BRCAddict

Harnessing BRCAness as a therapeutic target in high-risk pediatric solid tumors

Project Coordinator:

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Project Abstract:

Despite a concerted European effort to widely apply next-generation molecular diagnostics, cure rates for pediatric solid tumors at relapse remain dismal. Approximately 50% of cases do not have an obvious genetic drug target. Our recent pediatric pan-cancer study (www.pedpancan.com) suggests that a large proportion of Ewing sarcoma, osteosarcoma, glioblastoma, medulloblastoma, neuroblastoma and rhabdomyosarcoma, all of which are entities of high medical need, show a mutational signature compatible with BRCAness, implicating sensitivity to PARP inhibition. We hypothesize that a fraction of pediatric solid tumors with a BRCAness mutational signature will be sensitive to PARP inhibition.

We aim to (i) assess the sensitivity of BRCAness positive tumors (and negative controls) to combinations of PARP inhibitors and DNA-damaging chemotherapy in vivo and (ii) tune our BCRAness calling algorithm by using preclinical in vivo response data for its first clinical application. As secondary aims, we strive to understand the "degree of BRCAness" necessary to sensitize for PARP inhibition, the underlying genetic causes, resistance mechanisms, and the predictivity of in vitro testing. The preclinical phase II trial "BRCAddict" will be performed in an n=1 fashion with 10 different PDX models from six different entities in each treatment arm. BCRAness will be assessed by whole-genome and transcriptome sequencing of the models using an established bioinformatic algorithm. We expect 30-80% of BRCAness positive cases in the entities of interest. In vitro testing of the same combinations will be performed in a cell line panel and drug responses will be compared with in vivo data.

The results of this preclinical trial and the accompanying biomarker evaluation will lay the groundwork for a molecularly stratified phase II study across pediatric solid tumors within the European Innovative Therapies for Children with Cancer (ITCC) network, in which all applicants are involved.

EuroTCLym

Translational Research in Peripheral T-Cell Lymphomas: from characterization to novel targets

Project Coordinator:

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Project Partners:

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Project Abstract:

Background. Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of rare lymphoid malignancies. With current treatment options, the majority of patients do not achieve remission or experience relapse after completion of therapy, generally with dismal outcome [1-4]. Mechanisms of progression and relapse remain elusive and predictive biomarkers do not exist, precluding clinical progress.

Hypothesis. We hypothesize that utilizing a unique collection of clinically annotated samples from multiple European trials and registries for detailed pathologic assessment and comprehensive characterization of the (epi-) genetic landscape will unravel pivotal mechanisms determining the unique biology and clinical behavior of PTCL.

Aims. Aim 1: Collect a clinically annotated, comprehensively characterized and centrally reviewed sample collection of PTCL. Aim 2: Perform a comprehensive genetic and epigenetic characterization and identify prognostic (epi-) genetic biomarkers. Aim 3: Identify molecular targets and develop novel therapeutic strategies.

Methods. This study will be based on biopsy samples of patients treated in prospective European clinical trials and from population-based cohorts that are collected via the national pathology reference centers. Whole exome sequencing, genome-wide DNA methylation profiling and targeted sequencing results will be correlated with clinical parameters, including progression and outcome. (Epi-) Genetic alterations will be addressed with drug screening assays in pre-clinical models and ex vivo in primary PTCL samples.

Expected results & impact. This study will provide a comprehensively characterized catalogue of clinically annotated samples across the major subtypes of PTCL. The integrated analysis of (epi-) genetic alterations will elucidate pathogenic mechanisms and the correlation with clinical endpoints will provide insight in prognostic biomarkers. Finally, novel therapeutic strategies will be explored on the basis of these data.

LIQUIDHOPE

Advancing Liquid Biopsies for Monitoring and Personalized Treatment of Children with Neuroblastomas

Project Coordinator:

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Project Partners:

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Project Abstract:

The embryonal tumor, neuroblastoma, accounts for 11% of all cancer-related deaths in children. Its heterogeneous tumor biology creates clinical variability spanning spontaneous regression to rapid metastasizing progression. Long-term survival of high-risk disease remains poor, with <40% overall survival after first-line treatment and <10% after relapse, despite considerable international efforts to improve treatment over the last decades. Liquid biopsies have the power to revolutionize clinical care for children with high-risk neuroblastoma by reflecting precise disease status at any time during treatment and care. Blood and bone marrow samples are a less invasive source of biomarkers for patient monitoring and therapeutic decision-making. The LIQUIDHOPE consortium combines internationally recognized experts in neuroblastoma pan-omics and computational discovery with leading pediatric oncologists to advance this emerging clinical paradigm change. LIQUIDHOPE aims to accelerate transfer of liquid biopsy approaches into the clinic within 3 parallel research arms designed to overcome current hurdles in (1) therapy response assessment, (2) minimal residual disease (MRD) monitoring and (3) actionable target identification, and define the best marker/analysis method or combination thereof for patient monitoring as its secondary aim. LIQUIDHOPE will apply targeted metabolomics; cfDNA whole-exome sequencing; cfDNA transcriptional start site and methylation profiling; unbiased total RNA profiling to monitor long noncoding and circular RNA disease markers; droplet digital PCR of DNA/RNA disease markers; automated multiple marker imaging and sophisticated bioinformatics. LIQUIDHOPE can identify and validate predictive markers for treatment response, MRD, relapse and treatment choice in blood/bone marrow surrogates to advance unique liquid biopsy-based innovations for patient monitoring and personalized treatment of children battling neuroblastoma.

MOLCARUTUC

Comprehensive genomic characterization of upper urinary tract urothelial carcinoma and paired bladder recurrences

Project Coordinator:

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Project Partners:

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- Bernardo Herrera (Spain), Virgen de la Victoria University Hospital, Dept. of Urology, Malaga
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Project Abstract:

Background: Upper urinary tract urothelial carcinoma (UTUC) patients have poor outcomes and a high risk of future urothelial carcinoma of the bladder (UCB) after radical surgery. Currently, diagnostic tools that predict the risk of a UCB recurrence are lacking and more effective therapies are needed to improve survival. This project envisions the identification of novel genetic leads for improved diagnostics and therapy by large-scale genomic characterization of UTUC and paired UCB recurrences as the solution to address these clinical needs.

Hypothesis: 1) UTUC and UCB recurrences are clonally related, enabling surveillance by molecular urine diagnostics. 2) UTUC is characterized by molecular alterations that lead to high tumor mutational burden (TMB), offering a target for immunotherapy.

Aims: Primary: to clarify the clonal origin of UTUC and paired UCB recurrences. Secondary: to identify genomic alterations of UTUC and to investigate the potential of these aberrations as novel draggable targets and predictors of response to therapy.

Methods: A retrospective cohort of 199 UTUC + 99 UCB recurrences (discovery set) and a prospective cohort of 170 UTUC samples (validation set) are compiled. Whole exome sequencing, microsatellite instability analysis, and immunohistochemistry are done to assess TMB, mismatch repair deficiency, immune infiltration and molecular subtypes. The genomic profile of UTUC and paired UCB is compared and molecular alterations of UTUC are correlated with clinical outcome and therapy response.

Expected results and potential impact: This project provides novel insights on the clonality of UTUC and paired UCB. This can be applied to replace cystoscopies by patient-friendly urine assays for surveillance after surgery. Moreover, it enables the identification of new actionable genomic changes of UTUC that serve as targets for therapy, such as precision-guided immunotherapy in UTUC patients with high TMB leading to durable responses and improved outcome.