WWTF Project LS18-111

Ultra-high-risk pediatric cancer - combinatorial drivers and therapeutic targets for precision medicine

Abstract

Ultra-high-risk (UHR) cancer patients are frequently ill-served by classical treatment options such as combination chemotherapy, but also require therapies focused on specific (epi-)genetic targets. This is often hampered by a lack of knowledge of the driver genes affected by large structural aberrations. We have identified UHR patients within the European high-risk neuroblastoma trial cohort (CCRI/St. Anna Children's Hospital). Preliminary genomic analyses of UHR patients demonstrated that lack of treatment response and reduced survival are driven by loss-of-function mutations in ATRX and/or frequently co-occuring loss of 19q and 1q indicating risk-relevant genes in these regions. We propose to (1) identify genes on 1q and 19q that drive the UHR phenotype in an ATRX deleted background by a CRISPR knock-out screen combined with single cell RNA-sequencing (CROP-seq), followed by thorough molecular validation in patient samples and functional validation in zebrafish xenografts. (2) Based on the identified genes we will perform a genome-wide screen for synthetically lethal genes and aided by computational models prioritize and test potentially synthetic lethal compounds. (3) Finally, we will pilot the first real-time functional drug testing on patient-derived xenograft zebrafish to enable personalized treatment recommendations for UHR patients. Altogether, this strategy will provide clinical decision makers with a solid rationale to integrate the identified drugs in the clinic.

Scientific disciplines:
602051 - Translation studies (60%) | 302055 - Oncology (20%) | 301904 - Cancer research (20%)

Keywords:
cancer, neuroblastoma, ATRX, CRISPR screen, (epi-)genetics, synthetic lethality, zebrafish, patient-derived drug testing, personalized medicine

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Further links about the involved persons and regarding the project you can find at
https://archiv.wwtf.at/programmes/life_sciences/LS18-111