THE CANCER LETTER INTERACTIVE

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Vol. 25 No. 26
July 2, 1999

Advisors Approve $50 Million NCI Effort To Attack Cancer On A Molecular Level

The NCI Board of Scientific Advisors at a meeting June 23 approved the Institute's plan to form two programs that would fund about 16 grants for research to identify promising molecular targets for cancer therapy and the development of therapies to attack those targets.

NCI officials said the $50-million, five-year effort would propel the Institute's drug development program into the era of rational drug design, in which therapies are specifically engineered to affect one or more processes within the cancer cell.

Since its inception in 1955, NCI's Developmental Therapeutics

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In Brief:

NCCN, ACS Write Prostate Cancer Guideline For Patient Use; Gates Gives $4.5M To UPCC

NATIONAL COMPREHENSIVE Cancer Network and the American Cancer Society have written a version of the NCCN prostate cancer practice guidelines suitable for use by patients and their families. Among the topics covered are types of treatments, stages of disease, treatment options, and a glossary. Last March, NCCN and ACS released a similar document for breast cancer. NCCN is an organization of 17 comprehensive cancer centers. To obtain copies of the prostate cancer or breast cancer guidelines, contact NCCN at 888-909-NCCN or ACS at 800-ACS-2345, or visit the web sites at http://www.nccn.org or http://www.cancer.org. . . . **WILLIAM H. GATES FOUNDATION** has donated $4.5 million to the University of Pennsylvania Cancer Center to support a team of researchers studying adoptive immunotherapy for the treatment of non-Hodgkin's lymphoma. The gift is the largest amount given to date by the Gates Foundation that is solely dedicated to cancer research. The gift will support the immunotherapy research and clinical trials led by **David Liebowitz**, associate professor of medicine at the University of Pennsylvania and an investigator at the cancer center's Abramson Family Cancer Research Institute. The cancer center director is **John Glick**. . . . **RONALD BLUM** was named director of the cancer center and programs at **Continuum Health Partners Inc.**, a health system that includes Beth Israel, St. Luke's Roosevelt and Long Island College Hospital. Blum is the former medical director at St. Vincent's cancer center, which is being developed by Salick Health Care Inc., a unit of AstraZeneca. . . . **PORTLAND,** OR, has a new cancer research facility. The Northwest Veterans Affairs Cancer Research Center opened

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Grant Programs To Change Focus Of Drug Development

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Program has been highly regarded. Many of the anti-cancer drugs used today came through the program at a time when few pharmaceutical companies were interested in developing cancer therapies. As a result of these efforts, the interest in cancer therapeutics has flourished within industry and academia. That interest, as well as the explosion of knowledge in molecular biology, seemed to remove some of the luster from the NCI program in the past decade.

It is no longer good enough to find a drug that works like all the others, a review panel examining the DTP said in a report last year. "The goal is to foster the discovery of drugs which are not simply antiproliferative agents, but rather have unique and novel mechanisms of action," said the report of the Developmental Therapeutics Program Review Group. The report was presented last fall to the BSA (**The Cancer Letter**, Nov. 6, 1998).

The DTP budget is $205.9 million, of which $170 million, or 83 percent, is spent on extramural research, while $35.6 million, or 17 percent, is spent in-house. The DTP Review Group report recommended that the ratio of extramural to intramural funding should be 85 to 15.

The two grant programs approved by the BSA last week were developed in response to the report.

THE CANCER LETTER

Member, Newsletter Publishers Association

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Subscription $275 per year worldwide. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc.

Founded Dec. 21, 1973 by Jerry D. Boyd

At the June 23 meeting, NCI officials gave the BSA a point-by-point response to the report, which indicated that most of the report's recommendations have been incorporated into the Institute's overhaul of the program.

One aspect of the NCI program that seemed to generate the most criticism from scientists outside the Institute was the DTP's heavy investment in the empiric screening of hundreds of thousands of compounds in the hope of finding a few active drugs. Though the NCI 60 cell-line screen has been valuable in finding molecules that may target DNA or any protein targeted by known anti-cancer agents, the screen cannot suggest a likely target for small molecules with novel activities, according to the review group's report.

Earlier this year, the program cut back the use of its 60-cell-line screen to test compounds for anticancer activity. NCI now uses a less expensive "pre-screen," with three cell lines, to test most agents, reserving the use of the more expensive 60-cell-line screen for compounds with prior evidence of activity in the pre-screen.

In its discussion of one of the grant programs, the BSA suggested that NCI's funding commitment may be too low. However, the board indicated that it would be loathe to recommend a shift of funds away from investigator-initiated research grants (R01s and P01s) toward directed grants solicited by the Institute through Requests for Applications.

Recent NCI RFAs have been successful in generating grant applications—almost too successful—NCI Director Richard Klausner said in his report to the board. Klausner listed a number of recent RFAs for which NCI could fund only one-fifth to one-third of the amounts requested.

"These are new types of RFAs and they are critical to NCI," Klausner said.

The excerpted text of the concept statements and their discussion by the board appear below:

Molecular Target Drug Discovery Grants.

Concept for a new RFA (cooperative agreement), 10 awards, estimated cost $16.6 million over four years. Program director: Mary Wolpert, phone 301-496-8783, email: wolpertm@exchange.nih.gov

The past 20 years have seen an explosion in our understanding of how cancer cells work. Specific molecules have been identified which cause the initiation and progressive growth of tumors. From this work, a fundamental re-ordering of our approach to cancer drug discovery and development can emerge. There is the

opportunity to move away from empiric screening of agents discovered merely by their effects on tumor cell growth in vivo or in vitro. While it remains true that such assays may engender enthusiasm for the development of a clinically useful "anti-proliferative" agent, they may not be optimal for detecting a lead compound targeted to a particular molecule or pathway of biologic importance in cancer establishment or progression. Rather, the initial focus of attention in the new approach to cancer drug discovery is the elucidation of a novel structure's activity against a single molecular target, or a target operating in the context of a defined pathway. The nature of the screen may thus make the value of a lead structure apparent.

While the desirability of this approach might seem obvious, the tools for accomplishing this task are only now becoming routinely available. These include sequence information defining the primary structure of relevant target molecules; expression vectors for their large scale production; physical (X-ray and NMR) and computational techniques to allow routine elucidation of three dimensional structure; advances in screening technology to allow ever increasing efficiency in assessing large numbers of candidate lead structures; and combinatorial or parallel synthesis approaches to generating large numbers of candidate lead drug structures.

The evaluation of drugs in the clinic which have emerged from these types of approaches is beginning. Examples would include the farnesyl transferase inhibitors (FTIs), protein kinase (PK) antagonists of various sorts, matrix metalloprotease inhibitors, and growth factor receptor or other effecter antagonists (endothelin, TRAIL, etc.). It is striking that in this process the pharmaceutical industry has clearly seized a defining role in expeditiously advancing potentially useful molecules to a clinical test. However, in each of the instances cited, the initial definition of the targets to which these drugs are directed occurred largely (if not exclusively) in the academic sector. A legitimate concern is that commercial involvement will be directed at candidate drug molecules with the surest path to regulatory approval and largest potential for recouping of investment. Targets of less certain commercial value may be underserved in this process.

Paradoxically, such targets may be the most important in connoting useful biologic effect. That is, they may prevent the occurrence of a clinically troublesome neoplasm by arresting its progress in early stages; by preventing the occurrence of metastatic disease following occurrence of a primary tumor; or they may act in a defined pathway, cell lineage, or molecular phenotype of tumor, so that disease is apparent in a small (from a commercial point of view) but clinically important population of patients. Such targets may require large numbers of patients followed for long periods of time to assess benefit. So a fundamental need remains provision of an incentive for the involvement of academic investigators in defining molecular targets for cancer drug discovery, and in the early evaluation of leads generated in this process.

What are the elements for success in cancer drug discovery efforts addressing these needs? First, investigative activities establishing a molecule as a potential cancer drug discovery target can have as their focus any aspect of cancer cell biology that may create a vulnerability in the cancer cell. These might include cell cycle checkpoint, DNA repair, cell stress, or cell death pathways; cassettes of altered transcription factor activity; or activation of pathways allowing cell growth in hypoxic or hypo-vascularized conditions. In fact, any "difference" between a cancer and normal cell could potentially be exploitable as a therapeutic maneuver. Modern science has afforded numerous opportunities to demonstrate the likely value of an approach. These include engineered animals of various sorts (transgene-expressing, knock-out, etc.); "smart" screens where the target molecule is placed in a pathway or organism where differential response of a readout of the pathway or the organism's viability conveys information as to the function of the target in that milieu; and array technology, where the action of a candidate drug lead against its target can be placed rapidly in the context of expected action against other cellular and indeed organ-specific molecules. So the first requirement is for a molecular target to acquire a mature biologic pedigree indicating that it likely affects important aspects of cancer cell function. A second requirement is a tractable assay for the target's function that can be converted into a screen for small molecule effecters of the target's function. These aspects are critical components which would form the thrust of any molecularly focused drug discovery effort, and are actually well encompassed by activities funded by the more usual types of funding instruments (traditional grants, program projects, and cooperative agreements).

In addition, the ideal cancer drug discovery effort would contain additional components not well addressed by the usual funding mechanisms, and which will be critical components of the Molecular Target Drug Discovery (MTDD) initiative. Routine access to additional NCI contract research resources will be a distinguishing feature of successful MTDD grants. The readiness of a particular MTDD grant-derived opportunity for supplementation will be made by NCI staff with the valued and continuing advice of a "Compound Decision Group," comprised of senior members of the extramural community knowledgeable in drug discovery and development.

Activities and resources to be allied to MTDD grantees include:

Expression of Target: Successful applicants whose program involves production of quantities of expressed target protein for either structure elucidation and/or piloting of assays will be routinely eligible for supplements to achieve this goal. This will be accomplished either through production at their own institution or at a contract research facility using constructs emanating from the applicant's laboratory. Authority for this supplement will

rest with NCI Program staff.

Structura1 Analysis of Target: Applicants will be strongly encouraged to include at the outset of the funding period an ongoing relationship with a structural biologist who will be responsible for analysis of structure using relevant physical techniques including X-ray crystallography or NMR. Funding through, for example, a sub-contract to the structural biologist, will be flexibly available to stimulate this interaction as needed when the opportunity for successful structural analysis presents itself. Authority for implementation of the sub-contract will rest with NCI Program staff.

Access to Chemistry/Screening: Following definition of a candidate assay relevant to the target, efforts to create libraries of compounds and conduct screening activities that are based on the target's structure may be undertaken. This effort will use contract research resources available to NCI, but which will be paired in their management with the MTDD PI and NCI staff. Libraries may be "made to order" or emerge from existing collections available to NCI. All new libraries funded from an outside source under the overall umbrella of an MTDD grant will be the property of the originating PI, but a "voucher collection" will remain on deposit with NCI and may be offered to additional MTDD grantees or other peer-reviewed NCI-sponsored drug discovery efforts under appropriate Material Transfer Agreements. In the event that an MTDD grantee produces their own libraries, these would remain the property of the originator, and maintenance of a voucher collection by NCI would not be required. Screening might also be supported by contract research resources in the event it cannot be practiced in the originating PI's laboratory, or it might be conducted by supplementation of the PI's grant to include the cost of screening. Authority for implementation of chemistry or screening efforts would occur following advice to NCI from the extramural "Compound Decision Group."

Access to Preliminary Pharmacology: A key issue in early compound development may be the toxicologic, pharmacologic and/or pharmaceutic properties of a lead. NCI-directed contract research resources may be made available to assess initial pharmacologic features of leads, or of subsequent versions of the lead that may include efforts to optimize activity or pharmacology.

The cost of informatics related to management of compound flow into screens and cataloging the output data will be borne by the NCI.

Proposals responsive to the initial RFA will clearly outline a path to the design and implementation of new approaches to new targets important to the molecular pathophysiology of cancer. The ideal outcome would be the elucidation of entirely novel drug candidate structures directed at such targets. These targets may address the treatment of established cancers or the "prevention" of molecular changes which may cause cancer. The MTDD effort is designed to attract the participation of academicians who may have access to "state-of-the-art" science in target definition, yet lack access to chemistry, structure determination, screening, and initial pharmacology. Instead, focus will be maintained by the PI on the excellence of the scientific opportunity, the novelty and persuasiveness of the target as relevant to cancer, and the likely success of the effort ultimately leading to a candidate for pre-clinical and clinical development. In short, this initiative seeks to promote the participation of the very best academically-based scientists in molecularly targeted drug discovery. The RFA will require that the proposed target(s) in each grant be truly novel-not directly approached by molecules already approved for clinical use. Structural or functional analogs of currently licensed therapeutic agents would also not be considered responsive to the RFA.

The vehicle for offering this initiative will be through Cooperative Agreements (U01s) that would promote substantial NCI involvement. Following the initial solicitation as a set-aside, subsequent offerings of the initiative, also utilizing the U01 mechanism, would be by a standing "Program Announcement with Institute Review" without a set-aside from the Research Project Grant pool.

Represents A First Step

Stuart Schreiber, BSA member and co-director, Institute of Chemistry and Cell Biology, Harvard University, said the Molecular Target grants are a good first step in NCI's exploration of the small-molecule-based approaches. However, bolder steps will be required in the future, he said.

"These proposals will be target idenfication, pathway characterization studies," he said. "Then, if something is promising, chemistry and screening may be folded in.

"Alternatively, there is another way to go about doing this," Schreiber said. "The way we'd like to do it in the future is to bring chemistry and small-molecule screening right up front, not screening for specific targets, but screening for pathways and specific processes relevant to cancer. That would be a very powerful way to define those new targets. That's where NCI can play a big role. it's essentially not done in industry because industry focuses in on those targets, commits to those targets, and screens for them.

"We can envision some day in the future, 10 to 15 percent of proposals that come in from cancer biologists start from the beginning with screening, using small molecules to explore their favorite pathways," Schreiber said. "We can't do that right now because we haven't put all that in place. Given that, I am happy with this [RFA] as a start, but I

hope we just keep moving in that direction, because I think in the future we need to be more bold than this, thereby allowing small molecule based approaches to have an even bigger impact."

NCI Director Klausner said the grants would be a first step. "This is only one part," he said. As research continues, NCI would set up assay contracts for pathways, design libraries, and match investigators with pathway assays. "As we get that in place, we can imagine RAID-like programs that are not for taking a particular compound to the clinic, but taking a biologic process through screening, assay development, and access to libraries," Klausner said.

A Challenge For Reviewers

Joan Brugge, professor of cell biology, Harvard Medical School, said the program may need to weed out applications that focus on untested targets.

"There are tens of hundreds of targets and there are going to be more," Brugge said. "I would submit that perhaps we should look at things that are fairly well validated, or perhaps genetic screens, or identify multiple protein targets, rather than [funding] an individual who just identified a new fusion protein in some form of leukemia."

EDWARD SAUSVILLE, director, NCI Developmental Therapeutics Program: "You focus on what is precisely going to be a big challenge in putting forth this opportunity, to run between the rock of a too well-defined target and the hard place of something that is rather amorphous. Or, as our chairman would say, the Scylla and Charybdis of those respective poles."

DAVID LIVINGSTON, BSA chairman and the Emil Frei Professor of Medicine and Genetics, Harvard Medical School: "That's before your time."

SAUSVILLE: "In all seriousness, I am pretty optimistic that at least for this initial go, peer review will be very sensitive to the issue. The reason I would argue in favor of trying to steer it away from anything that vaguely resembles platinum or Taxol, not that those things are bad—they are very good—it's just that we need to really try to move ahead."

ROBERT WITTES, NCI deputy director for extramural science: "It might be hard for peer review to sort out what makes one better than another."

BRUGGE: "I think what's going to make one thing better than another is if somebody is going to use gain of function and loss of function approaches to demonstrate the role of the protein, then it's something brought further forward than a casual kind of association. I think you are going to get a lot of new proteins."

KLAUSNER: "As we've talked about the review criteria, Bob [Wittes] has referred to this as a 'credentialing' of the potential targets. The reviewers will build up a sense of comparing credentialling AKT versus something else, based upon the natural genetics, the pathways in lower organisms, the overexpression…. I think we can learn to do that as we go."

Greater Funding May Be Needed

Board members said NCI may not be committing enough funds to the Molecular Target concept.

"I think nobody has a unique lock on best way to do things," said Allen Oliff, BSA member and vice president for discovery, Dupont Pharmaceuticals. "We can't make the assumption that if industry is looking at something, they are going to do it the best way. We need to bring more people into the process. You might not be putting enough money into this."

Wittes agreed, noting that the research would be as applicable to prevention as to treatment. "This may be significantly under-budgeted, so we will have to look at that as we go along," he said.

OLIFF: "You are going to fund 10 ideas. You need to fund 100 ideas."

LIVINGSTON: "Maybe a thousand."

WITTES: "I'd like record to show that the chairman of the board thinks that this is under-funded by a factor of 100."

LIVINGSTON: "This is so under-funded that it isn't funny."

The concept was approved unanimously.

Centers of Excellence in Interventions Directed to Molecular Targets.

Concept for a new RFA (cooperative agreement), four to six awards, estimated cost $32 million over five years. Program director: Louise Grochow, phone 301-496-8798, email: grochowl@ctep.nci.nih.gov

This initiative will create a series of multidisciplinary and translational research teams. Each team will focus on a critical biological process that is currently thought to contain high-priority targets for cancer drug discovery for the treatment of established cancers or the prevention of molecular changes that may cause cancer. Examples include, but are not limited to, signal transduction, angiogenesis, invasion and metastases, cell-cycle control, apoptosis, vaccines, cellular therapies, and growth-factor physiology. For a particular class of targets, each team will advance the state of the pertinent science to facilitate

the development of tools, probes, and assays suitable for assessing in vivo the effects of drugs on that target class. They will validate the most promising probes in preclinical models and then in early clinical trials of drug candidates possessing suitable target specificity. Note that the purpose of these awards is not the support of new-agent testing per se. To the extent that that assessment of a biomarker of a molecular process may reflect the effect of an agent (e.g., downstream effects assessing inhibition of raf-kinase), projects may include research in novel big-marker development. However, these awards are not intended to support assay development for markers of individual tumor characteristics or measures of tumor burden. The purpose of this initiative is to create, develop, and validate the tools that will make mechanism assessment in clinical trials a reality.

Each team will be headed by a principal investigator of international stature in the subject area, and will include distinguished co-investigators in the areas of science needed. Teams are not limited to a single institution. These multidisciplinary research teams will develop and validate novel imaging, biochemical, pathological or other assays in proof-of-principle laboratory models and clinical trials.

The specific structure of each Center will be determined by the research plans of the applicant. NCI expects that innovative approaches to most target classes will require inclusion of diverse expertise including many or all of the following: basic biology pertaining to the target (molecular, cellular, immunologic); synthetic chemistry or radiochemistry; in vivo models suitable for assessment of the relevant target effects; pharmacokinetics and pharmacodynamics; clinical investigations incorporating pharmacodynamic endpoints; functional imaging; interventional radiology; pathology and molecular analysis of tissues.

Collaborating investigators may be from academic, industrial, or government institutions. In their research plans, COE investigators may incorporate promising new agents originating from any source (in-house, other academic, industry, NCI) that is appropriate to their target.

NCI expects that these Centers of Excellence will serve as important resources to other investigators developing new agents directed at the same target.

A Center of Excellence By Any Other Name…

The board balked at the concept's original request for a $64-million set-aside for 12 awards. Also, the name of the program got negative reviews from BSA members who supported the concept, as well as those who were critical of it.

"This could be renamed 'Translational Research, Put Up or Shut Up Time,'" said John Minna, BSA member and director of the Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center. "In any case, you need to come up with a good acronym so we can remember it."

ELIAS ZERHOUNI, BSA member and professor and chariman of radiology, Johns Hopkins University School of Medicine: "I agree, the name is not right. Beyond that, as written, it's too directed. It should be more generic."

MICHAELE CHRISTIAN, director of the NCI Cancer Therapy Evaluation Program and the presenter of the concept: "It wasn't meant to be directed."

SHARON MURPHY, BSA member and chief of hematology/oncology, Children's Memorial Hospital, and professor of pediatrics, Northwestern University School of Medicine: "I am having trouble with this concept of centers. You have a lot of mechanisms supporting this. There is nothing preventing people from doing this now. Why not contract it out?"

CHRISTIAN: "Maybe the people who said the name was wrong were right."

WITTES: "Think of it as a SPORE. It's a grant. It's not anything created in stone and steel."

TYLER JACKS, BSA member and associate professor of biology, Massachusetts Institute of Technology: "You can't simply contract this out, because there is nothing to contract right now."

LIVINGSTON: "What's the reason for not calling this a Program Announcement and carrying it out over a couple of years? Because it ain't even a field yet. It's a field you'd like to see get to be a field. Maturity isn't necessarily going to come in an organized and predictable way."

WITTES: "The reason why this is a better route is that, because these teams do not exist now, a surer way of assembling them is by setting aside money. That's No. 1.

"No. 2, they are going to be cooperative agreements; they need special review. We could do that with a Program Announcement, I suppose, but an RFA is a more conventional way of doing it."

WILLIAM WOOD, BSA member and professor and chairman of surgery, Emory University School of Medicine: "I want to express enthusiasm for this. Here, for the first time, we're moving from generations of trying empiric agents to actually some designed molecules and designed probes. To try and stimulate that process and make it work, is worth significant set-asides, recognizing that it may not work."

ZERHOUNI: "Our experience in our institution

is that if you don't set aside money, people won't get the energy to get together for a Program Announcement that may or may not have money."

Waiting For Rick

Louise Strong, BSA member and professor of experimental pediatrics and medical genetics, M.D. Anderson Cancer Center, had a question: Would approval of the concept cut into the R01 grant pool?

STRONG: "I have a question that's really more for Rick."

[LIVINGSTON *gestures toward Klausner's empty chair. The NCI Director had left the room some time earlier. Noticing that the chair is askew, Livingston turns it to face the table properly.*]

STRONG: "[Klausner] has often given us the breakdown of the money that is in the RFA pool compared to the investigator-initiated research program, and I think it's about 15 percent. Just looking at what we have gone over today, I wonder if we are shifting that balance. These are things that have major long-term commitments, and I understand the need for that flexibility, particularly when you put together big groups of people. But I just wonder if we have changed the balance here, and I'd love to know that."

LIVINGSTON: "That's the reason for my question about a Program Announcement. Bob?"

WITTES: "Well, if Rick were here, he would say something like this [*leans forward and to his left to look at Strong.*]: You know, I'm really glad you asked that question, because this whole thing is actually very much on our minds, and, in fact, the reason—"

[*Laughter.*]

LIVINGSTON: "This is going to take about 20 minutes."

WITTES [*continuing in character*]: "—and, it's basically the reason why I presented the budget issues that I did this morning. You are absolutely right."

[*More laughter.*]

WITTES [*as himself*]: "O.K., I'm no longer trying to be funny. But there actually is a shift. What's been happening is that as a result of all of the great input we've been getting from everywhere, and a lot of thinking that's been going on within the Institute, a whole collection of RFAs has arisen that are qualitatively different from the kinds that existed in prior years. I think what his budget discussion was meant to do this morning was to set the groundwork for further follow-up at subsequent board meetings, because you are going to be asked to help us with very tough decisions about how one trades off the value of things like this, with an ever-rising payline in the RPG pool, for example."

LIVINGSTON: "It's not been ever-rising for the past few years. It's at a very nice level."

WITTES: "It's comfortable now. The question is, as our appropriation does whatever it does over the next year or two, it's very clear that there's going to be more call on that money, no matter how generous the appropriations process is with that money. So, we'll come back to Louise's question in subsequent years."

Wittes said the current payline for investigator-initiated research is about 24 percent, not including the NCI Accelerated Executive Review program, which provides funding by exception for some proposals that miss the payline.

LIVINGSTON: "Louise raises the question, following this track, even with continued funding at some elevated level, will those number be in play?"

WITTES: "What's the balancing act we have to do to make sure that those numbers are protected, but also that there are these highly interactive, high interdisciplinary, highly consortial kinds of things that are not going to arise spontaneously from the RPG pool?"

LIVINGSTON: "But still, to prevent those numbers from being in play, what kinds of decisions need to be made that still protect the entrepreneurial, initiative-creating spirit of the Institute?"

ROBERT YOUNG, BSA member and president of Fox Chase Cancer Center: "I don't understand how anything is not 'in play,' at some level. I recall at two board meetings ago that Rick said that we are on a trajectory which requires roughly a 10 percent per year increase in budget in order to keep our R01 and P01 pool protected. Well, that's not much protection if we require that kind of increase just to do that. So, I don't think there is any concept of having protected pools, except for the extent to which we, and you, set out to protect them with a variety of strategies. We have embarked on a reasonably aggressive feeding frenzy in funding new, alternative mechanisms for research, and they are all good, particularly in isolation.

"But one of the things you said just a minute ago which has always troubled me is, you said that, 'You all are going to have to help us make some of these hard decisions depending on what the budget is.' I can understand that at some level, but it seems

to me, we are already making decisions which commit us to a certain trajectory independent of any sort of effort to compare apple and oranges. That's a hard comparison to make. I'm not sure it's even feasible for a group like this to do. But I don't see any format to be able to engage in that, in any meaningful way.

"We can address these [concepts], and unless they're fundamentally flawed or disturbing in their own right, we'll ultimately pass them. But that doesn't get us engaged in exactly what you just said. It may be ultimately that you are the ones who are going to have to make those decisions because you are the ones that are going to swing if they're not the right one. Maybe that's the right answer. But I'm not sure we're helping you in the way we've got this structured."

LIVINGSTON: "But you can imagine a scenario in which, given a report at some meeting, at which one was presented with a proposal that a payline decrease of a serious nature, or any nature, is coming, that this board would react, and I predict it would react significantly and unhappily."

YOUNG: "I would not want to have an RFA on the table the day that report was made. But what about the RFAs at this meeting? We are already on a trajectory which assumes something that's really quite robust."

LIVINGSTON: "We need to talk to Rick Klausner when he comes back."

ELLEN SIGAL, BSA member and founder of Friends of Cancer Research: "I don't know what balance is right, and I don't think anyone knows what the budget is going to be in three to five years—"

LIVINGSTON: "Three to five months from now."

SIGAL: "Exactly. The question is, is there a need for this [program]? Is the opportunity there? This is what's important. Then, when we get a budget, if we have to take a cut, we deal with that. This is a very important project, and I fully support it."

FREDERICK APPELBAUM, BSA member and director, clinical research division, Fred Hutchinson Cancer Research Center: "Our job is to spend money on research, not put it in the bank. You're hearing a certain squeamishness of absolutely wanting to protect the independent grant process above all else."

Continuing Doubts

Jacks proposed that the program be started with a smaller amount of money, $32 million that would fund four to six grants.

Some board members questioned the appropriateness of the concept. "My squeamishness is not based on the budget," said Murphy. "I don't think it's going to achieve the goal in terms of trying to make a translational connection of the preclinical developmental to the validation piece. It's not coherent to me."

ZERHOUNI: "You get that impression from the way the proposal is written, and the way it restricts itself to very defined targets. I think if we did not focus on that and if we said the goal of these grants is to develop, including generic, assays or targets, that are not necessarily biological, if you could do that and really challenge the field to put things that can measure, for example, cell death, in a manner that is applicable to clinical trials—If we change the scope of the proposal, your issues may evaporate."

WITTES: "What you are saying is totally compatible with this."

HERBERT KRESSEL, BSA member and president and chief executive officer, Beth Israel Deaconess Medical Center: "Not doing it will create a big gap in the cancer program," said "There is a big issue in getting the proper groups together, so I think putting a decent pot of money out there will help stimulate that."

OLIFF: "I'm not as enthusiastic about this as about the previous proposal. It's not clear to me that this is the best way to do it.… It's not clear to me that you need to spend this money and bring teams together."

Livingston called the question. The concept was approved by a vote of 19 to 6. BSA members opposing the concept were Brugge, Oliff, Young, Murphy, Enrico Mihich, of Roswell Park Cancer Institute, and Nancy Mueller, of Harvard School of Public Health.

New Cancer Research Facility

(Continued from page 1)

June 24, built and funded by the U.S. Department of Veterans Affairs. The center houses joint research projects of the Portland VA Medical Center and the Oregon Health Sciences University, with 66 labs and 150 staff. The center will specialize in research on the genetic basis and biological pathways of cancer. The director of the center is **Grover Bagby**, chief of hematology and oncology at the Portland VA Medical Center, and professor and chairman of hematology and oncology, Oregon Health Sciences University.

THE CANCER LETTER

Vol. 14 No. 6
June 1999

Business & Regulatory Report

Formerly "Cancer Economics"

Pharmacia & Upjohn Says Sugen Purchase Will Expand Its Foothold In Oncology

Pharmacia & Upjohn Inc. (NYSE: PNU) of Bridgewater, NJ, and **Sugen** (Nasdaq: SUGN) of South San Francisco said they have signed an agreement under which Pharmacia & Upjohn will acquire complete ownership of Sugen.

The acquisition, valued at about $650 million on a net basis, gives Pharmacia & Upjohn a portfolio of cytostatic and angiogenesis inhibiting drugs as well as its genomics and bioinformatics expertise. Sugen has three anticancer agents in clinical development.

The agreement has received the approval of the Boards of Directors of both Pharmacia & Upjohn and Sugen and is subject to the approval by Sugen's stockholders and regulatory approvals.

"Sugen's target-driven approach to drug discovery and development is supported by an outstanding scientific team and proprietary technology that we can leverage across our company's core research areas," said Fred Hassan, CEO of Pharmacia & Upjohn. "With the addition of the

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Abbott Laboratories To Buy ALZA Corp., Gaining Urology And Oncology Products

Abbott Laboratories (NYSE: ABT) of Abbott Park, IL, and **ALZA Corp.** (NYSE: AZA) of Palo Alto, CA, said they have entered into a definitive agreement for Abbott to acquire ALZA, a company focused on oncology and urology.

Under the agreement, Abbott will acquire all of ALZA's outstanding stock in a stock-for-stock merger transaction intended to be tax-free.

"Our acquisition of ALZA is an excellent strategic fit and an important step that builds our pharmaceutical business and accelerates Abbott's long-term growth," said Miles White, Abbott chairman and CEO.

"ALZA brings a number of key assets to Abbott that provide both short- and long-term value, including: a portfolio of pharmaceutical products that Abbott can rapidly grow and expand through its strong global sales organization; new products in development; strong technical relationships with pharmaceutical industry partners; and important scientific expertise in drug delivery technologies that enhance patient care and provide a strategic technology platform for application across all of Abbott's diverse businesses," White said.

ALZA's marketed products and its research and development portfolio in urology and oncology complement Abbott's pharmaceutical

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Pharmacia & Upjohn To Buy Sugen; Phase III Trial On Track

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cytostatic platform represented by Sugen, we position P&U to become the new challenger in the oncology category."

Stephen Evans-Freke, Sugen chairman and CEO, said the acquisition provides Sugen with the resources and global infrastructure to commercialize the cancer drugs in its development pipeline. "It will also enable us to apply our unique capabilities to other important disease areas in which our efforts to date have been severely resource constrained," Evans-Freke said.

Clinical Trials Moving Forward

Sugen recently said that FDA had agreed with the company's proposed clinical trial design for phase III trials of SU5416, its lead angiogenesis inhibitor, in colorectal and non-small cell lung cancer.

FDA plays an advisory role in reviewing protocols.

"The success of this meeting with the FDA helps validate Sugen's development strategy for SU5416 to move rapidly forward into phase III trials," said Stephen Carter, a pharmaceutical industry consultant who also serves as Sugen's senior vice president, clinical and regulatory affairs.

SU5416 is a small molecule angiogenesis inhibitor that prevents the formation of new blood vessels required for tumor growth by blocking the signaling pathway of the vascular endothelial growth factor (VEGF) receptor.

The trials, which are expected to begin later this summer in the U.S. and Europe, will compare SU5416 against standard chemotherapy regimens in patients who have not received chemotherapy. Both trials will provide for scheduled interim analyses. The primary endpoint is survival, with secondary endpoints of time-to-disease progression and objective response rate. The studies will analyze tumor samples, using Sugen's proprietary gene expression array technology.

Sugen is also working with the AIDS Malignancy Consortium on a registrational phase II trial in AIDS-related Kaposi's sarcoma, expected to begin this summer.

To date, more than 135 patients with end-stage disease have been administered SU5416 in seven phase I and phase I/II clinical trials. Results from the phase I studies of SU5416 showed that the drug was well tolerated with mild side effects.

There were also observations of lesion shrinkage in Kaposi's sarcoma, colorectal and basal cell cancer patients, and of disease stabilization in a considerable number of patients, including non-small cell lung patients, the company said.

Ten patients have been treated with SU5416 for greater than six months and individual patients have remained on study for greater than one year, with no evidence of cumulative toxicities, the company said.

Following the merger with Pharmacia & Upjohn, Sugen is expected to remain at its headquarters in South San Francisco, the companies said.

Peter Hirth, Sugen's executive vice president and chairman of the research and development committee, will become president of Sugen.

Under the deal, each of 23.5 million shares of Sugen stock will be exchanged for about $31 worth of Pharmacia & Upjohn stock, so long as the price of Pharmacia & Upjohn stock is between $60.16 and $49.22 at the close of the transaction.

In no event will SUGEN stockholders receive less than .515 share of Pharmacia & Upjohn common stock, nor more than .630 share of Pharmacia & Upjohn stock for each share of Sugen common stock.

The exact exchange ratio will be based on the average price of Pharmacia & Upjohn stock prior to closing. The transaction will be accounted for as a pooling of interests and will qualify as a tax-free exchange.

THE CANCER LETTER

Member, Newsletter Publishers Association

World Wide Web: http://www.cancerletter.com

Business & Regulatory Report

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Business & Regulatory Report (formerly Cancer Economics) is published 12 times a year as a supplement to The Cancer Letter. ISSN 1053-9611.

Venture Capital Fund Plans Investments In Health Care

ProQuest Investments of Princeton, NJ, has closed its oncology-focused venture capital fund at $100 million in committed capital.

Fund officials said limited partners include financial institutions, foundations and one pharmaceutical company, which represent 70 percent of the funds as well as individuals and family trusts.

Along with the sponsor fund, Domain Associates, ProQuest will invest from seed stage through public companies across health care, including pharmaceuticals, devices, health care internet and services.

Fund investments will range between $500,000 to $10 million per deal, and potentially larger with co-investment from ProQuest's institutional investors, fund officials said.

ProQuest intends to play an active role in its portfolio companies, and has board seats as part of two of the three current investments.

The fund partners are Jeremy Goldberg and Jay Moorin.

Goldberg is a founder of several biopharmaceutical companies, including Versicor, a spin-out of Sepracor Inc., Mitotix Inc., operating roles at SmithKline Beecham and Becton Dickinson, and venture consulting role at Robertson Stephens & Company Fund IV.

Moorin is the former president, CEO and chairman of Magainin Pharmaceuticals, managing director of Bear, Stearns & Company, and vice president, marketing and business development, of a division of Squibb. Pat DeAngelis will serve as the chief financial officer.

The fund will draw on the expertise of scientific and clinical advisors from Johns Hopkins, Memorial Sloan-Kettering, and Cedars Sinai, officials said.

So far, the fund has made three investments: Ablation Technologies, a San Diego device company with proprietary seed implants for localized prostate cancer, Epic Therapeutics, a Boston-based drug delivery company with a product in human pivotal trials, and U.S. Bioscience, a public company which ProQuest Investments and Domain Associates invested in during January 1999.

Partners Goldberg and Moorin or CFO DeAngelis can be reached at 609-430-1560, or through the fund's website at the following URL: http://www.proquestinvestments.com.

Deals & Collaborations:

Genentech Stays Independent In Roche Purchase Of Stock

Roche Holding AG has exercised the option to purchase 33 percent of **Genentech Inc.** of South San Francisco.

The purchase could have made Genentech a subsidiary of the Swiss drug company. However, in a move that appears to be calculated to allow the biotechnology company to retain its independence and its corporate culture, Roche said it would sell 19 percent of Genentech stock to the public.

As a result, Genentech will remain independently traded. The company will have independent directors. The redemption is being made pursuant to an agreement approved by the Genentech shareholders in 1995.

Genentech's callable putable common stock will be sold for $82.50 per share in cash. Genentech has appointed Chase Manhattan as the depository bank that will make payments to shareholders with respect to the redemption. The redemption date is June 30. Trading of Genentech stock ended on June 16.

J.P. Morgan Securities Inc. is acting as lead manager for the offering of the new stock. Goldman, Sachs & Co., Merrill Lynch & Co., Warburg Dillon Read LLC and BancBoston Robertson Stephens are co-managers.

In a related development, Genentech and Immunex Corp. (Nasdaq: IMNX) of Seattle said they agreed to jointly develop TRAIL/Apo2L, a TNF-related apoptosis-inducing ligand.

The agent appears in animal models to suppress tumor growth and causes remission of tumors, by apoptosis, the companies said. In preclinical research, TRAIL/Apo2L has been shown to cause a wide variety of tumor cells to undergo apoptosis while sparing normal cells, the companies said.

Immunex and Genentech have each conducted extensive preclinical testing of different forms of TRAIL/Apo2L. Under the collaboration agreement, the companies will share all development and commercialization costs.

The companies will form a steering committee and project team to select a single lead molecule for development, manage the development process, and allocate clinical, manufacturing and marketing responsibilities to each company.

* * *

AutoCyte Inc. (Nasdaq: ACYT) of Burlington,

NC, and **NeoPath Inc.** (Nasdaq: NPTH) of Redmond, WA, said they have entered into a definitive agreement to merge the two companies in a tax-free stock exchange.

NeoPath's shareholders will receive .7903 shares of AutoCyte common stock in exchange for each share of NeoPath common stock in a transaction that is expected to be accounted for as a pooling of interests. The new company will be headquartered in Burlington, NC.

The merged companies will offer liquid-based thin-layer slide preparation technology with the AutoCyte PREP System, as well as the NeoPath AutoPap Primary Screening System, the only FDA-approved device for automated primary screening of conventional Pap smears.

The companies said they are conducting a joint clinical trial for the screening of PREP slides by AutoPap. This supplement is expected to be submitted to the FDA in the second half of 1999, the company said.

The transaction will require shareholder and regulatory approval.

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Targeted Genetics Corp. (Nasdaq: TGEN) of Seattle announced an alliance with **Alkermes Inc.** (Nasdaq: ALKS) that provides Targeted Genetics with exclusive rights to a seminal patent for the manufacture of Adeno-Associated Viral vectors.

Under the agreement, Targeted Genetics will issue 500,000 shares of common stock as payment for an up-front license fee to Alkermes for exclusive rights to the issued patent and related pending patent applications.

Targeted Genetics will issue to Alkermes warrants to purchase up to 2,000,000 shares of common stock at substantial premiums to the current market price for periods of up to ten years. Targeted Genetics also will make milestone payments and pay royalties to Alkermes on products manufactured using the licensed technology.

The patent (US# 5,658,785 entitled "Adeno-Associated Virus Materials and Methods") and related pending patent applications, which Alkermes exclusively licenses from Children's Hospital in Columbus, Ohio, cover the use of cell lines for the manufacture of AAV vectors, which is the key to making AAV-based products in a commercially viable, cost-effective manner.

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Corixa Corp. (Nasdaq: CRXA) of Seattle and **Ribi ImmunoChem Research Inc.** (Nasdaq: RIBI), of Hamilton, MT, signed a definitive agreement whereby Corixa will acquire all outstanding shares of RIBI in a merger valued at about $56.3 million.

The transaction will combine Corixa's antigen discovery and immunotherapeutic expertise with RIBI adjuvant expertise and manufacturing resources to develop therapies for the treatment or prevention of cancer, infectious diseases and autoimmune diseases.

At the close of the merger, projected to be completed in September, the combined Corixa and RIBI product portfolio is expected to include nine programs in clinical development, 15 preclinical or discovery programs and six corporate partnerships focusing on cancer, infectious disease or autoimmune disease.

The combined Corixa and RIBI portfolio will range from products in preclinical stage of development to products that have completed initial pivotal phase III clinical trials.

The estimated $56.3 million purchase price is based on the purchase of RIBI's current outstanding shares of nearly 21 million for approximately $47.5 million in stock, and an additional $8.8 million in cash attributed to the purchase of shares currently held as preferred by Rose Glen Capital, stemming from a July 1998 financing by RIBI.

Corixa expects to continue operations in Montana.

In a related development, Corixa said it has entered into a research collaboration and license agreement with the pharmaceutical division of **Japan Tobacco Inc.** to support Corixa's development of therapeutic lung cancer vaccines.

The agreement provides JT with exclusive rights to vaccine and antibody-based products aimed at treating lung cancer and potentially other solid tumors in humans, principally in Japan and North America, as well as co-exclusive rights, with Zambon Group spa, in China.

Under the agreement, JT receives certain rights to develop vaccine products containing Corixa's novel lung cancer antigens, including antigens formulated using Corixa's microsphere delivery system and proprietary adjuvant technologies.

Corixa also may receive over $40 million in license fees, research funding and milestone payments based upon successful clinical and commercial progress, and royalties will be paid on annual net sales achieved by JT or its partners.

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IDEC Pharmaceuticals (Nasdaq: IDPH) of San Diego and **Schering AG** of Berlin said that they have entered into a licensing agreement valued at approximately $47.5 million granting Schering AG exclusive marketing and distribution rights to IDEC's investigational drug, Zevalin (ibritumomab tiuxetan), formerly known as IDEC-Y2B8.

IDEC will retain U.S. rights to Zevalin, which is a monoclonal antibody stably linked to the radioisotope yttrium-90. Zevalin is currently completing two pivotal phase III trials in low grade and/or follicular non-Hodgkin's B-cell lymphoma.

Under the agreement, Schering will pay IDEC $13 million as an upfront licensing fee and $15 million in committed funding for the development of Zevalin. Further, $19.5 million will be paid as milestone payments based on the achievement of certain development goals. Also, Schering AG will pay IDEC an undisclosed royalty on eventual product sales outside the U.S.

IDEC is concluding two multi-center, phase III studies of Zevalin in low grade and/or follicular non-Hodgkin's lymphoma, both of which are in advanced stages of patient accrual. One study is a randomized, controlled trial that compares a regimen of Zevalin and Rituxan with Rituxan alone. The second is a single-arm trial in post-Rituxan patients.

Product Approvals & Applications:
BMS Files SNDA For Taxol Combination With Herceptin

Bristol-Myers Squibb Co. (NYSE: BMY) of Princeton, NJ, has filed a regulatory application to FDA to gain marketing approval for Taxol (paclitaxel) in combination with the **Genentech Inc.** agent Herceptin (trastuzumab).

The BMS sNDA seeks approval for the indication of Taxol in combination with Herceptin as first-line therapy for women with metastatic breast cancer who overexpress the HER2 protein, the company said. Approximately 25-30% of all breast cancer tumors overexpress HER2, which is a poor predictor for patient outcome.

The filing follows a deal between BMS and Genentech in which the two companies agreed to continue clinical research and enhance the use of Herceptin and Taxol in the treatment of metastatic breast cancer.

The Taxol/Herceptin sNDA is based primarily on a multi-center, randomized controlled study, conducted by Genentech, involving 469 female patients with HER2 overexpressing metastatic breast cancer.

The women received either chemotherapy consisting of doxorubicin plus cyclophosphamide, or in those receiving prior adjuvant doxorubicin, Taxol. Patients were randomized to receive chemotherapy alone or chemotherapy in combination with Herceptin. The response rate for patients receiving Taxol plus Herceptin was 38% (N=92) versus 15% (N=96) with Taxol alone.

"We are very encouraged by this study which supports the submission for the use of Herceptin in combination with Taxol as an effective treatment for HER2 metastatic breast cancer," said Rick Winningham, president of BMS Oncology and Immunology. "Taxol's continued versatility shows that this anti-cancer agent will benefit thousands of cancer patients in the years to come."

Taxol is approved as first-line (in combination with cisplatin) and subsequent therapy, for the treatment of advanced carcinoma of the ovary, and for the treatment of breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. The drug is also indicated for use in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy, and for the second-line treatment of AIDS-related Kaposi's Sarcoma.

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Fujirebio Diagnostics Inc. (formerly Centocor Diagnostics of Pennsylvania Inc.) of Malvern, PA, said it has submitted to FDA a Product Development Protocol for premarket approval of it's globally-recognized CA19-9 RIA test kit.

Approval would allow commercial distribution of the CA19-9 RIA in the U.S. for use as a diagnostic adjunct to radiological imaging techniques in the detection of pancreatic, biliary or gallbladder cancer.

This application was identified during a clinical study at the Mayo Clinic, the company said. The study demonstrated that the CA19-9 RIA, when used with existing imaging techniques, significantly improved the sensitivity of detection of cancer in the target organs. The (PDP) proposes to validate this use for the assay with the results from a prospective study performed at 12 clinical sites in the US.

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Implant Sciences Corp. of Wakefield, MA,

said FDA has granted 510(k) clearance for marketing and distribution of Implant Sciences I- Plant radioactive Iodine-125 seed.

The I-Plant seed (small encapsulated radiation sources approximately half the size of a grain of rice) is used for the primary treatment of early stage prostate cancer and other cancers that are treated brachytherapy.

Oncology Management:

IMPAC Among Top 10 Firms On Leading IT Companies List

IMPAC Medical Systems Inc. of Mountain View, CA, said it has been named to the Healthcare Informatics 100 Leading IT Companies list for the third year in a row.

The magazine's annual survey, which compares information technology companies servicing the healthcare industry as ranked by revenue and growth, recognized IMPAC as one of the top 10 revenue gainers for 1998. IMPAC's revenue figures for 1998 grew almost 60 percent over 1997. IMPAC ranked 74th overall for 1999 — up from an 83rd place ranking the prior year.

IMPAC, a privately held company, develops practice management, electronic medical record, image management, and decision support software solutions, IMPAC has an installed customer base of over 1,100 cancer sites in 43 countries worldwide. IMPAC software manages the care of over 30,000 cancer patients daily.

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PhyMatrix Corp. (Nasdaq: PHMX) of Providence, RI, and its wholly-owned subsidiary, Clinical Studies Ltd., a clinical trial management organization, said they have entered into agreements with North Shore Hematology Oncology Associates and Hematology Oncology Associates of Long Island.

Both practices are part of the Long Island Oncology Network, located primarily on Long Island, NY. LION is an oncology independent practice association that represents over 70 oncology-specific sub-specialists.

The agreements add both group practices to CSL's Oncology Research Network, expanding the geographical reach of CSL to the Long Island area.

The Oncology Research Network links community-based oncology physician practices, academic medical centers and hospital systems with CSL's clinical research processes that ensure the collection and reporting of consistent, quality data.

The addition of these two practices brings the total number of medical oncologists within the research network to 64. Since the Network's inception in 1998, it has initiated and is currently enrolling in over 36, multi-site clinical research trials in breast cancer, colorectal cancer, lung cancer, prostate cancer, lymphoma, ovarian cancer and hematologic disorders for 18 pharmaceutical & biotechnology companies.

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American Oncology Resources Inc. of Houston has completed the merger with **Physician Reliance Network** of Dallas, following approval at their shareholder meetings in San Antonio.

Terms of the transaction call for Physician Reliance Network shareholders to receive a fixed ratio of 0.94 shares of common stock of American Oncology for each PRN share held. As a result, AOR and PRN shareholders will each own approximately 50% of the combined company on a diluted basis.

The new company, US Oncology Inc., will be headquartered in Houston. The company's common stock is traded on the Nasdaq Stock Market under the name USON. US Oncology provides comprehensive management services to over 750 physicians in 25 states.

Clinical Trials:

Allogen Enters Phase I Trial In Hematologic Malignancies

Osiris Therapeutics Inc. of Baltimore said it has begun a phase I trial for Allogen in cancer patients receiving chemotherapy and hematopoietic stem cell transplantation for the treatment of high-risk hematological malignancies, including acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia and non-Hodgkin's lymphoma.

Allogen is an infused, allogeneic adult mesenchymal human mesenchymal stem cells, or hMSCs. The product is targeted to improving transplant engraftment and reducing GVHD, the company said. The trial involves the co-administration of human mesenchymal stem cells with hematopoietic stem cells obtained from matched related donors.

Human MSCs are isolated from a small sample of bone marrow obtained from a matched relative of the patient and expanded until the number of adult

stem cells has increased over 3,000 fold. The resulting Allogen product is then shipped and stored frozen until the stem cells are thawed and infused into the patient. The multicenter Allogen clinical trial is being conducted in seven U.S. and European cancer centers as a part of the Osiris program of worldwide clinical collaboration.

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Matrix Pharmaceutical Inc. (NNM: MATX) of Fremont, CA, said it has completed the planned enrollment in a phase II trial of IntraDose Injectable Gel in primary liver cancer, and that it has extended enrollment in view of the encouraging results seen to date.

Thirty seven patients, the original enrollment target, have been entered on study at medical centers in the U.S., France, Germany, and Hong Kong. Total enrollment is projected between 45 and 55 patients.

Patients with three or fewer primary liver tumors who are not candidates for surgery are eligible for the phase II study.

IntraDose (cisplatin/epinephrine) Injectable Gel delivers cisplatin directly into tumors. The cisplatin is delivered in a collagen-based gel that also contains epinephrine. IntraDose delivers much higher concentrations of cisplatin into the tumor than can be administered intravenously and facilitates the retention of drug in the tumor for several hours.

In addition to the trial in HCC, IntraDose is being studied in randomized phase III clinical studies for the treatment of head and neck cancer and in a phase II study in colorectal cancer that has metastasized to the liver (metastatic liver cancer). IntraDose has also completed open-label phase III trials in locally recurrent breast cancer, melanoma, esophageal cancer, and other solid tumors. Results of those studies were reported at the May 1999 meeting of the American Society of Clinical Oncology.

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Proxima Therapeutics, an Atlanta-based privately held medical device company, said trials of GliaSite Radiation Therapy System are being initiated at five medical centers.

GliaSite places a high dose of radiation directly into the tissue most likely to contain residual cancer cells following tumor removal, the company said. The studies are being conducted under the NCI New Approaches to Brain Tumor Therapy program, the company said.

The investigational treatment combines the patented positioning GliaSite balloon catheter with Iotrex, a liquid radiation source specifically developed to treat patients with malignant brain tumors. During surgery, a neurosurgeon positions the balloon portion of the GliaSite catheter into the cavity created after the malignant brain tumor is removed. The other end of the catheter extends to the outside of the skull and is concealed underneath the skin at the top of the head. When the patient recovers from surgery, Iotrex is injected into the catheter and fills the balloon. After delivering a specified dose of radiation for three to seven days, the Iotrex is withdrawn and the balloon catheter is then removed during a brief surgical procedure.

The company said the approach enables delivery of site-specific internal radiation that limits exposure to healthy brain tissue. The company said the treatment is less disruptive and may avoid side effects associated with chemotherapy. The treatment also costs 25 to 50 percent less than existing therapies, the company said.

Up to 40 patients will participate in the GliaSite RTS clinical trials. All must have a recurrent, malignant brain tumor and prior treatment including surgery, radiation therapy and possibly chemotherapy, the company said.

The five U.S. academic medical facilities participating in the GliaSite RTS clinical study include Johns Hopkins University School of Medicine, Wake Forest University School of Medicine, Emory University School of Medicine, Henry Ford Hospital, and University of Texas Health Science Center at San Antonio.

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Techniclone Corp. (NASDAQ:TCLN) of Tustin, CA, said the University of California Los Angeles and Temple University will take part in a phase II trial of the drug Cotara in malignant glioma.

Timothy Cloughesy is the principal investigator at UCLA. Douglas Laske is the PI at Temple. The trial was started at the Medical University of South Carolina.

Cotara binds only to DNA in cells having porous nuclear and cellular membranes, and since only necrotic cells are porous, the DNA functions as a highly abundant but selective target, the company said. Once concentrated in necrotic regions throughout the tumor, the drug is able to expose neighboring living tumor cells to beta radiation, the company said.

The phase II trial, which began last December at MUSC, has a planned enrollment of 60 patients, comprised of 20 newly diagnosed glioblastoma

multiforme patients and 20 patients each with recurrent and anaplastic astrocytoma.

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Novopharm Biotech Inc. (TSE:NVO) of Toronto has begun treating melanoma patients in a phase I/II trial of NovoVAC-M1, its fully human antibody vaccine.

The single site study is being conducted at the University of Alabama at Birmingham Comprehensive Cancer Center by principal investigator Donald Miller. The study is accruing a minimum of 15 patients into three groups of five, each measuring the immune response to GD2 (a melanoma-associated antigen).

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AVI Biopharma Inc. (Nasdaq: AVII, AVIIW) of Portland,OR, said it will begin a multicenter phase II trial of the therapeutic cancer vaccine, Avicine, in pancreatic cancer.

The randomized trial, involving at least 50 patients at seven centers nationwide, is designed to evaluate the safety and efficacy of Avicine alone and the potential synergistic effects of Avicine in combination with the **Eli Lilly & Co.** (NYSE: LLY) drug Gemzar (gemcitabine).

John Marshall, of Georgetown University, will serve as lead principal investigator. The study will be managed by Premier Research Worldwide, a clinical research organization located in Philadelphia, PA.

In phase Ib/II trials, Avicine was well-tolerated and exhibited no systemic toxicity, the company said. The median survival in the 10 pancreatic cancer patients treated with Avicine was 33 weeks without drug-related toxic side effects, compared to the 23 week median historical survival for this disease for patients treated with chemotherapy.

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Introgen Therapeutics Inc. of Austin, TX, announced the initiation of a phase I trial utilizing Adenoviral-p53 gene therapy (RPR/INGN 201) in cancer patients with solid tumors.

This is the first clinical trial to deliver the p53 gene by intravenous administration, the company said. IV administration expands p53 treatment to potentially all solid tumors, increasing the accessible patient population to more than 1.5 million.

The phase I trial, led by Gail Eckhardt and Daniel Von Hoff, will enroll patients with nonresectable solid tumors and for whom all prior therapies have failed. The trial is being conducted at the Institute for Drug Development/Cancer Therapy & Research Center in San Antonio.

Patents:

Cytran Wins Patent For IM862, An Angiogenesis Inhibitor

The U.S. Patent and Trademark Office has awarded Kirkland, WA, based **Cytran Inc.** a patent for the anti-angiogenesis effects of the company's drug, IM862, Cytran said.

The U.S. patent covers claims for IM862 to inhibit angiogenesis in a number of pathological conditions, including malignant tumors, age-related macular degeneration and vascular diseases.

IM862, a small peptide comprised of two amino acids, is in a phase III trial. Results of a phase I/II trial using IM862 in Kaposi's sarcoma were presented at the annual meeting of the American Society of Clinical Oncology last month. The findings, presented by Parkash Gill, of the University of Southern California, demonstrated that over one-third of KS patients in the trial showed a major response—either complete resolution of the KS lesions or partial reduction in tumor size—within a median response time of six weeks of beginning treatment. The trial was conducted at USC Norris Cancer Center, led by Gill, and at Massachusetts General Hospital, led by David Scadden, Harvard University.

Cytran is a privately held company.

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Cell Genesys Inc. (Nasdaq: CEGE) of Foster City, CA, said the company has been issued U.S. patent No. 5,904,920 for GVAX cancer vaccine technology.

Abbott To Purchase ALZA

(Continued from page 1)

franchise areas, said Arthur Higgins, senior vice president, pharmaceutical operations at Abbott.

In 1998, ALZA's sales were $646.9 million and net earnings $108.3 million, with diluted earnings per share of $1.07.

ALZA shareholders will receive a fixed exchange ratio of 1.20 shares of Abbott common stock for each share of ALZA. Abbott intends to account for the transaction as a pooling of interests.

The transaction is expected to be completed by the end of the year, subject to approval by ALZA stockholders and regulatory agencies, the companies said.

ALZA Corp. was advised by Chase Securities Inc. and Merrill Lynch & Co.

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