Hypoxia, Normal Tissue Effects and LhARA Generated Ions

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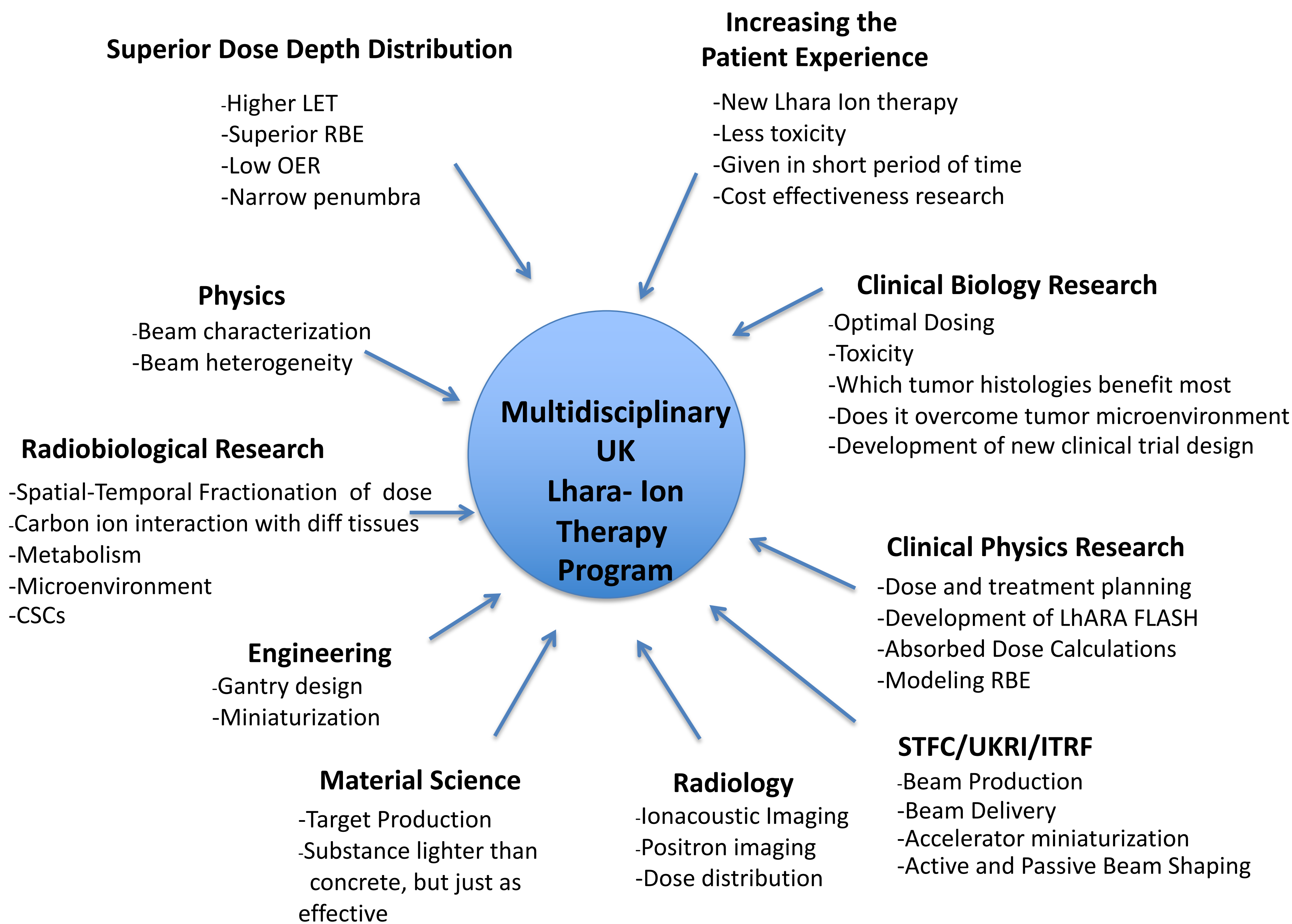

Superior Dose Depth Distribution
-Higher LET
-Superior RBE
-Low OER
-Narrow penumbra
Increasing the Patient Experience
-New Lhara Ion therapy
-Less toxicity
-Given in short period of time
-Cost effectiveness research
Physics
-Beam characterization
-Beam heterogeneity
Clinical Biology Research
-Optimal Dosing
-Toxicity
-Which tumor histologies benefit most
-Does it overcome tumor microenvironment
-Development of new clinical trial design
Multidisciplinary UK Lhara- Ion Therapy Program
Radiobiological Research
-Spatial-Temporal Fractionation of dose
-Carbon ion interaction with diff tissues
-Metabolism
-Microenvironment
-CSCs
Clinical Physics Research
-Dose and treatment planning
-Development of LhARA FLASH
-Absorbed Dose Calculations
-Modeling RBE
Engineering
-Gantry design
-Miniaturization
STFC/UKRI/ITRF
-Beam Production
-Beam Delivery
-Accelerator miniaturization
-Active and Passive Beam Shaping
Material Science
-Target Production
-Substance lighter than concrete, but just as effective
Radiology
-Ionacoustic Imaging
-Positron imaging
-Dose distribution

Advantages of LhARA for Radiobiologic Studies

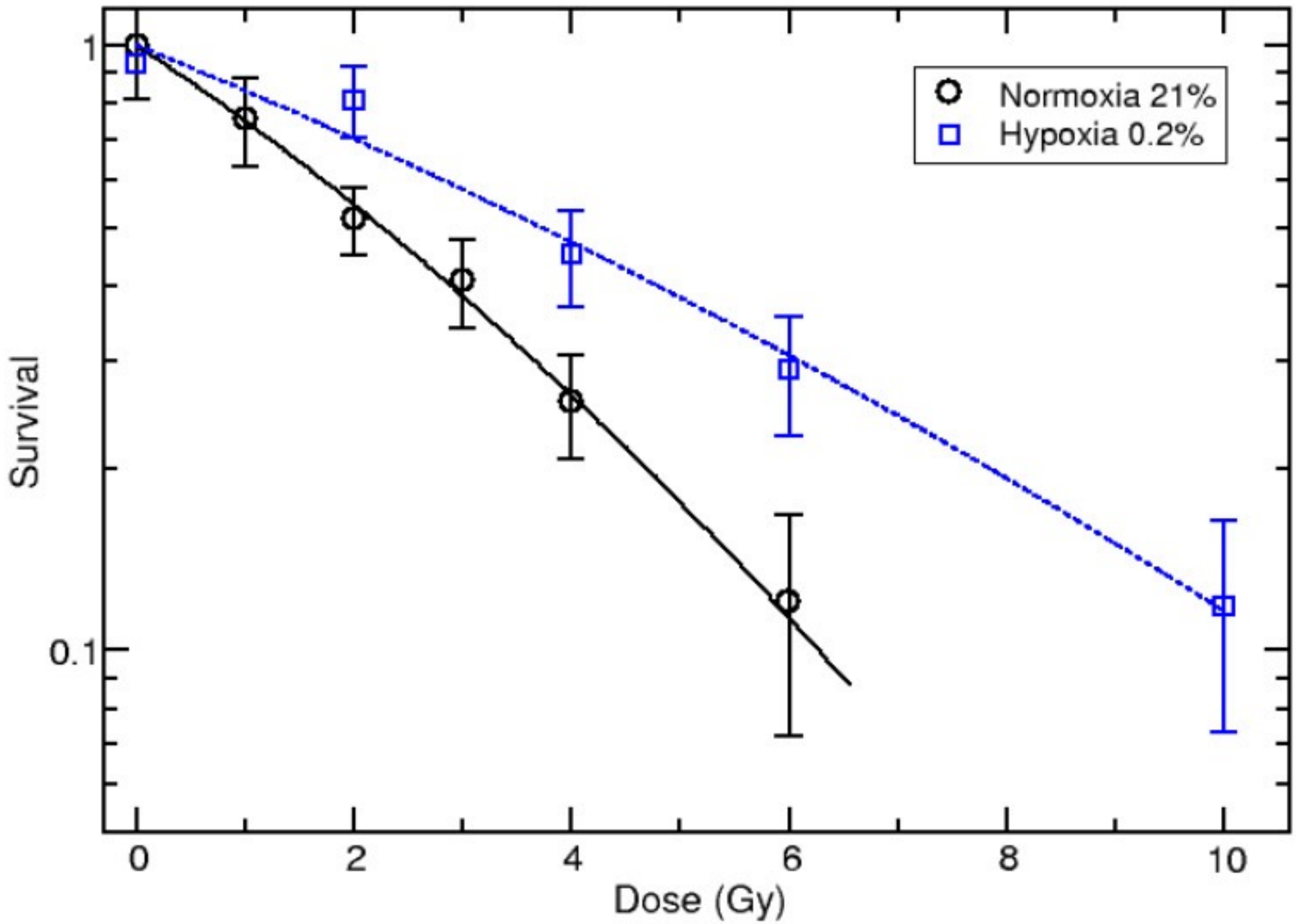
Ultra High Dose Rate of Protons and Ions generated by LhARA and their ability to overcome Hypoxia

Investigate the role of Hypoxia in LhARA Driven Proton FLASH Protection of Normal Tissue

Effect of LhARA Driven Ions on Cancer Stem Cells

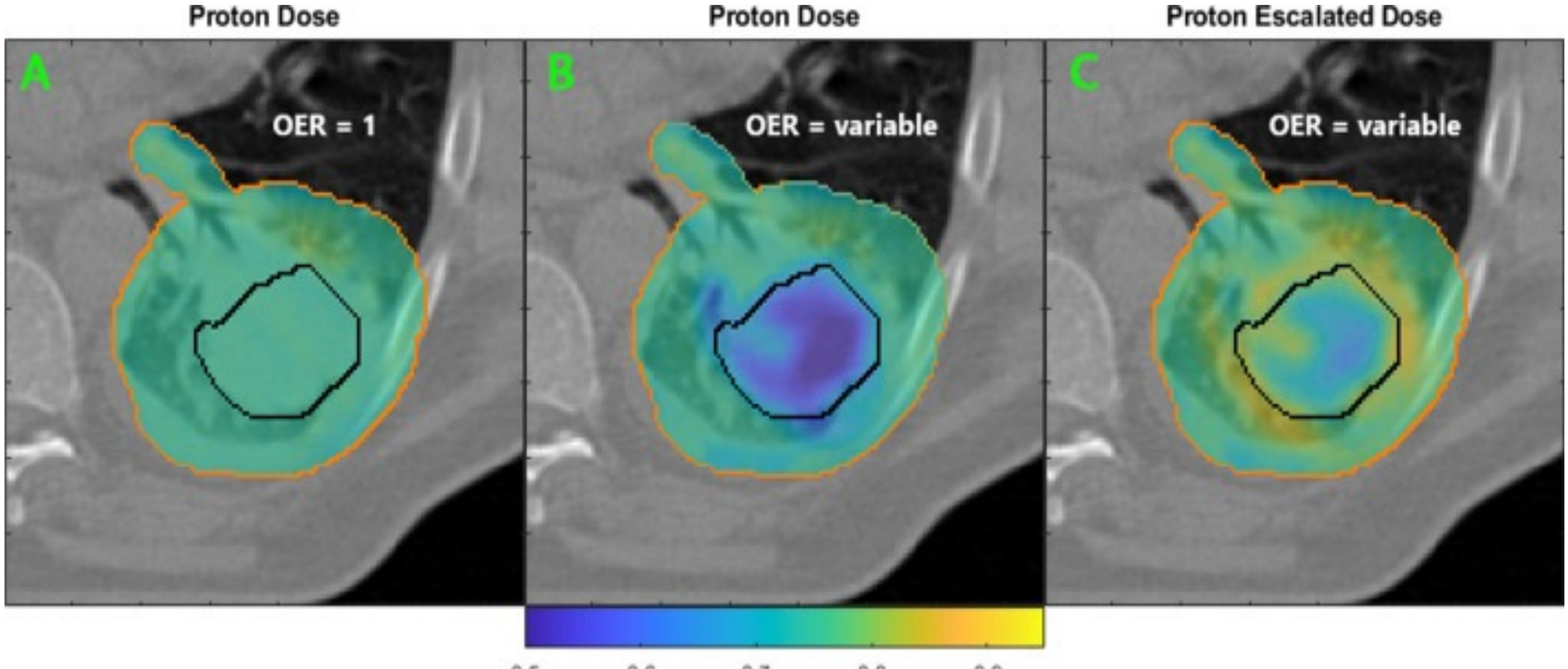
Potential to Manipulate the Temporal Delivery of Ions to understand how they affect normal tissues, Including both viability and transformation (sub lethal effects)

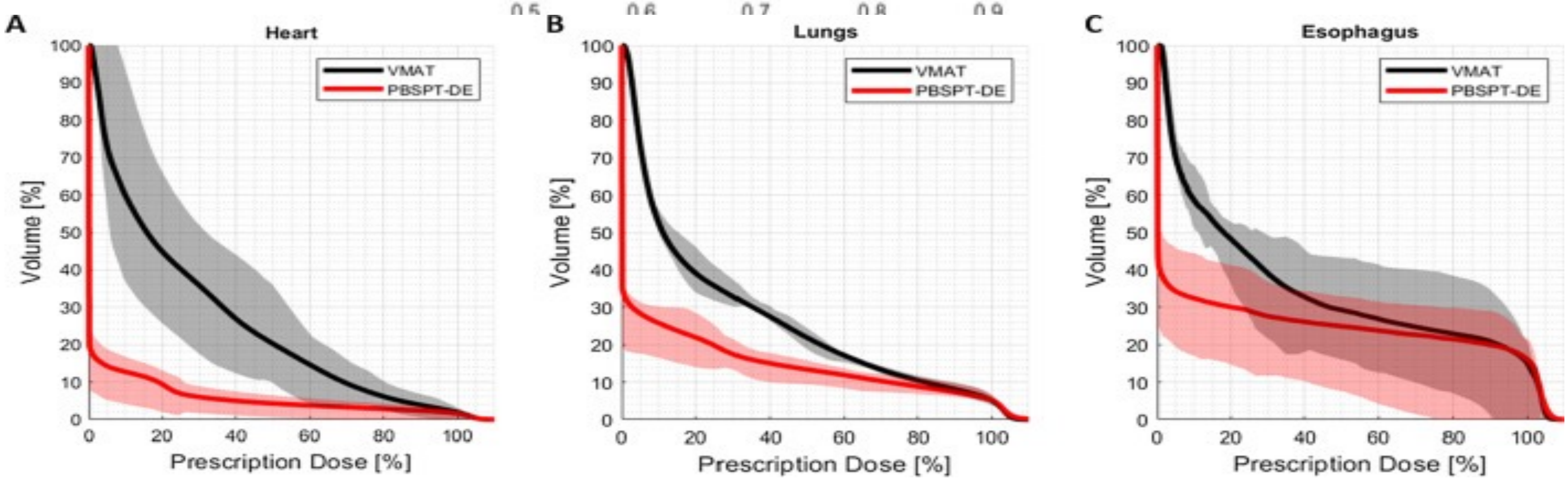
Effect of Hypoxia on U87 Tumor Cells Irradiated with 62 MeV Protons



Bravata et al, 2021

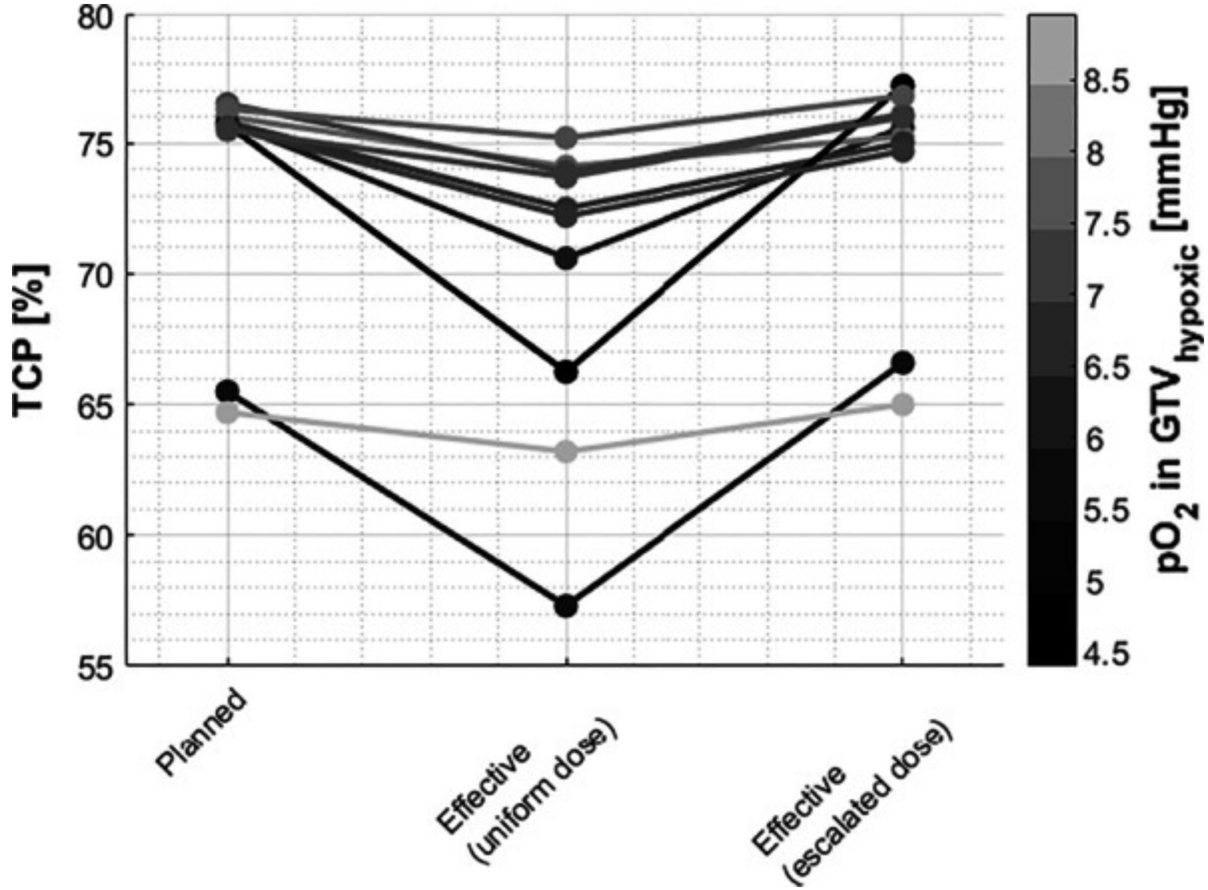
Example of Escalating Dose to Treat Hypoxic Tumor Regions





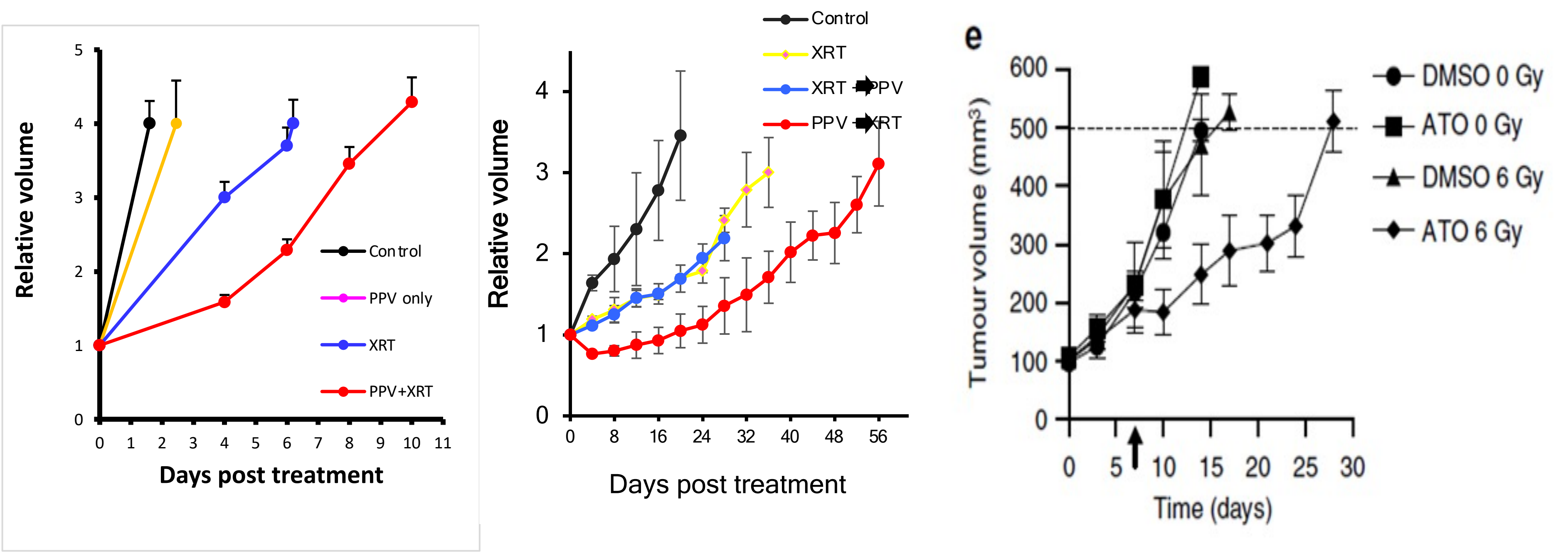
Kothe et al, 2021

TCP for Patients with Uniform Dose vs Escalated Dose

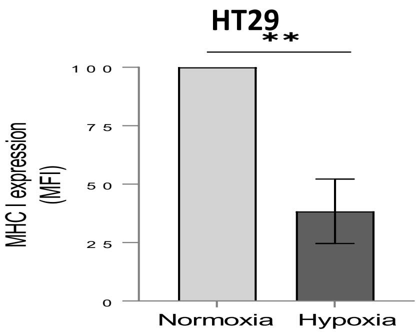


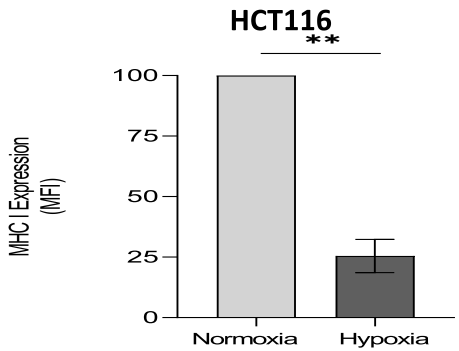
Kothe et al, 2021

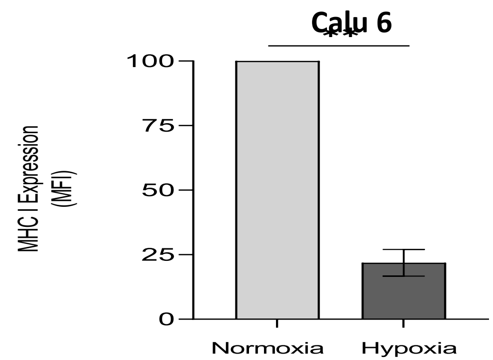
Effect of Mitochondrial Complex 1 and 3 Inhibitors on Increasing Tumor RadiosensitivityBy Making tumors more Oxic

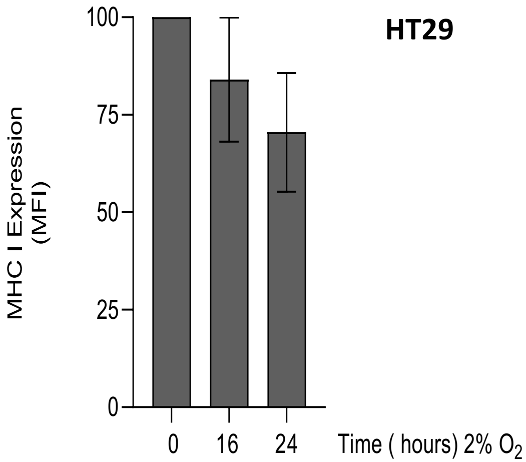


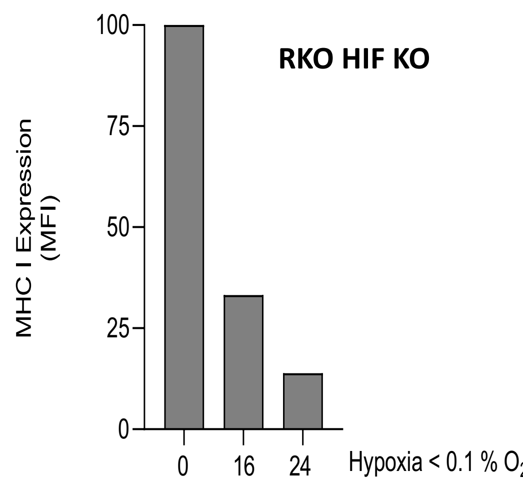
Hypoxia Induces a Decrease in MHC I Expression in a HIF Independent Manner





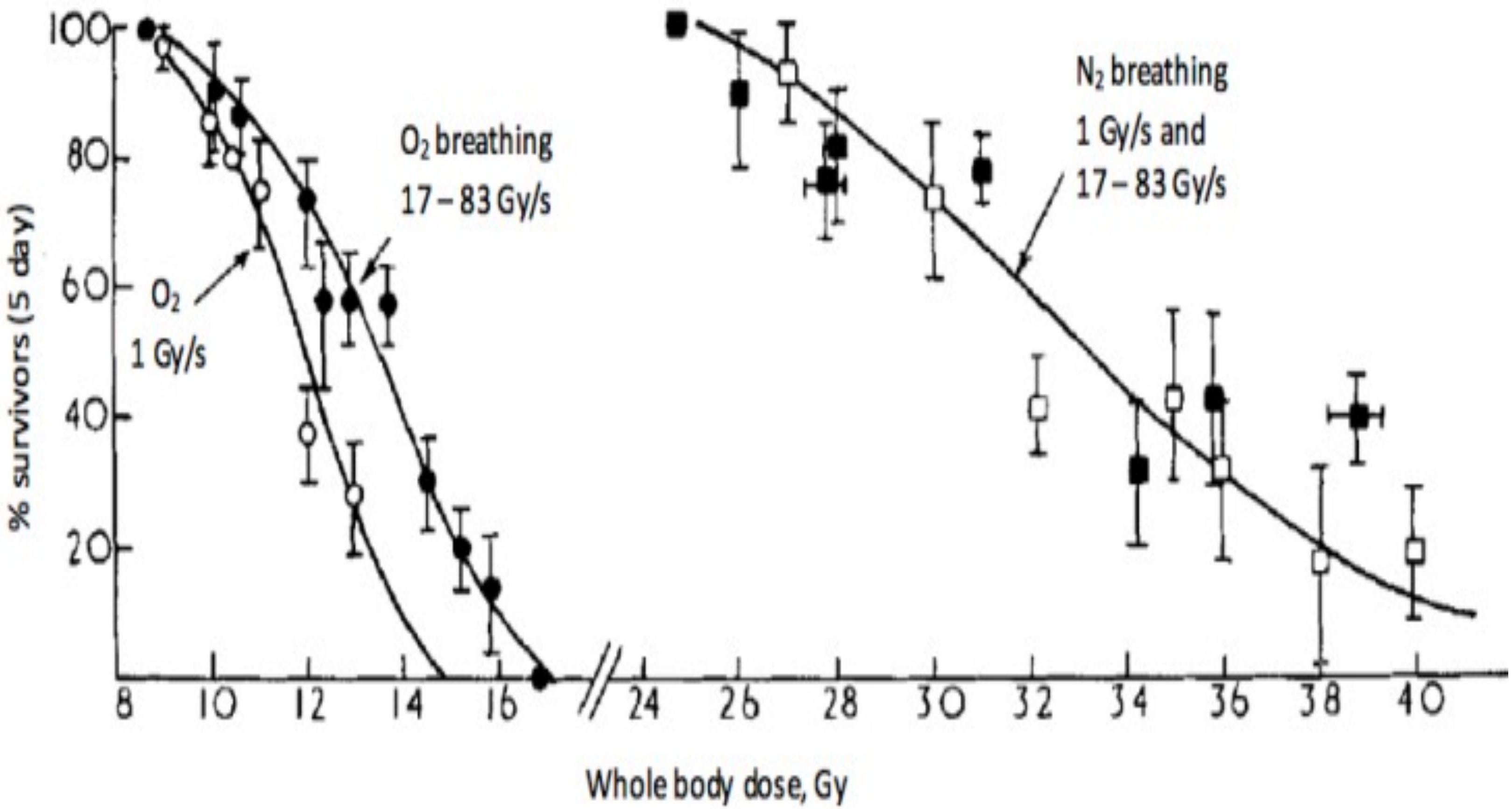






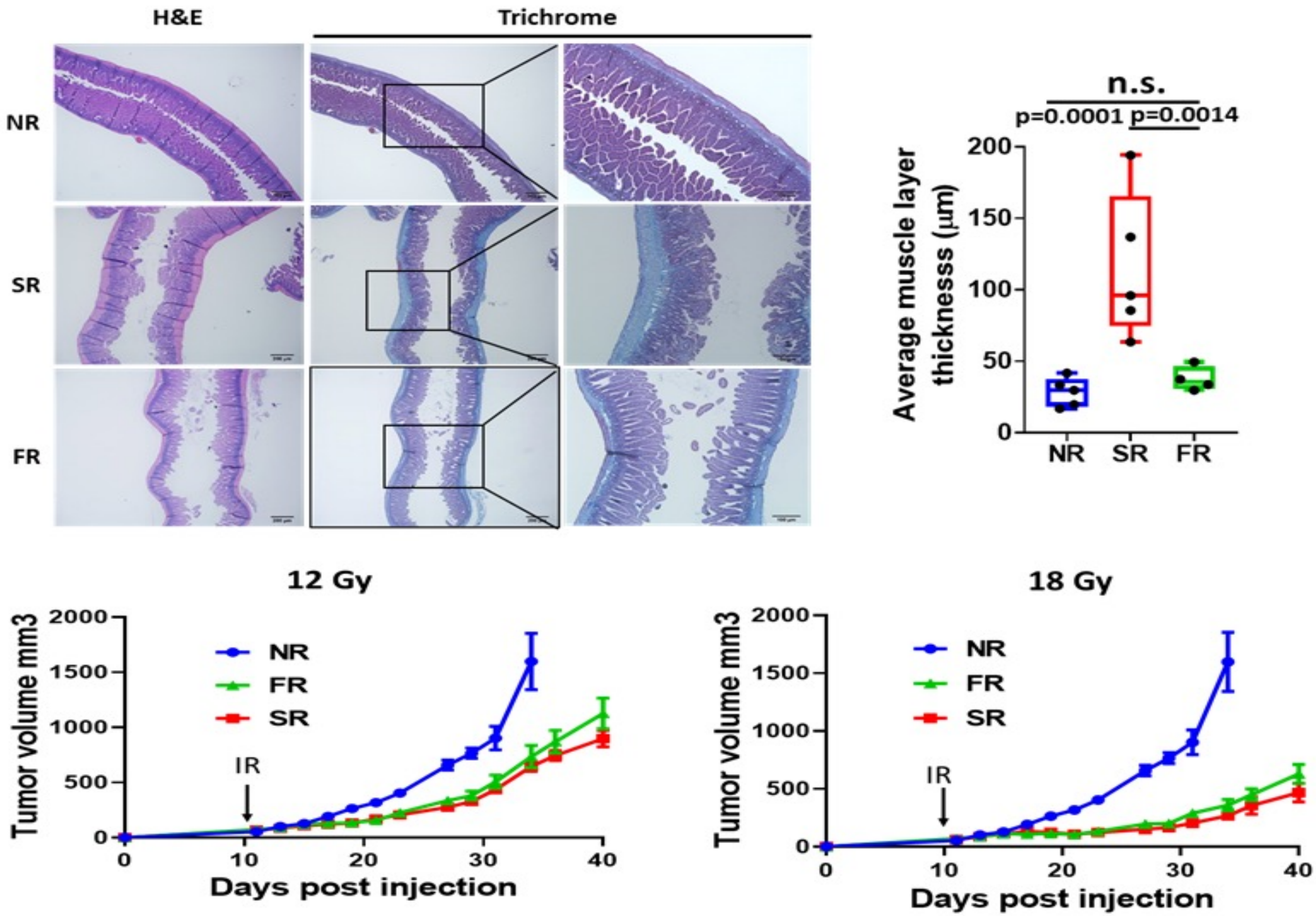
Can LhARA Radiation increase MHC1 Expression in combination with metabolic agents?

The Origins of FLASH Radiotherapy



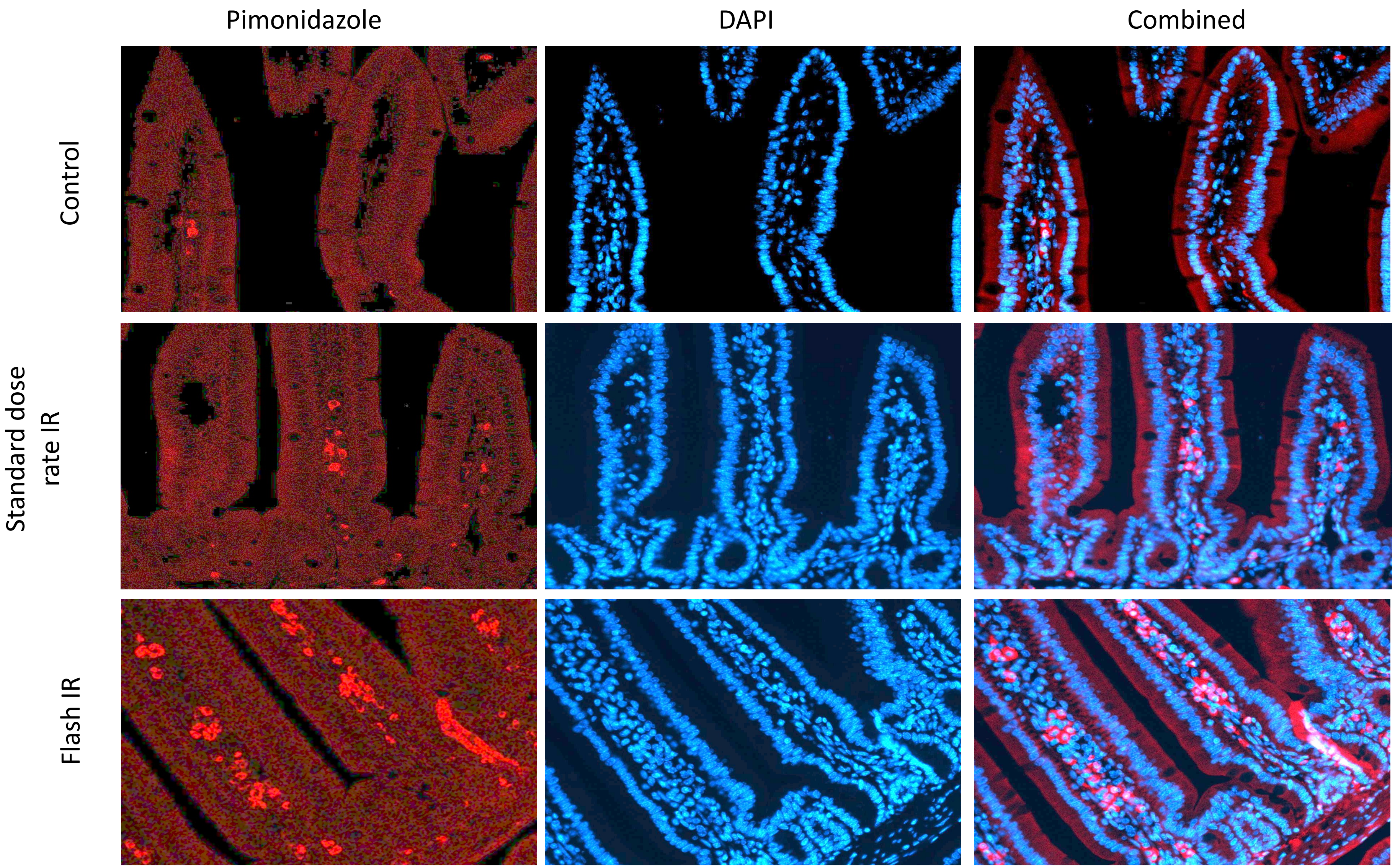
Hornsey S, Bewley DK. Hypoxia in mouse intestine induced by electron irradiation at high dose-rates. *Int J Radiat Biol Relat Stud Phys Chem Med.* 1971;19(5):479-483.

Flash-Proton Radiotherapy Highly Effective in Controling Pancreatic Tumor Growth and Reduces Normal Tissue Toxicity



Koumenus et al, unplublished

How does FLASH RT Protect Against Normal Tissue Toxicity?
Hypothesis: FLASH induces normal tissue hypoxia.

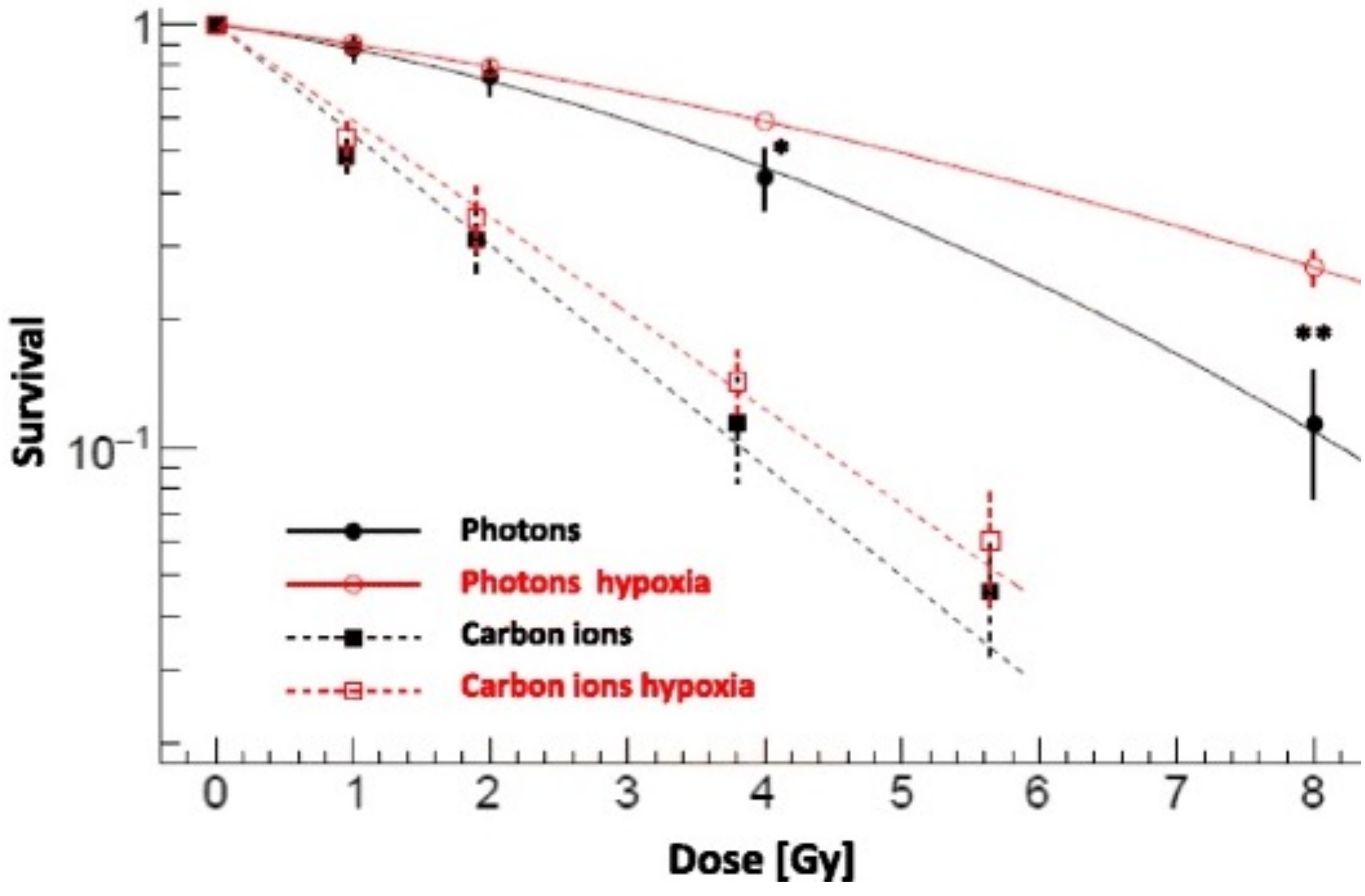


FLASH RT protection correlates with hypoxia in normal tissues

LhARA Proton FLASH Mechanisms to Explain Differential Normal vs Cancer

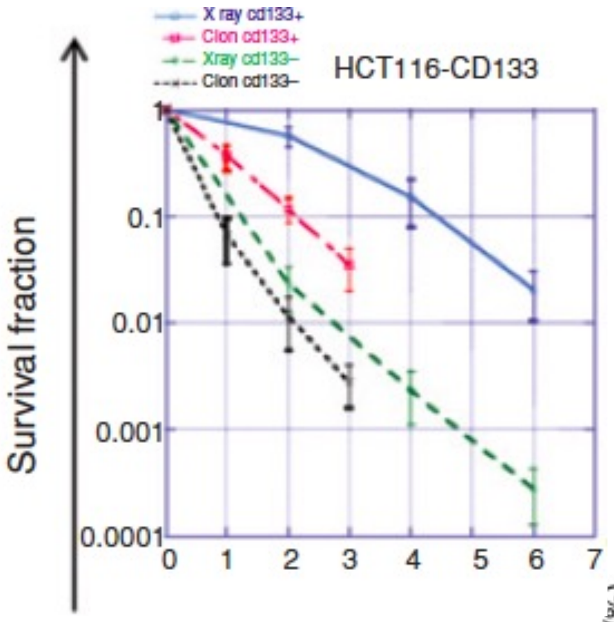
- Removal and decay of hydroperoxides and free radicals
- Oxygen saturation of irradiated normal tissues
- Effect of Different Beam Pulses
- Genetic Approaches to Understand FLASH Effect in Normal Tissue

Effect of Hypoxia on Photon and Carbon Ion Killing of A549 Cells

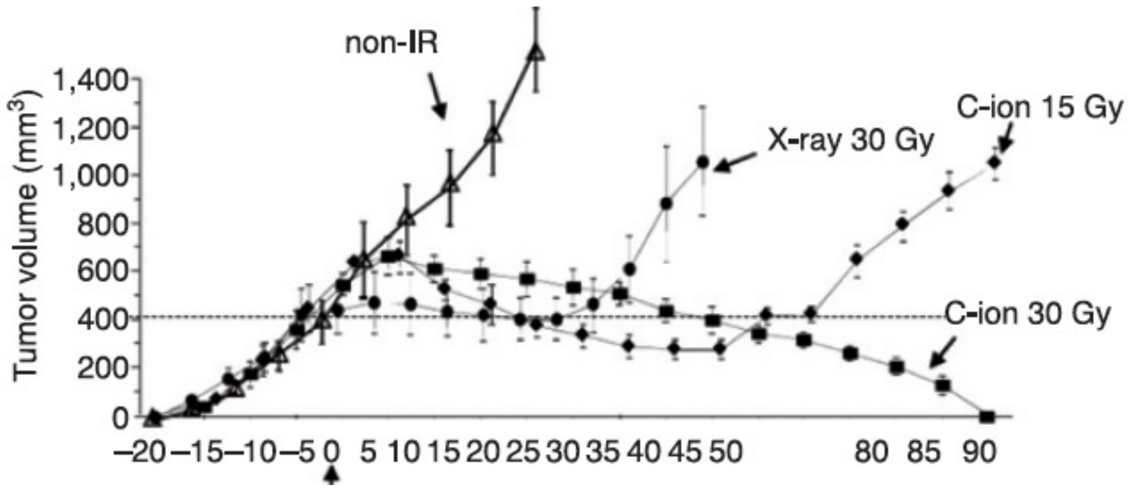


Carbon is More Effective In Killing Cancer Stem Cells

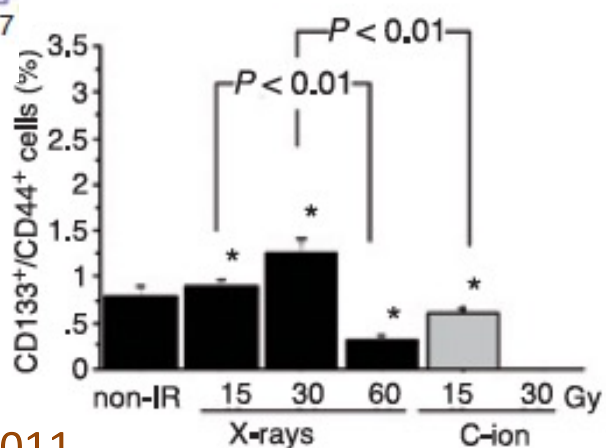
In vitro clonogenic survival

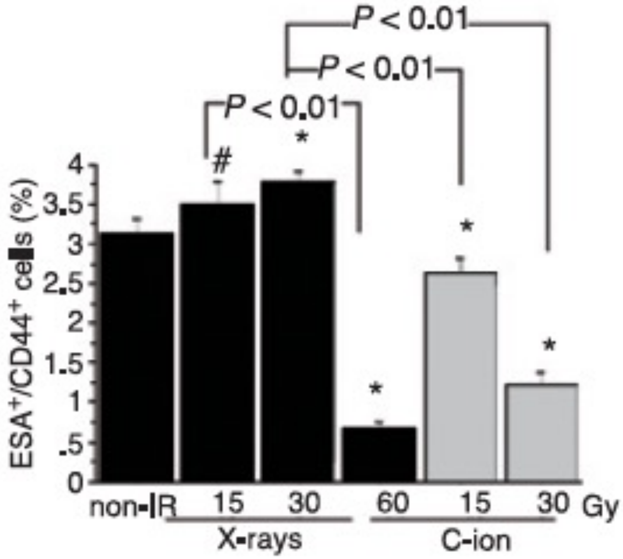


In vivo growth by beam type and dose



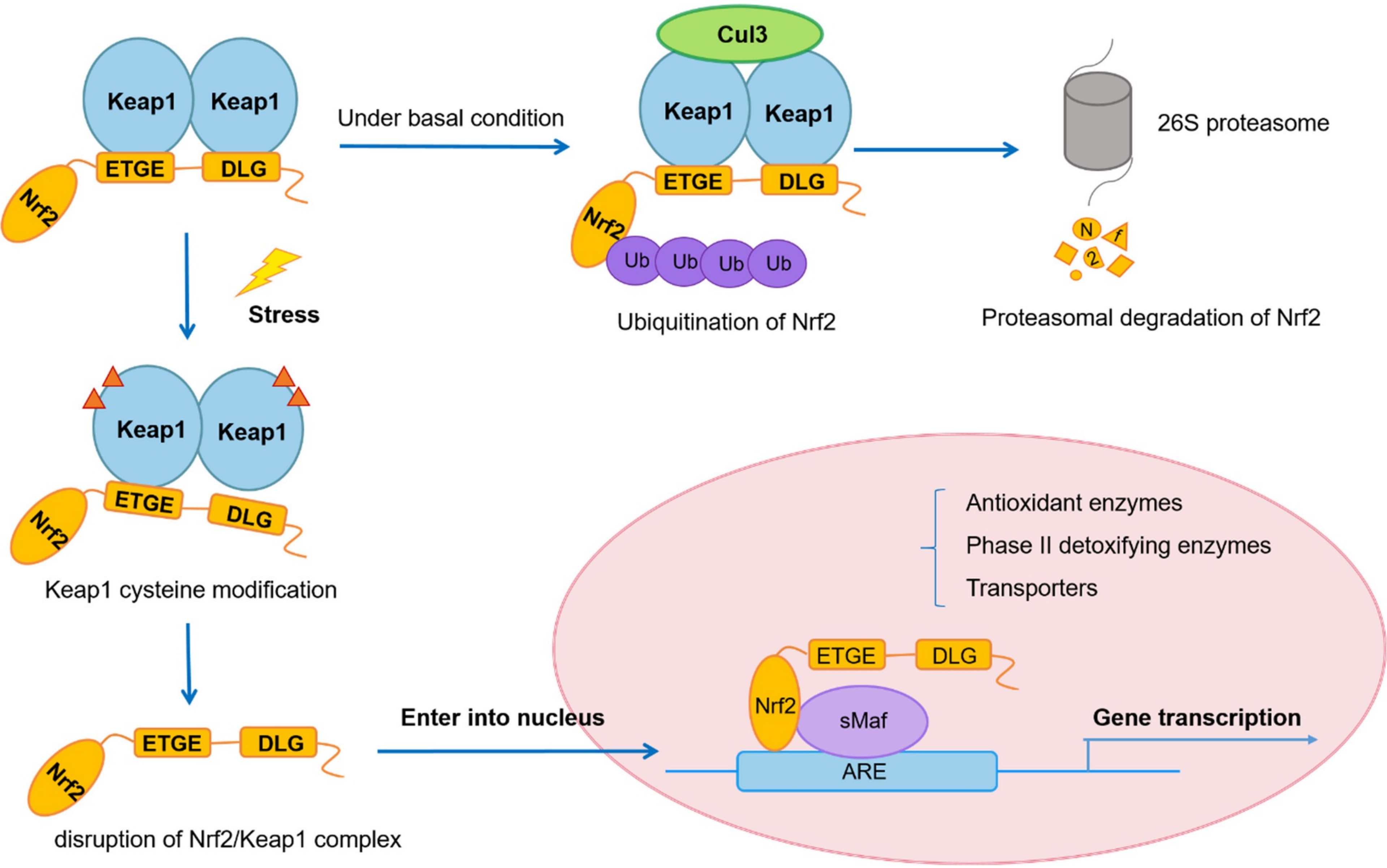
% putative CSC- like *in vivo* after RT





Cui X et al, Cancer Research 2011

Nrf2-Keap1 Pathway

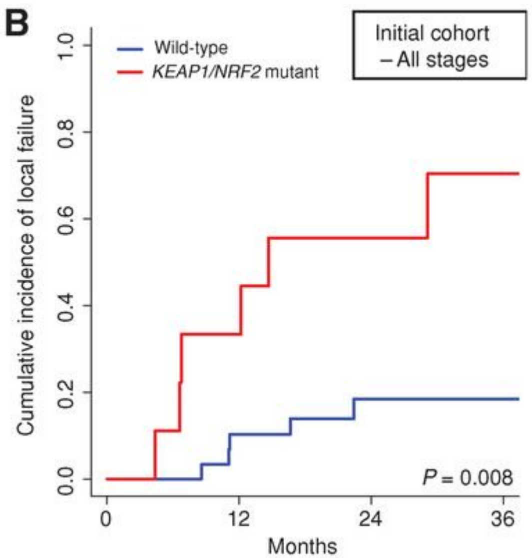


KEAP1/NRF2 Mutation Status Predicts Local Failure after Radiotherapy in Human NSCLC

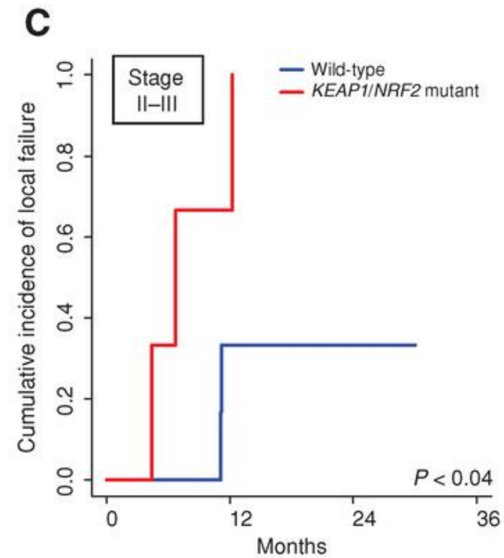
A

		Wild-type (*n* = 33)	*KEAP1/NRF2* mutant (*n* = 9)	*P*
Sex	M	9 (27%)	5 (56%)	0.23
	F	24 (73%)	4 (44%)	
Median age, years (range)		70 (42–91)	66 (56–91)	0.45
Median follow-up, mo. (range)		24 (6–53)	25 (7–63)	0.47
Histology	SCC	5 (15%)	1 (11%)	0.85
	Adenoca	25 (76%)	7 (78%)	
	Other	3 (9%)	1 (11%)	
Stage	I	22 (67%)	5 (56%)	0.54
	II	6 (18%)	1 (11%)	
	III	5 (15%)	3 (33%)	
Median tumor volume, mL (range)		16.2 (0.8–569.8)	16.1 (1.0–218.5)	0.48
Radiation type	SABR	25 (76%)	6 (67%)	0.68
	CFRT	8 (24%)	3 (33%)	
Chemotherapy	Yes	7 (21%)	3 (33%)	0.66
	No	26 (79%)	6 (67%)	

B



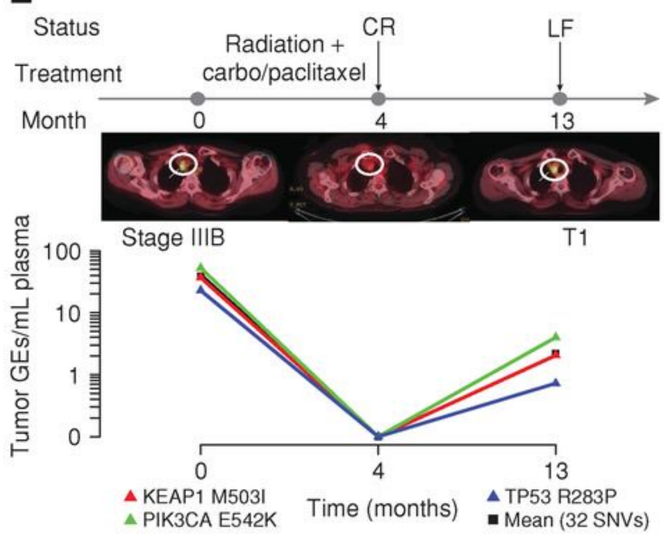
C



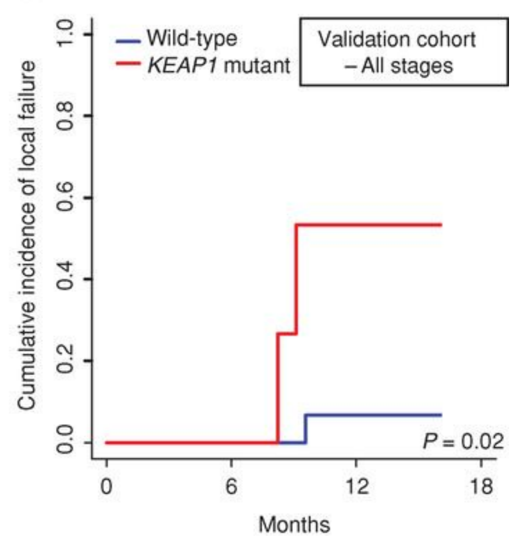
D

Patient	Age	Sex	Stage	*KEAP1* mutations: Tumor variant	*KEAP1* mutations: ctDNA variant (%AF)
T1	56	F	IIIB	M503I	M503I (3.38%)
T2	56	F	IIIB	R483C	R483C (0.44%)
T11	46	F	IIA	Wild-type	Wild-type
T13	81	F	IB	Wild-type	Wild-type
T14	78	M	IB	Wild-type	Wild-type
T23	51	F	IIIA	Wild-type	Wild-type
T35	48	F	IIIB	Wild-type	Wild-type

E

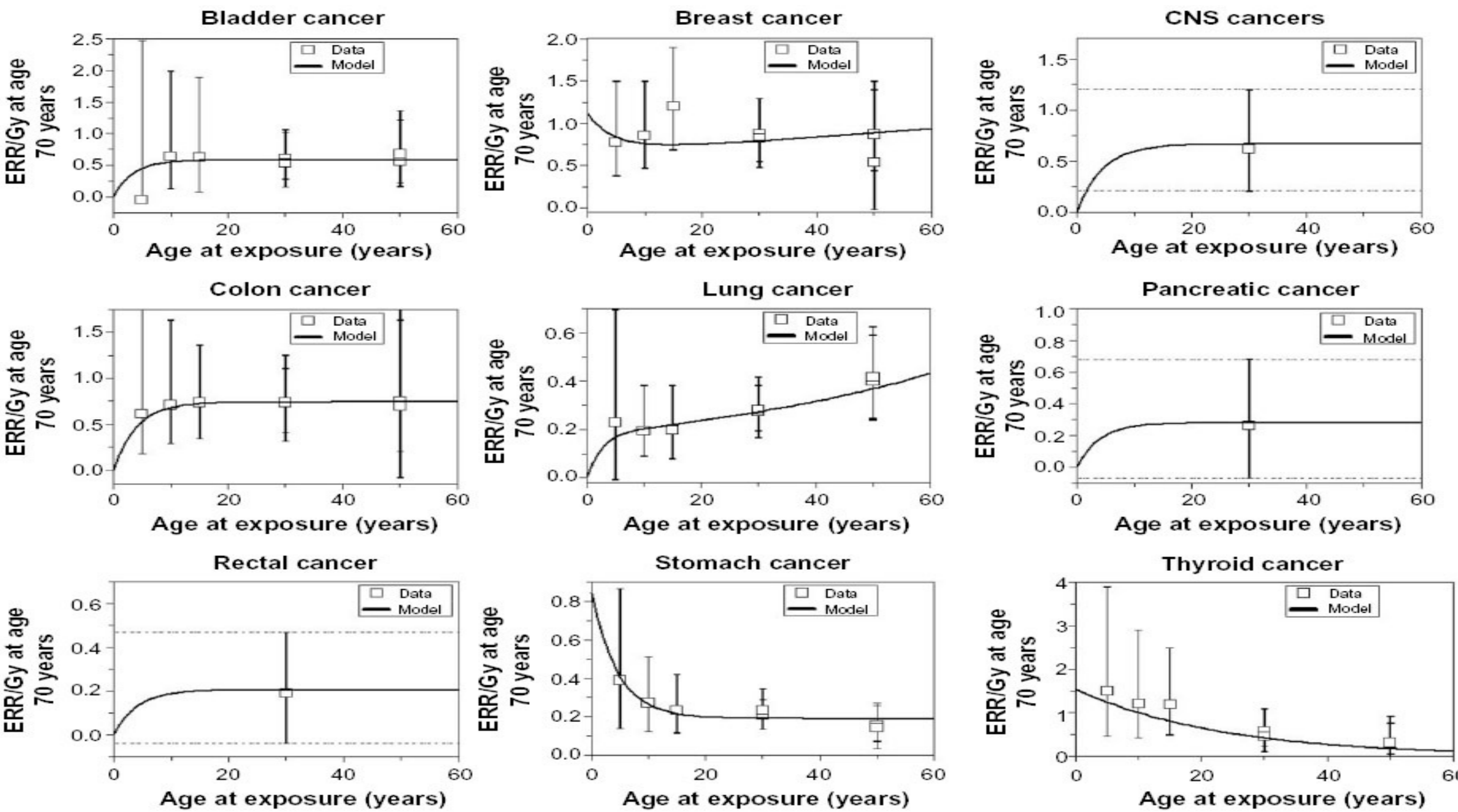


F



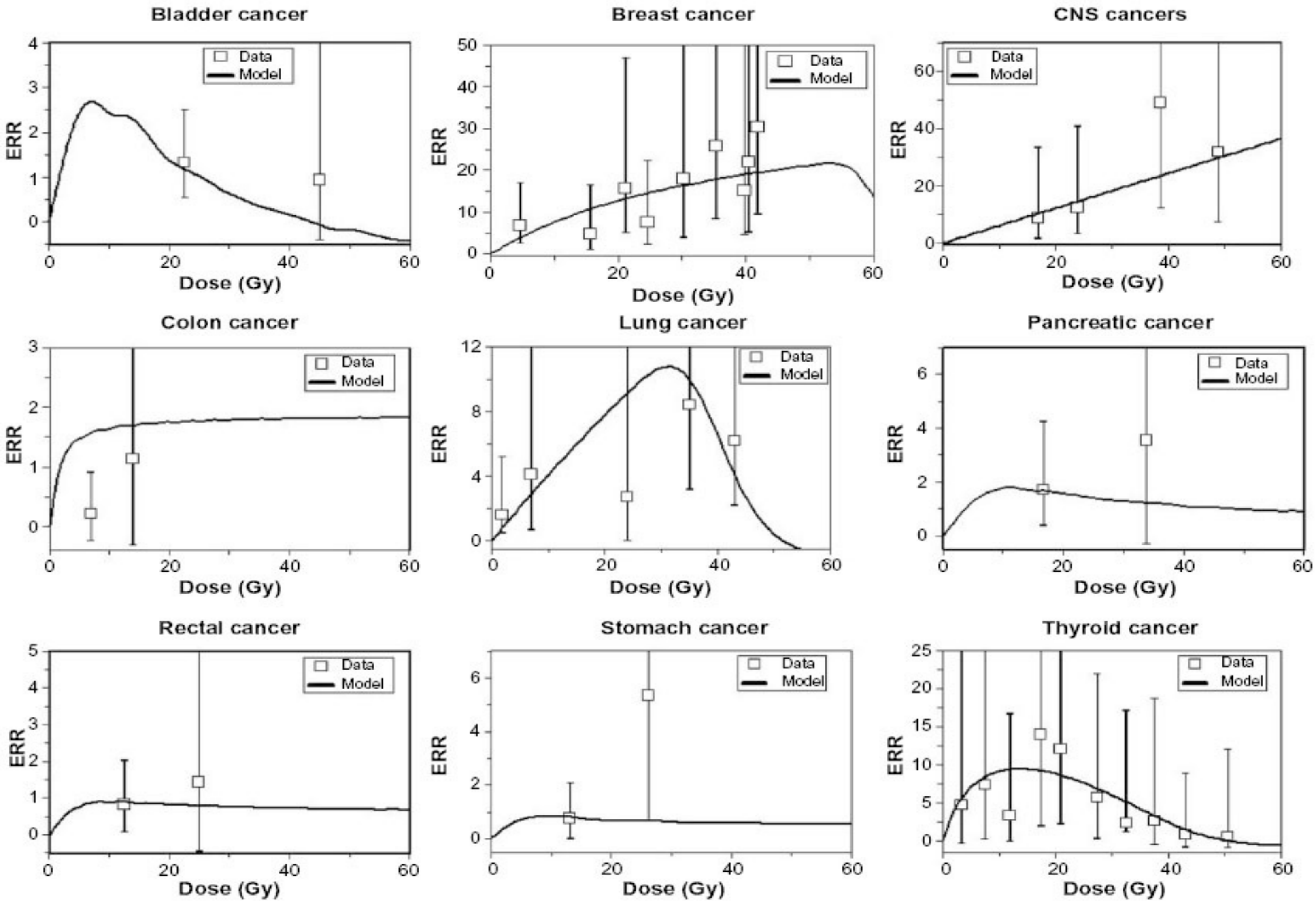
Youngtae Jeong et al. Cancer Discov 2017;7:86-101

Excess Relative Risk of Tumors after RT



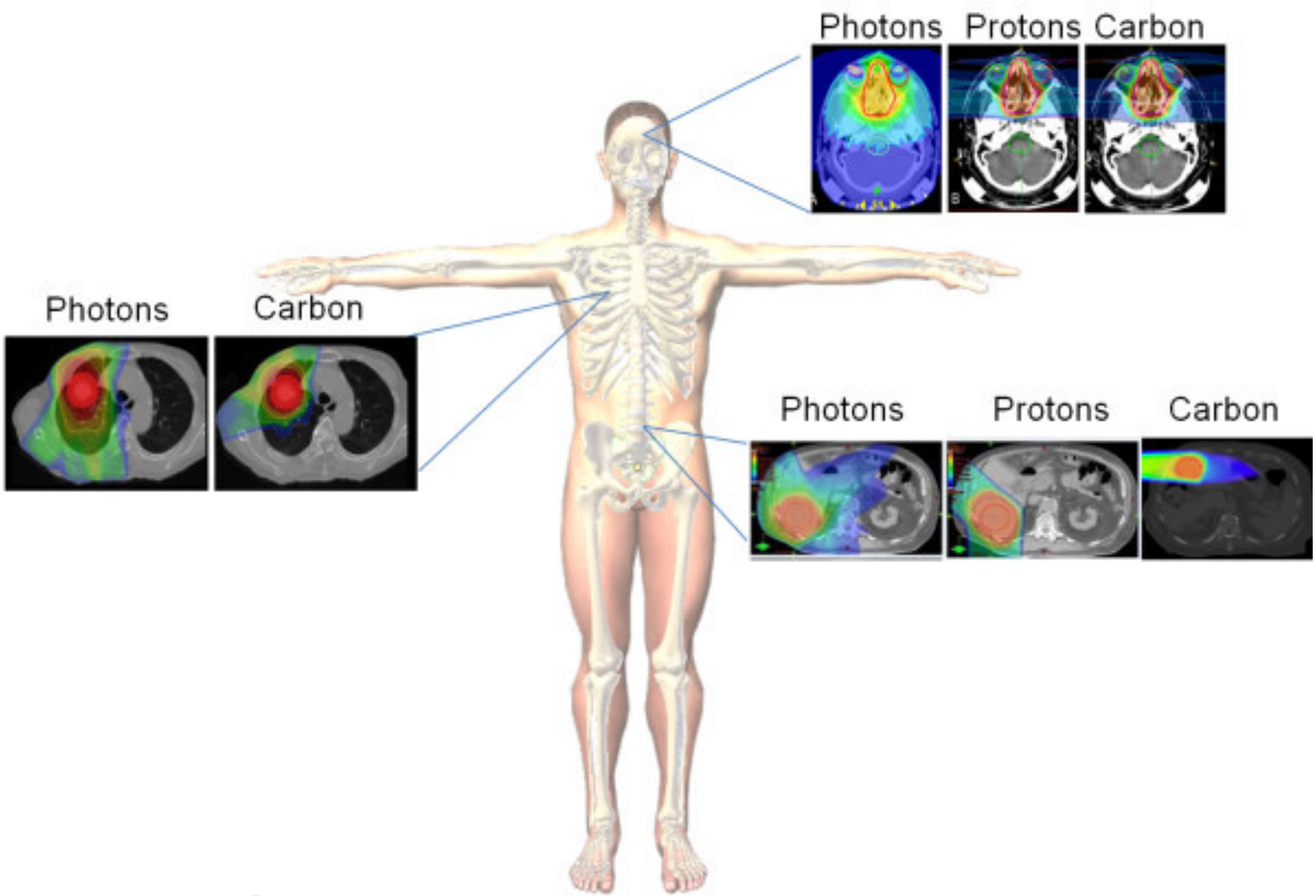
Ng and Shuryak, 2014

Excess Relative Risk of Second Cancer with High Dose Fx RT



Ng and Shuryak, 2014

Superior Dose Distribution of Carbon Ions Compared to Protons and Photons



Secondary Cancer Risks after RT

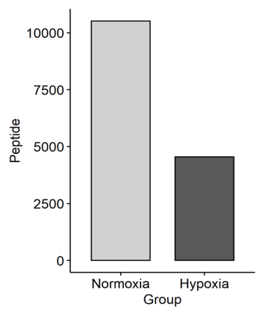
- Patient Age-younger more risk
- Genetic Risk Factors-?BRCA, ATM, p53, 6q21,PRDM1?
- Organ and Tissue Cite being Irradiated
- Dose and Volume of Tissue Irradiated and Modality

After tumor recurrence, second cancers are most common cause of treatment related death

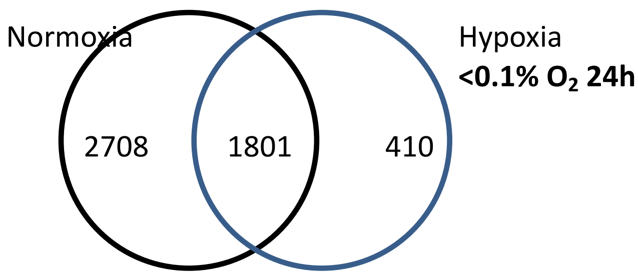
Field has mostly been risk assessments and time is right to move to more biology-based experiments

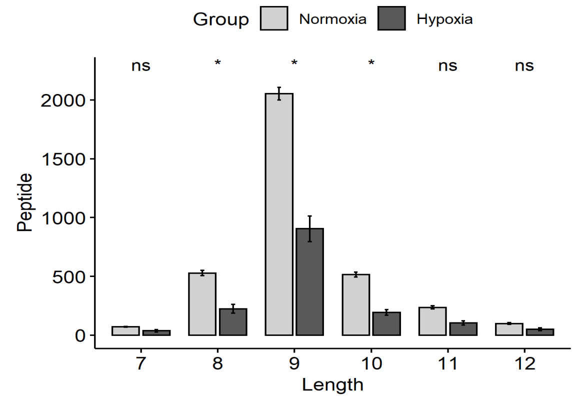
Hypoxia Leads to Decreased Antigen Presentation

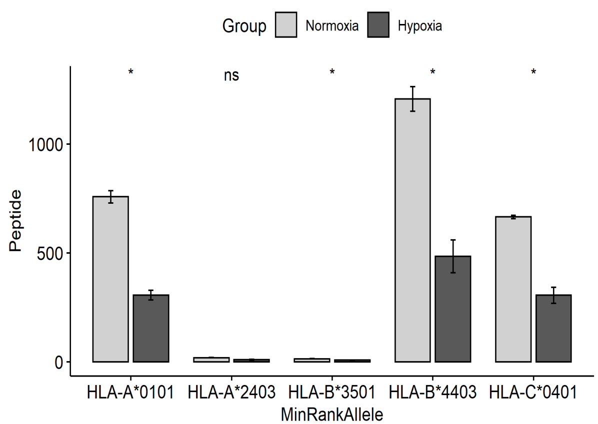
Total number of peptides



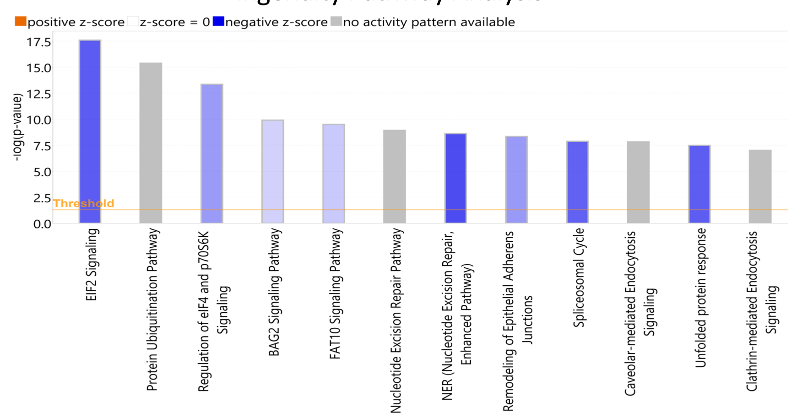
Specific peptides



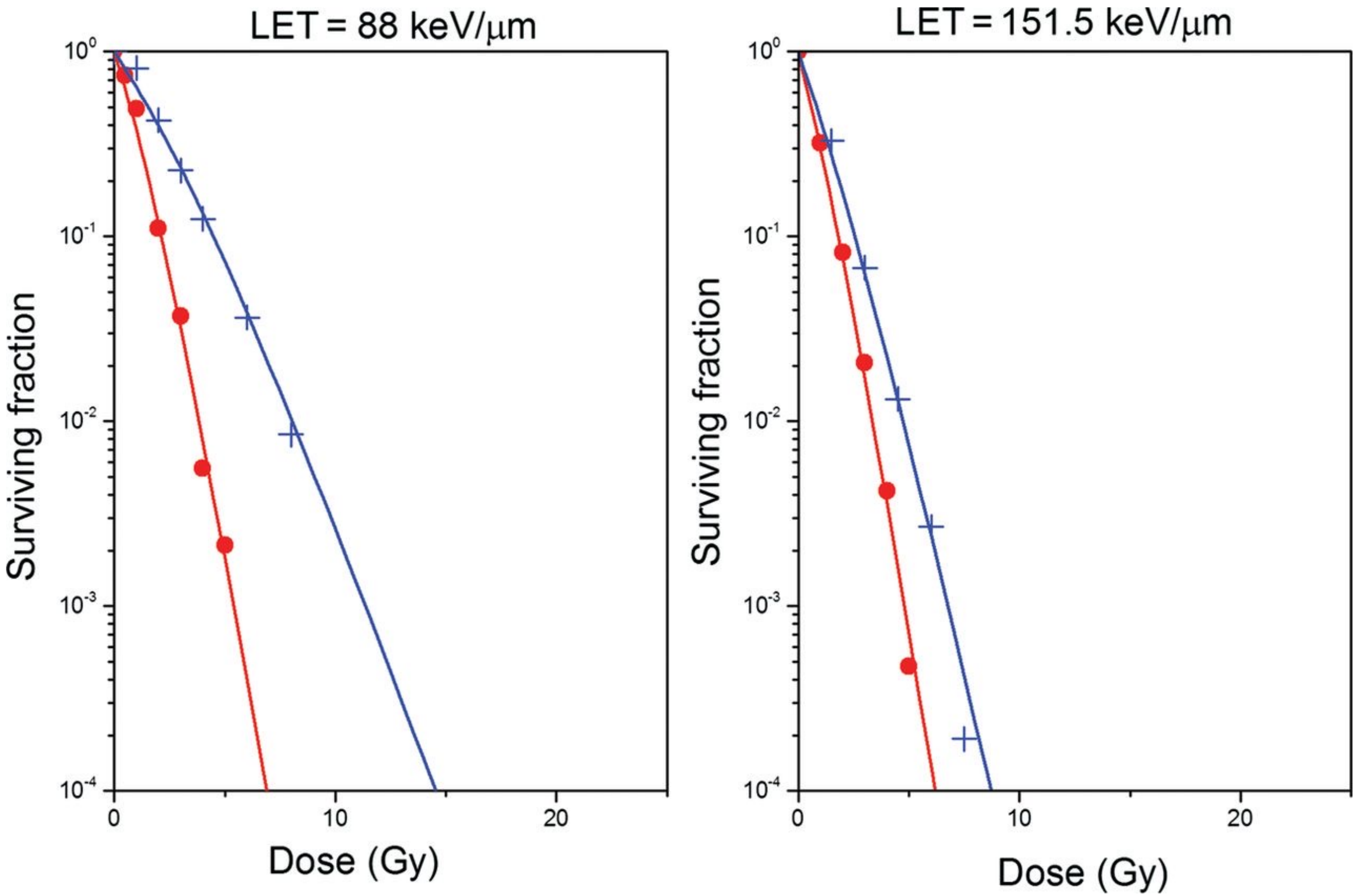




Ingenuity Pathway Analysis



Survival of Cells Irradiated with Carbon Ions in Oxic (red curves) and Hypoxic conditions (blue curves) for Two Different LETs



Antonovic L et al. J Radiat Res 2013;54:18-26