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AACI Commentary

The Broad Relevance of Pediatric Cancer Research

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Commentary Overview

- Significant scientific advances in pediatric cancer biology and new therapeutic approaches, coupled with NCI reporting requirements, are generating greater interest in pediatric cancer at leading cancer centers.
- Researchers are learning more about the distinct mechanistic underpinnings for many types of childhood cancers that differentiate them from adult cancers.
- Now more than ever it is critical that we work together as a national and global scientific community to develop new tools to advance cures for childhood and adult cancers alike.

Pediatric cancer is drawing increasing interest in cancer centers across the U.S. Contributing to this trend is the National Cancer Institute's (NCI) Childhood Cancer Data Initiative coupled with significant scientific advances in pediatric cancer biology and new therapeutic approaches. As more children are cured of cancer, there is also increasing focus on long-term health outcomes as survivors of childhood cancer have decades of life ahead.

The NCI requires that comprehensive and clinical cancer centers make specific efforts to address childhood cancer. Evidence of such activity must be demonstrated both in the NCI's Cancer Center Support Grant application and during site visits, when the agency evaluates whether an institution merits public financial support. Consequently, centers must actively pursue and be prepared to discuss their efforts in this evolving field.

From a research perspective, there are compelling reasons to focus on pediatric cancer. For

example, we're increasingly learning of distinct mechanistic underpinnings for many types of childhood cancers that differentiate them from adult cancers and that may demand distinct therapeutic approaches. A **2018 paper** by my St. Jude Comprehensive Cancer Center colleague, Dr. Jinghui Zhang, in collaboration with the NCI-funded Children's Oncology Group[1], analyzed somatic alterations in 1,700 childhood cancers. A central finding was that 55 percent of genes recurrently mutated in pediatric cancer are not mutated in adult cancers.

Consequently, in light of the building excitement for targeted therapies, it is important to realize that the standard approach of developing therapies for adult cancers and expecting them to "trickle down" to childhood cancers will not work for over half of the drivers of pediatric cancer. This scenario represents a substantial challenge and means that dedicated focus will be required on studying pediatric-specific mechanisms and searching for potential synthetic lethalities that can pave the way to targeted therapies.

It is equally important to highlight the corollary of the finding above: 45 percent of recurrent mutations in childhood cancers *are* found in adult cancers. In adult cancers these mutations often exist in the setting of remarkably complex aneuploid genomes that contain myriad additional mutations. This complexity can make it challenging to elucidate the role of a single mutation. In contrast, the genomes of childhood cancers are often much simpler, providing advantages to pediatric models in the elucidation of function and identification of vulnerabilities conferred by a driving mutation.

Underlying Mechanisms

Indeed, the study of pediatric cancers can yield key insights that are broadly relevant to cancer. For example, it was study of a rare childhood cancer of the eye, retinoblastoma, that led to recognition of tumor suppressor genes and the first identification of the key role of the Rb gene family in tumor suppression. Subsequently, independent studies by Drs. Olivier Delattre and Jaclyn Biegel of rhabdoid tumors—rare but highly aggressive cancers that strike babies and toddlers—uncovered the first evidence of a role for mutation of genes encoding a subunit of SWI/SNF chromatin remodeling complexes in driving cancer. It was not until a decade later, via human cancer genome sequencing efforts, that it was discovered that at least nine different genes that encode SWI/SNF subunits are recurrently mutated across a wide variety of cancer types. It is now clear that genes encoding SWI/SNF subunits are mutated in more than 20 percent of all human cancers, both adult and pediatric.

As a post-doctoral trainee in the 1990s in the laboratory of Dr. Stuart Orkin at Boston Children's Hospital, immediately inspired by the findings of Dr. Delattre, I sought to develop genetically engineered SMARCB1/INI1 mouse models in order determine whether this SWI/SNF gene was a bona fide tumor suppressor. We found that inactivation of SMARCB1 led to extremely rapid cancer onset at a median of only 11 weeks, with 100 percent of mice developing cancer. This was a remarkable finding as SMARCB1 inactivation led to cancer in less than half the time that it takes cancer to form following p53 loss. Study of the genomes of human rhabdoid tumors led to an equally surprising finding: the genomes were diploid and had an average of only four base pair changes across the exome, and a single recurrently mutated gene was identified – SMARCB1. Consequently, not only did cancer rapidly result from SMARCB1 loss, but the mechanism was novel as the genome otherwise seemed nearly pristine.

Subsequent study of the underlying mechanisms in my own laboratory revealed that SMARCB1/INI1 mutation resulted in unopposed activity of the EZH2-containing Polycomb Repressor Complexes and a potential therapeutic vulnerability via targeting of EZH2. With this discovery as a foundation, clinical trials of newly developed EZH2 inhibitors were pursued and it was less than a decade later that FDA approval came for use of an EZH2 inhibitor—Tazemetostat—in SMARCB1-mutant epithelioid sarcomas.

A New Era of Discovery

This story is just one example of the potential power of studying childhood cancers. Not only did the work yield mechanistic insights into cancer development, it led to an FDA approval for a new treatment of an adult cancer as well.

We are now poised at the brink of a new era of pediatric cancer discovery and therapies. To truly take advantage of this opportunity, now more than ever it is critical that we work together as a national and global scientific community to explore new biology, uncover new mechanisms and

vulnerabilities, and develop new tools in our armamentarium to advance cures for childhood and adult cancers alike.

This AACI Commentary *is adapted from Dr. Roberts' presentation at the 2020 AACI/CCAF Annual Meeting, where he moderated a panel discussion entitled, "Lessons from Pediatric Cancer: Genomics, Targeted Therapies, and Survivorship". Dr. Roberts was joined by* ***Smita Bhatia, MD, MPH****, Professor & Director, Institute for Cancer Outcomes & Survivorship, O'Neal Comprehensive Cancer Center at the University of Alabama at Birmingham;* ***Kimberly Stegmaier, MD****, Professor of Pediatrics, Harvard Medical School Dana-Farber Cancer Institute, Harvard Medical School; and,* ***Jinghui Zhang, PhD****, Chair of Department of Computational Biology, Comprehensive Cancer Center, St. Jude Children's Research Hospital.*

[1]Ma, X., Liu, Y., Liu, Y. et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. Nature 555, 371–376 (2018).

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