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Research on Molecular Targets to Diagnose, Prevent and Treat Cancer

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Good afternoon. I am J. Carl Barrett, Ph.D., from the National Cancer Institute (NCI) of the National Institutes of Health within the Department of Health and Human Services, where I am director of the Center for Cancer Research, one of the Institute's intramural research programs. Thank you, Senators Feinstein and Brownback, for inviting me to speak to you about molecular targeting. First, I would like to introduce you to the concept of molecular targets and discuss how they can be exploited throughout the full continuum of cancer care, from treatment and prevention to diagnosis and early detection. I would then like to describe the NCI's investments in this area to develop more effective therapies that will be given to the individuals most likely to benefit from them.

Molecular targets are critical changes that drive the growth and spread of the cancer cell. Interruption of those targets can inhibit, impede, or destroy the cancer cell. Molecular targeting uses information about basic biology to develop new strategies against disease. Specific proteins in the cancer cell become molecular targets that can be used for treatment, prevention, detection, or diagnosis of disease. By precisely choosing a target, a medical intervention is "targeted" to a specific cell. This approach results in interventions that are less toxic than traditional therapies since only diseased tissues are affected while normal tissues remain undisturbed.

Dr. Andrew von Eschenbach, the Director of NCI, recently issued the challenge goal of eliminating the suffering and death due to cancer and accomplishing this goal by 2015. This goal is attainable. New technologies developed in the past decade-such as gene, protein, and tissue microarrays-have enabled scientists to dissect biological pathways and identify precise molecular mechanisms underlying cancer. We can look at the cell's genes and proteins globally-approaches known as genomics and proteomics-to find patterns associated with cancer. We are increasingly able to describe cancer in terms of the interactive biological pathways and processes that lead to disease.

Progress will continue to accelerate. To quote Dr. von Eschenbach, "I believe we are at what I call a strategic inflection in biology, which means a point of unprecedented growth in three key areas related to cancer research: knowledge, technology, and resources. The

integration of growth in these three sectors provides an opportunity for exponential progress." Molecularly targeted therapies are one of those opportunities.

Molecular targets can be exploited along the full continuum of medical intervention from the treatment, prevention, early detection, and diagnosis of cancer to the development of improved technologies for patient assessment and monitoring. Every molecularly targeted agent is designed to interfere with a specific biological process essential to cancer progression and uncontrolled growth with minimal toxicity.

Molecularly targeted approaches to cancer intervention will give clinicians the ability to help treat or prevent cancer or to manage it as a chronic disease, preventing it from progressing to its later, more virulent stages. Treatments will become tailored to the molecular characteristics of the individual patient's disease.

It is likely that molecularly targeted therapeutic agents will most often be used as components of combination treatment regimens designed to disrupt multiple molecular pathways in order to slow or halt disease progression.

Some of the other panel members will discuss the specific molecularly targeted agents they have been involved in developing. I would like to place molecular targeting within the broader context of the continuum of cancer interventions, to suggest how the approach will transform the entire landscape of cancer prevention and control.

Classes of Molecularly Targeted Agents

Two broad categories of molecularly targeted agents exist that are actively under clinical development or are already in clinical use. The first comprises small-molecule compounds that act on the cancer cell to modulate gene expression or key proteins in pathways essential to disease progression. The other speakers will discuss several of these compounds.

The second category includes biological agents derived from components of the immune system that target cancer cell molecules to activate the immune system to block cancer cell functions or to deliver toxins to the cancer cell. Intramural investigators are presently examining multiple immune therapy approaches that target cancer cells in early-phase clinical trials, including biologically engineered vaccines, signaling proteins to boost immune responses, a variety of complex antibodies, and adoptive cell transfer.

Researchers have discovered that genes may allow us to predict patient outcome in response to immunotherapy. A recent pilot study has led to the identification of a set of genes regulating T-cell response that are highly expressed in metastatic lesions that regressed after patients had been treated with an immunotherapeutic agent. This finding raises the possibility that pathways enhancing immune responses against tumors may become a clinically useful tool to predict treatment response and may reveal novel therapeutic targets.

Molecular Diagnosis of Cancer

Diagnostic categories for cancer have traditionally been based upon anatomical location and the appearance of cancer cells under the microscope. However, samples of cancer tissue may appear identical under the microscope, yet respond differently to treatment. Thus, traditional diagnostic categories often fail to distinguish among molecularly distinct disease types. This discovery explains why significant numbers of patients diagnosed with specific cancers often fail to respond to standard treatment with conventional agents. Classifying cancers on the basis of molecular characteristics would provide profound clinical benefits. Additionally, it would drive the continued development of targeted interventions, and ultimately, the individualization of cancer therapy.

NCI has issued a Director's Challenge to support research aimed at developing a molecular classification of tumors. To date, the initiative has supported more than twenty intramural and extramural research groups. In one study, gene expression profiles have been identified that separate clinically different subsets of stage I lung cancer patients. Up to 40 percent of stage I non-small cell lung cancers recur despite surgical removal. A study has been initiated to confirm these exciting results in a separate, large-cohort study of archived frozen lung tumors with associated clinical outcome data. The study is using standardized protocols so that the data generated will be comparable. If confirmed, these molecular signatures will be developed onto clinical diagnostic tests that can inform the patient and clinician about the likelihood of cure by surgery alone. In addition, molecular profiling used for tumor classification may lead to the discovery of novel molecular targets for the development of new treatments or the development of improved imaging modalities.

Another study has focused on the most common type of non-Hodgkin's lymphoma called diffuse large B-cell lymphoma (DLBCL). Standard chemotherapy for this disease is effective in only 40 percent of patients. Intramural research begun in the late 1990s has recently allowed the reclassification of DLBCL into two major subclasses based on molecular characteristics. Researchers analyzed thousands of genes in lymphoma biopsy samples from patients with DLBCL and identified patterns of genes that are active in tumor cells that can predict whether patient patients are likely to be cured by chemotherapy. These results will lead to the development of more targeted treatment and the delivery of more accurate prognostics to patients. Following these findings, the NCI researchers involved in the initial study initiated the Lymphoma/Leukemia Molecular Profiling Project, an international consortium made up of seven clinical groups. The consortium's primary goal is to redefine the classification of lymphoma in molecular terms.

Early Molecular Detection of Cancer

Cancers are often initially detected at advanced stages, after invasion and metastasis have already occurred. For many cancers early detection increases the chance that medical intervention of any type will work. The early detection and diagnosis of ovarian cancer

are particularly challenging. When the disease is detected early, 95 percent of affected women survive for at least 5 years after undergoing conventional chemotherapeutic and surgical interventions. However, more than 80 percent of all cases are detected only at advanced, highly metastatic stages when women's five-year survival rate falls to 35-40 percent.

Investigators used proteomic-based technology to develop a simple blood test to diagnose early-stage, pre-metastatic disease in women with ovarian cancer. The test, which detects altered protein patterns associated with disease, has a sensitivity of 100 percent and a specificity of 95 percent, suggesting it has great promise as a routine diagnostic procedure. NCI researchers have established a joint Clinical Proteomics Program with colleagues in the Food and Drug Administration (FDA) to expedite the further development of proteomics-based technology for early detection. The collaboration has enabled researchers to set up a Clinical Reference Laboratory in support of an application for FDA Premarketing Approval. The laboratory will accept serum samples taken from women at high risk of developing ovarian cancer and submitted by physicians throughout the country. Dr. von Eschenbach has recently announced that the NCI and the FDA have negotiated a far more extensive interagency agreement that will build upon each agency's strengths to dramatically shorten the time needed to deliver novel technologies and molecularly targeted therapeutic agents into the clinic.

Molecularly Based Approaches to Prevention

Personal lifestyle choices can play a significant role in modifying an individual's risk for cancer development. A wealth of evidence exists linking the adverse effects of obesity and certain behaviors such as smoking, overexposure to ultraviolet light, physical inactivity, and dietary choices to cancer risk and mortality. Weight, diet, and physical activity cause alterations in many biological pathways that can contribute to cancer initiation and progression. Consumption of more calories than are expended through physical activity results in a condition known as positive energy balance, a term that demonstrates the relationship between obesity, inactivity, and heightened cancer risk. The challenges that face the NCI research community are to identify the precise molecular alterations resulting from lifestyle factors; to validate their relevance to cancer initiation or progression; and to develop preventive interventions using chemopreventive agents or alterations in behavior.

NCI supports clinical trials of mechanistically targeted agents to examine various chemopreventive agents. Every trial funded includes measurement or identification of the molecular targets involved in the cancer process. In the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the molecular genetics of cancer risk and associations between diet and cancer will be assessed. In the Breast Cancer Prevention Trial (BCPT) and the study of tamoxifen and raloxifene (STAR), the agents studied focused on the estrogen-receptor as a key to breast cancer risk. NCI has also begun an initiative that funds investigator-initiated research focused on two key aspects of this problem: validating surrogate biomarkers, which can be modulated by preventive agents for estrogen receptor (ER)-negative breast cancer, and identifying potential targets that are

observed in human ER-negative breast cancer to test potential chemopreventive agents directed against these targets.

The Rapid Access to Prevention Intervention Development Program (RAPID) is a mechanism of support for the development of molecularly targeted agents for cancer prevention. RAPID helps academic investigators expedite preclinical and early clinical drug development of investigational agents with the potential to prevent, reverse, or delay carcinogenesis. RAPID is designed to accomplish the tasks that are rate-limiting in bringing discoveries from the laboratory to the clinic by making the preclinical and early clinical drug development contract resources of NCI available to academic investigators. Through 20 currently funded projects, NCI supports clinical trial development of mechanistically targeted agents to examine the effects of various chemoprevention agents on molecular targets.

This program also provides preclinical agent development resources to academic institutions-specifically for potential cancer preventive agents-and program support extends to initial FDA regulatory filings and clinical phase I studies. Current projects include a second-generation human papillomavirus (HPV) vaccine that is both economical and stable; chemicals with specific efficacy in lung and colon cancer prevention models; and modified components of dietary crucifers with efficacy in preclinical cancer prevention models of breast, prostate, and HPV replication.

Molecularly Targeted Treatments

In order to support the commitment to develop molecularly targeted treatments to cancer patients, the NCI has a number of programs designed to discover and develop the next generation of Molecularly Targeted Drugs. Included in this process are identifying molecular targets for drug development, identifying drugs that act on identified molecular targets, and delivering molecularly targeted drugs to the cancer patient. The programs described below are designed to facilitate the development of agents to be used by the public.

Identification of Molecular Targets for Drug Development

Much of the NCI's research and development of novel molecularly targeted agents occurs under the auspices of the Developmental Therapeutics Program (DTP), which acts as a partner to both intramural and extramural investigators. The program provides resources needed for drug discovery (compounds, bioinformatics systems, cell lines, and screening) and drug development (formulation, testing in animal models, pharmacology, and toxicology). Its services expedite early refinement of candidate compounds and late development of candidate drugs until the time when investigators file for FDA permission to study an agent's effects in human clinical trials

Through the Molecular Target Drug Discovery (MTDD) program investigators are identifying novel molecular targets, validating these as targets for cancer therapy, and developing tests that determine how well potential agents work on these targets. One

discovery through this program involves a breast cancer-relevant gene that showed some differential expression between white and African American patients. This could have important implications in understanding differences among races in susceptibility to breast cancer. NCI provided a one-year supplement to firm up this observation.

The Chemical Genetics Institute (formerly the Molecular Targets Laboratory) was first funded in FY 2002 to capitalize on the opportunities emerging from advances in genomics, molecular biology, combinatorial chemistry, informatics, and imaging. Through this initiative scientists are applying advances to create a resource of biological assays and chemical probes (compounds used to study molecular targets) to study cancer-related targets. This work enables biological studies of cancer, including physiological and biochemical monitoring, and provides a platform for drug discovery.

A new initiative, called the Academic Public Private Partnership Program (AP4), has been created to support the discovery of new cancer agents and their rapid translation to human clinical trials. With this program, the NCI creates collaborations between universities, pharmaceutical companies, biotech companies, and non-profit organizations. A new funding mechanism to accomplish this goal was called for by several Progress Review Groups. The AP4 initiative represents a new paradigm in drug discovery, development, and delivery for the NCI.

Identification of Drugs that Act on Identified Molecular Targets

Through several NCI initiatives, chemists and biologists are collaborating to create libraries of synthetic, biological, and natural compounds that will be evaluated for therapeutic potential in molecular target assays, or tests used to screen the compounds to identify those that modulate the biological activity of defined target molecules.

The National Cooperative Drug Discovery Groups (NCDDG) program supports innovative, inter-disciplinary, multi-project approaches to discover new anticancer treatments. Thirteen funded groups are progressing in a variety of areas.

In Biology-Chemistry Centers, multi-disciplinary teams of scientists use a combination of chemical and biological techniques to create libraries of chemically diverse structures with potential anti-cancer effects. Using "smart" assays, scientists screen the compounds to identify those that will interact with cancer-specific molecular targets. The six teams funded through this initiative have screened hundreds of thousands of compounds for anti-cancer activity. A recent discovery used combinatorial chemistry to uncover a small molecule that disrupts the interaction of two proteins involved in angiogenesis (blood vessel development) and inhibited the growth of a skin tumor in an animal model.

The Rapid Access to NCI Discovery Resources (R*A*N*D) program expedites the development of drug research capabilities in academic institutions. R*A*N*D focuses on laboratory-based studies that are the starting points for new drug development, supporting early formulation, pharmacokinetic, pharmacology, and toxicology studies. R*A*N*D assists in the development of high-throughput laboratory assays to screen large numbers

of promising chemicals. The program supports the development of libraries of chemicals that scientists can draw upon for study. NCI provides, at no cost, samples of synthetic chemicals, collected natural products, and biological materials to investigators who want to screen them against molecular targets. More than 100 research groups engaged in targeted cancer research have been supplied with these samples.

The Mouse Models of Human Cancers Consortium (MMHCC) is a collaborative program designed to derive and characterize mouse models, and to generate resources, information, and innovative approaches to the application of mouse models in cancer research. Through the MMHCC, groups of academic researchers have created and are making available to researchers mice with defined genetic alterations that predispose the animals to certain types of cancer. More than 75 strains were available as of 2003. These mouse models could serve as a basis for testing new molecular targeting treatment and prevention strategies. (http://emice.nci.nih.gov) The consortium will develop partnerships with pharmaceutical industry sponsors to facilitate the testing and evaluation of new compounds identified by consortium members.

The Drug Development Group provides support for academic and corporate-derived compounds when NCI is responsible for conducting and monitoring the drug's clinical development. A number of promising agents have been developed to clinical trials through this program: A synthetic improvement on a naturally-occurring antitumor antibiotic was produced. Its biological activity is exerted by binding to DNA, and it is highly active in animal models against ovarian, melanoma, and breast tumors and is less toxic in animal studies than the parent compound. Clinical trials will be scheduled in both the United Kingdom and the United States. Another agent is a synthetic compound derived from a marine sponge that has shown anticancer activity in animal models against breast and lung cancers, producing tumor-free animals in both cancers. The compound is currently in Phase I clinical trials in the United States.

The Flexible System to Advance Innovative Research (FLAIR) provides funds to small businesses to develop cancer therapeutic and prevention agents from basic discovery to clinical trials. Through five rounds of competition, the program has awarded 50 FLAIR grants, including novel drug delivery systems, imaging, anti-angiogenesis, the design of small compounds able to mimic the action of proteins, newly designed agents that sensitize cancer cells to radiation, and anti-metastatic agents.

Delivery of Molecularly Targeted Treatments

NCI is committed to facilitating the discovery and development of molecularly targeted treatments to use in the clinical setting. Unique opportunities to deliver novel molecularly targeted therapies to cancer patients exist, and NCI is committed to the rapid, efficient translation of basic scientific advances into the clinic. NCI supports a variety of programs to facilitate the delivery of molecularly targeted therapies to cancer patients.

NCI's Cancer Therapy Evaluation Program (CTEP) funds an extensive national program of cancer research and sponsors clinical trials to evaluate new anti-cancer agents with a

particular emphasis on translational research to elucidate molecular targets and mechanisms of drug effects. CTEP trials are using molecularly targeted agents in areas that industry was not pursuing. Examples of this are: farnesyltransferase inhibitor (FTI) (R11577) to treat acute myelogenous leukemia; Depsipeptide to treat a form of lymphoma, Bevacizumab to treat kidney cancer; and Imatinib to treat glioblastoma. In addition, CTEP is currently succeeding in working with multiple companies to study combinations of molecularly targeted agents. They currently have agreements with nine industry co-sponsors to use these innovative and unprecedented combinations of targeted agents in clinical trials.

The Rapid Access to Intervention Development (RAID) program provides preclinical drug development resources to academic institutions. Ten molecularly targeted interventions developed through RAID reached readiness for clinical trials by the end of 2002.

A new program, the Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA), enables interdisciplinary teams of scientists to develop molecular assays, molecular and cellular imaging probes, and other tools to assess the effects of targeted interventions in preclinical models and in early clinical trials. Groups are targeting angiogenesis, the ability of tumors to form new blood vessels, survival and proliferation signals for tumors, new ways of measuring the effectiveness of tumor vaccines, and the structure of tumor chromosomes.

The Radiation Modifier Evaluation Module (RAMEM) program serves individual investigators and industry in the design and development of treatment programs for the use of novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. Integration of molecular imaging, molecular signatures, and molecular therapeutics with radiation therapy is a high priority of NCI's Intramural Program because new anti-cancer agents may ultimately be used in combination with radiation therapy.

The Radiation Research Program (RRP) is responsible for NCI's clinically-related extramural radiation research program. The Molecular Radiation Therapeutics Branch was established within RRP with the goal of developing target based strategies for enhancing tumor sensitivity and protecting normal tissue during radiotherapy. Its objectives include: identifying molecules/processes that regulate the radio-response of tumors and normal tissue, i.e., define novel molecular targets for radiation modifiers; evaluating currently available agents for their ability to enhance tumor cell radiosensitivity and protect normal tissue; and developing high throughput screening procedures for identifying novel radiation modifiers and for evaluating analogues of lead compounds.

NCI investigators have shown that a technique known as adoptive transfer is a promising approach to treating patients with refractory metastatic melanoma and has potential applications to other tumor types. Cells of the immune system are harvested from the patient, activated against the tumor antigen, and re-introduced into the patient where they

attack the tumor. Another laboratory in the intramural program synthesized an agent, zebularine, to inhibit gene silencing. Silenced tumor suppressor genes are obvious targets for reactivation. Zebularine is the first drug in its class available by oral administration. This drug is being jointly developed, and a patent is being pursued with university partners.

Future Directions

Technological initiatives are now being pursued at NCI that show great promise in helping us achieve our vision of eliminating death and suffering due to cancer by 2015. The earliest cDNA microarray technology was developed in 1995. The first microarrays could measure the activity levels of approximately 1,000 genes simultaneously. Today, microarrays have been developed that can simultaneously measure the activity levels of more than 40,000 genes or gene variants and tens of thousands of proteins. The entire human genome can now be represented on a single microarray chip. The effects of specific genes on the control of the cancer cell can now be examined by an exciting new approach called small interfering RNAs, which can reduce the expression of genes overexpressed in cells to interrogate their role in the cancer process.

We believe that the rapid pace of technological development in biomedical research will continue to accelerate, exponentially improving our ability to investigate the basic biological mechanisms that cause cancer or drive its progression. More important, technological progress will allow us to develop more finely targeted, and hence more effective, interventions to counteract those molecular mechanisms.

Nanotechnology is one such promising initiative that has the potential to be applicable to multiple aspects of cancer care. The term refers to technologies that can manipulate submicroscopic objects, including individual molecules or clusters of atoms. The NCI plans to establish multidisciplinary teams of intramural and extramural researchers to work with the leaders in other government agencies, academic institutions and private-sector organizations to apply nanotechnology to biomedical research and, ultimately, to cancer patient care.

On the therapeutic level, nanotechnology-based approaches include the development of enhanced delivery systems that will localize molecularly targeted preventive or therapeutic compounds to disease sites, thereby maximizing therapeutic benefit. Nanoengineering can be used to develop new methods for constructing complex anti-cancer vaccines or other biomolecules to trigger protective mechanisms in the host. Implantable submicroscopic sensors can be developed to monitor changing proteomic patterns that reflect individual responses to treatment and disease progression. Such sensors, since they would be minimally invasive, could be employed to screen wider populations. In diagnostics, nanoparticles can be developed to serve as selective contrast agents, enhancing the accuracy of diagnostic imaging modalities.

Conclusions

Given the molecular complexity of cancer, it is unlikely that the disease can be eliminated by 2015. But, as Dr. von Eschenbach has observed, a cure is not necessary to end the worst aspects of the human cancer experience: suffering and premature death. Our rapidly expanding knowledge of the precise molecular processes underlying cancer are already yielding new clinical tools: more effective means for early detection and patient monitoring; more biologically accurate diagnostic categories to guide prognostic evaluation and treatment selection; molecularly targeted therapeutic agents that avoid the most debilitating aspects of conventional treatment; and mechanism-based prevention strategies. With these advances and continued progress, cancer can be brought under control as a manageable chronic disease. To quote Dr. von Eschenbach again, "What is foreseeable is to expand our ability to preempt the suffering and death caused by cancer. That is why we have issued this challenge goal-to focus ourselves on reducing the burden of cancer."