Accelerator Based Neutron Capture Therapies

AB-NCT

A project of a demonstrator in France

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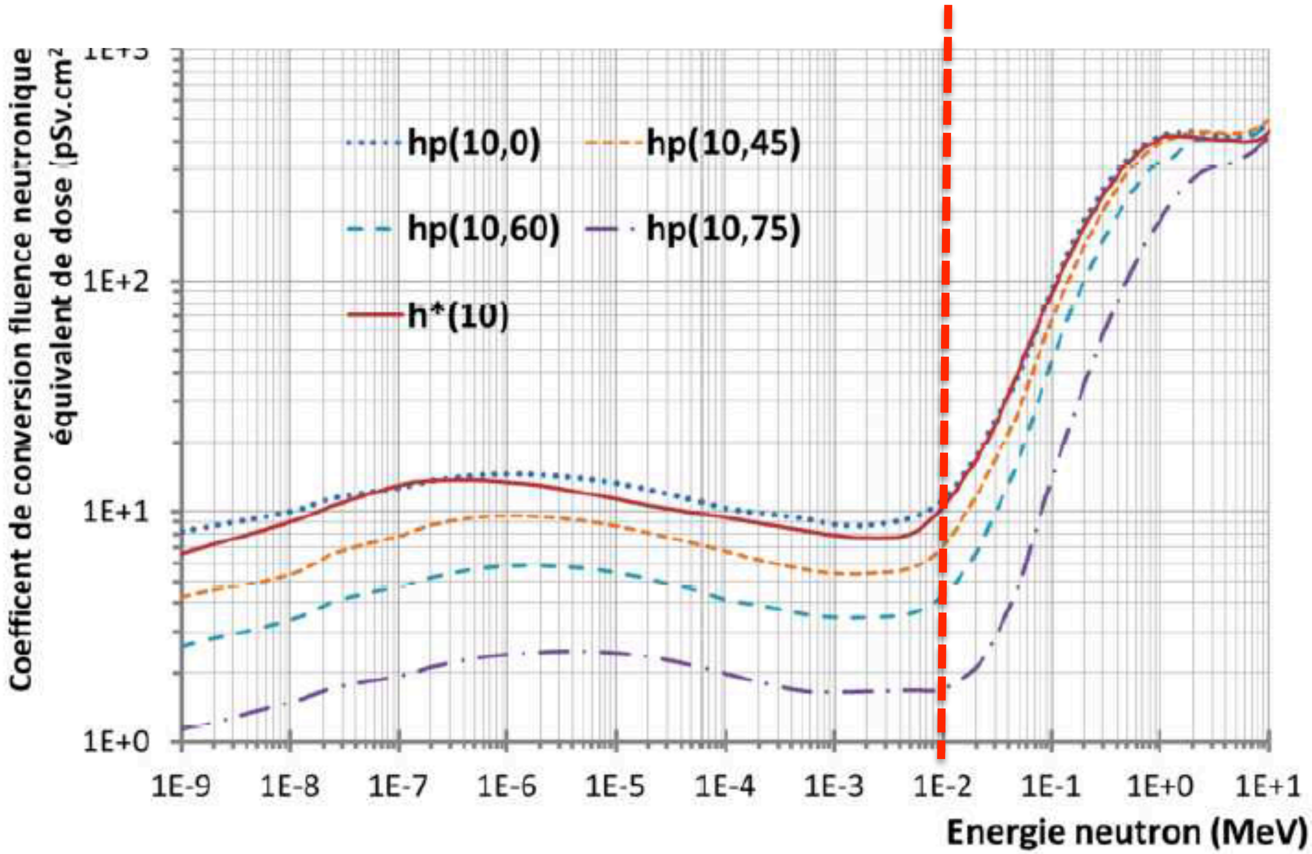
Presentation Plan

- ✓ Interest of an AB-NCT project
- ✓ AB-NCT Demonstrator Project in France
- ✓ LPSC contributions to the Project
  - Targets (^{9}Be, ^{7}Li) (J. Giraud's talk tomorrow)
  - Beam Shaping Assemblies (BSAs)
  - Fast and thermal neutron detection (N. Sauzet's talk tomorrow)
  - Gamma detector for on-line dose mapping (D. Dauvergne's talk tomorrow)
  - Radiobiology studies and experiments.(U. Koester's talk tomorrow)
- ✓ AB-NCT French project strategy.

Sending epithermal neutrons (En < 10 keV)

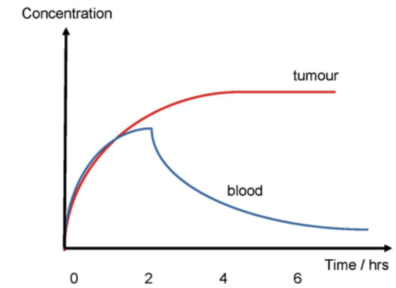
the dose keeps low !

$H_p(d)$: Total dose absorbed by a tissue at a depth d *$h = H / n^0$ fluence*



ICRP, 1996. Conversion Coefficients for use in Radiological Protection against External Radiation. ICRP Publication 74. Ann. ICRP 26 (3-4). http://www.icrp.org/publication.asp?id=ICRP%20Publication%2074

BNCT : Two approved carriers BPA and BSH
(healthy tissue / tumoral tissue) between 3 to 4.

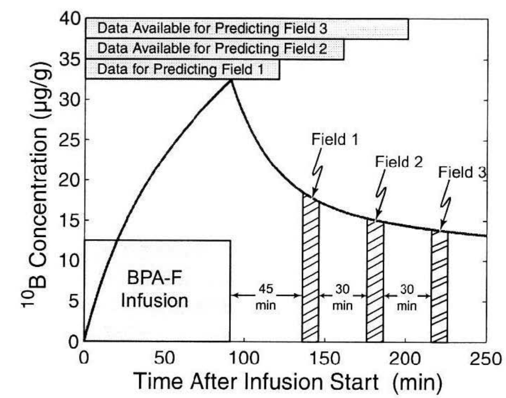


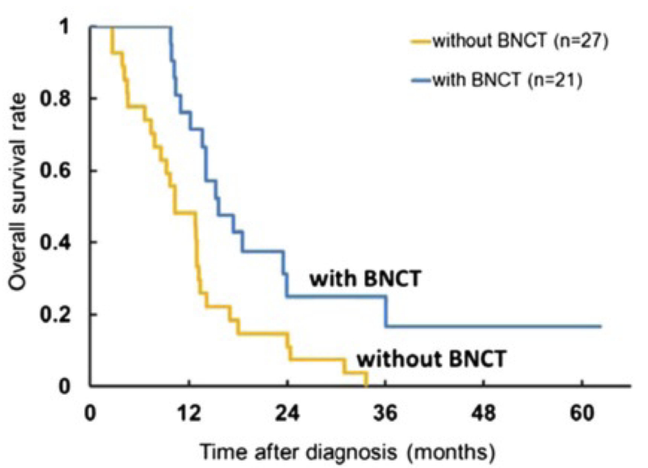
BSH : *sodium borocaptate* $Na_2\,{}^{10}B_{12}\,H_{11}\,SH$

BPA : *para-borophenylalanine* $C_9\,H_{12}{}^{10}BNO_4$

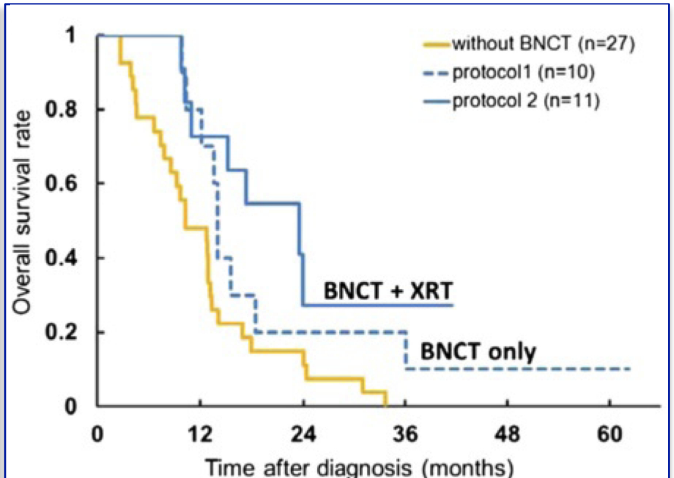
BPA pharmacokinetics

From Kiger et al, *Journal of Neuro-Oncology* **62:** 171–186, 2003.





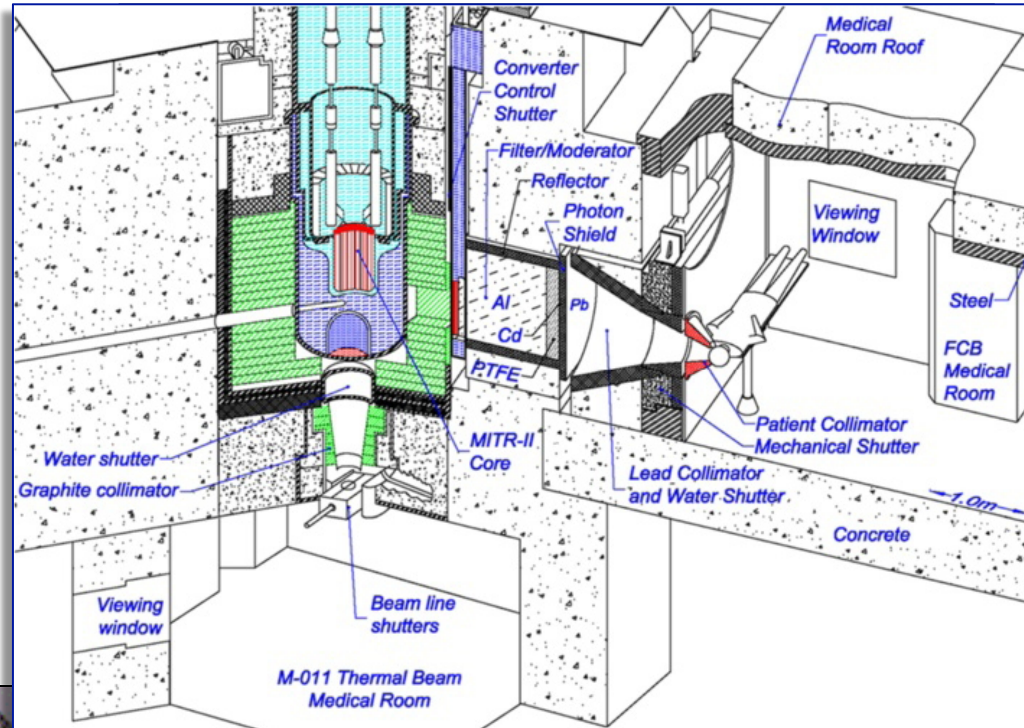
Kaplan-Meier estimates of overall survival for all newly diagnosed glioblastoma (WHO grade 4, n = 21). The median survival time of boron neutron capture therapy (BNCT) group (blue line) is 15.6 months. There is statistical significance between both group Log-rank test (p = 0.0035)

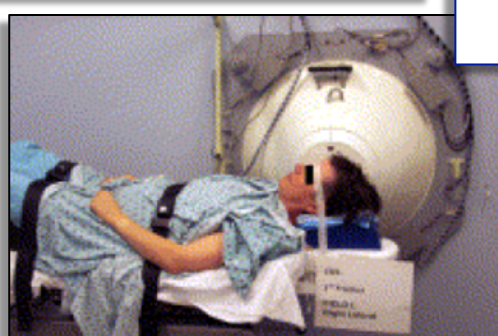


Kaplan-Meier estimates of overall survival for all newly diagnosed glioblastoma (protocol 1 and 2). External beam X-ray irradiation (XRT) boost after boron neutron capture therapy (BNCT) was carried for the latter 11 cases. This improved the median survival time to 23.5 months (from 14.1 months for BNCT only, protocol 1, dotted line in blue).

From Barth et al., Radiation Oncology 2012, 7:146 ,
Showing data from Kawabata et al., Appl. Radiat. Isot 2009 67:S15-18

The BNCT has been experimented in USA, Japan, UK, Russia, Finland, Italy, Argentina, China… but never in France





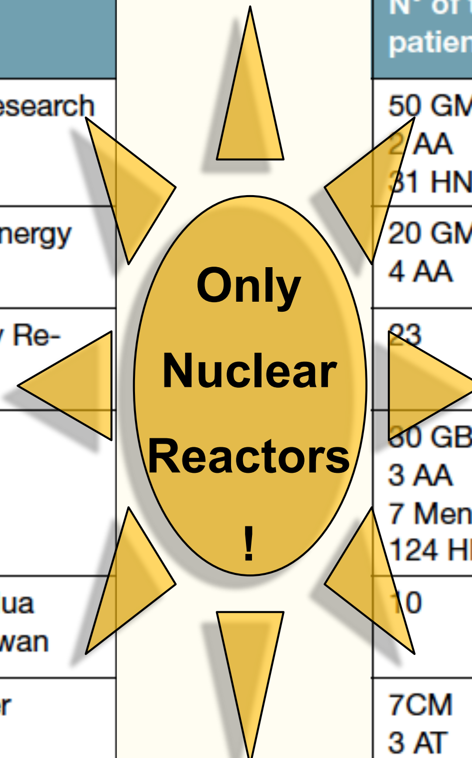
MIT reactor facility

NuPECC 2014 Report: Operative BNCT centres today !

Table 10.1. Operative BNCT centres

Centre	States	Neutron source	N° of treated patients*
Helsinki University Central Hospital, Helsinki, Finland	Europe	FIR-1, VTT Technical Research Centre, Espoo	50 GM 2 AA 31 HN
University of Tsukuba, Tsukuba City, Ibaraki	Japan	JRR-4, Japan Atomic Energy Agency, Tokai, Ibaraki	20 GM 4 AA
University of Tokushima, Tokushima	Japan	JRR-4 (Kyoto University Research Reactor, Osaka)	23
Osaka Medical College and Kyoto University Research Reactor, Kyoto University, Osaka and Kawasaki Medical School, Kurashiki	Japan	KURR	30 GBM 3 AA 7 Men 124 HN
Taipei Veterans General Hospital, Taipei, Taiwan	Republic of China	THOR, National Tsing Hua University, Hsinchu, Taiwan	10
Instituto de Oncología Angel H, Buenos Aires	Argentina	Bariloche Atomic Center	7CM 3 AT

* GM: glioblastoma multiforme; CM: cutaneous melanoma; AA: anaplastic astrocytoma; HN: head and neck cancer; Men: meningioma; AT: anaplastic thyroid cancer



TARGETS CHOICE

Accelerator based BNCT: Neutron-producing targets

Reaction	Bombarding energy (MeV)	Neutron producing rate (n/sec-mA)	Average neutron energy (keV)	Maximum Neutron energy (keV)	Target melting point (ºC)	Target thermal conductivity (W/(m·K))
$^{7}Li(p,n)$	1.91	$2.4 \cdot 10^{10}$	34	67.1	181	71
$^{7}Li(p,n)$	2.5	$8.9 \cdot 10^{11}$	326	786		
$^{9}Be(p,n)$	4	10^{12}	1060	2120	1287	201
$^{9}Be(d,n)$	1.5	$2.16 \cdot 10^{11}$	2010	5810		
$^{13}C(d,n)$	1.5	$1.82 \cdot 10^{11}$	1080	6770	3550	230

Lithium “fragility”

Larger the neutron energies,
harder to moderate them….

Accelerators and Targets of the present AB-NCT projects worldwide

Current status and performance of the different accelerators intended for AB-BNCT facilities worldwide.

Institute-location	Machine (status)	Target and reaction	Beam energy (MeV)	Beam Current (mA)	Reference
Budker Institute Russia	Vacuum insulated Tandem (ready)	Solid $^{7}Li(p,n)$	2.0	2	Aleynik et al (2011)
IPPE-Obninsk Russia	Cascade generator KG-2.5 (ready)	Solid $^{7}Li(p,n)$	2.3	3	Kononov et al. (2004)
Birmingham Univ. UK	Dynamitron (ready)	Solid $^{7}Li(p,n)$	2.8	1	Culbertson et al. (2004)
KURRI Japan	Cyclotron (ready)	$^{9}Be(p,n)$	30	1	Tanaka et al. (2011)
Soreq Israel	RFQ-DTL (ready)	Liquid $^{7}Li(p,n)$	4	1	Halfon et al. (2011)
Legnaro INFN Italy	RFQ (under construction)	$^{9}Be(p,n)$	4-5	30	Ceballos et al. (2011)
Tsukuba Japan	RFQ-DTL (under construction)	$^{9}Be(p,n)$	8	10	Kumada et al. (2011)
CNEA	Single ended	$^{9}Be(d,n)$	1.4	30	Kreiner et al. (2011)
Argentina	Tandem Electrostatic Quadrupole (under construction)	Solid $^{7}Li(p,n)$	2.5	30	

NIM 2013, Kreiner et al.

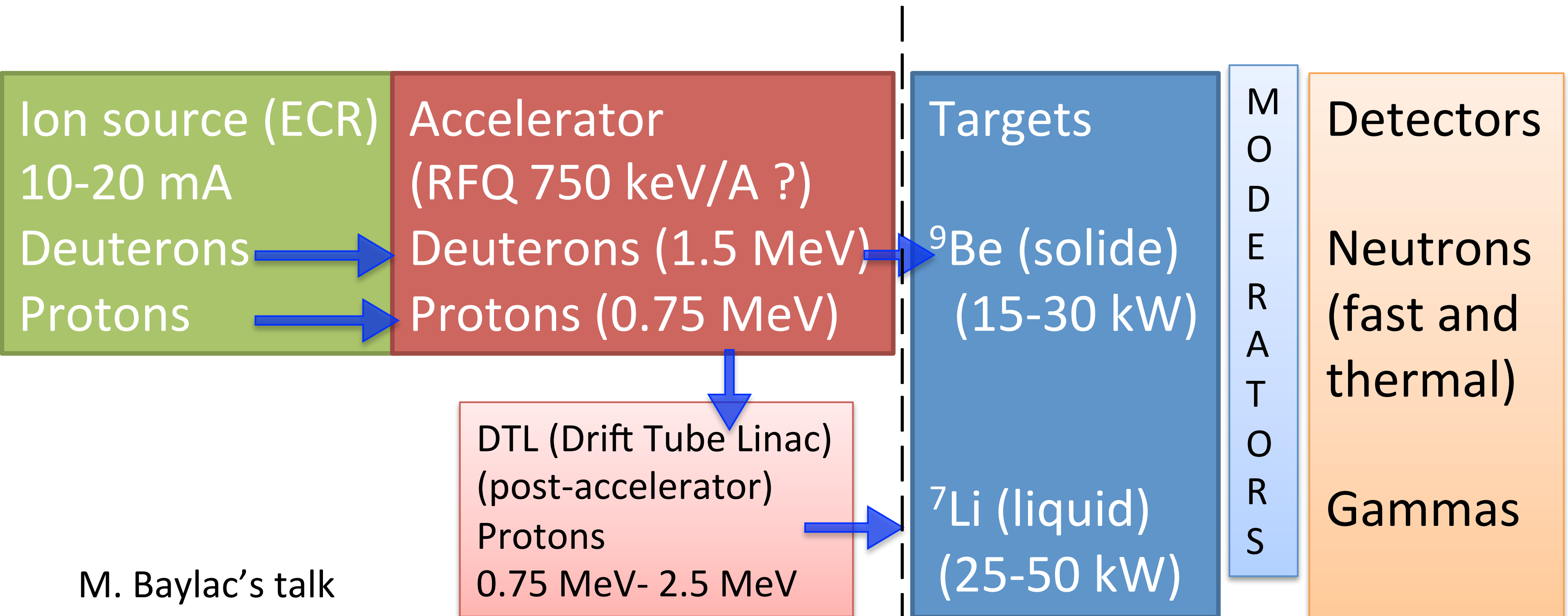
AB-NCT Challenges:

- To bring 10^9 $n_{th}/(cm^2.sec)$ to the tumor (30' irradiation time) using a compact and safe facility installed at a hospital.
- To build a target coping with 30-50 kW on 10 cm^2 (3-5 kW/cm^2)
- Caracterizing the neutron fields getting out the targets and the moderators (Beam Shapping Assemblies)

Project of an AB-NCT demonstrator in France

Two possibilities :

1) deuterons (1,5 MeV) on a ^{9}Be target
2) protons (2,5 MeV) on a liquid ^{7}Li target



M. Baylac's talk
J. Schwindling's talk
J-M. Lagniel's talk

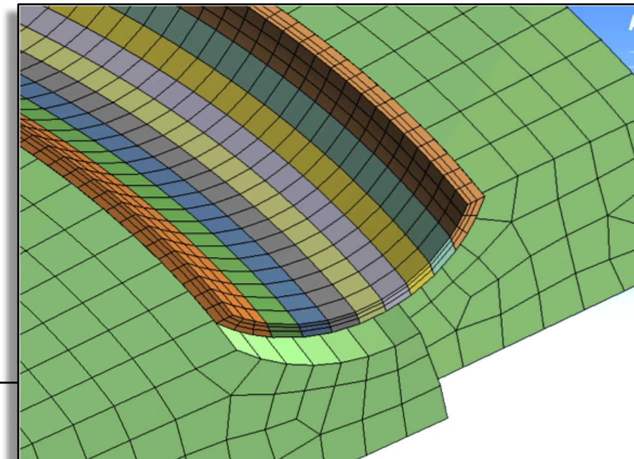
J. Giraud's talk

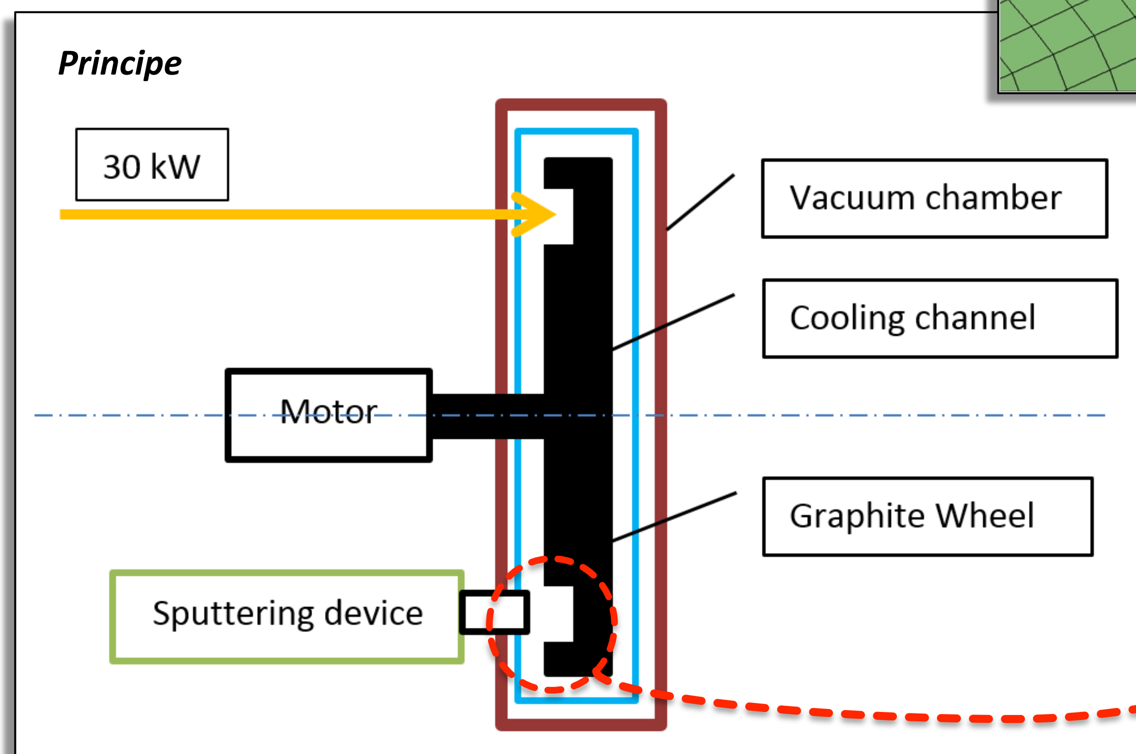
N. Sauzet's talk
D. Dauvergne's talk

Targets and Thermal Test Facility

Target for deuteron beam on ^{9}Be layer

Current status :
Target material : Beryllium layer
Backing material : Graphite
Backing diameter : 1000 mm
Thermal power dissipated : 30 kW
Cooling of the backing material : radiation mechanism
Regeneration of target





Production and regeneration of the ^{9}Be layer

Thermal test facility

Context

- The targets must work in acceptable thermal conditions

  must dissipate the thermal power

  ⟹

- Total thermal power on the targets: 30- 50 kW (on 10 cm^2)

  Power density of 3- 5 kW/cm^2

  ⟹

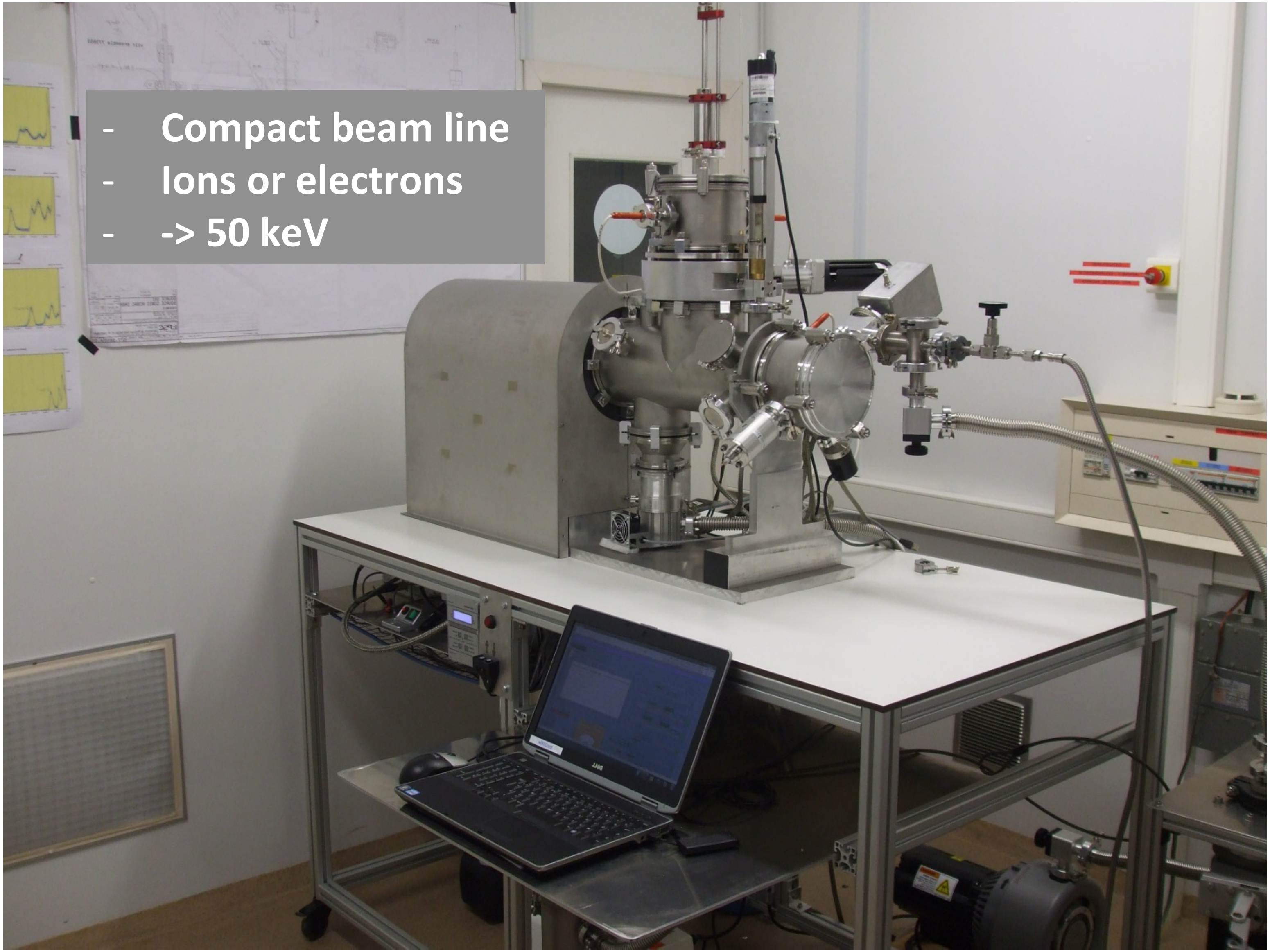
- Problem : How could we produce this thermal power density ?

⟹

Using an electron beam line :

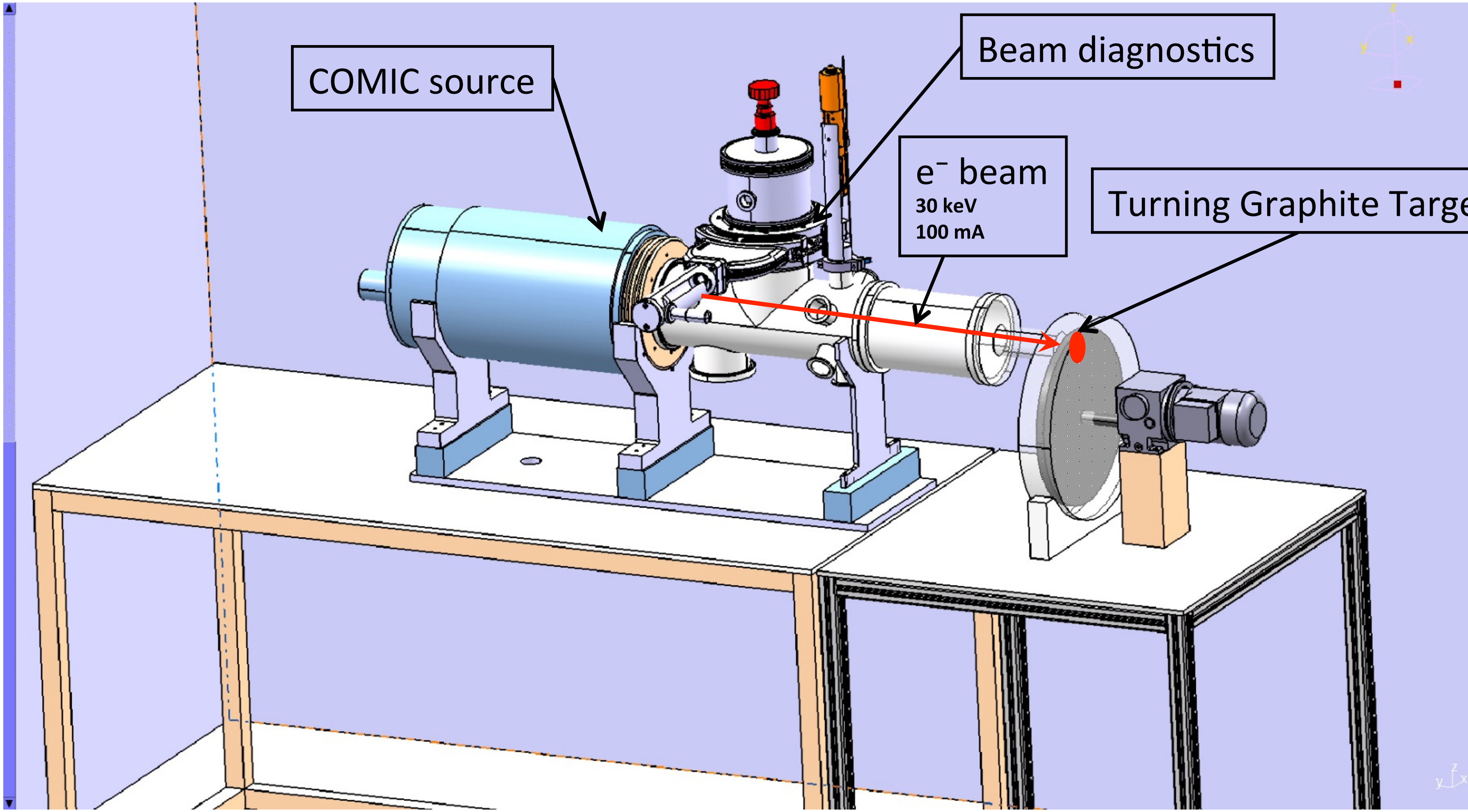
- *Energy : 30-50 keV*
- *Current : 100 mA*
- *Beam spot size : 1 cm^2*

COMIMAC



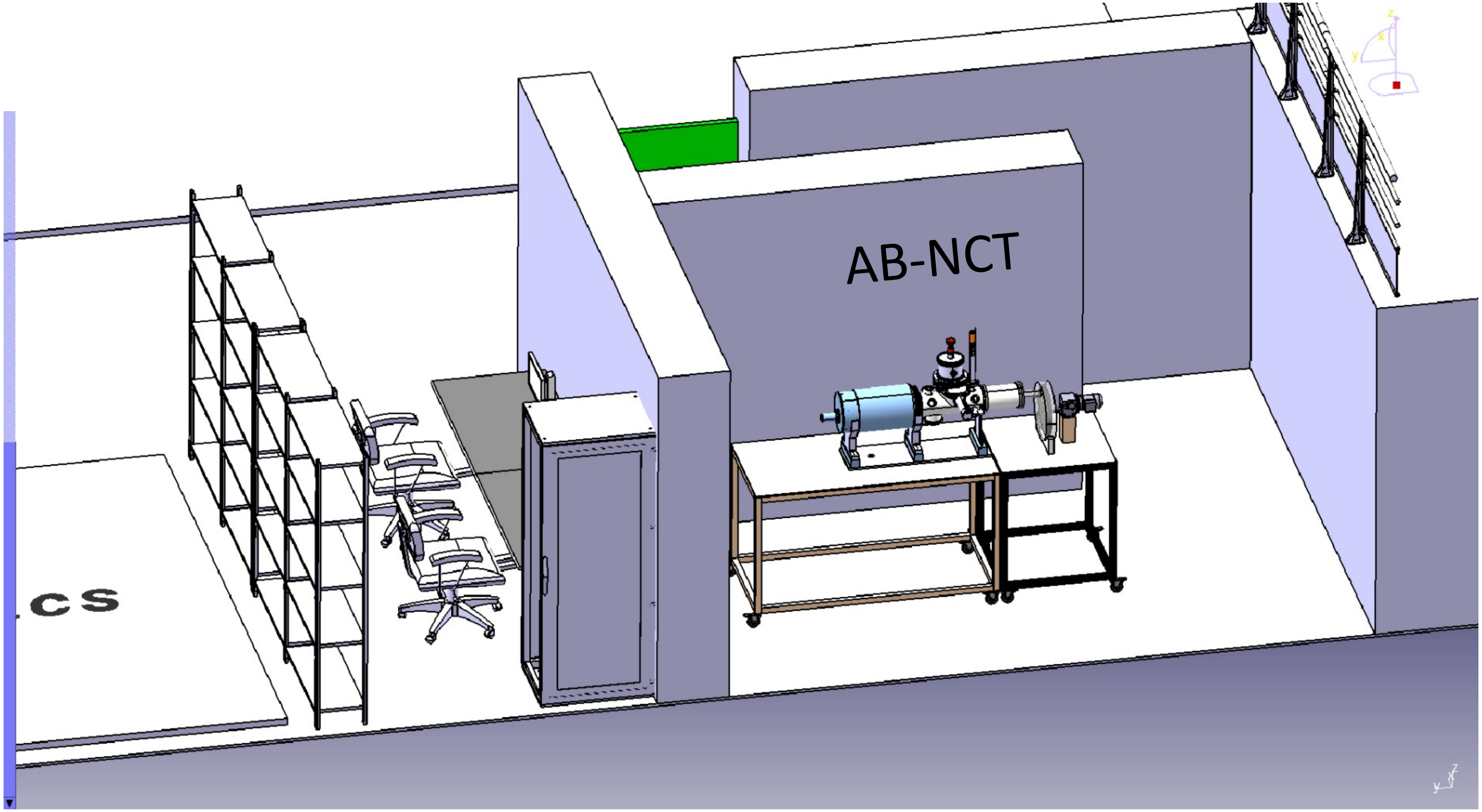
Test Facility

- COMIMAC coupled to the test target



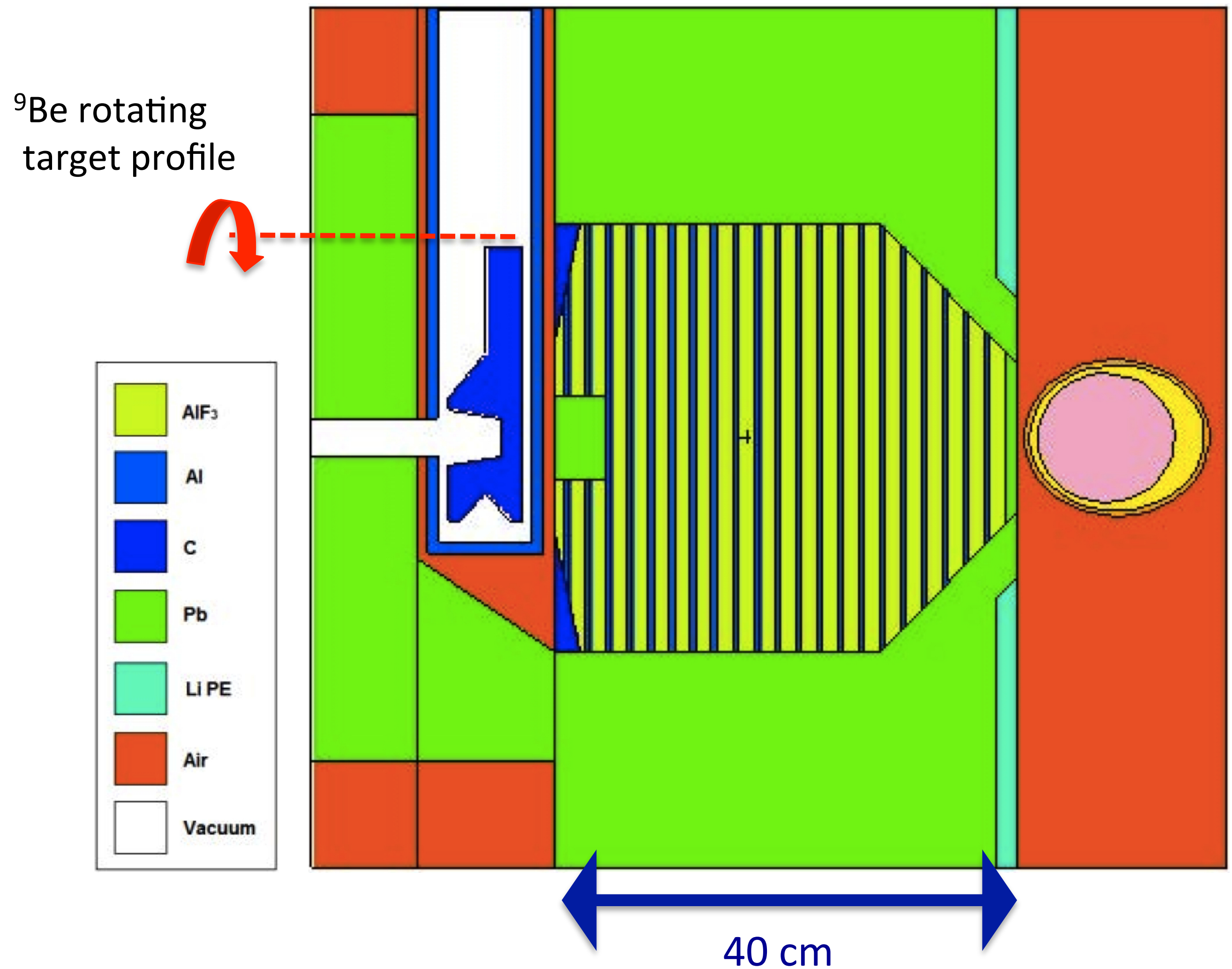
Experimental area

- Experimental area and radiation shielding at the LPSC

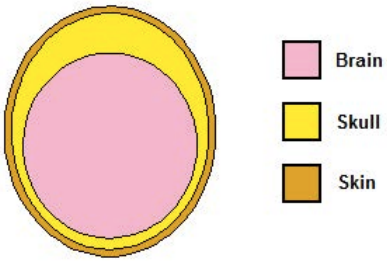


Moderation and detection of fast and thermal neutrons

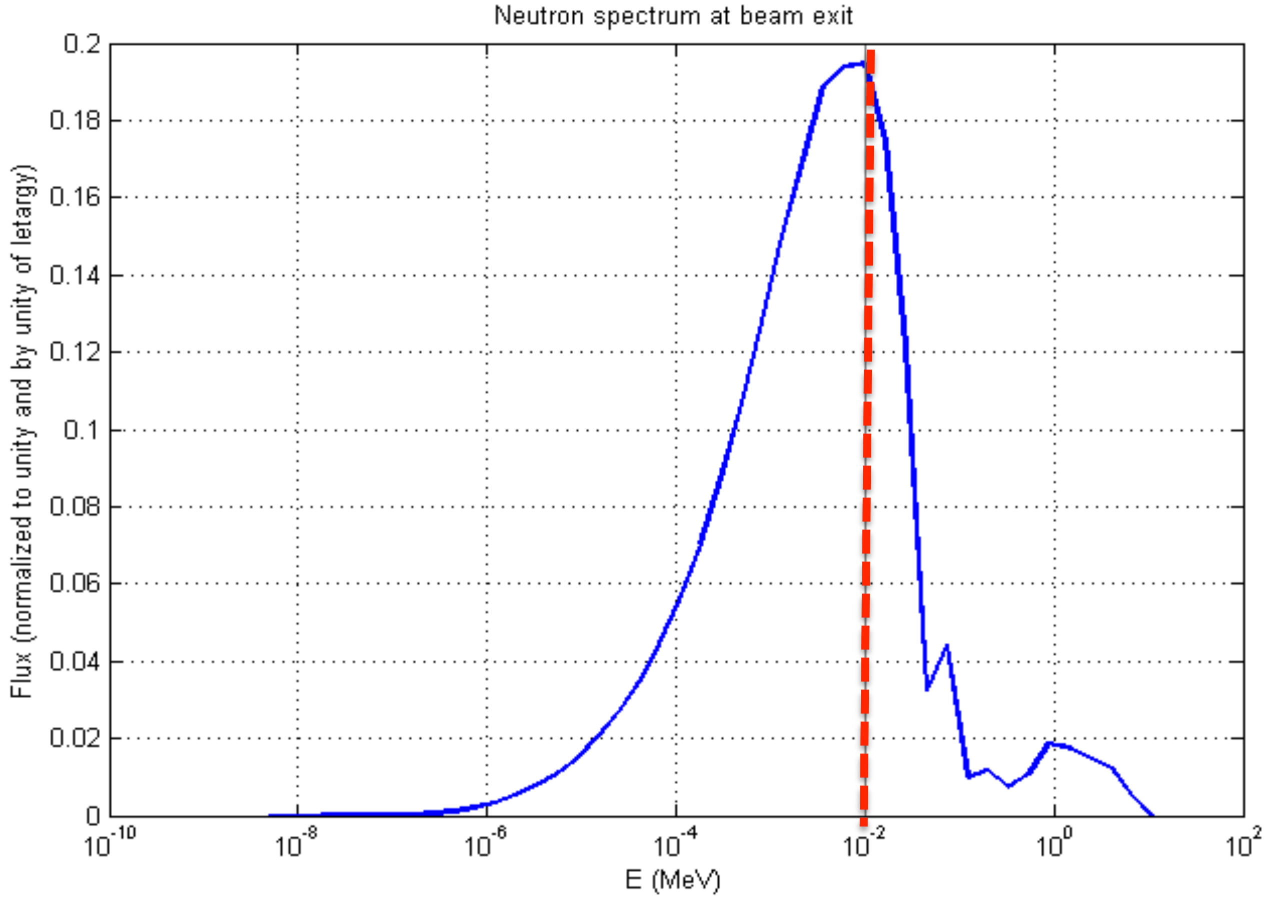
Simulation of a BSA for the ^{9}Be target (M.Tacca, D.S et al. (LPSC,2015))

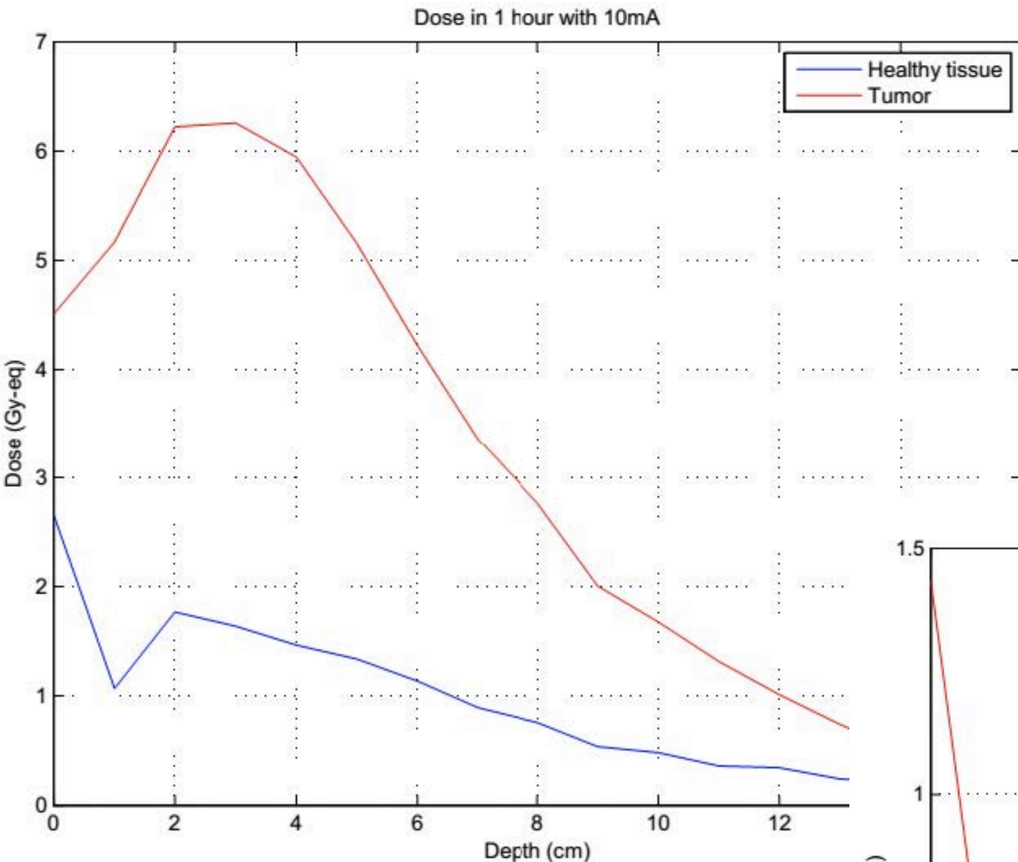


Snyder model (phantom)

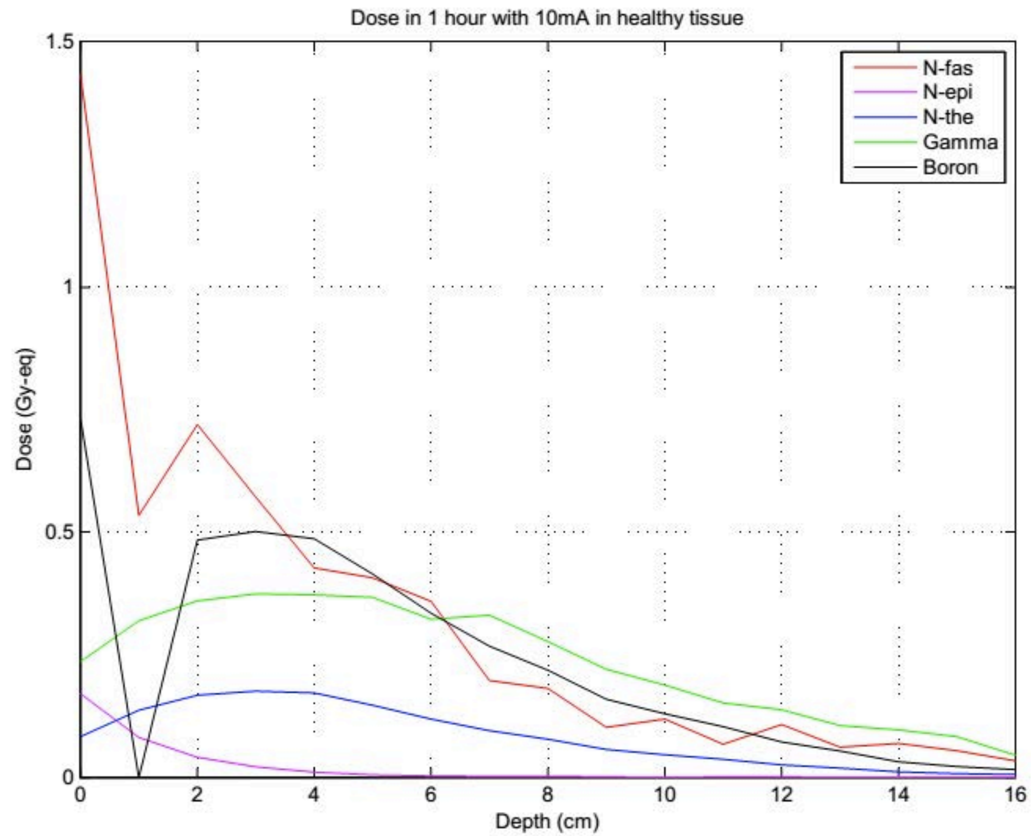


Neutron spectrum getting out the BSA around the ^{9}Be target simulated by Geant4 and MCNP (M. Tacca, D.S et al. LPSC,2015)





Dose calculation on the tumor and on the healthy tissue in 1 hour irradiation (10 mA of deuterons on the ^{9}Be target)
(contrast factor: 3,5)

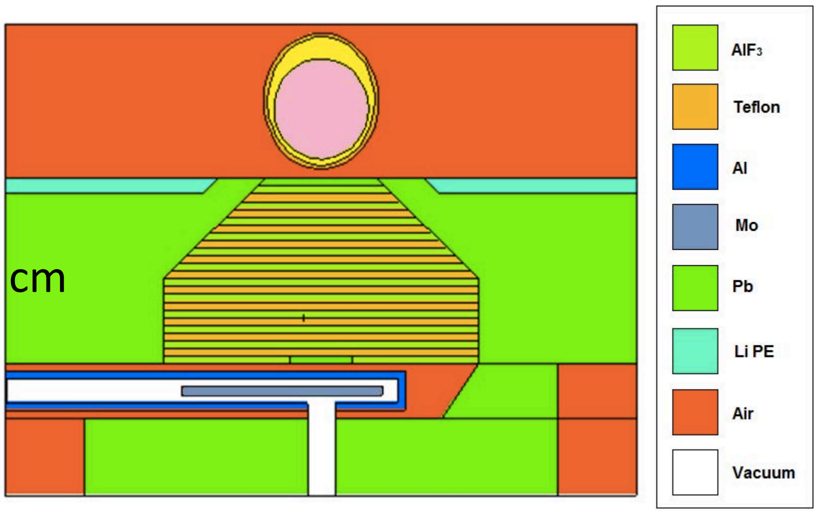


We need to improve a factor 6.4 the dose at the tumor…
But the design of the Be target has been improved since then…

^{7}Li liquid target

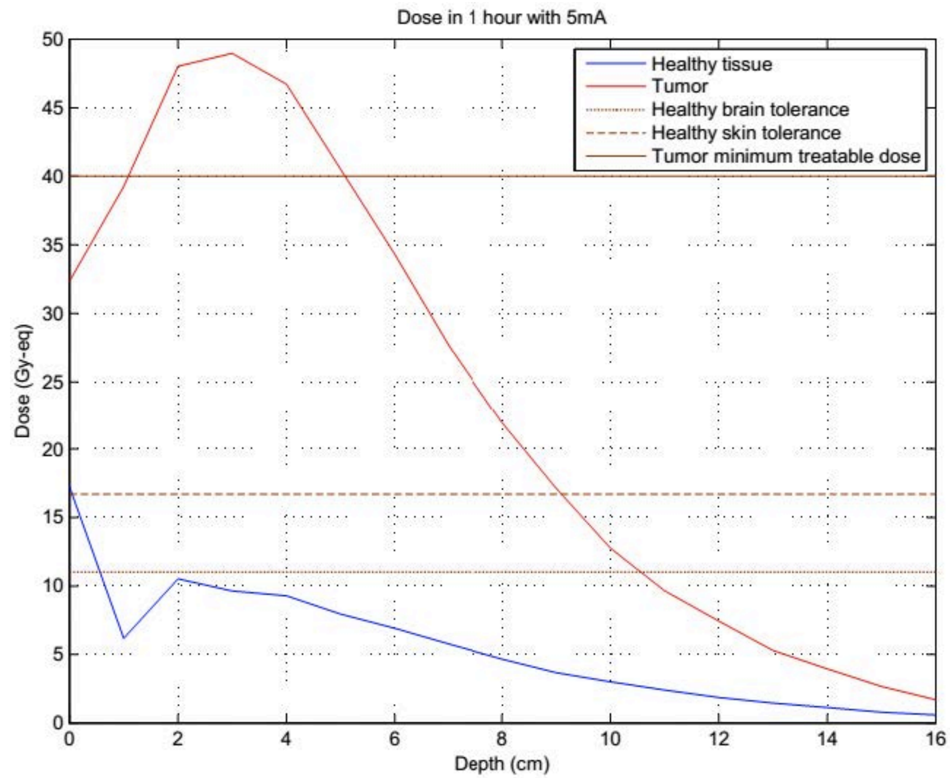
Simulation and dose calculation using the ^{7}Li target (M.Tacca, D.S. et al (LPSC-2015)

23 cm



All the quality parameters are fullfilled !!

Free beam parameter	*Li* BSA	Recommended
ϕ_{epi} (n/cm^2s)	$1{,}07+08\ mA^{-1}$	$>1{,}00E+09$
$\dot{D}_{fast}/\phi_{epi}$ $(Gy.cm^2)$	$9{,}88E-14$	$<2{,}00E-13$
$\dot{D}_{\gamma}/\phi_{epi}$ $(Gy.cm^2)$	$9{,}13E-14$	$<2{,}00E-13$
ϕ_{th}/ϕ_{epi}	$0{,}02$	$<0{,}05$
J_{tot}/ϕ_{tot}	$0{,}59$	$>0{,}7$



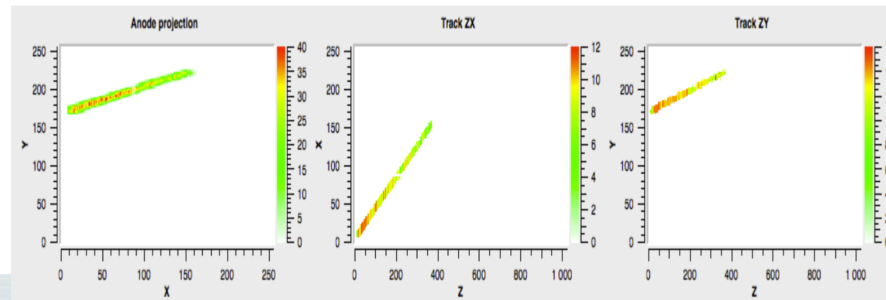
MIMAC-FastN: fast neutron detector

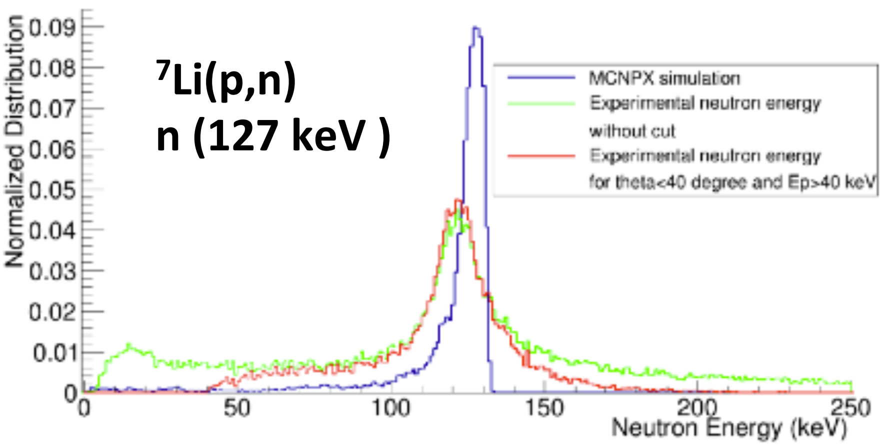
Neutron monochromatic field:

AMANDE facility at IRSN of Cadarache

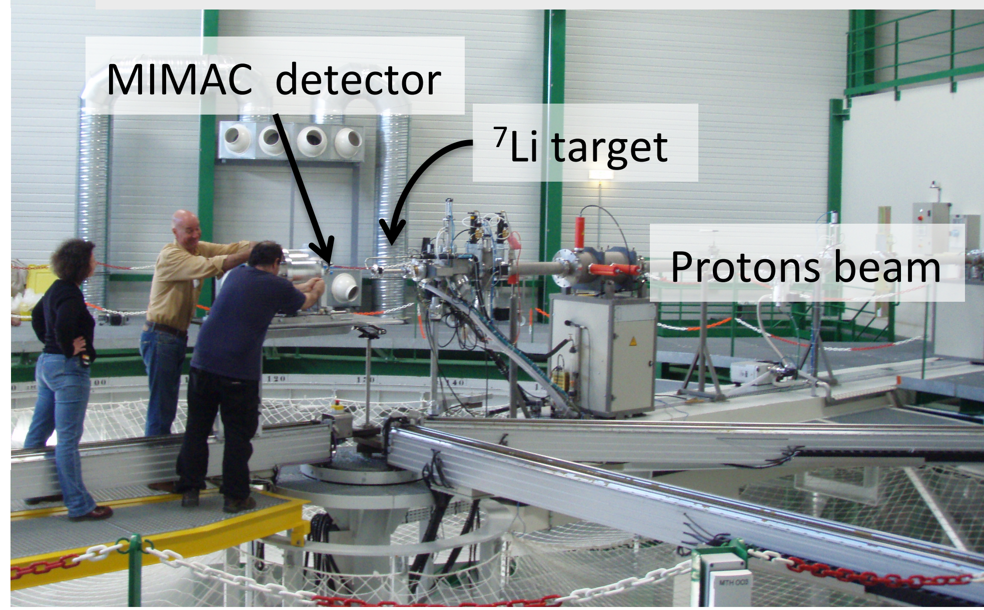
- Neutrons with a well defined energy from resonances of **^{7}Li(p,n) reaction**

$$E_{\mathrm{Recoil}} = 4\frac{m_n m_R}{\left(m_n + m_R\right)^2} E_{neutron} \cos^2\theta$$





D. Maire *et al.,* IEEE transactions on nuclear science, vol. 61, (2014) arXiv:1310.6837

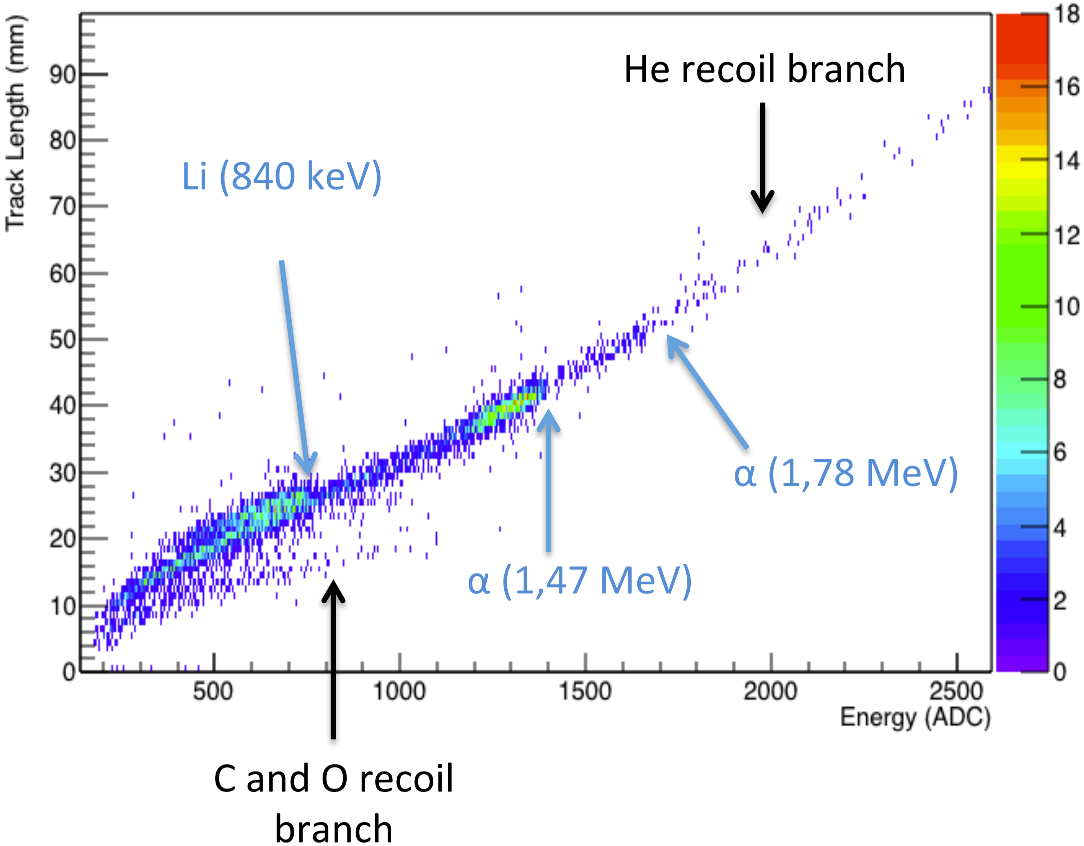


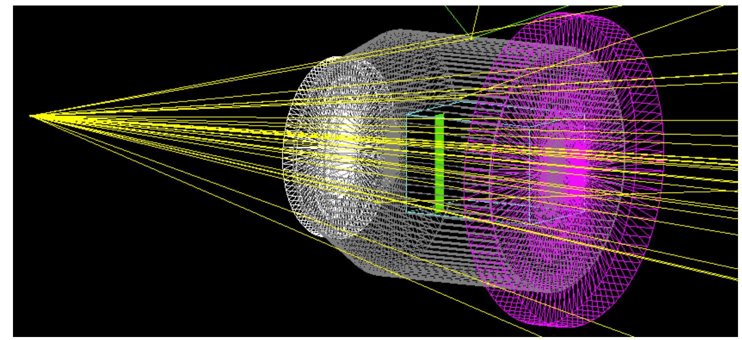
MIMAC-FastN: A fast neutron directional detector
To caractherize the neutron fields produced at the target and at the phantom

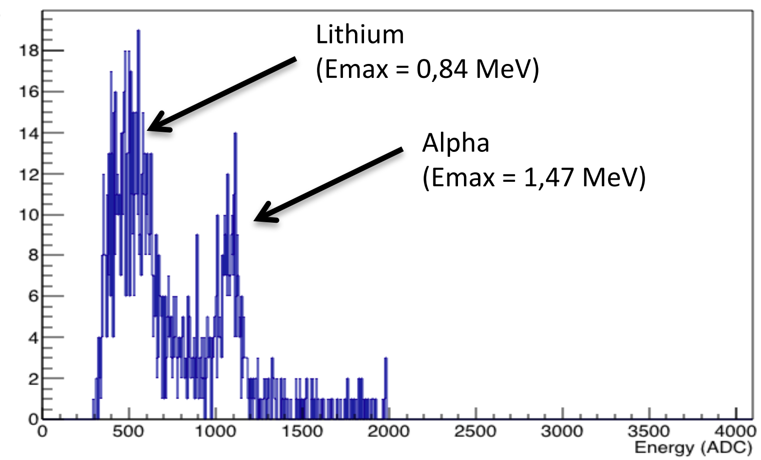
^{10}B layer inside the detector volume

One measures the fragments produced by the neutron capture at the "tumor position"

Track length vs. Recoil Energy







N. Sauzet et al, (2015)

Radiobiology experiments and simulations

- In collaboration with the ESRF *(ID-17, H. Elleaume)* and the ILL *(U. Koester)* :
  - Experimental studies and dosimetry of different biochemical compounds :
    - ✓ Cells experiments: Comparison of radiosensitivity due to BNCT/GdNCT (ILL) versus photo-activation radiotherapies (ERSF)
    - ✓ Micro-dosimetry studies by simulation comparing GdNCT and BNCT
    - ✓ Tests of GdNP and BNCT with thermal neutrons *(ILL)*
  - Damages on healthy tissues close to tumors :
    - ✓ Study on the nitrogen present in the DNA as the main source of the dose on healthy tissues

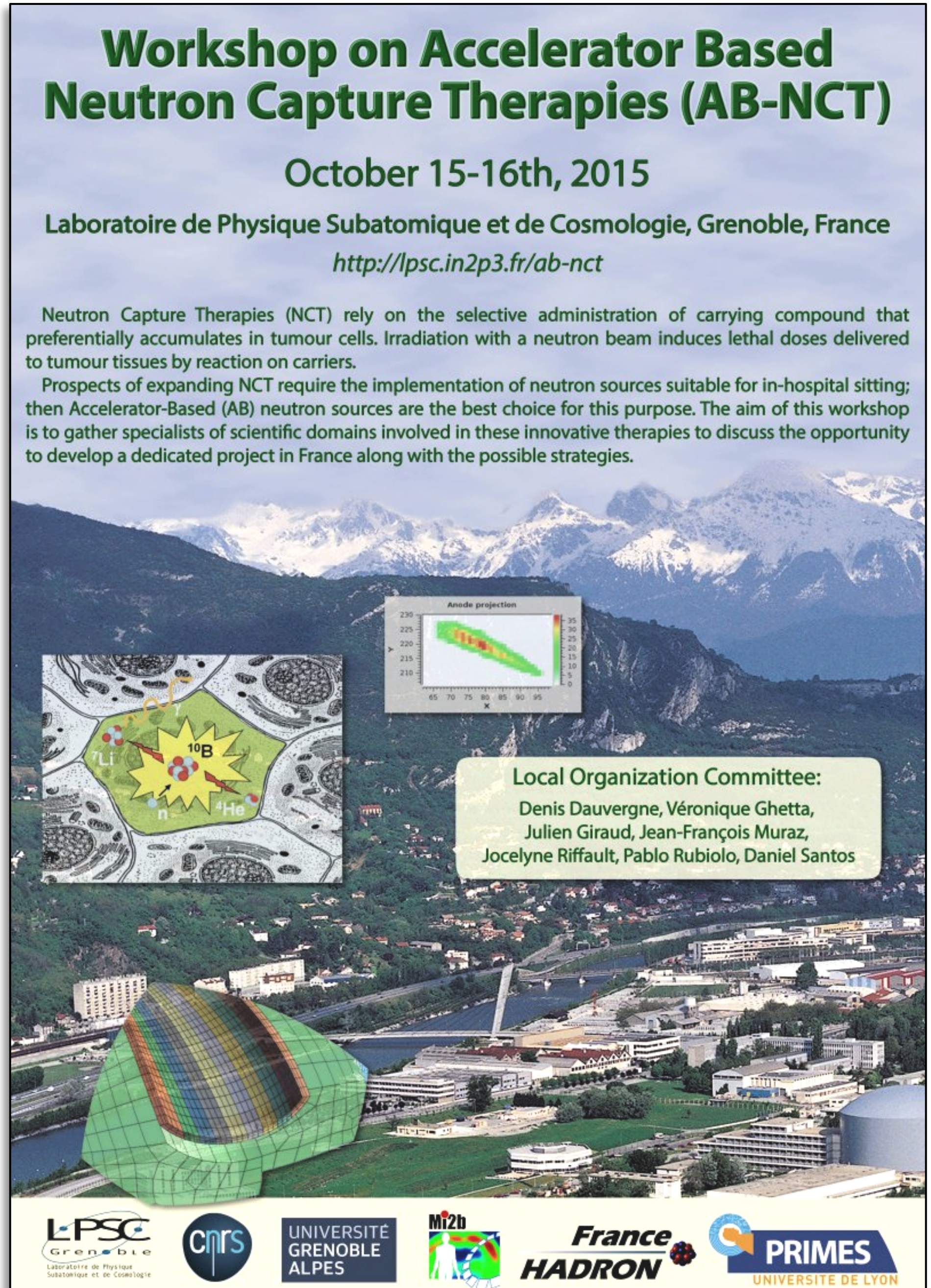
AB-NCT Project

LPSC – Grenoble Team:

D. Santos	(*Project Manager, Neutron detection and BSA simulation*)
J-F. Muraz	(*Technical Coordination, Thermaltarget tests*)
P. Cavalli	(Targets)
D. Dauvergne	(Gamma detection)
R. Delorme	(Simulations, radiobiological experiments)
J. Giraud	(Target thermal and mechanical calculations)
V. Ghetta	(Targets responsibility)
O. Guillaudin	(Neutron detector)
P. Rubiolo	(Simulations and Neutron detection)
N. Sauzet	(Simulations and Neutron detection)

AB-NCT French project strategy

- The NCTs are a subject of **Medical Research** → Physicians and Biologists in France have to define and « build » a clinical research project
- Local (Grenoble) and Regional (Rhône-Alpes) context:
  - LPSC (ion source + accelerator, targets, moderators, neutron and gamma detectors)
  - ILL (U Koester et al.) and ESRF (H. Elleaume, JF Adam et al) Cell irradiation experiments
  - CHU Grenoble (J. Balosso et al)
  - LabEx PRIMES: WP1 Innovative Radiotherapies, WP3 Radiobiology
    - Nanoparticles as carriers
    - Gamma imagery
- National context:
  - Ion sources and RFQs (LPSC, Ganil, Saclay)
  - France Hadron support
- Joining the International effort on AB-NCT
  - Workshop on AB-NCT - Grenoble (October 15^{th},16^{th} 2015)
  - Collaboration with the Argentina Group: TANDAR (CNEA) A. Kreiner et al.
  - Finland, Germany, Italy, Japan, United Kingdom…



Workshop on AB-NCT

October 15th, 16th 2015

Grenoble (France)

More than 50 participants…