Destructive potential of low-dose proton therapy (LDPT) on neurodegenerative disorders

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FCT Fundação para a Ciência e a Tecnologia

Introduction
Motivation

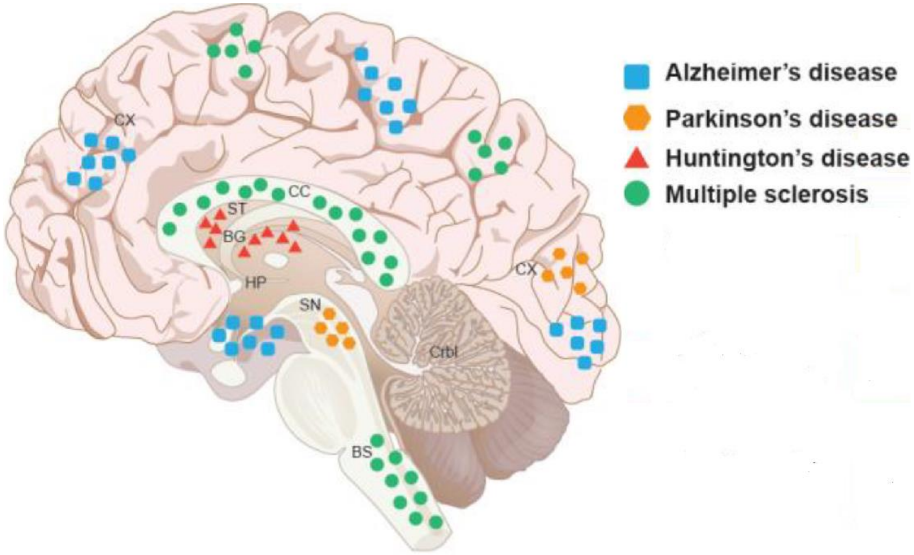


Fig. 1 - Major neurodegenerative diseases and their associated regions (Hussain *et al.* 2018)

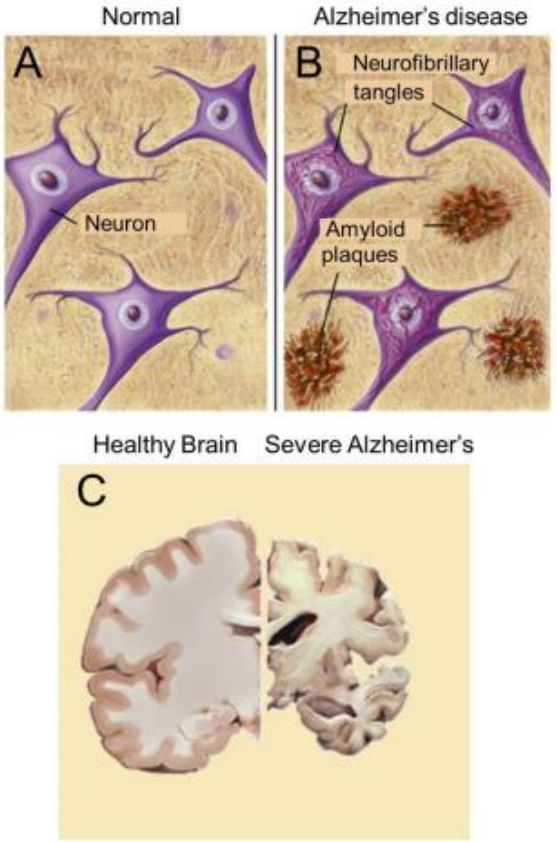


Fig. 2 – Healthy brain tissue (A) vs Alzheimer's Disease brain (B). Brain apoptosis in later stages of the disease development (C) (De Loff *et al.* 2019)

Introduction
Motivation

- Radiotherapy
  - Safe and well-established
  - Destruction of vital cellular components
  - Applications beyond cancer
- LDRT
  - Extra-cranial amyloidosis
  - Neurodegenerative disorders?!?
- On going clinical trials

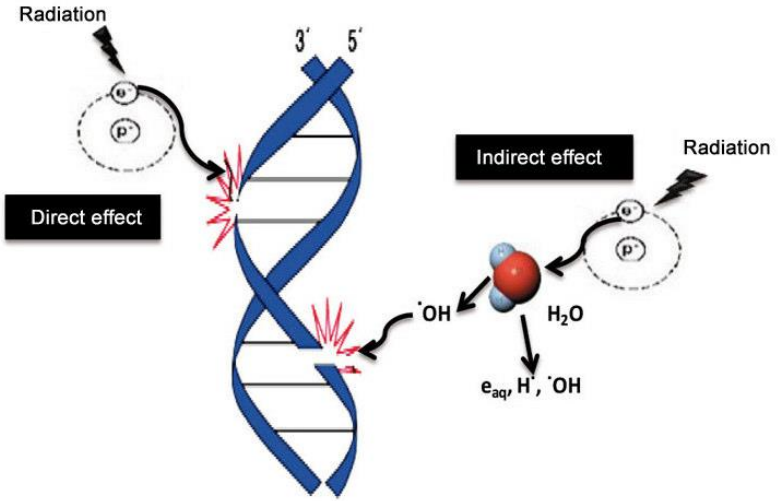


Fig. 3 – Representation of the direct and indirect effect of ionizing radiation in DNA (Džinić 2017)

Introduction
Motivation

- **Proton Therapy**
  - Finite range
  - Minimal lateral scattering
  - Higher precision
  - Lower integral dose
  - Reduced toxicity

Introduction
Study results

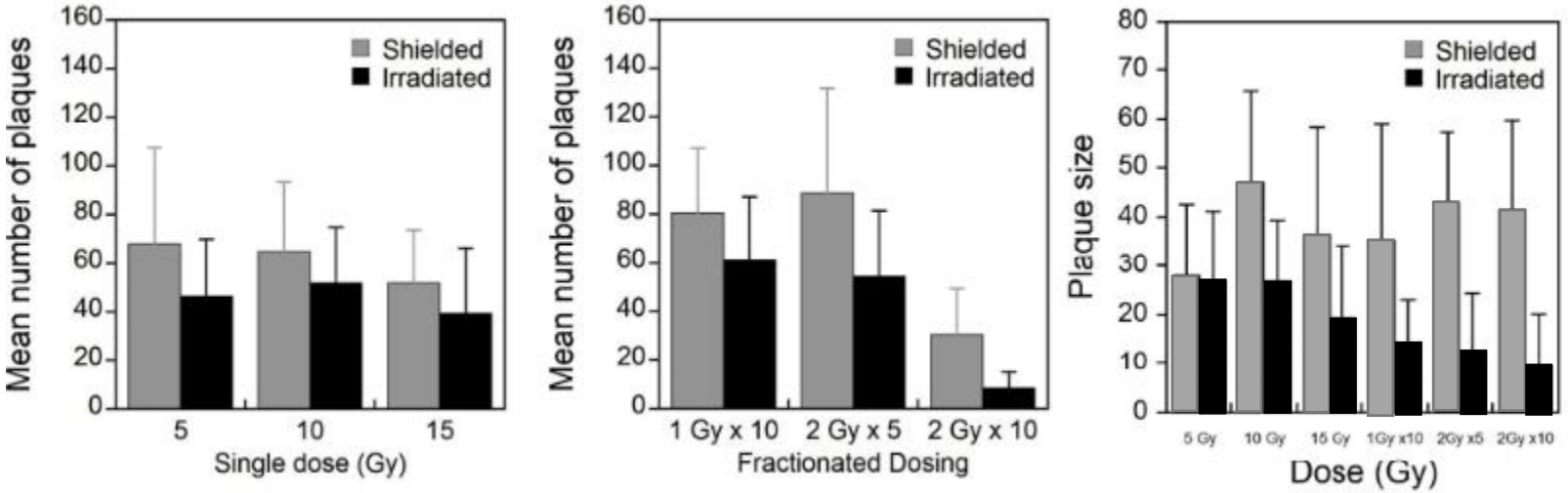
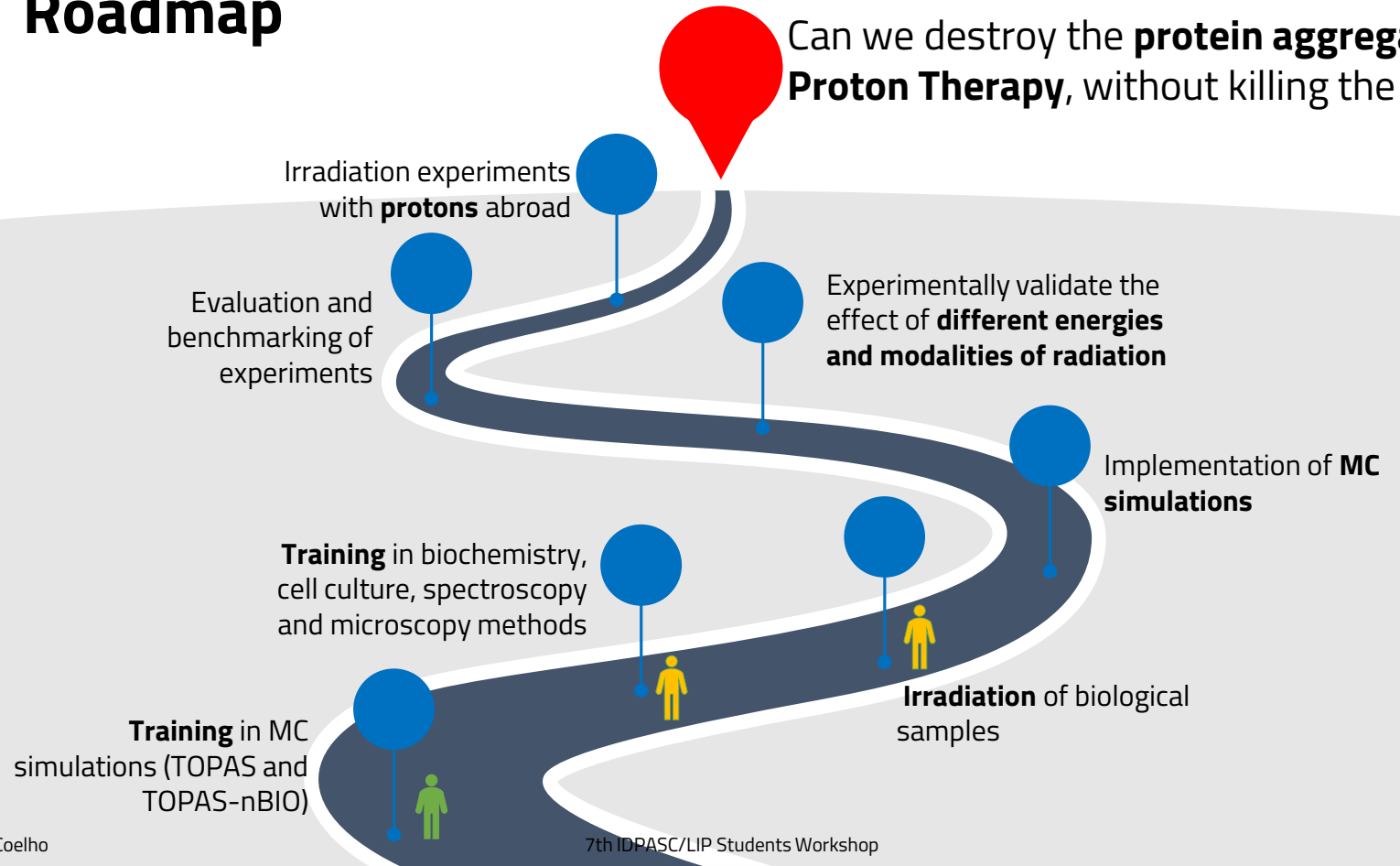


Fig. 5 – Mean number of plaques and plaque size measured 4 weeks after irradiation (Marples *et al.* 2016)

Roadmap


Can we destroy the **protein aggregates** with **Proton Therapy**, without killing the cells?
Irradiation experiments with **protons** abroad
Evaluation and benchmarking of experiments
Experimentally validate the effect of **different energies and modalities of radiation**
Implementation of **MC simulations**
Training in biochemistry, cell culture, spectroscopy and microscopy methods
Irradiation of biological samples
Training in MC simulations (TOPAS and TOPAS-nBIO)

Preliminary Results
Geometric design and irradiation

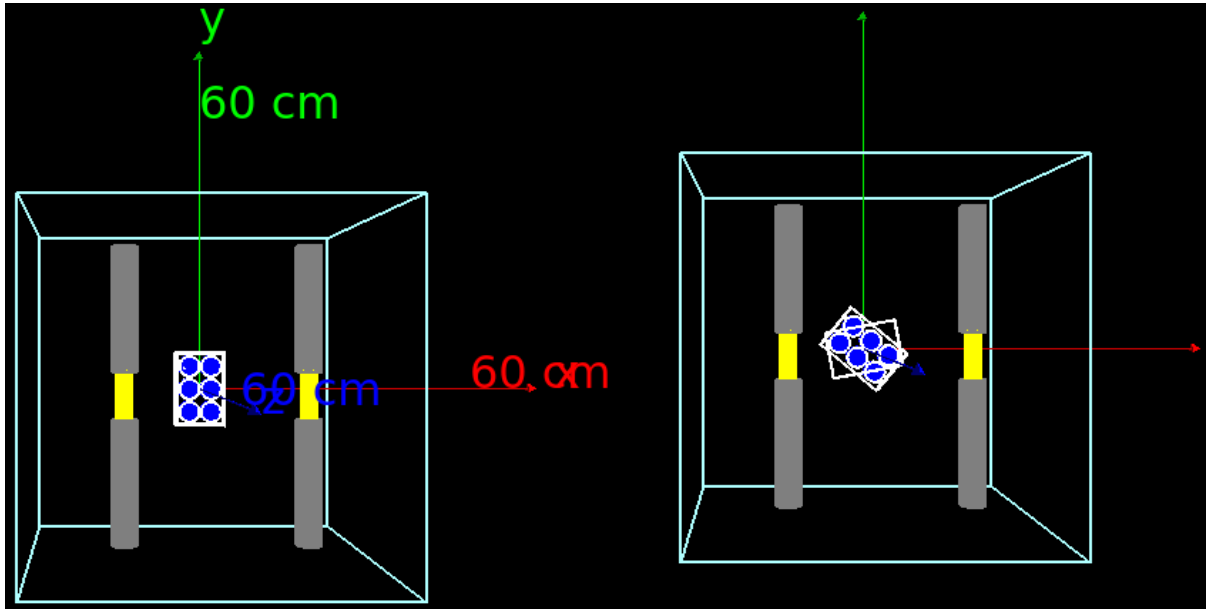


Fig. 6 – Representation of the geometric design used in TOPAS to simulate the irradiations done experimentally

Fig. 7 – PRECISA22 – 60Co irradiator used in the performed irradiations (Santos *et al. s.d.*)

ROS

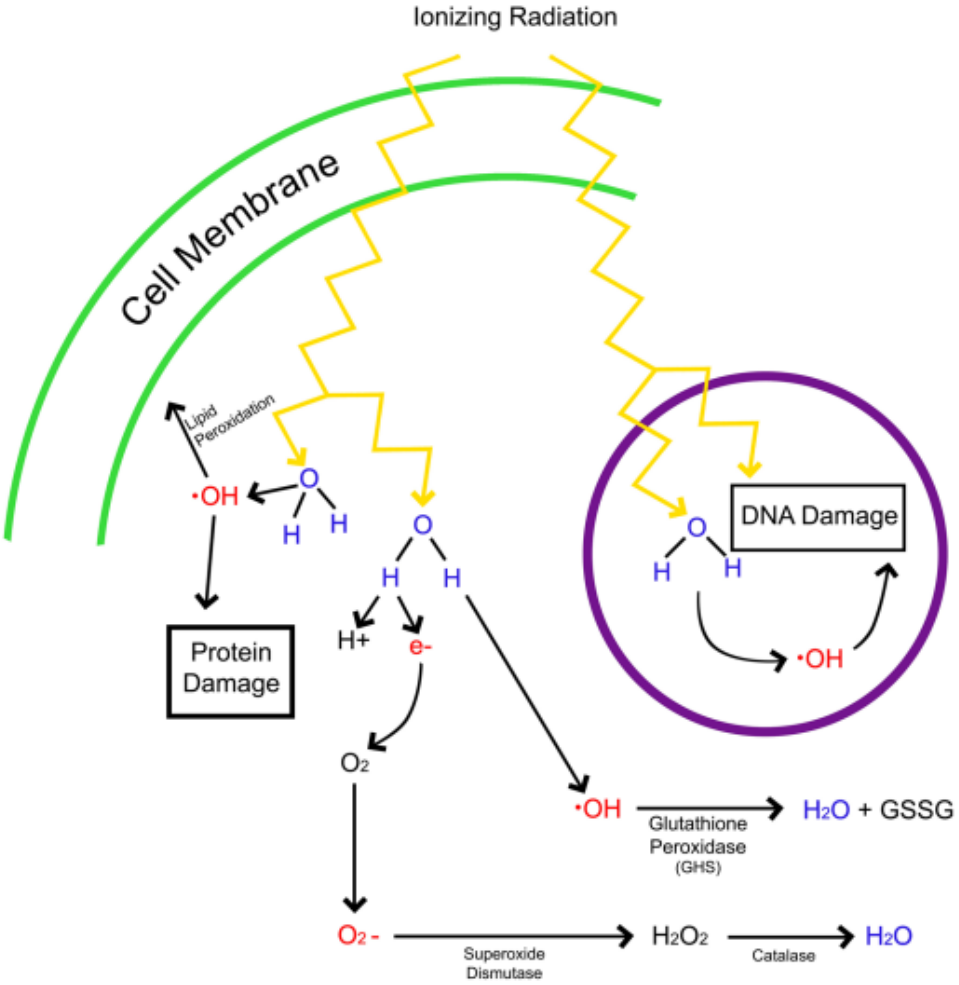


Fig. 4 – Generation of reactive oxygen species (ROS) in response to ionizing radiation (*Smith et al.* 2017)

Preliminary Results
ROS production

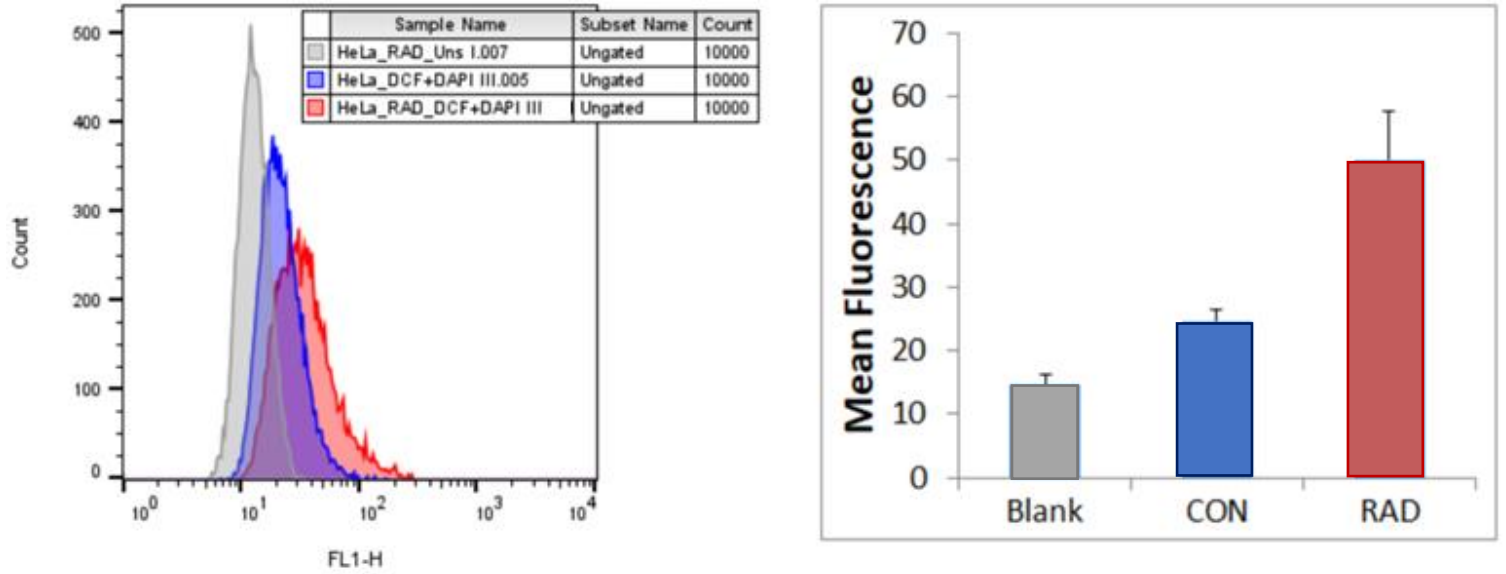


Fig. 8 – Flow cytometry measurements of fluorescence in cells irradiated with 10 Gy and using a gamma-ray source (60Co irradiator)

Preliminary Results
ROS production

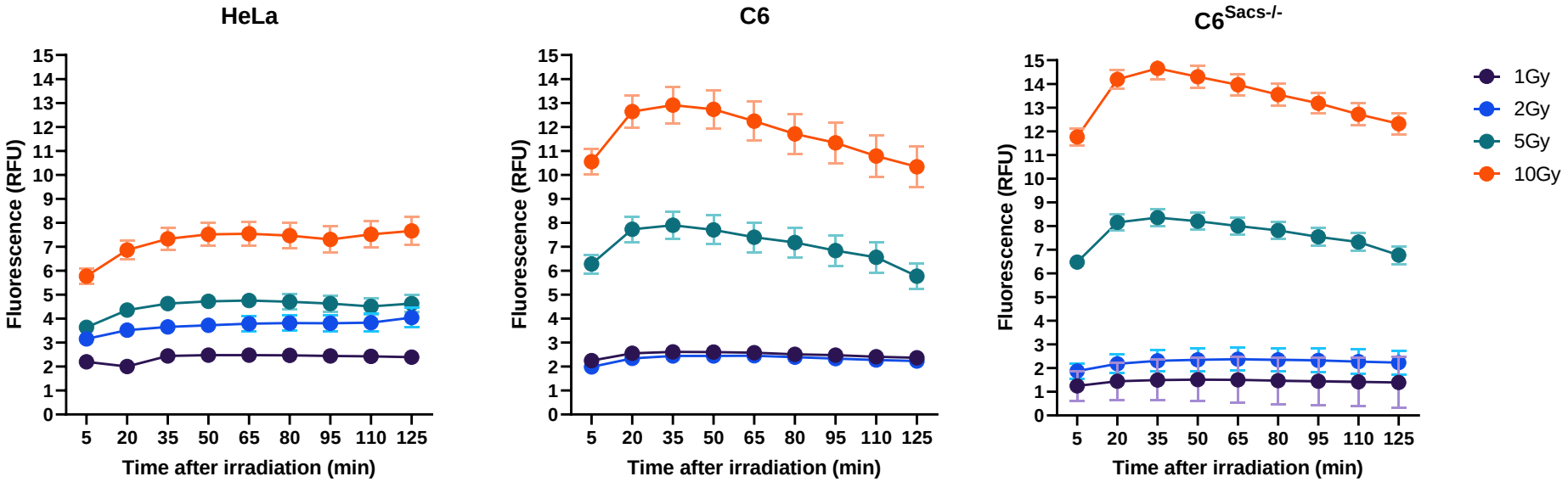


Fig. 9 – Measurements of ROS production by the DCFH-DA assay for 3 different cells lines, irradiated with a gamma-ray source (60Co irradiator)

Preliminary Results
Protein detection

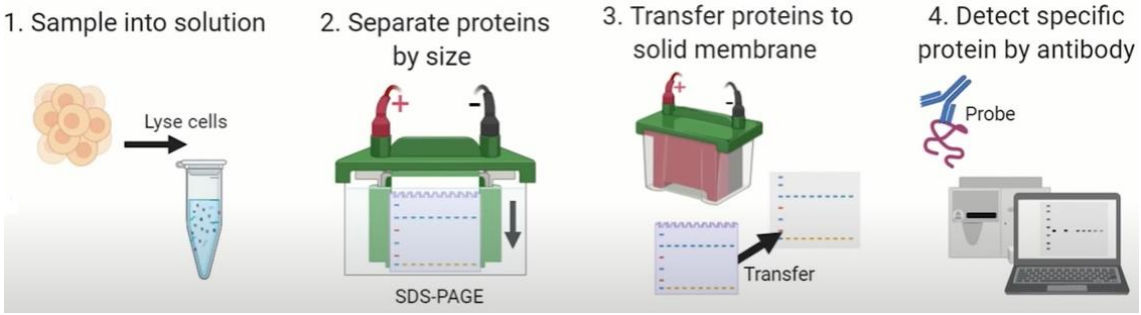


Fig. 10 – Process used to detect a specific protein (Western Blot)

Fig. 11 – Electrophoresis setup

Fig. 12 – Protein expression levels in a rat glioma cell line 2h after irradiation

Summary
Future work

- Irradiation of biological samples
  - X-ray source (CHLN)
  - **Proton** source (CMAM)
- Simulations
  - Peptide breaks
  - H-bonds breaks

(…)

It's an ongoing project!

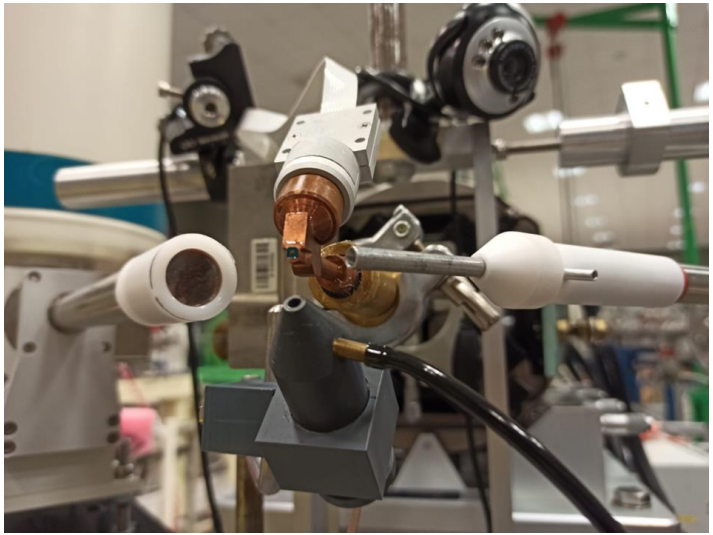


Fig. 13 – The beam line of the CMAM proton accelerator

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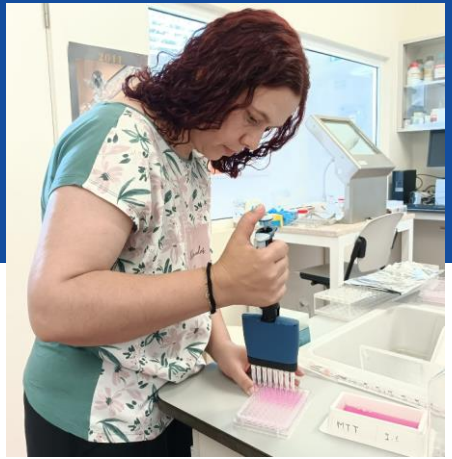
Thanks!



Any questions?

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On going clinical trials

University Hospital of Geneva	10 patients (observation) + 10 patients (LDRT)	10 Gy in 5 x 2 Gy	PET scan (8-12 weeks) Neurocognitive tests (6 months) RT side effects (12 months)
William Beaumont Hospital	15 patients (arm 1) + 15 patients (arm 2)	10 Gy in 5 x 2 Gy (arm 1) 10 Gy in 5 x 2 Gy (arm 2)	PET scan, neurocognitive tests and treatment toxicity (6 weeks, 3, 6 and 12 months)
Kyung Hee University Hospital	5 patients (arm 1) + 5 patients (arm 2)	5,4 Gy in 3 x 1,8 Gy (arm 1) 9 Gy in 5 x 1,8 Gy (arm 2)	PET scan, neurocognitive tests and treatment toxicity (6 weeks, 3, 6 and 12 months)
Virginia Commonwealth University	10 patients	10 Gy in 5 x 2 Gy	Neurocognitive tests (12 months)