Review of Accelerator-based Boron Neutron Capture Therapy IPAC16

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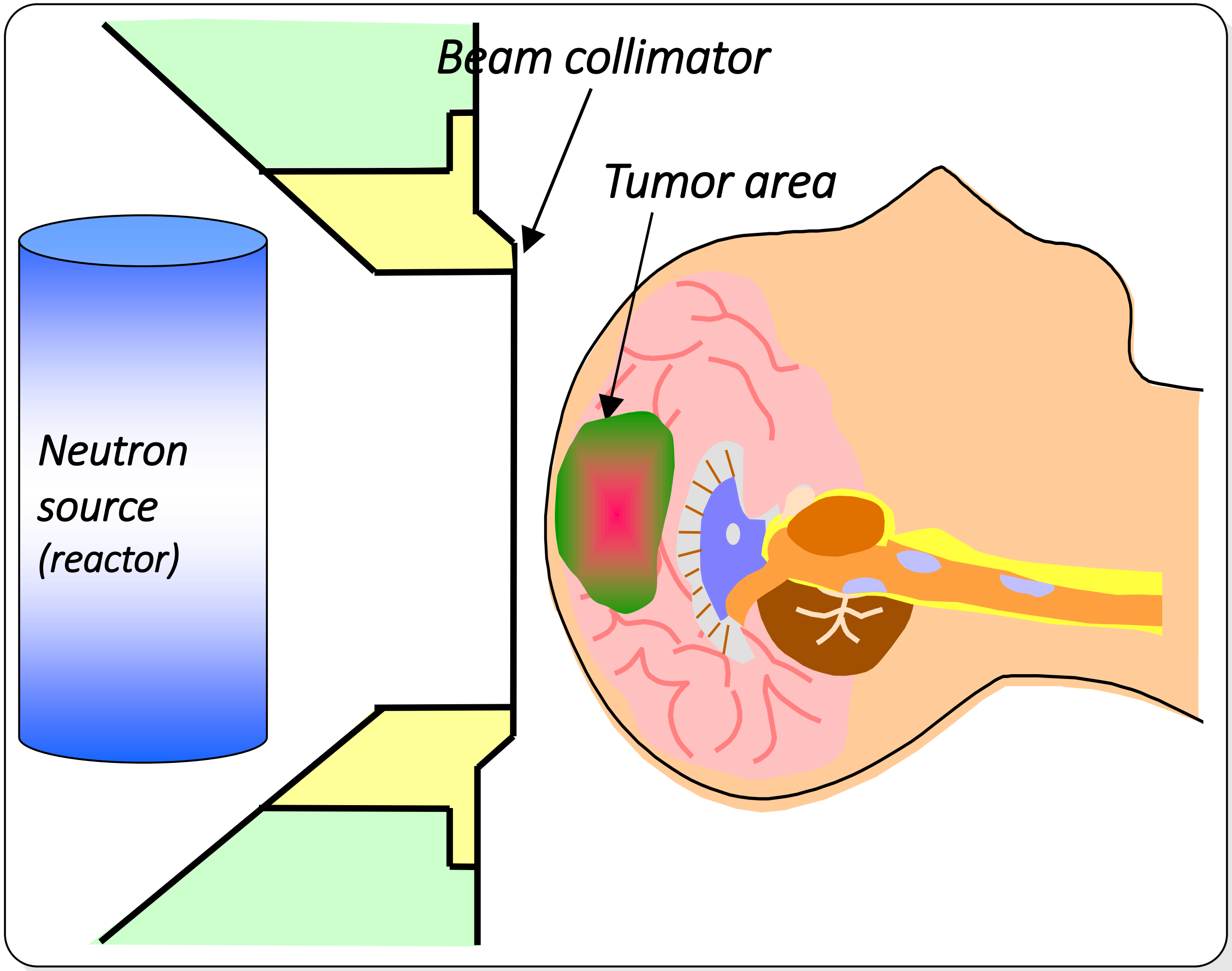
Okinawa Institute of Science and Technology (OIST)

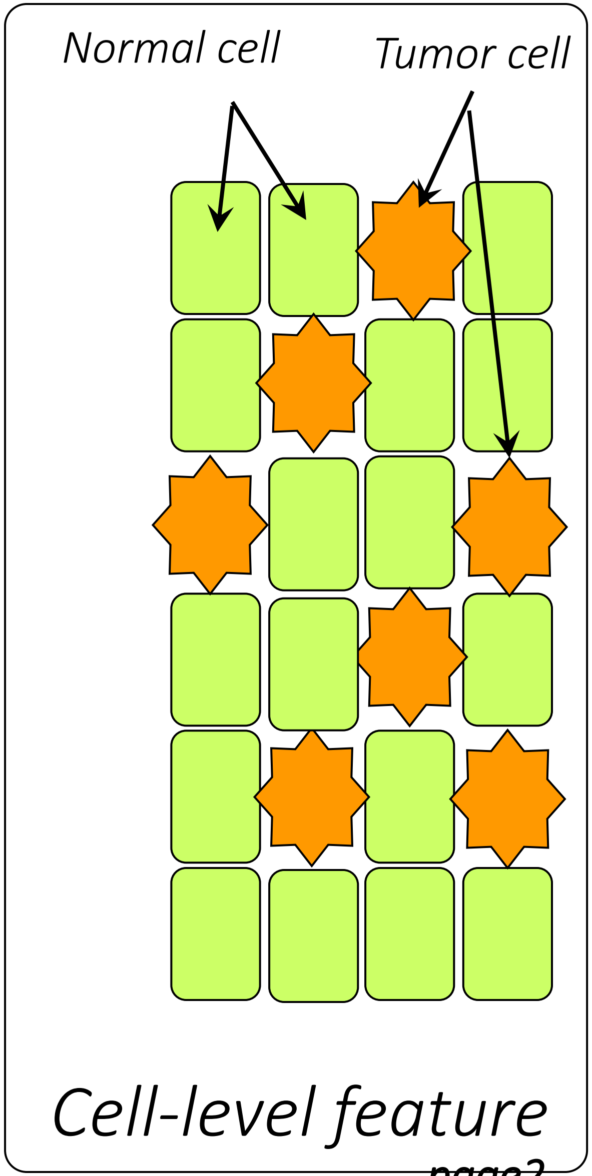
May 12, 2016

OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY GRADUATE UNIVERSITY

Courtesy of H. Kumada

Principle of BNCT





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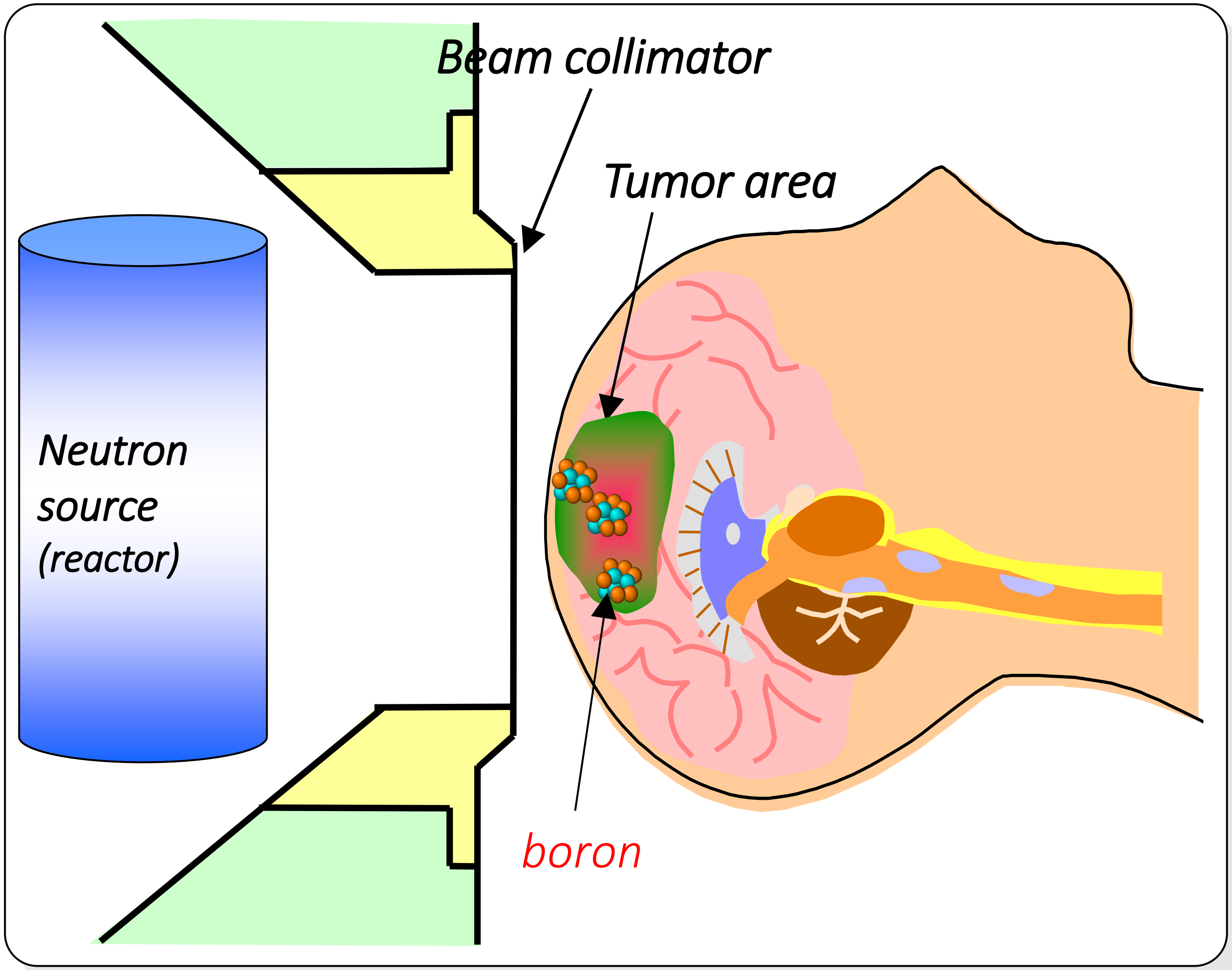
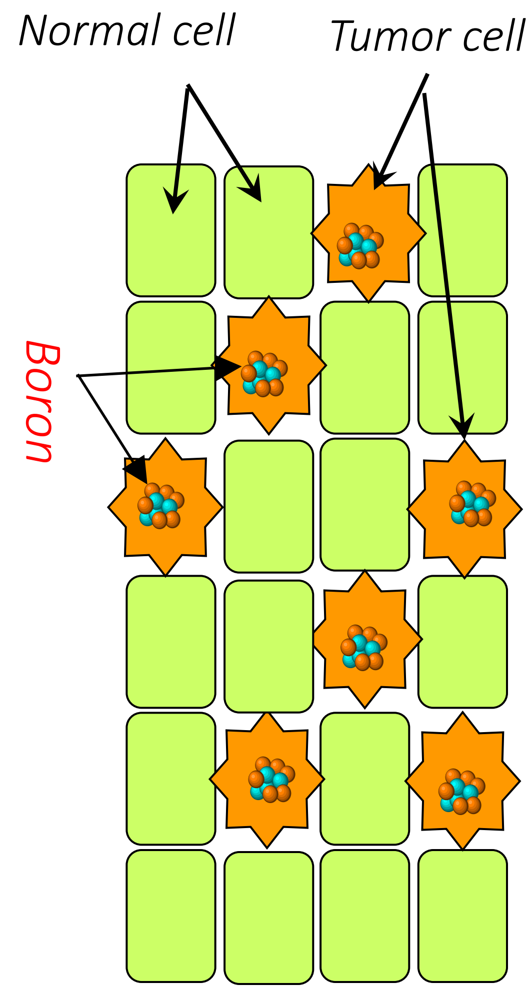


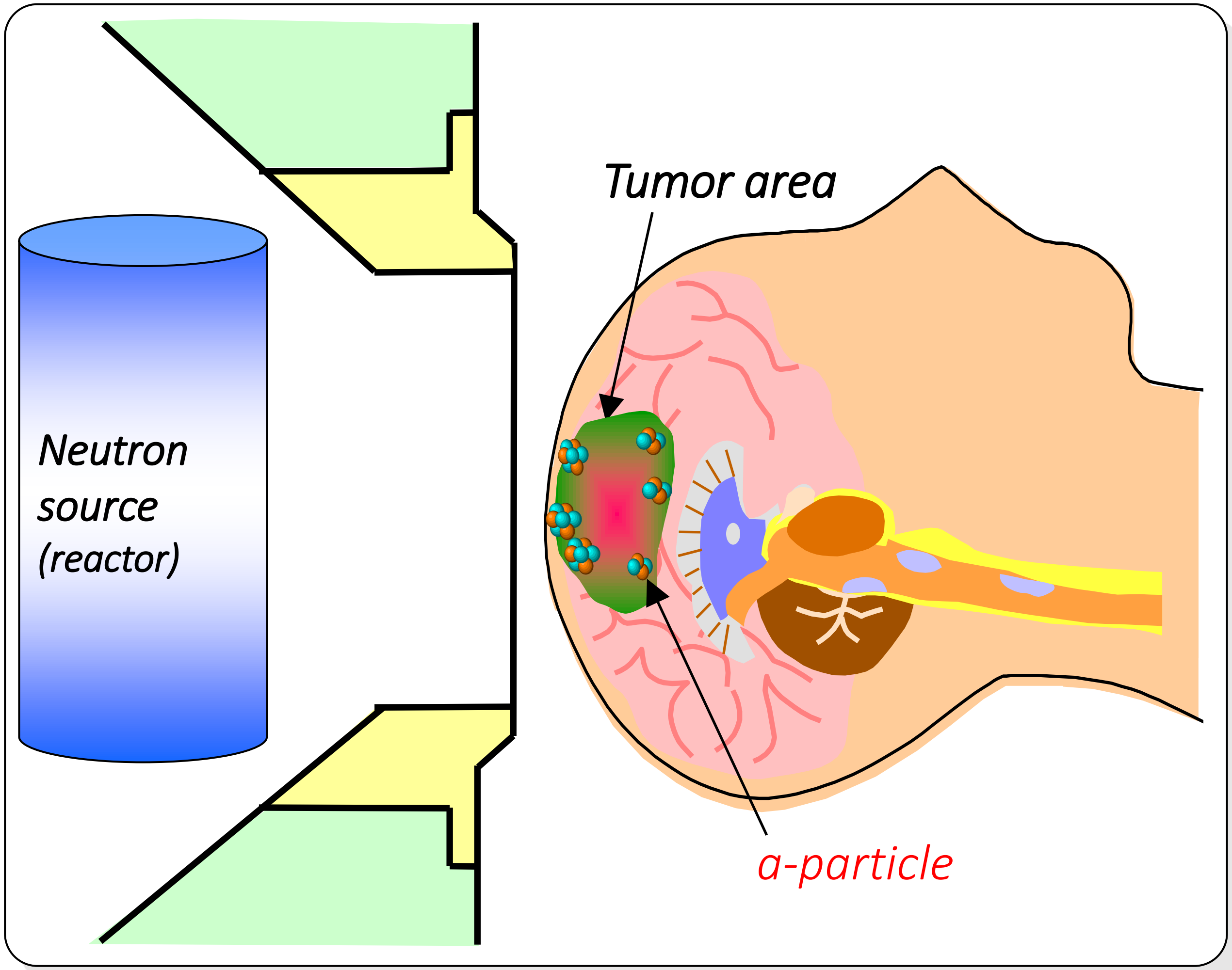
Transfer Boron to tumor cell with selective drug-delivery

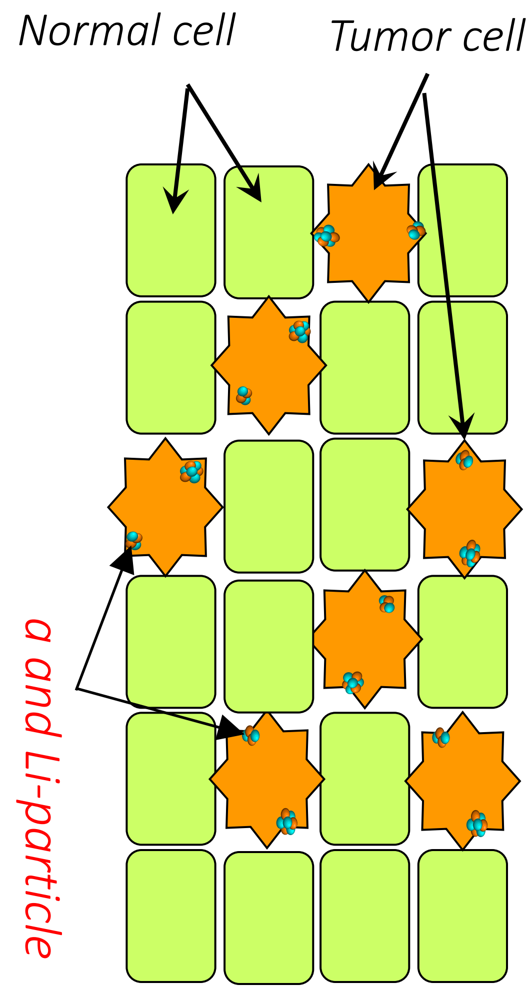


Cell-level feature

Courtesy of H. Kumada

Principle of BNCT



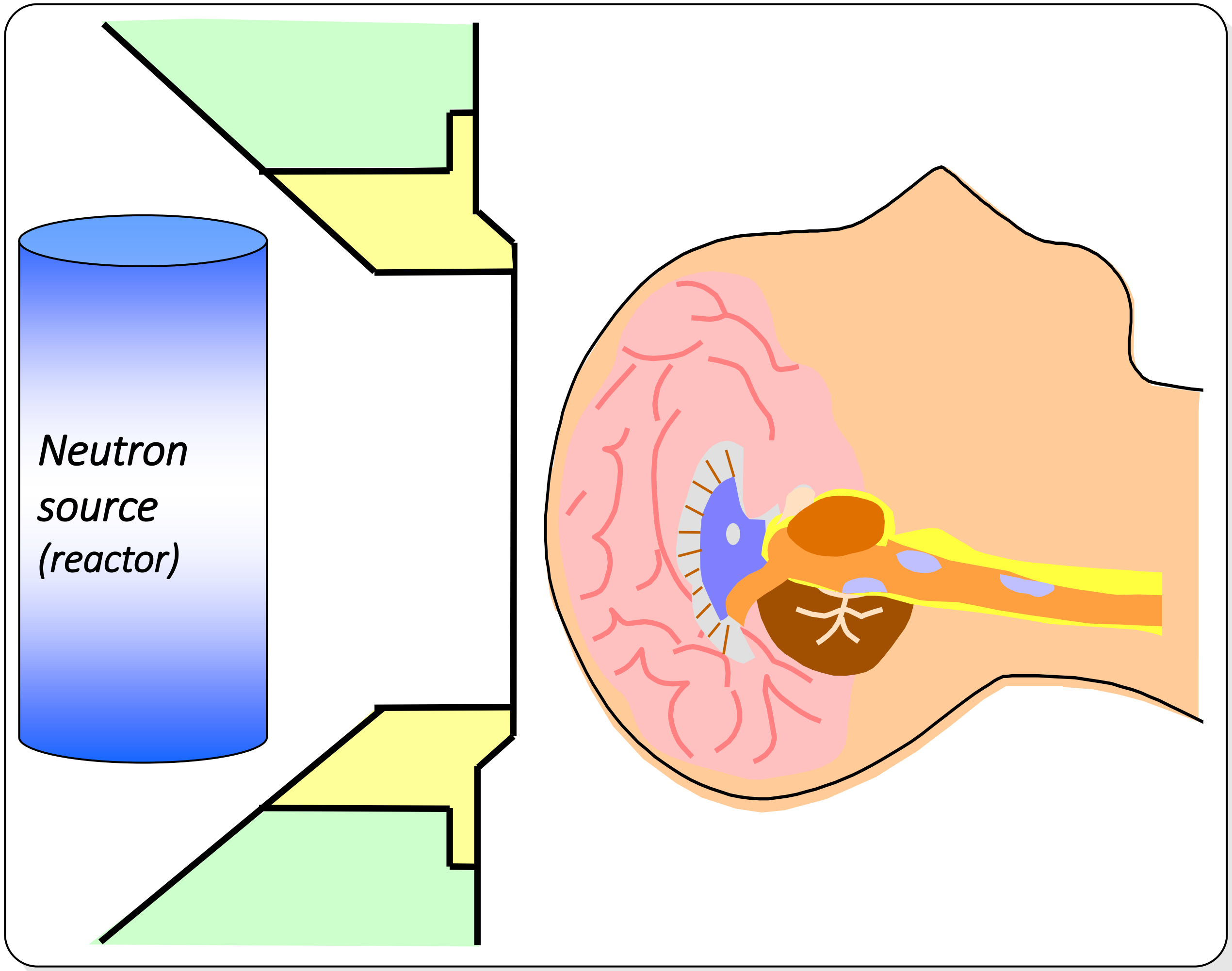


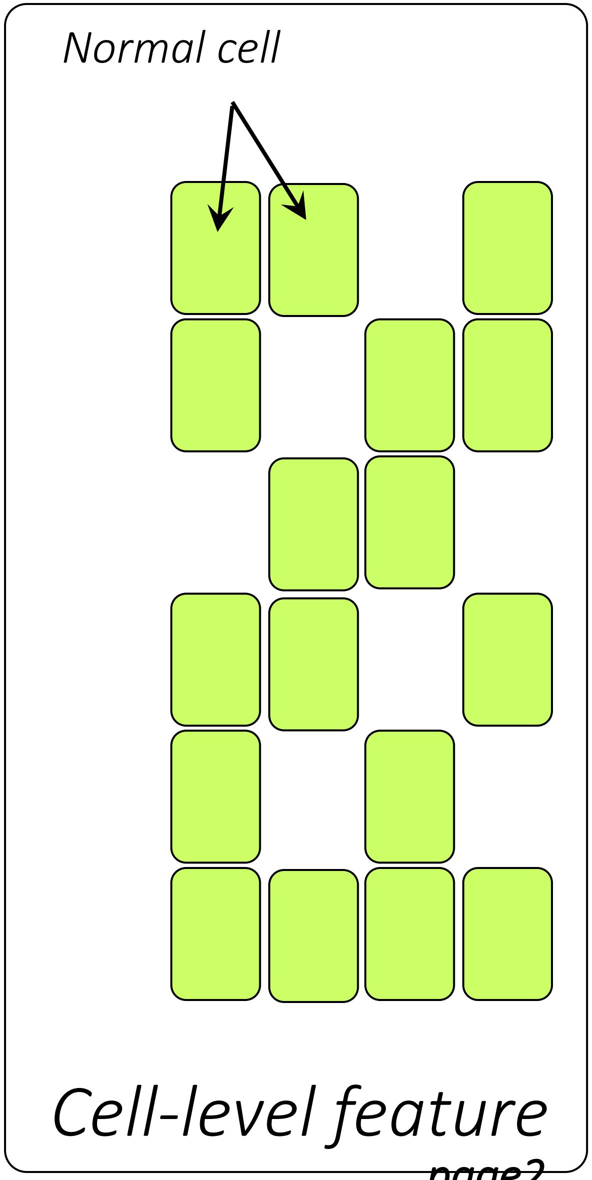
Cell-level feature

Neutron reacts with boron and emits
a-particle

Courtesy of H. Kumada

Principle of BNCT

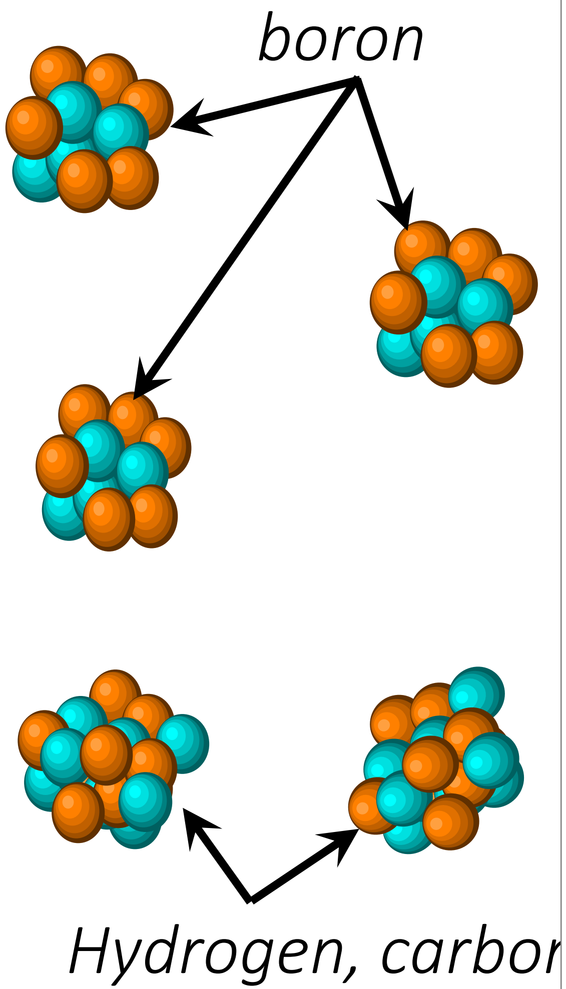


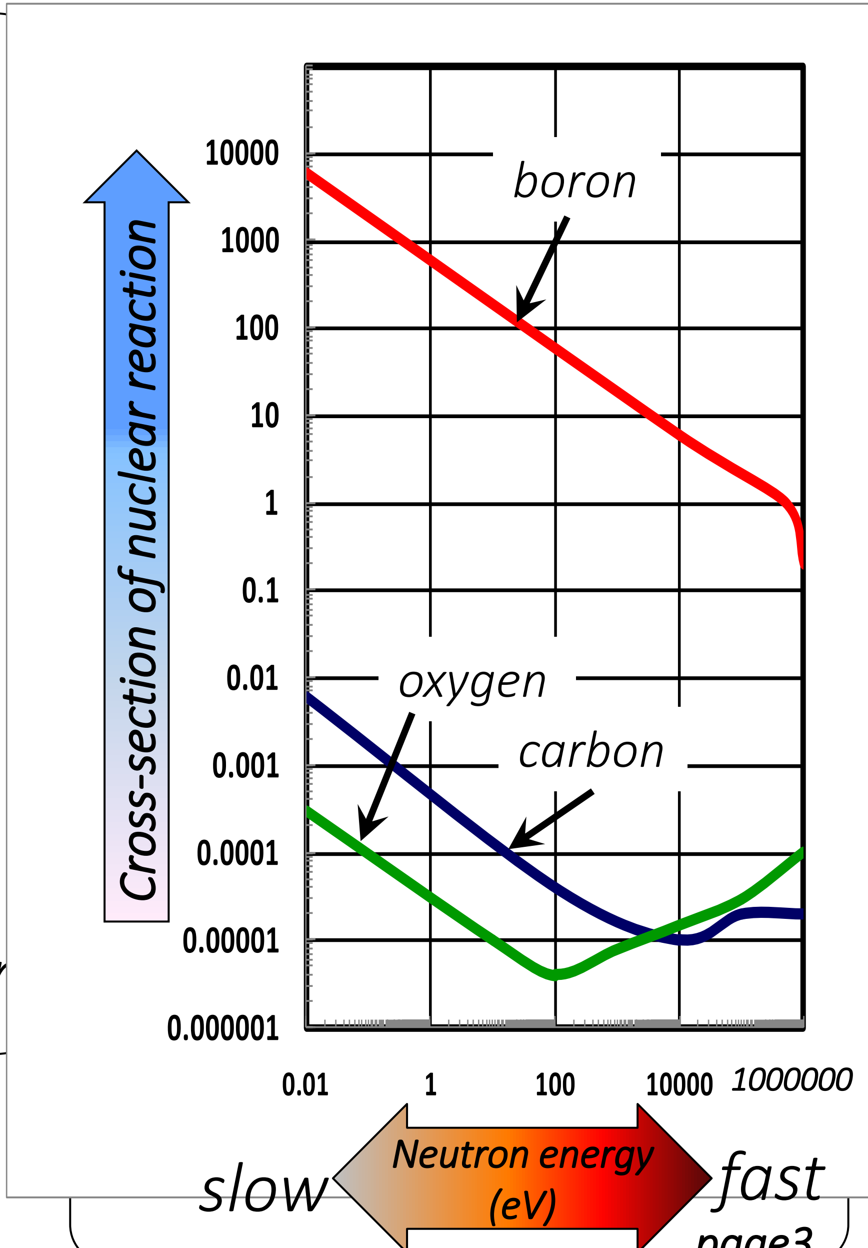


a and Li-particle
kills tumor cell selectively

Only Slow neutron reacts with boron

Courtesy of H. Kumada





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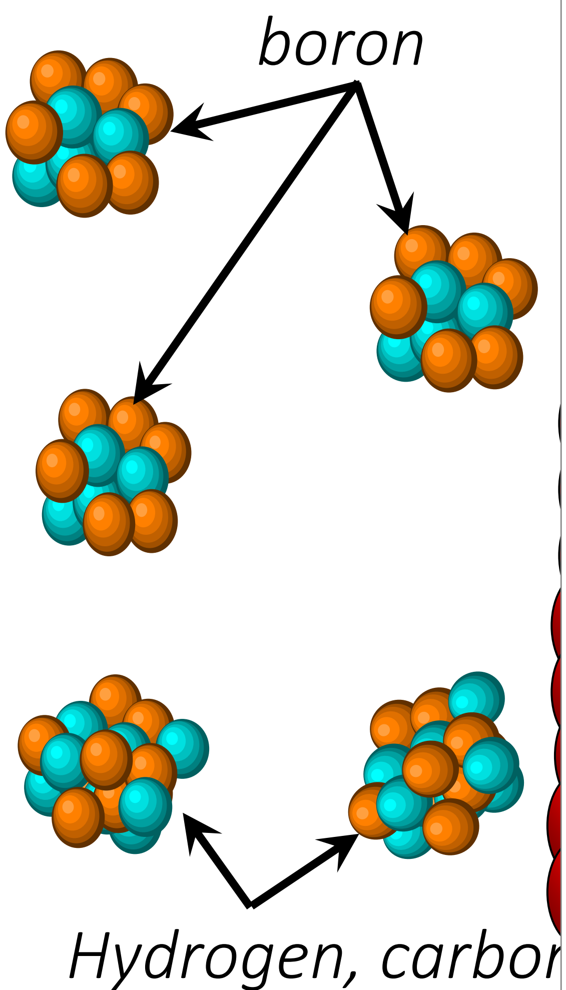
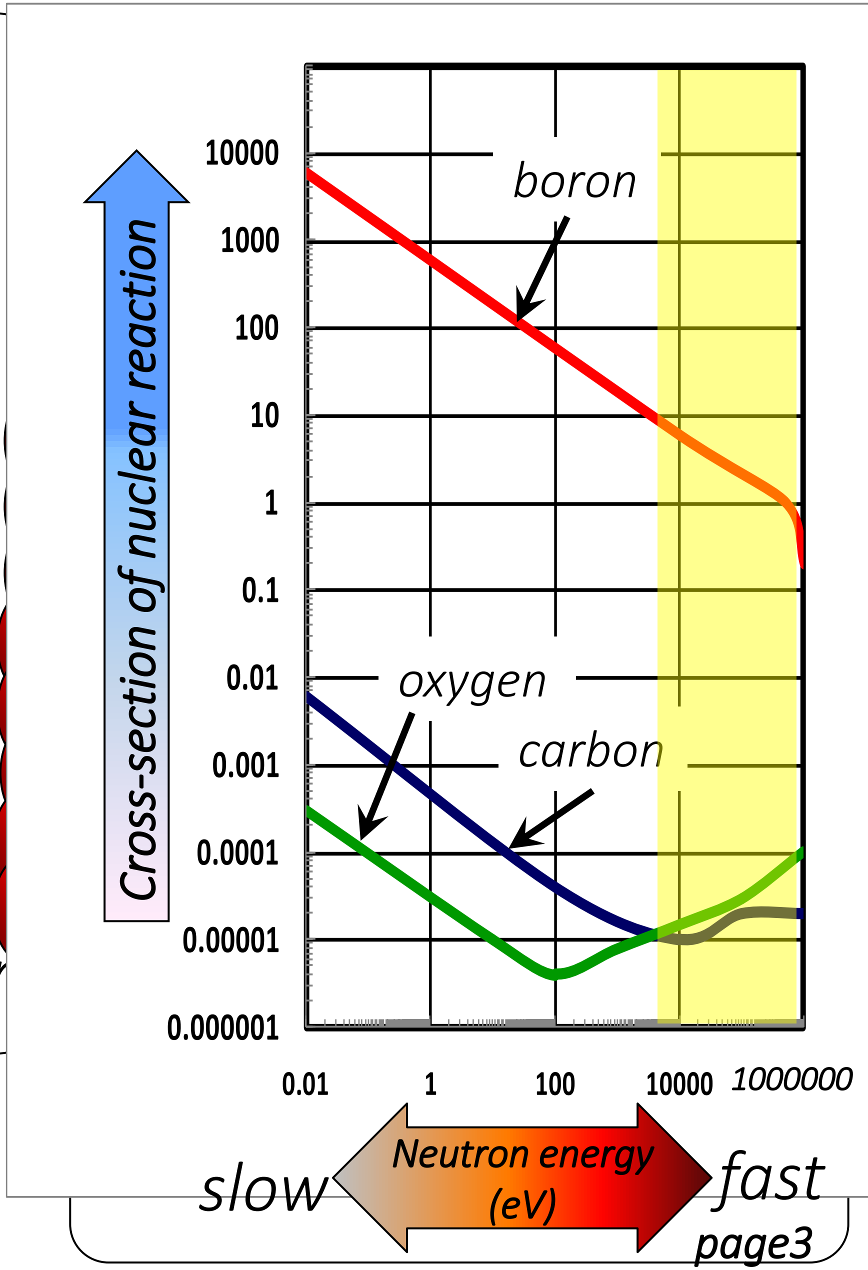


Fast neutron



Only Slow neutron reacts with boron

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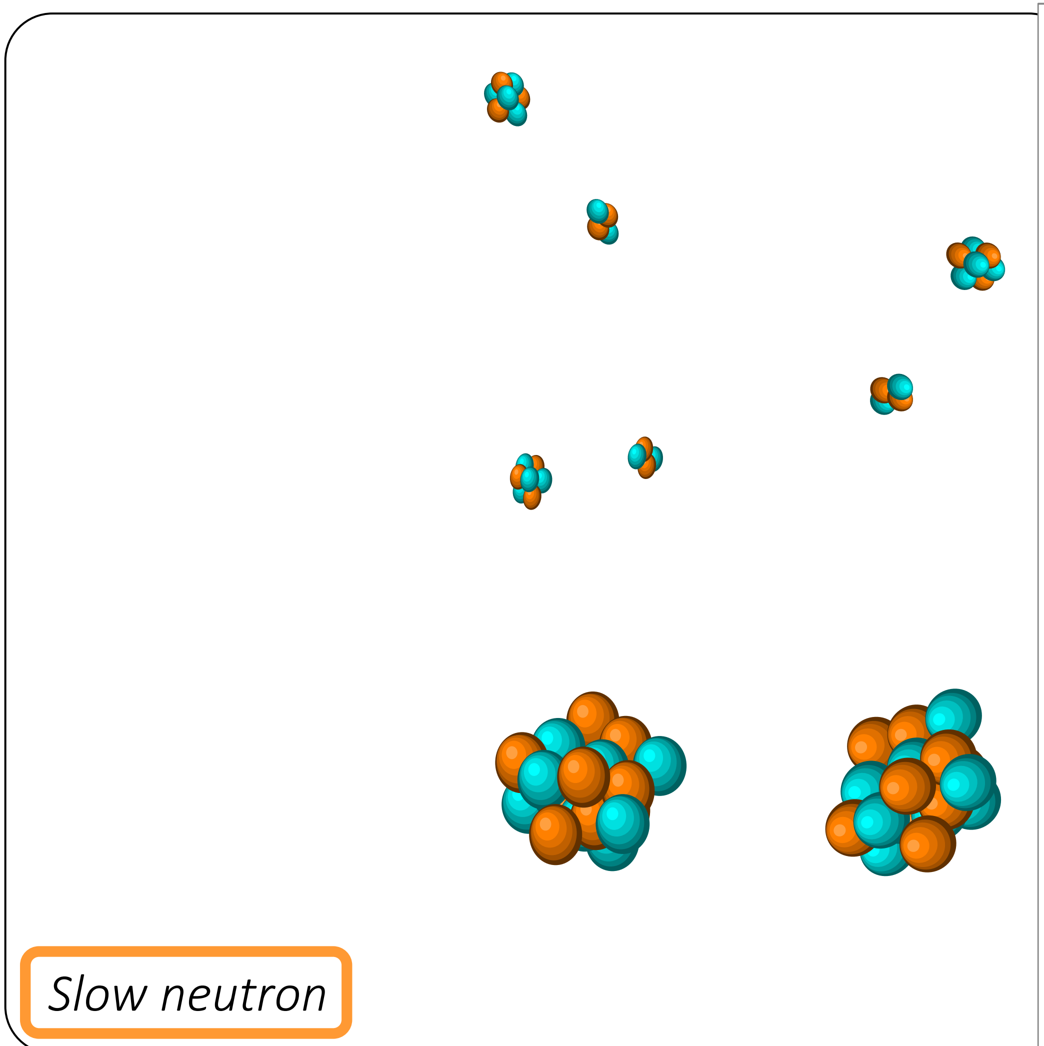
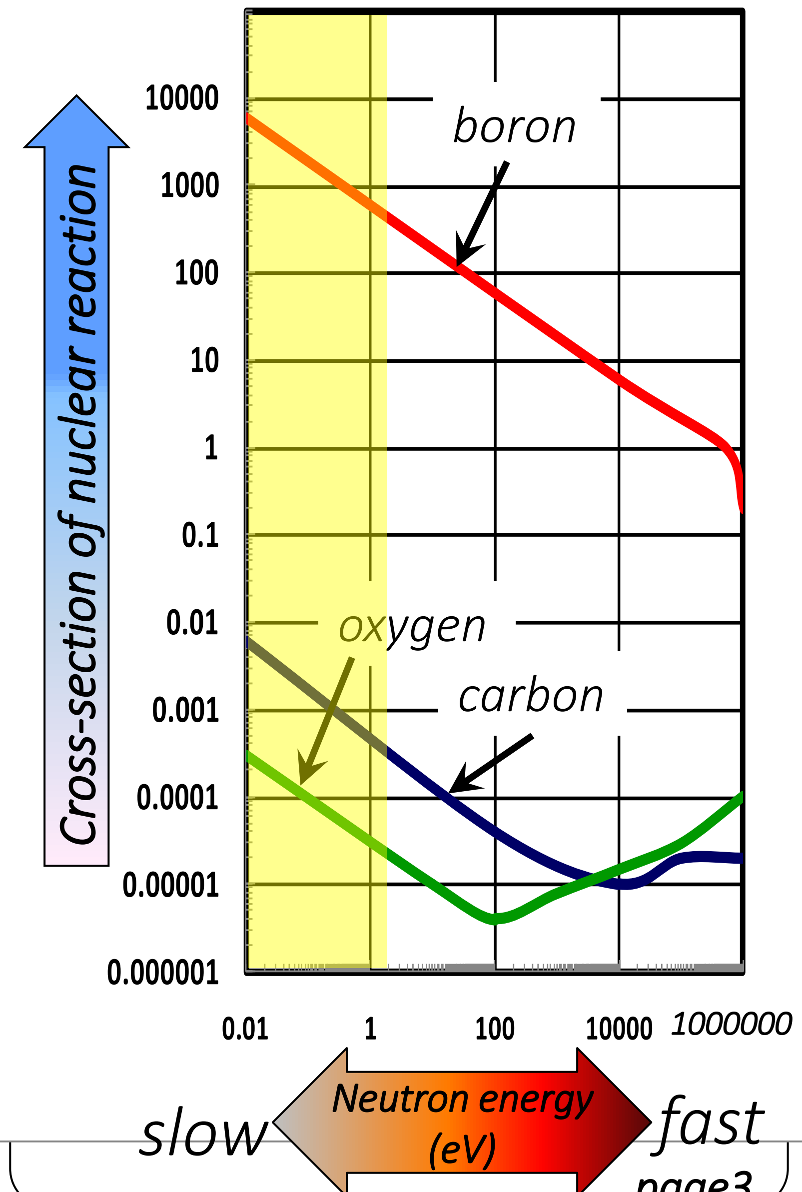
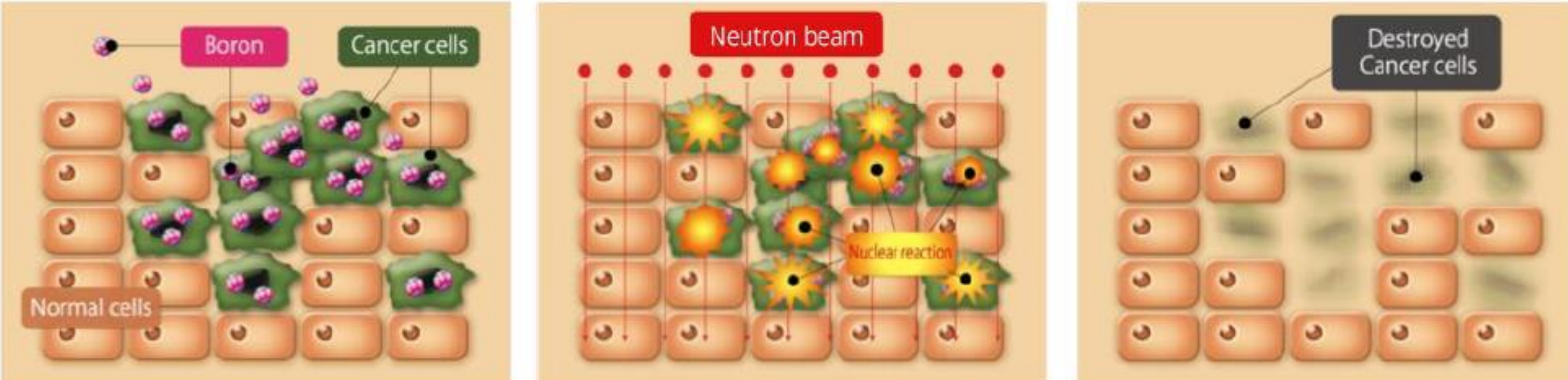




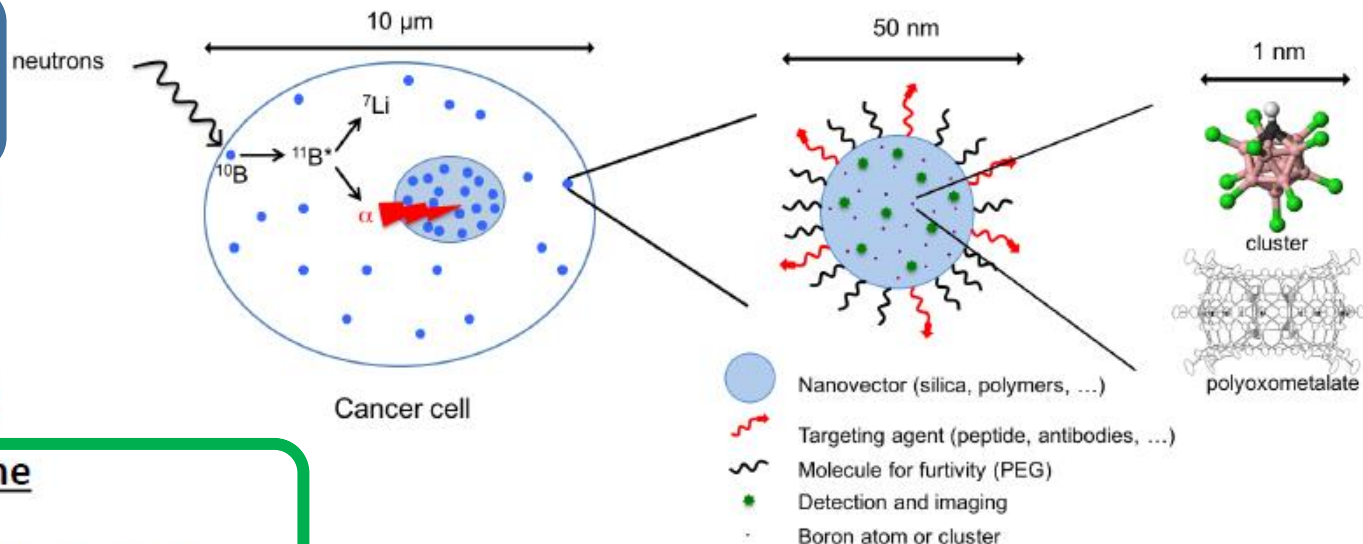
$n + B(10) = Li + \alpha + \gamma$ *Boron Neutron Capture Therapy*



Physics
Neutron source
Imaging

Chemistry
Boron sources
Encapsulation
Vectorization

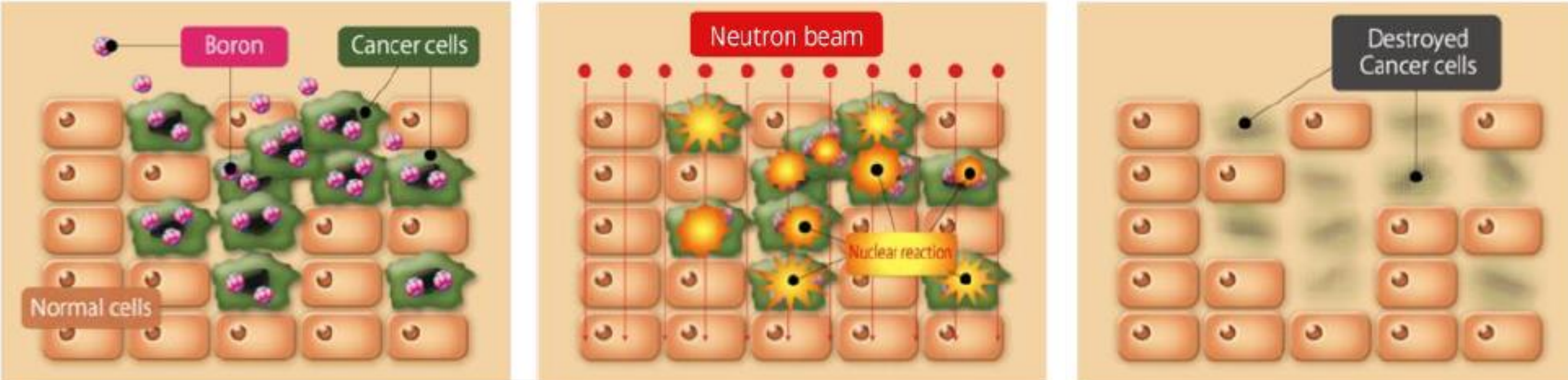
Biology/medicine
Cellular studies
Clinical trials and investigations



Moss, R. L. Critical Review, with an Optimistic Outlook, on Boron Neutron Capture Therapy (BNCT). *Appl. Radiat. Isot.* **2014**, *88*, 2–11.

$n + B(10) = Li + \alpha + \gamma$

Boron Neutron Capture Therapy



Physics
- Neutron source
- Imaging

Chemistry
- Boron sources
- Encapsulation
- Vectorization

Biology/medicine
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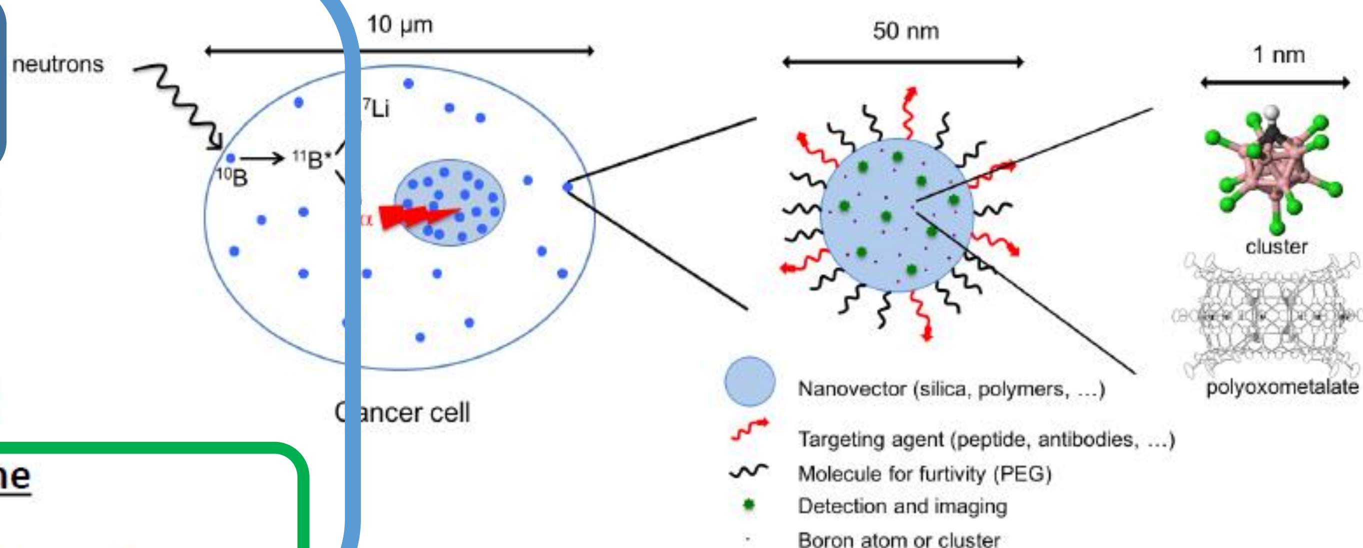
- Clinical trials and investigations



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Collaborative work of different fields is essential

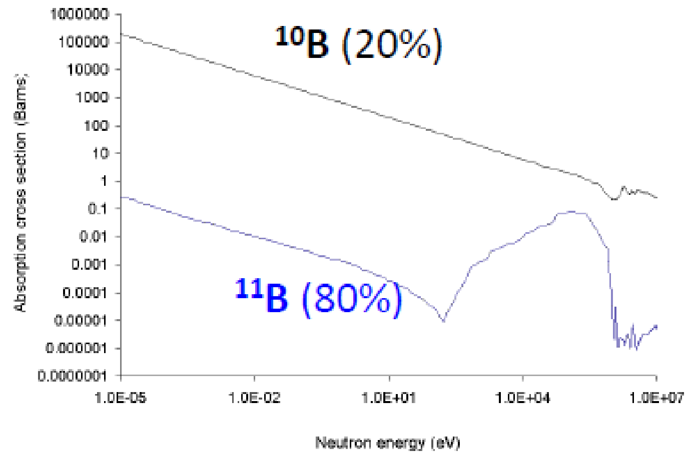
$n + B(10) = Li + \alpha + \gamma$ *Main molecules used in BNCT*

Requirements

- millions of ^{10}B near or inside cell => 20-35 µg $^{10}B/g$
- tumour-to-tissue ratio > 3
- low toxicity

20 g !!

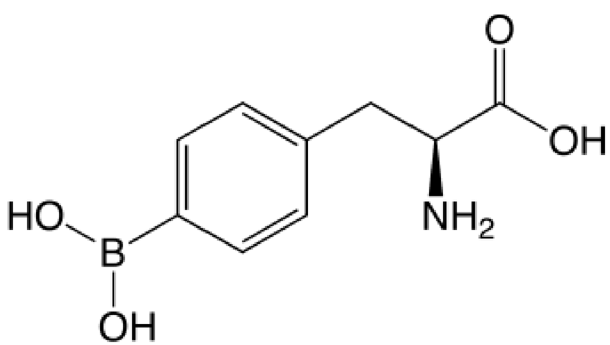
2.5 ~ 3.5 so far !!



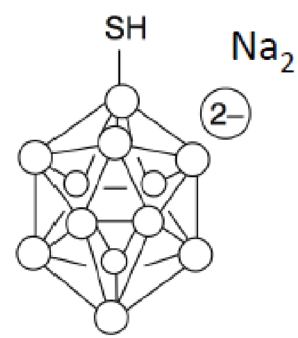
STELLA PHARMA CORPORATION (Japan) is the only drag company

⇒ enrichment in ^{10}B

L-p-boronophenylalanine (L-BPA)



Sodium mercaptoundecahydrododecaborate (BSH)



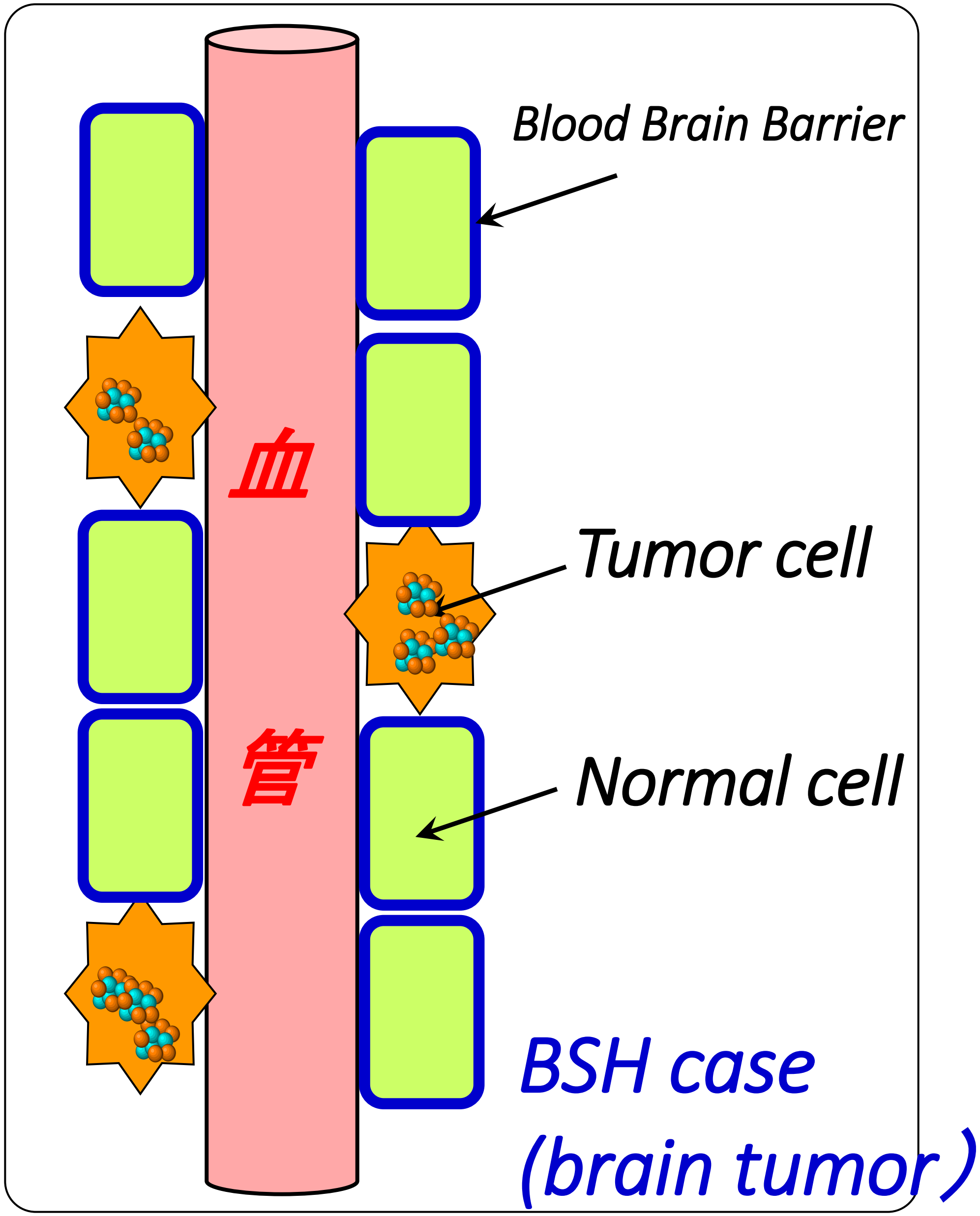
Main issues

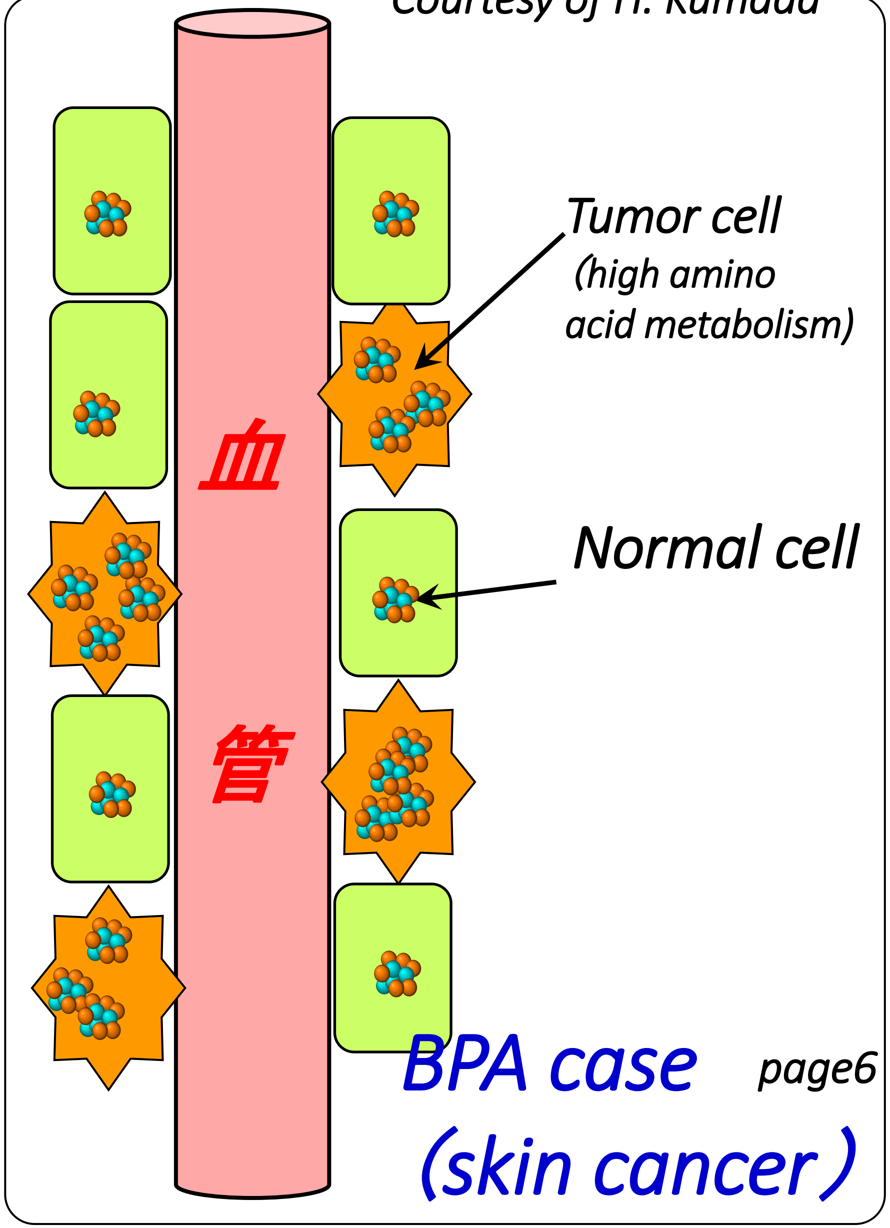
⇒ Not patentable => design of new boron-containing molecules and nanoparticles

⇒ Well known => encapsulation and vectorization inside tumours

Mechanism of boron delivery to tumor cell through blood vessels

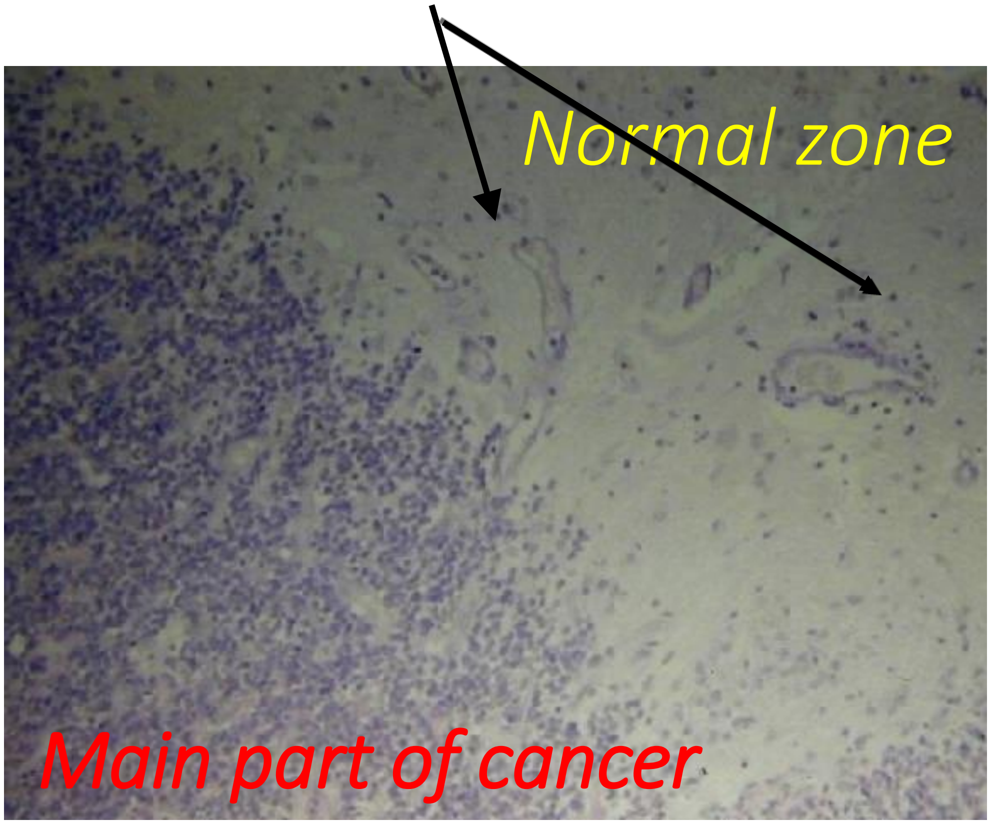
Courtesy of H. Kumada

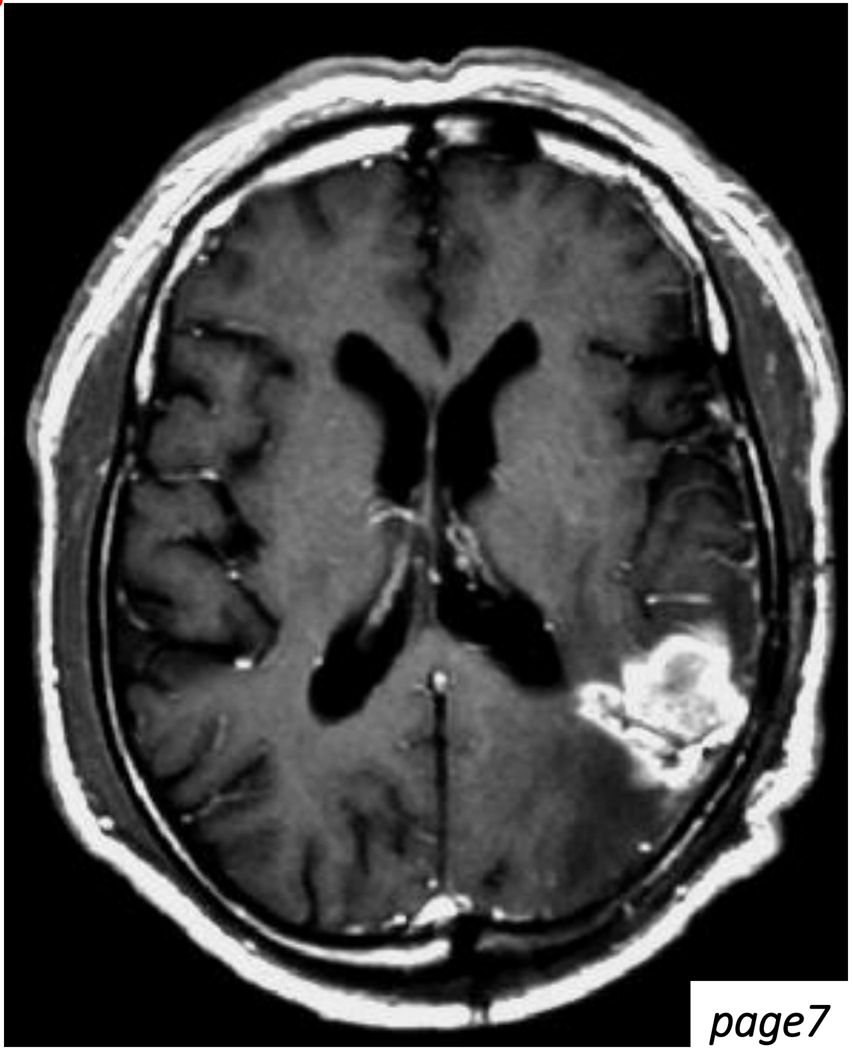




Courtesy of H. Kumada

Obstinate cancer therapy (brain cancer case)





Malignant glioma :

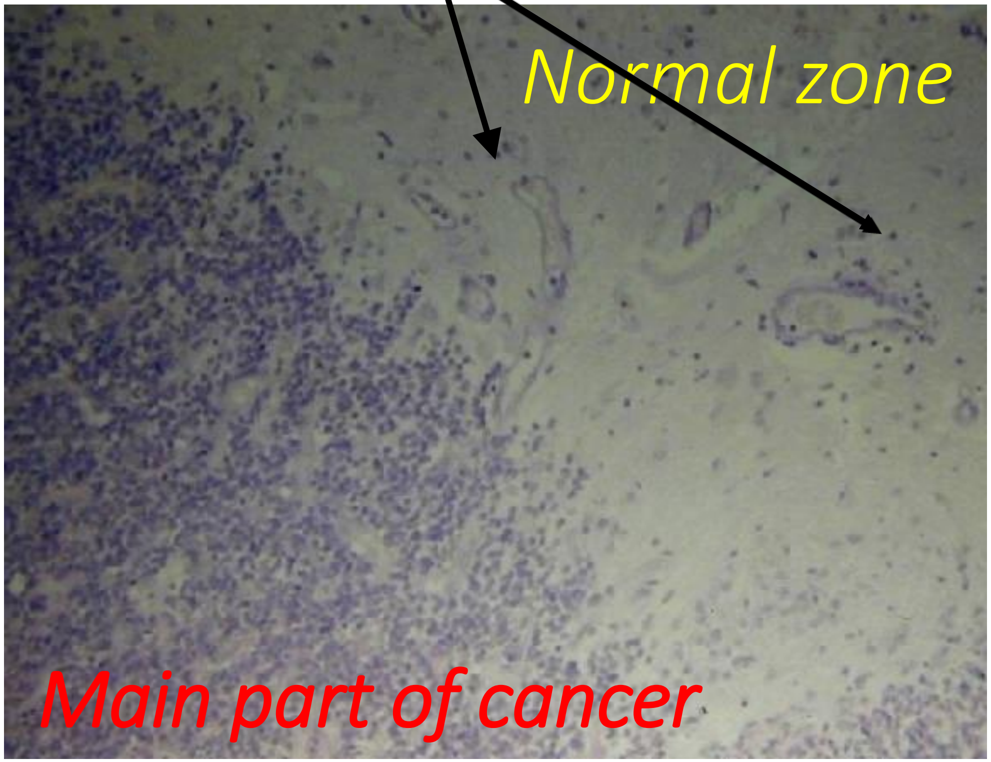
- *3 months to live without therapy*
- *12 months to live with standard therapy*

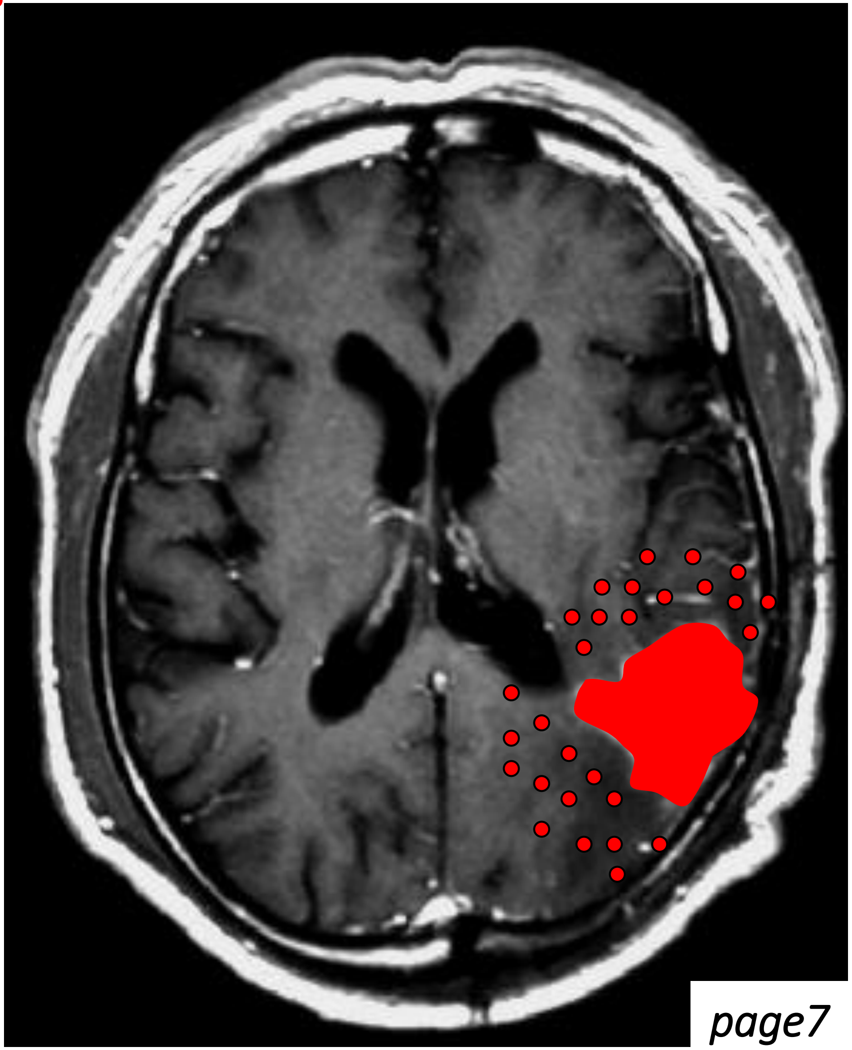
Brain cancer

Courtesy of H. Kumada

Obstinate cancer therapy (brain cancer case)

Tumor cells invasion to normal brain zone





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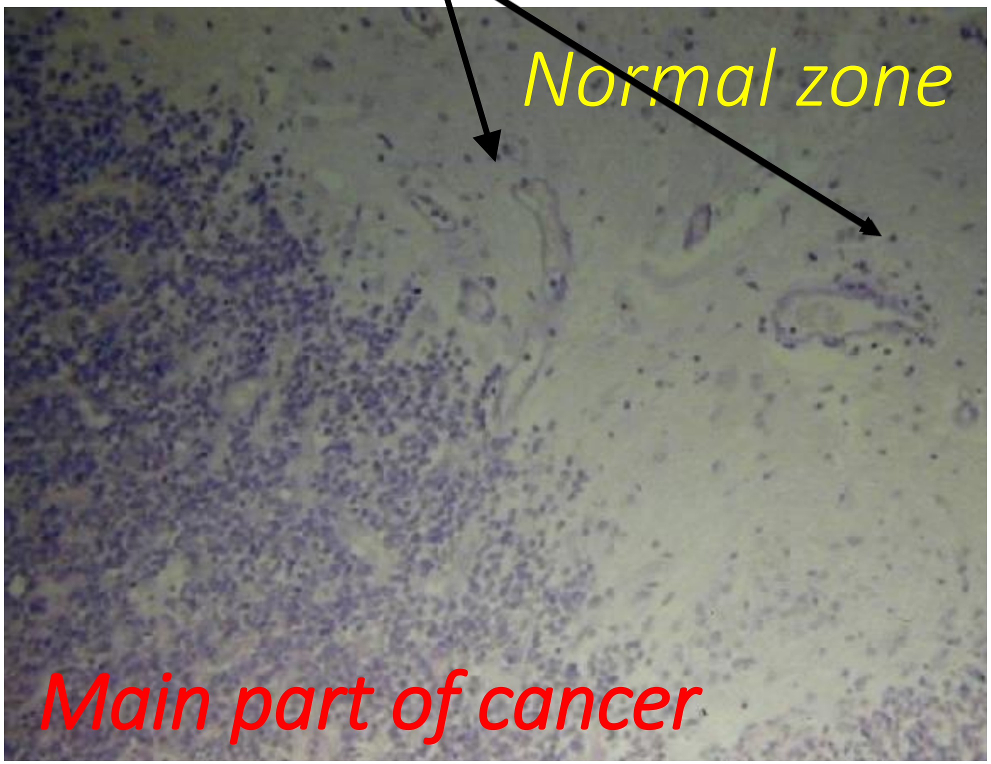

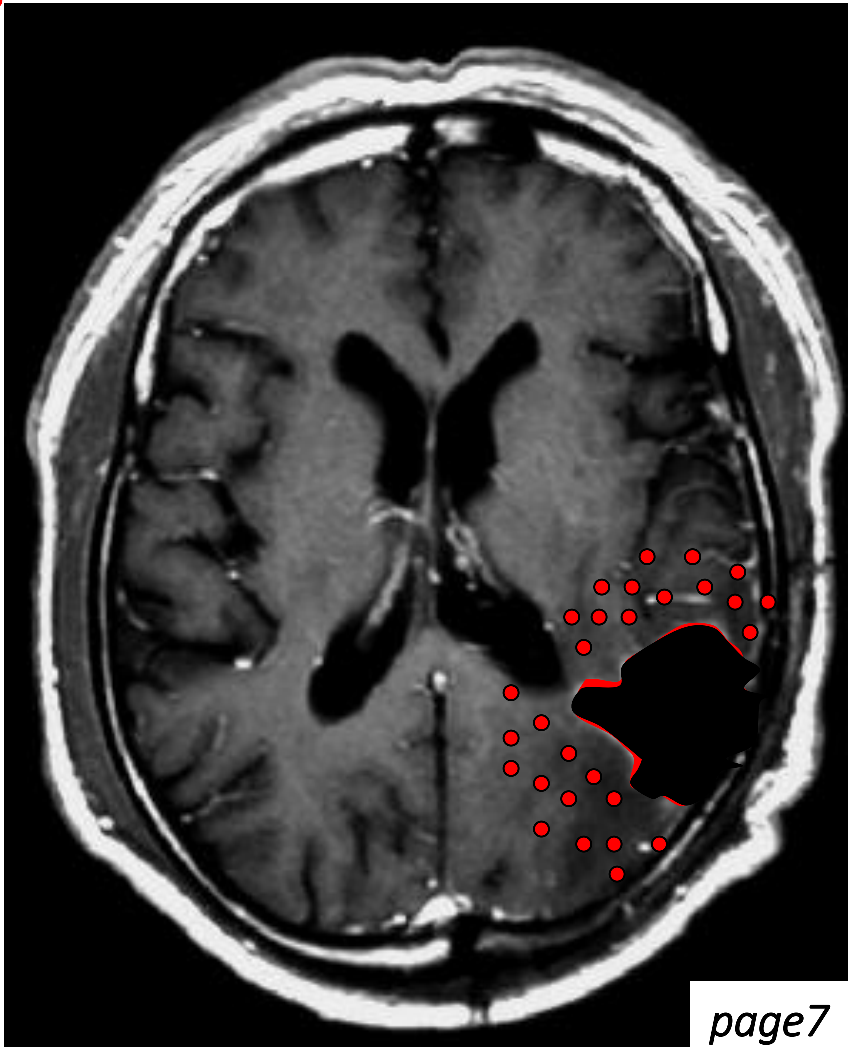

Excision with surgery

Malignant glioma :

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Courtesy of H. Kumada

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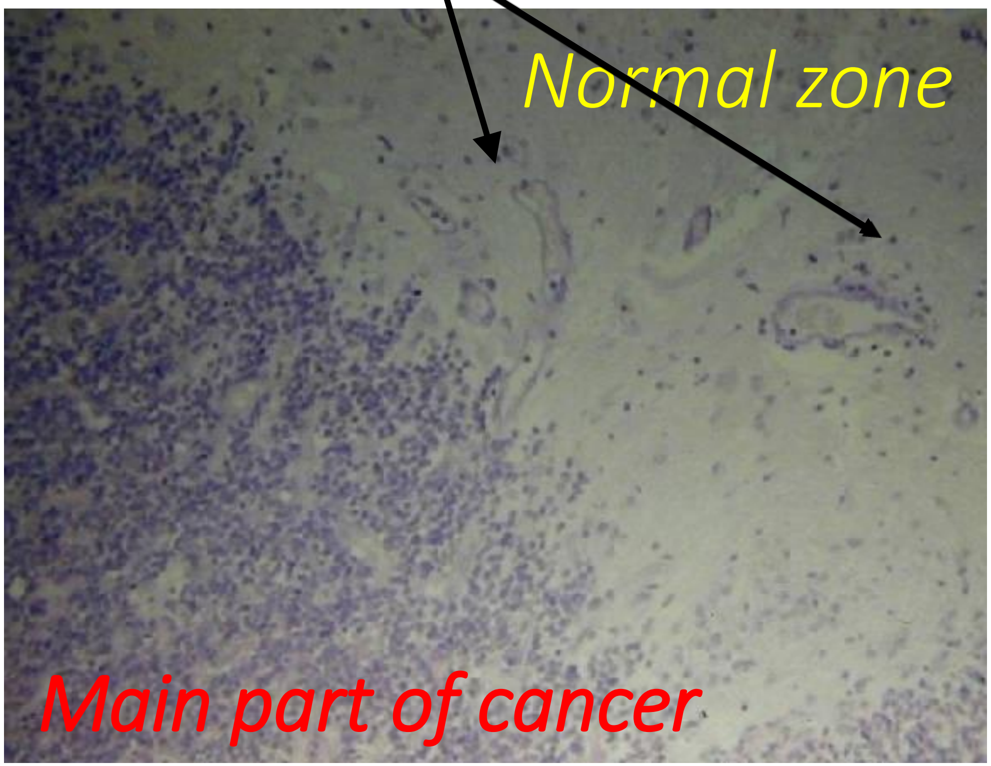

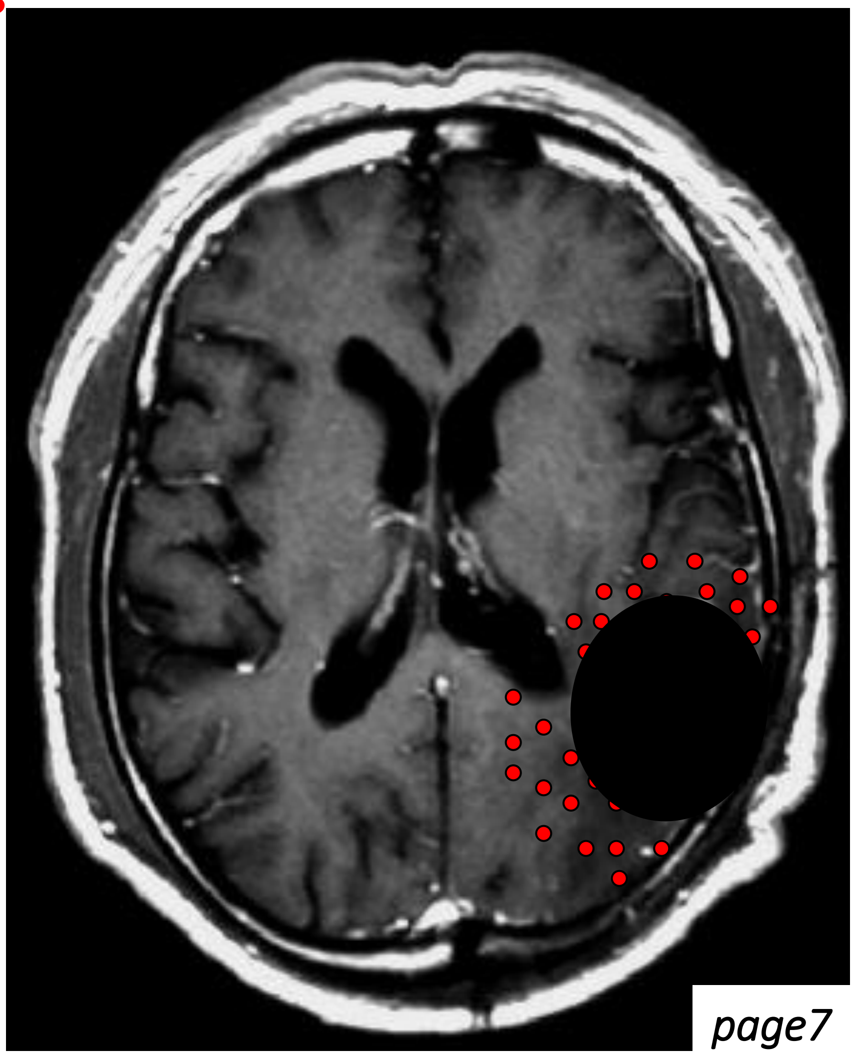

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Standard X-ray therapy

Malignant glioma :

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Courtesy of H. Kumada

Obstinate cancer therapy (brain cancer case)

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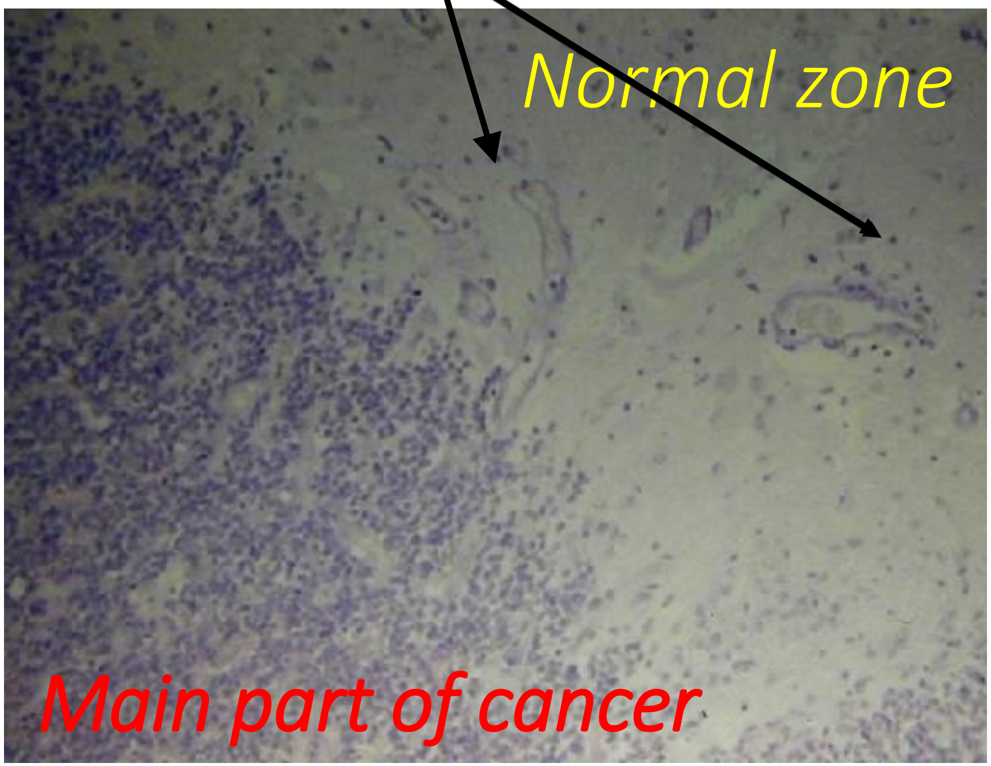

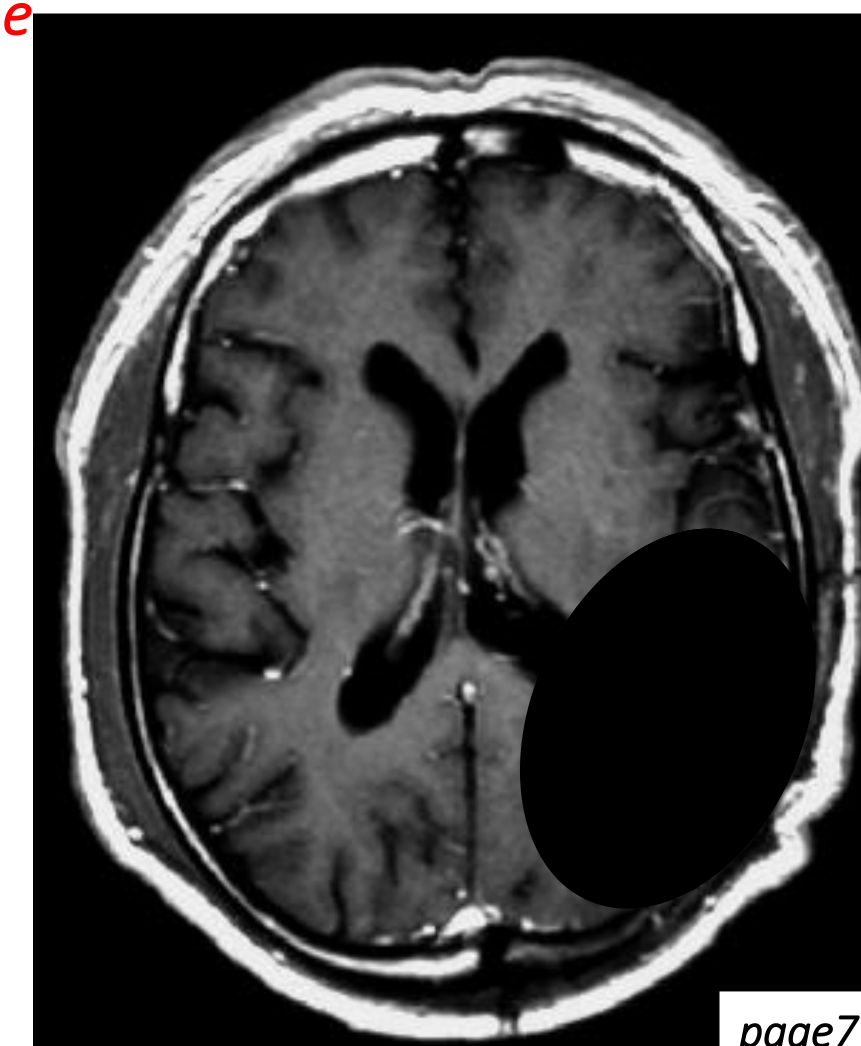

Malignant glioma :

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Standard X-ray therapy

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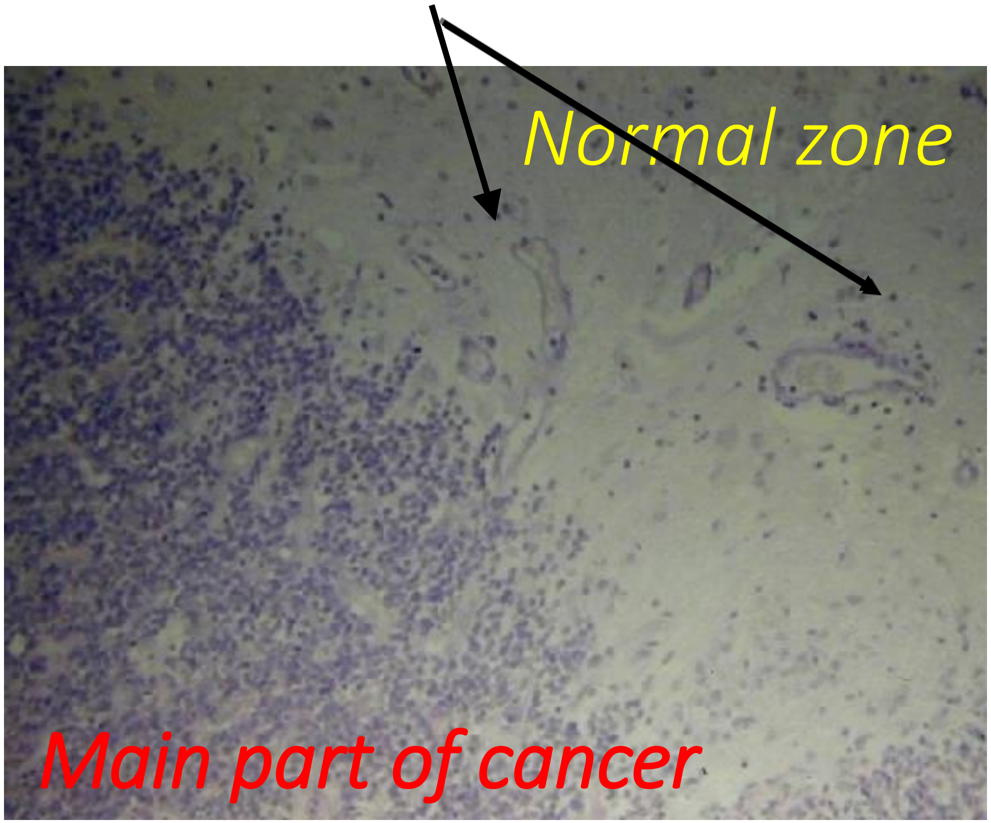
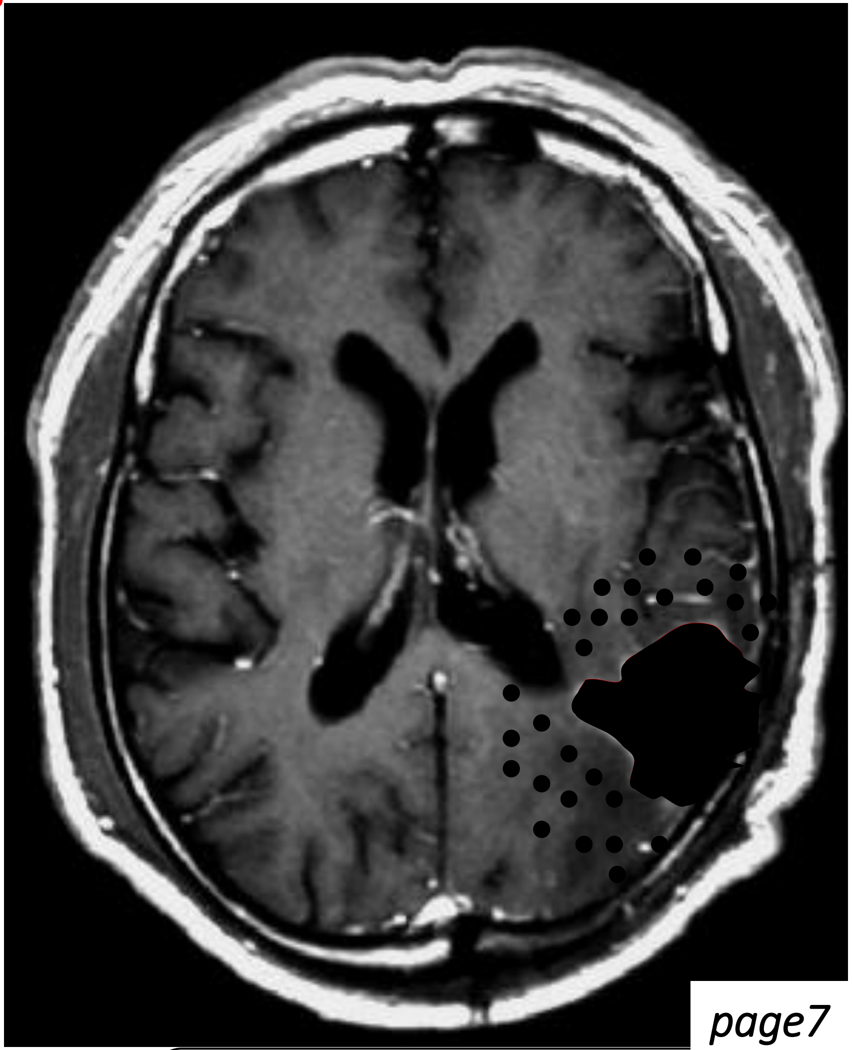




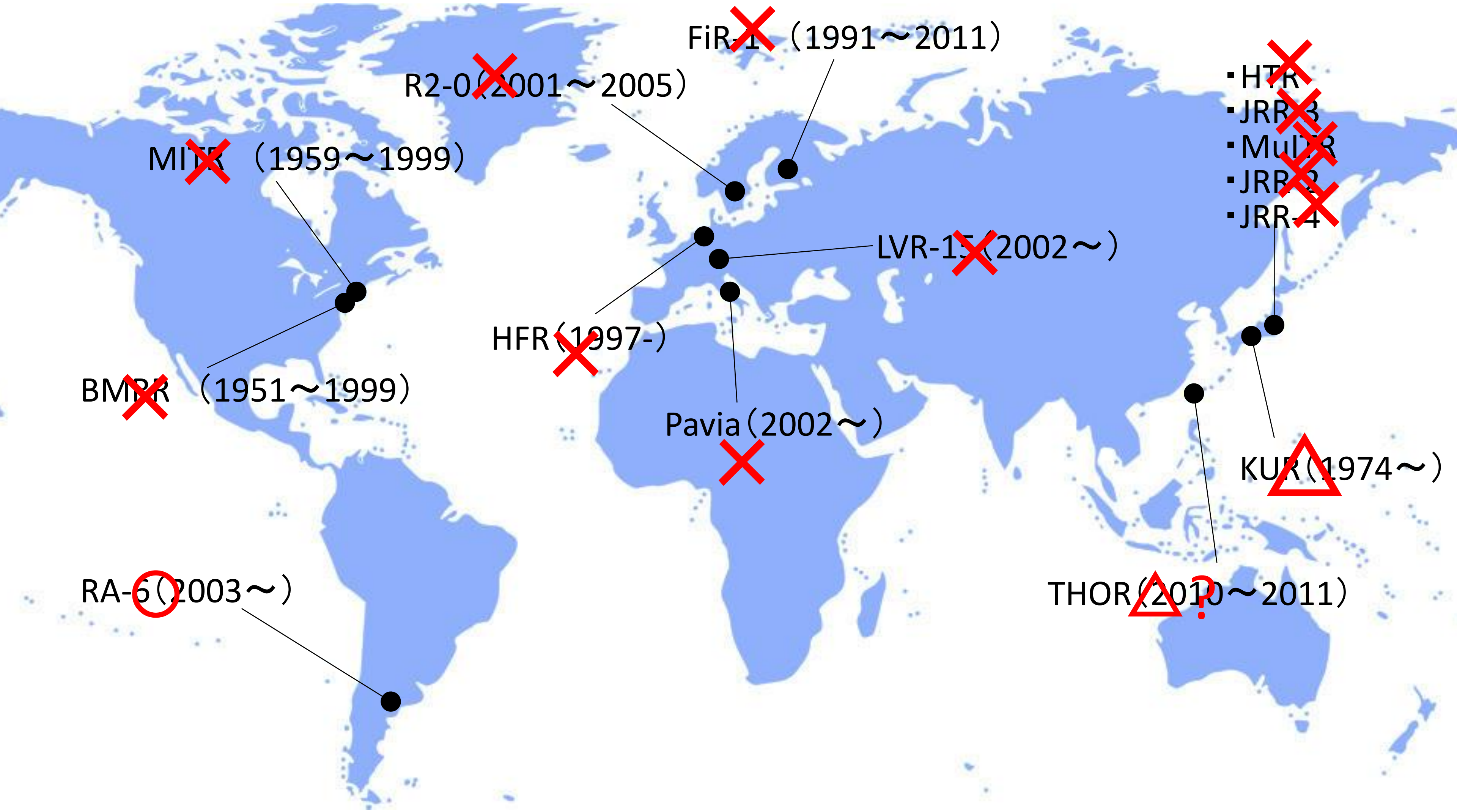
Cell-level therapy is indispensable

Malignant glioma :

- *3 months to live without therapy*
- *12 months to live with standard therapy*

Reactor-based BNCT facilities in the world

Courtesy of H. Kumada



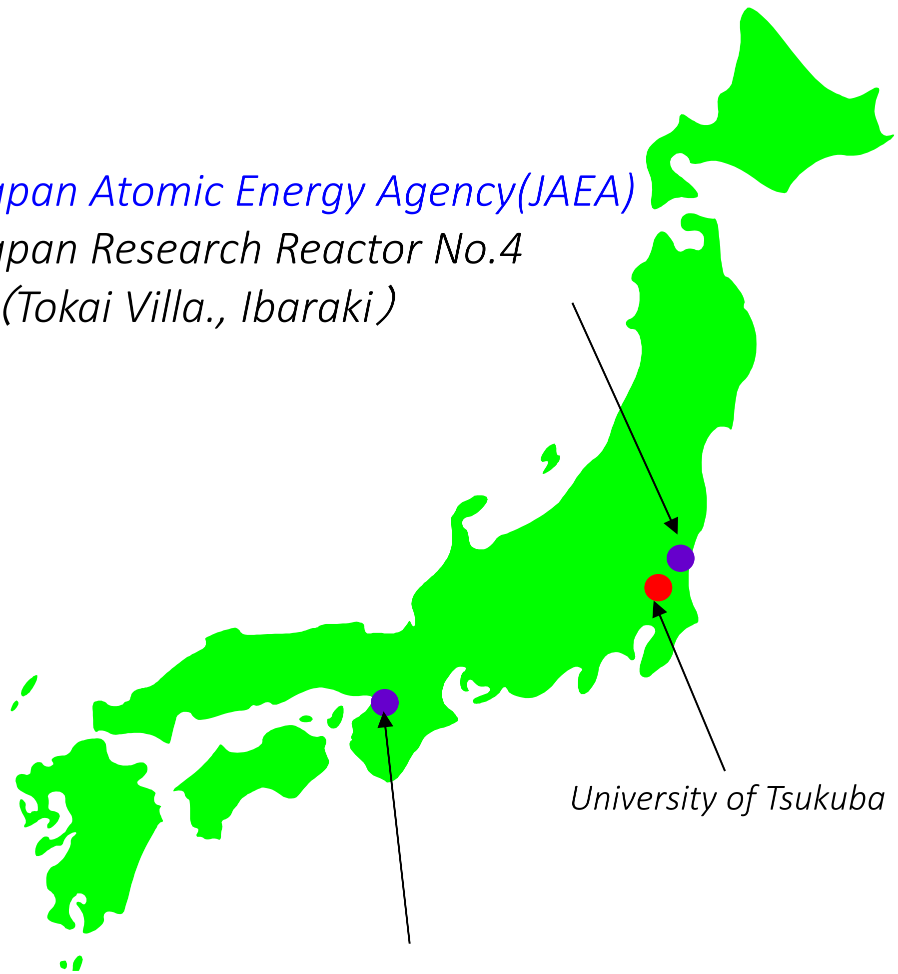
By Hiroaki Kumada (Tsukuba Univ.)

Reactor-based BNCT facilities in Japan

Courtesy of H. Kumada

Recent BNCT Facilities in Japan

Japan Atomic Energy Agency(JAEA)
Japan Research Reactor No.4
(Tokai Villa., Ibaraki)



University of Tsukuba

Kyoto Univ. Research Reactor Institute (KURRI) Research Reactor, KUR"(Osaka)

JAEA, JRR-4

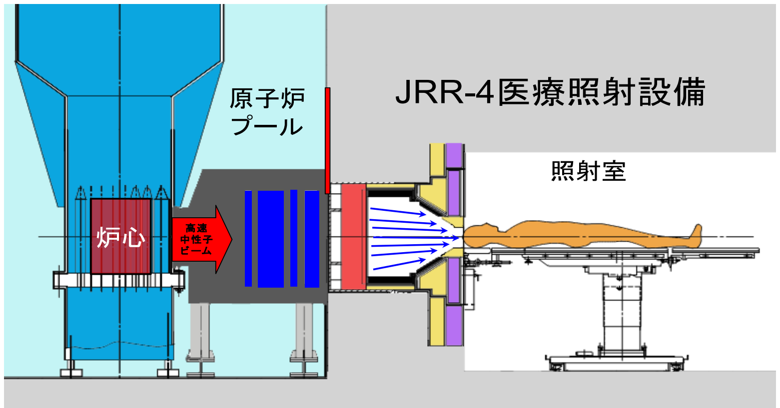
KURRI, KUR

By Hiroaki Kumada (Tsukuba Univ.)

Courtesy of H. Kumada

Reactor-based BNCT facilities in Japan

Reactor-based BNCT in Japan



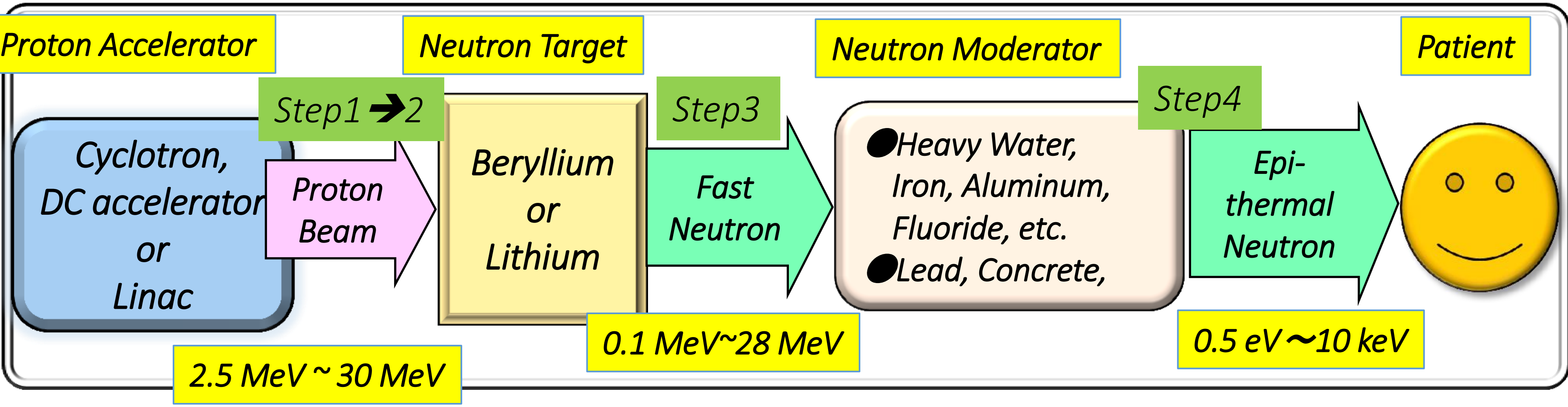
- Reactor can be used only for clinical study.
- Reactor has to be stopped about a few months in a year for the inspection and maintenance by law.
- The number of the BNCT facilities was only two, and unfortunately JRR-4 has stopped by the huge earthquake in 2011.
- It is almost impossible to develop new reactor-based BCNT facility in Japan

JAEA, JRR-4

KURRI, KUR

By Hiroaki Kumada (Tsukuba Univ.)

Methodology of accelerator-based neutron source design



Step1 :Protons are accelerated up to 2.5 〜 30 MeV.
Step2 :Protons are injected to Li or Be target to produce neutrons.
Step3 :Fast neutrons are generated.
Step4 :Slow down fast neutrons by moderator to "BNCT epithermal" neutrons.
(Step 4 is in common with a reactor-based BNCT)

Steps in designing of an accelerator-based neutron source for BNCT,

Step1: We should choose the neutron production target material (Be or Li),
Step2: Proton beam power can be decided from the necessary neutron flux for patient treatment,
Step3: We choose accelerator technology by considering required proton energy and current.

Starting point ➔ **IAEA-TECDOC-1223**

1.2. Epithermal beam intensity

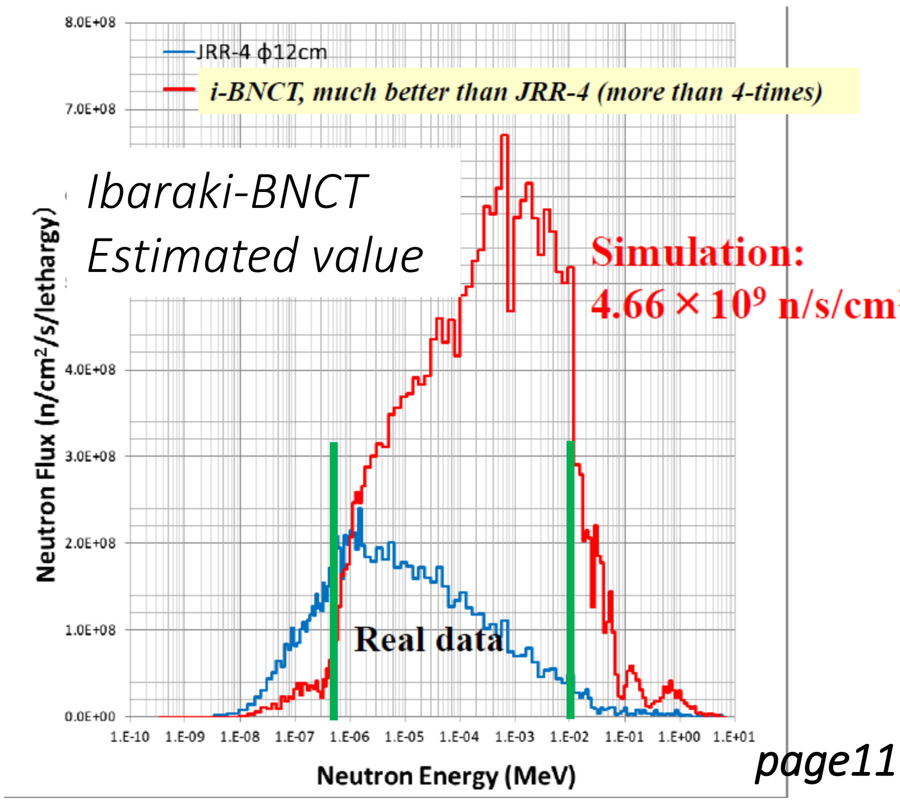
For the purposes of reporting beam intensity, the common definition for an epithermal energy range should be used, namely 0.5 eV to 10 keV. If other energy limits are used, they should be clearly reported.

Current experience shows that a desirable minimum beam intensity would be 10^9 epithermal neutrons $cm^{-2}\,s^{-1}$. Beams of 5×10^8 n $cm^{-2}\,s^{-1}$ are useable, but result in rather long irradiation times.

Energy range of "BNCT epi-thermal"
➔ (0.5 eV ~ 10 keV)"
Neutron flux ➔ > 1 X10^9 n/cm^2/s

INTERNATIONAL ATOMIC ENERGY AGENCY IAEA

May 2001



1.3.1. *The fast neutron component*

Upper limit of harmful component for patient

In BNCT the energy range for fast neutrons is taken as >10 keV. Fast neutrons, which invariably accompany the incident beam, have a number of undesirable characteristics such as the production of high LET protons with a resulting energy dependence of their induced biological effects. Therefore, it is one of the main objectives of BNCT beam design to reduce the fast neutron component of the incident beam as much as possible.

Another major objective is clearly to have as high an epithermal flux as possible. In existing facilities the range of dose from this component is from 2.5 to 13 $\times 10^{-13}$ Gy cm^2 per epithermal neutron. A target number should be 2 $\times 10^{-13}$ Gy cm^2 per epithermal neutron.

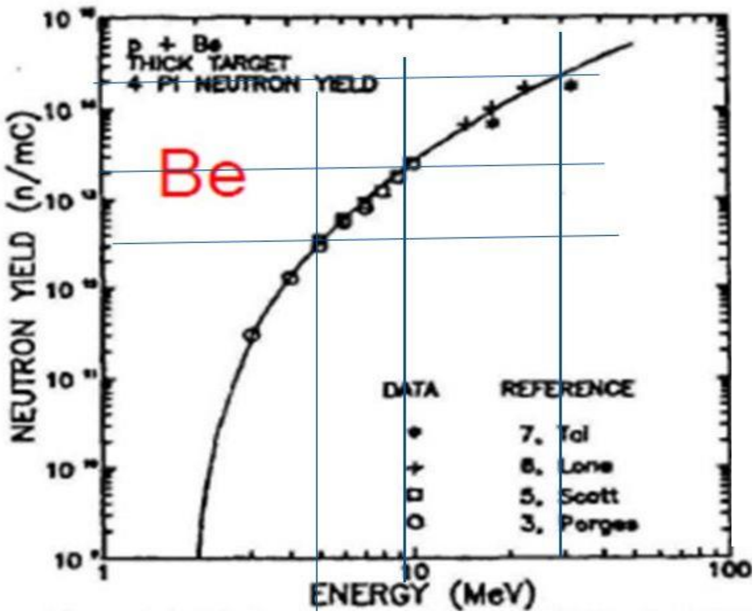
1.3.2. *The gamma ray component*

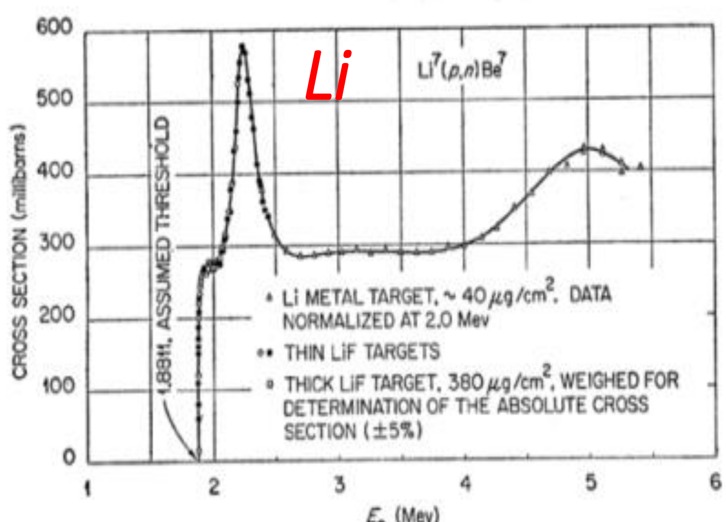
Upper limit of harmful component for patient

Because of the energy range of the gamma radiation, it results in an non-selective dose to both tumour tissue and a large volume of healthy tissue. Hence it is desirable to remove as much gamma radiation from the beam as possible. Since there are also (n,γ) reactions occurring inside the patient, the importance of this component in the incident beam is somewhat reduced. Nevertheless, a target number for this should be 2 $\times 10^{-13}$ Gy cm^2 per epithermal neutron. The range in existing facilities is from 1 to 13 $\times 10^{-13}$ Gy cm^2 per epithermal neutron.

Comparison between Lithium and Beryllium

$^{7}Li(p,n)^{7}Be$ $^{9}Be(p,n)^{9}B$

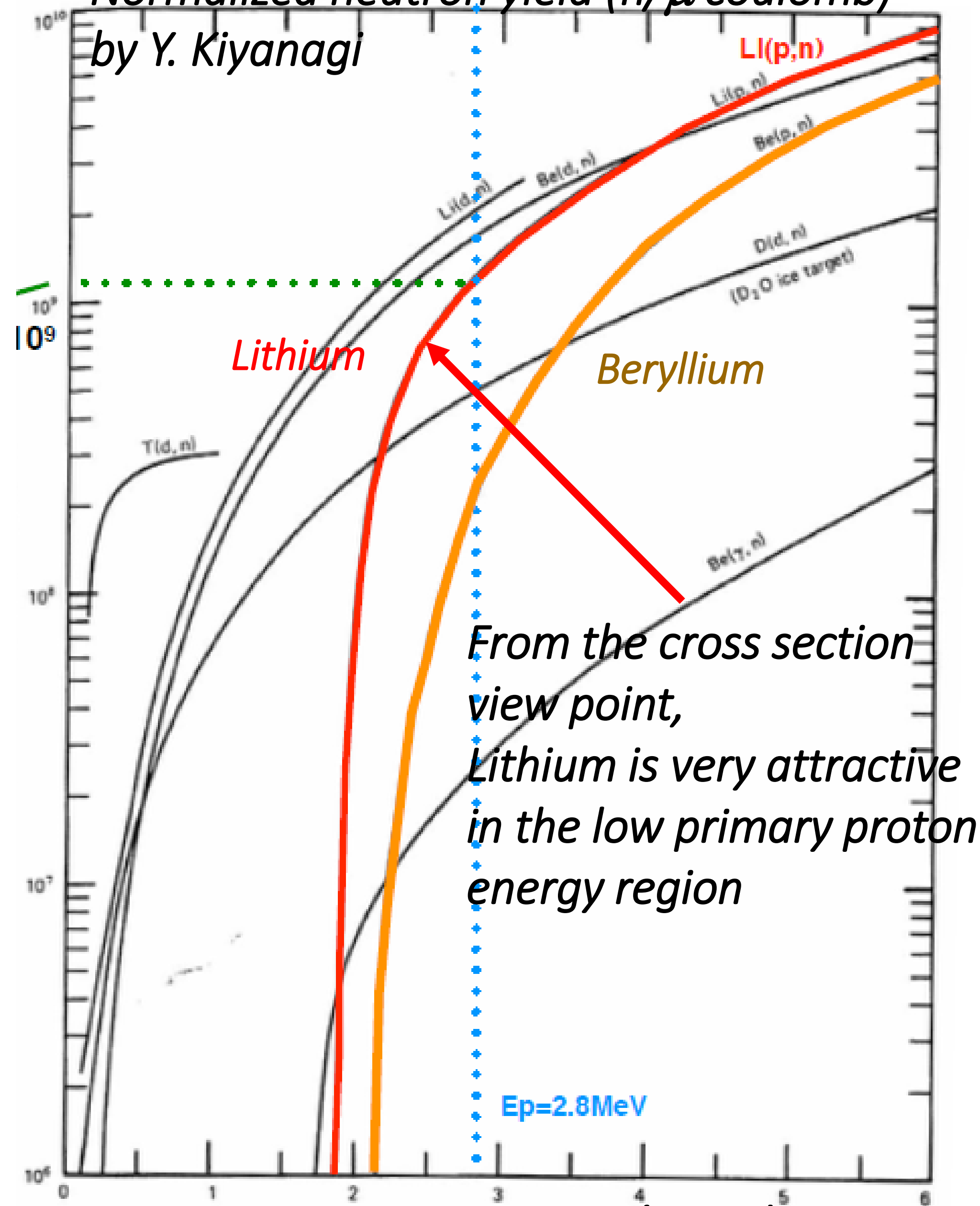




H. Tanaka, Kyoto Univ. Research Reactor Institute

Normalized neutron yield (n/μ coulomb)

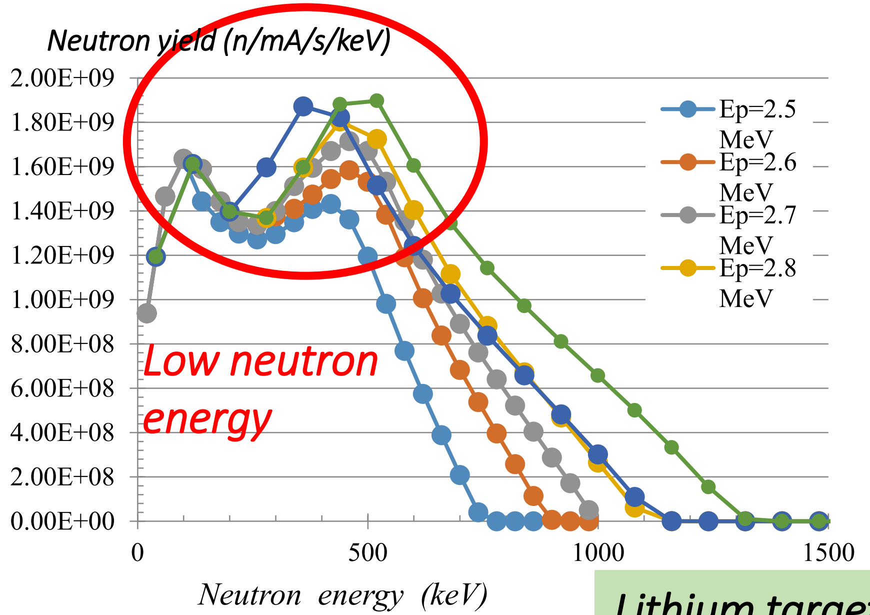
by Y. Kiyanagi

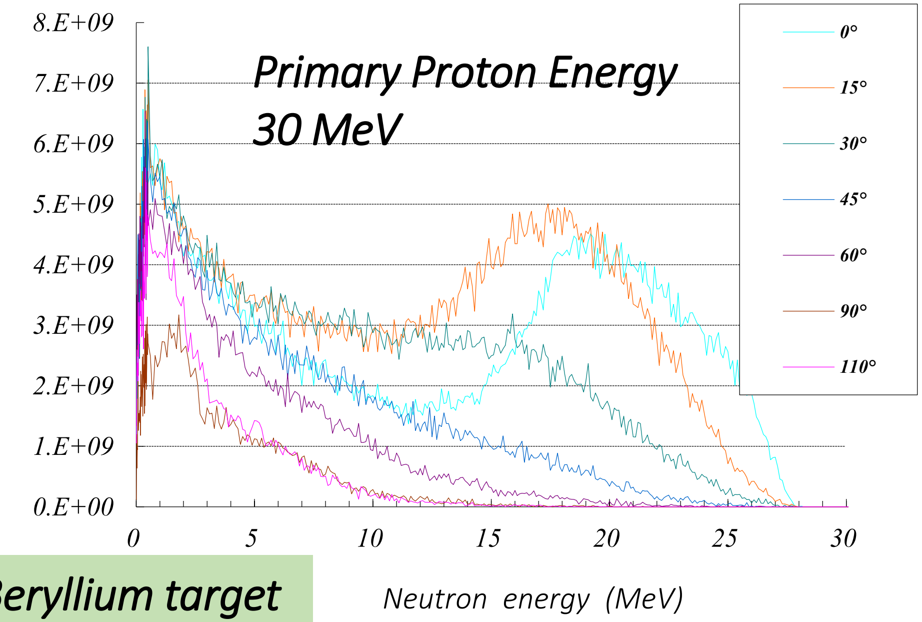


From the cross section view point,
Lithium is very attractive in the low primary proton energy region

Primary proton energy (MeV)

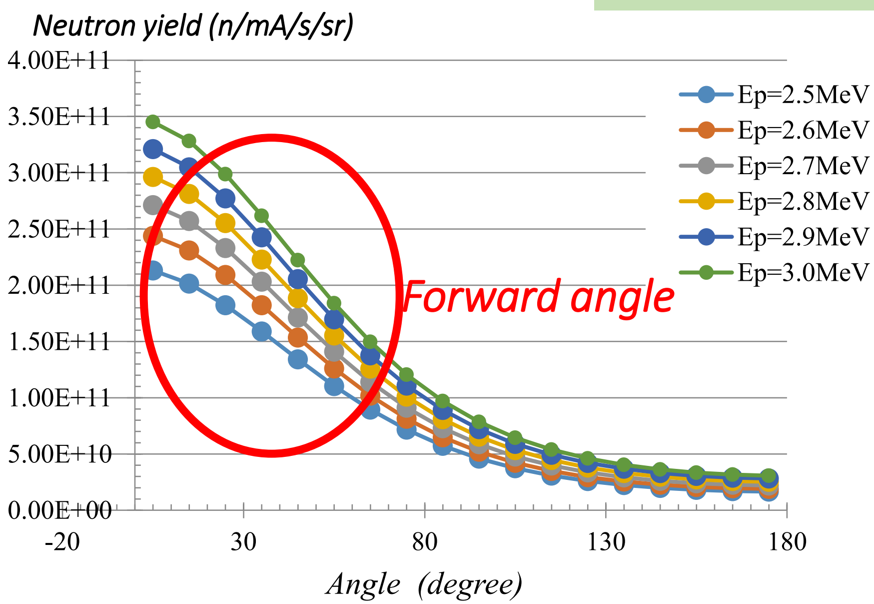
Neutron energy spectrum of lithium and beryllium for various production angle (by Yoshiaki Kiyanagi)

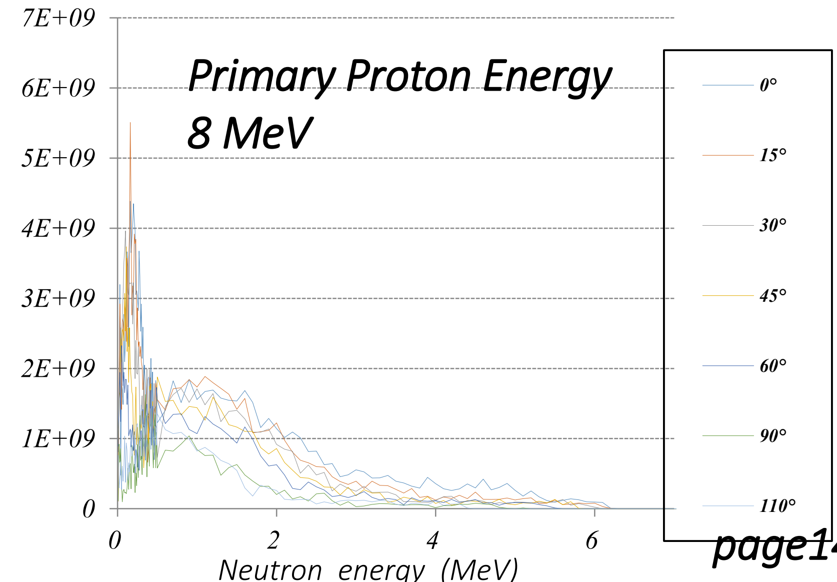




Lithium target

Beryllium target





Criteria of the technology choice

Target	Proton Energy	Problems to be solved
Solid Lithium	$^{7}Li(p,n)^{7}Be$ 2.5~3 MeV	➢ Low melting point (180.5° C) → heavy target heat load must be cooled effectively to avoid evaporation ➢ Generation of ^{7}Be (radioactive nuclide with half-life of 53 days) ➢ Generation of tritium by reaction of $^{6}Li(n,t)^{4}He$ → ^{6}Li / ^{7}Li (7.59/92.41%) ➢ Vigorous reaction with water and easy-oxidization
Liquid Lithium		➢ Generation of ^{7}Be and Tritium (same as above). ➢ Need to handle liquid metal in a hospital cautiously.
$^{9}Be(p,n)^{9}B$ Beryllium	> 13 MeV	➢ High energy neutrons produce many kind of active nuclides. → Heavy residual radiation (> 100 mSv/h) ➢ High energy neutrons may give damages to healthy tissues (need more study).
	< 13 MeV	➢ Lower yield → Need to develop a high current accelerator. ➢ Heavy target heat load must be cooled efficiently. ➢ Avoid target damage by blistering (Blistering: stopped proton in the metal easily capture free electrons and generate hydrogen in the target ➔ flaking/peeling takes place).

Current status for accelerator-based BNCT in the world

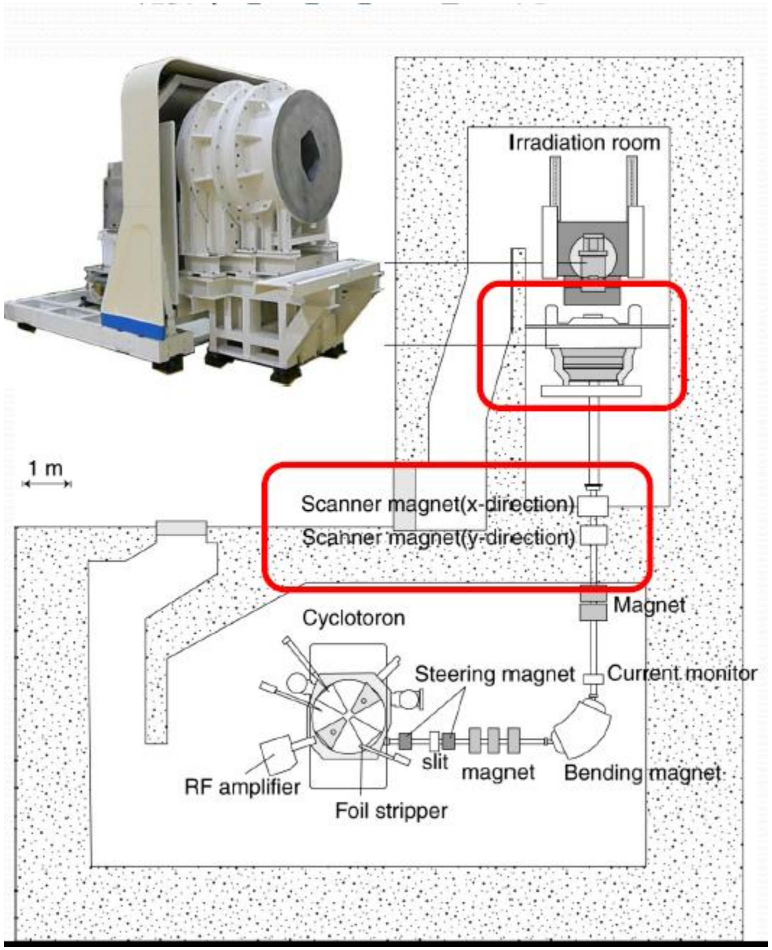
Location		Machine (Status)	Target & reaction	Beam Energy (MeV)	Beam current (mA)
Budker Institute (Russia)		Vacuum insulated Tandem (Ready)	Solid ^{7}Li(p, n)	2	2
iPPE-Obninsk (Russia)		Cascade generator KG- 2.5 (Ready)	Solid ^{7}Li(p, n)	2.3	3
Birmingham Univ. (UK)		Dynamitron (Ready)	Solid ^{7}Li(p, n)	2.8	1
Soreq (Israel)		RFQ-DTL (Ready)	Liquid ^{7}Li(p, n)	4	1
Legnaro INFN (Italy)		RFQ	Be(p, n)	4-5	30
CNEA Buenos Aires (Argentina)		Single ended Tandem Electrostatic Quadrupole (TESQ)	Be(d, n)	1.4	30
			Solid ^{7}Li(p, n)	2.5	30
Japan	KURRI	Cyclotron (Clinical Trial)	Be(p, n)	30	1
	University of Tsukuba	RFQ-DTL	Be(p, n)	8	10
	NCCenter, CICS	RFQ	Solid ^{7}Li(p, n)	2.5	20
	Fukushima South Tohoku Hospital	Cyclotron	Be(p, n)	30	1
	Osaka University	Neutron target system only	Liquid ^{7}Li(p, n)	~2.5	-
	Nagoya University	Dynamitron	Solid ^{7}Li(p, n)		
	Planning and designing : OIST (Okinawa) , Osaka Medical College (Osaka), Edogawa Hospital (Tokyo)				

By Hiroaki Kumada (Tsukuba Univ.)

In Japan, many institutes and hospitals are developing an accelerator-based BNCT facility, in which most combinations of accelerator and target technologies are included. As a typical example of these technologies, I will show following six cases.

Various technology choice

Group	Accelerator	Beam Energy	Power	Target material
1. Kyoto University	Cyclotron	30 MeV	33 kW	Thick beryllium (5.5 mm)
==Clinical trial==				
2. National Cancer Center	CW RFQ	2.5 MeV	50 kW	Solid lithium
==Passed radiation facility inspection==				
3. Nagoya University	Dynamitron	2.8 MeV	50 kW	Hermetic liquid lithium
==Accelerator commissioning and target development phase==				
4. Tokyo Institute of Technology		------------	---------	Liquid lithium target
==Target development only==				
5. Tsukuba University	Pulsed RFQ + DTL	8.0 MeV	80 kW	Thin beryllium (0.5 mm)
==Accelerator commissioning==				
6. OIST	Pulsed RFQ	3.0 MeV	30 kW	Solid lithium
==Design phase based on new solid lithium target technology==				

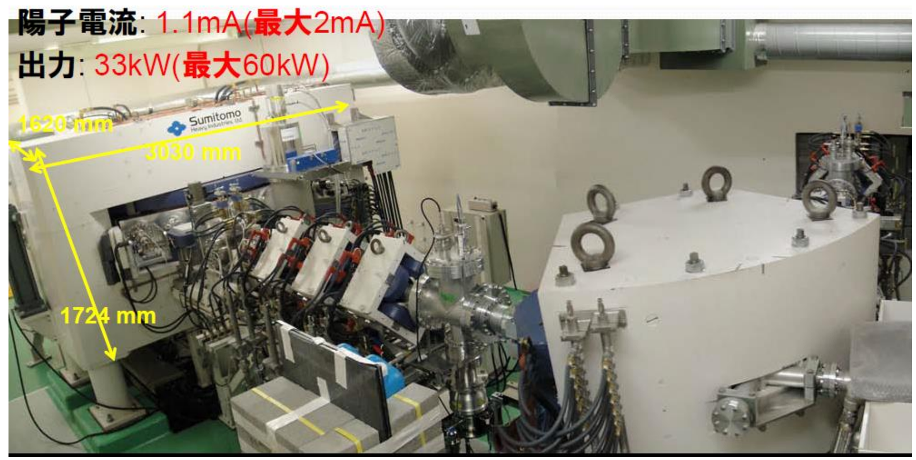


Technology-1:

30 MeV, 1.1 mA (33 kW) cyclotron
+ beryllium target

Kyoto University & Sumitomo Heavy Industries, Ltd.

The most advanced group and
in clinical trial phase

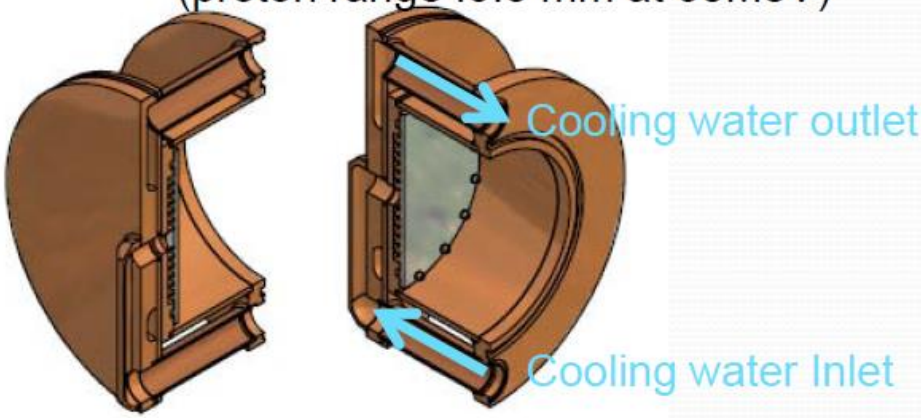


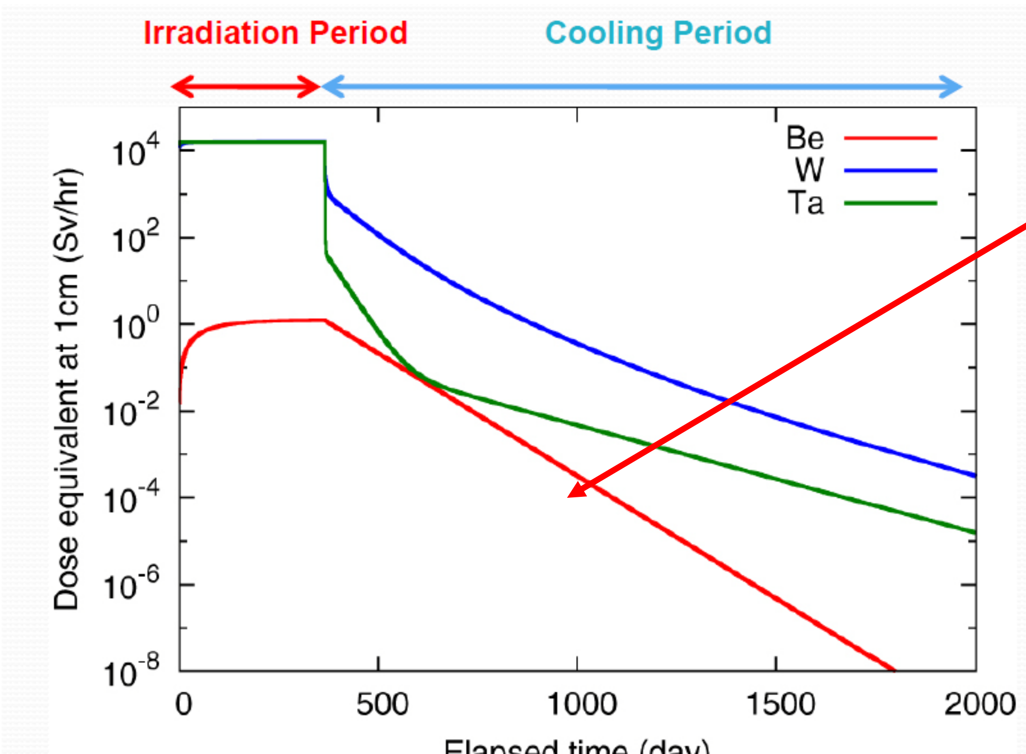
Characteristics:

- *Cyclotron is a mature technology*
- *5.5 mm thick target ➔ no risk on the target manufacturing technology*
- *Proton beam stops in water ➔ free from the blistering problem*

Photos and the figures are by
Motoki Tanaka (Kyoto University)

Be target thickness is 5.5 mm
(proton range :5.8 mm at 30MeV)





Risk:

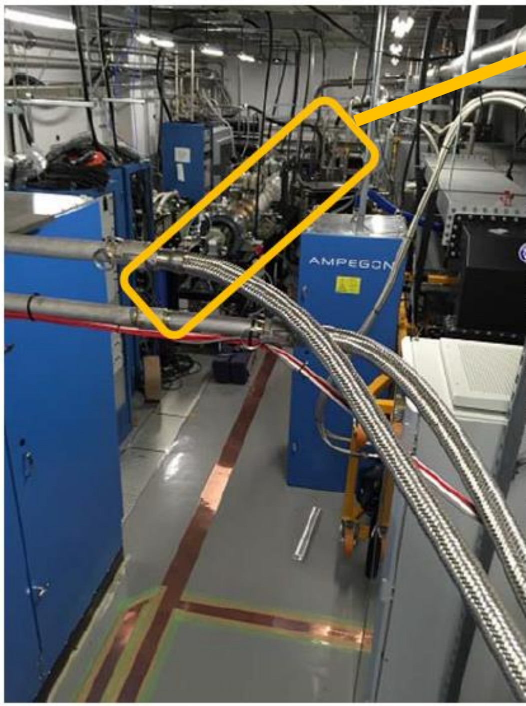
- *High residual radioactivity*

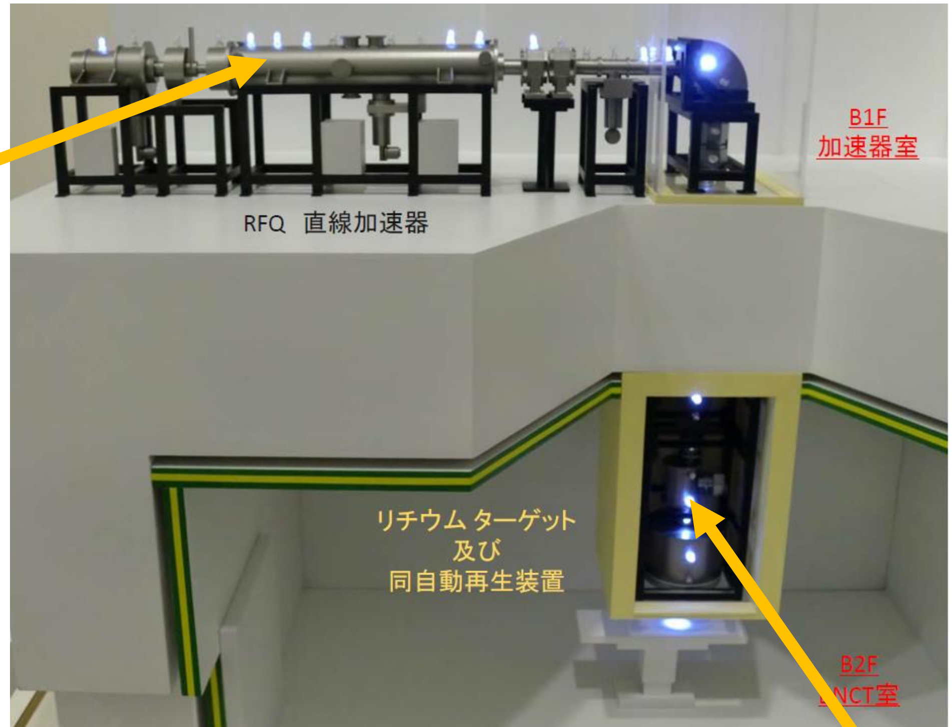
By Motoki Tanaka (Kyoto University)

Technology-2: *2.5 MeV, 20 mA (50 kW) RFQ (CW) + solid lithium target*

National Cancer Center & CICS, Inc.

Passed the radiation facility safety inspection in March 2016



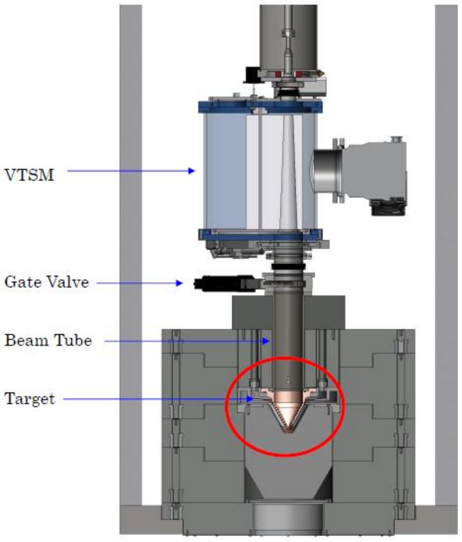


Characteristics:

- *Low risk for CW RFQ linac operation*
- *Simple moderator design and structure*

Risk:

- *Complex target design, structure and operation*



How to avoid concentration/accumulation of ^{7}Be.

Three rotating units are used

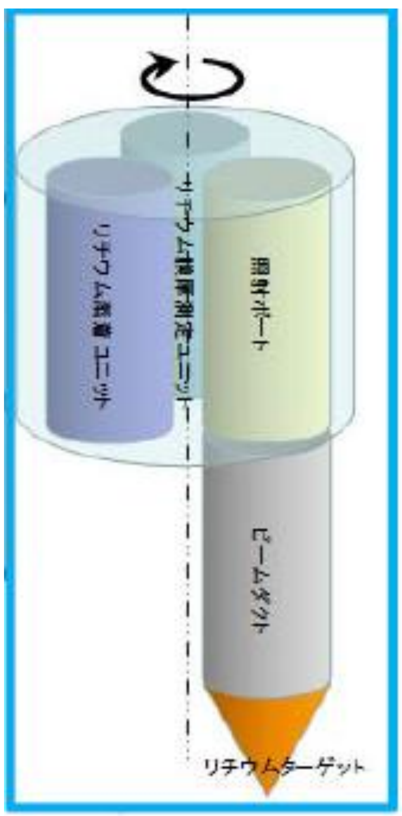
① Port 1: irradiation port

② Port 2: wash out port

- (utilizing that lithium reacts with water actively)
- Lithium target layer can be washed out with water before accumulating ^{7}Be frequently and waste liquid is stored in a tank.

③ Port 3: vapor deposition port

- New lithium layer is developed on the heat sink with vapor deposition method.



The photo and drawings are from Home Page Of National Cancer Center, CICS and paper by Linac Systems INC.

Figure 3: Channelized heat exchanger.

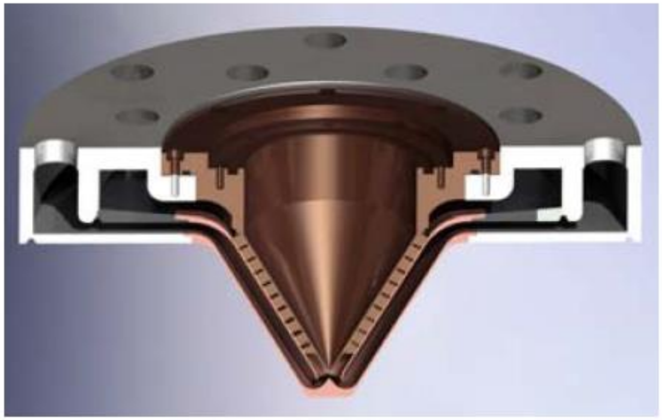


Figure 4: Manifold with target heat exchanger installed.

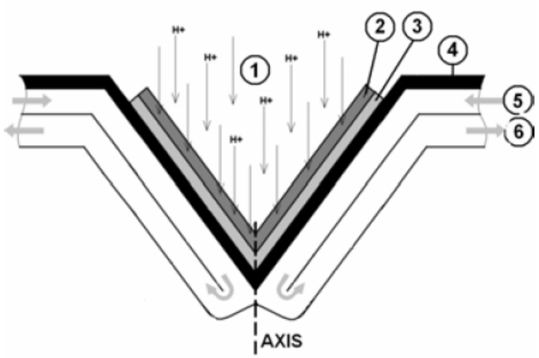


Figure 1: Protons (1) strike a 50-µm lithium metal layer (2) that is deposited on a Pd anti-blistering substrate (3), supported by a channelized conical heat exchanger (4). Coolant (5) flows through a conical-annular duct that encompasses the channels of the heat exchanger; reverses at the apex; returns via an outer conical-annular duct, and exits (6).

Issues

① Layer thickness control is difficult.

② Storage of waste liquid is troublesome.

===Unsealed Radioactive material====

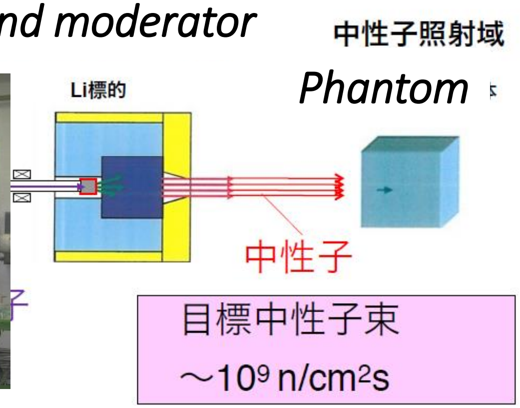
Technology-3: NUANS

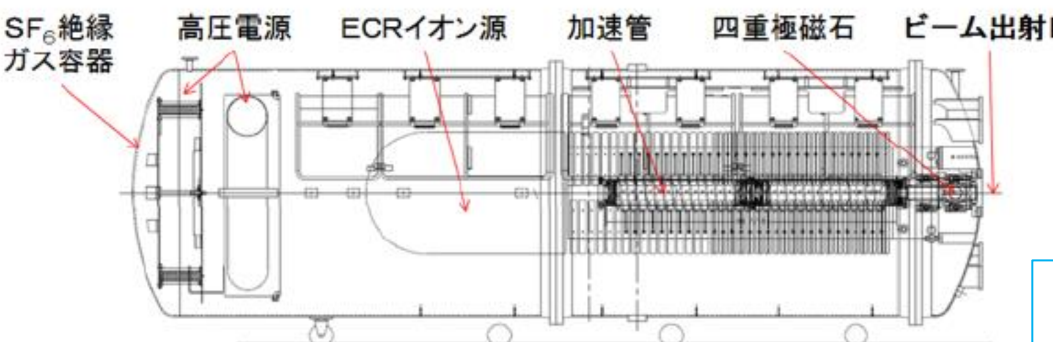
2.8 MeV, 15 mA (42 kW) Dynamitron
+ solid lithium target

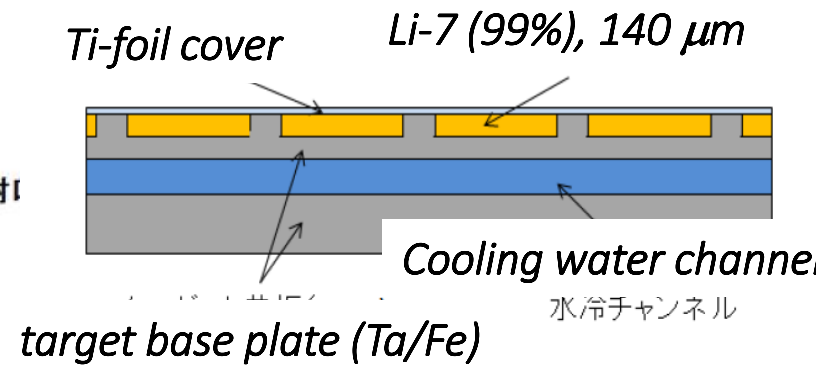
Nagoya University & YAGAMI Co., Ltd.

- *Accelerator commissioning*
- *Target development*

Lithium Target and moderator





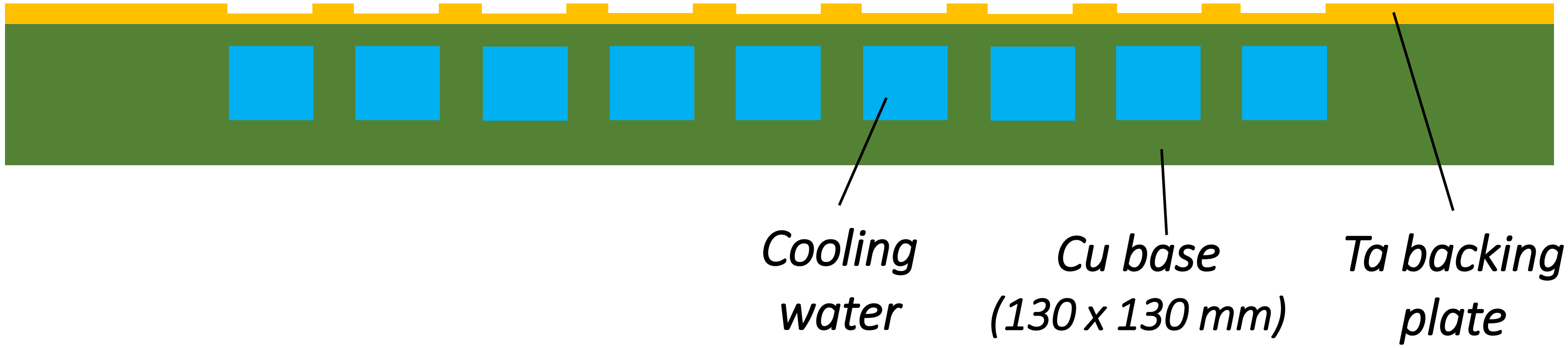


Titanium thin foil is used as a cover to prevent evaporation or oxidization
===sealed radioactive material===

Figures: by Yoshiaki Kiyanagi of Nagoya University

Cross sectional view of the Compact Sealed Li target

(1) Ta backing plate is connected to a Cu cooling base by HIP process.*
The emboss-structure is prepared on the surface of Ta plate.
Ta : High threshold for blistering (H^+ fluence > 1.6×10^{21} H^+/cm^2)
High corrosion resistance and good wettability for liquid Lithium



Courtesy of Y. Kiyanagi

(*HIP : Hot Isostatic Press)

Cross sectional view of the Compact Sealed Li target

(1) Ta backing plate is connected to a Cu cooling base by HIP process*.
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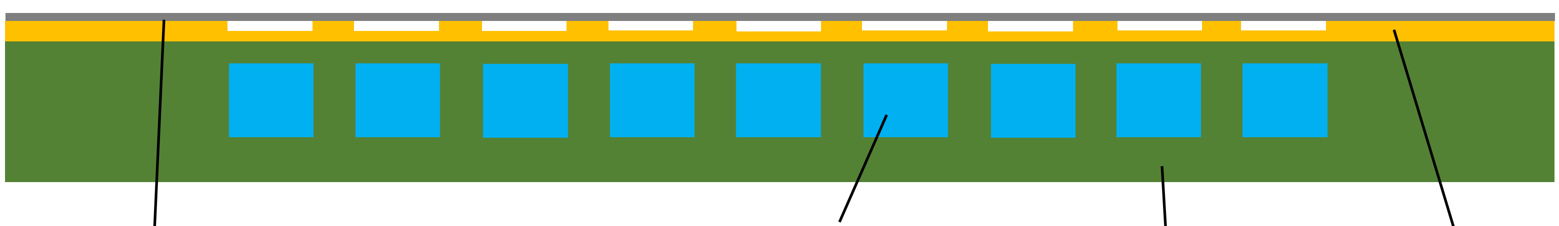
High corrosion resistance and good wettability for liquid Lithium

(2) Thin Ti foil is jointed to the Ta plate by Hot press process.
Ti : High corrosion resistance and good wettability for liquid Lithium



Courtesy of Y. Kiyanagi

(*HIP : Hot Isostatic Press)

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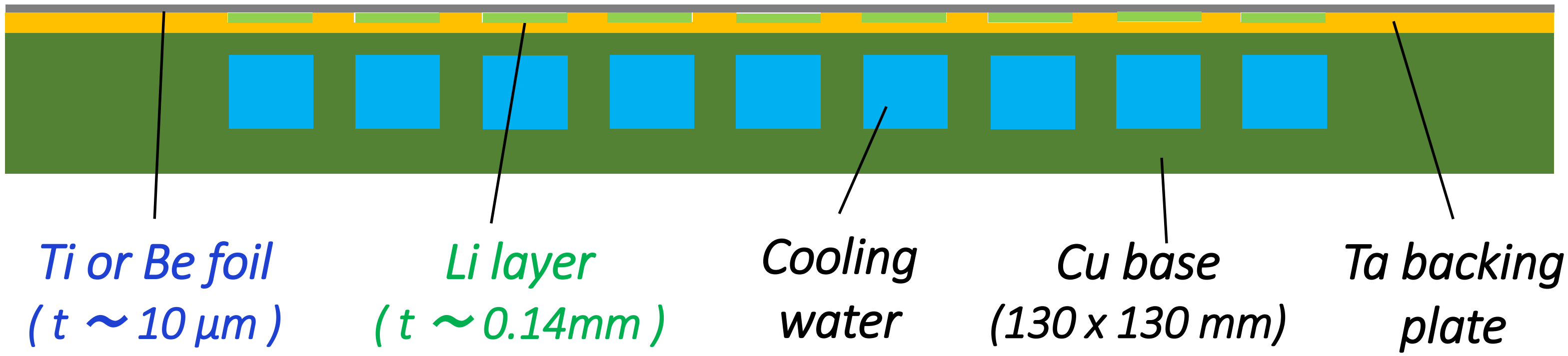
Ti : High corrosion resistance and good wettability for liquid Lithium

(3) Li is set in the thin space of the emboss structure.



Courtesy of Y. Kiyanagi

(*HIP : Hot Isostatic Press)

Cross sectional view of the Compact Sealed Li target

Completed

(1) Ta backing plate is connected to a Cu cooling base by HIP process*.
The emboss-structure is prepared on the surface of Ta plate.
Ta : High threshold for blistering (H^+ fluence > 1.6 x 10^{21} H^+/cm^2)
High corrosion resistance and good wettability for liquid Lithium

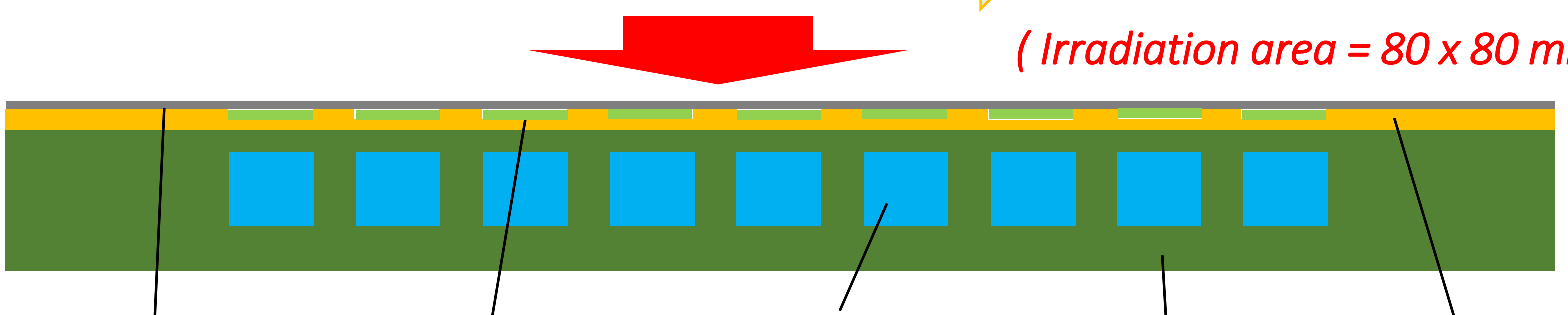
(2) Thin Ti foil is jointed to the Ta plate by Hot press process.
Ti : High corrosion resistance and good wettability for liquid Lithium

(3) Li is set in the thin space of the emboss structure. ← Under development

(4) Proton beam is irradiate to the Li through the Ti foil.
Li and Be-7 can be confined in the target by the Ti foil.

Proton Beam (>2.8MeV, 42kW)

Power density : 6.6 MW / m^2
(Irradiation area = 80 x 80 mm^2)

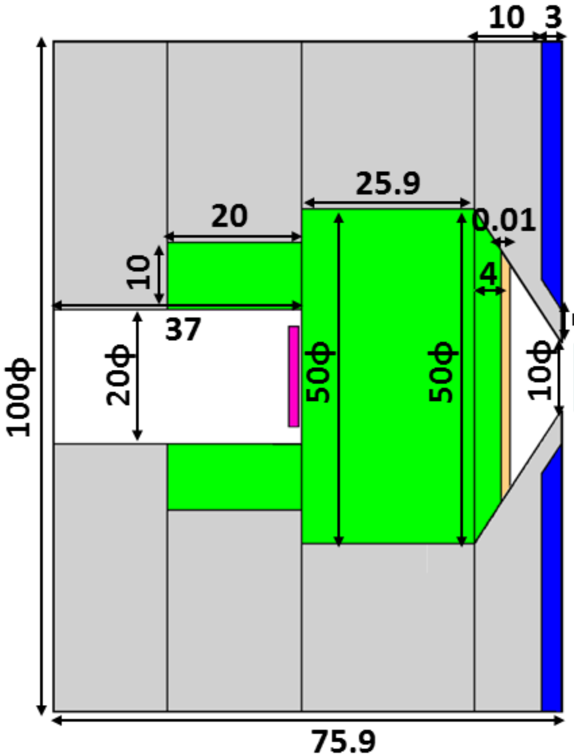


Courtesy of Y. Kiyanagi

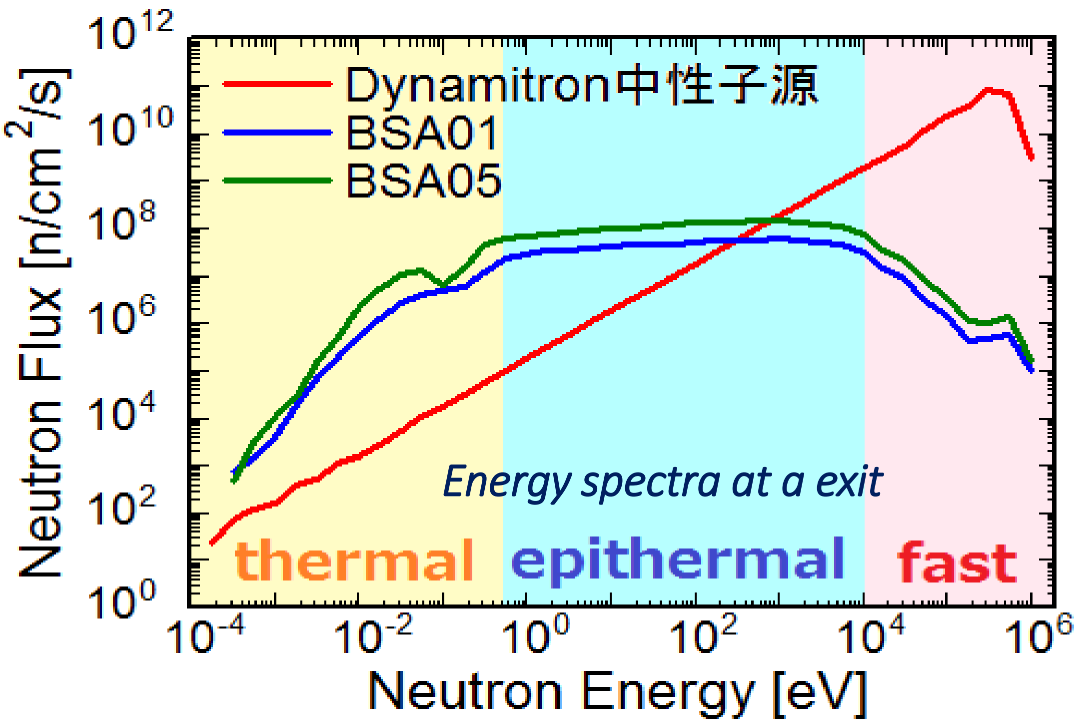
(*HIP : Hot Isostatic Press)

Beam shaping assembly

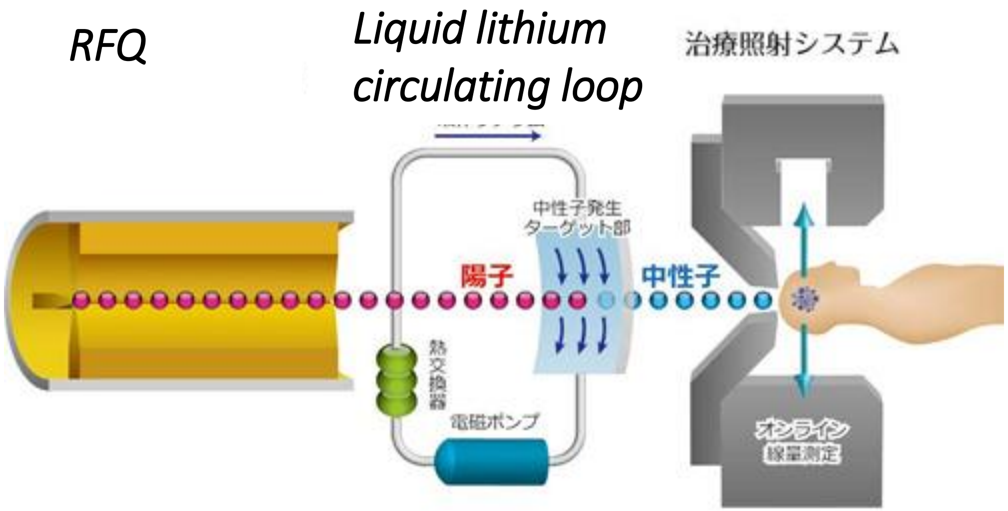
Courtesy of Y. Kiyanagi



Improved (BSA5)



	Original	Improved (Total weight :5.46 t)		
N_{epi} [$\times 10^9$ n/cm^2/s]	0.78	1.89	≧1	Epi-thermal
D_f [$\times 10^{-13}$ Gy・cm^2]	1.99	1.99	≦2	Fast neutron rate
D_g [$\times 10^{-13}$ Gy・cm^2]	1.79	1.69	≦2	γ ray rate
$N_{t/e}$	0.036	0.047	≦0.05	Thermal neutron rate
C/F	0.785	0.704	≧0.7	Current/Flux

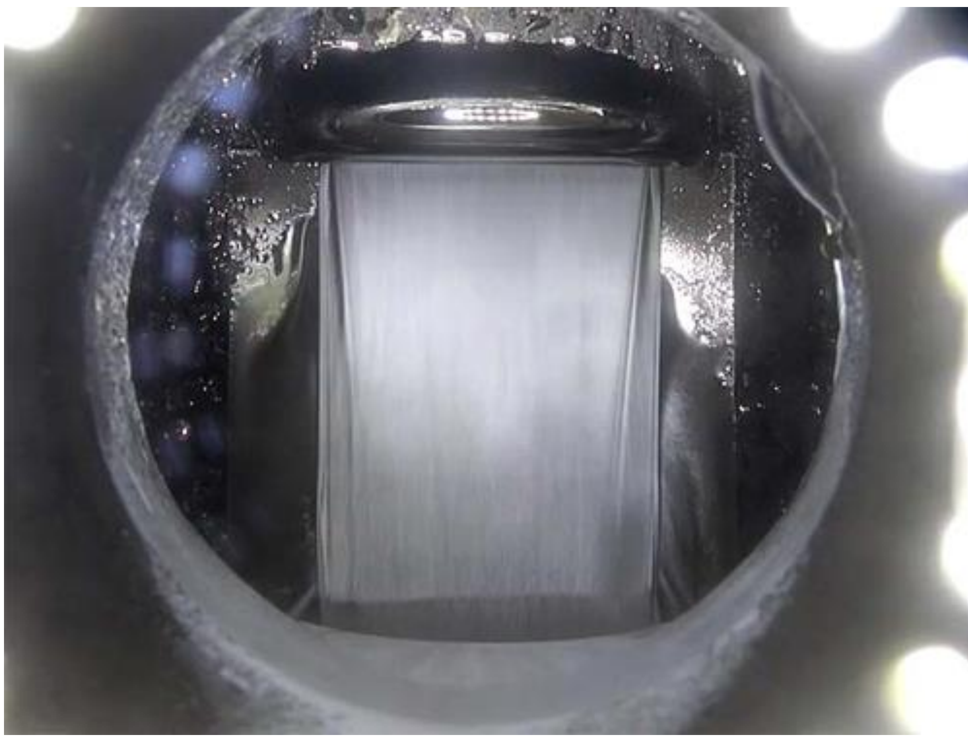


Technology-4:

Liquid lithium target development

Tokyo Institute of Technology & SUKEGAWA ELECTRIC CO., Ltd.

- *Verification test only*



Liquid lithium flow is successfully realized

Temperature	*220 º C*
Flow speed	*30 m/s*
Vacuum pressure	*10^{-4} Pa*
Layer width	*45 ~ 50 mm*
Length	*50 mm*
Liq. Li circulation	*electromagnetic pump*

Figures: Home page of Tokyo Institute of Technology

Ibaraki-BNCT

> ## *Technology-5:*
>
> *8 MeV, 10 mA (80 kW) RFQ + DTL linac + beryllium target*
>
> *Tsukuba University, KEK, JAEA, Ibaraki prefecture*
>
> - *Accelerator commissioning phase*

Accelerator Parameter:

- *Energy* *8 MeV*
- *Peak beam current* *50 mA (max)*
- *Beam pulse width* *1 ms (max)*
- *Repetition rate200 Hz (max)*
- *Duty* *20 % (max)*
- *Ion source* *50 keV ECR + Low Energy Beam Transport*

Characteristics:

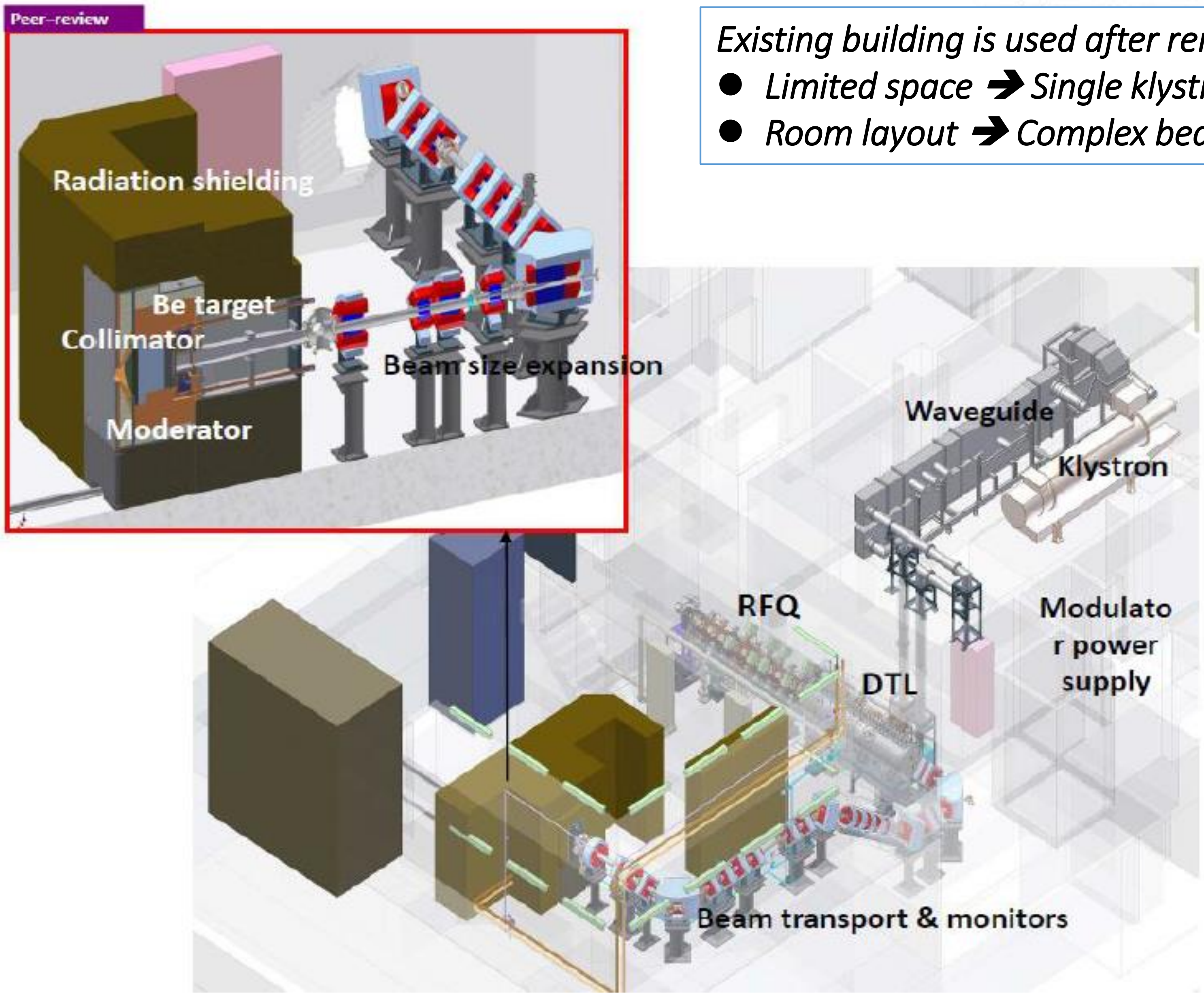
- *J-PARC design base* *RF frequency 324 MHz*
- *Pulsed linac*
- *High peak current ➔ ECR ion source (pulse operation) with 60 mA peak current*
- *Long pulse width and high repetition rate ➔ innovative water cooling system*

New developments in the linac system:

- *Long pulse and high duty klystron modulator power supply*
  ➔ KEK + DAWONSYS CO., LTD. (Korea)
- *Cooling water system for high duty RFQ and DTL with a large temperature difference (ΔT=10 º C) and dynamic temperature control ➔ KEK and MHI*

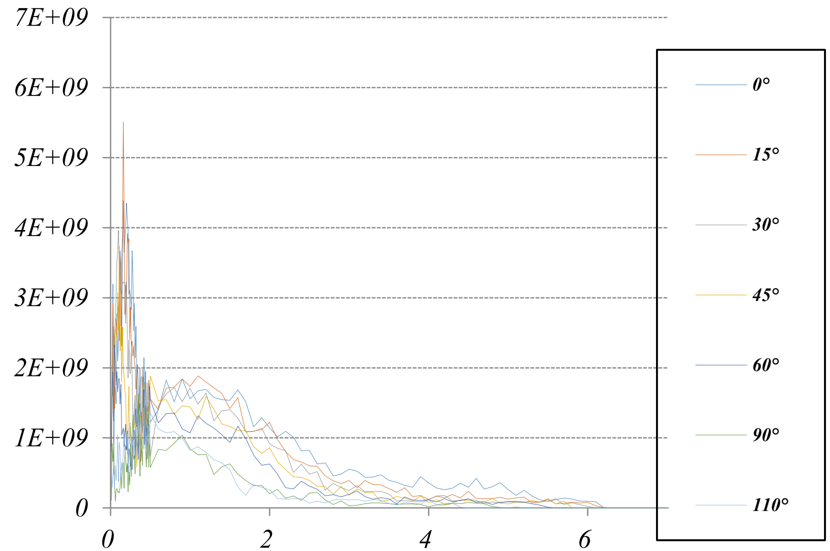
Technology-5 (continued):

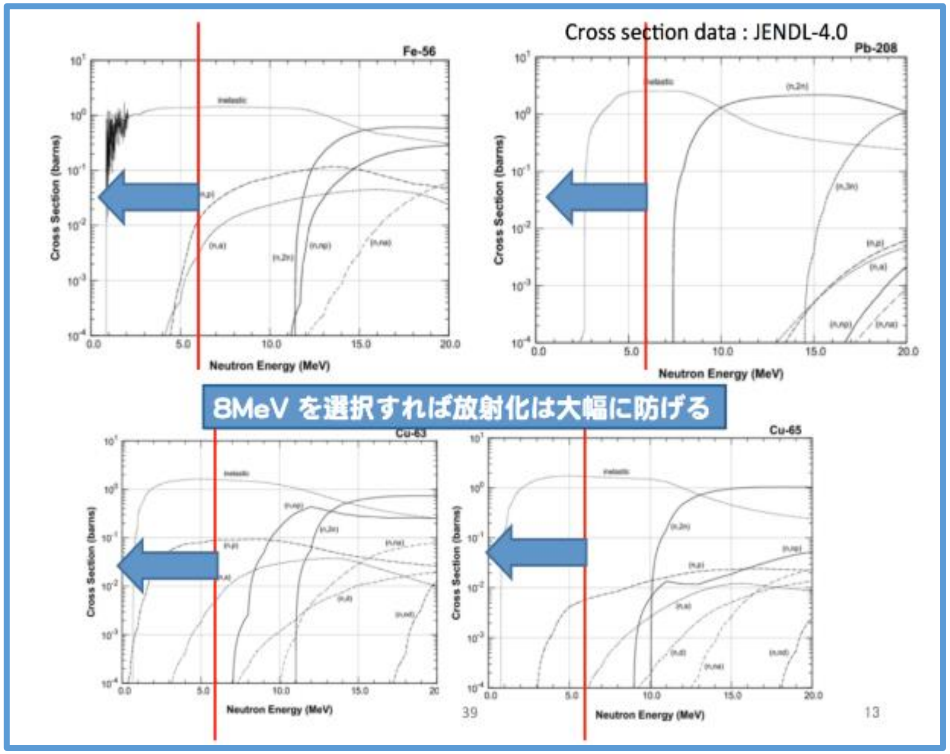
Existing building is used after remodeling
- *Limited space ➔ Single klystron*
- *Room layout ➔ Complex beam transport*



Why 8 MeV ?

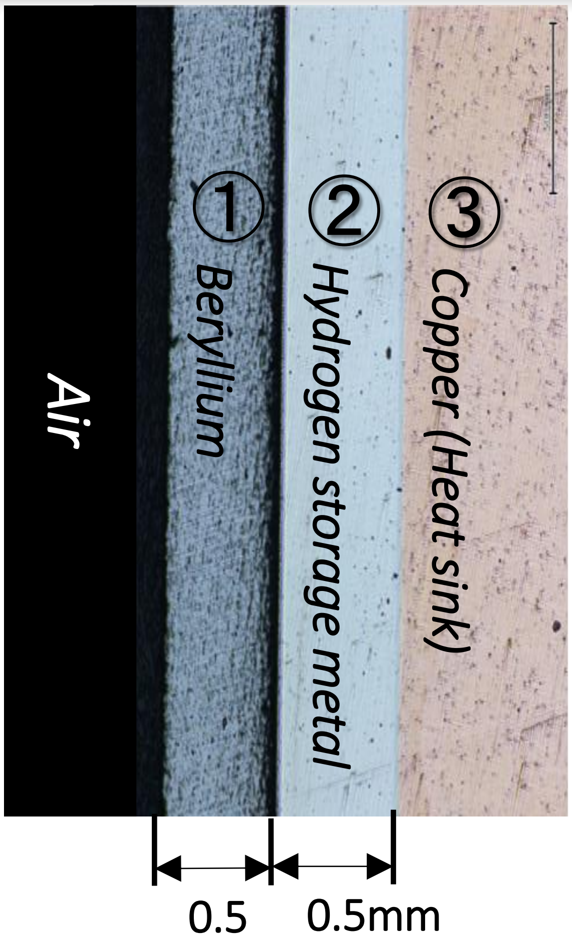
- *Neutron energy < 6 MeV*
- *Below threshold energy of many nuclear reaction channels*



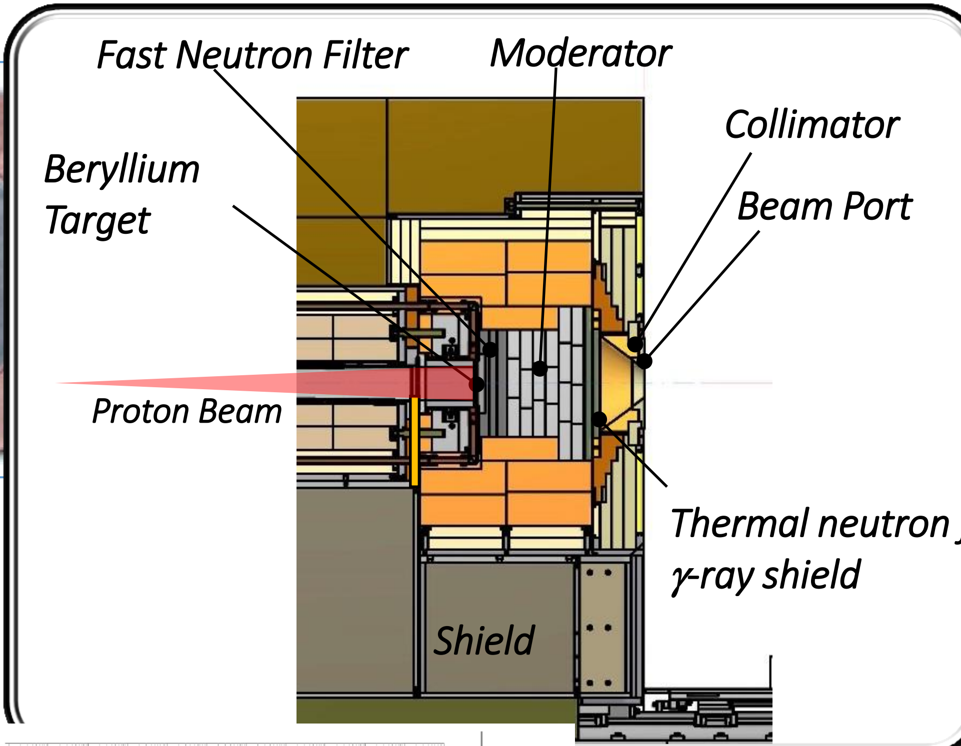


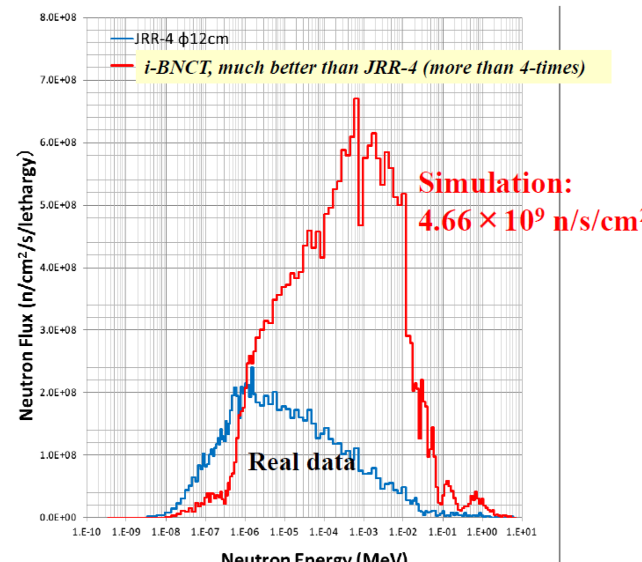
Target and moderator development

Technology-5 (continued):



Diffusion bonding with hot isostatic pressing (HIP)





Design of OIST-BNCT frontend based on solid lithium target

Beam energy	*3 MeV*
Max. peak current	*50 mA*
Beam pulse width	*0.1～1ms*
Repetition rate	*SS, 1～200Hz*
Max. duty	*20%*
Max. power	*30 kW*

Subsystem (red frame only)

1. *50kV-ECR ion source* ➔ *Ibaraki type*
2. *Low Energy Beam Transport*
3. *352MHz RFQ* ➔ *New, higher than Ibaraki*
4. *Multi-beam Klystron* ➔ *New*
   600 kW, 352 MHz
5. *Klystron modulator* ➔ *Ibaraki type but lower HV*
   HV < 35 kV
   Capacitor Charging PS
   Droop Compensation circuit
6. *Cooling water system* ➔ *Ibaraki type*

Require more consideration

1. *Larger size solid lithium target manufacturing (50mm so far)*
2. *Neutron moderator design* ➔ *learn from Nagoya*

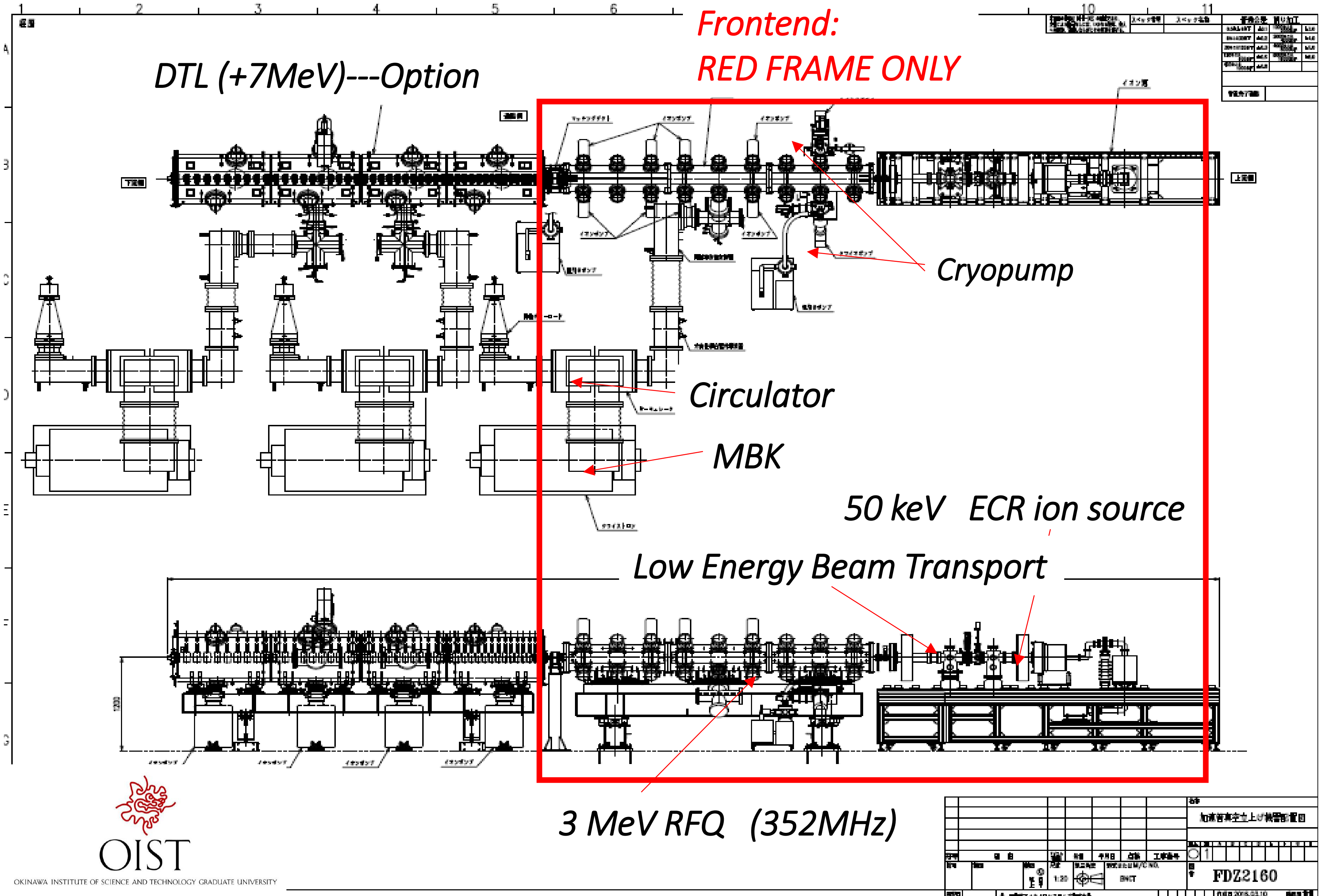
Technology-6:

3 MeV, 10 mA (30 kW) RFQ linac + solid littium target

OIST

- *Design phase*

OIST
OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY GRADUATE UNIVERSITY



OIST
OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY GRADUATE UNIVERSITY

Innovative solid lithium target development by
ULVAC, Inc. and SANKI INDUSTRY
----- Stable and tractable ----

Courtesy of ULVAC, Inc and SANKI INDUSTRY, Inc.

Bonding a thin solid lithium plate on copper heat sink in the glow box (left photo) ----- Good thermal contact at the layer boundary and special water flow channel structure to make an effective heat removal are realized by -----

① Layer boundary is cleaned up before bonding
② Copper heat sink structure
③ Lithium surface is covered with stable thin film (a few micron)
===sealed radioactive material===

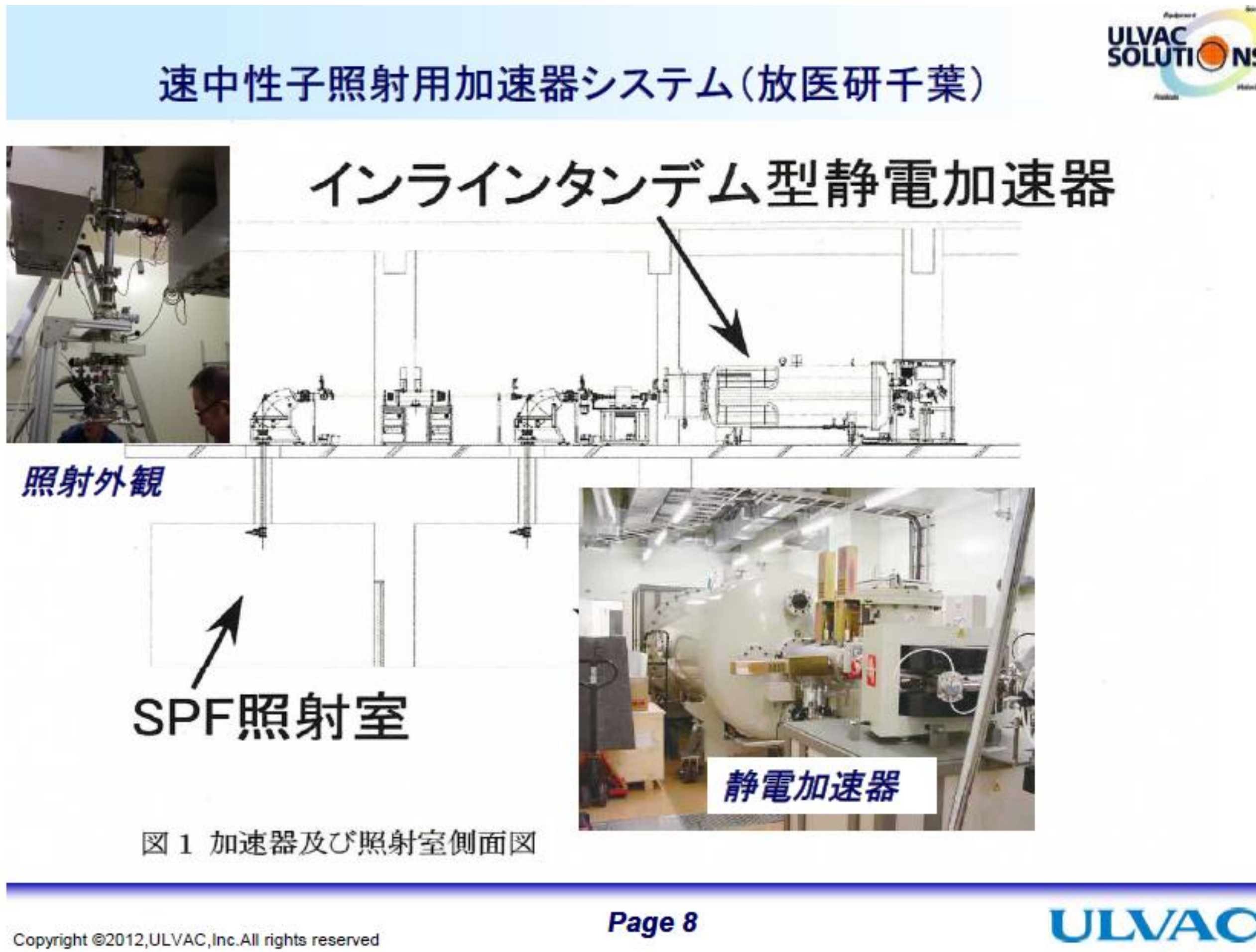
Irradiation experiment with the DC accelerator (right figure)

- *Beam energy* 3MeV,
- *Beam current (DC)* 60 μA,
- *Beam spot diameter* 5 mm

➔ *No damage by blistering, no evaporation of lithium*

Courtesy of ULVAC, Inc and SANKI INDUSTRY, Inc.

Equivalent to 34 mA average current for 120 mm target and beam spot diameter.



Summary and conclusion, my personal view

Various technology choice

Group	Accelerator	Beam Energy	Power	Target material
1. Kyoto University	Cyclotron	30 MeV	33 kW	Thick beryllium (5.5 mm)
==Clinical trial==				
2. National Cancer Center	CW RFQ	2.5 MeV	50 kW	Solid lithium
==Passed radiation facility inspection==				
3. Nagoya University	Dynamitron	2.8 MeV	50 kW	Hermetic liquid lithium
==Accelerator commissioning and target development phase==				
4. Tokyo Institute of Technology	------------		---------	Liquid lithium target
==Target development only==				
5. Tsukuba University	Pulsed RFQ + DTL	8.0 MeV	80 kW	Thin beryllium (0.5 mm)
==Accelerator commissioning==				
6. OIST	Pulsed RFQ	3.0 MeV	30 kW	Solid lithium
==Design phase based on new solid lithium target technology==				

1. *The most advanced project in Japan is the group-1 (Kyoto University). Southern TOHOKU General Hospital in Fukushima, Japan has already constructed the same type and ready for the clinical trial. A few more hospitals are going to introduce the same type.*

2. *It should be mentioned that we still need more studies and experiences to establish the real mass production type for the wide application.*

3. *We should not forget that the accelerator and target are the only frontend of the facility.*

4. *Important development items are the better drag delivery system, the method of clinical treatment planning including imaging technology and understanding of cancer mechanism.*