Preface

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Pediatric malignancies remain a leading cause of disease-related death in many countries, despite significant advances in therapeutic modalities initiated by Dr. Sydney Farber in the 1940s. Modern-day management of pediatric cancers encompasses a multi-modality approach that is constantly being refined and individualized resulting from advances in diagnosis, surgery, radiation, and personalized medicine. Over the span of 80 years, pediatric malignancies such as leukemia, lymphoma, and brain cancers have gone from being a death sentence in virtually all children to being treatable diseases with many patients achieving cure. The advancements in clinical medicine have been driven by key scientific discoveries. As we continue to elucidate the complex pathophysiology of pediatric cancers, we will continue to uncover additional targetable vulnerabilities of cancer leading to the development of more efficacious and less toxic therapeutic agents and approaches. This special two-issue series on pediatric cancers in *Cancer Metastasis & Reviews* includes 17 comprehensive review articles authored by leaders in pediatric oncology research that detail the exciting new directions this research is taking.

Many pediatric malignancies require a diagnosis prior to treatment initiation, in order to avoid unnecessary toxic therapy and to best individualize treatment selections. However, invasive biopsies can be difficult to obtain in children. In this issue, Weiser et al. from Albert Einstein College of Medicine and the Children's Hospital at Montefiore explore the growing evidence supporting the use of liquid biopsies in pediatric cancers. They expertly evaluate the benefits and limitations of this minimally invasive technique in common extracranial tumors and discuss the exciting new frontiers ahead for this innovative diagnostic technology.

Cancer is driven by incessant cell division and is thus commonly treated with cytotoxic (cell-killing) agents that target rapidly dividing cells. Cytotoxic cancer therapies, such as chemotherapy and radiation, have drastically improved pediatric cancer survival since their introduction in the late 1940s. However, they are highly toxic and can significantly impair patients' quality of life. It is now appreciated that the immune system plays a paramount role in preventing tumorigenesis and cancer progression. The evasion of anti-tumor immune mechanisms, in addition to rapidly dividing malignant cells, drives tumorigenesis and cancer progression. Thus, current cancer therapy development has focused on targeting immune cells and their interactions with tumor cells. In this issue, Hutzen et al. methodically discuss the development, mechanisms, and clinical applications of various FDA-approved adult immunotherapies in pediatric cancers as well as the cutting-edge immunotherapies currently in clinical trials. Another excellent review by Inaba and Pui further characterizes the critical role of immunotherapy in pediatric acute lymphoblastic leukemia (ALL). This rapidly emerging interest in harnessing the immune system to fight cancer has sparked interest in the development of T cell-based cancer therapies. While T cells mediate anti-tumor immune surveillance, tumor antigen variation and T cell inactivation within tumor micro-environment poses a challenge to T cell-based therapy development. Rauwolf and Rossig from the University Children's Hospital in Münster, Germany, provide new insights into chimeric receptor engineering in T cell therapies and other innovative solutions to recruit active T cells to tumors. Other novel therapeutic strategies explored in this issue include targeting fusion oncoproteins in sarcomas (Knott et al.), targeting genetic aberrations in renal tumors (Walz et al.), and preventing central nervous system (CNS) leukemia relapse *via* CNS-directed therapies (Chen et al.).

Another critical aspect of refining pediatric cancer therapy is recognizing pediatric cancers as biologically distinct from adult cancers. Novel cancer therapies are primarily studied in adult populations, and thus cannot be used in the pediatric setting without first understanding the etiologic, genetic, and molecular differences between adult and pediatric cancers. In this issue, Kattner et al. emphasize the need for effective

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translation of cancer therapies from adults to children, while simultaneously highlighting the importance of recognizing the biologic differences between cancers of these two populations. Spreafico et al. approach this important topic from another angle by asking whether pediatric protocols and treatments should be applied to adults with classically pediatric cancers such as Wilms tumor, medulloblastoma, and rhabdomyosarcoma.

Surgery remains a first-line treatment for many pediatric cancers. Surgical oncology has recently evolved with a focus on minimizing invasiveness, decreasing complications, and increasing postoperative function as well as quality of life. In this issue, Prof. Harold N. Lovvorn III and Dr. Hannah Phelps at Vanderbilt University Medical Center intricately explore the application of minimally invasive surgery to treat common pediatric embryological malignancies. Other surgical topics explored in this issue include the growing use of joint-preserving surgery (JPS) in pediatric osteosarcoma of the knee joint (Takeuchi et al.) and a comprehensive summary of neurosurgical approaches for a broad array of intracranial brain tumors (Aquilinia et al.).

This issue additionally features reviews on specific cancers that highlight the global impact of pediatric malignancies. Kamiyango et al. paint a vivid portrait of lymphadenopathic Kaposi Sarcoma (KS) in central and eastern Africa. The authors highlight the clinical differences in adult and pediatric KS, as well as the heterogeneous patterns of disease and

treatment responses observed in each pediatric KS phenotype. Similarly, an insightful review by Rashed et al. from the Children's Cancer Hospital in Cairo, Egypt, provides a global overview of the epidemiology, diagnosis, and treatment of pediatric diffuse intrinsic pontine glioma (DIPG).

The remaining reviews in this issue focus on recent pathophysiological discoveries and how they inform clinical care. Messenger RNA (miRNA) has long been known to act as both tumor suppressors and oncogenes in many cancers. This issue explores the novel role of miRNA as a prognostic biomarker in pediatric acute lymphoblastic leukemia (Rashed et al.) as well as miRNA dysregulation in pediatric abdominal and CNS tumors (Salomao et al.; Pezuk et. al). Matrix metalloproteinases (MMPs) are also known to be dysregulated in certain cancers. Hsiao et al. characterize MMP dysregulation and evaluate MMPs as novel therapeutic targets in childhood leukemia.

This impressive collection of reviews highlights cutting-edge research spanning the pathophysiology, diagnosis, and treatment of various pediatric malignancies. While great strides have been made in the treatment and cure of these cancers, there are many more discoveries and clinical advancements to be made. In this issue, we highlight the importance of basic and clinical scientific research and of the “bench to bedside” translation that turns scientific discoveries into clinical treatments and cures for pediatric cancer.