LS25-090 - Functional Identification of Response Biomarkers to Advance Precision Oncology in Childhood Cancers

Zusammenfassung

Every year, 35,000 European children and adolescents are diagnosed with cancer. While survival rates have improved overall, they remain below 70% for many solid tumors. As conventional therapies reach toxicity limits, there is an urgent need for precision oncology that uses molecular biomarkers to personalize therapy regimens. However, the scarcity of 'druggable' driver mutations and the low mutational burden in pediatric cancers pose major challenges for the development of targeted and immunotherapies. At the same time, many chemotherapeutics and targeted agents still lack molecular biomarkers for predicting therapy responses.

CRISPR screens offer a transformative tool for deciphering drug response and resistance mechanisms. By developing optimized CRISPR libraries and scalable screening workflows, we have established a platform for high-throughput drug modifier screens, which we have so far applied to characterize drug-gene interactions for 38 cancer therapeutics. Strikingly, we find that many genes whose loss strongly sensitizes to specific anti-cancer agents are homozygously deleted in pediatric cancers, suggesting that such deletions could serve as biomarkers to predict exceptional drug sensitivities. Although such genetic events are rare, their cumulative frequency scales with the number of drugs, and we predict that drug-sensitizing deletions can be found in at least 30% of high-risk pediatric cancers.

By combining cutting-edge platforms for high-throughput CRISPR screening, automated cell culture, and image-based drug sensitivity profiling, FIREBACC aims to systematically identify drug-gene interactions for 96 established cancer therapeutics in three high-risk pediatric cancers. Functional-genetic data generated by FIREBACC will provide deep insights into drug response and resistance mechanisms, establish a new class of response-predictive biomarkers to guide the use of existing drugs, and thereby advance precision oncology for pediatric patients.

Wissenschaftliche Disziplinen:
Cancer research (40%) | Oncology (30%) | Medical molecular biology (30%)

Keywords:
Pediatric cancerPrecision oncologyFunctional genomicsCRISPR technologyDrug modifier screensMolecular diagnosticsDrug response profilingBiomarker discovery

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https://www.wwtf.at/funding/programmes/ls/LS25-090/