Facility for Antiproton and Ion Research in Europe GmbH

ENLIGH Meeting
France, CAEN. July 1-3, 2019

# Is hypoxia sensitive to particle therapy?

Walter Tinganelli

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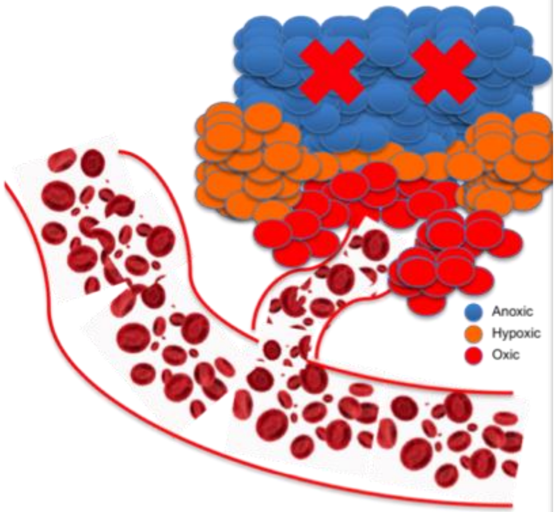
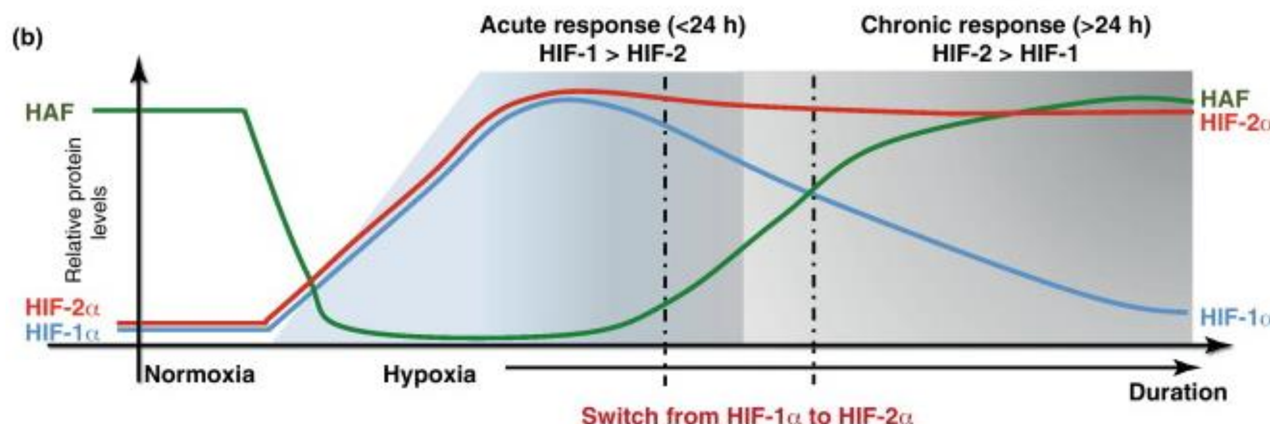
**Biophysics Department**
**Clinical Radiobiology Group**
**Darmstadt, Germany**

- The transition from acute to chronic hypoxia requires from 30 min to several weeks




HIF1-α > HIF2-α
LOW HAF

Death and necrosis
Apoptosis
Cell cycle arrest

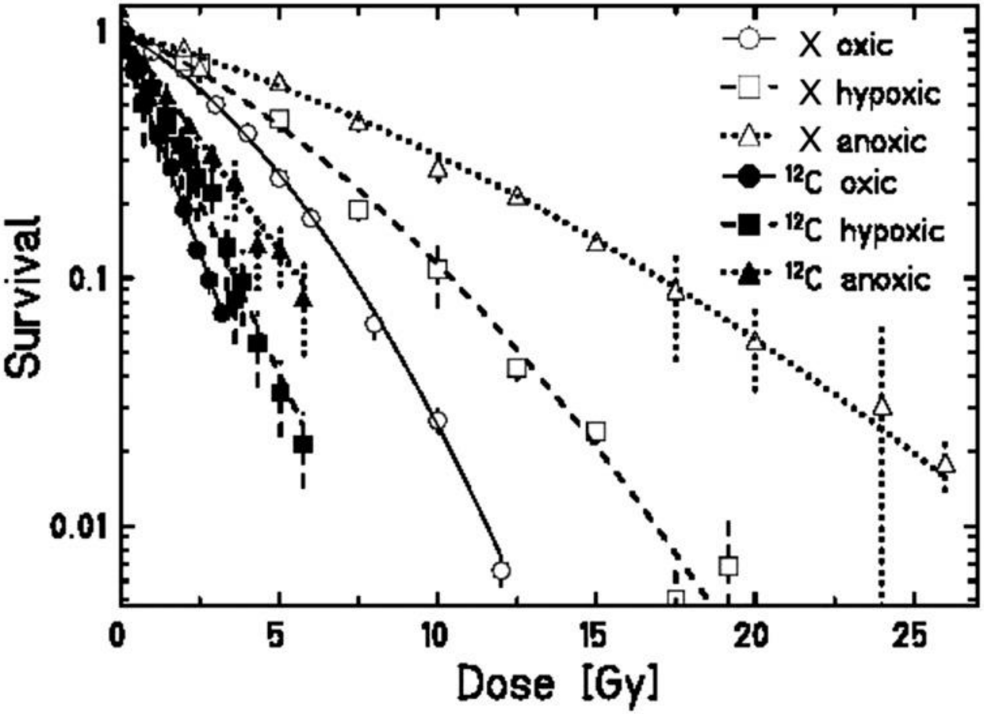



Hypoxia-Associated Factor (HAF)

Modified by the author:
Mei Yee Koh and Garth Powis. Passing the baton: the HIF switch.
Trends in Biochemical Sciences September 2012, Vol. 37, No. 9

Tinganelli et al. 2013






OER in Acute anoxia/hypoxia

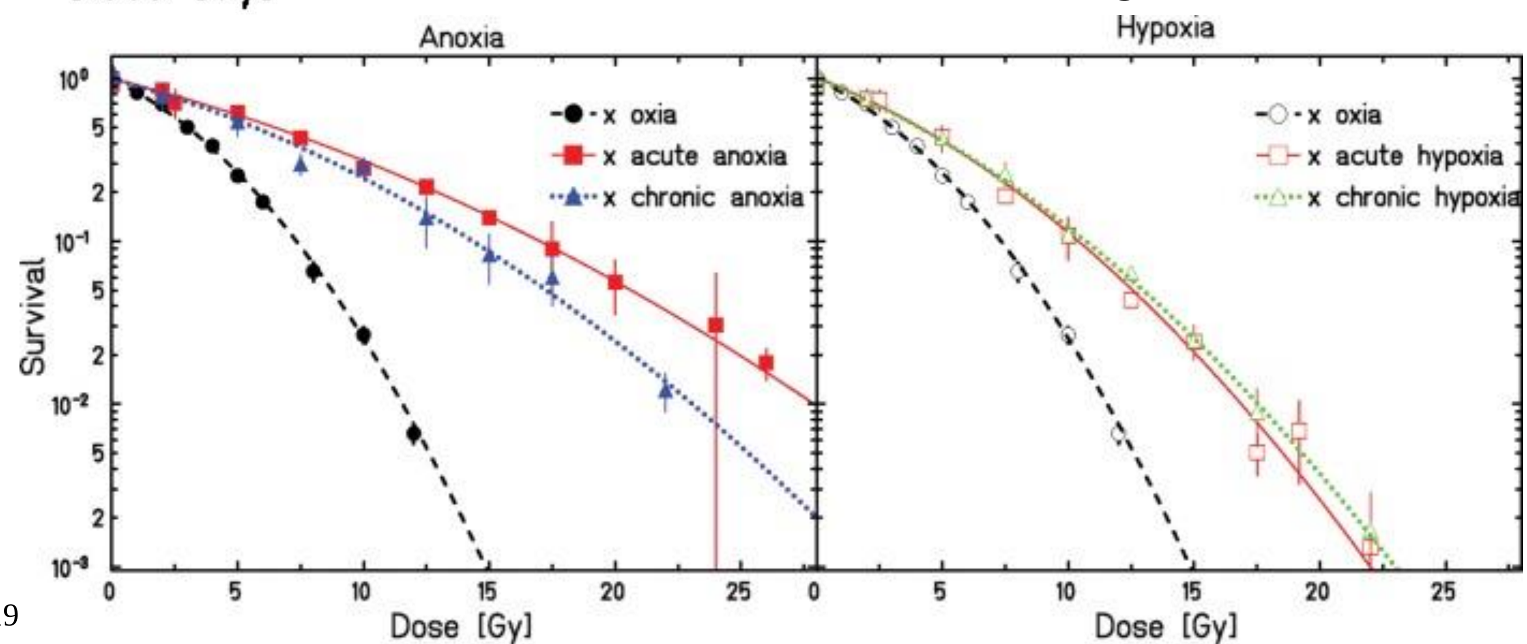
Oxygen Enhancement Ratio (OER)

$$\text{OER} = \frac{\text{Radiation dose in hypoxia}}{\text{Radiation dose in air}}$$

For the same biological effect

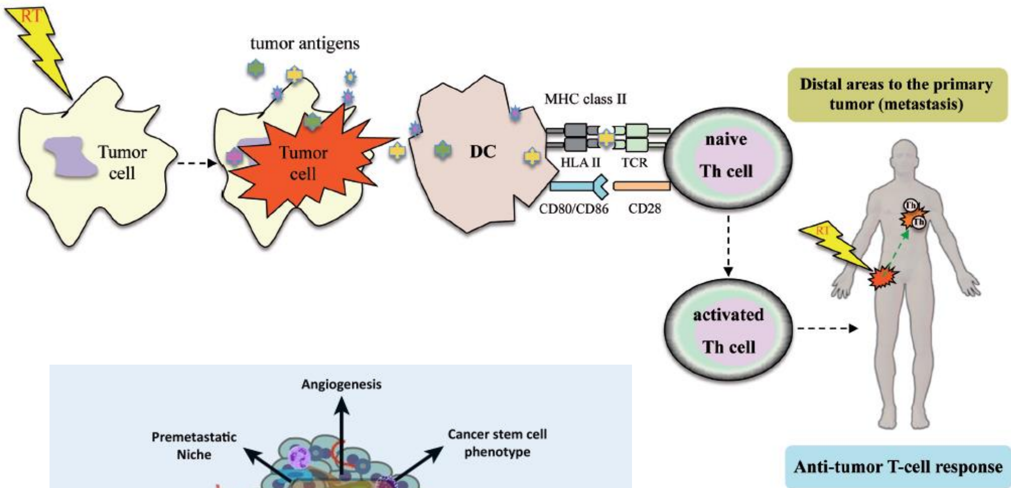
Ma, Tinganelli et. al. 2013

OER in chronic anoxia/hypoxia

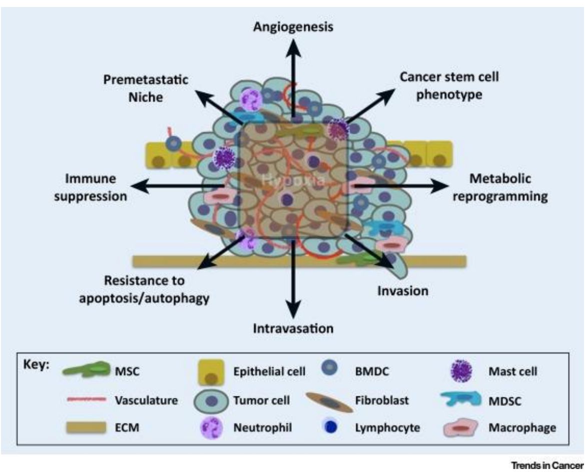


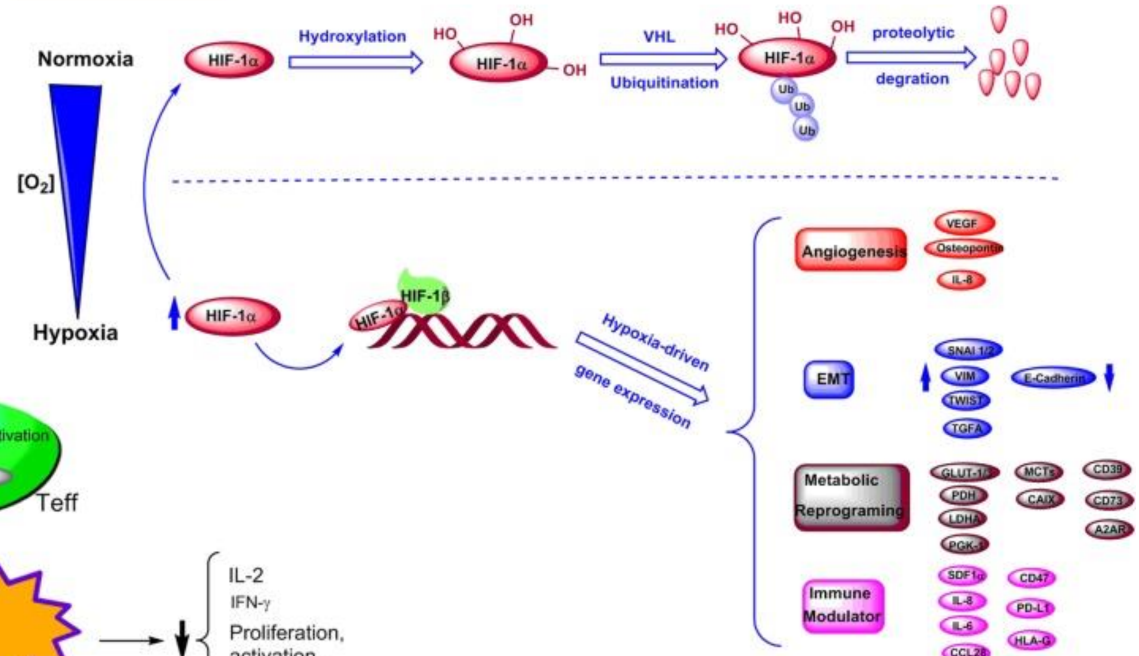
Hypoxia-Driven Immunosuppressive Metabolites in the Tumor Microenvironment: New Approaches for Combinational Immunotherapy

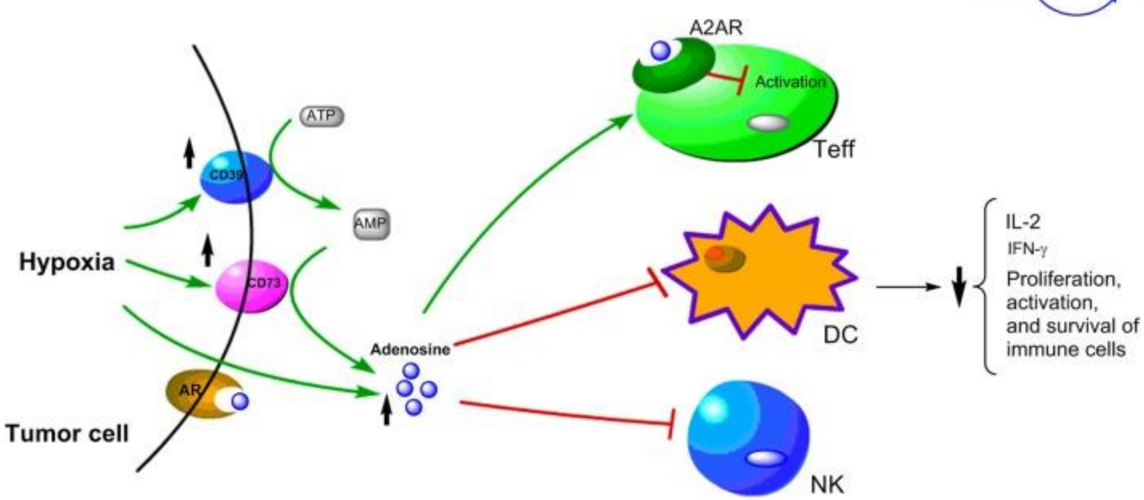
Yiliang Li,[1] Sapna Pradyuman Patel,[2] Jason Roszik,[2] and Yong Qin[2,*]




# Hypoxia and immunosuppression

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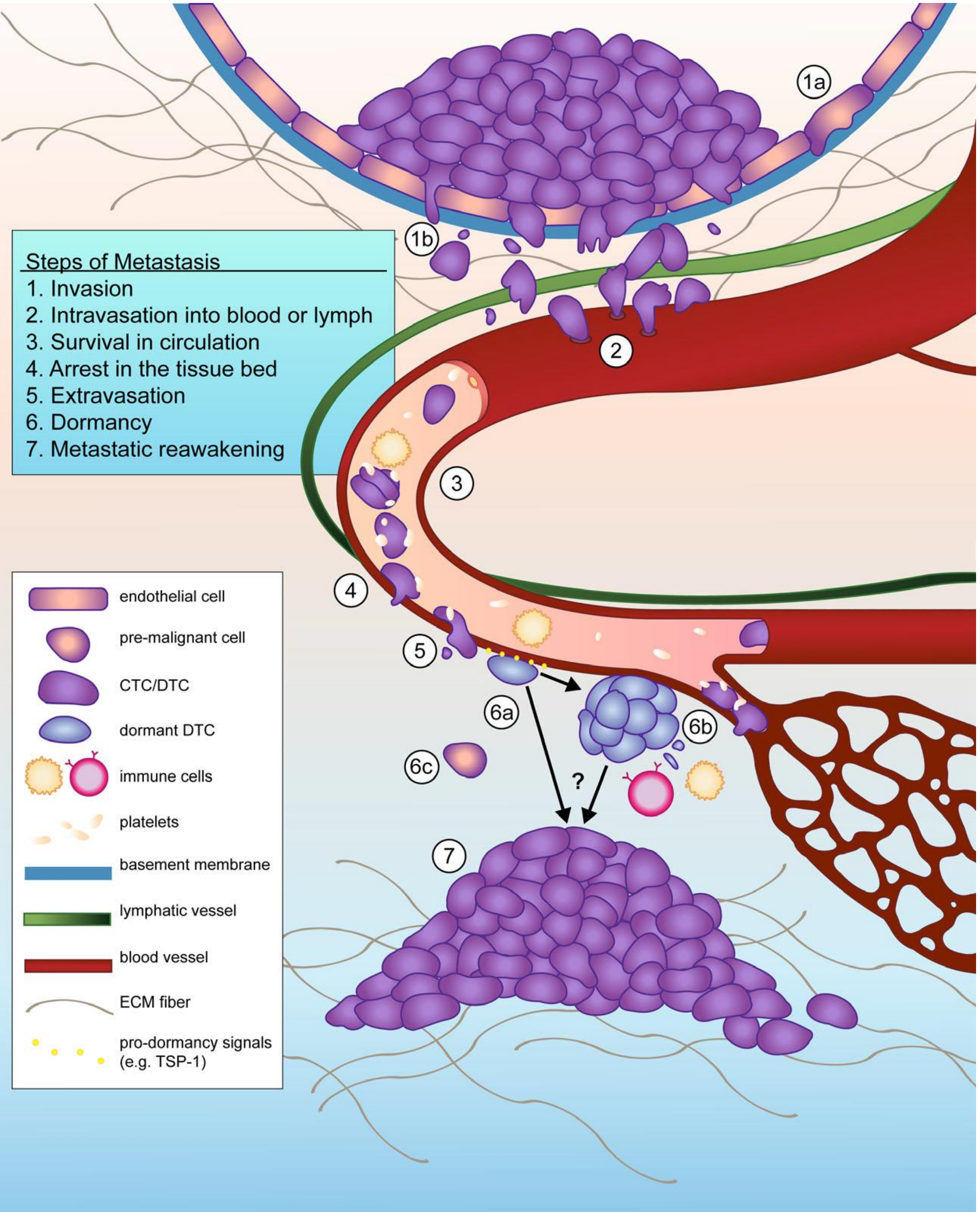
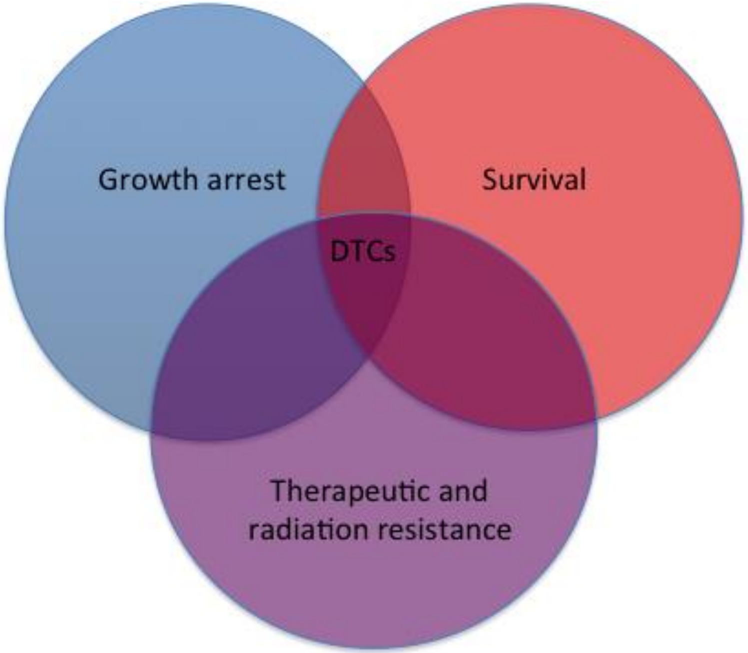
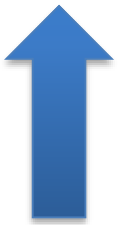
Mol Oncol. 2017 Jan;11(1):40-61. doi: 10.1002/1878-0261.12022.

# Circulating and disseminated tumor cells: harbingers or initiators of metastasis?

Dasgupta A[1], Lim AR[1,2], Ghajar CM[1].



ANOIKIS

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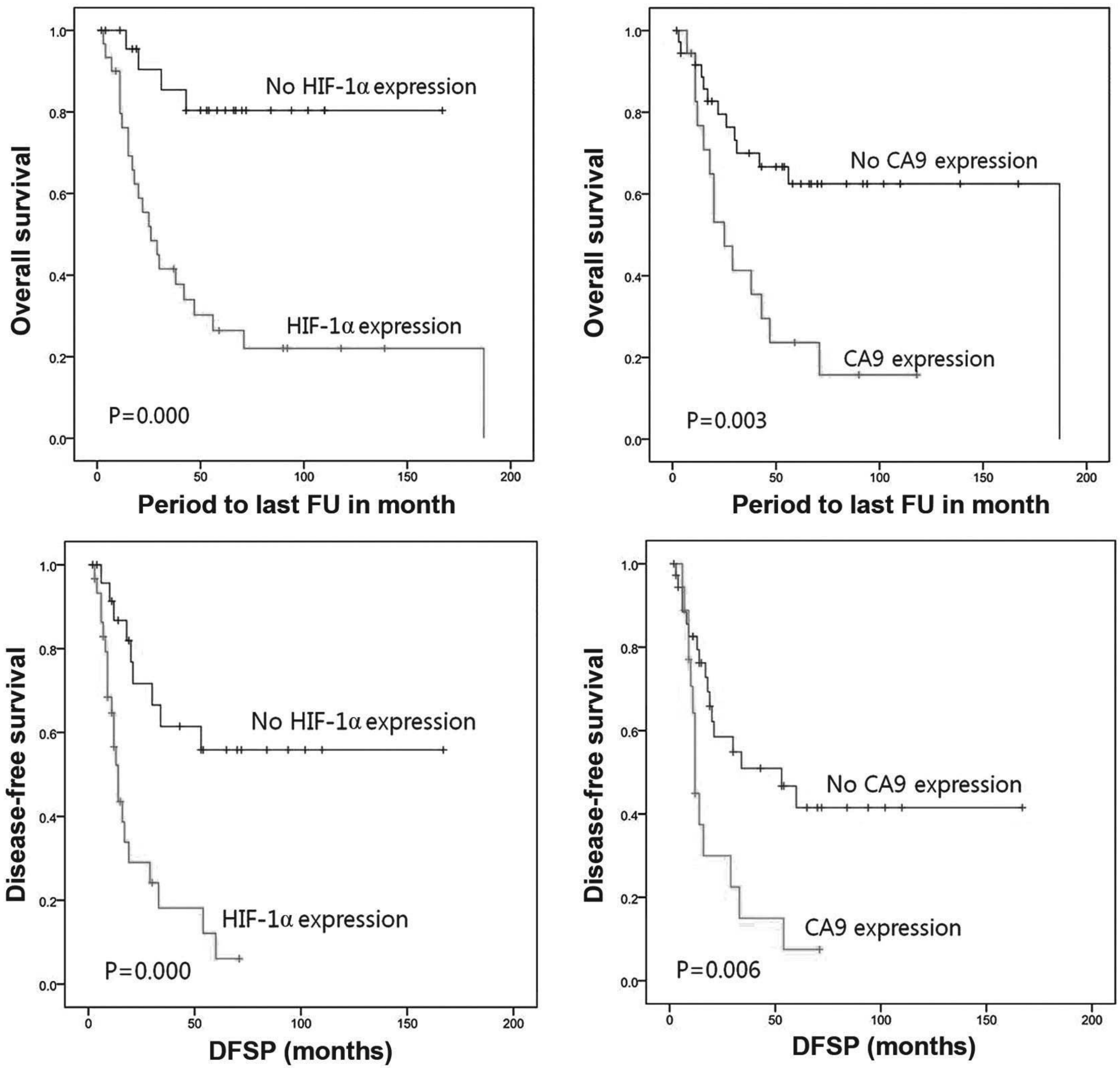
# Expression of hypoxic markers and their prognostic significance in soft tissue sarcoma

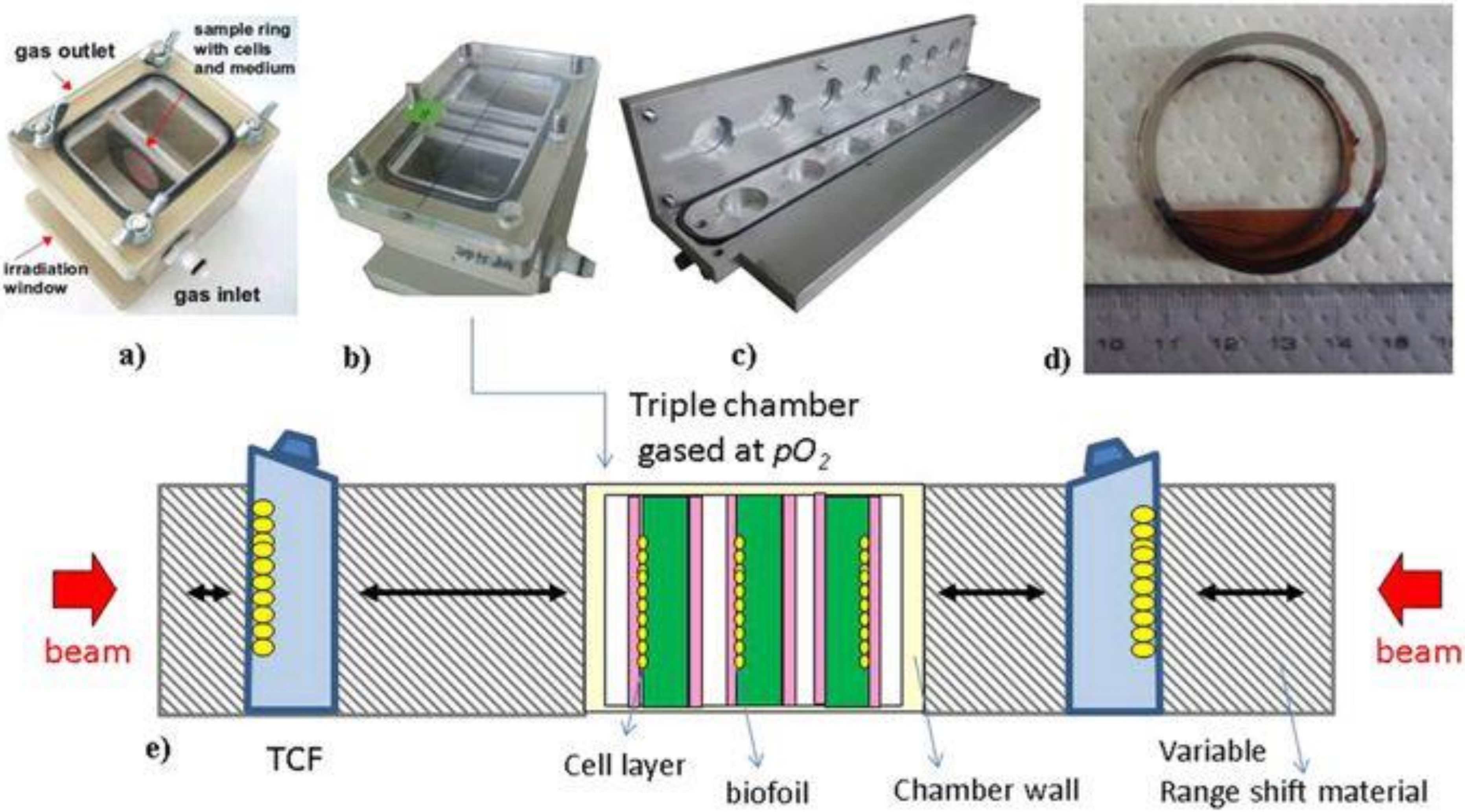
**Authors:** Jeung Il Kim, Kyung Un Choi, In Sook Lee, Young Jin Choi, Won Tack Kim, Dong Hoon Shin, Kyungbin Kim, Jeong Hee Lee, Jee Yeon Kim, Mee Young Sol




Kaplan-Meier survival curves showing disease-free survival and overall survival for soft tissue sarcoma patients with HIF-1α and CA9 expression.

**HIF-1α, hypoxia-inducible factor 1α; CA9, carbonic anhydrase 9; FU, follow-up; DFSP, disease-fee survival period.**

# Hypoxic CHAMBERS

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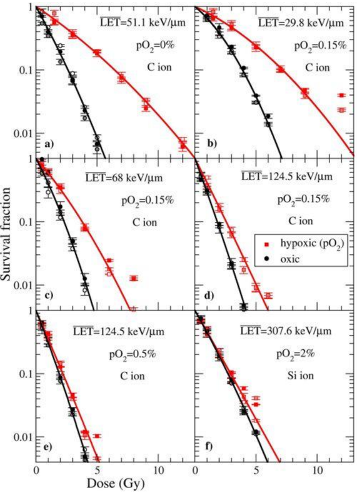
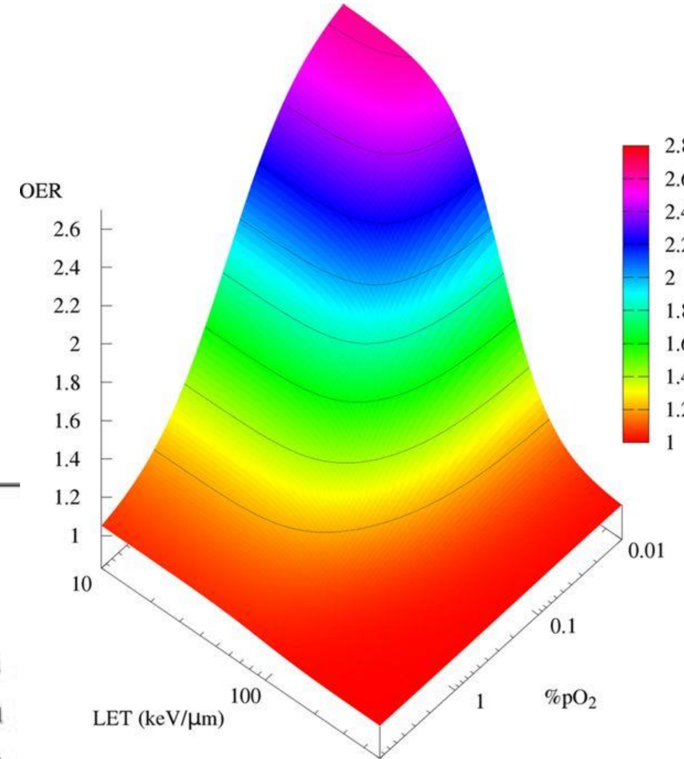
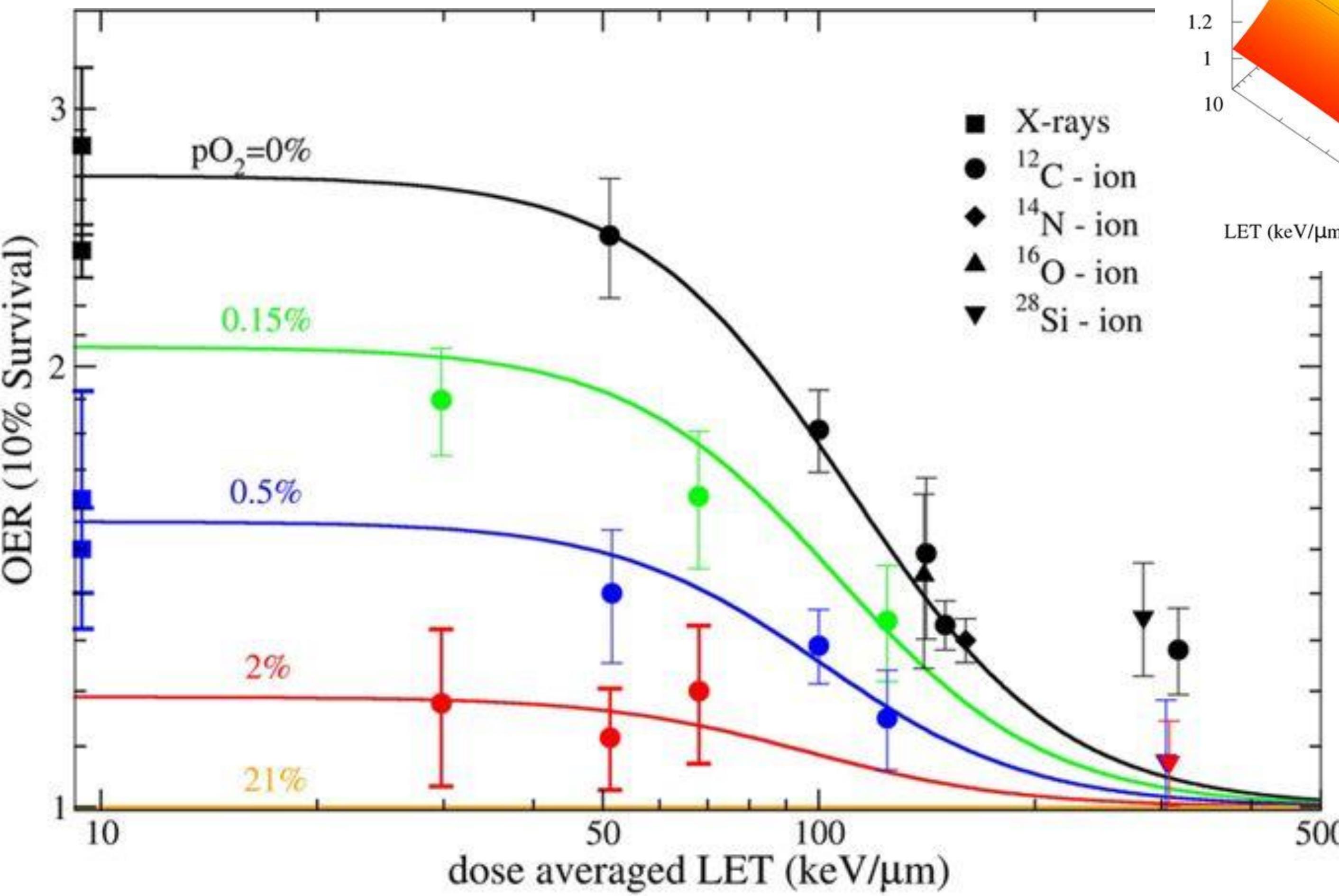
# OER(LET,$pO_2$) model




Walter Tinganelli et al.
Kill-painting of hypoxic tumours in charged particle therapy.
Sci Rep. 2015:17016.

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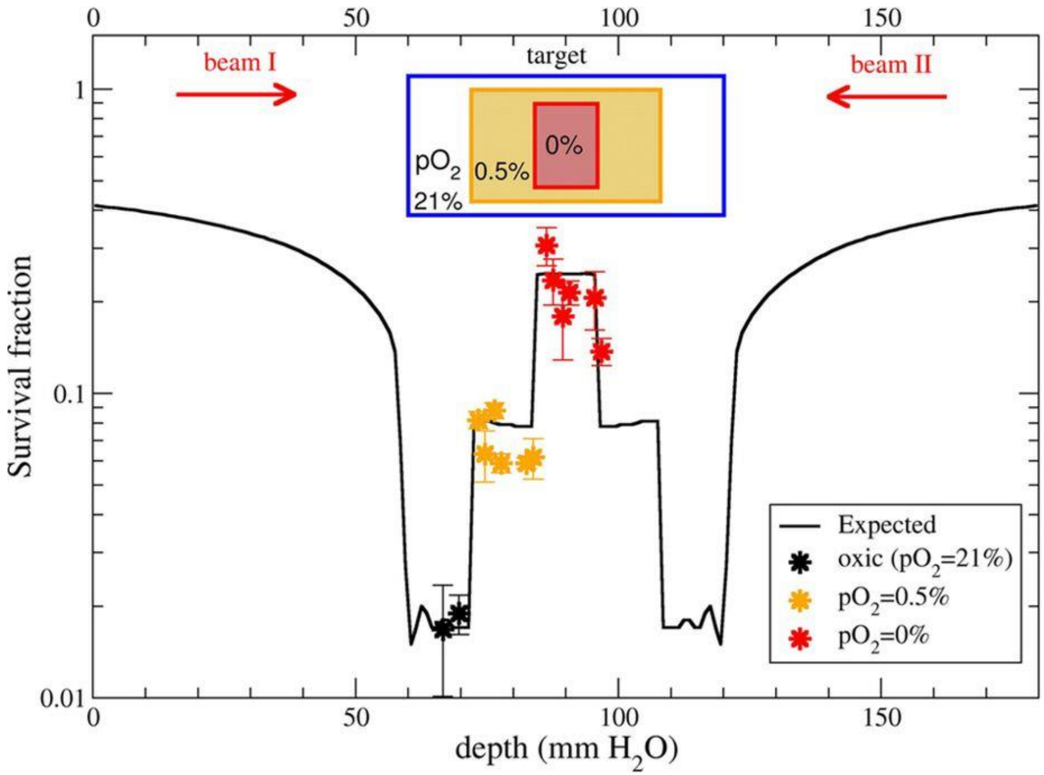
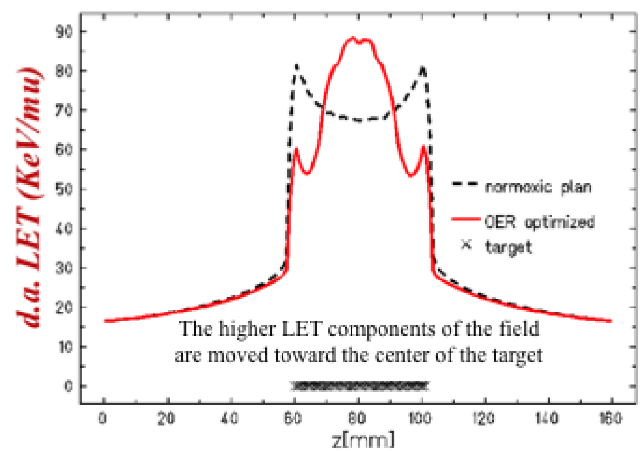



Extended target survival measurements performed at HIMAC compared with the calculation by our new TPS version. A beam of 290 MeV/u 12C-ions was used from both sides, passively modulated in a SOBP of 6 cm, on a phantom of 18 cm. Dose in the target was recalculated from the oxic control as 9.5 Gy (RBE)

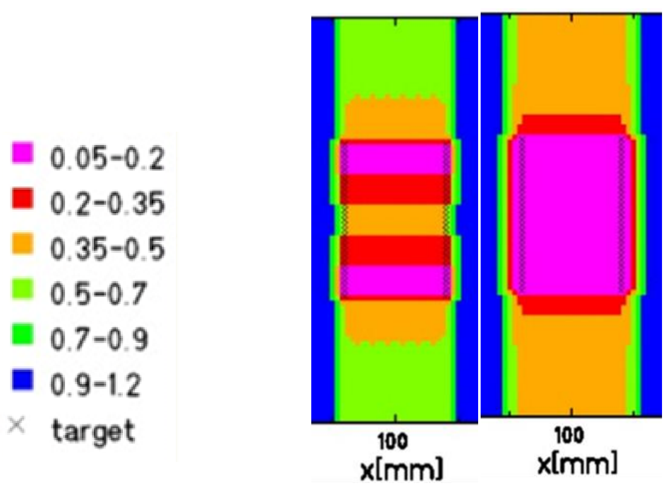
TRiP98-OER:
OER *vs* LET dependence

- **Biologically effective Dose (RBE weighted)= TRiP98**

LET distribution automatically adjusted from the optimization through the "hypoxic gradients" to the oxygen distribution
Krämer, Scifoni, Schmitz, Sokol, Durante, *EPJD 68 (2014)*




- **Biologically isoeffective Dose in the local microenvironment: TRiP98-OER**

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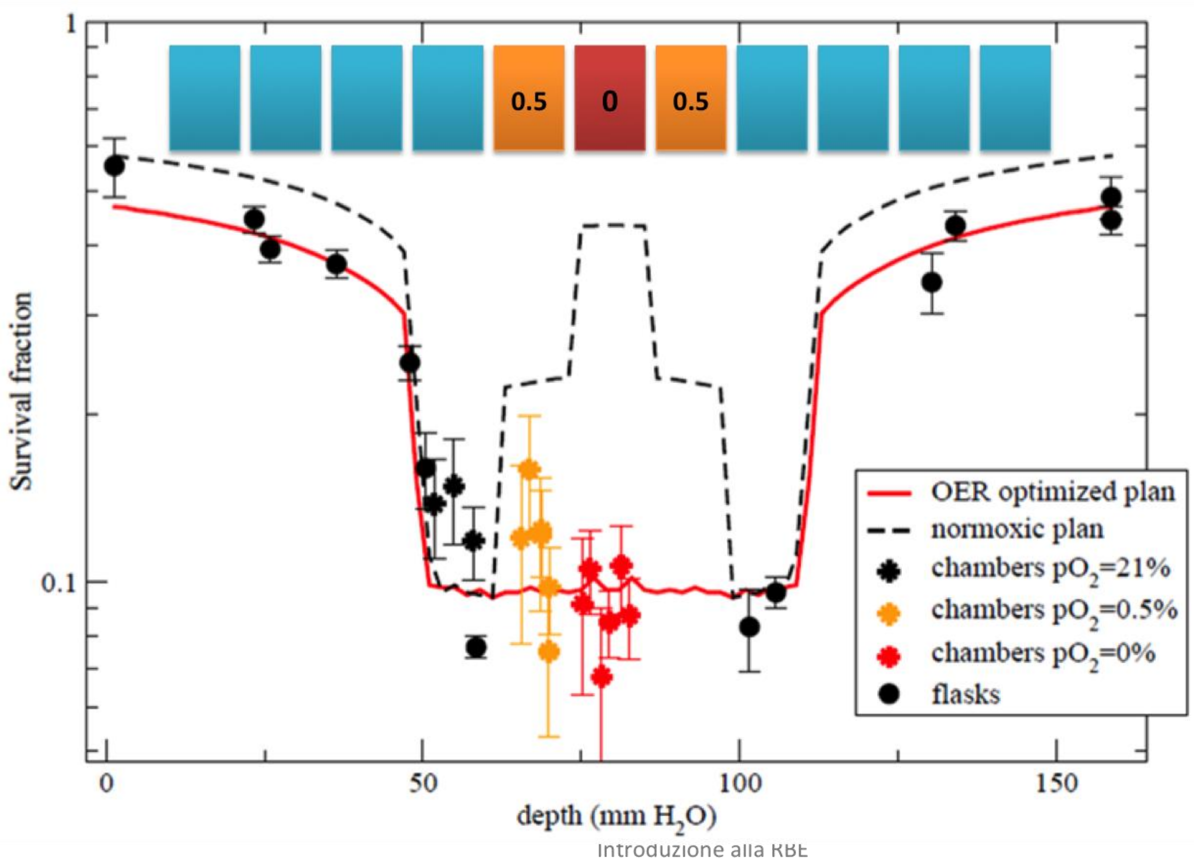
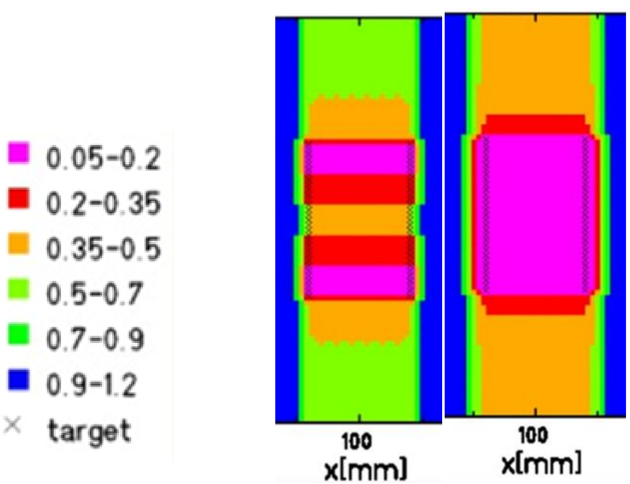



Walter Tinganelli et al.
Kill-painting of hypoxic tumours in charged particle therapy.
Sci Rep. 2015:17016.

Comparison of expected survival in an OER optimized plan with experimental results, performed at GSI. An actively scanned 12C ion beam, composed of 17 monoenergetic slices ranging from 234.64 to 155.26 MeV/u was used from both sides. The target length was 6 cm on a phantom of 16 cm. The beam was optimized with a prescribed survival level in the target of 0.1, corresponding to a RBE-weighted dose of 6.5 Gy (RBE) in normoxia. RBE-weighted dose in the entrance is 2.8 Gy(RBE). The dashed curve represents the expected survival across the phantom, when a normoxic plan is applied (similar to previous figure). Absolute measured and calculated data are shown, with no recalculation adjustment applied.




**Most relevant question:**
**-Do we need ions heavier than carbon to overcome hypoxia?**

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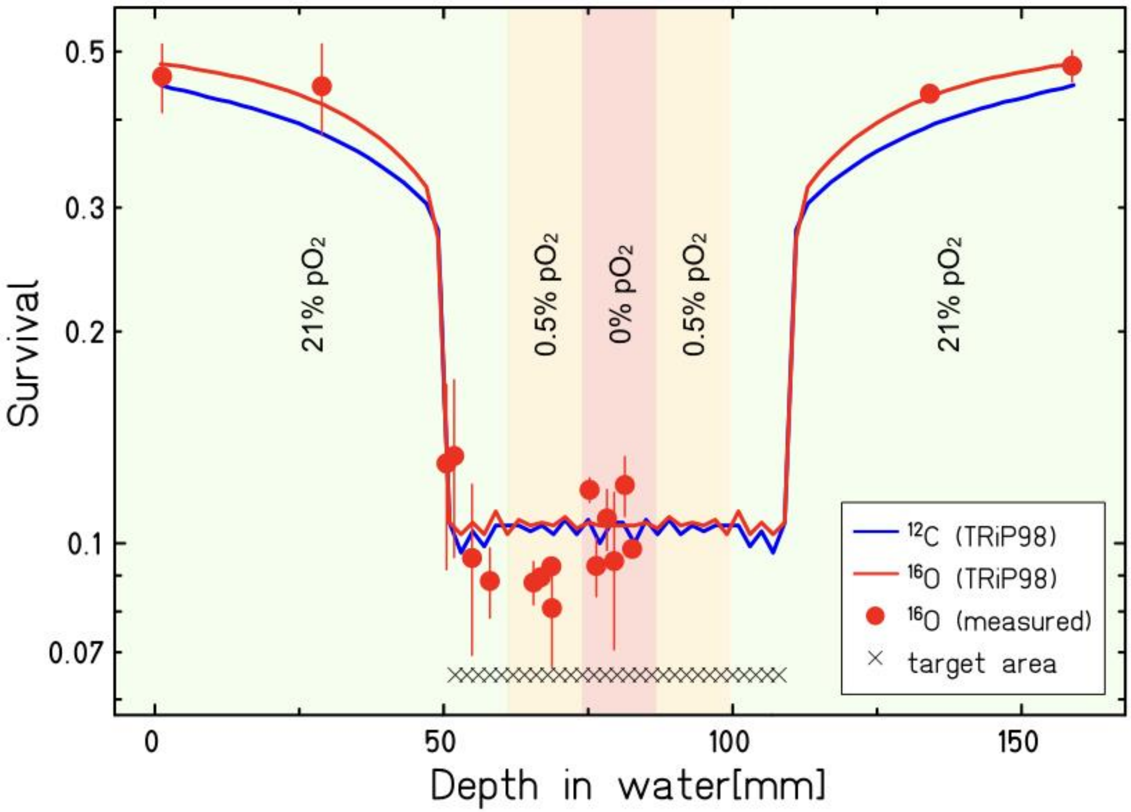
# Oxygen beams for therapy: advanced biological treatment planning and experimental verification

O Sokol[1], E Scifoni[1,2], W Tinganelli[1,2], W Kraft-Weyrather[1], J Wiedemann[1], A Maier[1], D Boscolo[1], T Friedrich[1], S Brons[3], M Durante[1,2] + Show full author list

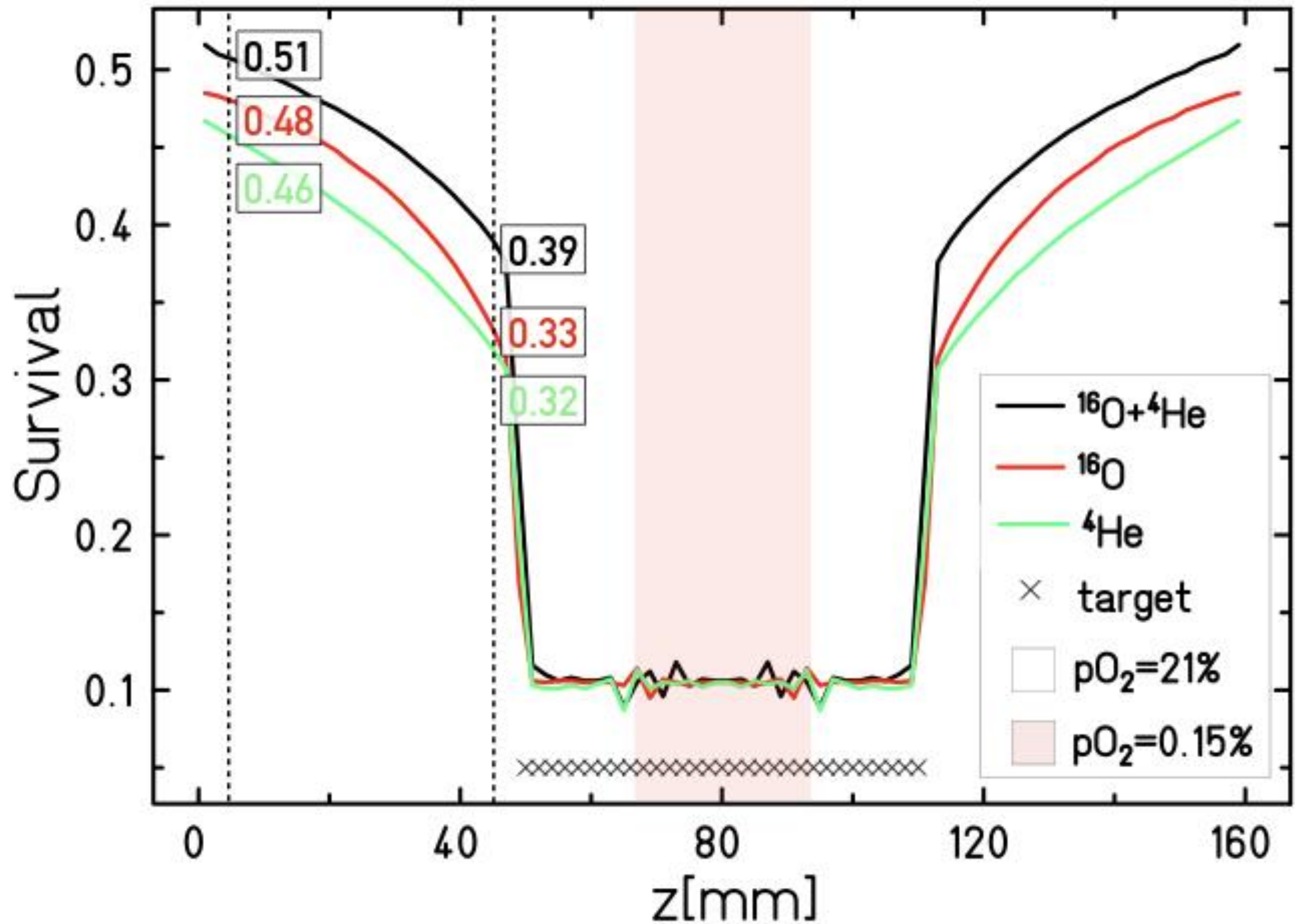
Published 20 September 2017 • 

Physics in Medicine & Biology, Volume 62, Number 19

"It emerges that for more hypoxic target regions (partial oxygen pressure of ≈0.15% or lower) and relatively low doses (≈4 Gy or lower) the choice of 16O over 12C or 4He may be justified".

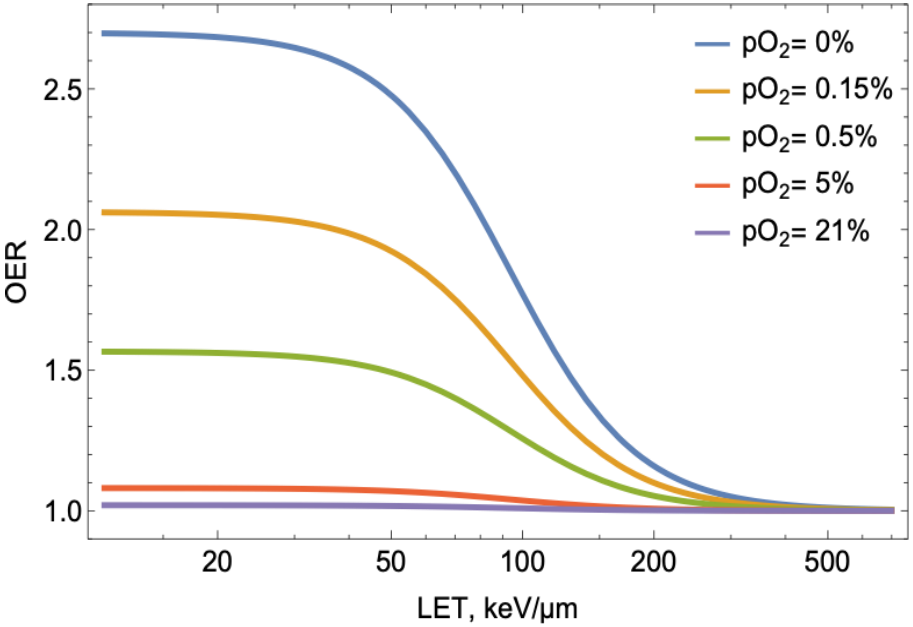


# What about a combination of more ions?




Kill painting of hypoxic tumors with multiple ion beams
Olga Sokol et al 2019 Phys. Med. Biol.

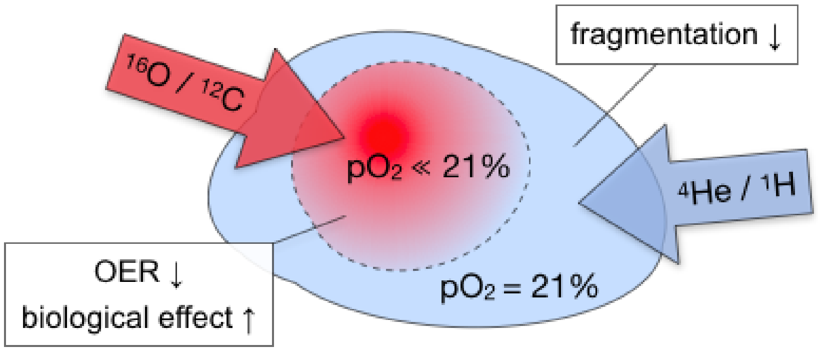
## GSI: to improve the treatment outcome for hypoxic tumors




**TRiP98-MIBO**

**(Multi-Ion Biological Optimization):**

**Mixed Oxygenation → Mixed Beams**




**Noticeable reduction of OER for high-LET ions**

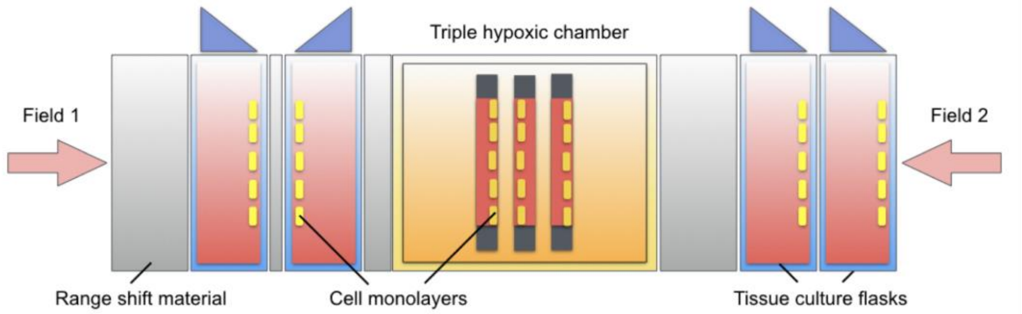
- Heavier ions for hypoxic parts (higher LET -> lower oxygen enhancement effect -> increased total biological effect)
- Lighter ions for normoxic regions (less fragmentation, lower RBE values -> better sparing of surrounding residual tissue and OARs)

# Experimental verification

**Pilot test of combined p + $^{12}$C irradiation using GSI hypoxic phantom**

- 10% survival in the target (6.5 Gy(RBE,OER) dose)
- 36 mm central region w. pO2 = 0.5%
- Two pairs of opposite fields of p and 12C
- CHO-K1 cell line, colony forming assay

$pO_2$ = 21%  $pO_2$ = 0.5%




Sketch of the experimental setup

Verification of combined $^{16}$O + $^{4}$He plans vs. single-ion plans in collaboration with HIT, Heidelberg, done last week

# Conclusions

- The treatment with **particles** is **undoubtedly** more suitable for the treatment of **highly hypoxic tumors**.
- Heavier than carbon ions, such as **oxygen ions**, are an excellent alternative for the treatment of **highly hypoxic tumors**
- **Multiple-ion strategy has to be chosen wisely** - it is not necessary beneficial and might worsen the planning outcome.
- **TRiP98-MIBO - the only research TPS** able to calculate the biological effect of several ion beams simultaneously in one treatment plan, by optimizing their contributions accounting for the target oxygenation. **Particle type and the particle fluences are optimally chosen automatically** by the TPS based on the 3D hypoxic imaging input.

However:

- **The difficulty to obtain a proper and sufficiently resolved oxygenation map, also accounting for its rapid temporal variation** in the course of a treatment is a strong limitation.

# Thank you for the attention

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