EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Proposal to the ISOLDE and Neutron Time-of-Flight Committee

Measurement of the ^{176}Yb(n,γ) cross-section at EAR1 and its application to nuclear medicine

[submission date]

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for the n_TOF collaboration

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UNIVERSIDAD DE GRANADA

Outlook

- **Scientific motivations.**
  - ^{177}Lu in nuclear medicine. Complementary production in new facilities.
  - Data needs of the ^{176}Yb(n,γ)^{177}Yb (→ ^{177}Lu).

- **Status ^{176}Yb(n,γ) experimental data and evaluations.**
  - No data in the 1/v region (meV-keV).
  - No resolved resonances.

- **Proton beam request at EAR1.**
  - **1.5e18**

Scientific motivations

New facilities for complementary 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.

2009

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comments on this story

Published online 23 October 2008 | Nature | doi:10.1038/news.2008.1186

News

Europe's isotope shortage will continue into 2009

Hospitals forced to use substitute procedures for medical scans.

Paula Gould

A Europe-wide shortage of medical isotopes will continue for at least three months while a Dutch nuclear reactor is repaired. Governments and regulators are now bending their rules concerning the use and transport of radioactive materials so that patients can still undergo diagnostic tests during the supply crisis.

The High Flux Reactor in Petten has been out of action since the end of August (see 'Isotope shortage could delay cancer treatment') after tiny bubbles of gas were found escaping from a pipe into the reactor's cooling system during a routine maintenance inspection. Although the cause of the leak has now been traced

The High Flux Reactor in Petten, the Netherlands, is facing an extended shut-down. NRG

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- Hospital
- Reactor closure
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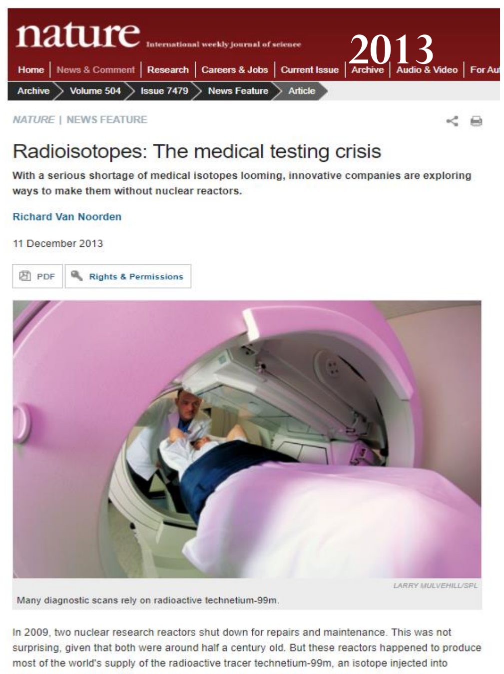
2013



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NATURE | NEWS FEATURE

Radioisotopes: The medical testing crisis

With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors.

Richard Van Noorden

11 December 2013

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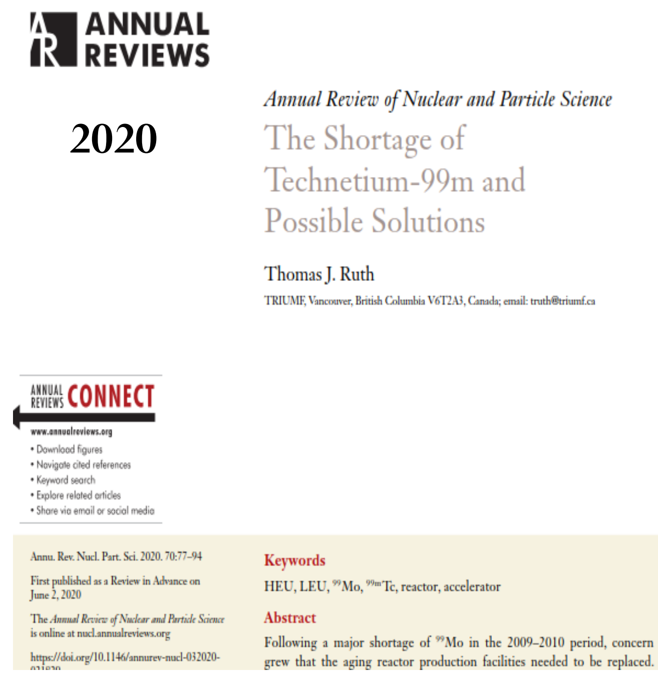
LARRY MULVEHILL/SPL

Many diagnostic scans rely on radioactive technetium-99m.

In 2009, two nuclear research reactors shut down for repairs and maintenance. This was not surprising, given that both were around half a century old. But these reactors happened to produce most of the world's supply of the radioactive tracer technetium-99m, an isotope injected into patients in 70,000 diagnostic scans a day. Hospitals around the world went into a panic.

2020



ANNUAL REVIEWS

Annual Review of Nuclear and Particle Science

The Shortage of Technetium-99m and Possible Solutions

Thomas J. Ruth

TRIUMF, Vancouver, British Columbia V6T2A3, Canada; email: truth@triumf.ca

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Annu. Rev. Nucl. Part. Sci. 2020. 70:77–94

First published as a Review in Advance on June 2, 2020

The *Annual Review of Nuclear and Particle Science* is online at nucl.annualreviews.org

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

Keywords

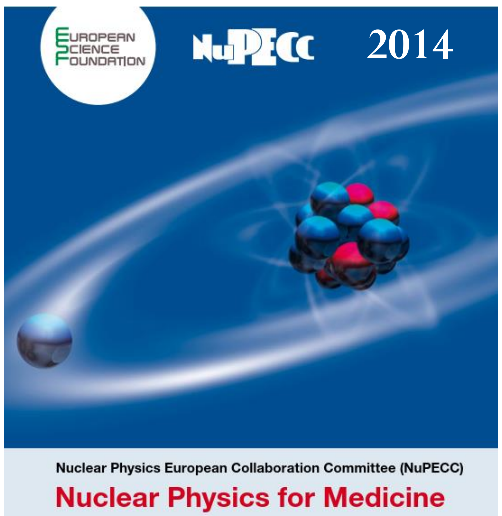
HEU, LEU, ^{99}Mo, ^{99m}Tc, reactor, accelerator

Abstract

Following a major shortage of ^{99}Mo in the 2009–2010 period, concern grew that the aging reactor production facilities needed to be replaced.

New facilities for complementary radioisotope production

Many working groups and international agencies have pushed for the use of nuclear facilities for radioisotope production with application to nuclear medicine (therapy and diagnosis). Not only "industrial" production is needed…



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 astatine 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 astatine 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.

^{211}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 ^{211}At labelled antibodies are under preparation.

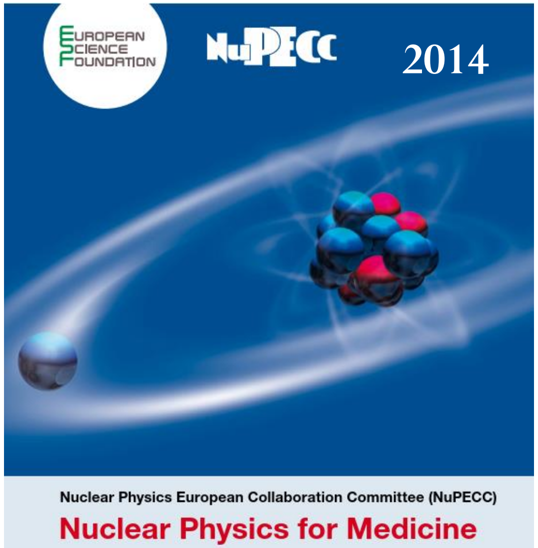
Preclinically ^{211}At-labelled antibodies have been used against acute myeloid leukaemia as well as cancers of the ovary and intestine.

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

New facilities for complementary radioisotope production

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 ^{60}Co, ^{153}Sm, ^{169}Yb and ^{177}Lu can be produced with appreciable specific activity ($R > 0.05$) in this way.

NuPECC
Long Range Plan 2017
Perspectives
in Nuclear Physics

European Science Foundation

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.

New facilities for complementary radioisotope production

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05392-2

EDITORIAL

Check for updates

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]

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 ^{99}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 ^{99}Mo production alone, can also produce the full range of other required medical isotopes.

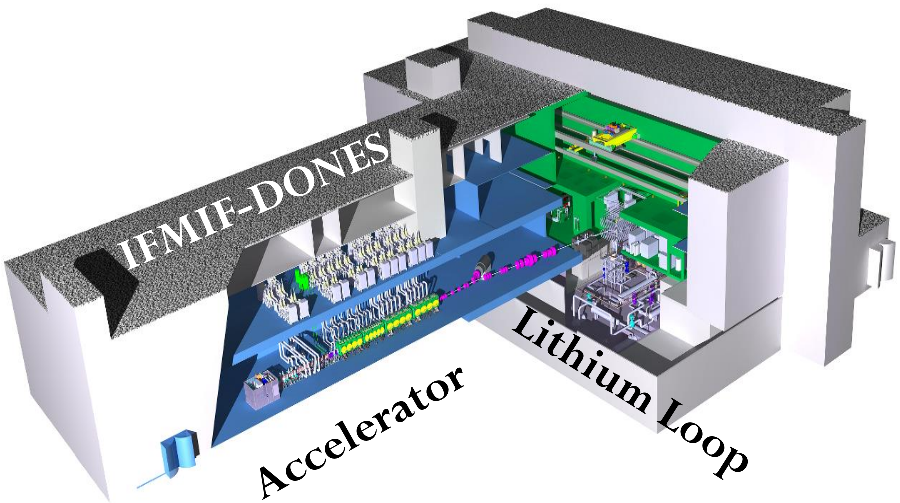
We identify ^{177}Lu, which already is an indispensable isotope for radionuclide therapy and will become even more so with increasing number of treatable prostate cancer patients, as an important candidate isotope that may not be produced in sufficient quantities in the near future, in case of insufficient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

New facilities for complementary radioisotope production

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.



EPJ Web of Conferences **239**, 23001 (2020) https://doi.org/10.1051/epjconf/202023923001
ND2019

Radioisotope production at the IFMIF-DONES facility

Javier Praena[1,*], *Francisco* Garcia-Infantes[1], *Rafael* Rivera[1], *Laura* Fernandez-Maza[2], *Fernando* Arias de Saavedra[1], and *Ignacio* Porras[1]

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[2]Hospital Virgen de la Arrixaca, Murcia, Spain

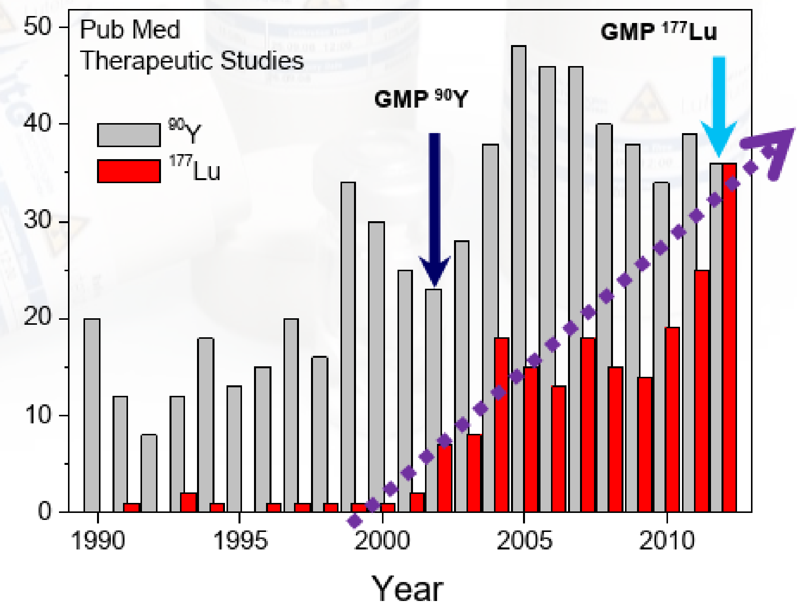
^{177}Lutetium in medicine

^{177}Lu, rising demand

- Theragnostic = diagnosis and therapy.
- Versatile radioisotope and one the most important emergent radioisotopes.
- Good good success in gastroentero-pancreatic neuroendocrine tumours [11].
- Currently, Lu177 is under study for several other tumours with good results [12].
- At present, it is produced in nuclear reactors.
- Rising demand radioisotope.

Number of scientific publications vs time:

Therapeutic applications of ^{90}Y and ^{177}Lu



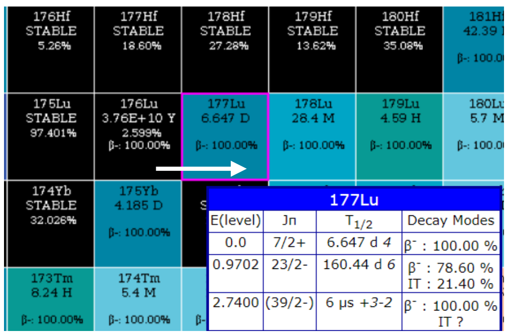
^{177}Lu production routes

“Carrier Added”

^{176}Lu(n,γ) → ^{177}Lu + ^{177m}Lu

Higher production. Lower specific activity.

^{177m}Lu is produced (0.05%), 160 days.

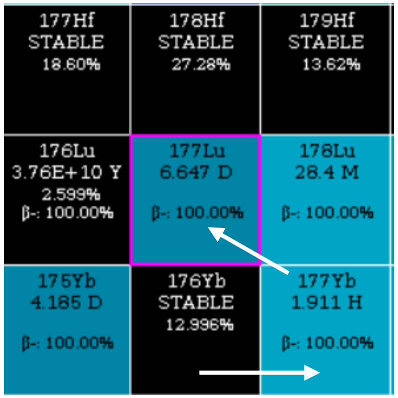


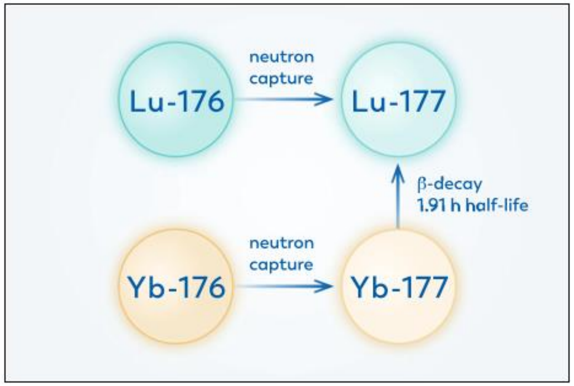
“Non Carrier Added”

^{176}Yb(n,γ)^{177}Yb (→ ^{177}Lu)

Lower production. Higher specific activity.

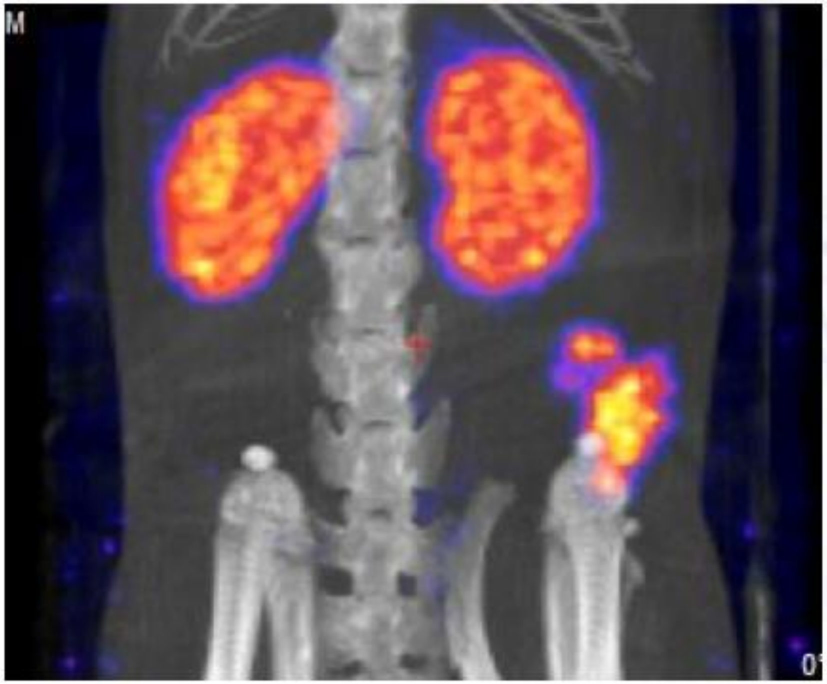
^{177m}Lu is negligible (<0.0001%)





Specific activity: impact on tumor uptake

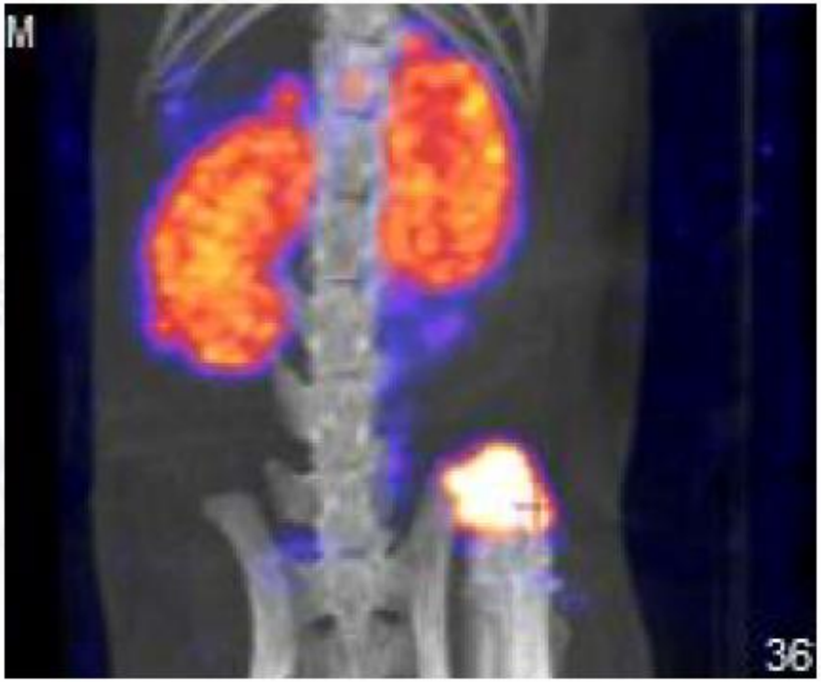
"Carrier Added"



300 MBq of ^{177}Lu c.a.

Dose to tumor - 35 Gy

"Non Carrier Added"



300 MBq of ^{177}Lu n.c.a.

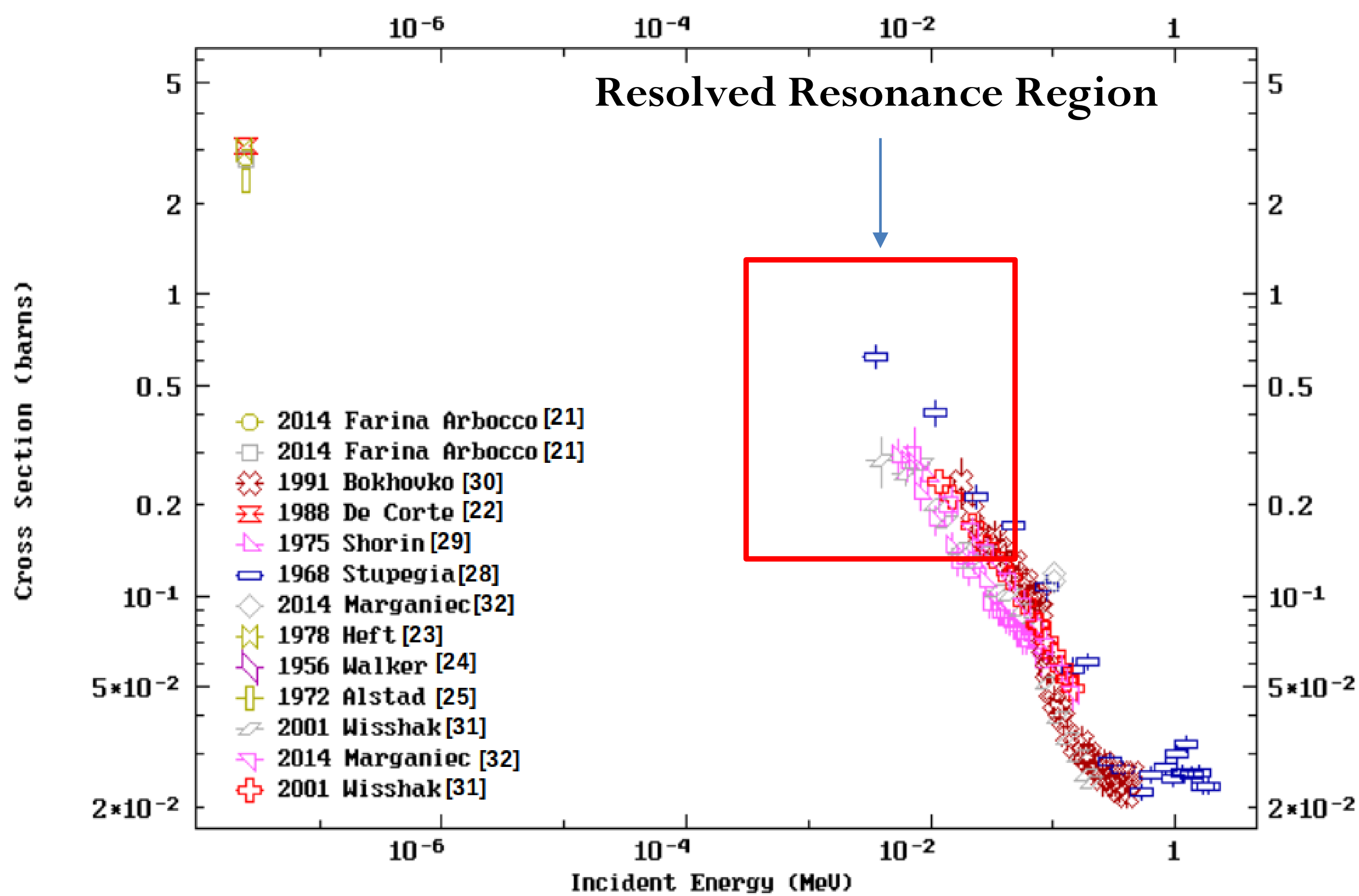
Dose to tumor - 70 Gy

Marion de Jong et al.; 2012 ICTR-PHE

$^{176}Yb(n,\gamma)^{177}Yb$
Data status. Proton request.

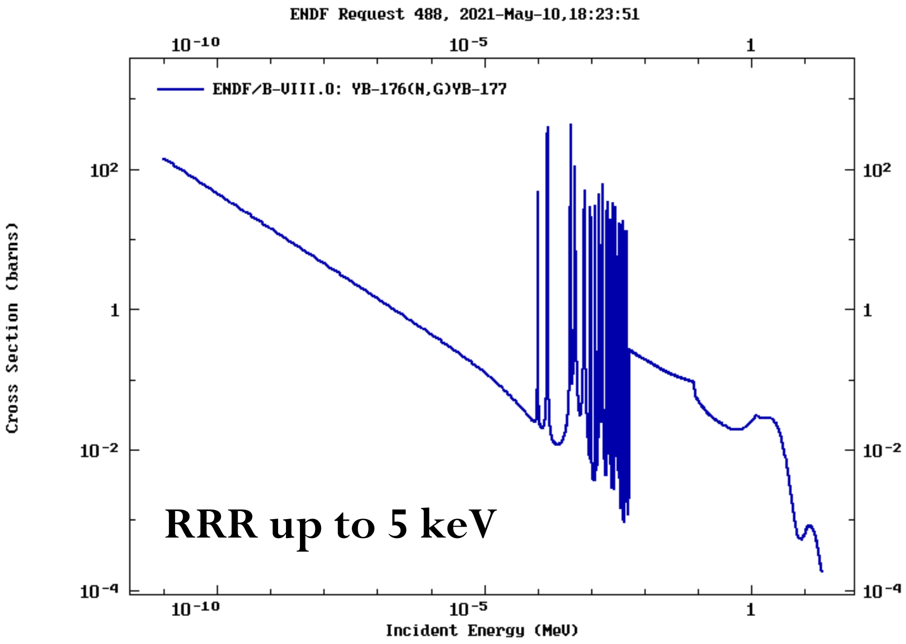
Experimental data $^{176}Yb(n,\gamma)$

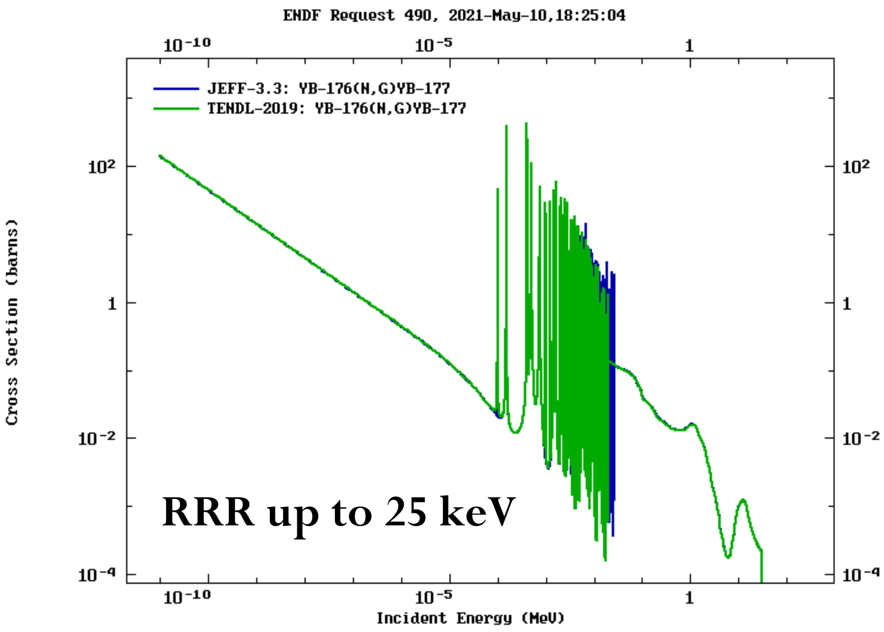
- No data in the 1/v region
- No resolved resonances. Resonances detected in transmission experiments.



Evaluations ^{176}Yb(n,γ)^{177}Yb

Evaluations foreseen resonances in the ^{176}Yb(n,γ) due to the results of transmission experiments. However, (n,γ) have not been detected





Sample and setup at EAR1

For the sample we will follow the method of Wisshak *et al.* [31], powder in Al can container.

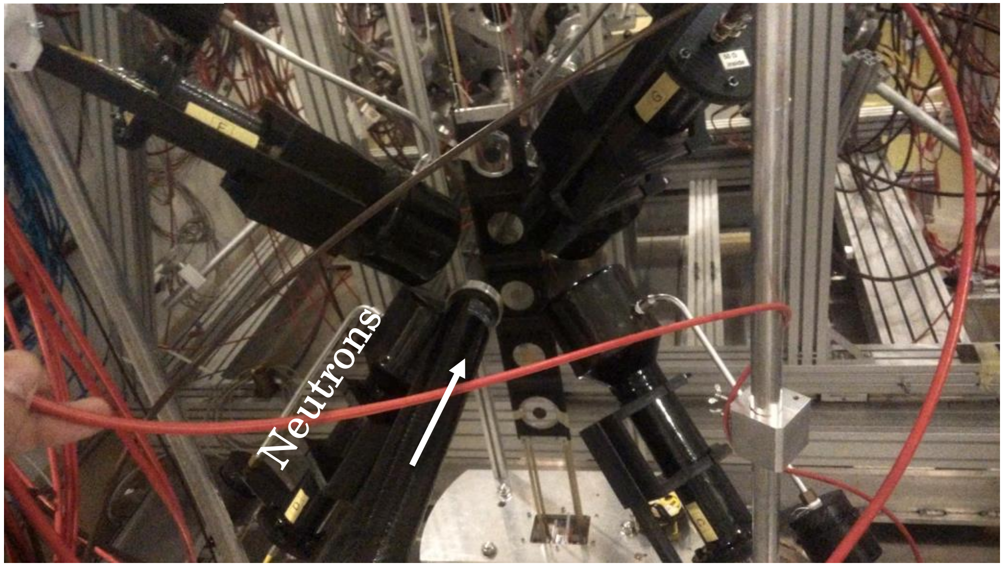
Trace Science Inter. provides the material with a higher enrichment than Wisshak *et al.* [31].

Contaminations of ^{168}Yb and ^{176}Lu are not expected, private communication Trace Science.

Table 1. Sample enrichment, mass and area density of the $^{176}Yb_2O_3$.

$^{176}Yb_2O_3$	
Enrichment [%]	>96%
Mass [g]	0.5
Area density [at/barn]	$3.857\cdot10^{-4}$

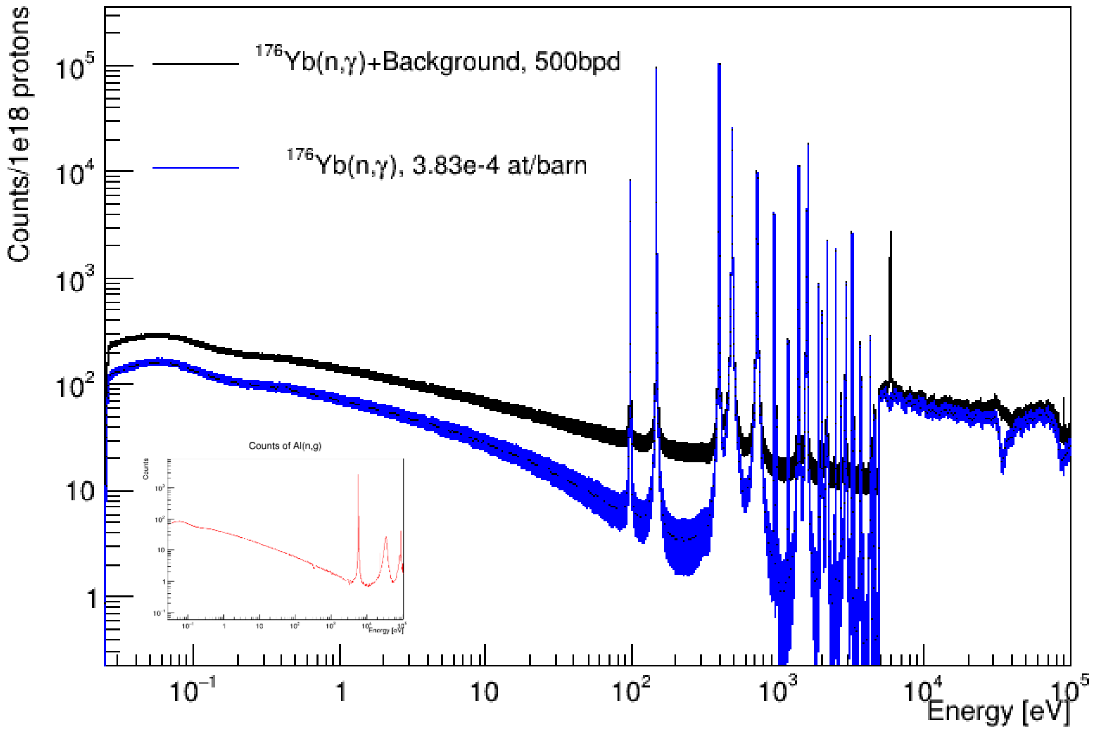
Four C_6D_6 detectors



Counts for 1e18 protons at EAR1: 500 bpd

Considering the setup with 4 C_6D_6, ENDF and the sample 3.8e-4 at/b.

Most important background is expected from the Al can.



Background can be substrate

Energy [eV]	Average Statistical uncertainty
1 - 70	10 - 30 %
1st and 2nd at WHM	5 %
Valleys 1st and 2nd	30 %

Sample by TRACE SCIENCE: no ^{168}Yb

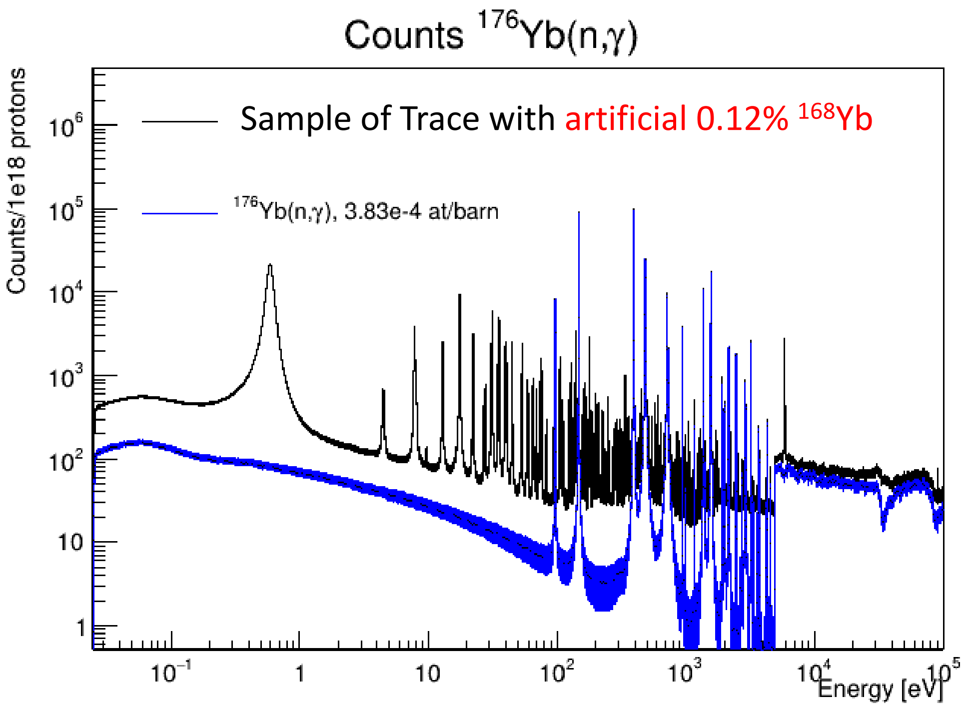
^{176}Lu and ^{168}Yb are the most undesirable isotopes in the sample. Both will not be present in the sample.

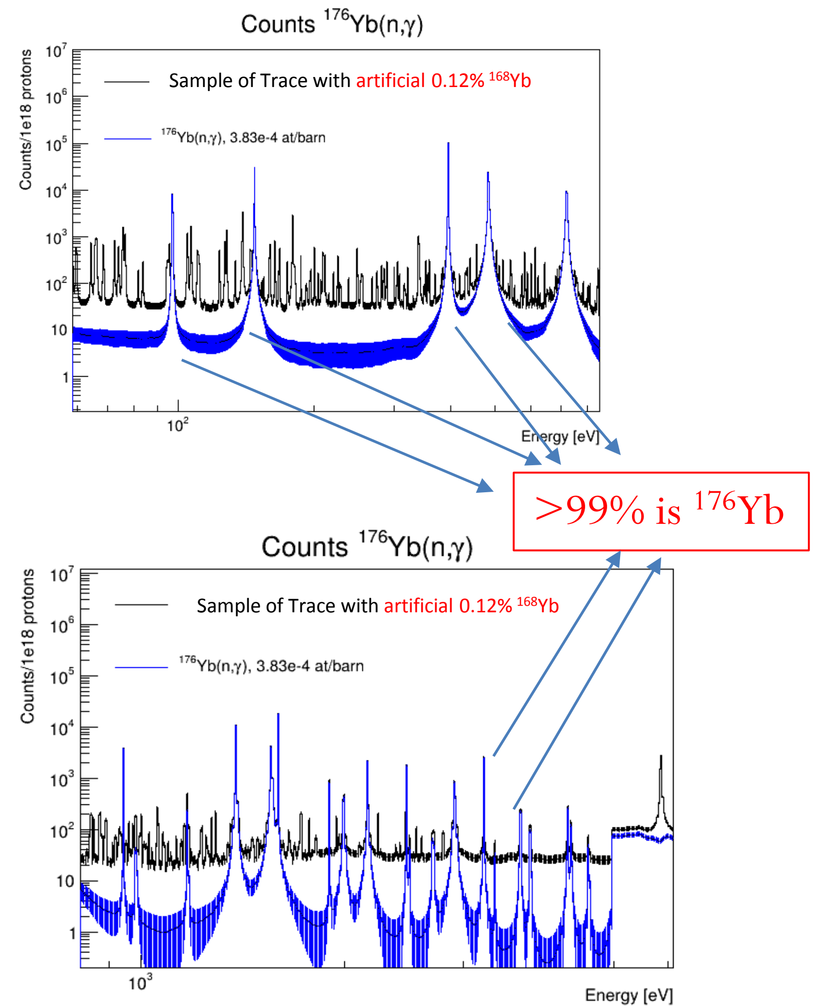
Isotopes	Abundance
^{171}Yb	0.41 %
^{172}Yb	0.69 %
^{173}Yb	0.51 %
^{174}Yb	1.99 %
^{176}Yb	96.4 %
	100 %

However, let us consider that the ^{168}Yb isotope would be present in the sample of TRACE.

Most unfavorable sample for background

Sample for the experiment considering an **artificial** contamination of 0.12% of the ^{168}Yb isotope.





Even in this artificial less favorable situation the background can be substrate

Conclusions and proton request

- ^{177}Lu is an important theragnostic radioisotope in nuclear medicine.
- It is considered for its production in accelerator-based neutron sources by means of the ^{176}Yb(n,γ) reaction as complementary to the production at nuclear reactors.
- A complete lack of data of the ^{176}Yb(n,γ) cross-section in the 1/v region (meV-keV).
- Important ^{176}Yb(n,γ) resonances, never detected, are expected because they have been detected in transmission experiments.
- At n_TOF, we will provide data in 1/v and will resolve the resonances for the first time, in a reasonable beam time.
- At present, it is not an objective of n_TOF to produce radioisotopes.

Summary of requested protons at EAR1: A total of $1.5\cdot10^{18}$ protons are requested.

$1\cdot10^{18}$ for the ^{176}Yb(n,γ)

$0.4\cdot10^{18}$ for background measurements.

$0.1\cdot10^{18}$ for ^{197}Au normalization

Thank you

Javier Praena

Universidad de Granada (Spain)
CERN Scientific Associate (EP-SME-62)
n_TOF Physics Coordinator

UNIVERSIDAD DE GRANADA

Sample by TRACE SCIENCE: no ^{168}Yb

^{176}Lu is not present in the sample. ^{168}Yb is the other isotope that could give noticeable background.

Contaminations of ^{168,170}Yb are not expected.

Isotopes	Abudance
^{171}Yb	0.41 %
^{172}Yb	0.69 %
^{173}Yb	0.51 %
^{174}Yb	1.99 %
^{176}Yb	96.4 %
	100 %

Isotopes	Experimental Enrichment *Kappeler
^{170}Yb	0.10 %
^{171}Yb	0.53 %
^{172}Yb	0.87 %
^{173}Yb	0.73 %
^{174}Yb	2.47 %
^{176}Yb	95.3 %
	100 %

IFMIF-DONES

ESFRI facility. City host: Granada

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Part 3

PROJECTS & LANDMARKS

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ENERGY / PROJECT

IFMIF-DONES

International Fusion Materials Irradiation facility - DEMO Oriented NEutron Source

lead country
ES

prospective member countries
HR

prospectives entities
EUROfusion

The full list of research institutions involved must be found in the website of the RI

TIMELINE

Roadmap Entry
2018

Design Phase
2007-2015

Preparation Phase
2015-2019

Implementation/Construction Phase
2019-2029

Operation Start
2029

ESTIMATED COSTS

capital value
710 M€

design
150 M€

preparation
40 M€

construction
420 M€

operation
50 M€/year

TYPE

single-sited

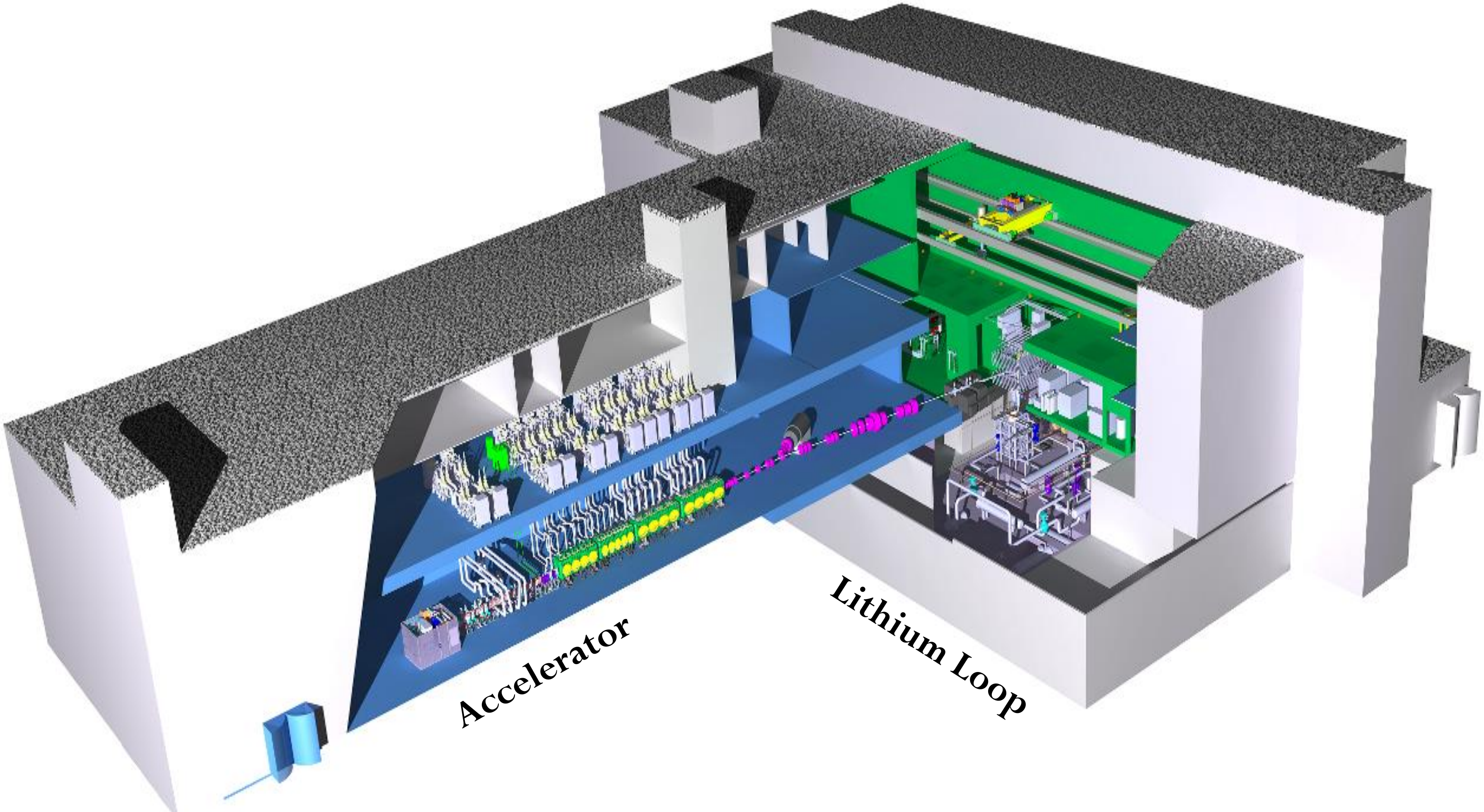
LEGAL STATUS

pending

POLITICAL SUPPORT

Spain-Croatia. City host: Granada

The facility goal: produce neutrons

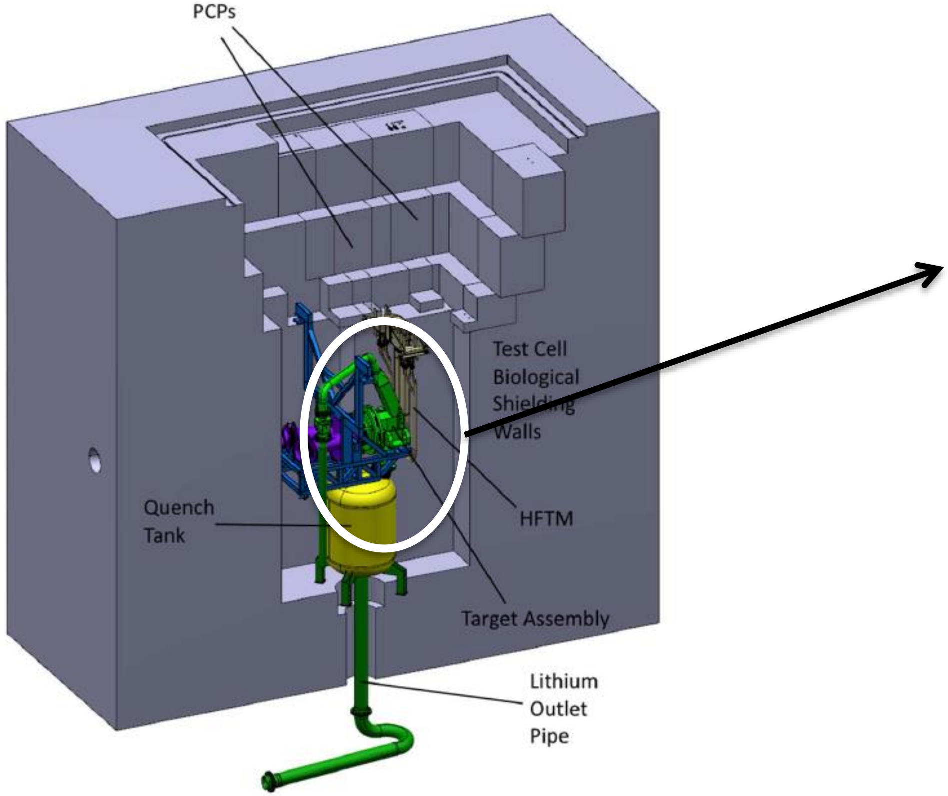


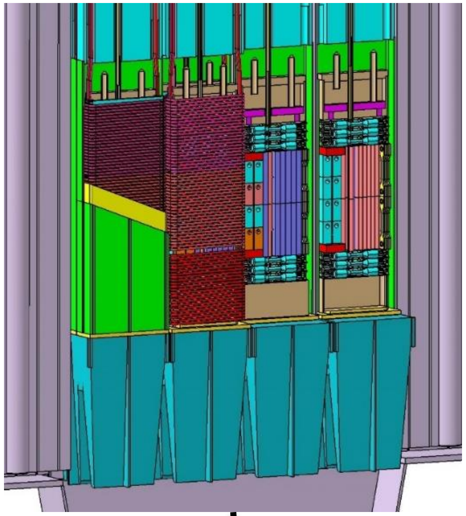
Neutron damage in key pieces of fusion reactors

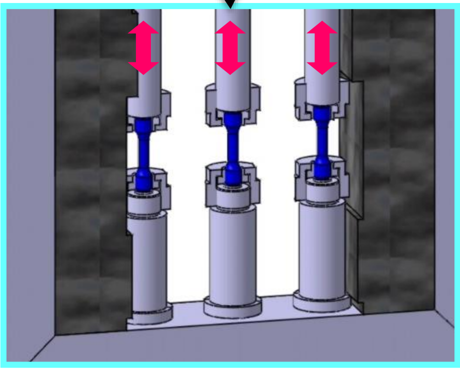
The goal of IFMIF-DONES is to produce neutrons-like DEMO fusion reactor.

Study the behaviour of several key pieces of DEMO.

Irradiations will last several months.

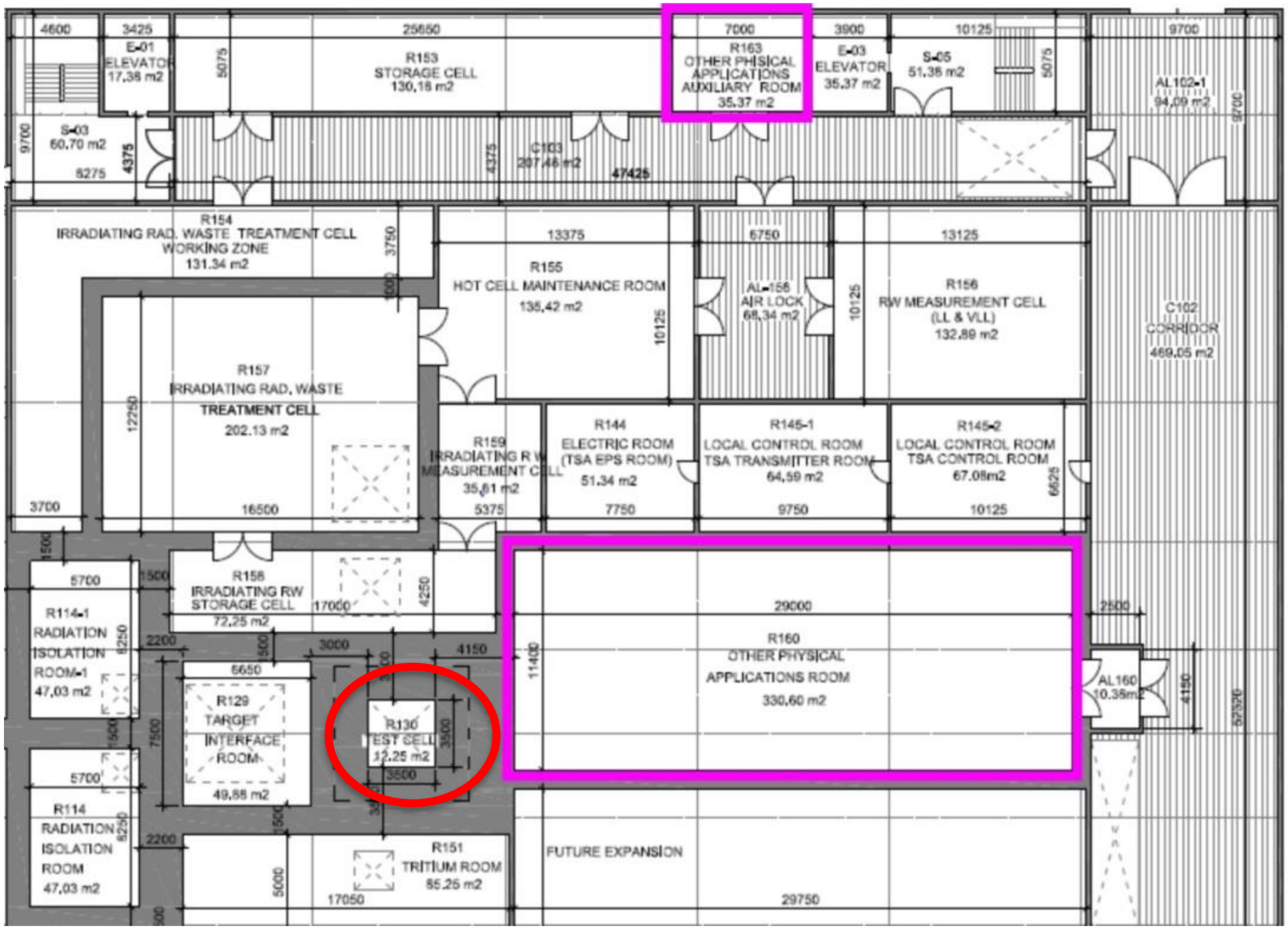






Other applications: in and out the bunker.

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.

EUROfusion	Power Plant Physics & Technology	IFMIF DONES

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)	
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RU:	CIEMAT / University of Granada (Spain)

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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

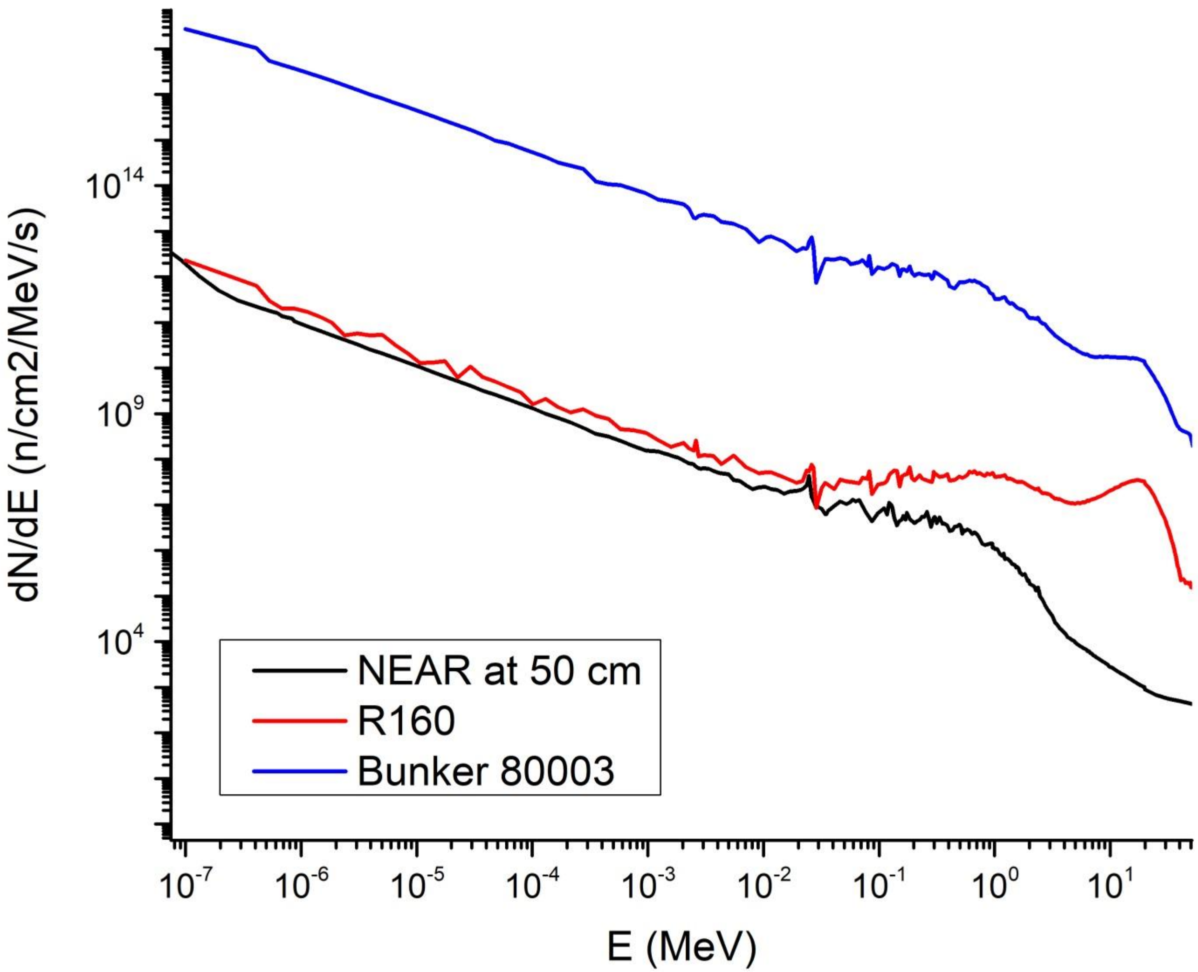
EPJ Web of Conferences **239**, 23001 (2020) https://doi.org/10.1051/epjconf/202023923001
ND2019

Radioisotope production at the IFMIF-DONES facility

Javier Praena[1,*], *Francisco* Garcia-Infantes[1], *Rafael* Rivera[1], *Laura* Fernandez-Maza[2], *Fernando* Arias de Saavedra[1], and *Ignacio* Porras[1]

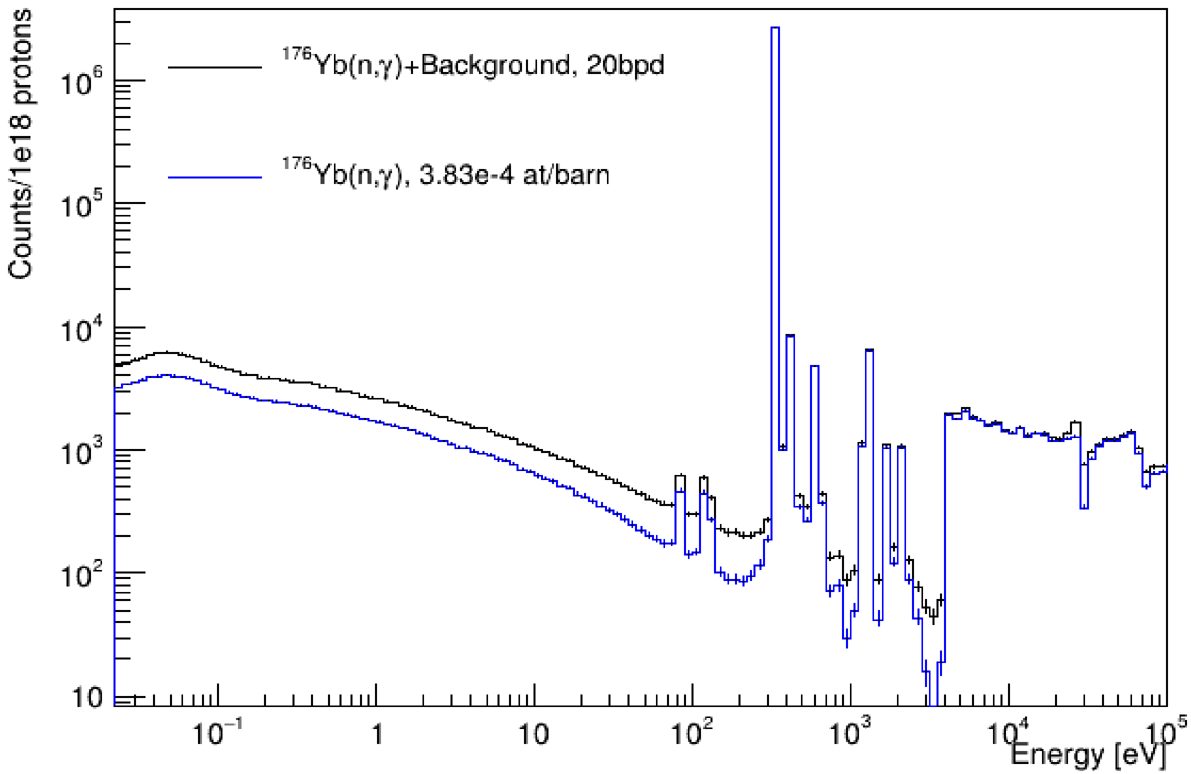
[1]Universidad de Granada, Granada, Spain
[2]Hospital Virgen de la Arrixaca, Murcia, Spain

N_TOF versus DONES



Counts for 1e18 protons at EAR1: 20 bpd

The low statistics in the 1/v could be improved with a smaller number of bpd



However, the low statistic of the valleys will remain.

Counts for natural enrichment of ytterbium