Development of molecular ion beams for extraction and mass-separation of ^{43,44g,47}Sc radioisotopes from irradiated natural titanium targets at the CERN-MEDICIS facility

Edgars Mamis
T. Stora, S. Rothe, E. Pajuste, C. Duchemin, M. Radziņa

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 Therapy and Diagnostics, and refers to the strategy of utilising radioactively labelled drugs for both purposes:
  - Most commonly for cancer treatment;
  - Ability to conjugate in the same pharmaceutically active agent;
  - So called ”Treat what You see” technique

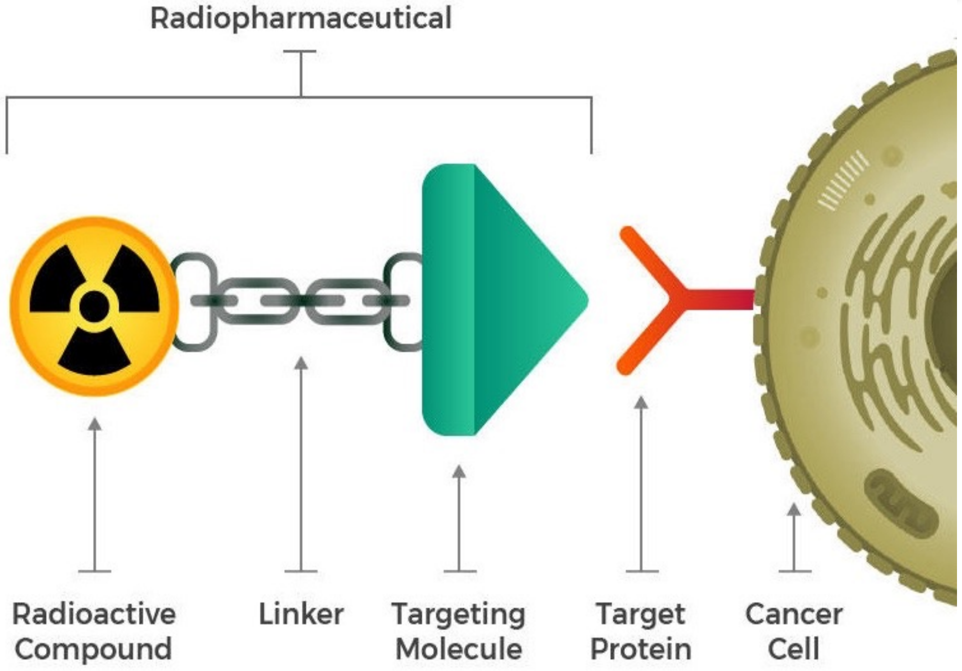
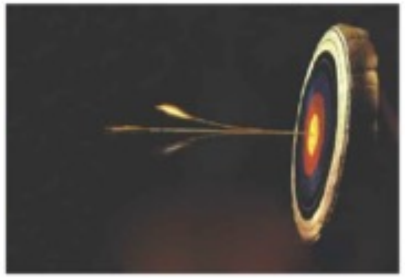


Fig. 1. Illustrative structure of a ligand radiopharmaceuticalradiopharmaceutical and its cell binding

External Beam Therapy

Radionuclide Therapy



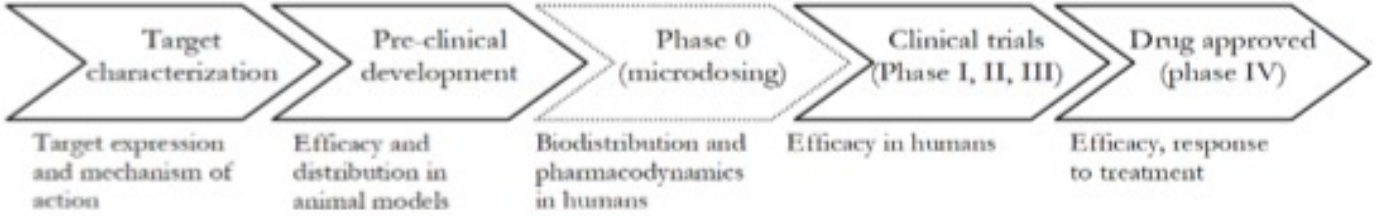


Fig. 2. Illustrative structure of drug develoment *Current Radiopharmaceuticals*, 2012, *5(2) 90-98.*

Why Scandium ?

- Cost and efficiency:
  - Sc radionuclides can be obtained from natural Ti 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;
  - Only the mass of atoms is different;
- Scandium radionuclides can be produced and decay to the most biocompatible stable chemical elements such as Ca and Ti;
- Trivalent metal, with similarities to lanthanides and rare earth elements.
- Chemical properties of Sc enable stable coordination with a DOTA chelator. This allows the use of targeting ligands, such as somatostatin analogs (e.g., DOTA-TOC, DOTA-NOC.

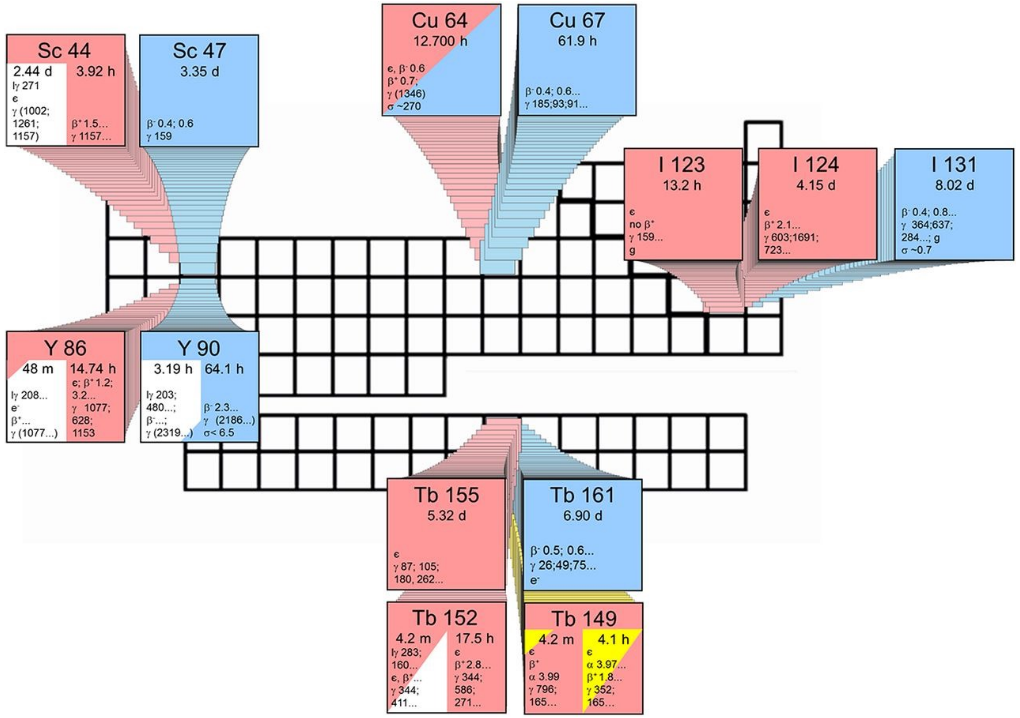
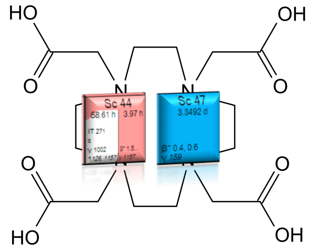


Fig. 3. Theragnostic principle: matched pairs of radionuclides for PET and SPECT imaging and for therapeutic application in nuclear medicine.
C. Müller, et. All. Promising Prospects for 44Sc-/47Sc-Based Theragnostics: Application of 47Sc for Radionuclide Tumor Therapy in Mice, *The Journal of Nuclear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

DOTA -



RFP – radiopharmaceutical

Nat-Ti as target material for ^{xx}Sc radionuclide production

- Relatively cheap metal titanium is light, corrosion resistant, 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
- Feasible for desired isotopes to be mass-separated (purified) from single production batch with MEDICIS and Isotope Seperator OnLine (ISOL) technique

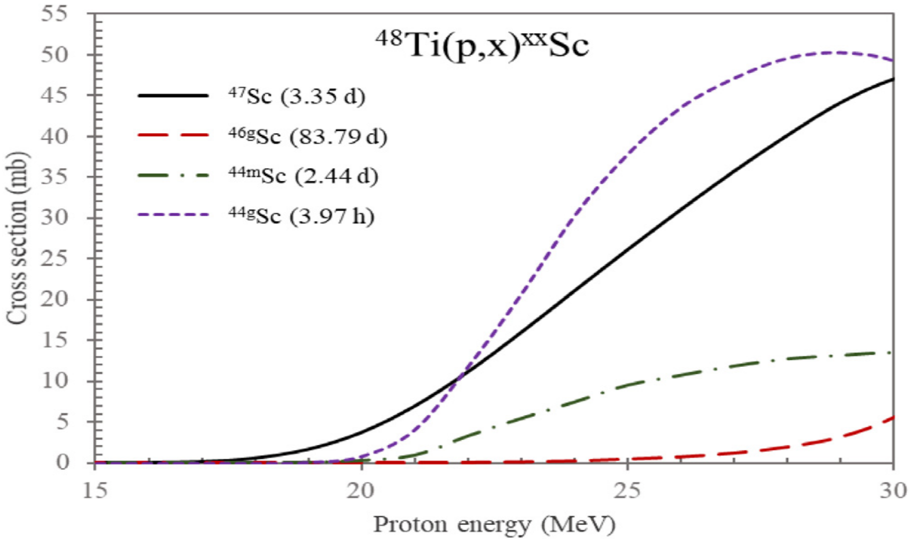


Fig. 4. Excitation function of ^{48}Ti(p,x)^{xx}Sc reaction by the TALYS-1.9 code
A. Jafari, et. All. Cyclotron-based production of the theranostic radionuclide scandium-47 from titanium target, *Nuclear Inst. and Methods in Physics Research,* vol. 961, no. Elsevier B.V., 2020

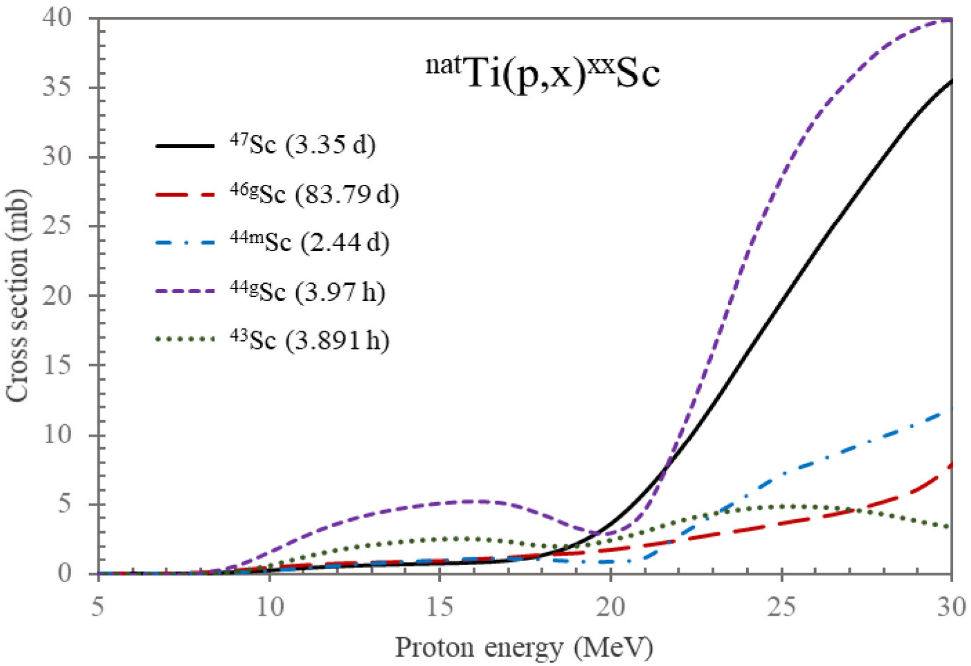


Fig. 5. Excitation function of ^{nat}Ti(p,x)^{xx}Sc reaction by the TALYS-1.9 code
A. Jafari, et. All. Cyclotron-based production of the theranostic radionuclide scandium-47 from titanium target, *Nuclear Inst. and Methods in Physics Research,* vol. 961, no. Elsevier B.V., 2020

Production of ^{47}Sc radionuclide from Ti

- Direct reaction on Ti targets for proton and deuteron bombardment:
  - **^{50}Ti(p,α) ^{47}Sc;**
  - **^{49}Ti(p,3He) ^{47}Sc;**
  - **^{48}Ti(p,2p) ^{47}Sc;**
  - ^{50}Ti(d,αn) ^{47}Sc;
  - ^{49}Ti(d,α) ^{47}Sc;
  - ^{48}Ti(d,3He) ^{47}Sc;
  - ^{47}Ti(d,2p) ^{47}Sc;
- Direct reaction on Ca targets for proton, deuteron and α particle bombardment:
  - ^{48}Ca(p,2n) ^{47}Sc;
  - ^{48}Ca(d,3n) ^{47}Sc;
  - ^{46}Ca(d,n) ^{47}Sc;
  - ^{44}Ca(α,p) ^{47}Sc;
- Direct reaction on V target for proton:
  - ^{51}V(p,αp) ^{47}Sc;
- Indirect reaction on Ti targets for proton and deuteron bombardment:
  - **^{50}Ti(p,p3He)^{47}Ca →^{47}Sc ($t_{1/2}$=4,536 d);**
  - **^{49}Ti(p,3p)^{47}Ca → ^{47}Sc;**
  - ^{50}Ti(d,αp)^{47}Ca → ^{47}Sc.
- Indirect reaction on Ca targets for proton and deuteron bombardment:
  - ^{48}Ca(p,d)^{47}Ca →^{47}Sc;
  - ^{46}Ca(d,p)^{47}Ca →^{47}Sc;
  - ^{48}Ca(d,t)^{47}Ca →^{47}Sc.

IAEA, Therapeutic Radiopharmaceuticals Labelled with
Copper-67, Rhenium-186 and Scandium-47, 2021.

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**

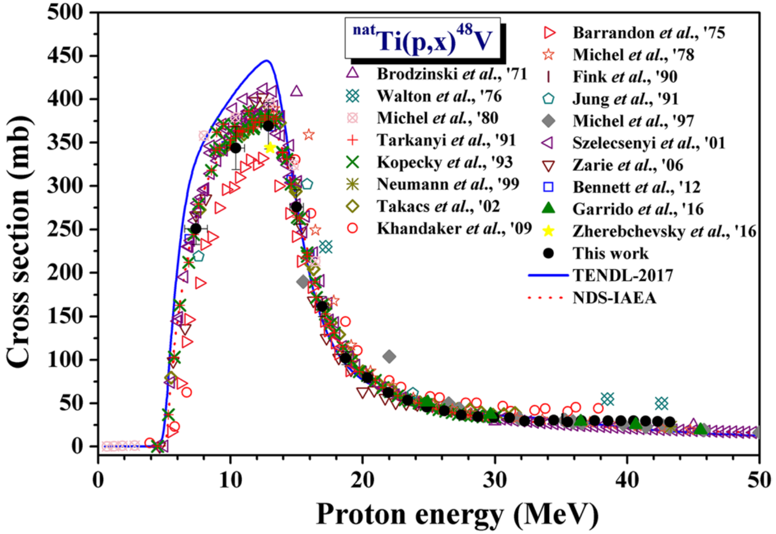


Fig. 6. Excitation function of ^{nat}Ti(p,x)^{48}V reaction compared with the literature data as well as the data from TENDL-2017 library based on the TALYS 1.9

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,γ)	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,α)	−3.07	3.14
		β$^+$ (88.1)			^{47}Ti(p,nα)	−11.95	12.21
					^{48}Ti(p,2nα)	−23.58	24.07
					^{49}Ti(p,3nα)	−31.72	32.37
^{44m}Sc	2.44 days	IT (98.8)	271.2	86.7	^{47}Ti(p,α)	−2.25	2.30
		EC (1.2)	1002	1.2	^{48}Ti(p,nα)	−13.88	14.17
^{44g}Sc	3.93 h	EC (5.73)	1157.0	99.9	^{49}Ti(p,2nα)	−22.02	22.47
		β$^+$ (94.27)			^{50}Ti(p,3nα)	−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,^{3}He)	−14.37	14.67
					^{49}Ti(p,α)	−1.94	1.98
					^{50}Ti(p,nα)	−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,^{3}He)	−11.87	12.11
					^{50}Ti(p,α)	−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,^{3}He)	−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. The maximum frequency of this pulsed beam is one pulse every 1.2 seconds with up to $3*10^{13}$ protons per pulse;
- 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.

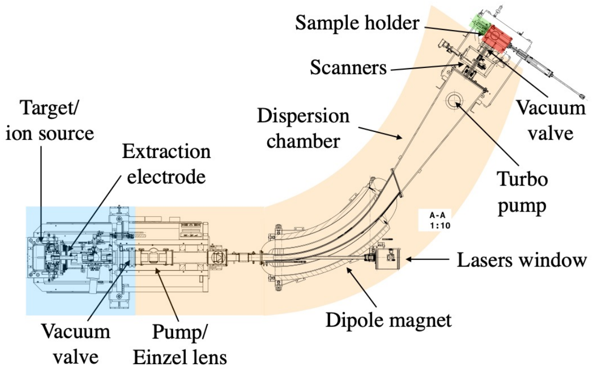


Fig. 7. MEDICIS isotope mass-separator structure

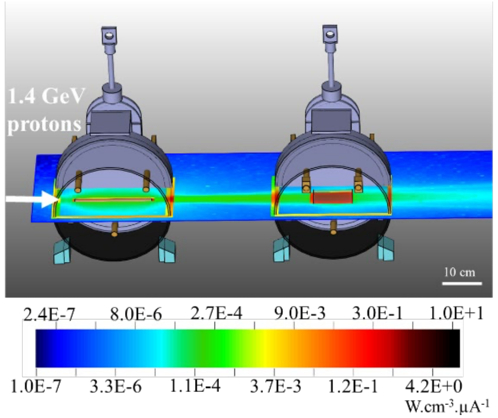


Fig. 8. Visualisation of the ISOLDE (left) and MEDICIS target (right) irradiated by the 1.4 GeV proton beam.

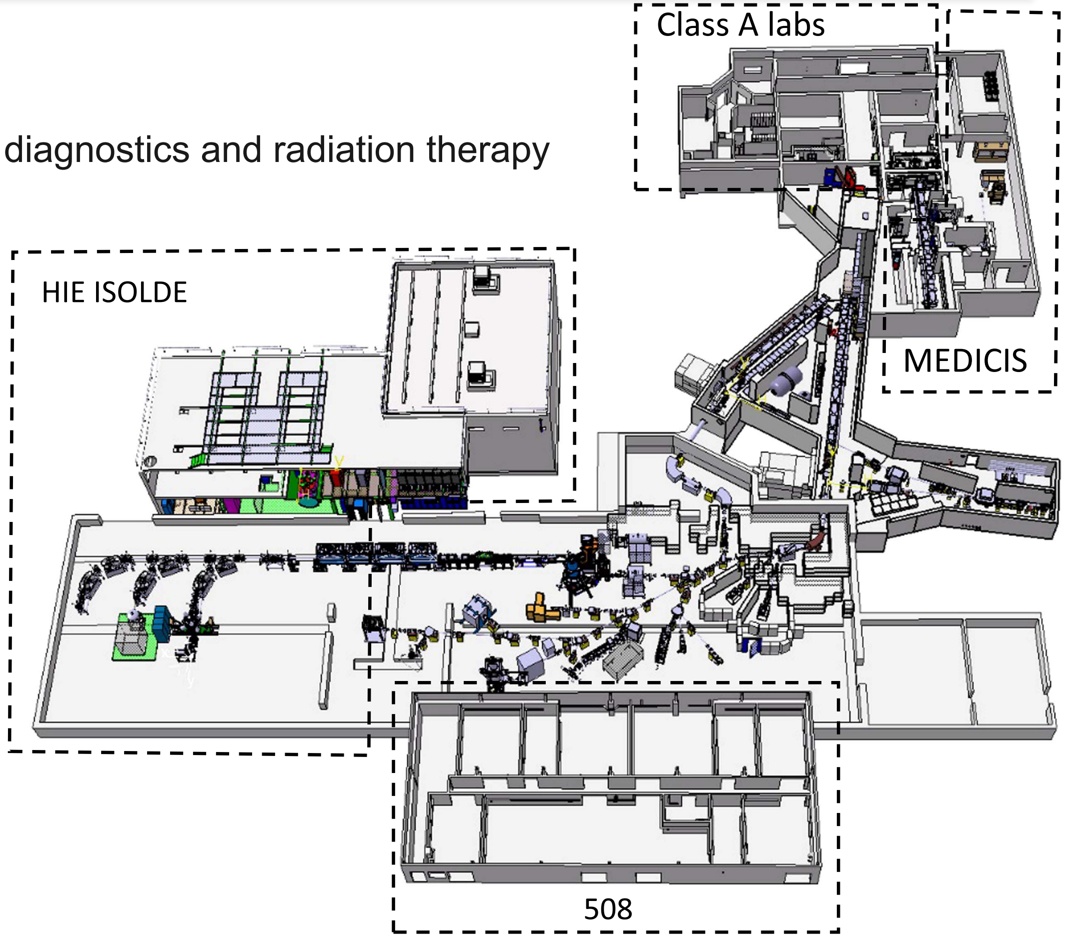
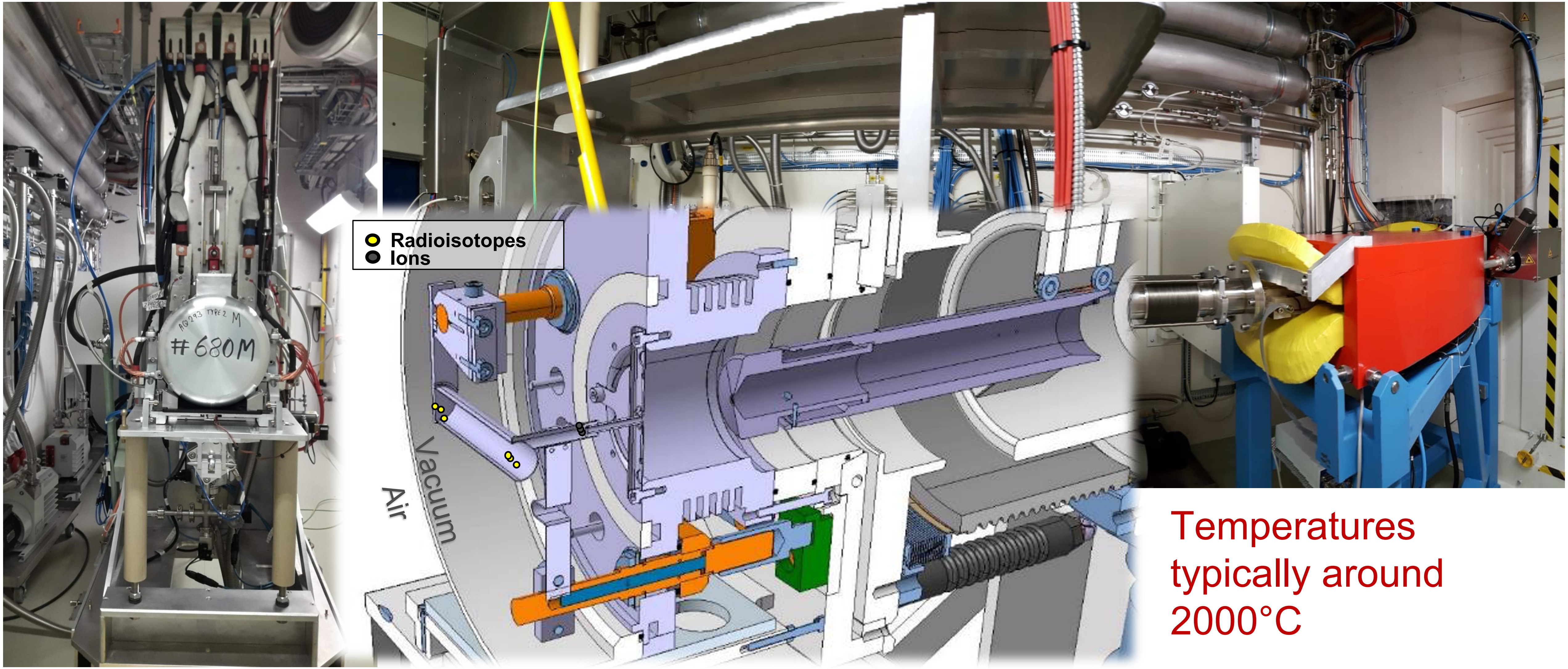


Fig. 9. 3D model of the ISOLDE-MEDICIS facility in 2017.

CERN-MEDICIS – view inside the bunker



Temperatures typically around 2000°C

Courtesy of C. Duchemin

Molecular beams

- Desired isotope extraction efficiency in most cases is enhanced by increasing temperature;
  - Up to a point where target material melts!
- Extraction of rare earth refractory metals such as Ti and Sc is challenging due to high boiling points and low vapour pressures;
- Refractory metals are very reactive by nature and 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 the isotopes;
- Collection of desired element/molecule can be shifted to an atomic mass region without increased background (isobars) from structural or gas contamints;

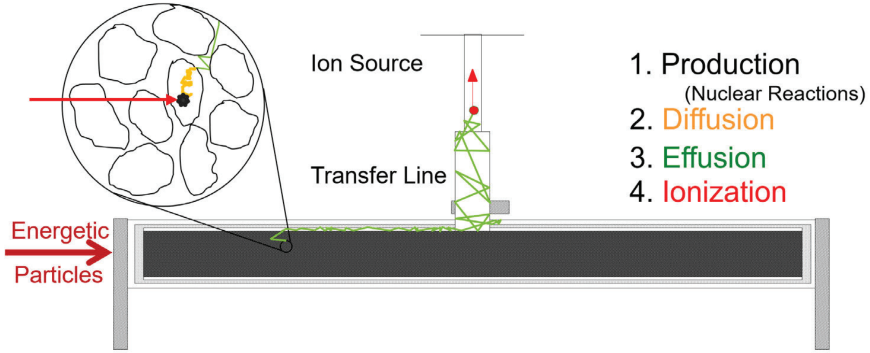


Fig. 10. Schematic of the ISOL method production, diffusion, effusion and ionization steps.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE FÉDÉRALE DE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

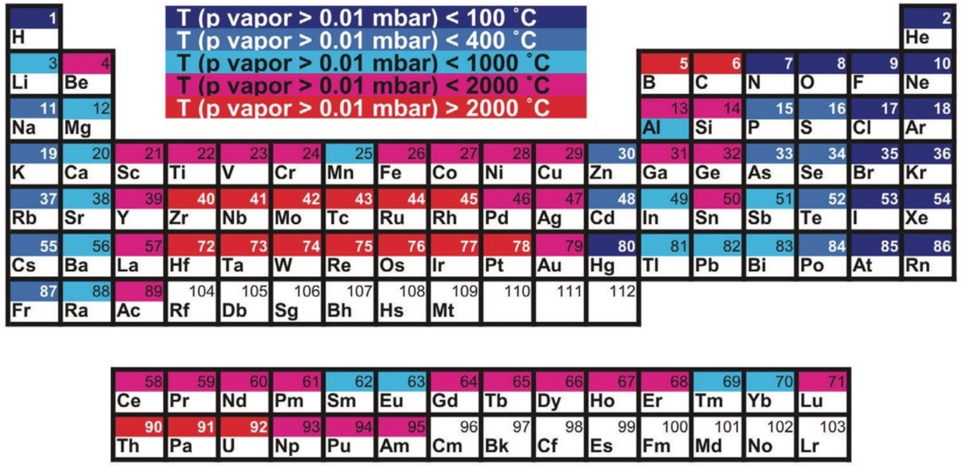


Fig. 11. Periodic table representing the temperature at which each element has a vapour pressure of 0.01 mbar.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE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

Target unit with FEBIAD ion source system

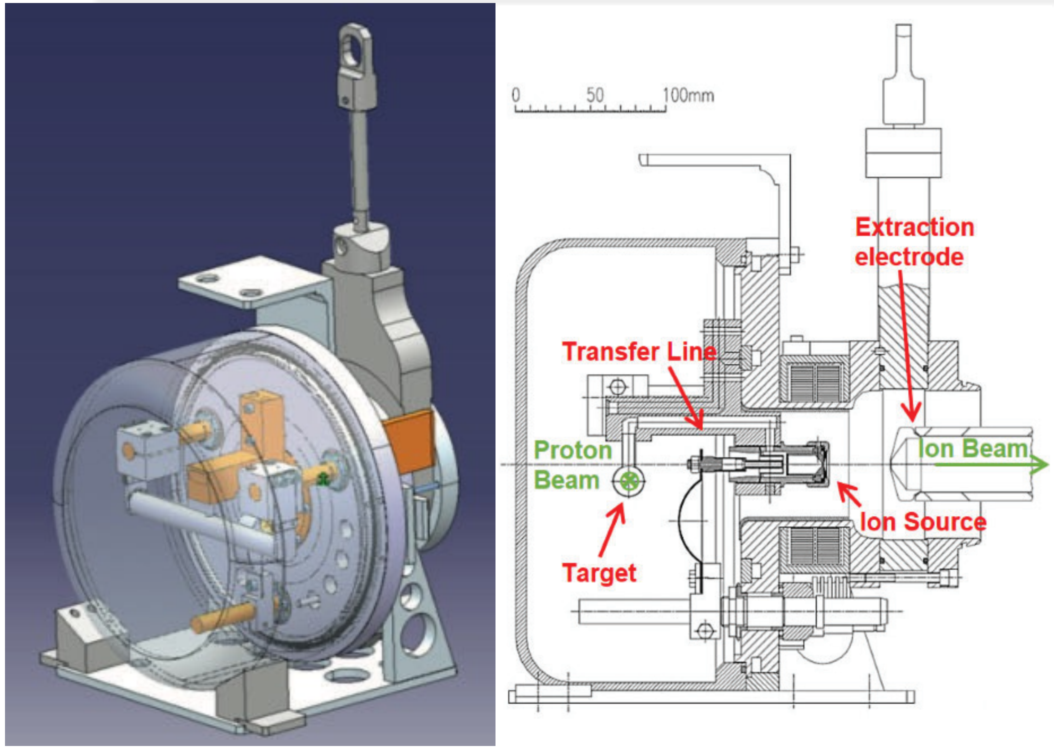


Fig. 12. Modern target and surface ion source unit at ISOLDE. The diameter of the confinement box (seen in transparency) is 30 cm.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, 2017.

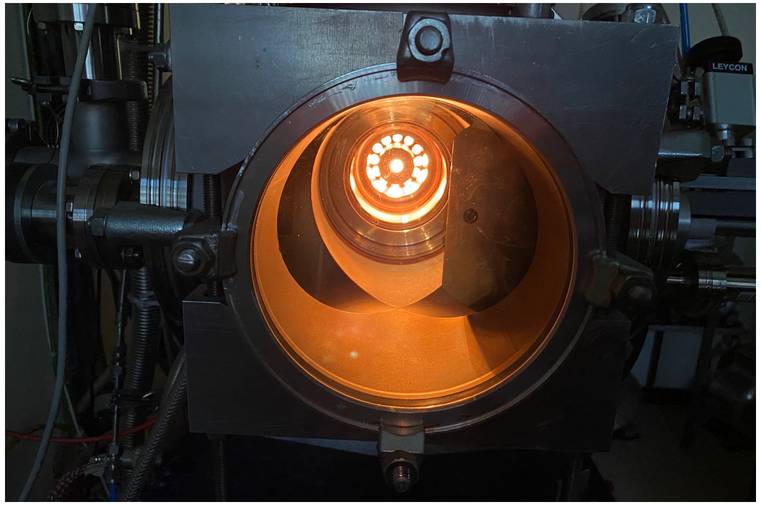


Fig. 13. Open front look of VD-5 target unit during temperature calibration on pump stand. Temperature ~ 2000 °C

Fig. 14. Target unit assembly on Offline-1 (Offline isotope mass separator) frontend.

Molecule ionization - VADIS VD-5

- Previousely surface and laser ion sources were used to ionize Sc elements and sometimes molecules;
  - When ionizing to q = +1 ions, molecules can dissociate in the ion source.
  - In some cases the cross section for the dissociation exceed the cross section for direct ionization by orders of magnitude.
- By using surface ionizer the release of Sc molecular beams release delay from target unit may be in order of several hours;

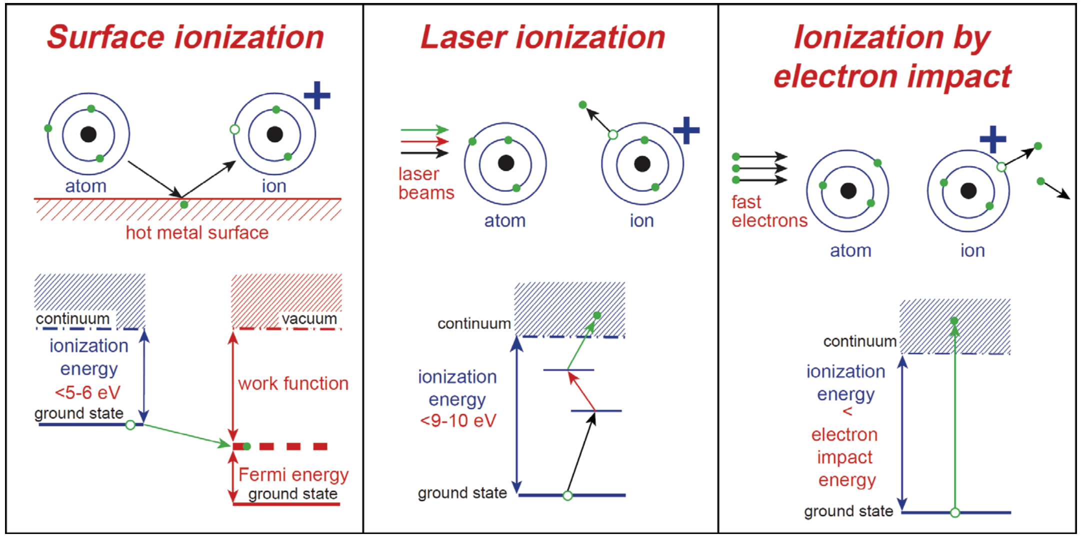


Fig. 16. Ionization mechanisms used in ISOLDE: surface, laser and electron impact ionization.
J. P. F. P. Ramos, *Titanium carbide-carbon porous nanocomposite materials for radioactive ion beam production: processing, sintering and isotope release properties,* Lausanne: ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, 2017.

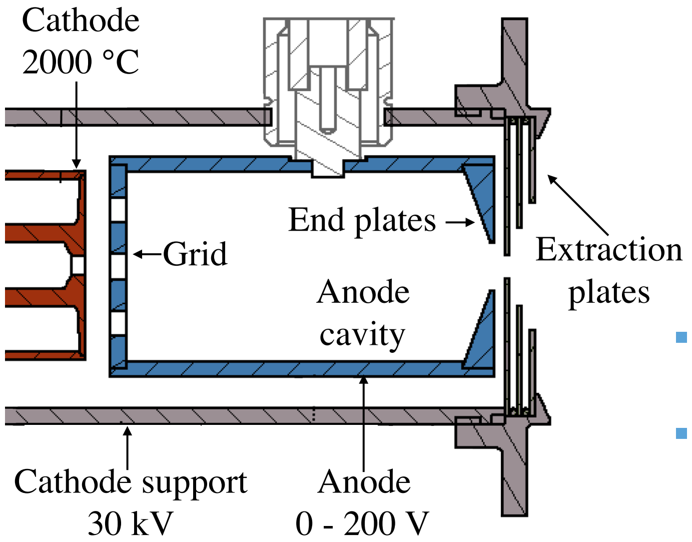


Fig. 15. Geometry of ISOLDE FEBIAD ion source (VADIS).
Y. M. Palenz, *Characterization and optimization of a versatile laser and electron-impact ion source for radioactive ion beam production at ISOLDE and MEDICIS,* Belgium: KU Leuven – Faculty of Science, 2019.

- 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 and can therefore ionize basically any element.

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

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

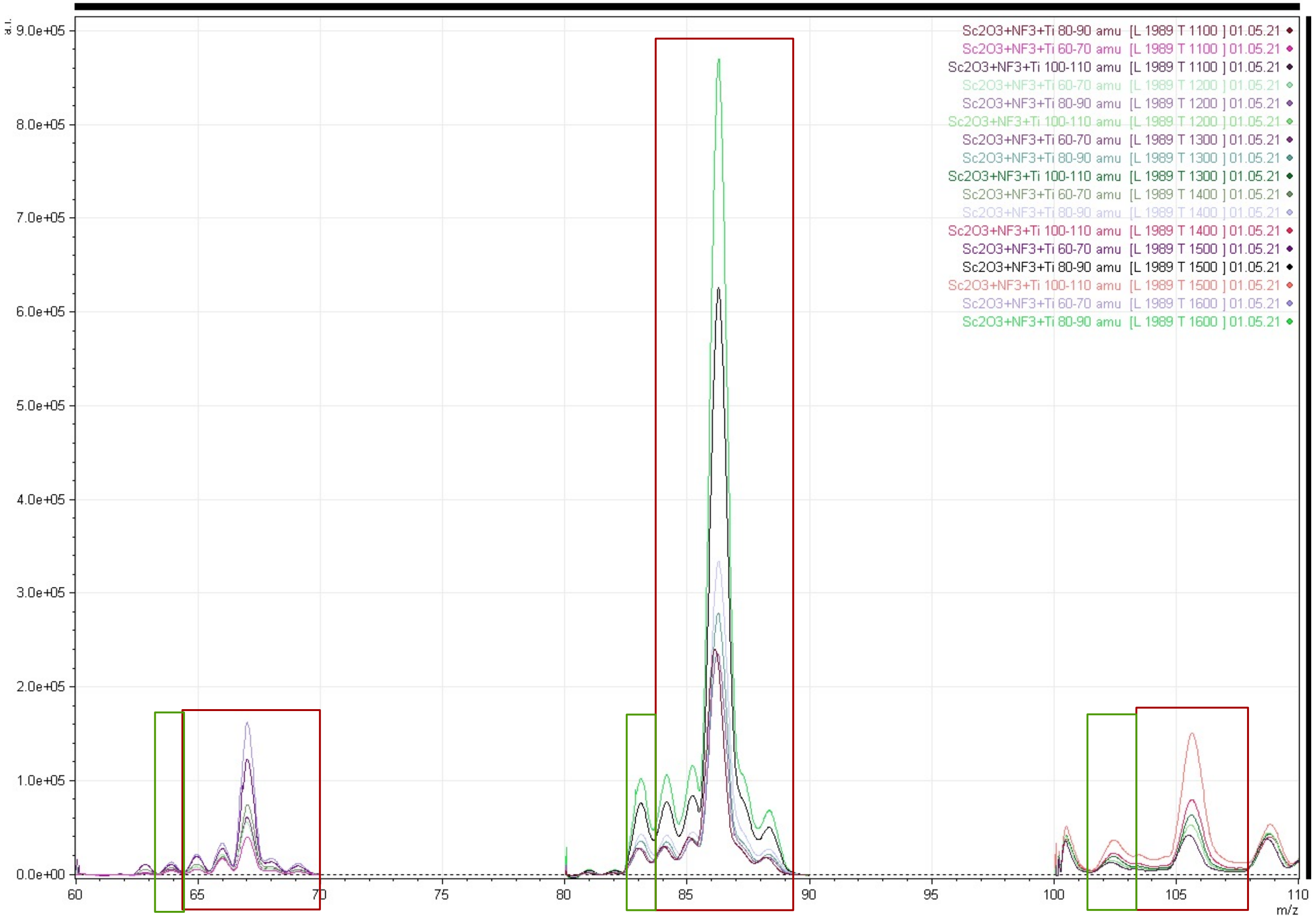


Fig. 17 Stable TiF_x^+ and ScF_x^+ molecular beam mass scans by gradually increasing target container temperature.

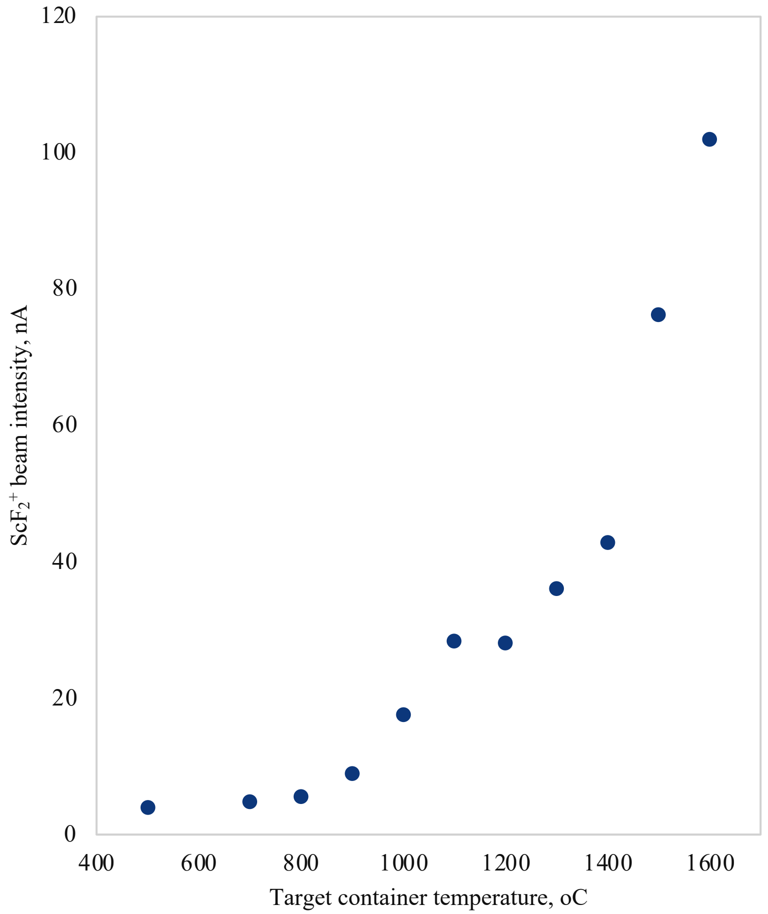


Fig. 18. Correlation between ScF_2^+ molecular beam formation/ extraction and target container temperature

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

- ScF^+; ScF_2^+ and ScF_3^+ molecular beams could be observed and extracted, <u>but so does</u> TiF^+; TiF_2^+ and TiF_3^+;
  - ScF_2^+ and TiF_2^+ molecular beams dominant;
- Whole mass spectra description;
  - Main other contaminants from Si, B, Be, C, Ta and O;
  - Large portion of total ion beam is taken by N_2, CO, BeF_2, SiF_x, TaF_x and TaO_xF_y;
  - Main contaminants for collection of $[^{47}Sc]ScF_2^+$ beam are $[^{47}Ti]TiF_2^+$ and fraction SiF_3^+molecules and have to be separated chemically or “baked out”;
- Total beam intensity must be monitored with increased sample quantity;
  - VADIS ion source capacity must be respected;
  - Total intensity could be controlled by choosing appropriate fluorinating gas (NF_3; CF_4; SF_6; ect) and supply to the target container;
- There is a clear correlation between target container temperature and beam intensity;
- Collection of separated isotopes:
  - Implantation in target foils;
  - Efficiency of extraction;
  - Purity from isobars.
- Molten targets can hinder the release or damage target unit.

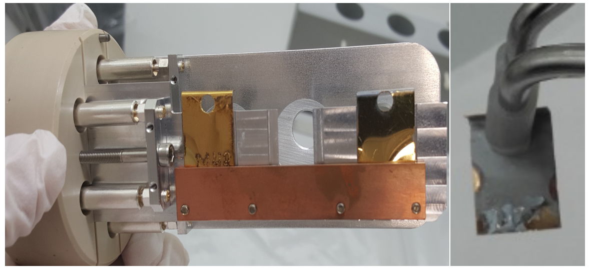


Fig. 20 MEDICIS separated isotope collection foils

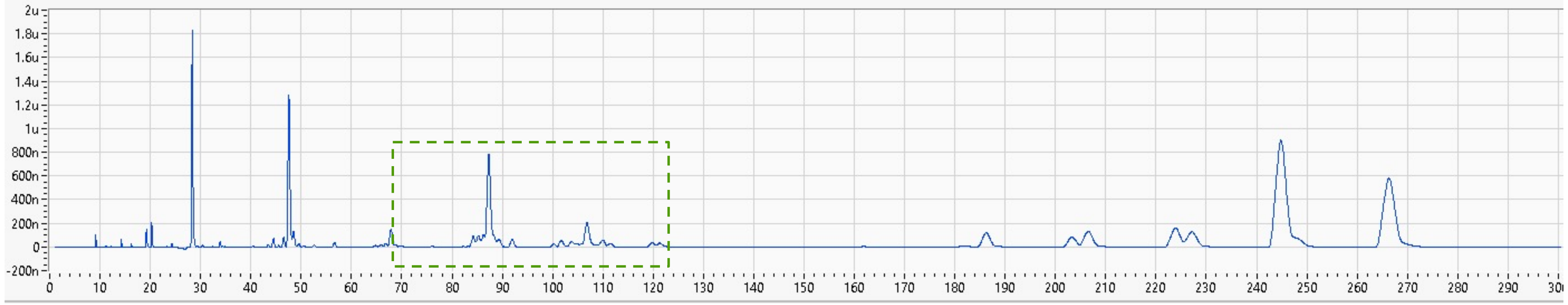


Fig. 19 nat-Ti + $[^{45}Sc]Sc_2O_3$ + NF_3 system full range mass scan – beam current distribution.

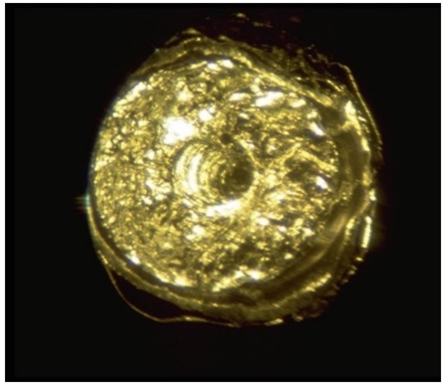
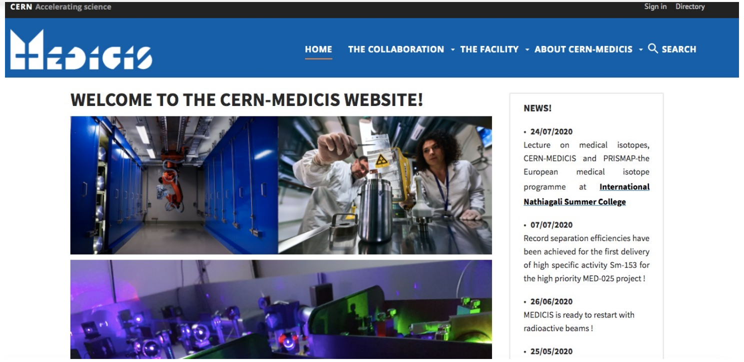


Fig. 21 Molten target material. Previously – stacked 20 mm annular Ta disks

Courtesy of C. Duchemin, L. Lambert and T. Stora

MEDICIS in 2021 and beyond

MEDICIS Website!
https://medicis.cern/



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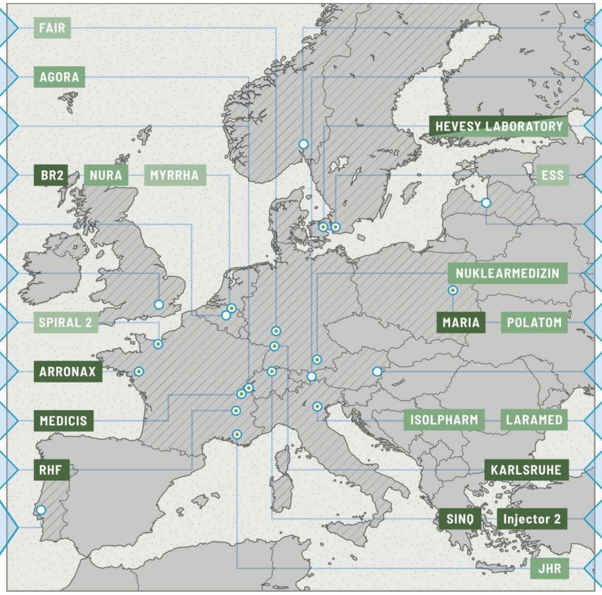
NEWS!

- **24/07/2020**
  Lecture on medical isotopes, CERN-MEDICIS and PRISMAP-the European medical isotope programme at **International Nathiagali Summer College**
- **07/07/2020**
  Record separation efficiencies have been achieved for the first delivery of high specific activity Sm-153 for the high priority MED-025 project !
- **26/06/2020**
  MEDICIS is ready to restart with radioactive beams !
- **25/05/2020**

- Sc radionuclides have been already studied by MEDICIS collaboration members across Europe and are soon to come towards clinical trials.
- Proton beam is now back at **CERN-MEDICIS** !
- **PRISMAP started on 1st of May!**
  - 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.

GSI	GSI Helmholtzzentrum für Schwerionenforschung GmbH
CHUV	Centre hospitalier universitaire vaudois
SCIPROM	SCIPROM Sàrl
SCK CEN	Studiecentrum voor Kernenergie / Centre d'étude de l'énergie nucléaire
KULeuven	Katholieke Universiteit Leuven
NPL	National Physical Laboratory
GANIL	Grand Accélérateur National d'Ions Lourds
ARRONAX	Groupement interet public ARRONAX
CERN	European organization for nuclear research
ILL	Institut Max von Laue - Paul Langevin
IST-ID	Associação do Instituto Superior Técnico para a Investigação e Desenvolvimento



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Danmarks Tekniske Universitet	DTU
European Spallation Source ERIC	ESS
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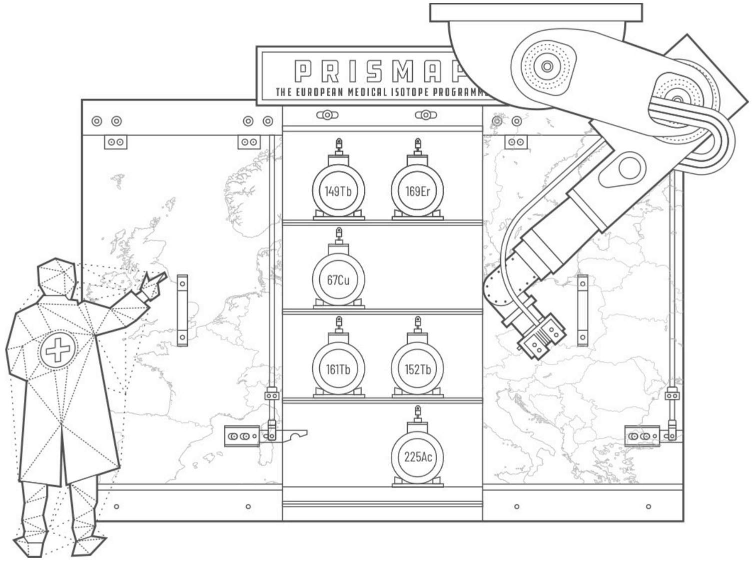
Klinikum rechts der Isar der Technischen Universität München	TUM
Narodowe Centrum Badań Jądrowych	NCBJ
Entwicklungs- und Betriebs-gesellschaft MedAustron GmbH	MedAustron
Istituto Nazionale di Fisica Nucleare	INFN
Joint Research Centre - European Commission	JRC
Paul Scherrer Institut	PSI
Commissariat à l'energie atomique et aux énergies alternatives	CEA

🟩 TNA2　🟩 TNA3　🟩 Future Facility



PRISMAP Website (coming soon)! INFO:
https://medicis.cern/prismap-european-medical-isotope-programme

Courtesy of C. Duchemin and T. Stora

Thank you for your attention,
and let us bring ISOL to Baltic!

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