Development of radiochemistry and production of medical isotopes

Radionuclide generators for medicine

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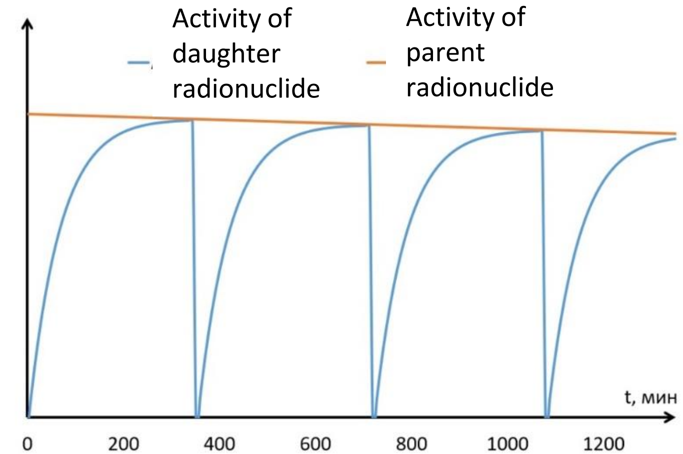
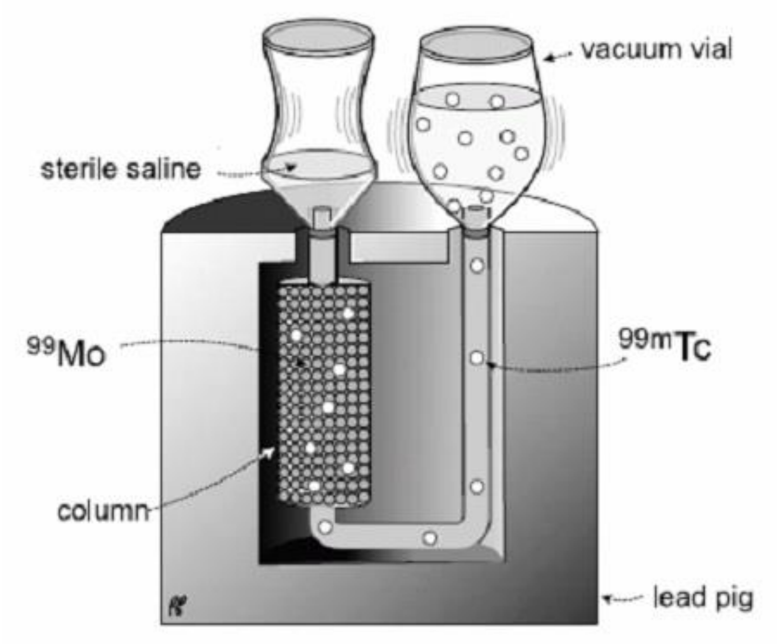
Radionuclides generators

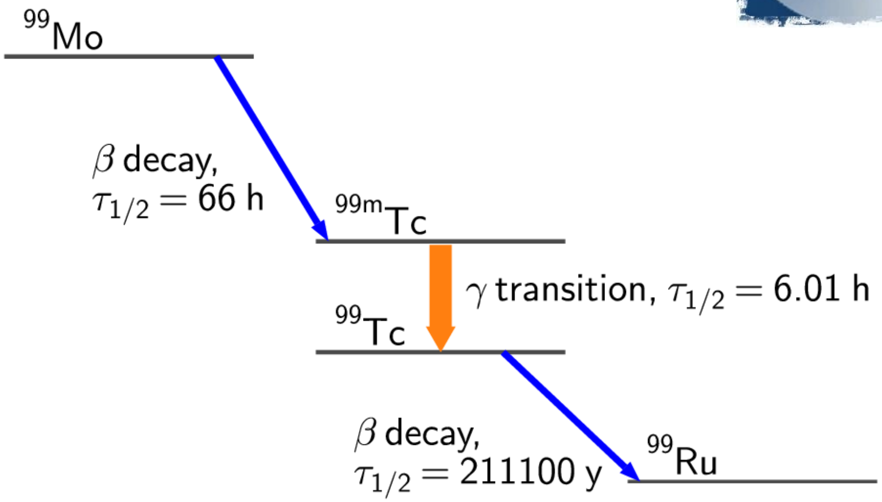
Parent	Parent $t_{1/2}$	Nuclear reaction	Daughter	Daughter $t_{1/2}$	Mode of daughter decay	Principal photon energy (keV) (% abundance)	Column	Eluant
^{99}Mo	66 hr	Fission $^{98}Mo(n,\gamma)$	^{99m}Tc	6 hr	IT[a]	140 (90)	Al_2O_3	0.9% NaCl
^{113}Sn	115 days	$^{112}Sn(n,\gamma)$	^{113m}In	99.5 min	IT	392 (64)	ZrO_2	0.05 *N* HCl
^{87}Y	80 hr	$^{88}Sr(p,2n)$	^{87m}Sr	2.8 hr	IT	388 (82)	Dowex 1 × 8	0.15 *M* $NaHCO_3$
^{68}Ge	271 days	$^{69}Ga(p,2n)$	^{68}Ga	68 min	β^+	511 (178)	Al_2O_3 SnO_2	0.005 *M* EDTA 1 *N* HCl
^{62}Zn	9.3 hr	$^{63}Cu(p,2n)$	^{62}Cu	9.7 min	β^+	511 (194)	Dowex 1 × 8	2 *N* HCl
^{137}Cs	30 yr	Fission	^{137m}Ba	2.6 min	IT	662 (85)	Ammonium molybdophosphate	0.1 *N* HCl + 0.1 *N* NH_4Cl
^{81}Rb	4.6 hr	$^{79}Br(\alpha,2n)$	^{81m}Kr	13 sec	IT	190 (67)	BioRad AG 50	Water or air
^{82}Sr	25.5 days	$^{85}Rb(p,4n)$	^{82}Rb	75 sec	β^+	511 (190)	SnO_2	0.9% NaCl
^{191}Os	15.4 days	$^{190}Os(n,\gamma)$	^{191m}Ir	4.9 sec	IT	129 (26)	BioRad AG1	4% NaCl
^{195}Hg	41.5 hr	$^{197}Au(p,3n)$	^{195m}Au	30.6 sec	IT	262 (68)	Silica gel coated with ZnS	Sodium thiosulfate solution

Data from Browne E, Firestone RB. *Table of Radioactive Isotopes*. 1st ed. New York: Wiley; 1986.
[a] IT, isomeric transition.



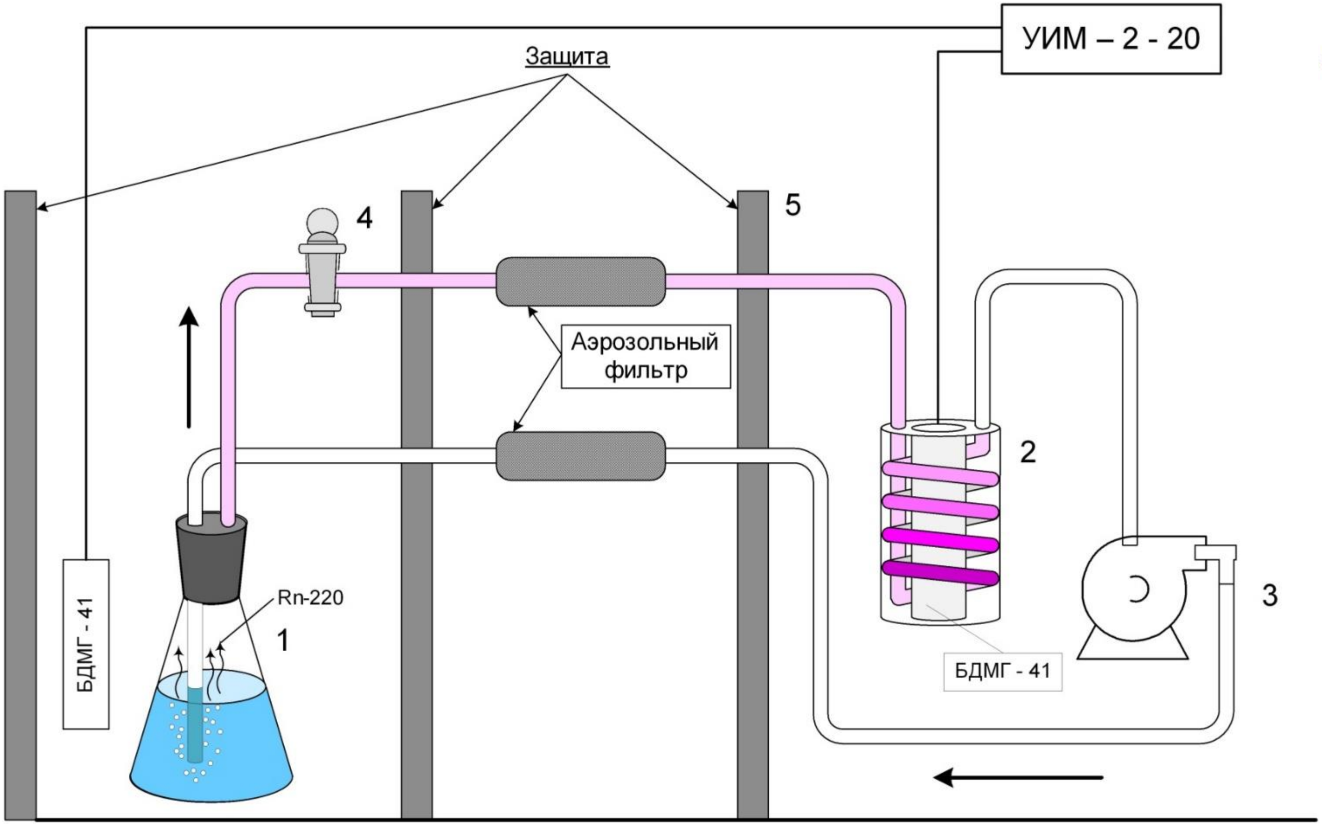
Mo-99/Tc-99m generators

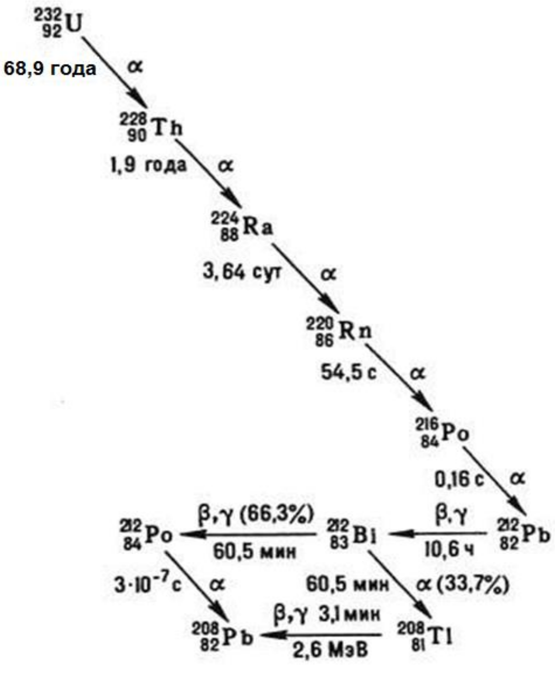




Usually ^{99}Mo is fixed on an oxide carrier in the form of molybdate (MoO_4^{2-}) or phosphomolybdate ions ($H_4[P(Mo_2O_7)_6]^{3-}$). In a slightly acidic solution, a stable heteropolymer is formed with Al^{3+} cations.

Radon generator of ^{212}Pb





Kurchatov Institute, Russia

$^{68}Ge/^{68}Ga$ generator

Параметр	Генератор ЗАО «Циклотрон» - Обнинск	Генератор IGG, Eckert & Ziegler (Германия)	Генератор iThemba LABS (ЮАР)	Генератор ITG (Германия)
Сорбент	**TiO_2** *модиф. ZrO_4*	**TiO_2**	**SnO_2**	**Силикагель** *модиф. 3,4,5-тригидрокси бензоатом*
Элюент	0,1 M HCl	0,1 M HCl	0,6-1,0 M HCl	0,05 M HCl
Проскок ^{68}Ge, %	< 0,005	< 0,001	< 0,01	< 0,005
Выход ^{68}Ga, %: *-начальный период* *- после 200 элюир.*	> 75 ~ 60	> 65 > 65	80 нет данных	80 нет данных
Объём элюата, мл	5	5-7	2-4	5
Активность ^{68}Ga во фракции 1 мл, %	80	65-70	нет данных	нет данных
Гарантированное время использования	≥ 1 год или ≥ 400 элюирований	1 год или 300 элюирований	нет данных	6 месяцев
Рекомендуемое время использования	Определяет потребитель (возможно до 3-х лет)	Пока проскок ^{68}Ge не превысит 5×10^{-3} %	нет данных	6 месяцев

$^{68}Ge/^{68}Ga$ generator

"Eckert & Ziegler receives approval for gallium-68 generator for cost-effective diagnosis of cancer

Berlin, December 4, 2014.

Eckert & Ziegler Radiopharma GmbH has received approval from the Federal Institute for Drugs and Medical Devices (BfArM) for its pharmaceutical $^{68}Ge/^{68}Ga$ generator for the German market. Germanium penetration, an essential factor for patient safety, is < 0.001% over its entire one-year shelf life…"

Test parameter	Specification
Appearance	Clear, colorless solution
Identity ^{68}Ga	Half-life 62 - 74 min
Content	> 60 % of nominal activity
Chemical impurity	Fe < 10 µg / GBq Zn < 10 µg / GBq
Radionuclidic purity (γ-emitting impurities)	< 0,001 % of nominal activity
Radiochemical purity	> 95 % free $^{68}Ga^{3+}$
pH	0,5 – 2,0
Microbiological quality	Sterile
Bacterial endotoxines	< 30 EU / ml

Eckert & Ziegler

*http://www.ezag.com/home/press/press-releases

^{68}Ge/^{68}Ga – generator regularly used in clinical practice with PET at A.M.Granov Centre of Radiology and Surgery

Ge-68 is produced by Cyclotron Co. at 22 MeV protons

The ^{68}Ga — generator of a chromatographic type is a glass column with a sorbent based on modified titanium dioxide. The parent radionuclide ^{68}Ge ($T_{1/2}$=271 d) is fixed on this sorbent. ^{68}Ga ($T_{1/2}$=67.71 min.), which is formed as a result of ^{68}Ge decay, is eluted from the column by 0.1 M HCl.

The breakthrough of ^{68}Ge is not more than 0.005 %

^{68}Ga yield in 5 ml of eluent is not less than 70 % at the first time of the operation and not less than 45% in 3 years or after 400 elutions

^{68}Ga— generator is produced with a nominal activity of ^{68}Ge: from 10 mCi (370 MBq) to 100 mCi (3700 MBq)

Kodina G.E. et al. / Russian patent #2126271

CYCLOTRON Co.,Ltd
Obninsk, RUSSIA

cyclotronzao.ru

Collaboration with Eckert & Ziegler, manufacturing authorization for pharmaceutical Gallium-68 generators obtained

Development of $^{72}Se/^{72}As$ PET Generator

^{72}Se (8.4 days)$\rightarrow$ ^{72}As (26 hr)

β+ emitter (PET application), γ 834 keV (77%)

Chemistry and concept has been developed:

- Chemical recovery based on metallic Se precipitation (Los Alamos)
- Distillation $AsCl_3$ in HCl - gas flow (Mainz-Juelich-Dubna)
- High temperature separation on MnO_2 in air flow (Troitsk)
- Solid state extraction from metallic Se (Mainz-Juelich-Dallas-Brussels)
- Anion exchange chromatography (Columbia-Los Alamos-Brookhaven)
- Extraction chromatography on o-diamines (Warsaw)
- Extraction chromatography on Se-selective resin (Troitsk -TrisKem Int.)

$^{82}Sr/^{82}Rb$ generators for PET

GR-01
Sr/Rb-82 Generator, Russia
in W-container
21/38 kg, 50-160 mCi,
60-78 days of utilization

CardioGen-82®
Sr/Rb-82 Generator, USA
10/30 kg, 100-120 mCi,
42 days of utilization

RubiJet
INR / LEMER /
NAOGEN, France

Ruby-Fill
DRAXIMAGE,
Canada

$$^{82}\mathrm{Sr} \xrightarrow{25.3\ \text{days}} {}^{82}\mathrm{Rb} \xrightarrow{76\ \text{s}} {}^{82}\mathrm{Kr} + 2e^{+}$$

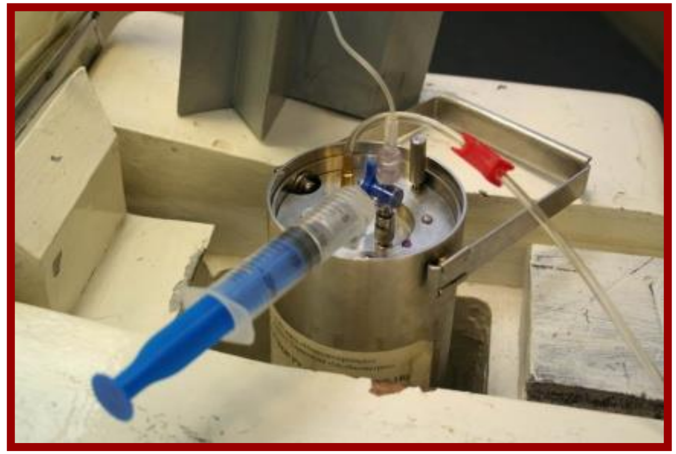
Chudakov V.M., Zhuikov B.L., Kohanuk V.M. / Russian patent #2546731

Chudakov V.M. et al. // Radiochemistry, 2014

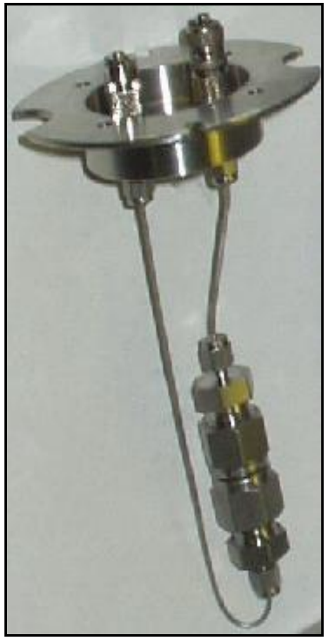
Sr-82/Rb-82 generators for PET

GR-01

GR-02



GR-01 in the injection system



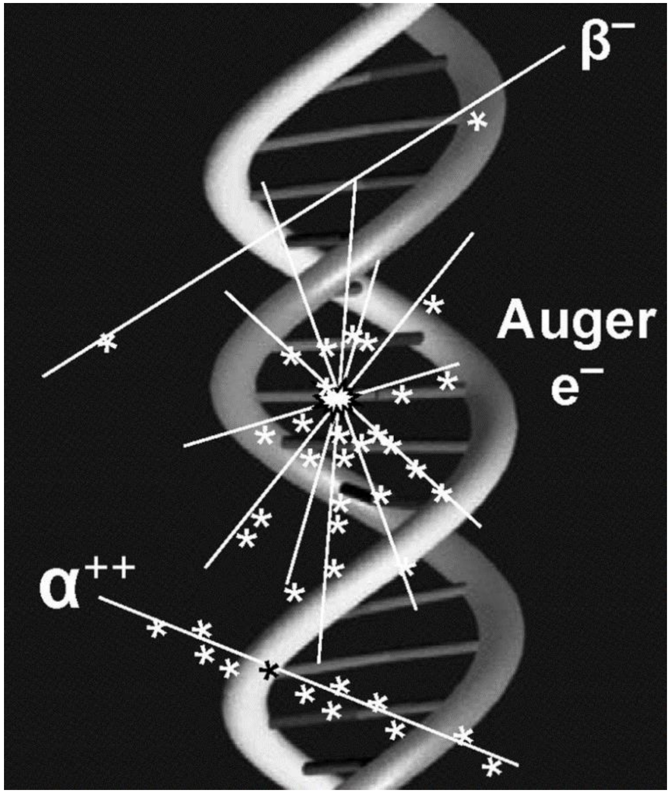
The application of the Sr/Rb-82 generator for diagnosis by positron emission tomography in Russian Scientific Center of Radiology and Surgical Technologies

Patient in PET scanner

Generator
in the injection system

Ac-225 and Bi-213

- α-Particles have high linear energy transfer (up to 100 keV/μm) and a short pathlength in comparison with β-particles;
- ^{225}Ac emit four α-particles in the decay chains providing a higher impact;
- Intermediate half-live of ^{225}Ac (10.0 d) is suitable for manufacturing and therapeutic treatment;
- ^{225}Ac may be also used as generator of the short-lived isotope: $^{225}Ac \rightarrow ^{213}Bi$ ($T_{1/2}$=46 min) providing α-particles.



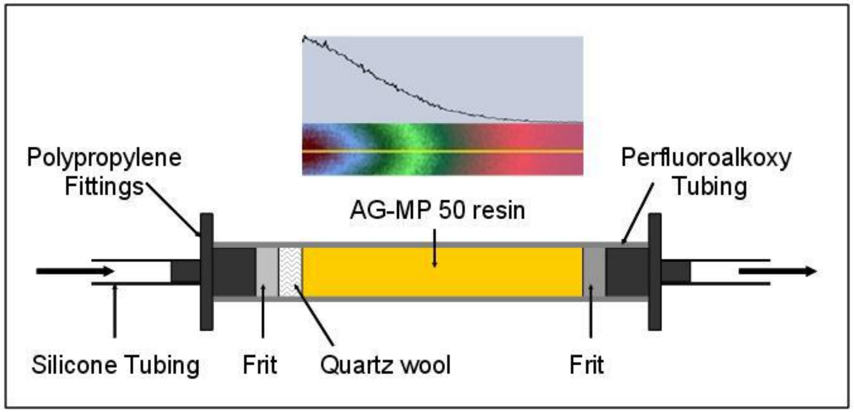
9.9 d		4.8 min		0.032 s		45.6 min		
Ac-225	→	Fr-221	→	At-217	→	Bi-213	→	Pb-209

$^{225}Ac/^{213}Bi$ generators

- A **direct** generator, where the parent ^{225}Ac is firmly retained by the sorbent, and ^{213}Bi is eluted with various complexing agents;
- The **inverse** generator, where the accumulated ^{213}Bi is periodically selectively sorbed from the ^{225}Ac solution, and then stripped off for use.
- The **direct** generator, where the parent ^{225}Ac is firmly retained by the sorbent, the short-lived ^{221}Fr is washed away from this sorbent, and the ^{213}Bi formed as a result of the ^{221}Fr decay accumulates and concentrates on the second sorbent.

Sorbent	Generator type	Media	Reference
AG-MP 50	direct	1-1.5 M HCl or 0.1 M HCl + 0.1 M HI	McDevitt et al, 1999 Bond et al, 2003
Ac Resin	direct	sorb. – 1 M HCl des. – 0.1 M HI	Wu et al, 1997
Anex (anion-exchange resin)	inverse	sorb. – 0.5 M HCl des. – 0.1 M NaOAc	Bray at al, 2000
UTEVA Resin	inverse	sorb. – 0.1 M HCl des. – 0.5 M NaOAc+0.75 M NaCl	McAlister et al, 2009

Scheme of direct $^{225}Ac/^{213}Bi$ generator with AG-MP 50 (ITU, Karlsruhe)



Scheme of $^{225}Ac/^{213}Bi$ generator with ^{225}Ac distribution profile

$^{225}Ac/^{213}Bi$ generator in lead shielding with peristaltic pump for semiautomatic elution

Typical $^{225}Ac/^{213}Bi$ generator performance:

- ✓ *elution:* with **600µl** 0.1M HCl/0.1M NaI
- ✓ *yield:* **75 ± 10%**
- ✓ ^{225}Ac breakthrough is lower than **2·10^{-5}%**

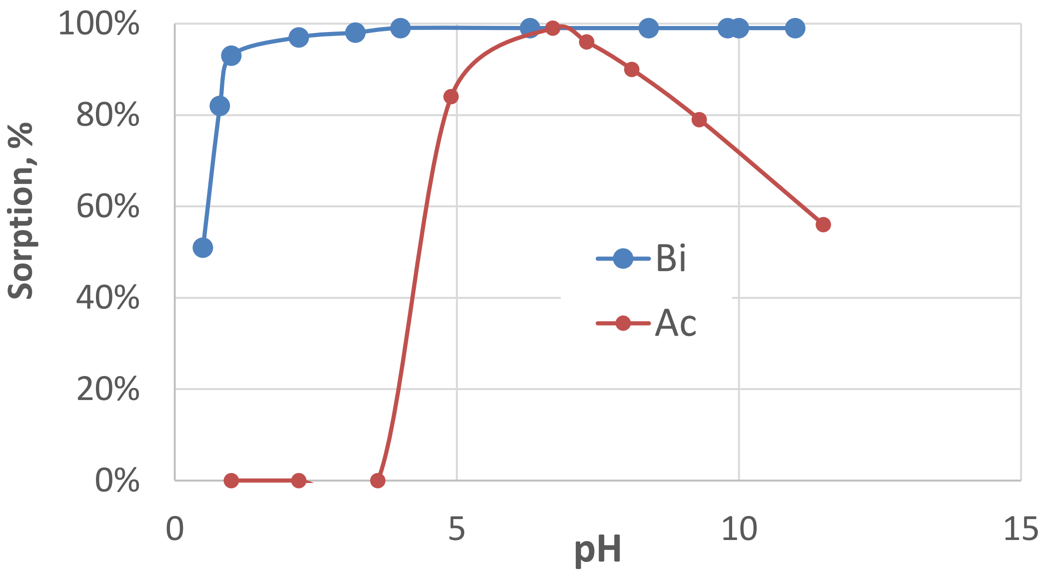
Processing time for Bi-radiopharm preparation is **15 min**

Deficiencies:

- ○ Low radiation resistance;
- ○ Need addition purification from the products of ^{227}Ac decay

Institute for Transuranium Elements, Annual Report 2006. ISBN 978-92-79-05001-5

TIG: Sorption on T-39 in static conditions



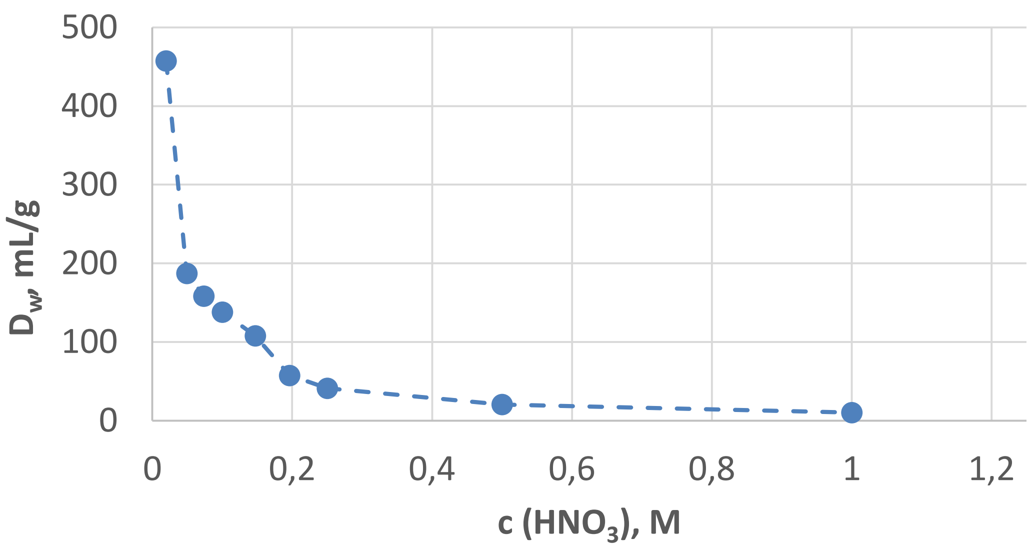
Chemical composition, mol. %:

96% - ZrO_2

4% - Y_2O_3

- High radiation and radiolytic resistance;
- High selectivity;
- Low price…

I = 0.1 M $NaNO_3$
m (T-39-950°C) = 1 g
V (sol) = 20 mL



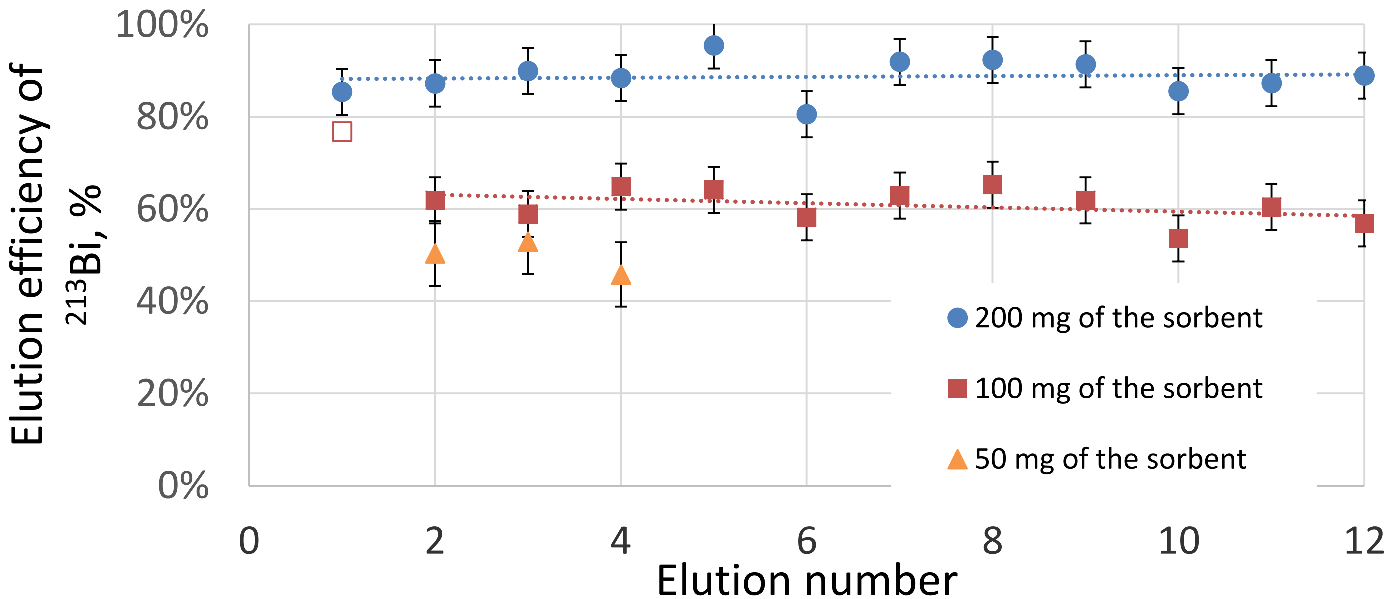
Sorbent Termoxide-39 (T-39) was supplied by Termoxide Company, Russia.

$$D_w = \frac{A_0 - A_s}{A_s} \cdot \frac{V}{m_s}$$

m (T-39-950°C) = 0.05 g
V (sol) = 5 mL

TIG: Efficiency of inverse $^{225}Ac/^{213}Bi$ generator

Sorption with single passing of Ac/Bi solution through the column



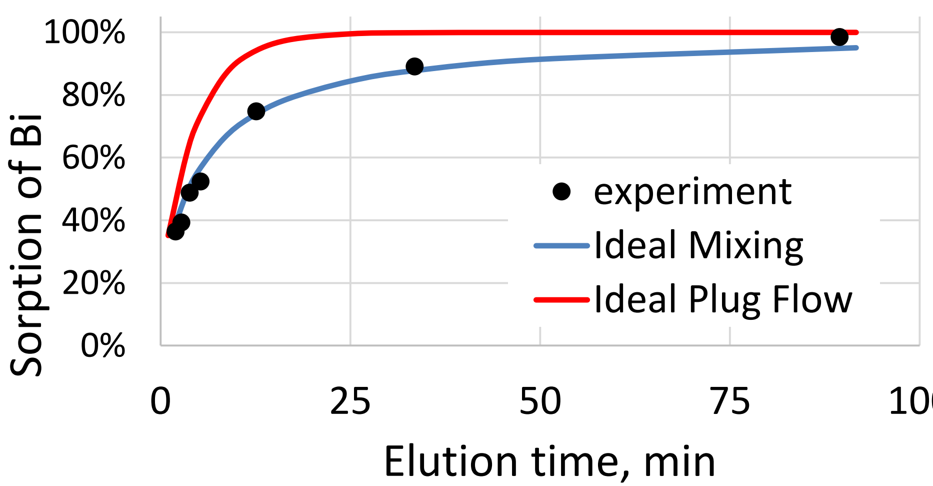
Sorbent T-39:

ZrO_2 + 4 mol.% Y_2O_3 ,

Burned at 950 °C

υ = 1.0 mL/min

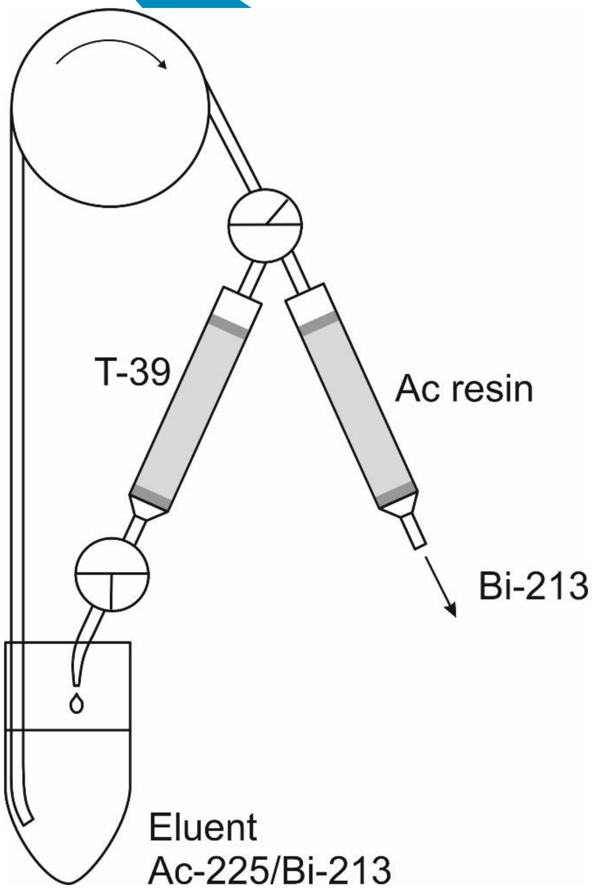
V ($^{225}Ac/^{213}Bi$ solution) = 5 mL



Kinetics of sorption

Elution of ^{207}Bi from the column with T-39 (100 mg) with different flow rates

TIG: Upgrade of the inverse $^{225}Ac/^{213}Bi$ generator



υ = 1.0±0.1 mL/min
V ($^{225}Ac/^{213}Bi$ solution) = 5 mL

Milking procedure:

1. Circulating $^{225}Ac/^{213}Bi$ (0.1M HNO_3) 40 min;

2. Rinsing with 0.1M HNO_3;

3. Stripping off ^{213}Bi with 1M HCl through Ac resin column;

4. Column regeneration

Typical $^{225}Ac/^{213}Bi$ generator performance:

— Period of recirculation: **50 min**

✓ *elution:* with 0.5 mL of 1M HCl

✓ *yield:* ≈ **80 %** for 100 mg column

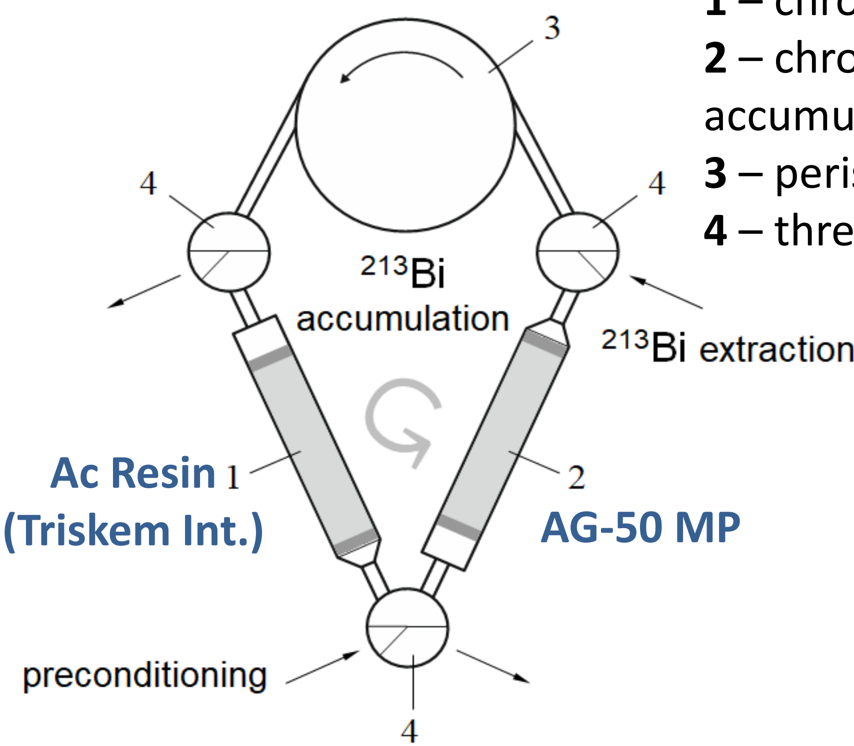
✓ ^{225}Ac breakthrough is lower than **10^{-6} %**

✓ Processing time for ^{213}Bi elution is **4-5 min**

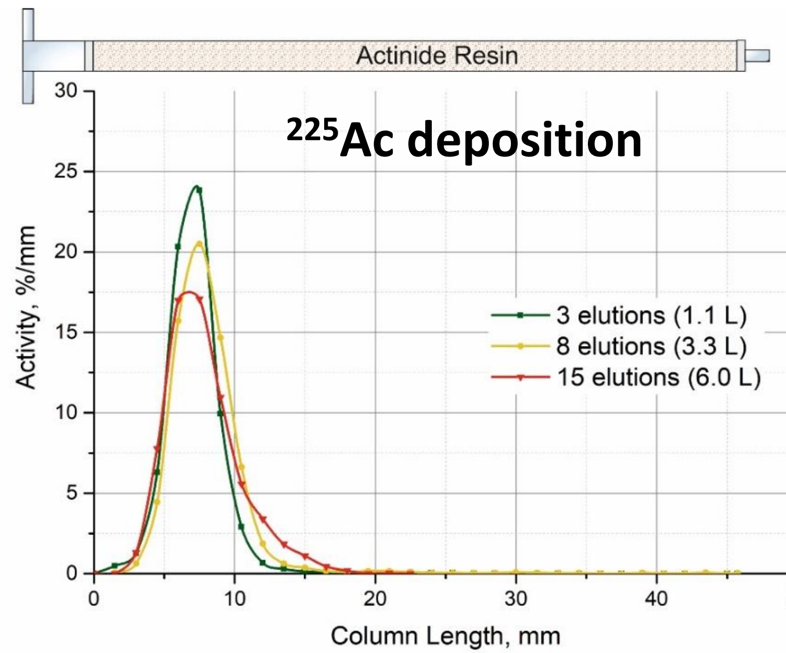
Vasiliev A. N., Ermolaev S. V., Lapshina E. V. et al // Radiochimica Acta, 2019

Scheme of direct $^{225}Ac/^{213}Bi$ generator with Ac-resin via ^{221}Fr («Afrabis», INR RAS)

1 – chromatographic column with parent ^{225}Ac;
2 – chromatographic column for ^{213}Bi accumulation;
3 – peristaltic pump;
4 – three-way cock



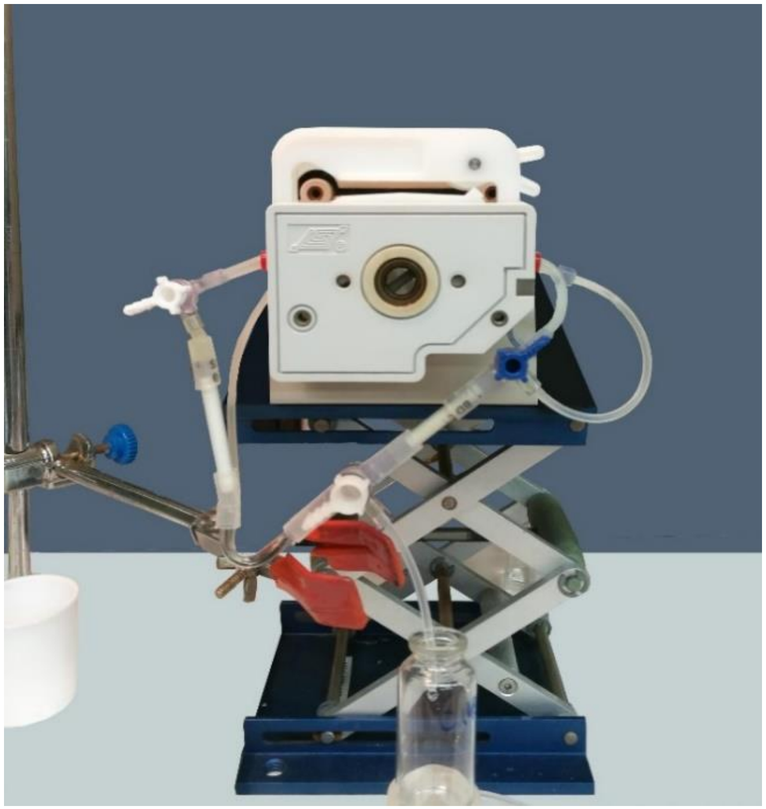
Cycling scheme
^{225}Ac (10 d) → ^{221}Fr (5 min) → ^{213}Bi (46 min)



Ermolaev, S.V., Skasyrskaya, A.K., Vasiliev A.N. Pharmaceutics, 2021

Direct $^{225}Ac/^{213}Bi$ generator

with Ac-resin via ^{221}Fr («Afrabis», INR RAS)



Typical $^{225}Ac/^{213}Bi$ generator performance:

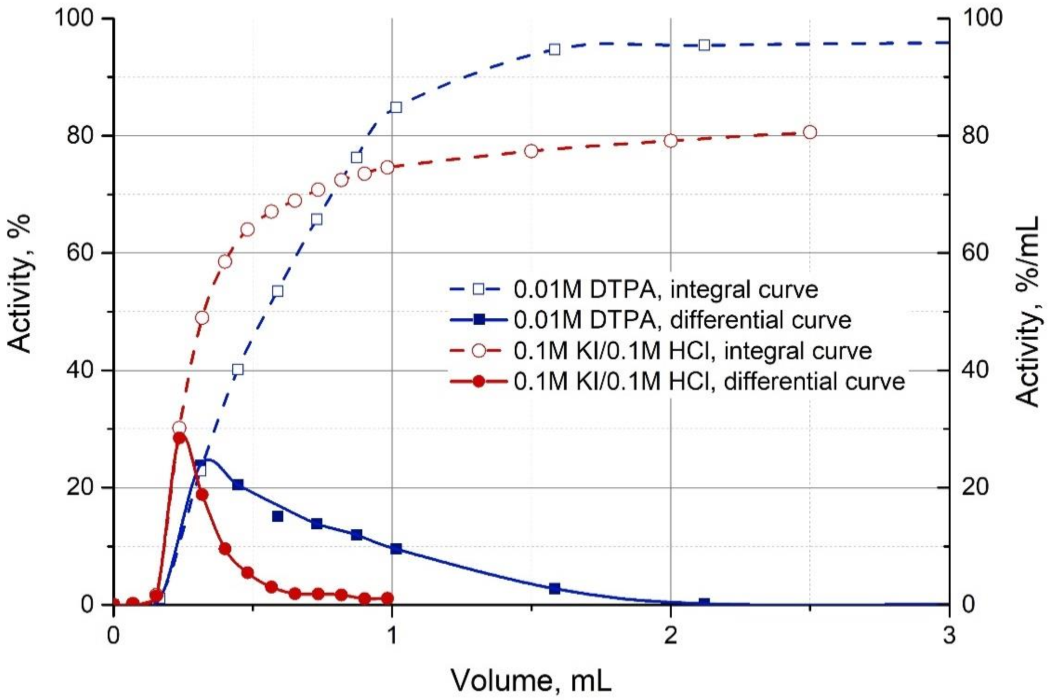
— Period of recirculation: **3-4 hr**

- ✓ *elution:* with 0.1M HCl/0.1M KI;
- ✓ *yield:* > **73 % in 0.5 mL;**
- ✓ ^{225}Ac breakthrough is lower than **10^{-6} %;**
- ✓ **^{227}Th and ^{223}Ra** breakthrough is lower than **10^{-6} %;**
- ✓ Processing time for ^{213}Bi elution is **2-3 min**

Ermolaev, S.V., Skasyrskaya, A.K., Vasiliev A.N. Pharmaceutics, 2021

$^{225}Ac/^{213}Bi$ generator «Afrabis»

^{213}Bi elution with chelators and conjugates

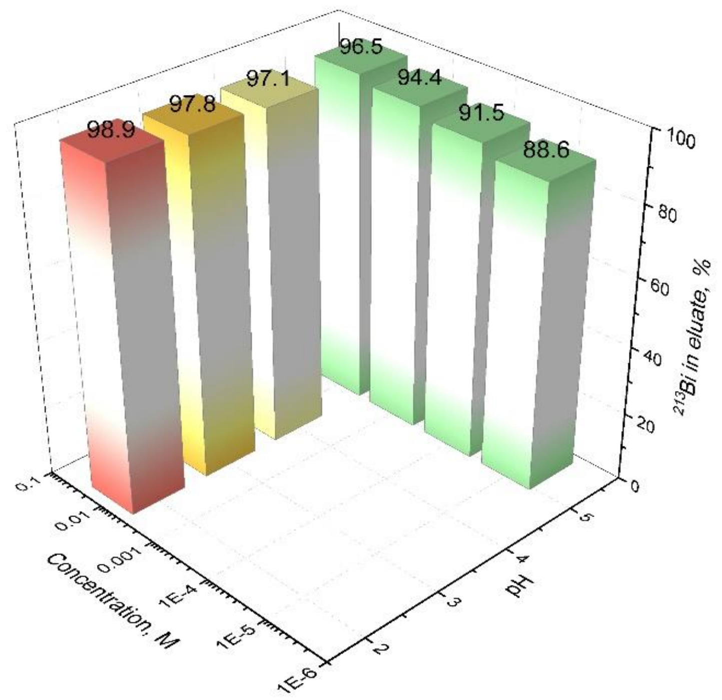


Integral and differential **Bi elution curves** with 0.1M HCl/0.1M KI and 0.01M DTPA (pH 5.3) from the column with 0.33-0.4 mL AG MP-50.
Flow rate – 1.0 ± 0.1 mL/min.

Ermolaev, S.V., Skasyrskaya, A.K., Vasiliev A.N. Pharmaceutics, 2021

Desorption of ^{213}Bi with 10^{-5}M **DTPA** and 10^{-5}M **DOTA** solutions directly from AG-MP 50 column was demonstrated.

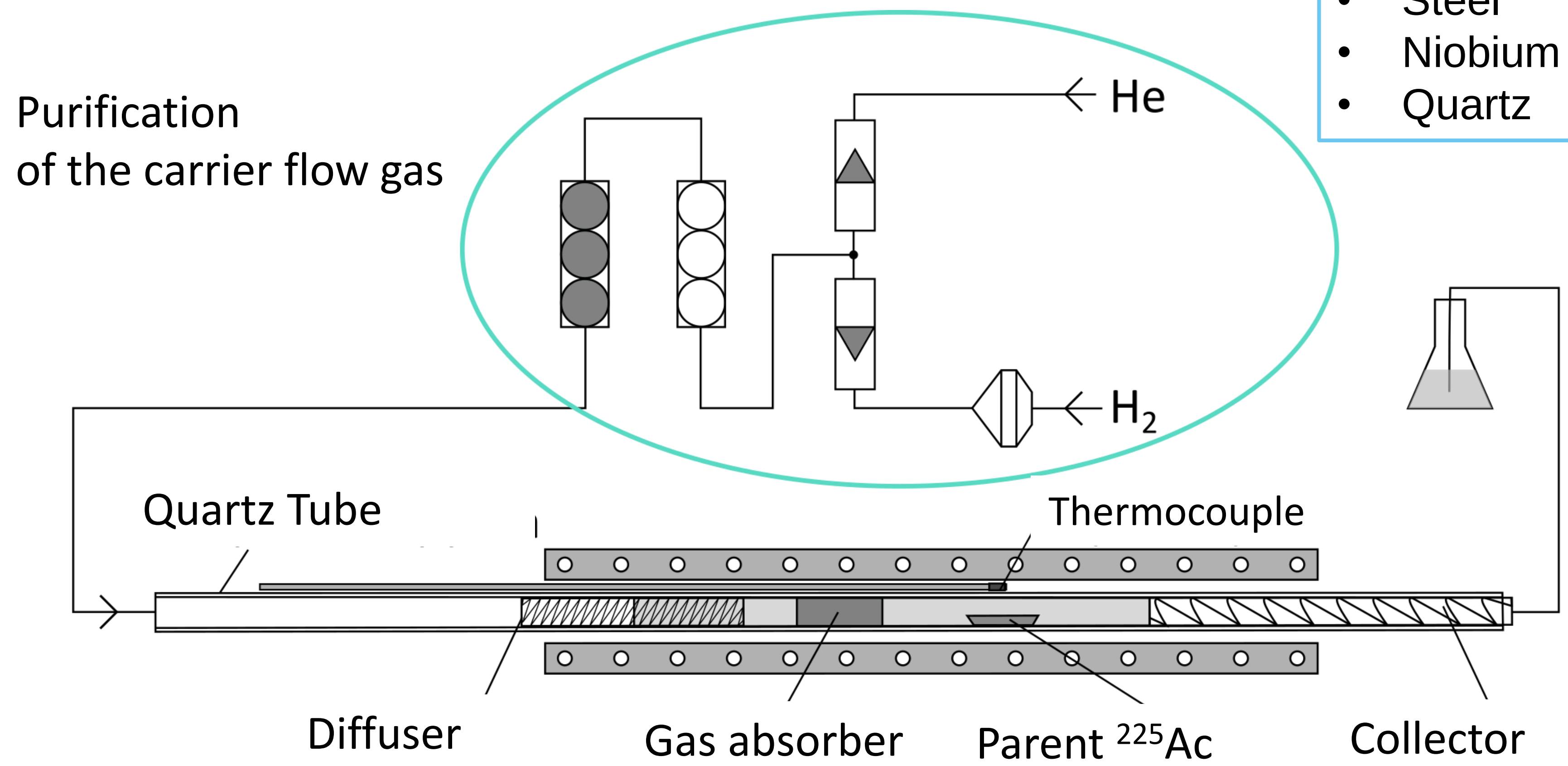
Elution with DTPA



$^{225}Ac/^{213}Bi$ generator

New approach

He/Ar + 10% H_2
Base:
- Steel
- Niobium
- Quartz



$^{225}Ac/^{213}Bi$ generators

	Sorbent	Type	^{213}Bi Yield	^{225}Ac breakthrough	^{223}Ra and ^{227}Th impurity	Time	Rad. resistence
	AG 50 MP	direct	75 % (in 0.6 mL)	$< 2 \cdot 10^{-5}$% (ITU) $< 3.5 \cdot 10^{-5}$% (INR)	10^{-4}-10^{-3}%	7-8 min	low
	Ac Resin	direct	85%	< 0.05%	-	7-8 min	low
	MSIG (an-exchanger)	inverse	≈ 85% (in 1 mL)	≈ 0.07%	-	-	high
	UTEVA Resin	inverse	≈ 87% (in 2 mL)	$< 10^{-7}$%	-	19 min	high
INR RAS	**TIG (Termoxide based)**	inverse	≈ 80% (in 0.5 mL)	$< 10^{-6}$%	-	4-5 min	high
INR RAS	**Afrabis**	direct	≈ 73% (in 0.5 mL)	$< 10^{-6}$%	$< 10^{-6}$%	2-3 min	medium

Thank you very much for your kind attention!

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Vladislav A. **Zobnin**

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Olga V. **Nastoyaschaya**