NEPTUNE:
Nuclear process-driven Enhancement of Proton Therapy UNravElled

WP1 - Modeling

December 14th 2018

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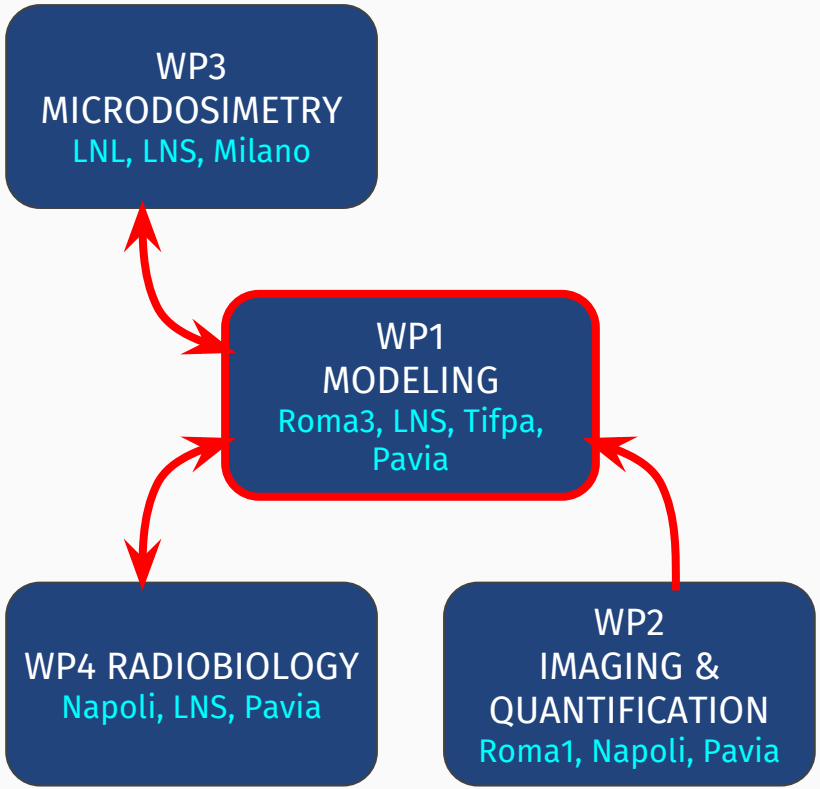
On behalf of LNS, INFN-RM3, TIFPA, INFN-Pavia

Istituto Nazionale di Fisica Nucleare

NEPTUNE WP1: Proton Boron Capture Therapy (PBCT) Modeling

WP1 (A Attili, P Cirrone) *Modeling*
Roma Tre, LNS, Pavia, TIFPA

- The main aim of the WP1 is the investigation of the radiobiological role of the α particles and other production channel in the p + $^{11}B \rightarrow 3\alpha$ and p + $^{19}F \rightarrow {}^{16}O + \alpha$ by means of computational modelling.
- The WP1 plays a key role in linking the microdosimetric data obtained in (WP3) to the experimental radiobiological outcome (WP4), taking into account the uptake data measured in (WP2).
- This task ultimately will help to untangle the role of the nuclear interactions and to indicate possible further mechanisms that could play a role in PBCT/PFCT.



NEPTUNE WP1: Proton Boron Capture Therapy (PBCT) Modeling

Three main steps have been identified:

S1. The experimental set-up used at INFN-LNS will be simulated with Geant4 to estimate the particle spectra generated by the nuclear reactions. The spectra will be used as an input for the radiobiological simulations based on the *Microdosimetric Kinetic Model* (MKM) & *BIophysical ANalysis of Cell death and chromosome Aberrations* (BIANCA) model.

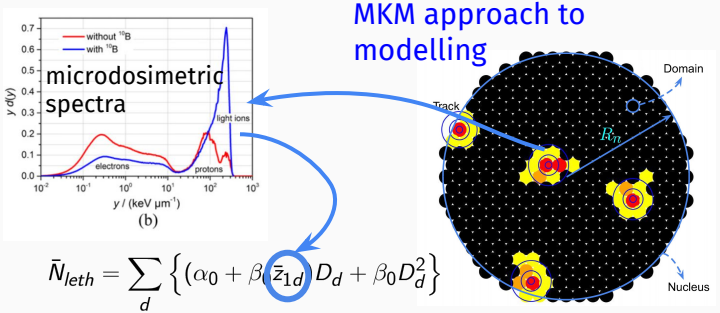
- Links: microdosimetric data (WP3), B and F cellular uptake (WP2) and cell survival (WP4) measurements.

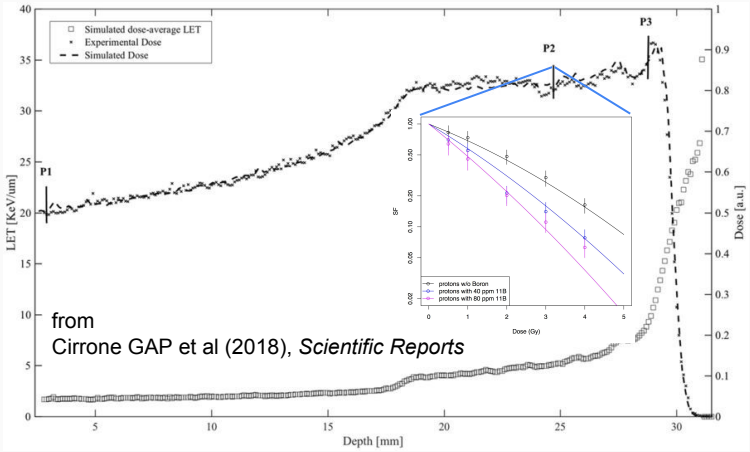
S2. A chemical-physics characterization of the reactive species following p + ^{11}B and p + ^{19}F reactions, will be carried out via two MC codes, Geant4-DNA and TRAX-CHEM.

- Links: reactive oxygen species (ROS), rate of double strand breaks (DSBs), chromosomal aberrations (CAs) and foci measurements (WP4).

S3. Other indirect mechanisms, such as non targeted effects (NTEs) will be implemented in the MKM.

- Links: Bystander effect measurements (WP4)



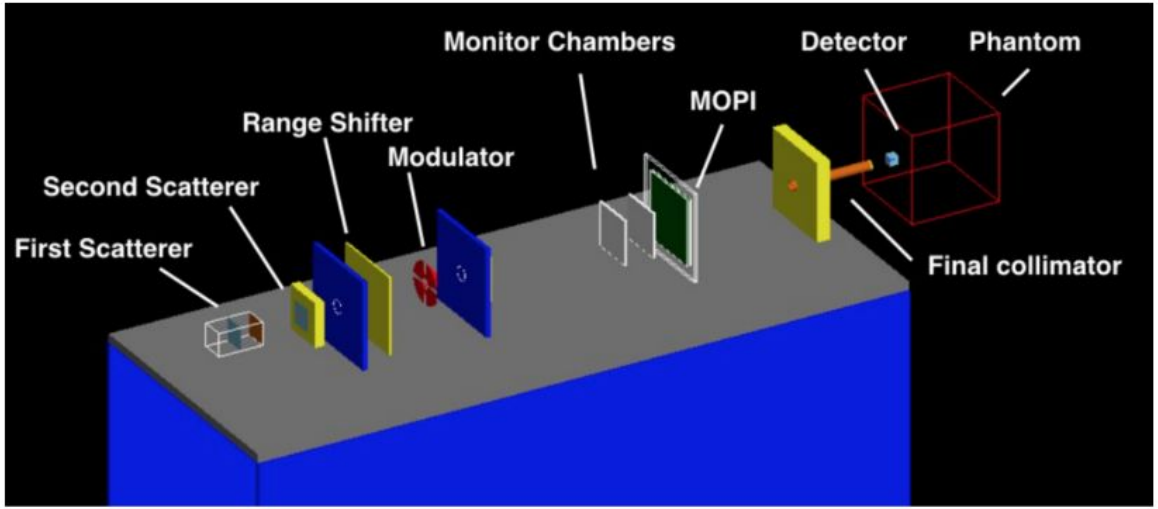


Profile of proton spread out bragg Peak (SOBP). Inset: cell survival fraction vs. dose w/ and w/o ^{11}B @ P2 (measurements & simulations)

Modeling -
First approach (S1)

S1: MC Simulations with Geant4

- A first part of the modelling activity will be the implementation of Monte Carlo (MC) simulations to estimate the particle spectra generated by the nuclear reactions. The whole experimental set-up at LNS will be simulated using the Geant4 toolkit.



The CATANA beamline geometry implemented inside Hadrontherapy application

S1: MC Simulations with Geant4 - α production channels

Reaction channels

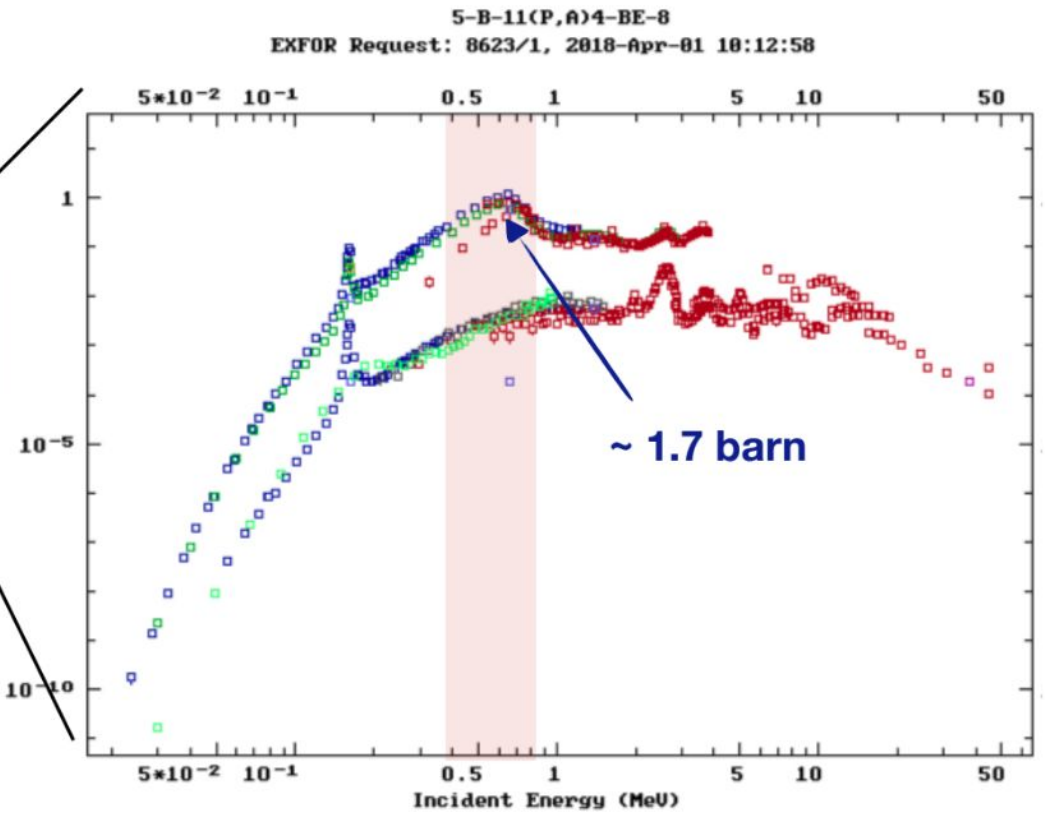
$$^{11}B + p \rightarrow {}^{12}C^{*} \rightarrow {}^{8}Be + \alpha_0 \rightarrow \alpha_{01} + \alpha_{02} + \alpha_0$$

$$^{11}B + p \rightarrow {}^{12}C^{*} \rightarrow {}^{8}Be^{*} + \alpha_1 \rightarrow \alpha_{11} + \alpha_{12} + \alpha_1$$

$$^{11}B + p \rightarrow {}^{12}C^{*} \rightarrow \alpha_2 + \alpha_3 + \alpha_4$$

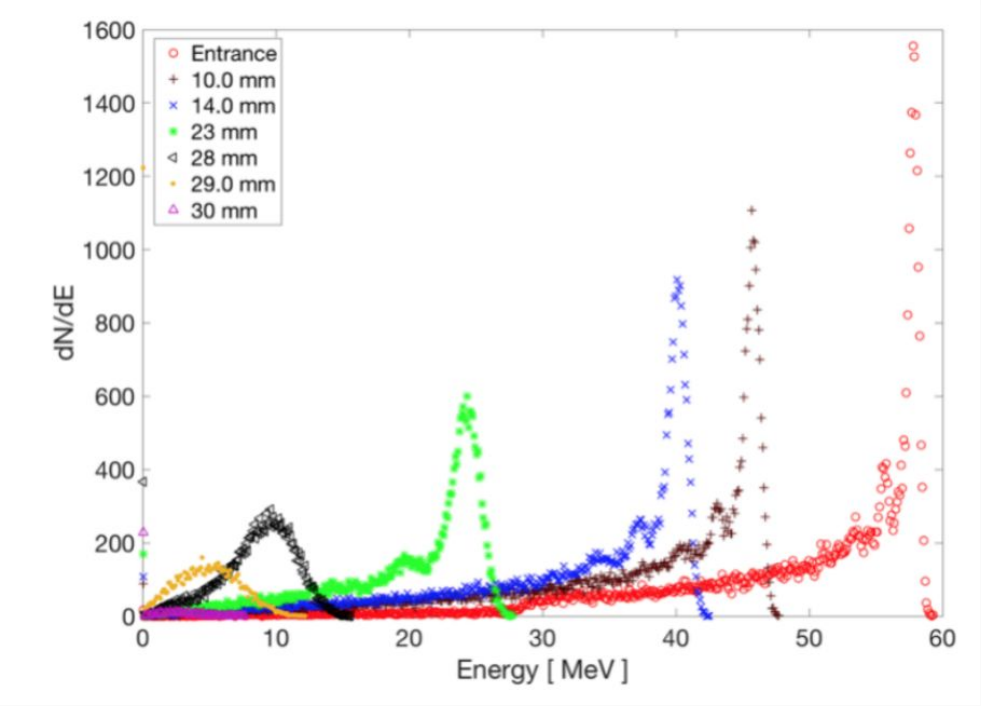
$$^{11}B + p \rightarrow {}^{12}C^{*} \rightarrow {}^{12}C + \gamma.$$

The reaction exit channels have a maximum cross section of 157 ub for incident proton energy under 1 MeV

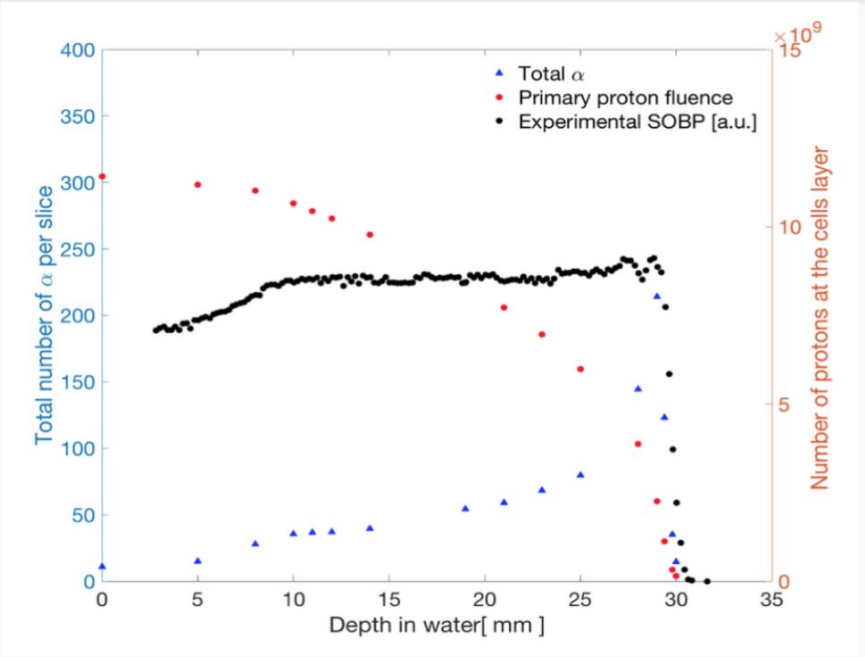


See next presentation by Davide Chiappara (PD)

S1: MC Simulations with Geant4 - preliminary studies



Energy spectra protons beam calculated at several depths along SOBP (Petringa 2018)

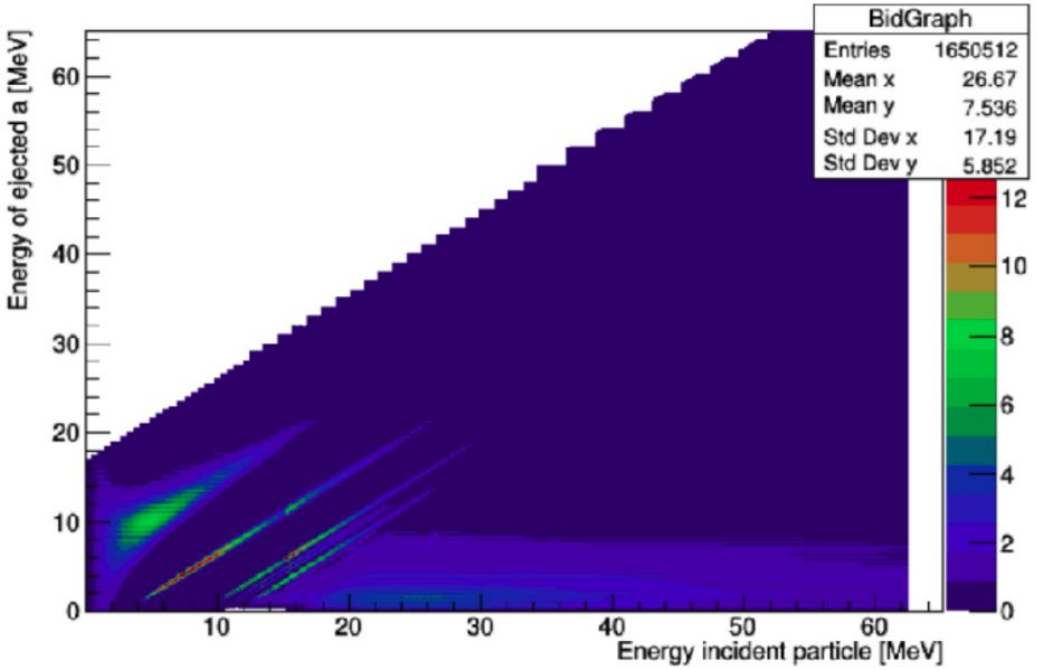


Number of α particles generated in the p-B reaction. Fluence of primary protons and total α from the reaction 11B(p, α)2α produced in each slice. The experimental dose distribution is also shown in arbitrary units. (Petringa 2018)

S1: MC Simulations with Geant4 - α production channels

Target: 11B	Maximum Cross Section
$^{11}B(p,\alpha)^{8}Be$	2000 mb at ~ 600 KeV
$^{11}B(p,n)^{11}C$	500 mb at ~ 5MeV
$^{11}B(n,p)^{11}Be$	10 mb at ~ 15MeV
$^{11}B(n,\alpha)^{8}Li$	200 mb at ~ 8 MeV

Target: 10B	Maximum Cross Section
$^{10}B(p,\alpha)^{7}Be$	100 mb at ~ 100KeV
$^{10}B(p,n)^{10}C$	10 mb at ~ 10 MeV
$^{10}B(n,p)^{10}Be$	100 mb at ~ 2.5 MeV
$^{10}B(n,\alpha)^{7}Li$	10000 mb at ~ 200 KeV



M.E. Kormaz, "INVESTIGATION OF REACTION CROSS SECTIONS OF ^{10,11}B WITH PROTONS AND NEUTRONS OF 0 – 30 MEV INCOMING ENERGY USING NUCLEAR MODELS "BPL, 20, 201035, pp. 293 - 300 (2012)

S1: MC Simulations with Geant4 - α + Li production by Neutron mediation

- Neutron Capture Enhanced Particle Therapy (NCEPT) : central hypothesis is that if a sufficient thermal neutron fluence is generated during proton or heavier ion therapy, it can be exploited therapeutically via the administration of a suitable non-toxic neutron capture agent containing 10B or 157Gd (Safavi-Naeini et al. 2018)

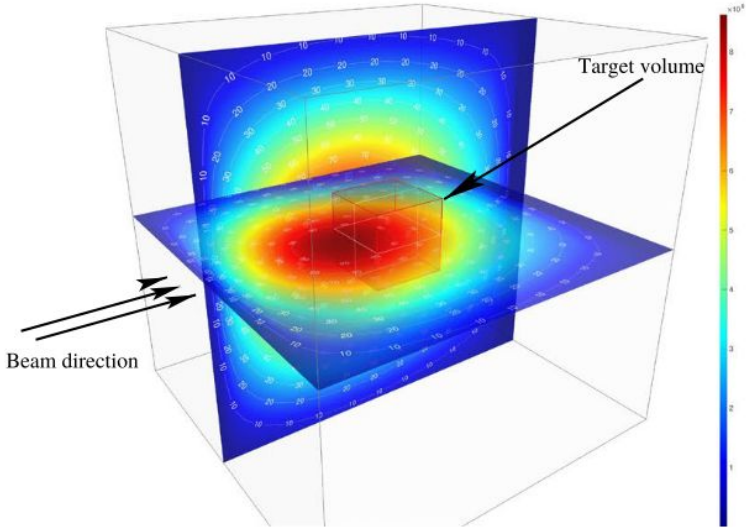
$$^{10}\mathrm{B} + n_{th} \rightarrow [^{11}\mathrm{B}]^{*} \rightarrow \alpha + {}^{7}\mathrm{Li} + \gamma(2.31\ \mathrm{MeV})$$

$$^{157}\mathrm{Gd} + n_{th} \rightarrow [^{158}\mathrm{Gd}]^{*} \rightarrow {}^{158}\mathrm{Gd} + \gamma + 7.94\ \mathrm{MeV}$$

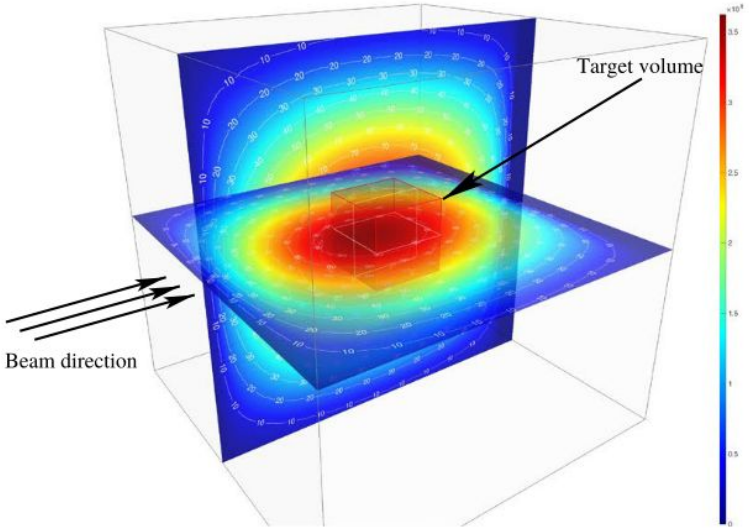
Target Depth (mm)	Primary Ion	Thermal neutron fluence per GyE primary dose ($n/cm^2/GyE$)		
		Minimum	Mean	Maximum
100–150	Proton ^{12}C	5.96×10^8	7.79×10^8	9.06×10^8
		2.86×10^8	3.34×10^8	3.60×10^8
140–190	Proton ^{12}C	6.26×10^8	8.82×10^8	1.09×10^8
		3.17×10^8	4.08×10^8	4.68×10^8

Thermal neutron fluences obtained for each target volume and treatment plan, assuming a target volume average proton or heavy ion biological dose of 1 GyE. (Safavi-Naeini et al. 2018)

S1: MC Simulations with Geant4 - α + Li production by Neutron mediation



(e) 3D (proton)



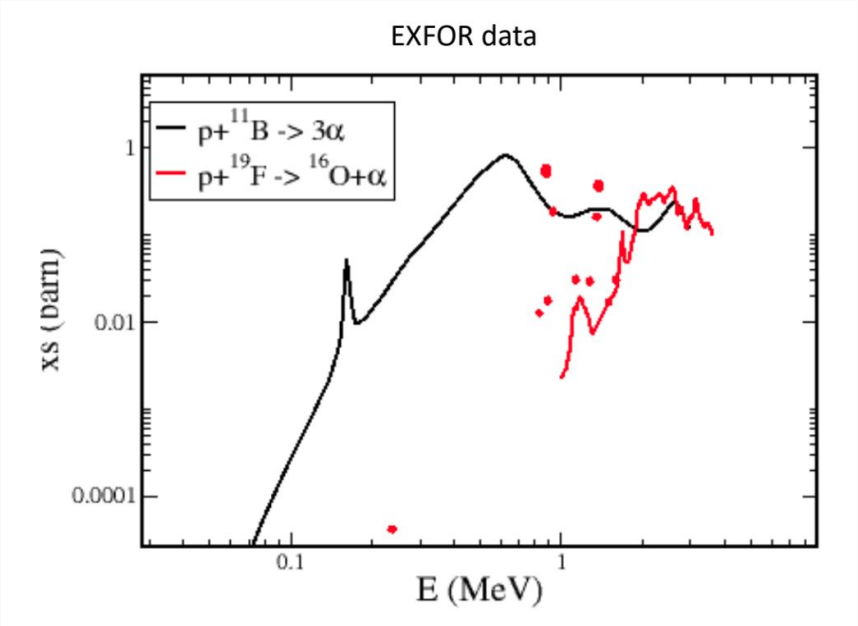
(f) 3D (carbon)

Normalised thermal neutron fluence resulting from irradiation of the 100–150 mm target volume. colourbars in the 3D figures show absolute fluence. (Safavi-Naeini et al. 2018)

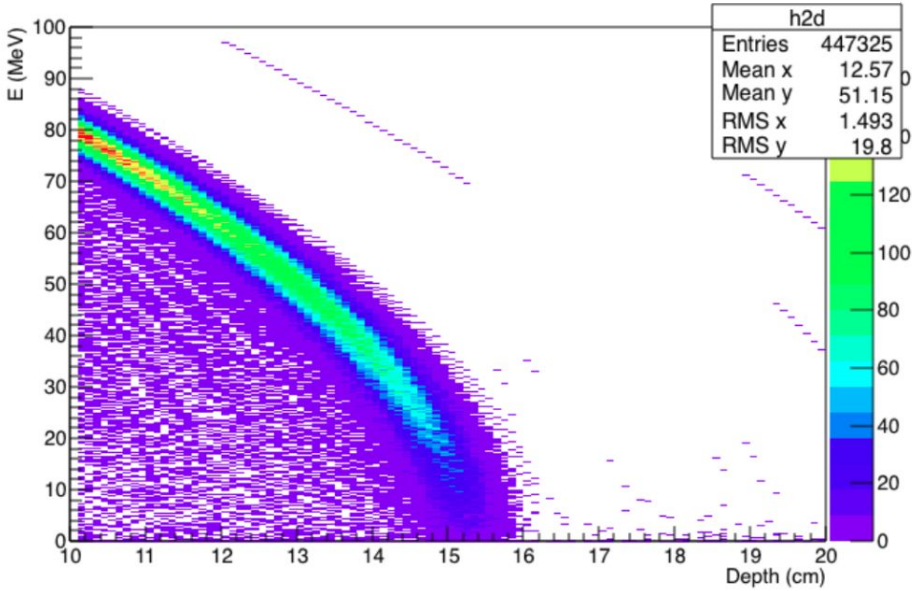
Target Depth (mm)	Primary	^{10}B thermal neutron capture agent concentration (ppm)			
		BPA (brain)[24]	BSH (brain)[104]	BPA (liver)[26]	BSH (liver)[26]
		RBE = 3.8	RBE = 1.2	RBE = 9.94	RBE = 4.22
100–150	Proton ^{12}C	390 910	1240 2880	149 348	351 820
140–190	Proton ^{12}C	345 744	1090 2360	132 285	310 670

^{10}B-based thermal neutron capture agent concentrations required to obtain a 10% increase in biological effective dose. (Safavi-Naeini et al. 2018)

S1: MC Simulations - α production channels

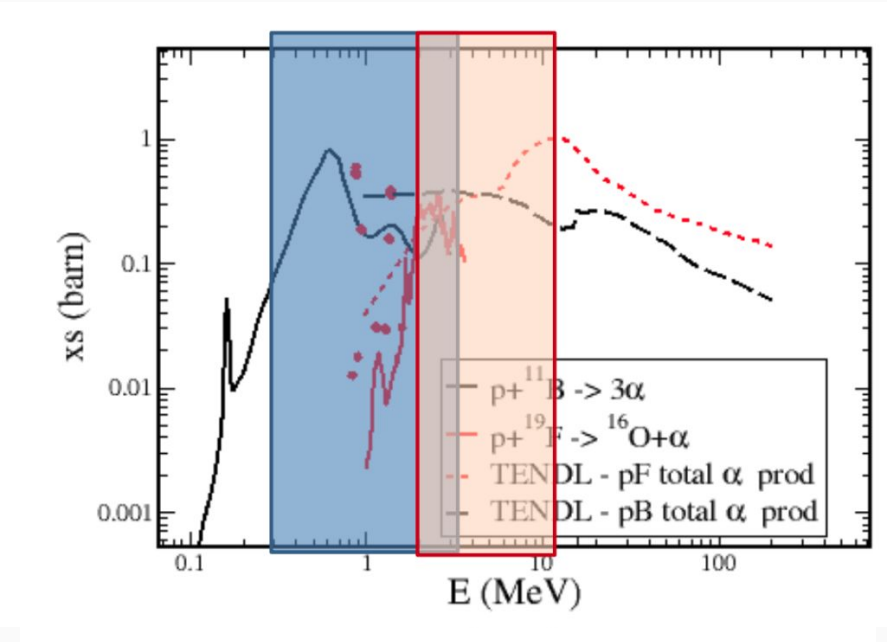


p Energy spectra vs Depth

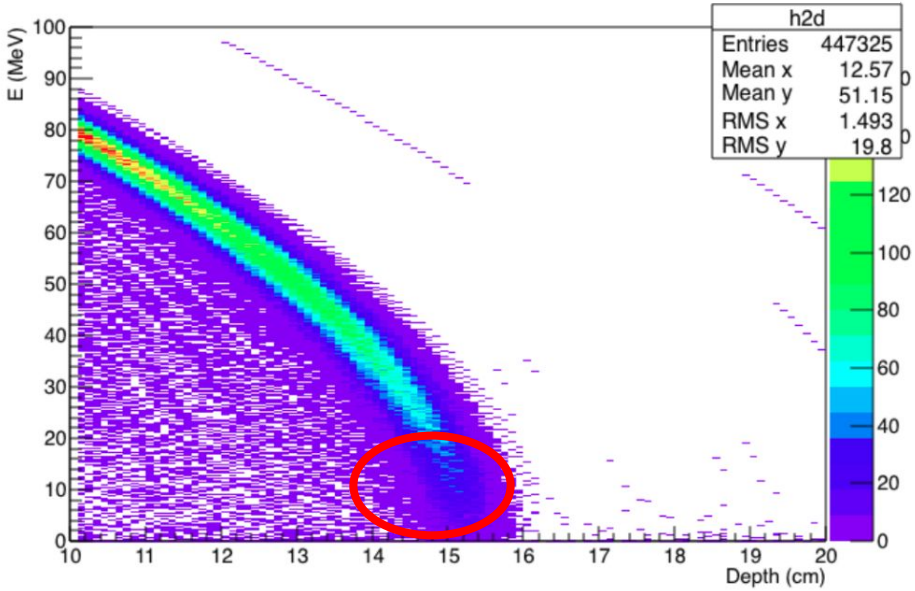


F. Tommasino (Tifpa)

S1: MC Simulations - α production channels



p Energy spectra vs Depth



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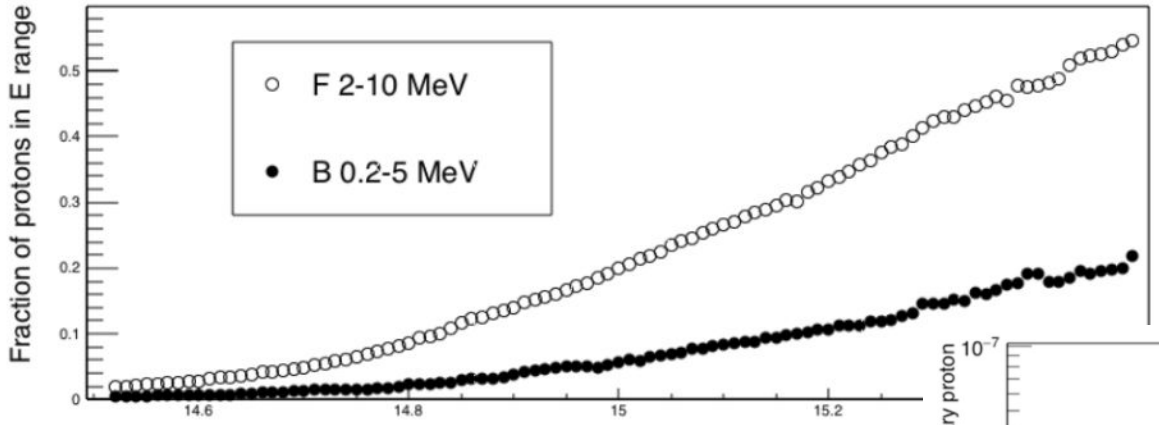
S1: MC Simulations - α production channels

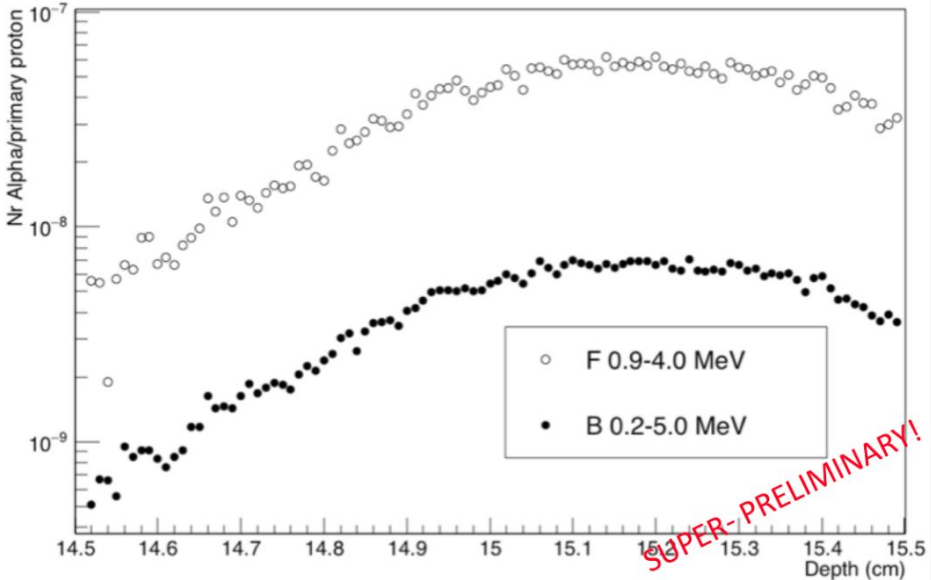


F. Tommasino (Tifpa)

See presentation by Emanuele Scifoni (Tifpa)

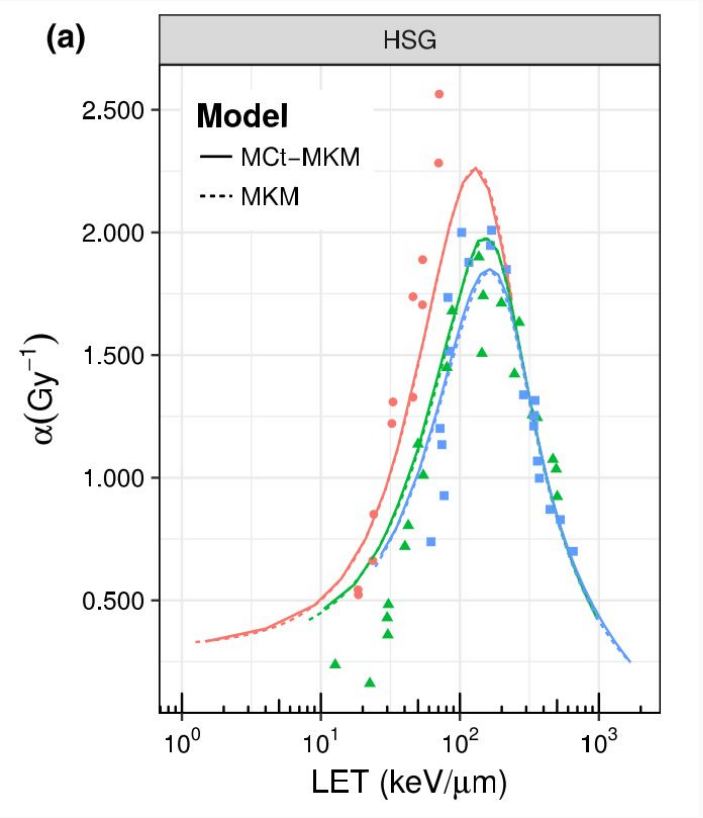
Difference basically driven by factor 3 / concentration rate

- Same impact of xs-



S1: Radiobiological modeling: MKM Approach

- The spectra generated by these simulations will be used as the physical input for the radiobiological simulations based on the **microdosimetric kinetic model** (MKM) (Hawkins 1996 & 2003), which was derived from the theory of dual radiation action (Keller & Rossi 1978) and has been already successfully used for the treatment planning for heavy charged-particle therapy in the Heavy-ion Medical Accelerator (HIMAC) in Chiba (Inaniwa et al. 2010, Kase et al. 2011) and for the estimation of the biological effect in boron neutron capture therapy (BNCT) (Horiguchi et al. 2015).
- The MKM has been also implemented by INFN-To/Roma3 in a code, "**Survival**", an open-source tool for radiobiological evaluations in the field of charged-particle therapy (Manganaro et al. 2018) with the possibility to be easily coupled with Geant4 MC simulations.

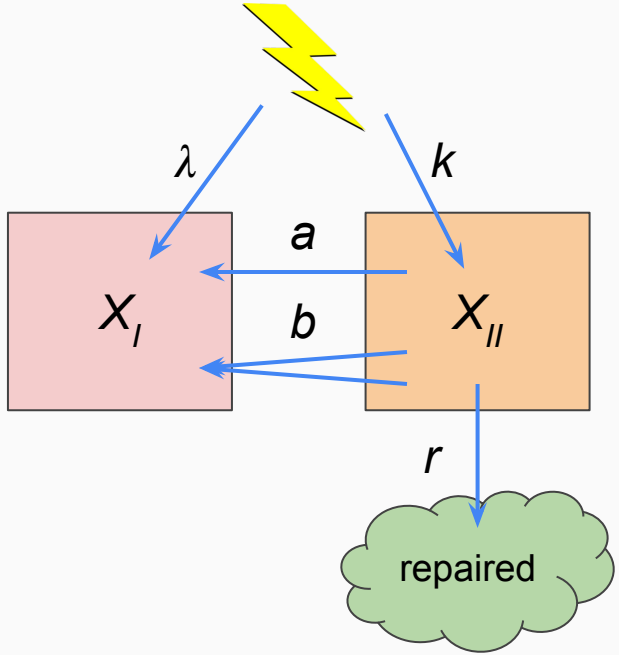


https://github.com/batuff/Survival

S1: Radiobiological modeling: MKM Approach

Kinetic equations:

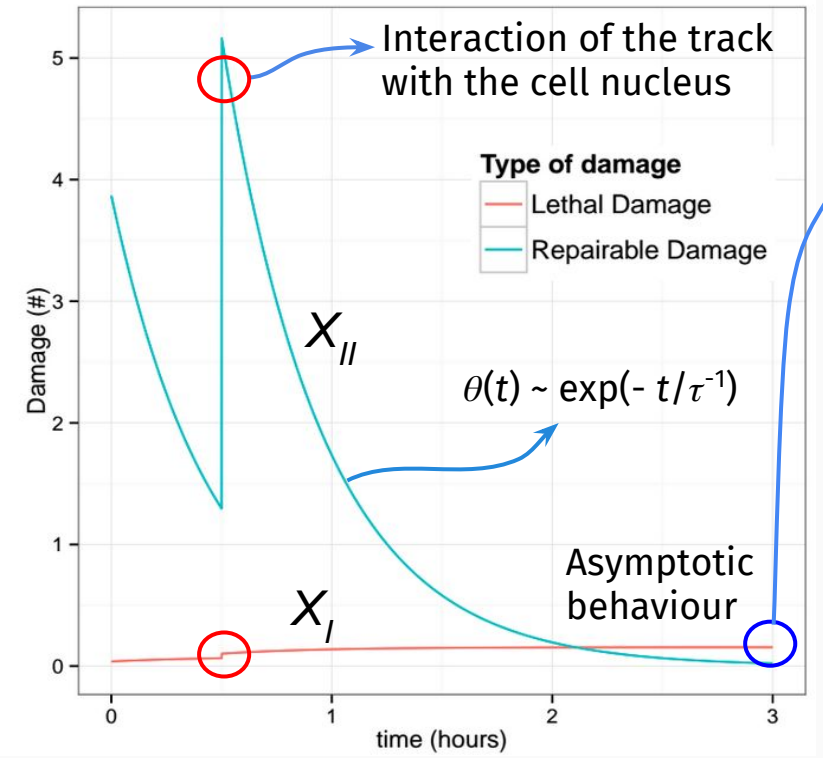
$$\begin{cases} \dot{x}_I^{(cd)} = \lambda \dot{z}^{(cd)} + a x_{II}^{(cd)} + b (x_{II}^{(cd)})^2 \\ \dot{x}_{II}^{(cd)} = k \dot{z}^{(cd)} - (a + r) x_{II}^{(cd)} - 2b (x_{II}^{(cd)})^2 \end{cases}$$



- z → microscopical absorbed dose
- x_I → type-I lesions: associated with clustered DNA damages which are **directly lethal** for the cell
- x_{II} → type-II lesions: non-directly lethal damages that may be **repaired**, spontaneously **converted to irreparable damages** or undergo **pairwise combination**.

Hawkins, R. B. (1996). *International Journal of Radiation Biology*

S1: Radiobiological modeling: MKM Approach



Hawkins, R. B. (1996). *International Journal of Radiation Biology*

Cell survival is derived from the asymptotic solution of the kinetic equations:

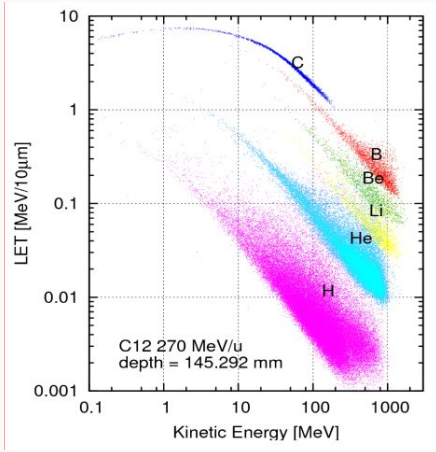
$$\langle N_{leth} \rangle = \langle x_I(t \to \infty) \rangle \simeq (\alpha_0 + \beta_0 \bar{z}_{1D}) D + \beta_0 D^2$$

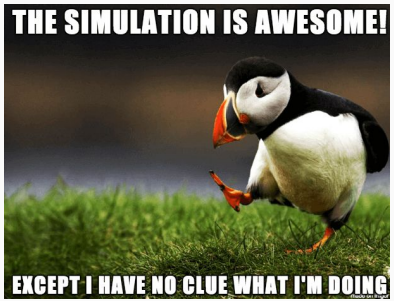
Where z_{1D} is the dose-averaged microscopical absorbed dose, α_0 and β_0 are functions of the rate parameters (λ, k, a, b, r). Since z_{1D} (x-rays) << z_{1D} (ions), $\alpha_0 \cong \alpha_X$ and $\beta_0 \cong \beta_X$

$$\Rightarrow \quad S \stackrel{?}{=} \exp(-\langle N_{leth} \rangle)$$

(note: to reproduce the correct high-LET non-Poissonian statistics a full MC computation or the use of “corrective factors” are needed.)

S1: Radiobiological modeling: Geant4 + “Survival” coupling





1

Fixed a voxel, at each particle step are retrieved the following infromations:

- Atomic number Z
- Atomic mass A
- Kinetic Energy E
- Deposited Energy dE
- Linear Energy Transfer LET
- Step Length dx

2

Precompiled LUT are recalled step-by-step for each particle.

The α and β parameters are then calculated by an interpolation procedure applied at the LUT values and based on particle energy E and LET.

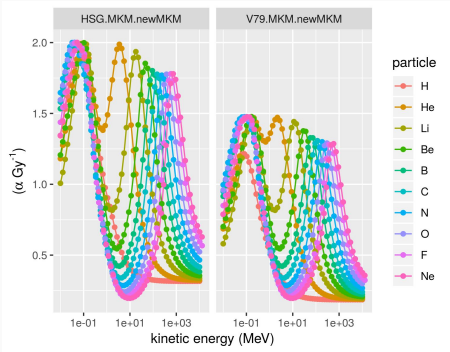
3

The weighted average of α and β parameters is calculated at the end of each event, taking into account the contribution of each particle.

4

The output variables, calculated at the end of a run are:

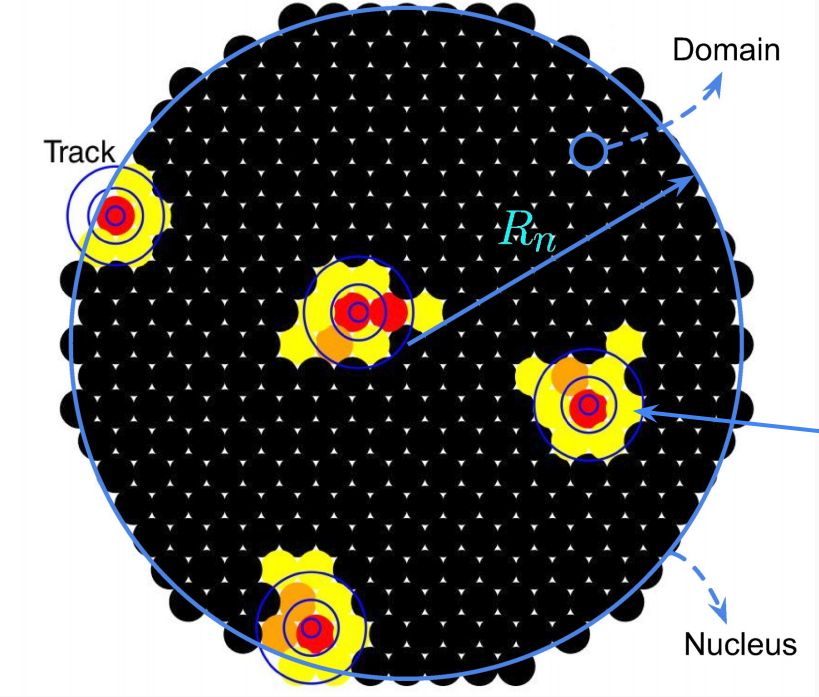
- α, and β, parameters
- Survival Fraction SF
- Relative Biological EffectivenessRBE
- Physical dose D_{phys}
- Biological dose D_{bio}



$$\bar{\alpha} = \frac{\sum_i \alpha(Z_i, \mathrm{LET}_i) D_i}{\sum_i D_i}$$

$$\bar{\beta} = \left(\frac{\sum_i \sqrt{\beta(Z_i, \mathrm{LET}_i)} D_i}{\sum_i D_i} \right)^2$$

S1: Links with other WPs - Microdosimetric Spectra



Hawkins, R. B. (1996). *International Journal of Radiation Biology*,
Kase, y., et al. (2006). *Radiation Research*

$$\bar{N}_{leth} = \sum_d \left\{ \underbrace{(\alpha_0 + \beta_0 \bar{z}_{1d})}_{\alpha_P} D_d + \underbrace{\beta_0}_{\beta_P} D_d^2 \right\}$$

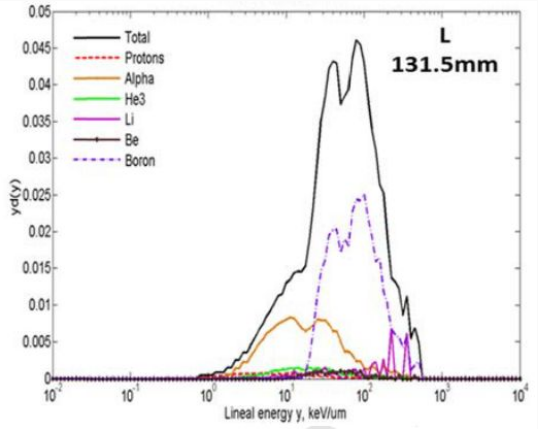
Particle energy spectrum

In simulations z_{1d} is obtained by means of a **track model**.

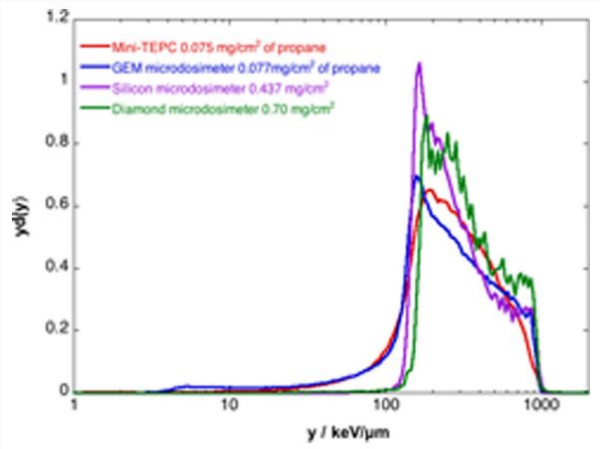
In principle, z_{1d} can be obtained “directly” from **microdosimetric measurements** of energy spectra, e.g. via a tissue-equivalent proportional counter (TEPC)

S1: Links with other WPs - Microdosimetric Spectra

- The spectra generated via the MC simulations will be also compared with the microdosimetric experimental data obtained by **WP3**. In particular, an important characteristic of the MKM is the possibility to use directly, as physical input, not only the simulation spectra, but also the experimental spectra obtained with the already available tissue- equivalent proportional counters (TEPCs) and the advanced dual microdosimeters that will developed at LNL (**WP3**).



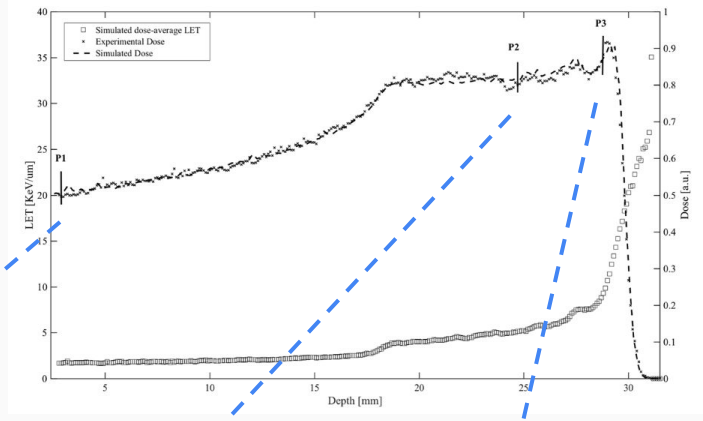
Microdosimetric spectra derived from the ΔE stage of E-ΔE telescope for a 290 MeV/u 12C beam. Separated dose weighted components are shown (Tran et al. 2018)



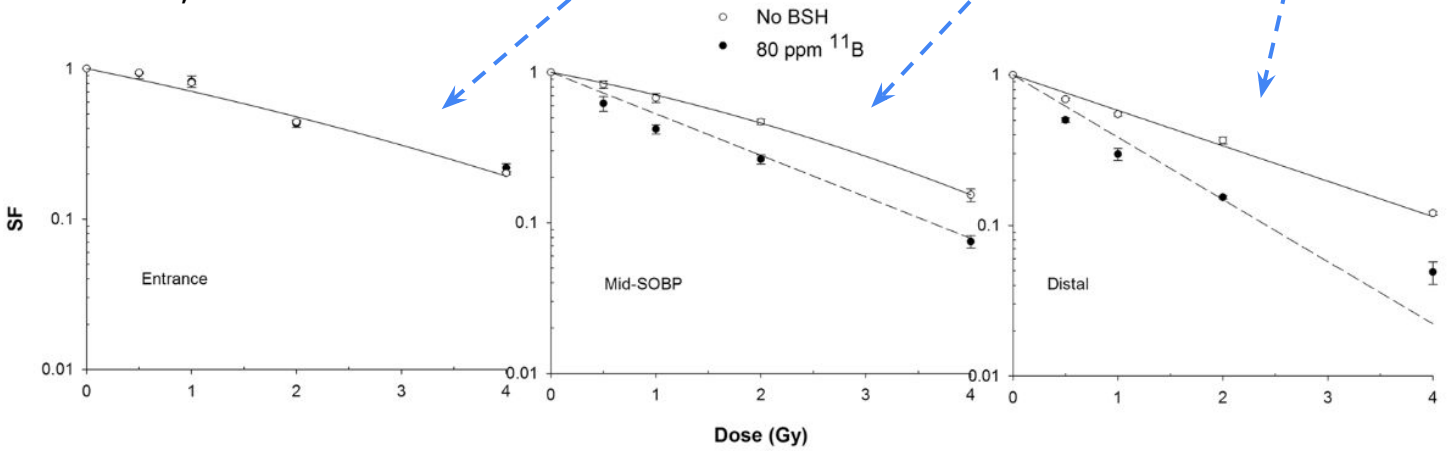
Microdosimetric spectra at 7.9 mm of water-equivalent depth for a 62 MeV/u 12C beam of INFN-LNS (Colautti et al. 2018)

S1: Links with other WPs - Cell Survivals

- The possibility to measure the B and F cellular uptake (**WP2-WP4**) will enable the development of survivals calculations and to compare the predictions with the cell survival measurements carried out w/ and w/out B and F, in the **WP4**.



Measured dose and calculated LET profile for cellular irradiation at different positions along the clinical proton SOBP at INFN-LNS (Cirrone et al. 2018)



Clonogenic survival along the proton SOBP. Data shown here refer to dose-response curves obtained at positions P1, P2 and P3 along the clinical proton SOBP (Cirrone et al. 2018)

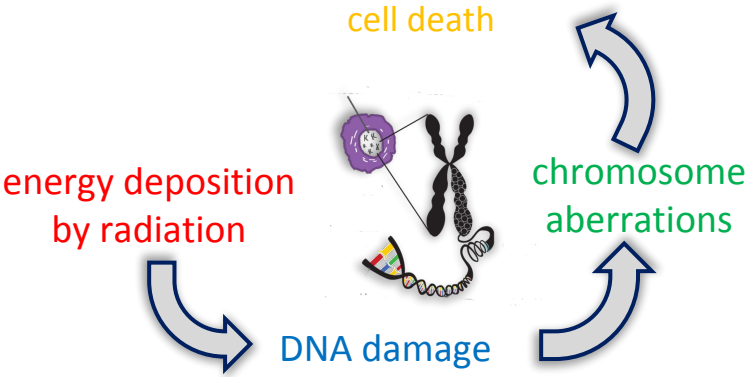
Pavia activity in WP1

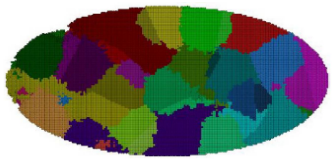
Personnel		
Name	**Title, Institution**	**FTE(%)**
Andrea Attili	Ricercatore, INFN-RM3	40
Pablo Cirrone	Ricercatore, INFN-LNS	10
Giada Petringa	Dottoranda, INFN-LNS	30
Elettra Bellinzona	Assegnista, INFN-TIFPA	20
Francesca Ballarini	Professore Associato, UNIPV - INFN PV	30
Silva Bortolussi	RTDb, UNIPV - INFN PV	10

- **General objective:** investigation of the role of α-particles produced in the p+^{11}B reaction, also in comparison with those produced in BNCT; in particular, cell survival experiments carried out in WP4 (BNCT treatment of *in vitro* cells) will be modelled by the BIANCA code

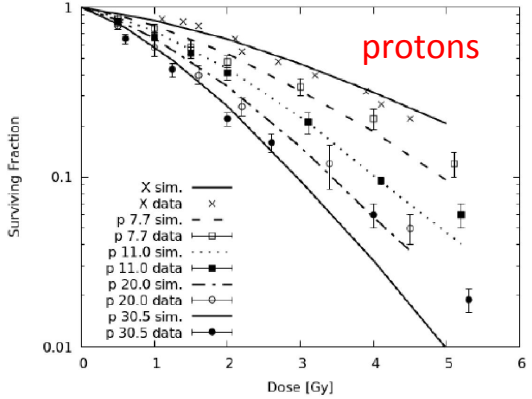
- **During the first year**, we plan to: a) evaluate the effect (survival) of a single α-particle traversing the cell nucleus, to estimate the number of particles needed to kill a cell; b) start to modify the code so that α particles can be originated from points inside the cell (instead of external irradiation), like it happens in BNCT

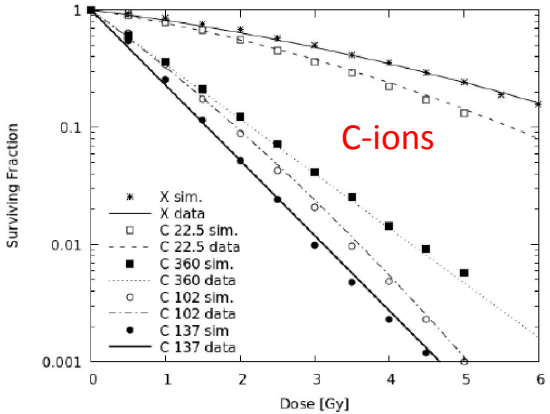
BIANCA (**BI**ophysical **AN**alysis of **C**ell death and chromosome **A**berrations), a model of cell death and chromosome damage developed in Pavia

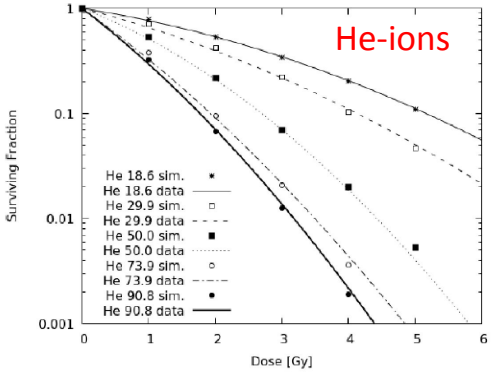




cell nucleus with chromosomes simulated by BIANCA *(Tello et al. 2017, DNA Repair)*







model validation against cell survival data for different radiation types and different LET values *(Carante et al. 2018, PMB 63, 075007)*

S1: Milestones/Deliverables for the first year

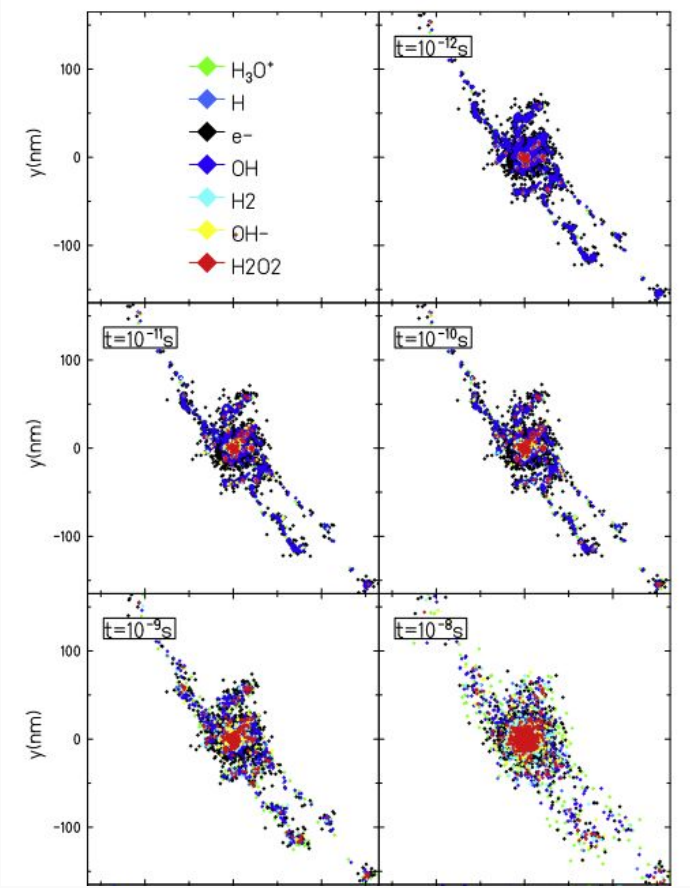
1st year

	Month	Milestone/Deliverable
D1.1	1-6	Implementation of MC simulations (Geant4) for p + 11B and p + 19F nuclear reaction spectra generated in the experimental setup.
M1.1	6-12	Integration of the simulated spectra evaluated in D1.1 in the radiobiological simulations (MKM + BIANCA)
...	...	...
M1.3	24-30	Comparison between simulation data (D1.1) and experimental data (microdosimetric spectra) taken by WP3. Inclusion of the experimental data in the radiobiological simulations (MKM).
M1.4	24-30	Comparison between simulation data (D1.1, M1.1, M1.6) with the experimental data (cell survival) taken by WP4.

Modeling -
Second approach (S2)

S2: MC simulations at the nanometer scale - Track structures

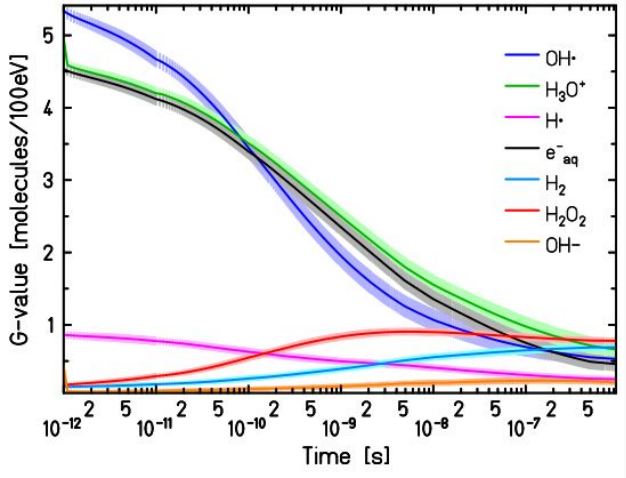
- In a second refinement of modelling study, the simulation of the track structures at the nanometer scale inside the cell will be added to the MC simulations developed in M1.1.
- Through these simulations the characterization of the reactive species clusters will be carried out using the recently developed extensions of the pre-chemical and chemical stage extensions of Geant4 and TRAX (Krämer Kraft 1994) codes, namely Geant4-DNA (Incerti et al. 2016), and TRAX-CHEM (Boscolo et al. 2018).



Chemical evolution of a 8 MeV/u carbon ion track in water in the time interval 1e-12 -- 1e-8 s, computed with TRAX-CHEM, shown in beam eye view. (Boscolo et al. 2018)

S2: MC simulations at the nanometer scale - Radiochemical processes

- As evinced in similar studies of enhanced proton-therapy, based on the combination of proton beam with nanoparticles absorbed in the irradiated tissue, and BNCT (Islam et al. 2018), radiochemical processes should play an important role in the cell damage. Such processes could be equally relevant in nuclear based enhanced proton-therapy, where the chemical pathway induced by the production of low energy α particles and other nuclear fragments could play a role in enhancing the radical production, with an important impact to the oxygenation, cell radiosensitivity and bystander effect (Kanike et al. 2015).



Time-dependent radiolytic yields for all the considered species generated by incident 20 MeV/u carbon ion radiation in a water cube of 5 x 5 x 0.5 μm3. (Boscolo et al. 2018)

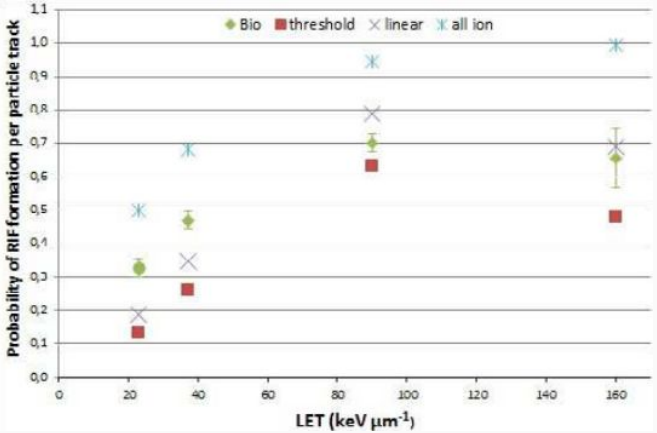
Chemical reaction	Reaction rate ($m^3\ mol^{-1} \cdot s^{-1}$)
Deoxyribose + OH•	$2.5 \cdot 10^6$
Adenine + OH•	$6.1 \cdot 10^6$
Guanine + OH•	$9.2 \cdot 10^6$
Thymine + OH•	$6.4 \cdot 10^6$
Cytosine+ OH•	$6.1 \cdot 10^6$

Chemical reactions included in the simulation of the chemical stage performed with Geant4-DNA (Villagrasa et al. 2017)

S2: Links with other WPs - ROS, DSBs

- The results obtained with the simulations will be compared with the **ROS** measurements, w/ and w/out B and F, performed in the WP4.

- The simulation of the reactive species production will be related with the measured production rate of DNA **double-strand breaks** (DSB), complex **chromosome aberrations** (CA) and foci. These characterizations will be used to tune the model repair kinetic equations and to provide insight for further mechanisms, both physical and biological, to be included in the modelling chain in order to reconcile the predictions with the observed biological damage.



Example of radiation-induced foci probability (RIF) per track evaluated via Geant4-DNA simulations, with different criteria of DSB formation. Experimental data of 53BP1 foci are reported with green circles for proton and green diamonds for α particles. (Villagrasa et al. 2017)

Ionization clusters and early DNA damage after the irradiation

$$\begin{cases} \dot{x}_I^{(cd)} = \lambda \dot{z}^{(cd)} + a x_{II}^{(cd)} + b (x_{II}^{(cd)})^2 \\ \dot{x}_{II}^{(cd)} = k \dot{z}^{(cd)} - (a+r) x_{II}^{(cd)} - 2b (x_{II}^{(cd)})^2 \end{cases}$$

S2: Milestones/Deliverables for the second year

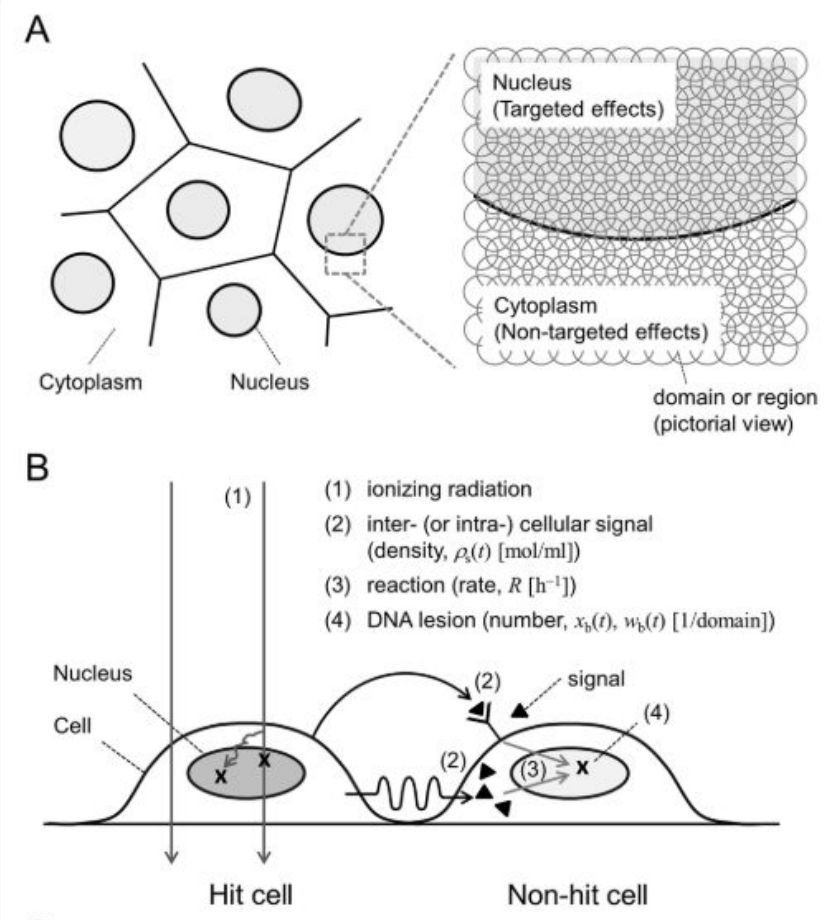
2nd year

	Month	Milestone/Deliverable
D1.2	12-18	Implementation of Geant4-DNA, and TRAX-CHEM simulations starting from the spectra obtained in D1.1.
M1.4	18-24	Coupling D1.2 simulations with radiobiological models to estimate cell survival, DSB, CA & foci.
...	...	...
M1.5	30-36	Comparison between simulation data (D1.2) and experimental data (ROS production) taken by WP4
M1.6	30-36	Comparison between simulation data from (D1.1, D1.2) + (M1.1, M1.2, M1.3, M1.4) with the experimental data (cell survival, DSB, CA, foci) taken by WP4.

Modeling -
Third approach (S3)

S2: Modeling of non targeted effects (NTEs)

- In order better reproduce the observed cell damage in presence of B and F a possible further mechanism to include in the modelling chain is the **bystander effect**. This effect will be included in a third refinement of modelling study. For this purpose an extension of the MKM, **I-MKM**, to include non targeted effects (NTEs) (Matsuya et al. 2018), will be implemented and coupled with the results of the simulations carried out in S1. and S2.



Conceptual illustration of the I-MKM model: (A) for micrometer-order targets (domains) in a cell population, (B) for processes that induce NTEs and The scenario of non-hit effects in (B) is as follows: (i) when a cell population is exposed to ionizing radiation, DNA lesions are generated along the track of ionizing radiation; (ii) hit cells emit initial signals which spread out and increase by cascade reactions as cell-killing signals (▲); (iii) the signals that reach to the non-hit cells induce potentially lethal lesions (PLLs) in proportion to the signal density (Matsuya et al. 2018)

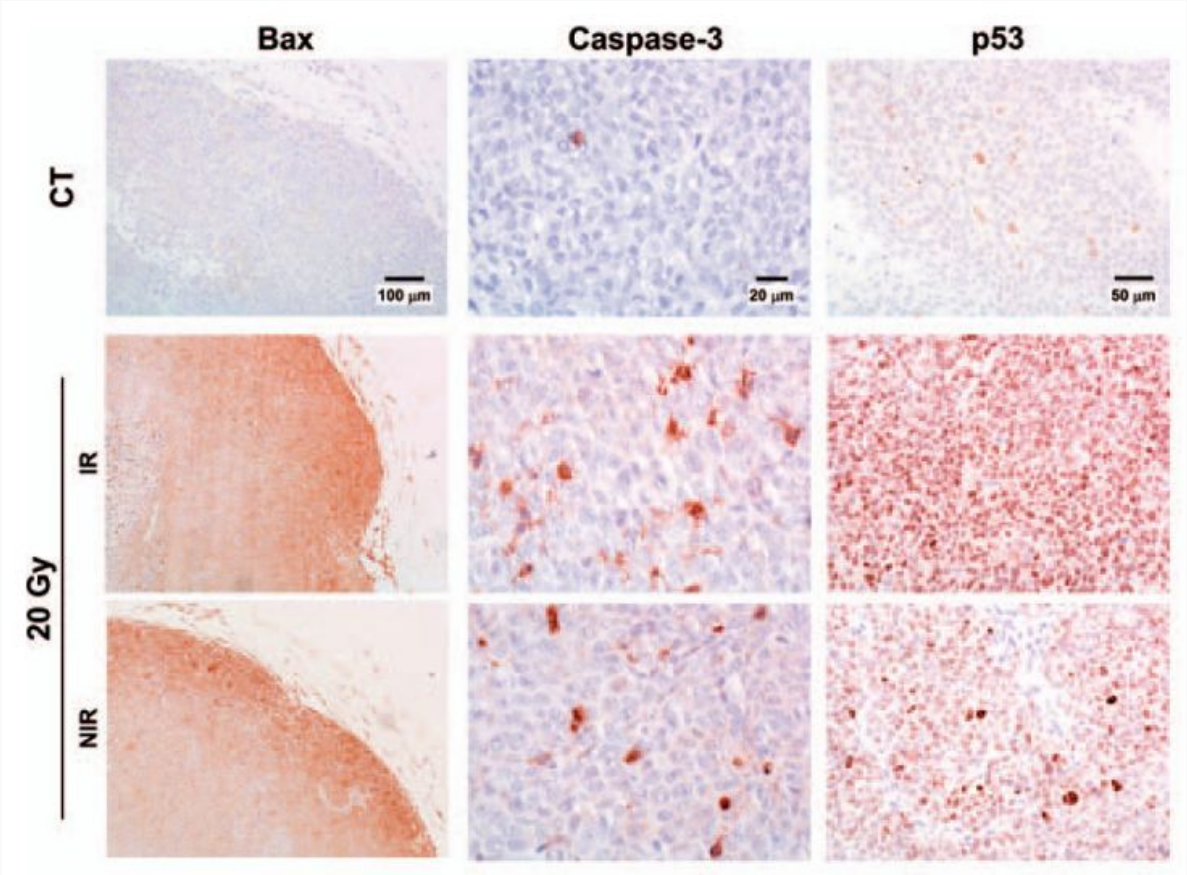
S2: Links with other WPs - Bystander effects

- The results obtained with the simulations will be compared with the bystander measurements, w/ and w/out B and F, performed in the WP4.

*"One of the ways to give your child solutions for bullying starts with understanding the **bystander effect**, a social phenomenon in which the more people who are present, the less likely they are to help a person in distress."*

S2: Links with other WPs - Bystander effects

- The results obtained with the simulations will be compared with the bystander measurements, w/ and w/out B and F, performed in the WP4.



Molecular analyses in wt-p53 tumours 4 h post-irradiation. Representative images of immunohistochemical staining carried out using antibodies directed against the pro-apoptotic factor Bax (left column), cleaved caspase-3 (middle column) and p53 (right column) (Strigari et al. 2014)

S2: Milestones for the third year

3rd year

	Month	Milestone/Deliverable
M1.3	24-30	Inclusion of the bystander effect in the simulations developed at D.1.1, M1.1.
...	...	...
M1.5	30-36	Comparison between simulation data (M1.4) with the experimental data taken by WP4.

That’s it.

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