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Facility Needs Panel Recommends $2.5-3 Billion, Seven Year Program To Be Run by NIGMS Or DRR

The "blue ribbon panel of experts" convened by NIH at the suggestion of Congress to study biomedical research facility needs and develop recommendations for meeting them will report that from $2.5 to 3 billion over a seven year program will be required to repair the infrastructure and expand it as determined by peer review. The program would not impinge

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In Brief

OMB Ends Apportionment; Carlo Croce To Head Fels Institute, Replacing Peter Magee Sept. 1

APPORTIONMENT, that old devil which in effect abrogated a portion of the National Cancer Act by severely limiting NCI's flexibility in reprogramming its funds, has been laid to rest by the White House. The President's FY 1989 budget specifies that NIH appropriations will go directly to the individual institutes, the practice followed prior to 1985. Legislation that year renewing biomedical research authorization, including the National Cancer Act, changed the word "shall" to "may" in directing the Office of Management & Budget to pass NIH funds to the institutes. OMB jumped on that language, which congressional staff members said was inadvertently changed, and began the practice which tied so many strings to any reprogramming efforts as to make them almost impossible to effect. Pressure from Cancer Program advocates, including members of NCI advisory groups, and from Congress forced OMB to back down. . . . **CARLO CROCE**, deputy director of Wistar Institute, will be the new director of Fels Research Institute at Temple Univ. School of Medicine, effective Sept. 1. Name of the Institute is being changed to Fels Institute for Research in Cancer & Molecular Biology. Croce will take over from **Peter Magee**, who is stepping down after more than 12 years as director. Magee will remain on the Fels faculty. Croce's field is the molecular and cellular biology of cancer. . . . **RICHARD ADAMSON**, director of NCI's Div. of Cancer Etiology, has made his selection of an associate director to head the Biological Carcinogenesis Program in his division. The recommendation has gone to the HHS secretary, who has final authority over the appointment since it is a Senior Executive Service position. Adamson expects the announcement to be made this month. . . . **NIH ADVISORY** group members and consultants are now receiving $150 a day for their time, up from $100.

Panel Recommends $2.5-3 Billion Over Seven Years For Facilities

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on existing construction authorities at NIH, such as NCI's, but would not specifically direct any of the new money to those authorities, according to the recommendations in the report.

The panel, chaired by Stephen Beering, president of Purdue Univ., met for two days last month to hear testimony from individuals who for the most part represented institutions involved in biomedical research. The first day was open, to hear the testimony, the second was closed to draft the report.

In last year's appropriations legislation, both houses asked for the report and cited the need for such information as the reason why no money was included for research facilities. The report has not been made public and probably will not until NIH Director James Wyngaarden presents it to Congress. However, **The Cancer Letter** has learned that:

*The report will recommend that from $100 to 200 million be made available for award through peer reviewed grants for each of the next two years, and that $500 million be available for each of the subsequent five years.

*The program would be administered either by the NIH Div. of Research Resources or the National Institute of General Medical Sciences.

*Awards would be based on merit review but allowances would be made for developing institutions.

*Awards would be made primarily for renovation of existing facilities, although the definition of "existing" and "new" can be vague and the lines fuzzy. Funds could also be used for acquisition of fixed equipment normal in functioning biomedical research laboratories, probably not for equipment such as MRI machines.

Neither NIGMS or DRR has a construction or facilities office with the capability of managing a construction grant program. One could be established rather quickly, either with former members of the NCI Research Facilities Branch, or by the transfer of present members of that staff.

Donald Fox, longtime chief of that Branch, which is located in the Div. of Cancer Prevention & Control, has been left without a lot to do, with no money to award. He does have several approved but unfunded applications waiting the day Congress turns construction money back on. In the meantime, Fox has been helping run the Centers & Community Oncology Program while the division searches for a replacement for Jerome Yates, who left as head of that program last October.

One issue discussed by the panel but not resolved was that of matching funds. NCI had required its facilities grantees to match NCI funds dollar for dollar. In practice, nearly everyone exceeded that, with institution and local support ranging from two to three times the NCI award all the way to the effort by the Arizona Cancer Center which came up with 15 times the federal money.

Some panel members felt that requiring grantees to provide 50 percent of the funds would be appropriate; others felt that 15 percent would be enough.

Over the last 10-15 years, NCI's construction budget has included money for renovation of intramural facilities, either on the NIH campus or at the Frederick Cancer Research Facility. There was no money for that either in the FY 1988 appropriations or in the President's budget for FY 1989. The pinch will be felt at FCRF this year, unless some of the $28 million NIH has that is earmarked for AIDS facilities can be used there.

Starting with the National Cancer Act of 1971 and even earlier, Congress has recognized the fact that if cancer research is to have any priority in the overall field of biomedical research, special authorities would be needed. That included construction, and it seems unlikely that Congress would initiate a multibillion dollar biomedical research program that bypasses NCI's authority and the expertise to manage a facilities grants program.

Without the means to support construction/renovation at cancer research centers, NCI would be unable to target high priority research needs.

Members of the panel in addition to Beering were Barry Bloom, Einstein School of Medicine; David Challoner, vice president for health affairs of the Univ. of Florida; Bernadine Healy, Cleveland Clinic Foundation; David Korn, dean of the Stanford Univ. School of Medicine and chairman of the National Cancer Advisory Board; Donald Langenberg, chancellor of the Univ. of Illinois School of Medicine; Chase Peterson, president of the Univ. of Utah; David

Satcher, president of Meharry Medical College; Benno Schmidt Jr., president of Yale Univ.; Edward Stemmler, dean of the Univ. of Pennsylvania School of Medicine; and Edwin Whitehead, chairman of Whitehead Associates.

Those making presentations represented the American Society of Microbiology, Assn. of Academic Health Centers, American Assn. of Colleges of Podiatric Medicine, American Assn. of Dental Schools, Assn. of American Medical Colleges, Assn. of American Universities, National Assn. of State Universities and Land Grant Colleges, Assn. of Independent Research Institutes and the Delegation for Basic Biomedical Research, Council on Government Relations, Federation of American Societies for Experimental Biology, Johns Hopkins Univ., Salk Institute, American Assn. of Colleges of Nursing, and the Univ. of California (San Diego).

Fox represented NCI, along with staff members from NIGMS, DRR, the Heart, Lung & Blood and the Eye institutes, and NIH headquarters.

CCOP Review Committee Member Objects To "Unwarranted Criticism"

James Mailliard, one of the reviewers in last year's recompetition of the Community Clinical Oncology Program, took issue with the contention by some of the unfunded CCOPs that the review was unfair (**The Cancer Letter**, Feb. 19).

"Your report. . .contains cricism of the ad hoc review committees which I believe is totally unwarranted," Mailliard wrote in a letter to the editor. "The alleged bitterness among those who were not given scores in the funding range is grossly unfair. The committee on which I served [Special Review Committee C which reviewed applicants affiliated with Cancer & Leukemia Group B] reviewed each applicant fairly, and as far as our committee is concerned, all CCOPs with a reasonably acceptable prior record received fundable priority scores. In my opinion, it is absolutely preposterous to suggest that good PIs with demonstrated experience and potential were turned down. We definitely rejected those who failed to provide satisfactory evidence that they could produce worthwhile data while accruing an acceptable number of patients to good phase 2 and 3 studies.

"A significant minority of the committee members lacked experience and, I agree, should not have been there, but most of our group are engaged in clinical trials in the community, and I strongly resent implication of inexperience.

"NCI staff input indeed was generally inadequate, especially in budget matters, an area where most physicians feel ill at ease. Exceptions were Drs. Robert Frelick [then the CCOP program director] and John Abrell [executive secretary of the review committees], who gave helpful support.

"I suggest that the next time around, we furnish a memorandum of 'helpful hints' to applicants. I don't want to put ELM Services Inc. out of business, but I suspect that some unofficial advice from the experienced would be very worthwhile for future applicants."

ELM assisted 19 CCOPs with their applications, 17 of which were funded.

Mailliard is director of the Div. of Oncology at Creighton Univ. School of Medicine.

Executive Search Exec New Executive VP of ACS; Murphy, Laszlo Sr. VPs

William Tipping, a principal in a Chicago executive search firm and longtime activist with the American Cancer Society, will be the new executive vice president of the Society.

Tipping, 56, was approved last week by the ACS Board of Directors for the position which will be vacated by the impending retirement of Robert Gadberry.

The Board also approved appointment of Gerald Murphy as senior vice president for medical affairs; and John Laszlo as senior vice president for research.

Murphy will take over the position held by Arthur Holleb, who wanted to retire last year but continued on while a search for his successor was conducted.

Laszlo will succeed Frank Rauscher, who decided to leave ACS rather than move to Atlanta, where the Society will relocate its national headquarters this year.

Tipping is partner and director of Hedrick & Struggles Executive Search Inc. of Chicago. He has been a volunteer with ACS since 1972, served on the Illinois Div. executive committee and was chairman of the division's board for two years. He has been vice chairman of the national board and chairman of its Public Information Committee.

Gadberry has been executive vice president since the retirement four years ago of the legendary Lane Adams. He had accepted the job

as an interim appointment until a permanent successor to Adams could be found.

Murphy, 54, is professor of urology at State Univ. of New York (Buffalo) and professor of biology at Niagara Univ. He has for many years been secretary general of the International Union Against Cancer, and is former director of Roswell Park Memorial Institute. He is a past national president of ACS.

Laszlo, 56, has been a member of the ACS national staff for two years, as vice president for research. He was formerly professor of medicine and director of clinical programs at Duke Univ. Comprehensive Cancer Center and had been an ACS volunteer for 20 years.

Tipping will be on the job within 60 days. Murphy will officially join the staff in July, by which time the move to Atlanta is scheduled to be completed. Rauscher also will leave by that time.

DCT To Renegotiate Terms Of Award, Possibly Revamp Cooperative Groups

The Board of Scientific Counselors of NCI's Div. of Cancer Treatment went along with the division's request for support of changes in the clinical trials program which could have a profound effect on the cooperative groups. Not all of the proposed changes were spelled out by DCT staff, but those that were included:

<>Terms of award in the cooperative agreements through which NCI supports the groups will be renegotiated "to allow more input (from staff) on the scientific quality and to terminate trials that aren't going anywhere," DCT Director Bruce Chabner said.

<>A greater emphasis on payment by case will be implemented.

<>The system in which high priority trials will be identified and physicians encouraged to participate whether or not they are affiliated with the groups conducting the trials will go forward.

Of perhaps greater impact on the cooperative groups was the significance of Chabner's remarks in summarizing the discussion following a presentation on clinical trials problems by Cancer Therapy Evaluation Program Director Robert Wittes.

"Streamlining the system might require a different structure than the cooperative groups," Chabner said. "We may want to try other models. We will not try to remake the entire system, and we do recognize the heterogeneity of the groups." He added that as groups come up for renewal of their cooperative agreements, "we will tie their funding plans to accrual, and we will ask the chairmen to renegotiate the terms of award."

The "terms of award" are provisions written into the cooperative agreements when they replaced grants as the funding mechanism for the cooperative groups. At that time, group chairmen were highly skeptical of the new mechanism and resisted anything that looked like increased control by NCI staff. The terms of award limits actions that can be taken by NCI in overseeing the program. With NCI's increasing concern over slow accrual (called by Director Vincent DeVita "a national disgrace"), staff's frustrations over being able to do anything about it is the basis for the discussions that have been going on for the past three years.

"We are going to explore restructuring some of the groups for case reimbursement," Wittes said. "That seems rational, and to us it makes more and more sense. It seems irrational to treat accrual differently from one group to another. We would like to have funds going out on the basis of accrual.

"That is not as revolutionary as it seems," Wittes continued. "Many affiliates are being paid now on that basis."

Wittes also said that "we are going to explore aggressively incorporation of surgical subspecialties" in clinical trials, "either by affiliating with present groups or by creating a new group." He cited head and neck surgeons as an example.

Wittes mentioned some of the restrictions imposed by terms of award that he would like to see changed. "We can't turn down a study on the basis of science but only on the basis of safety or similar flaws. I think the science can be better."

The present terms "are impossibly vague on the appeals process. It is impossible for us to say no without going through a process that is absurd."

Chabner noted that although the terms of award do include some provisions relating to accrual, "we can't really do anything about it." Even if an arbitrator agrees that accrual is too slow, a group can continue with the trial.

"We need some teeth in the system," Chabner said. "Accrual should be tied to the money. NCI should not have to pay for it if the study is not going to be completed in time to have any meaning. My feeling is that

once we pay for the base, the contribution of members has to be tied to funding."

Board member Ralph Reisfeld said it was not clear to him how the "carrot and stick" approach would be balanced.

"That will require intelligent interaction from us," Chabner responded.

Board member Charles Balch said "it is imperative that DCT staff have more flexibility. I'm a supporter of the cooperative groups, but I think we should bring in the surgical subspecialties. Surgeons play minor roles in cooperative groups now. To increase accrual, you're going to need more flexibility in using a range of options and funding of high priority options that you can't get through the existing cooperative group mechanism."

"That is a very important point," Chabner agreed. "Colon, lung and GU studies certainly need cooperation of surgeons."

Balch, head of surgery at M.D. Anderson, said there is "no way our urologists" to participate in the bladder cancer study approved as a high priority trial.

"Yes there is," Wittes insisted. "M.D. Anderson can affiliate with one of the groups just for this study."

In answer to Balch's question on how indirect funding would be handled in per case reimbursement, Wittes said, "There has to be a way to work it out. If not, we're in trouble."

Groups Said Unwieldy

Board Chairman John Niederhuber said, "It seems to me cooperative groups are almost unwieldy, that NCI is not getting its money's worth. It seems to me that we should move into the 1990s with disease oriented groups, with the leadership in house."

Board member James Cox, who is chairman of the Radiation Therapy Oncology Group, said, "The basic problem is that prestigious institutions with a lot of patients are not participating. They want to do creative studies. If those can be done with a cooperative group, okay. They need a carrot or a stick to encourage them. Anything that leads to better cooperation between the groups and the institutions with the tremendous scientific base and resources. It will work itself out."

Board member Emil Frei, who is chairman of Cancer & Leukemia Group B, said, "Speaking as a group chairman, I think you've done an extraordinary job of presenting the problem and developing some good proposals for improvements. A general administrative approach will not work. Groups are heterogeneous. Bernie Fisher (chairman of the National Surgical Adjuvant Breast & Bowel Project) has excelled working with only a few major centers, mostly with community physicians. But they can't do much far out stuff. At CALGB, we like to think we are primarily a science organization, with a majority of our centers doing phase 1 and 2 studies. . . My plea is what's going well does not need fixing. Leave it alone."

Frei continued, "John (Niederhuber) said that cooperative groups are no good. CALGB last year had three publications in the "New England Journal" and is presenting at two of the ASCO plenary sessions this year."

Alliance with ACS?

"We do not have to destroy CALGB," Chabner said, "but we may want to change it. We can't but up with taking six to eight to 10 years to complete a study."

Board member William Hryniuk said, "The American Cancer Society has an army out there. Why not dragoon them into the battle?"

Wittes agreed that an alliance with ACS might be helpful in convincing patients to participate in clinical trials. But, "If you sell the notion of clinical trials to consumers, you have to sell it as the best therapy. For the approach to patients to work, you have to sell the notion that they have to suspend judgment, and too many doctors say they have the answers, when no answers are available."

Board member Susan Horwitz suggested that the program should be pushed in the community, where most of the patients are. "That's why this (the plan for per case reimbursement) has a community thrust," Wittes said.

Board member John Mendelsohn said that the 10 top high priority trials "would not be a huge laundry list" to present to physicians. He suggested that NCI already has the mechanism to do that, through PDQ. Chabner suggested direct mail might be more effective. Wittes agreed but said that is also the most expensive.

"We have been assured by Dr. DeVita that if patient accrual is the most important issue facing NCI, and he says it is, funds will be made available to do what has to be done."

Chabner said that an extra $1 million will be available for clinical trials out of the current budget. "We'll see what we can do with that."

CTEP Drafts Approval Guidelines For FDA On Antineoplastic Agents

NCI's Cancer Therapy Evaluation Program has drafted its recommendations for FDA guidelines in approval of anticancer drugs. The guidelines are specifically for antineoplastics and emphasize endpoints in addition to survival benefit which should be considered in the approval process.

CTEP Director Robert Wittes presented the draft document to the DCT Board of Scientific Counselors. Members were asked to comment before the final draft of the document is sent to FDA for its consideration: The draft document follows:

Expeditious approval of anticancer agents that are beneficial to patients is a matter of highest priority. The demonstration that a new drug causes tumor regression and may improve the quality of life of patients who have cancers that are currently incurable should lead to approval for marketing even in the absence of supportive long term survival data. The criteria for approval need to be uniquely tailored to patients who have incurable, indolent or aggressive cancer, those who have failed on prior therapy or those who have disease for which there is no standard beneficial treatment. This degree of complexity requires participation by sophisticated clinical investigators with expertise in conducting such studies.

Assumptions

1. Safety and efficacy are appropriate requirements for drug approval.

2. Neither safety nor efficacy is an absolute concept in the context of cancer (or any other) treatment. Drugs are neither uniformly curative nor uniformly safe, nor are they ever likely to be. Thus, the approval process must approach flexibly the relation of risk and benefit in clinical settings having different underlying prognoses.

In particular, the approval process should be based on evidence that net benefit results from treatment for defined populations (or subpopulations) of patients. For example:

a. Agents showing significant benefit in patients with refractory cancer might be approved even in face of very substantial toxicity.

b. Agents that confer modest but reproducible levels of benefit in patients with refractory cancer should be approved if the level of toxicity is minimal.

c. For agents with intermediate degrees of benefit and toxicity, the weighing of this balance is more difficult, but the decision rests ultimately on whether demonstrated benefits to the treated population outweigh adverse effects.

d. Agents that avoid significant and specific organ toxicity may be approvable if they demonstrate benefit equivalent to a standard agent in a particular cancer.

3. Randomized clinical trials in support of an NDA or product licensing application (PLA) are generally the preferred means of drug evaluation. However, in patients who have refractory disease there characteristically is no standard therapy that provides reproducible benefit. In such cases alternative evaluative designs may be more appropriate medically and ethically. In such situations clinical trials cited in support of an NDA need not involve a comparative trial against a drug or placebo.

4. The premarketing experience with a drug should be sufficient to characterize its long and short term benefit and toxicity. Sufficient numbers of patients should be treated for long enough durations that uncommon but medically important tosicities, whether acute or chronic, will have a high probability of being detected. One would not have wanted to miss, for example, the cardiotoxicity of doxorubicin. Thus the appropriate length of followup should take into account the expected survival of the patients for whom the drug is intended.

5. Issues of relative effectiveness, i.e. how the new agent compares to other available treatments for the disease in question, are often medically important. Such questions can be addressed either in the pre or postmarketing period in randomized controlled trials. These comparative studies, however, should not be required for new agent approval if patient benefit can be established without them. Pivotal studies for an NDA or PLA may, of course, compare new therapy to a standard treatment but they must do this only when the labeling indications sought by the sponsor refer to a patient population for which effective standard therapy exists.

Approaches to the assessment of net benefit to the treated population

Acceptable endpoints include:

1. Survival benefit. Clearly an agent imparting a survival advantage to the treated population should be approved. Such a therapeutic effect is generally best shown in randomized control trials (RCT), although the effects of very potent agents or combinations of agents may be apparent even with historical controls (e.g. etoposide for the second line and ifosfamide for the third line treatment of metastatic germ cell tumors).

2. Time to treatment failure (or to disease progression) provides important information relating to drug efficacy and may be a useful parameter supporting approval. Involvement of TTF in the adjuvant setting is generally best shown in RCT.

3. Complete response rate. Across a variety of malignancies, a consistent increase in complete response rates has translated into increased survival and cure rates. Drugs that have reproducible and carefully documented complete response rates should be strong candidates for approval. Even in the presence of substantial toxicity, a significant complete remission rate, with responses of meaningful duration, may well justify drug approval, particularly for diseases having few good therapeutic options.

4. Response rate. Some have argued that virtually any drug with a response rate above some arbitrary level (e.g. 10-20% for many solid tumors) should be approved. Clearly any reasonable threshold level should be a function of the tumor type and stage in question (i.e. the threshold response rate for previously untreated indolent lymphomas might be very much higher than that for renal cell carcinoma or melanoma). The problem with this, however, is that it is not meaningful to consider response rate in isolation from duration of response and from the general level of toxicity.

5. Beneficial effects on disease related symptoms and/or quality of life. Qualify of life may be influenced by treatment induced decrease in symptoms of disease and/or reduction in the deleterious effects directly attributable to treatment. The aim here is to show improvement in tumor related symptoms, improved function, decreased reliance on medical support, gain in lean body mass, and other measures of patient benefit, in addition to tumor shrinkage. Such

improvement may be demonstrated by:

a. Comparison with standard therapy in an RCT. Here one must show equivalence or near equivalence in efficacy for the quality of life benefit to be medically meaningful, since ordinarily one would not want to sacrifice very much in survival for superior quality of life or symptom control. Individual patients and physicians might, however, come to rather different conclusions about the relative value of length of survival vs. a somewhat shorter survival that is of better quality.

b. Comparison of the post treatment status of the patient with his/her own pretreatment status. This approach has been used recently in the case of interferon alpha for hairy cell leukemia (reduction in transfusion requirement and infection rate after treatment) and in trials of somatostatin analogs in islet cell/carcinoid tumors (reduction in symptoms related to hormonal secretion). In other diseases, other parameters would have to be developed.

Illustrative Examples

1. Consider a hypothetical antiestrogen having response rate in previously untreated postmenopausal ER(+) patients about 30% (compared with about 50-60% for tamoxifen) and aabout 10-15% in patients who have previously responded to, and then failed, all other hormonal therapy including tamoxifen. Toxicity minimal.

Comment. For an indication centering on hormonally refractory patients, this drug should be approvable on the basis of a 10-15% objective response rate and essentially no toxicity. It should be very easy to show tangible patient benefit in the responders with an absence of treatment related toxicity. For an indication involving previously untreated ER (+) patients, however, comparison with tamoxifen in an RCT should be required. Indeed, the 30% response rate quoted above suggests that it might not be approved for this indication, since it appears to be only half as good as the established agent and has no other advantages.

2. Drug has a 20% response rate in kidney cancer, median duration 4 months, none lasting past 6 months. Severe refractory nausea and vomiting, lasting several days after each dose (q3w administration).

Comment. It is unlikely that the totality of data would support a claim of net patient benefit. Perhaps it might be approvable if the responders included patients with sympomatic liver, lung or brain disease who responded remarkably. It seems more likely that the short response durations and the severe nausea and vomiting would militate against approval.

3. Consider a hypothetical cytotoxic active against MOPP/ABVD failures with Hodgkin's disease. RR approximately 30%, all of which are PR. Median durations of responses are 5 months; none last longer than 8 months. Toxicity moderate: nausea and vomiting for 2-4 hours in 60-70%, grade 3 myelosuppression in 75%, urticaria in about 7%. Drug is given q 3 weeks.

Comment. A drug with these modest credentials seems unlikely to increase the effectiveness of initial chemotherapy if incorporated into primary combinations, though admittedly this 30% response rate may vastly underestimate its activity in less heavily pretreated patients. Nevertheless the drug should be approved for salvage use if the data in this group suggests medical benefit. Comparison with "standard therapy" in the salvage setting should not be required for approval since there is no standard therapy for this group that is medically meaningful. The basis for approval would be medical benefit to a group of patients for whom few other options exist. It is the sponsor's responsibility to show in its NDA application that this 30% response rate, plus the asociated toxicities, translated into overall benefit for the treated population. The best way of doing this would probably be to show better symptom control and quality of life in responders, compared to their pretreatment status, without strong adverse effects in the nonresponders.

4. Analog A, a chemical analog of Parent, has a similar spectrum of antitumor effect but with less toxicity (e.g. nausea and vomiting, major organ toxicity, whatever). Complete cross resistant with Parent.

Comment. If the sponsor can show net patient benefit, Analog A should be approvable for that patient population, without the necessity for comparative trials against Parent. The labeling indications of Analog A can be written narrowly without reference to Parent. Subsequent comparative trials can be done in the postmarketing period if a comparison is a medically important experiment in the particular clinical context. For example, the relative effectiveness and toxicities of 4-DMDR and daunorubicin, both in combination with Ara C, in the initial therapy of acute leukemia is a medically relevant issue, as is a comparison of cisplatin and carboplatin (each in combination with cyclophosphamide) in ovary cancer. On the other hand, a comparison of carboplatin and cisplatin (alone or in combination with 5-FU or bleomycin) in squamous head and neck cancer is much less important, because the role of cisplatin itself is less well defined in that disease.

5. Analog B is partially or completely noncross resistant to Parent.

Comment. Although this is a chemical analog of Parent, the lack of cross resistance means that the agent is likely to have a different spectrum of clinical activity. Analog B should be developed as a novel structure for both medical and regulatory purposes. Direct comparisons with Parent should not be required for approval unless the labeling indication requested is for a disease stage for which Parent is effective therapy and Analog B is being proposed as a substitute for Parent.

6. New drug with 30% response rate in kidney cancer, including 10-15% CRs that are relatively durable (median duration of PR about 6 months and of CR, >12 months). Mild toxicity.

Comment. Approve. Should be easy to show patient benefit, which should be presumed anyway because of the CRs.

(The draft document included one more hypothetical example along the same lines).

RFAs Available

RFA 88-CA-07

Title: In vitro transformation of human and animal mammary epithelial cells by chemical or physical carcinogens

Application receipt dates: May 6 or Oct. 17

Letter of intent receipt date: March 21

The Div. of Cancer Prevention & Control, through the Organ Systems Program (breast cancer) announces the availability of an RFA on the abaove subject.

Evidence suggests that carcinogenesis is a multistep, progressive process, with a number of heritable alterations accumulated during initiation and subsequent evolution to malignancy. It is important to define the specific alterations at each stage in this process. Toward this end, this RFA invites a search for methods by which we can succeed in obtaining efficient transformation of human and animal mammary epithelial cells to malignant cells in vitro by means of chemical or physical carcinogens. This research initiative seeks grant applicants with the following objectives: (a) to define in vitro conditions that allow high frequency transformation of rodent or human mammary epithelial cells using chemical or physical carcinogens; (b) to develop in vitro culture condi-

tions that optimally select for growth of mammary preneoplastic and neoplastic cells and favor this over growth of normal mammary cells; (c) to delineate markers (cytological, biochemical, molecular) that identify specific stages of in vitro mammary epithelial transformations and distinguish particular preneoplastic states in the multistep process; and (d) to develop improved in vivo systems for assaying tumorigenicity and to delineate functional growth assays, both in vivo and in vitro, that analyze mammary epithelial cell transformation and that correlate with tumorigenicity of the transformed cells in vivo (as in athymic, nude mice). Carefully designed studies are sought from investigators with expertise in cellular and molecular biology and experience in techniques of cell culture and transformation in vitro. The studies sought will require detailed exploration of specific experimental conditions for optimal transformation, and painstaking correlation of various phenotypic alterations with stepwise development of preneoplasia and neoplasia.

Laboratories with expertise in cell culture and in transformation are encouraged to turn their attention to mammary epithelial cell transformation by responding to this research initiative. Under this RFA, an applicant may apply for a period of support of up to five years. In addition, laboratories already involved in studies on mammary epithelial cell transformation are encouraged to expand their projects to focus on the aspects sought in this RFA; to facilitate such expanded focus on the aspects sought in this RFA; to facilitate such expanded focus, applications for appropriate for supplements to ongoing NCI grants may be submitted as responses to this RFA. A response is possible on either of the two response dates, i.e., as part of either, but not both, of the two competitions. Applicants are encouraged to submit a letter of intent and to consult with NCI program staff before submitting an application. The letter of intent should specify which response date the applicant is choosing. It is anticipated that approximately five awards (total over the two cycles) may be made as a result of this RFA.

Copies of the RFA and further information may be obtained from Dr. Elizabeth Anderson, Breast Cancer, Organ Systems Section, Cancer Centers Branch, DCPC, NCI-NIH, Blair Bldg Rm 721, Bethesda, MD 20892, phone 301/427-8818.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda MD 20892. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring MD, but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-85077-42
Title: Dietary surveys and food composition data
Deadline: Approximately April 17

The primary goals of this procurement are: (1) to obtain existing dietary survey and food intake data on individuals in various international populations and to establish a classification scheme, computerized data base, and retrieval software for these data; (2) to maintain a data exchange standard based on an international food language, convert various food component data sources to the standard, and develop a retrieval network.

These efforts will provide valuable research resources for better understanding the relationship between diet and cancer.

Contract Specialist: Joanne Feldman
RCB Blair Bldg Rm 2A07
301/427-8745

RFP NIH-NIAID-IAIDP-BAA-88-23
Title: Acquisition of data for developing improved strategies for conditions of bone marrow and to facilitate the transplantation of immune cell depleted marrow grafts
Deadline: Approximately April 18

The Genetics & Transplantation Biology Branch of the Immunology, Allergy & Immunologic Diseases Program of the National Institute of Allergy & Infectious Diseases is soliciting proposals for the acquisition of data, through preclinical studies, relevant to the development of improved strategies for conditioning bone marrow to facilitate the transplantation of immune cell depleted marrow grafts. Offerors are encouraged to submit proposals relevant to any one of the three general areas of research interest described in the broad agency announcement. Topics include:

Description of the host cell population participating in the rejection oif T-cell depleted bone marrow, including lymphokines secreted by each population; definition of the alloantigens recognized by the cells effecting the rejection of BM; the relationship of presensitization (i.e., prior transfusion) to increased rejection; optimization of the conditioning regimen to promote BM engraftment and prevention rejection; description of agents effective in inhibiting the growth and function of cells involved in BM rejection; the role lplayed by the marrow microenvironment, including marrow histocompatibility, in the rate of the recovery of marrow and immune function following BMT; the relationship of thymic function (i.e., age) to rate of recovery of T-cell function following the transplantation of HLA matched or mismatched BM; the role of cytokines (growth factors) IL-4 and IL-5 in the recovery of post transplant B-cell responses in recipients receiving grats depleted of both B and T-cells; the role of post transplant immunotherapy in the delayed onset of immune cell recovery; the role of different pretransplant conditioning regimens in altering the speed of immune cell recovery (i.e., alteration of thymic or marrow stromal cells); isolation and cultivation of pure populations of pluripotential hematopoietic stem cells; examination of the kinetics of engraftment following stem cell transplantation; and determination of the role of lpretransplant conditioning regimen and the role of specific cytokines (growth factors) in promotion of stem cell engraftment.

Three to 10 contract awards are anticipated as a result of the announcement. It is anticipated that the awards will be made on a cost reimbursement basis over a multiyear period.

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