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PERSPECTIVE

# Pediatric sarcomas: challenges and opportunities

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**Pediatric sarcomas are a heterogeneous group of rare mesodermal malignancies. These cancers, which affect children from infancy through adolescence and young adulthood, are in general challenging to treat with currently available therapies. Biologically, many are characterized by quiet genomes, fusion oncoproteins, immune "cold" microenvironments, and vast epigenetic deregulation that contributes to diverse and complex mechanistic drivers. Multifaceted advancements in research strategies, including high-throughput screening, new model systems, surfaceome profiling, and study of oncogenic fusion condensates have led to new opportunities for understanding the biology of pediatric sarcomas. To continue to make progress for these difficult to treat cancers, it will be critical to continue to improve access to bioinformatic data, approach patient care using innovative clinical trial frameworks, and foster interdisciplinary partnerships among medicinal chemists, scientists, clinicians, advocates, and industry partners.**

Sarcomas represent a diverse group of malignancies arising from primitive mesenchymal origins that typically occur in bone or soft tissue. Sarcomas of childhood represent ~21% of pediatric solid tumors; however, despite their rarity, these tumors are responsible for a large burden of morbidity and mortality among pediatric cancers. Particularly in metastatic or relapsed settings, sarcomas are extremely challenging to cure with currently available therapies.

Though more than 50 histologic subtypes of sarcomas exist, some are more prevalent in pediatric patients. Of pediatric bone sarcomas, osteosarcoma (OS) is the most common diagnosis, with 600 new cases per year in the United States, followed by Ewing sarcoma, which represents 450 new cases per year (Gorlick et al. 2013). The most common soft tissue sarcoma affecting children is rhabdomyosarcoma, of which ~60% of cases, or 350 new patients in the United States per year, are pediatric (Sultan et al. 2009). Nonrhabdomyosarcoma soft tissue sarcomas, which include synovial sarcoma, gastrointestinal stromal tumor, leiomyosarcoma, and pleomorphic

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liposarcoma, among other rare subtypes, represent an even smaller subset of pediatric tumors in the sarcoma group (Fig. 1; Lupo et al. 2021).

With some rare exceptions, sarcoma treatment is multimodal, involving cytotoxic chemotherapy and surgery and/or radiation for local control. Cooperative group clinical trials, many of which are run in the United States through the Children's Oncology Group (https://childrensoncologygroup.org/), and international through the European Organization for Research and Treatment of Cancer (https://www.eortc.org/) and others, have led to some improvements over time in pediatric sarcoma outcomes. This is true, for example, in nonmetastatic Ewing sarcoma, where increasing intensity of chemotherapy by decreasing the interval between cycles has led to improved outcomes and, with the addition of filgrastim, no significant increases in treatment-related toxicity (Womer et al. 2012). With long-term follow-up of these patients now completed, the overall survival advantage of patients treated with dose compression extends out to 10 years, and these findings have now been replicated in a European trial, making this the definitive standard of care for nonmetastatic Ewing sarcoma (Brennan et al. 2022).

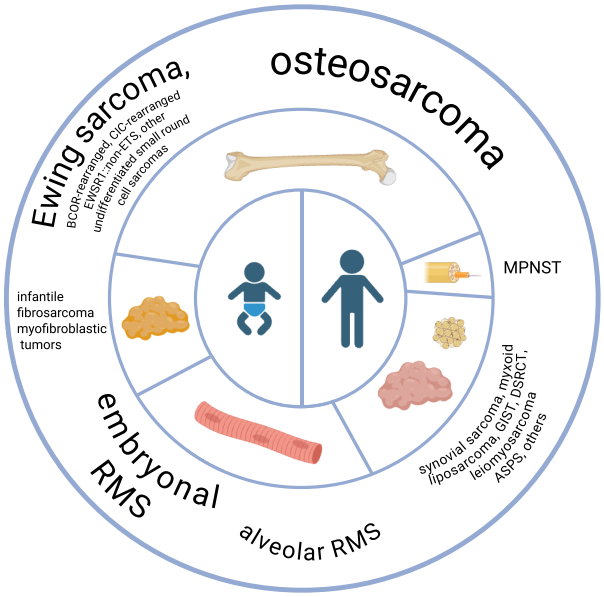


**Figure 1.** Schematic of pediatric sarcoma etiologies. Tumor names overlapping the *left* side of the circle represent those most common in young children, with the *right* side representing those most common in adolescent/young adults. Font size reflects the relative percentage of overall pediatric sarcoma cases. Bone tumors represent 43% of pediatric sarcomas, encompassed by osteosarcoma (60%) and Ewing sarcoma/other undifferentiated small round cell sarcomas (40%). Soft tissue tumors represent 57% of pediatric sarcomas, with RMS at 40%, miscellaneous soft tissue sarcomas (including synovial, myxoid liposarcoma, etc.) at 42%, infantile fibroblastic/ myofibroblastic tumors at 7%, soft tissue Ewing sarcoma at 6%, and MPNST at 5%. (RMS) Rhabdomyosarcoma, (GIST) gastrointestinal stromal tumor, (DSRCT) desmoplastic small round cell tumor, (ASPS) alveolar soft part sarcoma, (MPNST) malignant peripheral nerve sheath tumor. Created in BioRender.com (Ferrari et al. 2011; Sultan et al. 2025).

For many sarcoma subtypes, however, improvements in disease-free survival have stagnated for decades. This is particularly true in the setting of metastatic disease, but also relapsed/refractory disease, where there are limited effective treatment options available (Hernandez Tejada et al. 2020). For Ewing sarcoma, dose intensification strategies have been trialed, but have not improved survival for metastatic disease patients (DuBois et al. 2023). Similarly, metastatic osteosarcoma patients have a dismal long-term prognosis of <30% with standard therapies, suggesting therapeutic resistance (Smeland et al. 2019). Rhabdomyosarcoma and nonrhabdomyosarcoma soft tissue sarcomas fare similarly, with metastatic disease at presentation associated with a drastic reduction in long-term survival; however, in relapsed nonrhabdomyosarcoma soft tissue sarcomas, a signal of response to tyrosine kinase inhibitors in some phase I/II trials for patients with refractory disease has led to plans for incorporation of these agents into future up-front trials (Oberoi et al. 2023).

An understanding of the molecular drivers of pediatric sarcomas has deepened in recent years. Though diverse in disease location and cell type/histology, pediatric sarcomas are enriched in driver fusion oncoproteins, which are found in 17% of all cancers but a striking 40% of sarcomas (Brien et al. 2019; Wachtel et al. 2024). Fusion oncoproteins in pediatric sarcomas are comprised of two distinctive categories: fusions involving receptor tyrosine kinases, and fusions involving de novo oncogenic transcription factors or chromatin regulators. The successes of targeted therapy for tyrosine kinase fusions represent one of the biggest accomplishments in targeted therapeutics for pediatric oncology in the modern era. These include the use of larotrectinib for treating *NTRK*-rearranged congenital fibrosarcoma, BRAF inhibitors in some spindle cell sarcomas, and imatinib or pazopanib for pediatric dermatofibrosarcoma protuberans with *PDGFB* fusions, among others (Anderson et al. 2012; Drilon et al. 2018; Kao et al. 2018).

In the second category, fusions involving transcriptional or chromatin regulators, there are several well-studied pediatric sarcomas that are hallmarks of this biology. A disease-defining characteristic of Ewing sarcoma is the presence of the t(11;22) *EWSR1::FLI1* fusion, which encodes the EWSR1::FLI1 oncogenic transcription factor. EWSR1::FLI1 binds GGAA microsatellite regions and recruits BAF complexes and other coactivators to create de novo enhancers, driving aberrant transcription and oncogenesis (Delattre et al. 1992; Riggi et al. 2014; Boulay et al. 2017). Likewise, alveolar rhabdomyosarcoma, a rhabdomyosarcoma subtype with dismal survival, is characterized in ~80% of cases by the presence of the t(2;13) or t(1;13) *PAX3/PAX7–FOXO1* fusion, which results in the DNA binding domain of PAX3 or PAX7 coupled to aberrant activation of the FOXO1 transcription factor and downstream oncogenic transcriptional programs (Barr 2001; Sorensen et al. 2002). In rhabdomyosarcoma, the presence of the fusion itself is associated with inferior survival (Haduong et al. 2022). Synovial sarcoma, a rare but

aggressive nonrhabdomyosarcoma soft tissue sarcoma that is commonly diagnosed primarily in the adolescent/young adult (AYA) age group, contains a pathognomonic t(X;18) translocation between *SS18*, encoding a BAF complex subunit, and one of three transcriptional repressor genes: *SSX1*, *SSX2*, or *SSX4* (Clark et al. 1994). The SS18::SSX fusion evicts wildtype SS18 and retargets BAF to aberrant sites on chromatin, driving epigenetic dysregulation and tumor formation (Kadoch and Crabtree 2013).

Fusion proteins in cancer, including many of those involved in pediatric sarcomas, are enriched for a partner that contains an intrinsically disordered region (IDR), such as a transcription factor or chromatin coregulator (Hegyi et al. 2009). IDRs have increasingly been the subject of investigation in phase-separation condensate formation, contributing to their role in gene regulation (Quiroga et al. 2022). Additionally, fusion-driven sarcomas tend to have fewer collaborating genomic events, and hence have limited druggable oncoproteins for targeting with current therapies (Gao et al. 2018). Thus, a large emphasis of recent research efforts has been to employ novel chemistry to target driver fusion oncoproteins directly, their chromatin complex partners, or their specific condensate-related chromatin-regulatory mechanisms.

In March 2025, a group of experts spanning sarcoma biologists, chemical biologists, pediatric oncologists, pharmaceutical company representatives, and patient advocates met for 3 days at the Banbury Center of Cold Spring Harbor Laboratory to discuss the challenges in therapeutic target development for pediatric sarcomas. With emphasis on advances in understanding unique disease drivers in sarcomas, as well as therapeutic modulation of challenging protein targets, the discussion provided a forum for addressing critical questions and opportunities for improvement of outcomes in these difficult to cure pediatric malignancies. This white paper highlights the key principles and tools for discovery identified by the attendees to advance cures for young people with sarcomas.

## Clinical challenges in advancing treatment for pediatric sarcomas

### *Identification of molecular subtypes highlights the rarity of diagnoses*

Sarcomas represent only 12% of pediatric malignancies. Within many pediatric sarcomas there are new subtypes that have been recognized as distinct. For example, Ewing sarcoma with alternative FUS::ETS family member fusions and small round cell sarcomas previously described with the historical term "Ewing-like sarcoma," such as *BCOR*-containing fusions, or CIC::DUX4 rearranged sarcomas are now being recognized with next-generation sequencing methodologies (Underdown et al. 2025). While presenting opportunities for tailoring targeted therapies, these deeper characterizations of what were once thought to be single disease entities are highlighting challenges in building biorepositories of tumor samples for molecular characterization and model generation as well as for the development of clinical trials with limited patients diagnosed each year.

### *Adolescent and young adult (AYA) patient populations add to complexity of clinical trials*

Many sarcomas are classified as AYA malignancies, typically defined as occurring in teenagers and up to age 39; these young people face additional obstacles in treatment and in accessing clinical trials (Burningham et al. 2012). AYA patients with sarcomas have traditionally been treated in a range of settings across pediatric and adult institutions, with only recent efforts made to streamline care between pediatric oncology and medical oncology groups. Clinical trials, therefore, typically underenroll the AYA population, leading to challenges in studying these individuals' clinical course and collecting their tumor samples to support basic and translational research (Shaw et al. 2014; Whiteway et al. 2023). Supporting the realities of these challenges, multiple pediatric sarcoma diagnoses, including Ewing sarcoma, osteosarcoma and nonrhabdomyosarcoma soft tissue sarcomas, have inferior outcomes in AYA patients compared to children, highlighting a gap in knowledge and treatment of these patients (Keegan et al. 2024).

### *Sparsity of biomarkers*

Most biomarkers currently integrated into clinical practice for prognostication and/or treatment stratification in pediatric patients with sarcoma are based on stage/location, histology, or response to cytotoxic chemotherapy (Bielack et al. 2002; Kovar et al. 2016; Metts et al. 2024). There are numerous efforts underway to identify molecular biomarkers for risk stratification. For example, *TP53* mutations in rhabdomyosarcoma are associated with inferior prognosis (Shenoy et al. 2021; Shern et al. 2021). Interestingly, fusion partner subtypes in pediatric sarcomas, including Ewing sarcoma and synovial sarcoma, have not been previously validated as prognostically significant. However, in rhabdomyosarcoma, *FOXO1*-containing fusions are an adverse prognostic marker (Hibbitts et al. 2019). Specifically, it was recently shown that PAX3::FOXO1 fusion status (compared with PAX7::FOXO1) is an independent adverse prognostic factor for metastatic disease (event-free and overall survival) and localized disease (event-free survival only) (Koscielniak et al. 2025). Further efforts are underway to validate molecular biomarkers for patient stratification, such as *STAG2* loss in Ewing sarcoma, or *MYC* amplification in osteosarcoma (Shulman et al. 2022; Gillani et al. 2025; Marinoff et al. 2026). In addition to these classifications using tumor tissue directly, there are emerging efforts to utilize liquid biopsy to risk stratify patients with sarcoma and surveil for minimal residual disease (Shulman and Crompton 2025). Acquiring sufficient data to prospectively validate these findings in pediatric sarcomas remains a challenge.

*Metastasis and treatment failure*

Children with pediatric sarcomas are often diagnosed with metastasis because they spread rapidly and present with symptoms that can mimic common benign conditions of childhood, such as minor sports injuries or growth-related pain during adolescence. Even in the localized disease setting, sarcomas are considered a systemic disease, with micrometastases that, when left untreated, lead to distant relapse (Link et al. 1986). The presence of metastasis is a poor prognostic factor across bone and soft tissue sarcomas of childhood (Pappo et al. 1995; Bielack et al. 2002; Rodriguez-Galindo et al. 2003; Burningham et al. 2012). Thus, a clinical challenge recognized for young people with sarcoma is how to more adequately treat aggressive metastatic disease.

*Treatment-related late effects*

As the number of survivors of pediatric sarcomas grow, there is increasing awareness of toxicities that arise from standard chemotherapy treatment. Sixty percent to 90% of all childhood cancer survivors suffer from one or more chronic health conditions; accumulation of chronic health disorders predicts early mortality in these individuals (https://www.cancer.gov/types/childhood-cancers/late-effects-hp-pdq). Anthracyclines, a mainstay of many sarcoma regimens in high doses (>300 mg/m$^2$ body surface area), have been associated with higher rates of cardiac toxicity, including cardiomyopathy, in childhood cancer survivors (Armstrong et al. 2015). Fertility impairment in both males and females occur with exposure to high doses of cisplatin and cyclophosphamide, and rates of second malignant neoplasms are elevated in children after exposure to radiation used for local control, in addition to secondary acute myeloid leukemias from exposure to cyclophosphamide and etoposide. Furthermore, there are significant physical limitations and challenges associated with surgical resection of sarcomas in children, including amputations and limb salvage procedures (Khan et al. 2025). The increased recognition of late-term morbidity and mortality from effects of therapy in pediatric sarcomas has led to improved surveillance guidelines, as well as incentives to develop new targeted therapies.

## Biological challenges in advancing treatment for pediatric sarcomas

*"Undruggable" oncogenic drivers*

A substantial subset of pediatric sarcomas are driven by oncogenic fusions, which are difficult to target with small molecules due to their biochemical IDRs (Gröbner et al. 2018; Ma et al. 2018; Liu et al. 2023). These gene fusions typically encode aberrant transcriptional regulators, such as EWSR1::FLI1 in Ewing sarcoma, PAX3::FOXO1 in alveolar rhabdomyosarcoma, and SS18::SSX in synovial sarcoma, which reprogram the epigenome and transcriptional circuitry to maintain an undifferentiated, proliferative cell state (Linardic 2008; Kovar 2010; Ahn 2013). Despite their central role in disease initiation and maintenance, these fusion oncoproteins have remained largely undruggable, lacking the defined ligand-binding pockets or enzymatic activity exploited by conventional small molecules. In the absence of direct inhibitors, therapeutic strategies have shifted toward disrupting protein complexes that facilitate the transcriptional activity of these fusions or targeting their downstream effectors (Erkizan et al. 2009; Michel et al. 2018; Brien et al. 2018). However, the broad essentiality of these cofactors and the redundancy of transcriptional networks pose substantial barriers to selective targeting. Fusion-driven transcription factors thus represent a foundational challenge in the development of selective therapies for pediatric sarcomas, though recent advances in medicinal chemistry are beginning to overturn this view, as discussed below (see "Next-Generation Chemistry Targeting 'Undruggable' Proteins").

*Immune evasion and cold tumor microenvironment*

A second major biological challenge is the intrinsically immune-evasive nature of pediatric sarcomas, which exhibit features of so-called "cold tumors." In contrast to adult cancers, most pediatric sarcomas harbor a low mutational burden, resulting in limited neoantigen generation and weak immunogenicity that fails to elicit robust T-cell responses (Gröbner et al. 2018; Ma et al. 2018). Instead of being infiltrated by cytotoxic lymphocytes or antigen-presenting dendritic cells, these tumors are predominantly populated by immunosuppressive myeloid cells, including tumor-associated macrophages and myeloid-derived suppressor cells, that actively suppress antitumor responses(Fujiwara et al. 2011; Stahl et al. 2019; Fujiwara et al. 2021; Tumino et al. 2021). These features collectively pose major barriers to effective immune engagement and limit the success of currently available immunotherapies in pediatric sarcomas, suggesting a need to investigate immune augmentation strategies to mitigate this challenge.

*Developmental and epigenetic plasticity*

The developmental origins of pediatric sarcomas introduce a distinct layer of biological complexity, reflecting their emergence from undifferentiated mesenchymal or progenitor-like cells (Filbin and Monje 2019; Savary et al. 2022). Unlike adult malignancies, which typically arise from more differentiated tissues and accrue somatic mutations progressively over time, pediatric sarcomas often originate from developmentally immature cells that retain significant epigenetic plasticity and incomplete lineage specification (Tanaka et al. 2014; Filbin and Monje 2019; Danielli et al. 2023). This developmental immaturity contributes to a permissive chromatin landscape and flexible transcriptional programs, enabling tumor cells to transition between proliferative, migratory, and drug-tolerant states (Franzetti et al. 2017; Patel et al. 2022). Such plasticity underlies key hallmarks of sarcoma progression, including metastatic dissemination and therapeutic resistance. Fusion oncoproteins characteristic of

many pediatric sarcomas frequently co-opt these developmental pathways to enforce self-renewal and block lineage commitment, thereby stabilizing a tumorigenic cell identity. Recent single-cell transcriptomic and epigenomic studies have shown that pediatric sarcomas exist along a spectrum of transcriptional states, rather than fixed cell types, complicating efforts to define discrete therapeutic vulnerabilities (Aynaud et al. 2020; Wrenn et al. 2023; Danielli et al. 2024). Consequently, effective therapeutic strategies must overcome not only the oncogenic drivers of transformation but also the intrinsic developmental adaptability that enables tumor persistence and relapse.

## Emerging tools and incentives for pediatric sarcoma discovery

### *High-throughput dependency screening efforts*

Recent expansion of functional genomic and chemical library screening in pediatric sarcoma models is beginning to address key biological challenges by enabling a deeper understanding of disease mechanisms and uncovering previously unrecognized therapeutic targets. Multiple groups have capitalized on these technologies in order to highlight targets across cancer types spanning three continents (Behan et al. 2019; Dharia et al. 2021; Sun et al. 2023). One such effort is the Pediatric Cancer Dependency Map Accelerator (PedDep; https://www.peddep.org), a collaborative initiative driven by the Broad Institute, Dana-Farber Cancer Institute, and St. Jude Children's Research Hospital, that is integrated into the Broad Institute's Cancer Dependency Map. A major goal of PedDep is to expand the subtypes of pediatric sarcomas screened, including now many Ewing sarcoma, rhabdomyosarcoma, osteosarcoma, synovial sarcomas, clear cell sarcomas, and epithelioid sarcomas, among others. PedDep is seeking to integrate genome-scale loss-of-function CRISPR/Cas screening from cancer cell lines with next-generation sequencing, including whole genome, transcriptome and epigenetic characterization, in addition to single agent and combination small molecule screens. Efforts are also underway to increase screening in minimally passaged patient-derived cell lines and 3D tumoroid models for diseases where traditional cell line models are not available.

### *Imaging of oncofusion condensates*

Advances in imaging technologies, such as superresolution microscopy and live-cell single-molecule imaging, are transforming how fusion oncoproteins are studied at the biophysical and subcellular levels (McSwiggen et al. 2019). For instance, EWSR1::FLI1 and several other fusion oncoprotein drivers have been shown to form dynamic assemblies within the nucleus, which are essential for their transcriptional activity and chromatin remodeling function. These assemblies are driven by multivalent IDR–IDR interactions of the fusion oncoproteins and can develop into phase-separated condensates under specific conditions (Chong et al. 2018; Chong et al. 2022; Selig et al. 2025). These findings suggest that the oncogenic activity of sarcoma fusion proteins may depend on biophysical properties that are amenable to perturbation. The ability to visualize and quantify such behaviors in live cells offers a powerful platform to test hypotheses about protein organization, target engagement, and inhibitor response in physiologically relevant contexts (Tripathi et al. 2023).

### *Advances in immunotherapies and other targeted approaches*

In the past decade, pediatric sarcoma cell surface targets have been described in greater detail (density, disease status, expression, etc.), a necessary first step toward the application of targeted therapies for advanced disease (Gill and Gorlick 2021; Bailey 2024; Danielli et al. 2024; Mooney et al. 2024). CAR T cells, antibody-drug conjugates (ADCs), bispecific T-cell engagers (BiTEs) and targeting radiopharmaceuticals against many pediatric sarcoma cell surface targets (including but not limited to B7H3, GD2, EGFR, IL1RAP, STEAP1, and folate receptor-α) have emerged, as have areas of resistance or challenges that need to be investigated in order to realize the maximum benefit of these agents (NCT07297979) (Tian et al. 2023; Arnett and Heczey 2024; Kaczanowska et al. 2024). Understanding mechanisms to enhance tumor penetration of antibodies, nanobodies and targeted cellular therapies into pediatric sarcomas is a priority, as is understanding cell surface target heterogeneity and immunosuppressive factors that could render these therapies less effective. ADCs are often developed with adult carcinoma applications in mind and the appropriateness of the payloads utilized need to be considered for pediatric sarcomas with common targets (ineffective payload may not mean ineffective target). From an agent access standpoint, early recognition of shared surface targets between adult carcinomas and pediatric sarcomas and agents developed against these targets, such as STEAP1 (NCT04221542 and NCT07297979), may help establish timely collaboration with industry partners to test these agents in the pediatric population.

### *Next-generation chemistry targeting "undruggable" proteins*

Four converging advances in next-generation medicinal chemistry have transformed the landscape of tractable targets. First, direct chemical disruption of protein–protein interactions has proven a highly productive strategy for targeting onco-drivers considered undruggable. Recent advances include AI-10-49, which targets the CBFβ-SMMHC fusion in inv(16) AML (Illendula et al. 2015), and ziftomenib, the FDA-approved menin-KMT2A inhibitor for NPM1-mutated AML (Miao et al. 2026) that is now under clinical evaluation in KMT2A-rearranged leukemias, including pediatric patients. For fusion-driven pediatric sarcomas, this paradigm offers a direct route to antagonize the oncogenic driver itself. Second,

structure-guided drug design, now leveraging AI-based structural prediction, has provided the technical engine to identify druggable pockets on previously intractable protein targets. AlphaFold and related models now predict protein and protein-ligand complexes at near-experimental accuracy enabling virtual screening and pocket identification on targets lacking experimental structures (Jumper et al. 2021; Abramson et al. 2024). Third, targeted protein degradation has redefined therapeutic engagement by converting binding events into proteasomal elimination of the target, removing the requirement for a deep ligandable pocket or catalytic activity. Heterobifunctional degraders (PROTACs) and molecular glues now eliminate oncoproteins that classical inhibitors cannot productively engage, including transcription factors and chromatin complex subunits with intrinsically disordered regions. In pediatric sarcoma, this is exemplified by BRD9 degraders (FHD-609 and CFT8634) in clinical evaluation for SS18::SSX-rearranged synovial sarcoma (Brien et al. 2018), in which BRD9 is a selective dependency of the aberrant ncBAF complex. Fourth, chemoproteomic approaches to identify covalent modifiers of target proteins are emerging as a powerful route to ligands for difficult to target sites (Niphakis and Cravatt 2024). Because sarcoma fusion drivers often present only shallow surface pockets, such covalent strategies are particularly well suited to engaging them. Collectively, these advances are expanding the druggable space in pediatric sarcoma, bringing fusion oncoprotein drivers and their dependencies within therapeutic reach.

### *Surfaceome profiling for precision immunotherapy*

The systematic exploration of the cancer surfaceome offers new opportunities for selective targeting. Pediatric sarcomas, despite their low mutational burden, may express tumor-specific or lineage-restricted surface proteins that can be harnessed for targeted therapies, including antibody–drug conjugates, CAR T cells, or bispecific T-cell engagers. Recent efforts to comprehensively catalog surface protein expression across tumor types, especially when paired with transcriptomic and proteomic data, can reveal actionable antigens that are otherwise masked by transcript-level analyses alone (Lavoie et al. 2021; Wang et al. 2022). Collectively, these emerging platforms provide a new experimental framework to overcome the core biological barriers in pediatric sarcoma and lay the foundation for rational therapeutic development.

### *New model systems to interrogate sarcoma biology*

Model systems form the basis of many parts of cancer discovery science. In pediatric sarcomas, a diversity of models exists and are being built for answering wide-ranging questions, from interrogating tumor development in an immune competent context to preclinically testing drugs in settings closely related to patient disease. Banks of patient-derived xenograft (PDX) models have been built in the last decade by individual institutions and collaboratives of investigators that preserve the genomic qualities of multiple types of pediatric sarcomas and are accessible to investigators around the U.S. and the world (Stewart et al. 2016; Sayles et al. 2019; Dela Cruz et al. 2022). Building on this foundation, work is underway to develop iterative models of metastatic sarcomas as well as drug-resistant tumors to model tumor cell heterogeneity and to study resistance in an in vivo context (Loh et al. 2019; Nanni et al. 2019; Patel et al. 2022; Verma et al. 2024). Beyond immunocompromised mouse models, genetically engineered mouse models (GEMMs) provide an important tool for some pediatric sarcoma research, in particular for rhabdomyosarcoma, osteosarcoma, synovial sarcoma, clear cell sarcoma, and malignant peripheral nerve sheath tumor (Janeway and Walkley 2010; Hatley et al. 2012; Dodd et al. 2013; Jones et al. 2016; Langdon et al. 2021; Nirala et al. 2023; Ozenberger et al. 2023). In other pediatric sarcomas, such as Ewing sarcoma, where making GEMMs has not been successful, complementary models, including emerging zebrafish systems and humanized mouse models, are enabling new discoveries in an immunocompetent context (Minas et al. 2017; Daley et al. 2025; Vasileva et al. 2025; Dela Cruz et al. 2026). More recently, the technology to derive and manipulate induced pluripotent stem cells (iPSCs) to study early events in malignant transformation has allowed advances in our understanding of pediatric sarcomas as disorders of human development, including in the backdrop of cancer predisposition syndromes (Lee et al. 2015; Marin Navarro et al. 2018; Searcy et al. 2023; O'Donnell et al. 2025). Additionally, osteosarcoma is a common cancer that occurs in dogs, and the molecular features of the disease are similar to human patients. Therefore, the study of companion animals has allowed for a growth in our knowledge about osteosarcoma pathogenesis and response to drugs in canine clinical trials (Fan and Khanna 2015; Megquier et al. 2022).

## Summary and thoughts for the future

Addressing therapeutic challenges in pediatric sarcomas will require not only technological innovation but continued efforts on the part of the research community to collaborate, share knowledge, and translate discoveries. Several key opportunities have emerged to catalyze this progress:

### *Creating an open access platform for data and model sharing*

PedDep and related programs, including the Australian Childhood Cancer Model Atlas (https://www.hudson.org.au/ccma) (Sun et al. 2023), the Sanger Institute cancer cell line screening initiative (https://www.sanger.ac.uk/collaboration/human-cancer-models-initiative-hcmi) (Bashi et al. 2024), and other repositories, including St. Jude Cloud (https://www.stjude.cloud) (McLeod et al. 2021), the Childhood Cancer Data Initiative (https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative) (Flores-Toro et al. 2023), and the National

Institutes of Health (NIH)–National Cancer Institute (NCI) TARGET program (https://www.cancer.gov/ccg/research/genome-sequencing/target), have made significant progress in generating and integrating functional genomic data across pediatric cancer cell lines, including sarcomas. These resources have set a strong foundation for data accessibility and cross-study comparison. Looking ahead, a critical next step is the comprehensive multiomic characterization of newly established preclinical models, such as PDXs, tumoroids/organoids, and engineered cell systems, that may more accurately capture tumor heterogeneity and lineage context. Importantly, such efforts should be accompanied by centralized platforms that support not only model characterization but also the systematic sharing of preclinical experimental results. While peer-reviewed publications remain the primary vehicle for communicating scientific findings, they often favor positive results, leading to the underreporting of negative or inconclusive data. This publication bias can create duplication of efforts, obscure meaningful patterns across studies, and slow the iterative refinement of hypotheses. Dedicated repositories that capture both positive and negative outcomes, especially from in vivo preclinical efficacy studies, combination therapy screens, and pharmacodynamic biomarker efforts, would improve transparency and accelerate collective learning. These platforms could also include structured metadata (e.g., dosing regimens, model characteristics, readouts) to enable cross-study comparisons and reanalysis. Encouraging contributions from both academic and industry groups will be key to creating a truly comprehensive and sustainable resource. Ultimately, normalizing the sharing of negative results and unpublished preclinical findings will promote a more efficient and collaborative research environment, which is critical to ensure that only the most compelling therapeutics advance from preclinical investigation into human clinical trials.

### *Bridging pediatric and adult oncology through unified clinical infrastructure*

Many therapeutic agents developed in adult oncology remain untested in pediatric sarcomas, despite shared targets or pathways. One hurdle in this domain has been the formulation and access to investigational drugs. The Research to Accelerate Cures and Equity (RACE) For Children Act of 2017 requires pharmaceutical companies in the United States to provide access to relevant targeted anticancer agents for pediatric clinical trials. This legislation has led to increased opportunities for testing novel therapies in childhood malignancies (Zettler 2022), though challenges remain. Expanding trial networks that span both pediatric and adult oncology, as has already been done in some sarcoma contexts (Davis et al. 2017; Whiteway et al. 2023), could increase access to promising therapies and help address the persistent gap in clinical research for AYA patients. Moreover, integrating pediatric sarcoma biology into early-phase adult trials could enable timely assessment of efficacy in fusion-driven contexts, even when patient numbers are low. One recent successful example of this is in the case of *TRK* fusion-positive cancers, present where simultaneous trials were run in adult and pediatric patients, leading to accelerated FDA and European approval (Drilon et al. 2018). From an industry perspective, unified trials can lower barriers to entry for pediatric development, derisking investment and encouraging broader exploration of targeted therapies in younger populations. Importantly, early integration of pediatric cohorts into adult studies may accelerate pediatric labeling and reduce the time lag between adult drug approval and pediatric access, which remains a major hurdle in the current system.

### *Fostering multidisciplinary collaboration*

Breakthroughs in sarcoma therapy will increasingly rely on collaboration across disciplinary boundaries. Academic-industry partnerships are particularly essential for adapting advanced therapeutic platforms, such as antibody-drug conjugates, bispecific T-cell engagers, and targeted protein degraders, to pediatric sarcomas. While these technologies are primarily developed in industry, their successful application depends on disease-specific insights and models from academic research. Close collaboration ensures that cutting-edge modalities are guided by biological relevance and directed toward the most urgent clinical needs. Likewise, closer integration between biologists and medicinal chemists is essential for advancing the druggability of fusion oncoproteins and their associated complexes. While biologists define the mechanistic roles and structural features of these challenging targets, chemists bring the expertise to design molecules that can engage disordered regions, transient interfaces, or allosteric sites. This partnership is crucial for translating biological insights into tractable chemical matter, enabling the development of structure–activity relationships and the optimization of compounds for potency, selectivity, and in vivo performance. Without this synergy, many mechanistically promising targets may remain beyond the reach of drug development. Clinician–scientist collaborations will also be necessary to prioritize translational hypotheses with direct patient impact and to develop meaningful biomarkers for clinical trials.

Foundation and advocacy partnerships in pediatric sarcoma leading the way to provide critical funding mechanisms and forums for interinstitutional cooperation include the Osteosarcoma Institute (https://www.osinst.org), Break Through Cancer (https://www.breakthroughcancer.org), the Ewing Sarcoma Institute (https://www.ewingsarcoma.org), the Rhabdo Coalition (https://www.rhabdocoalition.org), Stand Up to Cancer (https://www.standuptocancer.org), and C-Further (https://www.c-further.org). Additionally, the US and international governments have dedicated significant resources toward multi-institution and international team science to make headway for pediatric sarcomas, including the NIH–NCI U54 collaborative grants for fusion oncoproteins (FusOnc2) program and the Cancer Research UK–NCI Cancer Grand Challenges (https://www.cancergrandchallenges.org). Continuing to build these collaborations

intentionally, through joint consortia, integrated training frameworks, or cross-disciplinary grant mechanisms, will be key to accelerating impact.

Together, these priorities underscore the need for a more interconnected research ecosystem that matches the complexity of the disease itself. As emerging tools continue to reveal new vulnerabilities in pediatric sarcomas, the challenge ahead lies in translating this knowledge into durable therapies, guided by collaboration, shared infrastructure, and a sustained commitment to bridging discovery and treatment.

## Competing interest statement

C.K. is the scientific founder, advisor to the Board of Directors, scientific advisory board member, consultant, and shareholder for Foghorn Therapeutics. C.M.L.'s spouse is a founder of Grid Therapeutics, which is evaluating therapeutic antibodies in adult lung cancers. K.M.B. is a Merck Data Safety Monitoring Committee member. F.J.R. is an employee of Deciphera Pharmaceuticals, LLC., a member of ONO Pharma. J.G. has a financial relationship with Kura Oncology, Inc. K.S. is a member of the scientific advisory board and has stock options with Auron Therapeutics. C.R.V. has received consulting fees from Flare Therapeutics, Roivant Sciences, and C4 Therapeutics; has served on the advisory boards of KSQ Therapeutics, Syros Pharmaceuticals, and Treeline Biosciences; and owns stock in Treeline Biosciences.

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