ITCC-P4 International Workshop
IMPROVING PEDIATRIC ONCOLOGY DRUG DEVELOPMENT THROUGH PRECLINICAL RESEARCH 2018

Breakout Session:
Design and use of orthotopic brain tumor models

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Reminder:
Orthotopic brain tumor testing

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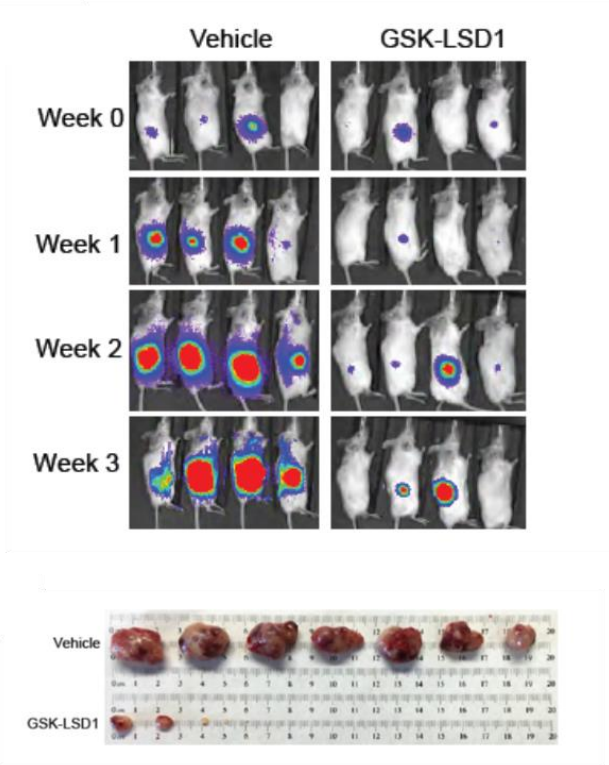
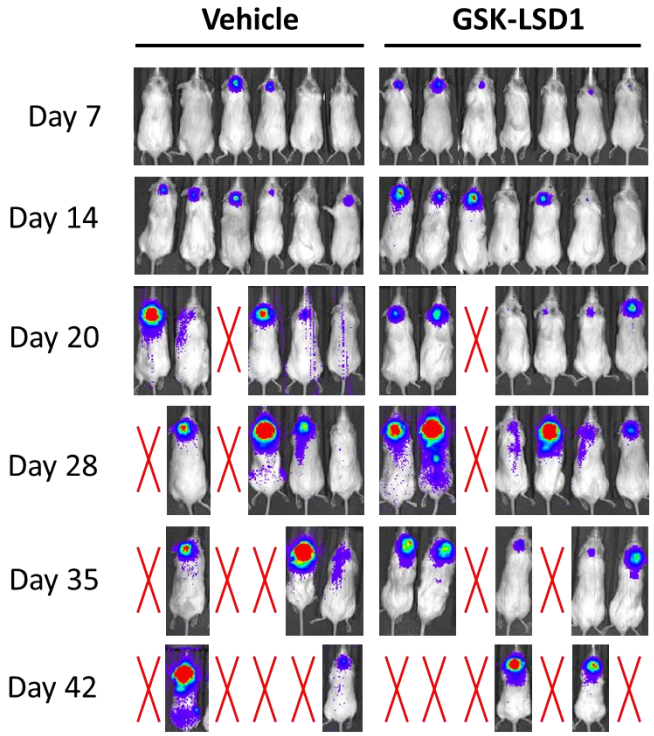
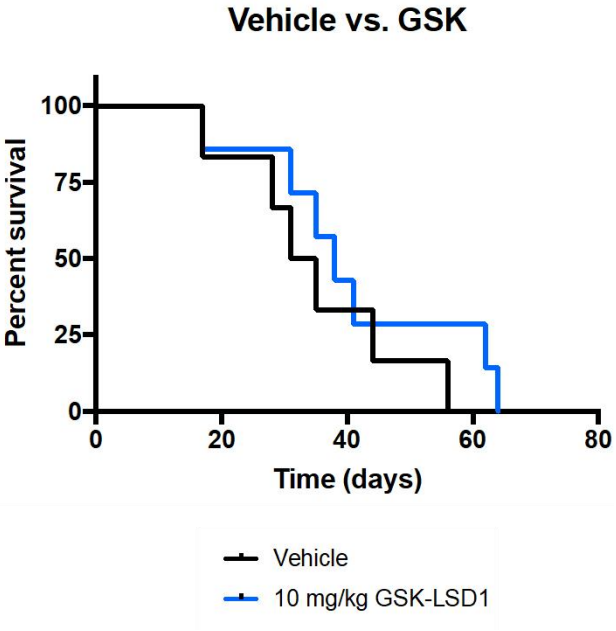
s.c.



orthotopic





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Some considerations/reminders

- A vast majority of drugs is actively designed not to penetrate the brain to prevent neurotoxicity
- A focally intact BBB might be critical to confer „clinical resistance“
- If a drug works in the brain, we typically conclude that it must be due to the disrupted BBB, and if it doesn´t work, we attribute it to an intact BBB
- There are reasons beyond the BBB for orthotopic testing (e.g., microenvironment, neuronal „firing“, etc.) as evidenced by morphology, „homing“ of metastases back to the CNS etc.

Pros and Cons of orthotopic versus subcutaneous models

- There is no optimal system
- Orthotopic models are more challenging and require specific training/expertise
- STX surgery might influence the BBB
- Luciferase labeling might change tumor heterogeneity/biology (→ not the experience of the cademic labs working with these models so far)
- More data needed on biological/genetic differences between orthotopic and sc implantation (e.g., ref Epo study in aldut glioma), but morphology nd transcriptomes are clearly different.
- Extent of clonal evolution might be different based on mutational burden/genomic instability
- S.c. models show a relevant difference in stiffness/collagen content (elastrography/imaging)
- S.c. overall tend to show better objective response
- Human stromal cells are getting eliminated over a few passages in case of PDX models
- Site of injection should be taken into account
- GEMMs are an important complement

Should orthotopic testing for brain tumors always be part of the minimal preclinical package? If so, would the „primary screen“ be s.c. and the „secondary screen“ orthotopic or do we suggest to start with orthotopic?

- Strategy might be different based on the individual target (e.g., dependence on faithful microenvironment) and based on the approach (one molecule versus hundrets).
- s.c. serves a different purpose (evidence of target relevance and effect of inhibiting it) → screening. PK and PD can be done sc for brain tumors, if this more cost-effective.
- However, we also all agreed that orthotopic efficacy testing using pediatric brain tumor models has to be part of the minimal preclinical package for these indications. If PK and PD is not done s.c., it has to be done orthotopic.
- Negative orthotopic efficacy data should trigger additional preclinical testing and preclude moving forward into a clinical trial for a brain tumor indication at this stage.

What are the best models to test BBB and tumor penetration?

- Objective orthotopic *in vivo* efficacy across several pediatric models (and model types) contributes strong evidence (while it could still be an off-target effect and negative controls are a mandate)
- BBB in healthy rat models is not necessarily predictive of brain tumor exposure (thus should not preclude preclinical evaluation)
- In silico prediction/*in vitro* assays for BBB (incl. drug transporters) comprise a standard part of the workup in pharma (but only a first step)
- PDX models may be predictive of tumor penetration in patients
- GEMMs complement PDX preclinical testing, also in regard to BBB/microenvironment

How does contrast enhancement clinically and preclinically factor in? Is this reflective of the entire tumor or just the „bulk“ that we can often treat with surgery? Are there examples for preclinical predictivity? Alternative/additional imaging modalities?

- Contrast enhancement characteristics not known for many models → is this relevant information from a clinical perspective? How does it evolve longitudinally?
- Maybe dependent on viability of transplanted cells?
- Question: Even if contrast enhancement was maintained, would clinicians accept this as a predictor of bbb status?

What are the procedures/evaluation criteria?

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- Knowledge about prior treatment
- Knowledge about growth kinetics
- Knowledge about contrast behaviour?
- Knowledge about molecular biology
- **Start of treatment at measurable tumor size**
- **Randomization by size**
- **Objective responses are requested as a minimum Solw-down of tumor growth is not sufficient.**

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Do we need in vivo exposure readouts for the minimal preclinical package for brain tumors? (e.g., endpoint measurement, longitudinal measurement, e.g., by microdialysis).

- Target engagement + PK should be part of the minimal required package in pediatric orthotopic models (at least if this data was not acquired sc)
- Appropriate negative controls *in vivo* to help distinguishing on target from off target effects
- Unclear to what extent clinical data on brain metastases are predictive for primary brain tumors?
- Imaging readouts may substitute pharmacologic concentration measures
- Need to acquire data on drug accumulation in the brain tumor

Should a drug with a poor brain penentrance, but some in vivo activity be moved forward to a clinical trial? („We should not be so picky for brain tumors“)

- No, not without additional supporting data.

How should radiation therapy be delivered in the preclinical setting (very preliminary)

- No clear proof that targeted radiotherapy is superior to whole-body irradiation in terms of efficacy readouts
- Mouse strain is critical re. tolerability of radiation (as it is for many drug treatments as well) – less immunosuppression is beneficial, if possible.
- Fractions of 2 Gy, max. 30 Gy (?) feasible

Possibility/relevance of a joint research project developed through a partnership between ITCC-P4 and PPTC?

- Establishing more evidence re. the use of luciferase imaging being an equally reliable efficacy readout as MRI imaging (or PET etc.)
- Systemic comparison between sc and orthotopic *in vivo* testing (ideally simultaneous) incl. contrast enhancement in comparison to the primary tumor that was transplanted. Combining with PD readout? Combining with microdialysis readout?
- Generate PDX from brain tumor metastases from (adult) patients with relevant targets? → Is this data predictive for primary brain tumors?