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## **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

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Roxane Autissier, Leslie Mazuel, J.-M. Bonny, Philippe Auzeloux, Sébastien Schmitt, et al.. Benefit of multimodal MRI to follow in vivo tumor microenvironment changes during therapy. 5th SFRMBM, Sep 2021, LYON, France. hal-03369601

**HAL Id: hal-03369601**

**<https://hal.inrae.fr/hal-03369601v1>**

Submitted on 7 Oct 2021

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

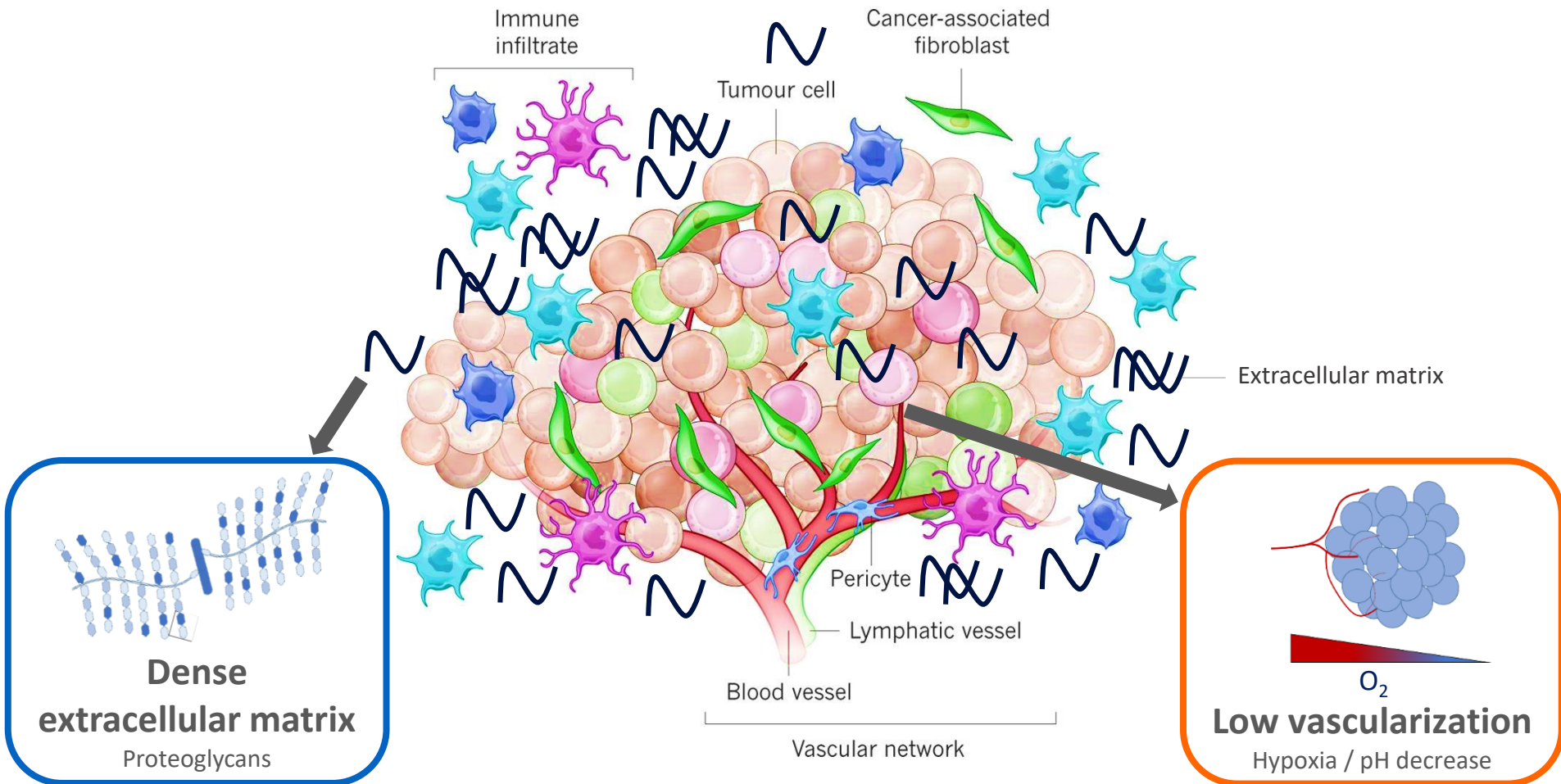
Roxane Autissier; Leslie Mazuel; Jean-Marie Bonny; Philippe Auzeloux;  
Sébastien Schmitt; Amidou Traoré; Elisabeth Miot-Noirault & Guilhem Pagés

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Roxane Autissier  
September 29<sup>th</sup>, 2021  
5<sup>th</sup> SFRMBM congress




# ➤ Context: Tumor microenvironment



## CHONDROSARCOMA

# ➤ Context: Previous work

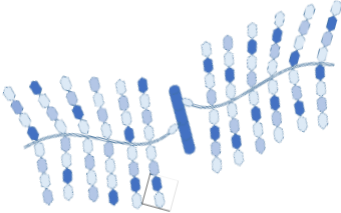
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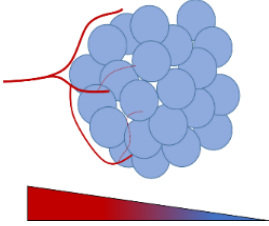
## Simultaneous proteoglycans and hypoxia mapping of chondrosarcoma environment by frequency selective CEST MRI

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

First published: 27 March 2021 | <https://doi.org/10.1002/mrm.28781>



**Dense extracellular matrix**  
Proteoglycans



**Low vascularization**  
Hypoxia / pH decrease



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## ➤ Working hypothesis

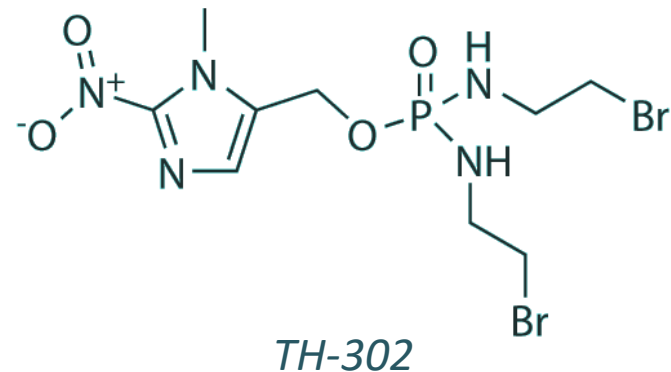
Is multimodal MRI able to detect tumor microenvironment changes during therapy ?

## ➤ 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



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Titre de la présentation

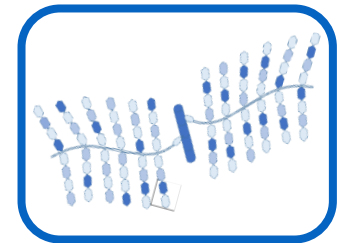
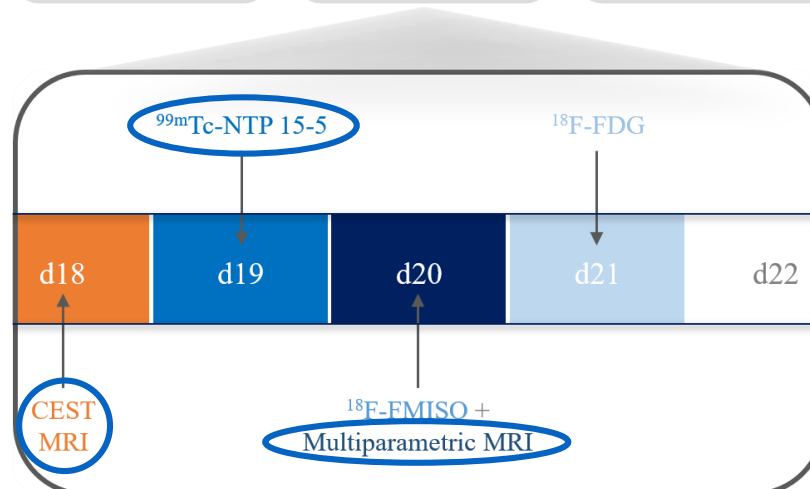
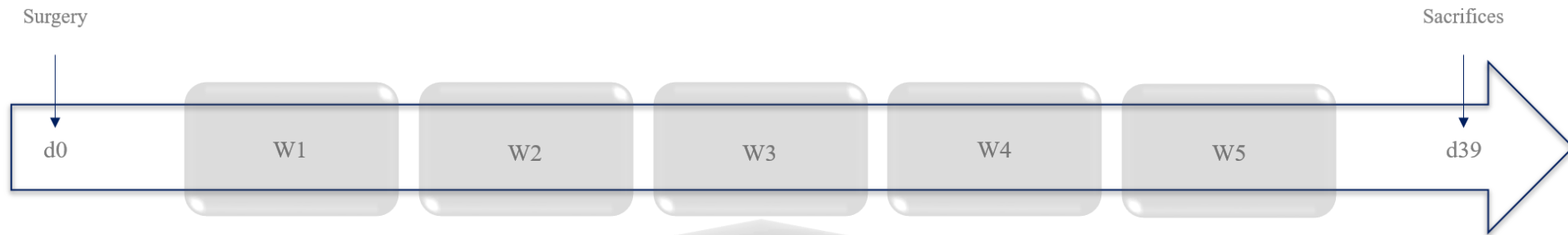
Date / information / nom de l'auteur

# ➤ Methods: Study design

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

## ❖ Treatment:

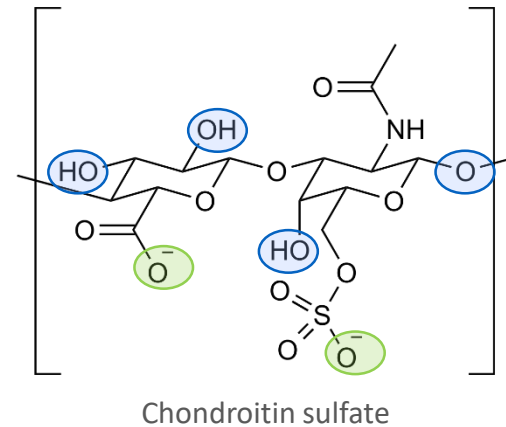
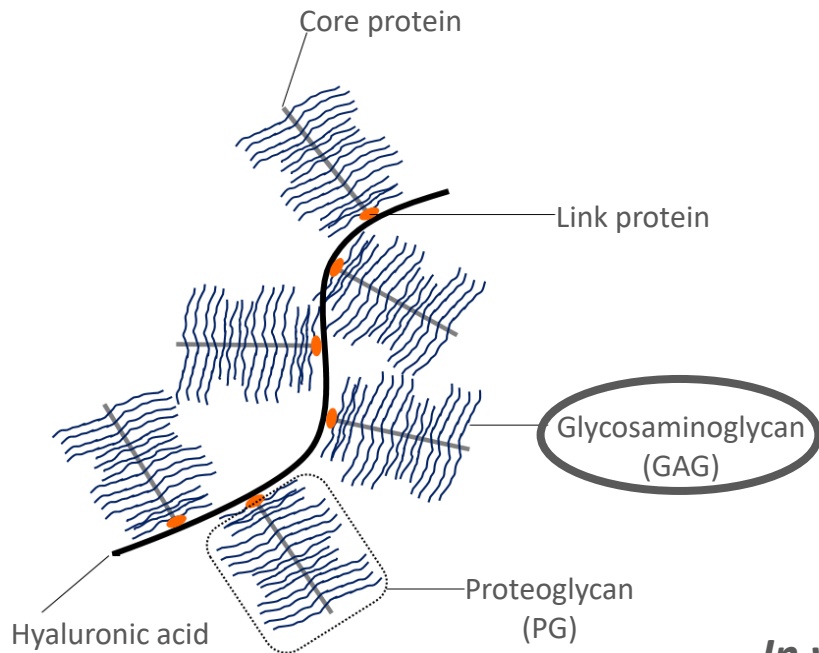
- 50mg/kg
- i.p injection once a day for 5 days followed by 2 days of rest
- d+11 to d+22



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# ➤ Methods: Extracellular matrix imaging



## *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**

**<sup>99m</sup>Tc-NTP 15-5**

*Negative charges targeting*

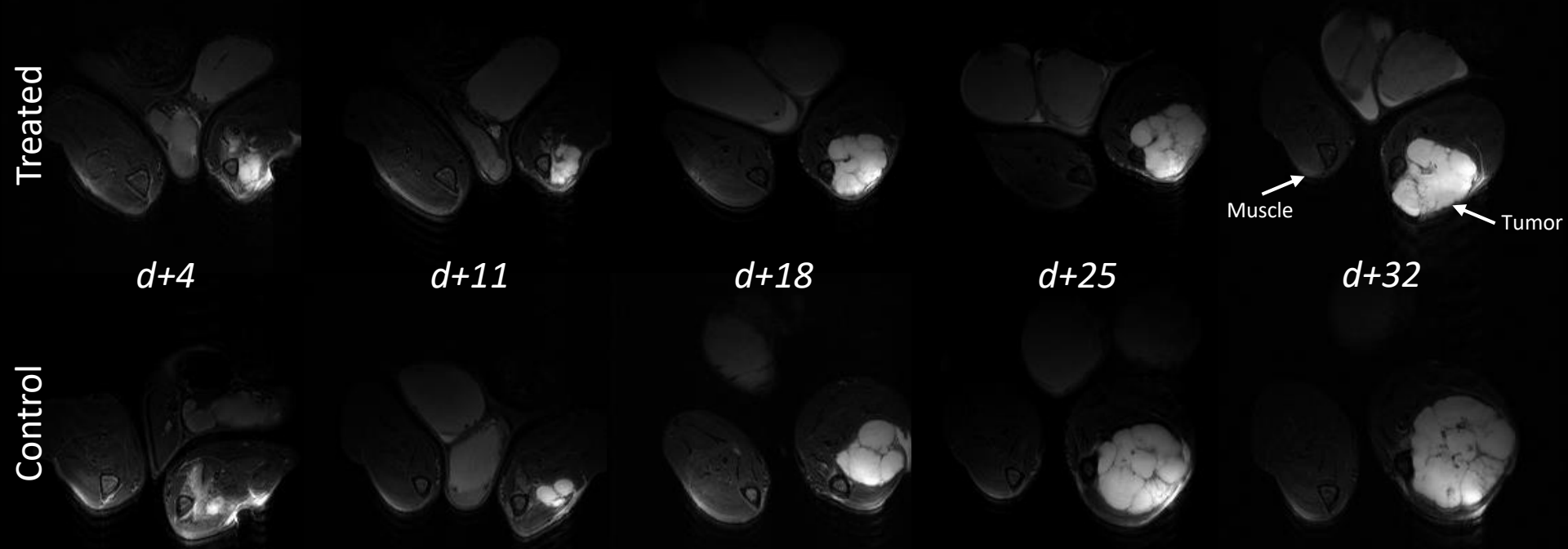


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Aigner T. et al., 2002, Cancer  
 Vidal A. et al., 2015, Appl. Radiat. Isot.  
 Ling W. et al., 2008, PNAS

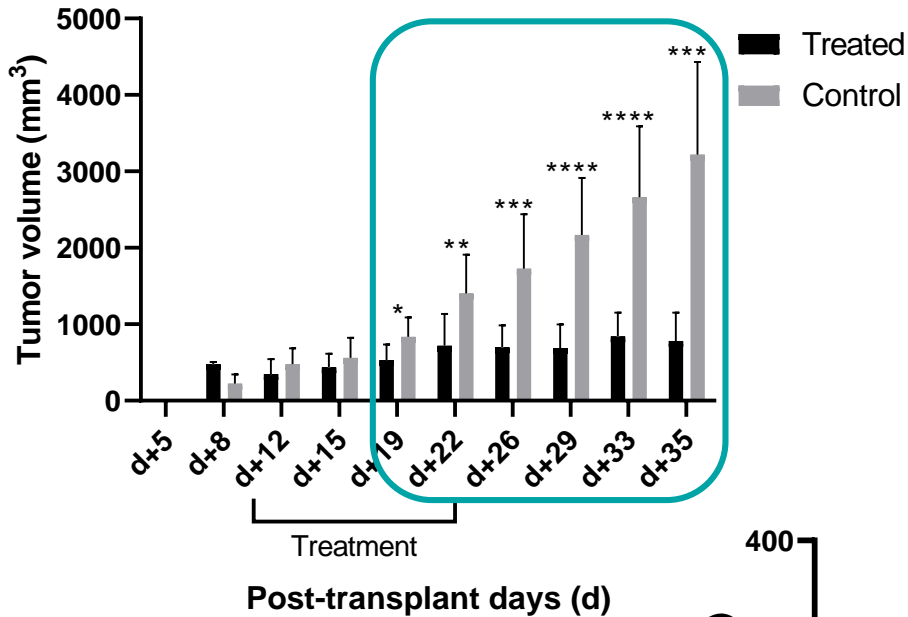
## ➤ Results: T2 weighted MRI at 11.7 T



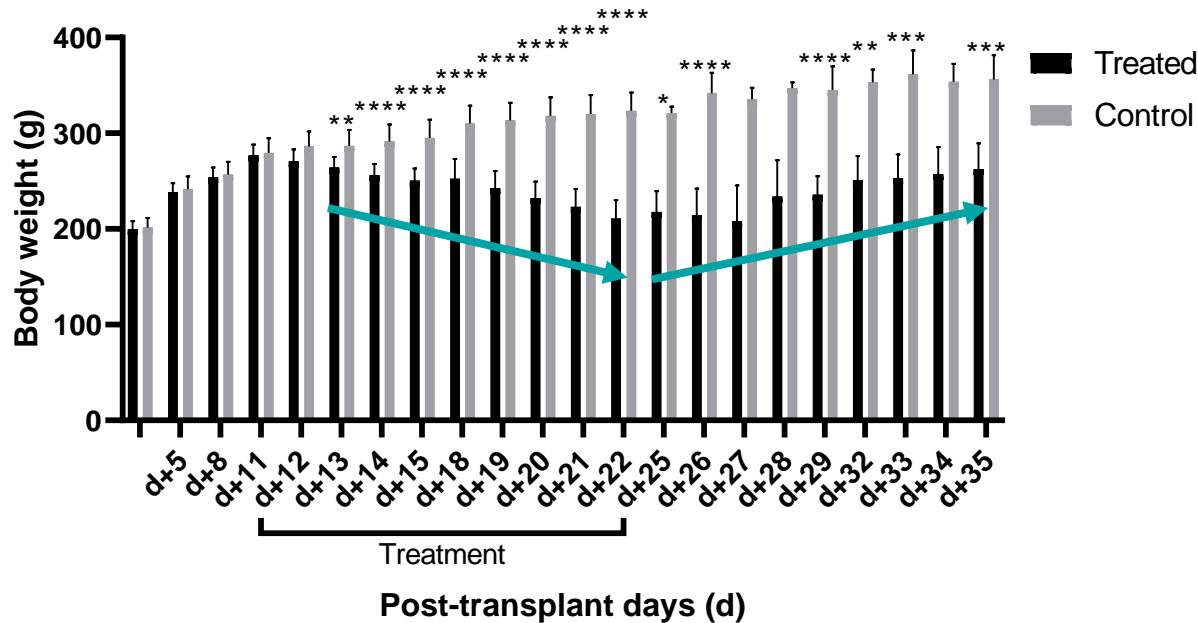
- ❖ Tumor has T2 hypersignal
- ❖ Cauliflower-shaped tumor
- ❖ Visual differences in tumor volumes between treated and control groups



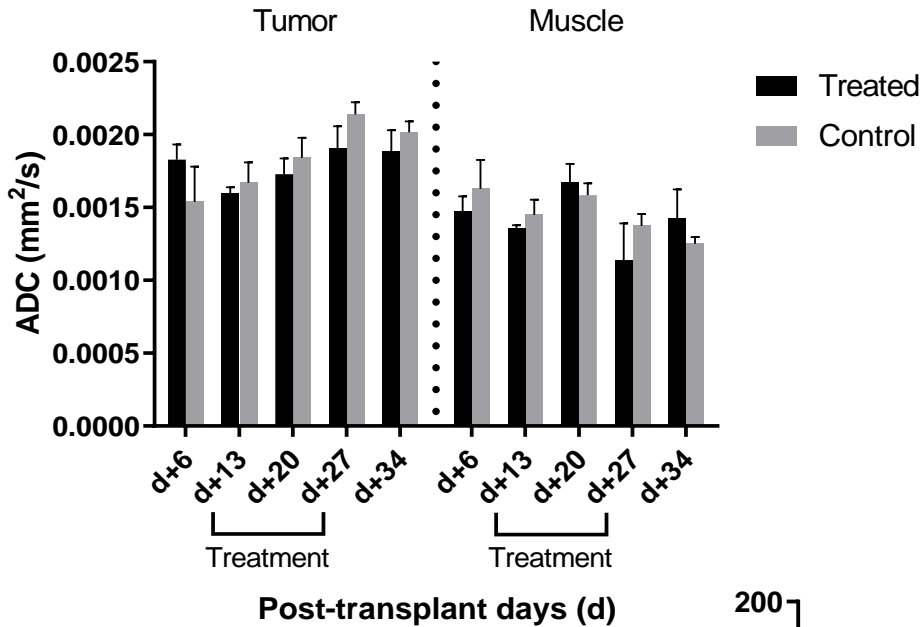
# ➤ Results: Tumor volume & body weight



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

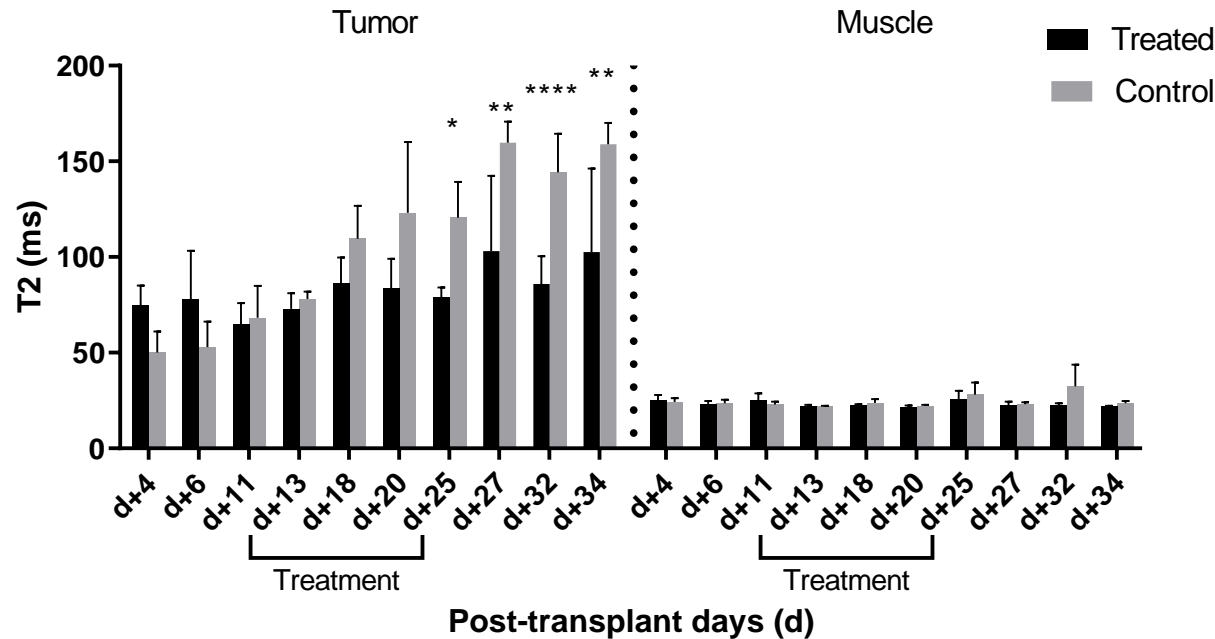


# Results: Multiparametric MRI

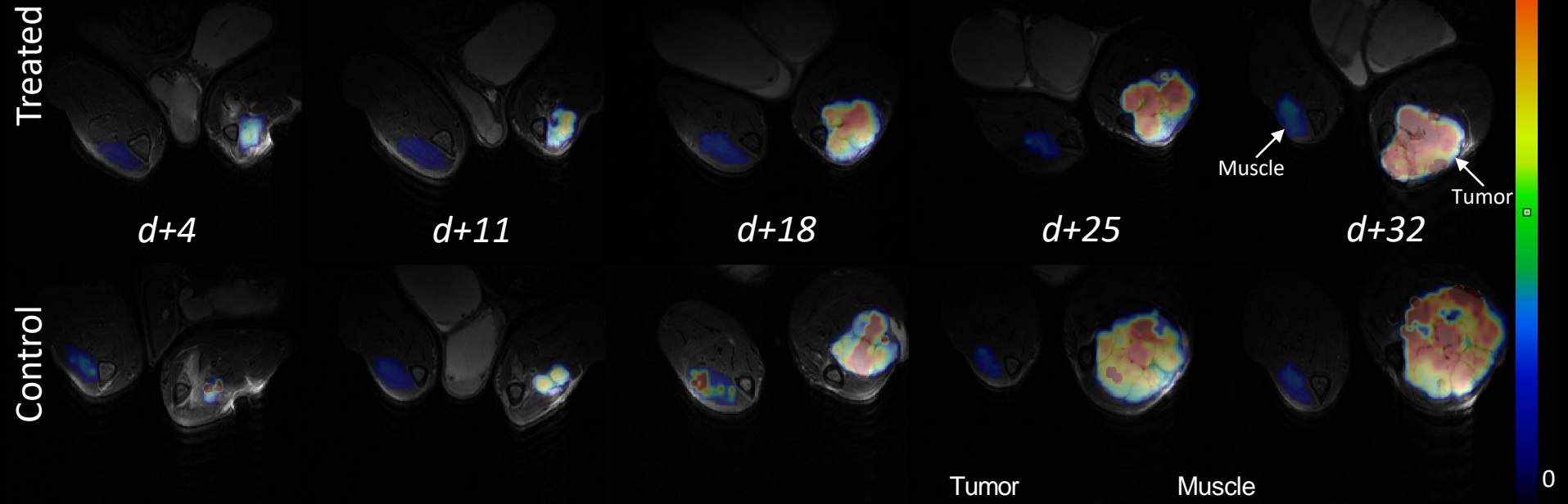


- ❖ ADC is higher in tumor than muscle
- ❖ ADC increases in tumor and remains stable in muscle over time
- ❖ No significant difference between treated and control groups

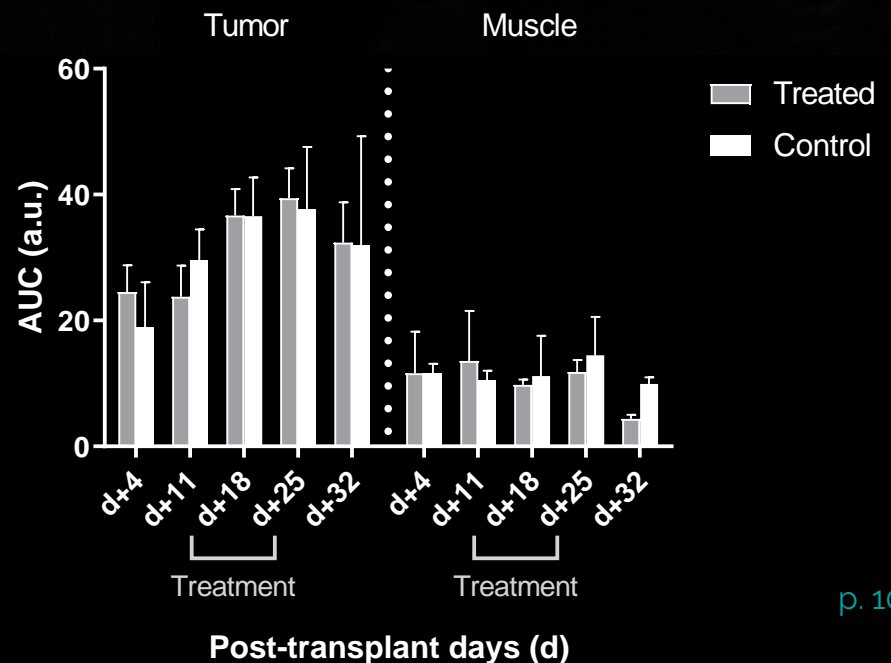
- ❖ T2 is higher in tumor than muscle
- ❖ T2 increases in tumor and remains stable in muscle over time
- ❖ Significant differences from the end of treatment



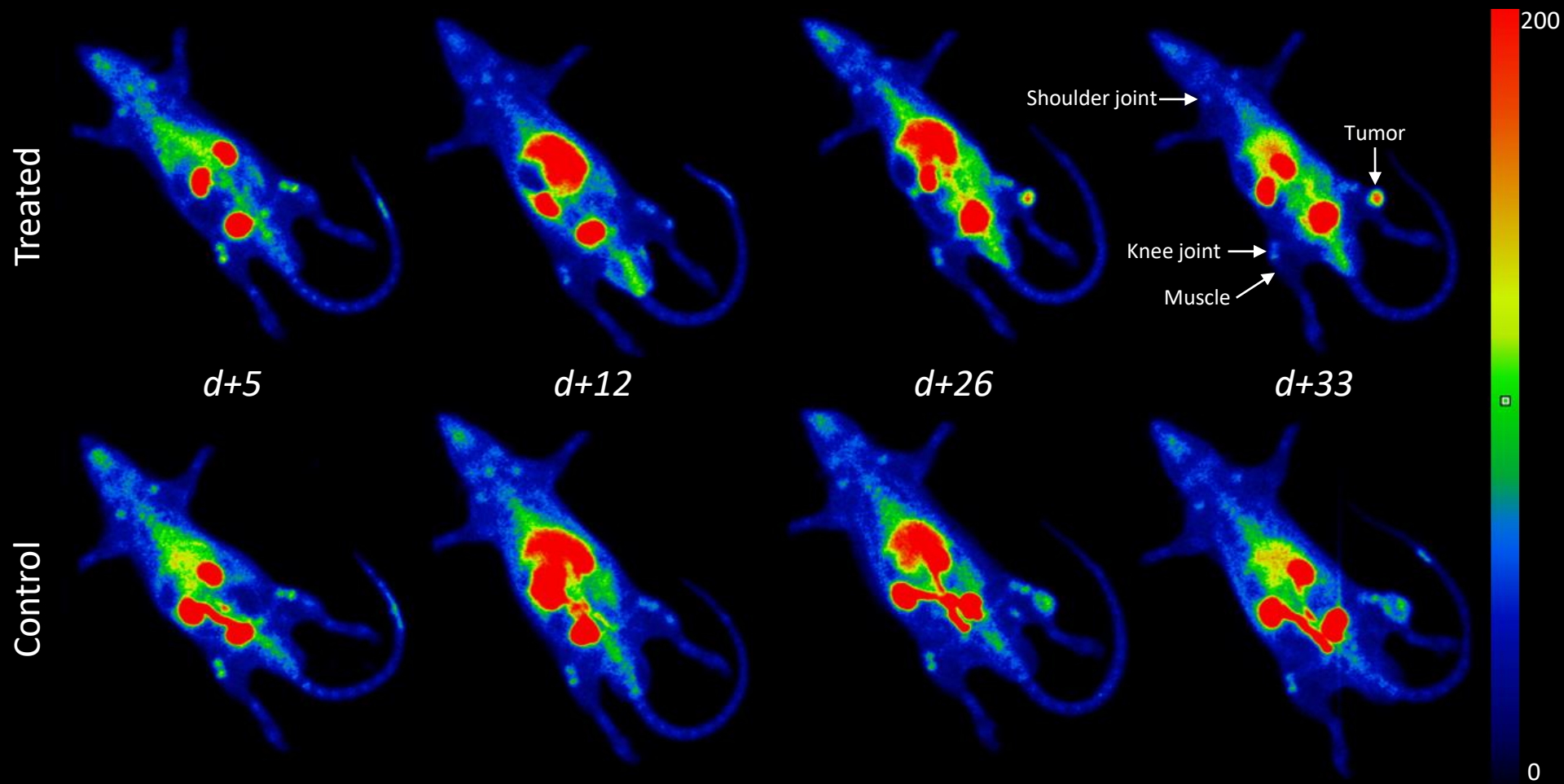
# ➤ Results: GAG CEST MRI



- ❖ 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 +++



# ➤ Results: $^{99m}\text{Tc}$ -NTP 15-5



Control

Treated

d+5

d+12

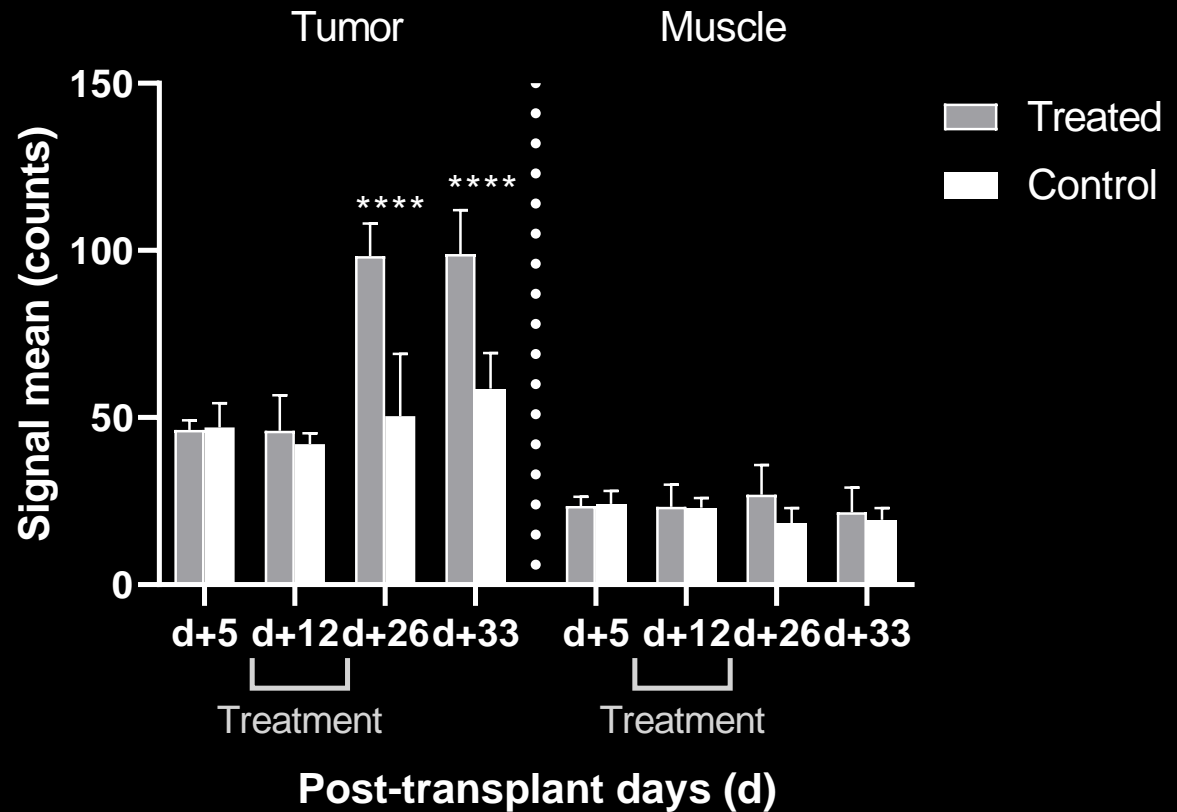
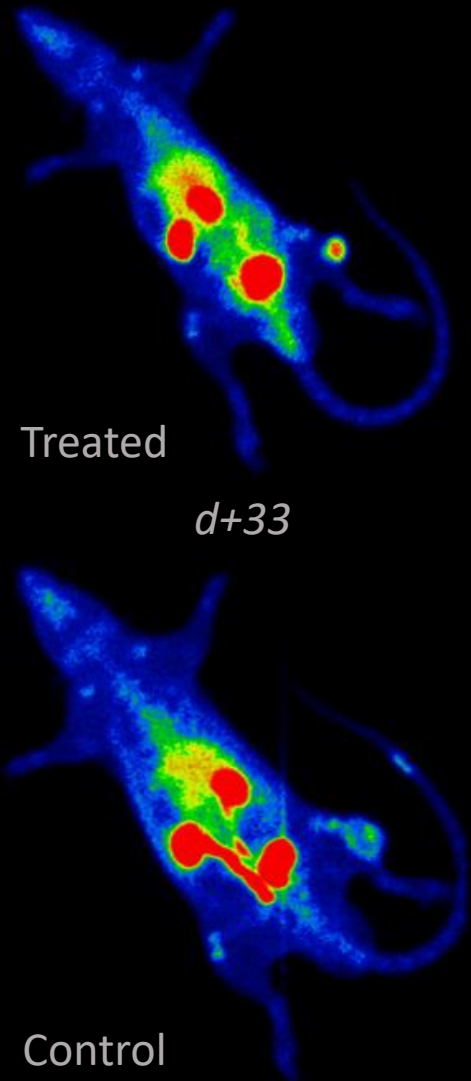
d+26

d+33

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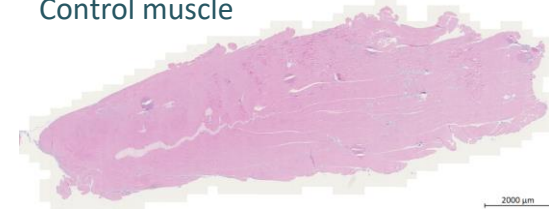
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# ➤ Results: $^{99m}\text{Tc}$ -NTP 15-5

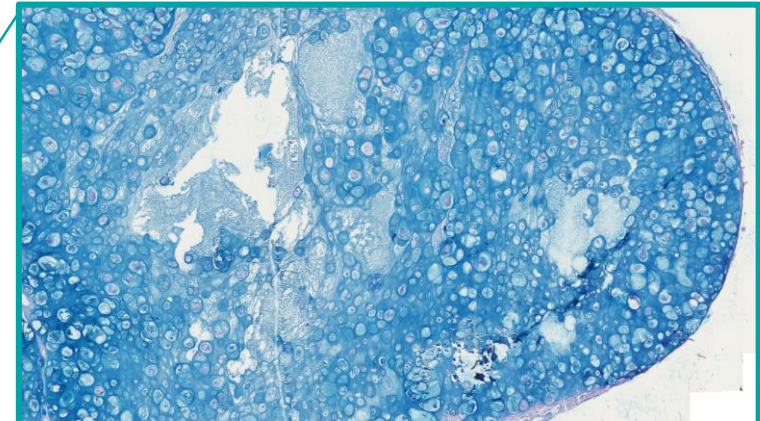
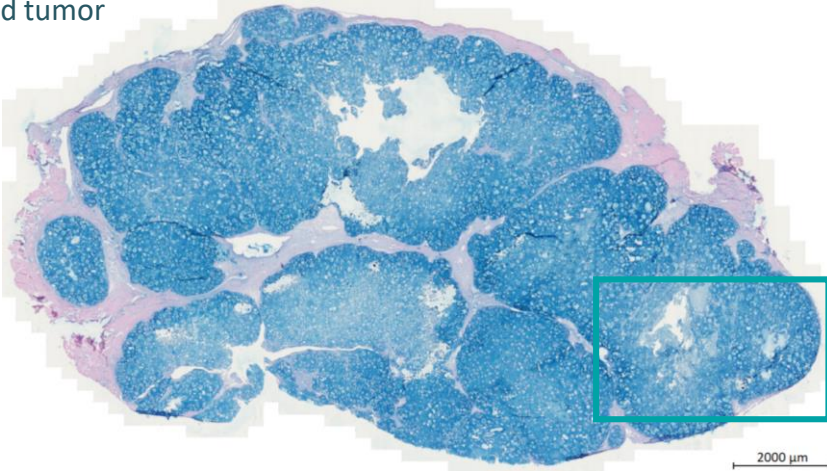


- ❖ Radiotracer signal is higher in tumor than muscle
- ❖ Activity increases in tumor and remains stable in muscle over time
- ❖ Significant differences in tumor between treated and control groups
- ❖ Are negative charges more accessible due to ECM modifications in treated tumors ?

# ➤ Results: Alcian blue staining

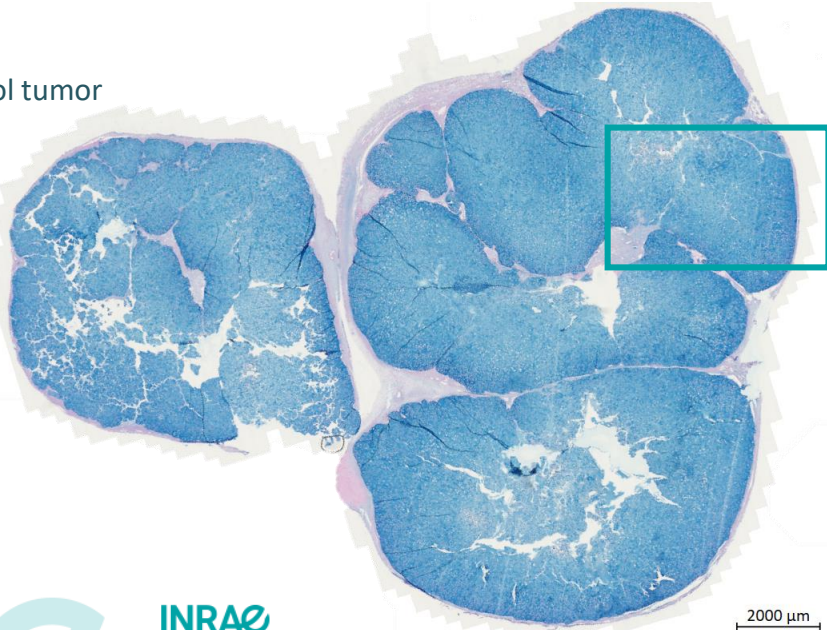


Treated tumor

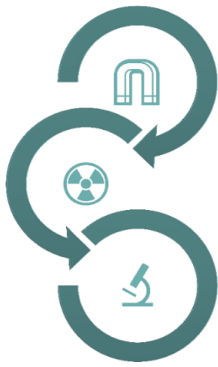


- ❖ Proteoglycans are distributed in the whole tumor ECM but with heterogeneities
- ❖ Morphological differences in tumor ECM between treated and control groups

Control tumor



## ➤ 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

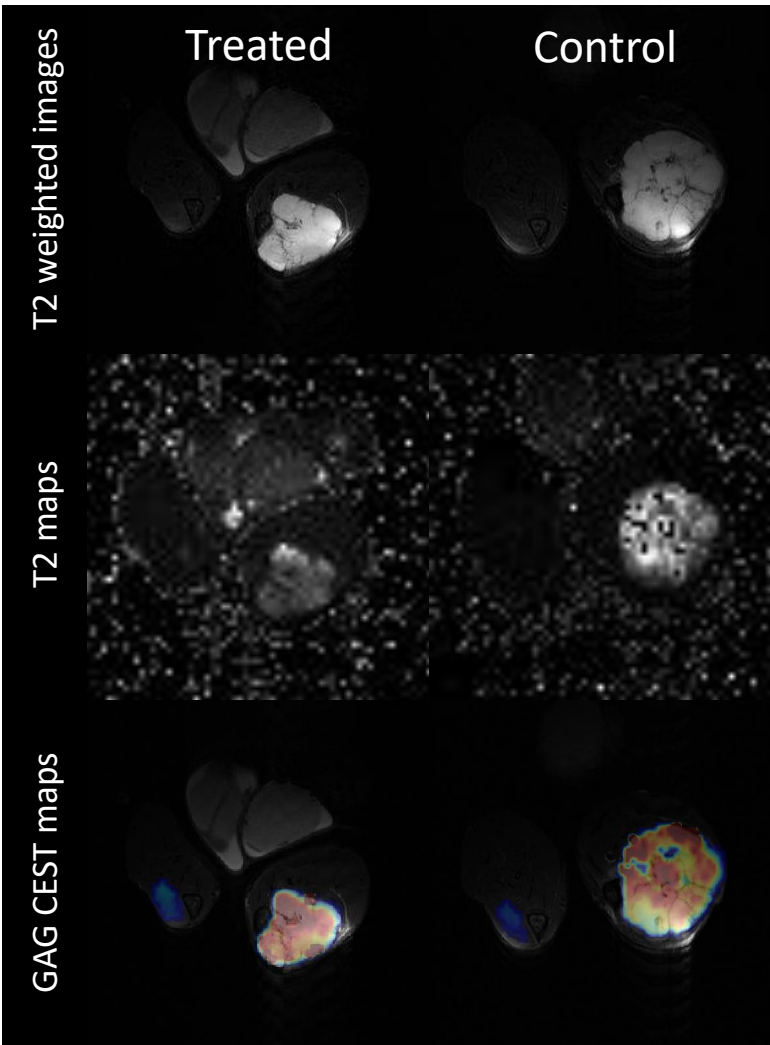
**Multimodal MRI is able to follow tumor ECM changes during therapy**



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## ➤ 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

- My supervisors:** Dr. Elisabeth Miot Noirault  
Dr. Guilhem Pagès  
Dr. Leslie Mazuel
- Radiochemists:** Dr. Philippe Auzeloux  
Dr. Sebastien Schmitt
- My lab's coworkers:** IMoST & AgroResonance teams
- Facilities:** IVIA - In Vivo Imaging in Auvergne  
Anipath (Christelle Damon-Soubeyrand)
- Grants:** Minister of Higher Education, Research and Innovation  
La Ligue contre le cancer

Doctoral school SVSAE & Clermont Auvergne university

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**Any questions ?**



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