THE CANCER LETTER

Vol. 29 No. 44
Nov. 28, 2003

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

NCI Plans 11-16% Grant Budget Cuts To Maintain R01 Payline At 20th Percentile

In an apparent change of policy, NCI Director Andrew von Eschenbach decided to maintain the R01 grant payline at the 20th percentile at the expense of fully funding new grants in fiscal 2004.

Maintaining the R01 payline at the 20th percentile, the same as last year, is the Institute's "No. 1 priority" for fiscal 2004, von Eschenbach said at a Nov. 13 meeting of the NCI Board of Scientific Advisors.

The new funding policy appears to have been made within the past two months. Institute officials told the National Cancer Advisory Board

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In the Cancer Centers:

Kevin Cullen Of Lombardi Named Director Of Maryland's Greenebaum Cancer Center

Kevin Cullen of the Lombardi Cancer Center at Georgetown University, was named director of the University of Maryland Greenebaum Cancer Center in Baltimore, beginning in January.

Cullen, a head and neck cancer specialist, will be appointed professor of medicine at the University of Maryland School of Medicine and will head its program in oncology.

A graduate of Dartmouth College and Harvard Medical School, Cullen completed his internship and residency at Beth Israel Hospital in Boston and received additional training at NCI. He served as interim director of the Lombardi center for two years and is a professor of medicine, oncology and otolaryngology at Georgetown University School of Medicine. He has been affiliated with Georgetown since 1988.

"We are very pleased to have recruited a medical oncologist of Dr. Cullen's stature and reputation to take the helm of our cancer center," said **John Ashworth III**, CEO of the University of Maryland Medical Center. "He is an outstanding choice for the job—a superb clinician and researcher and proven leader who is committed to strengthening our position as one of the finest cancer centers in the region."

As interim director of Lombardi, Cullen recruited more than 20 new faculty members and oversaw the renewal of the cancer center's NCI designation as a comprehensive cancer center.

The Greenebaum Cancer Center plans to significantly expand its clinical and research programs, renovate patient care areas, and open a new ambulatory center.

"The university and hospital have made a very strong commitment

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NCI Plans $19.5 Million Cut In Competing Grant Funding

(Continued from page 1)

at its Sept. 9 meeting that the payline for fiscal 2004 would drop to the 18th or 19th percentile (**The Cancer Letter**, Sept. 26).

The decision means that NCI would fund 80 to 100 more R01 grants than previously projected, but the grantees will get significantly less money than peer reviewers approved. To fund all R01s that fall within the fundable range—the top 20 percent of grants ranked by priority score—requires that NCI make cuts of 11 to 16 percent in the budgets of those same R01s.

Also, NCI plans to limit funding for other new grants, including R21s and P01s, to the same levels as fiscal 2003.

Last year, NCI made cuts of about 10 percent in grant budgets to meet the 20th percentile mark.

The budget scenario presented to the BSA assumed that NCI receives the appropriation approved by the House and Senate earlier this year, $4.77 billion, an increase of 3.8 percent, or $178 million. Congress has not finalized the fiscal 2004 appropriations for the Department of Health and Human Services, which includes NCI.

"Obviously, there is no way I can make absolute predictions, because I don't have a budget yet," von Eschenbach said to the BSA. **"**At the very top of the list of what we set as a priority was to maintain the R01 payline at 20 percent. With that pegged as our goal, then we will look at what we actually get in appropriation and work our way through the rest of the expenditures. I can only commit to that being our No. 1 priority for '04."

Commitment To Non-Competing Grants

Of the $178 million in expected new appropriations, more than $113 million is already obligated to pay non-competing grants, called Type 5s, awarded in previous years. NCI plans to set aside $1.470 billion to fund these grants.

The Institute also plans to provide $61.7 million for administrative supplements to grants, an increase of $8.5 million from last year.

Funding for grants submitted in response to Requests for Applications will increase by $28 million, from $30.6 million last year to $58.8 million.

Funding for the remainder of the competing grants, which includes the R01s, would decrease by $19.5 million, from last year's level of $466.9 million to $447.4 million.

Small business grants, which are Congressionally mandated to a percentage of the Institute's grants funding, would increase by $10.3 million, from $90.8 million to $101.2 million.

Altogether, funding for all Research Project Grants would increase by $140.9 million, or 7 percent, from $1.999 billion last year to $2.140 billion.

In his remarks to the BSA, von Eschenbach said the FY04 budget would provide relatively little flexibility to fund new initiatives. In contrast to the optimism with which he discusses the opportunities and promise of cancer research, von Eschenbach's budget review evoked an aura of difficulty and constraint.

The NCI budget staff has been "helping us cope with what are significant challenges as we look at the transitions that are occurring with regard to our funding streams and our ability to manage a very complex and very different portfolio than that which exists in many of the other Institutes and centers within NIH," von Eschenbach said.

"The NCI's budget has within it a number of very unique and very specific mechanisms that require different ways of viewing the portfolio, especially with regard to expectations regarding the long-term investment in that portfolio," he said. "The issue we have to continually remind ourselves about is that, when we talk about a budget increase of $178 million,

THE CANCER LETTER

Member, Newsletter and Electronic Publishers Association

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

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Subscription $305 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd

that does not translate into $178 million of new money that we could embrace new initiatives with.

"The fact of the matter is, because of out-year commitments, much of that increase is already spoken for," he said. "There has been a policy that we would always make good on the commitments we have made in previous years. So, we really do have great challenges with regard to our discretionary money.

"When one looks at the budget and defines dollars in terms of what is fixed in non-competing expenditures and what is available for competition… about 84 percent of our budget is fixed, and about 16 percent falls into that competing category," he said. "However, when one goes into that competing category, what we are talking about, for example, are competing cancer centers, and also, competing cooperative groups.

"Although the cancer center is competing, the program is, in fact, relatively fixed. So for example this past year, of the competing cancer centers, there were M.D. Anderson, Sloan-Kettering, Fred Hutchinson, and others, and those are programs that obviously, the NCI has a long and ongoing commitment to. Although they are in that competing pool, those are truly not flexible, discretionary dollars that we can simply say we're no longer going to fund…and then have that money to re-deploy to some other initiative, like our strategic priority in bioinformatics.

"We have within our portfolio a number of investments that, in fact, we have long and ongoing commitments to, and we must nurture and maintain. At the same time, we have so many emerging strategic opportunities.

"We have many issues with regard to the budget that are now going to be further amplified or complicated by projections for out-years in which the percentage of increases are going to be significantly less than what had been experienced in years past, where there was always ample new dollars coming into the budget to take care of commitments to non-competing renewals and new initiatives.

"Double-digit percentage increase are not what is considered by anyone realistic expectations for the future. So we have engaged in a long range financial planning process, and we have begun to model a number of scenarios that will take us all the way out to the year 2009, looking at how we enhance our strategic investments. That may be by redeployment of our investments as well as finding opportunities to partner with others."

The proposal by NCI and the National Dialogue on Cancer to create a National Biospecimen Network is one such initiative that would require co-funding, von Eschenbach said. The proposed biorepository could not be "totally and completely nurtured and supported simply by the NCI," he said. "So we have to find ways in which we can work effectively with other agencies that are funding cancer research, for example, [Department of Defense]."

Von Eschenbach said he plans to hold a meeting that would bring most of NCI's advisory groups together, including the NCAB, the Board of Scientific Counselors, and the BSA, to discuss financial planning.

Grant applications to NCI continue to increase, at a time when applications to NIH are "relatively flat," von Eschenbach said.

"As the number of applications goes up, we are funding more and more cancer research, but the percentage, especially in the R01 pool, the percentile, is affected not only by the numerator, but also by the denominator," von Eschenbach said. "And yet, the important message to take home is that there has never been before in the history of the enterprise as much money in cancer research. Never before has there been as many investigators in cancer research. So, it is, in fact, very good news, and it is my intention to continue to work aggressively and effectively to maintain that critical mass of investigators, because without research we have no hope, and without research we have no expectation of being able to create a world where no one suffers and no one dies from cancer."

BSA member Susan Horwitz, Falkenstein Professor of Cancer Research at Albert Einstein College of Medicine, said new cancer centers shouldn't be discouraged from applying.

"I think it's very important to realize that the discoveries that have been made in cancer, if one looks at them, have been made at a variety of places, and under all different kinds of circumstances," she said. "There are new places that would like to have a cancer center and that are deserving. Things change. I think it's very important to recognize this. One of the great things about the NCI and NIH has been the peer review system. New places should be encouraged to apply, even though it may be not at the best time."

"I couldn't agree with you more," von Eschenbach said. "We are looking at ways and

mechanisms to be able to make that more flexible and more possible. I only mention those three simply as examples of institutions in which, as a cancer center, there has been longstanding commitment and there has been obviously demonstrable success.

"One would not expect that tomorrow, just because that institution was coming in for competitive renewal, that it would go away, that we would simply take that allocation and re-deploy it somewhere else," von Eschenbach said. "If they did not recompete effectively, they would not be funded. The point I was making is to keep us aware that what is categorized as being discretionary money is not truly discretionary in the way in which we have invested our resources. When we start looking at other opportunities, the amount that's available is much less than one might think."

Separate Payline For Large R01s

In a change in funding policy established for fiscal 2004, the NCI Executive Committee plans to set a separate payline for R01s costing more than $700,000 in direct costs, which represents about $1 million in total costs.

"The intent of the Executive Committee will be to apply the common R01 payline whenever possible, but to reserve the right to reduce the payline based on budgetary constraints," according to the policy.

This case-by-case funding is similar to the way NCI funds program project (P01) grants, Stephen Hazen, chief of the NCI Extramural Financial Data Branch, said to the BSA.

"The real genesis of this occurred in 2001 when we had a very large number of large R01s submitted to the Institute," Hazen said. The grants were percentiled, and fell within the payline. "The consequence of that for those who were competing in 2001 was a significant 'downward negotiation'—that's the word we used then, we don't use that anymore. We are calling it a cut."

The pressure on the R01 payline is tremendous, Hazen said. "There are very high expectations in the grantee community for continuing the payline of the 20th percentile," he said. The number of R01 applications is increasing by about 8 to 10 percent, and the average cost of R01s is going up. P01 applications are increasing, and the number of R21 applications has increased 40 percent.

"Our goal is to achieve the 20th percentile for R01s in 2004," Hazen said. "In order to do that, we will have to take a greater than 11 percent average cut. We will also need to limit the numbers of R21s, P01s and other mechanisms so that we can put resources in the R01 payline."

Every percentage point in the payline represents about 60 R01s at about $350,000 per grant, or between $20 million to $30 million in total costs, Hazen said.

BSA member Thomas Curran, chairman of developmental neurobiology at St. Jude Children's Research Hospital, pointed out the projected doubling of the RFA funding. "This is the area where NCI can have influence, and you are moving from $30 million to almost $60 million there," he said. "So, putting things together, this committee has been responsible for influencing one percentile of the RPG pool. Is that a fair statement?"

"That's correct, congratulations," Hazen said.

Hazen said the budget cuts for new grants would range from 11 percent to 16 percent. "We will have to provide enough money to pay all the grants, and that's how we will have to do it," he said.

"It's a horrible thing to suggest, but looking at the numbers in the Type 5, has there been a discussion of a very modest percentile reduction in that number, which would, of course, give you a lot more flexibility?" Curran asked.

"Yes, there has been that discussion," Hazen said. "Dr. [Elias] Zerhouni, in a long line of NIH directors, has established a policy that our word is our bond. Two years ago, we were looking at budget options that were 2 or 3 percent cuts from the current level, and he was very insistent that we would not touch the Type 5s. Commitments that we made in the past are good.

"What it doesn't say is, are we wise when we make these competing grants to give some of them 3 percent cost-of-living increases over the next years?" Hazen said. "That's going to be a policy we are going to have to examine very carefully."

At a Nov. 12 meeting of the RPG Working Group of the NCAB, NCI staff presented different budget scenarios using a sliding scale based on review results, in which best scores would get smaller cuts. The NCI Executive Committee did not favor that policy. The working group agreed that a sliding scale would not help the grants with the best scores, and would cause greater problems for the grants close to the payline.

* * *

NCI plans to hold a meeting in March of all the directors of the NCI-designated cancer centers,

Institute Director von Eschenbach said.

"I plan now on a regular, formal basis of once a year to have a retreat with every one of the cancer center directors," he said to the BSA. "It's part of the strategy of how we can more effectively, as the NCI, add value to and continue to work effectively in the horizontal and vertical integration of the cancer centers. We are planning to do the same thing with the heads of the cooperative groups. That will be a very significant part of my effort for 2004."

Capitol Hill:

Medicare Reform Bill Enacted, Cuts Oncology Reimbursement

Congress has enacted a Medicare reform bill, creating a prescription drug benefit, but drastically cutting reimbursement for office-based oncologists.

After unsuccessful procedural maneuvering led by Sen. Edward Kennedy (D-Mass.), the Senate narrowly passed the bill Nov. 25, four days after it cleared the House on a razor-thin 220:215 margin.

While Kennedy and other critics blast the $400-billion bill for its generosity to insurance and pharmaceutical companies, office-based oncologists will see no evidence of federal largesse. Over the next 10 years, they will face cuts of $11.5 billion for Medicare reimbursement.

Even a cursory glance at the 678-page report reveals that things aren't going well for oncologists: the legislative language appears in the section titled "Combating Waste, Fraud and Abuse."

The conference report is posted at: http://energycommerce.house.gov/108/drafts/HR1-CONF_FIN.PDF

Under the bill, starting on Jan. 1, 2004, reimbursement for cancer drugs will drop to 80 to 85 percent of the "average wholesale price" from the current rate of 95 percent of AWP.

Reimbursement is set at the lower of 85 percent of AWP of the "widely available market price," which can be calculated with inclusion of wholesalers and distributors who get far lower prices than an average practice, observers say. With this downward pressure, reimbursement next year is likely to be closer to the lower end—at the floor level of 80 percent of AWP.

Starting in 2005, reimbursement will be set at the "average sales price plus 6 percent."

"The ASPs for drugs are not publicly known, but we have serious doubts that community physicians will be able to purchase drugs for 106% of ASP or less," ASCO said in its commentary on the bill. "The ASP system is wholly untested and is based on non-public price information, yet Congress has put it into effect… We have serious concerns about patient access if the reimbursement amount is less than the price of the drug, as it appears will often be the case."

For years, oncologists argued that Medicare underpays them for office expenses but overpays for drugs. Recognizing this argument, the government offset the cuts with an adjustment in practice expenses.

In 2004 and 2005, the adjustment will be around $380 million, and in subsequent years, it would drop to $340 million. This may amount to a 160 percent increase for practice expenses, far less than the 200 to 300 percent increase that would be required, ASCO estimates.

Starting in 2005, payments to oncologists would drop sharply, ASCO said.

"This decrease is based on the Congress's assumption that 3% of the drug payment (at 106% of ASP) will be profit to the physician that can be used to pay for practice expenses," the society said. "This assumption is wholly unwarranted—we have serious doubts whether drugs can be purchased by physicians for even 106% of ASP, and there is no reason to believe that the Medicare payment will be so much higher than the purchase price that 3% will be available to pay for office expenses."

Also, starting in 2005, Medicare would pay the lower of ASP plus 6 percent or the widely available manufacturer's price.

At least in principle, this could mean that the prices would enter a downward spiral, making it impossible for many physicians to purchase drugs. "Since the ASP is, by definition, an averaged price—meaning that there will always be prices above and below the average—there will always be a lower price," US Oncology said in its commentary on the legislation.

"By requiring the [HHS] Secretary to replace ASP with that lower price, the report will make it impossible for any purchaser above that lowest level to be able to cover the cost of the drug they are obtaining to treat their patients," the US Oncology analysis states.

The analysis is posted at http://www.legislink.com/site/DocServer/AV_DrugBil_Discrepancies.pdf?docID=1081

"We know that many in Congress have challenged our position that access to cancer care

will be jeopardized by just the cuts contained in this bill," ASCO President Margaret Tempero said in a statement. "But the fact is, the effect of these very substantial changes will be significant for oncology practices across the country.

"Among other things, we are concerned that these changes will have significant unintended consequences for cancer clinical trials, upon which we all depend to ensure progress in the fight against cancer for future generations," Tempero said.

Addressing another lingering problem in cancer care, the bill mandates an experiment with reimbursement for oral cancer drugs, including Gleevec, Iressa, and tamoxifen, through a two-year demonstration project, which would be launched in six states cover 50,000 patients.

* * *

Congress last week passed the Pediatric Research Equity Act, legislation that gives FDA the authority to require pediatric trials of drugs and biologics.

The bill, S. 650, was passed by the House on Nov. 19.

"The public health of children will be best served by enabling FDA to require testing of drugs for pediatric use, when drug firms do not test them voluntarily," HHS Secretary Tommy Thompson and FDA Commissioner Mark McClellan said in a joint statement. "This Department has long recognized the need for this testing so that parents and practitioners alike will have the information they need on how medications actually work in children."

The bill gives FDA an additional authority it can use when incentives fail to induce pharmaceutical companies to test drugs in children. The incentives are offered in the 2002 "Best Pharmaceuticals for Children Act," which grants six-month extensions of marketing exclusivity to sponsors who conduct FDA-requested testing of drugs with existing patents or marketing exclusivity.

In the past, FDA relied on the 1998 "pediatric rule" to compel reluctant pharmaceutical companies to test their products in children. However, in October 2002, the U.S. District Court for the District of Columbia ruled that the agency lacked statutory authority to enforce the rule.

"We strongly defended the pediatric rule in court yet lost," Thompson and McClellan said in a statement. "Instead of pursuing a time consuming appeal of the ruling, we called on Congress to work with us to craft the needed legislation to provide FDA with the authority to require pediatric studies."

The law will be triggered when the adult and pediatric disease or conditions are the same and when the product is considered to be either widely used (more than 50 000 children per year) or is a therapeutic advance. In the case of oncology products, the widely used criterion would not be met, so the product must be considered a therapeutic advance for the FDA to mandate pediatric studies.

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee met in a series of five meetings between September 2000 and November 2001 to establish principles that may apply to various malignancies. Historically, adult and pediatric cancers were considered different diseases, but a combination of new science and different therapeutic targets supports linkages based on pathophysiology and mechanism of action that would allow the FDA to apply the new law.

"We have an additional regulatory tool to ensure that children with cancer receive the same access to investigational agents and the same opportunity for new products as adults," said Steven Hirschfeld, a pediatric oncologist with the FDA.

Products developed for many adult cancers such as non-small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer will receive waivers for those indications. The new law will likely apply to hematologic malignancies, sarcomas, and brain tumors. In no case will the need for pediatric studies be allowed to delay approval for adults because compliance with the requirement can be deferred, Hirschfeld said.

Funding Opportunities:

RFP Available

NOT-CA-04-002: Cancer Information Service

NCI will award 15 base contracts to operate the CIS Partnership Program. Offerors may also choose to propose on one or more of the following four modules: CIS research coordination, CIS coordinating center, national Spanish call service, and e-mail response service. Fifteen cost-reimbursement, incrementally funded, completion type contracts (to include the modules) will be awarded for a five-year period of performance beginning on Oct. 15, 2004. The RFP will be electronically released on Dec. 3, 2003, with proposals due 45 days following the date of issuance. Text will be available at http://rcb.nci.nih.gov/.

Inquiries: Mary Landi-O'Leary, contracting officer, phone 301-435-3807; fax 301-480-0309; e-mail ml186r@nih.gov or Sharon Miller, team leader, phone 301-435-3783; fax 301-480-0241; e-mail sm103r@nih.gov.

In the Cancer Centers:

Maryland Plans Expansion; Winship Awarded NCI P20

(Continued from page 1)

to further develop the cancer center and promote its growth," Cullen said. "There is already a very strong scientific and clinical base there, and I intend to build on those strengths."

Cullen also plans to recruit more researchers and promote strong collaboration between clinicians and scientists. "That's really what a cancer center is about," Cullen said. "It's very patient-oriented. The mission of a cancer center is to translate basic science results into better ways to treat patients."

Maryland has earmarked Cigarette Restitution Fund Program monies for cancer research, awareness and screening, Cullen said. "There is tremendous opportunity for the University of Maryland Greenebaum Cancer Center to continue to capitalize on those resources to make significant progress in all of those areas," Cullen said.

* * *

WINSHIP CANCER INSTITUTE has been awarded a $1.9 million P-20 cancer center planning grant from NCI. The grant will provide a minimum of $250,000 each year for five years and represents a first step in attaining NCI comprehensive cancer center designation, an objective of the state cancer initiative, known as the Georgia Cancer Coalition.

"What is unique about Georgia is the state's substantial commitment of tobacco settlement funds through the Georgia Cancer Coalition," said **Michael Johns**, executive vice president for health affairs and CEO of the Woodruff Health Sciences Center at Emory University. "The GCC will serve to make the NCI program funding more efficient by developing a state-wide network of research centers, which will collaborate on investigations and develop clinical trials."

Emory opened a new building last July, which "will serve as a discovery accelerator where care of cancer patients is advanced through discoveries in genomics and molecular medicine," said WCI Director **Jonathan Simons**.

* * *

MEMORIAL Sloan-Kettering Cancer Center announced the recipients of the Paul Marks Prize for Cancer Research. The $125,000 award will be shared among three researchers: **YuanChang**, professor of pathology, Department of Pathology at the University of Pittsburgh Cancer Institute; **John Diffley**, principle scientist at Cancer Research UK London Cancer Research Institute; and **Nikola Pavletich**, chairman, structural biology program, Sloan-Kettering Institute. The prize, named after **Paul Marks**, president emeritus of MSKCC, recognizes significant contributions to the basic understanding and treatment of cancer by scientists no more than 45 years old at nomination.

* * *

ROSWELL PARK Cancer Institute has received more than $1.1 million in seed money pledges for genetic studies and for a Center for Genetics and Pharmacology. Benefactors include the Palisano Foundation, the Lo Vullo Family, Amgen, and the Pardee Foundation.

* * *

DAVID JANSEN has been appointed vice president of human resources at the Barbara Ann Karmanos Cancer Institute, said **John Ruckdeschel**, president and CEO of the Institute. Jansen was a partner with Mulhern Hastings Group LLC, a management consulting firm of Detroit.

* * *

YALE UNIVERSITY received the first NCI Graduate Program Partnership in Cancer Epidemiology and Genetics. Yale's Department of Epidemiology and Public Health will partner with the NCI Division of Cancer Epidemiology and Genetics to develop the training program. **Susan Mayne**, associate professor of epidemiology and public health, is principal investigator. The program supports tuition and dissertation research for four to six pre-doctoral students training in evaluating lifestyle factors associated with cancer risk, particularly nutritional, environmental, and occupational determinants. The program will include instruction at Yale and a summer at NCI. The dissertation research will be conducted at NCI. Yale will award the doctoral degree. **Harvey Risch**, professor of epidemiology and public health, and **Tongzhang Zheng**, associate professor of epidemiology and public health, serve on the steering committee with Mayne at Yale. **Demetrius Albanes** leads the partnership for NCI as head of the DCEG Office of Education, assisted by steering committee members **Aaron Blair**, chief of the Occupational and Environmental Epidemiology Branch, and **Arthur Schatzkin**, chief of the Nutritional Epidemiology Branch. Interested students may contact Mayne at susan.mayne@yale.edu or phone 203-785-6274. The application deadline for fall 2004 admission is Jan. 2.

NCCN National Comprehensive Cancer Network®

Medical Director

The National Comprehensive Cancer Network (NCCN), an alliance of nineteen of the world's leading cancer centers, is seeking an academic-based oncologist for the position of NCCN Medical Director. This is a full time position seeking to apply the Medical Director's scientific and clinical expertise in the development and work of NCCN Clinical Practice Guidelines, the NCCN Clinical Trials Network, Quality of Care initiatives, NCCN conferences, symposia and publications, NCCN managed care collaborations, etc.

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THE CANCER LETTER

Vol. 18 No. 10
November 2003

Business & Regulatory Report

Oncology Management:

Medicare Increases Reimbursement For Aranesp And Procrit, Changes Ratios

The Centers for Medicare and Medicaid Services earlier this month increased reimbursement for erythropoietin as part of revamping regulations for prospective payments to hospitals.

The increase affects Aranesp, an Amgen product, and Procrit, a Johnson & Johnson product. The rule is posted at http://www.cms.gov/regulations/hopps/2004f/.

There are no data for a definitive comparison of the two agents. Nonetheless, in November 2002, CMS ruled that Aranesp and Procrit are

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Clinical Trials:

Analysis Of ECOG Rituxan Study Finds Increase In Time To Treatment Failure

Genentech Inc. (NYSE: DNA) of South San Francisco, **Biogen IDEC** (Nasdaq: BIIB) of San Diego, and **Roche**, of Basel, Switzerland, said the Eastern Cooperative Oncology Group phase III study (E1496) evaluating Rituxan (rituximab) maintenance therapy has met its pre-specified primary efficacy endpoint early.

A pre-planned interim analysis of the study data by an independent ECOG Data Monitoring Committee demonstrated a statistically significant improvement in time to treatment failure in Rituxan maintenance therapy, the companies said. As a result, the DMC has stopped further randomization on the study.

The phase III study enrolled previously-untreated patients with indolent non-Hodgkin's lymphoma, the company said. All received a maximum of eight doses of induction therapy with cyclophosphophamide, vincristine, and prednisone. At the time that the study was stopped, 322 patients who responded or had stable disease following induction CVP chemotherapy had been randomized to receive either Rituxan maintenance therapy or no further treatment, the companies said.

Rituxan maintenance therapy consisted of four weekly doses of Rituxan every six months for two years, the companies said. Time to treatment failure was evaluated as the time from randomization to the first failure, defined as documented disease progression or death.

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GTx Inc.of Memphis, Tenn., said it has begun a phase III trial of Acapodene (toremifene citrate) tablets to reduce skeletal fractures and

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Deals & Collaborations:
GenPath, Merck Enter Multi-Year Collaborative Agreement

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CMS Increases Reimbursement For Aranesp And Procrit

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"functionally equivalent." The agency used the ratio of 260 units of Procrit to 1 microgram of Aranesp to set reimbursement. Amgen disputed this conclusion, arguing for a 400:1 ratio. After reviewing the data, CMS increased the conversion ratio to 330:1.

Payments for Aranesp increased from $2.37 per microgram to $3.24 per microgram. Payments for Procrit increased from $9.10 per 1,000 units to $9:83 per 1,000 units.

The excerpted text of the CMS rule follows:

Since publication of the OPPS final rule for 2003, we have continued to review and refine our analysis of the appropriate conversion ratio between these biologicals. In order to facilitate analysis of the non-peer reviewed materials submitted by Amgen and Ortho Biotech, we initiated a process in July 2003, in which each company shared with CMS, our contractor, and each other, a detailed description of the methods used in each of their unpublished clinical studies. Each company was then asked to submit to us their comments as well as the responses to questions raised by the other company's review. Finally, based on our analysis of this information, CMS submitted questions to each company to clarify their views…

The articles submitted by the manufacturers regarding treatment of chemotherapy-induced anemia (CIA) were all observational, retrospective, cohort studies. Several of these studies were conducted with a high degree of attention to minimizing avoidable bias and maximizing data integrity.

Observational studies are, however, unavoidably subject to patient selection bias since study subjects are not randomly assigned to the groups being compared. It is not possible to eliminate the possibility that the choice of erythropoetic agent was somehow systematically linked to characteristics of the patients treated. Similarities or differences in clinical response may reflect either baseline patient characteristics or the effects of the therapy being studied.

Another major limitation of observational studies is that the researcher typically has no control over the manner in which the intervention under study has been delivered. In this instance, an additional difficulty with using observational studies to assess the equivalence of dosages of epoetin alfa and darbepoetin alfa in chemotherapy-induced anemia in cancer patients is that the response to these drugs may be disease-driven, dosage-driven, or both (depending for example, among other factors, on the individual cancer patient's level of endogenous erythropoietin).

A large range of dosages of both epoetin alfa and darbepoetin alfa may show similar effects in any given patient and higher than necessary dosages may not be reflected in greater elevations of hemoglobin. More generally, the populations in the reported studies may show different results due to differences in demographics, health status, types of cancer, and cancer treatments.

Beyond these methodological concerns, the question of what constitutes the best indicator of drug effect remains unsettled. Studies in the literature have used one or more of the following end-points to analyze the effects of erythropoietic drugs:

Hemoglobin response – an increase from baseline of ≥2 g/dL (usually in the absence of transfusion in the preceding 28 days)

Hematopoietic response – Hemoglobin increase of ≥2g/dL from baseline or a hemoglobin ≥12g/dL

Mean change in hemoglobin – the mean increase in hemoglobin from baseline (usually in the absence of transfusion in the preceding 28 days)

Transfusions of red blood cells – the number (percent) of patients requiring transfusion measured at various time intervals.

Studies submitted by one of the manufacturers

THE CANCER LETTER

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Business & Regulatory Report

Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
E-mail: paul@cancerletter.com

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724

Business & Regulatory Report, a supplement to The Cancer Letter, is available separately for $185 per year. ISSN 1053-9611.

proposed additional measures such as "early hemoglobin response" (the hemoglobin rise from baseline at 4 or 5 weeks) and the "area under the curve" defined by hemoglobin increases from baseline. The FDA has not used these measures as criteria for registration (i.e., market approval) and they do not appear to be regularly used in the peer reviewed literature of erythropoietic drugs and their use either in kidney disease or in oncology. Therefore, their clinical significance is unclear at this time.

They do, however, raise the question of how hemoglobin response patterns affect symptoms that matter most to patients. Both companies are conducting additional clinical studies to address further the potential importance of front-loaded regimens that provide high initial doses of erythropoietic drugs in order to stimulate a more rapid clinical response.

During the process of exchanging and critiquing study methods, Amgen and Ortho-Biotech each raised significant methodological concerns about the study designs used to obtain new data. In addition to the overall concern about the observational methodology and selection of the outcome chosen for purposes of comparison, the following concerns were raised:

—the use of survival curves to analyze clinical data in this context

—the possible effect of patient functional status on erythropoietic response

—the technique for calculating mean values for drug dosages (arithmetic vs geometric means)

—the strategy for deciding how to handle data from patients who received transfusions

—the significance of an early rise in hemoglobin, and/or the significance of measures of hemoglobin response over the entire 12-16 week treatment interval

Each company provided extensive and compelling discussions of these and other issues, highlighting the fact that conclusions regarding the relative potency of these products are inherently limited by the nature and quality of the clinical data that currently exist. Despite the limitations of the available studies, CMS believes that it has sufficient data to establish a reasonable conversion ratio for payment purposes.

Amgen submitted several observational studies, including one community-based study and three medication use evaluations (MUE).

While interim results from two of these studies have been published in peer-reviewed journals, final results have not yet been subjected to full peer review. In one study (Vadhan-Raj, 2003), patients were started on darbepoetin at 3 mcg/kg every other week (QOW). The patients received up to 8 doses (16 weeks). The patients had hemoglobin (Hgb) responses comparable to that seen with epoetin 40,000-60,000 IU per week. The protocol allowed a dose increase and 43 percent of participants had their darbepoetin dose increased to 5 mcg/kg/QOW per the protocol. Virtually all of the Amgen studies produced results that suggested a conversion ratio of 400:1.

Ortho Biotech submitted early unpublished results from a multicenter head- to-head trial of 40,000 IU of epoetin weekly compared to 200 mcg of darbepoetin every other week. The primary end-point is the change in Hgb from baseline at week 5, and initial results show significantly greater increase in Hgb for patients treated with epoetin. Ortho Biotech also submitted data from several retrospective analyses of medical charts and electronic medial records, totaling several thousand patients. None of these studies have yet been peer-reviewed or published. All of the Ortho-sponsored studies provide results suggesting that the appropriate conversion ratio is 260:1 or less.

In the observational studies that directly compare Aranesp and Procrit for the treatment of CIA, and report total dose per patient per episode of both epoetin and darbepoetin, the ratio of mean total doses is 341:1 and the ratio of median total doses is 352:1. However, selection bias may affect the validity of these studies. CMS therefore believes that the above-mentioned ratios may still overestimate, at least modestly, the potency of darbepoetin alfa relative to epoetin alfa. An analysis of Medicare claims data from 2002 and 2003 determined that the ratio of utilization of Procrit to Aranesp in Medicare patients was 330:1 (units:mcg).

As noted above, a conversion ratio between the dosages of these two products is not meant to guide what should be done for individual patients in clinical practice. In addition, by using a conversion ratio CMS is not attempting to establish a lower or upper limit on the amount of either biological a physician can prescribe to a patient. CMS expects that physicians will continue to prescribe these biologicals based on their own clinical judgment of the needs of individual patients.

Based on our own review of the evidence, our consultation with the independent contactor who also

reviewed the evidence, and our discussions with Amgen and Ortho Biotech, CMS concludes that an appropriate conversion ratio for the purposes of a payment policy is 330 International Units of epoetin alfa to one microgram of darbepoetin alfa (330:1) for the purpose of treating chemotherapy-induced anemia.

* * *

M.D. Anderson Cancer Center said it has purchased the **Omnicell PharmacyCentral** system to automate pharmacy operations that support 60,000 patients annually.

The installation of the system is scheduled for November, the center said.

"Our current system is a manual perpetual inventory system, said Jane Kwan, manager of purchasing and inventory for the pharmacy division of M.D. Anderson. "The Omnicell system will automate this function and allow us to improve our accuracy and efficiency."

Omnicell PharmacyCentral is software linked to a carousel storage and retrieval device that enables hospital pharmacies to manage medication inventory in the central pharmacy while reducing medication errors, streamlining workflow for greater efficiency, and improving inventory control, the center said.

The M.D. Anderson installation is a four-carousel system, which includes the Omnicell PharmacyCentral MobileNet to manage off-carousel items.

* * *

National Comprehensive Cancer Network of Jenkintown, Penn., said it has updated its recommendations for adjuvant therapy following primary therapy for breast cancer. Based on the recently closed MA-17 trial, it is appropriate to use letrozole (Femara) in postmenopausal women with hormone receptor positive breast cancer who have completed 5 years of tamoxifen as adjuvant therapy, the NCCN panel said.

The MA-17 study does not address the adjuvant use of protracted or sequential aromatase inhibitors (e.g. letrozole following 5-years of anastrozole or indefinite anastrozole or tamoxifen following an aromatase inhibitor), the panel said. Therefore, Letrozole is not appropriate for premenopausal women.

NCCN Clinical Practice Guidelines in Oncology are available free of charge on CD-ROM at phone 215-690-0300 or at www.nccn.org.

* * *

PRA International Inc. of McLean, Va., said it has entered into a preferred provider relationship with the **Geriatric Oncology Consortium** for community-based geriatric oncology research and education.

"It will enable us to expand upon working relationships with the oncology community and provide greater access to cancer patients for clinical trails," said Patrick Donnelly, president and CEO of PRA.

Under the agreement, PRA will provide GOC with clinical services that support clinical development needs, the company said. The services allow GOC to affect cycle time of clinical trial activities including study start up, serious adverse event management and back end data management, and report writing, the company said. PRA, a clinical research organization, said it is conducting oncology trials at 3,000 sites globally.

Clinical Trials:

Phase III Trial Of Acapodene Begins For Prostate Cancer

(Continued from page 1)

other complications of androgen deprivation therapy for advanced prostate cancer.

The study will enroll 1,200 patients in the 24-month, placebo controlled U.S. trial, the company said.

Androgen deprivation therapy is accomplished either surgically by removal of the testes or chemically by treatment with LHRH agonists such as Lupron and Zoladex. Side effects include bone loss leading to osteoporosis and skeletal fractures, hot flashes and gynecomastia.

Acapodene is a nonsteroidal SERM, a small molecule that binds and selectively modulates the estrogen receptor, the company said. SERMs have been shown to stimulate estrogen receptors in bone and block estrogen receptors in the breast and could block estrogen receptors in the prostate.

GTx said it has licensed the right to develop, market and distribute toremifene, the active ingredient of the tablets, worldwide for prostate cancer, osteoporosis, hot flashes and gynecomastia as side effects of androgen deprivation therapy for prostate cancer, from Orion Corp, of Finland.

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I-Flow Corp. (Nasdaq: IFLO) of Lake Forest, Calif., said **M. D. Anderson Cancer Center** has begun a study with its ON-Q Post-Operative Pain

Relief System for breast reconstruction surgery.

The randomized study of 60 women measures the benefits of the device in allowing a faster return to normal life while reducing narcotics intake following surgery, the company said.

The study will be led by Charles Butler, director of the Plastic Surgery Clinic at M. D. Anderson Cancer Center in collaboration with Alicia Kowalski, assistant professor in anesthesiology at M. D. Anderson.

Patients will undergo a TRAM Flap, a surgical method that uses tissues from the body to reconstruct the breast following a mastectomy, and will receive an ON-Q pump, the company said. Half of the ON-Q pumps will be filled with a local anesthetic to be delivered to the surgical site and the other half will be filled with a placebo of saline.

In all cases, patients will be given the standard pain medications delivered through a patient controlled analgesia device in addition to ON-Q and will be continuously graded on a standard pain scale to determine comfort level. They will be evaluated on the amount of narcotics necessary to alleviate their pain and the pace of their overall recovery, for example, the length of their hospital stay.

"With TRAM Flap surgery, there is more pain than with other breast reconstructive surgeries, and it traditionally requires a longer hospital stay and a longer recovery time," said Butler. "The study will compare a technique that directly infuses pain medication into the surgical site to standard pain management to determine if patients experience less pain, side effects and, ultimately, a shorter recovery time."

The ON-Q Post-Operative Pain Relief System delivers a non-narcotic numbing medication directly to an incision site, the company said. It is a small, high-tech balloon pump that delivers local anesthetic, a pain-numbing medication, directly to the surgical site for up to five days. The anesthetic is administered through a tiny tube inserted during surgery. ON-Q is cleared for use by FDA, the company said.

* * *

Igeneon of Vienna, Austria, said it plans to start two additional trials with its cancer vaccine candidate IGN101.

The first is a placebo controlled phase III study in metastatic colorectal cancer in 24 European clinical centers, the company said. The second is a controlled phase III study in adjuvant breast cancer, which will be conducted in cooperation with the Austrian Breast & Colorectal Cancer Study Group. A placebo-controlled phase II/III trial in adjuvant NSCLC is ongoing.

In the placebo-controlled 700 patient metastatic colorectal cancer trial, patients will be given IGN101 or placebo in addition to first-line chemotherapy, the company said. The primary endpoint is overall survival. The secondary endpoint being time to disease progression.

In the 600-patient controlled breast cancer trial in 25 Austrian centers, patients in the adjuvant stage with increased risk for relapse will receive either standard chemotherapy or standard chemotherapy plus IGN101, the company said. Vaccinations will be started immediately after surgery, with the primary tumor removed and no metastases present. The primary endpoint is relapse free survival.

"To our knowledge, this is the first trial with and immunotherapy in adjuvant breast cancer worldwide", said Raimund Jakesz, head of the Vienna General Hospital and University Clinic4s Division of General Surgery and president of the ABCSG study group.

IGN101 is a candidate cancer vaccine that triggers an immune response to EpCAM (epithelial cell adhesion molecule), a membrane protein that is expressed—and often over-expressed—on epithelial cancer cells, the company said. It selectively destroys disseminated tumor cells and could prevent or delay the formation of metastases.

* * *

Medarex Inc. (Nasdaq: MEDX) of Princeton, N.J., said it has begun a phase II trial of MDX-010, a fully human anti-CTLA-4 antibody, for metastatic breast cancer.

In the multi-center, open-label trial, 33 patients receive a monthly dose of 3.0 mg/kg of the MDX-010 antibody for up to four treatment cycles and will be followed until disease progression, the company said. The study would evaluate tumor and immune responses.

MDX-010 is in multiple phase II trials metastatic melanoma, prostate cancer and other cancers, the company said. The drug is also in a phase I trial for HIV. Data from phase I/II studies conducted by Medarex and from an ongoing phase II study indicate that MDX-010 may induce anti-tumor activity in association with immune activation for metastatic melanoma and hormone refractory prostate cancer.

* * *

OSI Pharmaceuticals Inc. (Nasdaq: OSIP) of Melville, N.Y. said it has initiated a phase II dose-

escalation study of Tarceva (erlotinib HCl) for advanced non-small cell lung cancer where prior chemotherapy has failed.

Tarceva blocks tumor cell growth by inhibiting the tyrosine kinase activity of the HER1/EGFR receptor thereby blocking the HER1/EGFR signaling pathway inside the cell, the company said. The drug is being developed in a global alliance between OSI, Genentech and Roche.

The open-label study is evaluating the feasibility of dose escalation of Tarceva to induce tolerable rash with no other undue toxicities and to assess whether there is evidence of enhanced activity where a rash has occurred, the company said. The study is exploring a completed phase II study that observed that survival of patients who developed rash was longer than in those without rash, generating the hypothesis that rash might be a surrogate for patient benefit.

"The observed correlation between rash and survival previously reported with the drug and some other agents targeting the HER1/EGFR pathway is intriguing and of particular interest to the oncology community," said Eric Rowinsky, principal investigator and director of clinical research, Institute for Drug Development.

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OXiGENE Inc. (Nasdaq: OXGN, XSSE: OXGN) of Waltham, Mass., said Combretastatin A4 Prodrug, its investigational anti-tumor compound, would be tested in a clinical trial for newly diagnosed cancer without metastasis.

CA4P will be studied in combination with the chemotherapy drugs doxorubicin/cisplatin and radiation for newly diagnosed anaplastic carcinoma of the thyroid, the company said.

Thirty-three patients will be recruited for the dose-escalating trial, which is being conducted at Ireland Cancer Center at University Hospitals of Cleveland and Case Western Reserve University. Scot Remick, professor of medicine and program leader of the Cancer Center's Development Therapeutics Program, is the principal investigator.

"What makes this trial so significant is that it involves newly diagnosed patients who have not received prior therapy for the disease," said Fred Driscoll, president and CEO of Oxigene. "In the five other oncology trials in which CA4P is now being studied, the compound is administered only in advanced cancer patients who had failed all conventional therapies."

In the trial, therapy will be administered in three phases. In the induction phase, patients will receive a combination of doxorubicin and cisplatin, the company said. That will be followed by a combined modality phase, in which CA4P will be administered in an escalated dose with radiation. In the consolidation phase, patients will receive CA4P alone.

The Ireland Cancer Center also is the site of a complementary phase II single-agent trial of CA4P in advanced anaplastic thyroid cancer, the company said. That trial involves patients who failed first-line therapies and whose cancer has advanced regionally and/or metastasized.

"A large body of pre-clinical data suggests that CA4P has the potential to act synergistically with chemotherapy and radiation," said David Chaplin, chief scientific officer at Oxigene. "This trial opens the possibility of developing a new standard of care for a disease in which there is no established therapy."

CA4P attacks the vascular structure of solid tumors and other diseases characterized by the formation of aberrant blood vessels, the company said. The compound triggers a change in the shape of endothelial cells lining a tumor's blood vessels, and in turn, blocks the flow of blood to the tumor, depriving it of oxygen and nutrients.

The compound is a synthetic form of CA4, a natural substance found in the bark of the South African willow tree known as Combretum caffrum, the company said.

In June 2003, CA4P received FDA Fast-Track designation for ATC, the company said. In July 2003, FDA awarded orphan drug status to the drug for multiple forms of thyroid cancer including ATC.

* * *

Pharmacyclics Inc. (Nasdaq: PCYC) of Sunnyvale, Calif., said it has begun two phase I trials of its investigative drug Xcytrin (motexafin gadolinium) Injection in combination with Taxotere (docetaxel) for advanced solid tumors.

"Preclinical animal model studies have shown that Xcytrin improves the anticancer effects of several commonly used chemotherapy drugs," said Nithya Ramnath, principal investigator, Department of Medicine, Roswell Park Cancer Institute. The clinical studies are designed to evaluate the safety and benefit of Xcytrin in combination with docetaxel for common solid tumors that have failed prior therapies; a situation where currently available treatments are inadequate."

The phase I trials will each recruit 25 patients with relapsed prostate, breast, lung or ovarian cancers

that have failed initial chemotherapy, the company said. Each of the protocols is designed to evaluate Xcytrin in combination with different, but commonly used, docetaxel dosing regimens.

One will evaluate Xcytrin in combination with docetaxel given every three weeks. The study will be conducted at the James P. Wilcot Cancer Center, University of Rochester Medical Center, Rochester. The other protocol is designed to examine Xcytrin with docetaxel given weekly and will be conducted at the Roswell Park Cancer Institute.

Xcytrin, part of an investigational class of drugs called texaphyrins, is a tumor targeted generator of intracellular molecules known as reactive oxygen species, the company said.

After administration, the drug selectively localizes and accumulates inside cancer cells, due to their high rates of metabolism, including anaerobic glycolysis, the company said. Because Xcytrin is a paramagnetic compound, its presence is detectable with magnetic resonance imaging. Studies with MRI have confirmed the selective localization of Xcytrin in primary and metastatic tumors.

Within cancer cells, Xcytrin disrupts cellular metabolism, interferes with the flow of energy, and results in the generation of ROS, the company said. The mechanism of action of Xcytrin is believed to make cancer cells more vulnerable to the oxidative stress (i.e., specific types of damage involving oxidation-reduction reactions) caused by radiation therapy and chemotherapy, the company said. The generation of ROS within cancer cells promotes a process called programmed cell death, or apoptosis, leading to the selective destruction of the cancer cells.

Preclinical studies have shown that Xcytrin enhances the efficacy of radiation therapy and that of other chemotherapy agents, the company said. The drug is being investigated as a therapeutic in combination with radiation therapy and/or chemotherapy and as a single agent for various types of cancers in phase I and phase II trials sponsored by Pharmacyclics and/or NCI.

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Phoenix Pharmacologics Inc. of Lexington, Ky., said it has initiated a phase III study of ADI for terminal liver cancer.

The study is conducted at the Pascale National Cancer Institute in Naples, Italy, the company said. Phoenix Pharmacologics said it owns the patents to ADI and has manufactured all of the drug used for clinical trials in the U.S., Italy and Taiwan.

Phoenix, a privately held biopharmaceutical company, is searching for a commercial partner to manufacture the ADI drug and market it in Europe and North America once regulatory approval for sale is obtained, said Mike Clark, CEO of Phoenix.

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Synthetic Blood International Inc. (OTCBB: SYBD) of Costa Mesa, Calif., said it has begun a phase I trial of its perfluorocarbon based blood substitute for heart, stroke and cancer, and as a blood substitute and in organ preservation.

The first six, of 27 patients, have been infused with Oxycyte or a control fluid, the company said. The double-blinded study has gone well and the product appears to be safe at the starting dose level.

The company said it expects the study to be completed by the end of the year and phase II studies to begin in early 2004.

Deals & Collaborations:

GenPath, Merck Enter Collaborative Agreement

GenPath Pharmaceuticals Inc. of Cambridge, Mass., said it has entered into a multi-year collaborative agreement with **Merck & Co. Inc**. (NYSE: MRK) to identify cancer drugs.

Under the agreement, GenPath will use its proprietary cancer models to identify tumor maintenance genes as targets for small molecule oncology agents, the company said. GenPath will also use its inducible, spontaneous tumor models to guide candidate drug selection and optimization.

Merck will have an exclusive option to obtain exclusive worldwide license rights to a specified number of small molecule targets discovered and validated in a selected group of GenPath models, the companies said. The models will also be used in downstream drug discovery and optimization activities for candidate development.

Merck will be responsible for drug discovery, clinical development and commercialization of the products, the companies said.

GenPath will receive upfront payment plus annual research funding, as well as milestones and royalties from Merck, the companies said. Total payments to GenPath by Merck based on the successful commercialization of multiple products, exclusive of royalties, could exceed $100 million.

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Apollo Telemedicine Inc. of Falls Church, Va.,

said it has entered into an agreement with **Memorial Sloan-Kettering Cancer Center** to install its telediagnostic systems.

The patented software allows real-time visual connections between the pathologist and surgeons in the operating room, the company said. Biopsies can be sent to pathology from the operating room, prepared, and then analyzed. The results and the pathologist diagnosis will then be presented back to the operating room to discuss the results with the operating room team in real-time. The pathologist has the ability to annotate on any image being sent.

Twenty-three operating rooms will be connected via the network to the pathology department, the company said.

* * *

Genzyme Genetics, a unit of **Genzyme Corp**. (Nasdaq: GENZ), said it has entered into two licensing agreements with **Laboratory Corporation of America Holdings**, known as **LabCorp.** (NYSE: LH), and **Baylor College of Medicine** for access to its cancer diagnostic patent rights for the APC and p53 genes.

The companies have been granted non-exclusive diagnostic rights to the genes for use in diagnostic testing services, the company said.

Under each of the two agreements, Genzyme receives an up-front licensing fee and earn royalties on each diagnostic test performed, the company said.

Further financial details were not disclosed.

LabCorp said it would use the APC and p53 genes in its PreGen-Plus assay for colon cancer screenings for average risk individuals.

Under a separate license agreement, Baylor College of Medicine has licensed non-exclusive diagnostic rights to the APC gene for screening to detect mutations in the gene in high risk individuals.

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Ligand (Nasdaq: LGND) of San Diego said its cancer drug Ontak (denileukin diftitox) will continue to be manufactured by **Cambrex Bio Science Hopkinton Inc.** , a subsidiary of **Cambrex Corp.** (NYSE: CBM) of East Rutherford, N.J., under a five-year contract covering the existing commercial product as well as a second-generation formulation.

The products will be manufactured at the Cambrex Bio Science facility located in Hopkinton, Mass., the company said.

Under the agreement, which extends through 2008, Cambrex will be the primary supplier of the drug substance for Ontak and will also manufacture the drug substance for the second generation, improved purity, lyophilized formulation of the product, the company said.

Ligand said it intends to file for regulatory approval of the second-generation product by early 2005. Ontak had net sales of $16.4 million in the first half of 2003, up 21 percent compared to the same period of 2002, the company said.

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Miikana Therapeutics Inc. of Fremont, Calif., and **NovImmune SA** of Geneva said they are collaborating to develop fully human antibody-based therapeutics for cancer and immune diseases.

The collaboration would leverage the technologies of each company through a 50/50 sharing of costs and profits in order to develop therapeutic agents, the companies said.

* * *

Pintex Pharmaceuticals Inc. of Watertown, Mass., said it has acquired exclusive worldwide rights to Pin 1 enzyme related technology through **Garching Innovation GmbH,** the technology transfer agent for the **Max Planck Research Unit for Enzymology of Protein Folding**, an institute of the **Max Planck Society**, of Halle, Germany.

The Pin1 enzyme, which has been linked to human cancers, including prostate and breast cancer, may be one of the most prevalent tumor markers found to date, the company said.

Researchers from Pintex, Harvard Medical School, and Baylor College of Medicine described the Pin1 enzyme as "an independent marker that outperforms many other known and currently used indicators of prostate cancer disease-free survival, according to an article in Cancer Research.

Pintex said it would begin preclinical development on a small-molecule Pin1 inhibitor.

* * *

R2 Technology Inc.of Sunnyvale, Calif., said it has entered into a three-year distribution agreement with **Mammography Reporting System Inc**. of Seattle to distribute its MRS Mammography Reporting System.

The ImageChecker CAD system is approved by FDA for use in both film-based and digital mammography in minimizing false negative readings, the company said.

Clinical trials have demonstrated that the ImageChecker system as an adjunct to review by the radiologist can improve breast cancer detection rates up to 23.4 percent, the company said.

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