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In Sign-Off Of Two Orphan Drugs, ODAC Leaves Efficacy Interpretation To Docs

The FDA Oncologic Drugs Advisory Committee last week recommended accelerated approval for an intrathecal treatment for lymphomatous meningitis and full approval for a topical treatment of AIDS-related Kaposi's sarcoma skin lesions.

The committee's 6-1 vote for approval of the meningitis treatment DepoCyt is likely to demonstrate whether the accelerated approval mechanism can provide a shortcut for getting drugs to market on the basis of evidence that would be considered too slim to support full approval. DepoCyt is sponsored by DepoTech Corp. (Nasdaq: DEPO) of

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In Brief:

McDonald, Coolidge Lead ACS; Medals Awarded To Rosenberg, Boutwell, LeMaistre

AMERICAN CANCER SOCIETY elected officers at its annual meeting in Atlanta Nov. 15. New president is **Charles McDonald**, professor of medical science and chairman of the Brown University Department of Dermatology, and physician-in-chief of the Department of Dermatology at Rhode Island Hospital. He succeeds **David Rosenthal**, director of Harvard University Health Services. **Francis Coolidge**, partner in the Boston law firm of Ropes & Gray, was elected chairman of the board. He succeeds **Jennie Cook**, an accountant from Larkspur, CA. Elected vice president and president-elect was **Gerald Woolam**, clinical professor of surgery, Texas Tech University School of Medicine. Other officers: Chair-elect, **John Kelly**, director, Navy Family Service Center, Gulfport, MS; vice-chair, **John Baity**, senior partner in the New York law firm of Milbank, Tweed, Hadley & McCloy; Medical Affairs Committee chairman, **Dileep Bal**, chief, Cancer Control Branch, California Department of Health Services; Medical Affairs Committee vice-chairman, **Robert Young**, president of Fox Chase Cancer Center, Philadelphia. . . . **ACS MEDAL OF HONOR** Awards: **Saul Rosenberg**, of Stanford University School of Medicine, received the clinical research award for studies of malignant lymphomas and leadership in developing the field of medical oncology. **Roswell Boutwell**, professor emeritus in oncology, McArdle Laboratory for Cancer Research, University of Wisconsin, received the basic research award for advancing the understanding of carcinogenesis. **Charles LeMaister**, former president of M.D. Anderson Cancer Center, received the cancer control award for "being a prime mover against the tobacco industry."

ODAC Gives Drugs "Benefit Of The Doubt," Chairman Says

(Continued from page 1)

San Diego.

In another application, the committee voted 8-1 for approval of Panretin gel (alitretinoin). Though the therapy often substituted rashes for lesions, the committee was apparently influenced by the patients' perception of benefit from the therapy. The treatment is sponsored by Ligand Pharmaceuticals Inc. (Nasdaq: LGND) of San Diego.

Overall, the recommendations at the Nov. 16 meeting illustrate the inclination by ODAC to recommend approval of drugs based on evidence that the therapy may benefit small groups of patients, as well as the committee's willingness to leave it to physicians and patients to interpret the data on the package insert.

ODAC does not expect blockbuster drugs, said committee chairman Janice Dutcher, an oncologist at Our Lady of Mercy cancer center in the Bronx. "The committee's approach is to give drugs the benefit of the doubt," Dutcher said to **The Cancer Letter**. "We don't expect home runs. If there is an indication that a drug offers some benefit with acceptable risk, we recommend approval, and leave it to physicians to evaluate it for themselves when they see it in patients."

The committee's apparent generosity with the benefit of the doubt does not amount to an open invitation to NDAs that demonstrate little more than vague hints of efficacy. "I am not particularly concerned about this being precedent-setting," ODAC member Richard Schilsky said to **The Cancer Letter**. "I take the view that you have to evaluate each case on its own merits, and I wouldn't try to extrapolate from this to other circumstances."

Both DepoCyt and Panretin are orphan drugs intended for populations in which patient benefit resists objective evaluation. Studies supporting the two applications did not set increased survival as an endpoint. However, committee members said both applications provided a compelling theoretical basis to support potential efficacy.

—The application for DepoCyt, an injectable sustained-release formulation of the chemotherapeutic agent cytarabine (Ara-C), was based on a trial that enrolled 33 patients who were randomized to DepoCyt or unmodified Ara-C. With enrollment this small, the company barely cleared 14 patients per arm, the minimum number required to continue enrollment in preliminary phase II trials. Moreover, the study was marred by multiple violations of the protocol, FDA said in its review of the data. Flaws notwithstanding, the studies suggested that the drug produced responses in some of the patients.

—Though Panretin produced a response in 15 to 35 percent of patients, depending on criteria used, in 75 percent of patients the drug produced rashes. In 34 percent of cases, the rashes were painful, company data shows. The committee appeared to be convinced by the patients' perception of benefit from the therapy. The case for approval was further enhanced by the fact that Panretin is a retinoid compound, which places it into a class of therapeutic agents widely studied in cancer.

DepoCyt May Test Accelerated Approval

Now that ODAC has spoken, DepoCyt may well become the drug that will test the underpinnings of the accelerated approval mechanism.

Accelerated approval was established in 1992 in response to pressure from AIDS activists. To obtain accelerated approval, sponsors do not have to demonstrate conclusive evidence of clinical benefit.

Drugs may qualify "on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint" to predict clinical benefit.

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Sponsors who obtain accelerated approval must agree to continue studies that would "verify and describe clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome."

FDA regulations do not set deadlines for completion of the studies. However, the sponsors are expected to carry out the studies with "due diligence." ODAC would be expected to review the data if the drug is to be taken off the market or receive full approval.

In cancer, accelerated approval has been granted to Rhone-Poulenc Rorer's Taxotere, and Pharmacia & Upjohn's Camptosar. Both drugs have subsequently obtained full approval.

The DepoTech presentation was literally a last-ditch effort by the company to salvage its product.

"Your assessment today is critical to the future of this drug," said Stephen Howell, professor of medicine at the University of California at San Diego, and medical director of DepoTech. "As many of you may know, [DepoTech] has run out of money and will go out of business. The company has time to execute a merger and a transfer of this technology to another partner, but the level of enthusiasm that you express here today will determine whether any further studies of this drug will be undertaken."

The quality of data as well as the history of the product made it a challenge for ODAC to muster the "enthusiasm" Howell requested.

Last December, the committee said the trials were inadequate to support full approval of DepoCyt for neoplastic meningitis from solid tumors. Last May, FDA sent the company a "non-approvable letter" on the application. Last month, the company withdrew its European application for neoplastic meningitis for solid tumors when regulatory authorities determined that additional trials would be required.

However, last summer the company and FDA agreed that the data warranted a submission of an application for accelerated approval for the narrowed indication of lymphomatous meningitis, the company said. The application was based on the surrogate endpoint of response, defined as the disappearance of malignant cells in the spinal fluid in the absence of neurological progression.

Meanwhile, the company's losses mounted. As of Sept. 30, accumulated deficit reached $93 million, the company said.

Last month, DepoTech made an agreement to merge with Skye Pharma Plc., a London-based company that paid about $30.7 million to purchase all outstanding DepoTech stock. Sky Pharma would pay an additional $25.7 million if DepoTech could meet "performance milestones" that included getting DepoCyt approved and launched before April 2000.

DepoCyt is administered once every two weeks, as opposed to two to three times per week for unmodified Ara-C. However, FDA regulations do not name patient convenience among criteria for accelerated approval.

Accelerated approval regulations apply to drugs that provide "a meaningful therapeutic benefit over existing treatments." The benefit is defined as "ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response to available therapy."

The language of the regulations is difficult to interpret in relation to DepoCyt for lymphomatous meningitis, said Robert Temple, director of the Office of Drug Evaluation One of the FDA Center for Drug Evaluation and Research.

"We don't have anything approved for this use at all in this disease, and we are currently agonizing over what [existing treatment] means," Temple said. "Is it something we've approved? That's the FDA arrogant point of view. Or is it something people are using and think they are fine? We haven't actually pinned that down. But I would say that if there isn't anything approved, that goes some way toward saying that appears to work, has some credibility in saying that it is better than the available therapy."

The DepoCyt application was based on a five-year trial with the enrollment of 33 patients, including the control arm, which received unmodified Ara-C.

The company said it was unable to enroll more patients because lymphomatous meningitis is relatively rare. About 6,000 people per year develop the condition in the US. Since no more than 3 percent of all cancer patients enter clinical trials, at the most 180 patients would have been available for the study annually, the company said.

A large percentage of lymphomatous meningitis patients receive no treatment for the condition, which many clinicians view as a reasonable treatment option in the absence of an established therapy and criteria for defining patient benefit.

The picture was further clouded by numerous protocol violations, FDA officials said. According

to the agency's summary of protocol violations, two patients in the treatment arm received forbidden treatments, pathology samples were not reviewed at a central location, samples were collected late, and tumor sites that yielded abnormal samples were not consistently checked.

The company offered no apologies. Instead, it alleged evaluation errors by the agency staff, and said no additional studies would be possible because the company had spent its development funds, and was in the process of being sold.

"There are two ways of looking at this," Howell said. "We didn't get all the information that we had originally sought. One can take one approach of focusing on the deficiencies of the data set, looking at all the things we said we would do in the protocol and in the end could not do.

"Or one could celebrate the fact that a randomized trial has finally been done in a rare and difficult disease, and it provides evidence that these patients can effectively be treated with many fewer injections of a reformulated, established drug," Howell said.

To assess response, FDA suggested three "scenarios" for interpretation of data. According to a scenario that ignored all protocol violations, response was demonstrated among 12 of 16 evaluable patients receiving DepoCyt (75%), compared to seven of 15 evaluable patients receiving Ara-C (47%).

Under the least forgiving scenario, response was reported among three of seven evaluable patients receiving DepoCyt (43%), compared to one in eight receiving Ara-C (12.5%).

Another scenario, which ignored some of the violations but forgave others, response was reported among seven of the eleven evaluable patients in the DepoCyt arm (64%), and one in eight (12.5%) for Ara-C. Median duration of response varied between 38 and 59 days, depending on the scenario.

According to FDA evaluation, new onset headaches were the most serious side effect of DepoCyt therapy. On the DepoCyt arm, eight patients experienced new onset drug-related headaches, four of which were rated "serious." On the Ara-C arm, one patient experienced a serious headache.

Overall, side effects could not be easily separated from manifestations of the disease. Moreover, improvement is not expected in meningitis patients who suffer neurological damage from meningitis, which means patient benefit can be defined as slowing down of progression.

"I think you have to define what the existing treatment is," said committee member James Krook, principal investigator at the Duluth CCOP. "If you look at what the sponsor presented, they had trouble getting to agree to treatment. I don't think we have a reasonable existing treatment. There is a fair number of people with this disease that never get treated. Most of us struggle in these patient populations. When do you say they are better? When do you say they are worse?"

Clearly, the data did not generate a celebratory mood among committee members.

"The thing that I've been most persuaded by from the data we've seen today is that plain old Ara-C is pretty poor therapy for this group of patients," said Schilsky, director of the University of Chicago Cancer Center and chairman of Cancer and Leukemia Group B. "By comparison, this drug is not clearly worse, and clearly easier to give. I think that those things should cause us to think about value of having this therapy available."

Committee member Kim Margolin disagreed.

"If you look at the numbers, they are so small that if you decide to take the biggest numbers, which are intent to treat, or the smallest numbers, which are evaluable patients, we barely even come close to the usual two-stage rule for phase II studies, where you need one responder in 14," said Margolin, a medical oncologist from City of Hope National Medical Center. "So if you look at an eight- or 10-patient sample, we haven't even seen that plain old Ara-C is so lousy."

Since no therapy exists for the indication, it may be appropriate to approve DepoCyt, suggested patient representative Susan Krivacic.

"From the patient perspective, I suggest making it available, because there is not a whole lot out there," she said. "You've got dying patients. Give them a choice. I mean, we are a democratic society."

"I am not unsympathetic to that, but that would be an illegal act on our part," said Temple. "We have to reach a conclusion. There is obviously a great deal of flexibility how we reach that conclusion. These things have precedent-setting qualities."

Given these data, the committee could not possibly have relished having to decide whether response rates for DepoCyt and Ara-C "establish" that DepoCyt provides a meaningful advantage over "existing treatments."

"Can we change 'establish' to 'suggest'?" asked

ODAC Chairman Dutcher.

"I don't think that's strong enough for the regs," Temple replied.

After compromising on the word "support," the committee voted 7-1 in favor of DepoCyt.

Several FDA-watchers said to **The Cancer Letter** that it is unclear how the use of the change from "establish" to "support" would affect either the final approval of the drug by FDA or the agency's subsequent standards. However, observers agreed that if DepoCyt is approved, the industry would be likely to view this action as a relaxation of standards under the accelerated approval mechanism.

The committee recommended approval of the therapy in a 6-1 vote, with Margolin casting the vote in opposition, and Krivacic abstaining.

In a telephone interview, Dutcher said the sponsor will be expected to produce high quality data in post-approval studies. "They met the burden of proof for a lower threshold," Dutcher said to **The Cancer Letter**. "The committee was not happy with the quality of data, and will want to see further data."

Accelerated approval differs from "fast track," a mechanism that sets a six-month deadline for the agency to complete approval of drugs that treat life-threatening diseases and address unmet needs.

Recently, the agency published a draft "guidance to industry" on both mechanisms. The document is available at http://www.fda.gov/cber/gdlns/fsttrk.pdf

Patient Satisfaction Crucial For Panretin

Patient benefit was an elusive concept in the Panretin application.

AIDS Clinical Trials Group criteria for assessment of Kaposi's sarcoma are out of date, physician evaluation is subjective, and photographs are better at demonstrating progression of disease than its response to therapy.

According to Ligand's data, in a 12-week blinded phase of a phase III study, 35 percent of patients responded, in accordance with ACTG criteria. Based on physicians' global assessment, response rate was 19 percent, and based on photographs, response rate was 15 percent.

Side effects included rashes, reported in 75 percent of patients; pain, reported in 34 percent of patients; and pruritus, reported by 13 percent. However, patients overwhelmingly reported satisfaction with Panretin, company data showed.

"If it's at all helpful in terms of psychological and aesthetic effects, then, certainly, it's well worth looking at," said E. Carolyn Beaman, president of Sisters Breast Cancer Network and consumer representative on the committee.

The patients' satisfaction with the results was puzzling, said FDA medical reviewer Robert White.

"You may be able to speculate that with all this redness that the patients were seeing, they may have interpreted that as being activity," White said at the meeting.

ODAC member Krook said cancer patients often view side effects as an indication of activity of a therapy. "In medical oncology, we can give drugs, and as long as people get sick, they think they are getting better," Krook said. "If I don't get nausea and if I don't lose my hair, the drug is obviously not working. Some of this has to be the same thing: perception of redness as an improvement."

Ultimately, the treatment did not entail any serious negative effect, said Margolin. "I don't think we've seen anything that would suggest that patients who have had access to this kind of treatment—which the company is not claiming is not anything other than superficial benefit—have gone on to develop more life-threatening problems either due to their disease or due to this therapy," Margolin said.

The sole nay vote was cast by patient representative Michael Marco, director of opportunistic diseases at Treatment Action Group. "I can't see how the risk-benefit comes out for the drug or for the patient," Marco said. "To replace a lesion with a large red mark with pain, I just don't think is worth doing."

Dutcher said the majority of members vote to give patients a choice. "I think the rest of us are voting yes to have people have an option if they so choose," she said.

Though the company sought to have the drug approved as a first-line therapy for KS, the committee recommended against the "first line" designation.

"I have problems with 'first-line,'" said Krook. "I think we should leave it to the clinician whether it should be second, third, or fourth. I could see using this as first-line, but I don't think we saw anything that says this is better than radiotherapy or better than some of the other modalities."

In a vote that is most likely to set a precedent, the committee voted unanimously in favor of including "cosmetically beneficial response rate" based on photographs in the package insert for Panretin.

NCI Programs:

Tobacco Control Research To Get $142 Million Infusion

Advisors to the National Cancer Institute have approved the Institute's plan to spend $122 million over the next five years for research on tobacco control.

The NCI Board of Scientific Advisors unanimously approved two new grant programs designed to begin a five- to seven-year process of carrying out the recommendations of the Tobacco Research Implementation Group, an advisory panel that developed a blueprint for the Institute's tobacco research program.

With the addition of funding from the National Institute on Drug Abuse, the two new programs will provide $142 million in tobacco control research over five years. NCI spent an estimated $80 million on tobacco research in FY98, and $76 million in FY97.

In the first initiative, NCI will commit $50 million and NIDA will commit $20 million over five years to fund Transdisciplinary Tobacco Research Centers. These centers will be modeled on NCI's Specialized Programs of Research Excellence.

"These centers have the potential to dramatically alter the way tobacco research is conducted on a national level and to speed the pace of discovery, leading to a major public health benefit by reducing tobacco use," NCI Director Richard Klausner said in a statement.

"The collaboration between NCI and NIDA emphasizes the need to focus on all aspects of the problem, the causes, prevention, and treatment of nicotine addiction and its dramatic health consequences," said NIDA Director Alan Leshner.

For the second program, NCI will provide $72 million over four years for research on state and community tobacco control intervention. With last week's signing of a settlement agreement between 46 states and the tobacco industry, the states will have additional funds for tobacco control programs. The new research funded by NCI could give state officials better information on the most effective interventions, NCI officials and BSA members said.

NCI announced the funding in a Nov. 19 press release that emphasized the Clinton Administration's support for the new programs. "This implementation plan will focus the nation's commitment to forge a body of knowledge that will guide tobacco use research into the next century and help turn the tide on the epidemic of tobacco-related diseases," HHS Secretary Donna Shalala said in the statement.

The TRIG report's summary was presented to the BSA in September (**The Cancer Letter**, Oct. 16).

The full report, "The National Cancer Institute Tobacco Research Implementation Plan, Priorities for Tobacco Research Beyond the Year 2000," is available on the NCI website at http://dccps.nci.nih.gov/tcrb/trip/

The excerpted text of the concept statements follow:

Transdisciplinary Tobacco Research Centers. Concept for a new RFA, four to six awards, first-year set-aside $10 million, total cost $50 million over five years. Program Director: Glen Morgan, Tobacco Control Research Branch, phone 301-496-8584.

The purpose of the TTRCs is to facilitate a transdisciplinary approach to the full spectrum of basic and applied research on tobacco use, including: initiation of tobacco use (including the impact of advertising and marketing), prevention of tobacco use, addiction to tobacco and/or treatment of tobacco addiction and tobacco-related cancers as well as the identification of genes related both to addiction and susceptibility to harm from tobacco. Basic biological processes related to carcinogenesis and gene-environmental interactions as a consequence of exposure to tobacco also should be examined. The use of genetic information for tailoring treatments to genotype as well as various kinds of psychosocial tailoring should be topics of inquiry. Centers also can address questions about how to reduce the burden of tobacco-related illness among former smokers and how to disseminate and implement effective cessation strategies. Research on the interaction of tobacco use and other licit and illicit substances, e.g., alcohol, also could be undertaken.

There is an urgent need for new investigators who have the quality and breadth of training necessary to conduct cutting-edge research related to tobacco. Such training should expose young investigators to the multiple levels of research that address tobacco-related issues. Because tobacco scientists are widely dispersed by geography and discipline, this type of training is difficult to obtain. By emphasizing meaningful integration and collaboration among scientists, the centers would provide a challenging and unique venue for training the next generation of tobacco researchers.

The level of specialization in different aspects of tobacco research will vary from center to center. However, the centers should focus thematically on areas, such as adolescent smoking, in which there are significant gaps in our knowledge and critical needs, areas where focused, collective, transdisciplinary efforts could make a difference. It is hypothesized that the TTRCs will catalyze problem solving and lead to more rapid advances in

knowledge than would be possible by depending on individual investigators working in relative isolation. Such centers also, by their very organization, can apply successful concepts from private industry, such as the systematization of research, to enable knowledge gained from one target to be transferred to related targets.

Investigators located within a particular institution or institutions would be augmented by those from a distance, forming "virtual collaboratories." The centers also are encouraged to form partnerships with industry, e.g., in drug discovery. In addition, the centers themselves would come together for an additional level of synthesis. Thus, the centers will include a range of disciplines and investigations, consolidate expertise, and facilitate collaboration and the synergy that can result from diverse people working together. The result should be major scientific in knowledge about tobacco use and its prevention and treatment.

As an example, a center focusing on adolescent tobacco use might address such questions as: Why do some children experiment with tobacco and become addicted while others do not? This requires examination of genetic, social, cultural and economic factors. In the past, the question often has been approached from a discipline-specific perspective, at a single level of analysis. But that is not sufficient. The center would be expected to bring together investigators and propose research projects that incorporate the constructs and research tools of multiple disciplines. By testing broader conceptual models, the interactions between genetic and sociocultural factors, for example, could be examined within a single adolescent smoking research project. Similarly, studies of cessation might examine how the effectiveness of pharmacological methods interact with developmental stage, genotype, psychological functioning, and family history of tobacco use. The translation of basic tobacco-related research also requires transdisciplinary collaboration to insure that new interventions (e.g., school-based prevention programs) are informed by the latest research.

Support of this NCI-NIDA research program will be through the specialized center grant (P50) mechanism that has funded NCI's SPOREs. This mechanism supports any part of the full range of research and development from basic to clinical and intervention studies. The spectrum of activities will comprise a transdisciplinary attack on the tobacco problem. These grants differ from traditional program project grants in that they are more complex and flexible in terms of the activities that can be supported. In addition to support for transdisciplinary research projects, support is also provided for career development, pilot research projects, specialized resources and shared core facilities.

The P50 SPORE mechanism was chosen because of its stated objective of translating basic research findings to applied, innovative research with patients and populations, with the ultimate objective of reducing risk, incidence and mortality. SPOREs include innovative pilot projects, a career development program, cores, and other resources dedicated to translational research objectives.

Requirements:

—Strong PI who provides overall leadership.

—Evidence of institutional commitment.

—A transdisciplinary theme and focus.

—A minimum of three research projects.

—Shared/core resources.

—Career development. The TTRC should demonstrate a consistent commitment to career development, and a plan should be included with the application. NCI is committed to cross-training opportunities for scientists. The development of interdisciplinary scientists who have the facility to move from one scientific domain to another in solving problems is a critical need in tobacco research. At a minimum, all trainees should receive training in other areas; e.g., basic scientists should be exposed to behavioral research and vice versa.

—Developmental and pilot research.

—Intra- and inter-center collaborations.

NCI policy for SPORE grants establishes the following limits to the requested budgets: A new P50 SPORE application may request a maximum annual direct cost of $1.5 million and maximum annual total cost of $2.5 million. In complying with the direct cost cap of $1.5 million, the indirect costs related to subcontracts to other institutions or organizations will not apply toward the direct cost cap, but the total dollar request may not exceed $2.5 million. Future year increases are limited to three percent and may not exceed this cap. A TTRC grant application may request up to five years of funding.

Board discussion: BSA member Sharon Murphy, chairman of the Pediatric Oncology Group, said the tobacco centers concept "amounts to a whole new centers program" that should be reviewed more frequently than every five years when the grants come up for renewal. When the program is reviewed, it should be reviewed using the same metrics as proposed for the SPORE program, said BSA member John Minna, director of the Hamon Center for Therapeutic Oncology Research at University of Texas Southwestern Medical Center.

Barbara Rimer, director of the NCI Division of Cancer Control and Population Science, said a panel of extramural scientists would be formed to provide oversight for the program. "We are committed to making sure it works," she said.

BSA member Robert Greenberg, director, Norris Cotton Cancer Center, said he commended NCI for the program's "coherent research plan" and for involving NIDA. However, he disliked the use of the word "transdisciplinary," which, he said, wasn't in his dictionary. He advocated putting the word "use" in the

title to emphasize research on tobacco use, rather than the consequences of smoking.

In his presentation of the concept, Robert Croyle, NCI associate director for behavioral research, defined "transdisciplinary" as the "development and application of a shared, integrative conceptual framework based on discipline-specific theories, concepts, and methods. Instead of working in parallel, investigators collaborate across levels of analysis and intervention to develop a comprehensive understanding of tobacco use."

BSA member Caryn Lerman, director of cancer genetics, Lombardi Cancer Research Center, defended "transdisciplinary" in the title, saying that the research envisioned in the program "sort of transcends."

Research in State and Community Tobacco Control Interventions. Concept for a new RFA, 12 to 15 awards, first-year set-aside $18 million, total cost $72 million over four years. Program Director: Marc Manley, chief, Tobacco Control Research Branch, phone 301-496-8584.

The goal of this project is to support research on tobacco control interventions relevant to state and community tobacco control programs in order to inform program development and improvements. This will be achieved by investigating innovative tobacco prevention and control interventions at the community or state level. The results of this research will guide tobacco control programs in all 50 states.

Examples of research questions that may be addressed through this project are listed below:

In the context of a statewide program, what is the impact of a large counter advertising campaign on: 1) tobacco use behaviors, 2) readiness to quit, 3) attitudes toward tobacco advertising and tobacco use, and 4) other predictors of initiation and cessation?

What themes, techniques, and messages of mass media campaigns are most effective in achieving the goals of the campaign?

How should media interventions be tailored to influence high risk groups, such as heavy smokers, multicultural groups, and youth? Are tailored interventions more effective?

How can new communications tools, such as the internet, be used to reduce tobacco use at the community and state levels?

What public policies are most strongly predictive of reductions in tobacco use?

How do state laws that preempt local tobacco control legislation influence the public's knowledge, attitudes, and behavior related to tobacco?

In the context of comprehensive tobacco control programs, what are the relative contribution of media and policy interventions to reductions in tobacco use rates?

How do media interventions influence private and public tobacco control policies?

Research teams can choose to test interventions directed at one more population groups, at the state or local level. The interventions under study may be conducted in collaboration with state and local coalitions, voluntary health organizations, health departments, cancer centers, and other organizations. These collaborative relationships are strongly encouraged, as are in-kind contributions of staff end other resources from these organizations.

Investigators must describe in detail their research design and methods. Randomized, controlled trials of interventions are ideal, but other designs will be considered, if adequately justified. Applicants must describe in detail how the impact of the interventions will be distinguished from the impact of other tobacco control activities. Comparisons of different measurement tools are encouraged. Investigators may also choose to evaluate so-called "natural experiments" by examining the impact of interventions, policies, or regulations that are occurring or changing independently of the investigator. Large-scale trials, if proposed, should meet the criteria for such trials, as developed by the NCI Cancer Control Review Group.

The research team will have experience and expertise in tobacco control research at the community or state level, including behavioral science, advertising, communications, or policy research. An important objective of this research is to foster the development of cancer control researchers with experience in community and state level research.

It is anticipated that collaborative research will be fostered among the recipients of grants under this RFA. Projects that are testing the impact of similar interventions, using similar media, or focusing on similar populations will be encouraged to undertake collaborative research activities. These may include examining measurement issues, assessing complex interventions through different designs, assessing the impact of "contamination," or monitoring the responses of the tobacco industry to new interventions. Investigators will be convened at the time of award and frequently throughout the project to consider these issues and how they might be addressed through collaboration. At a minimum, investigators will be asked to consider the collection of common data elements in multiple projects.

A coordinating center will support the program, as needed, with data collection and analysis. The coordinating center will also monitor national trends in tobacco use behaviors and attitudes, news coverage of tobacco, tobacco advertising and promotion, and tobacco control activities. Through the coordinating center, NCI will make use of information technology to make discoveries widely available as soon as they are developed. NCI will coordinate large-scale research activities with ongoing investigator-initiated research projects to maximize the efficiency which new knowledge is generated, reported, and disseminated.