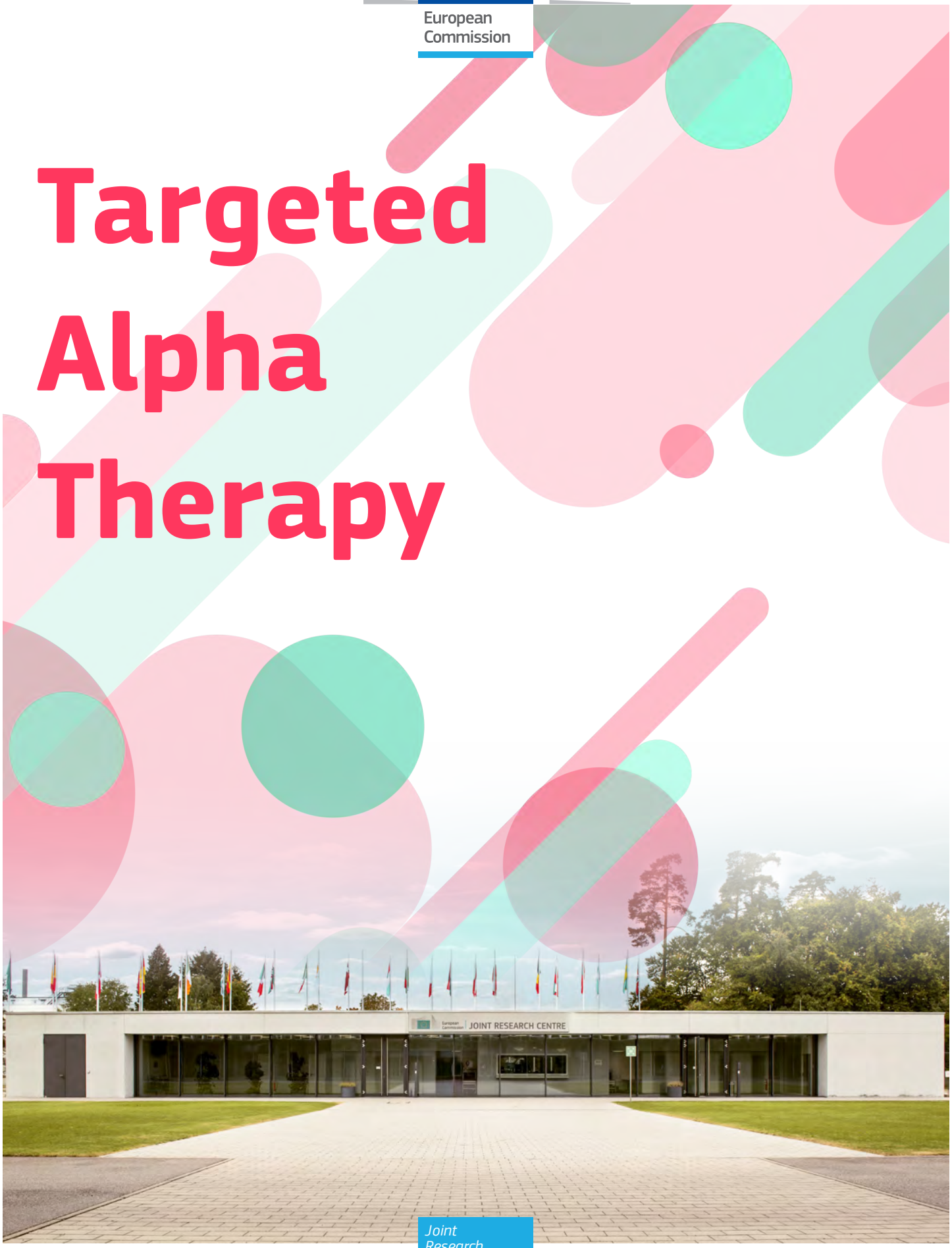
European Commission

Targeted Alpha Therapy



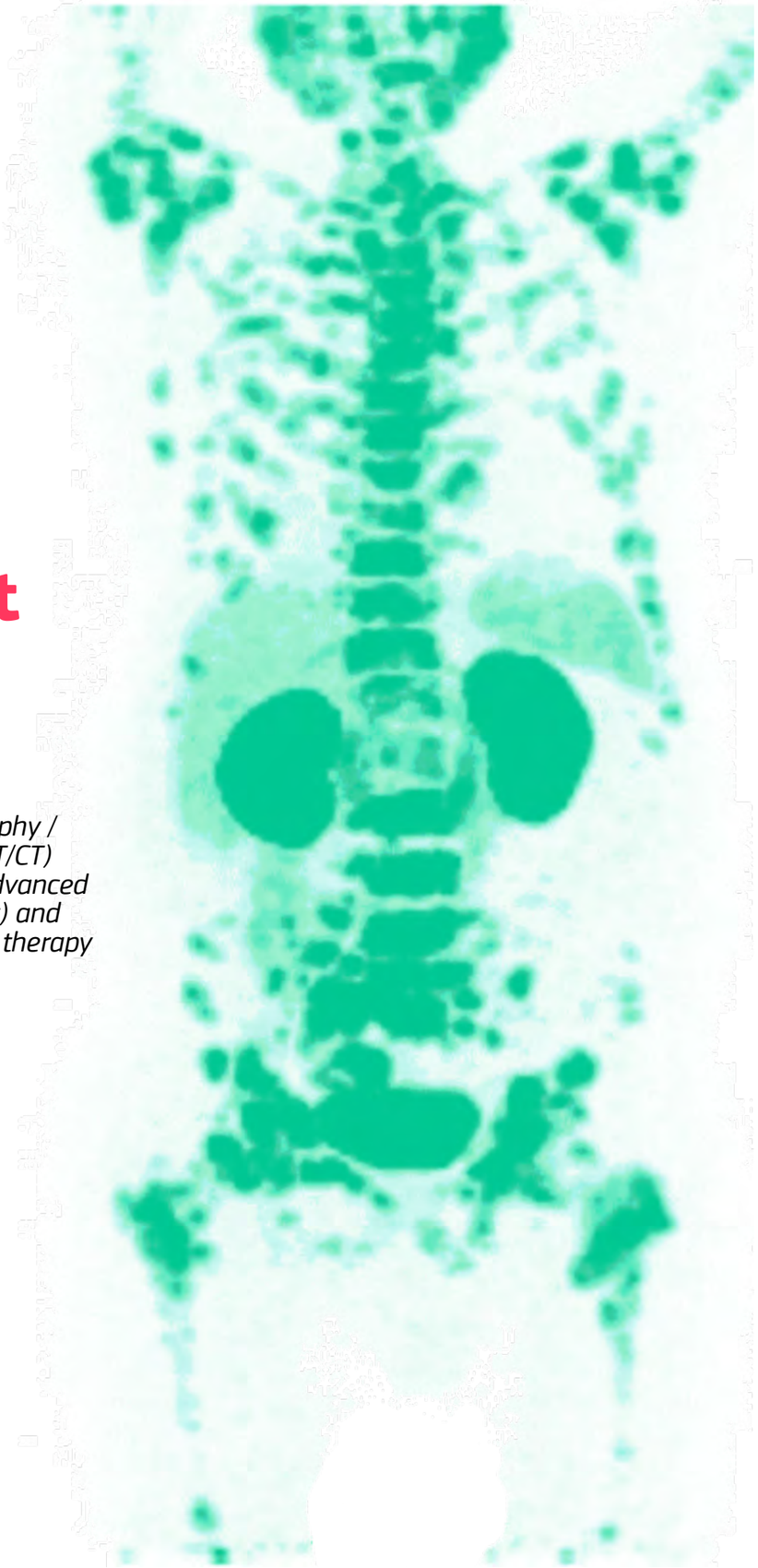
Joint Research Centre

Before Treatment

PSA* = 2923 ng/ml

Date: Dec 2014

Positron Emission Tomography / Computer Tomography (PET/CT) images of a patient with advanced prostate cancer before (left) and after (right) targeted alpha therapy with 225Ac-PSMA617.

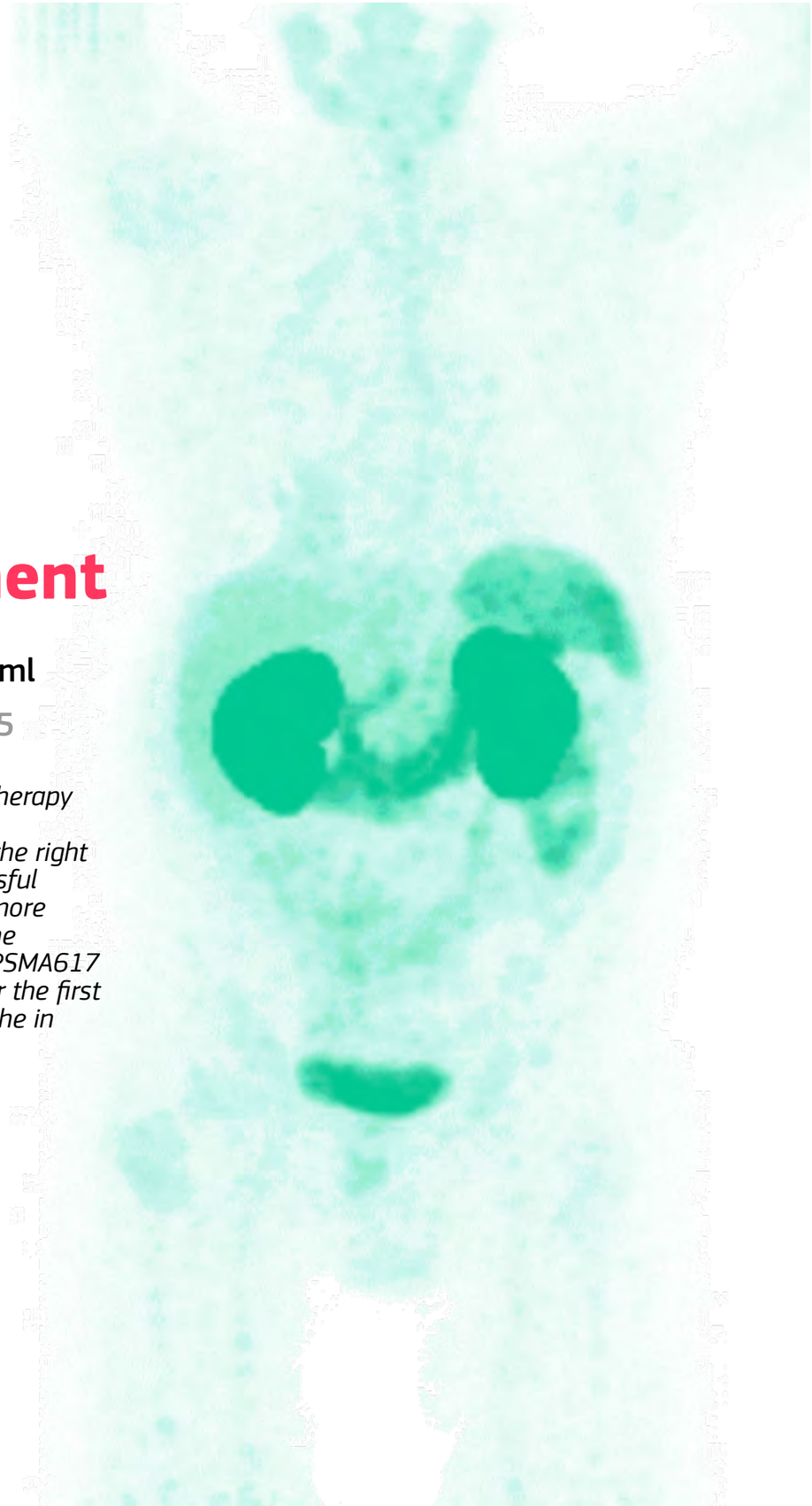


After Treatment

PSA = 0.26 ng/ml

Date: July 2015

The image before therapy shows widespread metastases, while the right image after successful therapy shows no more signs of disease. The compound 225Ac-PSMA617 was synthesized for the first time at JRC Karlsruhe in 2013.



**PSA = Prostate Specific Antigen*

How it Works

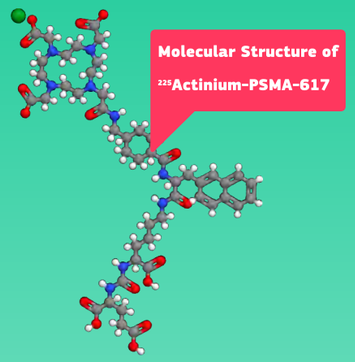
Alpha Radiation consists of the emission of alpha particles, charged nuclear particles formed by two protons and two neutrons. It is characterized by high energy and short penetration depth in human tissues.

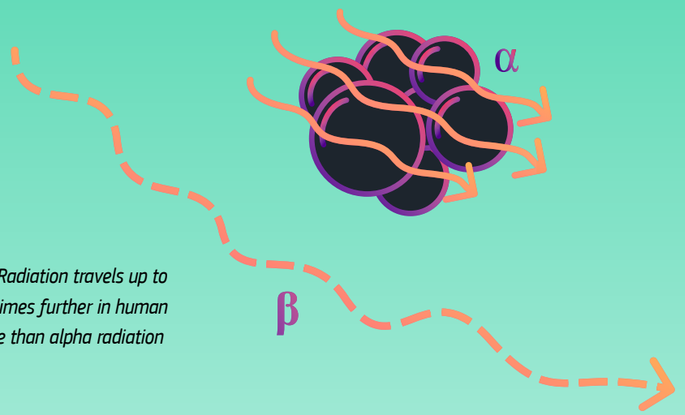
With the help of alpha radiation, it is possible to irradiate tumors selectively while sparing healthy tissues.

What does produce alpha radiation?

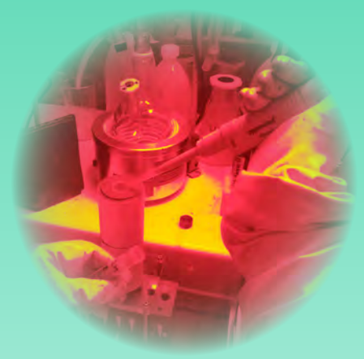
The emission of alpha particles is the result of a spontaneous nuclear transformation occurring mainly in nuclides with a large number of protons, where the electrostatic repulsion overcomes the cohesive nuclear force. As any other radioactive decay, alpha radiation is the result of a nuclear process and is not the property of a chemical element.

Several isotopes of radium, radon, polonium, actinium, uranium etc. Exhibit pure alpha decay.





Beta Radiation travels up to 100 times further in human tissue than alpha radiation



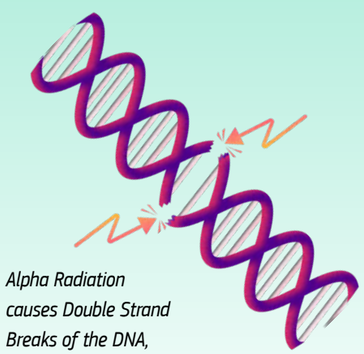
Why is Actinium so important?

Actinium-225 is one of the most effective radioisotopes for alpha therapy. Its decay chain provides four energetic alpha particles for destroying cancer cells, whilst its half-life of about 10 days is ideal for complementing the therapy cycle (from the preparation of the drug to the dismissal of the patient from the hospital).

Ac-225 can be gathered with the required radiochemical purity as a product of the radioactive decay of Thorium-229. The decay chain of Thorium-229 ends with the almost stable isotope Bismuth-209.

For medical applications it is very important that the radionuclide used as radiation emitter is chemically pure (absence of other chemical elements) and isotopically pure (absence of other isotopes of the given element).

For instance, the presence of Actinium-227 is not desired in a radio-pharmaceutical based on Actinium-225.



Alpha Radiation causes Double Strand Breaks of the DNA, that are very difficult to repair

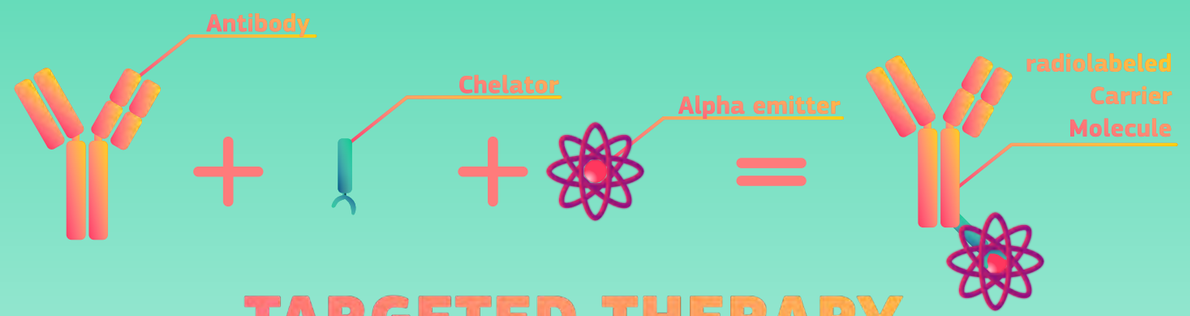
How does Alpha Radiation Reach the Tumor?

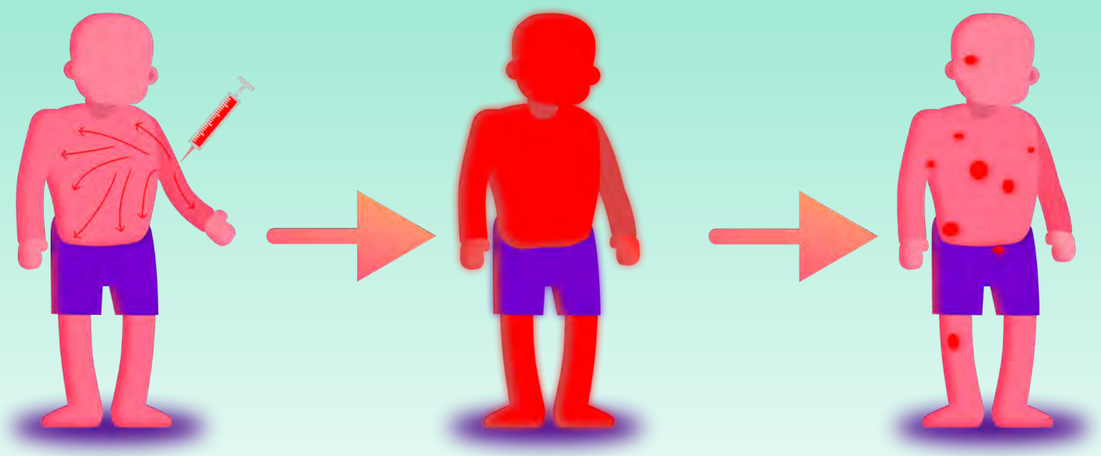
To be able to unfold its full potential, Actinium-225 has to be in close proximity of cancer cells (even better inside the cancer cell). This can be achieved if the tumor cell presents a characteristic biomolecule (a protein, for instance) on its surface that is absent in the healthy one. These tumor-specific biomolecules can be targeted by biomarkers, that is by chemical species having a strong tendency to form stable chemical bonds.

A Biomarker, modified with the addition of a part able to capture the radionuclide is called a radioligand and can be used to taxi the alpha emitter directly to the tumor cell. A good radioligand must be chemically stable and very fast in reaching the target (you don't want the taxi to break down during the transport or the radiation decay to occur while traveling).

Did you know that Thorium-229 has a half-life of 7940 years, which means it takes that many years for the number of Thorium-229 nuclei to fall o half of its initial value? It takes about two months for the concentration of Actinium-225 to saturate in a sample of Thorium-229.

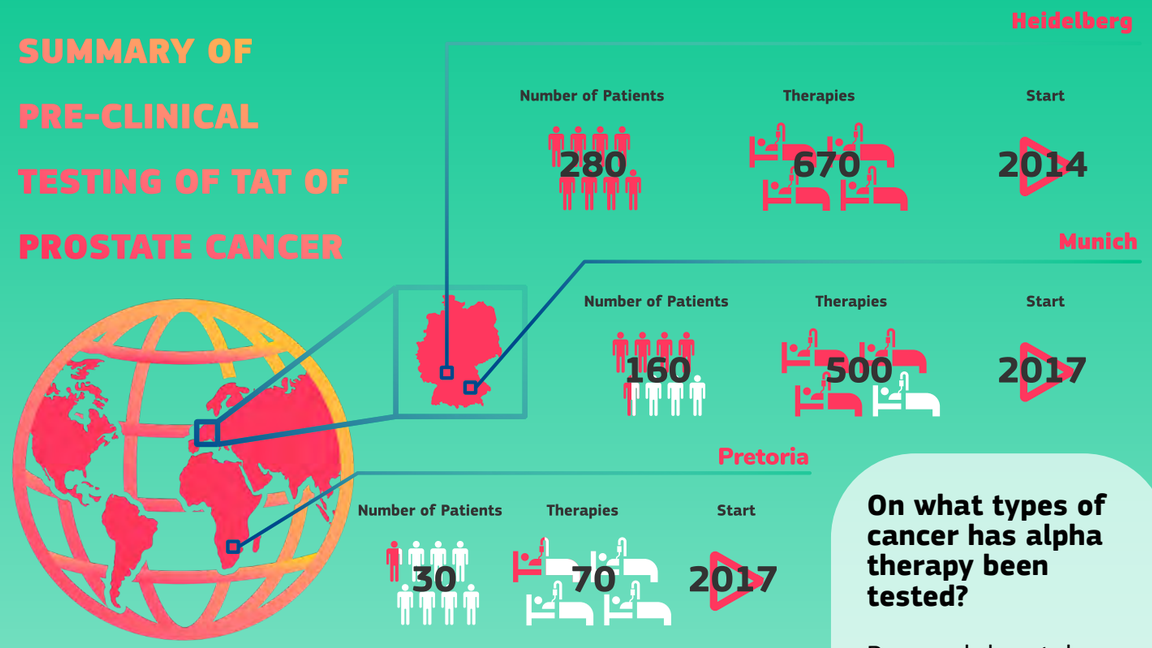
The research behind Biomarkers takes place in the field of theragnositcs. The combination of therapy and diagnostics.





Pre-Clinical Testing

SUMMARY OF PRE-CLINICAL TESTING OF TAT OF PROSTATE CANCER



On what types of cancer has alpha therapy been tested?

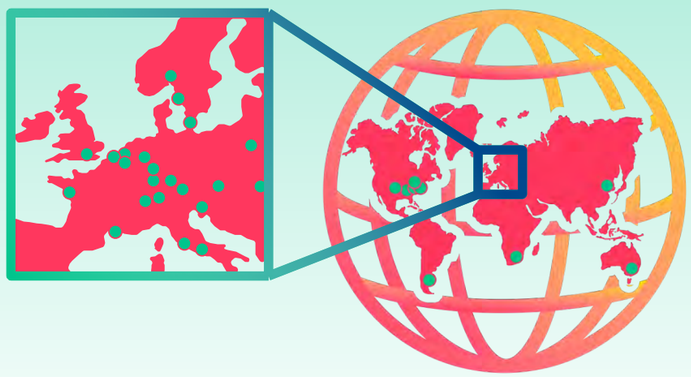
Research has taken place on many different types of cancer, like leukemia, lymphoma, melanoma, brain-tumors, neuroendocrine-tumors, bladder carcinoma and most importantly castration resistant metastatic prostate cancer

How has prostate cancer been treated?

The treatment used the radioligand ^{225}Actinium-PSMA-617, in which Actinium-225 is linked to a peptide having a strong chemical affinity for the protein PSMA, or “Prostate Specific Membrane Antigen”. PSMA decorates the surface of prostate cancer cells whilst not being present on healthy ones.

Clinical tests allowed the scientists to determine the optimal value of the radiation doses delivered to the patient. The efficacy of the treatment has been monitored by positron emission tomographic imaging techniques and by measuring the concentration PSA in the blood of the patient at different time intervals after the administration of the treatment.

COLLABORATIONS FOR PRE-CLINICAL TESTING



Contributions of Joint Research Centre to TAT*

Despite recent improvements in prevention, diagnosis and therapy, the majority of cancers, in particular in case of metastasized disease, remains incurable. For more than two decades Joint Research Centre (JRC) has gathered extensive experience in the development of a novel approach for therapy of advanced, metastasized cancers utilizing alpha emitting radionuclide, called Targeted Alpha Therapy (TAT).

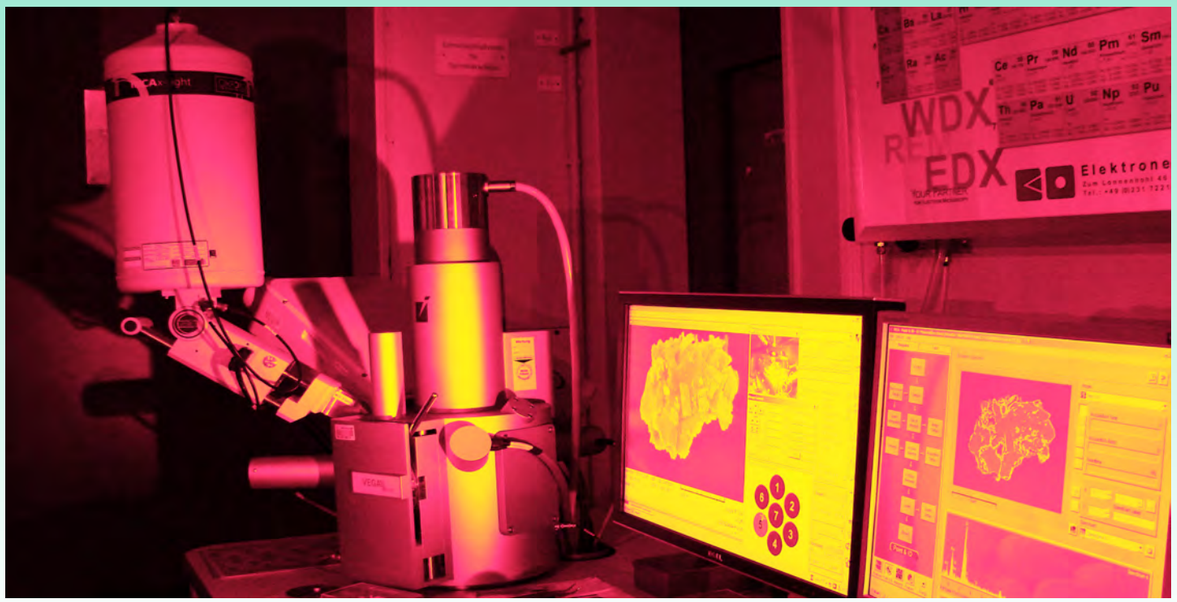
The activities of JRC related to TAT focus on the development and clinical testing of novel compounds for cancer therapy, the development and standardization of protocols for safe handling, synthesis, quality control and application of alpha emitter labelled compounds in clinical settings, as well as transfer of knowledge and provision of training to clinical staff in member states and worldwide.

More recently a breakthrough has been achieved with the development of a novel compound for therapy of advanced prostate cancer, ^{225}Actinium-PSMA-617. The compound, first synthesized at JRC Karlsruhe in 2013, shows remarkable efficacy for treatment of advanced prostate cancer and offers a new treatment option for the globally second most frequent cancer in men. Furthermore, it clearly demonstrates the significant potential of targeted alpha therapy for treatment of cancer in general. In addition, JRC and its partner hospitals are developing novel approaches for the treatment of rare diseases, such as glioblastoma multiforme and neuroendocrine tumors.

JRC has established a large network of clinical partners for joint development and clinical testing of alpha emitter labelled compounds. JRC is closely collaborating with IAEA** for the transfer of knowledge and provision of training to hospitals in Europe and worldwide and is organizing a bi-annual series of international symposia on TAT, bringing together 400-500 participants to present and discuss the newest development in TAT for cancer.

**TAT = Targeted Alpha Therapy*

***IAEA = International Atomic Energy Agency*



The European Commission's science and knowledge service

Joint Research Centre

JRC Mission

As the science and knowledge service of the European Commission, the Joint Research Centre's mission is to support EU policies with independent evidence throughout the whole policy cycle.

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conceived by: Lorenz Weber