

# THE USE OF PSI's HIGH INTENSITY PROTON ACCELERATOR (HIPA) COMPLEX TOWARDS MEDICAL-RADIONUCLIDE DEVELOPMENT

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INTERNATIONAL CONFERENCE ON  
**ACCELERATORS FOR RESEARCH  
AND SUSTAINABLE DEVELOPMENT**  
From good practices towards socioeconomic impact



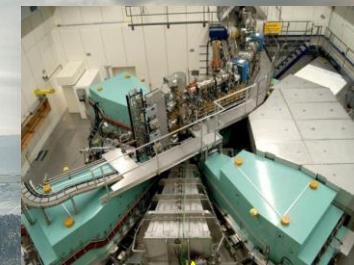
# Use of Large Facilities at PSI: Proton & Neutron Sources



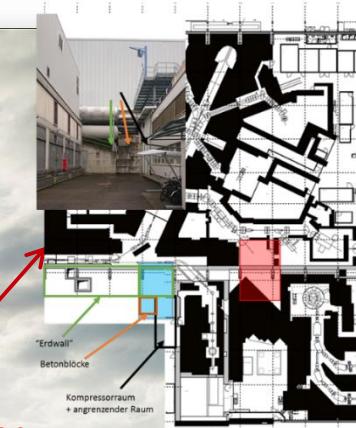
RADIOTRACER  
DEVELOPMENT



Proton Irradiation



Neutron Irradiation

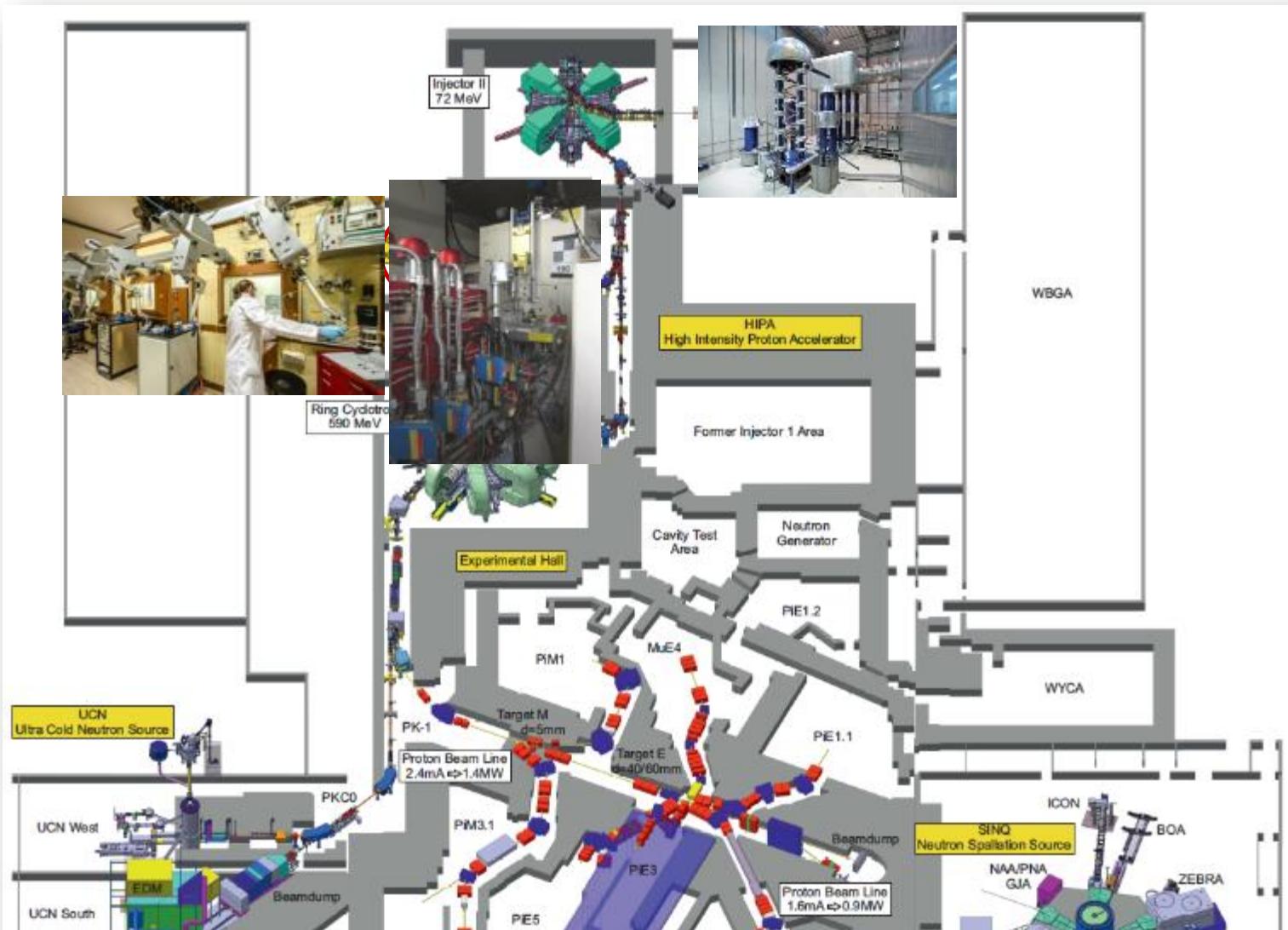


c/o Michel Jaussi Photography

Nicholas P. van der Meulen

International Conference on  
Accelerators for Research  
and Sustainable Development

# PSI's High Intensity Proton Accelerator Complex

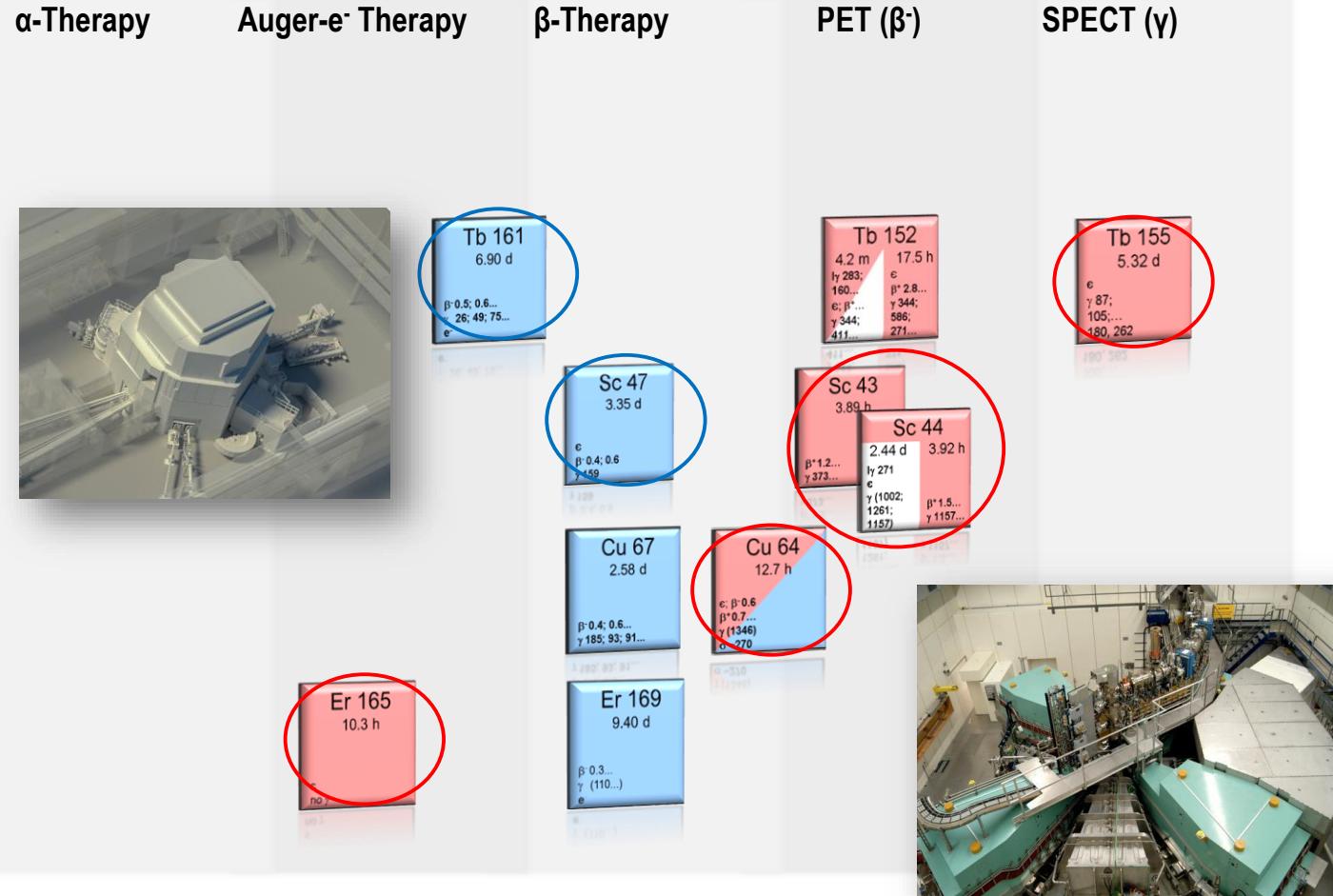


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International Conference on  
Accelerators for Research  
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# “Matched Pairs” of Radionuclides Towards Theragnostics



# Radionuclides: broadening the network for radiopharmaceutical application

Universities/cyclotron facilities



Tb 155 5.32 d	Tb 156 5.3 h
$\epsilon$ $\gamma$ 87, 105, 180 262...	$\epsilon$ $\gamma$ 534 199 50 1222
Gd 154 2.18	Gd 155 14.40
$\sigma$ 60	$\sigma$ 61000 $\sigma_{n,\alpha}$ 8E-5

Proton Irradiation

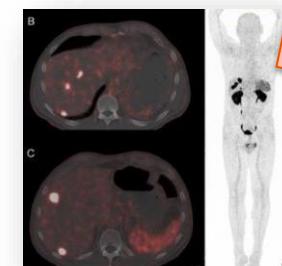
Research reactor facilities



Tb 161 6.89 d	Tb 162 7.76 m
$\beta^-$ 0.5, 0.6... $\gamma$ 26, 49, 75...	$\beta^-$ 1.4, 2.4,... 260, 808 108...
Gd 160 24.86	Gd 161 9.66 m 1.7... 361, 315 102... $\sigma$ 20000

Neutron Irradiation

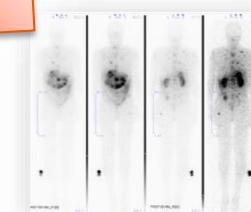
Patient Diagnosis



Preclinical groups;  
Groups determining dosimetry;  
The clinical fraternity



Chemical Separation  
Followed by...  
Preclinical research;  
Radiopharmaceutical  
Manufacture



Radionuclide Therapy

Groups determining dosimetry;  
The clinical fraternity



# <sup>44</sup>Sc: “From-Bench-To-Bedside”

Target Preparation



Proton Irradiation of Target Material



**Sc 44**

2.44 d  
 $\gamma$  271  
 $\epsilon$   
 $\gamma$  (1002;  
 1261;  
 1157)

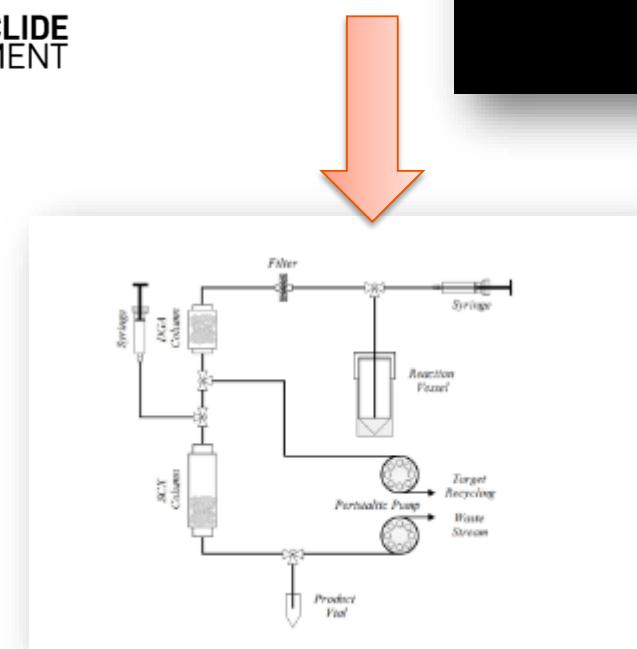
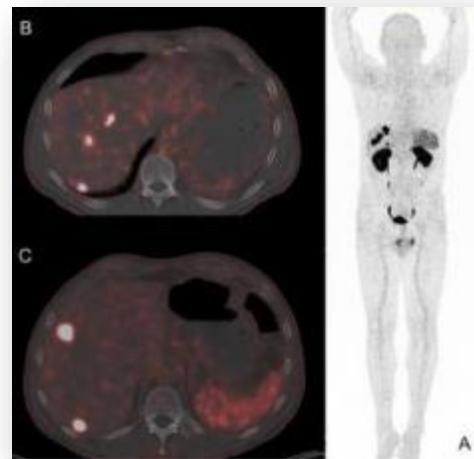
3.92 h  
 $\beta^+$  1.5...  
 $\gamma$  1157...

**Ca 44**  
 2.086

van der Meulen *et al.*, Nucl. Med. Biol. (2015);  
 Singh *et al.*, Cancer Biother. (2017);  
 van der Meulen *et al.*, Molecules (2020)



Radiolabelling and Imaging



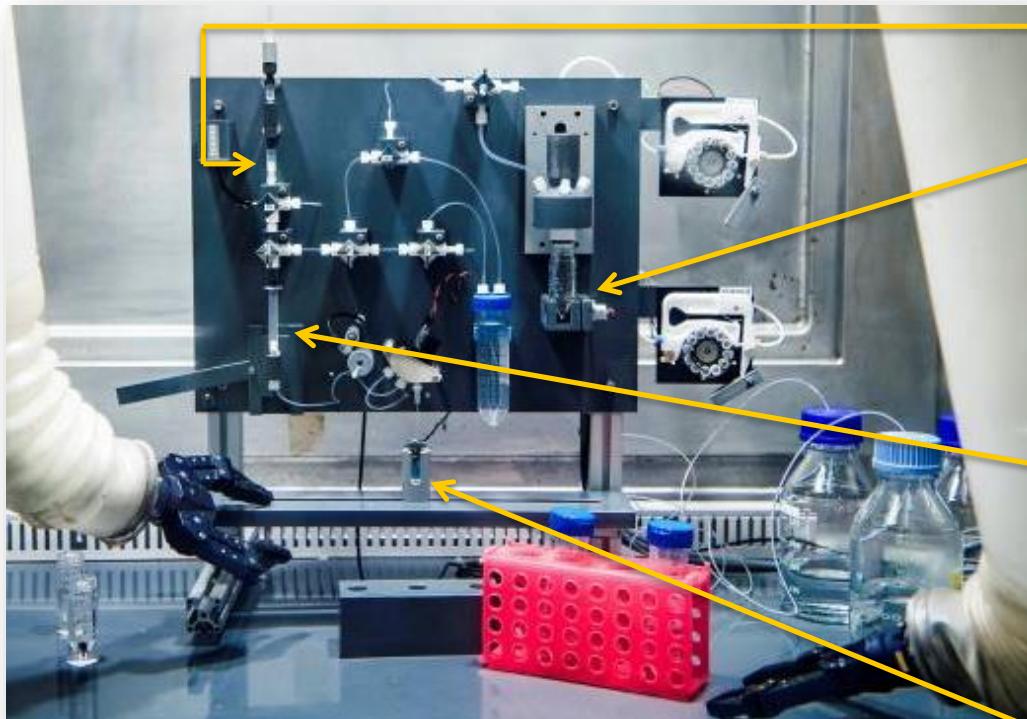
Chemical Separation and Processing



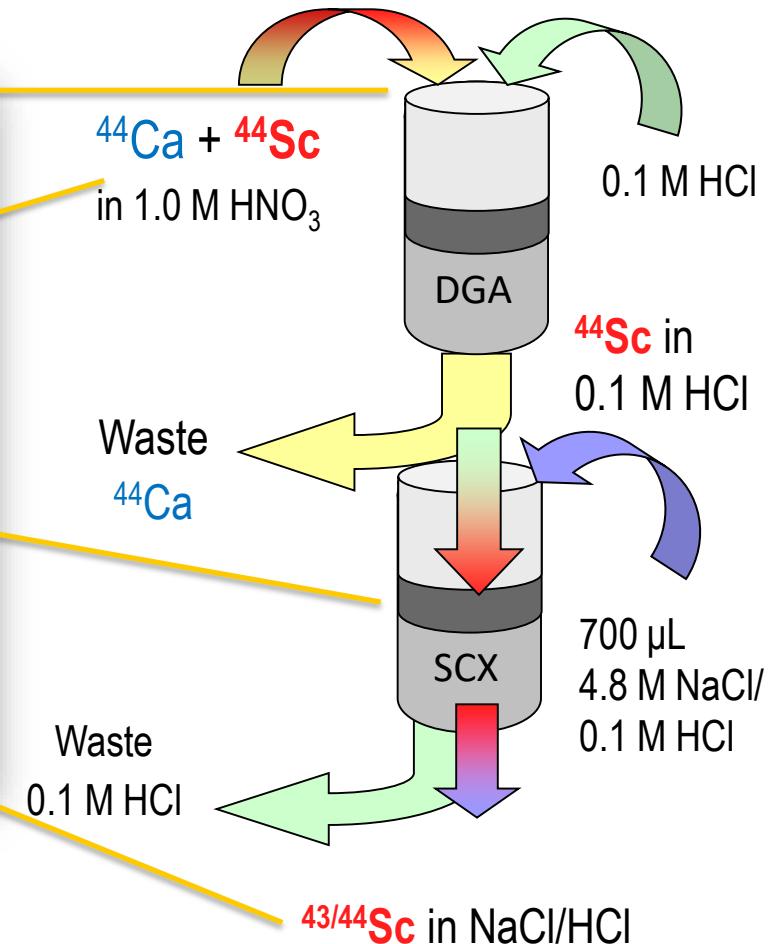
# Separation of Sc from Ca



RADIOISOTOPE  
DEVELOPMENT

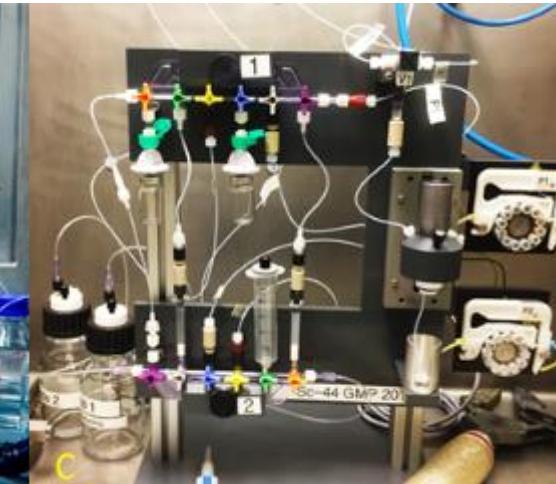
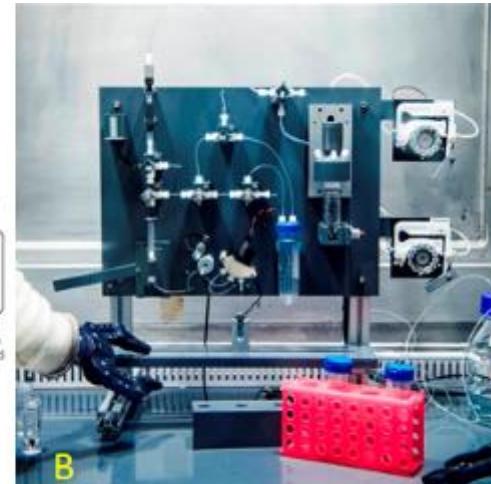
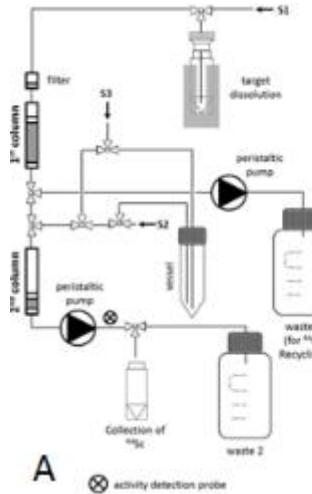


van der Meulen et al., Nucl Med. Biol. (2015)  
Domnanich et al., EJNMMI Radiopharm. Chem. (2017)  
van der Meulen et al. Molecules (2020)



Facility	m ( $^{44}\text{CaO}$ ), mg	Irradiation time	$^{44}\text{Sc}$ activity	Molar Activity (DOTATOC)
PSI-IP2	25 – 30	90 min	~4 GBq	Up to 25 MBq/nmol
UniBe	25 – 30	30 – 240 min	0.6 – 16 GBq	Up to 25 MBq/nmol





Initial PSI Target



Current PSI Target/ETH



UniBe Target

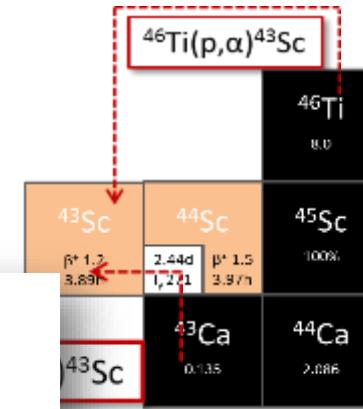


# $^{43}\text{Sc}$ : A Proposed Improvement in Radiometal PET

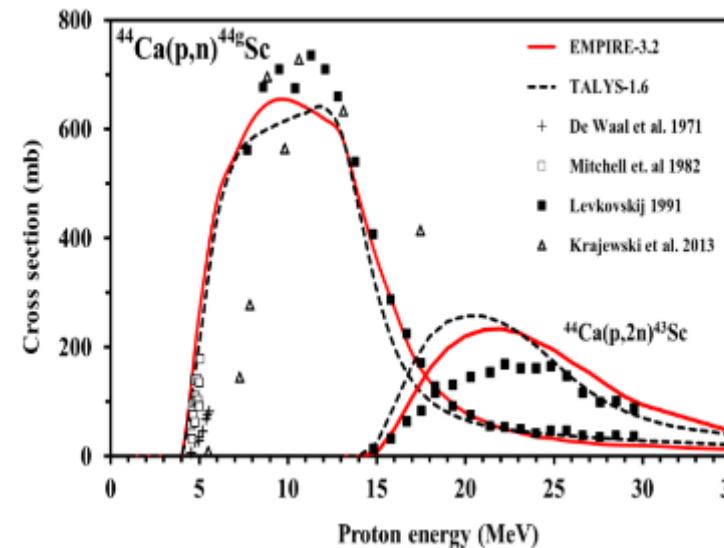
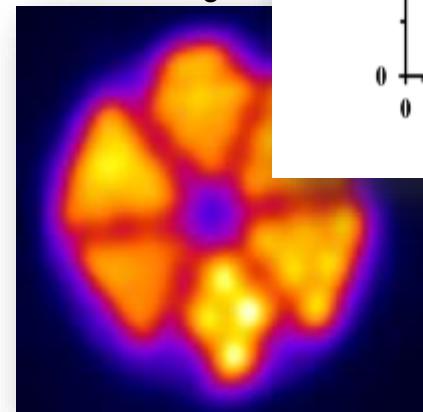
## Target Preparation



## Proton Irradiation of Target Material



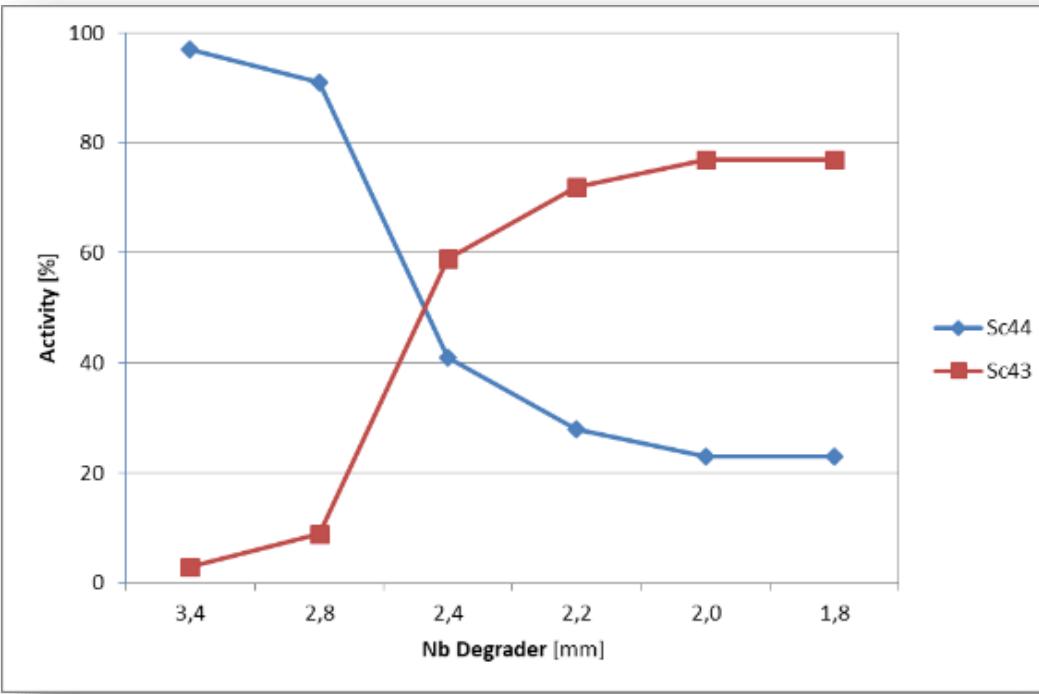
## Radiolabelling and Characterization



## Purification and Processing



# $^{43}\text{Sc}$ : $^{44}\text{Sc}$ at Various Energies

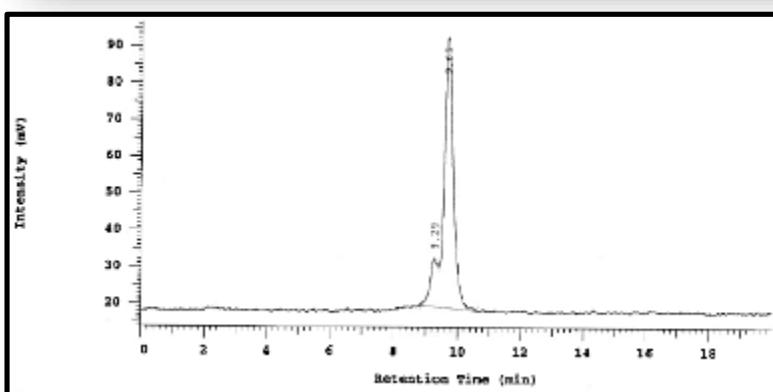


Reduction of proton energy @ PSI:

Nb Degrader [mm]	Proton energy [MeV]
3.4	10.3
2.8	18.6
2.4	22.8
2.2	24.7
2.0	26.4
1.8	28.1
1.0	34.1

$^{44}\text{Sc}$ : 26.2 %,  $^{44\text{m}}\text{Sc}$ : 0.8 %

$^{43}\text{Sc}$ : 73.0 %



DOTANOC labelling (100 %):

$^{44}\text{Sc}$ : 7.5 MBq/nmol ( $^{44\text{m}}\text{Sc}$ : 0.2 MBq/nmol)

$^{43}\text{Sc}$ : 20.9 MBq/nmol



RADIONUCLIDE  
DEVELOPMENT

van der Meulen and Hasler (2019)

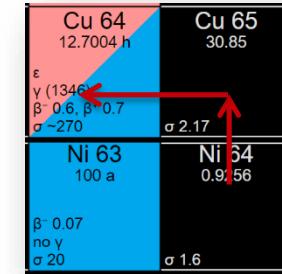


# $^{64}\text{Cu}$ : PET Radionuclide

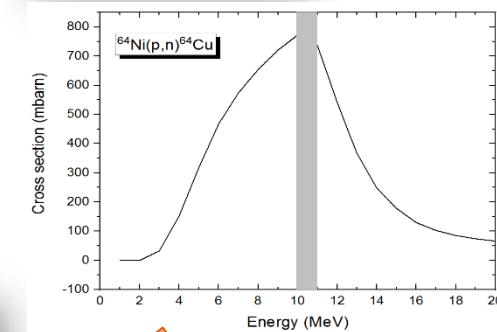
## Target Preparation



## Proton Irradiation of Target Material



## Radiolabelling and Preclinical Imaging

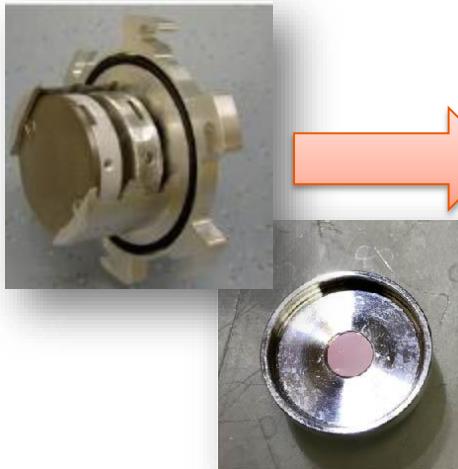


## Chemical Separation and Processing



# <sup>165</sup>Er: Potential Auger Therapy?

## Target Preparation

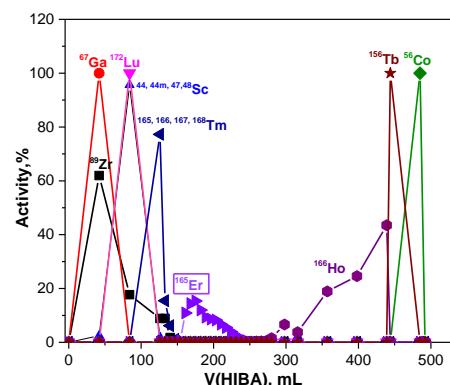


## Proton Irradiation of Target Material



<b>Er 165</b> 10.38 h	<b>Er 166</b> 33.503
$\alpha$ no $\gamma$	$\alpha$ 3 + 14 $\alpha_{\text{abs}} < 7E-5$
$\beta^-$ 38.4 m	$\beta^-$ 100
$\gamma$ 80, 97, 101, 123	$\gamma$ 3.1 + 58 $\alpha_{\text{abs}} < 2E-5$

<b>Tm 165</b> 30.08 h	<b>Tm 166</b> 7.70 h	<b>Tm 167</b> 9.25 d
$\beta^-$ $\gamma$ 243, 47, 297	$\beta^-$ 1.9... $\gamma$ 779, 2062	$\beta^-$ 632... $\gamma$ 100...
IT 200...	IT 164, 174...	IT 298
<b>Er 164</b> 1.801	<b>Er 165</b> 10.38 h	<b>Er 166</b> 33.503
$\alpha$ 18 $\alpha_{\text{abs}} < 0.0012$	$\alpha$ no $\gamma$	$\alpha$ 3 + 14 $\alpha_{\text{abs}} < 7E-5$
<b>Ho 163</b> 1.09 s	<b>Ho 164</b> 38.4 m	<b>Ho 165</b> 100
IT 298	$\beta^-$ 1.0... $\gamma$ 37, 57, 100	$\beta^-$ 3.1 + 58 $\alpha_{\text{abs}} < 2E-5$

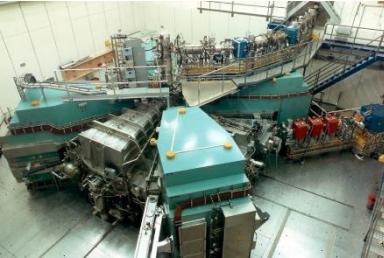


RADIONUCLIDE  
DEVELOPMENT

## Chemical Separation and Processing



# Terbium radioisotopes: novel radionuclides for radiotheragnostics



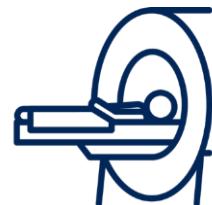
Dy 155 10.0 h	Dy 156 0.056	Dy 157 8.14 h	Dy 158 0.095	Dy 159 144.4 d	Dy 160 2.329	Dy 161 18.889	Dy 162 25.475	Dy 163 24.896
$\epsilon$ $\beta^-$ 0.9, 1.1... $\gamma$ 227...	$\sigma$ 33 $\sigma_{n,a} < 0.009$	$\epsilon$ , $\beta^-$ ... $\gamma$ 326...	$\sigma$ 43 $\sigma_{n,a} < 0.006$	$\epsilon$ $\gamma$ 58, $e^-$ $\sigma$ 8000	$\sigma$ 60 $\sigma_{n,a} < 0.0003$	$\sigma$ 600 $\sigma_{n,a} < 1E-6$	$\sigma$ 120 $\sigma_{n,a} < 2E-5$	
Tb 154 22.7 h $\epsilon$ 1248 347 1420 123... IT 1274...	Tb 155 5.32 d $\epsilon$ $\gamma$ 87, 105, 180 262...	Tb 156 24.4 h $\epsilon$ 88 199 ? IT 50 1222... $\epsilon$ $\gamma$ 534	Tb 157 71 a $\epsilon$ 10.70 s 180 a	Tb 158 100 $\epsilon$ $\gamma$ 944, 962 80... $\beta^-$ 0.9... $\sigma$ 570	Tb 159 100 $\epsilon$ IT (110) $\epsilon$ $\sigma$ 23.2	Tb 160 72.3 d $\epsilon$ $\gamma$ 879, 299 966... $\beta^-$ 0.6, 1.7... $\sigma$ 88...	Tb 161 6.89 d $\beta^-$ 0.5, 0.6... $\gamma$ 26, 49, 75... $\sigma$ 5000	Tb 162 7.76 m $\beta^-$ 1.4, 2.4... 260, 808 88...
Gd 153 239.47 d $\epsilon$ $\gamma$ 97, 103, 70... $\sigma$ 20000 $\sigma_{n,a} 0.03$	Gd 154 2.18 $\sigma$ 60	Gd 155 14.80 $\sigma$ 61000 $\sigma_{n,a} 8E-5$	Gd 156 20.47 $\sigma$ ~2.0	Gd 157 15.65 $\sigma$ 254000 $\sigma_{n,a} < 0.05$	Gd 158 24.84 $\sigma$ 2.3	Gd 159 18.479 h $\beta^-$ 1.0... $\gamma$ 364, 58...	Gd 160 21.86 $\sigma$ 1.5	Gd 161 3.66 m $\beta^-$ 1.6, 1.7... $\gamma$ 361, 315 102... $\sigma$ 20000

**155Tb**

Decay mode	$\gamma$ (87, 105,... keV) (Auger $e^-$ )
Half-life	5.32 d
Main application	SPECT

**161Tb**

Decay mode	$\beta^-$ (154 keV), Auger $e^-$
Half-life	6.96 d
Main application	$\beta$ -Therapy



<https://www.nndc.bnl.gov/nudat2/>

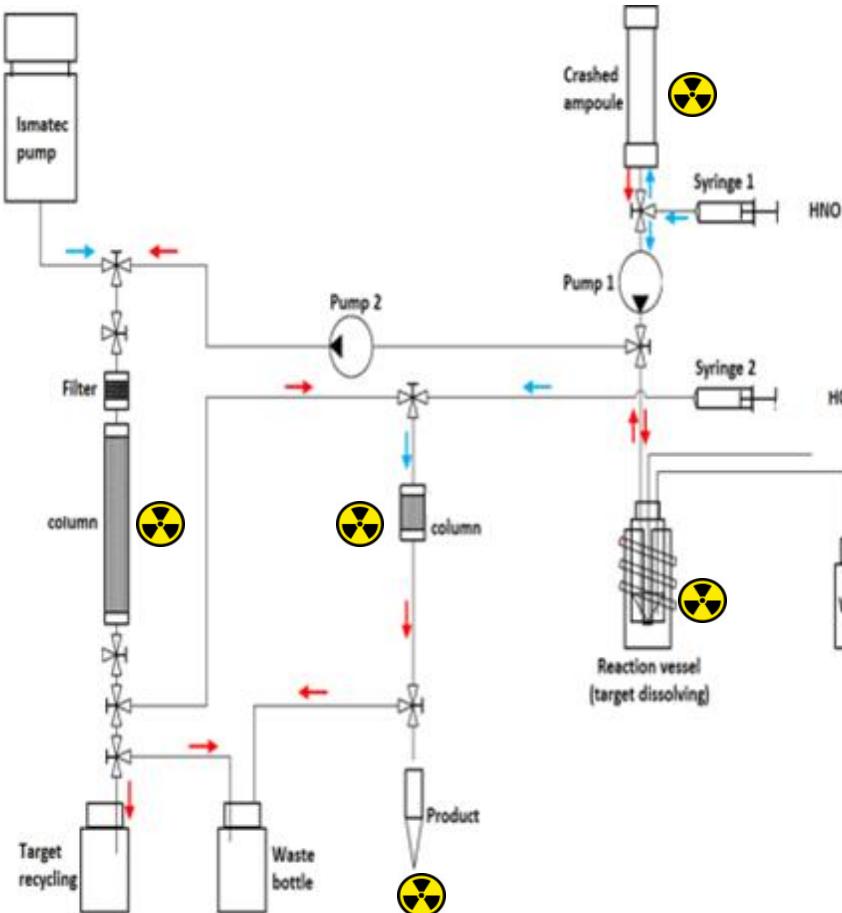


RADIONUCLIDE  
DEVELOPMENT

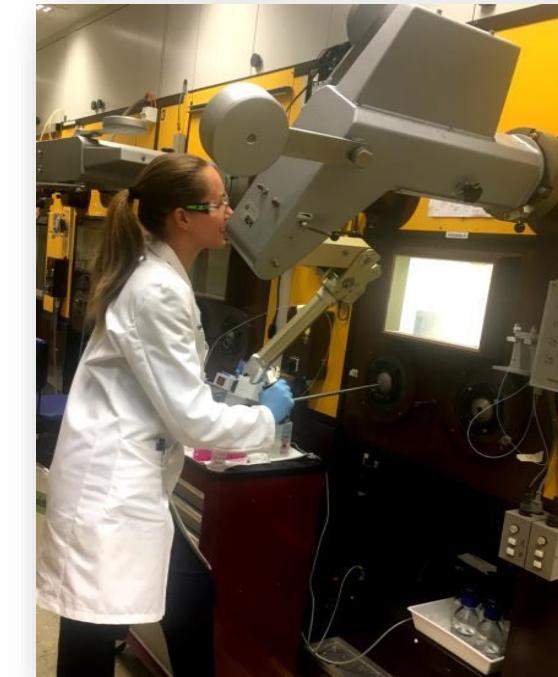


# Chemical Separation of Tb from Gd Target Material

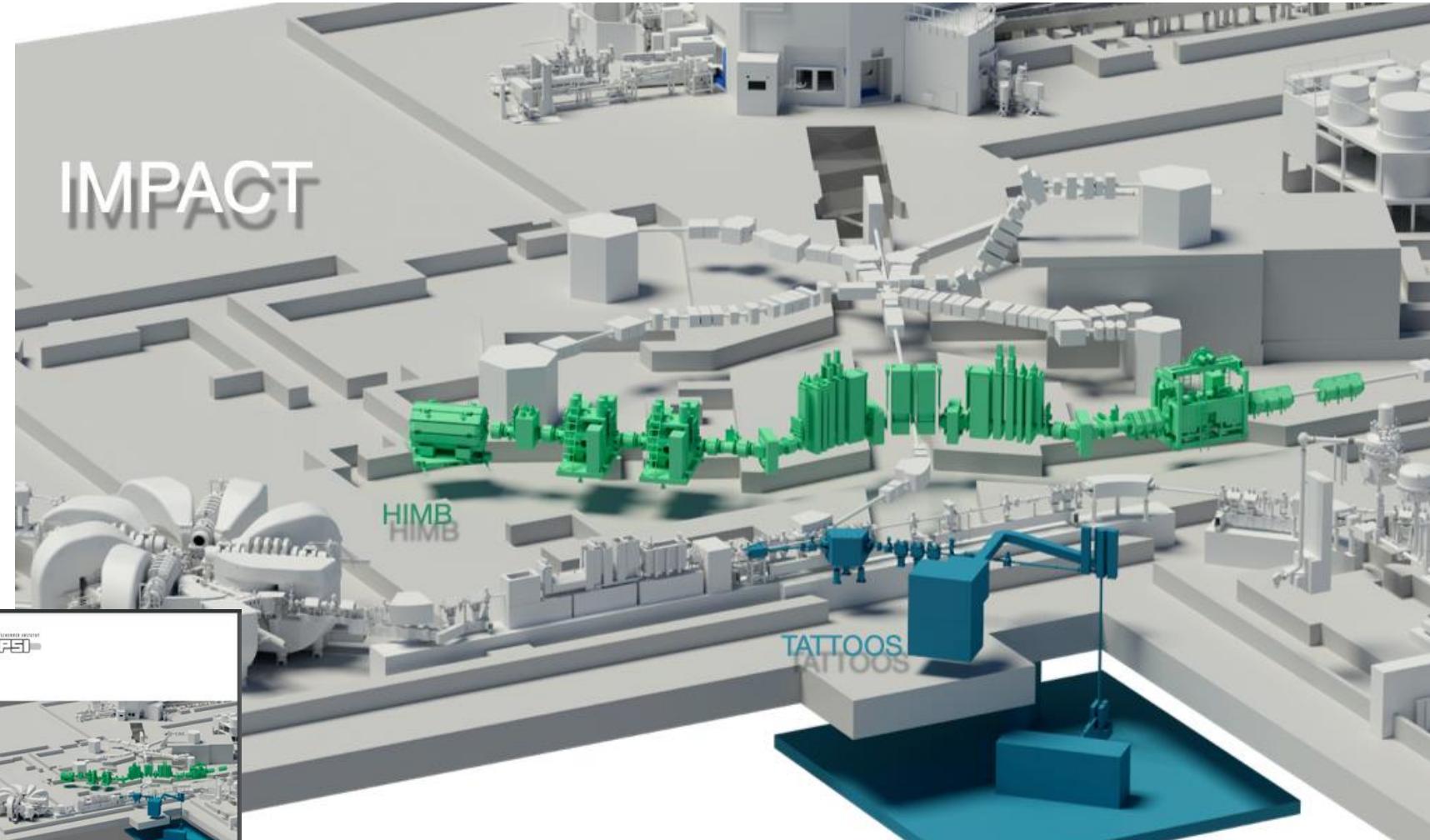
## Scheme concept of the Purification Process:



Separation process  
performed in a hot cell



Gracheva et al., EJNMMI Radiopharmacy and Chemistry (2019).  
Favaretto et al., EJNMMI Radiopharmacy and Chemistry (2021).



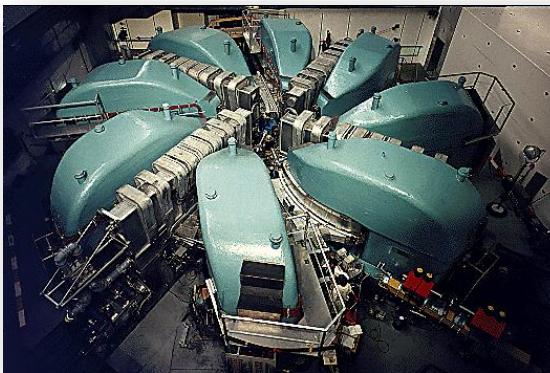
<https://www.psi.ch/en/impact>

CDR: <https://www.dora.lib4ri.ch/psi/islandora/object/psi:41209>



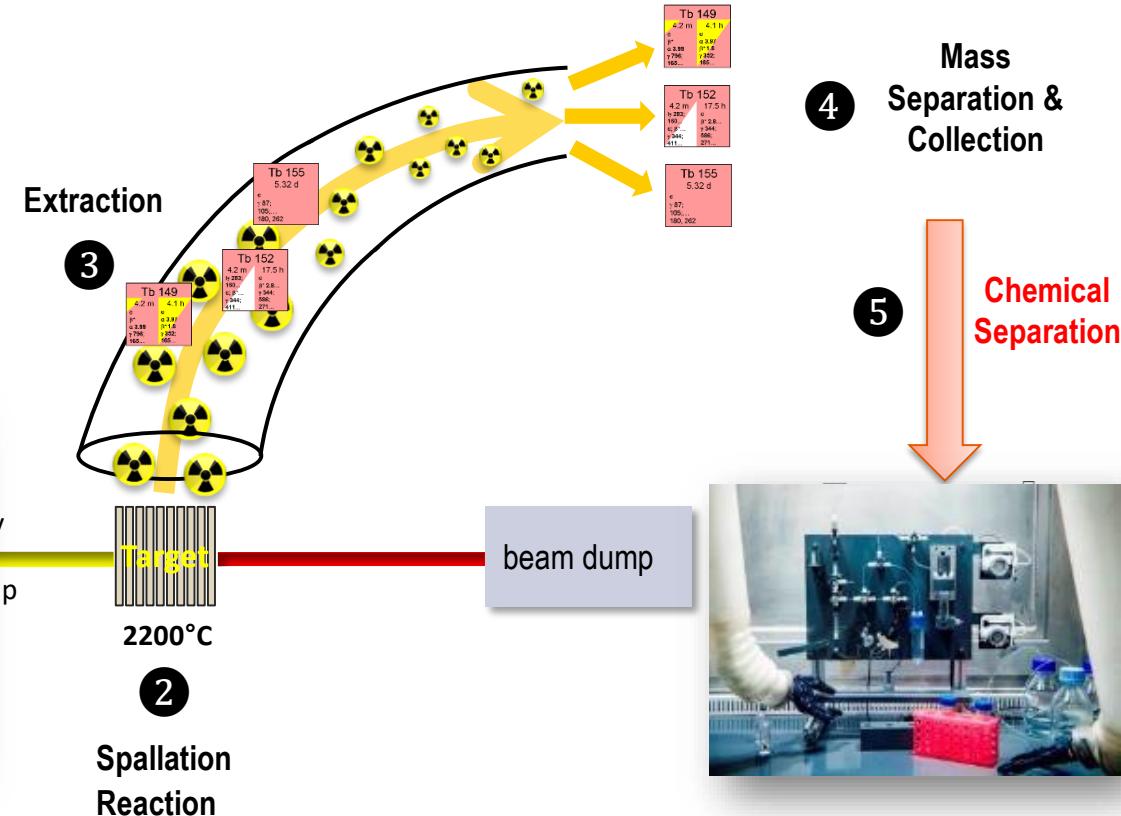
# Radionuclide Development using Isotope Separation OnLine (ISOL)

Cyclotron  
producing H<sup>+</sup>



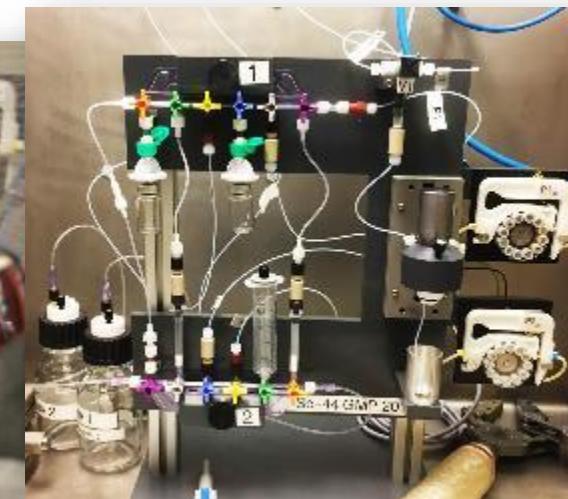
MeV  
μAmp

2  
Spallation  
Reaction



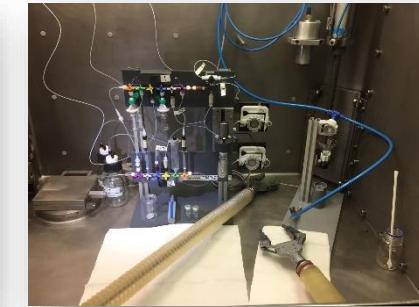
# Vital Aspects of Radionuclide Development often overlooked

- Targetry use and optimization requires development!
- The resultant (dependant on choice of target) **chemical separation** requires development!
- **Optimization** of the production of a radionuclide (incl. GMP/registration) takes years...
- Multidisciplinary: physics, chemistry, engineering.



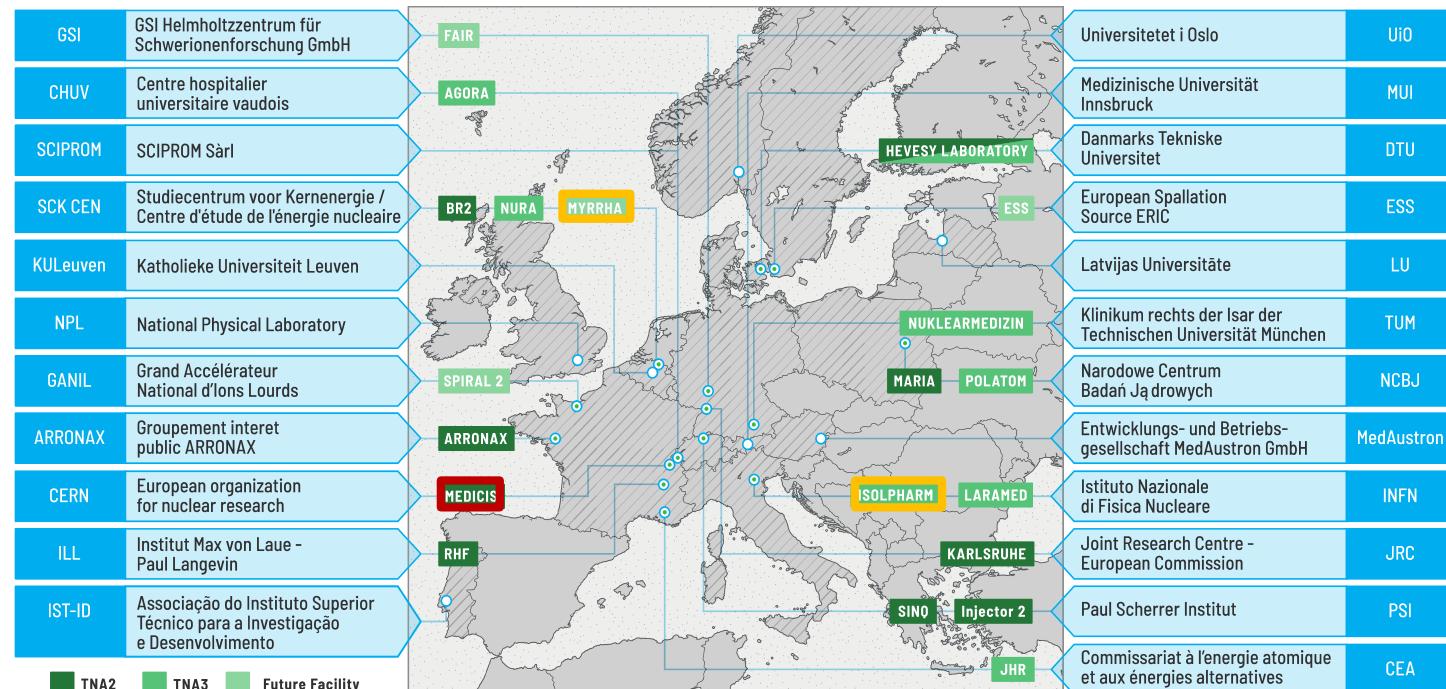
# Conclusions and Outlook

- PSI's HIPA facility is used extensively for the development of novel radionuclides.
- Developments can be implemented (technology transfer) for use at a medical cyclotron facility.
- Chemical separations can be upscaled.
- Production development can lead to the desired radionuclide reaching a patient in a clinical setting.



# The Future of Nuclear Medicine in the EU

## The PRISMAP consortium



- Facility with Isotope mass separation
- Facility planned with Isotope mass separation



European  
Medical  
Radionuclides  
Programme

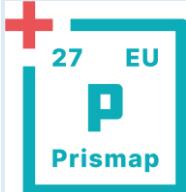


# Thank you

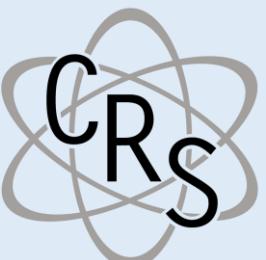


RADI<sup>\*</sup>NUCLIDE  
DEVELOPMENT

## Acknowledgements



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DEDICATED TO CURING NEUROENDOCRINE CANCER



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From good practices towards socioeconomic impact

