

Biological applications at DONES: fast neutron effects in biological samples

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**First DONES Users Workshop,
September 26-27, 2022**

Outline

Some radiation protection issues with neutrons

Neutrons in conventional radiotherapy

Neutrons in proton therapy

Neutrons in space missions

Boron neutron capture therapy

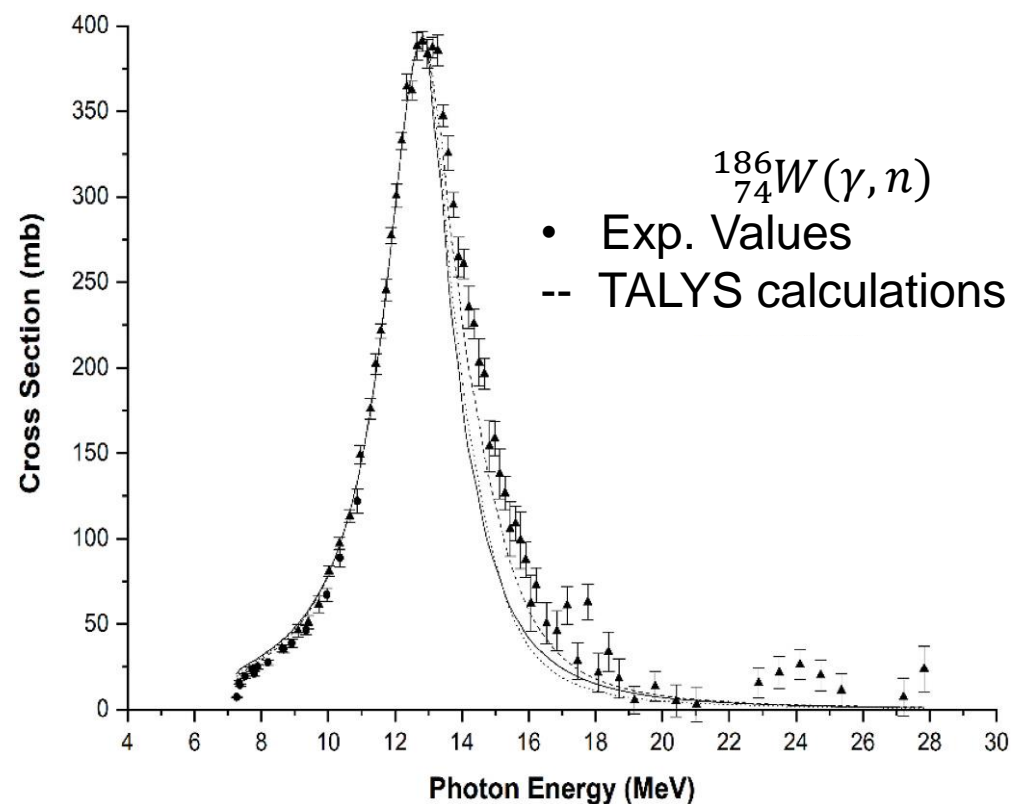
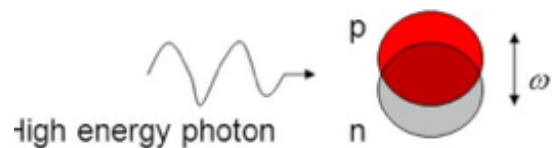
Accelerator-based neutron sources

Biological dose

Conclusions

Some radiation protection problems with neutrons

Neutrons in conventional photon radiotherapy



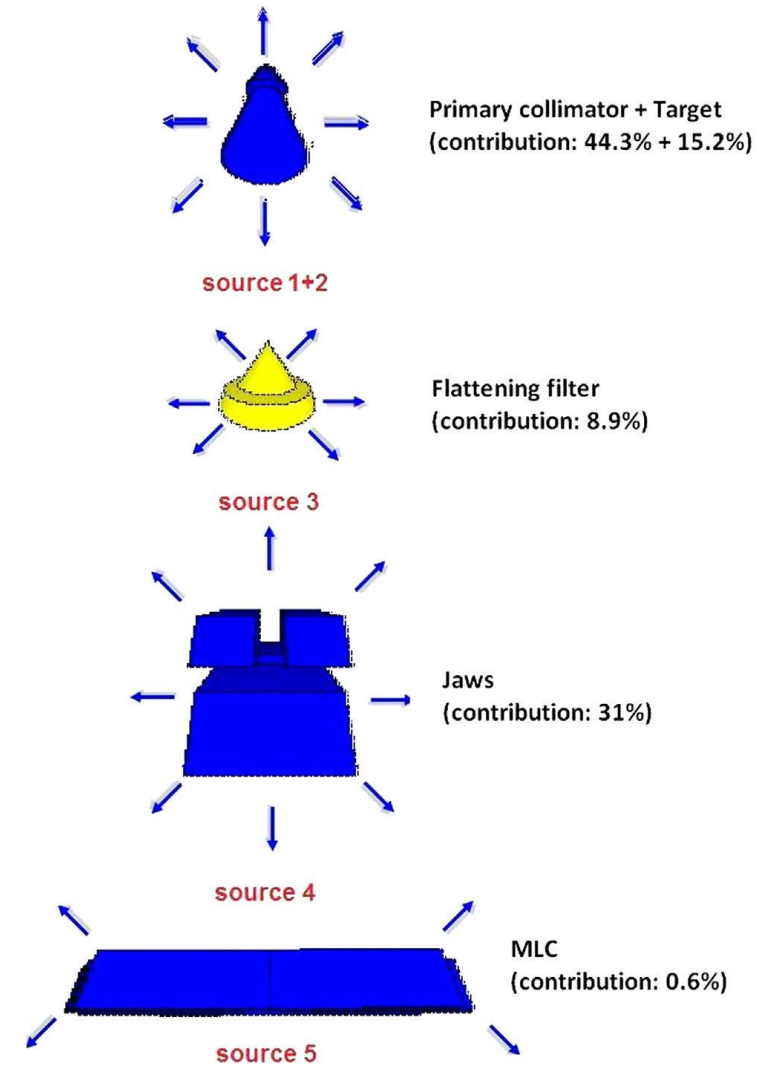
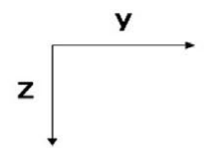
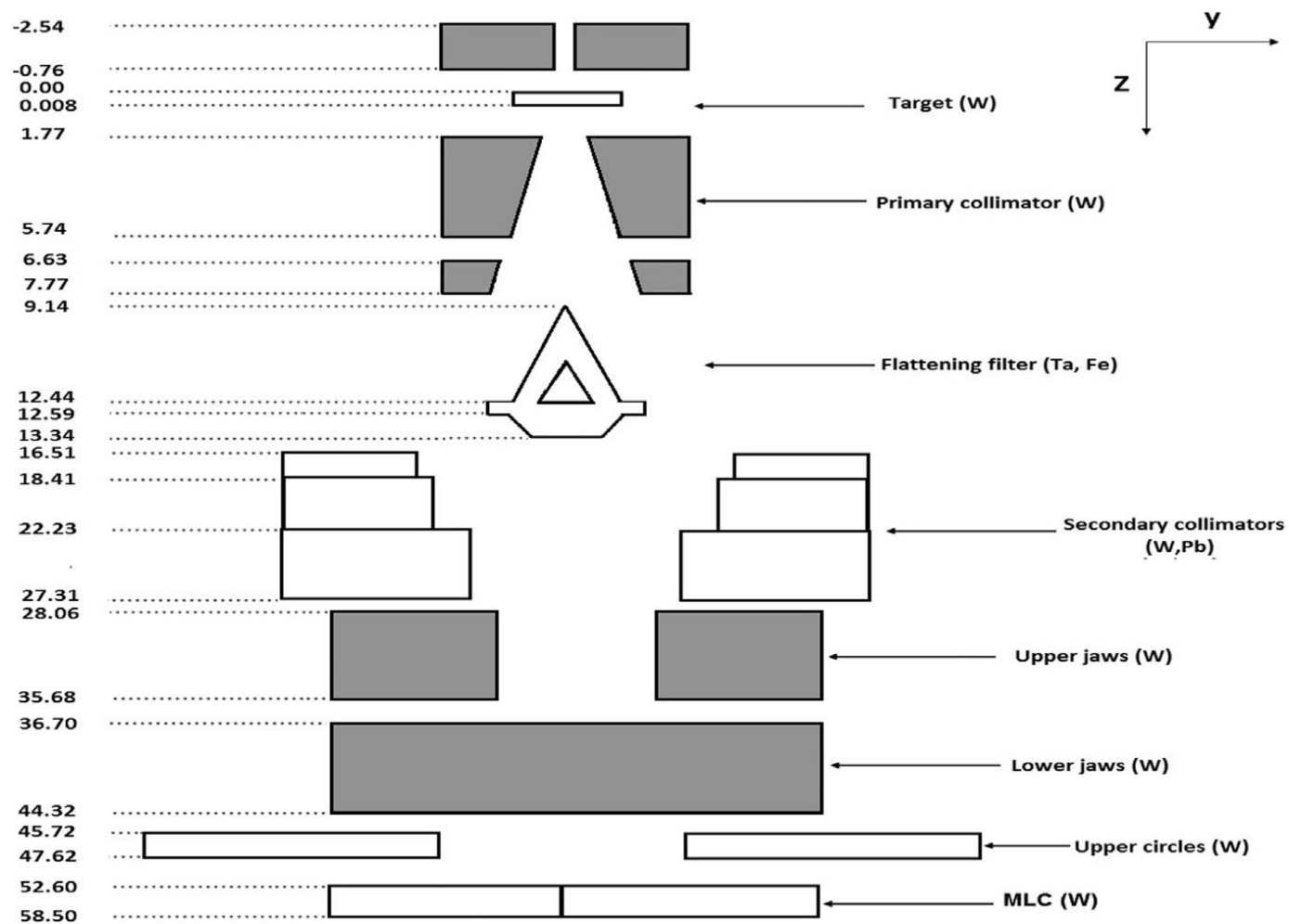
Giant Dipole Resonance (GDR) → photon-induced oscillations of protons and neutrons against each other.

Leading to neutron emission.

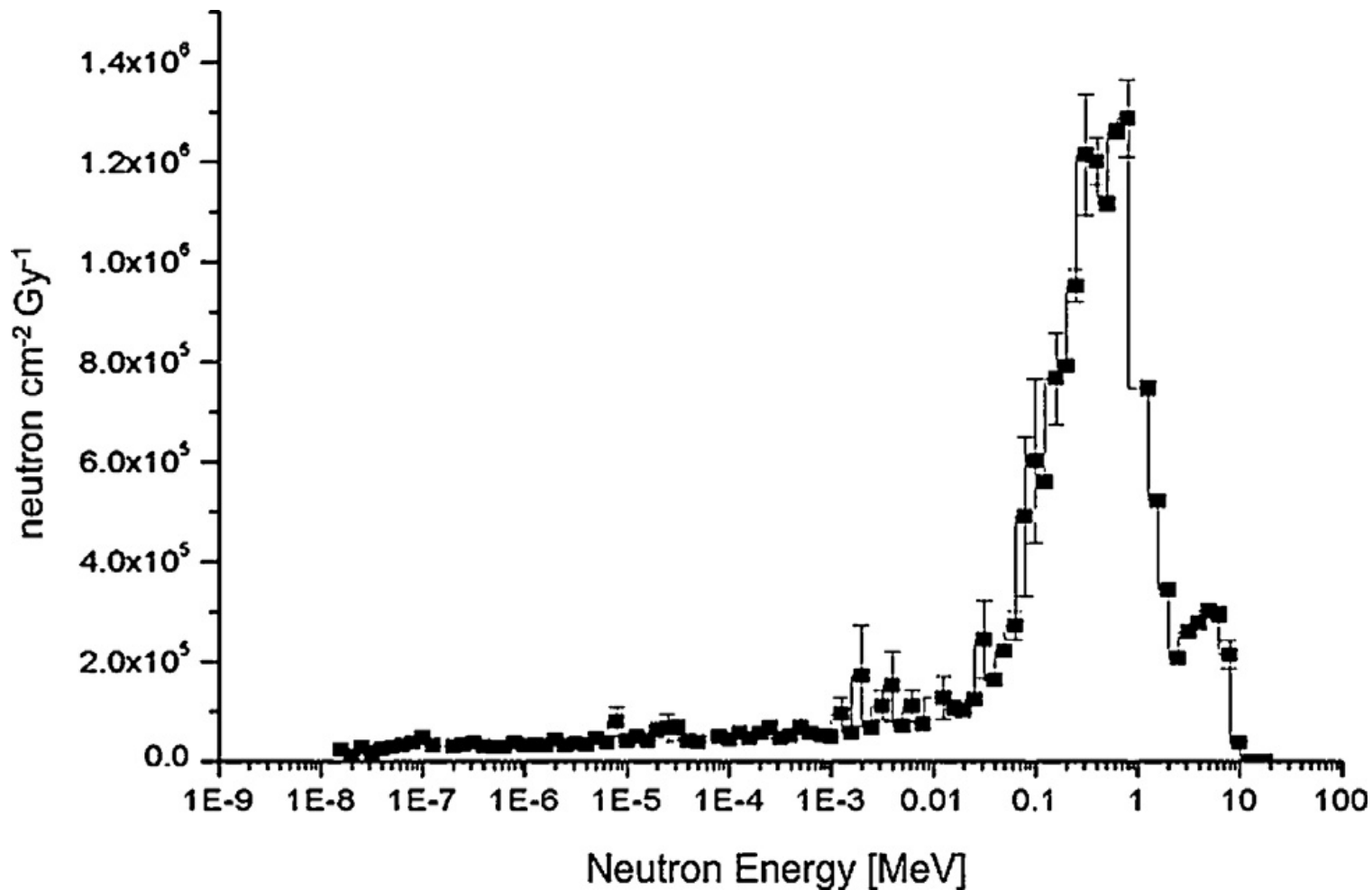
Incident photon energies from 10 MeV to ~30 MeV.

GDR neutron cross-section increases with Z number.

Neutrons in conventional photon radiotherapy



Neutrons in conventional photon radiotherapy



Neutron fluence per Gy at the patient plane during a classical radiotherapy treatment.

LINAC VARIAN 2300 CD18 MV.
SSD = 100 cm;
photon field = 10 × 10 cm;
jaws 10 × 10;
multileaf 40 × 40.

Simulation carried out by
MCNP4B-GN (NEA 1733) code
at 3 cm from isocenter.

Neutrons in conventional photon radiotherapy

Equivalent dose at the patient due to neutrons

Neutron equivalent dose	18 MV Varian		18 MV Elekta	
	TLD	50 mSv/Gy		44 mSv/Gy
MC simulation	7.06 mSv/Gy	423 mSv	2.37 mSv/Gy	142.2 mSv

Nedaie HA, et al. Neutron dose measurements of Varian and Elekta linacs by TLD600 and TLD700 dosimeters and comparison with MCNP calculations.

J Med Phys 2014;39:10-7 <https://doi.org/10.4103/0971-6203.125476>

Should be assessed accurately

TLD measurements not reliable

Depends on the Relative Biological Effectiveness factor

w_R

$$H = \sum_R w_R D_R$$

Dose Limits Recommended by ICRP	
Limit on Dose from Occupational Exposure	Limit on Dose from Public Exposure
20 mSv per year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv	average over 5 years does not exceed 1 mSv per year

Neutrons in conventional photon radiotherapy

Neutron detection is very important

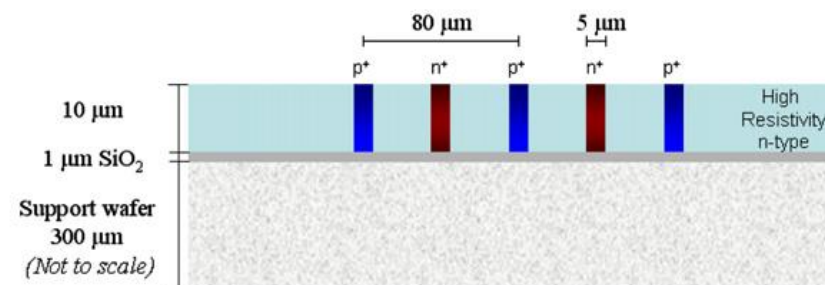
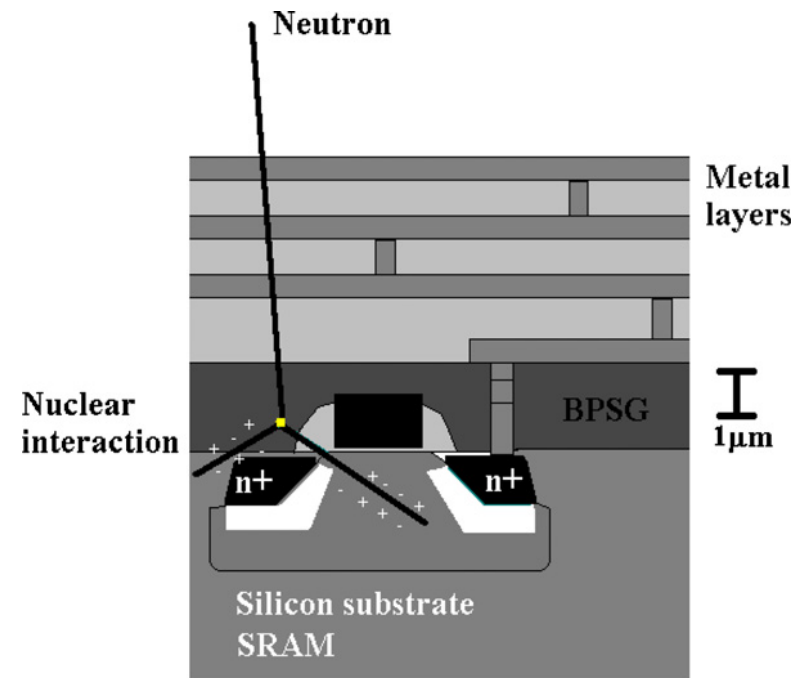
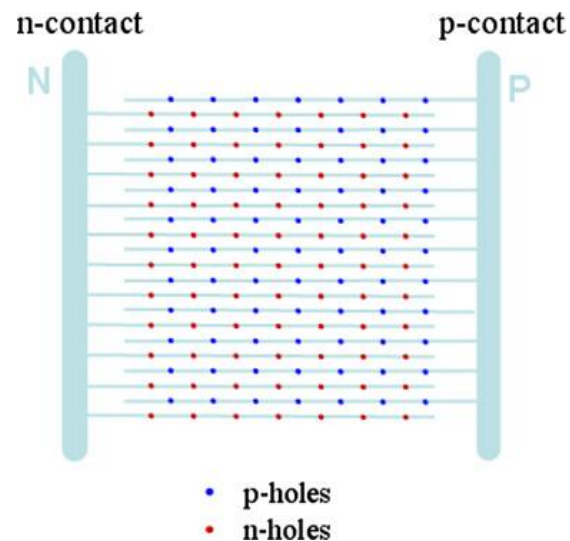
Passive methods:

Activation of foils in Bonner spheres

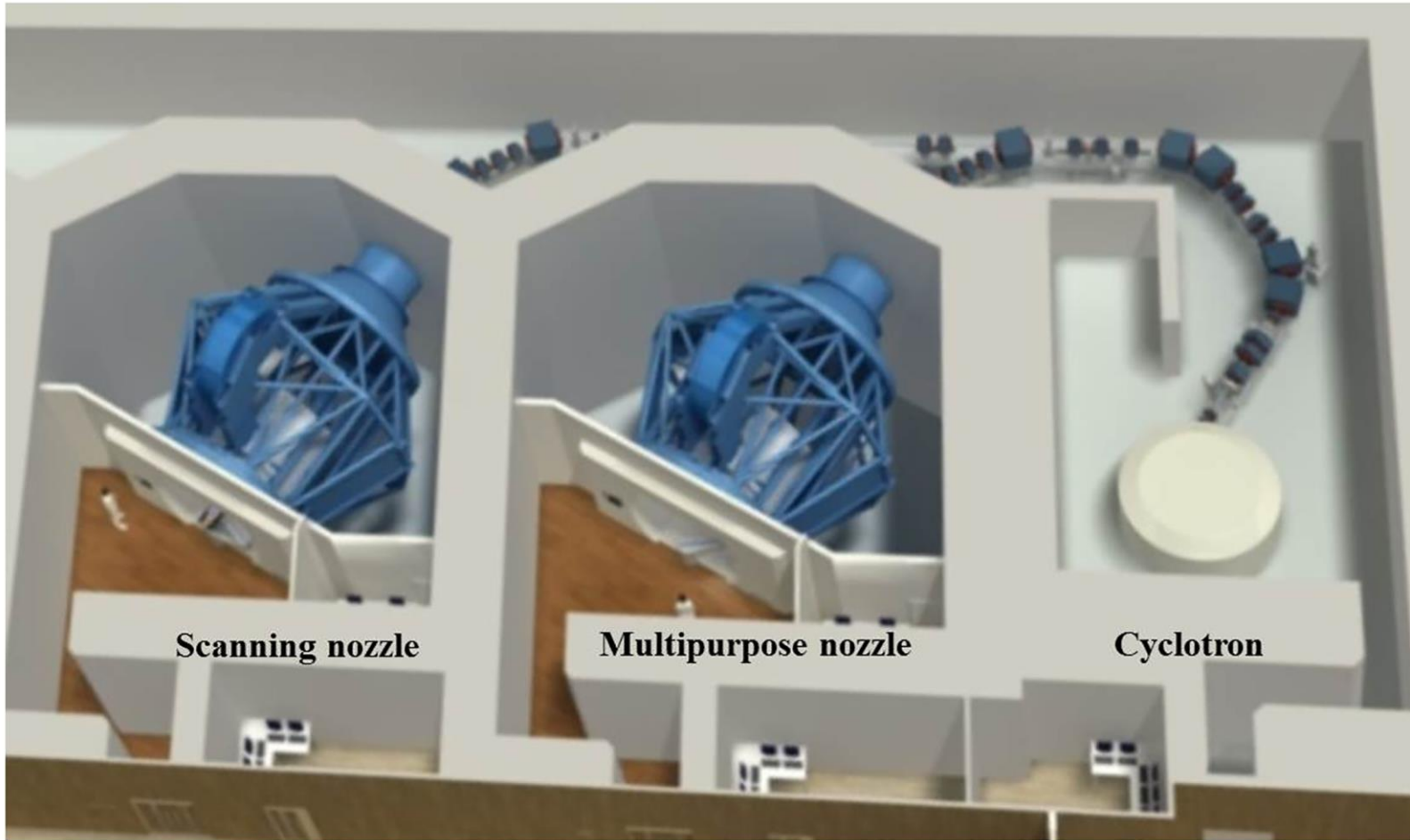
TLD dosimeters (Barquero et al Health Phys. 88 (2005) 48–58)

Active methods: effect on semiconductors
SRAM: Gomez, Iglesias & Sanchez-Doblado
Phys. Med. Biol. 55 (2010) 1025–39

Ultra-thin 3D silicon detector
Guardiola et al., Phys. Med. Biol.
58 (2013) 3227–3242



Neutrons in proton therapy



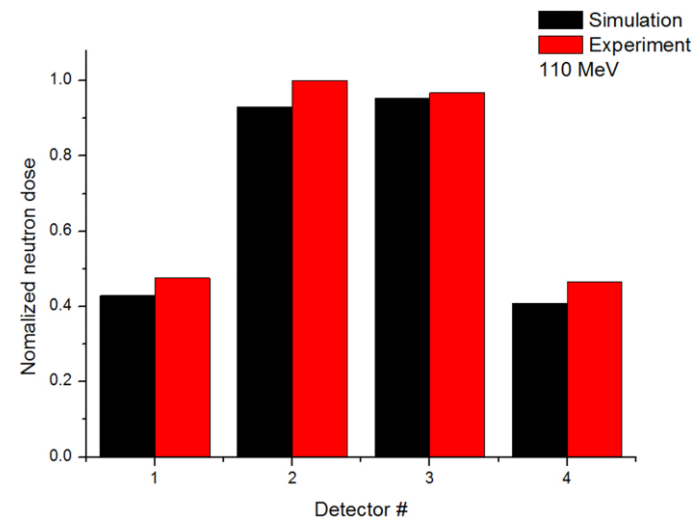
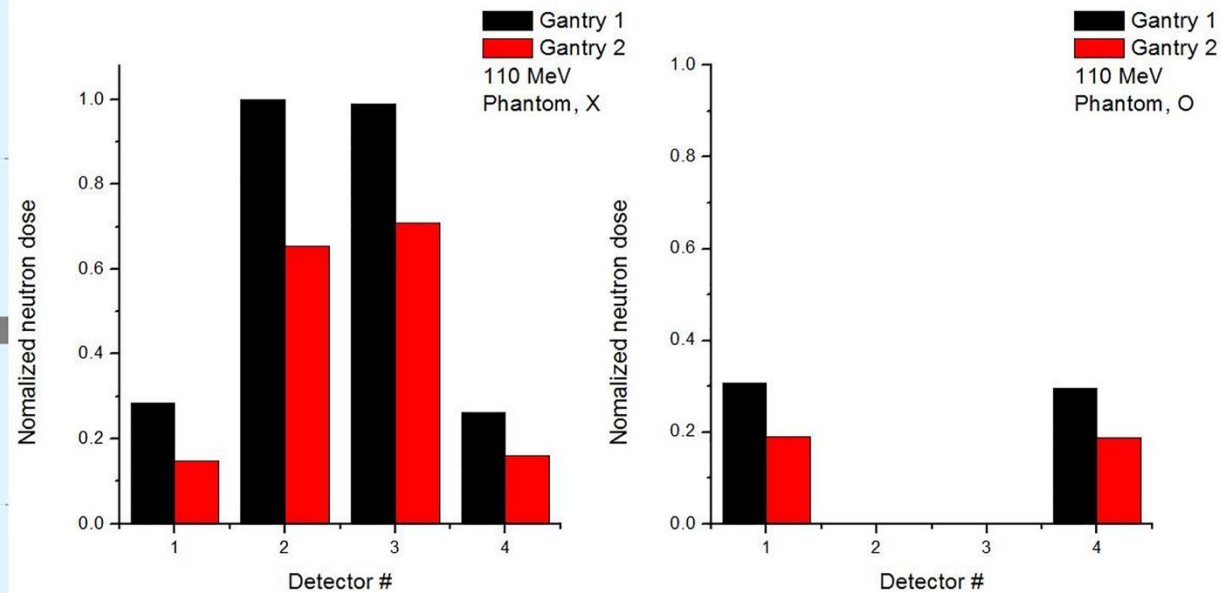
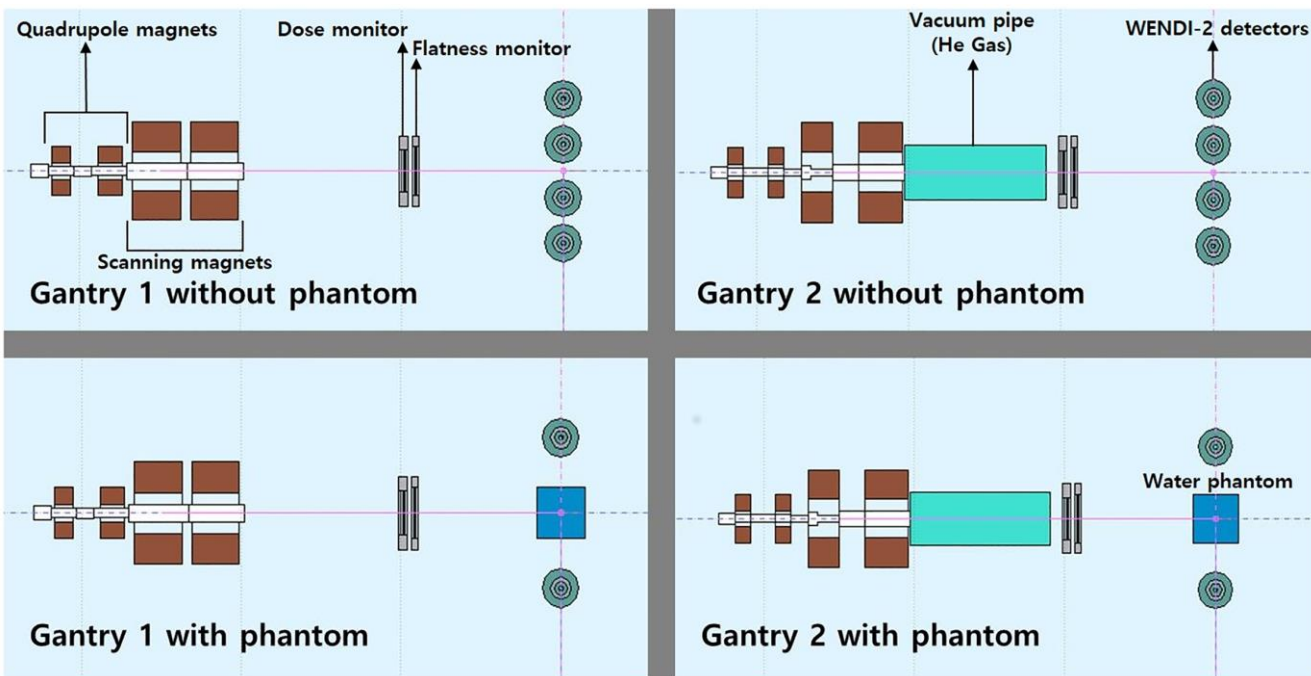
proton therapy at
Samsung Medical Center (SMC)

230 MeV cyclotron

Secondary neutrons:

- Produced at nozzles in gantries
- Produced in patient

Neutrons in proton therapy



Monte Carlo simulations with
FLUKA code
Lee et al Plos One (2017) 0186544

Neutrons in proton therapy

Table 2. Estimated effective dose by neutrons and primary radiation and resulting occurrence of fatal malignancies for a 1-Gy treatment dose with conventional photons (12), IMRT photons, and spot-scanned protons, respectively

Type of treatment	Effective dose (10^{-3} Sv)			Excess number of fatal malignancies per 100,000 patients per lifetime		
	Neutrons	Primary beam	Total	Neutrons	Primary beam	Total
Photons (conventional)	0.6–1.0	84	84.6–85	3–5	420	423–425
Photons (IMRT)	0.6–1.0	56	56.6–57	3–5	280	283–285
Protons (spot scanned)	0.9–3.6	28	28.9–31.6	4.5–18	140	145–158

Abbreviation: IMRT = intensity-modulated radiotherapy.

Neutrons in space missions

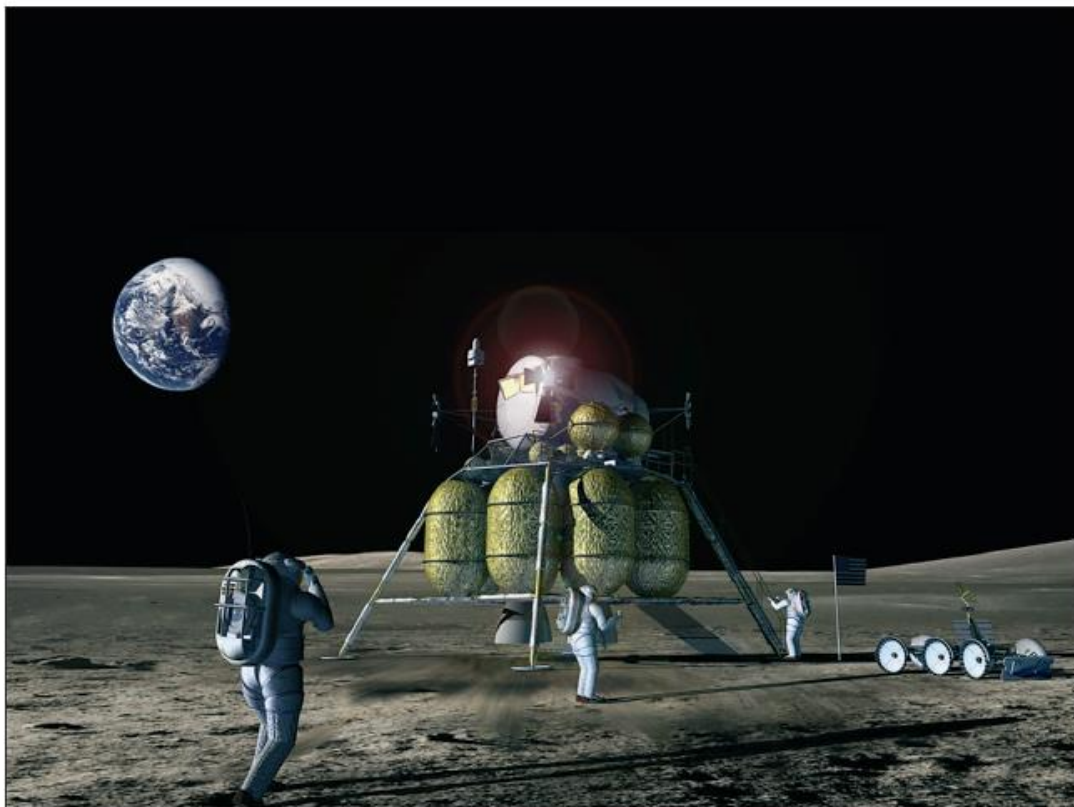
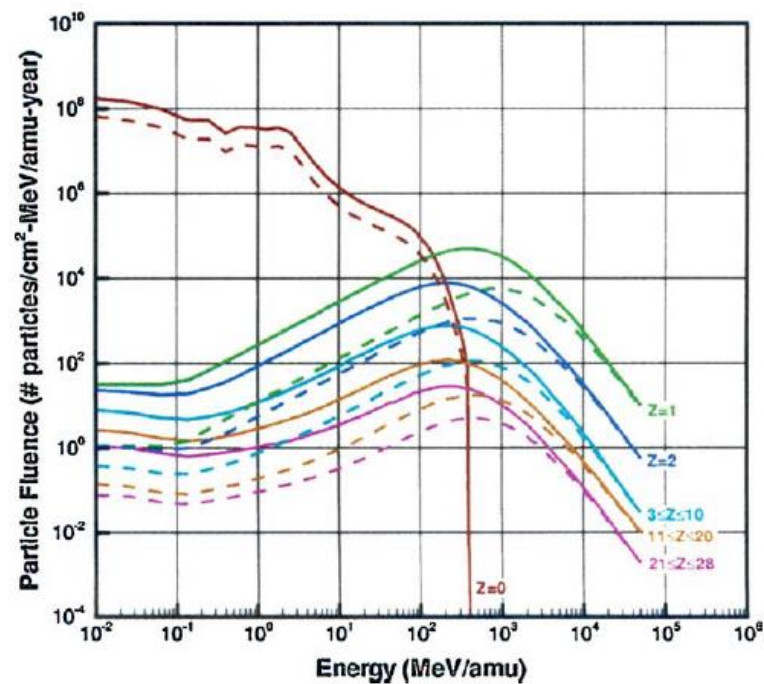


Figure 1: A future moon landing

According to the new Vision for Space Exploration (January, 2004), the National Aeronautics and Space Administration (NASA) plans to return to the moon in 2020. The present project anticipates four to six crew members who will complete lunar-surface exploration for 60-180 days. The Earth-moon cruise lasts about 4 days.

NASA/John F. Cassano and associates

Future lunar explorations 60-180 days
(trip in 4 days)



Radiation from cosmic rays at the lunar surface at two different years.

Wilson JW et al, Adv. Space Res. 34 (2004) 1281

Neutrons in space missions

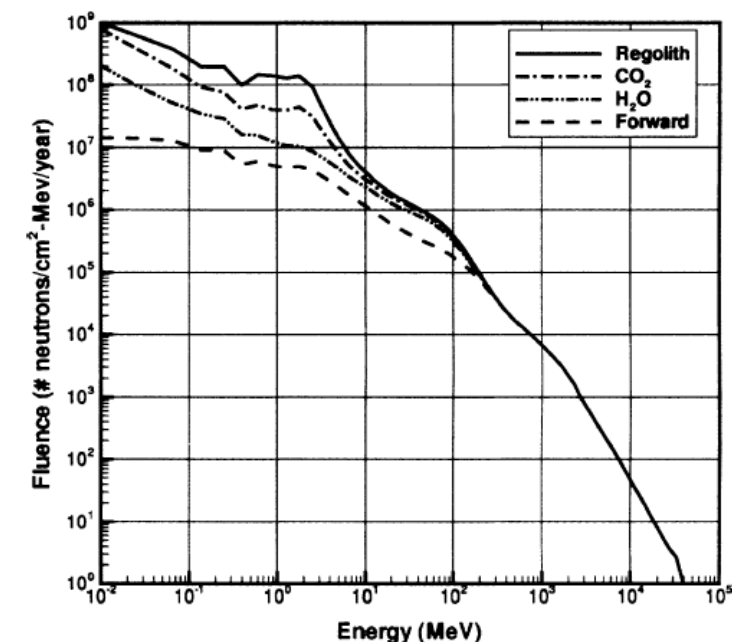


Artemis is the first step in the next era of human exploration. Together with commercial and international partners, NASA will establish a sustainable presence on the Moon to prepare for human missions to Mars.

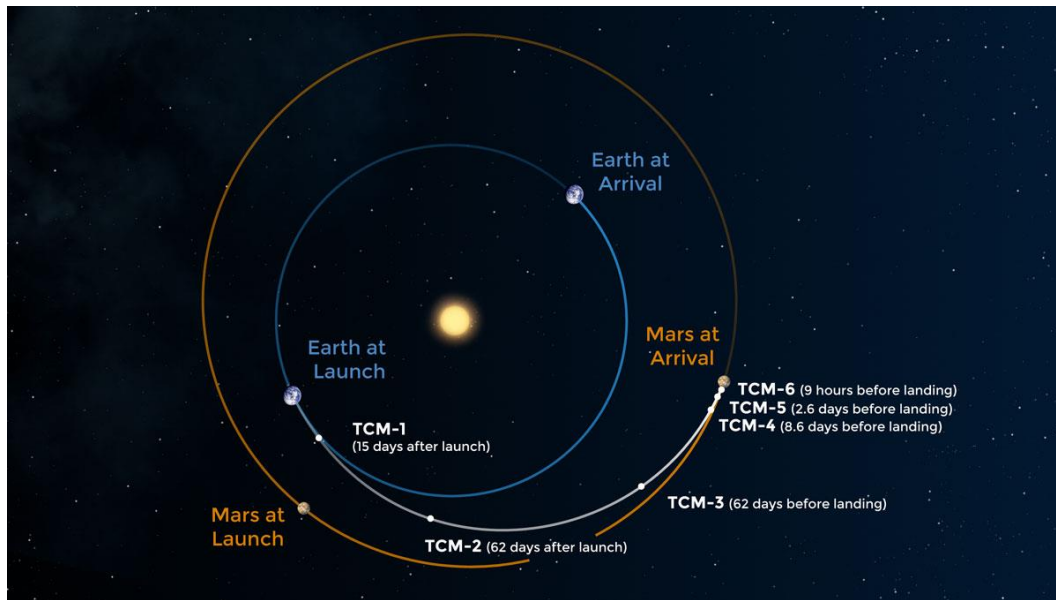


Estimation of neutron radiation in the surface of Mars from different materials

Wilson JW et al, Adv. Space Res. 34 (2004) 1281



Neutrons in space missions



The trip to Mars will take **about seven months** and about 480 million kilometers

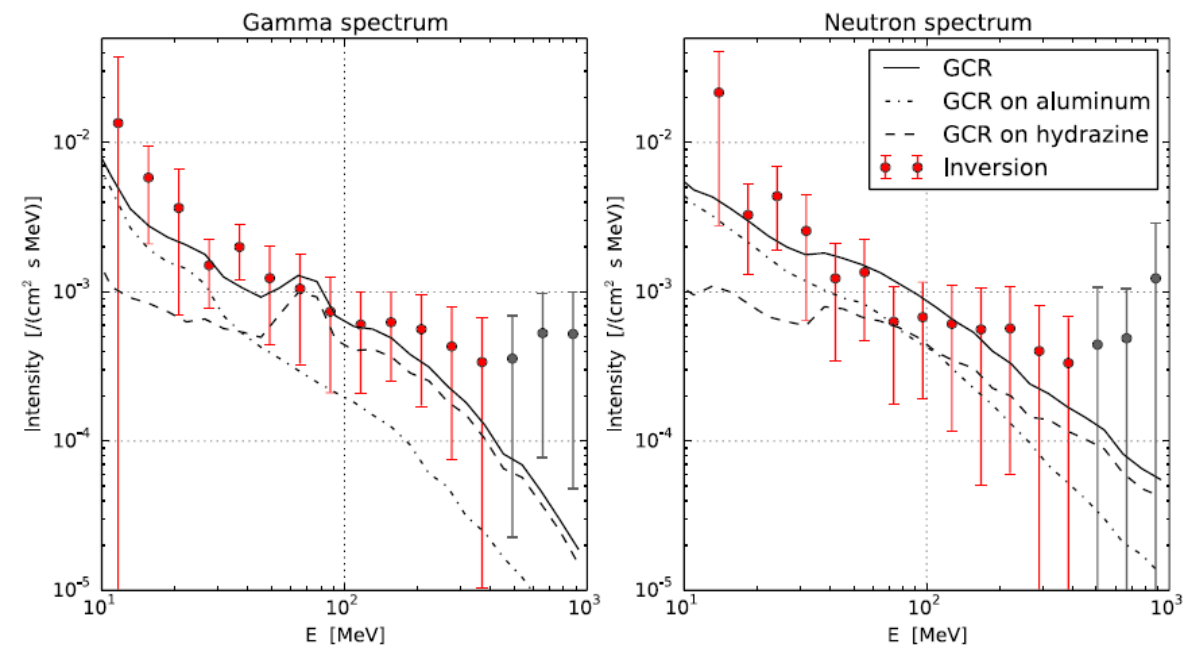
Dose equivalent rate neutrons: $19 \pm 5 \mu\text{Sv/day}$

Dose rate: $11 \pm 4 \text{ mSv}$

J. Köhler et al. Life Sci Space Res 5 (2015) 6

Mars Science Laboratory (MSL) mission: launched on November 26, 2011 and landed on Mars on August 6, 2012. On board the rover Curiosity was the Radiation Assessment Detector (RAD).

RAD was operated during most of the cruise from Earth to Mars, gathering the first science data of Curiosity's mission, providing a continuous radiation measurement from inside the spacecraft.



Neutrons in space missions

Passive shielding on the spacecraft

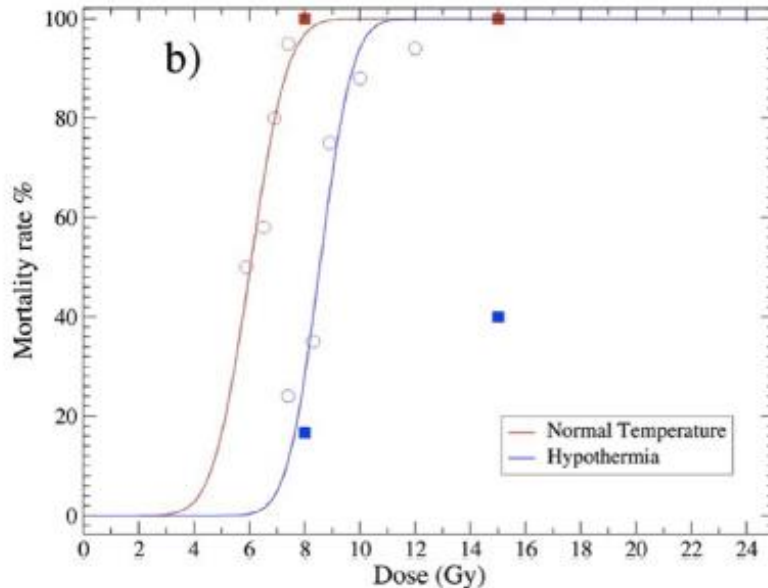
Efficient for charged particles, but produce secondary neutrons, increasing with shielding depth

Active shielding, especially magnetic fields using toroid or solenoidal configurations.

Biomedical countermeasures.

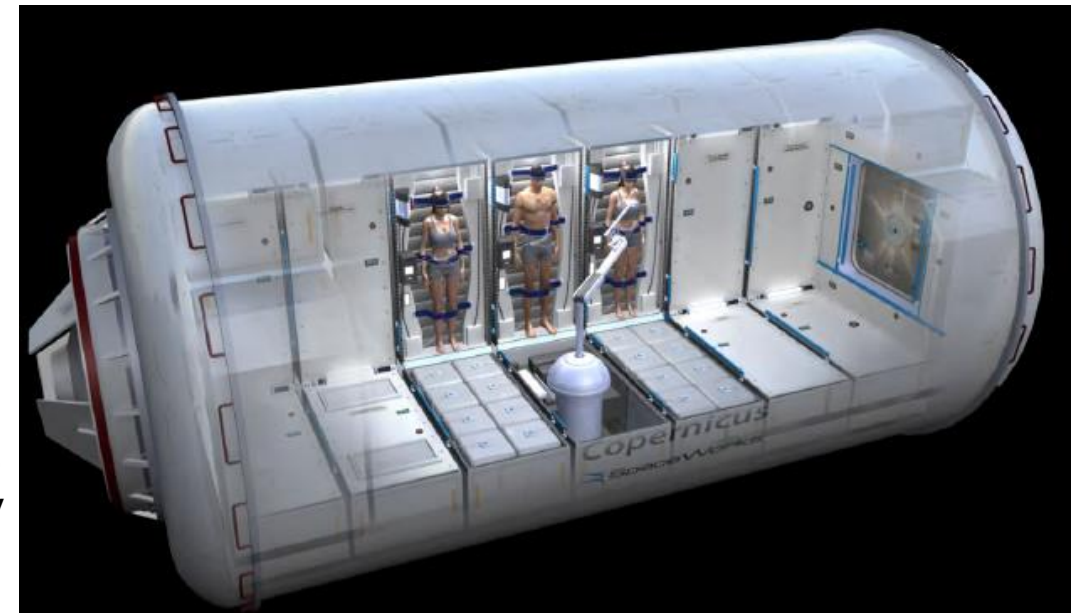
Hibernation has been reconsidered as a possible tool, **hibernation-like states** (synthetic torpor) can be induced in non-hibernating animals.

Animals in hibernation acquire **radioresistance**. The lethal dose is increased around 40%.

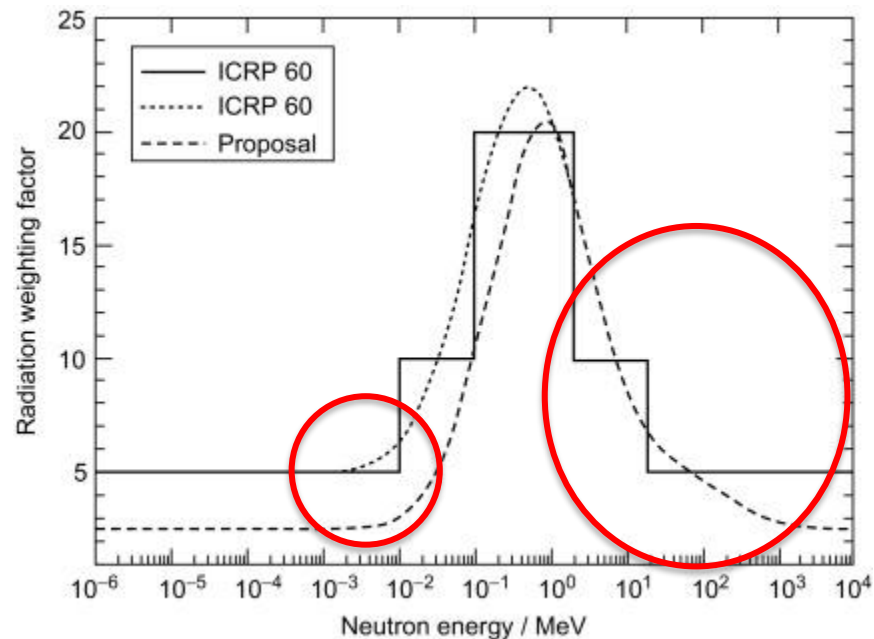


Radioresistance under gamma radiation (still not known with neutrons). Cerri, M. et al. Life Sci. Space Res. 11 (2016) 1

Mars transfer habitat design by SpaceWorks Enterprises, Inc.

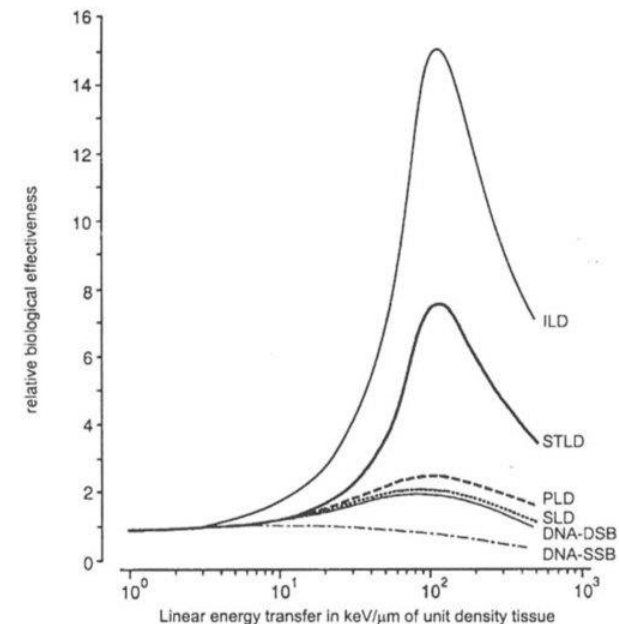


Neutrons relative biological effect

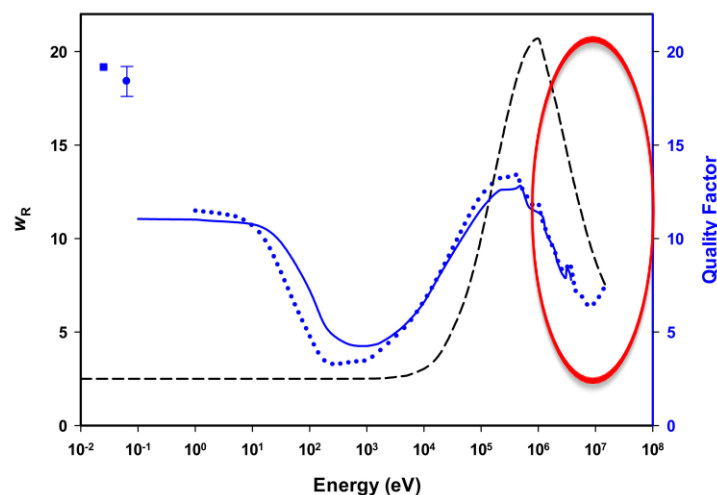
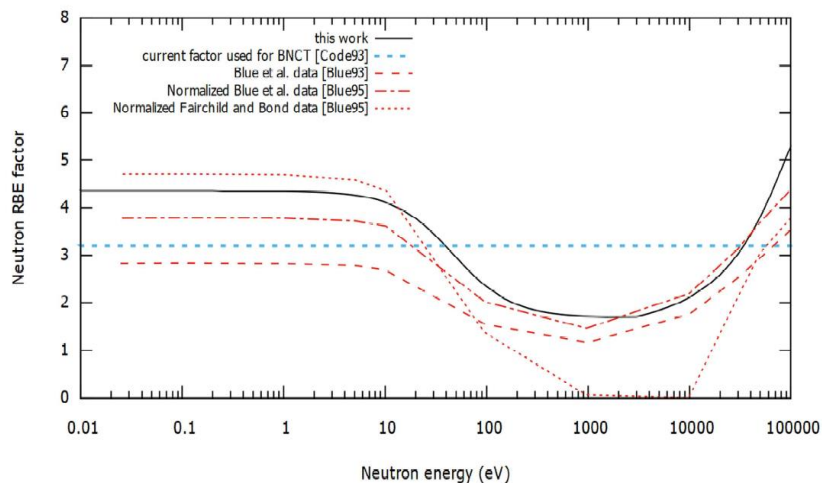


$$H = \sum_R w_R D_R$$

RBE depends on LET (keV/μm)



Combining secondary charged particle LET with RBE-LET relationship:



Pedrosa-Rivera M, Ph.D. Thesis (2020)
 Paterson et al. Int. J. Mol. Sci. 23 (2022) 878

Open problems

Radiobiological experiments with neutrons of different spectra are needed (specially for high energy)

Monte Carlo simulations are key for neutron transport

- Biological effective dose (as RBE varies with neutron energy)
- Neutron shielding designs

Cross section measurements of high energy neutrons are required (elements in tissue, materials for shielding)

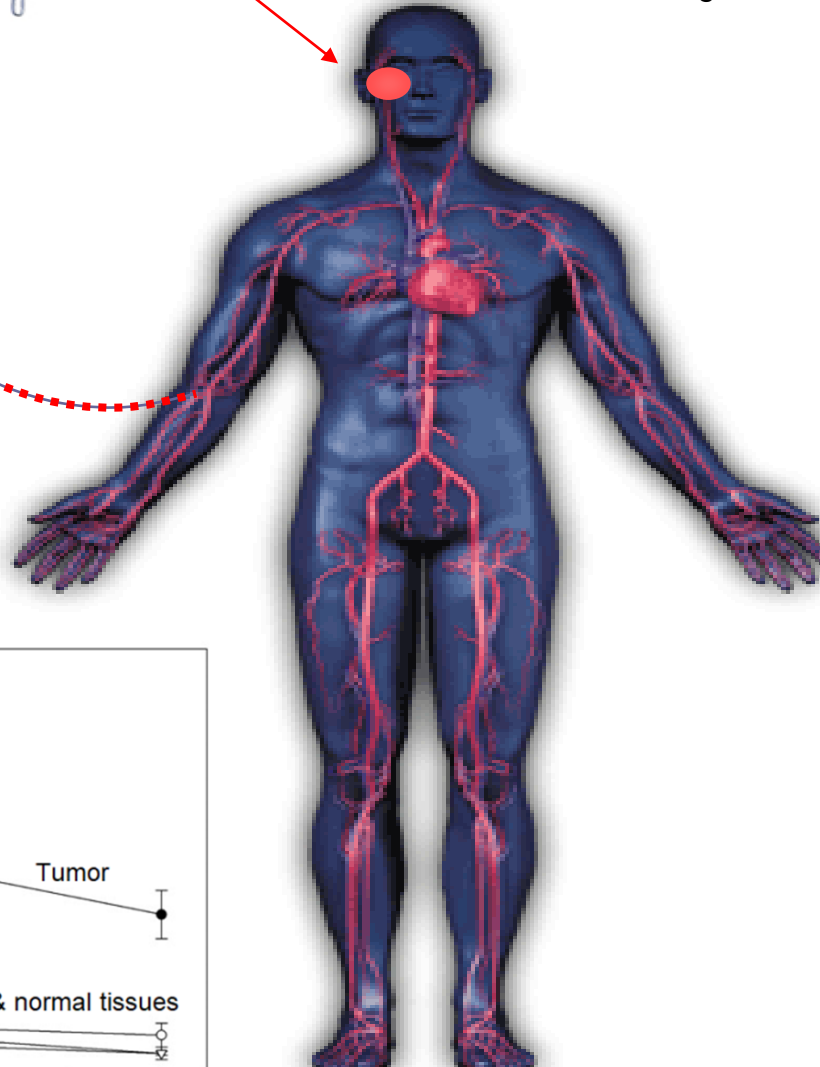
Neutron detection devices (precise dosimeters, monitors, spectrometers) development is a growing field

Boron Neutron Capture Therapy (BNCT)

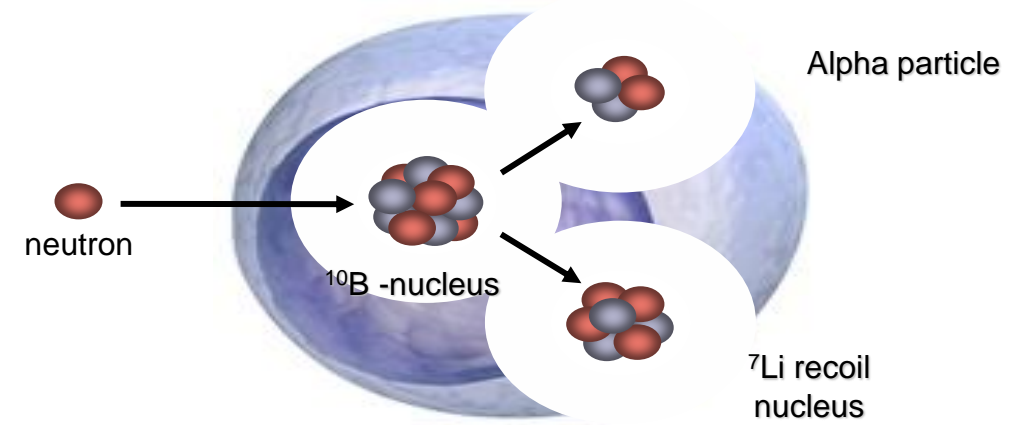
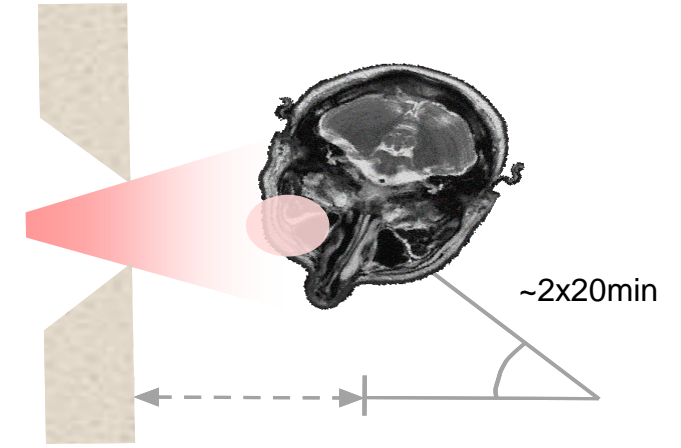
BNCT: Effective Treatment In One Day

BNCT treatment starts with a 2 hour intravenous boron compound infusion

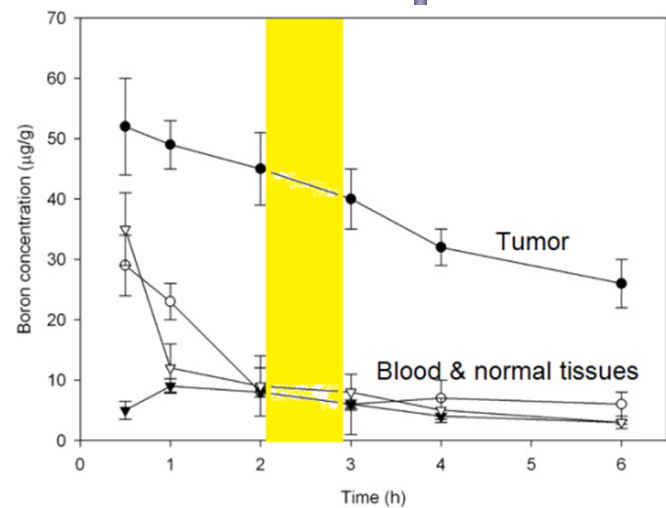
Boron is accumulating in the cancer cells



Targeted neutron irradiation is given according to the Monte Carlo dose plan



The boron atoms capture neutrons, leading to nuclear reaction emitting alpha and lithium recoil particles that cause extensive radiation damage in the cancer cells



Modern BNCT (from 1990), research reactors



Treatment Room at FiR1 Research Reactor, Helsinki

Phase II clinical trials

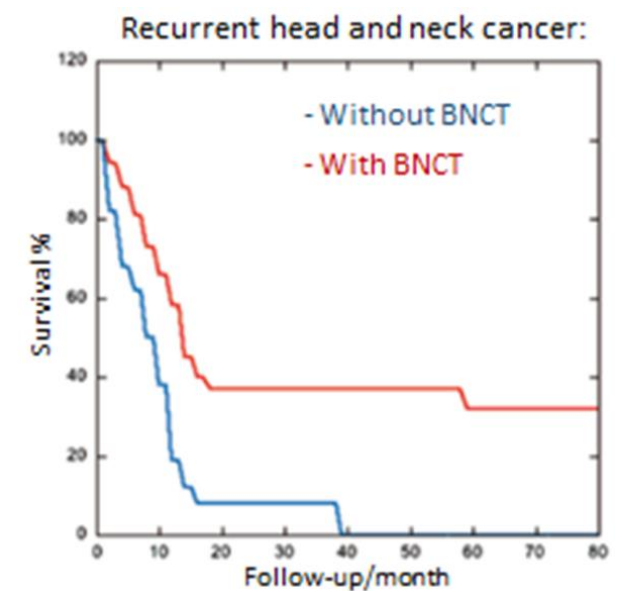
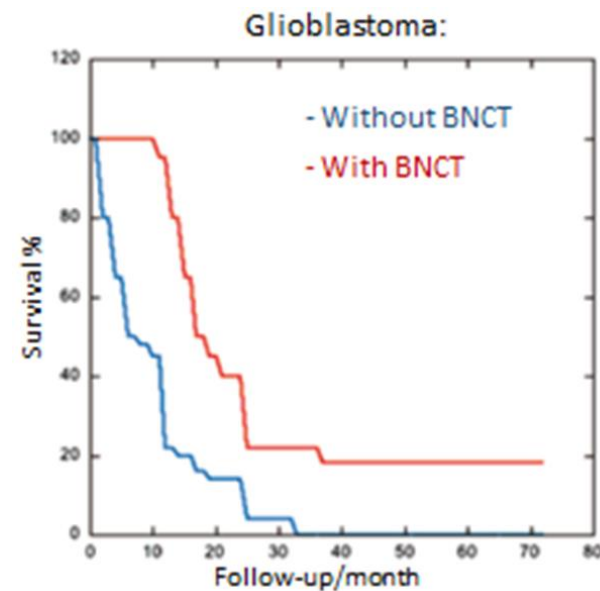
Epithermal neutron beams from reactors and BPA administration

Application to Brain tumors, local recurrent Head & Neck cancers

Other applications:

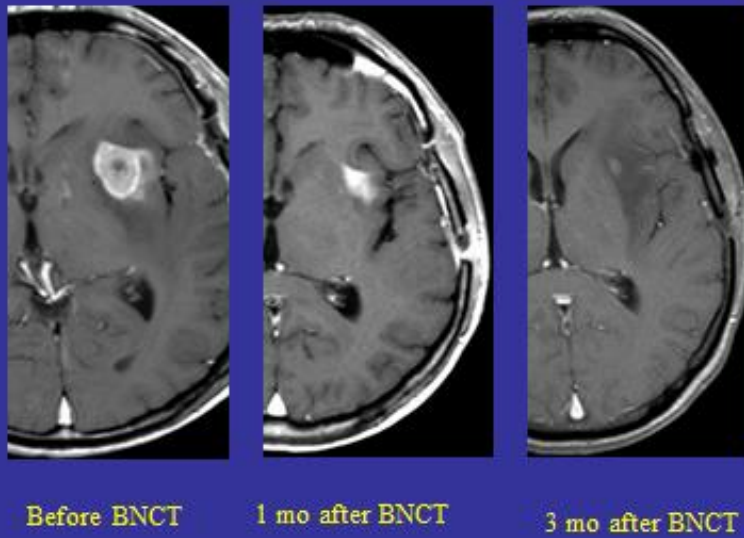
- melanoma
- liver metastasis (**extracorporeal**)
- other tumors are in study

**EU NUPECC Report
Nuclear Physics for Medicine (2014)**



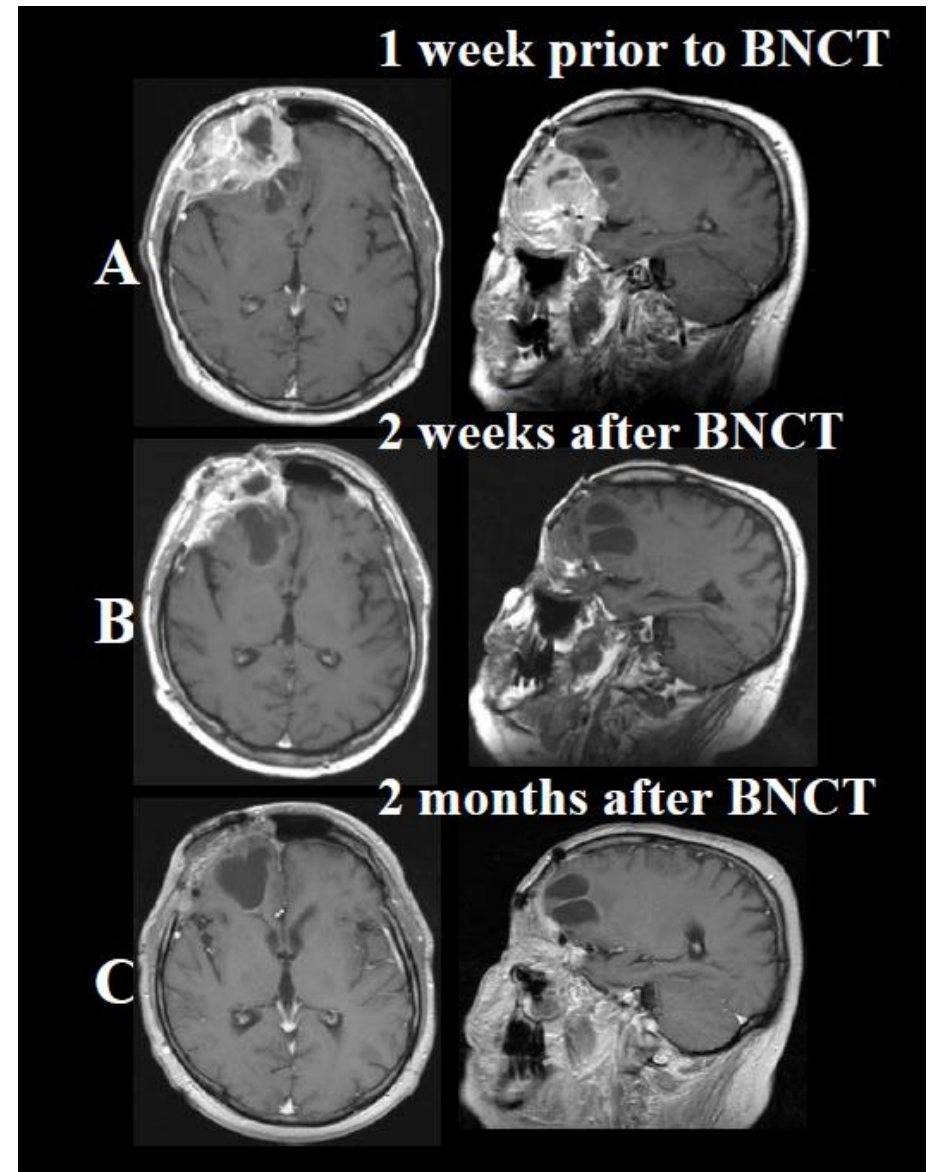
Clinical results

BNCT as first postoperative treatment in GBM



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

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



Biologically weighted dose (Gy-Eq or Gy(W))

Secondary particle	E	LET	Dose component
H recoil	5 keV	29 keV/ μm	Fast
Proton from ^{14}N capture	585 keV	57 keV/ μm	Thermal
Alpha from B reaction	1.46 MeV	160 keV/ μm	Boron
Gamma from H capture	2.2 MeV	low	Gamma

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

w_t, w_f also called RBE factors (assumed equal, also called neutron RBE)

w_B is compound dependent – called CBE

w_γ usually taken as 1, although a dose reduction factor < 1 has been proposed (Hopewell et al.)

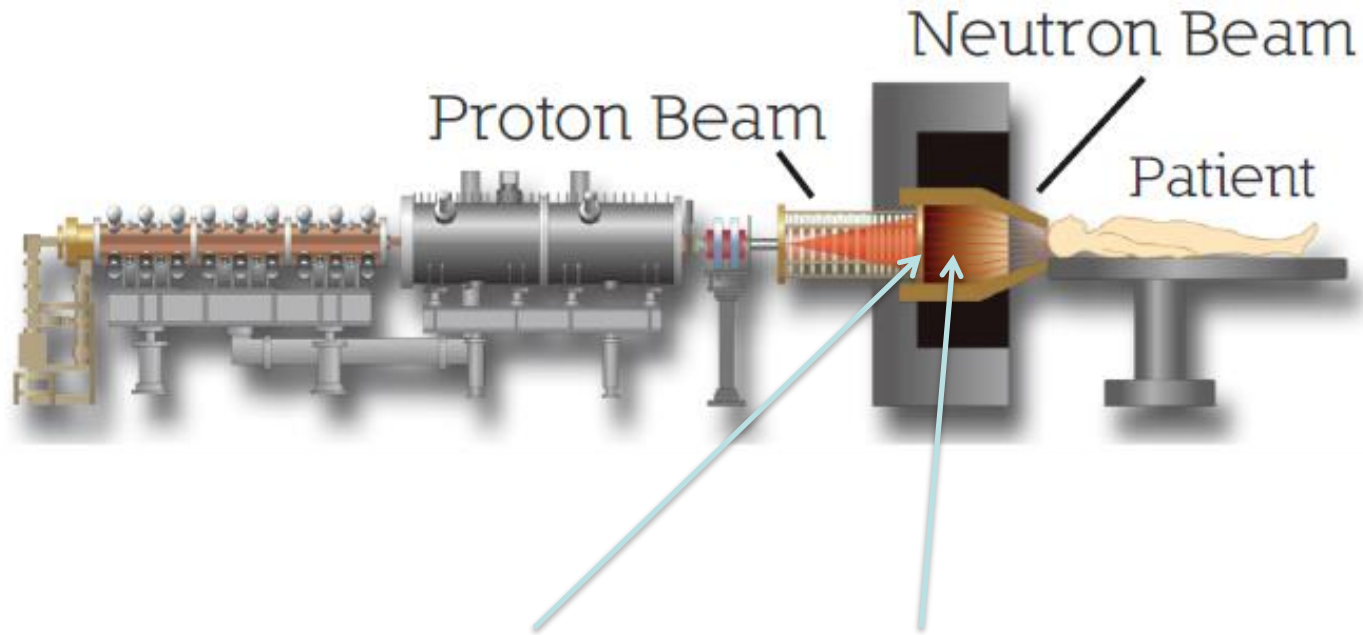
Uncertainty of weighting factors

Radiation	Tumor	Brain	Skin	Mucosa	Lung	Liver
Thermal Neutron	3.0	3.0	3.0	3.0	3.0	3.0
Epithermal Neutron	3.0	3.0	3.0	3.0	3.0	3.0
$^{10}\text{B}(n,\alpha)^7\text{Li}$						
BPA	3.8	1.35	2.5	4.9	2.3	4.3
BSH	2.5	0.37	0.8	0.3	?	0.9
γ-ray	1.0	1.0	1.0	1.0	1.0	1.0

In Finland and the USA, the thermal and epithermal neutron RBE were taken as 3.2 (Coderre and Morris 1998)

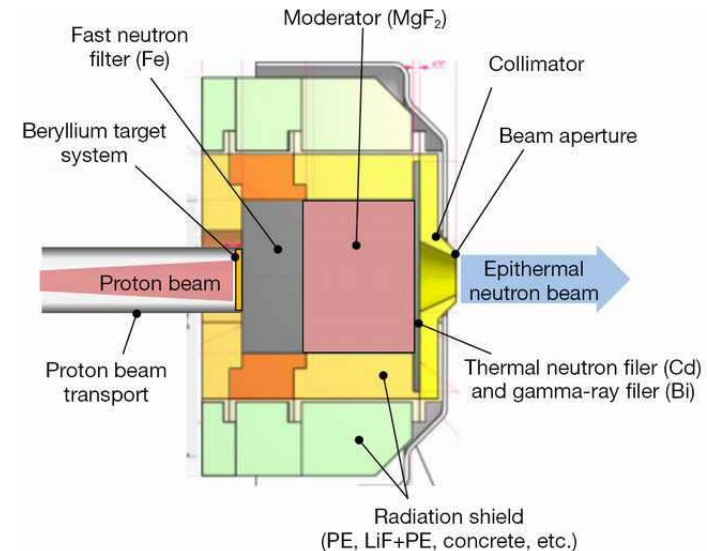
Accelerator based neutron facilities for BNCT

University of Tsukuba



Neutron producing target

BSA (Beam Shape Assembly): moderator (MgF_2 , AlF , etc.), reflector (Bi , Pb), filters (Cd , Bi), collimator and shielding (Li-poly , LiF)

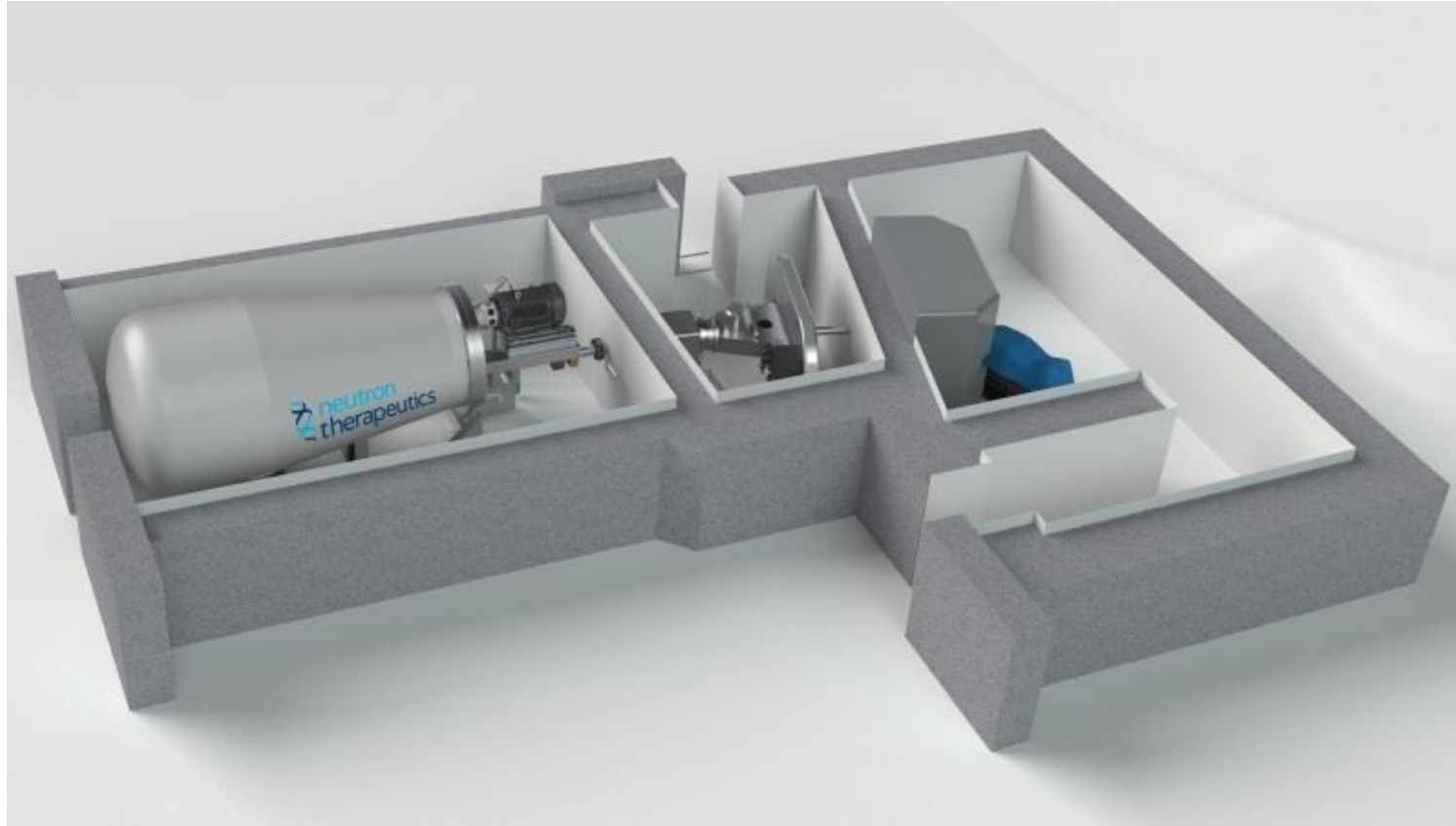


Current projects

Institute	Accelerator	Beam energy	Intensity	Reaction	Max. n energy
Kyoto Univ, Japan (in clinical trials)	Cyclotron	30 MeV	1 mA	${}^9\text{Be}(p,n)$	28 MeV
Helsinki Univ. Cent. Hospital, Finland	Electrostatic (Hyperion)	2.6 MeV	30 mA	${}^7\text{Li}(p,n)$	0.89 MeV
Budker Institute, Novosibirsk, Russia	Vacuum insulated Tandem	2.5 MeV	2 mA	${}^7\text{Li}(p,n)$	0.79 MeV
IPPE Obninsk, Russia	Cascade generator KG-2.5	2.3 MeV	3 mA	${}^7\text{Li}(p,n)$	0.57 MeV
Birmingham Univ., UK	Electrostatic (Dynamitron)	2.8 MeV	1 mA	${}^7\text{Li}(p,n)$	1.1 MeV
Tsukuba Univ., Japan	RFQ-DTL ^a	8 MeV	10 mA	${}^9\text{Be}(p,n)$	6.1 MeV
CNEA Bs. As., Argentina	Tandem Electrostatic. Quadrupole	1.4 MeV 2.5 MeV	30 mA 30 mA	${}^9\text{Be}(d,n)$ ${}^7\text{Li}(p,n)$	5.7 MeV 0.79 MeV
INFN, Italia	RFQ ^a	5 MeV	50 mA	${}^9\text{Be}(p,n)$	3.1 MeV
SOREQ, Israel	RFQ-DTL ^a	4 MeV	2 mA	${}^7\text{Li}(p,n)$	2.3 MeV
LBNL, USA	Electrostatic	2.5 MeV	50 mA	${}^7\text{Li}(p,n)$	0.79 MeV
National Cancer Center, Japan	RFQ ^a	2.5 MeV	20 mA	${}^7\text{Li}(p,n)$	0.79 MeV
Xiamen Humanity Hospital, China	Electrostatic (VITA)	2.5 MeV	10 mA	${}^7\text{Li}(p,n)$	0.79 MeV
Nagoya Univ., Japan	Electrostatic (Dynamitron)	2.8 MeV	15 mA	${}^7\text{Li}(p,n)$	1.1 MeV
Gachon Univ. Gil Med. Center, S.Korea	RFQ-DTL ^a	10 MeV	8 mA	${}^9\text{Be}(p,n)$	8.1 MeV
Southern Tohoku Hosp, Fukushima, JP	Cyclotron	30 MeV	1 mA	${}^9\text{Be}(p,n)$	28 MeV
Granada Univ., Spain	Electrostatic (Hyperion)	2.1 MeV	30 mA	${}^7\text{Li}(p,n)$	0.35 MeV

^a RFQ stands for Radio Frequency Quadrupole and DTL for Drift Tube Linac.

In-hospital projects

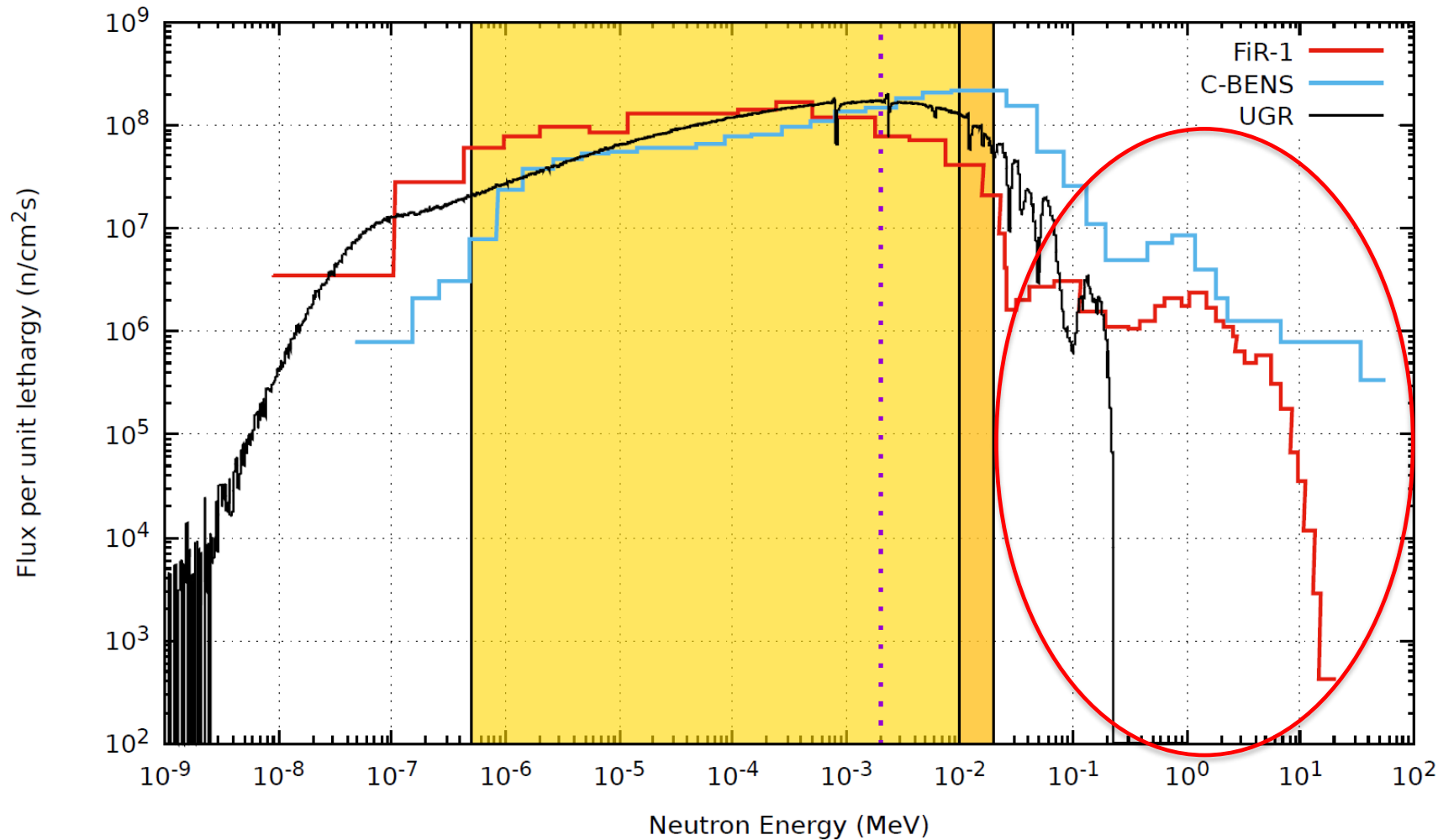


New facility in Finland
in commissioning at
Helsinki University
Hospital

Electrostatic
accelerator of
Neutron Therapeutics

Only facility in Europe
expected soon

Neutron spectra at different Accelerator-Based facilities



High energy tail very different between facilities
-> very important to assess **the biological effect of fast neutrons** for comparison (higher LET than epidermal neutrons, in yellow)

Biological dose in BNCT – big uncertainty

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

To introduce relative different biological effect:
Weighting factors (RBE).

Weighted dose:

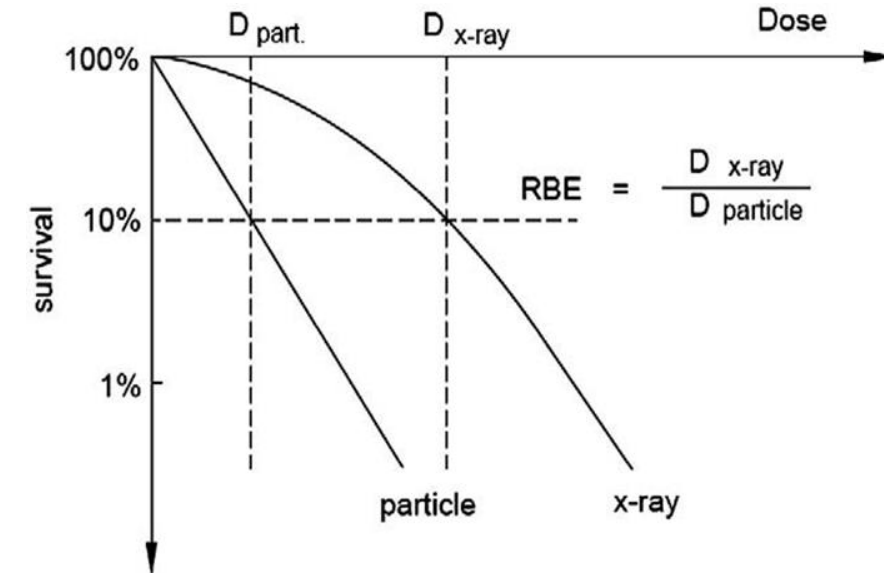
$$D_W \equiv w_t D_t + w_f D_f + w_\gamma D_\gamma + w_B D_B$$

weighting factors currently used
(Coderre et al.)

$$w_t = w_f = 3.2$$

$$w_\gamma = 1$$

$$w_B = 3.8 \text{ (tumour)}$$
$$w_B = 1.3 \text{ (Healthy tissue)}$$



A major source of uncertainty:

- w_t, w_f could not be separated (assumed the same)
- In current measurements of w_t , gamma dose is dominating -> loss of precision
- w_t, w_B should be measured in a pure thermal beam (or equivalent, like PF1b at ILL)
- w_f depends on facility, requires w_t
- w_γ assumed 1, should be confirmed

New biological dose concept

- Photon isoeffective dose $\rightarrow D_R$

$$\sum_{i=1}^4 \alpha_i D_i + \sum_{i=1}^4 \sum_{j=1}^4 G_{ij}(\theta) \sqrt{\beta_i \beta_j} D_i D_j = \alpha_R D_R + G(\theta') \beta_R D_R^2.$$

Gonzalez SJ, Santa Cruz GA, 2012
The photon-iso-effective dose in BNCT.
Radiat Res 178, 609-621.

- First-order approximation to photon isoeffective dose $\rightarrow D_p$

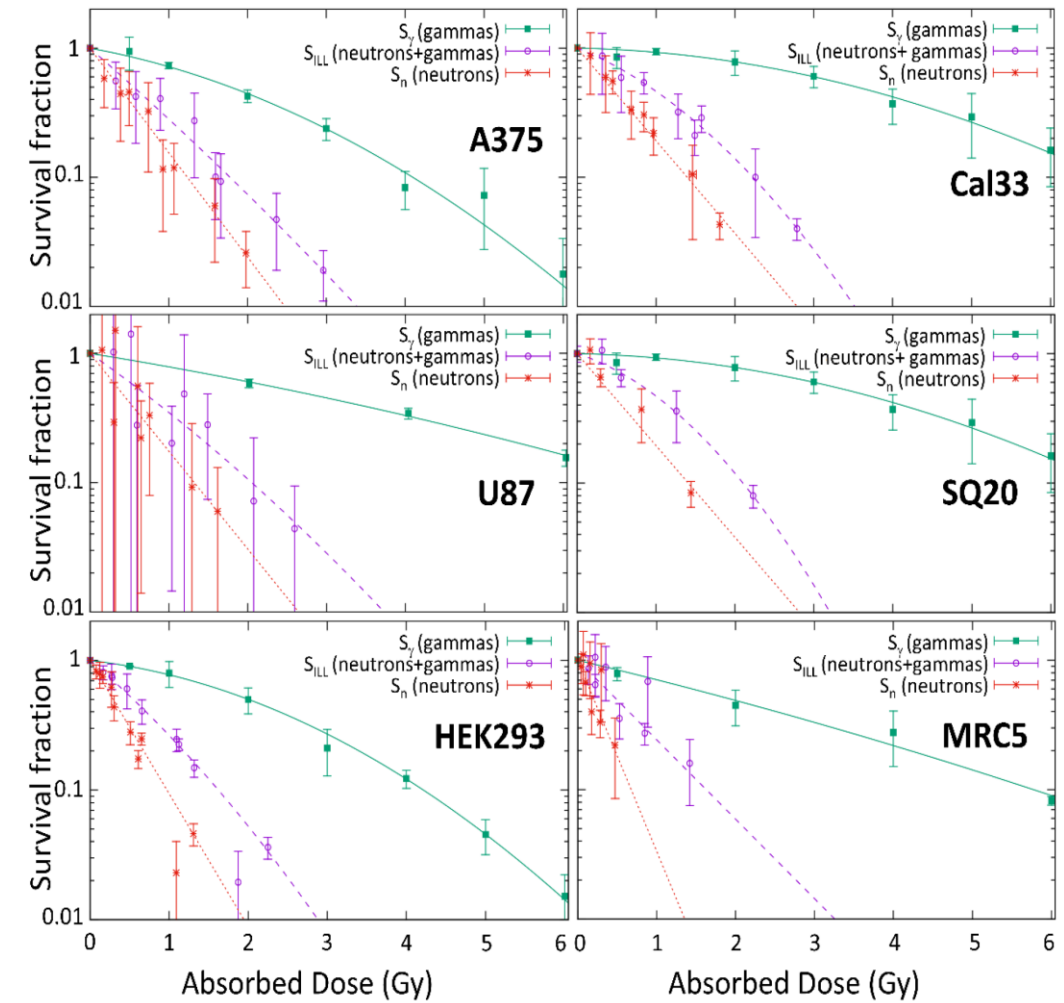
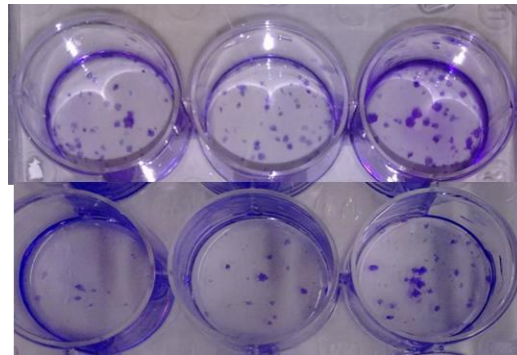
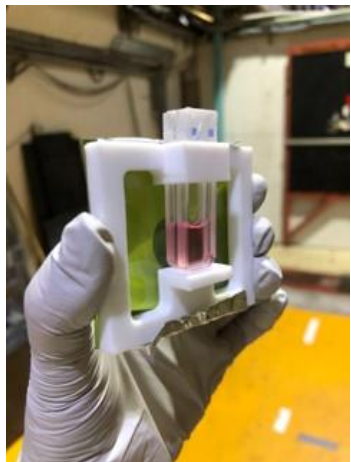
$$\frac{\alpha_f}{\alpha_p} W_f D_f + \frac{\alpha_t}{\alpha_p} D_t + \left(D_\gamma + \frac{D_\gamma^2}{\alpha_p / \beta_p} \right) + \frac{\alpha_B}{\alpha_p} D_B = \begin{cases} D_p + \frac{D_p^2}{\alpha_p / \beta_p} \\ n \left(d_p + \frac{d_p^2}{\alpha_p / \beta_p} \right) \end{cases}$$

A simple approximation for the evaluation of the photon isoeffective dose in BNCT
M. Pedrosa-Rivera, J. Praena, I. Porras, MJ Ruiz-Magaña, C Ruiz-Ruiz. Appl Radiat Isot 2020

The parameters α_i , β_i have to be determined by radiobiological measurements \rightarrow **Dose-response curves**

Determination of radiobiology factors for thermal n

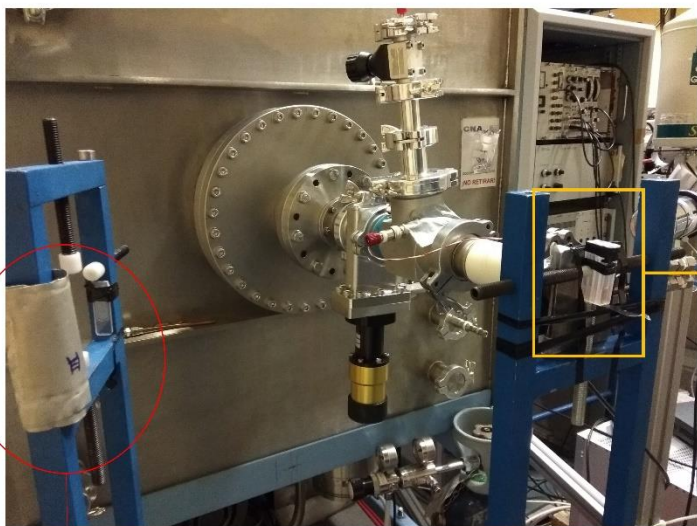
Institut Laue Langevin (Grenoble), PF1b neutron line



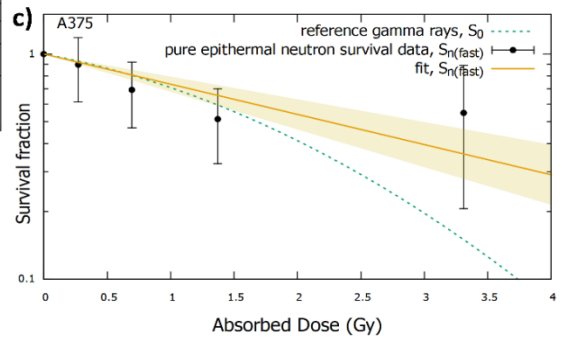
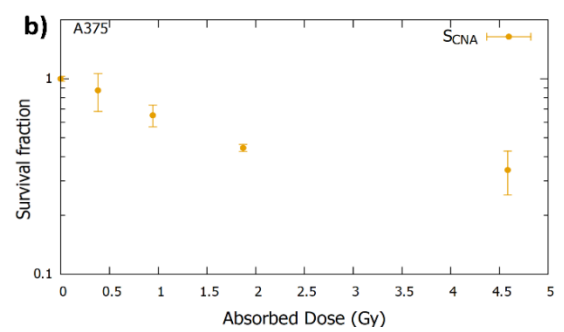
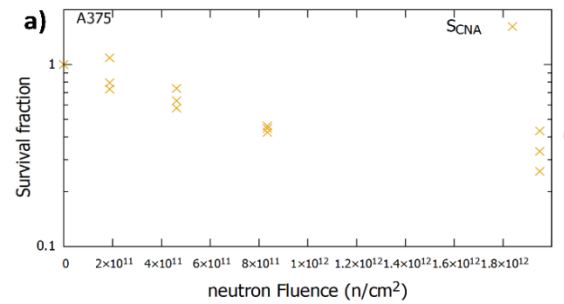
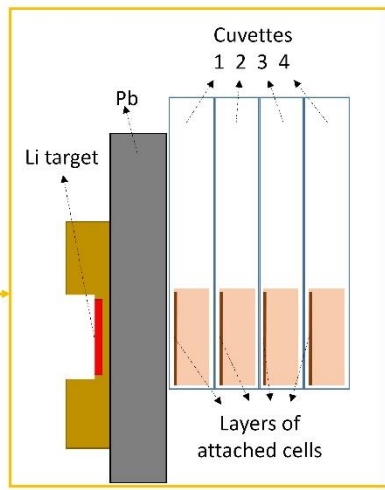
Cells **2020**, 9(10), 2144;

<https://doi.org/10.3390/cells9102144>

Irradiation with epithermal neutrons at CNA



Control cuvettes outside the beam



$W_f < W_t$, to be confirmed with more experiments

Radiobiological experiments with fast neutrons

- Clonogenic assays
- Other proliferation and cell viability studies
- Chromosome aberrations
- DNA damage
- Incomplete double-strand-breaks repair

Will produce results for determining both the weighting factors for therapy and the coefficients for the effective dose in radiation protection

Radiobiological experiments with fast neutrons

- System for inserting quartz cuvettes, filled with culture cells and médium
- Standard Bio Lab with incubator, centrifuge, laminar flow cabinet, microscope, ...
- Equipment for cell proliferation, viability and molecular studies



Conclusions

Determining biological response to fast neutrons is key for:

- Assessment of neutron radiation dose in patients during photon, proton therapy and BNCT.
 - Accurate tumor dose delivered
 - Sparing organs at risk
- Radiation protection assessments
 - Workers on radiation facilities
 - Space missions

A Bio Lab in IFMIF-DONES would provide essential data for different biological end points

- Stochastic effects for radiation protection
- Direct effects for therapies

UGR has an interdisciplinary group, open to collaborations world-wide, with experience in neutron radiobiology

- Running a bio Lab at the experimental hall of ILL Grenoble
- Supported by the UGR Chair Neutrons for Medicine, ISNCT, members of n_TOF (CERN) and users of CNA, INFN-LNL and ILL.

Thanks for your attention!!

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