Summer Student Program
Joint Institute for Nuclear Research
2015

Flerov Laboratory of Nuclear Reactions

Investigation on ^{195m}Pt production and processing of irradiated target

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Outline

1 Introduction

My name is Barbara Basarabová. I am Slovak, currently studying at the Czech Technical University in Prague in a doctoral program. My field of study is Nuclear Chemistry and I am dealing with understaning of radionuclide separation-mechanisms in order to develope a new way of radionuclide separation using ionic liquids.

I believe that for better understanding of separation mechanisms overall, it is very important to get a complex view on separation techniques in the field of Nuclear Chemistry. Thusly, since the Czech Republic is a member of JINR, I applied for participating in a Summer School Student Program in JINR for a period of two months.

JINR – The Joint Institute for Nuclear Research in Dubna, Moscow region, Russia – is an international research organization established in 1956 with the aim of uniting the efforts, scientific and material potentials of its Member States. [1]

Fig 1 Joint Institute for Nuclear Research

JINR consists of Directorate, six Research Laboratories, University Centre, Administrative Management Offices and AYSS – Association of Young Scientists and Specialists – which is a public organization. One of the laboratories is the Flerov Laboratory of Nuclear Reactions, FLNR, where I joined a research group during August and September, 2015.

Fig 2 Flerov Laboratory of Nuclear Reactions

FLNR was founded in 1957 by outstanding Soviet scientist Georgy N. Flyorov (Георгий Н. Флёров). Nowadays, it is one of the world's leading scientific centers in the field of Nuclear Physics. FLNR has now more than a dozen of scientific discoveries.

Along with two scientific groups in FLNR, there are eight scientific sectors in this laboratory. One of them is a sector of Chemistry of Transactinides, where Nikolay V. Aksenov is the head, currently. I was mainly working with Ph.D. student Alexander S. Madumarov led by above mentioned Nikolay V. Aksenov, on ^{195m}Pt production and investigation.[1]

2 Purpose of investigation

Since our society is constantly developing, technology environment goes forward as well. An increase of technology availability goes with an increase of needs and desires for further investigation, especially in the field of Nuclear Medicine.

Hence, in order to offer new possibilities of considerate treatment a new approach has been taken, videlicet theragnostics. Theragnostics is a treatment strategy that combines diagnostics and therapeutics using one specific drug. It implies diagnostic test that identifies patient's disease origin and a targeted therapy based on the diagnostic test.[2]

From the theragnostics point, radionuclides emitting radiation or non-radioactive Auger electrons offer a possibility of choosing a radionuclide with certain physical and nuclear characteristics that are suitable for a particular tumor type, or the disease under treatment. In particular, it is possible to select radionuclides suitable for particular purpose in theragnostic by considering their half-life, chemical, biochemical, physical and radioactive properties. [3, 4]

Suresh et al [5] have made a research on sorting and organization of number of theragnostic radionuclides providing the necessary pre-therapy information on biodistribution, dosimetry, limiting on critical organ or tissue, and the maximum tolerance dose (MTD), etc. following by performing higher dose targeted molecular therapy in the same patient with the same radiopharmaceutical.

Based on the results[5], Auger electron emitters, such as ^{195m}Pt, are suitable for tumor therapy (particularly for ^{195m}Pt, solid tumors – micrometastases) and for receptor-binding tracers (cellular (intracellular) antigens). Auger electron emitter ^{195m}Pt is therefore valuable to study.

One of the main goals of theragnostics is a preparation of a radionuclide in no-carrier-added (NCA) form in order to keep the level of harm as low as possible, which is mostly difficult to achieve. Moreover, one of the other constant issues in this field is the lack of availability, in sufficient and reasonable cost, of a majority of the best candidate in the NCA from. Thus, investigation on ^{195m}Pt radionuclide preparation in NCA form for theragnostic purposes has been launched. [6, 12]

3 Auger effect

Why are Auger electron emitters suitable for theragnostics?

Energy levels of electrons in atoms are divided into outer (valence) or inner (core) shells (levels) (see Fig **3**). Bombardment of solids by X – rays (photons) or electrons (incident electrons) with high kinetic energy may dislodge core electrons from their inner shells, and they may either escape the surface of the solid or they may be incorporated into neighboring ions.

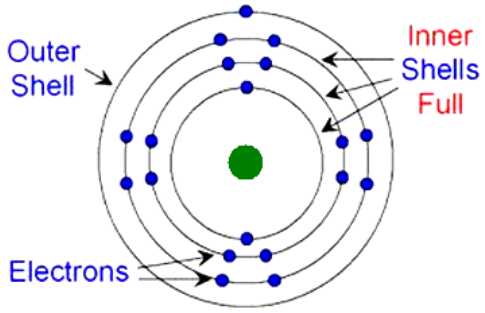


Fig 3 Image of energy levels of electrons

After the emission of the core electron from an atom, the resulting ion is energetically unstable. This formation of unstable (excited) ion proceeding with readjustment of remaining electrons in the central ion, and one of these adjustments is followed by Auger process, which is non-radioactive transition process (see Fig 2), called in honor of its discoverer, Pierre Victor Auger. [7,8]

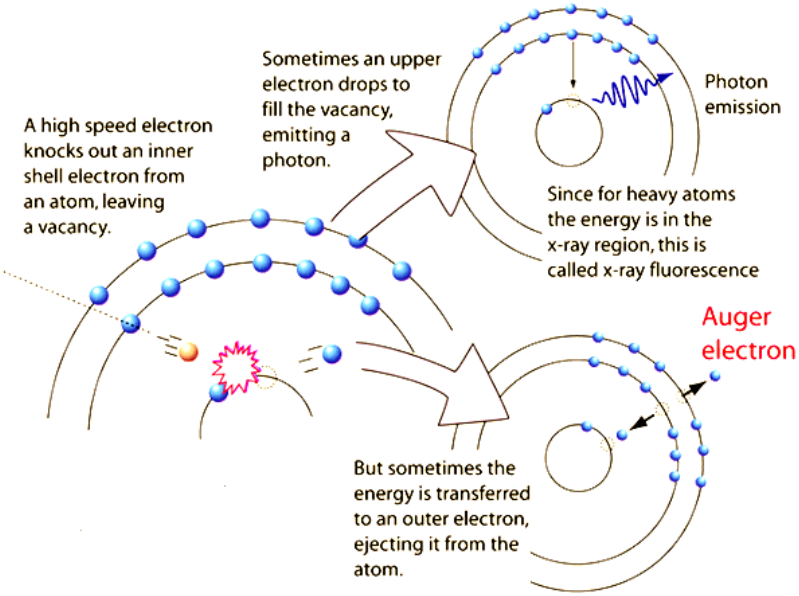


Fig 4 The Auger effect

Therewithal, the unstable ion may achieve a lower energy state by having another core electron jump from a higher-level shell into a lower-level shell. The jump is energetically favored, because electrons in higher-level shells have greater energy (kinetic and potential) than electrons in a lower-level shell.

Upon this movement of an electron from higher-energy level to lower-energy level, surplus energy may be processed into two ways, emission of X – rays or ejection of the second electron. Through this ejection of the second electron, energy is dissipated dominantly in the form of kinetic energy of the ejected electron. This ejected electron is an Auger electron. The energies of Auger electrons depend on the atomic binding energies of the atom. The most energetic Auger electrons result from transitions to the K-shells (25 – 27 keV), but the most of the electrons are produces by transitions between the outer orbitals.[7]

At the end, atom lacks two electrons, photoelectron and Auger electron, what leads to the formation of doubly-charged ion. However, the vacancy created by the second ejected electron (Auger electron) may also be filled by electrons from still higher-energy level. This process may continue by the net charge on the resulting increases. Anyway, a minimum of three electrons are associated with the production of one Auger electron. Based on this, it is apparent that Auger process does not occur in Hydrogen and Helium atoms. Auger electrons are emitted by about one-half of known radionuclides that decay by electron capture and internal conversion. Both processes result in the formation of vacancy in inner shell which may lead in auger electron creation.

Therapeutic particle emissions consist basically of Auger electrons, alpha, beta particles, and conversion electrons. Except for the beta particles, all of these are classified as high-linear energy transfer (LET) electron emitters, thus Auger electrons are very effective in cell kill in cellular proximity which is a necessary requirement. [2, 5]

In fact, the Auger-electron emitters represent very attractive source for malignant disease therapy in case of placement into cells within target area. Incorporation of Auger-electron emitters and photoelectrons is the most efficient way, capable of inducing cell death with virtually no damage to the surrounding cells, because they cannot penetrate into tissue more than a few atomic diameters from their side of generation (approximately 50 Å). [6 – 8] Such Auger electron emitters and currently widely used in nuclear medicine, e. g. ^{67}Ga, ^{99m}Tc, ^{111}In, ^{123}I and ^{201}Tl. [7, 8]

In addition, cellular and organ studies demonstrates when Auger emitters are introduced into the cytoplasm of cells, the effects are typical of those caused by radiations of low-linear energy transfer. Alike, when Auger emitters are incorporated into the DNA of cells, the resulting survival curves are similar to those for high-LET alpha particles. Along with, there has been found also biomolecules that are known to contain platinum. [6, 7, 9]

Thus, the possibility of transferring the potential of tumor therapy and diagnostics (theragnostics) based on the emission of Auger electrons from experiments to patients is a goal that now seems more within reach during any prior period. [6]

4 ^{195m}Pt production and investigation

Radionuclides are artificially produced by transforming a stable nuclide into an unstable state by bombardment with nuclear particles mainly neutrons, protons, deuterons, alphas, gammas, etc. [5] Radioisotopes for medical applications can be produced in accelerators, reactors, from the processing of reactor fission products, and from radionuclide generator systems using reactor- or accelerator-produced parents.

Soft gamma radiation, the capability of forming chemical compounds with many different biomolecules and moderately half-life, that ensures high initial specific activity and rapid decay are the properties of importance followed in clinical applications and ^{195m}Pt, Auger electron emitter, is now in the interest of further investigation on tumor diagnostic and therapy. [3]

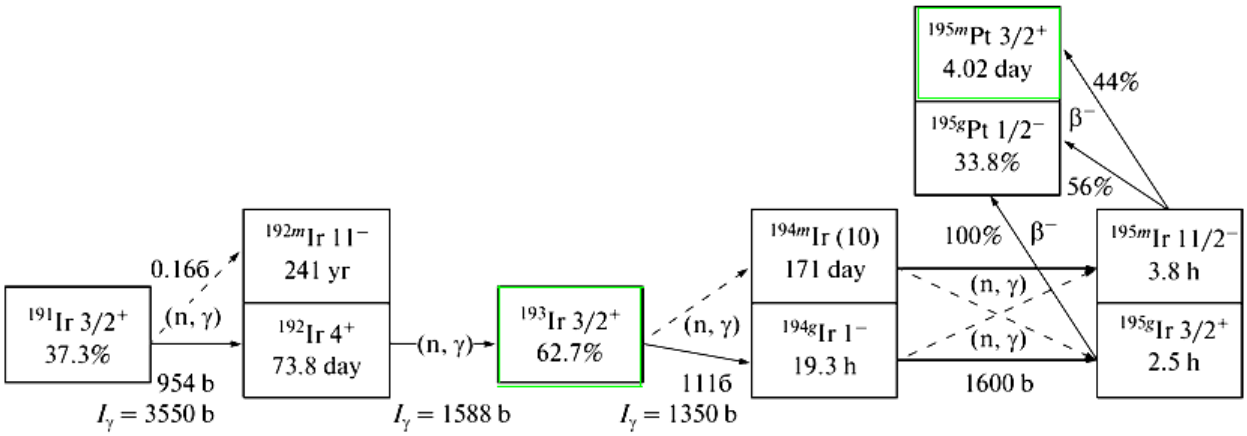
^{195m}Pt is characterized by nice nuclear properties (soft gamma-radiation 99 keV, suitable half life of 4 days), and decay results in the multiple generating of Auger electrons and it makes it suitable for use in the field of nuclear medicine.

However, current methods for this radionuclide obtaining are not very effective and the isomer of interest is accumulated in the bulk of the stable Pt material and cannot be isolated by chemical means.

Therefore, with the stress on a requirement to avoid to use an expensive cyclotrone, there is considered an indirect production method for accumulating of ^{195m}Pt as a result of double neutron capture (see also Scheme 1):

$$^{193}\text{Ir}\ (n,\gamma)\ ^{194g,m}(n,\gamma)\ ^{195g,m}\beta^{-} \rightarrow\ ^{195m}\text{Pt} \qquad \textbf{(1)}$$

The final product can be separated from the target (Ir) by chemical means. This method was taken for development of ^{195m}Pt from irradiated Ir target separation method. [6]



Scheme 1 The scheme for producing the ^{195m}Pt isomer by means of double neutron capture.[6]

^{195m}Pt isomer produced by Karamian et al by irradiation of iridium foils of natural isotopic composition with a modest neutron flux offers a possiblity to obtain ^{195m}Pt isomer in sufficient amount for use in Nuclear Medicine. However, further research on neutron cross-sections is needed. [6]

Fig 4 Microtron Mt-25 in JINR, Dubna

*Bremsstrahlung radiation is defined as an electromagnetic radiation produced by an acceleration or especially decceleration of a charged particle after passing trough the electric and magnetic fields of a nucleus.

The MT-25 microtron accelerates electrons to energies of 25 MeV with beam current of up to 20 μA and beam powers of 0.46 kW. A design contains a converter for transforming the electron energy to *****bremsstrahlung radiation, a secondary target for the generation of fast neutrons, and neutron moderator. Namely, it contains 4 mm-thick tungsten converter for generating bremsstrahlung radiation, thick lead and beryllium plates for producing neutrons in the (γ, n) and (n, 2n) reactions, and a graphite cube for neutron moderation. [6, 10]

5 Experimental part

The preparation of theragnostics radiofarmaceuticals strongly depends on the technically achievable specific activity of radionuclides. Because of the low achievable specific activity of ^{195m}Pt it cannot be used for radiolabelling. Therefore, ^{195m}Pt is considered to be produced in NCA form with high specific activity utilizating Szilard-Chalmers effect.

The Szilard-Chalmers effect is defined as a break of a chemical bond between an atom and the molecule of which in atom is part, as a result of a nuclear reaction of that atom. Its discovery belongs to L. Szilard and T. A. Chalmers, who represented an isolation possibility of an iodine radioisotope from the irradiated target material, produced by neutron irradiation of ethyl iodine. [11] For finding and investigating an effective separation method for ^{195m}Pt in with high specific activity we have demostrated a procedure Szilard-Chalmers effect keeping in our mind.

At the very beginning we have prepared a solution of H_2PtCl_6. The compound was prepared by mixing of HNO_3 and HCl in a molar ratio of 1:3 to make the aqua regia. We added a solid Pt into this aqua regia solution. The solid Pt was dissolved in aqua regia by heating up and evaporated in order to get a pure compound of H_2PtCl_6 in a beaker (see Tab 1). Just before complete evaporation we added 5 ml of HCl, and then evaporated it three times more with water to avoid presence of HCl.

$$Pt\ (s) + 4NO_3^-\ (aq) + 8H^+\ (aq) \rightarrow Pt^{4+}\ (aq) + 4NO_2\ (g) + 4H_2O\ (l) \quad \textbf{(2)}$$

$$Pt^{4+}\ (aq) + 6Cl^-\ (aq) \rightarrow PtCl_6^{2-}\ (aq) \quad \textbf{(3)}$$

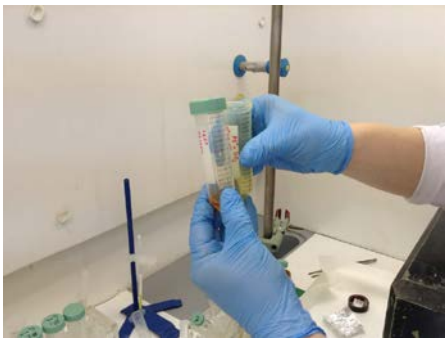


Fig 5 Preparation of aqua regia

We quantitatively transferred H_2PtCl_6 into SiO_2 material. We put this mixture of SiO_2 and H_2PtCl_6 into an aluminium foil and irradiated by gamma radiation on MT-25 for a time of 3 days as it is desribed above (Karamian et al). [6]

Tab 1 Used chemicals

	SiO_2 (s)	Pt (s)	H_2PtCl_6 (s)	HCl (l)	HNO_3 (l)	H_2O (l)
V [ml]	-	-	-	4.5	1.5	1
m [mg]	150	67.8	15	-	-	-

V – volume; *m* – weight; *ml* – mili liter; *μg* – mili gram

After irradiation we transferred a sample into a beaker and rinsed with destilled water three times with the volume of 15 ml (see Tab 1). After rinsing, we measured SiO_2 material with ^{195m} Pt recoiled active atoms on HPGe detector, Canberra. Measurement did not show any gamma lines, thus all the active Pt was rinsed with water, evidently.

Fig 6 Measurement of ^{195m}Pt sample on HPGe detector

Experiment stands on solubility of particlular components in a system. The system consists of Pt on SiO_2 carrier in the form of H_2PtCl_6.

Therefore, we prepared ^{195m}Pt by activation of H_2PtCl_6 on MT-25, but developing of the technique for ^{195m}Pt isomer saturation is still required.

6 Conclusion

Theragnostics, as a new approach in nuclear medicine, may change the usual business model of pharmaceutical companies from the classic blockbuster model toward targeted therapies and create a new-more efficient and convenient way of patient treatment. [2]

Taking account of properties of radionuclides such as existance in no-carrier-added form, Auger electrons emission and moderately short half-life, additional radiopharmaceuticals for cancerous cells targeting that are in absence of residual radioactive pollution in a human body, can be developed.

In order to achieve high specific activity of ^{195m}Pt isomer, which seems necessary today, special interest takes the Szilard–Chalmers effect. To produce ^{195m}Pt indirectly by double neutron capture, it is relevant to separate this Pt isomer from its parent. Effective method has to be developed.

We have used the photonuclear reaction ^{195}Pt(g,g‘)^{195m}Pt to get a product with high specific activity of ^{195m}Pt, which stands on solublity and Szilard-Charmel effect.

At the very end there was no observed ^{195m}Pt isomer sepration from the target. It can be caused by very short distances in SiO2 lattice, thus Szilar-Chalmers effect did not occur, apparently. Additional carrier materials, has to be investigated. Further investigation is needed.

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I am very grateful for visiting Dubna. It was great experience. I have learned a lot of new things and met a lot of kind andsmart people. My knowledge has enlarged. It would be pleasure to visit Dubna again.

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Abbreviations

α – alfa

β – beta

γ – gamma

μA – micro amper

aq – aqueous solution

Å – angström

DNA – Deoxyribonucleic acid

kW – kilo watt

l – liquid

LET – linear energy transfer

MTD – minimal tolerance dose

NCA form – no-carrier-added form

s – solid

MeV – mega electron volt