High-frequency Ultrasound Detection of Tumor Vascular Hypoxia as a Targeting Modality for Focused Ultrasound Ablation to Complement Chemoradiation

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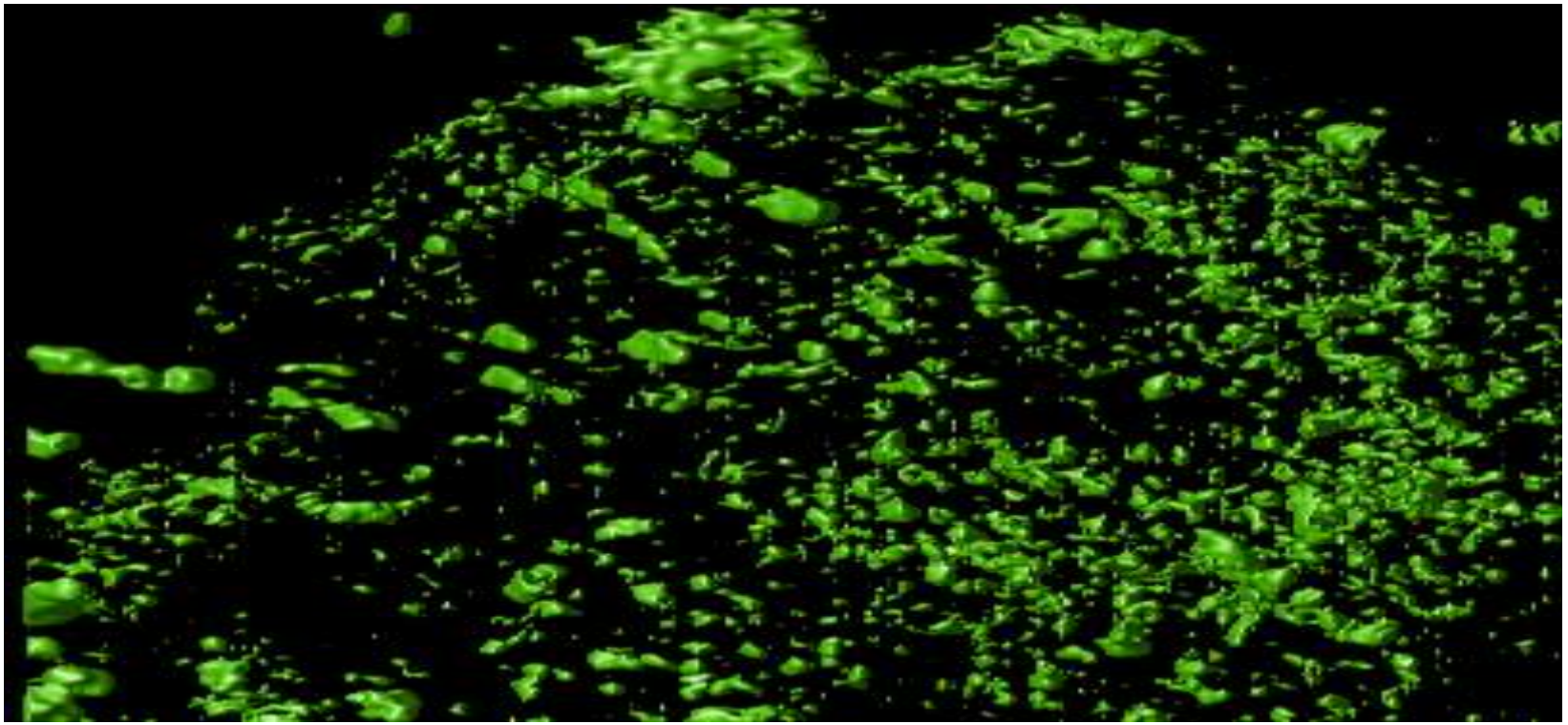
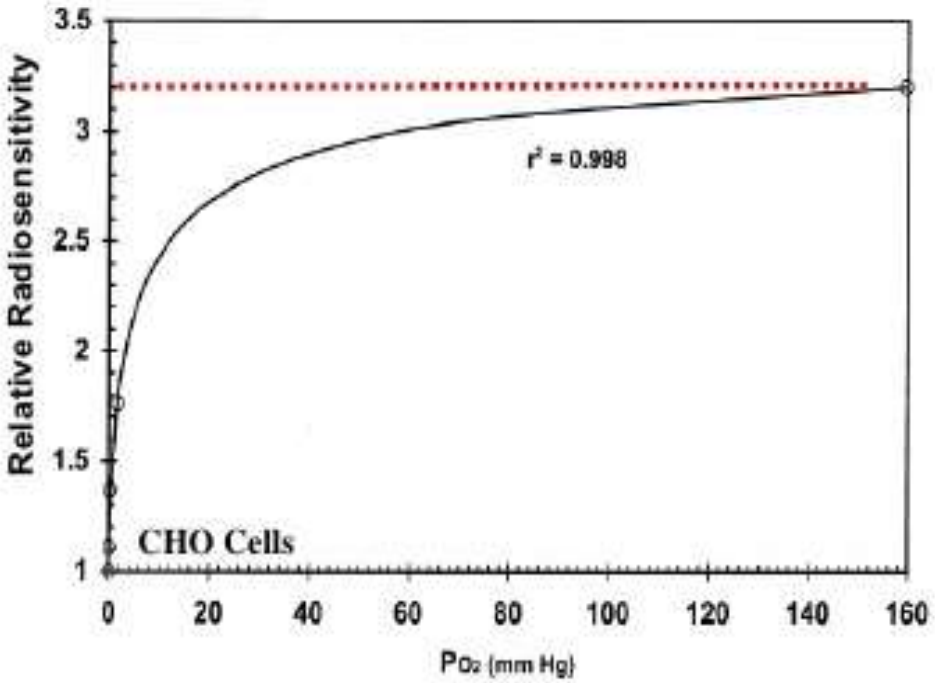


Background

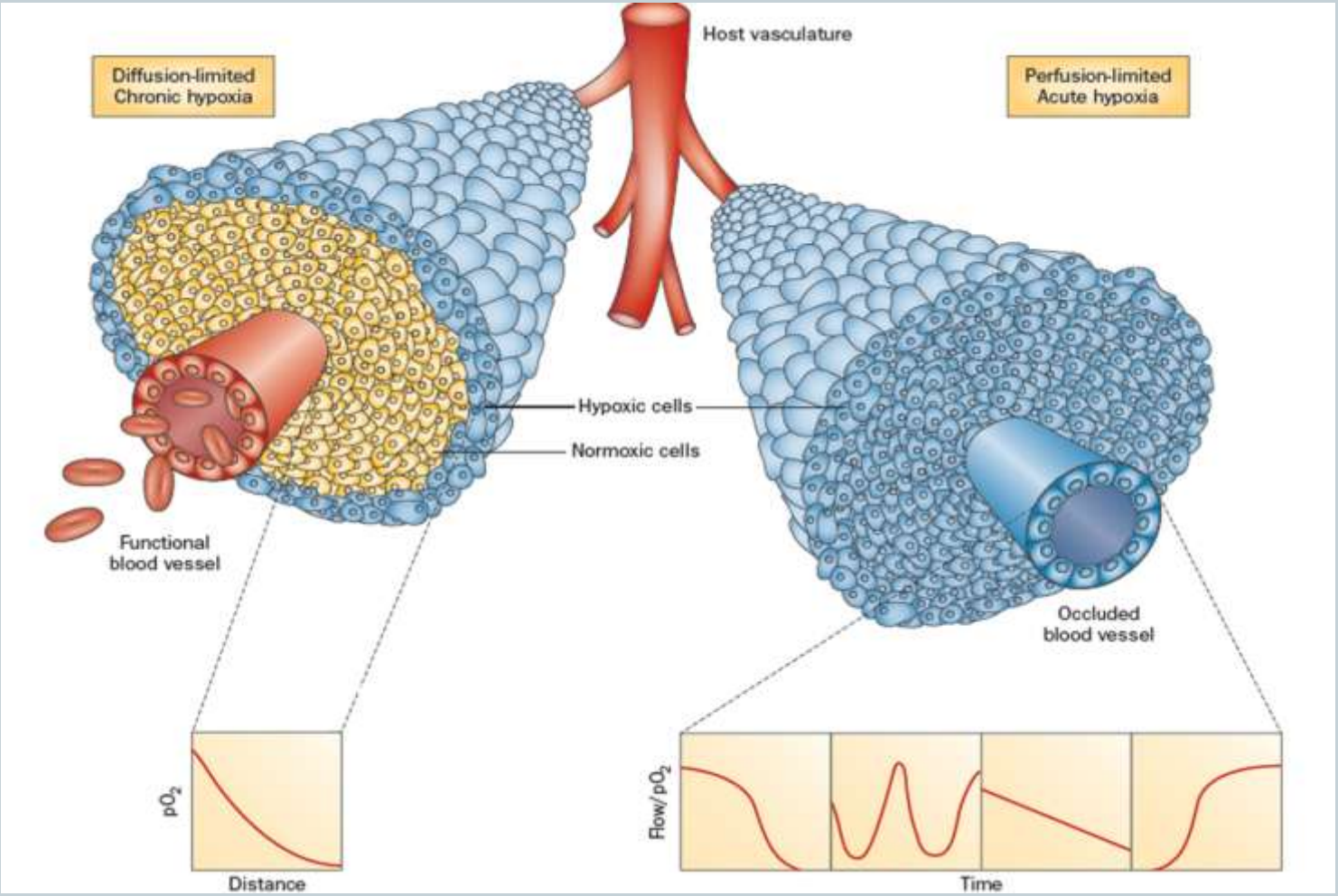
Fundamental Radiation Biology: Hypoxia



Kirkpatrick JP, et al. Intl. J. Rad. Oncol. Biol. Phys. 59:822, 2004

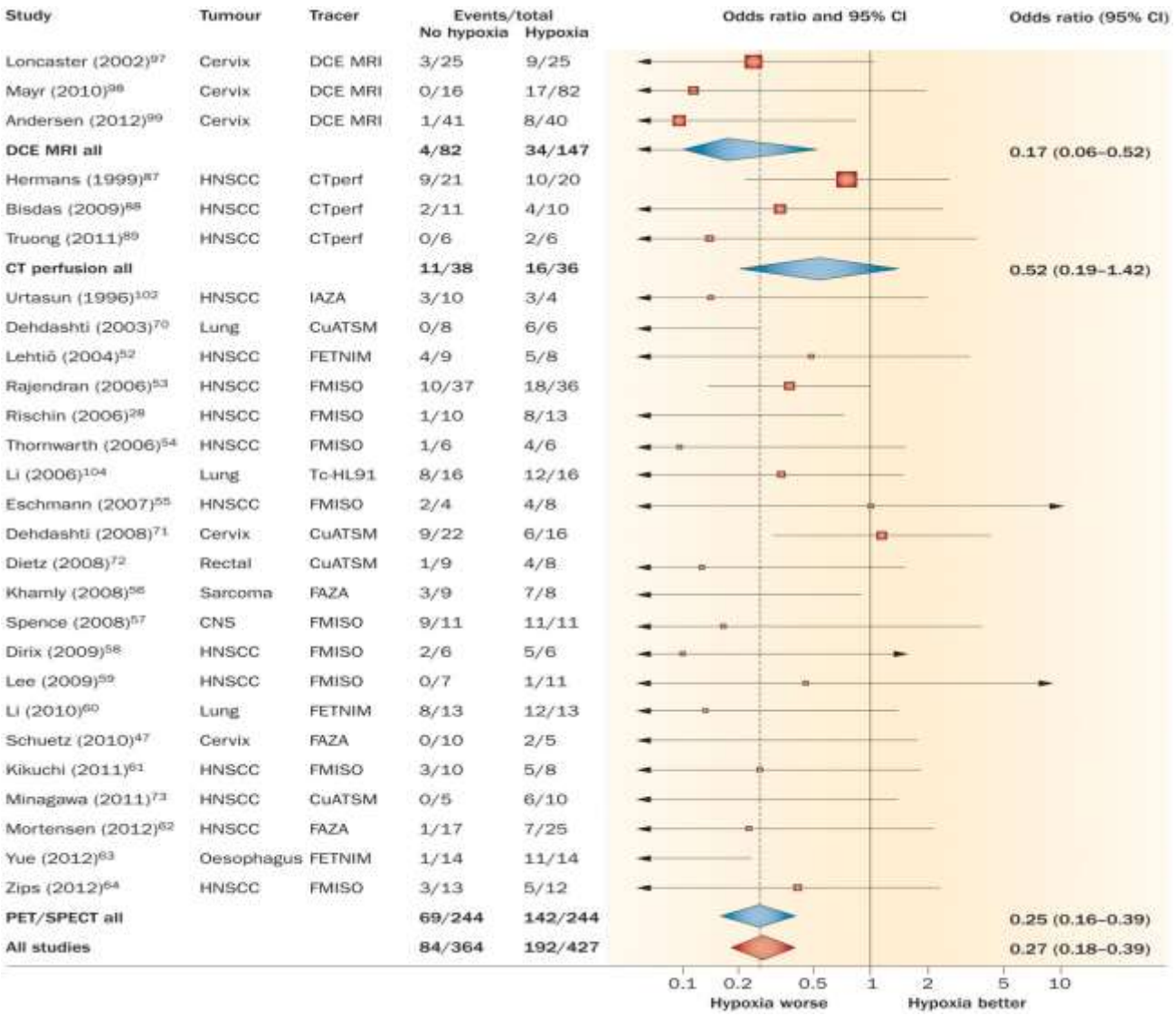
Palcic et. al, **Radiation Research 1984**

Background
Fundamental Radiation Biology: Hypoxia



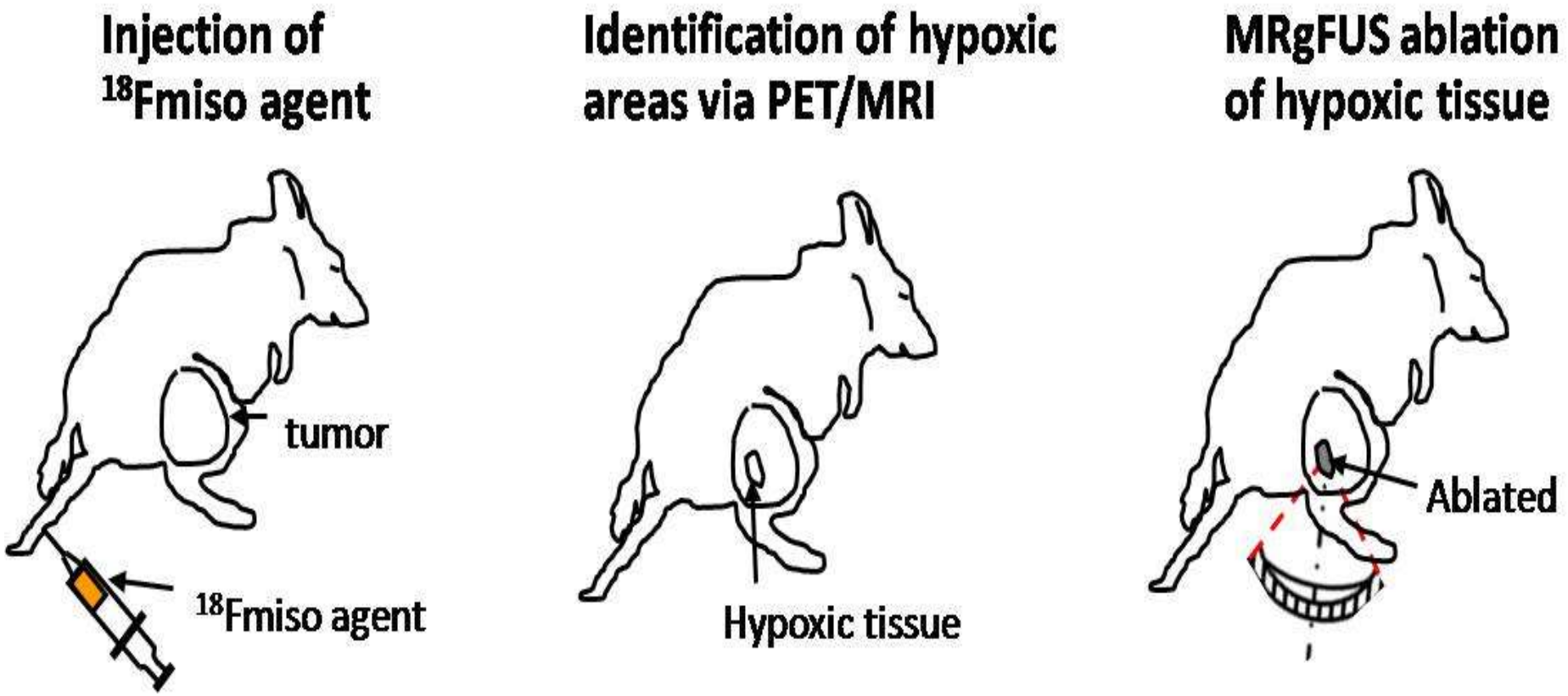
Horsman et. al, **Nature Reviews 2012**

Meta-analysis showing a forest plot of the relationship between hypoxia imaging and the outcome to radiation therapy

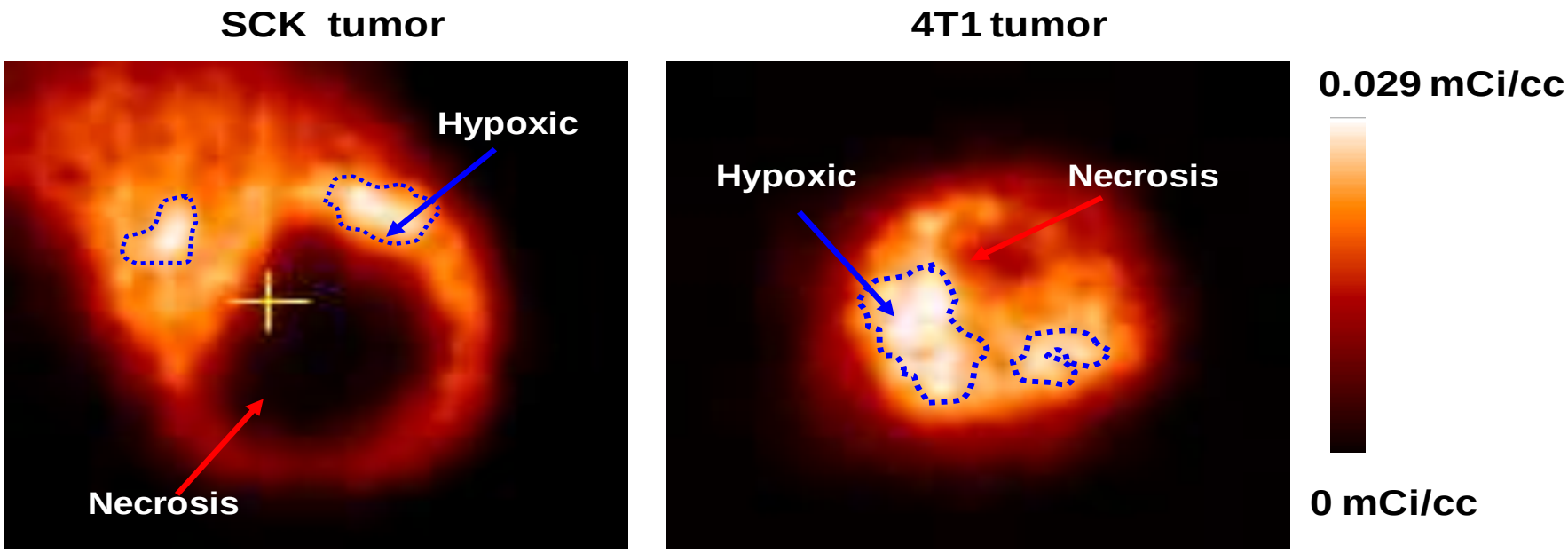


Horsman, M. R. *et al.* (2012) *Nat. Rev. Clin. Oncol.*

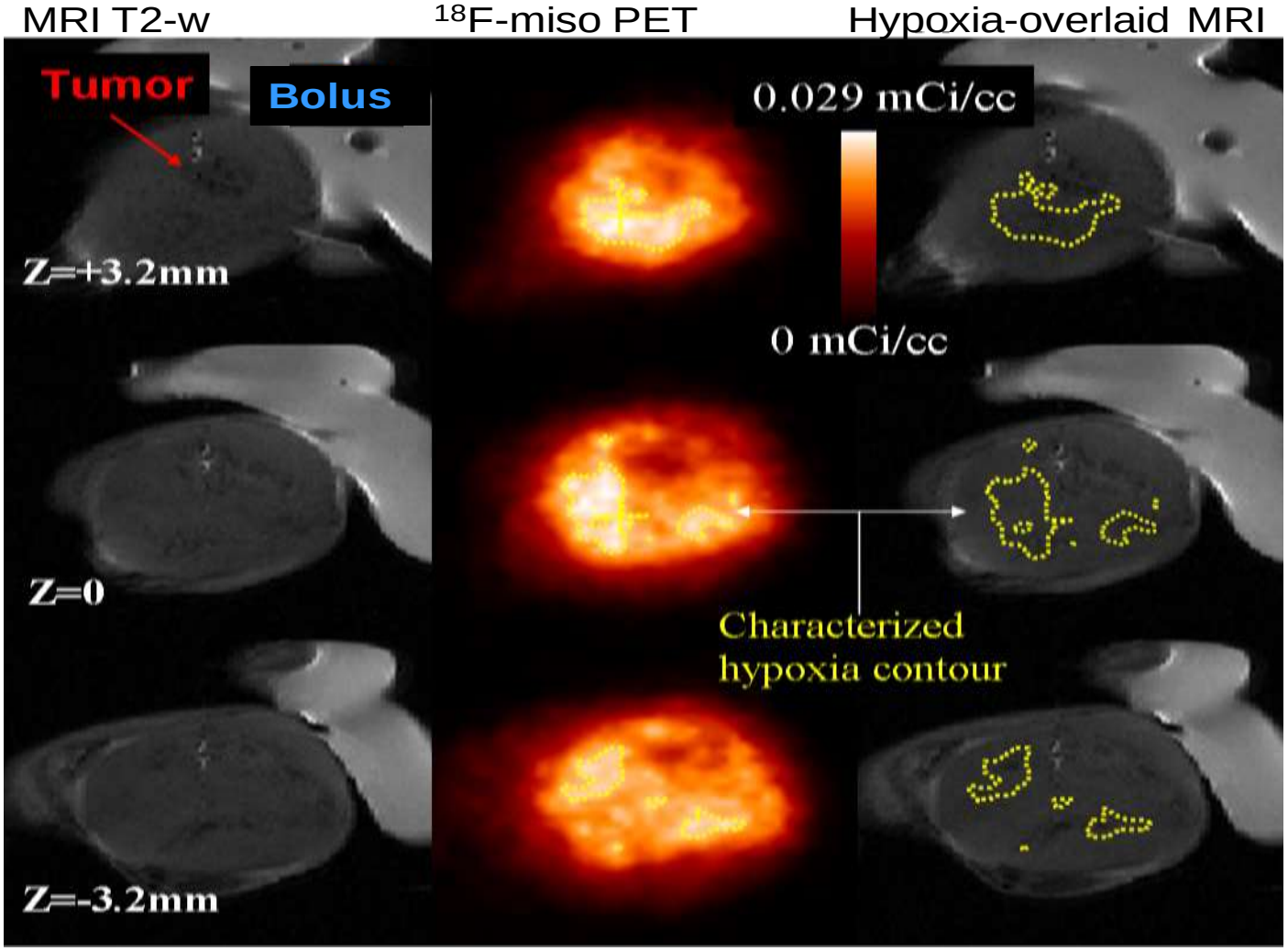
nature REVIEWS CLINICAL ONCOLOGY



Initial approach to reduce tumor hypoxia using ultrasound ablation to complement radiotherapy: Three basic steps of PET/MRI-guided FUS hypoxic-tissue ablation.



PET images of 4T1 and SCK mammary carcinomas, respectively. Attempt to target 'most hypoxic' regions with FUS.



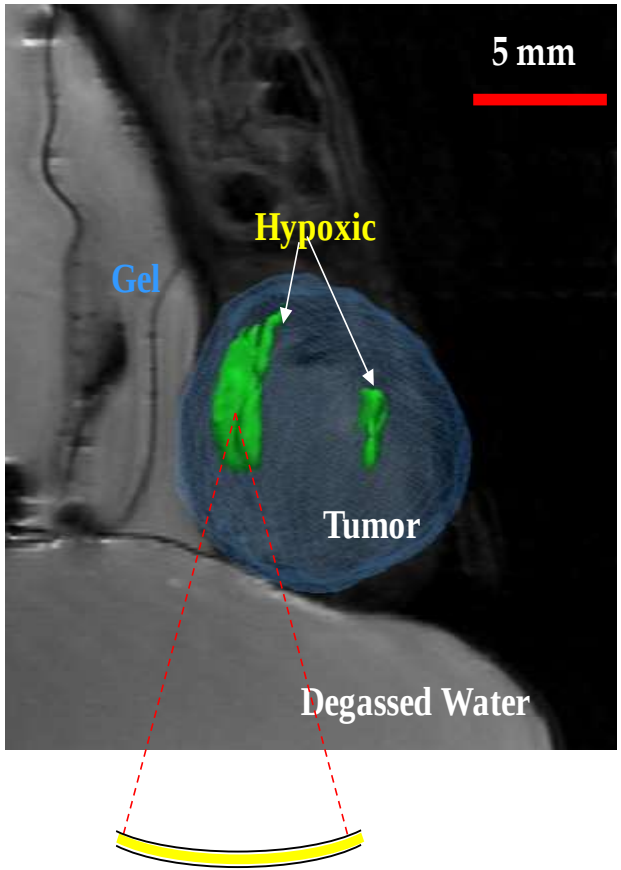
Registration of MRI T2-weighted and ^{18}Fmiso PET images of three transverse slices of a 4T1 tumor. The hypoxic areas characterized by contours of tumor/muscle (T/M) ratio >1.2. The water bolus used is shown in the MRI T2-weighted images but not in the PET images.

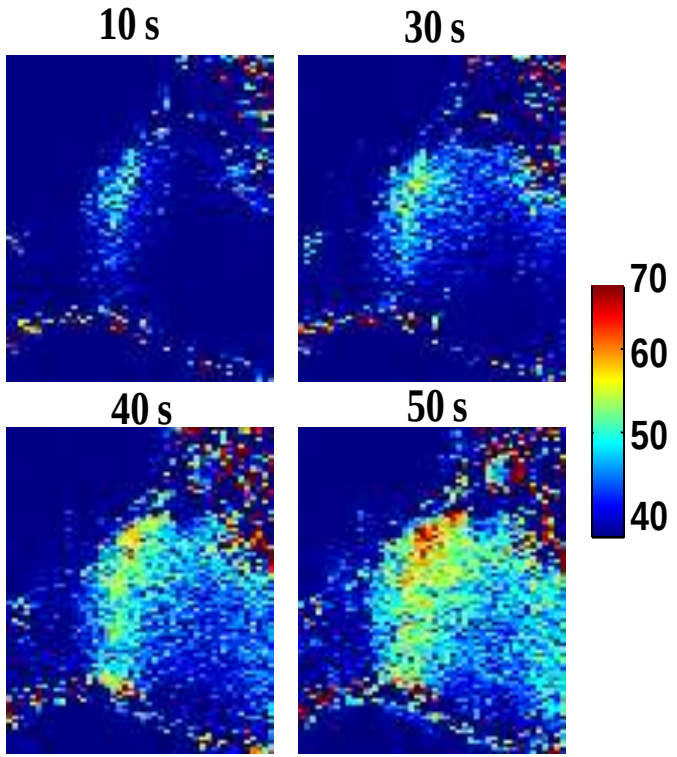
MRgFUS ablation of the hypoxic region in rear-limb tumor implant:

Advantages: **reduced ablation times for large tumors, improved radiation outcomes**

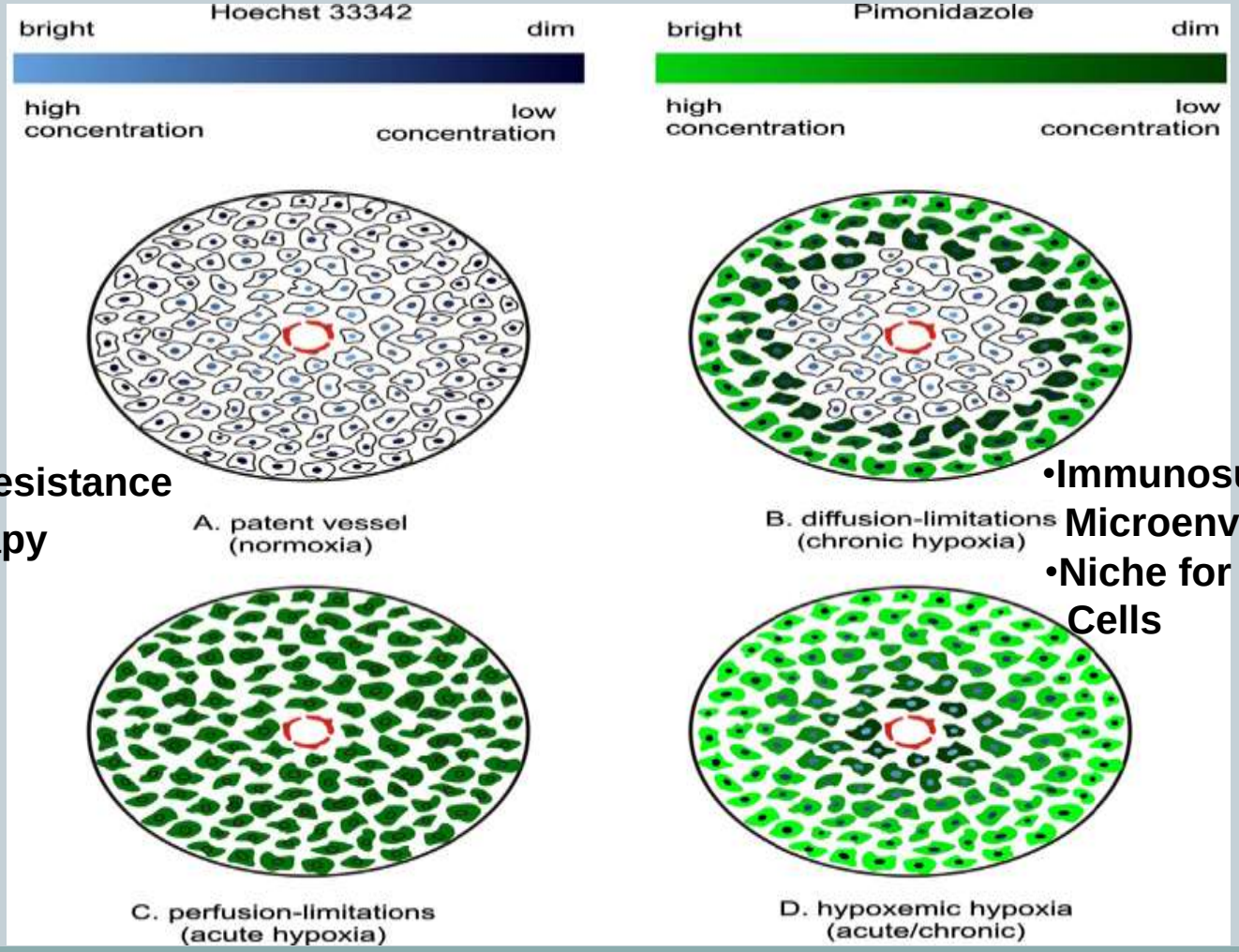
Disadvantages: **Difficult co-registrations, tedious set-up and targeting- are we really getting what we want?**

IS THERE ANOTHER WAY TO FIND AND TARGET 'IMPORTANT' HYPOXIA?





Evidence of Hypoxemic Tumor Vessels: hypoxia is not a 'yes' or 'no' phenomenon.



- **Radiation Resistance**
- **Chemotherapy Resistance**

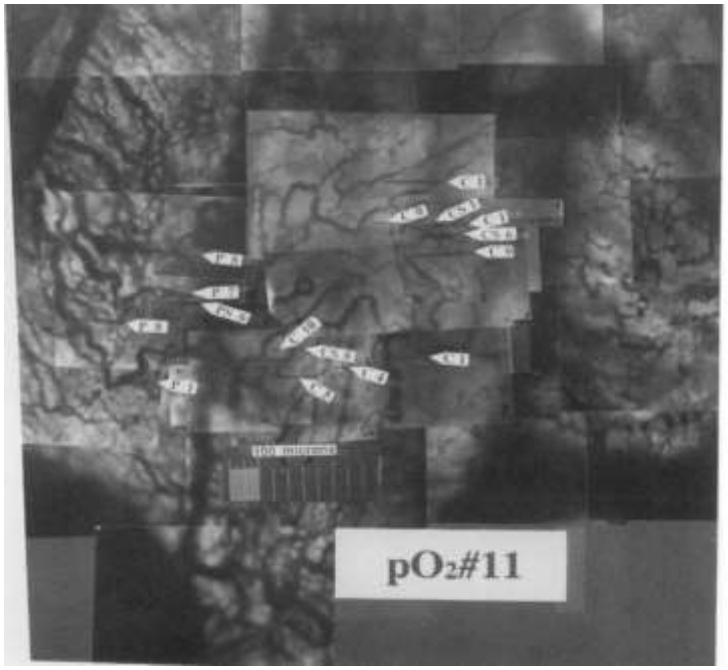
- **Immunosuppressive Microenvironment**
- **Niche for Cancer Stem Cells**

Mafeti et al. (2011) *Radiotherapy and Oncology*

Background
Evidence of Hypoxemic Hypoxia

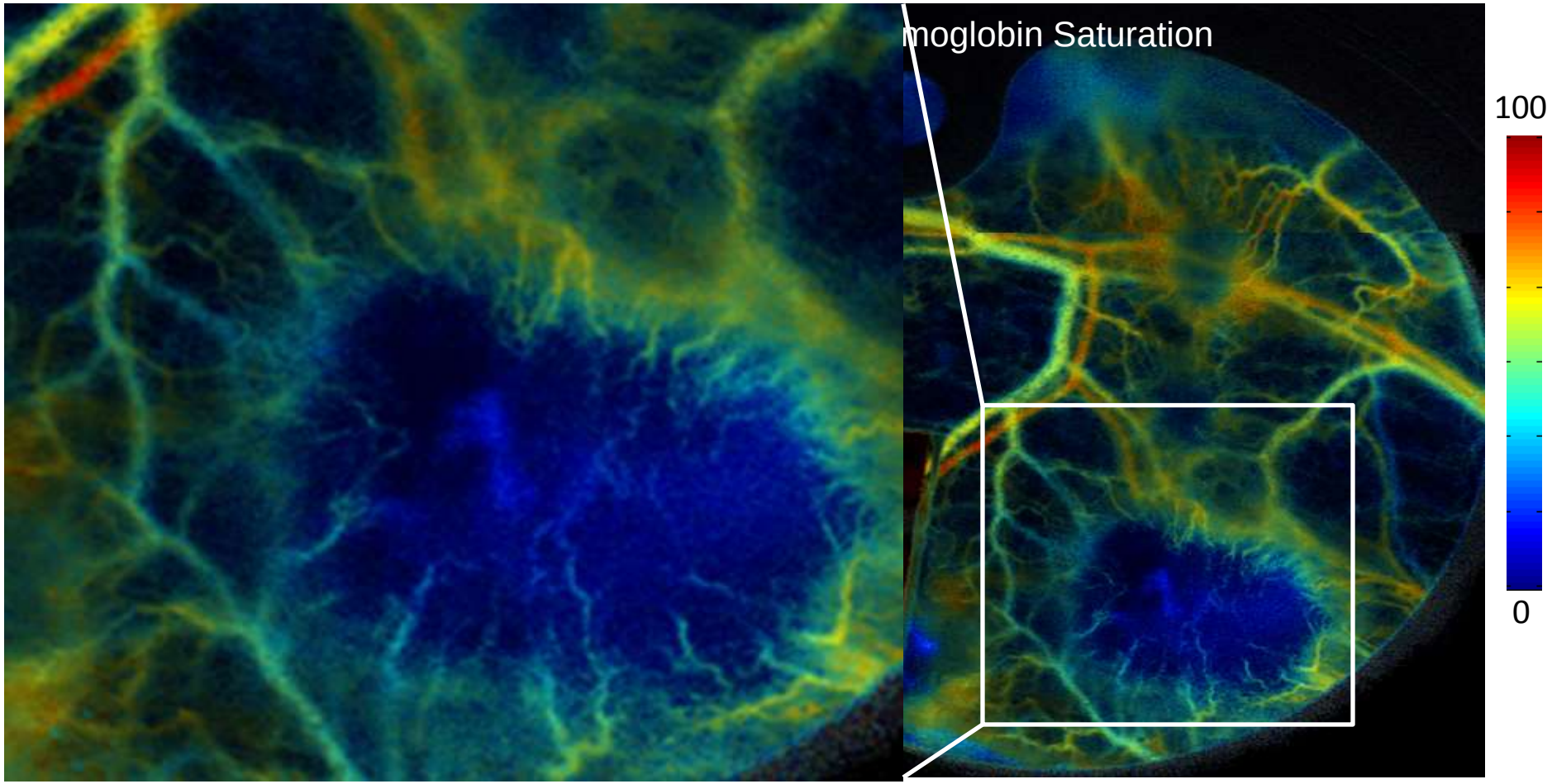
Perivascular oxygen tensions

Normal tissue vessels	72±13 mmHg
Tumor peripheral vessels	26±5 mmHg
Tumor central vessels	12±3 mmHg



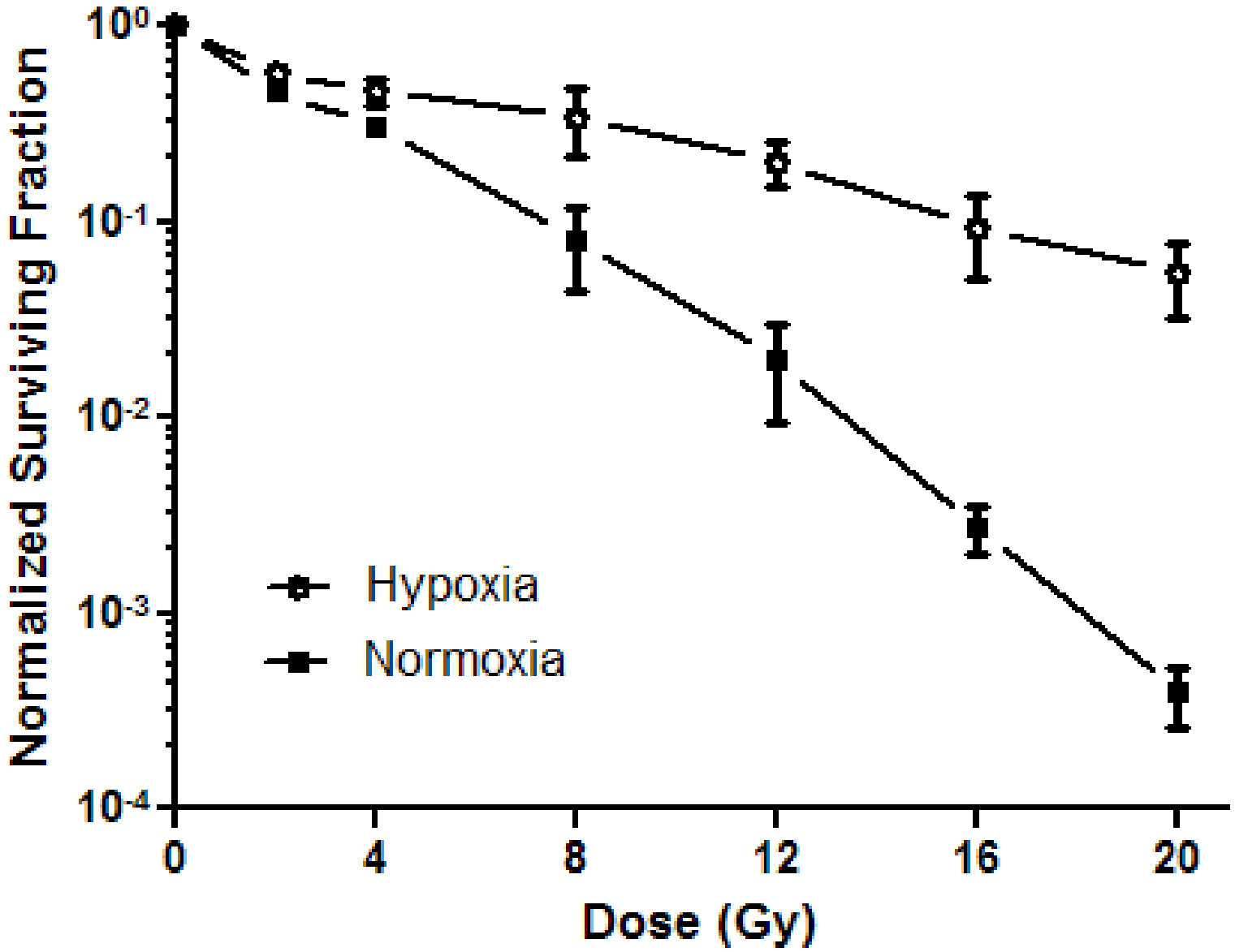
Dewhirst et. al **Radiation Research, 1992**

Background:
Imaging Vascular Hypoxia



Provided by
Andrew Fontanella, Dewhirst Group

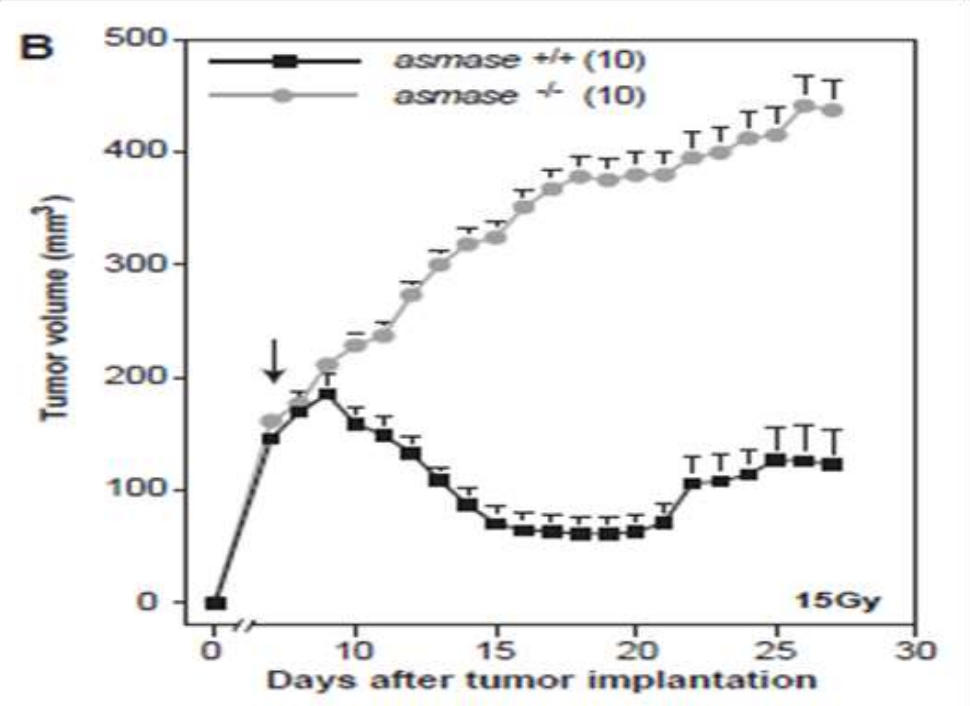
Hypoxia protects endothelial cells from radiation induced cell death



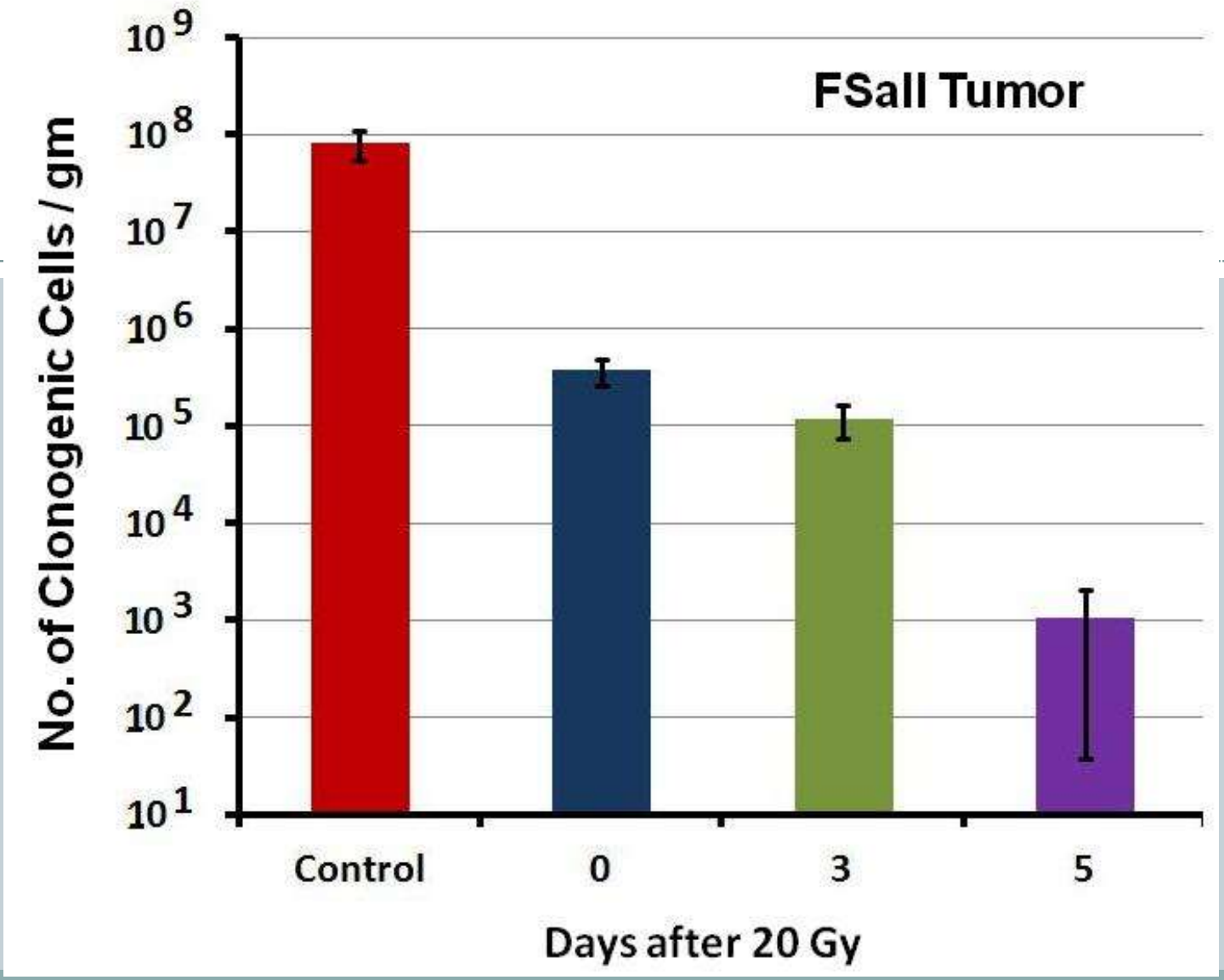
Vasculature key component of high dose radiation response…. Can we specifically detect and eliminate hypoxemic vessels?

Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis

Monica Garcia-Barros,[1] Francois Paris,[1] Carlos Cordon-Cardo,[2] David Lyden,[3] Shahin Rafii,[5] Adriana Haimovitz-Friedman,[4] Zvi Fuks,[4*] Richard Kolesnick[1*†]

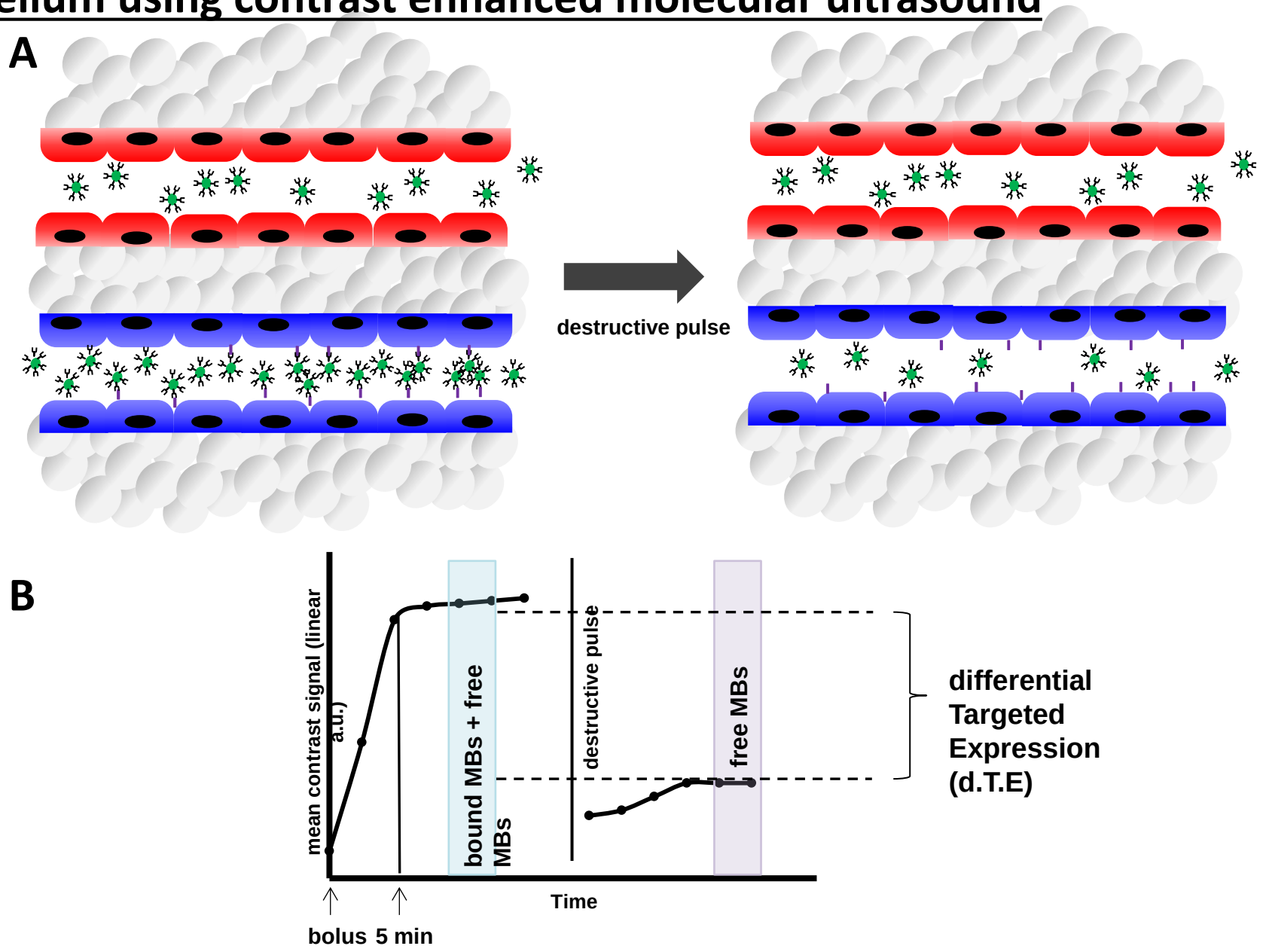


Evidence of indirect cell death caused by radiation induced vascular damage



Song CW, et al. unpublished

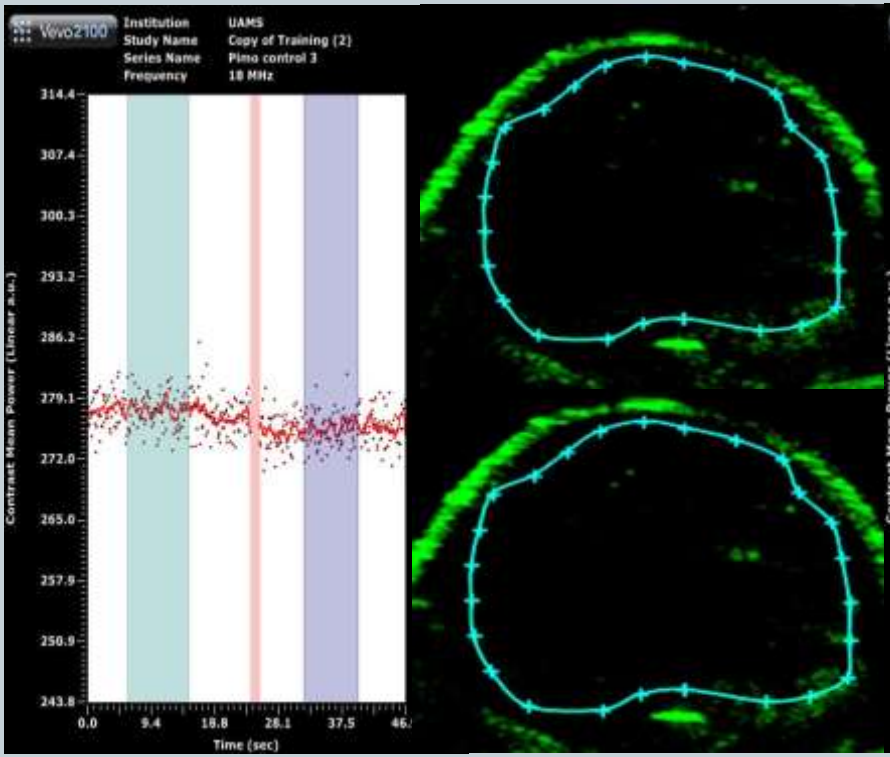
! Detect hypoxia via pimonidazole adducts on the surface of hypoxic endothelium using contrast enhanced molecular ultrasound

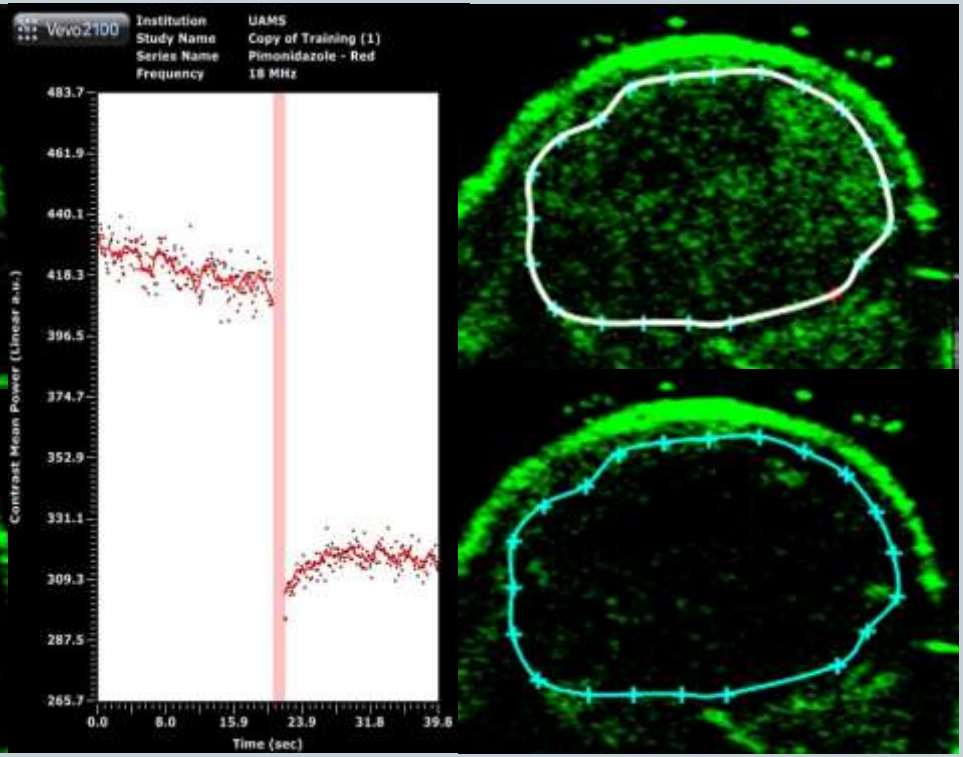


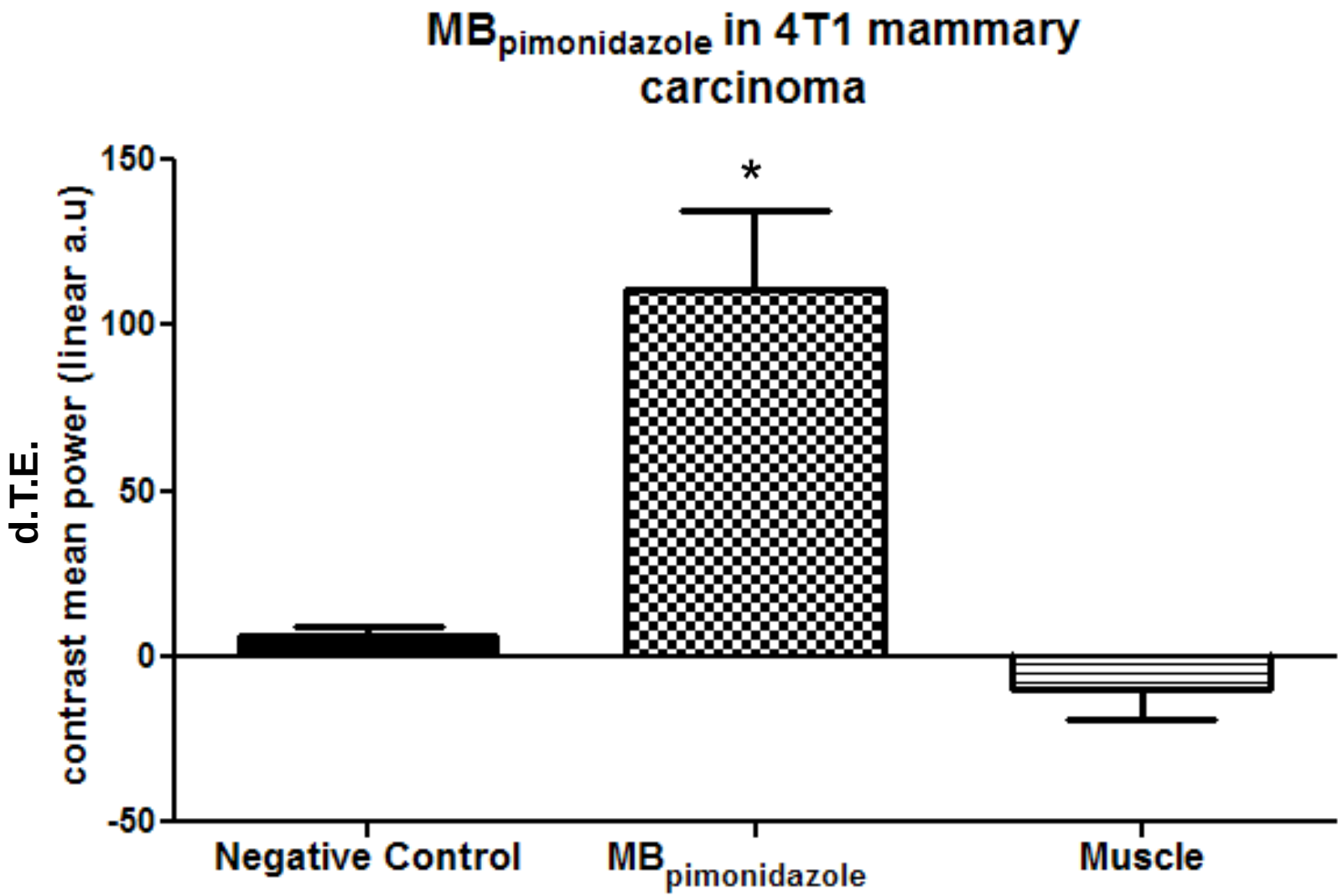
Detection of Hypoxemic Vessels in 4T1 murine breast tumor model

negative control – no pimonidazole

pimonidazole

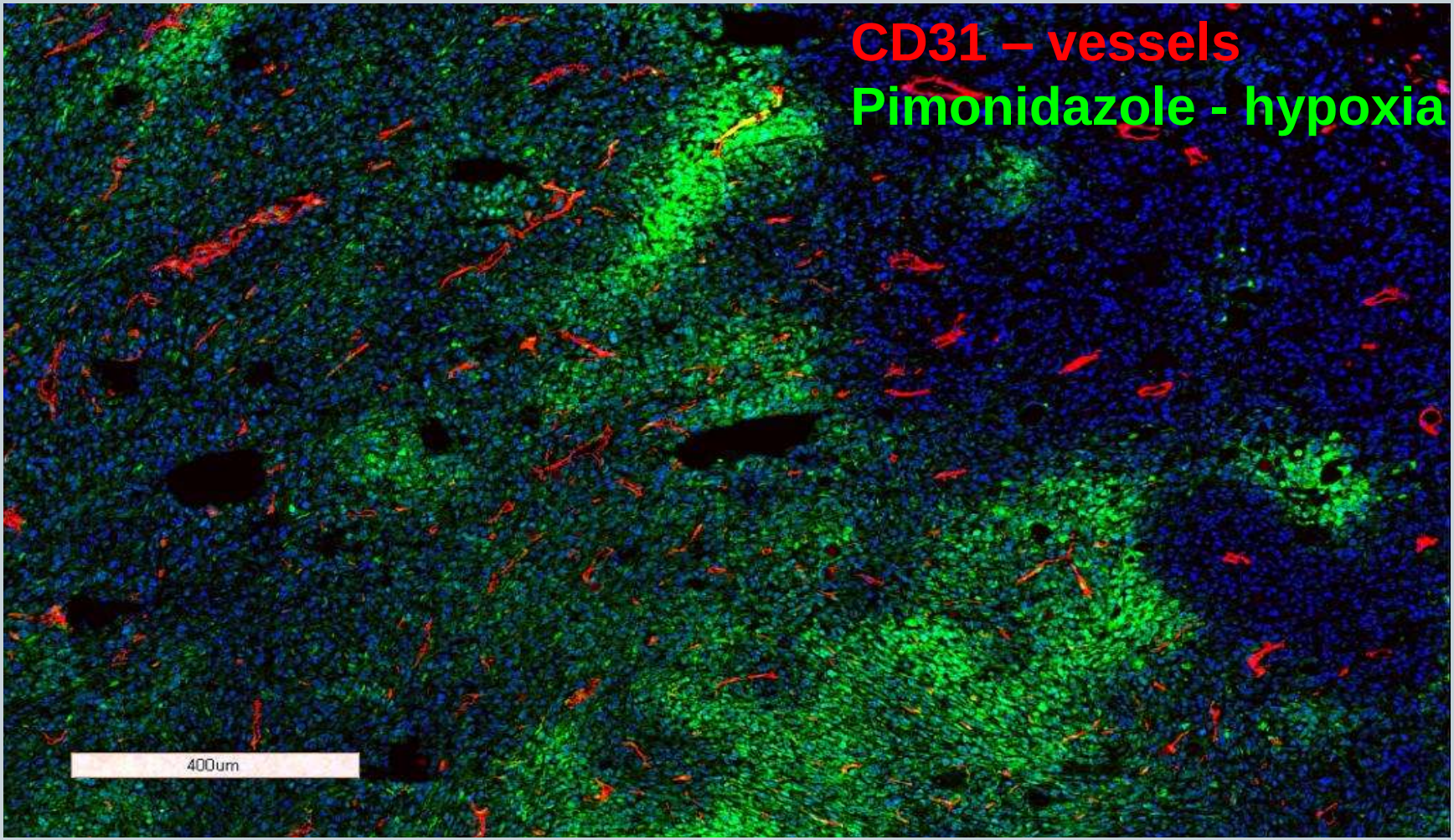





MBpimonidazole in 4T1 mammary carcinoma
d.T.E.
contrast mean power (linear a.u)
150
100
50
0
-50
*
Negative Control
MBpimonidazole
Muscle

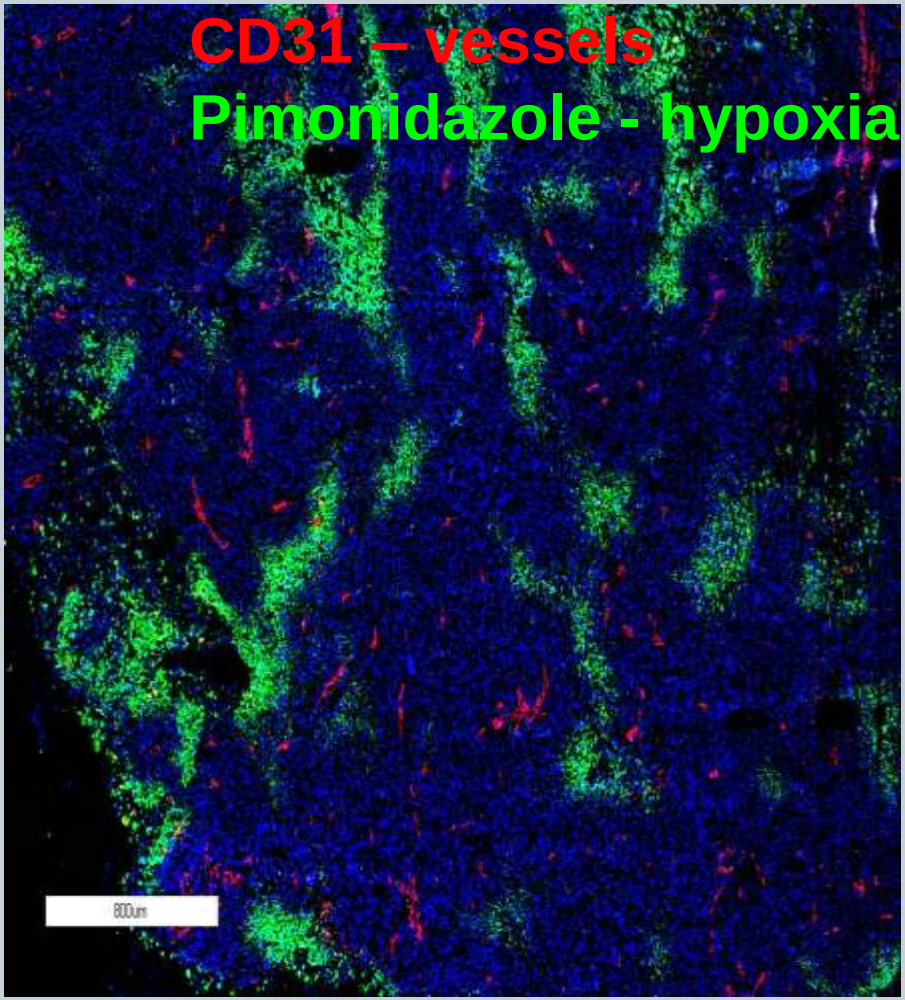
4T1 Mammary Carcinoma

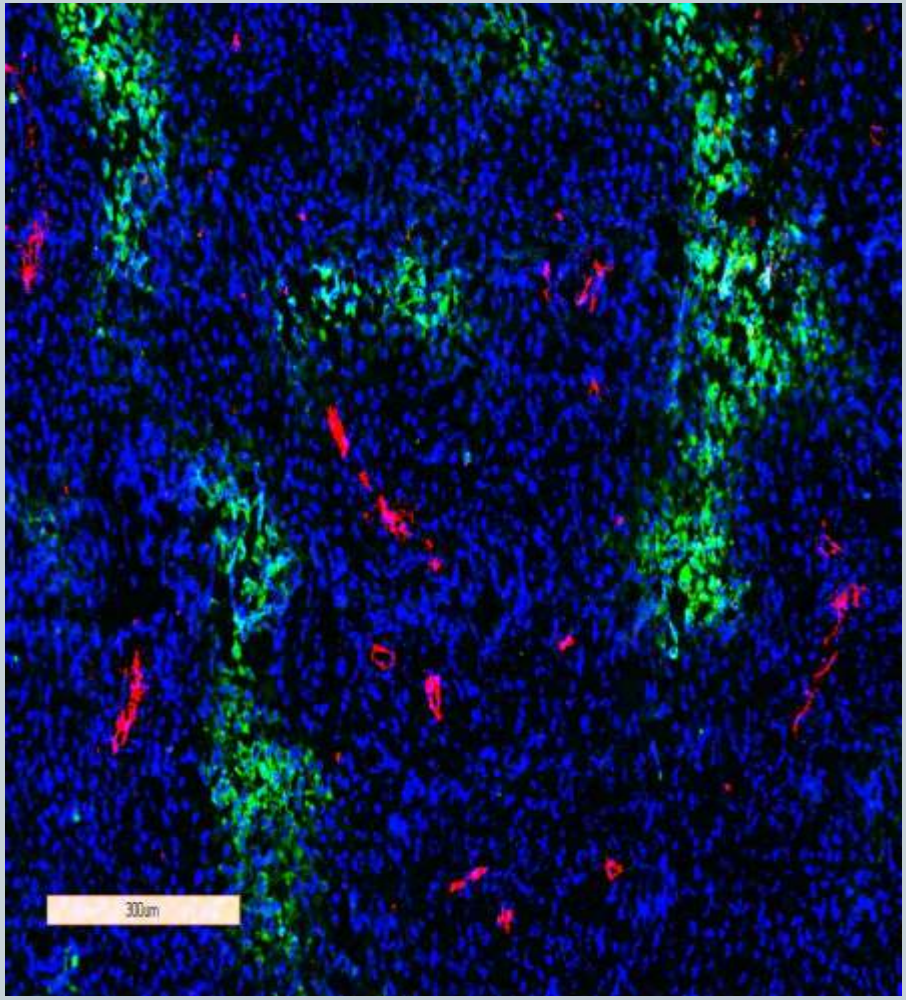
Evidence of Hypoxemic Vessels

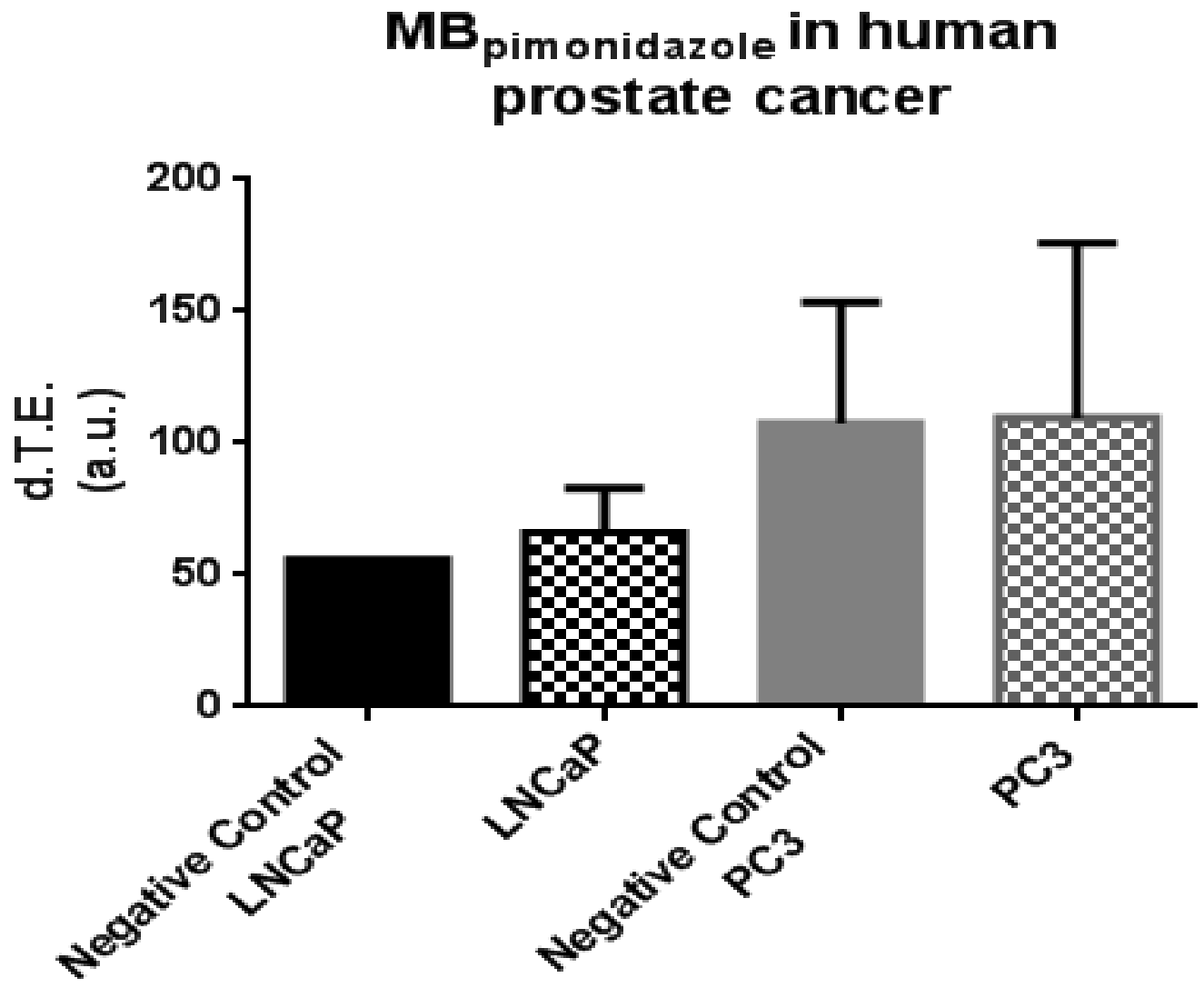


LnCap xenograft human prostate cancer model

Chronic Hypoxia seems to dominate

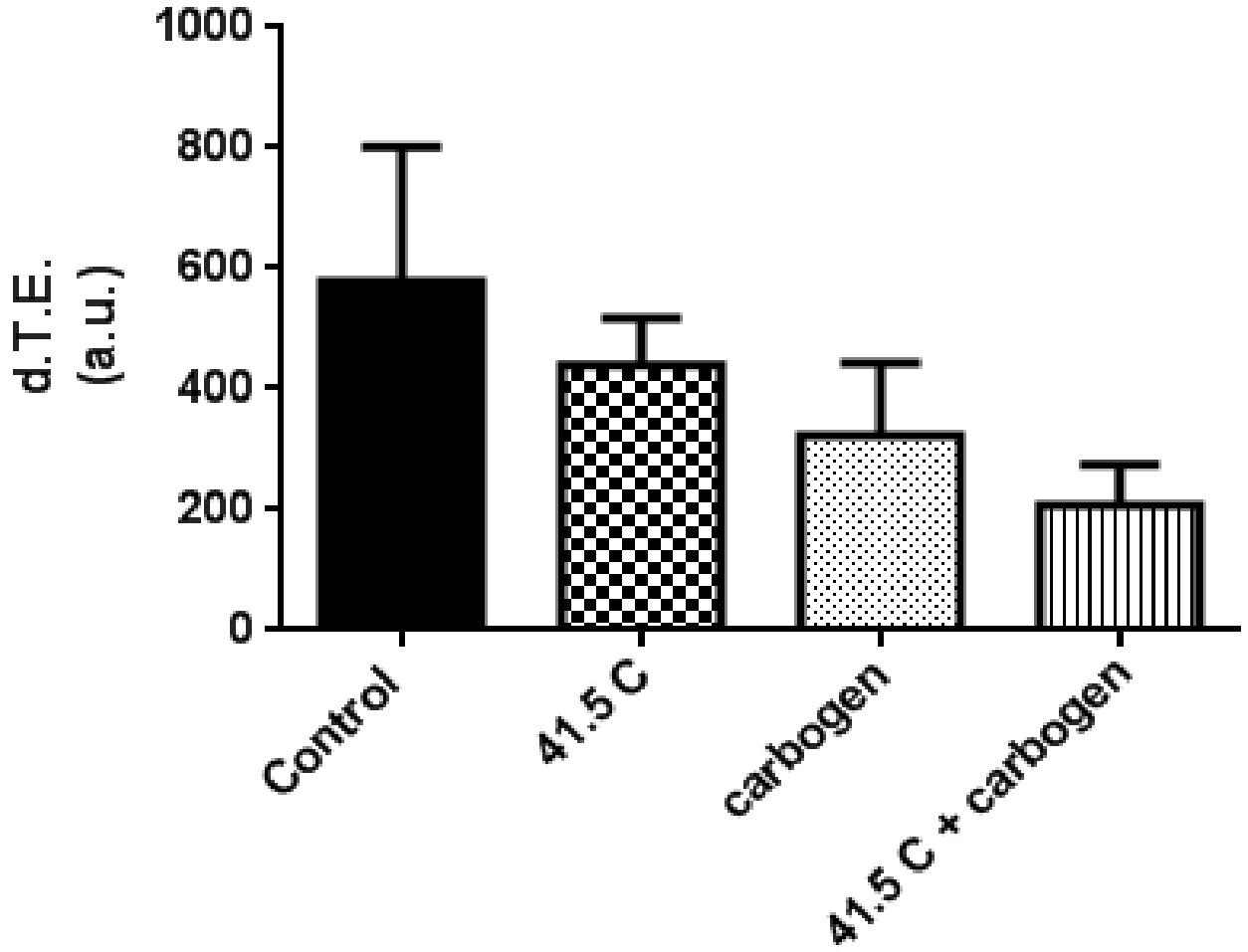




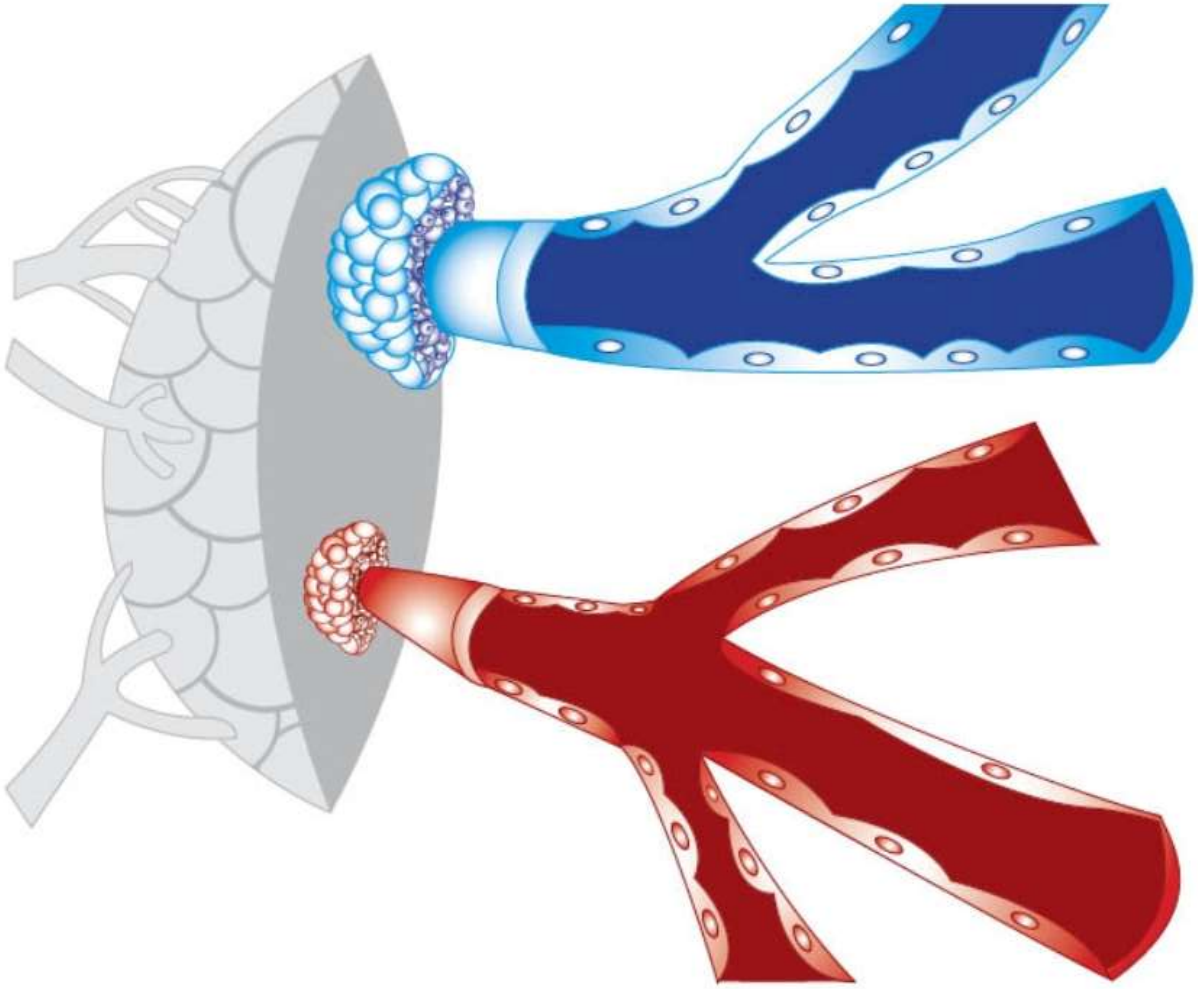

MB pimonidazole in human prostate cancer
d.T.E. (a.u.)
200
150
100
50
0
Negative Control LNCaP
LNCaP
Negative Control PC3
PC3

Hyperthermia as a tool to understand changes in vascular hypoxia following therapy

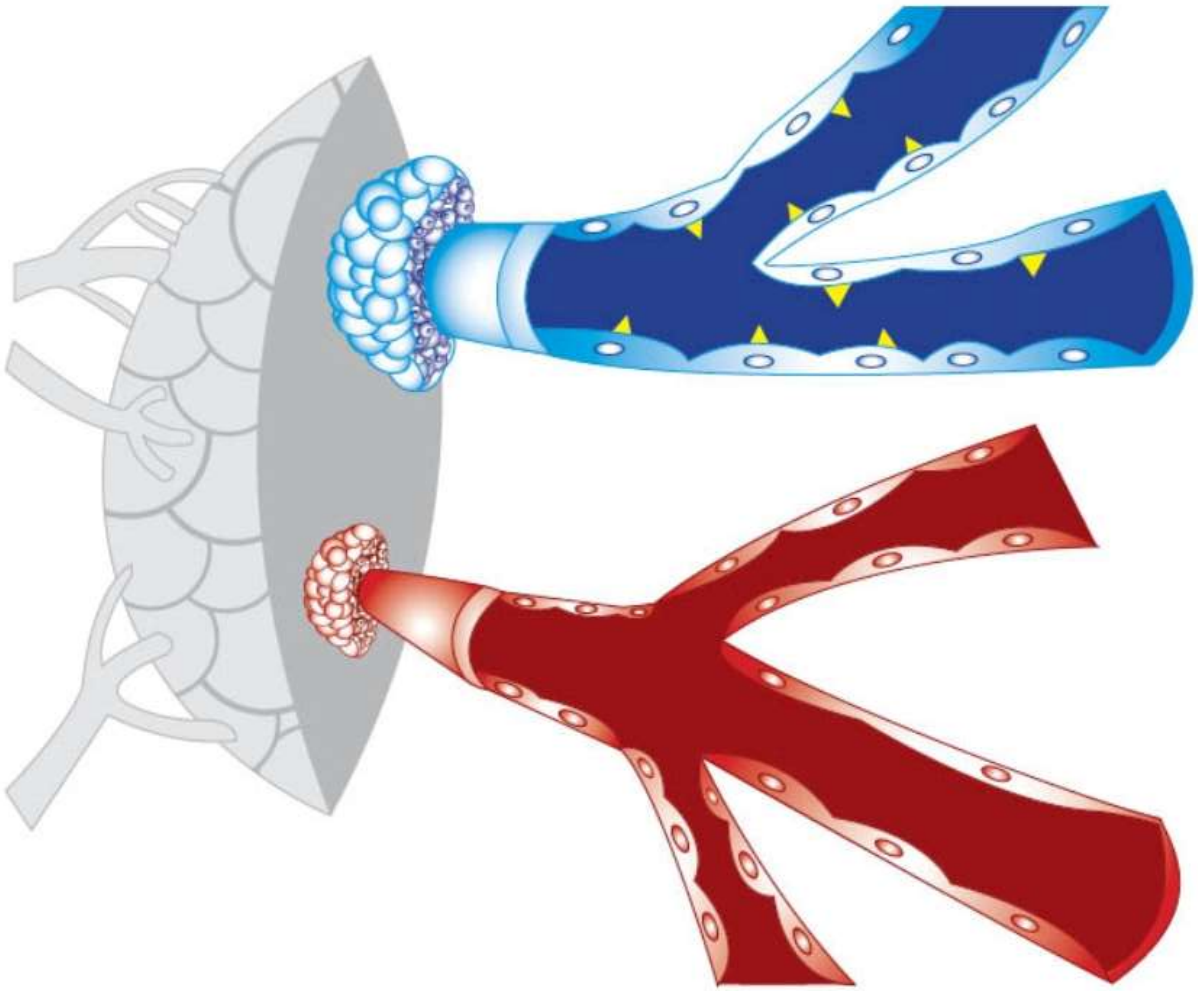
Mild hyperthermia and 95% oxygen breathing combine to reduce vascular hypoxia: Link to improved radiation response observed in numerous studies.



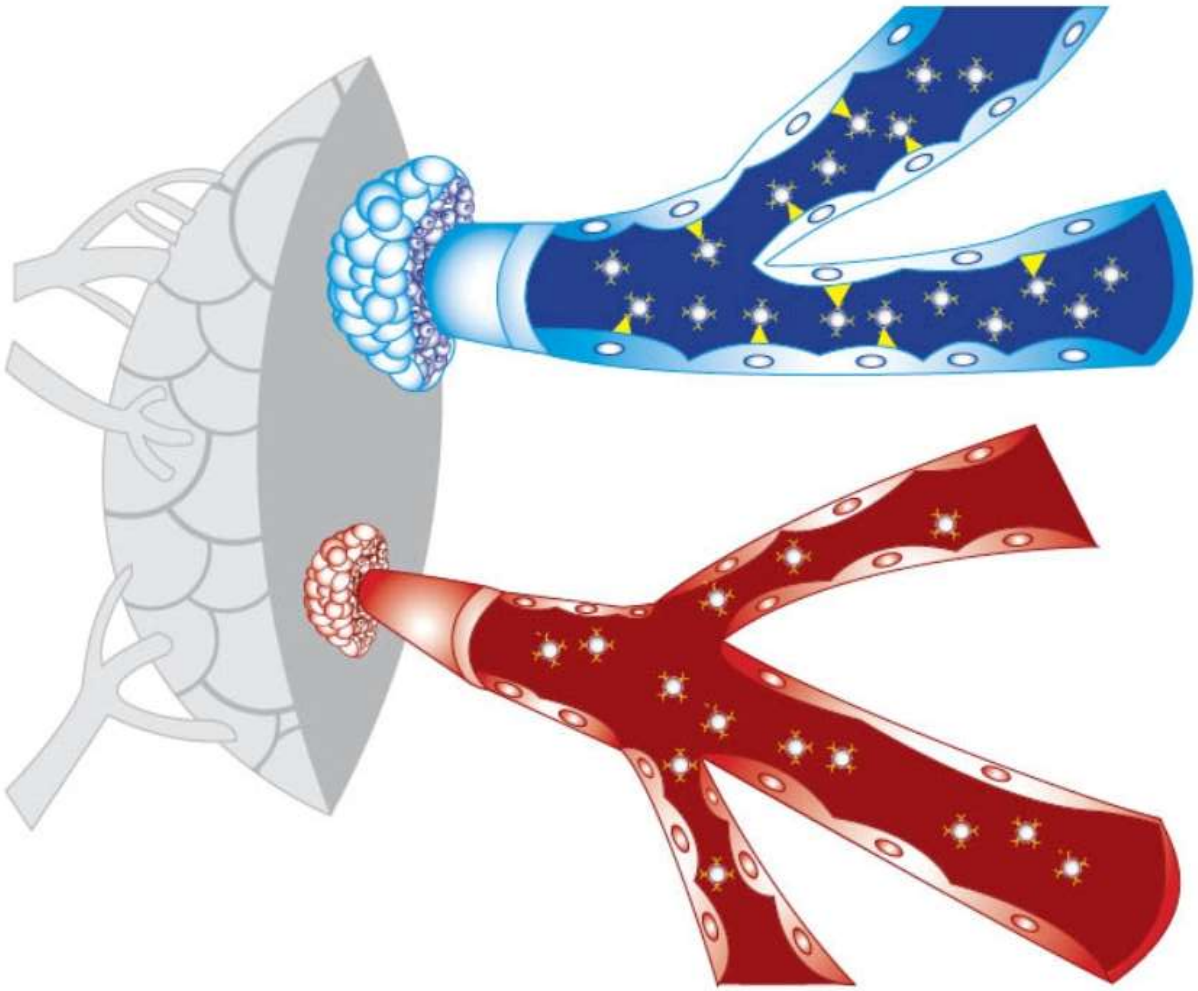
A concept of selective drug/nanomedicine therapeutic targeting of vascular hypoxia



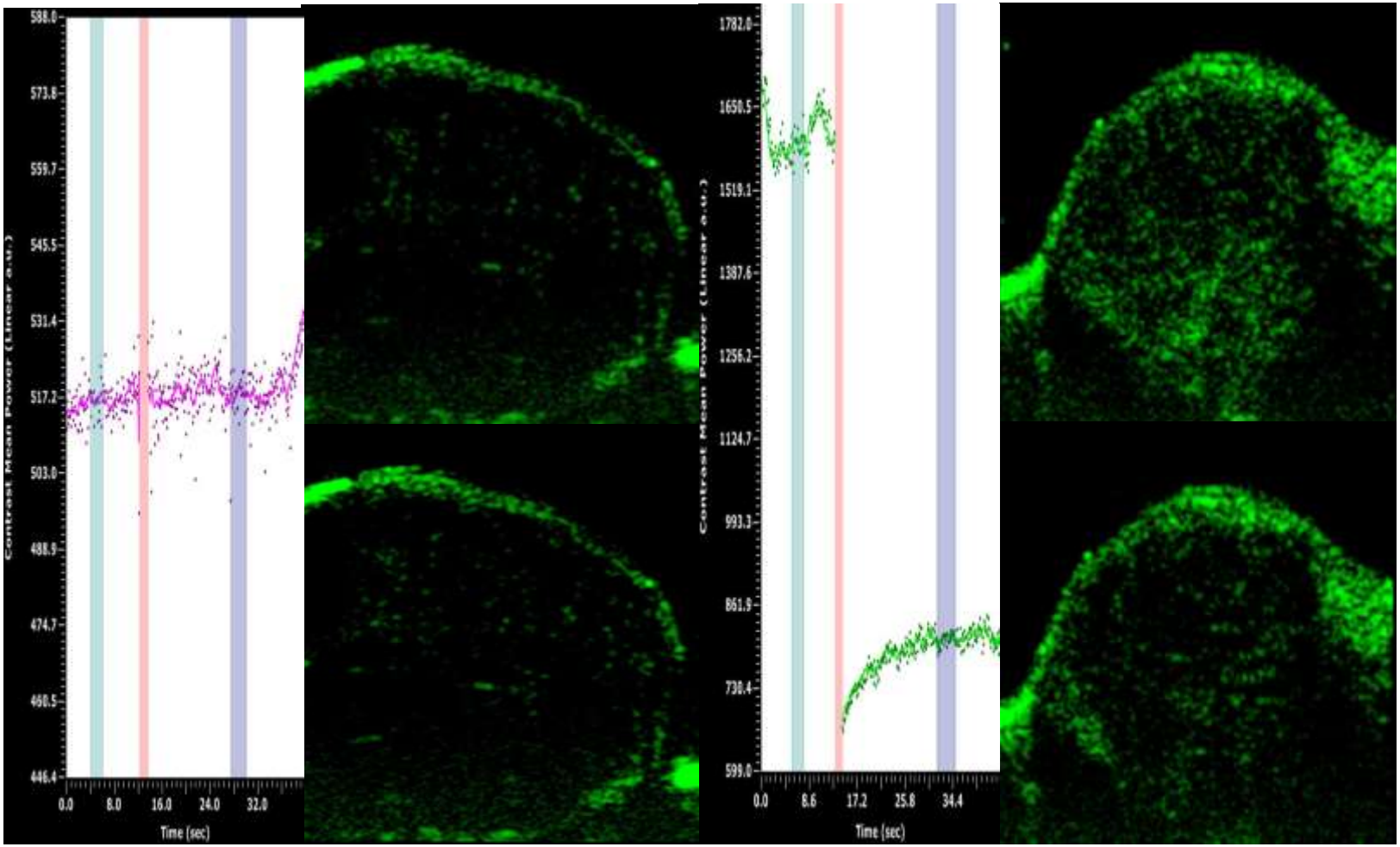
Inject pimonidazole i.p., allow addu ct formation in hypoxic vessels



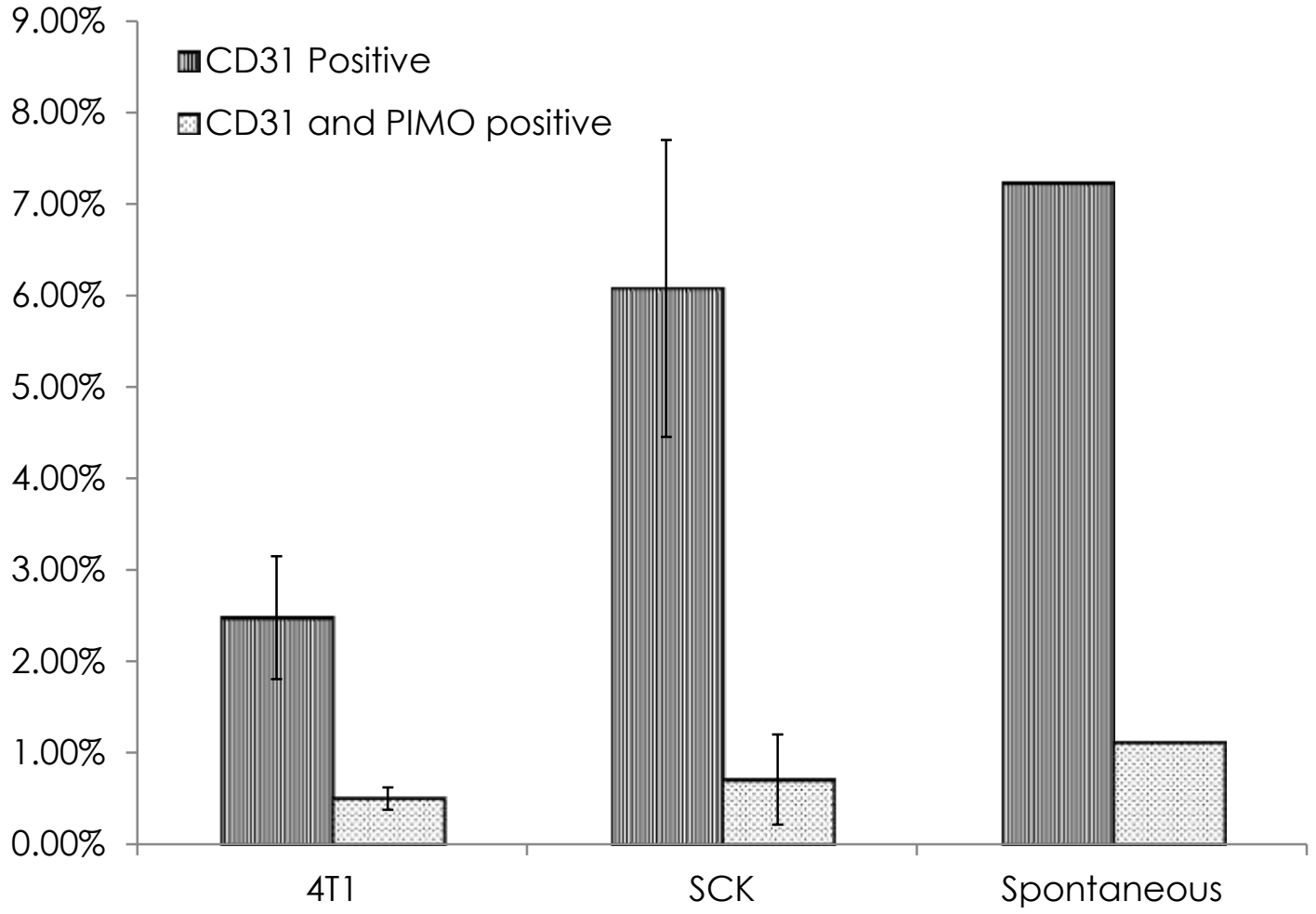
Infuse pimonidazole-targeted drug delivery vehicles to selectively target hypoxic vasculature



Contrast-enhanced US analysis of vessel hypoxia in transgenic breast cancer model MMTV-Wnt-1

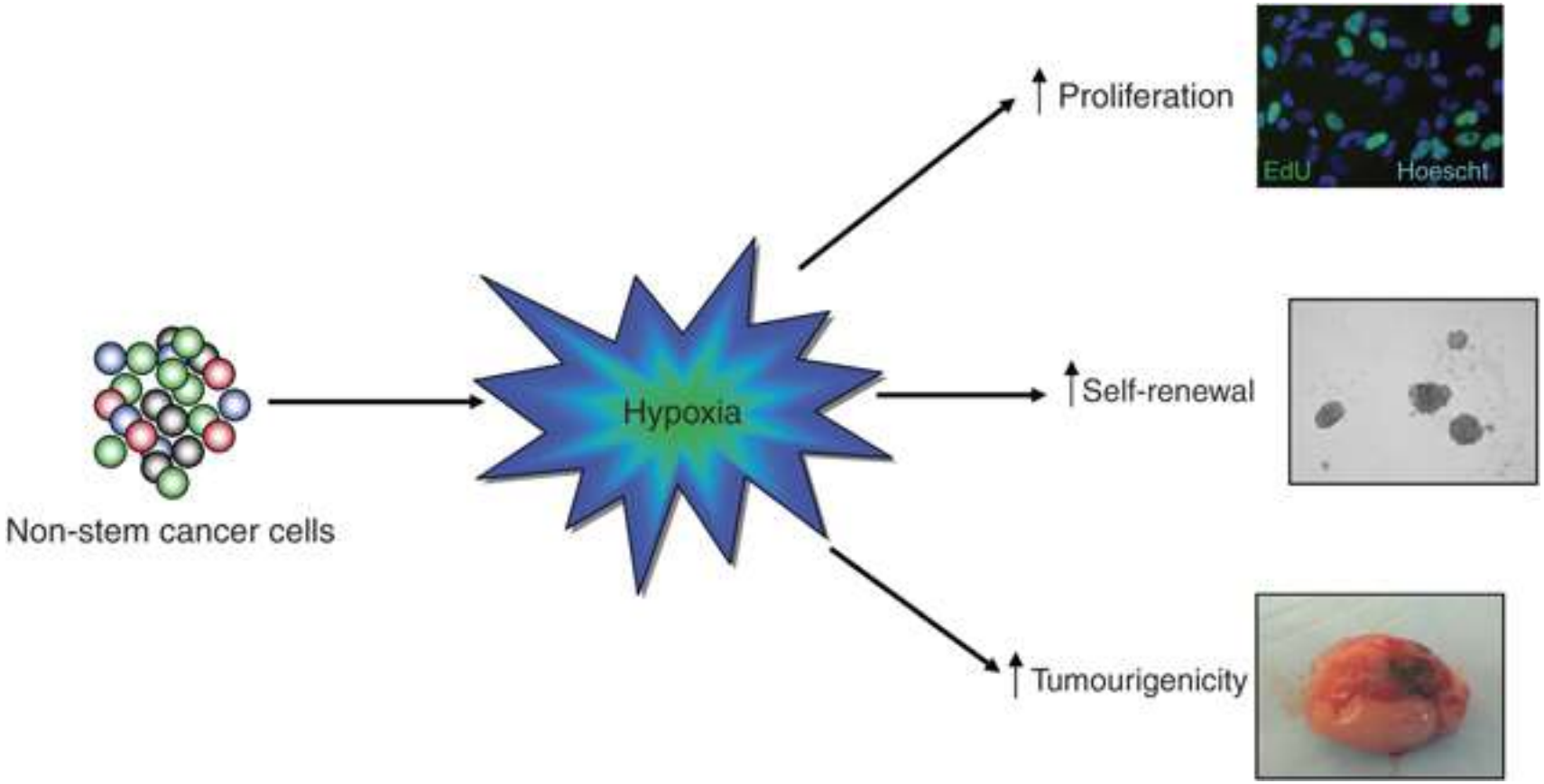


Colocalization analysis of hypoxic vessel presence: transgenic breast cancer also displays traits

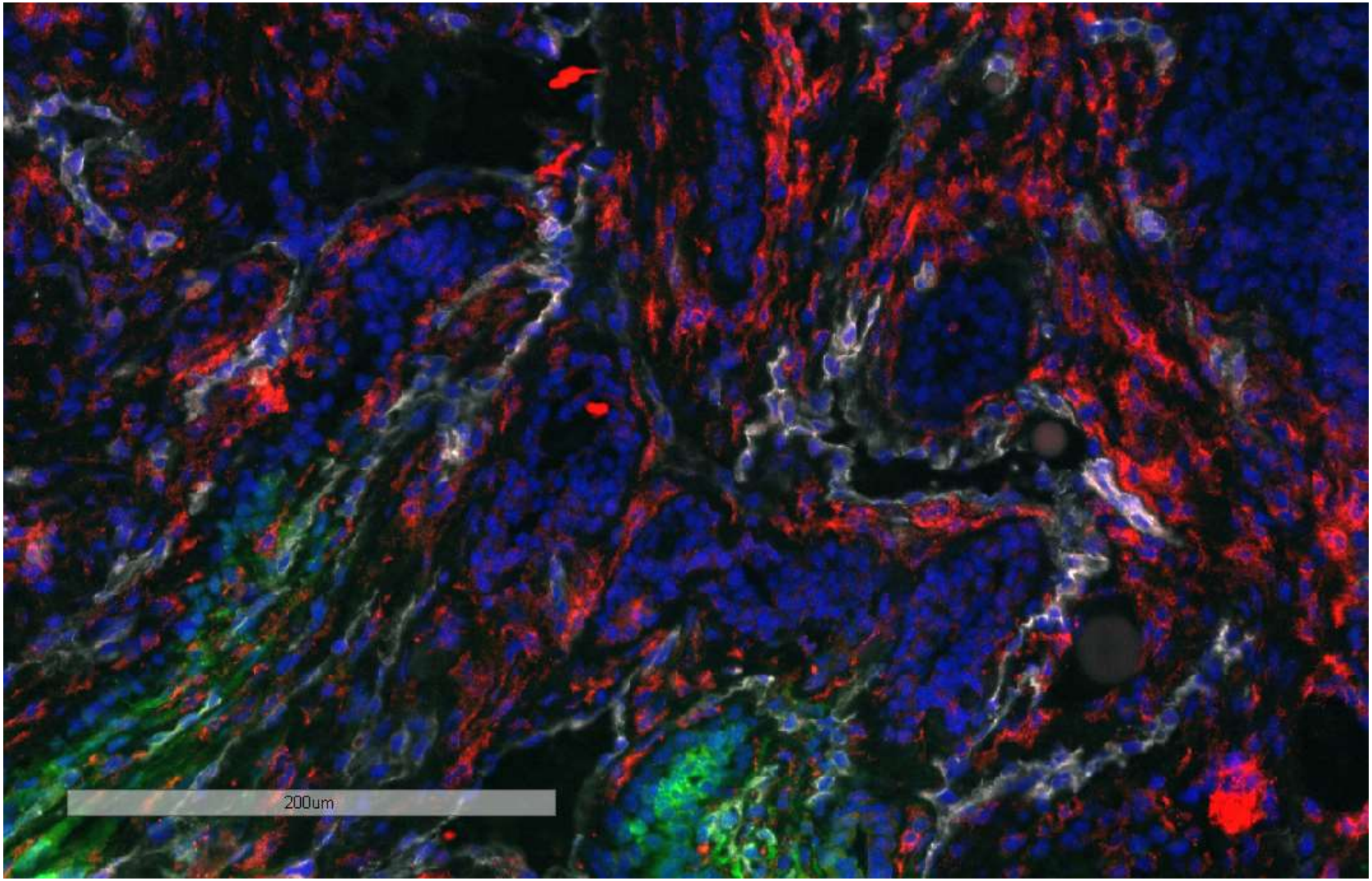


Further importance of destroying/targeting the hypoxic, peri-vascular niche

Hypoxia linked to cancer stem cells



White: CD31+ endothelial cells, Red: ALDH stem cell marker, Green: PIMO, hypoxia in transgenic murine breast tumor line MMTV-Wnt-1



Conclusions

- Development of a novel method for detecting hypoxemic vessels with contrast enhanced US may lead to improved methods for specifically targeting/removing hypoxic tissue
- Resistance of tumor vasculature/stroma a major factor in overall tumor control with chemoradiation
- Potential new target for drug/nanomedicine delivery to areas associated with therapeutic resistance
- An ultrasound-based imaging and treatment approach against cancer initiating cells?

Acknowledgements

- Eduardo Moros, PhD, Moffitt Cancer Institute
- Joseph Levy
- Azemat Jamshidi-Parsian

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Focused Ultrasound Surgery Foundation
NIH CA-44114

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