Radiobiology with laser-driven ions at the CLF

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[2] *Patrick Johnston Centre for Cancer Research, QUB*
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CLF/LHARA workshop, RAL, 2/11/26

Radiobiology activities within large consortia (2011-now)

EPSRC
Engineering and Physical Sciences Research Council

LIBRA — Basic technology (2007-13)

A-SAIL
ADVANCED STRATEGIES FOR ACCELERATING IONS WITH LASERS
Programme grant (2013-20)

IMPULSE — UHDpulse
EU networks (2021-24)

HORIZON 2020

GEMINI
15 J, 40 fs,
300 TW



CLF central laser facility

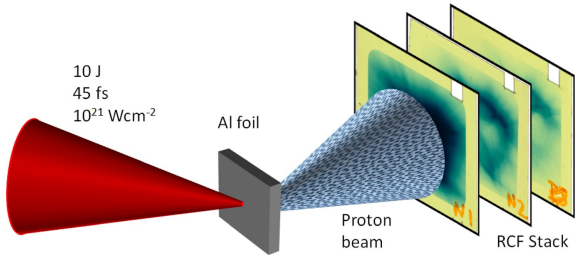
VULCAN PW
500 J, 500 fs,
1 PW



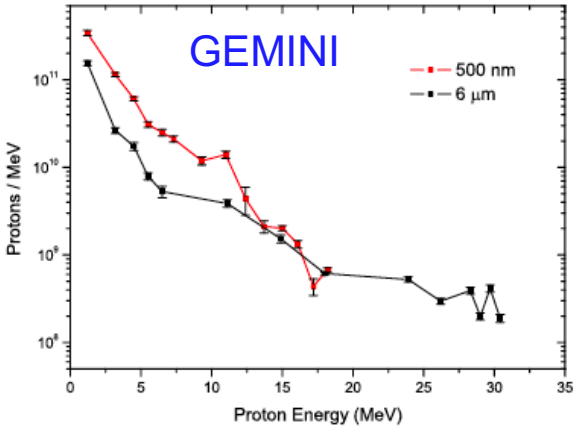
TARANIS (QUB), LULI2000 (France),
ELIMAIA (ELI, Cz)

Ion beams at CLF facilities

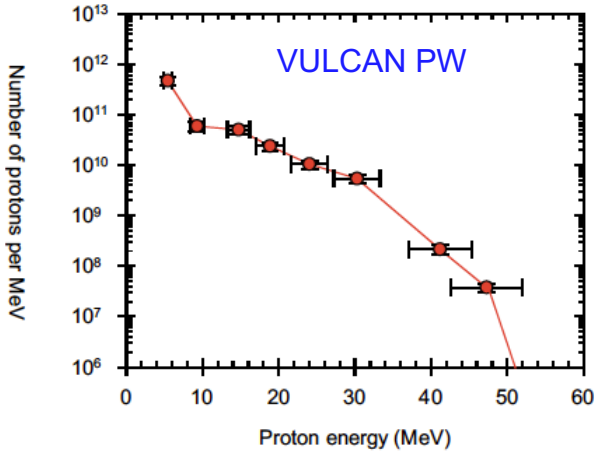
- Diverging, laminar beams
- Broad spectra
- Highly pulsed emission



TNSA protons (~μm foils)

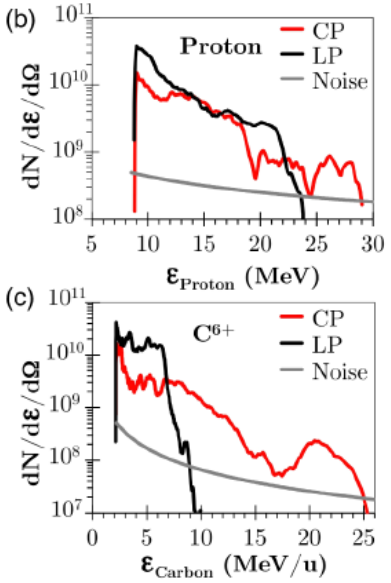


J. Green, APL (2014)



High-contrast (plasma mirrors) allow ultrathin foil interactions

Volumetric acceleration



GEMINI

Bulk carbon acceleration via Radiation Pressure

C. Scullion, PRL (2017)

Radiobiology at Extreme Dose Rate

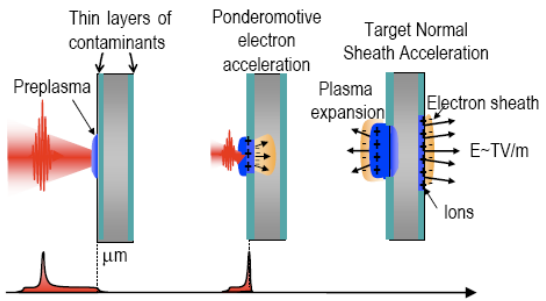
Conventional dose-rate
0.01-0.1 Gy/s

⟺

FLASH regimes
40 -1000s Gy/s

⟺

Laser-driven particles
>10^9 Gy/s



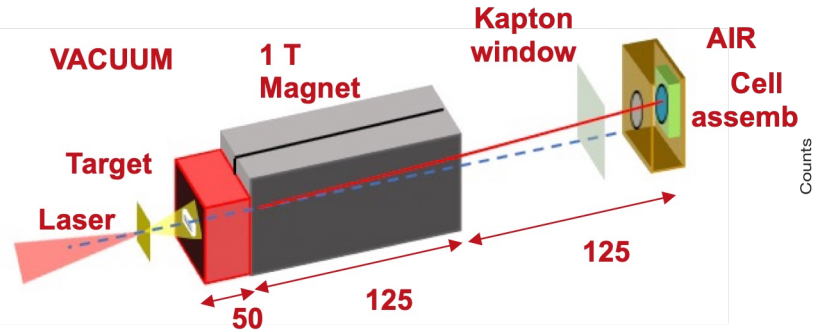
Laser-ion accelerators:
- Ultrashort sources (ps to ns)
- High brightness

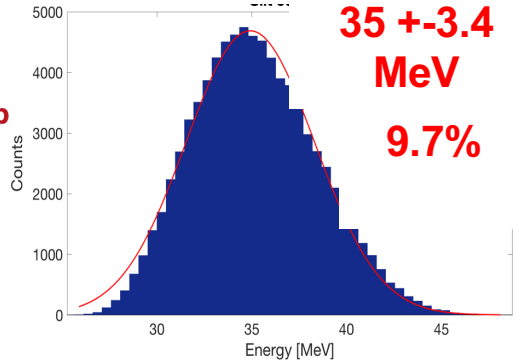
TNSA proton source (surface acceleration)

Unexplored, extreme regimes of radiobiology:

- Spatio-temporal overlap of independent tracks
- Local depletion of oxygen
- FLASH effects ?

Review: Chaudhary P, *et al* (2021), *Front. Phys.* **9**:624963





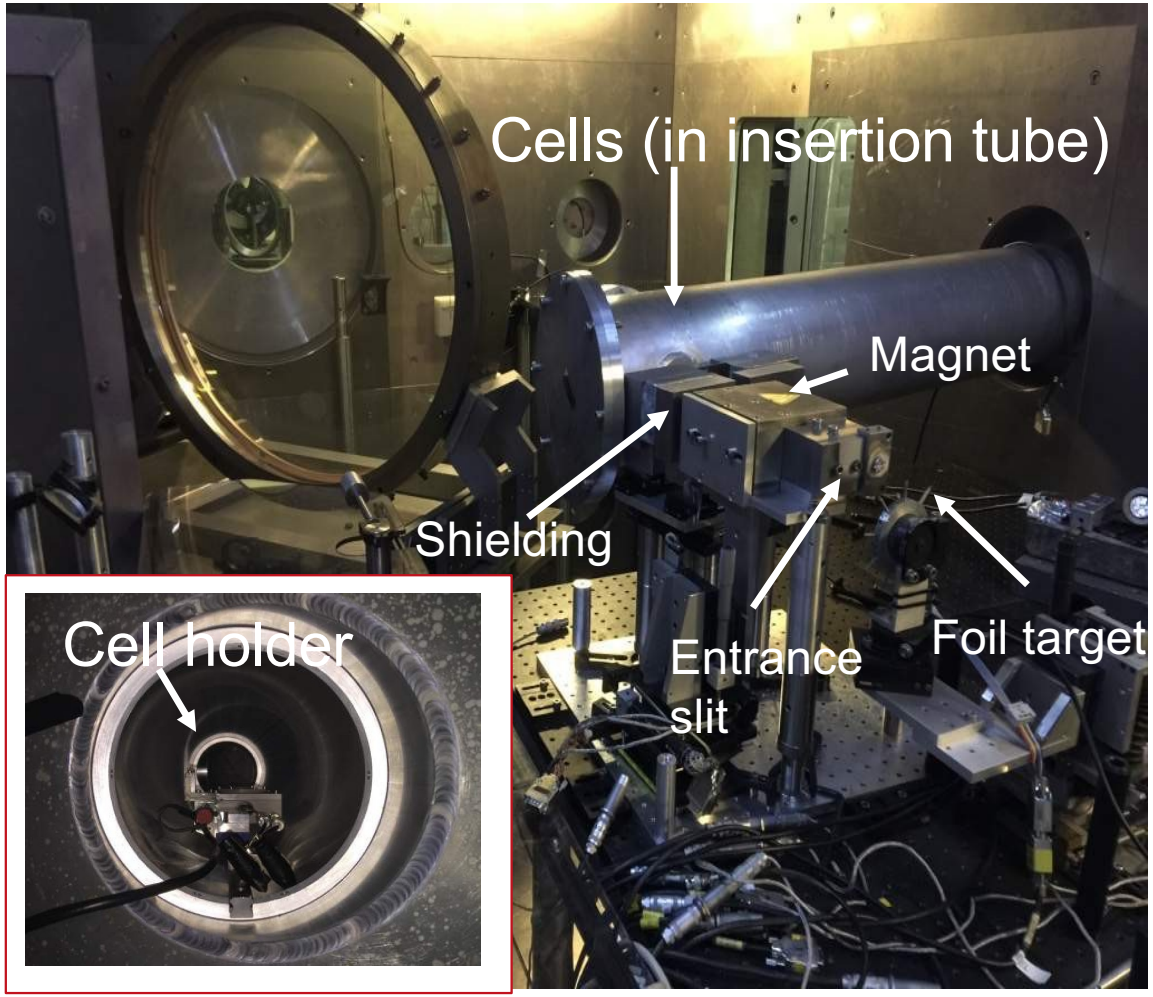
VULCAN, CLF

Multi-Gy dose in a single pulse

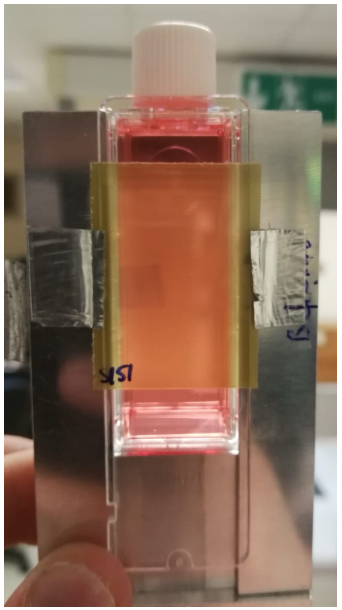
ΔT~ 350 ps (35 MeV protons)

Dose rate: 0.1-2 x 10^{10} Gy/s

Example: irradiation set-up @ VULCAN PW (CLF-RAL)

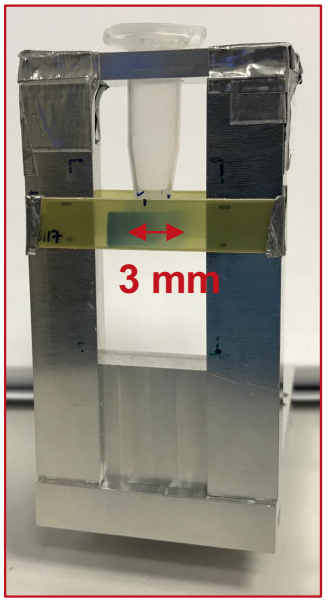


Slide flask



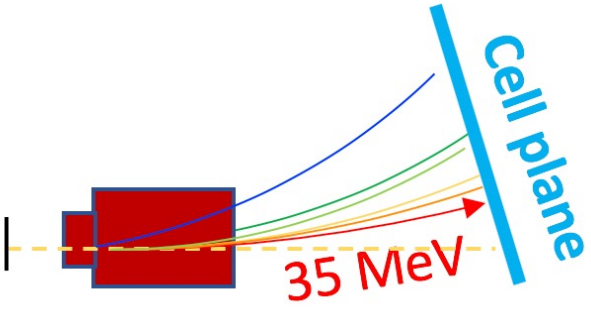
Monolayer (10 um) cells

Eppendorf tubes

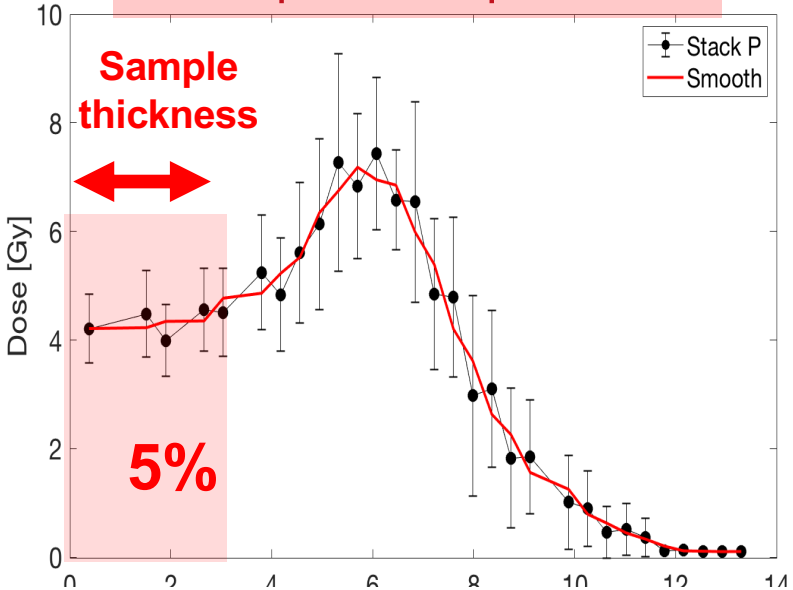


3D cell model in medium

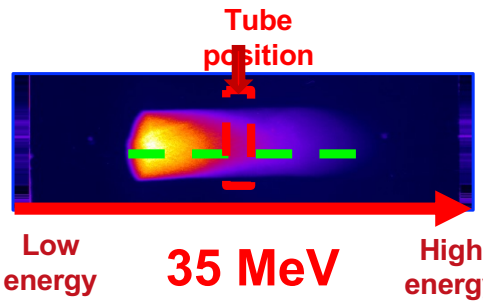
Beam transport and dosimetry



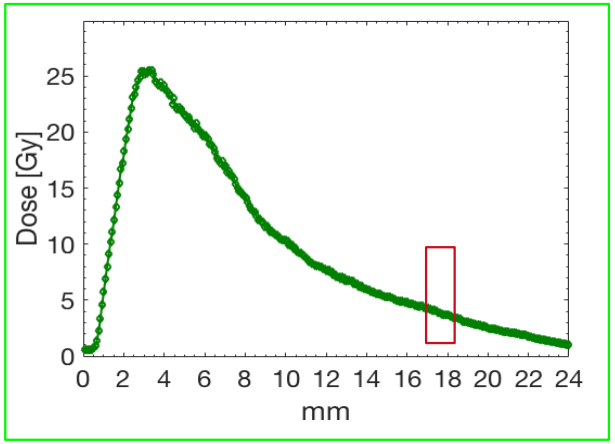
Depth-dose profile



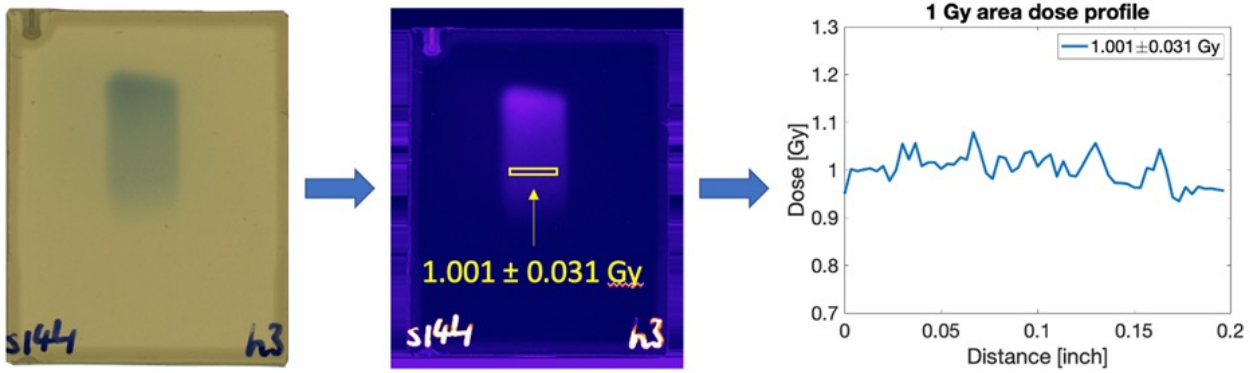
Dose distribution in RCF @ cell plane



Dose along dispersion direction

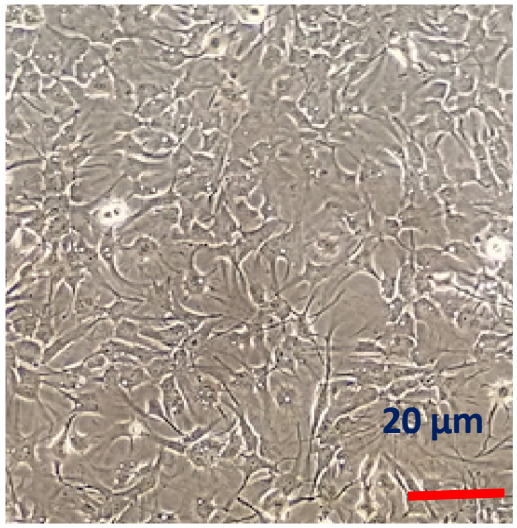


Dose reconstruction from calibrated RCF

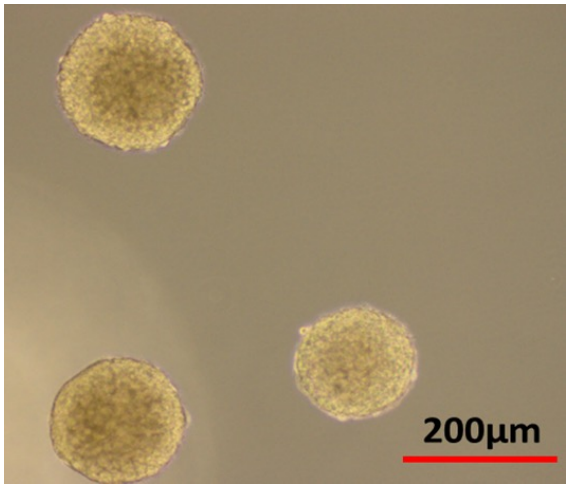


Cellular Models

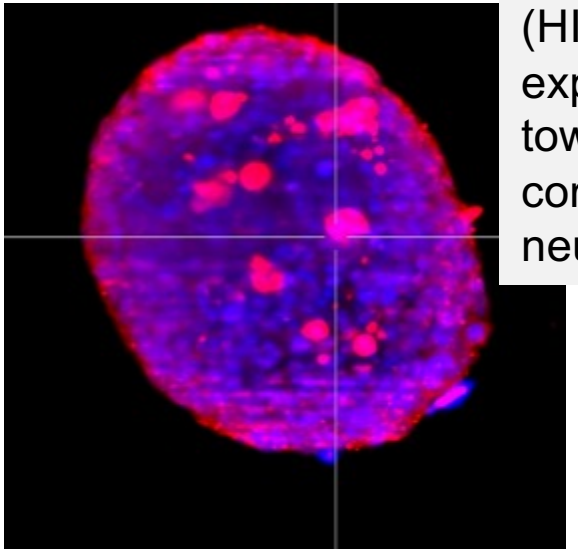
Cells :
1) V79 cells: hamster lung cells
2) Human normal skin Fibroblasts –AG01522
3) Patient derived GBM stem cells 2D and 3D models



Cells grown as **2D** monolayers



3D neurospheres developed from patient derived 2D GBM stem cells



Hypoxia marker (HIF-1α) expression (red) towards the inner core of a neurosphere.

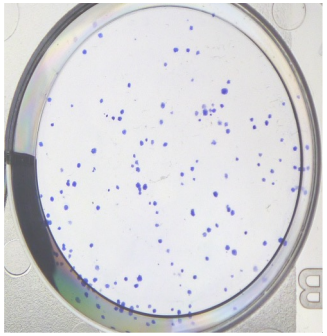
Hypoxic regions within core of neurospheres are a cause of **radioresistance**

Main assays employed

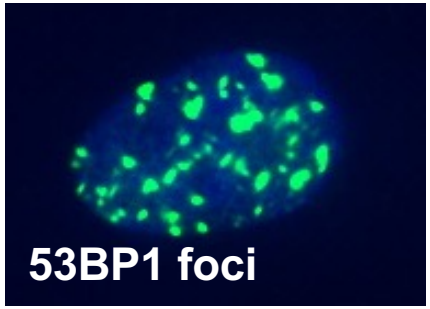
Clonogenic assays (cell survival studies):

1 week

Cell irradiation → Cell culturing → Counting of colonies → Survival fraction



DNA damage and repair (53BP1 immunofluorescence):



Cell irradiation → Cell fixing → Cell staining → Counting of foci

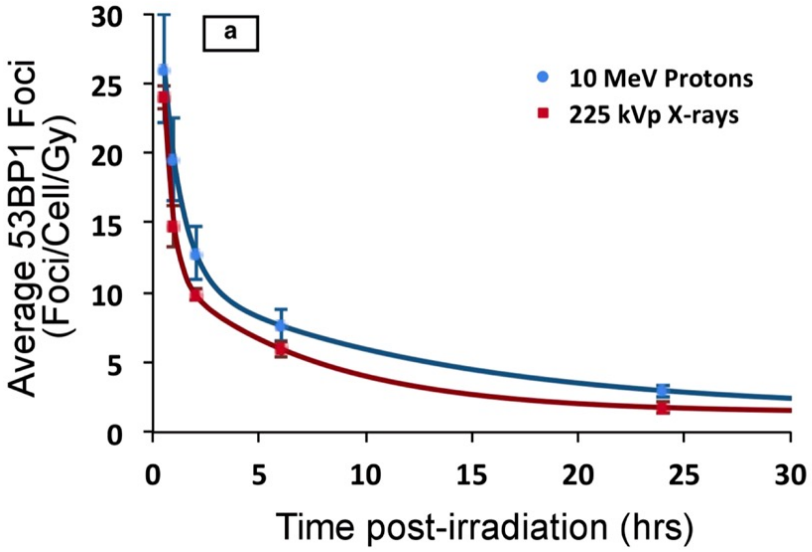
0.5- 24 hr

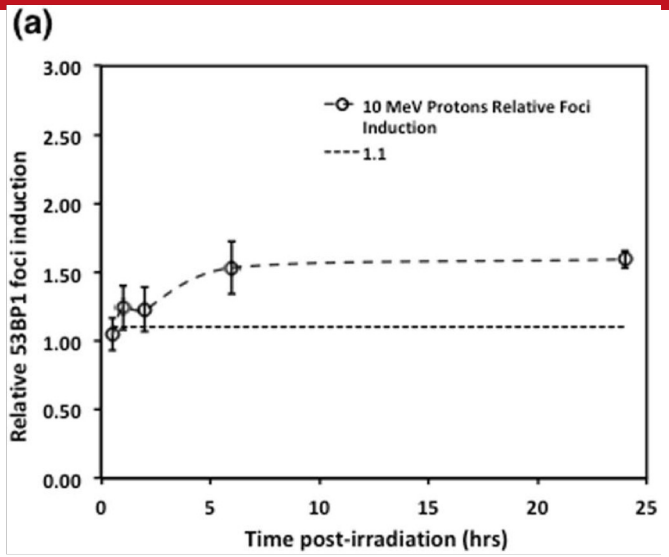
Process involving an agent which binds to DSBs

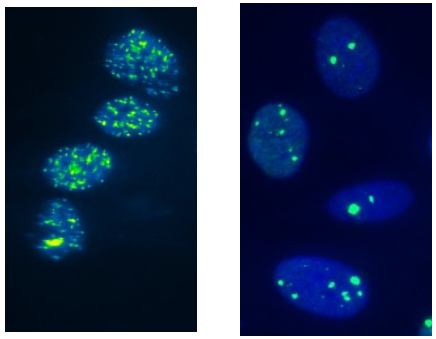
Foci (regions of accumulation of the agent) are highlighted , e.g. by fluorescence

DNA repair dynamics following UHDR exposure (oxic)

GEMINI, RAL: F. Hanton *et al*, Sci. Report, **9**, 4471 (2019)

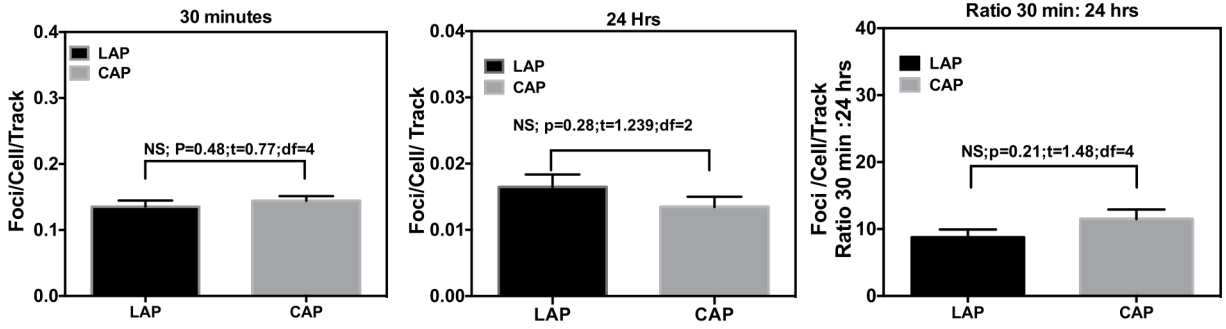






30 mins 24 hrs

AG01522 Human fibroblast
10 MeV protons

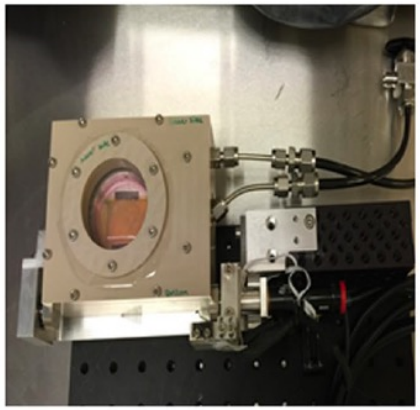


Results in line with expectations from conventional irradiations

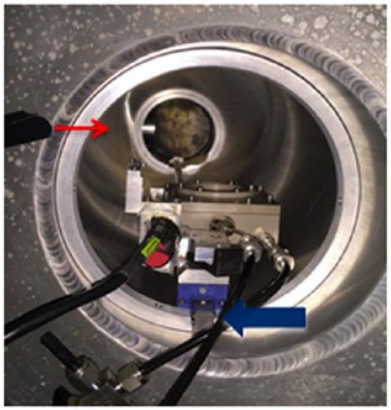
See review:
P. Chaudhary et al, Front. Phys.,**9**, 624963 (2021)

Hypoxia chamber developed for irradiations at controlled oxygen level

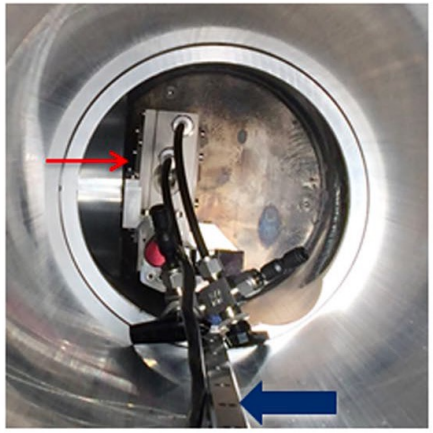
a

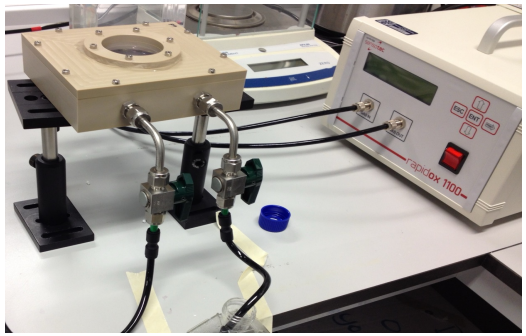


b



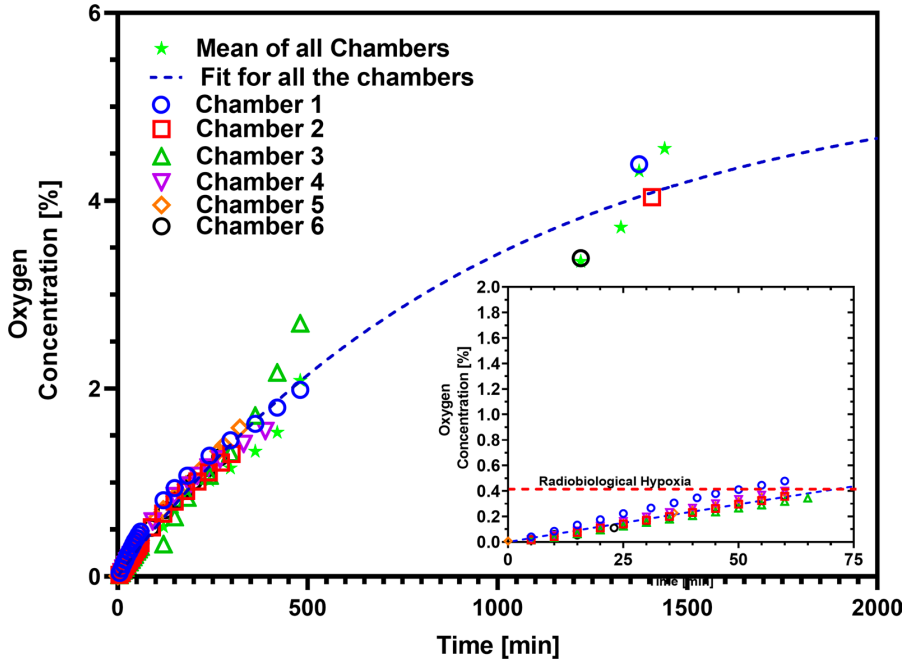
c





Hypoxia induction through gassing with 5% CO_2, 95% N_2

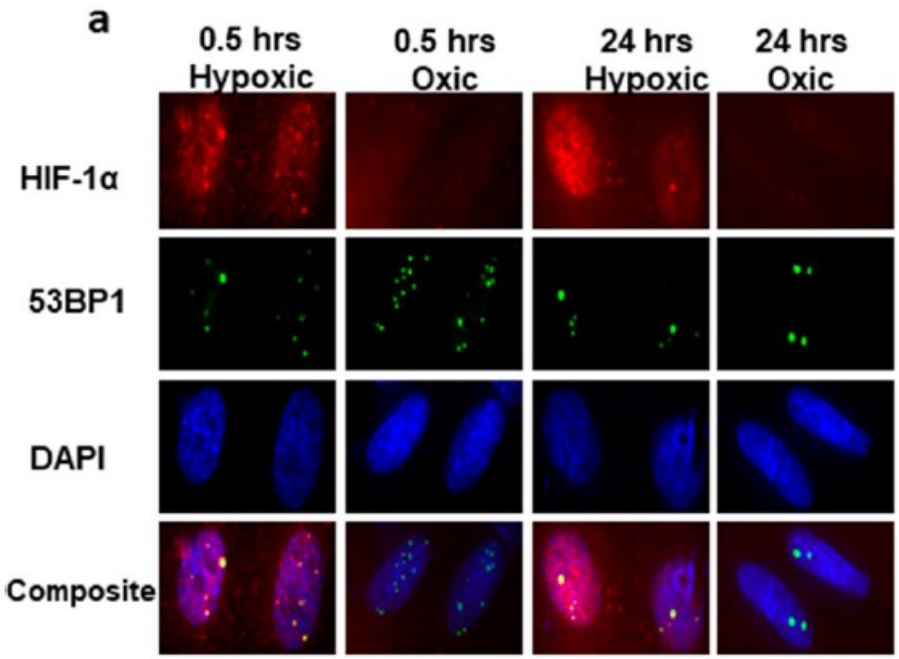
P.Chaudhary *et al*, Rad Oncol., **17**,77 (2022)

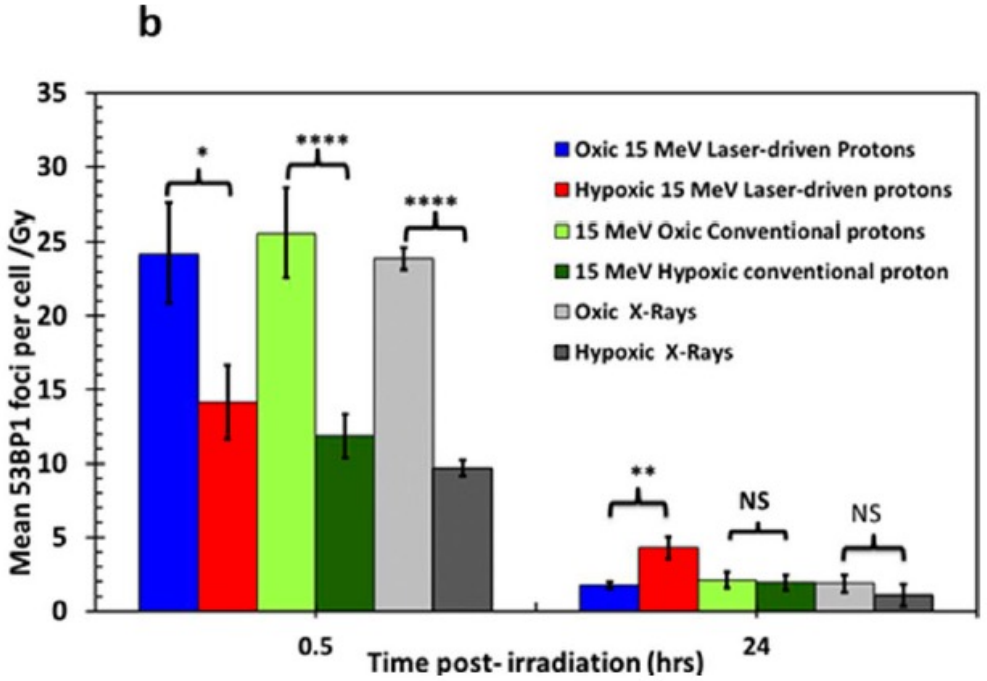


Time needed for each shot after gassing was < 45 minutes

More persistent damage observed under hypoxia at UHDR

VULCAN, RAL: P.Chaudhary *et al*, Rad Oncol., **17**,77 (2022)



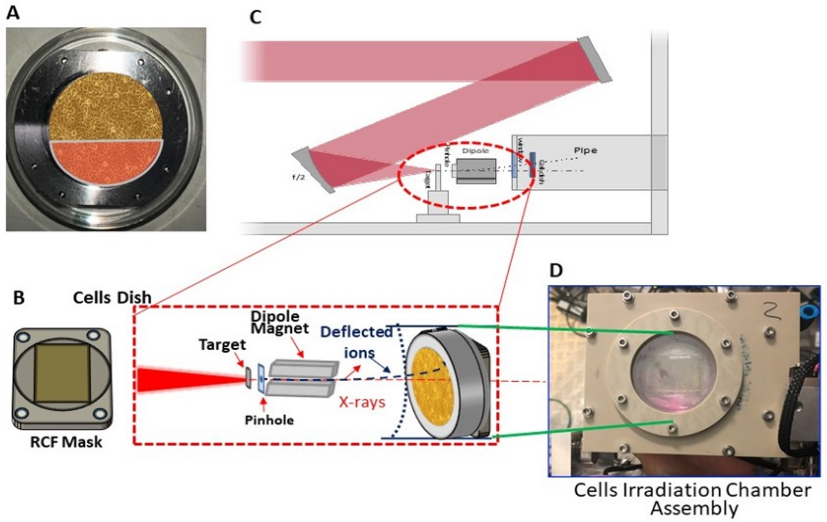


AG01522B cells, irradiated at ~1 Gy, by 15 (± 1) MeV protons

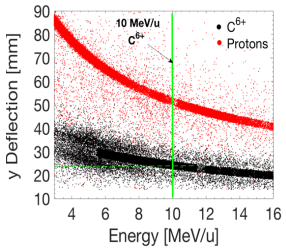
Dose rate ~ 2 10^9 Gy/s

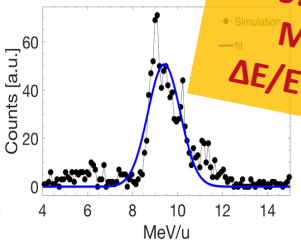
UHDR carbon radiobiology

P. Chaudhary *et al*, Phys Med Biol. **68**, 025015 (2023)



GEMINI laser @ CLF (UK)
~10 MeV/n C^{6+} pulses
1 Gy at 2.5 x10^9 Gy/s





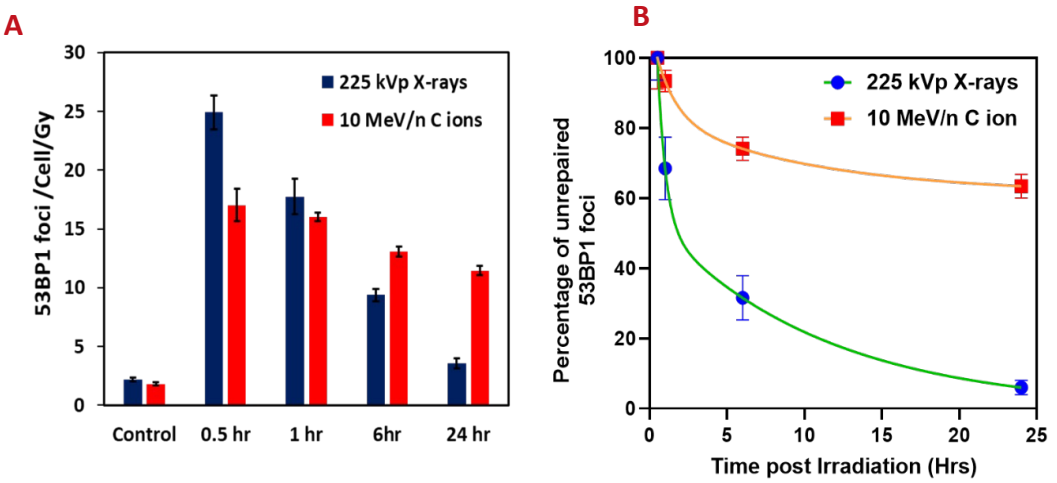
9.5 ±1.6 MeV/u
ΔE/E ~ 15 %

C ion

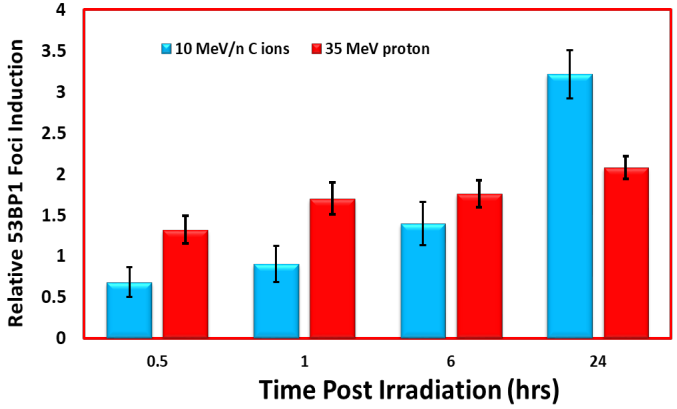
225 KV X-rays

Carbon irrad

ge

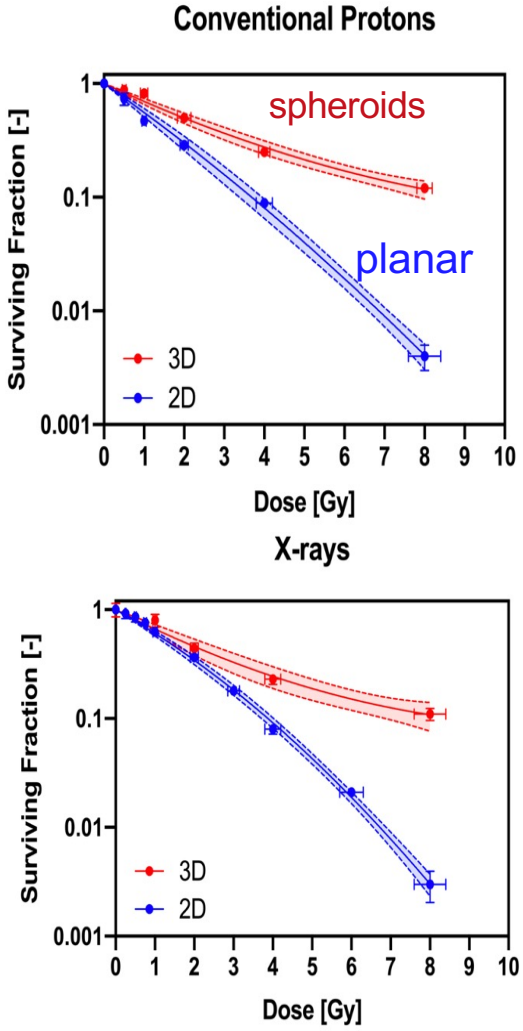


Repair dynamics

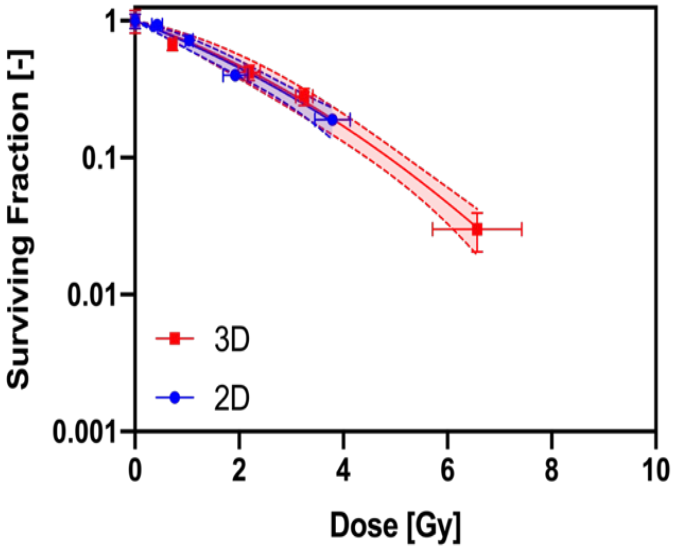


Cell survival: 2D vs 3D cell models

P.Chaudhary *et al*, submitted



VULCAN laser, 35 MeV protons



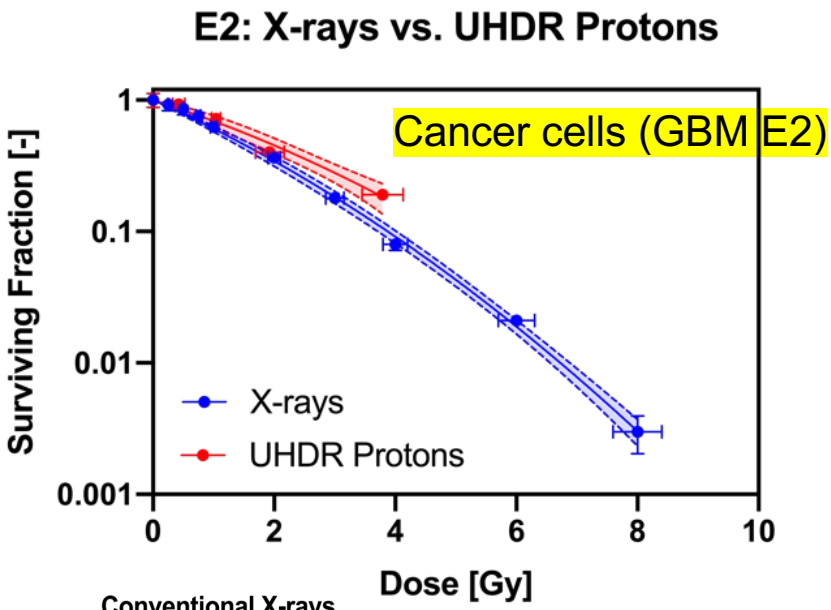
3D	Cyclotron	UHDR
RBE_{50}	0.65±0.05	0.94±0.30
RBE_{10}		1.79±0.49

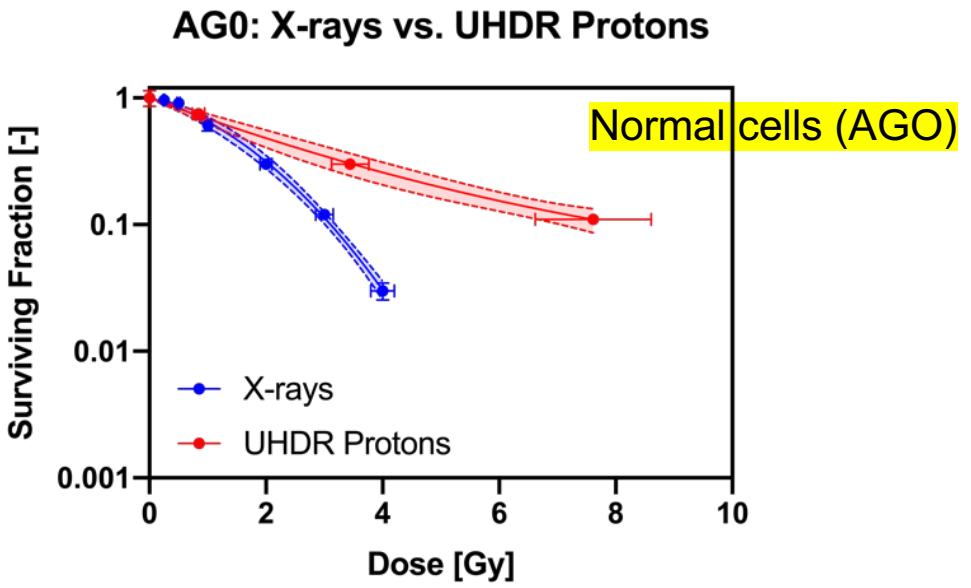
- Enhanced cell killing in 3D model @UHDR
- UHDR overcomes hypoxia-induced radioresistance
- Some analogy with in-vivo FLASH results?

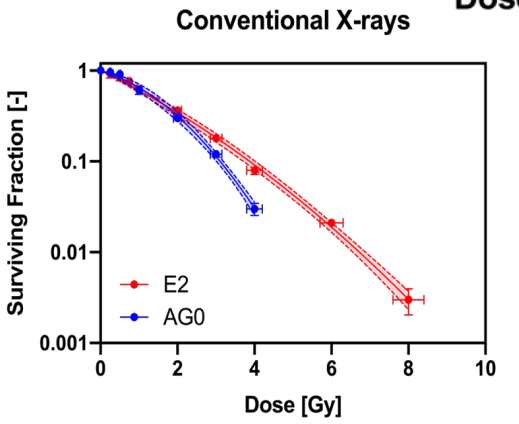
R.J.Leavitt *et al*, *Acute Hypoxia Does Not Alter Tumor Sensitivity to FLASH Radiation Therapy,* Int J Radiat Oncol Biol Phys, **5**, 1493 (2024)

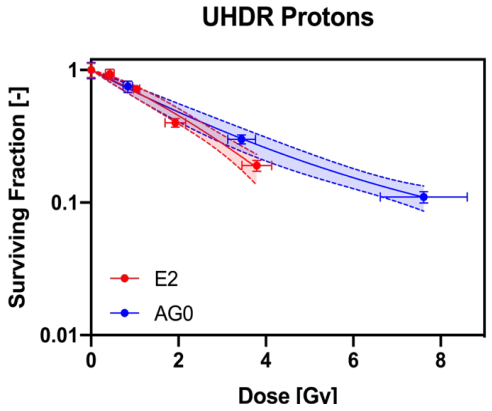
Survival studies (2D): differential cell response

B. Odlozilik *et al*, PhD thesis







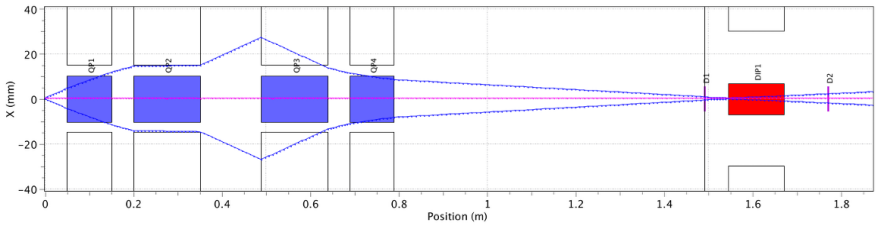


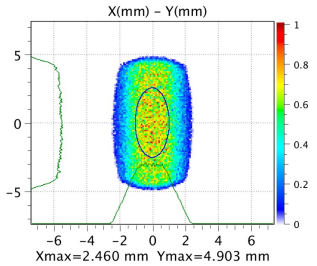
Enhanced sparing at UHDR for normal cells (AG01522) compared to cancer cells (GBM)

Potential relevance to FLASH radiotherapy?

More advanced studies require enhanced dose control

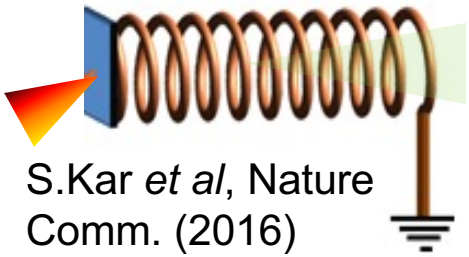
Quadrupoles for EPAC:





~10 Gy @10 MeV/n C6+ on GEMINI/EPAC

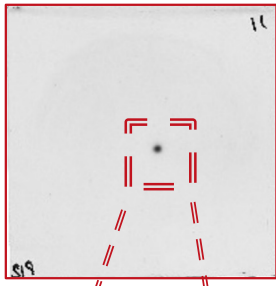
Advanced targetry for beam collimation



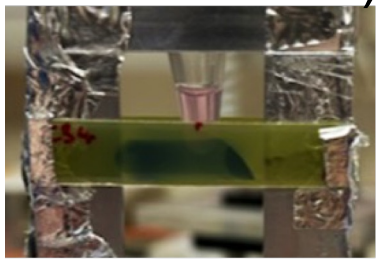
S.Kar *et al*, Nature Comm. (2016)

H.Ahmed *et al*, Sci. Rep.(2021)

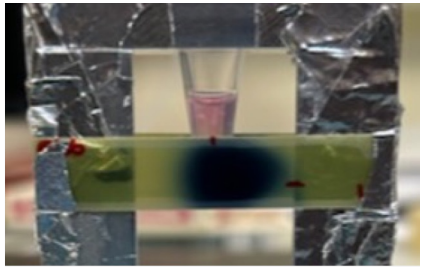
45 MeV



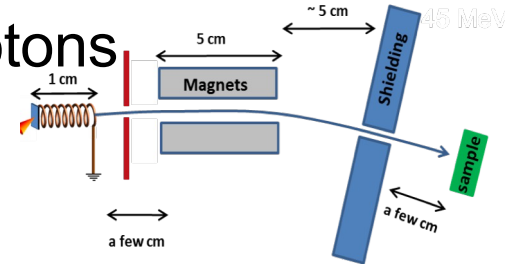
Up to 70x dose increase observed with protons (VULCAN PW)

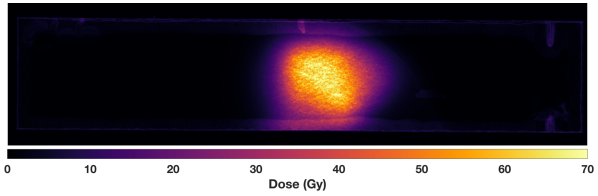


Flat foil dose @ 35 MeV
~ 1 Gy

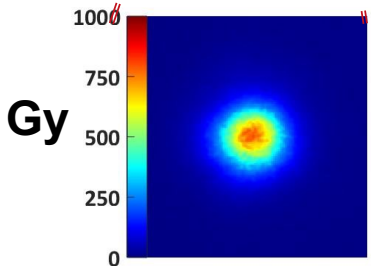


Foil/coil: dose @ 35 MeV
~ 70 Gy



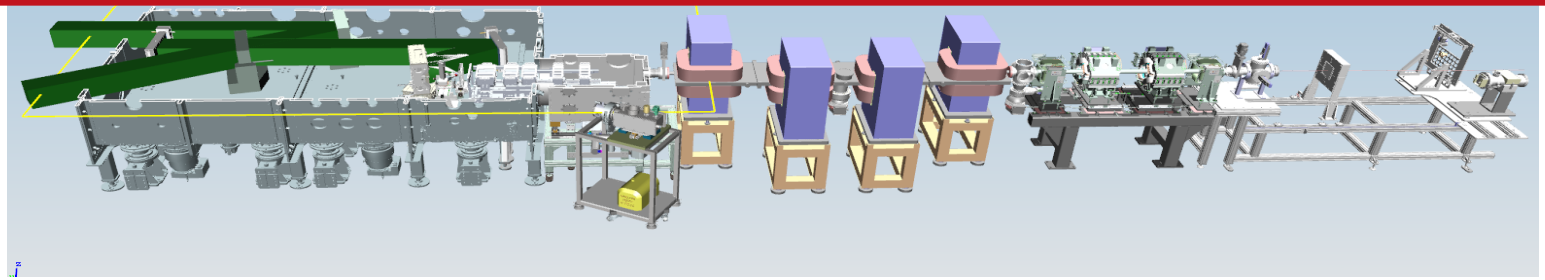


Divergence
< 0.5 °



ELIMAIA : experience with beamline approach

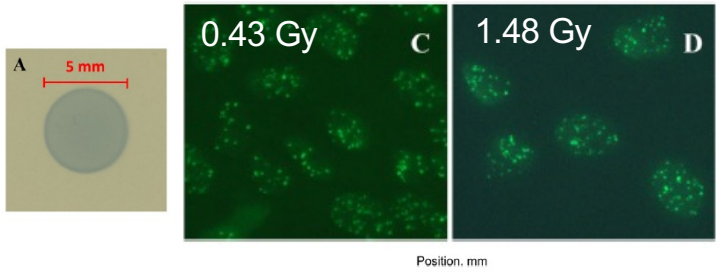
P.Blaha *et al*, Front Phys. (2025)



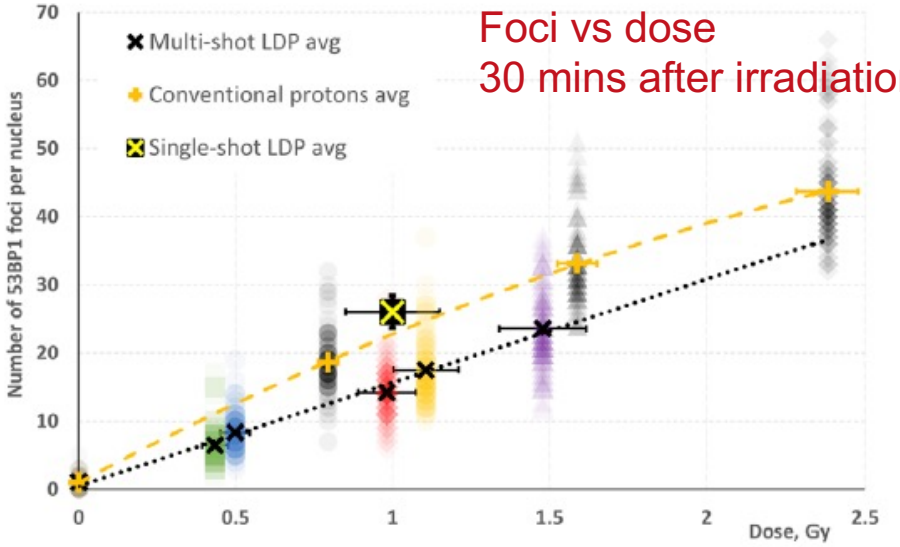
Accelerator-type approach:
transport-line, uniform dose, energy definition…

E~23 MeV (+- 7%)

AG01522 cells



Excellent beam uniformity



Foci vs dose
30 mins after irradiation

Dose per shot ~ 2-15 mGy
1Gy required at least 70 shots (and > 30 minutes)
Peak dose rate ~1-3 10^{6} Gy/s
Mean dose rate ~ $10^{-3\text{-}4}$ Gy/s

Planned improvements ~ 100 mGy per pulse, 3.3 Hz operation

Conclusions/perspectives

UHDR radiobiology
Compact set-up
Multi-Gy doses, >10^9 Gy/s
Beyond FLASH regimes

Emerging evidence of non-standard cell response at UHDR, enabled by
- moving to more complex models
- Using higher energy beams
- Single-shot irradiations

EPAC:
Stable, dedicated beamline arrangement
Single shot and multi-shot (10Hz) capability
New investigations: effect of pulse sequencing, FLASH (?) regimes, ….more data !
Capability for both TNSA proton acceleration and bulk acceleration (e.g carbon)

Needs:
- High-rep targetry (tape drive, liquid, cryo)
- Energy/LET definition, dose uniformity
- Sizeable dose per shot
- Bio-lab near laser (!)

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