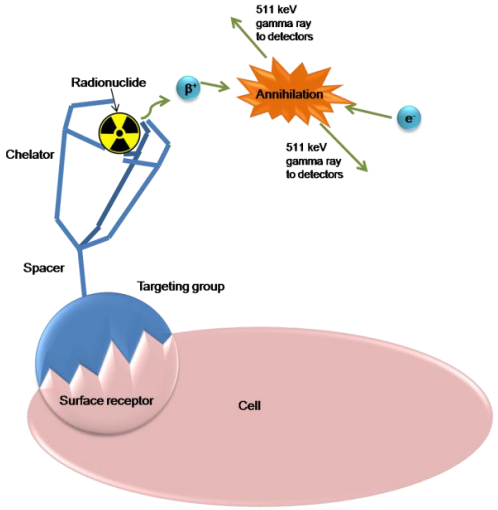
Project objectives

Current directions in radiochemistry and nuclear medicine highlight the importance of Positron Emission Tomography (PET) imaging, and subsequently the significance of optimal utilization of a growing number of β^+ emitting radiometal ions. PET imaging technique based on the measurement of radiation produced during positron (anti-electrons) annihilation - the collision with electrons of body cells, which generates two quanta of radiation propagating in opposite directions. This process is recorded by detectors, which allows to locate the source of radiation in the body. Radiation is received by the decay of radioisotopes with a reasonably short half-life, which are administered to the patient (Scheme 1). The combination of PET with the techniques of computed tomography (CT) and magnetic resonance imaging (MRI) has contributed to the development of diagnosis of various diseases, resulting in the increasing popularity of this method: number of studies in 2010-2013 increased in Europe by 20%, in Poland up to 73%. In the literature one can find many examples of compounds that bind radiometal ions, which are "good enough" imaging agents, but the relationship between the metal ion and a binding agent and its biodistribution in the body are a complex problem, clearly showing that these relationships are only superficially understood.



Scheme 1. Cartoon depicting the fundamental principle of positron emission tomography (PET).

The main objective of the project is to develop novel chelators for non-invasive *in vivo* imaging agents. By capitalizing upon our understanding of coordination preferences of metal ions and our previous achievements in the design of efficient metal chelators, we will focus specifically on ^{64}Cu, ^{68}Ga and ^{86}Zr radiometals – the most promising candidates for PET imaging.
Novel chelators will be developed possessing efficient metal binding groups (e.g. hydroxamic, phenoloxazoline, hydroxyquinoline, or pyridine-hydroxamic) in a linear, tripodal or tetrapodal arrangement.
This specific structures of the ligands have been elaborated in order to ensure (i) a strong association with metal ions and high thermodynamic stability of complexes in a broad range of pH (pH = 1–8), (ii) a good inertness towards *in vivo* transmetallation and transchelation reactions by endogenous metal ions and ligands, and (iii) fast complexation of the radiometal under high dilution and mild labelling conditions.

The development of preparative methods, proper organic synthesis and description of new chelators proposed in our project will be ensured by a collaboration with three groups specialised in organic synthesis: the group of Prof. Abraham Shanzer (Weizmann Institute of Science, Rehovot, Israel), the group of Prof. Oleg Varzatskii (Vernadskii Institute of General and Inorganic Chemistry NAS of Ukraine, Kiev, Ukraine), and the group of Prof. Igor Fritsky (National Taras Shevchenko University of Kiev, Ukraine).
A combination of physic-chemical methods will be used to determine the stoichiometry, stability and coordination structure of metal complexes, and their interactions with selected proteins. The determination of complex interactions with biomolecules (like albumin and transferrin) and biologically relevant metal ions (e.g. Ca(II), Zn(II), or Fe(III)) will allow the prediction of *in vivo* behaviour of complexes.

Expected impact of the research project on the development of science, civilization and society

We expect that the project will impact the research field on several levels, (i) bringing a large contribution to the general knowledge of the coordination chemistry of studied systems, and (ii) delivering novel, non-invasive chelators – the candidates for *in vivo* imaging agents. Moreover, benefiting from the scientific collaboration, project participants will (iii) develop flexibility and innovation in their scientific research (especially important for the scientific creativity of young researchers) and (iv) allow to establish solid collaborations for future research projects. The development in the area of imaging probes will have continuous impact on the pharmaceutical companies, clinicians and patients. Society as a whole will benefit from investment and further expansion in medicinal inorganic chemistry, represented here by the proposed project.