poster #171

Molecular profiles and drug response of ITCC-P4 patient-derived xenograft (PDX) pediatric cancer models for target identification and prediction of targeted therapies

Dennis Gürgen[1], Apurva Gopisetty[2,3,4], Eva-Maria Rief[4], Aniello Federico[3,4], Danny A. Zwijnenburg[5], Marcel Kool[2,3], Alexandra Saint-Charles[6,7], Gudrun Schleiermacher[6,7], Gilles Vassal[4,10], Jan Koster[5], Stefan M. Pfister[2,3,4,9,10], Jens Hoffmann[1]

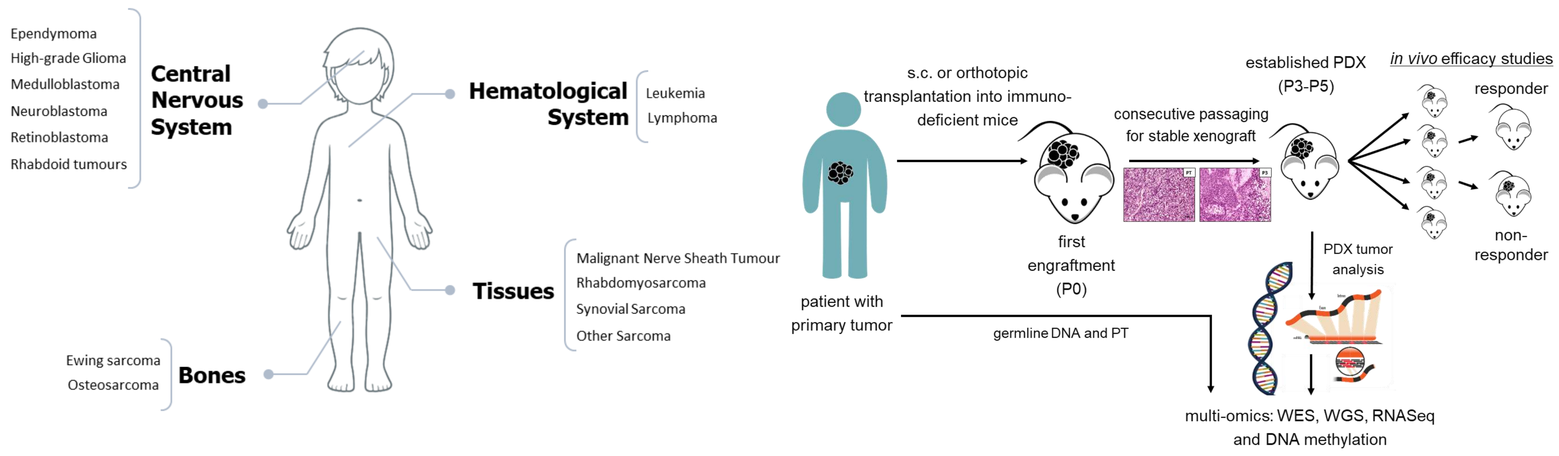
Experimental Pharmacology and Oncology (EPO) Berlin-Buch GmbH, Germany; Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany; German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK); ITCC-P4 gGmbH, Heidelberg, Germany; Center for Experimental and Molecular Medicine, Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, The Netherlands; RTOP (Translational research in Pediatric Oncology),INSERM U830, Équipe Labellisée LNCC, Diversity and Plasticity of Childhood Tumors, PSL Research University, SIREDO Oncology Centre, Institut Curie Research Centre, Paris, France; SIREDO Pediatric Oncology Center (Care, Innovation and Research for Children, Adolescents and young Adults with Cancer), Institut Curie, Paris, France; Center for Experimental and Molecular Medicine, Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, The Netherlands; National Center for Tumor Diseases (NCT), Heidelberg, Germany; European consortium for Innovative Therapies for Children with Cancer (ITCC-P4), Paris, France

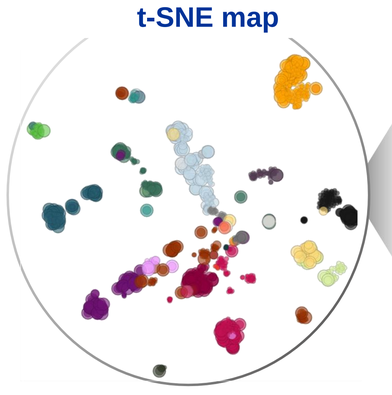
Background

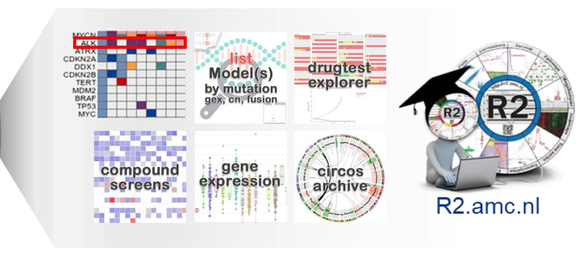
Childhood cancer oncogenesis occur from developing cells and consequently result in high tumor heterogeneity and low mutational burden. These molecular characteristics of pediatric cancer lead to highly variable clinical outcomes in patients. Clinical trials for pediatric cancers fail to provide groundbreaking progress, especially not in relapse or high-risk entities. Lack of molecular and genetic data on pediatric tumors, in particular from relapsed patients, were limited. Facilitating comprehensive preclinical drug testing in patient-derived xenograft (PDX) models is needed in order to initiate more successful clinical trials enabling future development of more effective treatments for children with cancer.

Aim and Methods

Our main objective was to establish a preclinical platform with a representative collection of *in vivo* PDX mouse models. Deep molecular characterization of PDX and the matching primary tumor biopsy and germline controls will enable extensive bioinformatics, biomarker verification and distinct selection of preclinical models for drug testing. The Innovative Therapies for Children with Cancer (ITCC-P4) platform, a European consortium of academia and pharma partners, established >400 characterized PDX models. Molecular and *in vivo* drug testing data (>250 PDX models) were clustered and analyzed by the R2 Genomics Analysis and Visualization Platform.

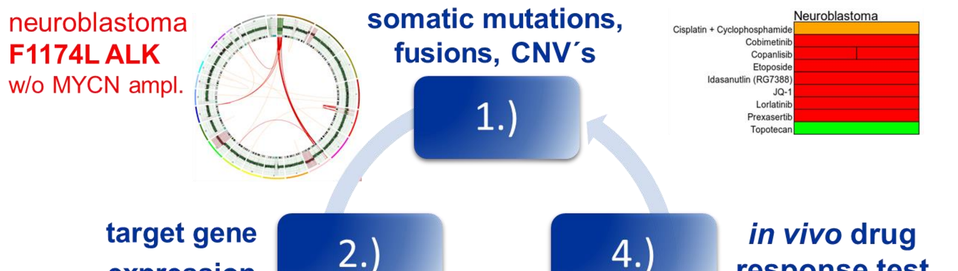




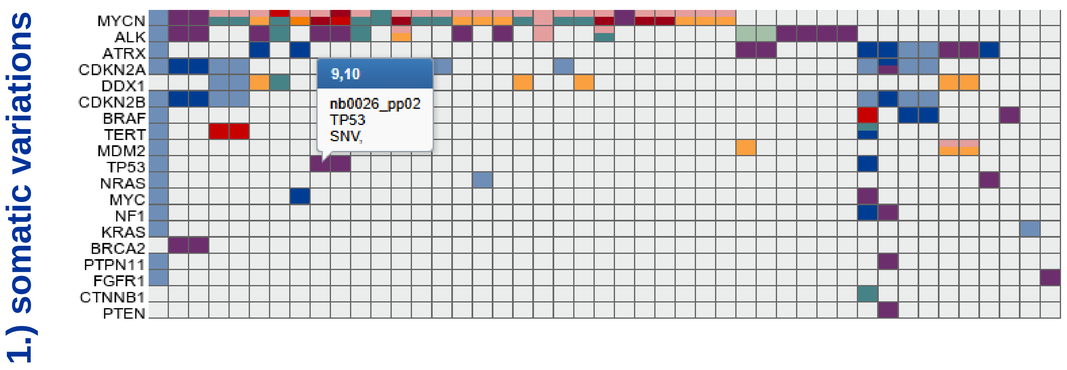


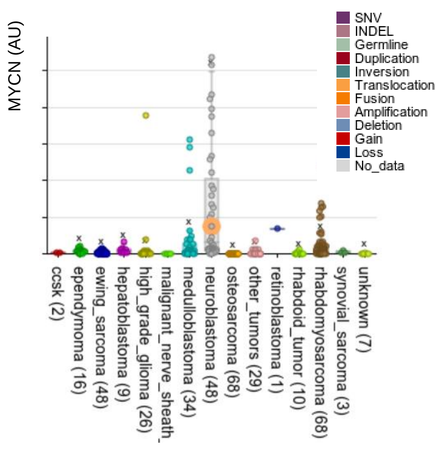
Results

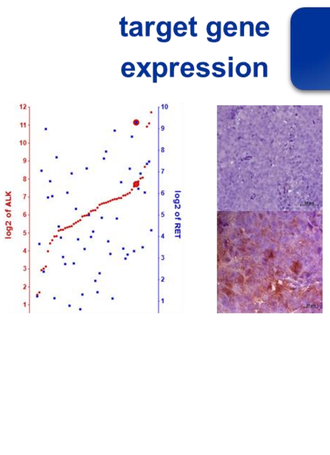
Molecular and *in vivo* drug testing data can easily be analyzed and processed via R2 genomics data base. Comprehensive target identification with deep molecular characterization data will enable suitable PDX model selection based on: somatic mutations, fusions, CNV´s, target gene expression and drug response characteristic of desired PDX models. Finally, target validation on protein level via IHC, and on the cellular level via FACS, deliver highly suitable preclinical model candidates for designated research projects.

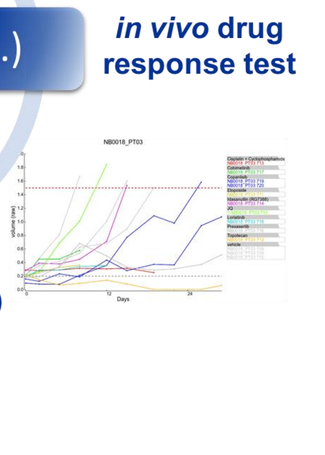


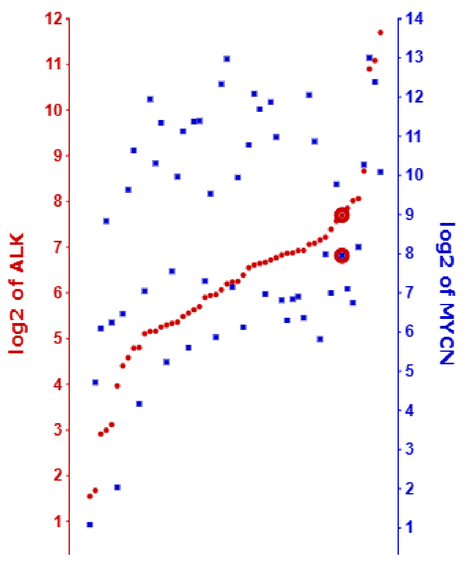
Neuroblastoma PDX cohort

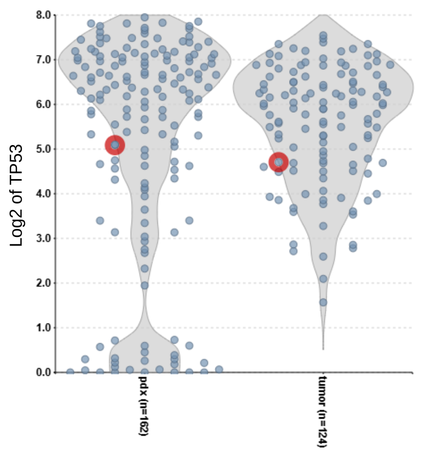




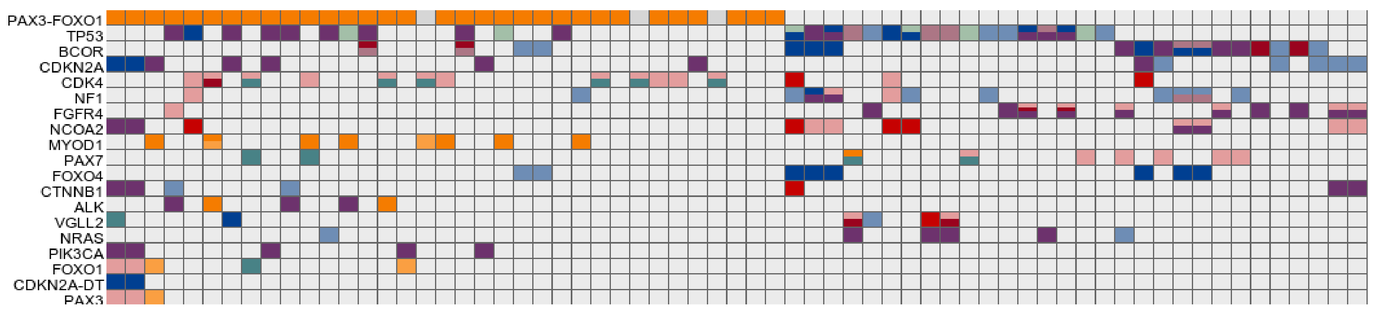


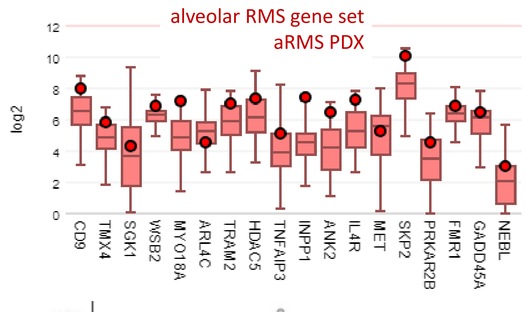


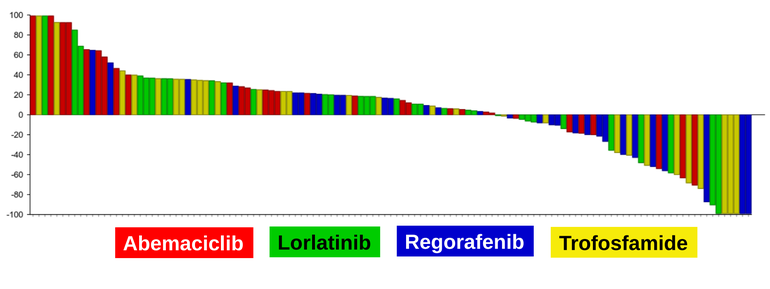




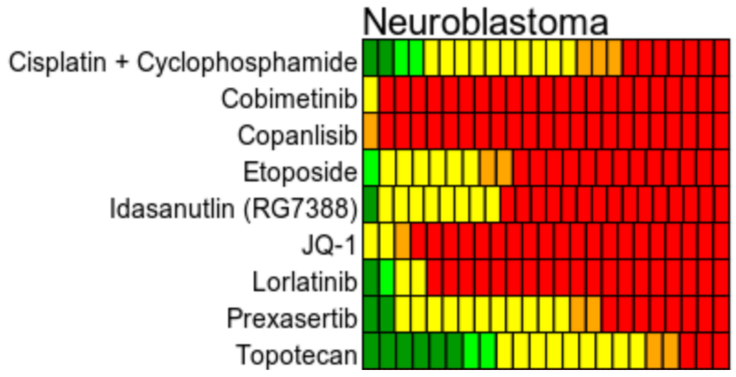
Rhabdomyosarcoma PDX cohort

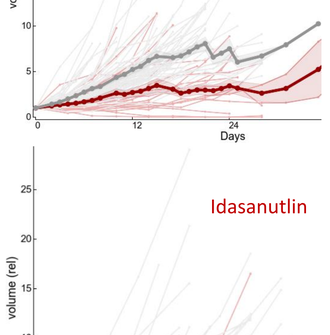


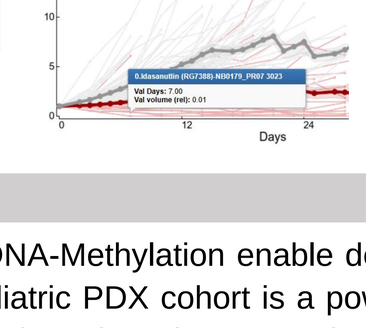


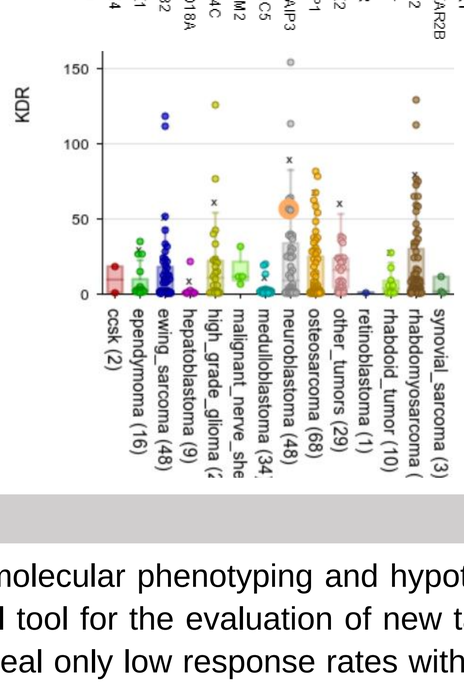


4.) PDX drug response (NB n=23 models)

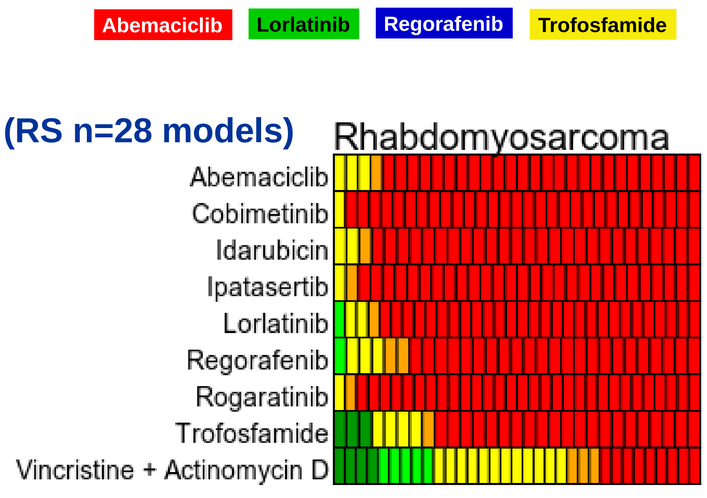








4.) (RS n=28 models)



Summary and Outlook

Comprehensive data from WES, WGS, RNASeq, DNA-Methylation enable deep molecular phenotyping and hypothesis driven PDX model selection for preclinical testing of novel drug candidates. Therefore, the ITCC-P4 pediatric PDX cohort is a powerful tool for the evaluation of new targeted therapies and biomarker identification for pediatric indications. Our *in vivo* drug testing of NB (n=23) and RS (n=28) PDX models, reveal only low response rates with targeted therapies compared to SoC chemotherapy. More effective preclinical filtering and combination drug test strategies (poster #169) were needed in order to address the high clinical need in high-risk pediatric cancer therapy.

correspondance: dennis.guergen@epo-berlin.com

itccp4.com r2.amc.nl epo-berlin.com