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Drug Discovery Groups Recompetition Approved, But DCT Advisors Scale Back Model Development

Advisors to NCI's Div. of Cancer Treatment recently gave concept approval to the recompetition of the National Cooperative Drug Discovery Groups and committed $4 million in first year funding for the four year grant program. But the DCT Board of Scientific Counselors also refused to set aside funds for the recompetition of the National Co-

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In Brief

NCI Scientist Accused Of Taking 'Payoffs' From Drug Firms; GM-CSF Wins FDA Approval

NCI SCIENTIST Prem Sarin, former administrator of the Laboratory of Tumor Cell Biology, was accused of accepting three payoffs totalling $33,000 for conducting research for drug companies, investigators for the General Accounting Office testified last week. GAO investigators Leo D'Amico and Fred Chasov told the House Energy & Commerce subcommittee on oversight and investigations that Sarin used federal labs and staff to conduct research for the companies, Pfizer Laboratories and Asta Pharma, and then directed the funds into his personal bank accounts. Documents used to clear the lab work apparently contain the forged signature of Sarin's boss, Laboratory Chief Robert Gallo, the investigators said. Sarin was not available for comment, but Gallo testified that Sarin denied that he had done work for drug companies. The case is under investigation by the HHS inspector general and the U.S. attorney's office. . . . **IMMUNEX CORP.** received FDA approval last week to market GM-CSF, trade name Leukine, to speed myeloid recovery in patients undergoing autologous bone marrow transplant to treat non-Hodgkins lymphoma, Hodkin's disease and acute lymphoblastic leukemia. The drug is available immediately. Hoechst-Roussel Pharmaceuticals Inc., which collaborated on GM-CSF, will co-market the drug under the name Prokine. . . . **NCI SIGNED** a collaborative research and development agreement with Bristol-Myers Squibb for the development of taxol. NCI will share its preclinical and clinical data on taxol exclusively with Bristol-Myers, and the company will undertake development of the agent. NCI and the Dept. of Agriculture are working on an interagency agreement to ensure access to USDA-owned stands of the Western yew tree, from which taxol is derived. . . . **RAYMOND LENHARD** has been appointed director of community programs at John Hopkins Oncology Center. He is professor of oncology at the School of Medicine and vice chairman of American Cancer Society professional education committee.

Drug Discovery Groups Recompetition Ok'd, But Model Groups Scaled Back

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operative Anticancer Model Development Groups, which currently funds two groups. NCI staff had requested $2 million in first year funding for the grant program. Instead, the board approved the concept as a program announcement.

The board also gave concept approval to two new RFAs: one that would fund five multi-institutional groups to study biological response modifiers and a second that would provide three grants for three-dimensional radiologic imaging studies.

Following are the concept statements:

National Cooperative Drug Discovery Groups. Recompetition of an RFA, first year award $4 million, four years.

The Developmental Therapeutics Program drug discovery effort has been restructured to attain a more desireable balance between rational approaches to the elucidation of new and improved anticancer treatments and the traditional, more empiric screening approaches such as the in vitro and in vivo screening projects in operation at the Frederick Cancer Research & Development Center in conjunction with other contract laboratories.

The goals of the multi-institutional NCDDGs are 1) the conceptualization and creation of new drugs and strategies to improve cancer treatment and curability, 2) the establishment of preclinical assays to examine the new drugs and strategies for both relevance to the rationale underlying their synthesis as well as to assessment of their potential for clinical efficacy; culminating in 3) the selection of new agents and strategies for development to the clinic.

DTP is seeking concept approval to reissue to RFAs, this for National Cooperative Drug Discovery Groups with either a disease oriented or general mechanism of action based strategy, and a companion RFA for National Cooperative Anticancer Model Development Groups. Currently there are 21 funded groups with a total budget of about $13 million. Two groups funded at $833,311 have expired. During FY1991, three additional groups funded at $1,692,343 will begin their final year. We expect them to respond to one of these RFAs and thus compete against applications from new groups. In this way, we envision continued improvement in the quality of the NCDDG program while maintaining a substantially level total budget.

It is proposed that cooperative agreements be established to form NCDDGs for treatment specific human malignancies or to exploit new molecular targets as sites of action for the discovery of more effective therapies. Each group will be assembled by a principal investigator to form a multidisciplinary and multi-institutional consortium of those skills needed to prosecute successfully the conceptualization, development and preclinical investigation of new, rationally based treatments. The biological or biochemical targets for attack will be selected by the applying group. If a specific tumor type target is selected by an applying group, they will be expected to show the relationship between the proposed research and anticipated preferential efficacy against the chosen malignant disease.

The PI will be the conceptual focus of the group, and, depending on the needs of the project, will extend invitations to appropriate scientists, regardless of their institutional affiliations, to participate as group members. The cooperative agreements may involve academic, nonprofit and/or commercial institutions.

Michael Grever, acting director of the Developmental Therapeutics Program, said NCI's in vitro screening system for anticancer drugs became operational last April and 6,000 drugs went through the chemical screen last year. The objective of the drug discovery group program is to "get drugs to phase 1 investigators," he said. About half of the effort is devoted to drugs with known chemical structures and half to natural product extracts.

Last year the drug discovery groups referred 210 possible anticancer compounds to the Biologic Evaluation Committee. Of those, 108 were reviewed and 67 were selected for further evaluation. The BEC for AIDS is working on 15 anti-HIV candidates and expects to select two for clinical testing in 1991: "Uniroyal Jr." and a protease inhibitor.

"We do need a special mechanism for drug discovery groups," said board Chairman John Niederhuber.

DCT Director Bruce Chabner noted that pharmaceutical firms "are putting more into these drugs than we are."

"Even those groups that weren't funded established ties with industry, so it has been very beneficial," said Phillip Crews, Univ. of California (Santa Cruz).

"How do we know whether the amount of money is appropriate? Why not put the money in the R01 pool?" asked Ronald Levy, Stanford Univ.

Chabner said the R01 pool could not provide the ties to industry that this program provides. He noted that the idea for the program came from R01 investigators.

"I would rather see money put into R01s," said board member JoAnne Stubbe, Massachusetts Institute

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of Technology. "I'm wary about ties between industry and academia."

"Many bright investigators don't know how to get from the lab to clinical research," replied Grever.

The program has generated "a tremendous amount of excitement," said Crews. "To decrease the program at this point would be a mistake."

The concept was approved, with Stubbe opposed.

National Cooperative Anticancer Model Development Groups. Recompetition of an RFA, proposed first year award $2 million, four years.

While the DTP screening and NCDDG programs are devoted to the discovery of new anticancer agents, the ultimate value of a new agent will depend on the extent to which the preclinical model used for its selection predicts for clinical efficacy. Thus, there is a continuing need for the development of highly sophisticated preclinical assays that might discriminate for more effective clinical candidates. Also, it is important to recognize that there are creative biologists, molecular biologists, biochemists, immunologists, pathologists and other scientists whose primary interests may not relate to drug discovery per se and who may not be in a position to enlist the collaboration of appropriate medicinal and organic chemists to form viable drug discovery groups in the tradition of the NCDDG program. Nevertheless, these scientists are in a position, with NCI assistance, to translate fundamental findings to practical and predictive preclinical models for anticancer treatment discovery.

Currently DTP supports two model development groups. One project, headed by Geoffrey Wahl of the Salk Institute for Biological Studies, is developing methods to detect, characterize, and eliminate episomes from cancer cells. Episomes, a potential drug target, consist of small circular pieces of DNA that contain oncogenes, drug resistance genes, or other amplified DNA sequences. Another project led by Ralph Reisfeld of the Research Institute of Scripps Clinic is developing a model of metastases of human melanoma in mice with severe combined immunodeficiency. The mice have been successfully repopulated with human peripheral blood lymphocytes to establish a human immune system in these otherwise immunodeficient animals. This model provides a method for evaluating the efficacy of genetically engineered recombinant fusion proteins between antitumor antibodies and cytokines.

It is proposed that the National Cooperative Anticancer Model Development Group program be expanded to assist investigators in the development of preclinical assays to be used in discovering and evaluating the anticancer potential of new drugs and strategies. Unlike the NCDDG program where the main emphasis is on the design of the agents to be tested, the main objective of this program is the development of preclinical assays of potential clinical predictiveness.

A group could consist of a consortium of multidisciplinary and/or multi-institutional laboratory programs from academic, nonprofit, or commercial organizations whose research activities are clearly interrelated and aimed at a well define objective. Alternatively, a groups could consist of a single laboratory program working in collaboration with NCI extramural staff under the provisions of a cooperative agreement. In either case, application for cooperative agreement will be assembled by the principal investigator to include those skills needed for successful development of new preclinical assays for the identification and preclinical therapy related evaluation of new anticancer treatments. Model development may be either mechanistically oriented or specific disease oriented. Successfully competing groups will be funded via cooperative agreements.

Four groups could have been funded with the $2 million requested in the RFA concept, but several board members said they were concerned about setting aside that amount from the research project grant pool. That amount could fund eight RO1 grants, Chabner said.

Levy said he thought the group studying multidrug resistance "would have done well in an RO1 study section."

Chabner said the concept could be advertised as a program announcement. "I sense a lot of concern about pulling a lot of money out of the RPG pool," he said.

"It just seems a little harder to defend this," Niederhuber said.

The board unanimously approved the concept as a program announcement.

National cooperative groups for the study of cancer therapy with biological response modifiers. Proposed new RFA, five awards, $200,000 per award per year, for a total of $1 million for the first year; project period four years.

The Biological Response Modifiers Program proposes to create a mechanism by which innovative, peer reviewed, investigator initiated approaches may be fostered to evaluate new agents or concepts.

It is proposed that cooperative agreements be established to form National Cooperative Groups for the study of cancer therapy with biological response modifiers for the design and execution of novel clinical trials of BRMs. Applicants will be expected to propose a novel plan for early clinical development, adequately supported by their own prior preclinical, and if appropriate, clinical results. The proposal should include evidence of access to the agents proposed for study, preclinical evaluation indicating that an investigational new drug filing is appropriate, and a detailed plan for a pilot clinical trial. NCI will facilitate the institution of a peer reviewed, investigator initiated trial, providing as needed, 1) NCI contractor supported production of agents, 2) where desireable NCI holding of the IND (in which case CTEP approval of the clinical protocol will be required), 3) assistance with toxicology testing, if necessary and appropriate, through a preclinical coordinator from DTP, 4) assistance with planning and support of a wider range of subsequent clinical trials, if appropriate, and 5) regulatory and technical expertise. Commitment of substantial NCI resources would also require DNC approval of the agents being tested.

Each group will be composed of the following elements: a principal investigator, one or more laboratory programs with the demonstrated expertise to design and carry out assays for the appropriate monitoring of patients on the study, one or more clinical programs each headed by a program leader with demonstrated expertise in conducting clinical trials of BRMs, and an NCI coordinator. The principal investigator will be the conceptual focus of the group. The proposal may include collaborators from the principal investigator's own institution, other institutions, or industry.

The structure of the NCGBRMs will thus parallel that of the national Cooperative Drug Discovery Groups. We anticipate that

participation in NCGBRMs will include academic, nonprofit, and/or commercial institutions. The multi-institutional approach may improve access to a wider range of creative talent. Application under this RFA may also be a logical step to develop agents arising in NCDDGs, P01s or R01s. Support for successful applicants will be via cooperative agreements.

Dan Longo, director of DCT's Biological Response Modifiers Program, which is the sponsor of the above concept, likened the structure of the proposed BRM "cooperative groups" to the National Cooperative Drug Discovery Group program. But board member Paul Carbone said the concept's title suggested the clinical cooperative group program. Carbone asked that the title be changed to reflect the fact that the program intends to "develop early clinical studies in biological therapy."

The concept was approved unanimously.

Quantitation of tumor response to treatment: a three dimensional approach. Concept for a new RFA, proposed first year funding $500,000, three grants each for three years.

Clinical investigations in oncology depend heavily on two dimensional radiologic techniques to determine tumor response to treatment. The major focus of this proposal is to optimize mathematical analysis of tumor volume based on three dimensional radiologic images in order to enhance evaluation of therapeutic efficacy of various treatment modalities/regimens in cancer patients and to facilitate comparison of clinical trials.

While the role of diagnostic imaging modalities in detection and delineation of neoplasms has been extensively studied, a fully adequate approach to serial evaluation of tumor response to treatment has not been developed. Until the present time, it has been difficult to obtain accurate tumor measurements, and volumetric analysis of tumor response to treatment has been usually subjective and qualitative rather than quantitative in nature. Major limitations in the accuracy and reliability of tumor measurements stem from the 2-D nature of imaging data display currently used for tumor volume analysis. Tumor response to treatment, however, is a complex 3-D phenomenon, and the use of 2-D imaging techniques is frequently inadequate for its full evaluation. The Diagnostic Imaging Research Branch workshop, "3-D Data Display and Analysis for Cancer Treatment Planning," in July 1990 confirmed the need for accurate tumor measurements in oncology and concluded that a 3-D approach is optimal for serial volumetric tumor analysis.

The workshop demonstrated that 3-D imaging can provide unique information for spatial tumor display and tumor volumetric analysis, which cannot be obtained by an other means. The participants agreed that there are two closely intertwined basic scientific areas of highest priority to the future advancement of tumor volumetric analysis: 1) automated "segmentation," or "tumor delineation," and 2) multimodality image "registration," or "superimposition" (e.g., CT, PET, conventional and metabolic chemical shift MRI, immunoimaging).

The specific goal of this proposal is the development and optimization of a quantitative analysis of tumor response to treatment based on 3-D medical imaging. The proposed research will stimulate the achievement of optimal tumor volumetric analysis by means of the development of advanced approaches to two critical basic computer science topics, automated image segmentation and multimodality image registration, and their validation and testing. This proposed RFA is expected to support three or four R01 grant applications in the area of volumetric tumor analysis.

Board members Mark Groudine, Robert Holden and William Hryniuk, responding to concerns about setting aside funds from the R01 pool, spoke in support of this program. "The technology is just now coming into play," Holden said.

"Here we do have clear evidence that the ideas are there," Hryniuk said. "I think this should be judged on its merits."

The concept was approved unanimously.

The board also unanimously approved a concept for an interagency agreement that would provide $100,000 over two years to the National Institute of Standards & Technology to carry out therapy simulated "Monte Carlo" calculations for proton particles.

DCT Advisors OK Recompetition Of Anticancer Drug Contracts

The National Cancer Institute's Div. of Cancer Treatment Board of Scientific Counselors recently approved the recompetition of four large contracts for the development of anti-cancer and anti-AIDS drugs.

Altogether, the board committed $6.57 million to the contracts, all of which last for five years. The concept statements were approved unanimously.

In addition to these four, the board also approved an RFP concept for recompetition of "Preparation of Anti-AIDS Bulk Drugs and Chemicals," at an estimated annual amount of $1.99 million, to be funded 100 percent with AIDS money (**AIDS update,** March 8).

Following are the concept statements:

Production of pharmaceutical dosage forms. Recompetition of a contract held by Univ. of Iowa. Estimated annual amount $434,000 (two thirds cancer funds, one third AIDS funds); five years; estimated total $2.17 million.

This contract makes available to the Div. of Cancer Treatment a facility for the manufacturing of freeze dried and liquid filled parenteral investigational drug products. The contractor also provides the capability of solid oral dosage formulation and production. Specifically, the contractor is engaged in 1) developmental studies of chemical agents leading to the formulation of clinical dosage forms, 2) small scale production and packaging of parenteral dosage forms for clinical use, 3) assay and quality control of prepared dosage forms. Data from final production reports are supplied to FDA as part of NCI's IND application. As a manufacturer of clinical drug products, the contractor must be registered with FDA and must comply with Good Manufacturing Practices.

We anticipate that several new compounds that have been approved by DCT's Decision Network Committee will require extensive formulation development and production of clinical dosage forms during the next contract period. More insoluble

compounds will be developed as sterile emulsions, and scale up studies will be required.

Each year, Iowa is involved with phase 1 batches of new clinical dosage forms for animal studies as well as the initial human studies. These products are manufactured and filed with FDA as well as the original IND filings. It is anticipated that four to six new drugs each for cancer and AIDS will be developed for clinical use each year during the contract period. In addition, drug supplies will be produced for ongoing clinical studies.

Currently, the production of parenteral dosage forms (lyophilized, liquid filled, large volume parenteral) takes place under three separate contract efforts:

--Development and production of dosage forms of anti-AIDS drugs (contract currently with Ben Venue Laboratories, concept for recompetition of this contract was approved by the BSC in Feb. 1990, first year funds $550,000).

--Production of clinical dosage forms of antitumor agents (contract currently with Ben Venue Laboratories, concept for recompetition approved by BSC in Oct. 1990, first year funds $1,116,300).

--Production of pharmaceutical dosage forms (contract currently with Univ. of Iowa, concept being considered here).

Upon approval of this project by the Feb. 1991 Board of Scientific Counselors, the parenteral portion of this contract will be consolidated with the other contract efforts for parenteral production into a generic RFP. The single RFP will result in a contract package for all parenteral manufacturing for the DTP. The small oral production component of this effort will be consolidated in a contract package for oral dosage form production.

Development of dosage forms and delivery systems for antitumor and anti-AIDS agents. Recompetition of contracts held by Univ. of Kansas, Univ. of North Carolina, and Univ. of Utah. Estimated annual amount $490,000 (50 percent cancer, 50 percent AIDS funding); five years, total amount $2.45 million.

The primary objective of this effort is to develop pharmaceutically acceptable parenteral dosage forms of new compounds with potential utility for the treatment of cancer and AIDS. As indicated, these compounds frequently do not inherently possess adequate solubility and stability for intravenous injection. For a number of years, the program has supported a contract effort to specifically resolve difficulties presented by these compounds. The complexity of the formulation development is expected to vary, and difficult assignments may require substantial development work. The contractor will be expected to carry out solubility determinations, evaluate approaches to improve water solubility, study the effects of pH, heat, oxygen, etc., on stability, prepare dosage forms on a pilot scale, and evaluate the delivery of the drug under simulated use conditions (after reconstruction and in intravenous fluids). The target of these investigations is a pharmaceutical dosage formulation that can be transferred to a contractor with manufacturing capability for scale up to a batch size for clinical evaluation.

Data from these studies will be transmitted to 1) contractors responsible for scale up manufacture, 2) FDA in support of investigational new drug applications, and 3) medical personnel handling these formulations.

Shelf life evaluation of clinical drugs. Recompetition of a contract held by Univ. of Georgia. Estimated annual amount $266,000 (100 percent cancer), five years, total amount $1.33 million.

The shelf life program has performed successfully in evaluating products prepared by DCT's contract manufacturers. Univ. of Georgia is conducting stability evaluations on over 200 separate lots of about 70 different chemical entities. The analytical methods must be validated in a way acceptable to FDA. In accordance with FDA guidelines, samples are held at -10, 4, 25, and 50 degrees C. Samples from each temperature are evaluated at the following time points: 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months. Cumulative reports are prepared at each time point on each lot and forwarded to DCT for review and filing. Annual inspections of reserve samples retained from every lot manufactured by DCT contractors are conducted as required by FDA. Approximately 400 inspections are performed each year.

It is anticipated that 20 to 30 new lots of formulated drug products will require shelf life testing each year during the new contract period. Six to eight of these will be new chemical entities. In addition, continuing studies on 150-200 lots will be completed.

Pathology and veterinary support for preclinical toxicology studies. Recompetition of a contract held by Pathology Associates. Estimated annual amount $125,000, (50 percent cancer, 50 percent AIDS), five years, total amount $625,000.

The Toxicology Branch of the Developmental Therapeutics Program of NCI is responsible for the preclinical evaluation of new antineoplastic and anti-HIV agents with clinical potential. This contract provides the branch with the ability to perform independent pathology peer review of the Investigational New Drug application directed drug toxicity studies; to conduct special reviews across studies in order to determine background incidence of various lesions; to perform special histological procedures; and, with a repository for storage of all pathology materials from past IND studies, to meet the requirements of the FDA for storage of these materials.

This contract also provides veterinary support to develop and implement new veterinary procedures for drug administration such as continuous intravenous infusion in different species and a central facility for storage, maintenance, and shipment of the infusion equipment used in the toxicology studies.

Pathology Associates Inc. set up a new pathology materials repository and moved all related materials from the previous repository. The repository routinely receives and ships pathology materials to and from the contract toxicology laboratories and other interest parties such as pharmaceutical companies.

Pathologists from PAI have performed 20 pathology quality assessment (peer) reviews on mouse, rat, and dog studies that were conducted on anti-AIDS drugs prior to study report finalization and filing with FDA as part of NCI's IND application. Another aspect of the contract is the ability to have a single pathologist review specific tissues across all studies at all contract laboratories.

Refinement of infusion procedures for drug administration has received considerable attention in the form of 1) developing procedures for performing continuous intravenous infusions in rats for up to 240 hours and in dogs for up to 30 days, 2) determining compatibility of infusion equipment with various experimental formulations and 3) continuously reviewing or evaluating infusion catheters, ports, and pumps for use in these studies. As an adjunct to this PAI has assembled and shipped all of the necessary infusion materials to the various contract laboratories on 16 occasions to support infusion studies being conducted at these laboratories.

In the area of veterinary support, PAI has conducted five site visits to contract toxicology laboratories to train and evaluate laboratory personnel in techniques including continuous infusion procedures, cardiac monitoring, cerebral spinal fluid sampling, and other related surgical procedures.

Emphasis on an independent pathology peer review will

remain an integral part of this contract as will the use of special histology procedures and the development or refinement of drug administration procedures.

ICCCR Participants Honor Cullen, Savagely Attack Tobacco Industry

The recent ICCCR International Conference on Cancer Prevention was dedicated to the memory of Joseph Cullen, a world leader in cancer prevention whose most important and far reaching contribution was his role in leading the federal government's campaign against tobacco use.

Cullen was director of the AMC Cancer Research Center in Denver at the time of his death from a malignant brain tumor last November. Before that he was deputy director of NCI's Div. of Cancer Prevention & Control, head of NCI's Smoking, Tobacco, & Cancer Program, and coordinator of all Dept. of Health & Human Services antitobacco efforts.

The conference, held at NIH's National Library of Medicine, featured a savage attack on the "tobacco cartel" for "exporting death" to third world countries and for targeting advertising and promotional efforts to youth, minorities, and the poor. Speakers described some of the steps being taken to combat the industry.

One of the more effective efforts appears to be the 25 cent per pack increase imposed by California starting January 1989. The revenue generated by the tax is earmarked for antitobacco education and health research.

David Burns, Univ. of California (San Diego) Medical Center, said that per capita consumption of cigarettes declined in California during the period 1980-1990 from 13 to less than nine. There was a five percent drop from 1987-1990, most of it after the tax went into effect. "California has a lower per capita rate of consumption than the rest of the U.S., and the decline is accelerating," Burns said.

Judith Mackay, who in the words of panel moderator Michael Pertschuk "conquered the tobacco industry in Hong Kong and has terrorized the tobacco industry and tobacco flacks," described the threat of U.S. tobacco exports to third world countries.

"One half billion people alive today will be killed by tobacco," said Mackay, who is director of the Asian Consultancy on Tobacco Control in Hong Kong. "Fifty million Chinese children alive today will die of tobacco related disease." Global tobacco related mortality will rise from the current 2.5 million a year to over 10 million annually by the year 2050.

"The bulk of this increase will lie in developing countries, where legislative and other measures, which in industrialized countries succeed in limiting the use of tobacco, do not exist or are at best inadequate," Mackay said.

"Of particular concern is the penetration of developing countries by the transnational tobacco companies, with aggressive promotional campaigns which include specific targeting of women, few of whom currently smoke in those countries," Mackay continued.

"The transnational tobacco companies advertise and market in ways long banned in the United States, for example selling cigarettes without health warnings, advertising on TV, and selling cigarettes with higher tar content than the same cigarettes sold in the U.S. Also, tobacco advertising revenue is a powerful influence in silencing the media from reporting on the hazards of tobacco, a particularly serious problem in developing countries where awareness of the harmfulness of tobacco is low.

"Transnational tobacco companies attempt to interfere with developing countries' own national public health laws, using political and commercial pressures to open markets and to promote foreign cigarettes. This has led not only to an increase in market share by foreign cigarettes, but evidence also points to market expansion, especially among young people.

"The entry of the transnationals leads either to a collapse of national tobacco monopolies or to their changing from a simple, unsophisticated government department which may still cooperate with health initiatives on tobacco, to an agency which copies the aggressive marketing and promotional behavior of the transnationals."

Mackay said that when efforts were made to ban smokeless tobacco in Hong Kong, they were defeated after interference by the U.S. State and Commerce departments and several U.S. senators, including Robert Dole (R-KS). Similar interference was effective in blocking antitobacco import efforts in Japan, led by Sen. Jesse Helms (R-NC).

"The president of Philip Morris gave credit to intervention of U.S. trade negotiators," Mackay said. "The president of RJR said, 'We expect such support from Congress. That's why we vote them in.'"

Mackay suggested that the United States could help limit growth in tobacco use in other countries by requiring the industry to adhere to the same standards required in the U.S.; by refraining from exerting pressures on foreign governments by both the industry and U.S. government related to opening markets to U.S. tobacco exports; and by sharing U.S. expertise in antitobacco efforts.

"The United States should be an exporter of health, not disease," she said.

Gregory Connolly, who, Pertschuk said, led the successful worldwide effort "to choke off expansion of smokeless tobacco sales," presented more details of the "transnational" tobacco companies.

Five transnational tobacco companies produce 40 percent of the 5.4 trillion cigarettes consumed each year and have assets in excess of $100 billion, said Connolly, who is director of the Office of Nonsmoking in the Massachusetts Dept. of Health. Philip Morris and British American Tobacco control approximately 20 percent of the world's market. Monopolies in nations with centrally planned economies produce 33 percent, and monopolies in capitalistic nations 17 percent.

"As smoking rates decline in the developed world and barriers to world trade become freer, the transnational tobacco companies expand operations to developing markets," Connolly said. "Once established, the transnationals introduce competition, transform how cigarettes are made, priced, and advertised, and come to dominate the market in time. Westernization of the market results in an increase in per capita cigarette consumption and in smoking among females in the developed world.

"Most developing countries protect their tobacco market for economic reasons and resist entry of the transnationals through bans or quotas, high tariffs, or bans on advertising. The transnationals counter these measures by sale of contraband cigarettes, direct or indirect advertising, support of local tobacco companies, joint manufacturing arrangements, and use of trade leverage by developed countries to open the market."

U.S. Dept. of Agriculture credits support tobacco exports, Connolly said. "Iraq was a major recipient of this program. Saddam smokes Marlboros. Some of the money he made from U.S. tobacco sales helped pay for his missiles."

Alan Blum, assistant professor of family medicine at Baylor College of Medicine, blasted the tobacco industry for its advertising and promotional policies and the media companies which accept it.

He also criticized NCI, which he said has "failed abysmally to look at the tobacco industry," and he charged media corporations and cigarette advertisers with carrying out a "conspiracy"to oppose efforts to ban that advertising.

"Who is worse," Blum asked, "the tobacco industry or media corporations?" Antismoking ads do not exist, he added.

Blum heads an organization called DOC (Doctors Ought to Care), which was founded in 1977 to educate the public, especially young people, about the major preventable causes of poor health. DOC employs paid media advertising laced with humor and ridicule of tobacco products and the tobacco industry, he said.

"Cigarette sales have not been seriously damaged by warnings of the dangers of smoking, because danger has become part of the formula for selling cigarettes, especially to the adolescent. But while the health consequences may not be a deterrent, ridicule by consumers of the product and the pusher holds great potential for hurting cigarette profits," Blum said.

Daily newspapers in Houston refused to accept DOC advertising, Blum charged, although weekly newspapers in the area did.

"U.S. tobacco companies are corporate criminals," Blum charged. Pointing out that most of those companies have diversified into food product and other fields, he said, "Every time you buy Post cereal, you're helping to sell cigarettes to kids. . .

Cancer's 'Seven Warning Signs'

"The tobacco industry is vibrant and dynamic, and we have to track it as we would a parasitic disease. The biggest obstacle to tackling the tobacco pandemic is complacency--on the part of the public and health professionals alike--stemming from the belief that the war on smoking has been won. We need to move beyond patient education and health promotion. An activist model provides an additional dimension to reinforce health outside the comfortable confines of the hospital or clinic and into the mass media, the streets, and the day to day context of patients' lives in the community at large.

"Cigarette advertising has grown larger than ever around the world, yet we still have failed to mobilize public anger toward it," Blum continued. ". . . Nowhere has the tobacco industry been more successful in creating a positive association with cigarettes than through sports sponsorship. In the United States the rising tragic trend is that of ethnic marketing. More than 56 million Americans still smoke, and their average age and educational attainment is lower than ever.

"Tobacco companies continue to provide research funding to medical schools, as if to imply that more research is necessary to settle what the industry calls the smoking and health 'controversy.' It is essential that tobacco companies be identified by the public for that they really produce.

"Hence, in the U.S., it is essential that we refer to them as Cancer's Seven Warning Signs: Philip Morris, RJR, Nabisco, BAT, American Brands, Loews, Liggett, and UST."

New Study May Resolve Gallo's HIV Discovery Controversy

NCI's Robert Gallo, who has been accused of seizing the credit for the discovery of the AIDS virus from French researchers, has released a new study that could completely exonerate him of those accusations.

Gallo's claim to the virus has been the subject of a much publicized investigation by the NIH Office of Scientific Integrity since 1989. Investigators have questioned whether Gallo either intentionally or unintentionally appropriated viral samples sent to his laboratory by the Pasteur Institut in 1983 and then claimed to have discovered them himself.

Late last year, NIH cleared Gallo of charges that he deliberately stole the virus on the basis of other information; but there was still some question about whether Gallo had mistakenly mixed his own viral samples with those from the French.

Gallo and a research team that included Pasteur Institut AIDS researcher Jean-Claude Chermann recently employed polymerase chain reaction technology to reanalyze DNA sequences of the samples sent to NCI by the French and those later described by Gallo's team.

The results, published in the Feb. 28 issue of "Nature," seem to eliminate any doubt that Gallo discovered HIV independently of the French; but they also raise further questions about the origins of the LAV virus discovered by the French.

"We have now clearly identified the original isolate provided to us by Pasteur Institut scientists in 1983," Gallo said in a statement. "I am pleased [to] confirm that [the French and American viruses] were indeed distinct viruses. We do not believe that proper identification of the first reported HIV isolate in any way detracts from the respective contributions of our laboratories on the study of AIDS."

The study, reported in the article "Sequence Analysis of the Original Isolate of HIV-1," redefines relationships between the viral samples. In 1985, Gallo and his team at NCI's Laboratory of Tumor Cell Biology reported that they had isolated and sequenced a virus then called IIIb, which they identified as the cause of AIDS.

The IIIb virus, said Gallo and his colleagues, was one strain that grew in culture from a pool of 10 viral samples the researchers had created.

Almost simultaneously, researchers at the Pasteur Institut reported their discovery of the AIDS virus, which they labelled LAV-1/BRU, or lymphadenopathy virus-1 from a patient with the initials BRU.

In 1983 the Pasteur Institute's Luc Montagnier and Jean-Claude Chermann sent four samples of a virus from patient BRU to Gallo's lab because the French team was having trouble growing it in culture. So when it was later discovered that the genetic sequences of IIIb and LAV-1/BRU were almost identical--an unlikely coincidence given the complexities of viral genetics--Gallo's claim to the virus came under scrutiny.

For the new study, Gallo, Chermann, and their collaborators retrieved frozen specimens from three of the four BRU samples and the original IIIb sample. PCR sequencing of a 900 base-pair portion of the virus' envelope gene showed that the BRU samples were very similar to each other (98.4-100 percent sequence identity).

However, the researchers said in the "Nature" article, the BRU samples "differ markedly" from both the corresponding IIIb sequences and the LAV/BRU sequences published by the two groups in 1985--with only 90.5-94.6 percent sequence identity.

The researchers concluded that "this data clearly show that none of the LAV samples received in...1983, which are still available for analysis...was the source of HTLV-IIIb. Nor could the materials of which these are the samples have been the origin of the published LAV sequence."

In her editorial commentary on the study in "Nature," editor Barbara Culliton noted that the apparent lack of a relationship between the three BRU samples and the published LAV/BRU "add a new layer of mystery to the case."

One of the four BRU samples sent to Gallo cannot be found, and another sample that Montagnier later sent with the label RUB was completely used in experiments. Culliton questions whether either could have been the real source of LAV/BRU; but, she says, "Chermann, who was working with Montagnier at the time, avows that they, too, came from BRU."

The patients who were the source of IIIb and LAV have never been identified, although NIH is working on the identification of the source of IIIb.

What the scientific community is left with, then, is a 180-degree turn in the conflict between Gallo's lab and the Pasteur Institut: the implication that Montagnier's lab somehow appropriated Gallo's virus to claim the discovery of the AIDS virus.

According to Culliton's commentary, Univ. of Wisconsin virologist and Nobel laureate Howard Temin's response to the new developments was that "'we now do not know where LAV or IIIb came from. Therefore, we can't accuse anyone of anything. Do we care further? No. This is a non-issue as far as the AIDS epidemic is concerned. Now it is a non-issue as to the character of Dr. Gallo. Let's get off with it.'"