Advantages of small animal imaging in the development of targeted radiopharmaceuticals

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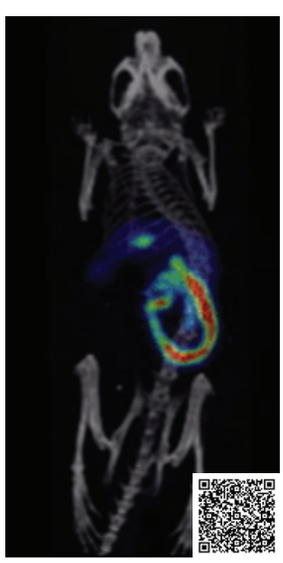
The gold standard among PET radiopharmaceuticals in the clinic is still 18F-FDG. This radiotracer visualises a basic biochemical function of most living cells, glucose consumption, which is up or down regulated in certain disease processes. However, FDG has known limitations, mainly caused by the non-specificity of metabolic changes. This results in a need for the development of alternative radiopharmaceuticals that are able to target specific receptors, cells, etc. In addition, radioligand therapy is more and more recognized as a prominent treatment strategy where PET radiotracers can assess drug-target expression in real time and identify potential responders. There are several reasons why the use of PET imaging in the development of targeted radiopharmaceuticals offers many advantages. The following points clearly demonstrate that PET imaging is an ideal, cost-efficient tool to follow up disease/therapy progression when studying the efficacy of newly developed targeted radiotherapies.

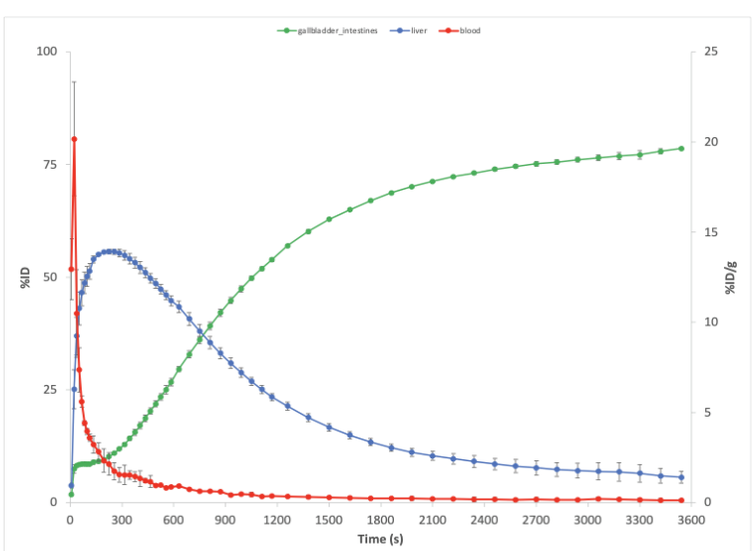
PET and SPECT imaging of targeted radiopharmaceuticals allows *in vivo*, non-invasive, longitudinal follow up and provides full body biodistribution data

Compared to cut and count (*ex vivo*) biodistribution studies, imaging offers full body biodistribution data of all organs at multiple timepoints in the same animal. This reduces the number of animals used in your study according to the 3Rs principle, and also reduces the overall study cost for example when using expensive animal models. There is no need to select the organs of interest in advance, as you'll get all organ information in one dataset. This is interesting in the case of new radiotracers, as it can be hard to predict the target organs. In addition, each animal serves as its own control, which lowers the standard error of your data. Lastly, imaging is a non-invasive *in vivo* technique that allows the researcher to evaluate the animals at multiple time points before reaching the end point, which results in an earlier/time-dependent therapy effect detection.

PET and SPECT imaging provides (dynamic) quantitative information

First, the resulting data provides a 3D image that shows the radiotracer distribution throughout the body. In addition, regions of interest can be drawn around the organs of interest, providing quantitative information of tracer concentration within that organ, and as a function of time in case of dynamic studies. By default, PET and SPECT data are expressed as radioactivity concentration in the organ of interest (kBq/cc), and can be converted into a (semi)-quantitative unit of choice, e.g. SUV, %ID/mL, etc. Lastly, kinetic modelling (compartment modelling) can be performed on dynamic PET data, which provides information on for example the binding potential of a radiotracer in a specific organ that is highly correlated with the receptor density.





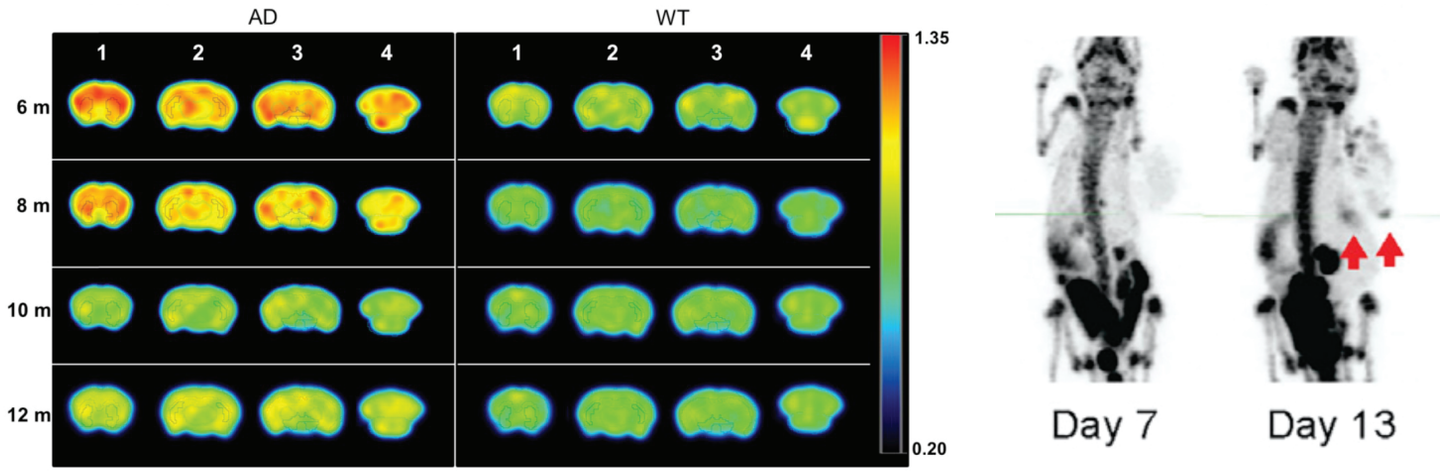
Dynamic radiotracer. 18F-Fluorocholic Acid, a bile acid analogue, providing quantitative kinetic information in multiple organs of interest. QR code contains link to dynamic movie.

Imaging of new compounds enables an efficient screening strategy

During the development process of new radiopharmaceuticals, imaging can be an attractive method for quick screening of new probes, thereby enabling the Go/No Go decision of the compound, before proceeding with more resource-intensive studies like ex vivo biodistribution. In addition, dynamic imaging, covering the time from injection of the tracer onwards, informs about tracer kinetics (including time needed to achieve optimal tissue to background ratio), clearance route, tumor and normal tissue uptake. With short-lived tracers, the same animal can be imaged with different tracers on subsequent days, again optimizing the use of lab animals.

Many radioisotopes with different half-lives are available, allowing you to evaluate biological processes of different length

A range of cyclotron and generator produced isotopes are available, including technetium-99m, indium-111, fluorine-18, carbon-11, oxygen-15, gallium-68, iodine-124, copper-64, zirkonium-89 and lutetium-177. The choice of the isotope mainly depends on the biological process that one would like to evaluate and radiochemistry. PET can for example be used for monitoring gene therapies. This requires the incorporationof an additional reporter gene into the vector containing the therapeutic gene of interest. A high-affinity PET radiotracer can bind to the corresponding reporter protein and is an indirect but proportional measure of therapeutic gene expression at a particular site, again in a non-invasive and longitudinal manner.



Left: Longitudinal follow up of 11C-Buterylcholylesterase as a potential marker of early onset Alzheimer's disease (Rejc et al., Theranostics 11, 2021).
Right: Imaging CAR-T imaging based on PET reporter genes.

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Imaging techniques can be divided into anatomical and functional techniques. The anatomical techniques, like MRI and CT, provide structural information with a high-resolution, where functional and highly sensitive techniques like PET and SPECT give insight in the molecular biology of disease processes. Each modality has intrinsic advantages and limitations, which can be overcome by combining modalities such as PET-CT or SPECT-CT. This multimodal approach provides complementary information about the pathophysiological process under study. At MOLECUBES, we believe that molecular imaging should be accessible to every research lab. It is therefore our mission to lower the barrier to preclinical PET, SPECT and CT imaging by providing compact, intuitive, flexible benchtop imaging solutions with the highest performance, supported by fast and simple workflows.

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