Pediatric cancer: case studies illustrate mechanisms to address significant challenges

Andrew L. Kung¹ and Elaine R. Mardis²

¹Department of Pediatrics, MSK Kids, New York, New York 10065, USA; ²Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, Ohio 43215, USA

The steady improvement in outcomes for children with cancer has in large part been achieved through risk-stratified therapy and maximum intensification of multimodality therapy for patients with poor prognostic disease. For most pediatric cancer types, further improvements in outcomes are unlikely to be achieved through further intensification of conventional treatment modalities and instead will require integration of more targeted therapies. Moreover, because a majority of survivors of childhood cancer have long-term toxicities attributable to the therapies used to treat disease, replacing conventional cytotoxic treatment modalities with more targeted approaches holds the promise of decreasing the toxicities incurred in the course of achieving a cure. Although very few cancer therapies are FDA-approved for pediatric cancer indications, recent approvals of targeted agents in a biomarker-based and tissue- and age-agnostic manner provides a framework for bringing new targeted therapies to impact children with cancer. The approval of larotrectinib for *NTRK* gene fusions, for example, provides a new therapeutic option for children with infantile fibrosarcoma driven by *ETV6-NTRK3*, without the need for clinical trials to prove efficacy specifically for this very rare indication. Likewise, the approval of pembrolizumab for all cancers with high microsatellite instability provides an FDA-approved option for the small number of children with DNA mismatch repair-deficient tumors. Comparative genomic studies have revealed some overlap in significantly mutated genes in both adult and pediatric cancers (Gröbner et al. 2018), which provides an impetus for using comprehensive cancer genomic characterization to identify genetic biomarkers predictive of response to targeted drugs in adult cancers for potential use in pediatric cancers sharing the same genetic biomarker.

Indeed, this special issue of *Cold Spring Harbor Molecular Case Studies* illustrates beautifully, through the published reports herein, how the landscape of pediatric precision medicine is emerging along these lines. In particular, several reports illustrate rare cases of high mutational burden due to different underlying genetic contributors to cancer predisposition. These reports include two cases wherein constitutional mismatch repair deficiency (CMMRD) was found (see Momen et al., this issue, doi:10.1101/mcs.a004408; Yang et al., this issue, doi:10.1101/mcs.a003863). One patient presented with a germline pathogenic mutation in polymerase epsilon (*POLE*), which is not a canonical mismatch repair gene, and a second case presented with a single *MSH6* mutation in the germline and both *MSH6* and *POLE* somatic mutations. In several of these ultra-high mutation load tumors, the patients responded to the use of checkpoint blockade therapy, which mirrors the clinical trial results that led to FDA approval of anti PD-1 therapy for patients with any tissue site and mismatch repair deficiency (Le et al. 2017).

Several rare cancer types also are being reported in this issue, with identified drivers that correspond to therapeutic vulnerabilities in the setting of off-label or nonstandard of care

Corresponding author:
elaine.mardis@
nationwidechildrens.org

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use. For those of us involved in the care of pediatric patients with these rare tumor types, this is familiar territory, and these results give us hope that the continuing use of NGS-based molecular characterization will reveal the clinical benefit of such approaches in the rare pediatric cancer setting. Two other reports outline support for new constitutional cancer predisposition genes in pediatric cancers, including *GNAS* in the setting of medulloblastoma (see Tokita et al., this issue, doi:10.1101/mcs.a004572) and *RECQL4* in osteosarcomas (see Maciaszek et al., this issue, doi:10.1101/mcs.a004218). There also are important reports of novel gene alterations in pediatric cancers that have corresponding treatment responses.

Taken together, these manuscripts illustrate the rationale behind *Cold Spring Harbor Molecular Case Studies*—namely, to provide a mechanism for describing novel case studies that can inform the medical field, benefitting future patients and their care, and broaden our perceptions about the genetic nature of human disease and how to address it using novel therapeutic approaches, when applicable. As these efforts have grown internationally, it appears that the paradigmatic use of clinical trials, although still important for new drug approvals, may be superseded by sharing the data and outcomes from individual pediatric cancer patients whose genomic results led to the use of indicated therapeutic modalities. In pediatric cancer, as in all rare diseases, the dissemination of knowledge is critically important and obstacles to data sharing toward this end should be nonexistent if we are to fully benefit from the promise of genomics-guided precision medicine. Speaking to these truths, we are very pleased to offer two front half pieces in this special issue. One is provided by the researchers involved in The Treehouse Initiative at the University of California at Santa Cruz, who have developed an important new database and toolkit for the advanced analysis of pediatric cancer data, based on the notion of unhindered access to computational tools that accomplish this aim (see Sanders et al., this issue, doi:10.1101/mcs.a004317). A second Perspective from Sharon Plon and colleagues (see Lindsay et al., this issue, doi:10.1101/mcs.a004499). Provides an overview of a critically important effort at ClinGen to curate information about somatic cancer mutations and their appropriate, research-guided interpretation for use by the clinical diagnostics and research community. These, and other publicly available resources, will ultimately facilitate the democratization and access to genomics-based diagnoses and treatments that are required for every child to benefit.

Competing Interest Statement

The authors have declared no competing interest.

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