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Further Restrictions Likely On ESA Use; Changes May Cut Market By 40-50%

By Paul Goldberg

Last year, the companies that market erythropoiesis-stimulating agents could still argue before Wall Street analysts that chemotherapy-related anemia was largely undertreated and that the franchise would once again continue to expand.

Now, expansion is no longer an option. As utilization of ESAs continues to decline amid safety concerns, FDA officials are discussing the recommendations they received at the March 13 meeting of the Oncologic Drugs Advisory Committee.

The sponsors will not be in a position of strength as they negotiate label changes, because FDA has been granted the power to act unilaterally and mandate studies in cases where safety issues are involved. The new authorities will become effective on March 25.

"Clearly, after March 25, if we decide that a risk evaluation and mitigation strategy will be required, under the statute, those will be required,"

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In Brief:

AACR 2008 Awards To Honor Scientists For Work In Prevention, Detection, Treatment

American Association for Cancer Research will honor the following researchers for their progress in cancer prevention, detection and treatment at the society's annual meeting next month:

Nancy Davidson will receive the AACR-Women in Cancer Research-Charlotte Friend Memorial Lectureship for her accomplishments in translational cancer science, including discoveries in the epigenetic regulation of estrogen receptors and clinical trials that have shaped the standard of care for breast cancer. She is professor of oncology and breast cancer research chairman in oncology at the Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center.

Arthur Gutierrez-Hartmann will receive the AACR-Minorities in Cancer Research-Jane Cooke Wright Lectureship for diversifying the cancer research community by recruiting minority scientists, for mentoring minority students, and for promoting the careers of young minority investigators. He is professor, Departments of Medicine and of Biochemistry and Molecular Genetics, and member, University of Colorado Cancer Center.

Sydney Brenner, professor at the Salk Institute for Biological Studies and a recipient of the 2002 Nobel Prize in medicine, is the recipient of the AACR-Irving Weinstein Foundation Distinguished Lectureship. Brenner is

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ODAC Advocates Excluding ESA Use In Adjuvant Setting

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John Jenkins, director of the FDA Office of New Drugs, said at a press conference immediately following the ODAC meeting. "We've already seen signals from the companies that they are eager to make the necessary changes in a timely manner."

Indeed, six days before the meeting, Johnson & Johnson and Amgen Inc., the sponsors of the agents in the U.S., issued a new label stating that ESAs "shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers when dosed to target a hemoglobin of greater than or equal to 12 g/dL." At the ODAC meeting, the companies broadly outlined a risk mitigation strategy for the agents.

If the committee's voting margins are a predictor of additional changes, it is likely that restrictions will be placed on the ESA use in patients whose treatment is administered with curative—as opposed to palliative—intent (the vote was 11-2 with one abstention). In a 9-5 vote, the committee recommended exclusion of breast and head-and-neck cancers from the label. Also, it is likely that the agency will require some form of a risk mitigation strategy, potentially including informed consent (the vote was 8-5 vote with one abstention).

According to Steven Harr, an analyst with Morgan Stanley, the changes recommended by ODAC could lower the sales of the Amgen drug Aranesp by as much as $400 to $500 million, or 40 to 50%. Meanwhile, the price of Amgen's stock has dropped from the high of $48 on March 13, the day of the ODAC meeting, to about $39.50.

Compared to this time last year, Amgen has lost more than a third of its shareholders value. This week's slide may have been influenced by an apparent advancement of the Roche version of an ESA to the U.S. renal market.

The advisory committee had the opportunity to recommend pulling ESAs off the market altogether, but voted 13-1 to continue to keep these agents available. "There was a clear signal that this class of drugs—the ESAs—should continue to be used in the oncology indication, which is anemia associated with cancer chemotherapy," Richard Pazdur, director of the FDA Office of Oncology Drug Products, said at a press conference after the meeting.

Similarly, ODAC voted 10-1 with two abstentions to reject the idea of placing ESAs into a restricted distribution system.

"We do have a few programs that have informed consent as part of their risk management plan," said Jenkins. "There are not very many. You really have to look at the logistics of where it fits under the overall programs. Interestingly, they voted for an informed consent, but they voted against a restricted distribution system. Places where have informed consents are generally in consort with some sort of a restricted access, restricted distribution. We need to take into account the vote, the discussion as we are deciding what's the best approach."

"Dancing With The Stars"

According to the sposors, ESA's are used by half the number of patients compared to this time last year.

It's unclear how this drop in utilization would affect Amgen's ability to continue the practice of "bundling" its ESA Aranesp with its white blood cell growth factor Neulasta. The bundling arrangement, built around offering discounts on Neulasta to oncology practices that meet specific targets in their Aranesp sales, had helped the Amgen ESA overtake the competing J&J product and become the preeminent ESA on the market in 2005.

In recent weeks, Amgen officials have said that they would be willing to discuss ending the controversial practice.

"The sponsors are fully prepared to work with government agencies and third-party payers as part of

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our risk management, as well as patient and provider groups to develop appropriate reimbursement policies that address the issues that have been raised by the FDA in the briefing book and the issues raised by others regarding perceived physician incentives," Joshua Ofman, Amgen vice president for reimbursement and payment policy, said at the ODAC meeting.

"I think that the previous speaker's answer was correct, but not complete," noted ODAC member Michael Perry, director of the Division of Hematology/ Medical Oncology at the University of Missouri Ellis Fischel Cancer Center. "I didn't hear the word 'bundling' used or explained. It's my impression that discount prices are given when you buy several of the sponsor's products at one time. If you buy Aranesp and Neulasta at the same time that you get a better rate which therefore influences, particularly in private practice, the rate at which you might prescribe those drugs. Is that an erroneous impression?"

OFMAN: "It is very important for everyone to recognize that when prescription data are evaluated in the United States, in the oncology setting, there currently does not appear to be overutilization of ESAs. In fact, if incentives were present and responsible for overutilization of ESAs in oncology, you'd expect to see a number of things:

"First, you might expect that large amounts of ESAs were being used to achieve higher hemoglobin levels, but, in fact, that's not the case. Fewer than 5% of all ESA administrations occur when hemoglobins are greater than 12 g/dL.

"Secondly, you might assume that you would see high doses of erythropoeic agents being used in clinical practice. And, indeed, this isn't the case. The mean weekly dose of Aranesp, for example, is approximately 20% less than the labeled dose.

"You also might expect to see that almost all patients with chemotherapy-induced anemia would be treated with ESAs if incentives were influencing utilization. In fact, that's also not the case. Up to 30% of patients in the oncology setting undergoing chemotherapy, who have hemoglobins less than 11 g/dL, are not receiving therapy with ESAs. And, finally, if incentives were playing an important role, you would note differences in ESA patterns of care among different systems with financial structures, such as, staff model HMOs, where they had salaried clinicians, as opposed to contracted or traditional managed care organizations. And, indeed, research shows that the patterns of care and the utilization of ESAs is quite similar in these two different settings.

"So, in general, when we look closely and interrogate the prescription data, we see in the United States prior to 2007 and in the current state, quite appropriate use of the ESAs."

PERRY: "Which doesn't answer my question. Maybe you ought to be on 'Dancing With the Stars' or something. You've tap-danced around the question. Is there bundling? Are there rebates? Yes or no."

OFMAN: "Yes, well, in the current system…"

PERRY: "There are?"

OFMAN: "Yes, there are. In the current system, as the government has set out Medicare Part B reimbursement, it is paid on what they call an average selling price. And what that means is that the government reimburses providers based on an average of the price that the purchasers pay.

"Market competition and price competition in the United States does take the form of rebates and discounts—and of course those are perfectly legal—and they do result in tremendous savings to government payers. But they have in fact fueled the perception…"

PERRY: "We are not debating that. All I want to ask is a simple question: 'Were there rebates and was there bundling?' And the answer to both those questions, if I'm correct, is 'Yes.' Is that correct?"

OFMAN: "There are rebates and discounts being provided and Amgen does have a contract that uses the portfolio of products..."

PERRY: "Can you say the word 'Yes'? 'Yes' twice."

OFMAN: "Yes."

PERRY: "Thank you."

Defending the Indications

In their joint presentation before ODAC, Amgen and J&J argued that the toxicity profile of ESAs changes when patients are treated with the goal of boosting the hemoglobin targets above 12 g/dL.

While the companies point out that adverse events have been seen it high-target trials, skeptics counter that the safety of these drugs hasn't been studied rigorously at lower targets, and that the dose-response curves for ESAs are simply not known.

"When we look at all of the data that have become available, including new data, other that those of the two studies that have shown harm, we believe that in the aggregate, these data, while raising concerns and guiding the need for appropriate use of ESAs, did not justify the significant actions of further restrictions at the level that have been suggested," said Paul Eisenberg, of Amgen's global regulatory affairs and safety division.

The committee was called to review data from two studies, a German neo-adjuvant trial and cervical cancer trial conducted by the Gynecologic Oncology Group (The Cancer Letter, Dec. 7, 2007). Altogether, the ESA label contains eight randomized trials, which produced inferior results on the ESA arms. However, company officials say that these trials have been selected from a database of 59 studies that show no harm.

Also, Amgen's Eisenberg said that the companies don't agree that the data point to tumor promotion as the explanation for disease progression and mortality. "The data, when looked at across indications, suggest that the increase in mortality is unexplained and that tumor progression as the only mechanism is unproven," he said.

The risk mitigation program proposed by the companies would accredit providers to administer ESAs, offer medication guides and other forms, directing physicians to obtain patients' signatures attesting to the fact that patients have been warned about the risks.

"This includes documentation and agreement by the healthcare provider and the patient of a discussion of benefit and risk, and an agreement to receive ESAs," said Adrian Thomas, of the J&J global safety and benefit. "This will be documented, placed in the patient's file and subject to audit."

The committee wasn't asked to comment directly on the hypothesis that ESAs are associated with tumor progression. However, one committee member, Bruce Redman, argued that the wording that tumor progression hasn't been demonstrated.

"The term 'tumor progression' should not be used," said Redman, associate professor of medicine at the University of Michigan Comprehensive Cancer Center. "The connotation of that term is severe. You have maybe decreased risk of local control or decreased control of a tumor type that may be host-related, but the study to do tumor progression, which is going to be ESA treatment versus best supportive care and doing actually tumor measurements, is probably never going to be done. I just have an aversion to the term 'tumor progression.'"

Later at the meeting, Redman said that it's "a very dangerous thing to cite that ESAs cause tumor progression. The data is not there to suggest tumor progression. They suggests that combining EPO with radiation therapy may decrease the efficacy of the radiation therapy. But you can't state that the EPO or the ESA is causing tumor progression. The data isn't there to support that."

"I would Rather Have The ESA"

The practice of medicine has changed dramatically since 1993, the year when ESAs were fist approved as an alternative to blood transfusion.

"At the time we were considering this application, we already had an approval for patients with chronic renal failure," Patricia Keegan, head of the FDA Division of Biologic Oncology Products, said at a press conference following the ODAC meetings. "We had safety information in another population, which we considered, as well as at that point in time there were different concerns about the safety of the blood supply than there are today. So I think part of the discussion is that the safety information as well as the amount of benefit has changed and evolved over time."

At the ODAC meeting, David Stroncek, a temporary voting member and chief of the laboratory services section of the NIH Clinical Center Department of Transfusion Medicine, said that transfusions are now given at lower hemoglobin levels than they were 15 years ago.

"I guess I'm the full-time transfusion medicine person on the committee," Stroncek said at the meeting. "[I have] a couple comments, one is that the transfusion triggers since this drug was approved for use in oncology have really decreased. And now for stable patients, guidelines suggest that a transfusion trigger be about 8 g/dL. Some studies are even suggesting that you can lower this down to seven. And the second comment is, availability of blood [is] always short. But that's been that way for years. And when there is a need to donate blood, people come forward. So, I'm confident that there will continue to be blood available."

Wyndham Wilson, head of the NCI Lymphoma Therapeutics Section, said the question of benefit of ESAs warrants reconsideration.

"I would like to get back to the other side of the question, which is benefit, although that's not been the focus," said Wilson, a temporary voting member. "What we have heard is that the benefit have been based on a reduction in the need for transfusions. But that is assuming that there is a downside to getting blood. And other than the convenience, that has not been shown, and some of the downsides, such as risks of getting viruses and GVH, have been through screening and the use of radiation of blood products.

"The other point that these studies have not looked at is actually the number of the transfusions that have been reduced by this. The patients that have the highest bone marrow toxicity from therapy are the ones in whom are going to have the greatest transfusions, where you'd

like to reduce that the most. They are probably also the patients who probably benefit from the use of these drugs the least.

"I've seen no data that actually looks at the reductions in number of the transfusions, just the reductions in numbers of the patients that have required them. So, I think in considering risk/benefit, we have to look back on the benefit piece. And to me currently, other than convenience, there is not hard data on this.

Perry disagreed, citing personal experience.

"I guess I take a slightly different view from my colleague," he said. "Transfusion is difficult. It is time-consuming. But it's also hazardous. The risk of infections may be reduced, but the risk of transfusion-related lung injury, which we didn't recognize years ago, is increasing. And we have to multi-transfuse people, it becomes more and more difficult every time to cross-match their blood. If they have to be multi-transfused, then they wind up with iron overload.

"So, it's not a very simple question to say, 'Well, well, we'll stop using ESAs and just substitute transfusions. The number of people in the United States who are eligible to donate—or rather who are donating—is smaller year-by-year. Fewer and fewer people choose to donate while the population continues to rise.

"If we stop using ESAs, it's likely that we will encounter a shortage of red blood cells at some point in the future. I have a unique perspective on this, I think. As far as I know—and I don't need to know anybody else's history—I'm the only person on this panel who's had both a transfusion and the ESA.

"If you give me the choice, I would rather have the ESA."

The Question of Trigger Points

The committee was unable to suggest an alternative to the currently labeled target of 10 g/dL.

"The question is, 'Where is your threshold for transfusion?'" said committee member Ronald Richardson, a consultant at the Mayo Clinic Department of Medical Oncology. "That would be your potential threshold for starting on ESA. But I would agree with Dr. Stroncek, from his comments this morning, that an otherwise a symptomatic patient without co-morbidities, that the hemoglobin level of 8 g/dL, which is the one that seems to be widely applied these days, is a very relevant one."

MICHAEL LINK [ODAC member and chief of the Division of Hematology/Oncology at Stanford University School of Medicine]: "I just have one comment. Maybe it's a question. If you use a threshold of eight, or whatever number it is, you're going to give a transfusion when they hit that thing, you know, we got to pull the trigger right then. So, in order for an ESA to work—since I don't have that much experience with it—how much in advance do you have to start the [ESA] continue in order to avoid getting a transfusion?"

GLENN BEGLEY [Amgen vice president for research]: "Because of the delay, you would need to start between two and four weeks before you see meaningful increase in hemoglobin."

LINK: "So I assume correctly that if you wait until you get to the trigger point, you've lost the opportunity to give an ESA, to prevent the transfusion."

BEGLEY: "That would be correct."

LINK: "So, you have to figure out how many grams people are dropping per week, and then sort of multiply by four and..."

WILSON: "I think the endpoints have been in these trials, if I understand them, as to whether or not you were able to avoid any transfusion. But certainly, if you were to start the EPO at a lower level, you may buy yourself a single transfusion, if you're in this window. But over the course of multiple cycles, you, in fact, may be able to reduce the actual number. And that's what I had mentioned before, that these studies haven't looked at the actual reduction in the number of transfusions, just whether or not a single patient had one or didn't.

"I would say that there is emerging evidence that the more EPO you give, the more risk there is to the patient. And it's already been noted that seven to eight is really our threshold these days, whereas it used to be higher back in the 1990s. So, I would say that you could certainly go as low as eight to nine.

"And even if you did buy yourself a single transfusion, if the drug worked, presumably you would be reducing subsequent ones."

REDMAN: "I think less than or equal to 10. It gives the physician the ability to manage the patient who's watching on the third—on the second cycle of hemoglobins. Initial second cycle is 12, third cycle it's 9.9 and goes, well, we'll have to wait for a couple more cycles until you do drop down to eight, when you know where that patient is going. I mean, chemotherapy-induced anemia is not, you got one cycle of therapy and you went from 14 down to 7 grams of hemoglobin. That's not chemotherapy-induced anemia, that's hemorrhaging.

"You have to allow the leniency of the physician managing the patient to have some leeway in the decisions and set guidelines. I think if you set eight and

then CMS comes up and says, you can't use EPO agent until somebody has a hemoglobin of 8, you are taking away that window."

ANTHONY MURGO [a temporary voting member of ODAC and head of Early Clinical Trial Development at the NCI Division of Cancer Treatment and Diagnosis]: "I think this depends on the individual patient, and this is where a physician's judgment has to come in. So having this cushion would be very important.

"We see many a patients who run around with hemoglobins of eight—but without any problem, and where you would feel comfortable just to continue to do that. But there might be some patients where, even with a hemoglobin of 10, whereas you might have some concern below 10, like nine. I think it has to be a physician's judgment on this."

HELEN SCHIFF [a patient representative on ODAC and a member of SHARE, a New York-based advocacy group]: "I think one of the problems is that you also have to look at the risks of treating people who might never go that low. They might need a transfusion and they might need an ESA. So, the more you raise it, the more you are subjecting people to risks who stabilize at 10, 11, or 9. And they don't really need anything. "

REDMAN: "The physician treating the patient is the best one, within certain guidelines, to make a decision whether a certain patient—and I have patients with nine grams of hemoglobin, and if I transfused them at 15, they still wouldn't be doing anything different than what they are doing now. We can make that decision as a treating physician. You just can't blanketly say, eight grams—we can start, but if you're between eight and 10, you can't get this agent."

WILSON: "I think we have to go back and look at the data. The discussion sounds as though most patients who were to get this drug at a hemoglobin of 10 are going to, in fact, benefit from it. But we know from the data that only one in three benefits from it. So, right off the bat we know a hemoglobin of 10 is not a very accurate number.

"I routinely treat patients with chemotherapy. And towards the end of their multiple cycles they can, in fact, cycle down around eight. But then within the week off they can come back up again. In fact, that's probably more the pattern we see than somebody who continues to sail down. And I think the reason for even considering a lower hemoglobin number is because, number one, we are not capturing very well those patients who really benefit. And, number two, because there is a worrisome association between the amount of EPO given and toxicity.

PERRY: "I would hate to think that a committee of 14 people, some of whom are actively treating patients, and some who are not, could take a hypothetical patient and, therefore, promulgate a regulation that effects millions of people. I think this is not good science. I think this is good talk in the bar, but I don't think it's the way you set levels.

"If you look at the levels that have been done, even where patients get the most improvement in their hemoglobin, most improvement in their ability to carry out their activities and their quality of life, it's usually between 10 and 11. So, I would prefer a level of 10, if we have to decide an arbitrary number. And I so move."

Though no vote was taken, the committee's discussion was intended to guide the agency's decision on targets for ESA use in the palliative setting.

Informed Consent

A similar discussion erupted when the committee turned to the question of mitigation of risks associated with ESA use.

Expressing the minority view, Perry said that no written informed consent documents were needed. "When we treat people with chemotherapy for whatever condition, there are a lot risks," he said. "We kill people with febrile neutropenia episodes all the time, hopefully always inadvertently.

"If we have to go through this process for every drug we give to patients, next we are going to be going through a long list of declarations, saying, 'If I give you Decadron as an anti-emetic to keep you from getting nauseated and vomiting and preventing electrolyte loss, I am going to ruin your diabetic control which possibly will lead to [retinopathy], blindness, etc.'

"We are approaching the point of silliness in trying to over-mandate things. I think a physician has incumbent upon himself or herself the responsibility to talk over with patients the side effects of everything they give and let the patient be involved in decision making. Mandating another signature for the patient and the physician is increasing work time and not improving the products.

"I don't think it's going to help your patients to have to sign a form—particularly if it's another 18-page form that they are going to read before they make the decision. They are going to sign it and say, 'Whatever you want, doc, I'll sign it to get on with things.' They are not going to be informed, or they are not going to get the drug."

Though the committee voted 8-5 with one abstention for informed consent, it was not at all

supportive of placing ESAs into a restricted distribution system.

This regulatory approach would be very different from the risk mitigation strategy proposed by the sponsors. While the sponsors proposed certifying the providers who would then distribute the drug, FDA asked ODAC to consider a plan that would certify each patient receiving an ESA.

"I think that if the FDA narrows the indications for this, and if there is an informed consent process, one could argue that to restrict access in the manner you have done for Revlimid would probably be overly onerous for a drug like this," said Wilson. "There are many drugs that we give where there are many drugs that we give where there are many toxicities that could accrued if in fact they were given wrong.

"That's one reason why we go to medical school."

In a related development on March 12, ODAC unanimously recommended approval for Nplate (romiplostim, by Amgen), a thrombopoietin mimetic peptibody, for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura.

ITP Is an autoimmune disorder characterized by thrombocytopenia, which causes bleeding events. FDA considers thrombocytopenia in adults with chronic ITP an unmet medical need.

The drug would be indicated for adults with chronic ITP who have not undergone splenectomy and have had an inadequate response or are intolerant to corticosteroids or immunoglobulins and patients who have had their spleen removed and have an inadequate response to the procedure.

Amgen agreed to place the agent into a risk management program that includes additional clinical studies and measures designed to ensure the agent's appropriate use.

In Brief:

AACR Awards For 2008

(Continued from page 1)

known for contributions that include the identification of messenger RNA.

John Dick is the recipient of the AACR-G.H.A. Clowes Memorial Award for his contributions to uncovering the biological origins and development of human leukemia. His work has provided a new understanding of leukemia pathogenesis and has suggested new insights into anti-neoplastic therapies for treatment of the disease. He is Canada research chairman in stem cell biology, division of cellular and molecular biology at Toronto General Research Institute, Princess Margaret Hospital.

Jose Baselga, director of medical oncology, hematology and radiation oncology at Vall d'Hebron University Hospital in Barcelona, will receive the AACR-Rosenthal Family Foundation Award for his contributions to the clinical development of targeted cancer therapies including studies with anti-EGFR agents, anti-HER2 monoclonal antibodies and biomarker-driven early clinical trials.

Robert Hoover, director of the NCI Epidemiology and Biostatistics Program, will receive the 17th Annual AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention for identifying environmental and genetic determinants of cancer, most notably bladder and breast cancer.

Joseph Bertino, interim director and chief scientific officer at The Cancer Institute of New Jersey, is the recipient of the AACR-Joseph H. Burchenal Memorial Award for Outstanding Achievements in Clinical Research. He is recognized for his contributions to cancer chemotherapy and mechanisms of action and resistance to anti-metabolites and development of novel cancer therapeutics.

Arul Chinnaiyan, S.P. Hicks Endowed Professor of Pathology and professor of pathology and urology at the University of Michigan Medical School, will receive the AACR Award for Outstanding Achievement in Cancer Research for research in genomic, proteomic, and bioinformatic approaches to cancer biology.

Steven Tannenbaum, Underwood-Prescott professor of toxicology and professor of chemistry at the Massachusetts Institute of Technology, will receive the AACR-CICR Award for Outstanding Achievement in Chemistry in Cancer Research.

Ellen Sigal, chairman of Friends of Cancer Research, was named the recipient of the AACR Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research.

Lawrence Loeb, professor of pathology and biochemistry at the University of Washington in Seattle is the recipient of the AACR Princess Takamatsu Memorial Lectureship for his distinguished career in cancer research, as well as for promoting collaboration between American and Japanese investigators.

Daniel Pinkel, professor-in-residence at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center and senior scientist, Lawrence Berkeley National Laboratory, will be honored, along with his team of researchers, with the

AACR Team Science Award. The team is recognized for their conception, technical implementation, dissemination and pioneering applications of comparative genomic hybridization and array CGH in molecular biology and genetics. Team members include: **Donna Albertson**, **Jane Fridlyand**, **Joe Gray**, **Ajay Jain**, **Robert Nordmeyer**, **Norma Nowak**, **Damir Sudar**, **Frederic Waldman, Anne Kallioniemi**, **Olli Kallioniemi** and **Antoine Snijders**.

Harald zur Hausen, will receive the American Association of Cancer Research Award for Lifetime Achievement in honor of his work in viruses and cancer. He is recognized for his research demonstrating the role of human papillomavirus as the etiological agent of cervical cancer. Zur Hausen's work has also linked HPV to several other cancers. From 1983 to 2003, he served as chairman and scientific member of the Management Board of the Deutsches Krebsforschungszentrum.

Funding Opportunities:

HHMI To Provide $300 Million To Early Career Scientists

The Howard Hughes Medical Institute announced a new program to support early career faculty, aimed at researchers who have run their own labs for two to six years.

Through a national competition, HHMI plans to select as many as 70 early career scientists in biology and medicine. These scientists, most of whom will be assistant professors at the time of the award, will receive six-year, non-renewable appointments to HHMI and receive the substantial research support necessary to move their research in creative, new directions.

HHMI will invest more than $300 million in this first group of scientists and plans a second competition in 2011.

"We decided to focus on scientists who have led their own laboratories for several years because many of these scientists are at a high point of their creativity just as they see their start-up funds and early-career awards ending," HHMI President Thomas Cech said. "Some of them may still be in line for their first NIH R01 grant, while others may have their first grant but are facing the very challenging first renewal of that grant. It is this period of career vulnerability that the HHMI Early Career Scientist Program aims to bridge."

HHMI is seeking scientists in all areas of basic biological and biomedical research, and areas of chemistry, physics, computer science and engineering that are directly related to biology or medicine.

Candidates should apply directly to HHMI and are expected to meet the following criteria:

—Have a doctoral degree.

—Hold a tenured or tenure-track position as assistant professor or higher academic rank at one of the eligible institutions; if the applicant is at an institution that does not have a tenure track, he or she should hold an equivalent appointment. Federal government employees are not eligible.

—Have at least two but no more than six years of experience since their initial appointment as an assistant professor (or equivalent). To meet this requirement the applicant's first faculty position as assistant professor must have begun no earlier than June 1, 2002, and no later than Sept. 1, 2006.

—Those selected as HHMI early career scientists may hold only one other early career award, such as those from The Pew Charitable Trusts, The Searle Foundation, The Burroughs-Wellcome Fund, The David and Lucile Packard Foundation, The Arnold and Mabel Beckman Foundation, The McKnight Foundation, or the NIH Director's New Innovator Award or the NSF CAREER Award.

—To be appointed as an early career scientist, the successful candidate must devote 75 percent of his or her time to the direct conduct of research.

Scientists who wish to be considered must indicate their intention to submit an application by April 30. The deadline for completed applications is June 10. Final selections are expected to be made by February 2009.

Further information is available at www.hhmi.org/research/competitions/earlycareer2009/.

RFAs, PAs, RFPs Available

RFA-CD-08-001: Elimination of Health Disparities through Translation Research. R18. Letter of Intent Receipt Date: April 2. Application Submission Receipt Date: May 2. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CD-08-001.html. Inquiries: Juliana Cyril, 404-639-4639; jcyril@cdc.gov.

PAR-08-105: Optimizing Technologies for the Preservation of Fertility. R21. Letters of Intent Receipt Date: Aug. 15. Application Due Date: Sept. 16. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-08-105.html. Inquiries: Diana Jeffery, 301-435-4540; jefferyd@mail.nih.gov.

RFP S08-031: Preclinical safety testing (Pharmacology/Toxicology) of non-radioactive forms of candidate medical imaging agents. Response Due date: March 24. Full text: http://www.fbodaily.com/archive/2008/03-March/12-Mar-2008/FBO-01528078.htm. Inquiries: Shannon Jackson, 301-228-4022, sjackson@mail.ncifcrf.gov.

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