CERN-MEDICIS: Production of Promising Radionuclides for Nuclear Medicine

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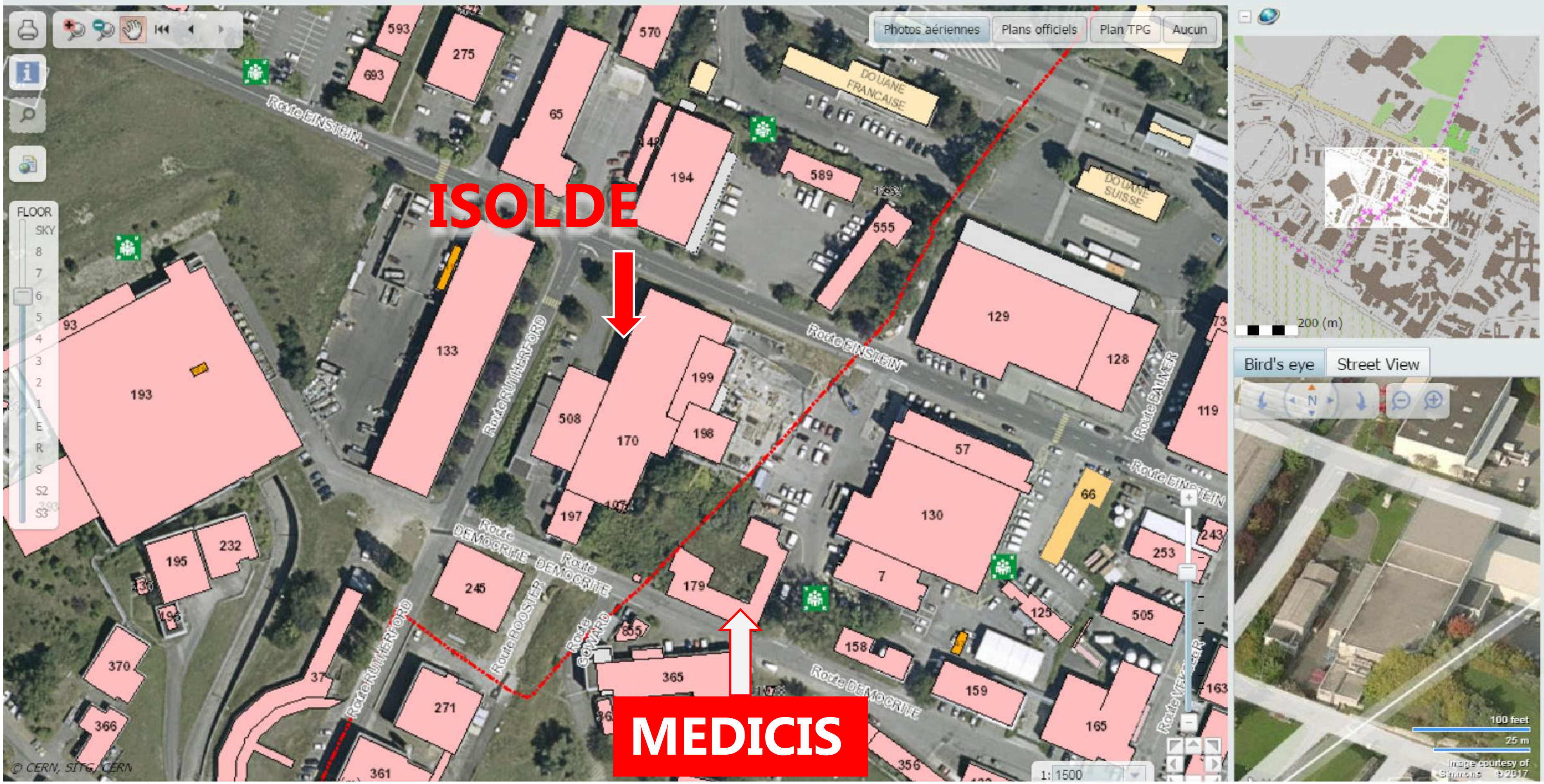
50 ЛЕТ НА ПИКЕ НАУКИ

CERN-MEDICIS (MEDical Isotopes Collected from ISolde)



CERN-MEDICIS (MEDical Isotopes Collected from ISolde)

First radioactive ion beam at CERN (Switzerland) in December 2017 to support the research and development in nuclear medicine using non-conventional radionuclides.

14 institutes (including CERN) have joined the collaboration to drive the scientific program of this unique installation and evaluate the needs of the community to improve the research in imaging, diagnostics, radiation therapy and personalized medicine.

The facility has been built as an extension of the ISOLDE (Isotope Separator On Line DEvice) facility at CERN.

Радионуклиды для персонализированной медицины

- Главным преимуществом персонализированной медицины является то, что можно учитывать индивидуальные патологии и свести к минимуму разрушение окружающих здоровых тканей путем тщательного подбора соответствующего радионуклида.
- Чтобы получить радиофармпрепараты для такого лечения, необходимо произвести конкретный радионуклид с наивысшей изотопной и химической чистотой в достаточных количествах и относительно не дорого (по какой-либо отработанной стандартной технологии).
- Эти радионуклиды могут быть получены на ускорителях частиц или в ядерных реакторах путем облучения стабильных изотопов. Однако для достижения уровня чистоты, необходимого для доклинических экспериментов и клинических испытаний, требуются дополнительные процедуры выделения целевого нуклида.
- В зависимости от того, какое количество и какой степени чистоты интересующего радионуклида требуются, такая очистка может быть достигнута методами:
  - ❑ физического разделения,
  - ❑ химического разделения,
  - ❑ масс-сепараторным методом
  - ❑ комбинацией методов.

Радионуклиды для пероснализированной медицины

В настоящее время **CERN-MEDICIS** является единственной европейской установкой, которая полностью посвящает свою программу производству и поставке изотопов медицинского назначения для исследований используя **масс-сепараторный метод** разделения изотопов.

CERN-MEDICIS также находится в центре нового европейского проекта под названием PRISMAP, который представляет собой консорциум из 23 институтов, целью которого является внедрение новых радионуклидов в медицинскую диагностику и лечение, в котором разделение изотопов играет важную роль для достижения соответствующей специфической активности и чистоты радионуклидов.

- Первые радионуклиды для медицинских исследований были получены на CERN-MEDICIS 12 декабря 2017 года.
- Tb-155 был первым радионуклидом, выделенным в MEDICIS, - один из четырех радиоизотопов тербия, которые являются весьма перспективными для диагностики и лечения рака.

в 2018, MEDICIS официально стала международной коллаборацией институтов, госпиталей и университетов.

Board number	Date	Number of institutes in the collaboration	Number of projects	Radionuclide(s) of interest
1	21/02/2018	12	13	C-11, Sc-43, Sc-44, Sc-47, Cu-67, Xe-131m, Xe-133m, Tb-149, Tb-152, Tb-155, Er-169
2	03/10/2018		3	Sc-44, Sc-47, Tb-149, Tb-155
3	20/03/2019		7	Fe-52, Fe-59, Tb-149, Tb-152, Tb-155, Tm-167, Er-169, Yb-175, Pt-191, Pt-193m, Pt-195m
4	18/09/2019		1	Ac-225, Ac-227
5	20/02/2020		1	Sm-153
6	17/09/2020		2	Cu-64, Ac-225
7	11/03/2021	14	4	Ba-128/Cs-128, Ce-134/La-134, Tb-149, Tb-152, Ac-225

Collaboration (2021):
GIP ARRONAX (France), CHUV (Switzerland), EANM (Europe), FABIS (Spain), HUG (Switzerland), ILL (France), IST (Portugal), JGU Mainz (Germany), JRC Karlsruhe (Germany), KU Leuven (Belgium), NPL (UK), PSI (Switzerland), PAEC (Pakistan), RTU LU (Latvia)

Isotope in-target production at CERN-MEDICIS

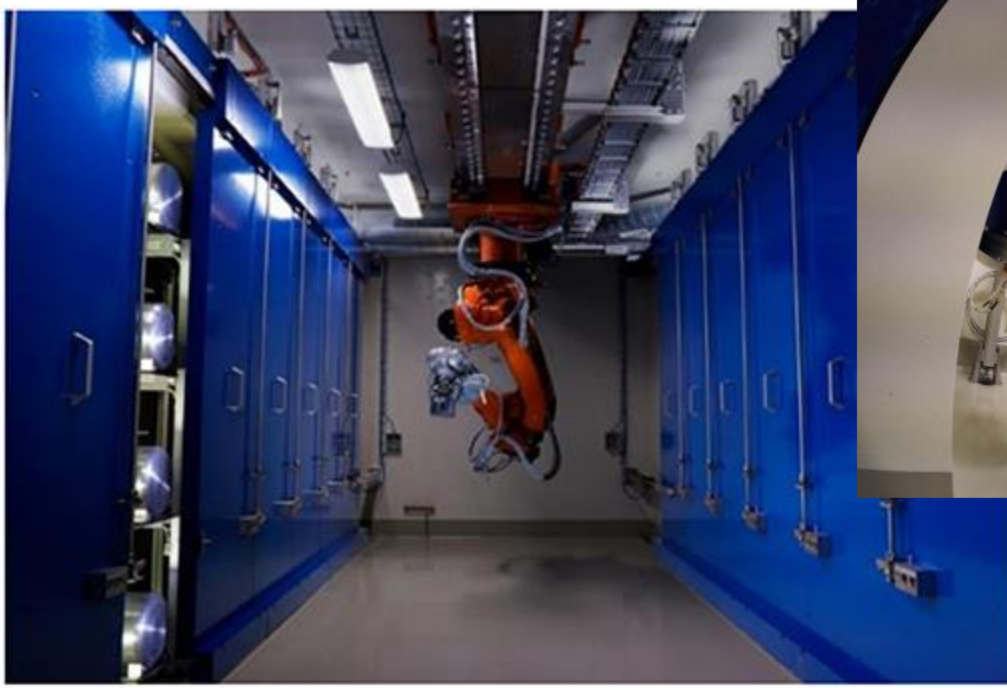
One of the main features of CERN-MEDICIS is that it can profit from several irradiation possibilities to produce its isotopes before proceeding to the off-line mass separation of the radionuclide of medical interest

The facility has the opportunity to irradiate targets at CERN in the ISOLDE primary area. Every target unit is compatible with both, the ISOLDE and MEDICIS facilities

The MEDICIS target can be:

- directly irradiated by the 1.4 GeV proton beam of the CERN Proton Synchrotron Booster;
- indirectly irradiated by the fraction of the primary proton beam (>65%) which did not interact with the HRS target, as well as by its secondary particle showers – so-called parasitic mode;
- irradiated at ARRONAX or PSI accelerators and delivered to MEDICIS facility.

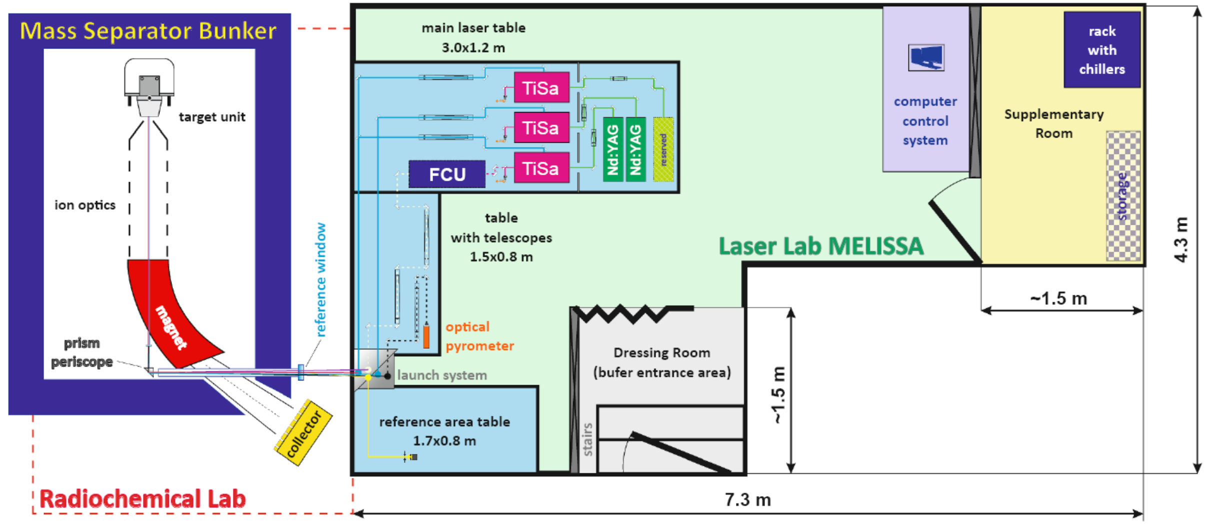
Once the MEDICIS target has been irradiated, it is transported to a decay point via an automatic rail conveyor system (RCS) handles the target and is used to safely connect the target to the MEDICIS target station to subsequently start with the collection of the radionuclide of interest.

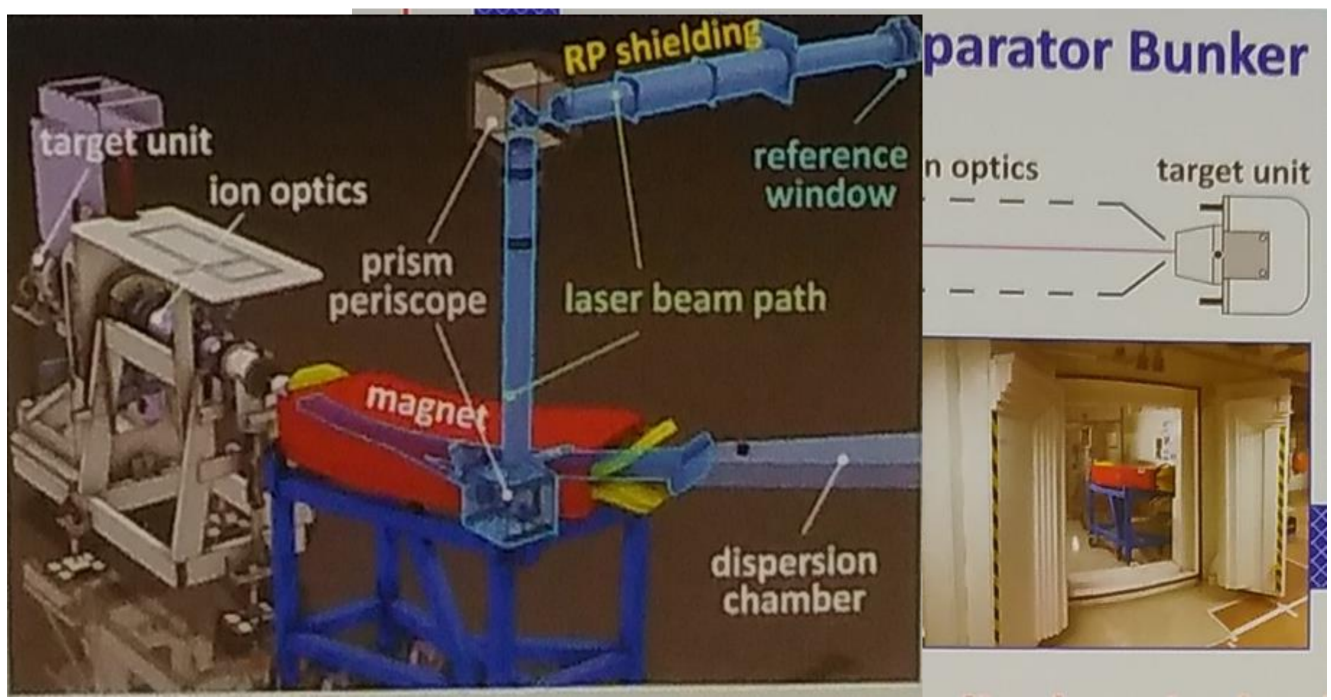


The MEDICIS consists of:

- a target-ion source assembly
- ion extraction system
- 55-degree double focusing magnet with a bending radius of 1.5m providing a mass resolving power of aboutd 400,
- the radioisotope collector is located in the Radiochemical Laboratory
- MELISSA Lab (MEDICIS' Laser Ion Source for Separator Assembly) – laser system for resonance ionization of selected isotopes

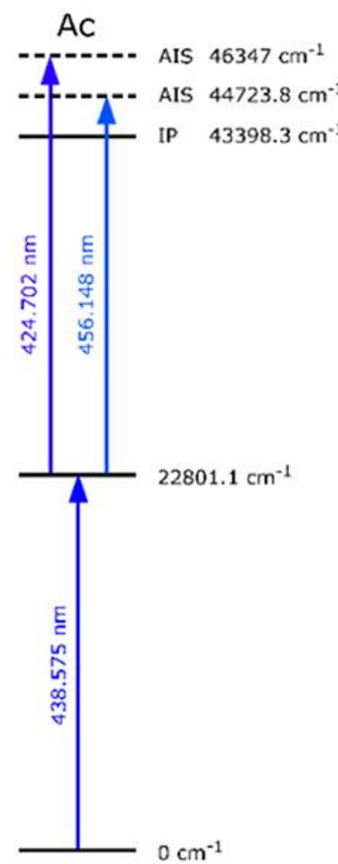
Preliminary irradiated target materials or samples containing radioactive isotopes of interest are enclosed in a target container, which is connected to a hot cavity ion source through a transfer line.
The container and ion source cavity can be independently heated to temperatures of 2000-2500◦C. This is necessary for the temperature-dependent release process of atoms from the target container into the cavity .
The atoms are then ionized via the element-selective laser ionization process.
The resulting ions are extracted by up to 60 kV accelerating potential, focused by ion optics, separated by their mass-to-charge ratio in the dipole electromagnet, and guided towards the collector.





Laser system of MELISSA Lab

- Two YAG pump lasers (commercial, InnoLas Nanio 532-18-Y)
- Two Ti-Sa tunable lasers (made by Mainz University)
- Wavemeter (Ангстрем, Новосибирск)
- Focusing and transfer optics



- MEDICIS is one of the very few facilities at CERN which was still operating during the second Long Shutdown (LS2).
- During the years 2019 and 2020, MEDICIS performed off-line mass separation of medically important radionuclides from materials irradiated at external partner institutes.
- In 2019 and 2020, CERN-MEDICIS received and used 34 externally irradiated target materials. These radioactive samples were provided by the GIP ARRONAX in Nantes (France), ILL in Grenoble (France), JRC in Karlsruhe (Germany), PSI in Villigen (Switzerland) and SCK CEN in Mol (Belgium).

This operation mode is being exploited since the first successful feasibility test carried out in 2018 with the mass separation and the collection of 18 MBq of Er-169 from naturally abundant Er-168, irradiated in the reactor of ILL in Grenoble (France)

Production of Mass-Separated Erbium-169

- Radiolanthanides are of particular interest in the field of nuclear medicine, offering attractive decay properties for both diagnosis and therapy (Cutler C, et al. *Current and potential therapeutic uses of lanthanide radioisotope* , Cancer Biother Radiopharm. (2000) 15:531–45. doi: 10.1089/cbr.2000.15.531)

- One of the most intriguing features of the radiolanthanides, other than having promising physical decay properties, is that they have similar chemical characteristics, and analogous coordination chemistry, which allows one to perform comparative pre-clinical studies. A significant disadvantage of lanthanides, however, is that they are difficult to chemically separate and isolate.

- Currently, the β−-emitting ^{177}Lu is used on a routine basis in clinics for targeted radionuclide therapy. The Center of Radiopharmaceutical Sciences (CRS) at Paul Scherrer Institute (PSI) has recently introduced ^{161}Tb as a potentially better alternative to ^{177}Lu due to its co-emission of conversion and Auger electrons. There is good reason to assume that conversion and Auger electrons emitted by ^{161}Tb, in addition to β−-particles, have an additive therapeutic effect. However, further studies are needed to investigate the contribution of conversion and Auger electrons in more detail. In this regard, the use of radionuclides with either β−- or Auger-electron emission would be ideal to investigate. The matched pair of ^{169}Er (pure β−-particle emitter) with the pure Auger-electron emitter ^{165}Er can, thus, represent an ideal model system to evaluate the additive therapeutic effect of Auger electrons on targeted β− therapy.

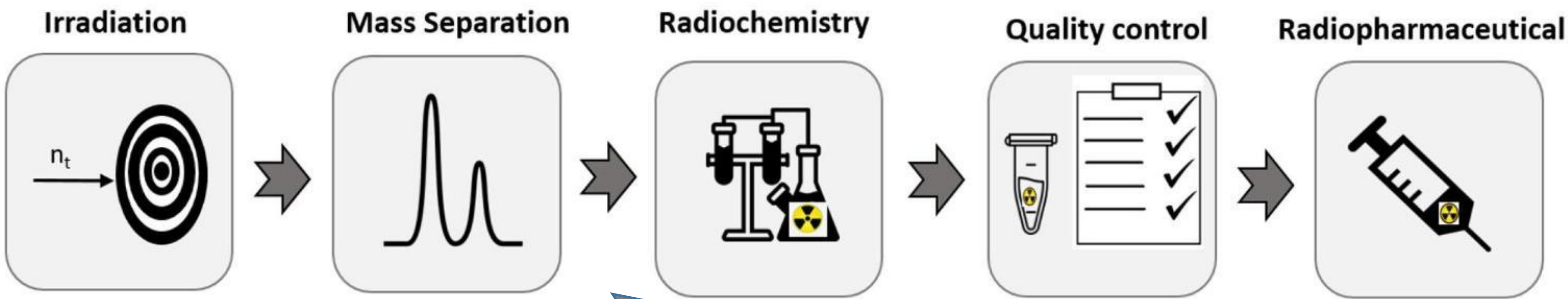
Comparison of decay properties and Auger electron/Conversion electron energies of ^{161}Tb, ^{169}Er, and ^{165}Er, respectively

- Относительно большой период полураспада ^{169}Er рассматривается как дополнительное преимущество, позволяющее избежать потери активности при транспортировке и хранении.
- С другой стороны, ^{165}Er является привлекательным радионуклидом для чистой оже-электронной терапии. Он распадается электронным захвата с последующим испусканием оже -электронов без сопутствующего γ-излучения, но с испусканием рентгеновских лучей со средней энергией 48,8 кэВ.
- Систематические доклинические исследования, сочетающие ^{169}Er и ^{165}Er с различными соотношениями активности, помогли бы изучить дополнительный терапевтический эффект от оже-электронов.

^{169}Er	9.39 d	100	CE M	6.1	36.0
			CE N	7.9	8.2
^{165}Er	10.36 h	_	Auger L	5.3	65.6
			Auger K	38.4	4.8

Only the high intensities are shown (data are taken from[1]).

Production of Mass-Separated Erbium-169



After the mass separation process, the subsequent chemical separation method was developed to obtain ^{169}Er in a solution of sufficient quality to enable radiolabeling of tumor-targeting agents.

The activity standardization of ^{169}Er was completed using the triple-to-double-coincidence ratio (TDCR) technique to perform precise activity measurements.

A preliminary in vitro experiment was carried out to assess tumor cell viability upon exposure to ^{169}Er-labeled PSMA-617 using cancer cells expressing the prostate-specific membrane antigen (PSMA).

Irradiation

Target:

Enriched $^{168}Er_2O_3$ (98.0%, ISOFLEX, USA and 98.2% Trace Sciences Int., Canada)

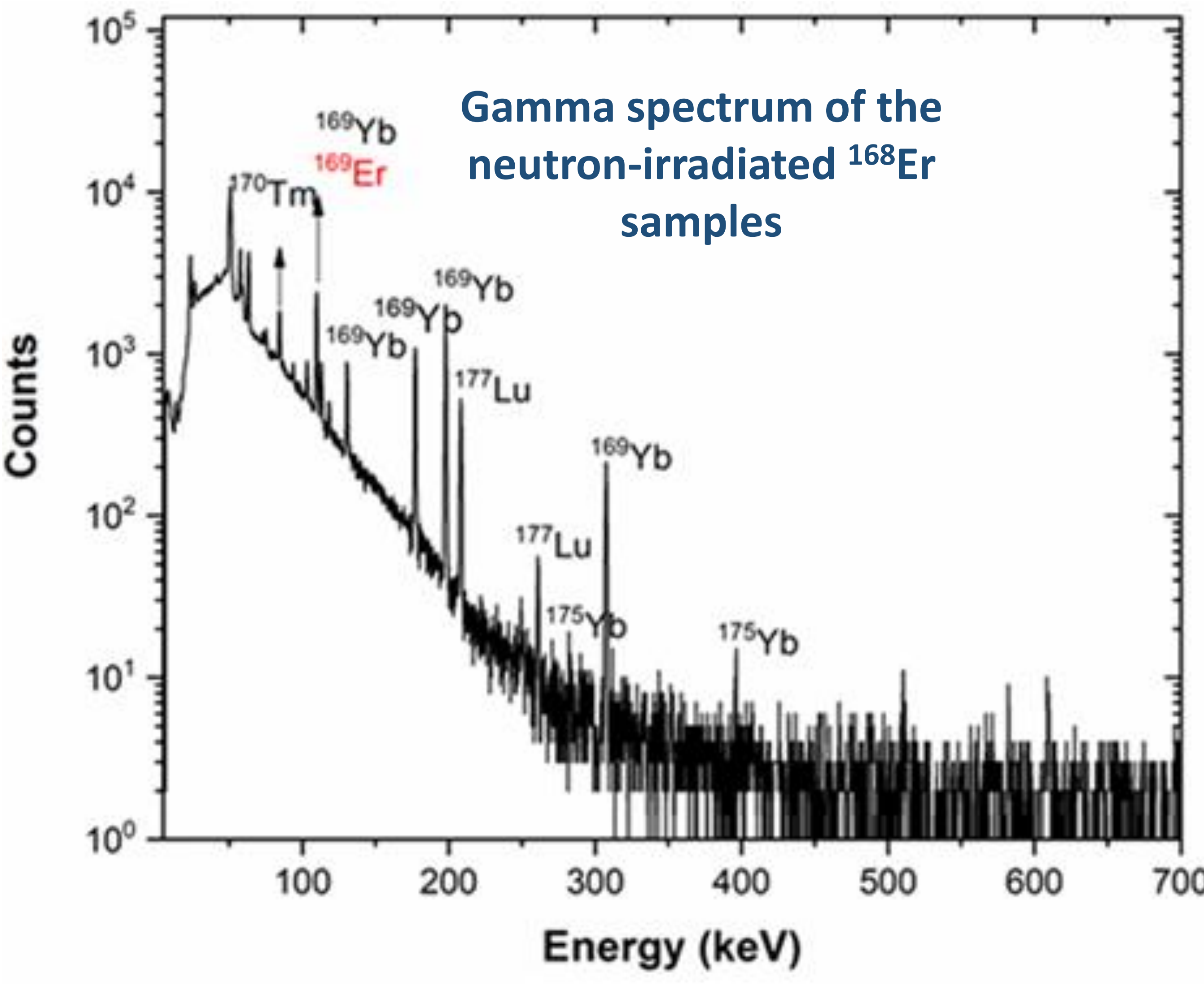
Nuclear reaction: production of **^{169}Er via $^{168}Er(n, \gamma)^{169}Er$**

Irradiation: the V4 irradiation position of the high-flux reactor at Institute Laue–Langevin (ILL), Grenoble, France

- thermal neutron flux :≈ **$1.1 \cdot 10^{15}$ n*cm²/s**,
- irradiation time: **7 days**
- ^{169}Er theoretical yield: **25-48 GBq**

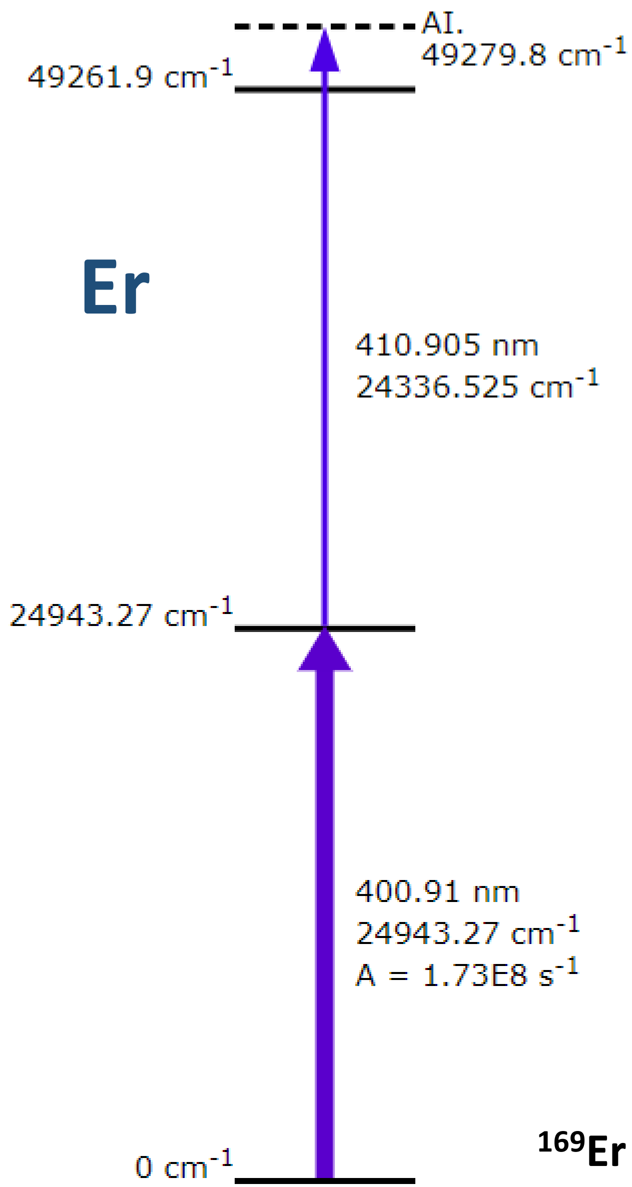
After irradiations, the ampoules were transported to the CERN-MEDICIS facility for the offline mass separation of A = 169.
Carrier-added ^{169}Er, supplied as a colloidal suspension of ^{169}Er-citrate was used as a representative sample for activity standardization.

Irradiation



Besides ^{169}Er

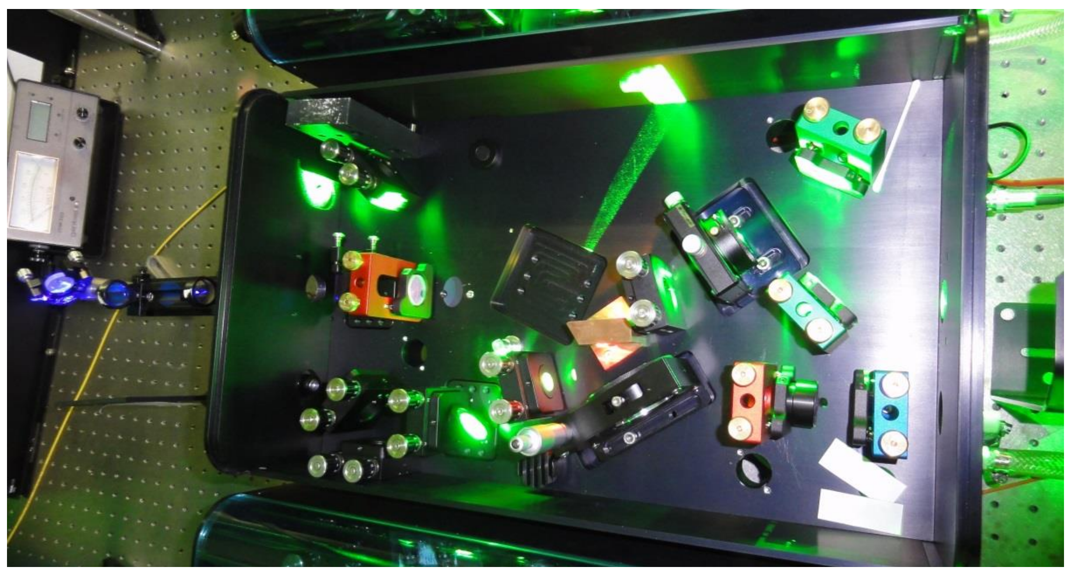
^{169}Yb, ^{175}Yb, ^{170}Tm, ^{172}Lu, and ^{177}Lu gamma-ray peaks were observed (because of impurities in the target material)



Mass Separation

MELISSA Lasers for ^{169}Er:

- The laser setup consists of two Ti:sapphire lasers, designed by Mainz University.
- Each pumped by a dedicated commercial InnoLas Nanio 532-18-Y laser system.
- The two-step laser resonance ionization scheme for erbium was used.



^{169}Er activities were increased up to a factor of four compared to the surface ionization technique.

Mass Separation

Target-ion source system for ^{169}Er:

- Target material was placed into an ISOLDE standard tantalum target container.
- The container was connected to a rhenium ion source via a transfer line.
- ^{169}Er was extracted from targets that were heated up to 2200 C.
- The ions were electrostatically accelerated to 60 keV and mass-separated with a magnetic sector field.

Mass Separation

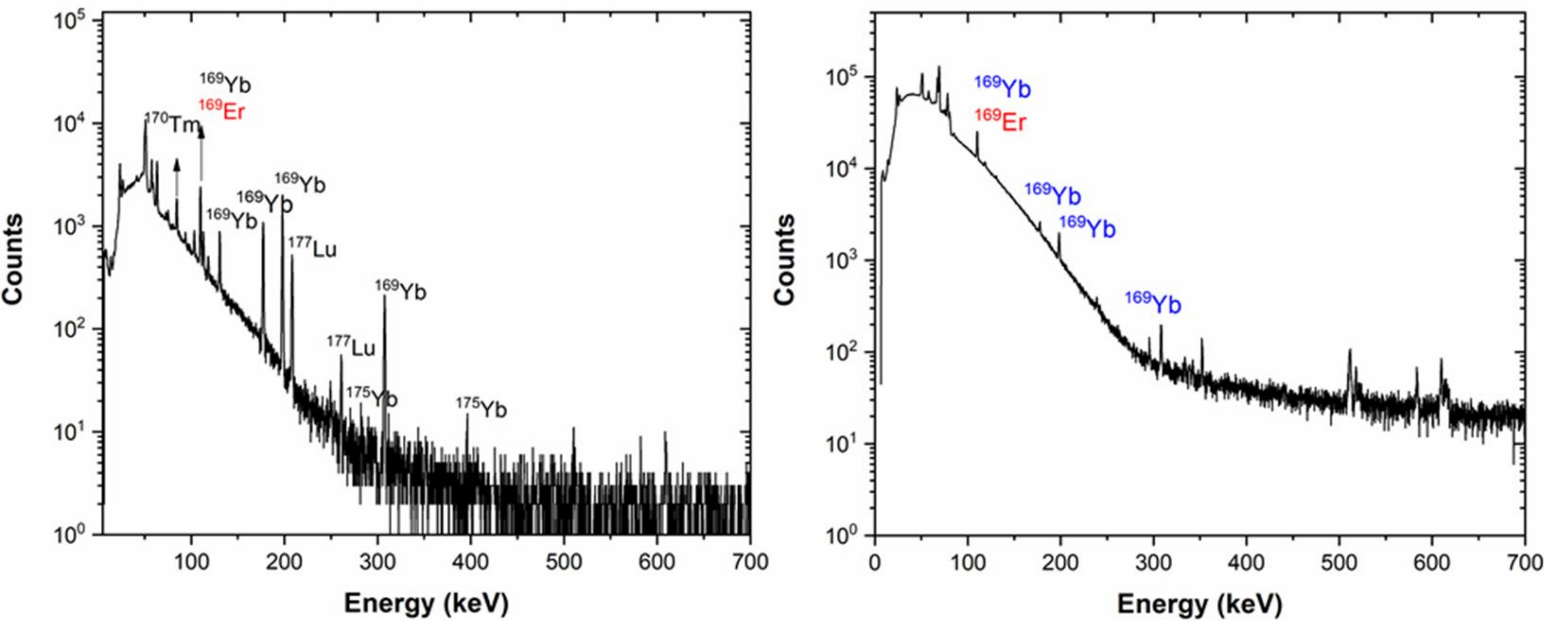
- The mass-separated A = 169 beam, containing ^{169}Er, was implanted into a solid catcher (zinc-coated gold foil).
- Gold foils (thickness: 0.1 mm, purity: 99.95%) were coated with 500 nm Zn (99.995%) layer using physical vapor deposition (PVD) technique.

In total, seven mass-separated samples were shipped to PSI for chemical separation, quality control, and an in vitro proof-of-concept experiment.

The mass 169 ion beam was implanted into solid catchers

Mass Separation

Gamma - spectrum of the neutron-irradiated ^{168}Er as compared to gamma-spectrum of the sample after mass-separation

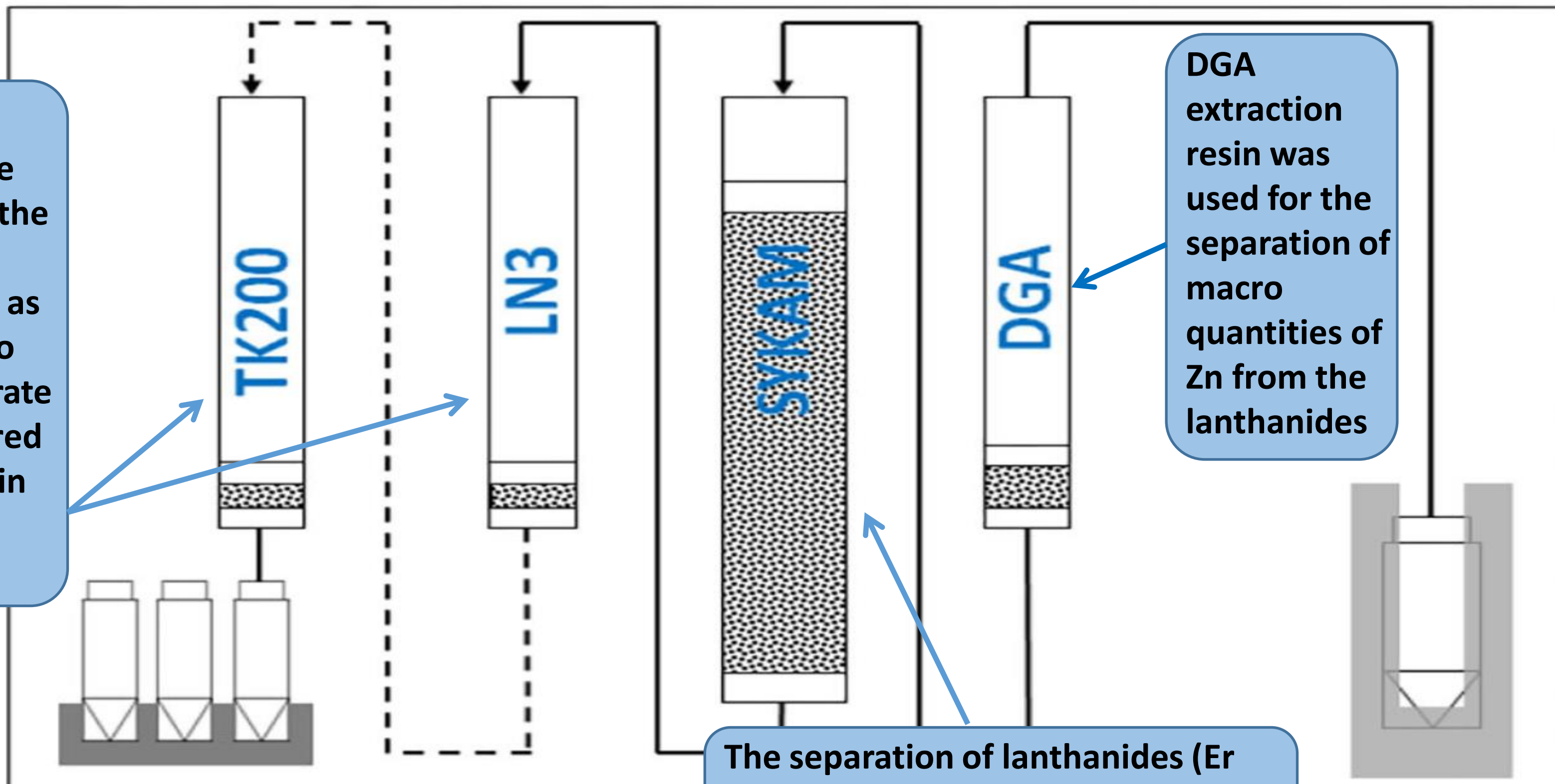


The presence of trace quantities of Yb (<400 ppm) in the target material ($^{168}Er_2O_3$) led to the production of ^{169}Yb ($T_{1/2}$ = 32 d) due to the high thermal neutron capture cross-section of ^{168}Yb . As a result, after the mass separation process, ^{169}Yb was observed as a radionuclidic impurity.

Radiochemical Separation

Cation and extraction chromatographic resins were used for the effective separation of ^{169}Er from isobars and zinc to obtain chemically and radionuclidically pure ^{169}Er.

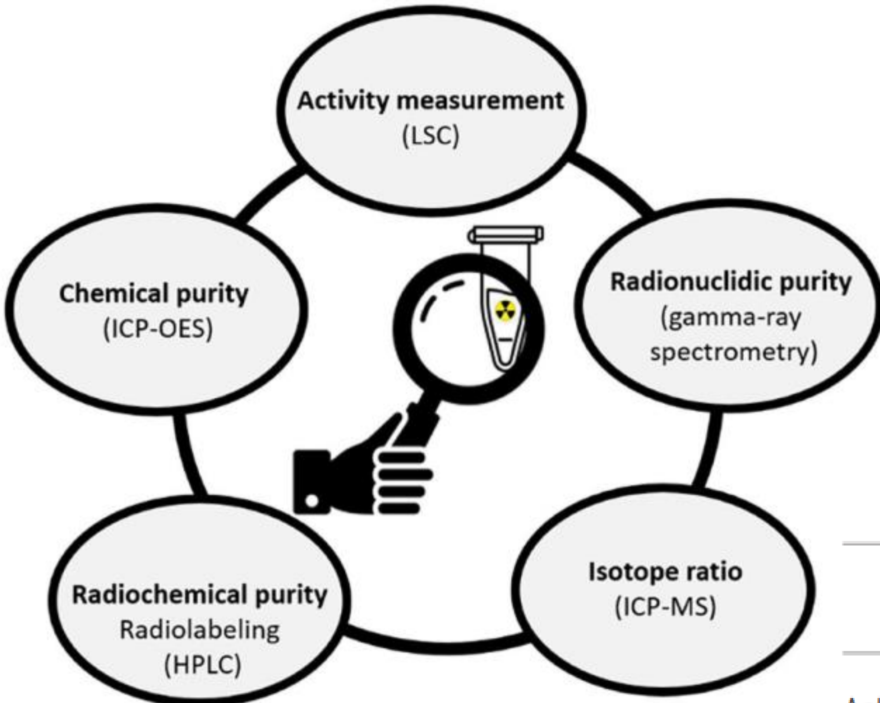
resin to eliminate Zn from the desired product, as well as to concentrate the desired product in a small volume



DGA extraction resin was used for the separation of macro quantities of Zn from the lanthanides

The separation of lanthanides (Er and Yb) was performed using Sykam cation exchange resin

Quality Control



Quality control analyses applied to the ^{169}Er samples after chemical separation (LSC, **Liquid Scintillation counting**, ICP-MS, **Inductively Coupled Plasma Mass Spectrometry**; HPLC, **High-Performance Liquid Chromatography**; ICP-OES, **Inductively Coupled Plasma—Optical Emission Spectrometry**).

Assessment of the quality control steps is crucial for the development of novel radionuclides toward nuclear medical applications .

Results obtained for the mass-separated ^{169}Er samples S1-S7

	S1	S2	S3	S4	S5	S6-7
Activity measurement (MBq)	52.9	23.4	8.59	4.70	73.2	93.4
Radionuclidic purity (%)	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
Isotopic ratio (168/169)	1.66	1.60	14.62	11.94	n.d	n.d
Chemical purity	n.d	n.d	n.d	n.d	0.49 μg Zn	n.d
Radiochemical purity (%)	n.d	n.d	n.d	n.d	0*	>98%

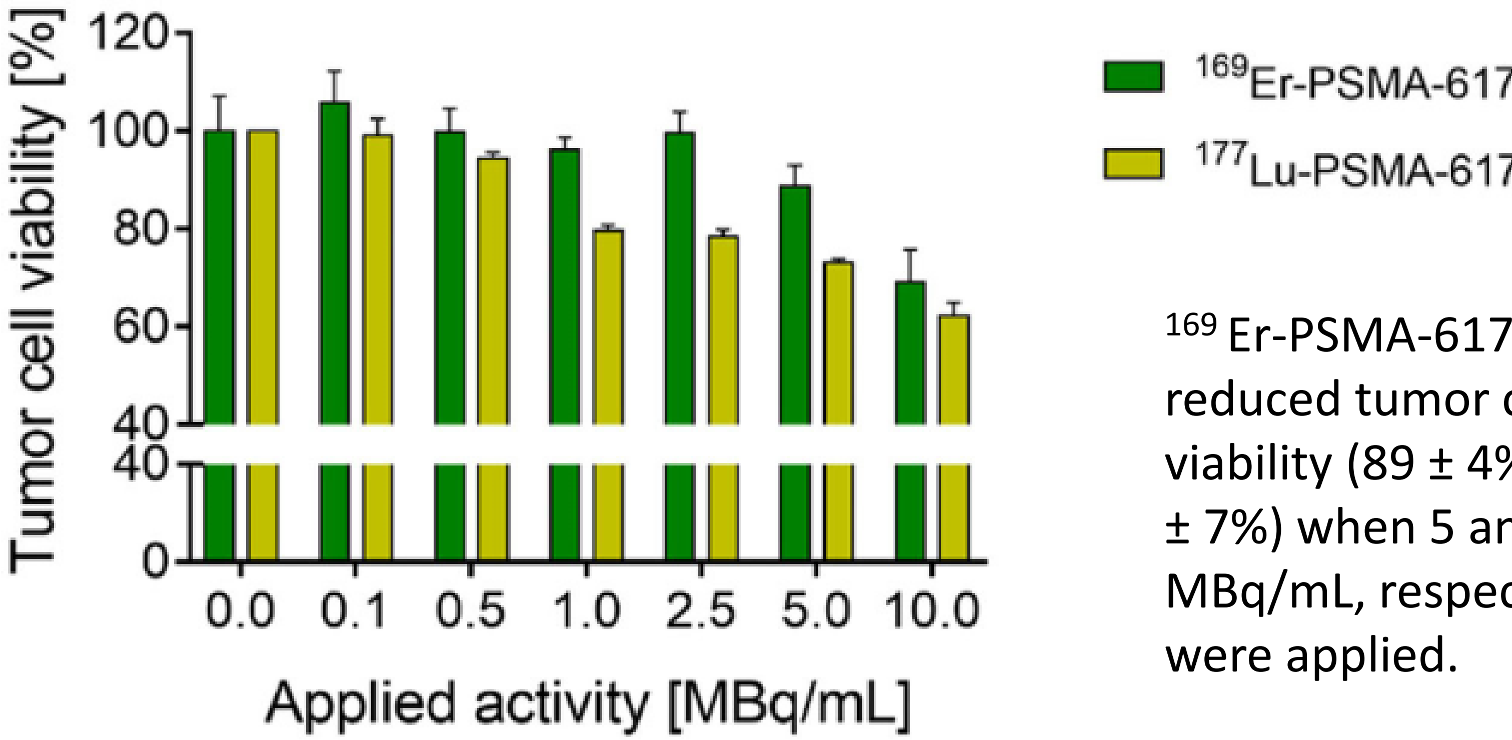
In vitro Viability Studies

- Samples S6 and S7 was used for preparation the radioligand ^{169}Er-PSMA-617 (**p**rostate-**s**pecific **m**embrane **a**ntigen) – specific molecule, accumulating by the prostate cancer cell membrane with high efficiency. It has a very low background accumulation in healthy tissue avoiding severe side effects and rendering the therapy safe with low toxicity.

- The radioligand ^{169}Er-PSMA-617 was tested in a tumor cell viability assay (in vitro) to investigate its therapeutic potential in comparison to the clinically-established ^{177}Lu-PSMA-617.

- Exposure of PC-3 human prostate cancer cell culture to ^{169}Er-PSMA-617 was tested for tumor cell viability at different doses.

In vitro Viability Studies



^{169} Er-PSMA-617 gave reduced tumor cell viability (89 ± 4% and 69 ± 7%) when 5 and 10 MBq/mL, respectively, were applied.

^{177}Lu PSMA-617 had a greater effect on tumor cell viability, resulting in 72 ± 1% and 62 ± 3% viable cells after exposure to 5 and 10 MBq/mL, respectively. Also, tumor cell viability was reduced at lower applied activity concentrations of 1.0 and 2.5 MBq/mL resulting in 80 ± 1% and 79 ± 1% viable tumor cells, respectively .

frontiers in Medicine

ORIGINAL RESEARCH
published: 22 April 2021
doi: 10.3389/fmed.2021.643175

Production of Mass-Separated Erbium-169 Towards the First Preclinical *in vitro* Investigations

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Specialty section:
This article was submitted to Nuclear Medicine, a section of the journal Frontiers in Medicine

The β^--particle-emitting erbium-169 is a potential radionuclide toward therapy of metastasized cancer diseases. It can be produced in nuclear research reactors, irradiating isotopically-enriched $^{168}Er_2O_3$. This path, however, is not suitable for receptor-targeted radionuclide therapy, where high specific molar activities are required. In this study, an electromagnetic isotope separation technique was applied after neutron irradiation to boost the specific activity by separating ^{169}Er from ^{168}Er targets. The separation efficiency increased up to 0.5% using resonant laser ionization. A subsequent chemical purification process was developed as well as activity standardization of the radionuclidically pure ^{169}Er. The quality of the ^{169}Er product permitted radiolabeling and pre-clinical studies. A preliminary *in vitro* experiment was accomplished, using a ^{169}Er-PSMA-617, to show the potential of ^{169}Er to reduce tumor cell viability.

Keywords: Er-169, electromagnetic isotope separation, lanthanide-separation, activity standardization, *in vitro* studies, laser resonance ionization

Conclusion

In this study, radionuclidically pure ^{169} Er was produced at high specific activities by means of neutron irradiation, followed by mass and chemical separation processes, respectively.

By combining surface ionization with resonant laser ionization, ^{169} Er activities were increased up to a factor of four compared to the previously-published study.

Further developments of the mass separation process, such as the application of an isotope-selective laser ionization scheme and optimization of the mass separator for high-flux ion-beam operation, are needed to increase the overall separation efficiencies and to provide higher activities of ^{169} Er in future.

The availability of the β –particle emitting ^{169} Er is particularly important to perform pre-clinical studies, in combination with the pure Auger electron emitter ^{165}Er. This combination will help us explore the additional therapeutic effect of Auger electrons to β-particles, as in the case of ^{161}Tb, which will certainly be of scientific relevance.

Enhanced knowledge of the additive therapeutic effects of Auger electrons will likely be well-received by the nuclear medicine community and ought to pave the way toward more efficient cancer treatment.

Проект комплекса «ИЗОТОП» для получения радионуклидов для исследований в ядерной медицине

Разработаны технические задания на:

- четыре мишенные станции, включая масс-сепараторную • масс-сепаратор
- системы установки и транспортировки мишеней • горячие камеры
- боксы для хранения облученных мишенных устройств

Проект комплекса «ИЗОТОП» для получения радионуклидов для исследований в ядерной медицине

- В отличии от MEDICIS, масс-сепаратор «ИЗОТОП», установленный он -лайн на ускорителе Ц-80 позволит проводить исследования с более широким кругом изотопов (например, с меньшим периодом полураспада)

Цитата из этой же статьи:

> for 7 days. For an industrial production, one could irradiate for longer, minimizing the activity loss during transport and chemical separation, and increasing the yield of ^{169}Er.

- Планируется создание трех мишенных станций для производства радионуклидов для диагностики и терапии

- Для получения радионуклидов высокой изотопной чистоты на одной из мишенных станций будет установлен масс-сепаратор

Радионуклиды, планируемые для получения на комплексе «ИЗОТОП»

Ge-68/Ga-68,
Sr-82/Rb-82,
Tc-99,
Cu - 64,
Cu - 67
In-111,
I-123
I-124,
Tb-149,
Pb-212/Bi-212,
Ra-223,
Ra-224,
Ac-225

Красным цветом отмечены изотопы, получение и выделение которых методами высокотемпературного разделения и с помощью масс-сепаратора уже протестировано на установке ИРИС

50 ЛЕТ НА ПИКЕ НАУКИ