THE CANCER LETTER

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PRESIDENT'S CANCER PANEL ROAD SHOW PRODUCES IDEAS FOR IMPROVING FUNDING MECHANISMS; NCI BUYS SOME

The President's Cancer Panel has gone on the road twice this year, the latest to Los Angeles, soliciting ideas from scientists in response to questions posed by Panel member Bernard Fisher last year on problems in funding biomedical research. *(Continued to page 2)*

In Brief

SBA WRITING GUIDELINES TO IMPLEMENT ACT GIVING 1.25 PERCENT OF R & D BUDGETS TO SMALL BUSINESS

SMALL BUSINESS Administration is writing guidelines to implement the new law requiring federal research agencies (including NIH and NCI) to reserve 1.25 percent of their R & D budgets for small businesses. Already decided: the base will exclude intramural research, and the percentage—to be phased in over four years—will be in addition to the amounts agencies already are channeling to small business. Yet undecided: whether it will include grants as well as contracts, whether it will require special study sections to review proposals. . . . **UNIV. OF SOUTHERN** California Comprehensive Cancer Center investigators need at least five patients with primary hepatocellular carcinoma to participate in a trial with partially purified human leukocyte (alpha) interferon. Patients should be positive for hepatitis B antigen. Those without prior therapy are preferred, but patients would be accepted if they have not received chemotherapy for one month before beginning the interferon trial. Physicians may call Drs. Raymond Kempf or Ira Felman at 213-226-4009, or Dr. Myron Tong at 213-440-5673. . . . **NOMINATIONS ARE** now being accepted for the sixth annual Bristol-Myers Award for Distinguished Achievement in Cancer Research, with its $50,000 prize. Saul Rosenberg is chairman of the Award Selection Committee, which includes a panel of judges form the 11 cancer research centers which participate in Bristol's $5.34 million a year grant program. Nominations will be accepted from medical schools, free standing hospitals and cancer research centers until Dec. 15. Only one nomination from each institution will be accepted. For forms and further information contact Secretary, Awards Committee, Bristol-Myers Co., 345 Park Ave Rm. 43-38, New York 10154. . . . **ANOTHER HONOR** for Richard Adamson, director of NCI's Div. of Cancer Cause & Prevention: The HHS Equal Opportunity Achievement Award "For extraordinary contributions to federal activities promoting equal opportunity and for sustained outstanding performance in the area of equal employment opportunity.' Also, John Moore, deputy director of the National Toxicology Program and director of toxicology research in the National Institute of Environmental Health Sciences: the HHS Executive Management Award "For improvements instrumental in the advancement of the National Toxicology Program."

SOME LOCAL REVIEW, MANDATORY STUDY SECTION SERVICE PROPOSED TO PANEL

(Continued from page 1)

Some of the suggestions proposed at the Boston meeting—establishing career investigator awards, five year peer reviewed renewable support for individual with excellent records; funding grants at less than recommended levels to spread the money over more grants—are being implemented by NCI.

The Los Angeles meeting produced its share of suggestions, some of which might well be adopted by NCI. Among them were:

—Decentralization of peer review, at least for some pilot projects and new investigator awards, by using institutional peer review systems suggested by Richard Steckel, director of the UCLA Jonsson Comprehensive Center.

—Mandatory service on study sections for all NIH grantees.

—Permitting carryover of unused grant funds, allowing investigators to build up an "insurance" fund to carry them through lean times.

—Discourage multiple grants for individual labs and place a dollar limit on the amount of money awarded to an individual.

—Return to closer collaboration between NCI program staff.

Lester Breslow, UCLA, put his finger on what really ails the NIH peer review system at the present time, if in fact it is ailing. "The underlying problem is. . . that the federal government will no longer support the growth of medical science and cancer research." Breslow said that efforts to improve peer review should be accompanied by an effort "to convince Congress and the Administration that too severe cutbacks threaten the very fabric of medical science for the long run."

Here are the questions submitted by Fisher which have been addressed at the Boston and Los Angeles meetings:

Does the present mechanism for research funding allow for the creation of an established population of scientists or does it favor the production of transient investigators who enter and leave research at a rapid clip?

What are the opportunities for young investigators in this system, and what are the opportunities for established investigators? Are they destined to exist forever from one grant review to the next with the attendent uncertainties thereof?

Should beginning and established investigators be evaluated by a separate process?

Does the present mechanism allow for uniqueness, innovation, and individuality?

To what extent does scientific fashion influence funding?

Is mechanism and process more important in a grant application than the concept of the investigator?

Do the mechanics involved with seeking funds, that is, writing the applications, preparing progress reports, interfere with research productivity?

Are there aspects of the peer review system which could be improved upon?

Is there a way in which there could be a better matchup between investigator and reviewer?

Could there be an opportunity for better communications between investigator and reviewer?

And what is the credibility of the priority scores, particularly those in the region of the cutoffs?

Fisher, who chaired the Los Angeles meeting in his last session as a Panel member, after Chairman Armand Hammer left following his opening remarks, described previous efforts to imrpove peer review.

"For the past 34 years, since the introduction of the peer review system, there have been 20 studies of this system carried out, and almost every aspect of the process has been examined," Fisher said. "Rarely, if ever, did they consider alternative methods. They warned against cronyism, recommended that members of the grant review committees be selected because of such qualifications as: 'Their professional attainment, their ability to make unprejudiced, statesmanlike judgments, for such reasons as they provided balanced representation from geographical regions or educational institutions.' These investigations demonstrated that priority scores were highly correlated with productivity, thus validating the system.

"The peer review system is based on the concept that grant applications submitted receive unbiased, objective evaluation by peers, equals, and investigators have expressed concern about whether their grants receive such review. The problem is that there may be varied perception of who a peer may be, and this may really be the Achilles heel of the system. The selection of a particular individual or a group of individuals to review a proposal may be in good faith and the selector of this group may perceive these persons really to be peers where the investigator, or even another selector may not.

"Well, it's fortunate that NCI is directed by one who is receptive and responsive to the concerns and ideas of the scientific community. And therefore, this process that we're going through today is not to be merely looked upon as an exercise. As you've already heard, many of the suggestions and comments made at the Boston meeting have been taken to heart and changes have been made."

Following are selections from a summary of the day's discussion prepared by Elliott Stonehill, executive secretary of the Panel.

Lawrence Alfred, Charles Drew Medical School—Study sections as they are presently constructed are composed of eminent scientists, and because of this, there is some assurance of a fair review of most grant applications. But I don't believe that this is true in a majority of cases. In my opinion the application itself, the grant application processes, the forms, and the total format is somewhat cumbersome and to a large degree discourages young investigators from applying. Consequently, young investigators must

rely upon their mentors for guidance and this leads to further inbreeding of conventional ideas.

I would like to suggest that NCI develop more effective RFPs for young clinical investigators. Secondly, I would like to encourage that there be more interaction between well known institutions involved in cancer research and smaller institutes and hopefully some new ideas might be encouraged through the application process for focus on areas of cancers in high risk groups.

Paul Boyer, UCLA—I chose four things that I would support that others have done. One is a peer review based primarily on past accomplishments. When investigators of merit take as much time to prepare their grants as they do to prepare their scientific papers, when they worry about the format and the grammar and the content therein you are losing research effort.

Second, I strongly think we need administrative simplifications to increase the effectiveness of peer review. There are certain agencies of the government, like OMB, that should be brought out of the health field.

Third, I feel that there are problems in abuses and uses of overhead charges that need consideration.

Fourth, I think that the question of stipends for those that are in training and those that are young investigators and the great group of postdoctoral fellows who have not even a beginning of an effective union needs consideration.

But in looking for things that might be a bit different than what has been said before, I've written a suggestion of some way in which an investigator might be allowed to have some increased buildup of carryover funds so that he could create his own insurance for a period of time, transferring the responsibility from NCI to the investigator.

Charles Heidelberger, USC—There are some inequities in the peer review system which are human frailties of members of study sections. What we have to do is to clean up the act a little bit. At least two years' service on a study section should be mandatory for everyone who received federal research funding. One has to pay one's dues. Political, minority, and other nonscientific considerations should be eliminated in choosing study section members and scientific criteria be applied more rigorously. It is essential that study section members have the perspective and judgment that usually accompany maturity.

I believe that it's necessary to alter the system so that applicants, after receiving their summary statements, be permitted to submit written rebuttals to the study section prior to the NCAB review. I think that a communication between the applicants and at least the primary reviewers on the study section, if instituted promptly enough, could eliminate a lot of hostility which is undoubtedly felt.

I think there should be a dollar limit on the total grants an individual principal investigator should be funded by. I would hesitate to suggest what that dollar limit should be.

More consideration should be given to innovative ideas than they are at present. Now the only perfect application can be one in which all the experiments have been already done so there's no risk.

Far too much of the investigator's time at present is spent in writing more and more complete grant applications and defending the paperwork that goes with it. When can be actually do the experiments?

It would be good for the applicant to be allowed at least to suggest what he or she considers to be the most appropriate study section for the review and also the name of some outside reviewers who should be expert and impartial in the field.

And finally, to emphasize points previously made by Dr. Arthur Pardee, I believe that people, not grants, should be supported, and that time and tranquility are needed for innovative research. The present insecurities in funding make that tranquility very difficult to achieve.

John Mendelsohn, Univ. of California (San Diego) We are not here because the peer review system is bad. To the contrary, the NIH sponsored research program in the biological and medical sciences has been one of the most successful government endeavors of the past few decades, and I believe that the peer review system had an important role to play in this achievement. I think we are here to deal with new constraints and problems which have had great impact on granting mechanisms.

There are at least four reasons for this situation: First, inflation, resulting in decreased funds available for research. Second, increased numbers of active, qualified investigators. Third, increases in the costs of research. And fourth, resubmissions of approved, unfunded proposals.

I am impressed that the NCI and its advisors are doing their homework. We must ensure that research funding is awarded to excellent research, regardless of the origin of the proposal. It is healthy that indivdiual research proposals are generated from intramural NCI sources and RFAs as well as via the R01 mechanism. The criteria for allocating point scores need to be expanded in a way that will ensure more equity and uniformity. Alternatively, we should consider rounding off or grouping priority scores. I also believe the study section should see an anonymous tabulation of their priority score votes and should be encouraged to reassess the mean priority score on a proposal if there is a wide disparity in the individual voted scores.

Third, there ought to be a ceiling on the amount of annual NCI funding distributed to an individual laboratory. This would allow funding of a greater number of approved research proposals.

Vincent DeVita, NCI director—I really am surprised

every time we do one of these exercises that there is a great deal of support for limiting the amount of dollars to an individual investigator. But I have never come out of one with any idea of how I'm going to do that. How do you arrive at what is a cap limit or do you set cap limits depending on the field of the investigator? Do we average up the costs of grants in certain areas? It's a very sticky problem. Every time we try to come to grips with it we just come away with no feeling that we've accomplished anything. Everybody likes the idea and no one knows how to do it.

Harold Amos, member, President's Cancer Panel–I wanted to ask a question, again, following the proposal about a ceiling on individual investigators, whether Dr. Boyer and Dr. Mendelsohn considered this may make a positive contribution to the quality of research in some laboratories?

Boyer–Yes. I would like to comment somewhat in favor of what Dr. Mendelsohn said. The knowledge that the study section has of the total range of activities of some investigators is not sufficient at the time of review, but rather than have a figure that you cut off, you peer review process will do this cutting for you if the knowledge is available.

Barbara Bynum, director, NCI Div. of Extramural Activities–The question really has to do with moving the path of young investigators into the mainstream of research support. Were your comments meant to suggest that we should again reemphasize or revitalize this mechanism, or in Dr. Alfred's case, direct it to a specific clinical focus?

Alfred–My comment for young investigatorship development did in fact point to specific health problems. But more specifically I think the young investigators are left out to a great degree in the review process.

DeVita–I didn't mention that the only grant program we have that took no cuts in 1982 was the Young Investigator Award. It's a small grant program as it is, so we made no cuts. I wonder if I could ask either Barbara or Steve Schiaffino (deputy director, NIH Div. of Research Grants) to comment on Charlie Heidelberger's point about grantees suggesting their study section and suggesting reviewers as ad hoc members of those study sections.

Bynum–There's never been anything that precluded this particular source of advising the executive secretary regarding either the choice of study section, or some concern with the study section to which an application has been assigned. The Div. of Research Grants has always been responsive to concerns on the part of the investigator regarding misassignment.

Wendy Clough, USC–Of the suggestions that I've heard discussed in making existing funds go further in a fair manner, I'd have to say that three of them have particularly impressed me with their fairness and possibly even are suggestions which could be implemented. First, there be a limit on the dollar amount that any one individual can receive. To make this effective it could not just be the dollar amount received from NCI.

The second suggestion is that there be the same review for intramural NIH grants as there are for extramural NIH grants. We're all aware that there is much very fine research at NIH in all the institutes–certainly NCI–that would pass any, even the most stringent, review process with flying colors and be handsomely funded.

The third point is that somehow we find some way to hold the line on indirect costs and fringe benefit costs which are eating away our grant applications. More and more money is going into overhead and fringe benefits, and this means that less and less money is actually available to do the research.

James Doroshow, City of Hope–I would like to begin by relating my impressions of the effect of the peer review process on investigators who are just beginning. My dominant impression of the process is of its sheer magnitude. The planning and execution of grants submission, its prolonged period in review, and the ultimate awarding or denial of funding–a process of gestation requiring at least nine months–may produce some profound and sometimes not altogether healthy changes in the principal investigator. By virtue of its all or nothing outcome the stakes in this process are perceived to be extremely high and may lead to a skewed appreciation of academic life.

I would like to comment on what I see are certain positive changes in the funding process, measures such as sliding scale award determinations and alterations in indirect cost reimbursement that increase the absolute number of awards as outlined by Dr. DeVita at the Panel's meeting in Boston and here have a potentially significant impact.

Carol Newton, UCLA–Research on cancer necessarily extends from understanding and manipulating molecular mechanisms within the cell to final evaluations of efficacy in clinical trials. It needs the new ideas of young researchers and it needs the continuing contributions of established investigators who also have new ideas.

What is meant by 'fund people, not proposals'? I've never participated in a review that did not weigh heavily an investigator's abilities and accomplishments. I know of nobody who extols enlarging the paperwork, least of all those who must carefully read it.

Perhaps there should be renewable, salary only proposals and awards for certain established investigators, similar to the RCDA, but all other research applications should be evaluated competitively on the basis of their merit as well as that of the investigators who wrote them. They are not disembodied, irrelevant pieces of paper. A good research concept without some idea of who is to pursue it is almost a con-

tradiction in terms.

Yosef Pilch, UC (San Diego)—Should the NCI, at this time, be embarking on major, new national programs requiring large initial investment and ongoing commitments of funds? The new regional cooperative oncology groups, the CCOPs, etc.

Too much time is spent writing and reviewing too many grants. Encourage investigators to submit a single application covering their entire research program. Discourage multiple grants from individual laboratories. Fund such grants adequately and for longer periods of time, thereby reducing the frequency of reapplication.

DeVita—I want to bring everybody up to date on the change in the peer review system in the Intramural Program of NCI. Some years ago we set up a process whereby members of each of the divisional boards of scientific counselors would chair site visit teams and spend two days site visiting each of the intramural laboratories. In advance of that site visit there is a document prepared that has all the characteristics of a P01 grant application, so that they are now in the process of preparing and submitting these. Key elements are that they must show their budgets. The 6.1 percent cut that we have made this year has frequently been made by closing entire laboratories or half of a laboratory and not by just giving everybody a 6.1 percent budget cut.

Fisher—Okay. One of the themes that has kept coming up is this business of setting a dollar amount for research. Is this the same philosophy which results in study sections cutting and slashing grant applications? How is that going to really help you in the long run?

DeVita—There may be some merit in limiting new grants to well funded investigators by requiring that they have a better priority score in order to get another new grant. In other words, make the cutoff line different. But we will need an extraordinary amount of support from the community, because the first time a Nobel laureate submits a grant with a 150 and it doesn't get funded, there will be a large outcry. But generally this is what we're hearing and I think it's very good. We're getting the sentiment that this is probably something we should consider.

Robert Spallone, chief, NCI Grants Financial Data & Analysis Branch—In looking at 1981 R01 awards, we found that there were 2,015 principal investigators. Of those, 1,608 had one R01 and no other support. That leaves 407 principal investigators with more than one R01 or an R01 with other grant support.

Amos—I think there is one important point, this question of overlap between P01s and R01s.

Heidelberger—We are concerned about the total dollar support. There are clearly some scientific entrepreneurs that have probably multimillion dollars worth of grants, and even though they may be great entrepreneurs and Nobel Prize winners, may not be using this money as efficiently as some others.

Jane Henney, NCI deputy director—Would you cap within specific areas of science, some areas that are just more costly than others? And then, how would you get at this whole point of how high should the cap be?

Heidelberger—I don't know. It seems reasonable that one should cap differently within different fields which cost more, but how to set those numbers, I don't know.

Newton—I find myself concerned about anything that's arbitrary in our grant system. I think it's going to be practically impossible to find a rule that people will agree to. There are some real concerns here about the quality of research of a person who is spreading himself too thin, and I think that is what we should look at. Alert the study sections to the need to be observant about that, but I'd be very concerned about replacing the judgment of scientific reviewers looking at a situation by some kind of arbitrary rule.

Richard Steckel, UCLA—The NIH peer review system is not perfect, but. . . it is the best nationwide mechanism yet developed to determine the quality and the fundability of research projects. There also seems to be a consensus that the present national peer review system has at least two major defects: number one, the long response time or turnaround time for NIH grant applications; and number two, the reluctance on the part of some reviewers to give sufficient priority to highly innovative, scientifically worthy, but sometimes unconventional research proposals, particularly when untested young investigators are involved in these proposals.

Many major academic centers already have established excellent internal peer review mechanisms for research within their own institutions to review pilot project applications—a study section and a council, in effect. We have two study sections, in fact, one for the socalled basic science or bridging applications, and one for patently clinic or patient related applications. We have three deadlines per year for applications to be submitted to the cancer center.

I would suggest in the future that approximately one percent of the NCI budget be targeted for decentralized peer reviews by approved research institutions for innovative pilot projects for one year to 18 months only, with an upper limit of perhaps $30,000 for each grant. The use of matching funds from institutional resources should also be encouraged to support these pilot projects.

David Golde, UCLA—Serving on the study sections is an onerous responsibility, and I don't think we get the best peer reviewers because it's not a pleasant undertaking. It's extremely difficult. A certain influx of funding into the study section mechanism that will make it a truly pleasant and educational experience will get us better peer reviewers, and as the

quality of the peer reviewer increases, so will the process.

The staff at NCI has improved dramatically over the years. I would like to see more money spent on administration at NCI rather than less.

Lastly, I'd like to make a request for continuation of support for training programs to the extent that these training programs produce academic oncologists.

Stuart Siegel, USC—I would like to strongly emphasize the need for renewed support of young investigators and in particular the rejuvenation of a program involved with Research Career Development Awards. Finally, I would like to offer strong support for the concept of the program project grant and the cancer center core grant.

I suggest the term of review section members be shortened to encourage qualified scientists to commit the time necessary to provide thorough and thoughtful review.

David Plotkin, community oncologist—There have been some of us the community that have been bucking for a bigger role in clinical investigation by the private sector for a number of years. Now, more than ever, with government cutbacks, with hundreds of research trained medical oncologists in the community practicing, we are finally on the verge of cultivating research in the community.

The Assn. of Community Cancer Centers, although speaking loudly for the community based physician, is, I submit, an essentially political organization with very little demonstrated experience in clinical cancer investigation. If indeed valid peer review is to take place in the implementation of the CCOP, an effort should be made to find people in the community who have done clinical research.

Richard O'Brien, USC—There is no better paradigm for scientific review than peer review. And I think that what we are talking about are ways to improve peer review in a climate where funding is less than adequate.

I am really very impressed by the leadership at the National Cancer Institute and the staff because they are very responsive to recommendations and advice from outside, and in fact have begun to introduce changes in the peer review system as it's practiced under the control of the National Cancer Institute.

I would very strongly favor the support, not of projects, not of grant applications, but groups, individuals, or laboratories which have scientific goals and means to achieve those goals, judged primarily upon the basis of their scientific talent and capability, mostly on the basis of recent productivity.

Fisher—Who would like to make some comments about, well, say, about Dr. Steckel's comments about internal peer review? I think that's a new thought that's been presented before us.

DeVita—I think there's nothing bad at all about that. I think some set aside funds like that have been used in the past. There is a little pulling and tugging going on with the Biomedical Research Support Grants, which are perceived as the mechanism for doing this internally, and we have core grants that give that flexibility.

Boyer—I'd like to speak in favor of this flexibility of a small amount of institutional support to get that small investigator going. The institutions knows how to choose someone to try to start better than the study section.

Steckel—I would second this, of course. We're talking about careful institutional peer review by criteria that are acceptable to NCI and to its consultants and a careful peer review of the track record of the institution in the use of these limited funds.

DeVita—What I'm hearing would be an institute equivalent of the Biomedical Research Support Grants?

Steckel—Except that there is no requirement in the BRSG that this peer review system take place; it's only a recommendation.

Fisher—Mandatory service has been recommended. I think at least two times, but one suggested that this be for a very short time and the other suggested that it be for a long time.

Amos—If I may comment, I think it is one of the worst ideas that's been proposed. It's hard enough to get a grant properly reviewed by people who are happy to be there.

Boyer—I don't think you want mandatory requirements, but I think you could have a little bit of peer group pressure, and this you can do by various ways.

Fisher—I think it would be a shame to let Dr. Boyer go scot-free for his remarks that there has been a change in NCI from basic research to clinical research. The reason that some of this has happened is because the information pool which has resulted from basic research has led to the very things that you would want it to do, and that is to clinical application, otherwise what good is it? I just do not accept the idea that there is polarization of 'clinical' versus so called 'basic' research.

Siegel—I do agree with you. I think that what distinctions there may have been are really blurring considerably now, and I think that some of the mechanisms I mentioned of funding are helping to bring the clinical scientist and the preclinical scientist together.

William Longmire, new member of the Panel—We have to save a pool, a purely esoteric 'Golden Fleece' award, sort of, for research that needs to be done and that has no relevance to anything that's going on, just purely investigator initiated. I think a small amount of research still has to be protected.

Fisher—I couldn't agree with you more. I'm absolutely dedicated to basic research, above everything else, but I don't think the priority must be established between basic research and clinical research.

Malcolm Mitchell, USC—I'd like to make two suggestions concerning peer review. Judgment with disinterest can be rendered best by established senior scientists. To ensure that mature scientists will serve on study sections, make three years service on a study section mandatory for anyone who has held, or holds, a federal grant for research, with personnel changing every three years, rather than four.

My second point is that more attention be paid to funding well established programs of scientific solid citizens, not simply individual grant proposals. Review groups should try to maintain funding for the consistently productive eminent individuals

Jay Levy, Univ. of California (San Francisco)—The inexperienced researcher really doesn't know how to apply for a grant. If you read your booklet, you don't know the study sections, you don't know the expertise on the study sections, you don't know when you can write and find out the report from the study section, and something should be done to improve that area.

The area of biology is not being supported, and I think it's mainly because we aren't getting study sections aimed towards this direction.

What could we do to try to improve the rating in the study sections? Two reviewers would send in their review. The study section's secretary would then send those reviews, without writing a summary, directly to the principal investigator with the comment, 'There is very little chance your grant will be funded. You can benefit from these responses and then have time to come in with a better grant.' The investigator knows, not on June 15, but in March, that there is no funding from that source.

Denman Hammond, USC—The first point begs that there be much closer collaboration and coordination between the program staff at NCI and the review staff. They have been separated by mandate of the Inspector General, and yet, I think the pendulum has gone entirely too far.

Once an investigator was advised of the results of the review, prior to that action being reviewed by the National Cancer Advisory Board, an investigator should be encouraged to have numerous ways of communicating, commenting on the review. There are errors in the review process. There are miscommunications and misperceptions.

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP, citing the RFP number. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs to the individual named, the Blair Building room number shown, National Cancer Institute, 8300 Colesville Rd., Silver Spring, Md. 20910. RFP announcements from other agencies reported here will include the complete mailing address at the end of each.

SOURCES SOUGHT

Project No. N01-CP-26005-72

Title: *Expert panel review of monographs on drugs, medical procedures and cosmetic ingredients*

Deadline for statement of qualifications: *Aug. 2*

The Office of Scientific Coordinator for Environmental Cancer acts as an information resource by NCI by maintaining various data bases on environmental media such as air and water. The scope of this data base is now expanding to include drugs, medical devices and cosmetic ingredients.

To address these issues, NCI has previously awarded contracts for the preparation of reports concerned with "Carcinogenicity of Drugs and Medical Procedures" (N01-CP-05633-01) and "The Potential Carcinogenicity of Cosmetic Ingredients" (N01-CP-05633-02). In each case, the contractor has prepared monographs on a number (approximately 180) of priority chemicals which were selected with the advice and guidance of an external steering committee. The format of these monographs is similar to that used by the International Agency for Research on Cancer and includes a summary of chemical, physical, carcinogenic, toxicological and epidemiological data from the published literature. The contractor has not evaluated the quality of the data with respect to the evidence for carcinogenicity in animals and/or humans.

Due to the sensitive nature of the chemicals that will be reviewed, NCI requires the consultant services of a scientific organization that commands the respect of the national and international scientific communities. It will be the responsibility of this organization to convene and administer an unbiased and prestigious multidisciplinary "Expert Panel" that will revise and update the contents in these monographs, if necessary, and provide their conclusions regarding the adequacy of the evidence for carcinogenicity of these chemicals. This conclusion would be similar in nature to the last section (4.3) of the IARC monograph series.

Since this is not an RFP, the NCI wishes to receive statements of interest and qualifications from respondents who are comparable in scientific stature to organizations such as the IARC, National Academy of Sciences or the Federation of American Societies for Experimental Biology. The imprimatur of such organizations is imperative for reviewing such documents which will be quoted and disseminated to interested individuals in government, academia and various portions of the private sector. In addition, decisions made by such an "Expert Panel" may have a major impact on the outcome of regulation and manufacture of these agents.

Contract Specialist: Jackie Matthews
RCB, Blair Bldg., Rm. 2A07
301-427-8771

RFP NCI-CM-37535-29

Title: *Prime contractor for performance of protocol toxicology studies*

Deadline: *Sept. 30*

NCI's Div. of Cancer Treatment is seeking an organization to serve as prime contractor and assume responsibility for the development of toxicologic data suitable for filing with the Food & Drug Administration as part of investigational new drug applications. Such a prime contractor must have both technical management and laboratory capabilities. Technical management capabilities are essential to select subcontractors to conduct preclinical toxicology protocol studies of new oncologic agents, to supervise, monitor and analyze the results of such studies and to develop new protocols for the toxicologic evaluation of various types of agents intended for clinical use in cancer patients.

The current protocol for the toxicologic testing of cytotoxic agents utilizes mice and dogs on a single dose schedule and daily times five schedule. Modifications to the existing protocols are necessary when the mouse cannot be used because of the unusual nature (limited solubility, instability, etc.) of various oncolytic agents. This is especially important since the mouse is the primary animal species used for the prediction of safe human starting doses of oncolytic agents being developed for phase 1 trials and since the data developed in the house studies serve as the basis for the testing done in the dog. Therefore, laboratory facilities that are in full compliance with the Good Laboratory Practice regulations are necessary for the rapid evaluation of proposed modifications to the existing protocols when these situations arise.

Laboratory capability is also essential so that the program director of the prime contractor and the technical subcontractor monitors can periodically spend time in the laboratory in order to maintain currentness in the rapidly developing field of toxicology and to be fully cognizant of the impact of the FDA Good Laboratory Practice regulations.

The prime contract is divided into four tasks for ease of monitoring by the government and because the nature of the work falls naturally into distinct categories. Task I is designed to cover protocol studies of oncolytic agents, radiosensitizers, biological modifiers, radioprotectors, etc. Protocols for cytotoxic agents have been developed to the stage where they are documented and workable for many of the drugs. However, insoluble drugs and drugs which are relatively nontoxic in the mouse at the maximum achievable doses demand development of new methodologies to elucidate the toxicities inherent in these drugs. Protocols for the testing of radiosensitizer drugs are also developed and tested. Protocols for biological response modifiers have not yet been developed and will require a literature search, protocol development and laboratory validation before they will reach a stage where the laboratory work can be subcontracted.

Task II is any part of the protocol study used in Task I or any portion of the earlier published protocol (1973, Prieur et al.) and is used to evaluate agents that have had previous clinical use preclinical study, etc., but where existing data are not considered adequate for investigational new drug applications.

Task III covers organ specific toxicity testing in vitro as well as in vivo, from development of protocols to the actual in house testing of the protocols to disclose any potential problems that might occur prior to being sent out to subcontractors for implementation.

Task IV covers cost management, subcontractor management, quality assurance monitoring, protocol development for each specific agent (as required by the GLP regulations), computerization of toxicology protocols and results, etc.

A well equipped laboratory component is mandatory for adequate assessment of the validity of the data obtained from all studies. Experience in the toxicologic evaluation of drugs intended for human use is an important aspect of any potential offeror which may propose for the toxicology prime contract. Evidence of such experience should be reflected in the curriculum vitae of the principal investigator, who should be trained in toxicology/pharmacology at the PhD or equivalent level at an accredited school, scientists and technical monitors employed by that organization and should be supplied to the government as part of a response to this solicitation.

Additionally, the offeror must supply documentation demonstrating its corporate stability and the management experiences of the actual staff involved in the conduct of the contract. Laboratory facilities and equipment must be described in sufficient detail to assess their capabilities and capacity. The prime contractor office facility must be within 35 miles of the NIH reservation to permit the proper level and frequency of interaction between the contractor, the Toxicology Branch and various other segments of the Div. of Cancer Treatment.

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