Tbilisi State University, Tbilisi, Georgia, Faculty of Exact and Natural Sciences, Department of Physical and Analytical Chemistry

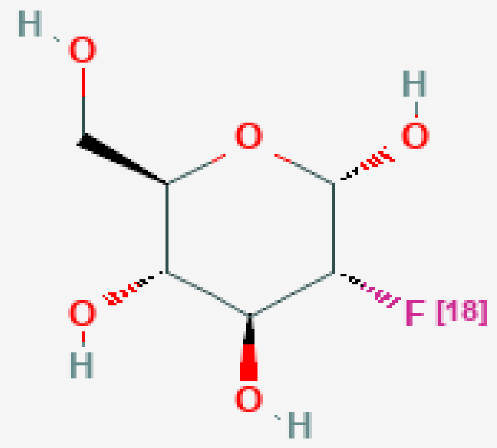
San Diego State University Georgia, Tbilisi, Georgia, Chemistry and Biochemistry Department

Characteristics and Applications of Non-Conventional Radionuclides in Radiopharmaceuticals for Medical Imaging

STUDENT: NATIA INADZE

What are Radiopharmaceuticals and Radioisotopes?

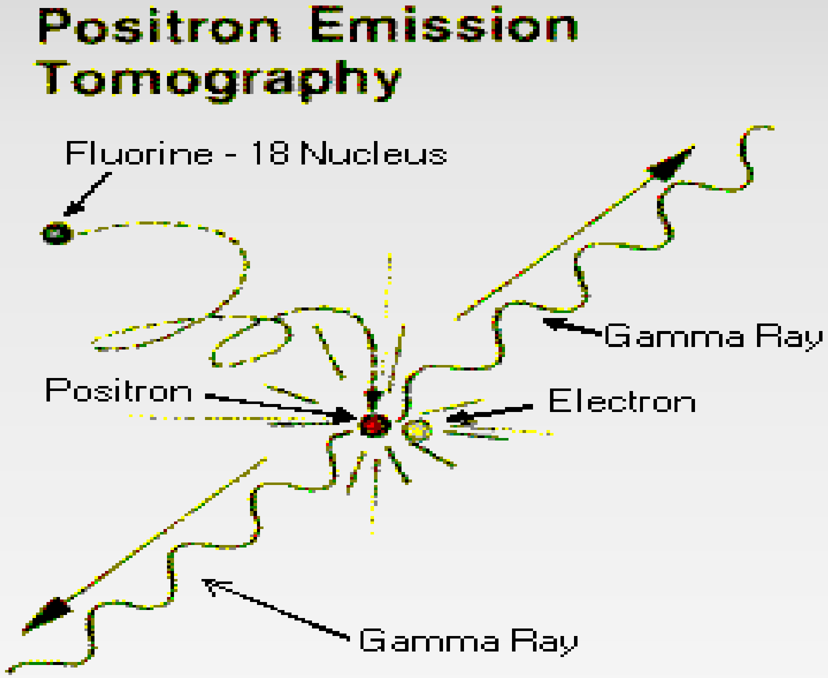
- Radiopharmaceuticals are a group of diagnostic or therapeutic agents synthesized by linking various radionuclides to biological molecules
- Radiopharmaceuticals labelled with b+-emitting radionuclides are utilized in medical imaging and are detected by their annihilation gamma quanta
- Radioisotopes are unstable isotopes, spontaneously dissipating excess energy in the form of radiation to produce a nonradioactive daughter atom
- Most common radionuclides used for diagnostic purposes are ^{99}Tc (T½ = 6 h) frequently used in SPECT, ^{18}F (T½ = 110min), ^{11}C (T½ = 20.4min), ^{13}N (T½ = 9.96min), ^{15}O (T½ = 2.04min), all used in PET



Duchemin, C., Fraile, P., Mario, L. (14 Sept. 2020). *In situ Gamma-spectrometry System for the Characterization of Non-conventional Radionuclides for Medical Research*. Retrieved November 09, 2020 from https://cds.cern.ch/record/2732064

Diagnostic Radioisotope Characteristics

- Their half-life should correspond to the residence time of the radiopharmaceutical in the organism
- The yield of the positrons should be maximum, and, correspondingly, the positron energy should be as low as possible
- The presence of high-energy gamma lines in the nuclide spectrum should be avoided
- The radioisotope should form kinetically and thermodynamically stable compounds *in vivo*

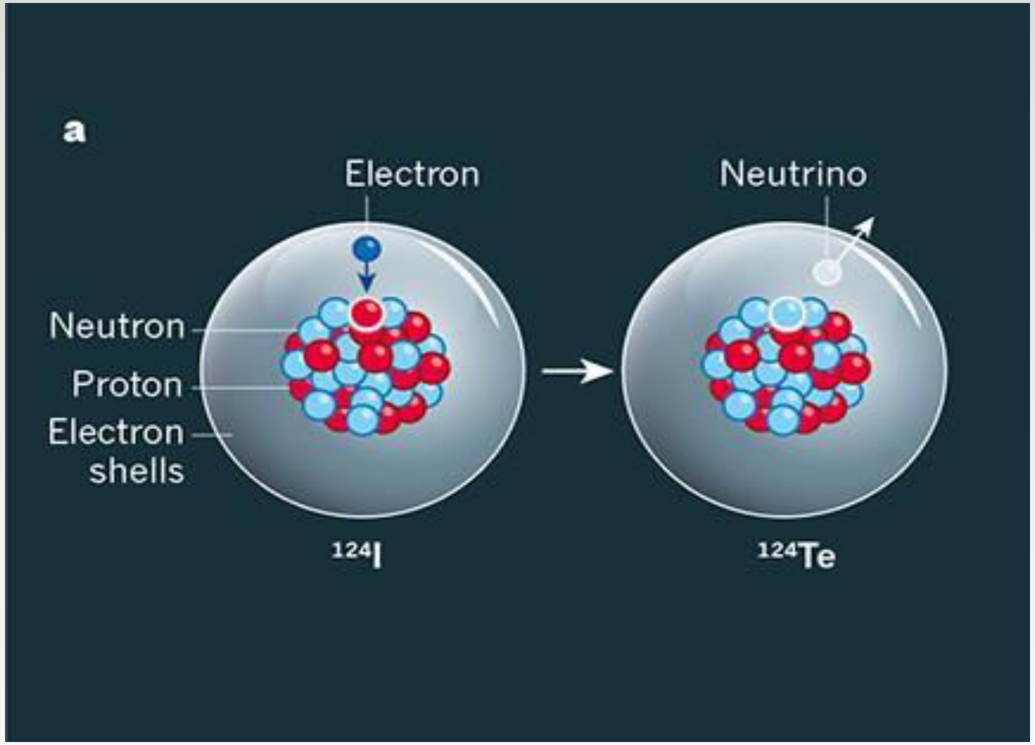


Qaim, M. S., Spahn, I. (06 Nov. 2017). *Development of Novel Radionuclides for Medical Applications.* Journal of Labelled Compounds and Radiopharmaceuticals. Retrieved November 09, 2020 from https://onlinelibrary.wiley.com/doi/full/10.1002/jlcr.3578

Krasikova, N. R., Aliev. A. R., Kalmykov, N. S. (March-April 2016). *The Next Generation of Positron Emission Tomography Radiopharmaceuticals Labeled with Non-conventional Radionuclides.* Mendeleev Communications. Vol. 26, Issue 2, pg. 85-94. Retrieved November 09, 2020 from https://www.sciencedirect.com/science/article/pii/S095994361600050X

Rise of Non-Conventional Radionuclides

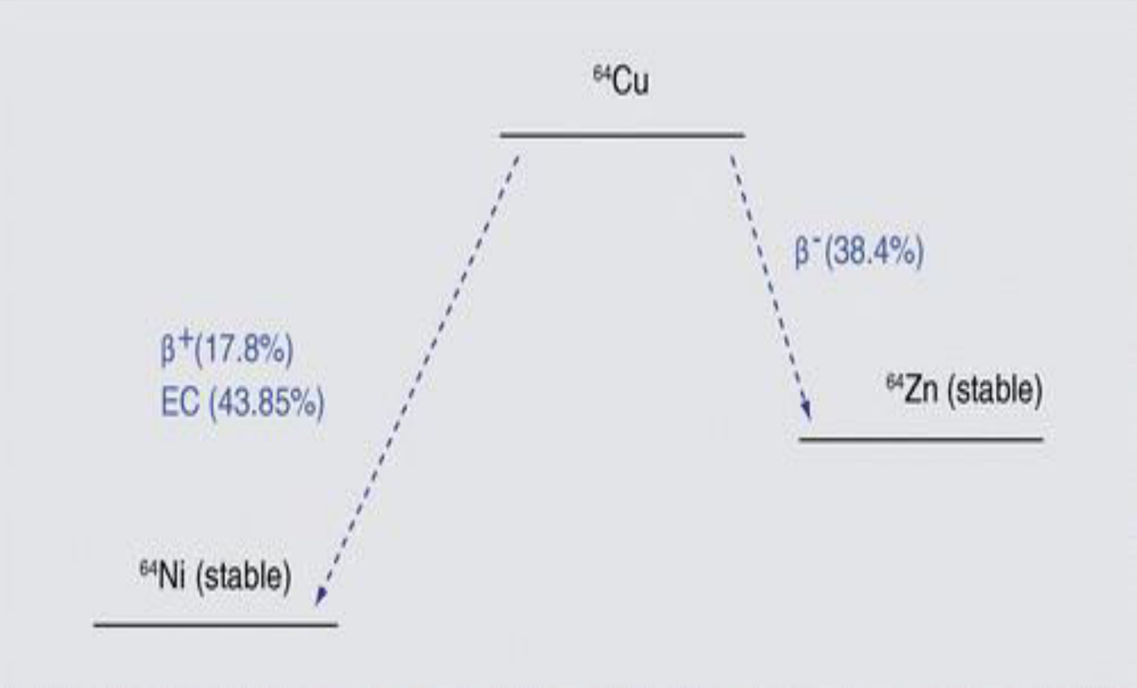
- For the purpose of studying slower functional processes, involving protein synthesis, cell proliferation, etc., nonstandard, longer-lived positron emitters are needed
- Some of them include ^{64}Cu (T½ = 12.7 h); ^{86}Y (T½ = 14.7 h), ^{89}Zr (T½ = 3.3 d), ^{124}I (T½ = 4.2 d), ^{73}Se (T½ = 7.1 h), and many others



Qaim, M. S. (2019). *Accelerator-based production of Non-standard Positron Emitters and Therapeutic Radionuclides*. Retrieved November 09, 2020, from https://juser.fz-juelich.de/record/872723

Copper-64

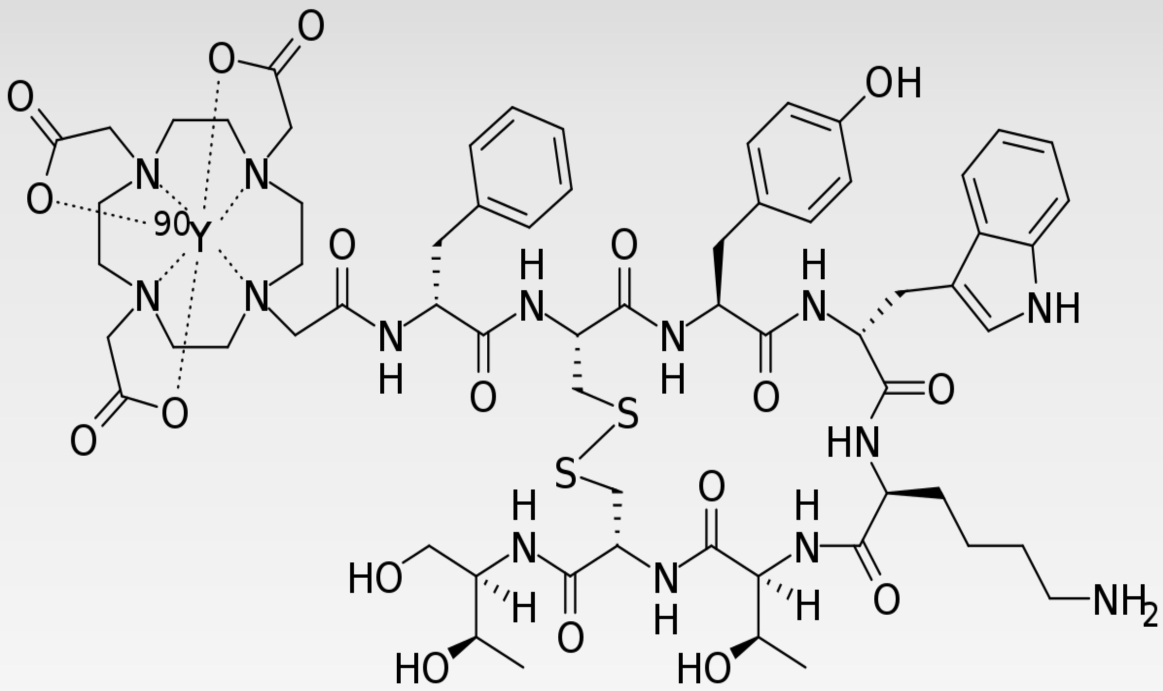
- The most commonly used non-conventional PET radioisotope
- The physical decay properties of ^{64}Cu include 18% β^+-, 38% β^-- emission and 44% by electron capture
- Relatively low β^+ energy of 0.653 MeV
- Cu-64 forms quite stable coordination complexes *in-vivo*



Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86.* Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

Yttrium- 86

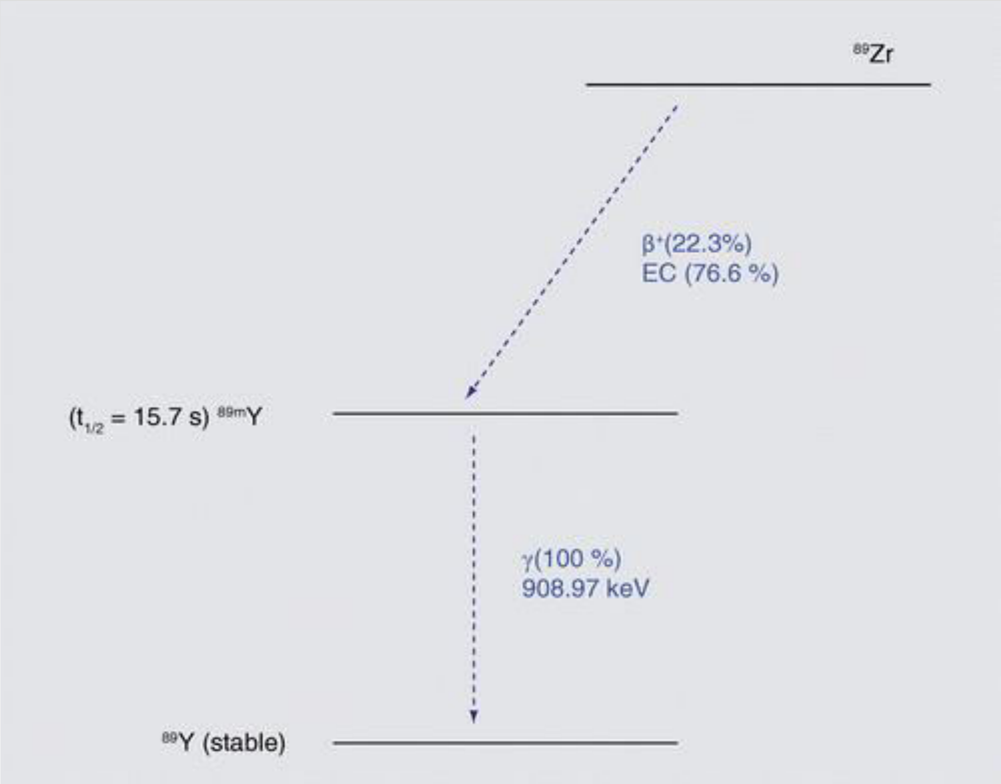
- Widely known metallic non-standard PET radionuclide
- ^{86}Y has a half-life of 14.7 h and decays by β^+- (34%) and γ-(77%) emission
- Tt has gained attention as an imaging pair for ^{90}Y, a therapeutic radionuclide currently used in nuclear medicine.
- The limitation of this β^+ isotope is relatively high positron energy of 3.15MeV and the presence of additional γ-rays that are emitted during ^{86}Y decay.



Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86.* Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

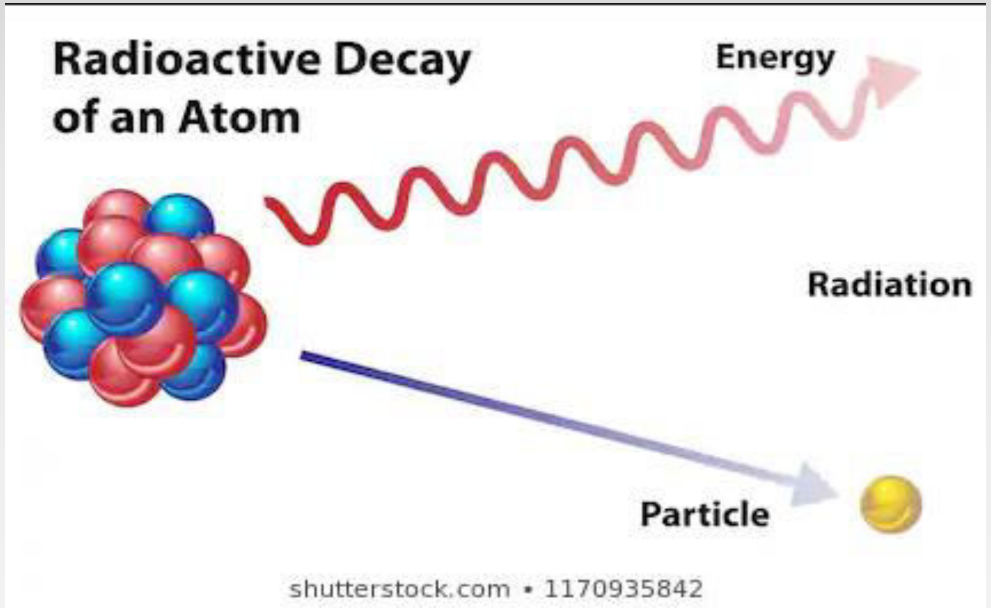
Zirconium-89

- It is a long-lived radionuclide with a half-life of 78.4 h and decays by electron capture, β^+-emission and γ-emission
- relatively low positron energy ($E_{\beta+} = 0.90$ MeV) results in high resolution of ^{89}Zr images that are comparable to those observed with ^{18}F and ^{64}Cu



Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86*. Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

Other Non-Standard Radionuclides



IODINE-124

- Is somewhat longer-lived ($T_{1/2}$ = 4.18d), and has relatively low positron branching of 22.0%.
- The β^+ endpoint energy amounts to 2.13 MeV, and several γ-rays are also associated with its decay.

SELENIUM-73

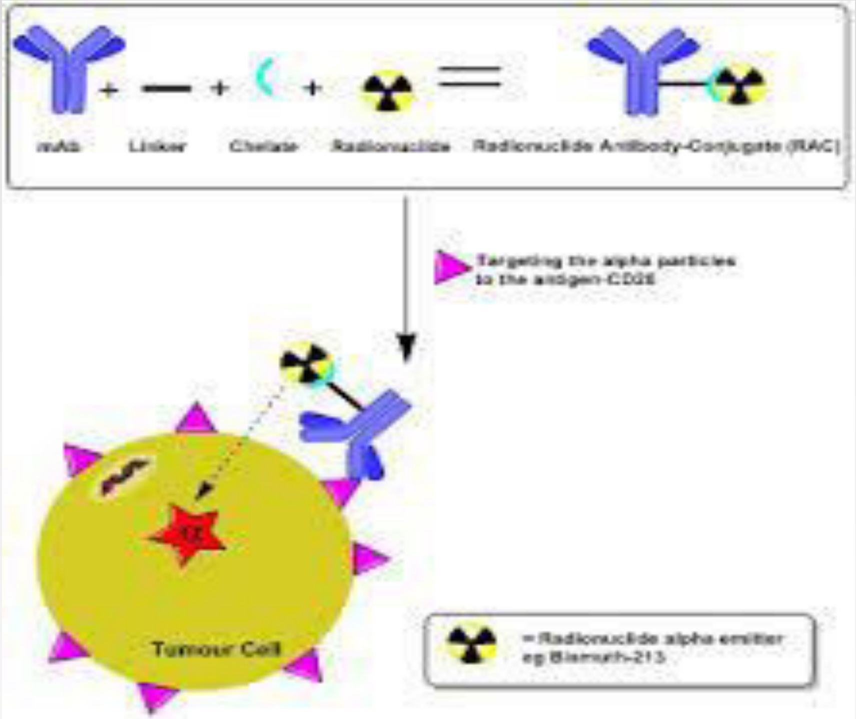
- It decays 65.4% via β^+ emission and 34.6% by EC. The positron endpoint energy amounts to 1.3 MeV and a few γ-rays are also emitted.

Many other non-traditional radionuclides are also known [^{43}Sc ($T_{½}$ = 3.9 h), ^{44}Sc ($T_{½}$ = 3.9 h), ^{45}Ti ($T_{½}$ = 3.1 h), ^{52}Mn ($T_{½}$ = 5.6 d), ^{55}Co ($T_{½}$ = 17.5 h), ^{61}Cu ($T_{½}$ = 3.3 h), ^{120}I ($T_{½}$ = 1.3 h), etc.]

Qaim, M. S., Spahn, I. (06 Nov. 2017). *Development of Novel Radionuclides for Medical Applications.* Journal of Labelled Compounds and Radiopharmaceuticals. Retrieved November 09, 2020 from https://onlinelibrary.wiley.com/doi/full/10.1002/jlcr.3578

Radiotracer Preparation - Chelators

- Incorporation of longer-lived metal isotopes is based on binding a radionuclide with a bifunctional chelating agent (BCA) that, in turn, can form covalent bonds with various biomolecules (vectors), with high specificity and selectivity
- Radiopharmaceuticals based on metal isotopes are not involved in cellular metabolism but bind to the target, for example, by interactions of the vector molecule with receptors expressed on the tumor surface.

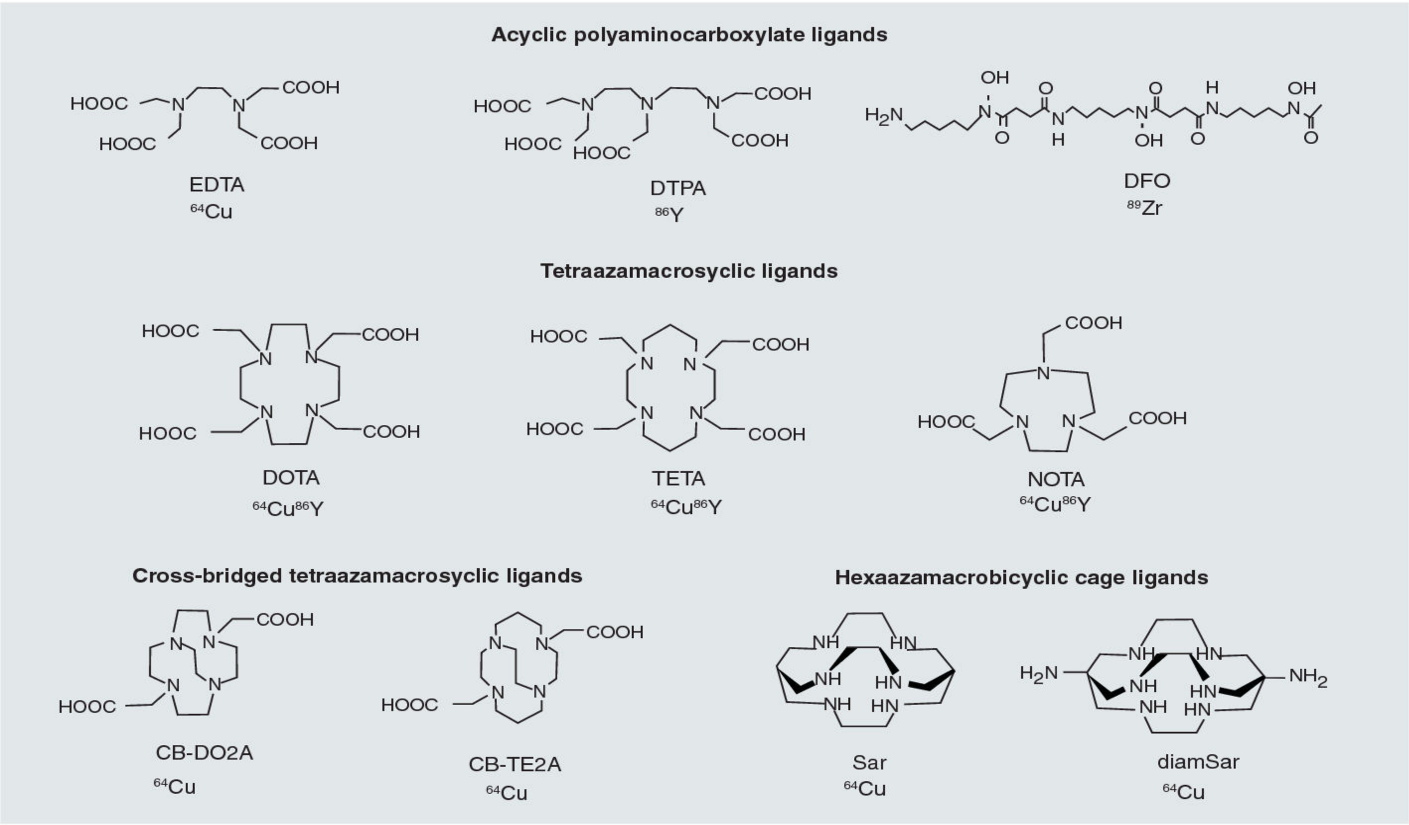


Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86.* Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

Krasikova, N. R., Aliev. A. R., Kalmykov, N. S. (March-April 2016). *The Next Generation of Positron Emission Tomography Radiopharmaceuticals Labeled with Non-conventional Radionuclides*. Mendeleev Communications. Vol. 26, Issue 2, pg. 85-94. Retrieved November 09, 2020 from https://www.sciencedirect.com/science/article/pii/S095994361600050X

Bifunctional Chelators (BCAs)

- The macrocyclic polyaminocarboxylates, 1,4,7,10-tetraazocyclododecanetetraacetic acid (DOTA) and 1,4,8,11-tetraazocyclotetradecanetetraacetic acid (TETA), as well as their derivates, are the most frequently used type of chelators, satisfying the necessary conditions for BCAs

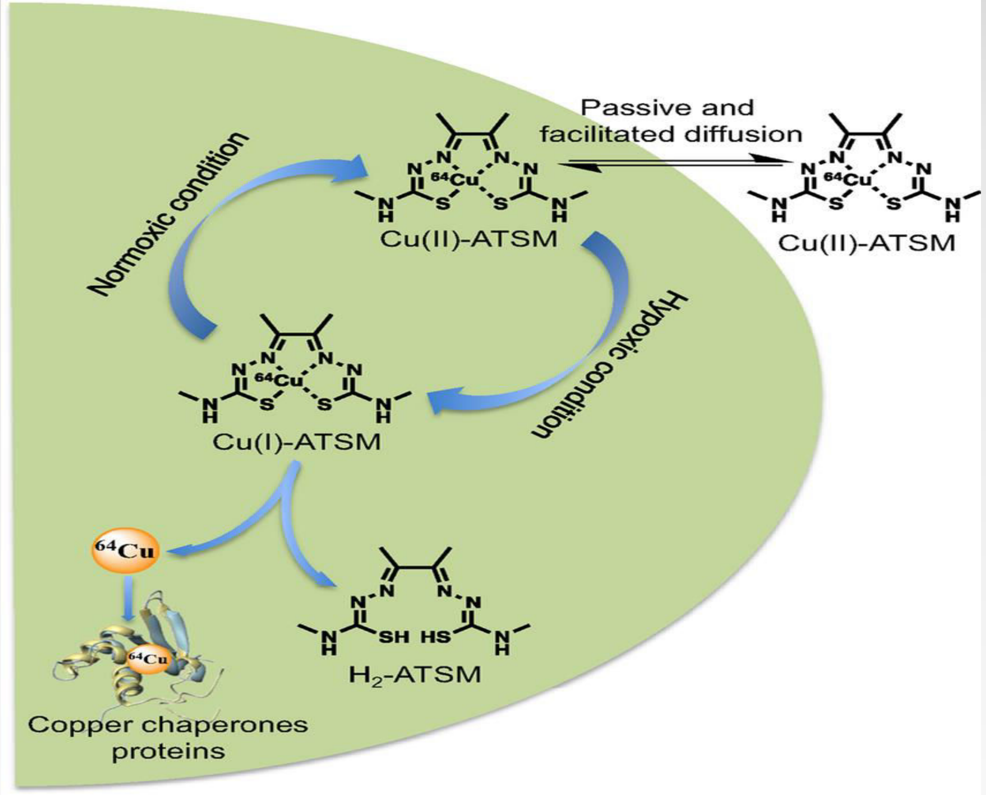


Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86.* Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

Krasikova, N. R., Aliev. A. R., Kalmykov, N. S. (March-April 2016). *The Next Generation of Positron Emission Tomography Radiopharmaceuticals Labeled with Non-conventional Radionuclides*. Mendeleev Communications. Vol. 26, Issue 2, pg. 85-94. Retrieved November 09, 2020 from https://www.sciencedirect.com/science/article/pii/S095994361600050X

Small-Molecule Probes

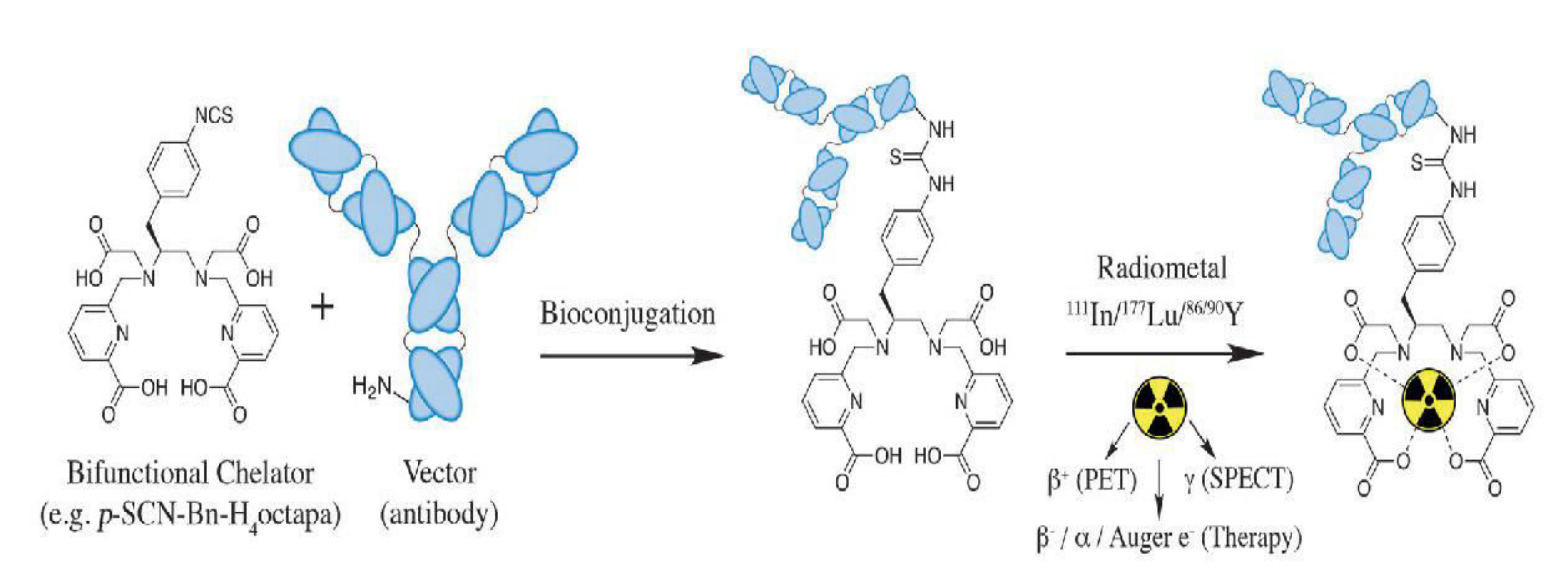
- One group of special interest is the semicarbazone ligand that has been complexed with ^{64}Cu and investigated to probe hypoxia
- With the semicarbazone ligand, diacetyl-*bis*(N^4-methylthiosemicarbazone) (ATSM), which has a maximum positron energy of 0.66 MeV, similar to that of ^{18}F, the resulting PET images are the best obtainable with any positron-emitting radionuclide of copper.



Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86.* Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

Peptide Probes

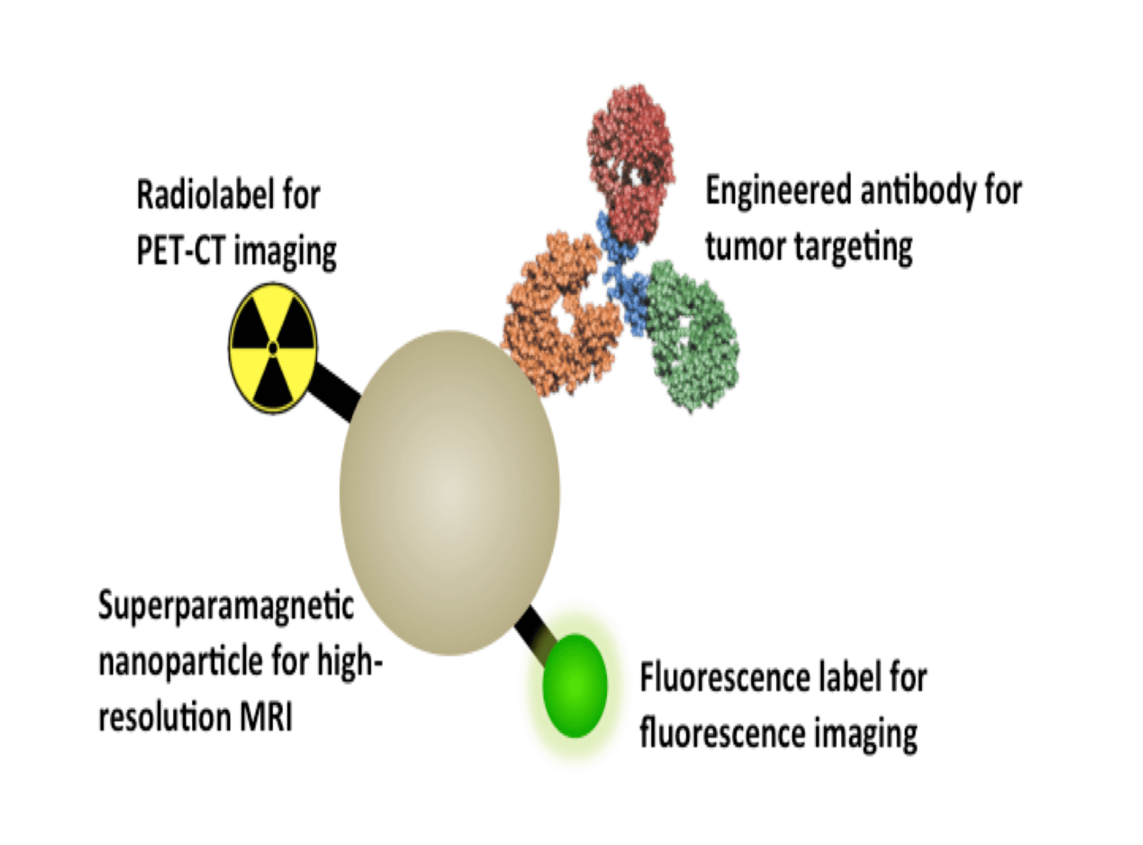
Peptide probes utilize the potential targets, such as somatostatin (SST) receptors, integrins and gastrin-releasing peptide receptors (GRPRs), which are overexpressed in many cancer cell types for imaging purposes.



Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86.* Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

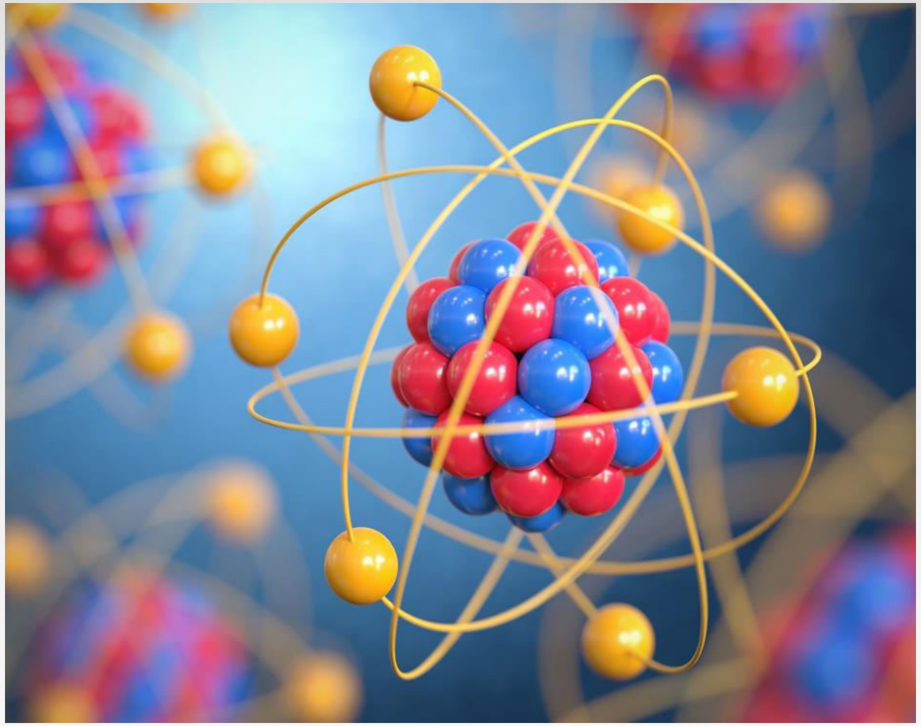
Nanoparticle Probes

- Nanoparticle probes are produced as diagnostic agents primarily because of their small size, large surface area and biokinetics.
- These properties permit greater functionality and wider *in vivo* distribution than can be accomplished with other molecular probes.
- A single nanoparticle can be conjugated with a large number of reporter molecules effectively, such as radionuclides or fluorophores, increasing signal-to-noise ratios.



Ikotun, F.O., E Lapi, S. (28 Apr. 2011). *The Rise of Metal Radionuclides in Medical Imaging: Copper-64, Zirconium-89 and Yttrium-86*. Future Medicinal Chemistry, Vol.3, NO.5. Retrieved November 09, 2020, from https://www.future-science.com/doi/full/10.4155/fmc.11.14

Summary



- The nonstandard isotopes play a key role in molecular imaging probe design utilized for studying slow metabolic process.
- The long half-lives and chemical versatility of these radionuclides have fueled novel probe development and enabled imaging of various biological processes.
- These isotopes have been effective in oncologic, cardiovascular and neurological imaging.
- Future research areas include further development of the strategies for radiopharmaceutical synthesis and production to avoid problems associated with the non-standard nuclides, such as non-specific tissue accumulation for example, as well as to increase the availability of these radioisotope radiopharmaceuticals in wider-scale medical applications.

Qaim, M. S., Spahn, I. (06 Nov. 2017). *Development of Novel Radionuclides for Medical Applications.* Journal of Labelled Compounds and Radiopharmaceuticals. Retrieved November 09, 2020 from https://onlinelibrary.wiley.com/doi/full/10.1002/jlcr.3578

Qaim, M. S. (2019). *Accelerator-based production of Non-standard Positron Emitters and Therapeutic Radionuclides*. Retrieved November 09, 2020, from https://juser.fz-juelich.de/record/872723

Thank You for Attention!