Ac-225, Ge-68 and Lu-177 – RADIOISOTOPES FOR DIAGNOSTIC AND THERAPY

ITM ISOTOPE TECHNOLOGIES MUNICH SE

DR. MARIAN MECKEL, VP RESEARCH AND DEVELOPMENT

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  - Manufacturing and lifecycle
  - Impurity profiles

ABOUT ITM

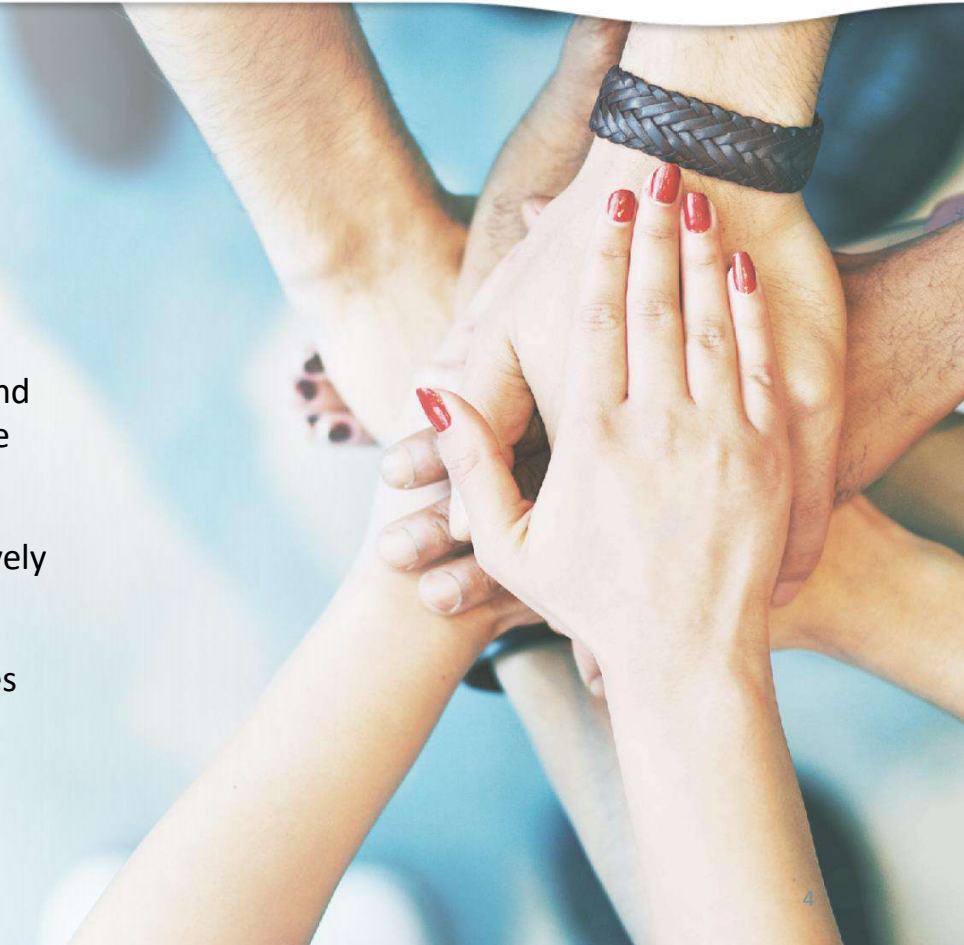
ITM Headquarters and Nuclear Reactor at the Research Campus in Garching / Munich.

… development, production and global supply of diagnostic and therapeutic radiopharmaceuticals & radioisotopes

Munich Airport

That's Us.

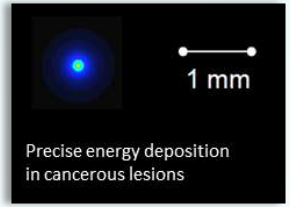
- Founded in 2004 in Garching/Munich
- Over 400 highly trained employees
- High-tech GMP infrastructure with over 900 m² of manufacturing and production area available today and approx. 4600 m² of additional space in the near future
- Unrivaled logistics network – guaranteed shipment within 24-48 h (Europe) and 72 h (Overseas) respectively
- All equipment and reagents required for the use and processing of diagnostic and therapeutic radioisotopes

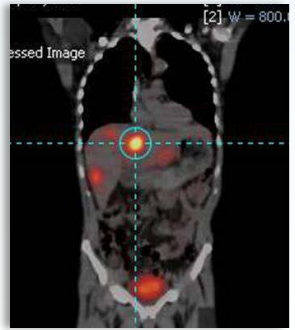


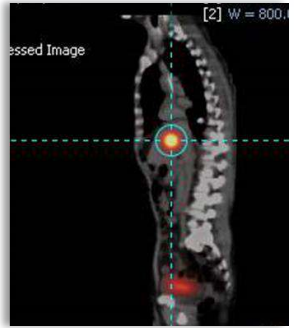
LUTETIUM-177
THERAPEUTIC BETA-EMITTER

Lutetium-177

- Low energy beta (ß-) emitter
  E_{max} = 0.498 MeV
  $T_{1/2}$ = 6.647 d
- specific activity of ≥ 3.000 GBq/mg (n.c.a. Lu-177) or ≥ 500 GBq/mg c.a. Lu-177
- cytotoxic radiation in relatively small areas with less damage to surrounding tissue
- Imagable Gamma radiation for precise dose localization during therapy:
  112.9 KeV (6.17%), 208.3 KeV (10.36%)
- radiolabeling of a variety of molecular carriers:
  small molecules, and peptides, proteins and antibodies
- excellent logistical to sites distant from the reactor production facility



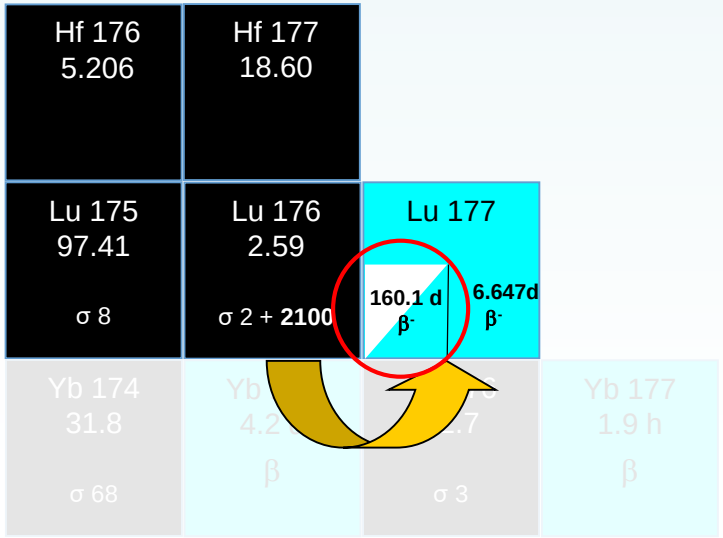




Source: Courtesy Prof. Brenner, Dr. Prasad, Charite Berlin

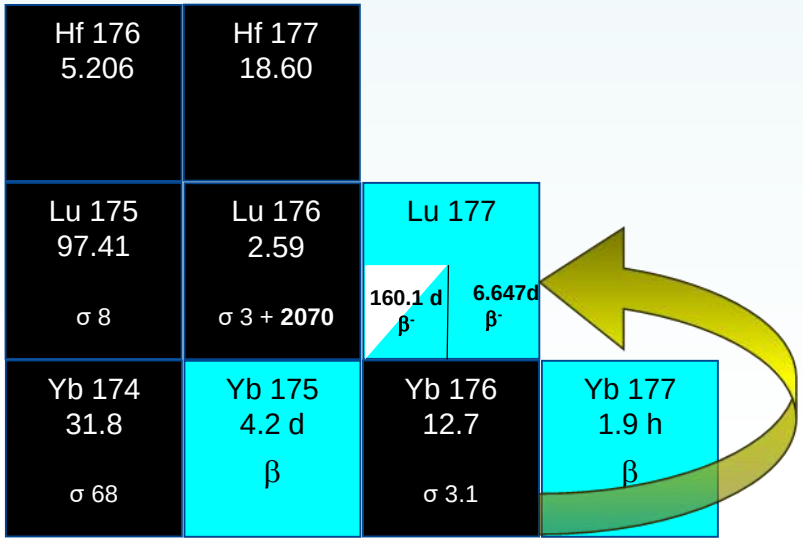
Therapeutic Lutetium-177 can be obtained on two different ways:

$^{176}Lu(n,\gamma)^{177}Lu$



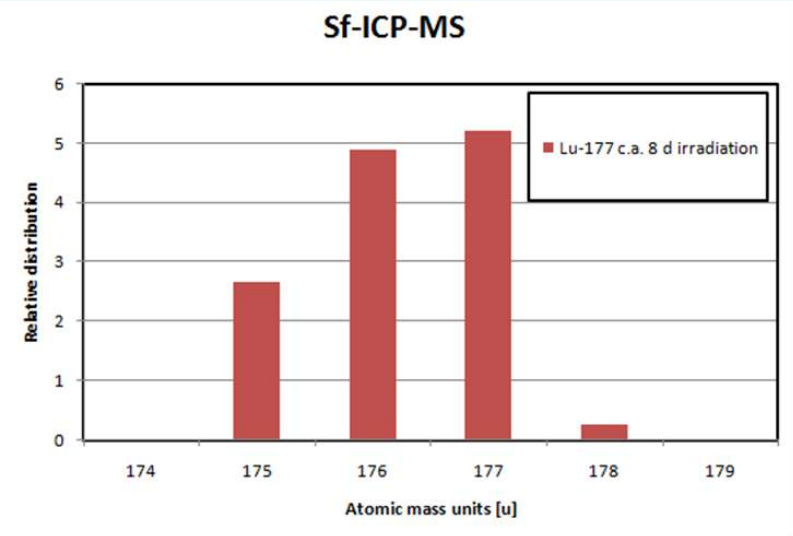
Carrier added (c.a.) Lu-177

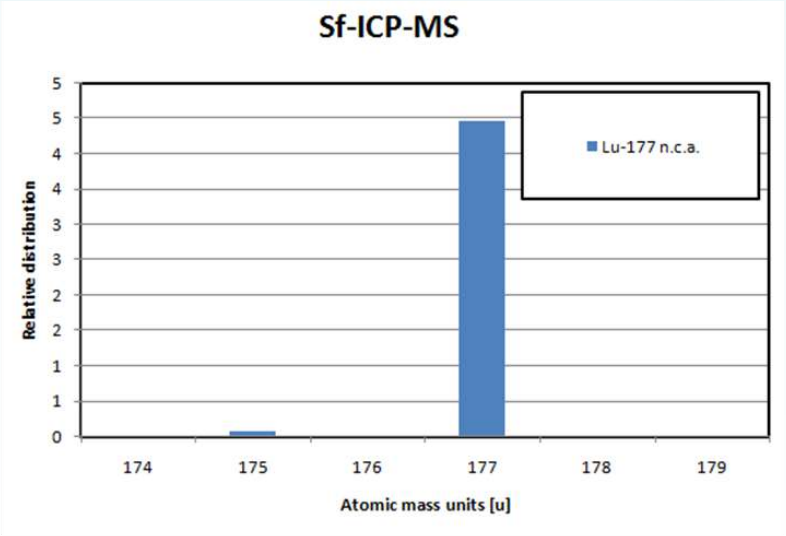
$^{176}Yb(n,\gamma)^{177}Yb \rightarrow {}^{177}Lu$



No carrier added (n.c.a.) Lu-177

Therapeutic Lutetium-177 can be obtained on two different ways:

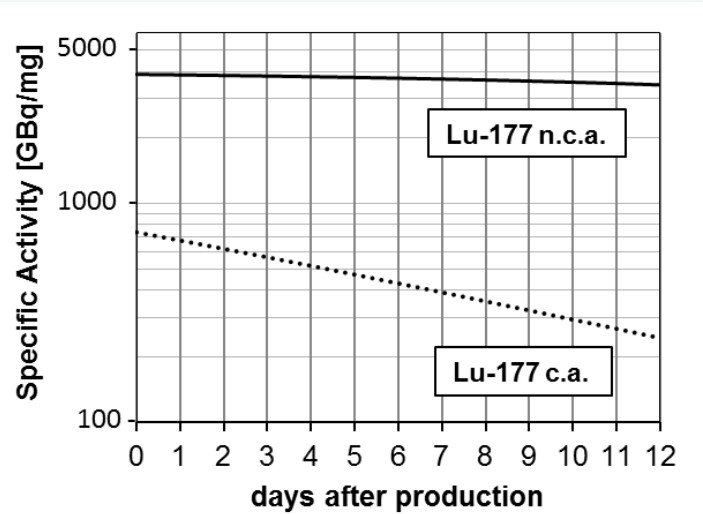


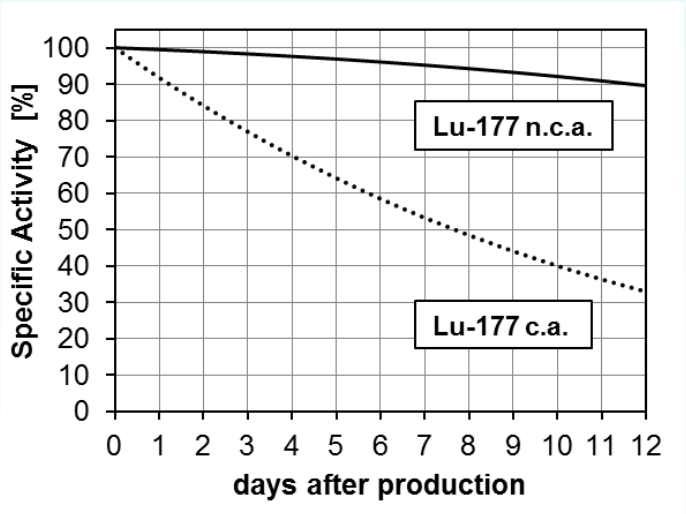


- Low specific activity:
  only 25 % "hot" ^{177}Lu atoms
- Long-lived radioactive impurities
  up to 0.1 % of long-lived ^{177m}Lu!
- *Limited radiolabeling performance*
- *Waste disposal problem*

- Highest specific activity:
  over 90 % "hot" ^{177}Lu atoms
- Highest radionuclidic purity
  No contamination with long-lived ^{177m}Lu!
- *Best radiolabeling performance*
- *Longer shelf-life of up to 2 weeks*

Impact on Shelf-life





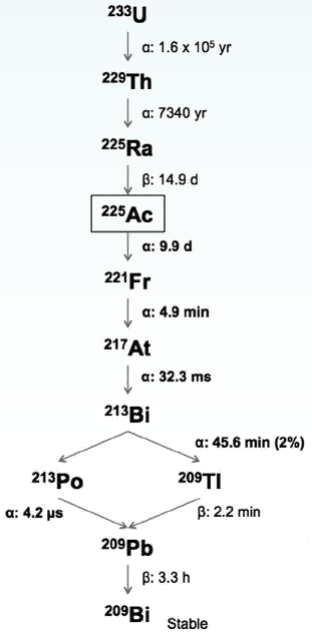
	Volumetric Activity	Specific Activity	^{177m}Lu content	Shelf-life	ART	Regulatory
c.a. Lu-177 #A	80 GBq/mL	≥ 500 GBq/mg	≤ 0.024 % @ART ≤ 0.05 % @ expiry	8 d	@ EOP	EMA registered
c.a. Lu-177 #B	> 18.5 GBq/mL	≥ 500 GBq/mg	≤ 0.02 % @EOP ≤ 0.05 %@ expiry	7 d	@ EOP	Registered in some EU countries
n.c.a. Lu-177	**40 GBq/mL**	**≥3000 GBq/mg**	**none**	**9 d**	**customer choice**	**EMA registered**

ART = Activity Reference Time

ACTINIUM-225
FOR TARGETED ALPHA THERAPY

Therapeutic Radioisotope ^{225}Ac for Targeted Alpha Therapy.

- Alpha emitter with small penetration range for highly precise cancer therapy
- Decay Chain with 5 alpha emissions
- Linear Energy Transfer with high cell killing probability
- Half-life of 9.9 days
- Longest living daughters: Pb-209, Bi-213, Fr-221
- Identification: Fr-221 (213 keV) and Bi-213 (440 keV)
- Similar complex chemistry like lanthanides

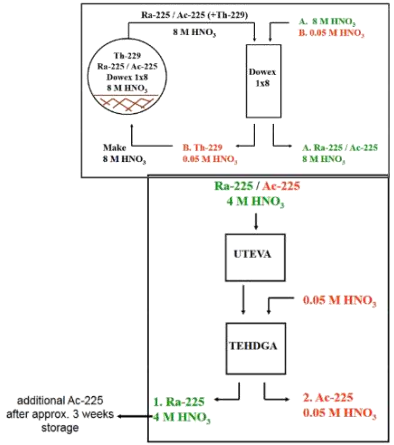


Manufacturer: ITM Medical Isotopes GmbH
For research purposes only.

POTENTIAL PRODUCTION ROUTES

1

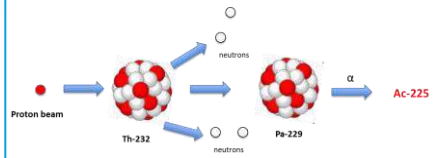
^{229}Th Generator



2

$^{232}Th(p, x) \rightarrow {}^{225}Ac$

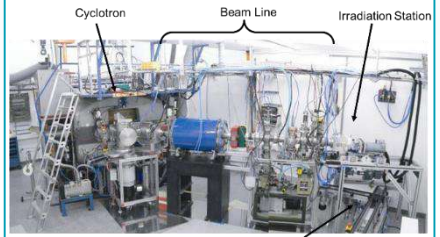
SPALLATION OF Th-232

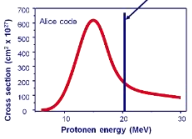


3

$^{226}Ra(p, 2n) \rightarrow {}^{225}Ac$

CYCLOTRON / PROTON IRRADIATION

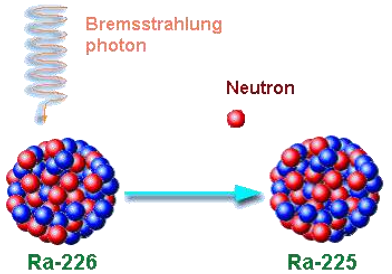




4

$^{226}Ra(\gamma, n)^{225}Ra \rightarrow {}^{225}Ac$

RHODOTRON, BETATRON OR LINAC PRODUCTION ROUTE

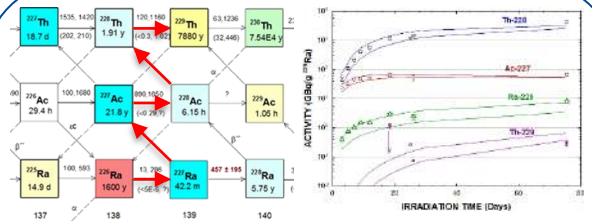


A.Morgenstern, Production and Pre-Clinical Testing of Ac-225/Bi-213 and U-230/Th-226, 6th Alpha-Immunotherapy Symposium, Toronto, June **2009.**
C. Apostolidis et al. Production of Ac-225 from Th-229 for Targeted α-Therapy, Anal. Chem. **2005,** 77, 6288-6291
G. Melville, B. J Allen, Cyclotron and linac production of Ac-225. *Applied Radiation and Isotopes,* **2009**; 67: 549-555

PROCESS 1: ^{229}Th GENERATOR

ELUTION OF THORIUM-229 "COW"

- Ac-225 eluted from Th-229 Generator
  - ($T_{1/2}$ = 7340 y)
- Amount of Th-229 is currently limited.
- Approx. 1,500 mCi/year are available (JRC, ORNL, IPPE)!
- Th-229 sources are >40 years old



Production of Thorium:
Neutron Irradiation of Ra-226 or Th-232 (n,γ) U-233

- High impurities of Th-228 (app. 5000:1)
  - Th-228 $T_{1/2}$ = 1.9 y
  - Rn-220 daughter
  - Tl-208 daughter 2615 keV γ-rays!
- Uncertainty in yield and cross-sections

1

^{229}Th Generator

- Decay and purification - presently best production method
- Limited by the present capacity of generators and access to ^{229}Th
- No scalable production route

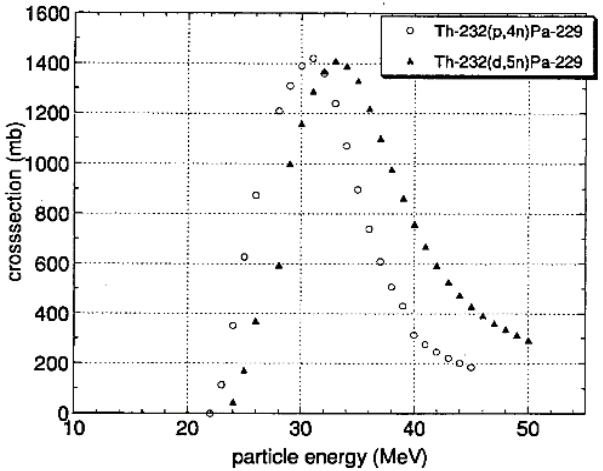
A.Morgenstern, Production and Pre-Clinical Testing of Ac-225/Bi-213 and U-230/Th-226, 6th Alpha-Immunotherapy Symposium, Toronto, June **2009.**
C. Apostolidis et al. Production of Ac-225 from Th-229 for Targeted α-Therapy, Anal. Chem. **2005,** 77, 6288-6291
S. Hogle, S. Mirzadeh et al. Reactor production of Thorium-229 . *Applied Radiationandlsotopes*, **2016**; 117: 19–27.

PROCESS 2: $^{232}Th(p, x) \rightarrow {}^{225}Ac$

SPALLATION OF Th-232

- Irradiation of Th-232 with high energy protons
- Currently done in the US
- Limited radionuclide purity (app. 0.3% Ac-227, $T_{1/2}$ 21.8a!)

Maybe applicable for Ac-225/Bi-213 Generator production



2

$^{232}Th(p, x) \rightarrow {}^{225}Ac$

High energy accelerator process

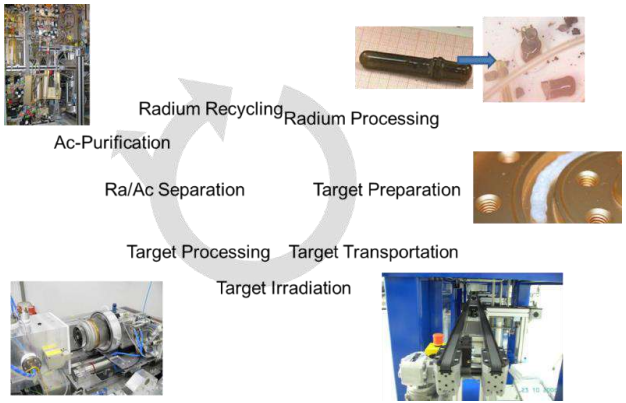
- High amounts of ^{225}Ac
- Contaminated by ^{227}Ac ($T_{1/2}$ = 21.8 a)

A.Morgenstern, Production and Pre-Clinical Testing of Ac-225/Bi-213 and U-230/Th-226, 6th Alpha-Immunotherapy Symposium, Toronto, June **2009.**
C. Apostolidis et al. Production of Ac-225 from Th-229 for Targeted α-Therapy, Anal. Chem. **2005,** 77, 6288-6291
G. Melville, B. J Allen, Cyclotron and linac production of Ac-225. *Applied Radiation and Isotopes,* **2009**; 67: 549-555

PROCESS 3: $^{226}Ra(p, 2n) \rightarrow {}^{225}Ac$

CYCLOTRON / PROTON IRRADIATION

- **2002-2008:**
  Actinium Pharmaceuticals and TUM collaboration
- Proof of principle regarding quantitative production accomplished at TUM cyclotron in Garching, Germany
- Normalized yield: Irradiation of 100 mg ^{226}Ra for 100 h with 100 µA result in 100 mCi ^{225}Ac (~4 GBq)



3

$^{226}Ra(p, 2n) \rightarrow {}^{225}Ac$

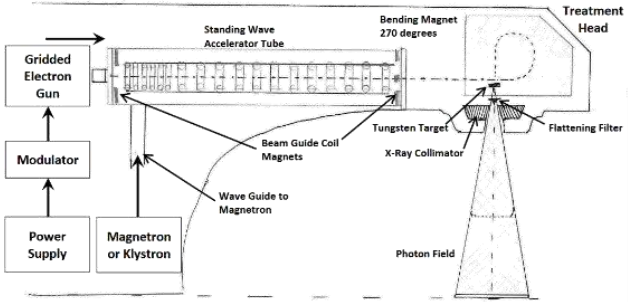
Cyclotron production route

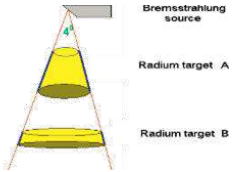
- ✓ Scalable production of clean ^{225}Ac successfully proven
- ✗ Significant investment required for large scale production

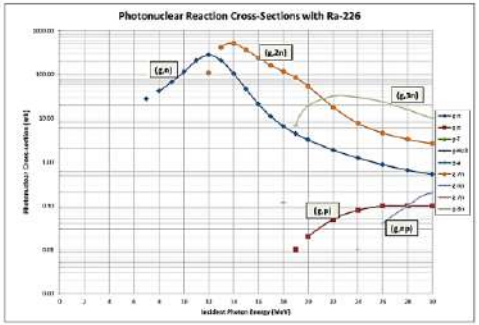
G. Melville, B. J Allen, Cyclotron and linac production of Ac-225. *Applied Radiation and Isotopes*, **2009**; 67: 549-555

PROCESS 4: $^{226}Ra(\gamma, n)^{225}Ra \rightarrow {}^{225}Ac$

RHODOTRON, BETATRON OR LINAC PRODUCTION ROUTE







4

$^{226}Ra(\gamma, n)^{225}Ra \rightarrow {}^{225}Ac$

- ✓ Side products have short $T_{1/2}$ can be separated
- ✓ Massive Ra-226 targets possible
- ✗ Very high photon energy required
- ✗ Proof of concept for large scale production still missing
- ✗ Significant investment required for large scale production

Therapeutic Radioisotope ^{225}Ac for Targeted Alpha Therapy.

ITM Medical Isotopes GmbH
Lichtenbergstrasse 1
85748 Garching / Munich, Germany

Certificate of Conformity

Actinium (^{225}Ac) chloride solution

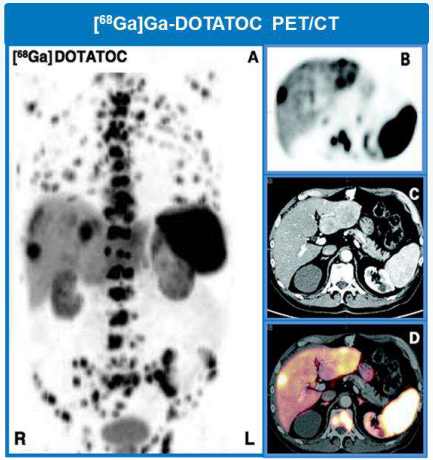
Lot No.:	Ac-01-111-11	**EOP [CET]:**	08.12.2021 12:00
Chemical Form:	**Ac^{3+} in aqueous 0.04 M HCl solution**		
Packaging	☒ 2 ml type I conical glass vial, closed with fluorotec coated bromobutyl stopper and center hole crimp cap		
	☐ 10 ml type I flat bottom glass vial, closed with fluorotec coated bromobutyl stopper and center hole crimp cap		

Test	Specification	Unit	Result
Activity per vial	90 - 110 of the ^{225}Ac activity	%	complies
Radioactivity Concentration	36 – 44 @ ART	MBq/ml	
Appearance	Clear and colorless solution	n.a.	complies
Identity ^{225}Ac	150 keV gamma line (Ac-225) 218 keV gamma line (Fr-221) 440 keV gamma line (Bi-213) 465 keV gamma line (Tl-209) 1567 keV gamma line (Tl-209)	n.a.	complies
pH	1 - 2	n.a.	complies
Radionuclidic purity (Impurities corrected to Ac-225 activity at TOM)	^{225}Ac ≥ 99.9 ^{225}Ra ≤ 0.001 ^{229}Th ≤ 0.0001 ^{227}Ac ≤ 0.0001	%	complies
Radiolabeling yield (Based on radiolabeling of DOTA-derivate)	≥ 97	%	complies

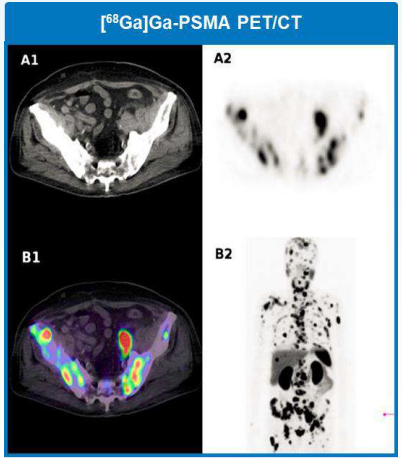
Manufacturer: ITM Medical Isotopes GmbH
For research purposes only.

DIAGNOSTIC RADIOISOTOPE
Germanium-68 / Gallium-68

GALLIUM-68

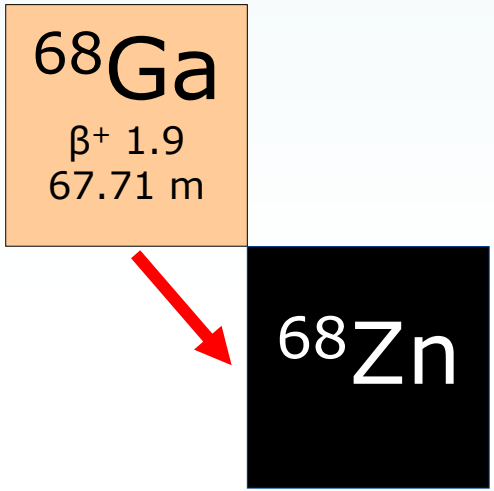


H. Wester et al. Clin Cancer Res. **2007**;13:3470-3481.



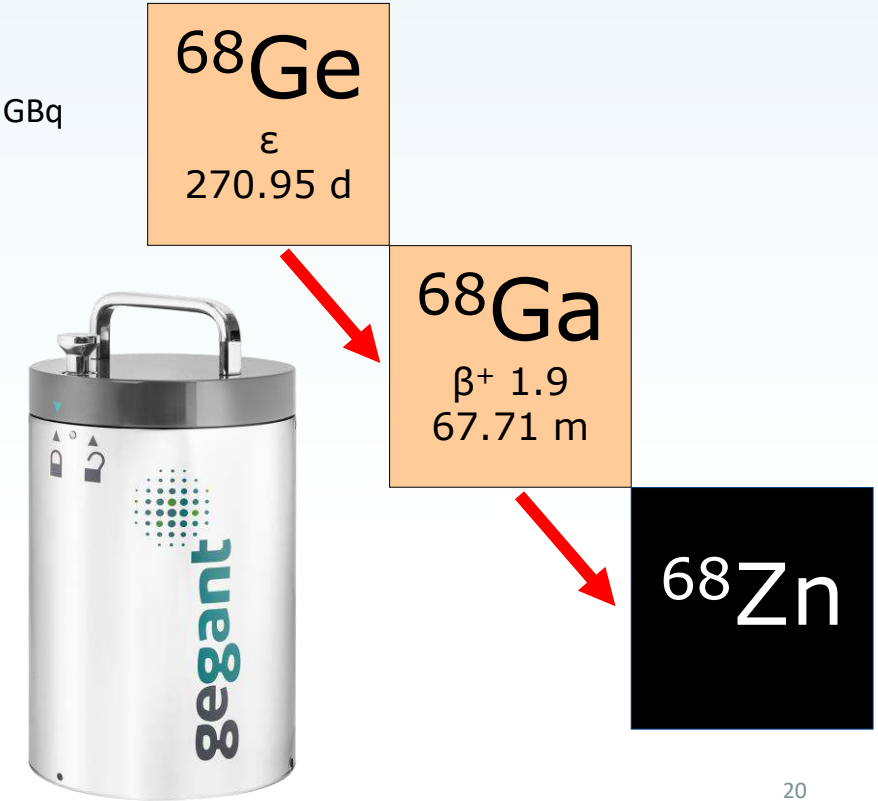
A. Afshar-Oromieh et al. *EJNMMI* **2013**, 40: 486–495.

- $T_{½}$ = 67.71 min
- 89 % β^+ branching
- E_{max,β^+} = 1.9 MeV
- Positron emission tomography
- Increasing interest in the last decade
- approved compounds/Kits: [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-PSMA-11 (FDA)

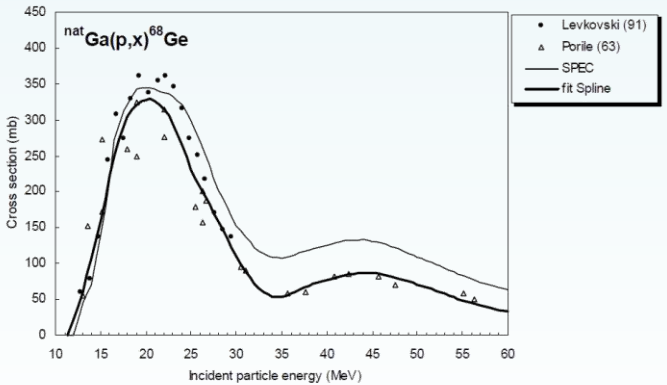


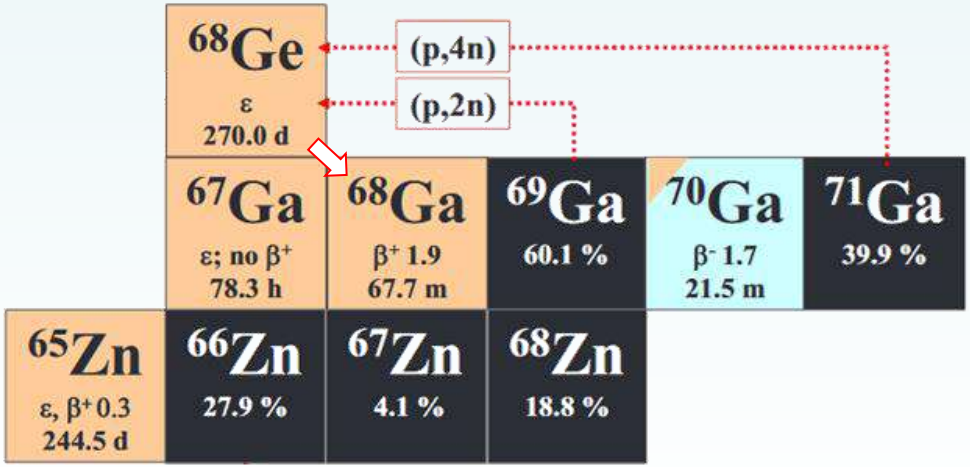
MAIN SOURCE Ge-68/Ga-68 GENERATOR

- Ge-68 trapped on solid phase for daily elution
- The generator sizes from 0.75 GBq, 1 GBq, 2 GBq and 4 GBq
- $[^{68}Ga]GaCl_3$ in accordance with Ph. Eur. 2464
- Low acidic eluent (0.05 M HCl) in 4 mL volume
- Yield ≥ 60%
- Breakthrough of ^{68}Ge ≤ 0.001% of total radioactivity
- Shelf-life 12 month



PRODUCTION OF Ge-68 IN CYCLOTRON





- 20 MeV protons with strong proton beam
- Natural or enriched Gallium/Nickel targets
- Long irradiation time
- Long cool down time after EOB

- Liquid-Liquid extraction from conc. HCl
- High radionuclidic purity

Ge-68 Breakthrough

- Estimated batch size of 1800 MBq Ga-68-Radiopharmaceutical in 20 mL
- Max 0.001 % of Ge-68 Breakthrough correlates to max 18 kBq Ge-68
- Usually, a factor 10 lower breakthough

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Original Article

Organ biodistribution of Germanium-68 in rat in the presence and absence of [^{68}Ga]Ga-DOTA-TOC for the extrapolation to the human organ and whole-body radiation dosimetry

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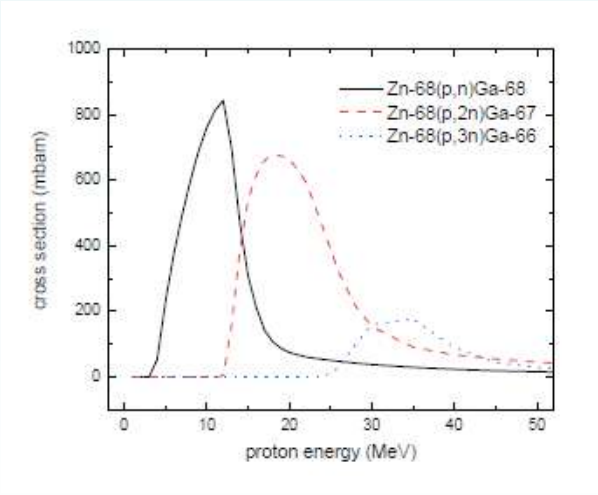
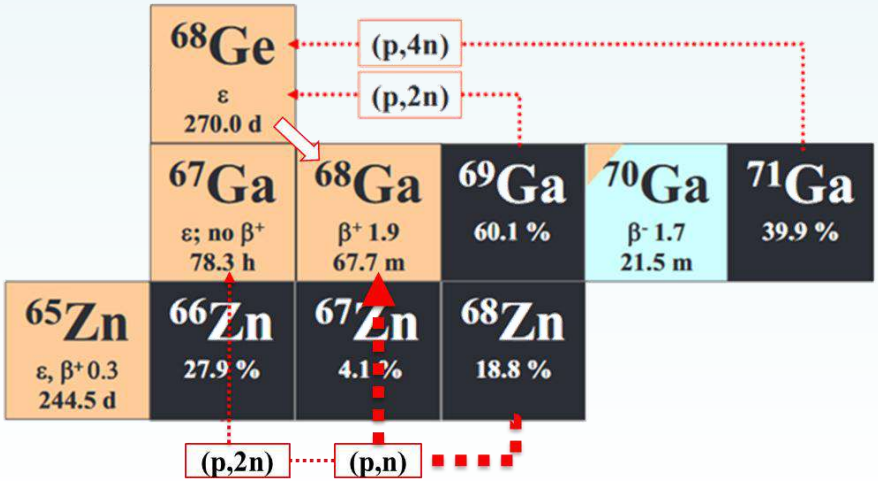
Table 2. Organ- and effective doses ([^{68}Ge]$GeCl_4$; [µSv/MBq]) for human females and males*

	FEMALE**	MALE***
Kidneys	185±54	171±38
Adrenals	83±41	40±10
Liver	38±0.4	19±7
LLI wall	23±7	15±0.2
ULI wall	17±5	12±0.1
Red marrow	13±4	12±4
Spleen	11±0.1	8.5±0.8
Osteogenic cells	11±3	6.9±1.6
Small intestine	10±0.8	9.7±1
Ovaries/Testes	9.2±1	1.8±0.5
Urinary Bladder Wall	7.7±1	7.0±0.5
Breasts	7.4±1	NA
Uterus	7.4±1	NA
Stomach wall	7.4±1	6.4±0.6
Thymus	7.4±1	6.4±0.6
Thyroid	7.4±1	6.4±0.6
Gall bladder wall	7.1±1	6.3±0.6
Skin	7.1±1	6.0±0.3
Lungs	3.2±0.2	3.2±0.3
Heart wall	2.6±0.9	2.1±0.2
Muscle	2.0±0.1	1.5±0.2
Pancreas	1.9±0.1	1.9±0.1
Brain	1.2±0.1	1.4±0.7
Total effective dose	15.5±0.1	±1.2

PRODUCTION OF Ga-68 IN CYCLOTRON





- 10 MeV protons
- enriched solid or liquid Zn-68 targets
- Relatively high activities
- Ga-67 main radionuclidic impurity

PASSION FOR PRECISION

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