Radiobiological studies for improving the treatment planning of Neutron Capture Therapy

María Pedrosa Rivera

Link to the thesis manuscript

Physique Nucléaire et Applications Médicales

LPSC Grenoble

Career

- University Degree and Master in Physics (Specialization in radiations):
  University of Granada

- PhD in Physics (July 2020): University of Granada, Granada, Spain
  Directors: Ignacio Porras & M.Carmen Ruiz
  ILL Supervisors: Ulli Köster & Trevor Forsyth
  Joint Research Center, European Commission, Geel, Belgium (6 months)
  Institut Laue Langevin, Grenoble, France(2 years)

- PostDoc in BNCT radiobiology: University of Granada (9 months)

Currently:

- PostDoc at PNAM group in LPSC in the project PICTURE (Planning Innovative Cancer Therapies Using RadioElements) under Rachel Delorme supervision
- Communication Task Force member of the International Society for Neutron Capture Therapy

UNIVERSIDAD DE GRANADA

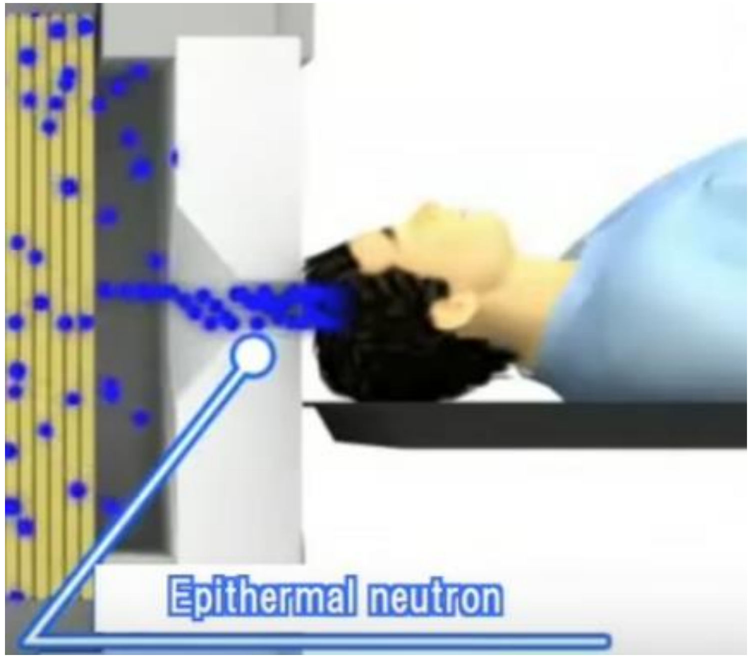
Joint Research Centre JRC

NEUTRONS FOR SOCIETY

LPSC Grenoble

Overview

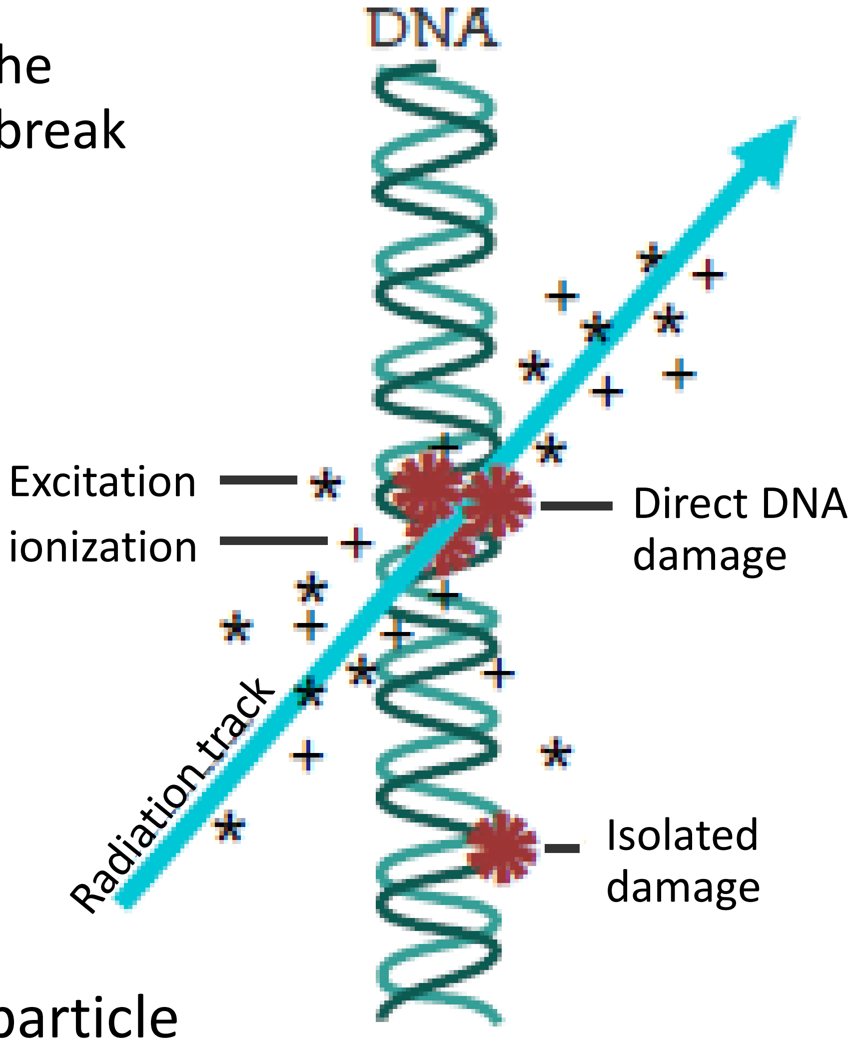
- Introduction
  - Radiotherapy
  - What is BNCT?
- PhD project
  - Current Biological Dose estimation
  - Theoretical developments
  - Experiments & Results (in 3 facilities)
- Conclusions and remarks



Introduction

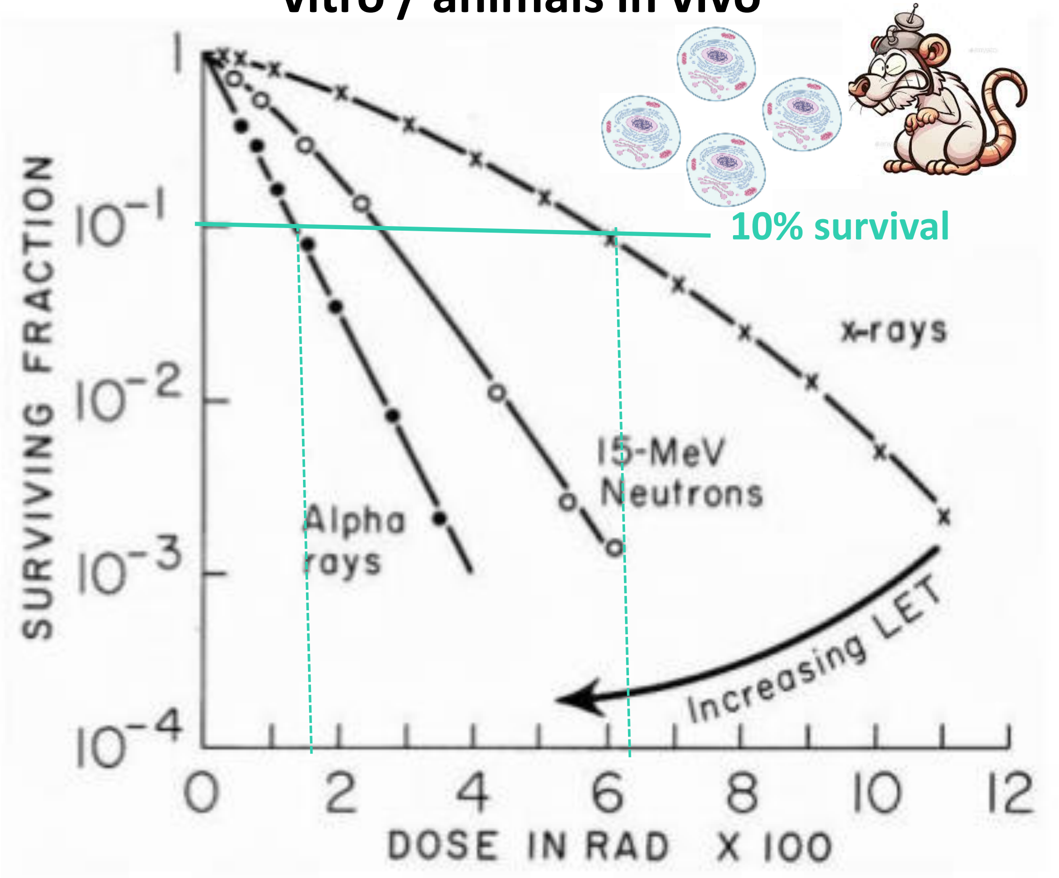
Effect of Radiations

- Direct damage to the DNA: *double* strand break
- Ionization starts chemical reactions which end in DNA damage. It can be repaired



It depends on the particle

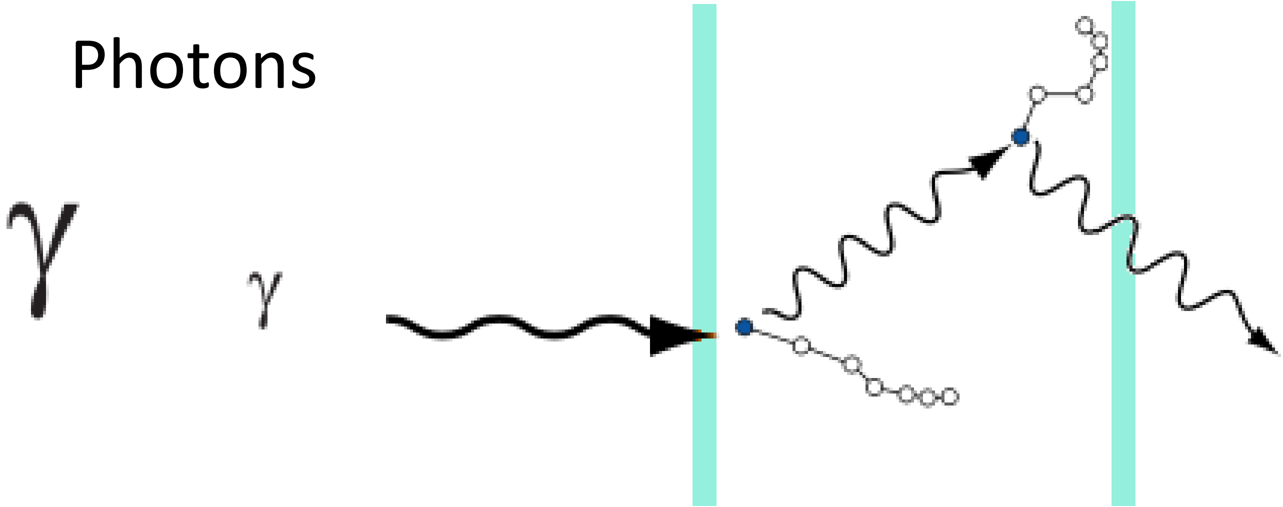
The effect is expressed in survival curves of cells in vitro / animals in vivo



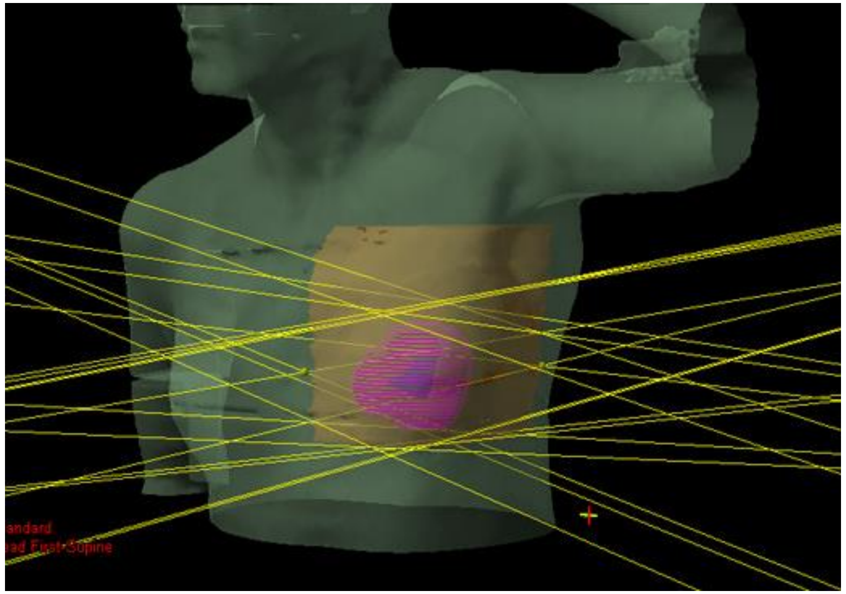
To have 10% survival it will be necessary to give a dose of 6 Gy with photons, but less than 2 Gy with alpha particles, because their damage is more direct.

Photon Radiotherapy (conventional)

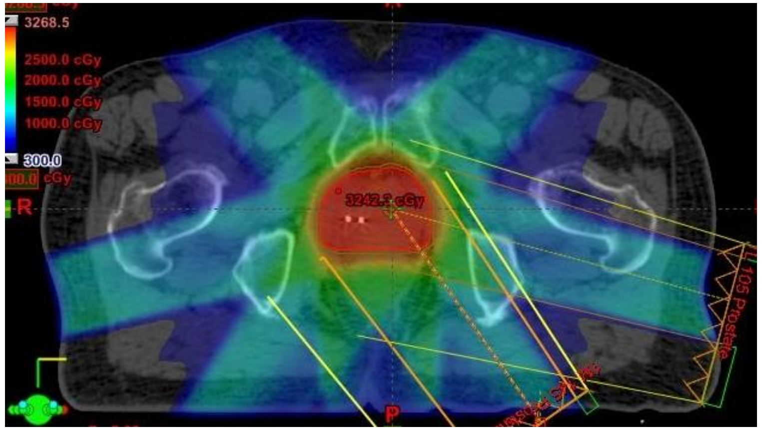
Photons



Ionization.
Damage the DNA on their track



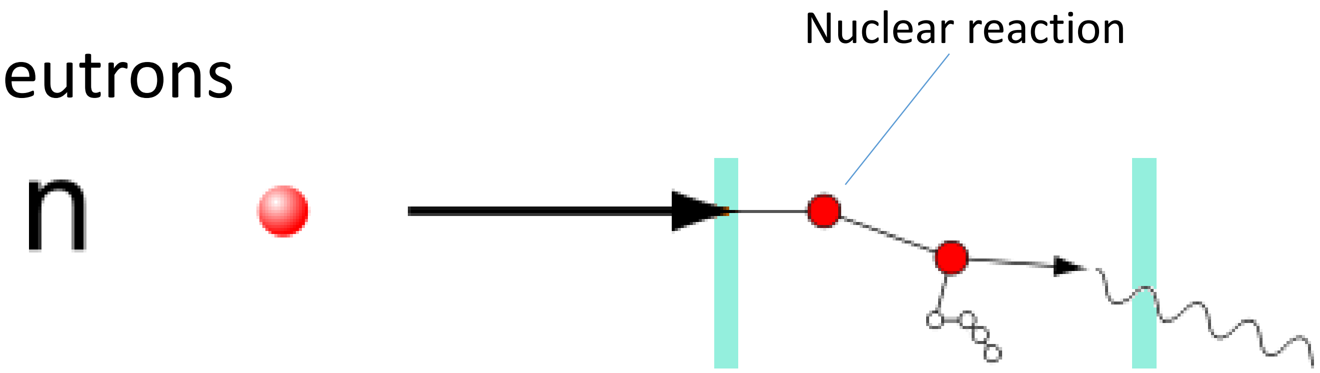
- External irradiation.
- The most important is the geometry.
- Healthy tissue is also damaged.



Boron Neutron Capture Therapy (BNCT)

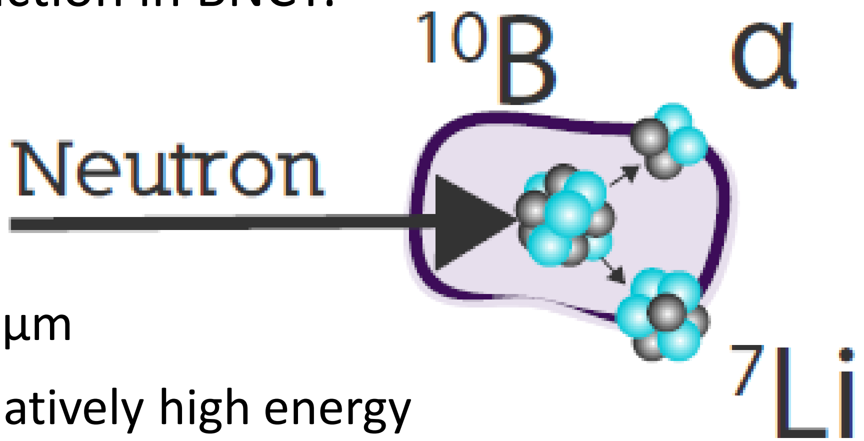
BNCT: Neutrons

Neutrons



<u>Indirect</u> ionization.
There is no damage until a nuclear reaction takes place

Nuclear reaction in BNCT:
$^{10}B(n,\alpha)^{7}Li$



Range < 10 µm

Li and α, relatively high energy

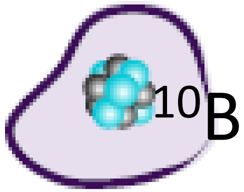
Lot of damage in a minimum space

↓

<u>The cell is totally destroyed after the reaction</u>

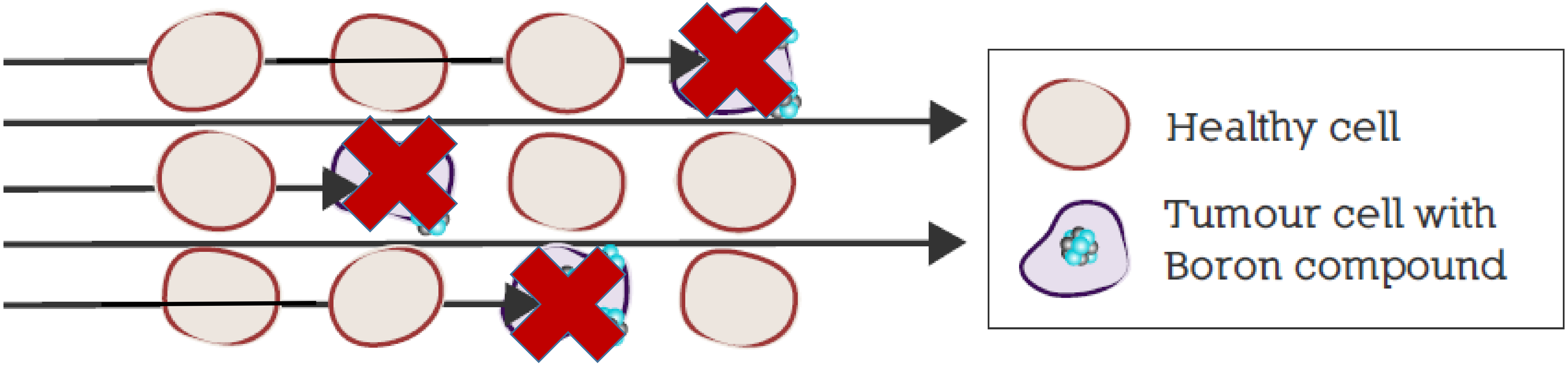
BNCT: How it works

Accumulate the boron in the tumour cells:



then

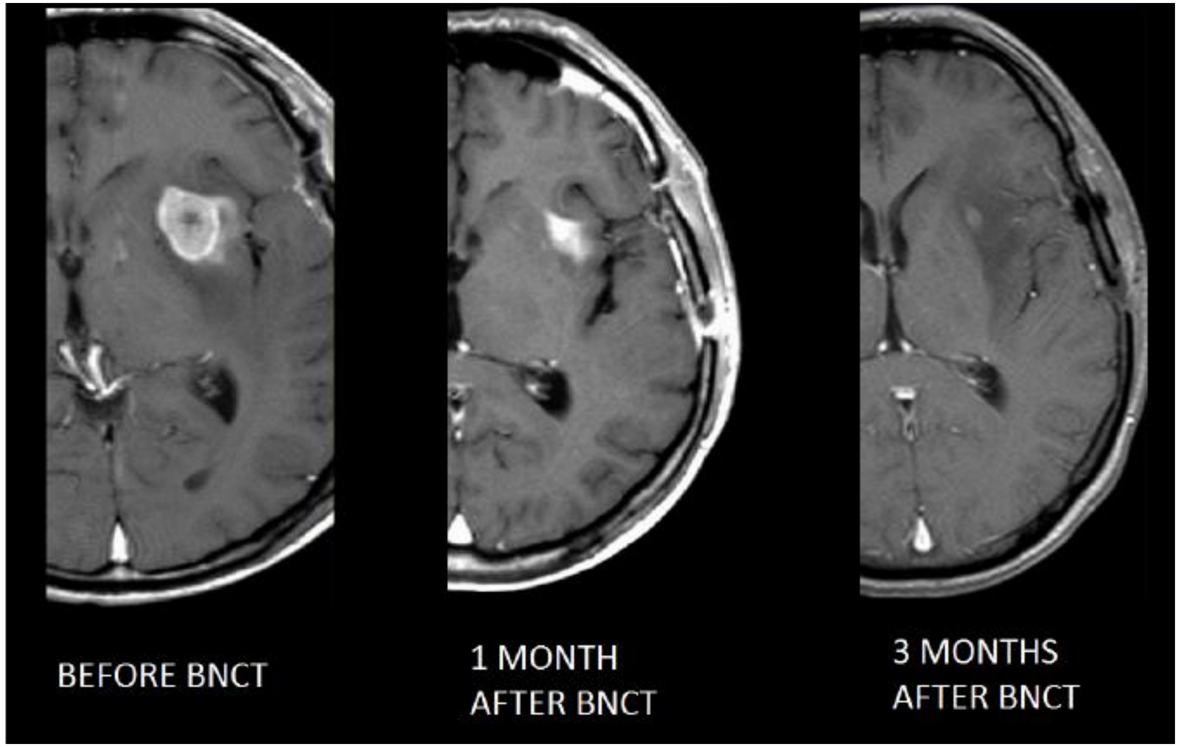
Irradiate with neutrons:



BNCT: dual radiotherapy selective at cell level

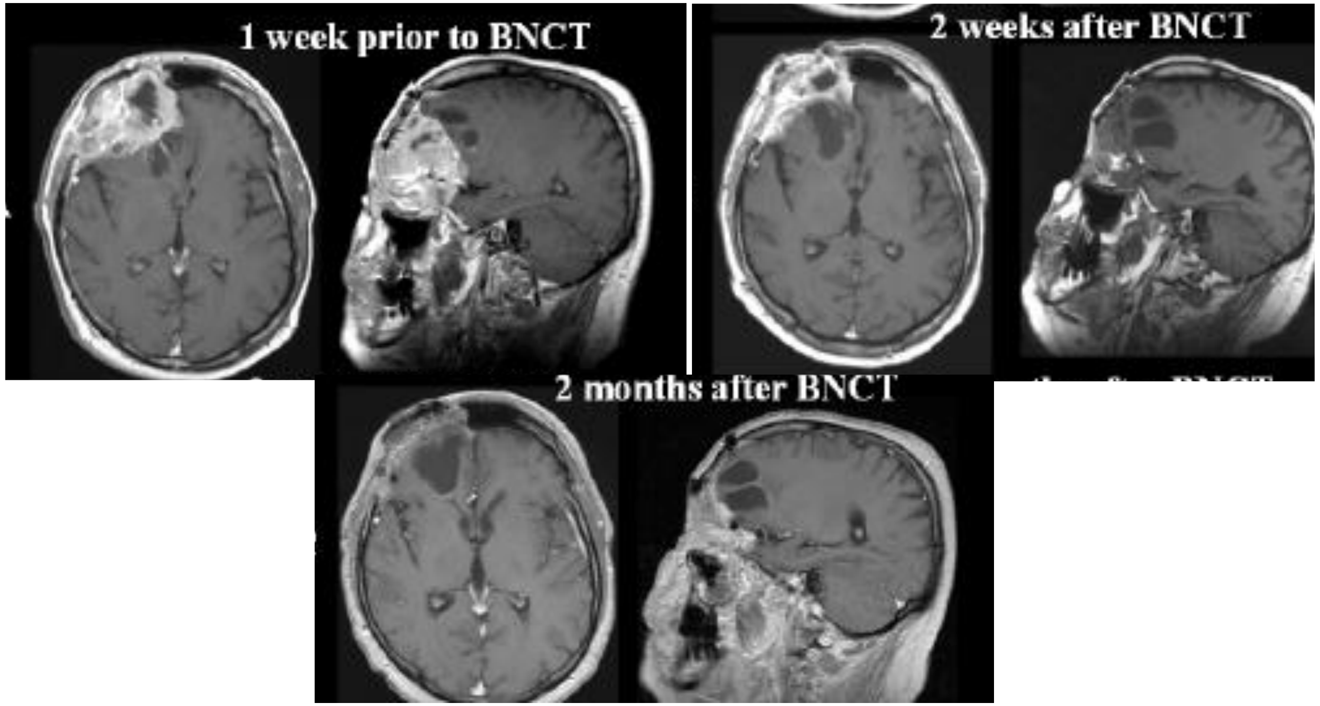
BNCT: Clinical results

Glioblastoma (mortal brain tumour)



Joensuu et al. *Journal of Neuro-Oncology*, 2003.

Recurrent head and neck cancers



Kouri et al. *Radiotherapy and Oncology*, 2004.

Also: melanoma, liver metastases, etc.

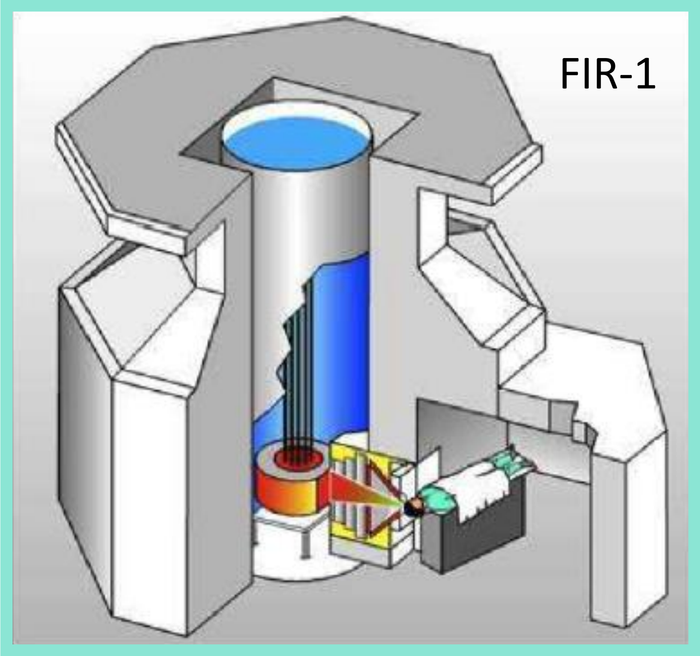
In all the cases there were good results on the palliative care.

The quality of life of the patient is improved.

1 day treatment

BNCT: neutron beam, reactors

Until now:
Reactors



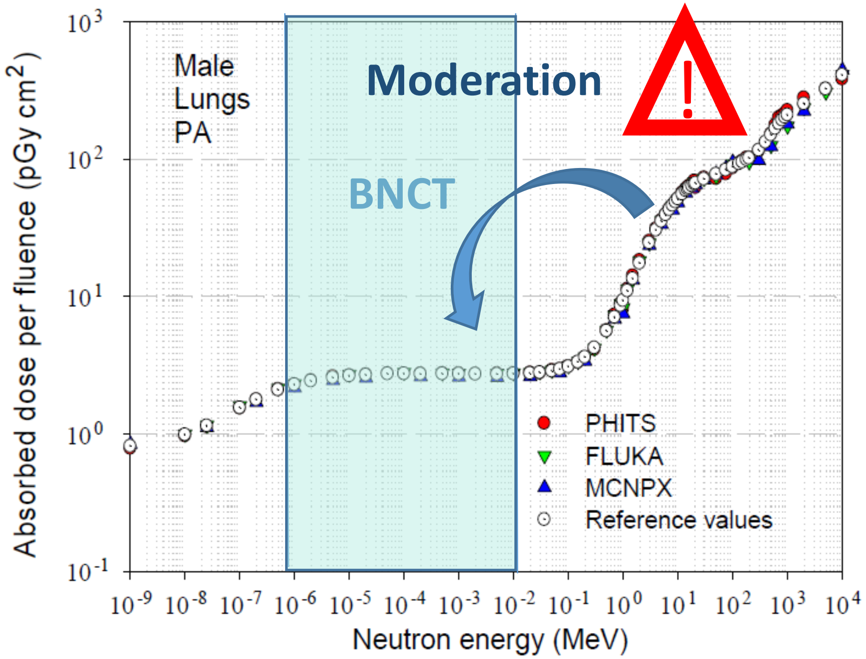
Patients at reactors in: Japan, Finland, Argentina, USA, Netherlands, Sweden, Taiwan…

> 1000 patients

Neutron beam requirements for BNCT:

Epithermal neutron flux	> 10^9 neutrons/cm^{2}s (at the therapy position)
Neutron energy	1 eV to 10 keV
Gamma dose rate	< 1Gy/h
Fast neutron dose rate	< 0.5 Gy/h

IAEA International Atomic Energy Agency



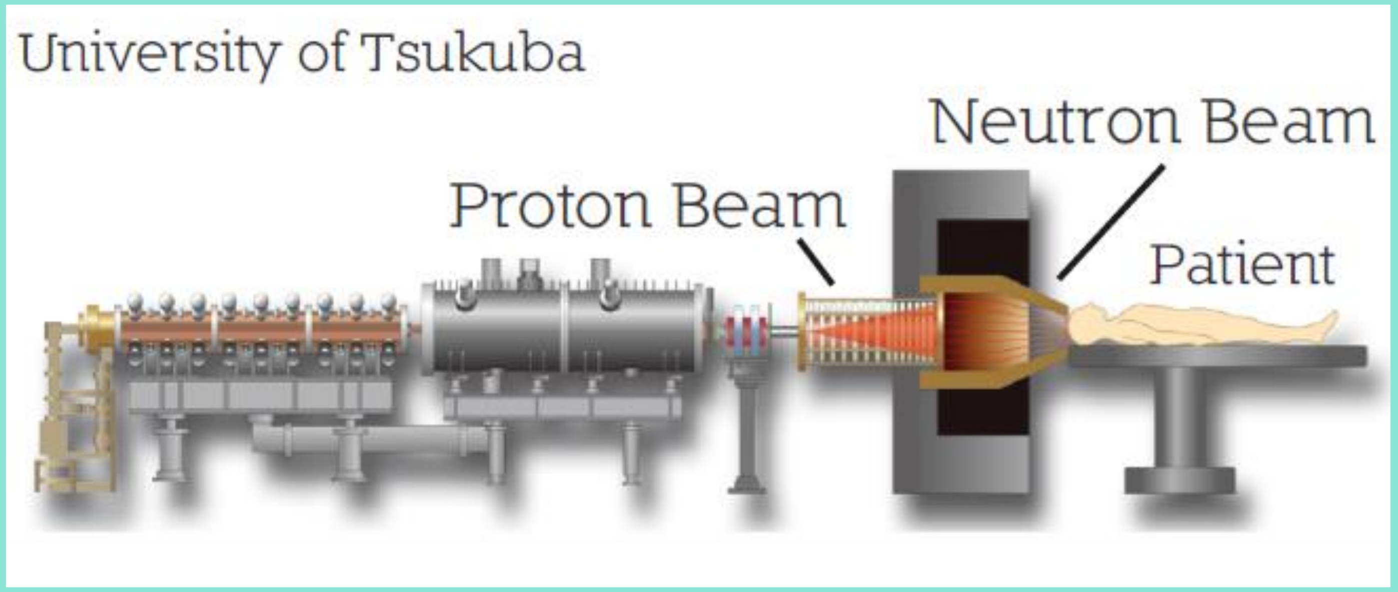
Loss of neutrons

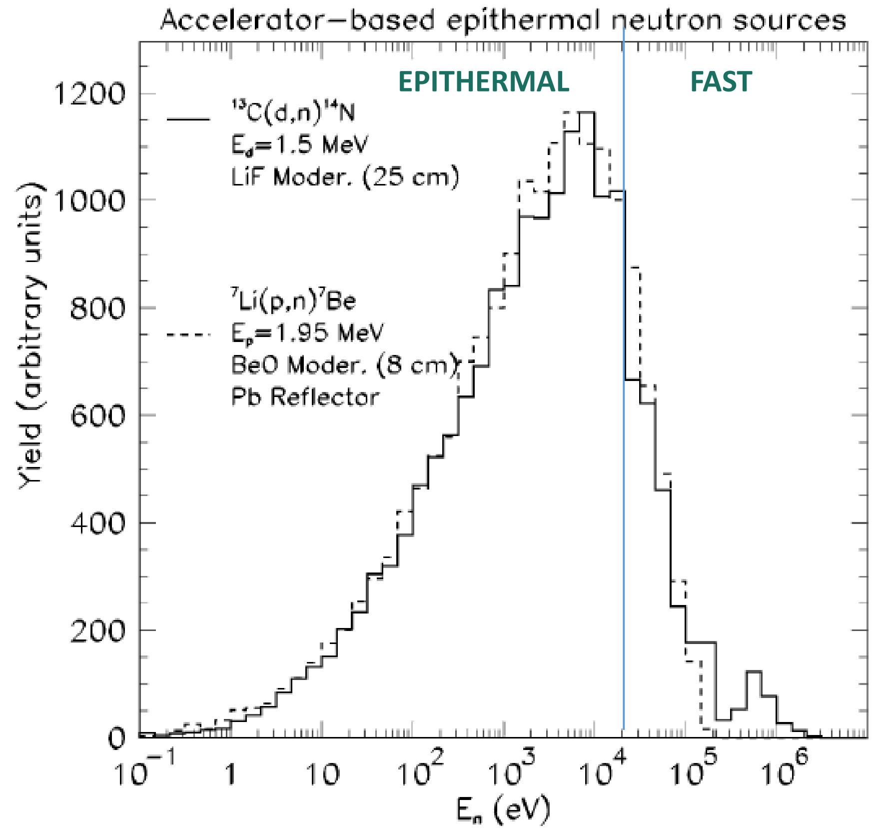
Gamma creation

Other Disadvantages:
Expensive
Far away from hospitals

BNCT: neutron beam, accelerators

Future:
<u>Accelerators</u>





Nuc. Inst. Met. Phy. Res. A 476 (2002) 123–126

Neutrons from (p,n) reactions

Almost no moderation required

Neutrons have the appropriate energies for BNCT

<u>Other Advantages:</u>
- They can be built at hospitals
- Less radioactive waste production

BNCT: Future

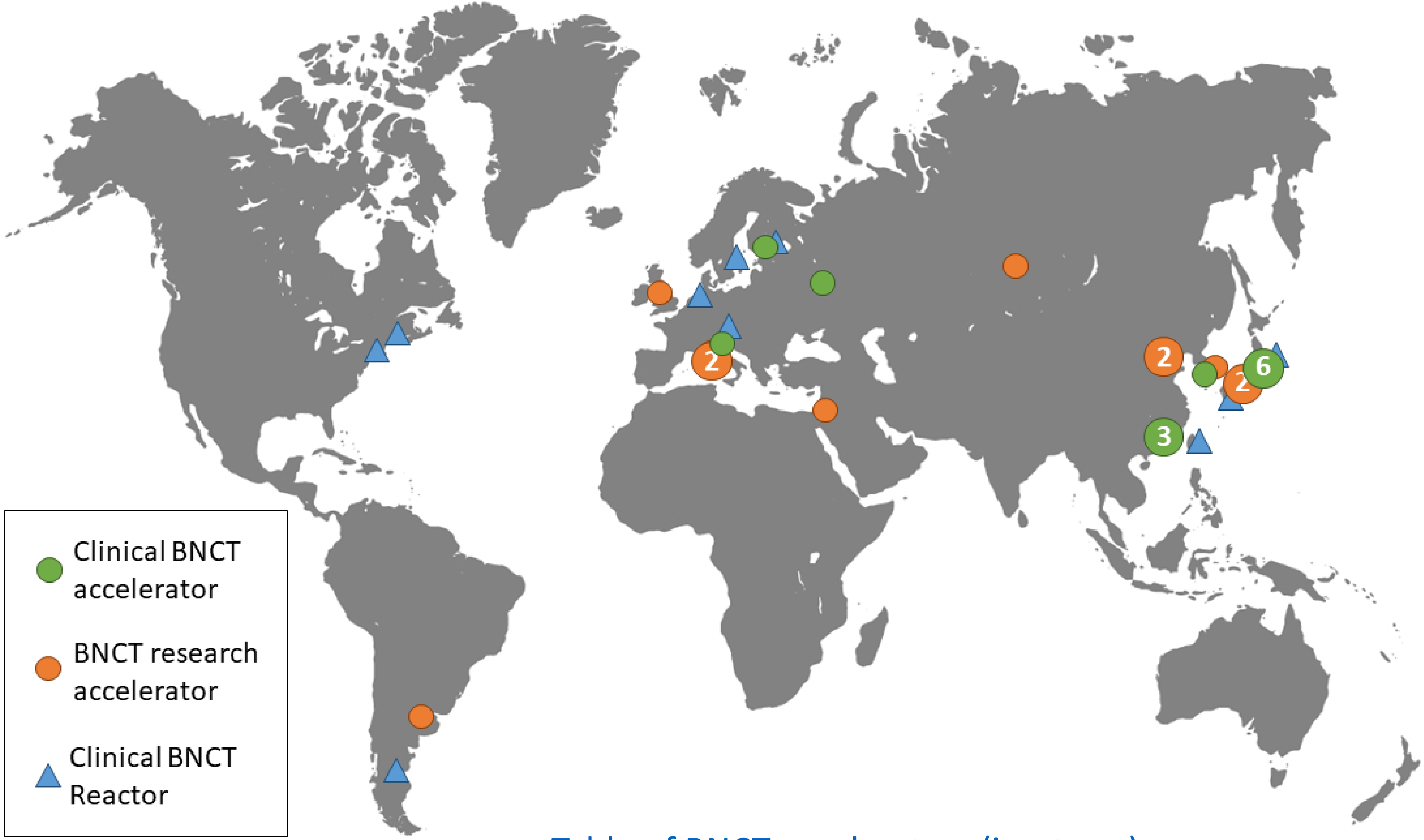


Table of BNCT accelerators (isnct.net)

More accelerators dedicated to BNCT

↓

more patients

↓

more clinical experience

It is expected to become a common radiotherapy in the future!

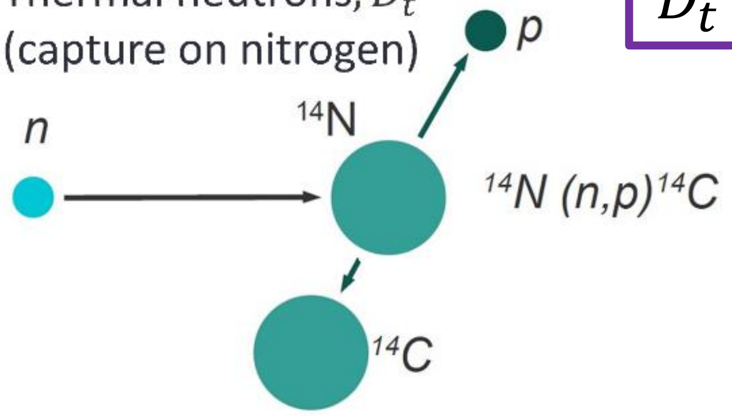
PhD Project

Biological Dose

Physical Dose in BNCT

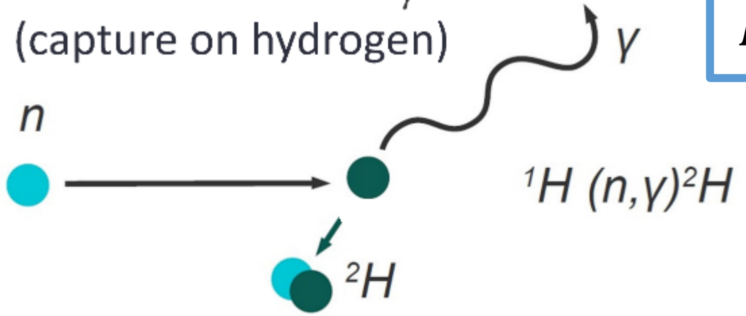
There are other reactions in the tissue

Thermal neutrons, D_t
(capture on nitrogen)



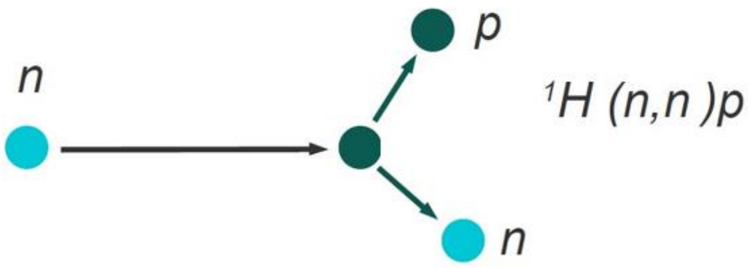
D_t

Gamma emission, D_γ
(capture on hydrogen)



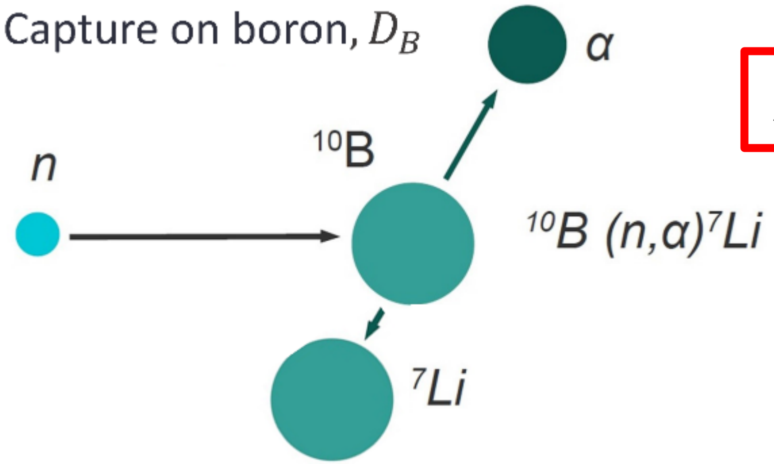
D_γ

Fast neutrons, D_f
(elastic collisions)



D_f

Capture on boron, D_B



D_B

Physical Dose: $D = D_t + D_f + D_\gamma + D_B$

Current biological dose in BNCT

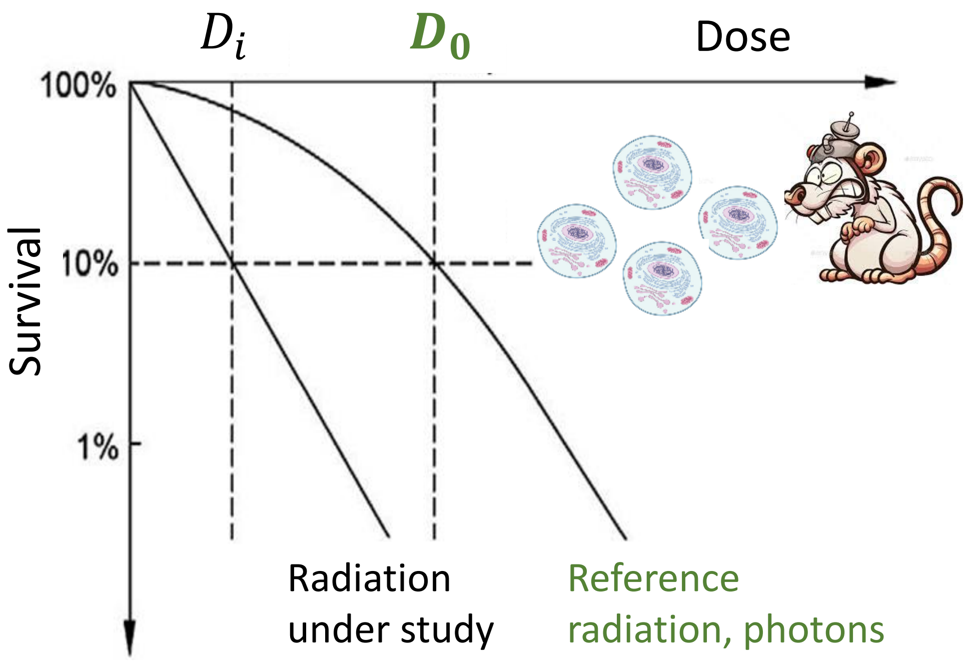
Physical Dose: $D = D_t + D_f + D_\gamma + D_B$

Biological Dose:

$$D_W \equiv \boldsymbol{w_t}\, D_t + \boldsymbol{w_f}\, D_f + \boldsymbol{w_\gamma}\, D_\gamma + \boldsymbol{w_B}\, D_B =$$

1. Weight each dose with a factor
   (*Relative Biological Effectiveness (RBE) or weighting factors*)
2. Compare with a known effect
   (*Reference photon Dose*)

Current biological dose in BNCT, w factors



From survival curves after *in vitro (cells)* or *in vivo (animals)* irradiations

$$RBE \text{ or } w_{factor} = \frac{D_0}{D_i}$$

They depend on the particle, energy of the particle, particle LET, tissue, dose, survival, etc..

$$D_W \equiv w_t\, D_t + w_f\, D_f + w_\gamma\, D_\gamma + w_B\, D_B = D_0$$

weighting factors (Coderre et al.)		
$w_t = w_f = 3.2$	$w_\gamma = 1$	$w_B(BPA) = 3.8$ (tumour) $w_B(BPA) = 1.3$ (Healthy tissue)

BNCT Dosimetry: Improvements

$$D_W \equiv w_t\ D_t + w_f\ D_f + w_\gamma\ D_\gamma + w_B\ D_B = D_0$$

weighting factors (Coderre et al.)		
$w_t = w_f = 3.2$	$w_\gamma = 1$	$w_B(BPA) = 3.8$ (tumour) $w_B(BPA) = 1.3$ (Healthy tissue)

- Simple formalism
- w_i used as constants, but by definition they are not constants

- w_i experimentation with few tissues and then extrapolated to others
- Thermal factor and fast factor assumed equal, $w_t = w_f$, due to the difficulty to separate them
- $w_\gamma = 1$ (effect equal to reference dose), due to the difficulty of isolate photon effect on a neutron beam

Theoretical developments

Experiments

Experiments in 6 different facilities

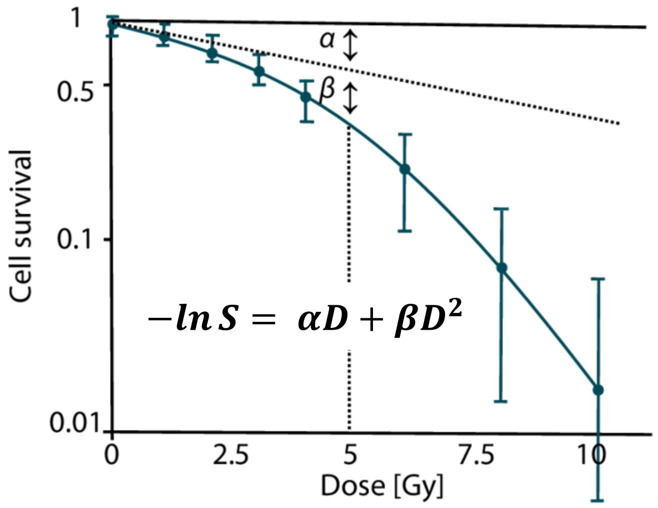
PhD Project

<u>Theoretical developments</u>

PhD: New formalism for biological effect

Introduce the LQ model and make equal the biological effect of BNCT and a reference photon irradiation:

$$-\log S \equiv \underbrace{\alpha_t D_t + \alpha_f D_f + \alpha_0 D_\gamma + \beta_0 D_\gamma^2 + \alpha_B D_B}_{\text{BNCT effect}} = \underbrace{\alpha_0 D_0 + \beta_0 D_0^2}_{\text{Photons effect}}$$



True constants
(only depends on the tissue)

$$E_{BNCT} \equiv w_f^* D_f + w_t^* D_t + w_B^* D_B + D_\gamma + \frac{D_\gamma^2}{\alpha_0/\beta_0} = \begin{cases} D_0 + \dfrac{D^2{}_0}{\alpha_0/\beta_0} & \textit{single fraction} \\ nd\left(1 + \dfrac{d^2}{\alpha_0/\beta_0}\right) & \textit{fractionated} \end{cases}$$

[Applied Radiation and Isotopes 157 (2020) 109018](#)

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

ELSEVIER

journal homepage: http://www.elsevier.com/locate/apradiso

A simple approximation for the evaluation of the photon iso-effective dose in Boron Neutron Capture Therapy based on dose-independent weighting factors

María Pedrosa-Rivera [a,b], Javier Praena [a], Ignacio Porras [a,*], María José Ruiz-Magaña [c], Carmen Ruiz-Ruiz [c]

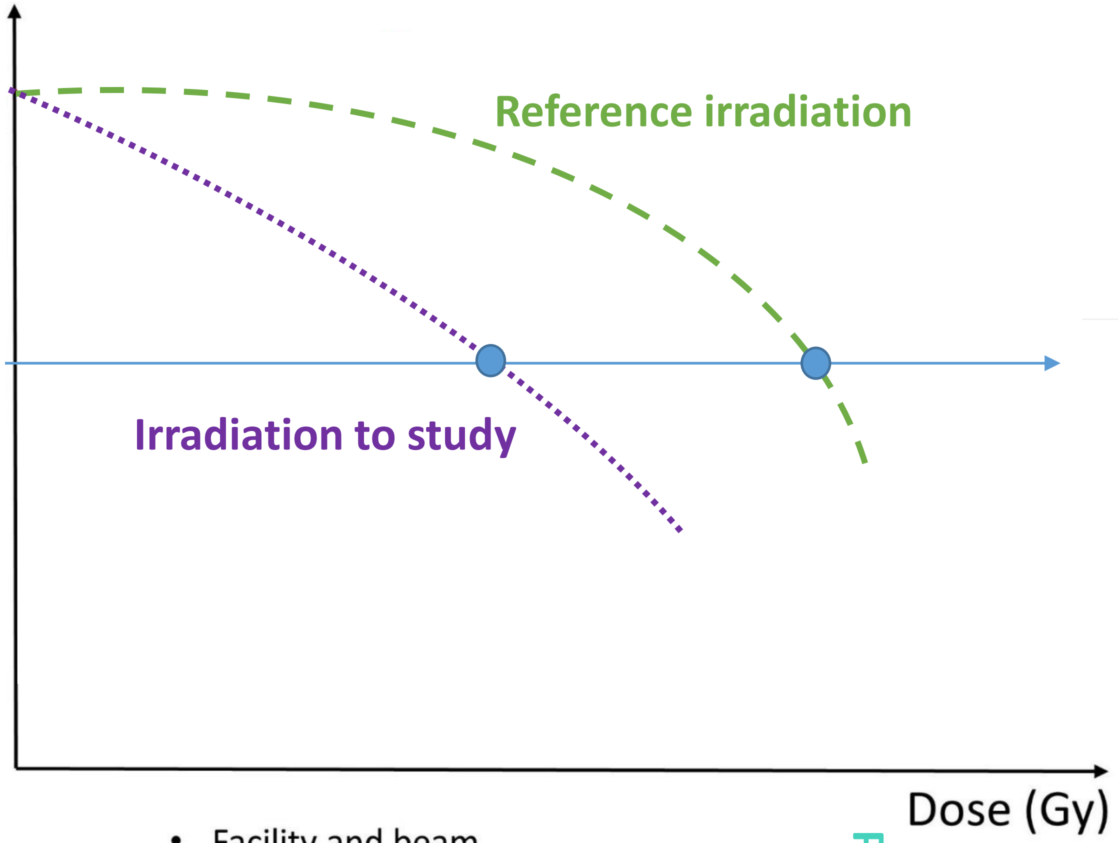
New factors: $w_i^* = \dfrac{\alpha_i}{\alpha_0}$

PhD Project

Experiments

PhD: The aim of the experiments

Survival after irradiation to study the biological effect

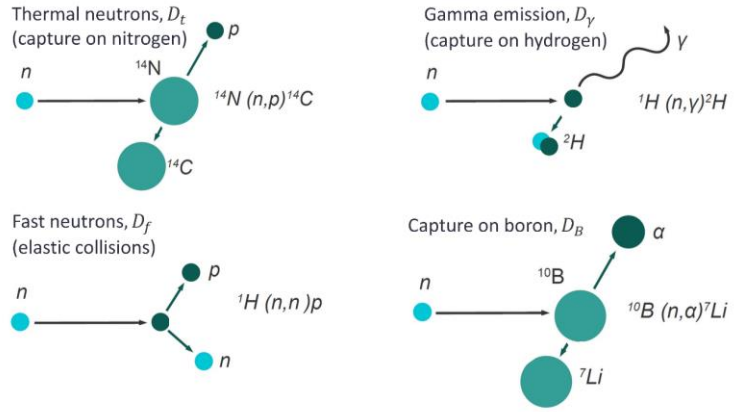


BIOLOGY

- Cell culture and cell lines
- Sample preparation
- Survivals assays

PHYSICS

- Facility and beam
- Set-up and Monte Carlo simulations



$$RBE\ or\ w_{factor} = \frac{D_0}{D_i}$$

$$w_i^* = \frac{\alpha_i}{\alpha_0}$$

1. **Sample preparation**
2. **Irradiation**
3. **Survival assays**

PhD Experiments(Physics): Facilities

Irradiation

Sample analysis

ILL:Low-energy neutrons → w_t, w_γ, w_B

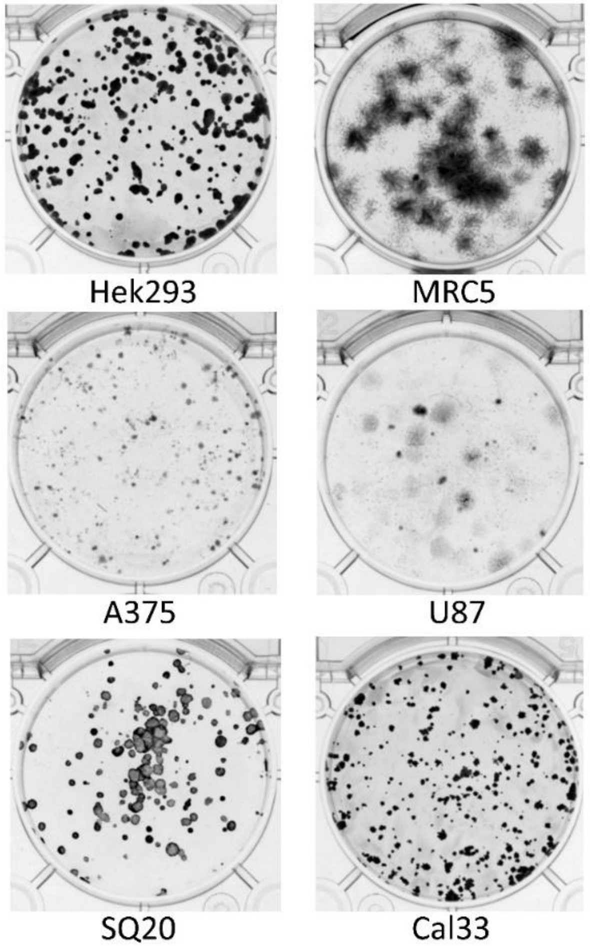
CNA:Epithermal neutrons → w_f

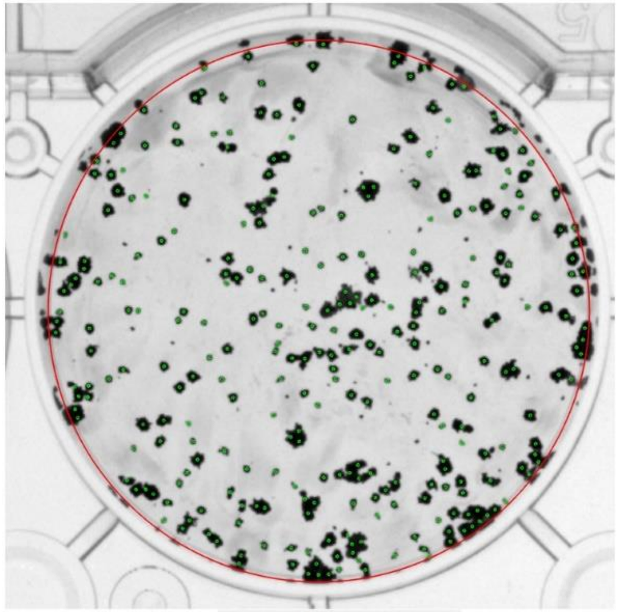
Hospital: Photons → Reference Dose, D_0

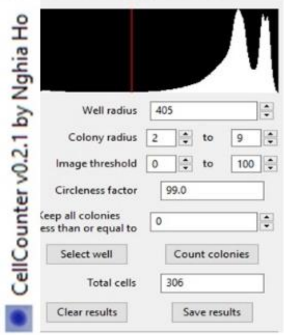
UNIVERSIDAD DE GRANADA

PhD Experiments(Biology): Assays after irradiation

Clonogenic assay:

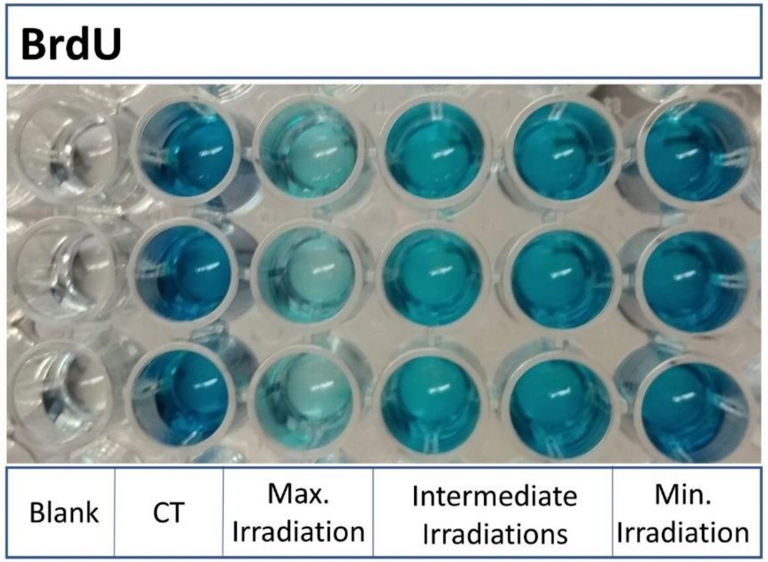


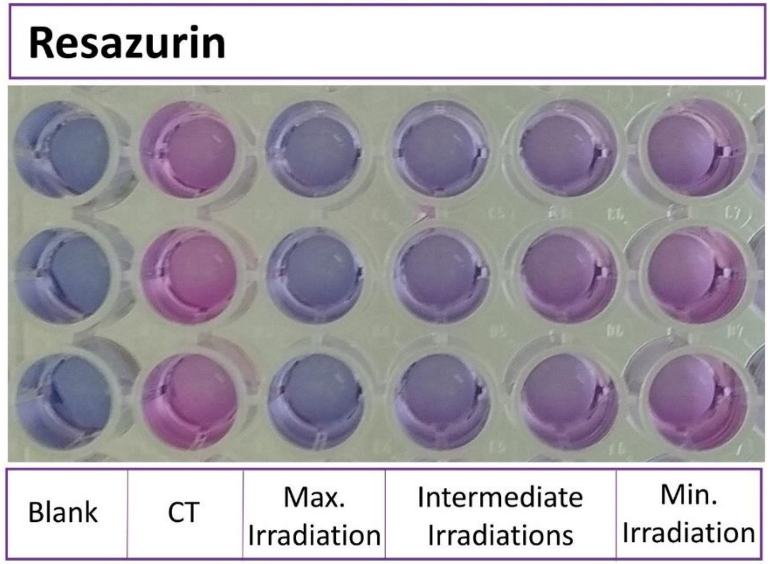




Survival results from this assay

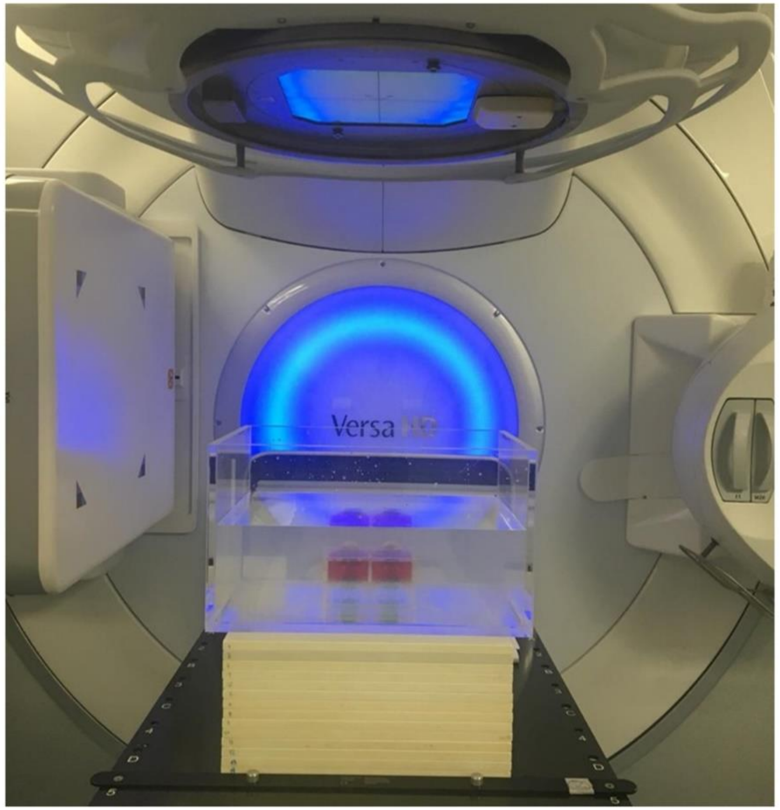
Colorimetric assay:

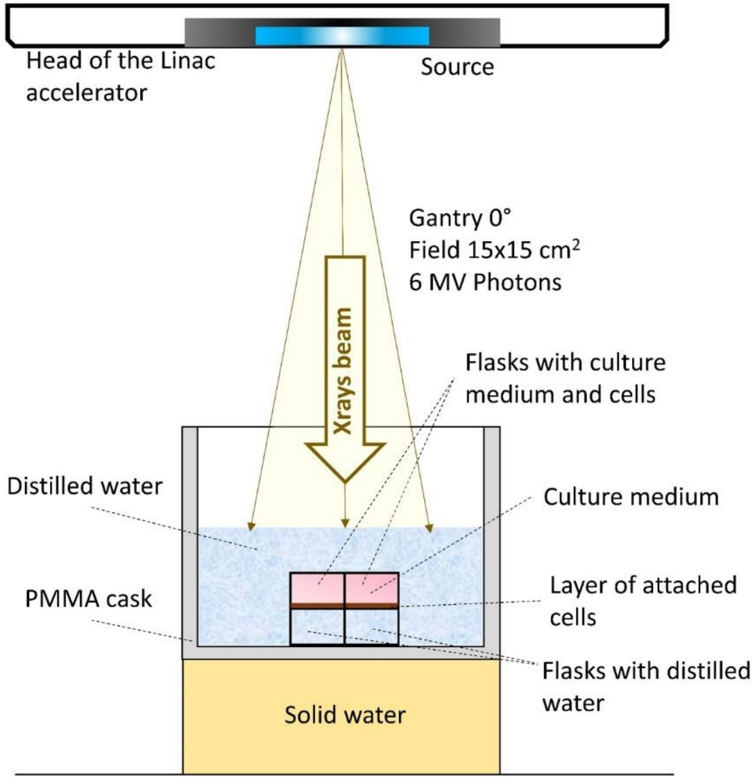


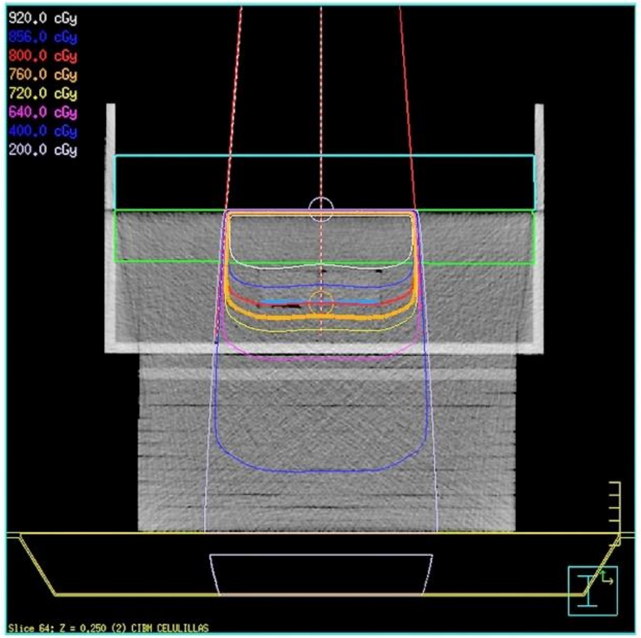


Experiment at the hospital LINAC

Experiment at LINAC: set-up





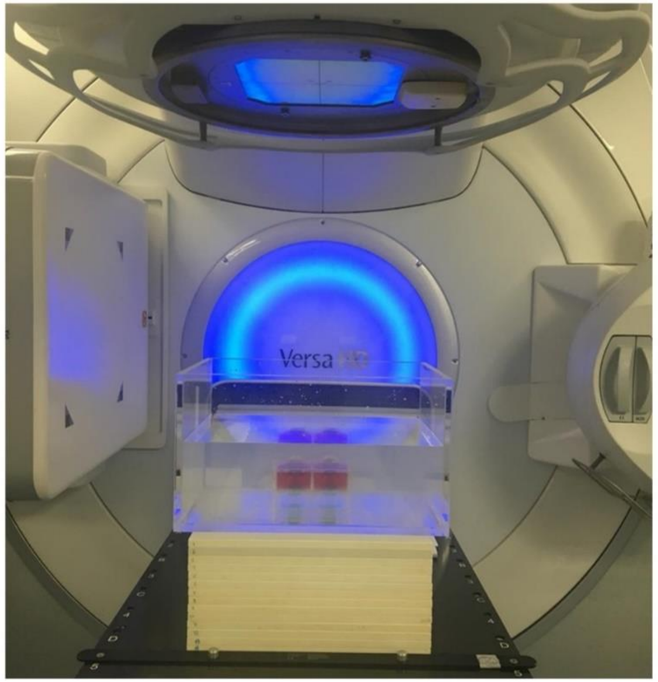


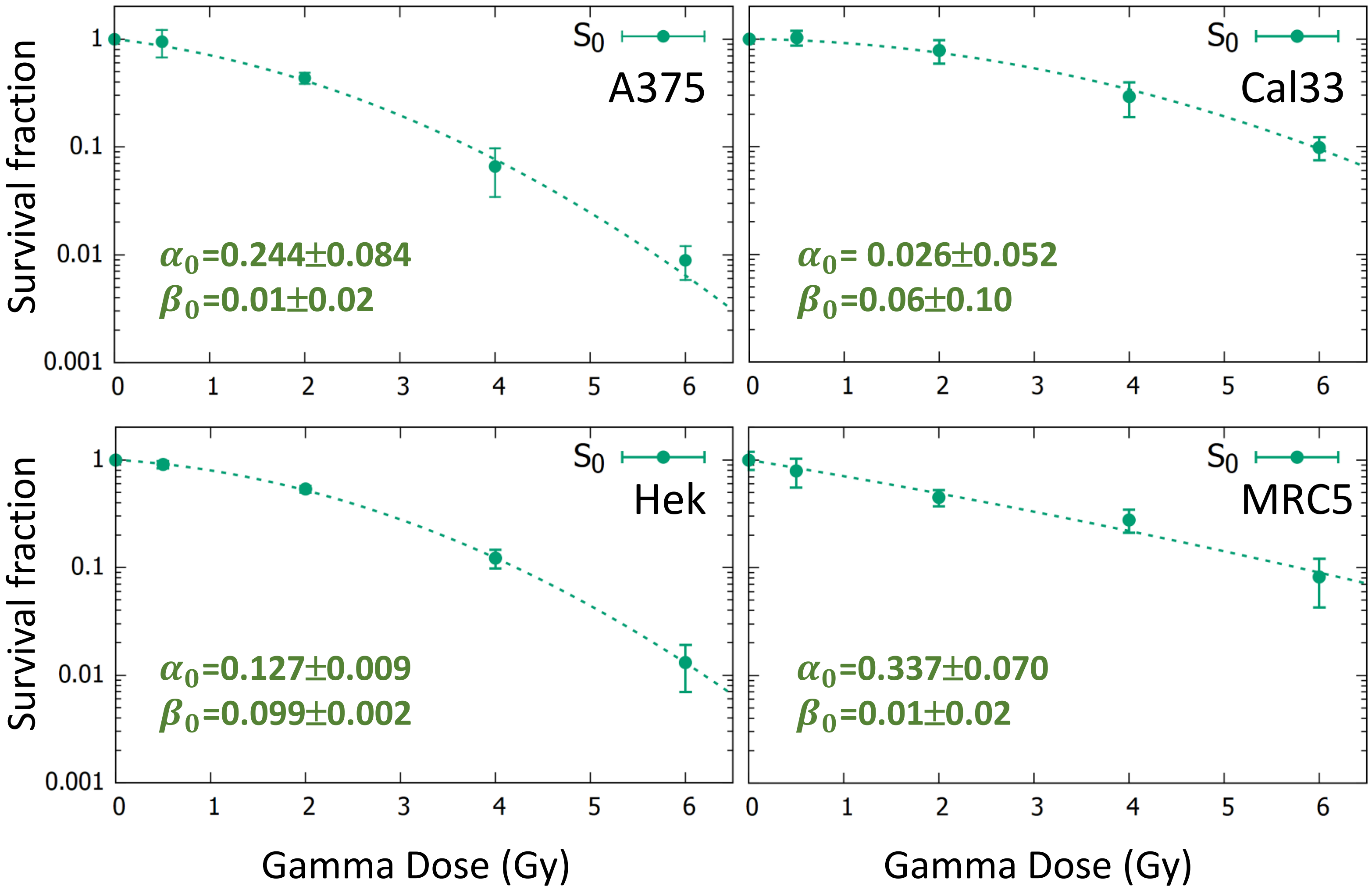
Exp.V: $D_{LINAC} = D_0$(reference dose=photons)

Experiment at LINAC: Results

HOSPITAL UNIVERSITARIO VIRGEN DE LAS NIEVES
HOSPITALES DE GRANADA

Exp.V: $D_{LINAC} = D_0$(reference dose)

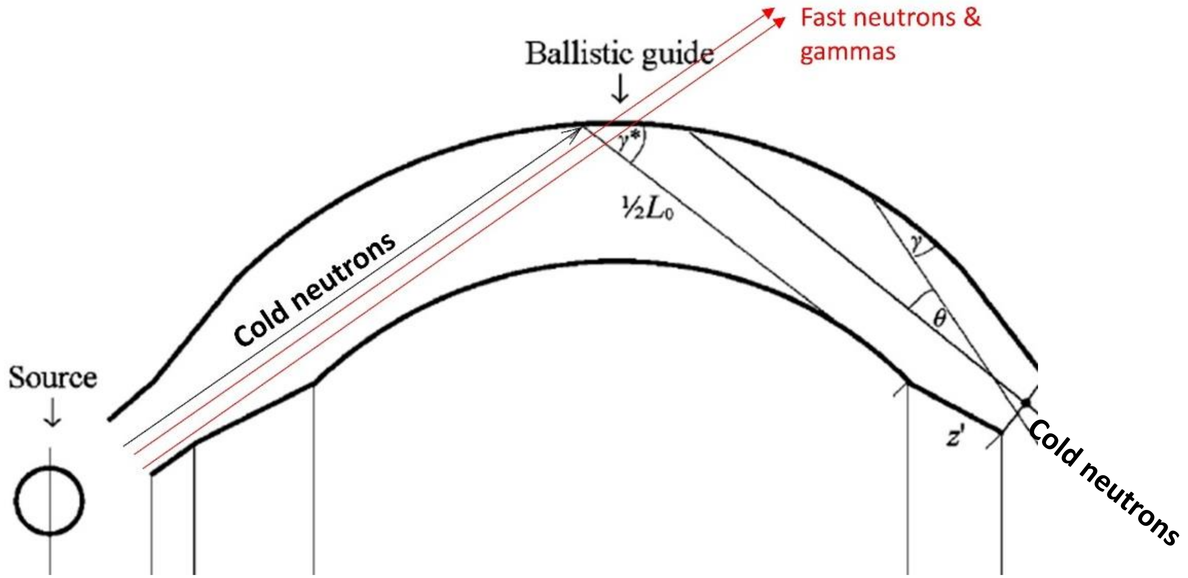


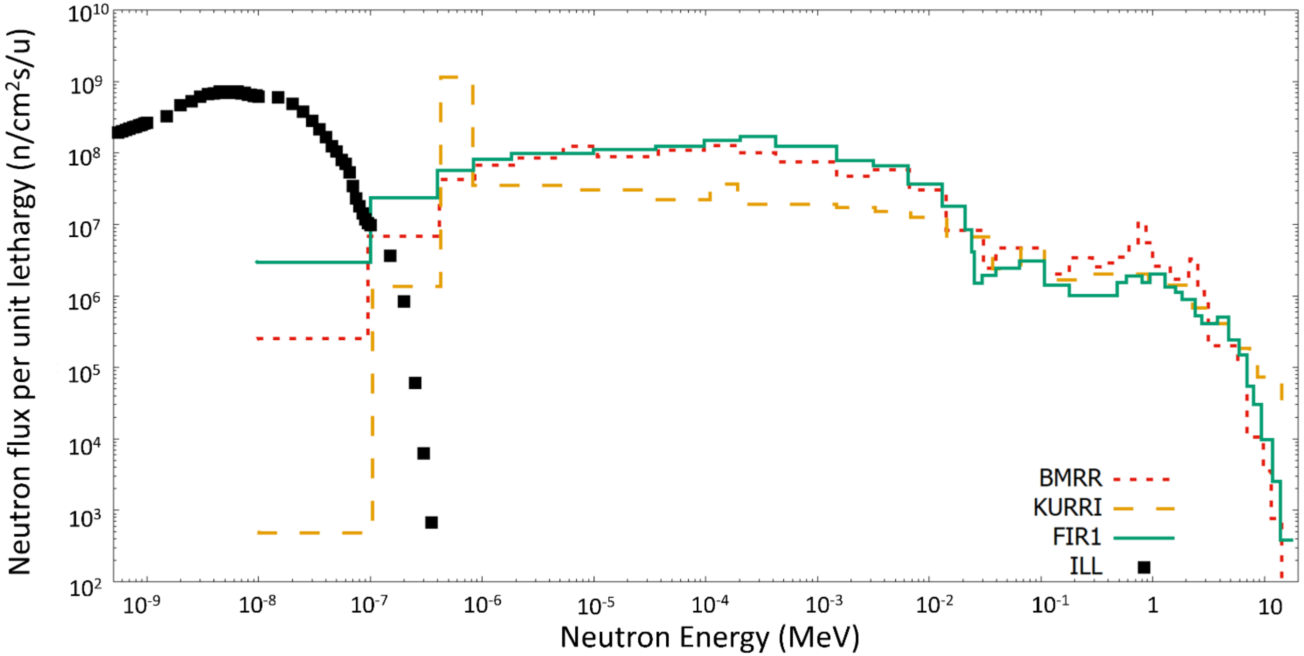


Experiments at ILL neutron beam

Experiments at ILL: Cold neutron beam

ILL beam: mainly low-energy neutrons





The bent guide allow cold neutron to follow the folded path while fast neutrons and gamma cannot

Compared to other beams (that have been used for BNCT irradiations and biological experiments), ILL beam is really “clean”

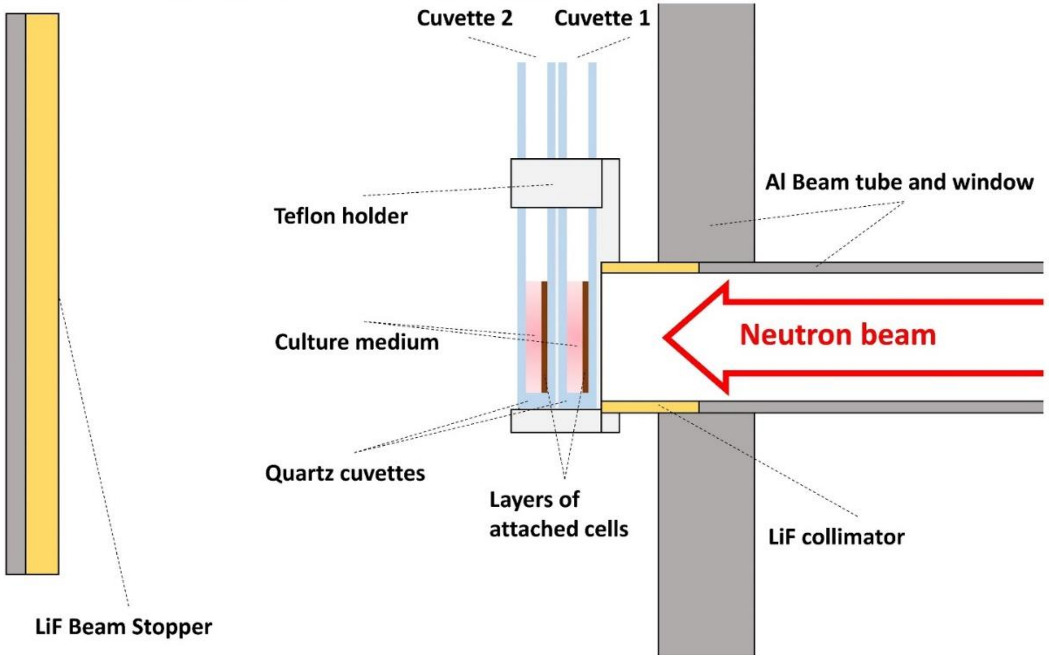
Experiments at ILL: Lab at the guide hall

- We need a lot of samples
- The samples need to be prepared in a level P2 lab

NEW!

P2 lab inside the ILL7 (instruments hall)

Experiments at ILL: Cold neutron irradiations

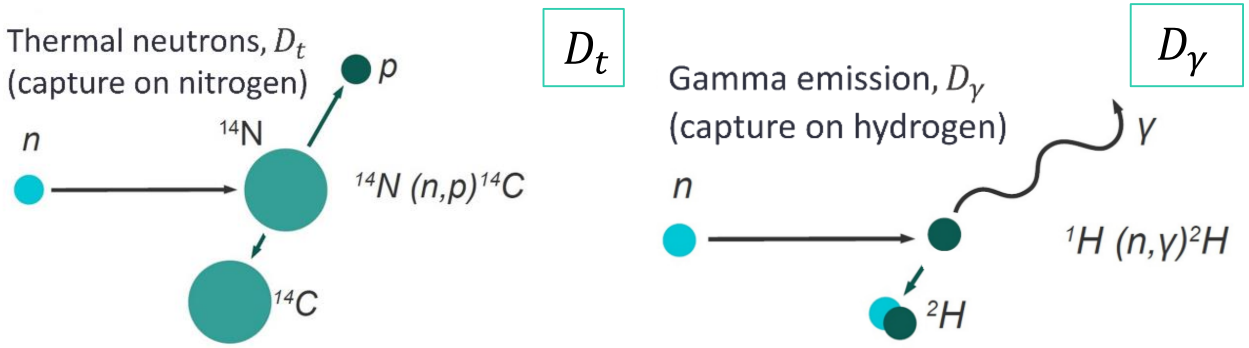


Materials with less gamma emission as possible: quartz cuvettes and LiF shielding

Cells need to be in culture media, but the more culture media, the more gamma creation (Hidrogen…): 2mm thick cuvettes

Limited irradiation time: two samples at the same time

ILL beam: mainly low-energy neutrons, with less gamma as possible



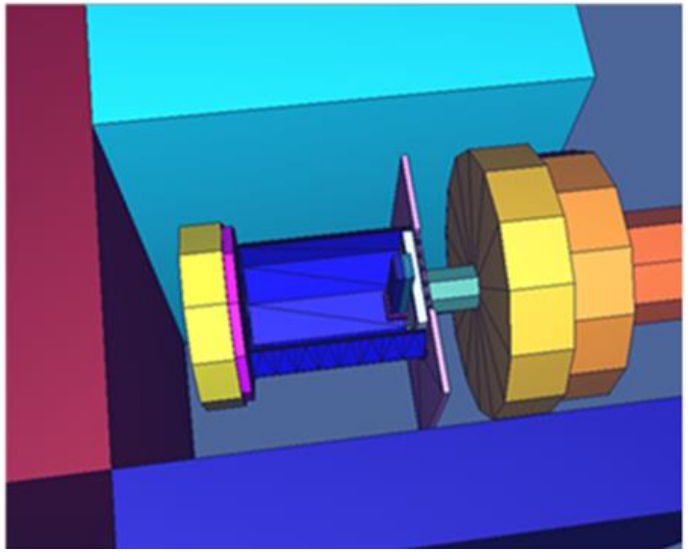
Exp.I: $D_{ILL} = \boldsymbol{D_t} + D_\gamma$ → $\boldsymbol{w_t}$

Experiments at ILL: Cold neutron simulations

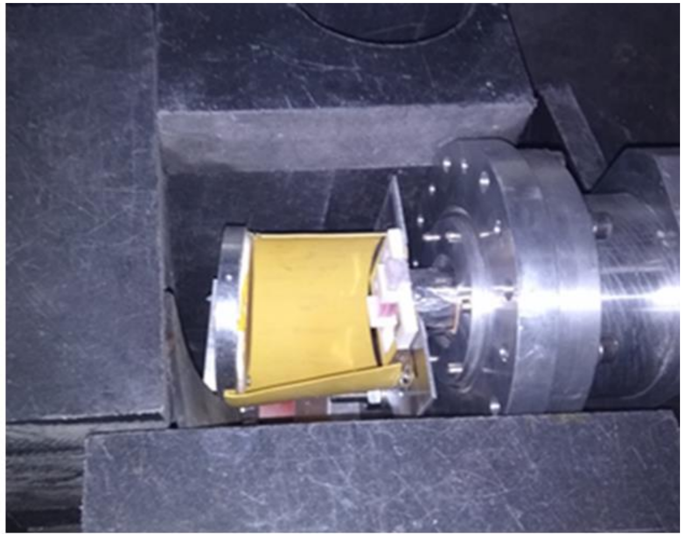
NEUTRONS FOR SOCIETY

MCNPX Monte Carlo simulations to "predict" neutrons behavior and calculate the doses

	Thermal dose, D_t (Gy/min)		Gamma dose, D_γ (Gy/min)	
	Cuvette 1	Cuvette 2	Cuvette 1	Cuvette 2
A375	0.095	0.044	0.021	0.016
Cal33	0.044	0.021	0.021	0.016
U87	0.037	0.017	0.021	0.016
SQ20	0.044	0.044	0.021	0.016
HEK293	0.027	0.013	0.021	0.016
MRC5	0.052	0.024	0.021	0.016



Neutron dose higher than gamma dose



Nuclear Inst. and Methods in Physics Research B 462 (2020) 24–31

Contents lists available at ScienceDirect

Nuclear Inst. and Methods in Physics Research B

journal homepage: www.elsevier.com/locate/nimb

ELSEVIER

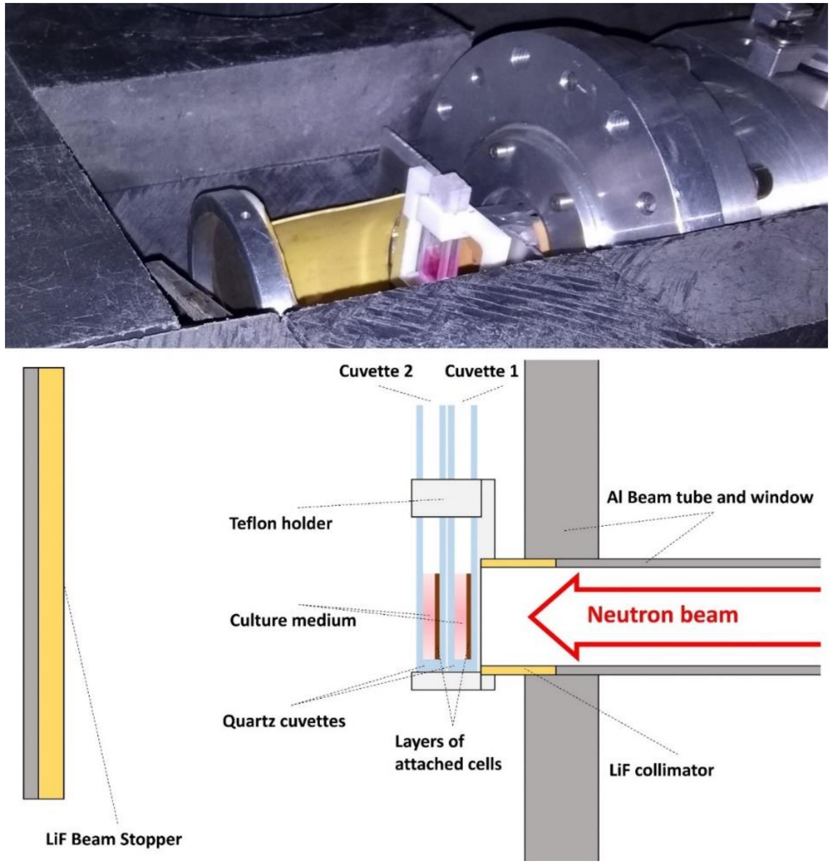
BEAM INTERACTIONS WITH MATERIALS AND ATOMS

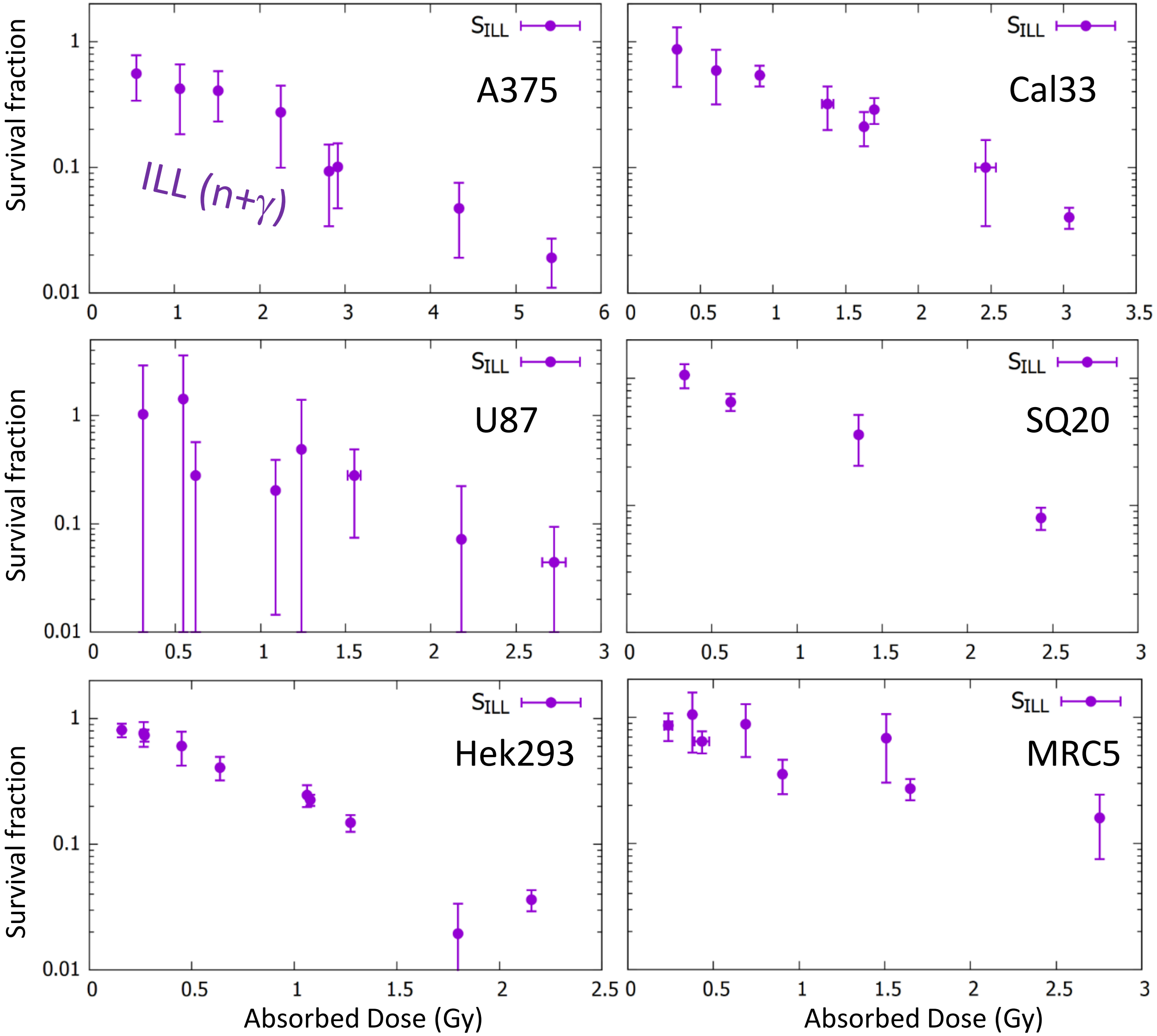
Neutron radiobiology studies with a pure cold neutron beam

M. Pedrosa-Rivera[a,b,*], M.J. Ruiz-Magaña[c], I. Porras[b], J. Praena[b], P. Torres-Sánchez[b], M.P. Sabariego[b], U. Köster[a], T. Forsyth[a], T. Soldner[a], M. Haertlein[a], C. Ruiz-Ruiz[c]

Experiments at ILL: Results, w_t

Exp.I: $D_{ILL} = \boldsymbol{D_t} + D_\gamma$





Experiments at ILL: Results, w_t

NEUTRONS FOR SOCIETY

S	A375	Cal33	U87	SQ20
50%	2.05±0.43	4.60±0.56	5.90±2.74	4.57±0.79
37%	1.83±0.42	4.05±0.52	5.79±3.03	4.02±0.73
10%	1.37±0.34	2.92±0.41	5.40±3.23	2.90±0.56
1%	1.04±0.26	2.18±0.31	4.90±3.07	2.16±0.42
S	Hek	MRC5		
50%	7.70±0.42	3.16±0.73		
37%	6.69±0.38	2.97±0.74		
10%	4.70±0.27	2.45±0.66		
1%	3.46±0.20	1.99±0.55		

$$w_t = \frac{D_0}{D_t}$$

cells

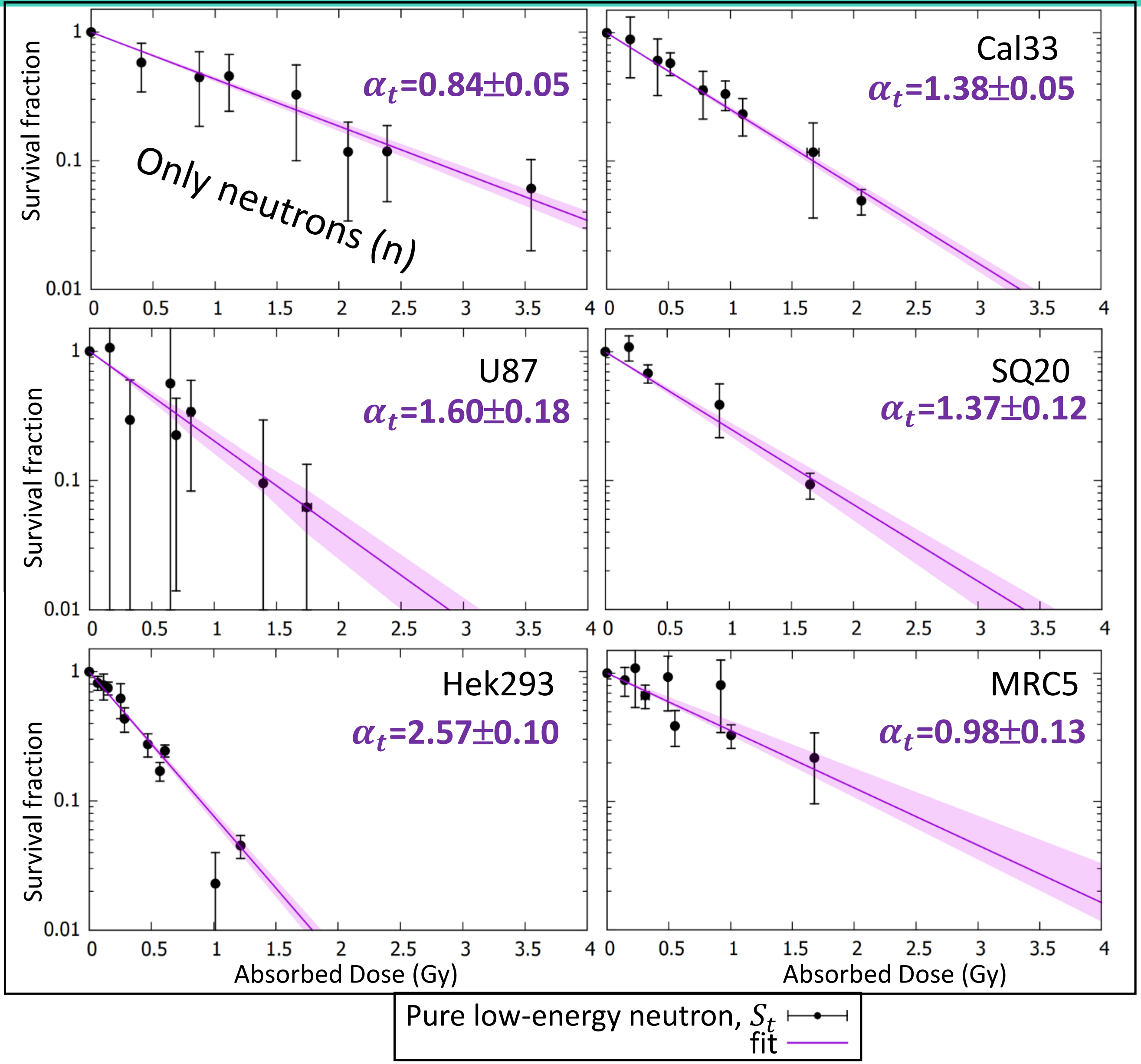
Cells 2020, 9(10), 2144

MDPI

Article

Thermal Neutron Relative Biological Effectiveness Factors for Boron Neutron Capture Therapy from In Vitro Irradiations

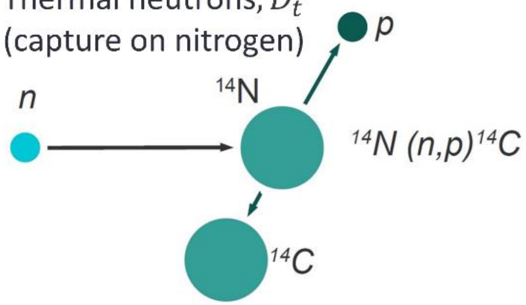
María Pedrosa-Rivera [1], Javier Praena [1], Ignacio Porras [1,*], Manuel P. Sabariego [1], Ulli Köster [2], Michael Haertlein [2,3], V. Trevor Forsyth [2,3,4], José C. Ramírez [5], Clara Jover [5], Daniel Jimena [5], Juan L. Osorio [5], Patricia Álvarez [6], Carmen Ruiz-Ruiz [6,*] and María J. Ruiz-Magaña [6]



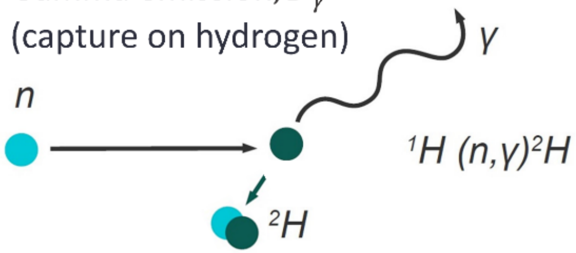
Experiments at ILL: Samples with boron (BPA)

Cold neutron irradiation

Thermal neutrons, D_t
(capture on nitrogen)

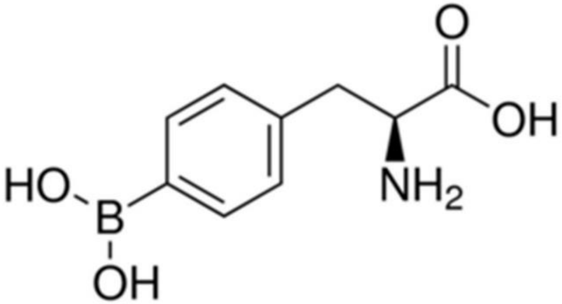


Gamma emission, D_γ
(capture on hydrogen)

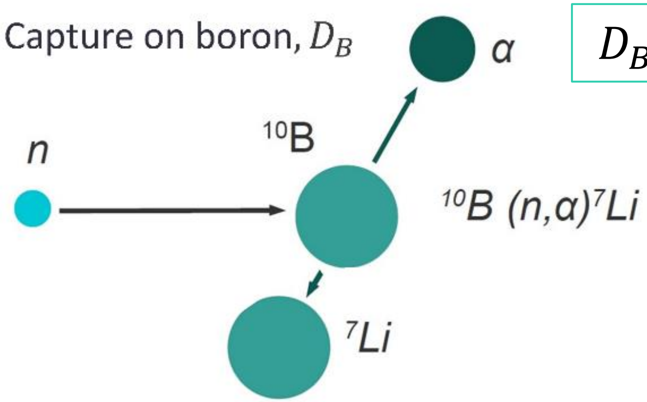


+

Boronophenylalanine (BPA), boron compound



Capture on boron, D_B

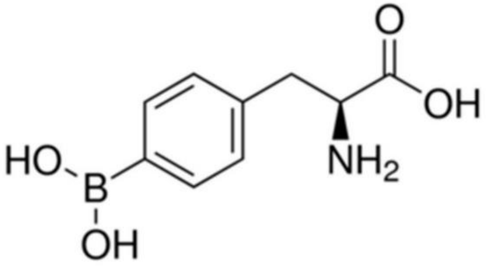


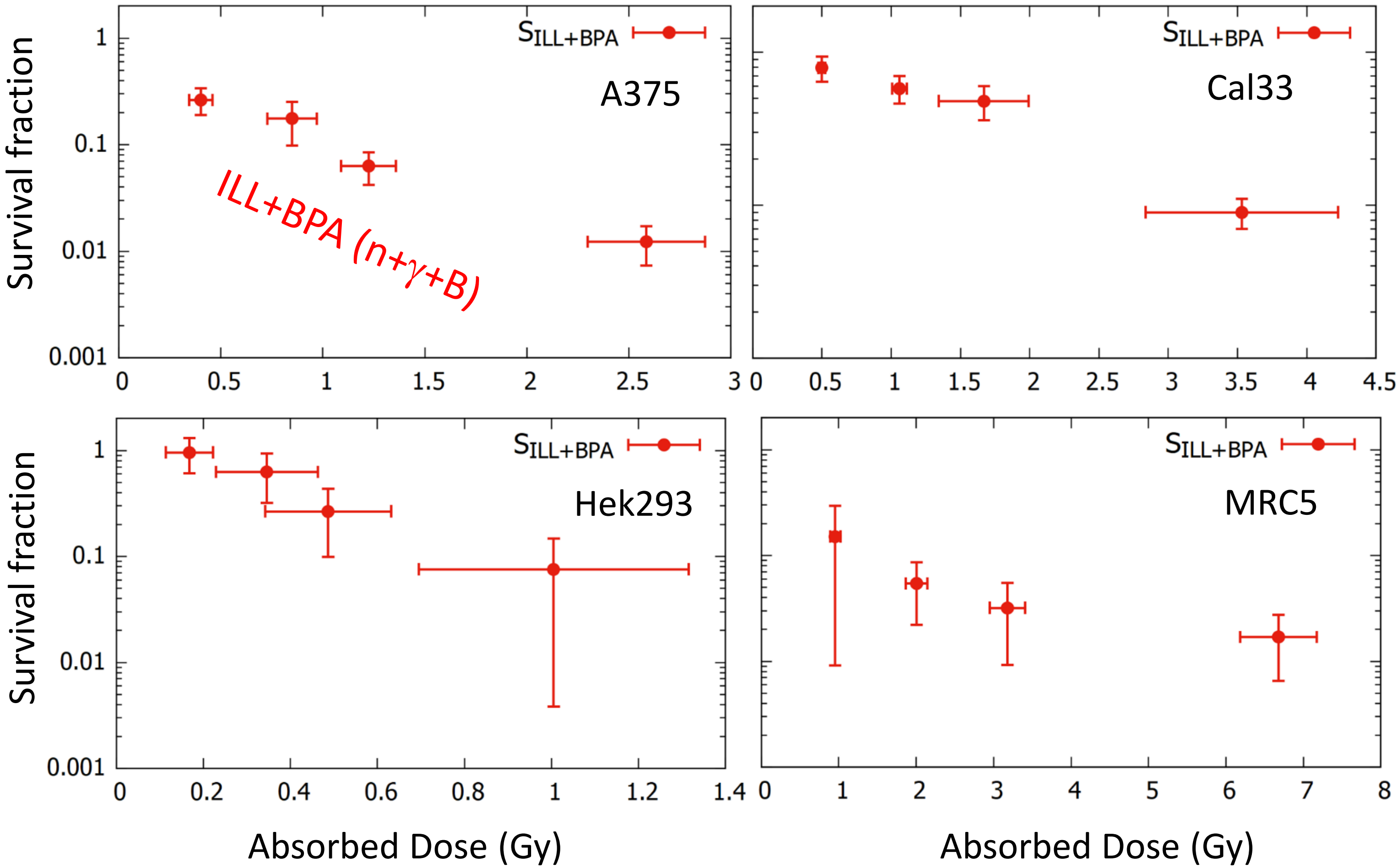
D_B

Exp.III: $D_{ILL+BPA} = D_t + D_\gamma$ → $\boldsymbol{w_B}$

Experiments at ILL: Results, w_B

Exp.III: $D_{ILL+BPA} = D_t + D_\gamma + \boldsymbol{D_B}$



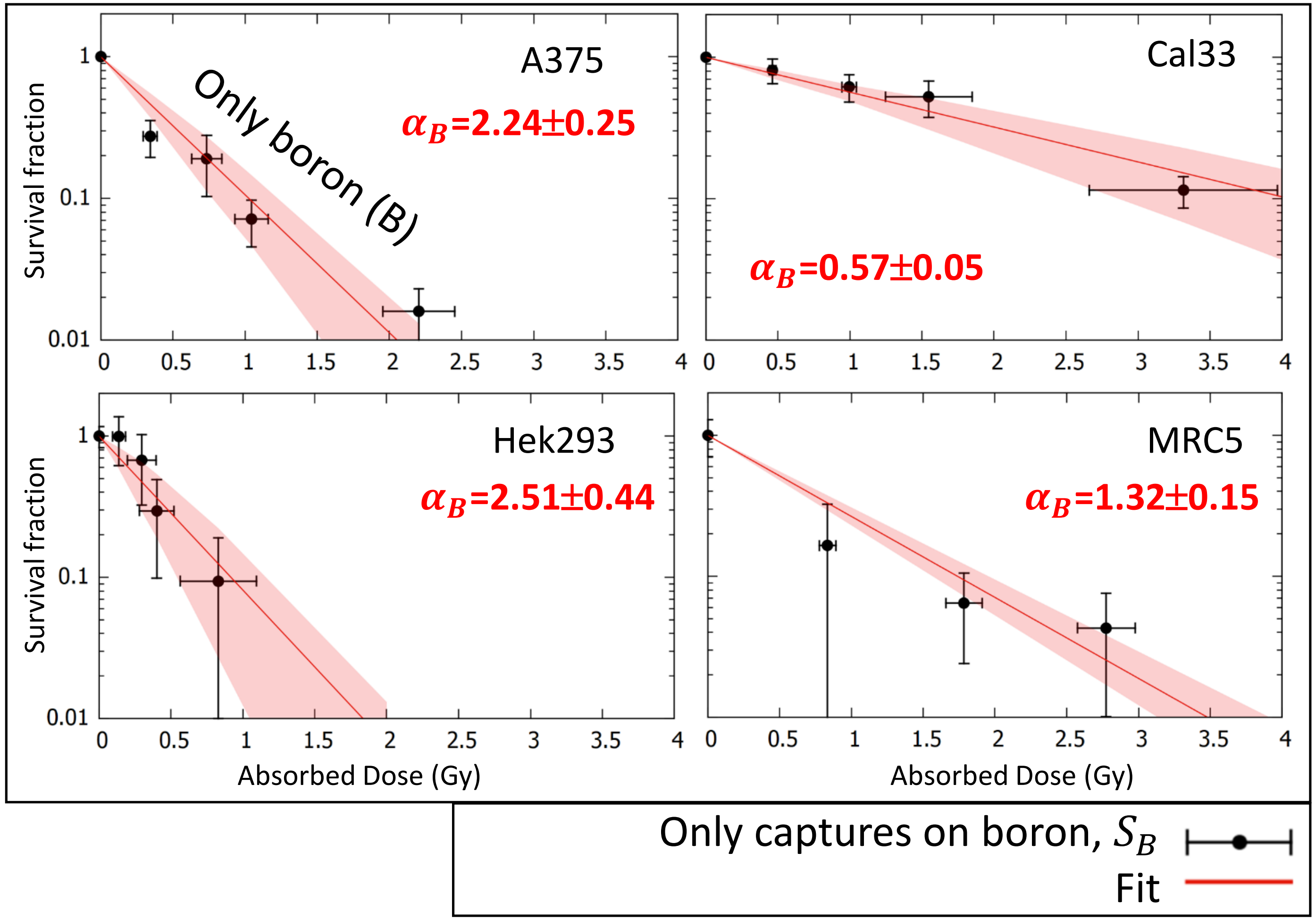


Experiment at ILL: Results, w_B

NEUTRONS FOR SOCIETY

S	A375	Cal33
50%	5.5±2.5	1.9±0.4
37%	4.9±2.3	1.7±0.3
10%	3.6±1.7	1.2±0.2
1%	2.8±1.3	0.9±0.2
S	**Hek**	**MRC5**
50%	7.5±1.5	4.1±1.1
37%	6.5±1.3	3.8±1.0
10%	4.6±0.9	3.1±0.9
1%	3.4±0.7	2.6±0.7

$$w_B = \frac{D_0}{D_t}$$



Applied Radiation and Isotopes 163 (2020) 109205

ELSEVIER

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso

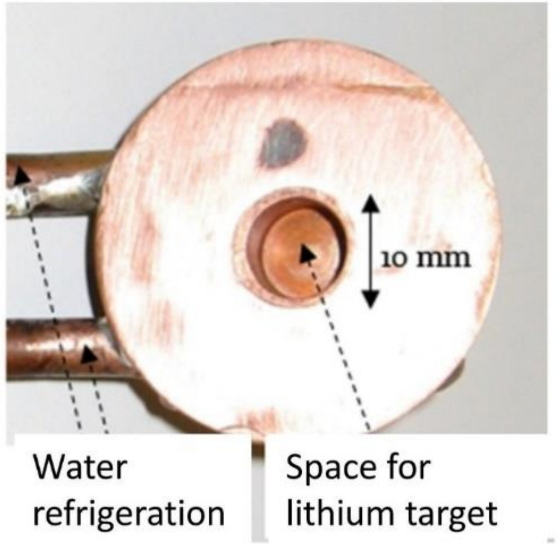
Radiobiology data of melanoma cells after low-energy neutron irradiation and boron compound administration

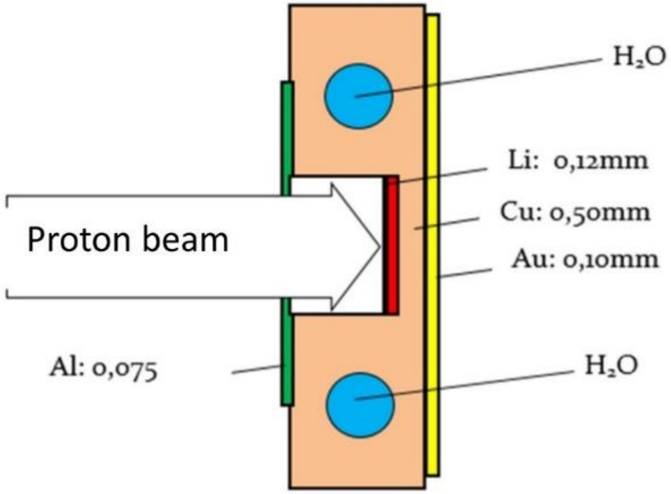
María Pedrosa-Rivera [a,b,*], M. José Ruiz-Magaña [c], Patricia Álvarez [c], Ignacio Porras [b], Javier Praena [b], Manuel P. Sabariego [b], Ulli Köster [a], Michael Haertlein [a], V. Trevor Forsyth [a,d], Torsten Soldner [a], José C. Ramírez [e], Clara Jover [e], Daniel Jimena [e], Juan L. Osorio [e], Ian Postuma [f], Carmen Ruiz-Ruiz [c]

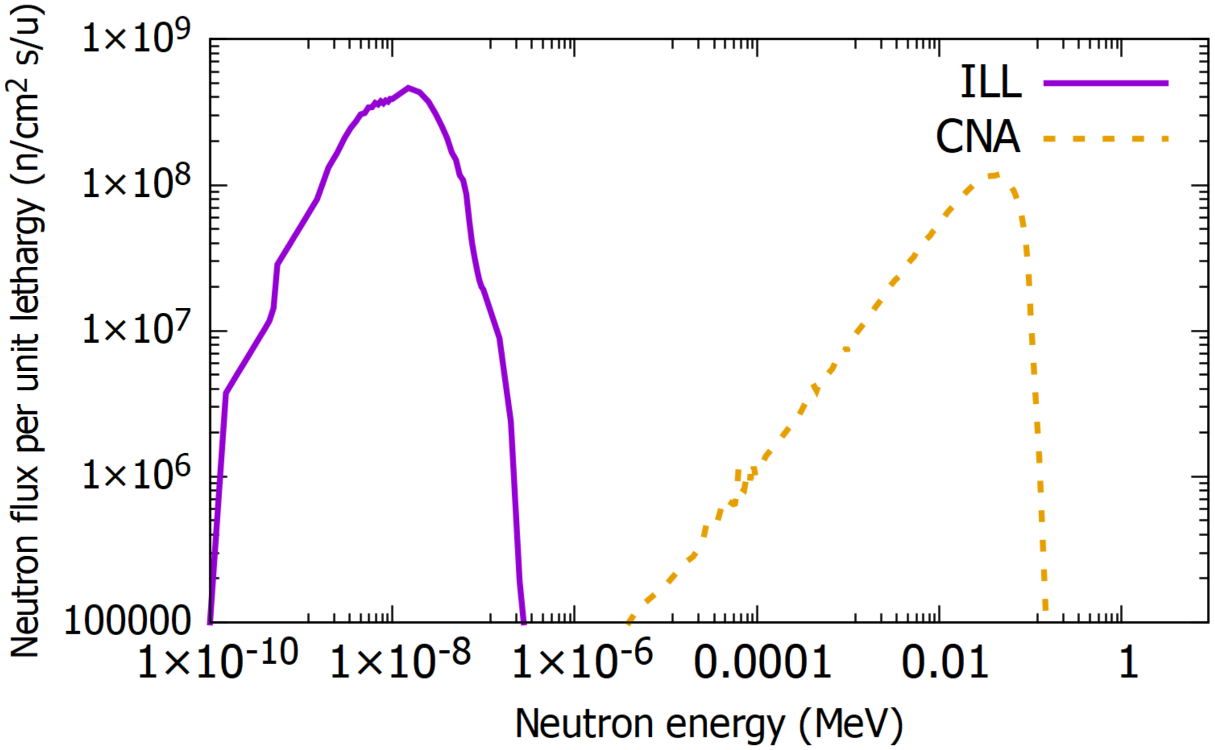
Experiments at CNA neutron beam

Experiments at CNA: Epithermal neutrons

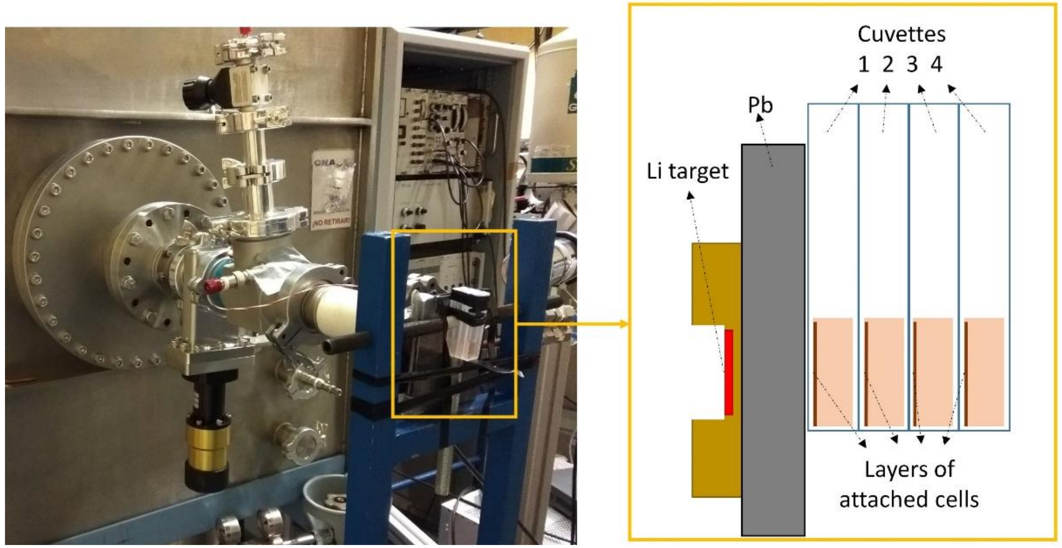
Epithermal neutron beam: protons in a Li target

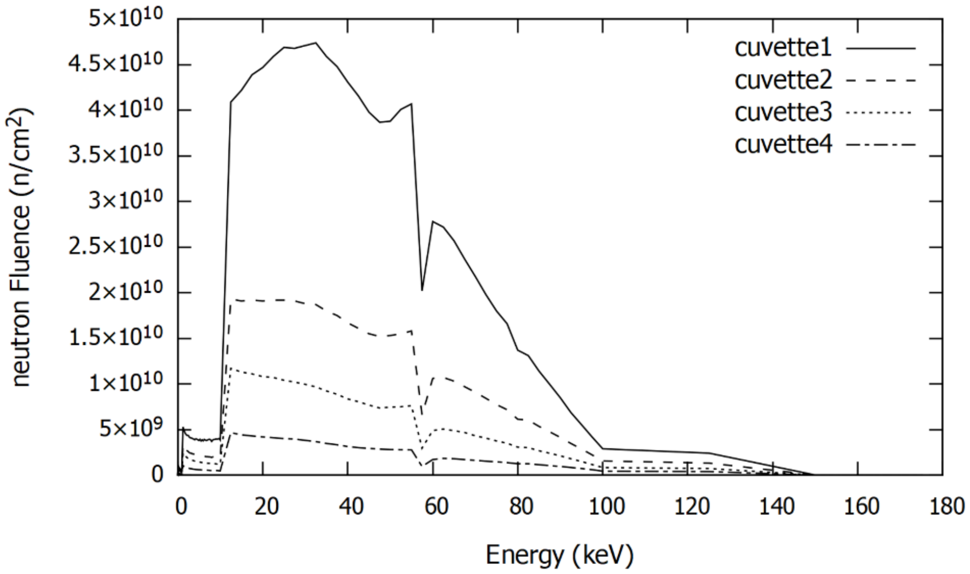






Experiments at CNA: Epithermal neutrons





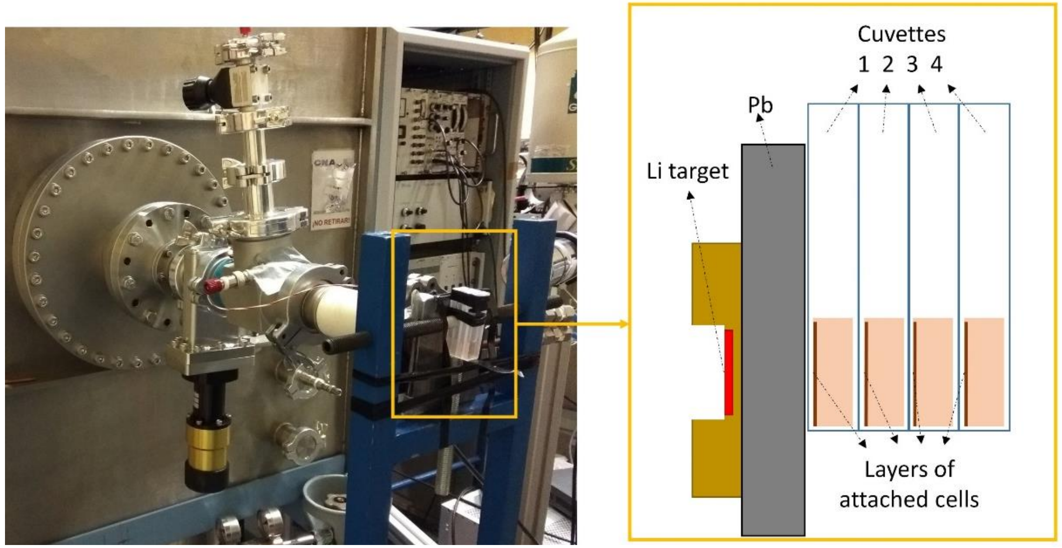
Photons generated in the target: Pb before samples to stop them

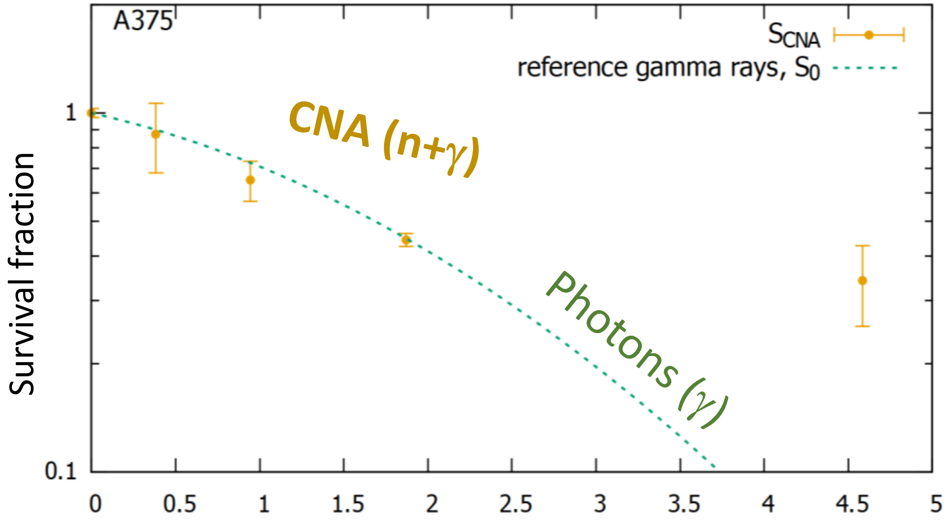
High neutron energies (higher penetration without high energies variation): we can irradiate 4 cuvettes at the same time

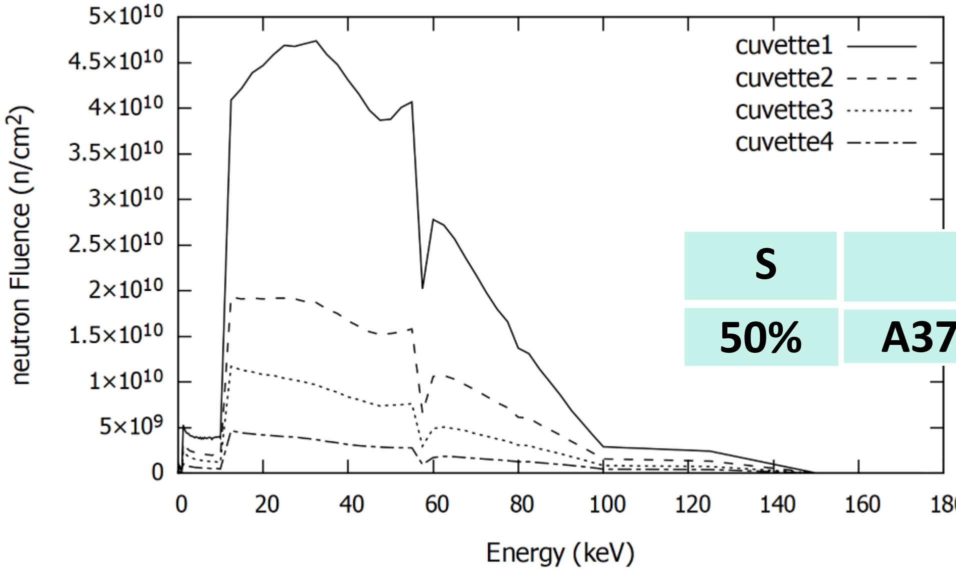
Neutron dose higher than gamma dose

Exp.IV: $D_{CNA} = \boldsymbol{D_f} + D_\gamma$ → $\boldsymbol{w_f}$

Experiments at CNA: Results, w_f (preliminary)

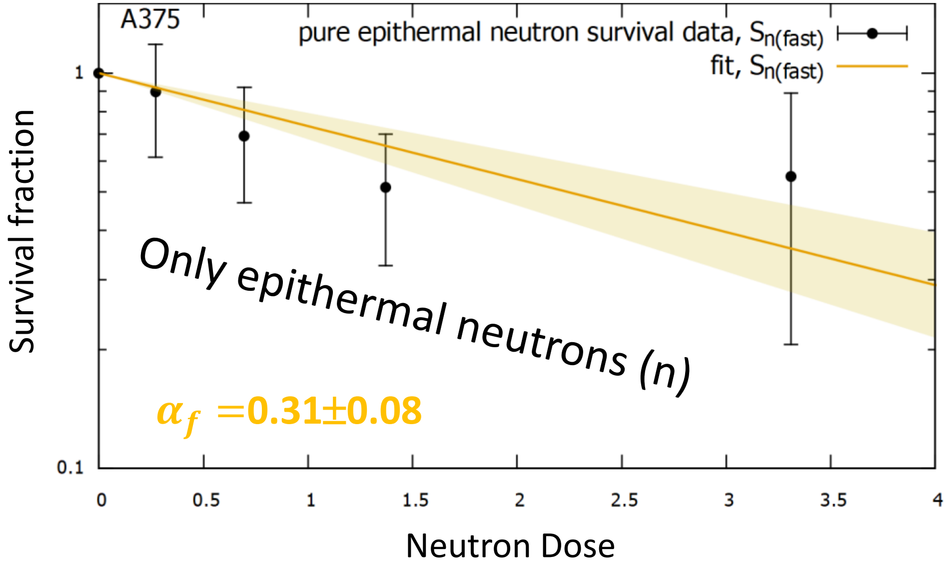






$$w_t = \frac{D_0}{D_t}$$

S		w_f
50%	A375	0.84±0.05



Summary and Conclusions

Experiments summary

Irradiation

Photons → α_0, β_0 (reference)

Low-energy neutrons →
- w_t for A375, Cal33, U87, SQ20, Hek, MRC5
- $\alpha_\gamma, \beta_\gamma$ induced from neutrons (for Hek)
- w_B for A375, Cal33, Hek, MRC5

$$D_W \equiv w_t\, D_t + w_f\, D_f + w_\gamma\, D_\gamma + w_B\, D_B = D_0$$

$$D_W^* \equiv w_t^* D_t + w_f^* D_f + w_B^* D_B + D_\gamma + \frac{D_\gamma^2}{\alpha_\gamma/\beta_\gamma} = D_0 + \frac{D^2{}_0}{\alpha_0/\beta_0}$$

Epithermal neutrons → w_f for A375 (preliminary data)

Experiments summary

Irradiation

Photons → α_0, β_0 (reference)

weighting factors (Coderre et al.)		
$w_t = w_f = 3.2$	$w_\gamma = 1$	$w_B(BPA) = 3.8$ (tumour) $w_B(BPA) = 1.3$ (Healthy tissue)

Low-energy neutrons →
- w_t for A375, Cal33, U87, SQ20, Hek, MRC5
- $\alpha_\gamma, \beta_\gamma$ induced from neutrons (for Hek)
- w_B for A375, Cal33, Hek, MRC5

A375 (melanoma) weighting factors		
Thermal	Fast	Boron
w_t =2.05±0.43	w_f =0.84±0.05	w_B =5.5±2.5
w_t^* =3.5±1.4	w_f^* = 1.03±0.08	w_B^* =9.2±6.8

Epithermal neutrons → w_f for A375 (preliminary data)

Concluding remarks

- BNCT is an experimental radiotherapy that showed promising results in patients.
- It is expected that became more important in the coming years due to the construction of accelerators.

- PhD motivation: A revision of the current model for biological effect estimation is advised. Since the cellular damage arising from neutron irradiation depends on different factors, its study requires a wide range of experimental data

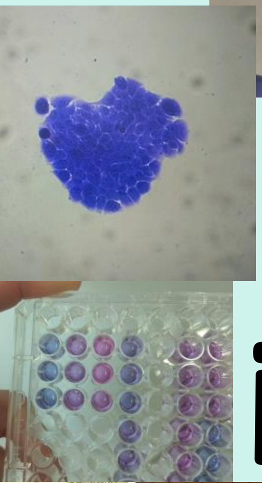
- A theoretical approach more realistic, but simple was proposed.
- Experiments in three different beams and for different cell lines (melanoma, glioblastoma, H&N and healthy tissues) allowed to get the RBE for the different dose components separately.
- The large amount of data obtained from the different irradiation studies of the various cell lines will be of value for a better understanding of BNCT dosing, and thus for a better individual adaptation of the treatment to patients.

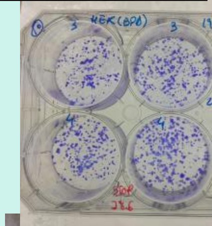
Link to the thesis manuscript

International Society for Neutron Capture Therapy website

UNIVERSIDAD DE GRANADA

NEUTRONS FOR SOCIETY





Thank you for your attention!

¡Gracias por vuestra atención!