LhARA Science Consultation Plan

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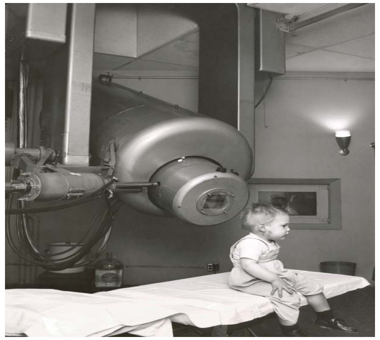
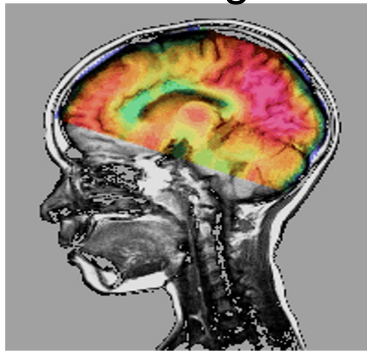
The Evolution of Technology to Increase Therapeutic Index

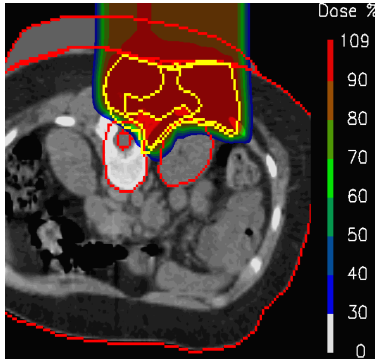
First Linac



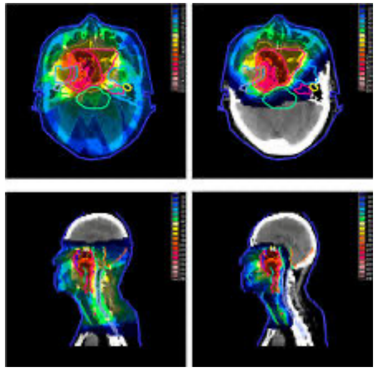
MRI & PET Scanning



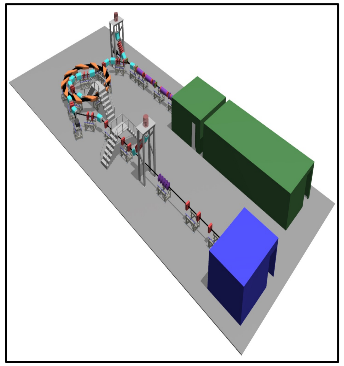
Proton Therapy



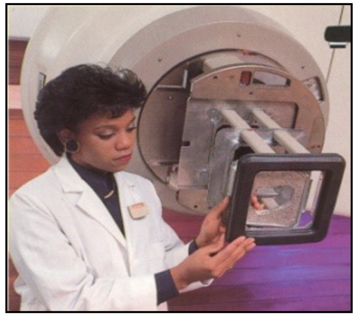
Hadron Therapy



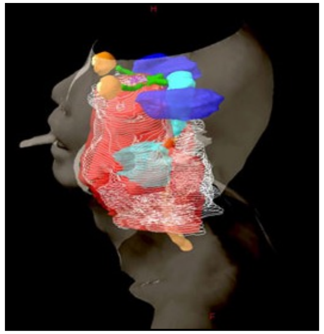
LhARA



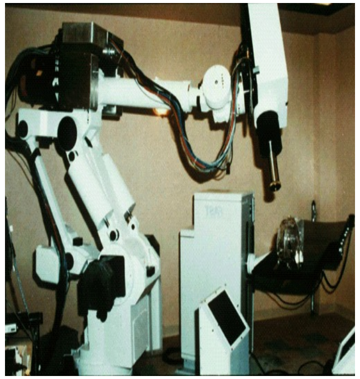
1960 1970 1980 1990 2000 2010 2020 2028



Shaped Electron Fields



Intensity Modulated Radiotherapy



SBRT

Adaptive Radiotherapy

Radiobiological Research Directions for LhARA

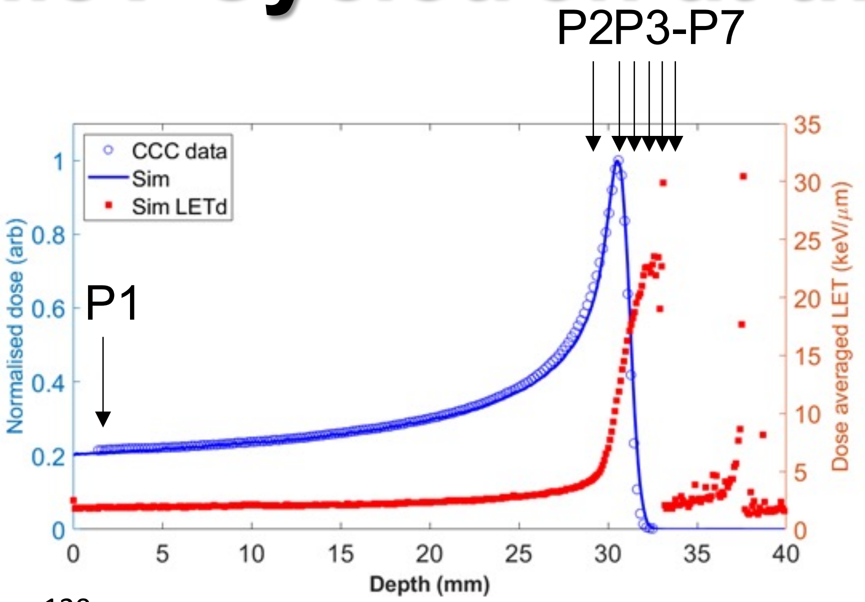
- Characterising the key biophysical characteristics of laser-driven ions compared to conventional ions by interrogating the response of different models. Specially those enriched in stem-cell populations.

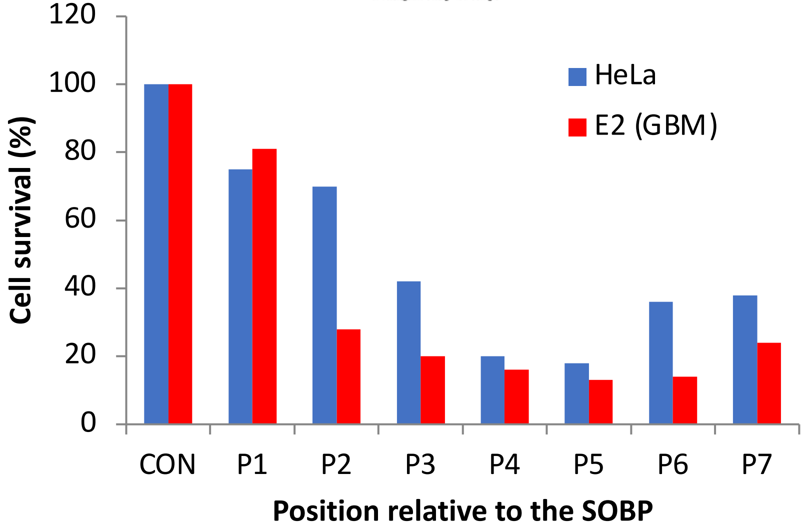
- Assessing the impact of oxygenation levels on DNA damage and immune responses in response to different temporal and spatial patterns.

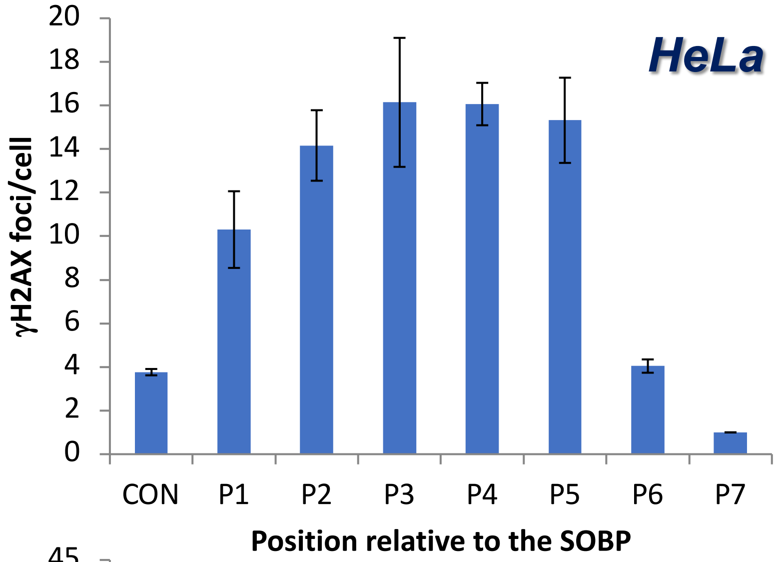
- Identify the impact of genetic mutations where ion beams would be effective.

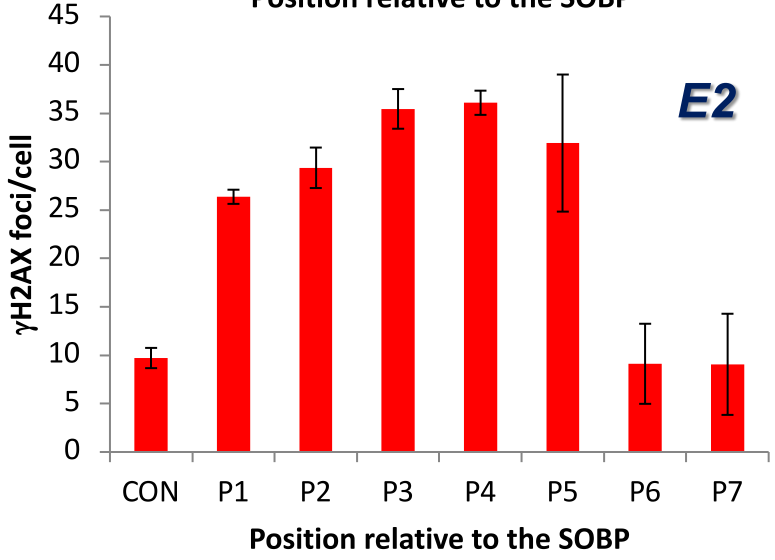
- Test the impact ultra-high dose-rate and spatially delivered ions on cell killing using in vivo mouse models and probe the impact of clinically relevant fractionation schedules.

Detailed Radiobiological Characterisation of the 60 MeV Cyclotron at the Clatterbridge Cancer Centre







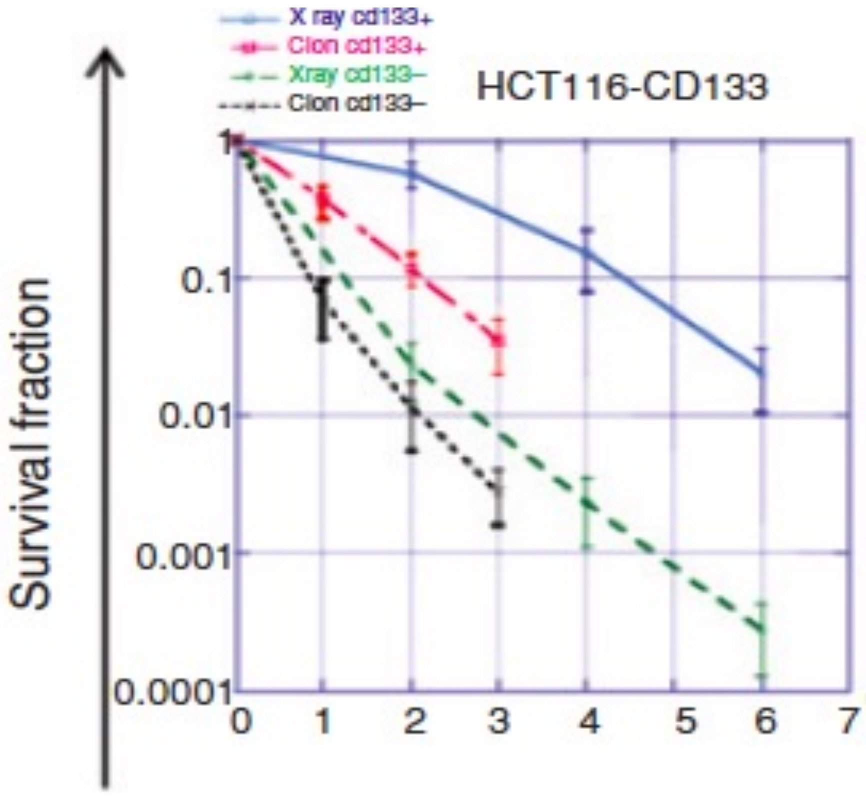


Cell survival and DNA damage/repair data will now be compared to the profile acquired using the MC40 cyclotron in Birmingham

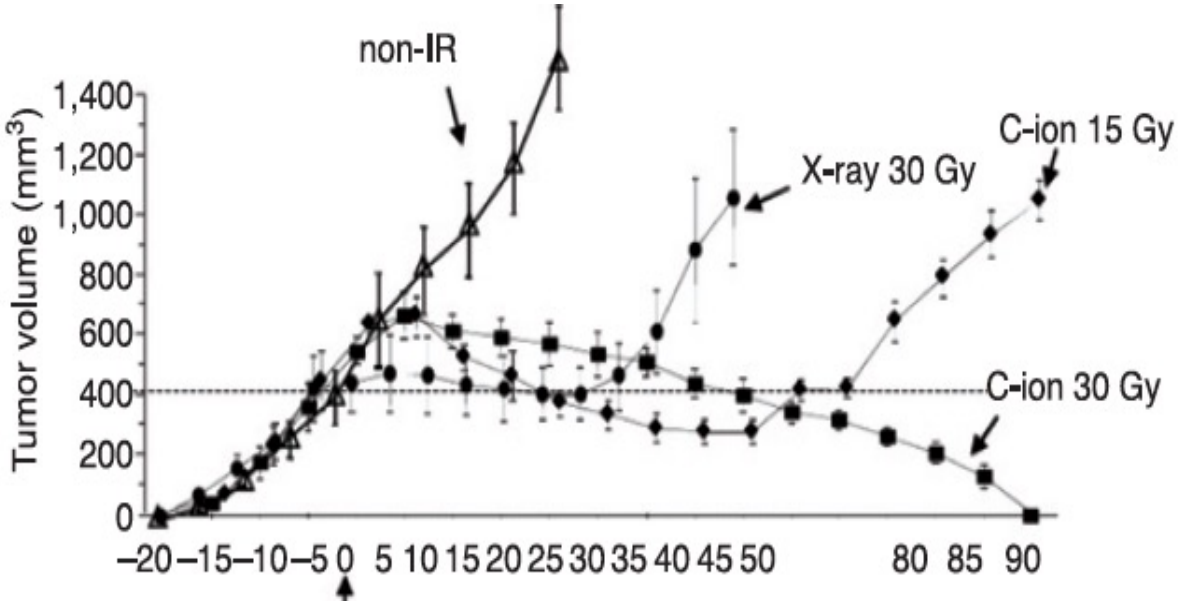
Aiyappa-Maudsley *et al., (Unpublished)*

Carbon Ions are More Effective In Killing Cancer Stem Cells

In vitro clonogenic survival

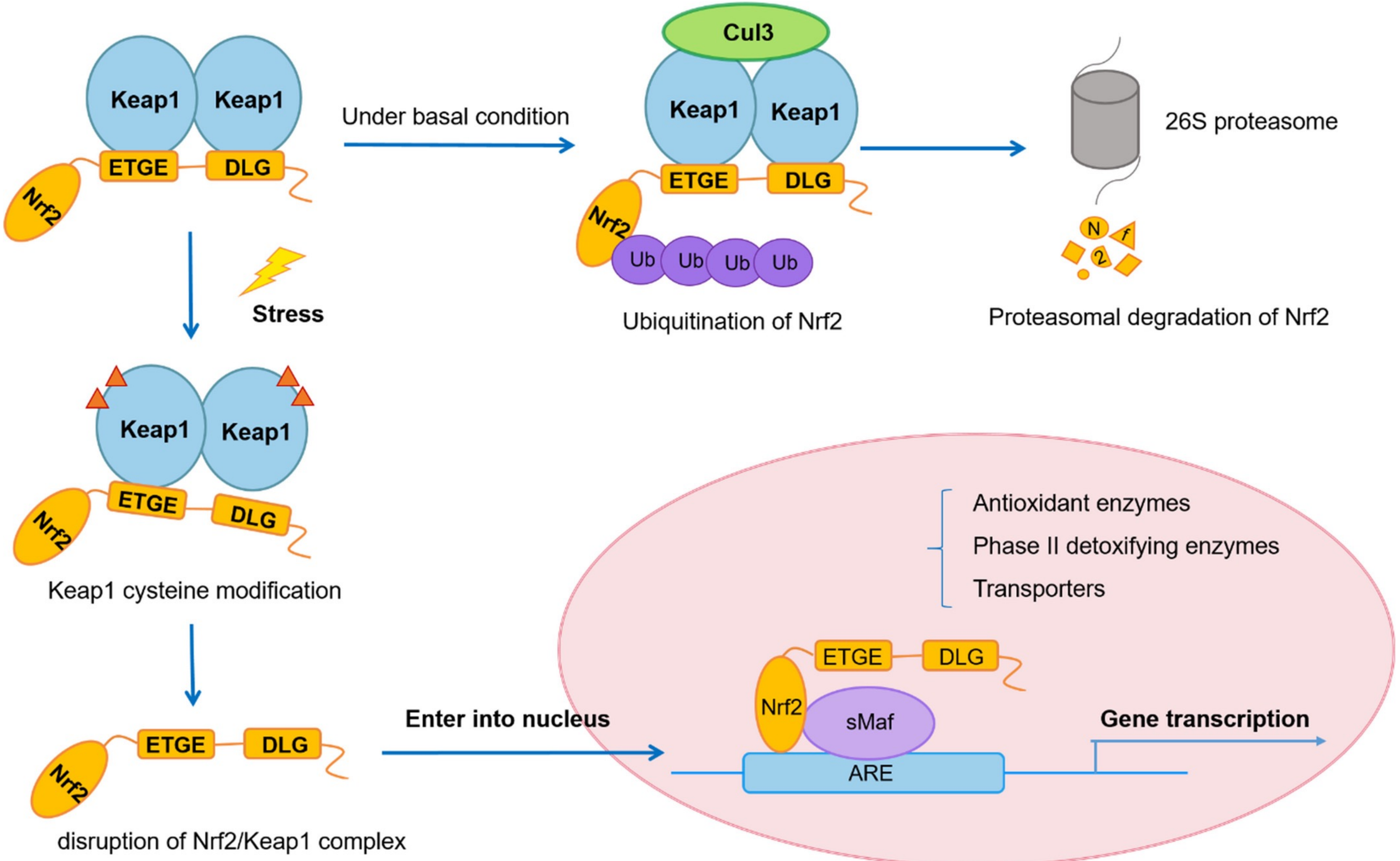


In vivo growth by beam type and dose



Cui X et al, Cancer Research 2011

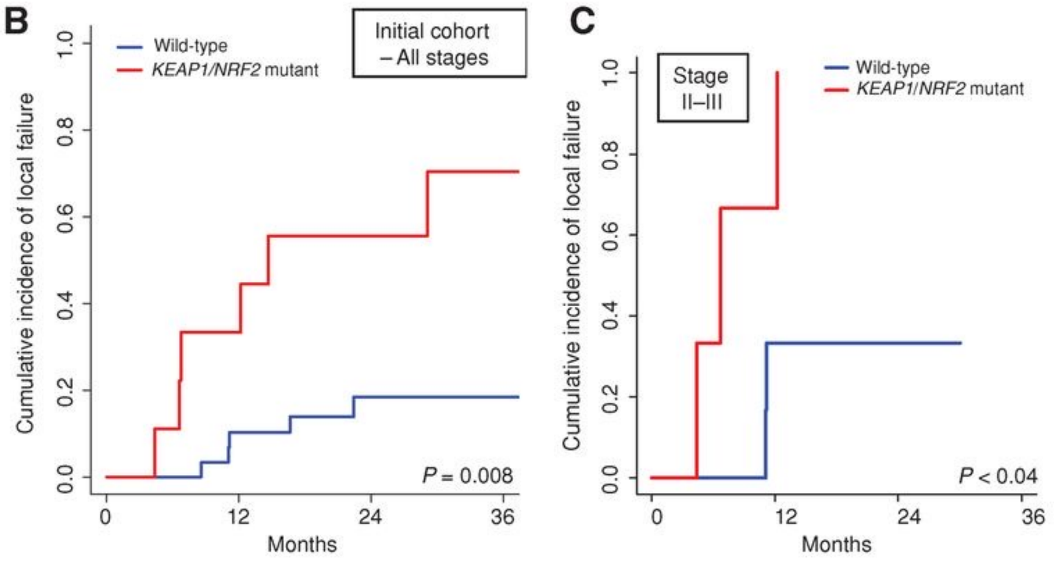
Genetic Pathways Potentially Benefiting from LhARA
Nrf2-Keap1 Pathway



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

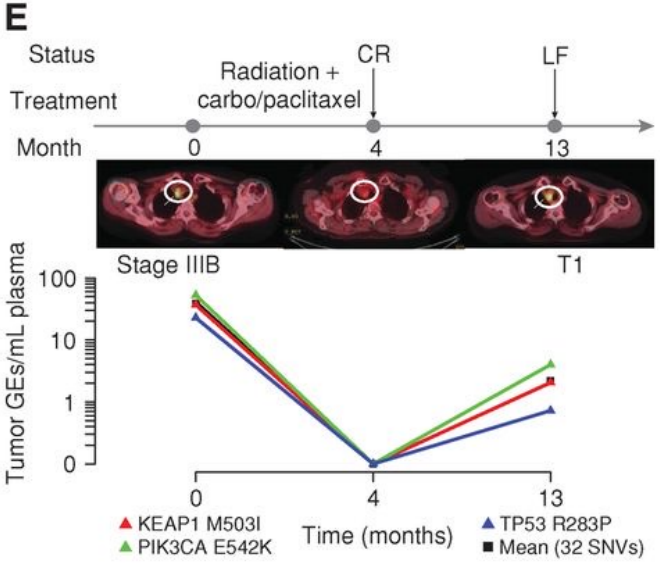
A

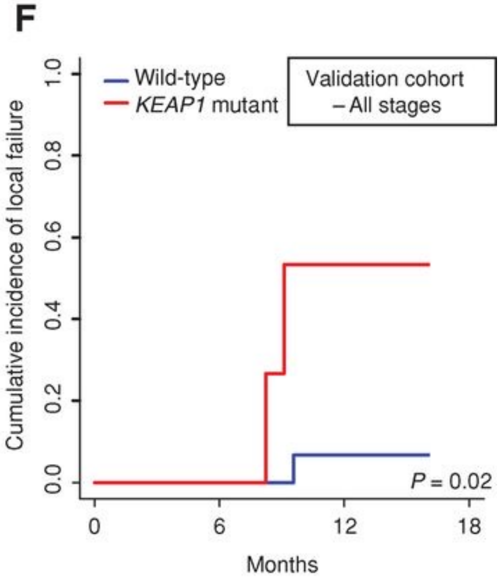
		Wild-type (n = 33)	*KEAP1/NRF2* mutant (n = 9)	P
Sex	M	9 (27%)	5 (56%)	0.23
	F	24 (73%)	4 (44%)	
Median age, years (range)		70 (42–91)	66 (56–91)	0.45
Median follow-up, mo. (range)		24 (6–53)	25 (7–63)	0.47
Histology	SCC	5 (15%)	1 (11%)	0.85
	Adenoca	25 (76%)	7 (78%)	
	Other	3 (9%)	1 (11%)	
Stage	I	22 (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%)	



D

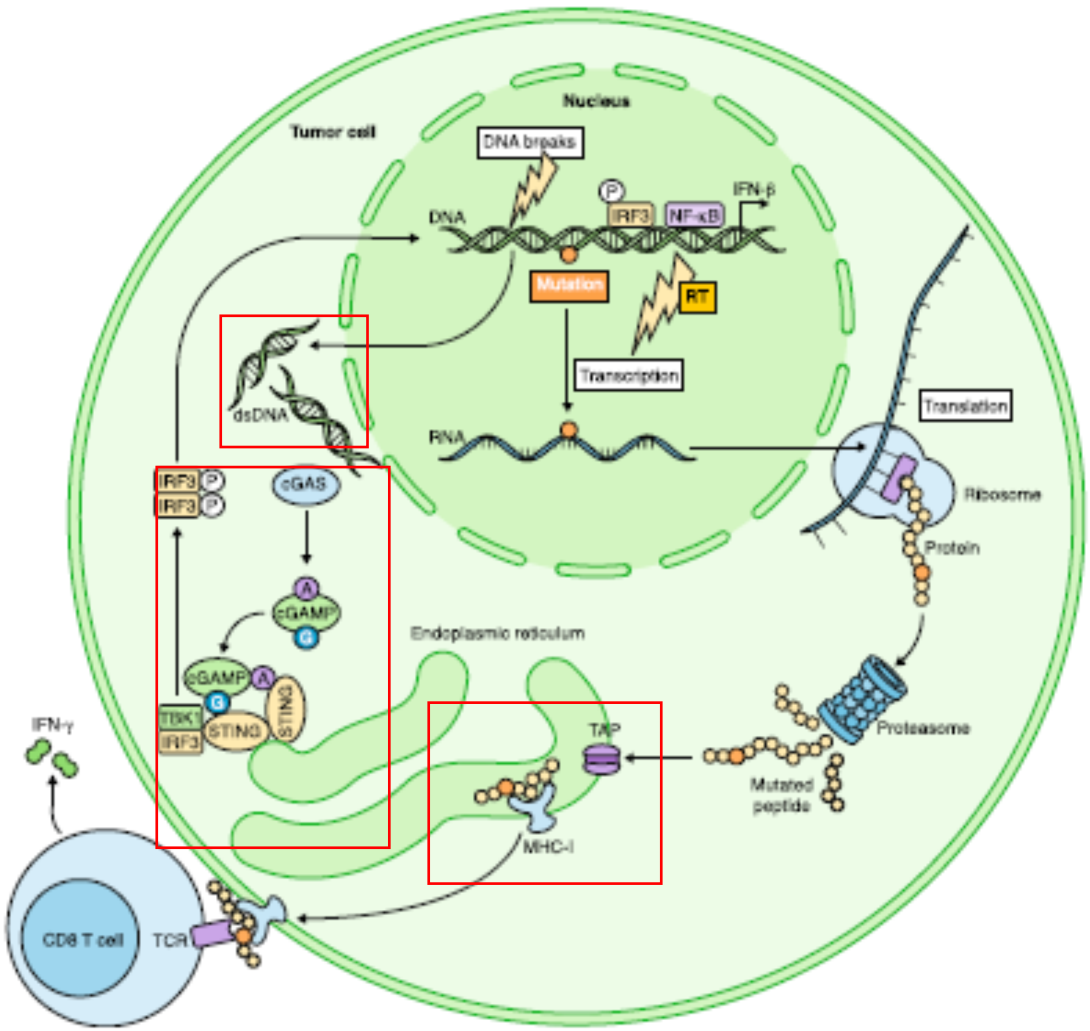
Patient	Age	Sex	Stage	*KEAP1* mutations: Tumor variant	*KEAP1* mutations: ctDNA variant (%AF)
T1	56	F	IIIB	M503I	M503I (3.38%)
T2	56	F	IIIB	R483C	R483C (0.44%)
T11	46	F	IIA	Wild-type	Wild-type
T13	81	F	IB	Wild-type	Wild-type
T14	78	M	IB	Wild-type	Wild-type
T23	51	F	IIIA	Wild-type	Wild-type
T35	48	F	IIIB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





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

Immune Effects of RT

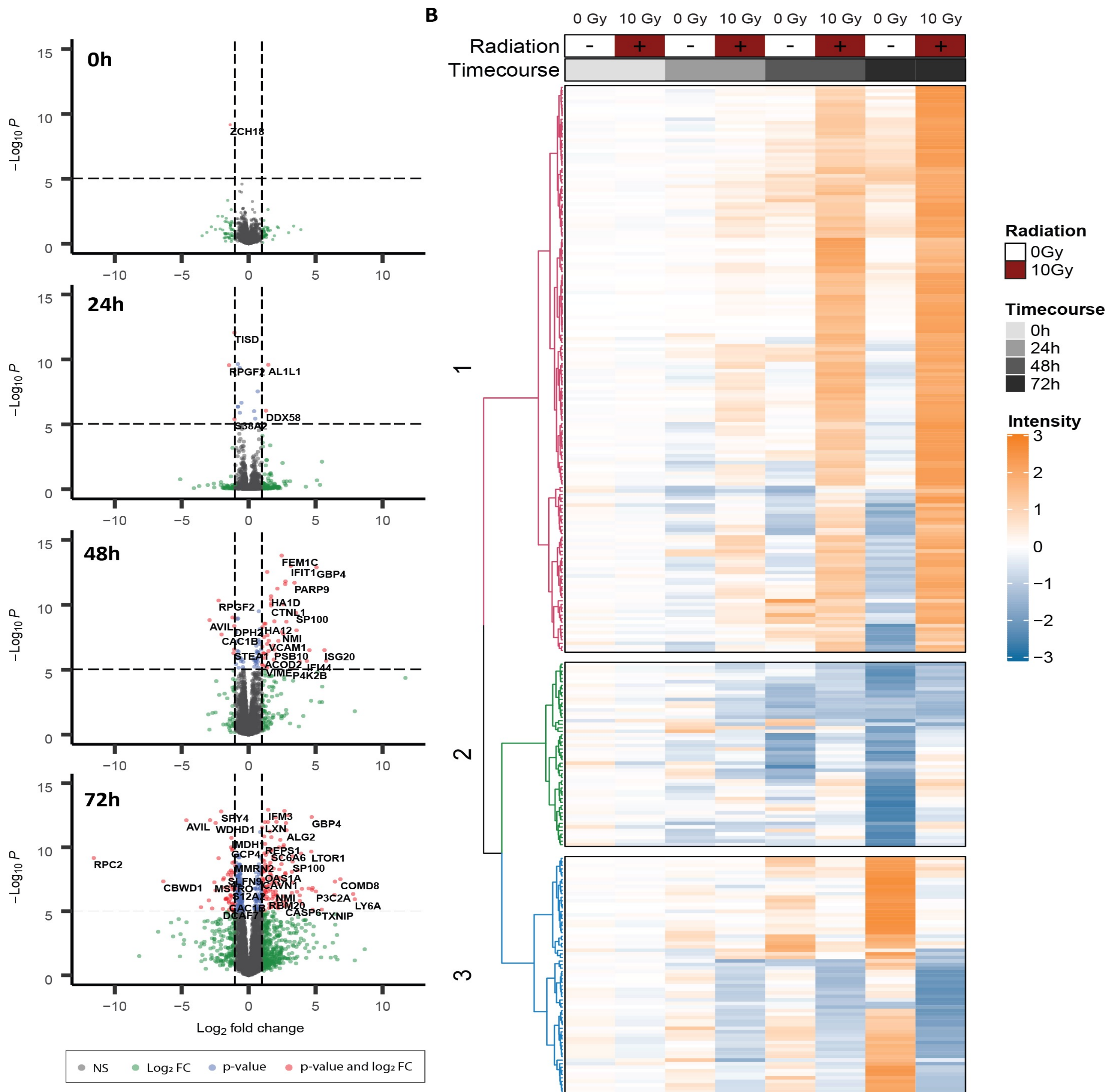


After RT:

- DNA damage results in genome instability and an increase in cytosolic DNA
- Cytosolic DNA can activate the cGAS/STING pathway which results in the transcription of type I interferons

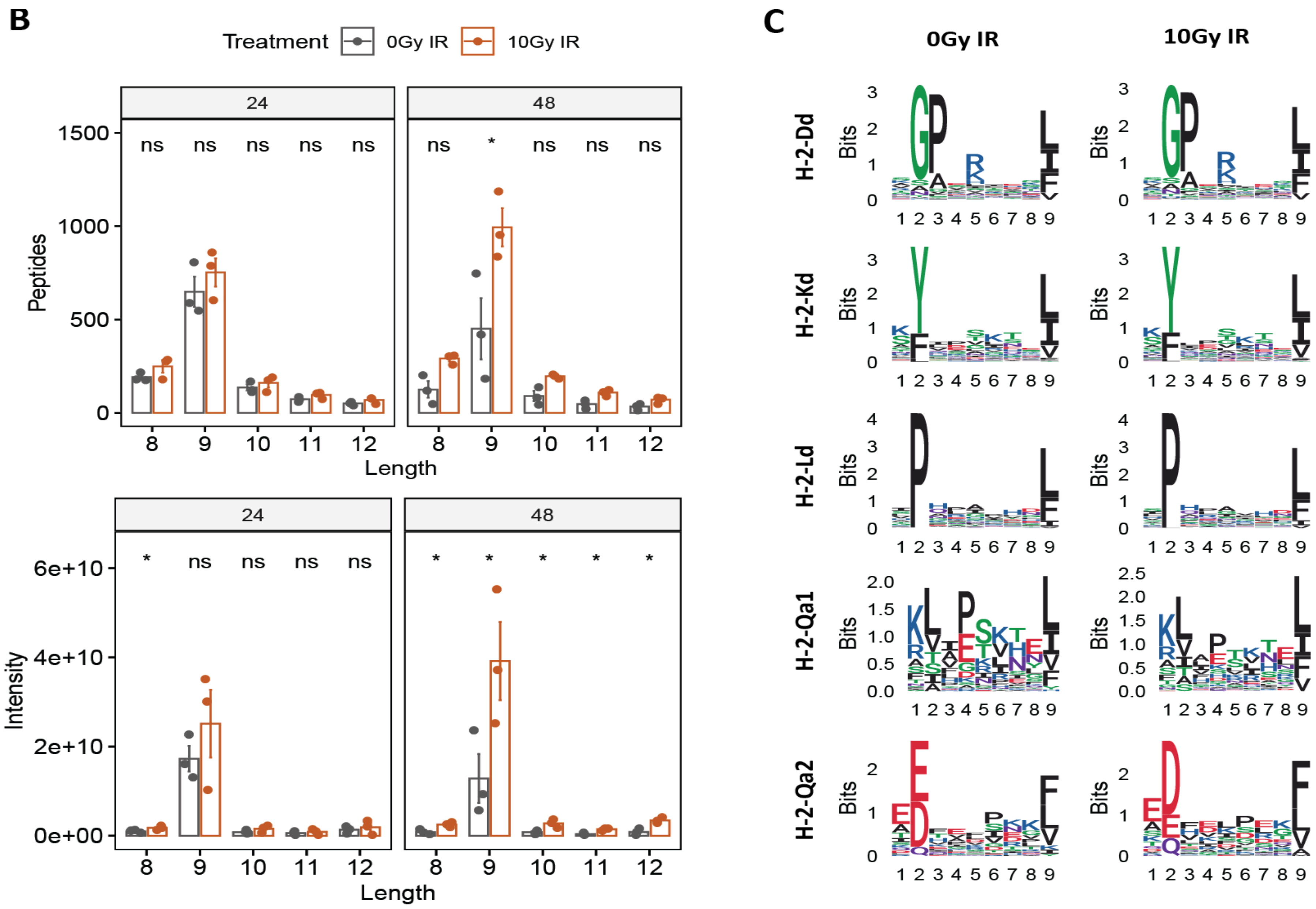
Lhuillier et al. Genome Medicine (2019)
Lhuillier et al. J Clin Invest (2021)

Analysis of Proteomic Changes after RT



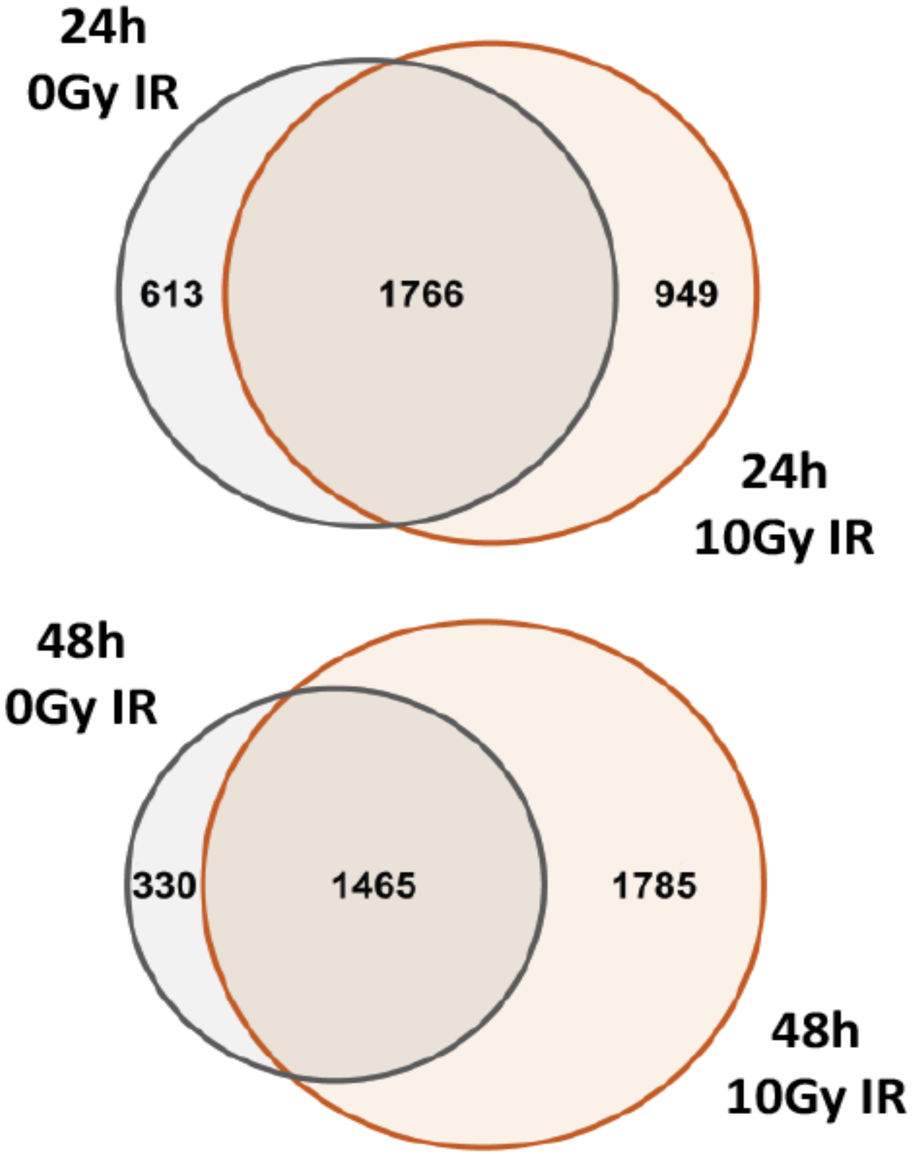
Tailor et al, 2022

Changes in Immunopeptidome after RT



Tailor et al, 2022

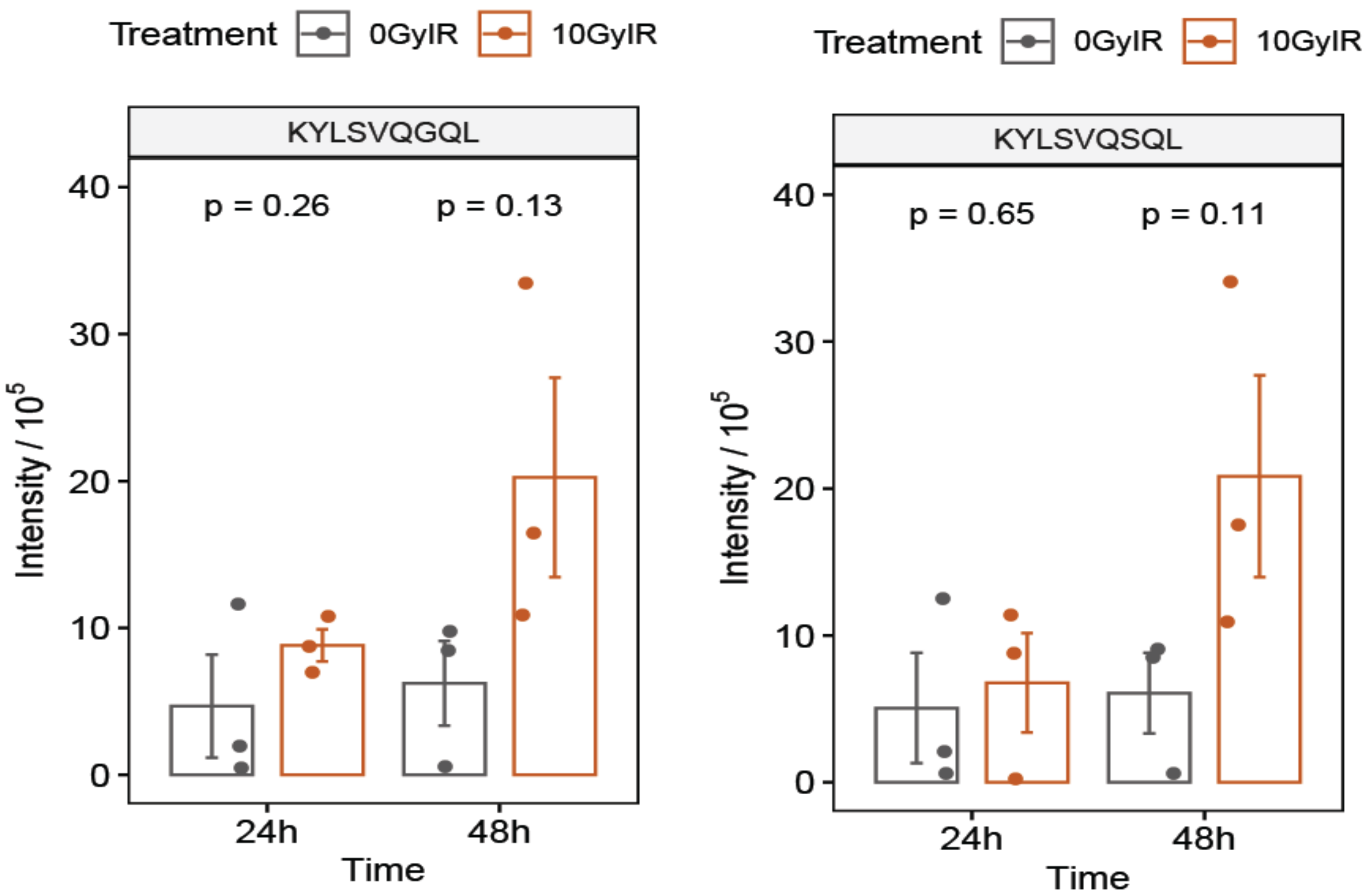
A Doubling of Peptides Bound to MHC after RT



Tailor et al, 2022

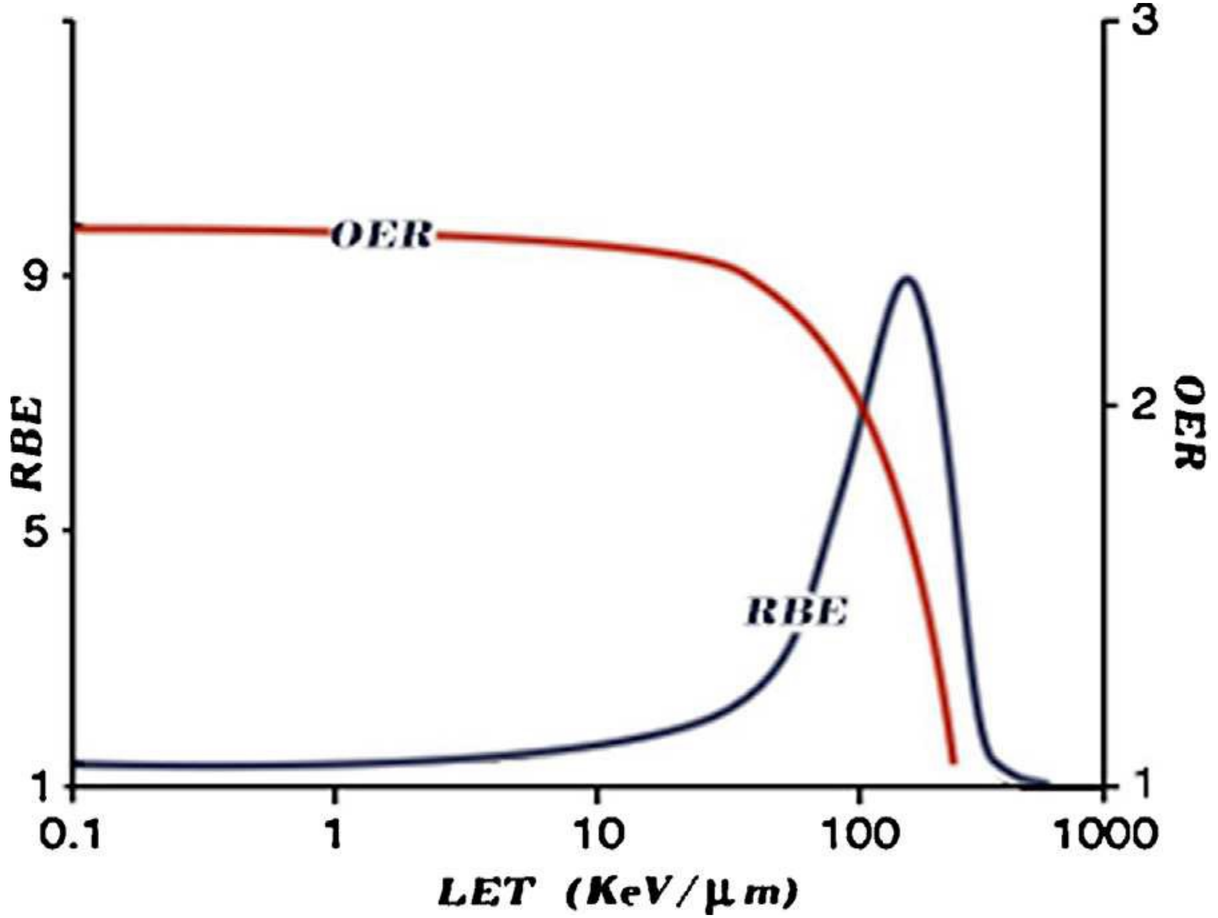
Example of a Unique Radiation Induced Peptide

E



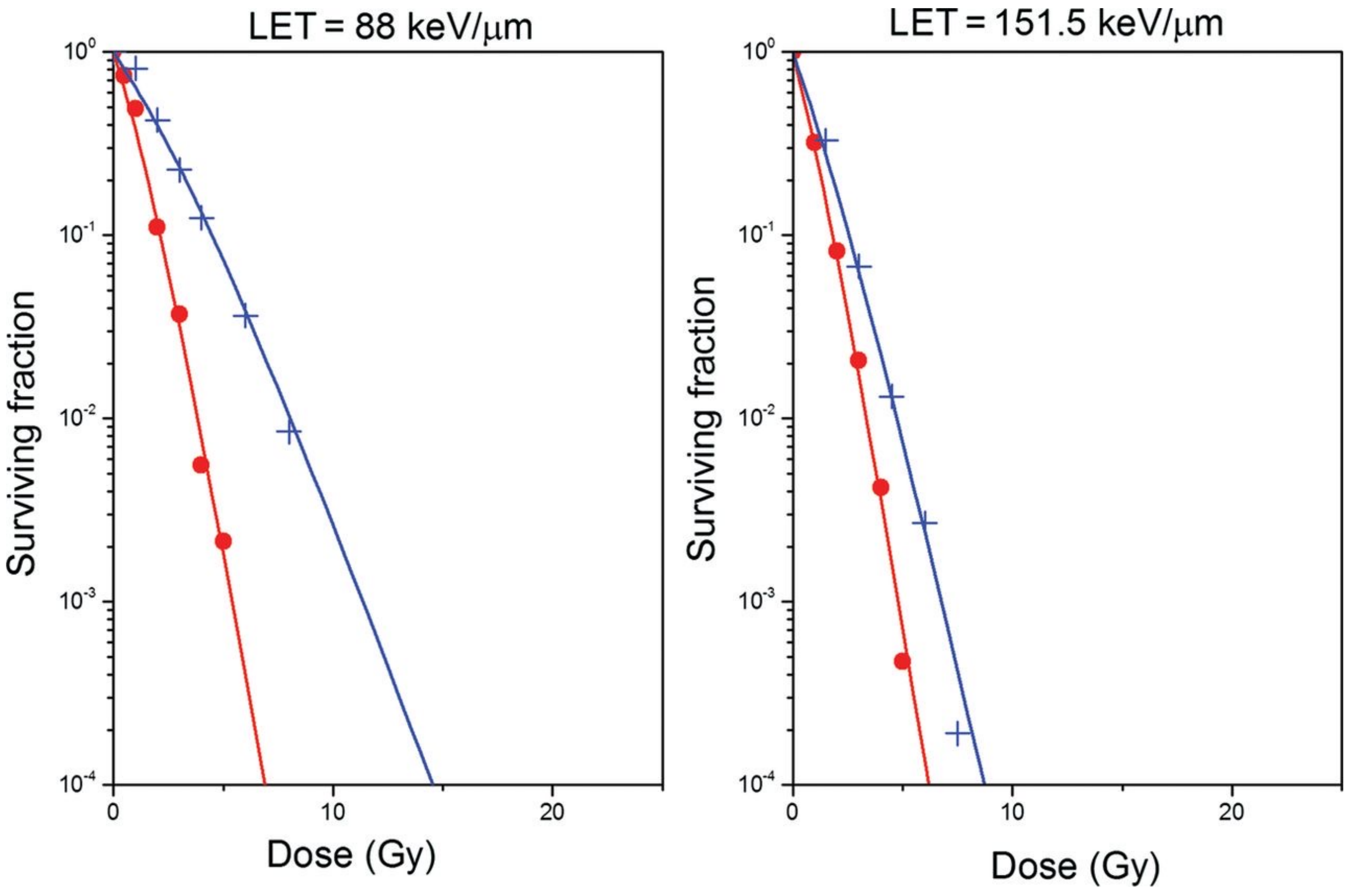
Tailor et al, 2022

The Relationships of RBE and OER vs LET.



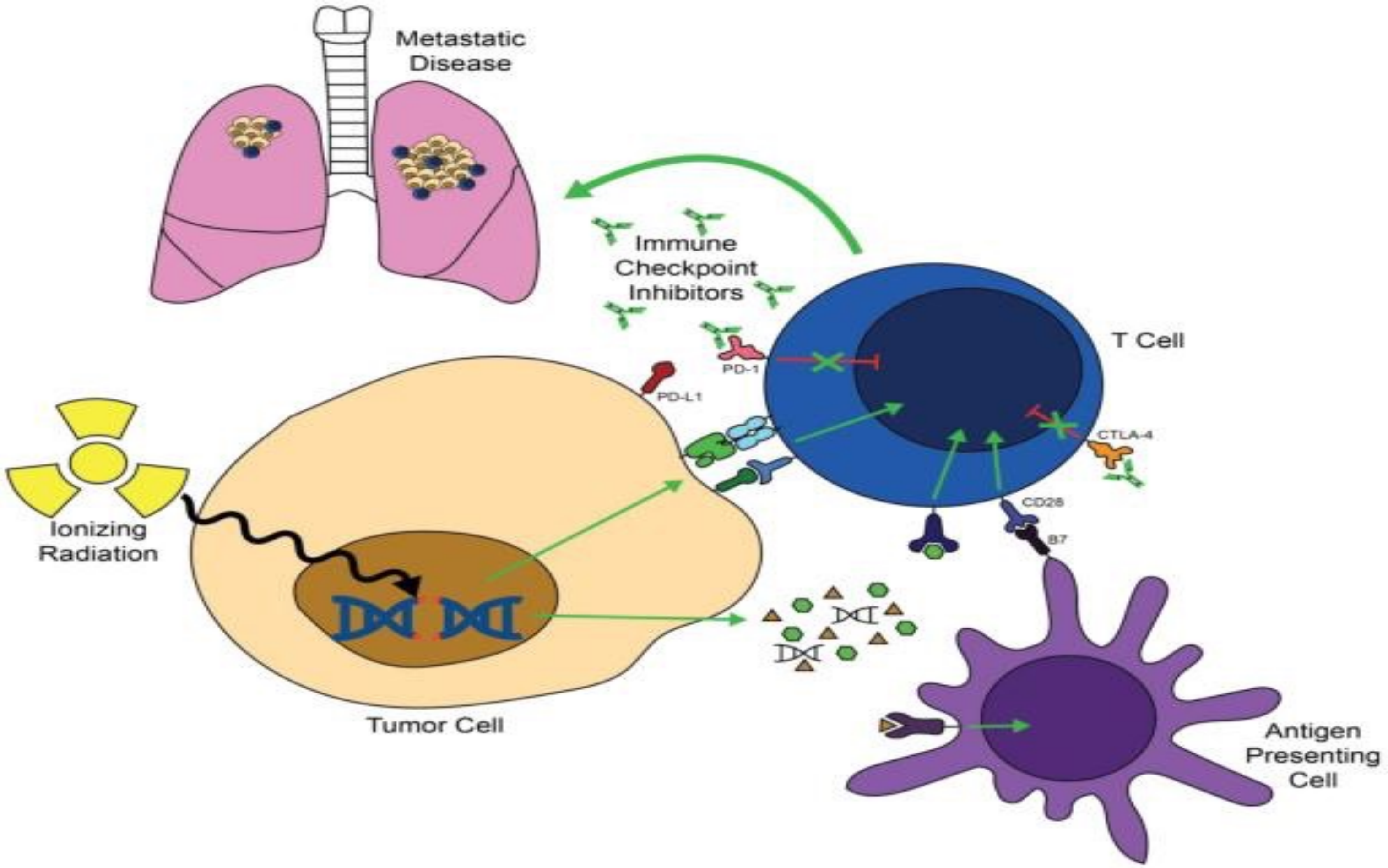
Desouky and Zhou, 2015

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

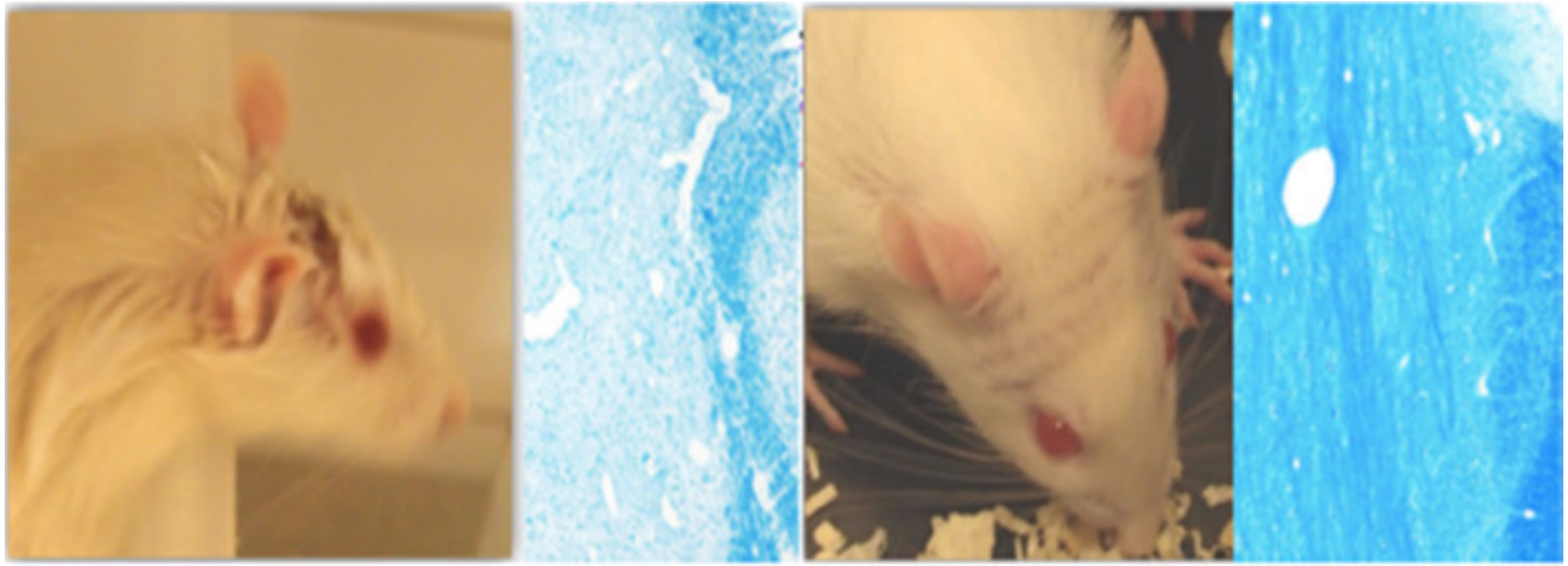


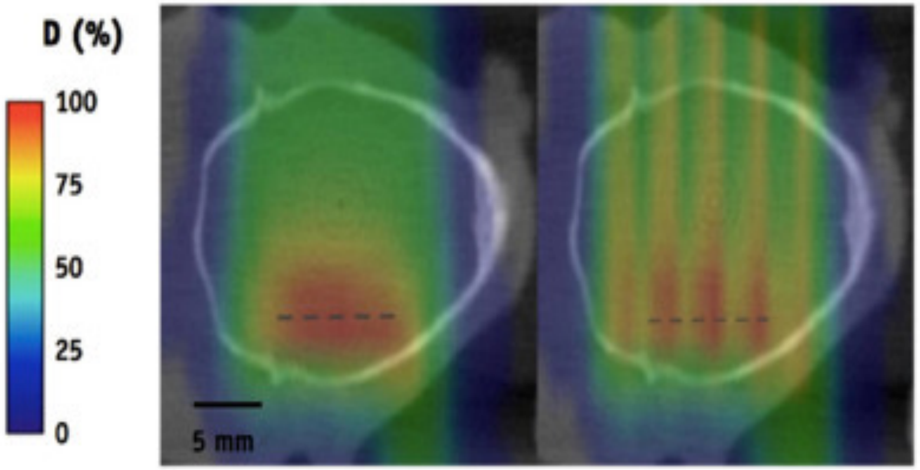
Antonovic L et al. J Radiat Res 2013;54:18-26

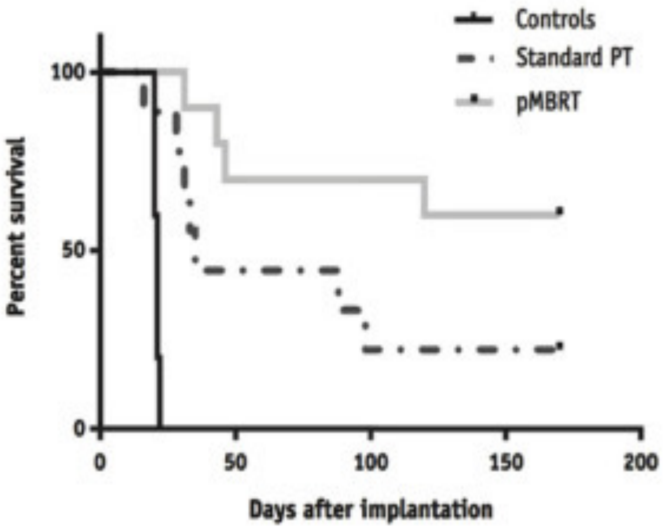
Combining LhARA Ion Therapy with Immune Checkpoint Inhibitors



Response to Proton Minibeam Irradiation

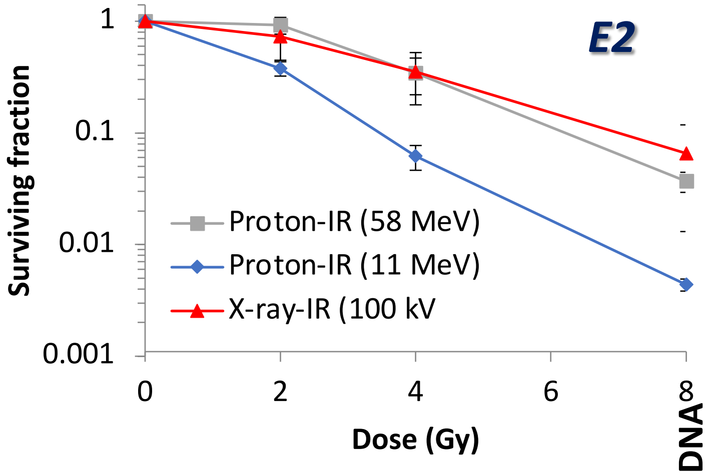




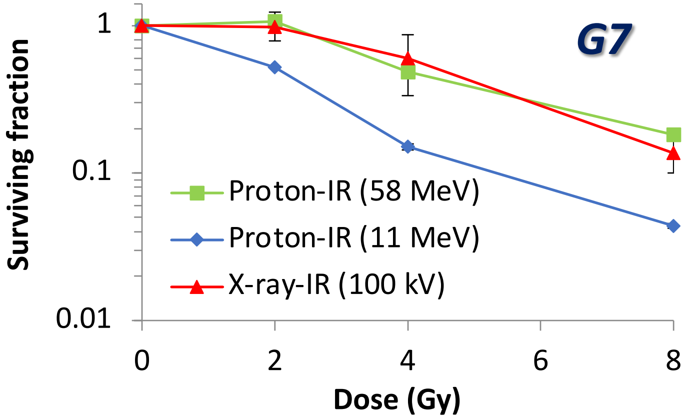


Br J Radiol. 2020 Mar; 93(1107)

"Relatively" high-LET protons cause a decrease in GBM cell survival due to CDD formation compared to low-LET protons

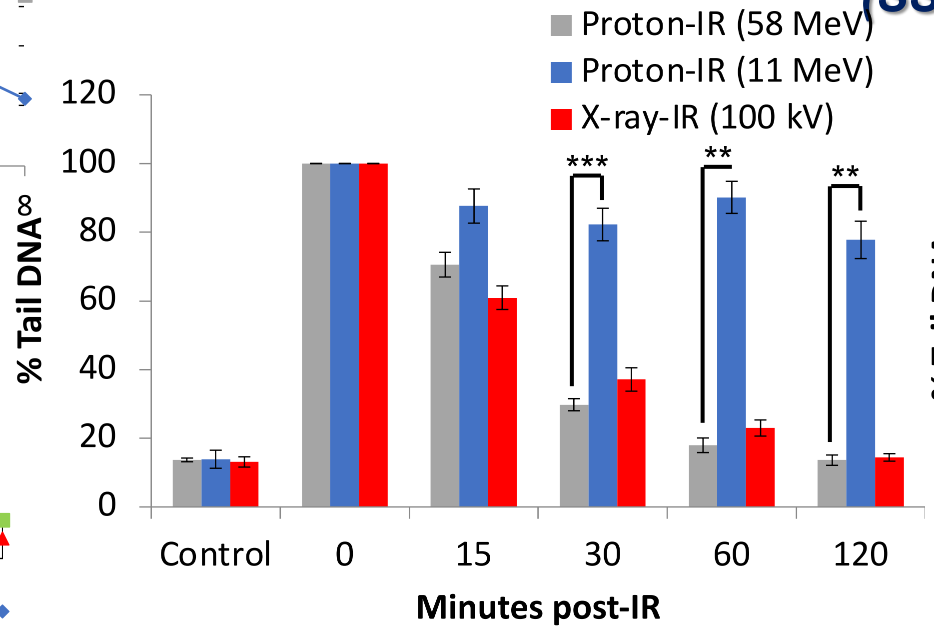


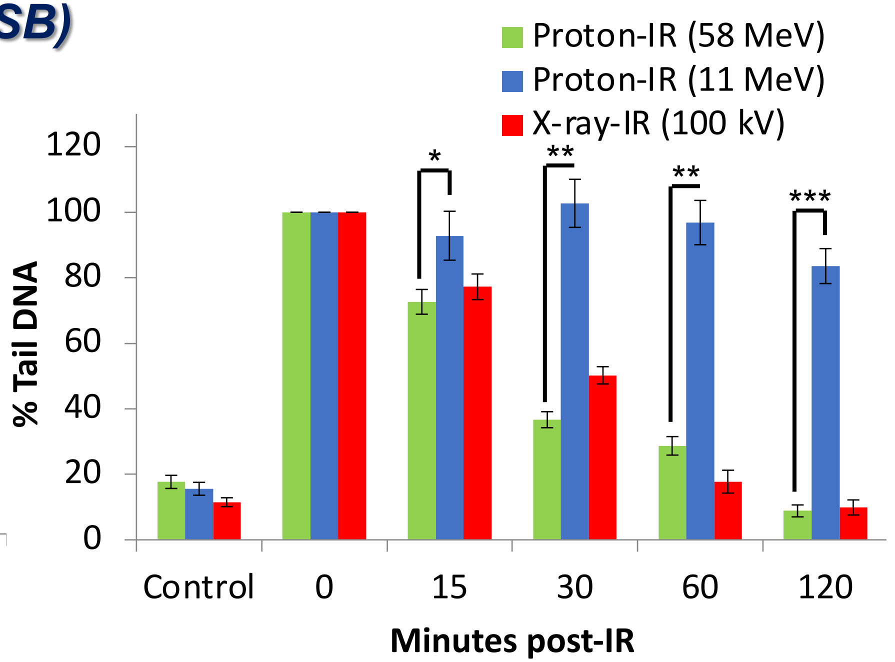
SF2;
RBE=2.4



SF2;
RBE=2.0

Alkaline (SSB)





*p<0.02, **p<0.005, ***p<0.002

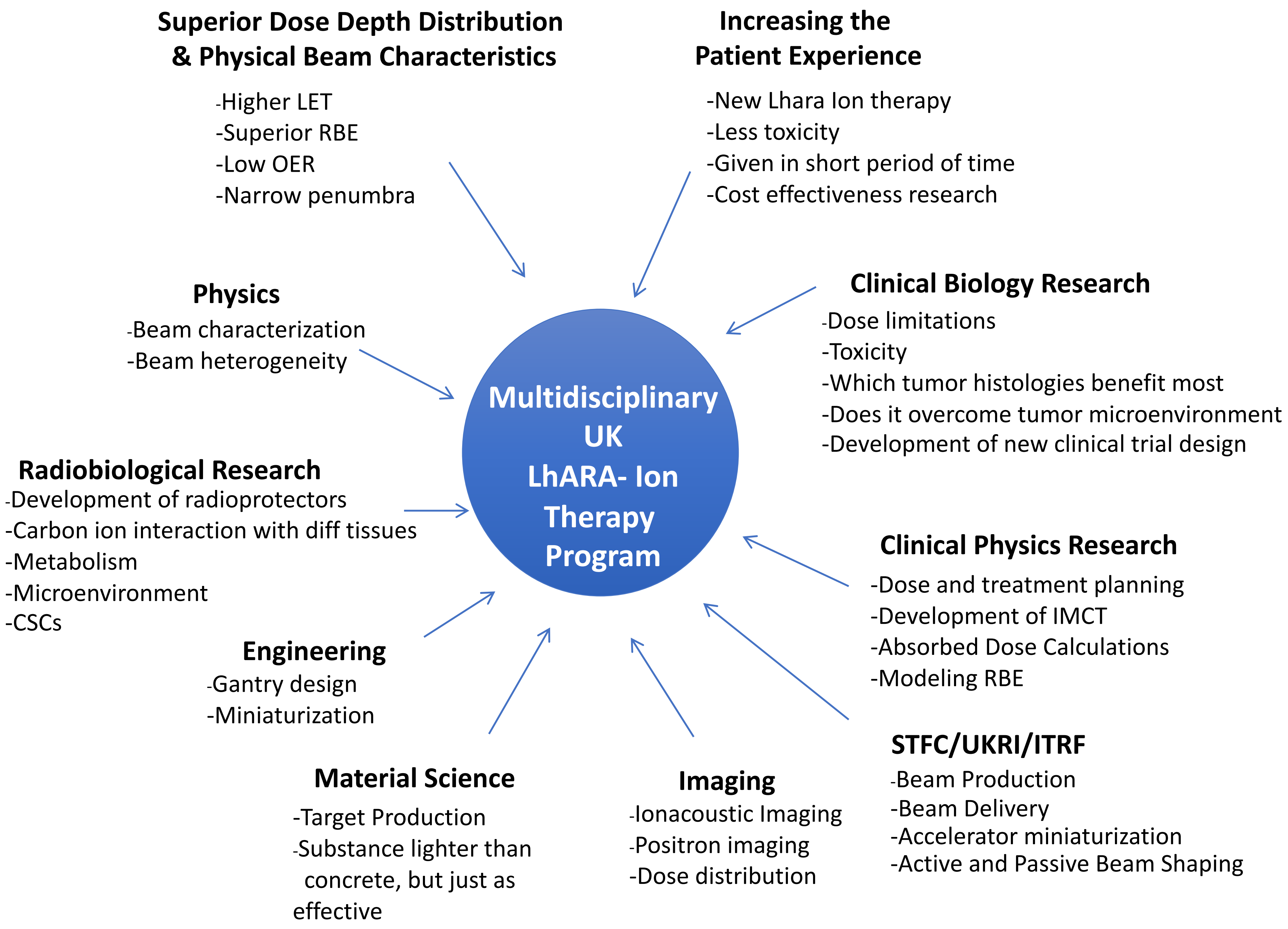
58 MeV (1 keV/μm); 11 MeV (12 keV/μm)

Aiyappa-Maudsley, Chalmers *et al.*, *(Unpublished)*

Summary

Technical advantages of the LhARA facility

- Provides a reproducible, stable and reliable beam critical for acquiring accurate radiobiological data, and for performing systematic evaluations of the biological response.
- Beam which is flexible, easily accessible, and potentially high throughput (unlike clinical facilities).
- Ions can be delivered in very short pulses (10-40 ns) and high repetition rates.
- Ability to deliver particle ions at different energies/LET (protons at 15 and 125 MeV; carbon ions at 30 MeV) and at different dose rates (e.g. FLASH).
- *In vitro* and *in vivo* end-stations both for routine cell culture experiments (with automated handling in controlled environments), but also animal irradiations.
- Stimulate the analysis of more complex biological end-points.
- Potential for live cell imaging, rather than single end-point measurements.


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