

Genetically Informed Therapies—A "GIFT" for Children with Cancer

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Abstract

The national investment that was made in oncology research with the passage of the National Cancer Act in 1971 is now coming to fruition. Nowhere is this more apparent than in the exciting prospects for genetically informed precision medicine as applied to the treatment of children with cancer. The wealth of information gleaned from intensive genetic analyses and NexGen sequencing studies has identified a number of viable targets in leukemias and solid tumors. Our rapidly evolving understanding of the enzymatic controls that regulate chromatin dynamics during normal differentiation of stem cells and their mutation or dysregulation in tumor cells is leading to a new library of therapeutically tractable tumor targets. The recent identification of germline variants associated with toxicity and/or response to therapy has further enhanced our ability to deliver individualized treatments for pediatric cancer patients. Our challenge today is to determine how best to use genomic data and integrate it into evolving clinical protocols to provide more efficacious therapies and a better quality of life for children with cancer. *Clin Cancer Res*; 18(10); 2735–9. ©2012 AACR.

Introduction

Significant advances in our ability to successfully prevent, detect, and treat malignant tumors have been made since President Nixon signed the National Cancer Act into law on December 23, 1971. As we are now some 40 years out from the historic challenge, a true appreciation of our progress and the challenges that await us necessitates a reflection on our treatments for children and the state of our knowledge about cancer cells, the immune system, and cancer therapy at the time the Cancer Act was initiated (Fig. 1).

In 1971, scientists could not readily clone or sequence genes, and the prevailing view was that viruses caused cancers. Although today it is known that only 15% of cancers have a viral etiology (e.g., Epstein-Barr virus and human papilloma virus), the role of the host's immune or inflammatory responses to viral infection as tumor-promoting causations remains to be resolved. From a study in 1969 of viruses in cancer (1) came the hypothesis that retroviruses isolated from animal tumors contain oncogenes that encode proteins capable of transforming cells. The subsequent identification of such oncogenes and their cellular localization and function led to the realization in 1978 that viral oncogenes have normal cellular homologs, called proto-oncogenes (2), and mutations in these genes cause tumors (3). In a landmark study in 1971 based on an

epidemiologic analysis of the inheritance of retinoblastoma tumors in children, Knudson (4) postulated the existence of a tumor suppressor gene, which led to the 2-hit model of tumorigenesis. Fifteen years later, the *RBI* tumor suppressor gene was isolated and cloned (5).

In 1971, the plasticity of cancer cells was noted in studies showing that tumor cells could differentiate into benign cells (6). In hindsight, this was indicative of a cancer stem cell, but only much later was this phenomenon described in leukemia [in 1997 (7)] and solid tumors [in 2003 (8)]. In 1971, the field of epigenetics was still restricted to model organisms, although modifications to histones and their effects on gene expression were known. Research into cancer epigenetics did not begin in earnest until a decade later with the identification of altered gene methylation in cancer (9). Only in the last decade have key enzymes that regulate the histone modifications that control stem cell lineage specification been identified. How mutations in these enzymes contribute to tumorigenesis is an area of intense investigation.

The effort to harness the immune system to fight cancer was also in its infancy in 1971. Lymphoid cells were categorized as B or T cells, and natural killer and dendritic cells had not yet been described. Commercialization of the fluorescence-activated cell sorter in the early 1970s (10), coupled with the development of monoclonal antibodies a few years later (11), facilitated the ever-expanding delineation of subsets of functionally important lymphoid cells.

These new discoveries in genetics and cancer biology, combined with advances in medical technologies and computational expertise that were not even imagined in 1971, have led to truly remarkable progress in understanding the pathogenesis of childhood cancer and the development of more effective therapies. Initial improvements in survival were observed with treatment regimens stratified by pathologic classification and tumor stage. However,

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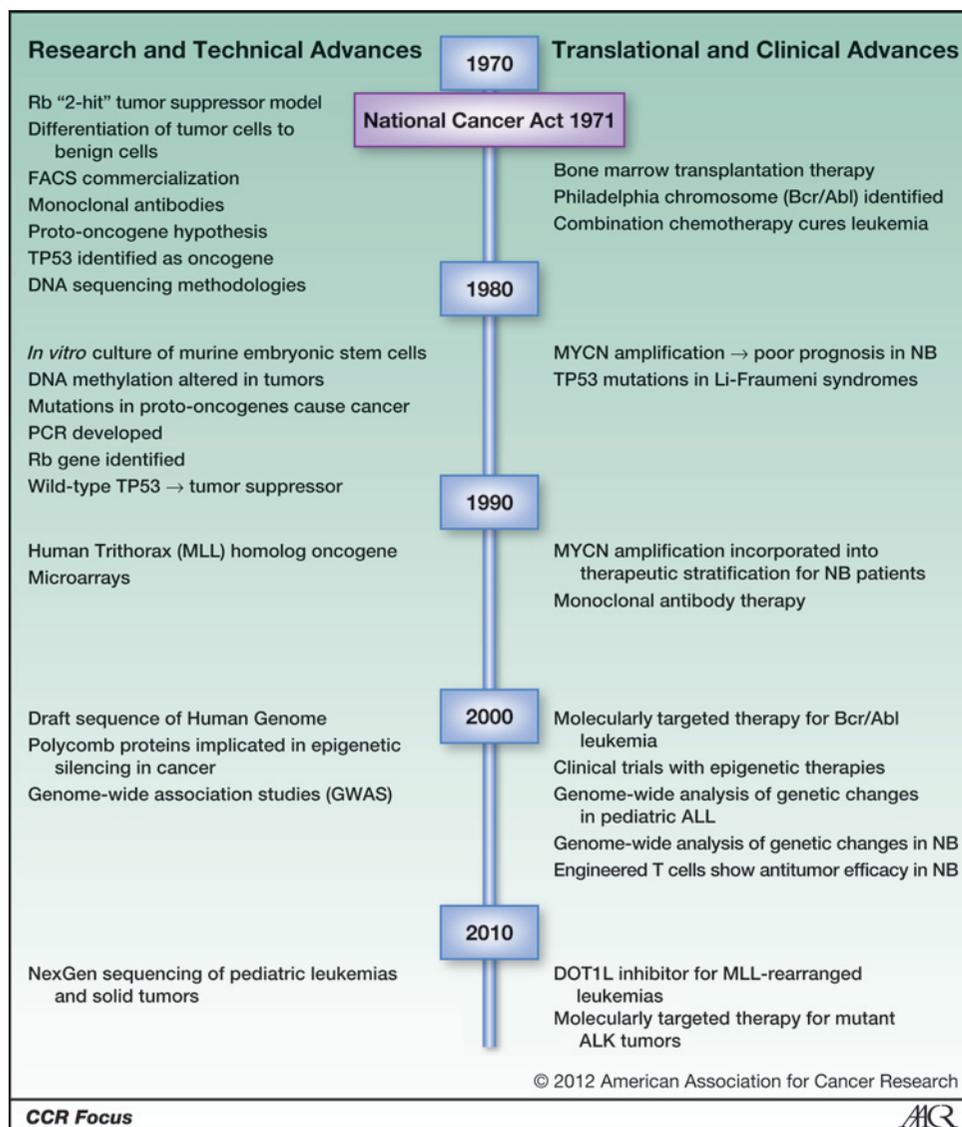


Figure 1. Timeline from 1971 to 2011, marking research and clinical advances achieved since passage of the National Cancer Act of 1971. The timeline shows selected research and technical advances, as well as translational and clinical advances, that have occurred in the last 40 years and have had a significant impact on our view of cancer biology and clinical practice, with a specific emphasis on pediatric oncology. Many of these findings relate to topics discussed in the articles that accompany this *CCR Focus* on pediatric oncology. FACS, fluorescence-activated cell sorter; NB, neuroblastoma.

the inadequacy of this approach became clear with the recognition of the biologic heterogeneity that exists within pathologically defined tumor types. The clinical significance of genetic tumor markers in pediatric cancers was first established in the 1980s (12, 13), and it soon became clear that more refined prognostication of risk of relapse could be achieved by combining tumor histology and stage with other clinical features, tumor genetics, and assessment of the response to therapy (14–16). Pediatricians were early adopters of risk-group-based treatment strategies in cooperative group clinical trials in acute lymphoblastic leukemia and solid tumors. This approach led to further improvements in outcome. In populations of patients with lower-risk disease treated with reduced therapy, high survival rates were maintained and less toxicity was observed, and increased survival rates were achieved in higher-risk populations treated with more intensive, multimodal treatment regimens. However, despite this

progress, cancer remains a leading cause of death in the pediatric population and long-term complications of therapy remain a pressing problem.

This *CCR Focus* section highlights many of the more recent translational and clinical studies in pediatric leukemia and solid tumors that have led to a better understanding of the key molecular events that drive tumorigenesis, including the identification of druggable targets and the development of biologically rational therapies. Of interest, despite the distinct pathologic origins of disease, in some cases the same molecular target identified in adult cancers is also detected in pediatric tumors, as exemplified by the anaplastic lymphoma kinase (*ALK*) aberrations that are seen in neuroblastoma, lymphoma, non-small cell lung cancer, and other cancer types (17). Our increasing understanding of the fundamental mechanisms that contribute to disruption of the epigenome in both pediatric and adult cancers is providing additional novel avenues for

targeting cancer (18). Targeted immunotherapies have led to dramatic improvements in outcome for children with neuroblastoma (19), and in more recent studies, response to treatment with chimeric antigen receptors (CAR) has been observed in patients with leukemia and solid tumors (20–22). It is also recognized that germline genetic variants influence response to therapy and outcome (23, 24). Thus, to optimally link pediatric oncology patients with effective, genetically informed therapies, we will also need to gain a deeper understanding of the host genetic variants that influence response and toxicity to chemotherapy.

Advances in Targeting Neuroblastoma

Matthay and colleagues (25) review the biologic rationale and clinical efficacy of three promising targeted therapies for neuroblastoma: (i) radiotherapy with ^{131}I -metaiodobenzylguanidine (MIBG), (ii) immunotherapy with monoclonal antibodies directed against the GD2 ganglioside, and (iii) biologic therapy with inhibitors of the ALK tyrosine kinase. MIBG targets the norepinephrine transporter, which is expressed in 90% of neuroblastoma tumors, resulting in cell-specific uptake and radiation-induced destruction of the cell (26). A number of early-phase studies and more recent trials in newly diagnosed patients have shown the activity of this agent in neuroblastoma (27). However, a randomized trial, such as the one planned by the Children's Oncology Group (COG), will be needed to confirm its clinical efficacy in high-risk neuroblastoma. Significant antineuroblastoma activity has also been observed with immunotherapy targeting a surface glycolipid molecule, disialoganglioside (GD2), which is uniformly expressed by neuroblastoma. A recently completed seminal randomized COG phase III trial showed a superior outcome for patients randomized to immunotherapy with ch14.18 antibody + cytokines and isotretinoin versus isotretinoin alone. In an effort to reduce the significant toxicities associated with ch14.18, second-generation anti-GD2 antibodies are being tested in early-phase clinical trials (19). Additional studies testing the efficacy of combining anti-GD2 antibodies with chemotherapy are under development in the COG. In recent studies, heritable oncogenic *ALK* mutations were shown to be the major cause of familial neuroblastoma, and somatic *ALK* mutations were detected in 5% to 8% of low-, intermediate-, and high-risk neuroblastoma tumors (28–31). Although the presence of activating *ALK* alleles is not sufficient to confer clinically aggressive, high-risk disease, *ALK* has been identified as a valid molecular target. Early-phase pediatric clinical trials testing crizotinib, a dual *ALK*/*MET* inhibitor that has shown efficacy in adults with *ALK*-rearranged cancers (32), have been rapidly developed, offering a truly personalized approach to treatment. Aggressive efforts to develop new *ALK* inhibitors are under way. In addition, the therapeutic efficacy of anti-*ALK* antibodies is being investigated (33) because *ALK* is expressed on the surface of most neuroblastoma tumor cells and is restricted to the brain following development. Although the development of individualized treatments for children with neuroblastoma remains a

considerable challenge, the great potential of these targeted approaches for children with high-risk neuroblastoma is now established.

Advances in Targeting Childhood Leukemias

In their comprehensive review of high-risk B-progenitor acute lymphocytic leukemia (ALL) and juvenile monomyelocytic leukemia (JMML), Loh and Mullighan (34) detail both the promise and the complexity of intensive genomic analyses and NexGen sequencing. In studying the mutational spectrum in genes associated with congenital disorders that are frequently accompanied by myeloproliferative disorders and JMML (e.g., *NF1*, Noonan syndrome, and *Cbl* syndrome), the challenge will be to understand the tumorigenic potential of different mutations. Here robust cell-based and animal modeling systems will be needed. It seems that a variety of different mutations in signaling proteins converge on a common pathway, the RAS/mitogen-activated protein kinase (MAPK) pathway, providing an opportunity for targeting a common downstream node.

Starting from leukemias that share the *BCR-ABL1* transcriptome without carrying the cytogenetic alteration, detailed genomic analyses revealed that some PH-like ALLs are marked by chromosomal rearrangements involving different cytokine receptors. These cytokine signaling receptors predominantly converge on a common signaling pathway, the Janus-activated kinase (JAK)/STAT pathway. With a high frequency of accompanying JAK mutations, there is the promise of therapies guided by precision genomic interrogation of patients' tumors. The discovery of activating *JAK2* mutations in other myeloproliferative disorders, and the observation that JMML cells are hypersensitive to cytokine stimulation and STAT activation, led to their inclusion in the recent COG clinical trial of ruxolitinib, which also includes ALL with JAK mutations. We will know in the next few years whether the promise of this targeted treatment strategy can be realized.

With the exception of imatinib (Gleevec; Novartis), the accumulating evidence from single-agent-targeted clinical trials indicates that although tumors may be initially responsive, the responses are not durable. This may be a particularly perplexing problem for ALL, because it is known to contain minor leukemic clones with unique but overlapping sets of genetic alterations. Do these clones or new ones appear at relapse? The authors point out that mutations in the acetyltransferase *CREBBP* emerge as a dominant clone in relapsed B-ALL (20%). On the basis of this finding, they propose the incorporation of histone deacetylase (HDAC) inhibitors for the treatment of this type of B-ALL.

Targeting the Epigenome in Pediatric Solid Tumors

Lawlor and Thiele (35) review recent advances in chromatin biology in the context of embryonic development, drawing parallels with the aberrant developmental programs in pediatric solid tumors such as the Ewing sarcoma family of tumors (EFT), neuroblastoma, and brain tumors. They present emerging data indicating that genetic

alterations characteristic of these tumors lead to fundamental dysregulation of the epigenome. This is exemplified by studies modeling Ewing sarcoma in normal neural crest stem cells. Upon transduction with EWS/FLI, the most common chromosomal translocation in EFT, increases in BMI-1 and EZH2 [key components of Polycomb repressor complex proteins 1 (PRC1) and 2 (PRC2)] are found. This leads to increased stemness, and blocks in differentiation similar to those found in EWS tumors.

Elevated EZH2 levels have been noted in neuroblastomas with an undifferentiated histopathology, and neuroblastoma cell models indicate that pharmacologic or genetic inhibition of EZH2 (directly or via destabilization of the PRC2 complex) with HDAC inhibitors relieves EZH2-mediated repression of genes with tumor-suppressor activity.

The finding that many of the enzymes that control chromatin dynamics, such as the histone methylase/demethylases and acetylases/deacetylases, are druggable has elicited much excitement. The challenge will be to determine how to best use them in clinical trials.

Targeting Childhood Cancer with Chimeric Antigen Receptors

Although investigators have long been tantalized by the sporadic successes of William Coley in using heat-killed bacteria to stimulate the immune system of patients with sarcomas in the late 1800s (36), proponents of cancer vaccines have been stymied up until now. Lee and colleagues (37) discuss the exciting advances that have been made in the use of tumor-focused CARs to target potent cytolytic T cells to tumor cells. This technology brings together the genetic engineering expertise garnered over the past 40 years from studies of the genetics of viruses, antibodies, and gene therapy, with a better appreciation of the complexity of cellular T-cell-mediated immune responses and host lymphoid homeostatic mechanisms.

The success achieved in neuroblastoma using anti-GD2 virus-specific T cells in a pilot phase I study stimulated interest in this therapeutic approach (20). Although anti-GD2 remains a validated target in neuroblastoma, a number of other pediatric tumors, such as Ewing sarcoma and osteosarcoma, express GD2, suggesting a wider application for anti-GD2 CAR therapy. Most clinical studies in pediatrics are targeting lymphoid tumors using CD19CAR engineered alone (first generation) or with costimulatory modules (second generation) transplanted into stimulated T cells. Although initially the focus was on transducing more cells into patients, the toxicity associated with cytokine storms limits the number of cells that can be transduced. The challenge now is to extend the lifespan of CART cells by genetically or immunologically enhancing their survival and/or infusing them into lymphopenic patients.

Individualizing Pediatric Cancer Treatments Using Germline Genetics

Pinto and colleagues (38) discuss a number of important germline pharmacogenetic and pharmacogenomic

studies that show the potential of using germline genetic biomarkers to personalize therapy and improve the overall care of children with cancer. Although the majority of these pediatric oncology studies have focused on identifying variants associated with toxicity, more recent research has shown that germline variants also contribute to response (24). Investigators have elucidated how germline genetic variation influences drug toxicity and/or efficacy largely by using candidate gene approaches, and specifically by evaluating variants known to be important in metabolic or pharmacokinetic pathways (39). However, clinically important genomic variants also have been identified with the use of whole-genome approaches (40). Well-genotyped human Epstein-Barr virus-immortalized lymphoblastoid cell lines derived from healthy individuals in the International HapMap Project have provided additional tools to identify genetic variants associated with chemotherapy resistance (41), and the potential of this cell-based approach was recently shown in adult cancer patients (42). Pediatric studies testing the association of chemotherapy-resistant genetic variants identified in the lymphoblastoid cell lines model with outcome in a cohort of neuroblastoma patients are ongoing. To develop more effective, personalized treatment regimens, it will be critical to evaluate heritable genomic variants associated with chemotherapy resistance so that patients at greatest risk for nonresponse to specific chemotherapeutic agents can be identified.

Conclusions

Clinical experience with targeted cancer therapeutics in the adult cancer population has revealed their great potential. Although the experience in pediatrics is more limited, the results of pediatric clinical trials are equally promising. Nevertheless, many challenges exist and considerably more work needs to be done before personalized therapy can become a reality for children with cancer. For many pediatric cancers, molecular targets have not been identified, emphasizing the need for more research and additional molecular profiling. However, even when a putative pediatric cancer target is identified, economic considerations can limit drug development unless there is also biologic rationale for using the agent in the more-common adult diseases. In addition to molecular profiling of tumors, additional knowledge regarding germline genetic variants associated with nonresponse and/or toxicity will be needed to facilitate the development of effective, individualized treatment strategies. Finally, until technologies are developed that can yield rapid and reproducible results in a cost-effective manner, the goal to link pediatric cancer patients with biologically relevant therapeutics efficiently and in a clinically relevant timeline will remain a substantial challenge.

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No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. J. Thiele, S. L. Cohn

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. J. Thiele

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. J. Thiele, S. L. Cohn

Writing, review, and/or revision of the manuscript: C. J. Thiele, S. L. Cohn

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. J. Thiele

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