The radiobiology of ultra-high dose-rate laser driven ion-beams: Challenges and opportunities

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Outline

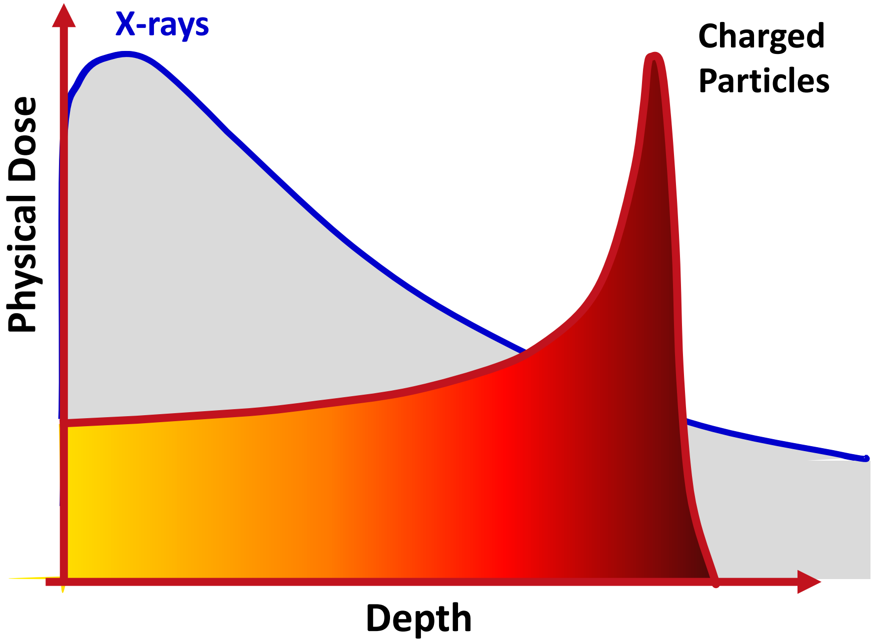
- Introduction to Ion-beams
- Introduction to the A-SAIL laser program
- Radiobiology studies
- Challenges and opportunities

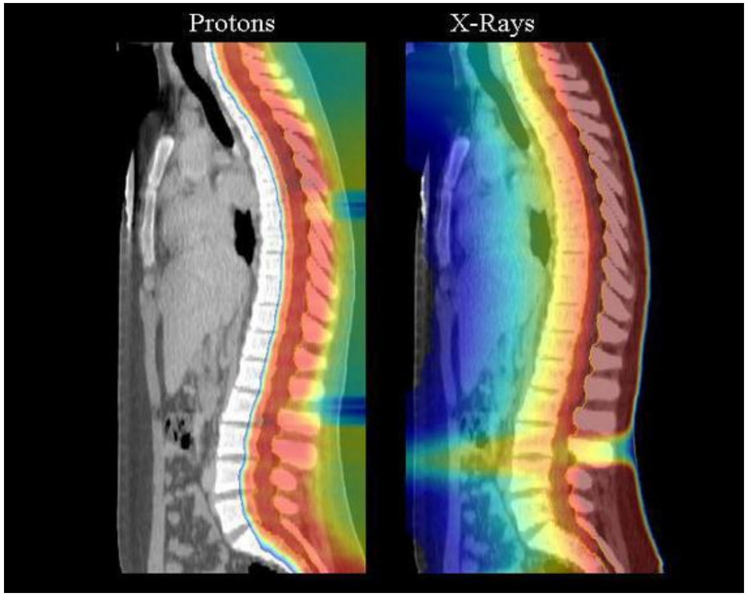
Background

Charged particles are being increasingly used in cancer treatment

By 2019, 260,150 patients had been treated, 222,425 with protons

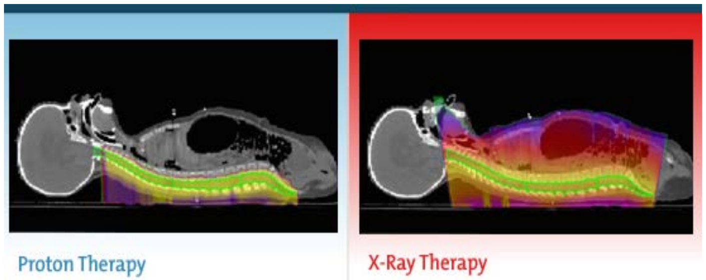
- Inverse energy deposition → Selective dose localization
- Elevated cell killing → Improved tumour control



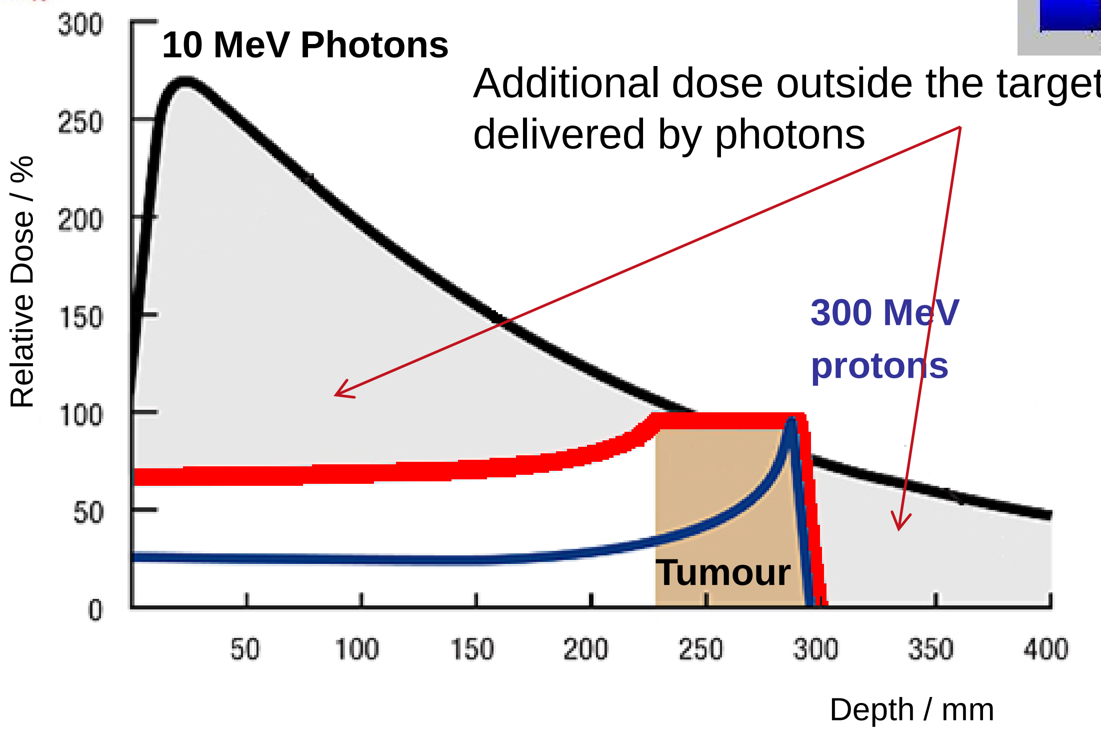


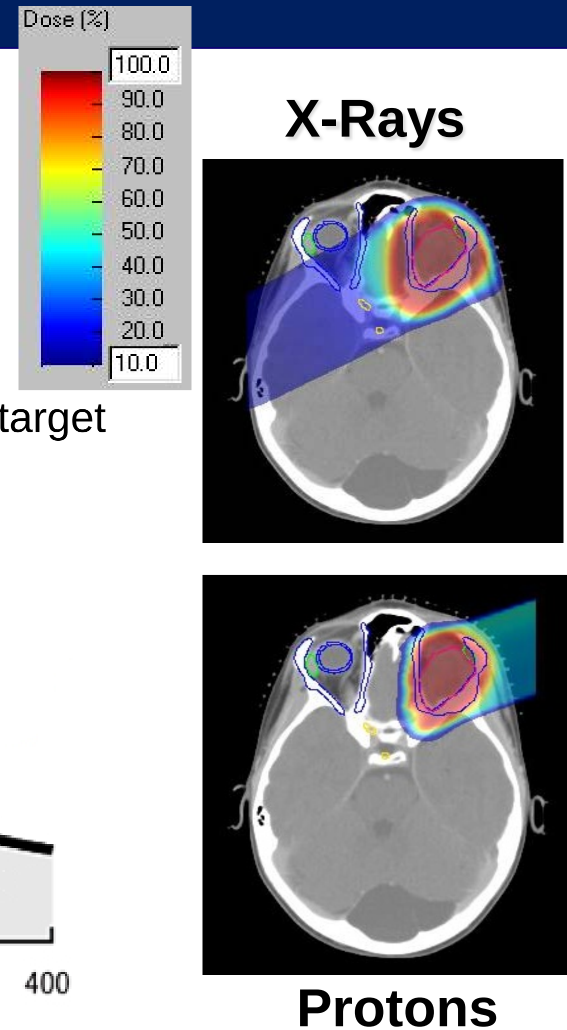
- The Bragg curve provides an opportunity for better protection of normal tissues in comparison to photons

Protons versus photons



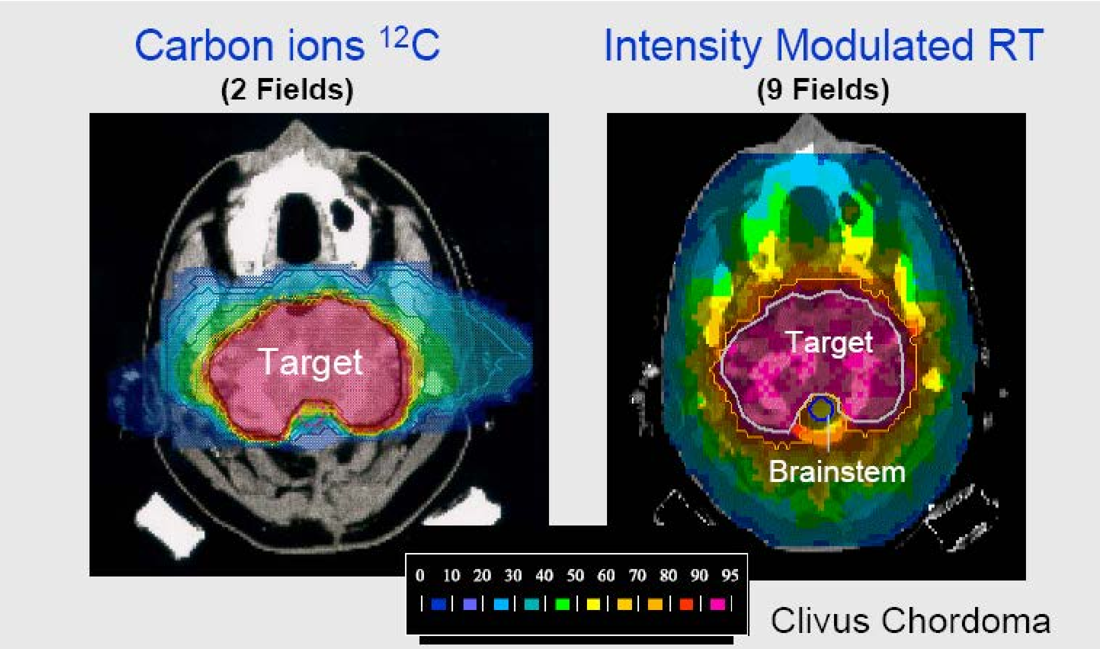
By producing a spread-out Bragg Peak (SOBP), uniform doses can be delivered at depth





Hadrontherapy treatment

Proton and Carbons from RF accelerators
are currently used for treating a number of different tumour types

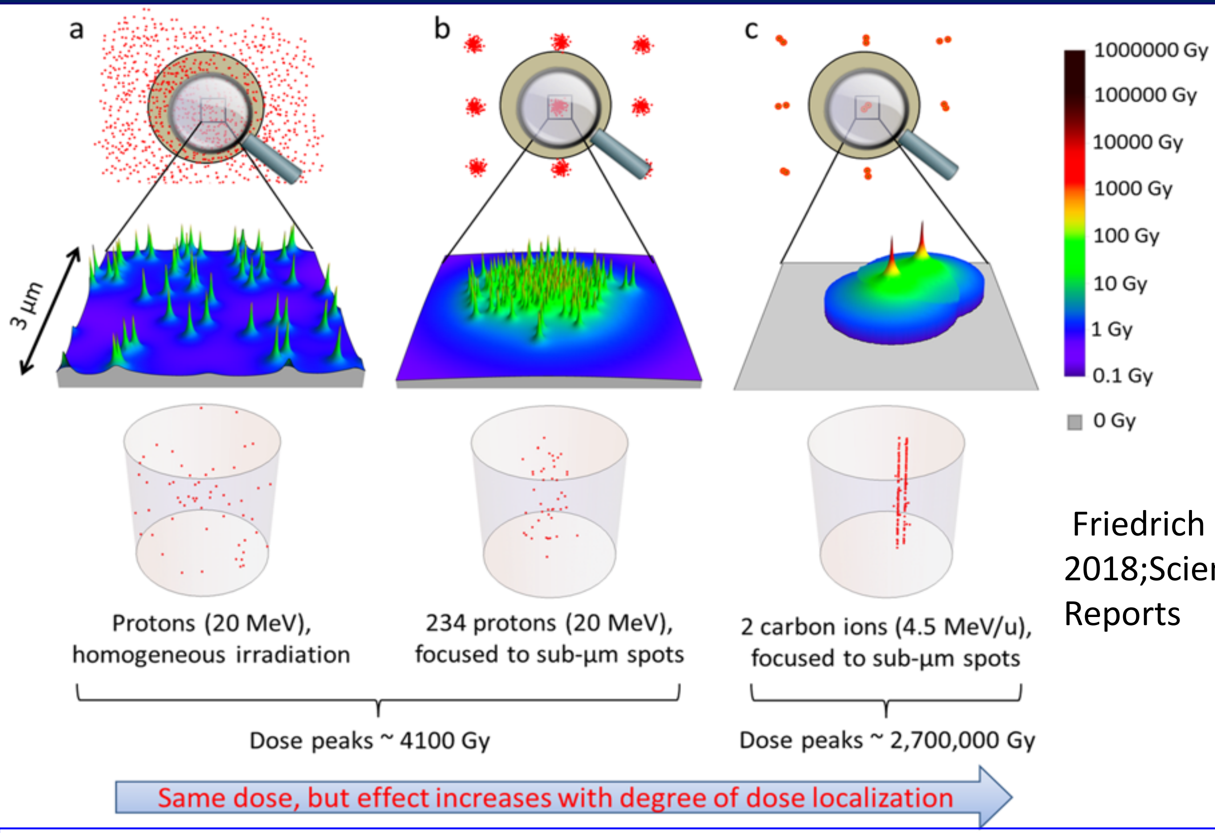


Energies required:
60-250 MeV (protons)
or 100-450 MeV/u (C-ion)

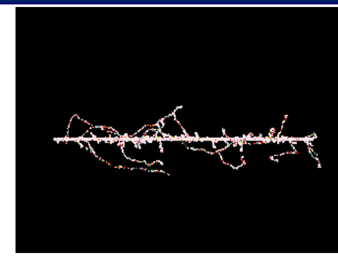
Typical dose fraction: 2-5 Gy
1 Gy ~ 10^{10} p+, ~10^{9} C in 5x5x5 cm^3
(delivered in few minutes)

Better localization + increased biological effectiveness leads to improved clinical outcomes for many prescriptions
~10% of cancer predicted to be better treated by ions, (0.1% at present)

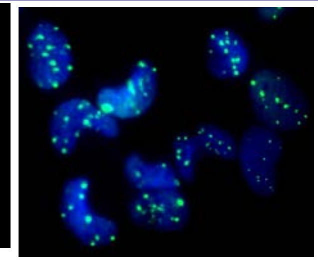
Spatial patterns – sub micron



Friedrich et al , 2018;Scientific Reports



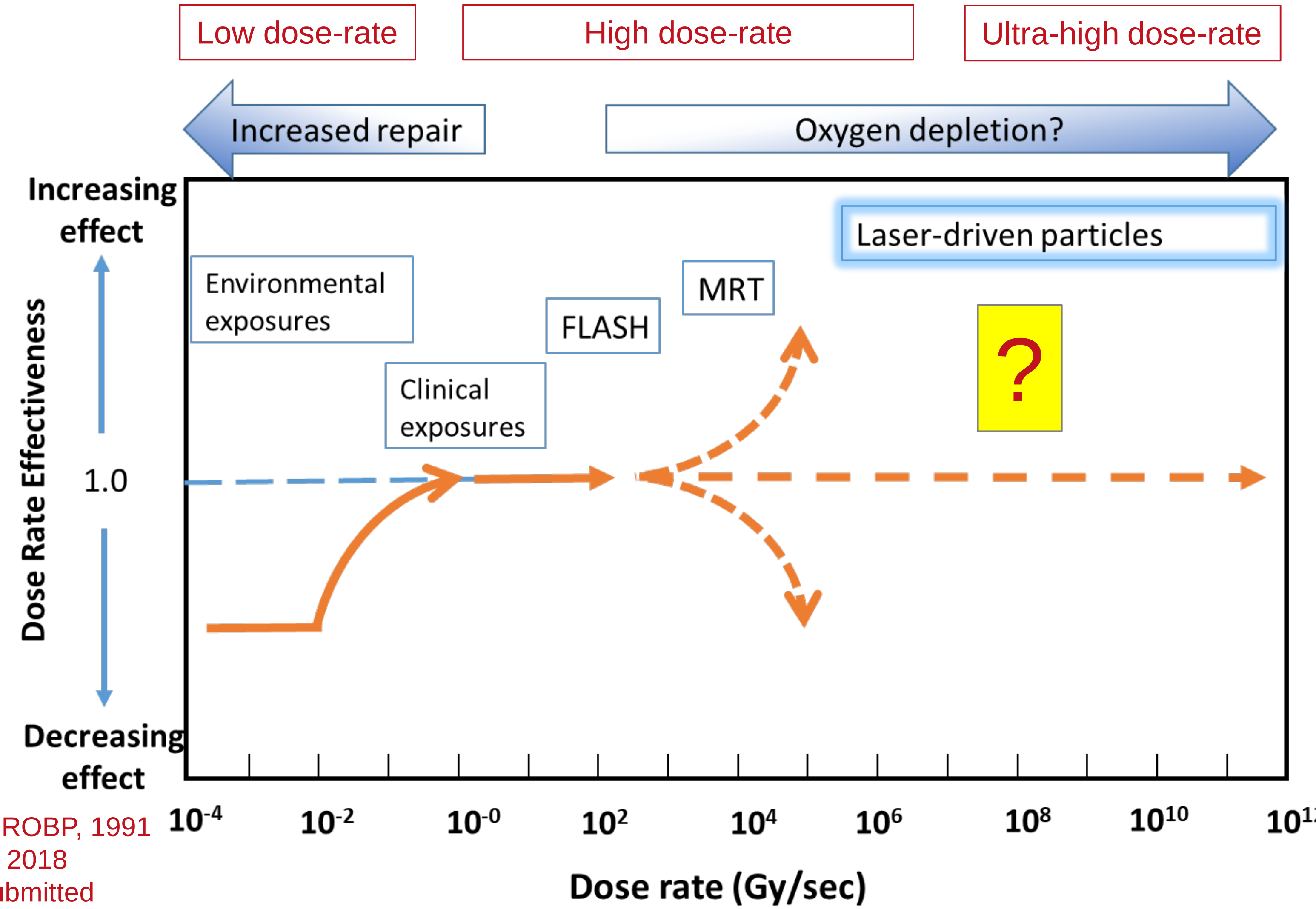
10 MeV Carbon ions track lateral view



10 MeV/n Carbon ion induced DNA Damage in GBM stem Cells

Due to the highly localized dose effects of carbon ions they are effective for radiotherapy , e.g. only 2 carbon ions deposit 700 times more dose than homogeneous or 234 protons at sub-µm scale

Dose-rate effects



Brenner and Hall, IJROBP, 1991
Durante et al., BJR, 2018
Chaudhary et al., submitted

The A-SAIL project

A-SAIL
ADVANCED STRATEGIES FOR ACCELERATING IONS WITH LASERS

Queen's University Belfast
University of Strathclyde
Imperial College London
CLF RAL - STFC

EPSRC
Pioneering research and skills

PROGRAMME GRANT, 2013-20

A-SAIL's aim

All-optical delivery of dense, high-repetition ion beams at energies of relevance to tumour treatment and diagnosis

INVESTIGATORS:
M. Borghesi (PI), S. Kar, K.M. Prise (QUB)
P. McKenna (Strathclyde),
D. Neely (STFC)
Z. Najmudin (Imperial)

eli beamlines project partner

A-SAIL structure

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1. Ion acceleration

Development and control:

Energy upscaling

Spectral control

Stabilization

2. Underpinning physics

Understanding and controlling the relevant interaction physics, e.g.:

surface dynamics

relativistic transparency

3. Technology developments

Development of enabling technologies.:

Targetry

Diagnostics

Beam transport

Optics

4. Pulsed radiobiology

Biological effectiveness at ultrahigh dose rates

Testing clinically relevant dose delivery patterns

Focus of current research

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- **Demonstrate feasibility of ion beam production**
  - High energy
  - Natively narrow energy distribution
  - High repetition, stability

- **Develop methods of beam transport/ delivery**

  - magnetic based or target based

- Assess the **biological effectiveness** of ultrashort ion bunches

- **Development of appropriate dosimetry**

What will it take for laser driven proton accelerators to be applied to tumor therapy?

Ute Linz[1,*] and Jose Alonso[2,†]

[1]*Forschungszentrum Jülich, D-52425 Jülich, Germany*
[2]*Lawrence Berkeley National Laboratory, Berkeley, California 94720, USA*
(Received 27 April 2007; published 24 September 2007)

In addition to having to develop an entirely new technology for effective beam delivery and dose conformation, the following challenges must be faced by the laser community: (i) verifying scaling laws for proton energy with laser power, (ii) improving proton flux by at least an order of magnitude, (iii) improving shot-to-shot reproducibility to the few-percent level, (iv) development of suitable dose-monitoring devices, (v) development of techniques for accurate dose control and cutoff, and (vi) addressing quality-assurance and patient-safety aspects. This is not to say that one should not work towards solving these tremendous problems! After all, it was realized over 100 years ago that orthovoltage x rays could be used for treating malignancies, but it took many decades—plus the

PRSTAB, 2007

Laser induced ions: Target Normal Sheath Acceleration (TNSA)

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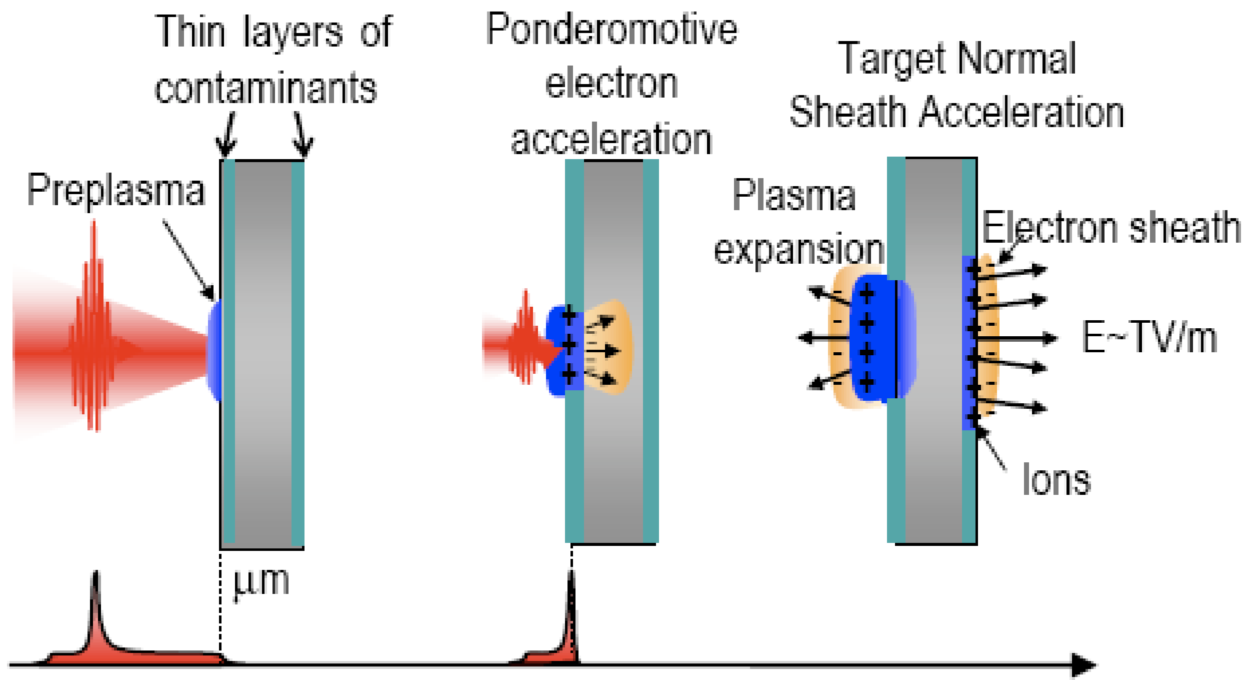
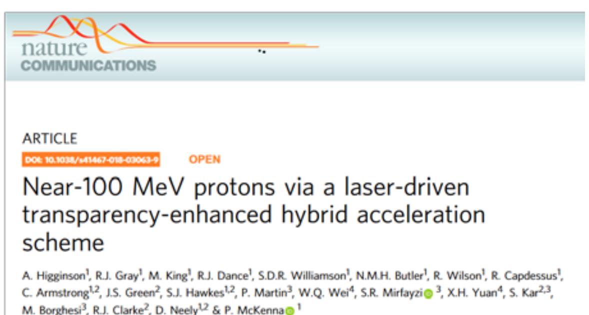
- Several mechanisms for producing laser-driven ions
- Currently ~100 MeV is possible
- For biology studies, pulse to pulse variations, rep rate, intensity and energy all require further developments




nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-03063-9 OPEN

Near-100 MeV protons via a laser-driven transparency-enhanced hybrid acceleration scheme

A. Higginson[1], R.J. Gray[1], M. King[1], R.J. Dance[1], S.D.R. Williamson[1], N.M.H. Butler[1], R. Wilson[1], R. Capdessus[1], C. Armstrong[1,2], J.S. Green[2], S.J. Hawkes[1,2], P. Martin[3], W.Q. Wei[4], S.R. Mirfayzi[3], X.H. Yuan[4], S. Kar[2,3], M. Borghesi[3], R.J. Clarke[2], D. Neely[1,2] & P. McKenna[1]

Lasers used for A-SAIL radiobiology

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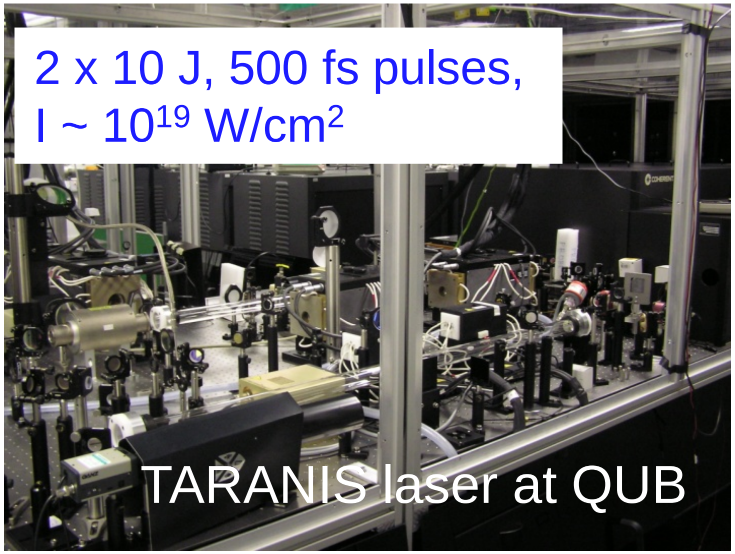
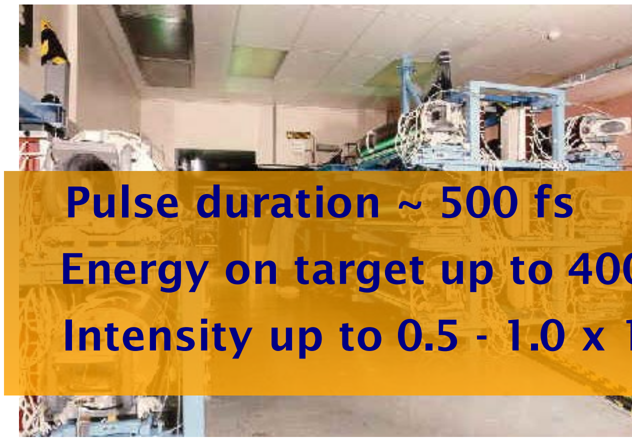


2 x 10 J, 500 fs pulses,
I ~ 10^{19} W/cm^2

TARANIS laser at QUB

VULCAN Petawatt

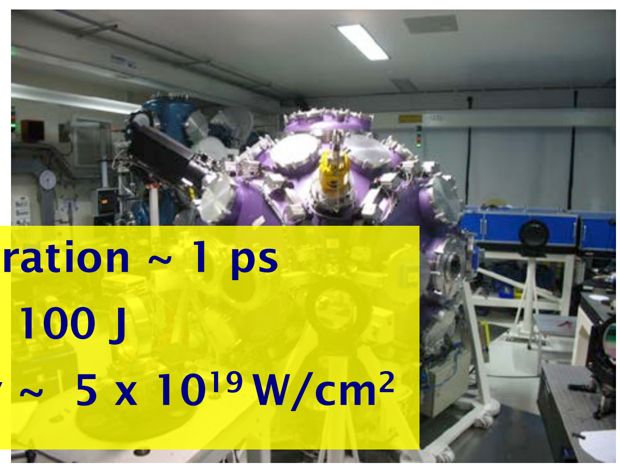


Pulse duration ~ 500 fs

Energy on target up to 400 J

Intensity up to 0.5 - 1.0 x 10^{21} W/cm^2

LULI 2000

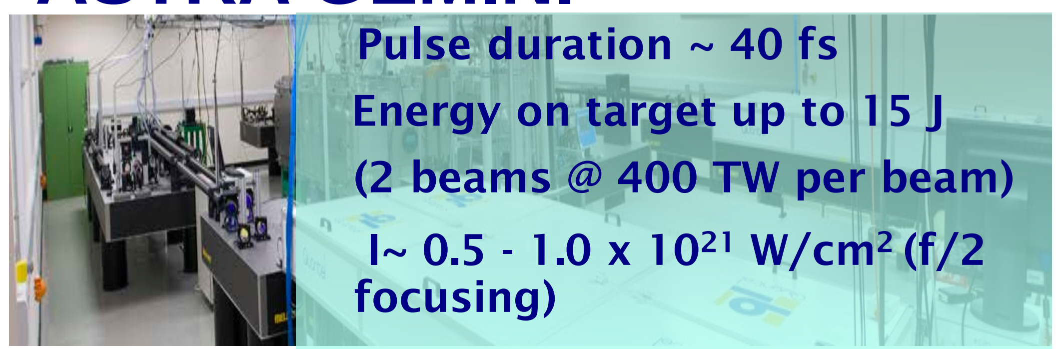


Pulse duration ~ 1 ps

Energy ~ 100 J

Intensity ~ 5 x 10^{19} W/cm^2

ASTRA GEMINI



Pulse duration ~ 40 fs

Energy on target up to 15 J

(2 beams @ 400 TW per beam)

I~ 0.5 - 1.0 x 10^{21} W/cm^2 (f/2 focusing)

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- Radiobiology studies

Current status of laser driven ion radiobiology experiments

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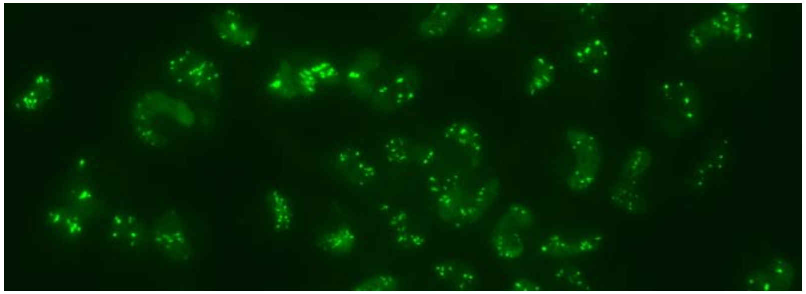
Goals:

1. Development of a methodology and demonstration of viability

2. Validation of laser-driven sources in view of future therapeutic use

3. Assessment of impact related to the short burst nature of the sources

4. Provision of an alternative, flexible source for radiobiological studies



Main groups active in this research over past 10 years

- **HZDR Dresden (Germany)**
- **APRC-JAEA (Japan)**
- **LMU/MPQ Munich (Germany)**
- **LOA (France)**
- **QUB (UK)**
- **HHU Dusseldorf (Germany)**

Planned activities at

- **ELI Beam lines (Czech Republic)**
- **ELI NP (Romania)**

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Two different approaches to laser-driven ion radiobiology

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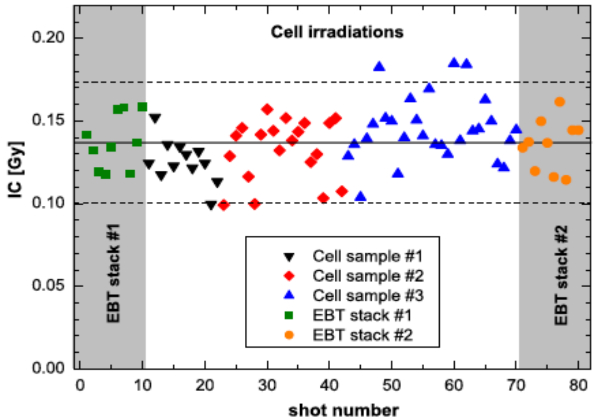
1. Multi-shot: Required dose is delivered in several fractions

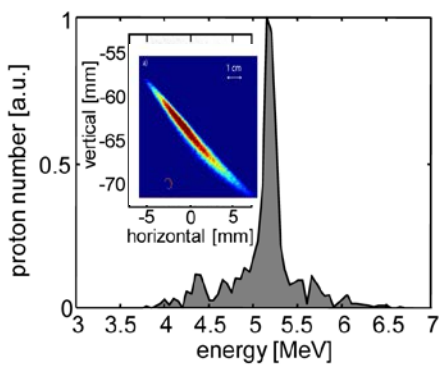


High-rep system
High-rep target
Typically Ti:Sa, fs systems
Dose control, transport

Average dose rate ~ Gy/min

e.g. S. Kraft et al, NJP, 12, 085003 (2010) (HZDR)
A. Yogo, et al, APL, 98, 053701 (2011) (JAEA)

2. Single shot irradiation: deliver of a single dose at Gy level in ~ 100s ps - ns pulses



Suited to low rep systems
More likely to highlight dose rate effects

Average dose rate >10^8 Gy/min

e.g. J. Bin et al., Appl. Phys. Lett. 101, 243701 (2012) (Munich)

+ Our work.....

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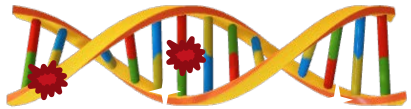
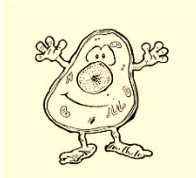
Radiation induced DNA Damage

- DNA is the primary target of radiation induced damage
- DNA DSB are more lethal and lead to cell death

low ionization density radiation induce simple repairable damage



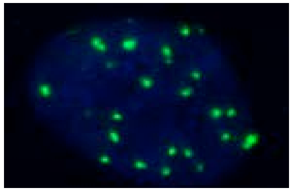


After DNA Repair cells survive

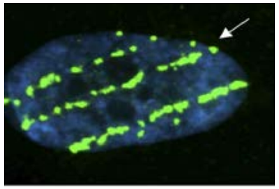
Ions with high ionization density induce complex non-repairable DNA DSB damage

Cell Injury and Cell Death

Low ionization density radiation induced DNA DSB



High ionization density radiation induced DNA DSB



Most important application of DNA DSB damage is for radiotherapy and chemotherapy aim is to kill maximum number of cancer cells by increasing yield of unrepairable DNA damage

Methodology – Biological Endpoints

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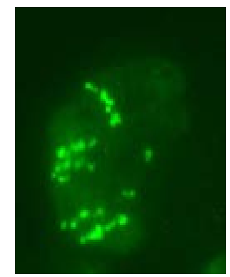
- What are the biological response of cells to ultrashort ion burst of proton and carbon ions?
- How does the presence of oxygen affect ultra-high dose rate radiobiology?

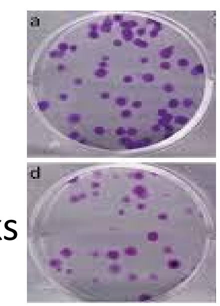
1. DNA DSB Damage and Repair Assay

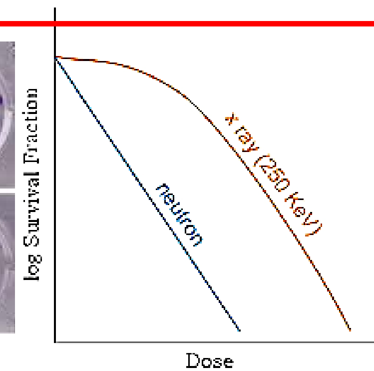
Cells → Exposure to Laser driven ions → Fixation, Staining with DNA DSB damage specific proteins- 53BP1 foci → Image Analysis



2. Cell survival Assay

Cells → Irradiate → Count → Plate → Incubate 1-2 weeks





X-rays are typically used as reference radiation

DNA Damage studies with Laser Driven protons

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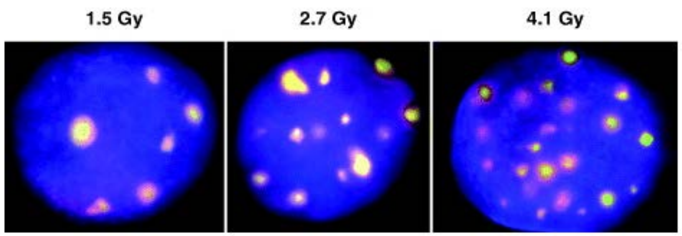
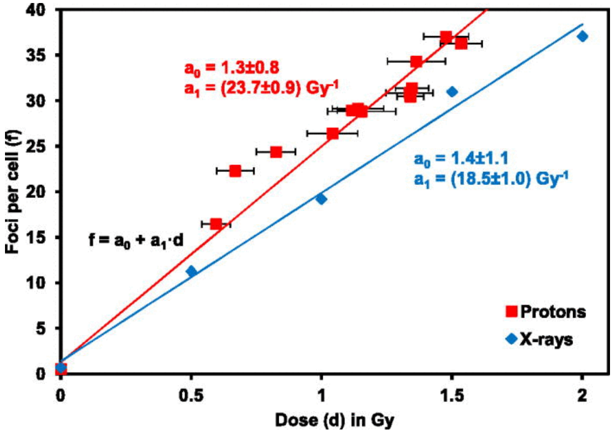
First method development for laser driven radiobiology study
HZDR Group Dresden, SD Kraft et al, 2010; New Journal Of Physics
Dose rate: 4 x 10 ^{7} Gy/ sec **Energy**: 5 MeV
Endpoint: DNA DSB damage
Cells: squamous cell carcinoma irradiated on 50µm surface
12- 29 pulses to deposit dose from 1.5 to 4 Gy
No comparison with reference radiation (X-rays)



LMU/MPQ Munich Group, J Bin et al , 2012; App Phy Lett
Dose rate: >10^{9} Gy/sec; **Energy**: 5-6 MeV
Endpoint: DNA DSB damage foci
Cells: HeLa Cells
Single pulses to deposit dose upto 7 Gy
Quadrupole magnet focused beam -1.5 Gy dose
Reference Radiation - X rays



Proton dose delivered in multiple or single pulses induced a dose dependent DNA damage more than X-rays. More comparisons with Cyclotron accelerated ions are still needed

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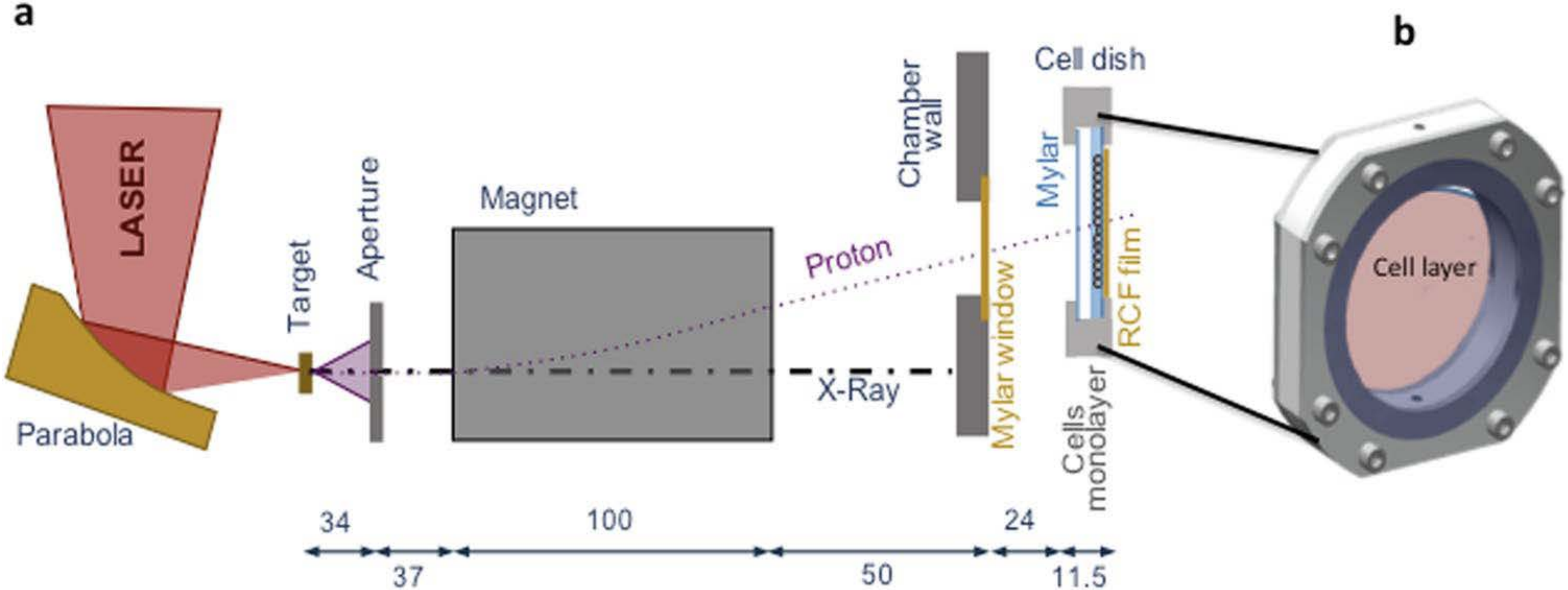
DNA damage studies on ASTRA GEMINI



- **f/2** off-axis parabola
- Linearly polarised beam with intensity **~3 x 10^{20}Wcm^{-2}**
- **25 nm** amorphous carbon targets.
- Magnetic spectrometer to disperse ions with respect to energy.
- Compact system to maximize dose and dose rate to cells

Hanton *et al,* Sci. Report, **9**, 4471 (2019)

- Energy - 10 MeV
- Dose - 1Gy
- Dose Rates - 10^9 Gy/sec
- Normal Human Fibroblasts
- Dose delivery: Single pulse

Dynamics of damage and repair can be studied

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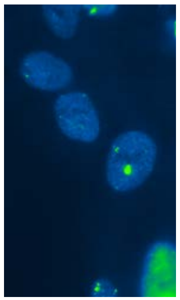
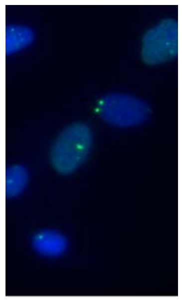
0.5 hours post irradiation

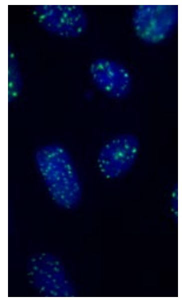


un-irradiated

proton

1 hour post irradiation

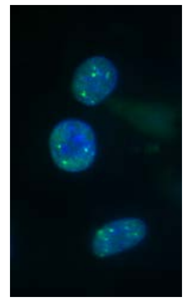


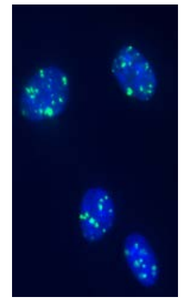


un-irradiated

proton

2 hours post irradiation

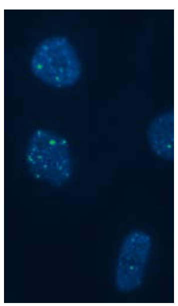


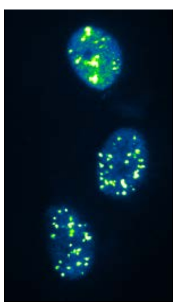


un-irradiated

proton

6 hours post irradiation

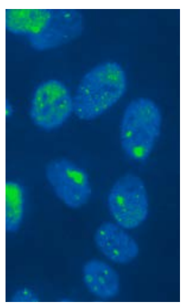


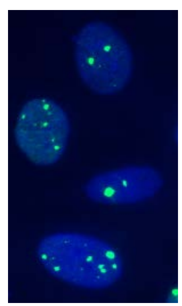


un-irradiated

proton

24 hours post irradiation





un-irradiated

proton

Cell line: **AG01522** Human fibroblast (1 Gy)
Fixed at 0.5-24 hr after exposure
Assay: 53BP1 Immunofluorescence

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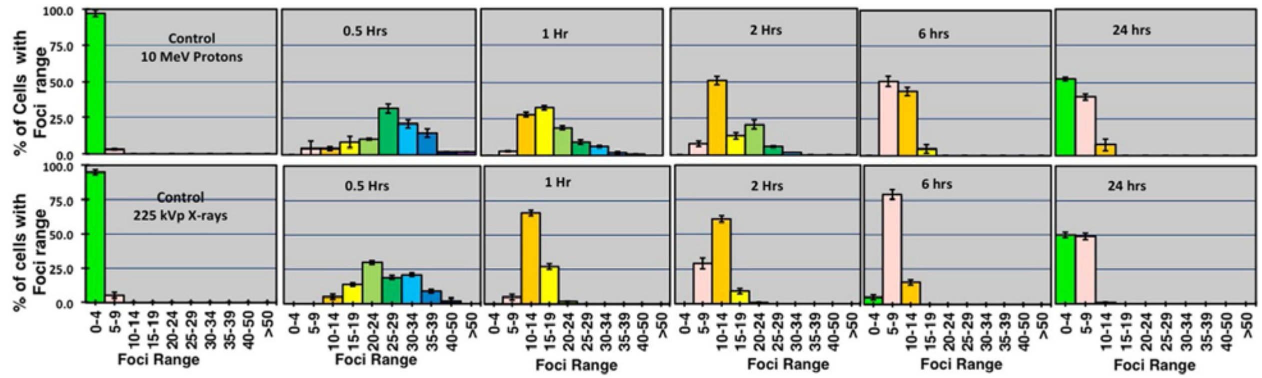
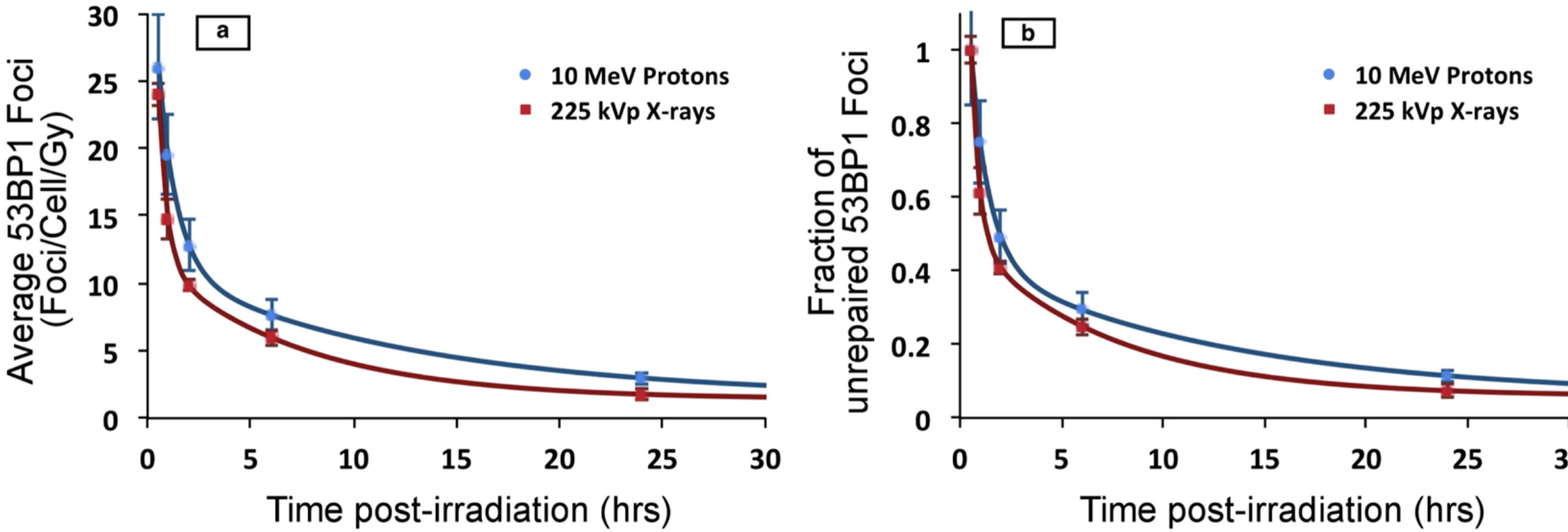
DNA repair dynamics investigated up to 24 hours

- Differences in foci distributions and repair kinetics relative to X-rays

- 10 MeV protons, 4.6 keV/μm



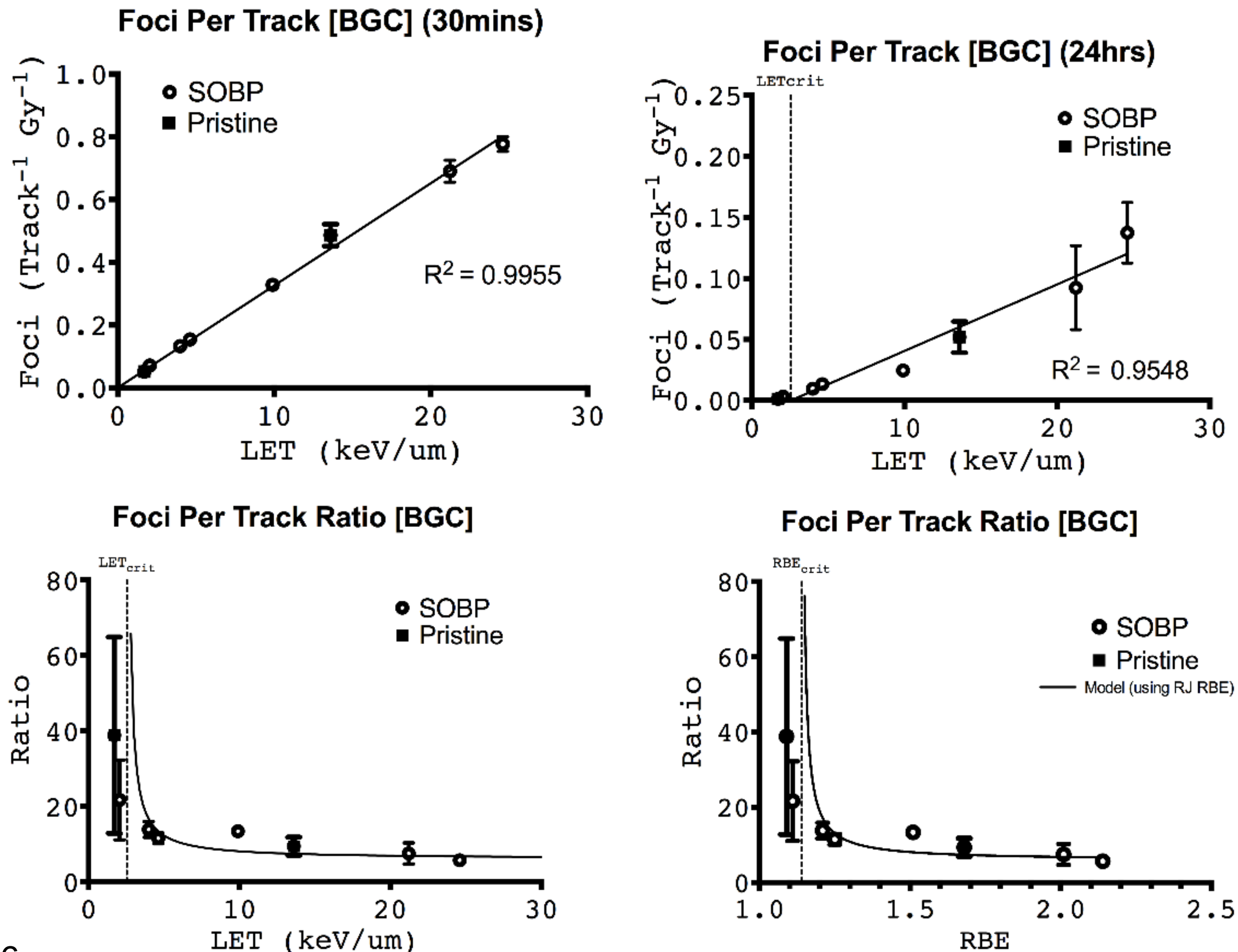


Hanton *et al*, Sci. Report, **9**, 4471 (2019)

Calibrations of DNA damage - protons

ADVANCED STRATEGIES FOR ACCELERATING IONS WITH LASERS

- Conventional protons delivered at ~ 2 Gy/min
- Linear relationship between foci per track and LET
- Slope dependent on repair time



Chaudhary *et al.* 2016
Int J. Radiat Oncol Biol Phys, **95,** 86

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Laser versus conventional beams

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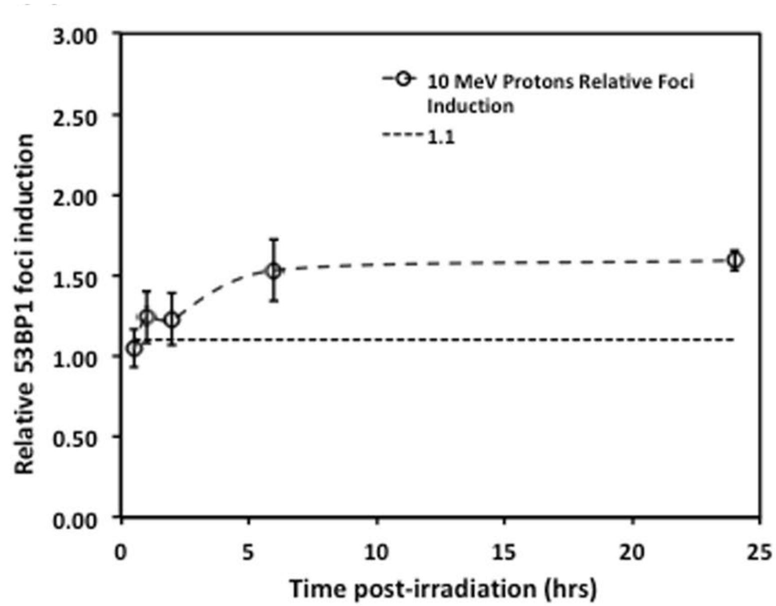
- Results from laser accelerated protons (LAP) in line with expectations from conventional accelerated protons (CAP)
- 10 MeV, 4.6 keV/µm
- 10^9 Gy/s single pulse



Hanton *et al*, Sci. Report, **9**, 4471 (2019)

Role of oxygen in laser driven ion radiobiology

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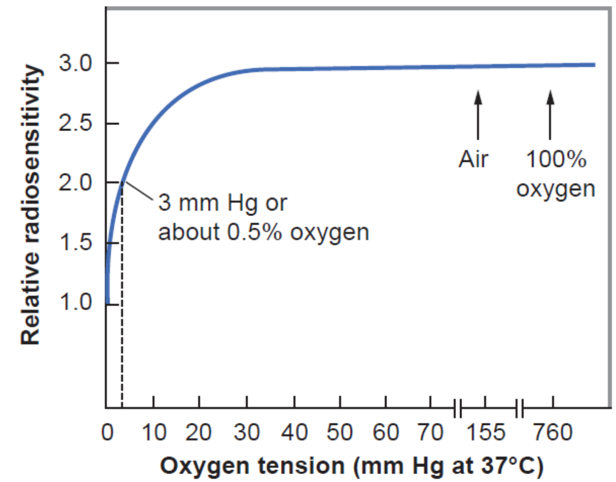
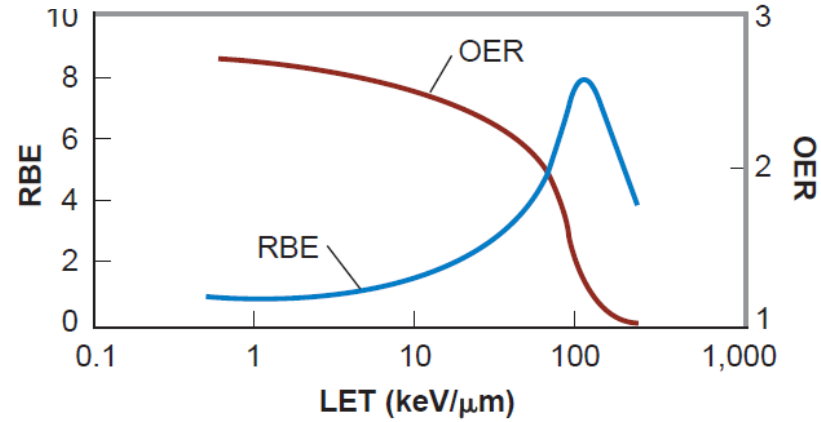
DVANCED STRATEGIES FOR
CCELERATING IONS WITH LASERS

- Cells and tissues can be up to **3 times more radioresistant** to photons in the absence of oxygen
- This is a major limiting factor in the treatment of **solid tumour with hypoxic regions** by photon radiotherapy
- With **increasing ionization density** (LET) the modulation by **oxygen (OER) decreases**
- This is one of the rationales for using ion beams with higher LETs for therapy
- Dose-rates higher than 10^9 Gy/s and 5 – 10 Gy **deplete cellular oxygen**





Jones *et al.*, 2012, BJR, 35, e933

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Vulcan Laser Facility

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Vulcan TAP
Laser Interaction chamber

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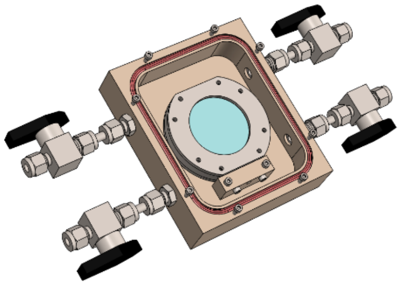
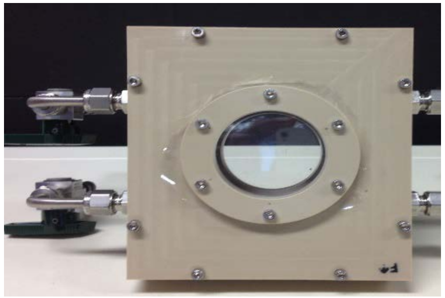
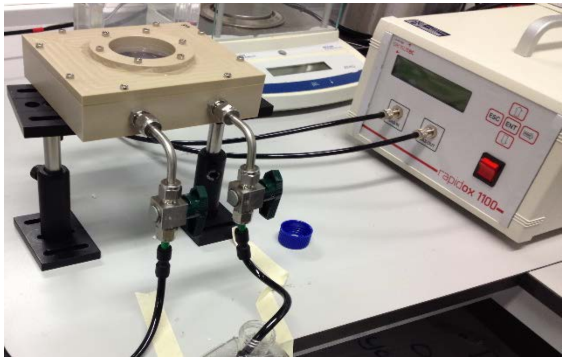
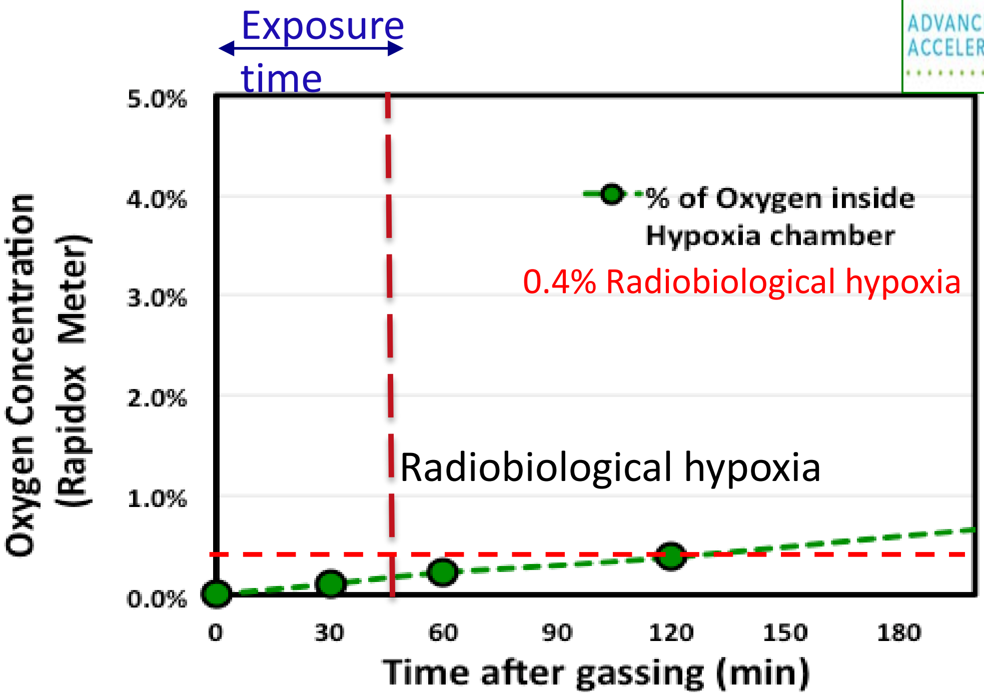
Hypoxia chamber for laser driven ion irradiations under controlled oxygen levels







Hypoxia induction with 5% CO_2, 95% N_2



Total Time needed for each shot after gassing is about 45 minutes maximum

Vulcan irradiation set up

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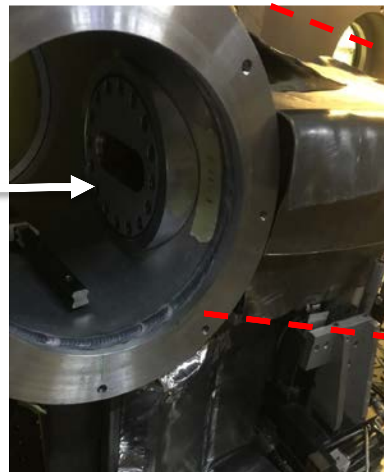
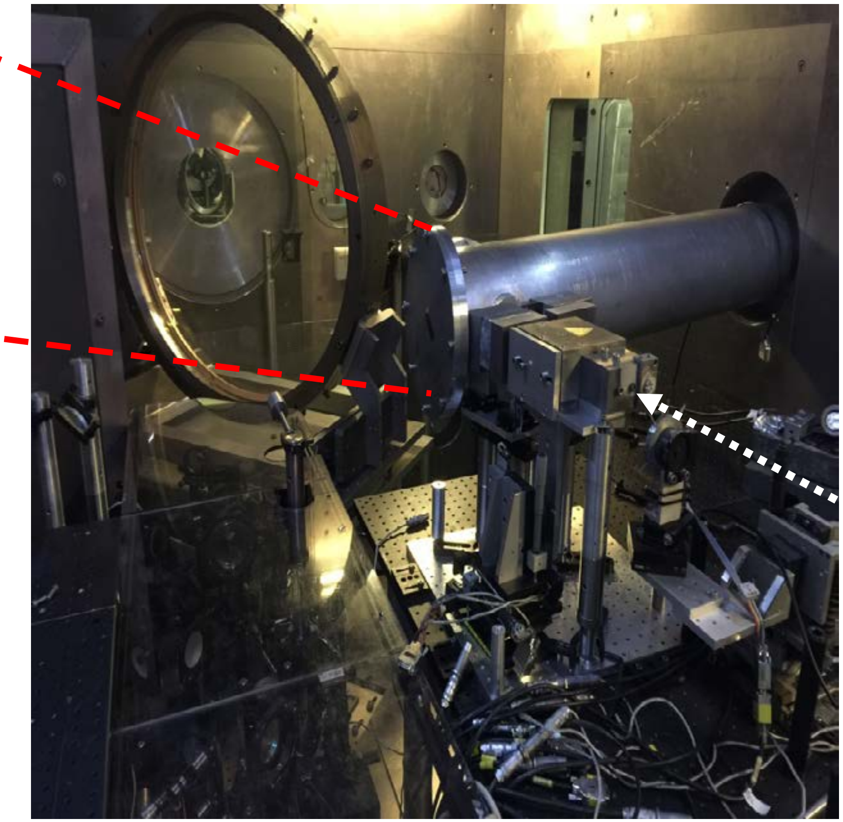
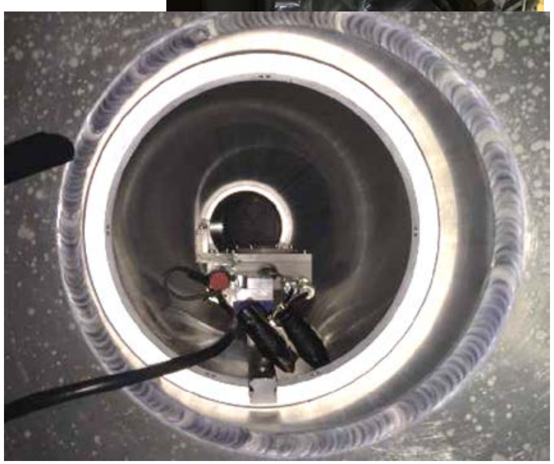
Sample Position





Direction of the laser onto the target

Sample holder sealed then raised 90^0 into irradiation position



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An example of results from hypoxic irradiation at ultra-high dose rates

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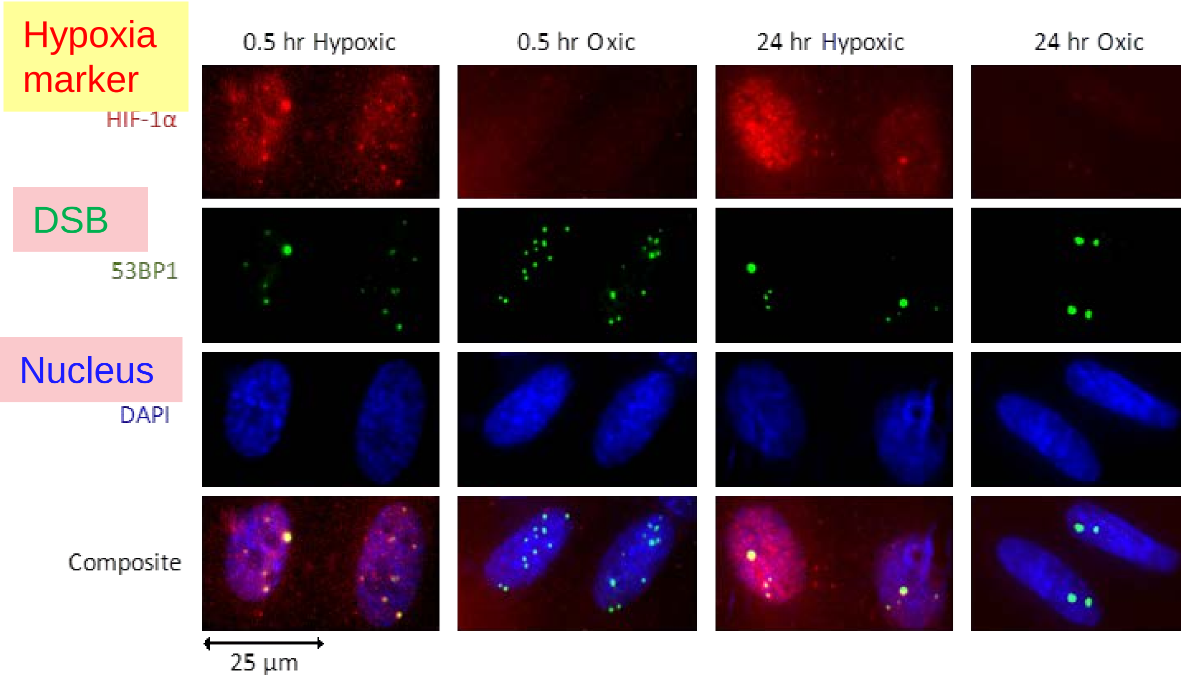
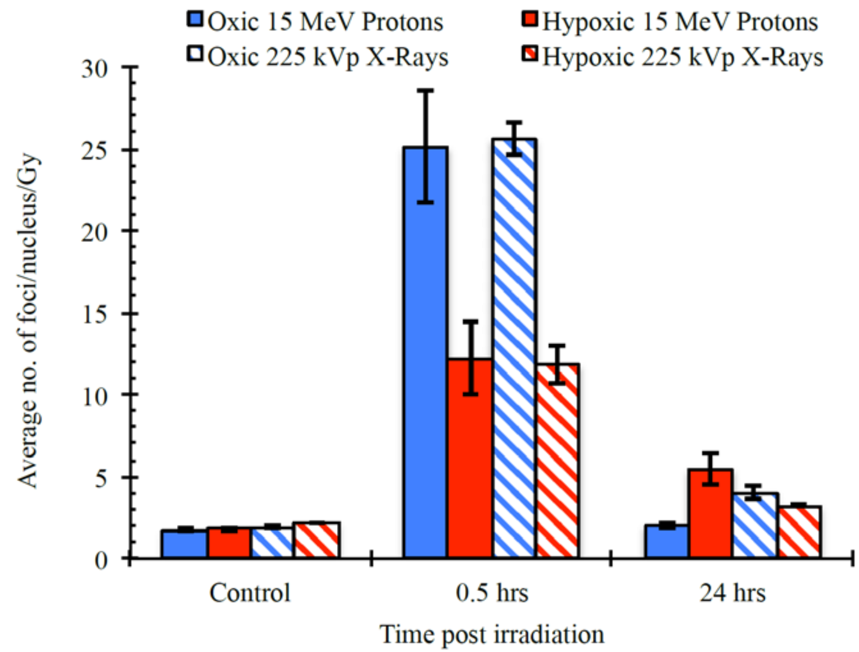
Gwynne, Chaudhary *et al.*, unpublished





- Data from 15 MeV laser-driven proton irradiation of AG01522B cells
- Increased residual damage with protons (2.6 keV/µm)

Other Endpoints

Cell killing studies with laser driven protons

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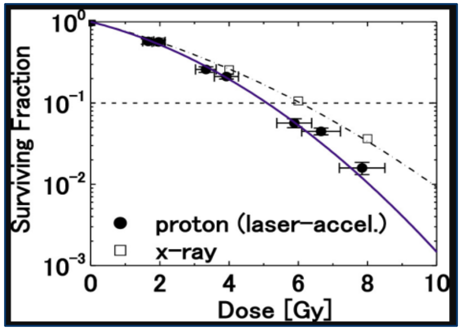
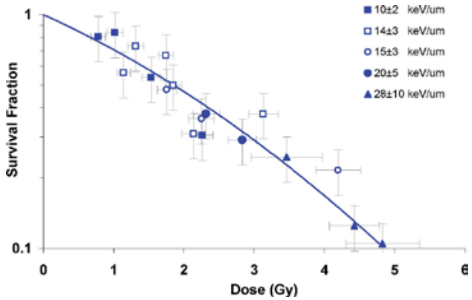
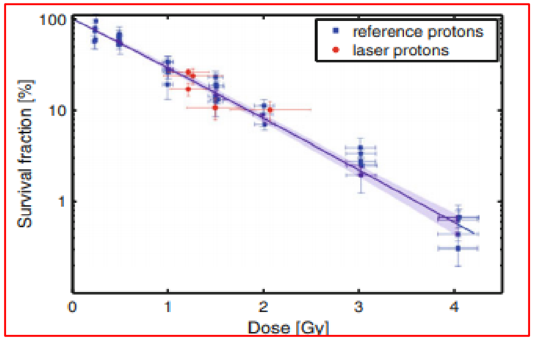
First comparison of cancer cell killing response of laser driven protons with reference X-rays Yogo *et al* 2011, Appl. Phys. Lett;98
Dose rate: 4 x10 ^{7} Gy/sec ; **Energy**:2.25 MeV
Cells : human salivary gland tumour cells ;
Relative Biological Effectiveness (RBE)= 1.2 compared to X rays
Dose delivery Mode: **multiple pulses**



First radiobiological study of laser driven protons at a dose rate of 10^{9} Gy/sec
Doria et al , AIP Advances 2012
Dose rate: 10 ^{9} Gy/sec ; **Energy** range: 1-5 MeV
Cells : V79 cells ; RBE- 1.4 compared to X rays
Dose Range: 1-5 Gy :Dose delivery Mode: **single shots**



First comparison of Cell killing response of laser driven protons with *cyclotron accelerated protons*
HZDR and Dresden Group, Zeil et al 2013, Appl. Phys Lett B; 110
Dose rate:4 x 10 ^{7} Gy/sec: Energy:2.25 MeV;
Cells: Squamous Cell Carcinoma
Dose delivery mode: **multiple pulses**



Laser driven protons show higher biological effectiveness than X-rays, but no difference with RF – accelerated protons in current experiments

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Temporal delivery of laser driven ions can change the biological response of cells

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LOA Group, Bayart *et al*, Scientific Report, 2019
Dose rate: 1.5 x 10 ^{8} Gy/sec;
Energy range: 1-6 MeV
Dose delivery mode: **multiple pulses**
Time interval between pulses : 3-60 seconds

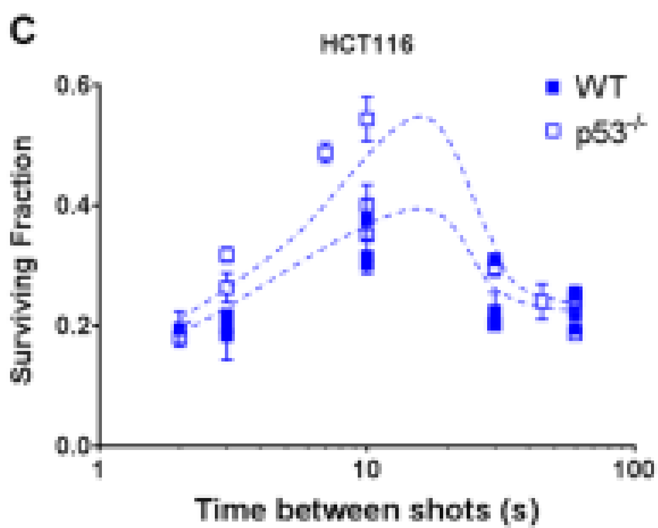
SCIENTIFIC REPORTS

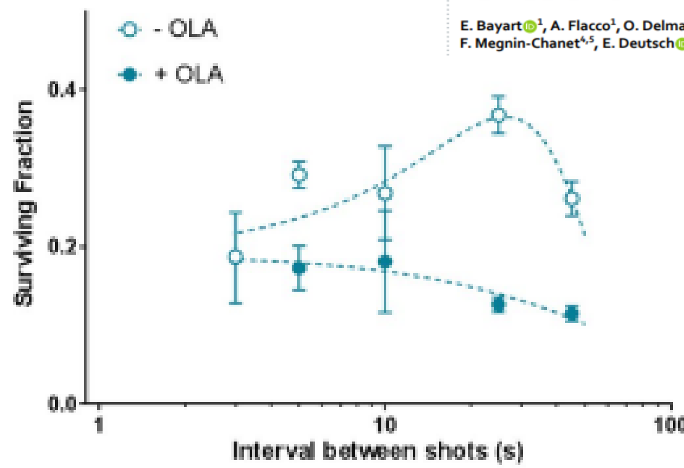
OPEN

Fast dose fractionation using ultra-short laser accelerated proton pulses can increase cancer cell mortality, which relies on functional PARP1 protein

Received: 25 February 2019
Accepted: 28 June 2019
Published online: 12 July 2019

E. Bayart[1], A. Flacco[1], O. Delmas[1], L. Pommarel[1,2], D. Levy[1,3], M. Cavallone[1], F. Megnin-Chanet[4,5], E. Deutsch[4] & V. Malka[1,3]

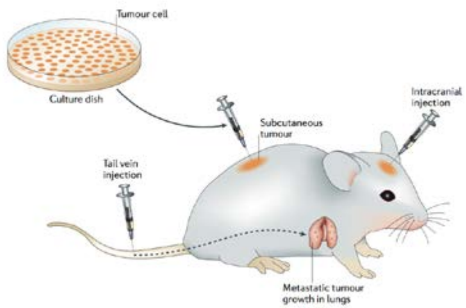




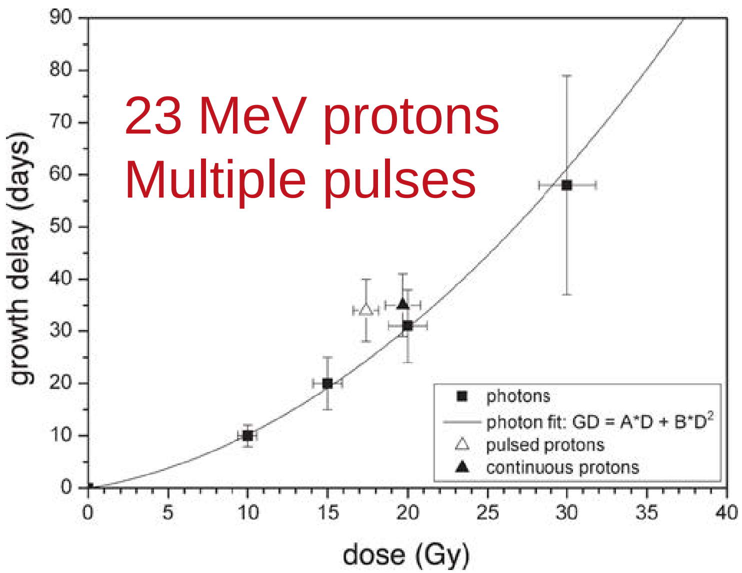
Cell survival of cancer cell lines was found dependent on +/- p53 and DNA repair inhibition along with the bunch repetition rate of laser driven protons – **Biology plays a role**

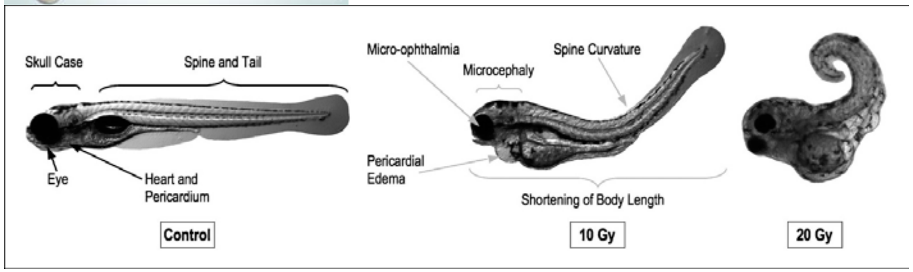
In vivo studies

- *In vivo* studies with laser driven protons have been started Using scanning ion microprobe SNAKE at Munich Tandem accelerator as surrogate of laser driven ions mouse tumour growth delay studies (Zlobinskaya *et al.,* 2014)
- In mice models also pulsed protons were found effective
- in delaying the tumour growth.
- Pilot studies with mouse tumours and zebrafish models carried out at HZDR (Brunner *et al.,* 2020).



Tumour cells can be injected to mice. After tumour formation, the tumours can be irradiated and growth monitored over time





Zebra fish embryo 24 hours post fertilization are irradiated and radiation induced changes recorded

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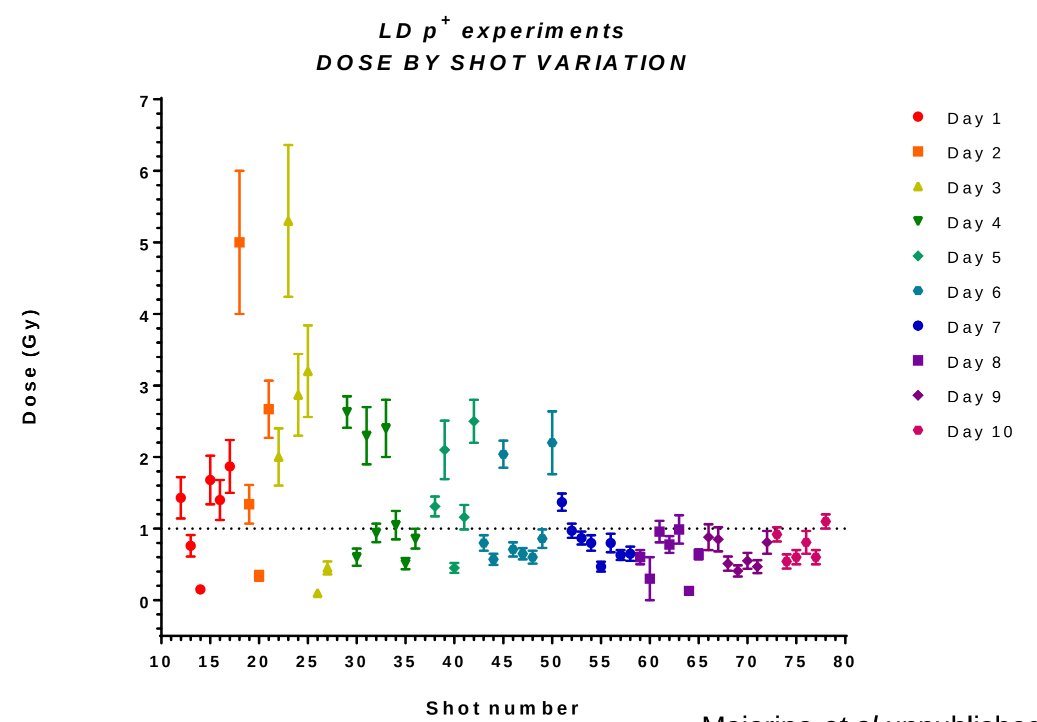
Challenges and opportunities

Challenges and Opportunities - 1

- Accessibility
- Pulse to pulse variation
- Energy resolution
- Frequency
- Beam size
- Other ions



Maiorino *et al* unpublished

Challenges and Opportunities - 2

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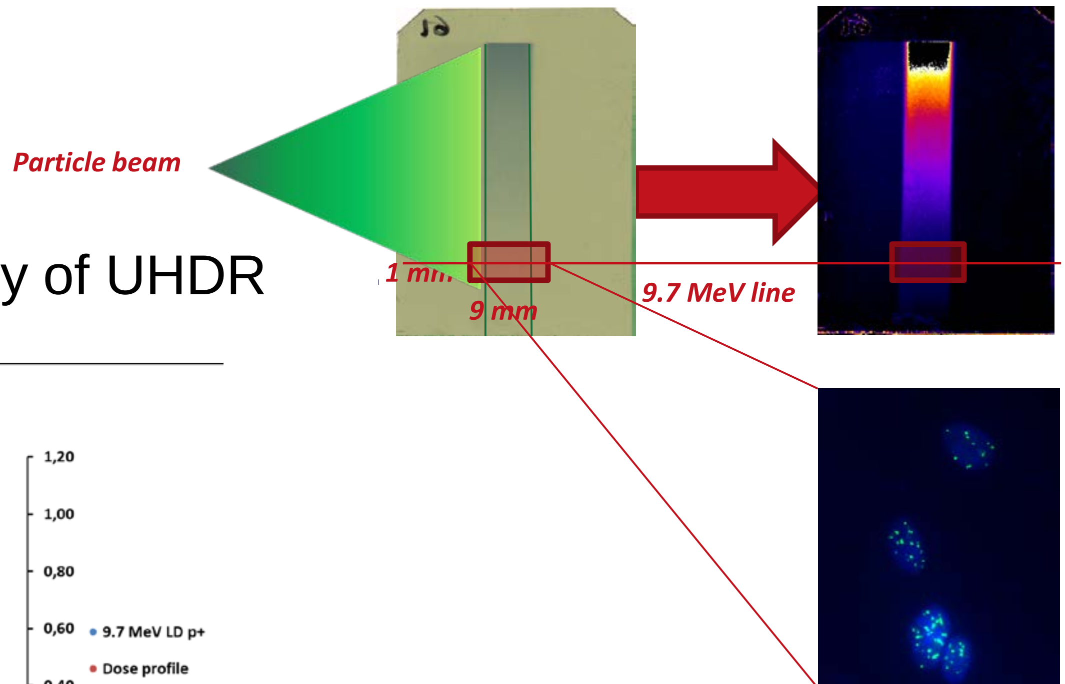
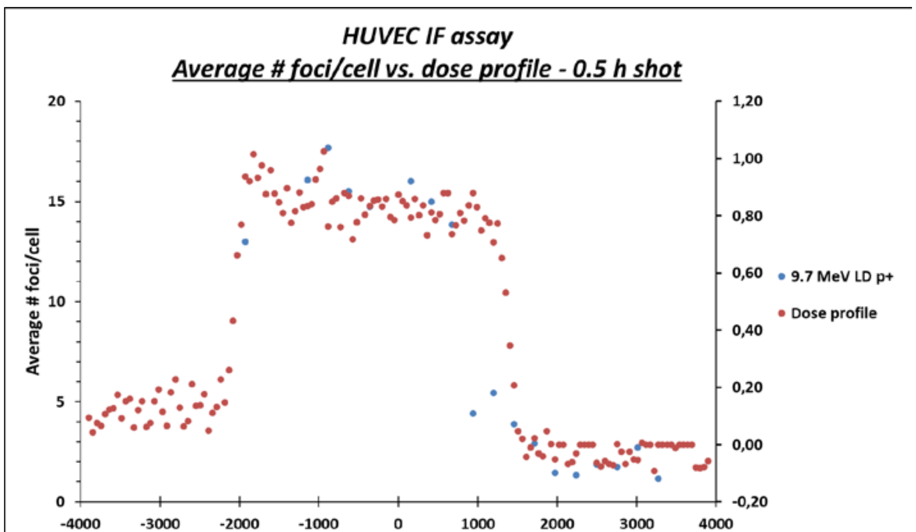
- Dosimetry
- Positioning accuracy
- End points
- Physics/Chemistry/Biology of UHDR





Maiorino *et al* unpublished

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Summary

- Radiobiology studies of laser driven ions are:
  - Validating the future applications of laser driven sources
  - Testing largely unexplored regimes of ultra-high dose rates
  - Validating new understanding of dose-rate effects.

- With the development and optimization of beam production and delivery techniques more energetic ion beams and species will be available.

- To properly understand the ultra high dose rate radiobiology more comparisons are needed at similar energies with cyclotron accelerated ions across a range of dose-rates and biological models.

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