Abstract 3571

The ITCC-P4 sustainable platform of fully characterized PDXs supports the preclinical proof-of-concept drug testing of high-risk pediatric tumor models

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Cancer represents a leading cause of death by disease in childhood. Pediatric tumors exhibit a high intertumoral heterogeneity, as different tumor types and subtypes have emerged with peculiar molecular and clinical features; however, compared to cancer in adults, pediatric tumors are rare and mostly present with lower mutational burden. The lack of specific therapeutic options represents the main current challenge; systematic, multi-disciplinary approaches are required to accelerate drug development and ultimately to find cures for all children with cancer. The EU funded “Innovative Therapies for Children with Cancer–Pediatric Preclinical Proof-of-Concept Project” (ITCC-P4; www.itccp4.eu) consortium consists of a public-private partnership including academic and industrial partners with the goal of developing a large-scale platform comprising >400 patient-derived xenograft (PDX) models representing high-risk pediatric cancers. Currently, this collection of PDX models includes the most common types of pediatric tumors, such as leukemia (n=28), bone and soft-tissue sarcomas (n=154), CNS tumors (n=96) and neuroblastomas (n=38), as well as other rare childhood cancers, such as hepatoblastomas (n=20) and malignant rhabdoid tumors (n=18); PDX models have been generated either from primary (n=206) or relapse (n=118) disease. In order to: a) investigate the biology of the pediatric PDX models in a high-throughput and systematic fashion, b) assess whether they accurately reflect the molecular features of the corresponding primary tumor and, c) identify potential new suitable biomarkers, we performed a comprehensive molecular characterization (whole-exome and low-coverage whole-genome sequencing; DNA methylation profiling; RNAseq and gene expression profiling) of the PDX models, as well as their matching human tumors and germline samples. These data contributed to the stratification of the PDX models based on their mutational status and emerging molecular vulnerabilities to inform in vivo drug testing in all these PDX models. This proof-of-concept drug testing has been conducted defining, for each group of models, a panel of single compounds (SOC n=3; novel targeted therapies, n=6) or combinations (with each other or with chemo- or radiotherapy). All processed molecular and drug-testing data are collected in the consortium´s centralized data repository (https://r2.amc.nl) allowing data downstream analysis, visualization and interpretation. Taken together, the ITCC-P4 sustainable platform represents a validated and powerful tool to investigate the biology of pediatric cancer based on the establishment, characterization and preclinical testing of pediatric cancer PDX models, ultimately envisaged to contribute the development of innovative therapeutic options for childhood cancer patients.