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PSI

CYC 2019 22–27 SEPTEMBER CAPE TOWN

Nicholas P. van der Meulen Ph.D.

Radionuclide Development

The use of PSI's IP2 beam line towards exotic radionuclide development and its application towards proof-of-principle preclinical and clinical studies

International Conference on Cyclotrons and their Applications
24 September 2019

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Use of Large Facilities at PSI

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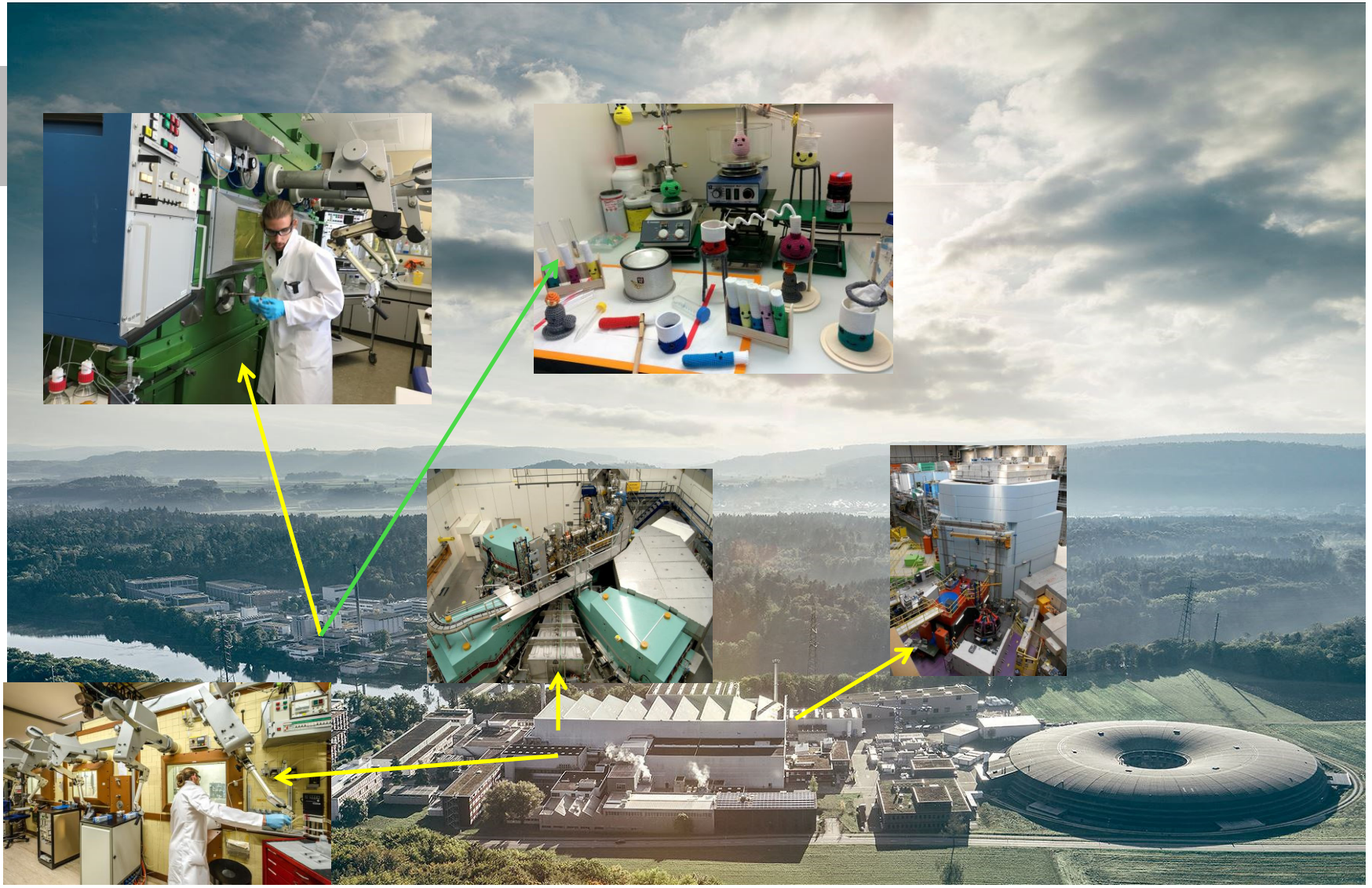
Use of Large Facilities at PSI



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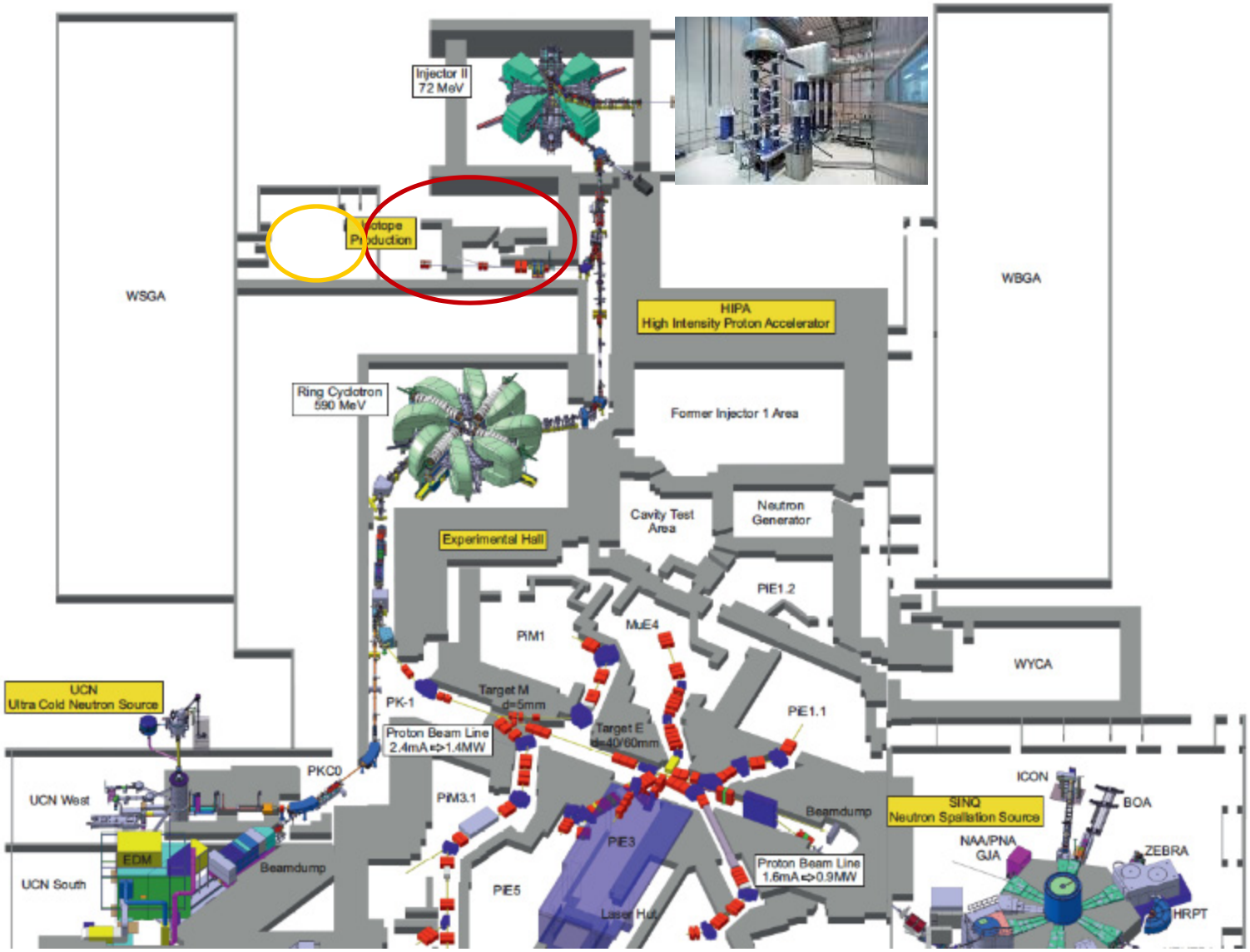
PSI's High Intensity Proton Accelerator Complex



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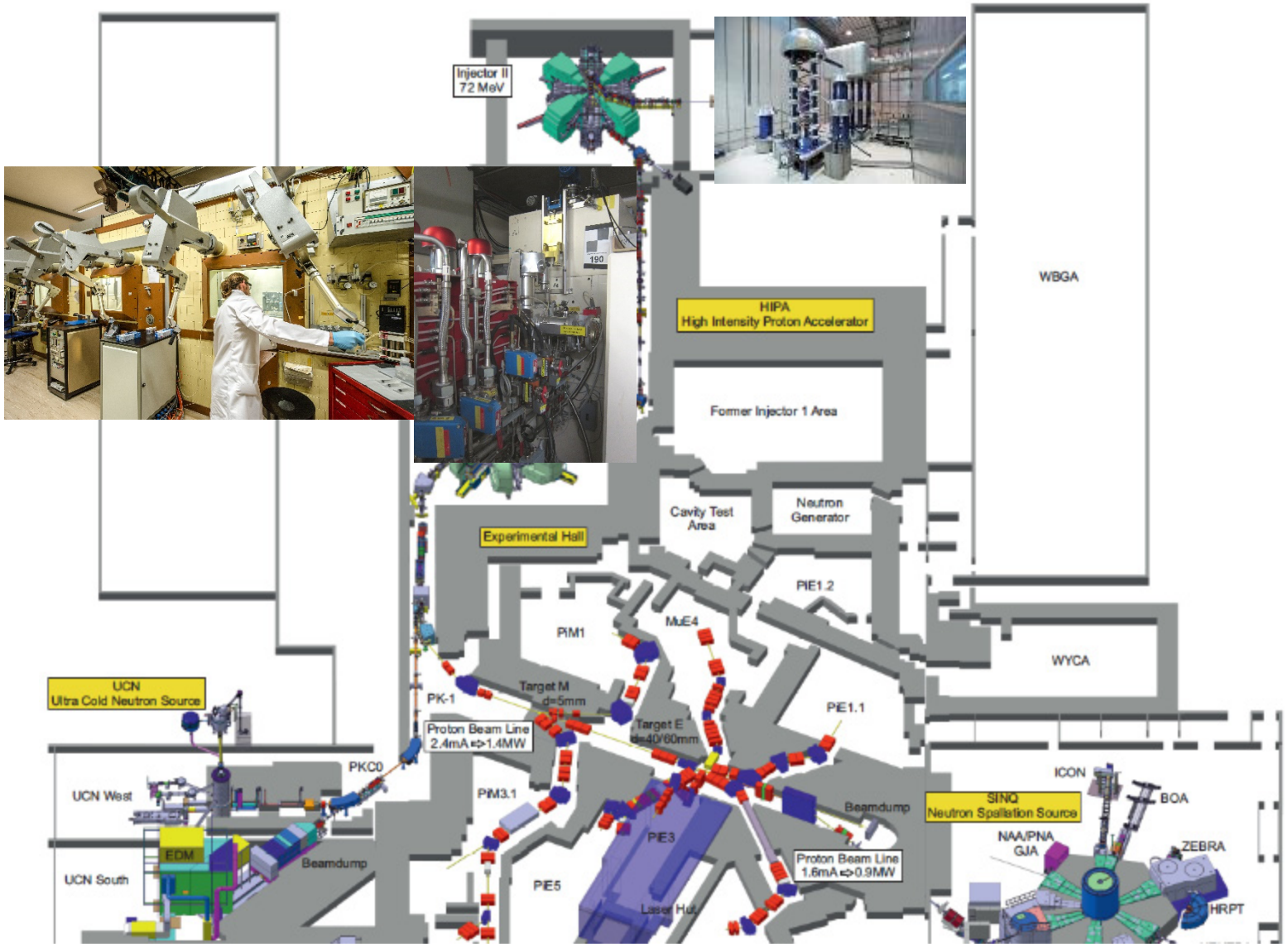
PSI's High Intensity Proton Accelerator Complex



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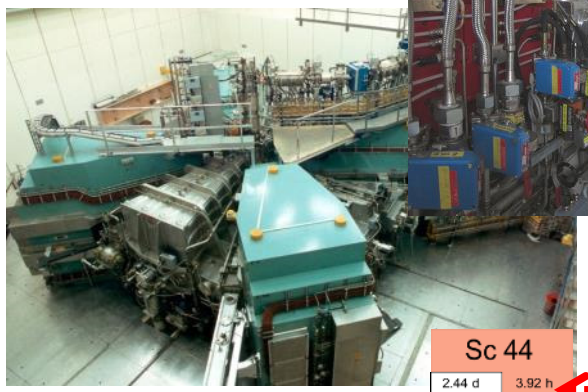
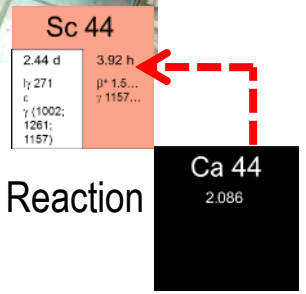
Radionuclide Development at PSI

Target Preparation & Encapsulation

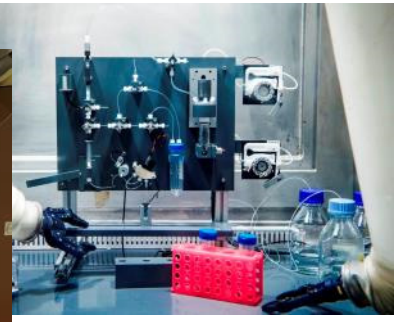
Target Loading into Irradiation Station

Target Irradiation with Protons

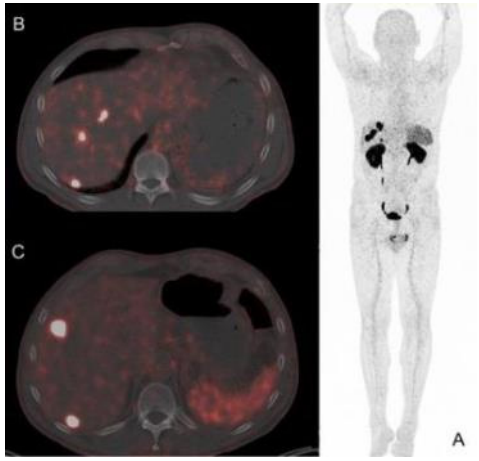




(p,n) Nuclear Reaction

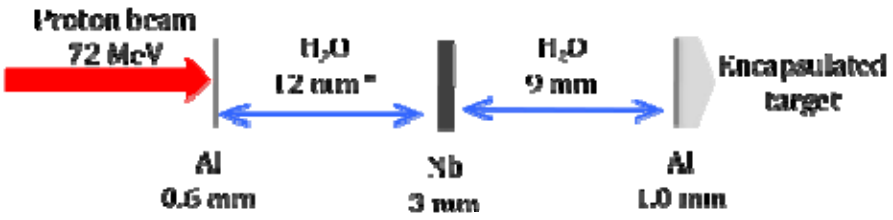


Chemical Separation and Processing



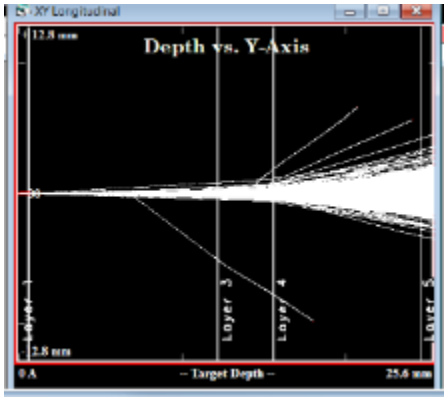
Radiolabelling and Imaging

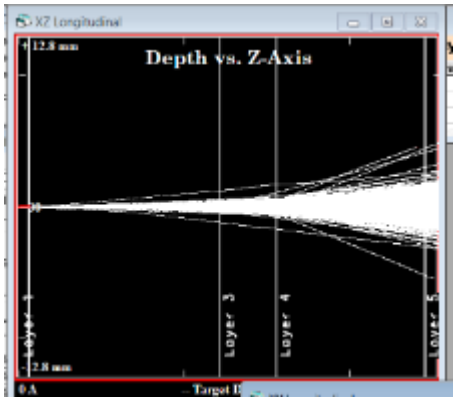
Energy Degradation @ IP2

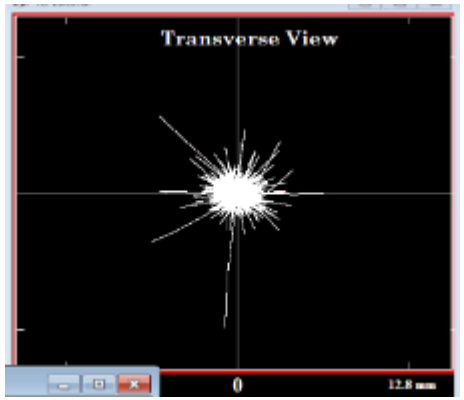


3.4 mm Nb Degrader

72MeV Proton beam - Al (0.6mm) – **11.6 mm H_2O – Nb – 9 mm H_2O** – Al (1mm) – Target → **10.3 MeV**



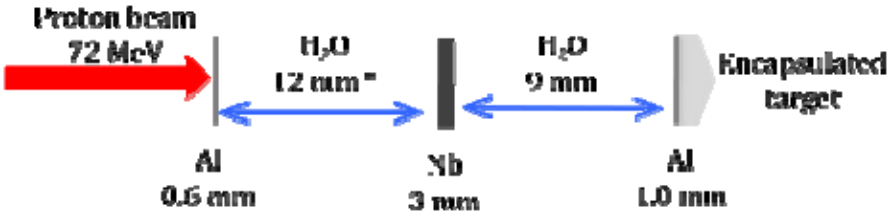




Calculations done with SRIM-2013; Average of 1000 Ions

Radionuclide Development

Energy Degradation @ IP2



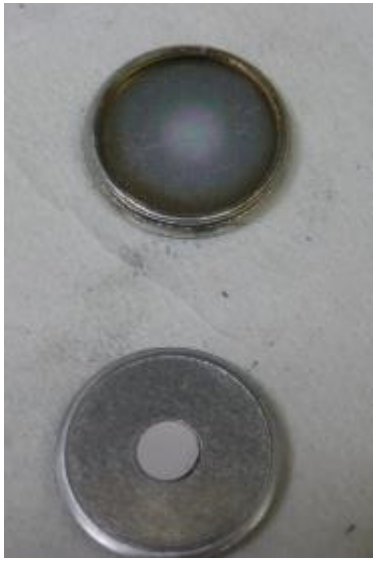
Reduction of proton energy @PSI:

Nb Degrader [mm]	Proton energy [MeV]
3.4	18.3
2.8	18.6
2.4	22.8
2.2	24.7
2.0	26.4
1.8	28.1
1.0	34.1

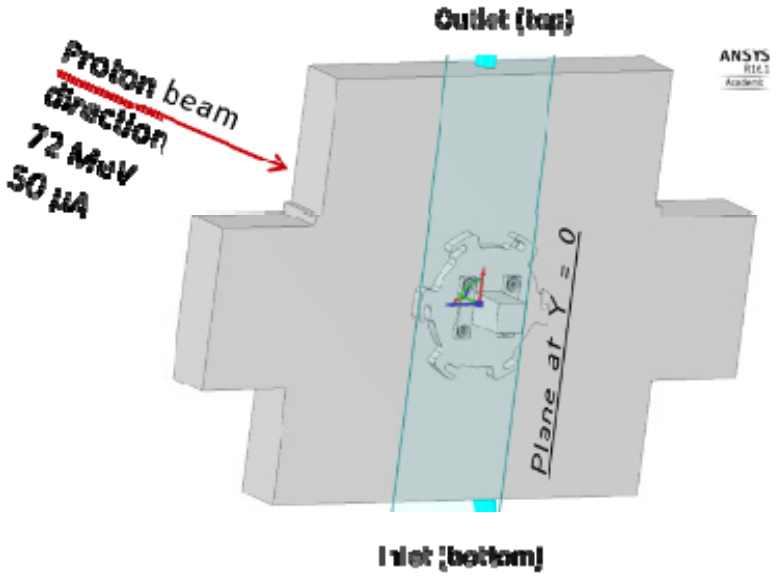
Radionuclide Development

Irradiation and its Effect on Target Cooling

- Cooling to be optimized – no rastering, wobbling or beam sweeping on target.
- Defocusing of beam has been performed.
- Cooling on target becomes an issue, particularly when it comes to longer irradiations.
- Beam settings are important: see Dr. H. Zhang's presentation on Wednesday (WEB04).

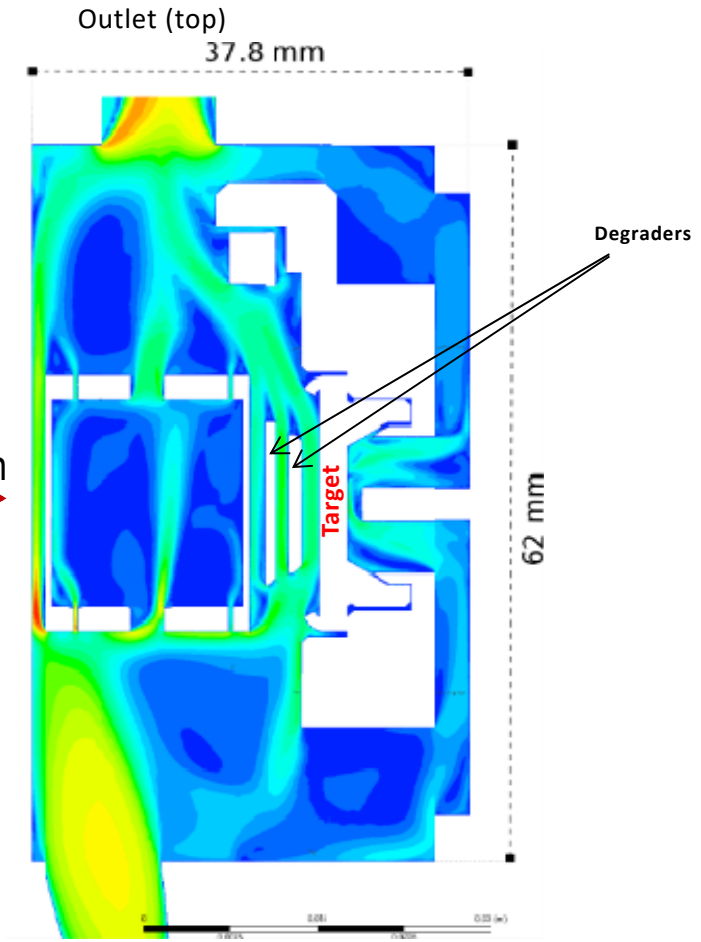


IP2 Geometry: cutting plane



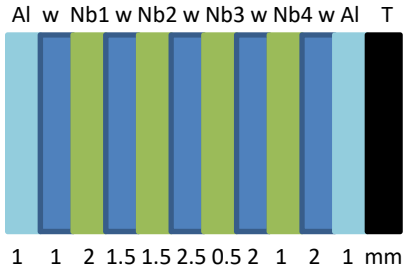
H⁺ beam direction
72 MeV
50 µA

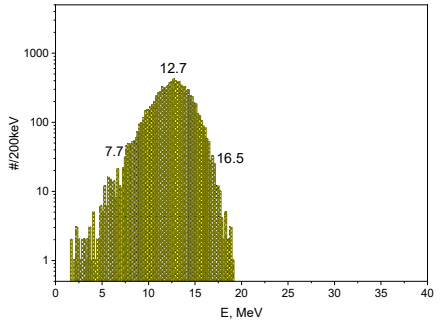
water channels



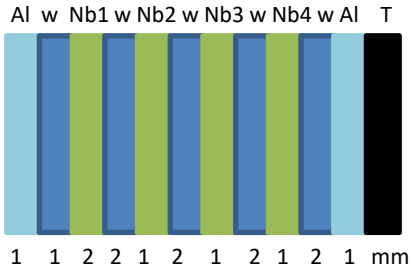
Upgrade of Degrading Concept To Improve Cooling

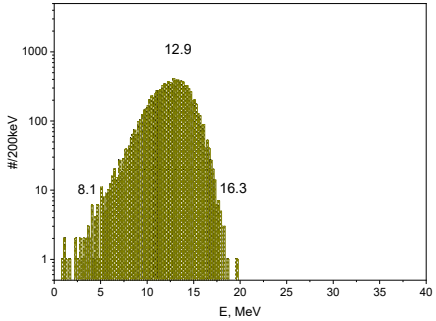
5mm Nb
9 mmH_2O
2mm Al





5mm Nb
9 mmH_2O
2 mm Al

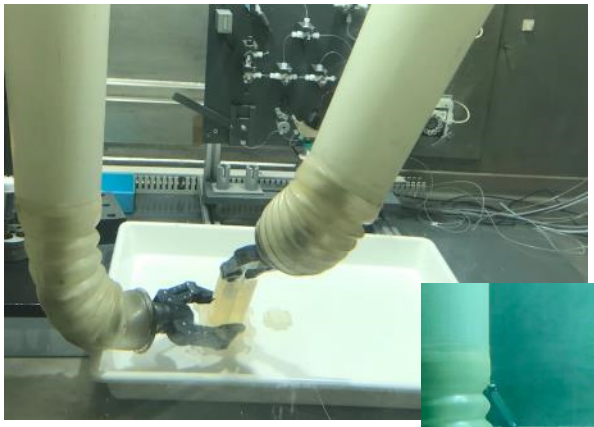


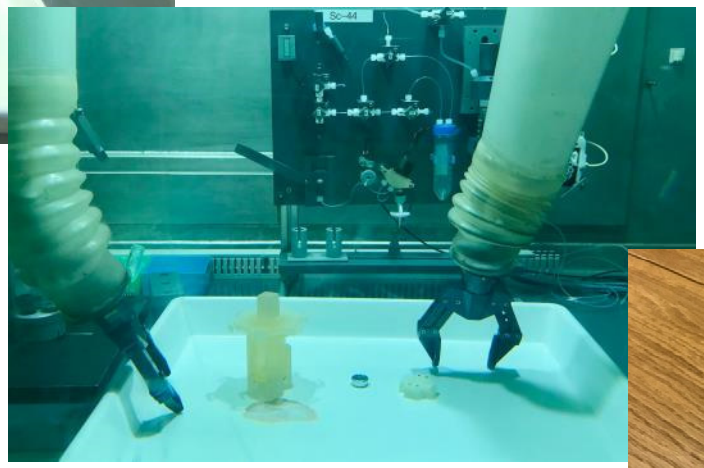


Various compositions with same thickness do not significantly change the result

YZ-Scattering: ~8 mm, i.e. target radius ~ beam radius + 4mm

Testing and Manipulation of Dummy Target



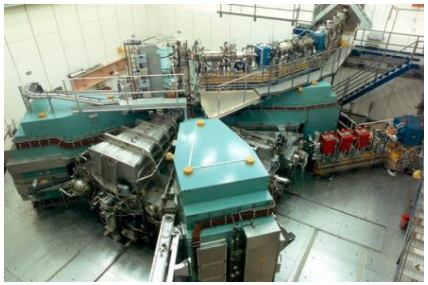


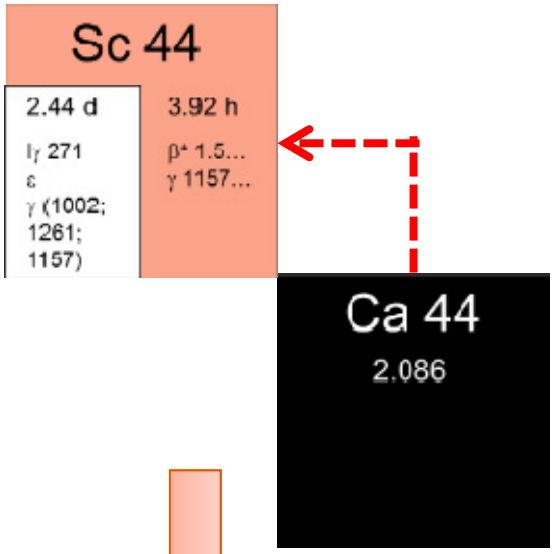
- After irradiation, the target has to be removed remotely
- Use of a hot cell necessary
- Target holder needs easy mounting/dismounting

^{44}Sc: “From-Bench-To-Bedside”

Target Preparation

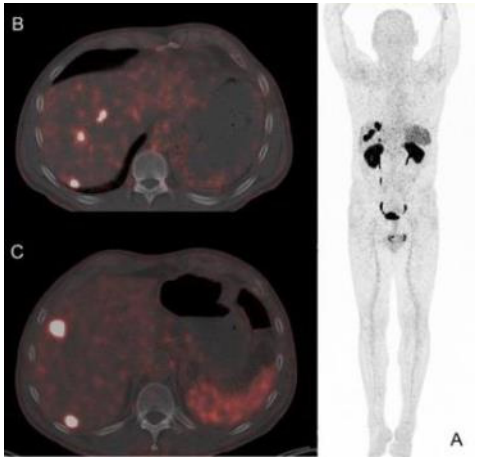
Proton Irradiation of Target Material

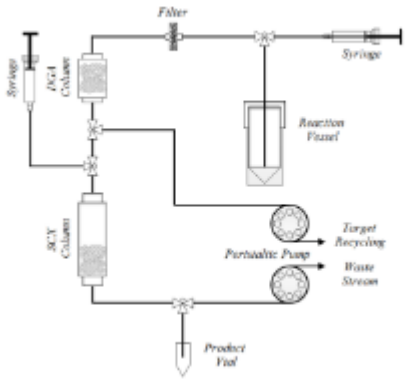




Radionuclide Development

Radiolabelling and Imaging





Chemical Separation and Processing

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

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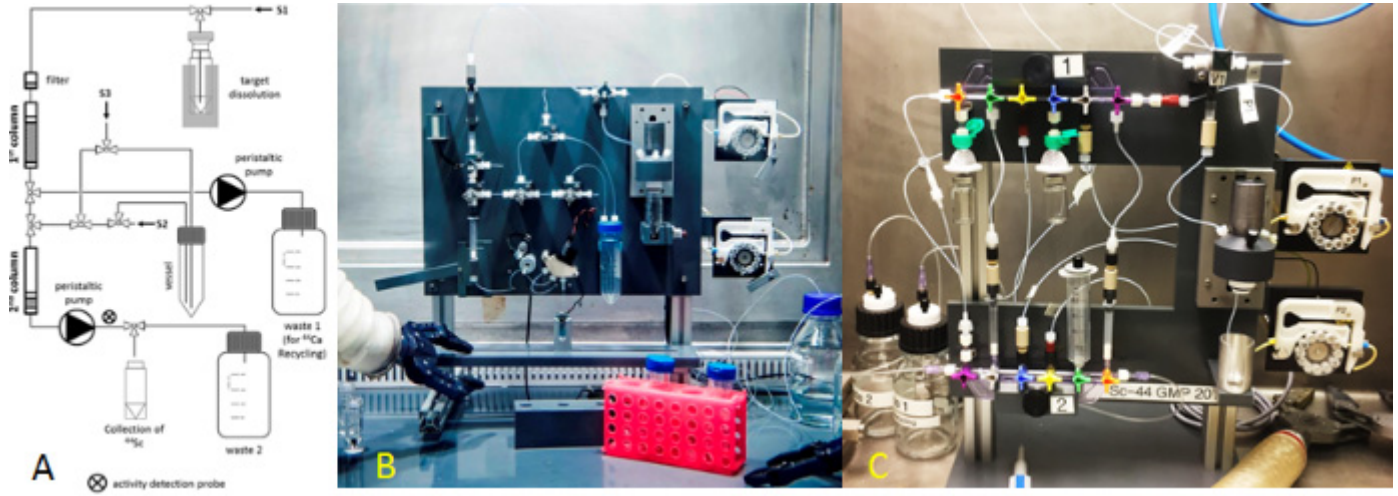
Radionuclide Development : ^{44}Sc



Initial PSI Target

Current PSI Target/ETH

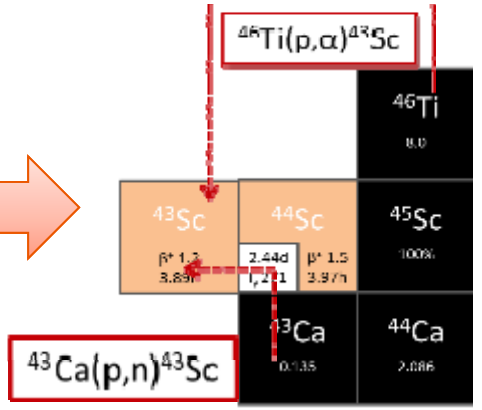
UniBe Target

van der Meulen *et al.* (2015); van der Meulen et al. (2018)

^{43}Sc: A Proposed Improvement in Radiometal PET

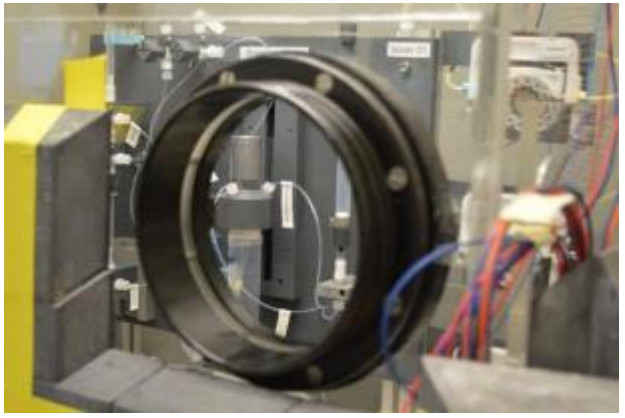
Target Preparation

Proton Irradiation of Target Material

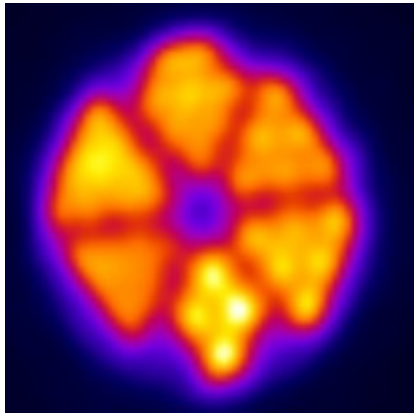


Radionuclide Development

Chemical Separation and Processing



Radiolabelling and Imaging

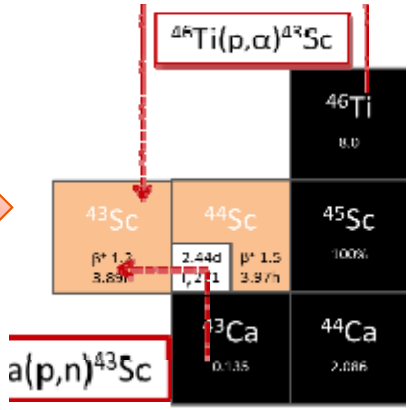


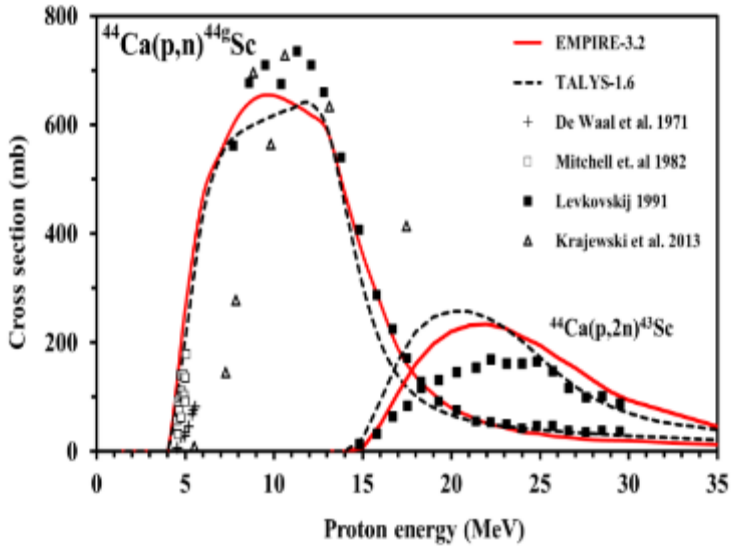
Domnanich *et al.* (2017); van der Meulen and Hasler (2019)

^{43}Sc: A Proposed Improvement in Radiometal PET

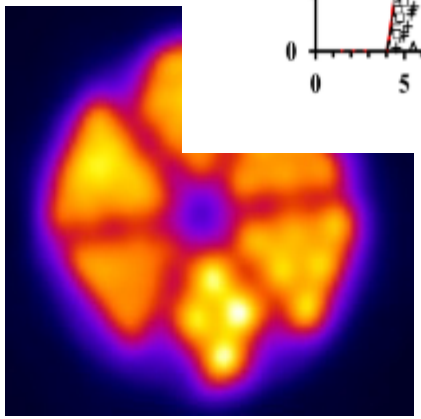
Target Preparation

Proton Irradiation of Target Material

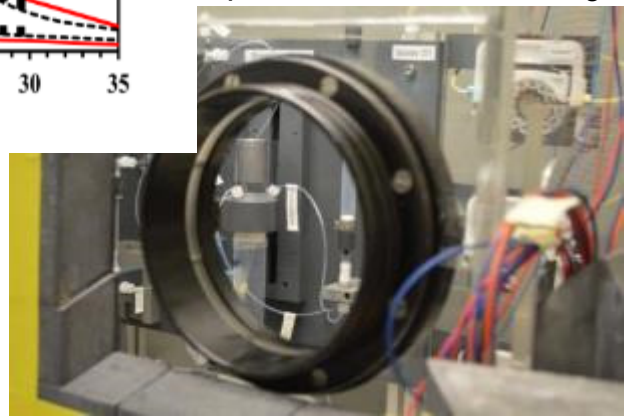




Radiolabellir

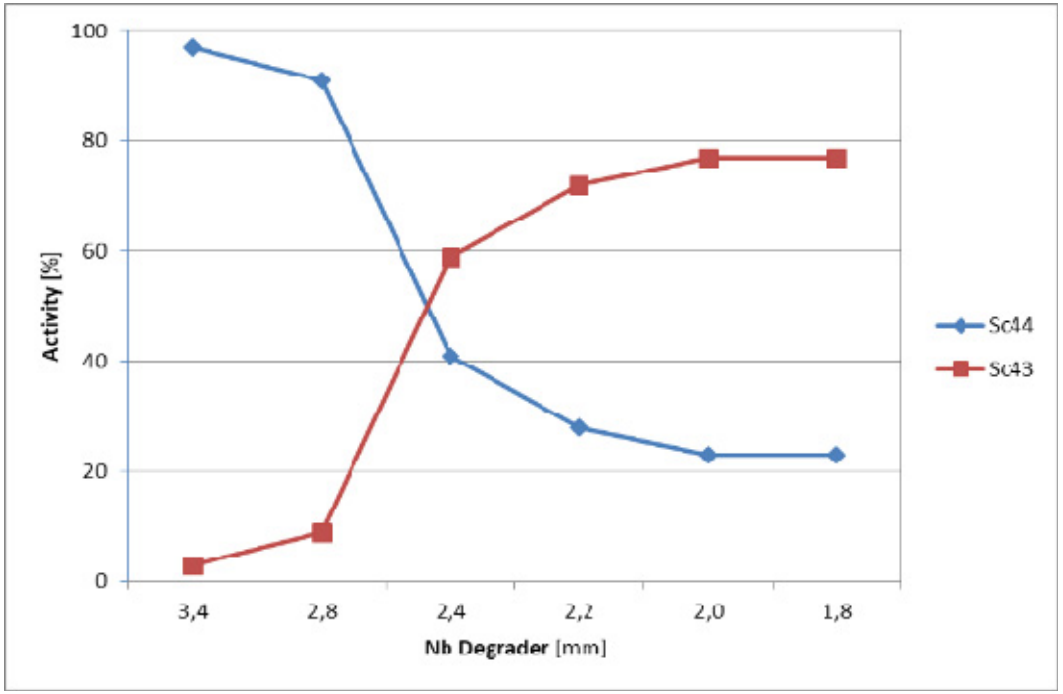


Separation and Processing



Domnanich *et al.* (2017); van der Meulen and Hasler (2019)

^{43}Sc:^{44}Sc at Various Energies

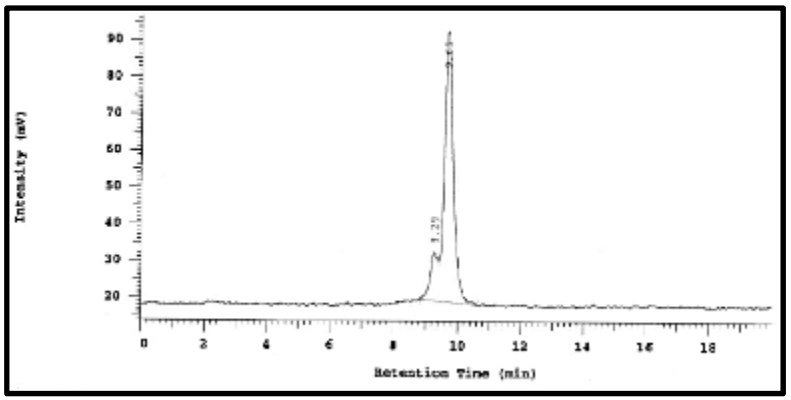


Reduction of proton energy @PSI:

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}Sc: 26.2 %, ^{44m}Sc: 0.8 %

^{43}Sc: 73.0 %



DOTANOC labelling (100 %):

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

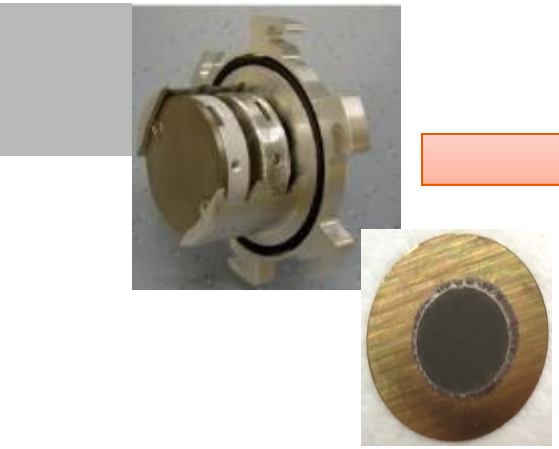
^{43}Sc: 20.9 MBq/nmol

Radionuclide Development

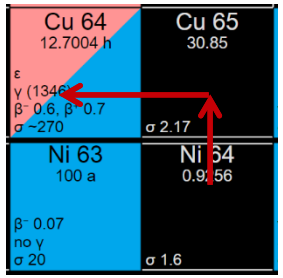
van der Meulen and Hasler (2019)

^{64}Cu: PET Radionuclide

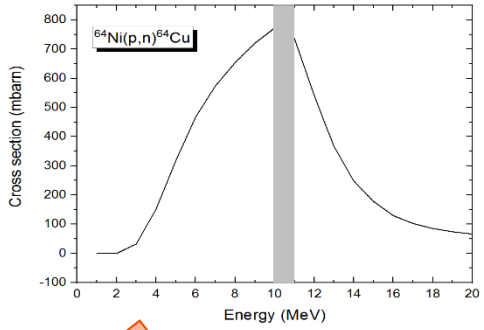
Target Preparation



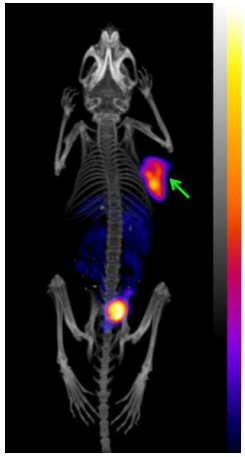
Proton Irradiation of Target Material

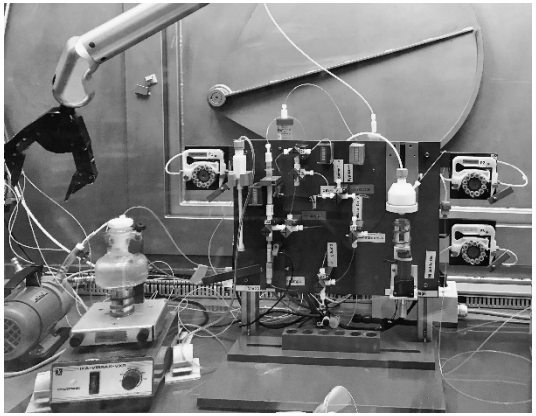


Radionuclide Development



Radiolabelling and Preclinical Imaging



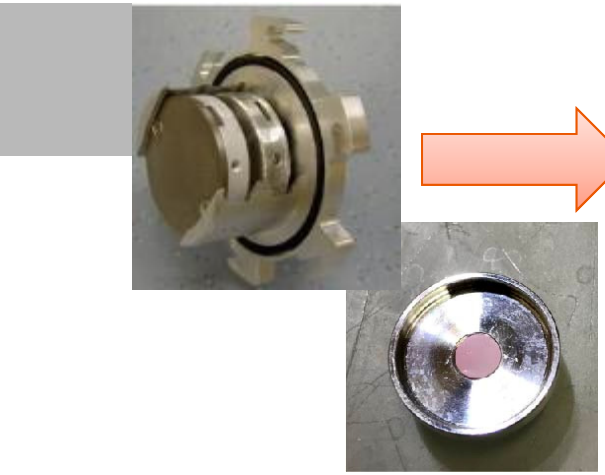


Chemical Separation and Processing

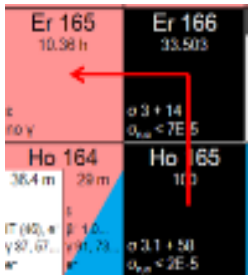
Van der Meulen et al. 2019; Farkas et al. 2016; Umbricht et al 2019.

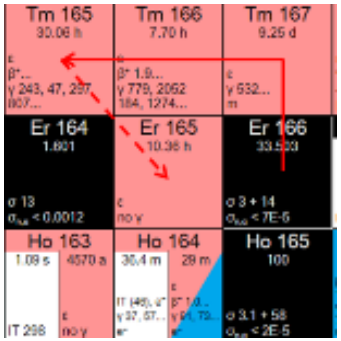
^{165}Er: Potential Auger Therapy?

Target Preparation



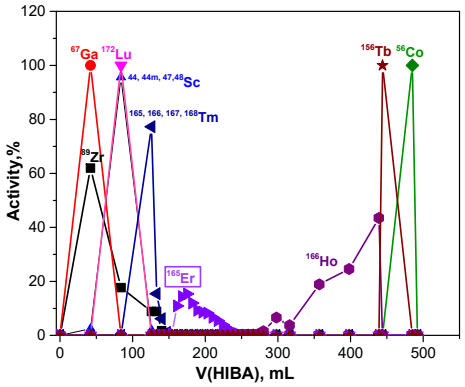
Proton Irradiation of Target Material





Radionuclide Development

Radiolabelling and Preclinical Imaging

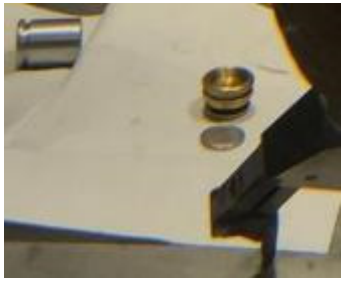


Chemical Separation and Processing

Gracheva et al. 2018; Gracheva et al. 2019.

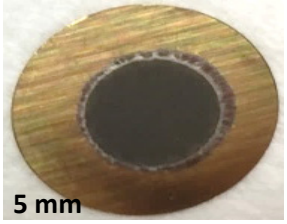
Implementation @ IBA Cyclone 18, Bern

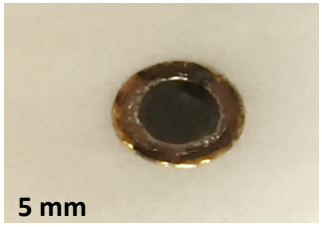
- Irradiation of ^{44}CaO(@ 5µA) → ^{44}Sc production;
- Irradiation of ^{64}Ni → ^{64}Cu production;
- Irradiation of Ho and $^{166}Er_2O_3$ → ^{165}Er production;
- Chemical separation @PSI;
- Proof-of-principle with medical cyclotron.



PSI: 10 mm

SWAN: 6 mm

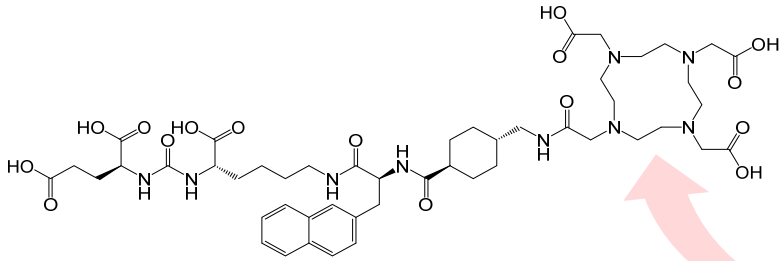




Radiolabeling of Biomolecules (e.g. PSMA-617)

Biomolecule

- Chemical synthesis: metal-free working environment
- Preparation of stock solution: in metal free environment (no metal spatula)



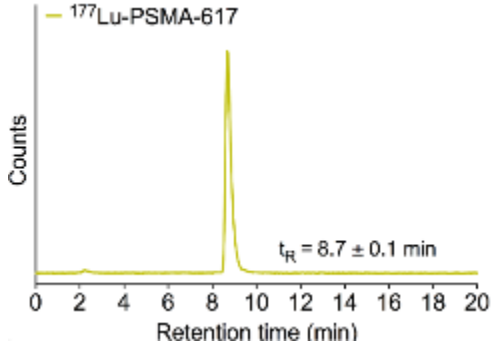
The macrocyclic chelator is NOT selective for the radiometal of interest, but will coordinate other (cold) metal ions.

Radionuclide

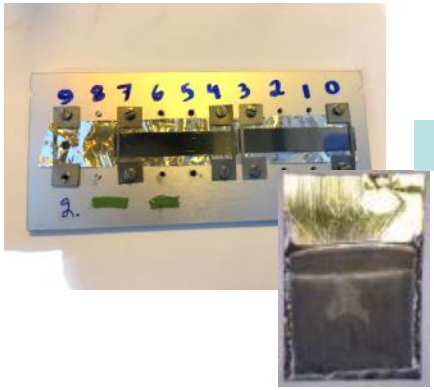
- **Radionuclidic purity:** **>99.9%**
- **Chemical purity:** **no metal ions (i.e. absence of Fe, Co, Cu, Zn, Gd, Pb etc.)**

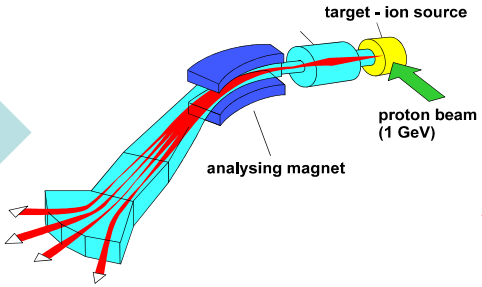
Labeling Conditions

- pH value: ~ 4.5
- Temperature: 95 °C
- Incubation time: 15 min
- Specific activity: **up to 150 MBq/nmol (^{177}Lu)**

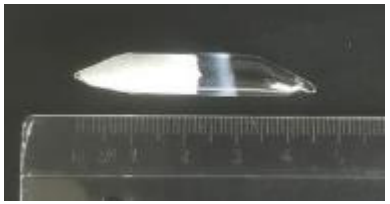


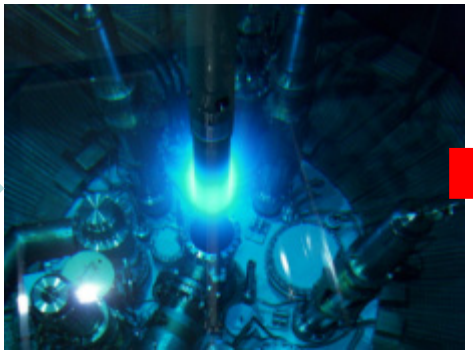
Vital Aspects of Radiochemistry often overlooked





Before introduction to GMP

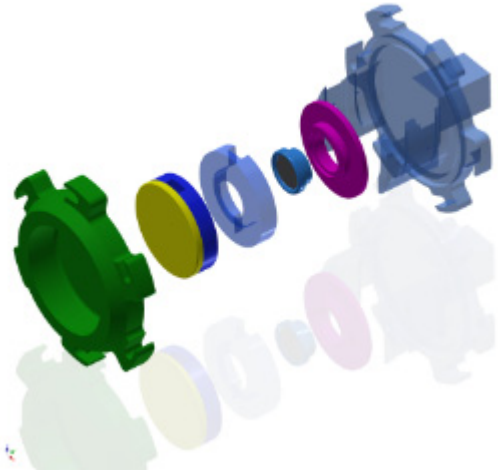


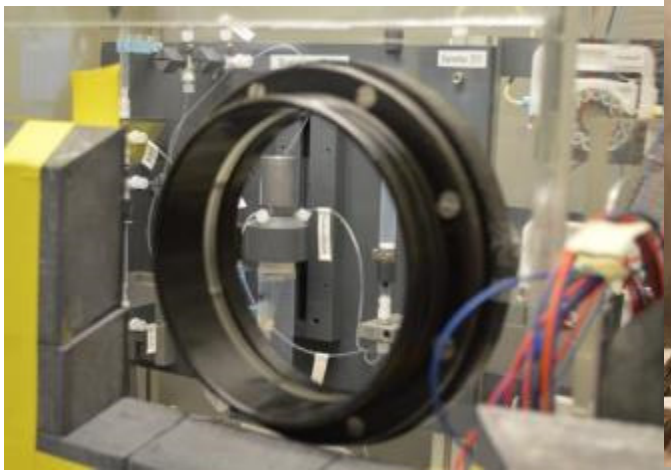


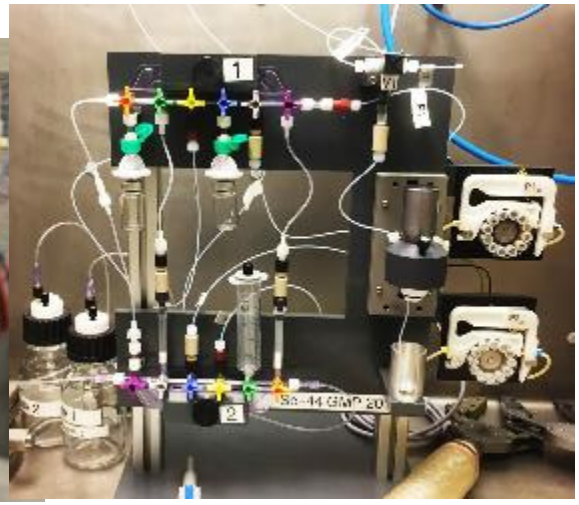
Targetry | Irradiation Facility | **Chemical Separation**

Vital Aspects of Radiochemistry 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 takes years…
- Multidisciplinary: physics, chemistry, engineering.

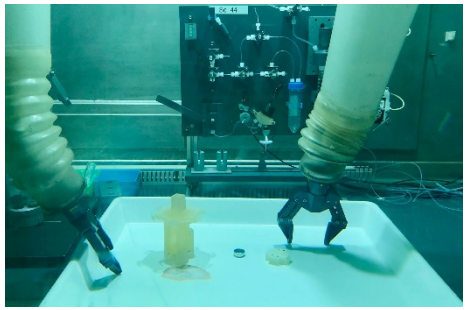
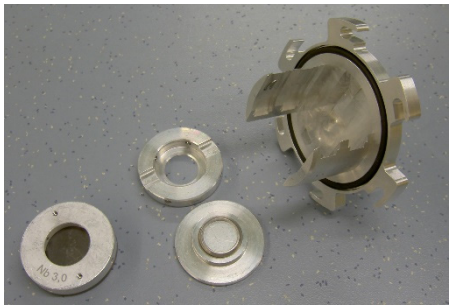


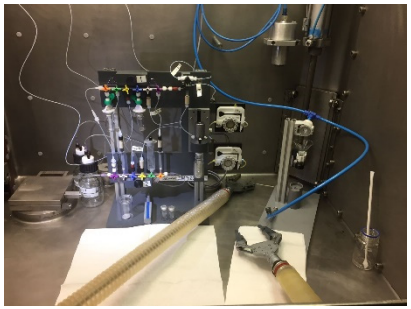




Conclusions and Outlook

- PSI's IP2 beam line is used extensively for the development of novel radionuclides.
- The use of degraders is important to degrade the 72 MeV proton beam.
- The cooling of target is important, therefore, target holder is being redesigned.
- Developments can be implemented (technology transfer) for use at a medical cyclotron facility.



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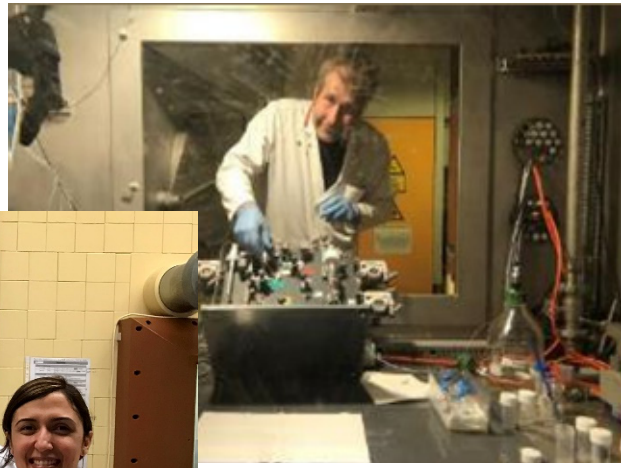

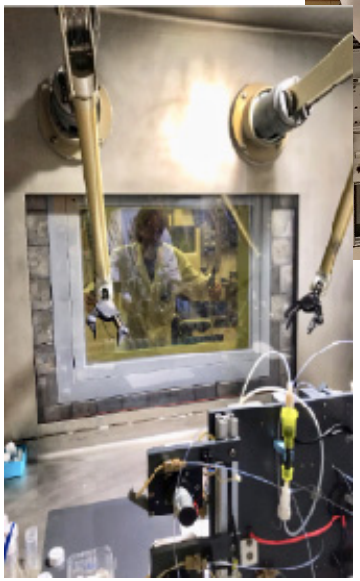

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