«New radionuclides for personalized medicine (theranostics)»

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Saint-Petersburg State University

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Outline

Basis of the radionuclide diagnostic and therapy

The new methods in radionuclide 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 disease.

Quick detect → effectively treat diseases → saving time and money → saving Life

How to reach

+ radionuclides

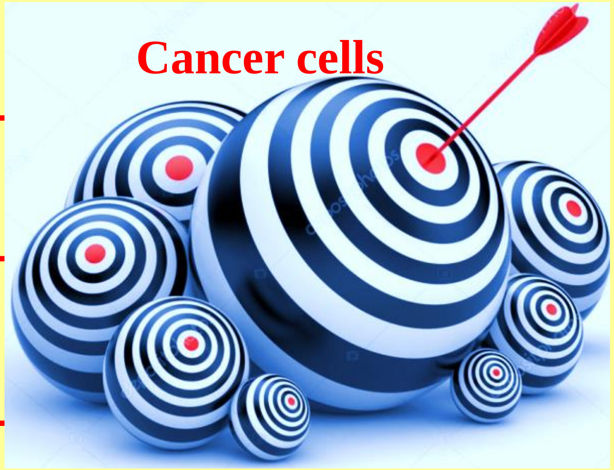
radionuclides distribution in the human body [1]

Radiation detectors

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

Basis of the radionuclide diagnostic and therapy

Radionuclide targeted therapy - RTT



Aims

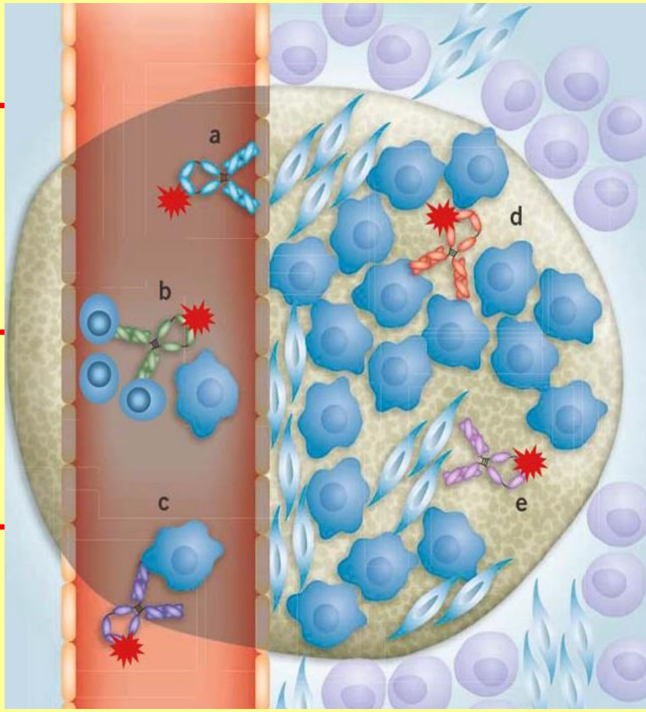
The ability to increase intracellar incorporation of the radiopharmaceutical without any toxicity

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



[2]

Basis of the radionuclide diagnostic and therapy

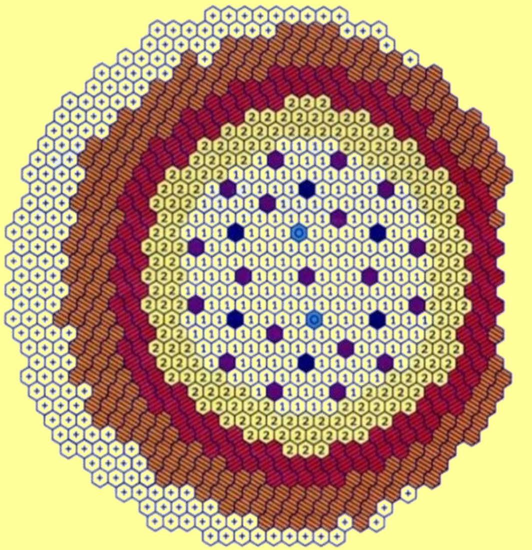
Radionuclide production

Cyclotrons

Nuclear reactions with:
^{1}p, d, α

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

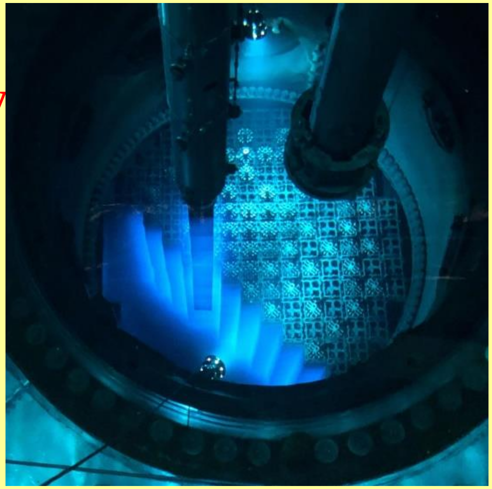
Nuclear reactor



Nuclear reactions with:
^{1}n

Fission fragments,

Neutron capture → decay



Basis of the radionuclide diagnostic and therapy

Diagnostics

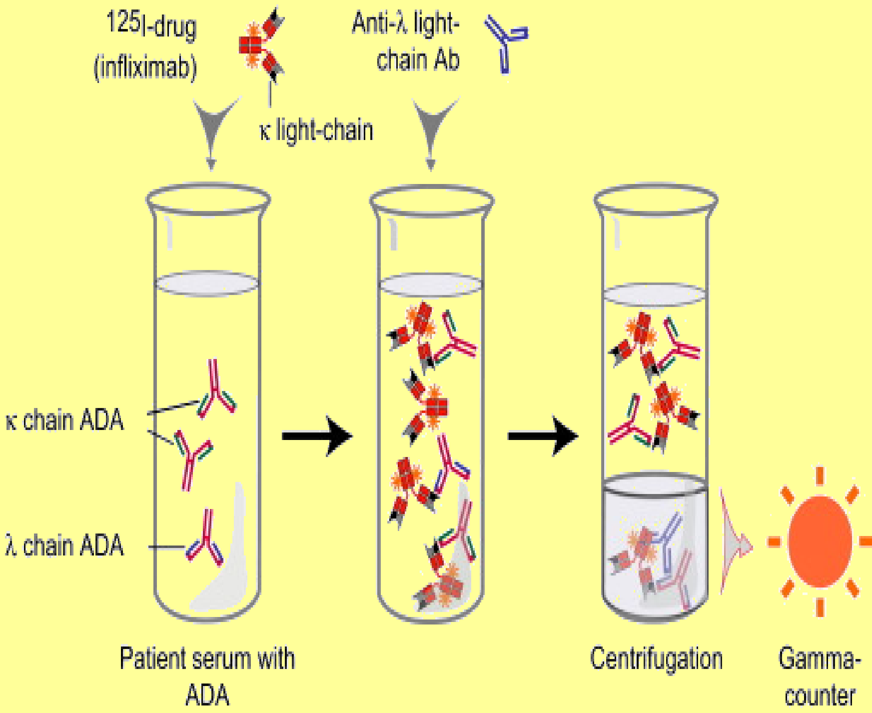
The following types of radionuclide diagnostics are used in clinical practice:

Imaging – visualization of the some organs by using radionuclides;

Measuring the accumulation of a radiopharmaceutical in the body;

A radioimmunoassay: antigens-antibodies

Rosalyn Sussman Yalow, Solomon Aaron Berson
the Nobel Prize for Medicine in 1977



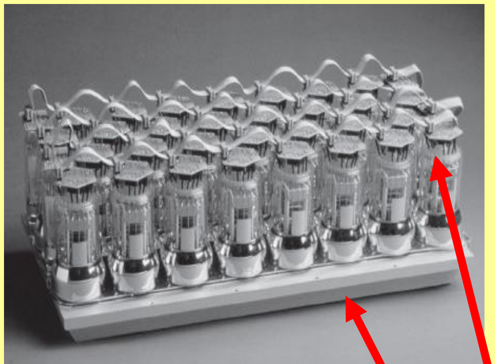
Basis of the radionuclide diagnostic and therapy

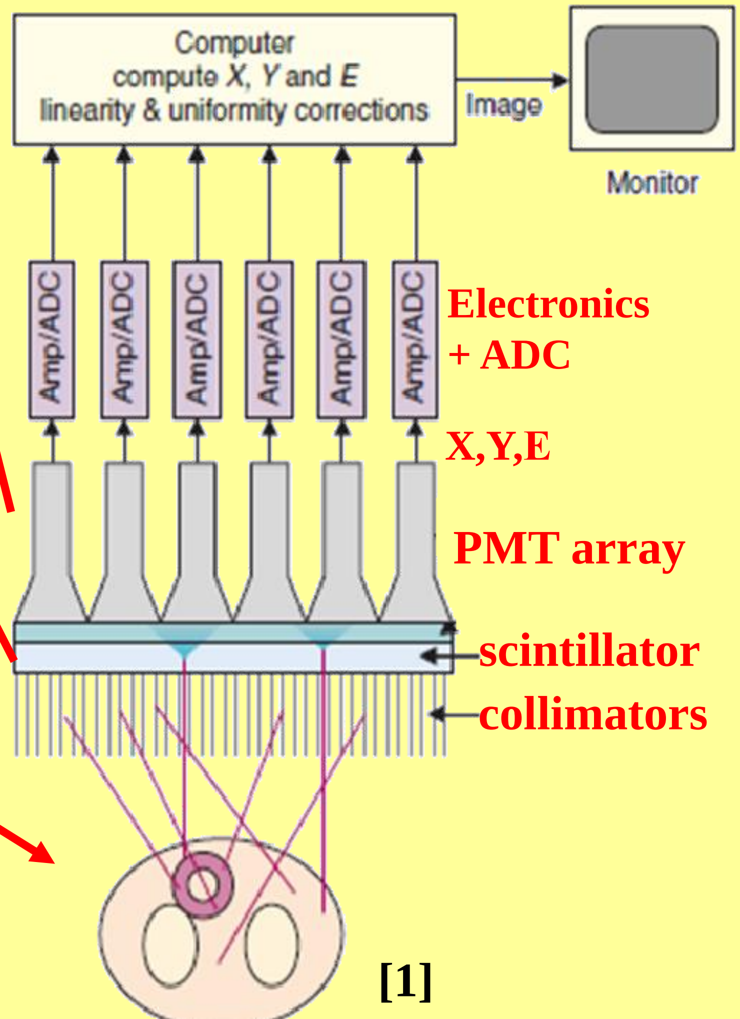
Diagnostics

Single-photon emission computed tomography (SPECT)

Gamma radionuclides → collimators+scintilatttor detector (nuclide image) → CT (3D image)

(Hal Oscar Anger)





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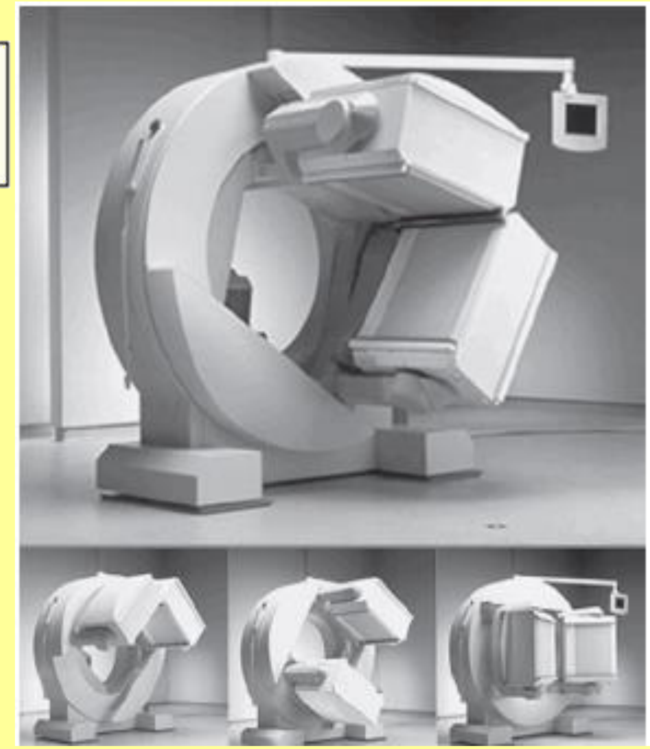


[1]

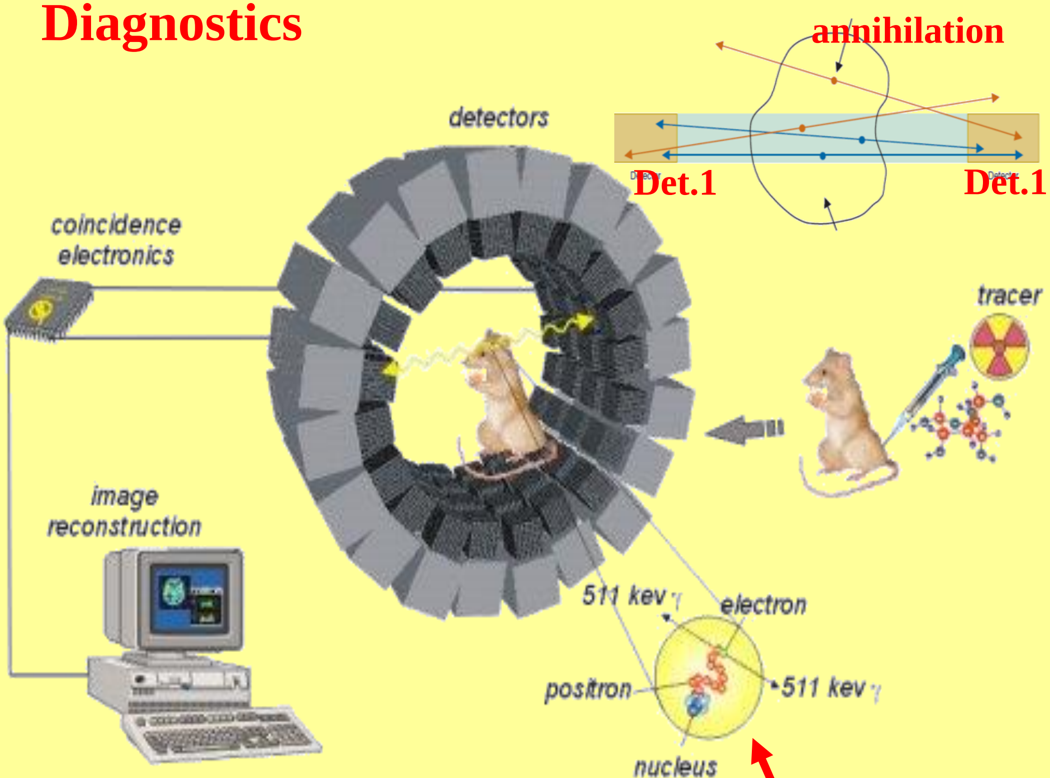
^{123}I → 792 мин

^{99m}Tc → 360 мин

Basis of the radionuclide diagnostic and therapy

Positron emission tomography (PET)

Diagnostics

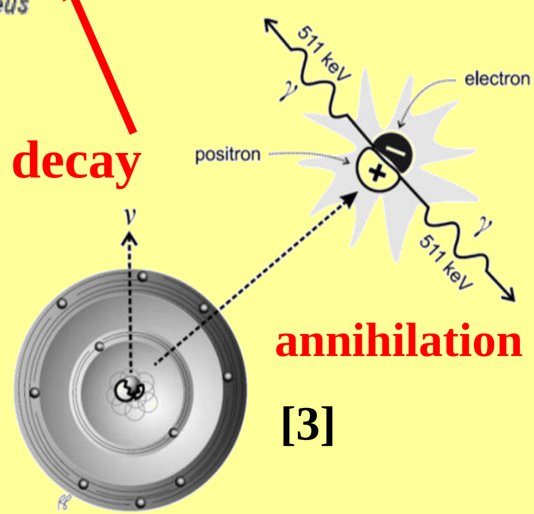


Positron radionuclides → annihilation two gamma quants registration (Scintillator counters in coincidence) → Image reconstruction

On-line visualization the biological processes in human body + CT (3D image).

^{68}Ga	^{11}C	^{18}F
↓	↓	↓
67 мин	20,4 мин	**109,8 мин**
↓		

β⁺ decay



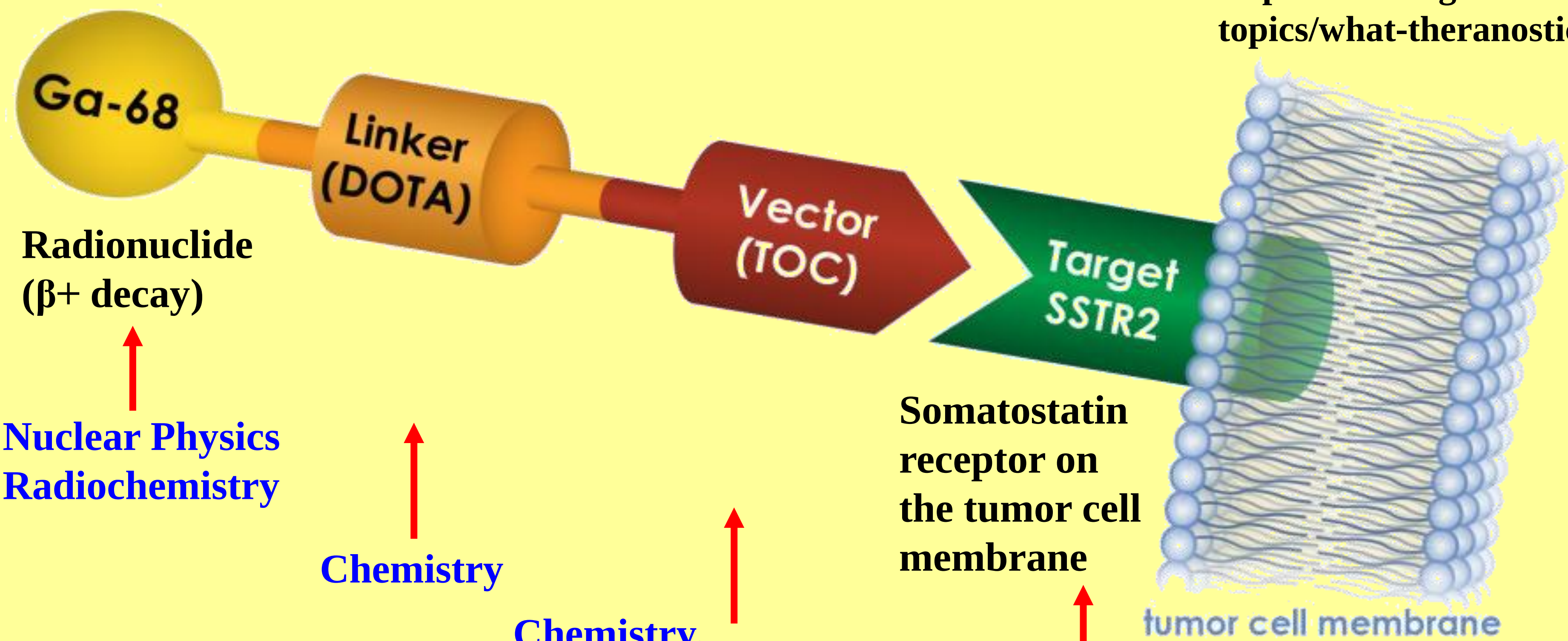
Basis of the radionuclide diagnostic and therapy

Positron emission tomography (PET)

Diagnostics

Tumor visualization by the PET

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



Radionuclide (β+ decay)

Nuclear Physics
Radiochemistry

Chemistry

Chemistry, Radiation-material science

Somatostatin receptor on the tumor cell membrane

Biology, Medicine

Basis of the radionuclide diagnostic and therapy

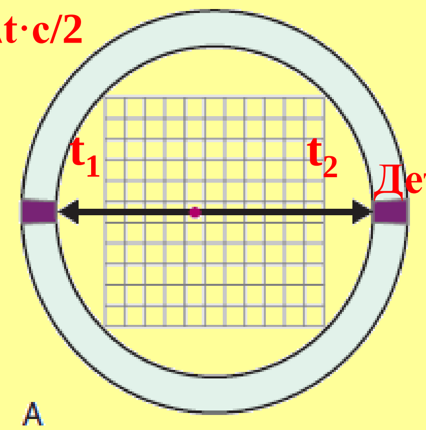
Diagnostics

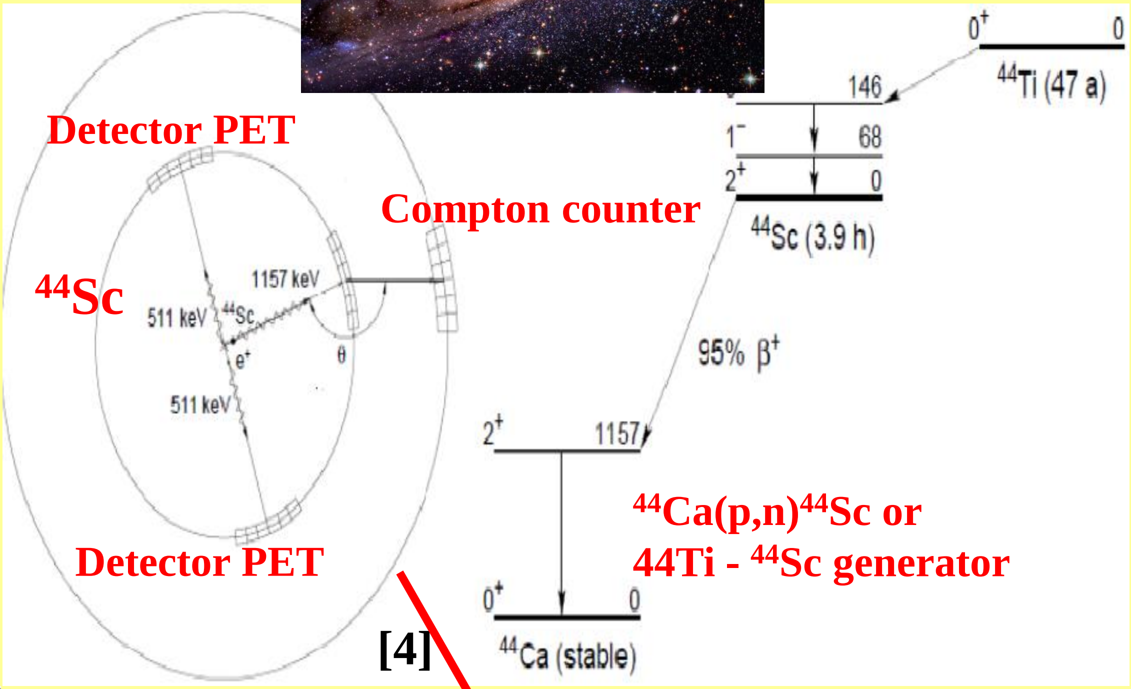
Advanced detector technologies for the PET

Gamma-PET method

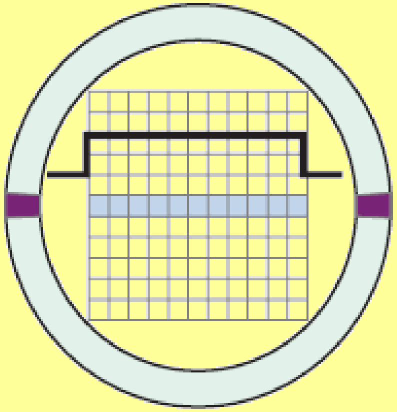
PET + Time of Flight (TOF) method

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

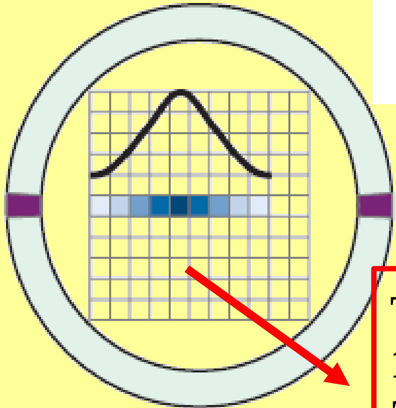




$^{44}Ca(p,n)^{44}Sc$ or
44Ti - ^{44}Sc generator



Standard PET
Position resolution

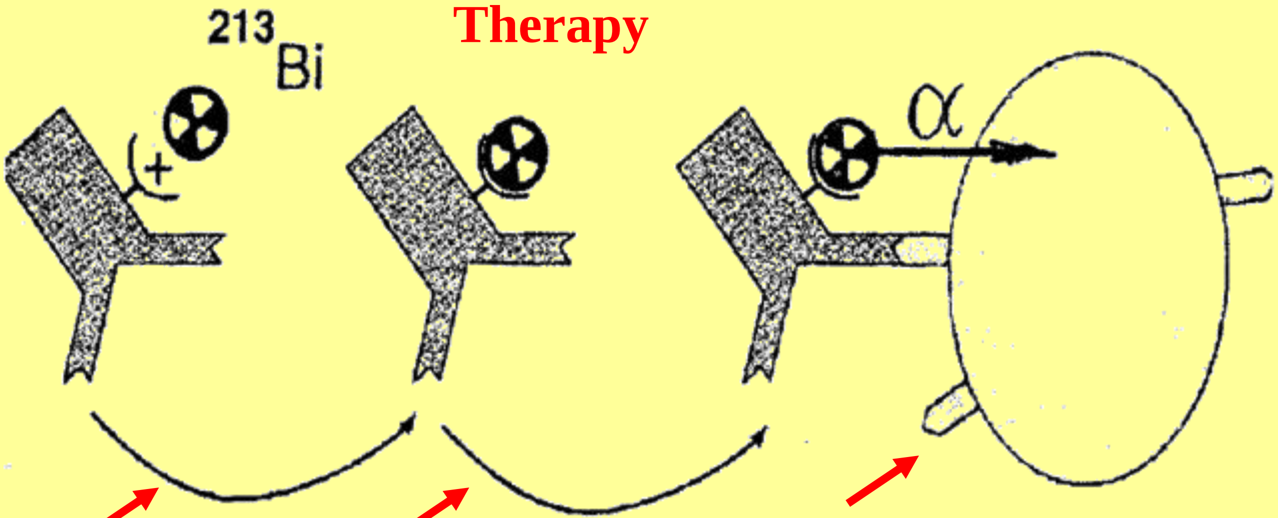


PET+TOF
Position resolution

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

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!

The new methods in radionuclide diagnostic and 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

Theranostic approach: couples diagnostic imaging and therapy using the same molecule

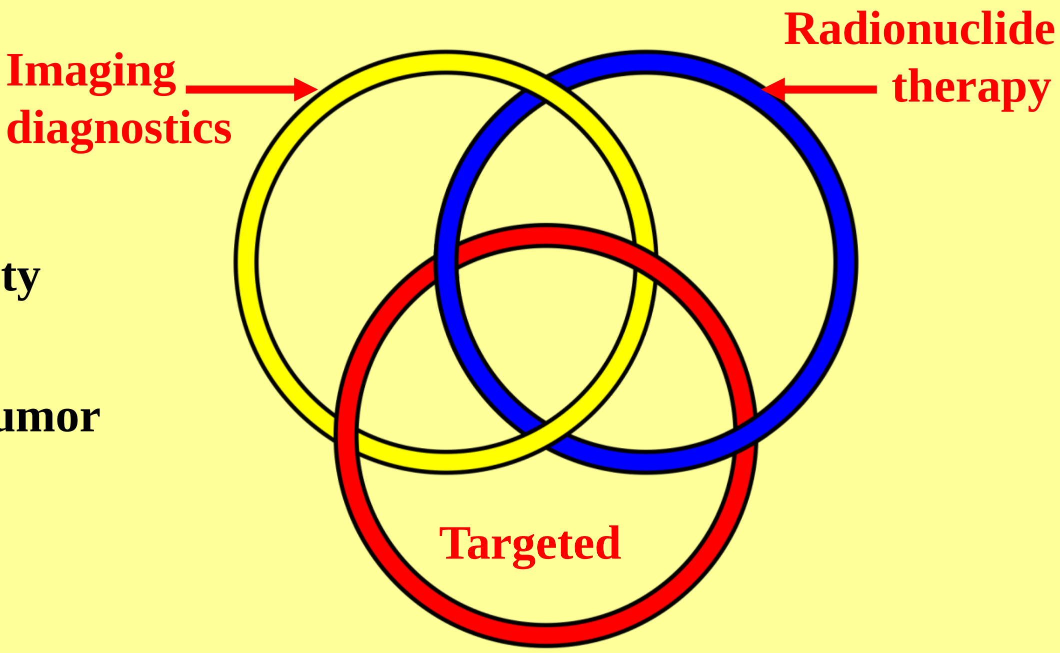
Combine both therapeutic and diagnostic capabilities in one dose.

Theranostics – goals:

Increase the tumor visualization quality

Increase the efficiency of the radiopharmaceutical delivery to the tumor

Control of the therapy processes



Minimum side effects at treatment and diagnostic of the cancer illness

The new methods in radionuclide diagnostic and therapy

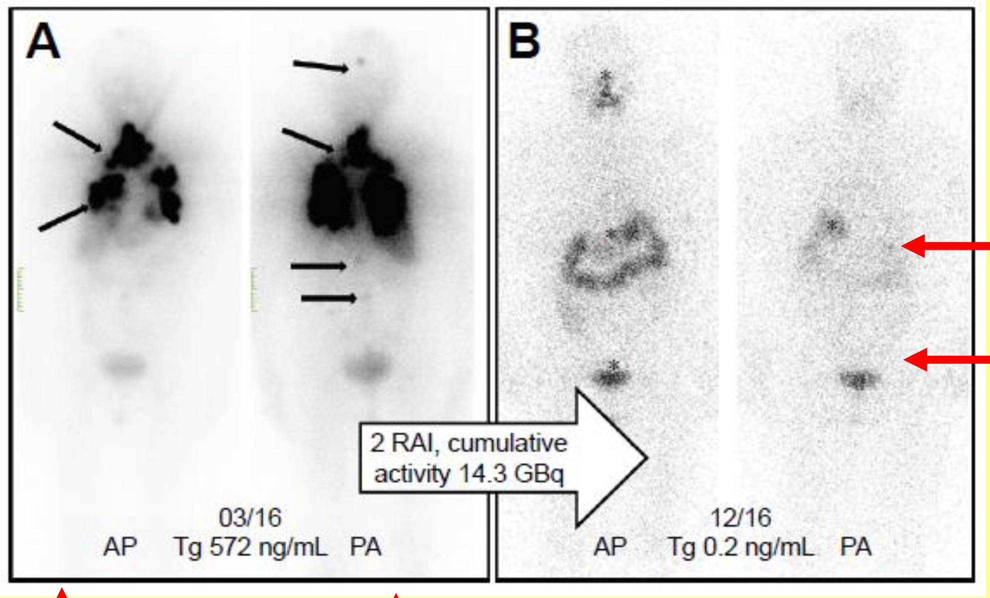
Theranostics: history

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

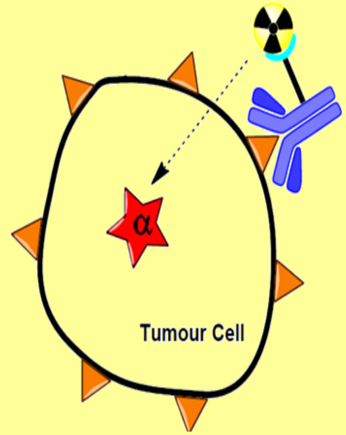
Theranostics today – new radionuclides and methods

Theranostics = **Diagnostic** + **Target therapy:**

Diagnostic
PET, SPECT
MRI, Optical methods

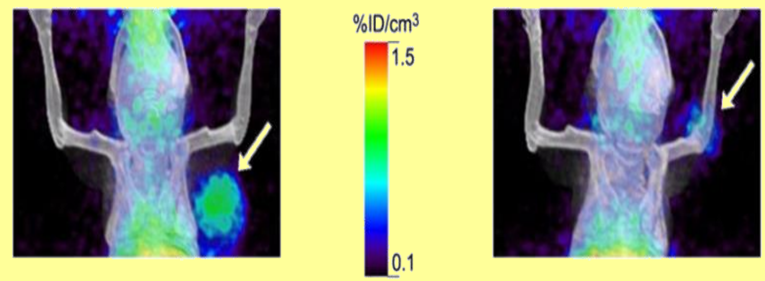
[7]

Target therapy:



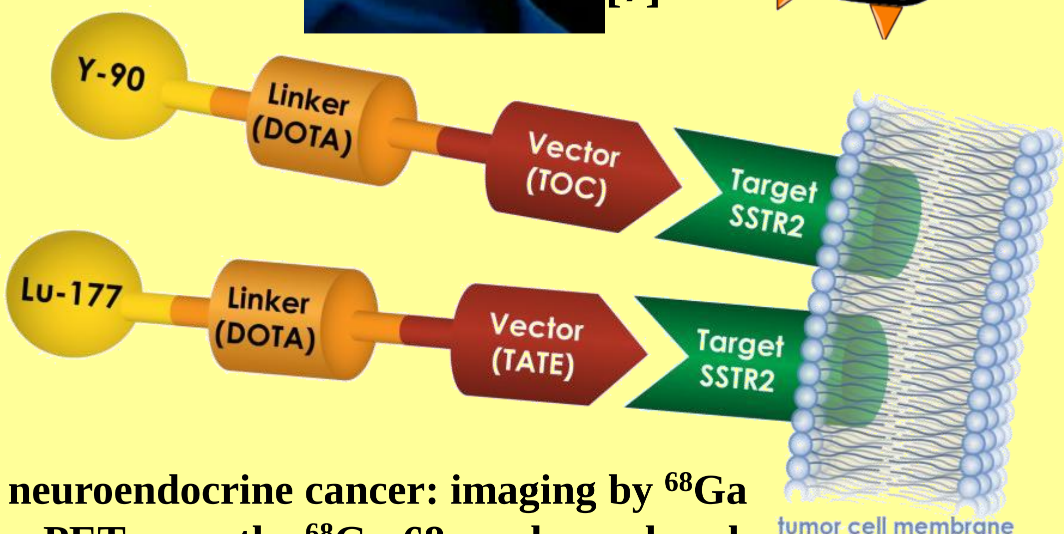
Example: 64Cu-DOTA-siRNA nanoparticles

nontargeted   targeted



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

[6]

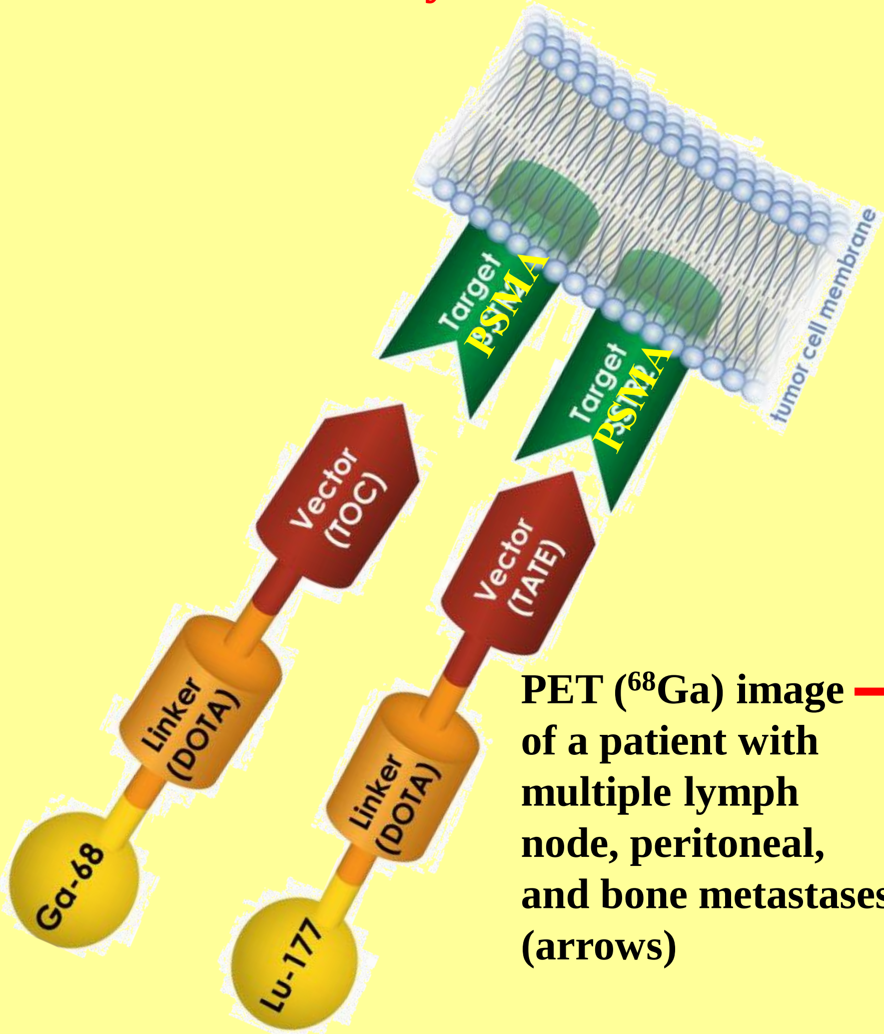


For neuroendocrine cancer: imaging by ^{68}Ga and a PET scan, the ^{68}Ga-68 can be replaced with another radionuclide: ^{177}Lu or ^{90}Y), that can target and kill tumor cells

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

The new methods in radionuclide diagnostic and therapy

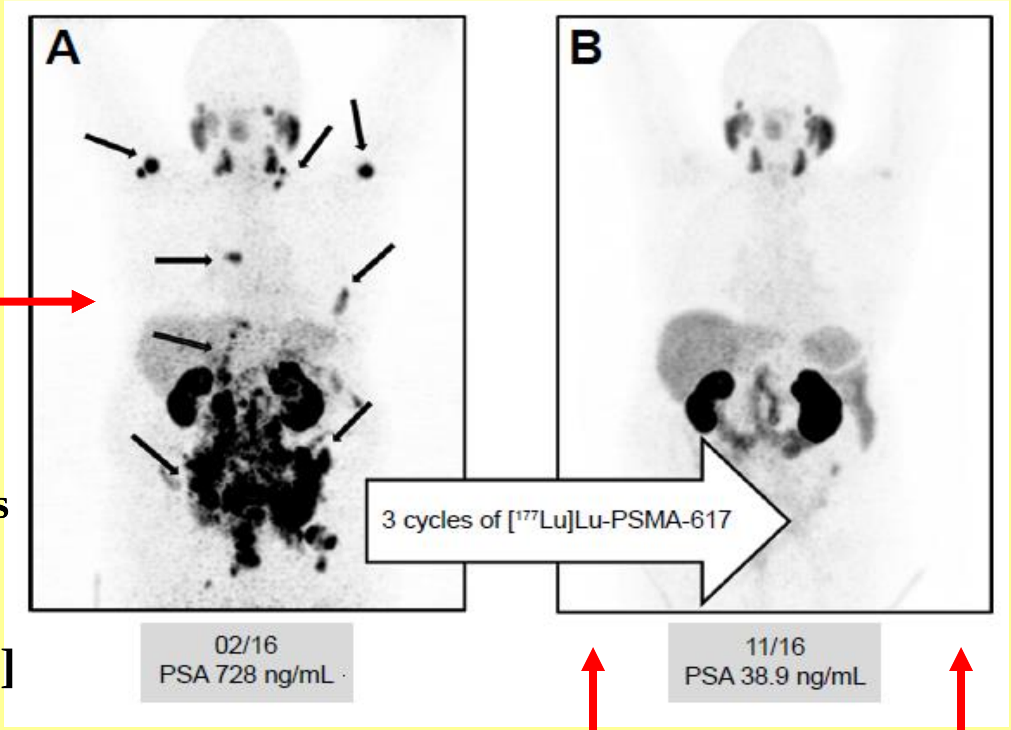
Theranostics today – novel radionuclides



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)



[5]

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

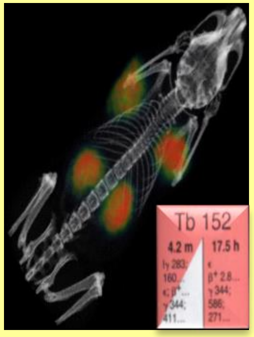
The new methods in radionuclide diagnostic and therapy

Theranostics today – novel radionuclides

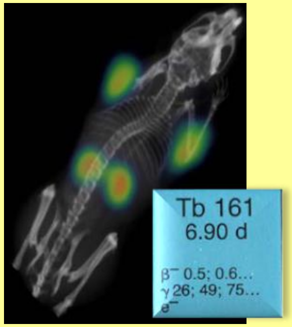
Terbium: Swiss Army Knife of Nuclear Medicine

^{149}Tb-therapy

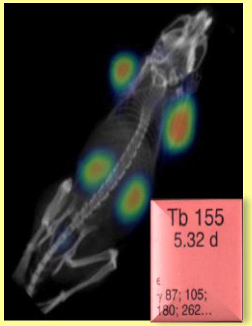
^{152}Tb-PET



^{161}Tb-therapy & SPECT



^{155}Tb-SPECT



Müller et al., JNM 2012

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

The new methods in radionuclide 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 have micron and submicron range and higher transfer energy, which increases the possibility of the cancer cells killing by the double breaking DNA. (Ionization in a volume of several cubic nanometers around the decay point)

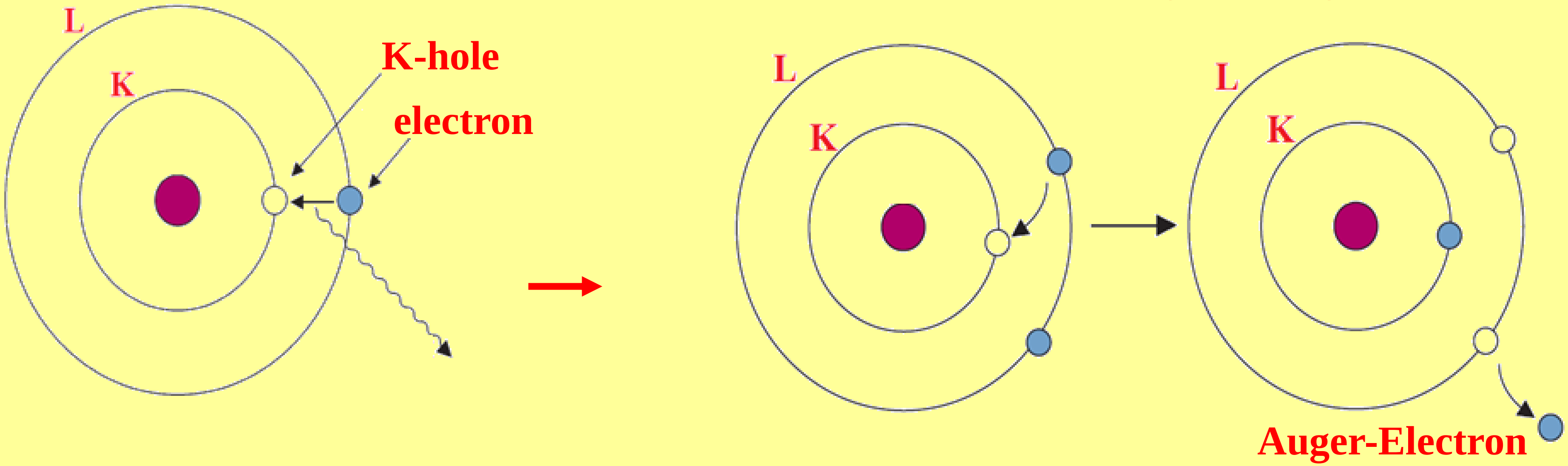
For Theranostic was proposed:

Radioisotope: ^{119}Sb (therapy) + ^{117}Sb (diagnostics, its gamma is suitable for the SPECT)

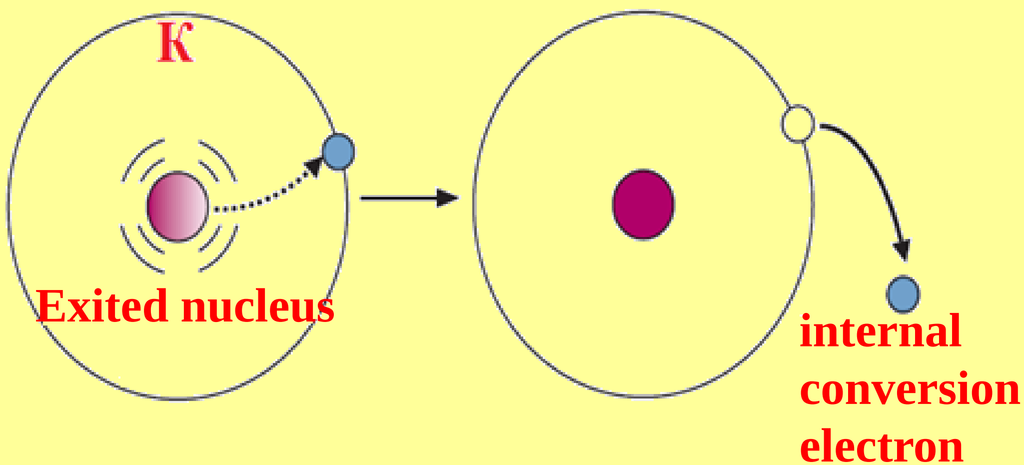
THERAPY + DIAGNOSTICS

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 Electron Emitting Radionuclides for the Therapy (requirements):

A) Number of the emitting electrons

B) Associated with this decay gamma and X-rays

C) Half -life time

D) Suitable "chemistry" for the radiopharmaceutical production

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

OUR Project:

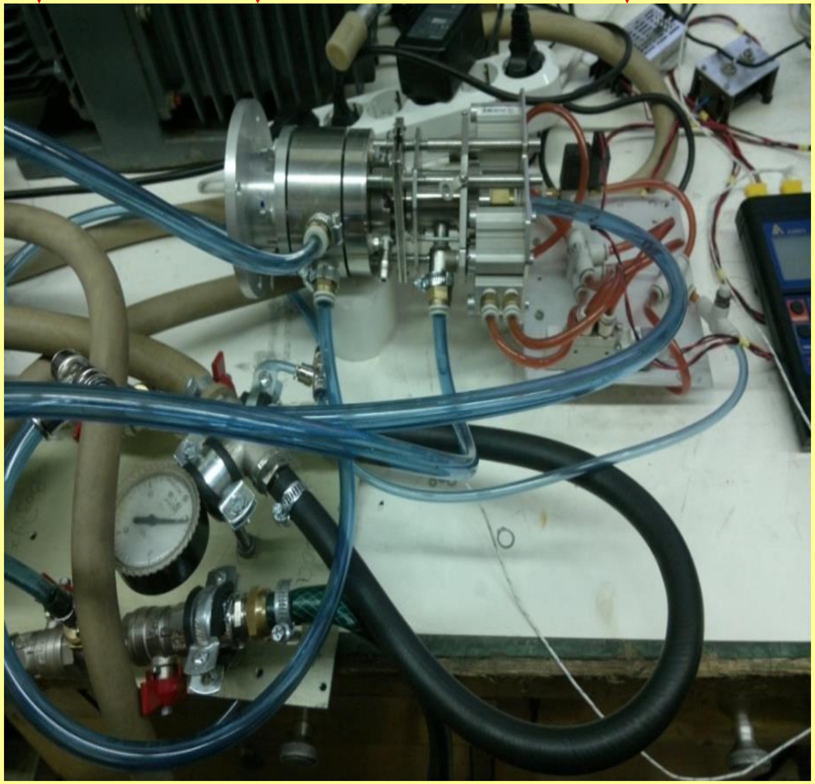
“The new radiopharmaceuticals based on biologically active synthetic polymers and Auger electron emitters for diagnostics and therapy of the oncological diseases”

COLLABORATION:

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

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

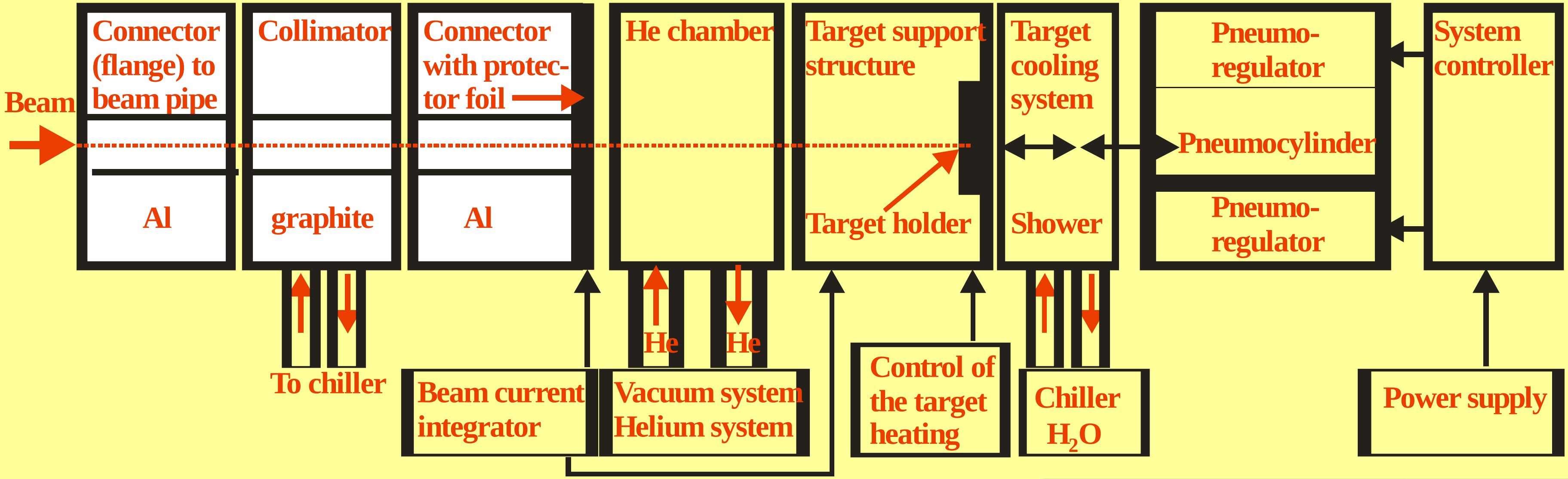


1. **Helium chamber**
2. **Innovative small diameter nozzle system (jet cooling of the target) for the high-effective cooling**
3. **Automatic target moving**
4. **The system for the control of the target heating**

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

Target system



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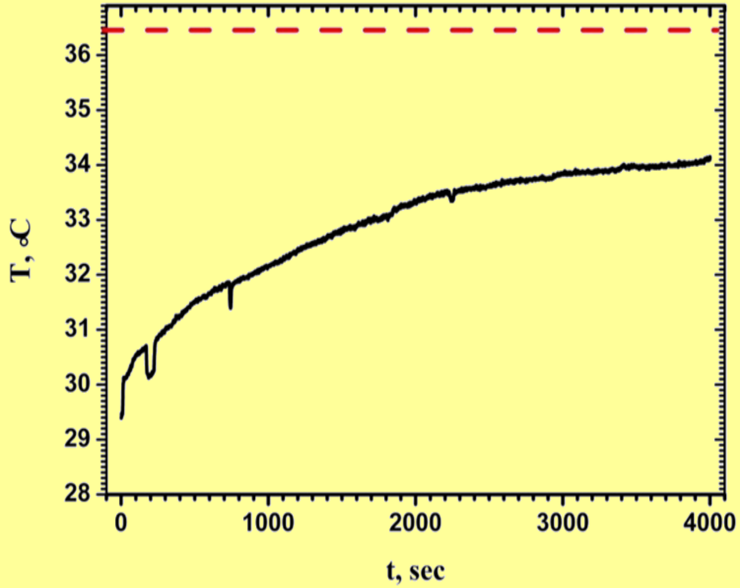


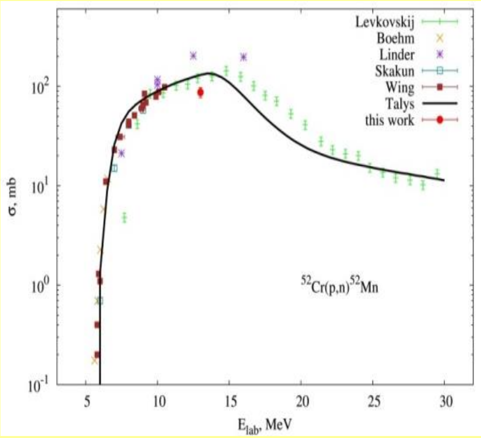
Power density up to 600 W/cm²
minimum water consumption
On-line monitoring of the target heating
Beam current measurements (at 3 point)

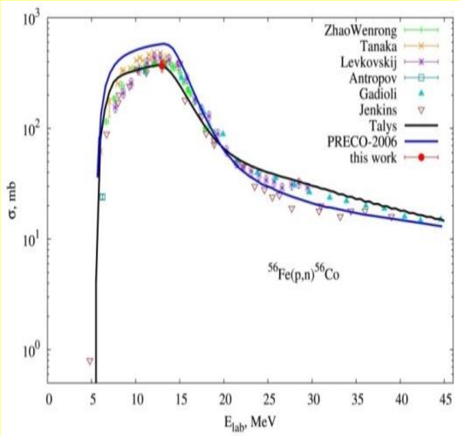
Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

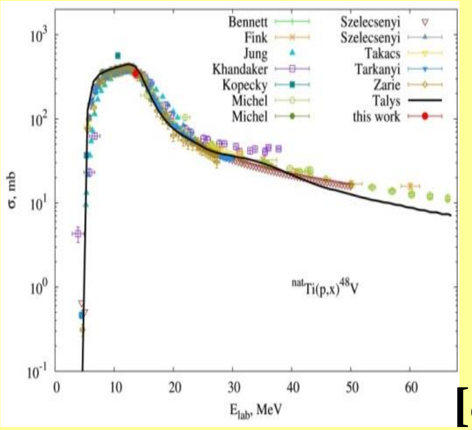
Investigations of the nuclear reactions excitation functions

Stacked foil method

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







[8]

Precise beam Characteristics (I, E) measurements

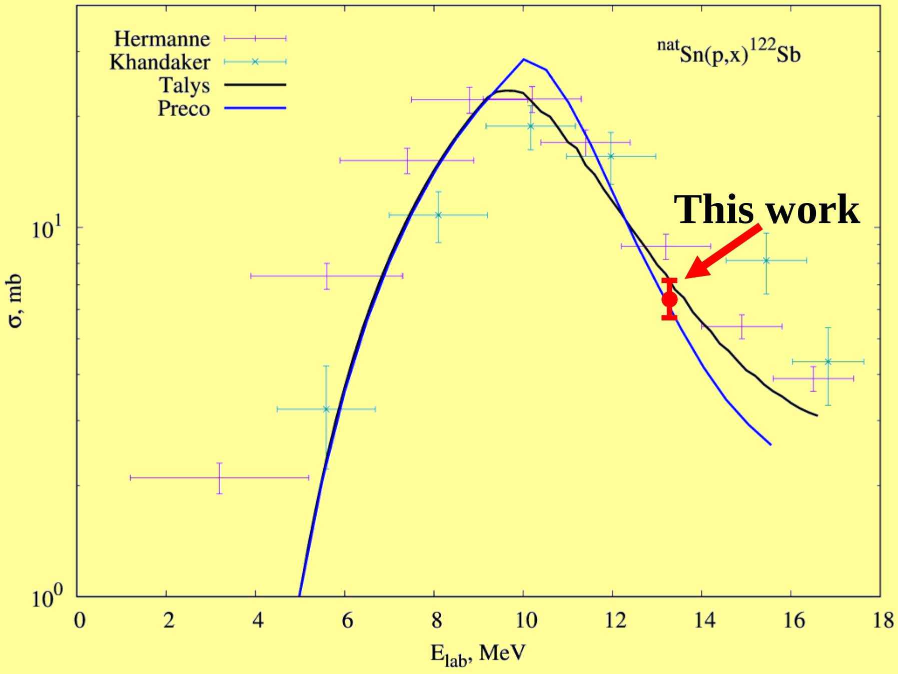
2. Investigation of the nuclear reactions excitation functions for the production of Sb
Tin targets. Two stages:

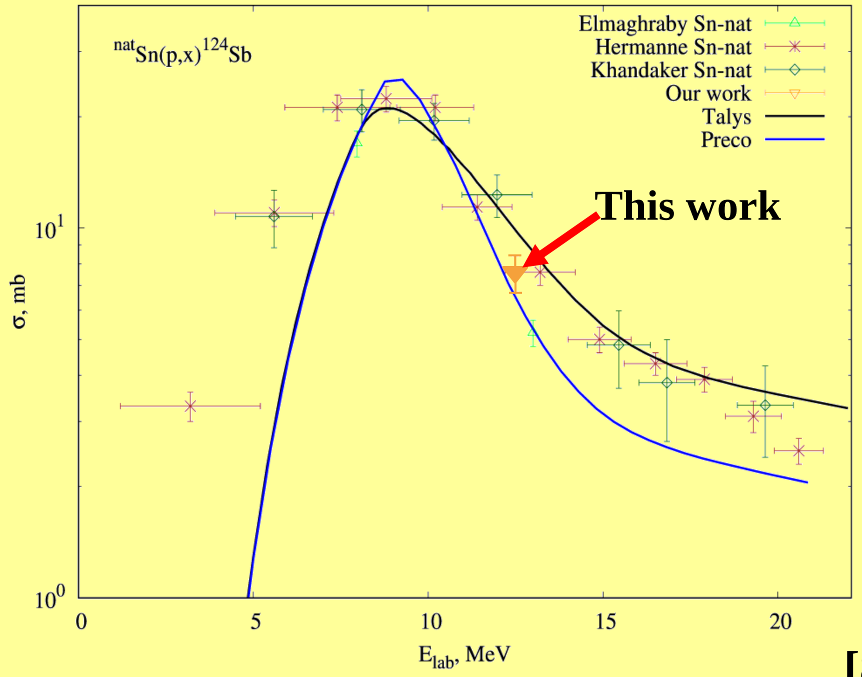
а) Investigations of the nuclear reactions on natural tin: ^{nat}Sn(p,X)^{122}Sb и ^{nat}Sn(p,X)^{124}Sb

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

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

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





[8]

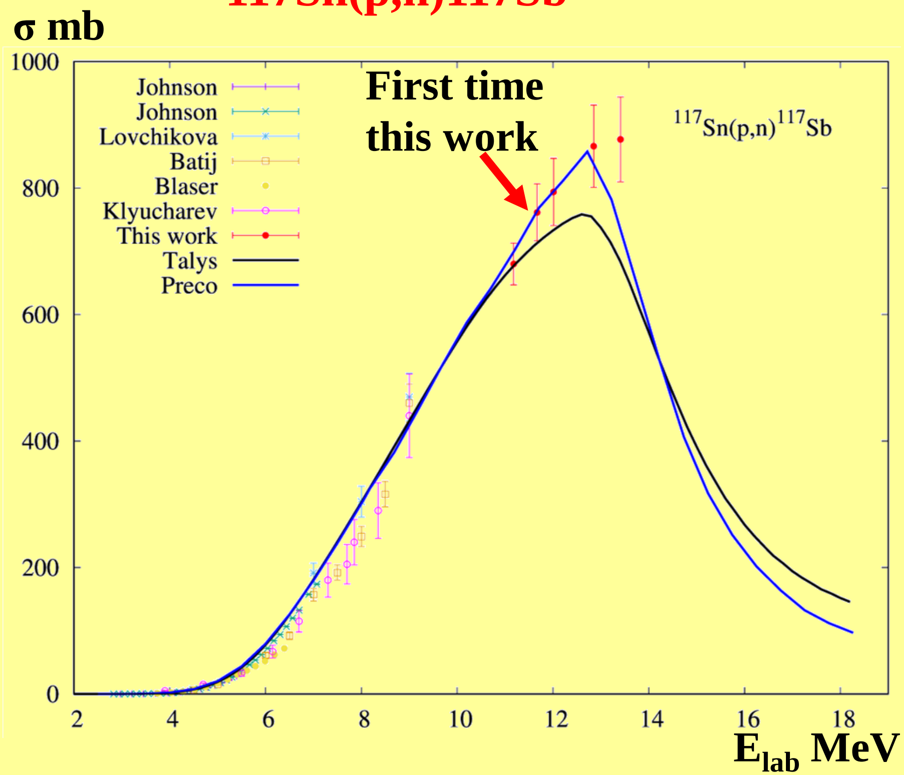
Theoretical models: pre-equilibrium, equilibrium processes, evaporation mechanism.

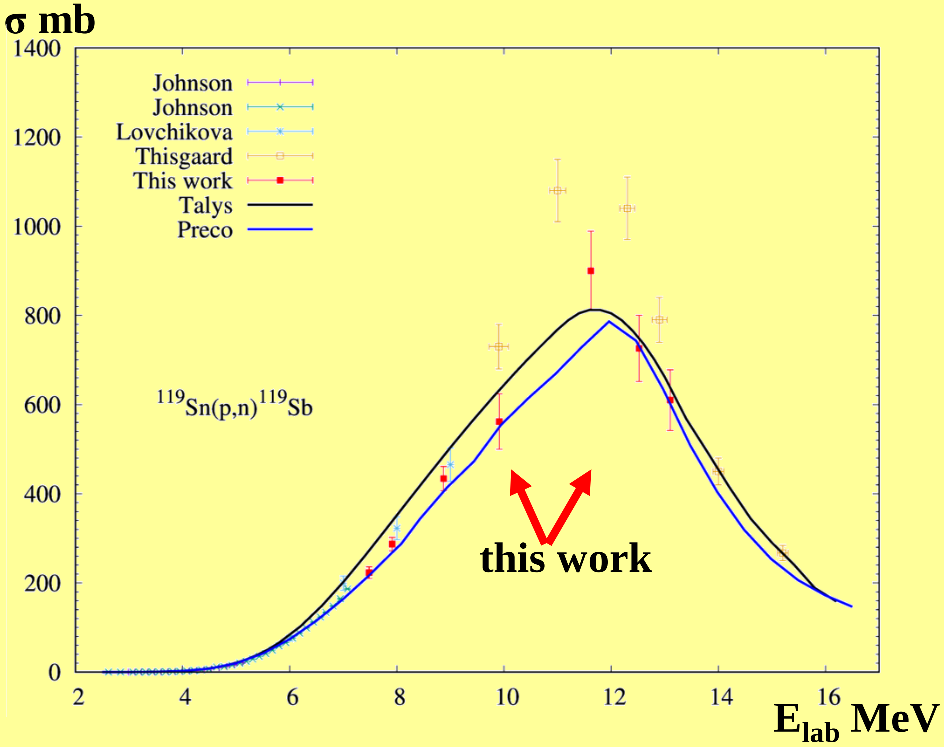
PRECO
TALYS

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

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

New Target system

Conclusion

1) Novel radionuclides for therapy and diagnostics:

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

2) New target system for radionuclide production

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

NEXT:

Synthesis and investigations of the biologically active polymers
Medical and biological research

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