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AACI Commentary

Joining Forces to Drive Progress Against Pediatric Cancer

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Commentary Overview

- Cancer remains the number one cause of death by disease for children in the U.S., and it can take decades in a research lab to understand mechanisms and develop new treatments – underscoring the need to identify vulnerabilities and translate them into better treatments.

- Through the Pediatric Cancer Dependencies Accelerator, the Broad Institute of MIT and Harvard, Dana-Farber Cancer Institute, and St. Jude Children's Research Hospital have joined forces in a collaboration that is designed to leapfrog barriers in the treatment of childhood cancers to make rapid progress.

- The first year of the project has already identified mechanistic and potentially therapeutic insights in cancers with some of the worst outcomes – with ongoing work to expand cancer vulnerability screens, develop novel models for research, and identify single and combinatorial treatment options.

- The exchange of ideas between institutions, interest groups, and investigators is fueling progress at a rate no one institution could achieve alone.

Alone, a comprehensive cancer center has the necessary tools, technology, and personnel to make important advances toward understanding and treating cancer. But what if two comprehensive cancer centers joined forces with one of the world's top research institutes? What could we accomplish?

When the world-class strengths of different institutions are united to answer the same questions and tackle the same problems, they can achieve far more than any one institution alone. By leveraging the expertise and capabilities of the Broad Institute of MIT and Harvard, Dana-Farber Cancer Institute, and St. Jude Children's Research Hospital, we kickstarted the Pediatric Cancer Dependencies Accelerator. This large-scale collaboration aims to transform and accelerate the identification of vulnerabilities in pediatric cancers and translate them into better treatments. Through this robust approach we have brought together remarkable innovation in mapping dependencies in cancer with in-depth experience with pediatric cancer to enable a vision of transformative progress.

The collaboration is supported by joint funding by all three institutions of more than $60 million over five years. This investment is supporting infrastructure development and scientific work by a team currently composed of more than 100 collaborating investigators, data scientists, trainees and project management staff.

Despite many advances, cancer remains the number one cause of death by disease for children in the U.S. It can take decades in a research lab to understand mechanisms and develop new treatments. Through collaborative efforts such as this project, we believe we can leapfrog barriers to rapidly identify therapeutic vulnerabilities in childhood cancer and translate those into targeted therapies in the clinic much faster.

Would you like to contribute a pediatric cancer cell line model for consideration for dependency screening? Please contact PedDepOps@broadinstitute.org.

Addressing Critical Gaps in Knowledge

By combining the intellectual leadership, technical expertise, and institutional resources of these three institutions, our collaboration is designed to address critical gaps in knowledge related to the biological basis of childhood cancer and how it might more effectively be treated. Launched in 2022, the Pediatric Cancer Dependencies Accelerator has already spurred progress in the development of new treatments for aggressive childhood cancers by:

- Developing and deploying genome-scale screening genetic perturbation approaches to identify vulnerabilities (dependencies) in a range of high-risk childhood brain, solid and blood cancers.
- Leveraging emerging technologies to characterize the genetic and epigenetic landscape of pediatric cancers.
- Amassing pediatric in vitro models from around the world and developing models where none had currently existed for high-risk childhood cancers that have poor outcomes.
- Identifying effective combination therapies with novel drug screening and functional genomics approaches and shortening the timeline for developing new therapies.
- Developing computational approaches to mine and integrate data and building innovative software tools for data sharing.

This collaboration builds on groundbreaking research initiatives from each of our institutions. Over the past decade, the St. Jude-Washington University Pediatric Cancer Genome Project and other large-scale sequencing efforts have yielded rich insights into the genomic landscape of pediatric cancers, including the understanding that most disease-driving genetic mutations are not currently druggable. Developing precision therapies will require identifying cancer dependencies and vulnerabilities that are not revealed by mining genomic datasets alone.

The Cancer Dependency Map (DepMap) Initiative developed at the Broad Institute in collaboration with Dana-Farber investigators has developed extensive, world-class datasets and computational infrastructure that has impacted research and target discovery programs worldwide. Launched in 2015, the Pediatric Cancer Dependency Map Project (PedDep) served as a proof-of-concept to apply the DepMap approach to childhood cancers. For example, large-scale CRISPR and drug sensitivity screens have now been effectively deployed at scale to identify vulnerabilities in many adult cancers, and proof-of-principle has been established that these approaches can also identify dependencies in childhood cancers, which often have much simpler genomes.

Collaboration Progress: Year One

In the first year of this project, we established cross-functional groups of investigators from the Broad Institute, Dana-Farber, and St. Jude which focus on three core disease areas (brain tumors, hematological malignancies and solid tumors) and two non-disease specific interest areas (pan-cancer and data science). These groups integrate expertise in childhood cancer, cancer biology, vulnerabilities, functional genomics, cancer genomes, large-scale sequencing, and computational analysis. Through these active working groups, we are enhancing and accelerating progress via technological innovation and by combining unique strengths and resources to address the greatest challenges toward understanding and treating pediatric cancers.

By screening models of pediatric cancers with some of the worst outcomes and by expanding the representation of pediatric cancer cell lines in the DepMap, we have already gained mechanistic and potentially therapeutic insights from our first vulnerability screens. As an example, we can now screen at genome-scale models that were previously not thought to be screen-able. The integration of drug screening, coupled with systematic identification of resistance mechanisms, and the addition of epigenetic characterization of models are also already generating substantial insights.

The exchange of ideas between institutions, interest groups and even individuals is fueling progress in ways we hoped – but weren't sure – were possible. Twice a month, scientists from all three institutions come together to talk about projects, processes, technologies, and new findings. Each specific interest group meets regularly, our joint steering committee meets monthly and we, as study PIs, meet monthly. Through these meetings there is an enormous amount of real-time collaboration and inter-institutional learning taking place. Using this time to learn from each other has been invaluable when we look at what we have already accomplished – and what is on the horizon.

The Pediatric Cancer Dependencies Accelerator is outperforming our expectations and stands as a testament to how much can be gained through collaboratively uniting diverse expertise from multiple centers to pursue opportunities with transformative potential for the field. Through this collaboration, we are committed to finding new therapeutic options for the most intractable cancers of childhood. To do that, we've committed to working together. What can we accomplish when we join forces? We can't wait to find out.

Our Mission

The Association of American Cancer Institutes (AACI) represents over 100 premier academic and freestanding cancer centers in the United States and Canada. AACI is accelerating progress against cancer by enhancing the impact of academic cancer centers and promoting cancer health equity.

About AACI *Commentary*

To promote the work of its members, AACI publishes *Commentary*, a monthly editorial series focusing on major issues of common interest to North American cancer centers, authored by cancer center leaders and subject matter experts.