UNIVERSITY OF CALIFORNIA
SAN FRANCISCO MEDICAL CENTER

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO — SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE — SAN FRANCISCO, CALIFORNIA 94122

Department of Microbiology

April 20, 1971

Dr. John H. Kreisher
Associate Scientific Director
THE COUNCIL FOR TOBACCO RESEARCH-U.S.A., INC.
110 East 59th Street
New York, N. Y. 10022

Dear Doctor Kreisher:

Thank you for your invitation to attend your Conference "Alterations in Gene Expression Carcinogenesis". I shall be happy to do so.

I assume the meeting will begin at 9 A.M. on the 5th, but would appreciate confirmation of this. If you have a list of these planning to attend, I would appreciate seeing it.

Yours,

Harold E. Varmus

Harold E. Varmus, M. D.
Department of Microbiology

HV:le.

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.
900 THIRD AVENUE
NEW YORK, N.Y. 10022

ROBERT F. GERTENBACH
PRESIDENT

May 7, 1985

Harold E. Varmus, M.D.
Professor of Molecular Virology
Dept. of Microbiology & Immunology
University of California
San Francisco, CA 94143

Re: Grant #1687RJ

Dear Dr. Varmus:

The Council For Tobacco Research - U.S.A., Inc. is pleased to award you a renewal grant in the amount of $133,099 for the period from July 1, 1985 through June 30, 1986 for the study proposed in your application dated November 20, 1984. It is understood that this grant is made subject to acceptance by the university authorities as heretofore.

The award is made without guarantee of support beyond June 30, 1986, even though we recognize that your application proposes a study extending beyond that date. Therefore, if by November 30, 1985 you submit to us a formal renewal application, including a report of your progress to date, your request will receive consideration in competition for available funds.

Your attention is called to the enclosed "Important Procedural Information for Grantees." Please fill in the attached "Notice of Research Project" and return it to me.

Drs. Vincent Lisanti and David Stone, Associate Research Directors, will represent our scientific staff as primary contact with your grant. The will be the persons to consult about any questions or problems that may arise, and should be kept informed about the progress of the study.

Cordially,

R. F. Gertenbach

Robert F. Gertenbach

RFG/s

Enc.

CC: Ms. Lorraine Petrakis

bcc: Auditor, LP, RO'K, MONITOR, DC, FILE

JD-093881

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE
Department of Microbiology
and Immunology

SAN FRANCISCO, CALIFORNIA 94143

November 7, 1983

Robert C. Hockett, Ph.D.
Research Director
The Council for Tobacco Research
110 East 59th Street (9th Floor)
New York, New York 10022

Dear Dr. Hockett:

In accord with the policy you described for me during our phone conversation last week, I am writing to outline the basis of a request I would like to make for funding from your Council.

For the past decade, my colleagues and I have been engaged in the study of retroviruses: the manner in which they replicate, the origin and nature of the genes they use to transform cells and induce tumors, and several other aspects of the behavior of this unusual class of agents. In the past few years, we have also been working with the hepatitis B viruses of man and ground squirrels, viruses with oncogenic potential that also prove to replicate in a manner that resembles retroviruses. Although it would be inappropriate here to review in detail the contributions our group has made in these areas, findings central to issues raised in this proposal include: the discovery that retroviral oncogenes are derived from normal cellular genes; descriptions of many steps in the retrovirus life cycle, including the structure and location of integrated (proviral) DNA; demonstration that retroviral proviruses can act as insertional mutagens to inactivate or activate genes at integration sites; identification of novel cellular oncogenes as rearranged genes in tumors; and definition of a transcriptional enhancer function in retroviral DNA that can affect expression of adjacent cellular genes.

Several of these ideas have stimulated our recent interest in the use of oncogenic retroviruses as insertion mutagens to identify cellular oncogenes. We have been pursuing this general notion in four experimental arenas. (i) Avian leukosis viruses (ALVs) initiate induction of B cell lymphomas by insertional activation of c-myc, a cellular oncogene first identified by its homology to the viral oncogene, v-myc. The c-myc gene has now been implicated as well in a variety of murine and human tumors, and novel genes related to c-myc have recently been implicated in additional human tumors. Nevertheless, we have only a primitive idea of what this gene and its relatives do in health or disease. (ii) Another group of avian tumor viruses, the myeloblastosis-associated viruses (MAVs), induce renal tumors (nephroblastomas) at high frequency and appear likely to cause significant insertion mutations in the process. We are now attempting to identify the mutational target(s) of the anticipated insertion mutations. (iii) The mouse mammary tumor virus (MMTV) acts as an insertional mutagen

during the induction of mammary carcinomas, and we have used the MMTV proviral DNA as a molecular tag to discover a novel oncogene, called int-1, that is normally silent in breast tissue but expressed as a result of the insertion mutations. (iv) DNA of hepatitis B virus (HBV) is frequently found in human hepatomas, though we as yet lack direct evidence for insertion mutations. On the other hand, we have recently found integrated HBV DNA and flanking cellular DNA to be ca. 50-fold amplified in one hepatoma, suggesting that unidentified genes in the vicinity may be instrumental in oncogenesis.

These four systems present a variety of opportunities based upon the gradient of knowledge we have about the mechanism of oncogenesis in each case. c-myc is clearly an important oncogene, associated with neoplastic potential by several criteria; the role of int-1 in cancer is thus far based mainly upon its involvement in MMTV-induced disease; and the mechanisms of MAV-induced and HBV-associated tumors are not yet established. The situation is further complicated by the considerable evidence for additional mutations---both at the sites of insertion mutations and in other cellular oncogenes---that contribute to tumorigenesis in the best-studied systems.

With the identification of c-myc and int-1 as probable instruments of oncogenesis and the likelihood of impeding identification of other oncogenes in renal and hepatic tumors, we wish to devote greater attention to the function of these oncogenes during neoplasia. We foresee several approaches---to be applied initially to c-myc and int---that go beyond the obvious (albeit necessary) identification of the protein products of such genes. (i) In vitro assays for the oncogenic activities of the genes (as cloned from both tumor and normal cells) will be developed. Weinberg and his colleagues have recently made a signficant step in this direction by devising an assay in rat embryo cells in which c-myc genes can collaborate with mutant ras genes to effect a neoplastic phenotype. We have learned this assay from Weinberg's laboratory and are attempting to modify it to produce short-term assays suitable for the alleles we have under study. We also wish to test cells from other lineages (e.g. mammary epithelium or B cell progenitors) as recipients in biological assays of putative oncogenes. (ii) Greater emphasis needs to be placed upon the use of cells from the appropriate lineage to attempt to "reconstruct" a tumorigenic cell by adding mutant oncogenes to it and returning the cells to the animal of origin. For example, we have in hand various mutant alleles from B cell lymphomas; we wish to introduce these into B cell precursors that are then returned to chickens to assess tumorigenicity. (iii) The function of oncogenes can be better assessed if they are conditionally expressed, e.g. if placed under the control of promoters responsive to hormones or other agents. We have been constructing recombinant molecules that have oncogenes under the control of MMTV (glucocorticoid-responsive) and metallothionein (heavy metal-responsive) promoters for this purpose; these now need to be introduced into appropriate biological contexts. (iv) Retroviruses can be used as genetic vectors to carry virtually any gene into a variety of host cells in vivo. We have constructed a number of suitable vectors for gene transfer into mice and now wish to use them to carry prospective oncogenes. These vectors may also be useful for the isolation of novel oncogenes. (v) Confidence in c-myc as an important oncogene has been greatly enhanced by finding it affected in several human tumors. In addition to exploring the

functional significance of mutant human c-myc alleles, we wish to search for involvement of int-1 (and other as yet unidentified oncogenes) in various human malignancies, starting with surgical samples and cell lines of breast, kidney, and liver cancers. These efforts will employ both the oncogenes in hand as molecular probes for rearrangements or altered expression and biological assays under development as means to identify new oncogenes.

The experiments to be proposed will require at least three years of support at a level of about $125,000 per annum. The expenses to be covered will include salary support for a technical associate, animal purchase and care (especially for nude mice), consumable supplies for cell culture, molecular cloning, and biochemical work; and a number of miscellaneous items. Although the funds will directly support only this laboratory, they will be used to assist efforts in which I collaborate with a number of other UCSF faculty; among these are Drs. J. M. Bishop, Director of the Hooper Foundation; E. Cadman, Director of the Cancer Research Institute; and D. Ganem, Assistant Professor of Medicine and Microbiology and Immunology.

I look forward to hearing from you at your earliest convenience about the suitability of this application.

Sincerely,

Harold Varmus

Harold E. Varmus, M.D.
Professor

HEV/jm

THE COUNCIL FOR TOBACCO RESEARCH-U.S.A., INC.

SUPPORTING BIOMEDICAL INVESTIGATION

900 THIRD AVENUE
NEW YORK, NY 10022
(212) 421-8885

JAMES F. GLENN, M.D.
CHAIRMAN OF THE BOARD
CHIEF EXECUTIVE OFFICER

February 1, 1995

James S. Todd, M.D.
Executive Vice President
American Medical Association
515 North State Street
Chicago, Illinois 60610

Dear Dr. Todd:

Your letter of November 8, 1994, addressed to the deans of a number of medical schools, has been brought to my attention. I feel that a response is required in view of the serious inaccuracies in your letter and, in particular, your misleading portrayal of the Council for Tobacco Research-U.S.A., Inc. as a public relations pawn of the tobacco industry.

You state that "the American Medical Association (AMA) has learned that many medical schools continue to accept funding from tobacco companies or 'research' institutes set up by the tobacco industry." Did you mean to imply that CTR is not "really" a research institute? If so, what basis do you have for such a statement? Have you, in fact, reviewed the research which CTR has sponsored or is sponsoring? Suspecting that you have not done so, I am enclosing a copy of our most recent annual report, including abstracts of scientific research supported during the past year at a level approximating 20 million dollars. The full publication of these various reports is contained in prestigious peer-reviewed journals.

Your statement suggests that the AMA has only recently learned of CTR's support for biomedical research, when in fact this support has been ongoing for some 40 years. During that same interval, the American Medical Association also distributed research funds on behalf of the tobacco industry, particularly in the investigation of nicotine and its physiological effects. Indeed, my laboratory at Duke University Medical Center was the recipient of such a grant some years ago.

You state that "tobacco research institutions such as the ... Center (sic) for Tobacco Research ... all funded fully by tobacco companies are used by the tobacco industry as part of its overall public relations strategy..." The tobacco industry, to the best of my knowledge, has certainly not used CTR in this manner during my tenure. Indeed, the tobacco industry does not participate in any way in selecting the research sponsored by CTR, nor does the industry seek to influence CTR grantees in any fashion. On the contrary, CTR encourages

these independent investigators to publish their results, whether findings might be favorable or unfavorable to the tobacco industry.

You further state that "tobacco research funds help the industry convince policy makers and the public that they have legitimate research projects underway that continue to search for links between smoking and ill health." The risk factor of smoking has long been known, not only in the scientific community but in the lay community as well. However, the fundamental process of many diseases remains obscure, and much of the research which CTR supports is directed toward an understanding of basic biomedical factors such as cellular and molecular biology, immunology and genetics, all predisposing to various disease processes. You will be interested to know that Dr. Harold Varmus, Director of the National Institutes of Health, recently explained at the annual Cold Spring Harbor Laboratory Symposium that "only through basic research will we uncover the general principles underlying the complexities of cancer ... out of basic cancer research will come new methods of assessing cancer risk and the best course of treatment." Dr. Varmus, incidentally, is a former recipient of a CTR grant which supported his early investigations, and he is one of three CTR grantees who have gone on to win the Nobel Prize in Medicine.

You then state that "the industry uses the funds to silence universities and researchers, and to link prestigious institutions with the industry, thus buying respectability." The clear implication is that investigators, deans and medical schools can be compromised for the price of grants-in-aid. This is not only a false statement, but is insulting to the medical research community at large. Were I still a medical school dean - and I have been a dean twice - I would be seriously offended by this thinly veiled attack on my integrity. I am confident that if you were to discuss the matter with investigators supported by CTR funds, none of them would support your insinuation that he or she has been compromised in any way. I would ask that you cite any examples to the contrary, and that you identify any "links" between any research institutions and the tobacco industry so that we can all know whom you are vilifying.

Your letter is also inaccurate with respect to the amount of funding afforded the biomedical research community by CTR and the numbers of projects and investigators supported. The facts are that through 1994, CTR has provided about 240 million dollars in research funding for over 1,400 grants and contracts to more than 1,000 different grantees. This research has resulted in a total of over 5,000 publications in numerous highly regarded journals through 1994. Arrangements for publication are made by the investigators, not by CTR. These are matters of public record, summarized in our annual reports.

Your comments comparing the levels of funding for research with advertising budgets are totally irrelevant. These comments are also unfair, since no comment has been made about how much funding by other U.S. industries (such as the petroleum, chemical,

automobile, construction, and food and dairy industries) have provided for basic biomedical investigation of diseases and disabilities that have been associated with their products.

You state that a "survey of industry-funded scientists revealed that nearly 80% of them indicated that none of their research had ever examined the health effects of tobacco use." The survey to which you allude was reported in The American Journal of Public Health and reflected responses of only 77 current or former grantees out of the more than 1,000 investigators whom we have supported. As indicated previously, the research which we have funded does not "focus on" tobacco and health, but rather attempts to elucidate basic disease processes. As a matter of fact, 20-25% of lung cancer victims have never been smokers and 90-95% of smokers never develop lung disease. These facts would suggest to a fair minded observer that there are numerous risk factors involved and that genetics may play a role, just as in retinoblastoma, familial colon cancer and a variety of other malignancies. You may be interested to know that CTR - along with the NIH, American Cancer Society, and other funding agencies - supported some of the fundamental genetic research upon which our current understanding of these particular diseases is based.

With regard to your comments concerning the opinions of Judge H. Lee Sarokin, your misleadingly incomplete information should be rectified. First of all, Judge Sarokin's opinion to which you refer was written in April 1988, more than six years ago, not in "the early 1990's." CTR was not a defendant in that action (or in any action before Judge Sarokin). Judge Sarokin therefore never has heard or seen a presentation by CTR, and to our knowledge he has never reviewed any CTR research data. Further, it is my understanding that the jury in this particular case rejected the charges of a fraud involving CTR.

You state that to keep its profits high, the tobacco industry creates public doubt about nicotine addiction, tobacco's role in disease and "twists research findings to its own ends." You seem to be asserting that CTR grantees' research has been misused or "twisted" by the industry. To the best of my knowledge that has never occurred. If you are asserting that it has occurred, I would request that you provide specific examples.

You state that "medical school use of tobacco profits to fund this research compromises the trust, built over decades, with the public." What trust, and in whom? Is it the trust that the medical schools generated during the last four decades during which they were receiving ongoing research support from CTR or while they were receiving funding from the tobacco companies through the American Medical Association? I would suggest that an accurate appraisal of public trust would find that there is a great deal more public confidence in our medical schools than in the American Medical Association.

In summary, your letter is misleading, inaccurate, unscientific and transparently political. The fact is that the American Medical Association abdicated its scientific responsibilities more than twenty years ago when it ceased to support its scientific program and chose to become a socio-economic and political body. I admit to great personal disappointment at that turn of events, particularly since I had worked diligently as both a Secretary and Chairman of one of the scientific sections of the AMA. It may be that this disappointment is widely shared in academic medicine since, it is my understanding, a majority of medical school faculty members in the United States do not belong to AMA. Certainly the AMA would not seem to be in any position to preach to the deans of our medical schools, who are people of highest integrity. I am sending a copy of this letter to each of them.

Sincerely,

James F. Glenn, M.D., F.A.C.S., F.R.C.S. (Hon.)

JFG:mm

cc: Deans, U.S. Medical Schools

The Scientific Advisory Board
of
The Council for Tobacco Research - U.S.A., Inc.
extends

CONGRATULATIONS

to

DR. LOUIS J. IGNARRO AND DR. FERID MURAD

co-recipients of the

1998 Nobel Prize in Physiology or Medicine

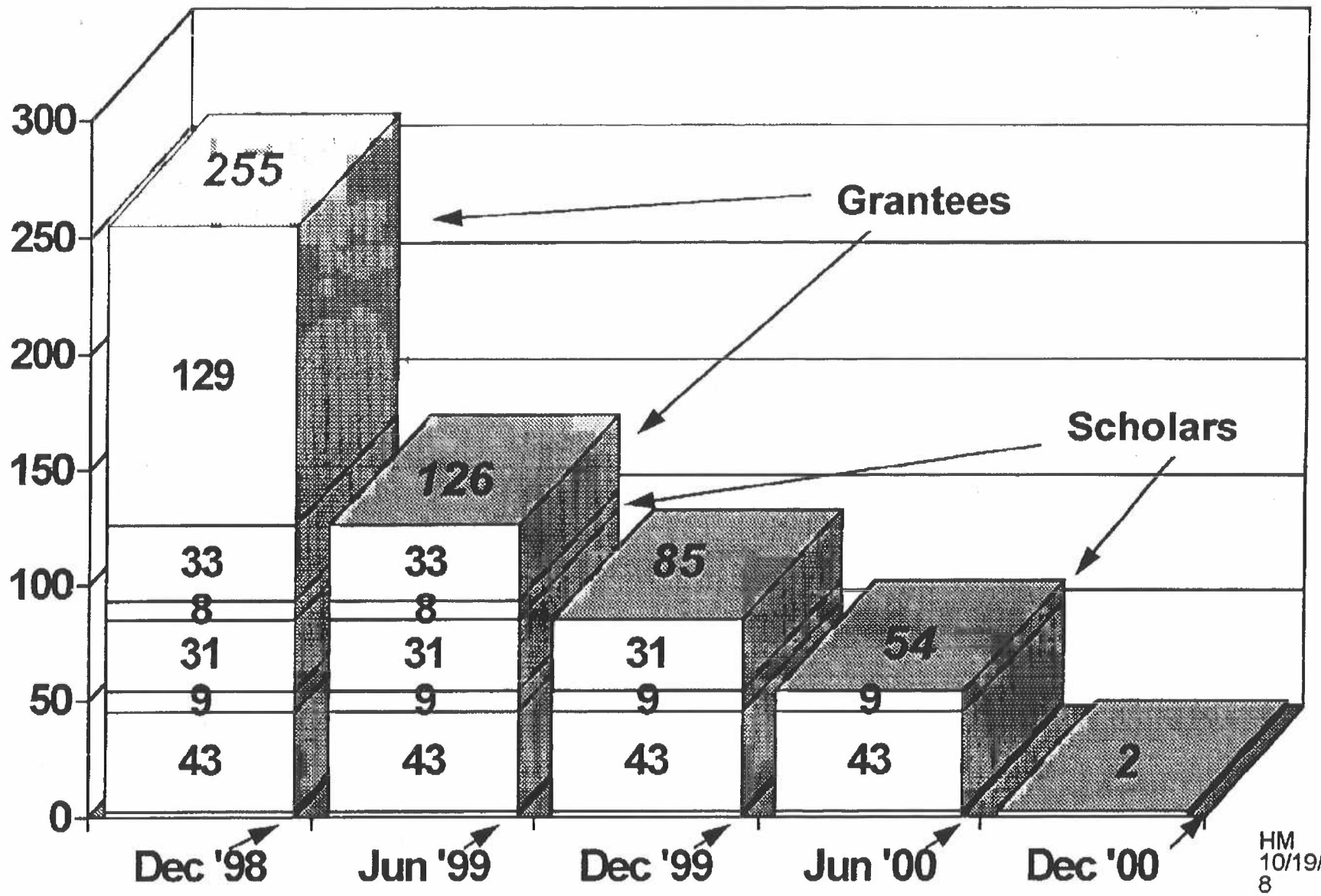
Dr. Ignarro and Dr. Murad have received financial support for their research under grants from The Council, as have three other Nobel prize winners:

Drs. Baruj Benacerraf, Stanley Cohen and Harold Varmus

The Council, its Scientific Advisory Board and its sponsor companies in the tobacco industry are proud to have participated in supporting the outstanding contributions of these five very distinguished biomedical investigators.

The Council for Tobacco Research-U.S.A., Inc.
900 Third Avenue
New York, NY 10022

NUMBER of ACTIVE CTR GRANTEES & SCHOLARS



HM
10/19/9
8