PET imaging for developing nanomedicine-based drug delivery systems

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School of Biomedical Engineering & Imaging Sciences, St Thomas' Hospital, London, UK

Declaration of Financial Interests or Relationships

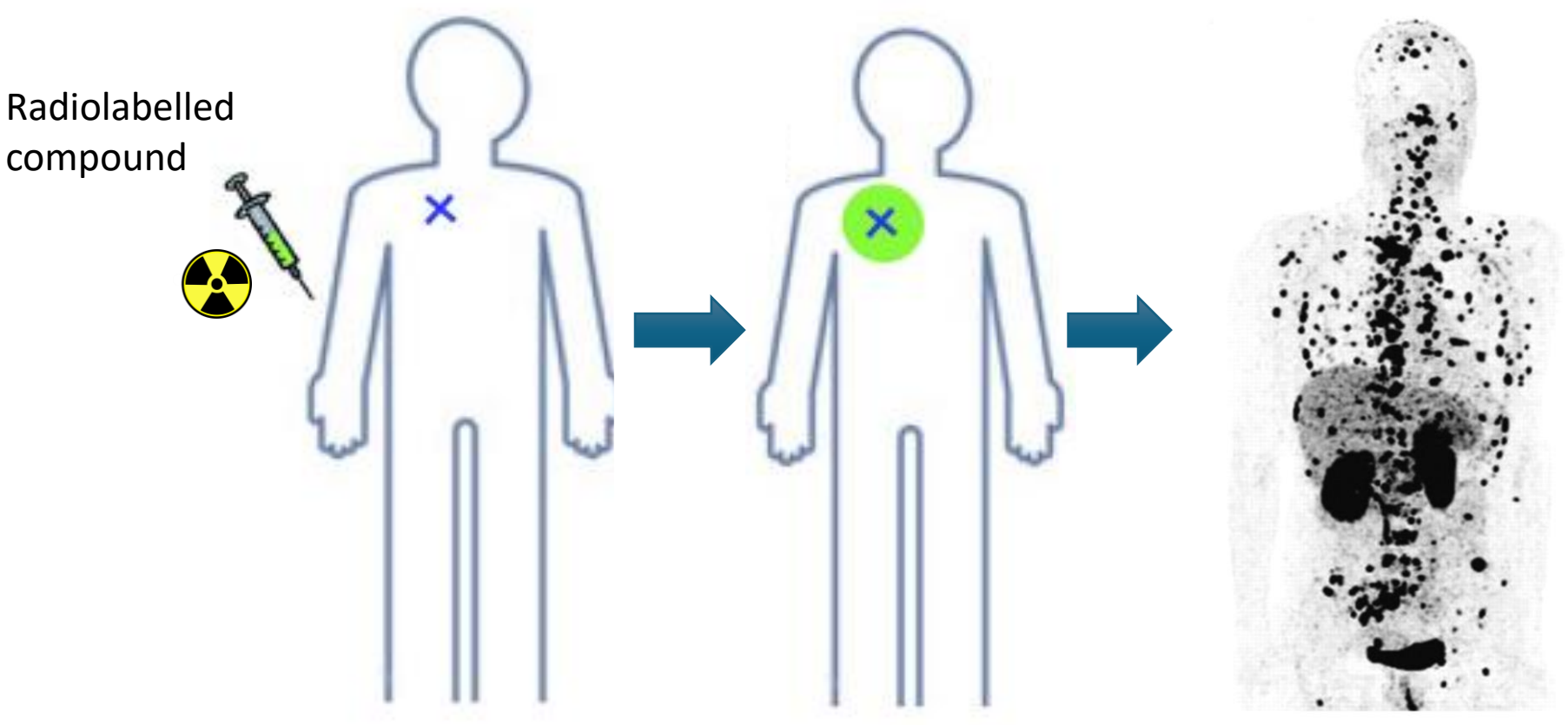
I or one of my co-authors have **the following financial interest** or **relationship(s)** to disclose with regard to the subject matter of this presentation:

Property rights/patents: Patent on Formulation for cell/liposome/exosome radiolabelling
Grant/research support: AstraZeneca, GlaxoSmithKline, Innomedica
Employment: King's College London
Consultant: ImagingAb
Other:

Radiometal chemistry to label and track drug delivery systems/nanomedicines and therapeutic cells *in vivo*

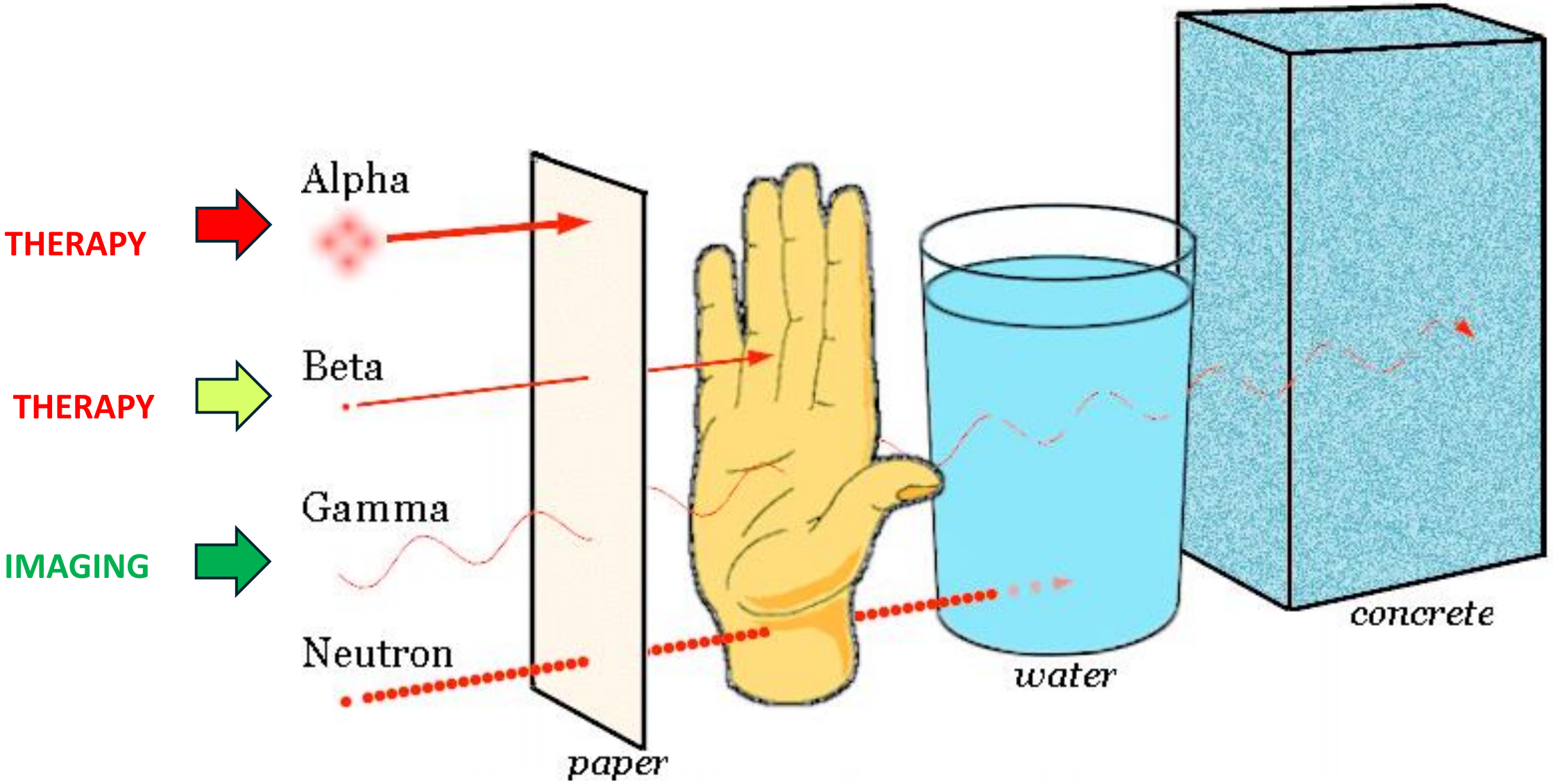
School of Biomedical Engineering & Imaging Sciences
King's College London

Nuclear Medicine



IMAGING
and
THERAPY

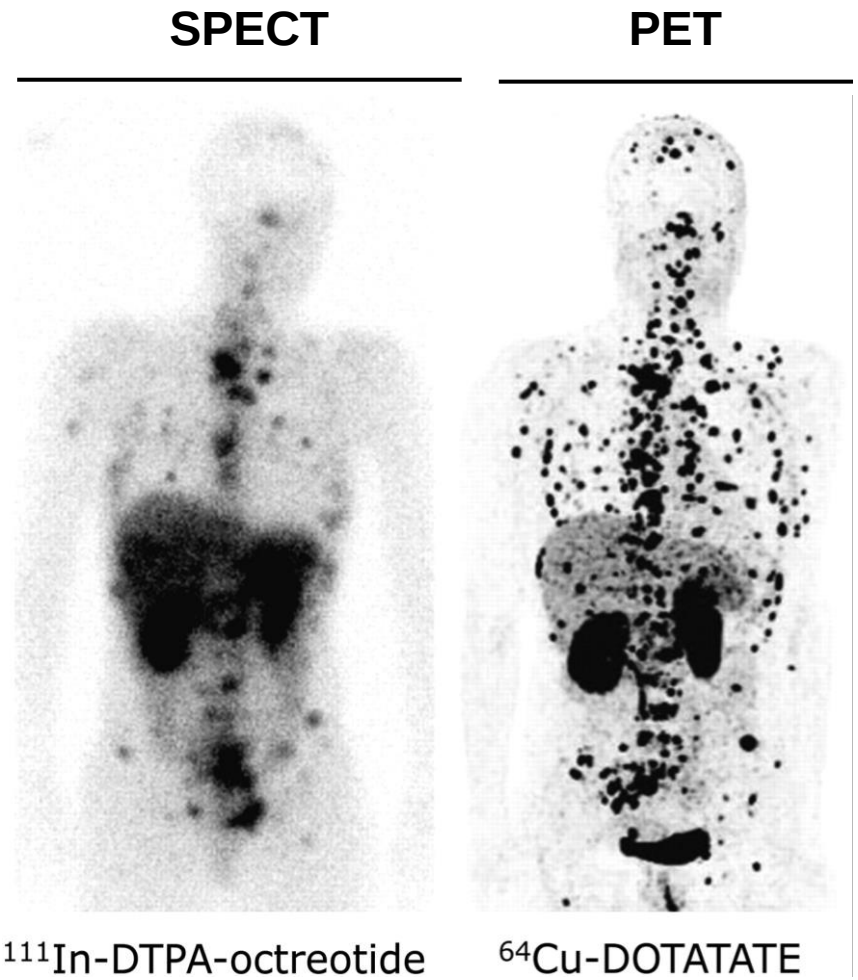
Radionuclide emissions




PET-CT


SPECT

Nuclear Imaging: SPECT and PET



Pfeifer *et al*. J Nucl Med 2012;53:1207

PROS:

- **Sensitive**: micrograms quantities, or less…(microdose imaging)
- **Hot-spot** → no endogenous background
- No **tissue penetration** issues
- **Whole-body (PET)**
- Dynamic → **kinetics (PET)**
- **Quantifiable (PET)**

CONS:

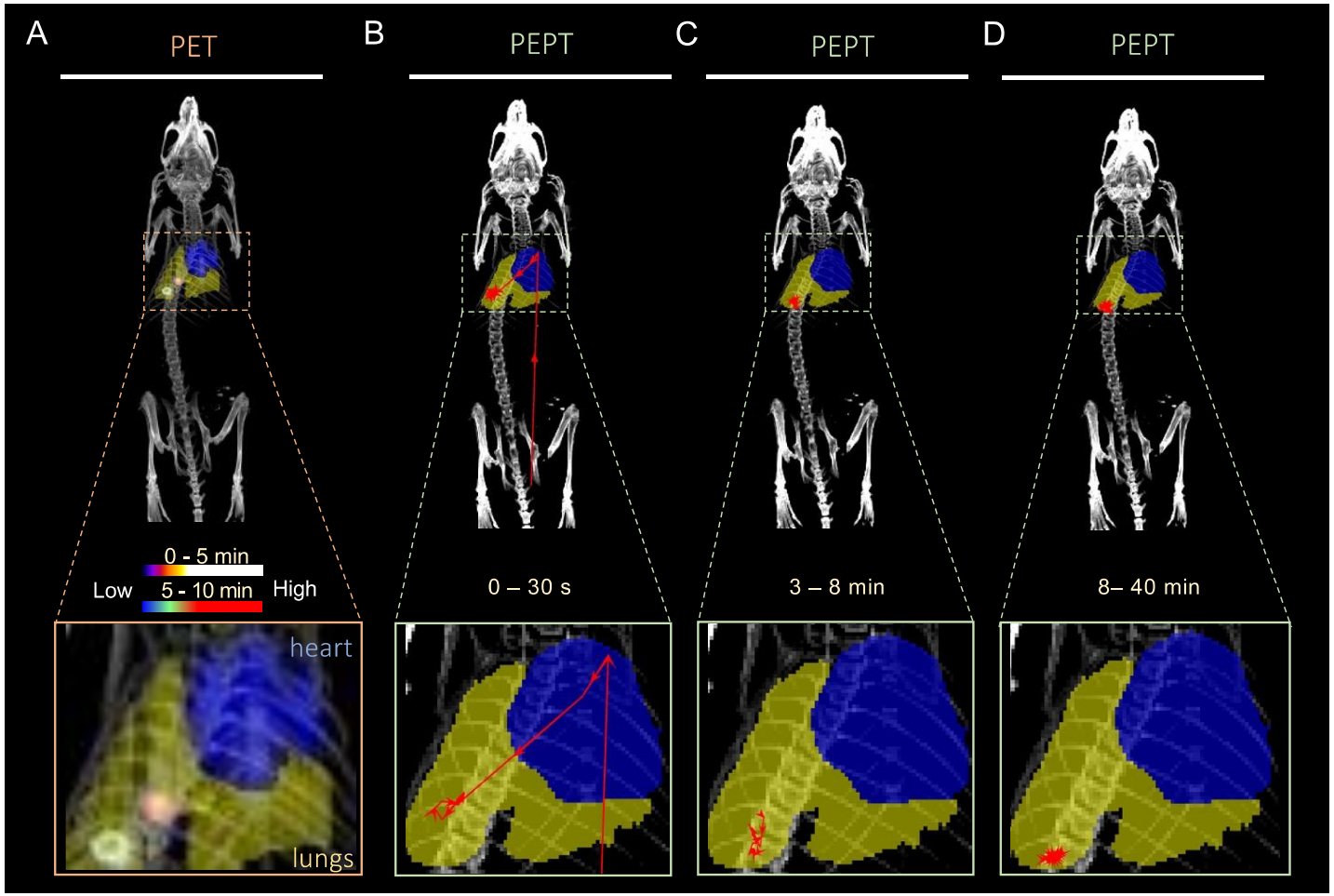
- Use of **radioactivity** → manageable risk

The sensitivity of PET

In vivo PET *and* PEPT imaging of a *single particle*

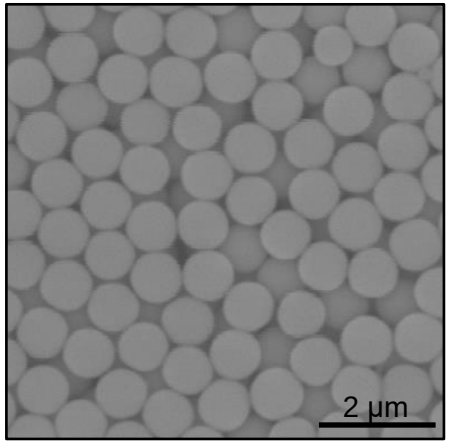
PET

Positron
Emission
Tomography



PEPT

Positron
Emission
Particle
Tracking



MASS DOSE: 1 silica particle → picogram range (10^{-11} – 10^{-12} g) *vs*. 10^{-6} g for standard PET tracer !!

RADIATION DOSE: 2 kBq (single particle) *vs*. 10,000 kBq (standard PET tracer) !!

nature nanotechnology

Article

https://doi.org/10.1038/s41565-023-01589-8

In vivo real-time positron emission particle tracking (PEPT) and single particle PET

Received: 16 May 2023

Accepted: 30 November 2023

Published online: 19 January 2024

Juan Pellico[1], Laurence Vass[1], Amaia Carrascal-Miniño[1], Francis Man[1], Jana Kim[1], Kavitha Sunassee[1], David Parker[2], Philip J. Blower[1], Paul K. Marsden[1] & Rafael T. M. de Rosales[1]

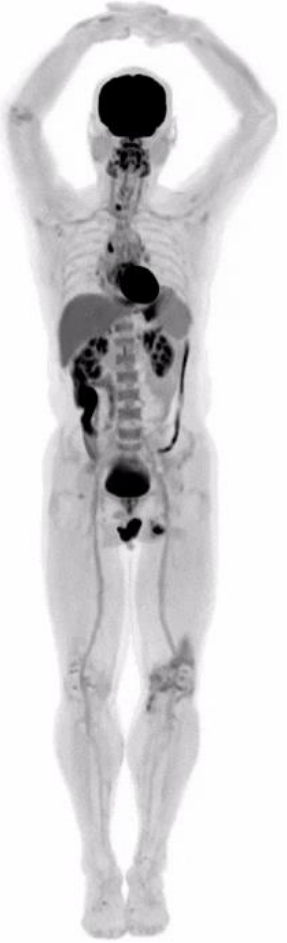
Nature Nanotechnology, **2024,** 19, 668

PET imaging as a drug development tool

KING'S College LONDON

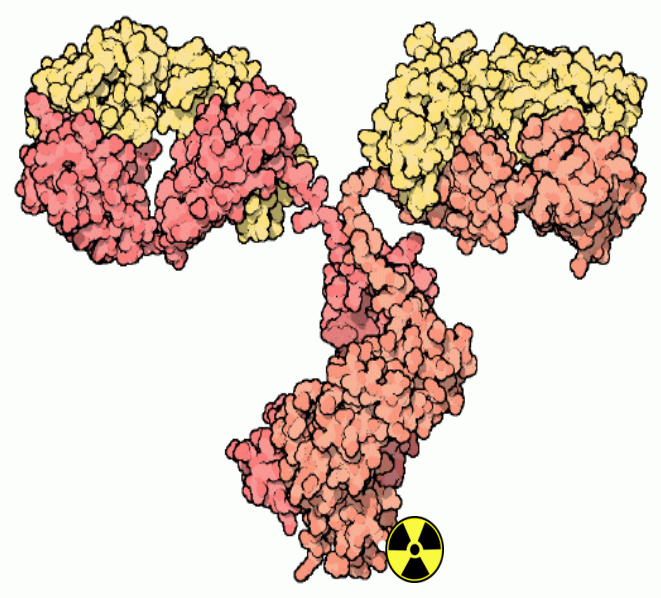
PET imaging allows:

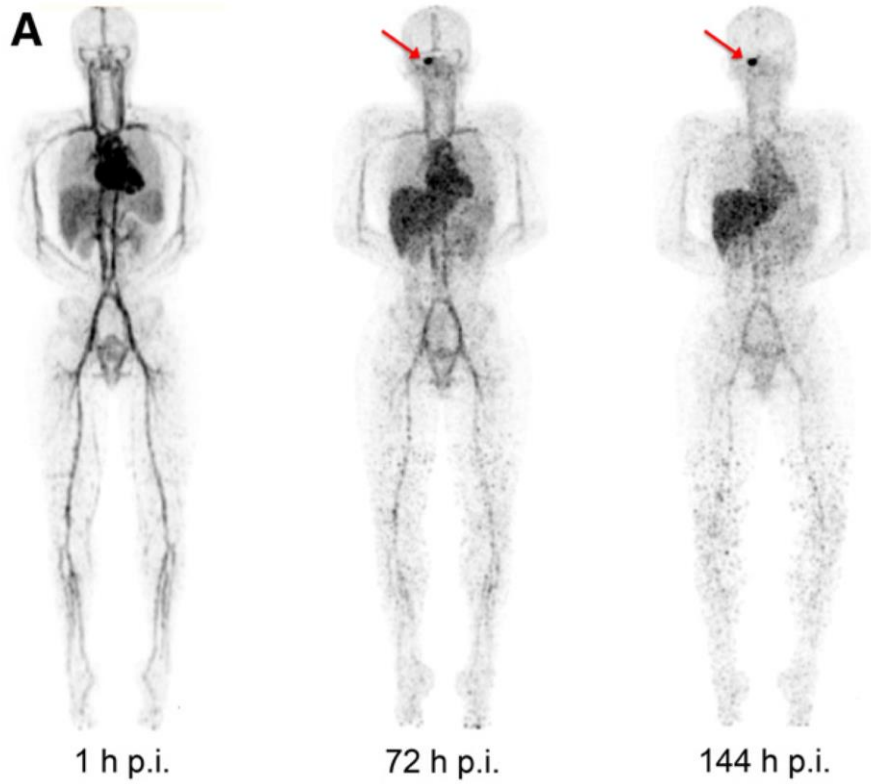
- See where is the drug is going *i.e.* biodistribution → whole-body! Using micrograms or less!!
- How fast, when? – pharmacokinetics → whole-body, 3D!
- How is it cleared? How fast? → Excretion
- Optimisation of dose and administration route
- Translatable: directly from animals to humans
- Patient-selection tool (personalised medicine / theranostics)



From SMALL MOLECULE drugs, to LARGE MOLECULES (e.g. Abs), to CELL THERAPIES

PET Imaging of Antibodies





- Easy to radiolabel
- Well-defined structure
- Well-established chemistry
- Radiolabel does not affect function

Correlation of tumor uptake of **[^{89}Zr]Zr-bevacizumab** with blood pool.

Molecular Drug Imaging: ^{89}Zr-Bevacizumab PET in Children with Diffuse Intrinsic Pontine Glioma, J Nucl Med 2017; 58:711–716

Why is PET not used more often for nanoDDS development?

DDS = drug delivery system

Main barriers

- Complex structures → (Radio)-chemistry
- Costs / infrastructure
- Only BioD/PK information
- Human studies → Radiation dose to patient

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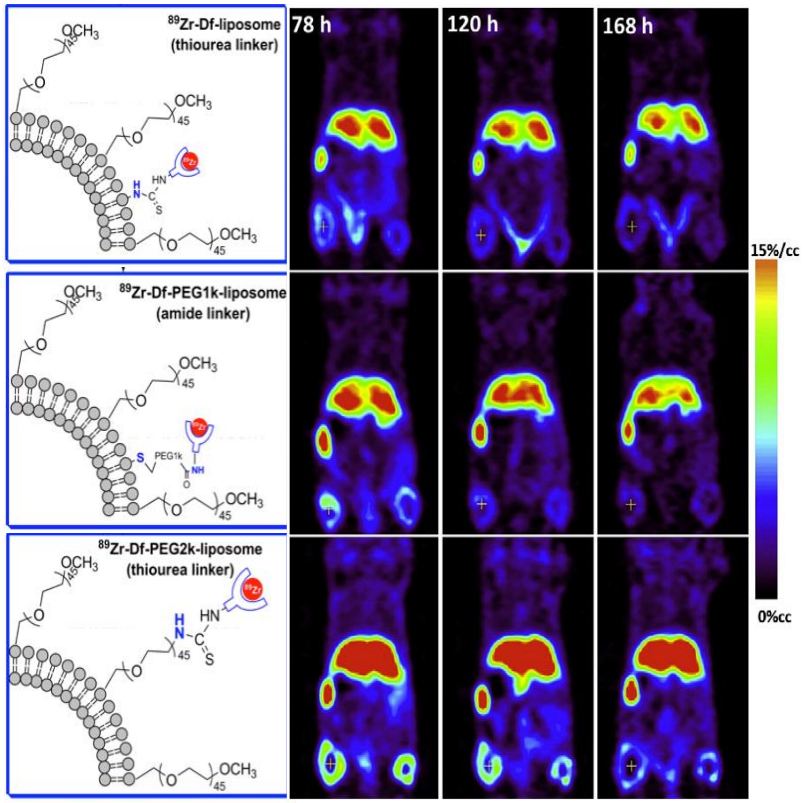
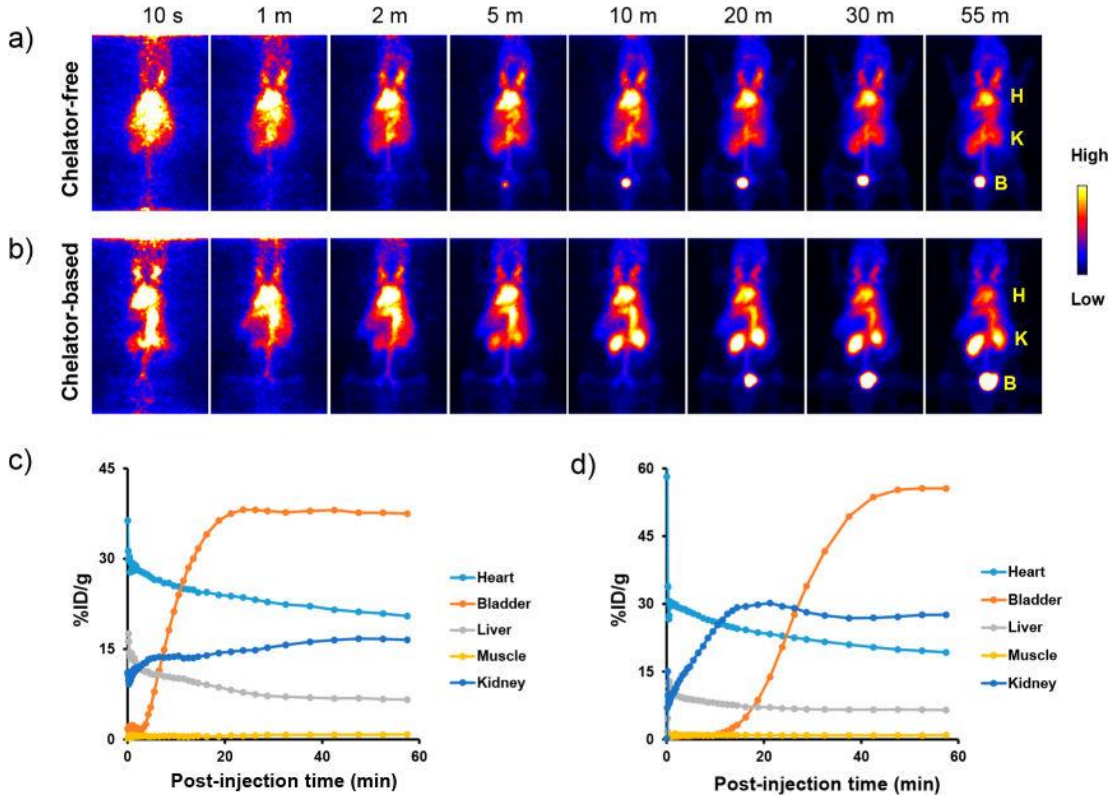
Labelling nano-DDS for PET imaging

NPs are not insensitive to labelling for imaging (*i.e.* how and where you label matters)



J. Seo *et al. Nucl. Med. Bio.* **2015**; 42: 155 – 163



Chen *et al.* Chem Mater. 2017 October 10; 29(19): 8269–8281

Chem Soc Rev

ROYAL SOCIETY OF CHEMISTRY

REVIEW ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Soc. Rev.*, 2021, **50**, 3355

Radiolabelling of nanomaterials for medical imaging and therapy

Juan Pellico, † Peter J. Gawne † and Rafael T. M. de Rosales *

70 pages, >700 references

Why is PET not used more often for nano-DDS development?

Main barriers

- Complex structures → (Radio)-chemistry
- **Costs / infrastructure**
- Only BioD/PK information
- Human studies → Radiation dose to patient

Why is PET not used more often for nano-DDS development?

Main barriers

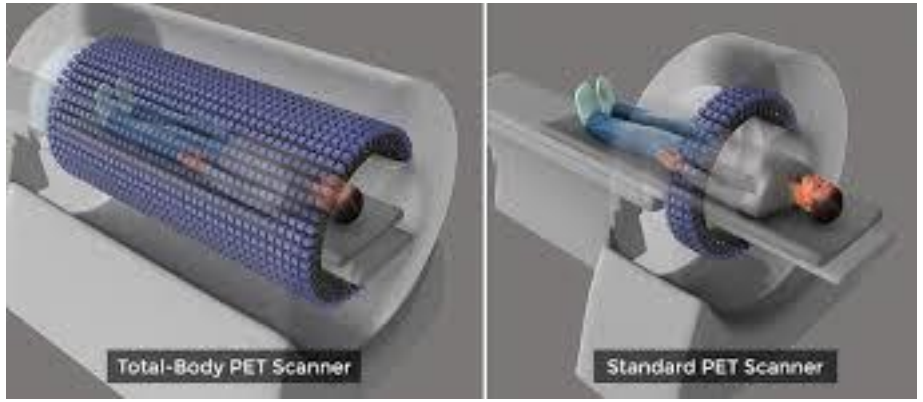
- Complex structures → (Radio)-chemistry
- Costs / infrastructure
- **Only BioD/PK information** → *multimodal imaging*
- Human studies → Radiation dose to patient

Why is PET not used more often for nanoDDS development?

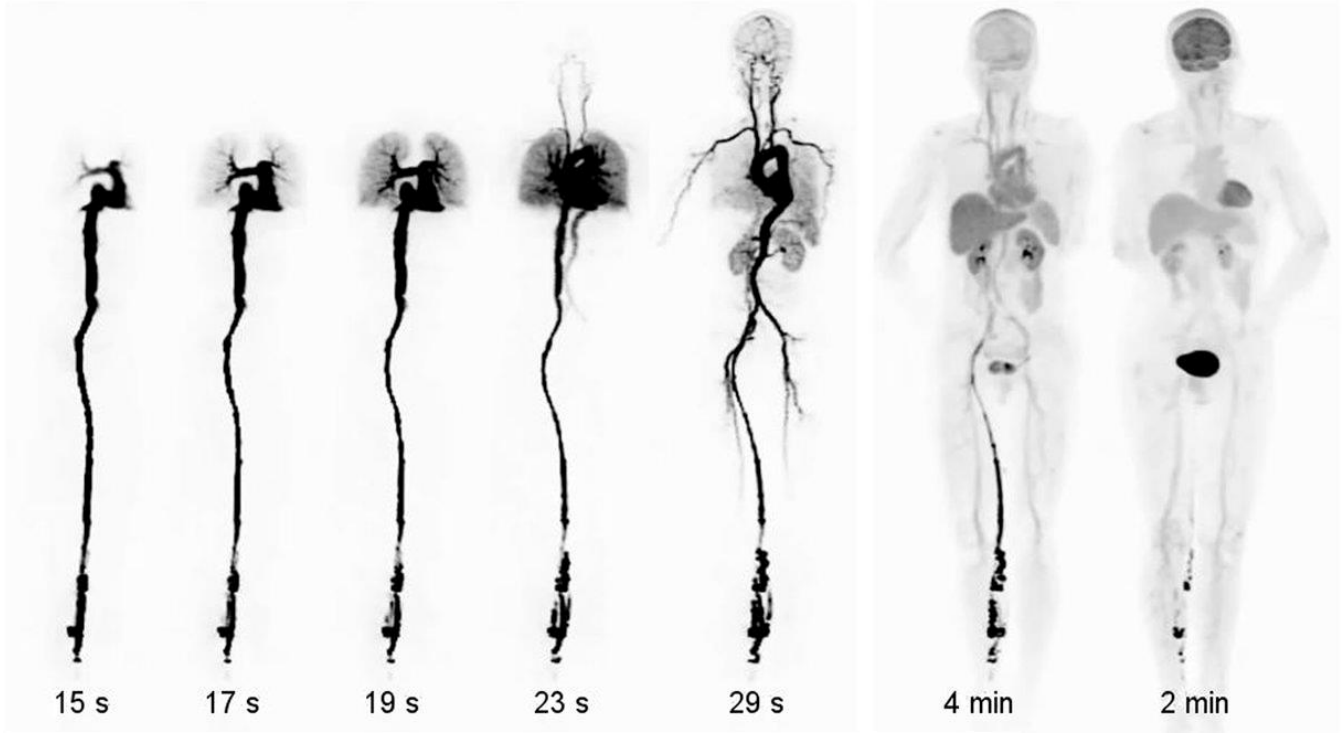
Main barriers

- Complex structures → (Radio)-chemistry
- Costs / infrastructure
- Only BioD/PK information
- **Human studies → Radiation dose to patient**

New technology: Total-Body PET

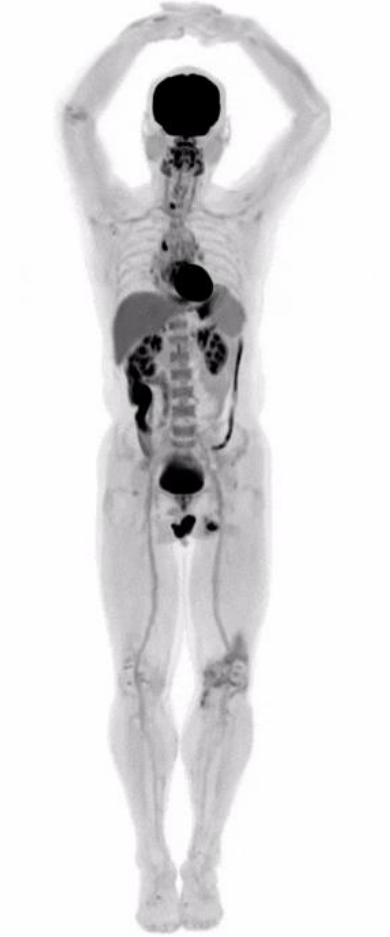


- 3D – whole body
- High sensitivity (up to 40x)
- High spatio/temporal resolution
- Quantification



S. Cherry et al. JNM *(2018) 59, 3-12*

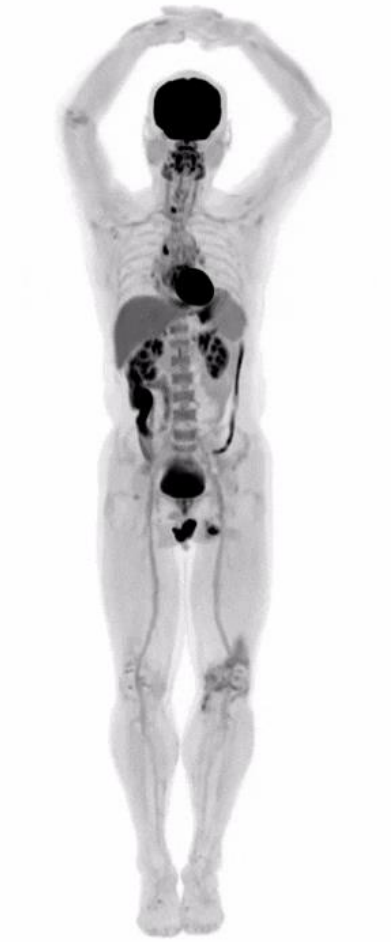
New technology: Total-Body PET



Two TB-PET now available at KCL !!
(50% of TB-PET scanners in the UK)

Fig WP4.1. Installation of the first TB-PET at GSTT (October 2024)

New technology: Total-Body PET



Current emphasis in my group:

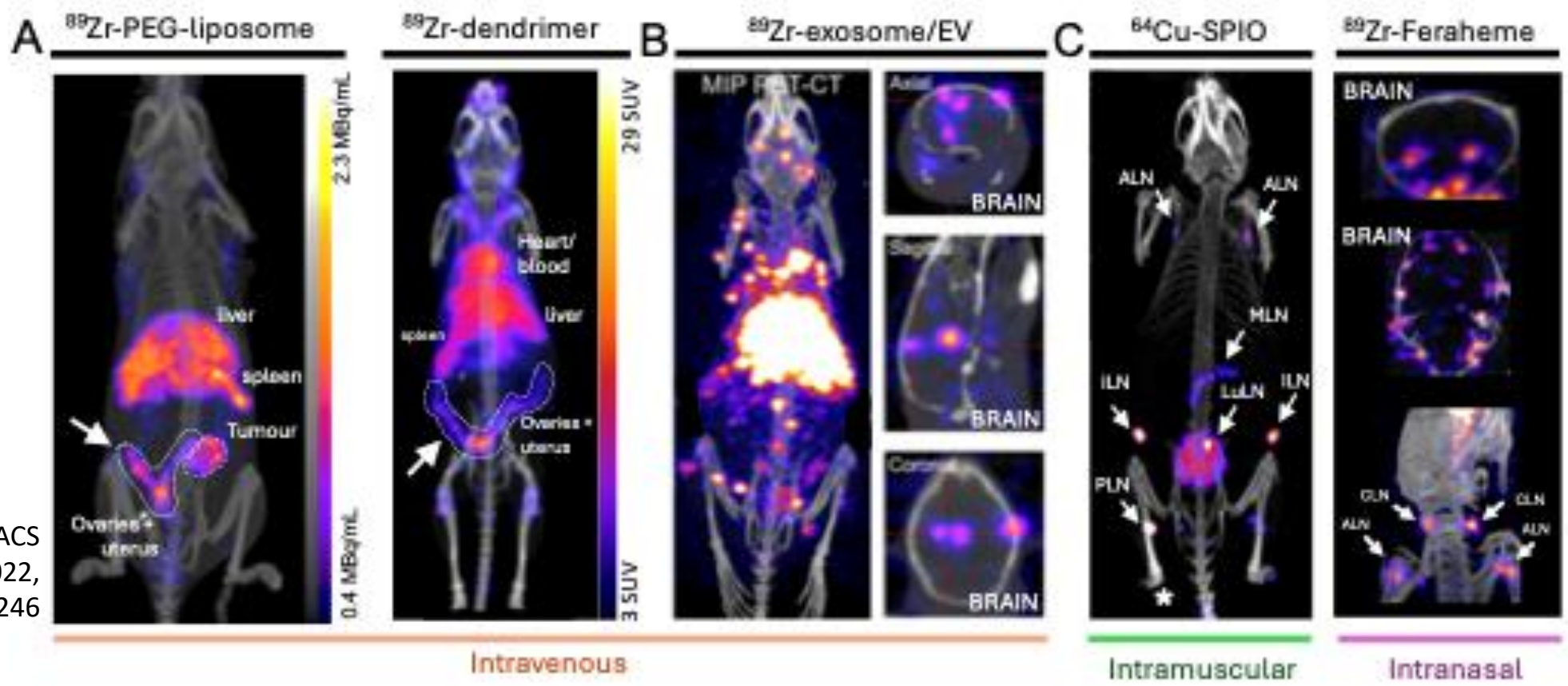
TB-PET will facilitate the evaluation of nano-DDS in humans for a better understanding of their *in vivo* behavior

Human heterogeneity
Disease heterogeneity
Novel materials / routes of administration

Support the selection of the best healthcare nanomaterials of the future

Total-Body PET for imaging nano-DDS: why?

Despite many multimodal imaging studies in preclinical models, We still don't fully understand how nano-DDS behave *in vivo*



Poley et al. ACS Nano, 2022, 16(4):5246

Total-Body PET for imaging nano-DDS: why?

nature medicine

Brief Communication

https://doi.org/10.1038/s41591-024-03453-1

Bioaccumulation of microplastics in decedent human brains

….The majority of MNPs found in tissues consist of PE and ***appear to be nanoplastic shards or flakes****. MNP concentrations in normal decedent* ***brain samples were 7–30 times greater than the concentrations seen in livers or kidneys****, and* ***brain samples from dementia cases exhibited even greater MNP presence****….*

Total-Body PET for imaging nano-DDS: why?

npj | vaccines

Article

Published in partnership with the Sealy Institute for Vaccine Sciences

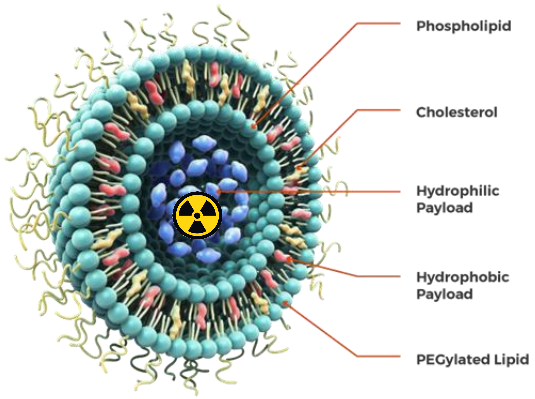
https://doi.org/10.1038/s41541-024-00911-2

The direct effect of SARS-CoV-2 virus vaccination on human ovarian granulosa cells explains menstrual irregularities

Check for updates

Hadas Bar-Joseph[1,7], Yael Raz[2,7], Anat Eldar-Boock[1], Nadav Michaan[2], Yoel Angel[3], Esther Saiag[4], Luba Nemerovsky[5], Ido Ben-Ami[6], Ruth Shalgi[5] & Dan Grisaru[2]

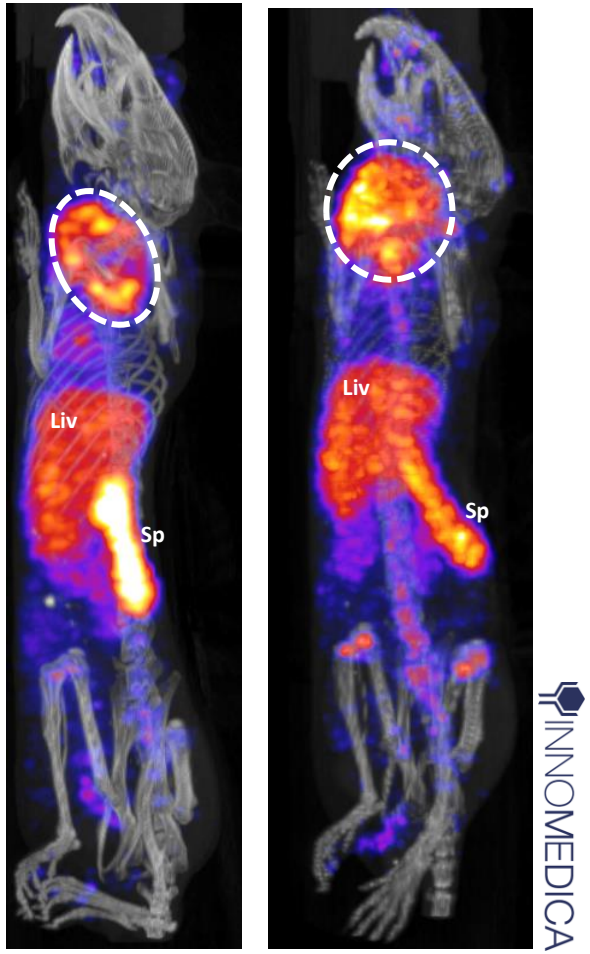
Total-Body PET for imaging nano-DDS: choosing the right radiochemistry



e.g. Liposomal doxorubicin (Caelyx/Doxil)

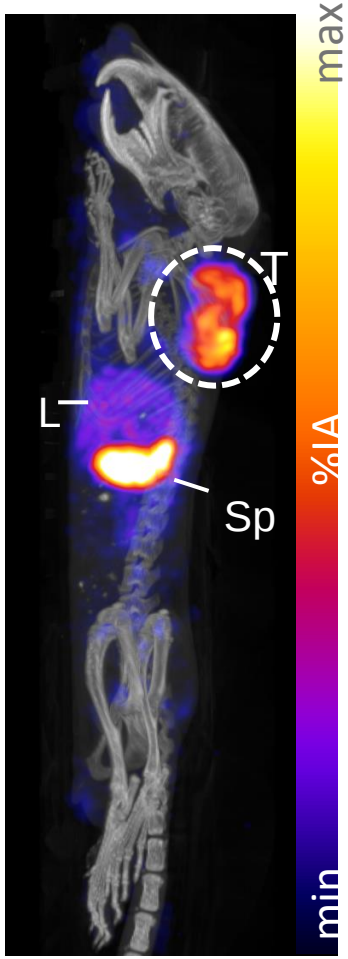
-Edmonds et al. *ACS Nano,* 2016; 10:10294
-Gawne et al. *Theranostics* 2020; 10(9):3867
-Gabizon et al. Pharmaceutics 2023; 15(11), 2606
-Minino-Carrascal, Preprint

Breast cancer



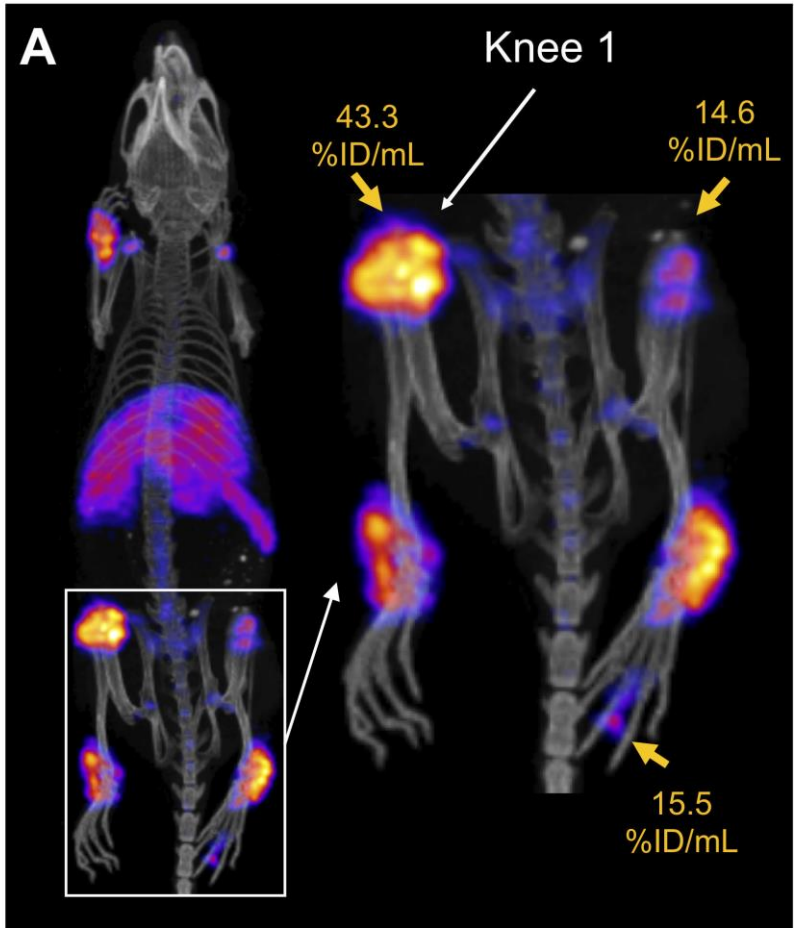
^{89}Zr-DOXIL ^{89}Zr-Talidox

Fibrosarcoma



^{111}In-PLA

Rheumathoid arthritis



^{89}Zr-PEGylated liposome (glucocorticoid)

Total-Body PET for imaging nano-DDS: choosing the right radiochemistry

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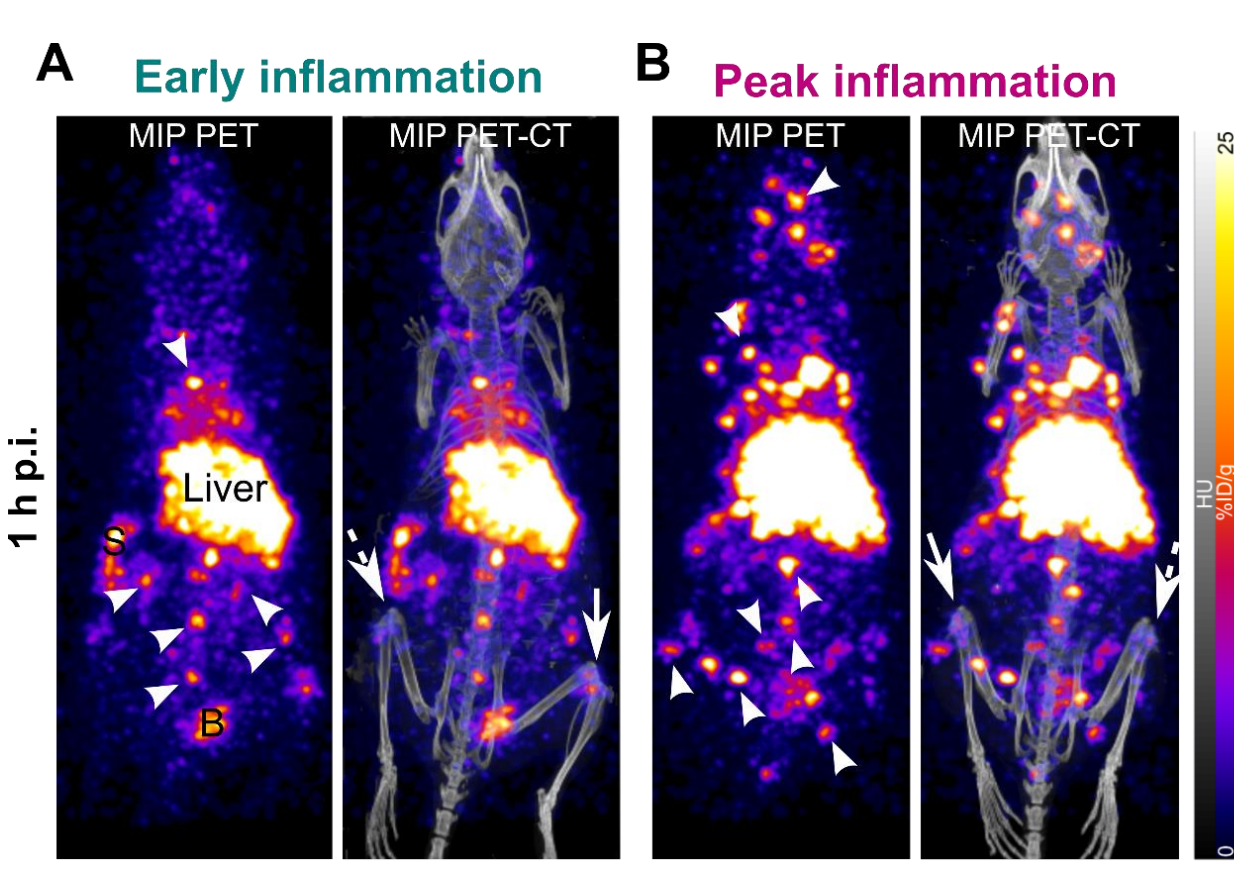
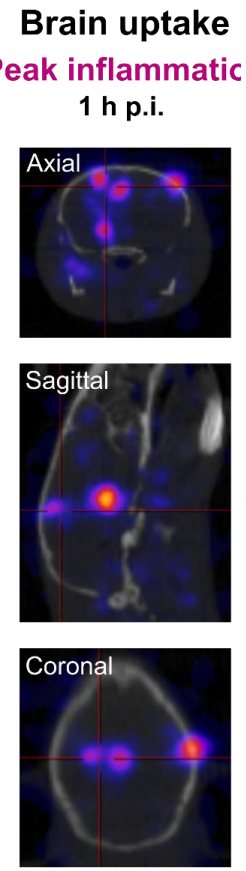
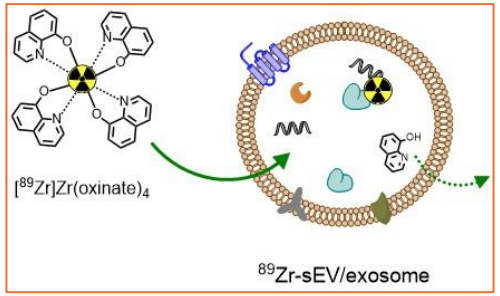
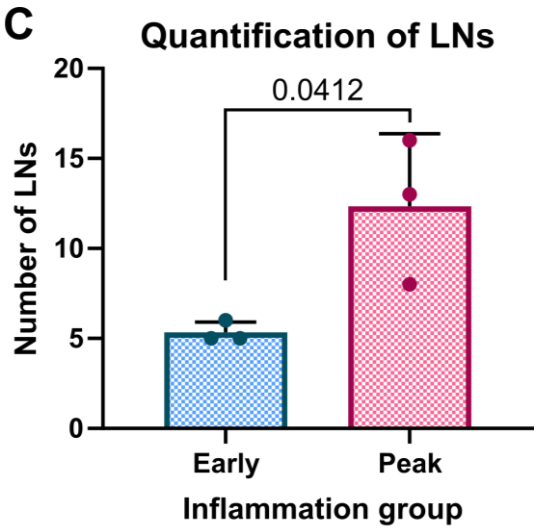
^{89}Zr-Neutrophil MVs exosomes in RA model (iv injection)







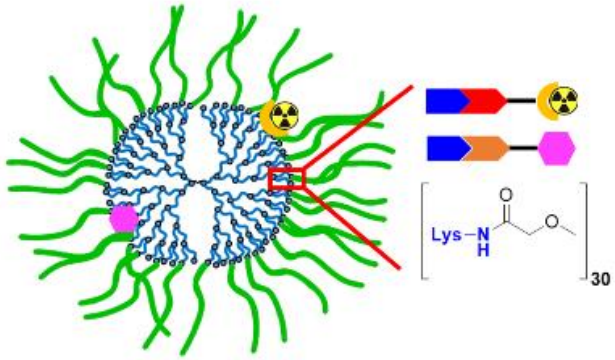
A. Khan



Exosomes/sEVs as DDSs seem to be well suited for delivering drugs to lymph-node resident cells and interact with the adaptive immune system

Unpublished data

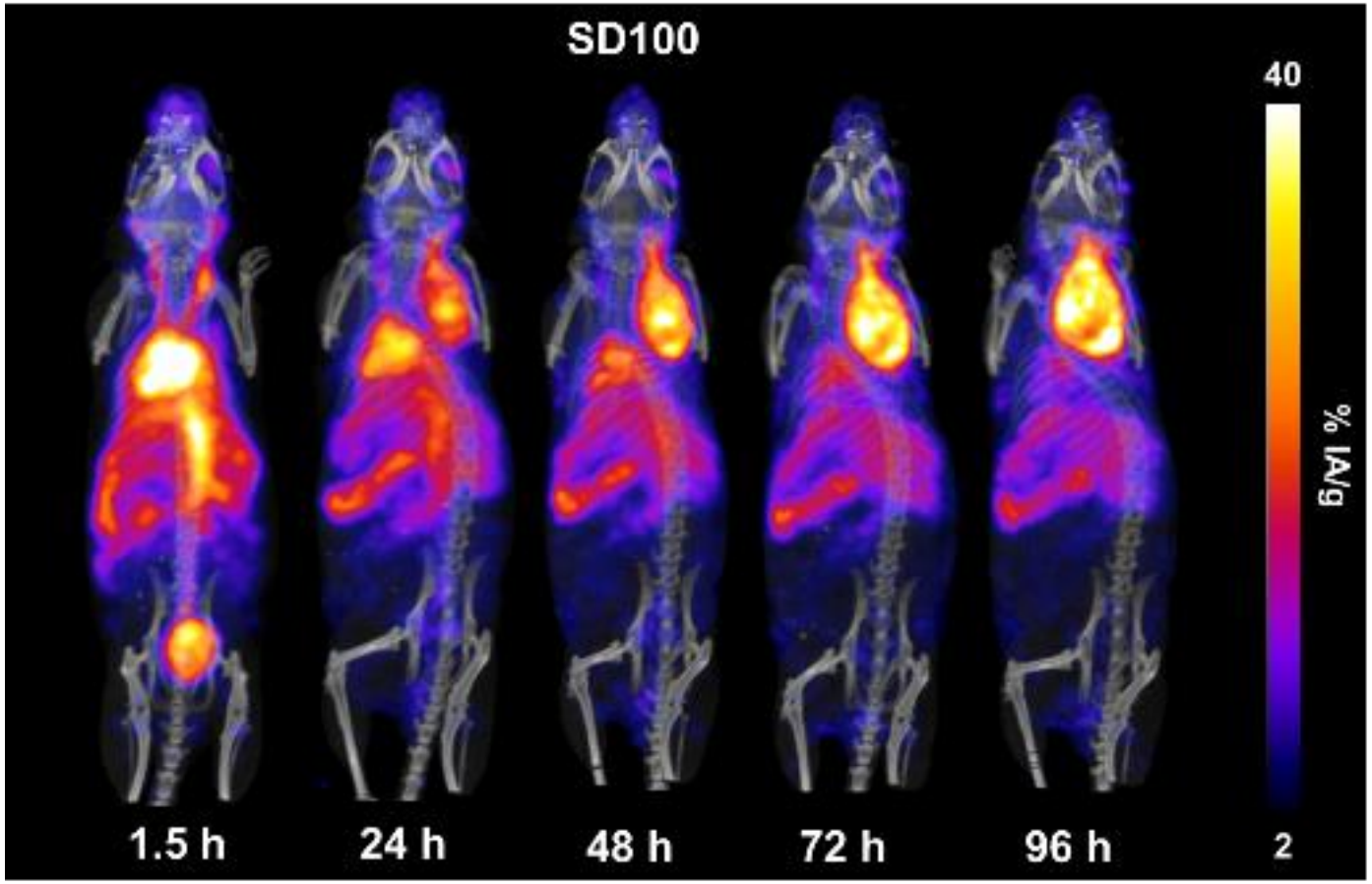
Total-Body PET for imaging nano-DDS: choosing the right radiochemistry



Polysarcosine – PEG alternative

→ Long circulation → high tumour uptake

Tia Gibson (Thu Tech session V – 10am)



Manuscript in preparation. Collaboration with AstraZeneca

Total-Body PET for imaging nano-DDS:
choosing the right radiochemistry

ACS OMEGA

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http://pubs.acs.org/journal/acsodf

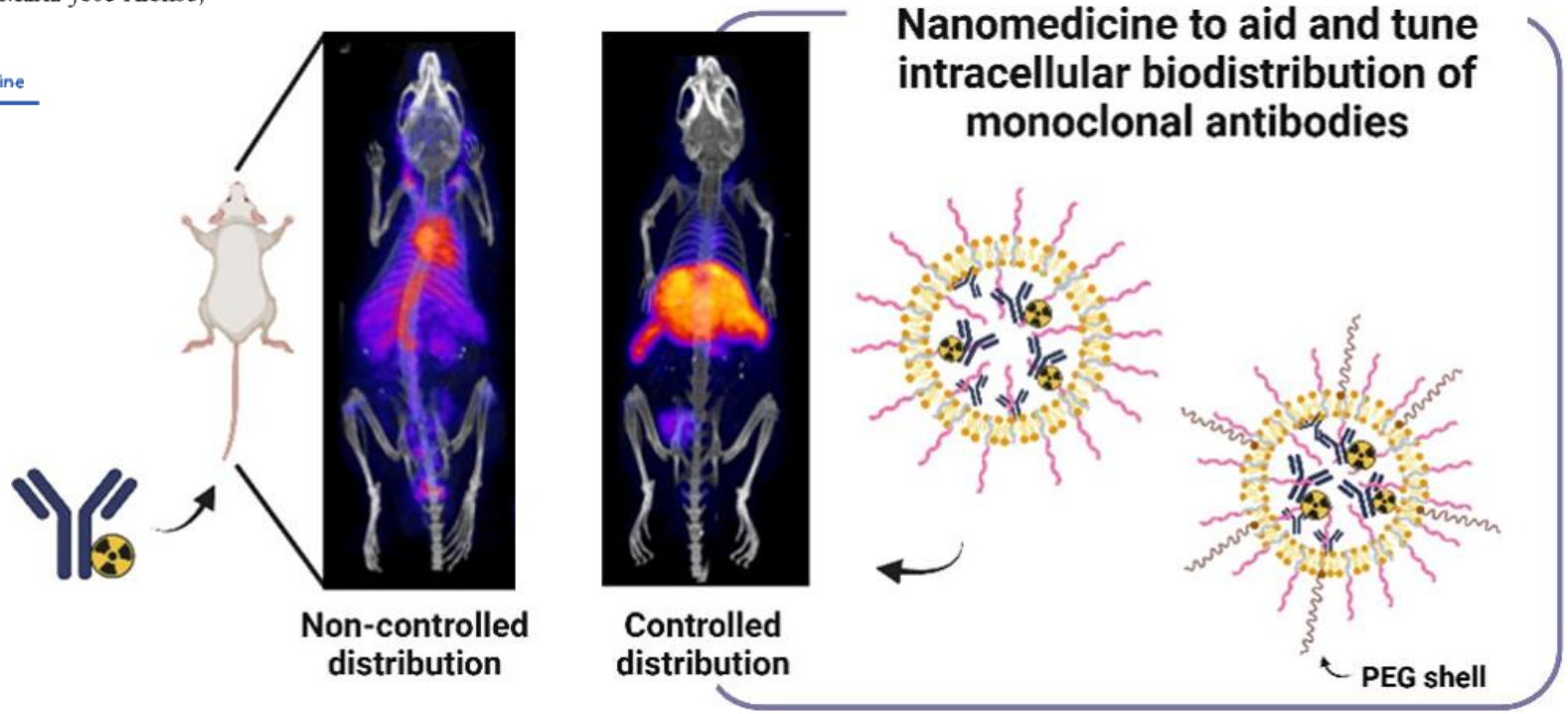
Article

Biodistribution of ^{89}Zr-Radiolabeled Nanoassemblies for Monoclonal Antibody Delivery Revealed through *In Vivo* PET Imaging

Ana M. López-Estévez, Amaia Carrascal-Miniño, Dolores Torres, María José Alonso, Rafael T. M. de Rosales,* and Juan Pellico*

Cite This: *ACS Omega* 2025, 10, 4763−4773

Read Online



Collab. MJ Alonso's lab (SantiagO)

Imaging the effect of external stimuli in the whole-body *in vivo* behaviour of nano-DDS

External X-ray radiation
&
FUS

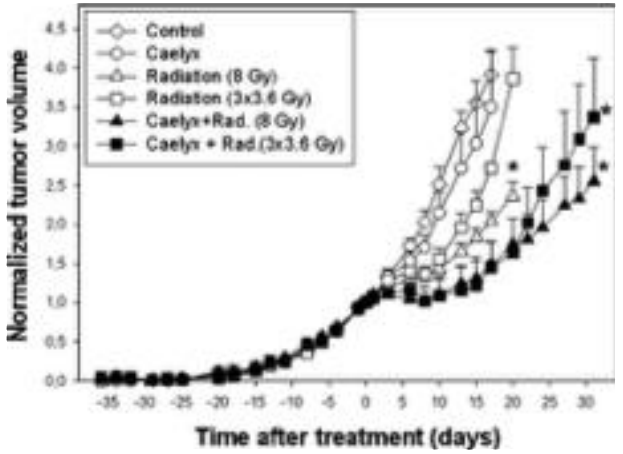
The effect of external beam X-ray radiation (EBRT) on the tumour delivery of nano-DDS

[CANCER RESEARCH 64, 547–553, January 15, 2004]

Radiation Improves the Distribution and Uptake of Liposomal Doxorubicin (Caelyx) in Human Osteosarcoma Xenografts

Catharina de L. Davies,[1] Lisa M. Lundstrøm,[1] Jomar Frengen,[2] Live Eikenes,[1] Øyvind S. Bruland,[3] Olav Kaalhus,[4] Mari H. B. Hjelstuen,[5] and Christian Brekken[5]

[1]Department of Physics, The Norwegian University of Science and Technology, Trondheim; [2]Department of Oncology, The University Hospital of Trondheim, Trondheim; Departments of [3]Radiotherapy and Oncology and [4]Biophysics, The Norwegian Radium Hospital, Oslo; and [5]Sintef Unimed MR Center, Trondheim, Norway

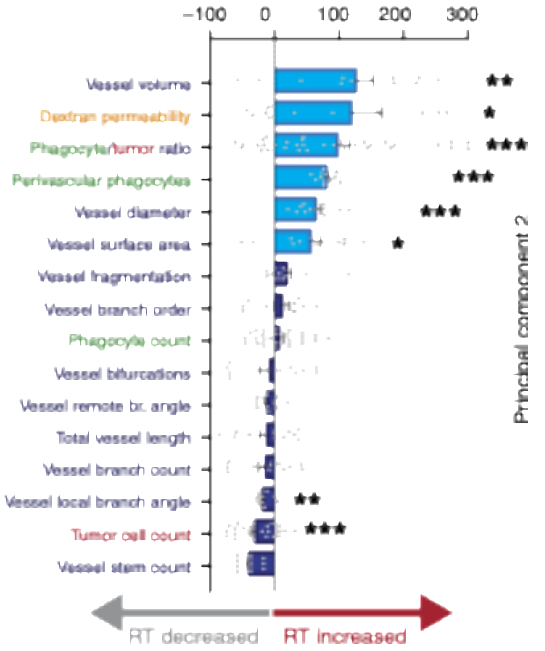


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE 2017

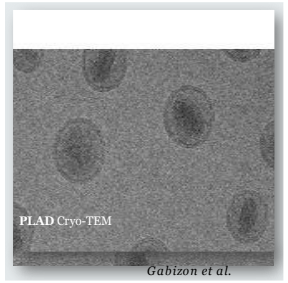
NANOMEDICINE

Radiation therapy primes tumors for nanotherapeutic delivery via macrophage-mediated vascular bursts

Miles A. Miller,[1,2] Ravi Chandra,[1,3] Michael F. Cuccarese,[1] Christina Pfirschke,[1] Camilla Engblom,[1] Shawn Stapleton,[1] Utsarga Adhikary,[1] Rainer H. Kohler,[1] James F. Mohan,[1] Mikael J. Pittet,[1,2] Ralph Weissleder[1,2,4]*



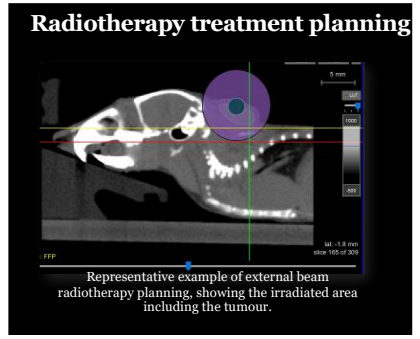
Imaging nano-DDS in combination with EBRT



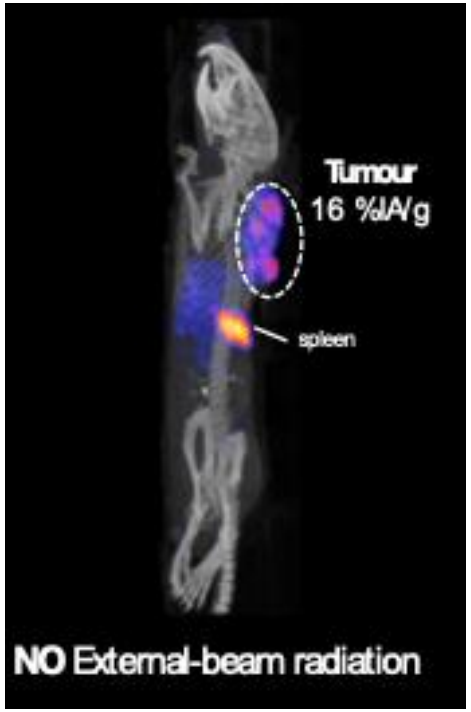
PLAD

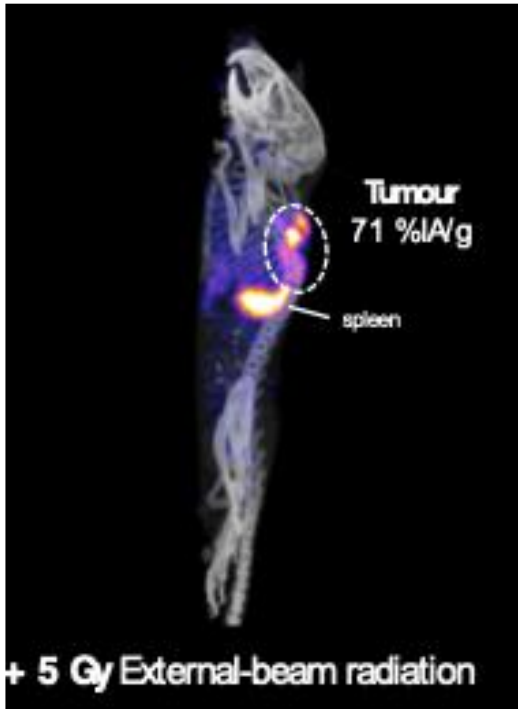
Doxorubicin (cytotoxic)
+
Alendronate (immune modulatory effects through interaction with TAMs (→M1) activation of some gamma-delta T Cells

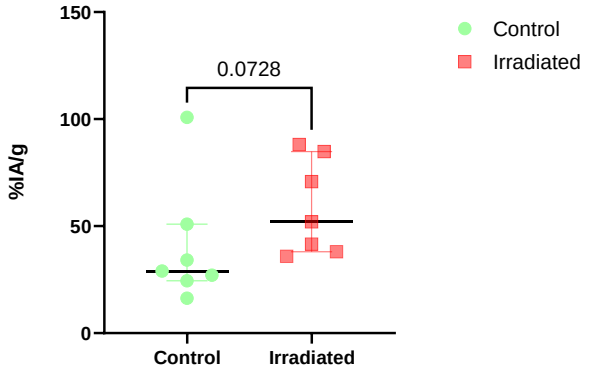
- *Islam, Gabizon, La Beck et al.* Nanotheranostics **2022**, 6, 451
- *Gabizon, La-Beck et al. Biomolecules **2023**, 13, 1309.*
- Gabizon et al. Pharmaceutics **2023**; 15(11), 2606



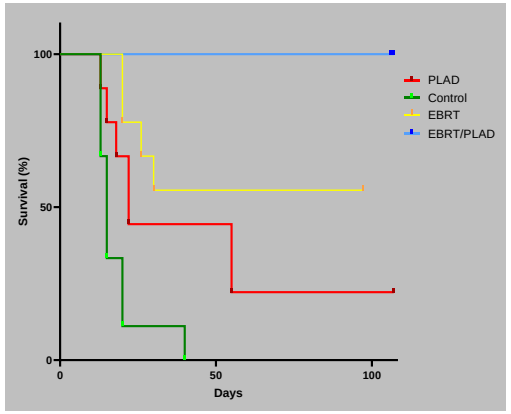
Fribrosarcoma tumour irradiation







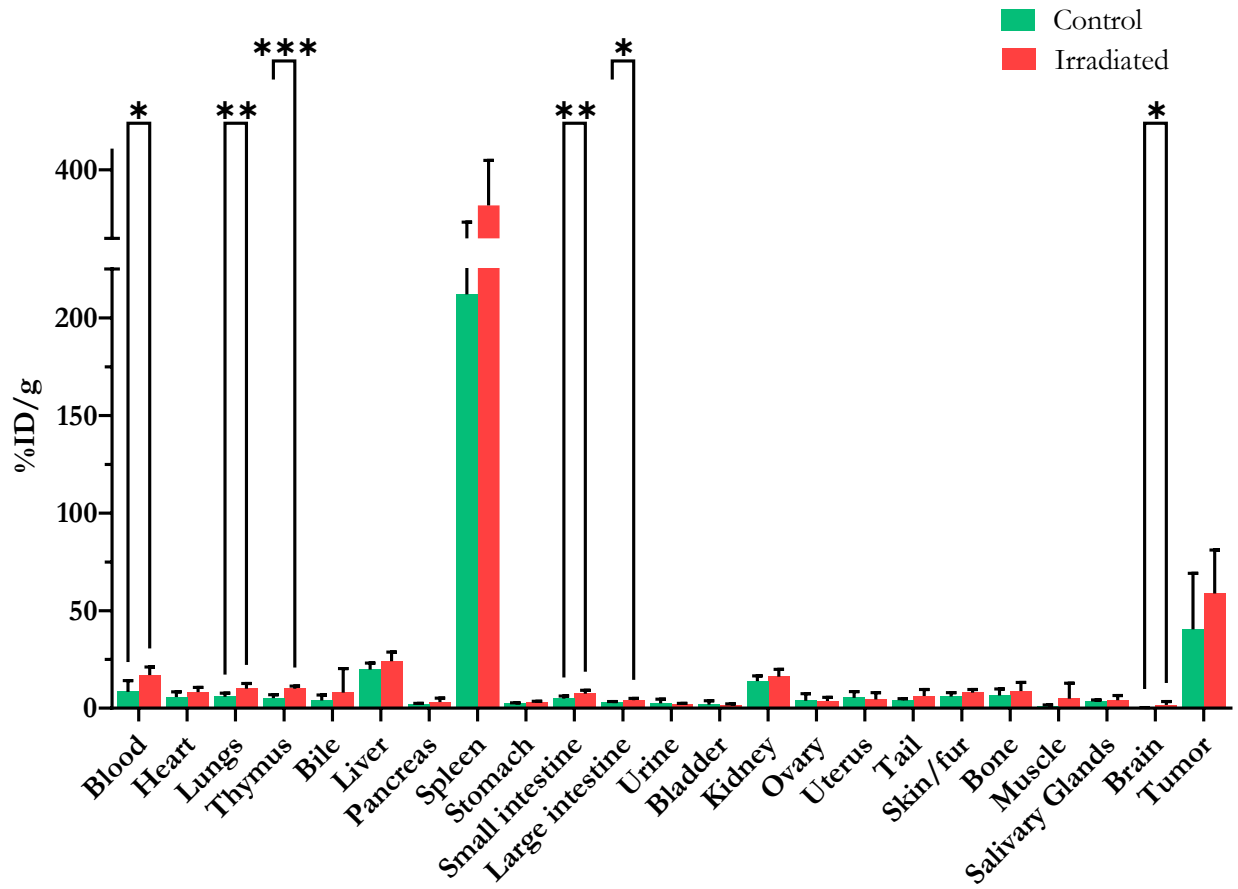
Tumour uptake



Therapeutic efficacy

Unpublished results

Imaging nano-DDS in combination with EBRT

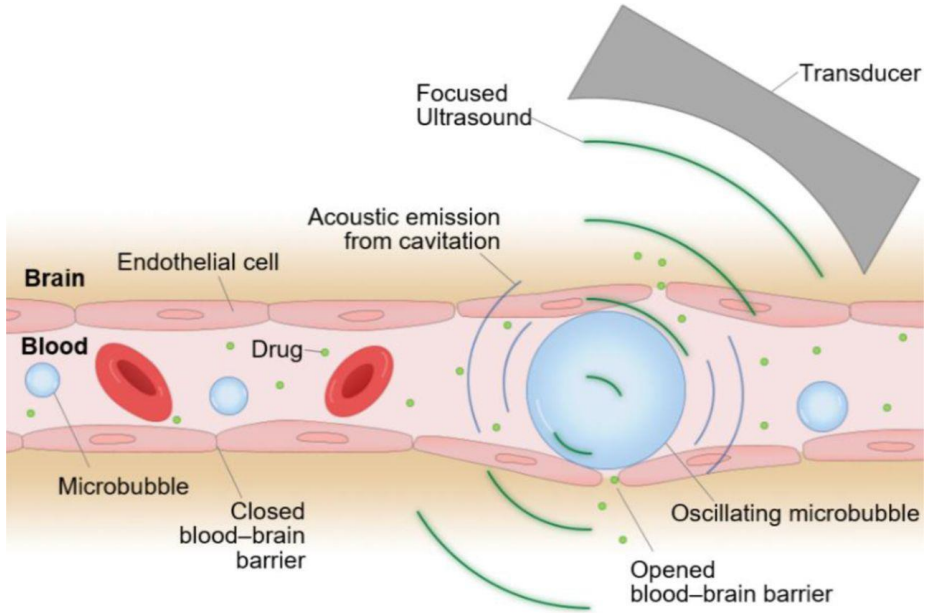


Significant differences were observed in several tissues, including blood suggesting **systemic effects** of the tumor targeted radiation (potential link to abscopal effect??)

Imaging the effect of external stimuli in the whole-body in vivo behaviour of nano-DDS

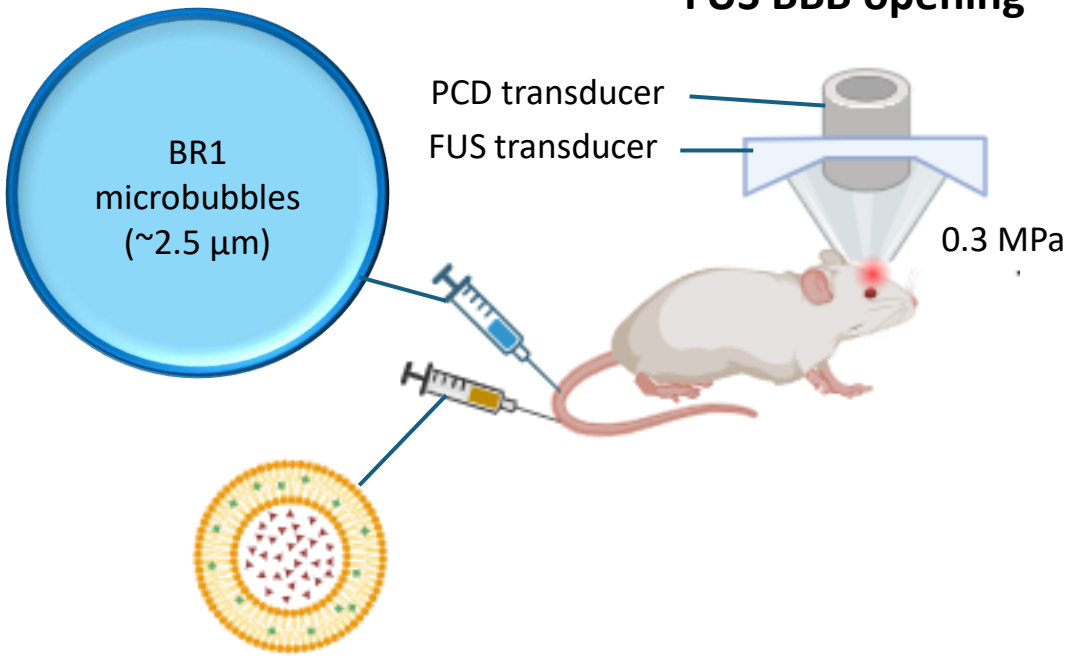
External X-ray radiation
&
FUS

Using PET to image FUS nano-DDS brain delivery



Bae et al. https://doi.org/10.1101/2023.12.21.23300222

FUS BBB opening



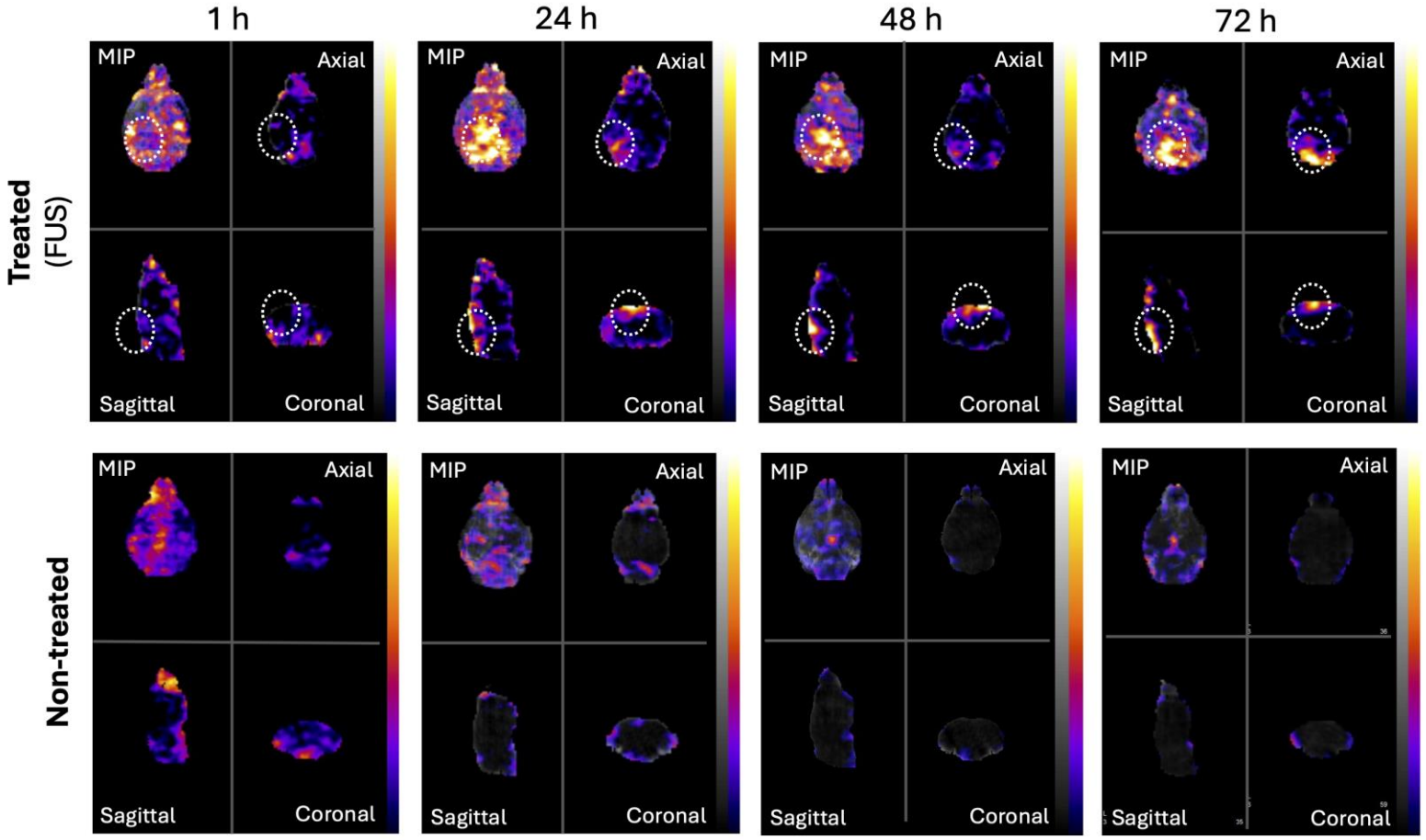
[^{89}Zr]Zr-Talidox (~36 nm)

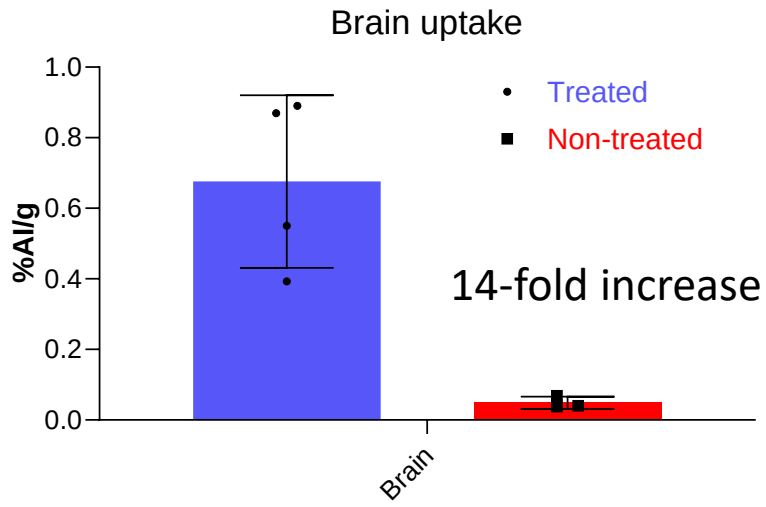
Dr Aishwarya Mishra

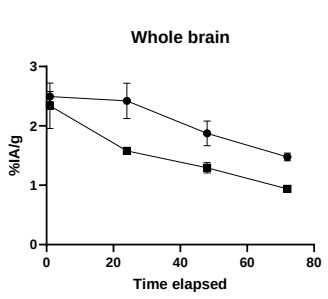
. **Collaboration**: Dr Antonis Pouliopoulos (KCL) and Innomedica

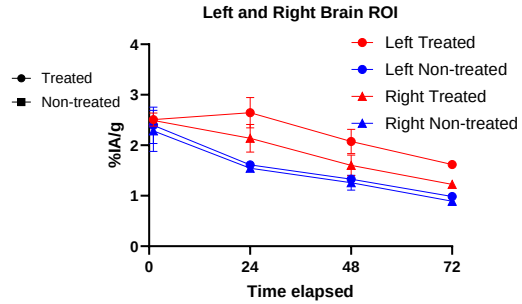
submitted

Using PET to image FUS nano-DDS brain delivery









KINETICS

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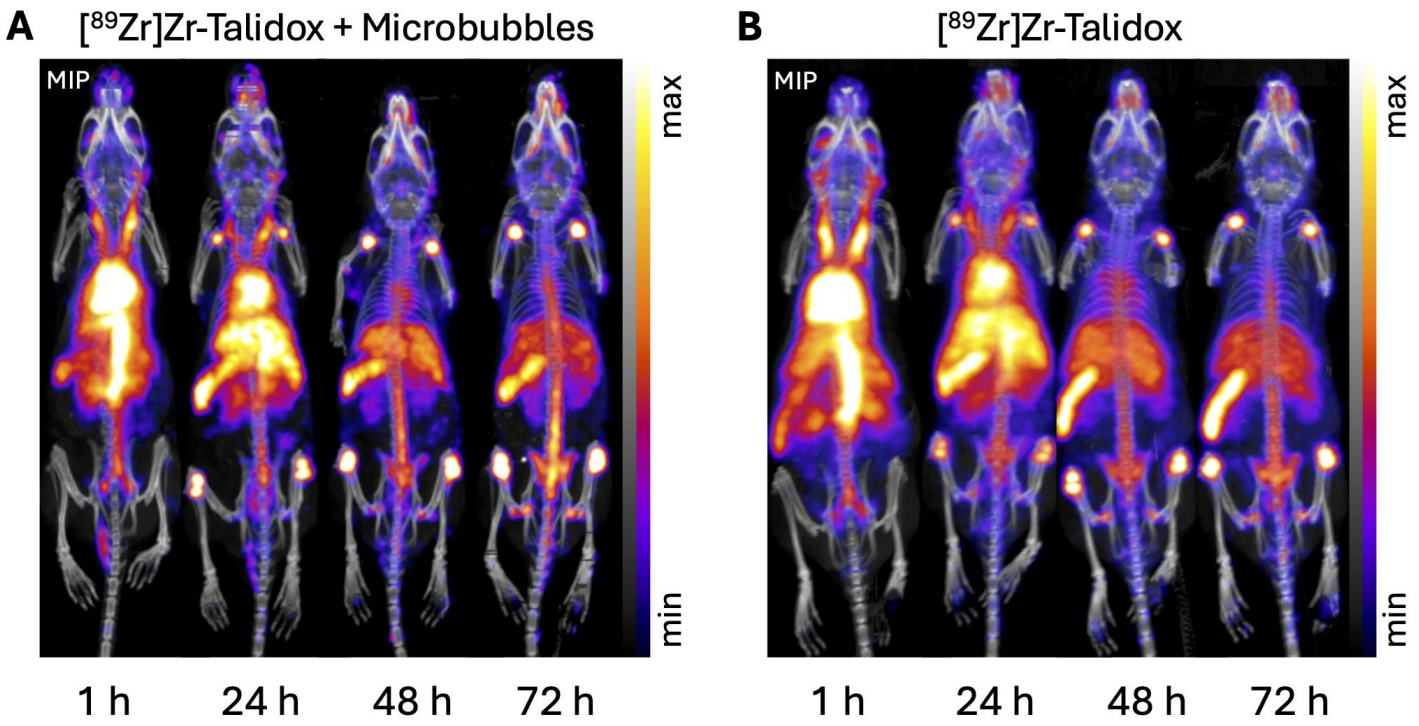
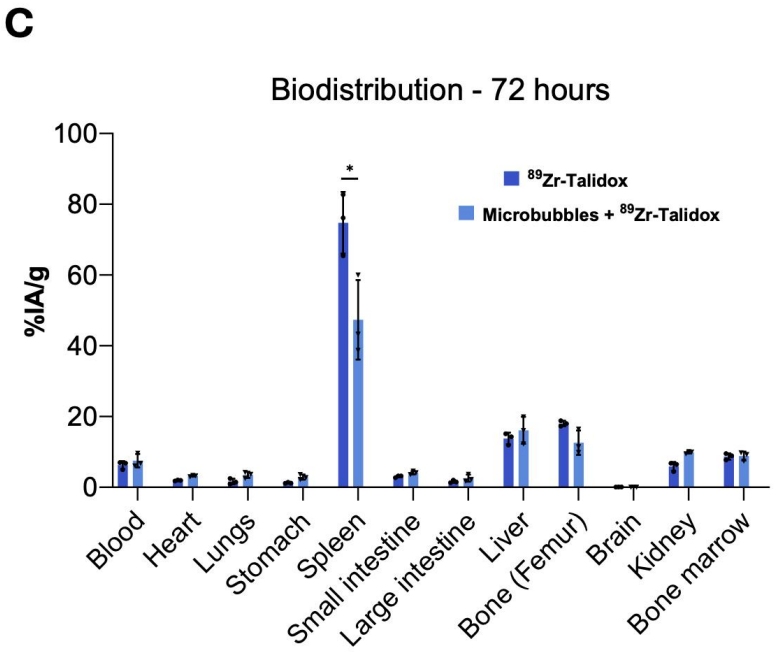
Using PET to image FUS nano-DDS brain delivery

Whole-body bioD





submitted

Conclusions

- **PET imaging** is well suited to study the whole-body bioD/PK of **DDSs** and inform their effective development (pre- and during clinical studies)
    - **Drug development tool** / optimise clinical trials / support regulatory approval.
    - Identifying **unexpected areas of uptake** (avoid off-target toxicities etc)
    - **(Nano)Theranostics** (using imaging to predict efficacy) → important due to human and disease heterogeneity)
- Choosing **the right radiochemistry and conditions to label the DDSs is important** → maintain original physicochemical properties of DDS
- **Total Body PET is a game-changing technique for human translation** → low dose of radiation and drug + whole body capability

EPSRC
Engineering and Physical Sciences Research Council

→ £10m funding to KCL to establish a world leading centre for total-body PET imaging of nano-DDS

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QUESTIONS?
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