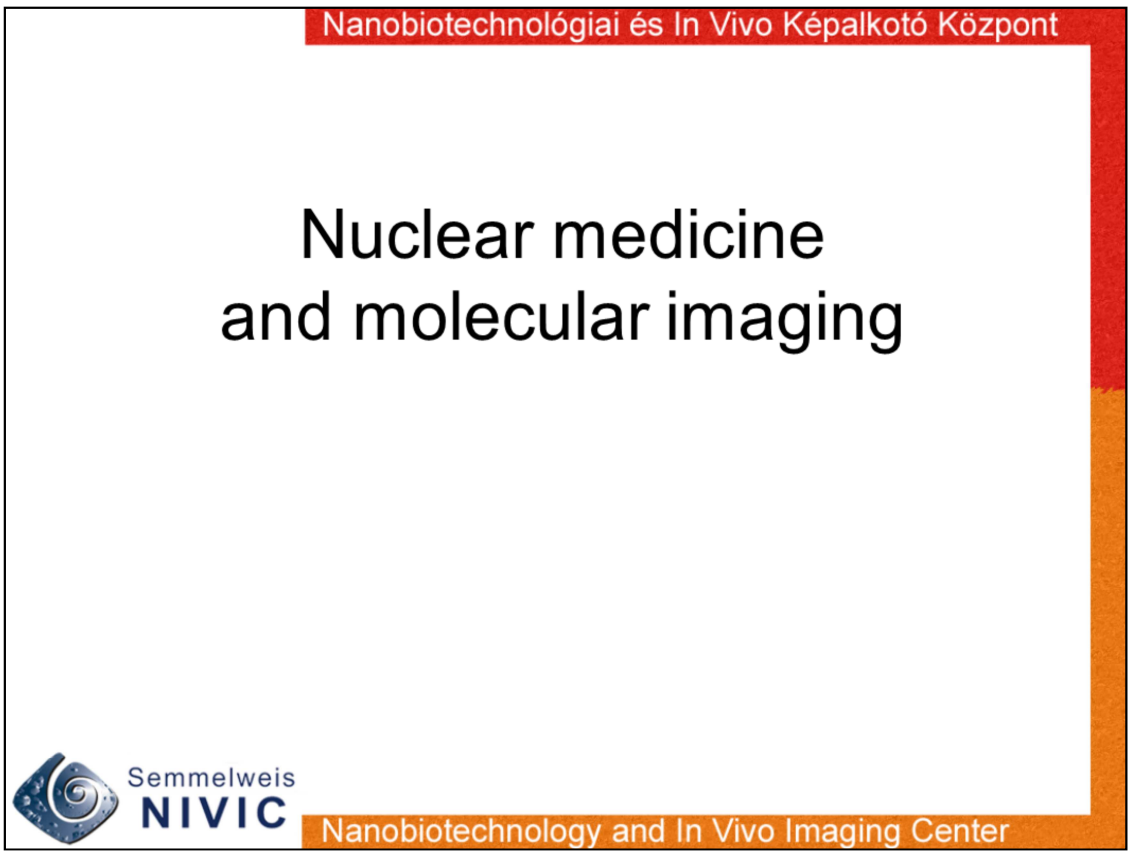
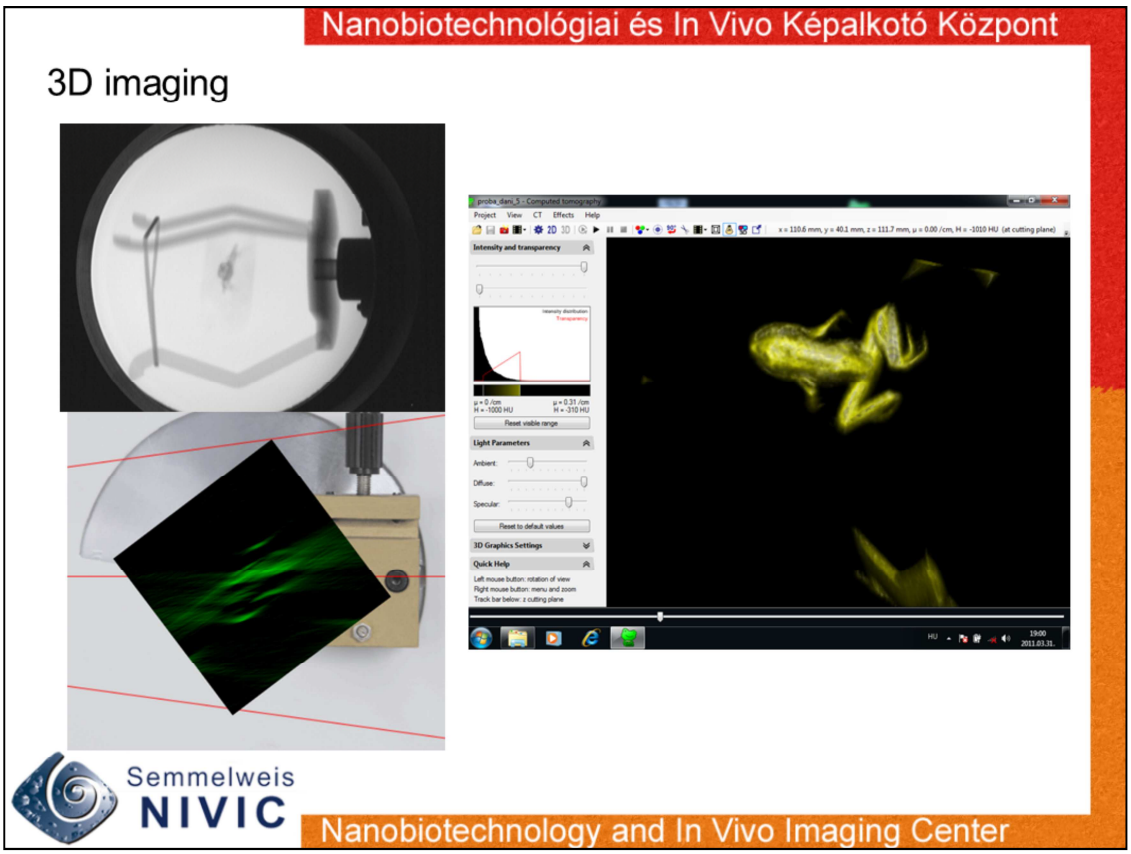


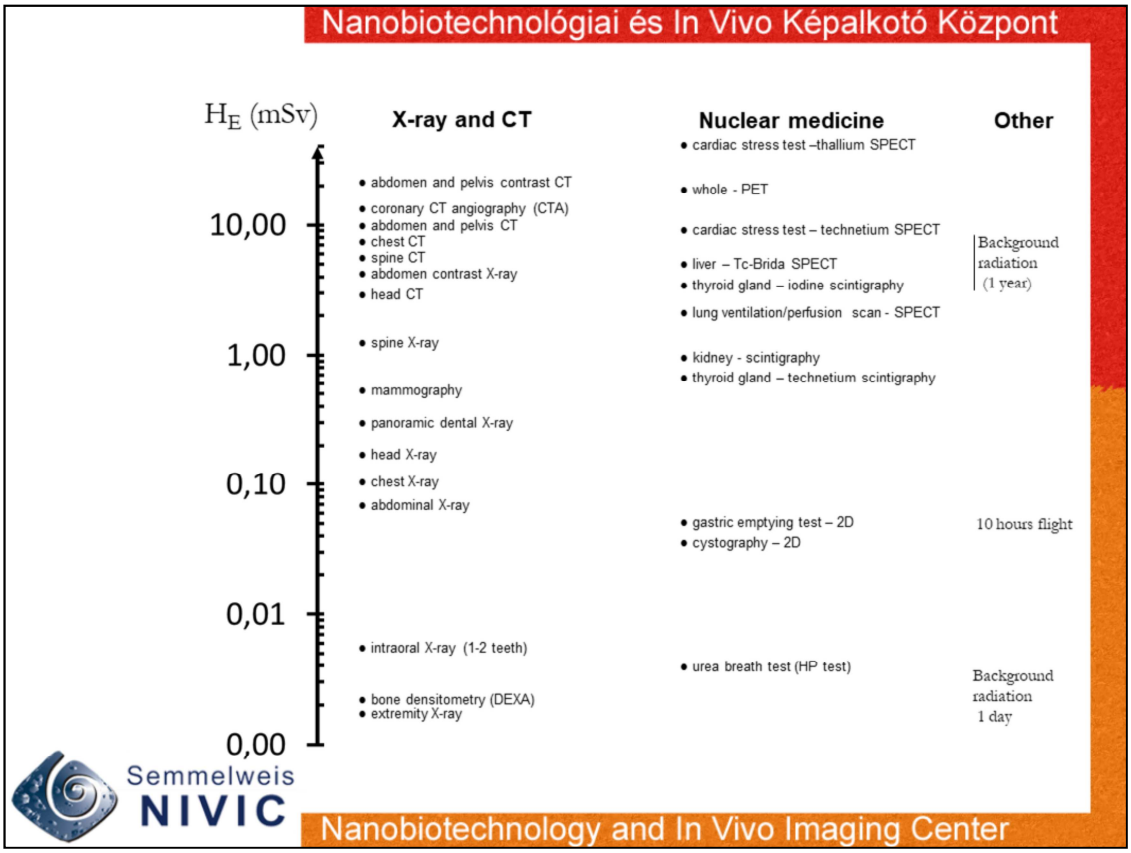
The anatomical knowledge plays an imortant role in the everyday medical care. The morphological imaging is based on the thesis, that the organic alterations show signs of changed anatomical structure. In numerous cases it is not enough to find the macroscopic changes, but to make a correct diagnose cell-level or subcellular examination is also necessary. These imaging techniques are called functional imaging in general and are involved in medical care for almost 30 years. We can state that this field of science undergoes significant changes and development as a consequence of information technologies and molecular biochemistry.



Nowadays the 2D planar scintigraphy (full body summation images) is replaced by 3D tomography (reconstructed images).

Questions: What can we see on the 2D image? – look at from another directions. Is the 3D image more informative?

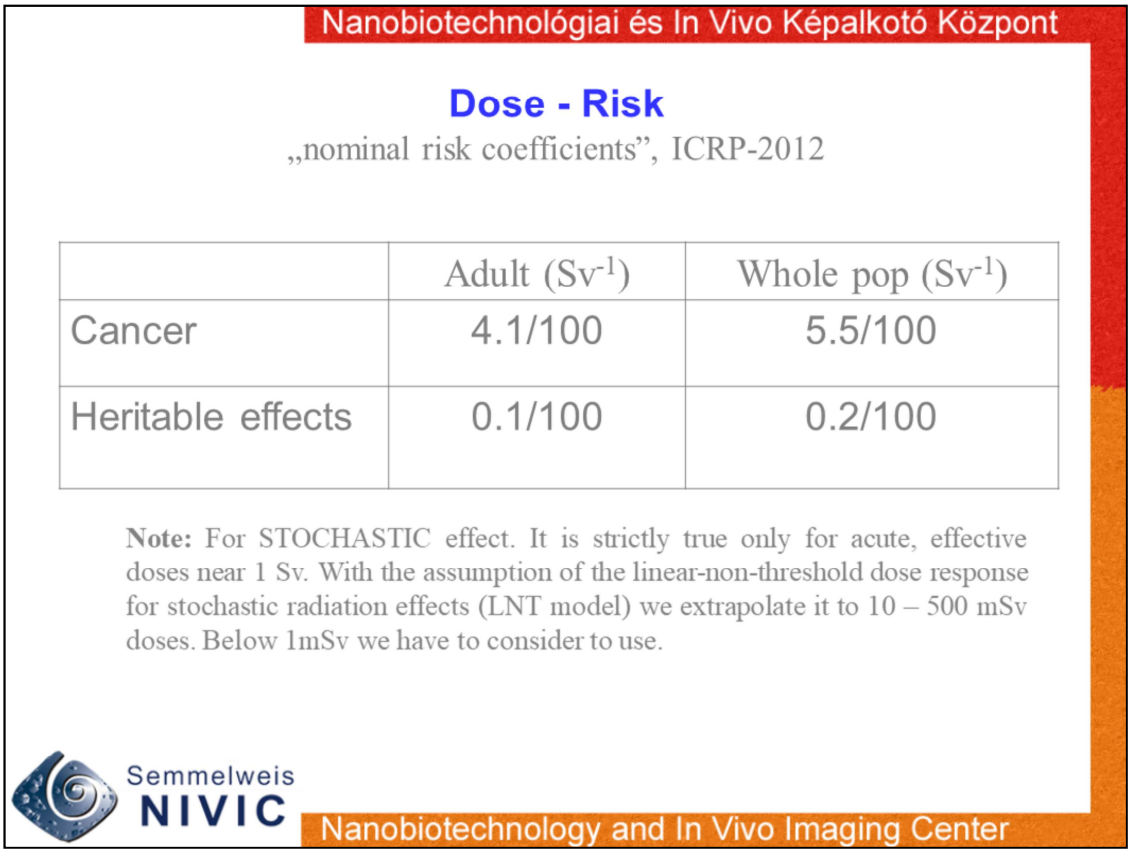
During this class we would like to show how can we make a 3D image from a series of 2D images (acquired from the same object but from different directions) during the reconstruction with our in-the-house X-ray equipment. During the step-by-step image acquisition from different directions it could be well observed how changes the recontructed 3D object continuously. Finally, we get the reconstructed datailed 3D image from the frog, which image is perpendicular to the projection's direction.



Equivalent dose of different X-ray, CT and nuclear imaging techniques.

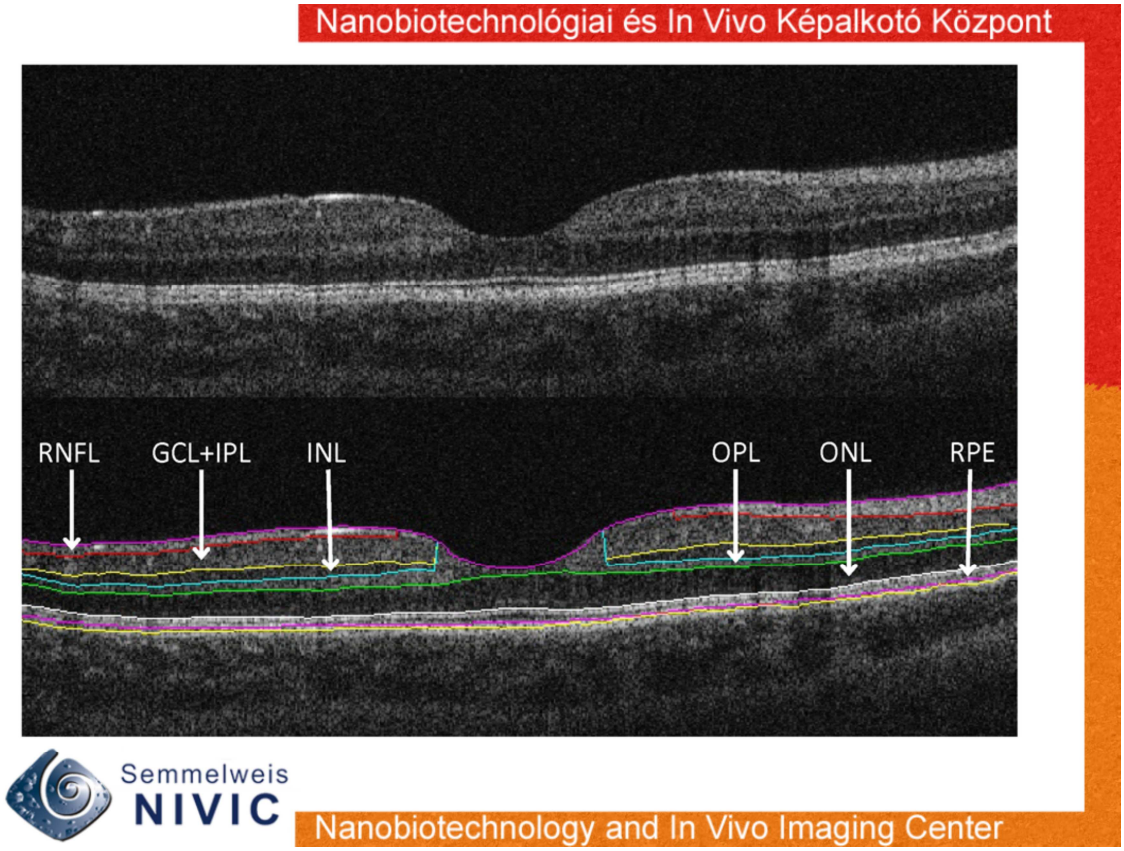
Questions:
What is the main difference between SPECT and PET?
Which one is the most dangerous imaging modality?
Why technecium is the most often used radioactive isotope in the case of SPECT scan?
What is the point of quantitative functional imaging?
Does radiology use quantitative imaging modalities?

(Supplementary info: DEXA: dual energy x-ray absorptiometry, HP: Helicobacter pylori)



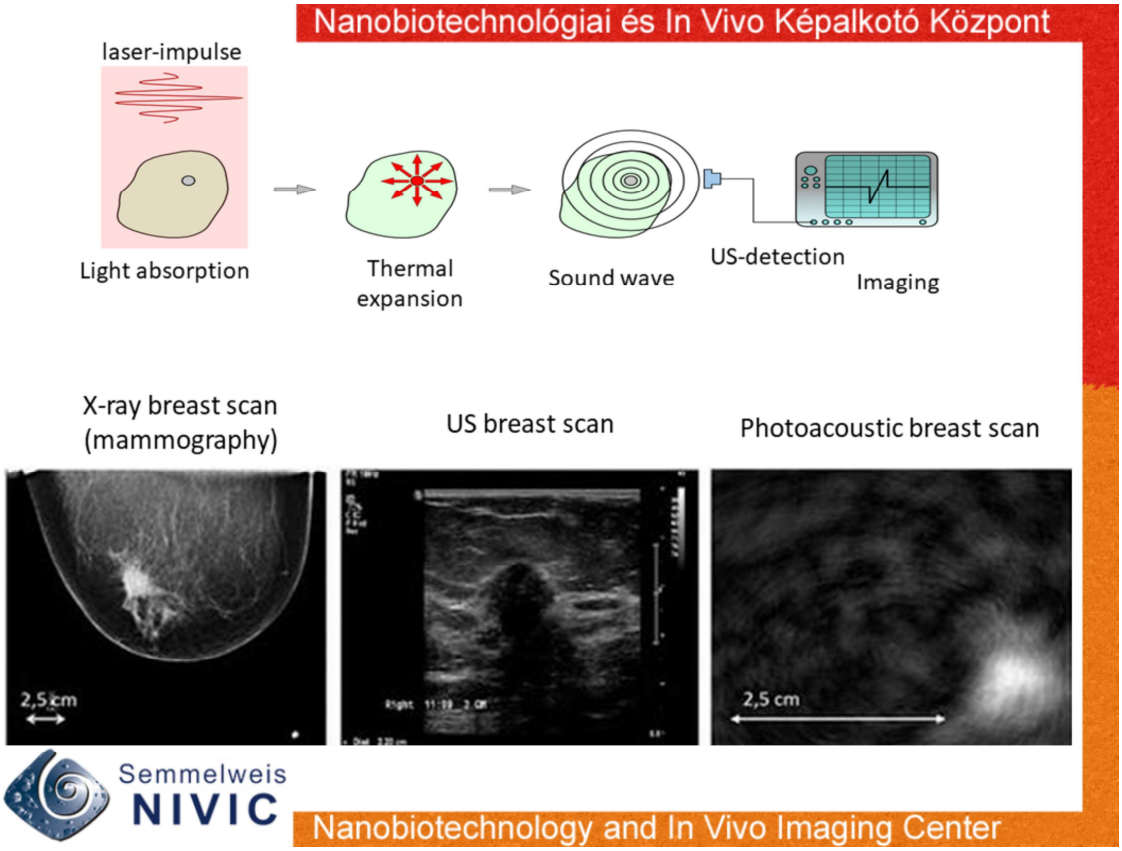
In the previous slide we showed the applied doses – but our real question is the probability of „harm" if we execute the imaging. Here we show a commonly used estimate.

These estimates based on phantoms (models for human body) and previous disasters (nuclear bombs, reactor accidents). These number shows in percentages the additive probability of a cancer or heritable effects for ionizing radiations. Eg. For 10 mSv effective dose (that is 1Sv/100): about 5.5/100/100 = 0.05% is the probability that somebody get a cancer because of this extra radiation.



The main advantage of optical imaging is its radiation free nature compared to the previous mentioned techniques. On the slide you can see an OCT (optical coherence tomography) image from the ocular fundus in cross-sectional view. This technique is a relative new measuring method which is available for the most hungarian ophthalmologist. Basically it uses a special laser beam to scan the fundus and gives high resolutional images about the retinal alteration (oedema) without the pupila dilatation, injection or direct contact of the eyes.

Image is from the following research atricle: A Morphological Study of Retinal Changes in Unilateral Amblyopia Using Optical Coherence Tomography Image Segmentation - Andrea Szigeti, Erika Tátrai, Anna Szamosi, Péter Vargha, Zoltán Zsolt Nagy, János Németh, Delia Cabrera DeBuc, Gábor Márk Somfai

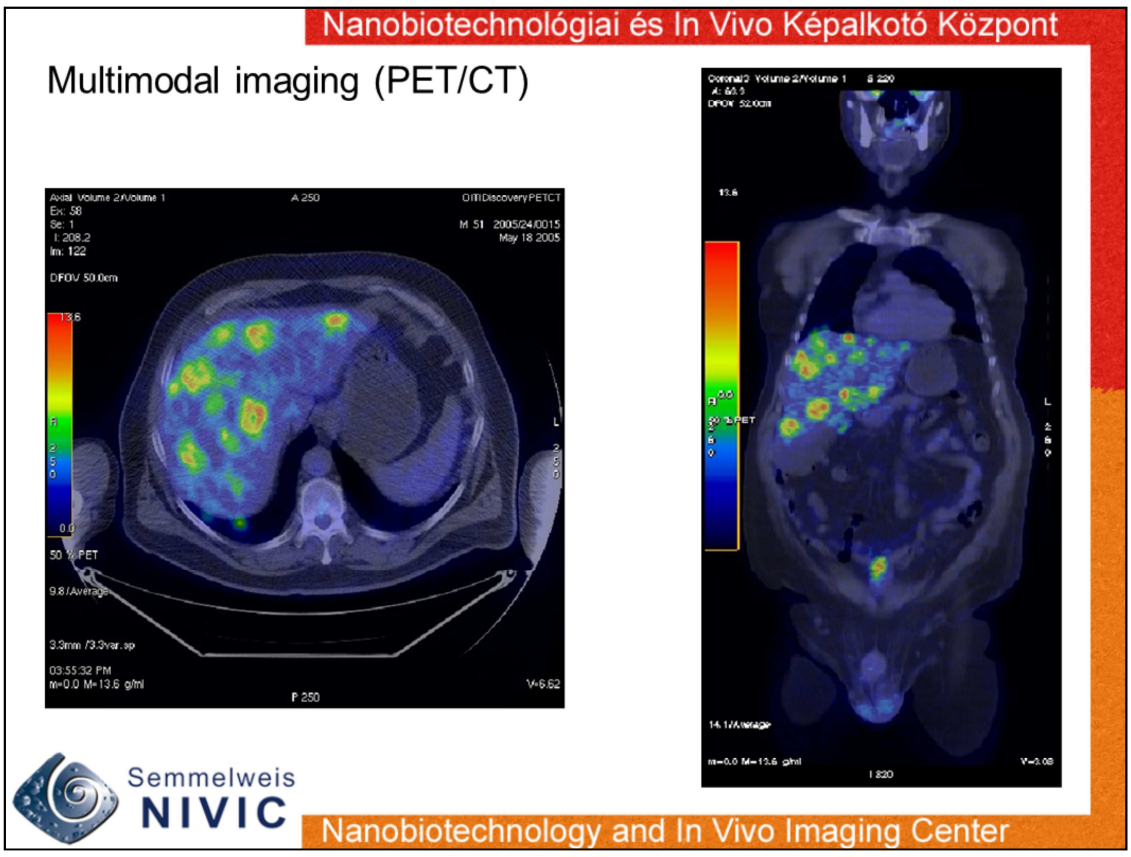


In the field of mammography the rutin diagnostic technique is the X-ray imaging still yet (breast cancer mortality 500000/year), despite of the technique's high radiation dose.

Other applied imaging techniques to breast cancer scanning are the US (mostly for young people and pregnant women) and the MRI (mostly in heritable cases, cancer recurrance, and other special cases). Those techniques suffer from the subjective analysis of US pictures and the limited availability of MRI equipment. Furthermore, the diagnosis of different alterations are difficult/ not possible to realize with this methods.

There is another new technique (photoacoustic tomography) to diagnose tissue alteration without the application any harmful radiation. The photoacustic tomography combines the advantages of US with the non-ionising selective laser excitation.

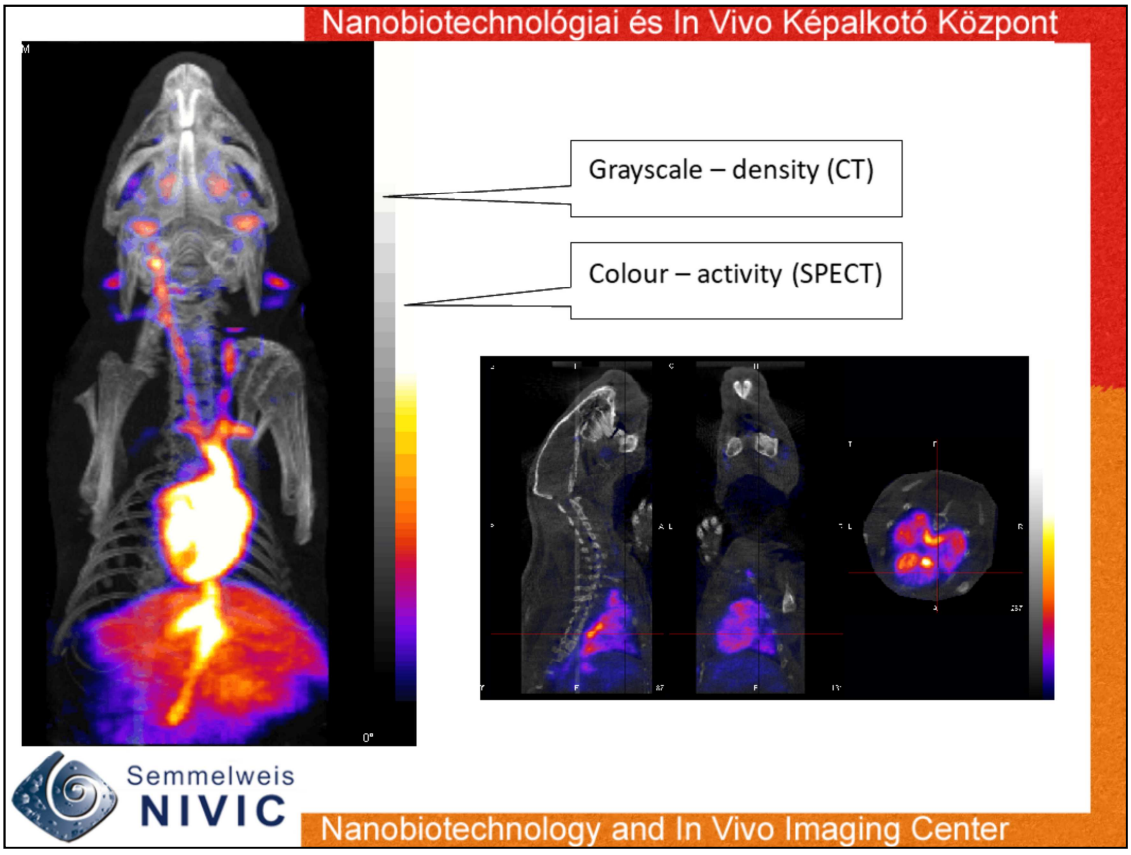
Photo from: http://www.diagnosticimaging.com/womens-imaging/photoacoustics-shows-promise-identifying-breast-cancer



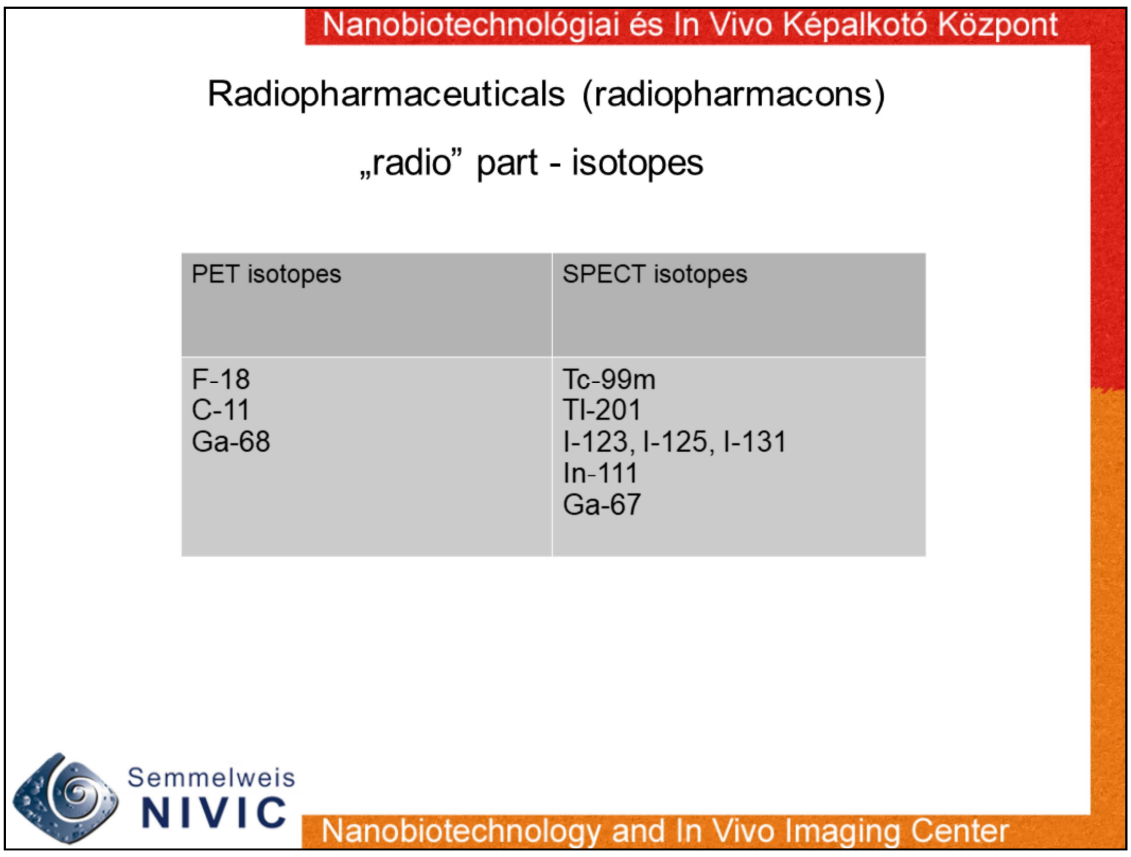
Some new imaging techniques have been discovered in the past decade giving stronger diagnostic support by combining the advantages of morphological and anatomical imaging.

The most represented hibrid imaging system is PET /CT with a typical application in oncology. I would like to clarify the efficiency of this method on the folowing example. In countless cases the tumours don't show well in a whole-body 3D CT image thanks to their small size/location. Using a PET, finding the tumour by its enlarged glucose metabolism becomes possible. In this case the CT image helps to plan the surgical intervention, because tumour location and size is definable by mulimodal imaging.

(Note: labels and scales are important thus we image arbitrary scale values.)



Multimodal imaging is based on the fusion of images from different imaging modalities which could be illustrated in different colors on the same image. (The colors are freely variable.)

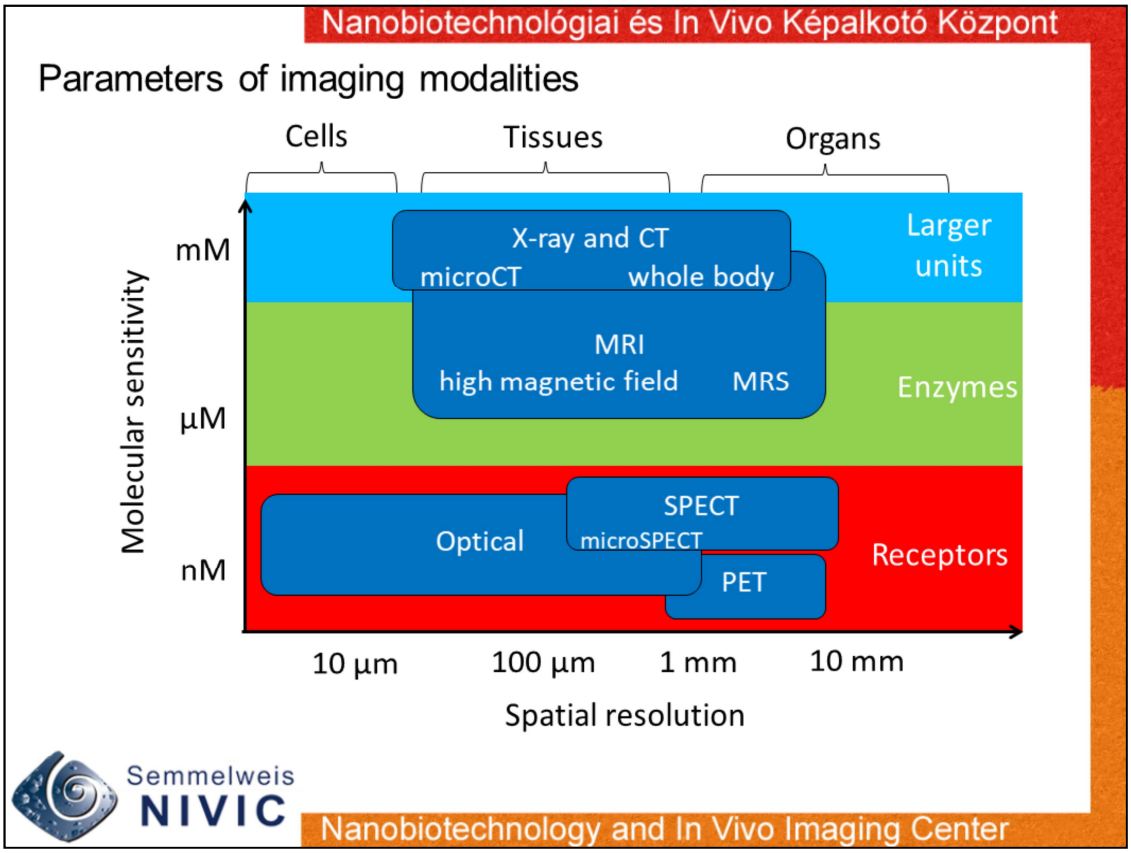


Using nuclear imaging we can gather information of the functional activity of a given cell / colony.
In the past decades a great number of special compounds were designed to detect the metabolic processes of different organs.

Radiopharmacons are constructed from two parts: a radioactive isotope as a radioactive source, and a pharmacon responsible for the selective delivery of the source to the target region.
In general F-18 (most often), C-11 and Ga-68 isotopes are used as PET radioisotopes, and Tc-99m (most often), In-111, I-123, I-125, I-131,Tl-201 and Ga-67 in SPECT imaging.

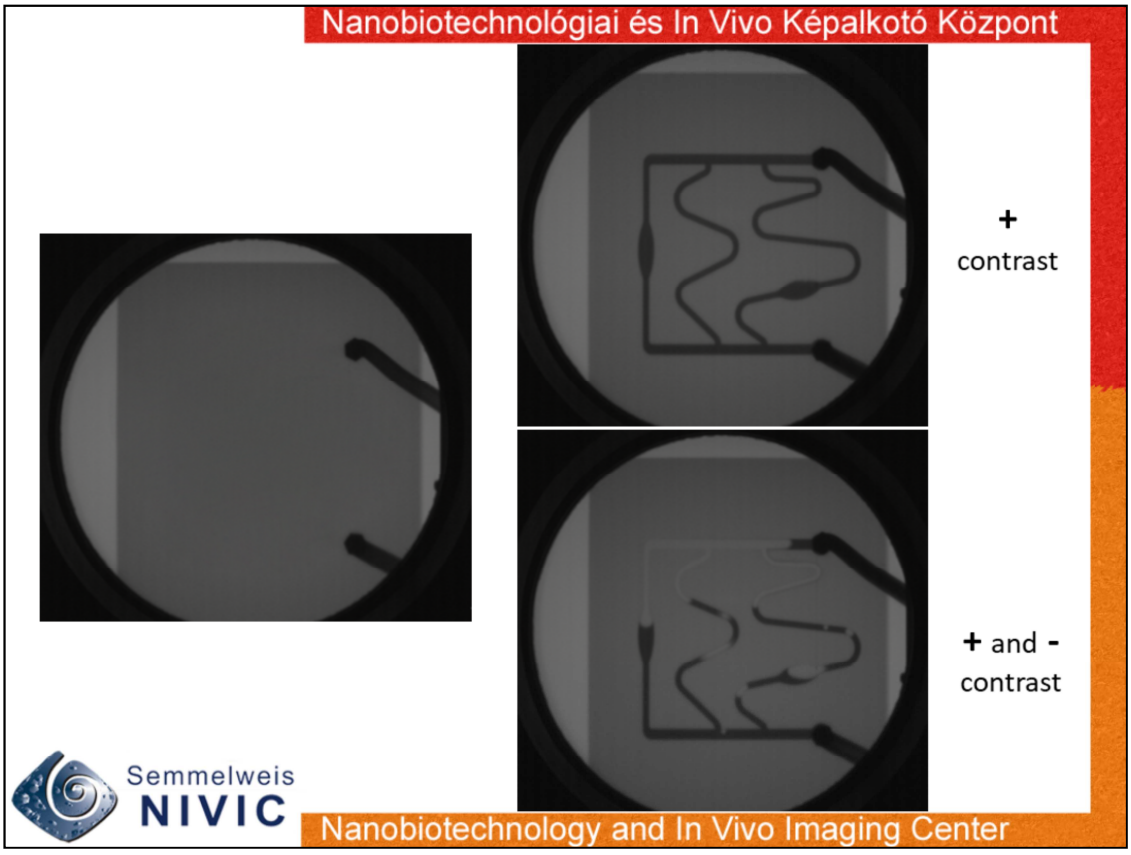
If it is possible we like to use Tc-99m in SPECT imaging. It has several benefits:
1. emitting only gamma-radiation (thus lower dose)
2. optimal gamma-energy
3. optimal half-life time
4. easy to create and bind to different pharmacons
5. cheap

I would like to show some examples to the in vivo detectation of different metabolic activities. Of course there are far more fields of use than shown here, the number of radiopharmacons is growing every single day.

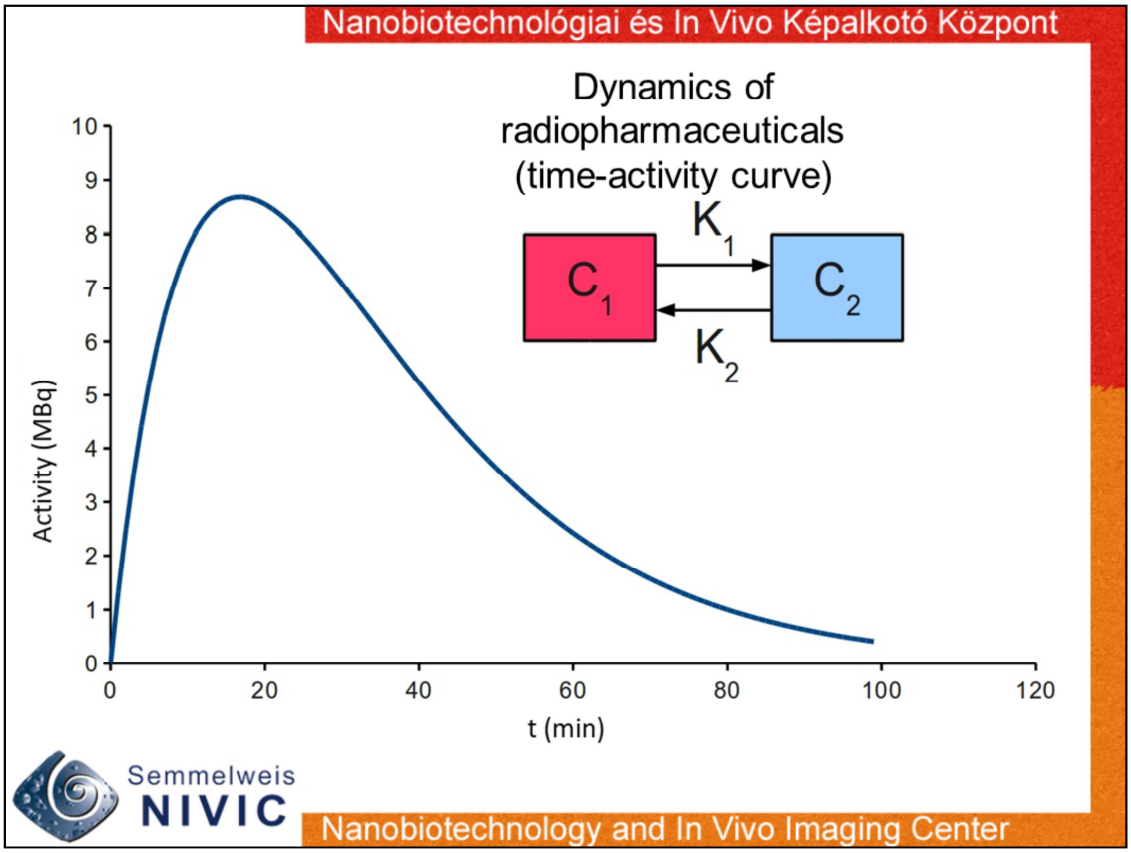


Creating contrast to emphasize the target in front of the background is a serious problem in imaging. The amelioration of contrast ratio is possible by applying compounds which accumulate selectively in the target area. The low sensitivity is the biggest problem of MRI and CT (angio) imaging, therefore it is required to apply contrast agents in high concentration which cause severe side effects and are disadvantageous to the patients.

In the other hand it is important to understand that the drug doses in nuclear and molecular imaging are very low compared to CT contrast agents. These doses are way under the ones necessary to the pharmacodinamic effect.

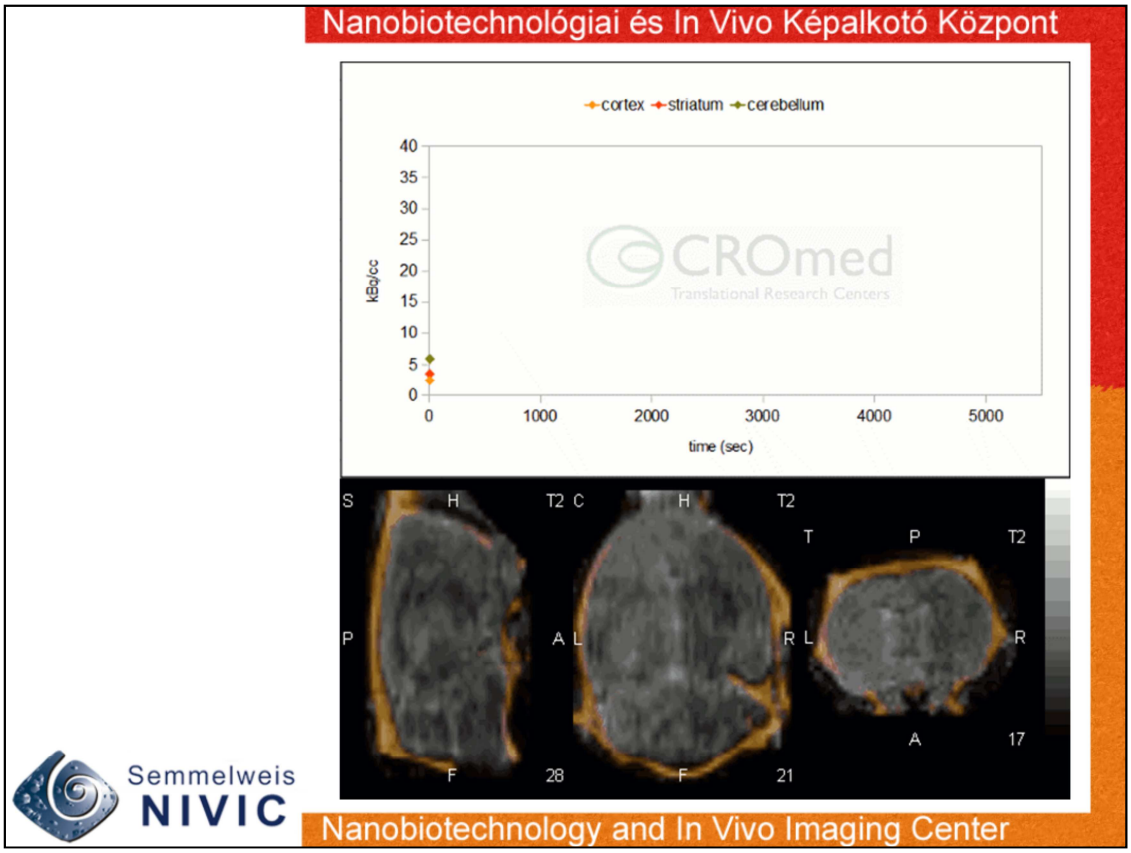


The radiological images must fulfill two different criterions to the anatomical structures be visible. First is the appropriate spatial resolution, second is contrast (density, echogenity, signal,...) difference.
On the pictures you can see the effect of kalium-iodidum (KI; + contrast agent, upper image) and the air (- contrast agent; lower image).

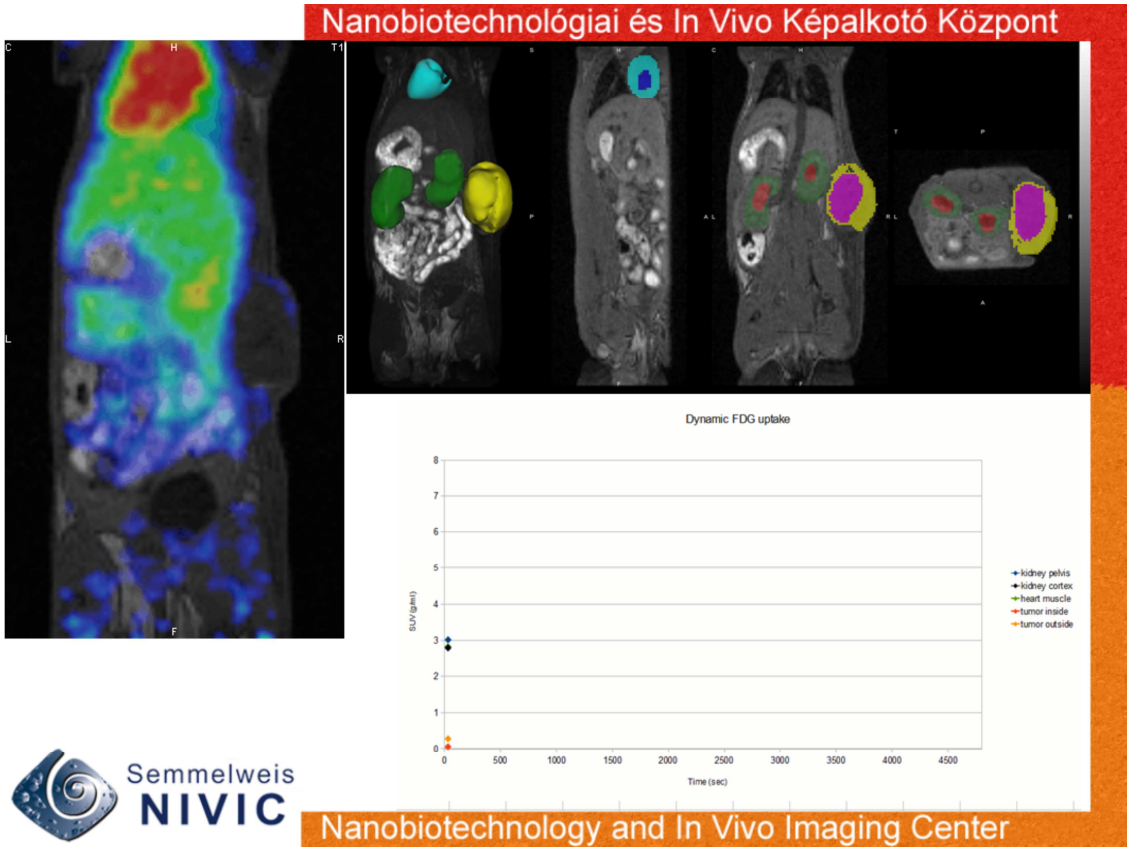


The other problem with contrast agents is that they are transformed and excreted in biological systems by the metabolism, so their quantity and contrast-building effectiveness is significantly lower by time. These time frames certainly depend on the properties of the biological system and also the chemical parameters of the contrast agent.

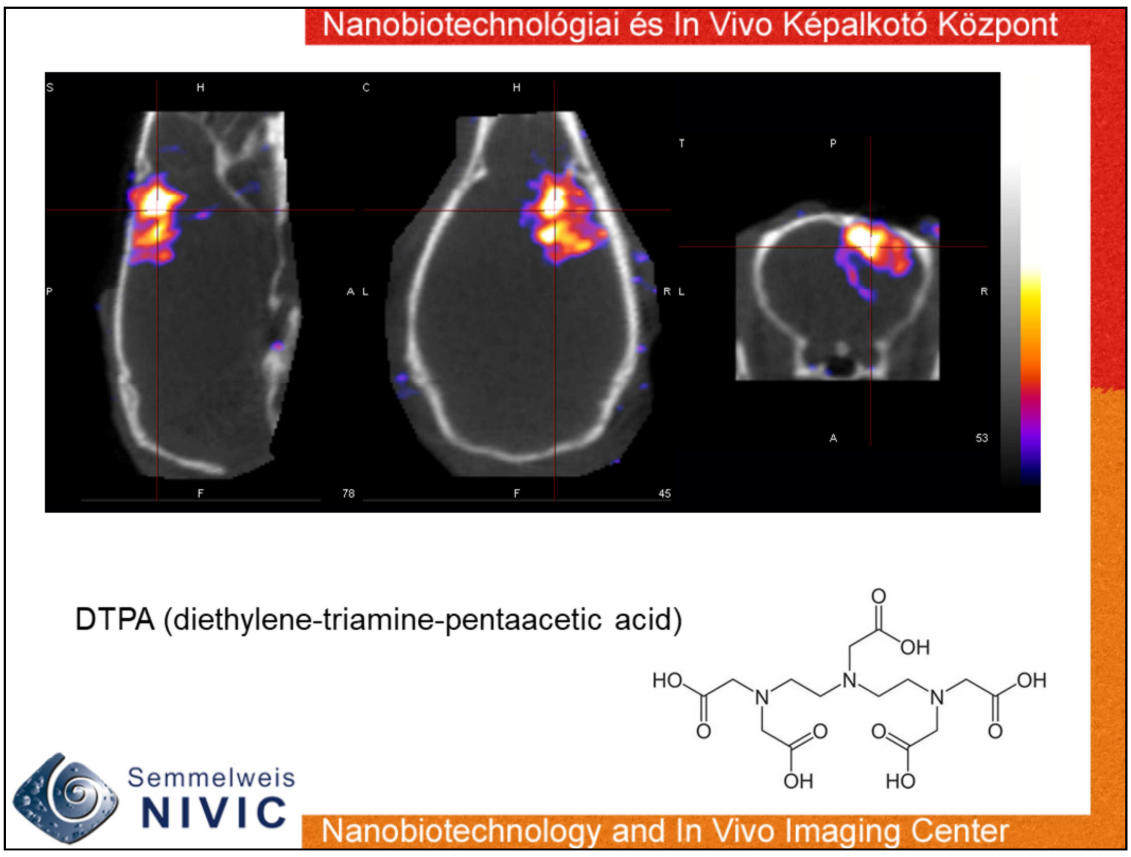
It is important to define the time axis of accumulation in different organs, excretion from blood and the wash-out from the given organ.



You can see a dynamic PET measurement on the slide. The distribution of activity in different central nervous system structures differs in time. This measurement was performed with a D2 receptor antagonist called raclopide marked with C11 isotope.

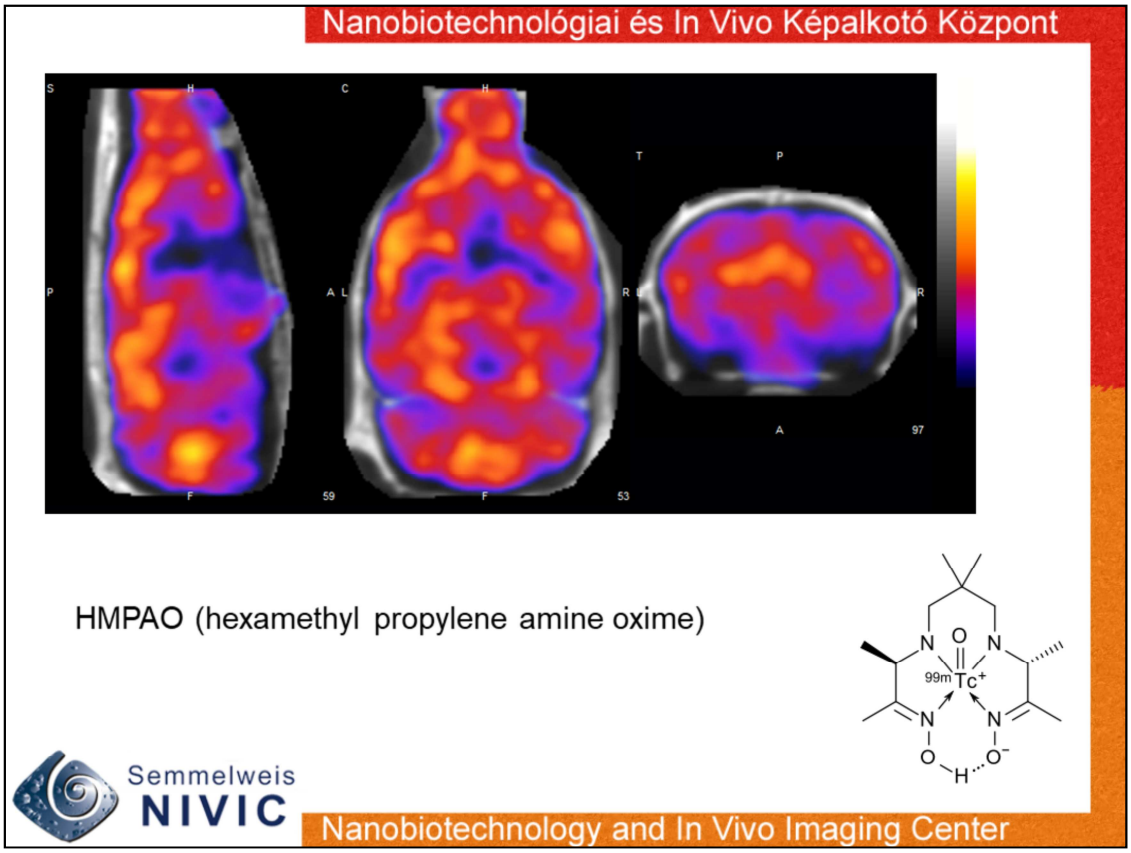


You can see a dynamic PET measurement with 18F-FDG on the slide.



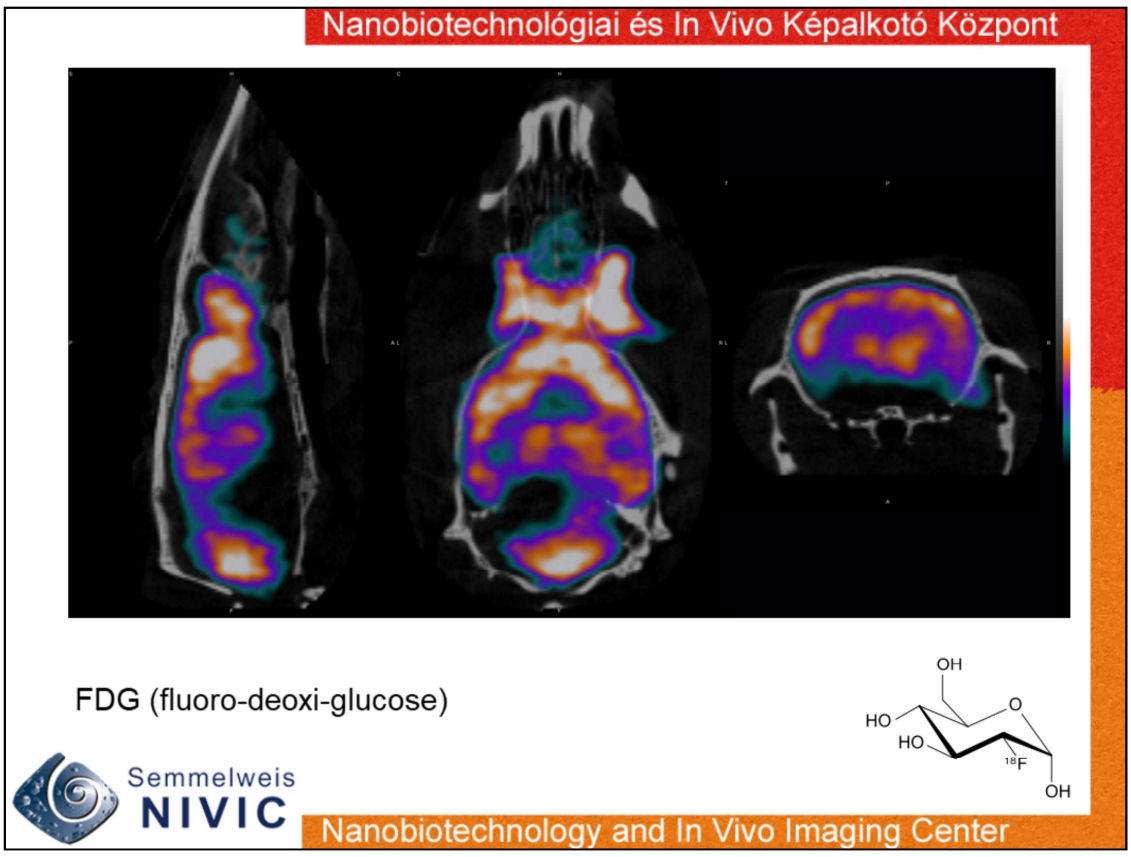
The radiopharmacons suitable for central nervous system imaging can be categorized by their capability to penetrate the blood-brain barrier. The ones, which are not able to go through the intact barrier are hidrophil and anionic molecules. In cases of altered permeability (ischaemia, tumor) they can penetrate the BBB, and can be detected in brain tissue.

One of these contrast agents is DTPA. This molecule -circulating in blood as a chelator- is suitable to detect endothel disfunction in the brain.



Tc-HMPAO, a BBB penetrating contrast agent is frequently used to measure brain perfusion. Because of its lipophilic character it can penetrate the barrier easily, then it is reduced in the cell membrane by the glutation peroxidase system. The hidrophilic complex is not able to sneak back to the blood, but the amount not entering the brain tissue is excreted quickly from blood.

Tc-HMPAO is used to measure the perfusion in different organs not only in the brain.

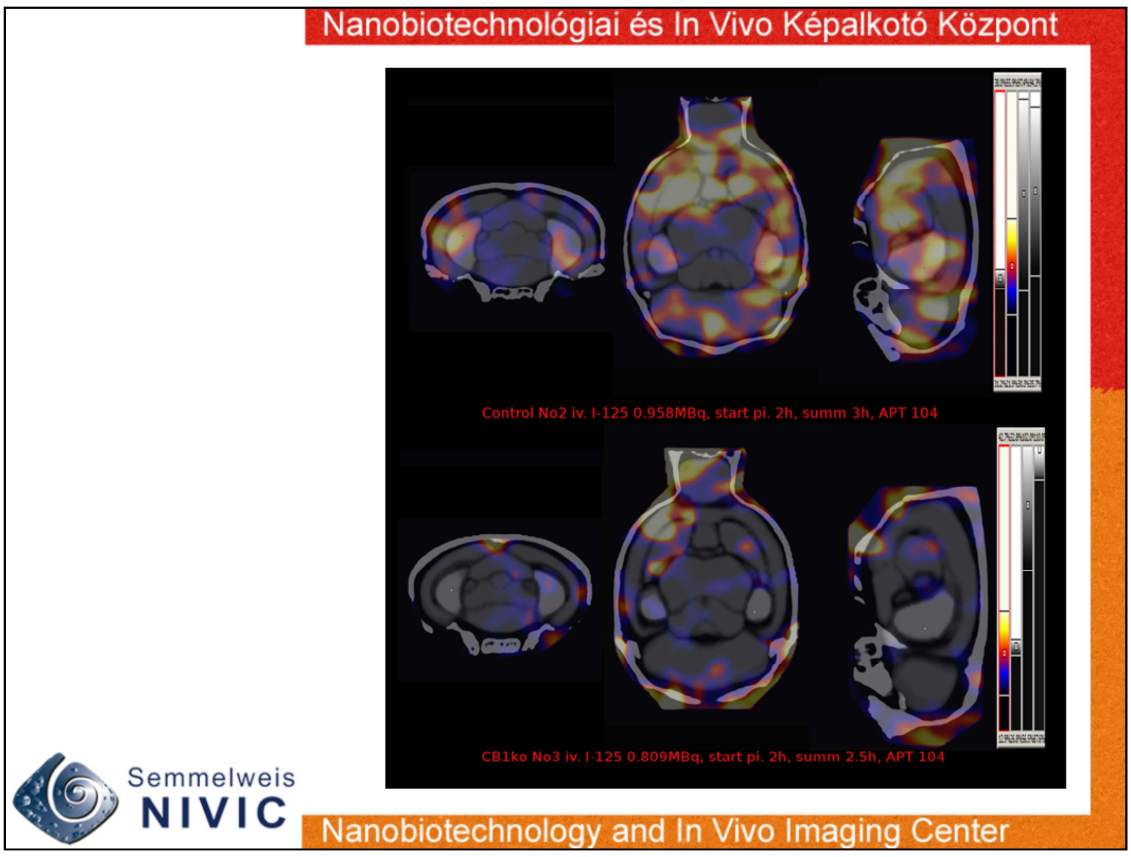


Unfortunately Pet imaging currently means only FDG-PET in Hungary. This moluecule – FDG – bound to F-18 isotope, can penetrate BBB and shows the speed of brain glucose meatbolism. It is phosphorilated by hexokinase in the cells, so it can stay in the brain for a long time.

FDG-PET is applyed for tumour classification and examination of CNS diseases in clinical use.

Question: Is it possible to detect the distribution of two or more isotopes at the same time? (=Is it possible to make dual labeling with SPECT?) – Yes, because we can (detect and) distinguish between two different radiopharmacons with different isotope, because they have different gamma energy.

But it is not possibly in the case of PET! (we have the same gamma-energy after annihilation)



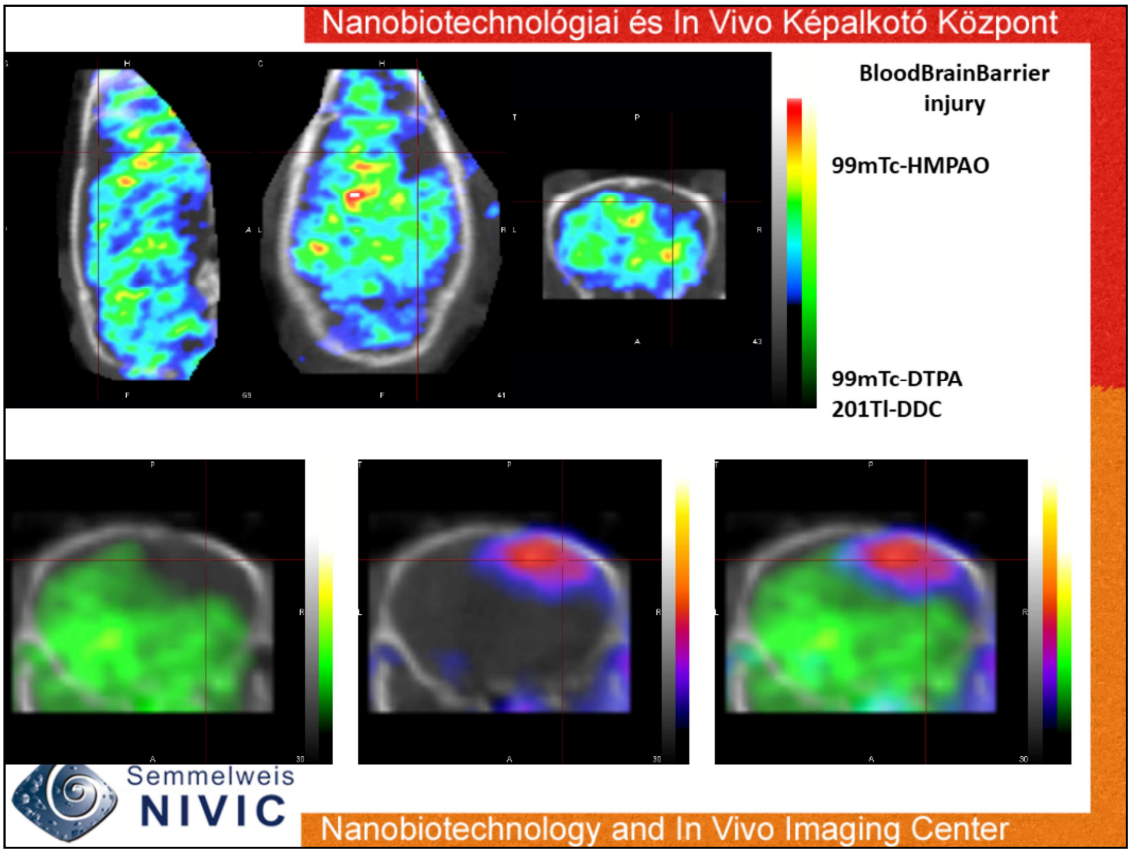
The spatial and temporal distribution of different receptors of the brain has a great importance. A lot of workgroups design special ligands to determine these distribution-values. One of these targets is CB1-R, having an important role in the diagnosis of epilepsy and alzheimer disease.

The easiest way to design PET ligands is to change one of the H-s of the receptor-ligand analogue molecule to F18,or a C to C11 with radiochemical procedures.

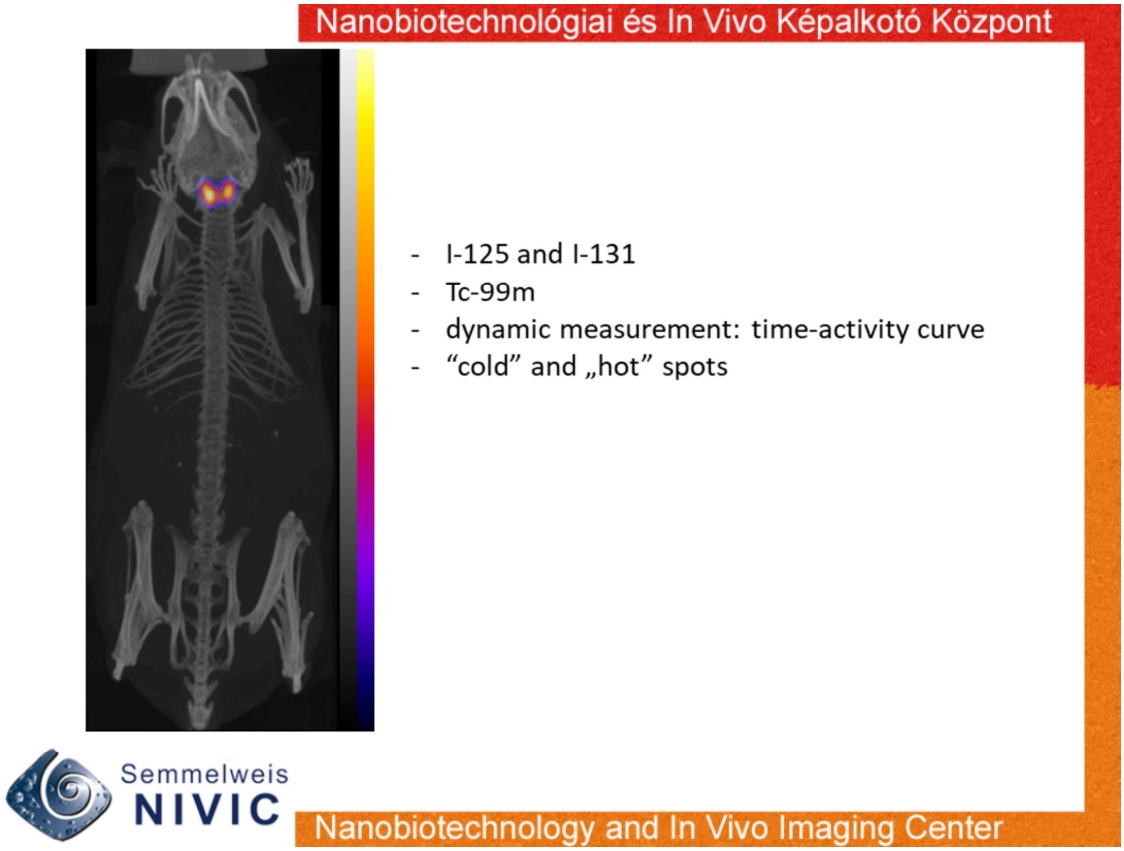
In the past years dozens of synthetic ligands were developed and tested in vitro and also in vivo to image CNS receptors.

Thanks to mulimodal imaging in the slide you can see the CNS distribution of a SPECT – not PET! – ligand in front of a brain Mri atlas and a skull CT.

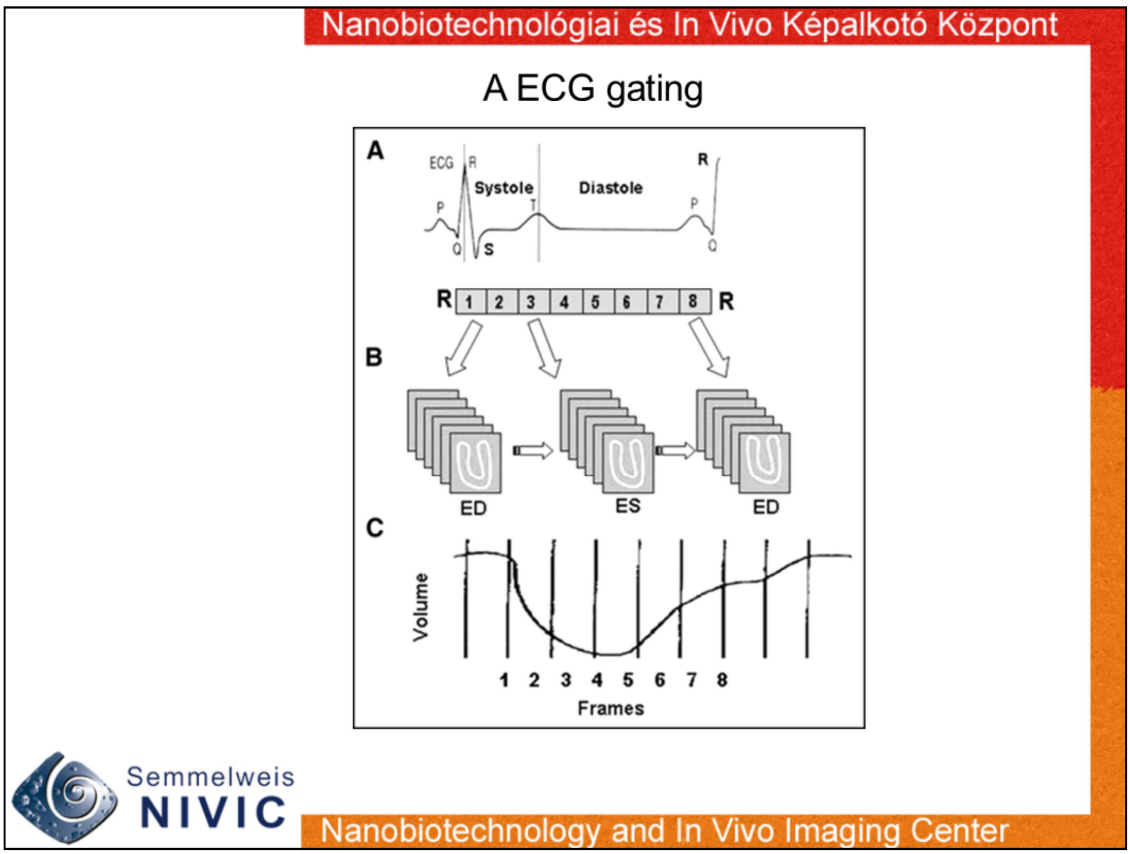
Brain blood flow can be seen using multi-isotope signaling (eg. with Tc-HMPAO) .



Investigation of BloodBrainBarrier injury using dual labeling technics.

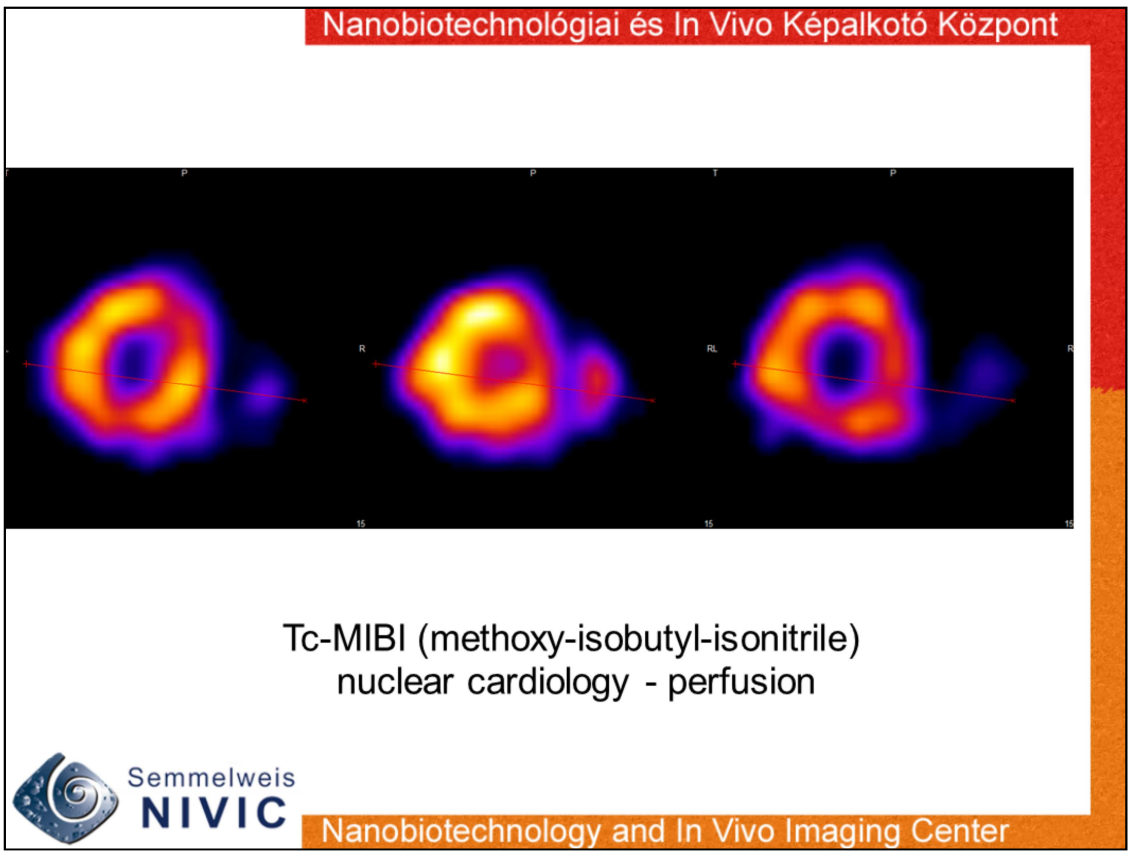


The thyroid gland scintigraphy is an often used imaging technique for years. Based on the intrinsic propety of thyroid glands, iodine is accumulated within the tissue, so the special in vivo targeting of isotopes are not necessary for imaging. Iodine isotopes (I-125, I-131) are often replaced by 99mTc. The uptake of 99mTc is a similar process like I-125 and I-121 uptake because Tc is a substrate of Na/I simporter.



3 types of examination are known in nuclear cardiology : measuring myocardial perfusion, helping to diagnose AMI or measure myocadial metabolism.

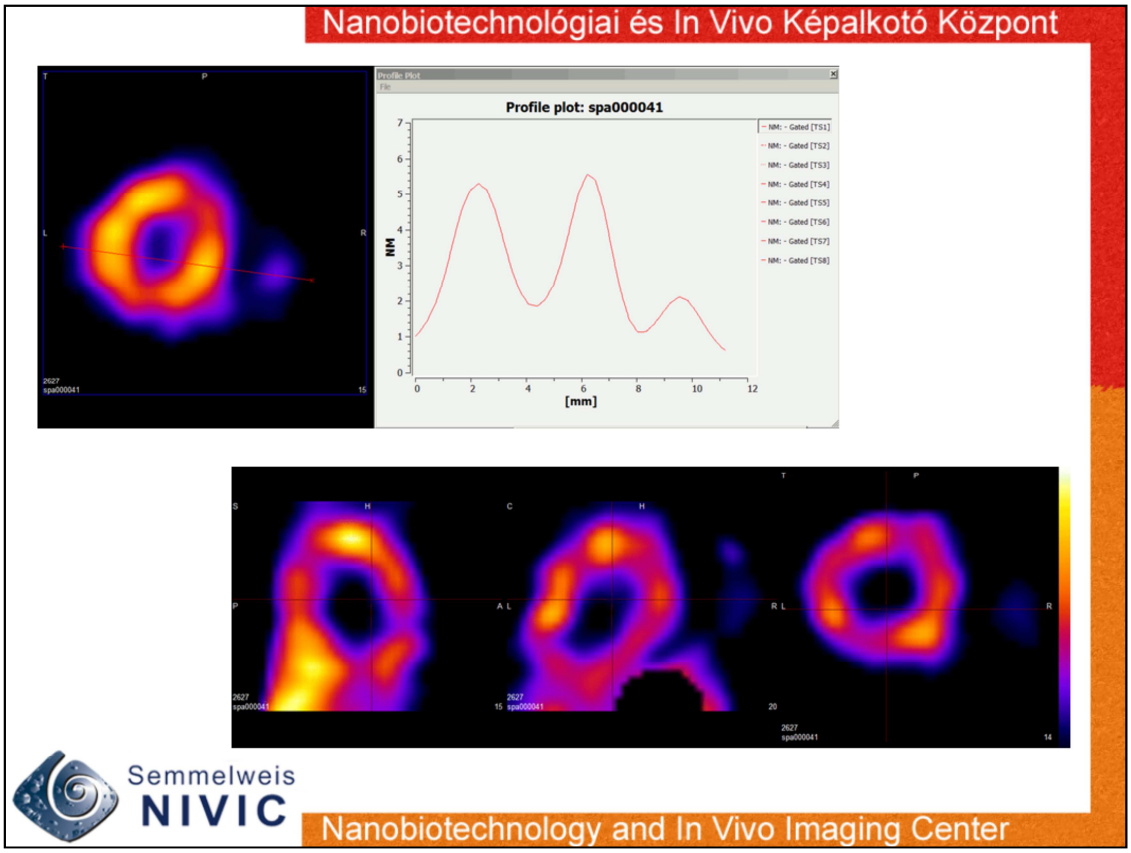
It is important to understand the basics of gated measurements used in nuclear cardiology: the projections and the phase of the synchrone administered EKG is connected. The images belonging to each phase are collected, than a reconstruction is made from them.



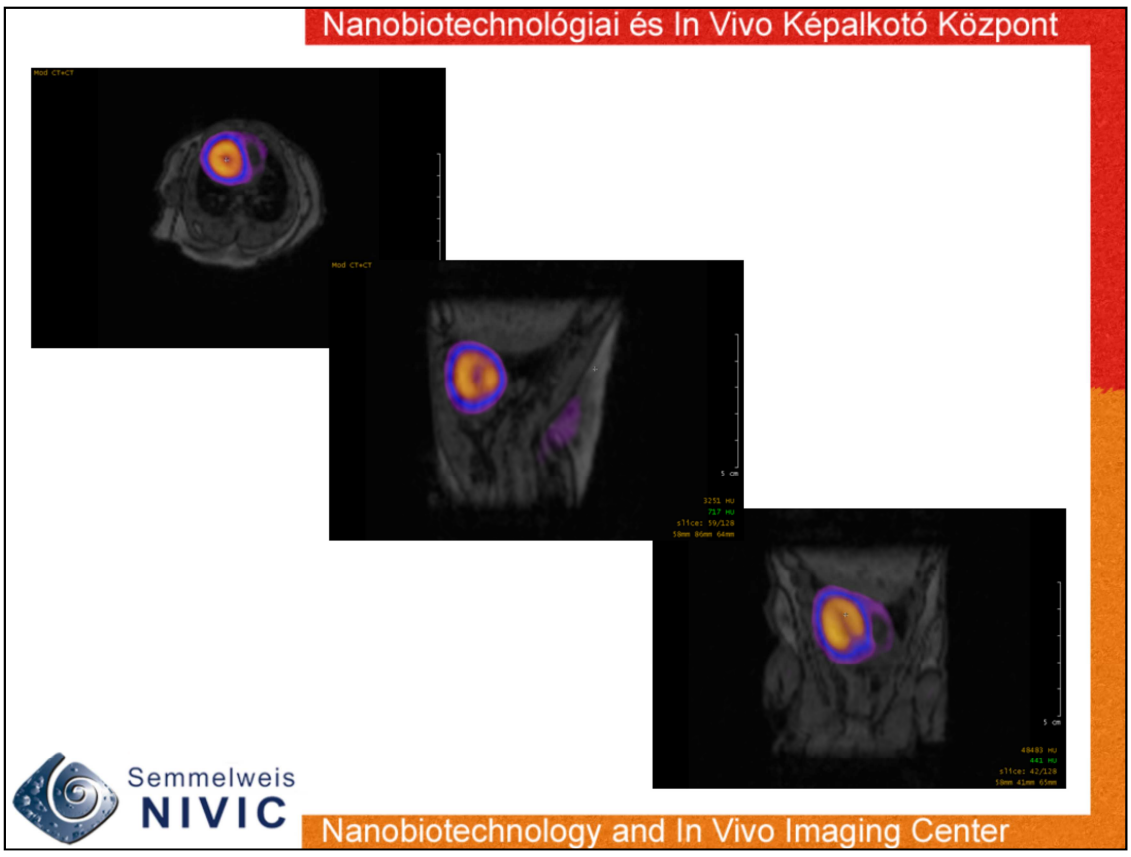
Potassium analogue Tl-201 is the most popular way to define tissue perfusion.

Tl has excellent physiological parameters (5-10 min uptake-time, 4 hours wash-out time), but weak physical parameters also (low energy gamma and long half-life) These parameters unnecessarily incease the dose of irradiation, and make the 3D reconstruction harder.

To eliminate these problems more compounds were developed, the most important is Tc-MIBI.

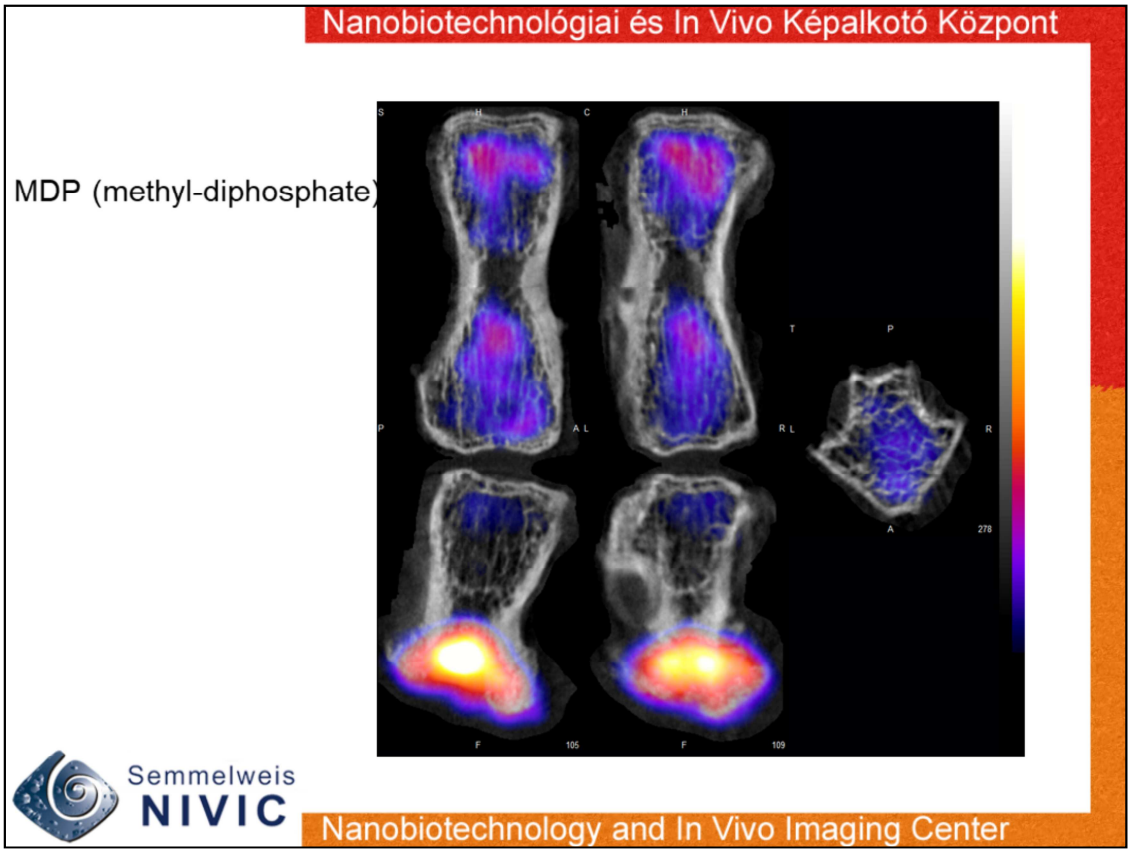


The set above shows a TC-MIBI perfusion measurement. Each and every frame was made in a different stage of the heart cycle.



Myocardial metabolism is measured by FDG or C11 marked glucose, because at low fatty acid levels the main source of energy is glucose in the heart.

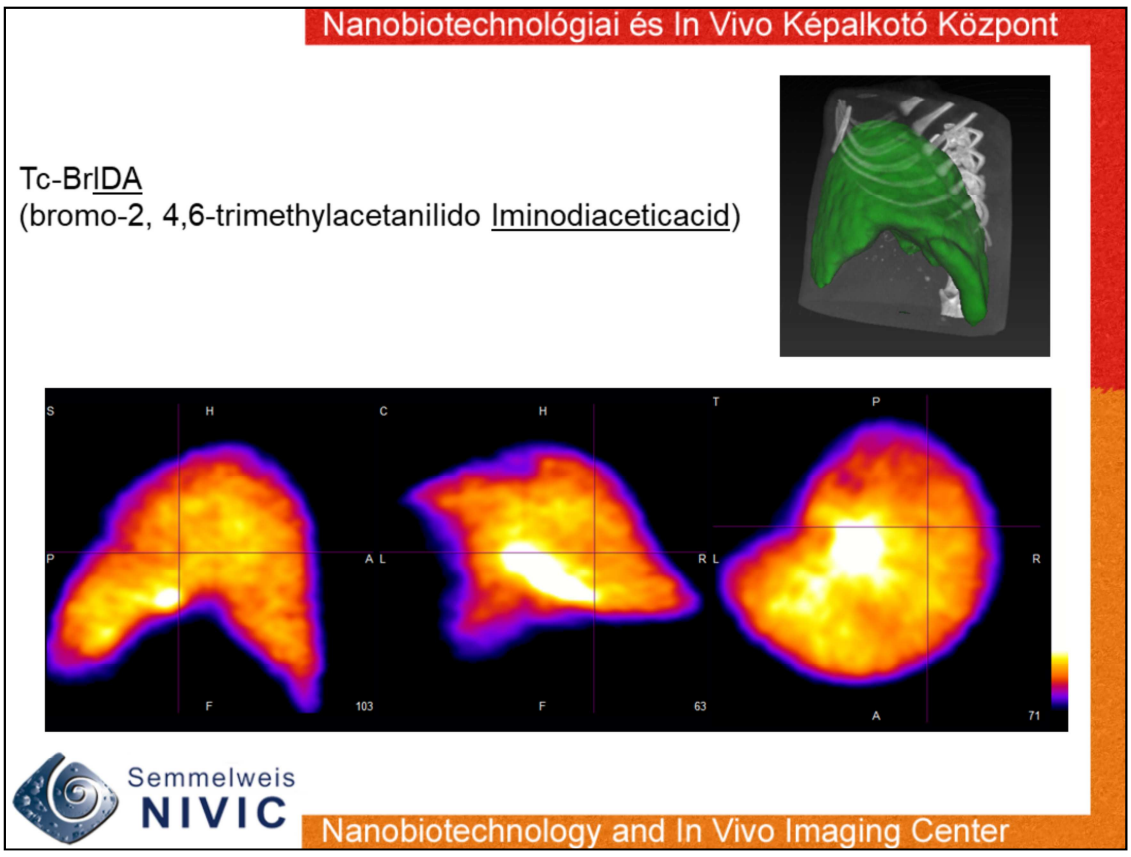
You can see an example for this process at the picture. Anatomy is demonstrated by the MRI image.



Up to now bone scintigraphy is a general examination in the diagnose of oncological diseases, bone metabolism and fracture. Using bone scintigraphy increased osteoblast and osteoclast activity and pathological hyperaemia can be revealed. The phosphate compounds marked with Tc bind to the free hydroxiapatite crystals of bones.

The most frequently used compound is the MDP (methyl-diphosphate).

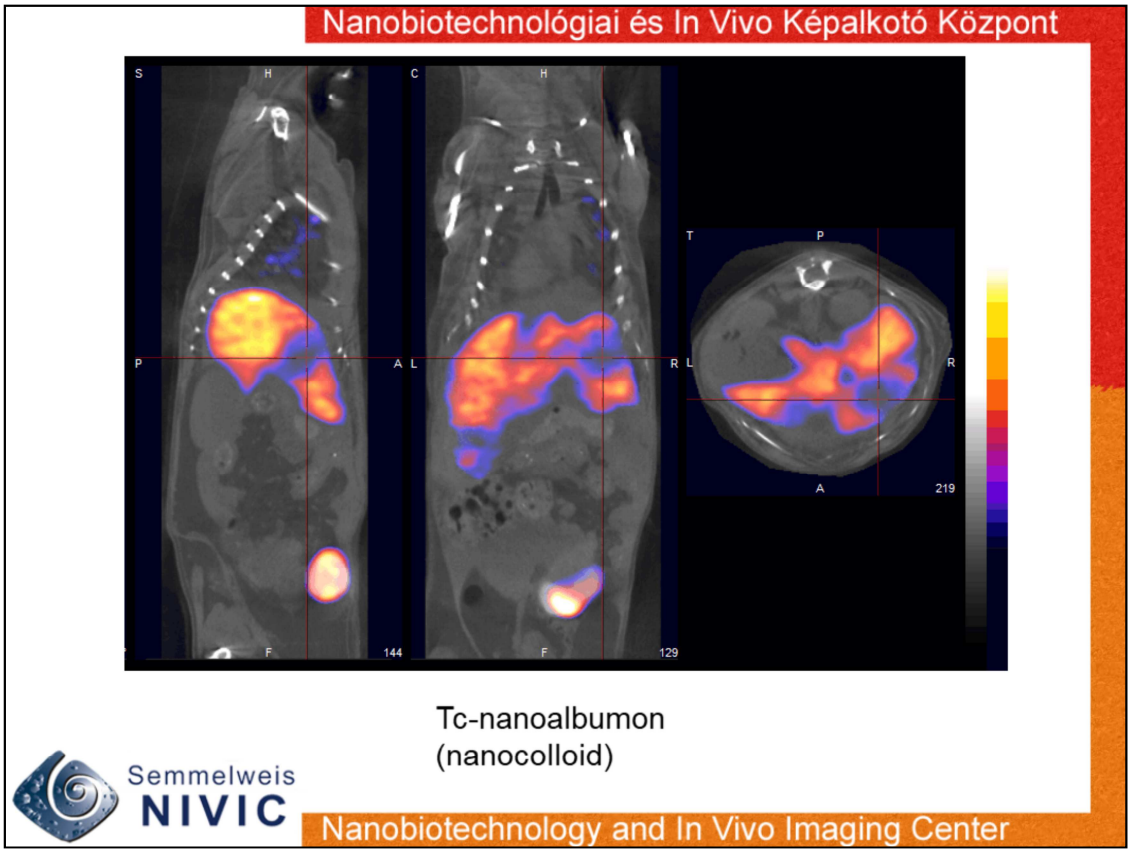
Question: Why is bone scintigraphy preferred against x-ray in paediatric relation? (higher sensitivity, lower dose)



Liver function can be measured by in vivo imaging methods. Using the 3D reconstructions not only the liver function in general, but also the function of each segment can be predicted.

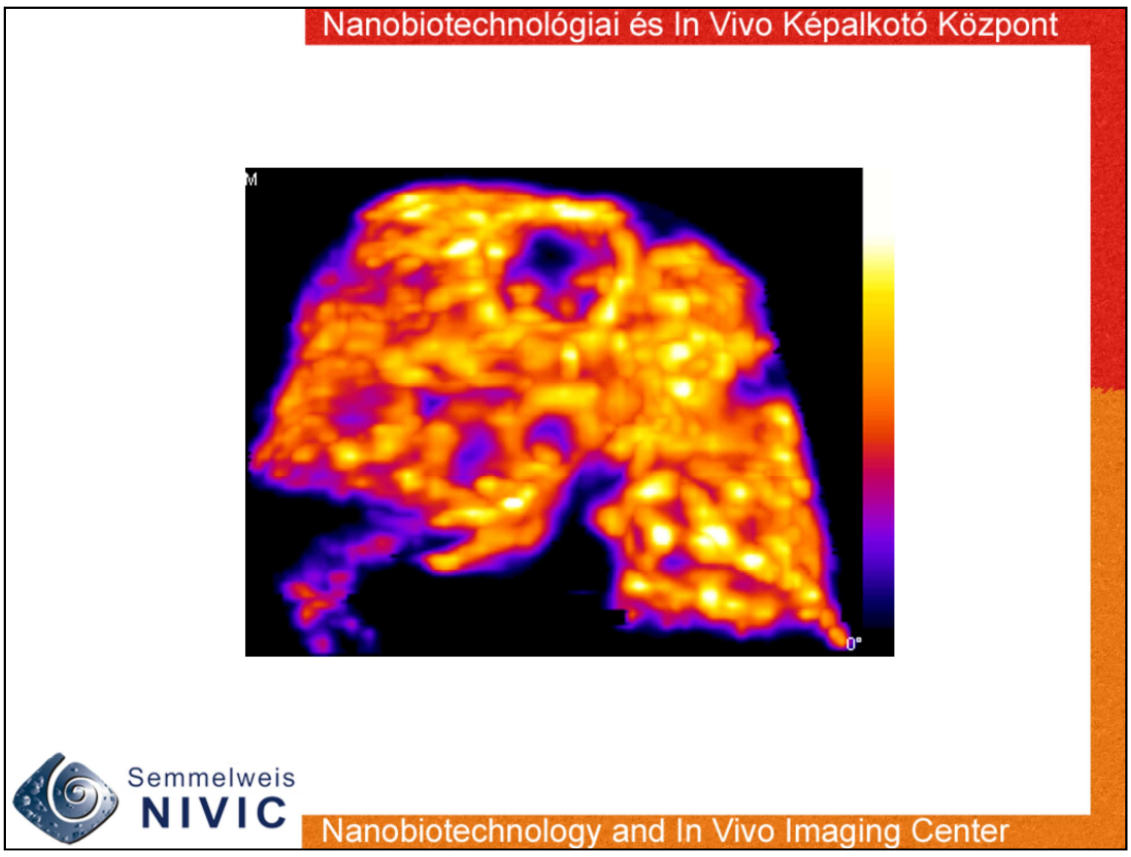
The derivates of IDA (iminodiaceticacid) are excreted by hepatocytes similar to bilirubin (ariving at first to the duodenum, then the intestines), so they can be used in imaging marked by Tc.

This method makes possible the non invasive examination of bile-excretion, bile flow and also bile ducts.

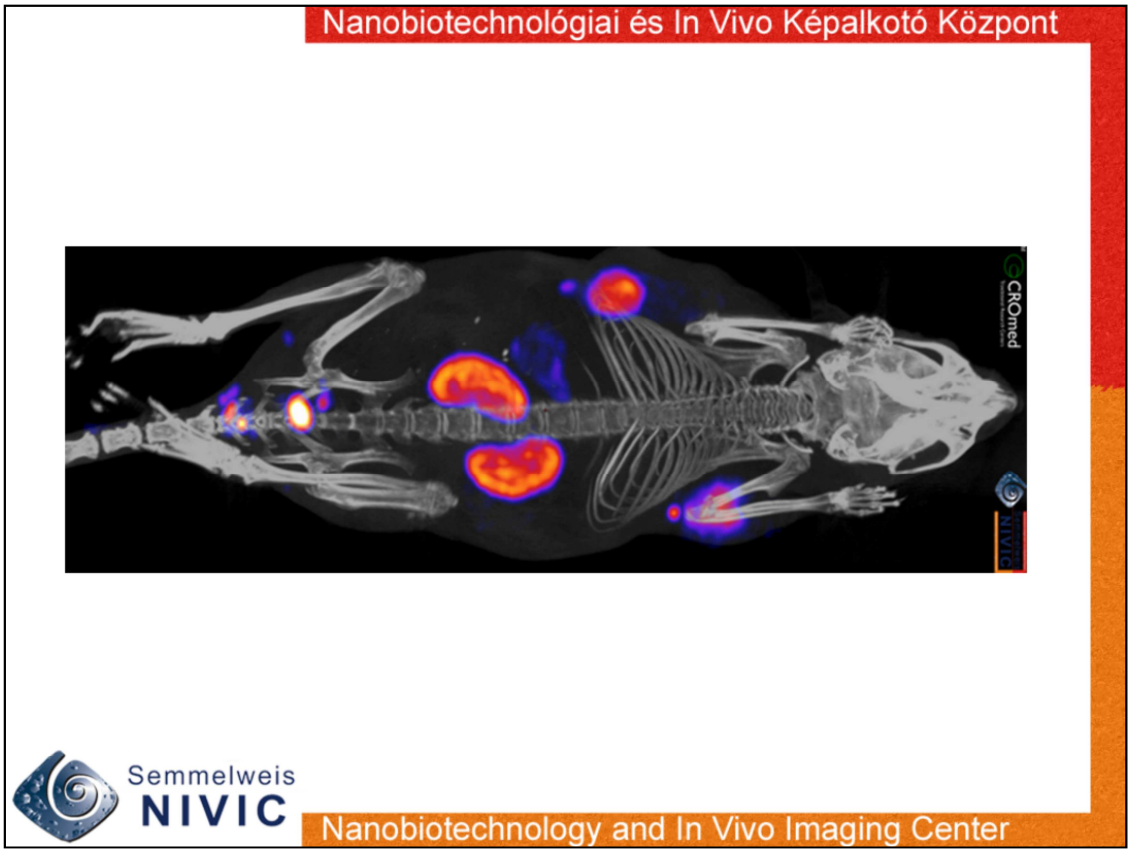


The Kupffer cells can also be found in the liver, as the part of the RES system. Their function is to filter the bacteria and endotoxines of the blood. The marking of Kupffer cells is performed with HSA nanobodies in the clinical practice.

The location of the marked cells can be used to identify morfological alterations such as tumors.



Metastatic tumour in the liver as cold spots. (cold spot=abse

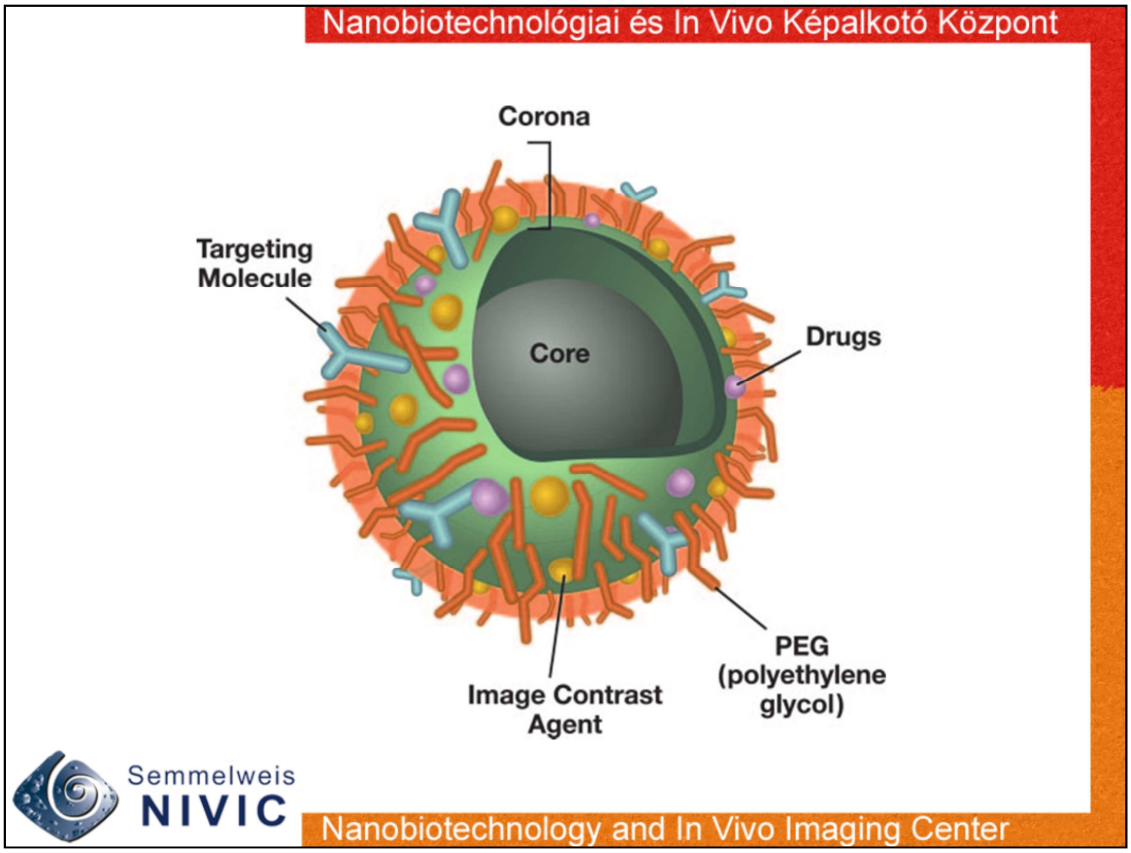


However nuclear imaging has a great importance in the diagnostics of metastatic tumors, it is still impossible to introduce the radiopharmaceuticals in use, due to the fact that they apply numerous various principles.

The imaging of SSR-2a receptors is used not only in the diagnostics, but also in therapy. By planning a suitable molecule it is possible to create a ligand analoge for the chelation of Tc or another B radiant ion in use. As the ligand analoge has selective binding potential to the given receptor, sketching the location and extension of the tumor becomes possible.

Despite of all advantages the position of SSR2a receptors in the human body still has to be acknowledged. For example they can be found in the kidney cortex too.

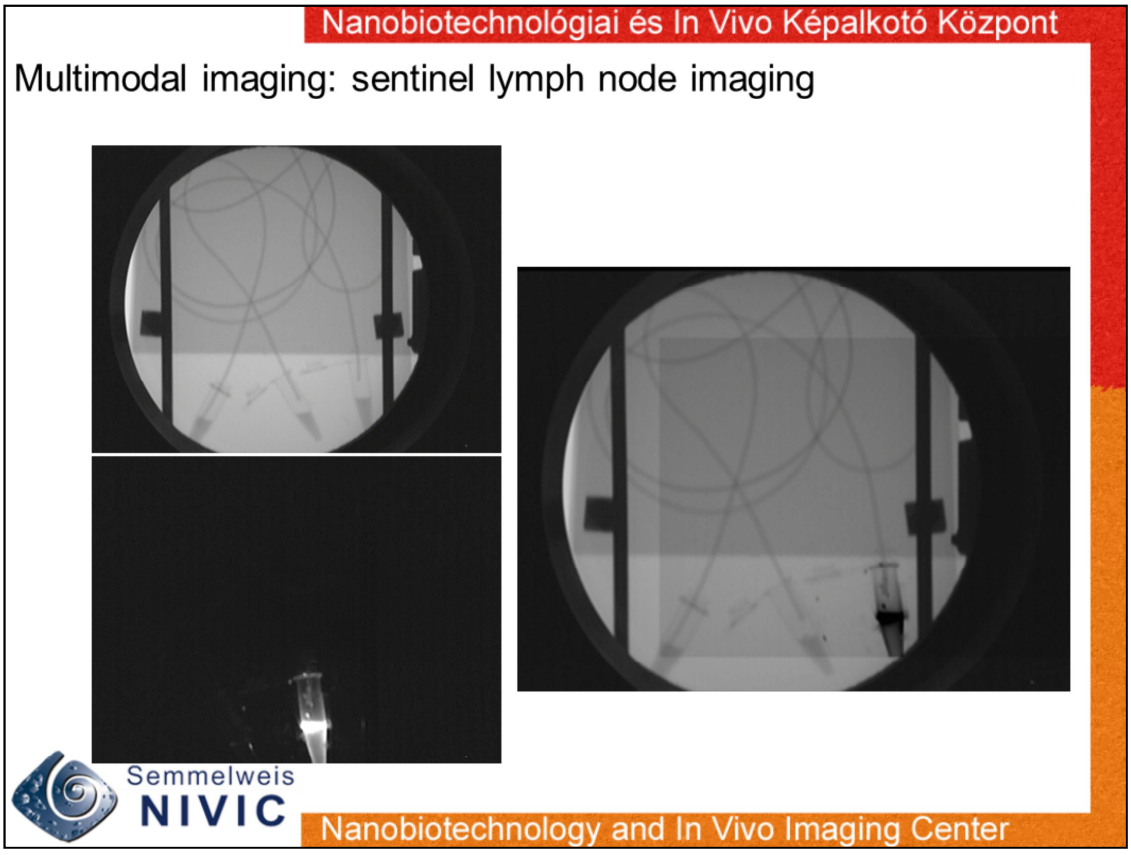
Numerous researchers aim the developement of agents with a lower kidney biding potential.



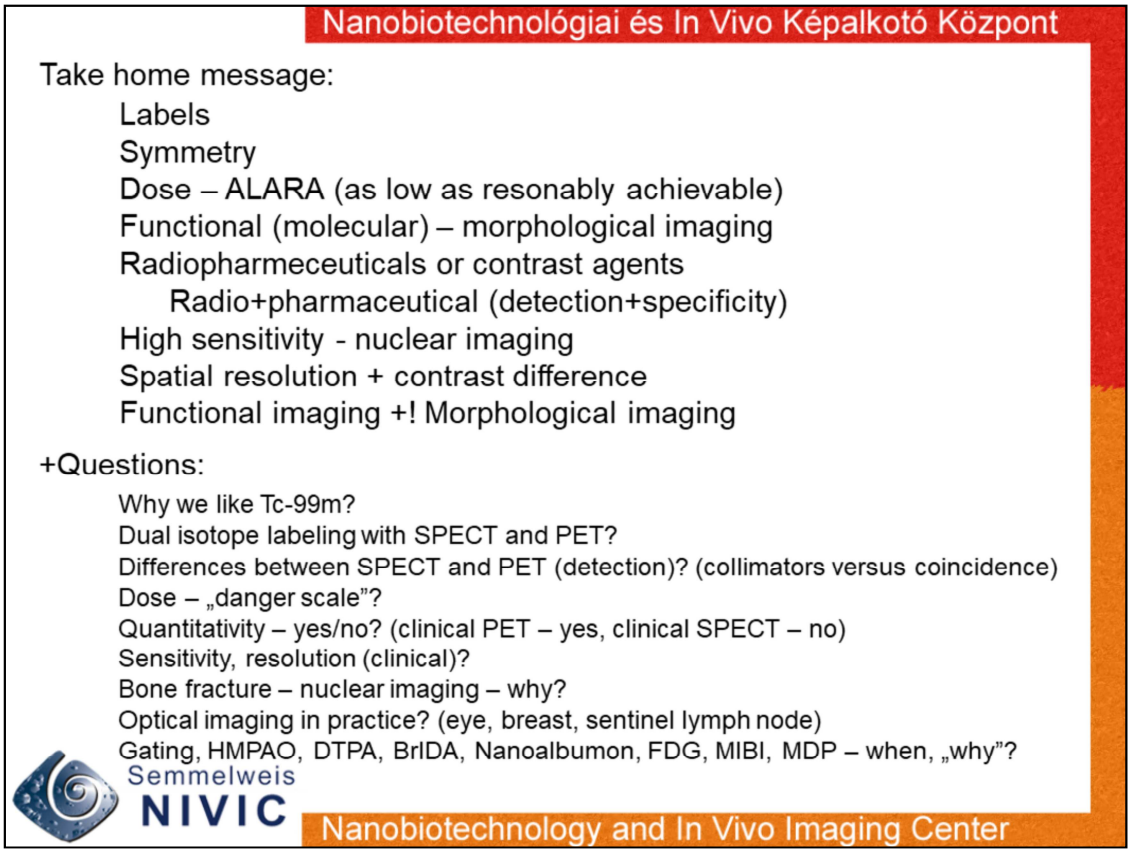
The nanobody based multimodal teragnosic showed on the image may become the most wide-spread device of individual therapy.

The nano body is suitable as a multimodal diagnostic contrast agent since its size.

(CT és MRI: core; PEG: disguise against the immune system; ICA: isotope for PET or SPECT detection; TM: aimed transport; Drugs: therapeutic isotope or pharmaceutical agent.)



The experiment shows in a network model how to find the sentinel lymph node. During the experiment both functional and multimodal imaging is presented, highlighting the benefits of multimodal imaging: a morphological and functional image can jointly provide the appropriate information.



In case of any questions don't hesitate to contact us:
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hegedus.nikolett@med.semmelweis-univ.hu.