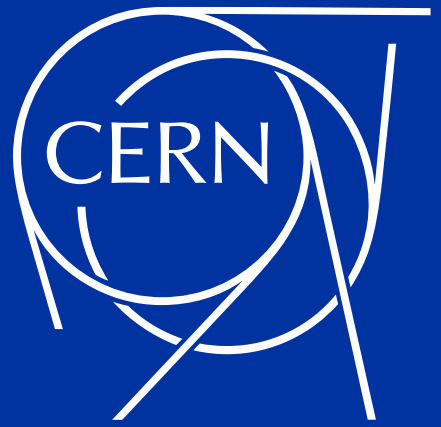

UNIVERSITY OF LATVIA
Institute of Chemical Physics

Production, extraction and mass-separation of medical ^{43,44,47}Sc radionuclides at the CERN-MEDICIS facility

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Supervisors: T. Stora (CERN); E. Pajuste (UoL); M. Radziņa (UoL)

12/10/2022

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, labelled with radioactive positron (β^+)/gamma or alpha and β^- emitters;

Theranostics - derived from Therapy and Diagnostics, and refers to the strategy of using radioactively labelled drugs for both purposes

- So called ”Treat what You see” technique

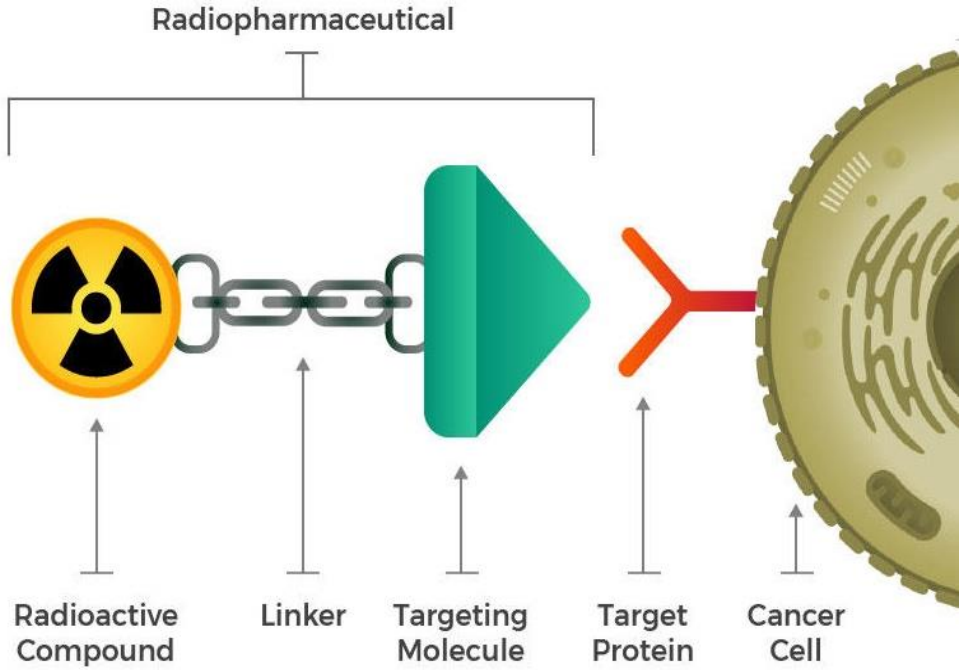


Fig. 1. Illustrative structure of a ligand radiopharmaceuticalradiopharmaceutical and its cell binding

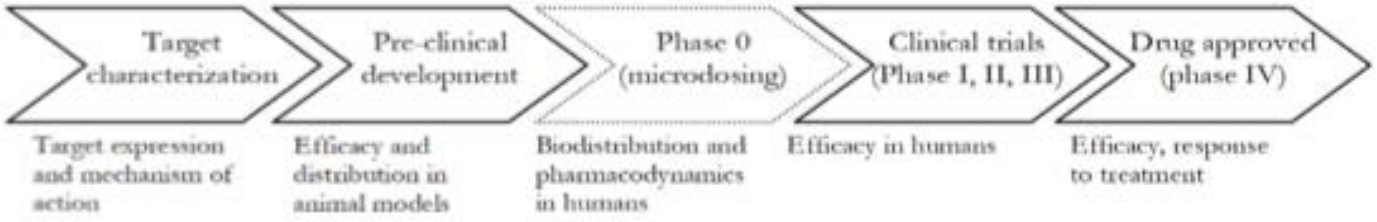
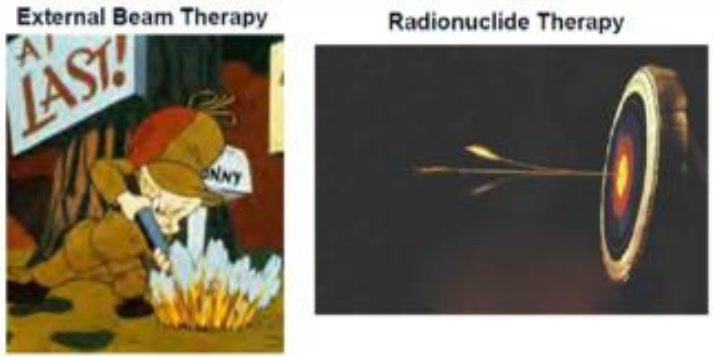


Fig. 2. Illustrative structure of drug develoment *Current Radiopharmaceuticals*, 2012, *5(2) 90-98.*



Why Scandium ?

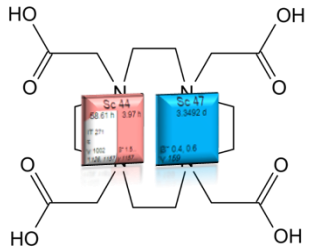
Cost and efficiency:

- 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;
- Good production cross-sections for medium energy (12-30 MeV) **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;
- Labelled with DOTA chelator combined with peptides

Scandium radionuclides can be produced and decay to the most biocompatible stable chemical elements such as Ca and Ti;

DOTA - 

RFP – radiopharmaceutical

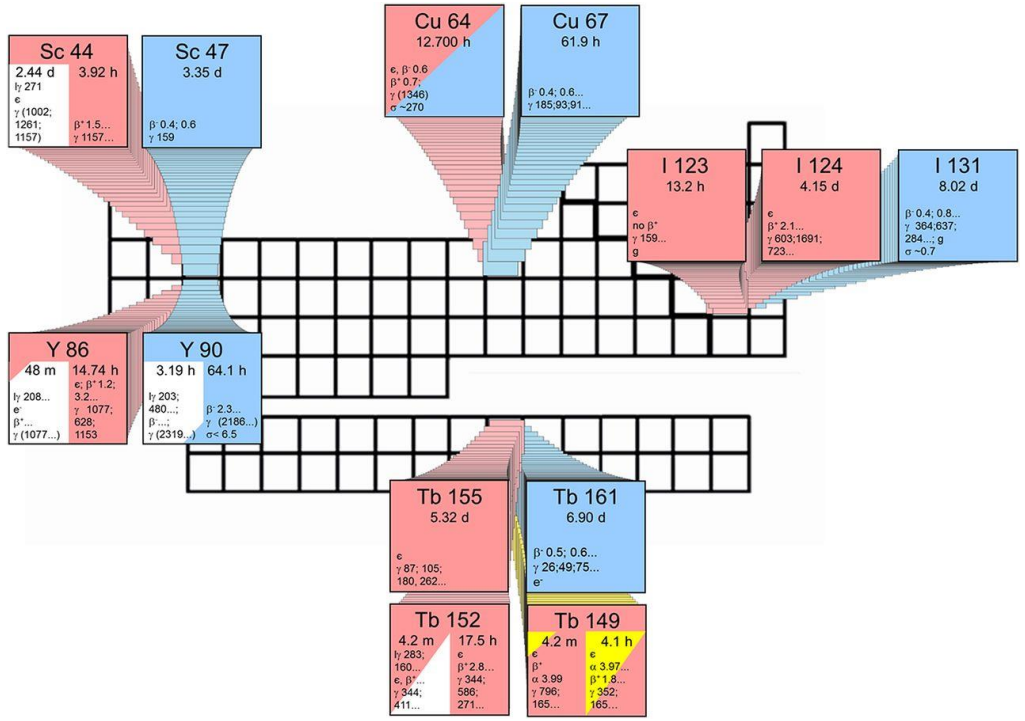


Fig. 3. Theragnostic principle: matched pairs of radionuclides for PET and SPECT imaging and for therapeutic application in nuclear medicine.
C. Müller, et. All. Promising Prospects for 44Sc-/47Sc-Based Theragnostics: Application of 47Sc for Radionuclide Tumor Therapy in Mice, *The Journal of Nuclear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

Nat-Ti as target material for ^{4x}Sc production

- Relatively cheap metal titanium is light, corrosion resistant, refractory and non-toxic;
- Natural titanium has five stable isotopes with different percentages, i.e. ^{46}Ti (8.25%), ^{47}Ti (7.44%), ^{48}Ti (73.72%), ^{49}Ti (5.41%), and ^{50}Ti (5.18%);
- Favorable theoretical nuclear reaction cross-sections of ^{44g}Sc and ^{47}Sc production compared to other Sc isotopes

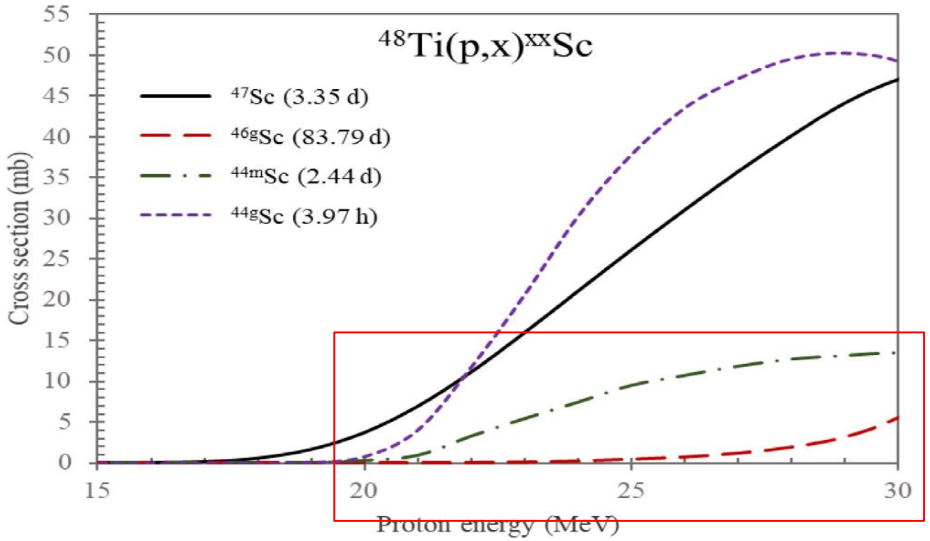


Fig. 4. Excitation function of ^{48}Ti(p,x)^{xx}Sc reaction by the TALYS-1.9 code
A. Jafari, et. All. Cyclotron-based production of the theranostic radionuclide scandium-47 from titanium target, *Nuclear Inst. and Methods in Physics Research,* vol. 961, no. Elsevier B.V., 2020

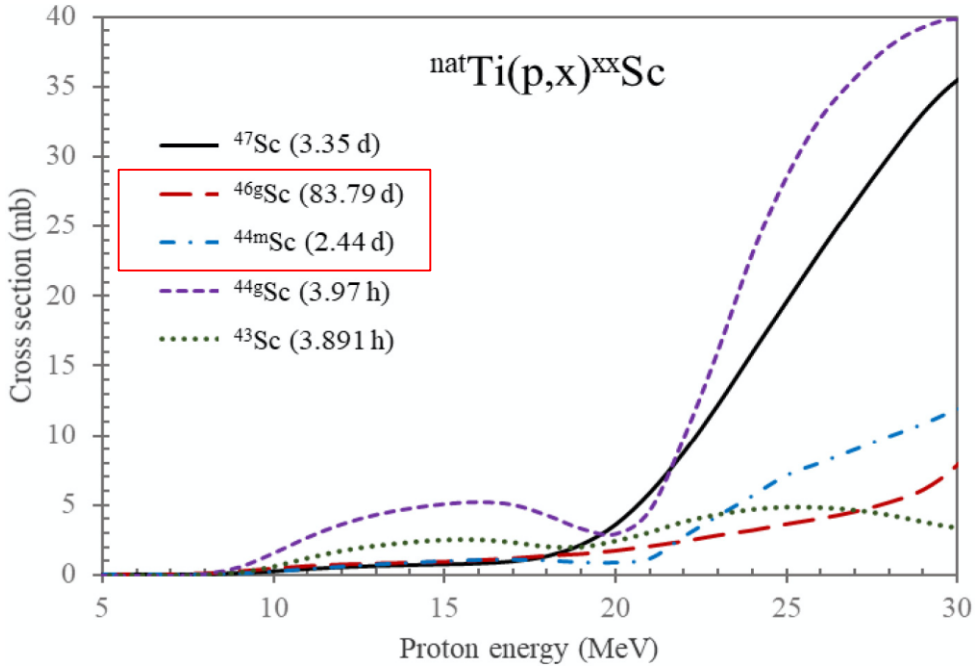


Fig. 5. Excitation function of ^{nat}Ti(p,x)^{xx}Sc reaction by the TALYS-1.9 code
A. Jafari, et. All. Cyclotron-based production of the theranostic radionuclide scandium-47 from titanium target, *Nuclear Inst. and Methods in Physics Research,* vol. 961, no. Elsevier B.V., 2020

Radionuclide separation

- Isotopically pure target material or …
- CERN-MEDICIS operates its mass-separator to obtain isotopically pure medical radionuclides.
- Combination with cyclotron produced target yields in high molar activity, high purity medical radionuclides

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

- Chemically pure radionuclides are obtained through radiochemical separation

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;

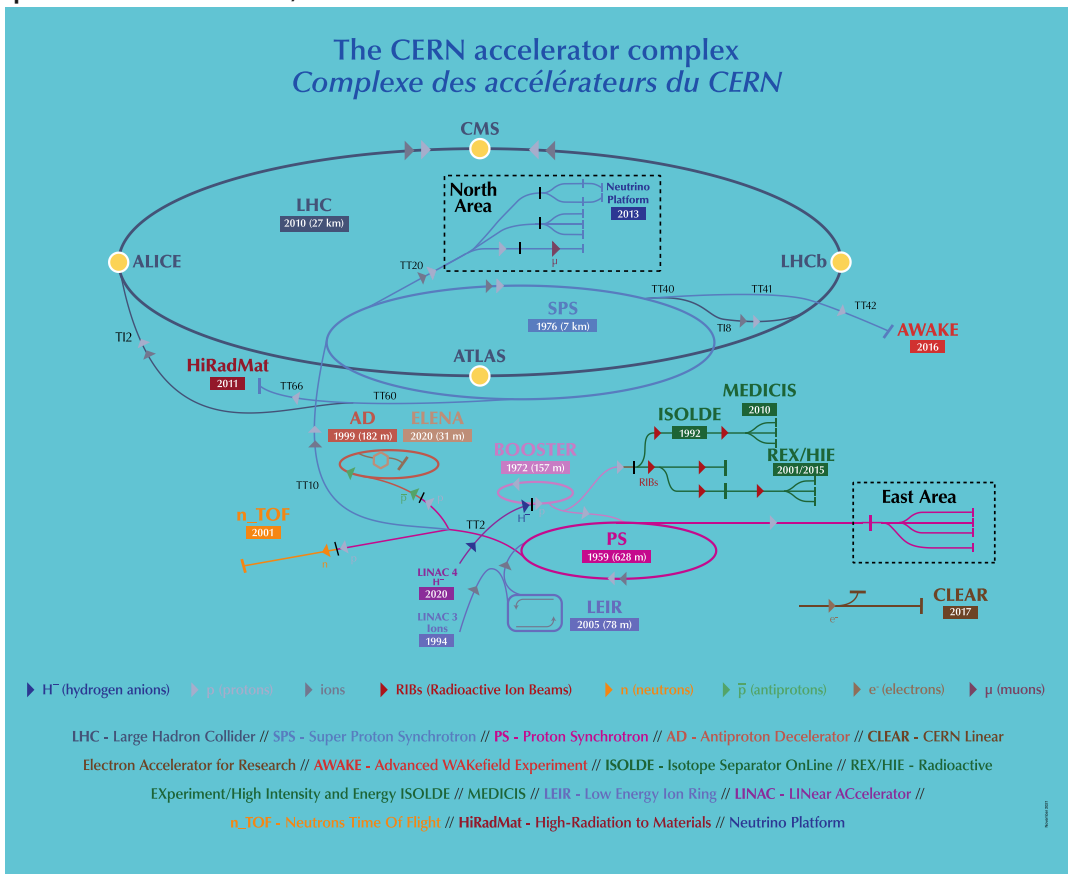


Fig. 6. CERN-MEDICIS in CERN accelerator complex

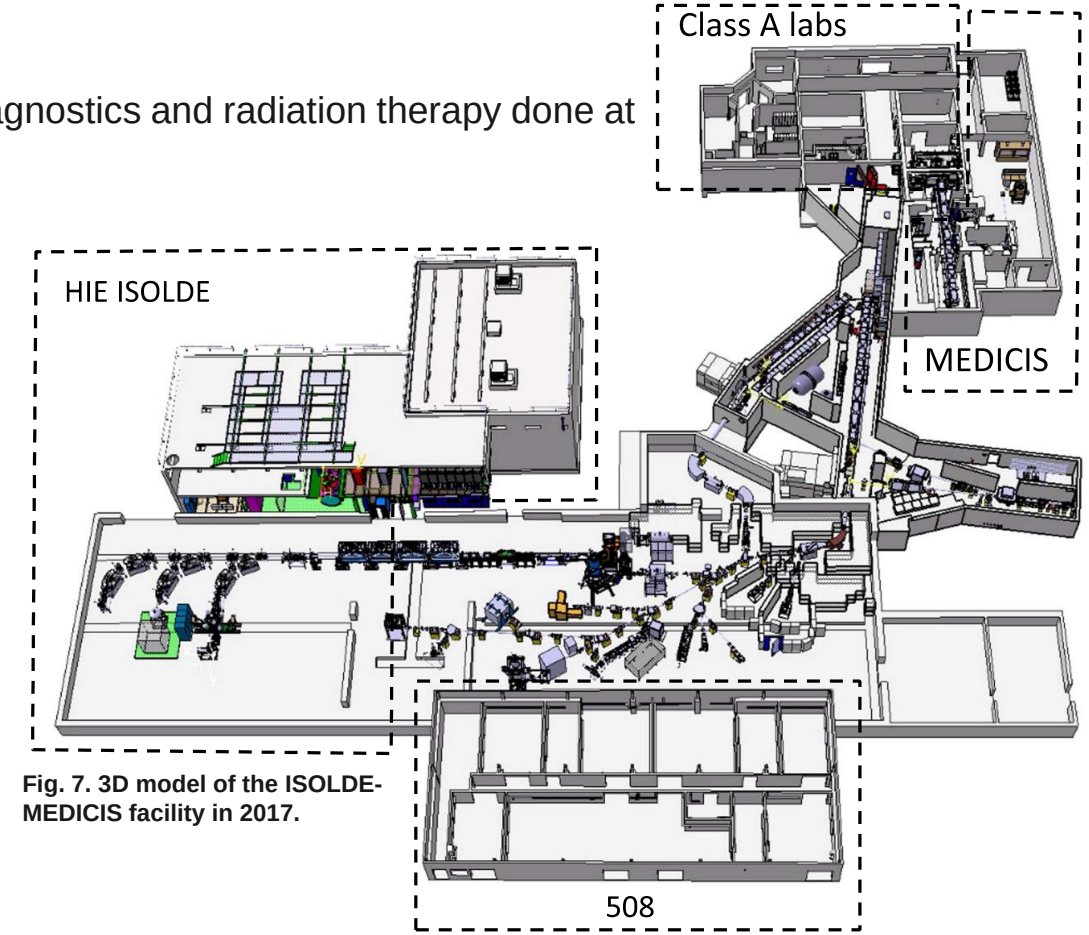
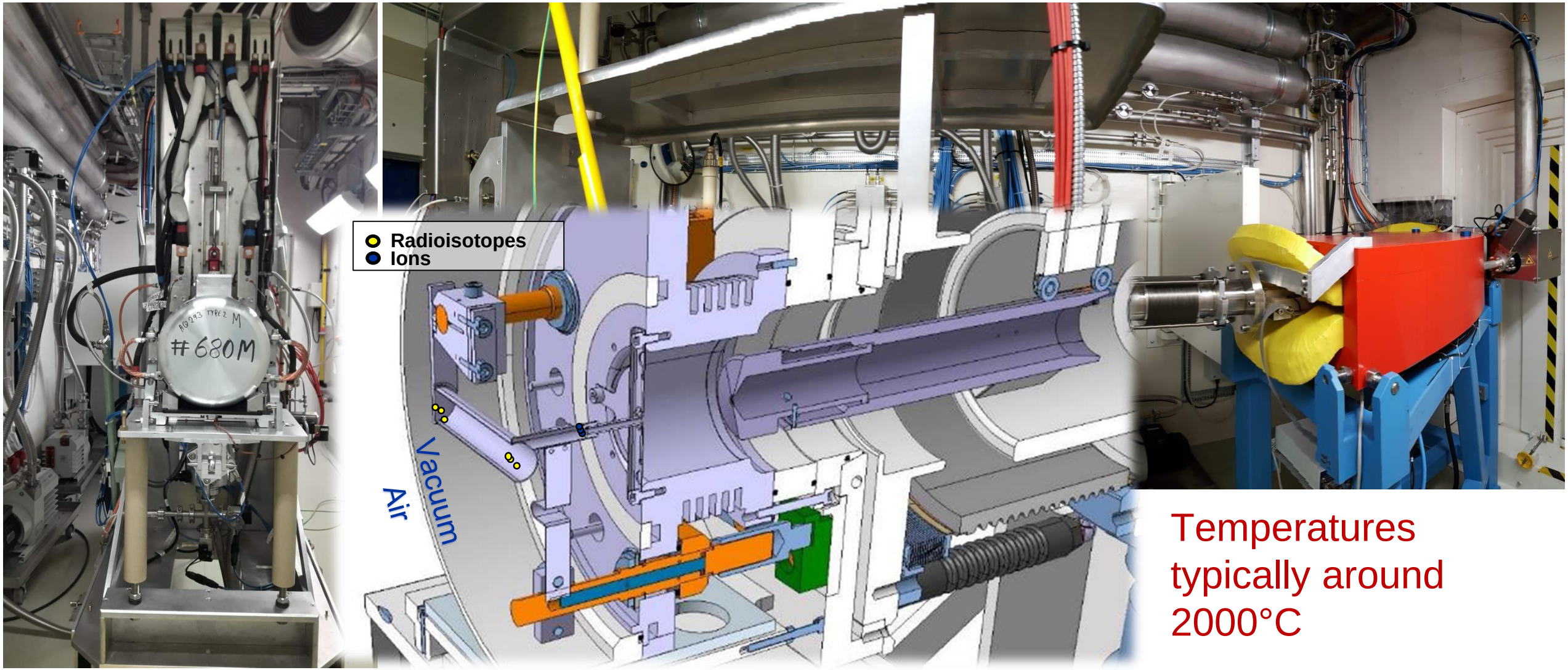


Fig. 7. 3D model of the ISOLDE-MEDICIS facility in 2017.

- Located after the PS Booster, it receives protons with an energy of 1.4 *(possibly 1.7 or 2 GeV in upgrade scenarios)*.

CERN-MEDICIS – view inside the bunker



Temperatures typically around 2000°C

Fig. 8. Animated MEDICIS mass-separator radionuclide extraction principle

History of Sc^+ and ScF_x^+ extraction at ISOLDE

- Sc extraction from irradiated ^{nat}Ti rolls as molecular halide beams was previously reported with W surface ion source at ISOLDE (1991);
  - Sc^+ and ScF^+ beams were observed, but no ScF_2^+ molecular ions alongside evaporation of Ti target
  - W surface source is not very suitable for molecule ionization

Note: Ti^+ beam current rose from 0.1 to 5 μA when fluorinating gas was added (Ti ionization efficiency is up to 1 % with surface source);

- During Sc radionuclide production contaminants such as ^{46}Sc ($t_{1/2}$=83d; Eγ= 889 keV; 1120 keV) sometimes cannot be avoided, even with enriched target materials;
  - Such high contaminant energy is bad for shielding and patient dosimetry;
  - **Mass-separation step therefore is mandatory**

- *No prior data of natural vanadium as target material for Sc production.*

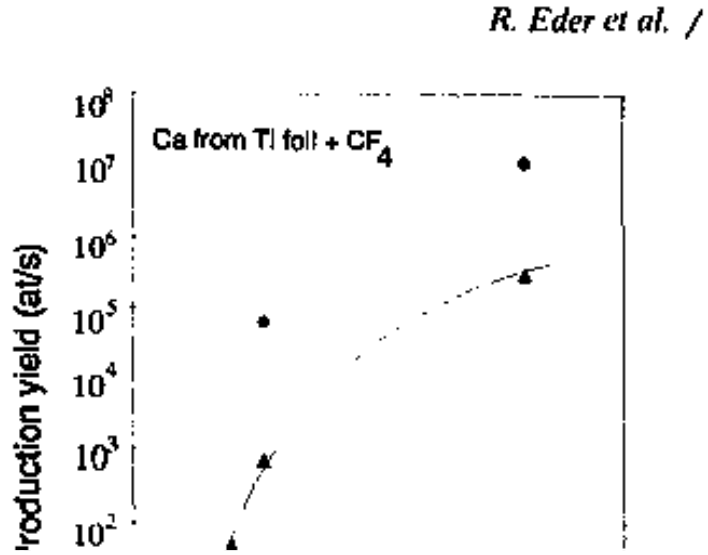


Fig. 9. Production yields of Sc^+ and ScF^+ ions from a 40 g/cm2 Ti foil target with a W surface ionizer. Irradiation 600 MeV protons.
R. Eder, et al. The production yields of radioactive ion-beams from fluorinated targets at the ISOLDE on-line mass separator, *Nuclear Instruments and Methods in Physics Research B62 (1992) 535-540, North-Holland*

Molecular beams

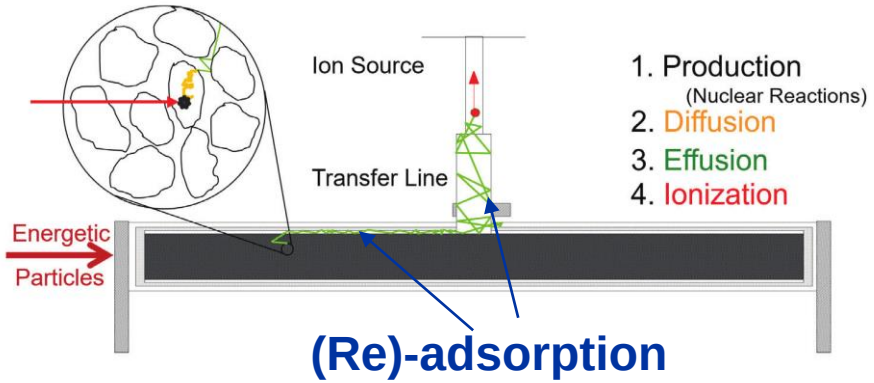


Fig. 10. Schematic of the ISOL method production, diffusion, effusion and ionization steps.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, 2017. CERN-THESIS-2016-247 ; EPFL-Thesis-nº7363

Fig. 11. Periodic table representing the temperature at which each element has a vapour pressure of 0.01 mbar.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, 2017. CERN-THESIS-2016-247 ; EPFL-Thesis-nº7363

- Desired isotope extraction efficiency in most cases is enhanced by increasing temperature;
  Up to a point where target material melts! Lower specific surface.
- Extraction of rare earth refractory metals such as Ti and Sc is challenging due to high boiling points and low vapour pressures;
- Refractory metals react to target materials, structures and make stable bonds;
- Formation of volatile molecules and beams such as halides - (ScF_x; $ScCl_x$; $ScBr_x$; ect. *x=1-3)* are used for effective results and extraction of desired isotopes;
- Collection of desired element/molecule can be shifted to an atomic mass region without increased background (isobars) s contamints;
- Re-adsorbtion (sticking) of Sc and ScF_x to Ta target structures hinders the extraction to ion source and collection.

Fig. 12. Intact (left) and molten (right) Ti roll target material.

Versatile ionization - VADIS VD-5

Previousely surface and laser ion sources were used to ionize Sc elements and sometimes molecules;

- Ionizing to q = +1 ions, molecules can dissociate in the ion source.
- The cross section for dissociation can exceed the cross section for direct ionization by orders of magnitude.

By using surface ionizer Sc molecular beams release delay from target unit may be in order of several hours to days;

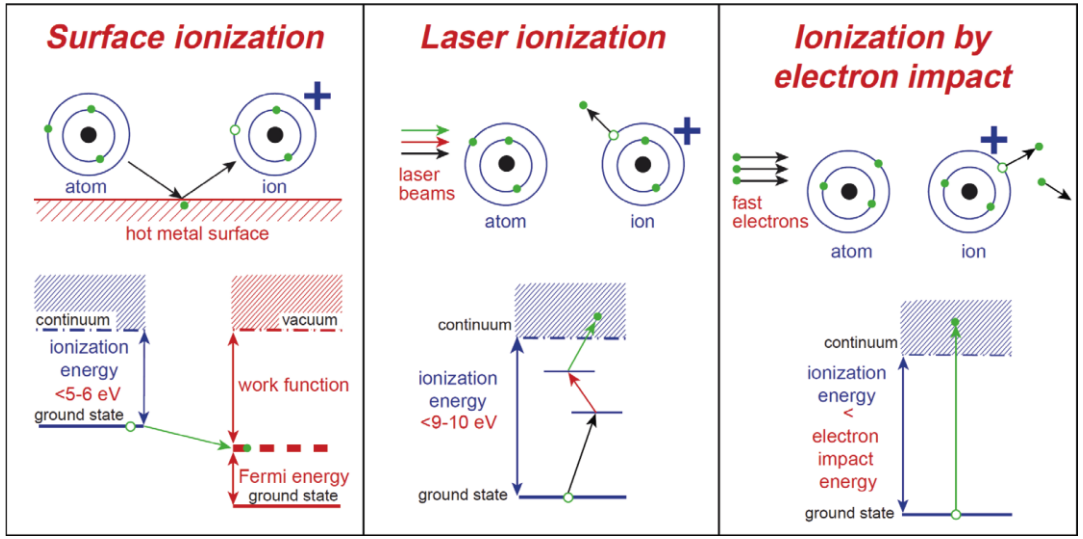
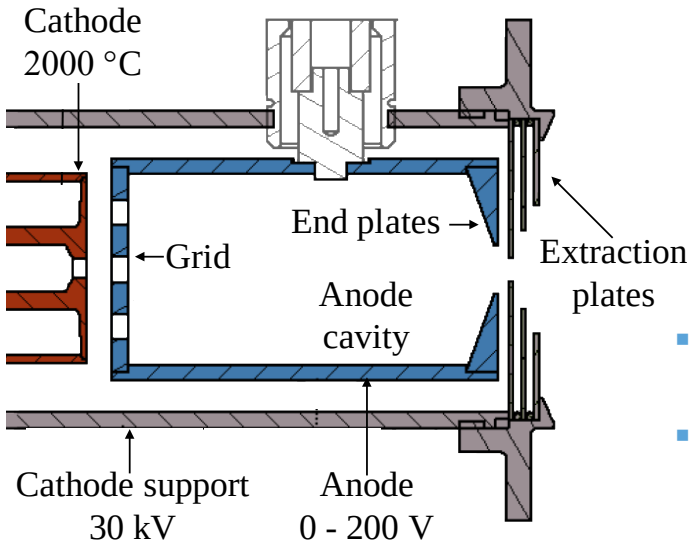


Fig. 13. Ionization mechanisms used in ISOLDE: surface, laser and electron impact ionization.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, 2017. CERN-THESIS-2016-247 ; EPFL-Thesis-nº7363



- VD-5 is an electron impact ion source with thermionic cathode as electron source and anode cavity for electron acceleration up to couple hundreds of volts with applied axial magnetic field.
- VD-5 can ionize elements/molecules with high ionization potentials (>10 eV).
  - Limiting factor is specific matrix, molecule/element ionization efficiency

Fig. 14. Geometry of ISOLDE FEBIAD ion source (VADIS).
Y. M. Palenz, *Characterization and optimization of a versatile laser and electron-impact ion source for radioactive ion beam production at ISOLDE and MEDICIS,* Belgium: KU Leuven – Faculty of Science, 2019. CERN-THESIS-2019-032

FEBIAD - Forced-Electron Beam Induced Arc-Discharge Ion Source
VADIS - Versatile Arc Discharge Ion Source

Stable ScF_x^+ and TiF_x^+;$TiOF_x^+$ molecular beams *(x=1-3)*

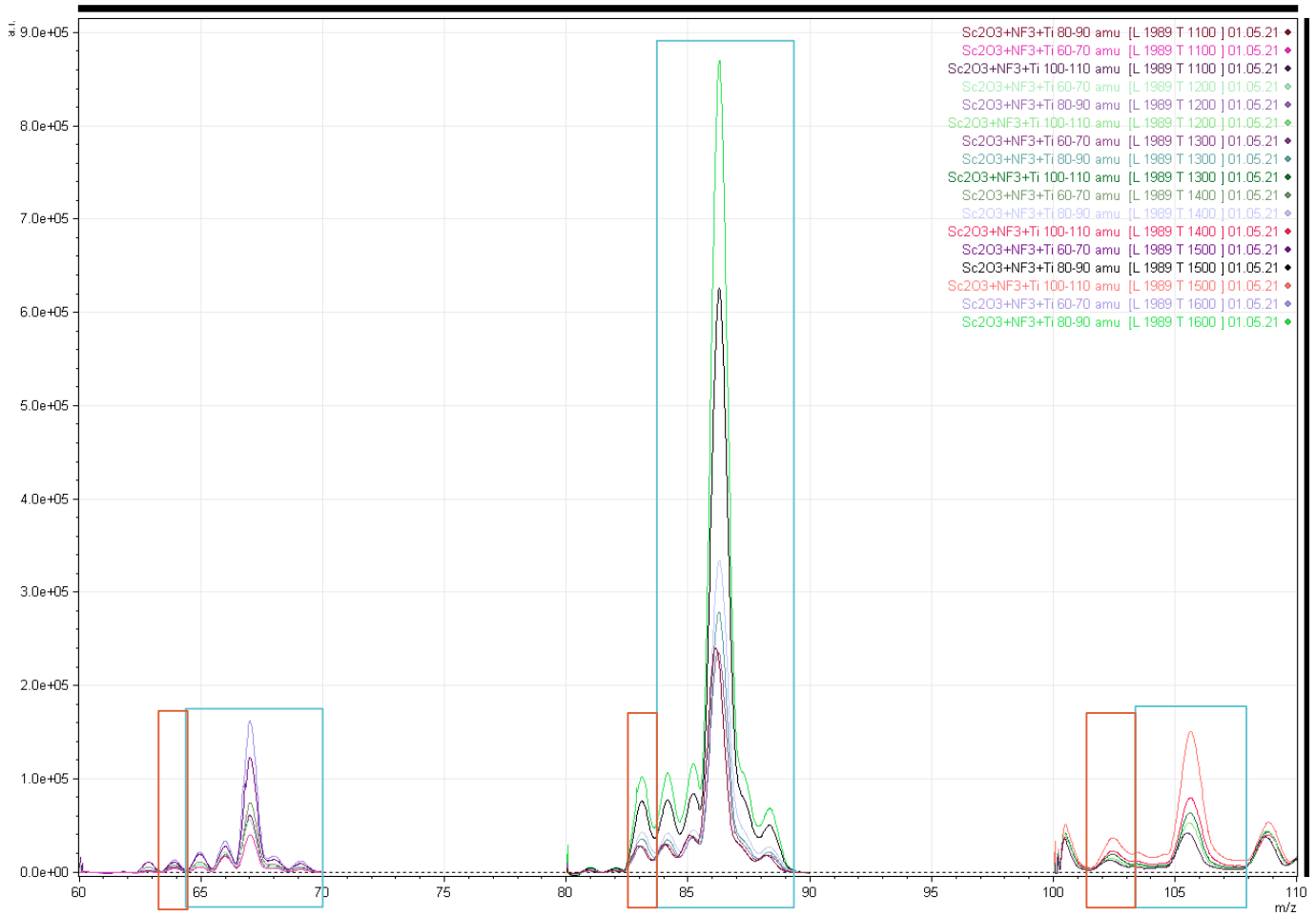


Fig. 15. Stable TiF_x^+, $TiOF_x^+$ and ScF_x^+ molecular beam intensity composition at various target temperatures

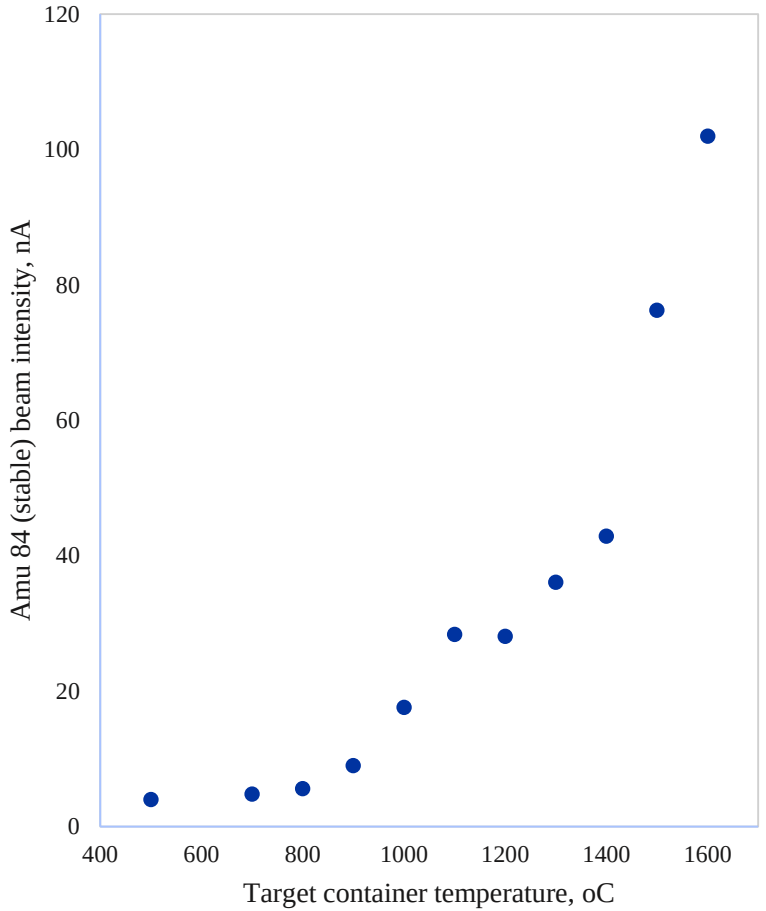


Fig. 16. Correlation between amu 84 (molecular) beam formation/extraction and target container temperature

Sc molecular beam target development and constraints

- Main total beam contaminants - Be, C, Ta. Large portion of total ion beam consists BeF_x, TaF_x and TaO_xF_y;
- Reduced the background of TaF_x and $TaOF_x$ molecular beam contribution to total beam by installing additional cooling of gas leak.
  - Reactive gas reaction with target structures mitigated at calibrated gas leak and Ta tube connection.
- Maximising production of radionuclides with double foil rolls.
- Target temperature cap at **1550 - 1600 ºC**.

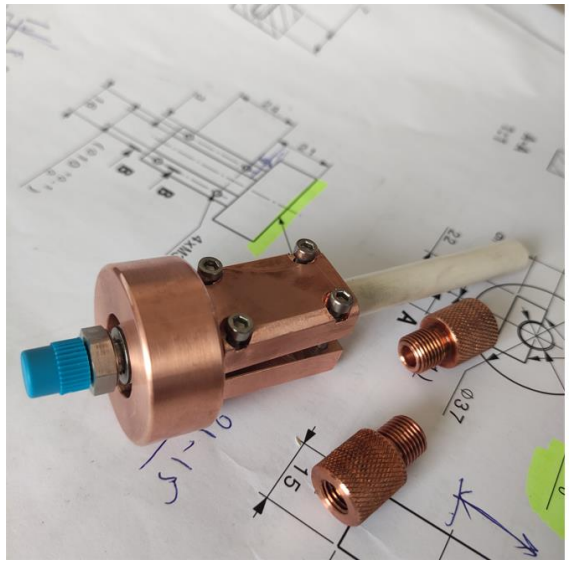


Fig. 18. ISOLDE/MEDICIS target gas supply leak modification (cooling)

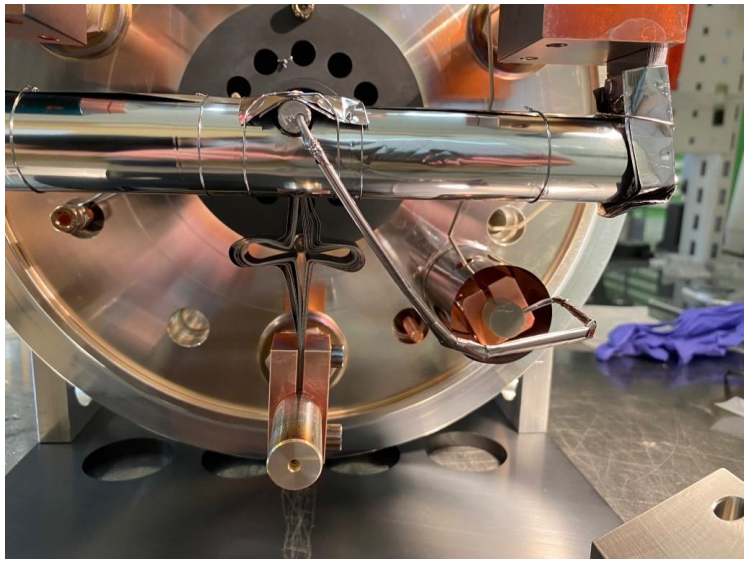


Fig. 19. MEDICIS separated isotope collection foils

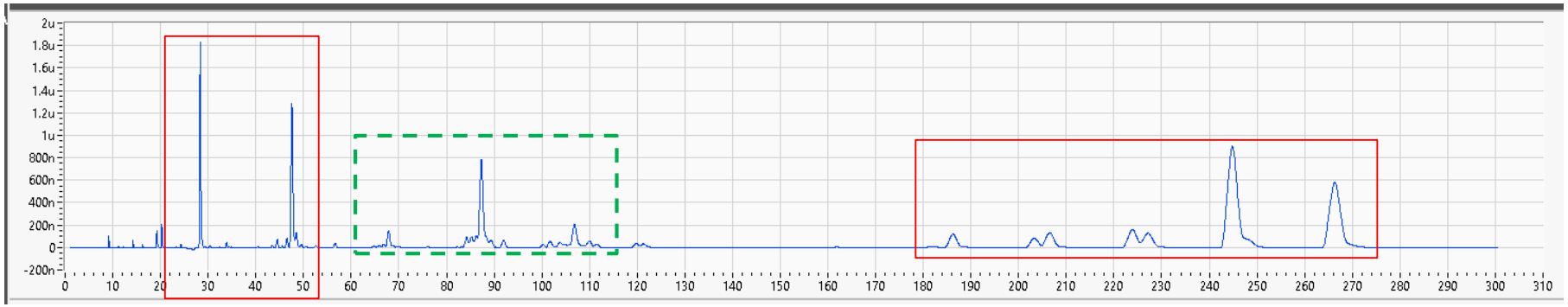


Fig. 17. nat-Ti + Sc_2O_3 + (x)NF_3 system full range mass scan – beam current distribution

Fig. 20. natTi double rolls used for Sc radionuclide production

^{44m,44g}Sc and ^{47}Sc fluoride collection

- Sc extraction from irradiated ^{nat}Ti rolls as molecular halide beams here was done with hot plasma VADIS VD-5 ion source target;
- ScF_x molecular beams were always acompanied/masked by TiF_x isobars due to reactivity and volatility of Ti halides;
- **Di-fluoride (TiF_2^+ , ScF_2^+) molecular beams are (and were expected) most dominant from the species**, with $^{48}TiF_2^+$ reaching ~1 μA beam intensities;
  - Dissociation of ScF_3 rather than direct ionization
- Conditions to separate ScF_2^+ in a hot plasma ion source were met, keeping TiF_x currents under control in order not to pollute/damage separator;
- **Successful separation from long lived ^{46}Sc and ^{48}Sc contaminants was achieved with MEDICIS mass-separator**;
- Identified strong 511keV (from positron annihilation) line during operation with target 741M
- Collected radionuclide activity in range of **few kBq**.

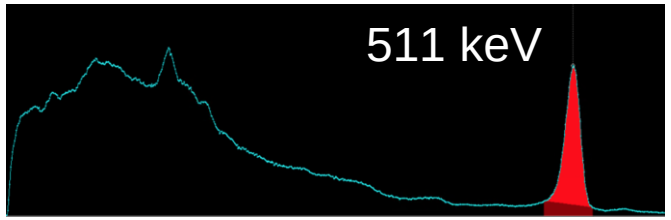


Fig. 21. Kromek γ-spectra during $^{44}ScF_2^+$ collection at MEDICIS (target 741M)

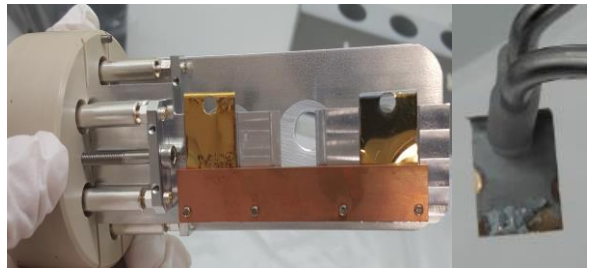


Fig. 23. MEDICIS separated isotope collection foils

Fig. 22. Mass scan fragments from medical Sc extraction by different fluorinating gases at same operation conditions, identifying strong TiF_x beams – MEDICIS, target #741M

^{51}V for targets

- ^{51}V(p,αp)^{47}Sc reaction with cyclotron
- **Melting point – 1910 ºC**
- Can be achieved with ^{nat}V targets (^{51}V: 99.750%, ^{50}V: 0.250%)
- ^{nat}V material is commercially available in metallic form, different geometries and purity up to 99,8%
- Does not require enriched target material
- Reported that at 18–30 MeV the production of ^{47}Sc is calculated to be 31 MBq/μA and 82 MBq/μA for 24 h and 80 h irradiation runs respectively.
  - Co-production of ^{46}Sc can be considered negligible - 0.01 MBq/μA and 0.03 MBq/μA.

Energy ^{nat}V foil (MeV)	^{47}Sc cross section (mb)	^{46}Sc cross section (mb)	Reference radionuclide	Energy monitor foil (MeV)	Monitor cross section (mb)
26.5± 0.8	4.3± 0.2		^{57}Ni	26.3± 0.9	180.2± 7.5
29.2± 0.8	7.4± 0.5		^{57}Ni	29.0± 0.8	162.9± 6.8
31.2± 0.7	9.0± 0.5	0.6± 0.1	^{57}Ni	31.1± 0.7	136.6± 5.7
33.3± 0.6	10.9± 0.6	2.6± 0.2	^{57}Ni	33.5± 0.6	113.9± 4.8
39.5± 0.6	8.3± 0.5	18.6± 1.1	^{57}Ni	39.3± 0.6	85.6± 3.6
48.1± 0.8	4.6± 0.3	30.8± 2.4	^{24}Na	48.1± 0.8	4.8± 0.3
51.0± 0.7	4.1± 0.3	27.8± 2.3	^{24}Na	50.9± 0.7	6.4± 0.5
53.6± 0.6	4.1± 0.3	25.1± 2.0	^{24}Na	53.7± 0.5	8.0± 0.6
55.7± 0.8	4.4± 0.4	23.0± 1.9	^{24}Na	55.6± 0.8	9.0± 0.6
58.3± 0.7	5.0± 0.4	21.6± 1.8	^{24}Na	58.2± 0.7	10.0± 0.7
60.7± 0.6	5.1± 0.3	18.6± 1.2	^{24}Na	60.7± 0.5	10.8± 0.5
65.5± 0.8	6.8± 0.4	16.7± 1.0	^{24}Na	65.5± 0.8	11.4± 0.5
67.8± 0.7	7.7± 0.5	16.7± 1.0	^{24}Na	67.7± 0.7	11.6± 0.5
70.0± 0.6	8.0± 0.4	16.4± 0.9	^{24}Na	70.0± 0.5	11.6± 0.4

Table 1. Data of the ^{nat}V(p,x)^{47}Sc,^{46}Sc nuclear cross sections and the values of the IAEA reference cross sections used.
Gaia Pupillo, et.all. Production of 47Sc with natural vanadium targets: results of the PASTA project, Journal of Radioanalytical and Nuclear Chemistry, 2019, https://doi.org/10.1007/s10967-019-06844-8

CERN FLUKA Monte-Carlo calculations of Sc production from Ti and V

Irradiation mode	Irradiation time	Decay time	Sc-44m activity Bq	Sc-44g activity Bq	Sc-47 activity Bq
Direct	1 hour	1 hour	1.176e+08 +/- 0.82%	1.389e+09 +/- 0.81%	2.244e+08 +/- 1.40%
Indirect			7.999e+06 +/- 1.47%	9.446e+07 +/- 1.46%	1.702e+07 +/- 5.80%
Direct	4 hours	1 hour	4.622e+08 +/- 0.82%	4.456e+09 +/- 0.79%	8.862e+08 +/- 1.40%
Indirect			3.131e+07 +/- 1.47%	3.018e+08 +/- 1.41%	6.720e+07 +/- 5.80%
Direct	14 hours	1 hour	1.527e+09 +/- 0.82%	8.824e+09 +/- 0.73%	2.973e+09 +/- 1.40%
Indirect			1.038e+08 +/- 1.47%	6.001e+08 +/- 1.30%	2.255e+08 +/- 5.80%

Table 2. Results of CERN FLUKA 4.1 ^{nat}Ti(p,x)Sc-44m, Sc-44g and Sc-47 production with 1.4 GeV proton direct impact (C. Duchemin)

Irradiation mode	Irradiation time	Decay time	Sc-43 activity Bq	Sc-44m activity Bq	Sc-44g activity Bq	Sc-47 activity Bq
Direct	1 hour	1 hour	4.691e+08 +/- 1.50%	8.133e+07 +/- 0.70%	9.604e+08 +/- 0.69%	9.202e+07 +/- 0.80%
Indirect			5.069e+07 +/- 4.10%	8.206e+06 +/- 2.10%	9.689e+07 +/- 2.06%	9.839e+06 +/- 2.40%
Direct	4 hours	1 hour	1.465e+09 +/- 1.50%	3.196e+08 +/- 0.70%	3.081e+09 +/- 0.67%	3.634e+08 +/- 0.80%
Indirect			1.583e+08 +/- 4.10%	3.225e+07 +/- 2.10%	3.109e+08 +/- 2.02%	3.886e+07 +/- 2.40%
Direct	14 hours	1 hour	2.638e+09 +/- 1.50%	1.056e+09 +/- 0.70%	6.102e+09 +/- 0.62%	1.220e+09 +/- 0.80%
Indirect			2.850e+08 +/- 4.10%	1.065e+08 +/- 2.10%	6.156e+08 +/- 1.86%	1.304e+08 +/- 2.40%

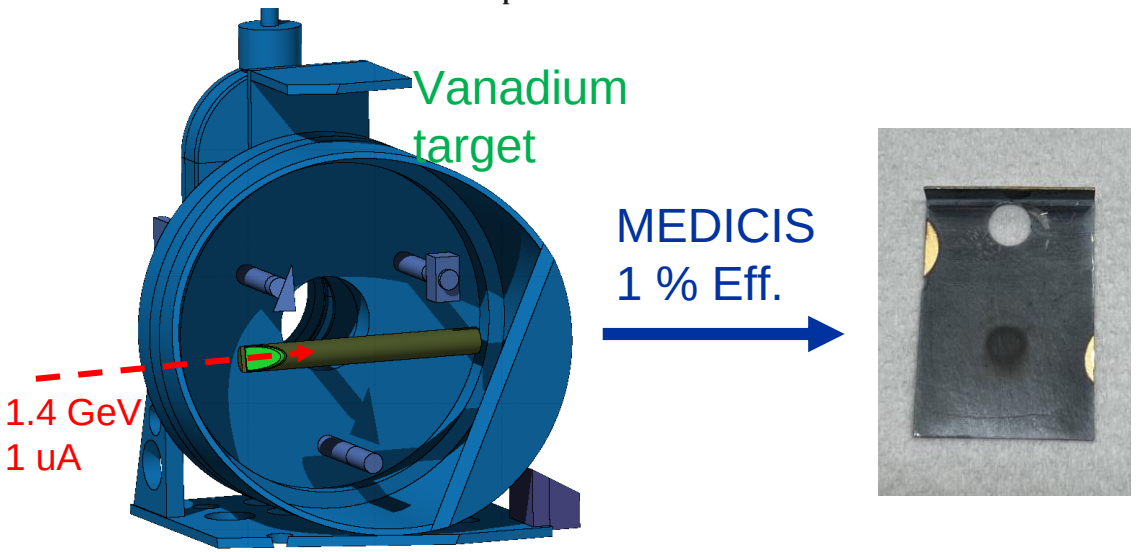
Table 3. Results of CERN FLUKA 4.2.2 ^{nat}V(p,x)Sc-43, Sc-44m, Sc-44g and Sc-47 production with 1.4 GeV proton direct impact

- In both cases direct irradiation with 6.25E+12 primary/second (1 µA) have been considered.
- Titanium target's density considered is 0.8 g.cm^{-3} and its volume is **30.17 cm^3 (mass of 24 g)**.
- Vanadium target's density considered is 0.87 g/cm^{-3} and its volume is **52.16 cm^3 (mass of 45,29 g)**.
- Calculations were done also for 1.7 GeV proton irradiation with less radionuclide production and favouring Ti as production material.

Element composition on MEDICIS collection foil

Element	Quantity (if OF are also collected), mol	Quantity (if no OF are collected), mol	Quantity with OF (if 1% efficiency), mol	Quantity no OF (if 1% efficiency), mol
Ca	4,05E-09	4,00E-09	4,05E-11	4,00E-11
Sc	3,46E-09	1,42E-09	3,46E-11	1,42E-11
Ti	2,97E-09	3,95E-10	2,97E-11	3,95E-12
V	3,57E-16	0,00E+00	3,57E-18	0,00E+00

Table 4. Sc-44 collection foil element composition contaminants



Element	Quantity (if OF are also collected), mol	Quantity (if no OF are collected), mol	Quantity with OF (if 1% efficiency), mol	Quantity no OF (if 1% efficiency), mol
Al	5,42E-14	5,42E-14	5,42E-16*	5,42E-16*
Si	1,80E-09	1,80E-09	1,80E-11*	1,80E-11*
Ca	5,55E-11	5,55E-11	5,55E-13	5,55E-13
Sc	2,05E-09	2,05E-09	2,05E-11	2,05E-11
Ti	1,47E-08	6,39E-09	1,47E-10	6,39E-11
V	1,28E-08	3,57E-16	1,28E-10	3,57E-18
Cr	4,67E-10	0,00E+00	4,67E-12	0,00E+00

Table 5. Sc-47 collection foil element composition contaminants. Al and Si compounds ure very unlikely to be extracted and expected.

- OF – Oxyfluorines. Oxyfluorines can form in presence of oxygen.
- Crude 1% Extraction efficiency presumed from a directly irradiated target.
- Not taken into account ratio of molecule species

Maximising output

- MEDICIS Double collection slit system installed and tested
- Collection of Sc-44 and Sc-47 silmutanously
- Successful Tm-165 and Tm-167 collection (100 MBq range)

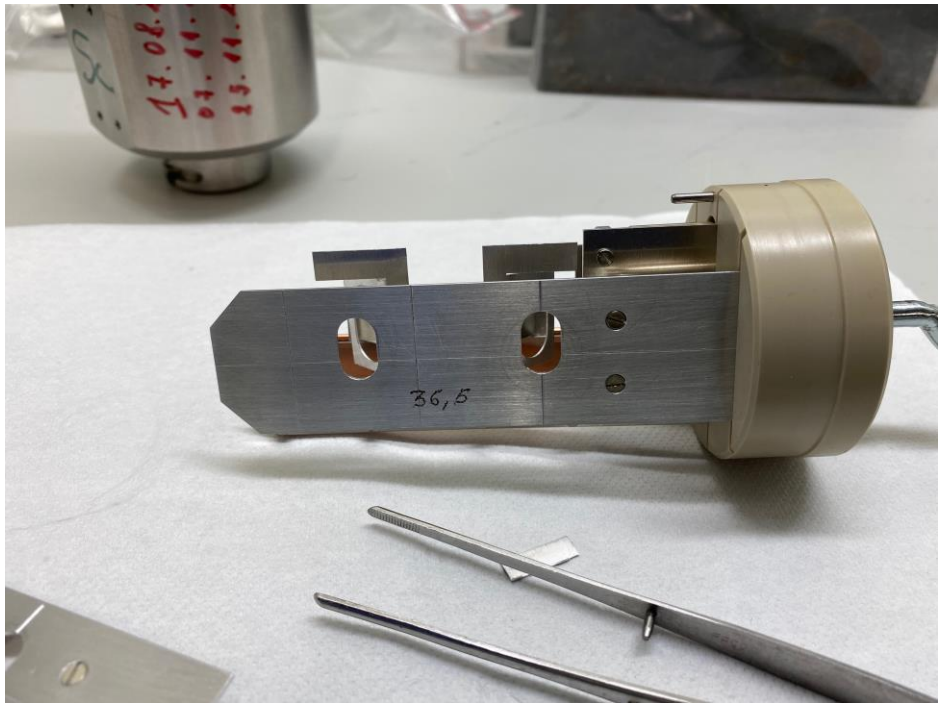


Fig. 24. Collection chamber for double collection with reduced sputtering

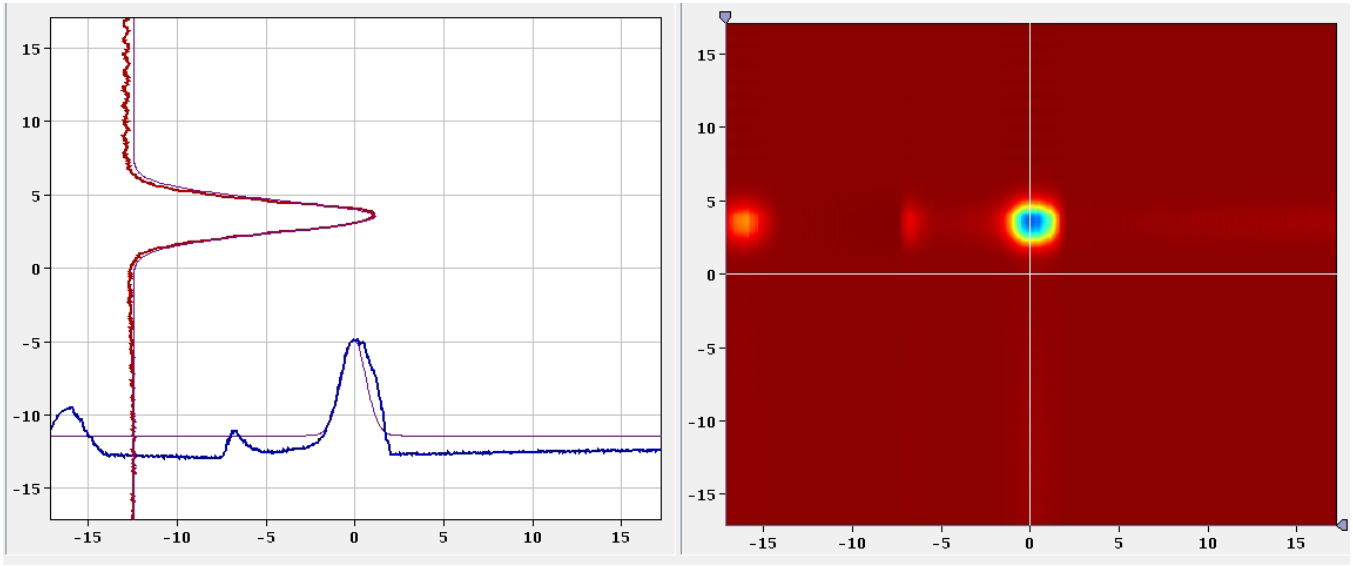


Fig. 25. Double beam collection profile of Tm-165 and Tm-167 silmutanously

Fig. 26. Kromek γ-spectra during double beam collection of Tm-165 and Tm-167 silmutanously

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 The European medical isotope programme: *Production of high purity isotopes by mass separation* started on 1st of May 2021.

In full swing!

PRISMAP will create a single-entry point for a fragmented user community distributed amongst universities, research centres, industry and hospitals.

27 EU
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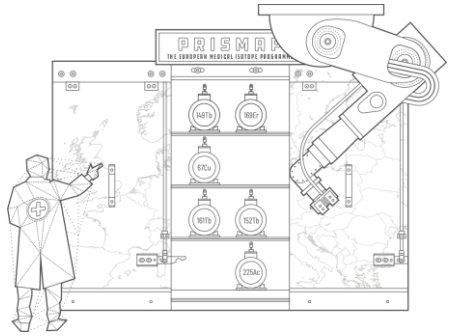
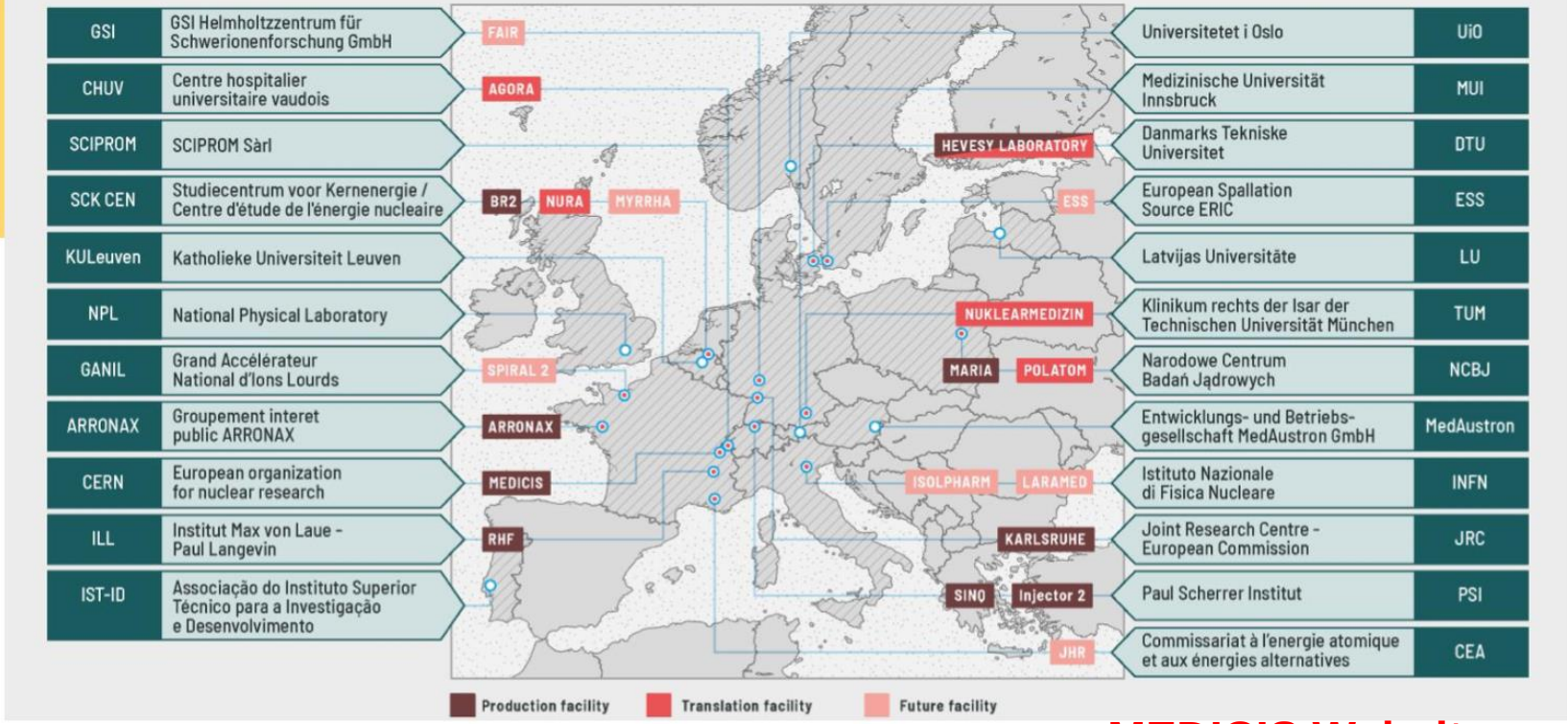
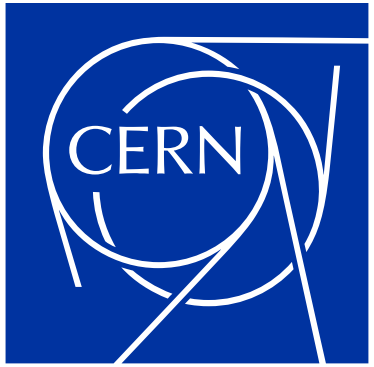




MEDICIS Website:
https://medicis.cern/



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