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

Maria Pedrosa¹,², Ignacio Porras², Javier Praena², M. José Ruiz-Magaña², M. Carmen Ruiz-Ruiz², Trevor Forsyth¹, Ulli Köster¹

¹ Institut Laue-Langevin
² Universidad de Granada
The chart of nuclides

Z
proton number

82
50
28
20
8
2

n 1
10.23 m

β⁻ 0.782

H 3
H 2
0.0115

σ 0.00051

He 4
He 3
He
4.002602

σ < 6E-6

σ < 0.05

σ

σ_n,p
0.00005
5330

He 1
99.9885

H 1
99.9885

σ 0.332

2

1
[1.00784; 1.00811]

28
20
8
2

neutron number N

126
Boron Neutron Capture Therapy

\[ \text{Li-7:} \ 6\% \ 1.01 \text{ MeV} - 94\% \ 0.84 \text{ MeV} \]

\[ \text{B-10:} \ 0.477 \text{ MeV Gamma} \ (94\%) \]

\[ \text{alpha:} \ 6\% \ 1.78 \text{ MeV} - 94\% \ 1.47 \text{ MeV} \]
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

[Diagram showing effects of different types of radiation on DNA, with annotations for beta (-), Auger electron (-), and alpha (+++) particles.]
Comparison of therapies

External beam radiotherapy
- X-ray/gamma
- protons
- carbon ions

Radionuclide therapy (intravenous)
- beta emitter
- alpha emitter

LET / RBE

physical localisation

biological localisation

BNCT
Comparison of therapies

- External beam radiotherapy
  - X-ray/gamma
  - protons
  - carbon ions
  - LET / RBE

- Radionuclide therapy (locoregional)
  - beta emitter
  - alpha emitter
  - BNCT

physical localisation

biological localisation
Glioblastoma multiforme
Clinical results

Survival curves of Japanese patients

Glioblastoma:
- Without BNCT
- With BNCT

Follow-up/month
Survival %

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

Recurrent head and neck cancer:
- Without BNCT
- With BNCT

Follow-up/month
Survival %

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

Which boron concentration is required?

Tolerable neutron fluence: \(< 2 \cdot 10^{13} \text{ cm}^{-2}\)

Probability that one \(^{10}\text{B}\) 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 \(^{10}\text{B}\) atoms per cell to assure >1 capture/cell:
\[
>> 10^7
\]
\[
>>10 \text{ million boron atoms per cell}!
\]

Boron concentration in tumor \(\approx 30 \text{ ppm}\)

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

Only metabolic targeting, no receptor targeting!

Tumor/blood ratio: \(\approx 3\)
Boron delivery agents

Until now:
- BPA

\[
\text{BPA} = \text{HO-B-CH}_{2}-\text{CH}_{2}-\text{CH}_{2}-\text{CH}-\text{COOH}
\]

- BSH

\[
\text{BSH} = \text{Na}_{2}\text{B}_{12}\text{H}_{11}\text{SH}
\]

New:
- boron-rich dendrimers with porphyrin nucleus
- Nanoencapsulation of carboranes
- Nanogels
- 10 B atoms in each carborane cage
Which neutron energy is required?
Which neutron energy is required?

![Graph showing neutron flux versus distance from water surface for different neutron energies.]

- 0.5 meV
- 10 meV
- 1 eV
- 10 keV
- 1 MeV
- 100 MeV

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 $^7\text{Li}(p,n)$ or $^9\text{Be}(p,n)$ reactions
• Challenging targetry ($\approx 10$ mA >2 MeV protons)
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

<table>
<thead>
<tr>
<th>Particle</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>3627</td>
</tr>
<tr>
<td>Electron</td>
<td>1113</td>
</tr>
<tr>
<td>Alpha</td>
<td>1346</td>
</tr>
<tr>
<td>Proton</td>
<td>666</td>
</tr>
<tr>
<td>Carbon ions</td>
<td>263</td>
</tr>
<tr>
<td>Auger</td>
<td>73</td>
</tr>
<tr>
<td>Thermal neutron</td>
<td>68</td>
</tr>
<tr>
<td>Neon</td>
<td>66</td>
</tr>
<tr>
<td>Pion</td>
<td>46</td>
</tr>
</tbody>
</table>
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?

Conversion Coefficients for Radiological Protection Quantities for External Radiation Exposures

Approved by ICRP in October 2010 and adopted by ICRU in November 2010
Neutron RBE

![Graph showing radiation weighting factor $w_R$ vs. neutron energy $E_n$ for different models: ICRP 103, ICRP 60, and U.S. NRC.](image)

- $w_R$ values range from 0 to 25.
- $E_n$ values range from $10^{-6}$ to 1000 MeV.

- ICRP 103 model shows a peak around $0.1$ MeV with a sharp increase followed by a gradual decrease.
- ICRP 60 model has a broader peak compared to ICRP 103.
- U.S. NRC model also peaks around $0.1$ MeV but with a more gradual increase.

The graph illustrates the relative biological effectiveness of neutrons at different energy levels.
Reactions relevant for neutron dosimetry

Fast neutrons (elastic collisions)

\[ ^1\text{H}(n,n')p \]

\[ D_f \]

Gamma emission (capture on hydrogen)

\[ ^1\text{H}(n,\gamma)^2\text{H} \]

\[ D_\gamma \]

Thermal neutrons (capture on nitrogen)

\[ ^{14}\text{N}(n,p)^{14}\text{C} \]

\[ D_t \]

Boron capture

\[ ^{10}\text{B}(n,\alpha)^7\text{Li} \]

\[ D_B \]
**BNCT biological dose**

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

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 (\(\gamma\) 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

<table>
<thead>
<tr>
<th>Component</th>
<th>Rad/MW-min</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>143.0</td>
<td>68.6</td>
</tr>
<tr>
<td>(^{14}\text{N}(n,P)^{14}\text{C})</td>
<td>47.4</td>
<td>22.8</td>
</tr>
<tr>
<td>H</td>
<td>18.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Total</td>
<td>208.4</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**BMRR**
A human as neutron target

<table>
<thead>
<tr>
<th>Element</th>
<th>Atom %</th>
<th>Captures</th>
<th>Gamma dose</th>
<th>Recoil dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>62</td>
<td>86%</td>
<td>82%</td>
<td>2%</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>0.2%</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>N</td>
<td>1.1</td>
<td>9%</td>
<td>1.7%</td>
<td>98%</td>
</tr>
<tr>
<td>O</td>
<td>24</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Cl</td>
<td>0.02</td>
<td>3.4%</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

- $^p$ 12 $\mu$m 12 keV/$\mu$m
- $^{14}\text{C}$ 0.25 $\mu$m 170 keV/$\mu$m
Microscopic nitrogen distribution?

### Nucleobases

<table>
<thead>
<tr>
<th>Element</th>
<th>Atom %</th>
<th>Captures</th>
<th>Recoil dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>36</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>C</td>
<td>32</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>O</td>
<td>7</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

![Cell diagram with labels: nucleus, cytoplasm, cytoskeleton, ribosomes, endoplasmic reticulum, mitochondrion, lysosome, Golgi body.]

![N 14: 99.636, sigma 0.080, sigma sub n,p 1.93; N 15: 0.364, sigma 2.4 E-5.]

![H 1: 99.9885, sigma 0.332; H 2: 0.0115, sigma 0.00051.]
The ILL Reactor

5.10^{18} \text{ neutrons/s}
generated at 57 MW
Neutron guides vs. light guides

Neutron guide:
\[ n_{\text{wall}} < n_{\text{vacuum}} = 1 \]

Light guide:
\[ n_{\text{core}} > n_{\text{cladding}} > 1 \]
Neutron guides: coated with Ni or multilayer
Guided neutron beams are “clean”

Fast neutrons and gamma rays are not transported.

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

## Growth in D$_2$O

<table>
<thead>
<tr>
<th>Organism</th>
<th>ATOM % D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>n/a</td>
</tr>
<tr>
<td>Algae</td>
<td>n/a</td>
</tr>
<tr>
<td>Yeast</td>
<td>n/a</td>
</tr>
<tr>
<td>Euglena (protiste)</td>
<td>n/a</td>
</tr>
<tr>
<td>Embryo plants</td>
<td>n/a</td>
</tr>
<tr>
<td>Mammals</td>
<td>n/a</td>
</tr>
</tbody>
</table>

### ATOM % D

Katz and Crespi (1970)

T. Forsyth, M. Haertlein, ILL.
The difficulty of NCT dosimetry

$$D_{BNCT} = \text{RBE}_B \times [^{10}\text{B}] \times D_B + D_\gamma \text{beam} + D_\gamma \text{capt.} +$$
$$+ \text{RBE}_{\text{fast}} \times D_{\text{fast}} + \text{RBE}_{\text{epi}} \times D_{\text{epi}} + \text{RBE}_{\text{th}} \times D_{\text{th}}$$

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

Thermal or cold beam from neutron guide:

$$D_{BNCT} = \text{RBE}_B \times [^{10}\text{B}] \times D_B + D_\gamma \text{beam} + D_\gamma \text{capt.} +$$
$$+ \text{RBE}_{\text{th}} \times D_{\text{th}}$$

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

$$D_{BNCT} = \text{RBE}_B \times [^{10}\text{B}] \times D_B + D_\gamma \text{beam} + D_\gamma \text{capt.} +$$
$$+ \text{RBE}_{\text{th}} \times D_{\text{th}}$$

*Deuterated* cells or $^{15}\text{N}$ enriched cells:

$$D_{\text{th}} = \text{RBE}_H \times D_H + \text{RBE}_N \times D_N$$