

**64th Meeting of the National Cancer Institute (NCI)  
Director's Consumer Liaison Group (DCLG)**

***Barriers to Drug Development in Pediatric Cancer Research***

**NIH Campus  
Building 31C, 6th Floor, Conference Room 6  
Bethesda, Maryland  
Friday, February 21, 2014**

**Members Present**

Mr. Max Wallace, Chair  
Mr. David Arons  
Ms. Susan Braun  
Dr. Adam Clark  
Ms. Andrea Ferris

Ms. Martha Gaines  
Ms. Joya Delgado Harris  
Ms. Linda House  
Dr. Michelle McMurry-Heath  
Mr. Jon Retzlaff

**Speakers**

Ms. Amy Bulman, Acting Director, Office of Advocacy Relations (OAR), NCI  
Mr. Max Wallace, Chair, NCI Director's Consumer Liaison Group (DCLG)  
Mr. John Czajkowski, Deputy Director for Management, NCI  
Dr. John Maris, Director, Center for Childhood Cancer Research, Children's Hospital of Philadelphia (CHOP)  
Dr. Malcolm Smith, Associate Branch Chief for Pediatric Oncology, Cancer Therapy Evaluation Program (CTEP), NCI  
Dr. Lee Helman, Scientific Director for Clinical Research, Center for Cancer Research, NCI  
Dr. Peter Adamson, Chief, Division of Clinical Pharmacology and Therapeutics, CHOP; Chair, Children's Oncology Group (COG)  
Dr. Greg Reaman, Associate Director, Office of Hematology and Oncology Products, U.S. Food and Drug Administration (FDA)  
Ms. Nancy Goodman, Executive Director, Kids v Cancer  
Ms. Lisa Tichenor, President, QuadW Foundation  
Ms. Maureen Lilly, Executive Director, Children's Cause for Cancer Advocacy (CCCA)  
Ms. Ruth Hoffman, Executive Director, American Childhood Cancer Organization (ACCO)  
Ms. Sarah Bogdan, Specialist, Federal Relations, American Cancer Society Cancer Action Network (ACS CAN)  
Mr. Peter Mayberry, Senior Manager of Legislative Affairs, St. Baldrick's Foundation  
Dr. Vicky Buenger, President, Coalition Against Childhood Cancer (CAC2)

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***Welcome and Opening Remarks***

*Ms. Amy Bulman and Mr. Max Wallace*

- Ms. Bulman and Mr. Wallace welcomed attendees, noting the large number of participants. The gathering included the DCLG members, NCI representatives, advocates, and others, with a number of parents of children who have and have not survived cancer.
- Mr. Wallace welcomed Martha (Meg) Gaines, the newest DCLG member. She is associate dean for academic affairs and experiential learning and director of the Center for Patient Partnership at the University of Wisconsin law school.
- DCLG member David Arons, senior director of public policy for the National Brain Tumor Society, was recognized for his role in advocating for the pediatric cancer meeting focus.
- The DCLG supports the larger cancer community in trying to find more efficient ways to prevent and treat cancer, and although this meeting will focus on pediatric cancer research, it is important that the DCLG consider pediatric issues in all of its discussions.

***NCI Update***

*Mr. John Czajkowski*

- Funding issues have forced NCI to take a hard look at not only its programs, but also internal processes, and unfortunately, the budget environment is not likely to improve soon. The relationship between NCI and the DCLG is important and the synergy with the DCLG means a great deal to NCI.
- Mr. Czajkowski will be leaving NCI to become executive dean of administration at Harvard University.

***The State of Pediatric Cancer Research***

*Dr. John Maris*

- Childhood cancer is a modern medical success story, but many childhood cancers have been resistant to progress. Cure rates remain low for acute myeloid leukemia (AML), high-risk neuroblastoma, and brain stem glioma, among others. The two thirds of children who are cured of any type of cancer are usually scarred for life by severe side effects.
- Childhood cancers have a lower number of mutations than adult cancers, meaning fewer targets for drugs. There have been unprecedented new therapeutic advancements in immunotherapy.

- The current research paradigm is definitely not sufficient for developing pediatric treatments. NIH funding is flat, with the potential loss of the next generation of physician-scientists.
- Optimally, a phase I study in adults would be completed before a drug is studied in children, but there are exceptions.
- Researchers have limited access to tumor cells at relapse and/or at autopsy, and they lack comprehensive strategies to define synergistic drug combinations and the mechanisms of drug activity and resistance in patients.
- Some approaches are working, such as growing investments from philanthropy and industry and increasing engagement from the advocacy community.
- Advances in research are translating to improved outcomes for children in a number of areas. Some groups are working to bring genomics and immunotherapy together to target childhood cancers with protein therapeutics.
- Positive developments in preclinical research include NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative and the Pediatric Preclinical Testing Program (PPTP), a screening initiative.
- To define the right questions, more pediatric-specific grant opportunities are needed.

*Dr. Malcolm Smith*

- Dr. Smith noted that the NCI annual budget for childhood cancer is about \$200 million. He mentioned that NCI tries to be involved in all types of pediatric cancer research. Examples are the TARGET discovery programs, PPTP, pediatric phase I clinical trials, and COG clinical trials. Other examples of NCI's investment in pediatric cancer research include the Pediatric Brain Tumor Consortium (PBTC), the NCI intramural program, the Childhood Cancer Survivorship Study, and many investigator-initiated research projects.
- A remarkable discovery about the relation of histone gene mutations to rhabdomyosarcoma as well as to diffuse intrinsic pontine glioma could be changing the landscape.
- PPTP, with principal investigator Dr. Peter Houghton, collaborated with more than 50 different companies and has evaluated more than 70 investigational agents. A number of agents have been transitioned from PPTP to the clinic. A number of compelling COG and Pediatric Brain Tumor Consortium (PBTC) trials are ongoing or in development.
- Agents must be specific for childhood cancer therapeutic targets and directly target genomic alterations and understanding molecular correlates of treatment failure must be a priority.

- There is a need to rescue orphaned drugs that were developed for adult cancer indications and abandoned before they could be tested on childhood cancers. Two examples are chimeric monoclonal antibody 14.18 (ch14.18), and insulin growth factor (IGF)-1R. Studying ch14.18 has led to a pharmaceutical collaboration with United Therapeutics and an important new treatment for children with neuroblastoma.
- The pediatric research community should be empowered to make prioritization decisions that are not based on adult cancer priorities. The DCLG could help address the problem of fragmentation in the study of childhood cancer.

*Dr. Lee Helman*

- One of the critical information gaps related to childhood cancers is the lack of understanding about why some tumors respond to treatment and others do not. He noted that it is necessary to understand what defines responders and nonresponders.
- Dr. Helman emphasized the need for mandated biopsies during the course of treatment. Lack of these biopsies is holding back the field; advocates can help advance this issue.
- Moving from a targeted agent to combined therapy takes too long. No examples of combined targeted agents in pediatric cancer exist yet. It is necessary to determine rational combinations as quickly and efficiently as possible.
- New strategies are needed for conducting clinical trials, and research in childhood cancer must address how to minimize the toxicities of treatment.
- More collaboration between the intramural pediatric program and COG can help inform the larger studies. Immunotherapies, imaging, and identifying patients who respond to a treatment are areas of interest.

Discussion highlights

- The promise of targeted development is nontoxic treatments.
- The model of placing the majority of newly diagnosed children in trials is changing. Trials are not needed for lower-risk tumors.
- Treatment is very difficult for relapse or refractory disease, with little past success.
- Researchers have seen an 86 percent response rate from T-cell therapy in children with refractory leukemias. One of the Pediatric Cancer Dream Team's goals is to move treatments from leukemia to solid tumors. Checkpoint inhibitors are an exciting discovery in the field.

- In preventive efforts, it has been difficult to identify precursors in childhood cancer, but some mutations and processes have been identified. The human papillomavirus (HPV) vaccine, Gardasil, is a pediatric intervention and the best example of a prevention strategy for a cancer caused by a virus.
- Biopsies in the course of a study probably cannot be mandated unless they are prespecified in the study design and demonstrate direct benefit. Biopsy could indicate how a child has responded to treatment, resulting in treatment changes (such as addition of a drug) where appropriate, and could be incorporated into study design.
- Approval of combined treatments depends on demonstration of benefits.
- Institutional review boards (IRBs) are reluctant to approve biopsy protocols because of concerns about coercion (i.e., that patients will think that they will not receive treatment if they refuse biopsy). Advocates can play a role by addressing IRBs.
- While resources for research are limited, the responsibility also is on researchers to come up with the right ideas. The field needs more money but could also spend its money more wisely. Drugs must be targeted in a faster way. Research that addresses scientific gaps will provide the best chance for success.

### ***The Potential Role of the Pediatric Cancer Advocacy Community in Reducing Barriers to Drug Development***

*Dr. Peter Adamson*

- The most important take-home message from this meeting for the DCLG is that the problem of childhood cancer has not been solved.
- Dr. Adamson noted that the presenters provided excellent background, but he hoped that DCLG members would leave this meeting outraged. Childhood cancer is the leading cause of disease and disease-related death in children in this country.
- What children have to endure in treatment is unacceptable. In treatment for high-risk cancers, four out of five children experience severe, life-threatening, or fatal toxicities in their treatments. Half of the children who are cured carry a lifelong burden from their treatment.
- The global regulatory environment is turning out to be an unexpected barrier.
- Pediatric oncology is entirely dependent on NIH funding. Childhood cancer has not registered on industry's radar. It will take extraordinary efforts to change that scenario.
- For childhood cancer, advocacy must become more global.

*Dr. Gregory Reaman*

- Dr. Reaman mentioned that the FDA is committed to the development of effective and safe therapies for childhood malignancies. He noted that pediatric oncology drug development should generally be coordinated with oncology drug development for adults.
- To be studied clinically, products should demonstrate biological plausibility of activity against a pediatric tumor, some expectation of potential benefit, a reasonable expectation of safety, and sufficient information to choose an appropriate starting dose.
- In the case of a scientific rationale and a population in need of treatment for which none is available, pediatric oncology clinical studies will be initiated, in most cases, immediately following adult phase I studies.
- With validated preclinical models, the necessity of adult studies prior to pediatric studies might diminish, and pediatric patients could be the first patients to receive a new agent.
- Pediatric patients should be given medicines that have been properly evaluated for their use, with an over-emphasis on safety and toxicity concerns. Product development should include pediatric studies when pediatric use is anticipated.
- Product labels first included a pediatric use section in 1979, but labeling pediatric drugs was not required until 1994. The 2003 Pediatric Research Equity Act (PREA) has had a profound impact on pediatric drugs.
- Some unique considerations are in play related to pediatric versus adult cancer drug development, including defining clinical benefit. Approaching cancer as a chronic disease is not a pediatric perspective. Cure and quality of survivorship are the most important aspects of treatment for children.
- The small size of childhood cancer study populations is an obstacle and combination therapies need more attention in treating childhood cancers.
- Constraints come from both industry and regulators. Current industry research and development models do not support pediatric development, and indication-based PREA triggers are not relevant for childhood cancers.
- Flexibility is important in regulatory decision-making in pediatric oncology. Early communication and thoughtful collaborative planning are key to effect change. Alternative endpoints to define clinical benefit include pharmacokinetics, pharmacodynamics, and prolonged event-free survival.

- A Pediatric Study Plan is required before a new drug is approved. Pediatric Study Plans frequently require modification.
- The priority review voucher incentive, known as the Creating Hope Act, is part of the FDA Safety and Innovation Act (FDASIA) and allows the Secretary to approve and award a priority review voucher to the sponsor of a rare pediatric disease product application. Vouchers may be transferred, including by sale. So far, there have been five designation requests; three have been granted and two denied. The voucher program is a demonstration of what advocacy can do.

*Ms. Nancy Goodman*

- Ms. Goodman's son Jacob was diagnosed with medulloblastoma and died 2 years later. His treatment caused many severe health problems in those 2 years.
- Reaching a 5-year survival mark is not the same as being cured.
- The role of government is to provide good to the public sector. A pipeline contains thousands of cancer drugs, but they are mostly for adults. NCI has not considered this in a way that is reflective of social values. NCI considers the best science. Industry is not willing to assume the burden. Pediatric cancers are orphan diseases with no possible return on investment.
- After Jacob died, Ms. Goodman and her husband formed Kids vs. Cancer to explore mechanisms available to fight cancer in children.
- One strategy for developing childhood cancer drugs is to repurpose a drug that failed trials for adults. Another is to develop new drugs for diseases that do not exist in adults. The PPTP program is a good start for finding drug targets but must be expanded.
- Additional funding is needed for pediatric trials and advocates can play an important role. A pediatric advocate should be on every NCI board and the Institute should not just be about the science, but also about saving lives when industry cannot take a role.

Discussion highlights

- Enrolling children in clinical trials has become the model for treating pediatric cancer, but more interest from industry would improve treatment.
- To attract quality scientists to pediatric cancer research, more RFAs must be created.
- The biology of some tumors (e.g., glioblastoma) is different in children and adults.
- A conference that included many cancer agencies and groups, industry, and investment capitalists could provide opportunities to move the field of pediatric cancer forward.



- HIV research advanced quickly because of advocates' willingness to fight. Childhood cancer might benefit from a similar approach. Companies do respond to argument.
- A number of examples were cited that illustrated the difficulty of getting industry to support childhood cancer drug development.
- This discussion has covered a range of topics, including the role of NCI, the role of industry, minimizing toxicity, biopsies, and incentives for industry. Advocacy groups want to know which barriers can be overcome by collaboration and which barriers, if removed, would provide the biggest paybacks.
- Under the current economic circumstances, the best way to bring down barriers would be to cultivate a climate that emphasizes the importance, for example, of NCI launching an initiative that emphasizes targeting therapy for pediatric cancers. Public/private partnerships can also play a role.

### ***Advancing Pediatric Cancer Research Through Advocacy***

*Ms. Lisa Tichenor, QuadW Foundation*

- Family and friends of Willie Tichenor, who died of osteosarcoma at age 19, formed QuadW—What Would Willie Want?—after his death. The foundation has worked to design efficient and leverageable grants. The bottom line is finding new treatments.
- Three drugs based on QuadW research will soon be in clinical trials. Since it began in 2008, work supported by QuadW has resulted in 12 articles published in scientific journals, with 6 more manuscripts awaiting publication. Two abstracts have been presented at major conferences.
- QuadW has helped establish a standard operating procedure for tissue collection that will be adopted by COG and a system of prioritizing investigational drugs targeting metastatic osteosarcoma.

*Ms. Maureen Lilly, Children's Cause for Cancer Advocacy (CCCA)*

- CCCA's approach has been to promote a national debate on public policy and legislature related to childhood cancer, with the goal of reducing barriers.
- Highlights of progress in policy changes to advance pediatric cancer research and drug development have included reauthorization of the Prescription Drug User Fee Act, permanent reauthorization of PREA and the 2002 Best Pharmaceuticals for Children Act (BPCA) under FDASIA, and making PREA more effective by removing the orphan disease exclusion and requiring that pediatric studies be based on targeted pathways. Ms. Lilly emphasized that drug trials should be based on pathways, not the sites of cancers.
- Biobanking can enhance the understanding of the molecular errors that cause cancer. CCCA works to advocate increasing biospecimen collection for childhood cancer.

- Advocates can affect change by making their case to members of Congress, working with the FDA to reduce regulatory barriers, and urging the FDA to adopt a mechanism to prioritize studies and expand targeted pathway studies.

*Ms. Ruth Hoffman, American Childhood Cancer Organization (ACCO)*

- Cancer is often compared to fighting a war, Ms. Hoffman noted, but in this battle, it is the little children who are the soldiers. Unfortunately, the arsenal is antiquated.
- Ms. Hoffman's daughter Naomi, diagnosed in 1987 at age 7 with acute myelogenous leukemia (AML), was one of first survivors of a bone marrow transplant. The high-dose chemotherapy drugs and radiation she was treated with are still used today and are associated with many toxic side effects.
- Naomi survived her treatment and her cancer but has suffered a long list of late effects including heart damage, lung damage, hypertension, cataracts, endocrine dysfunction, growth problems, destroyed tear ducts, dry mouth and tooth decay, and secondary cancer (metastatic thyroid carcinoma). She was told she was infertile—but then she became pregnant. She had cervical insufficiency, was hospitalized, and gave birth to Hope 4 months early. Hope has severe seizures, a direct result of her mother's toxic treatment.
- Marleigh, another child, was diagnosed with AML in 2012, at the age of 3, and treated with the same drugs Naomi received. Her parents were unsuccessful in obtaining a promising investigational drug and she died on December 12, 2013. Ms. Hoffman noted that half of all children diagnosed with childhood cancer die and they need better weapons to fight the war on childhood cancer.
- ACCO, which began in 1970 as the Candlelighters, was the first childhood cancer organization to lobby nationally for research. It has a national office, a network of 40 affiliates across the United States, and a global budget of more than \$15 million per year to provide direct services to families fighting childhood cancer. It is the largest publisher of childhood cancer resources in the country and provides them free to families and physicians.
- ACCO is a member of a number of alliances and coalitions that fight childhood cancer. It also provides patient navigation assistance.
- To address the challenges of childhood cancer, accurate messaging is important, funding is critical, and advocates can play a significant role. Pediatric cancer representation must be mandated on all boards.
- Other needs include funding for an epidemiological database and cross-Institute communication at the NIH.

*Ms. Sarah Bogdan, American Cancer Society Cancer Action Network (ACS CAN)*

- ACS CAN takes action on behalf of patients and their families and the priority of ACS CAN is to protect funding for cancer research.
- NIH, NCI, and the FDA must work together more closely.
- Guidelines are needed to explain to volunteers why these issues are so important.

*Mr. Peter Mayberry, St. Baldrick's Foundation*

- St. Baldrick's, formed in 2000 out of the work of three good friends and a challenge to shave their heads, is the largest private-sector source for funding of pediatric cancer research.
- A wide range of St. Baldrick's grants fund consortium research, COG, trial infrastructure, individual scholars and fellows, and improvement of supportive care.
- The Pediatric Cancer Dream Team is a 4-year, \$14.5 million grant with the goal of curing the most hard-to-treat childhood cancers and creating new treatments based on genetic abnormalities and the immune system.
- St. Baldrick's honors children with cancer and their families, with thousands of stories provided on the Foundation's website. Five children are selected as ambassadors each year. To emphasize that not all children survive this disease, one of the ambassadors is a child who has died.
- The Hero Funds are a way for individuals or groups to become involved with scientifically approved fundraising without red tape.

*Dr. Vickie Buenger, Coalition Against Childhood Cancer (CAC2)*

- Dr. Buenger's daughter was diagnosed with neuroblastoma in 2002 and survived for 7 years. Dr. Buenger learned how fragmented the childhood cancer landscape is and also about the many barriers to drug development.
- CAC2, a collaborative group with some private sources of funding, was founded in mid-2013. It includes representatives from 57 organizations, ranging in size from less than \$25,000 to over \$10 million in annual revenue; 15 unaffiliated individual advocates; and 3 student members.
- Thousands of advocates and advocacy organizations are working to close information gaps and expand the information reach.
- CAC2's mission is fourfold: coordinated action; information exchange; education and learning; and a broad-based collaboration for research and treatment, family services, advocacy support, and awareness building.

- CAC2's goals are to optimize the research efforts of CAC2 organizations to amplify the impact of funds raised, support policy and advocacy opportunities on childhood cancer issues, elevate childhood cancer awareness nationwide, and increase awareness of and promote collaboration among family and patient support organizations.
- Members of the coalition cooperate, establish enhanced personal relationships, and coordinate interest group activities and information sharing.

#### Discussion highlights

- The percentage of children with cancer who are involved in trials is not well defined. A reasonable estimate is about 50 percent. Not every child is eligible for a trial, and trials are not available for every disease.
- Advocates, particularly parents and grandparents, need talking points. Advocates must be able to talk about statistics and need in a meaningful way.
- Most of the complications children experience are related to treatment, particularly radiation. More toxicities are being seen now because more children are cured and living longer.

#### *Next Steps for the DCLG*

- DCLG members can learn from pediatric advocacy groups. Federal agencies and advocate groups are partners, not adversaries. This should not be the end of this discussion; it should be the beginning.
- Industry's voice was missing from the presentations and since most drugs are developed through industrial pathways, it would be beneficial to hear the industry perspective.
- Advocates could play an influential role addressing IRBs.
- The DCLG would benefit from having at least one pediatric advocate as a member in the group.

**Certification**

I hereby certify that the foregoing minutes are accurate and complete.

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**Date**

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**Chair**

**Director's Consumer Liaison Group**

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**Date**

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**Executive Secretary**

**Director's Consumer Liaison Group**