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Genetics Research Is Prevalent In Central Europe As Scientists Seek Answers To Related Questions

"Convergences of International Cancer Research," the seventh international symposium sponsored by the French Assn. for Cancer Research and the U.S. International Council for Coordinating Cancer Research, demonstrated the extent to which investigators around the world are working in similar directions on seeking answers to related questions. The field of genetics is dominating basic research in the U.S.,

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In Brief

Christopher Walsh Named Dana-Farber President; Sachs Leaves NCI; Acoustic Neuroma Conference

CHRISTOPHER WALSH has been appointed president of Dana-Farber Cancer Institute effective Jan. 1, by the institute's Board of Trustees. Walsh succeeds Baruj Benacerraf, Nobel laureate who has served as president for 11 years, and who will continue as president of Dana-Farber Inc., the institute's parent corporation. Walsh will continue as chairman of Harvard Medical School's Dept. of Biological Chemistry & Molecular Pharmacology. In 1989, Walsh was elected to the National Academy of Science and the Institute of Medicine. His current research focuses on the mechanism of action of immunosuppressive drugs and their role in transplant medicine and related areas. Prior to his appointment at Harvard, he was professor of chemistry and biology at Massachusetts Institute of Technology, and served as chemistry department chairman. He graduated Harvard in 1965, received his PhD from Rockefeller Univ. in 1970, and completed postdoctoral training in biochemistry at Brandeis Univ. . . . **DAVID SACHS,** Immunology Branch chief in NCI's Div. of Cancer Biology, Diagnosis & Centers, has left for a position as professor of surgery at Harvard Medical School and director of the transplantation biology research center at Massachusetts General Hospital. Sachs came to the Immunology Branch in 1972. "He has made major advances in transplantation biology and is now ready to take these advances into a clinical program," said Div. Director Alan Rabson. Sachs took the branch staff with him, and Rabson has no plans to replace them. . . . **MARK WILLINGHAM,** Ultrastructural Cytochemistry Section chief in DCBDC's Laboratory of Molecular Biology, is leaving for a job as professor of pathology at the Medical Univ. of South Carolina. . . . **NIH CONSENSUS CONFERENCE** on acoustic neuroma, a brain tumor, is scheduled for Dec. 11-13 at the NIH Masur Auditorium. Raymond Adams, Massachusetts General Hospital, is chairman of the consensus panel. To register contact Prospect Associates, 301/468-6338.

Genetics Research Prevalent In Europe, Budapest Symposium Finds

(Continued from page 1)

and that is becoming true in Europe, including, surprisingly perhaps, the countries in Central Europe now emerging from 40 years behind the Iron Curtain.

The symposium was held in Budapest, and Hungarian scientists outnumbered all other delegations. Investigators from Czechoslovakia, Poland, East Germany, Bulgaria, and Yugoslavia made it a conference dominated by Central Europe (a designation they all prefer over Eastern Europe, which they say starts at the border of the Soviet Union).

France and the U.S. were well represented, and two reports from those countries offered an intriguing look at the therapeutic potential that basic research laboratories are turning up.

Dominique Stehelin, director of the molecular oncology center at Pasteur Institute, described how transactivators of the ets family of proto-oncogenes are implicated in angiogenesis in the embryo of tumors.

"The formation of new blood vessels is essential in embryonic development, in tissue repair, and in the growth of tumors. This process is known as angiogenesis. We have examined the expression of c-ets1 by in situ hybridization during angiogenesis under different conditions in man. C-ets1 is expressed in the endothelia of developing vessels of embryos while mature vessels in adult tissues are essentially negative for c-ets mRNA. We demonstrated that c-ets transcripts accumulate in the sprouting capillaries of granulation tissue during wound healing, in the stromal capillaries during tumor vascularization and also in fibrocytes of tumor stroma. Carcinoma tumors themselves appear negative, as tested so far, with one notable exception: c-ets1 mRNAs are detected in the spindle cells of Kaposi's sarcomas, regarded as cells having an endothelial origin.

"This in vivo observations could be mimicked by in vitro experiments. In culture, c-ets mRNAs accumulated in growing endothelial cells and decreased by about 10 fold after these cells had reached confluence. Moreover, we found that angiogenic factors such as TNAa or PMA which in vitro modulate the expression of proteases and protease inhibitors also increase transiently the amount of c-ets1 mRNAs in confluent human umbilical vein endothelial cells.

"It has been show recently that the c-ets proteins activate transcription through specific ets binding sequences exemplified by the polyoma virus PEA3 motif which plays a role in the stimulation of transcription of urokinase type plasminogen activator, stromelysin and collagenase genes. Therefore we suggest that the c-ets1 proteins might regulate the transcription of the genes coding for these matrix degrading proteases which are necessary for both angiogenesis and tumor invasion."

Stehelin concluded, "We believe we have the tools now to allow us to modulate blood cell growth. If we have drugs to inhibit angiogenesis, we can control tumor cell growth."

Edward Mercer, who has been associate professor of genetics at Temple Univ.'s Fels Research Institute and who recently moved with Carlo Croce's laboratory to Jefferson Univ., has been studying the biology of the human p53 tumor supressor gene in cell cycle regulation.

"The p53 gene located on the short arm of chromosome 17 is a frequent target of mutation in a wide variety of human cancers. The wild type p53 protein encoded for by this gene appears to play an important role in cell cycle regulation. In vitro studies indicate that overexpression of wild type p53 protein (but not mutant forms) is antithetical to cell proliferation.

"We have established a series of human glioblastoma cell lines with wild type or mutant p53 cDNAs under transcriptional control of the mouse mammary tumor virus promotor. Although the endogenous p53 protein expressed in these cell lines is mutant at condon #273, induction of wild type p53 protein (but not mutant forms) is dominant and results in reversible growth arrest in G_1 phase of the cell cycle. Growth arrest of this model is accompanied by selective down regulation of proliferating cell nuclear antigen (PCNA) gene expressions. Since the PCNA gene encodes a nuclear protein that is an

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Editor: **Kirsten Boyd Goldberg**
Associate Editor: **Lisa M. O'Rourke**
Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
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auxiliary factor for DNA polymerase and part of the DNA replication machinery of the cell, our results suggest that wild type p53 protein may function to modulate the expression of genes necessary for cellular DNA replication.

"Biochemical analysis of the p53 proteins expressed in growth arrested cells indicates that two distinct populations of mutant (form 1) and wild type (form 2) p53 proteins consisting of several closely spaced phosphorylated isoelectric variants are present. Cascade immunoprecipitation with monoclonal antibodies that preferentially recognize mutant or wild type p53 indicates that a substantial amount of wild type p53 protein is present and not complexed with mutant p53 protein. The expression of wild type p53 protein is directly correlated with growth suppression and selective down regulation of PCNA gene expression.

"We are currently exploiting this model to investigate what other cellular pathways are altered in cells growth suppressed following induction of wild type p53 protein."

Mercer added that these findings should encourage investigators to look for a biochemical agent that could modify p53 and stimulate the activity which blocks cell proliferation.

Orsolya Csuka, head of experimental biology at the National Institute of Oncology in Budapest, described her studies which have potential for new therapy.

"Protein kinase C (PKC) has a great importance in signal transduction, growth regulation, and differentiation, and PKC might also function as a tumor suppressor gene. PKC belongs to a multigene family consisting of at least six distinct genes. These PKC isoforms are supposed to perform different roles in growth control and differentiation.

"The changes in PKC level and isoenzyme pattern have been evaluated during the process of induced differentiation of colon tumor cells and in multidrug resistant colon tumors. Hexamethylenbisacetamide (HMBA), retinoic acid (RA), sodium butyrate (NaBT), and mycophenolic acid (MA) have been applied for the induction of differentiation. Our results have shown that the ability of colon tumor cells for differentiation is dependent on the basal level of PKC.

"COLO 205 colon tumor cell line proved to be more sensitive to all types of inducers as compared to COLO 320 cell line. Inhibitors of PKC (staurosporine, H7) prevented the drug induced differentiation.

"All types of inducers caused an overall increase in PKC activity during the differentiation of colon tumor cells. Changes in PKC level may provide a common mechanism by which various agents regulate the differentiation of colon tumor cells. Modulation of PKC level influenced the chemotherapeutic sensitivity (5-FU, adriamycin) of the tumor cells. Our studies have also revealed that PKC might be a mediator in the mode of action of GnRH and somatostatin analogues.

"Our results suggest that PKC might be a novel target for the development of new therapeutic protocols."

Edith Olah, molecular biologist at the National Institute of Oncology in Budapest, has been studying epigenetic modulation of oncogene expression.

"In vitro experiments have shown that countermanding the actions of oncogenes may provide a new strategy to control malignant cell proliferation. Differentiation, which can be viewed as arising through a series of epigenetic changes, may alter the tumorigenic phenotype of cells.

"Tiazofurin (TR), an inhibitor of IMP dehydrogenase, the rate limiting enzyme of GTP biosynthesis, proved to be a potent inducer of erythroid differentiation of human K562 leukemia cells. We have also demonstrated that induction of the differentiation program is associated with an early (3 hr) decrease in the intracellular GTP pools and with concurrent down regulation of c-myc and ki-ras gene expressions. Furthermore, TR inducted the late expression of gamma globin gene, but had no effects on the level of c-abl transcripts. These results have suggested a role for guanine ribonucleotides in the regulation of c-myc and c-ras gene expression. Similar correlation was demonstrated in rat hepatoma 3924A cells contrary to presence of amplified and rearranged c-myc and over expressed ha-ras genes.

"The acquisition of TR resistance was associated with a moderate increase in the level of c-myc transcripts.

"Our current interest is to elucidate the oncogene pattern of human ovarian carcinoma cells derived from patients in order to find new molecular targets for anticancer therapy and also to reveal the impact of guanine ribonucleotides in modulation of expression of activated oncogenes."

Vladimir Vonka, Institute of Sera and Vaccine, Prague, described studies involving human papillomaviruses at the molecular level.

"For proving causal relationship between human papillomaviruses and cervical cancer suggested by molecular biological and histopathological findings, epidemiological studies are needed. They should provide an evidence that the infection is preceding the development of the disease and that there is an increased risk of developing the disease associated with previous infection.

"Utilization of immunological methods would be the

easiest way to deal with the problem. However, introduction of these methods has met considerable difficulties associated mainly, although not exclusively, with the inability to cultivate HPV in vitro. Thus it is not known, for example, how frequent is the antibody response in HPV infected subjects, what is the type specificity of the antibodies developed, what is the prevalence of HPV infections in general populations and whether there exists a relationship between the development of cancer the presence and/or level of antibody.

To address some of these questions, serological studies have been initiated in our laboratory. Three sources of antigens have been utilized: virions extracted from HPV induced lesions, genetically engineered HPV proteins, and synthetic peptides derived from known sequences of different HPV open reading frames. The results obtained suggest that in patients with warts, condylomata acuminata, and cervical cancer, the antibody responses to HPV infections are quite frequent and at least partially type specific."

Inhibitor Of Blood Vessel Growth May Be Tested As Cancer Therapy

A new drug that suppresses the growth of new capillaries around tumors may soon enter clinical trials as a cancer therapy, a researcher from Harvard Medical School told participants at a recent AIDS meeting in Washington.

The new drug is a synthetic analog of a fungal compound that cancer researchers stumbled upon in tissue cultures, said Donald Ingber, a researcher at Harvard Medical School's Dept. of Pathology, at a symposium on Kaposi's sarcoma at last month's meeting of the National Institute of Allergy and Infectious Diseases' AIDS Clinical Trials Group.

"We think we have...a new class of antitumor agents that inhibit both tumor growth and metastases based on their ability to interfere with angiogenesis...[and that] don't seem to have any toxicity," Ingber said.

Like the fungal compound on which it was modelled, the new drug, called TNP-470, inhibits the one of the cellular processes necessary for the growth of new capillaries.

In order to grow beyond one cubic millimeter in size, a tumor must stimulate the development of new capillaries that will supply it with nutrients and oxygen. So an agent that blocks angiogenesis can restrict the growth of blood vessels feeding a malignancy and thus the growth of malignancy itself, said Ingber.

Robert Gallo, chief of NCI's Laboratory of Tumor Cell Biology, said at the ACTG meeting that what he had heard about TNP-470 was "very impressive."

A Natural Angiostatic Antibiotic

The concept of fighting tumors by inhibiting the growth of their vascular lifelines is nothing new, Ingber said. After 20 years of research, scientists have identified and sequenced about a dozen different tumor angiogenesis factors, soluble endothelial cell mitogens that stimulate the growth of new blood vessels.

However, as investigators identified more of these growth factors they began to realize that "the idea of blocking the tumor angiogenesis factors wasn't going to work--there's just too much redundancy in the system," Ingber said.

In order to find a new approach, researchers returned to an examination of the angiogenic process, which involves three basic steps.

First, the basement membrane, or extracellular matrix, that surrounds an existing vessel must degrade locally to create an opening from which a new capillary can branch out.

Ingber and his colleagues at Harvard later showed that the next step was the deposition of new extracellular matrix into the surrounding connective tissue.

Then, he said, "as cells degrade and deposit an extended matrix they also exhibit large scale changes in cell shape. The cell and the nuclei literally extend in size as the cells begin to grow out into the neighboring connective tissue."

In the last few years, Ingber and his colleagues were studying this process using a special endothelial cell culture system. While working with this system, Ingber stumbled upon a fungus contaminating some of the tissue cultures.

The fungus was preventing the endothelial cells in those cultures from elongating to form new vessels; in fact, the cells were rounded near the fungus.

"This suggested to me that maybe this fungus was secreting some sort of soluble cell-shape regulator," Ingber said.

A pharmaceutical firm in Japan later determined that the active ingredient in that fungus was the antibiotic known as fumagillin.

A Potent Synthetic

When the Harvard investigators added fumagillin to a angiogenesis test system of chick chorioallantoic membrane systems they found that "this [agent] was not only inhibiting [capillary] growth but it was inducing regression of preexisting capillaries."

When tested in tumor-bearing animals, fumagillin

inhibited tumor growth. However, said Ingber, natural fumagillin also proved to be toxic in animal studies.

The Harvard scientists collaborated with the Japanese pharmaceutical firm to design analogs to fumagillin, "angiostatic antibiotics" that were less toxic than the natural compound.

The most potent one, labelled AGM-1470 and later TNP-470 by the Japanese firm, has proved to be "a potent inhibitor of endothelial cell growth...and angiogenesis in vitro," Ingber said.

The compound also strongly inhibited the continued growth of well-established tumors--measuring 100-150 mm^3 or more--in tumor-bearing mice.

When mice, rats, and rabbits with malignancies were given TNP-470 every other day, said Ingber, "the tumors in general don't regress, they just stay small; [the drug] did not interfere with tumor implantation, but completely inhibited tumor expansion."

TNP-470 also inhibited the growth of metastases, he said.

In addition, the compound "seems to have effects over a wide variety of tissues," Ingber said, including B16 melanomas, Lewis lung carcinoma, a mouse fibrosarcoma, and even one type of human tumor in the nude mouse model. The researchers have not yet tested the compound against Kaposi's sarcoma, in which the tumor itself is of vascular origin.

Effects on tumor growth translate into effects on survival as well. Tumor-bearing animals treated with the compound once a week lived twice as long as their untreated counterparts, Ingber said.

Keeping pediatric cancers in mind, Ingber's group treated young mice with TNP-470 and determined that it did not interfere with their growth rate.

The drug also appears to be dose-dependent but schedule-independent, so it could be given on different schedules without any net change in its effect if the dose is adjusted accordingly, Ingber said.

"Having a therapy where you don't have resistance and [the drug] is non-toxic is exactly what you want for something like cancer, where you can put patients on the drug for the rest of their lives," said Ingber.

The fumagillin analog meets these criteria. When mice in the experiments were taken off the fumagillin analog, their malignancies began to grow; but if given the compound again, the tumors--or more accurately, the tumors' network of blood vessels--remain sensitive to its effects.

Because the drug's activity is specific to growing endothelial cells, it does not harm normal, quiescent endothelial cells, which have extremely low turnover rates, Ingber said.

Some researchers at the AIDS meeting raised concerns that the drug would also inhibit natural wound healing. Ingber said it might be possible to take patients off a TNP-470 regimen for a few days or to block the effects of the compound locally if wound healing was necessary.

However, he said, future studies of TNP-470 must also examine the drug's effect on the normal menstrual cycle, which involves some angiogenesis.

Ingber's team is now trying to get the drug approved for phase 1 clinical trials through NCI.

"We believe that Kaposi's sarcoma would be an excellent target for this compound," Ingber said. The investigators plan to include patients with this form of malignancy in the phase 1 trials.

Grants Funding & The Budget: The View From The White House

"We'd like to get to know more about the Executive Branch," Assn. of American Cancer Institutes President Albert Owens said in explaining why he asked a former colleage of his from Johns Hopkins Univ., currently a White House science advisor, to speak at the annual AACI meeting recently in Baltimore.

Donald Henderson headed the World Health Organization team that eradicated smallpox, and then became dean of the School of Hygeine and Public Health at Hopkins "because I was an expert without a disease to study." After 14 years he retired as a dean, anticipating a return to "a life without some of those arcane discussions about indirect costs, policies regarding misconduct of science, proper care and feeding of animals, and all of those exciting things deans have to be involved with."

Then, Henderson was asked to join the White House Office of Science & Technology Policy as its associate director for life sciences, which encompasses biomedical research. "I assumed there was some mixup in someone's mail," he told the AACI meeting participants.

But eventually Henderson met the President's science advisor, the head of the OSTP, Alan Bromley, and was convinced that there is "a broad committment within the Administration to the advancement of science and the improvement of education."

The OSTP has had a checkered history: created during World War II, expanded during John Kennedy's administration, then abolished by Richard Nixon, resurrected by Congress in 1976, then languished during Ronald Reagan's administration. The office was "little heard of and little known," Henderson said.

A "major transformation" occured with the election

of President Bush, Henderson said. For the first time in history, the President's science advisor was named an assistant to the President, representing a small group of senior staff which includes John Sununu, Brent Scowcroft, the director of the Office of Management & Budget, and the chairman of the Council of Economic Advisors.

OSTP now has a staff of 40, and resides in the Old Executive Office Building. There are four associate directors working with Bromley, all confirmed by the Senate. Besides Henderson in life sciences, there is an associate director for industrial technology, for physics, engineering and physical sciences, and for international science policy.

Henderson explained that the President meets with his senior staff, including Bromley, daily at 7:30 a.m. At 8:15, Bromley and the OSTP senior staff meet. "Thus, when problems emerge, we have through that office, rather direct contact with the central policymaking people," Henderson said.

Another major change has been that as budgets come to the White House from the departments, those having to do with science are reviewed jointly by the OSTP and the Office of Management & Budget, rather than OMB alone. "So there is an opportunity for input into the decisionmaking process at the budgetary level," Henderson said.

But the issues Henderson said he hoped to leave behind in the dean's office have returned. His office is working to rewrite the notorious "OMB Circular A21"--the indirect cost document. At the time of Henderson's remarks to AACI, in late June, this work was taking place, Henderson said, "amidst a feeding frenzy of people on the Hill, and within the administration who see a number of institutions, in their view, getting very rich and very fat off government largess. It is very difficult in this environment to pursuade them that we don't fund now all the indirect costs and we can't cut the indirect costs without seriously compromising the biomedical research enterprise. We're having a difficult time in trying to walk the narrow path between doing irreparable damage and at least satisfyuing those who would go much further. I'm encouraged at the moment that we are in reasonably good shape, but, I must say, that damned document comes back to haunt one."

Prosperity Depends On Science

Two basic themes pervade policy and program development in the OSTP and the Administration, Henderson said. "The first is the belief that the future prosperity and well being of America depends very heavily on its ability to sustain a leadership position in science, and therefore we must support a science enterprise. And to sustain such a position requires in turn that there be an effective educational structure supporting it and providing people who can not only work in science but who understand it. The second theme is the belief that we need in government much more effective and much longer term plans across government, not just by deparment, with a need to emphasize the investment of federal funds for longer term investment for the future and less short term consumption mode."

For the latter theme, a group called the Federal Coordinating Council for Science, Engineering, & Technology, has been created, with the acronym FCCSET, or "Fixit." This is made up of Cabinet level or immediately sub-Cabinet level officers and agency heads, chaired by Bromley. It has seven subcommittees, including one on life sciences, which is chaired by Assistant Secretary for Health James Mason. This group has reviewed programs and plans across agencies, which Henderson called "a useful exercize."

Last year, the Administration announced three new initiatives as a result of cross-government planning: One was in high performance and communications, one in the math-science education, and the third in global warming.

This year, the Administration decided to embark on two major new intiatives, one in material science and one in biotechnology, Henderson said. These plans will be announced in January.

"We see in biotechnology tremendous opportunties for the future of industry. The U.S. now commands a very important lead, but we see problems in translating basic science into application," Henderson said. "The question is, what can be done to strenghten basic science."

Certainly, increased funding would help, Henderson acknowledged. "There's no question that we just have to have a healthy and stable biomedical research communty. There is a belief that the system today is not as healthy as it should be."

However, Henderson said, the NIH budget doubled from 1982 to 1990. In constant dollars, the NIH budget increased 40 percent, "not too bad an increase if one looks at this across the government."

For FY 1992, the President proposed an increase of $500 million for NIH, "the largest increase prposed by any President in 20 years," Henderson said. The President proposed a 9 percent increase in research project grants funding, for a total of $4.5 billion, funding some 22,000 research projects.

Henderson noted that concerns about "success rate," or the number of grants funded, are not limited to NIH, but are also being experienced by the National

Science Foundation.

"We've got to realize there are several factors that make this real success rate, which has to be interpreted with some caution. As many of you may know, the average duration of grants was deliberately extended beinging in the late 1980s. Everyone thought this was needed, so less time would be spent on renewals. This was viewed as desireable, but provided a blip in the awards, so that a lot of committments were made and new grants were more difficult to come by. At the same time, one sees that grants have increased in size."

The number of grant applications has increased by 30 percent over the past 10 years, Henderson said. However, he said some of the increase was due to a greater number of amended applications which are resubmitted. The resubmission rate increased from 8 percent to 30 to 35 percent. About 10 to 12 percent of researchers are submitting more than one application, compared to a "historical rate" of about 3 percent, Henderson said.

"There are other factors which have raised some troubling questions. One has to ask, when study sections approve 95 percent or more grant applications, compared to a figure of almost 70 percent a few years ago, one has to ask what is happening to the stringency of review," he said. "The arguments advanced that we have so many applications and only so many are approved and funded, those arguments within the Congress and the administration don't wash very well."

'Build A Solid Case' For Greater Funding

An interagency group has been created under the FCCSET panel to look at these issues, called the Working Group on the Structure and Support of Science. "One of the efforts that will be made is to try to get some reliable indecies so that we have some better measurement to give us a better sense of where we are with regard to quality grants which are not being funded," Henderson said.

"I think we could all make the case and appropriately so that more resources are needed. I noted that there is additional support in FY92. I can say with some certainty that increases for FY93 will compare as well. This is a basic committment on the part of the administration," Henderson said. "There is no reason now not to begin to make the case for additional resources and to make it well."

Henderson complained that some of his colleages in science come to Congress to say they are not adequately funded or to argue for making the provision for a certain number of new and competing grants. Those arguements, he said, are "no longer terribly compelling." Congress has asked, he said, "Why do you feel you are entitled to additional resources?"

"It seems to me that we do need to build a more solid rationally based arguement, based on priority needs and anticipated anccomplishements," Henderson said. "I think in the cancer field you have done an exeedingly good job in educating Congress and the public and you need to keep a focus on what research can do for people. Somehow we have to interpret for the general public what might we achieve. There is also the danger of overpromising, but there is a greater degree of sophistication than there was 20 years ago."

Henderson suggested investing in research a percentage of the amount the country spends on health care. Compared to other countries, the U.S. is underinvesting in science. About 1.8 percent of U.S. GNP is spent on nondefense research and development, while Germany spends 2.6 percent and Japan spends 2.8 percent of their respective gross national product.

Henderson said scientists need to do a better job of "developing a longer term rationale" for research funding that addresses the "different audiences"--the public, the science establishment, and industry.

Bypass Budget: As Appealing As A Phone Book

Owens asked Henderson whether NCI's annual Bypass budget, the professional needs budget developed by NCI and sent directly to the President, is useful. The Bypass budget, Owens said, is "about as appealing to the public as a telephone book."

"In a sense, each of the NIH institutes does have something like the Bypass budget which the director of the institute develops," Henderson said. "I think this is exceedingly important becasue what it says is, there are some things we're not doing. And then, there is the arguement that more funds should be made available. I can't say what the budget will be two years from now, but I will say now is the time to begin building a stronger case because we are not all that far away from the time when one could foresee much smaller expenditures in defense. We have to keep the case in front of us."

Commission On Cancer Seeks Data On Invasive Cervical Cancer

The American College of Surgeons Commission on Cancer is seeking comparative data to assess the current management of invasive cervical cancer.

The commission's Committee on Patient Care and Research annually conducts patient care evaluation

(PCE) studies of selected cancer sites. A data base of more than 365,000 cancer cases has been acquired through the voluntary participation of hospital based cancer committees. Data from these studies have shown trands in cancer patient care and have been used for professional education at the hospital, state, and national levels.

The formats for PCE studies of invasive cervical cancer have been mailed to hospital cancer registrars and central registries throughout the country. These studies include cases of patients initially diagnosed in 1984 and 1990. Complete confidentiallity is assured. Although each hospital will receive a summary of its data, only aggregate data will be released nationally. The analysis of the study results will be made available to hospitals, physicians, and allied health professionals. Hospitals will receive a summary of the results, and, when available, the published analysis. Participation in any commission PCE study is voluntary and does not affect the hospital's approval status.

Participants using these studies to fulfill their PCE requirements may use these invasive crvical cancer studies to meet their 1991 patient care evaluation requirement.

The deadline for receipt of the data forms is Jan. 1. For further information contact the Cancer Dept., ACOS, 55 East Erie St., Chicago, IL 60611, phone 312/664-4050, ext. 410 or 441.

Program Announcement: Lung Cancer

PA-91-83

Title: Cancer therapy research in lung cancer

Application Receipt Dates: June 1, Oct. 1, Feb. 1

NCI seeks grant applications to conduct therapeutic studies in lung cancer in human subjects. This Program Announcement encompasses a full range of therapeutic studies and clinical trials employing surgery, radiation, chemotherapies, or biologic response modifiers. The intent of the announcement is to encourage clinical researchers to translate new insights in the biology of lung cancer into clinical trials of innovative cancer therapies.

This type of grant solicitation is used to encourage investigator initiated research projects in areas of special importance to NCI.

In the past several years, research efforts into understanding the biology of lung cancer have been productive. Laboratory associations with both dominant (ras, myc) and suppressor (p53, Rb) oncogenes, growth factors and their receptors (EGF, HerB/neu), and recurrent cytogenetic abnormalities (3p deletion) have been made with either small cell or nonsmall cell lung cancer.

At the same time, promising developments have occurred in both pre-existing treatment modalities such as cytotoxics (new combinations of agents) and radiation therapy (new techniques of administration, radiosensitization and radioprotection), as well as new approaches such as differentiating agents/retinoids, biologic response modifiers, and photodynamic therapy and new drugs (taxol).

Unfortunately, neither the basic nor the therapeutic advances have yet translated into marked improvement in the treatment of lung cancer. Therefore, it is essential to facilitate collaborations between basic scientists and clinical investigators in order to promote the rapid incorporation of promising scientific advances into research on a well characterized lung cancer patient population.

The Div. of Cancer Treatment is requesting qualified investigators to develop research grant (R01) applications and First Independent Research Support and Transition (FIRST) Award (R29) applications involving therapeutic studies of lung cancer patients.

Studies should involve human subjects and be designed to ultimately improve lung cancer treatment. The applications may include single or multi-institutional (e.g., consortia, cooperative groups) research studies with appropriate biological correlates linked to these studies. New therapeutic studies may involve drugs, radiation, surgery, or biologic response modifiers, alone or in combination. Biological correlate studies that have clinical relevance to lung cancer therapies are also appropriate.

Some examples of therapeutic studies include, but are not limited to:

--immunotherapies based on surgically obtained tumor specimens

--therapies with novel mechanisms of action (e.g., retinoids)

--new radiation therapies, or radiation modifiers, to enhance cell kill or protect normal tissues

--biologic response modifiers (monoclonal antibodies, cytokines, tumor vaccines) alone or in combination with other therapies

--studies of drug or radiation resistance and reversal

--therapies aimed at interfering with growth factor action (e.g., suramin, bombesin analogs)

--innovative surgically based multimodality studies

Some examples of biological correlate studies include:

--phenotypic or genotypic alterations that appear to correlate with the development of drug or radiation resistance

--oncogenes, growth factors, and specific antigen expression on tumor cells

--pharmacokinetic and pharmacodynamic measurements

--biochemical pharmacologic parameters

--imaging studies to assess efficacy of treatment

Applicants from institutions that have a General Clinical Research Center funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. In such a case, a letter of agreement from either the GCRC program director or principal investigator must be inlcuded with the application.

Support of this program will be by the research project (R01) and FIRST award. Domestic applicants may request no more than five years of support, and foreign applicants may request no more than three years. Applications submitted in response to this PA will compete for funds with all other investigator initiated applications. The award of grants in response to this PA is also contingent upon the availability fo funds.

Nonprofit and for profit organizations and institutions, governments and their agencies, and occasionally individuals are eligible to apply. Both domestic and foreign applicants may apply. Applications may be submitted from a single institution or may include arrangements with multiple institutions. Applications from minority individuals and women are encouraged.

Written or telephone inquiries concerning the objectives and scope of this PA are encouraged and should be directed to Diane Bronzert or Dr. Roy Wu, Program Directors, Cancer Therapy Evaluation Program, Div. of Cancer Treatment, NCI, Executive Plaza North Rm 734, Bethesda, MD 20892, phone 301/496-8866, fax 301/480-4663.