Fighting for the Few: Advancing Research in Rare Childhood Cancers

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Abstract

Recently, the Cancer Burden Across Indiana Symposium hosted by Indiana University's Simon Comprehensive Cancer Center brought stakeholders together to address the cancer burden across Indiana. This event provided members of the Pollok Lab in the Herman B Wells Center for Pediatric Research with the opportunity to present data focused on osteosarcoma, a devastating pediatric bone cancer that often arises during the adolescent growth spurt and urgently requires better treatment options. This reflection highlights the significance of our findings, places our research within the broader field of pediatric oncology, and underscores how community-engaged research and advocacy are essential to progress. We discuss the urgent need for novel therapies, share key pieces of promising data, consider implications for policy and future research, and emphasize how collaborative efforts like these ultimately serve the well-being of families and communities across Indiana.

While childhood cancer is the leading cause of death by disease in children, its occurrence is considered rare, complicating the development of new therapies. From the 1970s until the 1990s, outcomes improved dramatically for children diagnosed with solid tumors (LaQuaglia, M. P. & Gerstle, J. T., 2022). However, for some types of cancer, such as osteosarcoma and rhabdomyosarcoma, there has been little to no improvement in outcomes since. The standard of care for many pediatric cancers was established decades ago, and outcomes remain poor in cases of metastasis or relapse. Further, the toxicity of the commonly used therapies for children with cancer leave a large percentage of them with a lifetime of medical conditions and challenges, such as secondary cancers, infertility, heart disease, kidney disease, and mental health challenges (Suh et al., 2020). There is rapid progress in developing improved methods of early diagnosis, prevention, and treatments for many types of adult cancers; however, there is a critical gap in developing new therapies for children, adolescents, and young adult patients. Therefore, there is a critical need for novel therapies specifically for childhood cancers in which earlier intervention will be key, representing a time before the tumor burden becomes unmanageable and refractive to therapy.

One of the difficulties in this field is the fact that tumors in children are very diverse at the genetic and molecular level, making it challenging to design “one-size-fits-all” targeted treatments. Our research delves into the genomic complexities underlying osteosarcoma. A key factor contributing to osteosarcoma progression is DNA replication stress. Replication stress occurs when DNA replication is hindered, leading to stalled replication and potential genomic instability. While moderate levels of replication stress can promote tumor growth, critically high levels can trigger death of the cancer cells, presenting a potential therapeutic opportunity. Bromodomain and extra-terminal domain (BET) proteins play a

critical role in regulating replication stress (Wang et al., 2023). We hypothesized that drugs that inhibit the activity of BET proteins, known as BET inhibitors, could increase levels of replication stress in the cancer cells, causing the cells to die in a process known as apoptosis. Before this theory could be tested in cancer patients, it must be tested in the lab using models.

Our lab utilizes in vitro methods such as osteosarcoma cell lines, as well as those that examine how patient tumors grown in mice respond to treatment. Cell lines allow us to treat cancer cells with a range of doses of the BET inhibitors to measure the ability of the drugs to inhibit cancer cells from growing. We can test multiple types of BET inhibitors to compare their efficacy. While we use a variety of osteosarcoma cell lines, including metastatic lines, and multiple inhibitors to ensure the results are consistent, cell lines do not fully capture the complexity of a tumor inside the body. Therefore, we also utilize patient-derived xenografts (PDXs) which involve typically small cancerous tumor specimens removed from a patient during surgery. These specimens are deidentified and are only obtained after sufficient tumor tissue is obtained for diagnosis and clinical trial studies. The specimen obtained by the Pollok lab is implanted into mice that lack a functional immune system. In this model, the tumor cells expand, are characterized at the molecular level, and are used for testing the efficacy and safety of new therapies, such as BET inhibitors. It is critical that our research is representative of and beneficial to all communities, so we are committed to testing PDXs from patients of diverse backgrounds, ethnicities, genders, ages, and treatment histories within the pediatric population. Our research objective was to evaluate the efficacy of clinically relevant BET inhibitors in osteosarcoma. We combined screening in cancer cell lines with molecular profiling and validation using PDXs. This allowed us to assess the efficacy of several BET inhibitors in these models and investigate the molecular changes induced by BET inhibition. Putting the data together, we evaluated BET inhibitors across different disease stages and prior treatment histories, reflecting real-world clinical scenarios. Our findings demonstrate compelling evidence for the therapeutic potential of BET inhibition in osteosarcoma. The cell line data showed growth suppression at clinically relevant doses of multiple BET inhibitors. Furthermore, one of the inhibitors significantly reduced tumor growth in numerous osteosarcoma PDX tumor models. This broad effectiveness across diverse patient samples is highly encouraging for future clinical therapeutic application.

While data such as this brings hope for improved outcomes for future cancer patients, there is much more work to do. In our future work, we will continue to investigate targeted therapies such as BET inhibitors, as well as combination therapies that involve different types of anticancer drugs working together to address tumor heterogeneity and invasion. Legislative support will be vital for realizing the full potential of precision medicine initiatives that integrate molecular techniques into patient care decisions . Policies that support data sharing and collaborative research across institutions can accelerate the identification of new biomarkers and therapeutic targets, ultimately benefiting patients sooner.

Multi-stakeholder engagement is key for achieving meaningful change in outcomes for

childhood cancer. However, meaningful engagement requires multi-stakeholder agreement on a model for working together, including agreed-upon processes for engagement and clear mission alignment. In addition, equitable engagement for all stakeholders is key, and a working model should aim for co-production. Elevate Childhood Cancer Research and Advocacy (Elevate), an Indiana incorporated nonprofit, proposed such a model at the Cancer Burden Across Indiana Symposium (Spoon et al., 2024). Previous work suggested that such a model should include recognition of eight key stakeholders (i.e., Product Makers, Principal Investigators, Program Managers, Policy Makers, Payers, Providers, Press, and the Public), with Patient Advocacy Groups serving as connectors, providing critical social capital to get things done. Patient Advocacy Groups (PAGs) have been an integral part of driving multi-stakeholder engagement in a range of rare diseases, including childhood cancers, such as rhabdomyosarcoma, osteosarcoma, neuroblastoma, and retinoblastoma.

For example, advocates play an important role in connecting patients with Principal Investigators for research (May et al., 2021; Merkel et al., 2106).

Advocates also regularly serve as catalysts, often initiating projects, providing seed money to launch initiatives, and helping build coalitions and consortiums (Moitra et al., 2017). The Indiana Pediatric Cancer Coalition (IPCC) was formed by a group of Hoosier families and nonprofits (i.e., Elevate, LG-30, Mighty Mason) who have been directly impacted by childhood cancer. IPCC is dedicated to fostering collaboration among advocates, increasing funding, and driving medical advancements.

The Coalition strives to ensure that the highest quality diagnostics, treatments, and survivorship care are accessible to children and families impacted by pediatric cancer throughout Indiana. IPCC envisions becoming a leading integrative resource for childhood cancer research and advocacy. Its goal is to drive the development of cutting-edge treatments that save lives, provide hope, and ensure a healthier future for Hoosier children and young adults. IPCC has been instrumental in expanding the Indiana Cancer Plan to include objectives for children, adolescents, and young adults impacted by cancer. In addition, IPCC works to actively bring about awareness through annual advocacy days at the statehouse, which include a range of stakeholders. In 2023, efforts by this group of advocates resulted in legislators drafting legislation to better understand childhood cancer research in Indiana through the Rare Disease Advisory Council. In 2025, persistent efforts to educate policy makers about the brilliant capacity of pediatric cancer researchers in Indiana and the desperate need for new therapies resulted in the passage of HB1453, which created a fund for pediatric cancer research in the state.

It is only with strong collaboration that we can make progress against childhood cancers. Researchers, advocacy groups, policy makers, and the community each have a crucial role to play. Scientists investigate disease mechanisms and new treatment possibilities; advocates connect families to research and amplify their voices; lawmakers create policies and funding streams to sustain progress; and communities ensure that rare pediatric cancers remain a public priority. Collaboration is key to developing more safe and effective therapies with the ultimate goal of giving children and young adults with cancer a chance to thrive. The lives of patients depend on our collective actions, and together we can transform today's hope into tomorrow's cures.

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