

# A Forceful Advocate for Young Cancer Patients

*“I consider our ability to cure a child with cancer the most important job in the world.” With these words, Peter C. Adamson, M.D., Chair of the Children’s Oncology Group—an NCI-supported consortium of more than 200 centers across North America, Australia, New Zealand, and parts of Europe—recently commented at a U.S. Food and Drug Administration briefing about the shortage of cancer drugs.*

(Photo: Peter Adamson)



Peter C. Adamson, M.D.

At the FDA briefing, I urged the agency to take the necessary steps to enforce early reporting of impending drug shortages. Moreover, I suggested that the government explore novel approaches, including incentives, which would result in the establishment of a strategic reserve of life-saving drugs for children with cancer.

The roots of my advocacy efforts can likely be traced back to my medical school training at Cornell University Medical College. It was during my first clinical rotations that I learned the importance of every patient having an advocate to help navigate the health care maze. I carry the importance

effectively advocate for children is an important skill for both pediatricians and pediatric subspecialists. Whether it is for an individual patient or a group of patients, advocacy for the children in our care has been stressed at various times throughout my pediatric training, both as a resident at The Children’s Hospital of Philadelphia (CHOP), and during my 12 years of subspecialty training and work in NCI’s Pediatric Oncology Branch.

During my time at NCI, in addition to the leadership and guidance of the then Chief of the Pediatric Oncology Branch, Philip Pizzo, M.D., I had the distinct privilege of having

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of advocacy with me these many years later, which in part led me to speak with the FDA on the cancer drug shortage crisis. Being able to

two of our fields’ most outstanding mentors, David Poplack, M.D., and Frank Balis, M.D. I was afforded tremendous research opportunities

early in my training. One of my first projects focused on understanding key elements of the clinical pharmacology of a unique type of targeted therapy for children and adults with acute promyelocytic leukemia (APL). All-trans retinoic

the world's largest organization devoted exclusively to childhood and adolescent cancer research. The COG unites more than 8,000 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers across North America,

efficiencies in all phases of clinical research.

There are a number of lessons from both the research realm and the clinical realm that influence how I now train pediatric residents and fellows. One common theme is that of the importance of time—whether it is the time to move an important idea from the laboratory into the clinic, or the time to deliver clinical test results to a patient and family. For families with children with cancer, there is perhaps no greater anxiety-provoking period than the time between the performance of a diagnostic test and the receipt of test results. Whether the news is good or bad, awaiting results in a remarkably stressful time for patients and families. So the delivery of results in a clear, compassionate, and straightforward manner is essential. Whether it is in the clinic, or in the development and execution of COG clinical trials, a key focus of our work will be to shorten the time it takes to get results.

Research examining the timeline between the creation of a new clinical trial concept and the actual start of the clinical trial shed important light on the inefficiencies of our national cancer clinical research enterprise, be it research at NCI-designated cancer centers or throughout the

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acid (ATRA, Tretinoin) was emerging as a major therapeutic advance for patients with APL, but the ability to maintain necessary drug exposures in patients appeared to limit its efficacy. Our work, first in pre-clinical models and then in adult and pediatric clinical trials, helped define the important clinical pharmacology of ATRA, which when administered on a continuous basis quickly induces its own metabolism. We went on to demonstrate that an intermittent schedule of drug administration could in part overcome this effect, and since then, an intermittent schedule of drug administration has become the standard way of administering ATRA to patients.

After my years at NCI, I returned to CHOP to start a new program of pediatric drug development that would extend beyond pediatric oncology. We established the Division of Clinical Pharmacology and Therapeutics, and our group led or supported a broad range of clinical trials that were being performed under the Best Pharmaceuticals for Children Act (BPCA). At CHOP, I more recently had the opportunity to support a broad range of clinical-translational research efforts, serving for a number of years as CHOP Research Institute's Director for Clinical-Translational Research.

About 18 months ago I was elected to lead the Children's Oncology Group (COG; [www.childrensoncologygroup.org](http://www.childrensoncologygroup.org)),

Australia, New Zealand, and parts of Europe in the fight against childhood cancer. Today, more than 90 percent of the 13,500 children and adolescents diagnosed with cancer each year in the United States are cared for at COG member institutions. Research performed by COG institutions over the past 50 years has helped transform childhood cancer from a virtually incurable disease to one with a combined five-year survival rate of 80 percent.

My role as Chair of the COG has enabled me to rethink how the oncology research community can best move its discoveries into pediatric clinics. Emerging research shows that even the more common childhood cancers are a mixture of diseases, with each subset

potentially requiring a unique and specific type of targeted therapy. It is clear that we must develop a better and more efficient way to move novel treatments from our labs into the clinic. Through COG, we can forge collaborations worldwide to improve

cooperative group system. The COG has taken a number of steps to shorten this timeline. One approach was to incorporate a new trial design for the conduct of pediatric phase I trials, the first-in-children studies we perform for new anticancer agents.

Our focus is now on target identification and evaluation of novel therapies. Not only is the goal to improve the cure rate, but also to decrease long-range deleterious effects of current-day treatment that too many of childhood cancer survivors face in young adulthood.

The pediatric phase I trial design we developed is called the rolling-six-method, and it allows us to reach a study endpoint, the recommended dose for children, in a significantly shorter period of time than was possible with prior designs. We used computer-based simulations to determine how the design would perform in the clinic, and have now moved to using the rolling-six as the standard approach to our phase I trials.

Since the introduction of chemotherapy for the treatment of childhood leukemia more than 60 years ago, the prognosis for children with cancer has indeed improved dramatically. The five-year survival rate for childhood cancers, many of which were uniformly fatal in the pre-chemotherapy era, is now approaching 80 percent. Despite these advances, several childhood cancers still have unacceptably low cure rates, and even when treatment is successful, the acute and long-term side effects can be substantial.

Our past success has come mainly through the more intense use of decades-old drugs, many of which were developed originally for adult cancers. But this approach to improving the outcome is, not

that too many of childhood cancer survivors face in young adulthood.

Relative to medical oncology, pediatric oncology faces some unique challenges in the development of novel approaches to the treatment of cancer. Despite a wealth of tantalizing

leads from basic science, there is a near-complete void in commercial research and development for drugs specifically targeting pediatric cancer. As devastating as cancer is in children, the numbers affected are too small to drive innovation in the private sector. To potentially address this gap, we have envisioned a public-private partnership that could establish a virtual drug development company. Our ideas emerged from an Institute of Medicine committee I participated on in 2005. The report, *Making Better Drugs for Children with Cancer*, serves as a blueprint of how this could emerge, and is modeled in part on efforts undertaken for other diseases or illnesses including cystic

venture, mitigating the major costs incurred by the private sector in drug development.

Cancer research is clearly entering into an age of discovery. We are using powerful analytical genomic tools—whose costs have fallen dramatically—

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to understand childhood cancer in terms of fundamental biology. Our ability to stratify patients for appropriate treatment continues to improve, and we foresee our lab-based efforts including genomics helping guide future research and therapy. The COG has a remarkable ability to partner with families in research, and this ability will provide a growing platform for discovery as we further link biology to outcome in the years ahead.

Our discovery efforts are clearly focused on understanding the biology of all the childhood cancers, finding the Achilles' heels for every type of pediatric tumor, no matter how rare, and developing and delivering treatments that maximize the likelihood of cure while minimizing the near- and long-term effects of therapy. As one of the pioneers in pediatric oncology Giulio (Dan) D'Angio, M.D., taught me many years ago, "for children with cancer, cure is not enough."

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surprisingly, paying diminishing returns. Thus our focus is now on target identification and evaluation of novel therapies. Not only is the goal to improve the cure rate, but also to decrease long-range deleterious effects of current-day treatment

fibrosis, tuberculosis, and malaria. A clear advantage that the pediatric oncology community has is that the clinical trial infrastructure afforded by the COG could conduct the full spectrum of pediatric clinical trials for drugs that result from such a