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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA MOLECULE PROGRAM ADVISORY COMMITTEE

MINUTES OF MEETING

DECEMBER 4-5, 1975

The Recombinant DNA Molecule Program Advisory Committee was convened for its fourth meeting at 9:00 a.m. on December 4, 1975 in the Galleria Room of the La Valencia Hotel, La Jolla, California. Dr. DeWitt Stetten, Jr., Deputy Director for Science, and Dr. Leon Jacobs, Associate Director for Collaborative Research, NIH, presided. In accordance with Public Law 92-463 the entire meeting was open to the public.

Committee members present were:

Drs. Edward A. Adelberg; Ernest H.Y. Chu; Roy Curtiss, III; James E. Darnell, Jr.; Stanley Falkow; Donald R. Helinski; David S. Hogness; Elizabeth M. Kutter; John W. Littlefield; Wallace P. Rowe; Jane K. Setlow; John Spizizen; Waclaw Szybalski; Charles A. Thomas, Jr.; and William J. Gartland, Jr. (Executive Secretary).

A Committee roster is attached. (Attachment I)

The following ad hoc consultants to the Committee were present:

Dr. Paul Berg, Stanford University School of Medicine, Stanford, California
Dr. Roy Britten, California Institute of Technology, Pasadena, California
Dr. Peter Day, Connecticut Agricultural Experiment Station, New Haven, Conn.
Dr. Rolf Freter, University of Michigan Medical School, Ann Arbor, Michigan
Dr. Edwin Geldreich, Environmental Protection Agency, Cincinnati, Ohio
Dr. Emmettee Redford, Lyndon Baines Johnson School of Public Affairs, Austin, Tex.
Dr. Maxine Singer, National Cancer Institute, NIH, Bethesda, Maryland

The following liaison representatives were present:

Dr. Richard Hedrich, National Endowment for the Humanities
Dr. Herman Lewis, National Science Foundation
Dr. Elena Nightingale, National Academy of Sciences

Other National Institutes of Health staff present were:

Dr. Emmett Barkley, NCI; Mrs. Betty Butler, NIGMS; Mrs. Sylvia Cunningham, NIAID; Dr. Irving Delappe, NIAID; Dr. Malcolm Martin, NIAID; Dr. Barbara Sanford, NCI; Dr. Bernard Talbot, OD; Dr. Alfred Webb, NIAID.

Others in attendance for all or part of the meeting were:

Mr. George Alexander, Los Angeles Times; Dr. Sidney Brenner, Medical Research Council, Cambridge, England; Dr. A.I. Bukhari, Cold Spring Harbor Laboratory of Quantitative Biology; Dr. J. Paul Burnett, Eli Lilly and Company; Dr. George Carsen, National Institute of Occupational Safety and Health; Dr. Stanley Cohen, Stanford University School of Medicine; Mr. John Collins, Stockheim, Germany; Dr. George Connell, Center for Disease Control; Dr. Denise Galloway, Cold Spring Harbor Laboratory of Quantative Biology; Dr. Rae Goodell, Massachusetts Institute of Technology; Dr. Vickers Herschfield, University of California, San Diego; Dr. Eva Mosharrafa, University of Minnesota; Dr. James McCullough, Congressional Research Services, Library of Congress; Dr. Louis Muschel, American Cancer Society; Mr. Colin Norman, Nature; Mr. Michael Rogers, Alfred Knopf Publishers; Dr. Winston Salser, University of California, Los Angeles; Dr. Joseph Sambrook, Cold Spring Harbor Laboratory of Quantitative Biology; Mr. Clifford Smith, San Diego Union; Dr. John Tooze, European Molecular Biology Organization; Ms. Pat Tucker, Time; Mr. Nicholas Wade, Science; Ms. Janet Weinberg, Science News; Dr. Richard Young, National Aeronautics and Space Administration.

I. CALL TO ORDER

Dr. Stetten called the meeting to order and expressed Dr. Fredrickson's regrets on being unable to attend the meeting. Dr. Stetten reminded the Committee that it is advisory to the National Institutes of Health, and that proposed guidelines are not regulations until officially adopted by the NIH. Dr. Stetten said that only members of the Committee may make motions and vote. The Chairman will vote only in the event of a tie vote. However, he said that anyone, who wished to enter into the discussion, will be recognized by the Chair. He asked that comments be limited to five minutes in duration. The Committee unanimously voted that it had no objection to Dr. Rae Goodell's request to tape record the entire meeting for the Massachusetts Institute of Technology Project on the Development of Safety Guidelines for Recombinant DNA Research.

Dr. Jacobs announced that an NIH Manual issuance dealing with recombinant DNA molecules has been prepared and is being commented upon at present. He also said that the NIH has prepared a letter to send to all grantees working with recombinant DNA molecules or who might potentially work with them for information about ongoing or proposed experiments.

II. CONSIDERATION OF MINUTES

The Minutes of the July 18-19, 1975 meeting were not considered, as Dr. Stetten said that the purpose of this meeting was in essence to reconsider the deliberations of the July meeting.

III. WORKSHOP ON DESIGN AND TESTING OF SAFER PROKARYOTIC VEHICLES AND BACTERIAL HOSTS FOR RESEARCH ON RECOMBINANT DNA MOLECULES

Dr. Helinski summarized the results of the workshop which was supported by the National Institute of Allergy and Infectious Diseases, and held in La Jolla on December 1-3, 1975. Approximately 60 scientists attended the workshop, organized by Drs. Helinski, Curtiss, Falkow and Szybalski, to consider host-vector systems. Dr. Helinski reported that there was a consensus that an EK2 plasmid and λ phage have been developed, which will meet the criteria for EK2 as stipulated in all 3 versions of the guidelines. (e.g. "Hogness", "Woods Hole" and "Kutter"). He emphasized that additional tests are required to confirm the EK2 properties of these 2 vectors, but it is anticipated that the vectors will meet the test. Therefore, it is hoped that EK2 vectors will be available soon. In general, EK3 host-vectors were not considered at the workshop. Dr. Helinski reported that a summary statement will be prepared by the organizing committee, and that it will be published in the Nucleic Acid Recombinant Scientific Memoranda, and possibly elsewhere.

IV. NIAID CONTRACTS FOR CONSTRUCTION AND TESTING OF SAFER HOSTS AND VECTORS

Mrs. Cunningham reported on the status of NIAID contracts for the construction and testing of safer hosts and vectors. She said that Requests for Proposals were issued on October 8, 1975 for the following 5 areas: construction of phage, plasmids and E. coli hosts, and survival testing and genetic testing of the constructed hosts and vectors. She said that the deadline for receipt of proposals is January 5, 1976, and that NIAID hopes to award contracts in March or April, 1976. She announced that copies of the RFPs were available at the meeting. In response to a question, Mrs. Cunningham said that applicants outside of the United States can submit proposals.

V. GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

The bulk of the two-day meeting was devoted to consideration of recommendations to the NIH for guidelines for research involving recombinant DNA molecules. For its deliberations the Committee used the Variorum Edition of the guidelines, which displayed the "Hogness", "Woods Hole" and "Kutter" guidelines side by side, paragraph by paragraph. The Committee voted to limit discussion of each paragraph to 10 minutes. If the discussion proceeded beyond 10 minutes, consideration of the paragraph was deferred until later in the meeting. The

Committee agreed that in cases in which there was no discussion of a specific item the Chairman would have the discretion to choose the version of his choice in preparation of the final document. The Committee then proceeded to consider the guidelines. In many cases the Committee did not comment on the different versions of specific items, thereby leaving the choice to the Chairman. In some cases the Committee voted to recommend one of the versions of a specific item with or without additional modifications. In other cases the Committee added new material or completely rewrote entire sections of the document. At the end of the discussion on the guidelines, the Committee unanimously voted for adoption of the document. The proposed Guidelines for Research Involving Recombinant DNA Molecules (Attachment II) represents the final form of the document prepared by the Committee and the Chairman.

The Committee went on record that the members had read all the communications received in response to the guidelines drafted at the July 1975 meeting, and that the Committee has taken into consideration all these points of view. The Committee felt that it has made improvements in the document in the light of new knowledge. Throughout the discussions it was understood that these guidelines will be subject to revision at future meetings.

It was agreed that the proposed guidelines will be sent to all attendees of the Asilomar Conference on Recombinant DNA Molecules. An announcement in the Federal Register will invite public comment on the guidelines. In addition, announcements on the availability of the guidelines will be placed in Nature, Science and the Proceedings of the National Academy of Sciences. The guidelines will also be distributed to industry and scientific societies for their information.

VI. IMPLEMENTATION

With regard to one aspect of implementation of guidelines, the Committee passed a resolution that for the time being responsibility for certification of putative EK2 strains and publication of information on which it makes its certification lies with the Committee. It was agreed that EK2 hosts and vectors should be published in the Nucleic Acid Recombinant Scientific Memoranda, and placed in central stock centers.

The Committee also passed a resolution that those workers who have constructed clones under the Asilomar guidelines should consult the Committee regarding their future use.

The Chairman was asked if the NIH would explore what impact the Committee can have on industrial applications of recombinant DNA technology. Dr. Stetten said that he will convey the concern to the Director of the National Institutes of Health, but that the NIH is not a regulatory agency. He will explore the possibility of inviting a lawyer versed in this area to the next meeting.

VII. A PROPOSED EXPERIMENT

Dr. Brenner proposed that an experiment be conducted to test whether biological mechanisms exist to transfer DNA from a lower organism to a higher organism. The experiments to be conducted under P4 conditions would in outline form be as follows: polyoma would be inserted in an EK1 plasmid, the plasmid would be put into an EK1 host, and used to populate new-born germ-free mice. The mice would be monitored by checking serum for antibodies, pathology, etc. Dr. Brenner estimated that an experiment with 100 mice would result in approximately 10^{13} genome doses per day. Controls would involve mice populated with bacteria carrying the plasmid without the inserted polyoma virus, and mice innoculated with polyoma virus. It was emphasized that other variations of this experiment and other controls need to be considered. Concern was expressed about the possible extrapolation and over-interpretation of a negative result. However, it was felt that such an experiment has a high probability of being informative. The Committee unanimously passed a resolution that the NIH with due haste facilitate the conduct of such an experiment under P4 conditions, and with the input of consultants. The Committee will comment on the design of the experiment.

VIII. SUBCOMMITTEE TO CONSIDER EXPERIMENTS

A subcommittee composed of Drs. Szybalski (Chairman), Hogness, Rowe and Spizizen was appointed to consider design of other experiments to be performed at NIH or under contract to provide information about biohazards.

IX. REVIEW OF RESEARCH PROTOCOLS

The Executive Secretary will select members of the Committee to assist on an interim basis in the review of a number of research grant and fellowship applications involving recombinant DNA molecules as to the adequacy of the physical and biological containment proposed by the applicants.

X. DATES OF NEXT MEETING

The Committee will meet in late March or early April 1976 on dates to be selected by the Executive Secretary.

XI. ADJOURNMENT

The meeting was adjourned at 10:30 p.m., December 5, 1975.