10 YEARS OF BREAKTHROUGHS
A HEALTHIER FUTURE

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

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Molecular characterization of patient-derived orthotopic xenograft models of pediatric brain tumors

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Facts & Figures

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Contributions	
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EFPIA in kind:	8 450 094 €
Other:	742 737 €
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Project website:	www.itccp4.eu
Social media:	LinkedIn:

Challenge

Solid tumors of the nervous system are the most common childhood cancers after leukemia. Even though we might be able to cure more and more patients, survivors still severely suffer long-term from the intensive treatments. Therefore, new treatment strategies are urgently needed. Patient-derived orthotopic xenograft (PDOX) models are an excellent platform for biomarker and preclinical drug development. However, the rarity of pediatric brain tumors hinders the generation of a large collection of PDOX models representing the wide spectrum of many different types of brain tumors, and makes it so far difficult to systematically assess efficacy of therapeutic options in a preclinical setting.

Approach & Methodology

Establishment of a sustainable comprehensive preclinical pediatric testing platform based on a panel of ~400 well-characterized patient-derived models of high-risk pediatric solid tumors to be used for rational pediatric drug development.

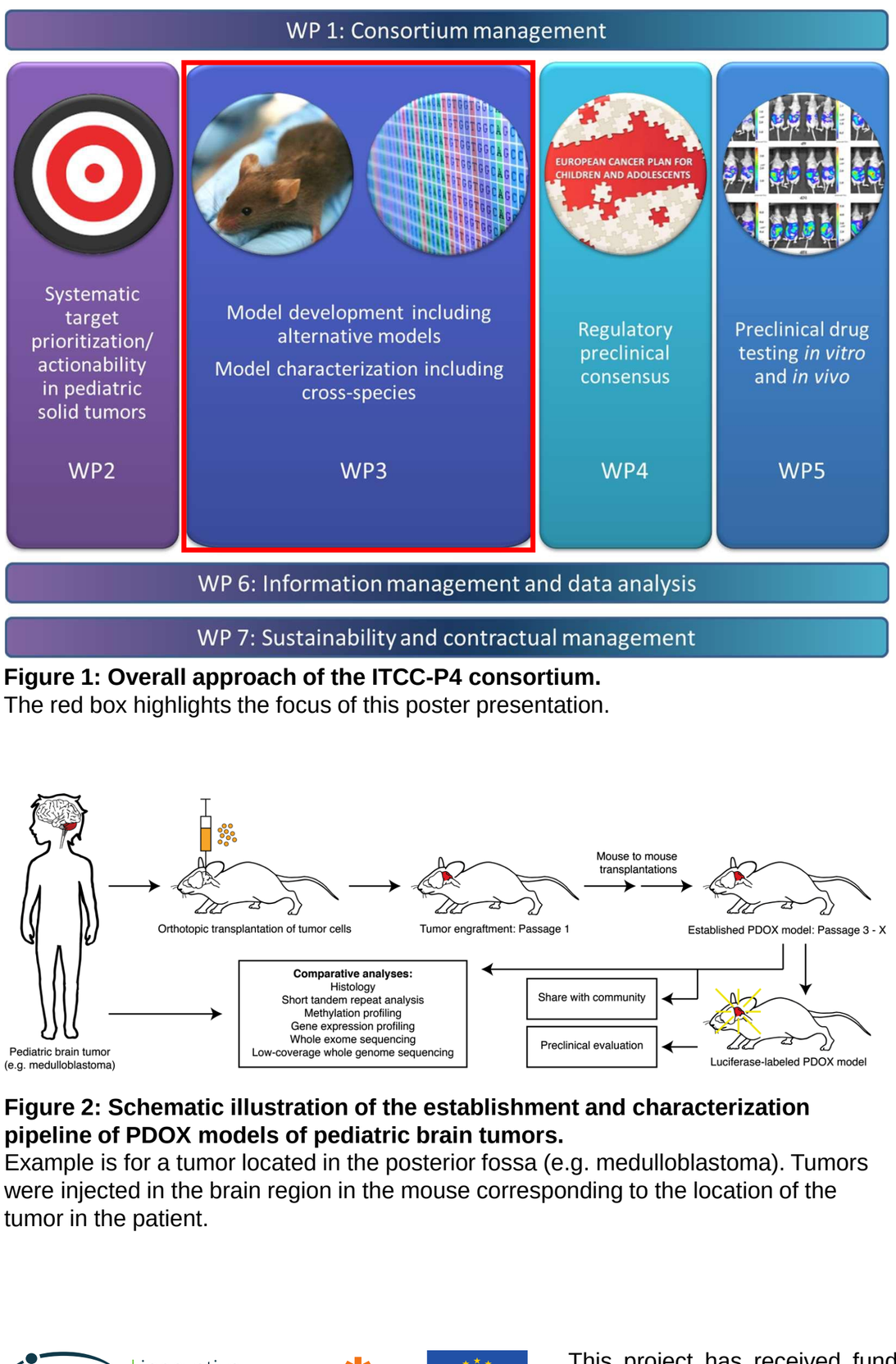

Figure 1: Overall approach of the ITCC-P4 consortium.
The red box highlights the focus of this poster presentation.

Figure 2: Schematic illustration of the establishment and characterization pipeline of PDOX models of pediatric brain tumors.
Example is for a tumor located in the posterior fossa (e.g. medulloblastoma). Tumors were injected in the brain region in the mouse corresponding to the location of the tumor in the patient.

Results

Molecular subtyping by methylation profiling of in total 130 PDOX lines identified 114 PDOX lines that fall into one of the four target brain entities and intra-entity subgroups for the consortium.

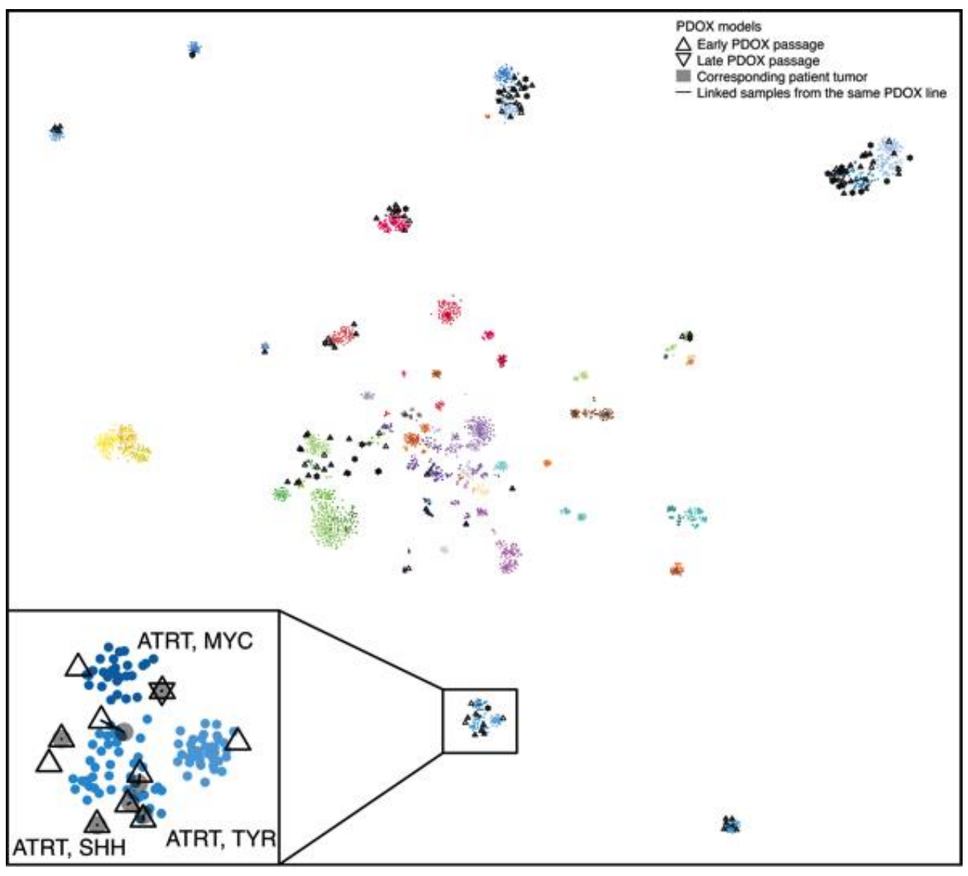

Figure 3: Molecular subgrouping of PDOX.
2D representation of pairwise sample correlations of methylation probes by tSNE dimension reduction. Colored dots represent reference patient samples.

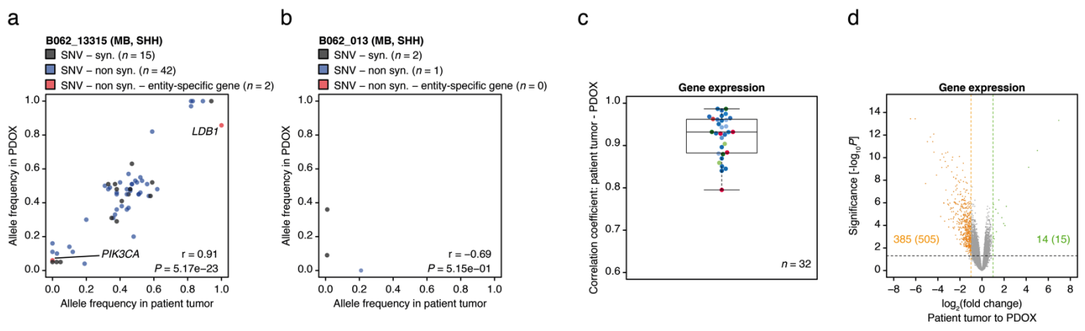

Figure 4: Molecular fidelity of PDOX.
(**a**,**b**) Correlations of allele frequencies for patient tumors and matching PDOX based on SNVs called from WES or WGS data. (**c**) Pairwise Pearson correlation coefficient of gene expression profiles of patient tumor PDOX pairs (*n* = 32), colored by tumor subgroup. (**d**) Mean expression level changes from human tumor to PDOX passage (*n* = 32 pairs). Significantly differentially-expressed probes are highlighted in orange (505 probes ~ 385 genes down-regulated in PDOX passage) and green (15 probes ~ 14 genes upregulated in PDOX passage) (*P* value < 0.05 and $\log_2$ (fold change) > 1).

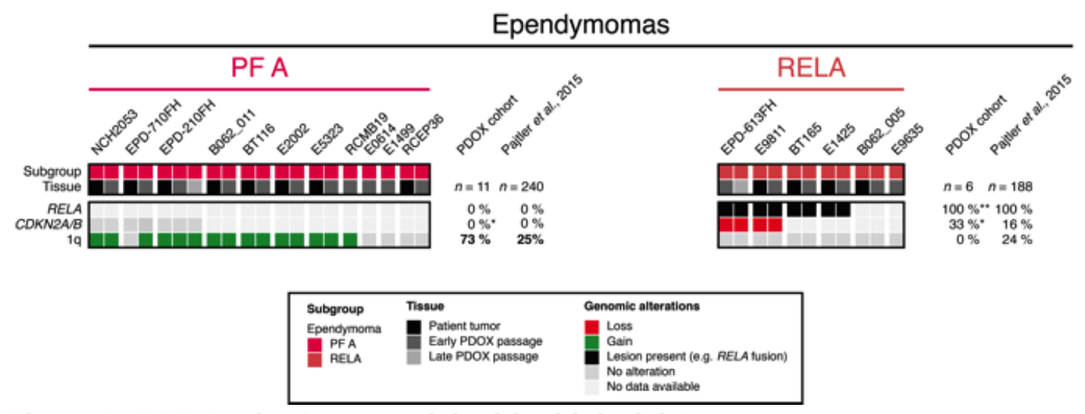

Figure 5: PDOX cohorts are enriched for high-risk tumors.
Hallmark genomic alterations including amplifications, deletions, and mutations are consistent between patient tumor and PDOX models at early and late passages in EPN. 1q gain is associated with a poor prognosis for PF A, but not RELA patients.

Value of IMI collaboration

- Systematic collection of rare preclinical pediatric model systems for academia and pharmaceutical industry
- Funding for in-depth molecular classification of model systems to match patient classifications
- Access to novel drugs through the pharmaceutical industry
- Large-scale preclinical drug testing by CROs

Impact & take home message

The preclinical-proof-of-concept platform will allow the systematic assessment of drug responses across various pediatric cancers. The PDOX models generated and characterized thus far faithfully recapitulate the tumors from which they were derived, but keep on continuously evolving over time. The bias for more aggressive tumor types within PDOX cohorts is a chance to study these deadly tumors better, but must also be taken into account when extrapolating results from the preclinical platform to clinical trials.

imi innovative medicines initiative efpia

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