



## 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

### ► To cite this version:

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-03369601>

Submitted on 7 Oct 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# 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

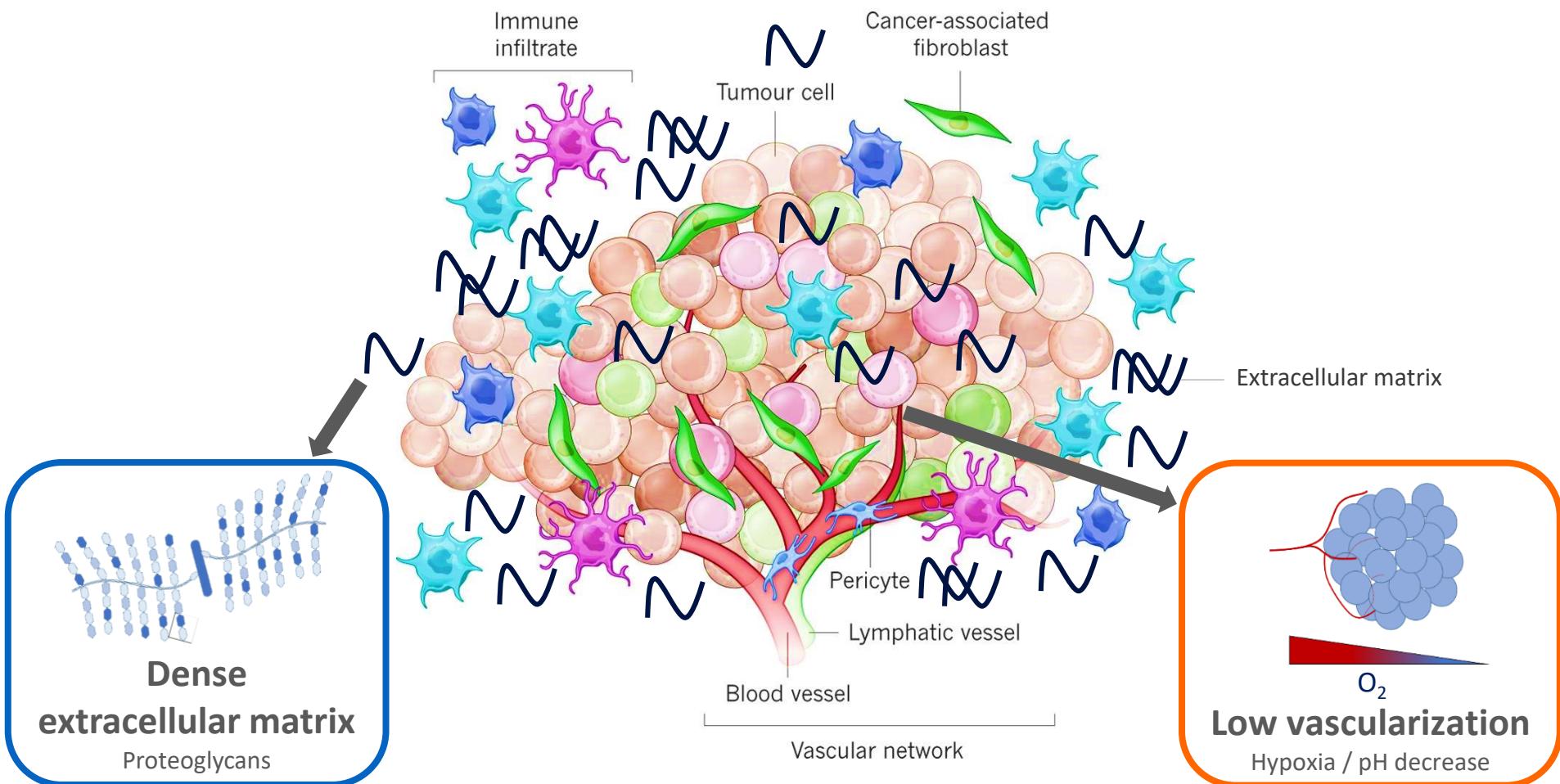


**INRAE**

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



## ➤ Context: Tumor microenvironment



## ➤ Context: Previous work

**MAGNETIC RESONANCE  
IN MEDICINE**

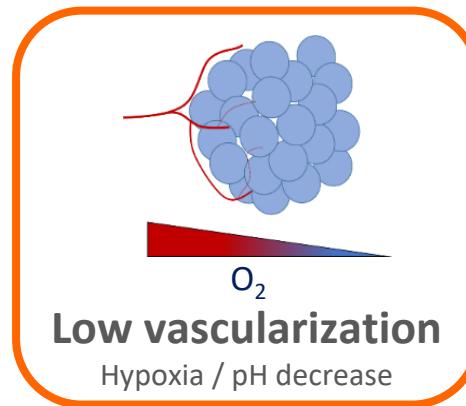
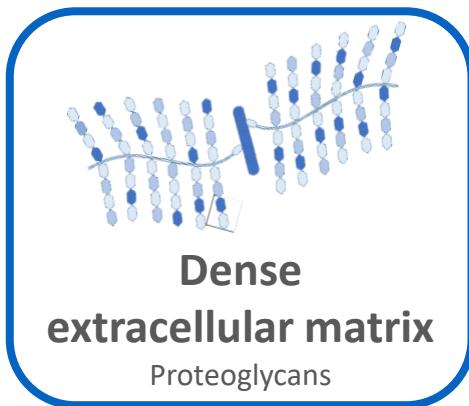
ISMRM ONE  
COMMUNITY FOR CLINICIANS AND SCIENTISTS

FULL PAPER |  Full Access

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 Peyrde, Elisabeth Miot-Noirault, Guilhem Pagés,

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



## ➤ Working hypothesis

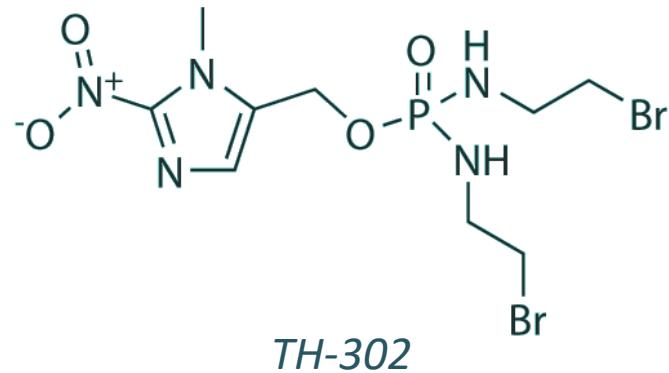
Is multimodal MRI able to detect  
tumor microenvironment changes during therapy ?

## ➤ 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

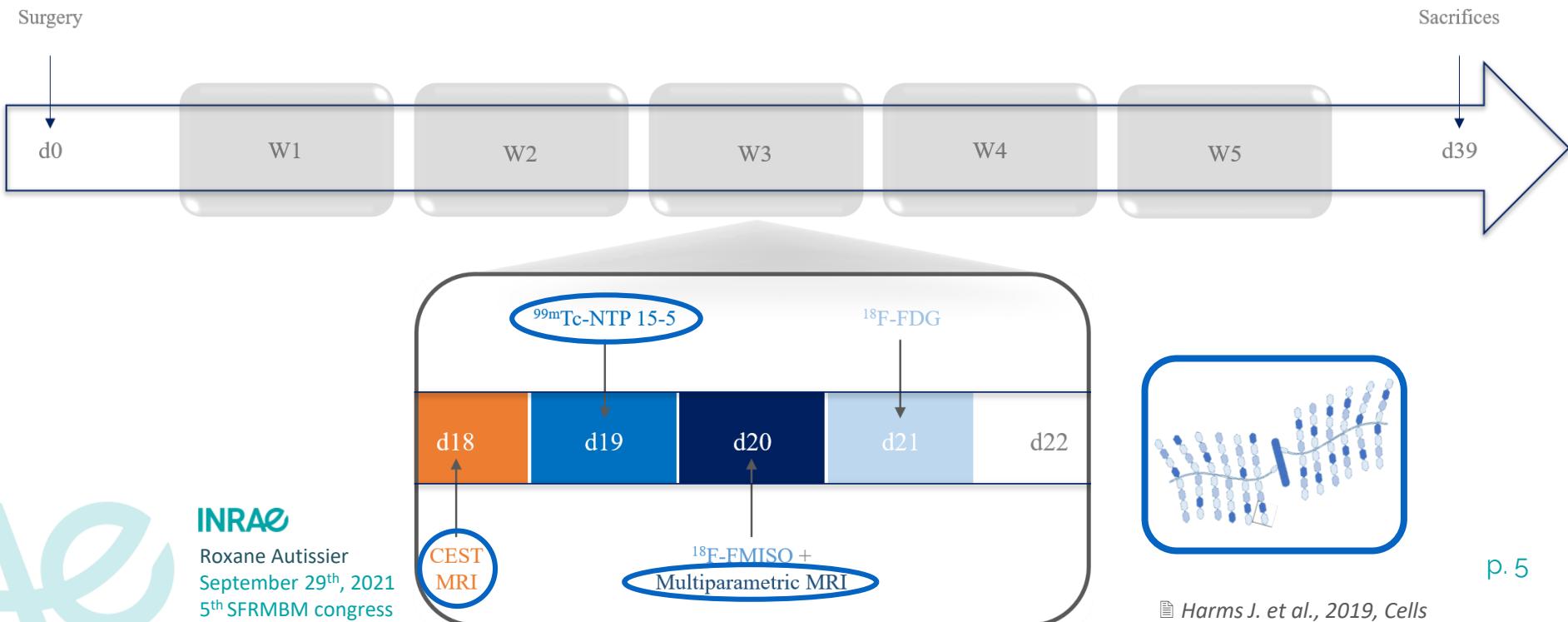


# ➤ Methods: Study design

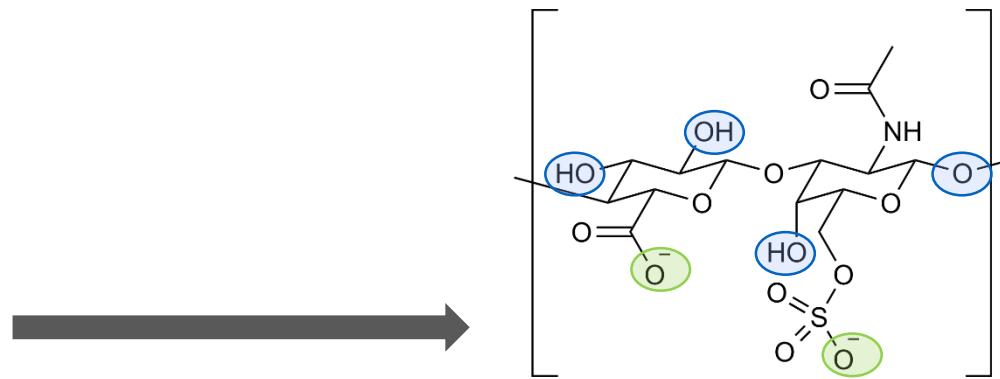
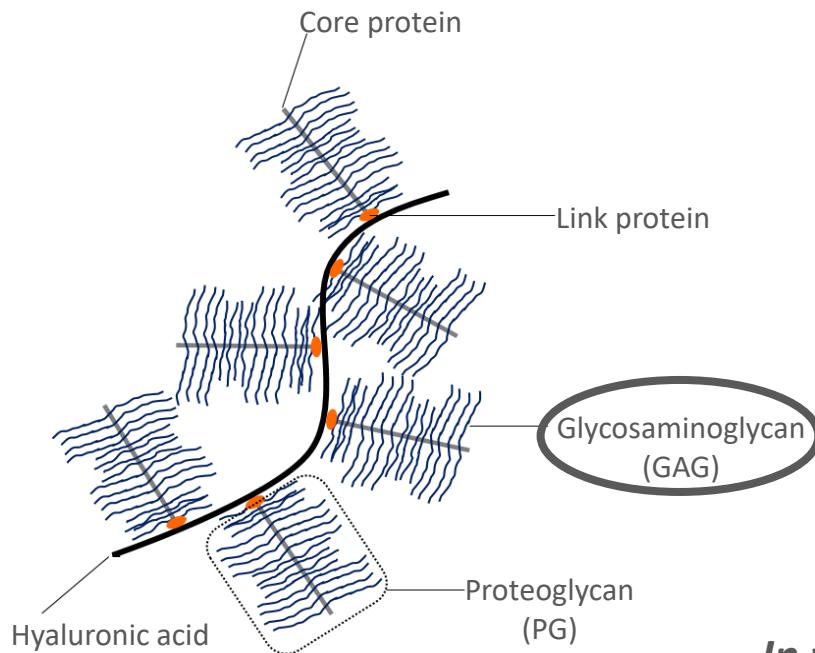
Paratibial Swarm rats follow-up during 5 weeks with TH-302 → (n=35)

❖ Treatment:

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



# > Methods: Extracellular matrix imaging



## In vivo Imaging

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



INRAE

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

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



Nuclear imaging  
 **$^{99m}\text{Tc-NTP 15-5}$**   
*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

Treated

d+4

d+11

d+18

d+25

d+32

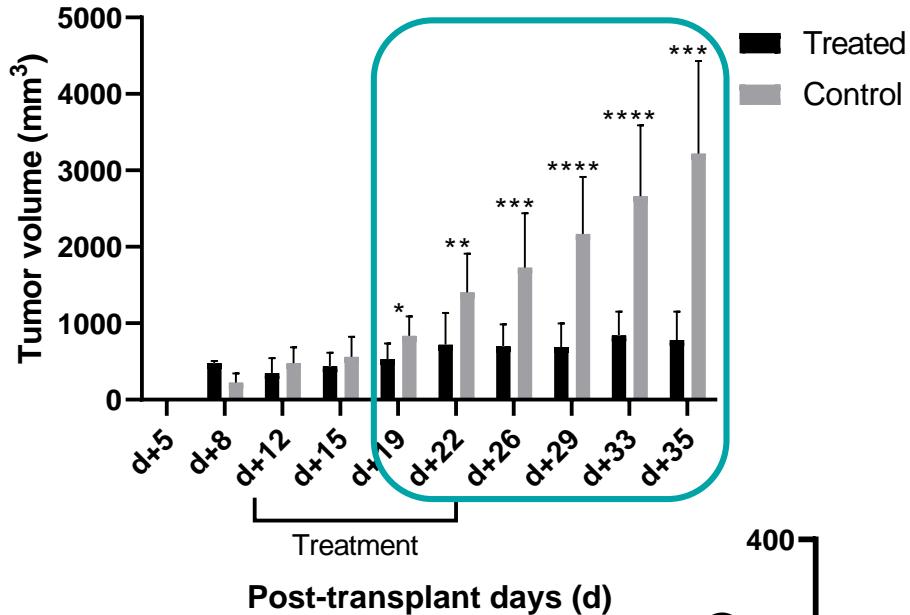
Muscle

Tumor

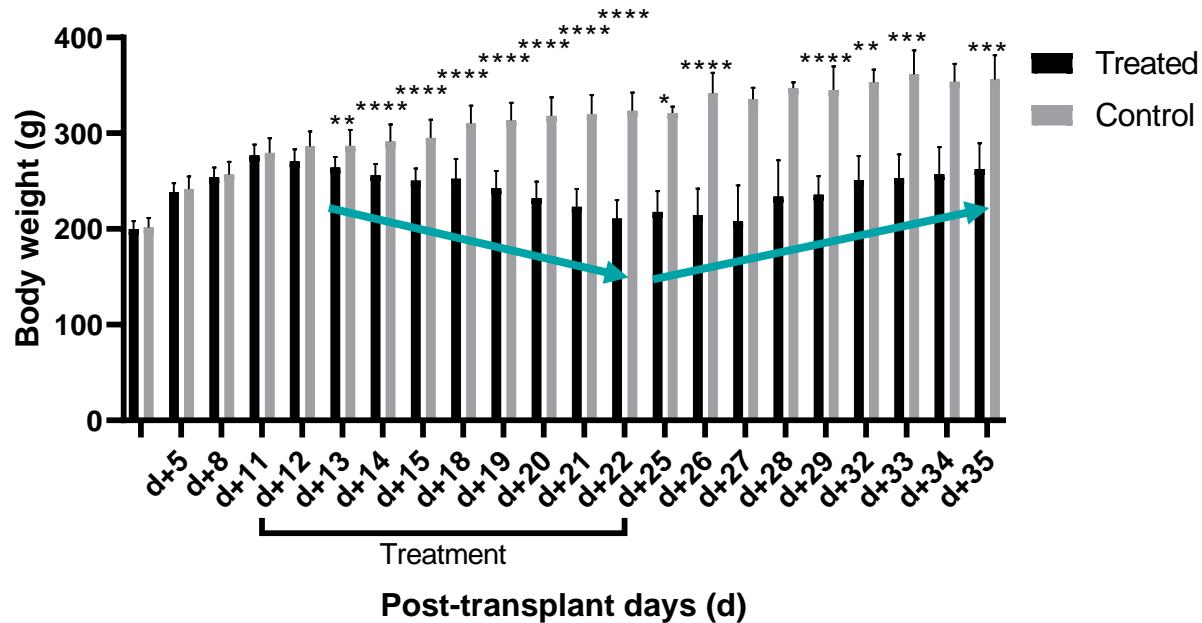
Control

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

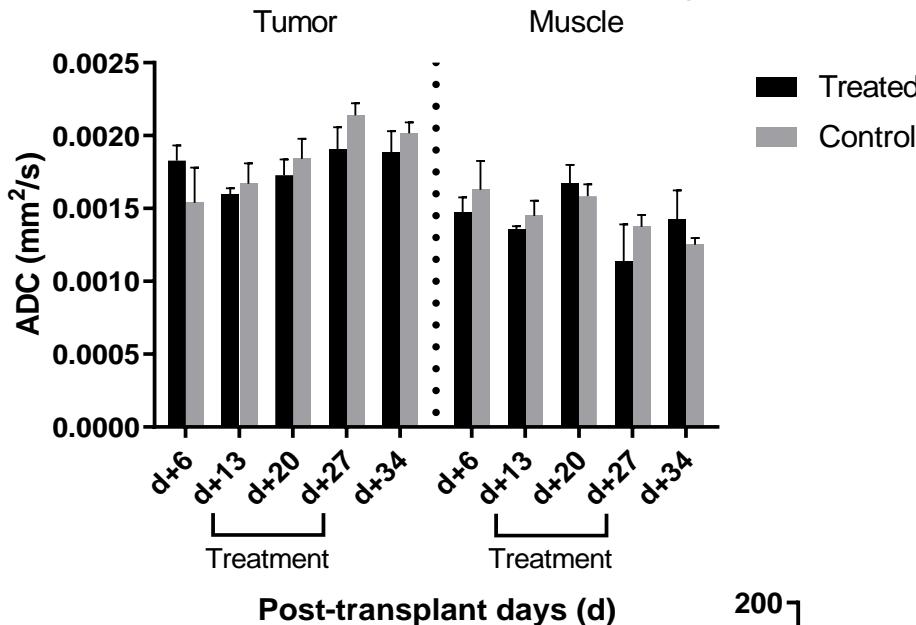
# Results: Tumor volume & body weight



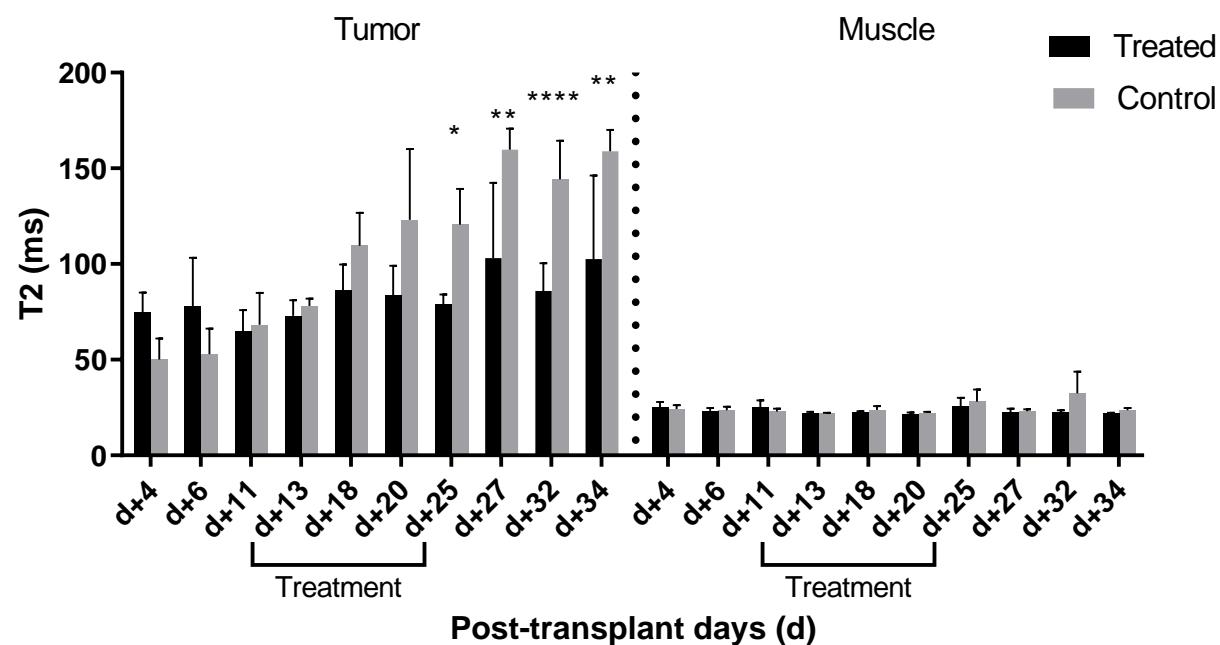
- ❖ The treatment reduces significantly tumor growth even after the end of therapy
- ❖ Side-effects tend to diminish after discontinuation of chemotherapy



# Results: Multiparametric MRI



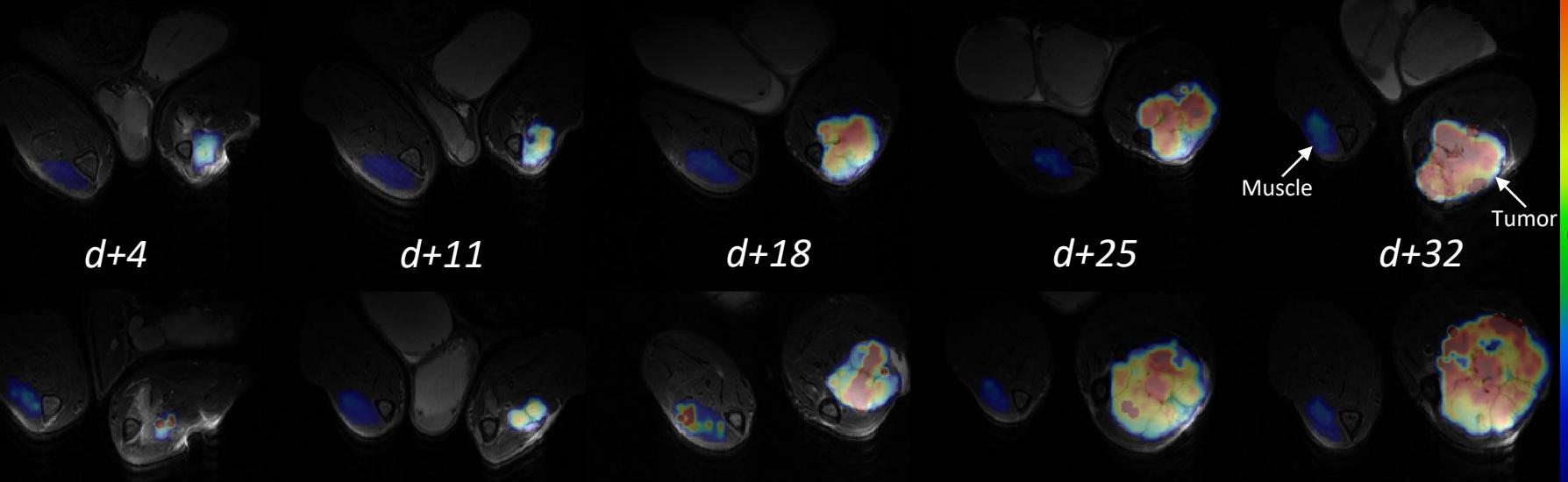
- ❖ ADC is higher in tumor than muscle
- ❖ ADC increases in tumor and remains stable in muscle over time
- ❖ No significant difference between treated and control groups



- ❖ 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

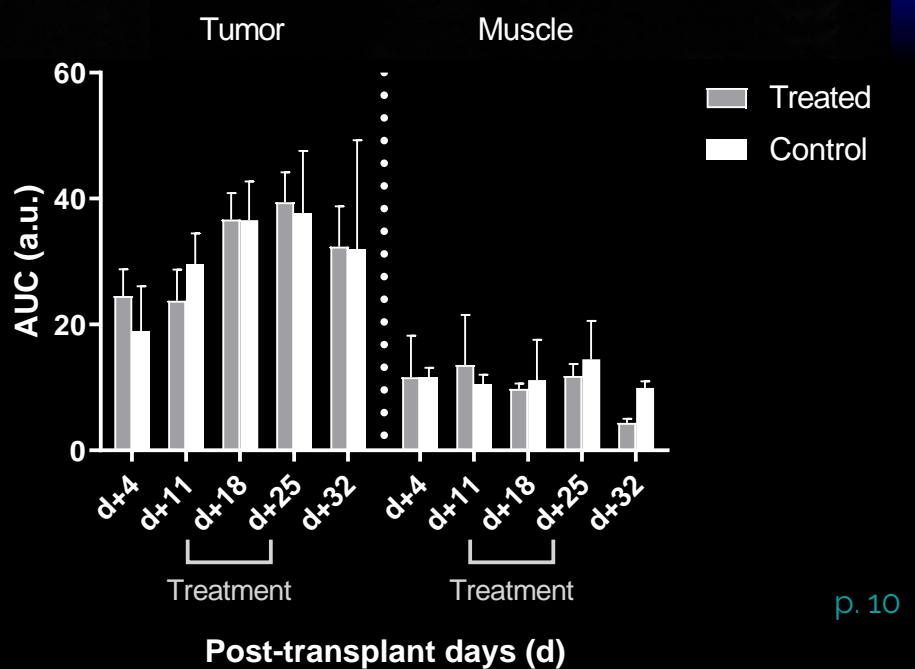
# ➤ Results: GAG CEST MRI

Treated



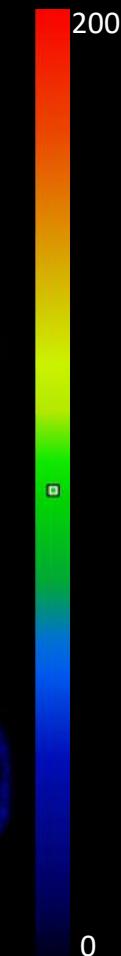
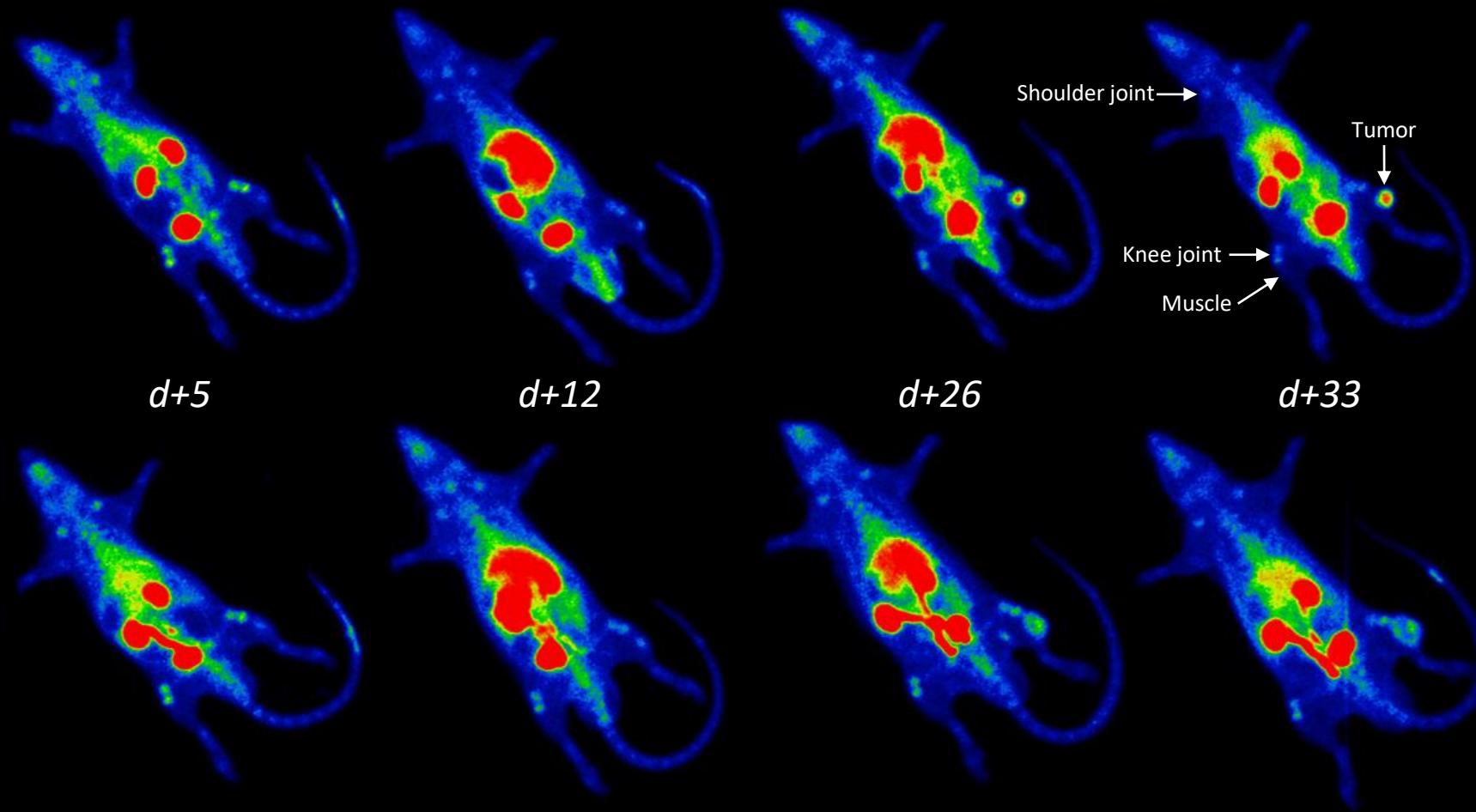
Control

- ❖ 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 +++

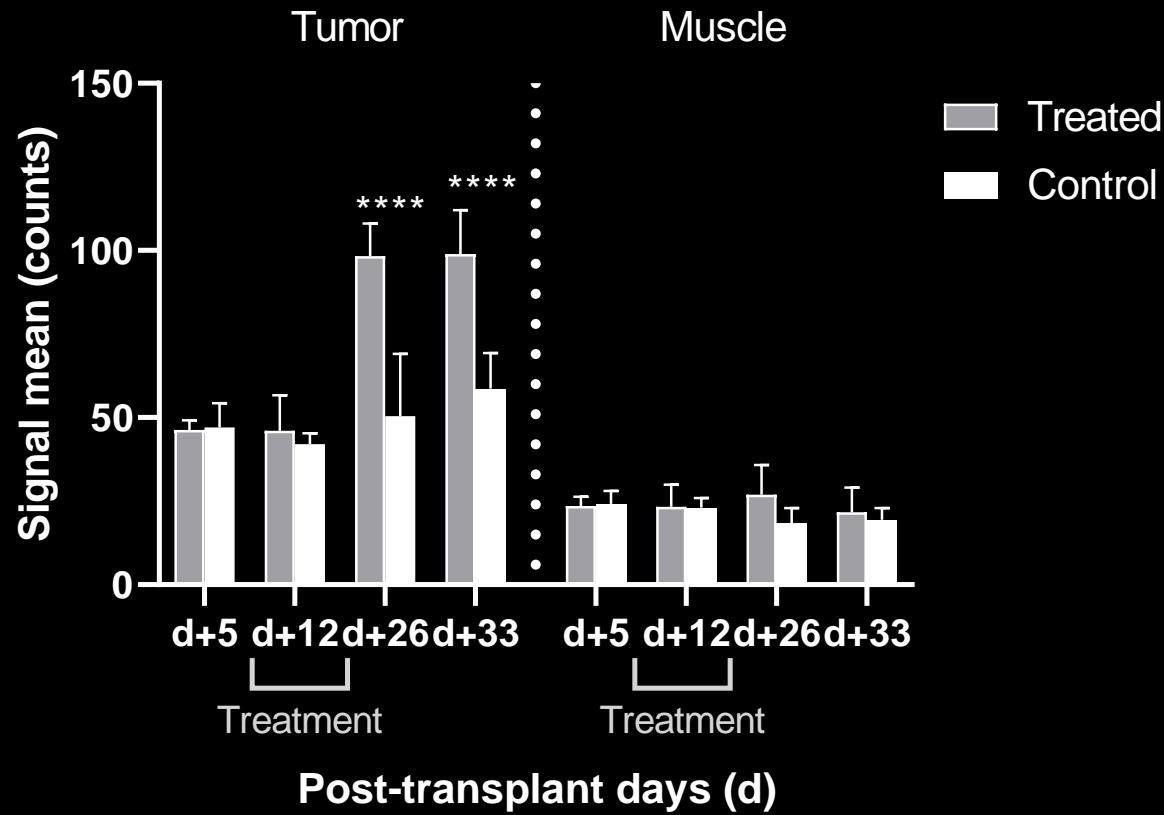
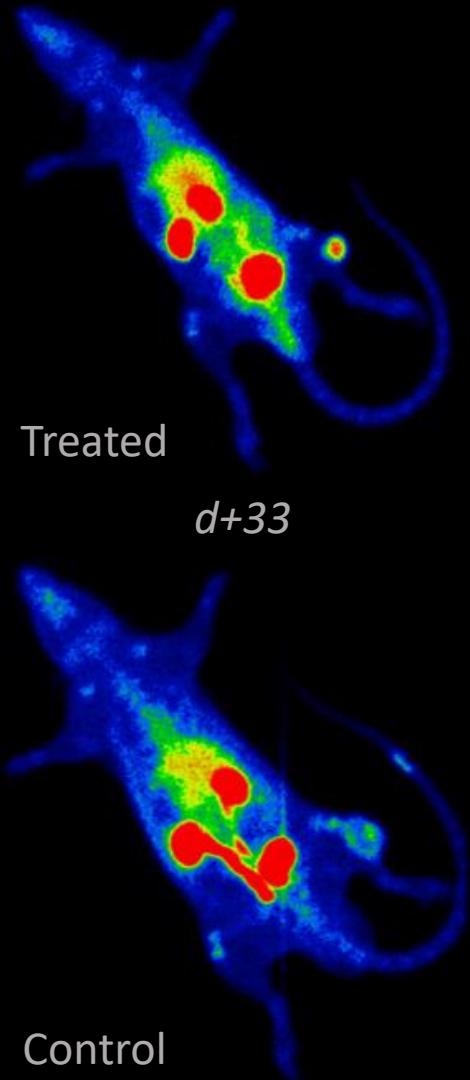


## ➤ Results: $^{99m}\text{Tc}$ -NTP 15-5

Treated



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

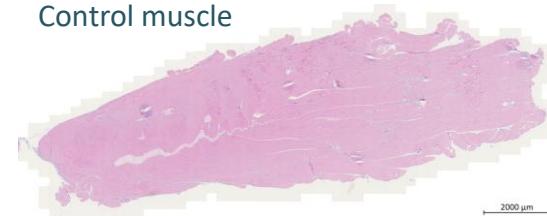


- ❖ Radiotracer signal is higher in tumor than muscle
- ❖ Activity increases in tumor and remains stable in muscle over time
- ❖ Significant differences in tumor between treated and control groups
- ❖ Are negative charges more accessible due to ECM modifications in treated tumors ?

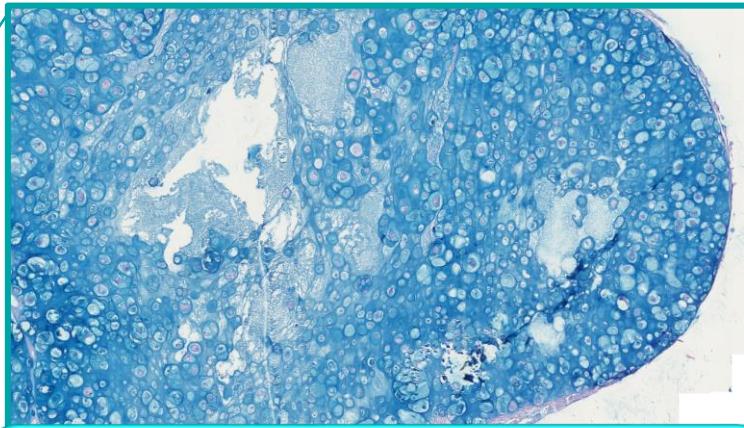
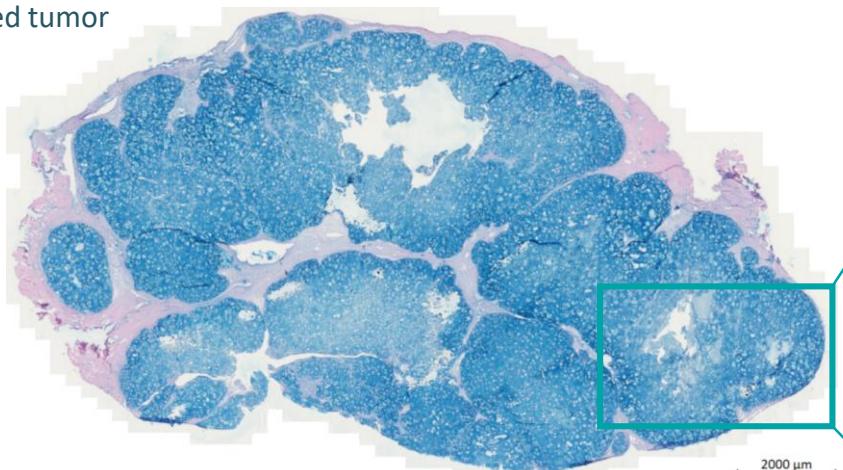


# Results: Alcian blue staining

Control muscle

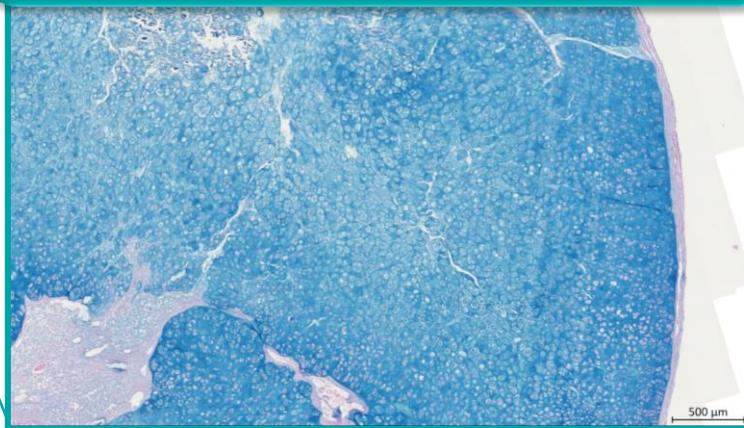
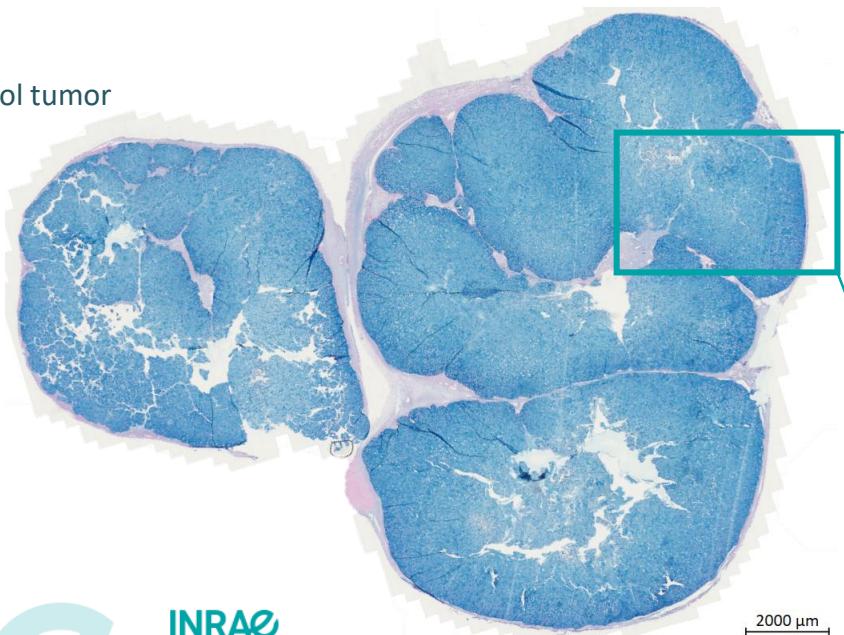


Treated tumor



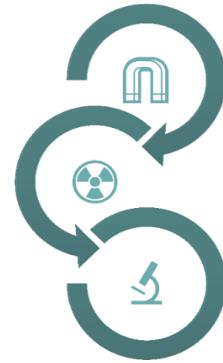
- ❖ Proteoglycans are distributed in the whole tumor ECM but with heterogeneities
- ❖ Morphological differences in tumor ECM between treated and control groups

Control tumor



INRAE

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



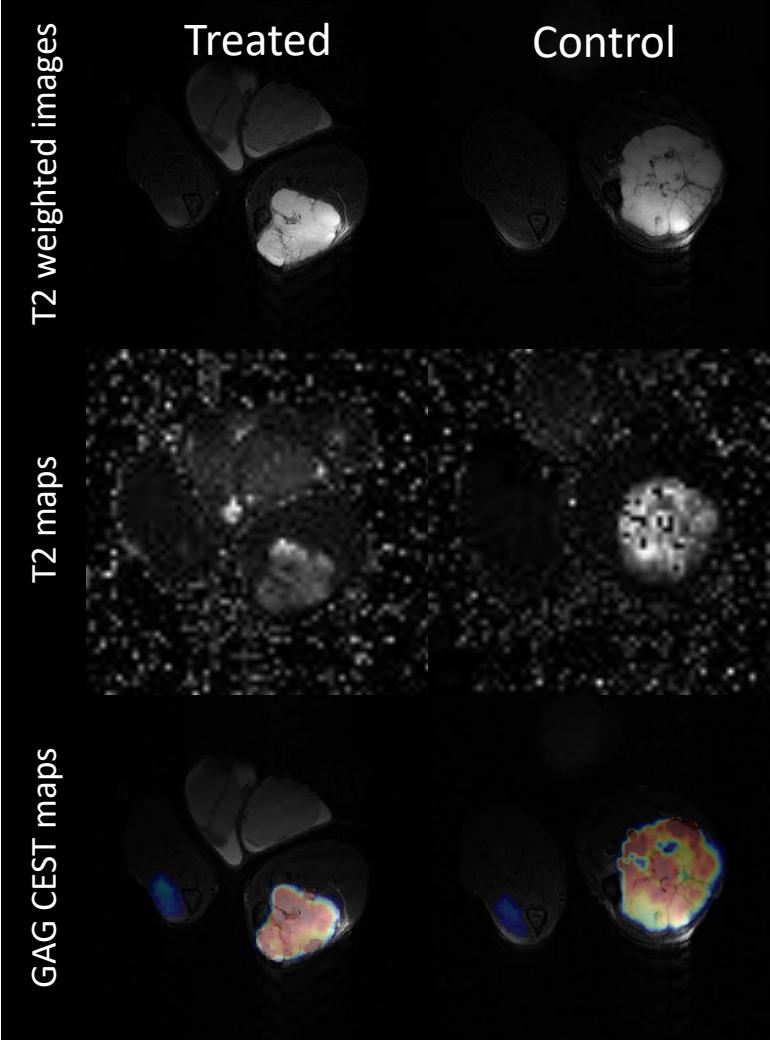
## Take home message



- ❖ 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



SFRMBM  
SOCIÉTÉ FRANÇAISE DE RÉSONNANCE  
MAGNETIQUE EN BIOLOGIE & MÉDECINE



INRAe  
la science pour la vie, l'humain, la terre



Inserm  
La science pour la santé  
From science to health



MINISTÈRE  
DE L'ENSEIGNEMENT  
SUPÉRIEUR,  
DE LA RECHERCHE  
ET DE L'INNOVATION  
Liberté  
Égalité  
Fraternité



UCA  
UNIVERSITÉ  
Clermont  
Auvergne

# 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. Sébastien 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