Optimising the Biodistribution and Pharmacokinetics of Polysarcosine-Based Star Dendrimers by PET/CT

Tia Gibson, Amaia Carrascal Miniño, Thomas Floyd, Aishwarya Mishra, Juan Pellico, Andrea Emanuelli, Mariarosa Mazza, Timothy Witney, Rafael T. M. de Rosales

KING'S College LONDON
EPSRC Centre for Doctoral Training
Smart Medical Imaging
UKRI Engineering and Physical Sciences Research Council
AstraZeneca

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

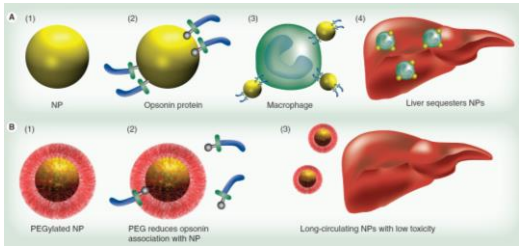
Stealth polymers in nanomedicine

↑ Blood $t_{1/2}$

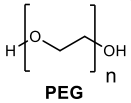
↓ Toxicity

↓ Immunogenicity

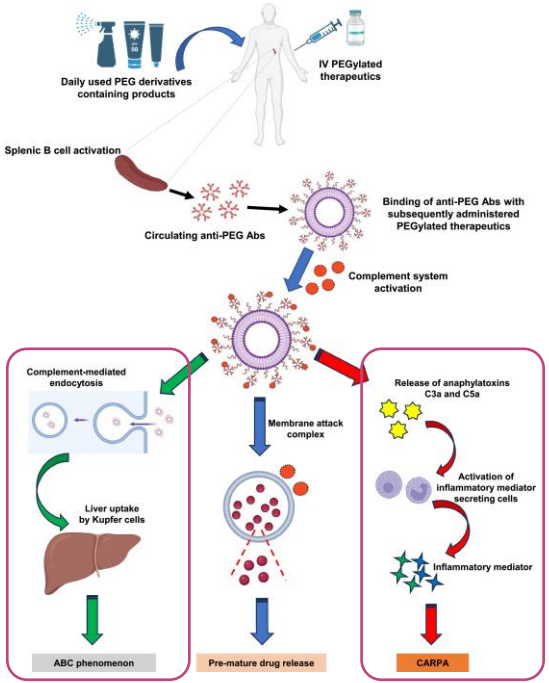
↓ Reticuloendothelial system (RES) scavenging



Polyethylene glycol (PEG)



- Anti-PEG immunity
  - Anti-PEG IgM and IgG
  - (pre-existing and induced)
- Hypersensitivity
  - Complement activation-related pseudo allergy (CARPA)
- Accelerated Blood Clearance (ABC) Phenomenon



JV Jokerst *et al, Nanomedicine*., 2011. SA Gaballa *et al*, *J. Pharm. Sci.*, 2024. ASA Lila *et al*, *J. Control. Release.*, 2013.

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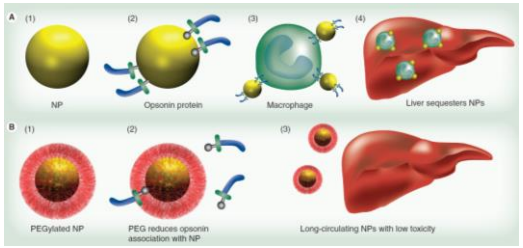

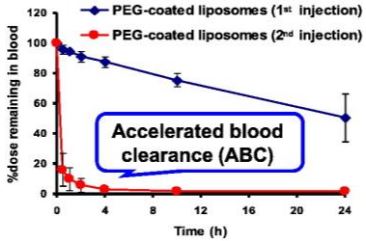

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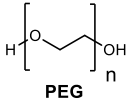

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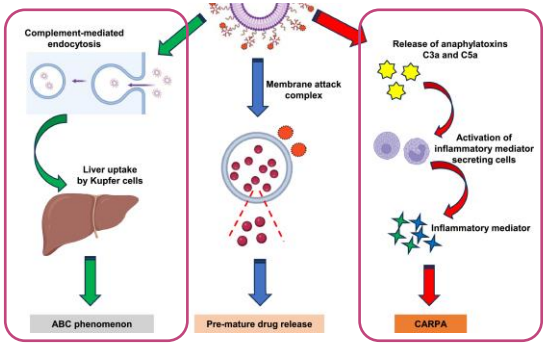

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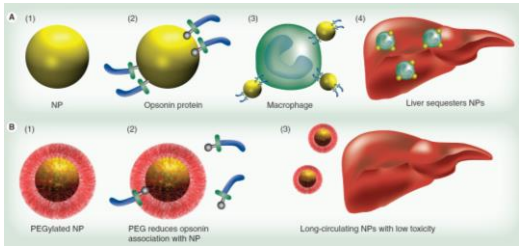

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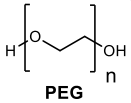

PEG

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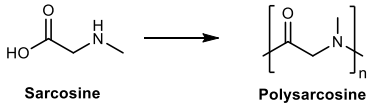
Alternatives to PEG

Polysarcosine (pSar)



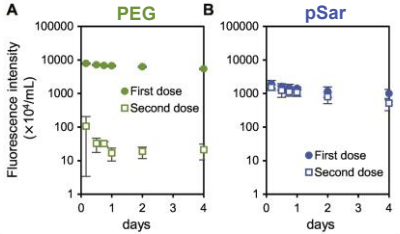
Sarcosine Polysarcosine

- Non-toxic • Non-immunogenic • Biodegradable

Uses:

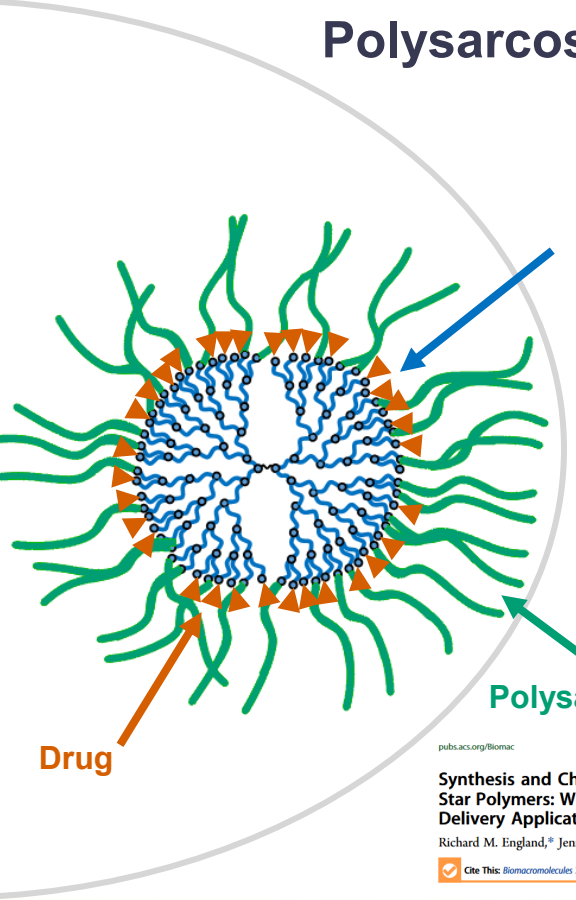
- Drug delivery – liposomes, polymeric micelles, conjugates
- Gene delivery

Liposome concentration in plasma



JV Jokerst *et al, Nanomedicine.*, 2011. SA Gaballa *et al*, *J. Pharm. Sci.*, 2024. ASA Lila *et al*, *J. Control. Release.*, 2013.

Polysarcosine star dendrimer drug delivery platform



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Article

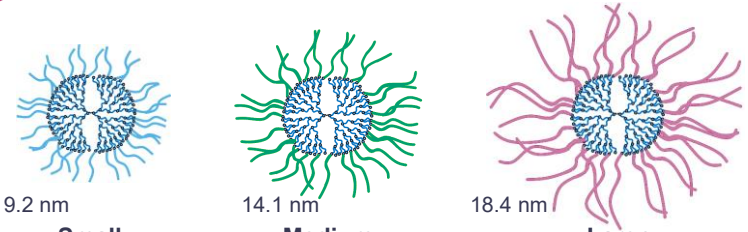
Synthesis and Characterization of Dendrimer-Based Polysarcosine Star Polymers: Well-Defined, Versatile Platforms Designed for Drug-Delivery Applications

Richard M. England,* Jennifer I. Moss, Anders Gunnarsson, Jeremy S. Parker, and Marianne B. Ashford

Cite This: *Biomacromolecules* 2020, 21, 3332–3341 Read Online

PET/CT

Three drug-free pSar star dendrimers for bioD/PK study



Aim:

Immunocompetent healthy mice

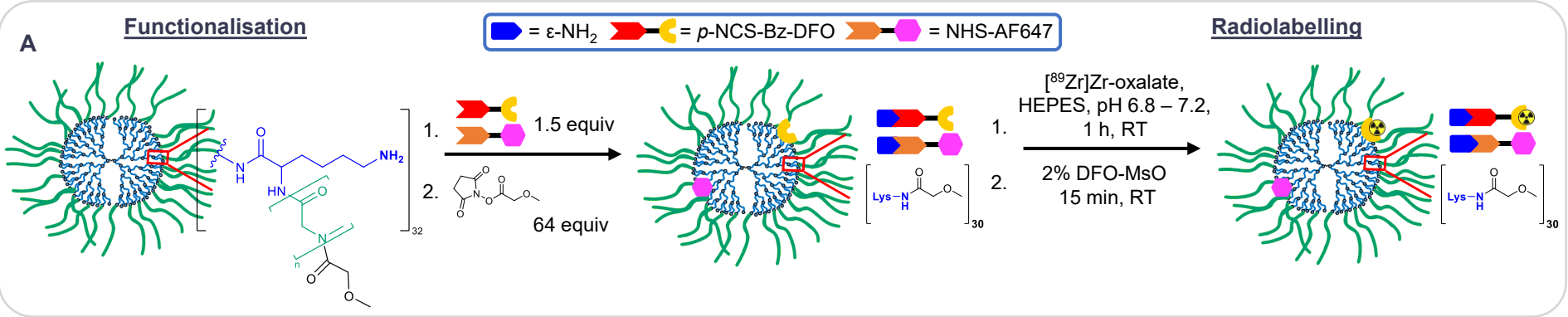
- Study the effect of pSar chain length on:
  - Biodistribution
  - Pharmacokinetics
  - RES uptake

Immunocompetent tumour bearing mice

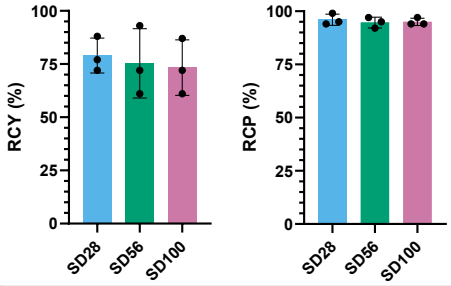
- Quantify tumour accumulation
- Study effect of disease burden on:
  - Biodistribution
  - Pharmacokinetics
  - RES uptake

RM England *et al, Biomacromolecules.*, 2020.

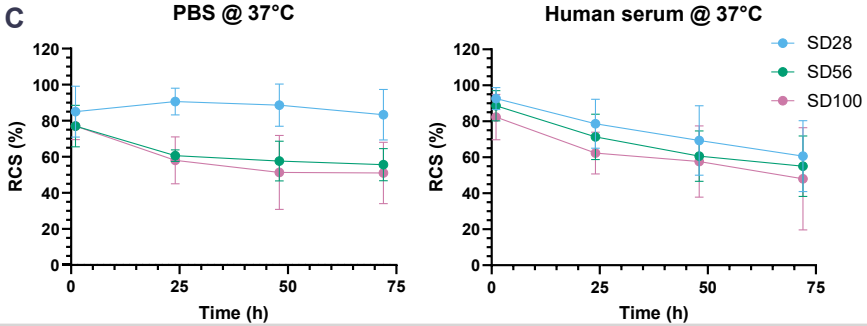
Zr-89 radiolabelling strategy



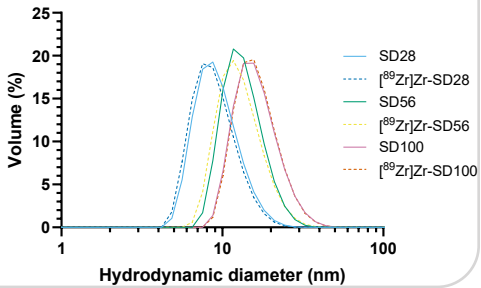
High radiochemical yield and radiochemical purity



Suitable radiochemical stability for *in vivo* imaging

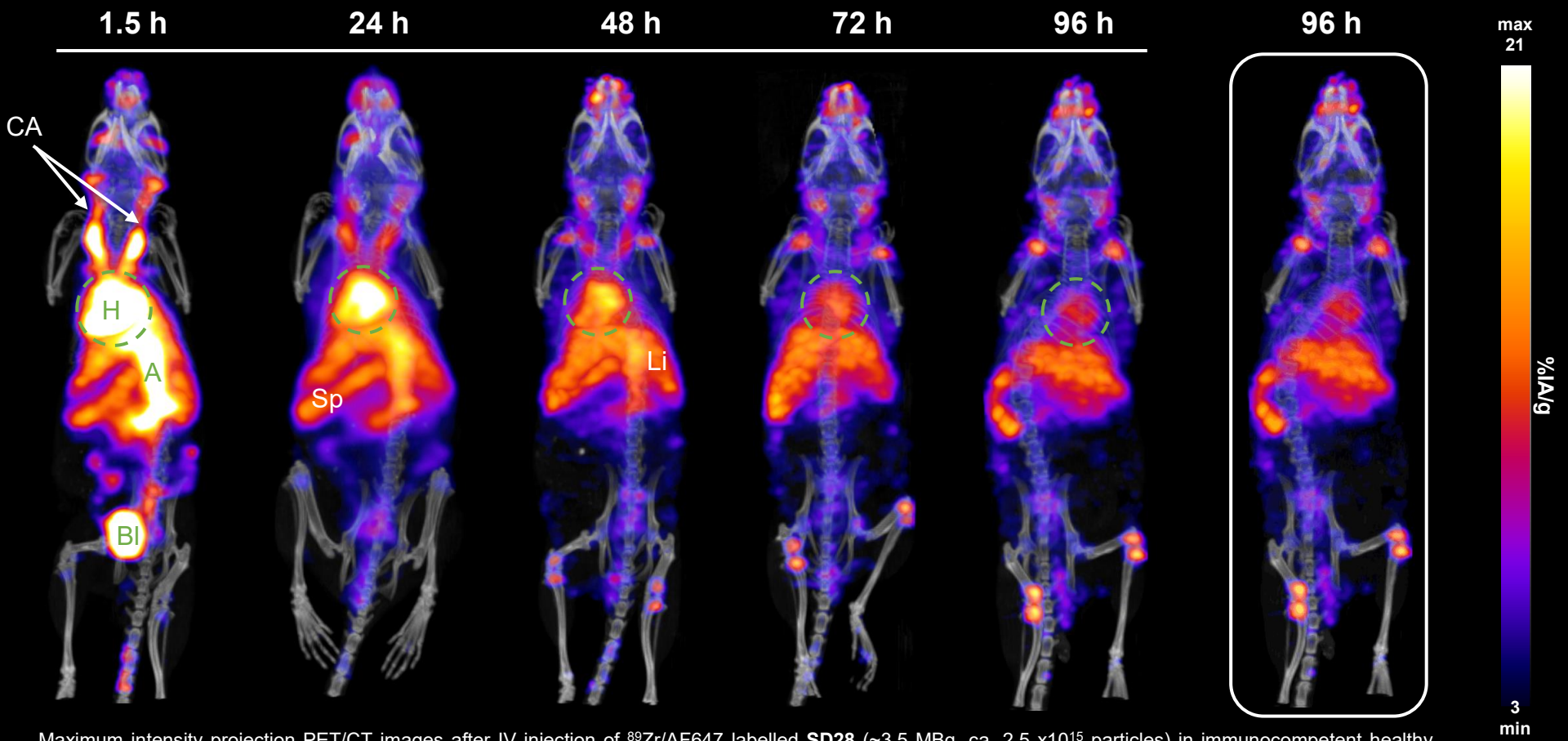


Size unaffected by radiolabelling



Data represent the mean ± SD (n= 3).

Biodistribution of pSar star dendrimer in healthy mice



Maximum intensity projection PET/CT images after IV injection of ^{89}Zr/AF647 labelled **SD28** (~3.5 MBq, ca. 2.5 x10^{15} particles) in immunocompetent healthy female BALB/c mice, (13 weeks, n= 4) at 1.5, 24, 48, 72 and 96 h p.i.

Data expressed as percentage of injected activity (activity in organ/total injected activity) per gram of tissue (%IA/g). Unpublished

Biodistribution of pSar star dendrimers in healthy mice

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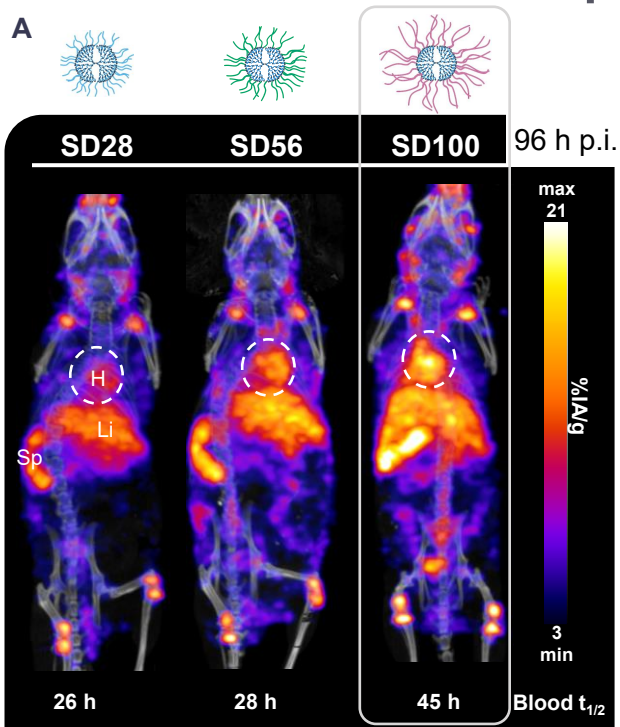
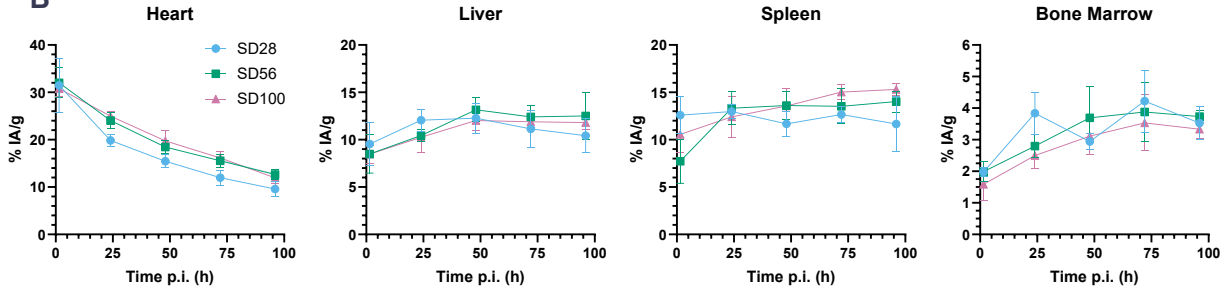
A



MIP PET/CT images after IV injection of ^{89}Zr/AF647 labelled SD28/56/100 (~2.8 MBq, ca. 2.5 x10^{15} particles) in immunocompetent healthy female BALB/c mice, (13 weeks, n= 4) at 96 h p.i.

In vivo biodistribution

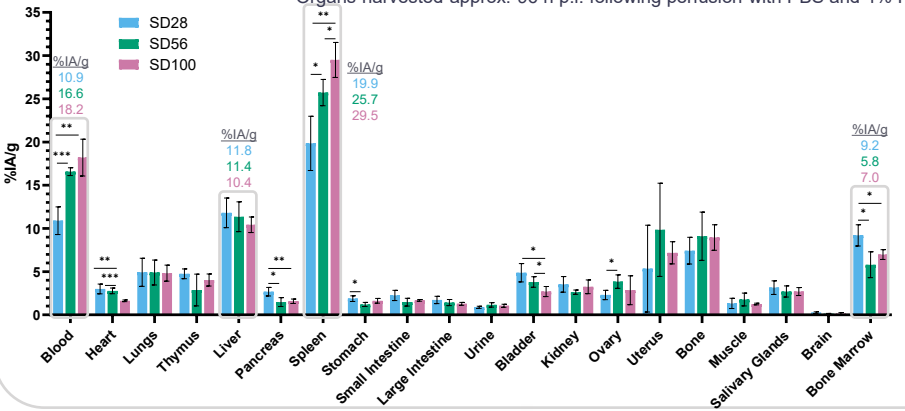
B



Ex vivo biodistribution 96 h p.i.

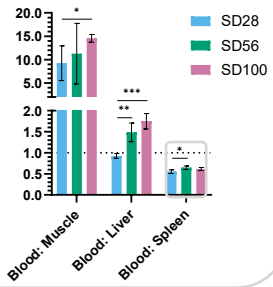
C

Organs harvested approx. 96 h p.i. following perfusion with PBS and 4% PFA.



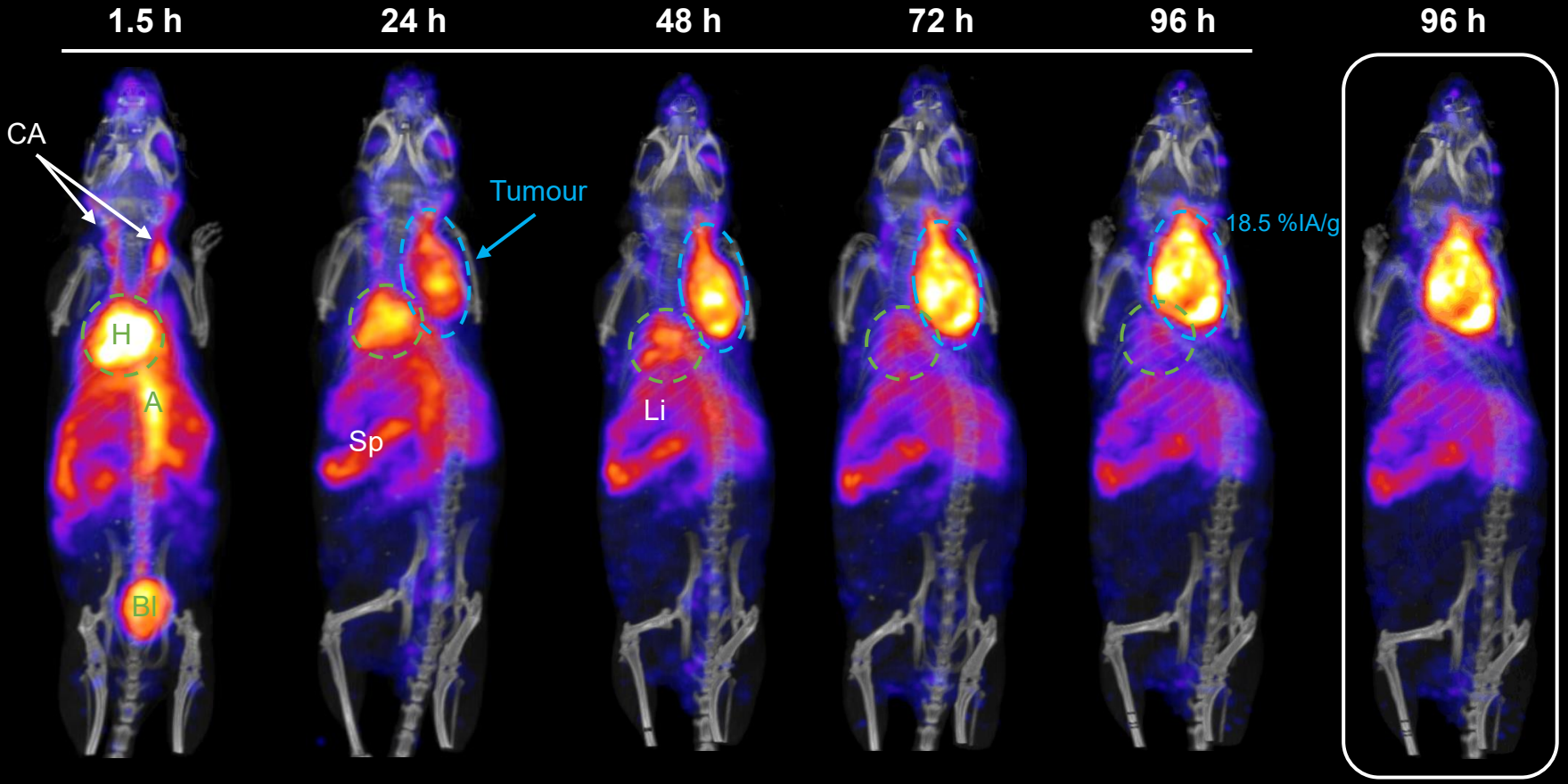
D

ex vivo blood ratios



Data expressed as percentage of injected activity (activity in organ/total injected activity) per gram of tissue (%IA/g). Data represent the mean ± SD (n= 3–4). p = * < 0.05, ** < 0.01, *** < 0.001

Biodistribution of pSar star dendrimer in 4T1 tumour bearing mice



Maximum intensity projection PET/CT images after IV injection of ^{89}Zr/AF647 labelled **SD100** (~2.5 MBq, ca. 2.5 x10^{15} particles) in 4T1 tumour bearing immunocompetent female BALB/c mice, (13 weeks, n= 4) at 1.5, 24, 48, 72 and 96 h p.i.

Data expressed as percentage of injected activity (activity in organ/total injected activity) per gram of tissue (%IA/g). Unpublished

Biodistribution of pSar star dendrimers in 4T1 tumour bearing mice

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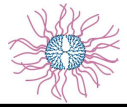
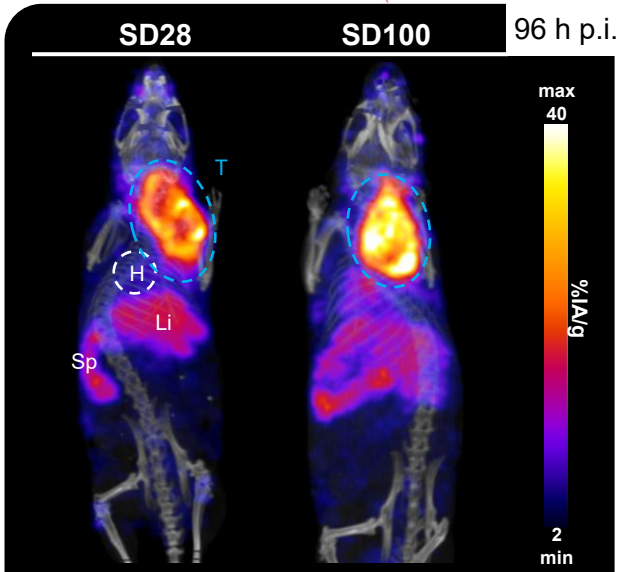
A

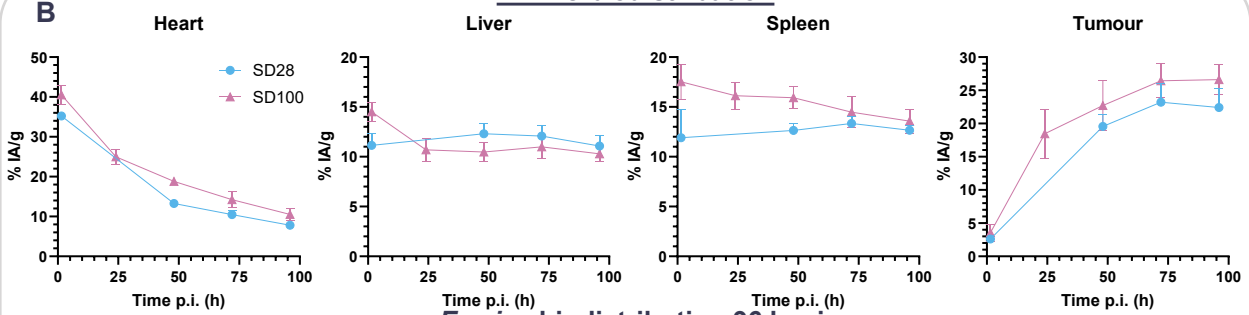




MIP PET/CT images after IV injection of ^{89}Zr/AF647 labelled SD28/100 (~3.9 MBq/~2.5 MBq respectively, ca. 2.5 x10^{15} particles) in 4T1 tumour bearing immunocompetent female BALB/c mice, (13 weeks, n= 4) at 96 h p.i.

In vivo biodistribution

B



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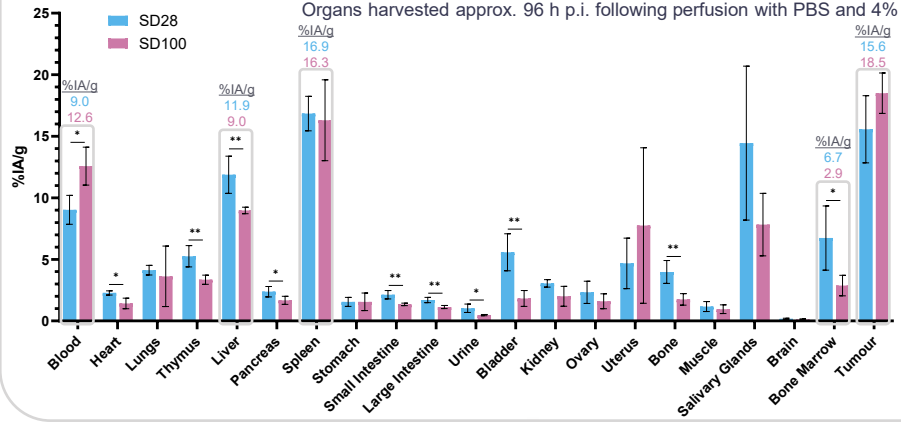
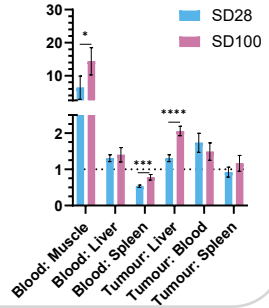


D *ex vivo* blood ratios



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Biodistribution of SD100 in healthy vs 4T1 tumour bearing mice

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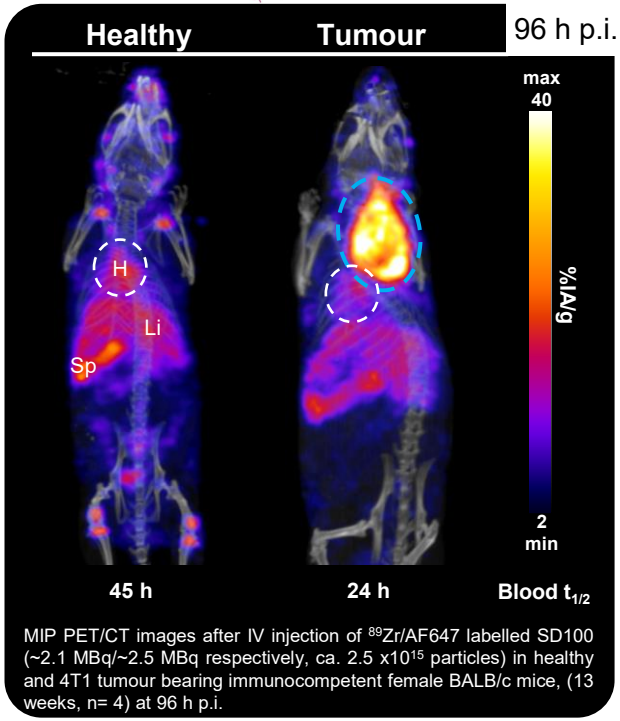
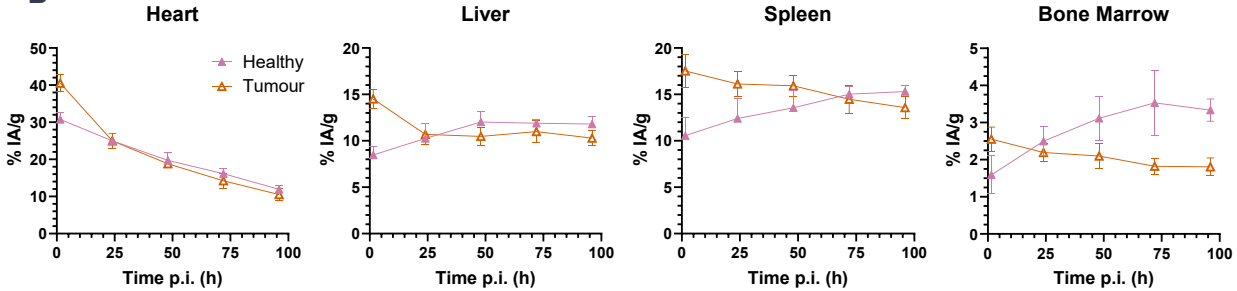
A



MIP PET/CT images after IV injection of ^{89}Zr/AF647 labelled SD100 (~2.1 MBq/~2.5 MBq respectively, ca. 2.5 x10^{15} particles) in healthy and 4T1 tumour bearing immunocompetent female BALB/c mice, (13 weeks, n= 4) at 96 h p.i.

B

In vivo biodistribution



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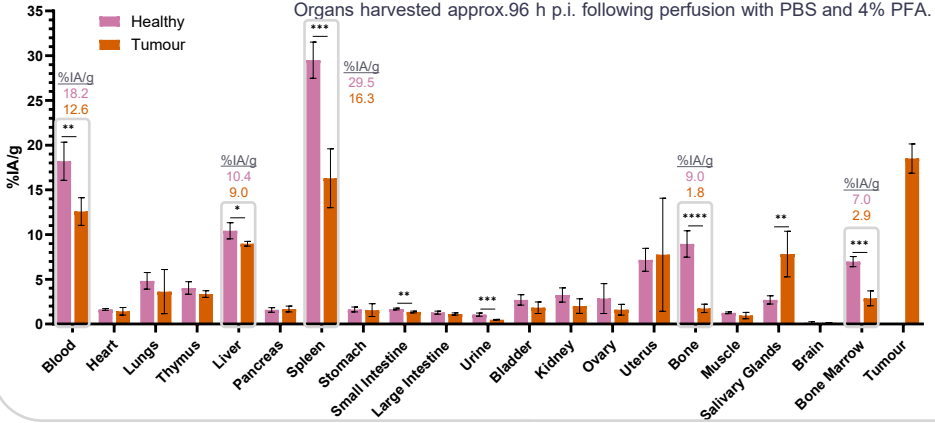

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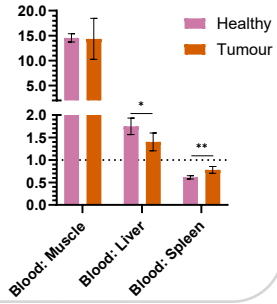

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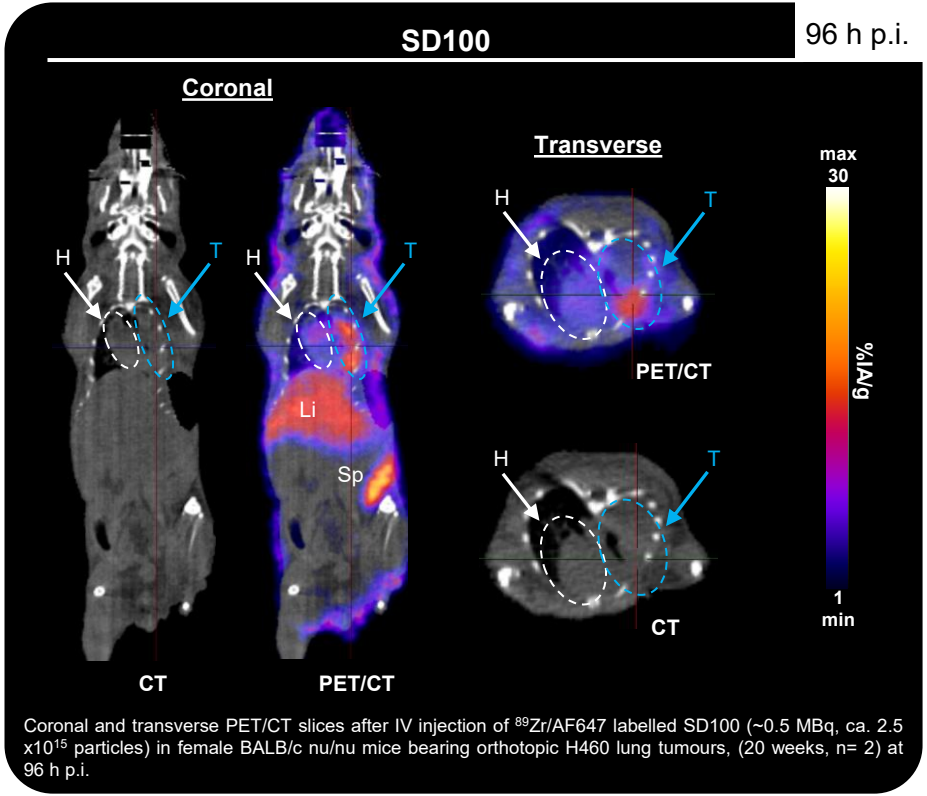
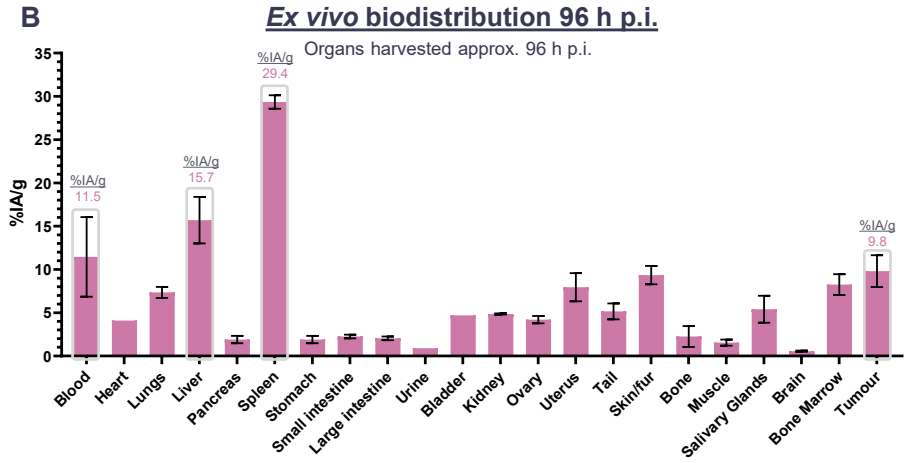
Uptake of SD100 in orthotopic model of NSCLC

A



Coronal and transverse PET/CT slices after IV injection of ^{89}Zr/AF647 labelled SD100 (~0.5 MBq, ca. 2.5 x10^{15} particles) in female BALB/c nu/nu mice bearing orthotopic H460 lung tumours, (20 weeks, n= 2) at 96 h p.i.

B



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Conclusions

- **pSar functionalisation** proportionally **prolongs the blood circulation time** of star dendrimers
  - Positive correlation between pSar chain length and blood $t_{1/2}$ (26 – 45 h, SD28 – SD100)
  - pSar SDends remain in blood circulation 96 h p.i. (11, 16.5 & 18 %IA/g for SD28/56/100 respectively in healthy mice)
- **High passive tumour uptake** for both SD28 and SD100
  - 15.5 and 18.5 %IA/g for SD28 and SD100 respectively
  - Longer $t_{1/2}$ = higher tumour uptake
- pSar SDends **preferentially accumulate in tumour over RES** organs
- pSar is **promising alternative stealth polymer** to PEG

Future work

- Evaluate biodistribution of pSar star dendrimers at a **cellular** level
  - Localisation in liver, spleen and tumour
- Evaluate effect of **drug loading** on the **biodistribution** and evaluate **therapeutic effect** (SD100)
- Investigate if **repeat administration** promotes **accelerated blood clearance**

Acknowledgements

Supervisors

- Dr Rafael T M de Rosales
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- Dr Mariarosa Mazza
- Dr Thomas Floyd

- Dr Amaia Carrascal Miniño
- Dr Aishwarya Mishra
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- Dr Andrea Emanuelli
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- Dr Adam Jones
- Dr Kavitha Sunassee

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Questions?

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