

# Dosimetry for proton irradiation of 3D cell models at ultra-high dose rate

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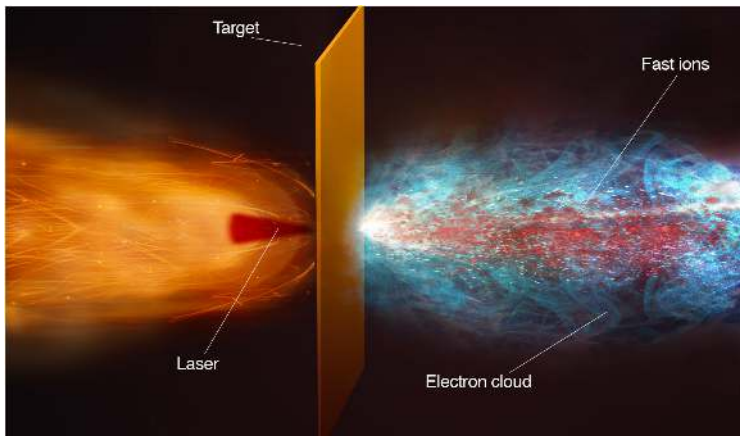
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# Laser-acceleration of ions for biomedical applications

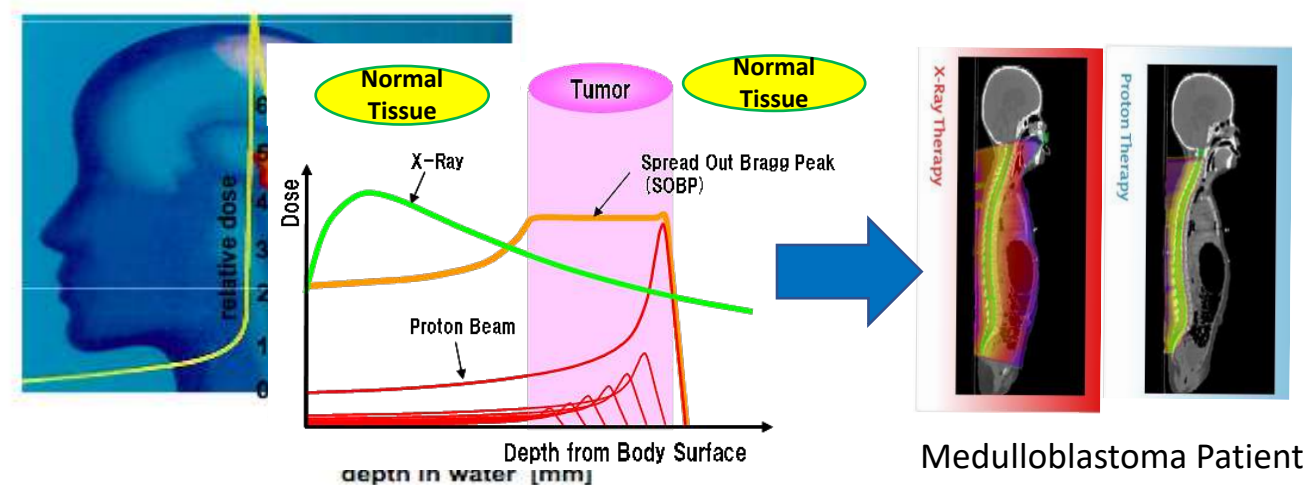


## Proton-hadron therapy

- Dose deposition in a unique pattern called Bragg Peak.
- Spares the normal surrounding tissues

## Activities

- WP1:** Exploration of different acceleration regimes
- WP2:** Investigation of the extreme interaction physics underlying the acceleration processes
- WP3:** Development of enabling technology (targetry, advanced optics, diagnostics)
- WP4:** Investigation of highly pulsed ion radiobiology



# Radiobiology at ultra-high dose rate

**Conventional dose-rate**  
0.01-0.1 Gy/s (1-10 Gy/min)



**FLASH dose-rate**  
>40 Gy/s (>2400 Gy/min)

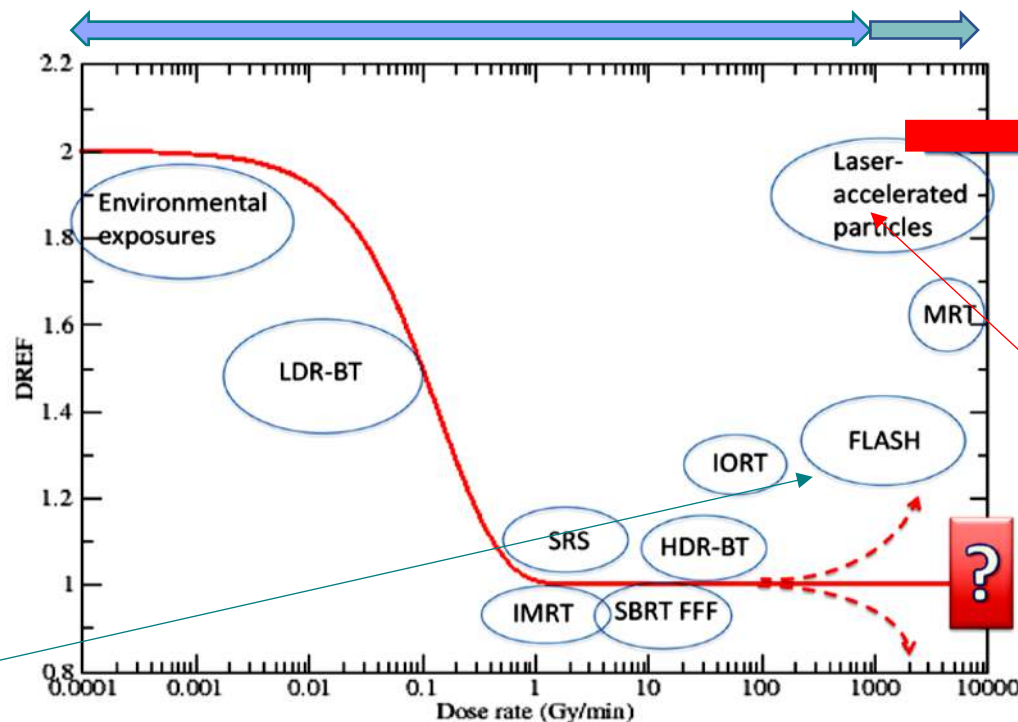


**Laser-driven dose-rate**  
>10<sup>9</sup> Gy/s (>10<sup>11</sup> Gy/min)

## Possible effects

- Spatio-temporal overlap of independent tracks
- Local depletion of oxygen
- Lack of interaction between prompt DNA lesions and indirect lesions

**Spare normal tissues preserving the anti-tumor activity**



M Durante *et al*, BJR, 2014

## Studies

- Investigations of DNA damage and repair dynamics
- Survival studies
- Sub-lethal damage investigations

**A Novel regime of radiobiology**

Hanton, F. et al., DNA DSB Repair Dynamics following Irradiation with Laser-Driven Protons at Ultra-High Dose Rates. *Scientific Reports*, 9(1), 4471.

<https://doi.org/10.1038/s41598-019-40339-6>

## PURPOSE

Irradiation of Glioblastoma stem cells irradiation in 3D and 2D configuration with 30-35 MeV protons

## CHALLENGE

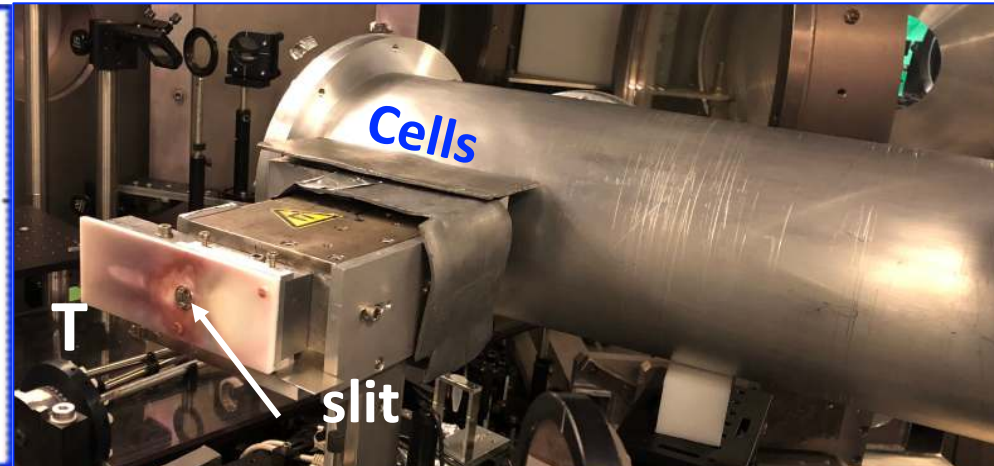
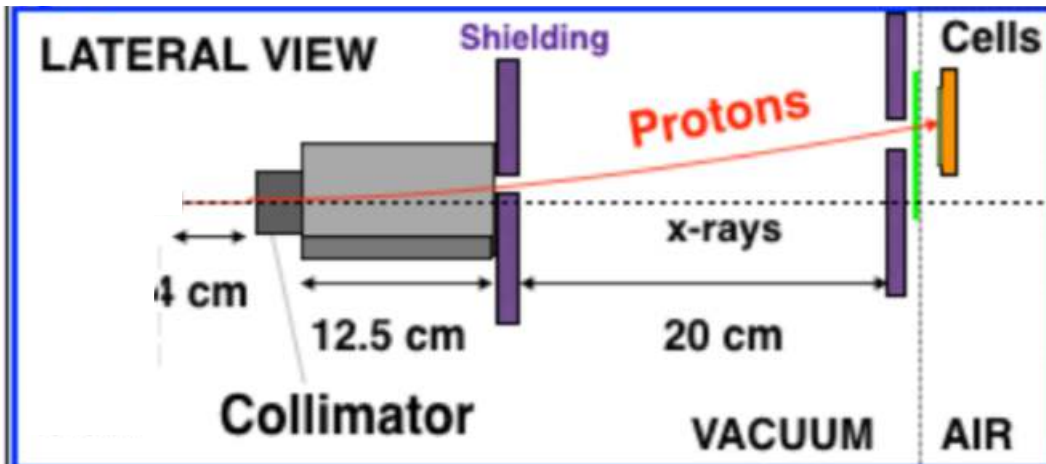
Sufficient dose at 30-35 MeV

Depth-dose distribution homogeneity (3 mm) for 3d cell irradiation

## Beam and setup parameters

- Dose- 0.5-4 Gy
- Variable slit (0.25-1 mm)
- Dose Rates-  $10^9$  Gy/s
- Dose delivery: Single pulse
- Radiochromic films (RCF-EBT3) for dosimetry

## Experimental setup



## Vulcan PW

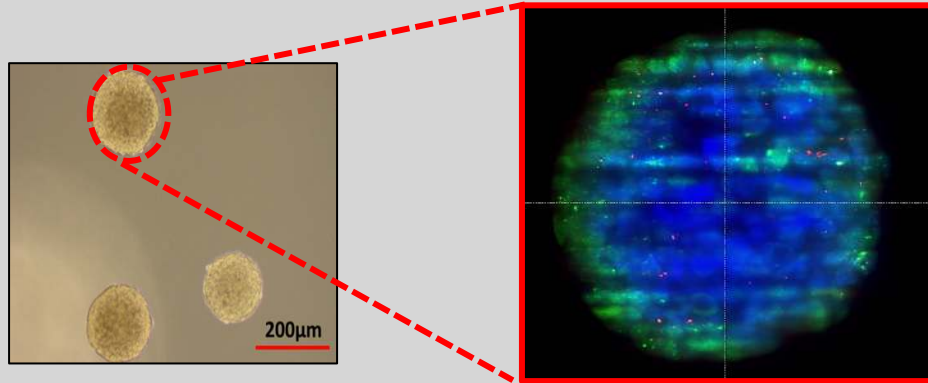
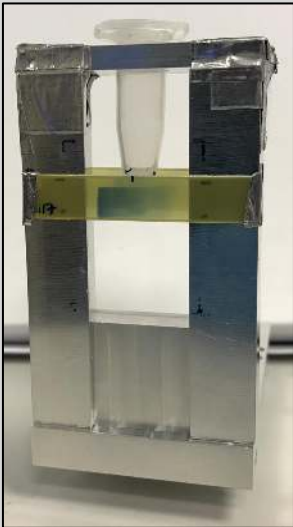
Power: 1 PW  
 Time pulse: 500 fs  
 Energy: 650 J  
 Intensity:  $10^{21}$  W/cm<sup>2</sup>  
 Target: 15 um Au

# Cell irradiation

## Biological Endpoints

- DNA DSB Damage and Repair Assay -> FOCI counting
- Clonogenical assay -> Cell survival fraction as a function of the absorbed dose

## Neurospheres GBM stem cells in Eppendorf tubes



DNA DSB damage in 3D neurosphere detected using Octopus Light Sheet Microscopy. Nucleus is shown in blue, green dots represent DNA DSB break in cells.

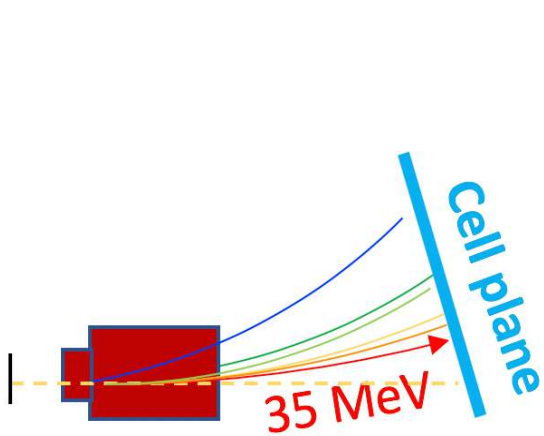
- Enhanced biological damage induced in 3D cell models neurospheres due to hypoxic regions in their interior
- 3D neurospheres are more realistic because they mimic the tumor architecture and provide a snapshot of the tumour physiological microenvironment

## 2D GBM cells in slide flask

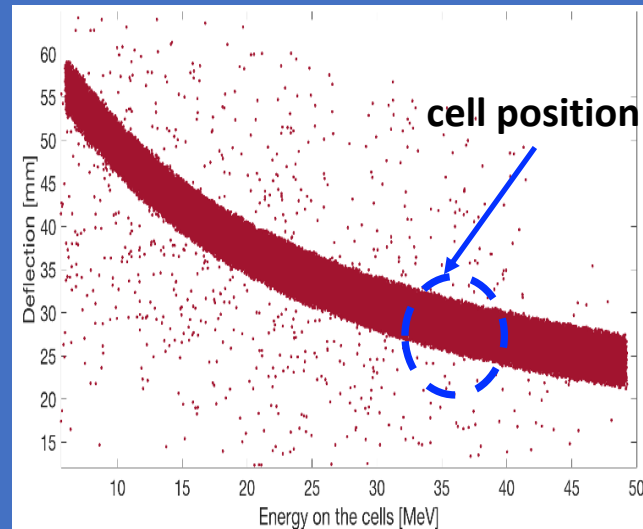


RCF-EBT3 in front for dose measurement  
Monolayer (10 μm) cells for comparison

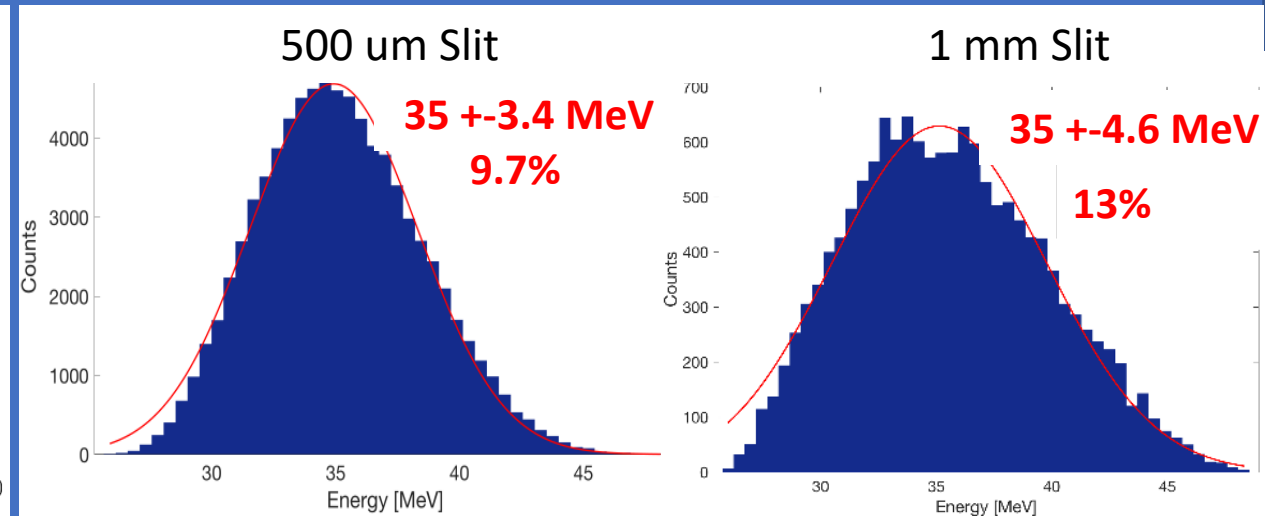
# Transverse profile and energy spectrum



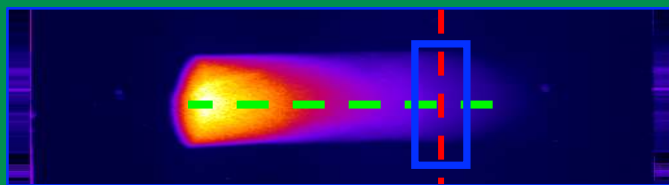
**G4** Energy dispersion



Energy spread VS slit aperture

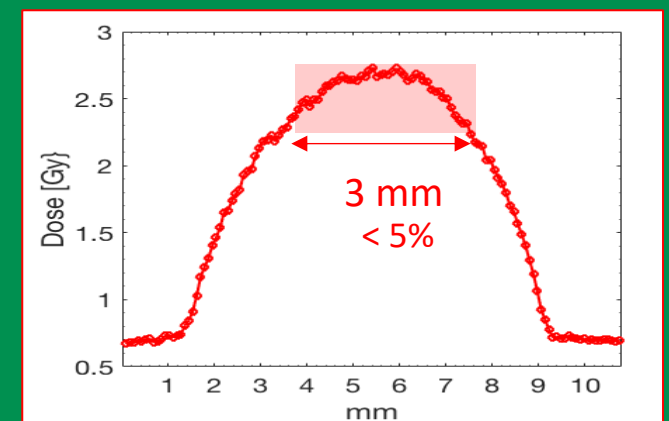
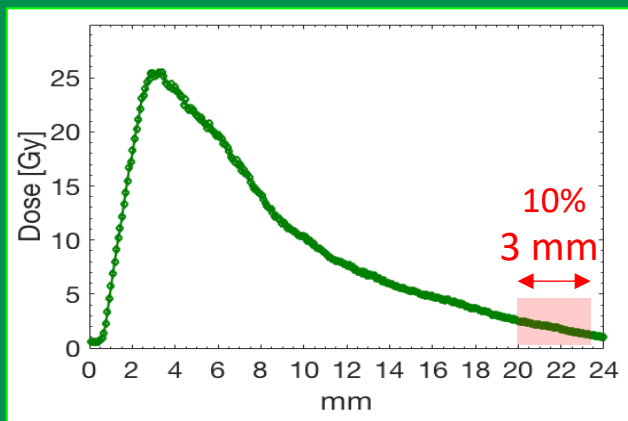


Dose distribution @ cell plane 0.5-30 Gy whole energy spectrum



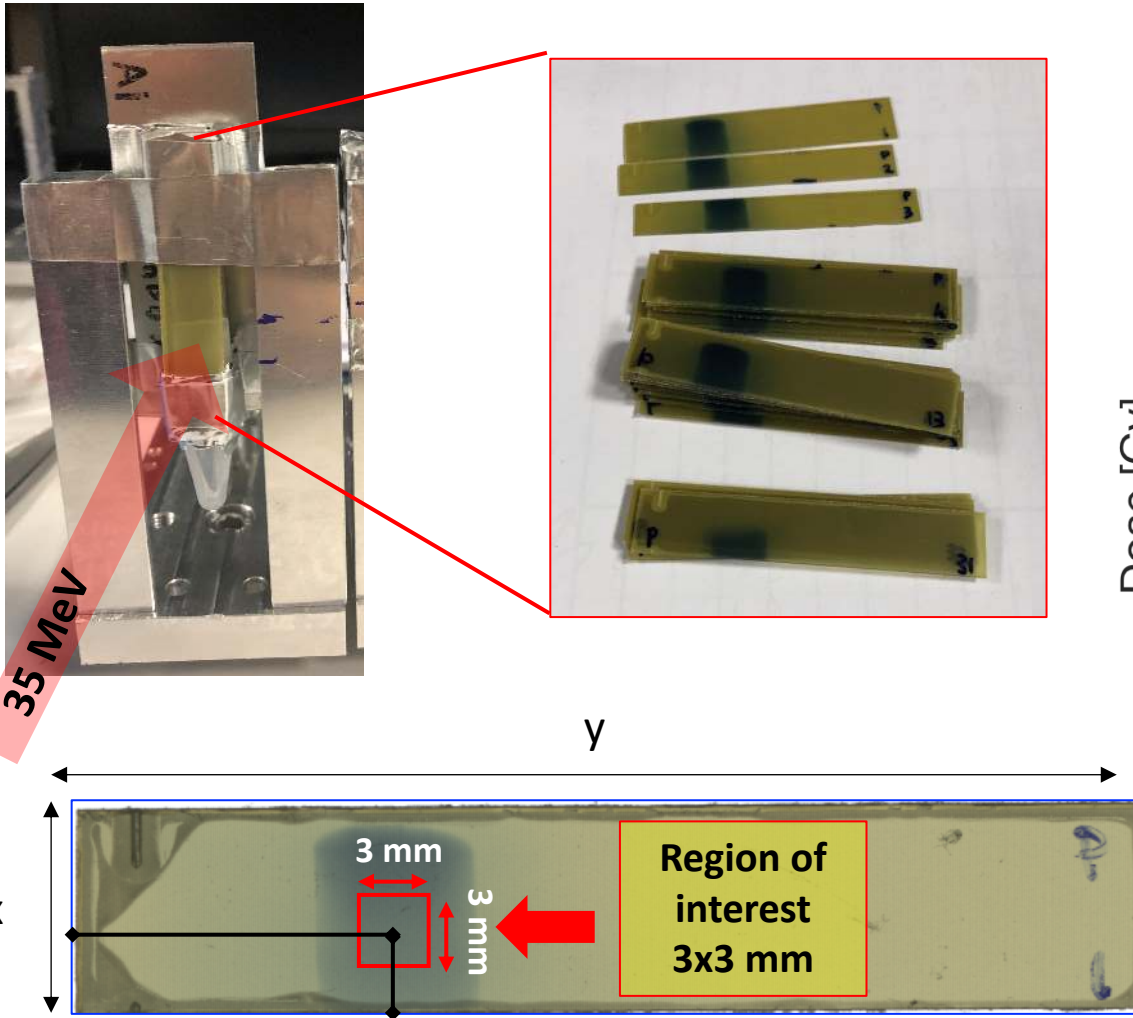
Low energy      Cells      High energy

0.2-3 Gy @35 MeV

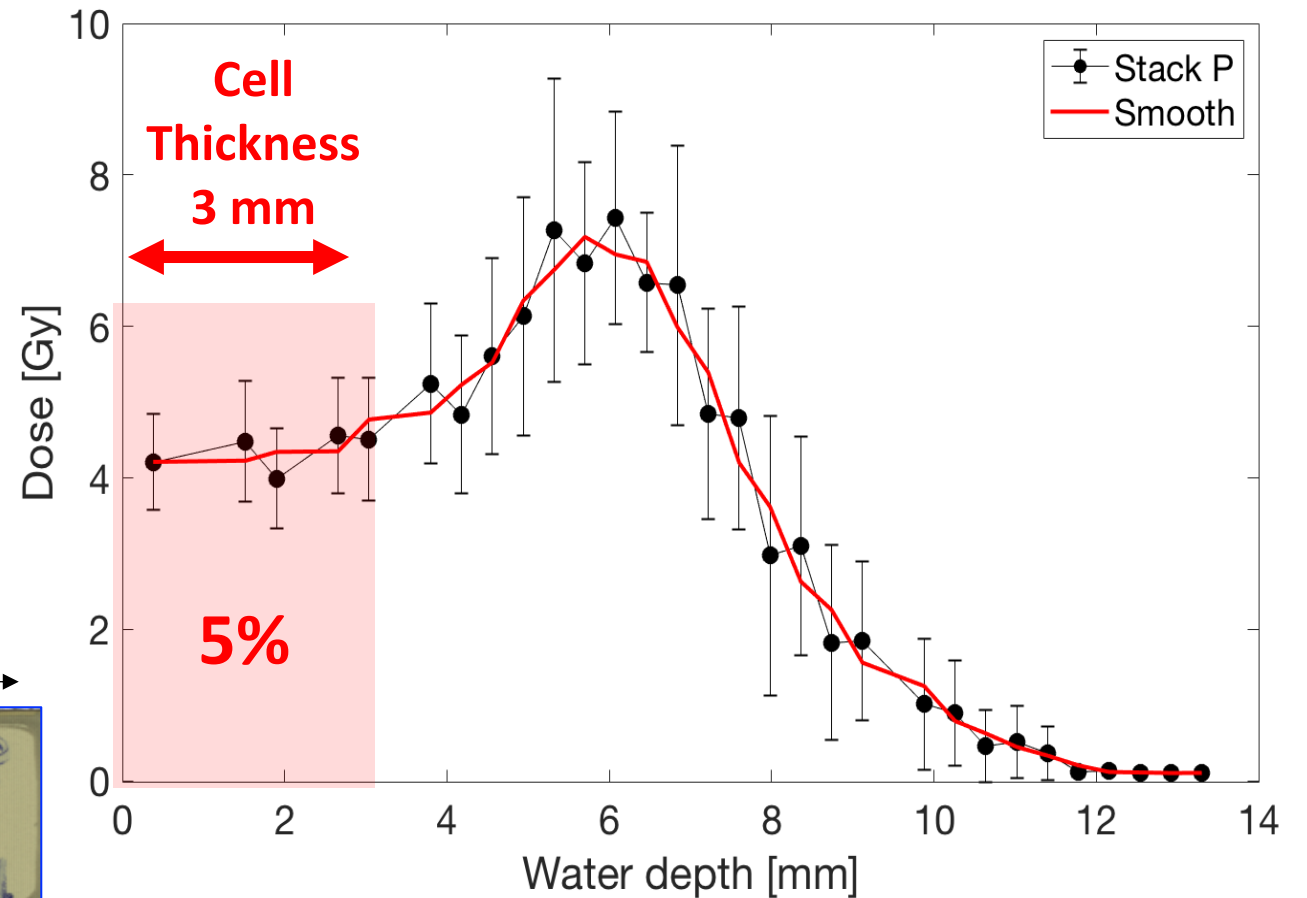


# Depth-dose profile at cell position

RCF stack at cell position

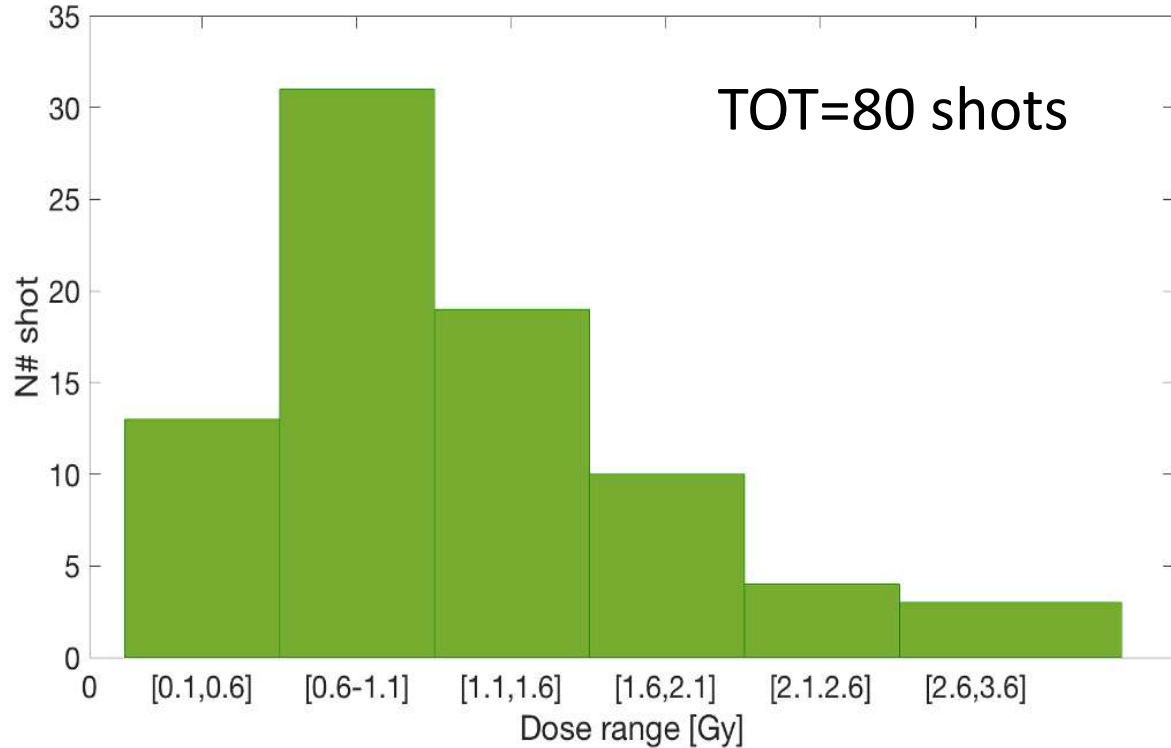


Depth-dose profile

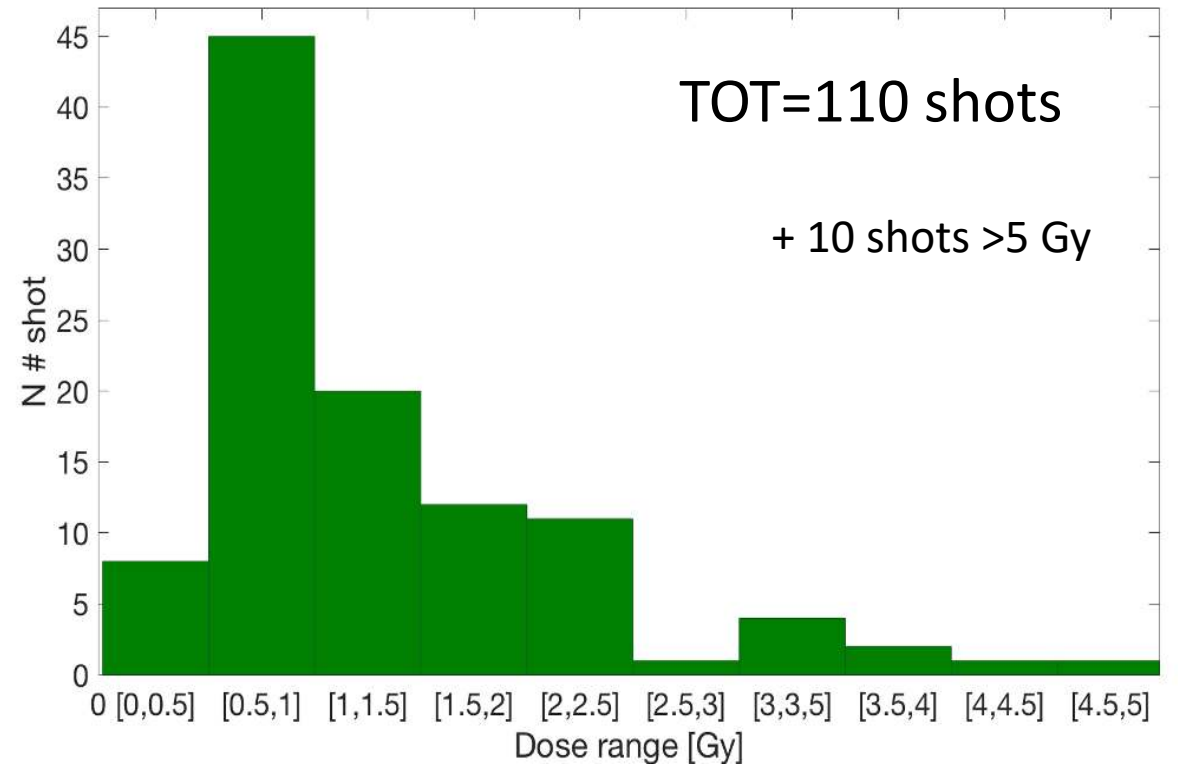


# ...a bit of statistics

## First exp run



## Second exp run



Reference measurements with conventionally accelerated protons (30-60 MeV) have been performed at LNS-INFN along CATANA beamline- analysis is ongoing



# Contributors

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# Thank you