

The past, present and future of ^{89}Zr -immuno-PET

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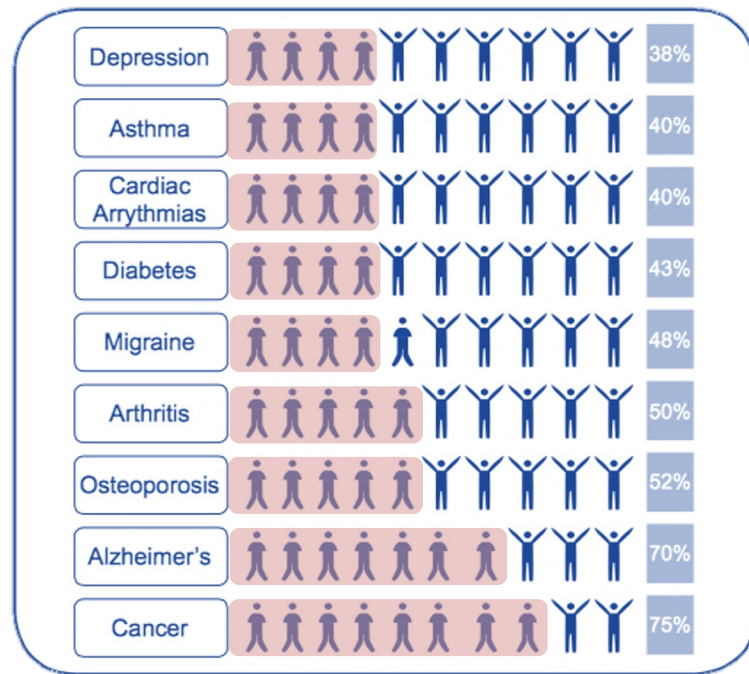
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Why ^{89}Zr -immuno-imaging?

- ❖ Only 10% of drugs that enter clinical development will reach the market
- ❖ Even approved drugs are only effective in a small part of patients
- ❖ Drug development is time consuming and expensive (demonstration of added value in phase III trials)
- ❖ Yearly worldwide sales: ~ **1000 billion** : **600 billion** spent in vain.



Is there a role for academic molecular imaging?



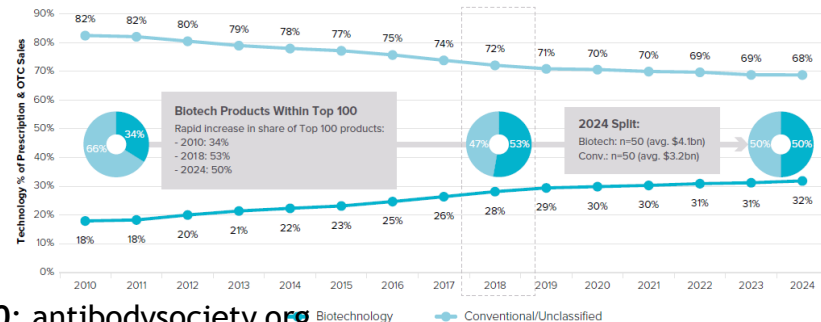
Why ^{89}Zr -immuno-imaging?

From small molecules to a diversity of biologicals

- Seven of the top-ten drug blockbusters were biologics in 2019.
- >120 mAbs approved by FDA and/or EMA of which ~50 for cancer
- Over 550 mAb therapeutics in clinical trials, of which ~80 in late-stage clinical studies (half for cancer)
- Biologicals contribute 50% of the Top 100 product sales by 2024

Figure 4: Worldwide Prescription Drug & OTC Pharmaceutical Sales: Biotech vs. Conventional Technology

Source: EvaluatePharma, May 2019



Evaluate pharma 2019 report; Antibodies to watch 2022, Mabs, 2020; antibodysociety.org



Imaging **drug** and/or target: most informative?

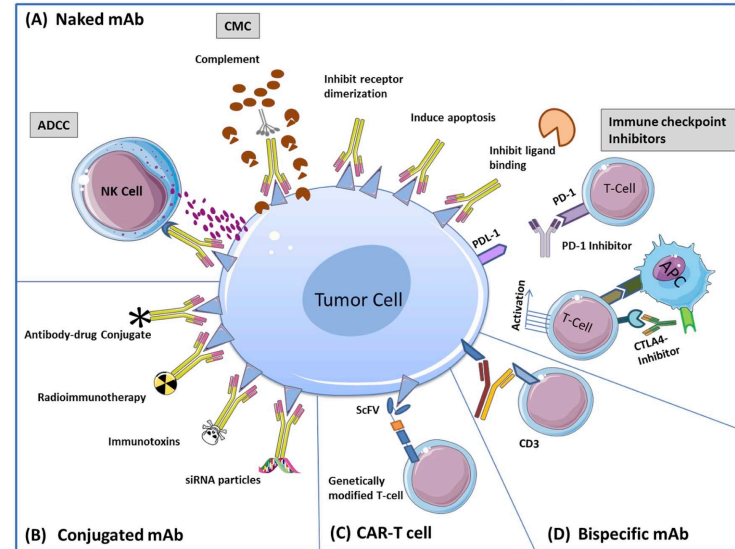
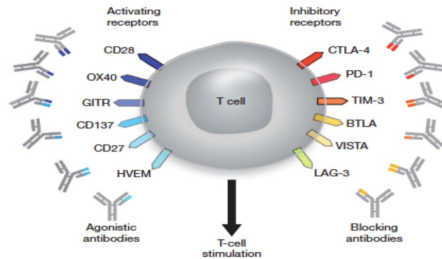
- * Assessment of expression and accessibility of target (also in e.g. brain)
- ➡ Assessment of pharmacokinetics and biodistribution of drug
 - * Whole body, non-invasive, quantitative and longitudinal
- ➡ Confirmation of selective disease targeting - anticipate toxicity
- ➡ Optimization of drug dose: avoiding “sinks”, homogeneous targeting
 - * Identification of patients group with highest chance of benefit
 - * Individualization of therapy (companion - complementary diagnostics)
- ➡ Mechanism of action: showing distinguished properties of a drug
- Labeled **drug** might be more informative and needs just one single lead product
- We call it often a **derisking** tool during drug development!



Sneak peek to the future: next generation targeted biologicals

More potent, multiple specificities and (immune) functions

- ✓ Antibody drug conjugates (ADCs)
- ✓ Immune checkpoint inhibiting antibodies
- ✓ Fusion antibodies, e.g. immunocytokines
- ✓ Bi- and multispecific antibodies
- ✓ Antibody fragments, antibody-like scaffolds
- ✓ Oligonucleotides
- ✓ Nanoparticles
- ✓ Cells

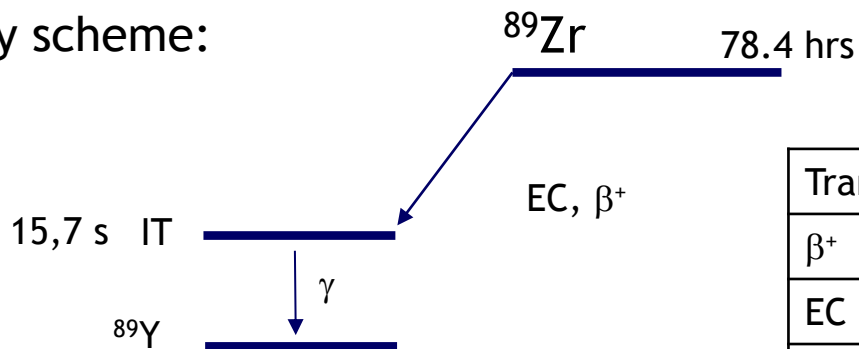


Charmsaz et al, Exp Hematology, 2017.



Zirconium-89

Decay scheme:



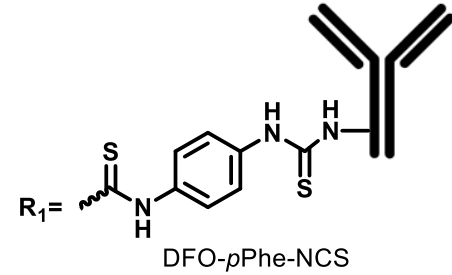
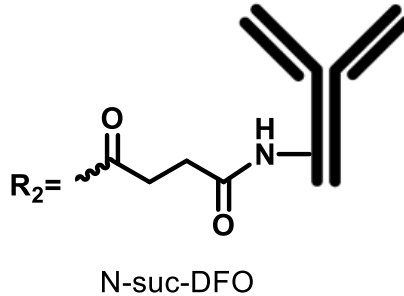
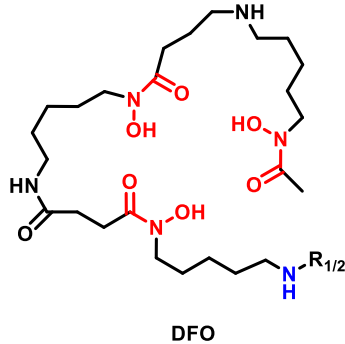
Transition	Energy (MeV)	Abundance (%)
β^+	0.897	22.6
EC		77.0
γ	0.909	99.0

- Production: nuclear reaction $^{89}\text{Y} (p,n) ^{89}\text{Zr}$, obtained as ^{89}Zr in Yttrium disk
- Work up: dissolve in 6M HCl, affinity chromatography



Clinical situation of ^{89}Zr -immuno-PET

Chelator and bifunctional linker:



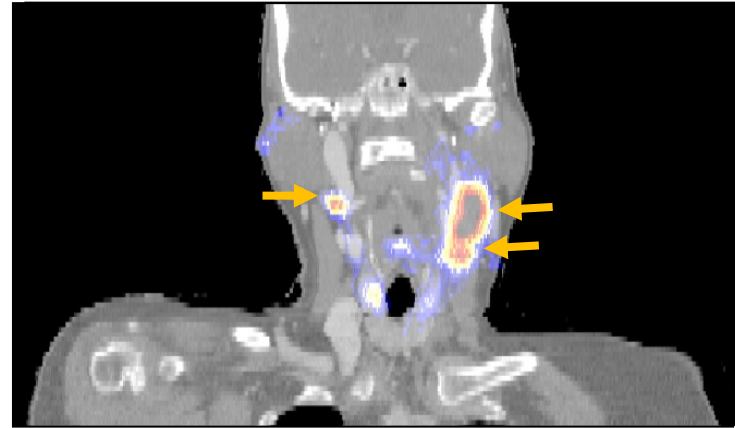
- In mice uptake of ^{89}Zr in bone $\rightarrow$ instability of ^{89}Zr in chelator, discrimination between specific uptake and non-specific uptake difficult
- In man: ??



Past: first clinical trial ever

^{89}Zr -cU36 – CD44v6 – head and neck cancer:

- First clinical immuno-PET study ever
- Feasibility and safety proven
- All primary tumors detected
- 10 mg mAb dose, since between 2-52 mg no mAb dose dependent PK was observed
- Dosimetry determined: ~ 0.6 mSv/MBq
- Image derived quantification of blood-activity possible



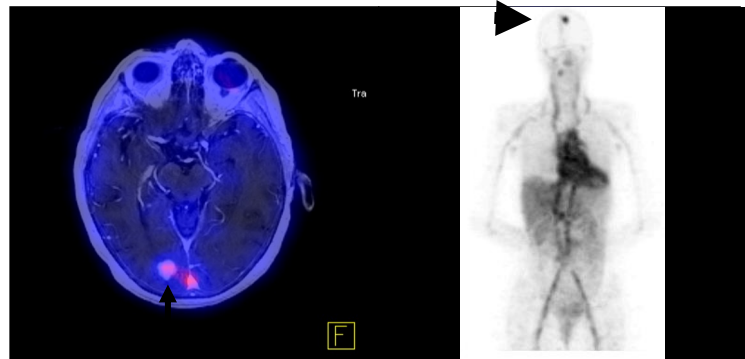
Detection lymph node metastases



Past: what did we learn from first clinical trials

^{89}Zr -trastuzumab – HER2 – breast cancer:

- mAb dose at least 50 mg, otherwise bound to extracellular HER2 shed in blood → fast PK
- Detection of most of the known lesions
- Liver lesions sometimes missed (3 out of 7)
- Brain metastases could be visualized



Dijkers *et al*, Clin. Pharmacol. Ther. 2010; Oude Munnink *et al*, J. Clin. Oncol. 2010.



Present:

- Use of ^{89}Zr -immuno-PET in early phase clinical trials
- Not restricted to mAbs, also nanoparticles, oligonucleotides, ...
- New chelators for zirconium-89
- Also application outside oncology domain

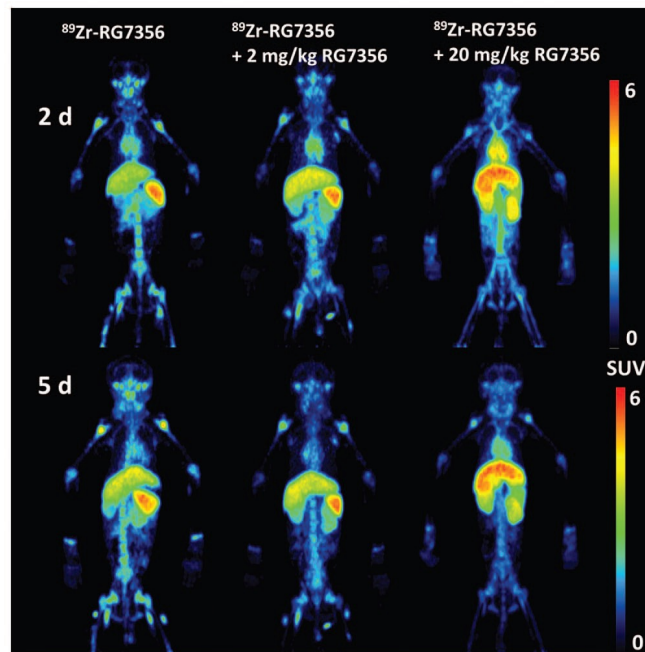
- What will be discussed:
 - CD44 example (mouse-monkey-man)
 - Nanoparticle imaging (clinical)
 - SAP imaging (clinical)
 - DFO* chelator (preclinical)



Present: CD44 imaging in mouse, monkey, man

CD44 overexpression → tumor aggressiveness and metastatic potential
= attractive therapeutic target

- Imaging to anticipate “sinks” and toxicity: CD44
- Decreasing uptake in spleen, bone marrow and salivary glands with increasing mAb dose
- Uptake related to CD44 expression

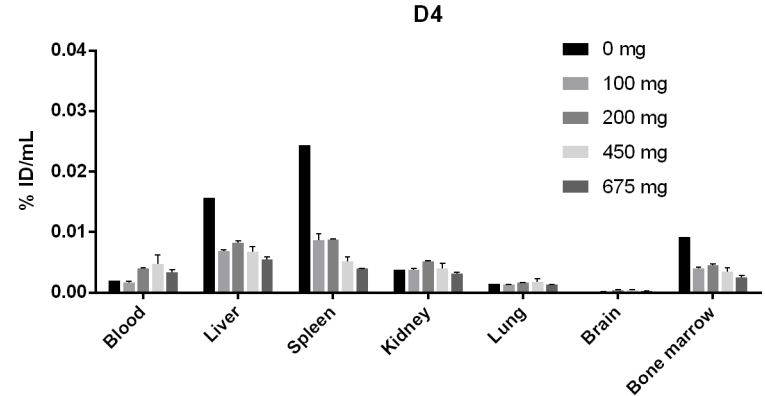
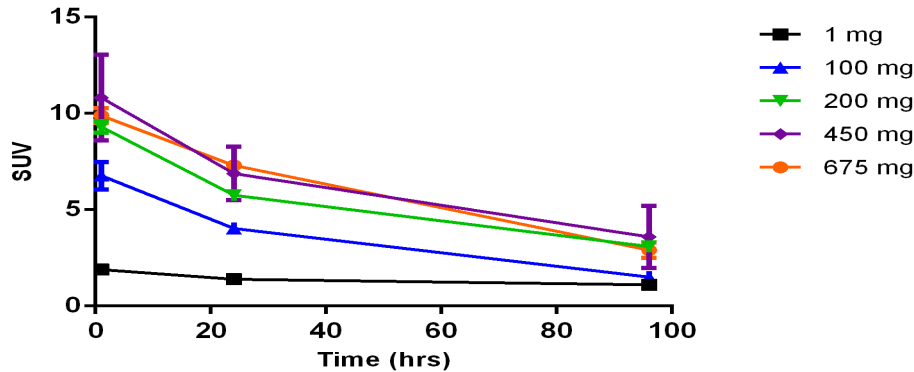


Vugts *et al*, mAbs 2014, 567.



CD44 imaging: mouse, monkey, man

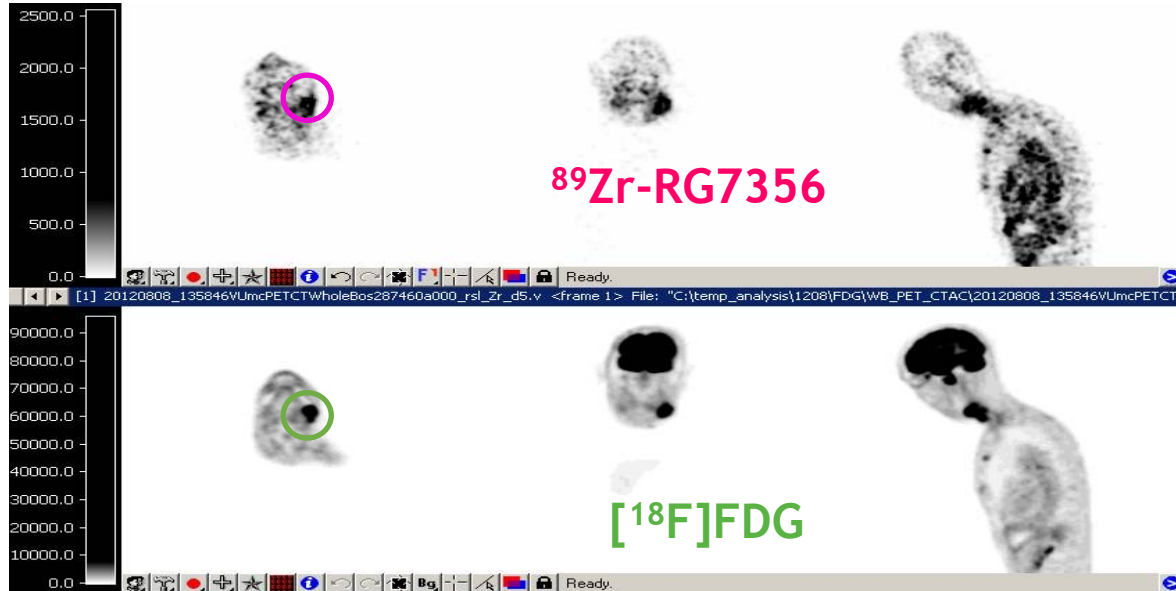
- Thirteen subjects were included
- Dose escalation study
- Quantification of ^{89}Zr -RG7356 in blood pool as a function of time





CD44 imaging: mouse, monkey, man

Patient 8 head&neck cancer (449 mg cold)



- Antibody sink for lower dose cohorts, might be related to CD44 expression in these tissues
- Tumor targeting of ^{89}Zr -RG7356 confirmed for doses ≥ 450 mg

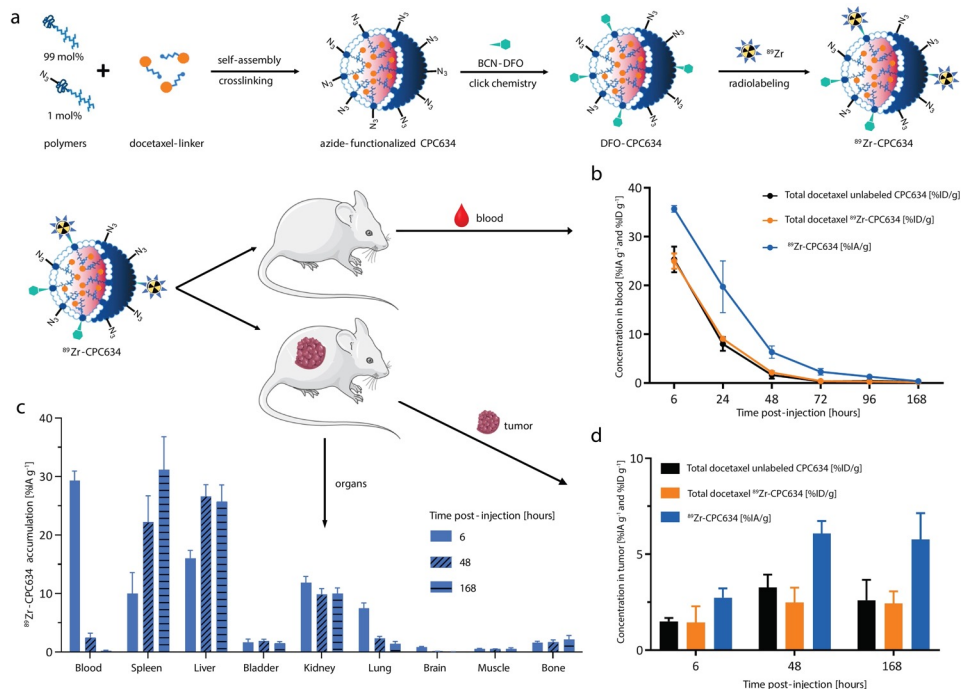


Nanoparticle imaging: background

- **CPC634** is a 65 nm polymeric nanoparticle with covalently linked docetaxel that has demonstrated improved pharmacokinetics and toxicity profiles compared to its conventional chemotherapeutic counterpart
- **Unmet clinical need:**
 - To demonstrate tumor accumulation in a safe and reliable way
 - To ultimately identify patients who are most likely to benefit from nanomedicine treatment

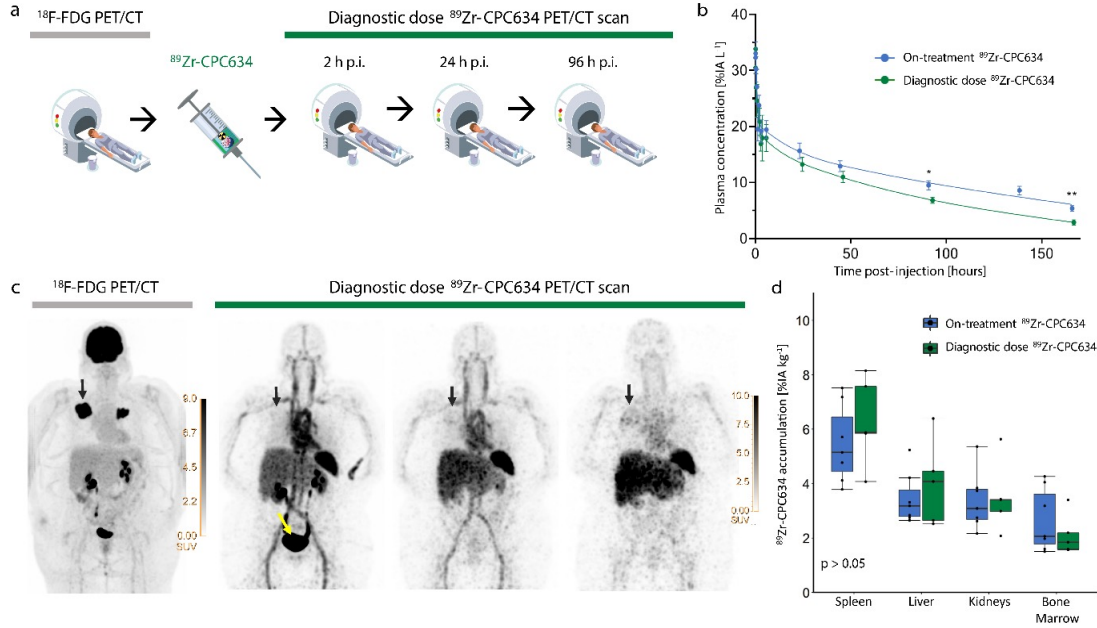
Nanoparticle imaging: preclinical

- Identical blood levels of total docetaxel (%ID/g) with CPC634 and ^{89}Zr -CPC634
- Expected biodistribution of ^{89}Zr -CPC634 with predominant accumulation in spleen, liver and kidney
- Similar intra-tumoral levels of total docetaxel (%ID/g) with CPC634 and ^{89}Zr -CPC634





Nanoparticle imaging: diagnostic vs on treatment imaging



- Effect of dose on PK and tumor targeting evaluated
- Similar PK and biodistribution
- Circulation up to 144h p.i.
- Accumulation in spleen, liver and bone marrow, known sites of nanoparticle entrapment and elimination.
- Tumor accumulation was observed (black arrow).

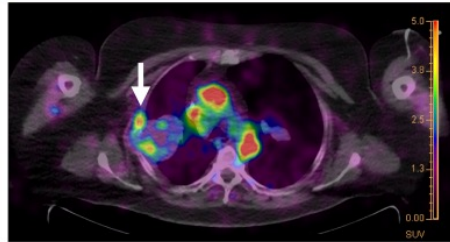


Nanoparticle imaging: tumor uptake

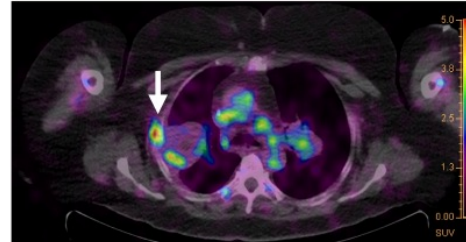
^{18}F -FDG PET/CT



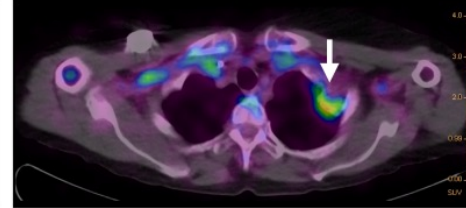
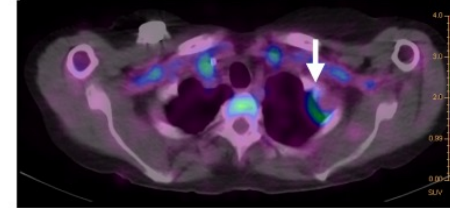
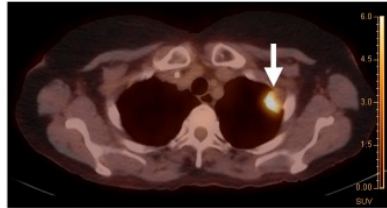
On-treatment ^{89}Zr -CPC634



Diagnostic dose ^{89}Zr -CPC634



Endometrial cancer
– Lung metastasis



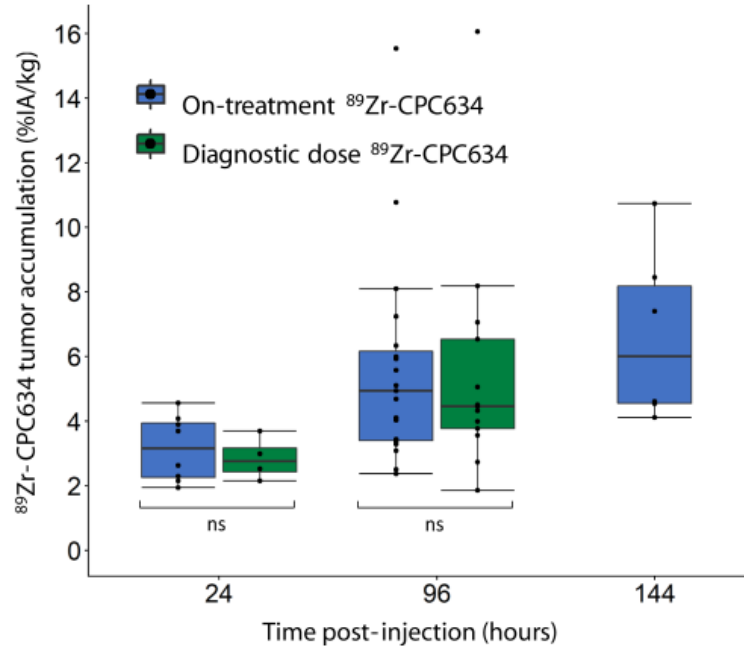
Colorectal cancer
– Lung metastasis

- Tumor accumulation in 6 out of 7 patients
- Heterogenous uptake

Miedema I *et al*, Adv Mat 2022, article nr 2201043



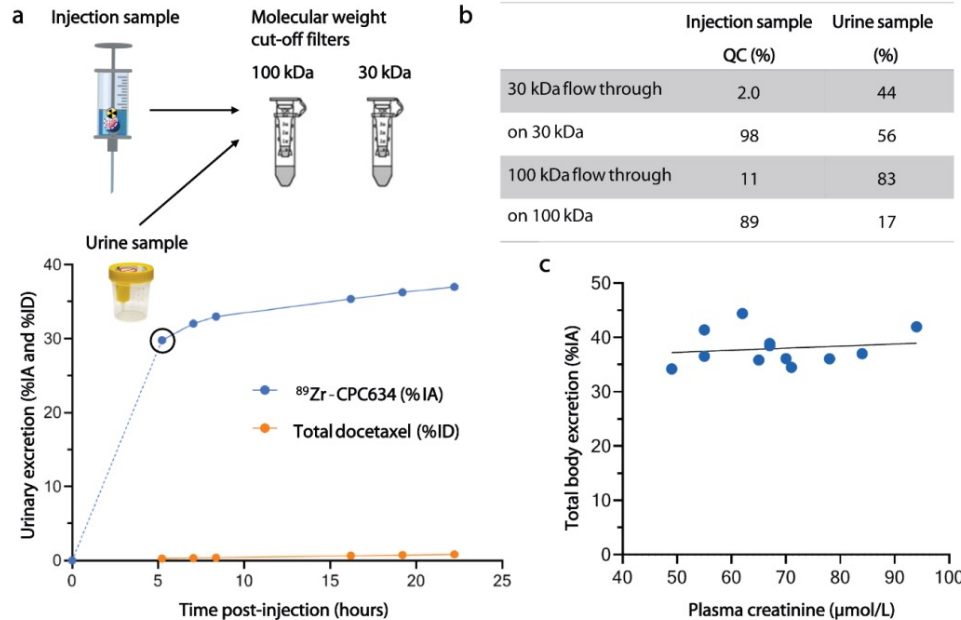
Nanoparticle imaging: tumor uptake



- Heterogeneous between patients, between tumor lesions of each patient and within the tumor lesions itself
- In 21/46 tumor lesions with on-treatment imaging (46%; in 7 patients)
- in 13/32 tumor lesions with diagnostic dose imaging (41%; in 5 patients).
- No significant difference between on-treatment and diagnostic dose imaging



Nanoparticle imaging: problem with NP batch



PROBLEM: Polymeric networks present which could not be detected by standard nanoparticle analysis methods



Nanoparticle imaging: conclusion

- Radiolabeling of CPC634 with ^{89}Zr has been succesful (same physicochemical properties as well as preclinical PK, biodistribution and tumor accumulation)
- ^{89}Zr -CPC634 PK and biodistribution in patients are similar on treatment vs. diagnostic dose
- Tumor accumulation of ^{89}Zr -CPC634 was observed in 6 out of 7 patients with a low, diagnostic dose
- ^{89}Zr -CPC634 PET imaging is safe and can be further developed as a potential tool for patient selection before start of treatment



SAP immuno-PET study

- Systemic amyloidosis is a progressive, often fatal disorder in which misfolded proteins form fibrils that accumulate in vital organs leading to progressive organ dysfunction
- In a Phase 1 clinical trial GSK demonstrated progressive removal of amyloid with up to three cycles of mAb therapy that targeted the plasma protein serum amyloid P component (SAP), which is universally present in amyloid deposits, and is therefore a target in all forms of amyloidosis.

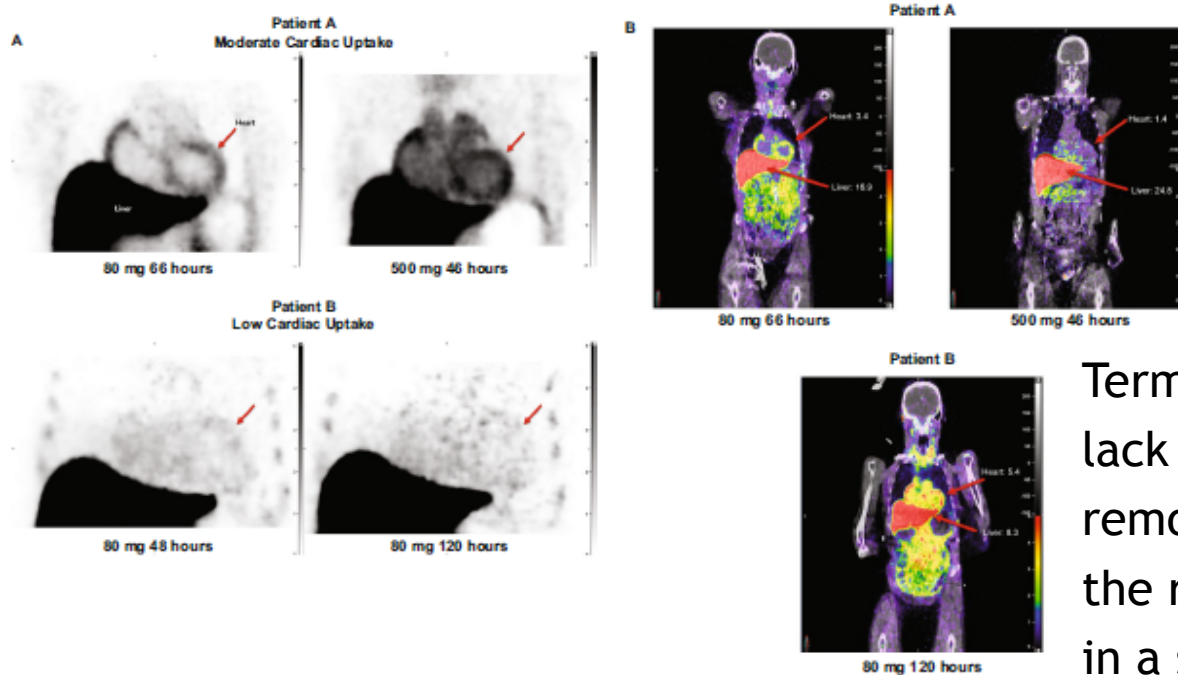


SAP immuno-PET study

- In a follow-up Phase 2 study was investigated:
 - What the impact of treatment on cardiac amyloid deposits?
 - What is the occurrence and nature of dermatological adverse events (AEs; mainly rashes), which were seen in 58% of patients in the Phase 1 study and seemed to occur with incremental dezamizumab doses?



SAP immuno-PET study



Termination of the study because:
lack of evidence of cardiac amyloid
removal or functional benefit, and
the reporting of a SAE of vasculitis
in a subject in the Phase 2 study

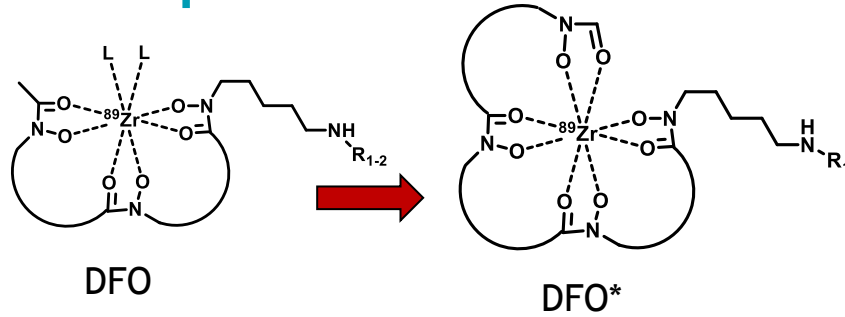


Future?

- Total-body PET
 - lower amount of Zr-89 and thus radiation dose reduced
 - Imaging at later timepoints after injection
 - Imaging of new drug formats, e.g. cell therapies, RNA/DNA based molecules
- Imaging outside the oncology domain

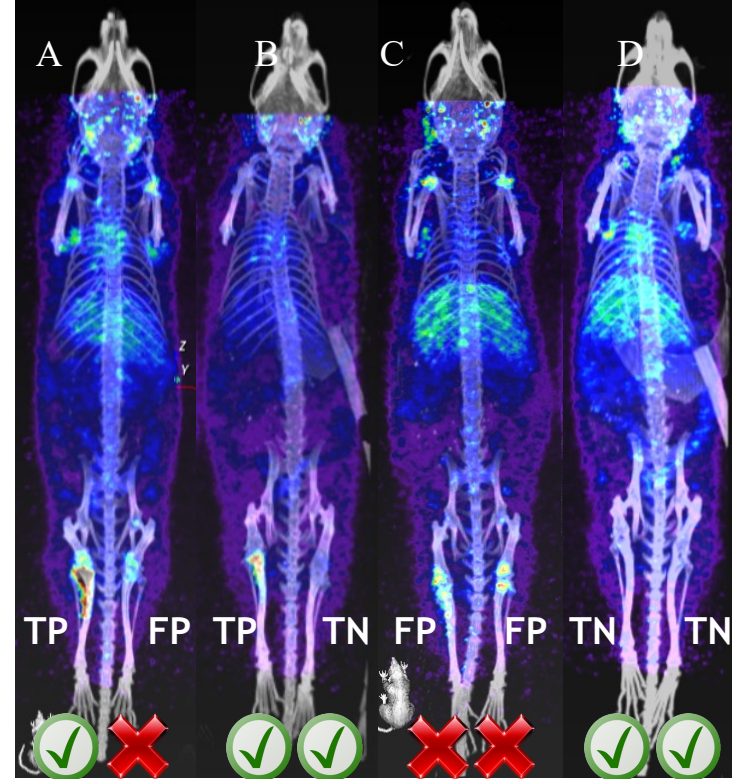


Sneak peek of the future: brain ^{89}Zr -immuno-PET



Bone metastasis model:

- A. DFO-NCS-trastuzumab
- B. DFO*-NCS-trastuzumab
- C. DFO-NCS-B12
- D. DFO*-NCS-B12

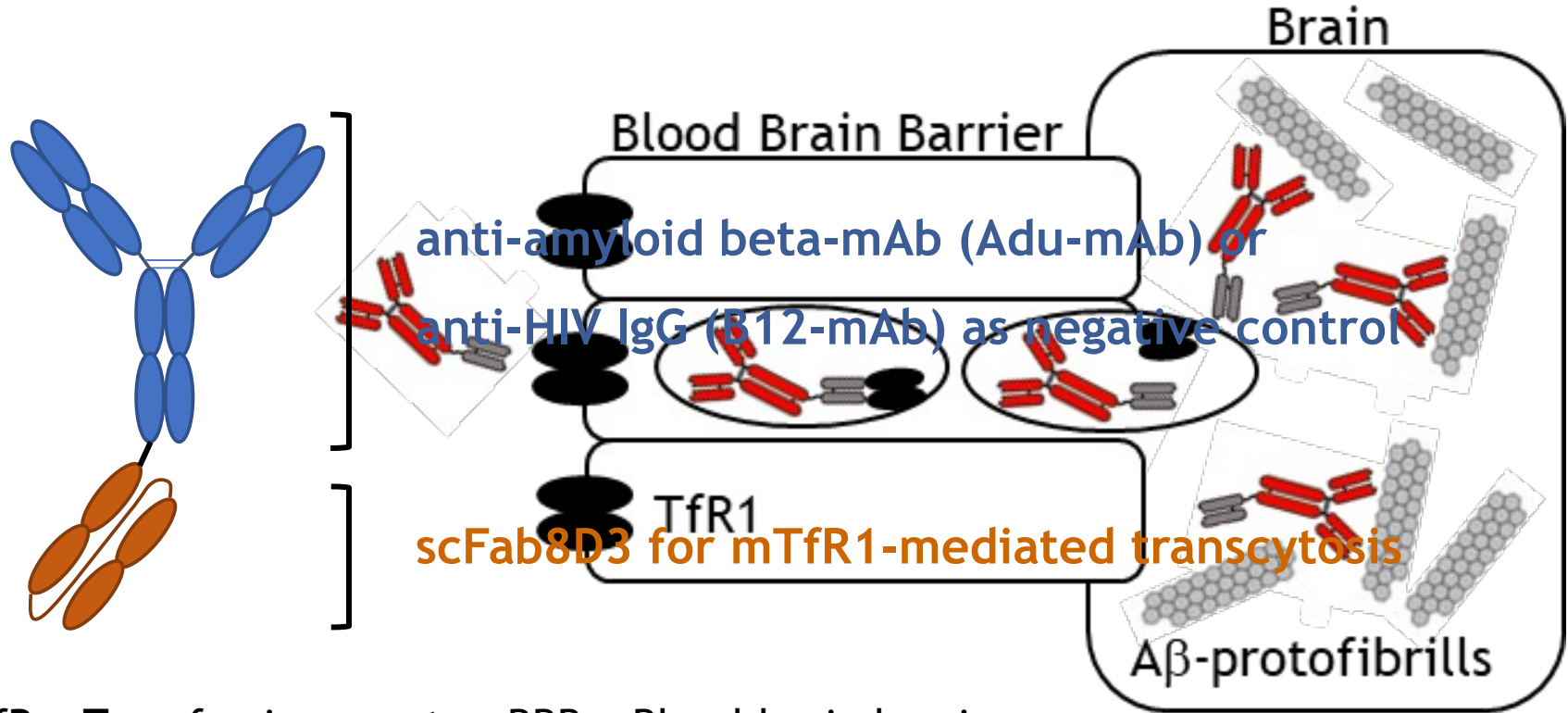


Chomet *et al*, EJNMMI 2021, 694.

TP=true-positive, FP=false-positive, TN=true-negative



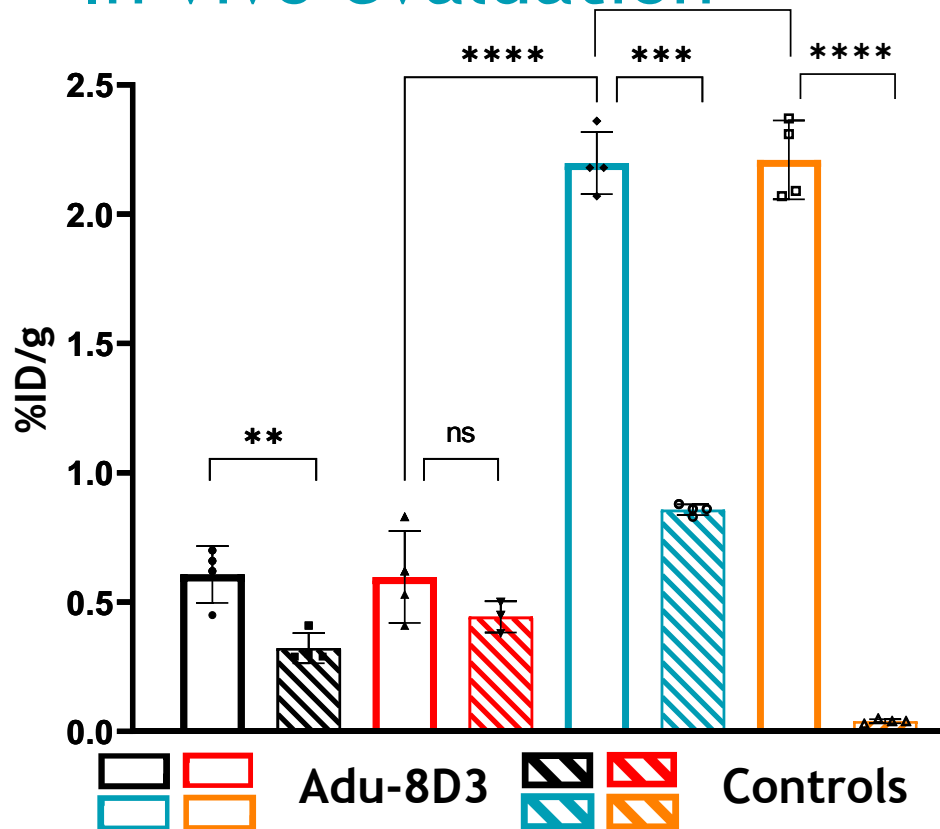
Brain ^{89}Zr -immuno-PET



TfR = Transferrin receptor, BBB = Blood-brain barrier



In vivo evaluation



[⁸⁹Zr]Zr-DFO-N-suc

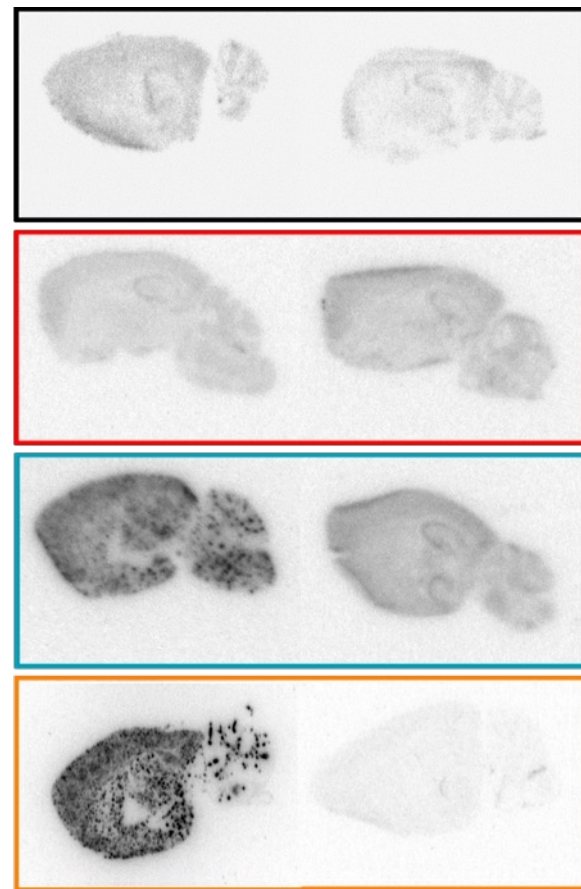
[⁸⁹Zr]Zr-DFO-NCS

[⁸⁹Zr]Zr-DFO*-NCS

[¹²⁵I]-

Adu-8D3

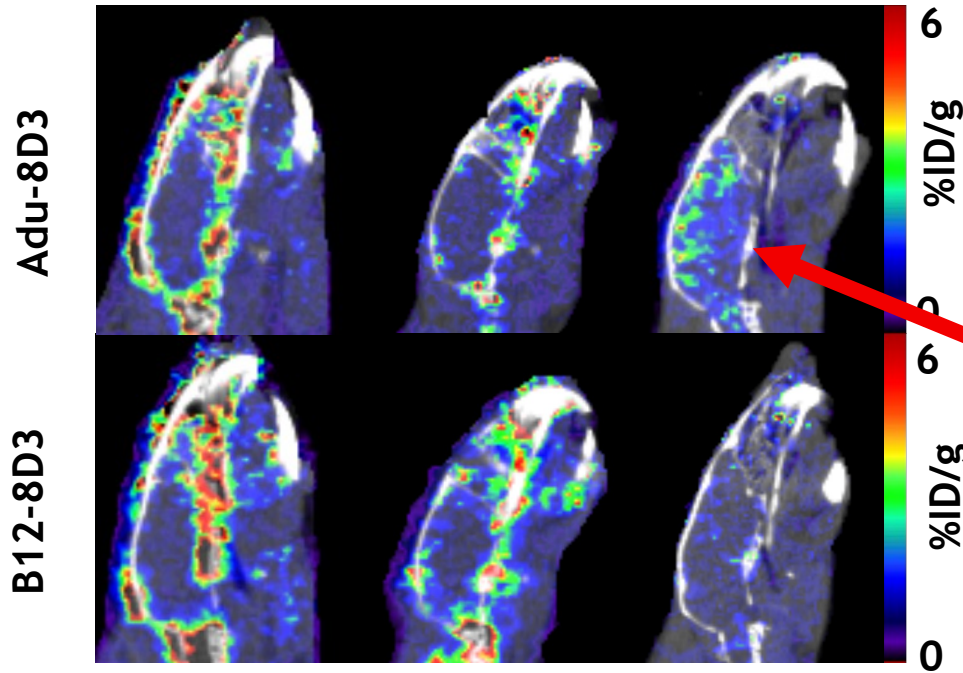
Controls





PET imaging day 7 p.i.

[⁸⁹Zr]Zr- DFO-*N*-suc DFO-NCS DFO*-NCS



No specific brain uptake for both DFO groups with abundant signal around the brain

High brain uptake with focal hotspots was only observed for [⁸⁹Zr]Zr-DFO*-NCS-Adu-8D3



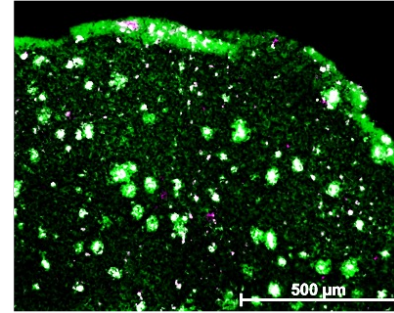
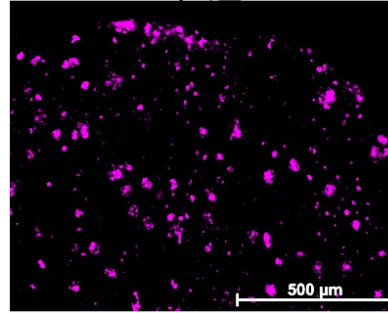
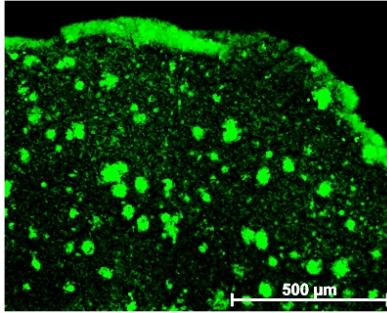
Immunofluorescence

A β plaques -
by Thioflavin S

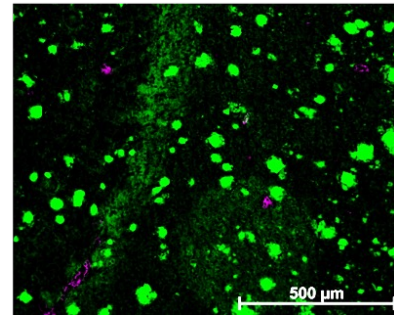
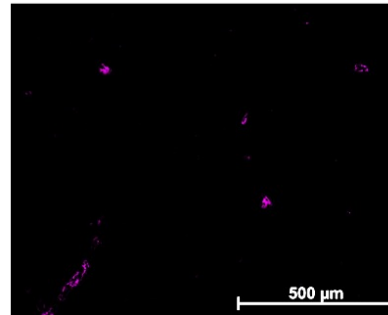
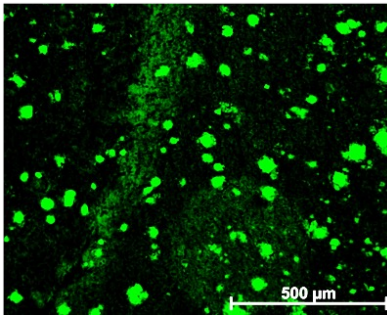
Injected mAb - by
anti-human IgG AF

merged

[⁸⁹Zr]Zr-DFO*-
NCS-Adu-8D3
(injected)



[⁸⁹Zr]Zr-DFO*-
NCS-B12-8D3
(injected)



➤ Co-localization of all Adu-8D3 constructs with amyloid beta plaques



Conclusion

- Multiple applications possible
- More and more pharmaceutical companies want to understand their products better in earlier phase clinical trials
- Multiple ways to include ^{89}Zr -immuno-PET, exact set-up depends on research question
- Not limited to proteins and oncology
- De-risking drug development program
- Use of total body PET → later scanning timepoints, lower amount of Zr-89, lower radiation dose (37 MBq results in around 20 mSv)

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