Radiolabelled peptidomimetic inhibitors of the VEGF/NRP-1 complex for imaging of pathological angiogenesis associated with early stage of malignant tumours formation

Cancers are among the most important challenges to be faced by modern medicine. According to WHO, as many as 8.8 million people died of cancer-related problems in 2015. Available treatments are frequently able to prolongue patients' lives (or even give a full remission). Still, in many other cases their efficacy is limited and their use is associated with many adverse effects that lower patients' quality of life (*e.g.* hair loss, nausea, vomiting *etc.*) or even threaten their lives (*e.g.* impairment of bone marrow function, immunodeficiency). Therefore, scientists have been in a continuous search of novel therapeutic strategies against cancer.

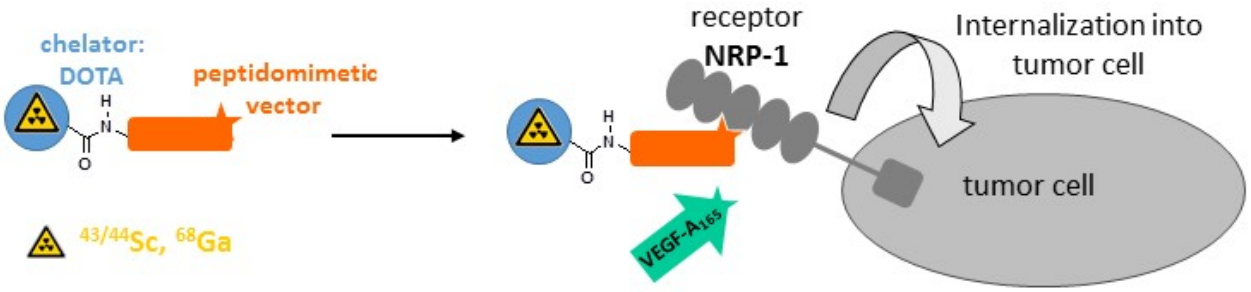
Recent years have witnessed a blooming development of several anti-cancer approaches, including **T**argeted **R**adio**N**uclide **T**herapy, TRNT. The principle of TRNT is an attempt to selectively deliver the radioactive cargo (radioisotope) to cancer tissues. In this fashion, harmful action of ionizing radiation kills the cancer cells, with the healthy cells left intact. The realization of the idea behind TRNT requires the design and synthesis of special chemical compounds suited for these purposes. First, we need a molecule (*vector)* with a high-affinity for some *molecular targets* (proteins) on the cell surface. Then, such a *vector* is attached with a ligand able to chelate (*i.e.* to complex) a radioisotope. The *molecular target* for the therapy is chosen so that it is prevalently present on the cancer cells (*overexpression*) and only to a limited degree on the healthy cells. This enables that the *vector* recognizing the *molecular target* delivers the radionuclide solely to the cancer cells.

Some radionuclides could be used for the treatment of cancers, but some others give the possibility to image the tumours. The imaging is also possible in the *targeted* approach, where a therapeutic radionuclide is attached to a *vector.* Just as in TRNT, the *vector* selectively delivers the isotope to the diseased tissues and so the cancer can be visualized by an appropriate detector. This in turn facilitates proper therapeutic decision-making and monitoring of the disease/treatment progress. In an ideal situation, one and the same *vector* could carry at one time a diagnostic radionuclide and at another time a therapeutic nuclide. Such **thera-nost**ic pair (from **thera**py and diag**nost**ics) enables a very precise tailoring of the treatment exactly to the needs of a patient and his/her specific cancer phenotype.

For the *targeted therapy* (and diagnosis), a key issue is the widest possible repertoire of available *molecular targets* and *vectors.* What we plan to show with our research is that the repertoire can be extended with a protein called Neuropilin-1 (NRP-1, a *target*) and its peptidomimetic inhibitors (*vectors*). Many researchers have found that NRP-1 is expressed on the surface of several types of cancers, including their most malicious forms. We suppose that targeting this protein should enable a precise delivery of the radioemitting cargo for diagnostic and therapeutic purposes.

In order to prove the correctness of our assumption we want:

1) to design and synthesize novel molecules targeting NRP-1 (novel *vectors*),
2) to test which of them will be the strongest binders of the *molecular target* (using *in vitro* tests),
3) for the best of the *vectors*: to label them with diagnostic radionuclides $^{43/44}$Sc and ^{68}Ga,
4) to administer our compounds (complexes *vector-radionuclide)* to mice that would be transplanted with human cancer cells,
5) to check whether our complexes are delivered to the tumour tissue – to this aim we shall attempt to image the cancers by the means of Positron emission tomography–computed tomography (PET-CT).



If our assumption is correct, we shall be able to extend the repertoire of *molecular targets* with Neuropilin-1. What is more, we shall provide novel *vectors* targeting the protein. A direct result of the project will be novel diagnostic tools for oncologists. If the project succeeds, another step to be taken will be an attempt to use the novel vectors for therapeutic purposes.