Importance of Radiobiology to Hadron Therapy

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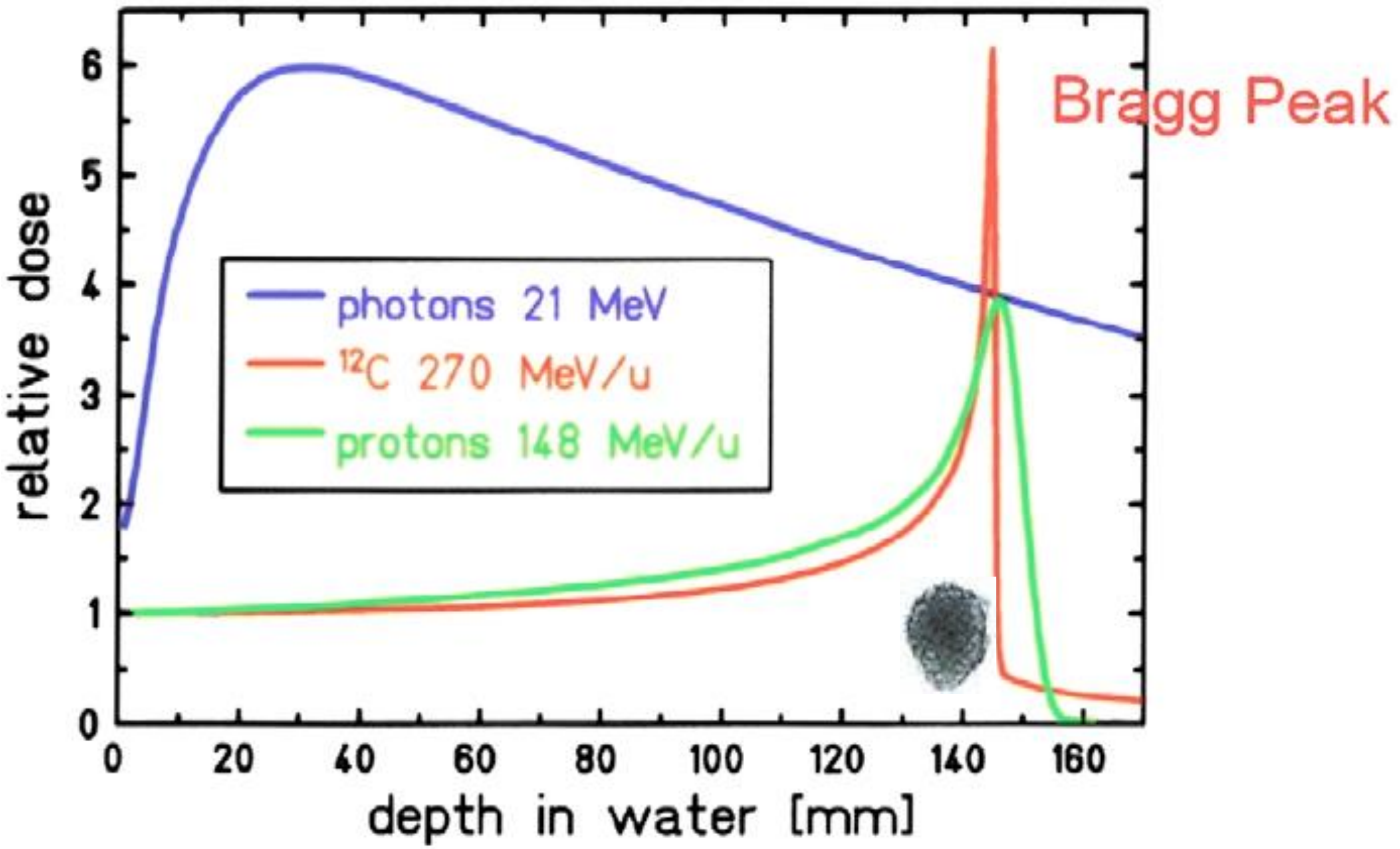
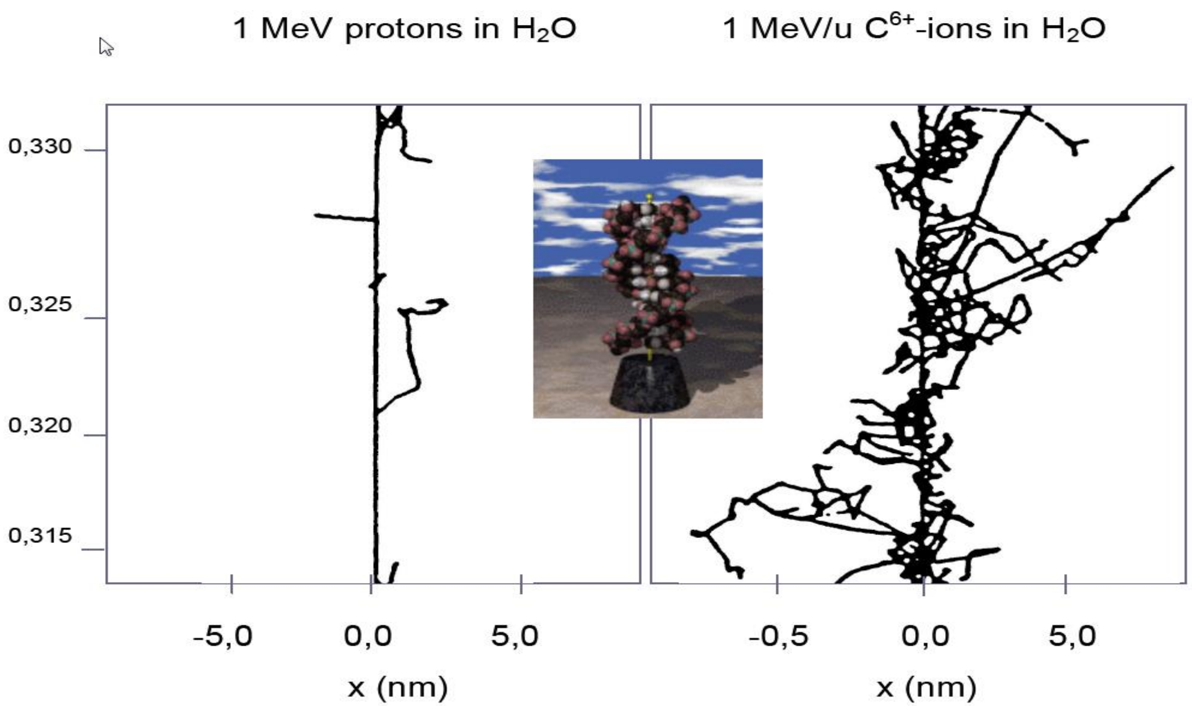
There is a strong rationale for the clinical benefit of proton and carbon therapies, but current evidence is limited

Therapy	Rationale for clinical benefit
Proton	▪ Deliver a higher, targeted radiation dose with decreased toxicity to surrounding tissue compared with photon therapy, especially near critical structures
Carbon	▪ Further increase target tissue damage with decreased secondary tissue affected compared with proton ▪ Specific potential benefit with intractable radio-resistant tumors

Dosimetry
Photons vs. Protons vs. Carbon



Carbon Ions Induce More Lethal Damage Per Unit Dose than Photons or Protons



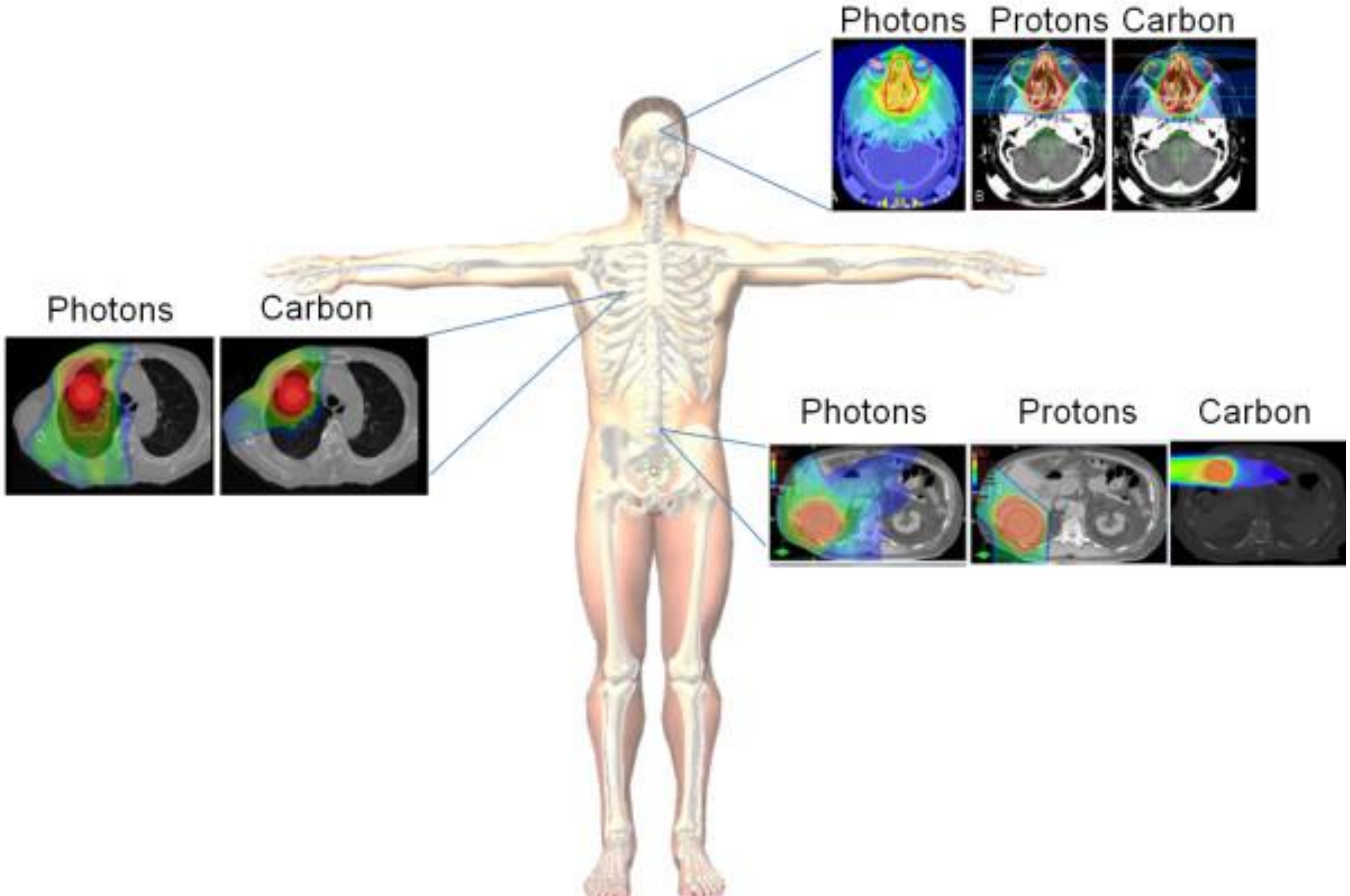
Increased Biological Effectiveness:

Relative Biological Effectiveness is 3 times protons

- Reduces # fractionations by ~ 2: greater patient throughput/compliance
- Countermands radio-resistance: non-repairable, double-strand breaks

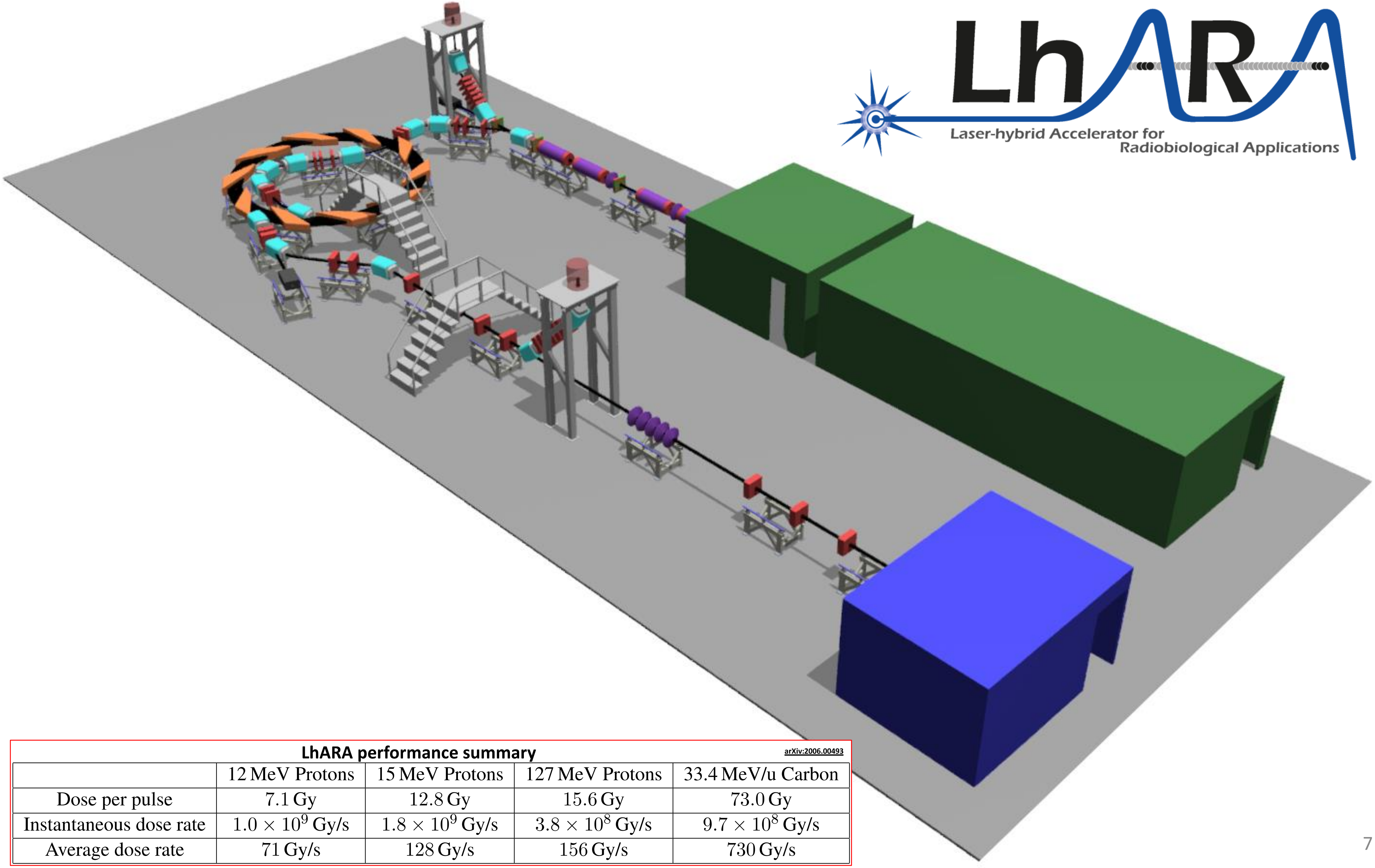
Production of positrons permits active monitoring using PET

Superior Dose Distribution and Biological Effectiveness of Carbon Ions Compared to Protons and Photons



Laser Driven Ion Accelerator for the UK

- Hadron Therapy while highly effective is expensive to build, run and service and requires greater technical experience
- High powered laser interaction with solid (foil) targets can generate significant magnetic and electric fields to accelerate ions
- State of the art currently is 2 digit MeVs at a high yield (10^{10}-10^{12}/pulse)
- Technology is still developing and needs work on energy bandwith, spatial profile uniformity, and repeat stability
- Major goal is to improve particle beam characteristics in a more reliable and streamlined manner that is more cost effective and efficient in a production type facility
- Ultimately, we want to develop a laser driven ion accelerator that can generate stable, well characterised and reliable beams that can be used for research and ultimately clinical purposes



LhARA performance summary

arXiv:2006.00493

	12 MeV Protons	15 MeV Protons	127 MeV Protons	33.4 MeV/u Carbon
Dose per pulse	7.1 Gy	12.8 Gy	15.6 Gy	73.0 Gy
Instantaneous dose rate	1.0×10^9 Gy/s	1.8×10^9 Gy/s	3.8×10^8 Gy/s	9.7×10^8 Gy/s
Average dose rate	71 Gy/s	128 Gy/s	156 Gy/s	730 Gy/s

Radiobiological Research Directions

-Examining relative biological effectiveness (RBE) of different ion species-What is the Proton RBE- 1.1 or varying?

-Advantages and disadvantages of different ways of beam delivery- FLASH, Minibeams, etc

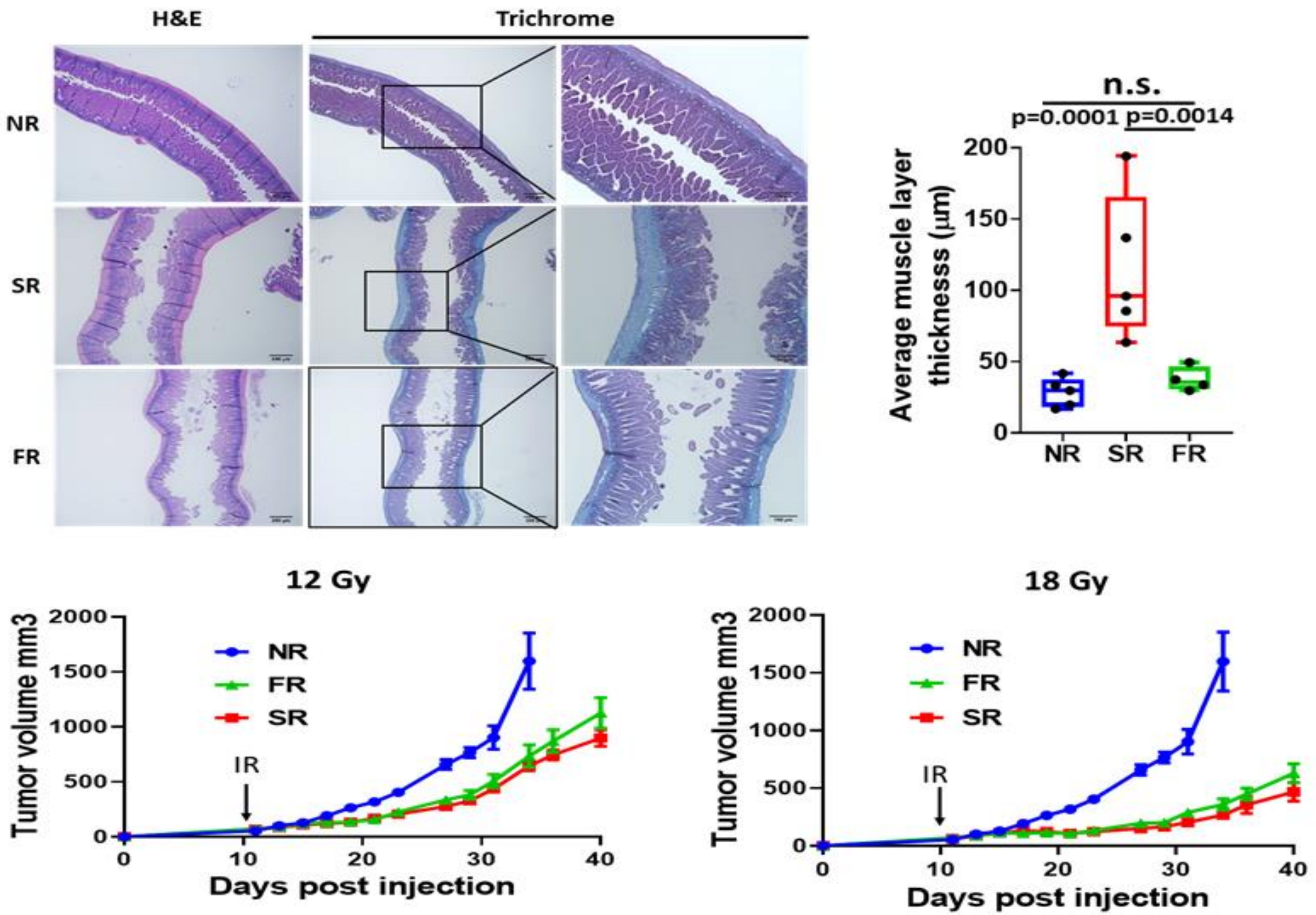
-Increased generation of tumour neoantigens for immune therapy

-Ion interaction with normal tissues-normal tissue tox

-Identifying genetic mutations where Ion beam is most effective- Nrf2/Keap1, Cancer Stem Celss

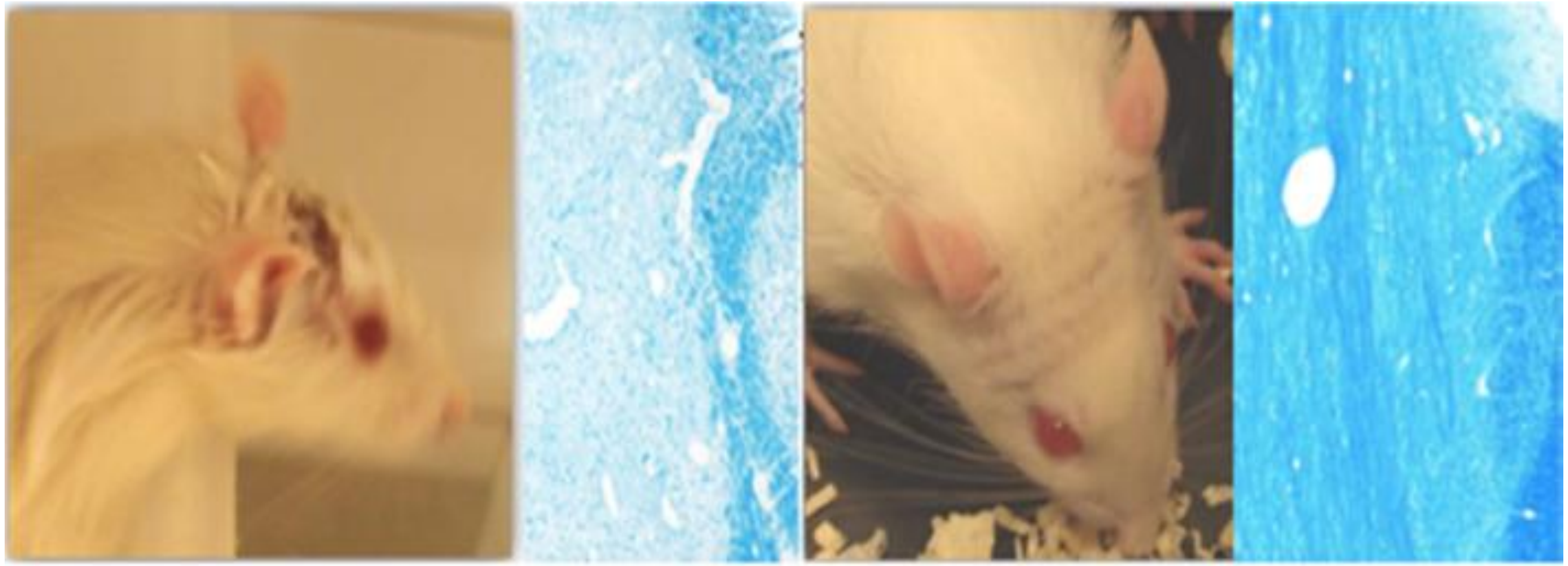
-Effect of Tumor Microenvironment on Ion Killing

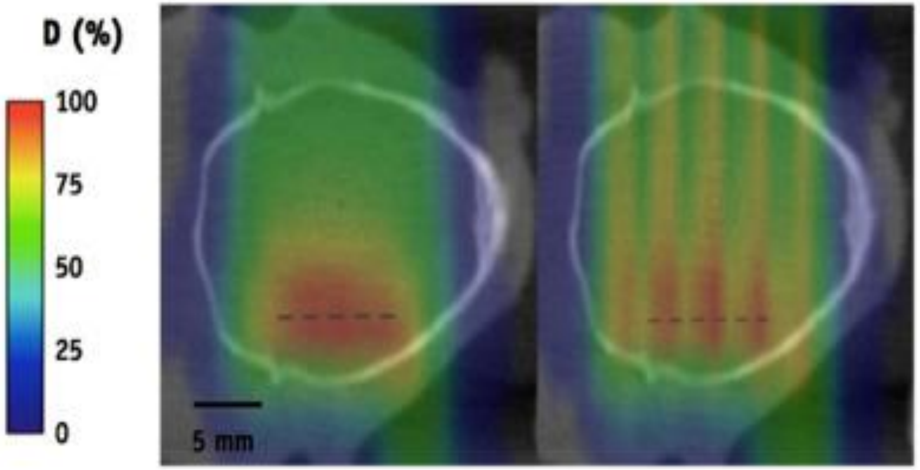
Flash-Proton Radiotherapy Highly Effective in Controling Pancreatic Tumor Growth and Reduces Normal Tissue Toxicity

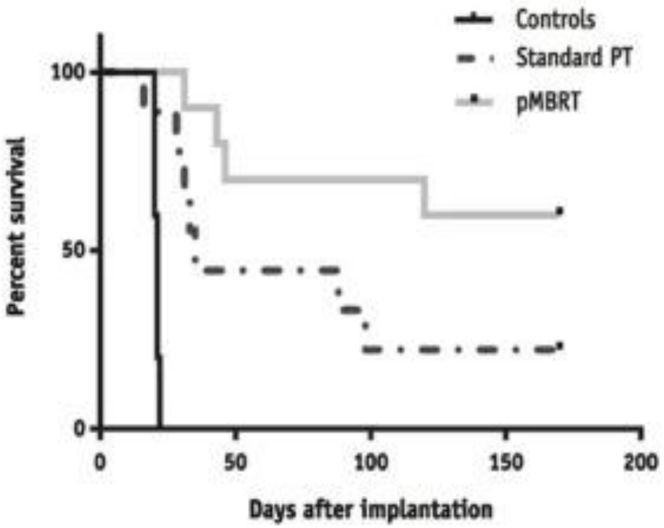


Koumenus et al, unplublished

Response to Proton Minibeam Irradiation

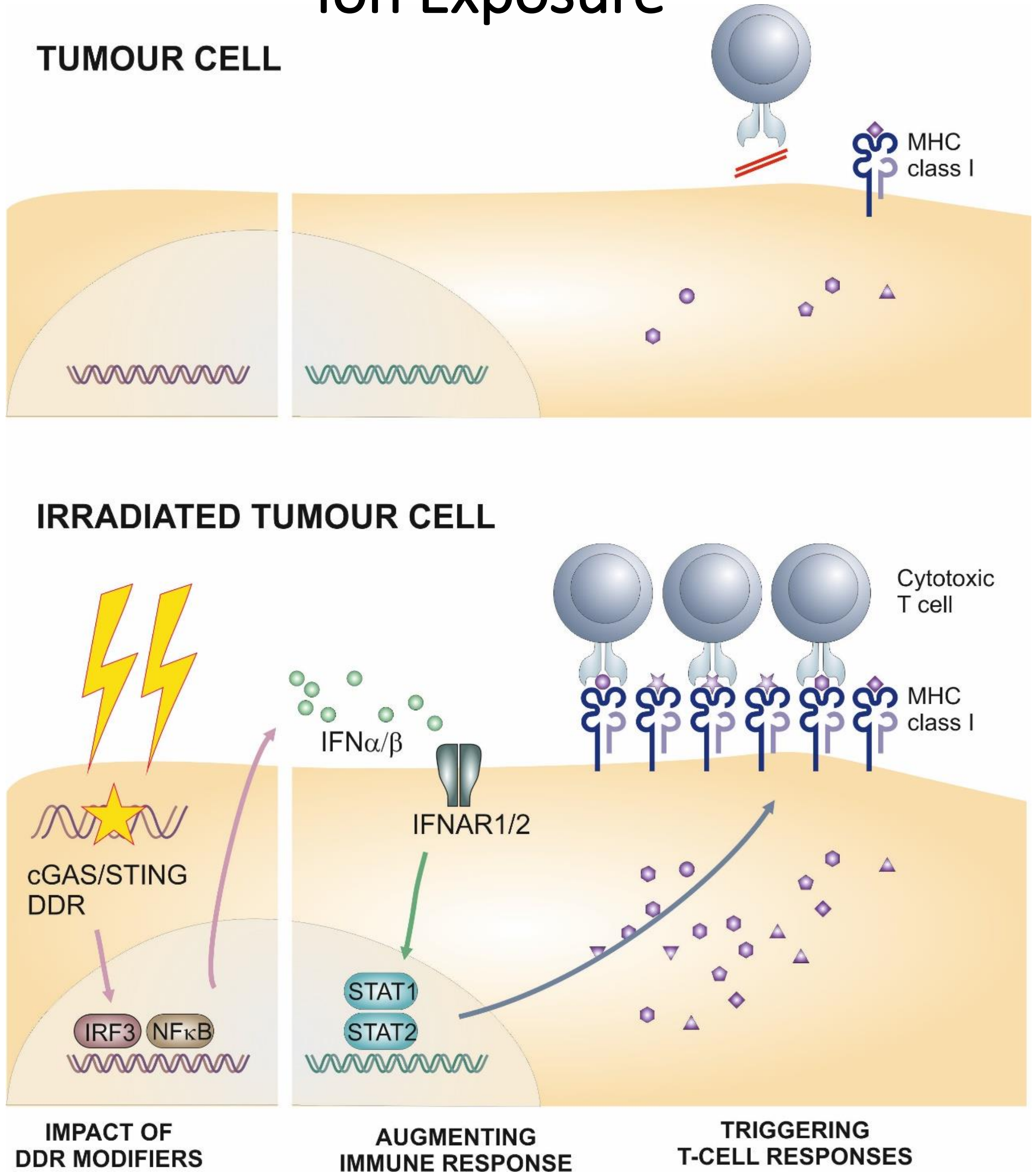






Br J Radiol. 2020 Mar; 93(1107)

Increasing Tumor Antigen/Neoantigen Formation after Heavy Ion Exposure

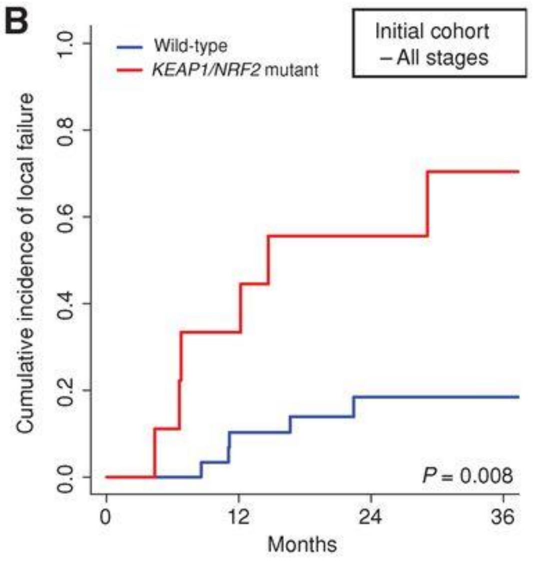


KEAP1/NRF2 Mutation Status Predicts Local Failure after Radiotherapy in Human NSCLC

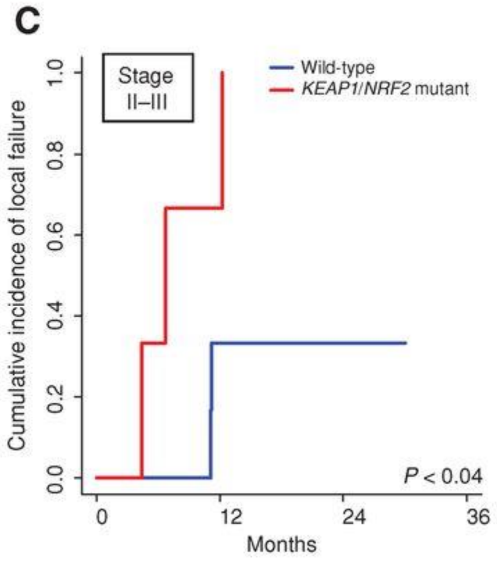
A

		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



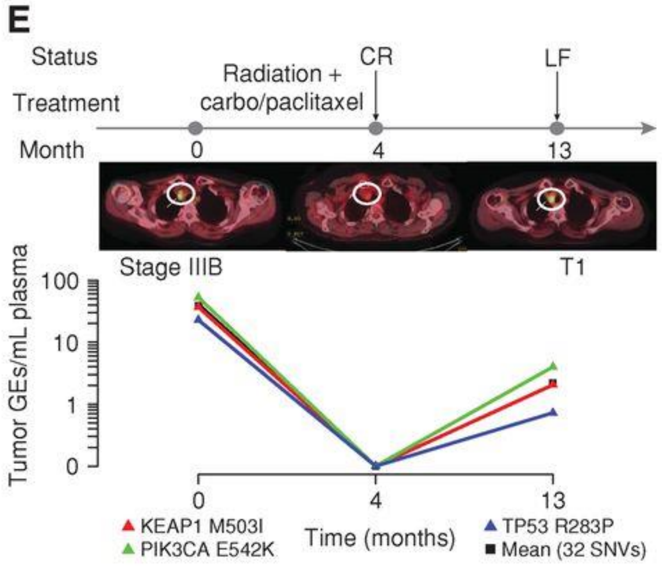
C



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



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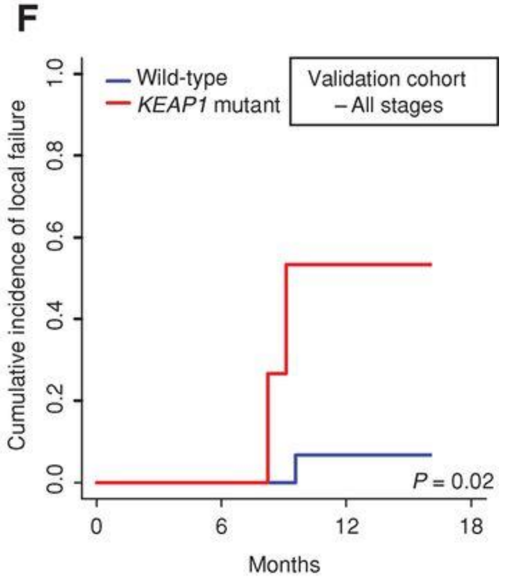
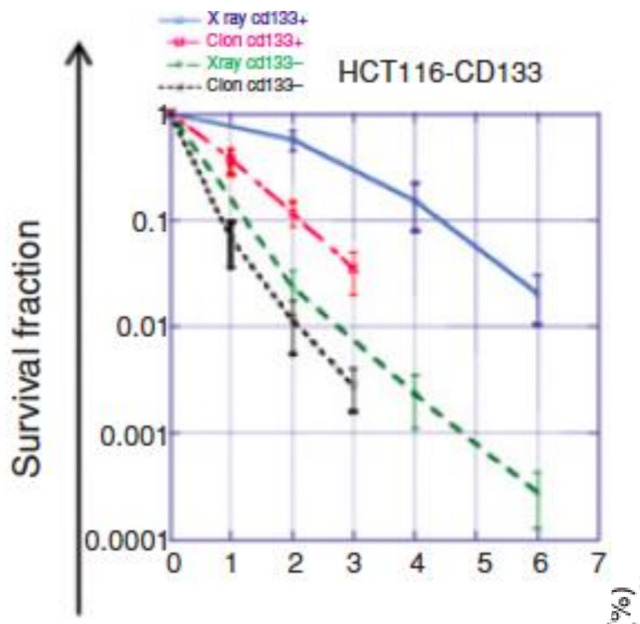


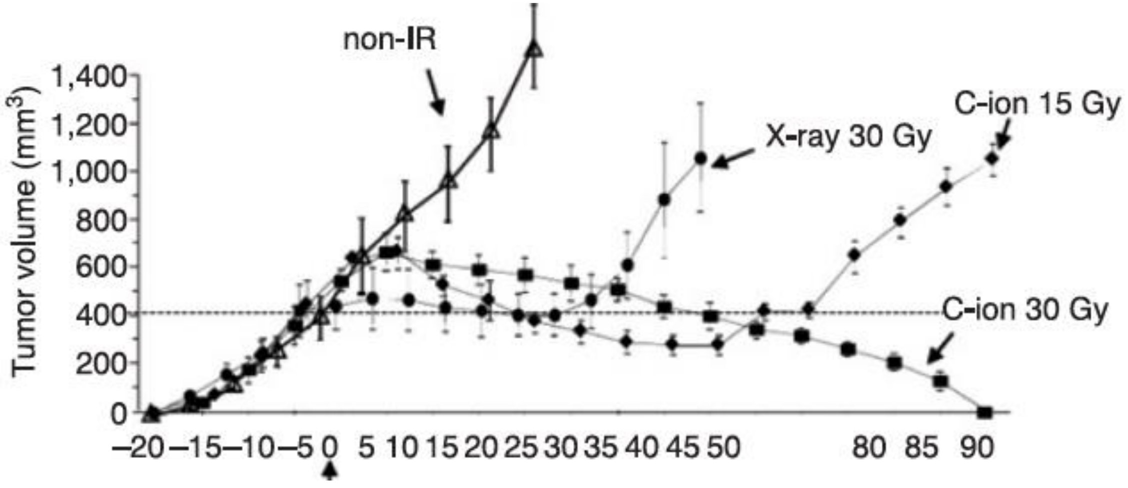
Youngtae Jeong et al. Cancer Discov 2017;7:86-101

Carbon is More Effective In Killing Cancer Stem Cells

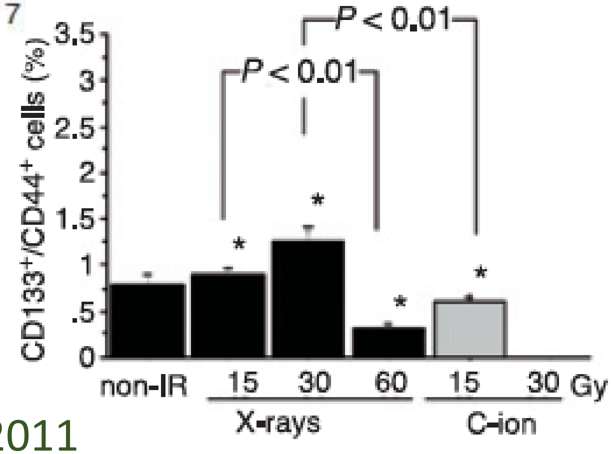
In vitro clonogenic survival

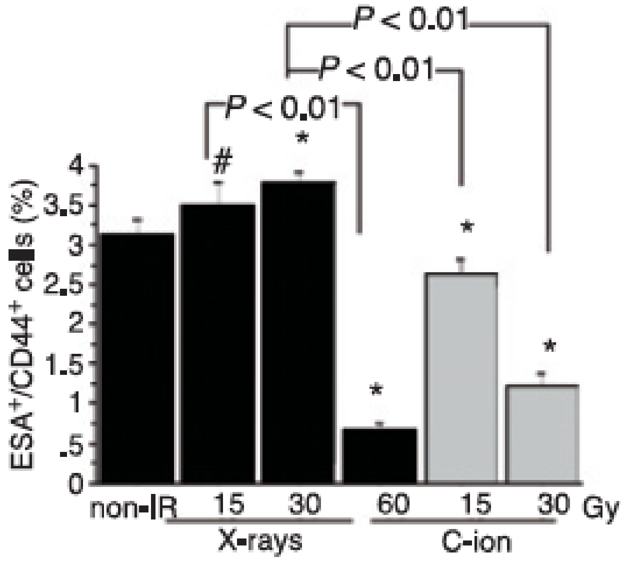


In vivo growth by beam type and dose



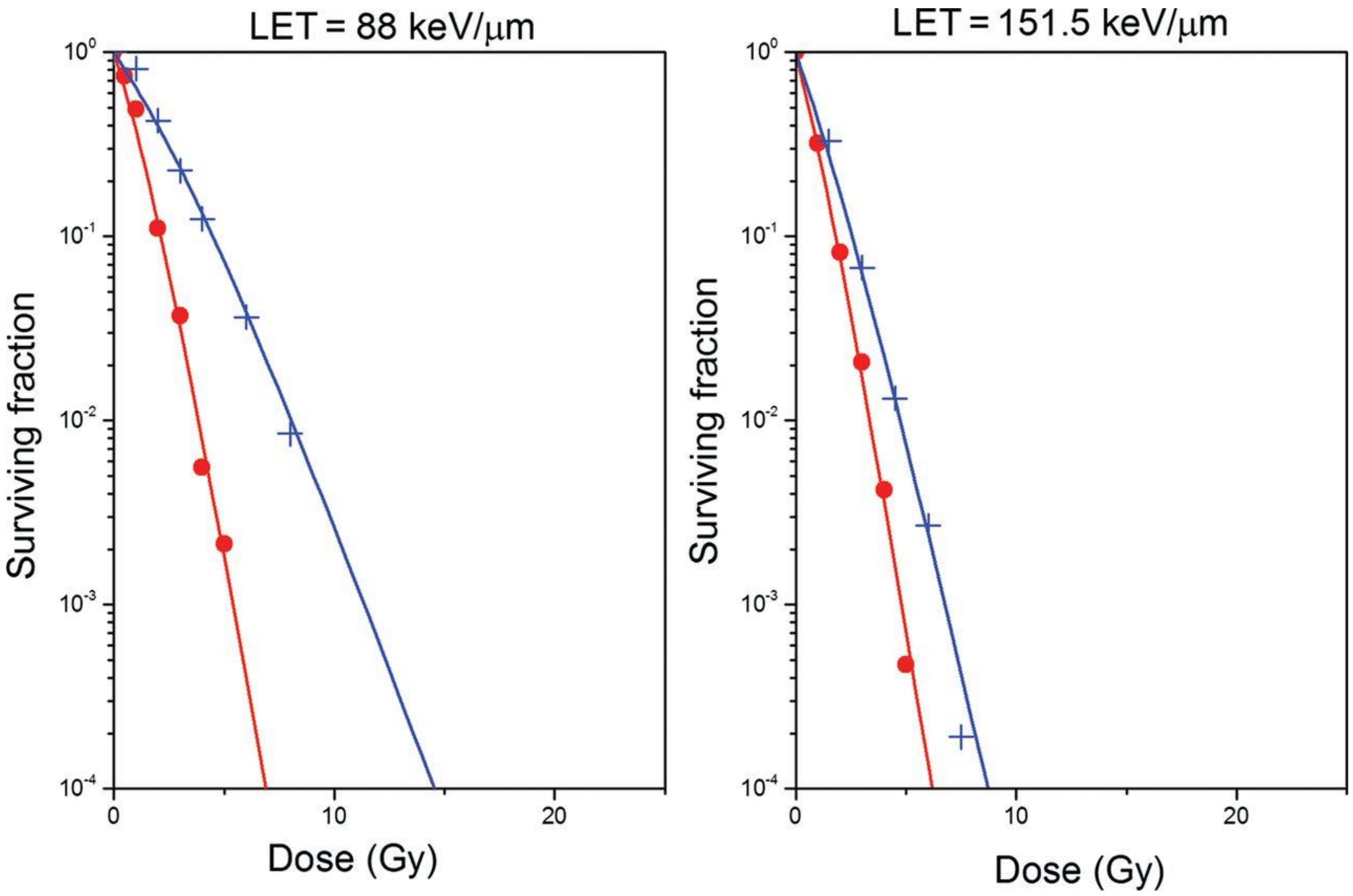
% putative CSC- like
***in vivo* after RT**



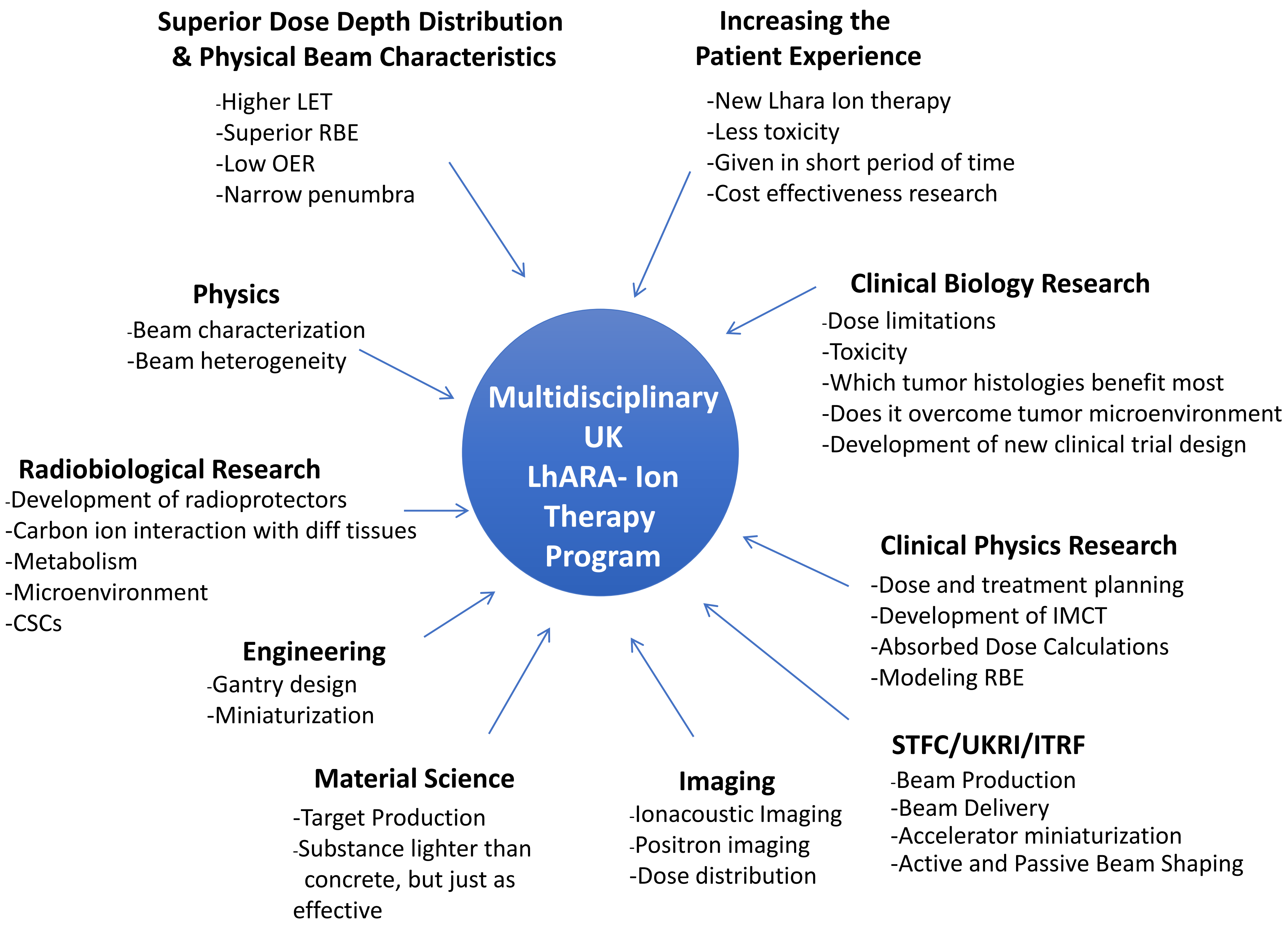


Cui X et al, Cancer Research 2011

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


Superior Dose Depth Distribution & Physical Beam Characteristics
-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
-Dose limitations
-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
-Development of radioprotectors
-Carbon ion interaction with diff tissues
-Metabolism
-Microenvironment
-CSCs
Clinical Physics Research
-Dose and treatment planning
-Development of IMCT
-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
Imaging
-Ionacoustic Imaging
-Positron imaging
-Dose distribution