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.

[FR Doc. 97–30274 Filed 11–17–97; 8:45 am]

BILLING CODE 4160–01–F

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, ins 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.