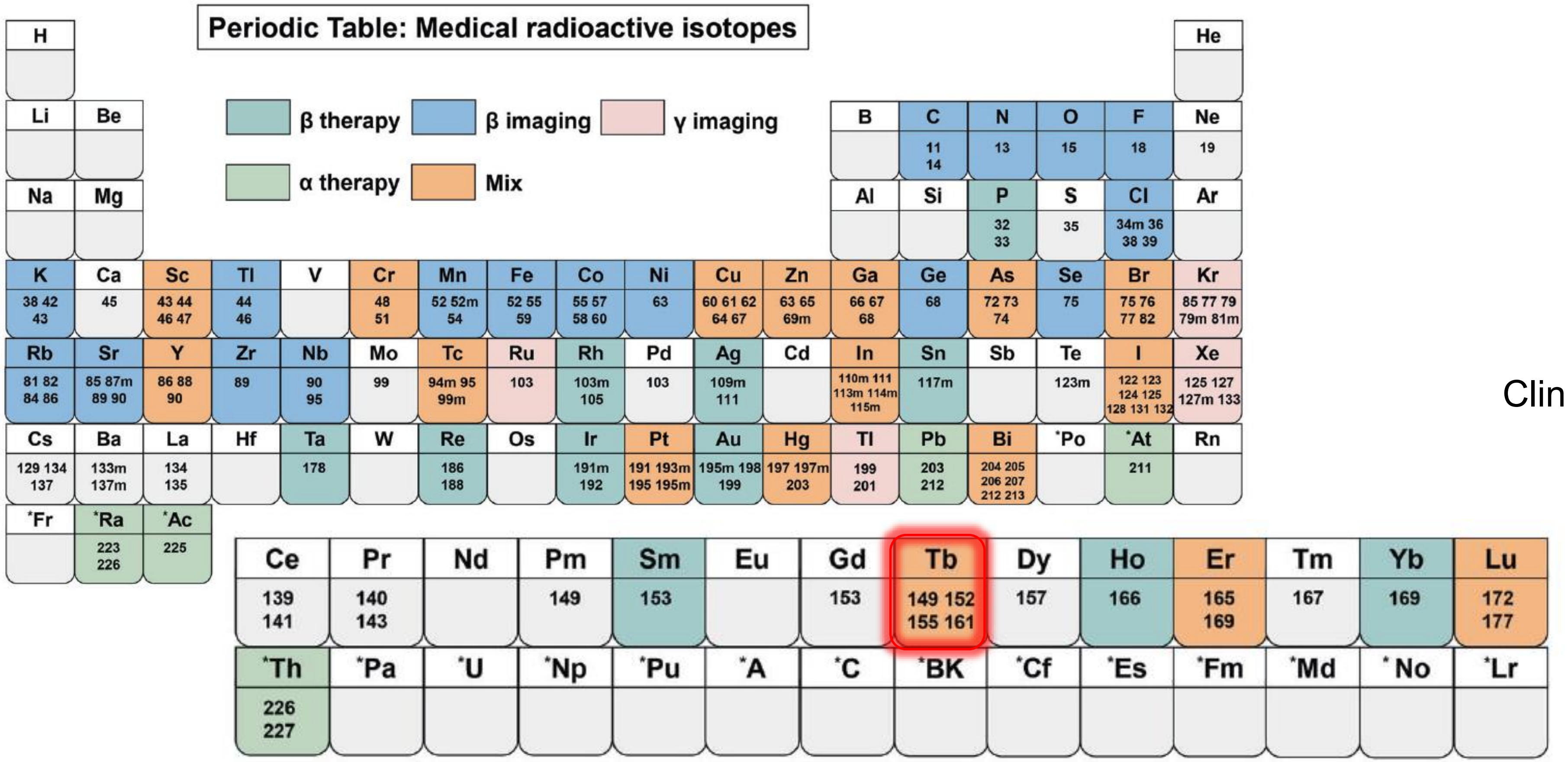
Development of Terbium Fluoride Beams for Medical Applications

EMIS XX 2025, Whistler, Canada

23rd October 2025

Wiktoria Wojtaczka, KU Leuven

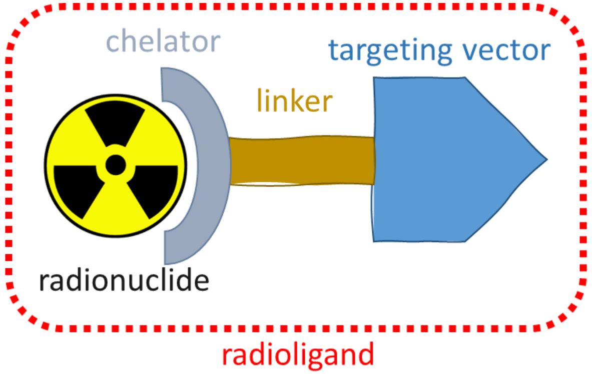
Why terbium?



S. Zhang, Signal Transduction and Targeted Therapy **10**, 1 (2025)

2 FDA-approved agents

Clinical trials for many indications

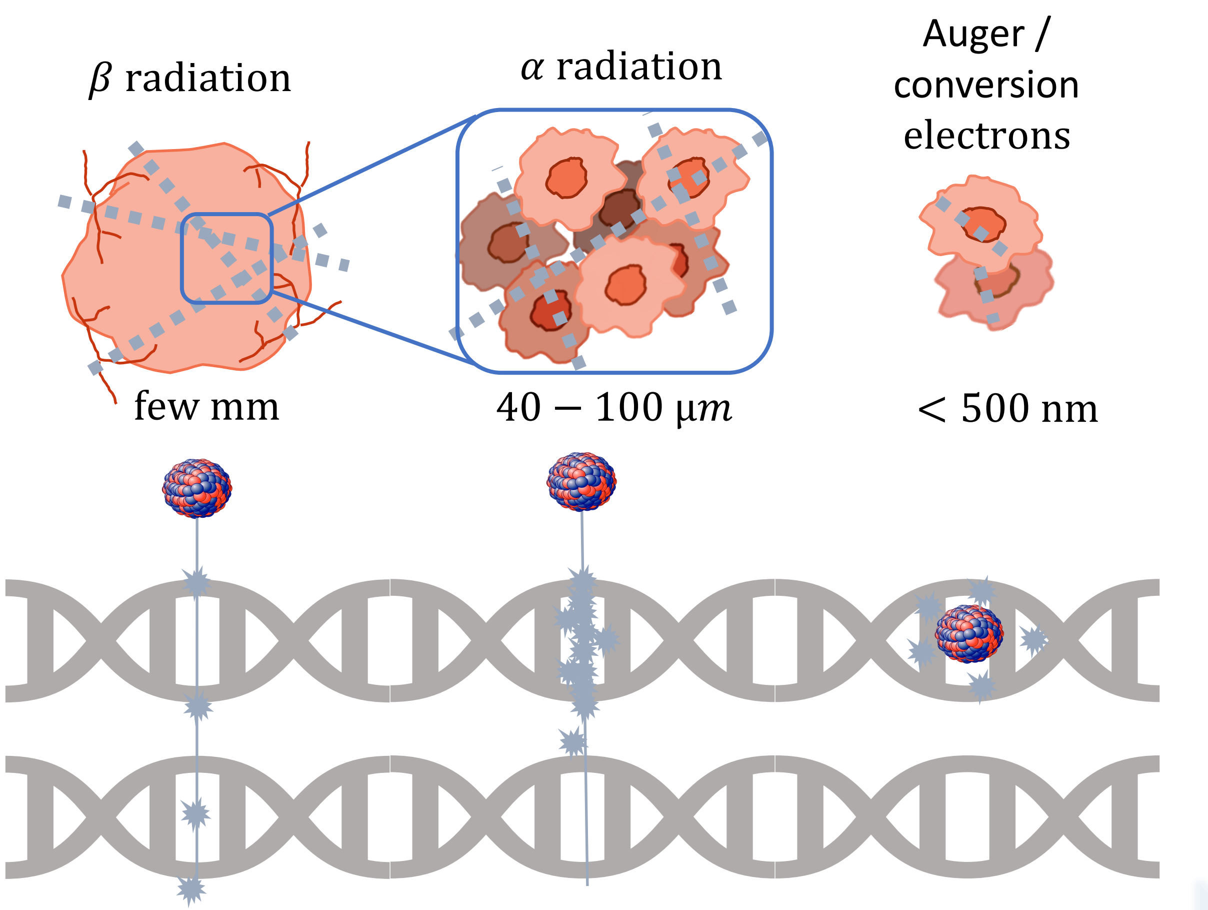


By studying Tb molecules, we also learn about other lanthanides

KU LEUVEN

Range

Ionisation pattern



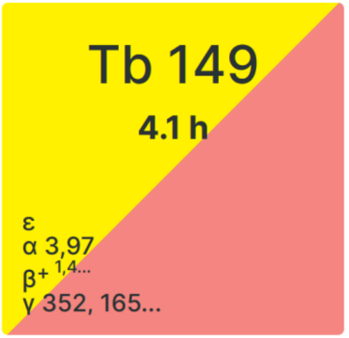
Long range
Less complex DNA damage

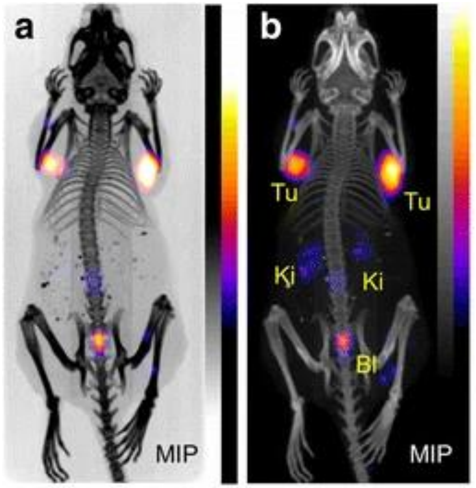
Short range
More complex DNA damage

All modalities in nuclear medicine
Chemically identical
Elegant theragnostics

C. Müller et al. J Nucl Med 53.12 (2012): 1951-1959.

α-Therapy
PET (β⁺)





C. Müller et al. **2017** EJNMMI radiopharm. chem. **1**, 5

EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

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

Terbium-149 for targeted alpha therapy

11 January 2023

Nick van der Meulen[1], Cristina Müller[1], Anzhelika Moiseeva[1], Colin Hillhouse[1], Pascal Grundler[1], Stuart Warren[1], Maryam Mostamand[1], Ana Katrina Mapanao[1], Avni Mehta[1], Karl Johnston[2], Ulli Köster[3]

α-Therapy
PET (β^+)

Tb 149

4.1 h

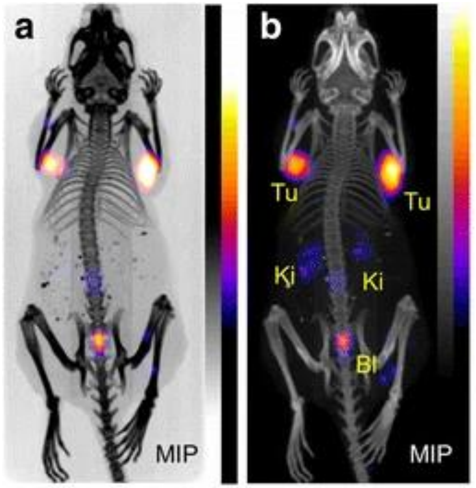
ε
α 3,97
β^+ 1,4...
γ 352, 165...

PET (β^+)

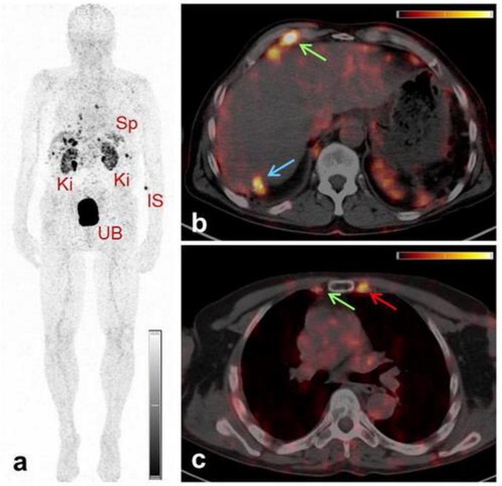
Tb 152

17.5 h

ε
β^+ 3.0, 2.6, 2.0...
γ 344, 271, 586...



C. Müller et al. **2017** EJNMMI radiopharm. chem. **1**, 5



R. Baum et al. Dalton Trans **2017**;46:14638–46

α-Therapy
PET (β^+)

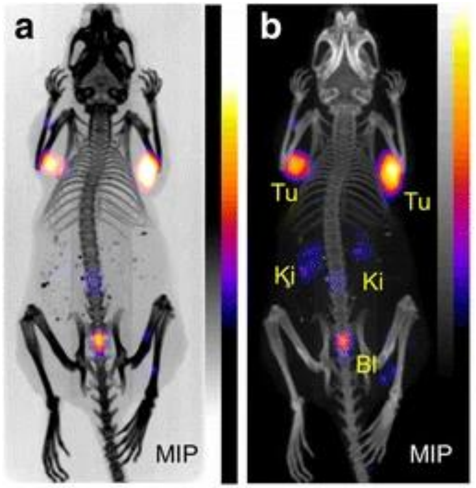
Tb 149
4.1 h
ε
α 3,97
β^{+} 1,4...
γ 352, 165...

PET (β^+)

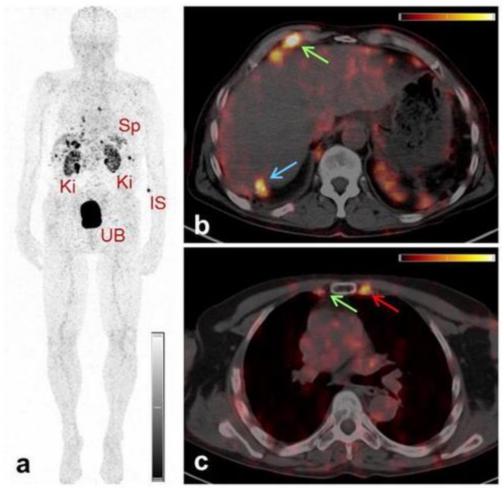
Tb 152
17.5 h
ε
β^+ 3.0, 2.6, 2.0...
γ 344, 271, 586...

SPECT (γ)

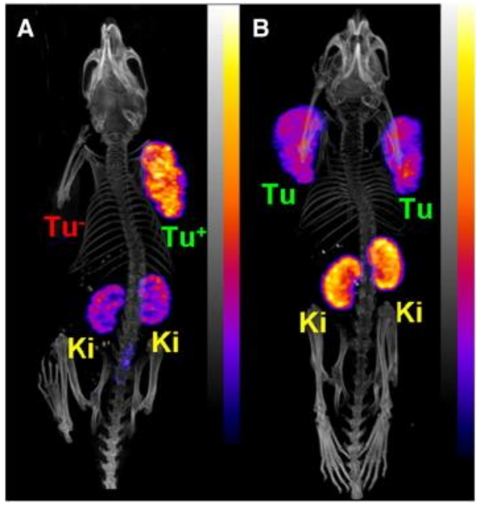
Tb 155
5.3 d
ε
γ 87, 105, 180...
e^-



C. Müller et al. **2017** EJNMMI radiopharm. chem. **1**, 5



R. Baum et al. Dalton Trans **2017**;46:14638–46



C. Müller et al **2014** Nuc Med Biol 41:e58-e65

α-Therapy
PET (β^+)

PET (β^+)

SPECT (γ)

SPECT (γ)
β^--Therapy
Auger-e^- Therapy

Tb 149
4.1 h

Tb 152
17.5 h

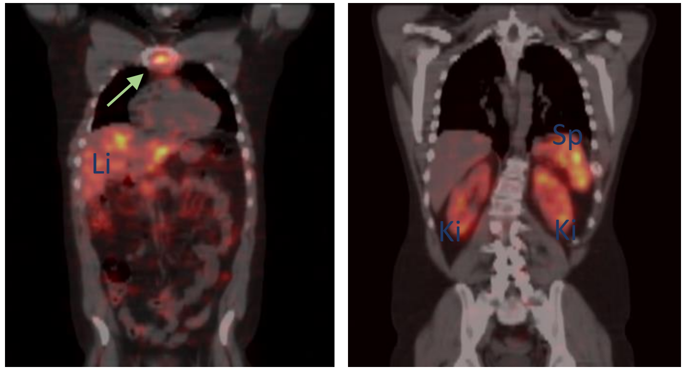
Tb 155
5.3 d

Tb 161
6.95 d
β^- 0.5, 0.6...
γ 26, 49, 75...
e^-

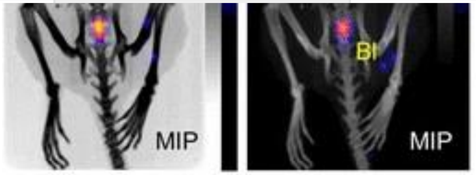
1	Combined Beta- Plus Auger Electron Therapy Using a Novel Somatostatin Receptor Subtype 2 Antagonist Labelled With Terbium-161 (**161Tb**-DOTA-LM3)	NCT05359146	Recruiting	• Neuroendocrine Neoplasia's (NENs) • Gastroenteropancreatic Neuroendocrine Tumour (GEP-NET)	• Drug: **161Tb**-DOTA-LM3 • Drug: 177Lu-DOTATOC	University Hospital, Basel, Switzerland	Interventional
2	EValuation of radIOLigand Treatment in mEn With Metastatic Castration-resistant Prostate Cancer With [**161Tb**]Tb-PSMA-I&T	NCT05521412	Recruiting	• Prostate Cancer • Metastatic Castration-resistant Prostate Cancer	• Drug: [161 Tb]Tb PSMA I&T	Peter MacCallum Cancer Centre, Australia	Interventional
3	Targeted Radionuclide Therapy in Metastatic Prostate Cancer Using a New PSMA Ligand Radiolabelled With Terbium-161 (**161Tb**-SibuDAB) - Dose Identification/Escalation Phase Ia/b Study	NCT06343038	Recruiting	• Castration-resistant Prostate Cancer	• Drug: Injection, **161Tb**-SibuDAB,1GBq • Drug: Injection, 177Lu-PSMA-I&T, 1GBq • Drug: Injection, **161Tb**-SibuDAB, Dose Escalation	University Hospital, Basel, Switzerland	Interventional

clinicaltrials.gov

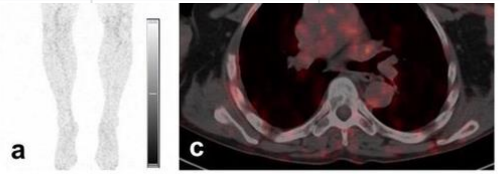
Patient with NEN (600 MBq ^{161}Tb-DOTATOC)



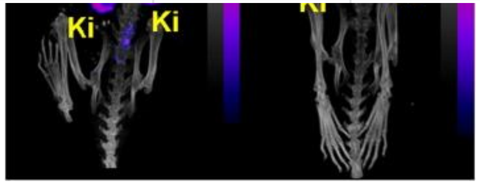
R. Baum & A. Singh et al. **2021**, J Nucl Med 62:1391.



C. Müller et al. **2017** EJNMMI radiopharm. chem. **1**, 5

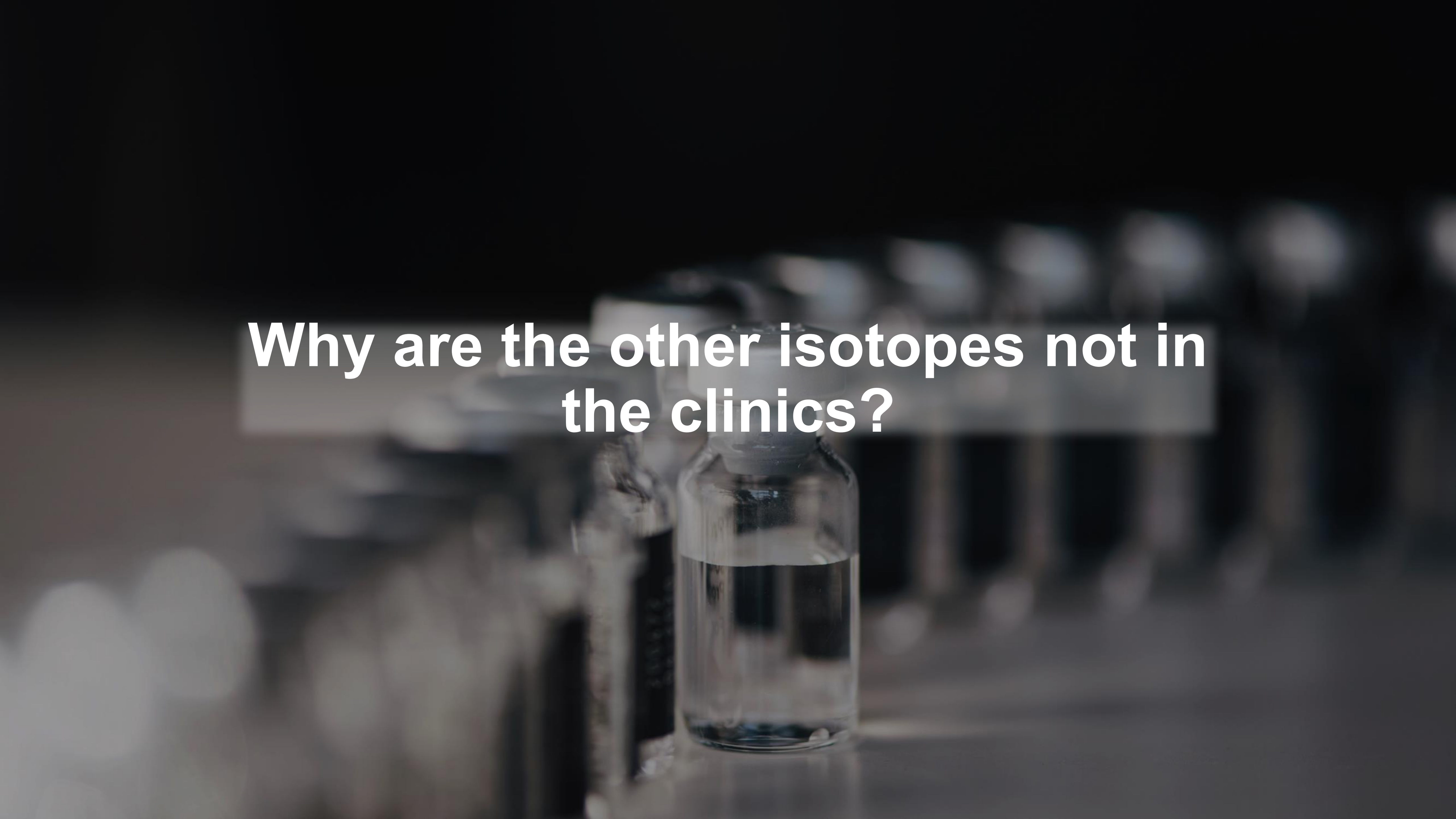


R. Baum et al. Dalton Trans **2017**;46:14638–46



C. Müller et al **2014** Nuc Med Biol 41:e58-e65

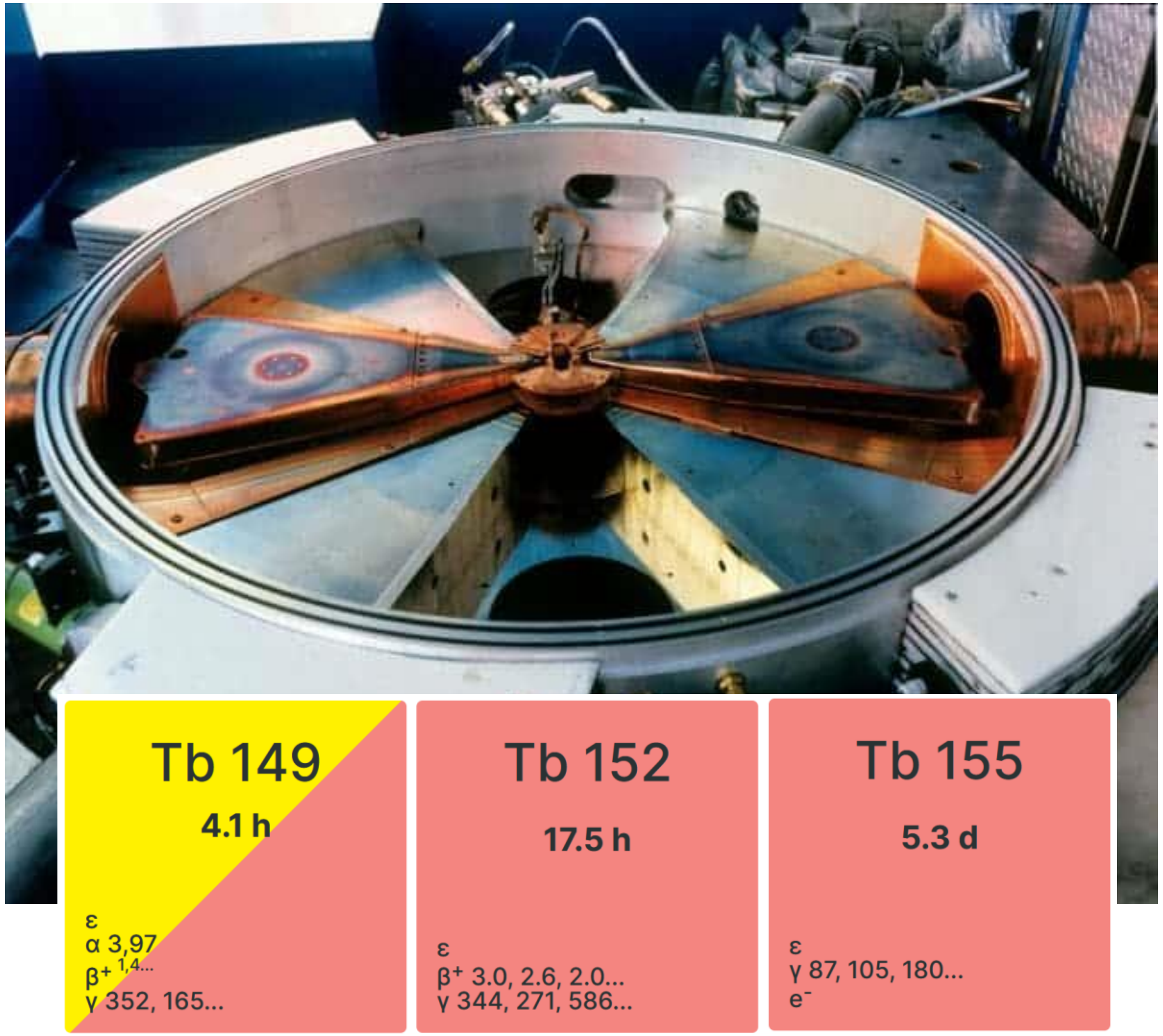
3 clinical trials ongoing
many cases of compassionate use



Why are the other isotopes not in the clinics?

Possible production routes of Tb

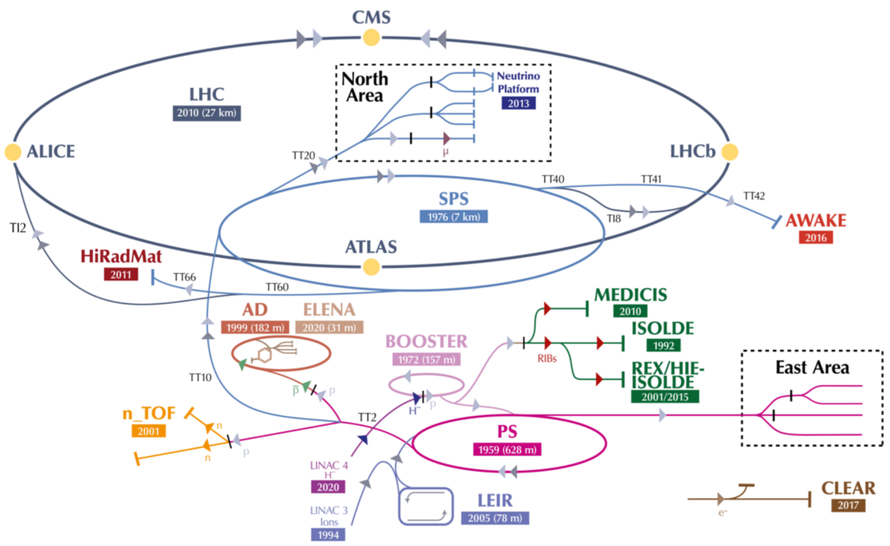
TERTHERA
TERBIUM THERANOSTICS



NEA (2020), BR2-reactor of SCK-CEN, OECD Publishing, Paris

in most cases mass separation required

Producing Tb at CERN



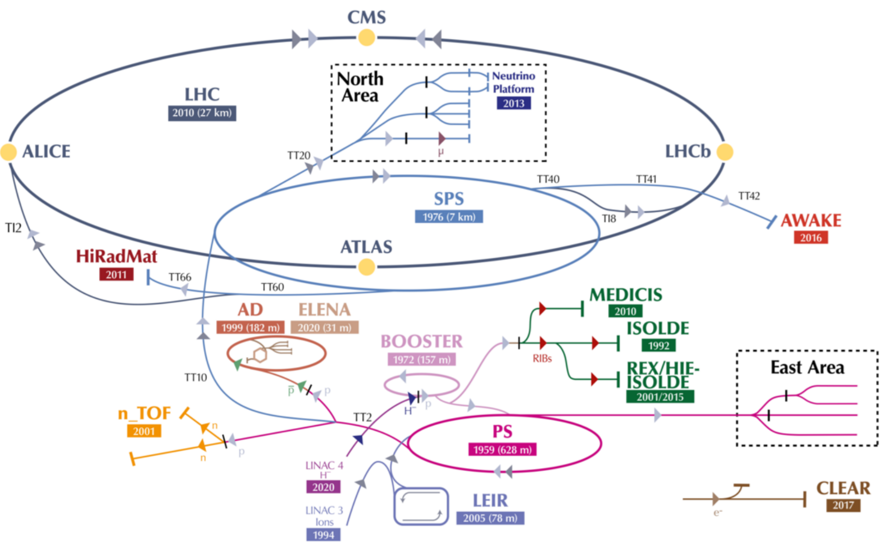
Overview of ISOL facilities and production techniques — *João Pedro Ramos*

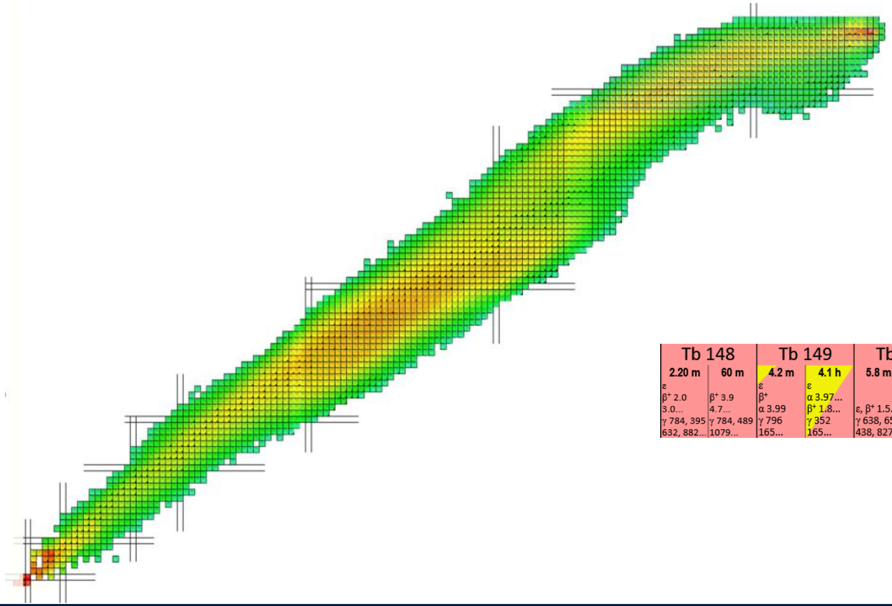
MacDonald AB, Fairmont Chateau Whistler — 10:30 - 11:00

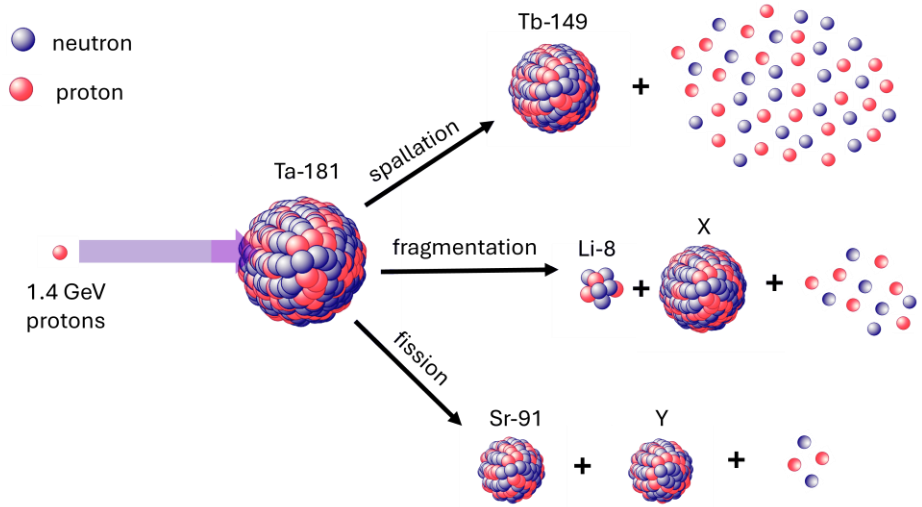
Development of molecular beams at ISOLDE — *Mia Au*

MacDonald AB, Fairmont Chateau Whistler — 08:30 - 09:00

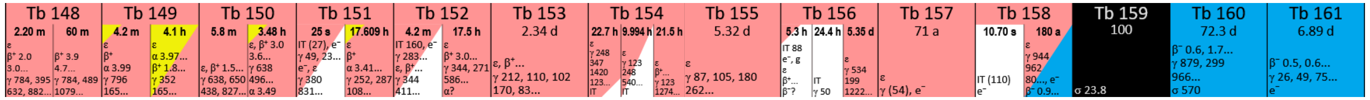
Producing Tb at CERN







1.4 GeV protons, spallation on Ta



many Tb isotopes produced

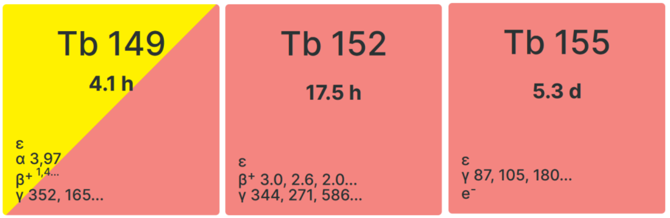
KU LEUVEN

Medical grade ^{149,152,155}Tb product

Mass separation for isobaric selection

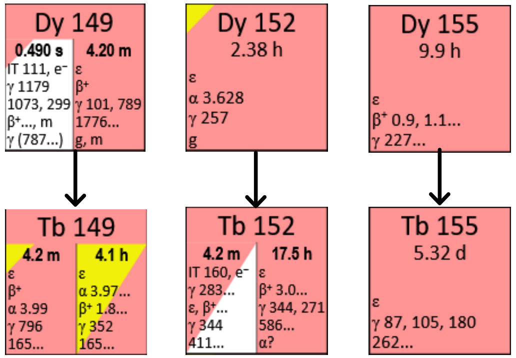
+

Chemical separation for elemental selection



Isotopically pure $^{149,152,155}Tb$

(in Europe)



Online

CERN ISOLDE

Tb 149
4.12 h

Tb 152
17.5 h

Tb 155
5.23 d

Spallation on Ta M.P. 2996°C

+

mass separation

Atomic

Dy Tb

B.P. 2567°C B.P. 3230°C

Offline

Tb 155
5.23 d

Spallation on Ta

Mass separation CERN MEDICIS

Atomic

Dy then Tb **Tb**

Gd irradiation

PSI Arronax Nantes

Radiochemistry

Mass separation

Atomic

Tb

Isotopically pure $^{149,152,155}Tb$

Online

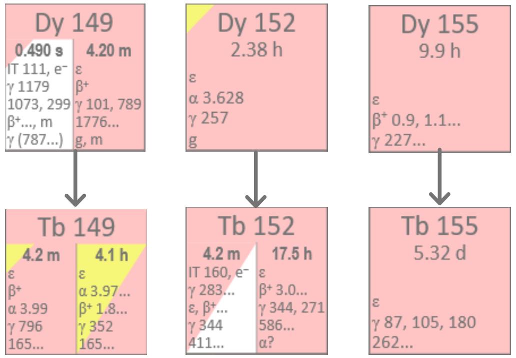
Tb 149
4.12 h

Tb 152
17.5 h

Tb 155
5.23 d

Offline

Tb 155
5.23 d



Spallation on Ta

Gd irradiation

PSI

Arronax Nantes

Radiochemistry

Spallation on Ta M.P. 2996°C

m

	Tb-149	Tb-155
ISOLDE	> 1GBq/night	100s MBqs/week
MEDICIS	x	few MBqs/week

on

Mass separation

Atomic

Atomic

Atomic

Dy

Tb

B.P. 2567°C

B.P. 3230°C

Dy then Tb

Tb

Tb

Isotope Separation OnLine

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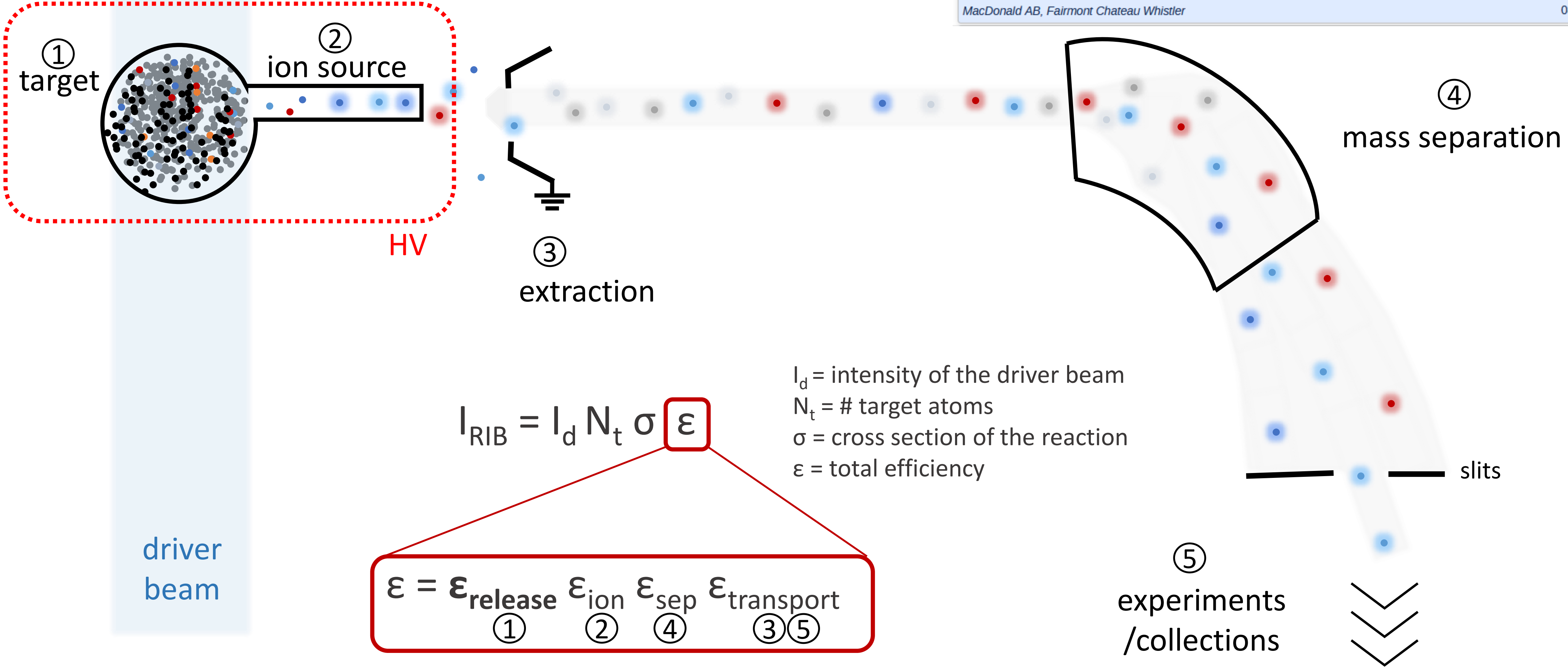
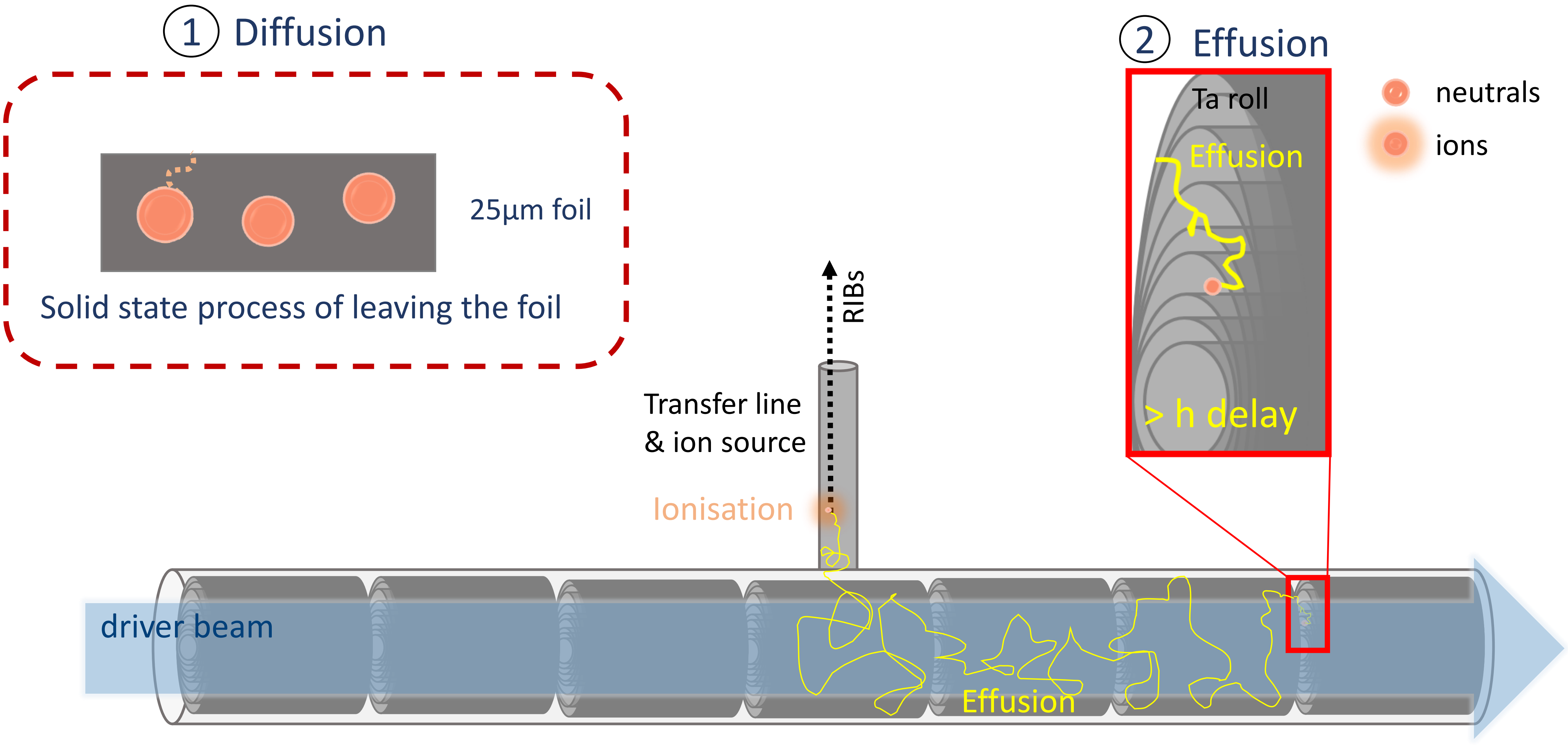


$$I_{RIB} = I_d N_t \sigma \boxed{\varepsilon}$$

I_d = intensity of the driver beam
N_t = # target atoms
σ = cross section of the reaction
ε = total efficiency

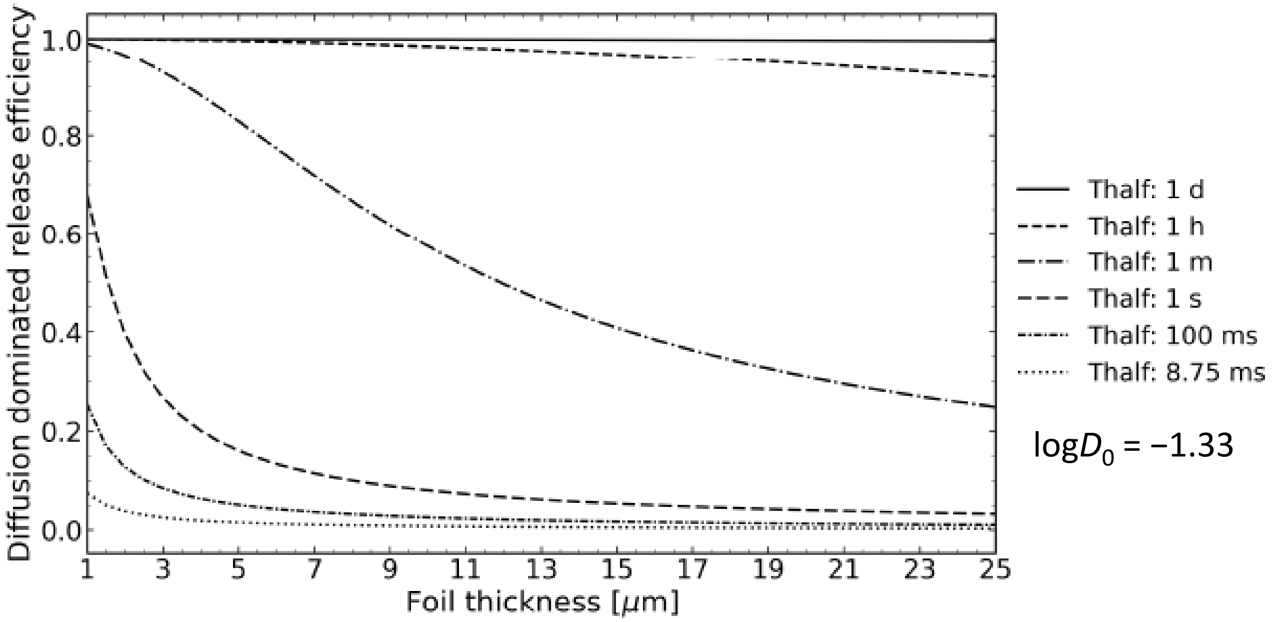
$$\varepsilon = \underbrace{\boldsymbol{\varepsilon}_{\mathbf{release}}}_{①} \underbrace{\varepsilon_{ion}}_{②} \underbrace{\varepsilon_{sep}}_{④} \underbrace{\varepsilon_{transport}}_{③⑤}$$

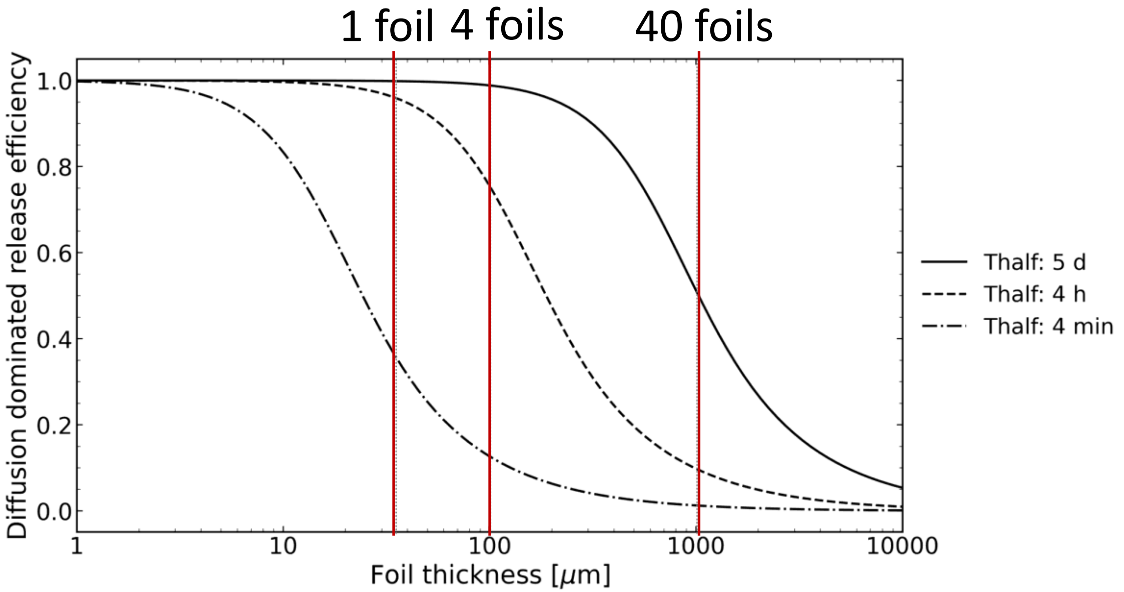
Release



1 Diffusion
25µm foil
Solid state process of leaving the foil
2 Effusion
Ta roll
Effusion
> h delay
neutrals
ions
RIBs
Transfer line
& ion source
Ionisation
driver beam
Effusion
Target container

1. Diffusion





for 25um foil >95% of Tb with half-life 1h should leave the foil

In the case of foil welding, the release efficiency decreases

R. Kirchner NIMB **70**,186–199 (1992)

G.J. Beyer et al NIMB **204**, 225–234 (2003)

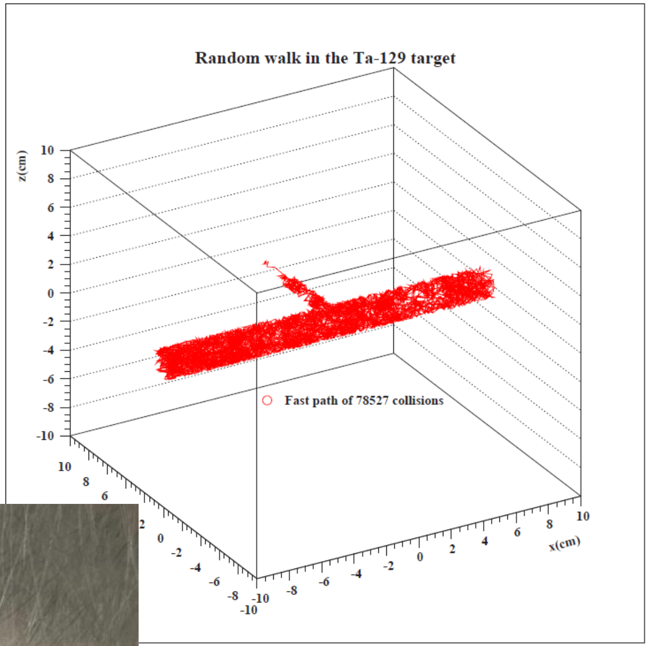
2. Effusion

>> 60 000 collisions in a Ta target

Tb 0.03s sticking time at 2400^{o}C for Ta*

→ average delay on the order of **hours**

(Dy ~0.0003s sticking time – 100x faster)

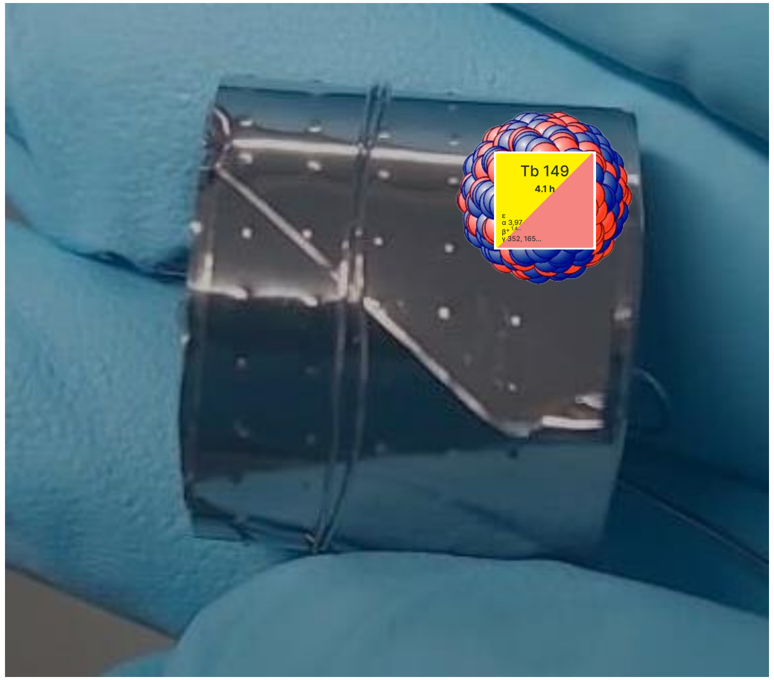


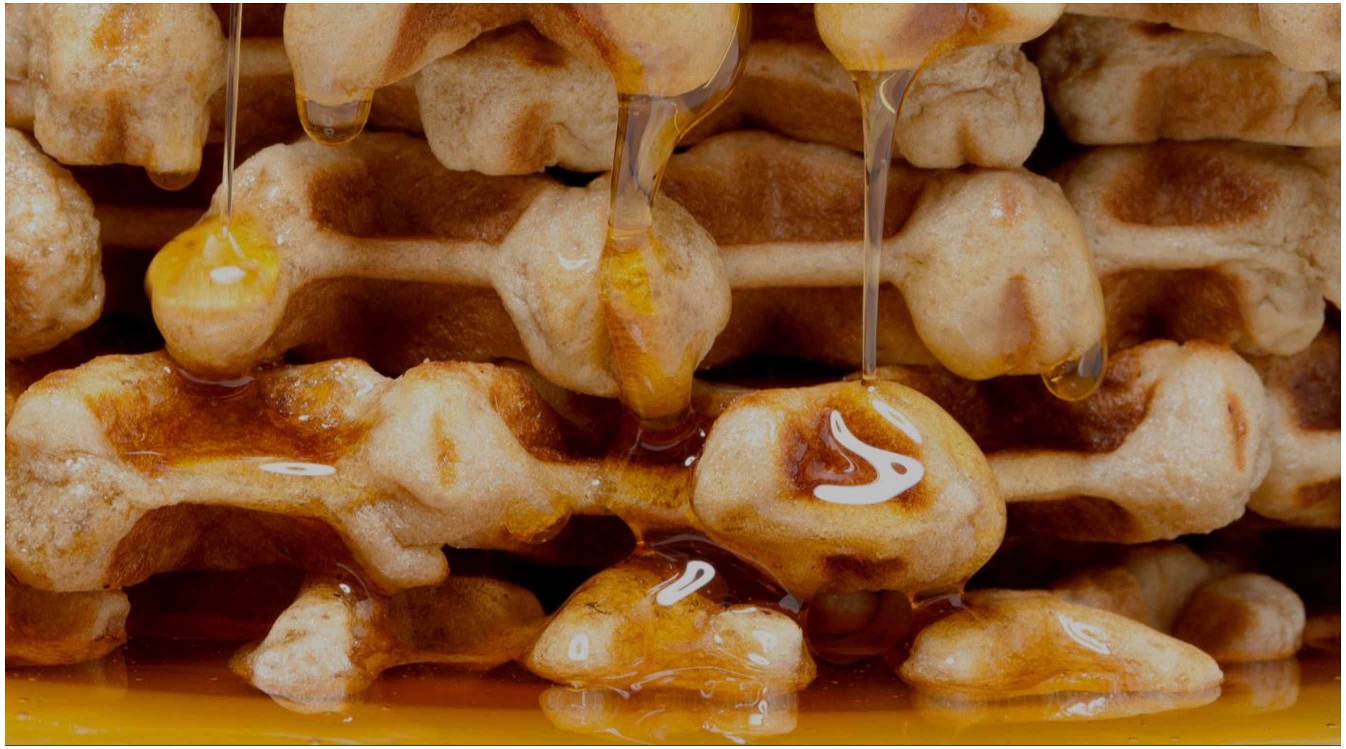
Leitner PhD thesis 2005

$$\tau_a = \tau_0 \, e^{\frac{-\Delta H_{ads}}{RT}}$$

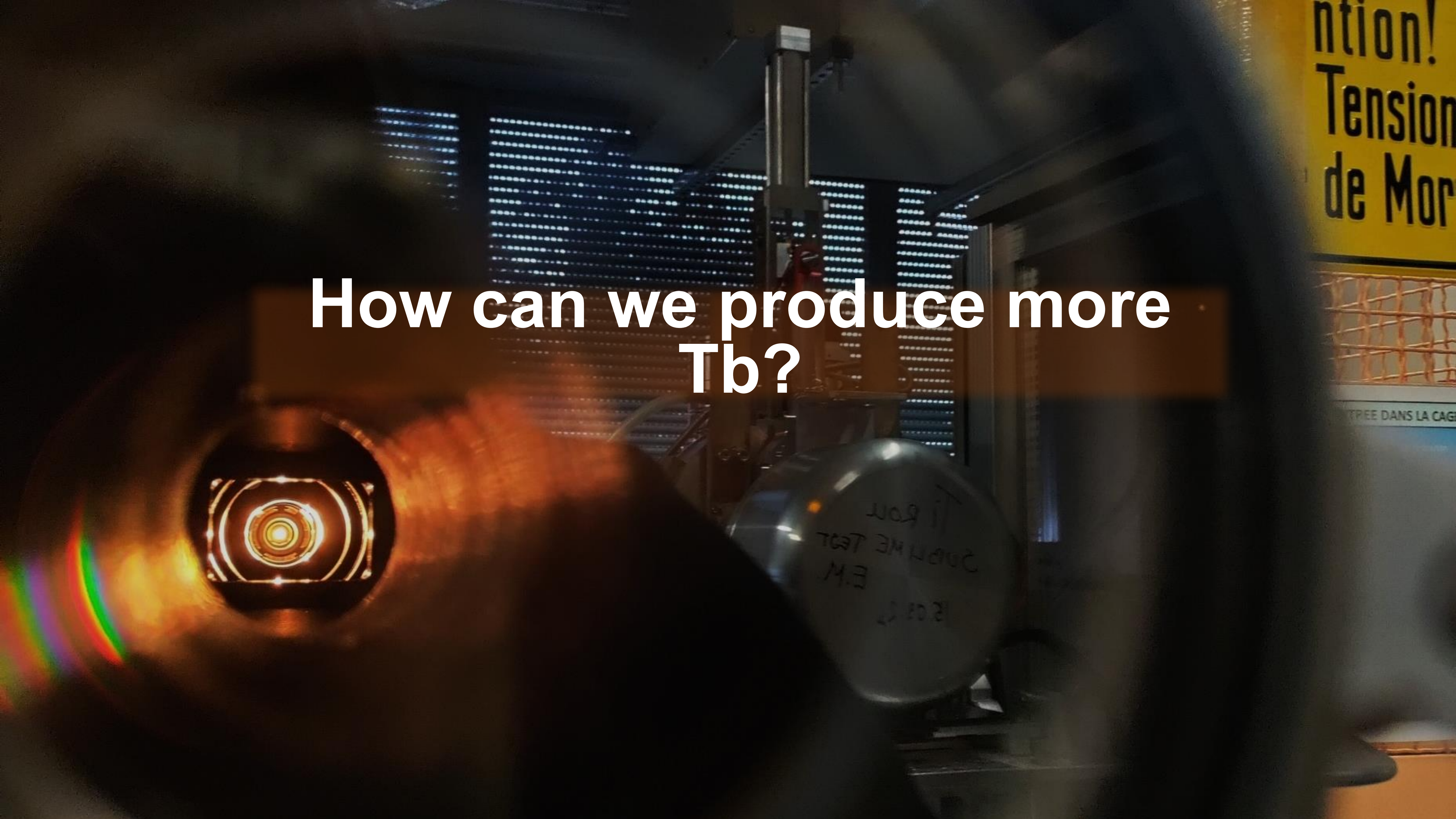
*lower limit! Estimated through Eichler systematics. U. Koster PhD thesis 2000

Tb is “sticky”

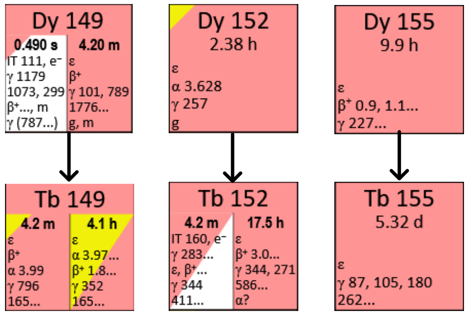


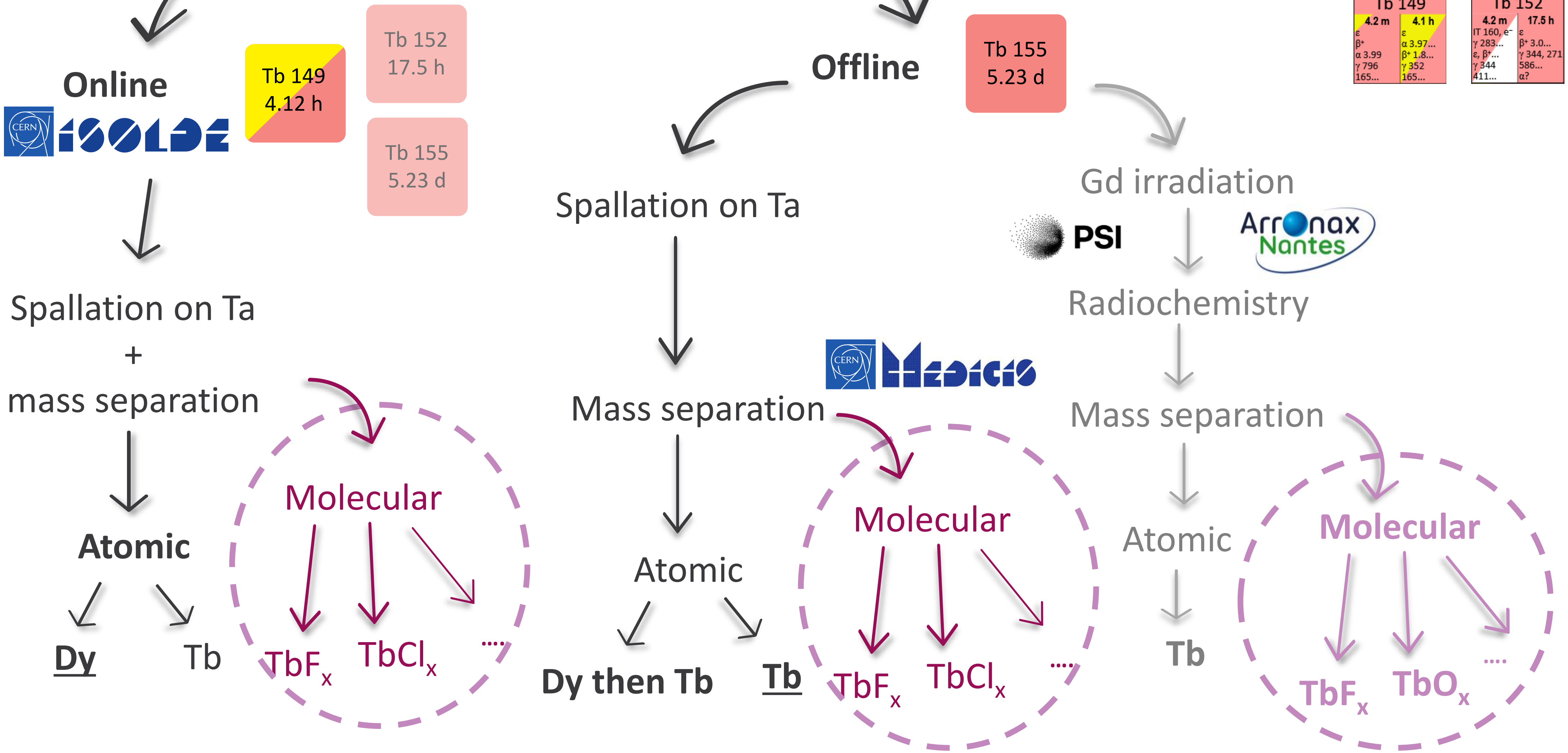


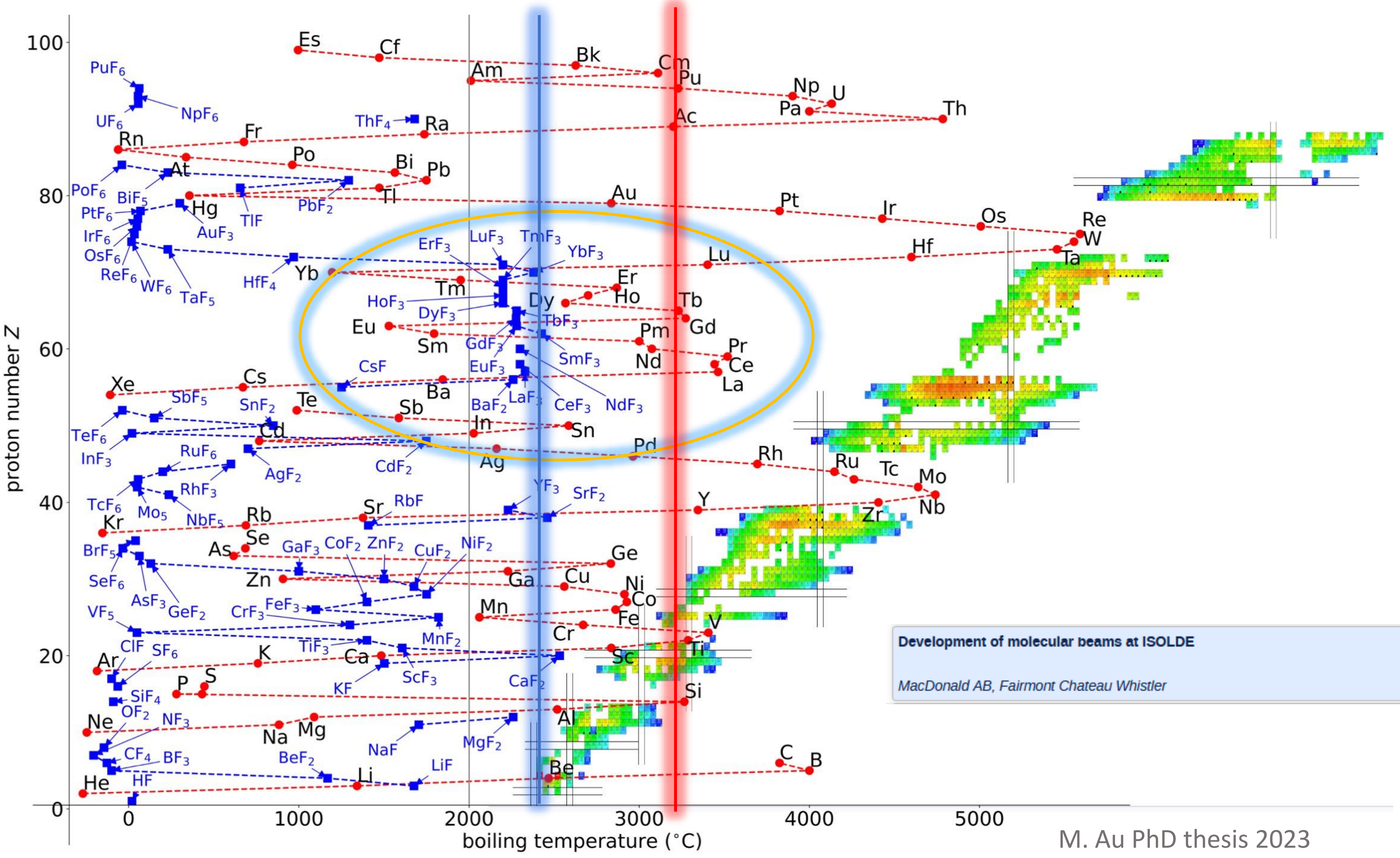
How can we produce more Tb?



Isotopically pure $^{149,152,155}Tb$





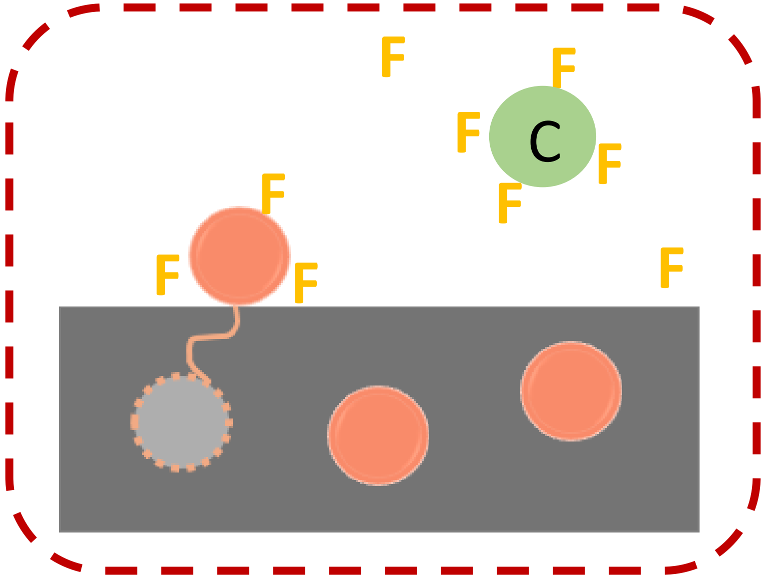


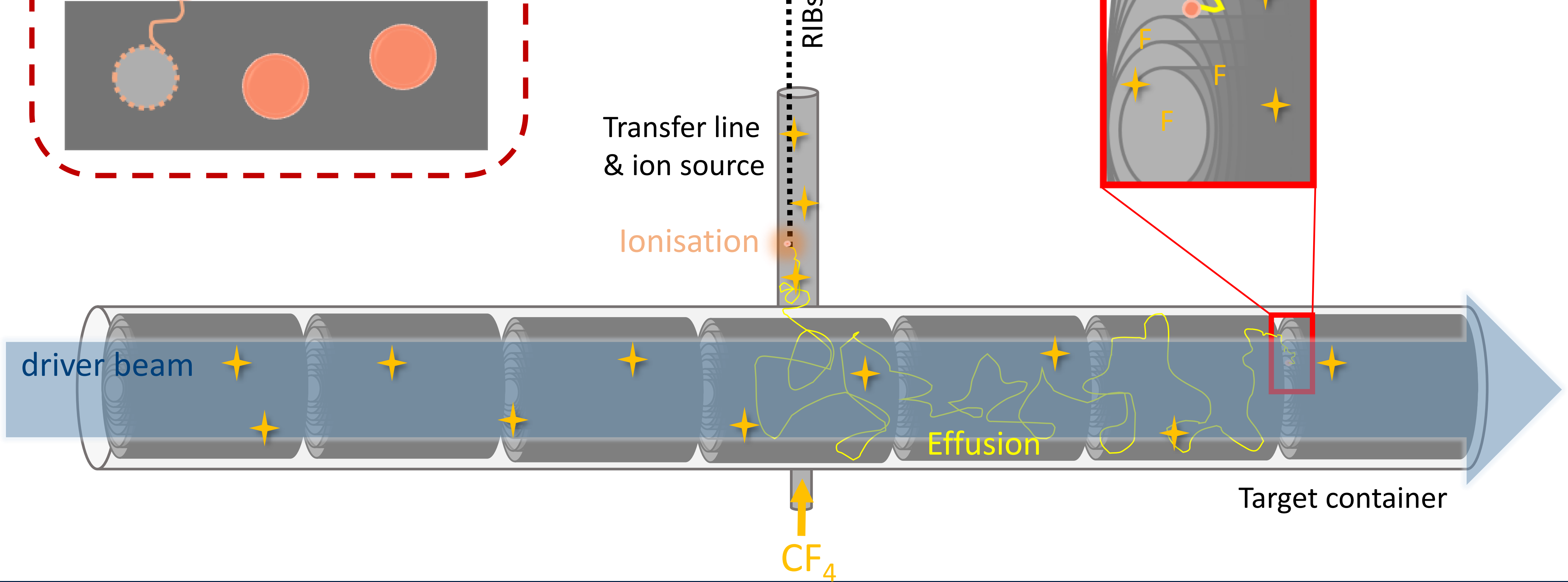
Development of molecular beams at ISOLDE *Mia Au*

MacDonald AB, Fairmont Chateau Whistler 08:30 - 09:00

M. Au PhD thesis 2023

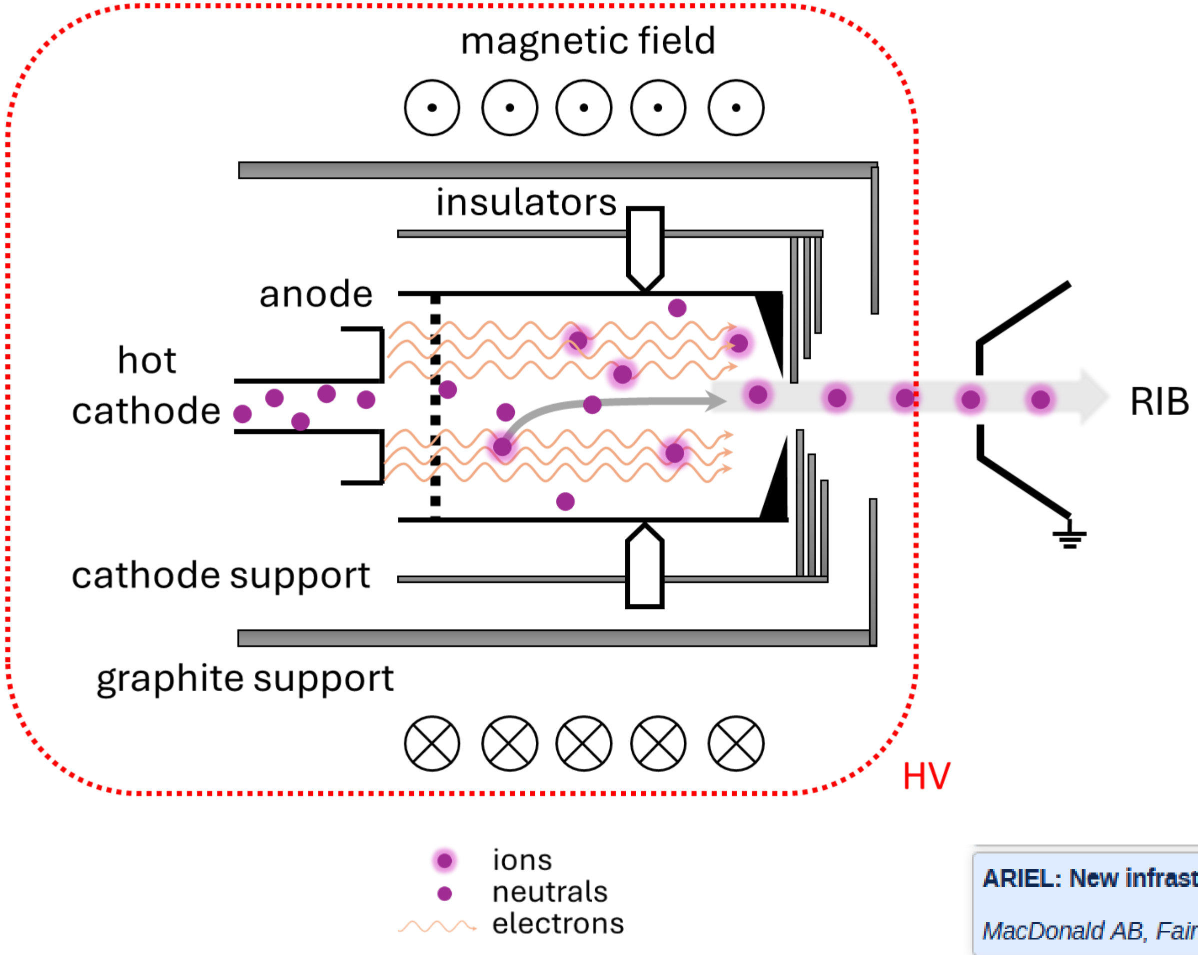
Fluorination





Forced Electron Beam Induced Arc Discharge

At ISOLDE referred to as VADIS (Versatile Arc Discharge Ion Source)



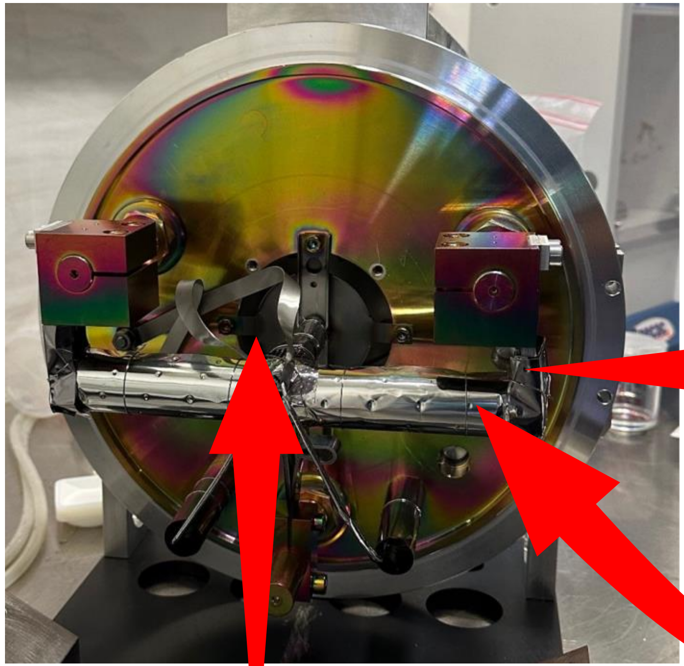
What can we optimise?

	Variable parameter	Effect
target	temperature	release ion load neutral load equilibrium point for chemical reactions over long times: target microstructure evolution
ion source	anode voltage magnetic field cathode temperature	electron energy electron trajectories electron density ion survival dissociation\ionisation plasma conditions beam shape (extraction and transport efficiency)
gas injected	composition partial pressure time since fluorination	fluorine availability neutral species pressure fluorine saturation chemical equilibrium on target surfaces

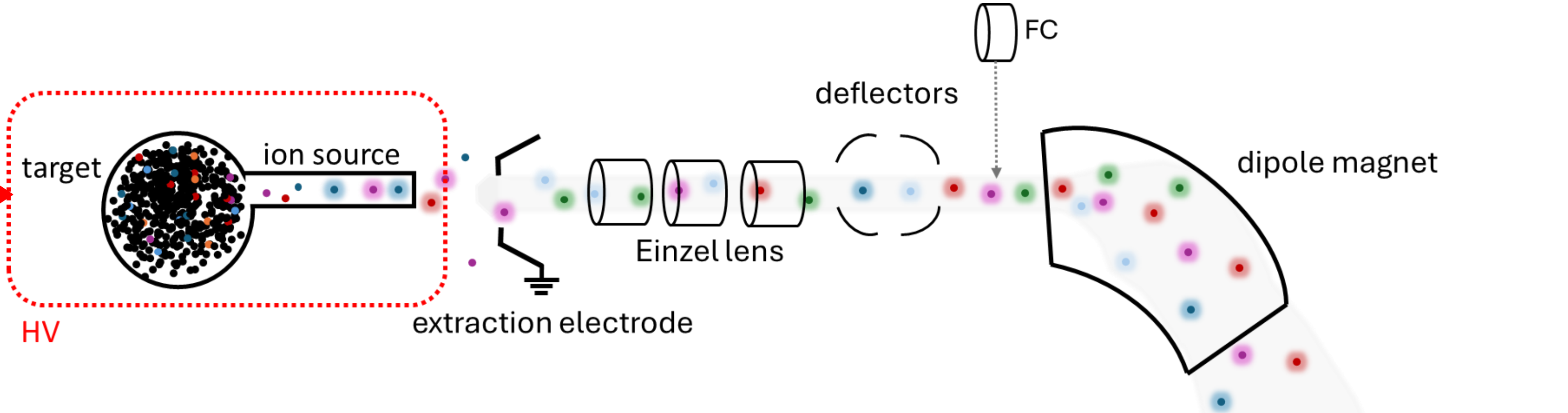
ARIEL: New infrastructure, new opportunities for target and ion source development *Fernando Alejandro Maldonado Millan*

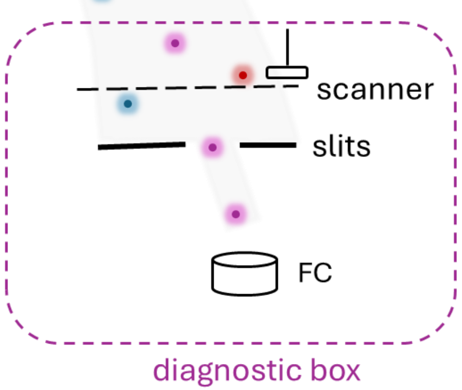
MacDonald AB, Fairmont Chateau Whistler 09:20 - 09:40

Offline tests

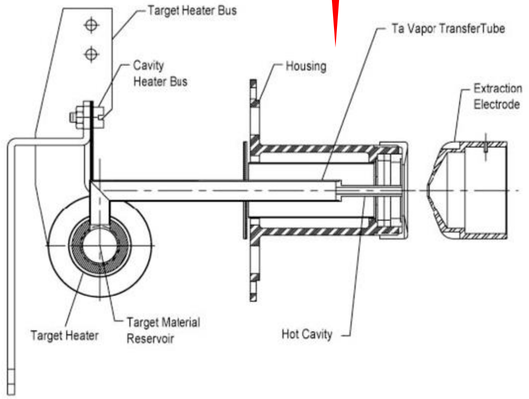


ISOLDE Offline 1





TbF_3 powder

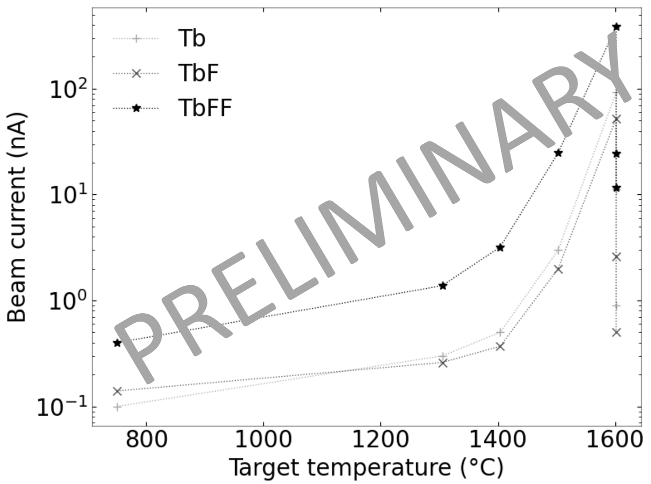


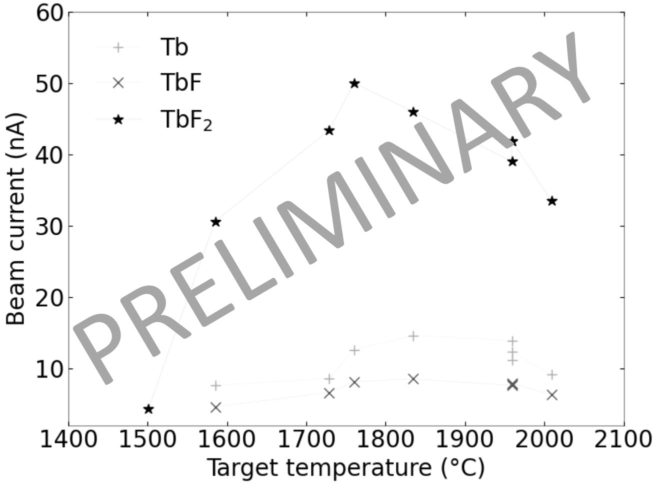
FEBIAD ion source

Temperature dependence

→Already observed <1500°C

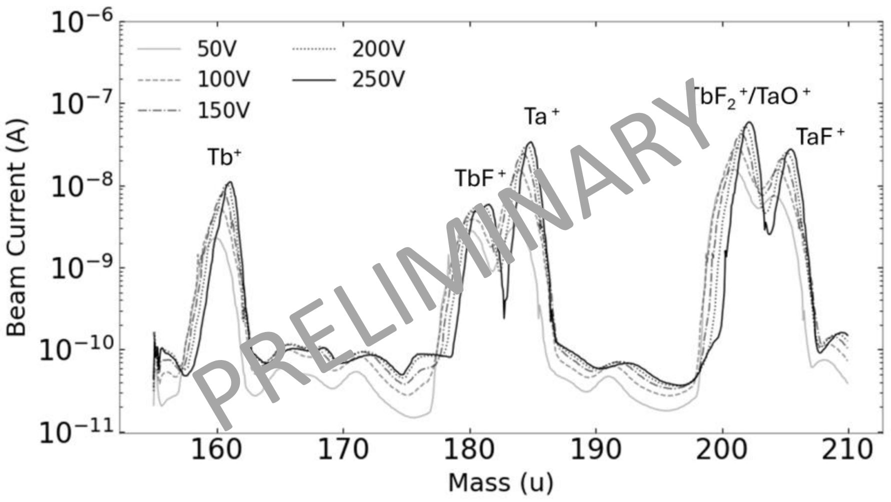
→ Appearance temp. depends on oxygen content and CF_4 saturation



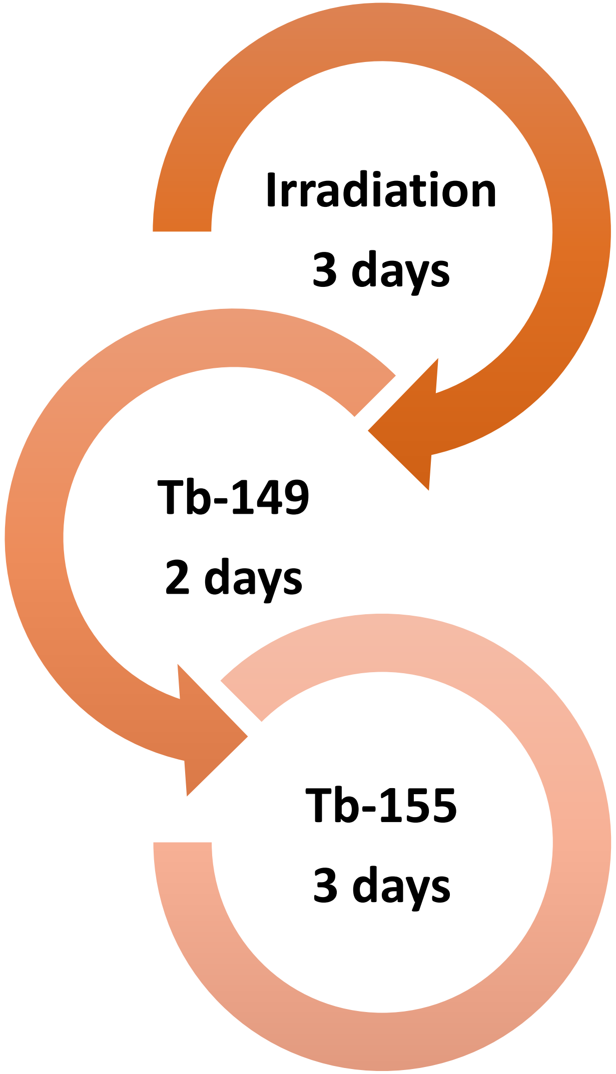


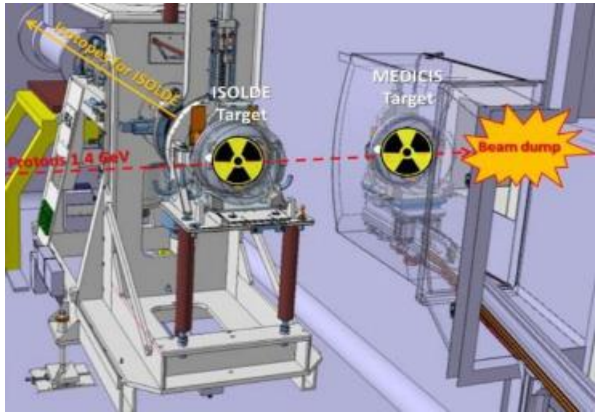
Response to change in electron bombardment energy

→ Cannot shift sideband distribution



Offline extraction at MEDICIS



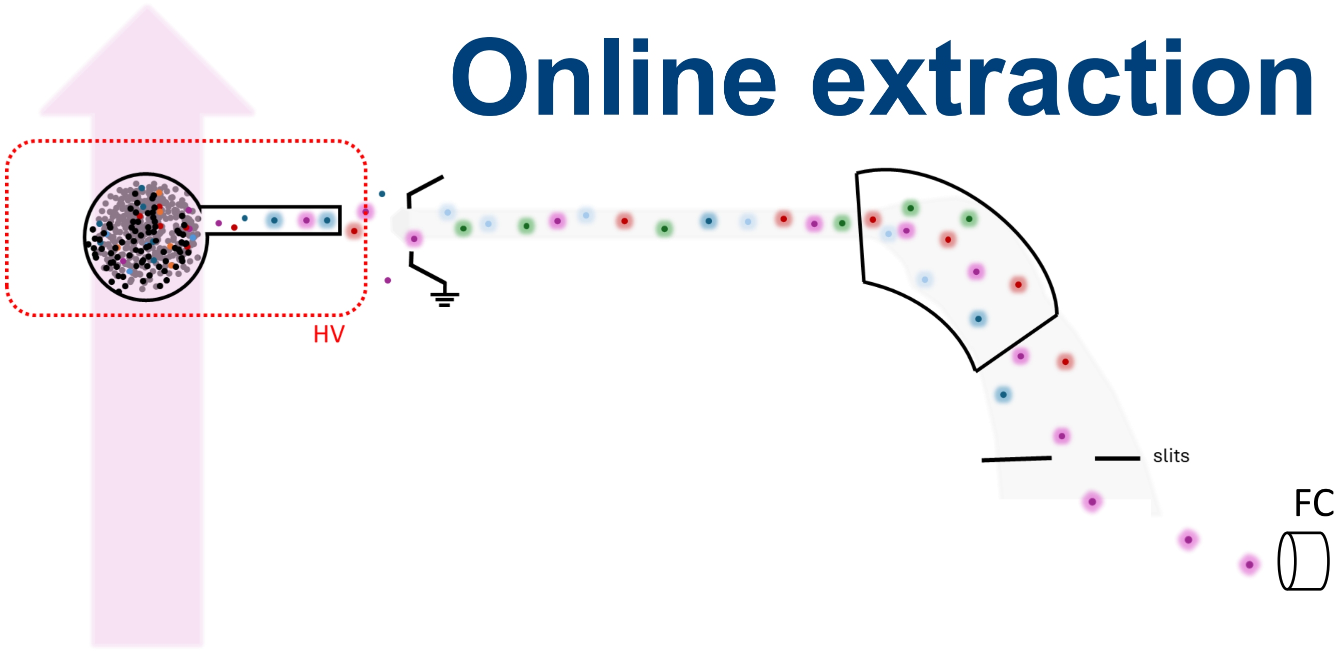


Isotope	Sideband	A/q	$A_{in\text{-}target}$ [MBq]	A_{foil} [MBq]	$A_{collimator}$ [MBq]	Efficiency %
Gd-149	GdF_2	187	748 (11)	1.27 (7)	5.45 (2)	0.17 (1)
Tb-149	TbF_2	187	3090 (90)	0.015 (3)	0.045 (6)	0.0005 (1)
Tb-155	TbF_2	193	1130 (20)	1.25 (4)	–	0.11 (3)

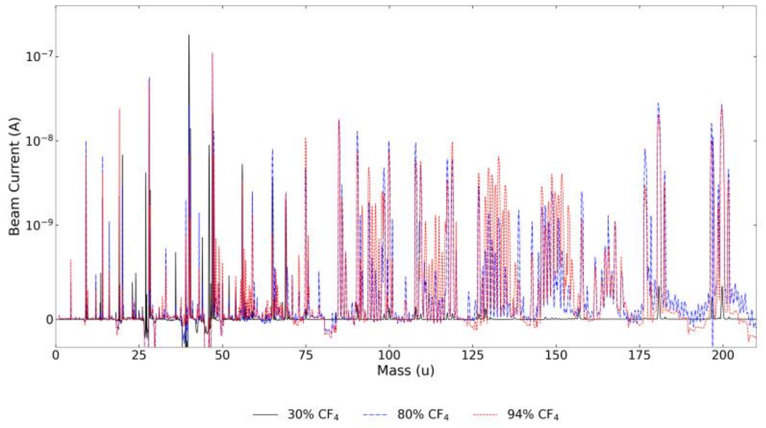
Difluoride extraction
Tb-155 efficiency 0.1%
- **comparable to laser ionised Tb @ MEDICIS**

Difficult to disentangle influence of different parameters

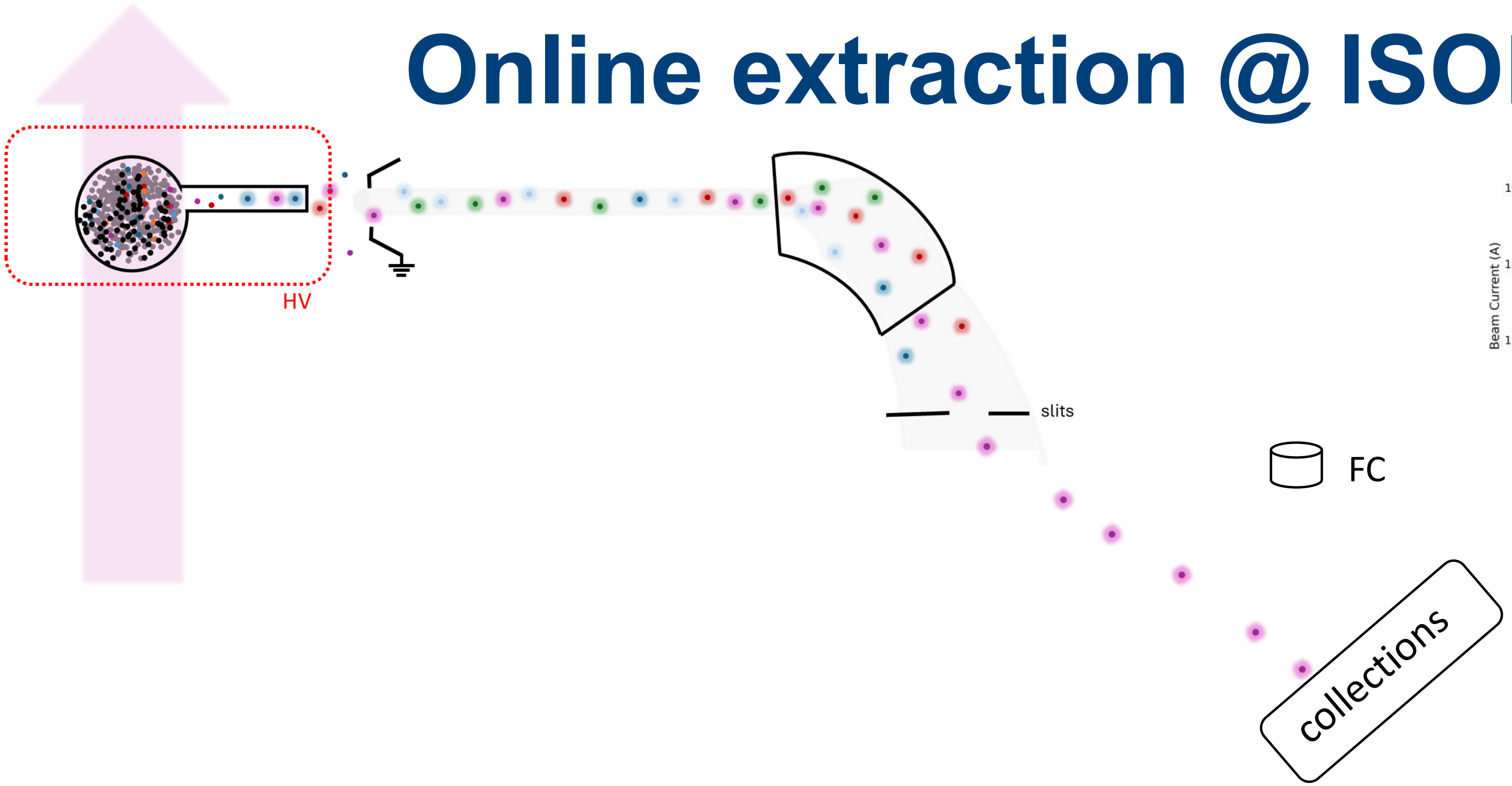
Online extraction @ ISOLDE



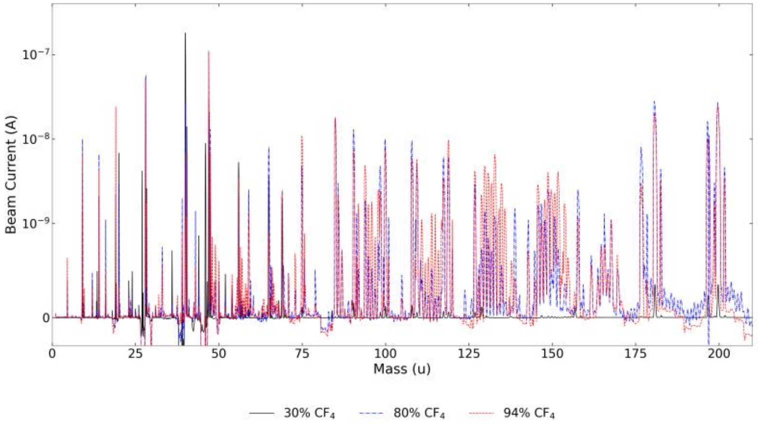
Mass scans



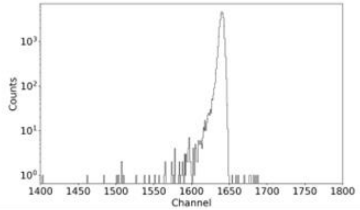
Online extraction @ ISOLDE



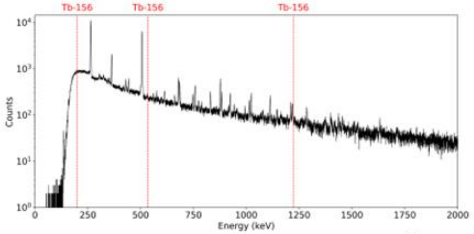
Mass scans



Alpha spectrometry



Gamma spectrometry



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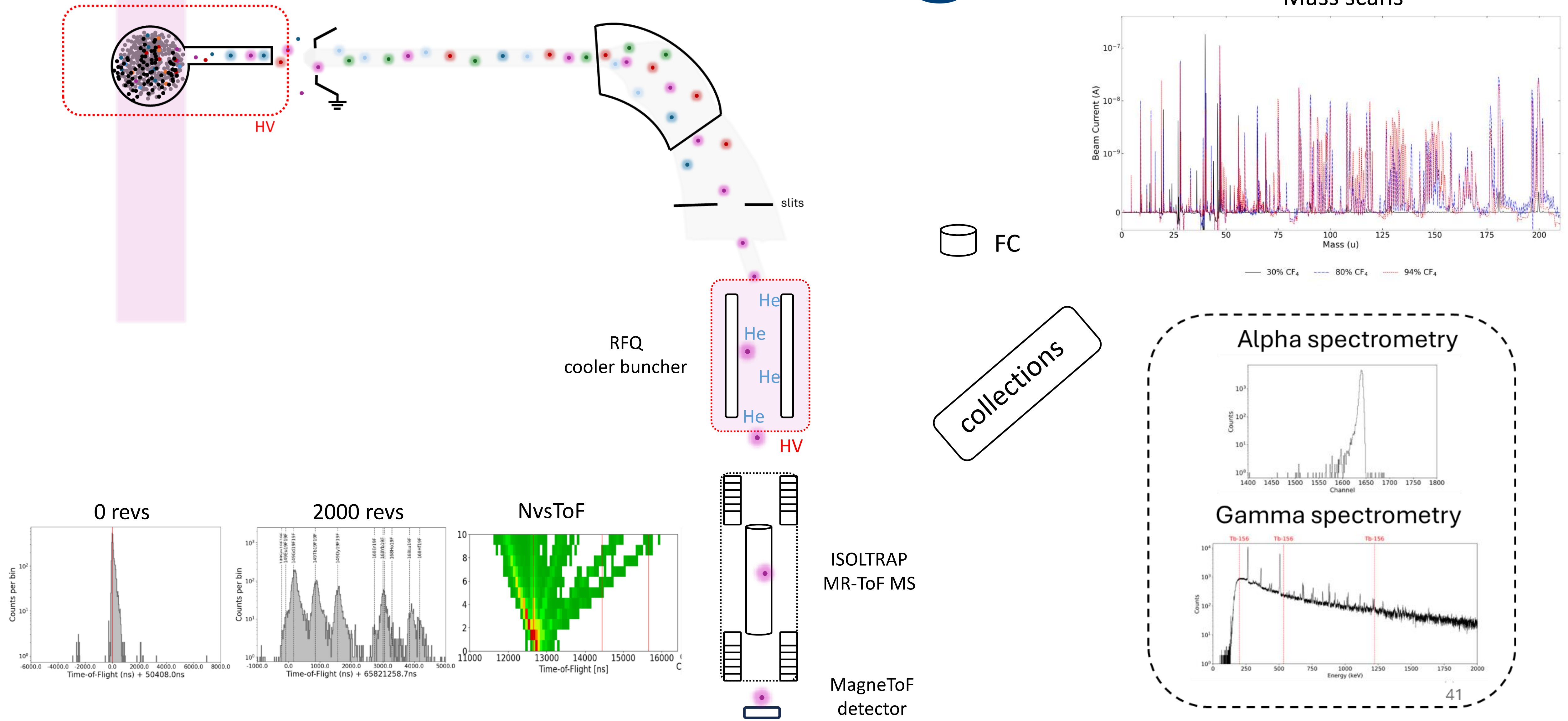
Online extraction @ ISOLDE



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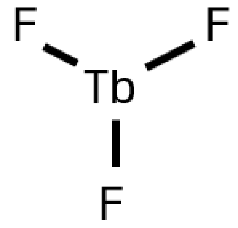
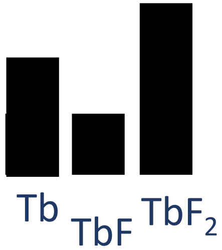
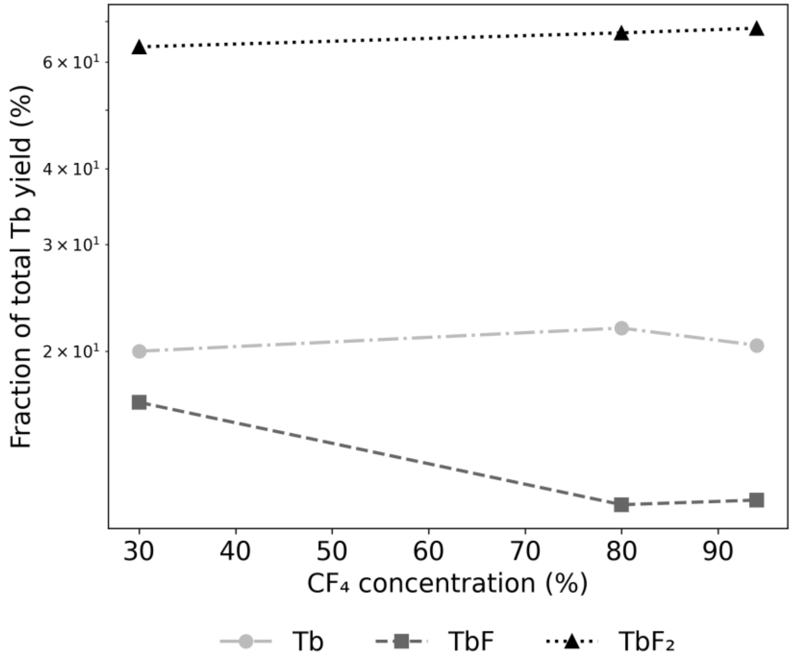
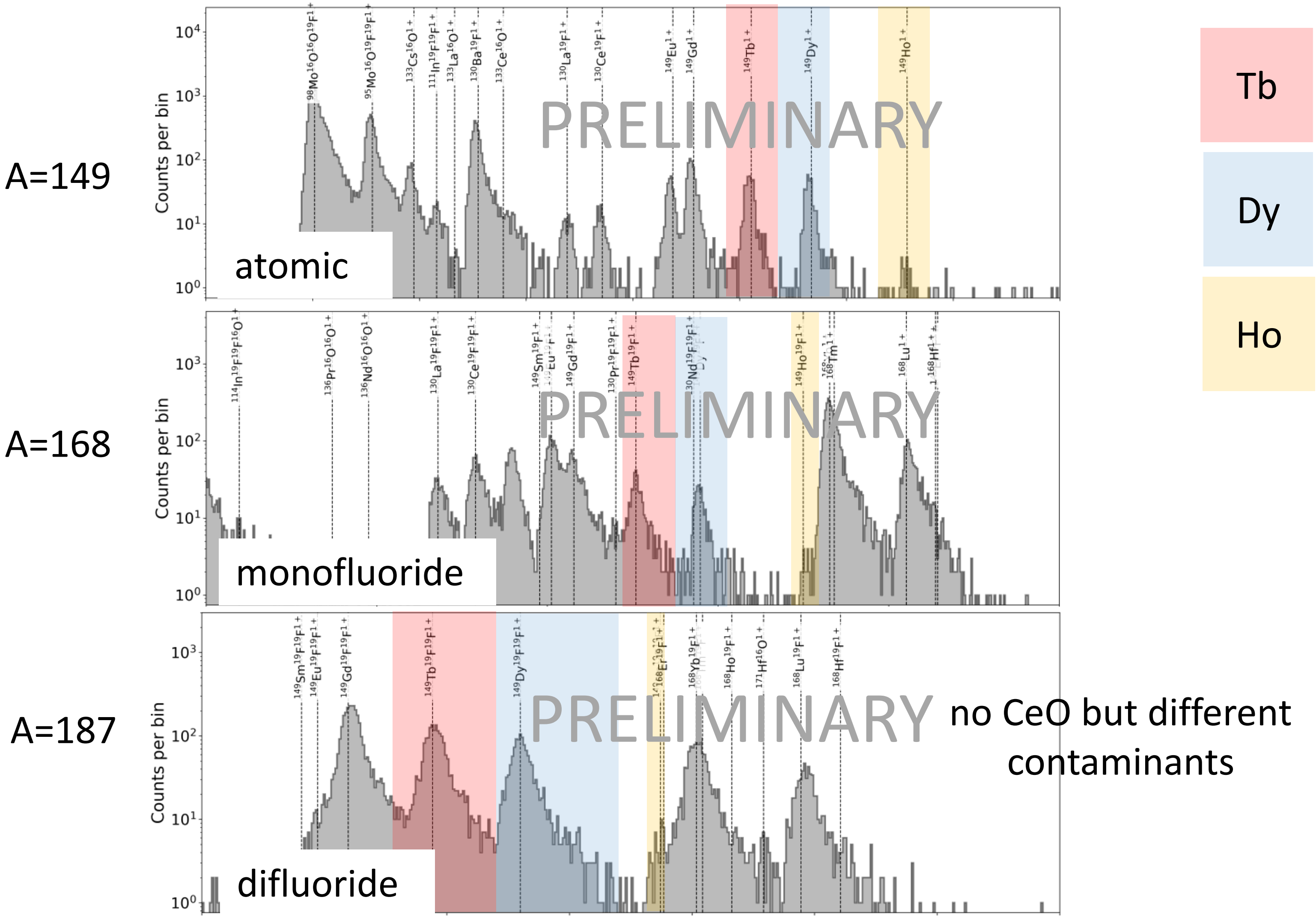


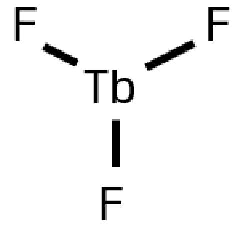


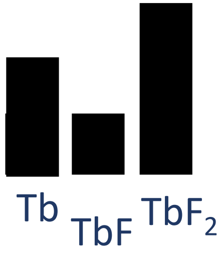


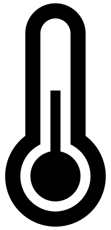
TbF_2 strongest (and cleanest) sideband

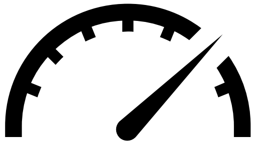


no CeO but different contaminants

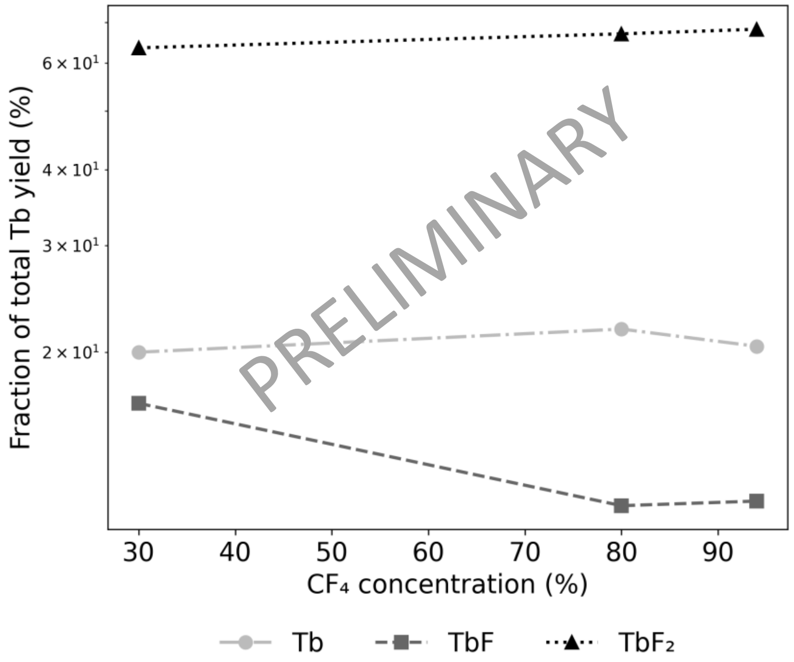




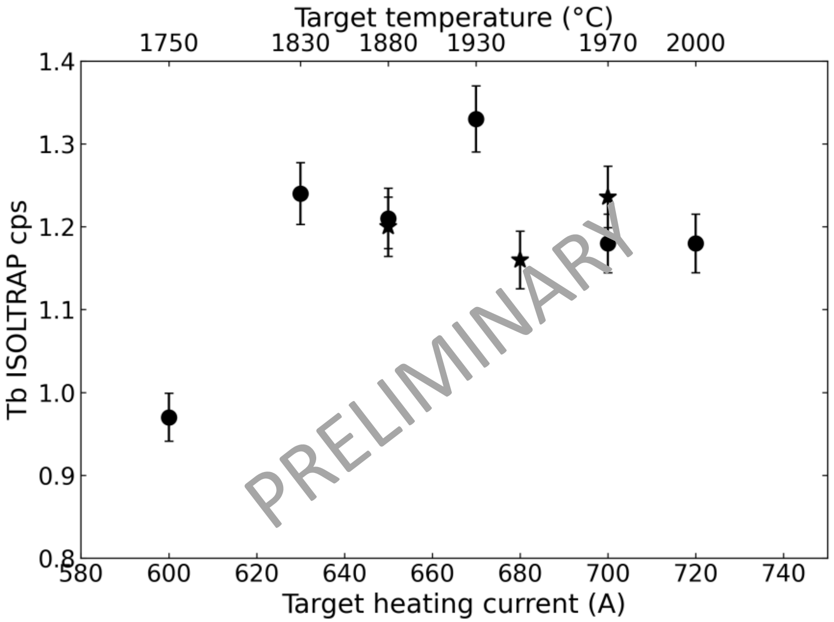




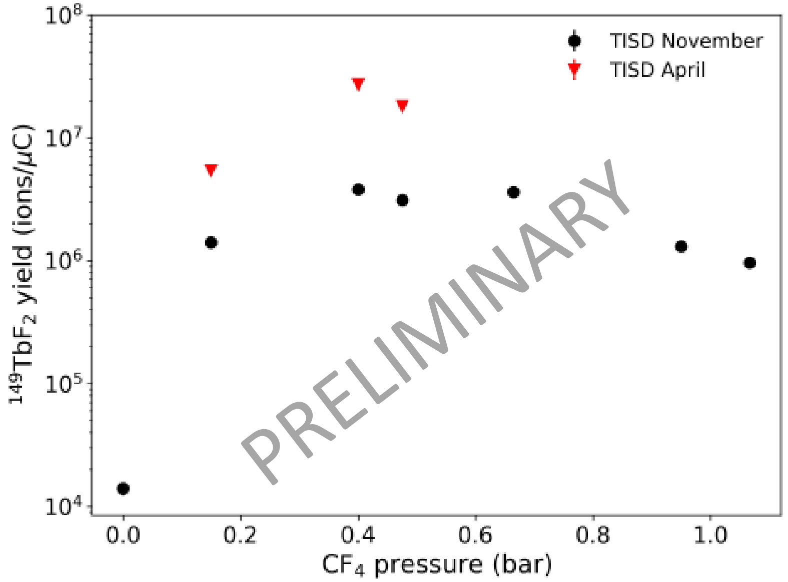
CF_4



TbF$_2$ strongest (and cleanest) sideband



Tb beam <1900°C



Optimal fluorine concentration

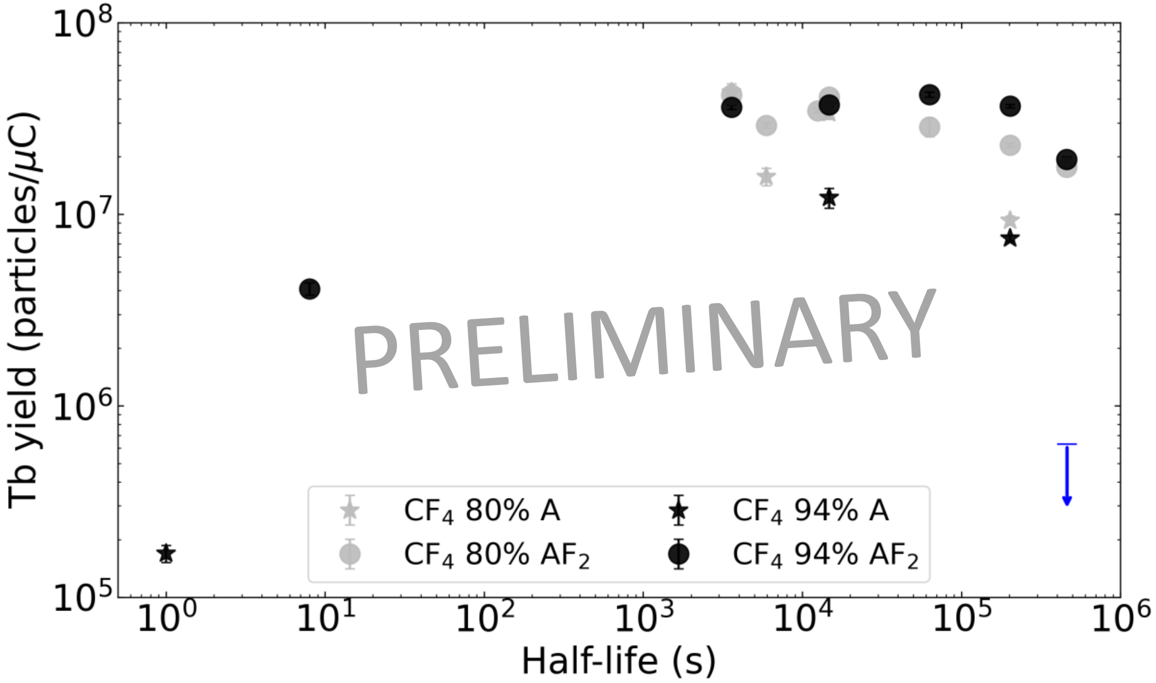
What we saw, what we didn't see

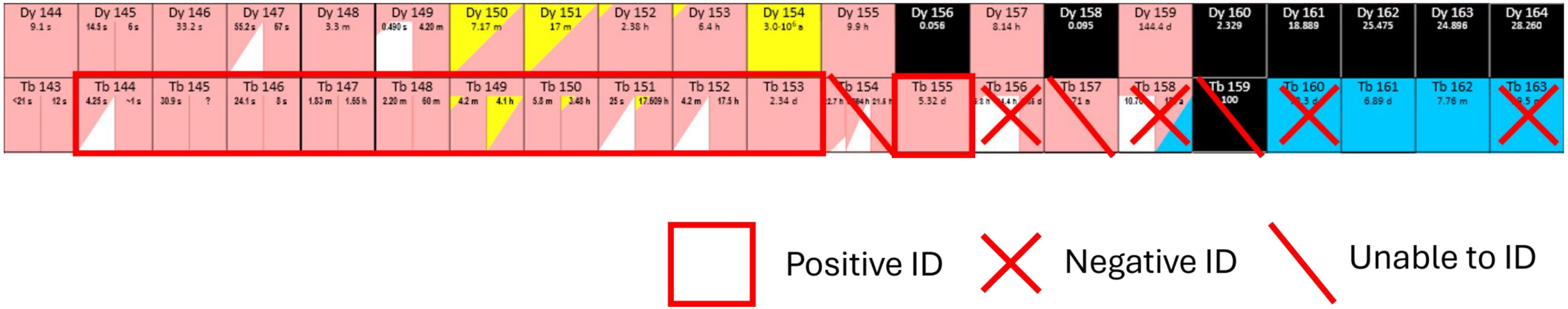
Higher yields than RILIS Tb

No neutron rich Tb observed

No Tb on Dy shielded masses

- 154, 156, 158, 159 not observed





What’s limiting Tb release?

Production limit

- Not a lot of Tb is directly produced in the foil
  → most of the Tb is a decay product of Dy

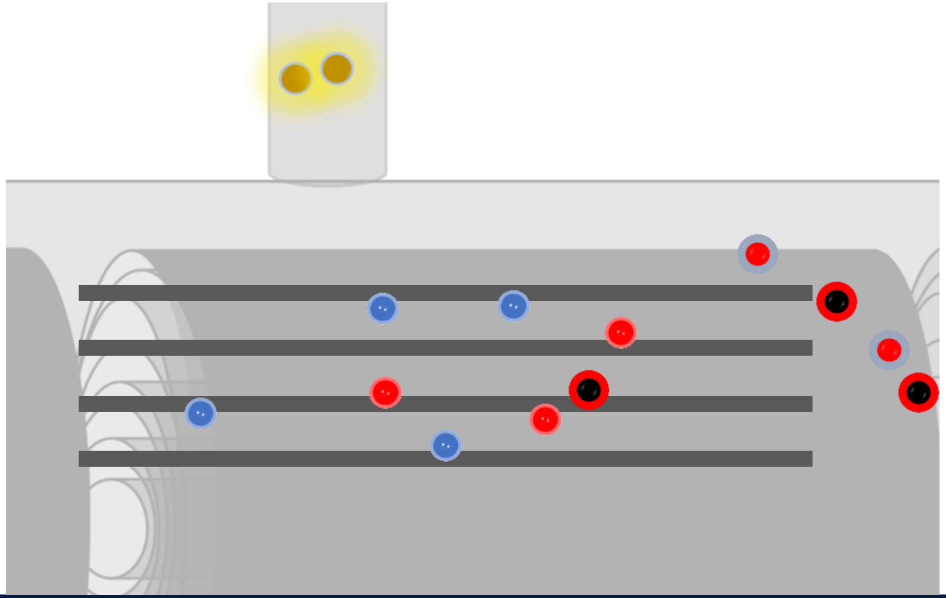
What’s limiting Tb release?

Effusion limit

- Tb produced in the foil is not released
- Tb we see is the decay product of Dy
  → Dy completed part of the pathway

Proposed mechanism:
Dy assisted release

Dy Tb Gd



What's limiting Tb release?

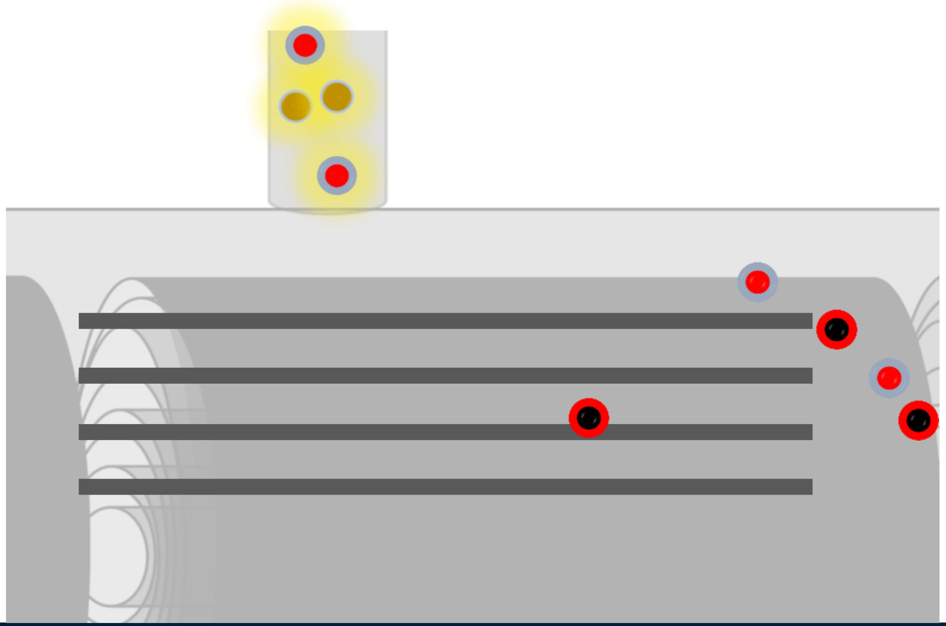
Effusion limit

- Tb produced in the foil is not released
- Tb we see is the decay product of Dy

  → Dy completed part of the pathway

Proposed mechanism:
Dy assisted release

Dy Tb Gd



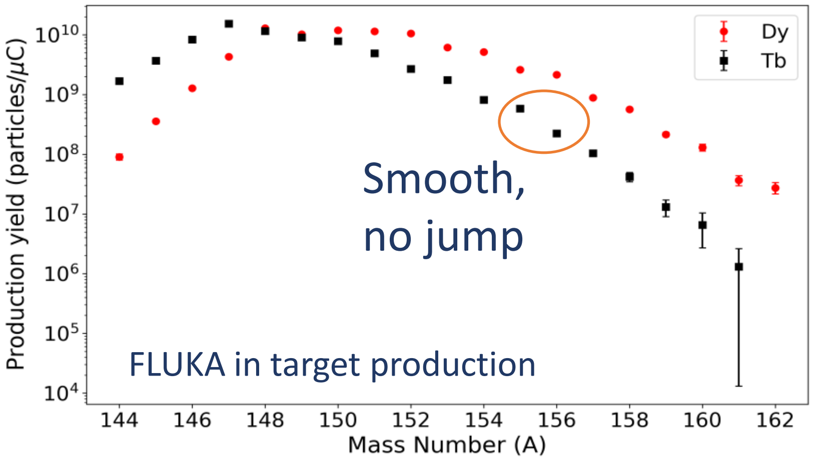
What's limiting Tb release?

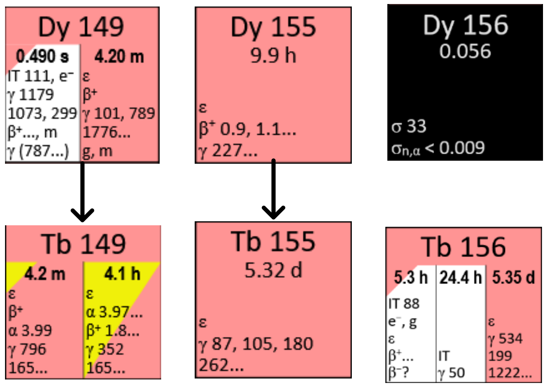
Production limit
or effusion limit

- No ^{156}Tb observed
- No n-rich Tb observed
- No stable or long-lived Tb observed when there is no feeding from Dy

Effusion limit

- Offline extraction:
  $^{149}TbF_2$ efficiency: 0.0005(1)%
  $^{155}TbF_2$ efficiency: 0.11(3)%





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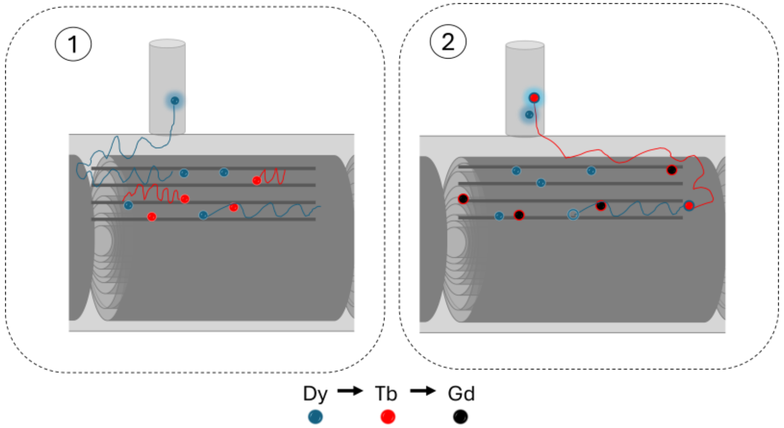
Molecules allow for co-collection of Tb and its parents <1900°C

Dy facilitates release of Tb

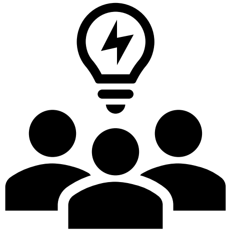


TbF_2 yields not competitive with RILIS Dy for medical isotopes online

^{149}Dy RILIS > **$^{149}TbF_2$** > ^{149}Tb RILIS

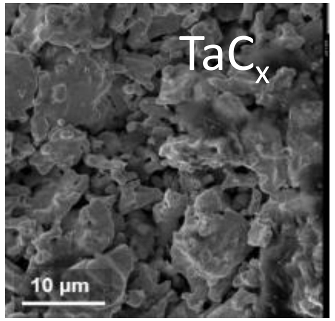
Molecules advantageous for offline extraction

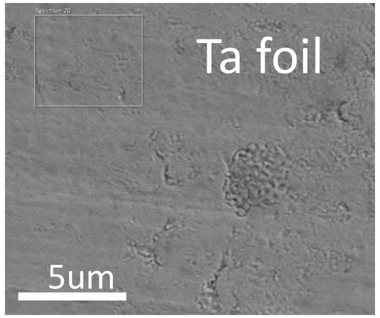
What's next? Short-term

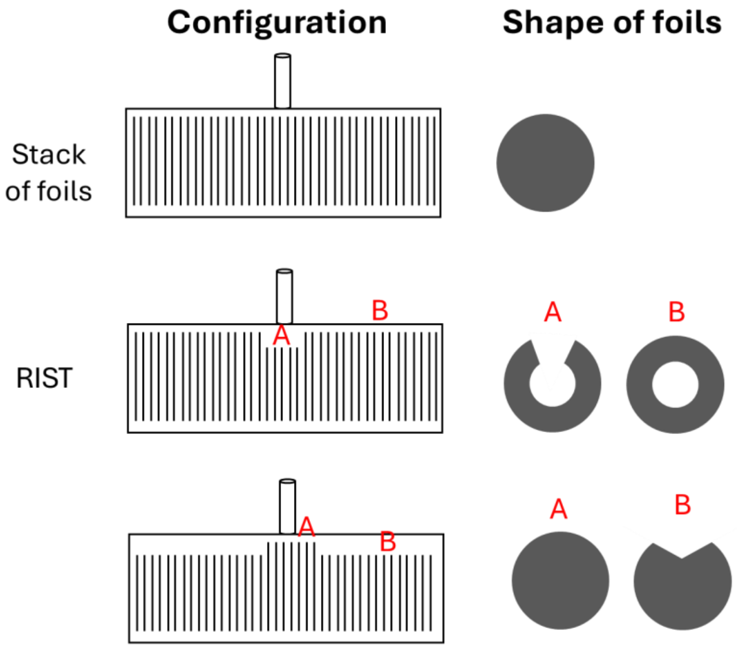


We need to rethink the target itself

- New materials – TaC? Others?
- New geometries







Long term: Tailored systems

Redefine what is needed for medical isotope production

"standard" ISOL	medical mass separation
Efficiency	Efficiency
Rapidity	~~Rapidity~~
Selectivity	Selectivity
Versatility	~~Versatility~~
	Scalability

New facilities with more powerful proton beams

→ New challenges

There is a lot still to be done.

Acknowledgements

Mia Au, Maroua Benhatchi, Mathieu Bovigny, Nadine Conan, Thomas Elias Cocolios, Bernard Crepieux, Marie Deseyn, Charlotte Duchemin, Alexandre Dorsival, Isabel Frank, Paul Fischer, Paul Florian Giesel, Hanne Heylen, Michael Heines, Jake Johnson, Ulli Köster, Daniel Lange, Lukas Nies, Mike Owen, Edgar Reiss, Ralf Rossel, Simon Stegemann, Thierry Stora, Jonas Stricker, Sebastian Rothe

ISOLDE operations team, ISOLDE targets and ion sources team

F. Maldonado for FEBIAD discussions

Thank you for your attention.

Questions?