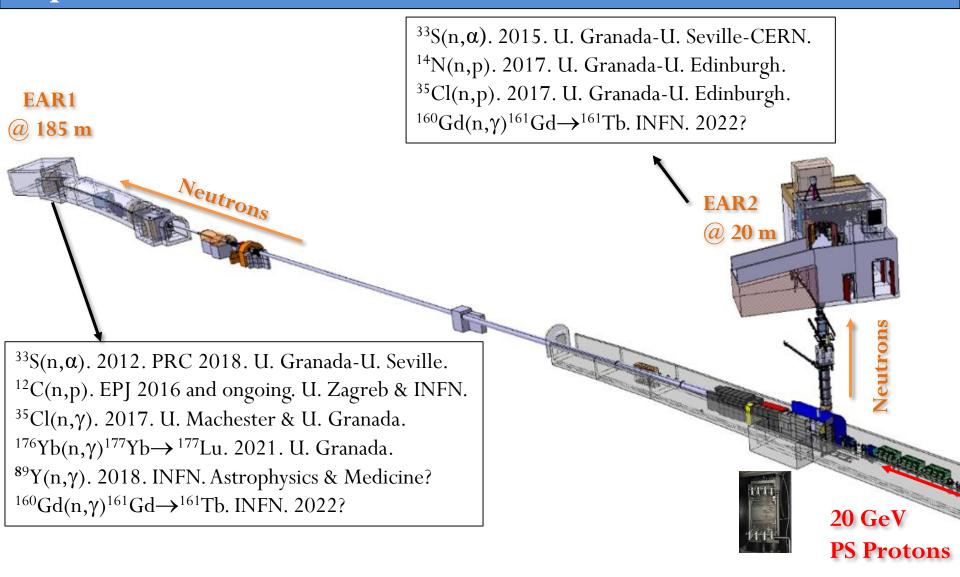
## **Nuclear Data at n\_TOF for Medicine**

#### **Javier Praena**

Prof. Universidad de Granada (Spain) CERN Scientific Associate (EP/SME) n\_TOF Physics Coordinator



### **Experiments for medicine**









## Experiments at n\_TOF: motivations and results

- Dosimetry related to fast neutrons in protontherapy/photontherapy. Secondary tumours.
  - $^{12}C(n,p)^{12}B$  in EAR1. Integral finished. Angular-energy distribution, ongoing.
- Dosimetry in Boron Neutron Capture Therapy (low energy neutrons).
  - $^{14}N(n,p)$  in EAR2.

Provides the most important biological dose to healthy tissue.

Data status opens to variations in the dose of at least 12%, depends on the neutron beam.

At n\_TOF, we have found a further reduction of the 1st resonance, as Wallner by integral.

•  $^{35}Cl(n,p)$  in EAR2.

Significant dose in healthy tissue in high sensible organs. Ongoing.

•  $^{35}$ Cl(n, $\gamma$ ) in EAR1.

Significant dose in healthy tissue in high sensible organs (15%). Ongoing.

- New target in Neutron Capture Therapy (low energy neutrons).
  - ${}^{33}$ S(n, $\alpha$ ) in EAR1.

We solved the discrepancies in the resonances between ORNL and Geel measurements.

•  ${}^{33}$ S(n, $\alpha$ ) in EAR2.

For the first time data from thermal to 10 keV were measured.

- Production of radioisotopes for medicine in accelerator-based neutron facilities.
  - $^{176}$ Yb $(n,\gamma)^{177}$ Yb $\rightarrow$   $^{177}$ Lu in EAR1. Theranostics, well stablished. No resonances had been resolved.
  - $^{89}Y(n,\gamma)^{90}Y$  in EAR1. It was proposed for astrophysics. It is also demanded radioisotope.
  - $^{160}\mathrm{Gd}(n,\gamma)^{161}\mathrm{Gd} \rightarrow ^{161}\mathrm{Tb}$  in EAR1 and EAR2. Production of  $^{161}\mathrm{Tb}$ , on study for theranostics.







# Boron Neutron Capture Therapy

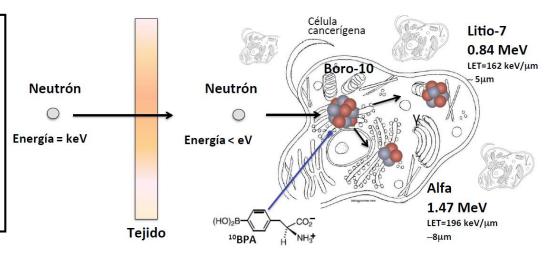


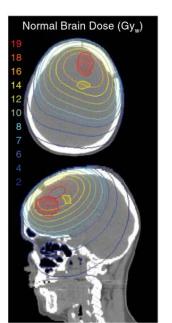


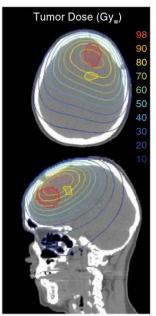


### Boron Neutron Capture Therapy: bases and motivations

Boron-10 compound (BPA) is injected in the blood stream. BPA is preferably absorbed in tumor cells. Tumoral area is irradiated with neutrons in keV-eV rage. Neutrons are moderated in tissue and reach the tumor with thermal energy maximizing the  $^{10}$ B(n, $\alpha$ ) $^{7}$ Li (2.4 MeV) reaction probability.







The dose on healthy tissue is lower (>factor 4) than in tumor tissue with <sup>10</sup>B-load.

The dose in healthy tissue is lower than in photon or proton therapies. No fractioning.

The dose in healthy tissue is the limiting factor in whatever radiotherapy treatment. Nuclear data on key reactions must be measured as accurate as possible (n\_TOF).







### BNTC: achievements as experimental treatment (in one day)

Barth et al. Radiation Oncology 2012, 7:146 http://www.ro-journal.com/content/7/1/146



REVIEW

pen Access

Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer

Rolf F Barth<sup>1\*</sup>, M Graca H Vicente<sup>2</sup>, Otto K Harling<sup>3</sup>, W S Kiger III<sup>4</sup>, Kent J Riley<sup>5</sup>, Peter J Binns<sup>6</sup>, Franz M Wagner<sup>7</sup>, Minoru Suzuki<sup>8</sup>, Teruhito Alhara<sup>9</sup>, Itsuro Kato<sup>10</sup> and Shinji Kawabata<sup>11</sup>

BCNT was always an experimental therapy (patients who suffered other therapies or radiotherapies).

Since 2012, important evolutions in BNCT community:

Japan, Finland, Argentina, Italy, Taiwan (old and new BNCT)

UK, Russia, China, Israel (new BNCT), Spain.

#### Substitution of the neutron sources:

New accelerator-based facilities are substituting nuclear reactors (new reactors?).

### New status of the therapy in each country where BNCT was carried out:

From experimental treatment to conventional one.

Japan: BNCT for melanoma is already included in the Public Health-Care System.

#### New Boron compounds.

Improvements in BPA and BSH. New targets or cooperative targets.

### New data for accurate treatment planning.

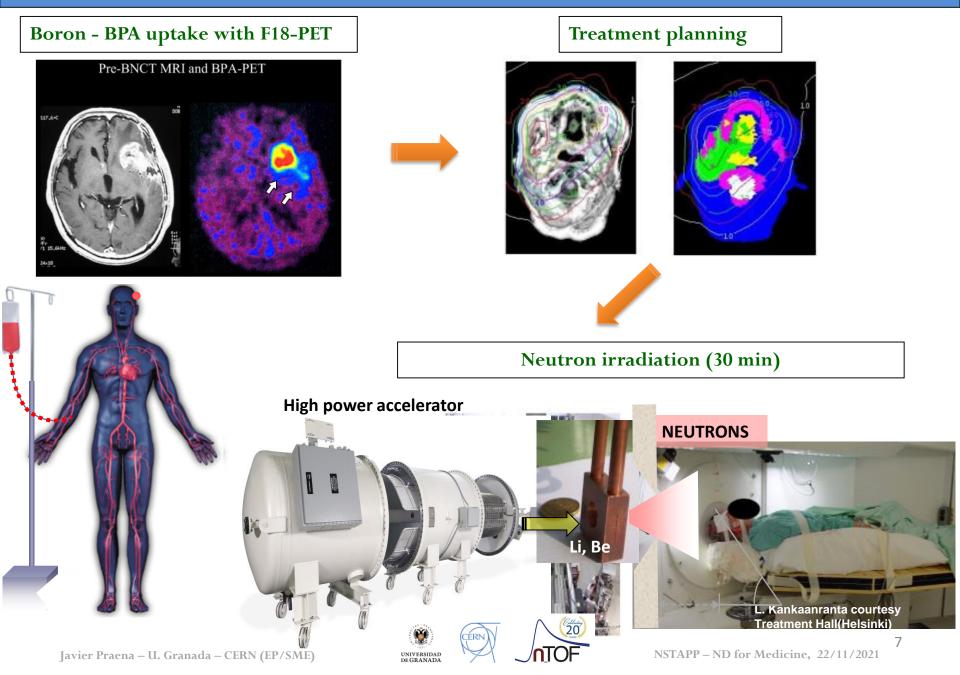
NCT treatment planning systems rely exclusively on Monte Carlo simulations for dose calculations because of the complex, scatter-dominated nature of neutron transport.







## Boron neutron capture therapy: one day treatment (no fractioning)



### BNTC: some achievements with nuclear reactors

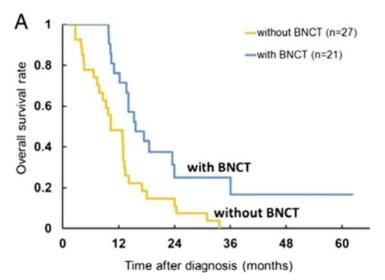


Figure 6 A. Kaplan-Meier estimates of overall survival for all newly diagnosed glioblastoma (WHO grade 4, n = 21). The median survival time of boron neutron capture therapy (BNCT)

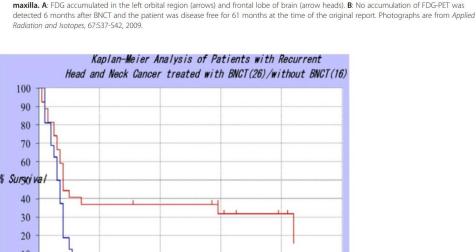


Figure 4 18FDG-PET study prior and 6 months after BNCT of a 56 year-old male patient with recurrent squamous cell carcinoma of the

% Sursoi va 10 0 20 60 80 100 0 Months after BNCT

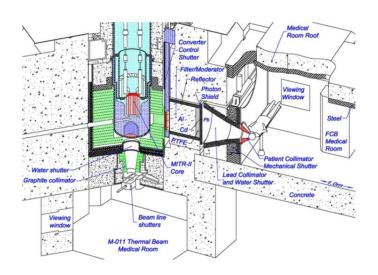
Figure 10 Kaplan-Meier survival plots of patients with recurrent HNC treated by Kato et al. (6) with BNCT (26 cases, red line) and those who treated with other than BNCT (16 cases, blue line). The outcomes for the 26 patients: Mean survival time: 33.6 months, 4-year Overall survival (OS): 37.0%, 6-year OS: 31.7%. Most of the 26 patients had either recurrent or far advanced cancers of the head and neck region and 15 (58%) had regional lymph node metastases and 6 had developed distant metastases. Nineteen of the patients had squamous cell carcinomas, 4 salivary gland carcinomas and 3 had sarcomas. All but one had received standard therapy and developed recurrent tumors for which there were no other treatment options.

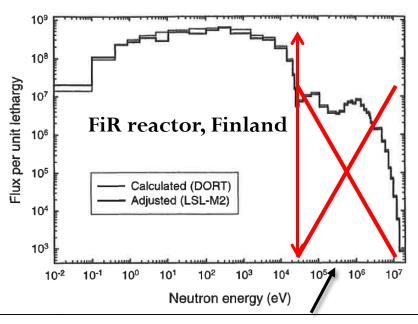


of high grade gliomas and recurrent head and neck cancer

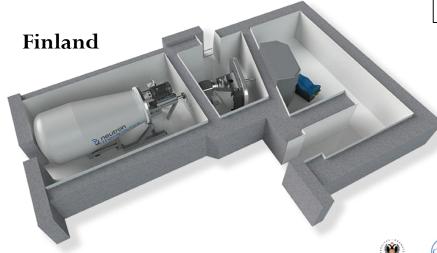
Rolf F Barth<sup>1\*</sup>, M Graca H Vicente<sup>2</sup>, Otto K Harling<sup>3</sup>, W S Kiger III<sup>4</sup>, Kent J Riley<sup>5</sup>, Peter J Binns<sup>6</sup>, Franz M Wagner<sup>2</sup> Minoru Suzuki<sup>8</sup> Teruhito Aihara<sup>9</sup> Itsuro Kato<sup>10</sup> and Shinii Kawabata

### BNTC neutron source: from reactors to accelerators.





With accelerators the fast tail is reduced, however a neutron fraction is above 300 keV, <sup>14</sup>N(n,p) reaction!!!



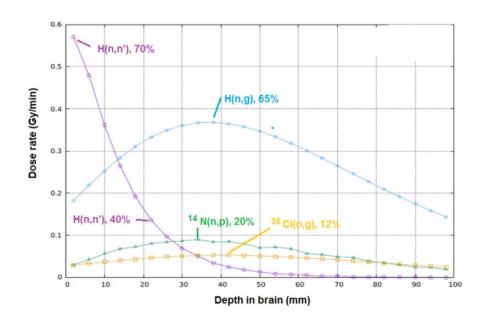
Neutron Therapeutics Company in Finland has already finished the installation. p+Li+BSA.

Dosimetry measurements have been performed. Permits for therapy are on going.





### Dosimetry in healthy tissue is fundamental



Contribution to the dose on healthy tissue for a 10 keV neutron beam.

 $^{14}N(n,p)^{14}C$ ,  $^{35}Cl(n,p)^{35}S$ ,  $^{35}Cl(n,\gamma)^{36}Cl$  have measured at n\_TOF.

Contribution to the dose on healthy tissue for a 0.4 keV neutron beam

Proceso	D global (Gy/min)	$\%$ de la $D_{Total}$ global	% del total de colisiones
$^{1}H(n,n)^{1}H$	$1.82 \cdot 10^{-3}$	0.74	90.84
$^{12}C(n,n)^{12}C$	$1.37 \cdot 10^{-5}$	$5.54 \cdot 10^{-3}$	1.97
$^{14}N(n,n)^{14}N$	$3.20 \cdot 10^{-6}$	$1.30 \cdot 10^{-3}$	0.53
$^{16}O(n,n)^{16}O$	$3.19 \cdot 10^{-5}$	$1.29 \cdot 10^{-2}$	5.84
$^{35}Cl(n,n)^{35}Cl$	$5.34 \cdot 10^{-8}$	$2.16 \cdot 10^{-5}$	$3.85 \cdot 10^{-2}$
$^{37}Cl(n,n)^{37}Cl$	$1.78 \cdot 10^{-9}$	$7.22 \cdot 10^{-7}$	$7.36 \cdot 10^{-4}$
$^{14}N(n,p)^{14}C$	$3.21 \cdot 10^{-2}$	12.99	$5.37 \cdot 10^{-2}$
$^{35}Cl(n,p)^{35}S$	$3.09 \cdot 10^{-3}$	1.25	$5.26 \cdot 10^{-3}$
$^{1}H(n,\gamma)^{2}H$	0.177	71.76	0.66
$^{35}Cl(n,\gamma)^{36}Cl$	$3.26 \cdot 10^{-2}$	13.21	$6.17 \cdot 10^{-2}$
$^{37}Cl(n,\gamma)^{38}Cl$	$7.65 \cdot 10^{-5}$	$3.10 \cdot 10^{-2}$	$1.65 \cdot 10^{-4}$



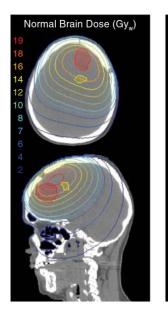


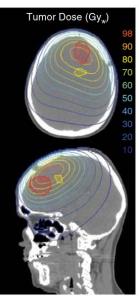


### Dosimetry: ${}^{14}N(n,p){}^{14}C$ , ${}^{35}Cl(n,p){}^{35}S$ , ${}^{35}Cl(n,\gamma){}^{36}Cl$

Although the dose in healthy is much lower, the better nuclear data will provide a more realistic Monte Carlo planning, better duration of the neutron irradiation, possible second or third irradiation depending on organ...

The data at n\_TOF are very important, and they will be used in the codes.



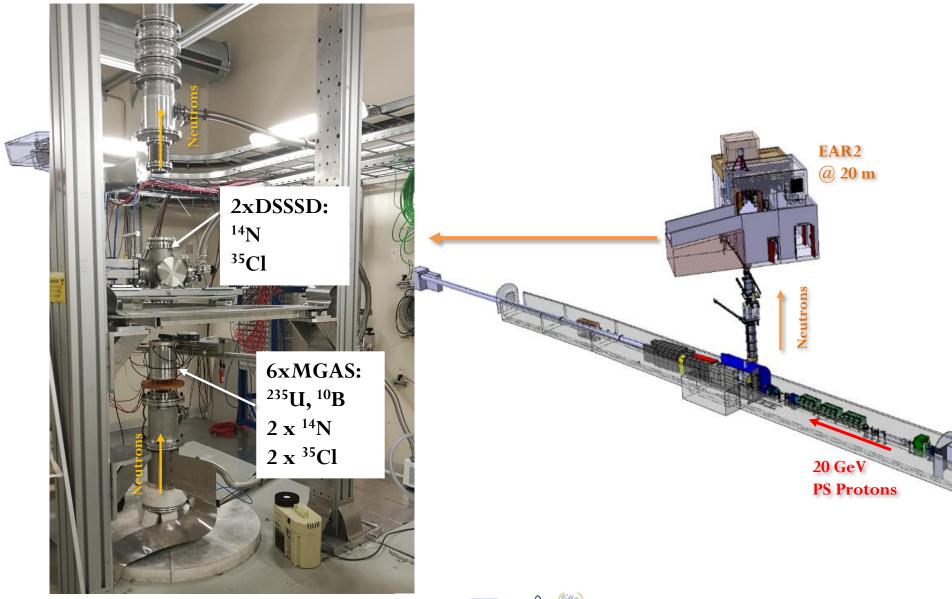








## EAR2 setup for ${}^{14}N(n,p){}^{14}C$ and ${}^{35}Cl(n,p){}^{35}S$ .







## <sup>14</sup>N(n,p)<sup>14</sup>C at EAR2: covering all the energy range.

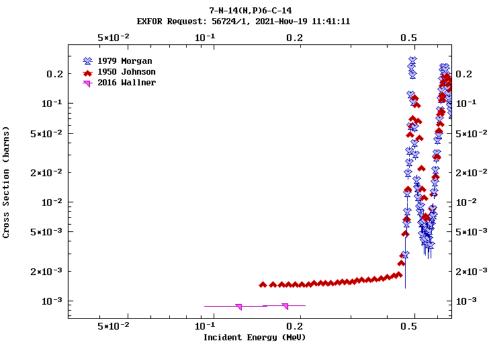
Only partial measurements in the energy for AB-BNCT:

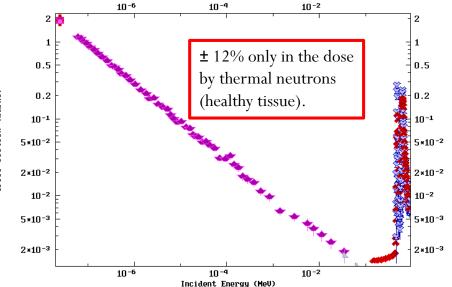
Thermal

Above thermal to 80 keV

Above 100 keV

At n\_TOF, we cover the whole energy range.





Johnson: first measurement of the first (493 keV) resonance.

After, Morgan provided a lower strength that Johnson

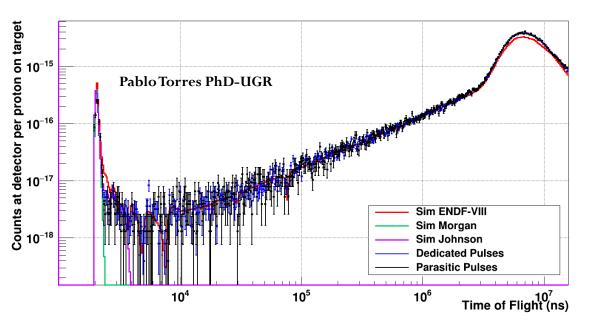
After, Wallner *et al* showed a further reduction factor 3.3 by activation.

At n\_TOF, we have found a reduction.





## <sup>14</sup>N(n,p) <sup>14</sup>C at EAR2: covering range partial previous experiments



It is covered the energy range from thermal to 500 keV.

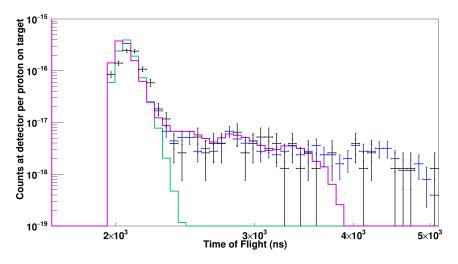
For the first time.

Purple and Green are Johnson and Morgan experimental with the RF-EAR2.

Black points, n\_TOF data.

Reduction of factor 1.5 the area of the resonance.

Impact in the dose on healthy tissue and BNCT planning.









# Radioisotope production





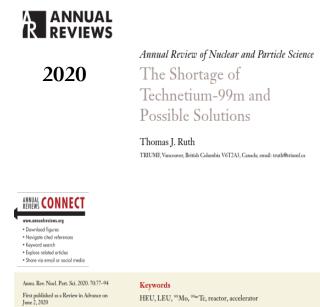


There is a trend since a decade to use existing and new nuclear facilities for producing radioisotopes (Medicis-Isolde).

The Technetium world crisis in 2009-2010 was an alarm about the way to supply radioisotopes for nuclear medicine. Few reactors world wide.













Following a major shortage of 99Mo in the 2009-2010 period, concern

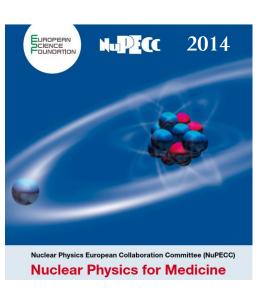
grew that the aging reactor production facilities needed to be replaced.

The Annual Review of Nuclear and Particle Science

https://doi.org/10.1146/annurev-nucl-032020

is online at nucl.annualreviews.org

# International agencies and groups pushed for the use of accelerator-based facilities, as a complementary option.



Another "longer-lived" alpha emitter is 211 At. The difficulty of its application resides more in its (bio-) chemistry. Astatine is a heavier homologue of the halogen iodine, but it is also close to the metalloids. For therapeutic applications it is essential to ensure a stable bond to the targeting vector to minimise in vivo delabelling. Efforts are ongoing to improve the understanding of a tatine chemistry by experiments with trace quantities supported by computational chemistry [Cha11]. Interestingly, the ionisation potential of astatine, one of the fundamental atomic properties of an element, was only experimentally determined by laser spectroscopy with a tatine isotopes produced at ISOLDE (CERN) [Rot13]. This value can now serve as experimental benchmark to support "in silico" design of astatine compounds for nuclear medicine applications.

<sup>211</sup>At-labelled antibodies have been used clinically for treatment of brain cancer [Zal08]. Phase I trials for treatment of prostate cancer micrometastases and of neuroblastoma with <sup>211</sup>At labelled antibodies are under preparation.

Preclinically <sup>211</sup>At-labelled antibodies have been used against acute myeloid leukaemia as well as cancers of the ovary and intestine.

R&D activities in nuclear facilities as ISOLDE provided a better understanding in nuclear medicine

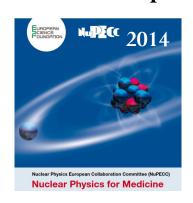
To overcome this restriction a new project called MEDICIS is now under construction. It will make use of the protons that have traversed the ISOLDE targets for additional beam dump irradiations of





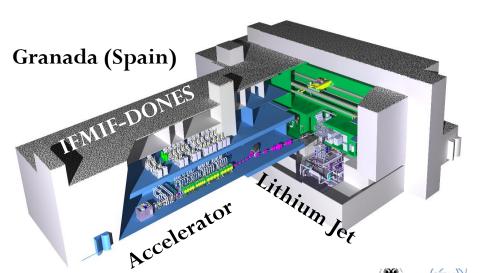


Also, accelerator-based neutron facilities has been considered for the production of radioisotopes for nuclear medicine.



Thus high neutron flux *and* a high capture cross-section are essential to achieve a high specific activity by converting a large fraction of the stable target into the wanted radioisotope. Only <sup>60</sup>Co, <sup>153</sup>Sm, <sup>169</sup>Yb and <sup>177</sup>Lu can be produced with

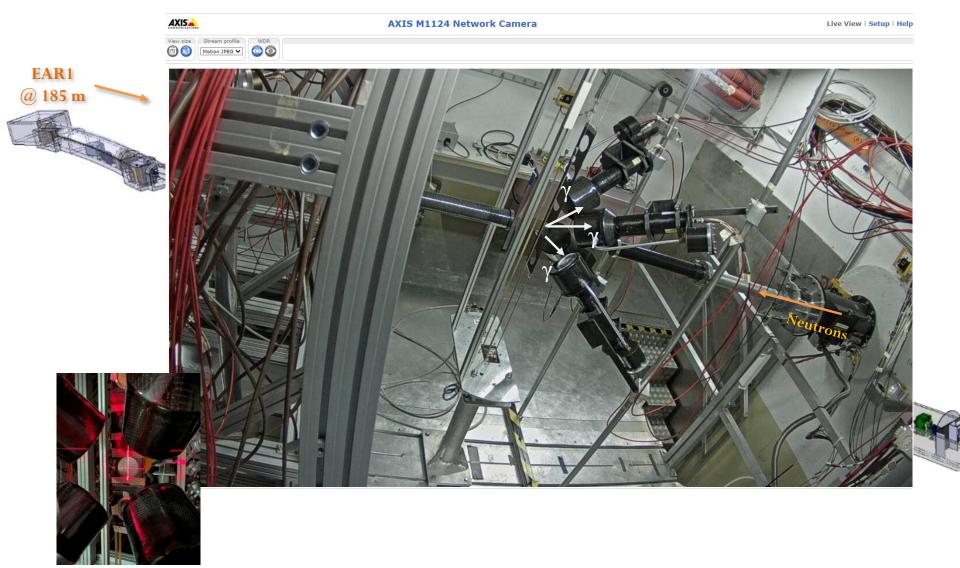




To be used in nuclear medicine, large radionuclide production is required which implies the use of highly intense particle beams (hundreds to thousands of µA) or secondary neutron sources. Targetry to be used in such conditions (kW of power over few cm²) are not an easy task requiring dedicated developments. Such R&D activities are ideally suited to be performed in nuclear physics research laboratories. Production capabilities of some specific nuclei using electron and gamma beams should also be investigated.



# $^{176}$ Yb $(n,\gamma)^{177}$ Yb $(2 h) \rightarrow ^{177}$ Lu(6.5 d) at EAR1



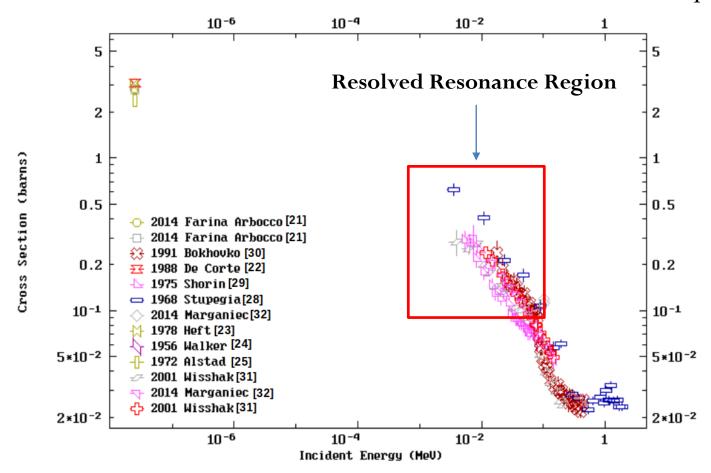






# Previous experimental data <sup>176</sup>Yb(n,γ)

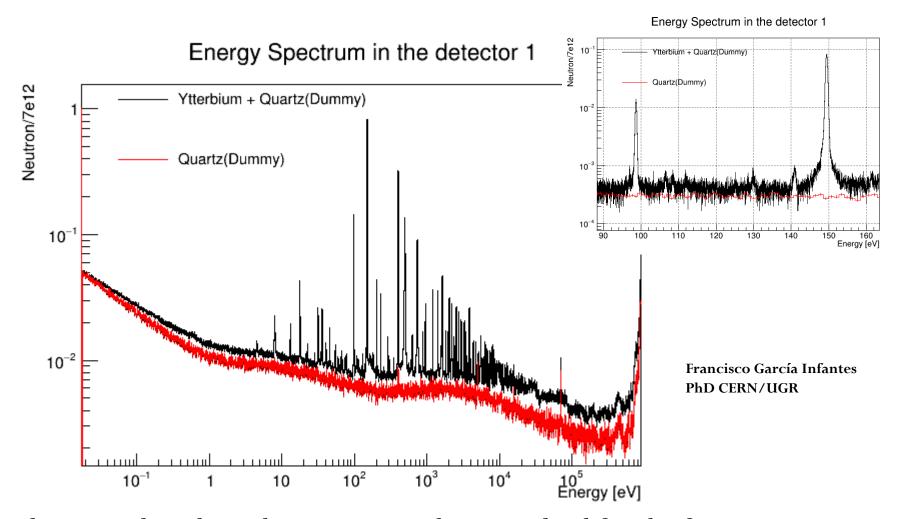
- No data in the 1/v region
- No resolved resonances. Resonances detected in transmission experiments.







# n\_TOF experimental data <sup>176</sup>Yb(n,γ)



Preliminary data show that resonances have resolved for the first time and data in the 1/v region.

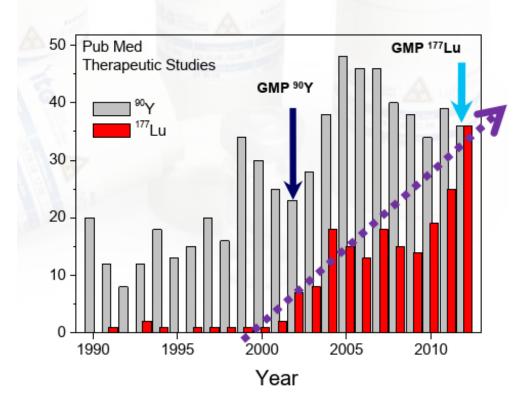


## <sup>177</sup>Lu rising demand & <sup>90</sup>Y well established

- Theragnostic = diagnosis and therapy.
- At present, it is produced in nuclear reactors.
- Rising demand radioisotope.
- Y-90 is also of interest for complementary production.

Number of scientific publications vs time:

### Therapeutic applications of 90Y and 177Lu









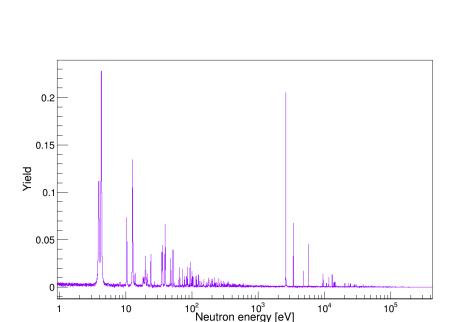
# <sup>90</sup>Y well established: again, unique data

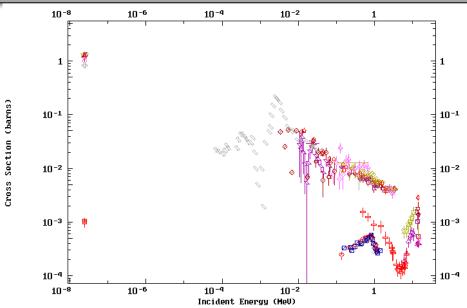
EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH Proposal to the ISOLDE and Neutron Time-of-Flight Committee

Neutron capture cross section of 88Sr and 89Y

[08/01/2016]

G. Tagliente<sup>1</sup>, M. Barbagallo<sup>1,8</sup>, N. Colonna<sup>1</sup>, S. Cristallo<sup>2</sup>, L. A. Damone<sup>1</sup>, A.C. Larsen<sup>3,4</sup>, M. Lugaro<sup>5</sup>, C.Massimi<sup>6</sup>, M. Mastromarco<sup>1</sup>, P.M. Milazzo<sup>7</sup>, F. Mingrone<sup>8</sup>, and the n\_TOF collaboration.





Preliminary data show that resonances have resolved for the first time and data in the 1/v region.







### **Conclusions**

### The n\_TOF facility is providing unique data for medicine.

 $^{160}\mathrm{Gd}(\mathrm{n},\gamma)^{161}\mathrm{Gd} \longrightarrow ^{161}\mathrm{Tb}$ , will provide data for new radioisotope

### AB-BNCT is opening a new framework and market:

Accelerators, targets, BSA and treatment planning codes.

Companies: Neutron Therapeutics, TAE Life Sciences...

Public institutions: Japan.

### Radioisotope market, Reuters Report:

10 billion€ in 2017 and it is expected to grow 12.3% until to 2023.

The major hindrance is the high capital investments required, cyclotron.

CERN MEDICIS facility is an excellent example to be followed and synergies should be found.

NEAR opens new possibilities for medicine applications: to be studied.









# Thank you

### **Javier Praena**

Prof. Universidad de Granada (Spain) CERN Scientific Associate (EP/SME) n\_TOF Physics Coordinator







# <sup>177</sup>Lu production routes

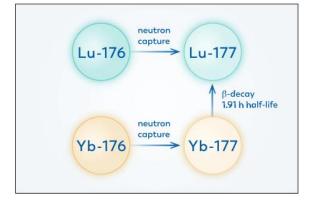
#### "Carrier Added"

 $^{176}$ Lu(n, $\gamma$ )  $\rightarrow$   $^{177}$ Lu + $_{\underline{\phantom{0}}}^{177m}$ Lu

Higher production. Lower specific activity.

177mLu is produced (0.05%), 160 days.

176Hf STABLE 5.26%	177Hf STABLE 18.60%	178Hf STABLE 27.28%	179 STAI 13.6		180 STA 35)		181Hi 42.39 I β-: 100.0
175Lu STABLE 97.401%	176Lu 3.76E+10 Y 2.599% β-: 100.00%	177Lu 6.647 D β-: 100.00%	178 28.4 β∹ 100	M	179 4.59 β-: 100	H	180Lα 5.7 M β-: 100.0
174Yb STABLE 32.026%	175Yb 4.185 D β-: 100.00%	E(level) 0.0 0.9702	Jn 7/2+ 23/2-	6.64	'Lu 1/2 7 d <i>4</i> 14 d 6	β-: 1	y Modes 00.00 %
173Tm 8.24 H β-: 100.00%	174Tm 5.4 M β-: 100.00%	2.7400 β-	ŕ		+3-2	İT : 2 β <sup>-</sup> : 1	78.60 % 21.40 % 00.00 % T ?



#### "Non Carrier Added"

 $^{176}\mathrm{Yb}(\mathrm{n},\gamma)^{177}\mathrm{Yb} \ ( \longrightarrow ^{177}\mathrm{Lu})$ 

Lower production. Higher specific activity.

<sup>177m</sup>Lu is negligible (<0.0001%)







## Specific activity: impact on tumor uptake

### "Carrier Added"

300 MBq of <sup>177</sup>Lu c.a. Dose to tumor - 35 Gy

### "Non Carrier Added"



300 MBq of <sup>177</sup>Lu n.c.a. Dose to tumor - 70 Gy

Marion de Jong et al.; 2012 ICTR-PHE







### Perspectives during the YETS and after

- To finish the analysis regarding the commissioning.
- 28/02/2021 proton beam back, low intensity.
- Physics Program:  $^{79}$ Se(n, $\gamma$ ) (INTC-P-580) EAR1,  $^{94}$ Nb(n, $\gamma$ ) (INTC-P-577) EAR2,...

#### **Proton beam**

Fixed impact point of the proton beam on target.

#### Our Needs for Physics:

- Proton pulses with two different intensities: 7.5-8.5e12 and 2-3.5e12.
- 1.05e17 protons per day made in 30 days, in average, as the campaigns before the LS2.

### • Our Constrains from Target:

- Maximum average intensity on target = 160e10 p/s
- Dimensions for high intensity pulses  $\approx 215 \text{ mm}^2$ .
- Dimensions for low intensity pulses  $\approx 40 \text{ mm}^2$ .

Thanks to the PS team for the constant feedback for improving the quality of the proton beam







## ESFRI facility. City host: Granada













































Warsaw University of Technology







STRATEGY REPOR

LANDSCAPE ANALYSIS

**EVENTS** 

NEWS

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Part 3

### PROJECTS & LANDMARKS

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ENERGY / PROJECT

ROADMAP 2018

#### **IFMIF-DONES**

#### International Fusion Materials Irradiation facility - DEMO Oriented Neutron Source



#### Roadmap Entry

2018 Design Phase 2007-2015 Preparation Phase 2015-2019 Implementation/Construction Phase 2019-2029 Operation Start 2029

#### ESTIMATED COSTS

150 M€ preparation 40 M€ 420 M€ 50 M€/year

capital value 710 M€

### POLITICAL SUPPORT









# Spain-Croatia. City host: Granada





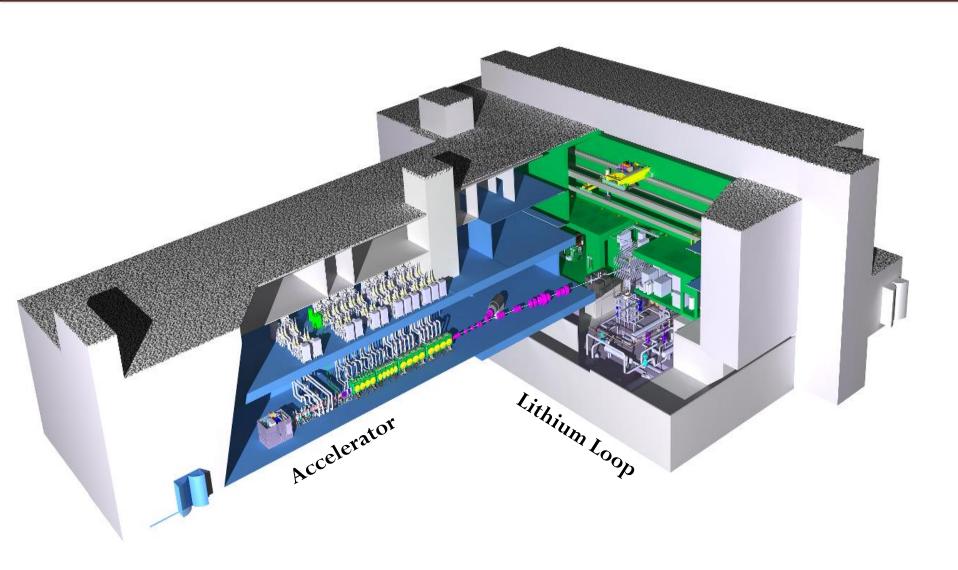






TERRENOS CEDIDOS POR
EL AYUNTAMIENTO DE ESCÚZAR
PARA EL PROYECTO DEL ACELERADOR

## The facility goal: produce neutrons







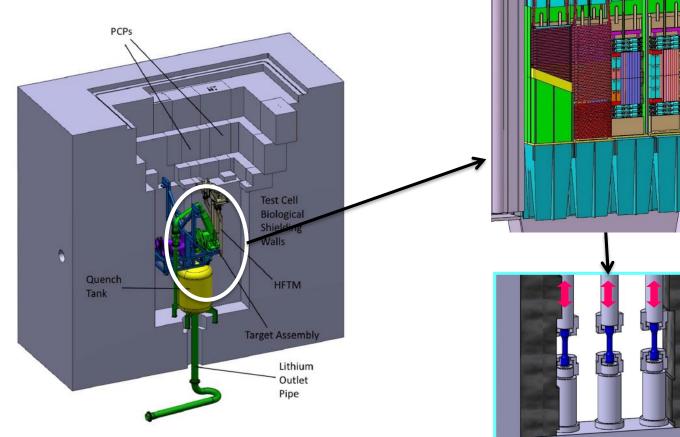


## Neutron damage in key pieces of fusion reactors

The goal of IFMIF-DONES is to produce neutrons-like DEMO fusion reactor.

Study the behaviour of several key pieces of DEMO.

Irradiations will last several months.





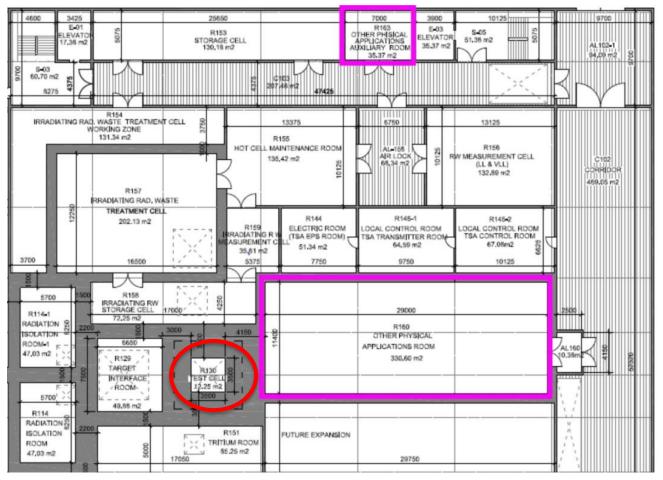






## Other applications: in and out the bunker.

The design of the building of IFMIF-DONES has already included an experimental hall (R160) next to the bunker where the neutrons are produced.







## UGR and the other applications.



#### Power Plant Physics & Technology



Report IDM Ref. No.	Version: see IDM

Report
ENS-7.2.3.1-T13-06-N1
Feasibility study of the use of DONES for radioisotope
production, electronics irradiation and neutron scattering

_	Deliverable			Technical Report
	Management Report		X	Technical Note
	Other	Specify:		·

		Document Id.	ENS-7.2.3.1-T13-06-N1		
Work Package: WPENS		Issue Date	21/01/2020		
Document/Report Authors (refer to first page of actual report/document for a complete list)					
Authors:	Authors: J. Praena, F. García Infantes, P. Torres-Sánchez, M. Macías, A. Roldán, I. Porras,				
	Arias de Saavedra	Arias de Saavedra			
RU:	CIEMAT / University of Granada	CIEMAT / University of Granada (Spain)			

Links to other files (CATIA CAD	Links to other files (CATIA CAD Files, Interface database,)				
Title:	n/a				
URL:	n/a				

IDM Report Review & Approval			
IDM role	Name(s)		
Author and co-author(s):	J. Praena, F. García Infantes, P. Torres-Sánchez, M. Macías, A. Roldán, I. Porras, F. Arias de Saavedra. (Authors of Section 1: A. Ibarra, U. Fischer, F. Mota)		
Reviewer(s) Technical Issues:	W. Krolas, J. Castellanos and F. Arbeiter		
Reviewer PMU:	No		
Approver:	A. Ibarra		

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#### Radioisotope production at the IFMIF-DONES facility

Javier Praena<sup>1,\*</sup>, Francisco Garcia-Infantes<sup>1</sup>, Rafuel Rivera<sup>1</sup>, Laura Fernandez-Maza<sup>2</sup>, Fernando Arias de Saavedra<sup>1</sup>, and Ignacio Porras<sup>1</sup>

<sup>1</sup>Universidad de Granada, Granada, Spain

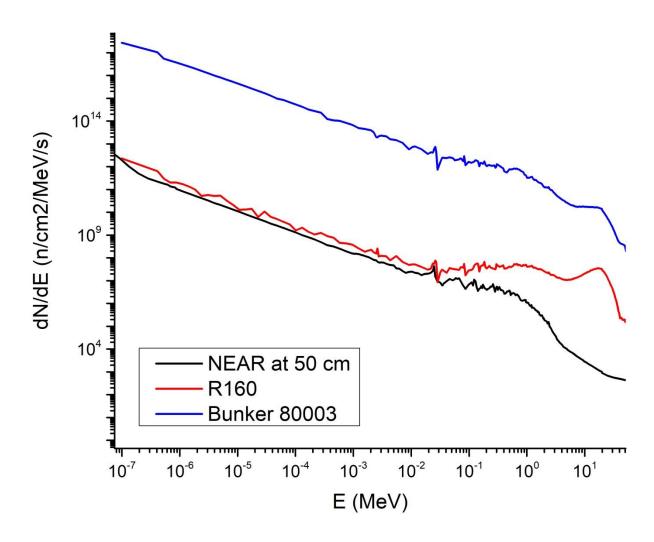
<sup>2</sup>Hospital Virgen de la Arrixaca, Murcia, Spain







## N\_TOF versus DONES





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**EDITORIAL** 



#### Challenges and future options for the production of lutetium-177

W. V. Vogel 1 · S. C. van der Marck 2 · M. W. J. Versleijen 1

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#### Discussion

In the coming years, production of medical isotopes will remain a matter of clinical, financial and political debate. There are multiple routes to production of <sup>99</sup>Mo, potentially involving investments in several current and new techniques. But it remains a vital question whether future facilities, of which an increasing number may be optimized for <sup>99</sup>Mo production alone, can also produce the full range of other required medical isotopes.

We identify <sup>177</sup>Lu, which already is an indispensable isotope for radionuclide therapy and will become even more so with increasing number of treatable prostate cancer patients, as an important candidate isotope that may not be produced in sufficient quantities in the near future, in case of insufficient availability of high-flux neutron irradiation facilities. In 2015,



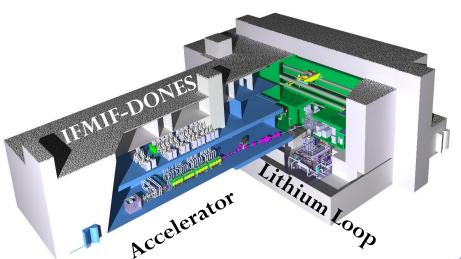




Facilities under designed and construction as IFMIF-DONES (Granada, Spain) considers the production of radioisotopes for medicine as an complementary application.

MEDICIS-ISOLDE-CERN is an excellent successful example.

Nuclear data are needed to calculate the specific activity of the most adequate radioisotopes.



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<sup>1</sup>Universidad de Granada, Granada, Spain
<sup>2</sup>Hospital Virgen de la Arrixaca, Murcia, Spair



