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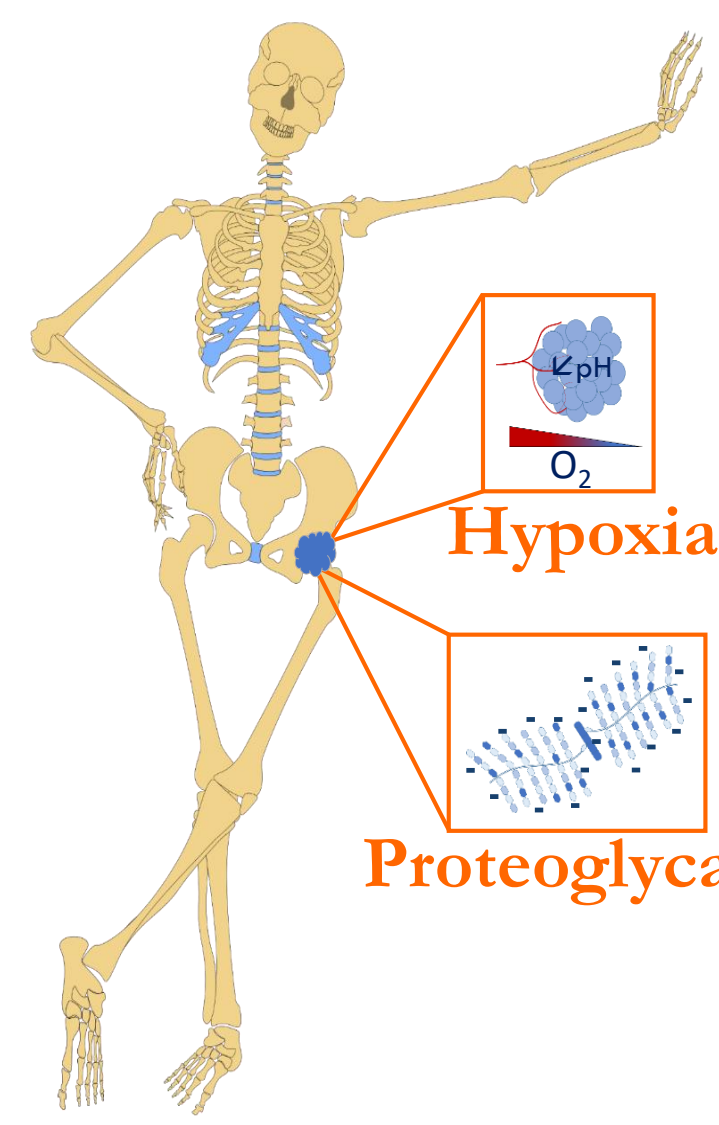
Interest of *in vivo* CEST MRI to study chondrosarcoma tumour microenvironment

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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.

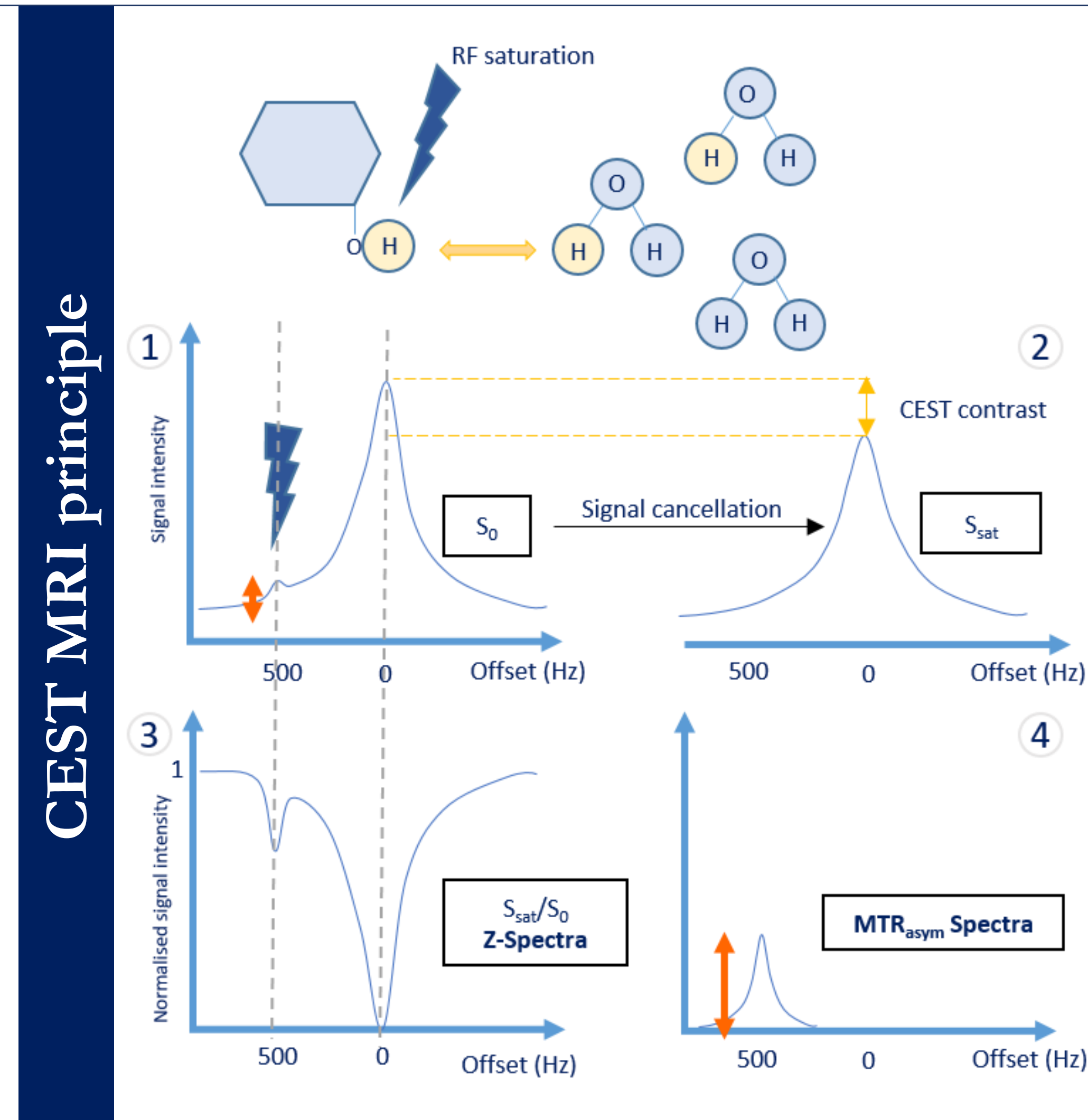
In this context, we propose to develop an MRI strategy based on Chemical Exchange Saturation Transfer (CEST) to simultaneously co-register both hypoxia (pH) and PGs content *in vivo*.

Materials and Methods:

In vivo model of chondrosarcoma: 5 week female nude NMRI mice (n=10) were implanted with rat chondrosarcoma SWARM xenograft (1 mm³ fragment) in scapula position. After 2 weeks growth (average tumour volume: 215.04 mm³ ± 86.27), xenografts were characterized in terms of PGs content by ²³Na MRI, ^{99m}Tc-NTP 15-5 radiotracer (developed in UMR 1240 INSERM, Peyrode *et al.* 2011) and hypoxia by ¹⁸F-FMISO (Rajendran *et al.* 2015). Then, both tumour characteristics were evaluated by CEST MRI.

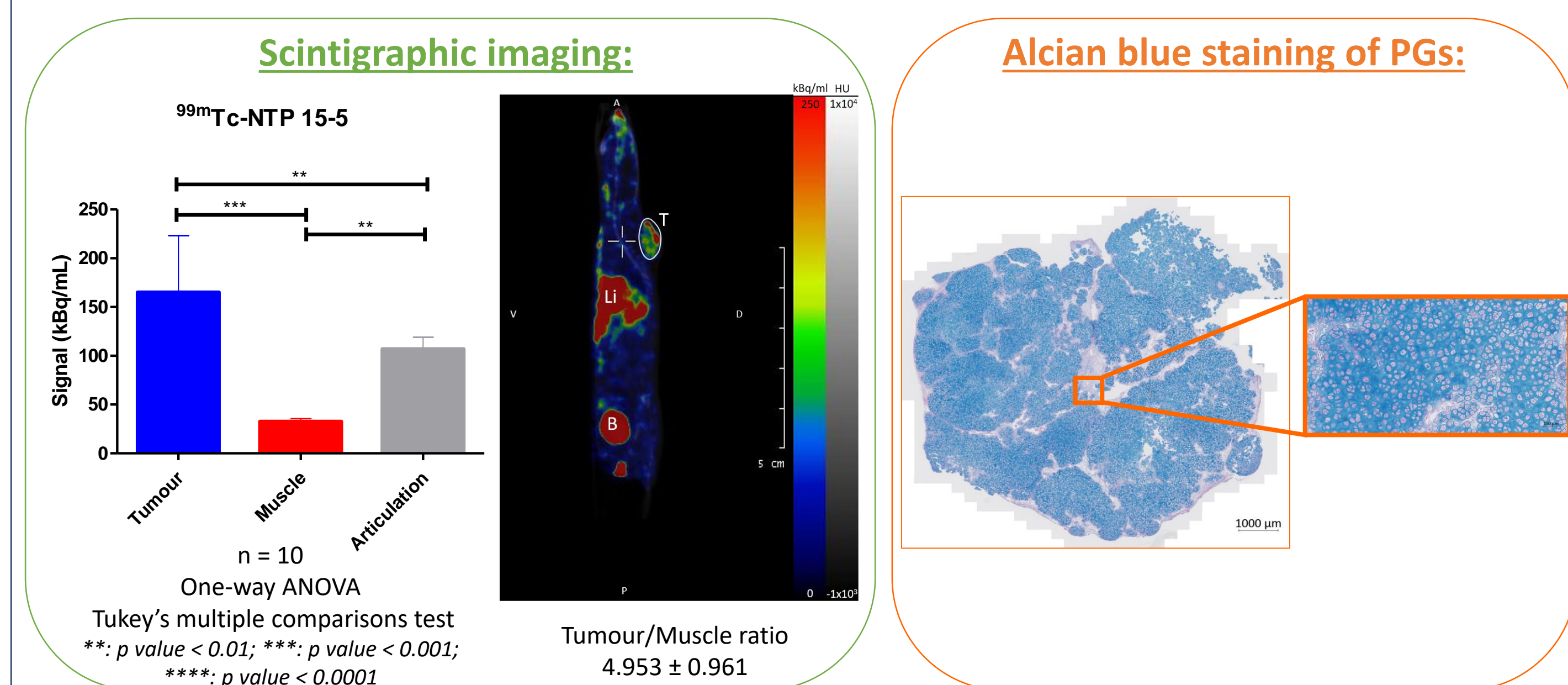
In vivo multimodal imaging: All acquisitions were performed on anesthetized mice (1.5% isoflurane in air/O₂ 70/30, v/v, mixture). **MRI acquisitions:** MRI images were acquired at 11.7 T using a 72 mm volume quadratic coil with surface reception. Diffusion weighted imaging (b=500 s.mm⁻²) was first performed to localize the tumour, then WASSR (B₁=0.1 μT for 1 s, Δω_{sat}=±1000 Hz in 20 Hz steps) and CEST Z-spectra (B₁=1.5 μT for 4 s, Δω_{sat}=±2500 Hz in 50 Hz steps) were acquired based on a RARE sequence. ²³Na 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 B₀ inhomogeneities, the CEST maps were generated and Area Under the Curve (AUC) were calculated at given frequencies on Z-spectra asymmetries with MTR_{asym} or three-offset measurement approaches (Wu *et al.* 2016 ; Jin *et al.* 2013). **Scintigraphic imaging:** ^{99m}Tc-NTP 15-5 (13 MBq/animal) and ¹⁸F-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:

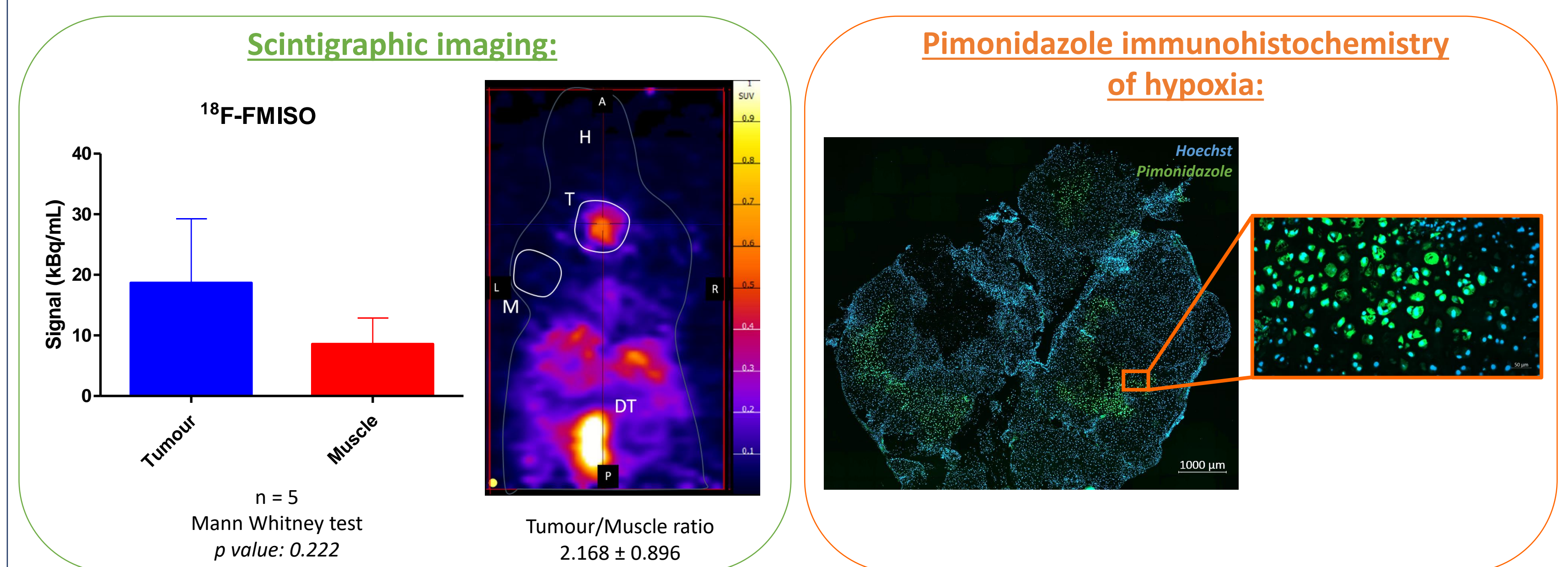
1/Evaluation of proteoglycans content



High accumulation of ^{99m}Tc-NTP 15-5 inside the tumour reflects the presence of PGs content

High alcian blue staining illustrates the high PGs content

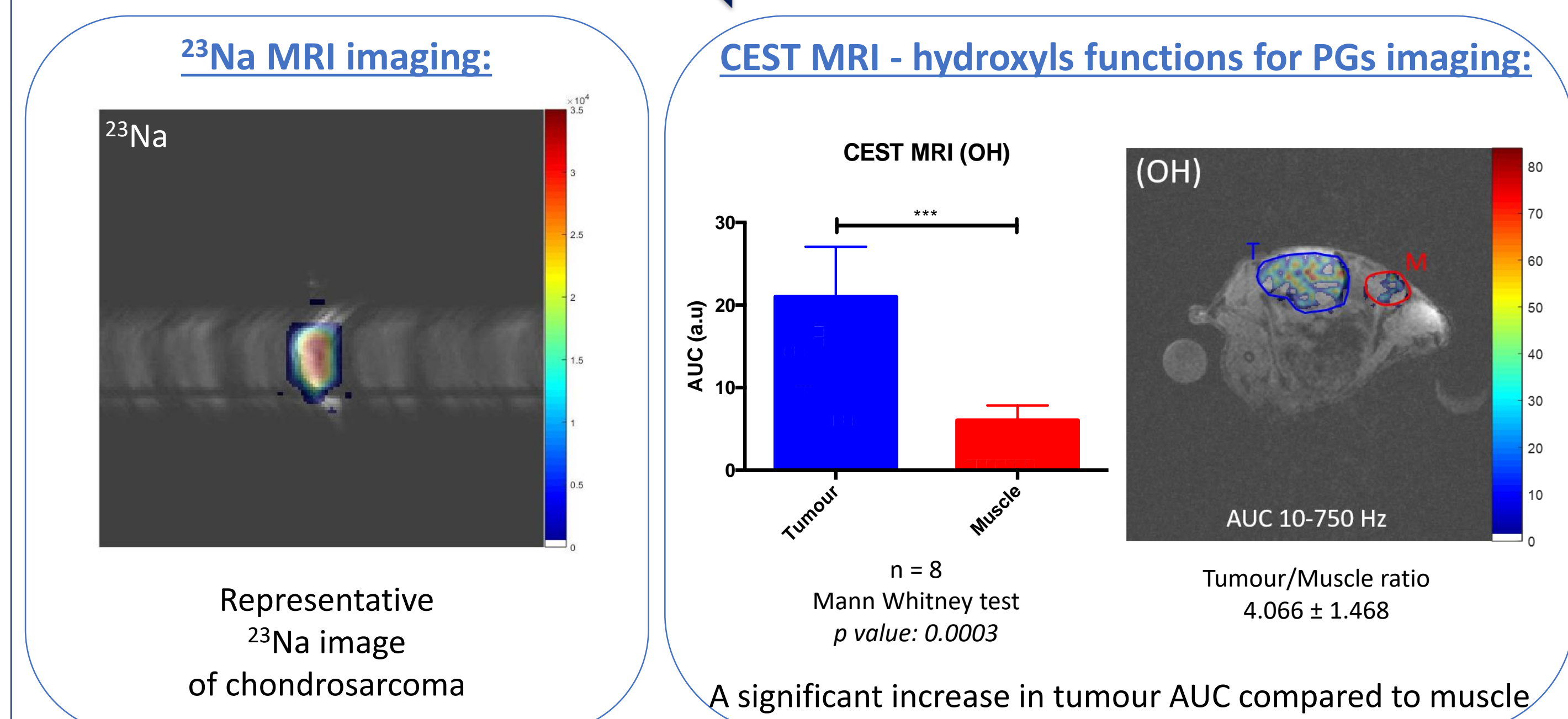
2/Evaluation of hypoxia (pH)



¹⁸F-FMISO uptake inside chondrosarcoma reflects mild hypoxia

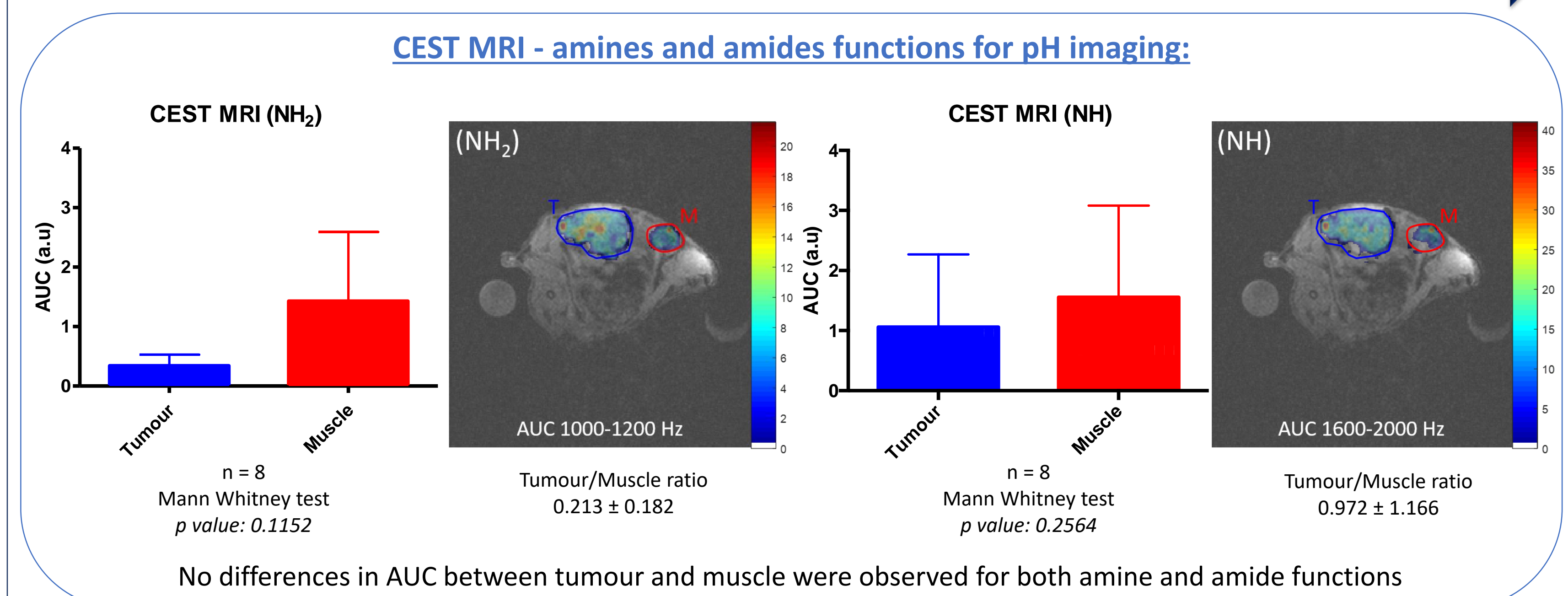
Pimonidazole staining confirms the presence of tumour hypoxic areas

CEST MRI



²³Na 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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