Challenges in the Boron Neutron Capture Therapy

Michał Silarski
Jagiellonian University

- Introduction
- Neutron sources for BNCT
- Boron carriers
- Dose and boron distribution monitoring
- Gadolinium Neutron Capture Therapy
- Summary

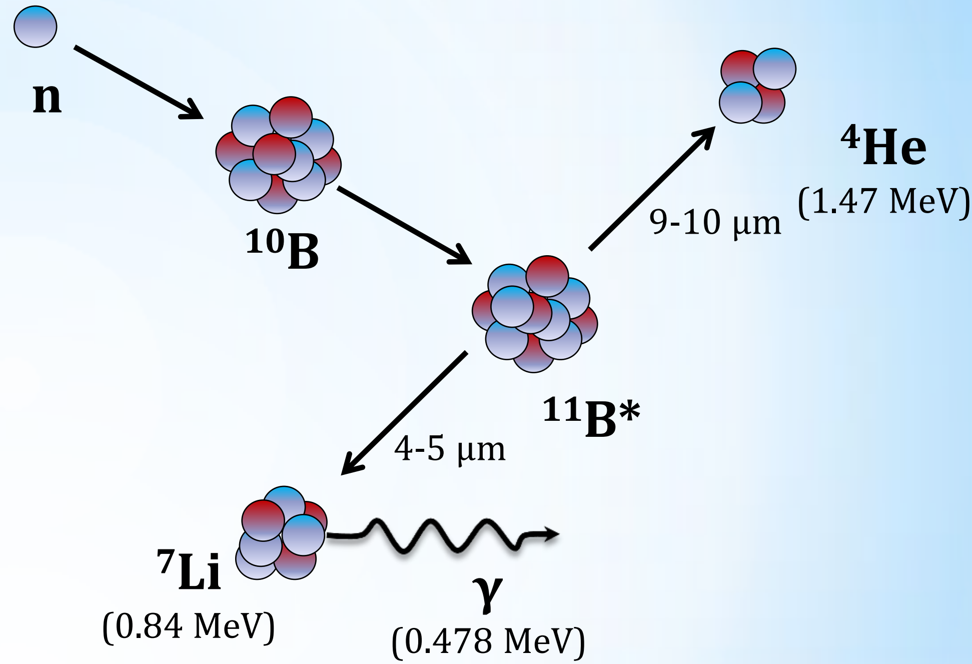
Narodowe Centrum Badań i Rozwoju

3rd Jagiellonian Symposium on Fundamental and Applied Subatomic Physics
Kraków, 23-28 June 2019

SABAT
Stoichiometry Analysis By Activation Techniques

Introduction

- Therapy used against highly malignant and therapeutically resistant tumors:
  - gliobastoma multiforme)
  - malignant melanoma
  - head and neck recurrent cancers
  - Malignant pleural mesothelioma
- Irradiation with (epi)thermal neutrons
- ^{10}B transfered selectively to the tumor cells
- High LET within a single cell



http://www.jsnct.jp/e/index.html; Kawasaki Medical School

Introduction

❖ So far only ^{10}B and Gd were considered as „targets” for NCT

$^{10}B(n,\alpha)^{7}Li$ $^{14}N(n,p)^{14}C$ p recoil $^{1}H(n,\gamma)^{2}H$

$$D_{tot} = CBE_B D_B + 3.2D_n + 3.2D_H + D_\gamma$$

Compound Biological Effectiveness

Relative Biological Effectiveness

❖ The in-air neutron beam recommendations by the International Atomic Energy Agency:

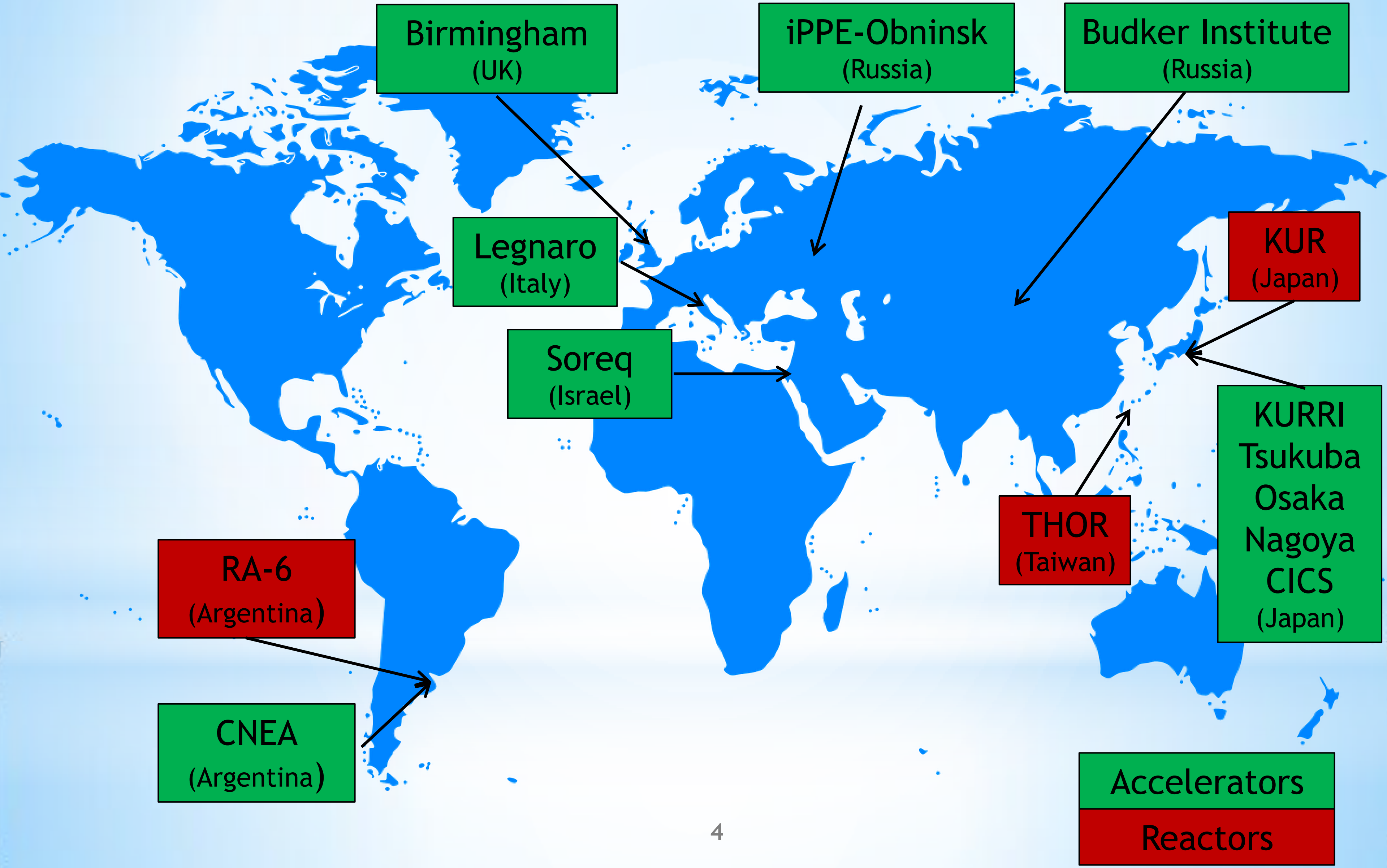
Parameter	Recommendations
Φ_{epi} (0.1 eV <E_n<10 keV) [$cm^{-2}s^{-1}$]	>10^9
Φ_{epi} /$\Phi_{thermal}$	> 20
Φ_{epi} /Φ_{fast}	>100
D_{fast}/Φ_{epi} [Gy cm^2]	< $2*10^{-13}$
D_γ/Φ_{epi} [Gy cm^2]	< $2*10^{-13}$

Nuclide	Reaction	σ [b]
^{3}He	(n,p)	5333
^{6}Li	(n,α)	940
^{10}B	**(n,α)**	**9835**
^{113}Cd	(n,γ)	20600
^{135}Xe	(n,γ)	2720000
^{149}Sm	(n,γ)	42080
^{151}Eu	(n,γ)	9200
^{155}Gd	**(n,γ)**	**61100**
^{157}Gd	**(n,γ)**	**259000**
^{147}Hf	(n,γ)	561
^{199}Hg	(n,γ)	2150

(Wolfgang A.G. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa „Neutron capture therapy”, Springer)

H. Naeem et al., Journal of the Korean Physical Society, 70 (2017) 816

BNCT facilities around the world (2016)



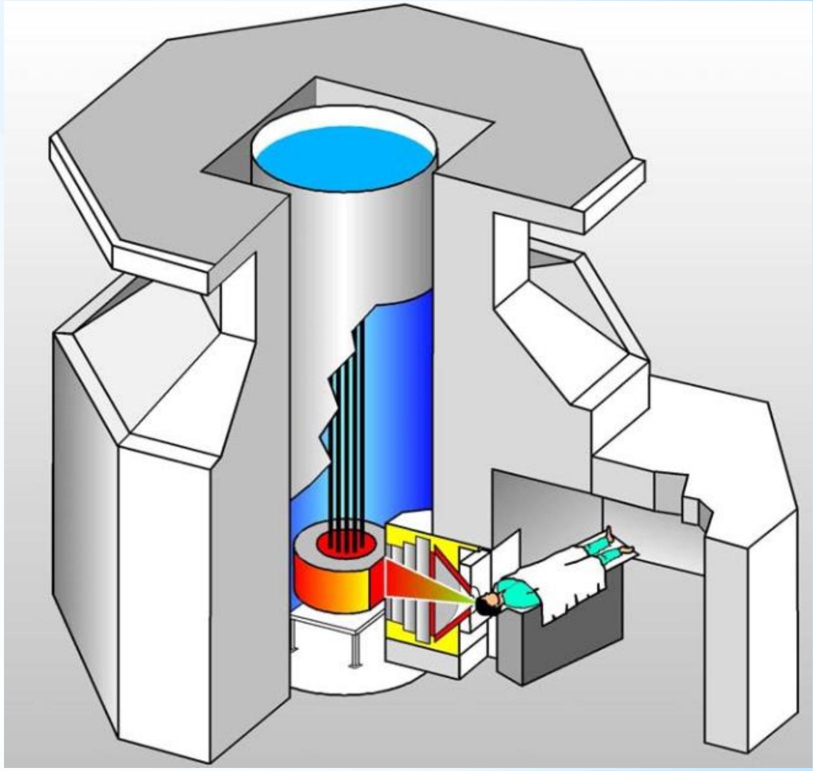
Neutron sources for BNCT

- **Reactors**
  - High neutron flux (e.g. Maria: ~10^{14} $cm^{-2}s$)
  - Expensive and complex
  - low public acceptability
  - require complicated licensing procedures

Reactor BNCT beams

core neutrons (fast→epithermal)

fission converter (thermal→ epithermal)

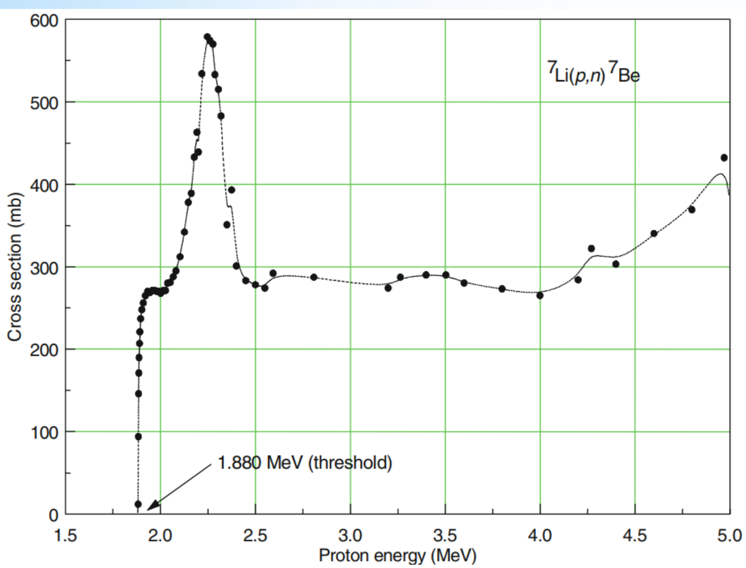


- **Isotopic sources (e.g. Sb-Be, Am-Be)**
  - High activities needed (orders of magnitude higher than therapeutic gamma sources)
  - Cannot be switchched off
  - Never used, simulations showed feasibility of such therapy [M. Golshanian et al., Nucl. Inst. Meth. A 835 (2016) 182]

Neutron sources for BNCT

- **Accelerator sources**
  - Expensive
  - Require a lot of space
  - Most popular reactions: $^{7}Li(p,n)^{7}Be$ and $^{9}Be(p,n)^{9}B$
  - Target cooling problems for high proton intensity

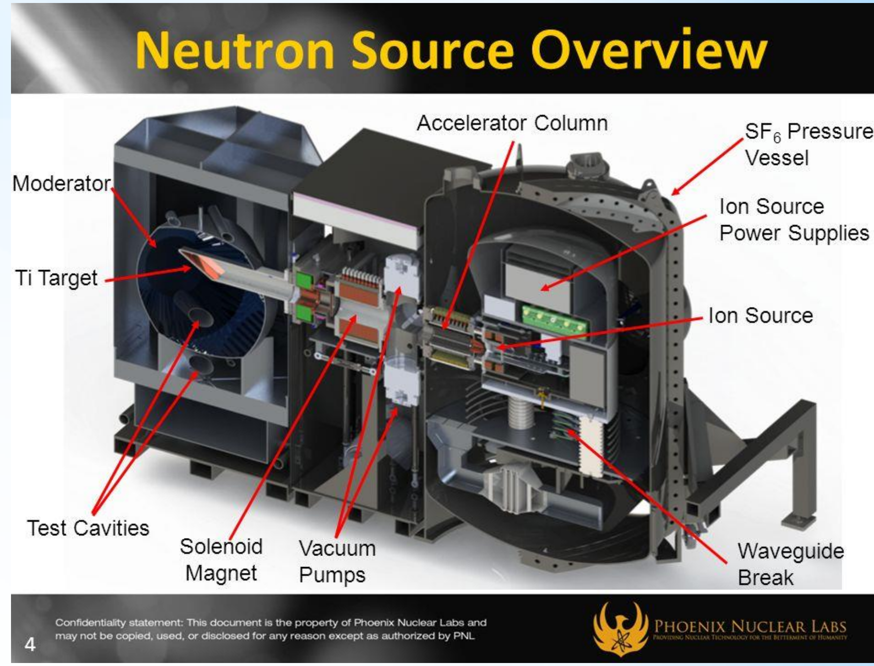
Reaction	E_{th} (MeV)	E_{in} (MeV)	Total production (n/mA s)	Fraction E_n<1 MeV (%)	$E_{n,max}$ (keV)	$E_{n,min}$ (keV)
$^{7}Li(p,n)^{7}Be$	1.880	1.880	0	100	30	30
		1.890	6.3×10^{9}	100	67	0.2
		2.500	9.3×10^{11a}	100	787	60
		2.800	1.4×10^{12b}	92	1,100	395
$^{9}Be(p,n)^{9}B$	2.057	2.057	0	100	20	20
		2.500	3.9×10^{10}	100	574	193
$^{9}Be(d,n)^{10}B$	0	0	0	50	3,962	3,962
		1.500	3.3×10^{11}	50	4,279	3,874
$^{13}C(d,n)^{14}N$	0	0	0	75	4,974	4,964
		1.500	1.9×10^{11}	70	6,772	5,616
$^{12}C(d,n)^{13}N$	0.327	0.327	0	100	4	3
		1.500	6.0×10^{10}	80	1,188	707
$d(d,n)^{3}He$	0	0	0	0	2,451	2,451
		0.120	3.3×10^{8c}	0	2,898	2,123
		0.200	1.1×10^{9}	0	3,054	2,047
$t(d,n)^{4}He$	0	0	0	0	14,050	14,050
		0.150	4.5×10^{10}	0	14,961	13,305

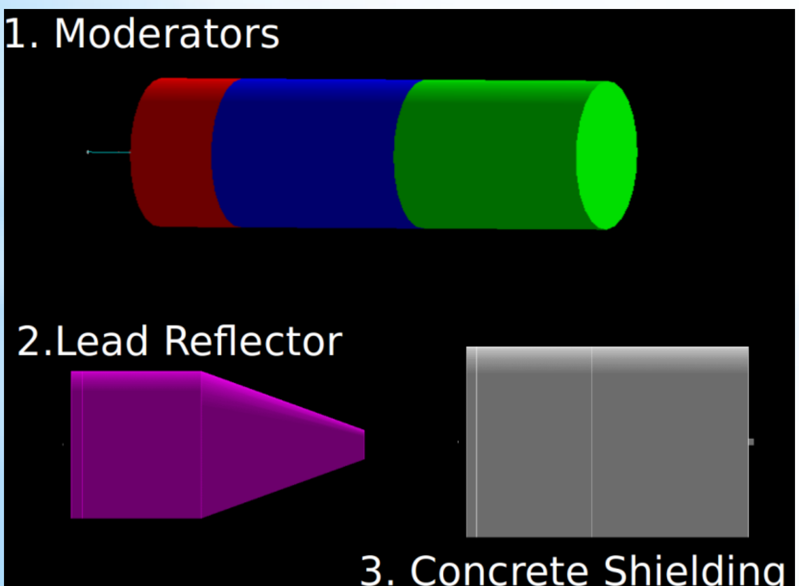


(Wolfgang A.G. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa „Neutron capture therapy", Springer)

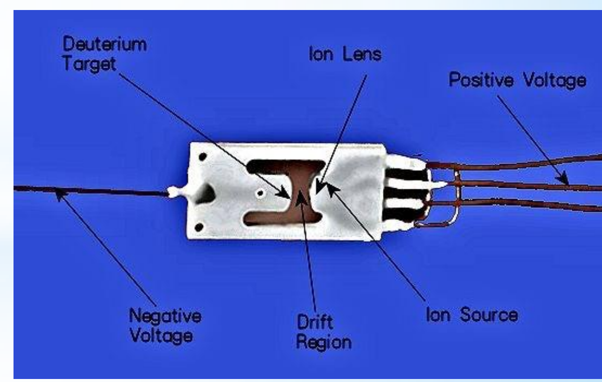
Neutron sources for BNCT

- **Neutron generators: DD or DT**
  - Small size and cost
  - Fast, monochromatic neutrons
  - Max. intensities ~ 10^{11}/s (DD) – 10^{13}(DT) [Phoenix]
  - Never used so far (too low neutron intensities)
- Each of the source need a Beam Shaping Assembly to form the desired epithermal neutron beam





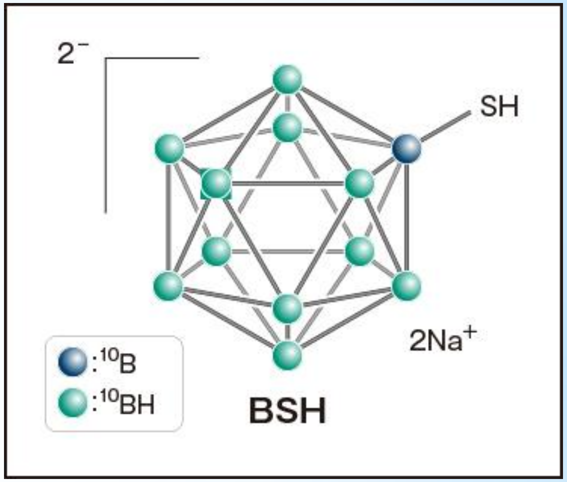
Courtesy of Vahagn Ivanyan



https://newatlas.com/sandia-neutristor-neutron-generator-chip/23856/#gallery

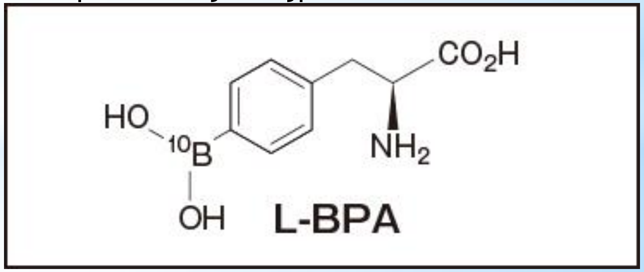
Boron carriers

- Selective accumulation (Tumor/Normal >3) with ^{10}B concentration of 20 to 40 ppm
- Low toxicity
- Not metabolized in the tumor
- No pharmaceutical effects themselves (boron delivery molecule only)



http://www.jsnct.jp/e/about_nct/houso.html

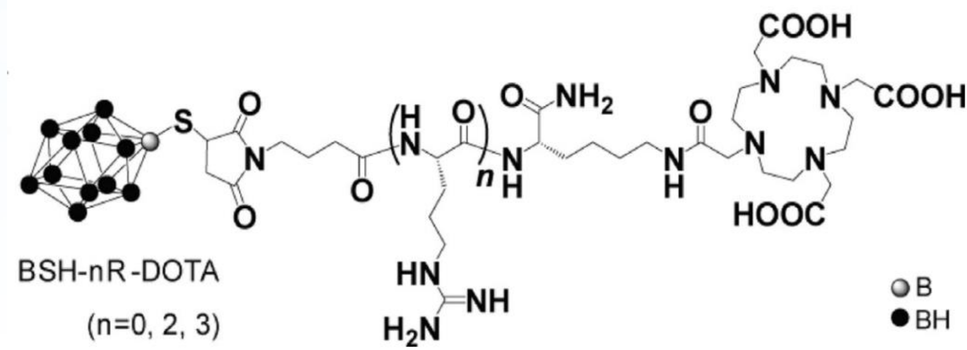
- BSH (disodium mercaptoundecahydrododecaborate)
  - Low accumulation inside tumor cells (it stays in the intercellular spaces)



- L-BPA (L-p-Boronophenylalanine)
  - Administered combined with a water-soluble substance such as D-fructose
  - does not accumulate in slowly proliferating malignant cells

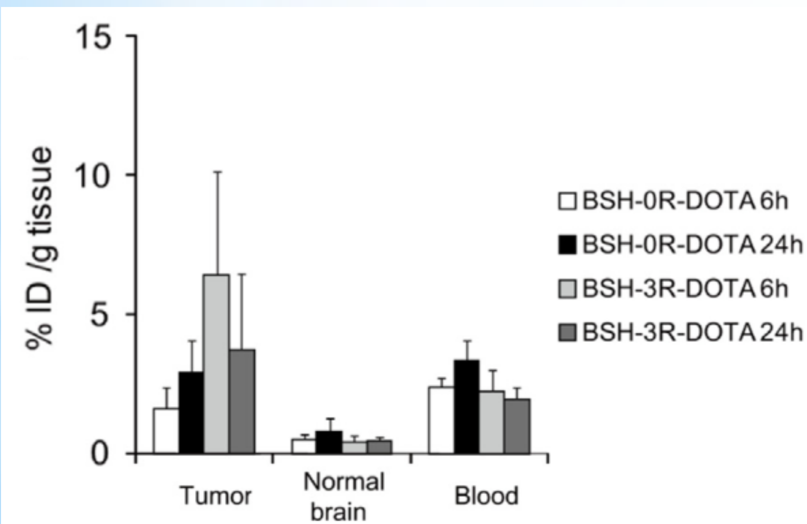
Boron carriers

- Intensive studies are ongoing to increase the tumor selectivity and intracellular delivery of ^{10}B-compounds
  - BSH connected to e.g. protein, peptide, small-interfering RNA…
  - Carborane-bearing pullulan nanogels [R. Kawasaki et al., Biochemical and Biophysical Research Communications 483 (2017) 147]
  - BSH-polymer conjugates, e.g. PEG-b-P(Glu-SS-BSH) [P. Mi et al., Journal of Controlled Release 254 (2017) 1]

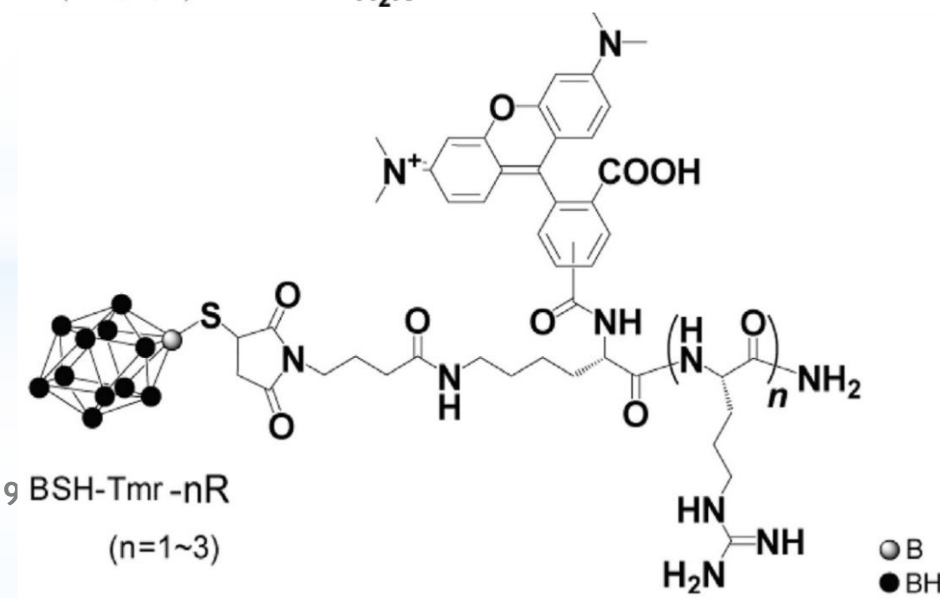


BSH-nR-DOTA

(n=0, 2, 3)



(Iguchi Y. et al. Biomaterials 56 (2015) 10-17)



9 BSH-Tmr -nR

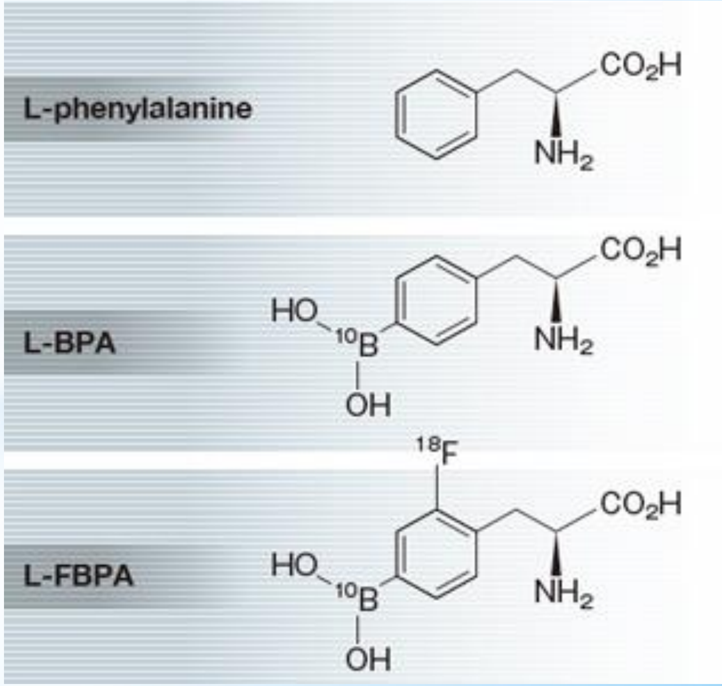
(n=1~3)

Dose and boron distribution monitoring

- **Magnetic Resonance Imaging (MRI)**
  - Non-invasive imaging of boron distribution
  - Sensitive to ^{10}B and ^{11}B isotopes

- **Activation Gamma Radiation Analysis**
  - Gamma quanta due to neutron capture on ^{10}B (E_{γ} = 0.478 MeV)
  - Radiation of tissue activation (H,C,N,…)
  - A fast method that allows in vivo imaging also during therapy

- **Positron Emission Tomography**
  - Boron carrier labeled with β^{+} active element:
  - L-F-Boronophenylalanine [Imahori Y. et al. J Nucl Med. 39 (1998) 325]
  - ^{64}Cu-labeled BSH-3R-DOTA [Y. Iguchi et al., Biomaterials 56 (2015) 10]
  - Non-invasive imaging of boron distribution in the patient's body at each stage of therapy (resolution ~ 4-6 mm)



http://www.jsnct.jp/e/about_nct/pet.html

Alternatives to Boron

- $^{157}Gd(n,\gamma)^{158}Gd$ reaction has 60 times bigger cross section than the capture on ^{10}B

- Easy assessment of the Gd concentration in the tissue to be used in the treatment by MRI

GdNCT = short range contribution (Auger electrons) + long range products (gammas)

- **Efficient therapy demands Gd transfer to the cell nucleus**
  [S. A. Enger et al., Radiation Measurements 59 (2013) 233]

Summary

physicsworld

Magazine | Latest | People

RADIOTHERAPY | RESEARCH UPDATE

Boron neutron capture therapy progresses towards clinical cancer treatments

17 May 2019 Tami Freeman

*BACKUP

Table 1.1 Isotopes with high values of thermal neutron capture cross sections [4–7]

Nuclide	Interaction	Cross section σ_{th} (b)
^{3}He	(n,p)	5,333
^{6}Li	(n,α)	940
^{10}B	(n,α)	3,835
^{113}Cd	(n,γ)	20,600
^{135}Xe[a]	(n,γ)	2,720,000
^{149}Sm	(n,γ)	42,080
^{151}Eu	(n,γ)	9,200
^{155}Gd	(n,γ)	61,100
^{157}Gd	(n,γ)	259,000
^{147}Hf	(n,γ)	561
^{199}Hg	(n,γ)	2,150
^{235}U[a]	(n,f)	681
^{241}Pu[a]	(n,f)	1,380
^{242}Am[a]	(n,f)	8,000

[a]Radioactive

(Wolfgang A.G. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa „Neutron capture therapy", Springer

Pierwiastki emitujące kw. Gamma po wychwycie: efekt biologiczny mniejszy od boru, ale dawka rozłożona bardziej homogenicznie w większych obszarach

- Gadolin daje jeszcze możliwość obrazowania z MRI, ale nie wykazano skuteczności tego obrazowania
- Po pochłonięciu neutronu emituje kwanty gamma o łącznej energii ~8 MeV
- Być może reakcja z litem byłaby dobra, ale przekrój czynny jest sporo mniejszy…