Preface: The Status of Pediatric Solid Tumors in 2015

Despite the progress of the past few decades in treating pediatric solid tumors, patients who present with these tumors continue to present challenges. We have collected "state-of-the-science" reviews for selected solid tumors occurring in children. Almost 24 years ago we wrote a review, "New Insights into the causes of Cancer" for a volume devoted to Solid Tumors in Children that was published by the Pediatric Clinics of North America. As we look at this special issue devoted to pediatric solid tumors, and as we consider future directions, it is important to consider from whence we came.

Presciently, we had discussed initiating genetic alterations arising in stem cells that could lead to a tumorigenic phenotype yet still retain the capability to "differentiate." While then the term dedifferentiation was met with skepticism, stem cell research and induced pluripotent cells have revealed a cell's amazing capability to "reprogram" itself and be induced to different developmental paths depending on the environment. To this point, McEvoy and Dyer, in their review "Genetic and Epigenetic Discoveries in Human Retinoblastoma," highlight findings that the transcriptome of retinoblastomas is a hybrid gene signature of the 3 retinal cell types, suggesting inactivation of retinoblastoma leads to fundamental disturbances in the coordination of developmental programs during development. Also, recent breakthroughs in our understanding of the epigenome and how enzymes regulating nucleosome positioning affect gene transcription have illuminated previously enigmatic tumors. One example is detailed in the review by Geller, Roth, and Beigel in "Biology and Treatment of Rhabdoid Tumor." Mutations of SMARCB1, a component of the SWI/SNF chromatin-remodeling complex, mark this developmentally obscure and highly aggressive tumor, which can arise in brain, kidney, and soft tissues during early childhood. New insights into the mechanism of action of these chromatin remodelers have suggested novel therapeutic options. Another adolescent and young adult tumor with a widely debated developmental origin is Ewing sarcoma. Lawlor and Sorenson, in their review "Twenty Years on: What Do We Really Know about Ewing Sarcoma and What Is the Path Forward," detail the progress that has been made in understanding how the chimeric EWS-FLI fusion oncogenes disrupt developmental pathways in cells of either the mesenchymal or neural crest lineages.

The "source and nature of genetic lesions" was another area of increasing debate. It was known that many viral oncogenes had normal cellular homologs, and there was a rapidly expanding list of 3-letter "proto-oncogenes" whose cellular localizations "dotted" discrete cellular locales. Oncogenes were classified as nuclear, cytosolic, or outer or inner membrane. Today, this view has been supplanted by an intricate system of interconnected signaling networks, and we know that post-translational modifications regulate different cellular localizations. MYC was one of the first oncogenes associated with human cancers; with its family members, MYCNL and MYCN, MYC is one of the most widely disrupted gene families in cancer. It is now known that MYC is a transcriptional amplifier and a critical factor capable of inducing reprogramming in normal cells. It was appreciated early on that the amplification of MYCN was important in both the pathogenesis of neuroblastoma as well as a clinical biomarker of high-risk disease, but a mechanistic understanding of how MYCN directly contributed to the formation of neuroblastoma was ill-defined. The review "Neuroblastoma," by Schulte and Eggert, details recent findings illuminating how mutations in ALK affect neuroblastoma tumorigenesis alone or in the setting of MYCN dysregulation. It was believed early on that transcription factors would not be "druggable," but the ability to target regulators of post-translational modifications to transcription factors and understanding of how transcription factors integrate with the transcriptional machinery offer new therapeutic approaches.

There were only 2 well-recognized tumor suppressors-RB and TP53; one of these, p53, had just switched from being an oncogene to a tumor suppressor gene. Now we know that use of differential isoform, level of expression, post-translational

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modifications, or cellular context may enable genes to have dual personalities, either promoting or inhibiting cancer cell growth. The review by McEnvoy and Dyer also highlights that the transcriptome of retinoblastomas is enriched in MDM4 isoforms that are more stable and thus more actively repress p53 function. The review by Morrow and Khanna, "Osteosarcoma Genetics and Epigenetics: Emerging Biology and Candidate Therapies," highlights that pervasive chromosomal instability is a hallmark of osteosarcomas that lack a canonical chromosomal alteration or gene mutation.

While the concepts of autocrine, intracrine, or paracrine tumor cell growth had been elaborated by the 1990s, the metastatic process was focused on processes mediating a cancer cell's ability to transit the extracellular matrix in vitro. The review "Physiological, Tumor, and Metastatic Niches: Opportunities and Challenges for Targeting the Tumor Microenvironment" by Muragi, Giles, and Kaplan details how mechanisms influencing the normal physiologic processes of tissue homeostasis, wound healing, and angiogenesis has expanded the cast of characters that affect the primary tumor niche as well as distant metastatic niches.

When we considered the therapeutic implications of genetic alterations identified in the 1990s, we thought that a "major goal of incorporating genetic analyses into newer classification schema" would be to identify prospectively subgroups of patients who did not respond to standard therapy." We studied genes, their RNA transcripts, proteins, and metabolites one at a time and indicated that initial evaluation of patient should include short-term cultures of cells for cytogenetic and DNA analyses. Now, in the era of precision medicine, -omics is attached to each of these, and we are able to assess globally a patient's cancer genome (and perhaps proteome), and we test primary tumor cells in high-throughput matrix screens of thousands of compounds to identify tumor vulnerabilities. Each of the tumor-centric reviews in this issue illustrates how different aspects of "-omic" analyses has provided insights into the complexity of their respective tumor types. In "Pediatric Rhabdomyosarcoma," Shern, Yohe, and Khan discuss how next-generation sequencing has revealed that rhabdomyosarcomas previously characterized as having fusion-negative alveolar histology do indeed have unique PAX3 fusions, just not with the canonical PAX fusion partner, FOXO1. In "Pediatric Brain Tumors: Genomics and Epigenomics Pave the Way," Fontebasso and Jabado show how integrated genetics, epigenetics, and next-generation sequencing have molecularly defined new subtypes of pediatric brain tumors, which are informed by an understanding of the basic biology and normal developmental potential of neuronal cells.

In the 1990s adoptive cellular immunotherapy with tumor-associated T cells was in its infancy, and the humanization of mouse monoclonal antibodies was the first step in making "chimeric antibodies." Yet even then it was noted that a critically important step for immunotherapy would be the in vivo delivery of genetically engineered antibodies. The progress we have made since then and the promise of its application to solid tumors is reviewed by Orentas and Mackall in "Emerging Immunotherapies for Cancer and Their Potential for Application in Pediatric Oncology." They highlight exciting studies of "chimeric antigen receptor" therapy in which cytolytic T cells engineered with tumor-specific chimeric antibodies have been developed and seem to be effective against relapsed leukemias.

We believe this special issue offers readers a comprehensive assessment of the critical questions and avenues of research related to these pediatric solid tumors that may shed light on disease pathogenesis and the directions needed to increase treatment efficacy.

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