

#### 4.8 Carcinogenicity Studies

Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. However, product-specific assessment of carcinogenic potential may still be needed depending upon duration of clinical dosing, patient population, and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.). When there is a concern about carcinogenic potential, a variety of approaches may be considered to evaluate risk.

Products that may have the potential to support or induce proliferation of transformed cells and clonal expansion possibly leading to neoplasia should be evaluated with respect to receptor expression in various malignant and normal human cells that are potentially relevant to the patient population under study. The ability of the product to stimulate growth of normal or malignant cells expressing the receptor should be determined. When in vitro data give cause for concern about carcinogenic potential, further studies in relevant animal models may be needed. Incorporation of sensitive indices of cellular proliferation in long-term repeated dose toxicity studies may provide useful information.

In those cases where the product is biologically active and nonimmunogenic in rodents and other studies have not provided sufficient information to allow an assessment of carcinogenic potential, then the utility of a single rodent species should be considered. Careful consideration should be given to the selection of doses. The use of a combination of pharmacokinetic and pharmacodynamic endpoints with consideration of comparative receptor characteristics and intended human exposures represents the most scientifically based approach for defining the appropriate doses. The rationale for the selection of doses should be provided.

#### 4.9 Local Tolerance Studies

Local tolerance should be evaluated. The formulation intended for marketing should be tested; however, in certain justified cases, the testing of representative formulations may be acceptable. In some cases, the potential adverse effects of the product can be evaluated in single or repeated dose toxicity studies, thus obviating the need for separate local tolerance studies.

#### Notes

##### Note 1

Animal models of disease may be useful in defining toxicity endpoints, selection of clinical indications, and determination of appropriate formulations, route of administration, and treatment regimen. It should be noted that with these models of disease there is often a paucity of historical data for use as a reference when evaluating study results. Therefore, the collection of concurrent control and baseline data is critical to optimize study design.

##### Note 2

There may be extensive public information available regarding potential reproductive and/or developmental effects of a particular class of compounds (e.g., interferons) where the only relevant species is the nonhuman

primate. In such cases, mechanistic studies indicating that similar effects are likely to be caused by a new but related molecule may obviate the need for formal reproductive/developmental toxicity studies. In each case, the scientific basis for assessing the potential for possible effects on reproduction/development should be provided.

##### Note 3

With some biopharmaceuticals, there is a potential concern about accumulation of spontaneously mutated cells (e.g., via facilitating a selective advantage of proliferation) leading to carcinogenicity. The standard battery of genotoxicity tests is not designed to detect these conditions. Alternative in vitro or in vivo models to address such concerns may have to be developed and evaluated.

Dated: November 12, 1997.

**William K. Hubbard,**

*Associate Commissioner for Policy Coordination.*

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#### DEPARTMENT OF HEALTH AND HUMAN SERVICES

##### National Institutes of Health

##### National Institute of Arthritis and Musculoskeletal and Skin Diseases; Notice of Closed Meeting

Pursuant to Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following National Institute of Arthritis and Musculoskeletal and Skin Diseases Special Emphasis Panel (SEP) meeting:

*Name of SEP:* Mechano Transduction in Bone.

*Date:* December 18, 1997.

*Time:* 8:00 a.m.-5:00 p.m.

*Place:* Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland 20814.

*Contact Person:* Tommy L. Broadwater, Ph.D., Scientific Review Administrator, Natcher Building, 45 Center Drive, Rm 5AS25U, Bethesda, Maryland 20892-6500, Telephone: 301-594-4952.

*Purpose/Agenda:* To evaluate and review a research grant application.

This meeting will be closed in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C. The discussion of this application could reveal confidential trade secrets or commercial property such as patentable material and personal information concerning individual associated with the application, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

(Catalog of Federal Domestic Assistance Program Nos. [93.846, Project Grants in Arthritis, Musculoskeletal and Skin Disease Research], National Institutes of Health, HHS)

Dated: November 10, 1997.

**LaVerne Y. Stringfield,**

*Committee Management Officer, NIH.*

[FR Doc. 97-30204 Filed 11-17-97; 8:45 am]

BILLING CODE 4140-01-M

#### DEPARTMENT OF HEALTH AND HUMAN SERVICES

##### National Institutes of Health

##### Prospective Grant of Exclusive License: Immunodampening Technology

**AGENCY:** National Institutes of Health, Public Health Service, DHHS.

**ACTION:** Notice.

**SUMMARY:** This is notice in accordance with 35 U.S.C. 209(c)(1) and 37 CFR 404.7(a)(1)(i) that the National Institutes of Health (NIH), Department of Health and Human Services, is contemplating the grant of an exclusive world-wide license to practice the invention embodied in U.S. Patent Number 5,585,250 and pending U.S. Patent Application Serial No. 08/764,575 both entitled "Dampening of an Immunodominant Epitope of an Antigen for Use in Plant, Animal and Human Compositions and Immunotherapies" and related foreign patent applications to Biological Memetics, Inc., of Frederick, Maryland. The patent rights in this invention have been assigned to the United States of America.

It is anticipated that this license will be limited to the field of vaccines for the treatment and prevention of infectious diseases in animals and humans.

**DATES:** Only written comments and/or applications for a license which are received by NIH on or before February 17, 1998 will be considered.

**ADDRESSES:** Requests for a copy of the patent and/or patent application, inquires, comments and other materials relating to the contemplated license should be directed to: Robert Benson, Patent Advisor, Office of Technology Transfer, National Institutes of Health, 6011 Executive Blvd., Suite 325, Rockville, MD 20852-3804; Telephone: (301) 496-7056, x267; Facsimile: (301) 402-0220.

**SUPPLEMENTARY INFORMATION:** The patent and pending patent application describe a broadly applicable method of redirecting the immune response to an antigen from an immunodominant epitope to another epitope by altering the immunogenicity of the immunodominant epitope. The method is most useful for those pathogens with a highly variable immunodominant epitope, such as HIV, HCV or gonorrhea.

By immunodampening the dominant epitope the immune system then reacts to other more conserved epitopes.

The prospective exclusive license will be royalty-bearing and will comply with the terms and conditions of 35 U.S.C. 209 and 37 CFR 404.7. This prospective exclusive license may be granted unless within 90 days from the date of this published notice, NIH receives written evidence and argument that established that the grant of the license would not be consistent with the requirements of 35 U.S.C. 209 and 37 CFR 404.7.

Applications for a license filed in response to this notice will be treated as objections to the grant of the contemplated license. Comments and objections submitted to this notice will not be made available for public inspection and, to the extent permitted by law, will not be released under the Freedom of Information Act, 5 U.S.C. § 552.

Dated: November 5, 1997.

**Barbara M. McGarey,**

*Deputy Director, Office of Technology Transfer.*

[FR Doc. 97-30202 Filed 11-17-97; 8:45 am]

BILLING CODE 4140-01-M

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Public Health Service

#### National Toxicology Program; National Toxicology Program (NTP), Board of Scientific Counselors' Meeting; Review of Draft NTP Technical Reports

Pursuant to Public Law 92-463, notice is hereby given of the next

meeting of the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee on December 9 and 10, 1997, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences (NIEHS), 111 Alexander Drive, Research Triangle Park, North Carolina. The meeting will begin at 1:30 p.m. on December 9, and at 8:30 a.m. on December 10, and is open to the public. The agenda topic is the peer review of draft Technical Reports of long-term toxicology and carcinogenesis studies from the National Toxicology Program. Additionally, there will be a presentation made concerning data obtained from transgenic mouse models on several of the chemicals being reviewed.

Tentatively scheduled to be peer reviewed on December 9-10 are draft Technical Reports of 10 two-year studies, listed alphabetically, along with supporting information in the attached table. All studies were done using Fischer 344 rats and B6C3F<sub>1</sub> mice. The order of review is given in the far right column of the table. Copies of the draft Reports may be obtained, as available, from: Central Data Management, MD E1-02, P.O. Box 12233, Research Triangle Park, NC 27709 (919/541-3419), FAX (919/541-3687), email: CDM@niehs.nih.gov.

Public comment on any of the Technical Reports is welcome. Persons wanting to make a formal presentation regarding a particular Technical Report must notify the Executive Secretary by telephone, by FAX, by mail, or by email no later than December 4, 1997, and provide a written copy in advance of the

meeting so copies can be made and distributed to all Subcommittee members, *ad hoc* expert consultants, and staff, and made available at the meeting for attendees. Written statements should supplement and may expand on the oral presentation. *Oral presentations should be limited to no more than five minutes.*

The program would welcome receiving toxicology and carcinogenesis information from completed, ongoing, or planned studies by others, as well as current production data, human exposure information, and use patterns for any of the chemicals listed in this announcement. Please contact Central Data Management at the address given above, and they will relay the information to the appropriate staff scientist.

The Executive Secretary, Dr. Larry G. Hart, P.O. Box 12233, Research Triangle Park, North Carolina 27709 (telephone 919/541-3971; FAX 919/541-0295; email hart@niehs.nih.gov) will furnish agenda and a roster of Subcommittee members and expert consultants prior to the meeting. Summary minutes subsequent to the meeting will be available upon request to Central Data Management.

Attachment.

**Charles E. Leasure, Jr.,**

*Acting Director, National Toxicology Program.*

#### SUMMARY DATA FOR TECHNICAL REPORTS TENTATIVELY SCHEDULED FOR REVIEW AT THE MEETING OF THE NTP BOARD OF SCIENTIFIC COUNSELOR'S TECHNICAL REPORTS REVIEW SUBCOMMITTEE

[December 9-10, 1997]

Chemical CAS No.	Technical route/report number	Primary uses	Exposure levels	Review order
1-Chloro-2-Propanol, Technical, 127-00-4.	TR-477	Chemical intermediate for propylene oxide & other organic compounds.	Dosed-Water (deionized water): Rats: 0, 150, 325, or 650 ppm; Mice: 0, 250, 500, or 1000 ppm (50/sex/group).	10
Coconut Oil Acid, Diethanolamine Condensate, 68603-42-9.	TR-479	Foam stabilizer in shampoos and dish-washing liquids; dyeing assistant in textile processing.	Topical (95% ethanol): Rats: 0, 50, or 100 mg/kg; Mice: 0, 100, or 200 mg/kg (50 sex/species/group).	2
Diethanolamine, 111-42-2 .....	TR-478	Production of textile lubricants. Rubber chemicals intermediate; emulsifier in agricultural chemicals, cosmetics, and pharmaceuticals; gas conditioning agent.	Topical (ethanol): Male Rats: 0, 16, 32, or 64 mg/kg; Female Rats: 0, 8, 16, or 32 mg/kg; Mice: 0, 40, 80, or 160 mg/kg (50/sex/species/group).	1