«New radionuclides for personalized medicine (theranostics)»


RFBR grant № 20-02-00295

Saint-Petersburg State University

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
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 intracellular incorporation of the radiopharmaceutical without any toxicity

**One of the main challenges**

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

**Radionuclide production**

**Cyclotrons**

Nuclear reactions with: $^1p$, $d$, $\alpha$

Main channel

**Target**($^1p$, $^1n$)**Product**

**Nuclear reactor**

Nuclear reactions with: $^1n$

Fission fragments,

Neutron capture $\rightarrow$ 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 + scintillator detector (nuclide image) → CT (3D image) (Hal Oscar Anger)
Basis of the radionuclide diagnostic and therapy

Positron emission tomography (PET)

Diagnostics

Positron radionuclides $\rightarrow$ annihilation
two gamma quants registration
(Scintillator counters in coincidence) $\rightarrow$
Image reconstruction

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

- $^{68}$Ga
- $^{11}$C
- $^{18}$F

$\beta^+$ decay

67 мин
20,4 мин
109,8 мин

PET+CT
Basis of the radionuclide diagnostic and therapy

Positron emission tomography (PET)

Diagnostics

Tumor visualization by the PET

Radionuclide (β+ decay)

Somatostatin receptor on the tumor cell membrane

Nuclear Physics
Radiochemistry

Chemistry

Chemistry, Radiation-material science

Biology, Medicine
PET + Time of Flight (TOF) method

\[ \Delta d = \Delta t \cdot \frac{c}{2} \]

1. Fast scintillators
2. Multi channel plate detectors

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

**Diagnostics**

Advanced detector technologies for the PET

**Gamma-PET method**

\[ \gamma \text{-quanta of } 44\text{Sc (1157 keV)} \text{ is detected (by Compton spectrometer) together with two annihilation gammas (by standard PET detectors))} \]

3D position visualization
The best position resolution!
The new methods in radionuclide diagnostic and therapy

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.

Monoclonal antibody
Peptide
Protein
Nanoparticle
Polymers

Carriers

Specific membrane antigen

Alpha - particles (5-7 MeV) are effective to destroy the tumors at the diameter several microns.
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 ($T_{1/2} = 8$ days) 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

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

**Diagnostic**
- PET, SPECT
- MRI, Optical methods

**Target therapy:**
- Example: $^{64}$Cu-DOTA-siRNA nanoparticles

Theranostics: $=\\begin{array}{c}
\text{Diagnostic} \\
\text{PET, SPECT} \\
\text{MRI, Optical methods} \\
\end{array} + \begin{array}{c}
\text{Target therapy:} \\
\text{Example: }^{64}\text{Cu-DOTA-siRNA nanoparticles} \\
\end{array}

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)

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

$^{149}\text{Tb-therapy}$

$^{161}\text{Tb-therapy \& SPECT}$

$^{152}\text{Tb-PET}$

$^{155}\text{Tb-SPECT}$

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: $^{119}\text{Sb}$ (therapy) + $^{117}\text{Sb}$ (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:**

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Energy (keV)</th>
<th>( ^{\text{e}} ) (on 100 mother nuclei)</th>
<th>Associated ( \gamma )</th>
<th>T1/2</th>
<th>Daughter nuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclide</td>
<td>Auger ( ^{\text{e}} )</td>
<td>IC</td>
<td>Auger ( ^{\text{e}} )</td>
<td>IC</td>
<td>Daughte r nuclide</td>
</tr>
<tr>
<td>55Fe</td>
<td>0.61 (L)</td>
<td>no</td>
<td>139.9</td>
<td>no</td>
<td>5.9 (0.16)</td>
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<td>67Ga</td>
<td>0.99 (L)</td>
<td>83.65 (K)</td>
<td>168.3</td>
<td>29.1</td>
<td>8.62 (0.17)</td>
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<tr>
<td>111In</td>
<td>2.72 (L)</td>
<td>144.57 (K)</td>
<td>100.4</td>
<td>8.07</td>
<td>171.28 (0.91)</td>
</tr>
<tr>
<td>123I</td>
<td>3.19 (L)</td>
<td>127.16 (K)</td>
<td>95.1</td>
<td>13.61</td>
<td>27.20 (0.25)</td>
</tr>
<tr>
<td>( ^{195}\text{mPt} )</td>
<td>7.24 (L)</td>
<td>17.01 (L)</td>
<td>140</td>
<td>69</td>
<td>65.12 (0.22)</td>
</tr>
<tr>
<td>117Sb</td>
<td>2.95 (L)</td>
<td>129.36 (K)</td>
<td>94.5</td>
<td>11.57</td>
<td>25.04 (0.23)</td>
</tr>
<tr>
<td>119Sb</td>
<td>2.95 (L)</td>
<td>19.40 (L)</td>
<td>147.1</td>
<td>67.5</td>
<td>3.44 (0.12)</td>
</tr>
</tbody>
</table>
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

Beam current measurements (at 3 point)

Power density up to 600 W/cm²
minimum water consumption
On-line monitoring of the target heating
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

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: $^{\text{nat}}\text{Sn}(p,X)^{122}\text{Sb}$ и $^{\text{nat}}\text{Sn}(p,X)^{124}\text{Sb}$
   b) Investigations of the nuclear reactions on highly enriched tin isotopes: $^{117}\text{Sn}(p,n)^{117}\text{Sb}$ и $^{119}\text{Sn}(p,n)^{119}\text{Sb}$
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

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

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

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

117Sn(p,n)117Sb

New experimental data:

a) The peak area of the 119Sn(p,n)119Sb 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 117Sn(p,n)117Sb were obtained for energy region: from 11.0 MeV up to 13.3 MeV - 5 new points
Investigations of the nuclear reactions for the production of new diagnostic and therapy radionuclides

New Target system
Concluding

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
References


