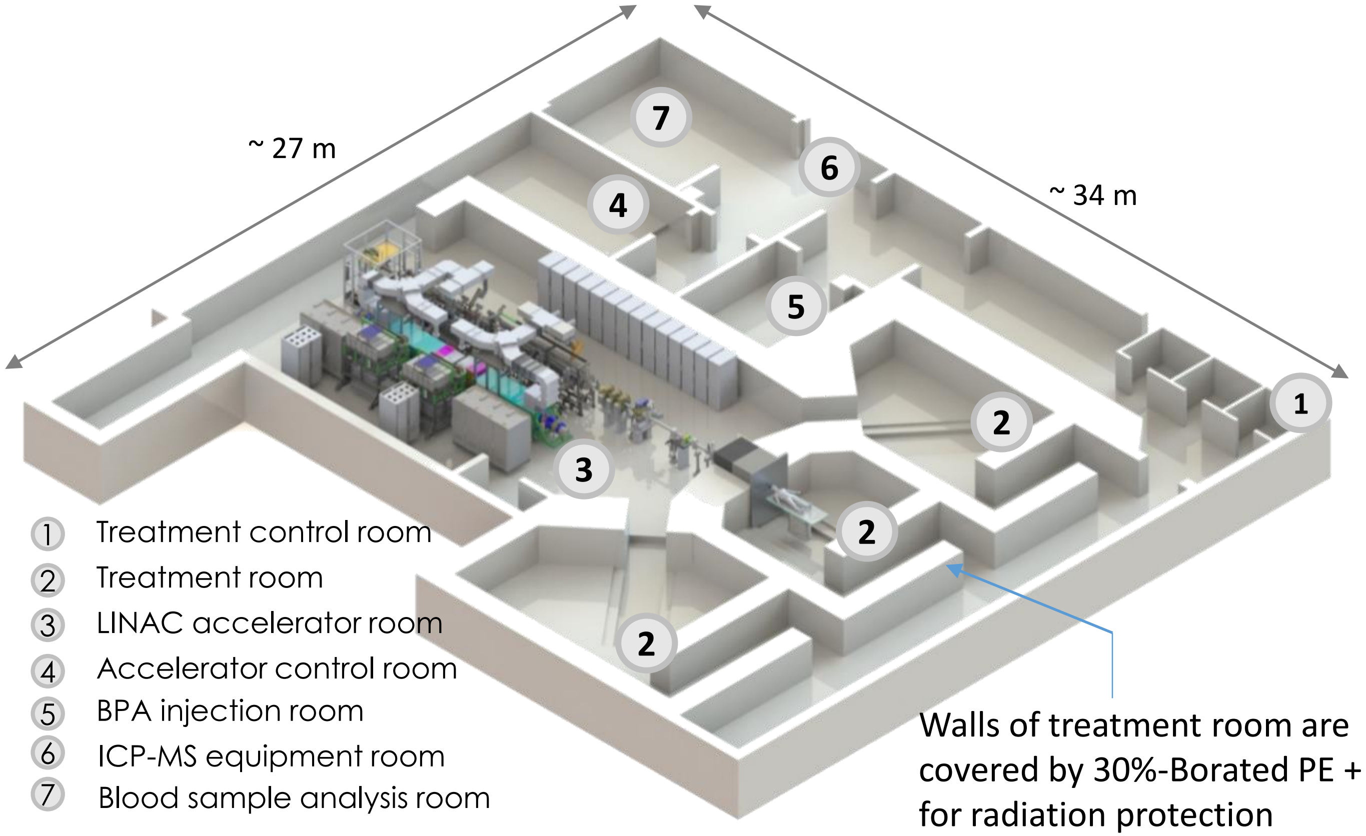
High Flux LINAC-driven Epithermal Neutron Source for BNCT in DawonMedax

2022. 10. 19

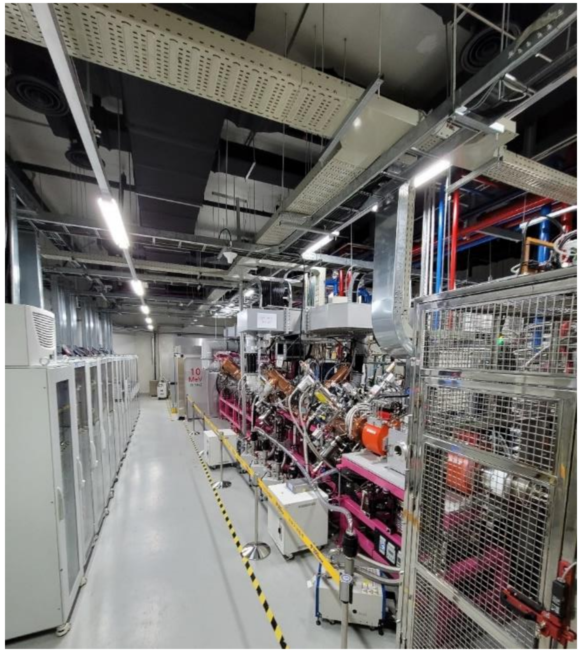
배 영 순
Chief Technology Officer
BNCT Center, DawonMedax

DawonMedax (DM) A-BNCT facility



1. Treatment control room
2. Treatment room
3. LINAC accelerator room
4. Accelerator control room
5. BPA injection room
6. ICP-MS equipment room
7. Blood sample analysis room

Walls of treatment room are covered by 30%-Borated PE + lead for radiation protection



- **Layout of DM A-BNCT facility in Bld 3B of BRC research center in Songdo**

How is Boron Neutron Capture Therapy Different?

- **Binary process**

Effective DNA damage with cellular precision

1st process: A non-radioactive boron pharmaceutical is infused

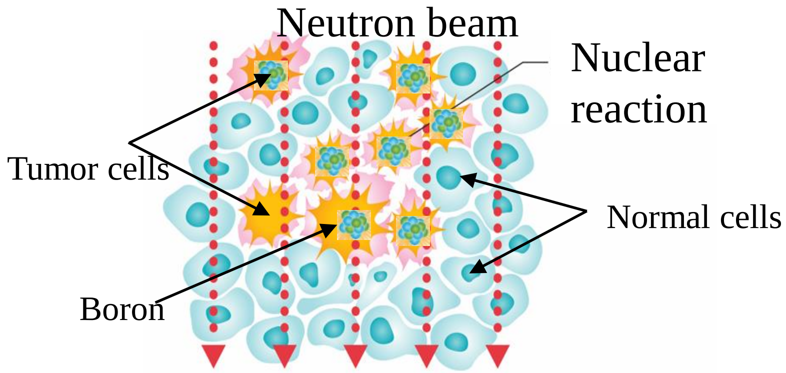
- BPA agency: high uptake ratio in cancer cells to normal cells (3.5:1)

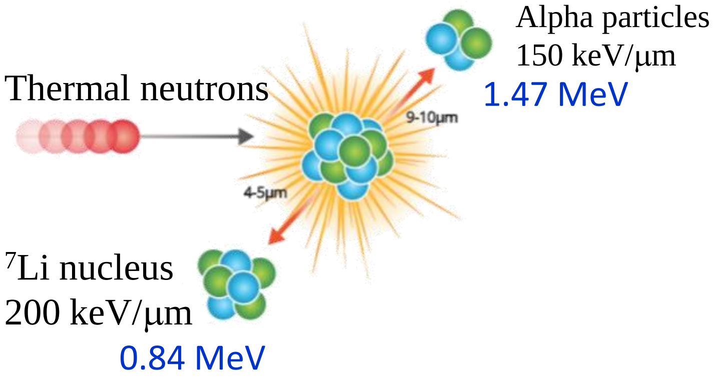
2nd process: A epithermal neutron beam is directed at the tumor

- ^{10}B reacts with thermal neutron, splitting into an alpha particle and 7Li nucleus
- The reaction products deposit massive energy within 10 μm with high LET

Promising radiotherapy

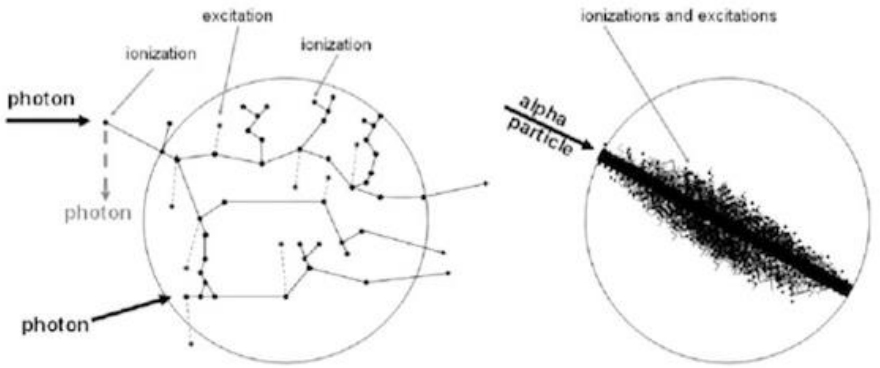
- Precision at a cellular level based on biology, not geometry
- DNA damage is more effective due to heavy charged particles with high LET





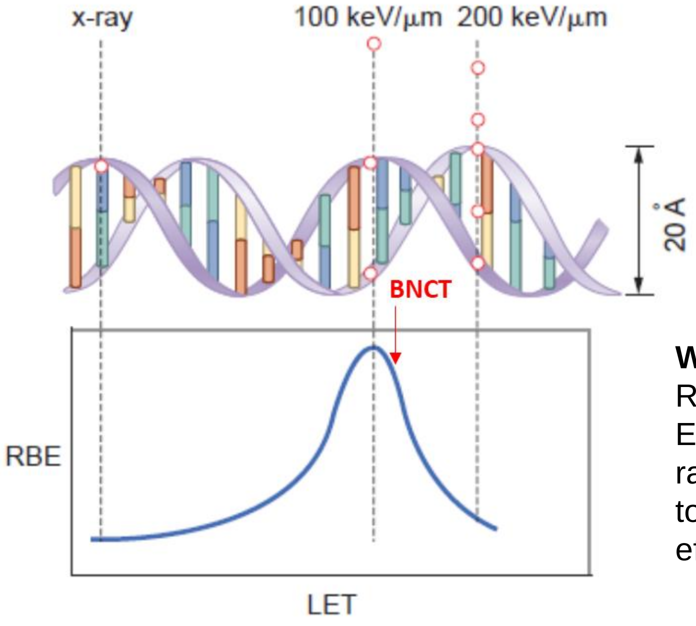
BNCT dose

What is LET?
LET (Linear Energy Transfer) is a measure of the ionization density along a radiation path



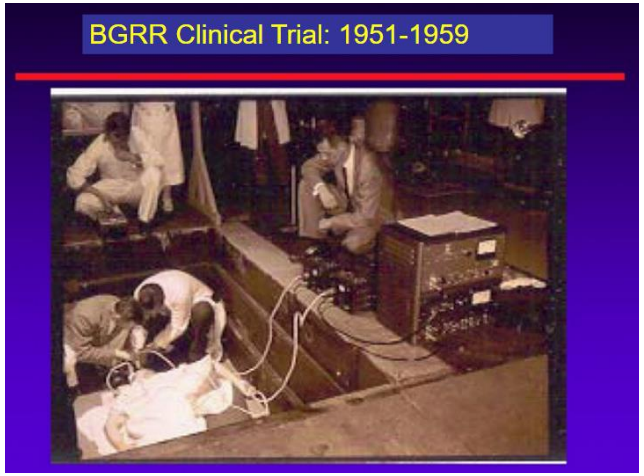
- Traditional radiation therapy sources, X-rays, gamma rays has low LET; low ionization density

- Heavy and charged particles such as neutrons, protons, alpha particles, have high LET



What is RBE?
RBE (Relative Biological Effectiveness; 생물학적효과비) is a ratio of D250 dose of 250-keV X-ray to Dr test radiation for equal biologic effect, i.e., D250/Dr

Research reactor has been used for early BNCT



US: BGRR (1951-59)
-Clinical trial

- (treatment) Efficacy: at least comparable to standard therapies.

Y. Mishima ('87)
-BPA
- Melanoma

New Clinical trials (1994-2011)

- Nuclear Reactor (US, Japan, Sweden, Finland, Netherland, Czech Republic, Taiwan, Germany)

- Development of Protocol (IAEA TECDOC2001)

- *Japan – JRR-4, KURR (thermal and epithermal)*
- *USA – BMRR, Brookhaven Phase I/II Trials 1994-1999 (Epithermal)*
- *USA – MITR, MIT/Harvard; 1994-2004 (two epithermal beam configurations)*
- *Netherland – Petten (epithermal)*
- *Finland – VTT/FiR1, HYKS (optimized epithermal)*
- *Sweden – Studsvik (epithermal)*
- *Czech Republic (epithermal)*
- *Argentina – Mixed thermal/epithermal beam*
- *Italy – Explanted liver, thermal neutron field*
- *Taiwan – THOR epithermal beam*

- **Reactor-based BNCT**
  - Remaining reactors for BNCT clinical trials; KUR in Japan, RA-6 in Argentina, THOR in Taiwan, BCTC in China
  - NOT adequate in terms of Safety & Commercialization
  - Difficult for the reactor to be licensed for BNCT treatment
  - Neutron spectrum is in thermal-epithermal range, which is not suitable for deep-seated cancers such as malignant glioblastoma multiforme (GBM; 악성뇌종양 혹은 교모세포종)

Kinds of accelerator-based neutron sources for BNCT in the World

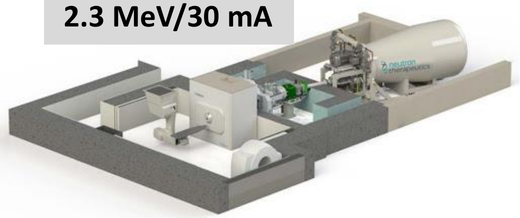
Li target +

ES accelerator-based BNCT

2.3 MeV/10 mA

Xiamen, China (US TAE-life science)

2.3 MeV/30 mA



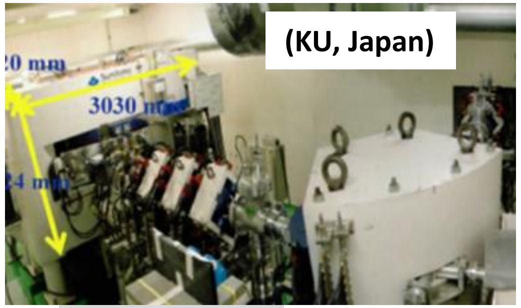
Finland (US Neutron Therapeutics)

Nagoya Univ. (Japan)

RF accelerator-based BNCT

Cyclotron-based BNCT

(KU, Japan)

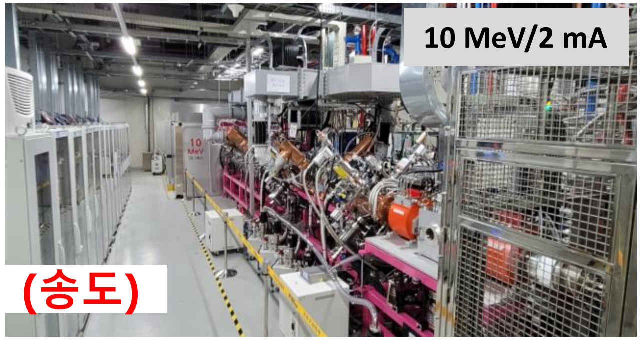


30 MeV/1 mA

C-BENS BNCT (Southern TOHOKU General Hospital)

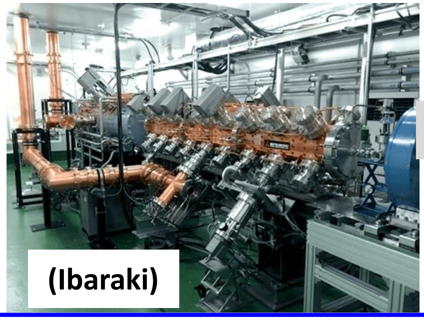
LINAC-based BNCT

10 MeV/2 mA



(송도)

+ Be target



8 MeV/2 mA

(Ibaraki)

2.5 MeV/10 mA

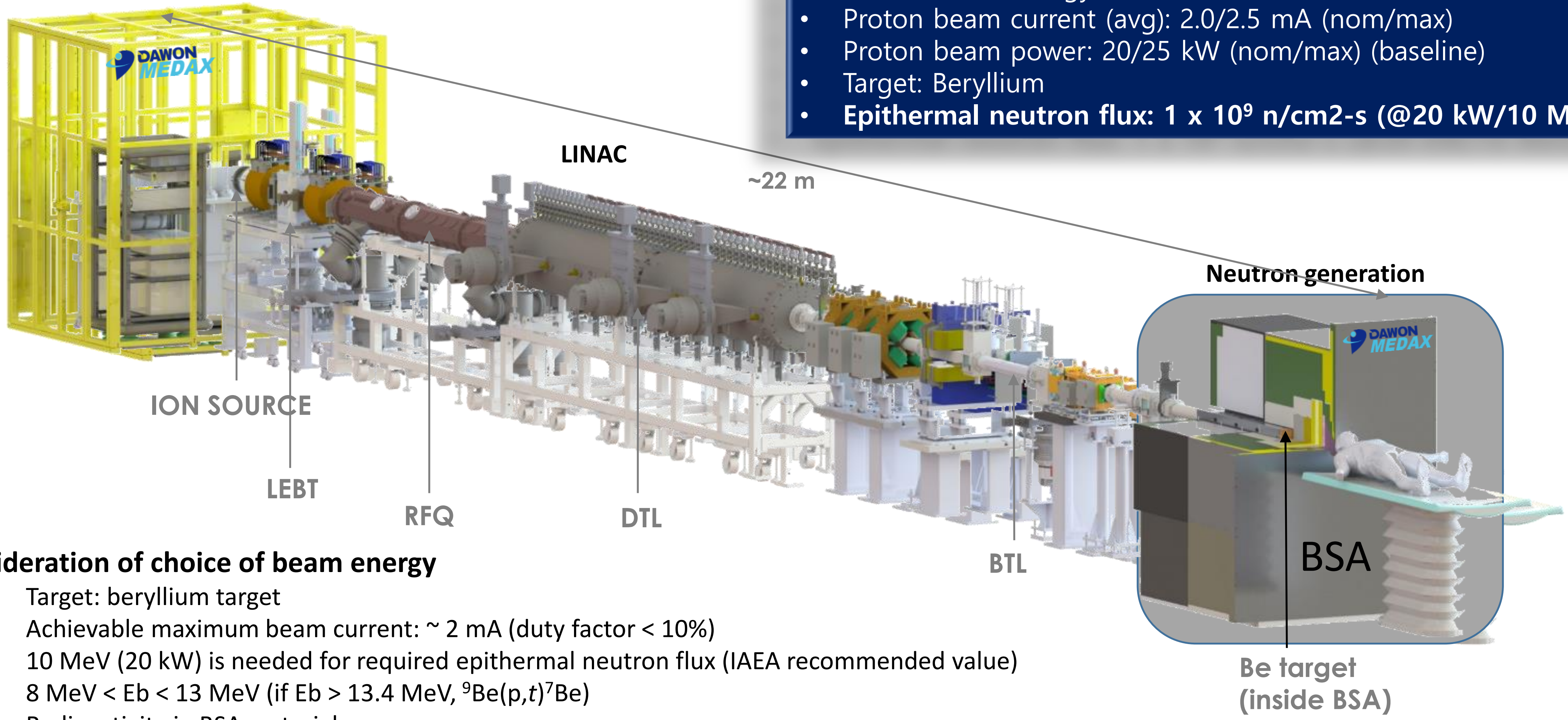
(Tokyo 암센터)

Single RFQ

+ Li target

High Flux LINAC-driven Epithermal Neutron Source for BNCT

- RF frequency: 352.0 MHz
- Proton beam energy: 10 MeV
- Proton beam current (avg): 2.0/2.5 mA (nom/max)
- Proton beam power: 20/25 kW (nom/max) (baseline)
- Target: Beryllium
- **Epithermal neutron flux: 1 x 10^9 n/cm2-s (@20 kW/10 MeV)**

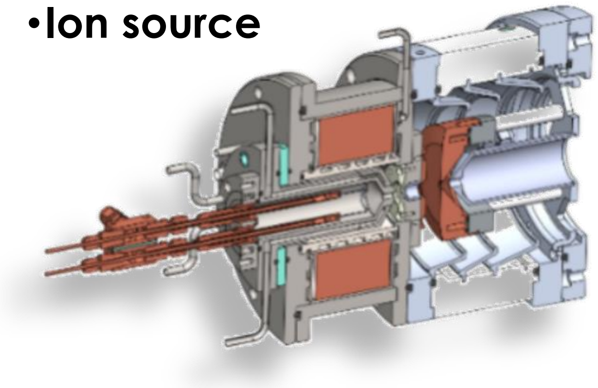


Consideration of choice of beam energy

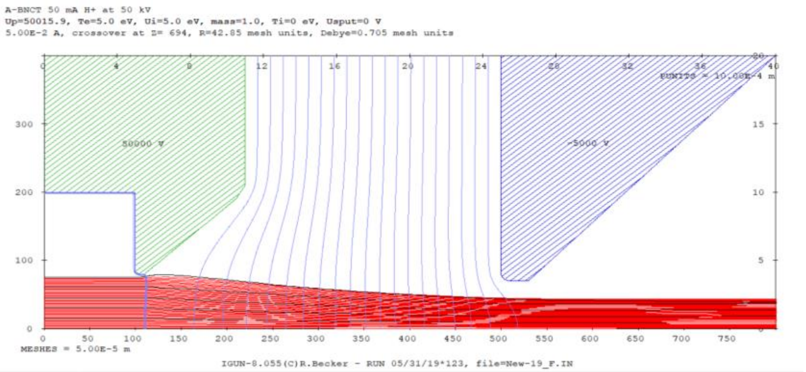
- Target: beryllium target
- Achievable maximum beam current: ~ 2 mA (duty factor < 10%)
- 10 MeV (20 kW) is needed for required epithermal neutron flux (IAEA recommended value)
- 8 MeV < Eb < 13 MeV (if Eb > 13.4 MeV, ^{9}Be(p,*t*)^{7}Be)
- Radioactivity in BSA materials

Ion Source (IS) and Low energy beam transport (LEBT)

• **Ion source**

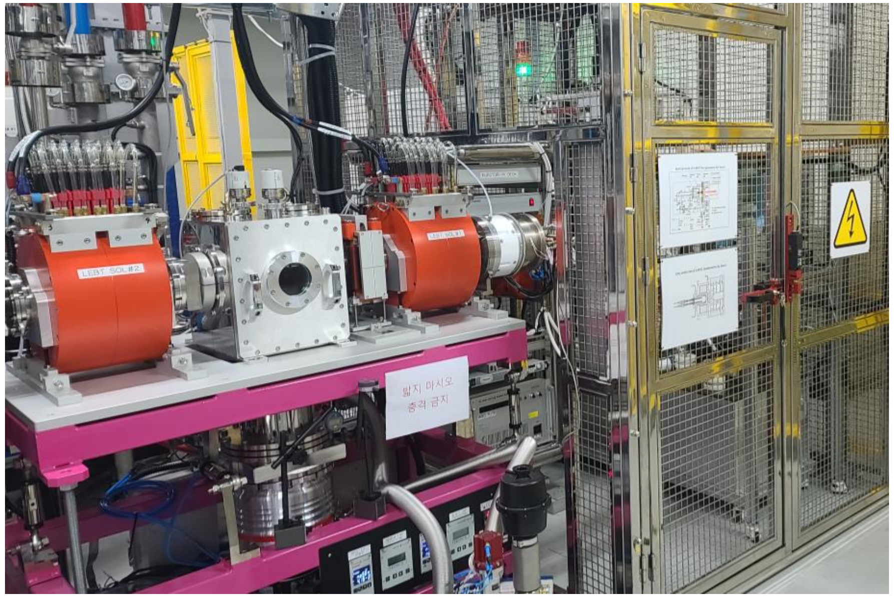


- Duo-plasmatron type H+ ion source
- 50 kV & > 70 mA
- Low emittance beam
- H^+ ratio > 80%



- **pulsed plasma operation**

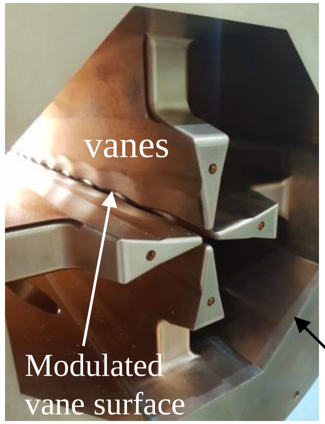
High stability with high rep. rate (2 ms, 120 Hz)

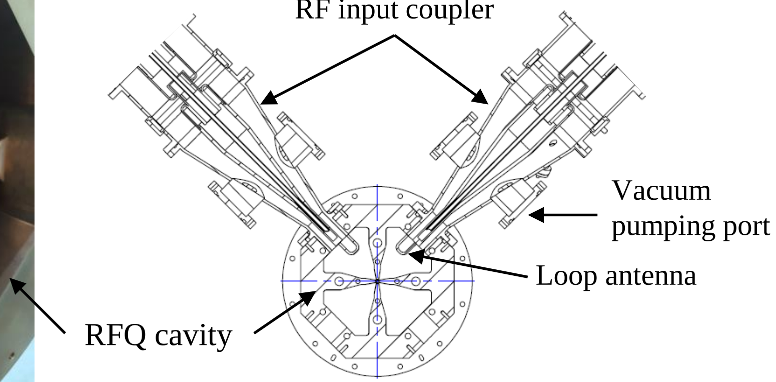


- Low energy beam transport (LEBT)
  - Two solenoids for beam focusing and matching into next accelerator
  - Steerer magnets for beam alignment
  - Orifice between solenoids for minimization of gas loading into RFQ and collimating outer beam edges

LINAC

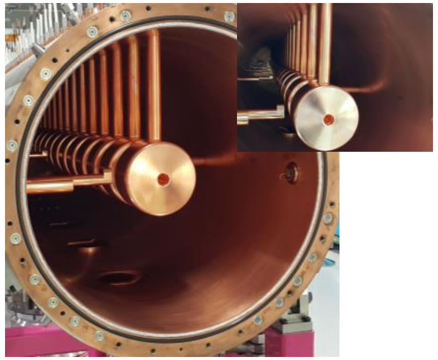
- Radio Frequency Quadrupole (RFQ) Linac
  - DC beam input → bunching, transverse focusing, acceleration by vane modulation
  - Input/output energy: 50 keV/3 MeV
  - Length: 3.18 m
  - 4-vane type
  - Number of segment: 3
  - No stabilizer rod, no coupling plate
  - Two coaxial RF input couplers

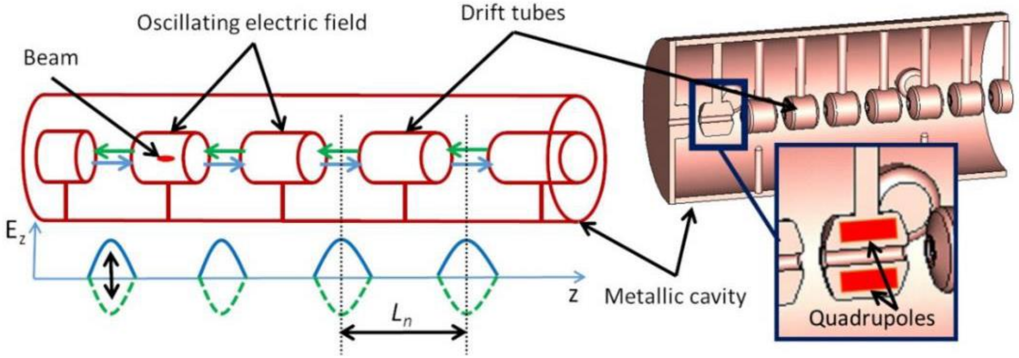




Longitudinal modulation on the electrodes creates a longitudinal component in the TE mode

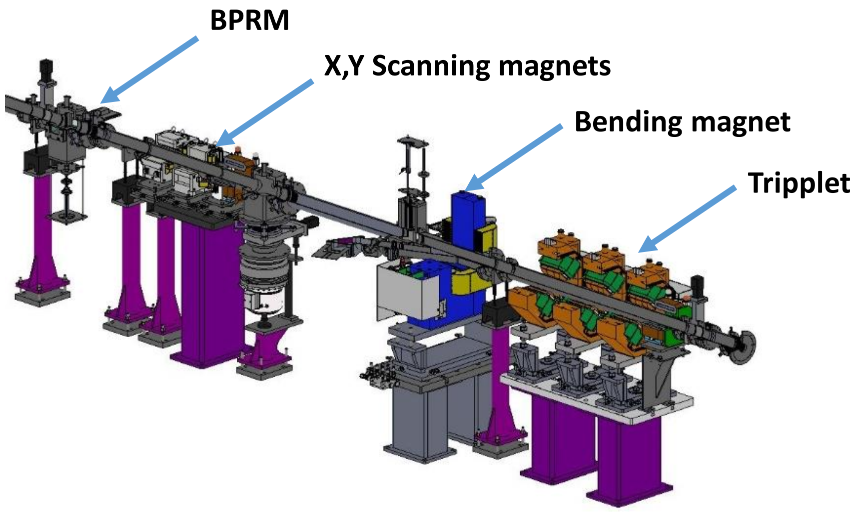
- Drift Tube Linac (DTL)
  - Input/output energy: 3 MeV/10 MeV
  - Length: 4.8 m (two segments)
  - Alvarez type linac
  - E0 = 2.2 MV/m
  - 47 cells (48 Drift Tubes)
  - EQM and FFDD lattice (G = 50 T/m)
  - Two coaxial RF input couplers

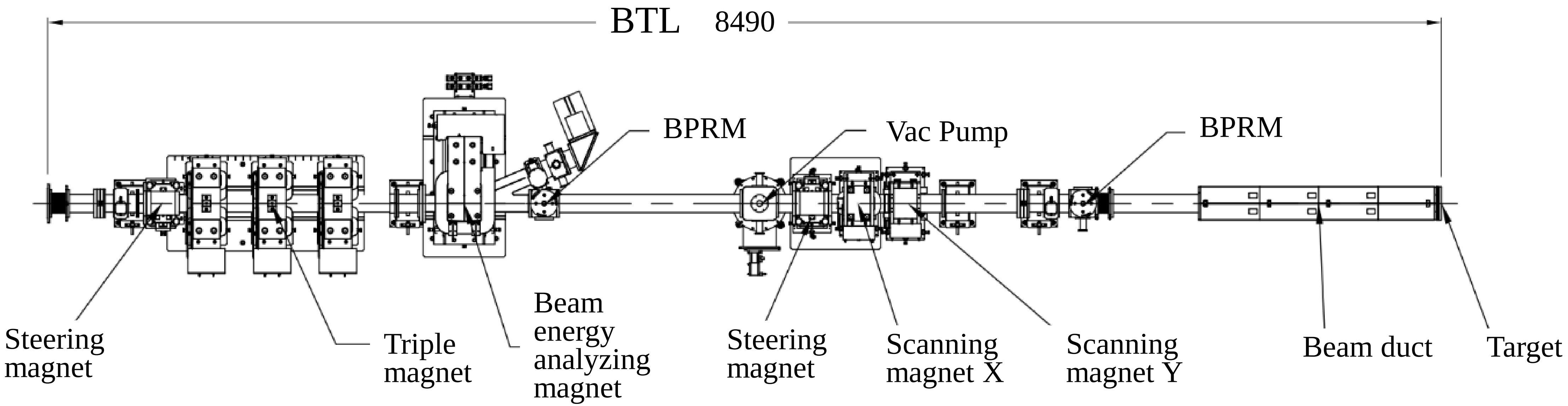




Beam Transport Line (BTL)

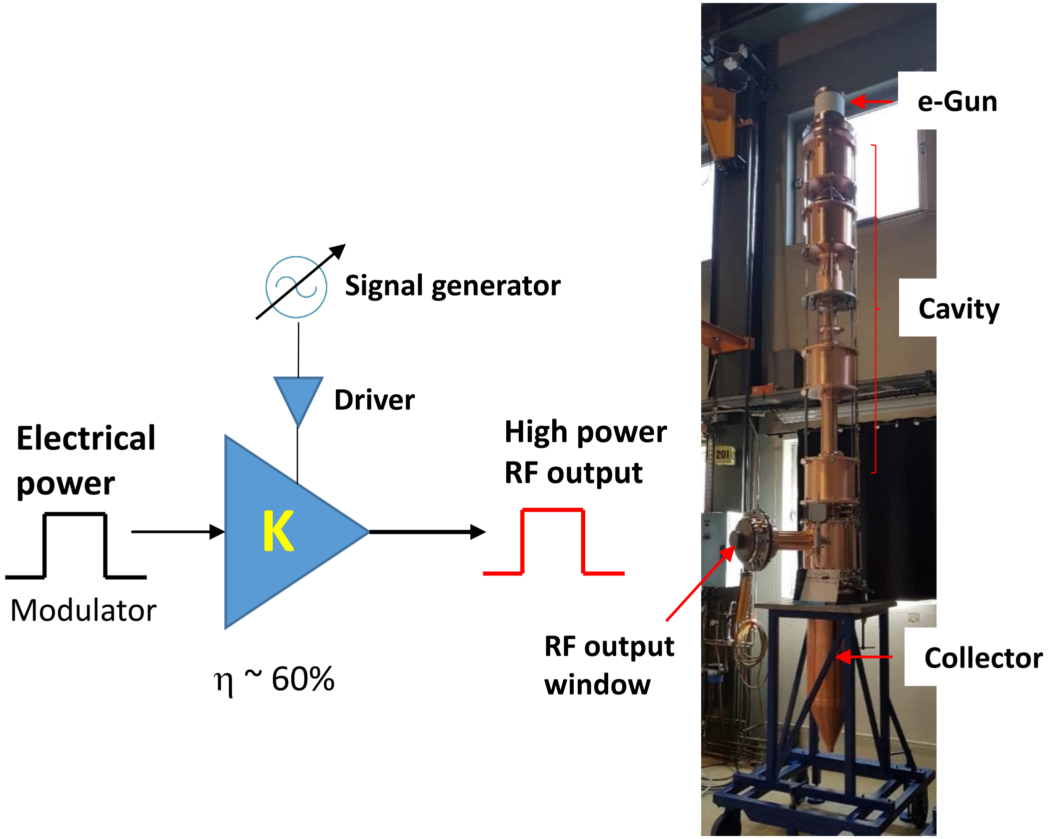
- Beam transport line (BTL)
  - TQM (triple quadrupole magnets) for beam profile control and focusing
  - Beam analyzer magnet (22.5°)
  - Steering magnet
  - Beam scanning magnets
  - Beam profile monitor
  - ACCT for beam current measurement





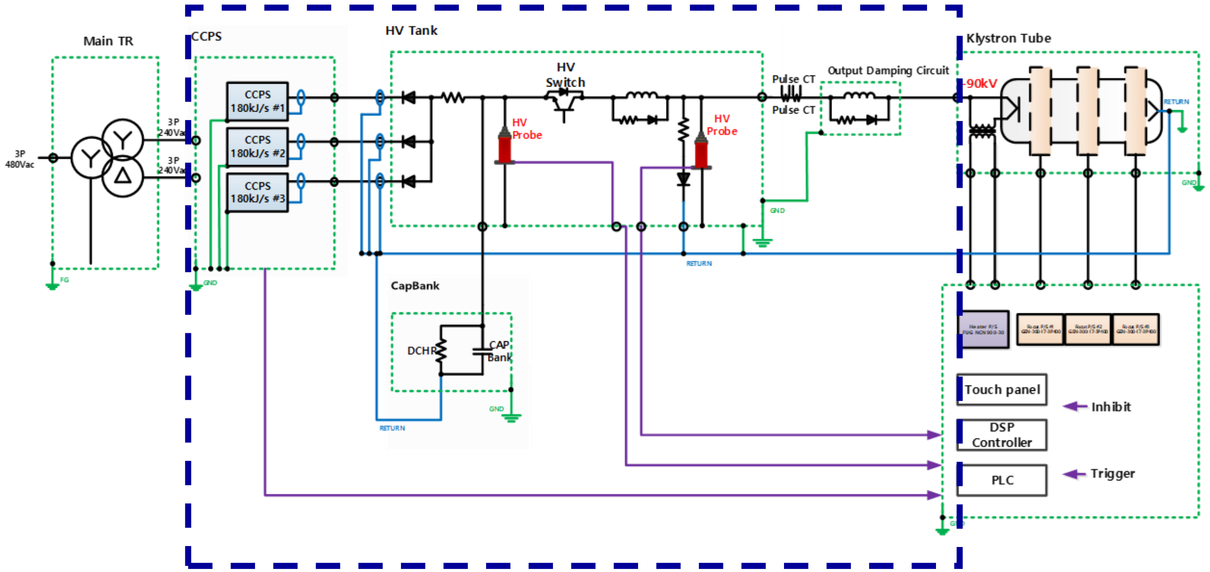
RF source and modulator

- RF source: Klystron



Klystron (Thales TH2179C)
- 352.000 MHz,
- 1.5 MW peak, 300 kW avg

Modulator circuit



Max. voltage: 90 kV
Max. current: 30 A
Capacity: 180 kW x 2 EA
Max. PPS: 120 Hz @ 1.8 ms pulse width
Voltage stability < 0.1%
Voltage droop < 2% (RMS)

Control and interlock systems

- **Instrument and control system**
  EPICS based control and monitoring system
  PLC as a local IOC
  Oscilloscope for precise monitoring of beam and RF traces
  Peak and average beam current (and charge accumulation onto the target) monitoring using fast digitizer

- **Interlock system**
  FPGA-based fast interlock ; modulator, LLRF, scanning magnet, etc
  PLC-based slow interlock; cooling, vacuum, temperature, etc

- **LLRF controller**
  Phase-locking of RFQ and DTL linacs
  RF amplitude and phase feedforward control during the pulse
  Beam loading compensation by beam trigger
  Fast turn-off by reflected power caused by RF breakdown, and auto turn-on after delay time (variable) with feedforward resonance frequency tracking for the fast recovery to resonance (RFQ)

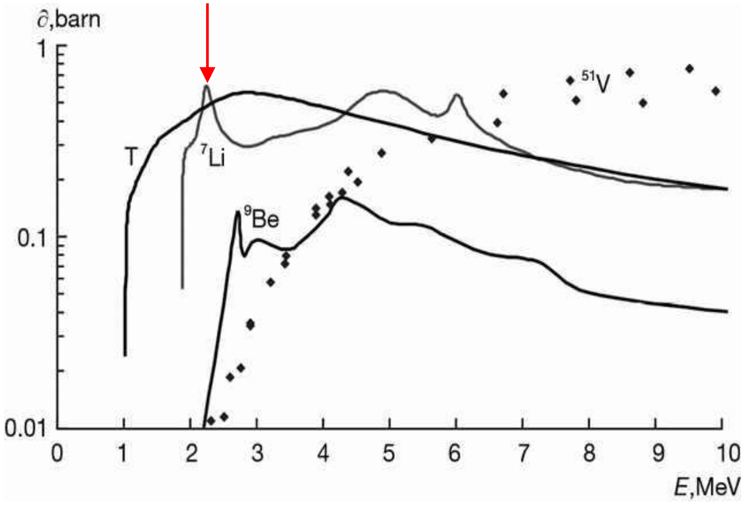
Target and neutron generation

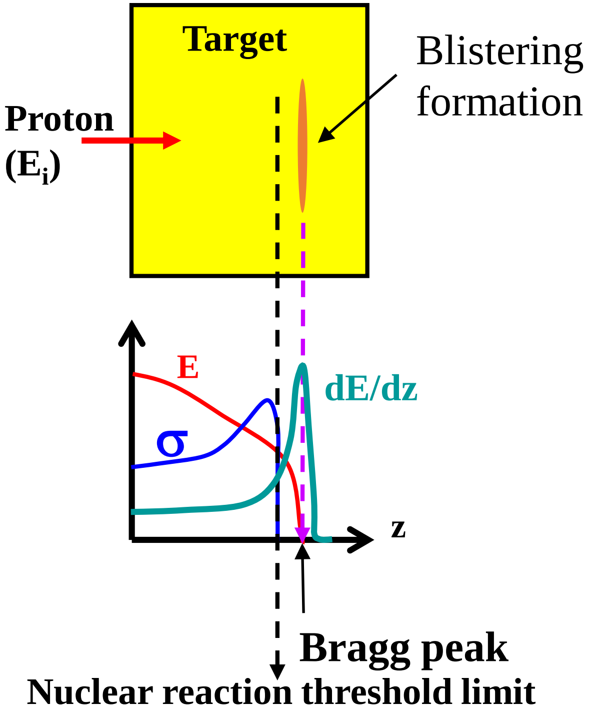
Two typical nuclear reactions for BNCT

p + ^{7}Li → ^{7}Be + n – 1.65 MeV
p + ^{9}Be → ^{9}B + n – 1.85 MeV

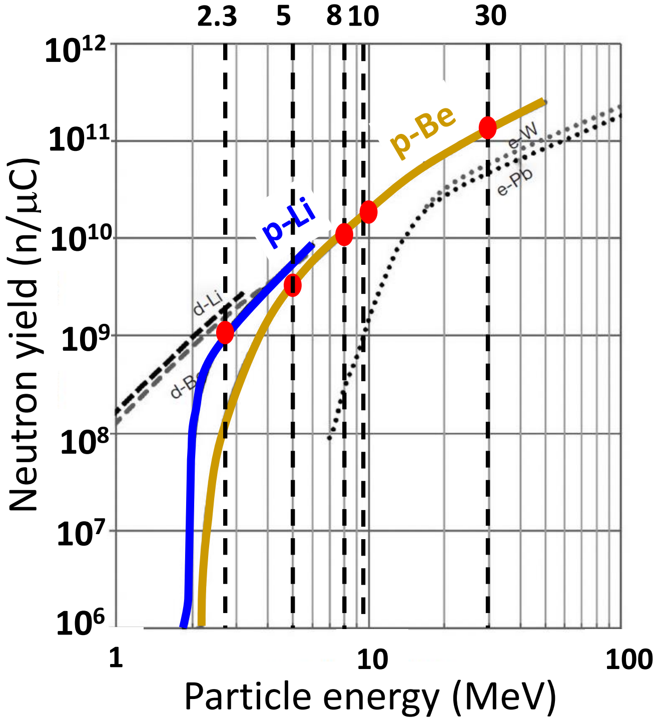
$$Y = \int_{E_i}^{0} \int N_p n_t \sigma(E) dV dE$$

Resonance peak @ 2.3 MeV





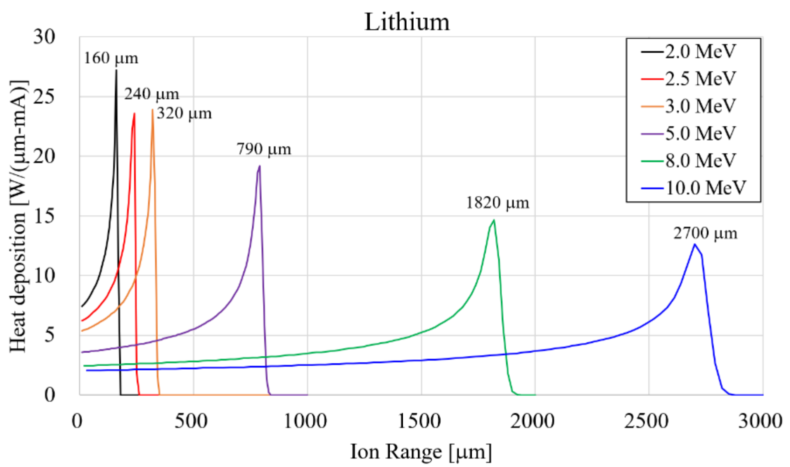
Li : 1.88 MeV, Be: 2.06 MeV

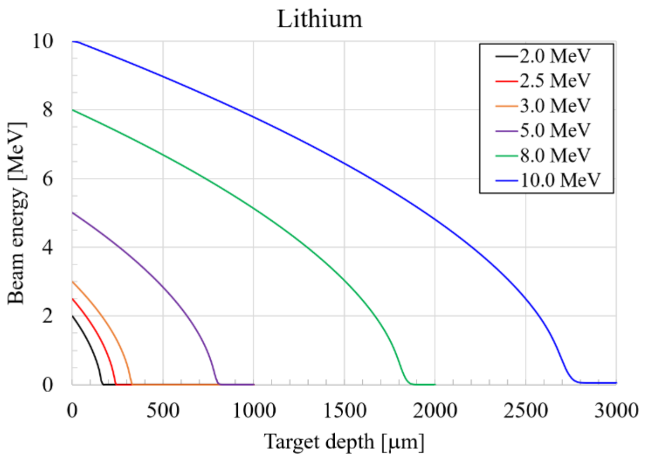


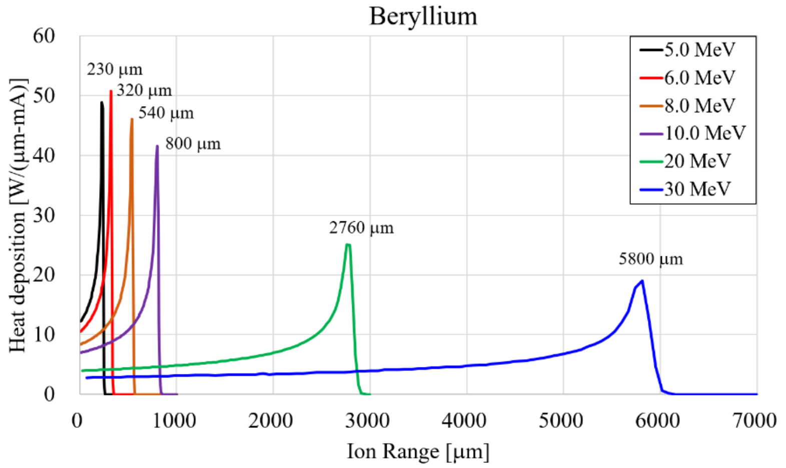
- 2.3 MeV/30 mA (ES) — Li target

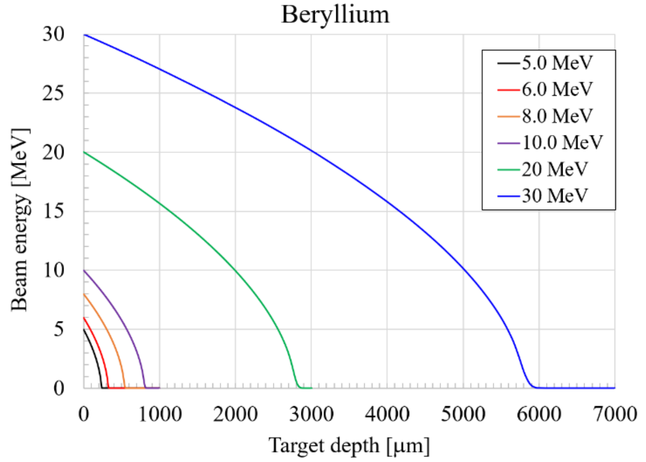
Be target:
- 5 MeV/20 mA (RFQ)
- 8 MeV/2 mA (RFQ+DTL)
- 10 MeV/2 mA (RFQ+DTL)
- 30 MeV/1 mA (Cyclotron)

Beam heat deposition and target thickness









	^{7}Li	^{9}Be
Nuclear reaction	^{7}Li(p,n)^{7}Be	^{9}Be(p,n)^{9}B
σ	~ 5 σ_{Be}	σ_{Be}
Threshold energy	1.84 MeV	2.0 MeV
Accelerator	2~2.3 MeV (ES acc.)	5~30 MeV (RF acc.)
Melting temp	180 deg-C	1300 deg-C
Therm. Cond.	85 W/m-K	216 W/m-K
Radioactivity	^{7}Be (γ-ray)**	-
Thickness	~0.1 mm	0.5 ~ 5 mm

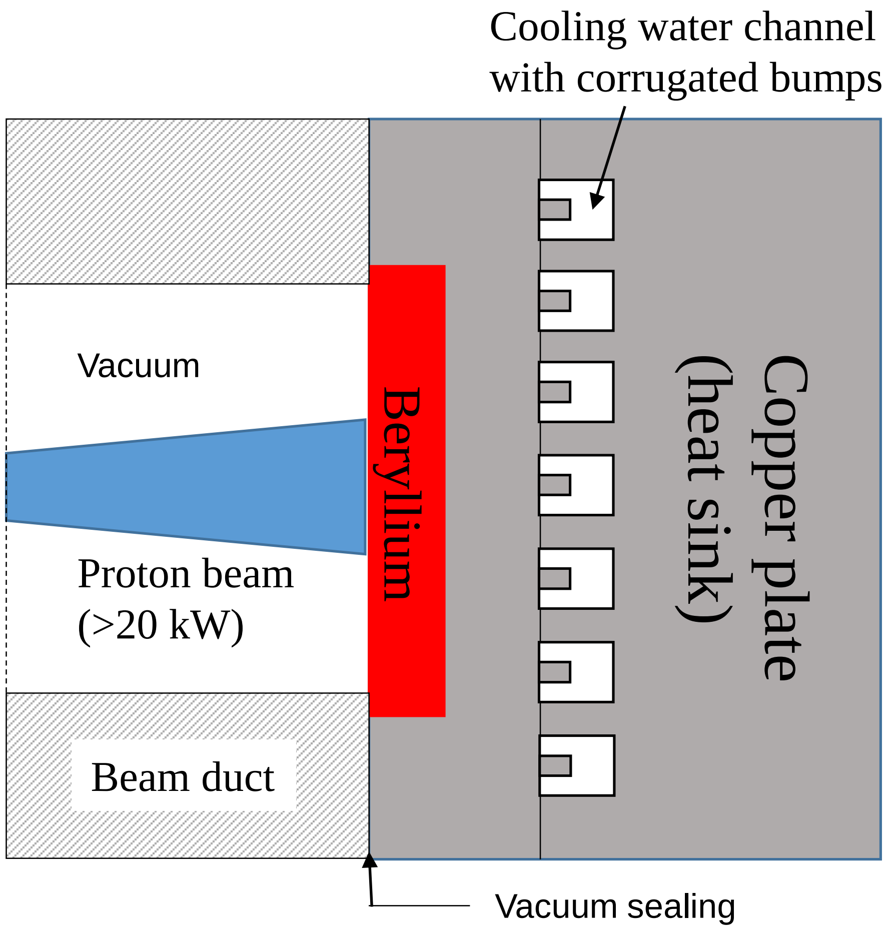
**gamma ray (478 keV, 53.6 days) with yield ~2x10^{12} s^{-1} (2.5MeV, 10 mA); comparable to neutron yield from target

- SRIM code calculation for lithium and beryllium target

Beryllium target assembly

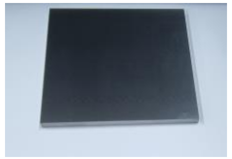
$p + {}^{9}Be \rightarrow {}^{9}B + n - 1.85\ MeV$

N Yield : 4.15×10^{13} n/s @10MeV/2mA(avg)



- Current beryllium target structure

- Target size: 100 x 100 mm^2
- Target thickness ~ 1 mm
- Brazing bonding: beryllium-OFHC
- Power density ~ 10 MW/m^2
- Water cooling structure
  - ➢ micro water channels (flow speed ~10 m/s)
  - ➢ High water pressure (max ~13 bar)
- Life time ~ 420 Coulombs



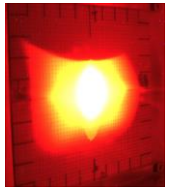
Beryllium plate

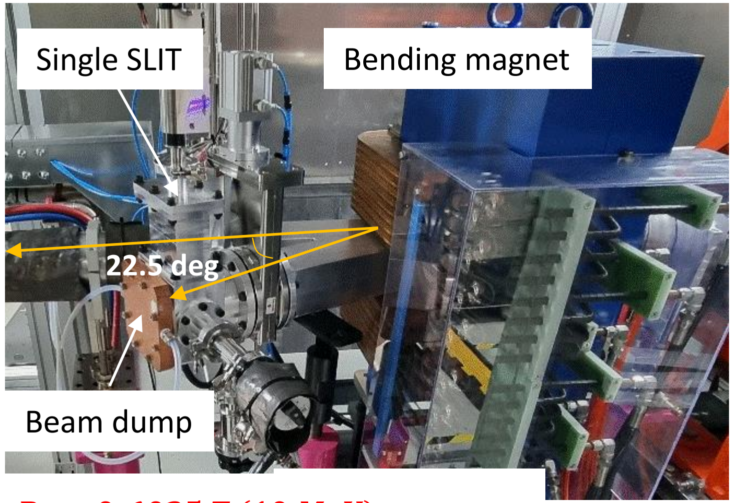
- **Longer life time target under development**
  Thinner target
  Anti-blistering backing material
  behind beryllium target (Pd, V, Ti,…)
  3-layer bonding

Proton beam measurements

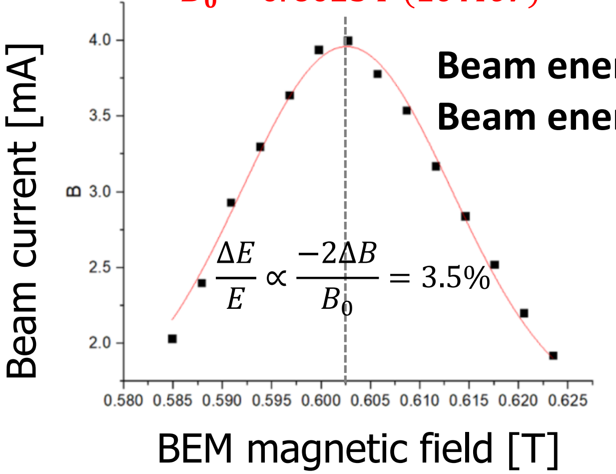
Beam energy

- **Beam energy analyzer magnet system**





$B_0 = 0.6025\ T\ (10\ MeV)$

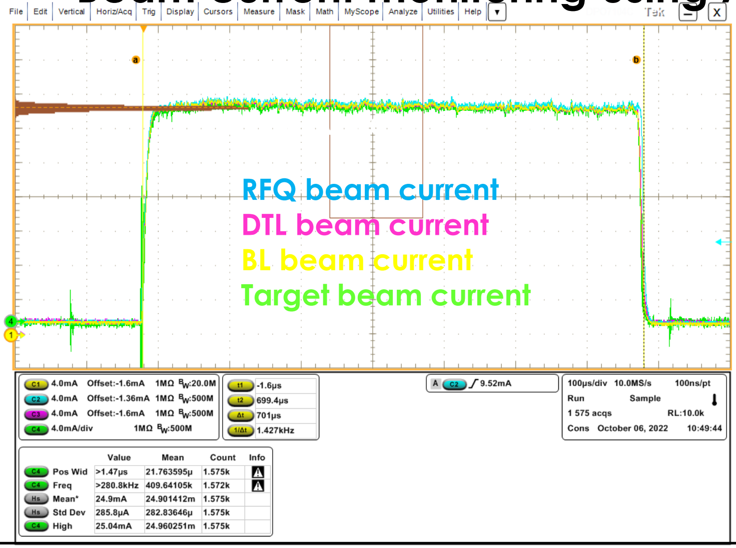


$$\frac{\Delta E}{E} \propto \frac{-2\Delta B}{B_0} = 3.5\%$$

Beam energy: 10.01 MeV
Beam energy spread < 5%

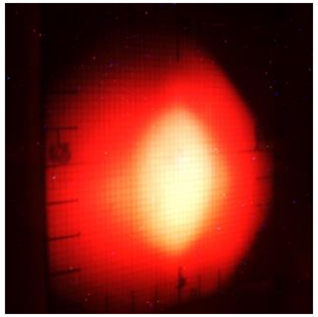
Beam current and profile

- **Beam current monitoring using ACCT and Shunt Resistor**

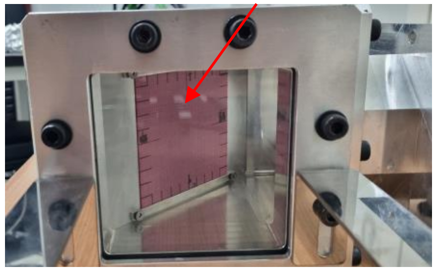


- **Beam profile measurement using Chromox screen at the target position**

Beam 1σ (radius)	
Horiz.	Vert.
19.1 mm	21 mm

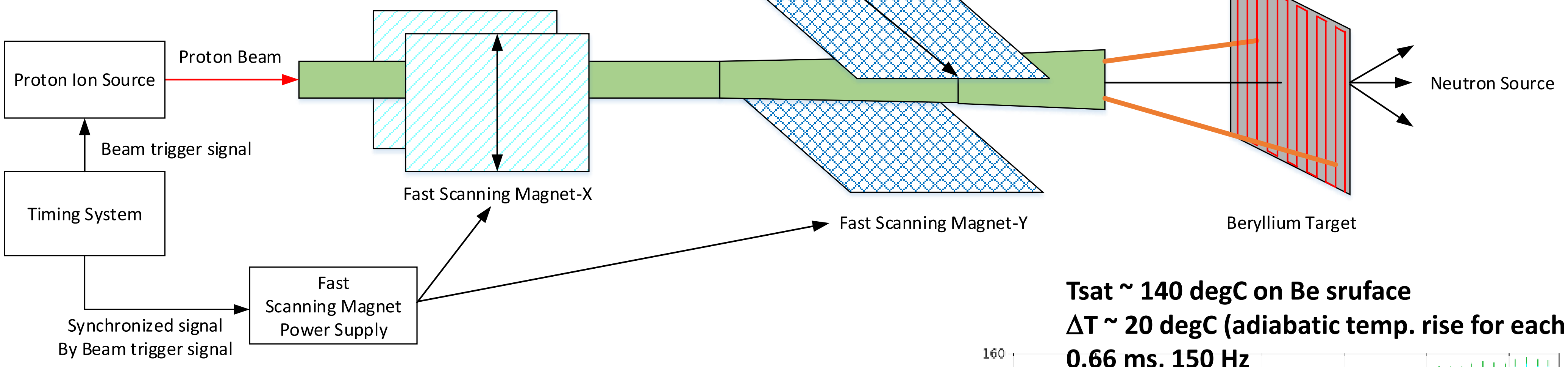


Chromox screen (Chrome-coated Al2O3 ceramic plate)

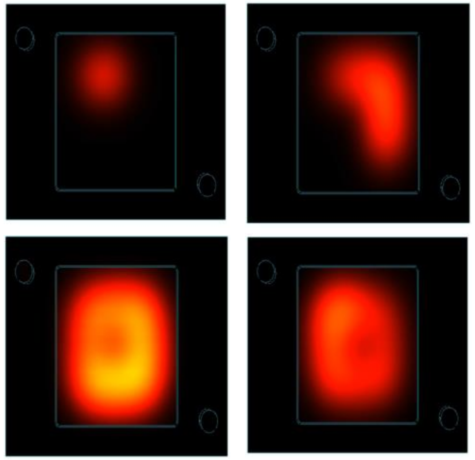


Fast beam scanning onto beryllium target

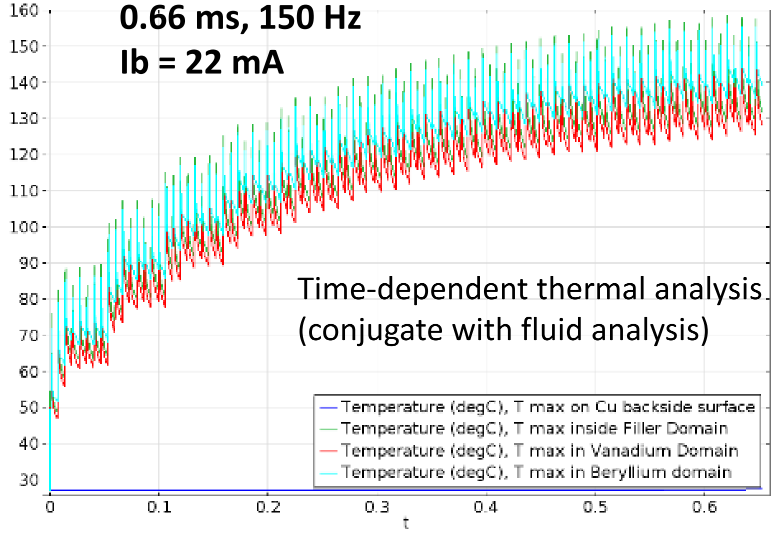
- **Beam deflecting using electromagnet**
- **Discrete change by DelX and DelY of beam center with sync. to beam-on time**



Beam-wobbling scan for heat dispersion on the target



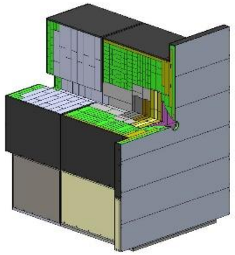
Tsat ~ 140 degC on Be sruface
ΔT ~ 20 degC (adiabatic temp. rise for each pulse)

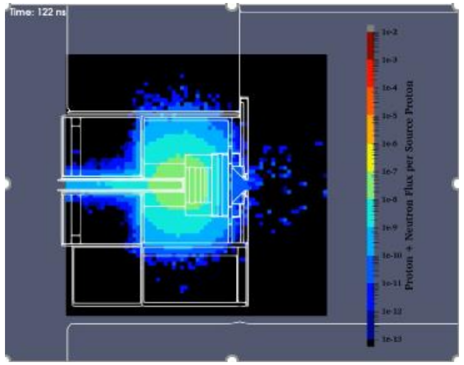


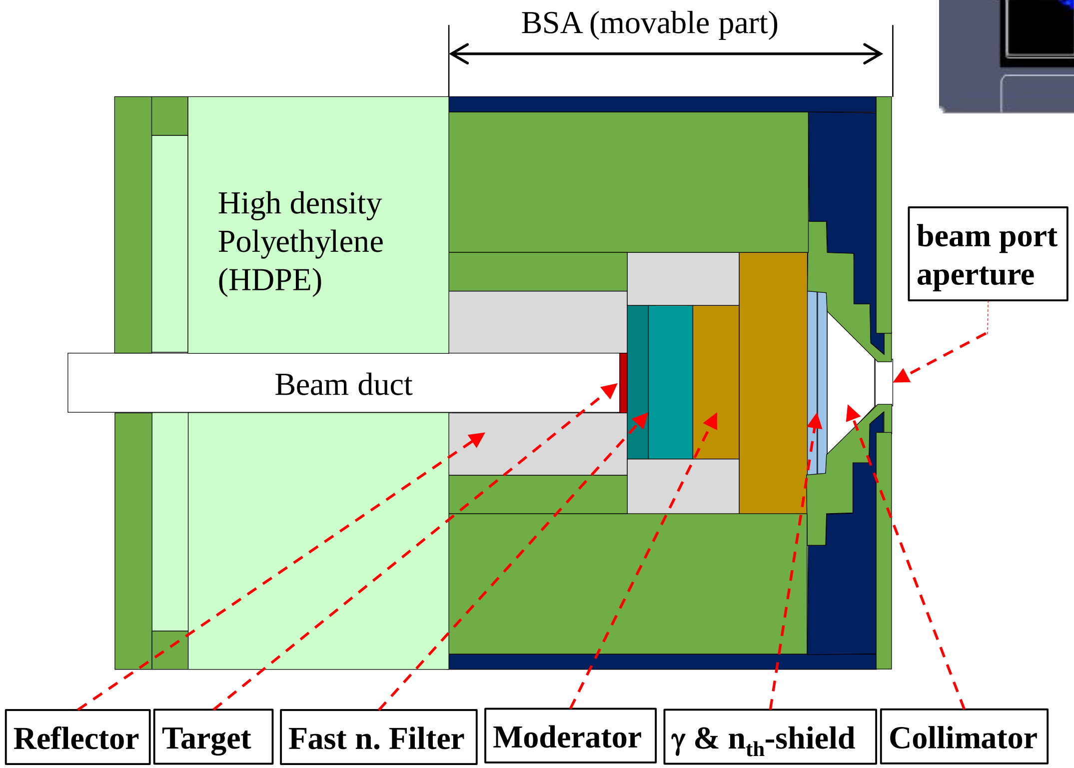
0.66 ms, 150 Hz
Ib = 22 mA

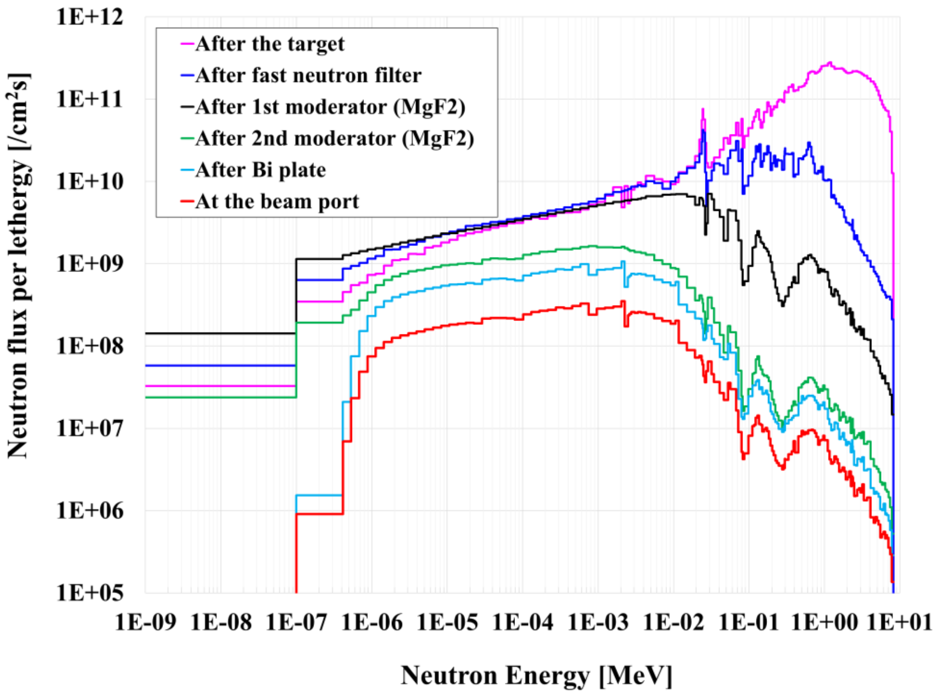
Time-dependent thermal analysis
(conjugate with fluid analysis)

(Neutron) Beam Shaping Assembly (BSA)









Optimization of BSA design has been reached using MCNP code with ENDF nuclear data for high epi-thermal neutron flux

Epithermal neutron beam quality factors and conversion efficiency

- **Neutron beam quality factors at beam port**

Parameters at beam port	Value	IAEA-recommendation
Epithermal neut. energy	0.5 eV ≤ E ≤ 10 keV	0.5 eV ≤ E ≤ 10 keV
Epithermal neut. Flux, Φ_{epi}	1.03×10^{9} n/cm²s	≥ 1.0×10^{9} n/cm² s
Φ_{th}/Φ_{epi}	~ 0.003	≤ 0.05
$\dot{D}_f/\Phi_{ep}$	3.3×10^{-13} Gy cm²	≤ 2×10^{-13} Gy cm²
$\dot{D}_\gamma/\Phi_{ep}$	0.9×10^{-13} Gy cm²	≤ 2×10^{-13} Gy cm²
J/Φ	0.71	≥ 0.7

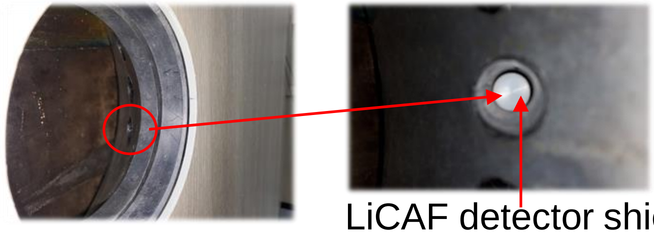
- **Epithermal neutron beam conversion efficiency (10 MeV, 2 mA)**

$Y = 4.15 \times 10^{13}$ n/s, $\Phi_{epi} = 1.03 \times 10^{9}$ n/cm²-s

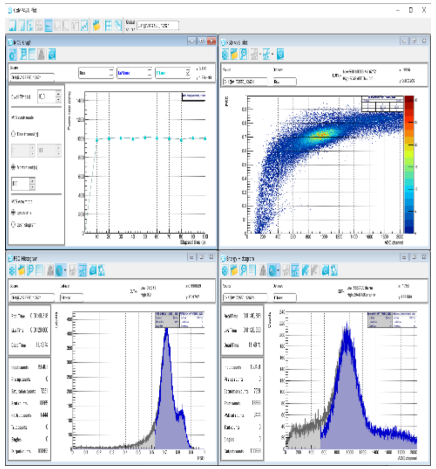
$\eta = \Phi_{epi}/Y = 2.48 \times 10^{-5}$ /cm²

On-line neutron beam monitoring

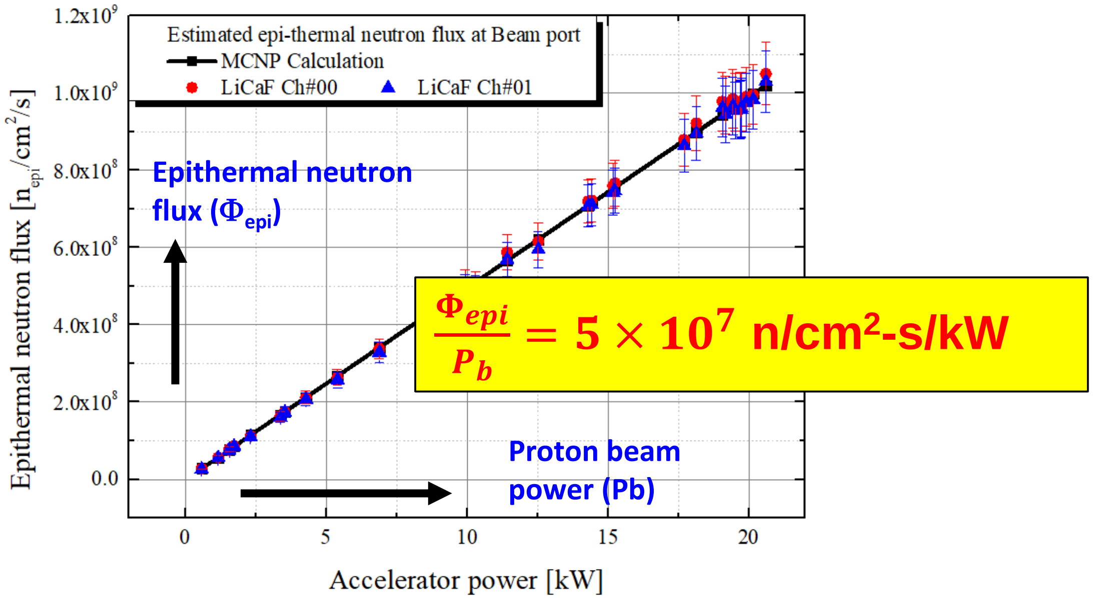
- **On-line neutron beam monitoring detectors are embedded in the neutron beam collimator material inside BSA**
  - LiCAF scintillator
  - Real-time accurate γ and neutron pulse shape discrimination (PSD) using fast digitizer and pre-amplifier
  - View directly epithermal neutron beam
  - Treatment dose are controlled by automatically terminating irradiation based on the neutron fluence reported by on-line beam monitoring detectors



LiCAF detector shielded by HDPE



- **Epithermal neutron beam flux vs p-beam power**



cf. Cyclotron-based BNCT: 1.7 x 10^7 n/cm^2-s/kW
Electrostatic accelerator-based BNCT: 2 x 10^7 n/cm^2-s/kW

BNCT Dosimetry

Neutron interactions and dose components in human body

Interaction type	Neutron energy range	Interaction	High LET products	Low LET products
Scattering	Fast	Elastic with ^{1}H	Scattered neutron + proton	-
	Fast	Inelastic with ^{14}N	Scattered neutron	Prompt γ
Radiative Capture	Thermal	$^{1}H(n,\gamma)^{2}H$	-	2.22 MeV prompt γ
	Thermal	$^{25}Na(n,\gamma)^{24}Na$	-	6.96 MeV prompt γ
Nuclear Reactions	Thermal	$^{14}N(n,p)^{14}C$	0.58 MeV proton	-
	Thermal	$^{10}B(n,\alpha)^{7}Li$	94%: 1.47 MeV α + 0.84 MeV $^{7}Li^{3+}$	94%: 0.48 MeV prompt γ

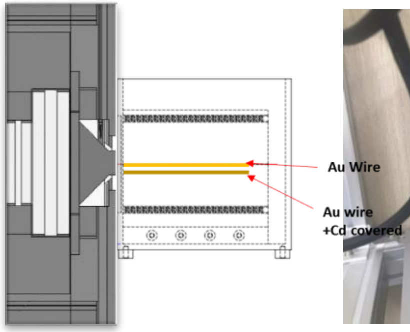
Heavy charged particles
- Short ranges
- High LET

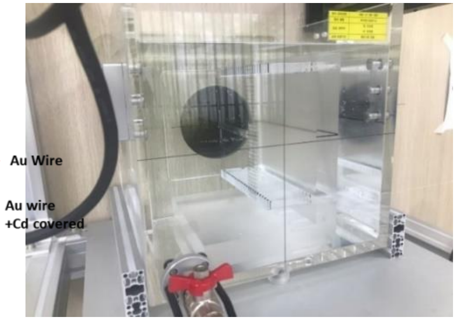
γ radiations
- Non-local dose
- High energies (up to ~ 10 MeV)

Dosimetry measurements and analysis

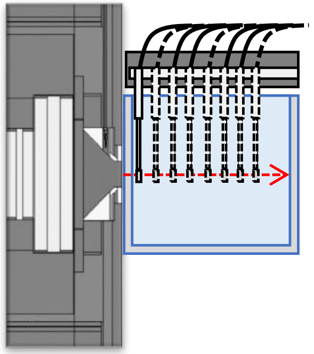
Neutron beam quality factors are verified with dosimetry of neutron beam in water phantom

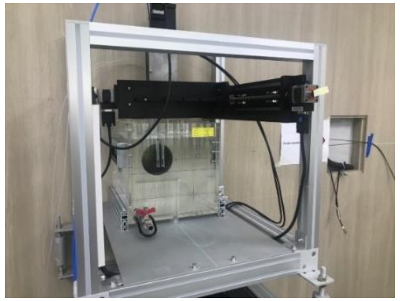
- **Thermal neutron dose (boron & nitrogen dose) using gold wires in water phantom**





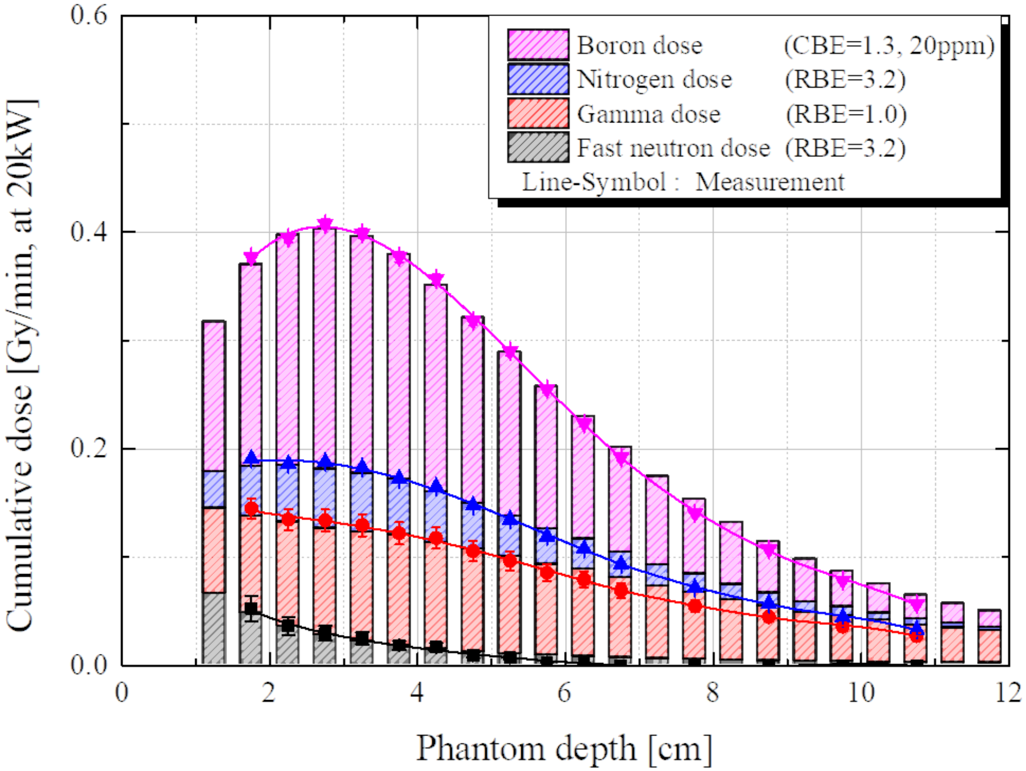
- **Gamma dose, fast-neutron dose (hydrogen dose) using two paired ion chambers in water phantom**





Two paired ion chambers:
1. Graphite chamber(0.1cc), CO_2 gas: gamma dose
2. Tissue Equivalent Plastic (A150) chamber (0.1cc), TE-methane gas: total dose (gamma + fast neutron)

- **Neutron Gy-eq measurement results**



Radioactivity in A-BNCT facility

- **Radiation protection is important issue in the use of A-BNCT facility in a hospital in the aspect of long-term operation and decommissioning**

- **Radioactivity in DM A-BNCT facility after 1-yr operation (1000-hr operation)**

  RI of half-life > 1 h impacting on radiation exposure to staffs

  - Be target (99.462%-^{9}Be, 0.06%-^{56}Fe): Co-56 (77.2d) is main RI after 5-day rad. cool-down
  - BSA

    30% BPE: no gamma emitters except prompt gamma radiation
    Al case: 1e5 Bq/g (Na-24, 14.96h)
    Iron filter & case : 3e5 Bq/g (As-76, 1.07d), 2e5 Bq/g (Mn-56, 2.58h), 1.7e3 Bq/g (Co-60, 5.27y)
    Moderator: 1.3e4 Bq/g (Na-24, 14.96h), 2.754 MeV-γ

  Most of RI is short & intermediate-lived β-γ emitters
  Co-60 will be a main radiation source after long-term operation

- **Generation of radioactivity should be As Low As Reasonably Achievable**

  The accelerator beam energy could be reduced for the use of Be target
  However, the high flux epithermal neutron requirement will need high current operation in LINAC
  Both energy and current will be lowered if new boron agency with high uptake ratio is developed in future!

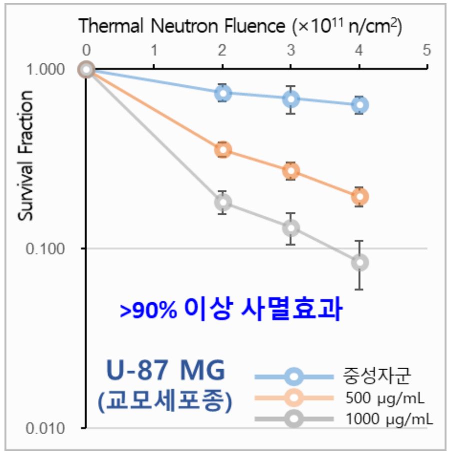
Pre-clinical study – cell & animal efficacy test

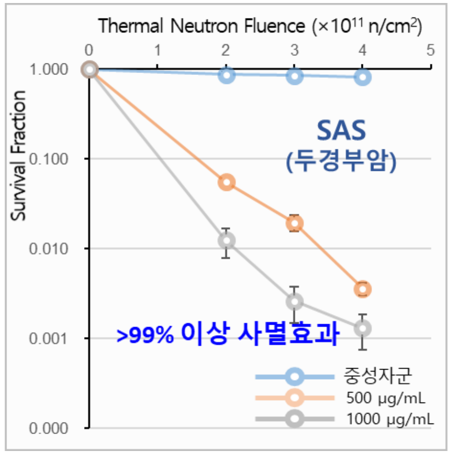
• In Vitro BNCT 효력 시험 프로토콜

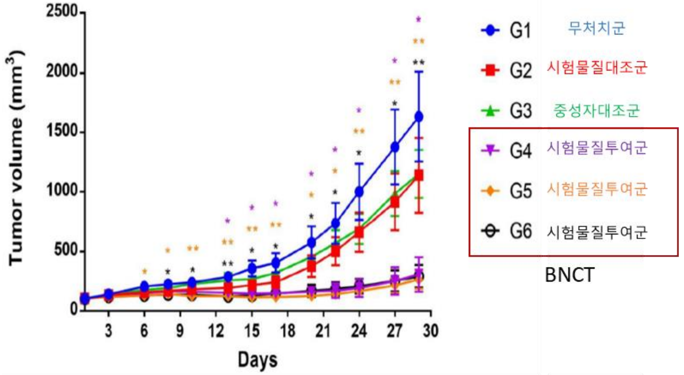
시험계	시험 내용
U87MG (뇌암 세포주)	• 고농도 1,000μg/mL (공비2, 2농도군) • 조사선량: 4개 선량 • 대조군 대비 BNCT 시험군의 세포 colony 감소 정도 평가 (Clonogenic assay)
SAS (두경부암 세포주)	• 고농도 1,000μg/mL (공비2, 2농도군) • 조사선량: 4개 선량 • 대조군 대비 BNCT 시험군의 세포 colony 감소정도 평가 (Clonogenic assay)

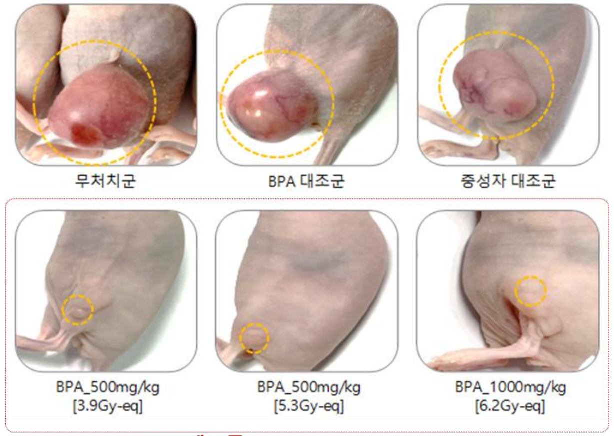
• In-Vivo BNCT 효력 시험 프로토콜

구분	시험계	투여방법	시험 내용
설치류	Balb/c nude mouse (U-87MG Xenograft model) (교모세포종)	정맥	• 고용량 1,000mg/kg (공비 2, 2용량군) • 조사 시간: 45분, 60분 (@20 kW) • 대조군 대비 BNCT 시험군의 종양 크기 변화 평가









교모세포종
종양 억제 효과 확인

Summary and Plan

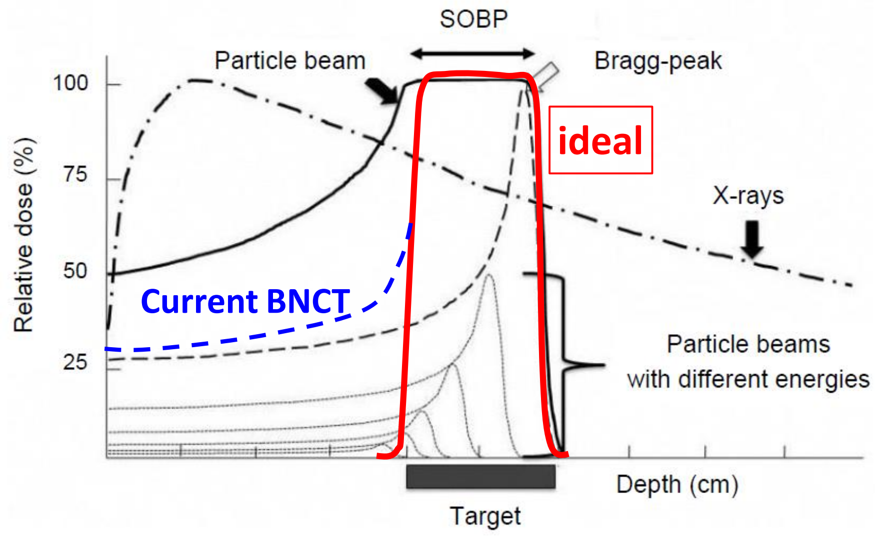
High efficient and high flux epithermal neutron source is developed

- RF LINAC
- Proton beam energy: 10 MeV
- Proton beam current (avg): max 2.5 mA
- Epi-thermal neutron flux: >1 x 10^9 n/cm^{2}s

Plan

- Design of 2nd beam line with improved BSA design for next-generation boron agency development, industrial application (memory SEE, neutron radiography, etc)
- Long-life beryllium target (with anti-blistering backplate) is under development
- Design of 2nd LINAC-based neutron source (with improved design of DTL linac, new layout of facility)

❖ **The promise (or potential) of BNCT is delivering radiation dose close to ideal**



Ref: Y. Matsumoto, J. Pers. Med. 2021. 11, 825

- **Next-generation boron agency will enable ideal radiation dose as well as short treatment time or compact low-energy accelerator facility**