Progress of D-BNCT Project

Tianjiao Liang

Institute of High Energy Physics, Chinese Academy of Science
Spallation Neutron Source Science Center

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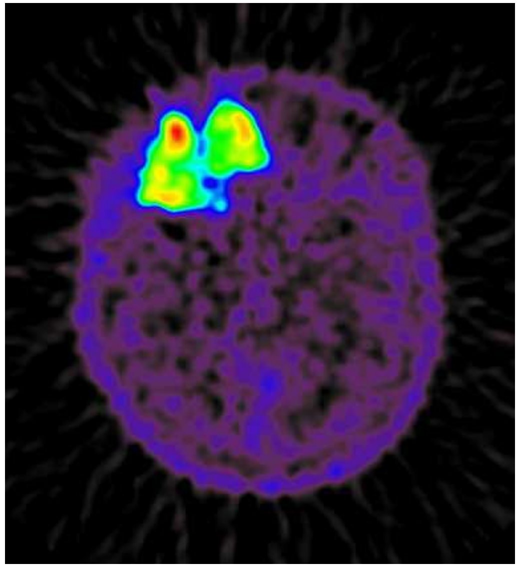
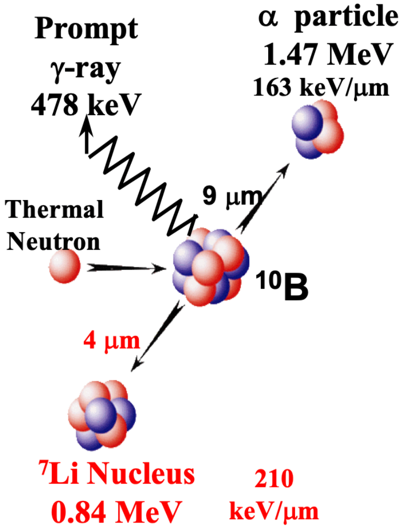
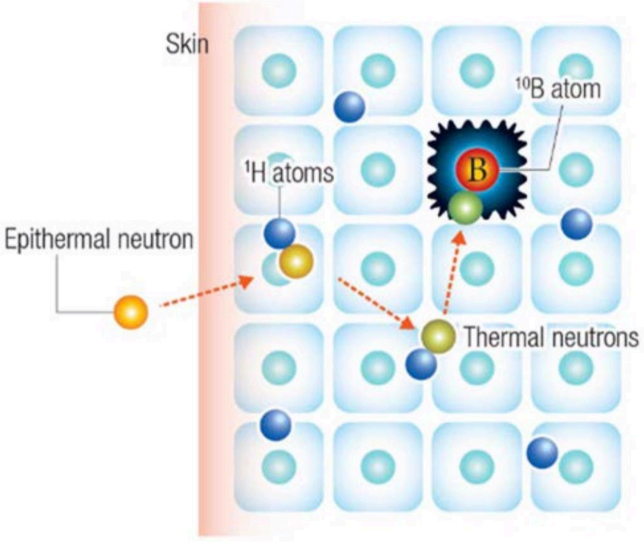
BNCT: Boron Neutron Capture Therapy







Cellular Targeted Heavy-ion Therapy

Targeted thearpy：Boron drugs are enriched in tumor cells, high dose gradient between tumor and normal tissues

Cellular level radiotherapy：7Li range 8-9 microns, α Particle range 4-5 microns in cells

Heavy-ion therapy: 7Li and α particle with high linear energy transfer（LET）, highly lethal to tumor cells.

High flux neutron source + High efficiency boron drug + Medicine

Requirement of B10 Concentration

Thermal neutron cross section of the major nuclide in the human body

^{10}B	3836
^{16}O	0.0002
^{12}C	0.0037
^{1}H	0.332
^{40}Ca	0.44
^{22}NA	0.536
^{14}N	1.75
^{40}K	2.07

- B10 concentration: 30ug/g

  ~10^9 B10 atom per cell

- B10 macroscopic cross-section: 0.7m^{-1}

  H macroscopic cross-section: 2.2m^{-1}

- ~1/4 neutron react with B10

  and 3/4 neutron react with H

□ Higher concentration and Tumor/Normal tissue Ratio (T/N) desired

Requirement of Integrated Neutron Flux

- B10 concentration: 30ug/g
- B10 macroscopic cross-section: $0.7m^{-1}$

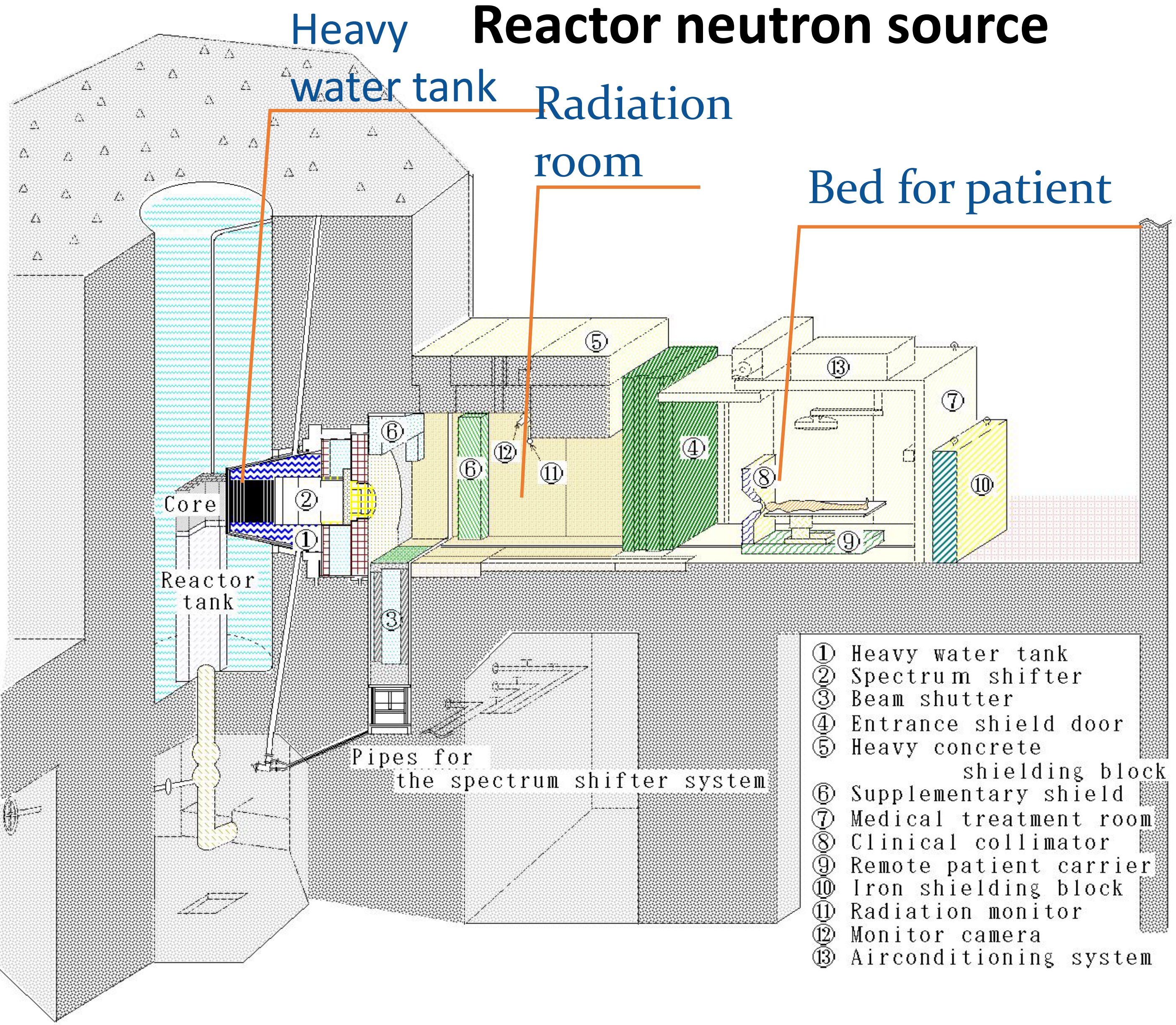
- Assume cell size: 10um， then the probability of B10 capture reaction of one incident thermal neutron: 7×10^{-6}
- Assume cell cross section area: $10^{-6}cm^{2}$ and integrated thermal neutron flux: $10^{12}n/cm^{2}$, then the probability of B10 capture reaction in the cell: 7

- $10^{12}n/cm^{2} = 5x10^{8}n/cm^{2}/s$ x 2000s (~half hour)

□ High flux neutron source compatible with hospital desired

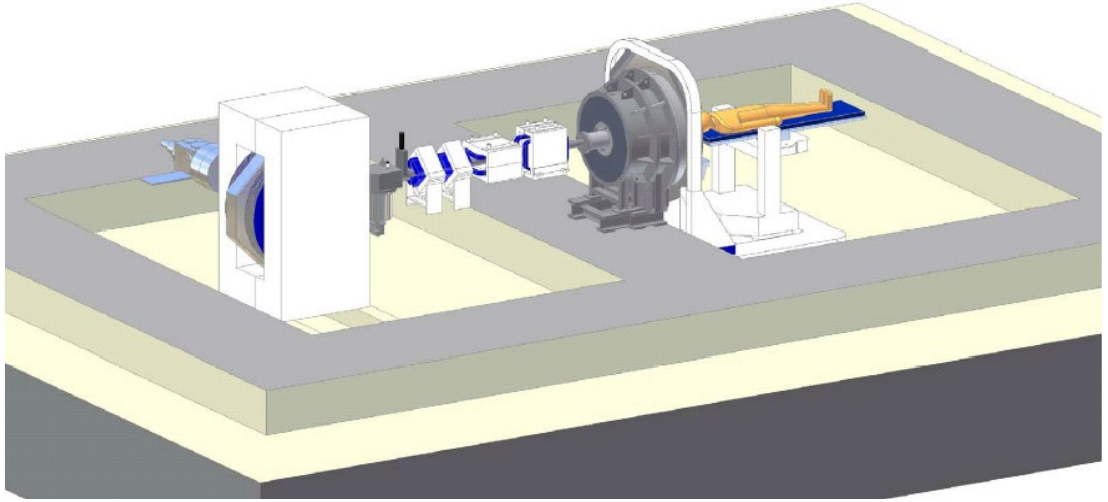
From reactor to accelerator based neutron source

Reactor neutron source



small., simple,safe

Accelerator based neutron source



New Era of Accelerator Based BNCT

In March 2020, Sumitomo Heavy Industries, Ltd. obtained approval from Japan's Ministry of Health, Labor and Welfare (MHLW) for the manufacture and marketing of a new medical device—the accelerator-based BNCT system (NeuCure b System) and its dose calculation program (NeuCure b Dose Engine). This product is among the world's first BNCT medical devices.

Until now, about 900 patients have been treated.

Reference Neutron Beam Quality Factors

TABLE 6. REFERENCE NEUTRON BEAM QUALITY FACTORS

Beam quality component	Symbol or definition	Reference value	Section	Ref.
Therapeutic epithermal flux[a]	ϕ_{epi}	$\geq 5 \times 10^{8}$ cm^{-2}·s^{-1} (e)	3.1	[1, 78[e]]
Thermal to epithermal flux ratio	ϕ_{th} / ϕ_{epi}	≤ 0.05	3.1	[1]
Beam directionality[b]	J / ϕ_{epi}	≥ 0.7	3.1	[1]
Fast neutron dose per unit epithermal fluence[c]	$D_H / \int\phi_{epi}(t)\cdot dt$	$\leq 7 \times 10^{-13}$ Gy·cm^2	3.2.1	Table 27
Gamma dose per unit epithermal fluence[c,d]	$D_\gamma / \int\phi_{epi}(t)\cdot dt$	$\leq 2 \times 10^{-13}$ Gy·cm^2	3.2.5	[1]

[a] ϕ_{epi} refers to the flux of epithermal neutrons in the energy range typically defined for BNCT (Table 1).

[b] Much lower values (e.g., 0.3) can be used for treatment of melanomas with more thermalized beams.

[c] These are doses per unit fluence of epithermal neutrons, where epithermal fluence is defined as $\int\phi_{epi}(t)\cdot dt$, in units of cm^{-2}.

[d] The range reported in reactor based BNCT facilities is 1–13 × 10^{-13} Gy·cm^2.

[e] Ref. [78] reports $\int\phi_{epi}(t)\cdot dt = 5.3 \times 10^{11}$ cm^{-2} used clinically in $t = 17$ min, corresponding to $\phi_{epi} = 5.2 \times 10^{8}$ cm^{-2}·s^{-1}.

TABLE 1. DEFINITION OF NEUTRON ENERGY RANGES USED IN BNCT

Range name	Thermal	Epithermal	Fast
Neutron energy	< 0.5 eV	0.5eV–10 keV	> 10 keV

Note: Neutrons with energies slightly in excess of 10 keV (e.g., 20–30 keV) can be useful for epithermal BNCT as relative biological effectiveness does not undergo a step change at 10 keV.

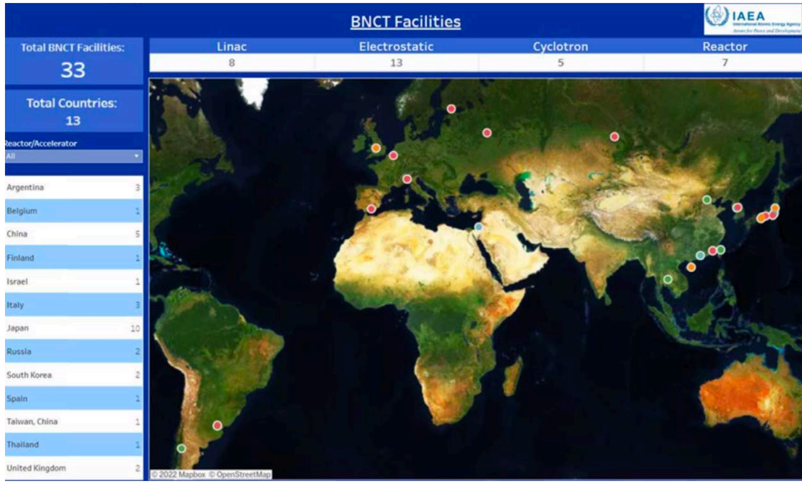
ADVANCES IN BORON NEUTRON CAPTURE THERAPY (June, 2023) IAEA

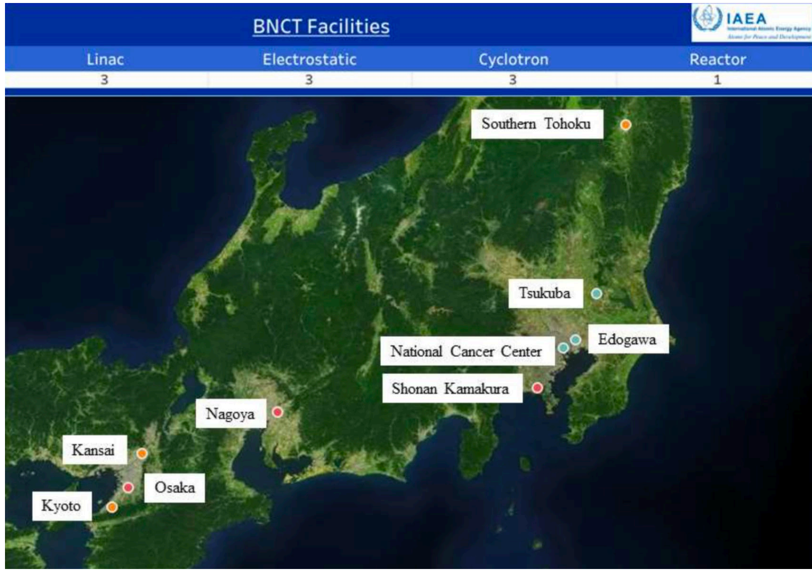
AB-BNCT Worldwide

TABLE 5. CURRENT STATUS AND PERFORMANCE OF ACCELERATORS INTENDED FOR AB-BNCT FACILITIES

Institute/location	Machine status	Target reaction	Beam energy (MeV)	Current goal (mA)	Final power (kW)	Refs
		CYCLOTRONS				
Kyoto University, Japan	Clinical trials and research	5.5 mm ^{9}Be(p,n)	30	1	30	[7, 28]
Southern Tohoku Hospital, Japan	Treatments covered by insurance	5.5 mm ^{9}Be(p,n)	30	1	30	[7, 28, 53]
Kansai BNCT Research Center, Japan	Treatments covered by insurance	5.5 mm ^{9}Be(p,n)	30	1	30	[7, 28, 30]
Pengbo Hainan BNCT Center, China	Project planning	5.5 mm ^{9}Be(p,n)	30	1	30	
		ELECTRODYNAMIC LINEAR ACCELERATORS				
A-BNCT, Dawon Medax, Rep. Korea	RFQ-DTL: Preclinical	Thick ^{9}Be(p,n)	10	8	80	[54]
Tsukuba, Japan	RFQ-DTL: Preclinical	0.5 mm ^{9}Be(p,n)	8	10	80	[31, 55]
SARAF, Soreq, Israel*	RFQ-DTL: Under development	Liquid jet Li(p,n)	2.5	20	50	[33]
INFN, Legnaro, Italy*	RFQ: Under development	Solid ^{9}Be(p,n)	5	30	150	[56]
IHEP, BNCT-01, Dongguan, China	RFQ: Operational	Solid ^{7}Li(p,n)	3.5	5	17.5	[57]
IHEP, BNCT-02, Dongguan, China	RFQ: Under construction	Solid ^{7}Li(p,n)	2.8	20	56	[57]
National Cancer Center, Tokyo, Japan	RFQ: Clinical trial	Solid ^{7}Li(p,n)	2.5	20	50	[32, 36–37, 58]
Edogawa Hospital, Japan	RFQ: Commissioning	Solid ^{7}Li(p,n)	2.5	20	50	[7]
		ELECTROSTATIC ACCELERATORS				
Budker Institute, Novosibirsk, Russia*	VITA: Operational	Solid ^{7}Li(p,n)	2.0–2.3	10	23	[45]
Blokhin Cancer Center, Moscow, Russia	VITA: Under construction	Solid ^{7}Li(p,n)	2.3	7	20	[59]
Xiamen Humanity Hospital, Neuboron BNCT Center, China	VITA: Clinical study and research	Solid ^{7}Li(p,n)	2.5	10	25	[45, 60–61]
CNAO, Pavia, Italy	VITA: Under construction	Solid ^{7}Li(p,n)	2.5	10	25	[45]
Nagoya University, Japan	Dynamitron: Commissioning	Solid ^{7}Li(p,n)	2.8	15	42	[62–63]
University of Birmingham, UK*	Single ended: Under installation	Solid ^{7}Li(p,n)	2.6	30	78	[64–65]
Helsinki University Hospital, Finland	Single ended: Commissioning	Solid ^{7}Li(p,n)	2.6	30	78	[66]
Shonan Kamakura Hospital, Japan	Single ended: Under installation	Solid ^{7}Li(p,n)	2.6	30	78	[67]
University Hospital of Brussels, Belgium	Single-ended: Project planning	Solid ^{7}Li(p,n)	2.6	30	78	[68]
University of Granada, Spain	Single-ended: Under development	Solid ^{7}Li(p,n)	2.1	30	63	[69–70]
CNEA, Buenos Aires, Argentina	ESQ: Under development	^{9}Be(d,n) thin 8 μm, ^{13}C(d,n) thick	1.45	30	43	[7–9]
KIRAMS, Rep. Korea	ESQ: Under development	^{9}Be(d,n) thin 8 μm, ^{13}C(d,n) thick	1.45	30	43	[7–9]

Note: The KIRAMS project is within a collaborative agreement with CNEA, Argentina. Facilities denoted with * are non-clinical facilities.





D-BNCT Project Team

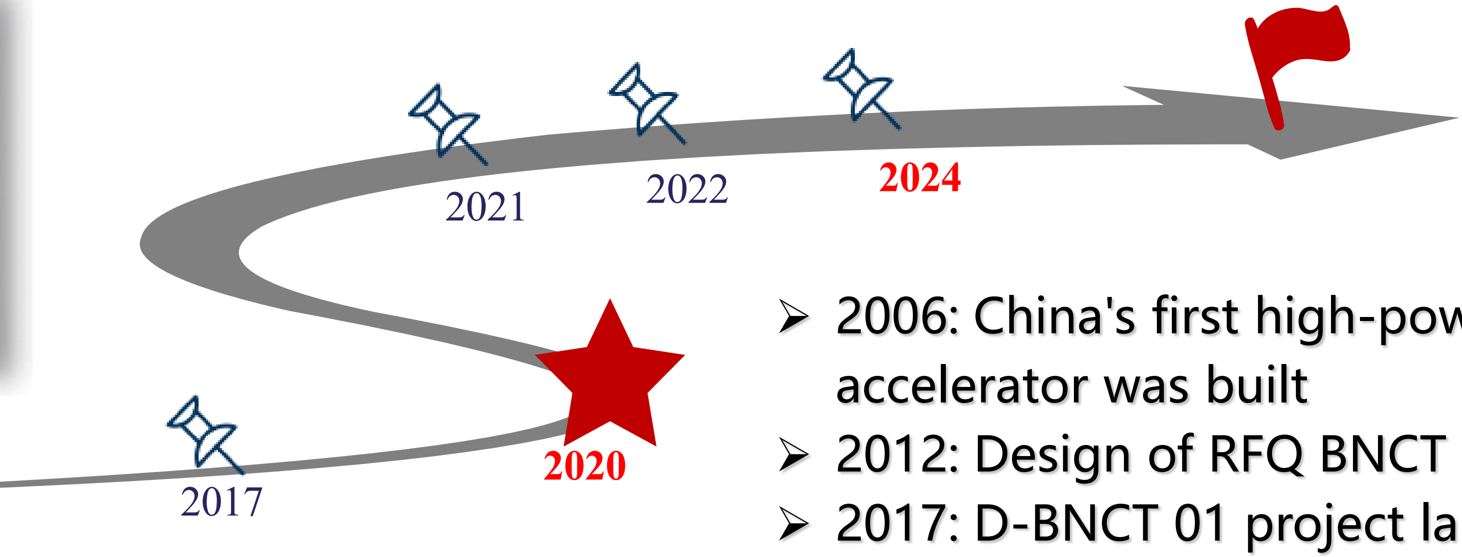
- China Spallation Neutron Source （CSNS），Institute of High Energy Physics (IHEP), Chinese Academy of Sciences.
- Over 50+ members
- Based on the experience from the design and construction of CSNS

- Dongguan People Hospital
- Founded in 1888. One of the earliest Western hospitals established in China
- Over 5000 employees
- Best hostpital in Dongguan

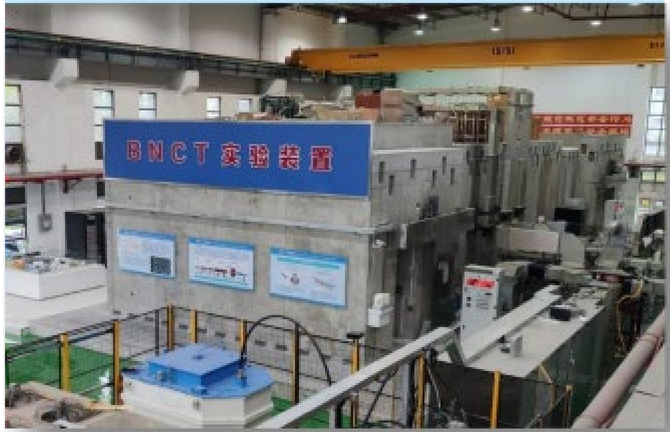
- Guoke neutron Medical Technology Co., LTD. （CASBNCT）
- Founded in 2021
- High-tech enterprise specializing in the R&D, manufacture and marketing of BNCT equipment

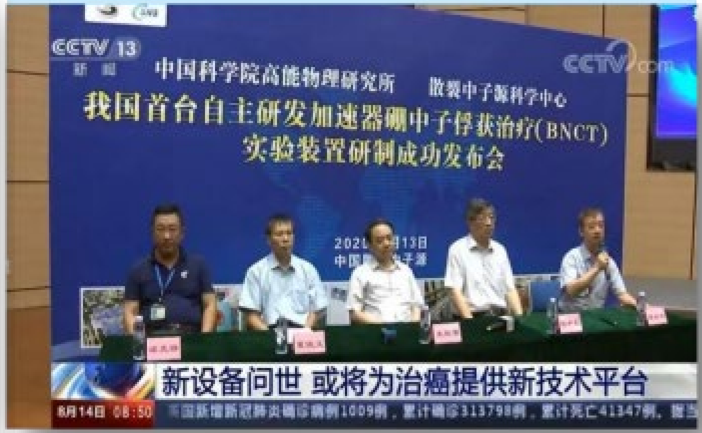
D-BNCT milestone

The development of the RFQ accelerator was supported by the 973 Program



BNCT experimental device The release of Chinas first BNCT experimental device in 202 0



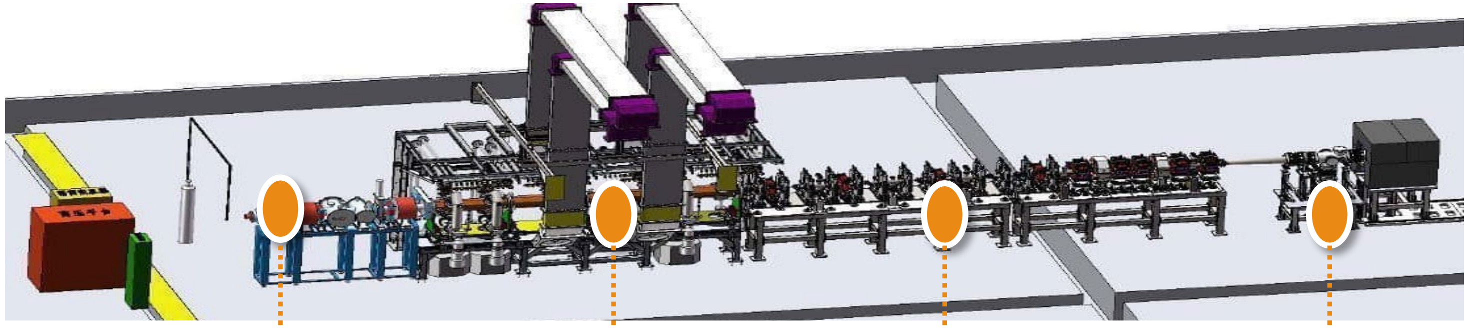


- 2006: China's first high-power RFQ accelerator was built
- 2012: Design of RFQ BNCT started
- 2017: D-BNCT 01 project launched
- 2020: D-BNCT 01, Chinas first BNCT experimental facility was built successfully
- 2022: The clinical equipment D-BNCT 02 project started
- 2023: D-BNCT 02 are installed in place.
- 2024: Type inspection and preclinical experiments of D-BNCT 02 .

D-BNCT 01

- The first accelerator BNCT experimental facility in China, located in the China Spallation Neutron Source with area of 1000㎡.
- Engineering verify and prototype for clinal facility
- Provide neutron beam for R&D of boron drug.
- Reuse some old accelerator components.

D-BNCT 01： Configuration and Parameters



ECR ion source

RFQ accelerator

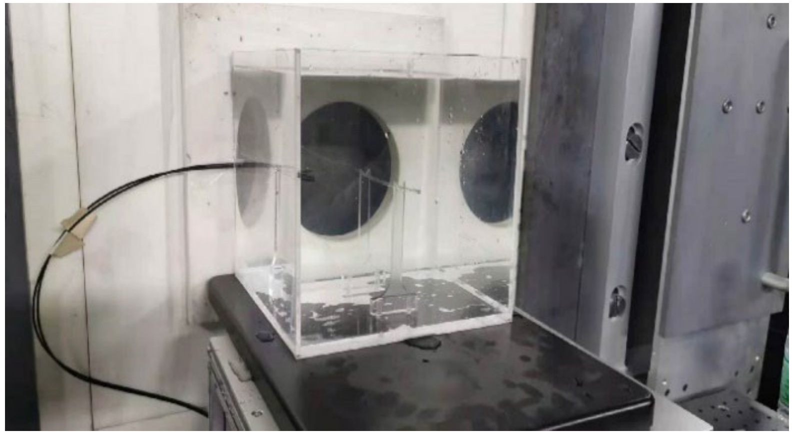
Transmission line

Target and BSA

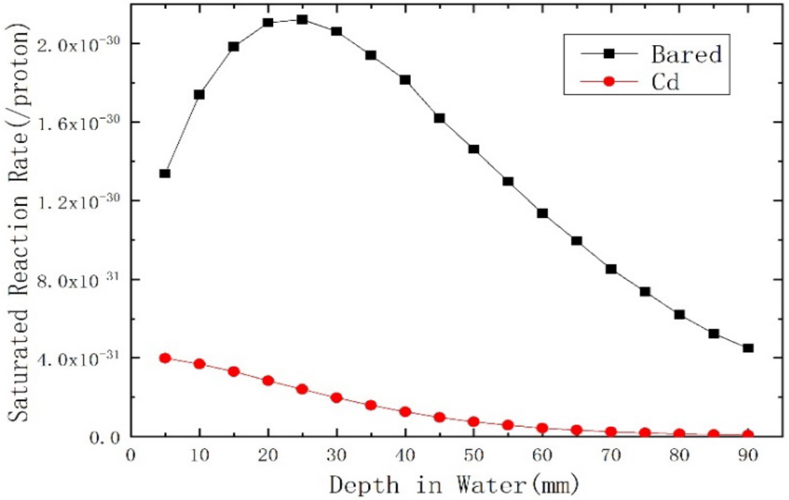
Accelerator Type	RFQ
Proton Energy	3.5MeV
Mean Current	5mA
Tartget Type	Solid lithium Target
Designed proton beam Power	17.5kW
Current proton beam power	5-10 kW
Epi thermal neutron	$2x10^{8}$ n/cm^{2}/s
γ compoent	< $2x10^{-13}$ Gy cm²/n_{epi}
Thermal neutron flux ratio	< 0.05

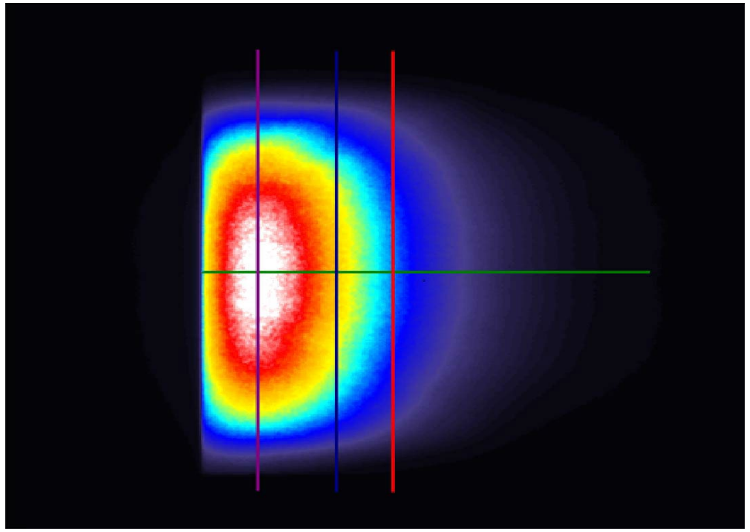
- Breakthrough in key technologies: lithium target, BSA, remote maintenance of target…

D-BNCT 01： Beam Characteristics

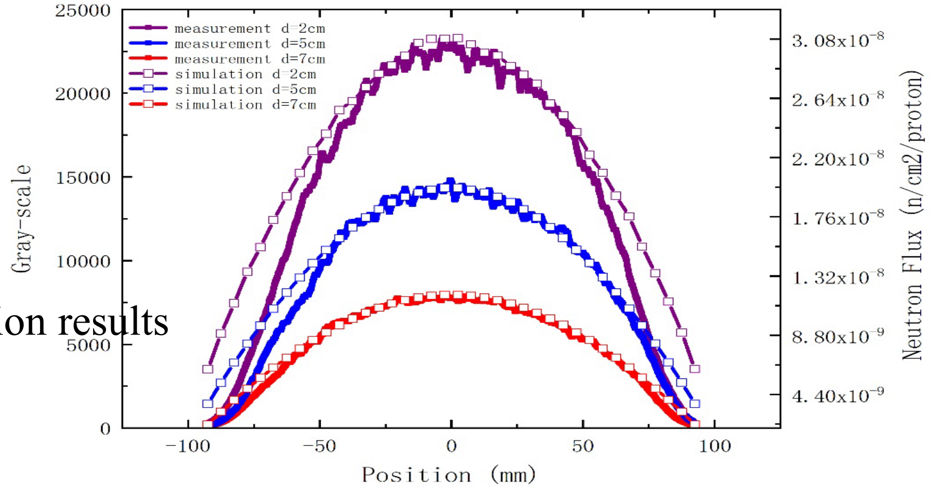


Water Phantom experiment





Copper foil activation results



JunYang Chen, etc. Evaluation of neutron beam characteristics for D-BNCT01 facility, NUCL SCI TECH (202

D-BNCT 01: Support for Drug R&D

Cell experiments

Fixed method of the mouse

Mouse experiments

Animal place

- More than 1,000 cell and animal experiments for dozens of university, institute and enterprises, including glioma, head and neck tumor, breast cancer, liver cancer, melanoma and esophageal cancer.
- Rich experience of preclinical experiment accumulated

D-BNCT 02: Cooperative Hospital

■ BNCT Treatment Center

- Loacted at Dongguan People’ s Hospital
- Capability for two sets of BNCT equipment
- Land area of about 4000㎡ and construction area of 18464㎡
- Four floors above ground and one floor below.

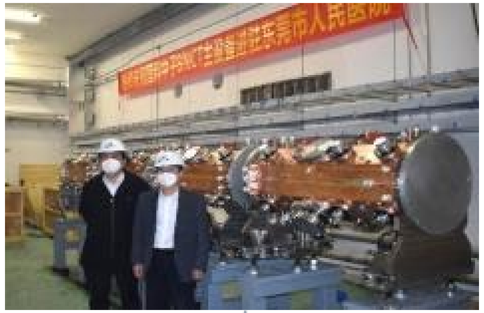
■ BNCT Research Center (under construction)

- Next to the BNCT treatment center
- 12 floors and approximately 300 research beds
- Improving and registering BNCT equipment
- Developing and evaluating boron drugs, as well as their clinical applications.

BNCT Treatment Center

BNCT Research Center

D-BNCT 02: Milestone



Jan 2022
Project launched

July 2022
The BNCT building topped out

Dec 2022
RFQ accelerator installed

Mar 2023
Accelerator commissioning

Dec.2023
Fisrt neutron beam beam

Apr 2024
Preliminarily commissioning completed

Aug 2024
Cell and animal cell experiment completed

D-BNCT 02: Overview

■ Product name: Boron neutron capture therapy system. Product model: CASBNCT-50kW-01

■ Design philosophy

- Combination of advanced accelerator technology (ECR ion source + RFQ accelerator + solid power source) and rotating solid lithium target

- High efficiency BSA design, supply high flux epithermal neutron with good therapeutic quality.

- Short treatment time, short waiting time after treatment, high clinical turnover rate.

- 2 horizontal treatment rooms + 1 vertical treatment room (reserved).

D-BNCT 02: Configuration and Parameters

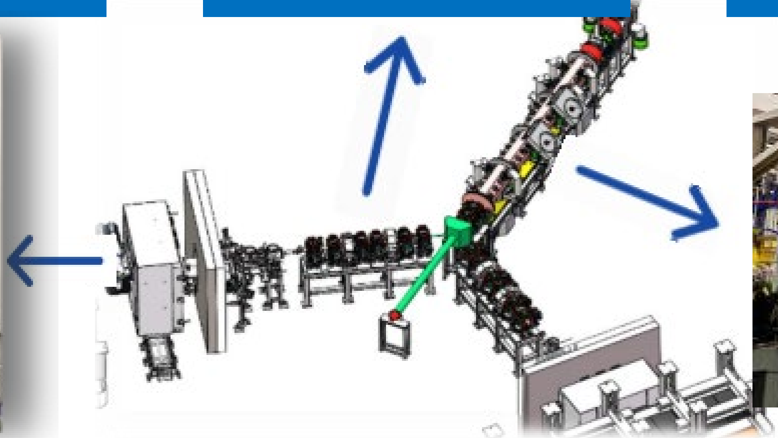
Accelerator	RFQ
Proton energy	2.78 MeV
Current	10 mA
Treatment rooms	2 horizontal + 1 vertical (reserved)
Target	Rotate lithium target
Maintenance mode	manipulator
Beam aperture	10,12,15cm
Epi thermal neutron flux	$>6\times10^{8}$ n/s/ cm^2
Fast neutron component	$< 5\times10^{-13}$ Gy .cm 2
γ component	$< 2\times10^{-13}$ Gy .cm 2

Control system

Transmission line

ECR ion source

Patient Support system



RFQ Accelerator

- The subsystem includes the ion source, low-energy transmission, RFQ accelerator, high-energy transmission, accelerator control, neutron target, target auxiliary system, the radiation head, patient support, laser positioning, neutron beam monitoring, treatment control system, treatment planning system, and other auxiliary equipment.

D-BNCT 02: Installation

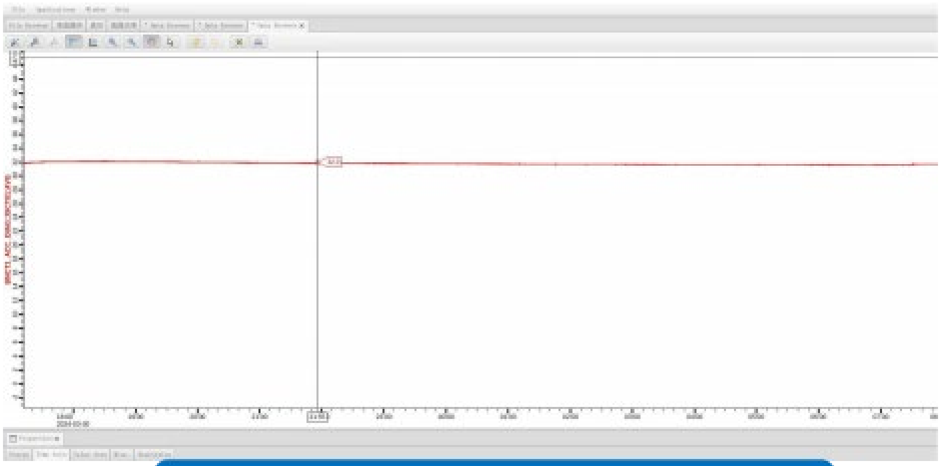
D-BNCT 02: Accelerator

- The scheme of ECR ion source + RFQ accelerator + solid state power source, is suitable for medical devices with the advantage of low proton energy, high beam power, good stability, long life and other advantages
    - Low proton energy is beneficial for radiation protection, neutron slowing down, reducing the size of BSA and shortening the waiting time between treatments
    - High beam power--high neutron yield, shortening the treatment time

D-BNCT 02: Accelerator

ECR ion source:

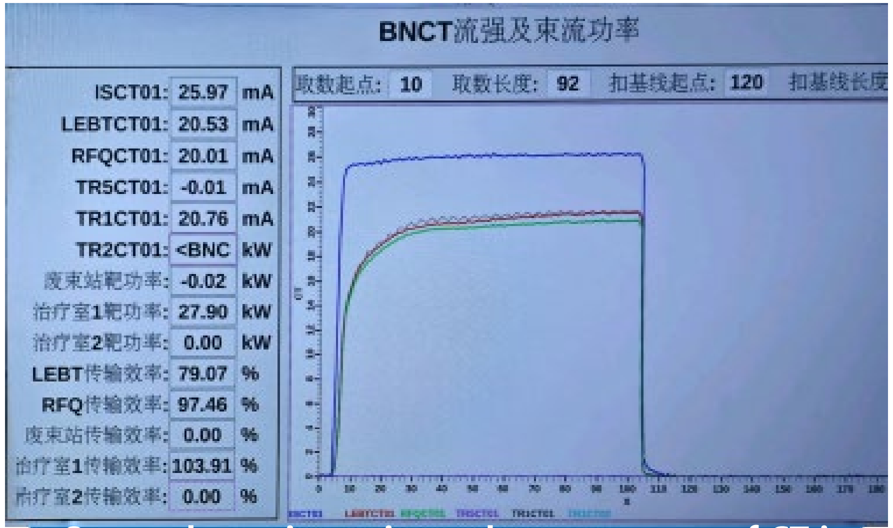
- With the advantages of high discharge efficiency, small beam emission and long life
- One-button mode is adopted to realize the rapid beam emission.



of CT pulse beam intensity at the ion source outlet

RFQ accelerator:

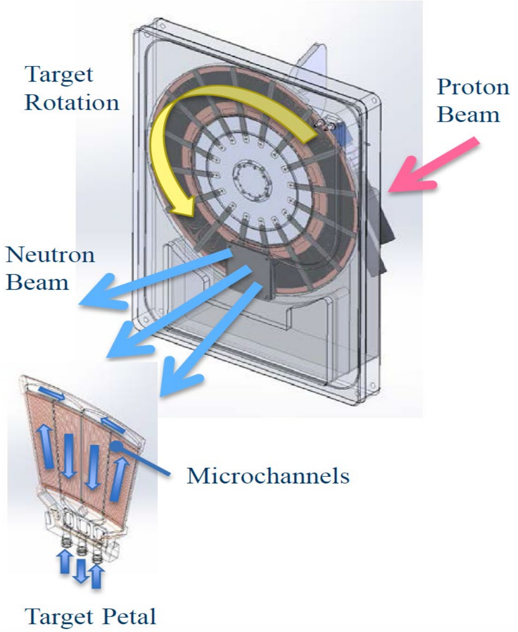
- Simultaneous beam convergence, focusing and acceleration, suitable for low energy of high current, high duty cycle and high power accelerator.
- pulse working mode with a beam repetition frequency of 200Hz, a pulse length of 4ms and an occupancy ratio of 80%.



Output beam intensity and target power of CT in each section of accelerator

D-BNCT 02: Target and BSA

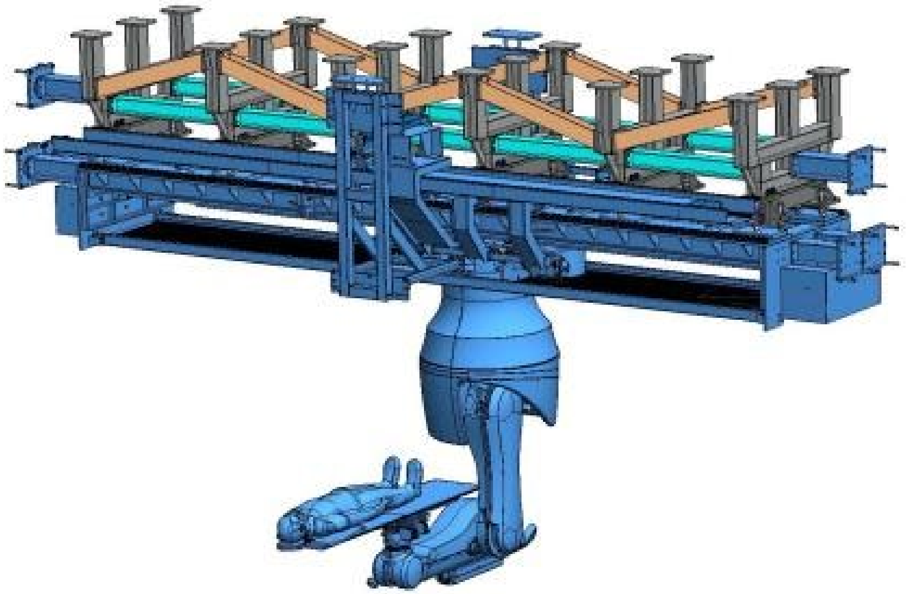
- The rotating target adopts rapid rotation, large beam spot, high flow water cooling and other technologies.
- Expected to be increased to 70 kW
- Long lifetime to reduce the frequency of target replacement.
- Automatic disassembly function, easy to maintenance.
- Compact BSA structure, meet the IAEA recommended value, low radiation activation and short waiting time after irradiation.



D-BNCT 02: Patient support system

Robotic arm patient support and positioning system

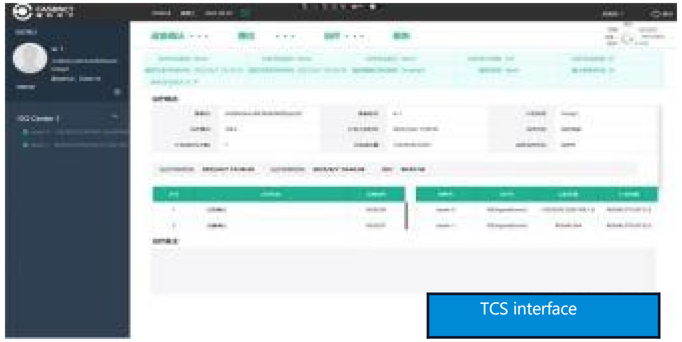
- Six-degree-of-freedom precision mechanical arm connected to a medical carbon fiber treatment bed;
- Top hanging installation, and equipped with a horizontal moving seventh axis.
- Horizonal motion deviation less than 1mm and motion deviation less than rotation motion deviation less than 0.5°
- Intelligent control to improve the operation efficiency.
- Reduced activation design, collision protection, highly stable and reliable performance



D-BNCT 02: Software system

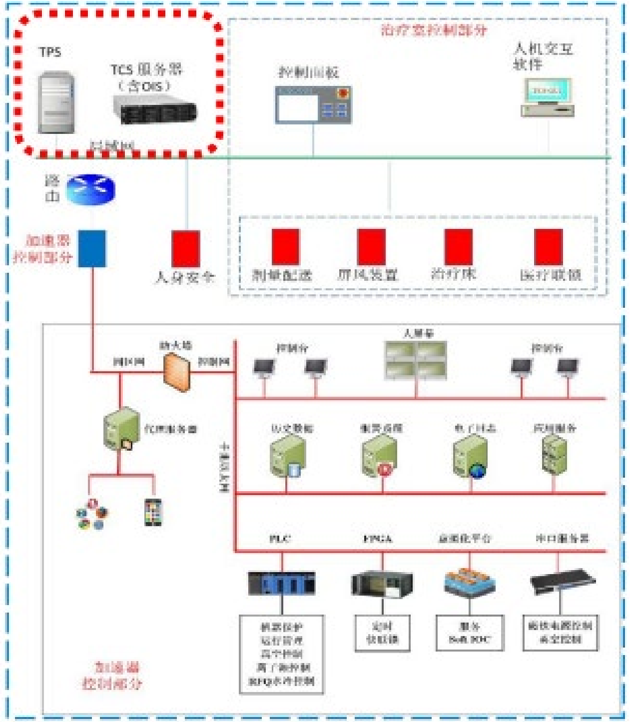
Core software system has been deployed

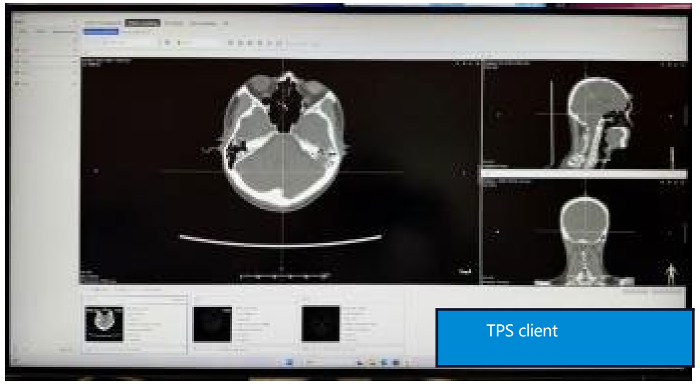

TCS client


TCS interface


TCS Panel

- High integration treatment control system (TCS) with visual operation.
- A fully functional high precision treatment planning system (TPS).

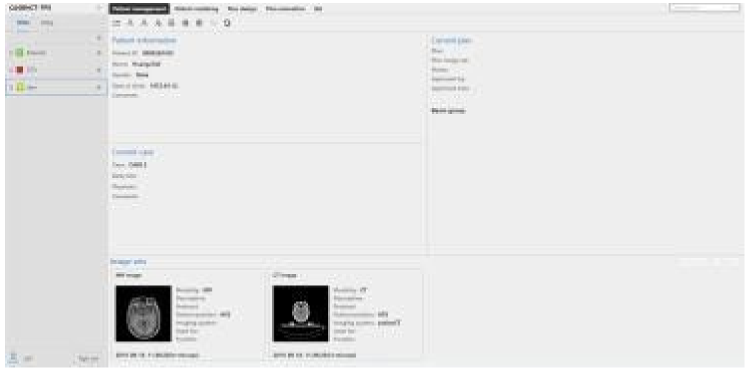



TPS client


TPS calculation

D-BNCT 02: Treatment Plan System TPS

Patient management



Patient import, export, open, query, treatment file report, DICOM treatment file export, etc

Patient modeling

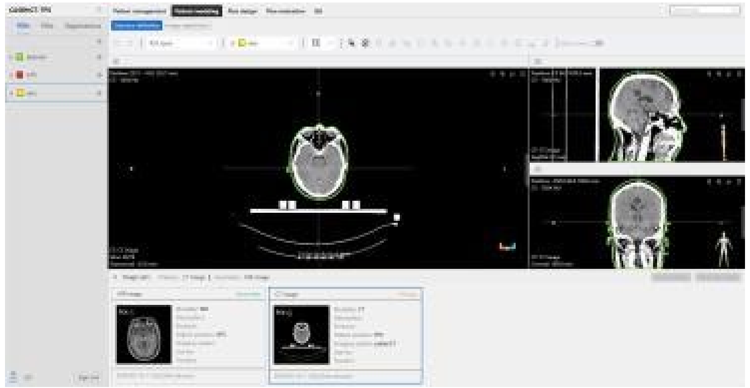
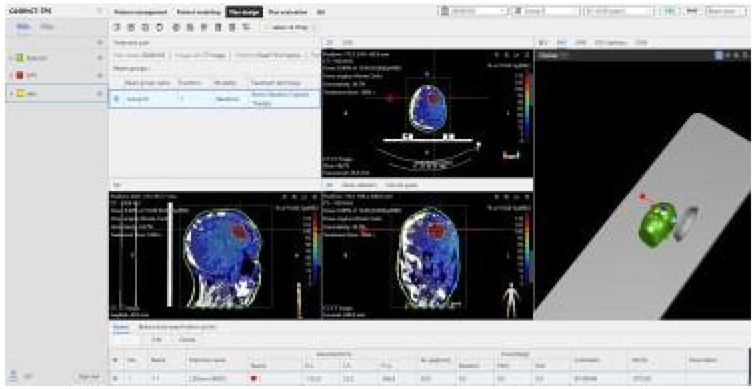


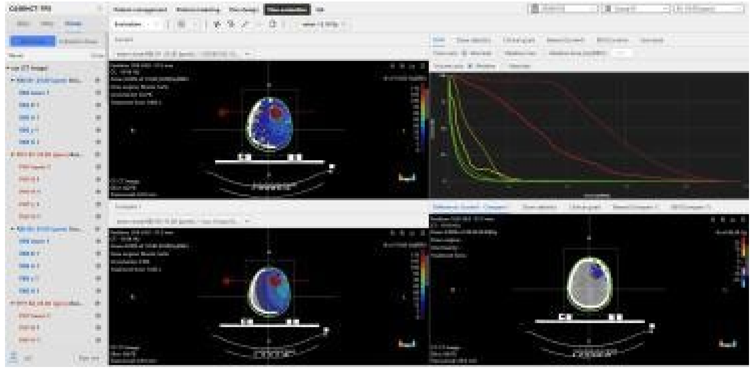
Image registration, ROI and POI drawing and definition

Plan design



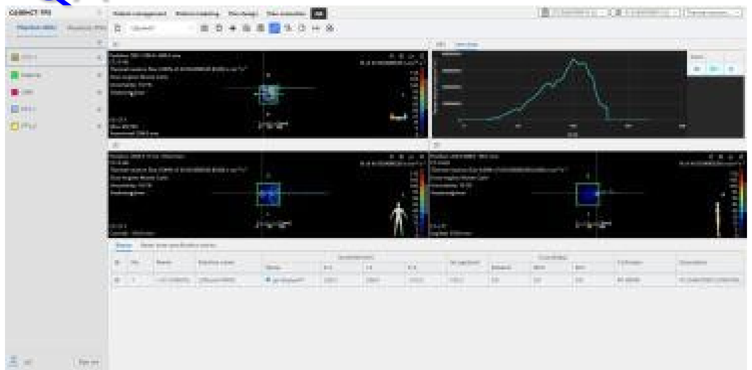
Design beam parameters and prescription dose, calculate dose distribution equip DVH

Plan evaluation



Provide a variety of evaluation tools and multi-plan comparison to evaluate the plan.

QA

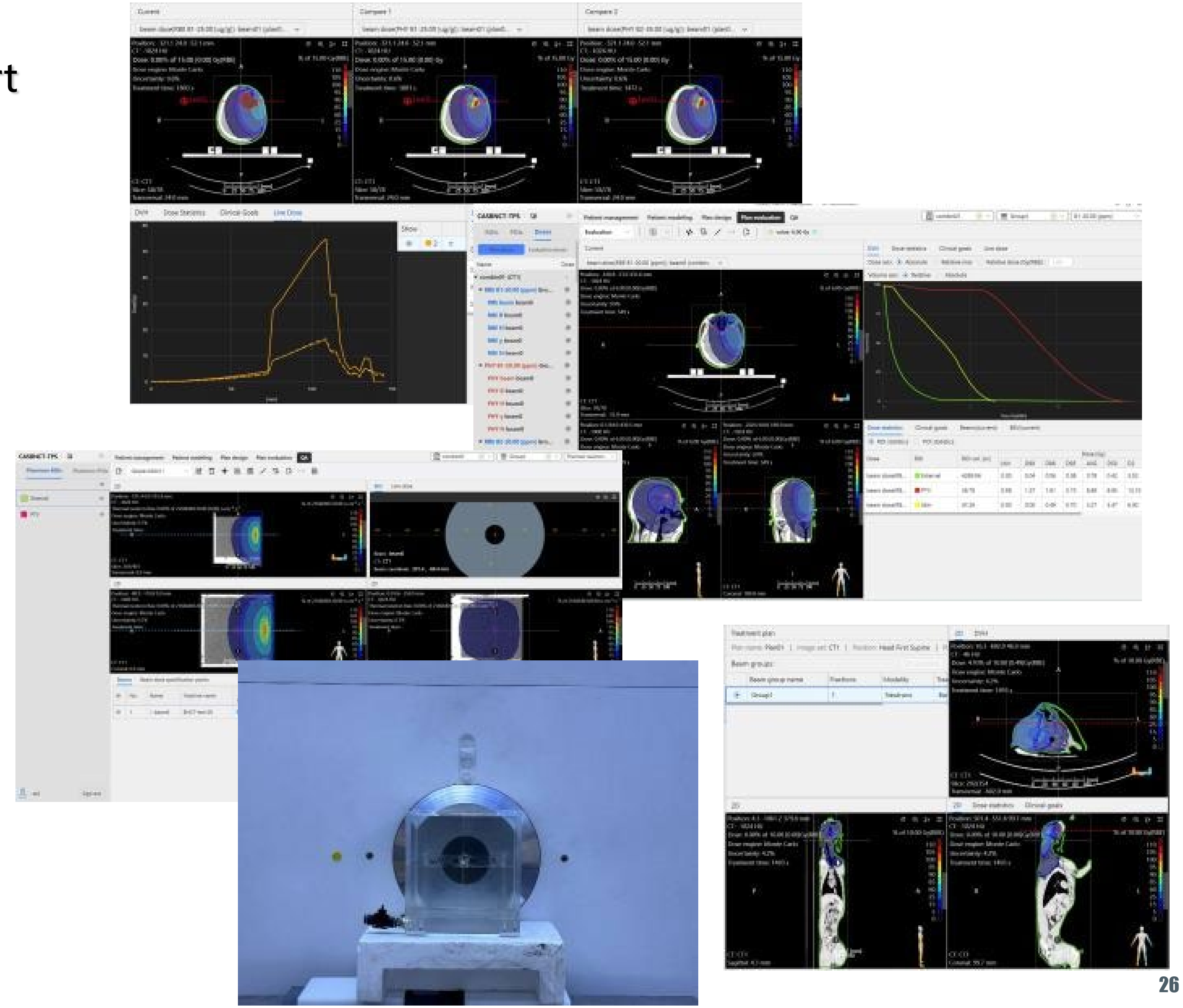


Provides QA verification of the thermal neutron flux and gamma dose rate for the patients treatment plan.

D-BNCT 02: TPS Dose Verification

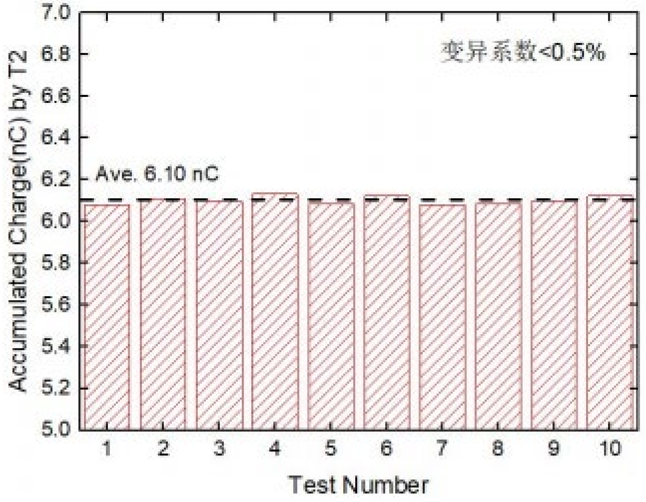
Core functions of TPS

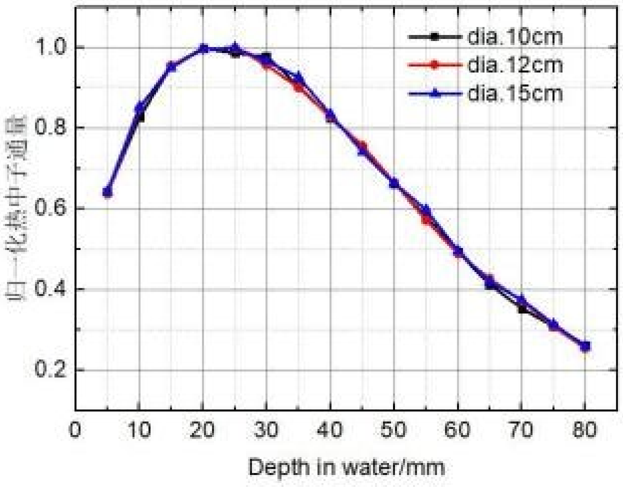
- Neutron and photon Monte Carlo transport simulation
- The neutron source term of device
- Import of CT/MRI/PET-CT data
- The elemental composition and the boron concentration of different tissues
- Blood boron concentration ratios and CBE, RBE for different tissues
- B/N/H/Gamma doses
- Physical dose and bioequivalent dose
- Multiple treatment plans compared
- Validation of treatment plan dose
- large animals experimental mode

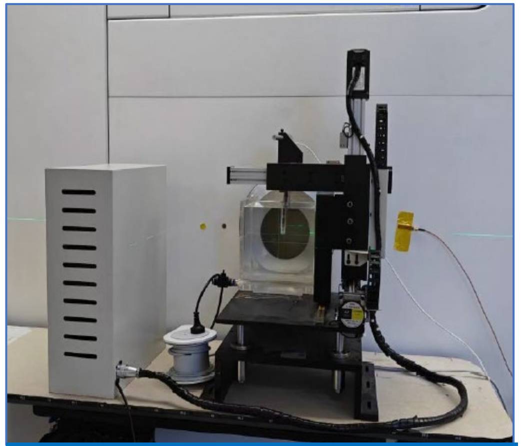


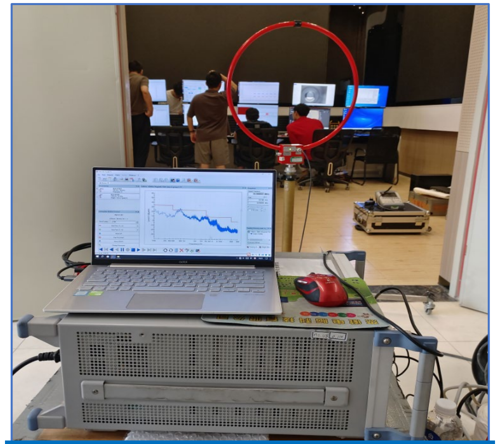
D-BNCT 02: Type Testing

- Peak flux in the water tank > 1.2×10^9 n/s/cm2
- Peak flux at beam port >6×10^8 n/s/ cm2
- The stability of BNCT system meets the clinical requirements.

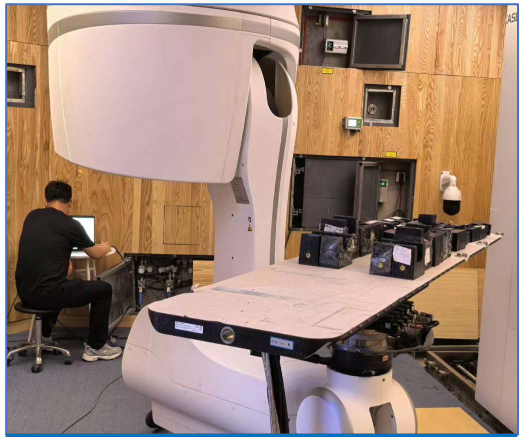





Neutron beam testing


EMC testing

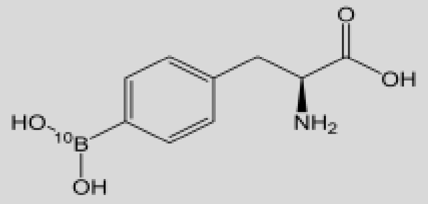

Software testing


Positioning testing

D-BNCT 02: Boron Drug

➢ BPA boron drug cooperate with Hainan Puli Pharmaceutical Co., Ltd.

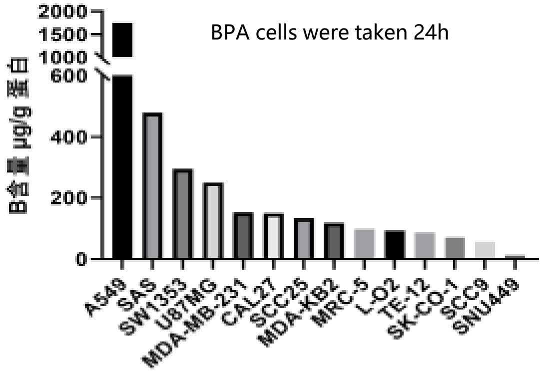
- Impurity of clinical batch BPA <0.5%, and the abundance of ^{10}B >99%
- ^{10}B flavenol for injection
- Clinical batch of API produced under GMP conditions
- The safety and pharmacokinetics completed

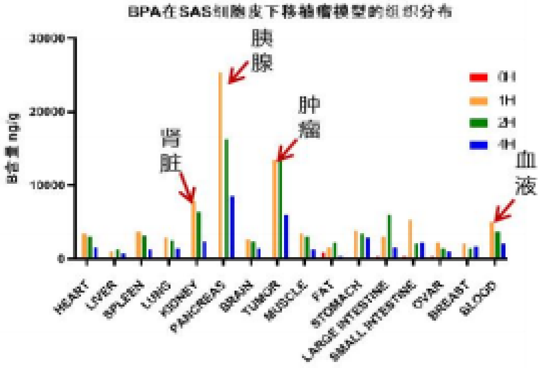


(S)-2-amino-3-[4-(10B)-dihydroxyphenyl]propanoic acid (L-BPA)

- The efficacy and safety of the drug + neutron irradiation experiments finished

Preliminary experiments demonstrate that significant inhibitory effect on tumor cell growth, dose dependency, with minimal toxic reactions and high system safety



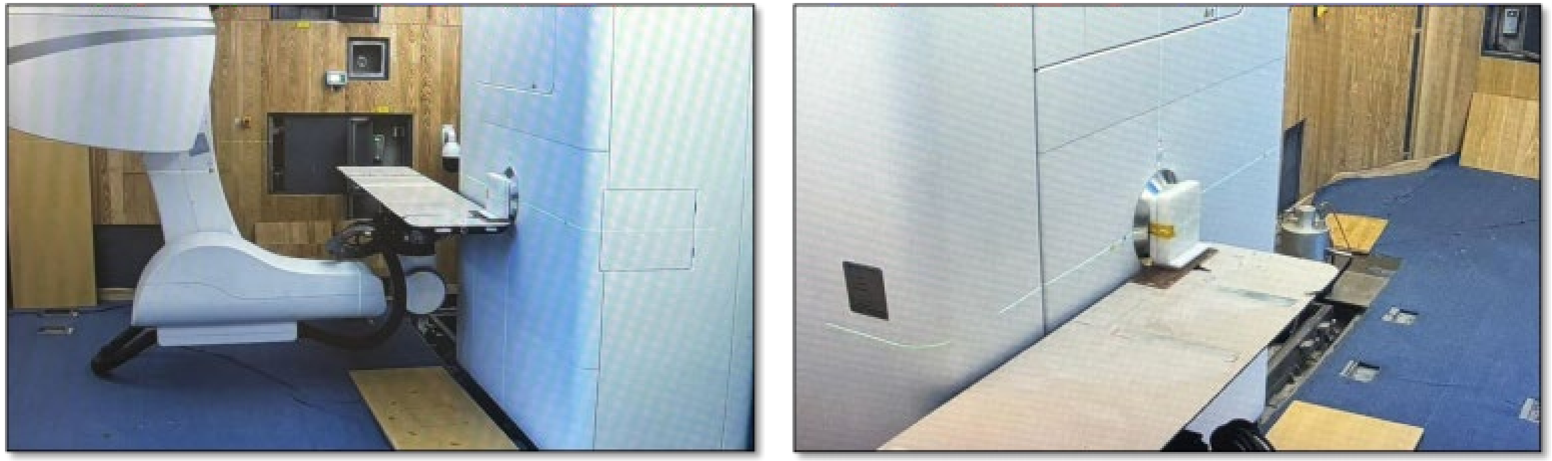


D-BNCT 02: Preclinical Study

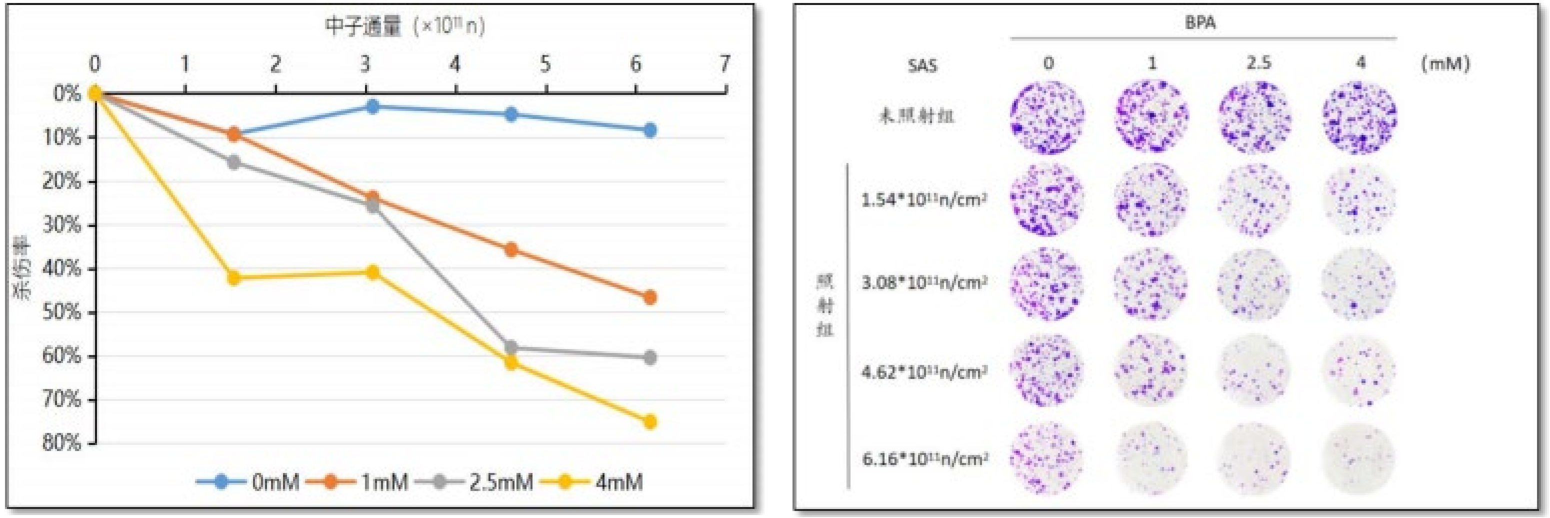
➢ Cell experiments were carried out using Puli BPA boron drug + neutron irradiation

- Verify the in vitro drug effect of BNCT on tumor cells.
- The effectiveness and repeatability of in vitro irradiation of tumor cell such as SAS, CAL27, SCC25 and U-87MG

The killing rate increases with the increase of irradiation dose and drug dose, and it is dose-dependent.



Neutron irradiation



results after irradiation

D-BNCT 02: Preclinical Study

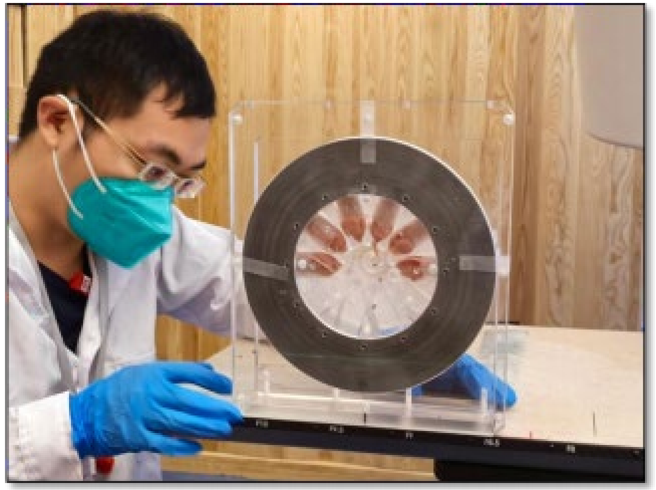
➢ Animal experiments were carried out using Puli BPA boron drug + neutron irradiation

The efficacy study

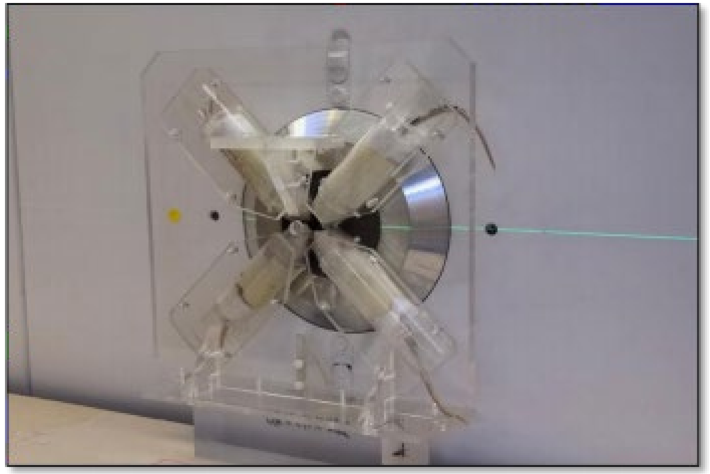
- The tumor suppression rate of SAS rats was increased with the increase of drug and irradiation dose. both medium and high doses achieved effective tumor suppression.

The Safety study

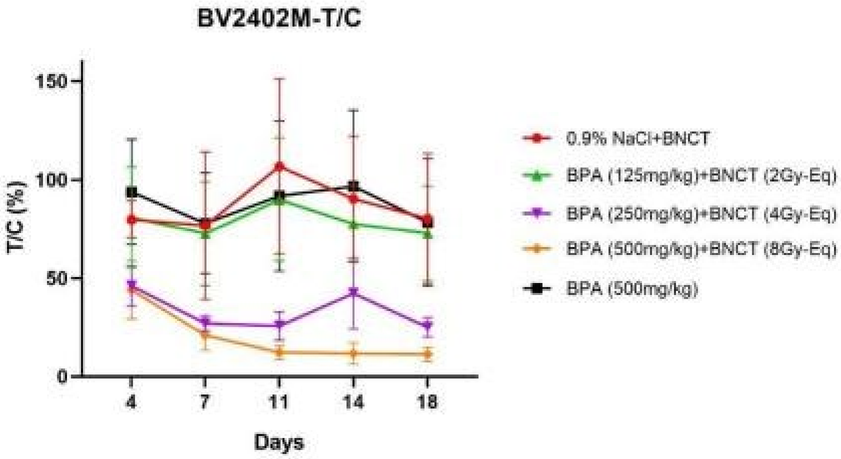
- The toxic effects were dose-dependent
- The toxicity of the high dose group is still small, and the system safety is high.



The mice were positioned before irradiation



Rat irradiation experiment



Relative tumor proliferation rate

Dogs were exposed to the irradiation

D-BNCT 02: Clinical Trial

Started the patient Pre-enrollment since Apr. 30

- Aged ≥18 years and ≤75 years, regardless of gender;
- Head and neck malignant tumor confirmed histologically ;
- Recurrent head and neck malignant tumor (squamous cell carcinoma, non-squamous cell carcinoma, nasopharyngeal carcinoma) who have failed to prior surgical treatment, standard radiotherapy;
- Laboratory test results meet the requirements;
- No other major concurrent diseases

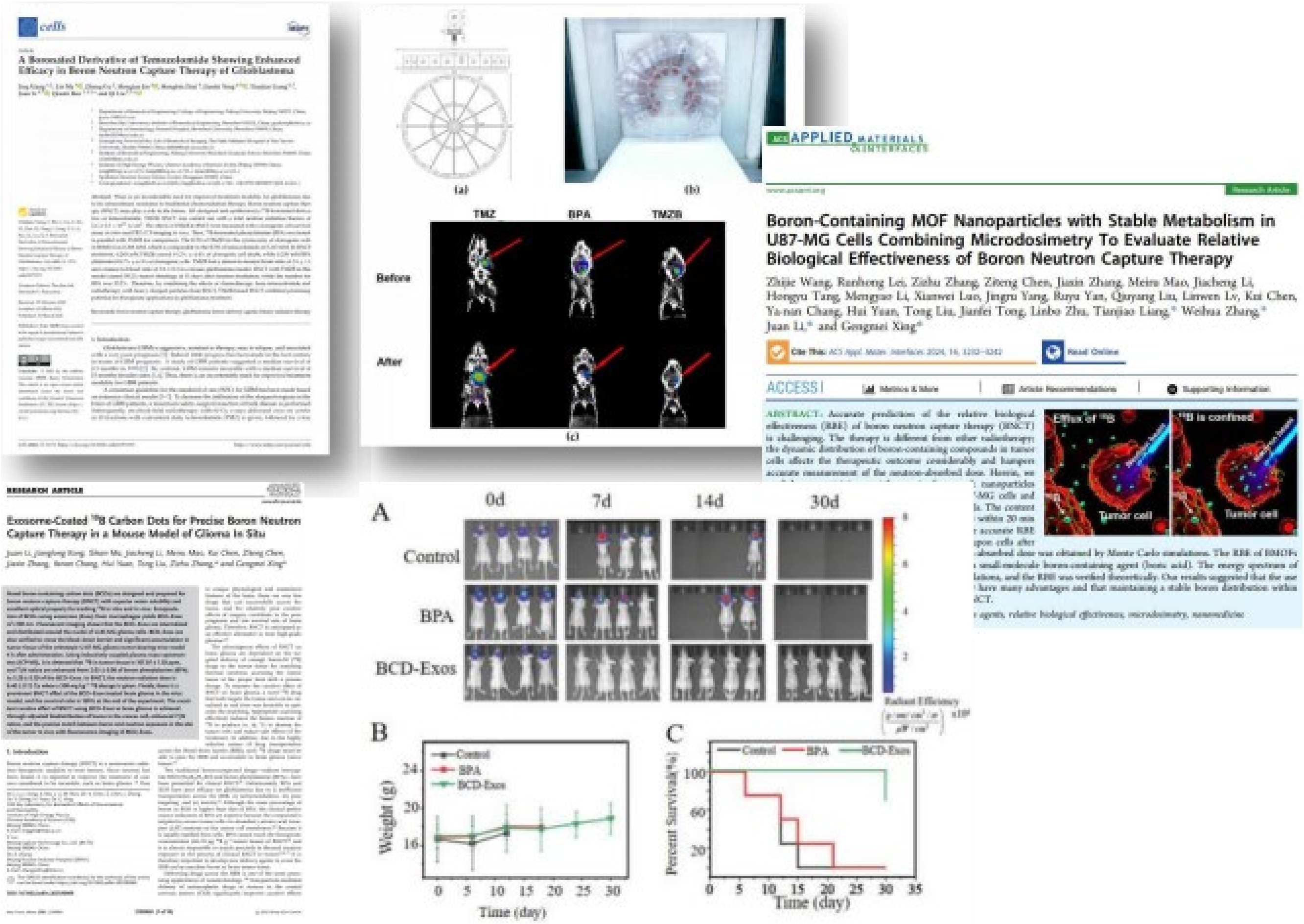
more 50 patients have been registered, and the enrollment will be continue

Plan to start the trial by the end of June after the approval of radiation safety license

Pre-clinical trial preparations have been initiated.

R&D on New Boron Drug and Medicine

- Third generation nano boron drugs
- Small molecule boron drugs based on amino acid transporters
- BNCT derivatives of chemotherapy drug
- Combination therapy of BNCT and immunotherapy
- Boron 10 delivery system based on biofilm structure
- Drug Integrated tracing and BNCT therapy



Summary

- BNCT is a new type of binary, targeted and cell-level precision radiotherapy combining radiation and drugs. It has a good application prospect in the field of tumor radiotherapy and has developed rapidly in China recent years.
- Our team are making full efforts to promote the clinical practice and application of BNCT
- Close international collaboration is desired.

D-BNCT, for people's health