R&D ACTIVITIES FOR THE PRODUCTION OF RADIOISOTOPES AT GANIL

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Agenda

- Motivations and opportunities
- Short terms projects
  - ^{211}At
  - Other α emitters
  - Dosimetry
- Conclusion and perspectives

Motivations and opportunities

A great density of skills

Nuclear Physics
Astrophysics
Applications

Atomic Physics
Material science

Life and health science

Radiobiology

Medicine
Hadrontherapy center

Centre de Lutte contre le Cancer François Baclesse
unicancer NORMANDIE - CAEN

CHU CAEN NORMANDIE

Motivations and opportunities

GANIL-SPIRAL 2 Layout

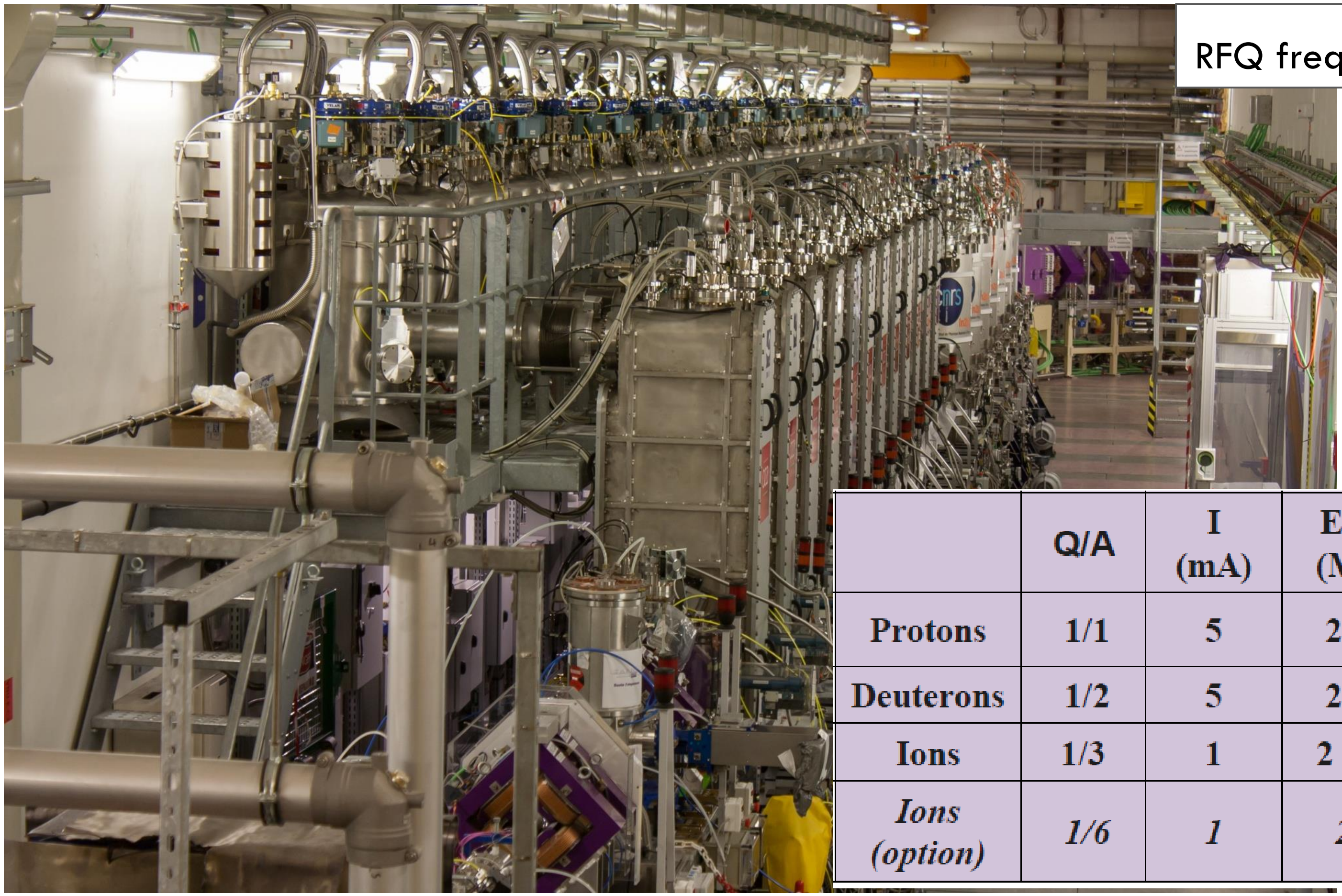
ESFRI landmark facility

SPIRAL2 & SPIRAL1 Upgrade

- ✓ High intensity stable beams
- ✓ High intensity neutron beams
- ✓ High intensity RIBs

Motivations and opportunities

The SPIRAL 2 Linac

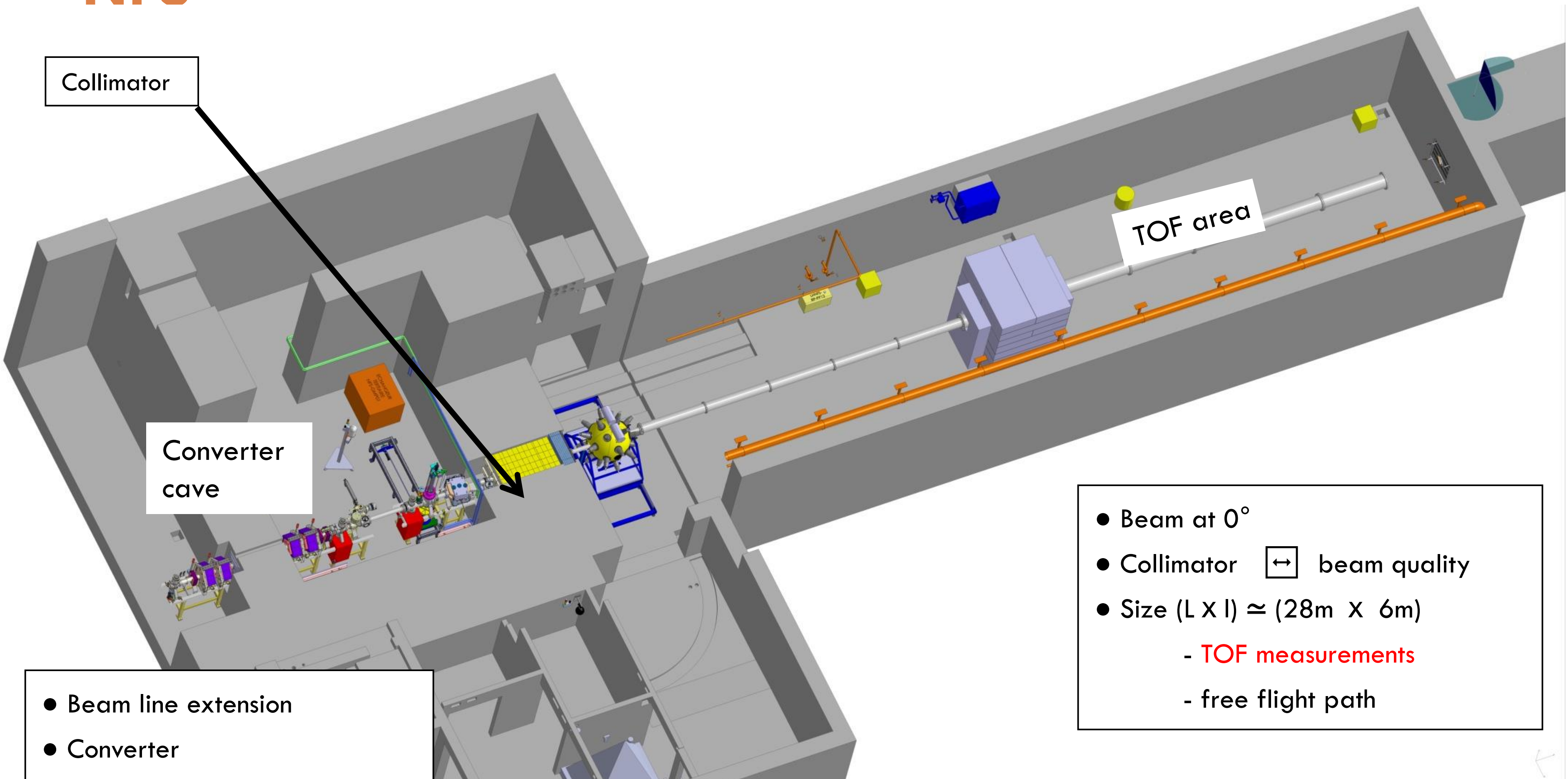


RFQ frequency F = 88MHz

	Q/A	I (mA)	Energy (Mev/u)	CW max beam Power (KW)
Protons	1/1	5	2 - 33	165
Deuterons	1/2	5	2 - 20	200
Ions	1/3	1	2 - 14.5	45
Ions (option)	*1/6*	*1*	*2 - 8*	*48*

Motivations and opportunities

NFS

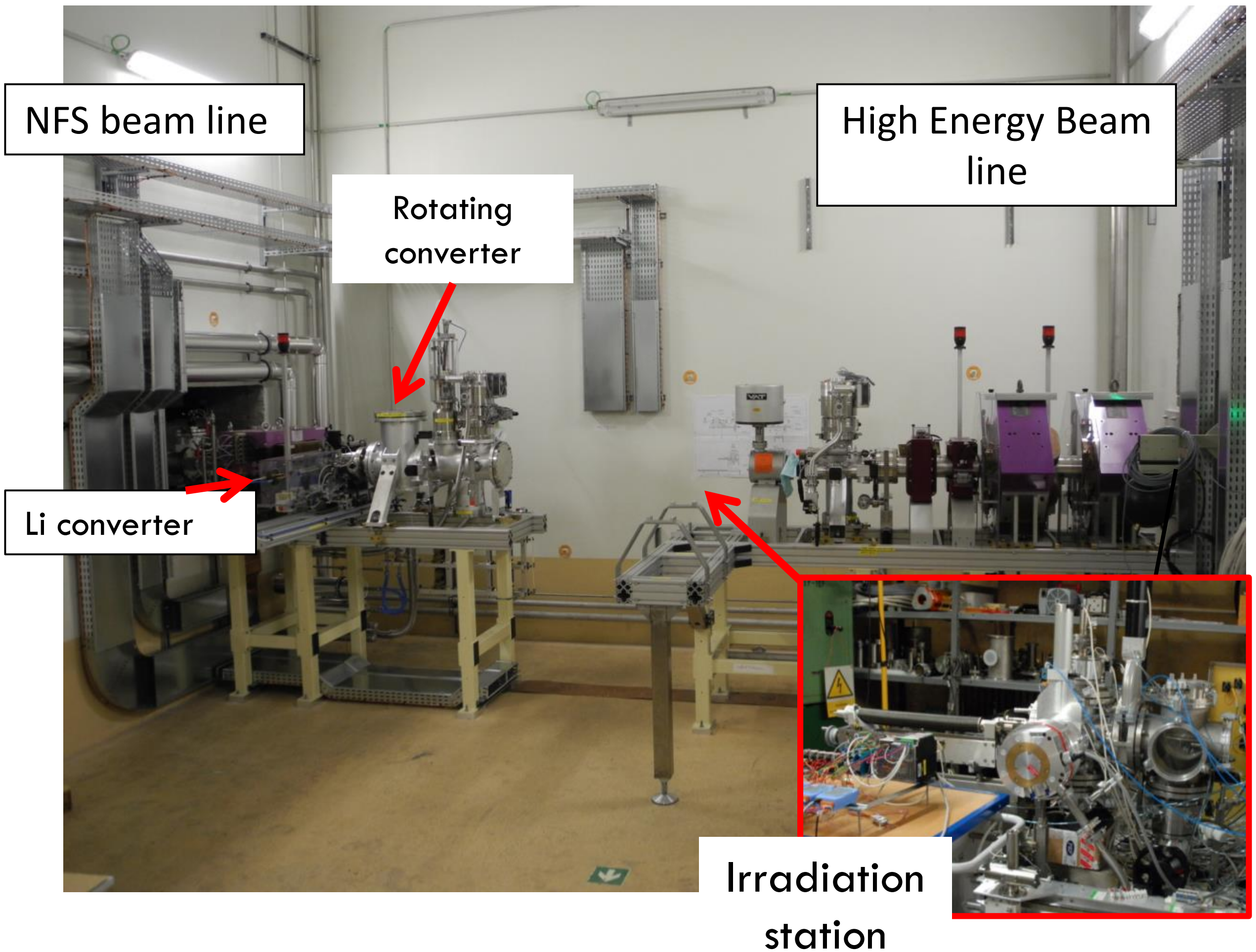


- Beam line extension
- Converter
- Magnet and beam dump
- Irradiation station (n, p, d)

- Beam at 0°
- Collimator $\boxed{\leftrightarrow}$ beam quality
- Size (L X l) ≃ (28m X 6m)
  - TOF measurements
  - free flight path

Motivations and opportunities

NFS Converter room



Motivations and opportunities

Opportunities at SPIRAL 2

- Limited current (cyclotrons):
  - Dedicated equipments, not optimized for R&D production of new isotopes (fixed energy) => cross-section, contamination,…
  - Only proton, deuteron and/or α-particles
  - Target not designed for high beam intensities

- New possibilities at SPIRAL2:
  - Very intense beams at variable energy (Imax=5 mA for 40MeV d)
  - New beams compared to existing production facility machines

Motivations and opportunities

Strategy for radio-isotopes studies

- Only R&D
- Collaboration
- Targeted goals
- Alpha emitters

- Current isotopes of interest:
  - ^{211}At (ARRONAX et al)
  - α+Th reaction products

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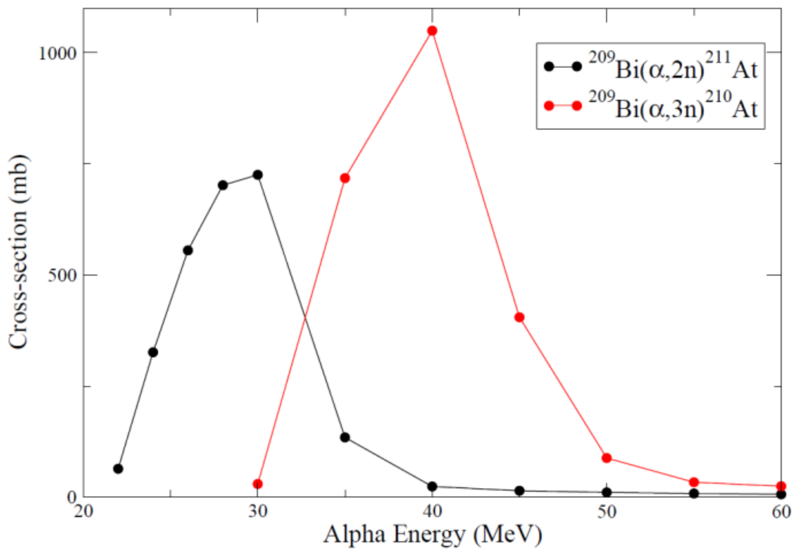
^{211}At at NFS

Production using $^{209}Bi(\alpha,2n)^{211}At$

- Reaction
  - Reaction threshold 20.718 MeV
  - Cross section max 700 mb at 30 MeV
  - Production of contaminant ^{210}Po $^{209}Bi(\alpha,3n)^{210}At \rightarrow {}^{210}Po$, $t_{1/2} = 138$ d, Et=28.613 MeV
  - At 30 MeV: ratio $N^{210}At/N^{211}At < 10^{-4}$

- Production estimate:
  - Alpha 28 MeV, 1 kW
  - Target : Bi on AlN backing
  - ^{211}At production : 9.6 GBq in 8h



^{211}At at NFS

Scenario

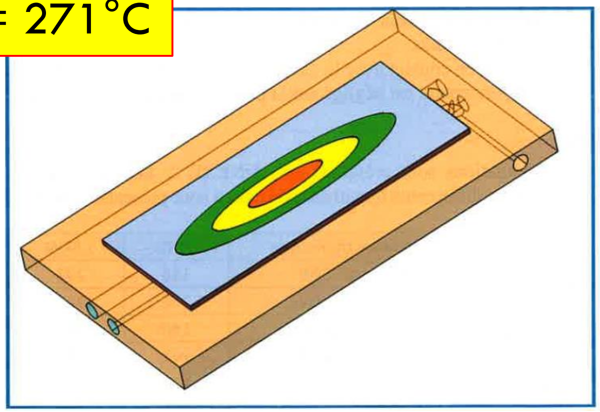
- Target from ARRONAX
- Irradiation at SPIRAL2
  - Irradiation station in the converter room
  - Beam: 28 MeV α, 70 μA (3.15^{e}14 α/s)
  - Tirr: 4 to 8h
  - Production of ~10GBq of ^{211}At
  - Dose Rate after 30 min cooling: 0.25 mSv/h at 30 cm
- Irradiated targets sent to ARRONAX
- Extraction, labelling, QC at ARRONAX

^{211}At at NFS

Thermal study

- 1kW deposited
- Two designs:
  - Target on cold copper
  - Direct backing liquid cooling
- Parameters:
  - Thermal resistance target-copper
  - Cooling liquid temperature

T_{fusion} Bi= 271°C



1 kW OK. Measurement of thermal resistance

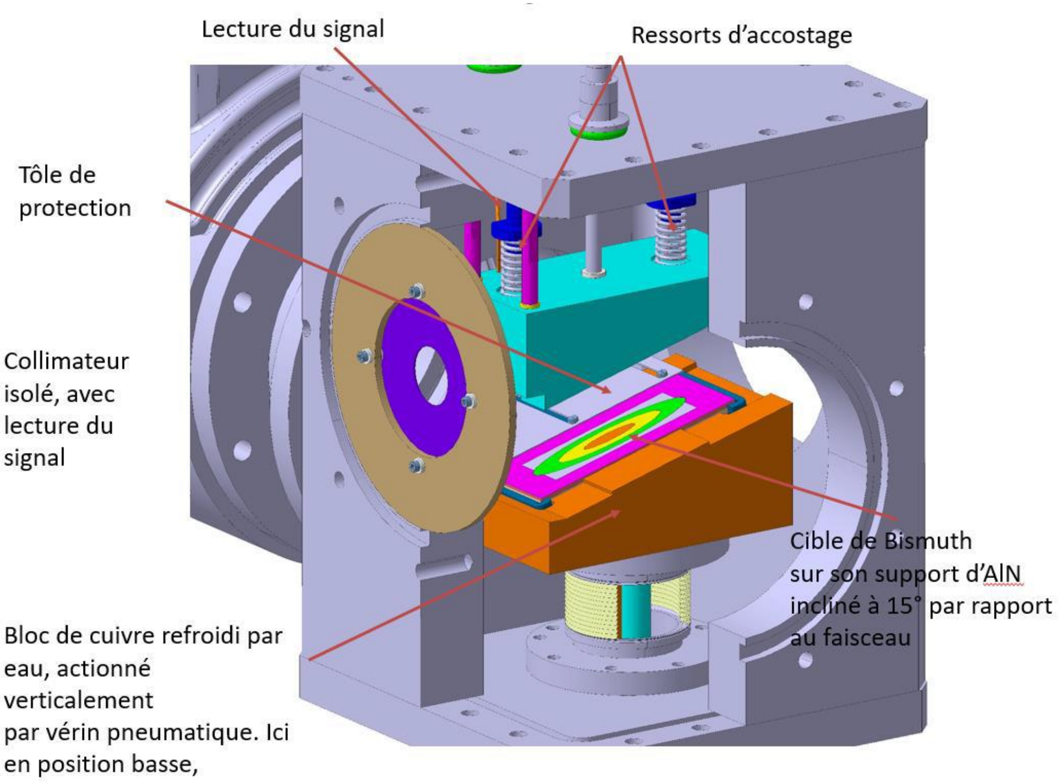
	résistance thermique	1KW	1,5KW	2KW
solution plaquée (eau 15°C)	100 mm².C/W	188	292	
	200 mm².C/W	252	387	
solution plaquée (éthanol -30°C)	100 mm².C/W	140	243	
	200 mm².C/W	202	340	
solution contact eau (eau 15°C)		156	228	309
solution contact eau (éthanol -30°C)		105	180	260

Tableau 4 : températures maximum de la cible calculées en °C

^{211}At at NFS

The irradiation station

- Manual load/unload
- Unload using vinyl confinement
- Dosimetry measurements
  - extremity : 480 µSv
  - Full body : 20 µSv
- Shipment : A type parcel



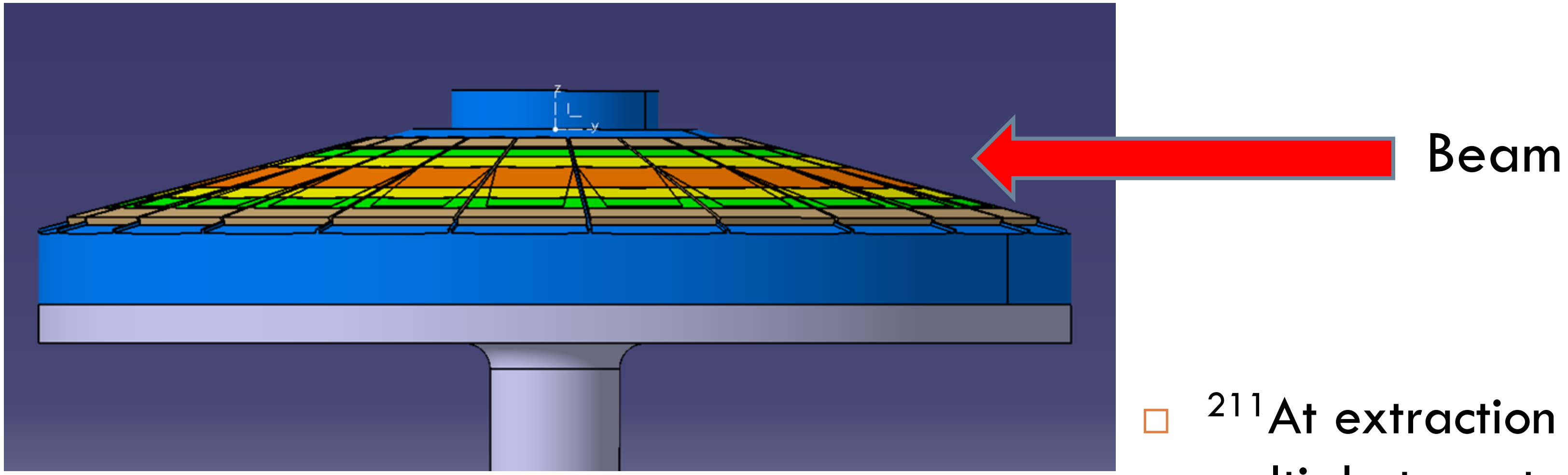
Collaboration NPI Rez (Tcheque Rep.)
Under manufacturing

^{211}At at NFS

Higher power dissipation

- Production via α + Bi
- Goal: ~10 kW
- Rotating target

Ø beam (+/-3 σ) = 24 mm
we kept the angle of the target of 15°



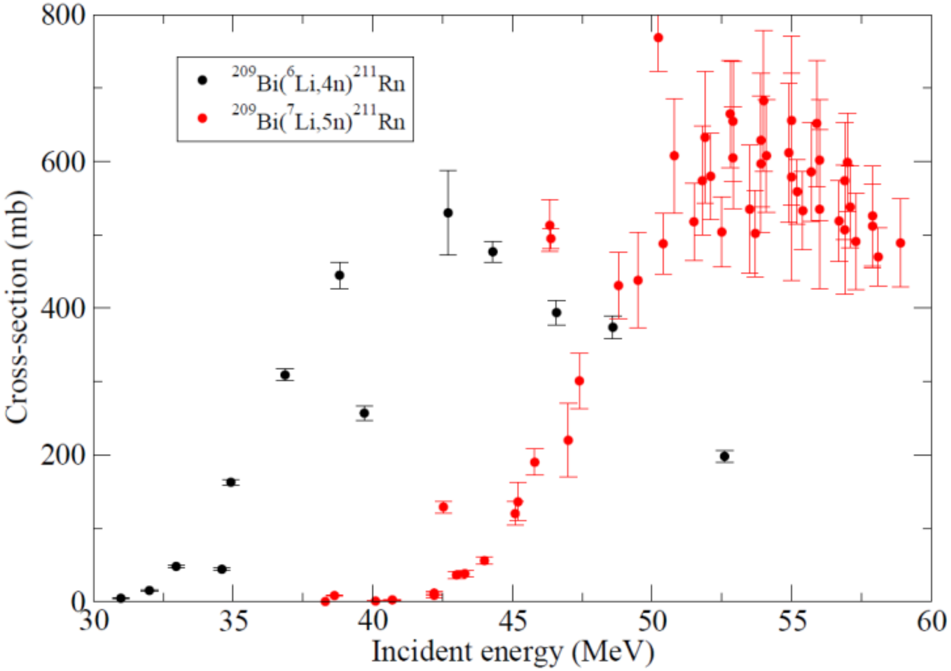
- ^{211}At extraction with multiple targets ?

Collaboration NPI Rez (Tcheque Rep.)
Feasibility study

^{211}At at NFS

Design of a generator using $^{209}Bi(^{6}Li,4n)^{211}Rn$ or $^{209}Bi(^{7}Li,5n)^{211}Rn$

- Reaction
  - Reaction threshold
    - 28.5 MeV for $^{209}Bi(^{6}Li,4n)$
    - 36.13 MeV for $^{209}Bi(^{7}Li,5n)$
  - ^{210}Po contamination
    - $E(^{6}Li)$> 36 MeV for $^{209}Bi(^{6}Li,4n)$
    - $E(^{7}Li)$> 48 MeV for $^{209}Bi(^{7}Li,5n)$
  - Energy domain of SPIRAL2



- Production estimate:
  - LISE code
  - Lithium beam stopped in target
  - Optimal irradiation time : 14h
  - Best reaction $^{209}Bi(^{7}Li,5n)^{211}Rn$

48 MeV	36 MeV	Rapport activité
Act-utile (Bq/µA)	Act-utile (Bq/µA)	
^{7}Li	^{6}Li	$^{7}Li/^{6}Li$
4,84E+05	1,83E+05	2,65

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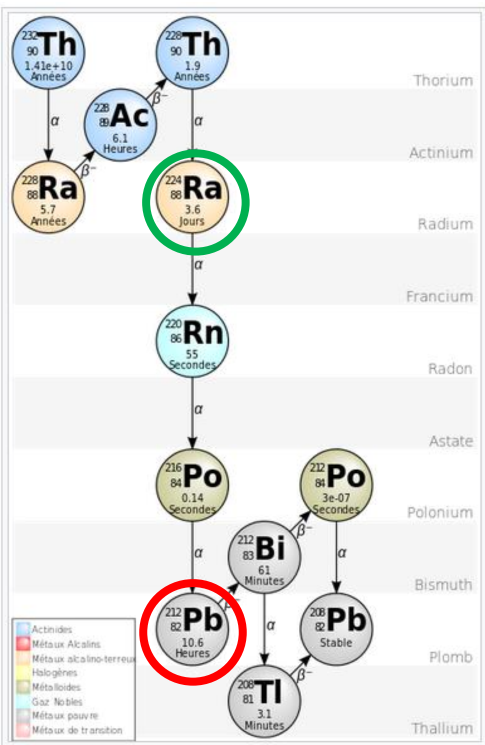
Other α-emitters

Generators from the α + ^{232}Th reaction

^{212}Pb from ^{224}Ra

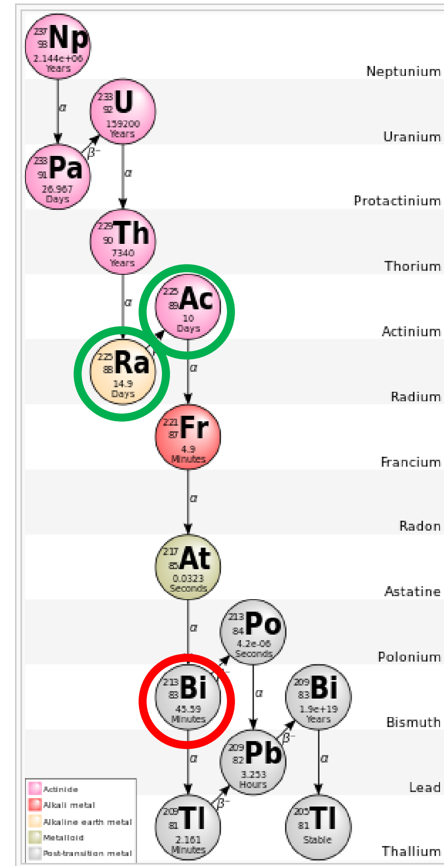
^{213}Bi from ^{225}Ra or l'^{225}Ac



Thorium 232 decay chain

Generators

Radio-isotopes of interest

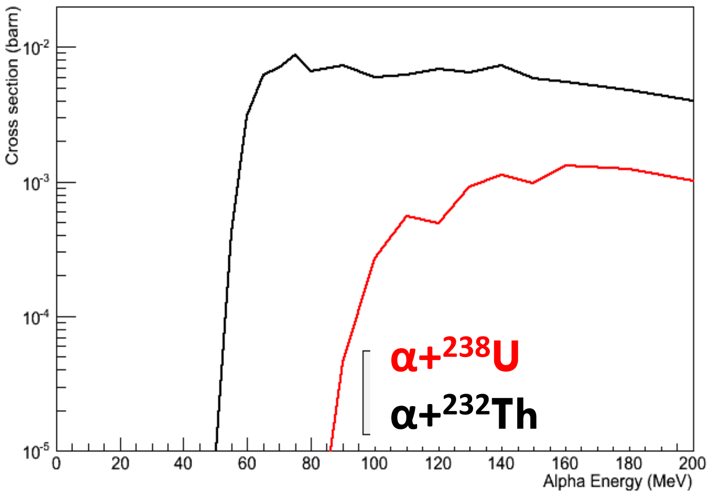


Neptunium 237 decay chain

Other α-emitters

^{224}Ra generator

- Database TENDL-2014: Reaction α + ^{232}Th
- Reaction threshold
  - ≈ 50 MeV for α + ^{232}Th
  - ≈ 100 MeV for α + ^{238}U



- Production rate calculations :
  - Natural thorium target 0.05 cm so that E_{out}≈ 50 MeV
  - 80 MeV, I=200 μA (6.2e14 α/s)
  - T_{irr}=1d
  - FISPACT-II vs PHITS : **huge differences**

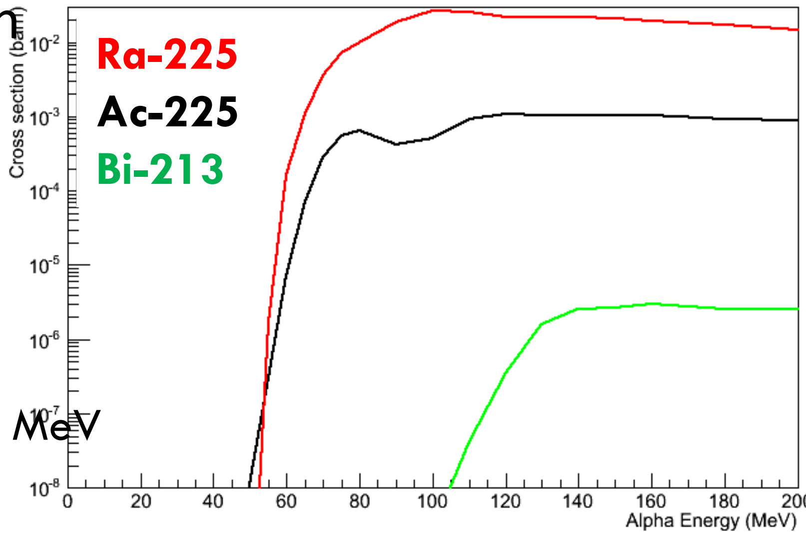
	MCNPX+FISPACT II	PHITS
^{224}Ra	3.56×10^{8} Bq/g	5.34×10^{6} Bq/g

⇨ First cross-section measurements to constrain models
⇨ Approved experiment at NFS

Other α-emitters

^{225}Ac generator

- Database TENDL-2014: Reaction α + ^{232}Th
- Reaction threshold
  - ≈ 50 MeV for ^{225}Ac and ^{225}Ra
  - ≈ 100 MeV for ^{213}Bi
- FISPACT-II calculations:
  - Natural thorium target 0.05 cm so that E_{out}≈ 50 MeV
  - 80 MeV, I=200 μA (6.2e14 α/s)
  - T_{irr}=1 and 10 d



	80 MeV	
	A(Bq/g)	% Atot
Irradiation 1j	1.24E+08	0.39%
Irradiation 10 j	9.30E+08	0.495%

⇨ First cross-section measurements to constrain models

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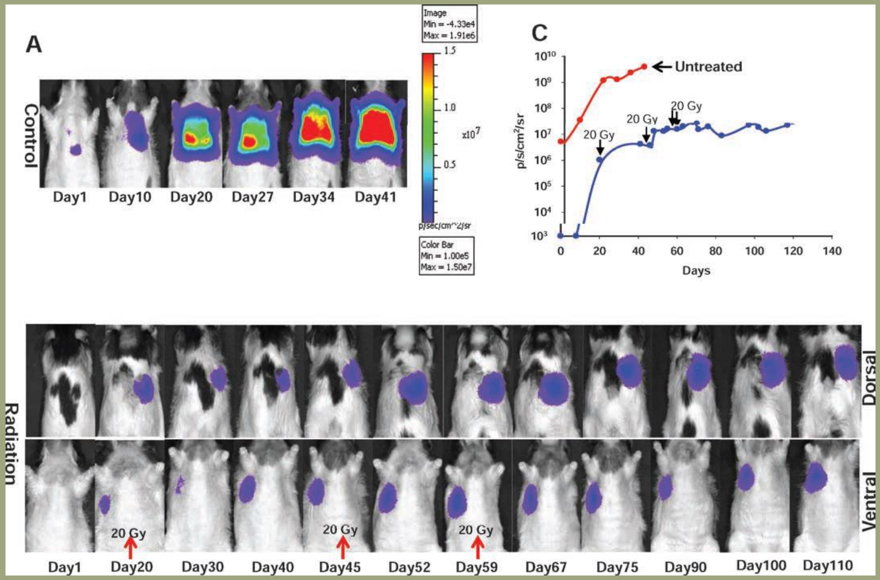
Dosimetry

Development of a new radiopharmaceutical → Evaluation / Trials **Preclinical** / clinic

PHYSICAL dose **vs.** BIOLOGICAL observable



e.g: tumour volume vs. delivered dose

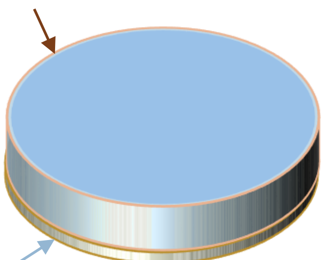
Tumor progression after (panel A) no treatment and (panel B) delivery of 60 Gy in three fractions on days 20, 45 and 59. The heat scale is given in signal intensity per unit area. Panel C: Tumor growth curve obtained by integrating the bioluminescence imaging signal over a region of interest. (reprint of Saha 2010)

Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

Dosimetry: MIRD Formalism

$$D(Gy) = \frac{E(J)}{m(kg)}$$

Case of *in vitro* irradiation



In radionuclide therapy:

Nb of radionuclide decays in a particular volume $\tilde{A}_S$

× energy emitted per decay E_0

× fraction of emitted energy absorbed by a particular (target) mass $\varphi_{T \leftarrow S}$

$$D_T = \frac{\tilde{A}_S \cdot E_0 \cdot \varphi_{T \leftarrow S}}{m_T}$$

???

Max range in water = 90 µm

⇨ *a small fraction of radionuclides is "seen" by the cells. HOW MUCH ???*

⇨ *cell thickness ?*

1) Determining the spatial (and temporal) activity observed by the target
2) Determining the fraction of energy left by radiations in the target

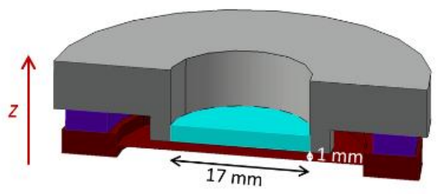
Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

1) Spatial and temporal distribution

- Experimental setup:

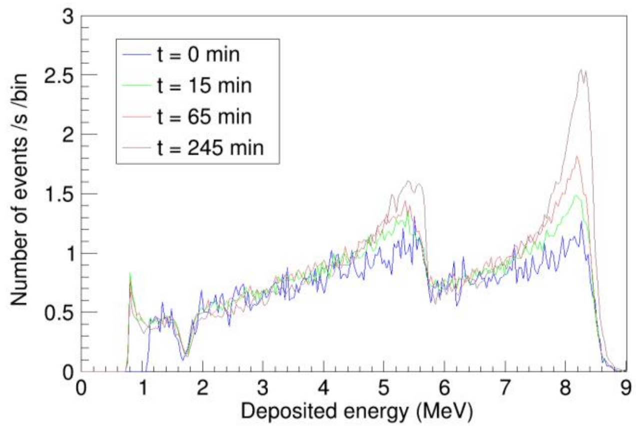
1,8 mm of culture medium
+15 kBq of vectorized isotopes

Custom-made plastic well
2,5 µm mylar base



CH1) Custom-made well, 2.5 µm mylar base

Silicon detector
⇩
Time of interaction
& Deposited energy

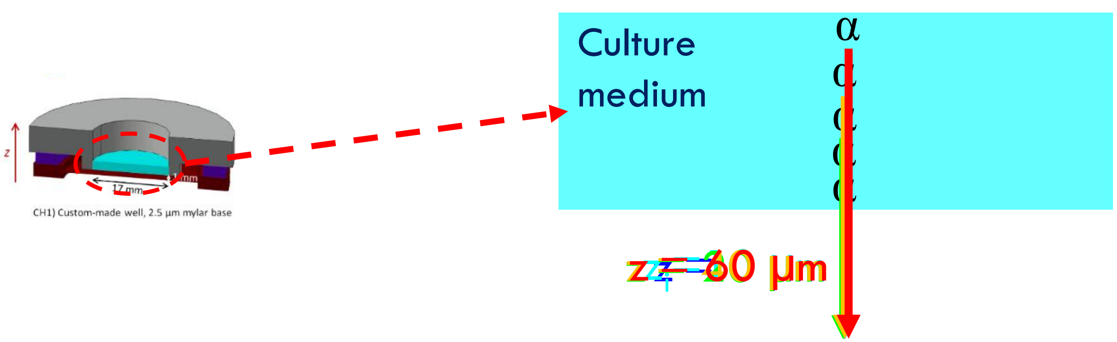


Experimental energy spectra

Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

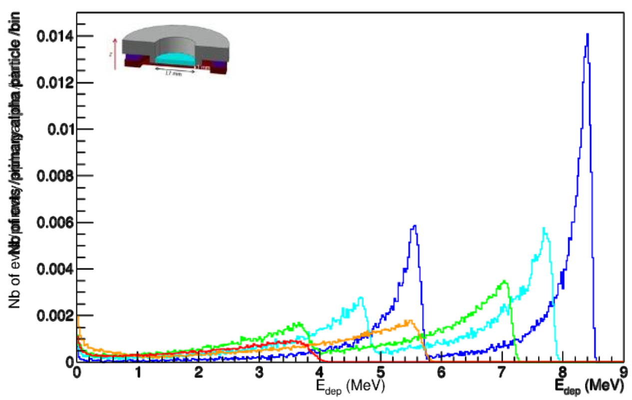
1) Spatial and temporal distribution

- Monte Carlo simulations



Position of alpha emission in the culture medium

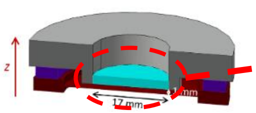
Simulated energy spectra



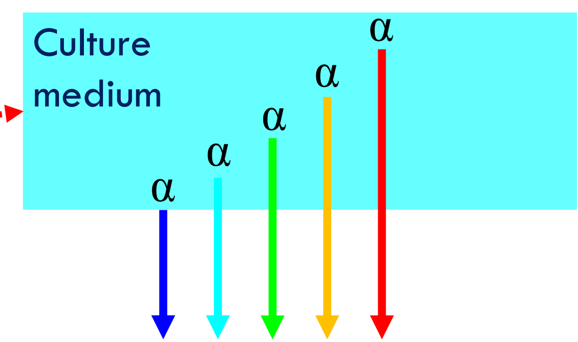
Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

1) Spatial and temporal distribution

- Monte Carlo simulations:



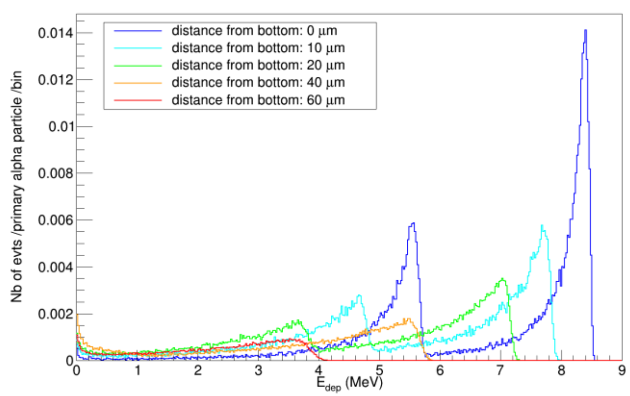
CH1) Custom-made well, 2.5 μm mylar base



Combination of the different emission positions

$$A(t, z_i) = h(t) + a(t) \cdot e^{-b(t) \cdot z_i}$$

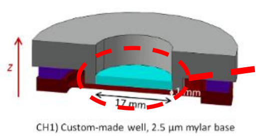
Simulated energy spectra

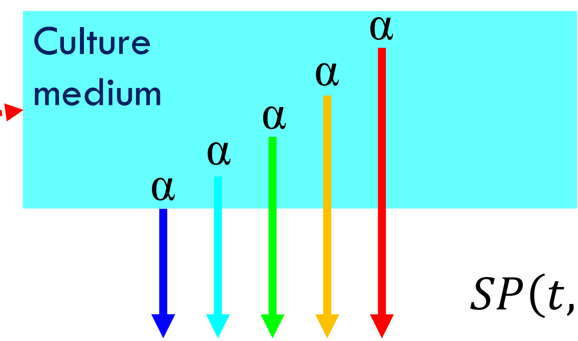


Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

1) Spatial and temporal distribution

- Monte Carlo simulations vs Experimental spectra:

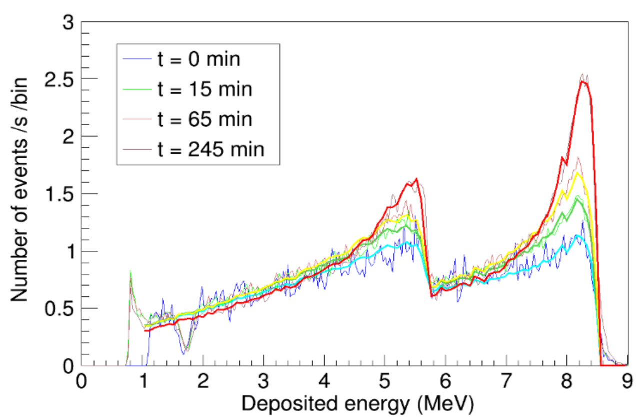




χ^2 minimization for each spectrum

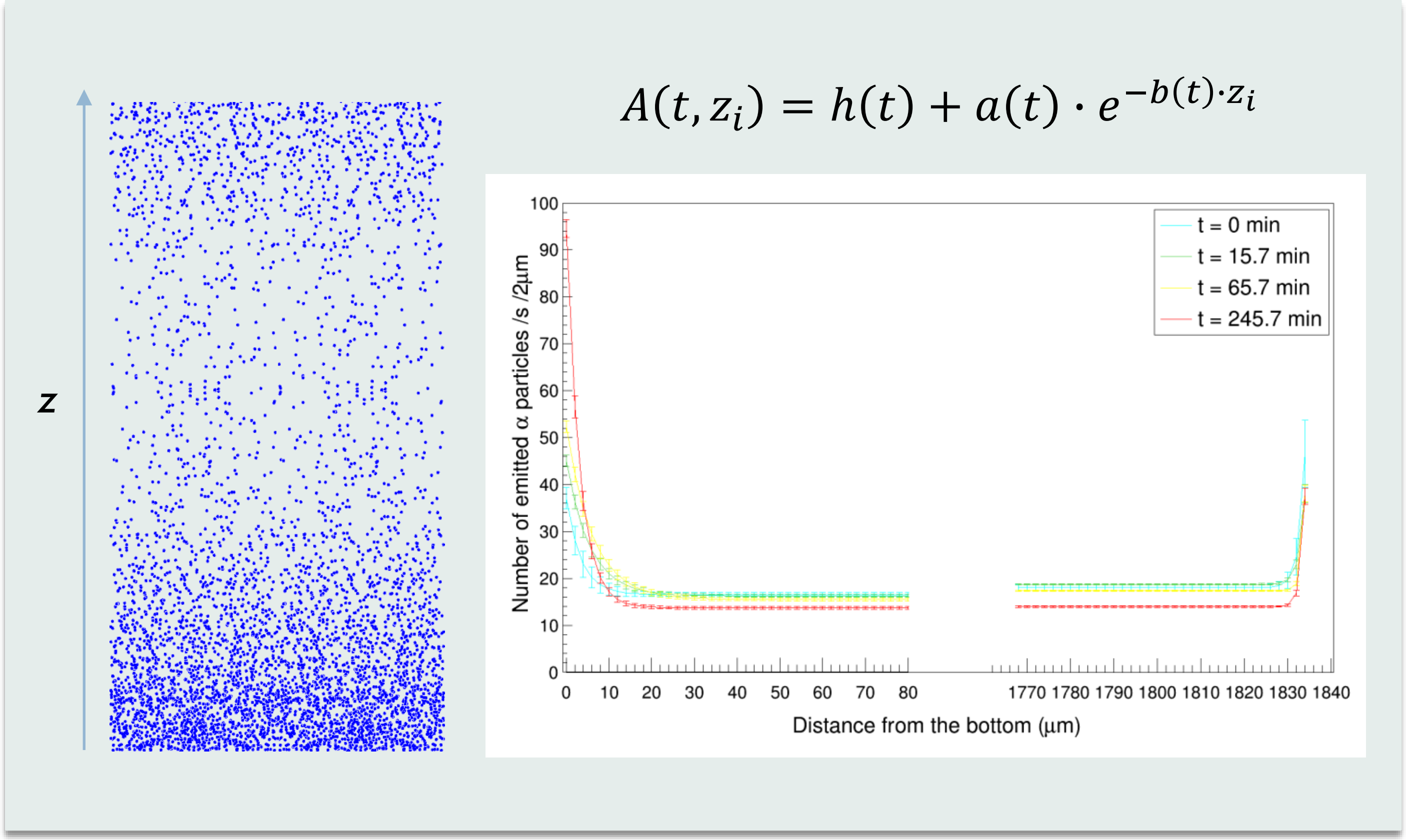
$$SP(t,E) = \sum_i A(t,z_i) \cdot SP_{MC}(z_i,E)$$

Convoluted energy spectra



Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

1) Spatial and temporal distribution



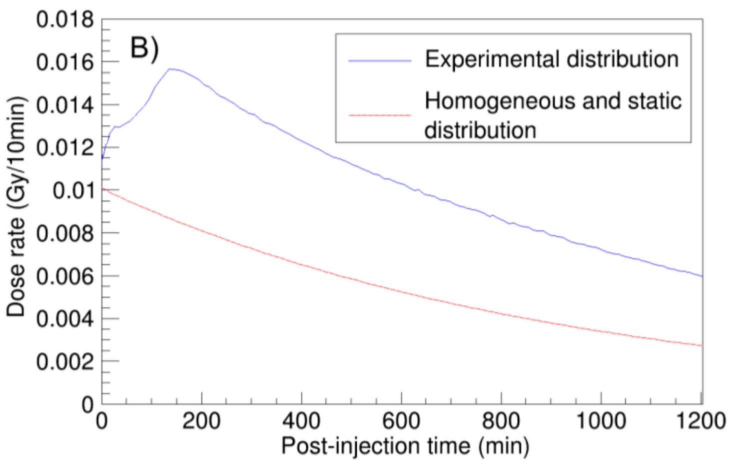
Spatial distribution of isotopes in the medium at different post-injection times

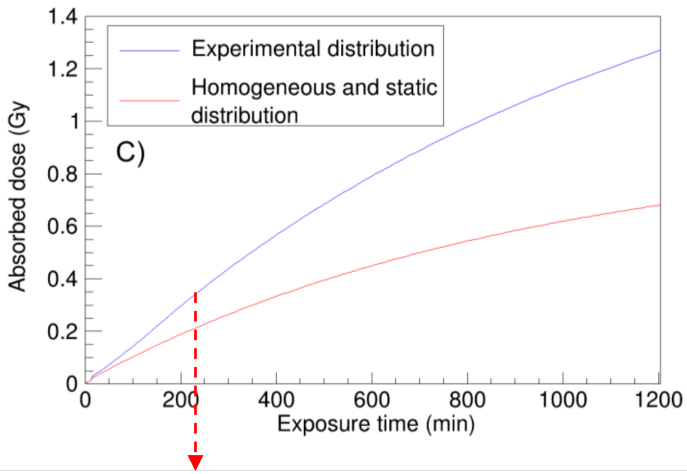
Dosimetry for *in vitro* assessment of Targeted Alpha Therapy (TAT)

2) Dose calculation

$$A(t, z_i) = h(t) + a(t) \cdot e^{-b(t) \cdot z_i}$$

$$\frac{dD}{dt}(t) = \sum_i A(t, z_i) \cdot S(z_i)$$





0,35 Gy

0,20 Gy

Error of 43% !

Almost a factor 2 in biological effect interpretation

Conclusion and perspectives

- SPIRAL-2 beams offer opportunities for R&D on production of innovative radioisotopes
- GANIL concentrate on alpha emitters
- Target irradiation: Astatine (with ARRONAX, SUBATECH, NPI Rez):
  - Irradiation station for Bi under construction
  - Design study for high power (10 kW; solid Bi)
  - Long-term: liquid bismuth target with continuous online extraction of At-211 or Rn-211
  - Measurements of $^{6,7}Li+^{209}Bi$ at NFS; impurities

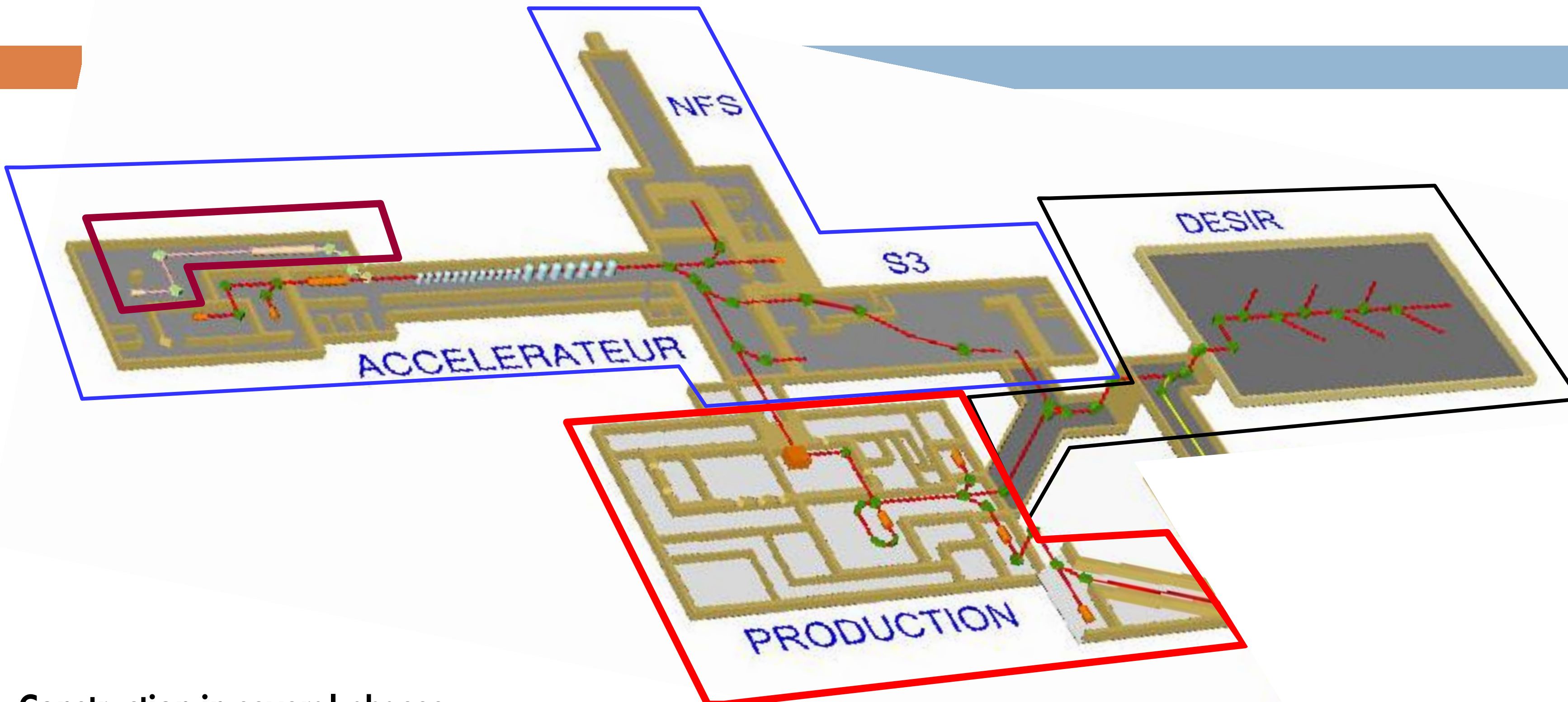
Conclusion and perspectives

- Other alpha emitters : Bi-213, Pb-212:
  - Production study using α + ^{232}Th. Approved experiment.
  - Cross-section measurements $\leftrightarrow$ nuclear data interest

- Development of dosimetry studies to evaluate new radioisotopes:
  - Focus on alpha dosimetry (detection methods; in-vitro distribution; effects;…). Very little done
  - Connection physics-radiobiology; interdisciplinary studies; CYCERON/ISTCT

Thank you for your attention

SPIRAL 2 construction phases

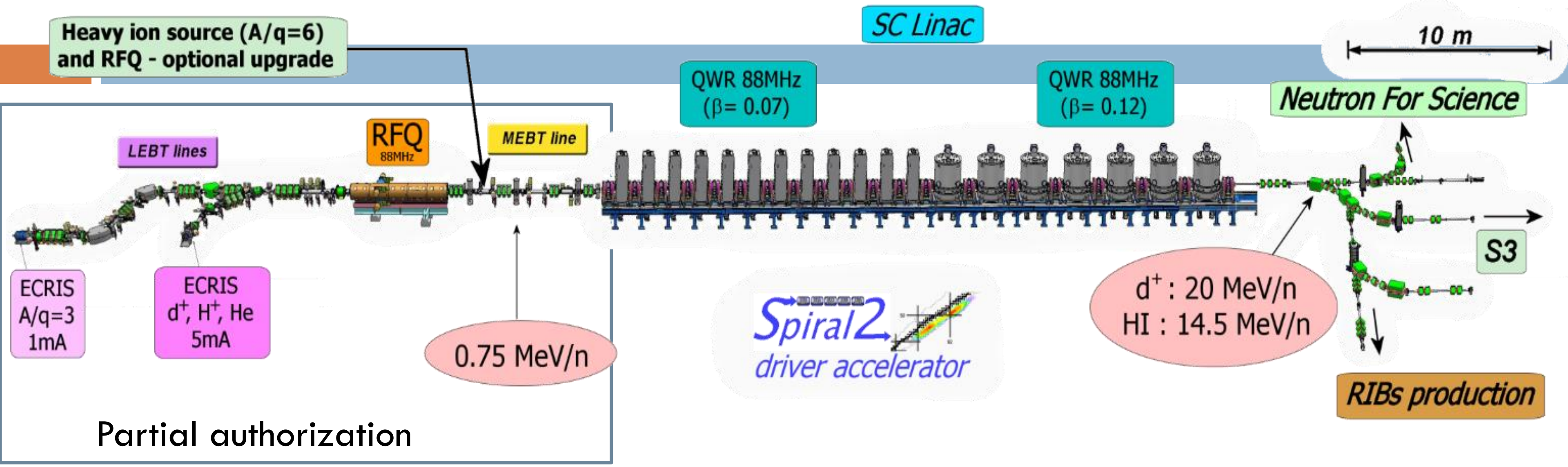


Construction in several phases:

Phase 1 : LINAC + NFS + S3	**Built**
Phase 1+ : DESIR	**Funded, call for tender for construction**
Phase 1++ : RFQ Q/A = 1/7	**Not yet funded**
Phase 2: Production building	**Standby**

SPIRAL-2 phase 1 building

The Linear Accelerator



RFQ frequency F = 88MHz

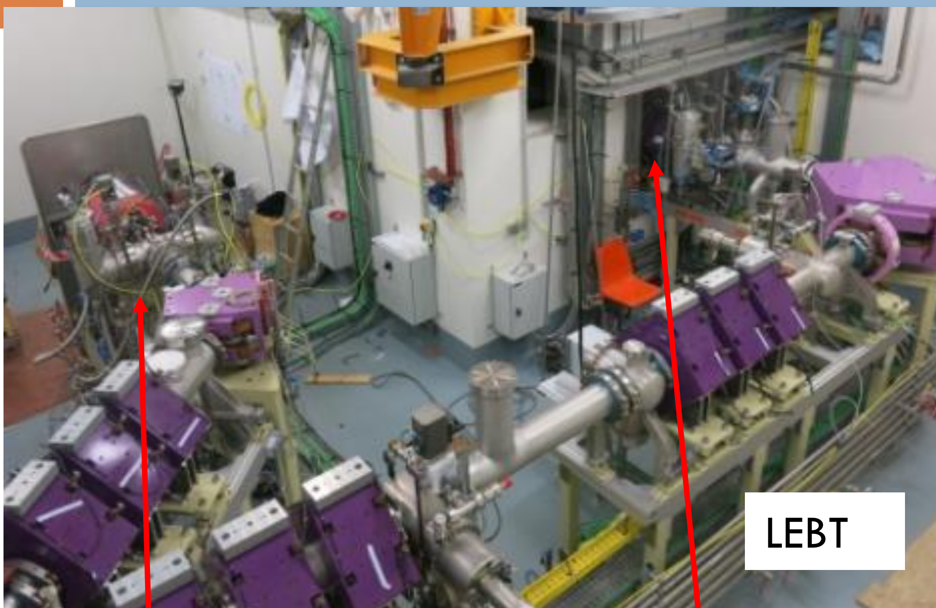
Total length: 65 m (without HE lines)

Slow (LEBT) and Fast Chopper (MEBT)
RFQ (1/1, 1/2, 1/3) & 3 re-bunchers

12 QWR beta 0.07 (12 cryomodules)
14 (+2) QWR beta 0.12 (7+1 cryomodules)
1.1 kW Helium Liquifier (4.5 K)
Room Temperature Quadrupoles
Solid State RF amplifiers (10 & 20 KW)

	Q/A	I (mA)	Energy (Mev/u)	CW max beam Power (KW)
Protons	1/1	5	2 - 33	165
Deuterons	1/2	5	2 - 20	200
Ions	1/3	1	2 - 14.5	45
Ions (option)	*1/6*	*1*	*2 - 8*	*48*

Sources and LEBT and RFQ



ECRIS A/Q=3
First beam (230 µA Argon 9+) July 10, 2015

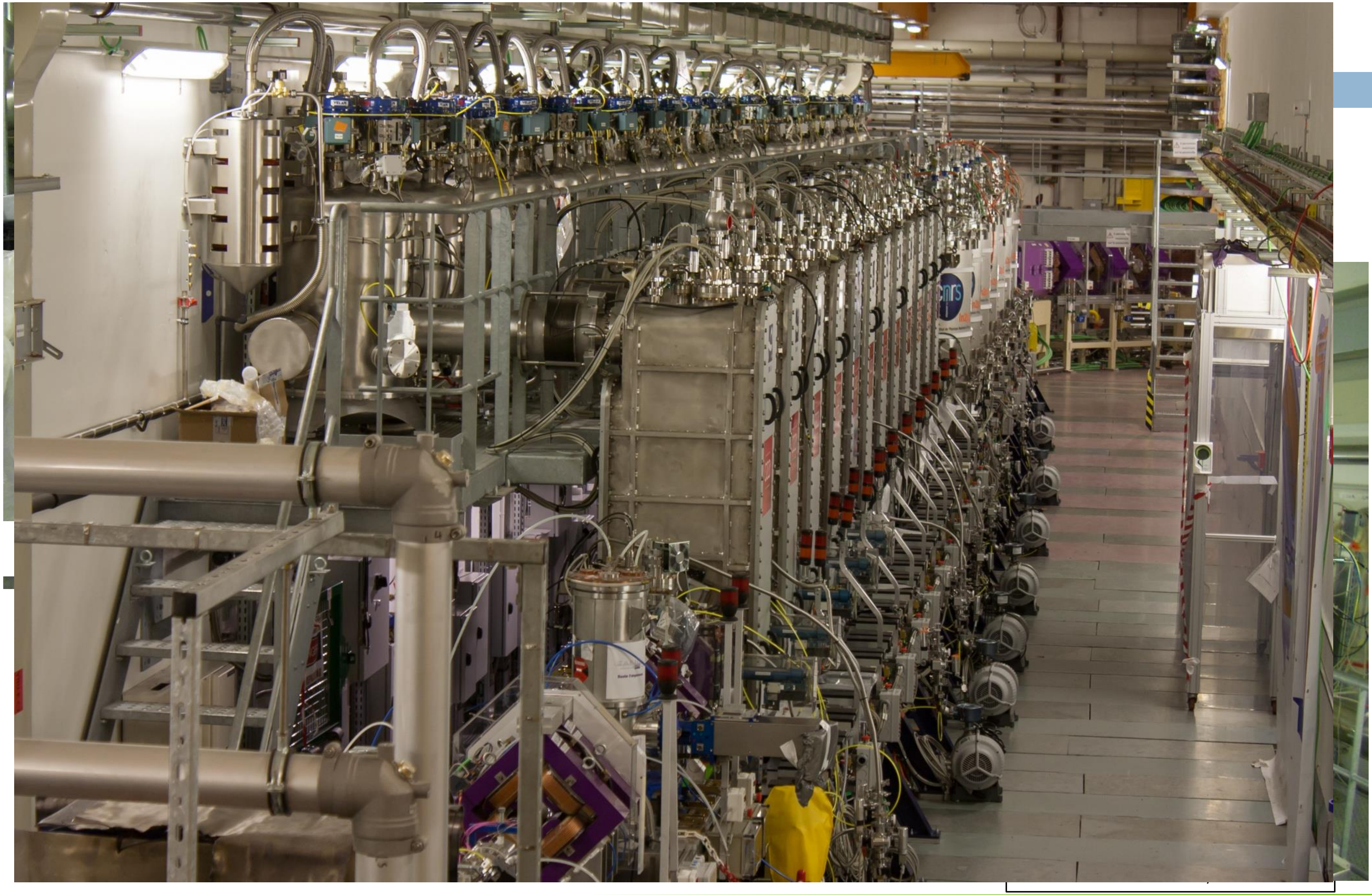
ECRIS A/Q=2
First beam (2mA H^+) Dec. 19th, 2014

RFQ: First beam (H+) Dec 3rd, 2015

RFQ Commissioning with beam :

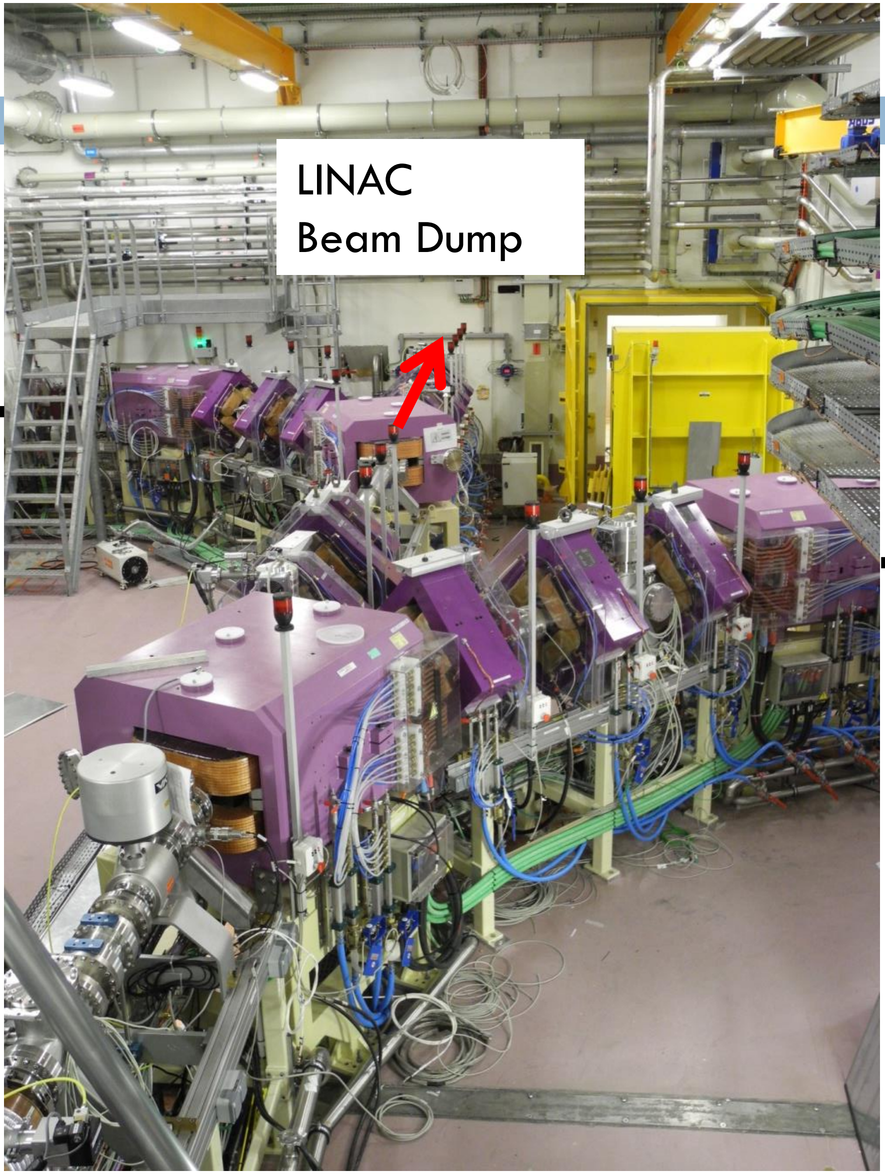
- **A/Q=1 (protons) with 5 mAe CW**
- **A/Q=2 ($^{4}He^{2+}$) with 1,3 mAe CW**
- **A/Q=3 ($^{18}O^{6+}$) with 600 µAe**

The LINAC



High Energy Beam Line

NFS

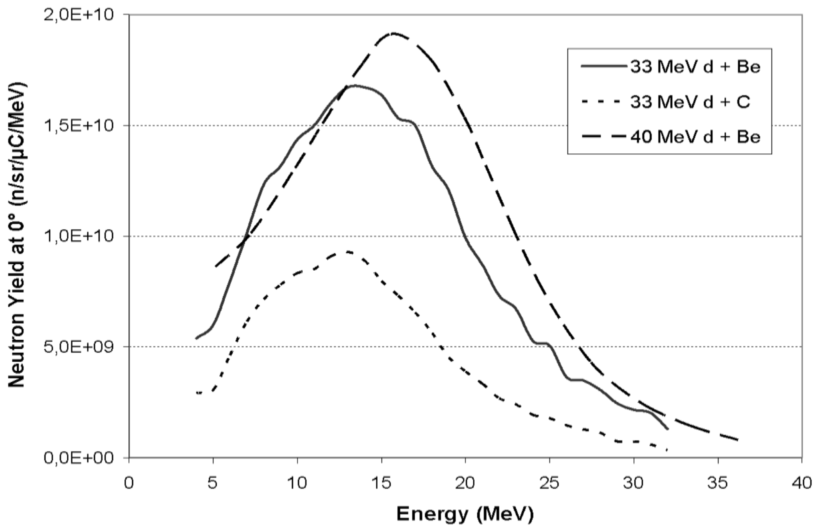


To S3 and Production Building

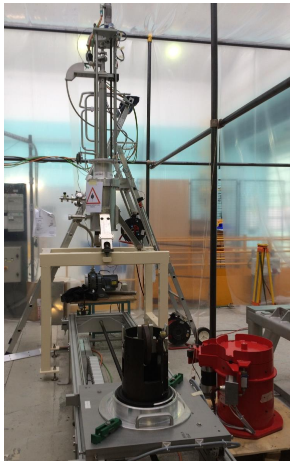
Neutron Spectra

Continuous spectrum

E_{max} = 40 MeV , <E> = 14 MeV



40 MeV d + Be at 50 µA



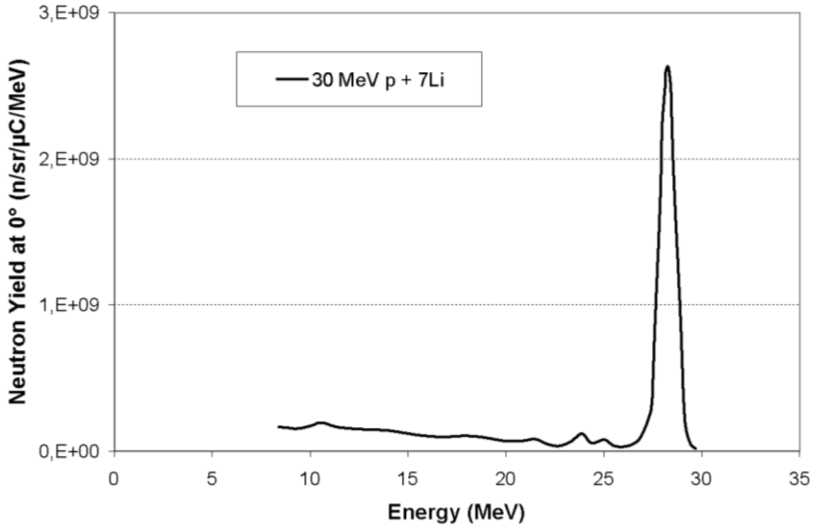
Rotating converter

thick target C or B (8mm)

P< 2 kW

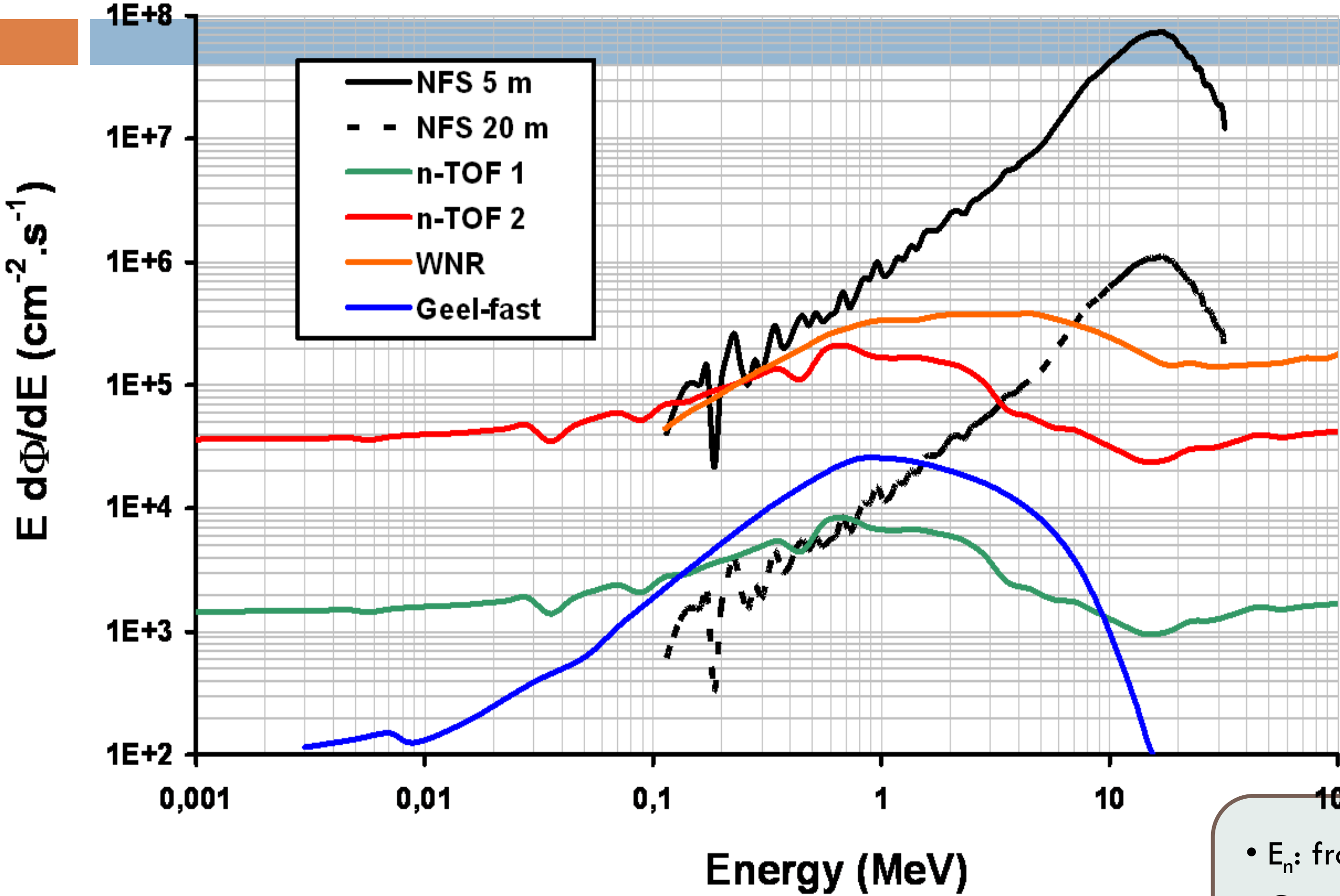
Quasi-monoenergetic spectrum

E_n = up to 31 MeV



p + Li (1mm) at 20 µA

Comparison with other Neutron TOF facilities



NFS : 40 MeV d + Be

WNR : Los Alamos

n-TOF 2 : CERN

n-TOF 1 : CERN

GELINA : Geel

- E_n: from 0,1 MeV to 40 MeV
- Good energy resolution
- Reduced γ flash
- Low instantaneous flux

Complementary to the existing facilities

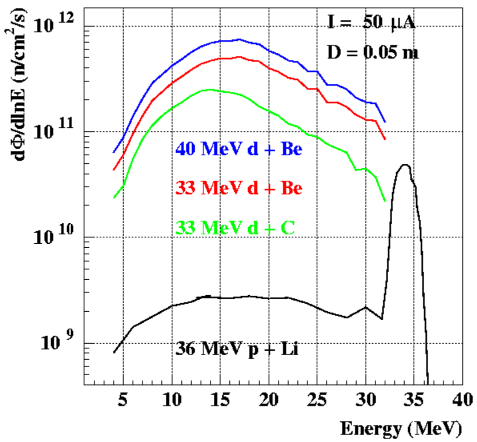
Measurement by activation method

1- Sample irradiation in the converter room

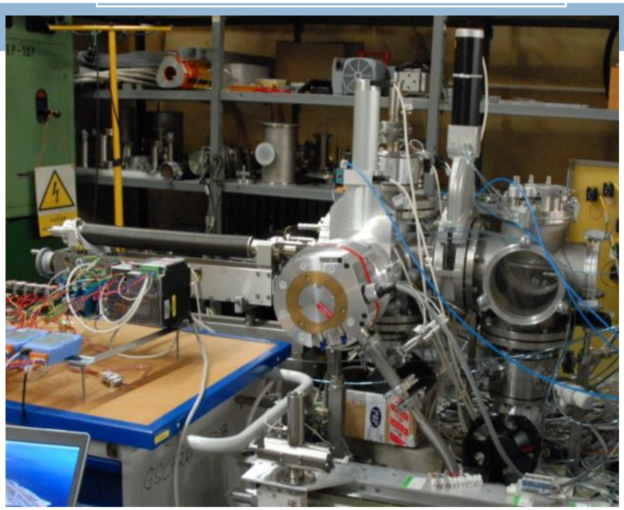
ion induced reactions

Neutron irradiation

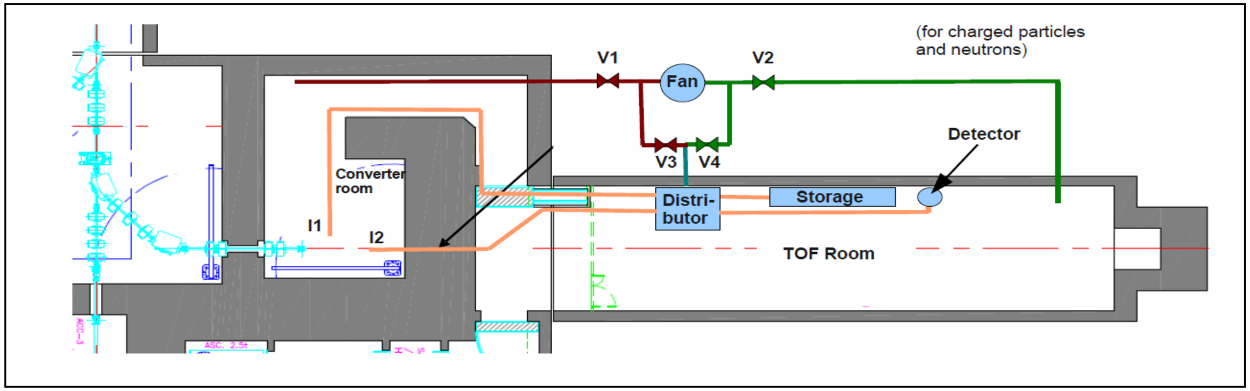
- Spectrum similar to IFMIF
- $\Phi > 10^{11}$ n/s/cm^2



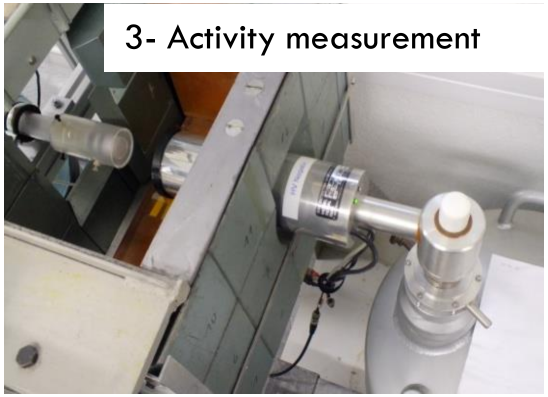
or



2- Transfer of sample to TOF room



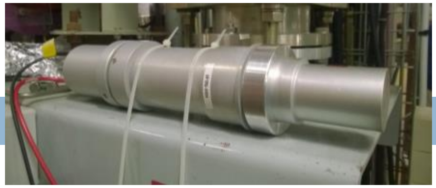
3- Activity measurement



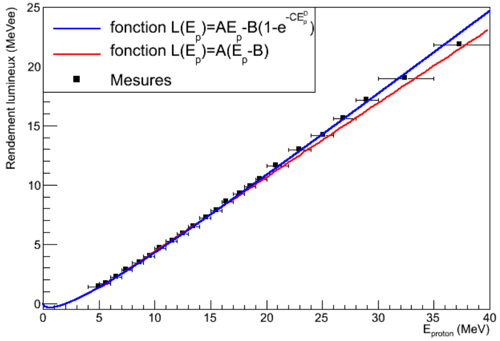
Cross-section measurements by activation method
Study of radioisotope production

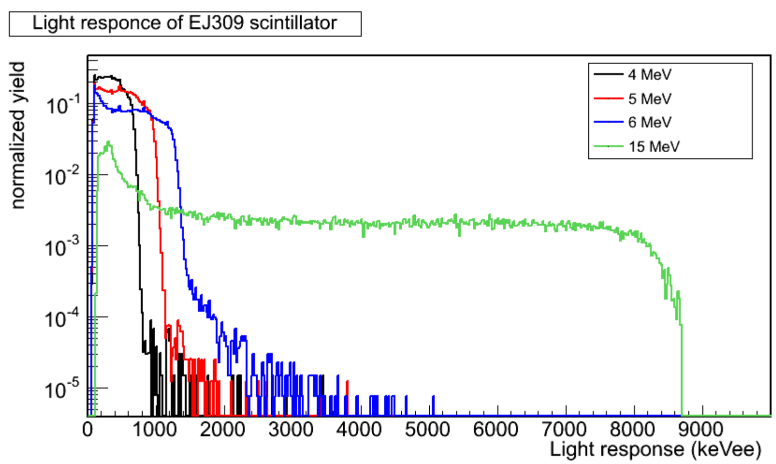
Neutron monitoring

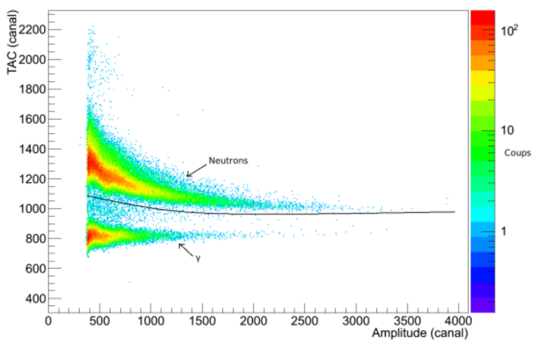
❑ Detector based on liquid scintillator EJ309



- Neutron spectrum and flux measurement by the TOF technique
- n-γ discrimination by pulse shape analysis
- Characterization
  - at Ganil reaction 10,5 MeV/A Kr + Cu
    - Light response between 5 and 30 MeV
  - at CEA/DIF
    - Mono-energetic neutrons at 4, 5, 6 and 15 MeV
    - Efficiency measurement







❑ Proton recoil telescope

- CH2 radiator + ΔE-ΔE-E Si telescope
- Prototype tested at GANIL

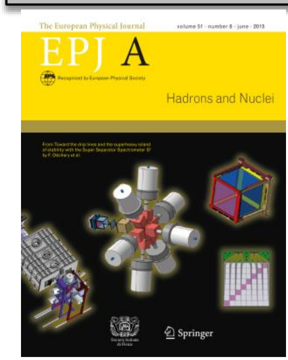
Super Separator Separator

Study of rare events in nuclear and a

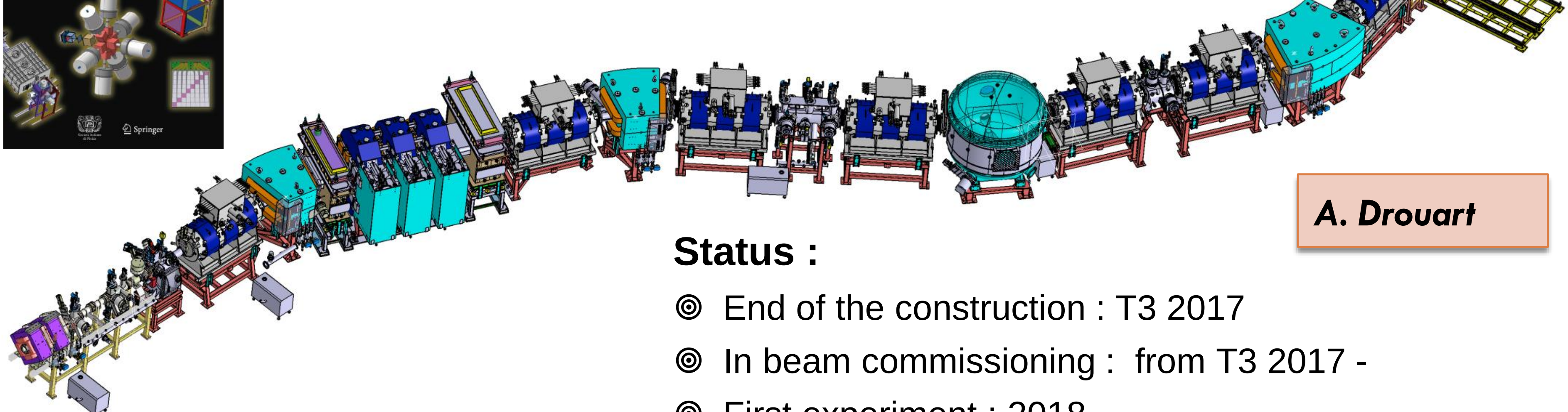
3 magnetic dipoles
7 superconducting quadrupoles triplets
1 Electric dipole

S3 Physics case (15 LoIs)

- VHE – SHE elements
- Proton drip-line and N=Z
- Nuclear astrophysics
- Atomic physics



- Global physics program has been defined – The collaboration is ready to work out detailed proposals
- Commissioning experiments
- Preparatory studies in different laboratories are underway
  - ✓ Feasibility of in-source laser spectroscopy (400 MHz)
  - ✓ VHE decay spectroscopy @ LISE
  - ✓ High power target station @ GANIL



A. Drouart

Status :

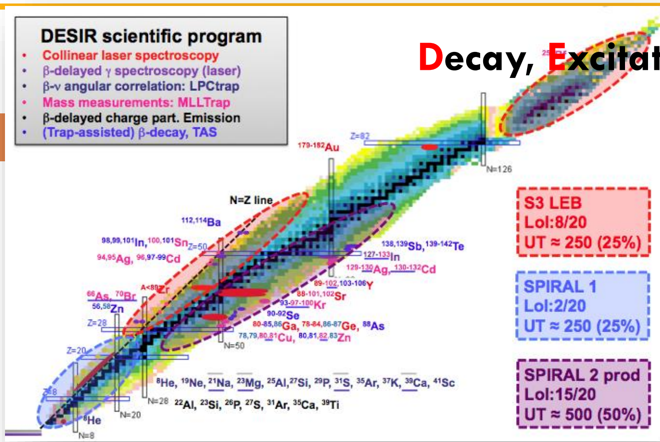
- End of the construction : T3 2017
- In beam commissioning : from T3 2017 -
- First experiment : 2018

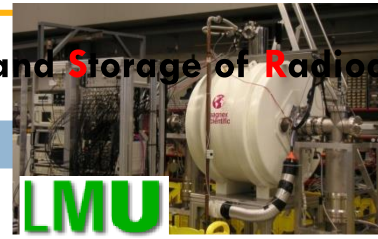
S3 experiments @ GANIL PAC (T2 2017)

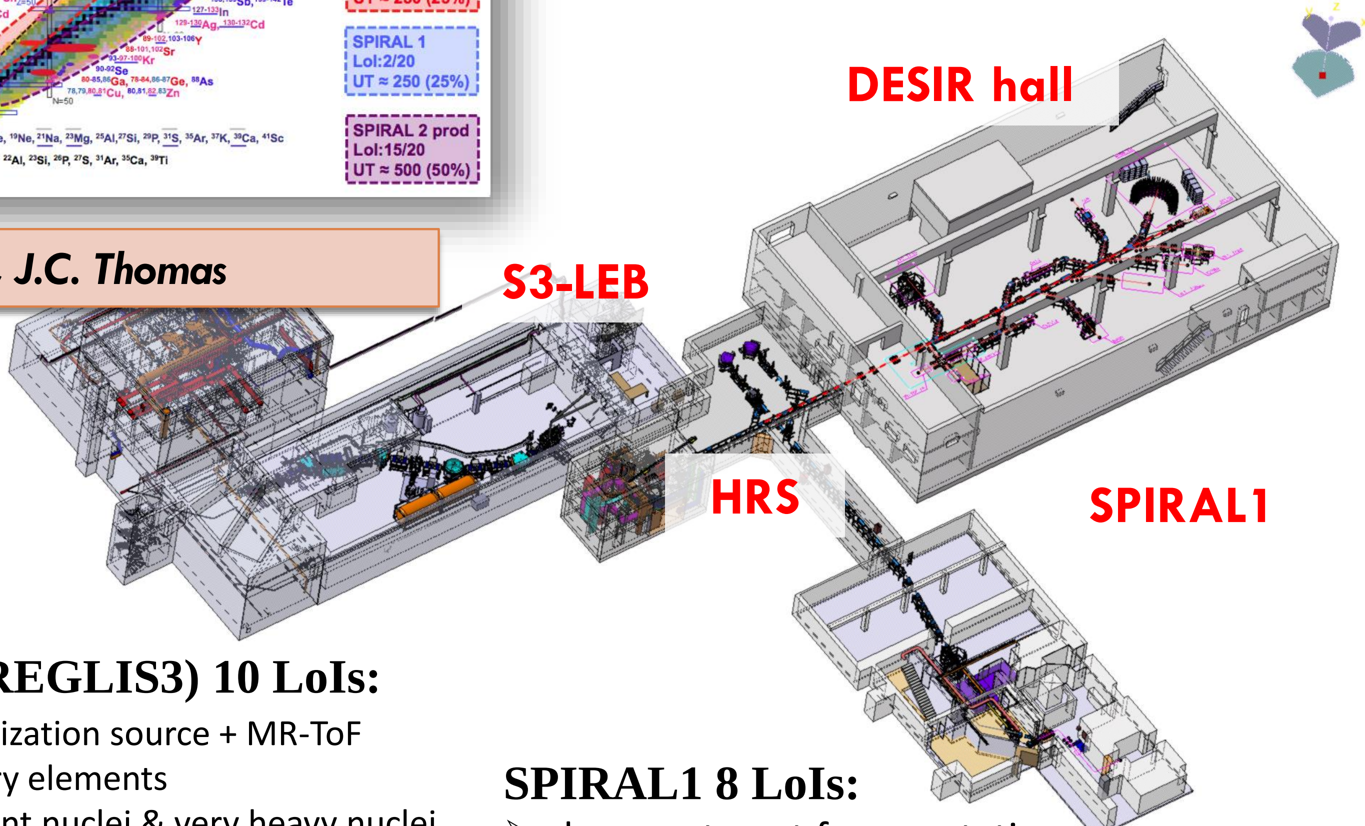
First campaign setting to be defined in 2016

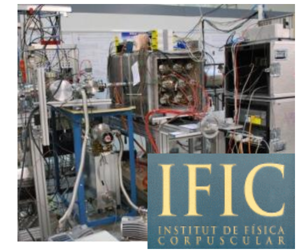
DESIR

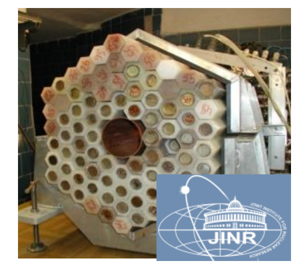
Decay, Excitation and Storage of Radioactive Ion











E. Petit, J.C. Thomas

S³ LEB (REGLIS3) 10 LoIs:

- laser ionization source + MR-ToF
- refractory elements
- n-deficient nuclei & very heavy nuclei

SPIRAL1 8 LoIs:

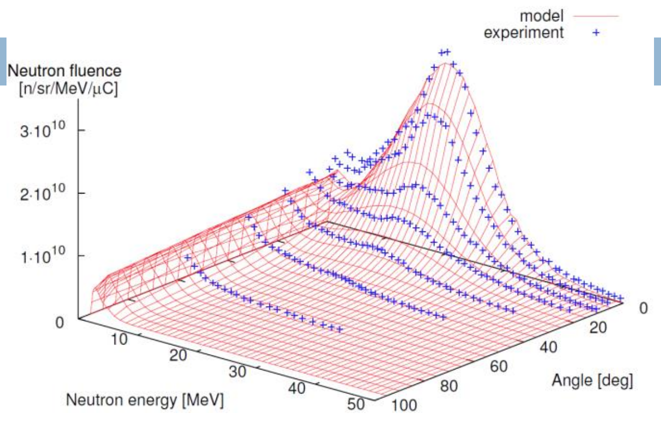
- beam + target fragmentation
- ECR + FEBIAD + Surface ionization
- light nuclei

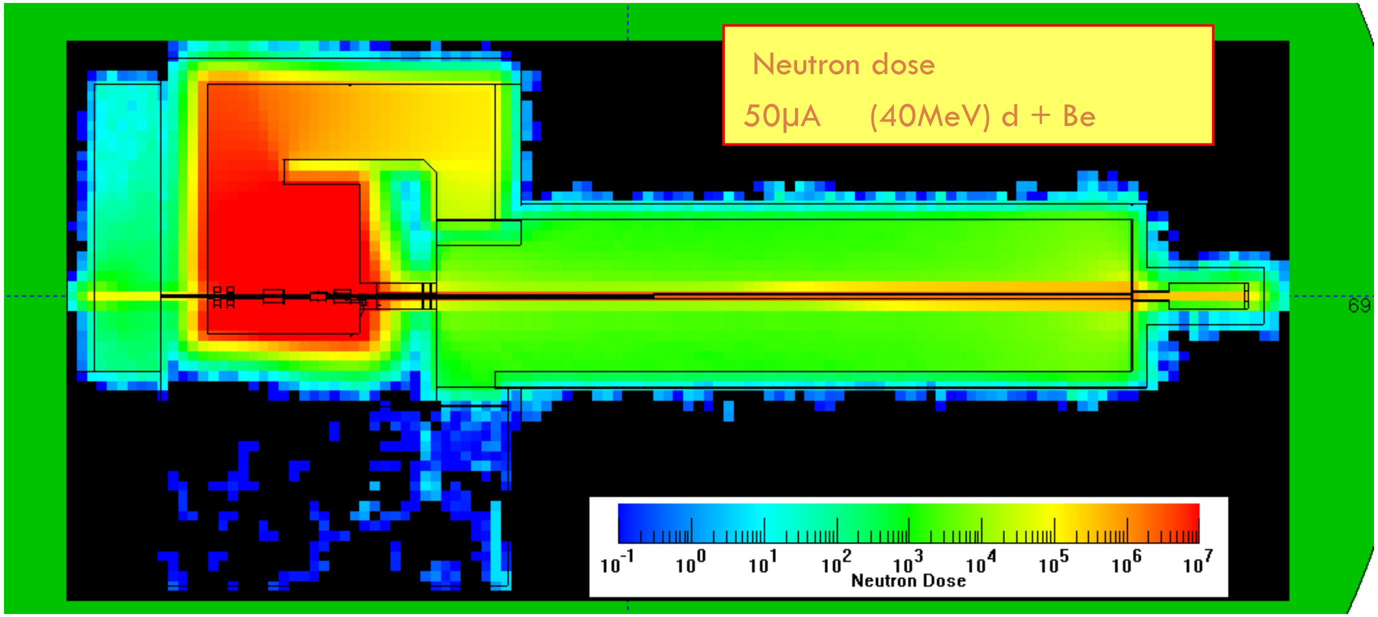
Funded (July 2015)

Design study phase: beginning 2016

Neutron transport simulations

- Neutron transport simulations are needed for :
  - Safety purpose (biological protection, activation, waste management…)
  - Background evaluation
- Simulations characteristics :
  - MCNPX neutron code
  - Neutron source d+Be and p+^{7}Li

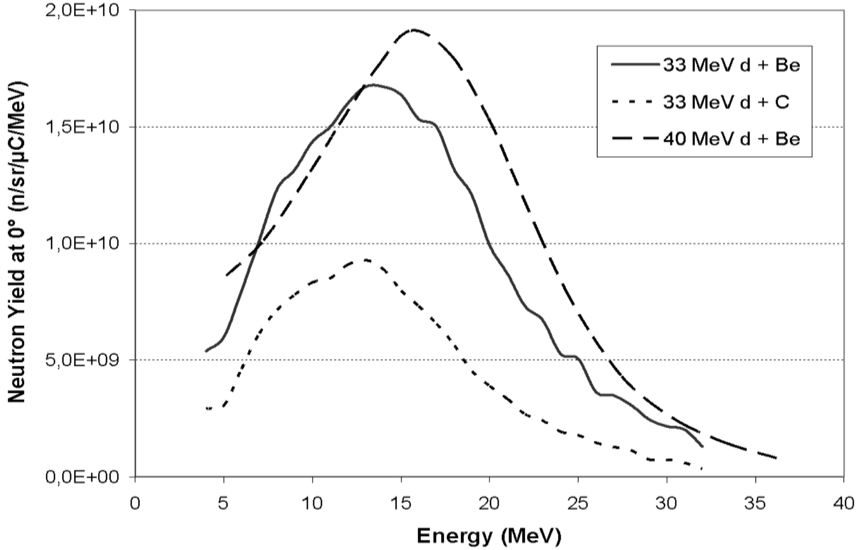




Continuous neutron spectra

Deuteron + thick converter (1cm)

E_{max} = 40 MeV , <E> = 14 MeV

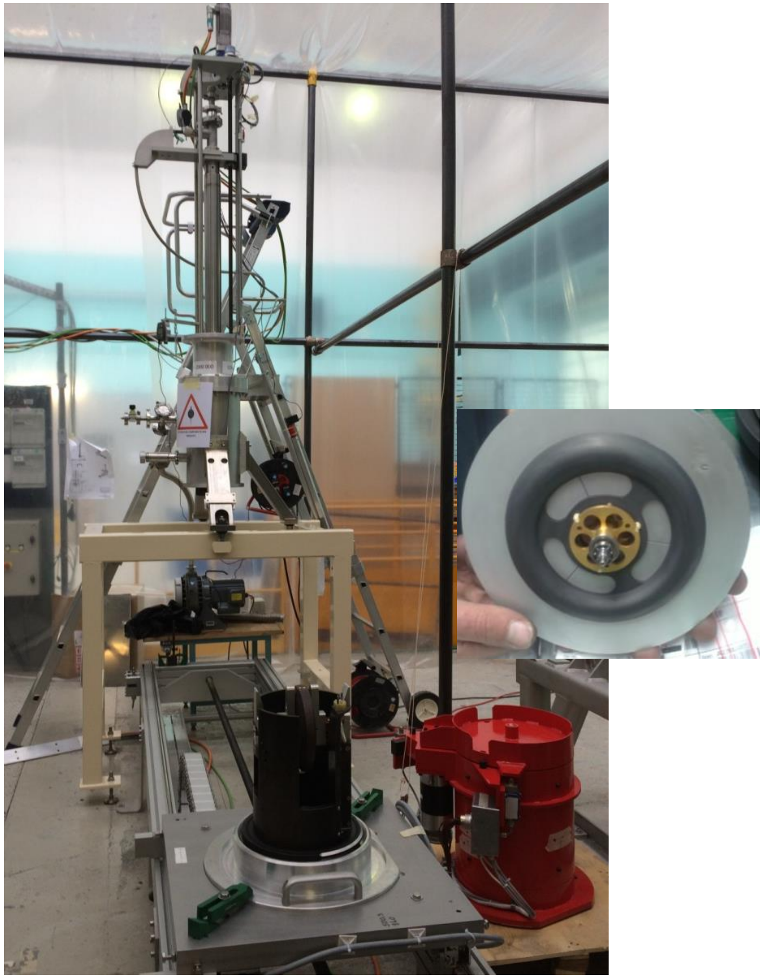


40 MeV d + Be at 50 µA

E MeV	Flux at 5 m
0-40	8.10^7 n/cm^2/s
5	2.10^6 n/cm^2/MeV/s
14	5.10^6 n/cm^2/MeV/s
30	6.10^5 n/cm^2/MeV/s

Rotating converter

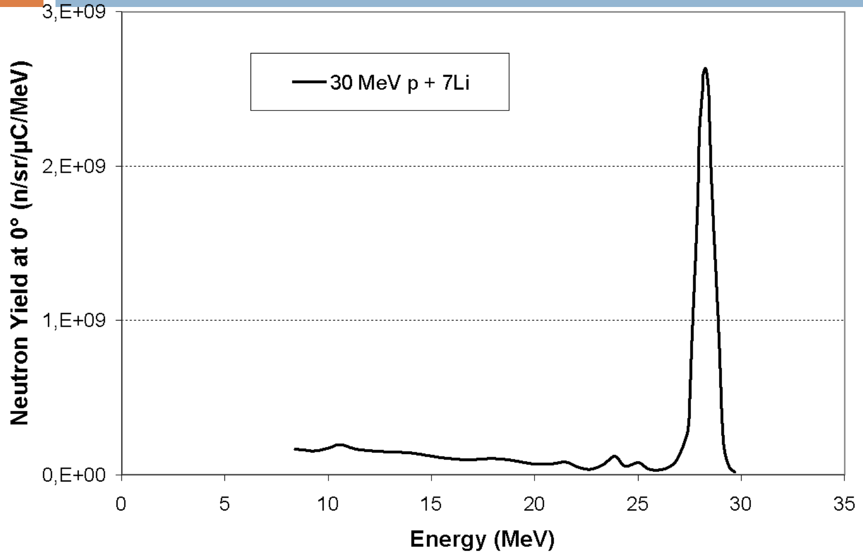
- thick target C or Be
- P< 2 kW



Quasi-mono-energetic neutron spectra

p + ^{7}Li thin lithium target

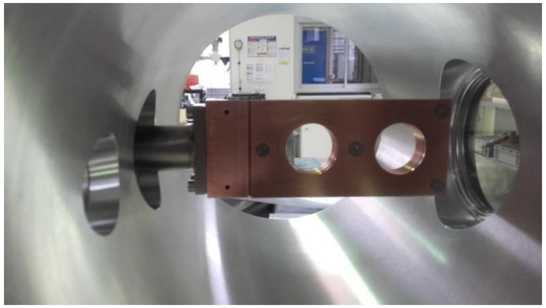
E_n = up to 31 MeV



Thin converter

- Li or Be
- Static target

Deflecting magnet for proton beam



p + Li at 20 µA

Li thickness ⇔ Δep=1MeV

E MeV	Flux at 5 m
5	1,7.10^{4} n/cm^{2}/MeV/s
10	5.10^{3} n/cm^{2}/MeV/s
20	2,3.10^{4} n/cm^{2}/MeV/s
30	1,2.10^{5} n/cm^{2}/MeV/s