The ITCC-P4 Paediatric Preclinical Proof-of-Concept Platform

Louis Stancato PhD, Eli Lilly and Company
On behalf of the ITCC-P4 Consortium
5th ACCELERATE Paediatric Oncology Conference
Paediatric Cancer Drug Development: The Need for Public-Private Collaboration

- >20% of all paediatric cancer remains incurable
- ~ 2/3 of childhood cancer survivors will experience significant long-term health consequences
- Lack of well-characterized paediatric cancer research tools limits the predictability of preclinical testing
- A close Academia/SME – EFPIA partnership is essential
  - Will bring all needed pieces together in a precompetitive platform

A public/private consortium would open doors to paediatric development in a concerted and rigorous fashion
### Genetic Determinants behind Paediatric Solid Tumors – Therapeutic Opportunities

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNV/Indel</th>
<th>Fusion</th>
<th>Copy number change</th>
<th>Expression change</th>
<th>Affected oncogenic pathways</th>
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<tbody>
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<td>Receptor tyrosine kinase (RTK) pathways</td>
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<td>NTRK</td>
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<td>TP53 regulation</td>
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<td>Sonic hedgehog</td>
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<td>Others</td>
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<td>Telomere maintenance</td>
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<td>SRC family</td>
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<td>Immunogenicity</td>
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<td>AKT</td>
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<td>TSC/MTOR</td>
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<td>Telomerase</td>
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</tr>
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<td>SNV count &gt;200</td>
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Other include e.g., Nephroblastoma, RCC, MPNST, undiff./other sarcomas, germ cell tumor, PNET, ETANTR
ITCC Pediatric Preclinical Proof-of-Concept Platform (ITCC-P⁴)

- 400 PDX models/5yrs; GEMMs
- Standard-of-care and targeted compound testing
- POC for immunotherapies in humanized models
- POC for organoids

ITCC-P⁴ Workflow

WP 1: Consortium management
- WP 2: Systematic target prioritization/actionability in pediatric solid tumors
- WP 3A: Model development including alternative models
- WP 3B: Model characterization including cross-species
- WP 4: Regulatory preclinical consensus
- WP 5: Preclinical drug testing in vitro and in vivo
- WP 6: Information management and data analysis
- WP 7: Sustainability and contractual management

Courtesy of S. Pfister, DKFZ
Patient Derived Xenograft (PDX) Models

10 major solid tumour types

Plan – 40 PDX per histology

Will be adjusted accordingly

Traditional Cell Lines vs. PDX Models

<table>
<thead>
<tr>
<th></th>
<th>Traditional Cell Lines</th>
<th>PDX Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Human tumor</td>
<td>Human tumor</td>
</tr>
<tr>
<td>Passaged</td>
<td>In vitro</td>
<td>In Vivo</td>
</tr>
<tr>
<td>Passage number</td>
<td>Usually high</td>
<td>Usually low</td>
</tr>
<tr>
<td>Cell histology</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
</tbody>
</table>

**Patient-Derived Colon Xenografts**

CXF 110

**Cell Line-Derived Colon Xenografts**

CXF 243 (20X magnif.)

CXF 243 (40X magnif.)

**Neuroblastoma**

**Sarcomas**

RMS

Synovial

MPNST

Ewing’s

Osteo

**CNS Tumours**

(orthotopic)

Medulloblastoma

HGG incl. DIPG

Ependymoma

ATRT
ITCC-P⁴: Model Generation

Academic sites

- SOP sample collection/consent forms

Frozen tumor samples/FFPE/germline/plasma

Viable tumor samples

GEMMs

Academic sites / SMEs / CROs / Oncotest

SOP PDX generation

Subcutane / orthotopic

PMC

SOP organoid generation

Roche

SOP humanized PDX generation

Academic sites

SOP GEMM (re)establishments

DKFZ / Curie

SOP
- Biobanking patient samples
- Molecular characterizations of germline/tumor/PDX/organoid/GEMM

Academic sites / SMEs / CROs

SOP data transfer histology / molecular characterizations to WP6

SMEs / CROs / Oncotest

SOP PDM/GEMM transfer to SMEs/CROs for preclinical testing in WP5

Brain tumors: Oncotest
Non-Brain tumors: EPO / Xentech / Pharmamar
# Target Actionability Review: MEK, ERK

## An Example

**Target/pathway:** RAS/RAF/MEK/ERK  
**Author:** H. Caron, Roche  
**Version Date:** Cotellic  
**18 Jan 2016**  
**Simko, Caron, Berger**

### Target Review Scores

<table>
<thead>
<tr>
<th>Disease scores</th>
<th>Target Review Scores</th>
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</thead>
<tbody>
<tr>
<td>suff. POC for clin. development</td>
<td>sufficient</td>
</tr>
<tr>
<td>needs more work</td>
<td>inconclusive ('needs more work')</td>
</tr>
<tr>
<td>no candidate for clinical dev.</td>
<td>negative</td>
</tr>
<tr>
<td>no data</td>
<td>not tested</td>
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</table>

### Target Actionability Review

#### Preclinical

1. Clinical target patterns
2. Molecular Target Validation (vitro)
3. Molecular Target Validation (vivo)
4. Compound Efficacy (vitro)
5. Compound Efficacy (vivo)
6. Biomarker Predictive
7. Resistance Mechanisms
8. Combination

#### Clinical

7. Safety in children (phase 1 trials)
8. Efficacy in children (phase 2 trials)
9. Efficacy in SOC (phase 3 trials)

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H. Caron, Roche
IT Infrastructure – “R2”

R2: Genomics Analysis and Visualization Platform

Somatic Mutations

Gene Expression/IC50 Correlation

PDX RECIST

Progressive Disease: > 10% ΔT/ΔC
Stable: -50% to +10%
Partial Regression: < -50%
Complete Regression: Volume < 1mm³

OncoPrint Annotation Overview

N=1 Mouse Trial Data
J. Koster, AMC
Pre-competitive Collaboration

- Academic and EFPIA partners to share in the models & technology including:
  - Testing Platforms
    - PDX models
    - Matching cell lines ($1^0$ cell lines/organoids)
    - GEMMs
    - Humanized immuno mouse models (limited subset of disease)
  - Complete molecular characterization data for all models
  - Standard-of-care testing data across models
Benefits to Paediatric Drug Development

- **Speeding** the development of the next generation of medicines to combat paediatric cancer
  - Increasing the number of *cures*
  - *Mitigating* the long term health effects assoc. w/chemotherapy

- *Data-driven, rational decisions* on which tumours to treat and with which combination of agents

- Paediatric drug development will be a *fully functional* research paradigm that rivals approaches created for adult malignancies
ITCC-P4 – Consortium Leadership

Executive Team
H. Caron, Roche
S. Pfister, DKFZ
L. Stancato, Lilly
G. Vassal, IGR

Target Actionability
H. Caron, Roche
J. Molenaar, PMC

Model Development & Characterization
M. Kool, DKFZ
D. Shields, Pfizer

Drug Testing
J. Hoffman, EPO
D. Zopf Bayer

Regulatory Consensus
Silvia Chioato, Pfizer
G. Vassal, IGR

Information Technology
J. Koster, AMC
L. Stancato, Lilly
# ITCC-P4 – Scientific Leadership

## Scientists, Clinicians, Informaticians and Project Managers from across the EU

<table>
<thead>
<tr>
<th>Neuroblastoma</th>
<th>PDX establishment &amp; labeling</th>
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</thead>
<tbody>
<tr>
<td>J.J. Molenaar (PMC), A. Eggert (Charite), J. Schulte (Charite), F. Westermann (DKFZ), G. Schleiermacher (ICU), L. Chesler (ICR)</td>
<td>Academic sites, EPO, Xen Tech, Oncotest</td>
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<table>
<thead>
<tr>
<th>Soft tissue sarcomas</th>
<th>Molecular characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Schäfer (UZH), J. Shipley (ICR)</td>
<td>WES, IcWGS, transcriptome, DNA methylation (DKFZ, IC), Immuno-profiling (Roche)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone sarcomas</th>
<th>Alternative models</th>
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<tr>
<td>H. Kavar (CCRI), K. Scotlandi (ACC), O. Delattre (ICU), A. Kulozik (Heidelberg), N. Gaspar (IGR), A. Montero Carcaboso (FSJD)</td>
<td>Organoids: H. Clevers &amp; M.v.d.Wetering (PMC), GEMM: J. Schulte (CB), L. Chesler (ICR), Humanized immuno mouse models: Roche</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Embryonal BTs Ependymoma</th>
<th>Preclin. testing &amp; pharmacology</th>
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<tr>
<td>F. Bourdeaut (IC), M. Kool (DKFZ), L. Chesler (ICR), W. Berger (MUW), O. Witt (DKFZ), M. Grotzer (UZH)</td>
<td>Preclinical testing: EPO, Xen Tech, Pharmamar, Oncotest Preclinical pharmacology: IGR, DKFZ, EPO, Xen Tech</td>
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<thead>
<tr>
<th>High-grade gliomas</th>
<th>Bioinformatics/database</th>
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<td>C. Jones (ICR), D. Jones (DKFZ), J. Grill (IGR), W. Berger (MUW), A. Montero Carcaboso (FSJD), M. Grotzer (UZH)</td>
<td>Jan Koster (AMC), Nathalie Jäger (DKFZ), Virginie Bernard (IC), Rogier Versteeg (AMC), Rolf Kabbe (DKFZ), Louis Stancato (El Lilly), Andreas Schlicker (Bayer)</td>
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