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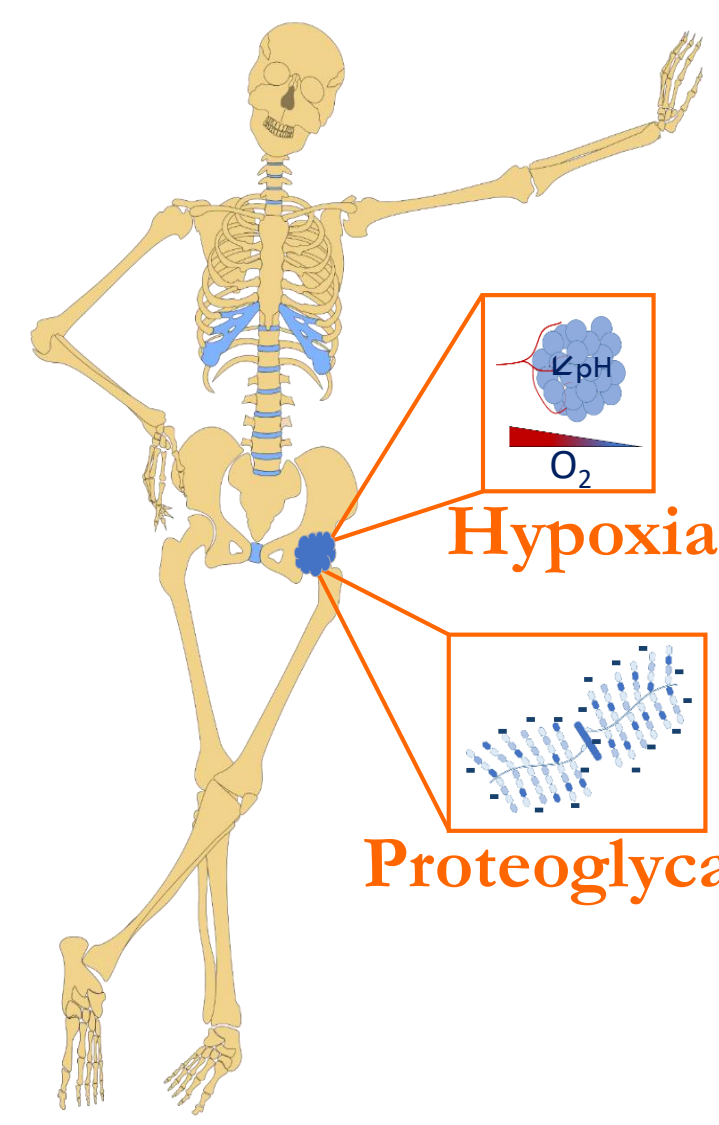
# Interest of *in vivo* CEST MRI to study chondrosarcoma tumour microenvironment

R. Autissier<sup>1,2</sup>, E. Maubert<sup>1</sup>, S. Schmitt<sup>1</sup>, P. Auzeloux<sup>1</sup>, C. Peyrode<sup>1</sup>, F. Degoul<sup>1</sup>, A. Traoré<sup>2</sup>, J. M. Bonny<sup>2</sup>, E. Miot-Noirault<sup>1</sup>, L. Mazuel<sup>1,2</sup> & G. Pagès<sup>2</sup>

<sup>1</sup> Université Clermont Auvergne, INSERM, UMR1240 IMoST, 63000 Clermont-Ferrand, France

<sup>2</sup> INRA, AgroResonance, UR370 QuaPA, 63122 Saint-Genès-Champanelle, France

Contact: [Roxane.Autissier@uca.fr](mailto:Roxane.Autissier@uca.fr)



## Introduction:

Chondrosarcoma is a malignant cartilage tumour and represents the second most common primary malignant solid tumour of bone. It accounts for approximately 25 % of all bone sarcomas (Bertoni *et al.* 2002). Poorly vascularized and rich in proteoglycans (PGs), chondrosarcomas are considered to be chemo- and radio-resistant with efficient treatment usually limited to surgical resection with large disease-free margins. If the hypoxic and PGs status of the tumour can be assessed by TEP imaging and scintigraphy, it requires however 2 separated exams.

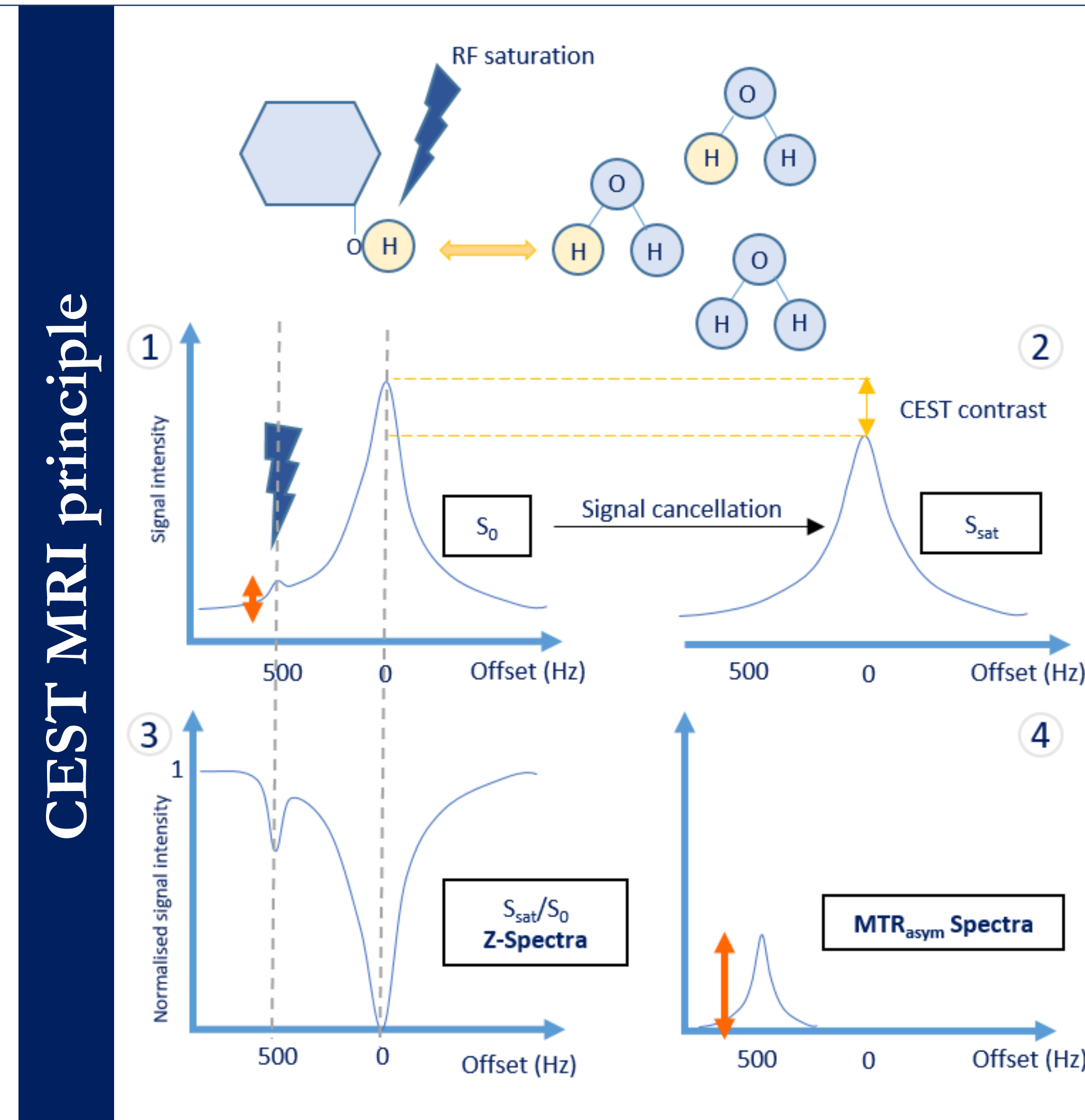
In this context, we propose to develop an MRI strategy based on Chemical Exchange Saturation Transfer (CEST) to simultaneously co-register both hypoxia (pH) and PGs content *in vivo*.

## Materials and Methods:

**In vivo model of chondrosarcoma:** 5 week female nude NMRI mice (n=10) were implanted with rat chondrosarcoma SWARM xenograft (1 mm<sup>3</sup> fragment) in scapula position. After 2 weeks growth (average tumour volume: 215.04 mm<sup>3</sup> ± 86.27), xenografts were characterized in terms of PGs content by <sup>23</sup>Na MRI, <sup>99m</sup>Tc-NTP 15-5 radiotracer (developed in UMR 1240 INSERM, Peyrode *et al.* 2011) and hypoxia by <sup>18</sup>F-FMISO (Rajendran *et al.* 2015). Then, both tumour characteristics were evaluated by CEST MRI.

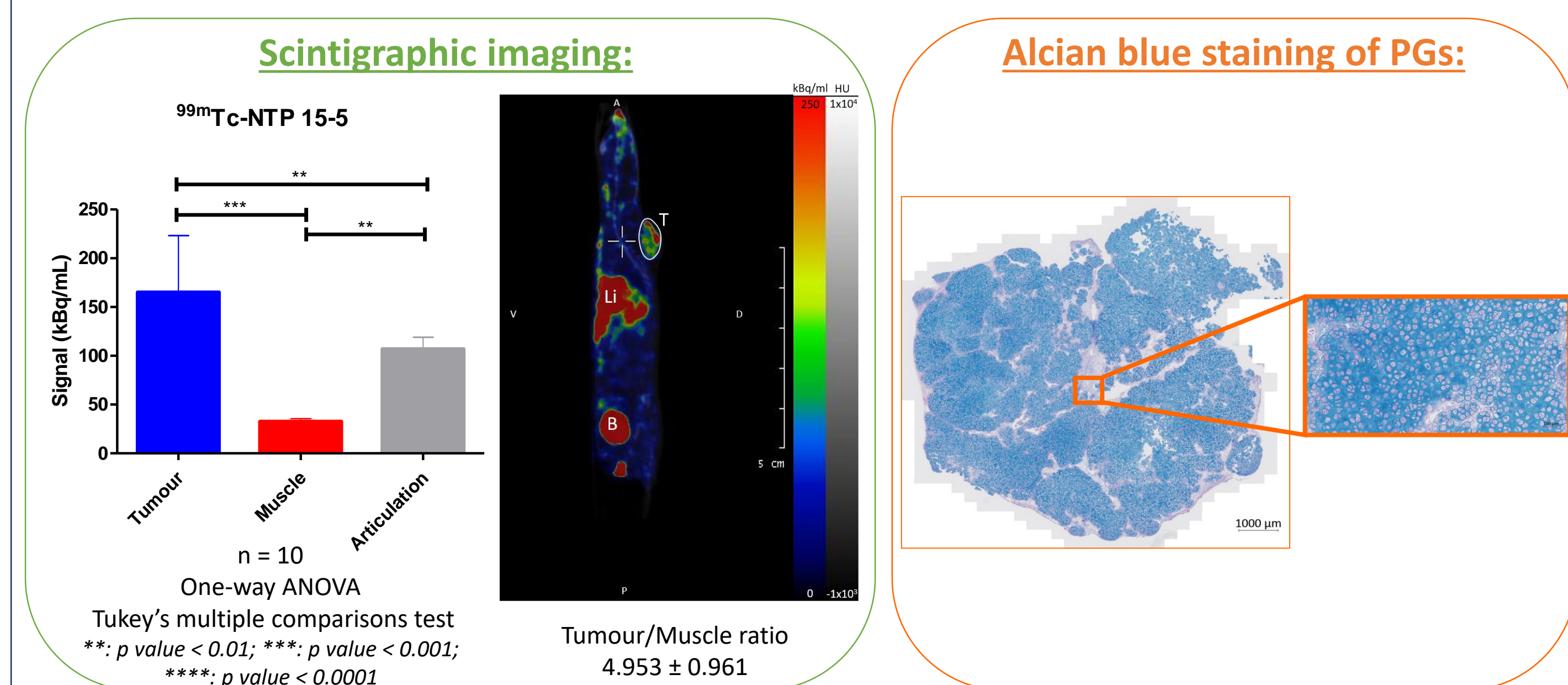
**In vivo multimodal imaging:** All acquisitions were performed on anesthetized mice (1.5% isoflurane in air/O<sub>2</sub> 70/30, v/v, mixture). **MRI acquisitions:** MRI images were acquired at 11.7 T using a 72 mm volume quadratic coil with surface reception. Diffusion weighted imaging (b=500 s.mm<sup>-2</sup>) was first performed to localize the tumour, then WASSR (B<sub>1</sub>=0.1 μT for 1 s, Δωsat=±1000 Hz in 20 Hz steps) and CEST Z-spectra (B<sub>1</sub>=1.5 μT for 4 s, Δωsat=±2500 Hz in 50 Hz steps) were acquired based on a RARE sequence. <sup>23</sup>Na MRI was recorded thanks to a FLASH sequence in axial plane. Data were analysed using an in-house program written on MathWorks®. After correction for B<sub>0</sub> inhomogeneities, the CEST maps were generated and Area Under the Curve (AUC) were calculated at given frequencies on Z-spectra asymmetries with MTR<sub>asym</sub> or three-offset measurement approaches (Wu *et al.* 2016 ; Jin *et al.* 2013). **Scintigraphic imaging:** <sup>99m</sup>Tc-NTP 15-5 (13 MBq/animal) and <sup>18</sup>F-FMISO (18 MBq/animal) were administered intravenously then acquisitions were performed 30 min or 4 h after injection with 15 min planar acquisition, respectively. Data were analysed using Interview™FUSION and VivoQuant™.

**Ex vivo analysis:** the presence of PGs and hypoxia was assessed by Alcian blue and pimonidazole staining respectively.



## Results:

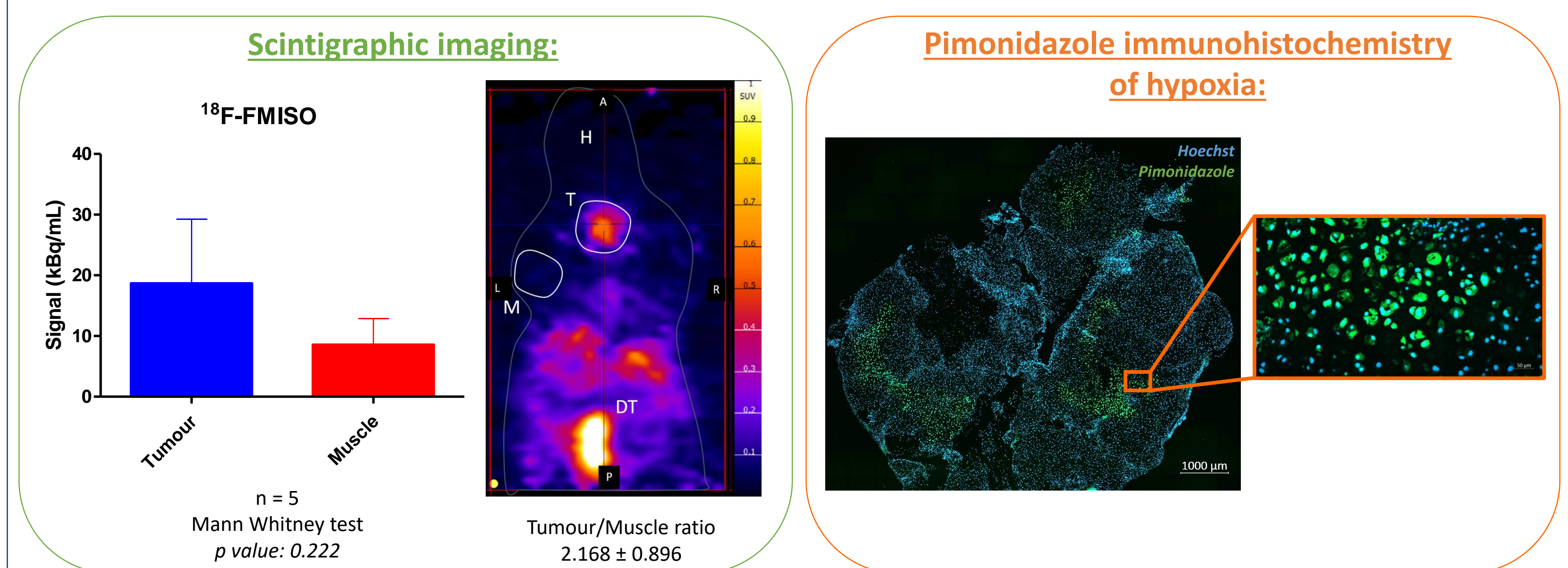
### 1/Evaluation of proteoglycans content



High accumulation of <sup>99m</sup>Tc-NTP 15-5 inside the tumour reflects the presence of PGs content

High alcian blue staining illustrates the high PGs content

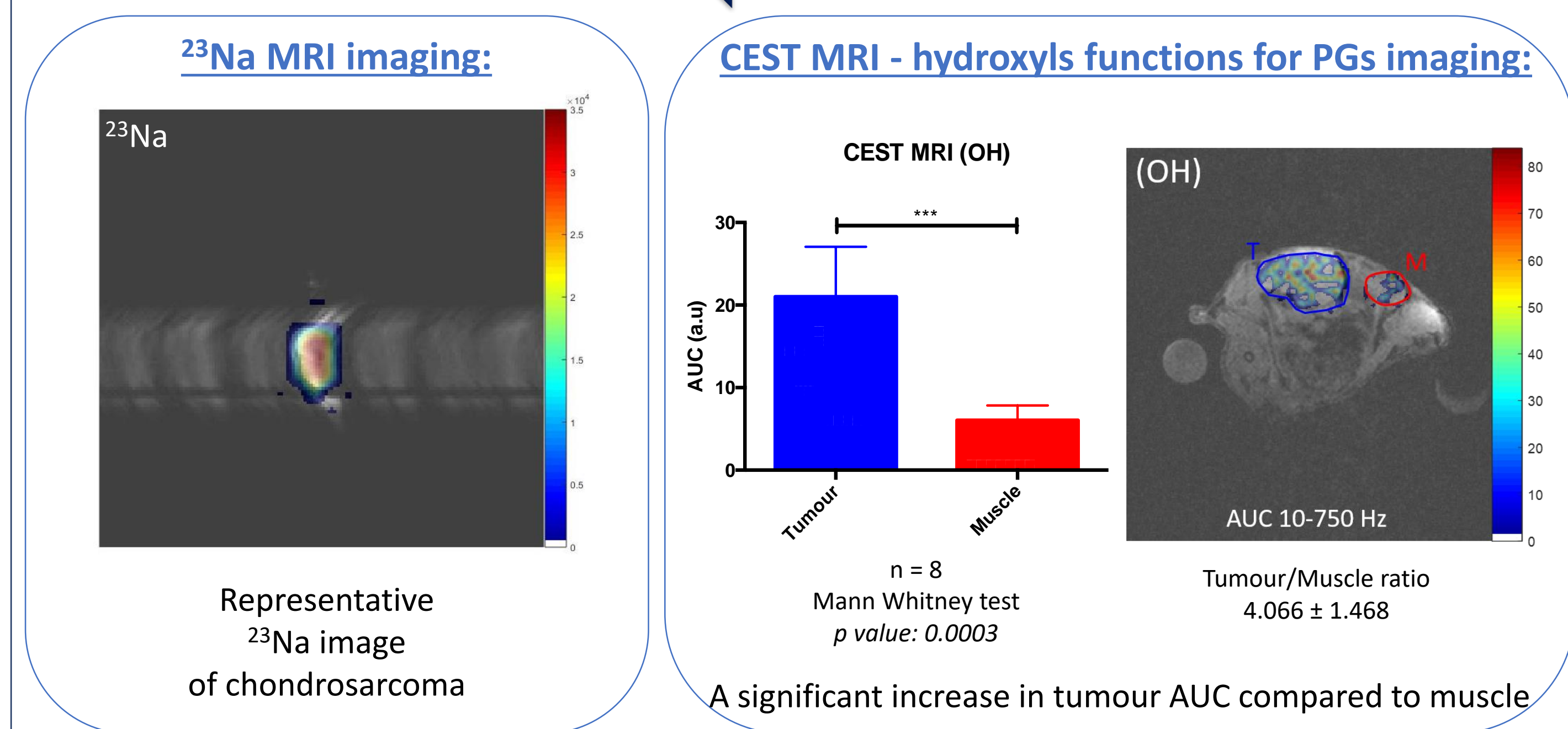
### 2/Evaluation of hypoxia (pH)



<sup>18</sup>F-FMISO uptake inside chondrosarcoma reflects mild hypoxia

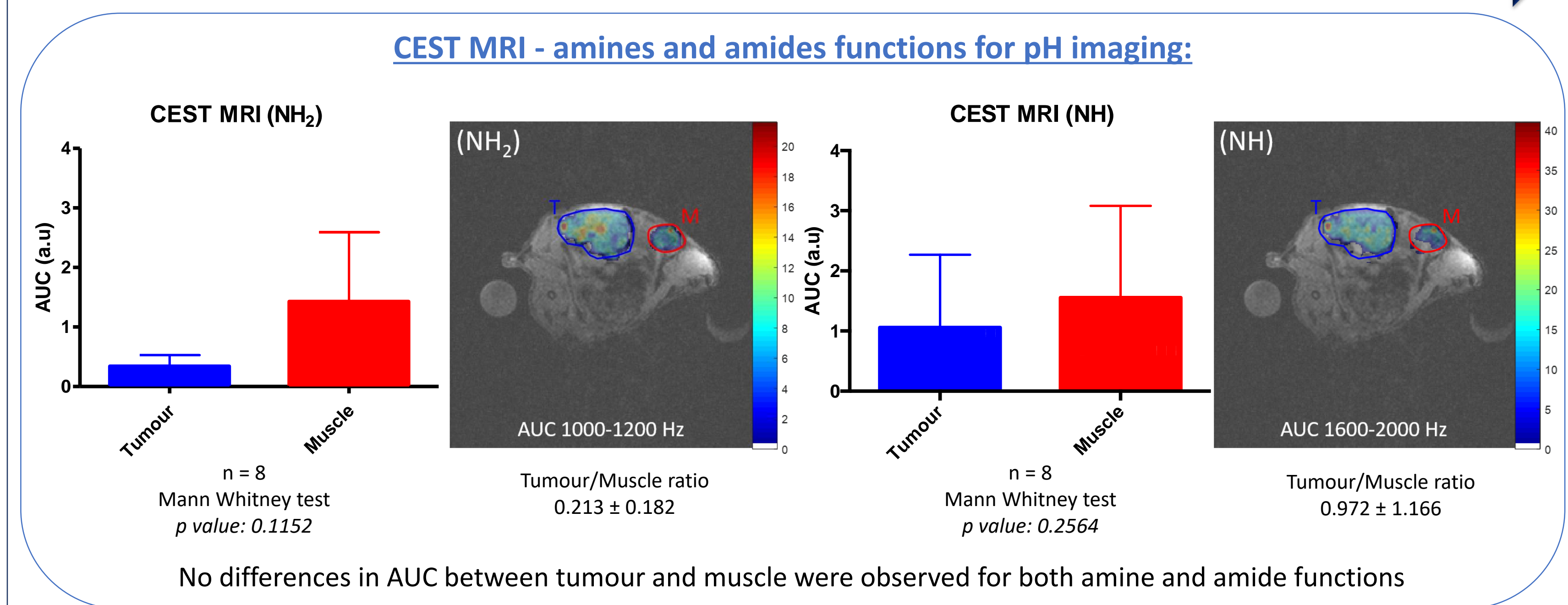
Pimonidazole staining confirms the presence of tumour hypoxic areas

## CEST MRI



<sup>23</sup>Na MRI reflects the presence of PGs

AUC of hydroxyls functions can confirm large presence of PGs inside the tumour



Cartography of AUC between 1000-1200Hz (amine moiety) suggests regional changes in pH within chondrosarcoma

## Conclusion – Discussion:

Preliminary findings reveal potential of CEST MRI as multimodal imaging approach. In a unique acquisition, CEST MRI provides *in vivo* quantitative data of extracellular matrix as well as a high resolution cartography of hypoxia.

Perspectives are now to evaluate CEST MRI as an *in vivo* method to assess response to therapy.

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