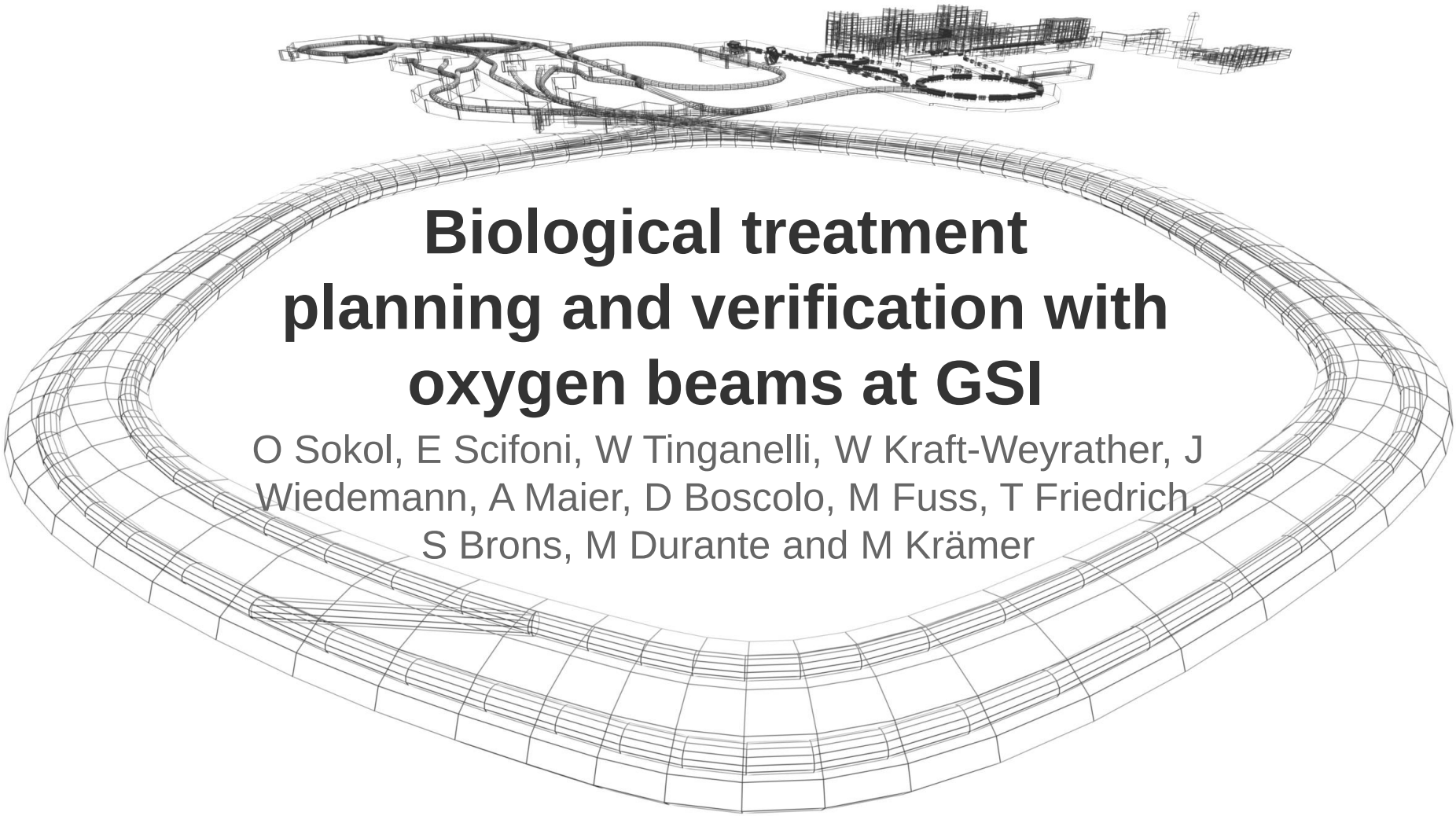
GSI Helmholtzzentrum für Schwerionenforschung GmbH



Biological treatment planning and verification with oxygen beams at GSI

O Sokol, E Scifoni, W Tinganelli, W Kraft-Weyrather, J Wiedemann, A Maier, D Boscolo, M Fuss, T Friedrich, S Brons, M Durante and M Krämer

Scope

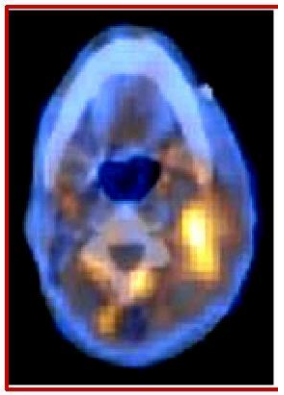
- First experimental verification of biologically optimized treatment plans with ^{16}O ions
- Generated with the GSI planning system TRiP98, accounting for RBE and OER
- Underlying experiments performed at HIT and GSI
- Analysis of differences/advantages compared to lighter ions

Why use oxygen beams for therapy?

- Current interest in O ions due to different advantages in the physical dose profile:
  - **higher LET**, very low lateral scattering

→ Biologically relevant advantages:

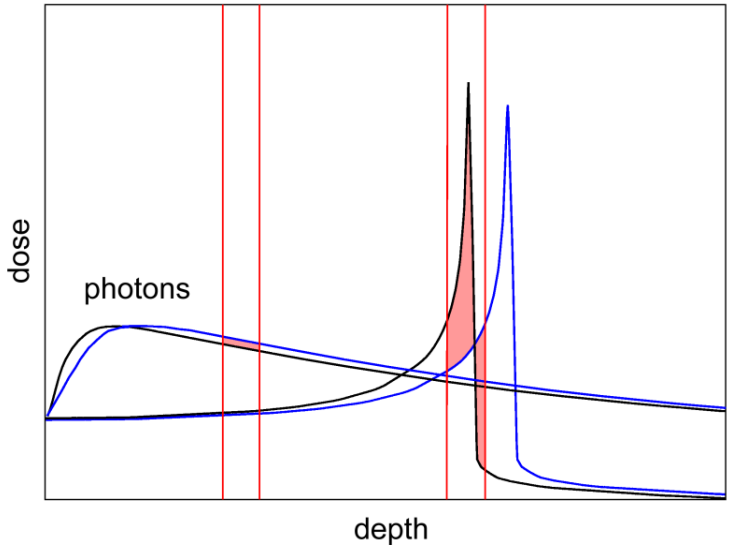
  - dense dose deposition pattern leads to a higher radiobiological effectiveness (**RBE**), particularly in the Bragg peak region before ions stop
  - this in turn makes it possible to compensate for **oxygenation effects** (tumour hypoxia) or treat otherwise radioresistant targets



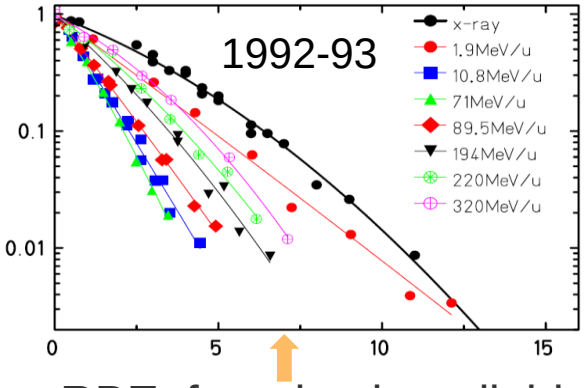
  - (the high-LET ion tracks induce sufficient direct damage and do not depend on indirect damage paths which are enhanced by the presence of oxygen)

Why use oxygen beams for therapy?

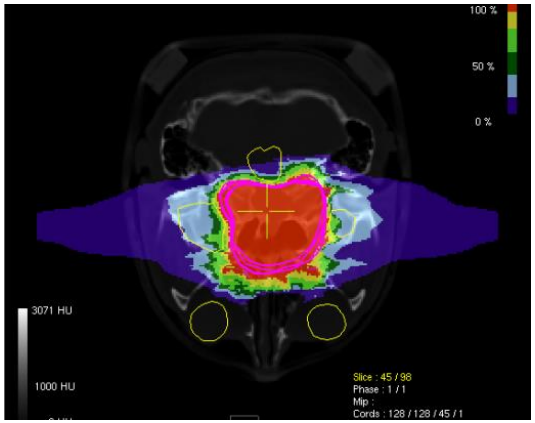
- O beams are available in some centers for research purposes with sufficient dosimetric quality, e.g. at HIT
- drawbacks to keep in mind:
  - larger uncertainties in **fragmentation** tail
  - shifts in density upstream can displace Bragg peak out of target volume
  - (and if this happens, the highly effective high-LET dose irradiates healthy tissue)



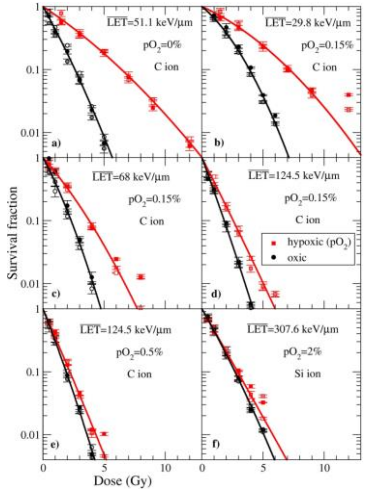
Ingredients



RBE: from basic radiobiology (survival curves) or local effect model LEM IV



influence of hypoxia: OER data



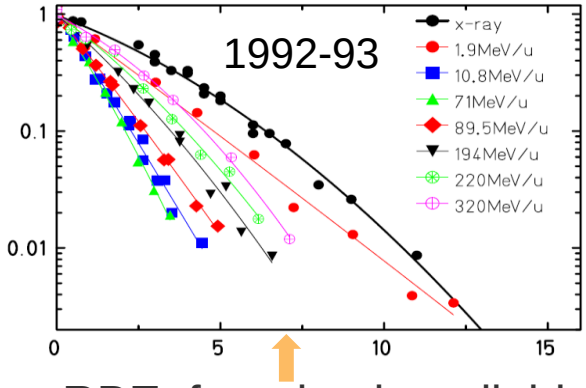
(Tinganelli et al. 2015) plus new data

inverse treatment planning system optimizing for the biologically effective dose (uniform survival level)

physical beam characteristics: attenuation, lateral scattering, fragmentation…

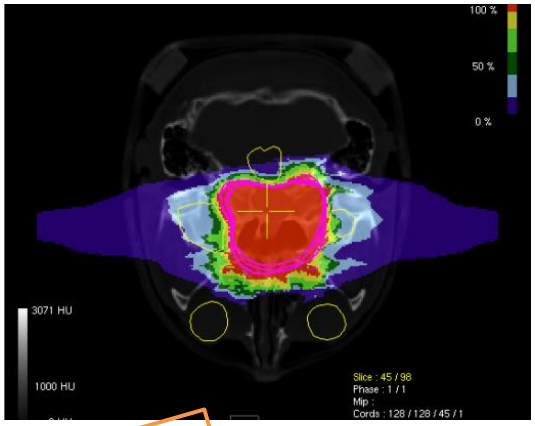
(Kurz et al. 2012)

Ingredients



RBE: from basic radiobiology (survival curves) or local effect model LEM IV

✓ Elsässer et al. 2010



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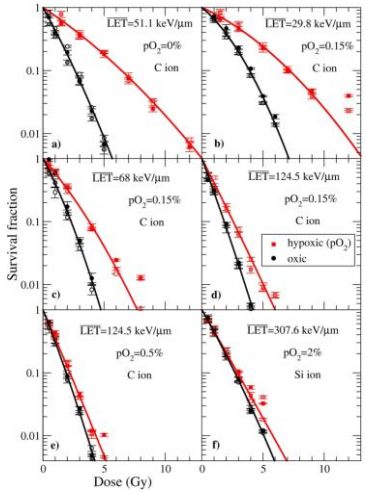


(Tinganelli et al. 2015) plus new data

inverse treatment planning system optimizing for the biologically effective dose (uniform survival level)

✓ TRiP98 "kill painting"

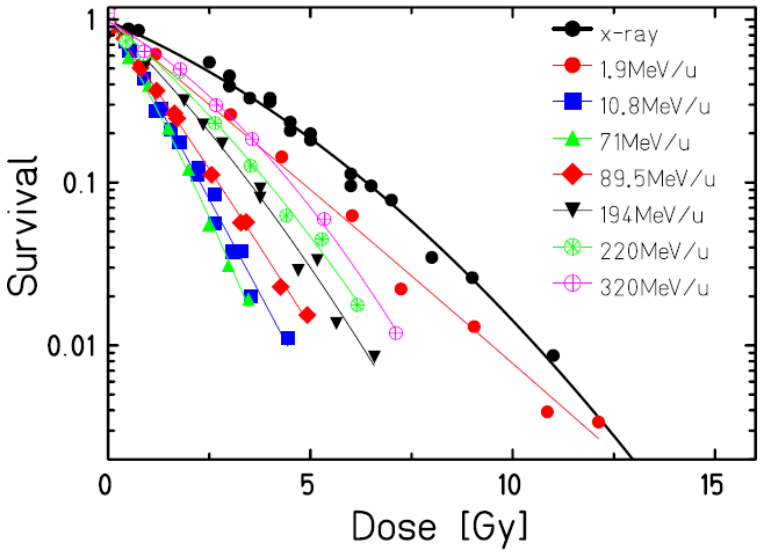
Krämer and Scholz 2000, Krämer et al. 2014, Tinganelli et al. 2015

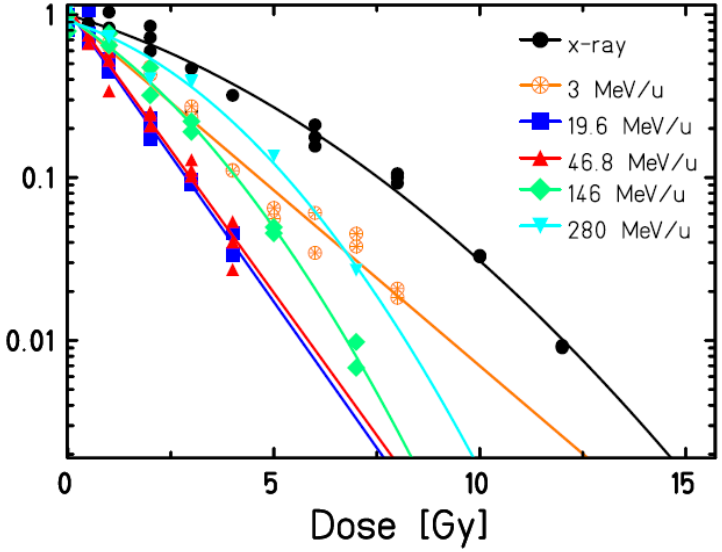
physical beam characteristics: attenuation, lateral scattering, fragmentation…

(Kurz et al. 2012)

Radiobiology: survival curves

- very scarce existing data for O in different cell lines
- CHO cells were used for all experiments
  - easy to handle, robust, regular growth
  - α/β similar to several human tissues
- Cell survival curves (→ RBE) were measured at different facilities (GSI UNILAC, GSI SIS18 and HIT)





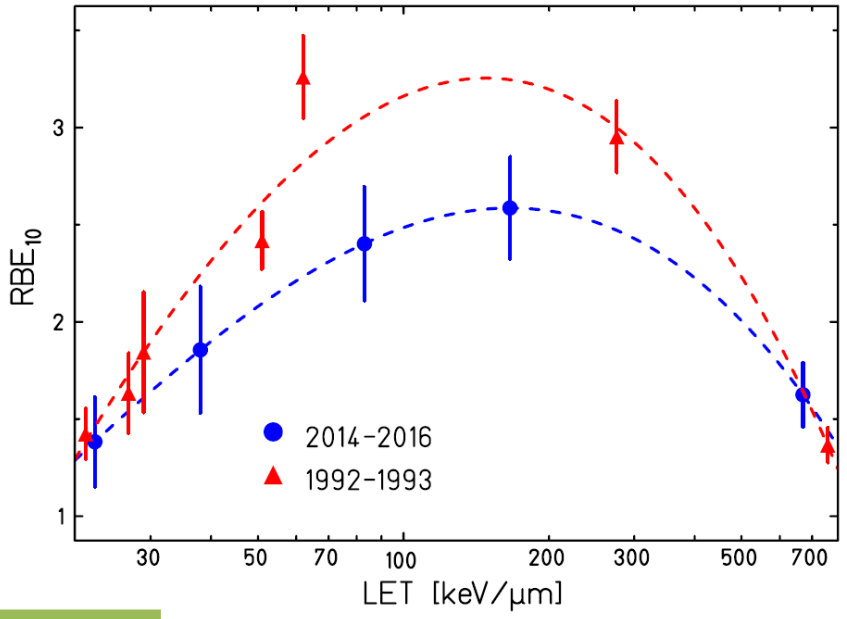
Fit functions:
E ≤ 46.8 MeV/u:
$lnS = -\alpha D$
E ≥ 146 MeV/u:
$lnS = -\alpha D - \beta D_2$

(Sokol et al. 2017, submitted to PMB)

- old curves steeper!

Radiobiological effectiveness

LET, keV/µm	RBE_{10}
23	1.383 ± 0.231
38	1.856 ± 0.326
83	2.402 ± 0.294
166	2.586 ± 0.263
670	1.625 ± 0.165



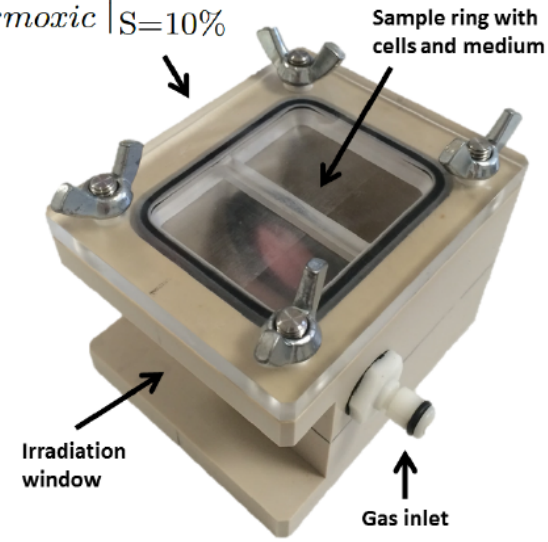
(Sokol et al. 2017 submitted to PMB)

Reference X-ray	
α = 0.176 ± 0.035 1/Gy	β = 0.017 ± 0.003 1/Gy^2

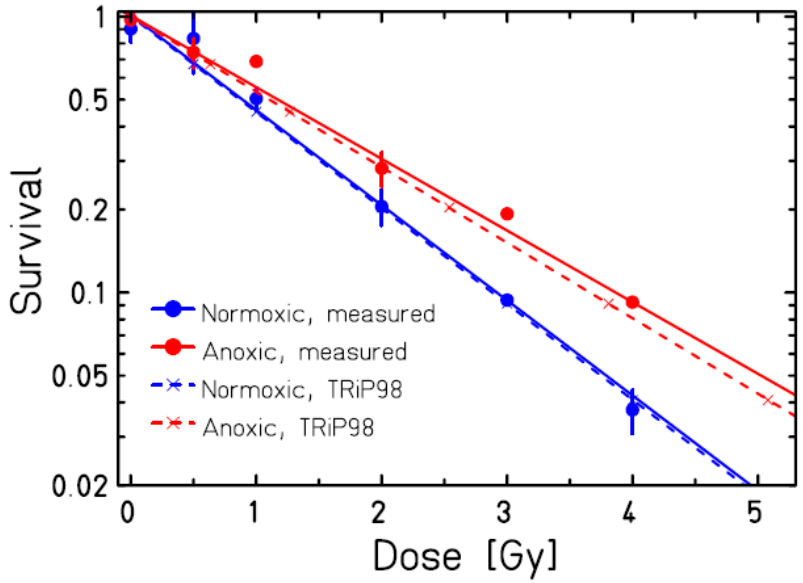
- RBE has changed over the many generations since 90’ (due to changes in cell line properties)
- compatible with LEM IV predictions, however these present larger variations for different LET
- maximum not accurately defined

Oxygen enhancement ratio

$$\mathrm{OER}_{10} = \left.\frac{D(pO_2)}{D_{normoxic}}\right|_{S=10\%}$$



Hypoxic chamber to irradiate a sample ring with cells under defined oxygenation conditions



Survival of CHO cells after irradiation with ^{16}O ions with dose-averaged LET = 166 keV/µm in normoxic and anoxic (pO_2 = 0%) conditions.

The symbols and solid lines are the measured values and its linear fitting. The dashed lines are TRiP98 calculations.

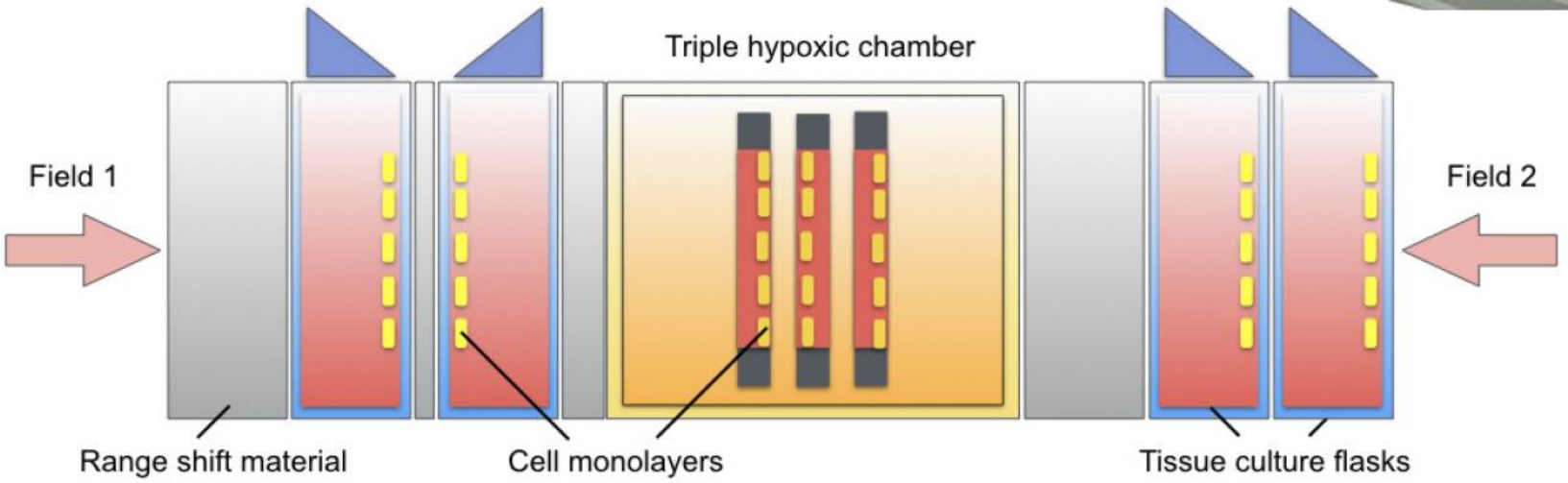
Oxygenation	α_{TRiP98}	α_{fitted}	$OER_{10,TRiP98}$	$OER_{10,exp}$
pO_2 = 21%	0.800	0.794 + 0.029	1.27	1.33 ± 0.05
pO_2 = 0%	0.630	0.598 + 0.002		

This good agreement confirms weak particle type interaction!

Radiobiology: treatment plan verification

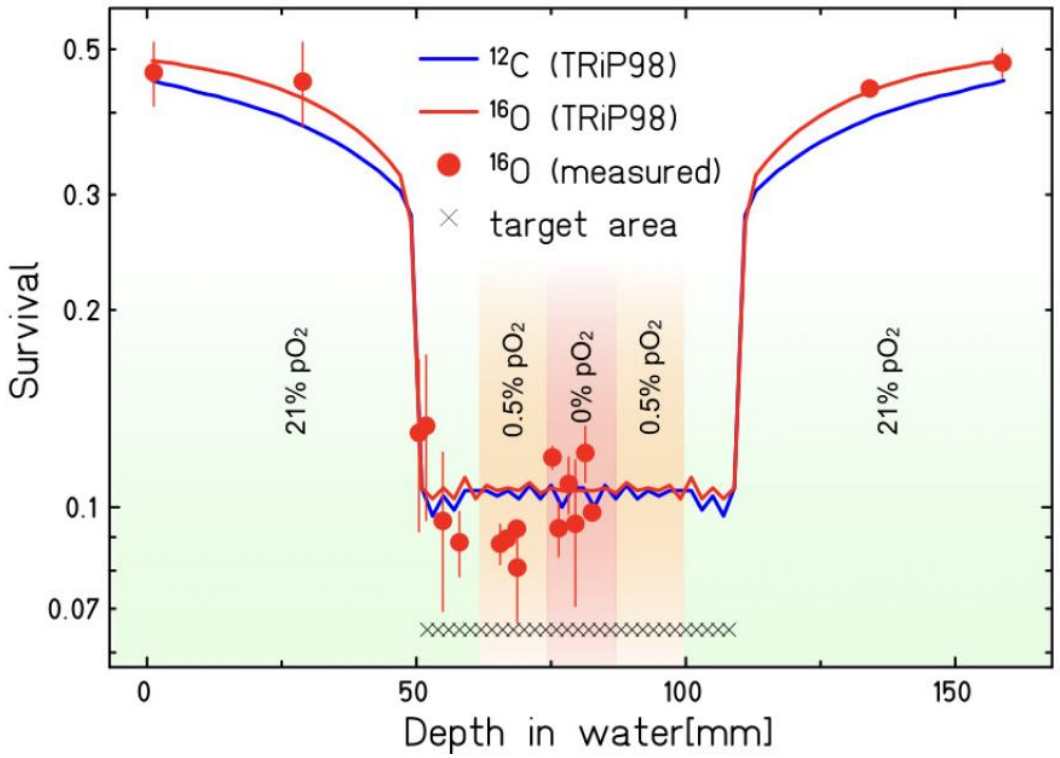
Setup for biological dosimetry including differently oxygenated regions:

- simulated volume 40x40x160 mm^3, target centered at 80 mm depth
- pO_2 distribution along the beam direction:
  - 20% for $z < 6.2$ mm and $z > 9.8$ mm
  - 0.5% for $6.2 \leq z < 7.4$ mm and $8.6 < z \leq 9.8$ mm
  - 0% for $7.4 \leq z \leq 8.6$ mm.



Radiobiology: treatment plan verification

Inverse treatment plan calculated using the kill-painting approach



(O: Sokol et al. 2017 submitted to PMB,
C: Tinganelli et al. 2015)

- simulated volume and target according to geometry on previous slide
- normoxic and two different hypoxic regions
- RBE-weighted prescription dose 6.5 Gy
  (= survival rate 10%)
- TPS predictions are very well confirmed for target and entrance channel
- for a given cell killing level in the target, the damage in the entrance channel is lower for O

Physical characterization (QA room at HIT)

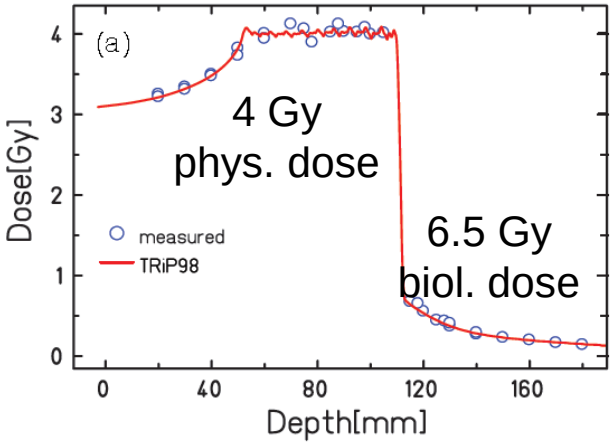
Target 60 × 40 × 40 mm, centered at a depth of 82 mm, single-field plan optimized for a uniform physical dose

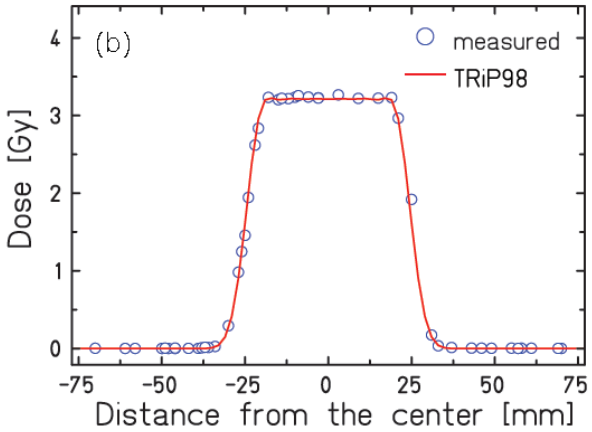
(a) PDD

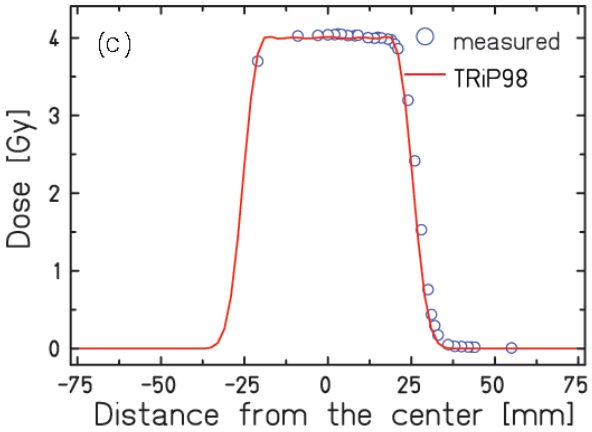
(b) Lateral dose profile, entrance channel (19.7 mm depth)

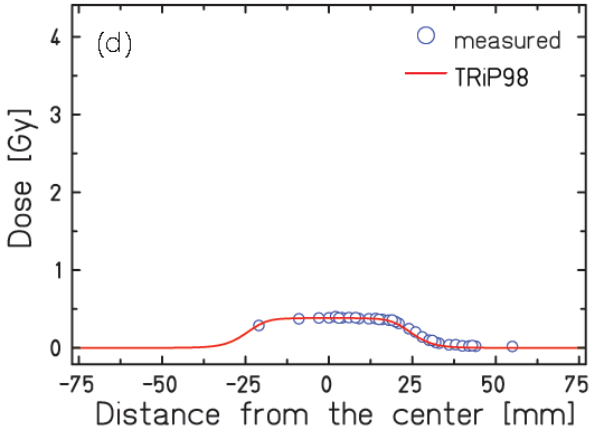
(c) Lateral dose profile, distal part of the target (89.7 mm depth)

(d) Lateral dose profile, fragmentation tail (19.7 mm depth)









physical dose measurements obtained in water phantom with array of 6x4 pinpoint ionization chambers (0.03 cm^3 sensitive volume)

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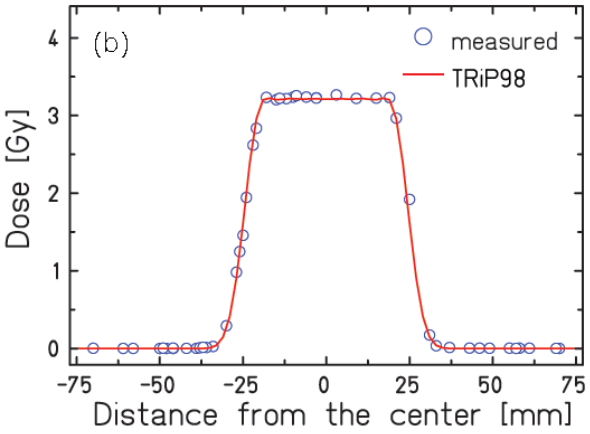
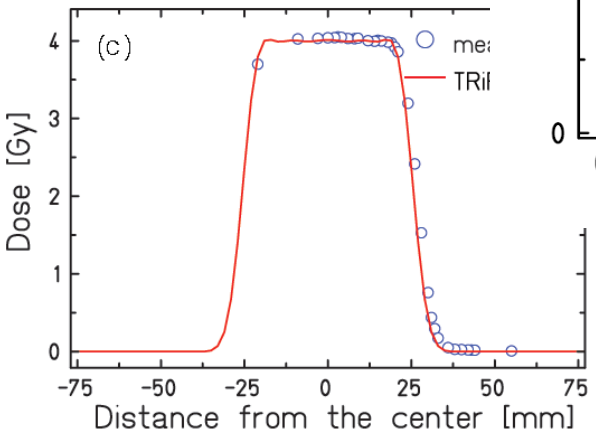
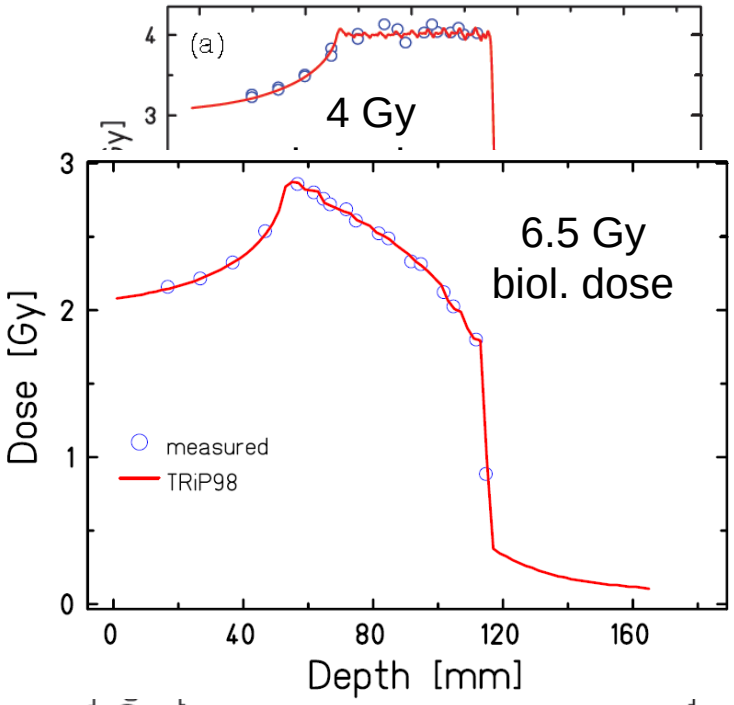
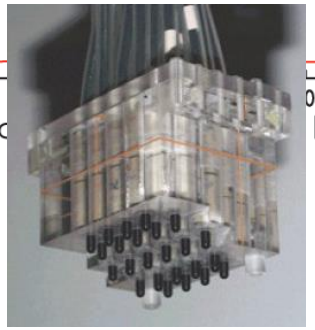


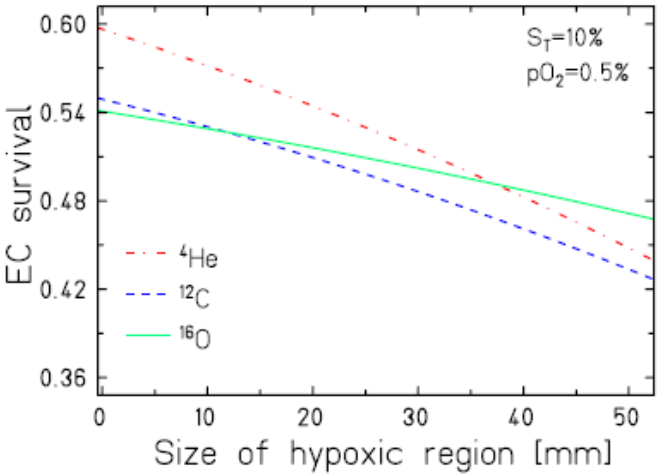


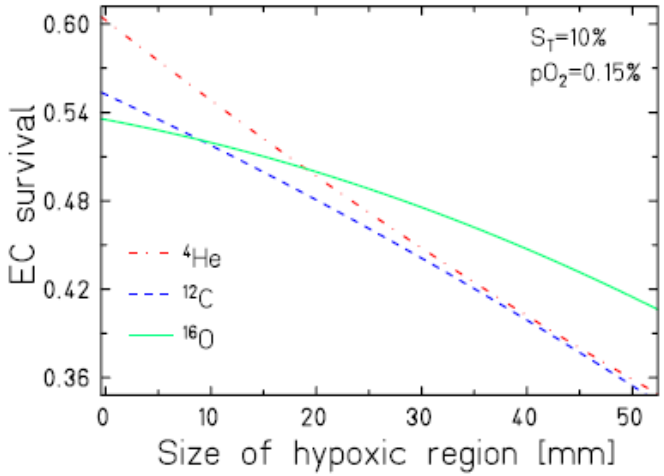


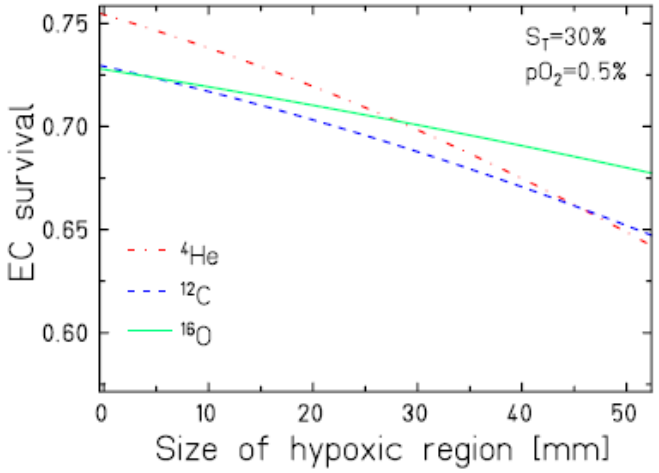


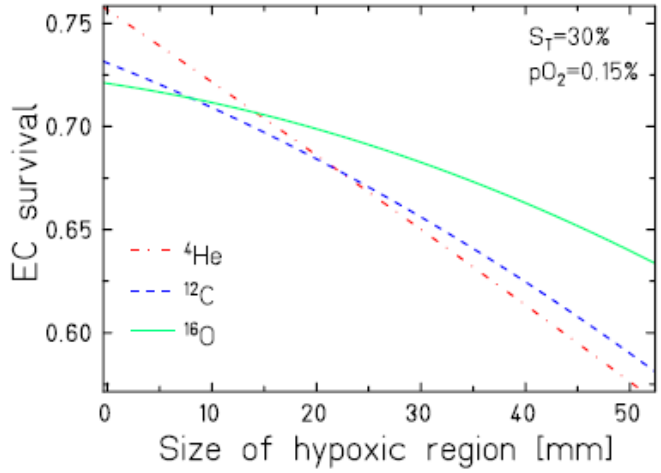
physical dose measurements obtained in water phantom with array of 6x4 pinpoint ionization chambers (0.03 cm^3 sensitive volume)

^{16}O vs. lighter ions: a comparative analysis









→ normoxic cases: He spares EC tissue best

→ O is generally better suited for very hypoxic environments (0.1-0.2%) where OER rises to 2.5 (survival increase in EC 13%)

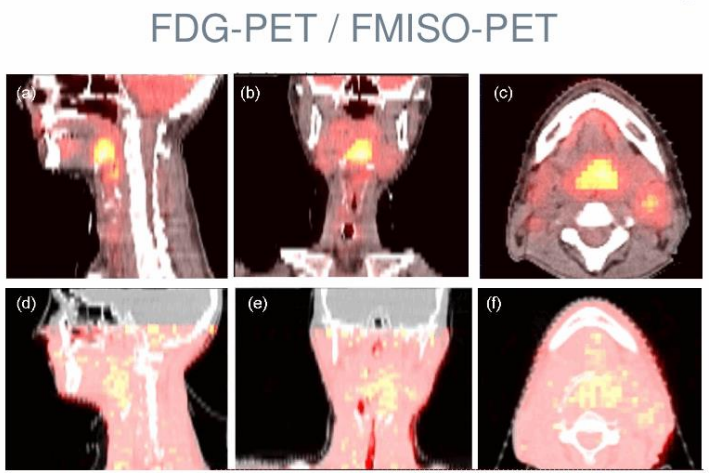
→ for large hypoxic parts O should also be preferred

Conclusions

- TRiP98 oxygen beam model is now validated for calculating biologically optimized (survival-level-based) treatment plans
- brings us closer to a future clinical application of O ions
- O can offer a better peak-to-entrance ratio in terms of cell killing than lighter modalities
  - depending on exact geometry, dose prescription and level of hypoxia
  - For hypoxic regions (0.15% or lower) and relatively low doses (4 Gy or lower) the use of O should be considered
- Some further “basic” RBE measurements in monoenergetic beams would be desirable

Persisting problems (wish list)

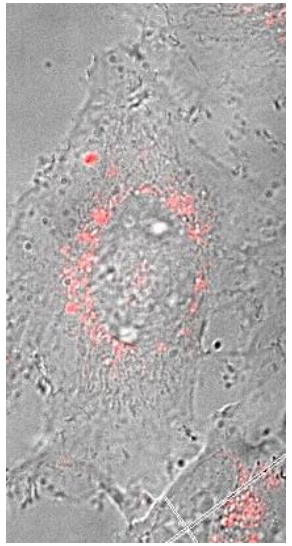
- O offers many theoretical advantages, but is for the moment not available in clinical practice
- Some physical parameters (nuclear fragmentation CSs!) needed in the TP could be improved (experiments) for a better accuracy; they affect range prediction
- In order to fully exploit the benefits O ions offer, methods to quantify hypoxia in vivo (such as PET imaging) still need to be improved (intra-tumour pO_2 distribution is needed)
- main problem:
  uptake ≠ concentration!



A. Brahme group, Karolinska Institutet

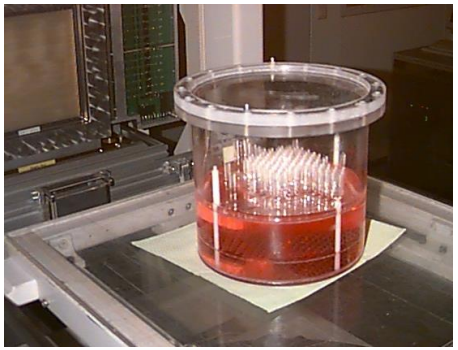
Future plans and ongoing projects at GSI

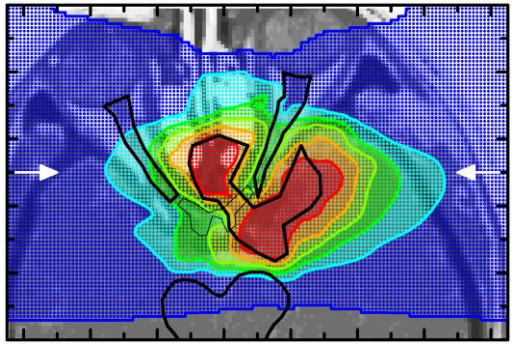
- Complimentary plans for oxygen:
  - measure **RBE** for LET values between 100 and 300, around the maximum, using monoenergetic beams
  - maybe use additional cell line
  - verify cell survival in a basic one-field plan (simpler = better defined conditions)
- TRiP optimization for **multi-ion plans** incl. OER in progress (p, He, C, O)
- Ongoing experiments on radiosensitization by **gold nanoparticles** and complementary model-ling of local dose enhancement, radiochemistry and biological endpoints (collaboration with ISMO from Université Paris-Sud, Prof. S. Lacombe and TIFPA, E. Scifoni)



Future plans and ongoing projects

- Further exploration of pseudo-3D biological dose verification methods, to continue providing a solid base for the increasingly sophisticated treatment planning possibilities
- Examine low-dose region





- Search for a beam while the FAIR facility is being built on campus

Thanks for your attention! …Questions?

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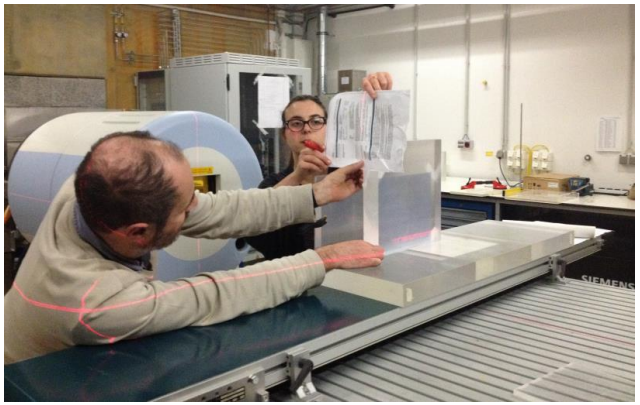

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Klaus-Josef Weber
Sylvia Trinh
(Heidelberg University Hospital)

and the Argent project