PARTNER final Project Meeting

Influence of Oxygen Status and Radiation Quality on Cell Survival

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*** GSI Darmstadt**
now: IOL- NIRS, Chiba-Japan

Motivation

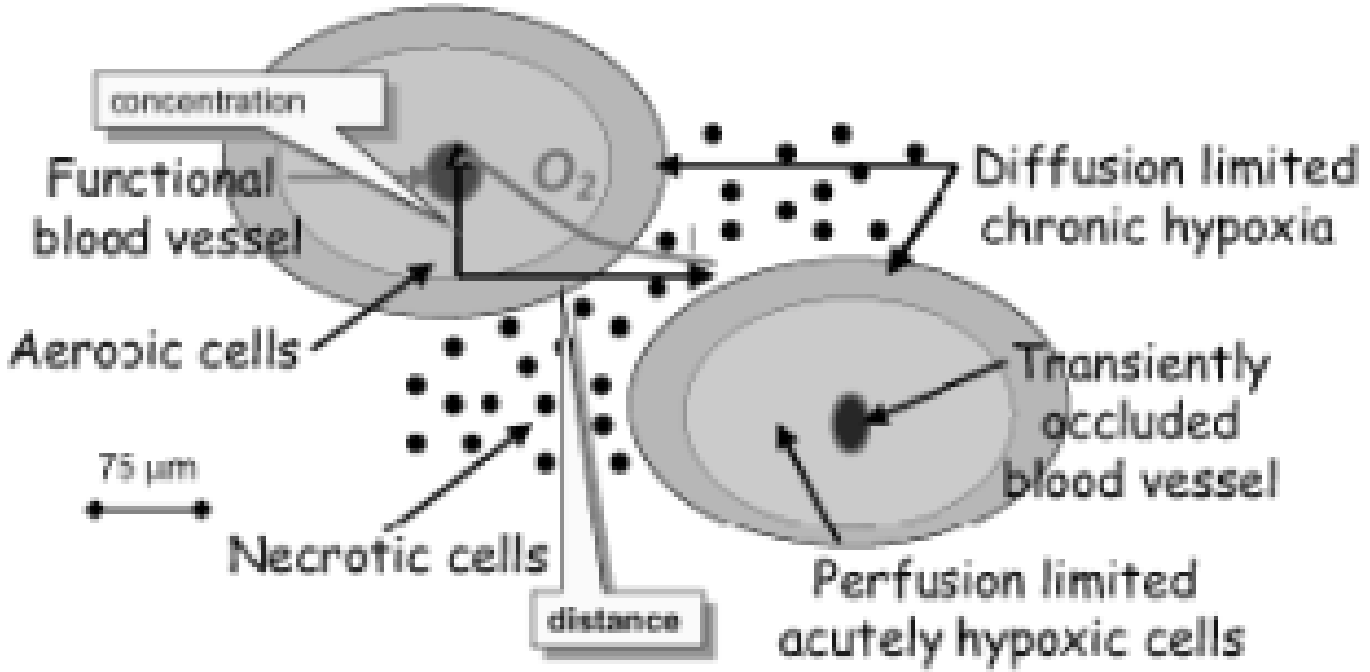
- Hypoxia – characteristic feature of locally advanced solid tumors
- Hypoxic cells are more radioresistent (Oxygen effect)
- Often responsable for local recurrences
- Source of metastasis
- Hypoxia in tumors: 0.1 – 1% O_2
- High LET irradiation can reduce the oxygen effect

Questions:

- Which are the most appropriate ions?
- How can we simulate realistic tumor conditions in cell experiments?

First Step: Construction of a suitable chamber

Hypoxia:
Acute and chronic



Hall&Giaccia 2006

"…HIF-1 drives the initial response to hypoxia (<24h) and HIF-2 drives the chronic response (>24h). Here, we review the significance of the HIF switch and the relation between HIF-1 and HIF-2 under both physiological and pathophysiological conditions…"

Trends Biochem Sci 2012 Sep;37(9):364-72. Epub 2012 Jul 18.
Passing the baton: the HIF switch.
Koh MY, Powis G

I. Effects of Acute Hypoxia

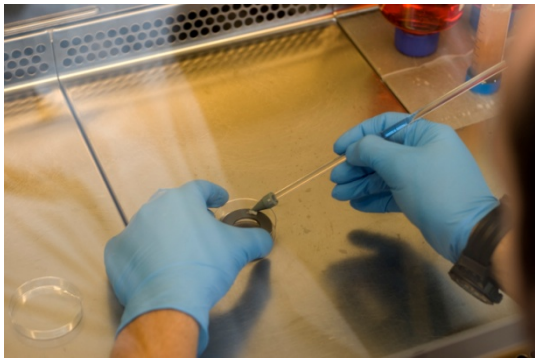
Tinganelli, Ma *et al.*

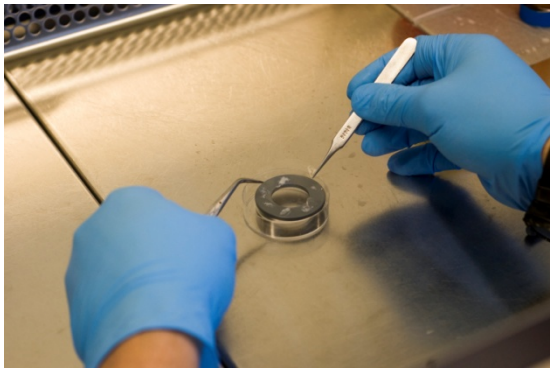
- Test of the hypoxic chamber with different cell lines
- Measurement of the oxygen dependence for x-ray irradiation
- Analysis of the dependence of the OER on dose and survival level
- Comparison to similar measurements with high LET irradiation
- Measurement of the influence of increasing LET and atomic number on OER and RBE

Definition:

OER (Oxygen Enhancement Ratio) = $\mathbf{Dose}_{\mathbf{hypoxic}} / \mathbf{Dose}_{\mathbf{oxic}}$

Hypoxia: GSI Experimental set up



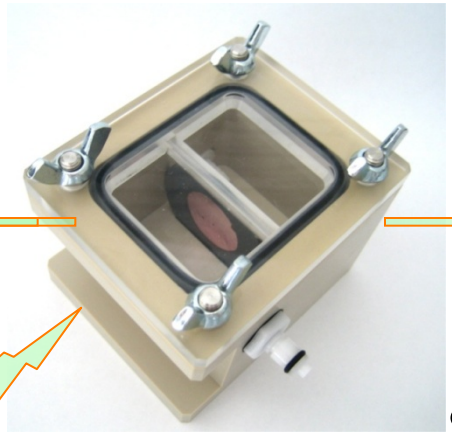


Polyvinyl chloride

- Growth support gas permeable 25 µm foil
- Growth area 4,5 cm^2
- Irradiation through chamber wall 1 mm thick (1.23 mm Water)
- 200 ml/min for 2 hours

Anoxia= 0%O_2

Hypoxia= 0.5%O_2

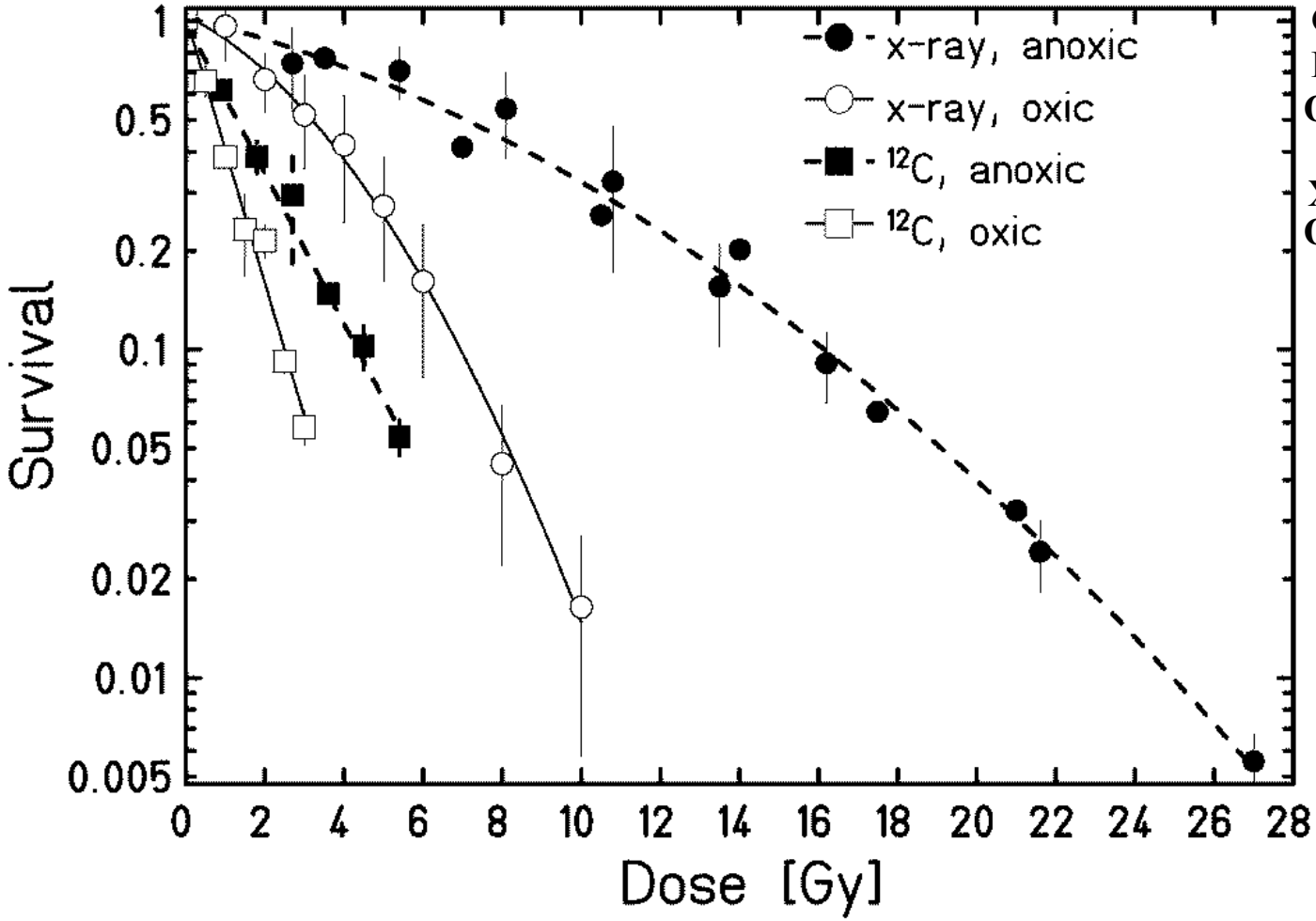


Polyetheretherketone (PEEK)

Construction: Corinna Schicker

First Tests:

RAT-1 Dunning Rat Prostate Cancer Cells (α/β= 4.69 Gy)



Carbon
LET 100 keV/ µm
OER 1.98±0.12

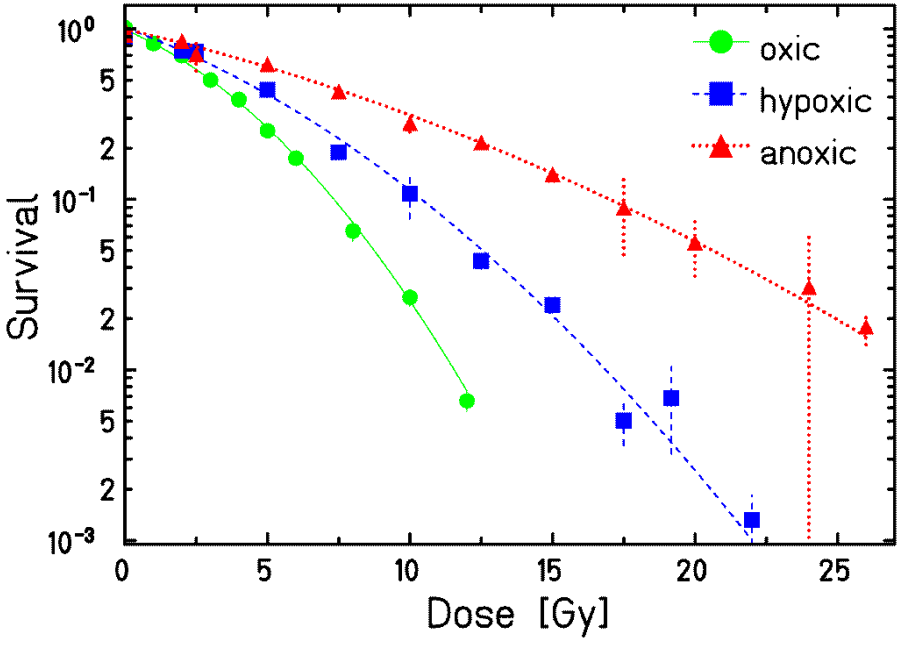
X-ray
OER_{10} 2.32 ±0.036

von Neubeck C.

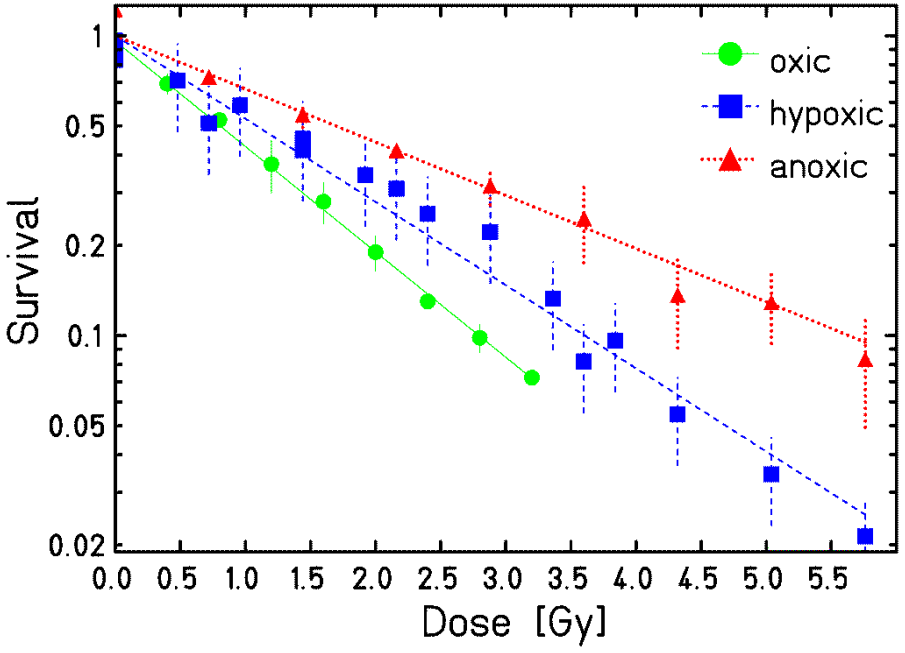
CHO-K1 cells (α/β= 8.2 Gy)

1) Dependence on Oxygen state

x-ray

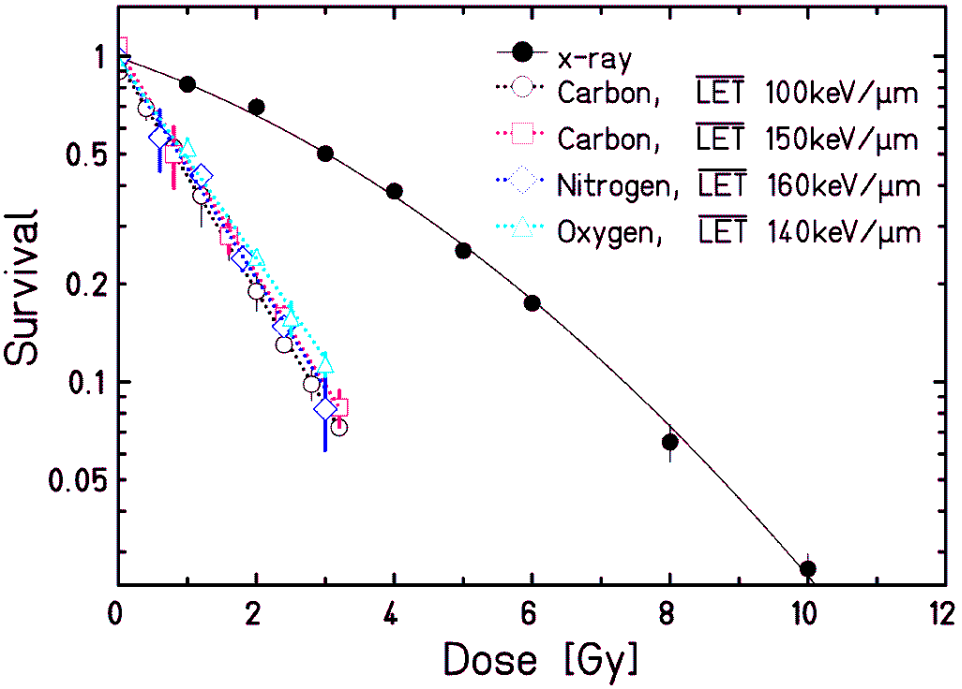


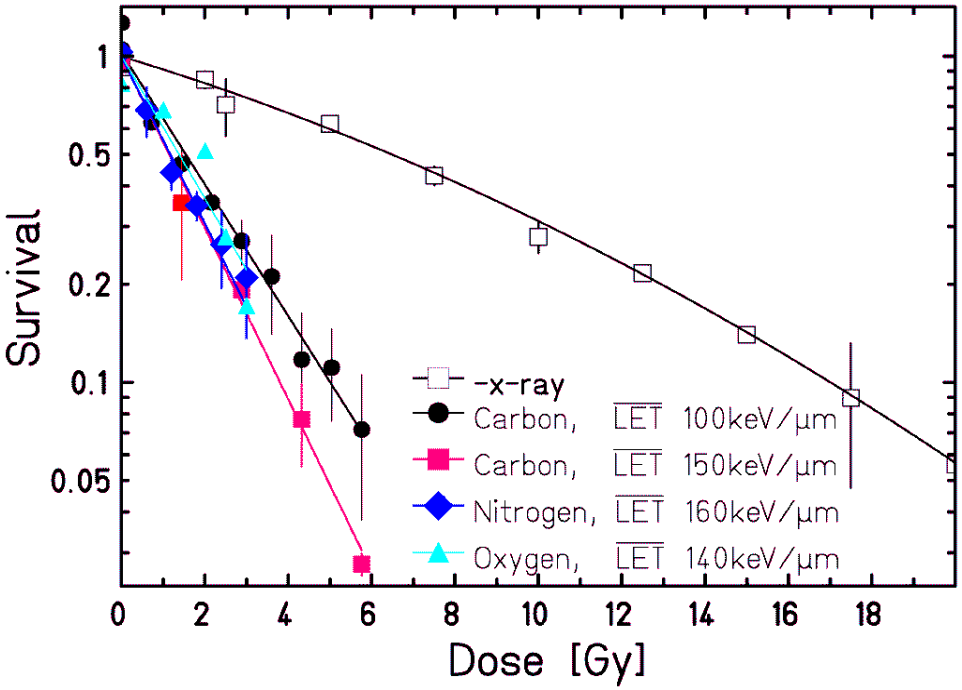
Carbon LET$_D$ 100keV/ µm



cell line	radiation	oxic state	RBE_{10}	OER_{10}
CHO-K1	x-ray	oxic	-	-
		hypoxic	-	1.4±0.04
		anoxic	-	2.31±0.08
	C-100	oxic	2.60±0.07	-
		hypoxic	2.88±0.21	1.27±0.09
		anoxic	3.03±0.19	1.98±0.12

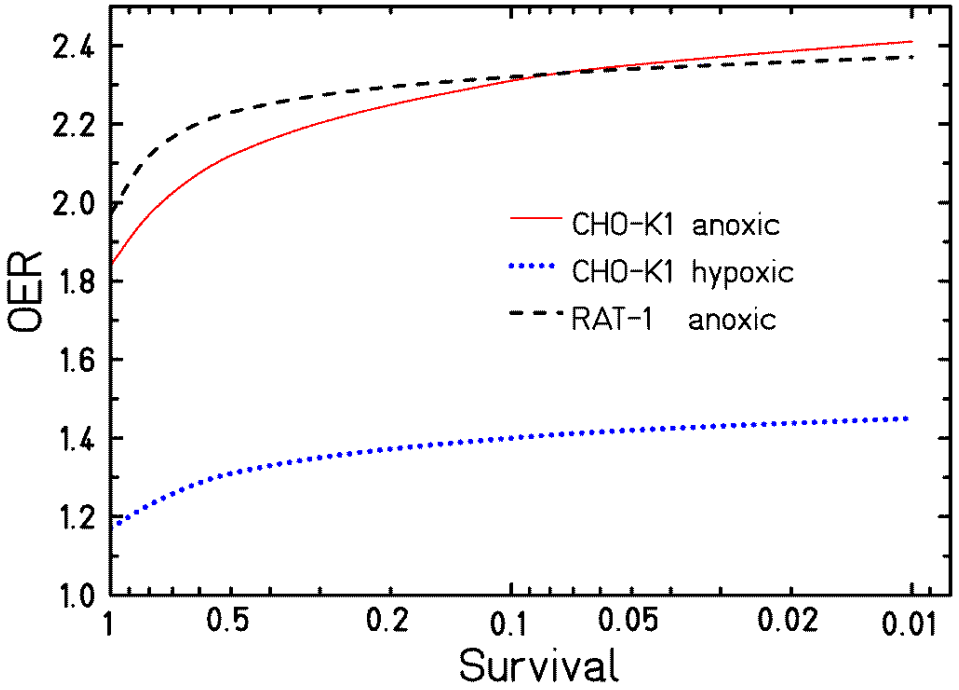
2) Dependence on Particle and LET

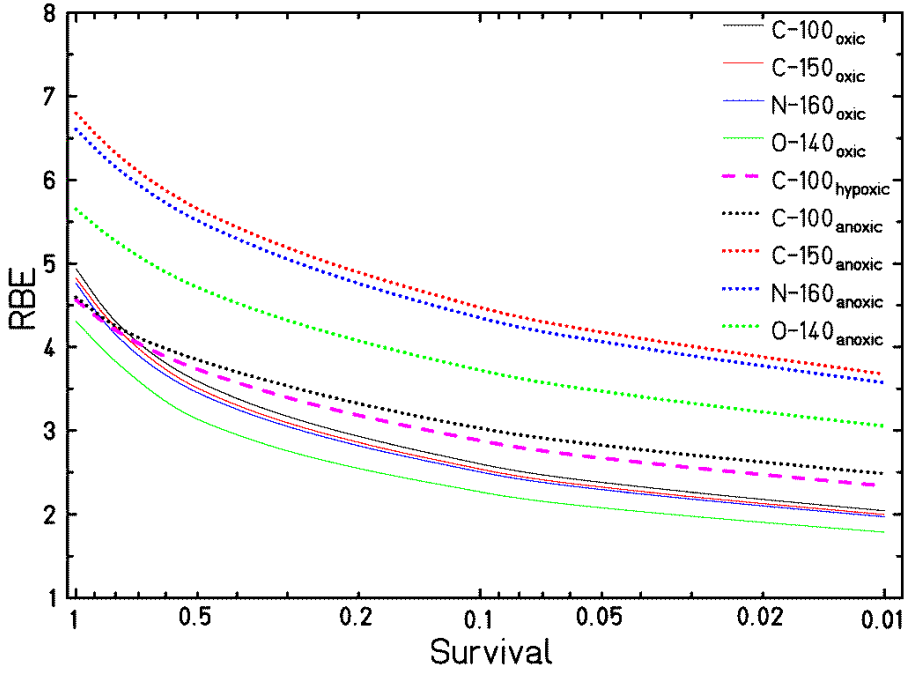




cell line	radiation	oxic state	RBE_{10}	OER_{10}
CHO-K1	C-150	oxic	2.54±0.14	-
		anoxic	4.48±0.15	1.31±0.08
	N-160	oxic	2.51±0.08	-
		anoxic	4.35±0.46	1.33±0.15
	O-140	oxic	2.27±0.09	-
		anoxic	3.72±0.86	1.40±0.33

Acute hypoxia:
OER and RBE survival dependence





Conclusions

- Applicability of the hypoxic chamber for x-ray and ion irradiation has been shown
- Both cell lines showed an increasing OER with decreasing survival
- This effect was less expressed for RAT-1 cells
- OER decreased with increasing LET
- Whereas the RBE under oxic conditions was in the same range for all LET values, there was still an increase in RBE with LET under anoxic conditions
- The influence of the LET on the OER was more expressed for RAT-1 cells

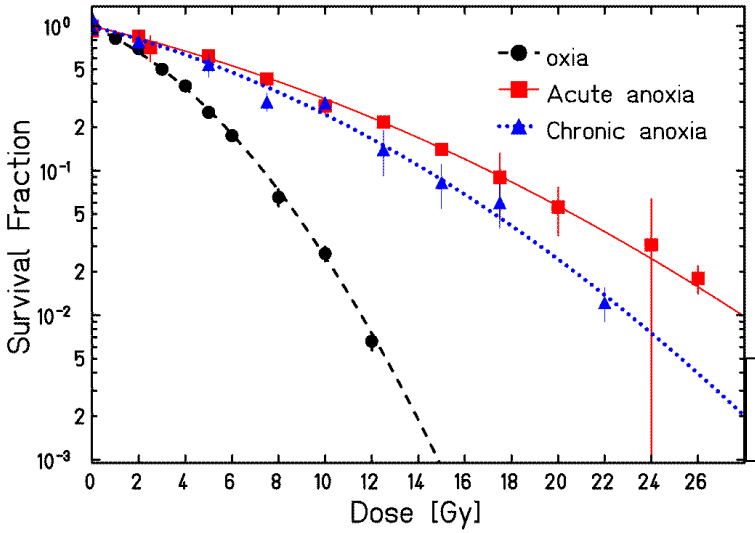
II. Effects of Chronic Hypoxia

Ma*, Tinganelli *et al.*

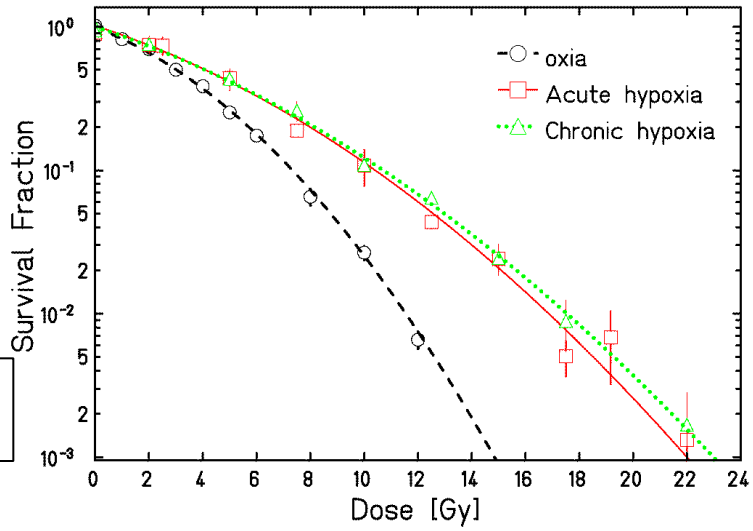
- Survival under chronic hypoxia and anoxia
- Cell cycle distribution
- Effects of reoxygenation
- Experiments performed with CHO-K1

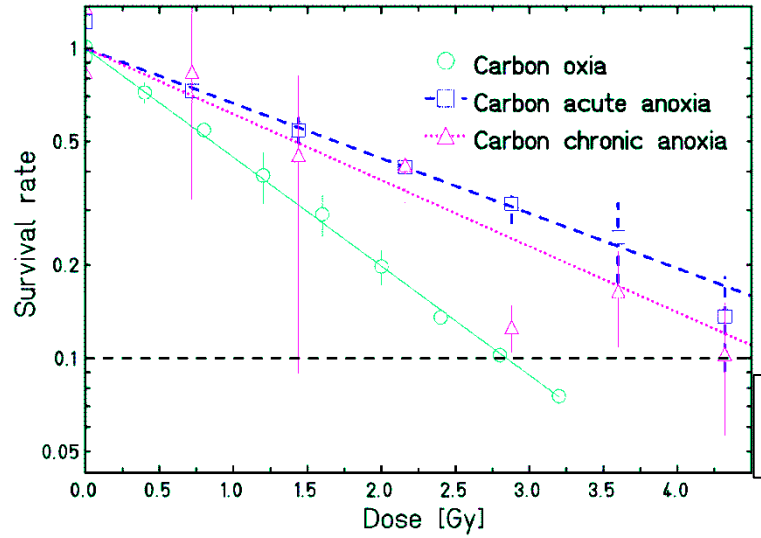
*Former GSI, Now: Fudan University Shanghai

1) Influence of Chronic Anoxia and Hypoxia

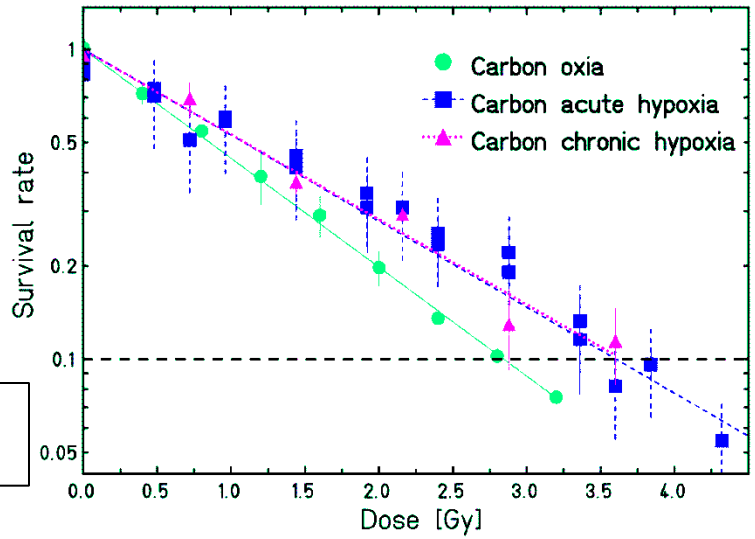


$OER_{acute} = 2.31$
$OER_{chronic} = 1.97$

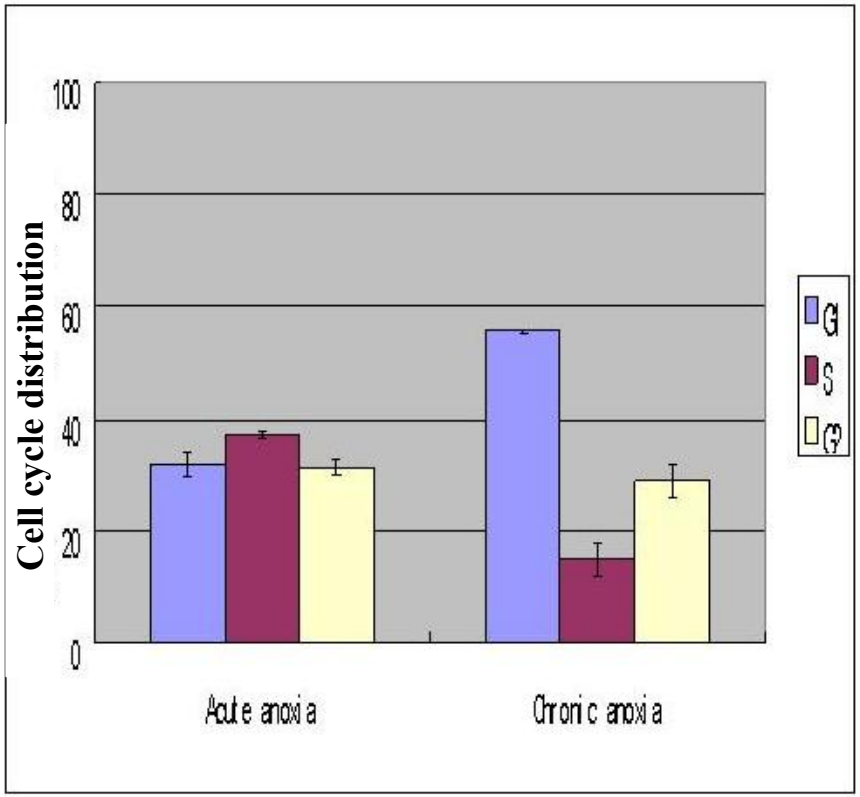


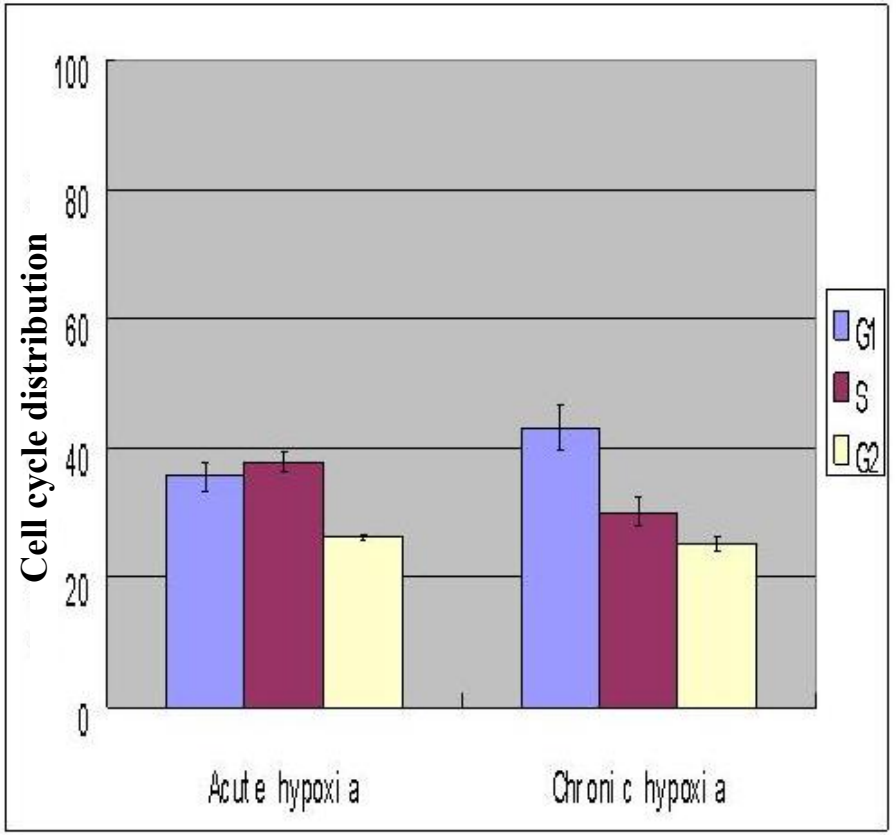


$OER_{acute} = 1.98$
$OER_{chronic} = 1.68$

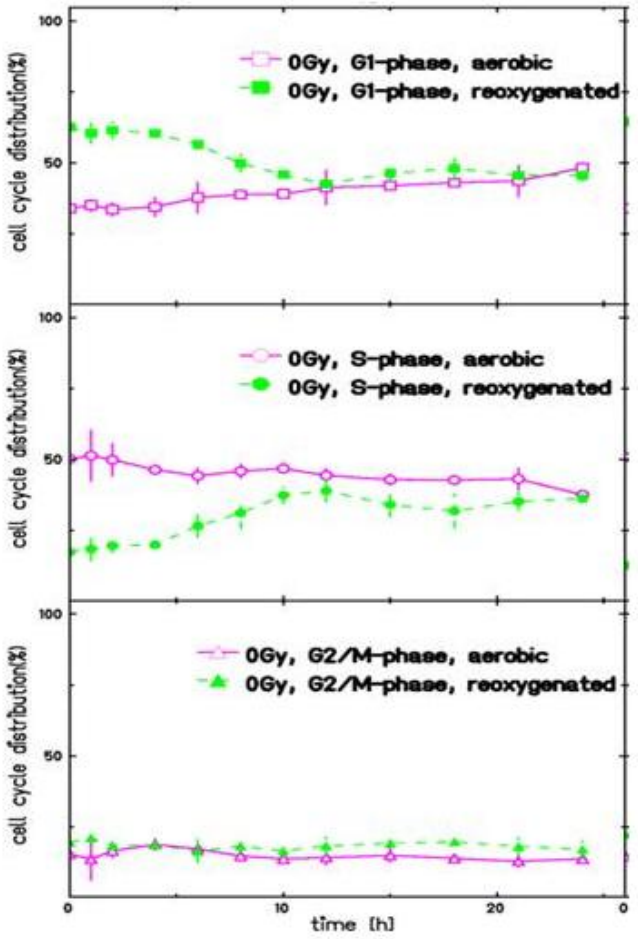


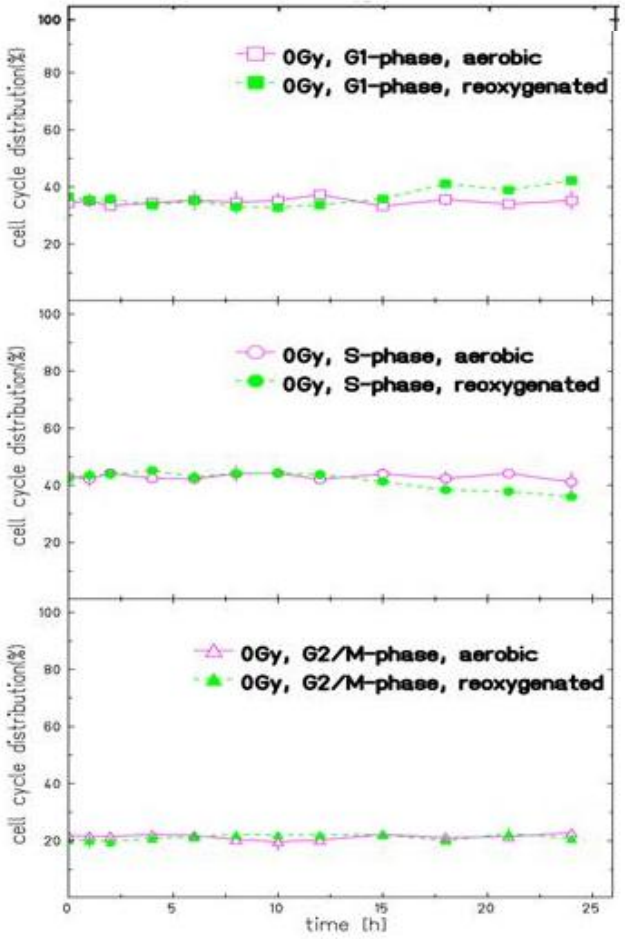
Cell Cycle Distribution



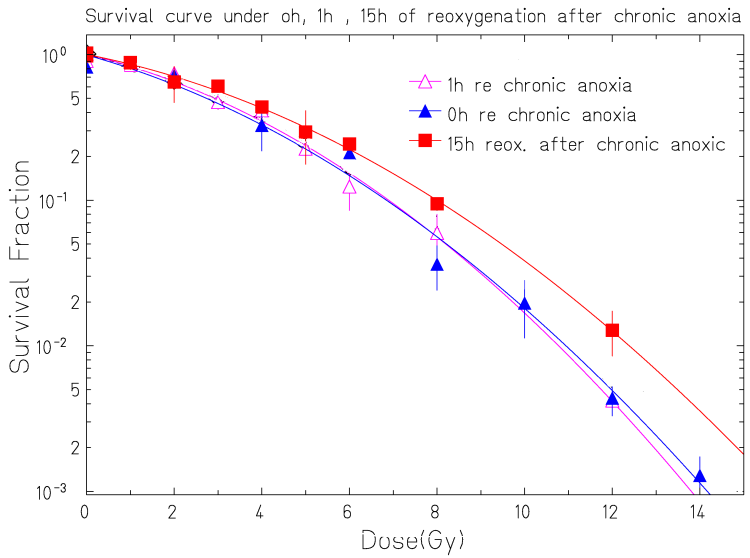


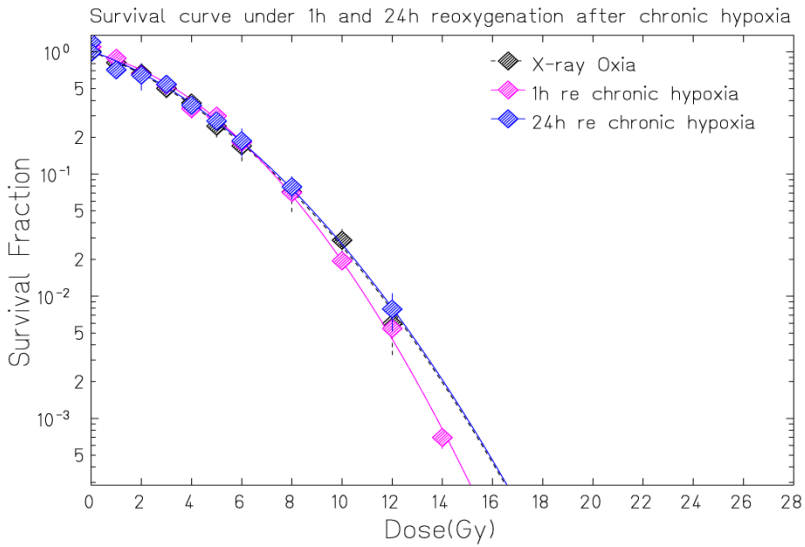
Effects of Reoxygenation

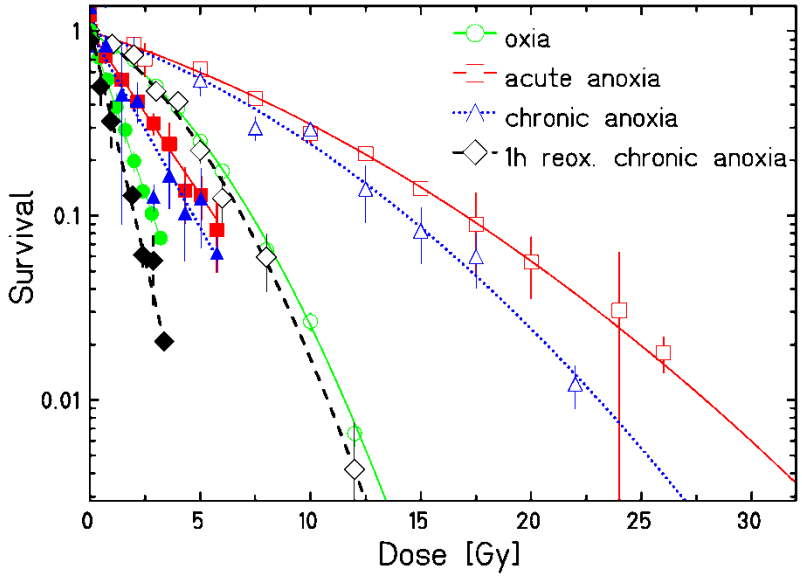




Effects of Reoxygenation







Conclusions

- RBE under anoxic conditions is reduced by chronic anoxia
- This effect has been found for x-ray and carbon irradiation
- Possible reasons are changes in cell cycle distribution
- Formerly anoxic cells are also more radiosensitive directly after reoxygenation
- For CHO-K1 cells chronic hypoxia in the measured frame has no similar influence

Thank you…

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