DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington DC 20201

JUL 19 2010

The Honorable Todd Tiahrt
Ranking Member
Subcommittee on Labor, Health and
Human Services, Education
and Related Agencies
Committee on Appropriations
House of Representatives
Washington, D. C. 20515

Dear Representative Tiahrt:

I am pleased to transmit this report, entitled "NCI's Pediatric Cancer Research and Pediatric Cancer-Related Activities," as requested in House Report No. 111-220, page 109.

Sincerely,

Ellen G. Murray
Assistant Secretary for Financial Resources

Enclosure

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Chairman
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

NCI's Pediatric Cancer Research and Pediatric Cancer-Related Activities

Francis S. Collins, M.D., Ph.D.
Director, NIH

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Executive Summary

In the fiscal year (FY) 2010 House of Representatives Report 111-220 (page 109), the Committee requested that the National Cancer Institute (NCI) intensify pediatric cancer research and provide a report on the actions it has taken to implement the research-specific portions of the Caroline Pryce Walker Conquer Childhood Cancer Act. The following is submitted in response to those congressional requests.

The Caroline Pryce Walker Conquer Childhood Cancer Act (CPWCCCA) authorized $30 million dollars per year for five years across HHS for a variety of purposes described in the law, including expansion of the National Childhood Cancer Registry, development of a public awareness initiative, and an intensification of cancer research efforts.

The FY 2010 Congressional appropriation for HHS specifically provided $3 million to the Centers for Disease Control and Prevention to enhance and expand its existing cancer registry, and $1 million to HHS to develop informational services for patients and families affected by childhood cancer. In March 2010, the Department provided this $1 million to NCI for expenditure through an intradepartmental delegation of authority. To invest these funds in keeping with the requirements and spirit of the CPWCCCA, on June 4, 2010, the NCI announced an opportunity for current grantees to compete for administrative supplements that would enable successful applicants to expand and implement activities focused on increasing awareness of pediatric cancers, including current state-of-the-art treatments for these diseases and clinical trials of new interventions, and/or on improving the long-term care and quality-of-life of pediatric cancer survivors and their families. Successful applicants are required to utilize a current partnership or establish a new partnership with one or more organizations who provide support and services in areas of childhood cancer and to individuals and families affected by those cancers, and who must be involved integrally in the development, review, and/or dissemination planning for the informational materials and resources. Priority in funding will be given to applications that address the needs of low income and ethnically diverse populations with regard to childhood cancers and persons affected by those cancers. NCI anticipates awarding four to seven administrative supplements in response to this initiative.

In the consolidated Appropriations Act Conference Report 111-366, the conferees commend NCI for its attention to the issues of pediatric cancers. The NCI continues to expand and intensify its robust pediatric cancer research program.

In 2008, NCI provided $189.7 million for pediatric cancer research. In 2009, NCI funded this research at $192.5 million within the annual appropriation and an additional $49 million from NCI's American Recovery and Reinvestment Act (ARRA) allotment. NCI estimates that its pediatric cancer research funding will reach $196 million in FY 2010. NCI uses this funding to support an ambitious research program designed to help children with cancer by bringing the Institute's most promising new technologies and ideas into our efforts to develop effective therapies and other interventions. NCI's strategy encompasses a broad spectrum of pediatric cancer research. It begins with basic biology research and preclinical testing to identify and validate new therapeutic targets, and extends through our comprehensive clinical trials program

that translates discoveries into clinical benefit for children with cancer. An important feature of our research program is our work addressing the special issues faced by childhood cancer survivors.

Introduction

In its report on the Fiscal Year (FY) 2010 budget for the Department of Health and Human Services (DHHS), the House of Representatives Committee on Appropriations stated:

> *Pediatric Cancer.* The Committee urges NCI to intensify pediatric cancer research, including laboratory research, to identify and evaluate potential therapies, preclinical testing, and clinical trials through cooperative clinical trials groups. This research should include research on the causes, prevention, diagnosis, treatment, and late effects of pediatric cancer. The Committee also requests that NCI report to the Committees on Appropriations of the House of Representatives and the Senate by June 1, 2010 on the actions it has taken to implement the research-specific portions of the Caroline Pryce Walker Conquer Childhood Cancer Act. (House of Representatives Report No. House Report 111-220, page 109).

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

Background

NCI supports a comprehensive pediatric cancer research program that extends from basic biology research and preclinical testing to identifying new therapeutic targets and an extensive clinical trials program that determines whether the preclinical discoveries can be translated into clinical benefit. Pediatric research in the laboratory includes studying the genetic and other mechanisms related to tumor formation and metastasis. NCI's Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatment (TARGET) Initiative applies high-throughput genomic analysis methods to identify novel therapeutic targets for childhood cancers and is an example of a synergistic and multidisciplinary program that begins in the laboratory and goes beyond. The Pediatric Preclinical Testing Program (PPTP), an NCI-supported research contract begun in 2005, generates preclinical data that informs decisions about the prioritization of new agents and combinations of agents for study against specific types of childhood cancers. NCI supports several consortia of institutions to perform clinical trials of novel agents and treatments, thereby allowing preclinical discoveries to move rapidly to the clinic and be studied by experienced pediatric oncology investigators. The Children's Oncology Group (COG) develops and coordinates cancer clinical trials available at over 200 U.S. and international institutions. The clinical trials conducted by COG, NCI, and other NCI-supported consortia play key roles in evaluating new treatment approaches.

Identifying and Evaluating Potential Therapies

The Childhood Cancer TARGET Initiative is a public-private partnership developed to harness the power of cutting-edge genomics technologies to rapidly identify valid therapeutic targets in childhood cancers. The underlying premise is that identification of genes that are consistently mutated or altered in specific cancers will provide critical leads for identifying therapeutic targets for these cancers. The TARGET program's initial focus was on neuroblastoma and acute lymphoblastic leukemia (ALL), but was expanded with funds from the American Recovery and Reinvestment Act of 2009 (ARRA) to include acute myeloid leukemia, osteosarcoma, and high-risk Wilms tumor. As a result of TARGET, there will be a virtually complete cataloguing of the gene mutations and other gene alterations that occur in these childhood cancers. Through TARGET, NCI has completed a comprehensive genomic analysis of several hundred neuroblastoma cases and sequenced approximately 100 genes. Several mutations have been identified that are undergoing secondary studies.

Discoveries through the ALL TARGET Initiative include identifying activating JAK family mutations, which appear to be driver mutations for a subset of the ALL cases studied. These mutations could be the key to identifying more and better treatments for the group of children who have leukemia with JAK mutations. The transforming activity of the JAK mutations was blocked by JAK inhibitors, providing strong rationale to pursue inhibition of JAK signaling as a novel therapeutic intervention for JAK-mutated ALL. This is important because the children with JAK-mutated leukemia do particularly poorly. Even with best available treatment, most children with this form of leukemia eventually have their leukemia recur. As an initial step in translating the TARGET Initiative discovery from the bench to the bedside, the Children's Oncology Group Phase 1 Consortium is developing a clinical trial of a JAK inhibitor for children with relapsed ALL.

The TARGET Initiative also discovered that the Ikaros gene (IKZF1) is altered in approximately 25 percent of children with high-risk ALL and is a highly significant independent predictor of treatment failure due to relapse. The discovery of a new biologically-defined subset of ALL tumors that reoccur with current treatment approaches has important prognostic and therapeutic implications.

The NCI, in collaboration with the Translational Genomics Research Institute (TGen), is developing a clinical protocol to treat pediatric cancer patients who have refractory or recurrent disease. The cure rate for pediatric patients with recurrent or refractory malignancies is less than 10 percent and there are no standardized methods for choosing therapy in this setting. NCI and TGen will perform a compressive genomic and proteomic analysis on patients who have failed first line therapy or whose cancer has grown despite standard therapy. This analysis will be used to determine an appropriate therapy for these patients, as treatment will be matched according to the genomic changes in their own tumor. This novel, innovative approach is a first for this type of personalized trial in pediatric cancers.

Preclinical Testing

The NCI-supported Pediatric Preclinical Testing Program (PPTP) is a comprehensive program designed to systematically evaluate new agents against childhood solid tumor and leukemia models (both *in vitro* and *in vivo* models). This program assists clinical researchers in selecting

study agents and combination therapies that are most likely to be effective for treating childhood solid tumors and leukemias. Some correlations have been observed between preclinical antitumor activity of agents tested in pediatric tumor models and clinical activity of these same agents. Although these examples support the potential predictive value of preclinical models, validation of the models across a broader range of pediatric cancers and therapeutic agents is needed.

Since 2005, more than 30 agents or combinations of agents have been tested against PPTP's molecularly characterized panel of childhood cancers. A key discovery was the sensitivity of neuroblastoma to Aurora Kinase A inhibition, which is currently being developed into clinical trials. The PPTP also discovered that a novel oncolytic virus, NTX-010, was highly active against pediatric preclinical models of selected childhood cancers, and NTX-010 has entered clinical evaluation in children with refractory neuroblastoma and rhabdomyosarcoma. Investigators at the NCI continue to profile microRNAs in this panel to identify novel biomarkers and therapeutic targets. NCI has recently committed to an additional five years of support so that the important work of the PPTP can continue.

NCI-Supported Pediatric Clinical Trial Groups and Consortia

The Children's Oncology Group (COG) is an NCI-supported cooperative group that develops and coordinates cancer clinical trials at over 200 member institutions throughout the United States, Canada, Europe, and Australia. Through the COG network of member institutions, children with cancer, regardless of where they live, can access state-of-the-art therapies and the collective expertise of world-renowned pediatric specialists.

The COG Phase I/Pilot Consortium aims to develop and implement expeditiously pediatric phase I and pilot studies, thus facilitating the integration of advances in cancer biology and therapy into the treatment of childhood cancer. The consortium includes approximately 20 institutions. Pharmacokinetic and biological correlative studies are key components of the consortium's phase I trials and are increasingly important for new agents with specific molecular targets. The consortium conducts pilot studies of promising multi-agent regimens. These studies are an important step in the integration of new agents into the therapy of specific childhood cancers and require careful monitoring for toxicity and safety. After their initial evaluation for safety in children by the consortium, agents and regimens can be studied within the larger group of COG institutions to determine their role in the treatment of specific childhood cancers.

Through a collaborative agreement between industry and the COG in 2009, several NCI investigators began work on whole genome and transcriptome sequencing of 50 rhabdomyosarcoma and 50 osteosarcoma tumor samples along with paired germ line DNA in an effort to comprehensively characterize the genomic changes that contribute to pathogenesis of these two cancers. The goals of these projects are to identify every expressed gene and every harmful mutation in these cancers. The information generated by this project will produce a quantum increase in the molecular knowledge of these cancers. This will be used to better diagnose these cancers and to develop new therapies targeting these specific mutations. This is an important step for developing personalized therapy for these cancers based on the genetic changes identified in a given cancer.

To improve outcomes for children with high-risk neuroblastoma, the COG is conducting studies of the monoclonal antibody ch14.18, which targets a molecule on neuroblastoma cells. In 2009, COG researchers presented results of their phase 3 trial that demonstrated that immunotherapy using this antibody improves survival for children with high-risk neuroblastoma when administered following high-dose chemotherapy and stem cell transplantation. The NCI manufactured ch14.18 so that COG could definitively evaluate this neuroblastoma-targeted agent. The agent is the first monoclonal antibody that has been shown to be clinically beneficial in children with cancer prior to a demonstration of efficacy in adults with cancer. NCI is continuing to support COG to enroll patients in this clinical trial as a way to allow children with high-risk neuroblastoma access to ch14.18. A second COG clinical trial of ch14.18 is collecting detailed data requested by FDA to support licensing of the agent. NCI is identifying a pharmaceutical collaborator that will be able to ensure its long-term availability as a licensed product.

The Translational Genomics in Neuroblastoma (TGiN) Consortium includes members of the COG, the International Society of Pediatric Oncology European Neuroblastoma Research Network, and researchers from Australia and Japan. The objective of TGiN is to harness the power of high throughput genomic studies to identify and validate functional gene targets which can be exploited to improve survival in neuroblastoma. A TGiN meeting was held in November 2009 to discuss developing personalized therapy for patients with neuroblastoma based on genomic studies.

The Pediatric Oncology Branch (POB) of the NCI, part of the NIH Clinical Center in Bethesda, MD, conducts a translational research program focused on tumor biology, drug development, genetics and genomics, immunology and immunotherapy, metastases biology, neuro-oncology, and psychosocial support. Recent accomplishments of the POB include creating a consortium between members of the NCI, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and academic institutions to study the rare pediatric cancer, Gastrointestinal Stromal Tumor (GIST). Experts from around the United States travel to the NIH to evaluate, first hand in a multidisciplinary clinic, patients with this rare disease. This clinic may serve as a paradigm in the investigation of rare diseases.

The POB has created resources providing information to the public on pediatric cancer, including the late effects of pediatric cancer treatment to ensure access to necessary long-term medical and psychological care and educational outreach for parents. Fifty-two researchers from 26 institutions helped the POB develop a pocket-sized reference book for pediatric oncology clinicians on the psychiatric and psychological dimensions of pediatric cancer symptom management that is being distributed to every fellowship training program in the U.S. The POB also initiated the first study, conducted at 10 institutions, to examine the experience of lone parenting with children living with cancer, and created an advance care planning guide for adolescents and young adults living with cancer and other life-limiting disease.

The New Approaches to Neuroblastoma Therapy (NANT) Consortium is collaborative group that brings together university and children's hospitals to test promising new therapies and combination therapies for high-risk neuroblastoma. The group is closely linked with laboratory

programs developing novel therapies for high-risk neuroblastoma. The group conducts limited clinical trials, with the goal that promising therapies will be tested nationally.

The Pediatric Brain Tumor Consortium (PBTC) is made up of nine leading academic institutions that have extensive experience with tumors of the brain that develop during childhood. The PBTC aims to rapidly conduct phase I and II clinical evaluations of new therapeutic drugs, intrathecal agents, delivery technologies, biological therapies, and radiation treatment strategies for children 0–21 years of age with primary central nervous system tumors. Another objective of the PBTC is to develop and coordinate innovative neuroimaging techniques.

Other large-scale pediatric cancer collaborations, such as the International Childhood Cancer Cohort Consortium (I4C), will further investigate the role of environmental exposures and genetic factors that may be linked to the development of pediatric malignancies. With over 700,000 individuals in participating early-life childhood cohorts, this study has the statistical power to detect significant associations between exposures and cancer outcomes.

Late Effects of Pediatric Cancer

The NCI-funded Childhood Cancer Survivor Study (CCSS), initiated in 1993, is a collaboration of 27 institutions coordinated by St. Jude Children's Hospital in Memphis, Tennessee. The CCSS is made up of a cohort of more than 20,000 individuals who survived five or more years after diagnosis of childhood cancer. The cohort cancer survivors were diagnosed before age 21 between 1970 and 1986; approximately 4,000 siblings of survivors serve as a control group.

Because treatment has improved since 1986, in 2007 the CCSS began recruiting an additional 14,000 adults who were treated for cancer as children between 1987 and 1999 to allow for the evaluation of late effects of newer types of cancer treatment. Late effects and health outcomes evaluated include second and subsequent cancers, reproductive and psychosocial outcomes, and survival. Late effects of chemotherapy, surgery, and hormonal therapy are also being evaluated. NCI researchers are providing expertise in measurement of radiation exposure and primarily focus their research on the risk of therapy-related late effects of second cancers of the brain, breast, thyroid, bone, and soft tissue, sites known to be especially sensitive to the carcinogenic effects of radiation. Attention is also given to the dependence of risk on factors such as gender, age at exposure to radiation, and time since exposure.

In 2006, NCI published a monograph on the risk of new malignancies among two million cancer survivors utilizing data from the U.S. Surveillance, Epidemiology, and End Results (SEER) Program, 1975-2000. Eighteen types of childhood cancer were included in the report. The analysis showed that the risk of new cancers was more than six times higher for survivors of childhood cancer compared to the general population, with patterns suggesting the effects of cancer therapy and genetic susceptibility. The risks were also increased about two- to three-fold among those whose first cancers were diagnosed as young adults. The monograph underscores the importance of long-term monitoring of cancer survivors for early detection of second cancers. In addition, quantification of the risk of therapy-related cancers is assisting physicians and their patients in making risk-benefit evaluations of specific treatments.

Among other studies on late effects, NCI is studying survivors of retinoblastoma (RB), a cancer of the eye that is diagnosed during infancy or early childhood. The study has shown that patients with hereditary RB, or who carry a mutation in the *RB1* gene, have a nearly 40 percent chance of developing a second cancer if they survive to age 50, whereas patients with non-hereditary RB have only a 6 percent chance of developing another cancer if they survived to that age. NCI researchers are examining whether specific mutations in the *RB1* gene may be responsible for the increased risk for specific types of second cancer in survivors of the heritable form of this disease. Survivors of the heritable form are particularly at risk for developing bone and soft tissue sarcomas, melanoma, leiomyosarcoma of the uterus, and brain cancer.

NCI researchers are also examining RB patients with melanoma or its precursor lesions in order to determine the genetic basis for the increased melanoma risk. RB patients are also at increased risk for developing lung cancer, which may be related to an increased sensitivity to tobacco smoke. Radiotherapy used to treat RB has been associated with an excess of soft tissue and bone sarcomas in the head. In 2009, as part of an ongoing effort to study second cancers and other late health effects in RB survivors as they age, NCI began using Web-based social networking techniques in an effort to educate survivors on the importance of life-long health screening and care, as well as to locate study participants previously lost to follow-up.

Conclusion

NCI funding supports a large portfolio, which includes studies to understand the biology of, identify causes of, and discover effective treatments for childhood cancers. NCI-supported studies are developing new treatment approaches that target critical cellular processes required for cancer cell growth and survival. Preclinical studies of new agents are identifying promising anticancer drugs that can be evaluated in clinical trials and clinical trials are identifying superior treatments for childhood cancers, thereby leading to improved survival rates for children with cancer. The portfolio also encompasses projects designed to evaluate new drugs that may be more effective against childhood cancers, have less toxicity for children, improve the health status of survivors of childhood cancers, and monitor U.S. and international trends in incidence and mortality rates for childhood cancers.

More than 10 million cancer survivors are alive in the United States, at least 270,000 of whom were originally diagnosed when they were under the age of 21. Although there has been some increase in the incidence of all forms of invasive pediatric cancer over the past 20 years, from 11.5 cases per 100,000 children in 1975 to 14.8 per 100,000 children in 2004, death rates have declined dramatically and five-year survival rates have increased for most childhood cancers during this same time. Advances in cancer treatment have meant that today almost 80 percent of children diagnosed with cancer are alive at least five years after diagnosis, compared to about 58 percent in the 1970s. This improvement in survival rates is due to significant advances in treatment, resulting in a cure or long-term remission for a substantial proportion of children with cancer.