Mass-separation of medical $^{43,44,47}Sc$ radionuclides at the CERN-MEDICIS facility

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Theranostics

- Radiopharmaceuticals - group of pharmaceutical drugs containing radioactive isotopes used for:
  - SPECT – Single Photon Emission Computed Tomography;
  - PET/CT – Positron Emission Tomography/Computed Tomography;
  - Radionuclide therapy.
- Biological molecules or sometimes artificial building blocks for specific targets, labeled with radioactive positron (β^+)/gamma or alpha and β^- emiters;
- Theranostics - derived from <u>Therapy and Diagnostics,</u> and refers to the strategy of utilising radioactively labelled drugs for both purposes
  - So called ”Treat what You see” technique

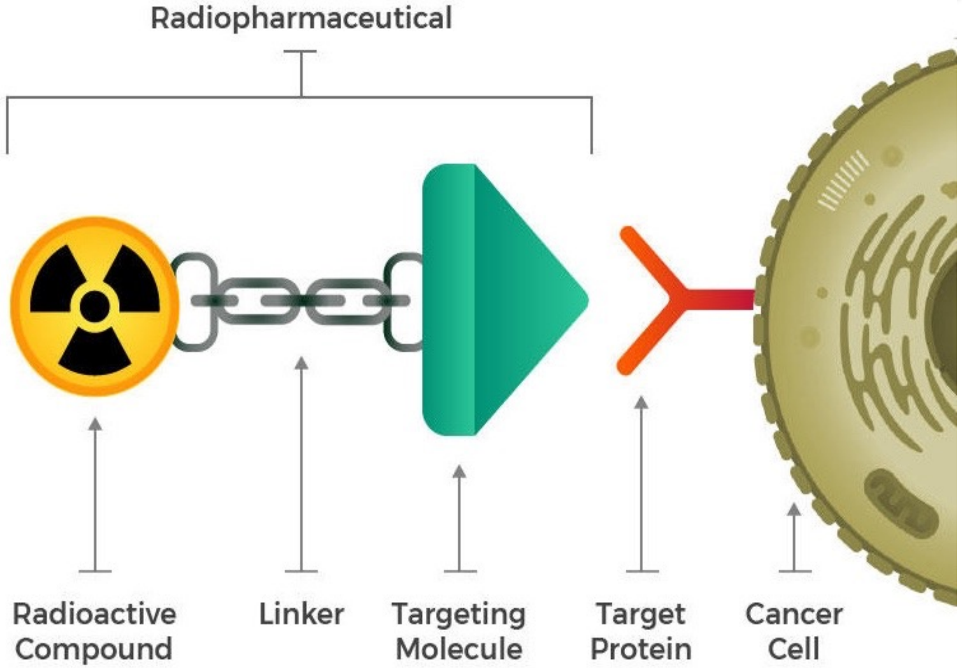
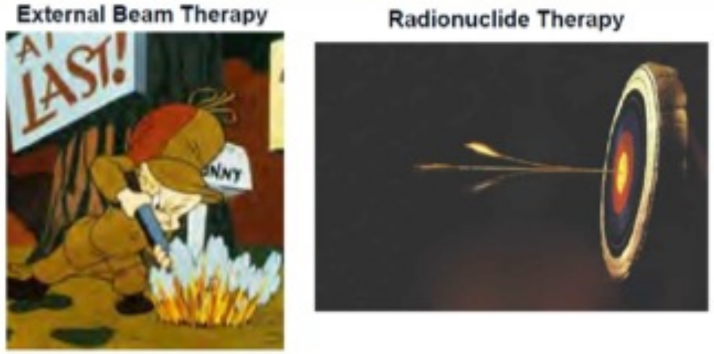


Fig. 1. Illustrative structure of a ligand radiopharmaceuticalradiopharmaceutical and its cell binding



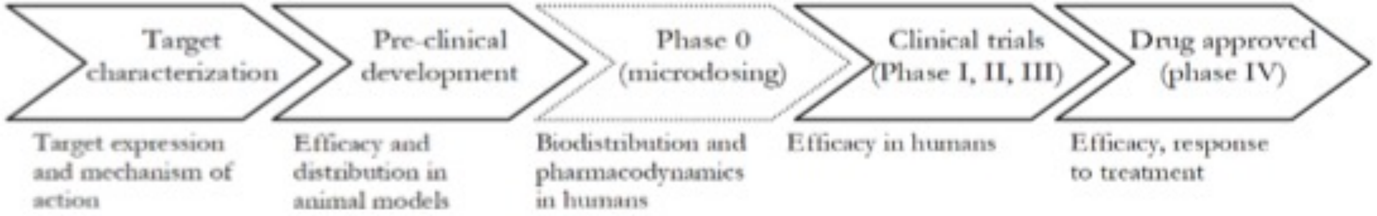


Fig. 2. Illustrative structure of drug develoment *Current Radiopharmaceuticals*, 2012, *5(2)* 90-98.

Why Scandium ?

- Cost and efficiency:
  - Sc radionuclides can be obtained from natural Ti and V targets – cost efficient;
  - No expensive, enriched, low abundancy isotopes required;
  - Sc from natural Ti can be obtained in suffiently large quantities for medical applications – GBq of radioactivity;
  - Can be produced by **cyclotrons** – no nuclear reactors needed.
- ^{43,44g}Sc have diagnostic and ^{47}Sc therapeutic application decay properties – perfect for so called “matched pair” RFP’s;
  - Same chemistry, different application;
- Scandium radionuclides can be produced and decay to the most biocompatible stable chemical elements such as Ca and Ti;

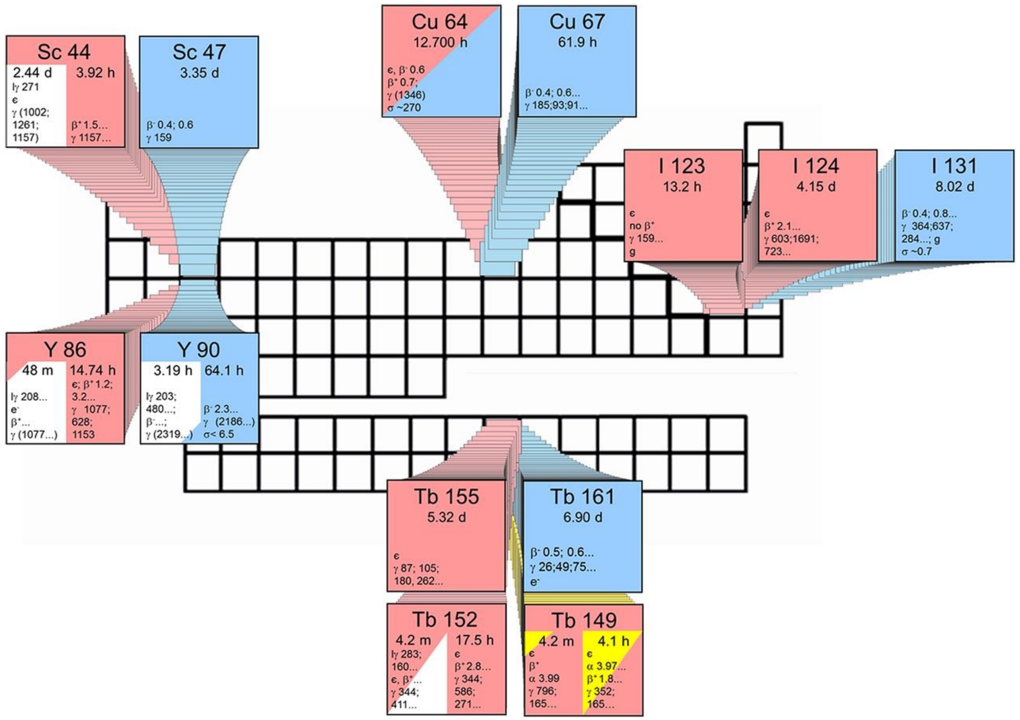
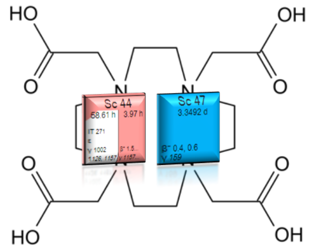


Fig. 3. Theragnostic principle: matched pairs of radionuclides for PET and SPECT imaging and for therapeutic application in nuclear medicine.
C. Müller, et. All. Promising Prospects for 44Sc-/47Sc-Based Theragnostics: Application of 47Sc for Radionuclide Tumor Therapy in Mice, *The Journal of Nuclear Medicine,* October 2014, 55 (10) 1658-1664; DOI: https://doi.org/10.2967/jnumed.114.141614

DOTA -



RFP – radiopharmaceutical

Impurities

- Purification methods:
  - Chemical – precipitate method or ion exchange columns.
    + Effective for ^{48}V and Ti element removal
    - **Use of strong and corrosive acids**
  - Physical – **Isotope mass-separation**

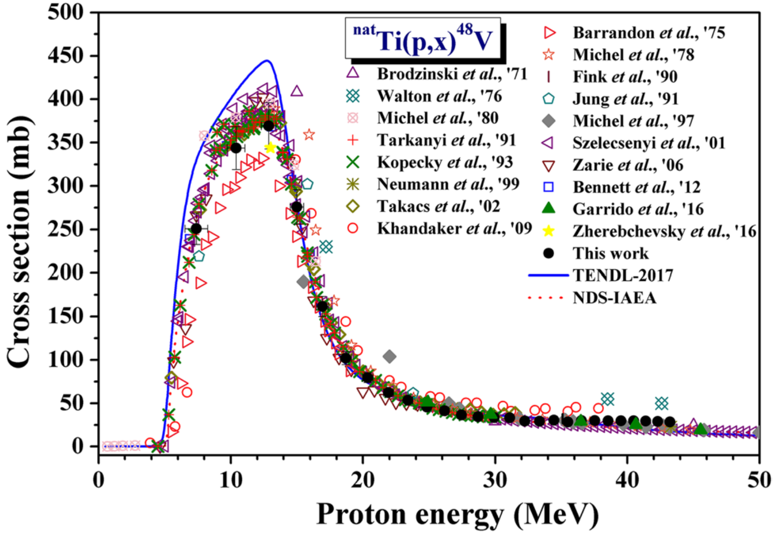


Fig. 4. Excitation function of $^{nat}Ti(p,x)^{48}V$ reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

M. Shahid, et. All. Measurement of excitation functions of residual radionuclides from natTi(p,x) reactions up to 44 MeV," *Journal of Radioanalytical and Nuclear Chemistry,* vol. 318, p. 2049–2057, 2018

Nuclei	Half-life	Decay mode (%)	E_γ (keV)	I_γ (%)	Production route	Q-value (MeV)	Threshold value (MeV)
^{48}V	15.97 days	EC (50.09)	944.13	7.87	$^{47}Ti(p,\gamma)$	6.83	0.0
		β^+ (49.91)	983.52	99.98	$^{48}Ti(p,n)$	−4.79	4.89
			1312.1	98.2	$^{49}Ti(p,2n)$	−12.93	13.20
					$^{50}Ti(p,3n)$	−23.88	24.36
^{43}Sc	3.89 h	EC (11.9)	372.8	22.5	$^{46}Ti(p,\alpha)$	−3.07	3.14
		β^+ (88.1)			$^{47}Ti(p,n\alpha)$	−11.95	12.21
					$^{48}Ti(p,2n\alpha)$	−23.58	24.07
					$^{49}Ti(p,3n\alpha)$	−31.72	32.37
^{44m}Sc	2.44 days	IT (98.8)	271.2	86.7	$^{47}Ti(p,\alpha)$	−2.25	2.30
		EC (1.2)	1002	1.2	$^{48}Ti(p,n\alpha)$	−13.88	14.17
^{44g}Sc	3.93 h	EC (5.73)	1157.0	99.9	$^{49}Ti(p,2n\alpha)$	−22.02	22.47
		β^+ (94.27)			$^{50}Ti(p,3n\alpha)$	−32.96	33.63
^{46g}Sc	83.79 days	β^- (100)	889.28	99.98	$^{47}Ti(p,2p)$	−10.46	10.69
			1120.54	99.99	$^{48}Ti(p,^3He)$	−14.37	14.67
					$^{49}Ti(p,\alpha)$	−1.94	1.98
					$^{50}Ti(p,n\alpha)$	−12.87	13.13
^{47}Sc	3.35 days	β^- (100)	159.38	68.3	$^{48}Ti(p,2p)$	−11.44	11.68
					$^{49}Ti(p,^3He)$	−11.87	12.11
					$^{50}Ti(p,\alpha)$	−2.23	2.28
^{48}Sc	43.67 h	β^- (100)	175.36	7.48	$^{49}Ti(p,2p)$	−11.35	11.59
			1037.52	97.6	$^{50}Ti(p,^3He)$	−14.58	14.87

Table 1. The decay data of ^{48}V and $^{43,44m,44g,46,47,48}Sc$ radionuclides produced from the $^{nat}Ti(p,x)$ reactions

M. Shahid, et. All. Measurement of excitation functions of residual radionuclides from natTi(p,x) reactions up to 44 MeV," *Journal of Radioanalytical and Nuclear Chemistry,* vol. 318, p. 2049–2057, 2018

CERN-MEDICIS

- MEDICIS - MEDical Isotopes Collected from Isolde;
- ISOLDE - Isotope mass Separator On-Line facility;
- Production of non-conventional radionuclides for R&D in cancer imaging, diagnostics and radiation therapy done at partner institutes;
- Located after the PS Booster, it receives protons with an energy of 1.4 GeV.
- ISOLDE leftover protons (80-90%) used to irradiate second (MEDICIS) target;
- **CERN has 60 years of experience** of producing radioactive beams and utilizing mass separation technique for purification/detection of exotic and novel radioisotopes.

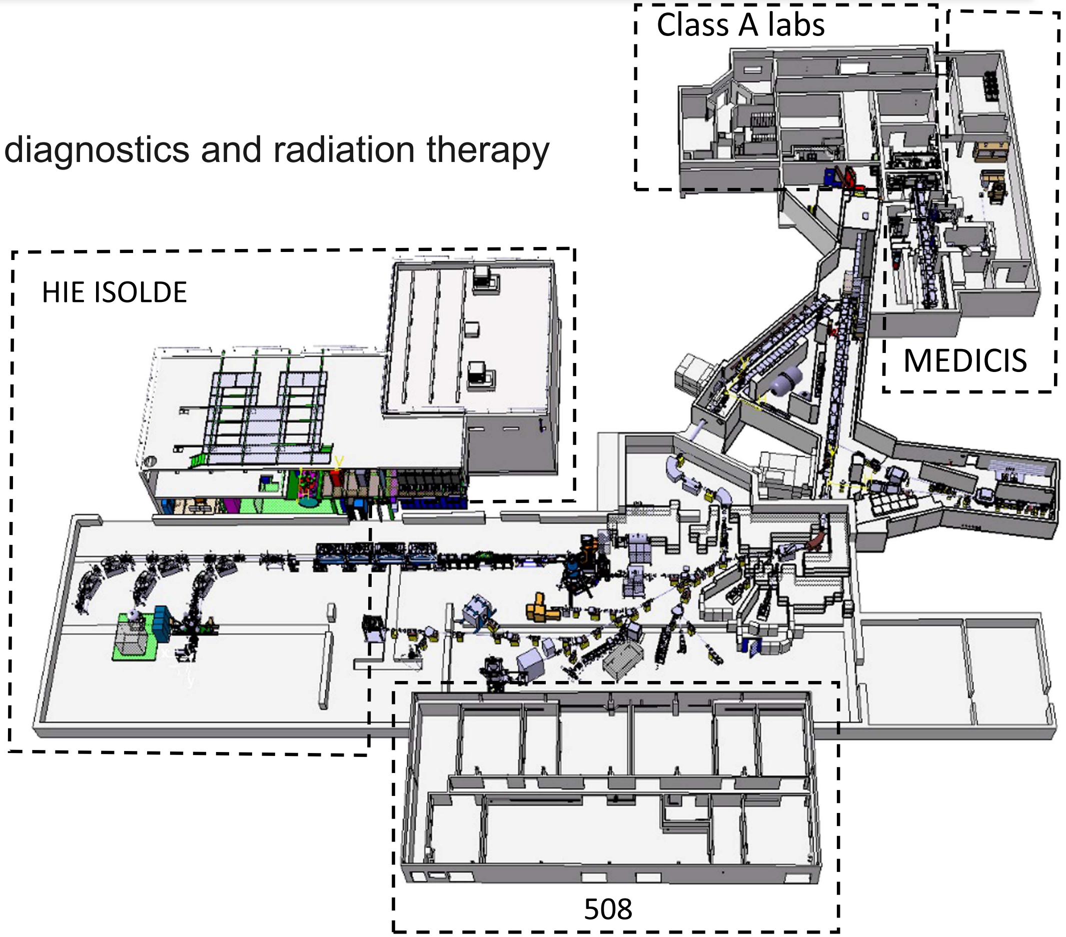


Fig. 6. 3D model of the ISOLDE-MEDICIS facility in 2017.

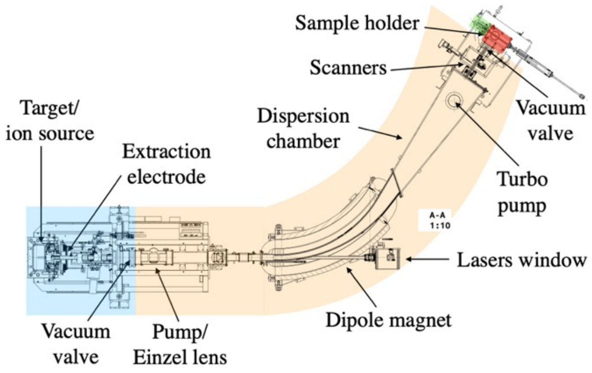
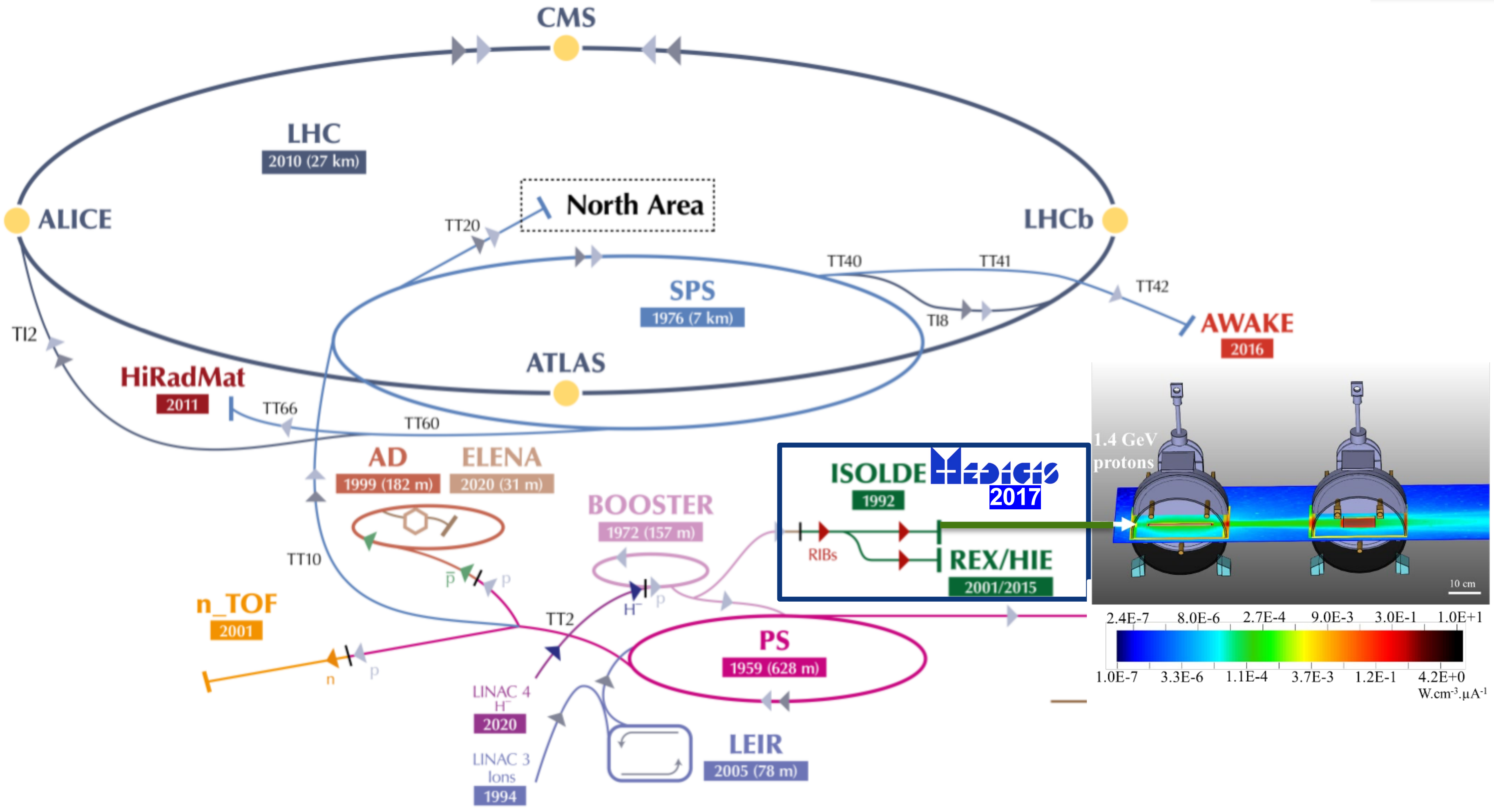


Fig. 5. MEDICIS isotope mass-separator structure

CERN Accelerator complex

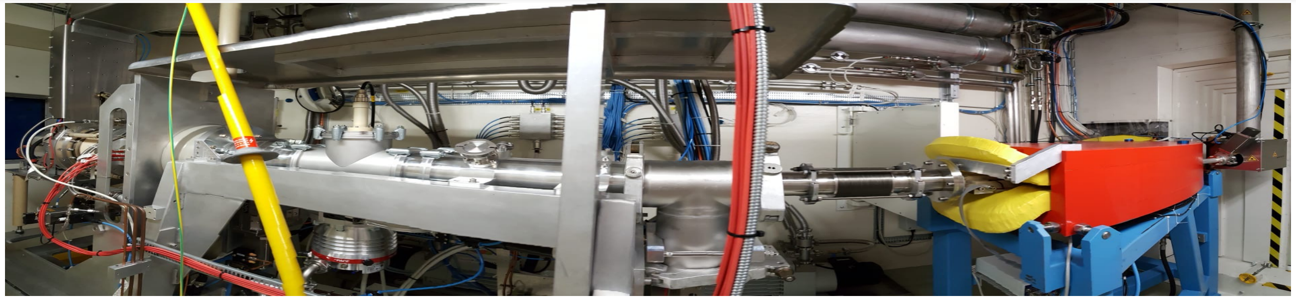


H⁻ (hydrogen anions) p (protons) ions RIBs (Radioactive Ion Beams) n (neutrons) p̄ (antiprotons) e⁻ (electrons)

Radionuclide separation

- CERN-MEDICIS operates its mass-separator to obtain isotopically pure isotopes
- Chemically pure radionuclides are obtained through a second step – radiochemical separation

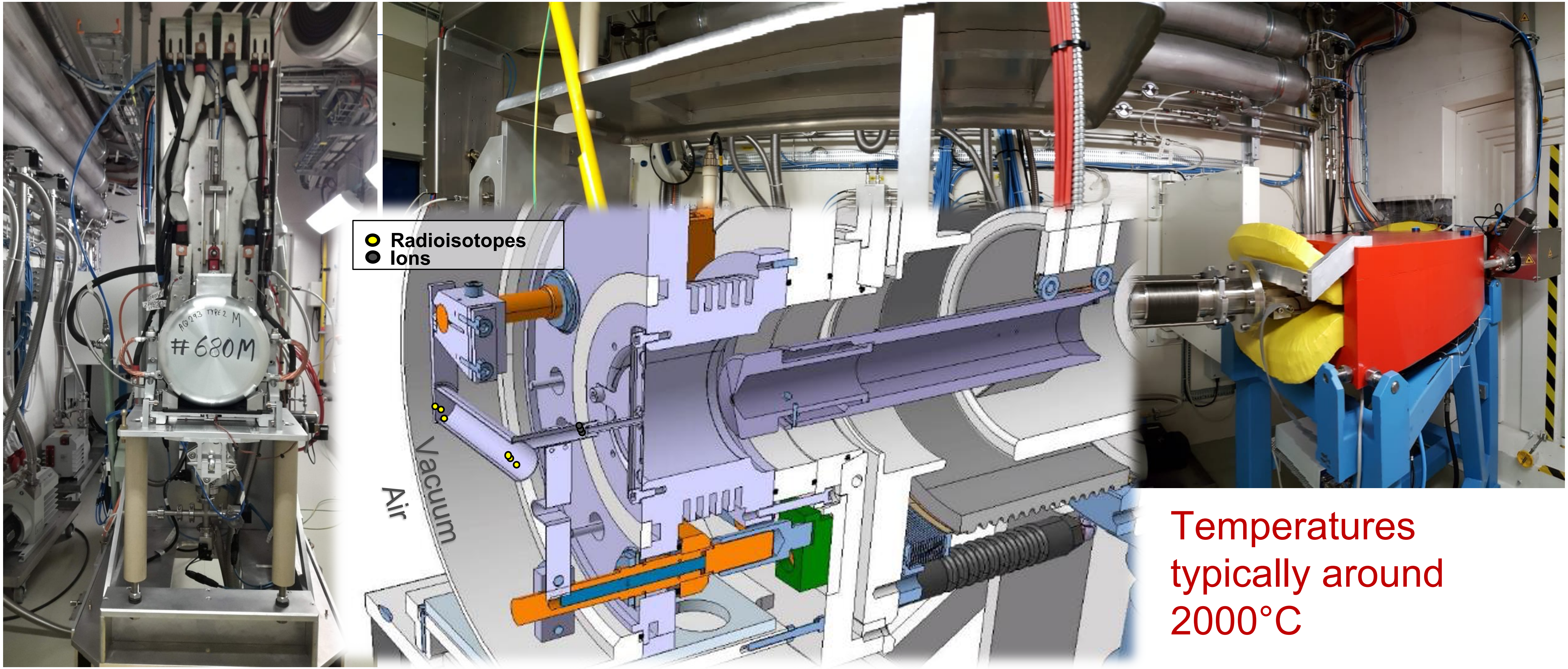
Mass-separator



V 45 6.36e+3 547 ms 6	V 46 1.10e+6 422.64 ms 0.05	V 47 5.82e+7 32.6 m 0.3	V 48 4.32e+8 15.9735 d 0.002	V 49 1.06e+9 330 d 15	V 50 2.23e+9 150 Py 40	V 51 4.01e+9 stbl	V 52 3.22e+9 3.743 m 0.005	V 53 3.46e+9 1.543 m 0.014	V 54 1.59e+9 49.8 s 0.5	V 55 1.41e+9 6.54 s 0.15
Ti 44 1.51e+7 59.1 y 0.3	Ti 45 6.01e+7 184.8 m 0.5	Ti 46 6.01e+8 stbl	Ti 47 1.16e+9 stbl	Ti 48 3.09e+9 stbl	Ti 49 2.83e+9 stbl	Ti 50 3.44e+9 stbl	Ti 51 1.46e+9 5.76 m 0.01	Ti 52 1.13e+9 1.7 m 0.1	Ti 53 3.54e+8 32.7 s 0.9	Ti 54 2.47e+8 2.1 s 1.0
Sc 43 1.30e+8 3.891 h 0.012	Sc 44 4.07e+8 4.0420 h 0.0025	Sc 45 1.40e+9 stbl	Sc 46 1.85e+9 83.80 d 0.03	Sc 47 3.19e+9 3.3492 d 0.0006	Sc 48 1.90e+9 43.67 h 0.09	Sc 49 1.80e+9 57.18 m 0.13	Sc 50 5.65e+8 102.5 s 0.5	Sc 51 3.54e+8 12.4 s 0.1	Sc 52 7.13e+7 8.2 s 0.2	Sc 53 3.80e+7 2.4 s 0.6
Ca 42 1.04e+9 stbl	Ca 43 1.26e+9 stbl	Ca 44 2.80e+9 stbl	Ca 45 1.77e+9 162.61 d 0.09	Ca 46 2.12e+9 stbl	Ca 47 8.67e+8 4.536 d 0.003	Ca 48 5.70e+8 45 Ey 6	Ca 49 1.21e+8 8.718 m 0.006	Ca 50 5.50e+7 13.9 s 0.6	Ca 51 7.92e+6 10.0 s 0.8	Ca 52 3.20e+6 4.6 s 0.3
K 41 1.25e+9 stbl	K 42 1.02e+9 12.355 h 0.007	K 43 1.59e+9 22.3 h 0.1	K 44 9.10e+8 22.13 m 0.19	K 45 8.20e+8 17.8 m 0.6	K 46 2.44e+8 105 s 10	K 47 1.43e+8 17.50 s 0.24	K 48 2.19e+7 6.8 s 0.2	K 49 1.18e+7 1.26 s 0.05	K 50 1.86e+6 472 ms 4	K 51 1.13e+6 365 ms 5
Ar 40 1.28e+9 stbl	Ar 41 8.28e+8 109.61 m 0.04	Ar 42 1.29e+9 32.9 y 1.1	Ar 43 6.47e+8 5.37 m 0.06	Ar 44 5.68e+8 11.87 m 0.05	Ar 45 1.35e+8 21.48 s 0.15	Ar 46 6.88e+7 8.4 s 0.6	Ar 47 7.42e+6 1.23 s 0.03	Ar 48 3.01e+6 415 ms 15	Ar 49 2.15e+5 236 ms 8	Ar 50 8.82e+4 106 ms 6

Radiochemistry

CERN-MEDICIS – view inside the bunker



Temperatures typically around 2000°C

TiF_x^+ and ScF_x^+ molecular beams – the full picture

- ScF^+ and ScF_2^+ molecular beams could be observed and extracted, but so does TiF^+; TiF_2^+ and TiF_3^+
- Main contaminants from B, Be, C, Ta;
- Unwanted beams can be reduced by target unit ugrades, such as additional cooling.
- Total beam intensity must be monitored with increased sample quantity
  - Ion source capacity must be respected;
- Collection of separated isotopes:
  - Implantation in target foils;
    - Double beam upgrade at MEDICIS'
  - Efficiency of extraction;
  - Purity from isobars and selectifity
- Molten targets can hinder the release or damage target unit.

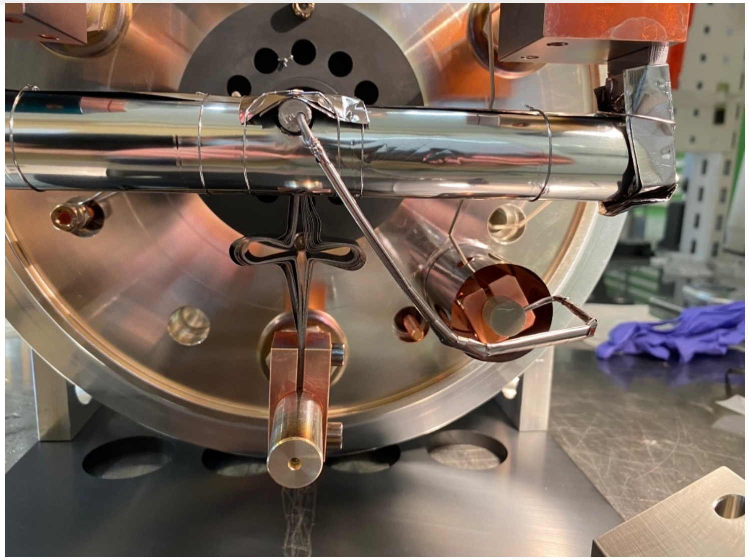


Fig. 8. MEDICIS separated isotope collection foils

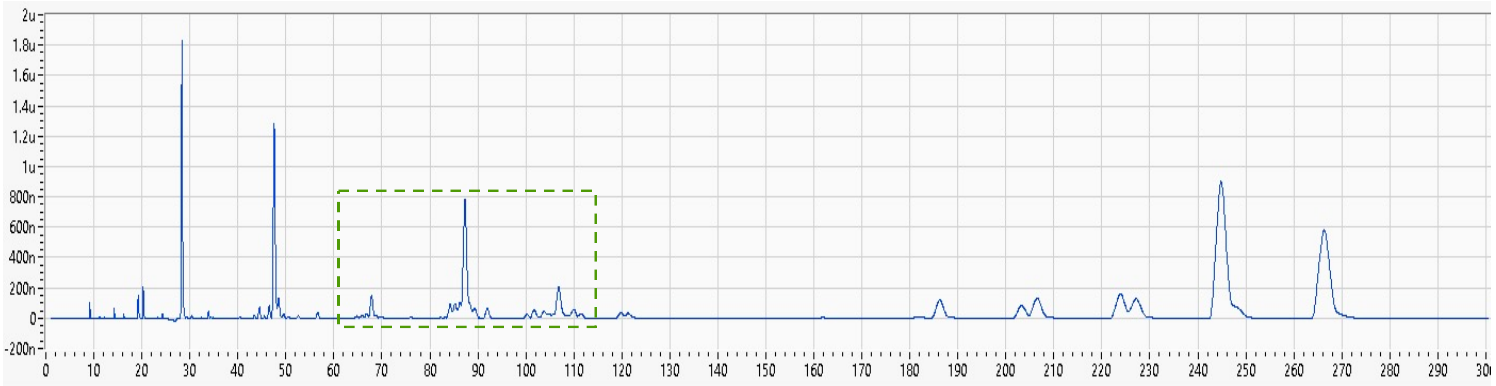
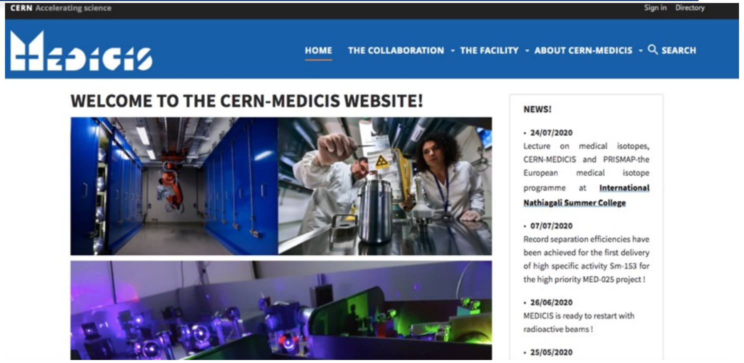


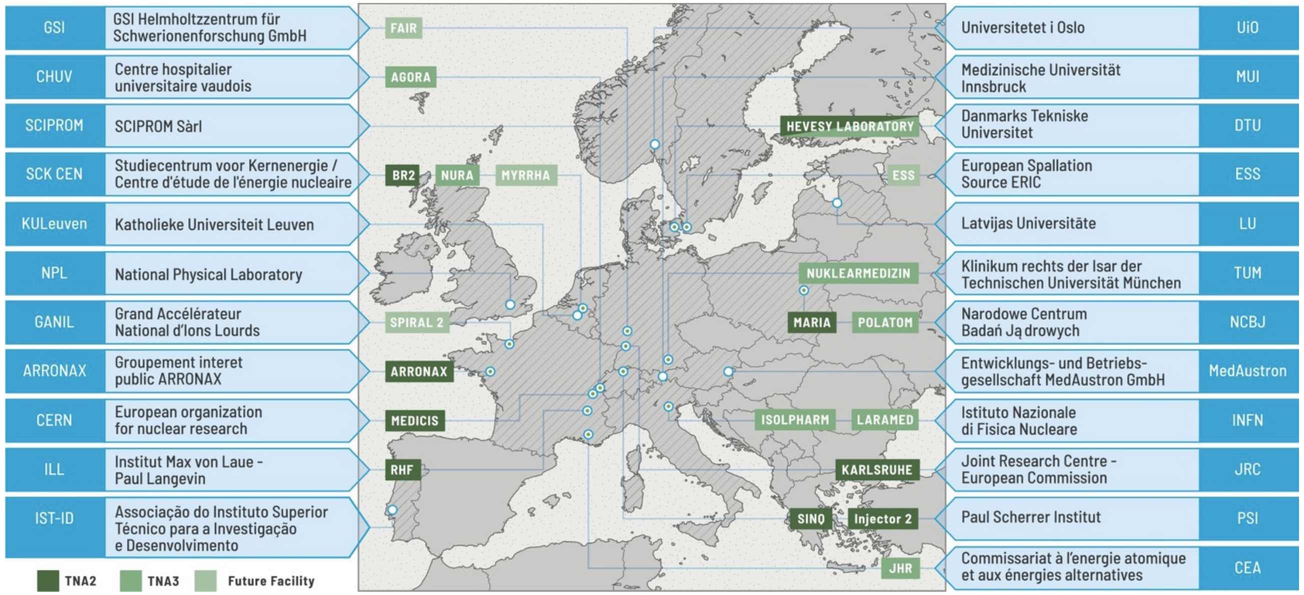
Fig. 7. nat-Ti + [^{45}Sc]Sc_2O_3 + NF_3 system full range mass scan – beam current distribution.

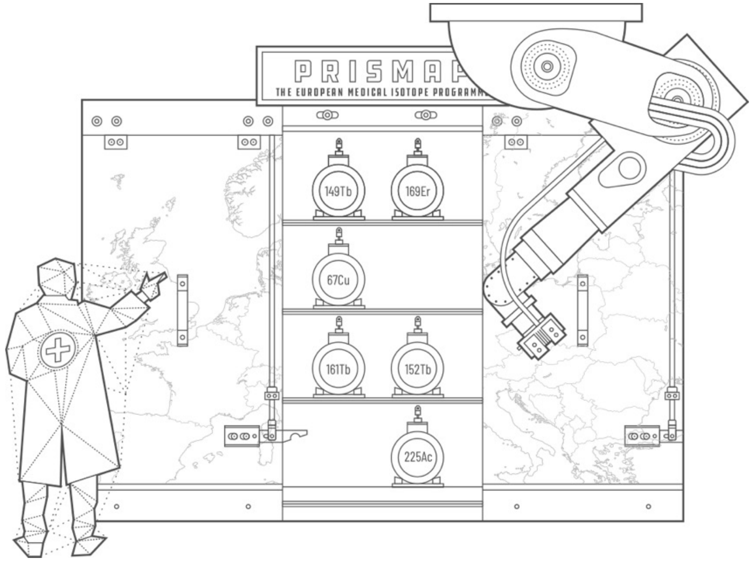
Fig. 9. Intact (left) and molten (right) Ti roll target material.

MEDICIS in 2022 and beyond

- Sc radionuclides have been already studied by MEDICIS collaboration members across Europe and are soon to come towards clinical trials.
- **PRISMAP started on 1st of May 2021!**
  - The European medical isotope programme: *Production of high purity isotopes by mass separation*
  - Consortium of 23 institutes funded by the Research Infrastructures program INFRA-2-2020 of Horizon 2020 of the European Commission
- PRISMAP will create a single-entry point for a fragmented user community distributed amongst universities, research centres, industry and hospitals.







PRISMAP Website: https://www.prismap.eu

MEDICIS Website: https://medicis.cern/

Thank you for your attention!