratory Animals* at 9; *Guide for the Care and Use of Laboratory Animals* at 8. Likewise, section 2143 of the Animal Welfare Act directs the Secretary of the USDA to promulgate standards to govern the humane handling, care, treatment, and transportation of animals by dealers, research facilities, and exhibitors, but states that the Secretary shall not promulgate rules, regulations, or orders with regard to the design, outlines, or guidelines of actual research or experimentation by a research facility. 7 U.S.C. §§2143(a)(1)-(6). The Animal Welfare Act also emphasizes the role of the IACUC to assess animal care and treatment in a research facility. 7 U.S.C. §2143(b).[2] The legislative history for both the PHS Act and the Animal Welfare Act confirm that the guidelines and rules are not intended to prescribe methods of research. (Letter from Dr. Varmus to Mr. Kimbrell and Mr. Mendelson at 8-11, *citing* H.R. Rep. 99-158, 99th Cong., 1st Sess., (1985); S. Rep. No. 1281, 89th

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[1] We do not agree with the argument raised in the supplemental petition, that prohibiting research methods does not prescribe methods. Prohibiting one method necessarily prescribes other methods.

[2] Implementing regulations and USDA policy also require the principal investigator and local IACUCs to assess alternatives to procedures that may cause more than momentary or slight pain or distress to animals. 9 C.F.R. §2.31(8)(d), USDA Animal Care Resource Guide Policy #12.

Cong., 2d Sess., (1966); H.R. Rep. 91-1651, 91st Cong., 2d Sess. (1970).)[3]

Section 404C of the PHS Act, which directs the NIH to prepare a plan regarding, among other things, methods of biomedical research and experimentation that do not require the use of animals, does not require the NIH to prescribe research methods, or mandate use of specific alternatives to animal methods. 42 U.S.C. §283e(a). The *National Institutes of Health Plan for the Use of Animals in Research* (the "*Plan*') that was developed pursuant to Section 404C of the PHS Act encourages use of alternatives, but does not mandate elimination of animal methods. In fact, the *Plan* recognizes that research using animals continues to be a valid scientific model. *Plan* at 2-3. Further, nothing in the statute indicates that the NIH must mandate particular alternatives to animal methods to give effect to section 404C of the PHS Act. The statute is given full effect by the development of a plan by the NIH, and its various activities to support alternatives, including those described in its response to AAVS's prior petition. (Letter from Dr. Harold Varmus to Mr. Kimbrell and Mr. Mendelson dated September 18, 1997.)

Under principles of statutory construction, statutes must be construed in harmony with other constitutional, statutory and common law. *See* Sutherland Stat. Cons. §53.01 (5th Ed), *citing* Schorr, V. Commodity Futures Trading Commission, 740 F.2d 1262 (D.C.C. 1984). Section 495 of the PHS Act, section 2143 of the Animal Welfare Act, and section 404C of the PHS Act must be construed together to direct the NIH and the USDA Secretary to promulgate guidelines and regulations for animal care and treatment, refrain from prescribing research methods, rely on local IACUCs to evaluate care and use of animals or use of alternatives on a case by case basis, and develop a plan for fostering alternatives. It is eminently reasonable for the NIH to interpret these statutes to mean that, while it should develop a plan for and support methods of research that do not use animals under section 404C of the PHS Act, it is not permitted to prescribe research procedures, as stated in section 495 of the PHS Act. Furthermore, the scientific necessity of research

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[3] It is appropriate to examine legislative history for these statutes because legislative history clarifies any ambiguity raised by language stating that the NIH guidelines and USDA rules should not prescribe research methods.

methods in individual projects or availability of alternatives should be assessed through local IACUC review, as required under section 495 of the PHS Act and section 2143 of the Animal Welfare Act and its implementing regulations.

Finally, the NIH's determination not to ban the use of the mouse ascites method for MAb production is based on available scientific evidence and recommendations made by a panel of independent experts. The decision has a clear, rational basis and is both legally and scientifically sound; it cannot be construed as arbitrary or capricious. The NIH's reasonable determination based on an expert assessment of available scientific evidence, and its interpretation of PHS statutes and policies are discretionary decisions that are entitled to judicial deference. Thomas Jefferson University v. Shalala, 512 U.S. 504 (1994); WWHT v. FCC, 656 F.2d 807, 817 (D.C. Cir. 1981); Natural Resources Defense Council v. SEC, 606 F.2d 1031, 1053 (D.C. Cir. 1979); *See also* Pharmaceutical Mfrs. Ass'n v. Food and Drug Administration, 484 F. Supp. 1179 (D.C. Del. 1980).

2) Immediately instruct all grant review panels to give higher ratings and preference in funding to proposals and renewal grant applications based on the use of in vitro MAb production techniques.

The NIH will not implement this request. In accordance with sections 405, 406, and 492 of the PHS Act, and relying on the applicant's compliance with section 495, the NIH funds research proposals based on the scientific and technical merit of those proposals, as evaluated by independent peers with expertise in the area proposed for research. 42 U.S.C. §§284, 284a, 289a, 289d. Instructing these reviewers to give higher ratings and thus preference in funding to certain applications would be inconsistent with peer review statutes and policies and antithetical to the concept of independent peer review. Peer reviewers selected are fully qualified to assess the scientific and technical merit of applications and carefully examine the use of research methods using animals or alternatives to animals.

Specifically, the evaluation by members of a scientific review group (study section) must take into consideration the investigator's response to the following 5 criteria, as listed in the grant application PHS Form 398: *See:* Review Procedures for Initial Review Group Meetings at http://www.drg.nih.gov/refrev.htm.

(1) Provide a detailed description of the proposed use of the

animals in the work previously outlined in the experimental design and methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.

(2) Justify the use of animals, the choice of species, and the numbers used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and their numbers.

(3) Provide information on the veterinary care of the animals involved.

(4) Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices where appropriate to minimize discomfort, distress, pain, and injury.

(5) Describe any euthanasia method to be used and the reasons for its selection. State whether this method is consistent with the recommendation of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

The NIH review process requires that any comments or concerns that review members may wish to express regarding the appropriateness of the choice of species and numbers involved, and the justification for their use be noted. A comment is an observation that will be communicated as a suggestion to the investigator. A concern is a finding regarding animal care or use that requires resolution by program staff prior to an award; NIH review and program staff and OPRR staff work together to resolve any concerns. No award will be made unless all concerns raised by the review group have been resolved. Applications containing procedures or conditions not adhering to policies related to animal welfare must be called to the special attention of National Advisory Councils and may require individual discussion and Council action.

3) Include funding in the next NIH budget to establish significantly more Core In Vitro MAb Production Facilities and educational programs on using in vitro methods.

The NIH will consider funding meritorious applications for the

support of core MAb production facilities. However, before the issuance of a request for applications (RFA), it will be necessary to consult with the NIH Institute and Center Directors to determine whether there is actually a need to support additional core facilities to meet programmatic priorities.

A core facility is a well-equipped laboratory at an academic institution that offers specialized laboratory services. Only those facilities that are dedicated to cell culture, MAb production, or both will be considered in this response. The mission of a cell culture laboratory is to provide investigators with cell culture systems, equipment, technical assistance, and education that will enable them to address important scientific questions. The hybridoma facility provides investigators with the following services: immunization of mice, fusion of B lymphocytes with myeloma cells to create hybridomas, subcloning and cryopreservation of hybridomas, and the production of MAbs by the mouse ascites and in vitro methods. In addition, the laboratory is expected to evaluate advances in the development of new methods for the production of MAbs and remain on the cutting edge of the technology. Using a core laboratory is a cost effective way for investigators to complete more work than they normally could accomplish given space and qualified personnel restraints. Many not-for-profit centralized facilities also offer similar services to investigators on a fee-for-service basis.

According to the NIH Computer Retrieval of Information on Scientific Projects (CRISP) database, an on-line computer-based information system for NIH extramural programs, the total number of tissue culture and monoclonal antibody core facilities supported by the NIH Institutes and Centers for Fiscal Years 1993 through 1998 has remained relatively constant (Appendix B). In Fiscal Year 1998, the NIH supported 303 core facilities (Appendix C). The dollar level of support has increased from $44.8 M to $52.4 M during this period. Sixty-three of the core facilities were devoted primarily to the production of MAbs. These facilities are reasonably well distributed geographically across the U.S. with clusters in areas where the heaviest concentrations of NIH-supported investigators are located (Appendix D).

However, the NIH is not and should not be the sole source of support for developing and implementing new methods for MAb production. In addition, the transfer of in vitro technology into the private sector for commercial production has made MAbs against a wide variety of antigens (epitopes) available to investigators. Altweb, the Alternatives to Animal Testing Web site which is partially supported by the NIH, is currently

preparing a list of organizations that sell MAbs produced by in vitro methods. The list is expected to be available soon at http://altweb.jhsph.edu. Recently, a supplement to *Lab Animal*, Autumn 1999, on "Small-Scale Monoclonal Antibody Production," lists resources that provide new technologies in MAb production.

4) Immediately provide regularly scheduled training courses where both intramural and extramural investigators are taught the latest in vitro methods for producing MAb.

This year, as noted above, the NIH Institutes and Centers have made 303 awards to research institutions in the U.S. to operate central core laboratories for cell culture and hybridoma technologies. Many of these facilities not only provide training to investigators (and laboratory personnel) who want to establish in vitro MAb systems in their own laboratories but also provide services, such as producing quantities of MAbs of desired specificity on a fee-for-service basis. In addition, the administrative components of these cores are responsible for keeping researchers apprised of new MAb systems by scheduling meetings and sponsoring seminar series.

Each year, the NIH, primarily through the OPRR, funds or co-funds a number of workshops and meetings dealing with animal welfare issues. These meetings, many with national importance, provide a forum for IACUC members, laboratory animal veterinarians, regulatory officials, research administrators, researchers using animals, animal care staff, and others to discuss issues related to the well-being of research animals. They often feature reports and panel discussions by experts on animal and non-animal methods, including MAb production.

Finally, the NIH will explore additional ways to disseminate new information on hybridoma technology.

CONCLUSIONS

Over the last several decades, MAbs have become an essential biomedical research and therapeutic tool. Continuing refinements and increased experience with cell culture technology have greatly reduced the need to use animals for the production of MAbs. Although the NIH declines implementing a total ban on the mouse ascites method for the scientific reasons stated above, it strongly advocates the use of in vitro techniques as the default method for MAb production. The NIH also declines to instruct

review panels to give preference to applications using in vitro MAb production techniques because doing so is inconsistent with peer review statues and policies. Independent evaluation of research proposals by knowledgeable experts is essential to encourage creativity and generate innovative approaches to support the best science. Appropriate review and approval mechanisms for protocols involving MAb production are currently in place at both the institutional and grant review levels to avoid unnecessary or "routine" use of the mouse ascites method. The NIH will continue to allocate funds to ensure that critical technologies for the in vitro production of MAbs are advanced as an agency priority. A similar letter will be sent to Mr. Mendelson and Ms. Letterman.

Sincerely,

Harold Varmus, M.D.
Director