Robustness and Reliability of PET-Based Quantification of Tumor Hypoxia (and Glucose Consumption)
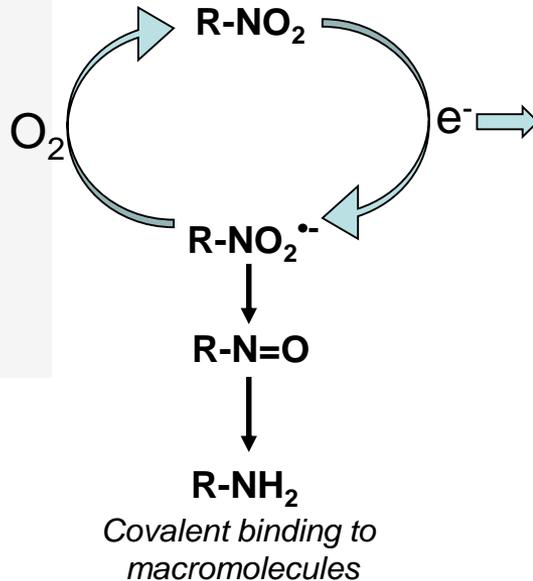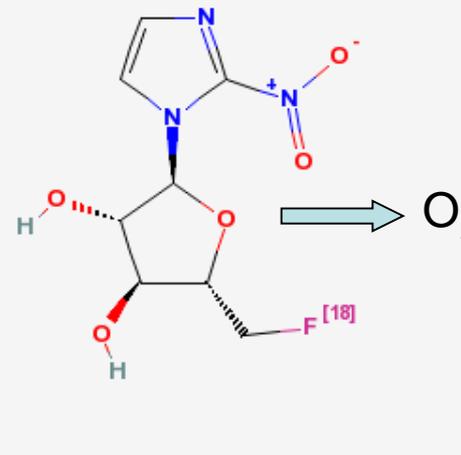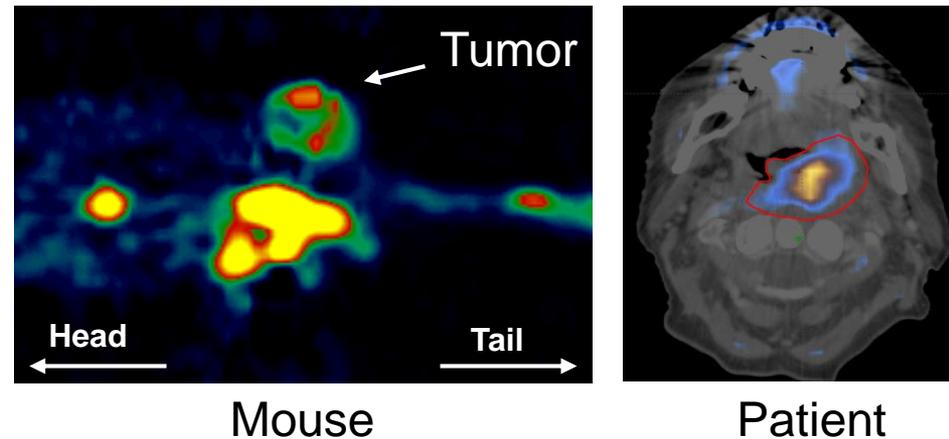
Hypoxia tracer

^{18}F-FAZA

O_2

R-NO$_2$

e$^-$

R-NO$_2$$^{\bullet-}$

R-N=O

R-NH$_2$

Covalent binding to macromolecules

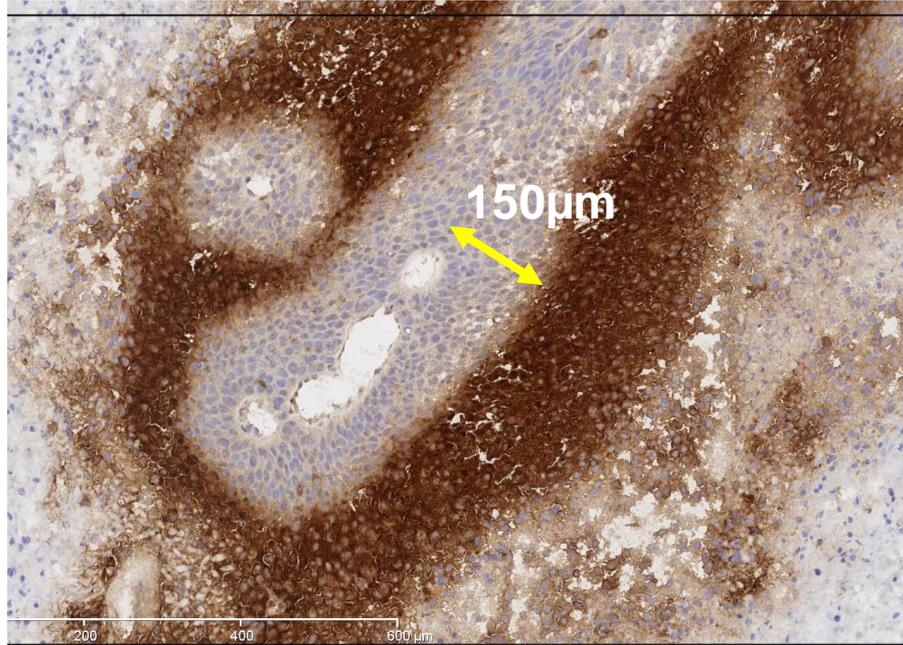Hypoxia PET

Tumor

Head

Tail

Mouse

Patient

What are the minimal requirements if hypoxia PET should guide decision-making in radiotherapy?

It depends on the context/application!

- If we prescribe a magic pill (could be Nimorazole) we may not even need hypoxia imaging

- If we want to dose escalate whole tumors it may be sufficient with a crude sorting of patients according to absence/presence of hypoxia (i.e., if one voxel is above a chosen threshold we escalate dose to the entire tumor- or prescribe the pill)

- If we want to do "hypoxic dose painting" we ideally need a tumor 3D map that is quantitatively accurate, i.e., proportionality between voxel signal and number of hypoxic cells (or rather averaged voxel radioresistance) and the target needs to be rather stable over time (at least from imaging to treatment)
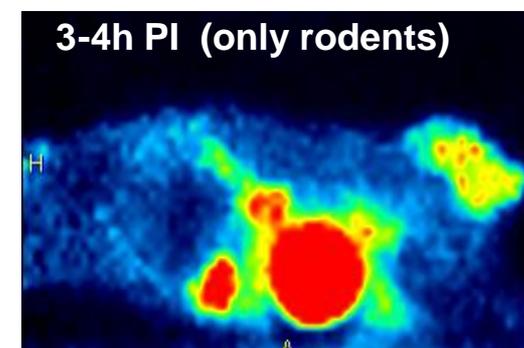
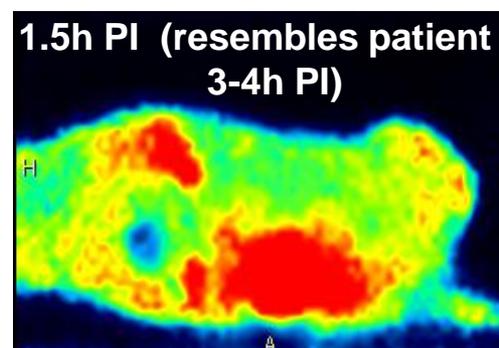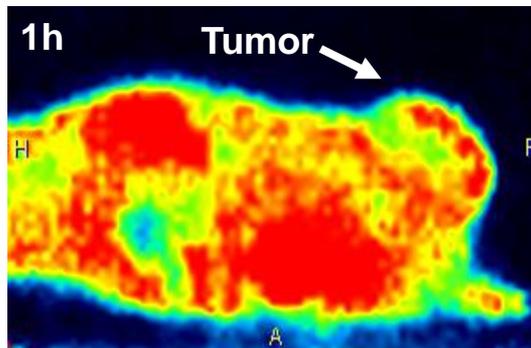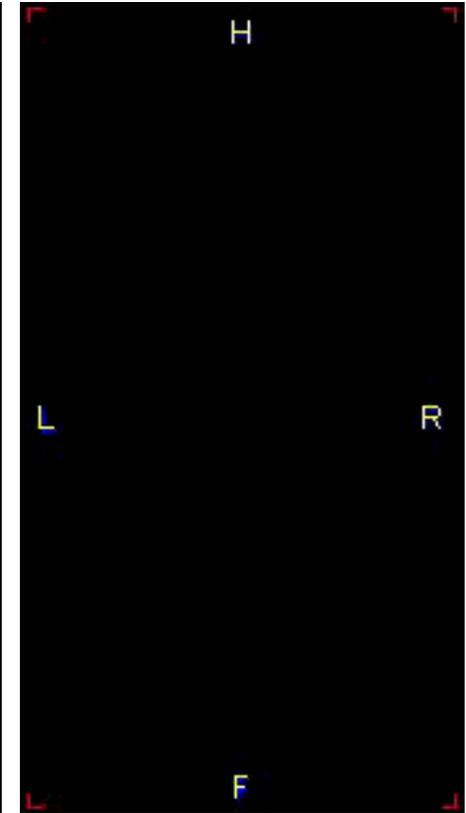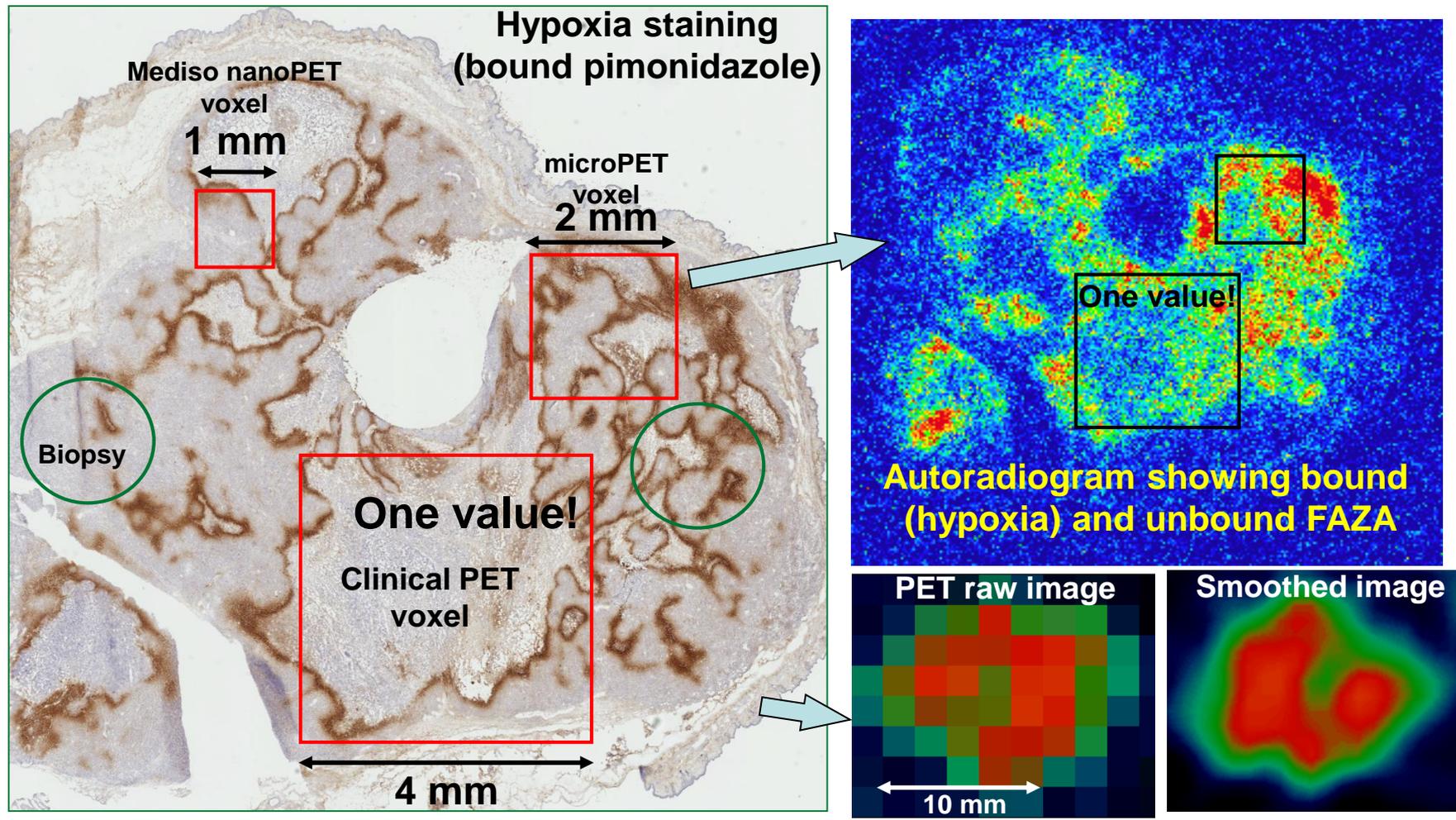# PET based target definition in radiotherapy: possibilities and challenges

Hypoxia (pimonidazole, brown staining)

150μm

MRI

0-3h FAZA-PET

T

1h   Tumor

1.5h PI (resembles patient 3-4h PI)

3-4h PI (only rodents)

The resolution/dilution problem aggravates the contrast problem

Hypoxia staining (bound pimonidazole)

Mediso nanoPET voxel
1 mm

microPET voxel
2 mm

Biopsy

One value!
Clinical PET voxel

4 mm

One value!

Autoradiogram showing bound (hypoxia) and unbound FAZA
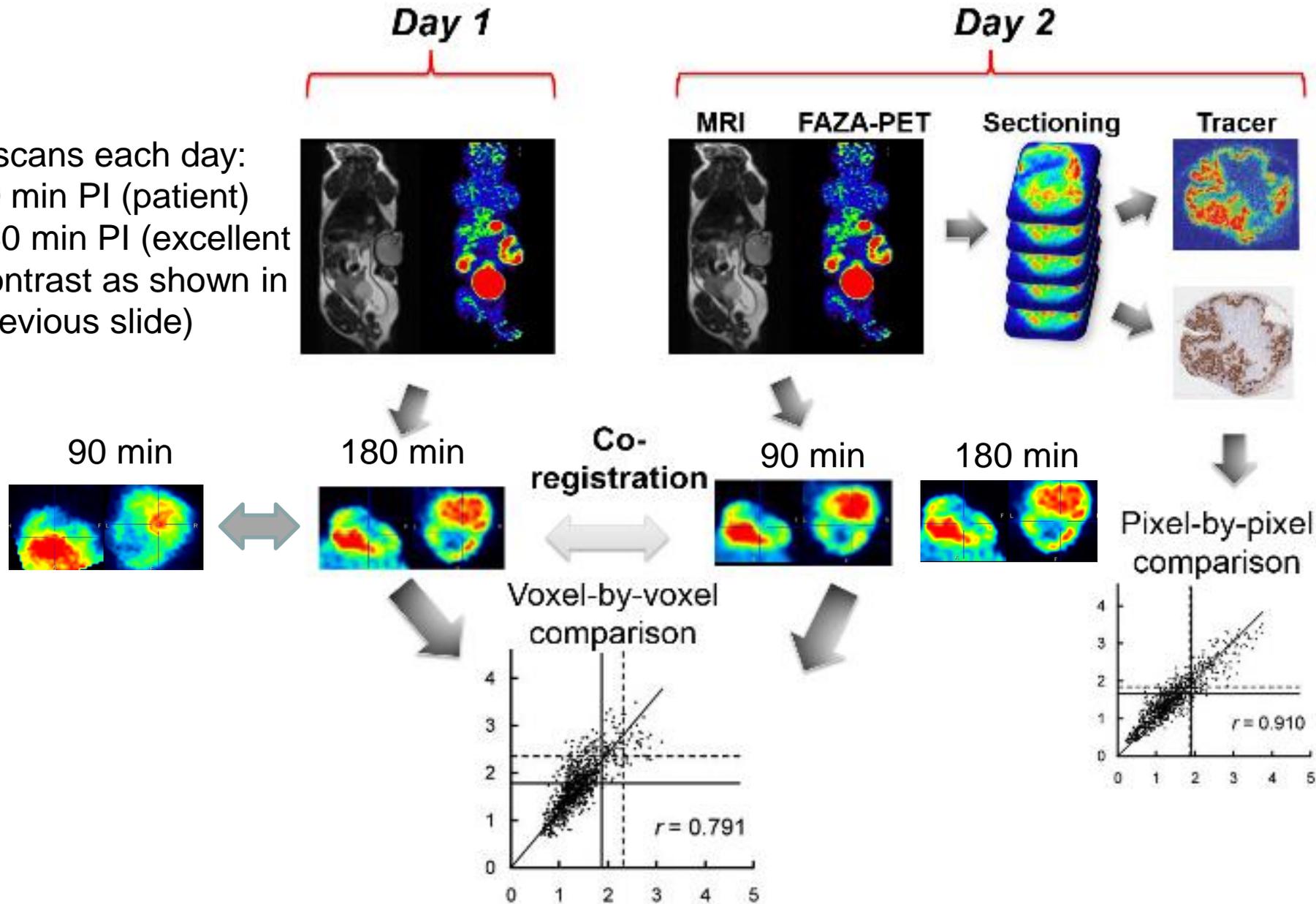
PET raw image

Smoothed image

10 mm

In rodents, at late time points (≥3h PI), excellent hypoxia specificity is reached meaning that we have "the true distribution of chronic hypoxia" against which scans at earlier (clinical relevant) time points can be compared!!!

| Pimonidazole | Segmented pimonidazole | FAZA (PET tracer) | Pimo-FAZA 2D match |

Similar results are obtained in a range of xenograft tumors at late (3-4h) scan time points!
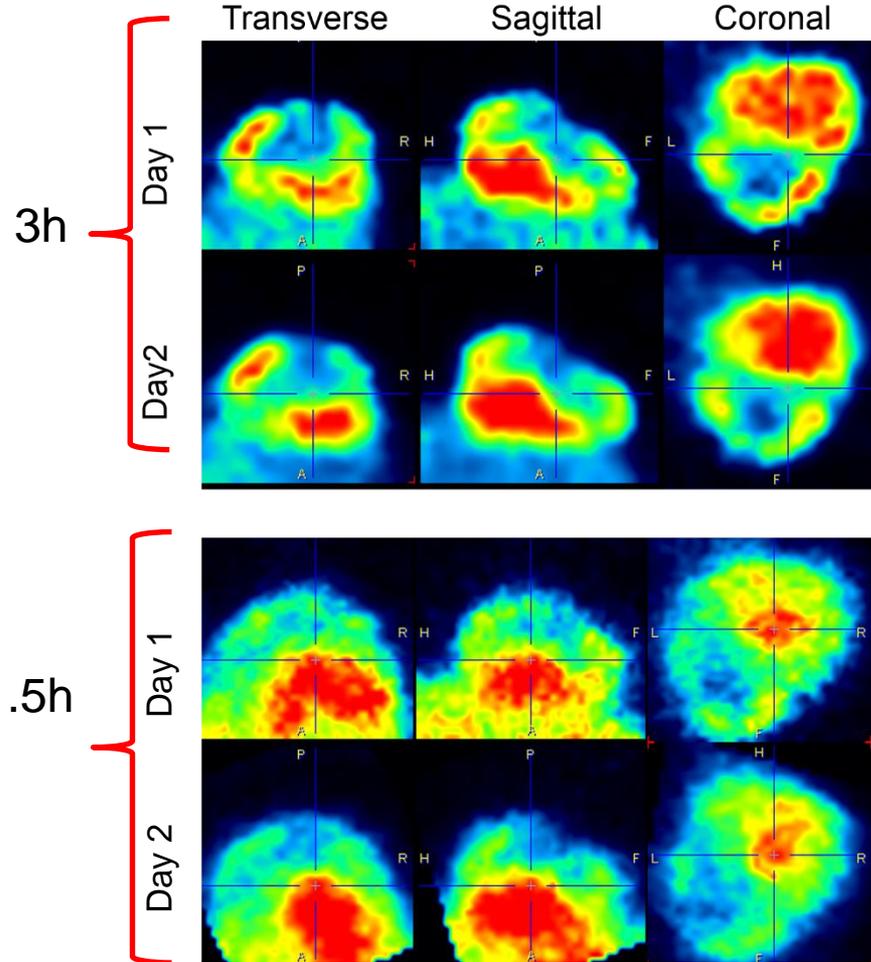
Reproducibility and contrast development

Two scans each day:
- 90 min PI (patient)
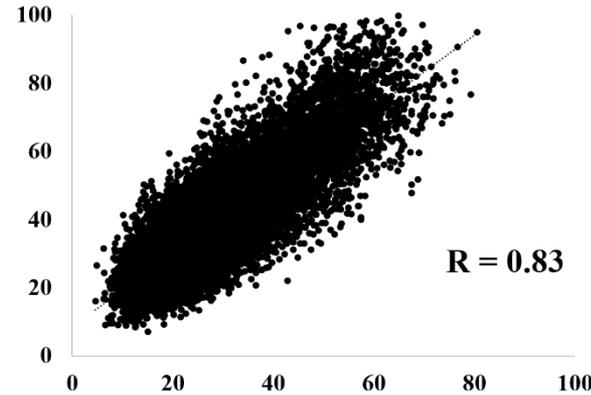- 180 min PI (excellent contrast as shown in previous slide)

Reproducibility and accuracy at high contrast (only achievable in mice) and low contrast mimicking the clinical scenario
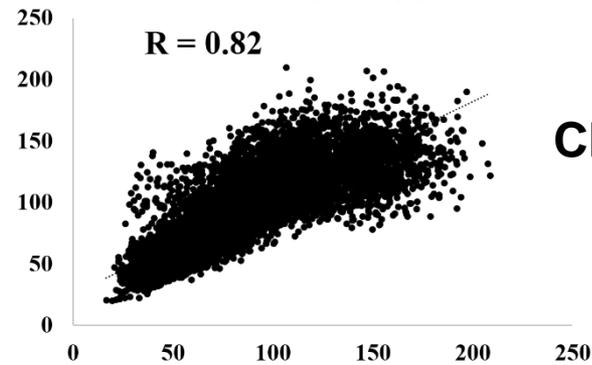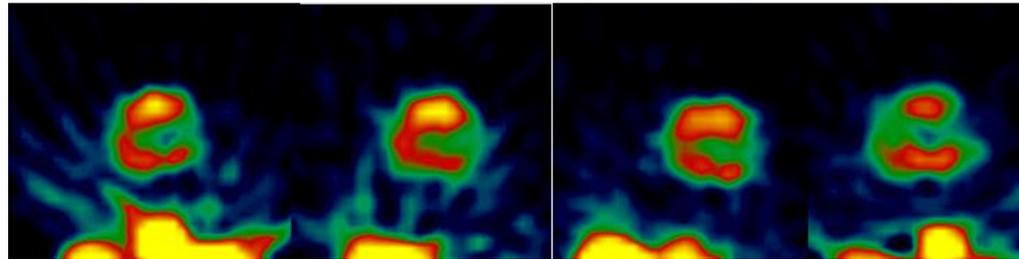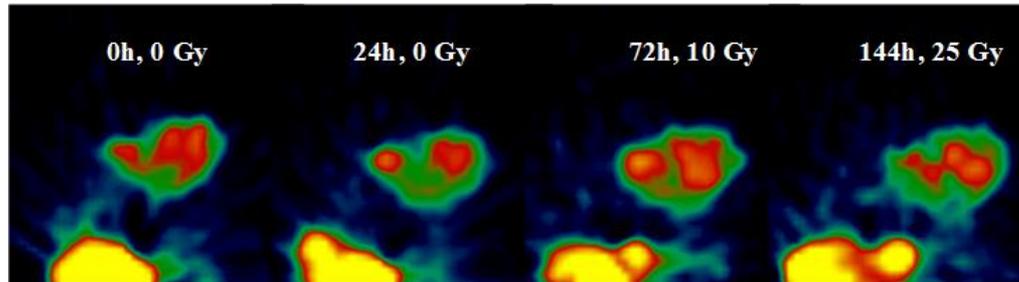
UMSCC47 HNSCC xenograft

Rodents only

Clinical simulation
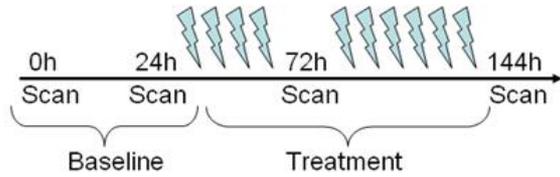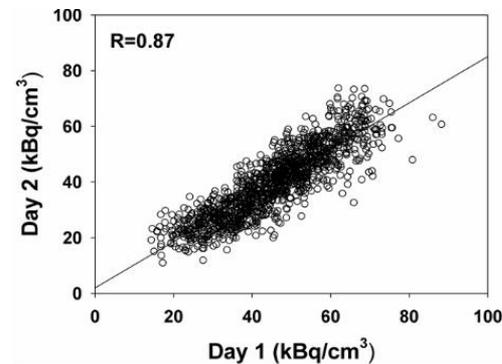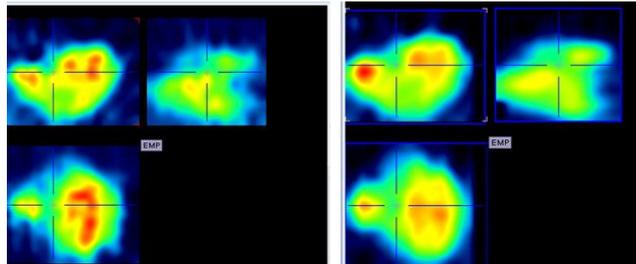
Importantly: reasonable correlations were also obtained when 90 and 180 min scans were compared suggesting that target definition is reliable. Equally encouraging results were obtained in a variety of tumor models
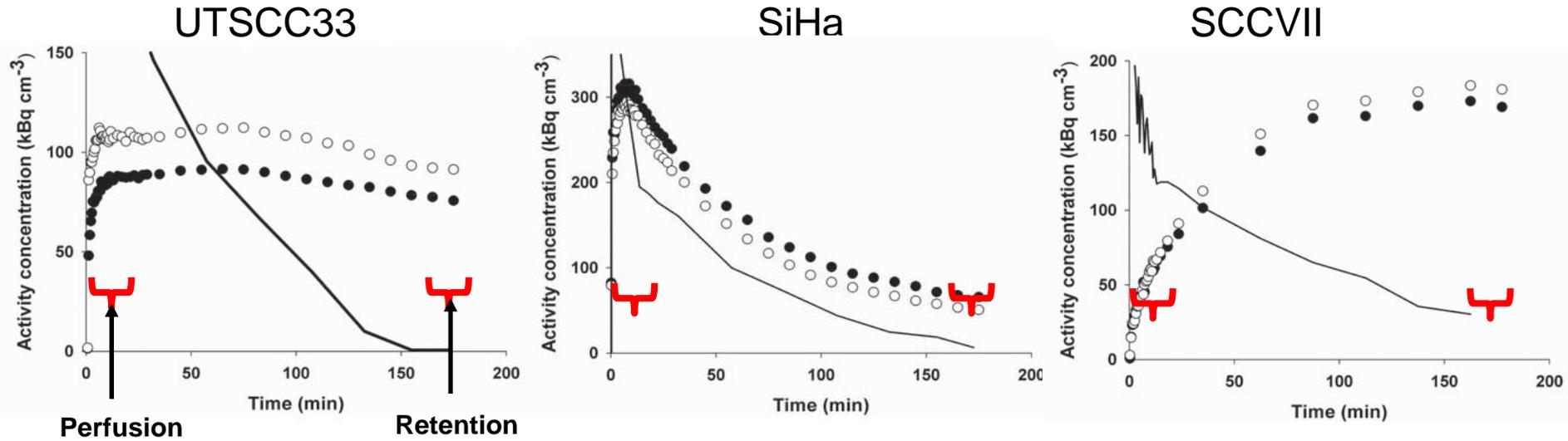
Reproducibility during treatment

0h, 0 Gy   24h, 0 Gy   72h, 10 Gy   144h, 25 Gy
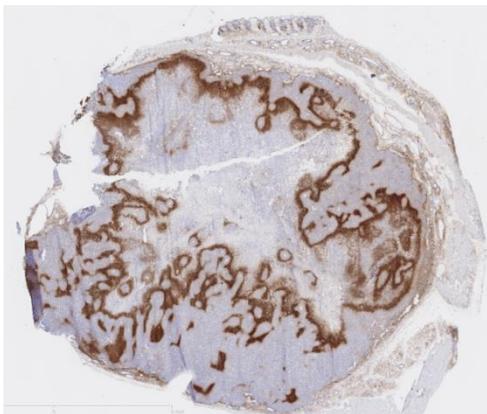
Day 1   Day 2

R=0.87

We can do better, in terms of improving contrast and accuracy, if we use the information hidden in dynamic scans (Alber/Thorwarth)
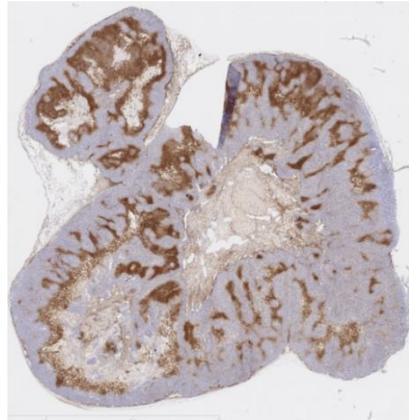
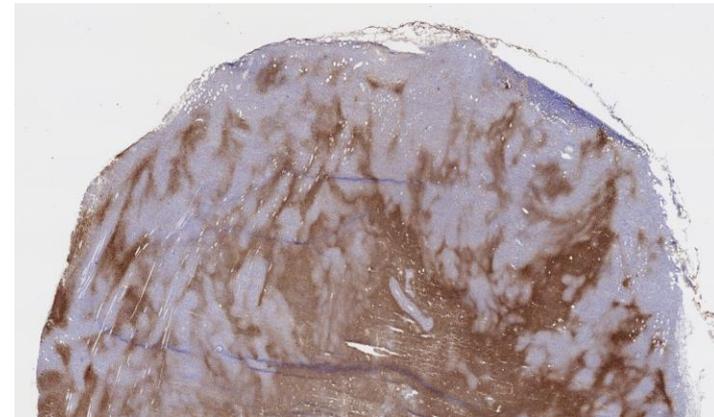Time activity curves for tumors reveals widely differing perfusion and tracer retention patterns

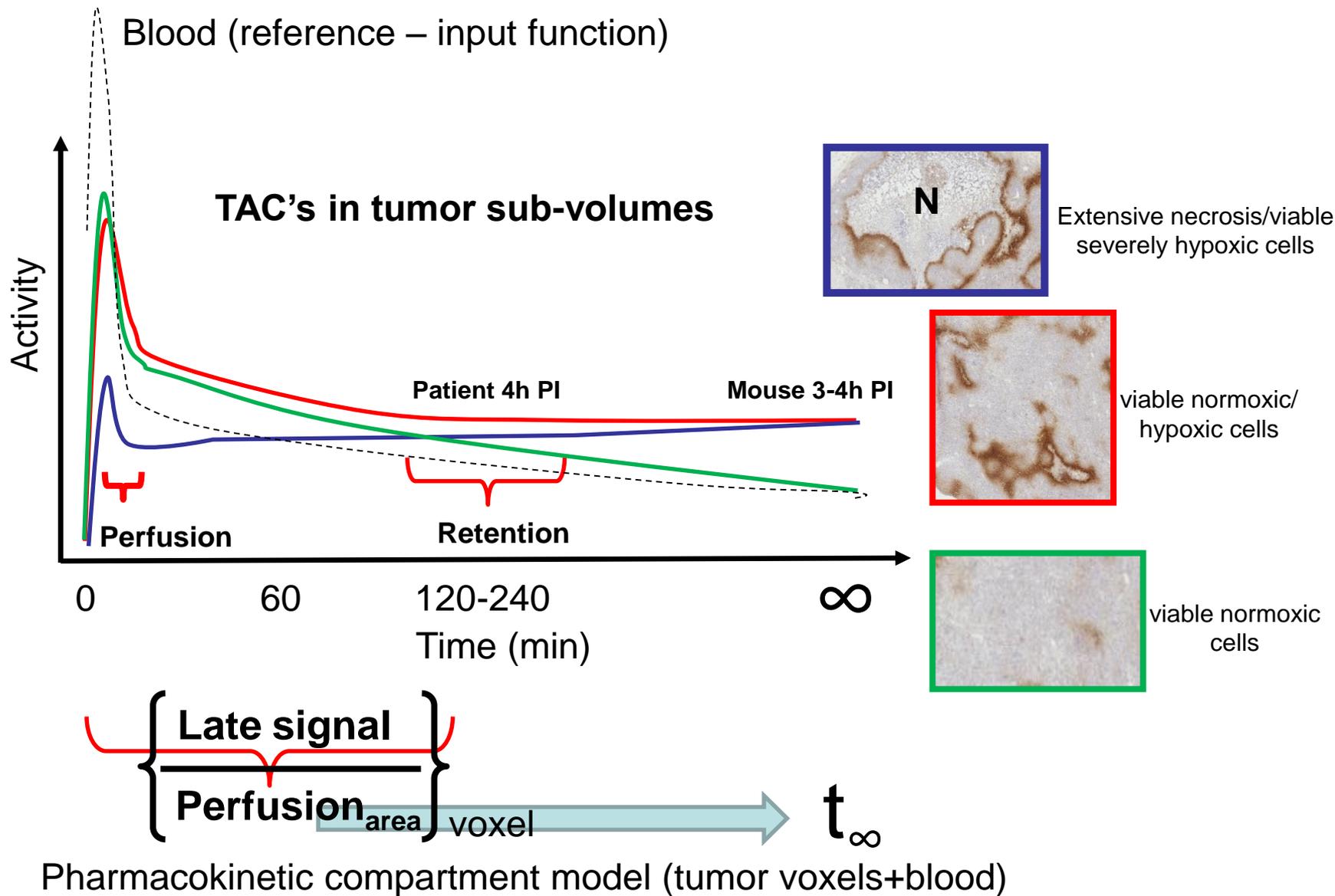Intratumoral distribution of hypoxic cells assessed in tissue sections

Full vs reduced (clinically feasible) dynamic PET scans (Alber/Thorwarth)

Blood (reference – input function)

TAC's in tumor sub-volumes

Activity

Patient 4h PI   **Mouse 3-4h PI**

Perfusion   **Retention**

0   60   120-240   ∞

Time (min)

N

Extensive necrosis/viable severely hypoxic cells

viable normoxic/ hypoxic cells

viable normoxic cells

$$\left\{ \frac{\text{Late signal}}{\text{Perfusion}_{\text{area}}} \right\}_{\text{voxel}} \quad t_{\infty}$$
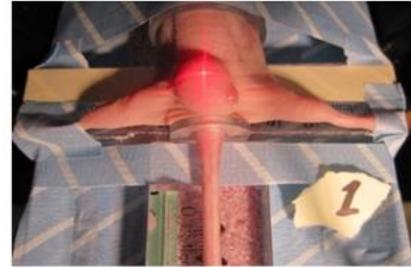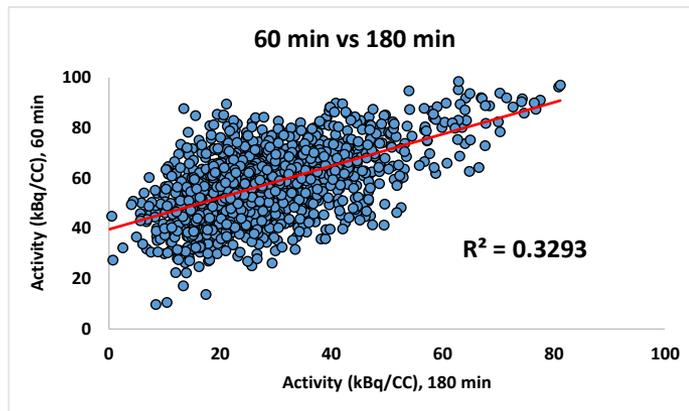
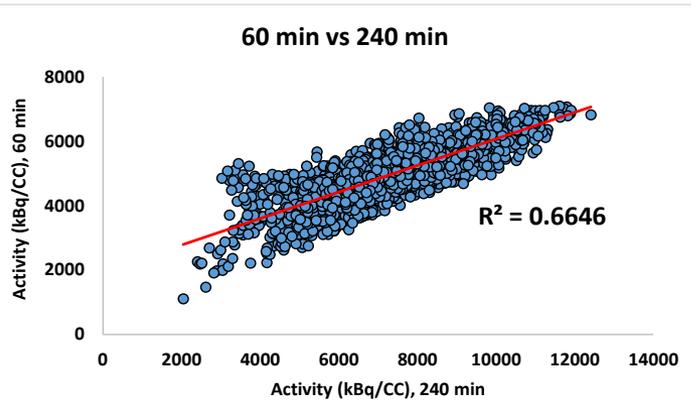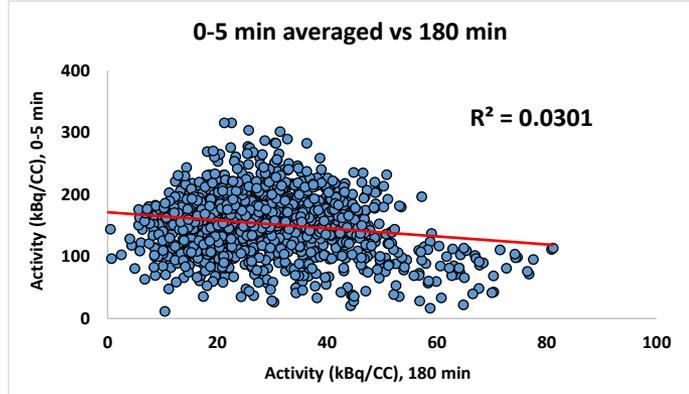Pharmacokinetic compartment model (tumor voxels+blood)

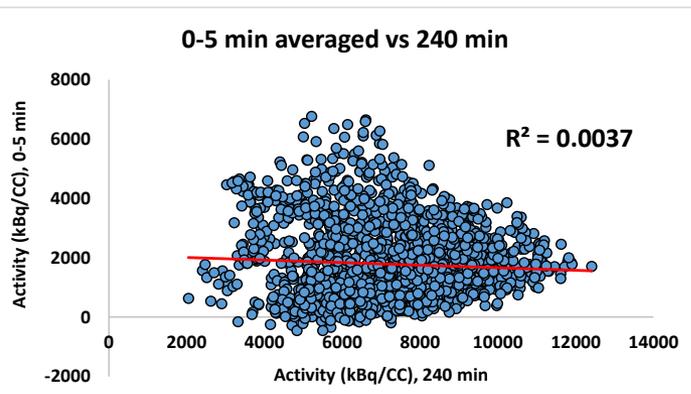# Dynamic microPET, voxel size: ~0.8, 0.8, 1.2 mm
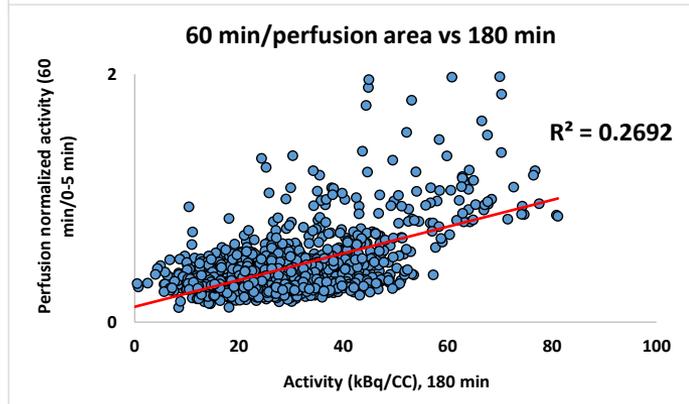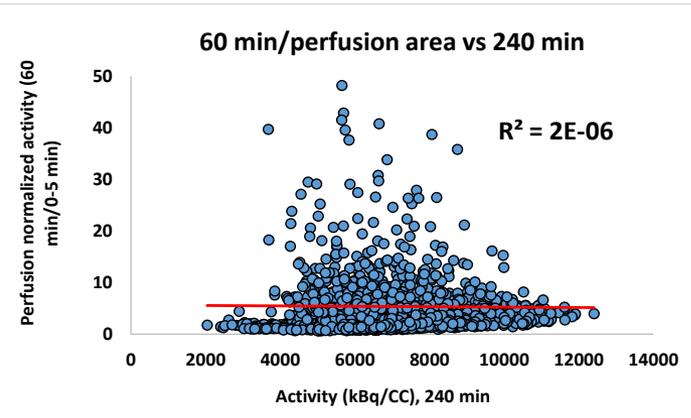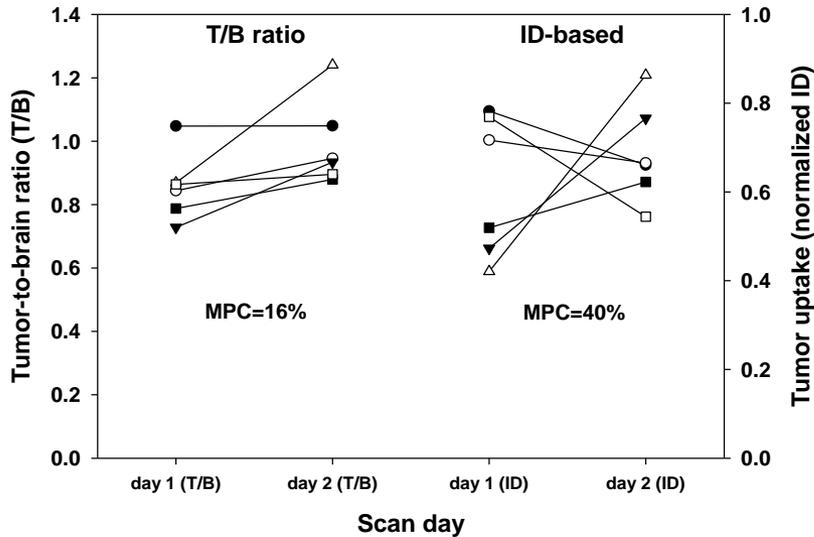

SCCVII – mouse flank tumor

R1 rat foot tumor

Early_{60 min} vs. Late_{180/240 min}

Perfus._{0-5 min} vs. Late_{180/240 min}
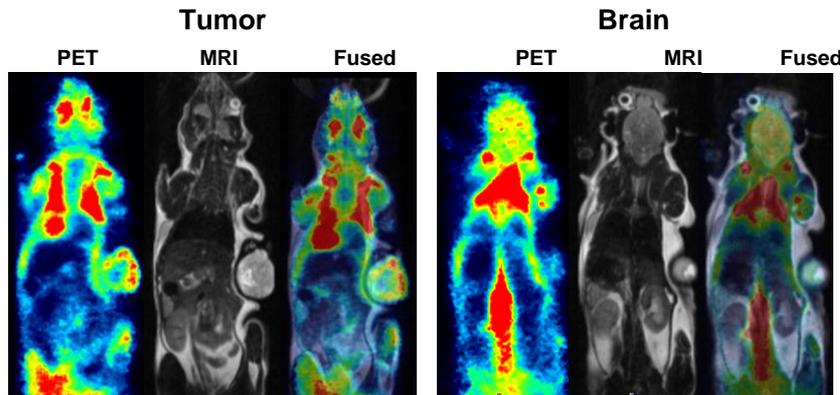
$\frac{Early_{60\ min}}{perfus._{0-5\ min}}$ vs. Late_{180/240 min}
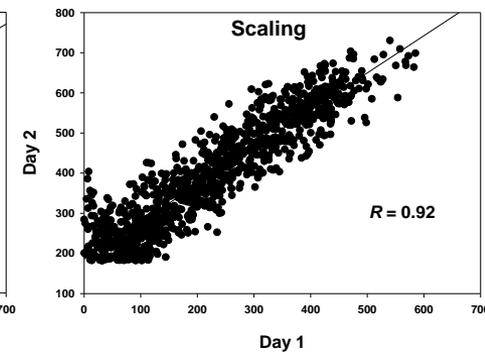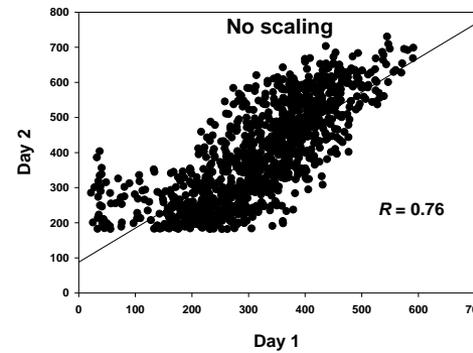
FDG-PET reproducibility in mice bearing C3H tumors – stability of target in 4D

Whole-tumor uptake

Intratumoral distribution
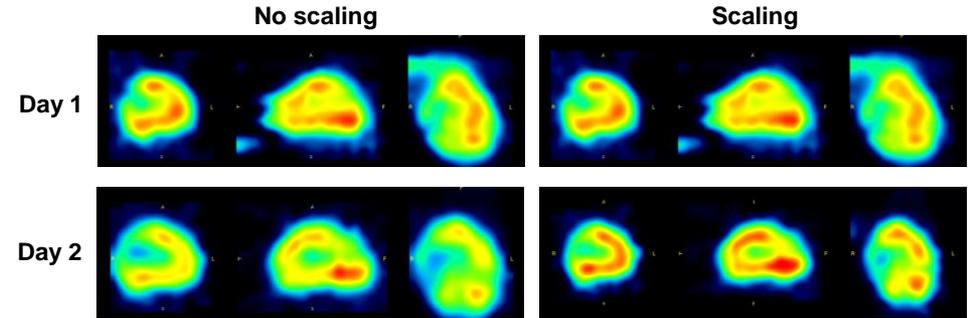
In summary

- PET provides reasonably accurate tumor hypoxia-maps (in mice) also at relatively low contrast (~1.5h PI) suggesting that hypoxia PET may be sufficient accurate to guide dose painting

- FAZA PET is reproducible at baseline and foci of intense tracer retention are spatially rather stable during therapy

- Reduced kinetic analysis combining perfusion related tracer distribution (first few min) and retention-potential (last frames) does not improve the quantitative accuracy of hypoxia PET in our models (voxel noise, no relationship between blood flow and O_2 delivery capacity)

- FDG-PET displays excellent reproducibility when using a brain normalization-approach. Further, the spatial reproducibility is high.

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- **Lene H Skjærris**

Glucose and hypoxia PET in tumor-bearing rodents

- Assess/define limitations in PET-based target definition, which may depend on intended treatment (e.g., chemotherapy, radiotherapy + magic pill, vs. dose painting)

- Improve current scan protocols to improve robustness and reliability

- Assess the usefulness of such protocols to guide and monitor treatment such as dose painting

Why are hypoxia and glucose metabolism interesting targets in (radio)therapy?

- Hypoxia is linked to chemo- and radio-resistance and aggressive disease progression

- Glucose is linked to overall metabolism, proliferation (Warburg effect), cell density and hypoxia (Pasteur) and excessive glucose consumption thus recapitulates many features of aggressive disease

Quantification of FDG PET in C3H tumor-bearing mice - using reference tissue normalization

Ex vivo biodistribution –interanimal variability
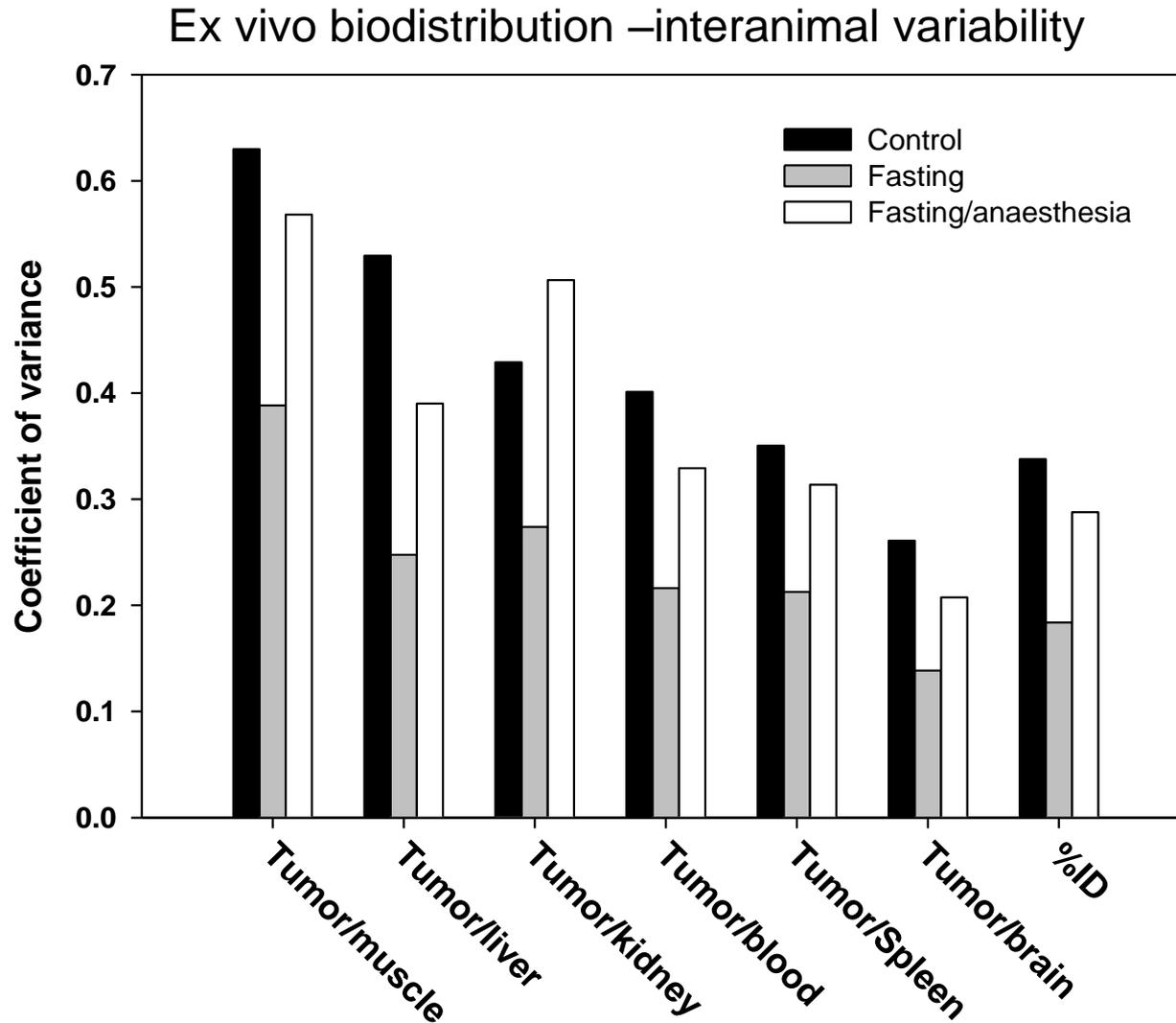
Clinically relevant partial dynamic protocol
(Thorwarth/Alber 2013)