Beams of the "lightest radionuclide useful for hadron therapy": neutron beams for BNCT

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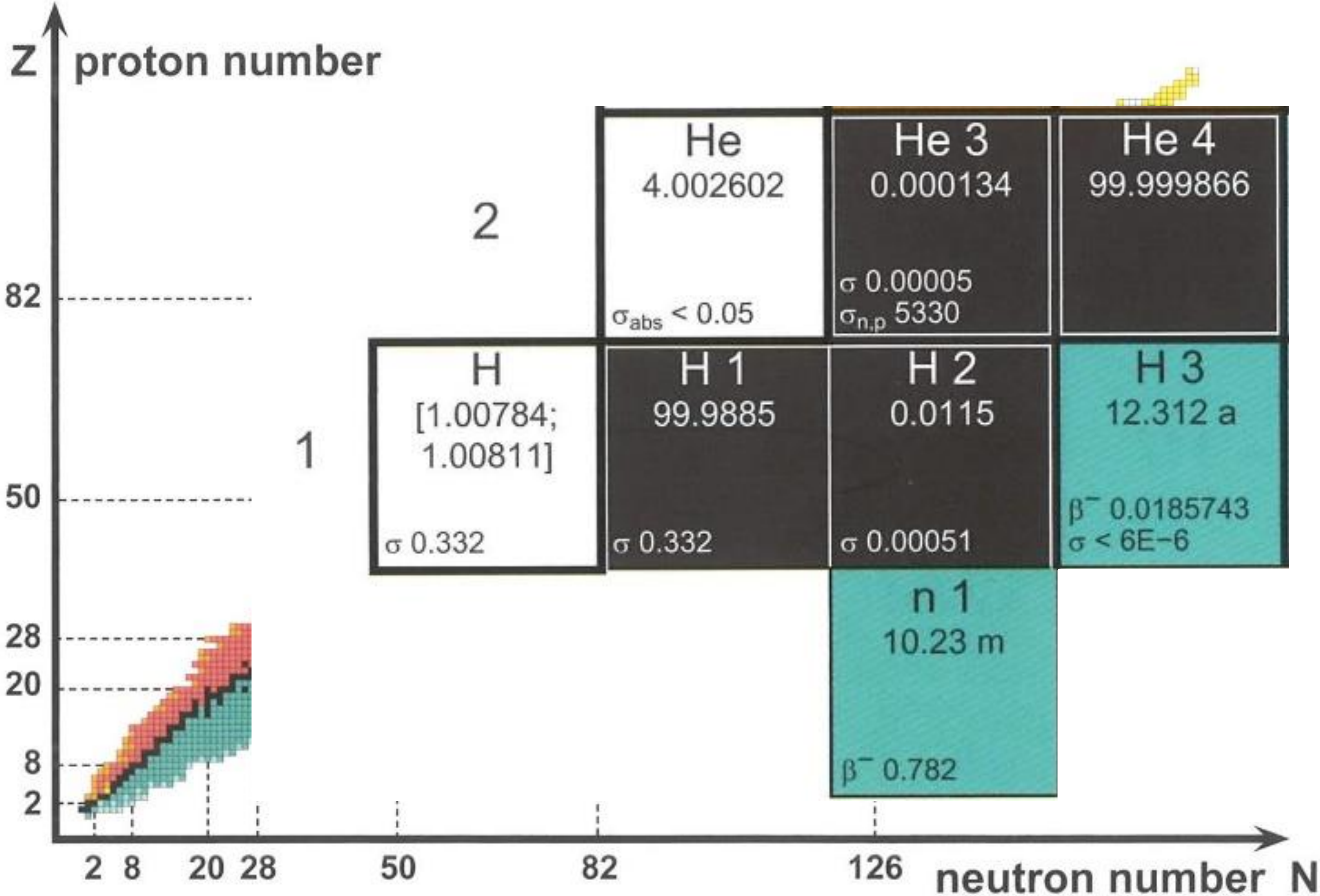
NEUTRONS FOR SOCIETY

UNIVERSIDAD DE GRANADA

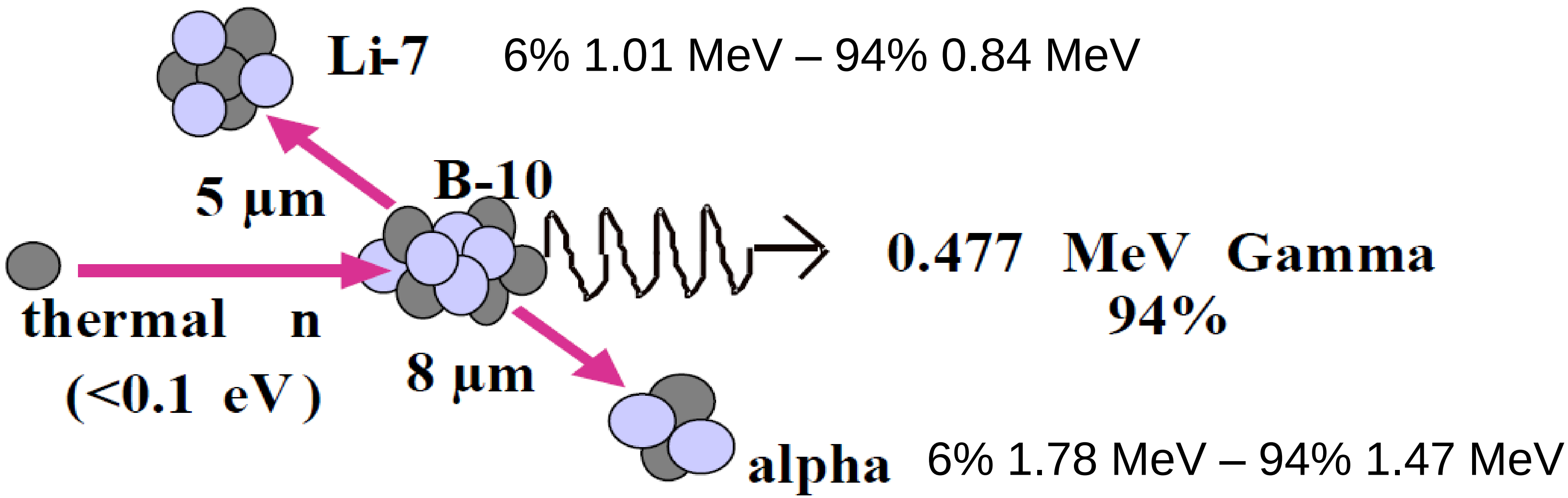
FUNDACION ACS

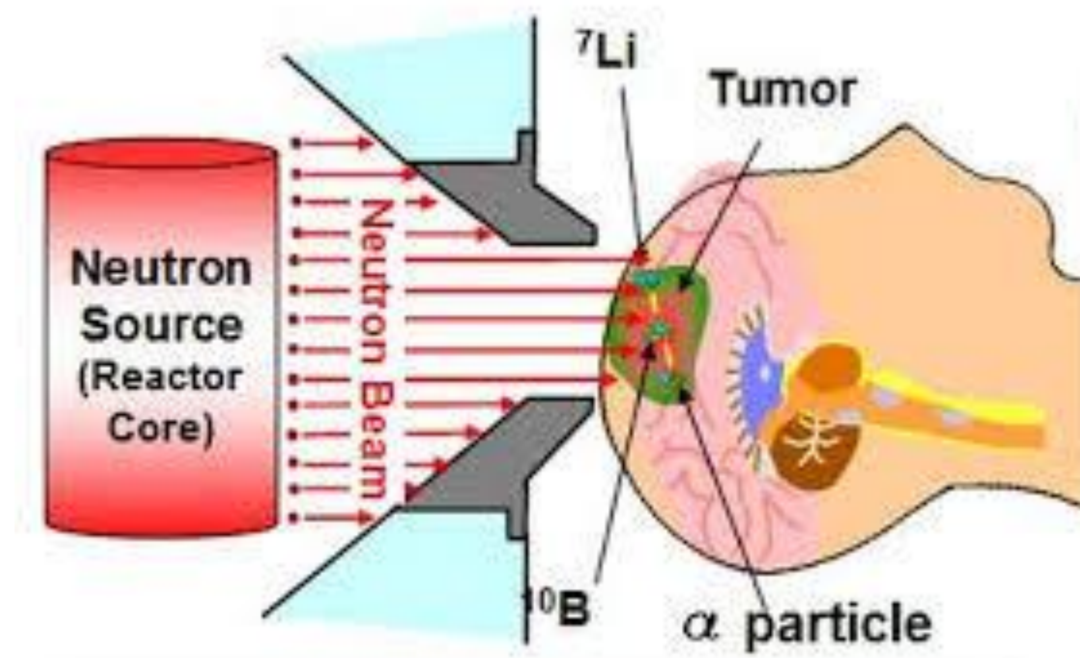
aecc Contra el Cáncer

The chart of nuclides



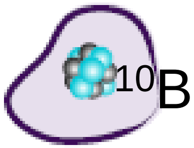
Boron Neutron Capture Therapy





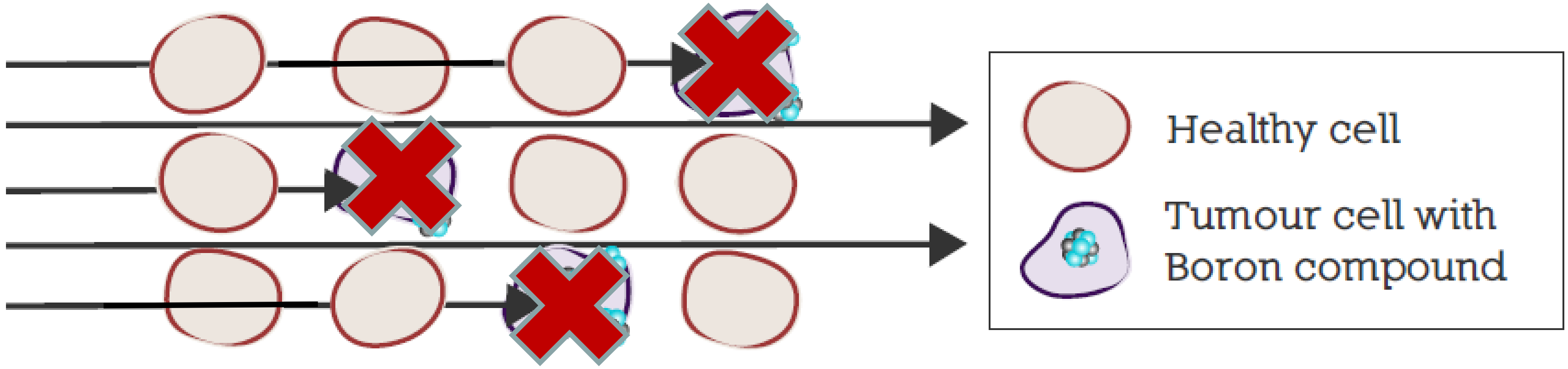
Principle of BNCT

Accumulate the boron in the tumour cells:



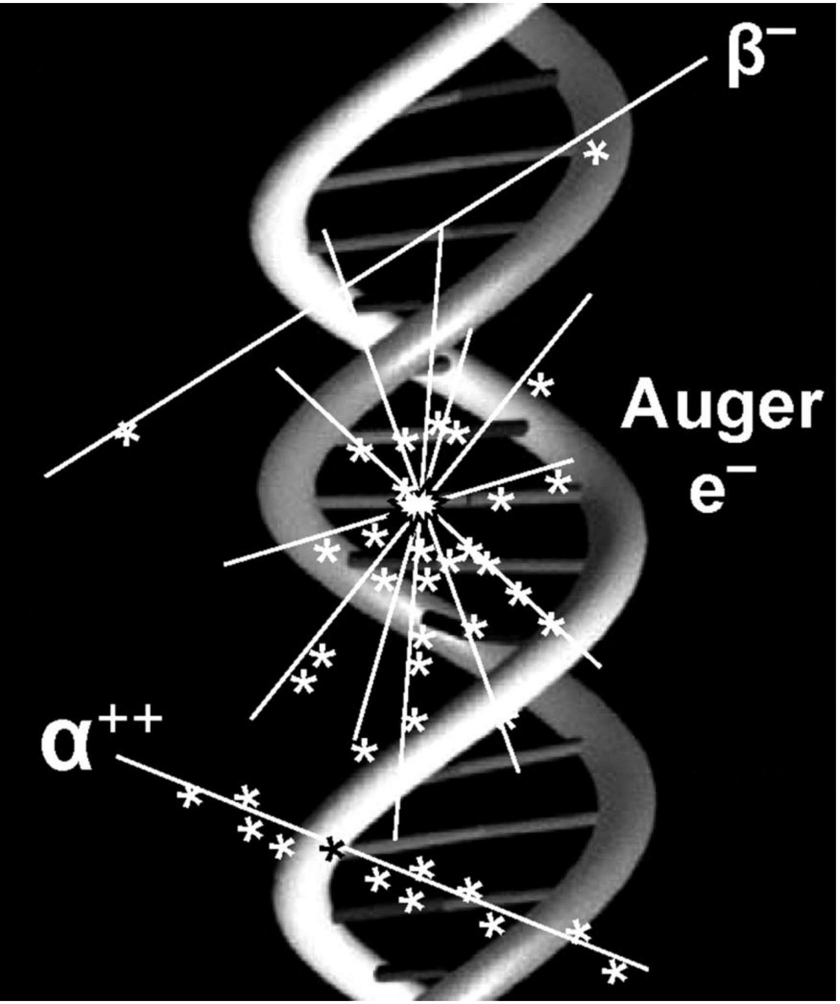
then

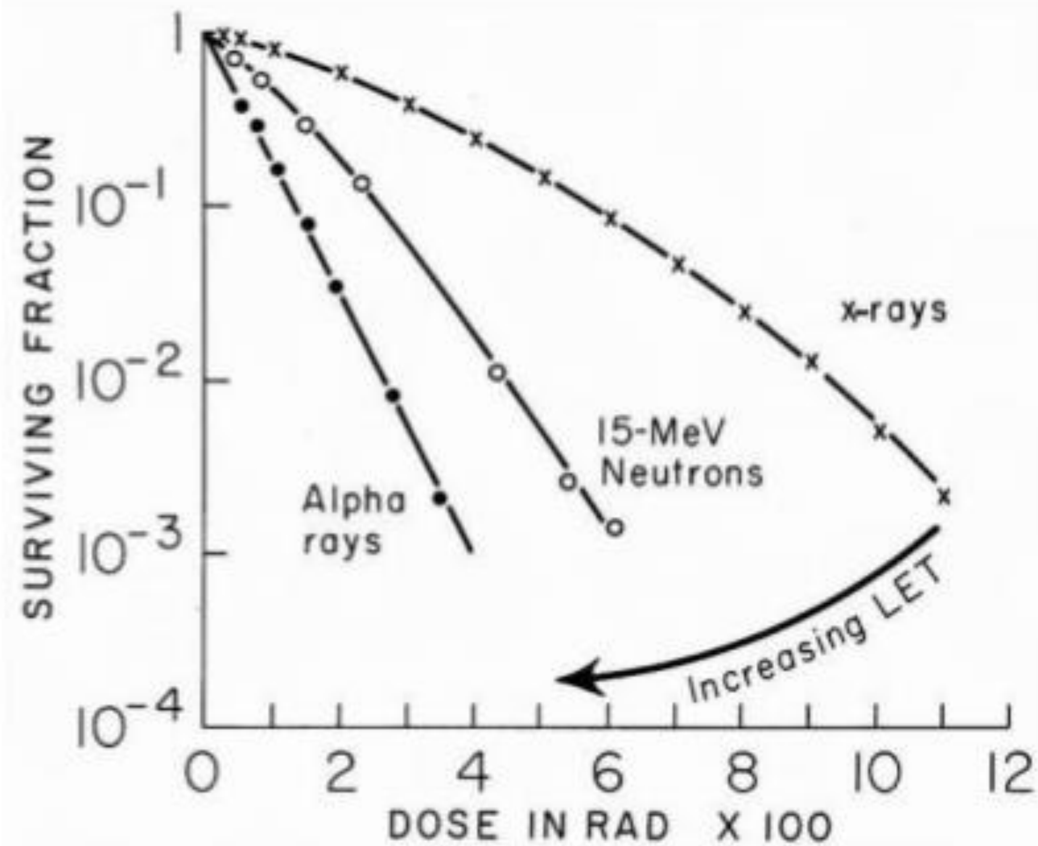
Irradiate with neutrons:



BNCT: radiotherapy selective at cell level

Effect of Linear Energy Transfer on cell survival





Comparison of therapies

External beam radiotherapy

Radionuclide therapy (intravenous)

X-ray/gamma

beta emitter

protons

LET / RBE

alpha emitter

BNCT

carbon ions

physical localisation

biological localisation

Comparison of therapies

External beam radiotherapy

Radionuclide therapy (locoregional)

X-ray/gamma

beta emitter

protons

LET / RBE

alpha emitter

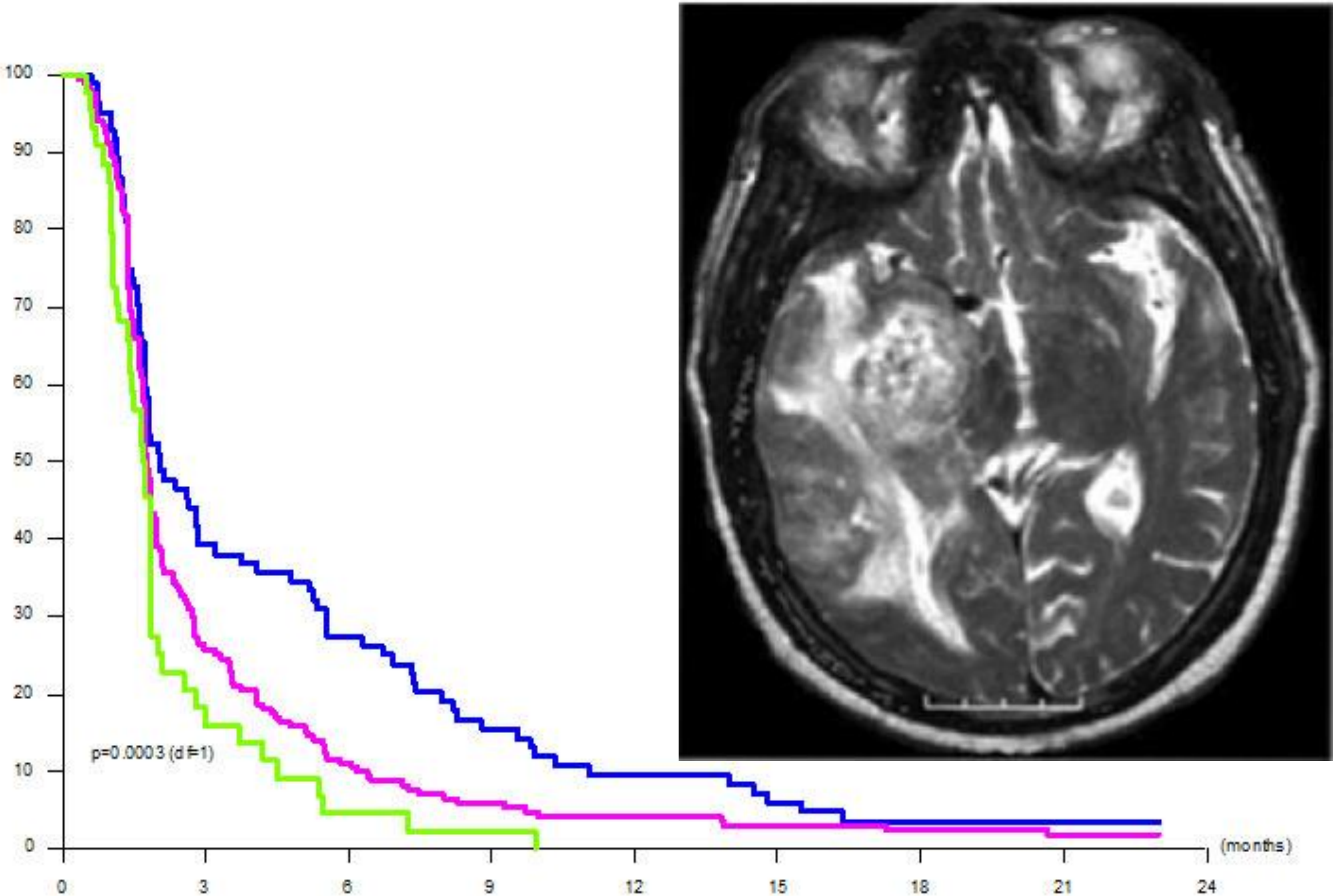
BNCT

carbon ions

physical localisation

biological localisation

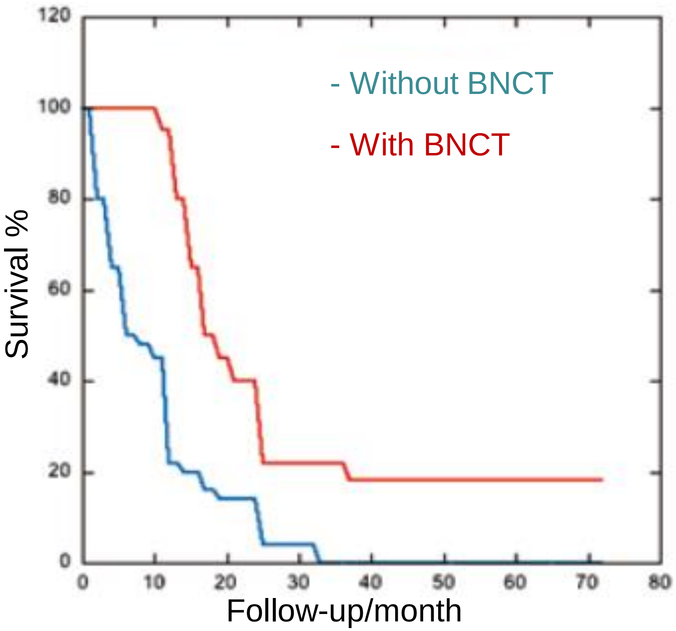
Glioblastoma multiforme



Clinical results

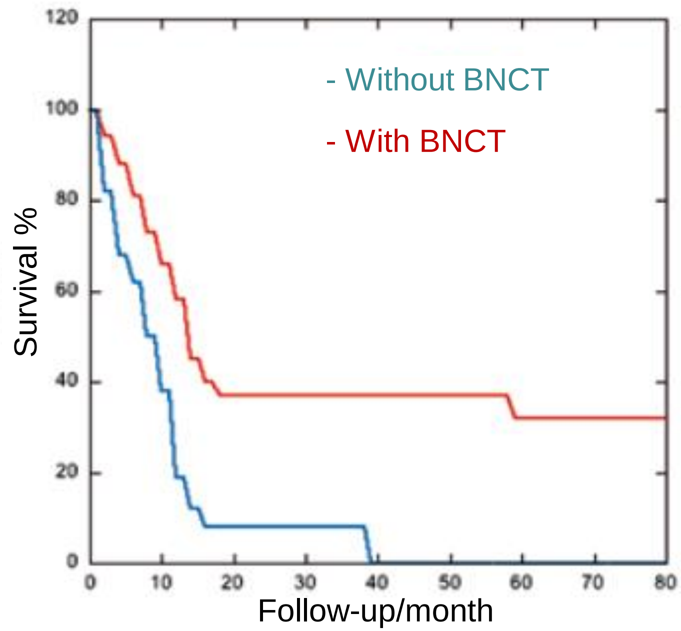
Survival curves of Japanese patients

Glioblastoma:



- Prognosis: 0% survival after 32 months
- With BNCT: 20% still living

Recurrent head and neck cancer:



- Prognosis: 0% survival after 40 months
- With BNCT: 40% still living

S. Miyatake et al. J Neurooncol 91 (2009) 199.
R.F. Barth et al. Radiat Oncol 7 (2012) 146.

Which boron concentration is required ?

Tolerable neutron fluence: $< 2 \cdot 10^{13}$ cm^{-2}

Probability that one ^{10}B atom captures a neutron:

$$3840 \cdot 10^{-24}\ \text{cm}^2 \cdot 2 \cdot 10^{13}\ \text{cm}^{-2} \approx 7.7 \cdot 10^{-8}$$

Number of ^{10}B atoms per cell to assure >1 capture/cell:

$>> 10^7$

>>10 million boron atoms per cell !

Boron concentration in tumor $\approx$ 30 ppm

Infusion of up to 100 mg BSH/kg or 900 mg BPA/kg

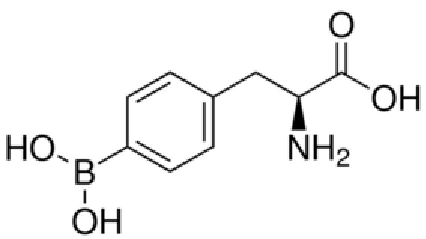
Only metabolic targeting, no receptor targeting!

Tumor/blood ratio: ≈ 3

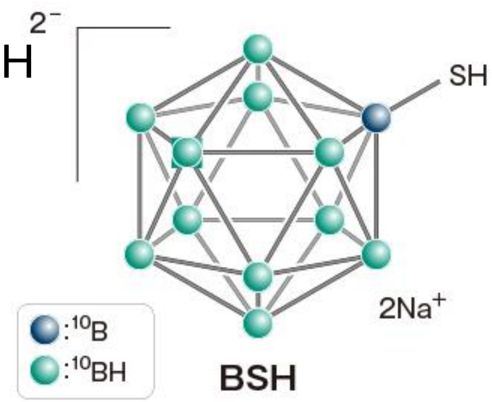
Boron delivery agents

Until now:

BPA

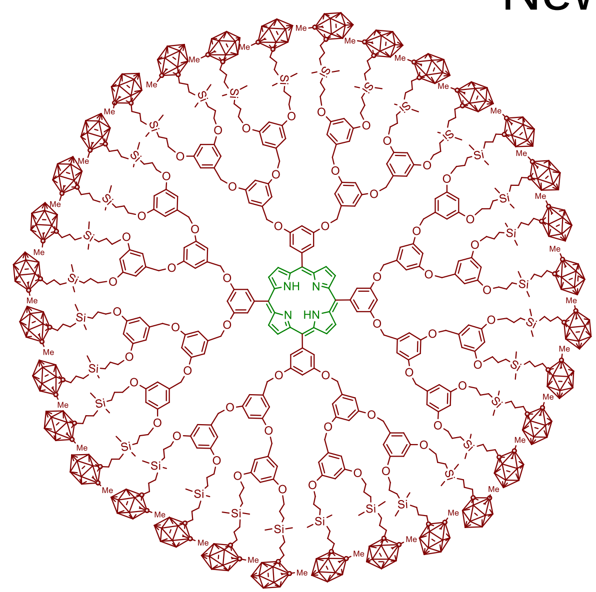


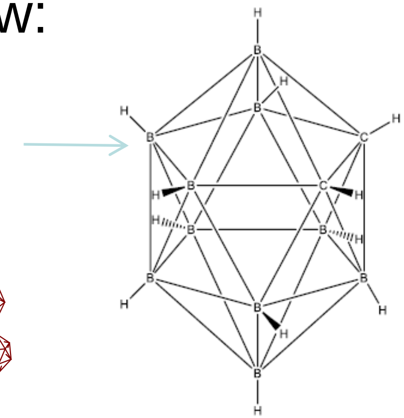
BSH



$Na_2B_{12}H_{11}SH$

New:



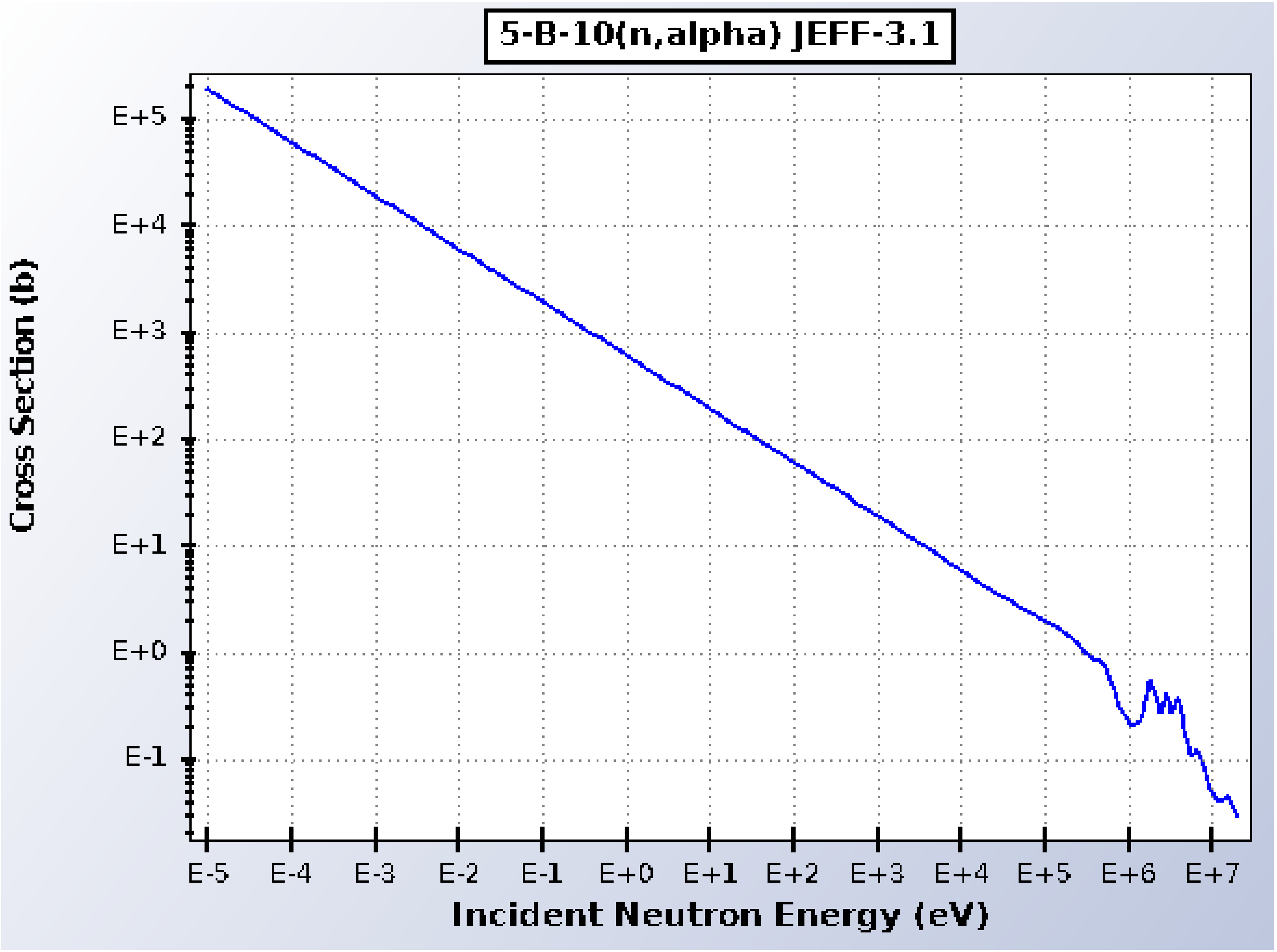


10 B atoms in each carborane cage

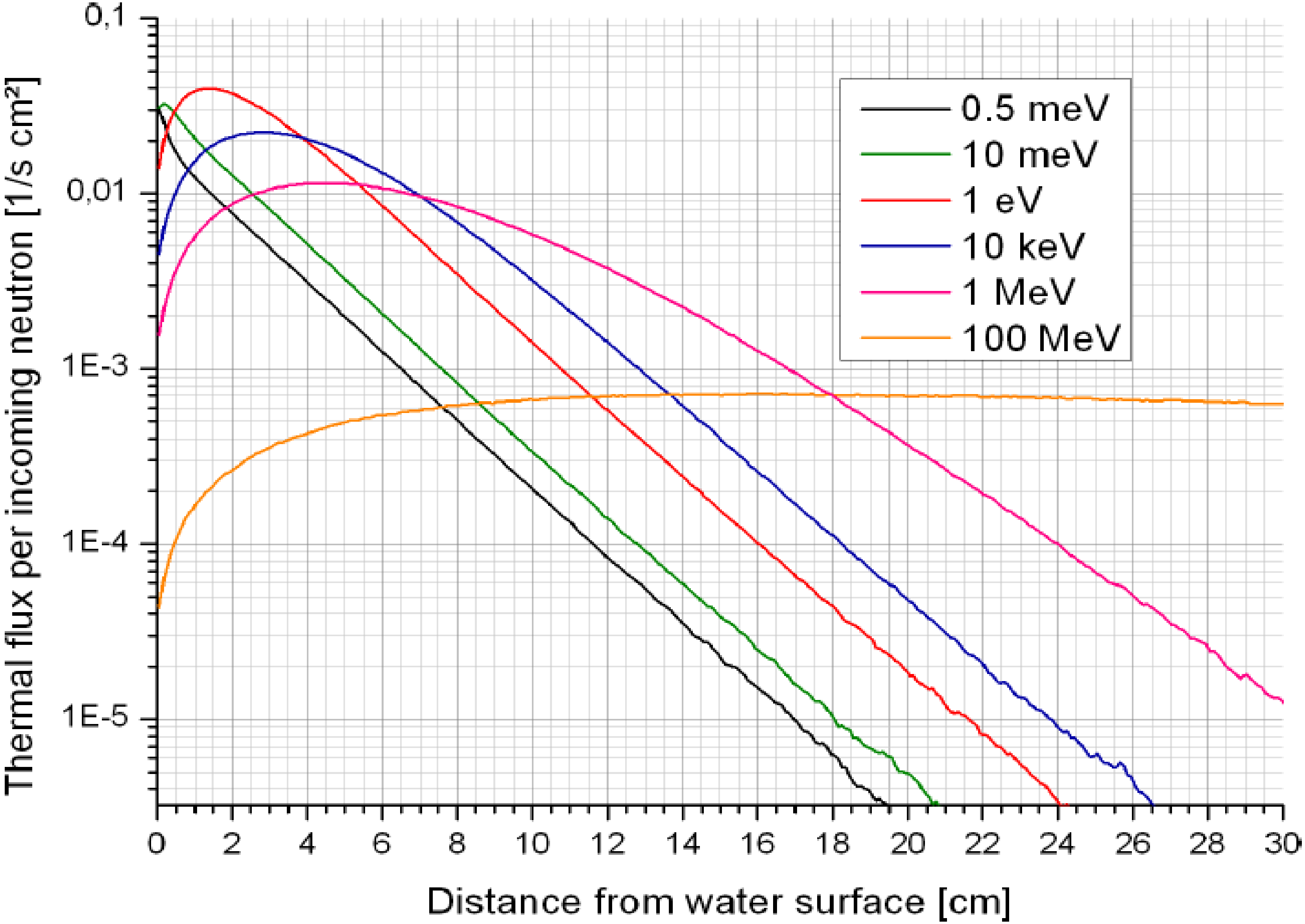
boron-rich dendrimers with porphyrin nucleus

Also:
- Nanoencapsulation of carboranes
- Nanogels

Which neutron energy is required ?



Which neutron energy is required ?

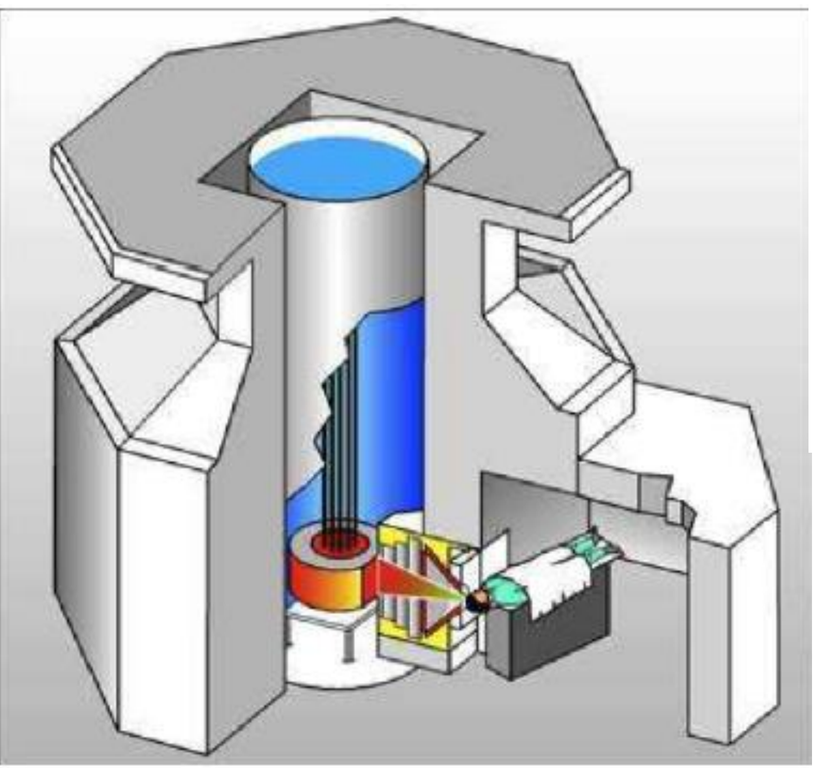


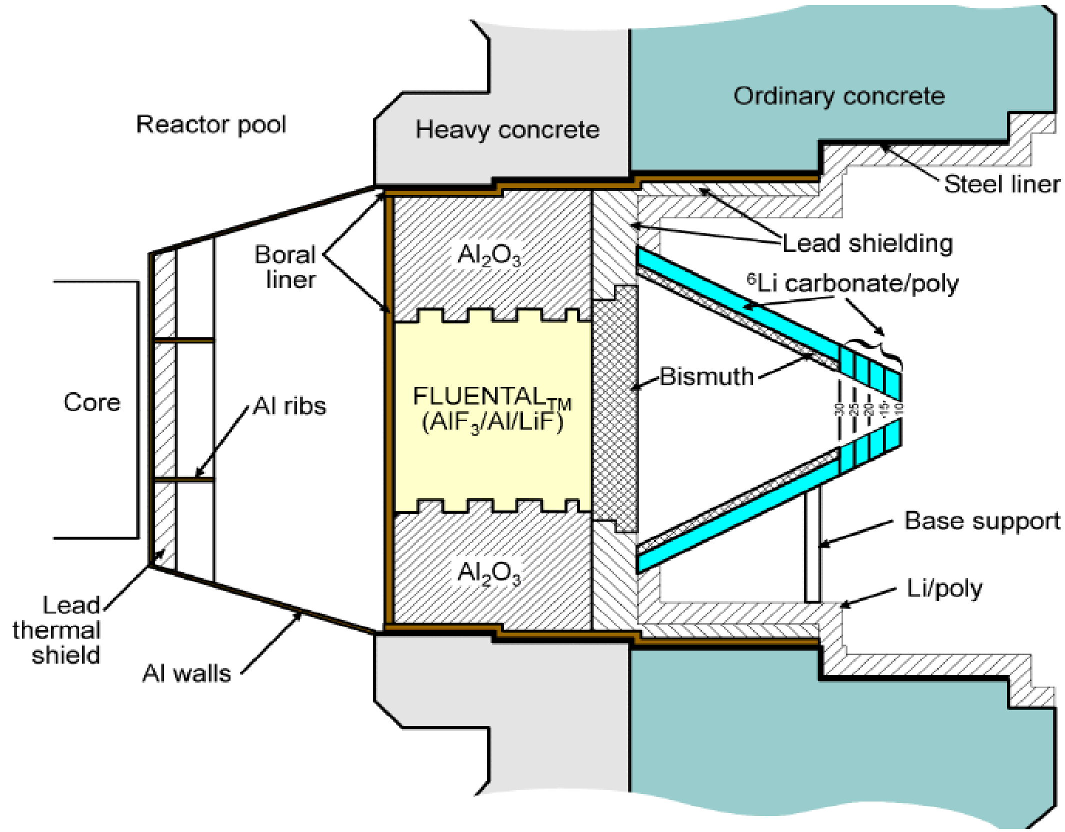
E. Bavarnegin et al., JINST 12 (2017) P05005

Neutron sources for BNCT

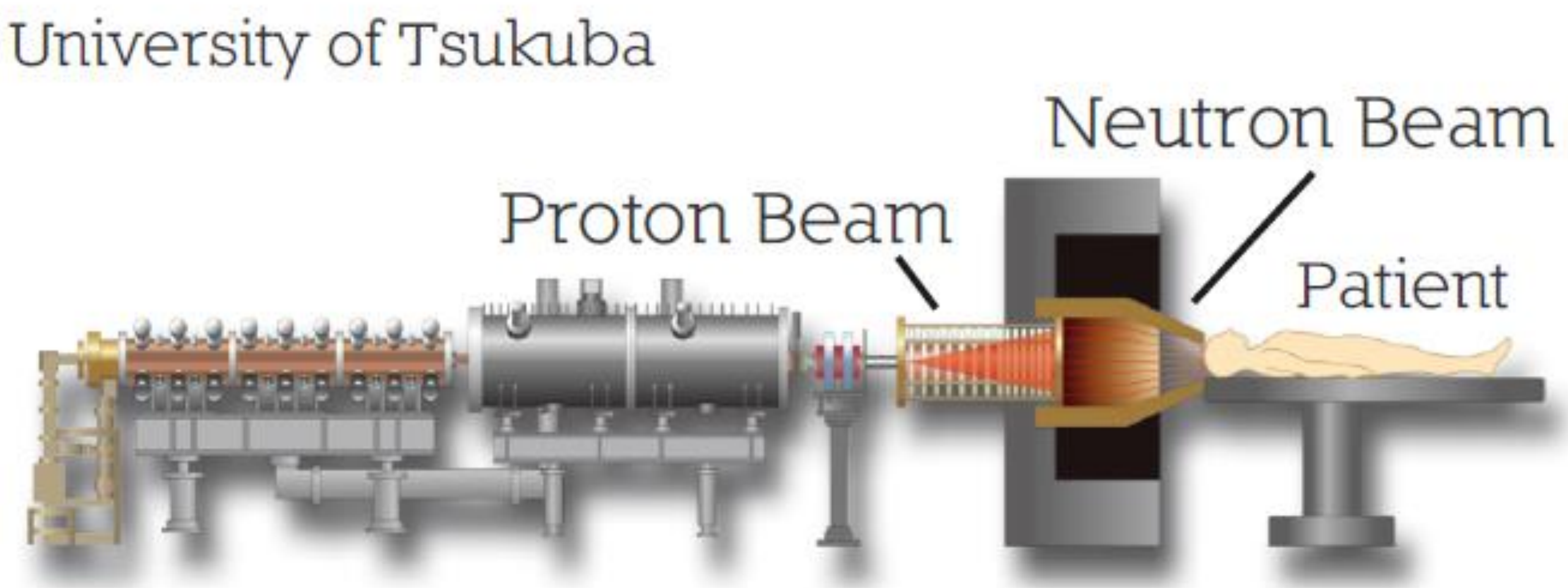
Over 700 patients treated at reactors in:

Japan, Finland, Argentina, USA, Netherlands, Sweden, Taiwan…





Future: accelerators



- Can be integrated into hospitals
- Epithermal neutron spectra from $^{7}Li(p,n)$ or $^{9}Be(p,n)$ reactions
- Challenging targetry (≈10 mA >2 MeV protons)

The MIT Nuclear Reactor Laboratory

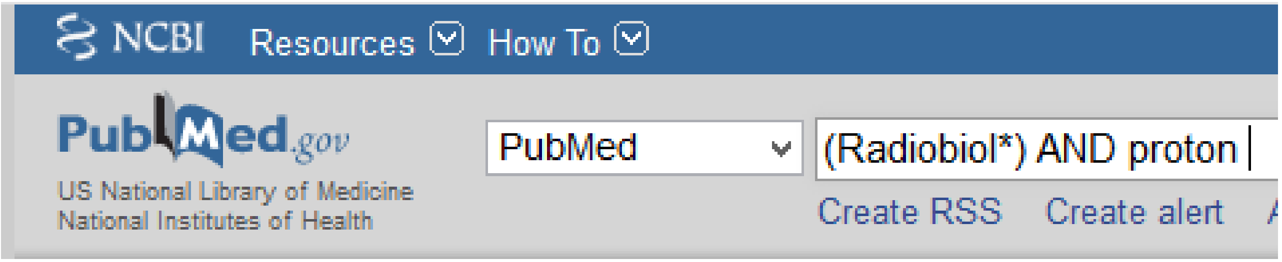
BNCT

The Basics of Boron Neutron Capture Therapy

?

BNCT is a binary radiation therapy modality that brings together two components that when kept separate have only minor effects on cells. The first component is a stable isotope of boron (boron-10) that can be concentrated in tumor cells by attaching it to tumor seeking compounds. The second is a beam of low-energy neutrons. Boron-10 in or adjacent to the tumor cells disintegrates after capturing a neutron and the high energy heavy charged particles produced destroy only the cells in close proximity to it, primarily cancer cells, leaving adjacent normal cells largely unaffected.

Radiobiology knowledge



Gamma	3627
Electron	1113
Alpha	1346
Proton	666
Carbon ions	263
Auger	73
Thermal neutron	68
Neon	66
Pion	46

Stopping of radiation

Charged particles:

- quasi-continuous stopping
- by Coulomb interaction with electrons at large distance
- non-destructive detection possible

Neutral particles:

- rare and catastrophic interaction
- destructive detection

How dangerous are slow neutrons?

ELSEVIER

ICRP Publication 116

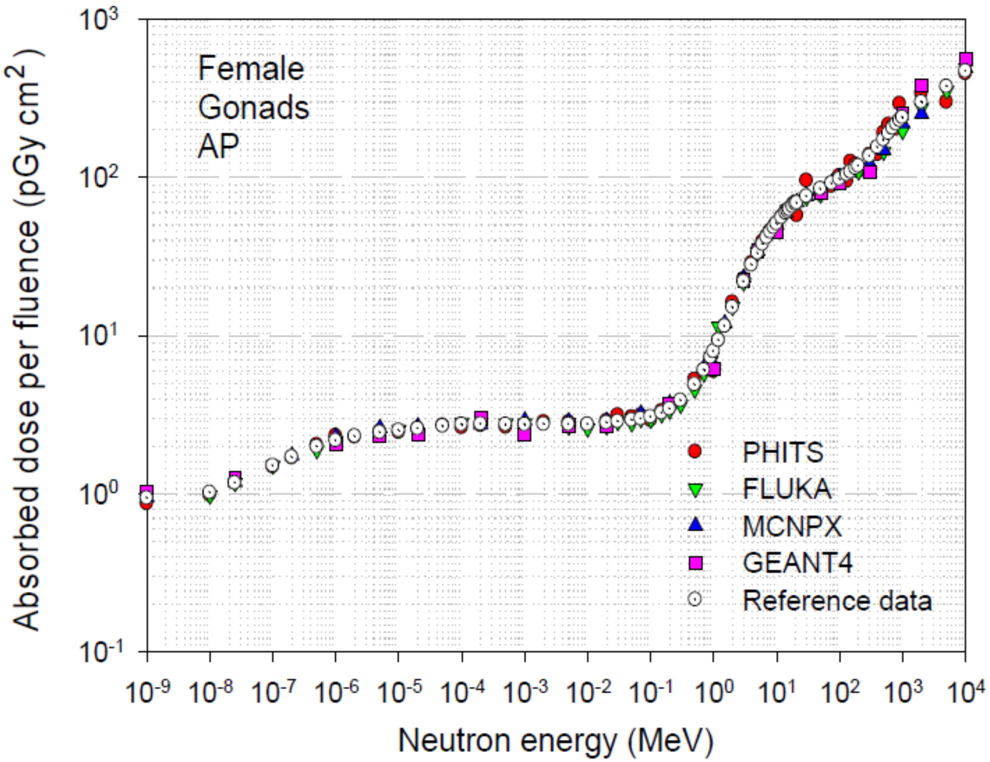
Annals of the ICRP

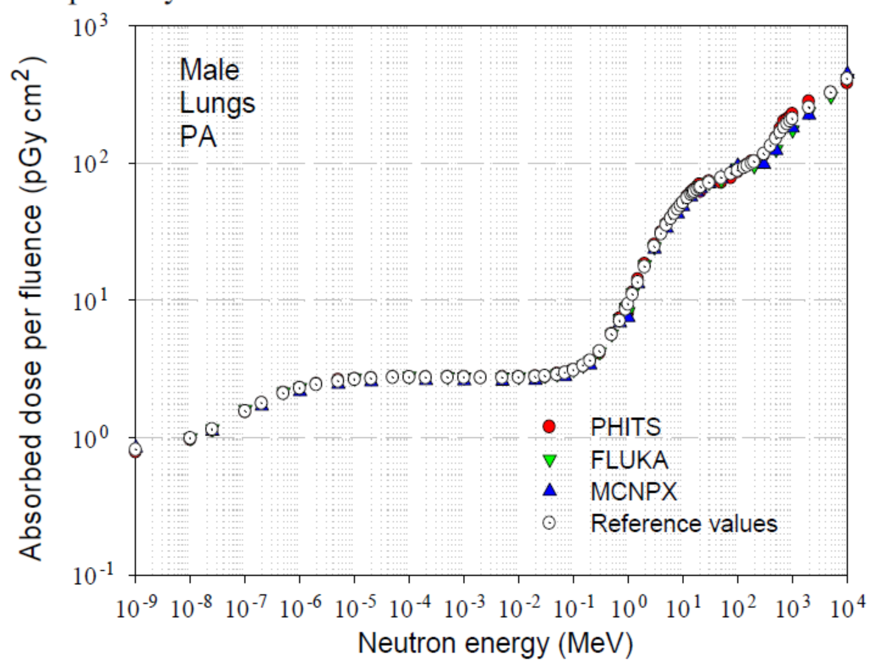
Conversion Coefficients for Radiological Protection Quantities for External Radiation Exposures

ICRP PUBLICATION 116

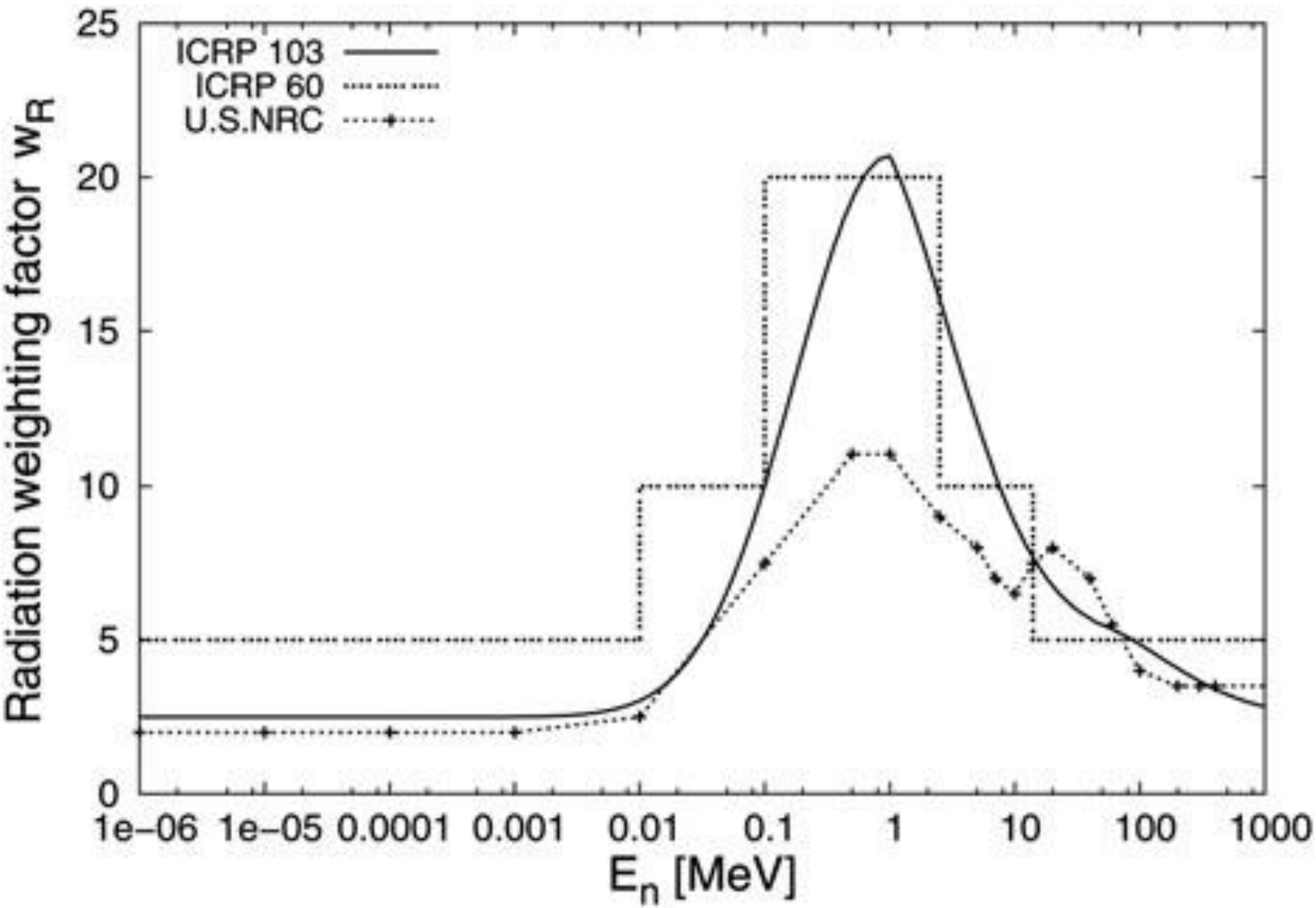
Approved by ICRP in October 2010 and

adopted by ICRU in November 2010



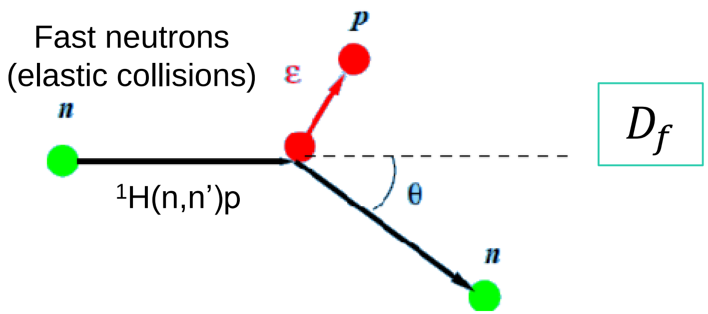


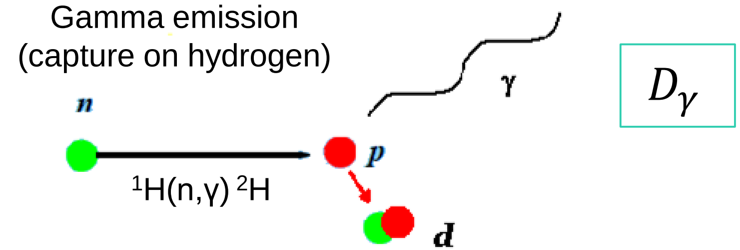
Neutron RBE

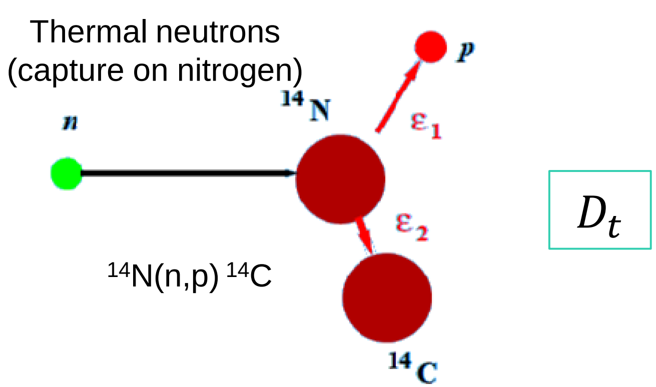


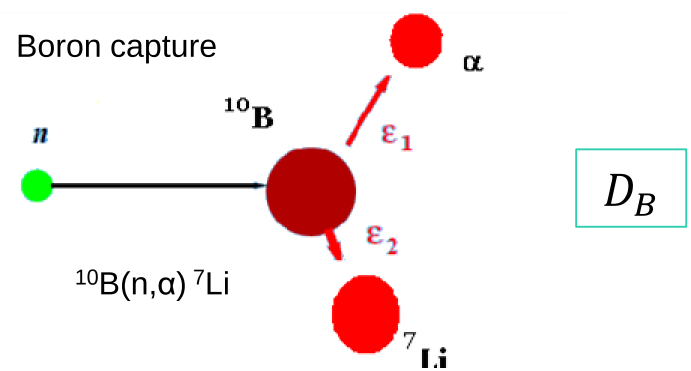
ICRP 103
ICRP 60
U.S.NRC
Radiation weighting factor w_R
25
20
15
10
5
0
1e−06
1e−05
0.0001
0.001
0.01
0.1
1
10
100
1000
E_n [MeV]

Reactions relevant for neutron dosimetry









BNCT biological dose

D_W – equivalent photon dose

$$D_W = w_t D_t + w_f D_f + w_\gamma D_\gamma + w_B \,[\mathrm{B10}]\, D_{B,1\mathrm{ppm}}$$

Both = 3.2 (FiR1), 3.0 (Osaka), for T and N

- Obtained from very few experiments
- Strong variability (1.9 – 7.1)
- Difficult to separate
- Assumed equal for epithermal beams from reactors (average energy of fast neutrons ~600 keV)
- Gamma contributions (substraction assuming linearity)

Assumed = 1

- D reduction factor < 1 proposed because of the low dose rate (γ from H capture)

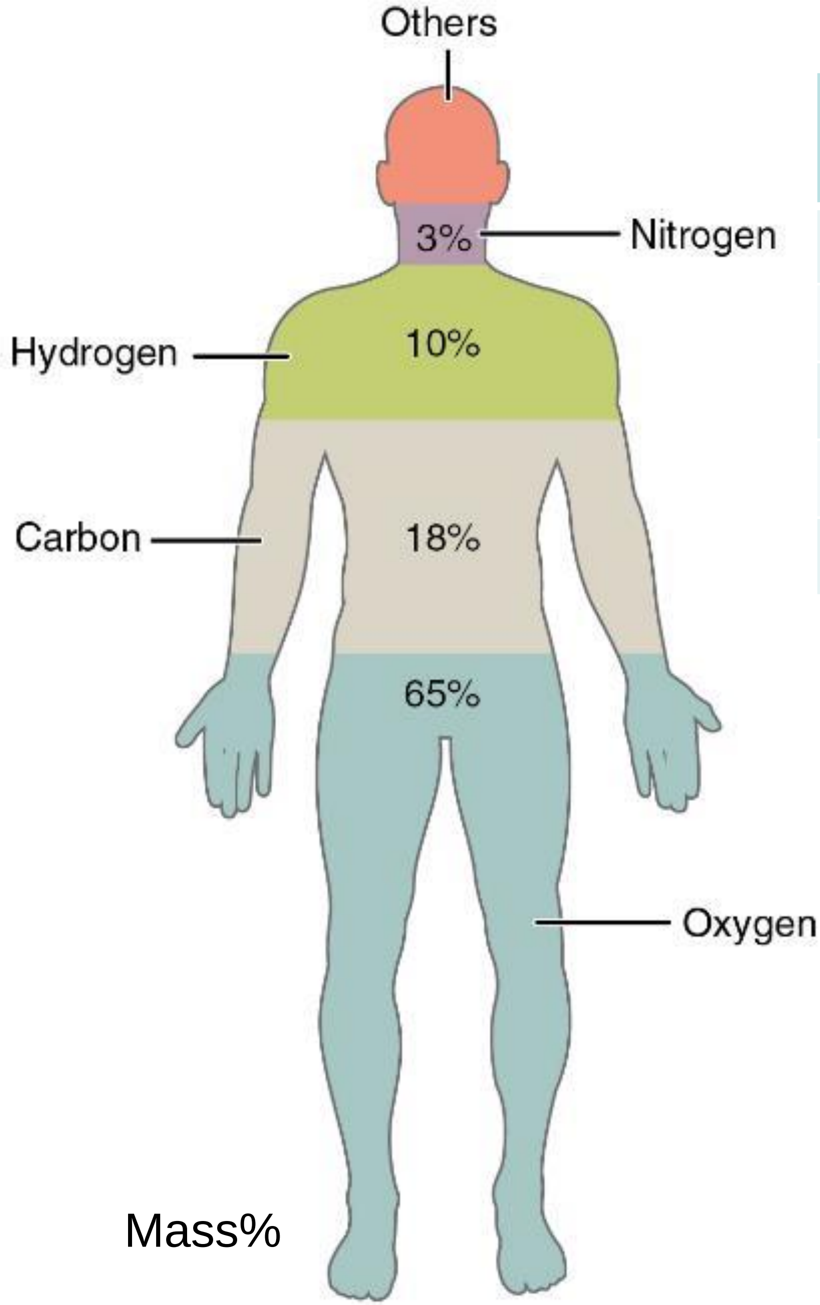
T = 3.8, N = 1.3, Skin = 2.5 (BPA)

- Obtained for therapy of brain tumors => applied to H&N
- Compound-dependent factor

BMRR

Component	Rad/MW-min	%
Gamma	143.0	68.6
$^{14}N(n,P)^{14}C$	47.4	22.8
H	18.0	8.6
Total	208.4	100.0

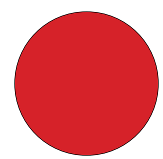
A human as neutron target

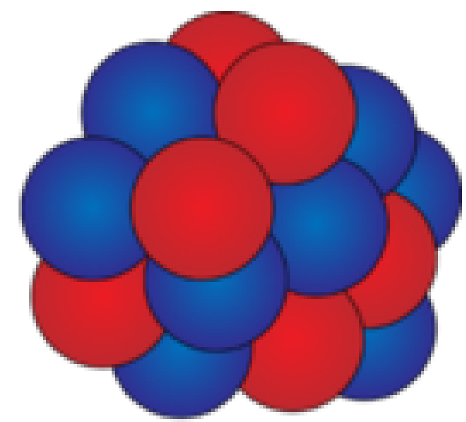


Mass%

Ele-ment	Atom %	Captures	Gamma dose	Recoil dose
H	62	86%	82%	2%
C	12	0.2%	0.4%	0%
N	1.1	9%	1.7%	98%
O	24	0.0%	0.1%	0%
Cl	0.02	3.4%	12%	0%

$^{14}N(n,p)$

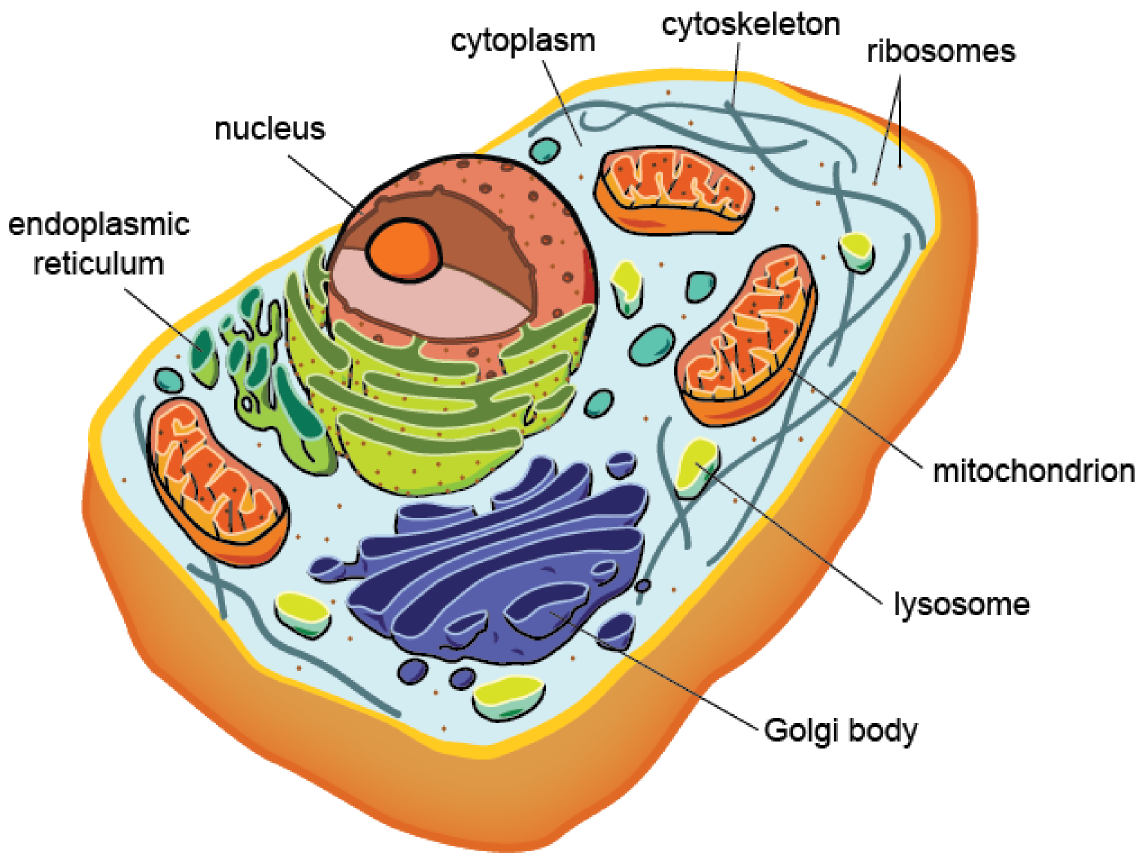




p
12 μm
12 keV/μm

^{14}C
0.25 μm
170 keV/μm

Microscopic nitrogen distribution?



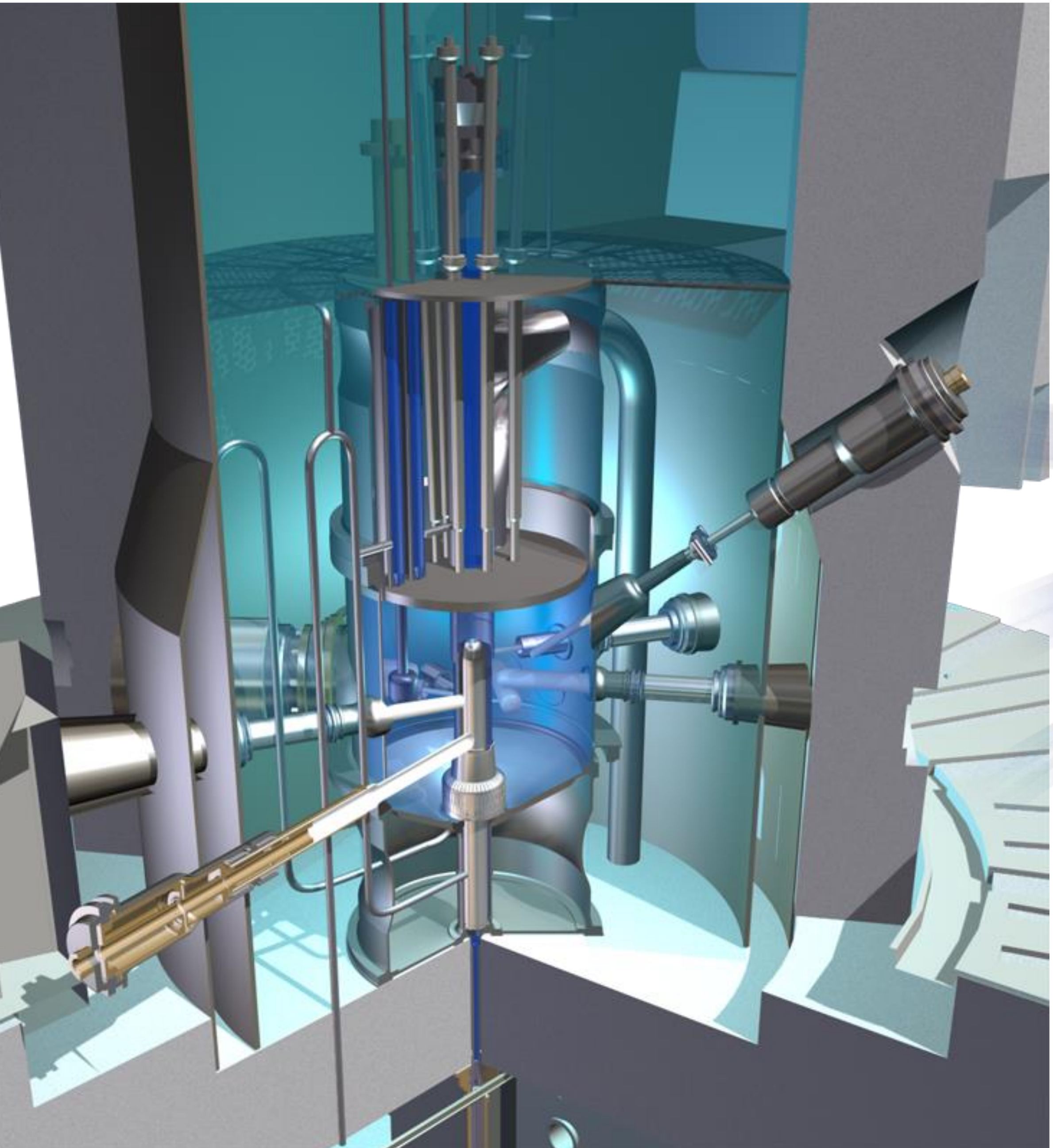
Nucleobases

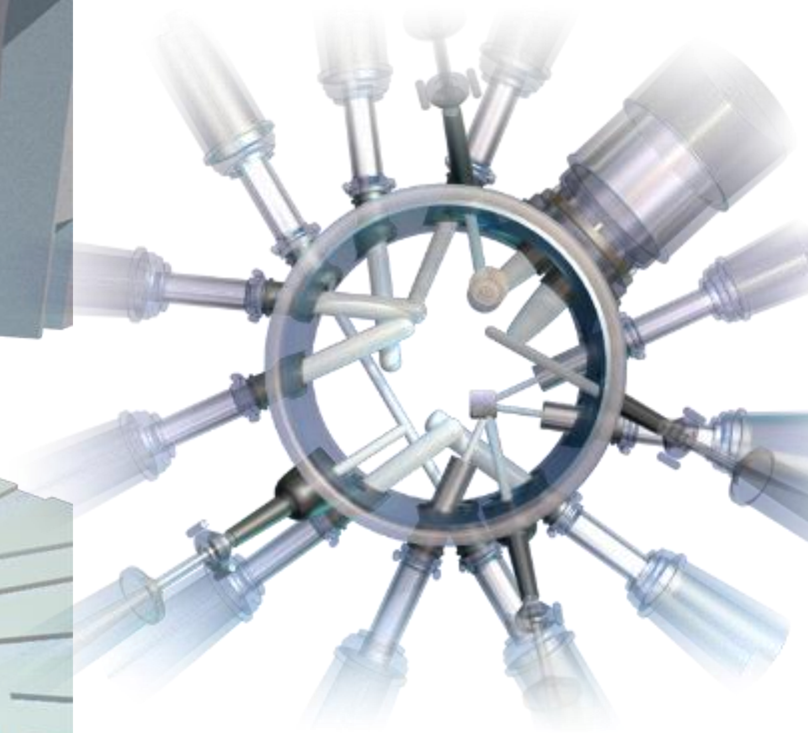
Element	Atom %	Captures	Recoil dose
H	36	15%	0%
C	32	0%	0%
N	35	85%	100%
O	7	0%	0%

N 14	N 15
99.636	0.364
σ 0.080 $\sigma_{n,p}$ 1.93	σ 2.4 E-5

H 1	H 2
99.9885	0.0115
σ 0.332	σ 0.00051

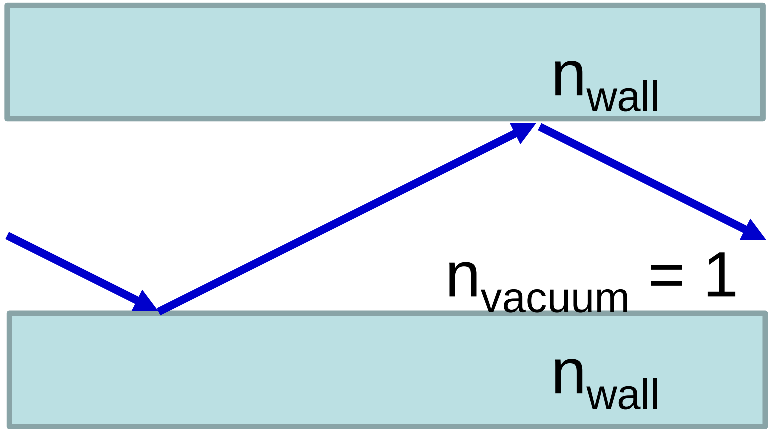
The ILL Reactor

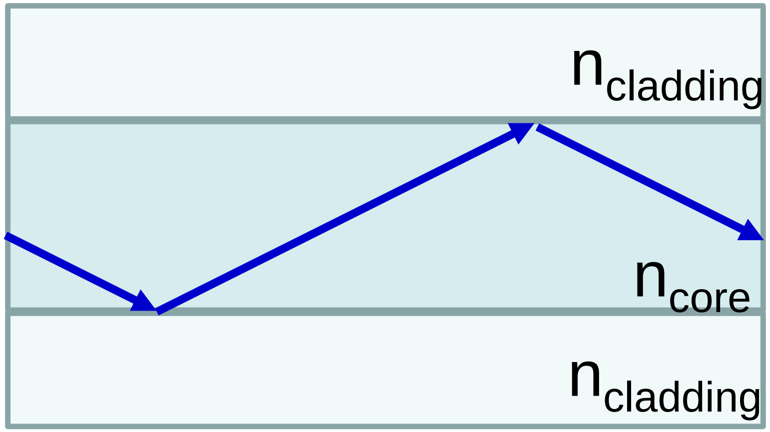




$5 \cdot 10^{18}$ neutrons/s generated at 57 MW

Neutron guides vs. light guides





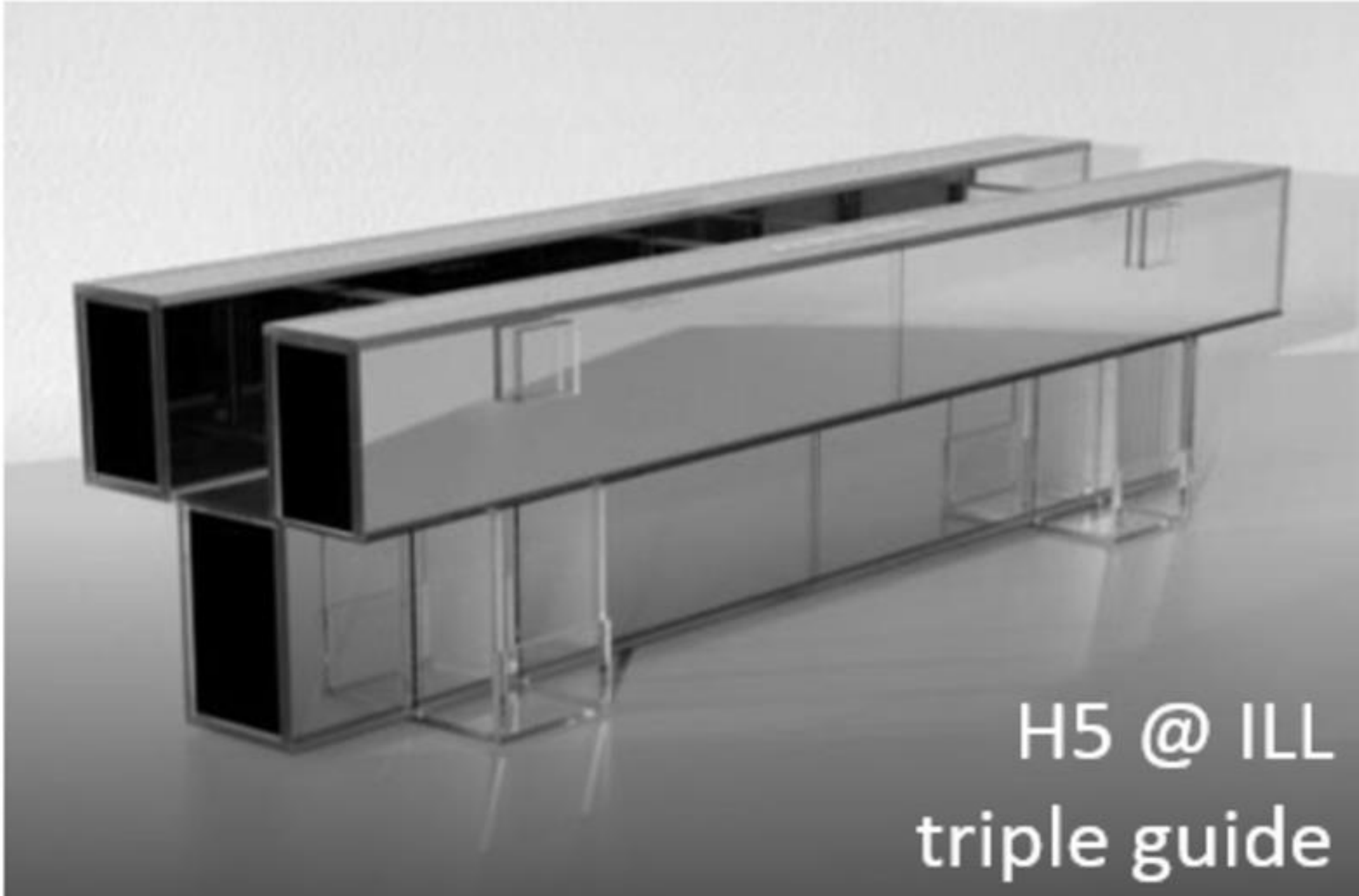
Neutron guide:

$n_{wall} < n_{vacuum} = 1$

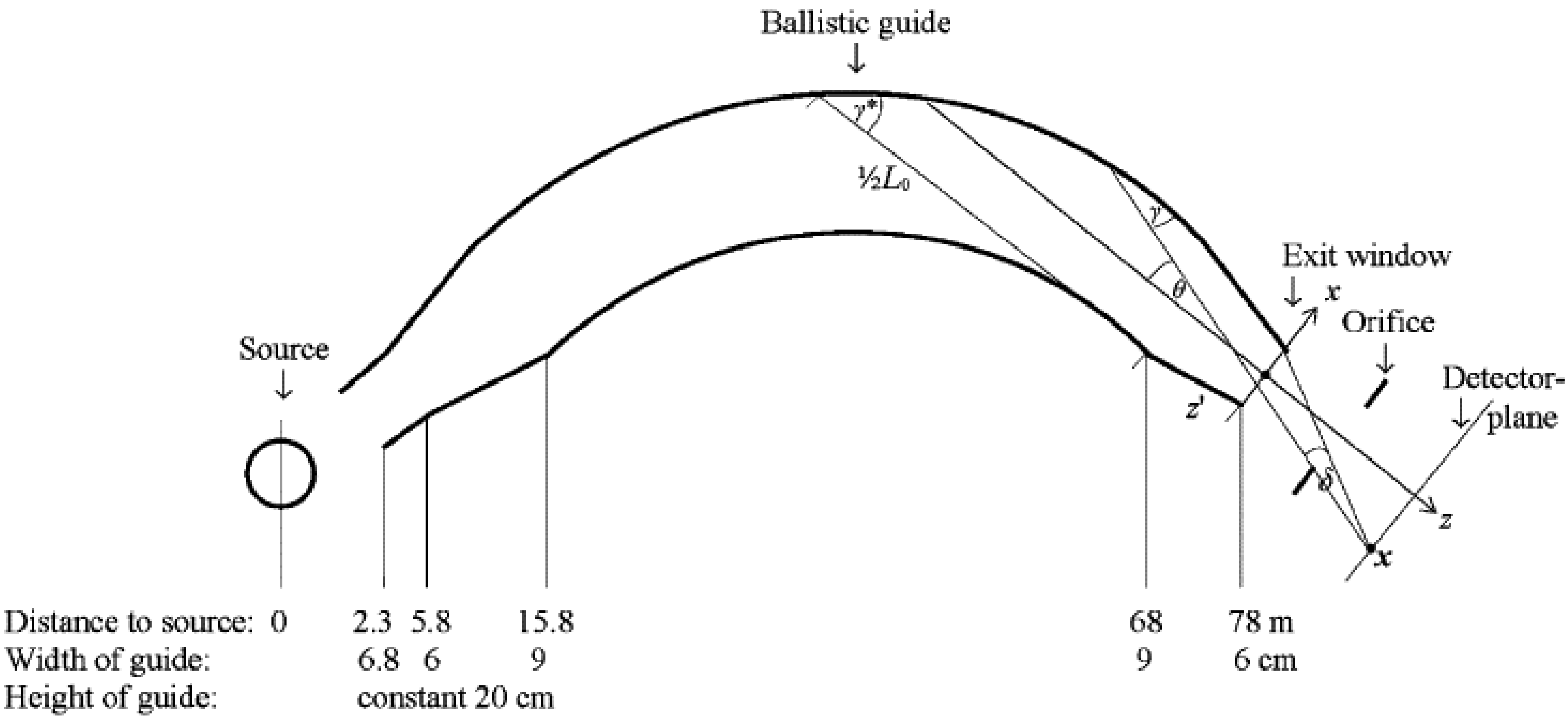
Light guide:

$n_{core} > n_{cladding} > 1$

Neutron guides: coated with Ni or multilayer



Guided neutron beams are “clean”

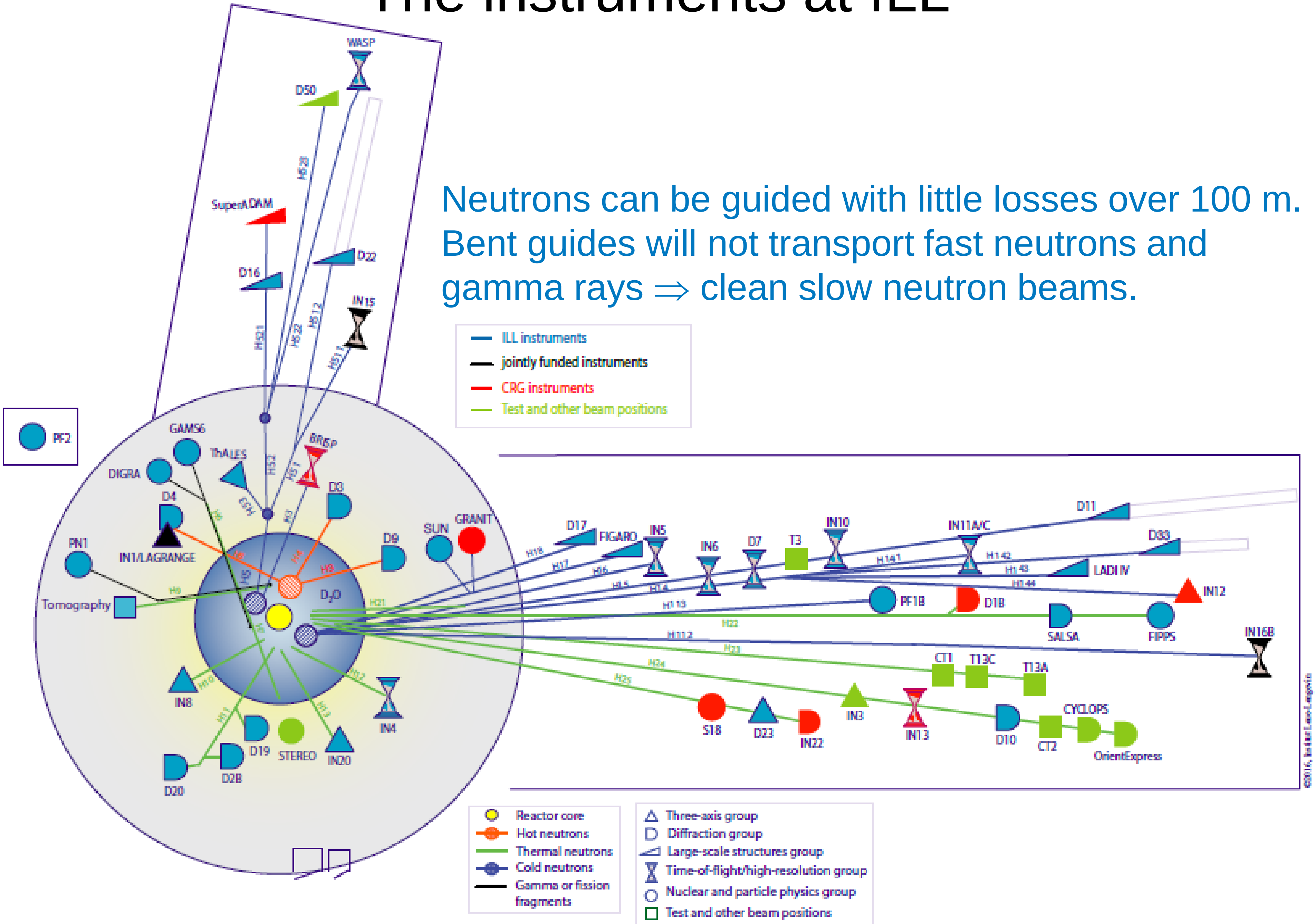


Fast neutrons and gamma rays are not transported.

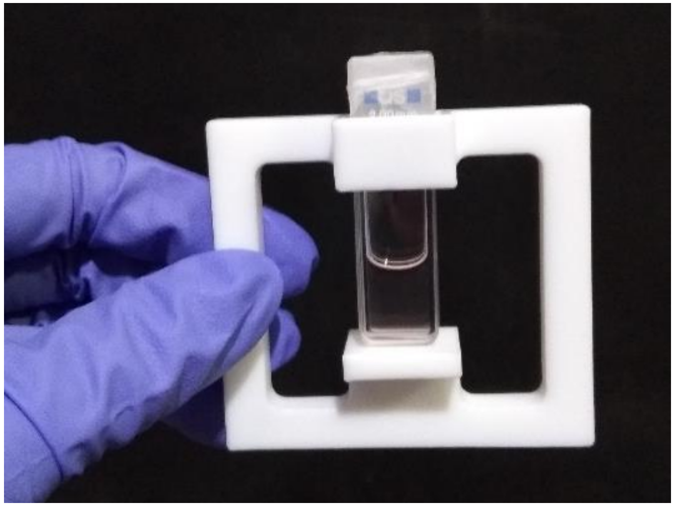
H. Abele et al. Nucl. Instr. Meth. A562 (2006) 407.

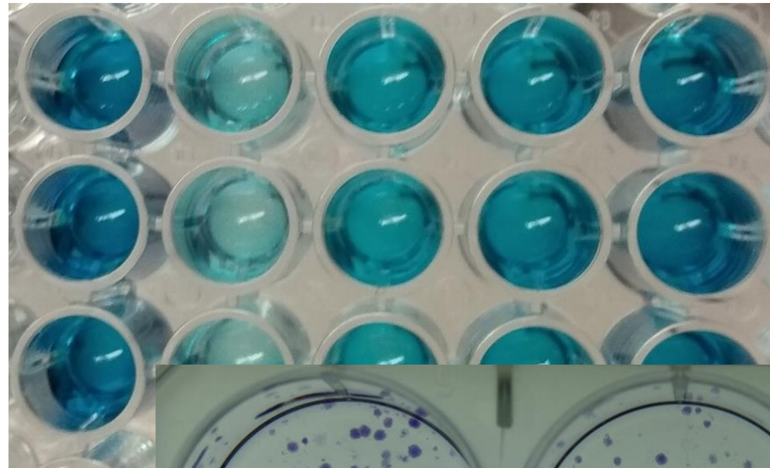
The instruments at ILL

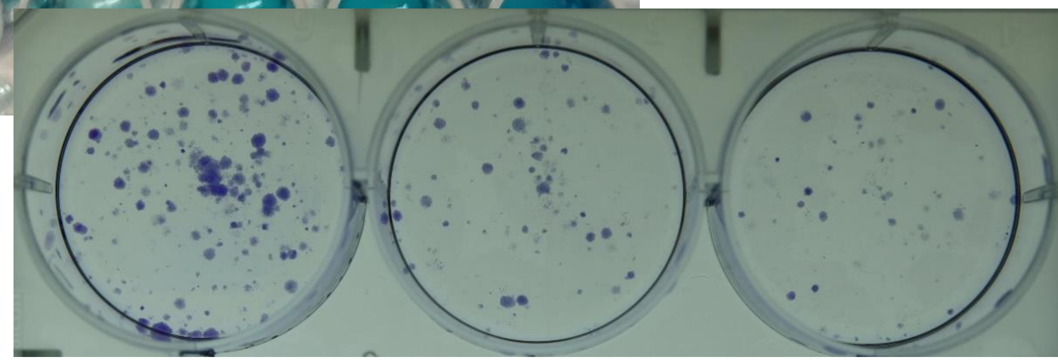
Neutrons can be guided with little losses over 100 m. Bent guides will not transport fast neutrons and gamma rays ⇒ clean slow neutron beams.

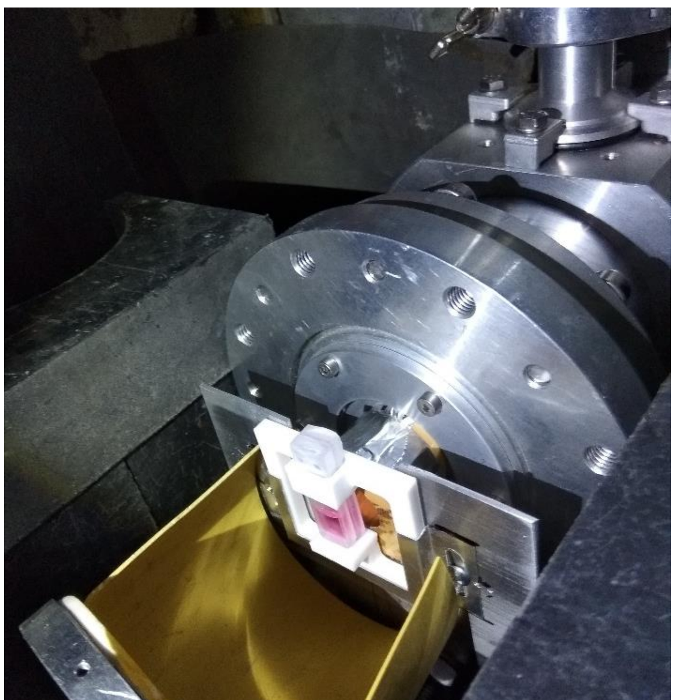


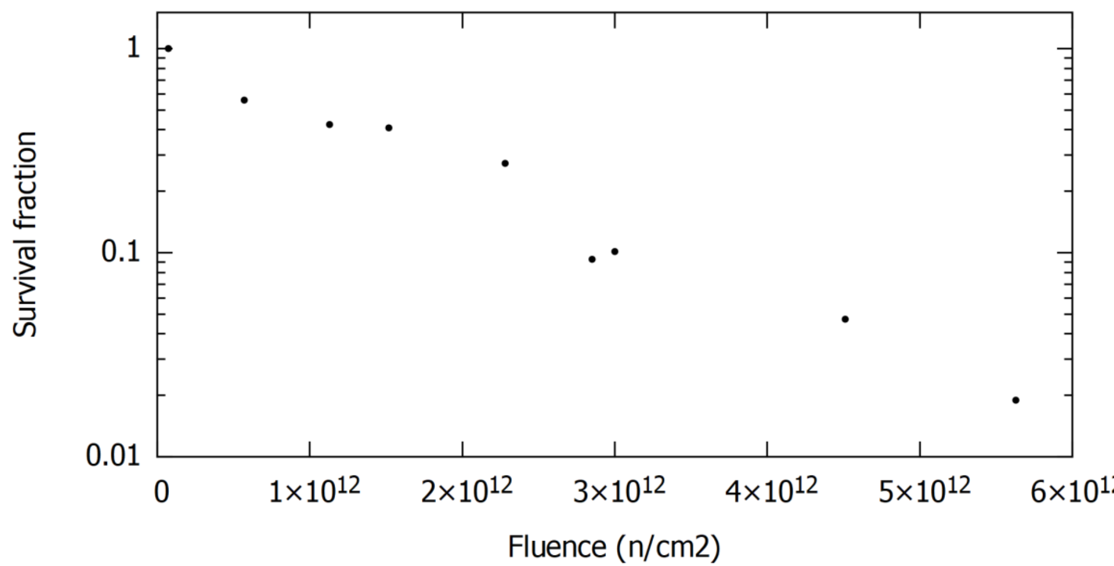
Experimental method validated



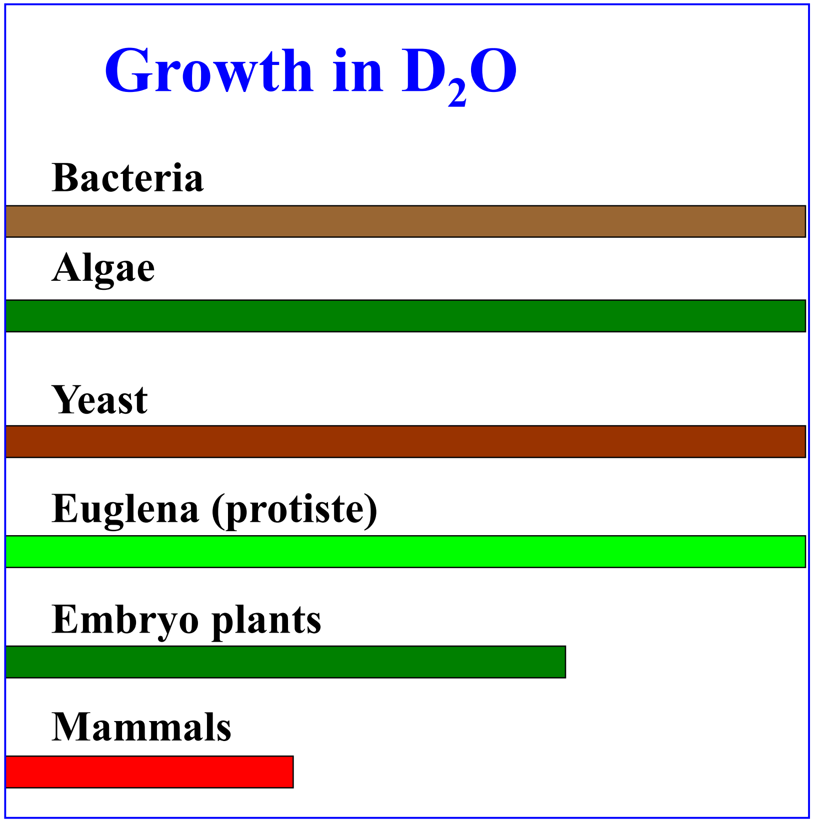






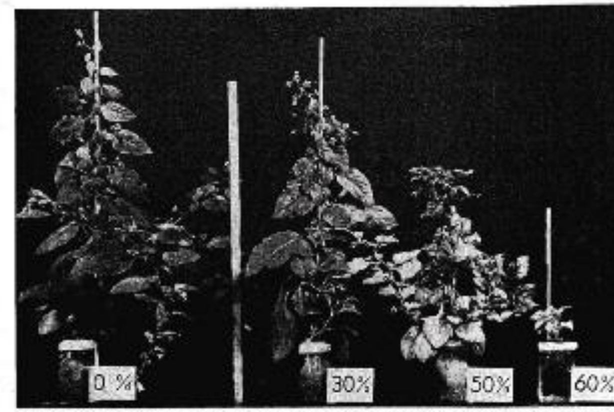


ILL's Deuteration Laboratory



ATOM % D

Katz and Crespi (1970)



...nts of *Atropa belladonna* grown hydroponically in nutrient solutions con-
...reasing concentrations of D_2O. [Uphaus *et al.* (29)]

N 14	N 15
99.636	0.364
σ 0.080 $\sigma_{n,p}$ 1.93	σ 2.4 E-5

T. Forsyth,
M. Haertlein, ILL.

The difficulty of NCT dosimetry

$$D_{BNCT} = RBE_B \times [^{10}B] \times D_B + D\gamma\ beam + D\gamma\ capt. + $$
$$+ RBE_{fast} \times D_{fast} + RBE_{epi} \times D_{epi} + RBE_{th} \times D_{th}$$

RBE factors are derived for a given cell type, dose, dose rate and end point.

Thermal or cold beam from neutron guide:

$$D_{BNCT} = RBE_B \times [^{10}B] \times D_B + D\gamma\ beam + D\gamma\ capt. +$$
$$+ RBE_{th} \times D_{th}$$

Thermal or cold beam from neutron guide, single cell layer:

$$D_{BNCT} = RBE_B \times [^{10}B] \times D_B + D\gamma\ beam + D\gamma\ capt. +$$
$$+ RBE_{th} \times D_{th}$$

Deuterated cells or ^{15}N enriched cells:

$$D_{th} = RBE_H \times D_H + RBE_N \times D_N$$