«Radiopharmaceuticals for diagnostic and therapy in modern nuclear medicine»

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Outline

Basis of the radionuclide diagnostic and therapy

The new methods in radionuclide diagnostic and therapy

Novel radionuclides for diagnostic and therapy

Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

Conclusion

Basis of the radionuclide diagnostic and therapy

Radionuclide diagnostics

Aims To diagnose the deviations in the vital functions of organs at all stages of the illness

Quick detect

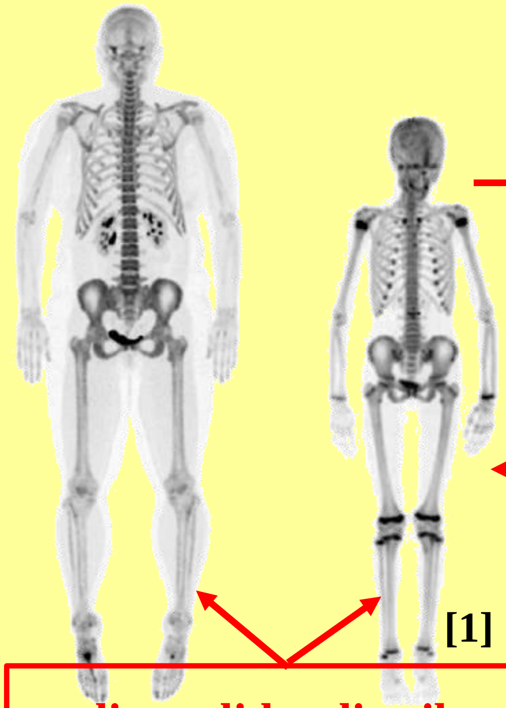
Effectively treatment of the illness

Saving

Saving LIFE

Human body radiometry

Radiation detectors



[1]

Radiation detectors

It is possible to obtain an image of the organs, tumors, metastases

How to reach

+ radionuclides

radionuclides distribution in the human body

Basis of the radionuclide diagnostic and therapy

Radionuclide targeted therapy - RTT

Aims

Cancer cells

The ability to increase intracellar incorporation of the radiopharmaceutical without any toxicity

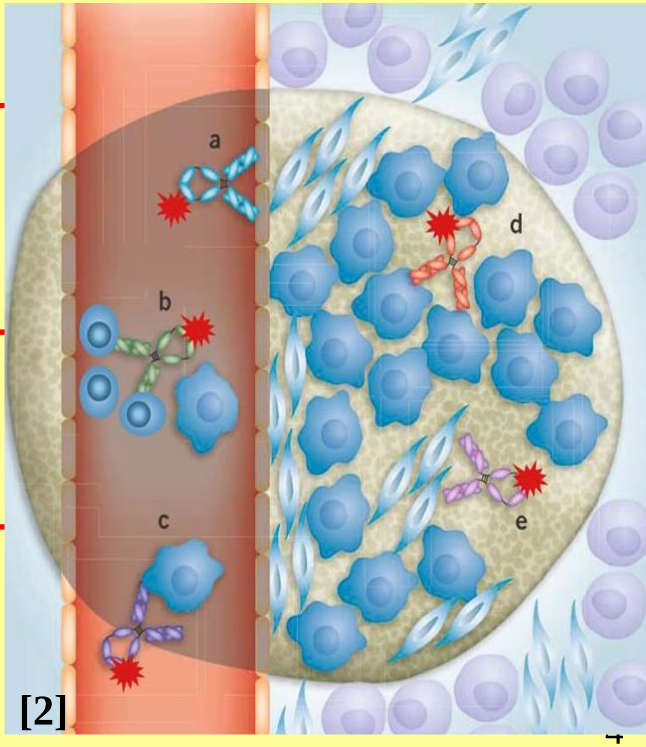
↓

One of the main challenges

of RTT remains in matching the physical and chemical characteristics of the radionuclide and targeting agent with the clinical character of the tumor

↓

How to reach



The radionuclide labeled agents are used to target cancer-associated structures

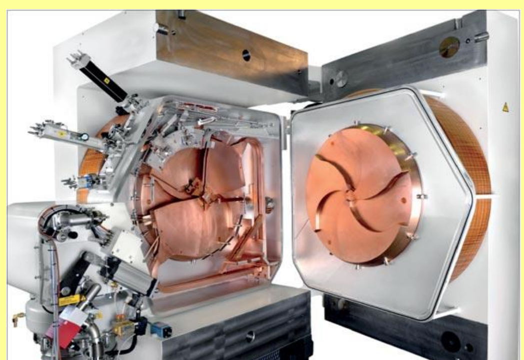
Basis of the radionuclide diagnostic and therapy

<u>Radionuclide production</u>

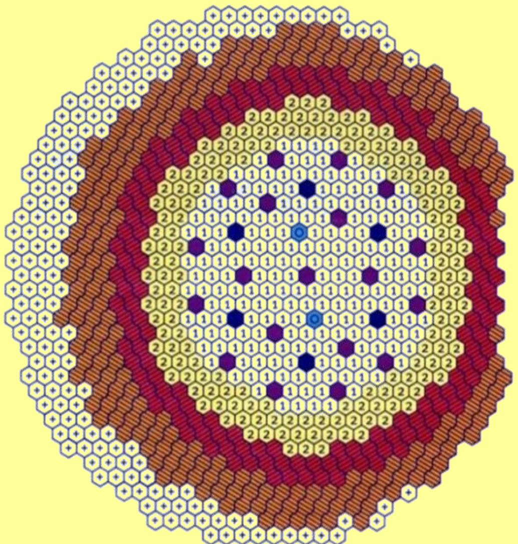
Cyclotrons

Nuclear reactions with:
^{1}p, d, α

Main channel:
Target(^{1}p,^{1}n)Product



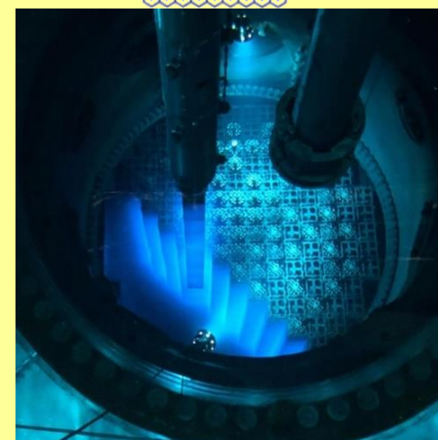
Nuclear reactor



Nuclear reactions with ^{1}n:

Neutron capture → decay

Fission fragments



Basis of the radionuclide diagnostic and therapy

Types of radionuclide diagnostics

In Vitro

1) Measuring the accumulation of a radiopharmaceutical in the biological samples

2) A radioimmunoassay: antigens-antibodies

Insulin

The blood has antibodies to insulin

Antiserum

+

^{125}I + Insulin

+

Patient serum

Centrifugation

<u>Rosalyn Sussman Yalow</u>

<u>Solomon Aaron Berson</u>

the Nobel Prize
for Medicine in 1977

In Vivo

1) Imaging – visualization of the some organs by using radionuclides

2) Measuring the accumulation of a radiopharmaceutical in the body

Basis of the radionuclide diagnostic and therapy

Single-photon emission computed tomography (SPECT) - Hal Oscar Anger

In Vivo

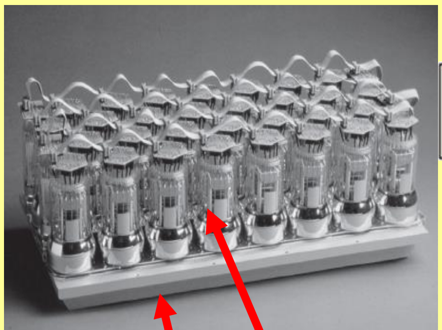
Gamma radionuclides

↓

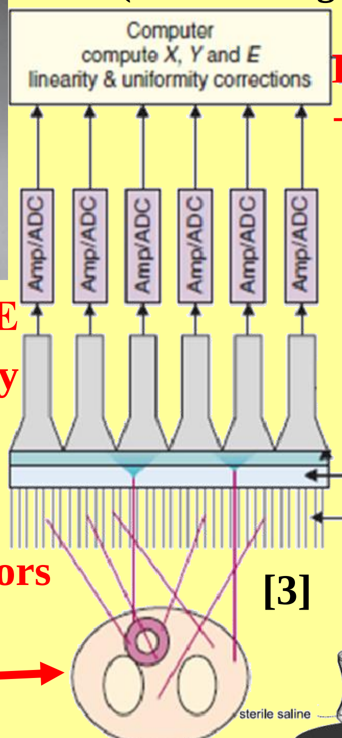
Collimators+scintilatttor detector

↓

CT (3D image)



(nuclide image)



Electronics + ADC

X,Y,E

PMT array

scintillator

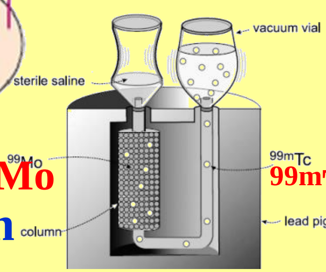
collimators

[3]

^{123}I ↓ 792 min.

^{99m}Tc ↓ 360 min.

140 keV



^{99}Mo

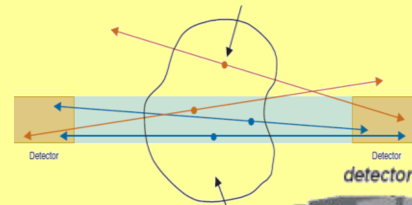
67 h

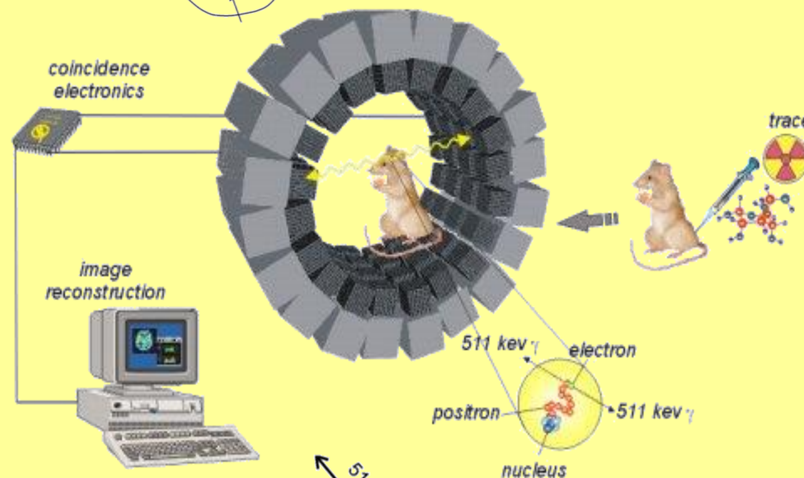
^{99m}Tc

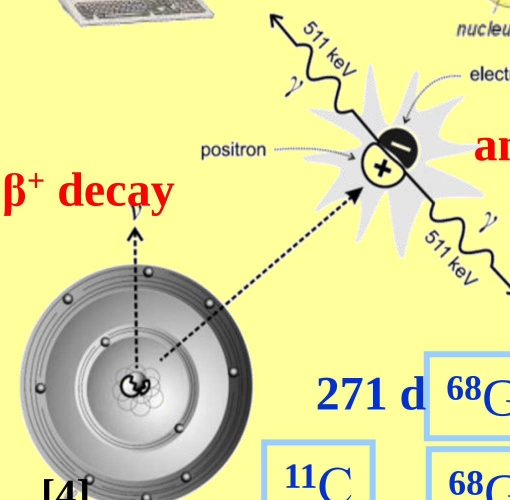
[4]

Positron emission tomography (PET)

In Vivo







annihilation

β^{+} decay

[4]

271 d ^{68}Ge

^{18}F

109 min.

^{11}C 20 min.

^{68}Ga 67 min.

Basis of the radionuclide diagnostic and therapy

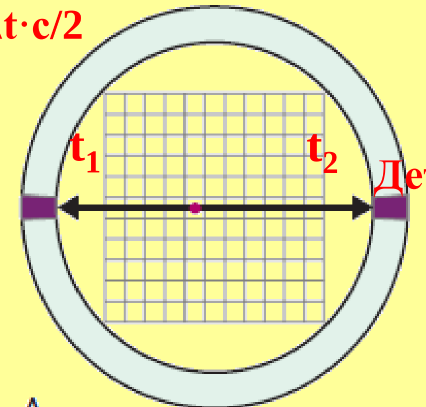
Diagnostics

Advanced detector technologies for the PET

PET + Time of Flight (TOF) method

$\Delta d = \Delta t \cdot c/2$

Detector 1 t_1 t_2 Детектор 2



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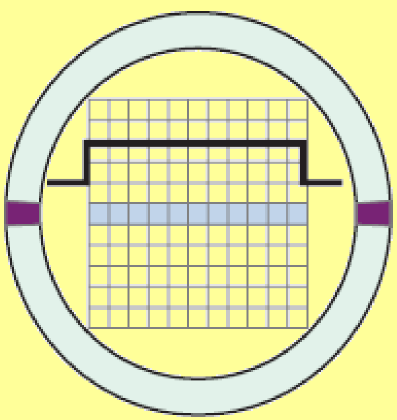
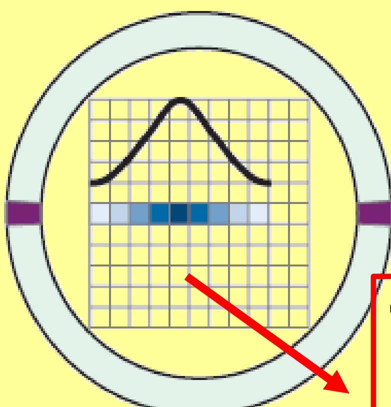




Standard PET
Position resolution

PET+TOF
Position resolution

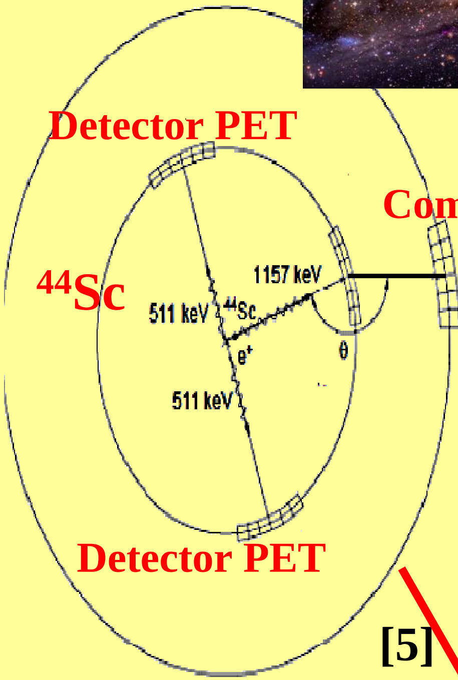
Time – ps. We need
1. Fast scintillators
2. Multi channel plate detectors

Gamma-PET method

Detector PET

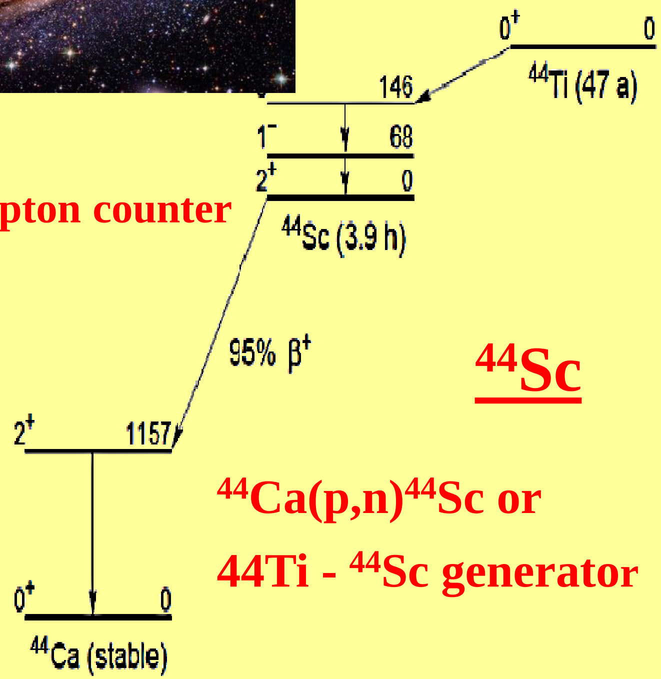
^{44}Sc

Compton counter



Detector PET

[5]



^{44}Sc

^{44}Ca(p,n)^{44}Sc or

44Ti - ^{44}Sc generator

γ-quanta of 44Sc (1157 кэВ) is detected (by Compton spectrometer) together with two annihilation gammas (by standard PET detectors)
3D position visualization
The best position resolution!

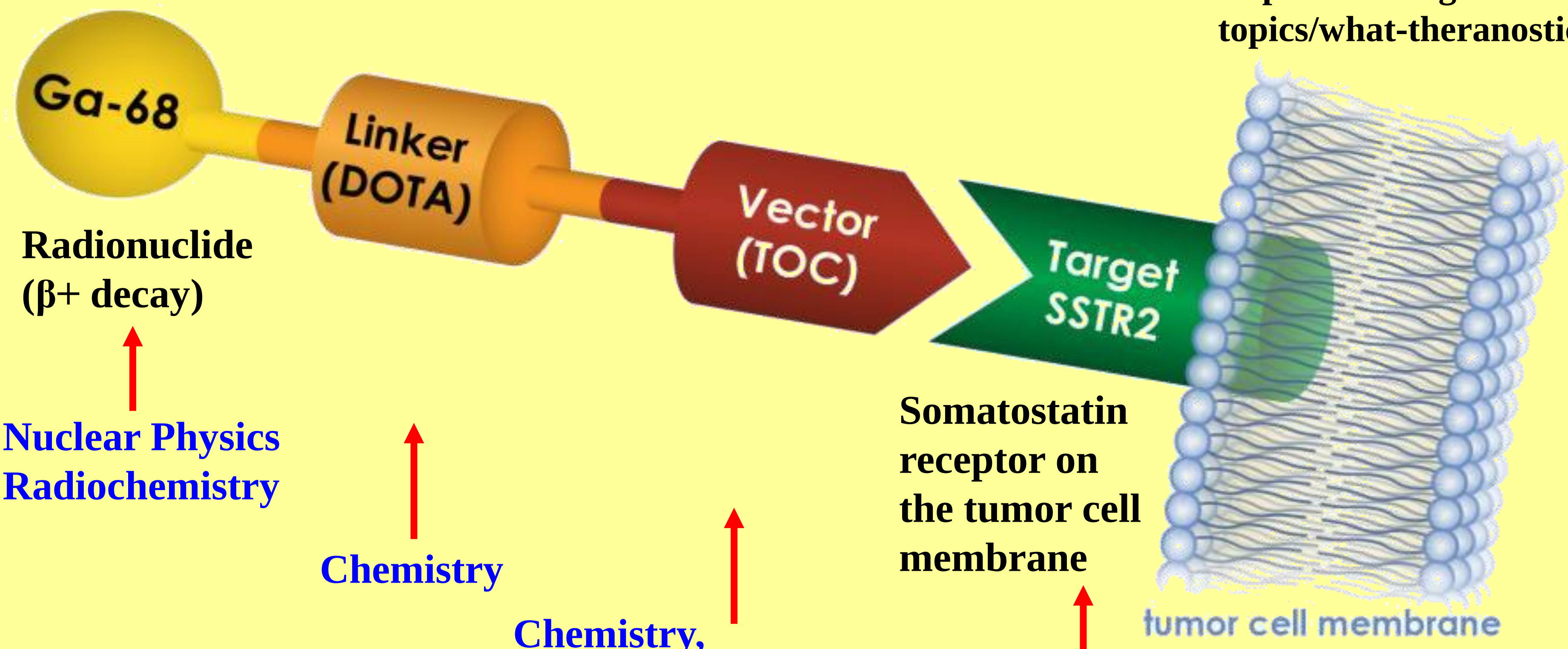
Basis of the radionuclide diagnostic and therapy

Positron emission tomography (PET)

Diagnostics

Tumor visualization by the PET

https://uihc.org/health-topics/what-theranostics



Radionuclide (β+ decay)

Somatostatin receptor on the tumor cell membrane

Nuclear Physics
Radiochemistry

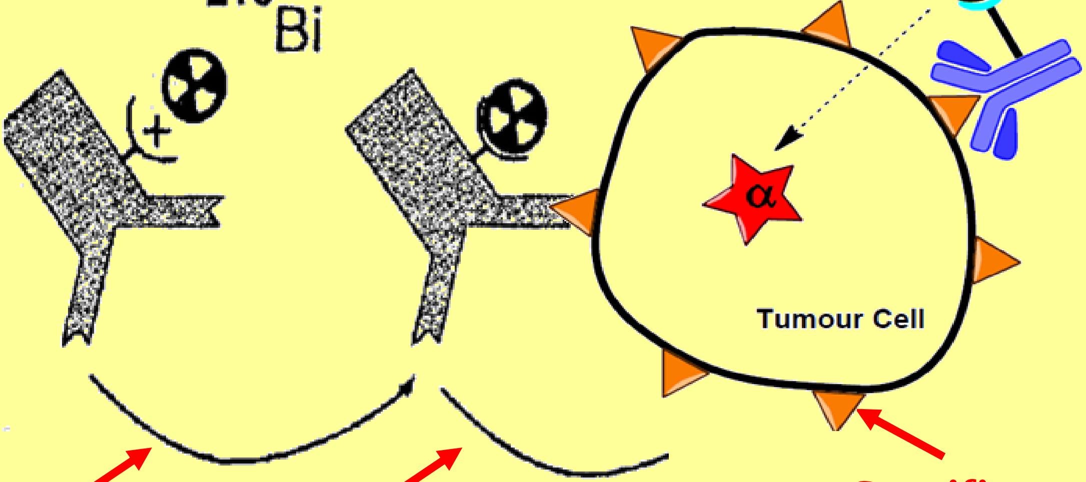
Chemistry

Chemistry, Radiation-material science

Biology, Medicine

The new methods in radionuclide diagnostic and therapy

Therapy



Alpha - particles (5-7 MeV) are effective to distroy the tumors at the diameter several microns

Specific membrane antigen

- Monoclonal antibody
- Peptide
- Protein
- Nanoparticle
- Polymers

} Carriers

Big problem – recoil nuclei

Recoil nuclei can kill of the vector molecules

α – decay ⟶ recoil nuclei kinetic energy ~ 100 - 110 keV
5-7 peptide molecules are destroyed, and finally the whole radiopharmaceutical also destroyed.

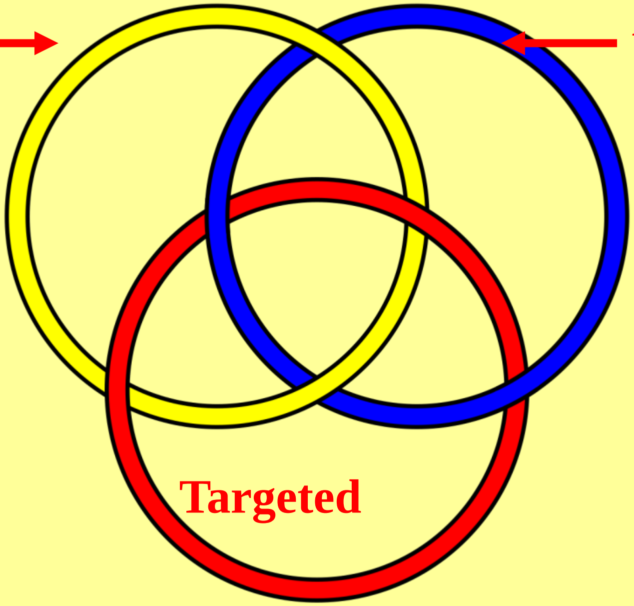
β - decay recoil nuclei kinetic energy ~ 25 eV.
There is no damaging, but continuous spectrum is not suitable for the optimal treatment planning.

The new methods in radionuclide diagnostic and therapy

Theranostics: therapy + diagnostic

Combine both therapeutic and diagnostic capabilities in <u>one dose</u>

Theranostics – goals:



1) Increase the tumor visualization quality
2) Minimum side effects diagnostic
3) Control of the therapy processes

Minimum side effects at treatment

Increase the efficiency of the radiopharmaceutical delivery to the tumor

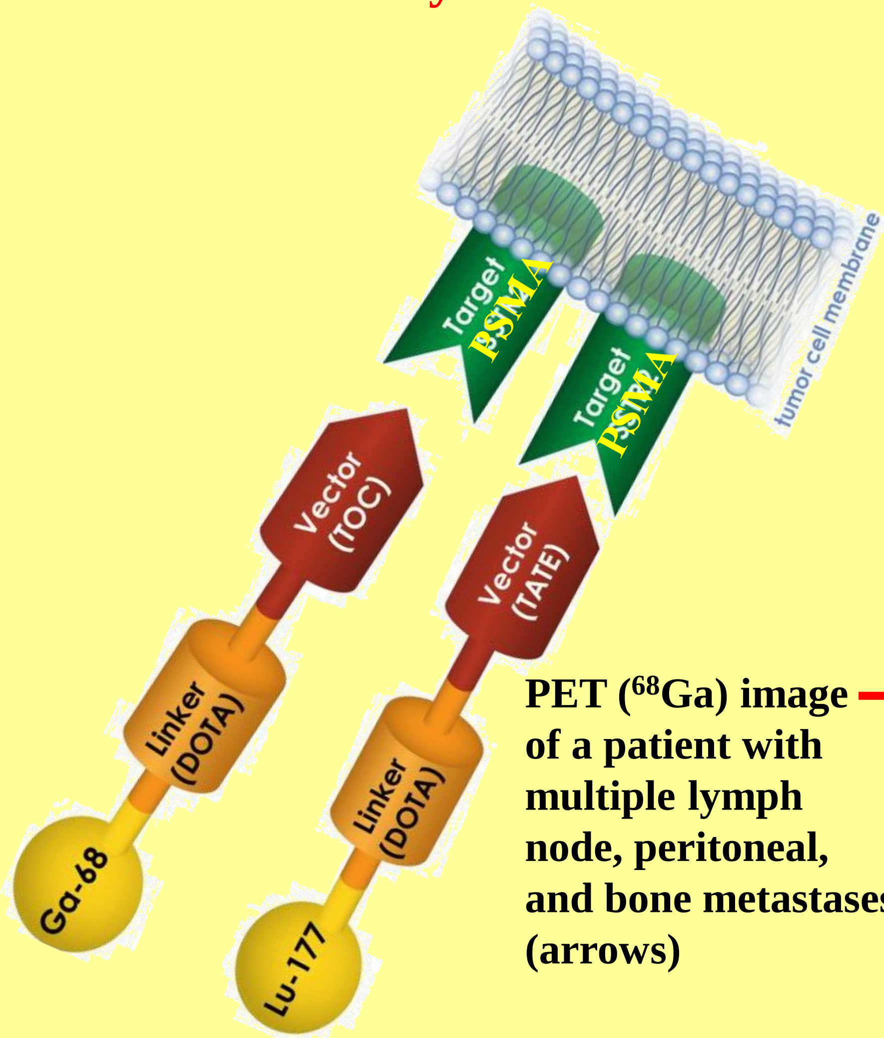
Theranostics: history

Radioiodine therapy: "the gold standard" in thyroid diseases

First radioiodine therapy with ^{131}I ($T_{1/2}$ – 8d) in patients with thyroid cancer was undertaken by Seidlin et al in 1946

The new methods in radionuclide diagnostic and therapy

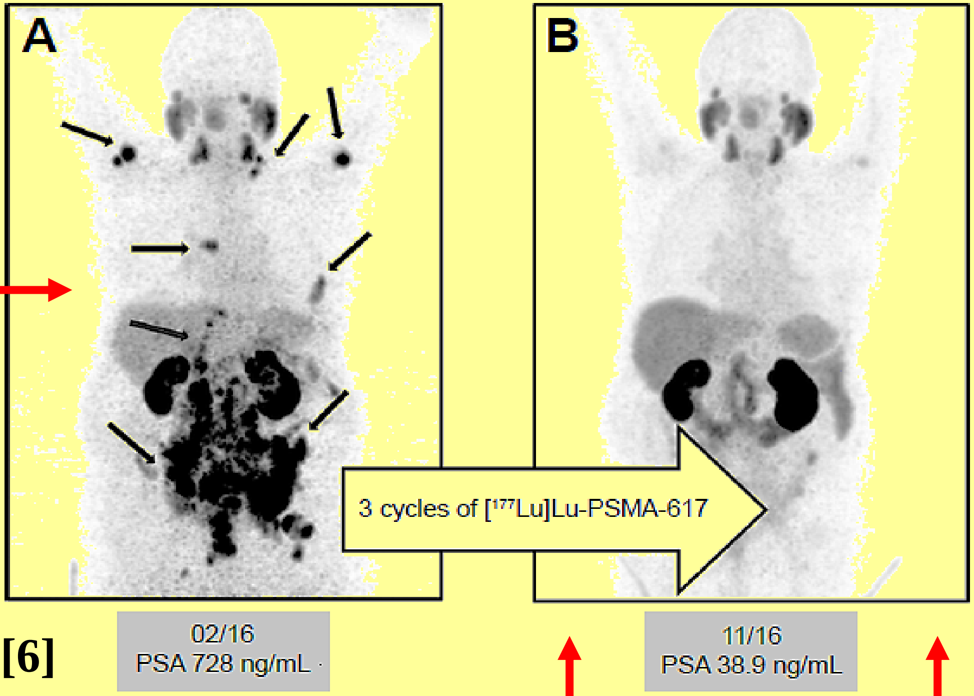
Theranostics today – novel radionuclides



Prostate cancer is one of the common cancer in men. Cancer cells has prostate-specific membrane antigen (PSMA) on the cell surface.

There are several available radiopharmaceuticals that target PSMA: ^{68}Ga + ^{177}Lu

PET (^{68}Ga) image of a patient with multiple lymph node, peritoneal, and bone metastases (arrows)



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PET (^{68}Ga) image of a patient after three cycles of ^{177}Lu therapy, showed a very good response

Novel radionuclides for diagnostic and therapy

Terbium: Swiss Knife of Nuclear Medicine

^{149}Tb-therapy
^{152}Tb-PET
^{155}Tb-SPECT
^{161}Tb-therapy + SPECT
^{155}Tb-SPECT

Manjit Dosanjh, X International Congress "Nevsky Radiology Forum – 2018" , 27-28 April, Saint-Petersburg

Production method – reactor
Advantages – high yield,
Disadvantages – targets, radiochemistry, Purity, high cost

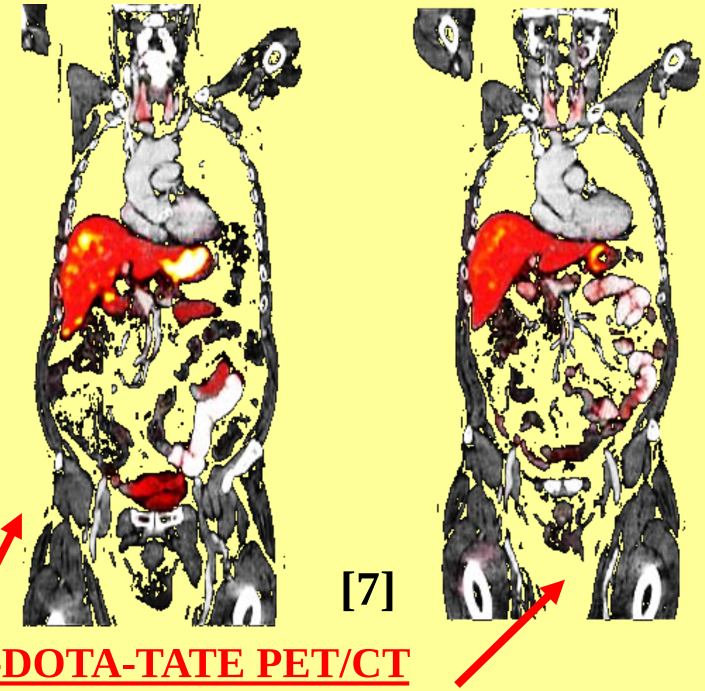
Production method – cyclotron
Advantages – purity,
Disadvantages – targets, radiochemistry, high cost

Theranostics today – novel radionuclides

^{46}Sc-therapy (bone palliation therapy include radiolabeled complexes of zoledronic acid)

^{44}Sc-PET

^{68}Ga + ^{177}Lu

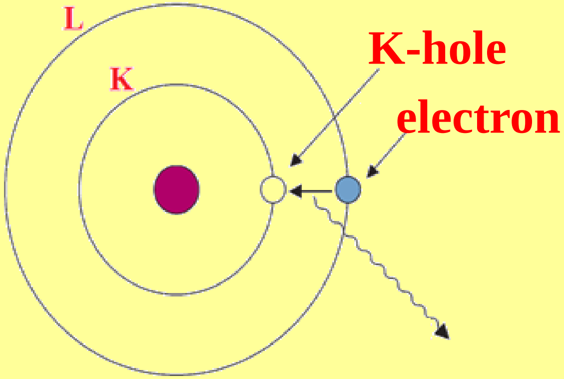


[7]

^{68}Ga-DOTA-TATE PET/CT before and after ^{177}Lu-DOTATATE therapy. Almost complete regression of the primary tumor and metastases

Production method – mass separation
Advantages – excellent purity,
Disadvantages – low yield, high cost

Novel radionuclides for diagnostic and therapy



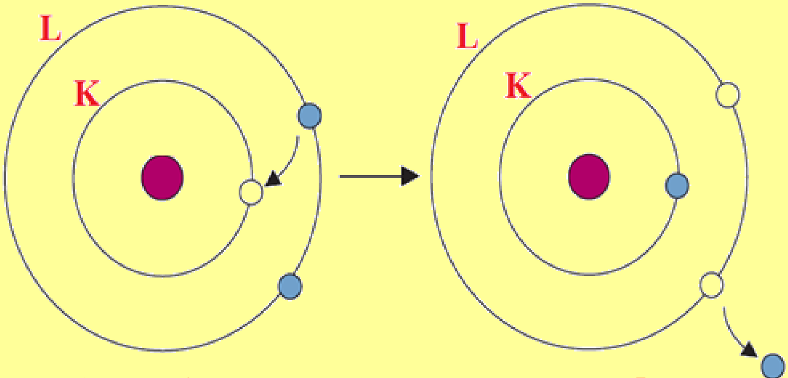
Auger-Electron Radionuclide Therapy

An effective tool for the destruction of specific tumor cells, micrometastases and small tumors with minimal side effects.

The Auger-Electron emitters:

1) Have micron and submicron range

2)Higher energy transfer (increases the possibility of the cancer cells killing by the double breaking DNA



Auger Electron Emitting Radionuclides for the Therapy (requirements):

1) Number of the emitting electrons
2) Associated with this decay gamma and X-rays
3) Half -life time
4) Suitable "chemistry" for the radiopharmaceutical production

For Theranostic were proposed:

^{119}Sb - therapy
$T_{1/2}$ = 38.2 h, Electron energy: 2.95 (L), 21.0 (K)
Emission 147, 12 (on 100 mother nuclei)

^{117}Sb - diagnostics, SPECT (gamma – 158 keV)
$T_{1/2}$ = 2.8 h, Electron energy: 2.95 (L), 21.0 (K)
Emission 147, 12 (on 100 mother nuclei)

Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

OUR Project:

“The new radiopharmaceuticals based on biologically active synthetic polymers and Auger electron emitters for diagnostics and therapy of the oncological diseases”

COLLABORATION:

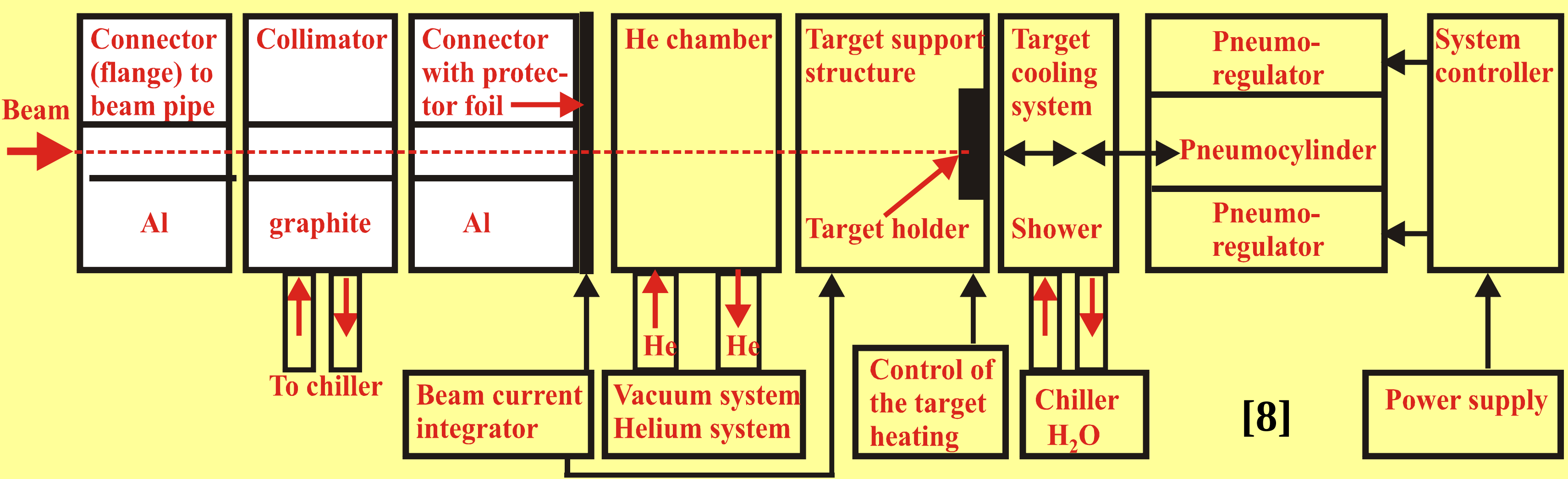
Saint-Petersburg State University, V.G. Khlopin Radium Institute

Target unit (solid targets)

Power density up to 600 W/cm^2

1) Helium chamber
2) Innovative small diameter nozzle system (jet cooling of the target) for the high-effective cooling
3) Automatic target moving
4) The system for the control of the target heating

Target system



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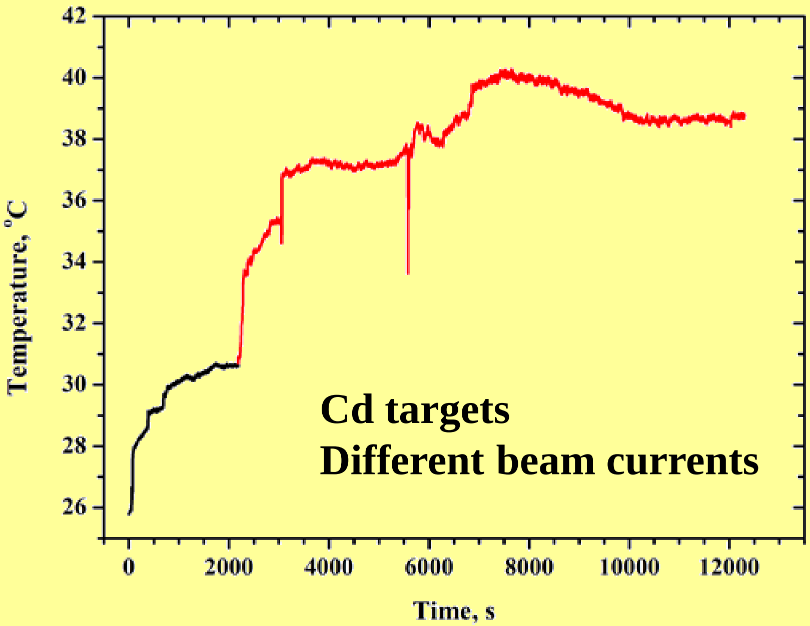
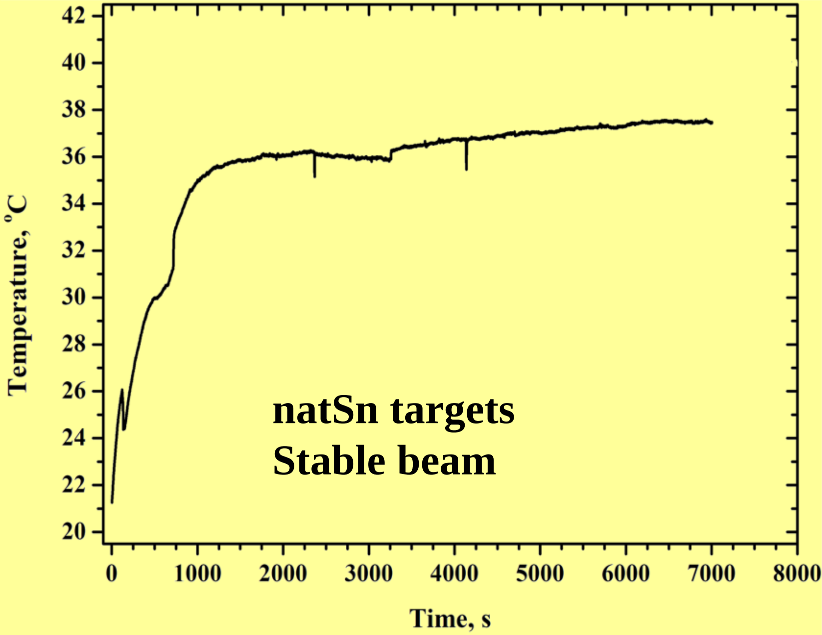
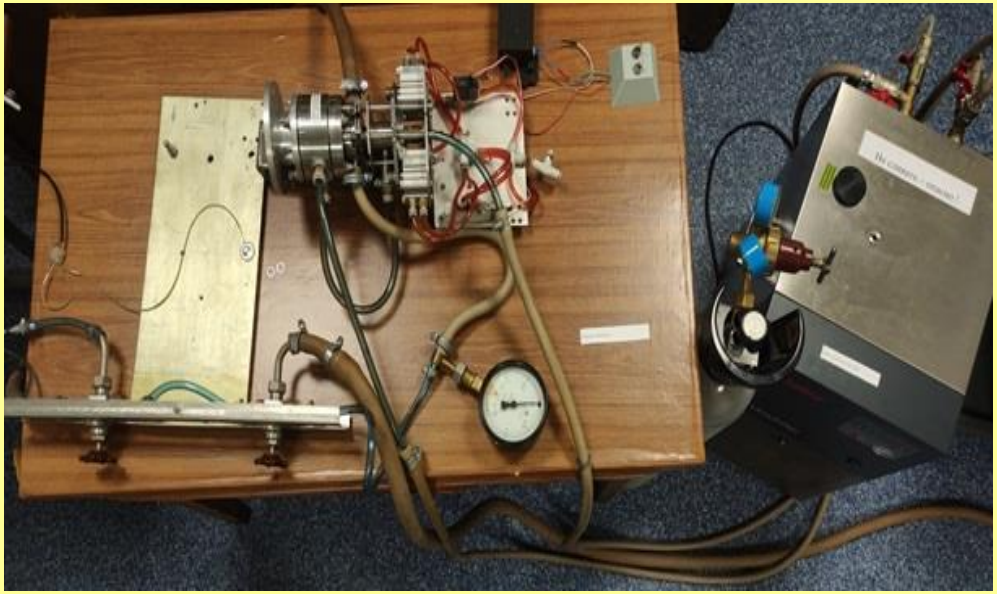
Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

Target heating measurements





Modernized target unit (solid targets)



1) New system for control of the target heating

2) Modernized cooling system

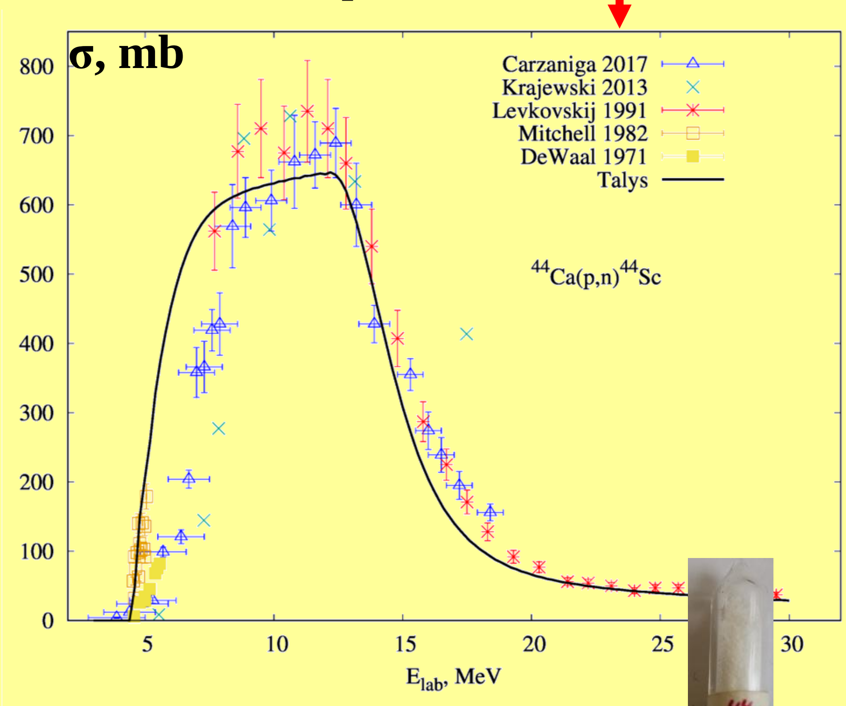
Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

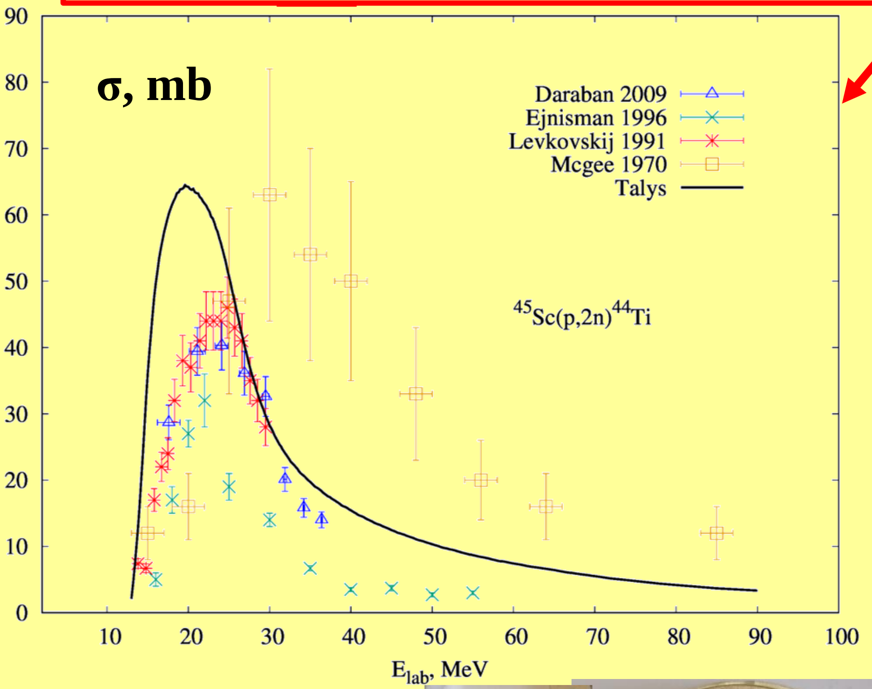
Investigations of the nuclear reactions excitation functions for ^{44}Sc production

^{44}Ca(p,n)^{44}Sc excitation functions **VS.** **^{45}Sc(p,2n)^{44}Ti excitation functions**

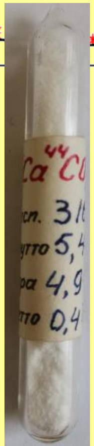
^{44}Sc commonly used generator

Our theoretical predictions





Proposal:



The powder ^{44}CCO$_3$ target

An especial target holder

Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

Investigations of the nuclear reactions excitation functions

Stacked foil method

1. Investigations of the monitor nuclear reactions excitation functions: Stainless steel foils, Ti foils, Fe-foils

Precise beam characteristics (I, E) measurements

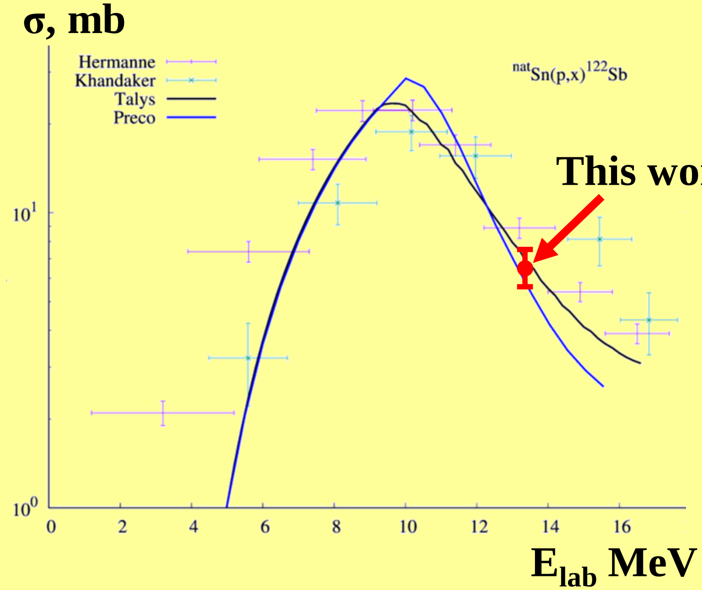
2. Investigation of the nuclear reactions excitation functions for the production of Sb Tin targets. Two stages:

a) Investigations of the nuclear reactions on natural tin: $^{nat}Sn(p,X)^{122}Sb$ and $^{nat}Sn(p,X)^{124}Sb$

б) Investigations of the nuclear reactions on highly enriched tin isotopes:
$^{117}Sn(p,n)117Sb$ и $^{119}Sn(p,n)^{119}Sb$

Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

2) experimental studies of the nuclear reactions on natural tin + theoretical formalism adapted for the nuclear systems of the medium mass nuclei



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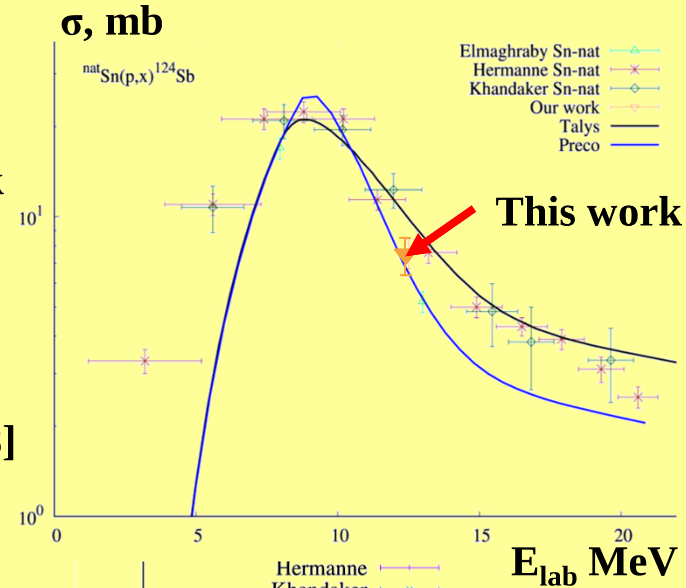
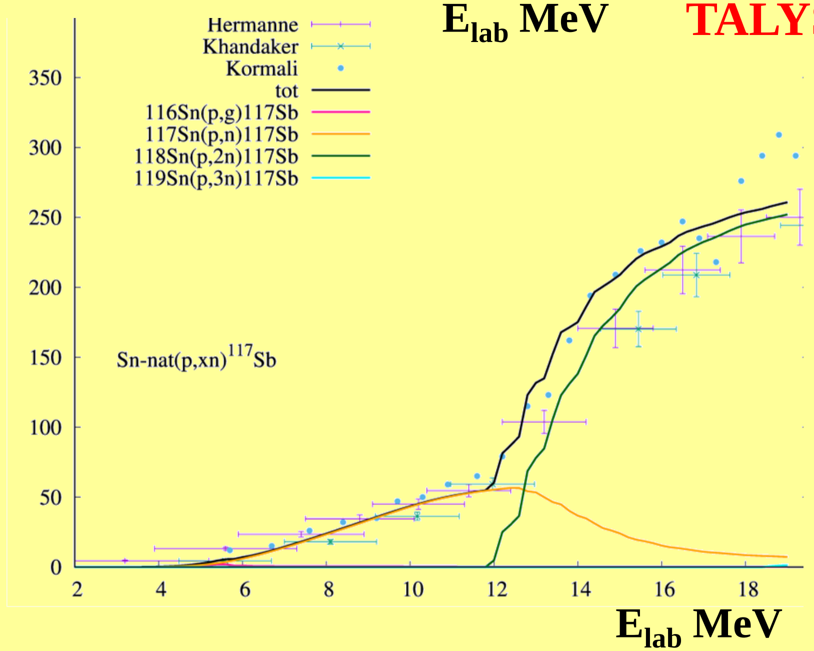


Theoretical models:

pre-equilibrium, equilibrium processes, evaporation mechanism.

PRECO
TALYS

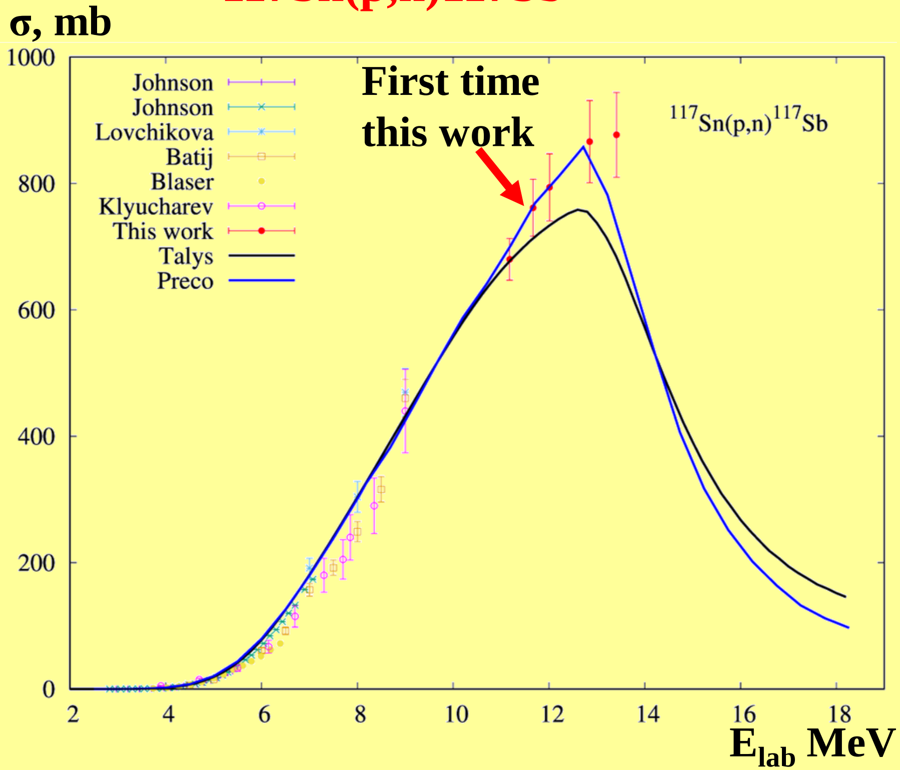
Analysis of proton reaction on nat-Tin isotopes with formation of ^{117}Sb in the exit channels

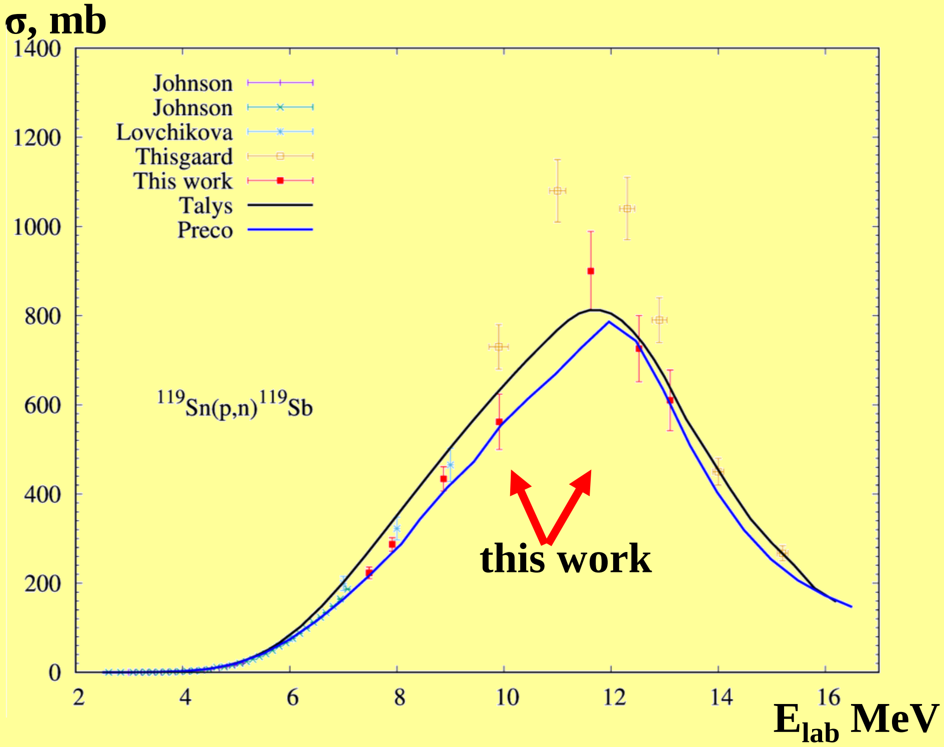


Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

б) Investigations of the nuclear reactions on highly enriched tin isotopes:

117Sn(p,n)117Sb **119Sn(p,n)119Sb**





New experimental data:

a) The peak area of the $^{119}Sn(p,n)^{119}Sb$ excitation function has been investigated from 7.5 MeV up to 13.0 MeV – 7 new points

b) The first time cross-sections for the reaction $^{117}Sn(p,n)^{117}Sb$ were obtained for energy region: from 11.0 MeV up to 13.3 Me - 5 new points

Conclusion

1) Novel radionuclides for therapy and diagnostics:

a) Auger-Electron emitters – target therapy
b) registration of satellite gamma quanta for dyagnostics

2) Modernized target system for radionuclide production

3) The studies if the nuclear reactions for the antimony radionuclide production

NEXT:

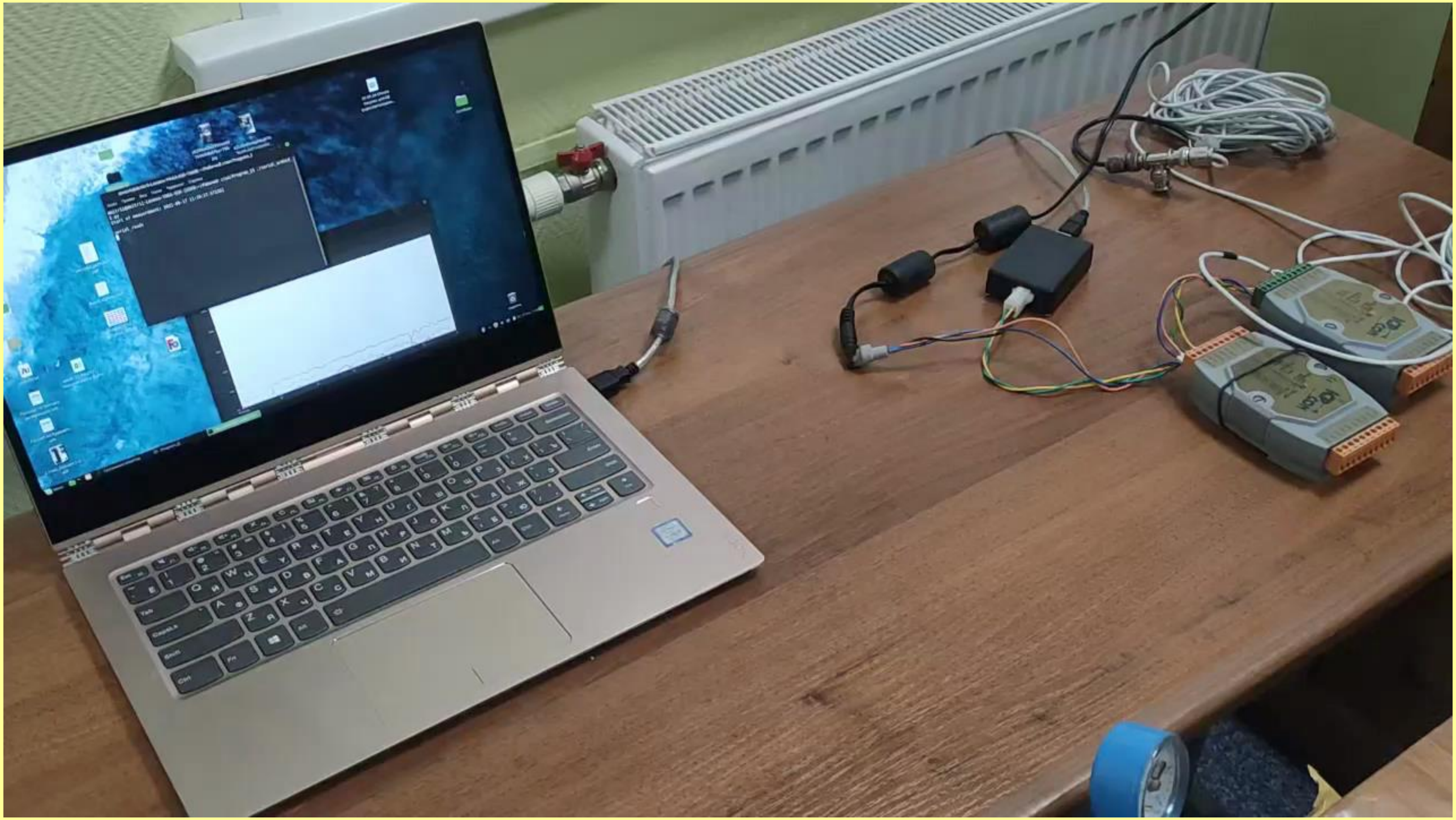
Continue of the nuclear reaction investigations in particular in the excitation function peak area

Studies of the radiation properties of new polymers using as radionuclide carrier

Medical and biological research

Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

Modernized Target unit



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BACK-UP SLIDES

The new methods in radionuclide diagnostic and therapy

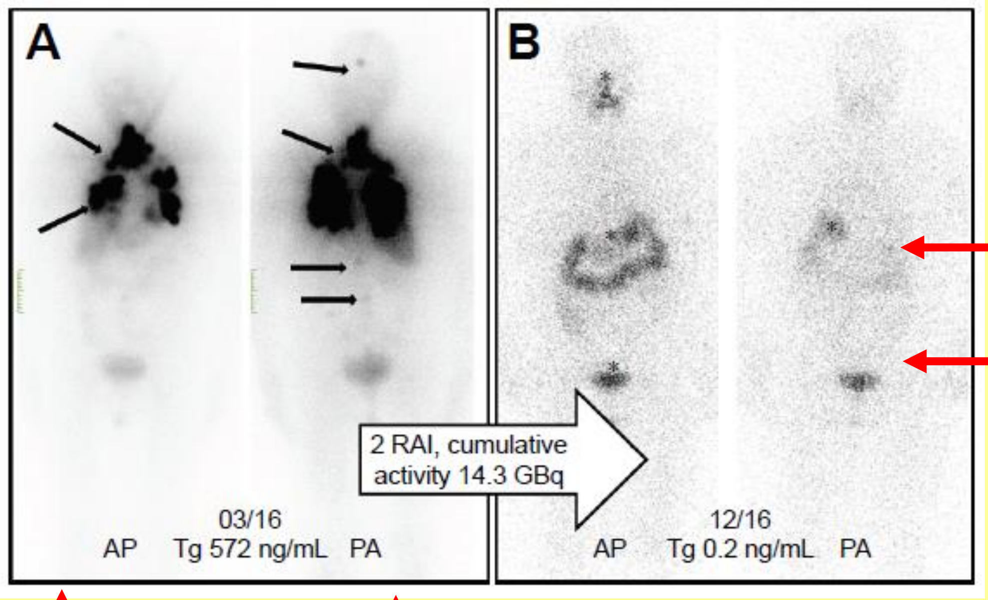
Theranostics: history

Radioiodine therapy: "the gold standard" in thyroid diseases

First radioiodine therapy with ^{131}I ($T_{1/2}$ – 8d) in patients with thyroid cancer was undertaken by Seidlin et al in 1946

Iodine Theranostics today: needed for thyroid cancer (TC) treatments

^{131}I combines the characteristics of a beta (90% of electrons, mean energy: 192 keV) and gamma (~81% of gammas, energy: 364.5 keV).



It can be visualized using a gamma camera or SPECT

After two administrations of radioiodine therapy (cumulative activity: 14.3 GBq), the patient was in complete remission

[5]

Initial ^{131}I planar images with metastatic TC (lung, bone, intracranial soft-tissue metastases)

The new methods in radionuclide diagnostic and therapy

Theranostics today – new radionuclides and methods

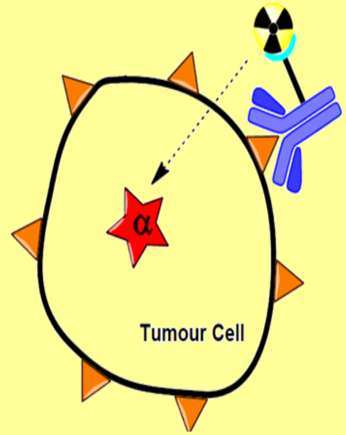
Theranostics =

Diagnostic
PET, SPECT
MRI, Optical methods

[7]

+

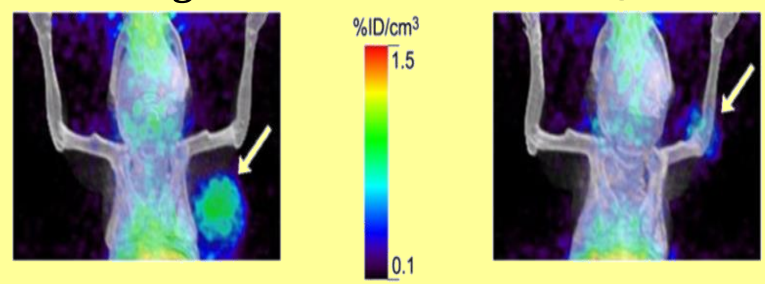
Target therapy:



Example: 64Cu-DOTA-siRNA nanoparticles

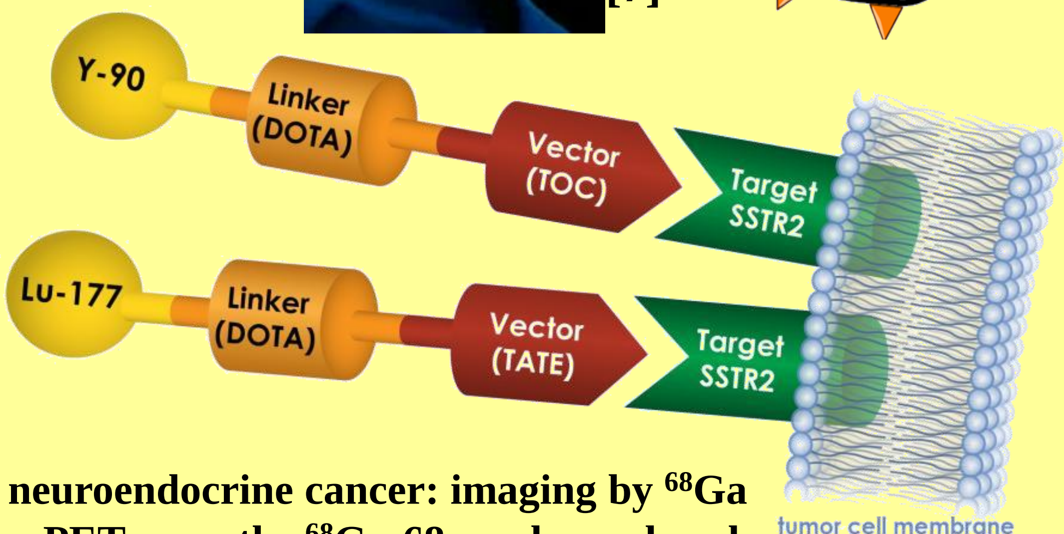
nontargeted

targeted



Micro (animal)-PET/CT image tumor (arrow) 1 day

[6]

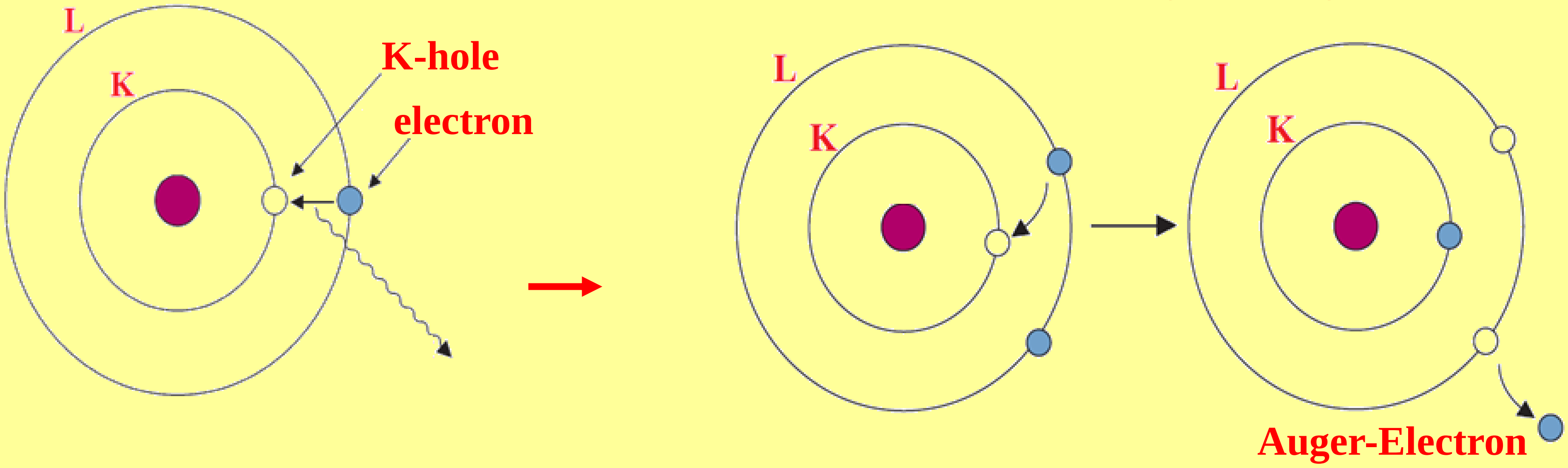


For neuroendocrine cancer: imaging by ^{68}Ga and a PET scan, the ^{68}Ga-68 can be replaced with another radionuclide: ^{177}Lu or ^{90}Y), that can target and kill tumor cells

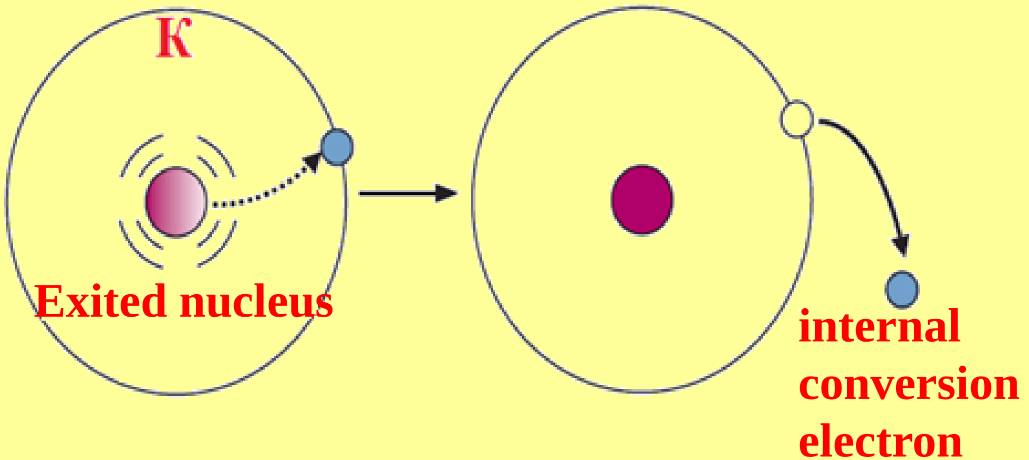
https://uihc.org/health-topics/what-theranostics

The new methods in radionuclide diagnostic and therapy

The origin of Auger-Electron



The origin of internal conversion electrons (IC)



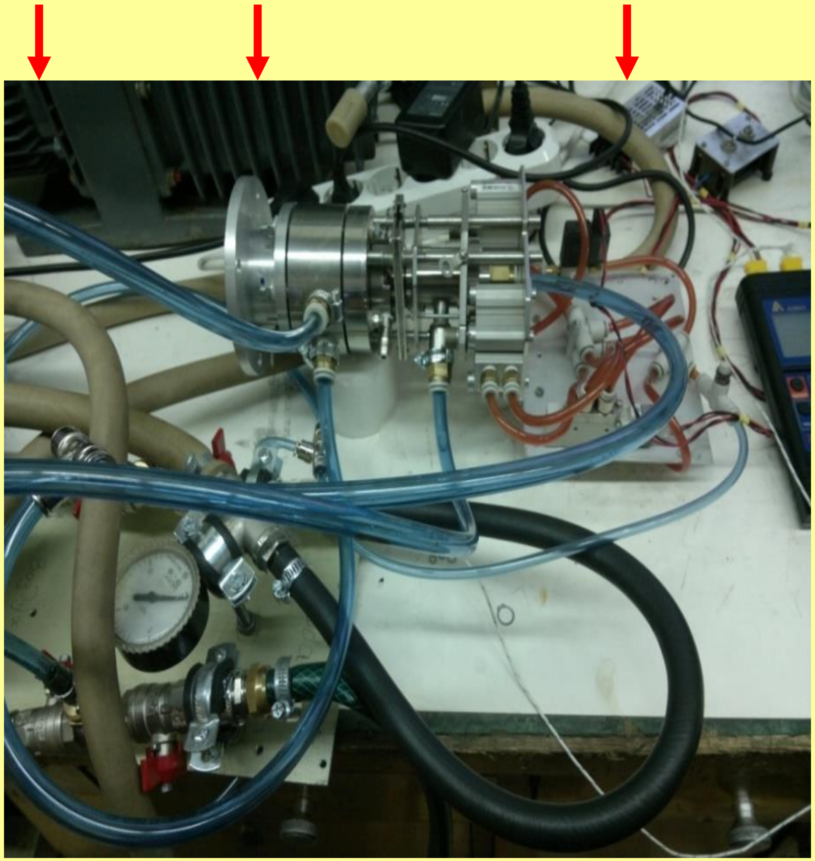
The new methods in radionuclide diagnostic and therapy

Auger and Internal conversion electron emitters:

Nuclide	Energy (keV)		^{-}e (on 100 mother nuclei)		Associated γ	T1/2	Daughter nuclide
	Auger ^{-}e	IC	Auger ^{-}e	IC			
^{55}Fe	0.61(L) 5.19 (K)	no	139.9 60.1	no	5.9 (0.16)	2.744 y	^{55}Mn (Stable)
^{67}Ga	0.99 (L) 7.53 (K)	83.65 (K) 92.1 (L)	168.3 60.7	29.1 3.57	8.62 (0.17) 8.64 (0.33) 93.3 (0.39) 184.57 (0.21) 300.21 (0.17)	3.26 d	^{67}Zn (Stable)
^{111}In	2.72 (L) 19.30 (K)	144.57 (K)	100.4 15.5	8.07	171.28 (0.91) 245.35 (0.94)	2.80 d	^{111}Cd (Stable)
^{123}I	3.19 (L) 22.70 (K)	127.16 (K)	95.1 12.4	13.61	27.20 (0.25) 27.47 (0.46) **158.97 (0.83)**	13.22 h	^{123}Te (> 9.2E+16 y)
^{195m}Pt	7.24 (L)	17.01 (L) 20.5 (K) 115.62 (L)	140	69 65 61	65.12(0.22) 66.83(0.37) 98.90(0.11)	4.010 d	^{195}Pt (Stable)
^{117}Sb	2.95 (L) 21.0 (K)	129.36 (K) 154.10 (L)	94.5 13.4	11.57 1.46	25.04 (0.23) 25.27 (0.44) **158.56(0.85)**	2.8 h	^{117}Sn (Stable)
^{119}Sb	2.95 (L) 21.0 (K)	19.40 (L) 22.99 (M)	147.1 11.9	67.5 13.3	3.44 (0.12) 23.87 (0.16) 25.04 (0.21) 25.27 (0.39)	38.19 h	^{119}Sn (Stable)

Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

New target unit (solid targets), irradiation of the targets by high-intensity charged particle beams for the production of diagnostic and therapeutic radionuclides



1. Helium chamber

2. Innovative small diameter nozzle system (jet cooling of the target) for the high-effective cooling

3. Automatic target moving

4. The system for the control of the target heating

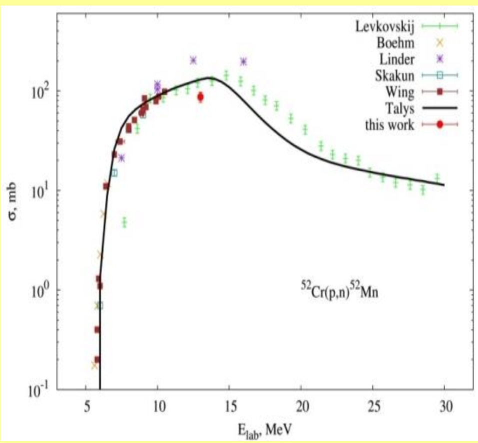
Central Research Institute of Structural Materials "Prometey“, Saint-Petersburg State University, Institute for Analytical Instrumentation

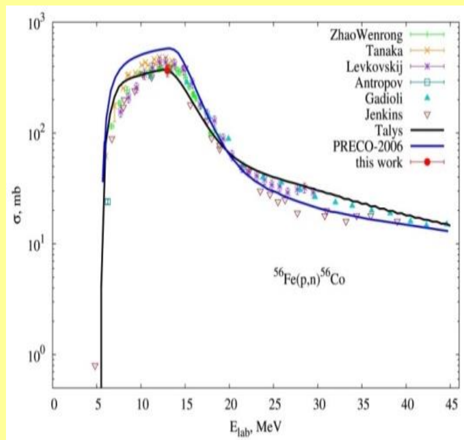
Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

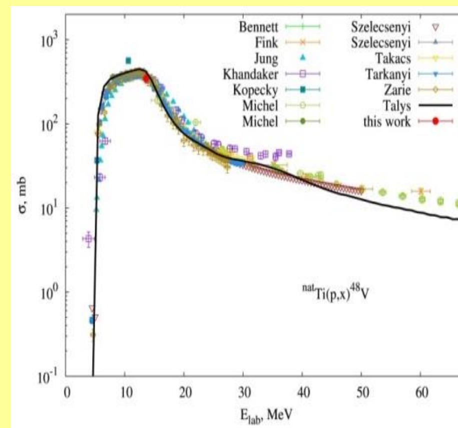
Investigations of the nuclear reactions excitation functions

Stacked foil method

1. Investigations of the monitor nuclear reactions excitation functions: Stainless steel foils, Ti foils, Fe-foil







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Precise beam Characteristics (I, E) measurements

2. Investigation of the nuclear reactions excitation functions for the production of Sb
Tin targets. Two stages:

а) Investigations of the nuclear reactions on natural tin: ^{nat}Sn(p,X)^{122}Sb и ^{nat}Sn(p,X)^{124}Sb

б) Investigations of the nuclear reactions on highly enriched tin isotopes:
^{117}Sn(p,n)117Sb и ^{119}Sn(p,n)^{119}Sb