Perspectives for radioisotope production at DONES

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Outlook

1) Justification.

2) First radioisotope with neutrons: **^{99}Mo.**

3) First radioisotope with deuterons: **^{177}Lu.**

New facilities for radioisotope production

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


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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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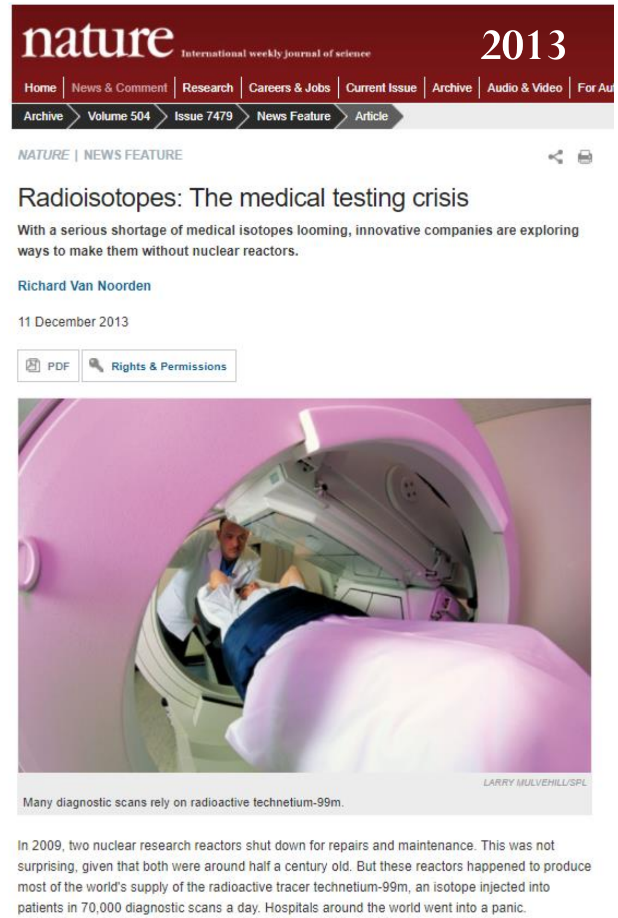
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NATURE | NEWS FEATURE

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.

New facilities for radioisotope production

Since the Tc99 crisis (SPECT), there is a new trend in nuclear medicine, the use of new facilities dedicated or not for radioisotope production.

ANNUAL REVIEWS

2020

Annual Review of Nuclear and Particle Science

The Shortage of Technetium-99m and Possible Solutions

Thomas J. Ruth

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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-032020-021829

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.

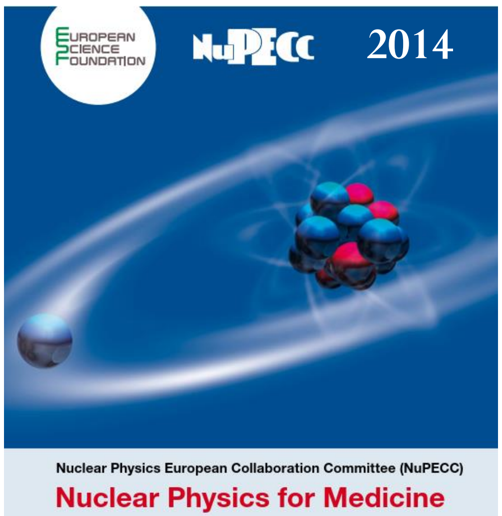
This trend also includes the fact that radioisotopes with shorter half-life cannot be supplied by few facilities world wide.

The production at regional levels of new radioisotopes could be enough for clinical use and research.

The production of many of them are not economically beneficial.

New facilities for 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.

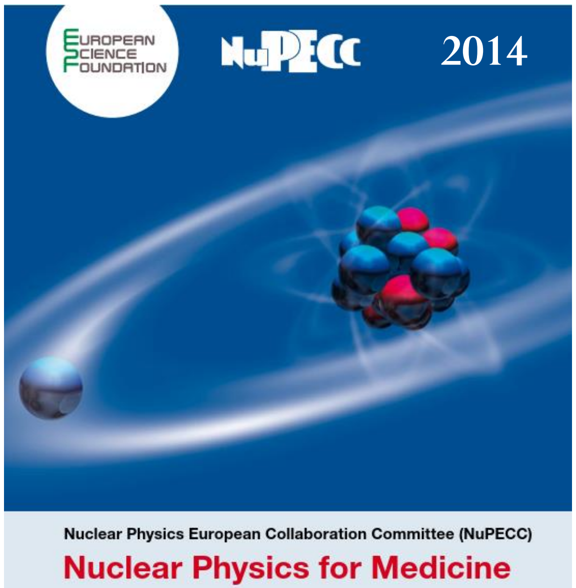
^{211}At-labelled antibodies have been used clinically for treatment of brain cancer [Zal08]. Phase I trials for treatment of prostate cancer micrometastases and of neuroblastoma with ^{211}At labelled antibodies are under preparation.

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

New facilities for radioisotope production

These R&D activities pushed the MEDICIS project with the aim to provide radioisotopes for nuclear medicine.



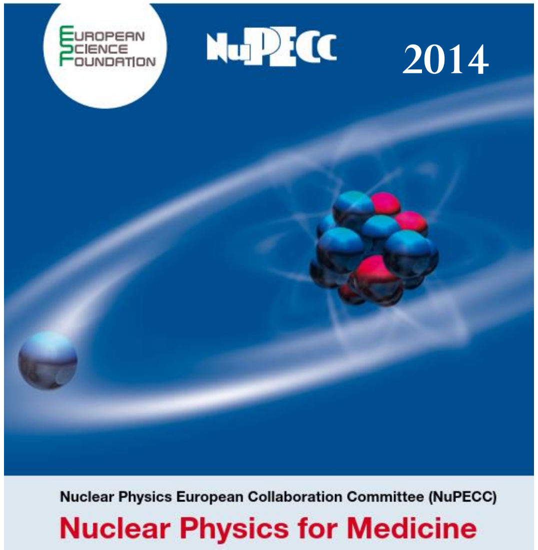
The isotope separation on-line facility ISOLDE at CERN provides over 1000 different radioisotopes in non-carrier-added quality by combining universal production via 1.4 GeV proton induced reactions with chemically selective ion sources and on-line mass separation. It gives access to high purity radioisotopes for R&D purposes in saturation activities up to ≈1 GBq. Thus promising radioisotopes that cannot be easily produced by established production methods can be supplied for fundamental research in radiobiology and preclinical studies before a dedicated production method has been developed.

Several disciplines (nuclear and atomic spectroscopy, mass measurements, nuclear astrophysics, nuclear solid state physics, etc.) depend on beams from this unique facility. Therefore radioisotopes for medical applications are only available a few times a year.

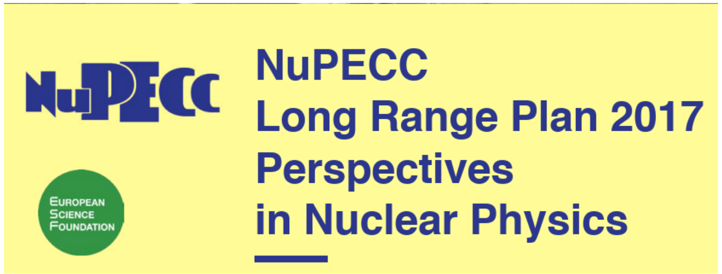
To overcome this restriction a new project called MEDICIS is now under construction. It will make use of the protons that have traversed the ISOLDE targets for additional beam dump irradiations of

New facilities for 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.



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.

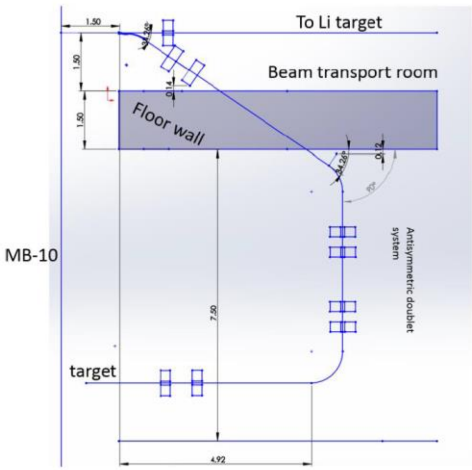
New facilities for radioisotope production

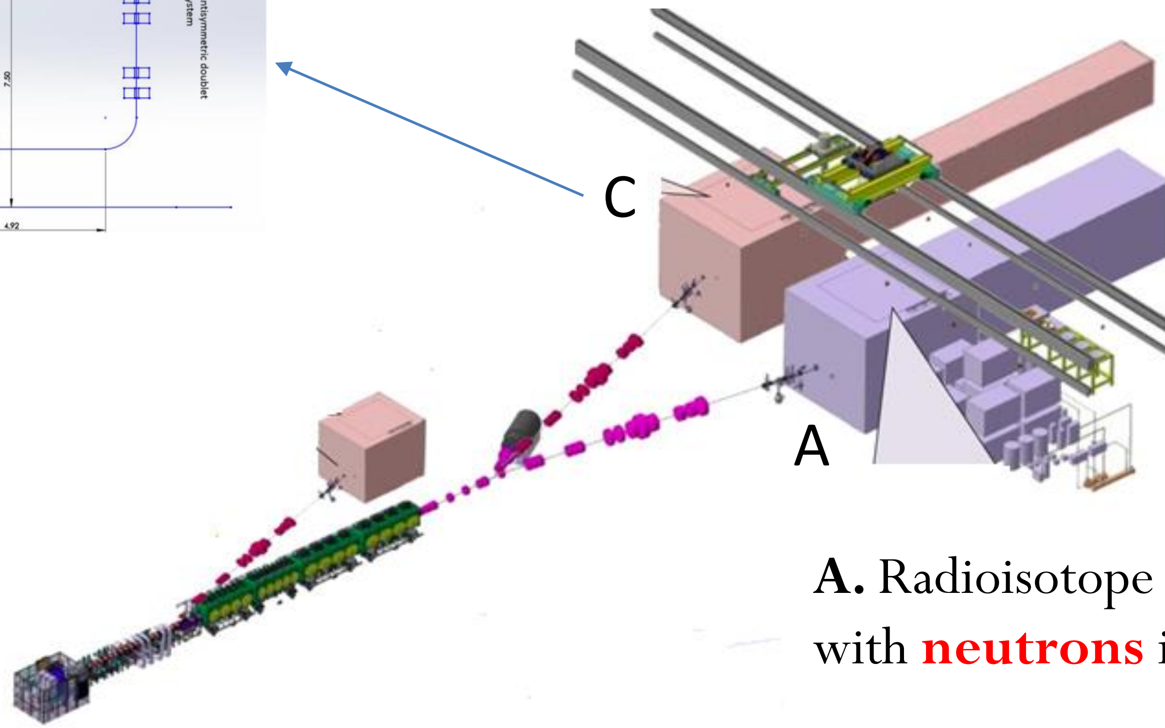
Accelerator-based could produce for R&D and regional quantities for clinical applications.

MEDICIS-ISOLDE-CERN is an excellent successful example.

Experimental Halls at DONES

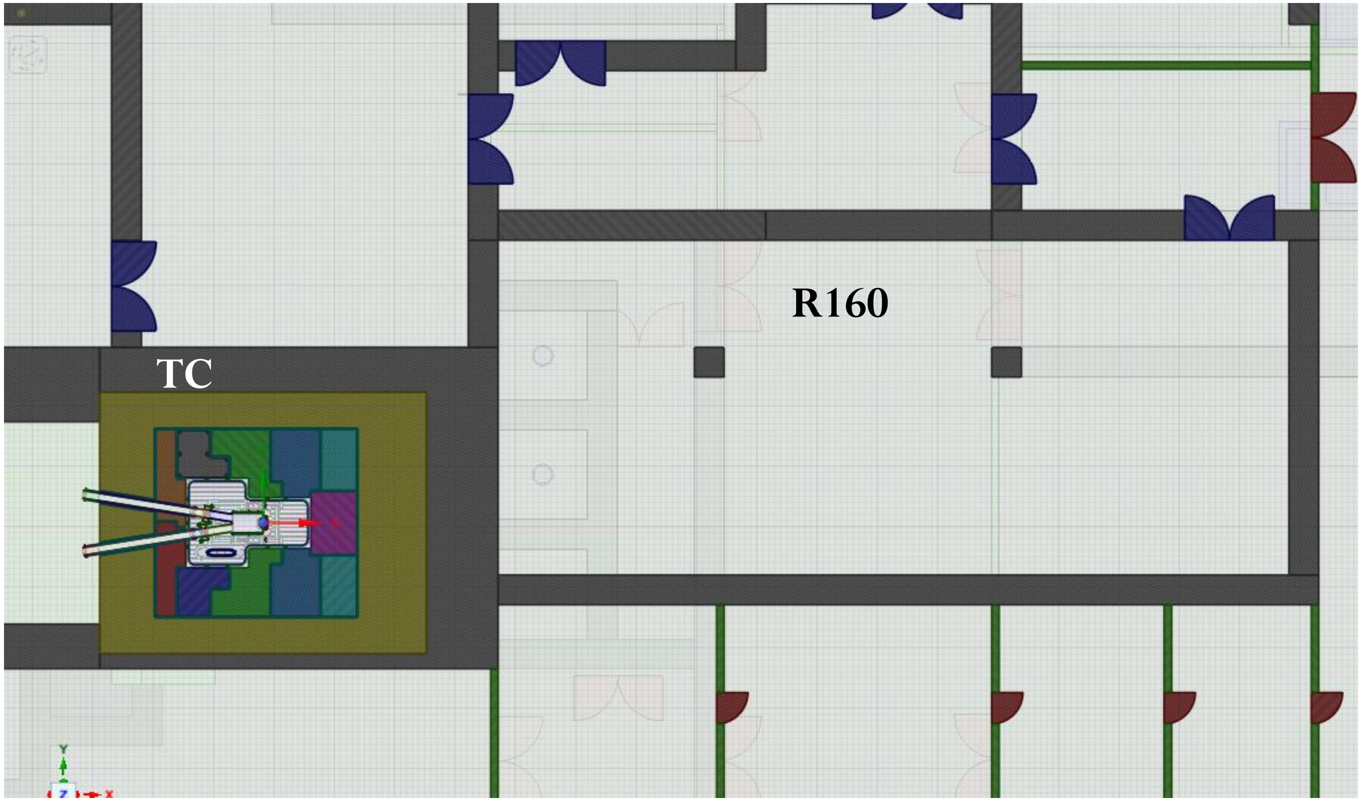
C. Radioisotope production with **deuterons**
Under study to deflect 1/100 beam ~ 1mA, 40 MeV





A. Radioisotope production with **neutrons** in the HFTM.

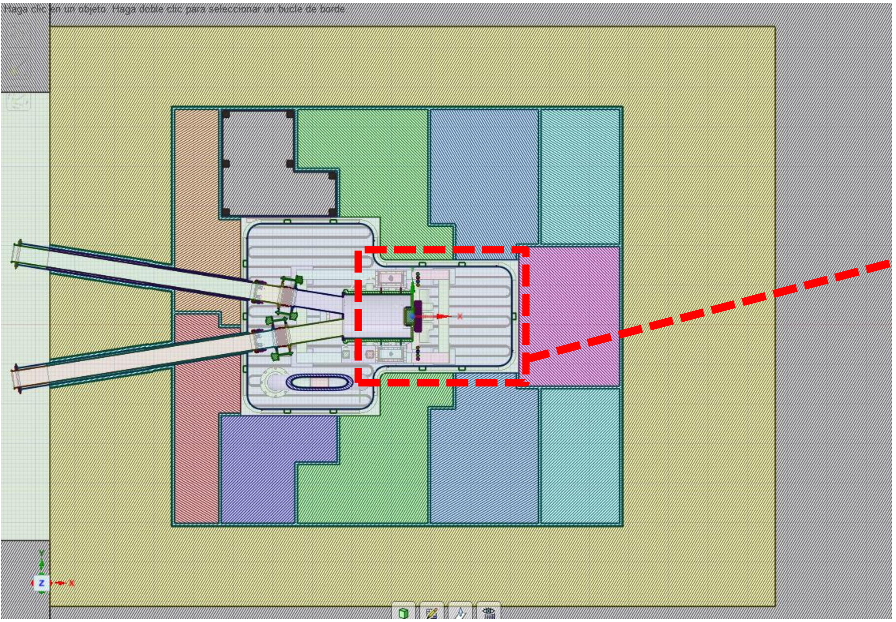
Neutrons: Test Cell and R160

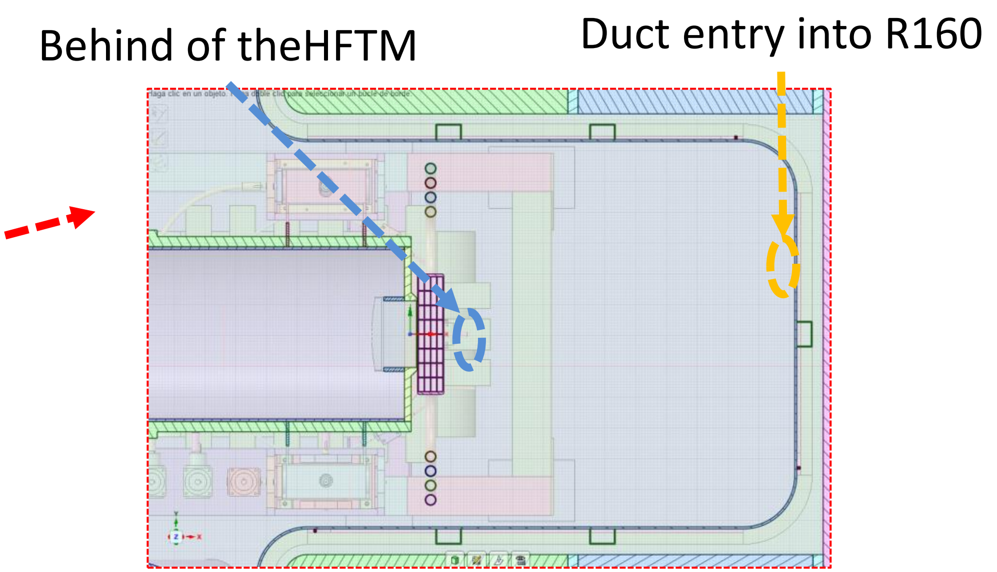


Lower neutron flux at R160.

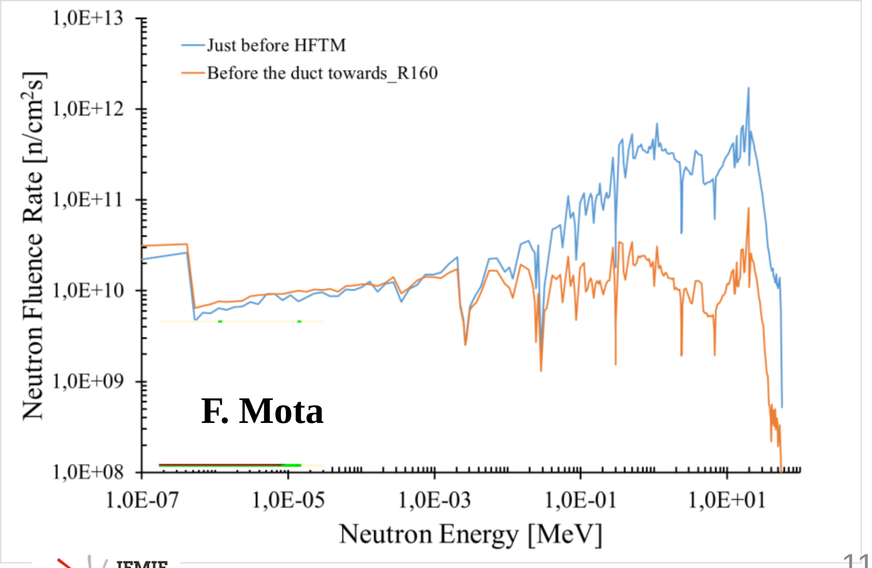
Only inside the TC radioisotope production would be significant.

Neutrons: Test Cell

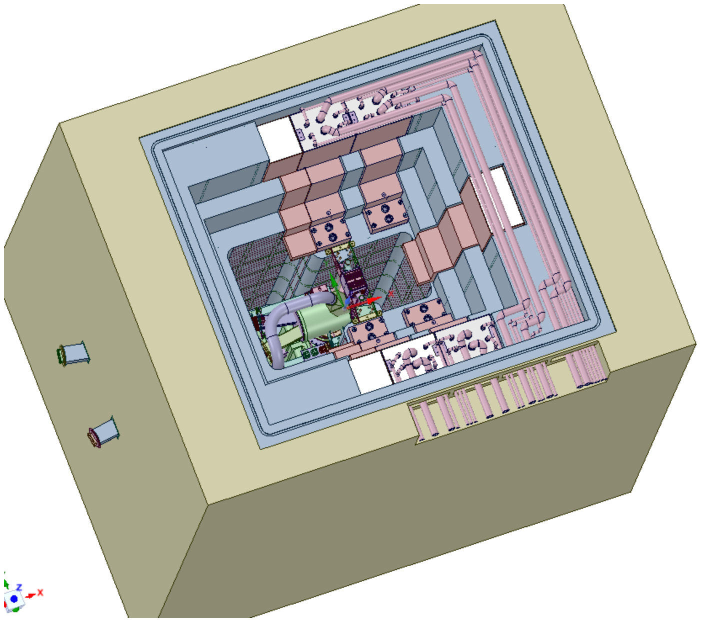


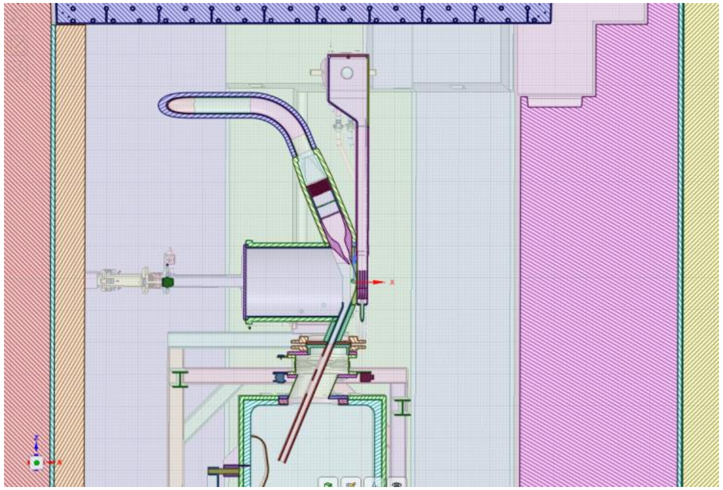


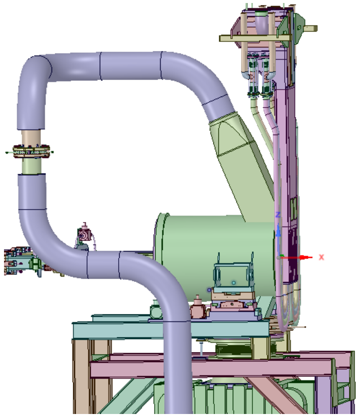
Even inside the TC, the fast neutron flux decreases significantly.



Neutrons: Test Cell



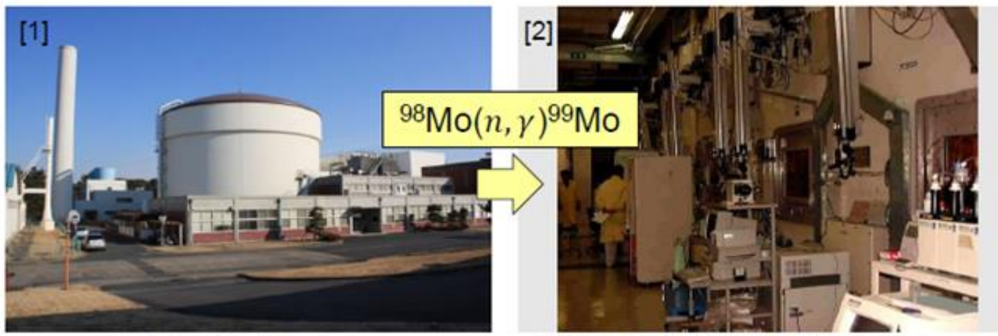




The design of the TC should consider a modification.
Tube crossing the TC keeping the properties of the inner atmosphere.

Mo/Tc production: benchmark case

We try to be as realistic as possible.
We have simulated the production of Mo/Tc at the JRR-3 nuclear reactor.
Neutrons have much lower energy than DONES neutrons
Thermal neutrons 8-9e13 n/(cm²·s)



JRR-3, JAEA, Tokai, Japan

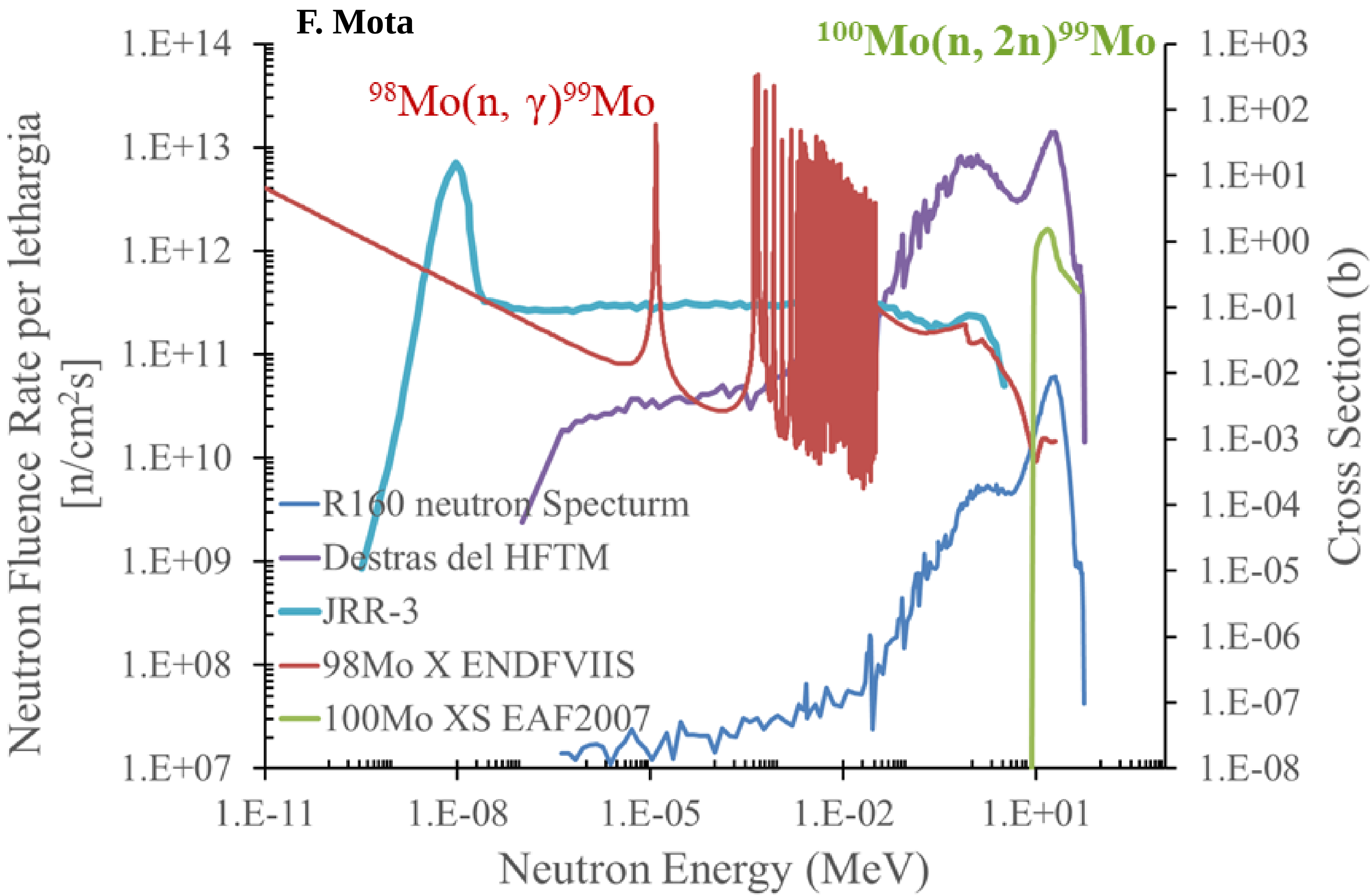
NUCEF-BECKY, JAEA, Tokai, Japan

MoO_3

Spark plasma sintering

RESULTS JRR-3		
7 days	Experimental	Simulated MCNP
Specific Activity (GBq/g ^{nat}Mo)	14.8	16.5

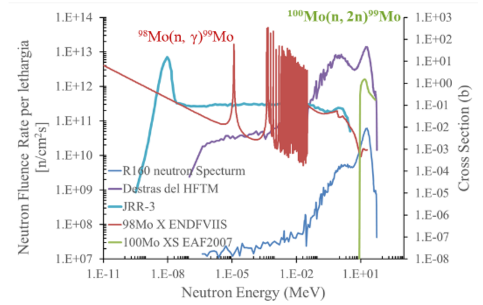
Mo/Tc production at DONES



At DONES the Mo/Tc production should be carried out with enriched ^{100}Mo samples

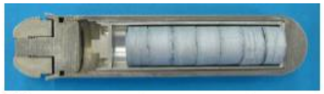
Mo/Tc production at DONES

We have studied the production with different realistic samples and in two possitions inside the TC:



Natural MoO_3 samples were irradiated with neutrons and the the Mo/Tc was extracted.

Enriched $^{100}MoO_3$ were irradiated at LINAC, (γ,n) and Mo/Tc was extracted.



Three such capsules, weighed 293.4 g (Mo: 195.6 g) in total,

ϕ10 mm, 3 mm-thick, 1.06 g

7 days of irradiation		
GBq/g Mo	Behind of HFTM	Entrance of duct
MoO_3 enriched 95% ^{100}Mo	56	2.24
MoO_3 with Mo nat	6.7	0.70

Mo/Tc production at DONES: conclusions

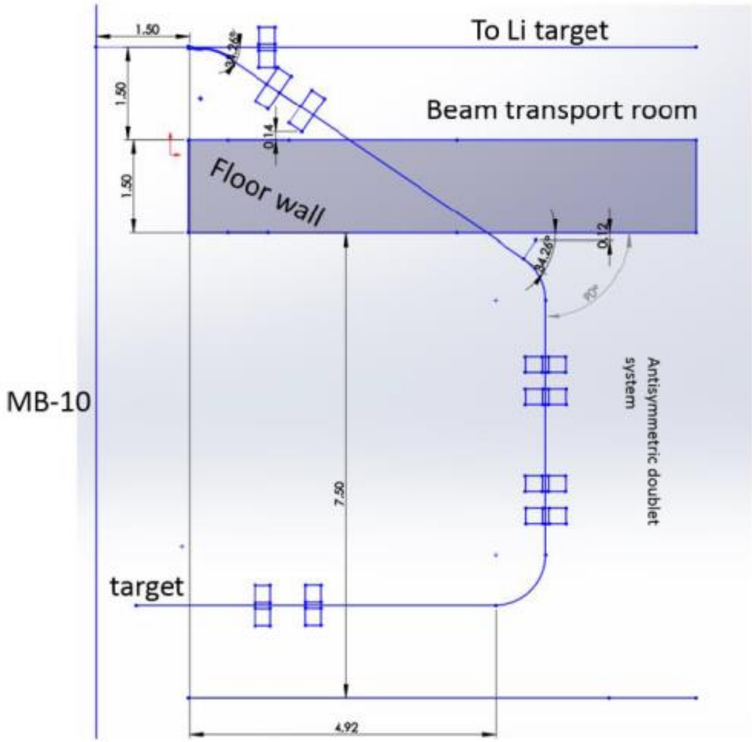
1) Considering the purification/extraction for $^{100}MoO_3$ enriched 95% as for the JRR Linac. Contaminations to be finally studied.

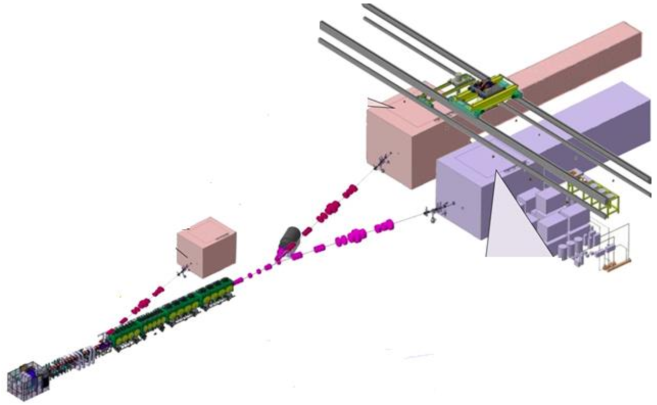
2) Tc Annual Demand in East Andalucia Health Area (3 Million people) is around 11 TBq (1 M€).

3) DONES could produce it in 4.5 months without or low impact in the irradiation of materials for fusion.

Deuterons at DONES

Experimental Hall at DONES

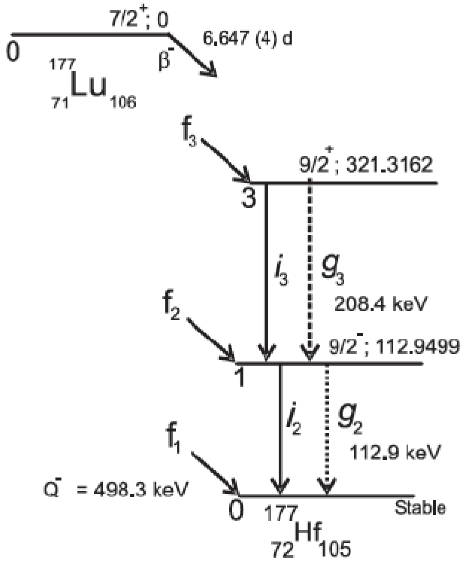




Radioisotope production with **deuterons.**

Under study to deflect 1/100 beam ~ 1mA, 40 MeV

^{177}Lu rising demand



Beta decay 40-150 keV.

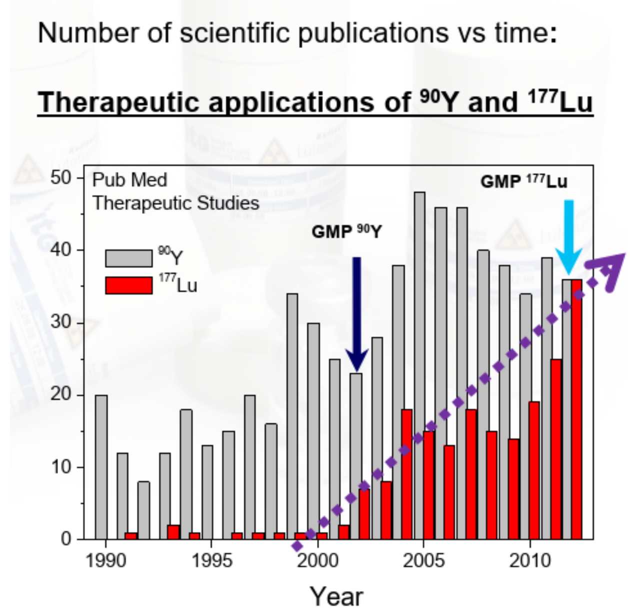
- ^{nat}Lu = ^{175}Lu (97.4%) + ^{176}Lu (2.6%)

- Electrons for therapy. Photons for imaging.

THERASNOSTIC

- ^{177}Lu – DOTA-TATE. Low toxicity (urine)

- Good results in gastroenteropancreatic neuroendocrine cancer.



^{177}Lu is one of the most demanding radioisotope.

It has been studied for many other kind of cancers.

^{177}Lu with neutrons at nuclear reactors

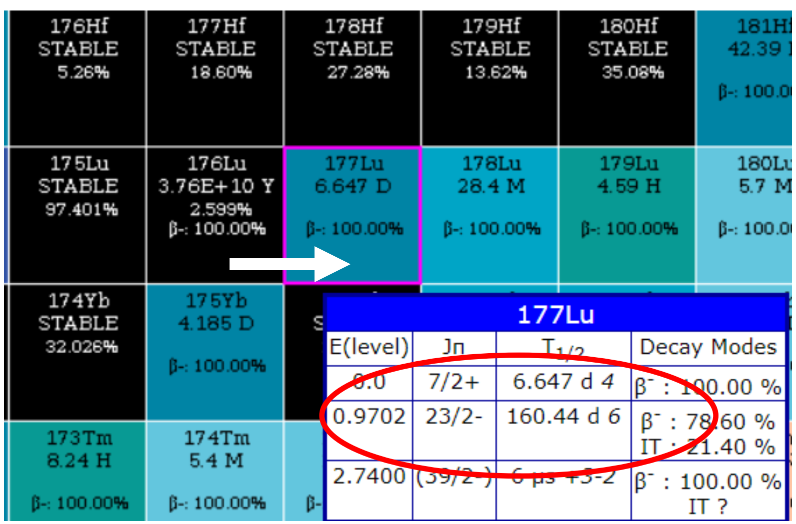
"Carrier Added"

^{176}Lu+n $\rightarrow$ ^{177}Lu+ ^{177m}Lu + γ

The more conventional in nuclear reactors

Higher production. Lower specific activity.

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

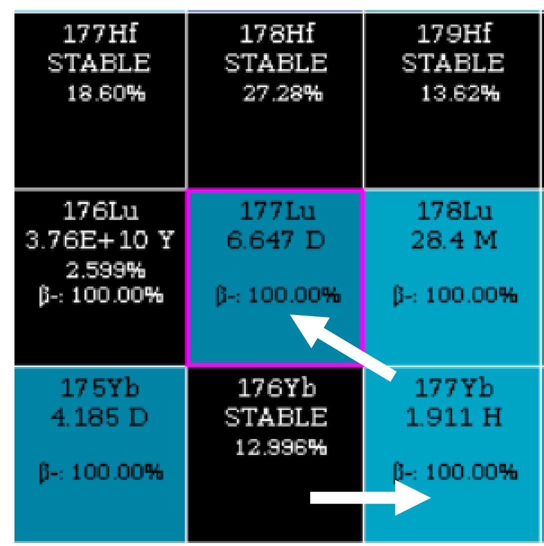


"Non Carrier Added"

^{176}Yb+n $\rightarrow \gamma$+ ^{177}Yb $\rightarrow$ ^{177}Lu

Lower production. Higher specific activity.

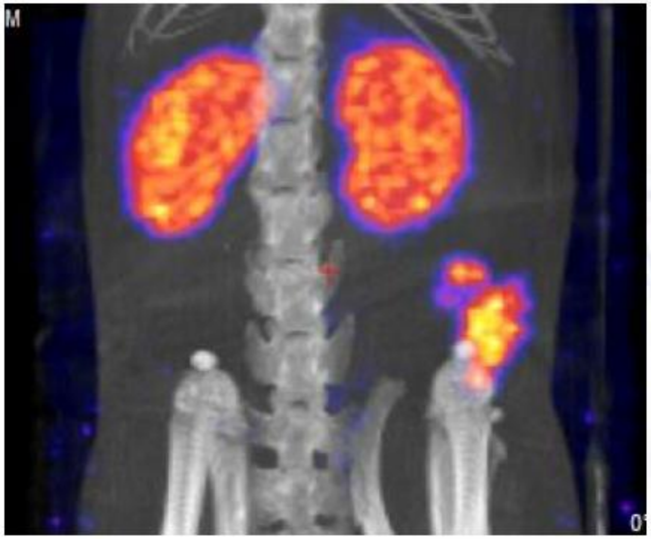
^{177m}Lu is negligible (<0.0001%)



^{177}Lu n.c.a. production is preferred

"Carrier Added"

$^{176}Lu + n$

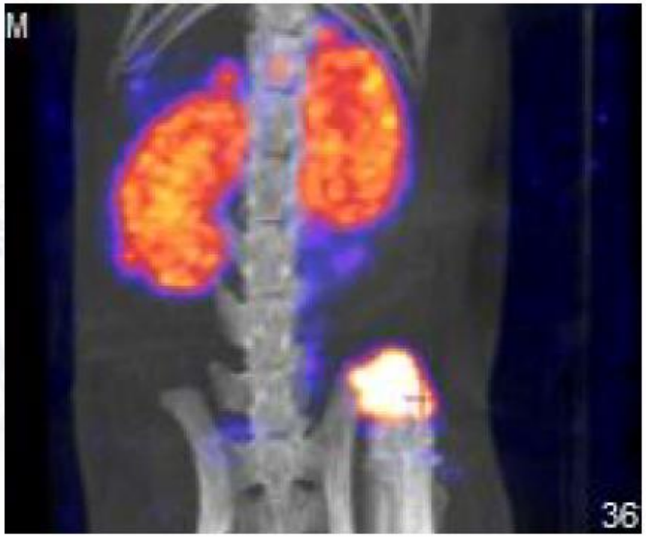


300 MBq of ^{177}Lu c.a.

Dose to tumor - 35 Gy

"Non Carrier Added"

$^{176}Yb + n$



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

Dose to tumor - 70 Gy

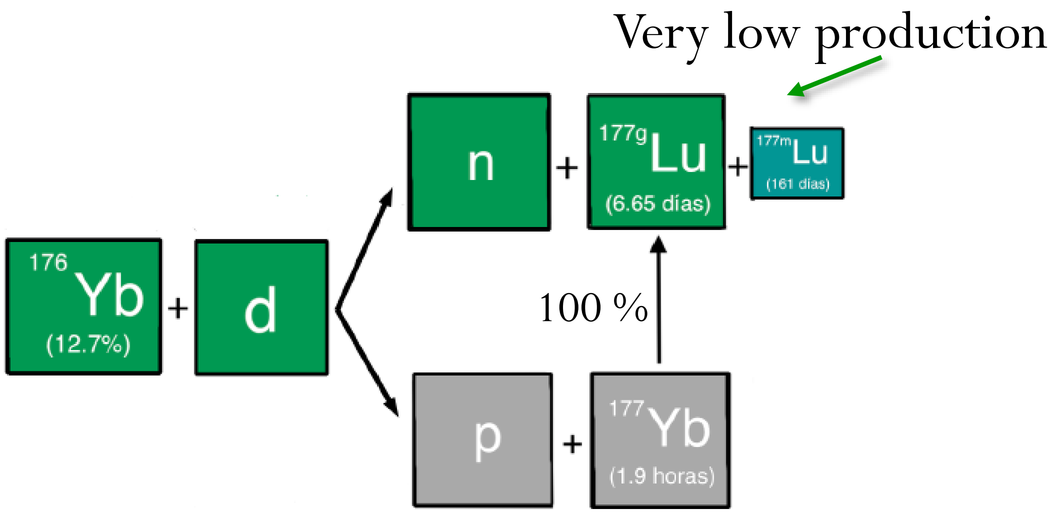
Marion de Jong et al.; 2012 ICTR-PHE

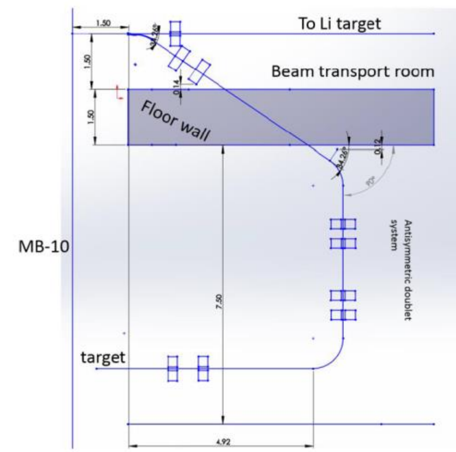
The "non carrier added" is the preferred production route with neutrons

Final specific activity and quality is higher after extraction

^{177}Lu with deuterons at DONES

With deuterium on ^{176}Yb two routes can be open: direct and indirect

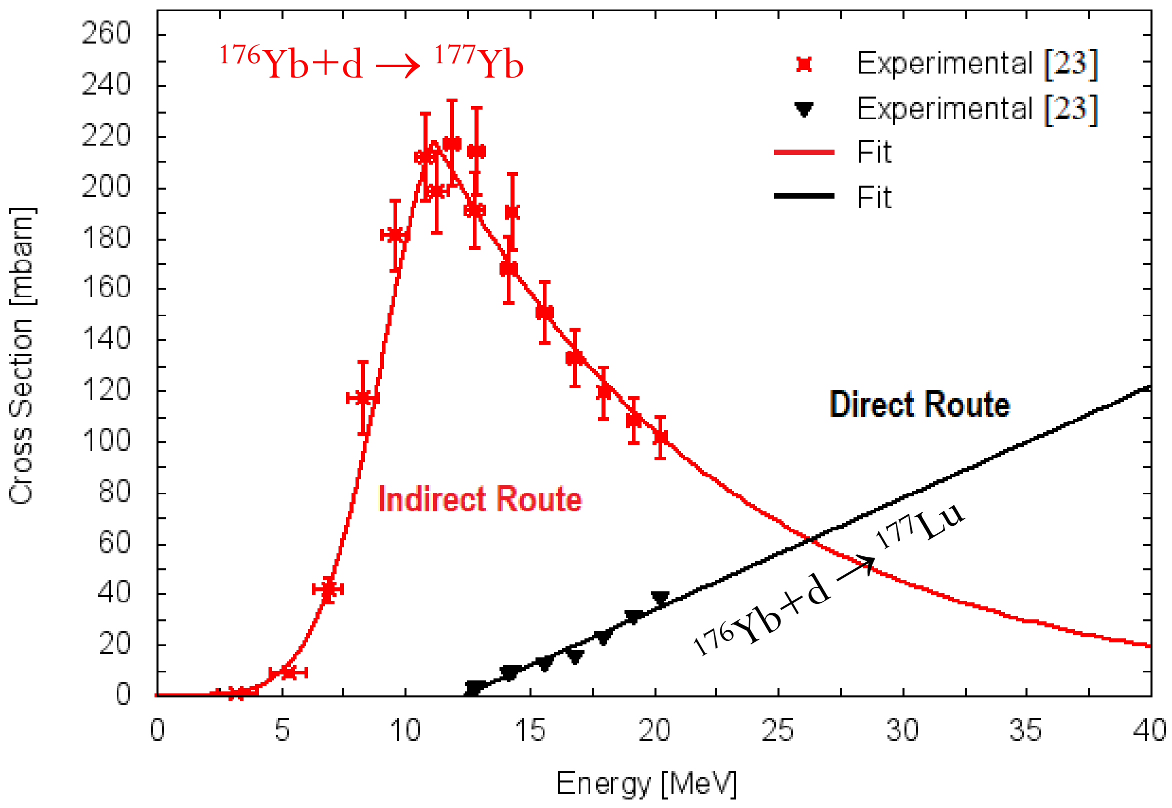




The deuterium production is as "added" compromise between the carrier added with negligible ^{177m}Lu and the non carrier added

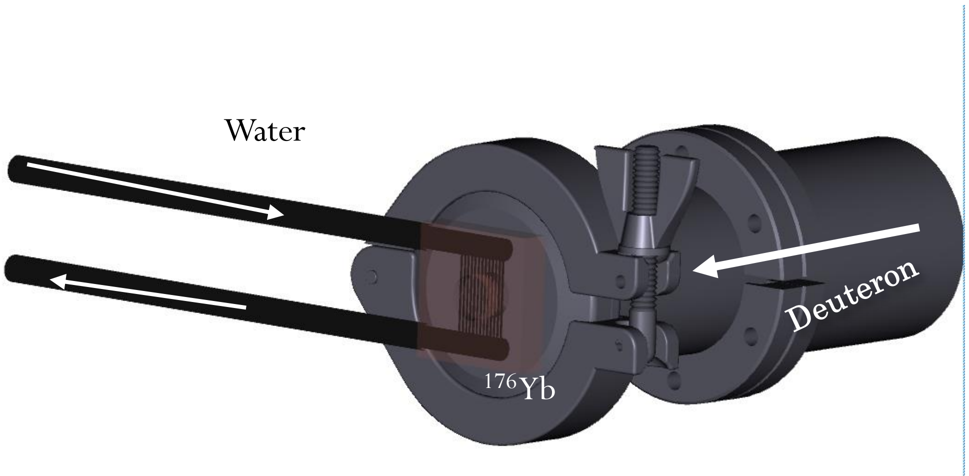
^{177}Lu with deuterons at DONES

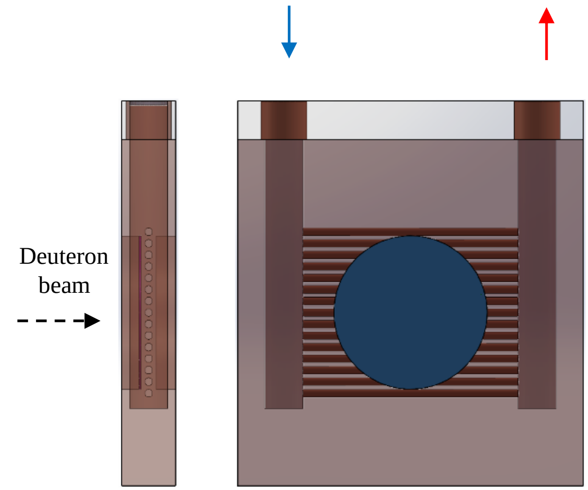
Experimental data available.

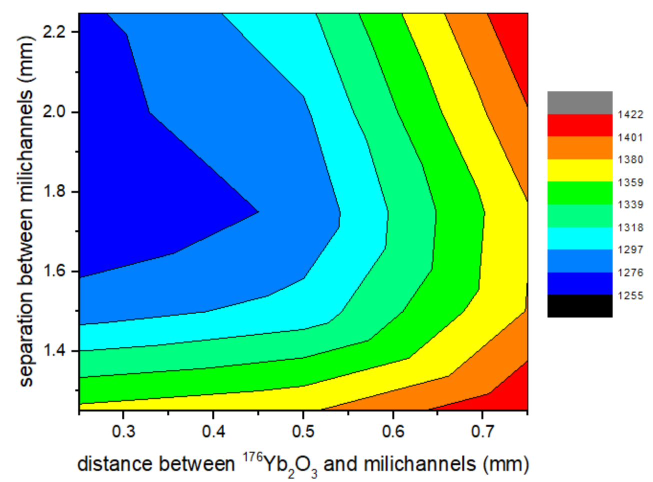


^{177}Lu with deuterons at DONES

We simulate a realistic Cu device water-cooled for sustaining the power delivered for the 40 MeV and 1 mA deuterium beam.



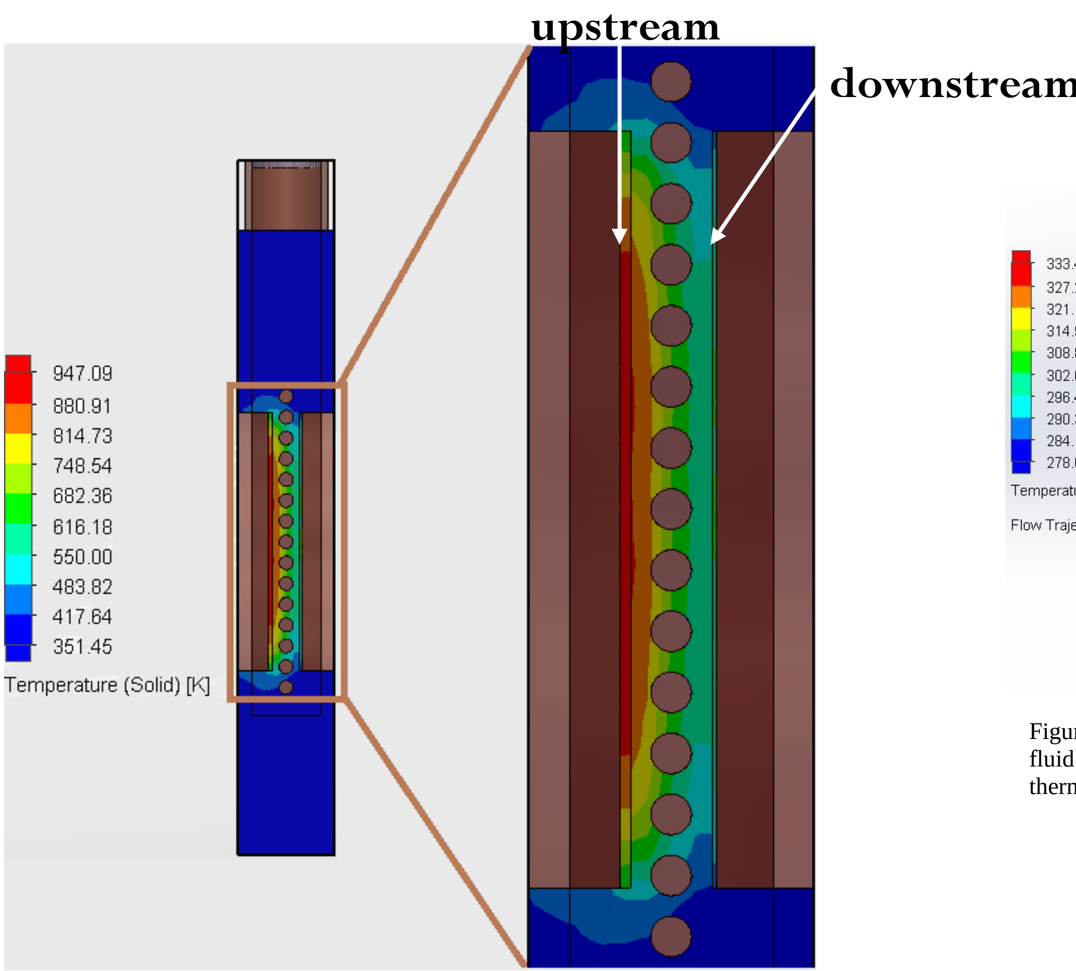




Exact dimensions of the backing are simulated with SolidWorks keeping the temperature well below the melting points.

^{177}Lu with deuterons at DONES

Two evaporated samples upstream and downstream the millichannels



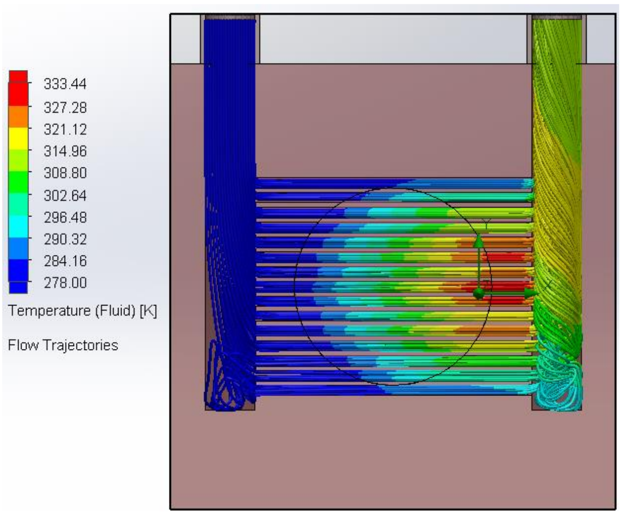


Figure 6. Temperature distribution of the cooling system fluid for a cooling water speed of 12 m/s and $4\cdot10^{-7}$ $K\cdot m^2/W$ thermal contact resistance.

^{177}Lu with deuterons at DONES

Reaction	Irradiation time (d)	Activity (GBq)	Specific Activity (GBq/mg)
$^{176}Yb(n,\gamma)^{177}Yb \rightarrow ^{177}Lu$	7	590	1.11
$^{176}Yb(d,n)+^{176}Yb(d,p)$	3.5	1st sample	
		234	0.37
		2nd sample	
		223	0.74

$^{176}Yb_2O_3$ samples enriched at 99%, we already used it at n_TOF-CERN experiment.

40 MeV and 1 mA Deuterium beam, the same SA is produced in half of the time than nuclear reactors with neutrons.

1 treatment with ^{177}Lu: 4 doses, 7.4 GBq/dose, 14 k€/dose.
1 day at DONES: 120 GBq after purification, 224 k€.

Conclusions

1) Production of radioisotopes is important from social and economical point of view.

2) Supply crisis could be avoided. March 2022 ^{177}Lu crisis in Andalusia hospitals.

3) Research on new radiopharmaceutical drugs would be pushed.

4) ^{99}Mo radioisotope with neutrons (fast) inside Test Cell shows preliminary promising results.

5) ^{177}Lu with deuterons in R026 shows preliminary promising results.

6) Work ongoing. Open new collaborations for experimental production with deuterons Tm165, Sc45-Ti44, Orleans (France). New routes need regulation.

Thank you for the attention