Nuclear Application in Medicine

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Barely a few months after Röntgen discovered X-rays, the discovery of the phenomenon of radioactivity by Becquerel and Curie was equally sensational. These discoveries were the basis for two important applications in medicine: **radiodiagnosis** and the **treatment by ionizing radiation**.

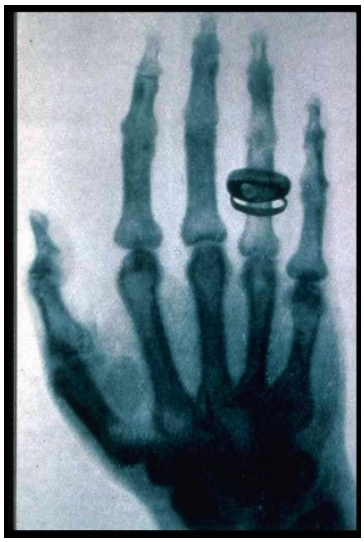

Figure 1 – Dr. von Kollikers hand, a friend of Röntgen, second known radiography ever.

Both **Radiodiagnosis** (using X-rays) and **Radiation Therapy** (use of X-rays or radionuclides, whether in sealed sources, or not**)** were used on an experimental basis in the years following their discovery. Marie Curie is known for having setup during WWI a series of mobile X-ray vans to allow detection of bullets and shrapnel in wounded soldiers close to the battle fields. These “Petites Curie”, and Marie herself, were also on the Flemish front to help wounded Belgian soldiers**.**

The latest development in nuclear medicine is bringing Diagnostics and Therapy together in what is often referred to as **Theranostics**. In this case, the combination of a radionuclide and a pharmaceutical product combines the advantages of both biology (which allows to bring a radioisotope to the desired location) **and of nuclear physics**, which uses the radiation of the isotope either as a localization signal (diagnostics and dosimetry) or to destroy specific target cells (radiation therapy).

Other radiation therapy applications make **direct use of Particles (p+, e-, α)** beams (generated in a Particle Accelerator) or neutron beams (generated in a Reactor – usually a research reactor). In general, the use of particles or radioisotopes for treatment offers **undeniable advantages because they impact at both the molecular and at the cellular levels**.

Each year, some 40 million patients around the world depend on the use of medical radioisotopes. The radionuclides used are mainly Technetium-99m (Tc-99m) and Fluor-18 (F-18), but recent developments induce an increase in the therapeutic use of radioactive isotopes, **able to treat numerous diseases**. Diagnostic and therapeutic applications with other radioisotopes are growing exponentially. The story of nuclear medicine is far from over, as this field continues to evolve and expand, unlocking new possibilities for diagnosis and treatment.

Medical imaging, both with X-rays and radioisotopes, is undoubtedly one of the medical fields in which spectacular progress has been made due to an increase of computer power to improve imaging quality and interpretation. Thanks to precise localization, it becomes easier to intervene surgically, which is the only possible treatment for some pathologies. Moreover, new techniques enable a deeper understanding of the functioning of certain organs, including the brain, about which much remains to be discovered.

Regarding the medical applications of ionising radiation, it is worth noting that one of the three basic principles of radiation protection, namely the pursuit of the lowest possible dose, does not necessarily apply here. Unlike the other applications, exposure to radiation, either for diagnostic or for therapeutic purposes, is in the interest of the patient. It is therefore up to the doctor to determine on a case-by-case basis to what extent the patient may be exposed to achieve the desired goal. Better understanding of the biological effects of radiation, low dose versus high dose, potential hormesis effects, making tissues more radiation resistant, etc., are also being investigated. Nevertheless, a major challenge remains to limit the impact of the radiation in the areas surrounding the location where the treatment needs to be focussed.

1 Radiography by X-ray

Radiology is the discipline in medical imaging that **includes the set of techniques to image the morphology of the human body by means of X-rays**. In December 1895, W.C. Röntgen, the discoverer of X-rays, made a first radiogram of his wife's hand (see Figure 1). The technique takes advantage of the fact that X-rays can partially pass through the human body and, depending on the nature of the crossed

tissue, are absorbed to a greater or lesser extent – This generates contrast on the created image that can thereby be interpreted by a specialist. For example, bones are more difficult to penetrate than muscles, which in a radiogram leads to areas that are darker and lighter. With this technique, radiograms can be made to reveal, for example, a bone fracture, damaged tissue in a lung radiogram, etc.

' **Conventional radiology'** still covers most of all radiological examinations that are carried out. These are mainly X-rays of bones, of the chest area and of the abdominal area. Today the classical photographic films have been replaced by digital read-out, allowing a much faster – or even instantaneous – diagnosis.

In a **CT** scan **(**Computerized Tomography), precisely focused X-rays, generated in an X-ray tube, rotate all the way around the patient's body. Image acquisition and processing software then allows to reconstruct a three-dimensional image of the organs and delivers more contrasted images of the organ structures. With a CT scanner, the brain, chest, abdomen or bones are among the organs or regions that can be studied. The scanner reveals abnormalities that are not visible on an ordinary radiogram or an ultrasound. And importantly, in quasi real-time.

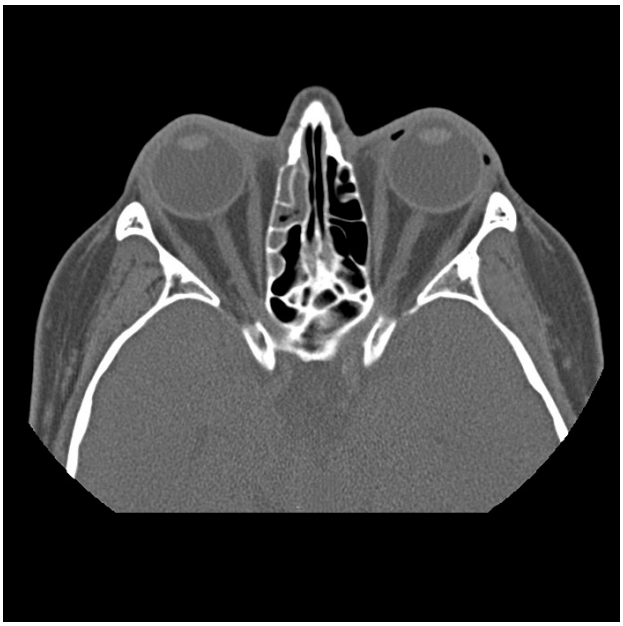

Figure 2 – Cross section at eye-ball level (CT-scan)

In addition to conventional radiology and the scanner, **more specialized techniques** expand the diagnostic range. Examples include **coronarography** (internal examination in which pictures are taken of the heart and coronary arteries to determine any constrictions) and **mammography** (X-ray examination of the breasts). **Dental X-ray equipment** occupie an important place in the total radiology park. A commonly used technique is the panoramic X-ray, in which an X-ray bam rotates around the patient's head for about ten seconds and makes an image showing both the lower and upper jaw.

Radiological examinations mainly concern the macroscopic structure of the various organs. In order to clearly visualize that structure, the difference in density of the different tissues must be sufficiently high

(e.g. the difference between bone tissue and soft tissue). If this is not the case, a 'contrast product' will often be injected (e.g. a iodine solution during a coronarography) to obtain a better visualisation.

Other techniques which do not use ionizing radiation

Magnetic resonance

The X-ray CT scanner, initially a true revolution in the radiological world, is now facing increasing replacement by MRI (magnetic resonance imaging).

In this technique, the patient is placed in a **powerful magnetic field**. Our organism contains large amounts of hydrogen nuclei, included in water molecules. When those molecules enter a magnetic field and are exposed to carefully selected radio impulses with a specific frequency, the **hydrogen nuclei** "respond" by emitting **radio waves** at a similar frequency. Images can be generated from this signal. This morphological research thus makes use of the magnetic properties of the atomic nuclei in the different structures of our organism. The advantage as compared to the X-ray scanner is that there is no exposure to radiation. The disadvantage, however, is that the examination takes a lot longer (several minutes rather than seconds). MRI has become the preferred method for imaging soft tissues with high spatial resolution and is particularly effective in cerebrospinal structures (brain and spinal cord). Through MRI, certain functions of the brain can also be studied, e.g. by locally measuring the changes in blood circulation. The technique is expensive but relatively safe.

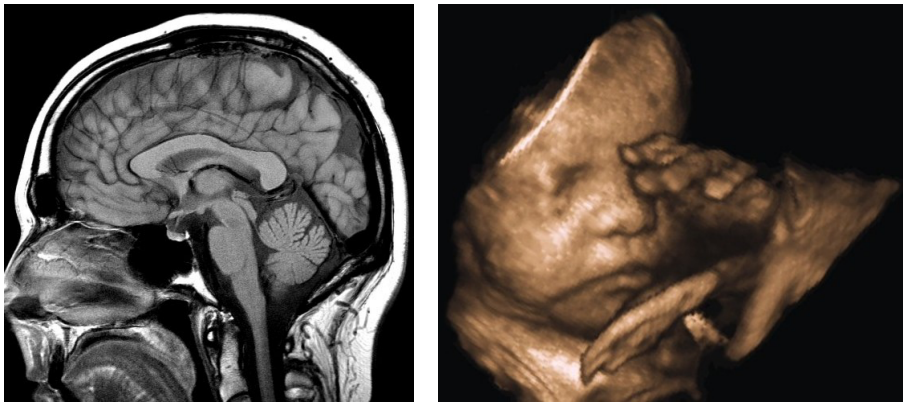

Figure 3 – (left) MRI-scan of the brain; (right) Ultrasound of a foetus in his mother's abdomen

Ultrasound (ultrasonography)

In ultrasound imaging, one uses an external source of **ultrasonic pulsating** waves. These waves are basically audio waves with a frequency higher than the human ear can hear. The moment and the direction of the waves are both known. At the interfaces between the different tissues, the waves are partially reflected. By measuring the time that elapses between the departing and returning wave, one can generate an image. Echograms are mainly used to image soft tissues and for the prenatal follow-up of babies. The technique is fast, harmless and cheap, which makes it very widespread worldwide.

2 Nuclear Medicine: diagnosis

The diagnostic applications of nuclear medicine are partly divided into **in vivo *techniques, in which the patient is administered radioisotopes***, and partly into ***in vitro techniques***, in which a **sample** taken from the patient (blood, urine, biopsy, etc.) is **examined in the laboratory**. Nuclear imaging is the most common in vivo application, while the radioimmunological assay (such as hormonal dosing in the blood) is the most widespread technique in in vitro radio diagnostics. This last one was very popular in the 80's and till early 21st century but has gradually been replaced with non-nuclear techniques.

Nuclear medicine imaging is essentially functional imaging at the molecular level and is therefore an **important addition to purely morphological imaging** via conventional radiology, CT scanner, ultrasound or magnetic resonance.

2.1 In vivo

This technique consists of studying the metabolism of an organ by means of a specific radioactive substance – the so-called radiopharmaceutical – that is administered to a patient. The nature of the radiopharmaceutical depends on the organ or disease to be examined. The **radioelement can either be used directly or attached to a vector** (molecule, hormone, antibody, etc.) with a high affinity for the organ being examined or for a particular biochemical process in the body.

The localization of the radioactive substance in the organism is done with a specific detector – the gamma or PET camera – which consists of a scintillator or semi-conductor detector, hardware and software for image acquisition and processing. With this equipment one can get a picture of the **functioning of organs (scintigraphy).** Scintillation literally means 'sparkle, brilliance'. In other words, it is based on measuring the flashes of light generated by radioactive radiation in a scintillation crystal or liquid. Recent cameras use semiconductor-based detectors, offering better quality images.

*The example that historically best illustrates the technique is the use of radioactive iodine to investigate the functioning of the thyroid gland or to treat thyroid disorders. The thyroid gland has a natural affinity for iodine, which it needs to secrete thyroid hormone. In Belgium, the thyroid gland of people who follow a normal diet contains 8 to 10 mg of iodine-127, which is a naturally occurring and non-radioactive isotope. However, if iodine-rich foods are administered (e.g. seafood), the thyroid gland will absorb the extra iodine like a sponge, until it is completely saturated. The thyroid gland does not distinguish between the different isotopes of iodine, regardless of whether they are radioactive. Consequently, if a very small but known dose of radioactive iodine is administered, e.g. iodine-131, the amount of this specific isotope found in the thyroid gland reflects the affinity of the organ for iodine, which thereby characterizes the thyroid function (diagnostics). The right amount of radioactive isotope best-suited for the measurement must be adequately determined. On the one hand, as with all physical measurements, the technique should not interfere with the functioning of the organ studied. If the dose of iodine being administered is too high, the actual thyroid function itself will be affected. That is why the smallest possible amounts of radioactive iodine are used in thyroid diagnostics: one speaks of a radioactive trace (and by analogy also of '**tracers**'). On the other hand, the radioactivity must also be sufficiently high to achieve an acceptable measurement quality (reliability).*

The above example also illustrates the main challenges for nuclear imaging:
- To select or develop a molecule capable of bringing the appropriate radioelement to the organ under investigation and then studying how it spreads (temporal and spatial).
- To determine the required dose administered for optimal diagnosis with minimal radiation.
- To avoid physiological effects of the molecule by administering only trace amounts.

The radioisotopes shall be chosen in such a way that their γ-emission can be detected externally. There are many of these radioelements or "pure γ-emitters" (they only emit photons) such as technetium-99m, iodine-123, thallium-201, indium-111, etc. **However, technetium-99m is by far the most widely used radio element** (more than 90% of all cases). It has excellent physical properties, is inexpensive and easily available and it has a radiant energy that is very appropriate for the patient from a dosimetric point of view. There is no stable technetium in nature: all isotopes are radioactive. Technetium-99m is the decay product of Molybdenum-99, which is itself a fission product of Uranium-235. The half-life is 6 hours, in most studies an ideal length for imaging, but too short for Tc-99m to be stored for more than a day. The half-life of molybdenum-99 is 66 hours. This makes it possible to store a molybdenum-99 generator and use the decay product, Tc-99m, according to the clinical needs. In Belgium, molybdenum-99 is obtained, among other things, by irradiating uranium in the BR-2 reactor of the Belgian Nuclear Research Centre, SCK CEN in Mol, followed by extraction and purification at the Institute for Radioelements, IRE, in Fleurus. Almost 7 million patients worldwide undergo a medical examination every year thanks to the Belgian production of molybdenum-99.

Cyclotron for short living isotope production

Another way to produce short living isotopes for the radioactive tracers is a Cyclotron. These compact accelerators will accelerate electrons, protons or even full nuclei to hit a "target" and produce the desired isotope through nuclear reactions. This technique not only enables the production of (very) short-lived isotopes but also allows for the creation of specific isotopes with minimal side products or waste by carefully selecting the beam energy, incident particles, or isotopically enriched targets.

Many larger hospitals or radiopharmaceutical production sites are equipped with cyclotrons to produce medical isotopes close to the nuclear medicine departments.

Ion Beam Application or IBA, based in Louvain-la-Neuve, is world leader in the manufacturing, installation, and start-up of these accelerators for medical applications.

In 1935, Nobel Laureate George de Hevesy injected a small amount of phosphorus-32 into rats. After measuring the radioactivity of the bones, he formulated a very controversial statement at the time: "*This result strongly supports the view that the formation of bones is a dynamic process, the bone continuously taking up phosphorus atoms which are partly or wholly lost again and are replaced by other phosphorus atoms*". This dynamic view of bone formation was diametrically opposed to all static theories at the time, but G. de Hevesy was right, and today **skeletal scintigraphy** (see Figure 4 below) is one of the most frequently used procedures in nuclear medicine. Prior to the study, Tc-99m labelled diphosphonate is injected. This tracer actively looks for areas where bone growth takes place. The picture of radioactivity reflects bone growth and bone metabolism.

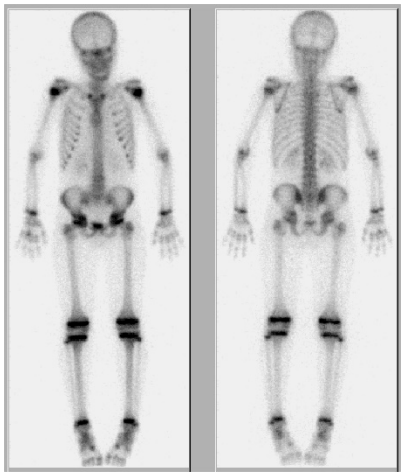

Figure 4 – normal bone scintigraphy, performed with a gamma camera. We see the bone metabolism of a young patient (front and back view).

Using SPECT (Single Photon Emission Computed Tomography), in which the camera rotates around the patient, **three-dimensional images** can be reconstructed from two-dimensional projections. D. Kuhl developed emission tomography from 1964 onwards. The spatial resolution of SPECT tomographic

imaging is similar to that of classical imaging, but because lesions are imaged with much more contrast, they are easier to detect and examine.

Positron Emission Tomography (PET-scan)

This technique allows to create cross-sectional images that show the distribution (temporal, spatial and quantitative) of a radioactive tracer emitting positrons (positive electrons, antiparticles of negative electrons).

The tracers are labelled with a radio element that emits positrons and thus become radio tracers. Since the production of the radioelements requires a cyclotron (See above) and since the radiation is only short-lived, the radio tracers can only be used close to the place where they were generated. The advantage of this form of labelling, with a very high specific radioactivity, is that only very ***small amounts of tracer*** *must be injected. F-18-FDG (fluoro-18-deoxyglucose) is well suited for this purpose. It has a half-life of 110 minutes and decays into stable oxygen-18 by emitting a positron.*

The emitted positron then "travels" until it collides with a free electron. The collision will result in their annihilation, leading to the simultaneous emission of two γ photons, which will travel in opposite directions, 180° apart. Those photons are then detected by the positron cameras connected to a processing unit.

2.2 In vitro

This analytical technique used in biomedicine does not involve administering radioisotopes to the patient but enables the measurement of specific components in **biological fluids, particularly in blood**: hormones, drugs, tumor markers, etc. This technique uses dosing methods based on immunological reactions (antibody-antigen reactions labelled with radioisotopes), hence the name radioimmunology or RIA (Radio Immunology Assay). In recent years, radioactive methods have gradually given way to non-radioactive alternatives, especially regarding growing concerns and issues of radiation protection nature, and regarding the cost of processing radioactive waste. However, some tests are still being performed by the nuclear medicine departments worldwide.

3 Radio Therapy

Ever since the first radium treatments[1] at the end of the 19th century, radiation therapy has evolved greatly. Along with surgery, chemotherapy and immunotherapy, it is **one of the most used techniques for treating cancerous tumours.** Radiation therapy uses ionizing radiation, coming from an external or internal sealed source, to destroy malignant cells. The administered doses are calculated in such a way that the radiation is concentrated as much as possible on the tumour while the surrounding, healthy cells, are irradiated as little as possible.

Prior to the radiation sessions, a patient-specific treatment plan is always drawn up. In the plan, the volume to be irradiated, the dosimetry, the trajectories that the beams must describe (ballistics) and the duration of each treatment are determined very precisely. The elaboration of this plan, which aims

[1] *The first radium treatments or 'curie therapies' were carried out a few years after the discovery of radioactivity by Becquerel and the discovery of radium by the Curie family. Marie Curie founded "L'Institut du Radium" and has personally calibrated more than 5,000 radium sources.*

to achieve a high and homogeneous radiation dose in the target volume while ensuring the maintenance of healthy tissues, requires close cooperation between the hospital physicist (radiation expert) and the radiation therapist (oncologist). Originally, simulations with Phantoms and small dosimeters were used for this planning but currently powerful software is available to do most modelling, often linked to diagnostic software to fine-tune the model.

3.1 External Radiation Therapy

Irradiation is carried out by "shooting" a beam with ionising radiation through the patient and hitting the tumour. Irradiation is carried out in different sessions from different incidence angles, limiting the dose to the healthy tissue but accumulating it in the tumour. The technique was often referred to as (tele)gamma therapy, as it was originally using a strong cobalt-60 (cobalt therapy) or caesium-137 source. The current instruments use a linear accelerator that creates a strong Bremsstrahlung (highly energetic X-rays). The accelerators have intricate collimators to create beams with very accurate forms, which can be adapted during the rotation of the irradiation head.

With linear accelerators, also electrons can be used directly for shallow tumours. Electrons have a penetration depth in the body (typically a few centimeters) that increases with their energy. By tuning the energy, the penetration depth can be very accurately chosen, such that the electrons generate X-rays, the energy of which is deposited much deeper in the body.

3.2 Hadron or Proton Radiation Therapy

A beam of charged particles generated by cyclotron is aimed at treatment volume (Tumour). The **beams** that are obtained are **extremely fine**, which can be steered with great precision by using a set of giant bending magnets.

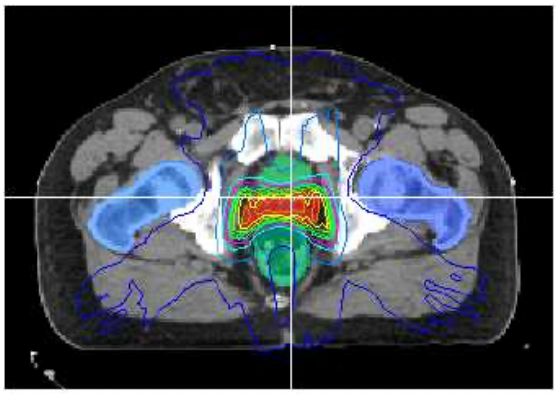

Figure 5 – Simulation of irradiation zones with corresponding radiation doses.

Proton therapy exploits two advantages of the way proton beams interact with other substances: (1) there is little lateral scattering (in the tissue) due to the weak diffusion of the protons during their trajectory; (2) at the end of the trajectory they release all their energy on a very short distance (the Bragg peak). The location of the maximal energy deposition can thereby be controlled very well (depending on the energy of the incident particles) and the dose at the peak is – as desired to kill

cancerous cells – very large. Thanks to this ballistic precision (controllability of the trajectory), each proton beam can be adjusted to adjust the dose distribution three-dimensionally to the shape of the target volume to be irradiated (the tumour). It thus enables **to increase the doses in the treated volume while at the same time minimize the dose, and therefore the associated complications, to healthy surrounding tissue**. For that reason, proton therapy is the preferred technique in radiotherapy when the treated tumour is close to radiation-sensitive structures (optical pathways, spinal cord, etc.).

Heavier particles can also be used and are then referred to as Hadron Therapy. But these require heavier accelerators and bending magnets and are so far only experimental.

The Belgian company IBA is not only the world leader in manufacturing and installing cyclotrons but also the world leader in Proton-Therapy installations.

3.3 Radiation therapy by in vivo implantation of sealed sources (brachytherapy or curie therapy)

Curie therapy is the oldest form of Radiotherapy and goes back to a few years after Radium was discovered. Today it is mainly called brachytherapy and it allows to treat **cancer tumors** in cavities or tissue in which small sealed sources can be introduced. The radionuclides most used in brachytherapy are Cesium-137, Iridium-192 and Iodine-125. They have definitively taken the place of Radium-226, which was used in the first half of the 20th century in the form of needles or tubes.

There are in fact three forms of brachytherapy:

1. if the radiant material radiates slowly (0.4 to 2 Gy/h) it is called Low Dose Rate or LDR treatment. The patient must then be hospitalized for several days. The applicator often has the shape of a fine wire of a few centimetres. Iodine-125 sources are or have been used to treat prostate cancer.
2. if the radiating material has a medium radiation rate (2 to 12 Gy/h), it is called Medium Dose Rate. A specific radiation source is used (iridium-192 in small dimensions). Since the dose flow rate is higher, the irradiation can also be divided into many small steps (Pulsed Dose Rate). This results in a higher comfort for the patient, who does not need to constantly have the radiation source present in the body;
3. High Dose Rate treatments (more than 12 Gy/h) use a strong radiation source and the treatment time is very short (at most a few minutes). As a rule, this is only done with a so-called “afterloading device” as an applicator.

Alternative to these are the use of “seeds” or small mechanical spheres or very small cylinders that can be placed in tumours that have sponge like or needle accessible tissue. These are very specific treatments.

3.4 In Vivo Radiation therapy by administration of open sources (Theranostics)

It is currently the hot topic in nuclear medicine and one of the most promising techniques in cancer treatment. Although many different names have been used, the generally accepted terms currently are **Radio Ligand Therapy** (RLT), **radioimmunotherapy** or **Theranostics**. In the diagnostic field or medical imaging field, A wide range of molecules has been designed to bind with high specificity to cancer cells or other harmful cells (Alzheimer, inflammations…). These range from small molecules (RaCl) to full

anti-bodies over nanobodies and smaller peptides. For the majority of simple ions and molecules, the affinity for the target volume is insufficient for therapeutic purposes. By using large molecules that bind with the antigens on the cancer cells, and not with the healthy tissues, the selectivity of the treatment can be increased as they have a high affinity for specific cancer cells or cells associated to tumours (Eg. Fibroblast cells).

The carrier molecules are referred to as “vectors” and the cell structures to be targeted as “Target”

The strategy is as follows:

1. a vector that is assumed to be highly specific to a specific cancer cell or associated cells is marked with a diagnostic or imaging isotope (often PET) and injected at diagnostic (low) doses.
2. images are generated to verify the extent to which the vector binds to the tumour and any metastasis;
3. If the selective binding (affinity) is sufficiently high, a second radio pharmaceutical will be prepared for injection. The same vector is used but the attached isotope is now selected to deliver a maximal dose to the target cells but a minimal one to surrounding tissue. These are by preference high energy Betas or Alphas with low gamma intensity.

Due to this dual isotope approach the technique is often referred to as “Theranostics”. A combination of “therapy” and “diagnostics”. The best-known combination today is PSMA (Prostate Signalling Metastases Antibody) marked with F18 or 68-Ga for PET imaging and Lu-177, a beta emitter, for therapeutic doses. But the use of Alpha emitters as At-211, Ra-223, Pb-212, Ac-225 is also used in clinical trial phases. Many more ligands as FAPi (Fibroblast Activation Protein Inhibitor), DOTATOC/TATE, Pentixapharm etc have been approved for medical use or are in pre-clinical and clinical trials.

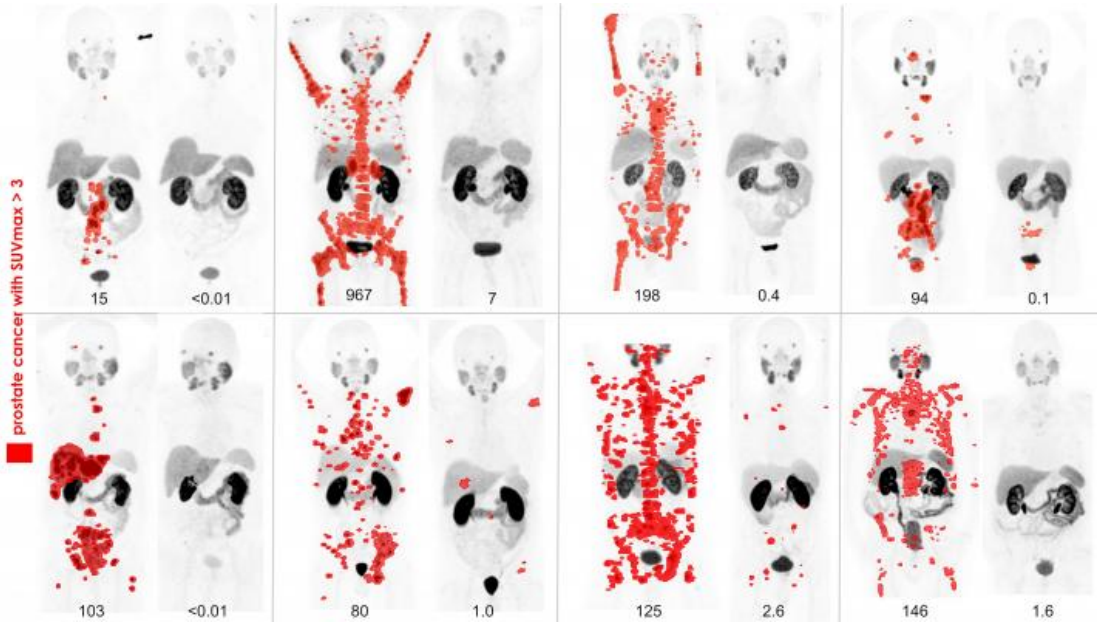

Figure 6 – SNMMI IMAGE OF THE YEAR 2018: PSMA PET before and after lutetium-177 PSMA617 theranostics in 8 patients with metastatic prostate cancer who exhausted standard therapeutic options.

It should be noted that this is also quite unique in the pharmaceutical field, whereby the diagnostic phase also provides a quantification of the doses that will be needed for the therapeutic phase. One popular technique is attaching the Radioactive isotope by a process that is known as chelating. The RA isotope is hereby caught in a small atomic cage, attached with a short inert chain (linker) to the active molecule. (Antibody, peptide, nanobody.)

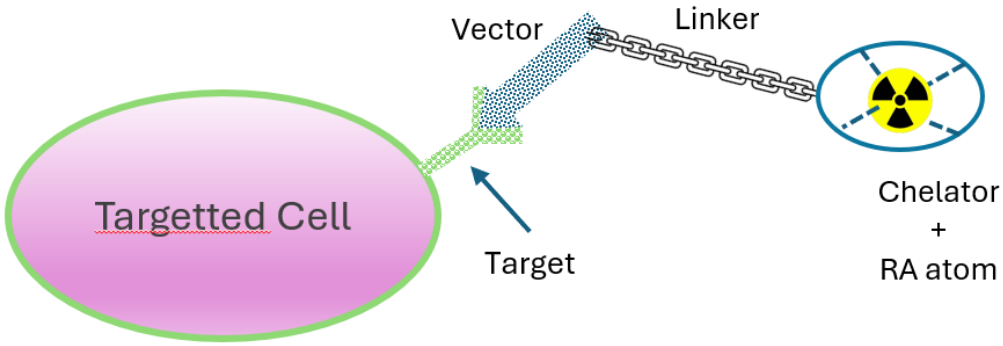

Figure 7

Advancements in this field are progressing rapidly, with numerous new vectors being discovered. While the current applications are primarily diagnostic and palliative, fully curative uses are also expanding at a remarkable pace.

Notably, Belgium has made significant contributions in this field, with several Belgian companies leading the way in the development of production tools (synthesis units) and quality control for radiopharmaceuticals. Companies such as Trasis, ORA Neptis, IBA Molecular, and Elysia are prominent worldwide, providing chemical robots to hospitals and radiopharmacies. Additionally, many of the essential quality control (QC) tests required for finished products before patient administration originate from Belgium.

Moreover, the production and availability of the necessary radioisotopes for these innovative therapies are critical and must be ensured for radiopharmacies. Pantera, a joint venture between the SCK CEN research center and IBA, is hoping to soon start producing Ac-225 based on a novel Ra-226 (ᵞ, n) Ra-225 reaction followed by a Beta decay to Ac-225.

Last but not least, recent years have witnessed the emergence of several startups offering innovative radiopharmaceutical services and development, ranging from research into new vectors to the commercial production of patient doses.