Benefit of multimodal MRI to follow in vivo tumor microenvironment changes during therapy

Roxane Autissier, Leslie Mazuel, J.-M. Bonny, Philippe Auzeloux, Sébastien Schmitt, Amidou Traoré, Elisabeth Miot - Noirault, Guilhem Pagès

BENEFIT OF MULTIMODAL MRI TO FOLLOW *IN VIVO* TUMOR MICROENVIRONMENT CHANGES DURING THERAPY

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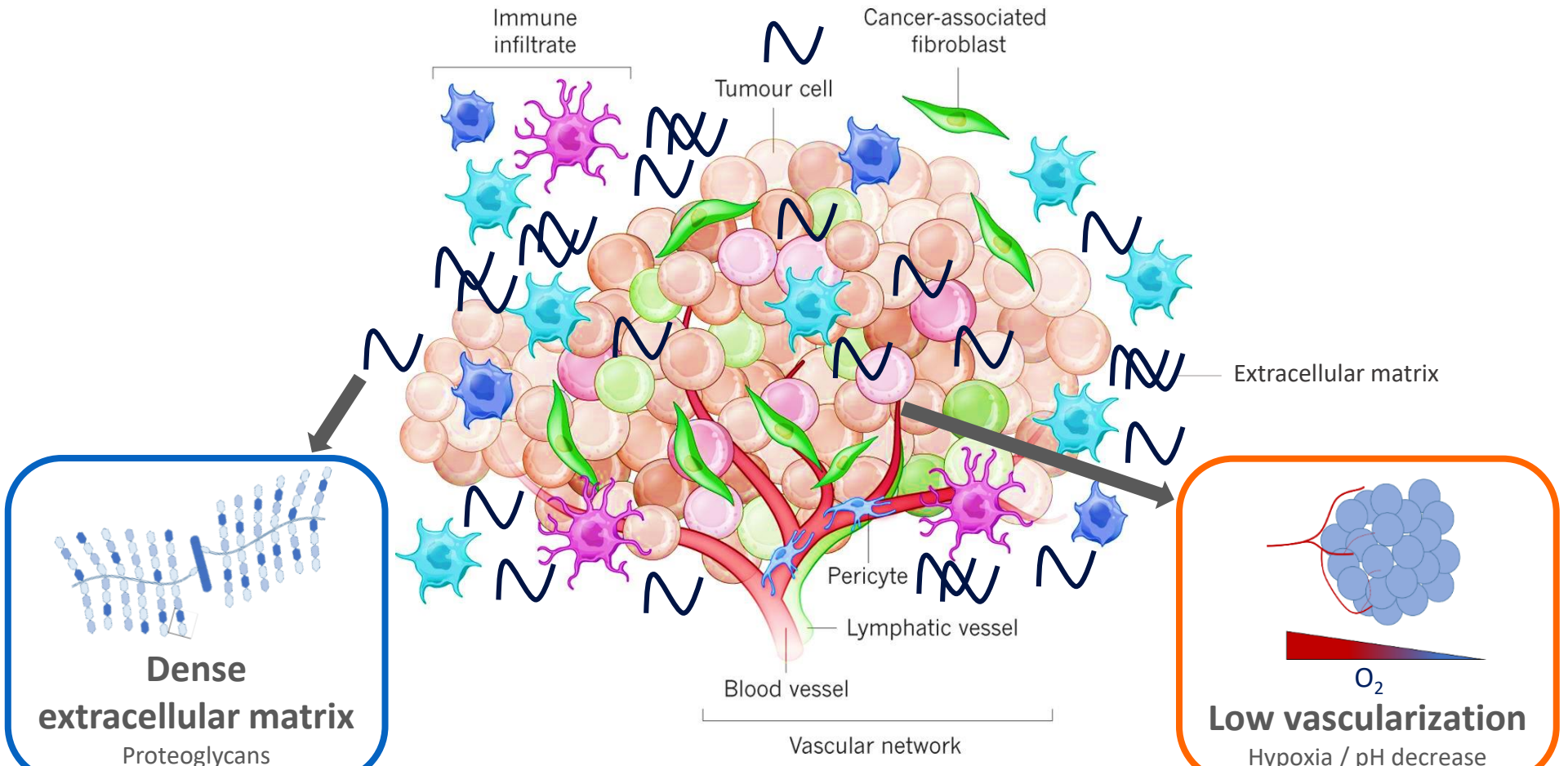
Context: Tumor microenvironment



CHONDROSARCOMA

Kouvaras E et al., 2019, Biotech Histochem
Sweet MB et al., 1976, Biochim Biophys Acta

Context: Previous work

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Simultaneous proteoglycans and hypoxia mapping of chondrosarcoma environment by frequency selective CEST MRI

Roxane Autissier, Leslie Mazuel, Elise Maubert, Jean-Marie Bonny, Philippe Auzeloux, Sébastien Schmitt, Amidou Traoré, Caroline Peyrode, Elisabeth Miot-Noirault, Guilhem Pagés,

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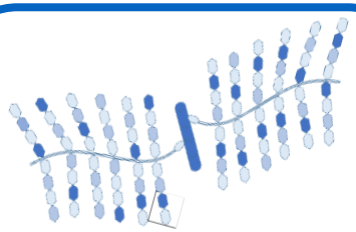
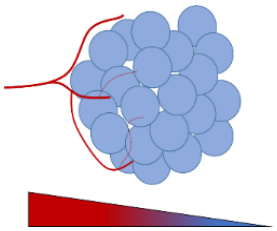


Dense extracellular matrix

Proteoglycans



O_2

Low vascularization

Hypoxia / pH decrease

Working hypothesis

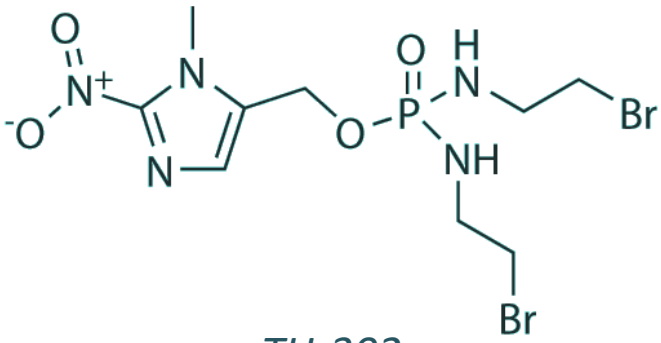
Is multimodal MRI able to detect tumor microenvironment changes during therapy ?

Context: TH-302, an innovative treatment

NIH - National cancer institute definition:

A **hypoxia-activated prodrug** […] introduces intra- and inter-strand DNA crosslinks in nearby cells; the crosslinks **inhibit both DNA replication and cell division**, and may **lead to apoptosis of cells** in the tumor. The inactive form of the prodrug is stable under normoxic conditions, which may limit systemic toxicity.

- Phase III clinical trials (x2)
- TH-302 is effective in osteosarcoma
- No information about chondrosarcoma



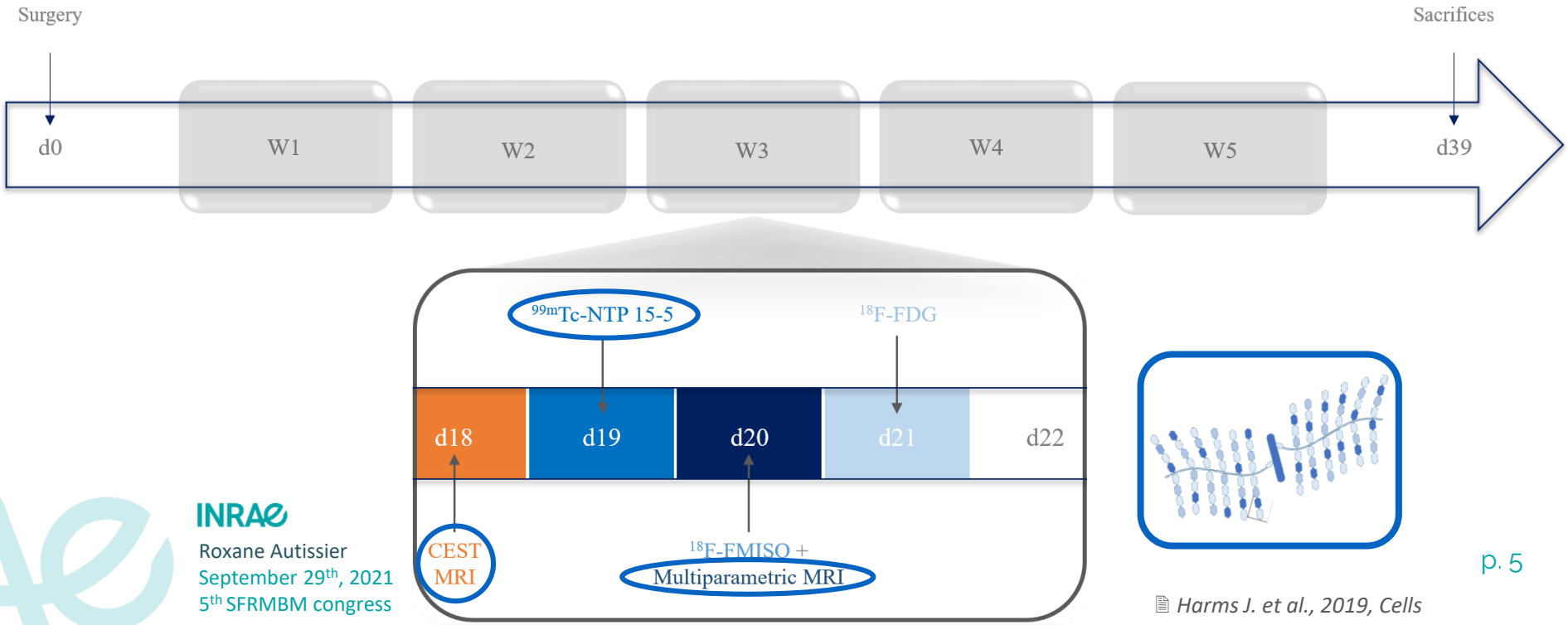
TH-302

Liapis V. et al., 2015, Cancer Lett.

Methods: Study design

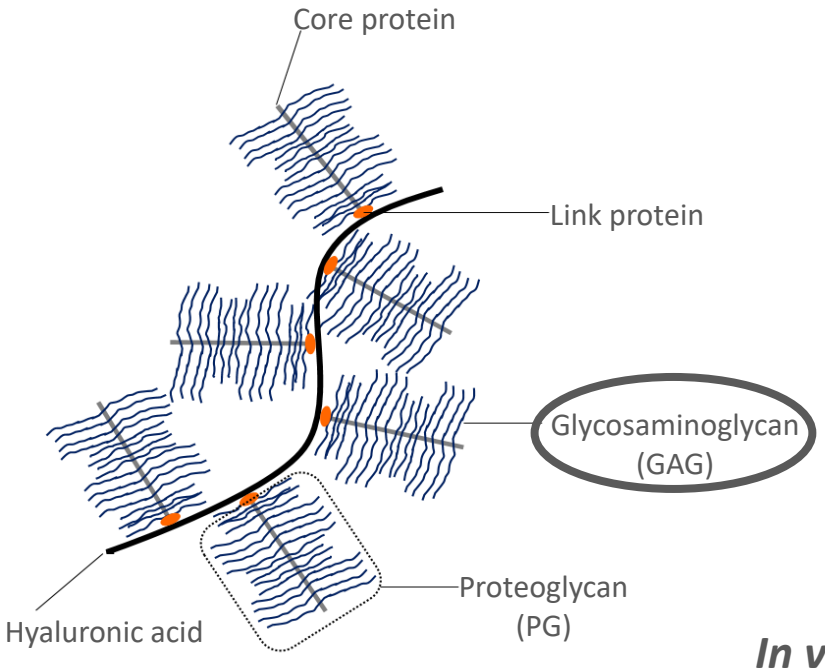
Paratibial Swarm rats follow-up during 5 weeks with TH-302 → (n=35)

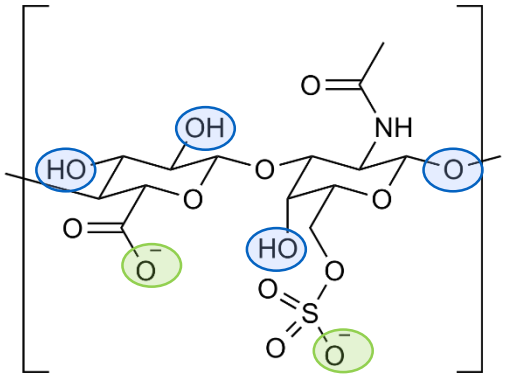
- Treatment:
  - 50mg/kg
  - i.p injection once a day for 5 days followed by 2 days of rest
  - d+11 to d+22



Harms J. et al., 2019, Cells

Methods: Extracellular matrix imaging





Chondroitin sulfate

In vivo Imaging

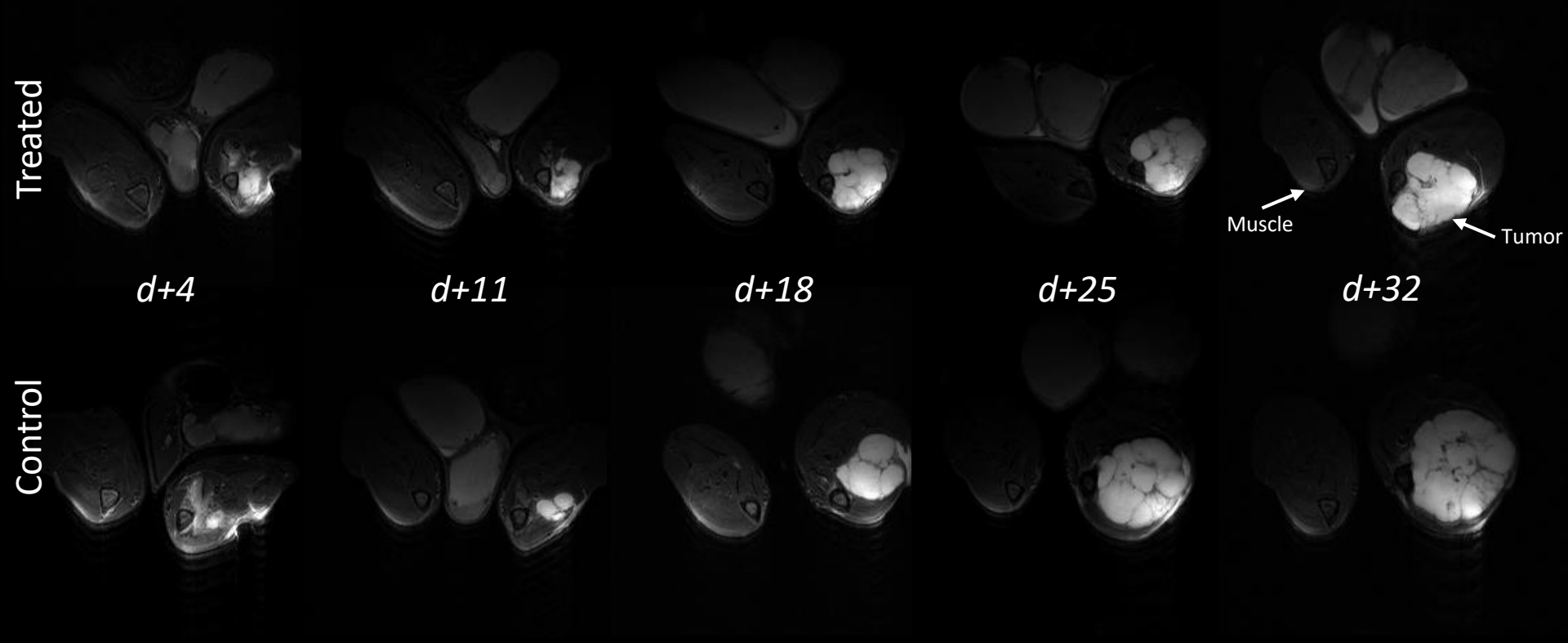
Magnetic resonance imaging
11,7 T
T2 / Diffusion weighted imaging

Magnetic resonance imaging
11,7 T
GAG CEST
Hydroxyl moieties signal

Nuclear imaging
^{99m}Tc-NTP 15-5
Negative charges targeting

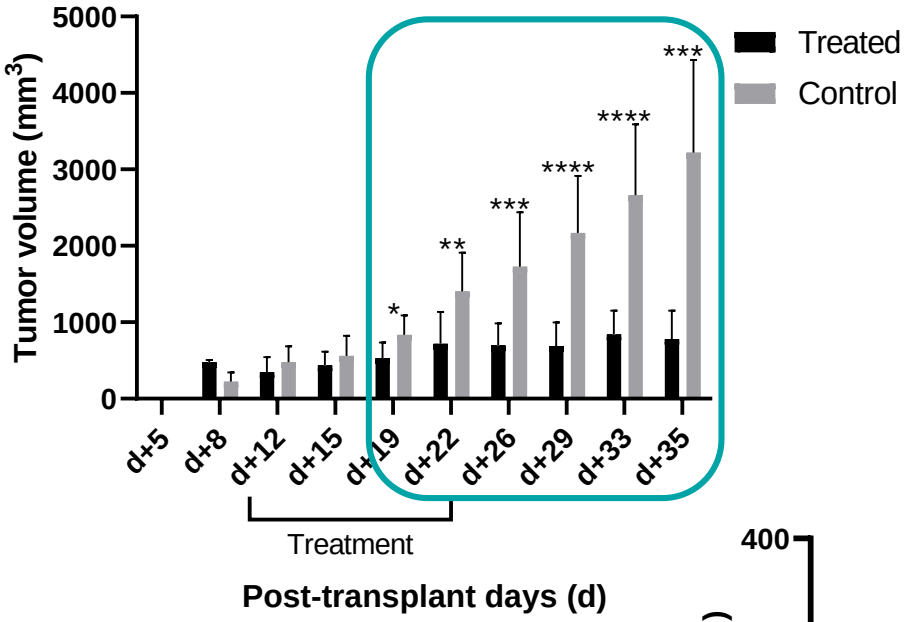
Aigner T. et al., 2002, Cancer
Vidal A. et al., 2015, Appl. Radiat. Isot.
Ling W. et al., 2008, PNAS

Results: T2 weighted MRI at 11.7 T

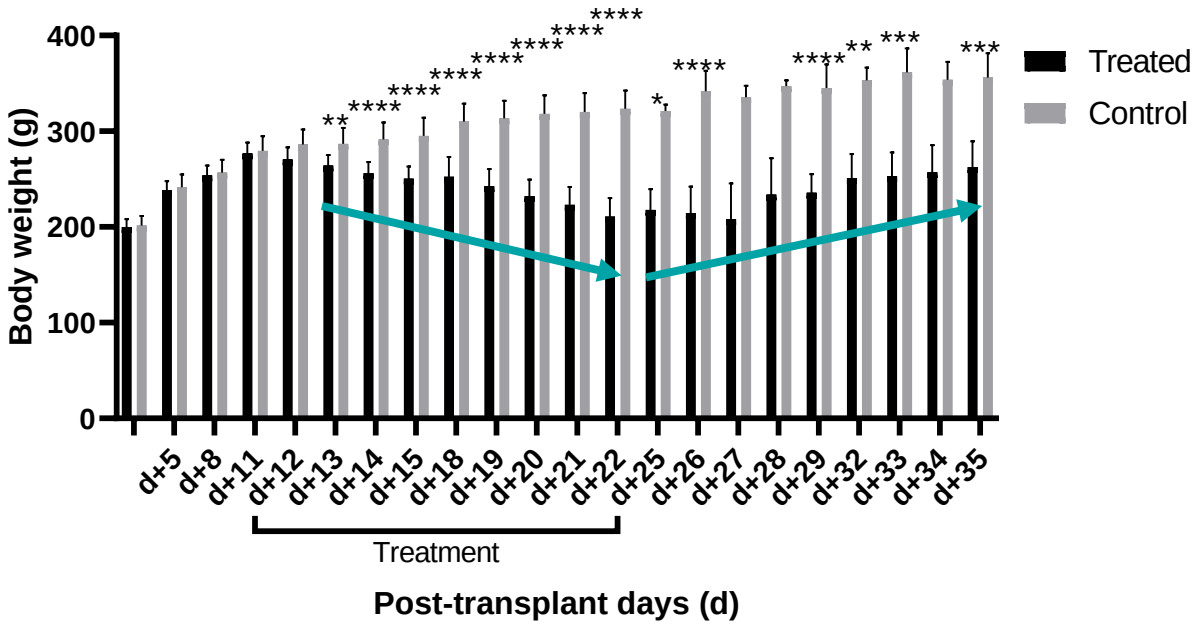


- Tumor has T2 hypersignal
- Cauliflower-shaped tumor
- Visual differences in tumor volumes between treated and control groups

Results: Tumor volume & body weight

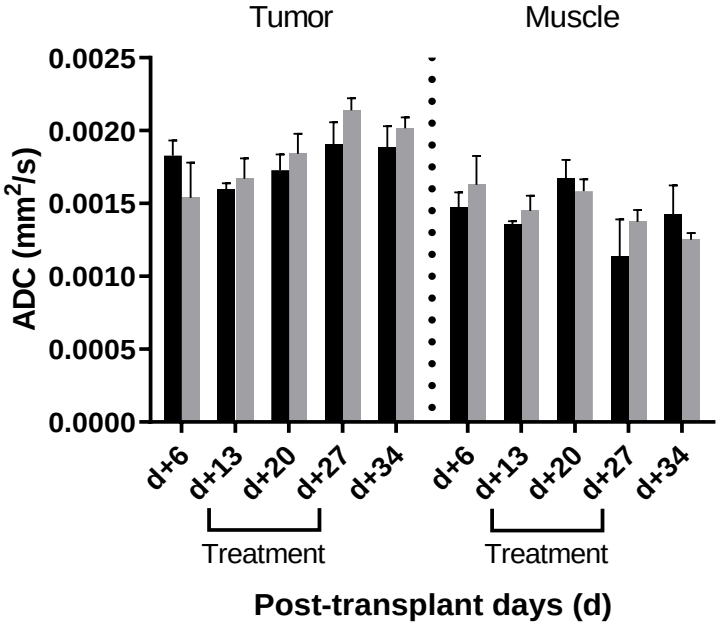


- The treatment reduces significantly tumor growth even after the end of therapy
- Side-effects tend to diminish after discontinuation of chemotherapy

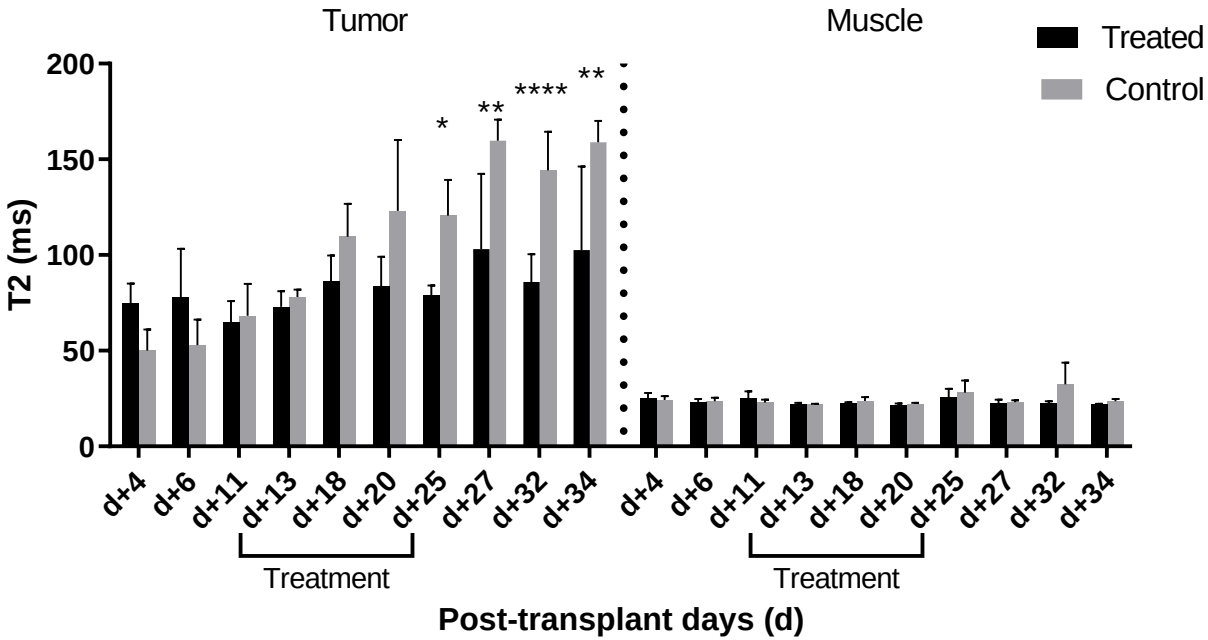


Mean±SD, Sidak's multiple comparisons test (n=35)

Results: Multiparametric MRI



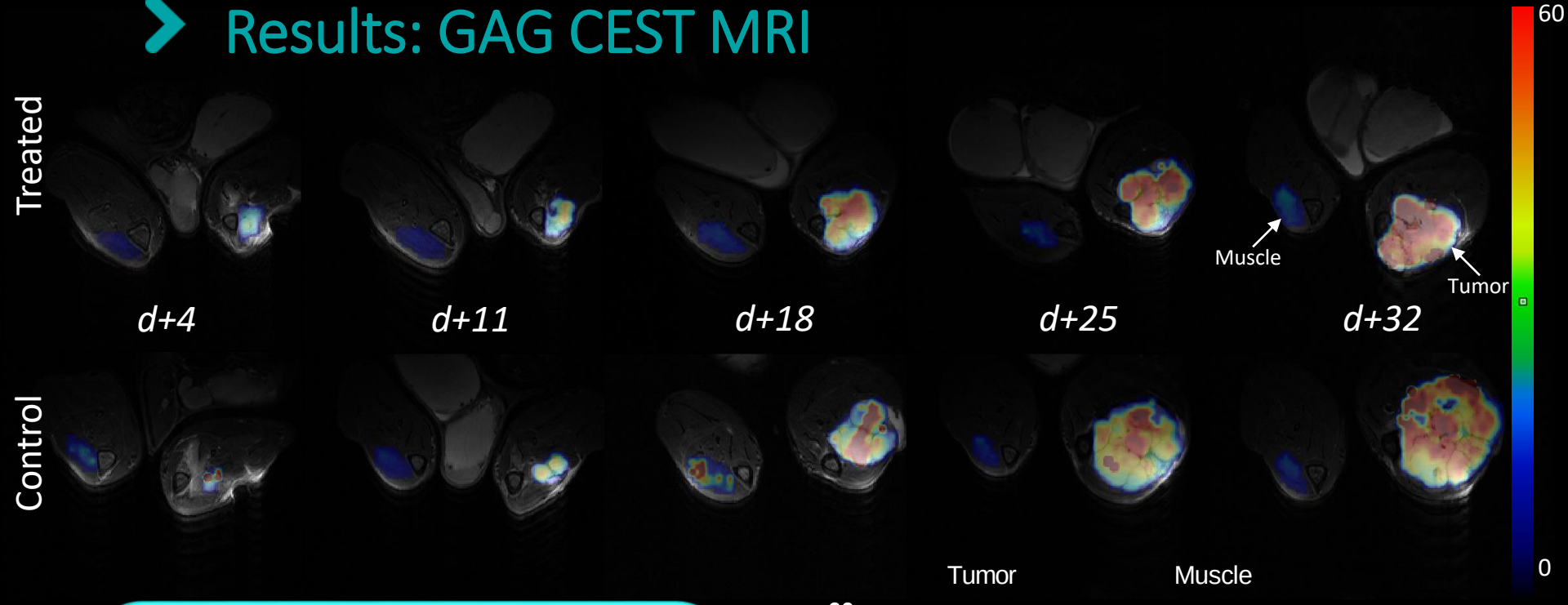
- ADC is higher in tumor than muscle
- ADC increases in tumor and remains stable in muscle over time
- No significant difference between treated and control groups



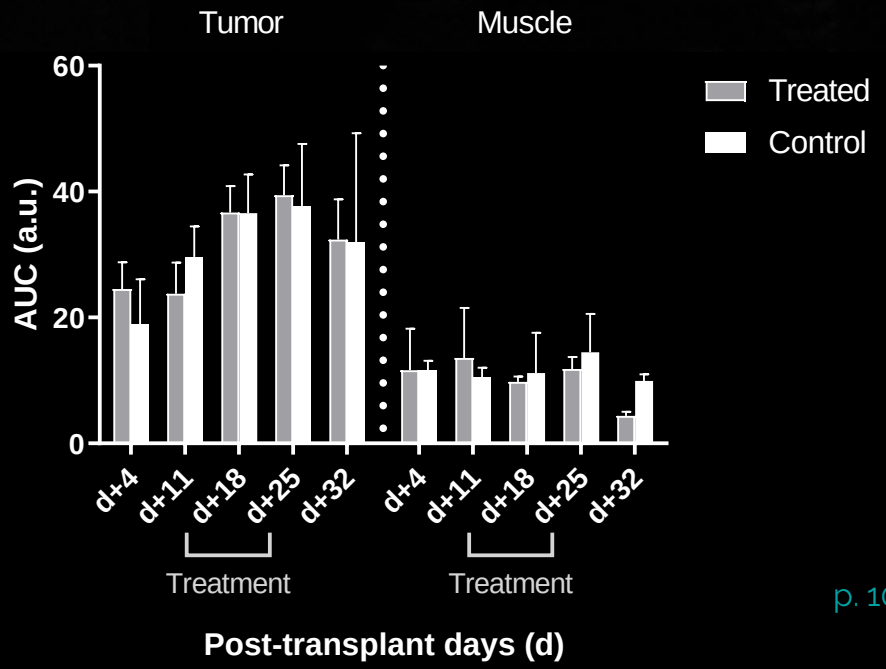
- T2 is higher in tumor than muscle
- T2 increases in tumor and remains stable in muscle over time
- Significant differences from the end of treatment

Mean±SD, Tukey's multiple comparisons test (n=8)

Results: GAG CEST MRI

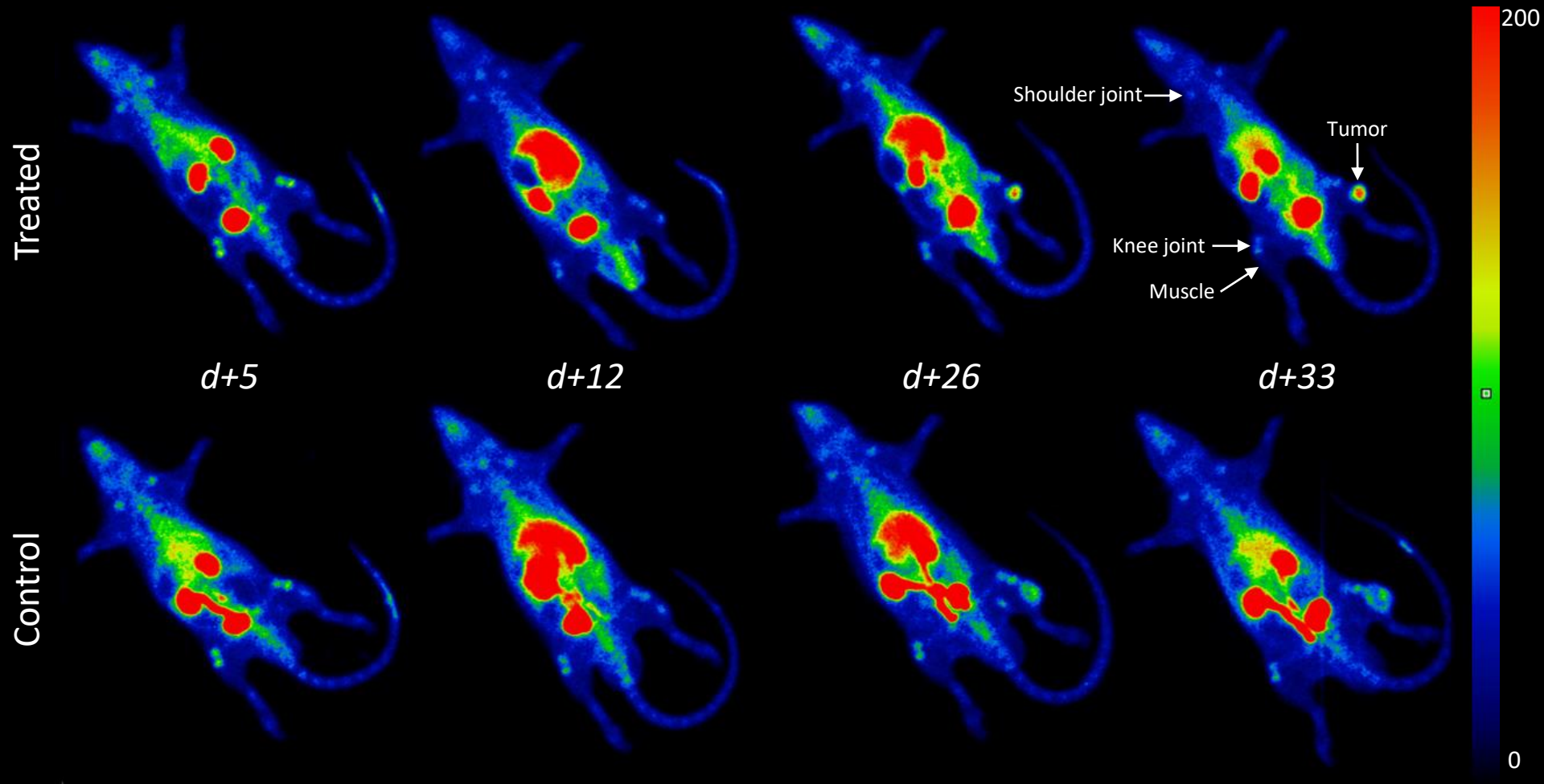


- GAG CEST effect is higher in tumor than muscle
- GAG CEST effect increases in tumor and remains stable in muscle over time
- No significant difference between treated and control groups
- High spatial resolution is provided by CEST MRI → Tumor heterogeneities +++

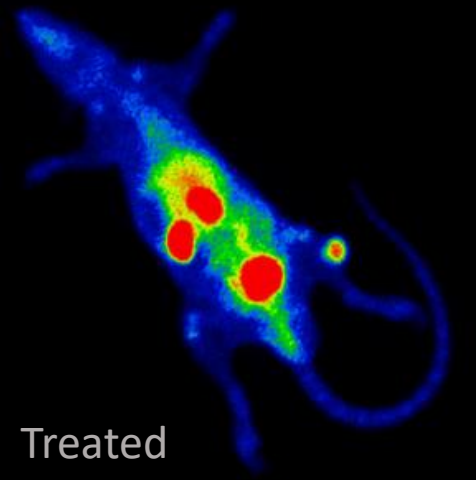


INRAE
Roxane Autissier
September 29th, 2021
5th SFRMBM congress

Results: ^{99m}Tc-NTP 15-5

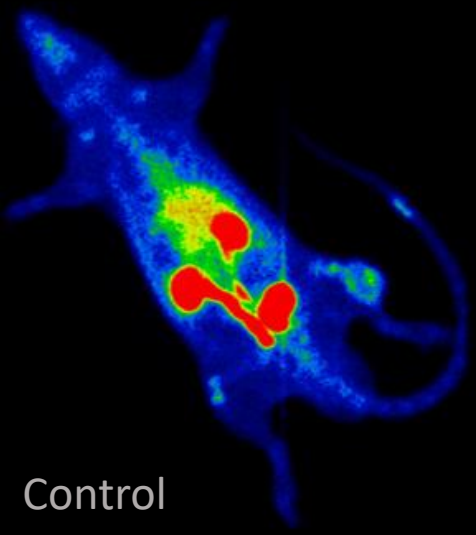


Results: ^{99m}Tc-NTP 15-5

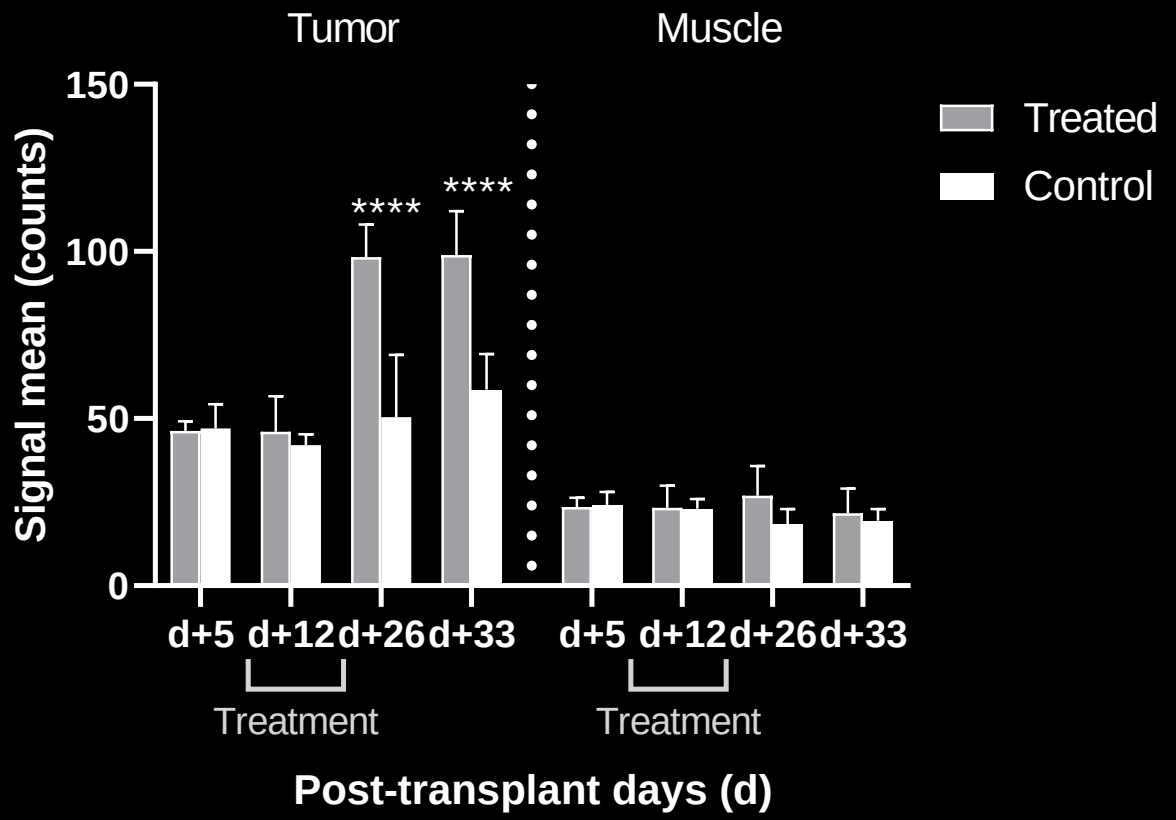


Treated

d+33



Control

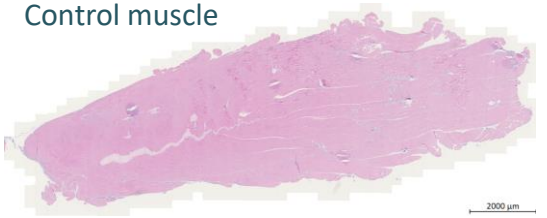


- Radiotracer signal is higher in tumor than muscle
- Activity increases in tumor and remains stable in muscle over time
- Significant differences in tumor between treated and control groups
- Are negative charges more accessible due to ECM modifications in treated tumors ?

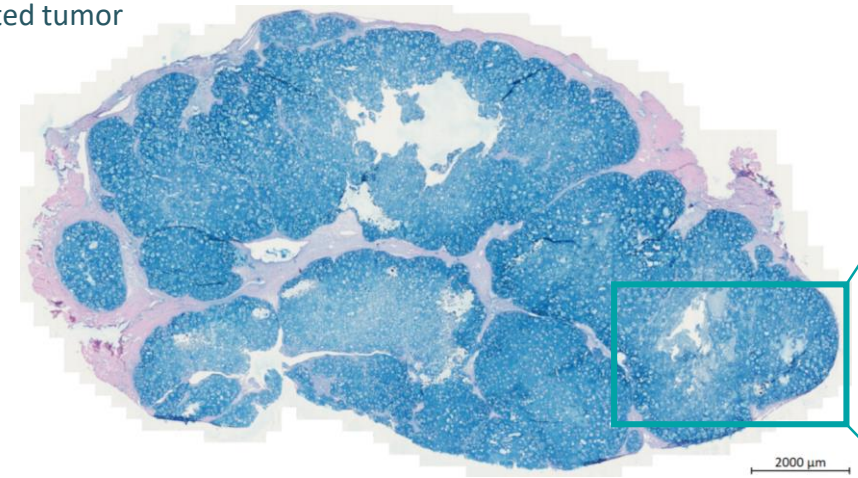
Mean±SD, Tukey's multiple comparisons test (n=8)

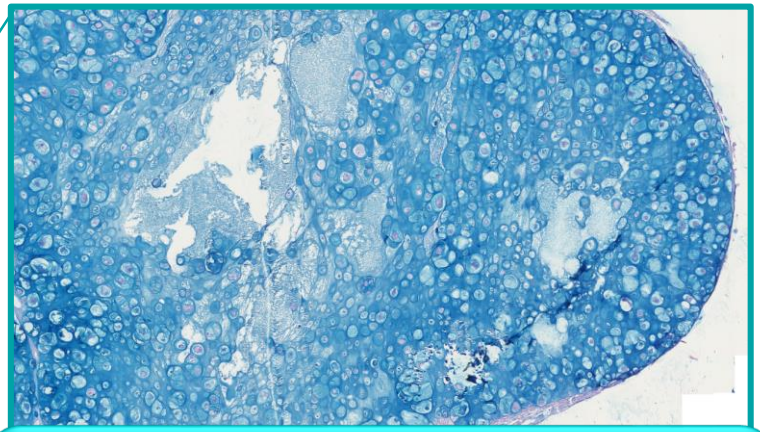
Results: Alcian blue staining

Control muscle

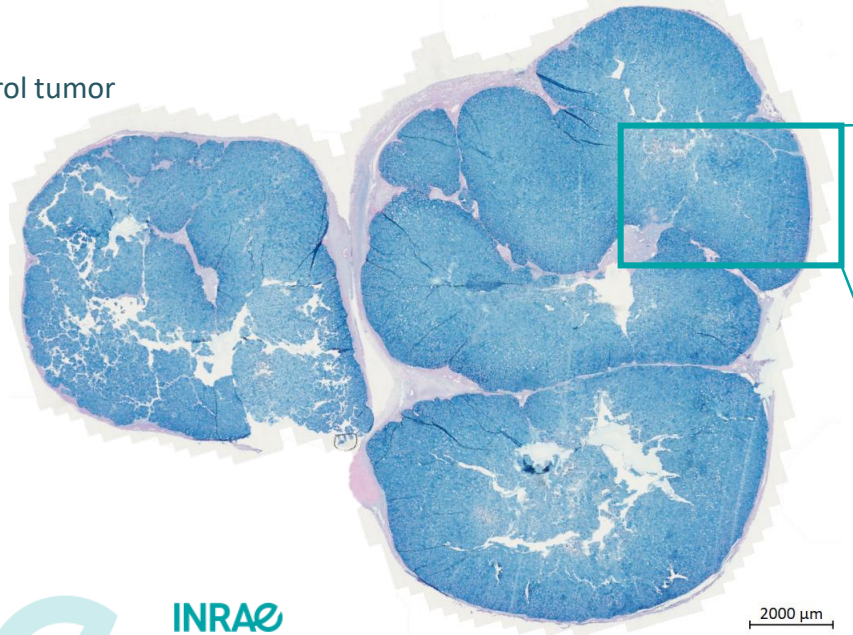


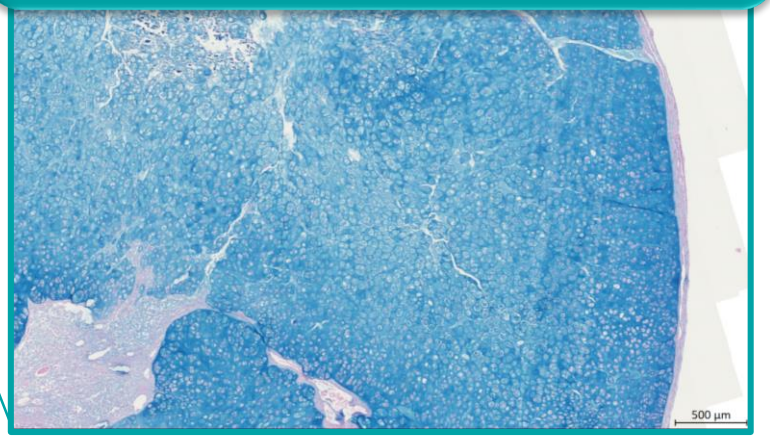
Treated tumor





Control tumor





- Proteoglycans are distributed in the whole tumor ECM but with heterogeneities
- Morphological differences in tumor ECM between treated and control groups

Take home message

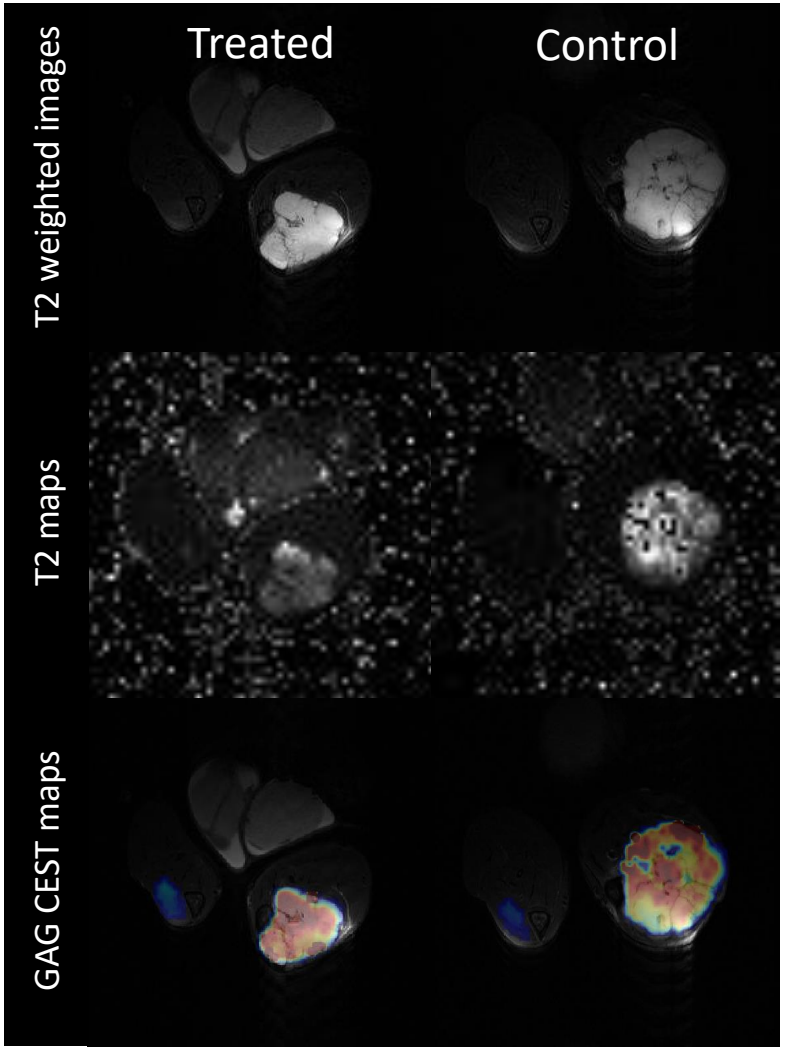
- TH-302:
  - Is effective on chondrosarcoma
  - has an impact on ECM

- T2 → loss of structural integrity
- CEST MRI → no proteoglycan content modification
- CEST MRI → heterogeneous proteoglycan distribution

- CEST MRI provides:
  - a non invasive method
  - contrast agent independence
  - high spatial resolution

Multimodal MRI is able to follow tumor ECM changes during therapy

To go further



- Take into account tumor heterogeneities for quantification
- Explore TH-302 effects on tumor hypoxia degree
- Use this original multimodal MRI approach to follow tumor microenvironment changes with other therapies

Acknowledgments

Thank you for your attention

Thanks to SFRMBM 2021 organization team

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Dr. Leslie Mazuel

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Any questions ?