Engineering nanoparticle systems to target lymphatics and their underlying cellular mechanisms

Immunoengineering GRC
July 11, 2024

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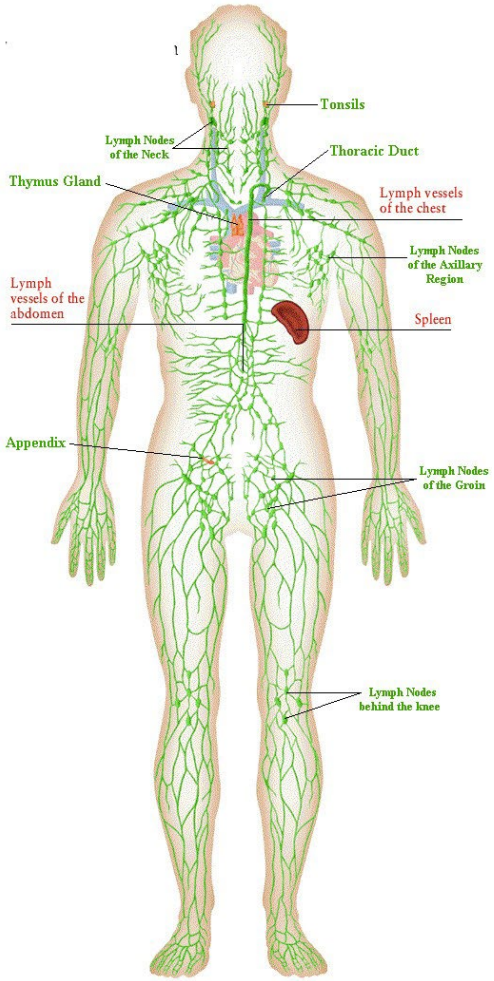
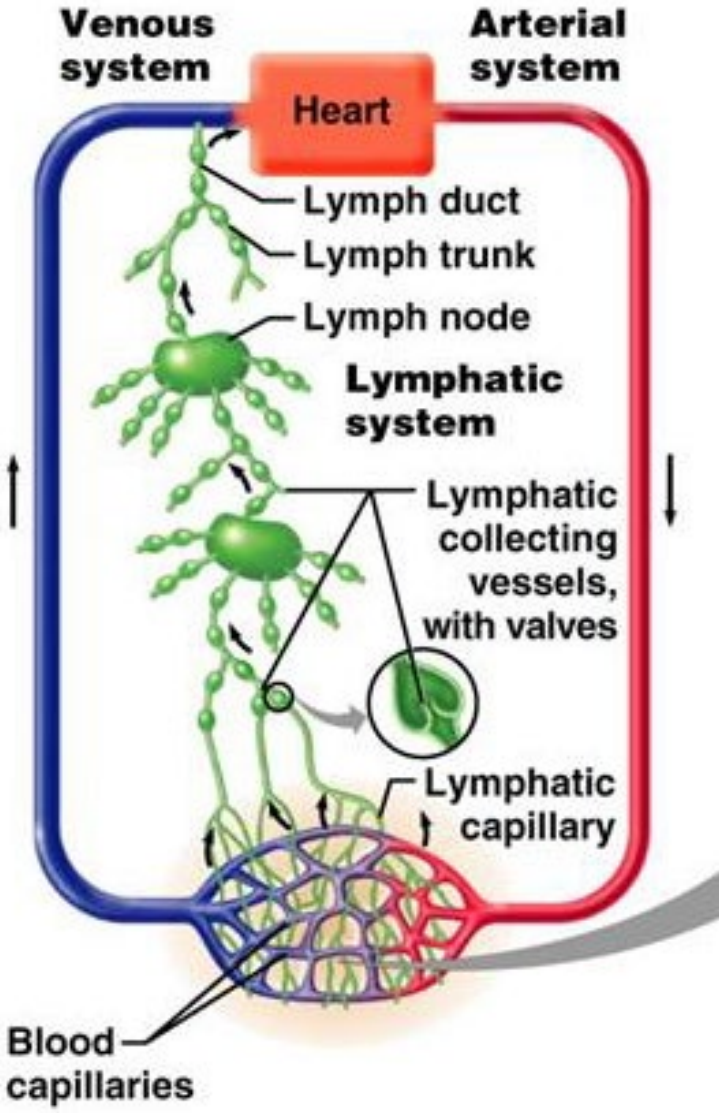
Maisel Lab

Mucosal Associated Immune System
Engineering and Lymphatics Lab

Lymphatics are crucial for tissue homeostasis





- Maintain fluid balance
- Transport materials from peripheral tissue to the **lymph nodes**
- Cellular trafficking to the lymph nodes
- Modulate immunity

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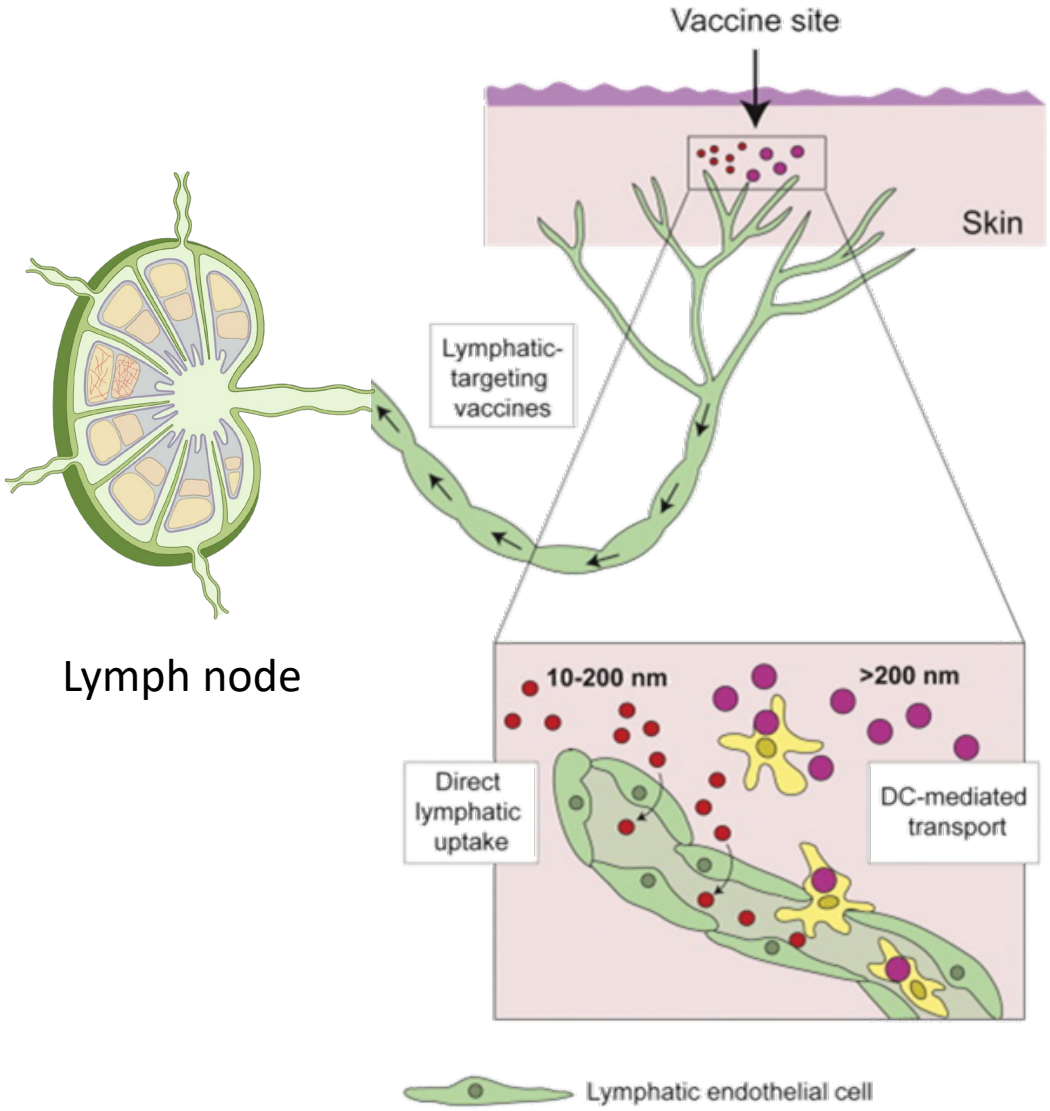
http://www.natureswarehouse.net/assets/images/Blog/Lymph%20system.jpg
http://anatomyandphysiologyi.com/wp-content/uploads/2014/01/Lymphatic-vessels.jpg

Lymphatics transport nanomaterials to the lymph nodes



Lymph node delivery improves immunotherapeutic efficacy

- Vaccines
- Allergen immunotherapy
- Cancer immunotherapy
- Tolerogenic treatments for autoimmunity

BioRender

Maisel et al. *Adv Drug Del Rev 2017*.

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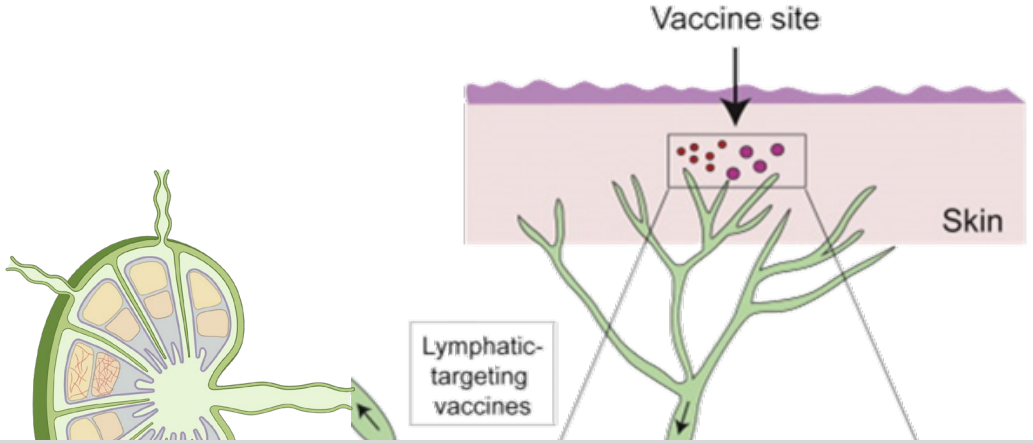
Lymphatics transport nanomaterials to the lymph nodes

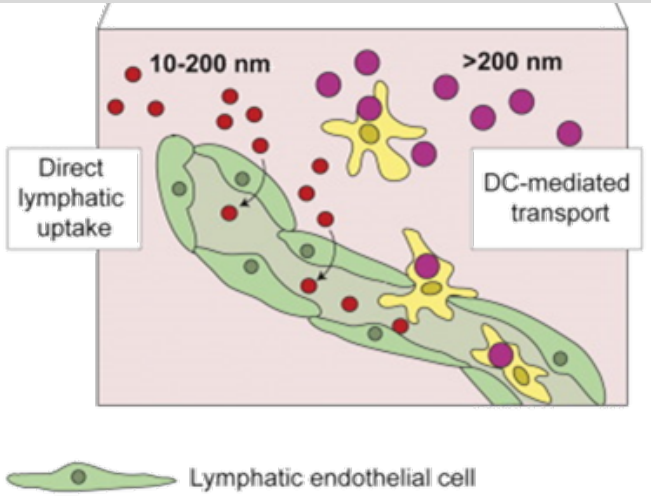


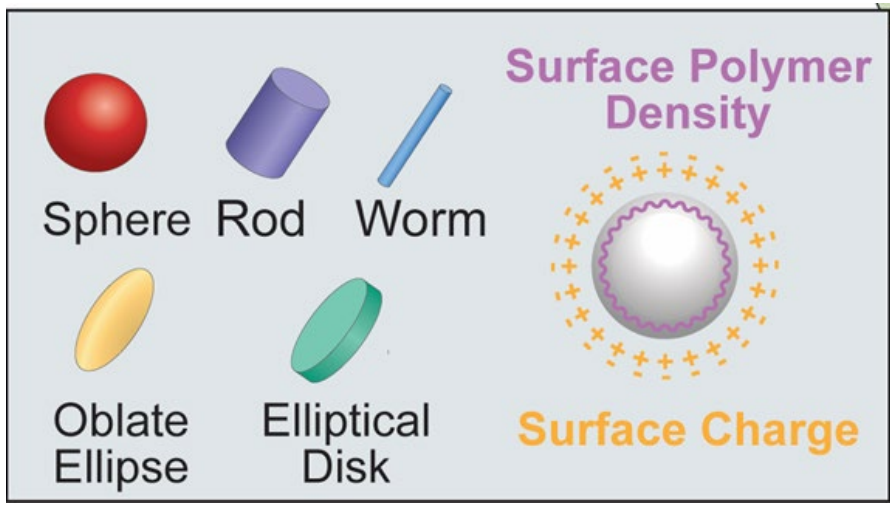
Lymph node delivery improves immunotherapeutic efficacy

- Vaccines
- Allergen immunotherapy
- Cancer immunotherapy
- Tolerogenic treatments for autoimmunity

What material properties are required to maximize nanoparticle transport into lymphatics?

Lymph node





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Maisel et al. *Adv Drug Del Rev 2017*.

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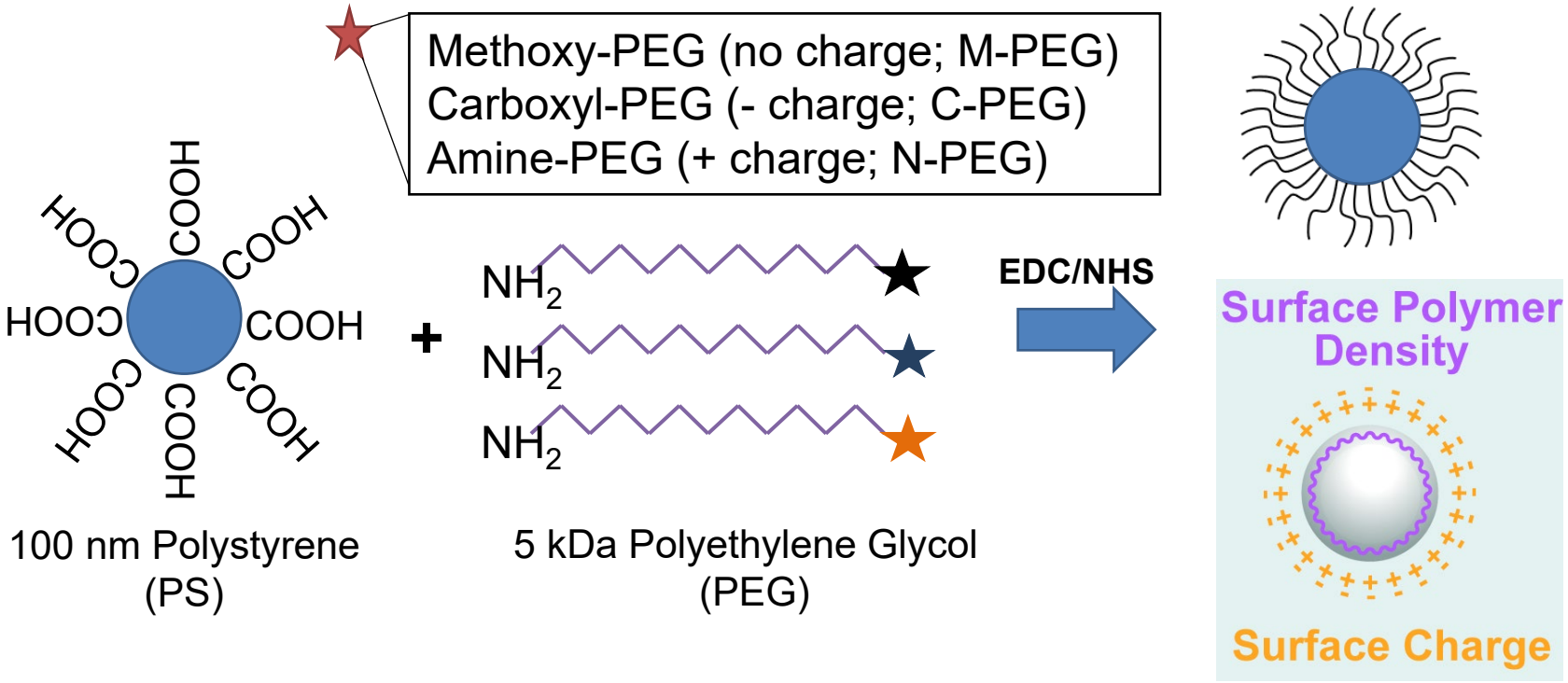
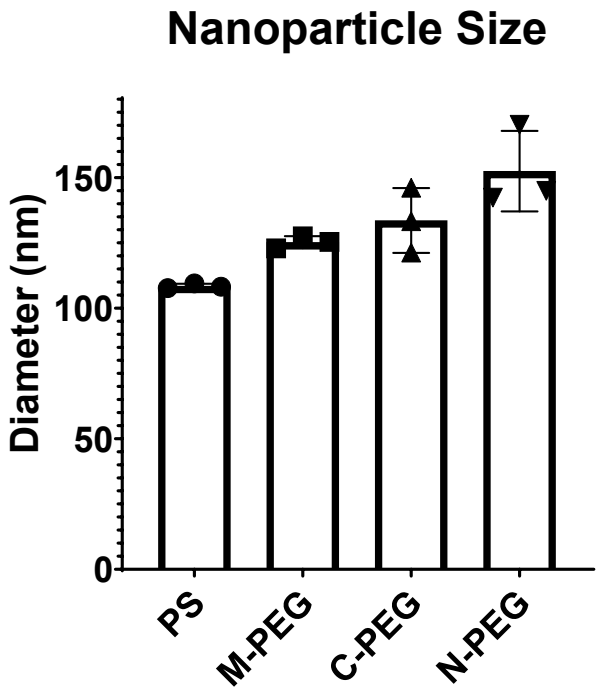
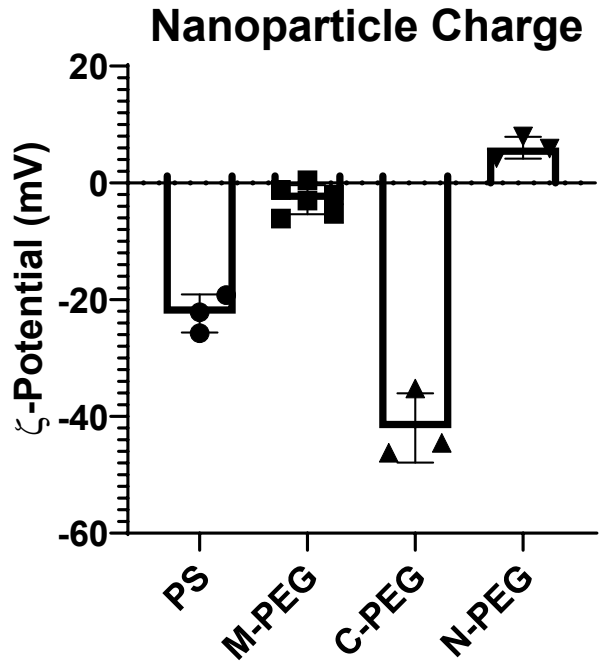
Nanoparticles can be formulated with PEG with positive, negative, or neutral charge







Nanoparticles 20-250 nm are effectively transported to the lymph nodes by lymphatics

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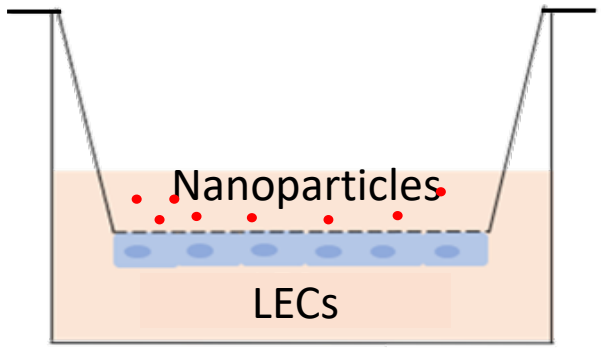
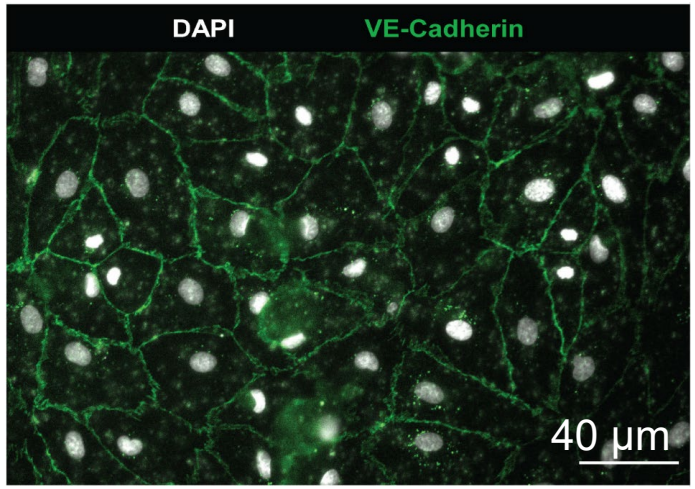
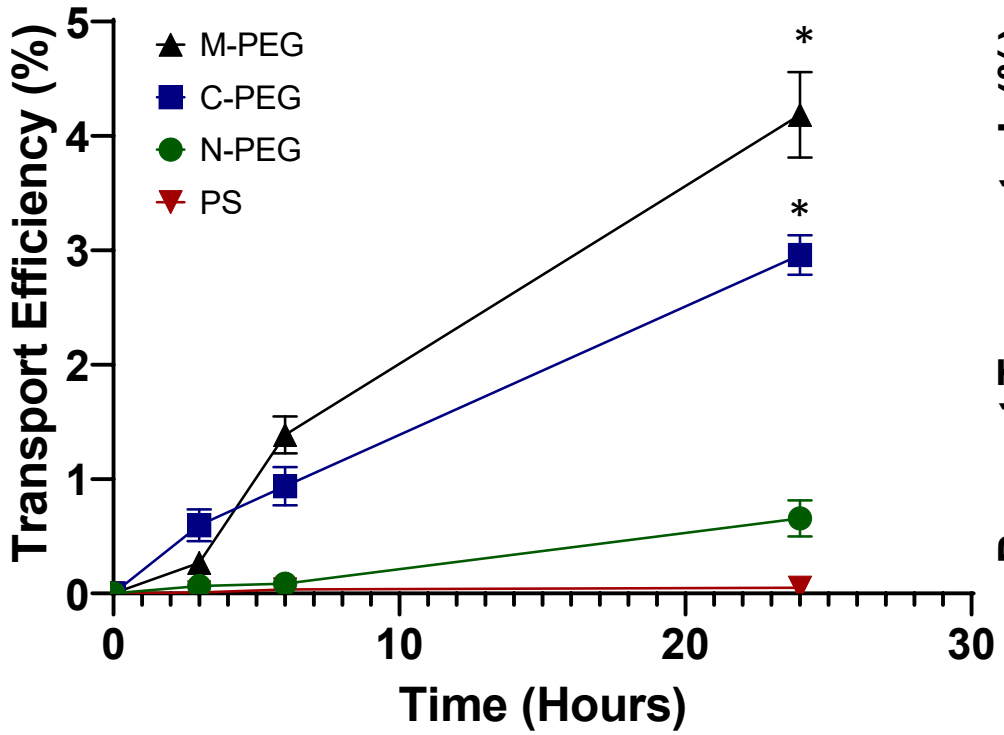
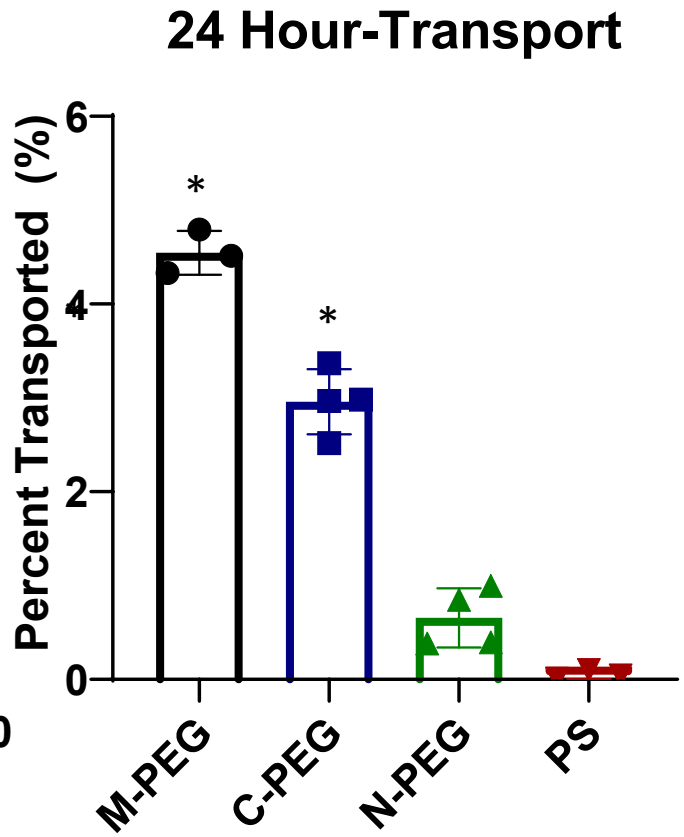
McCright et al. *Acta Biomaterialia 2022*.

Nanoparticle charge modulates their transport by lymphatics









Neutral surface charge maximizes ~100 nm nanoparticle transport across lymphatics

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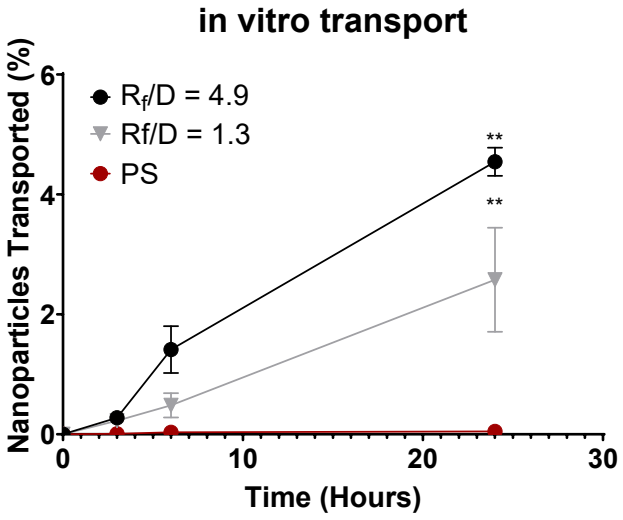
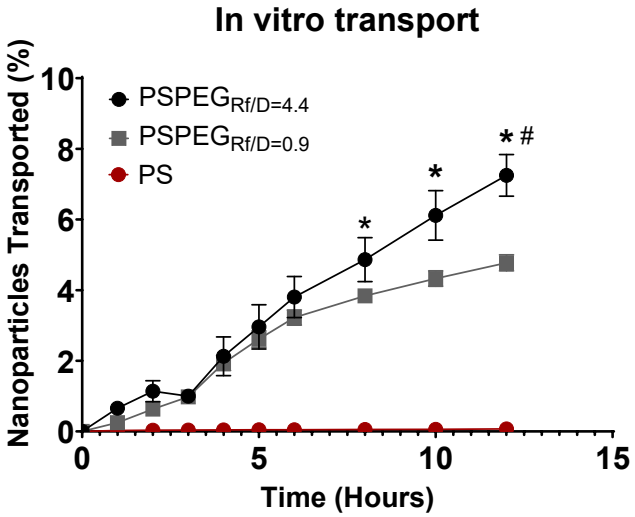
unpublished

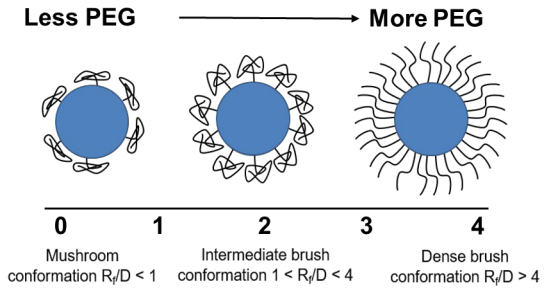
PEGylation enhances nanoparticle accumulation in the lymph nodes

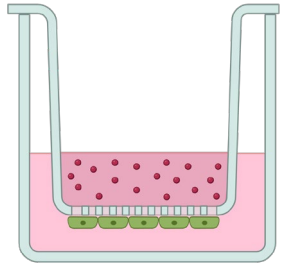
100 nm



40 nm







BioRender

McCright et al. *Acta Biomaterialia 2022*.

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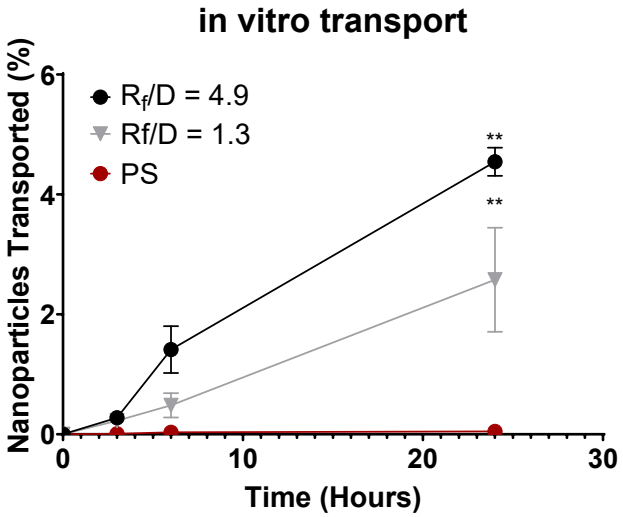
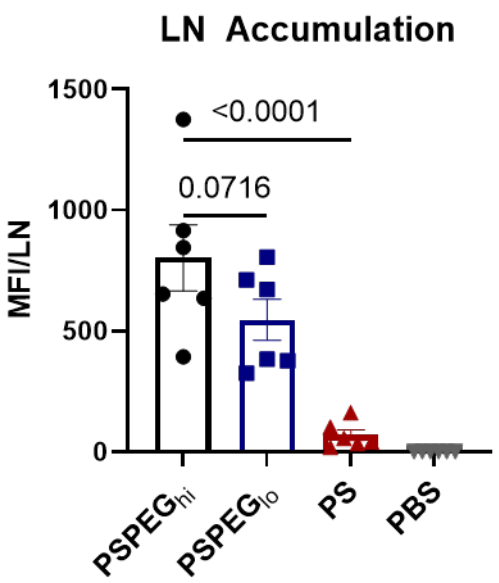
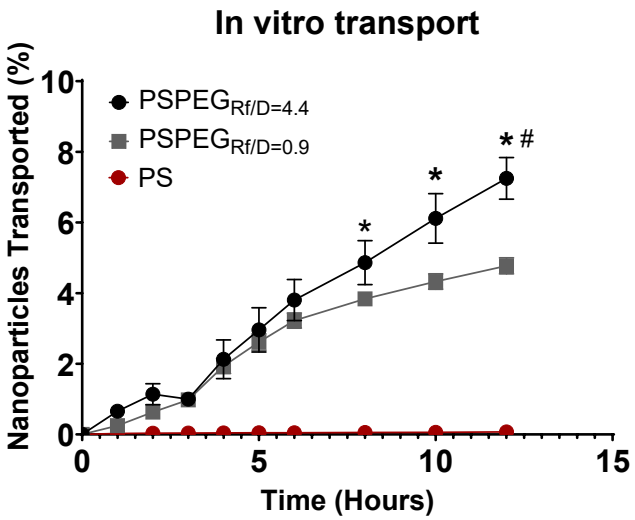
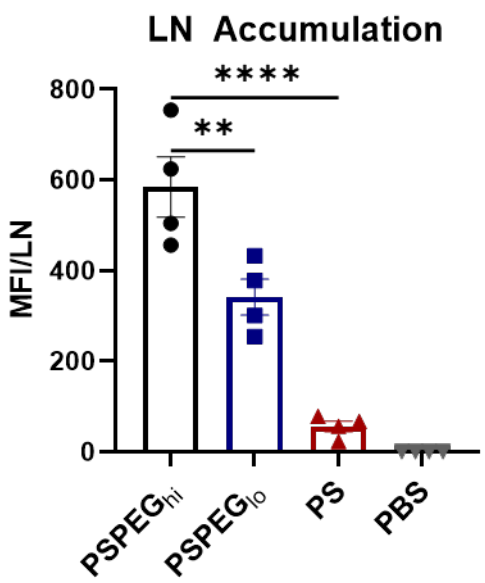
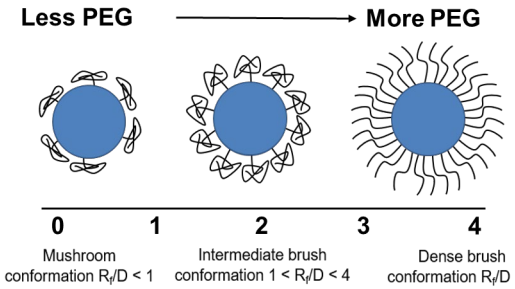


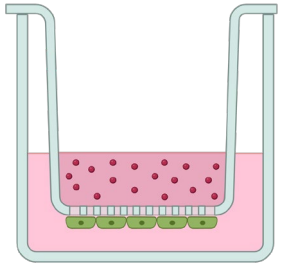


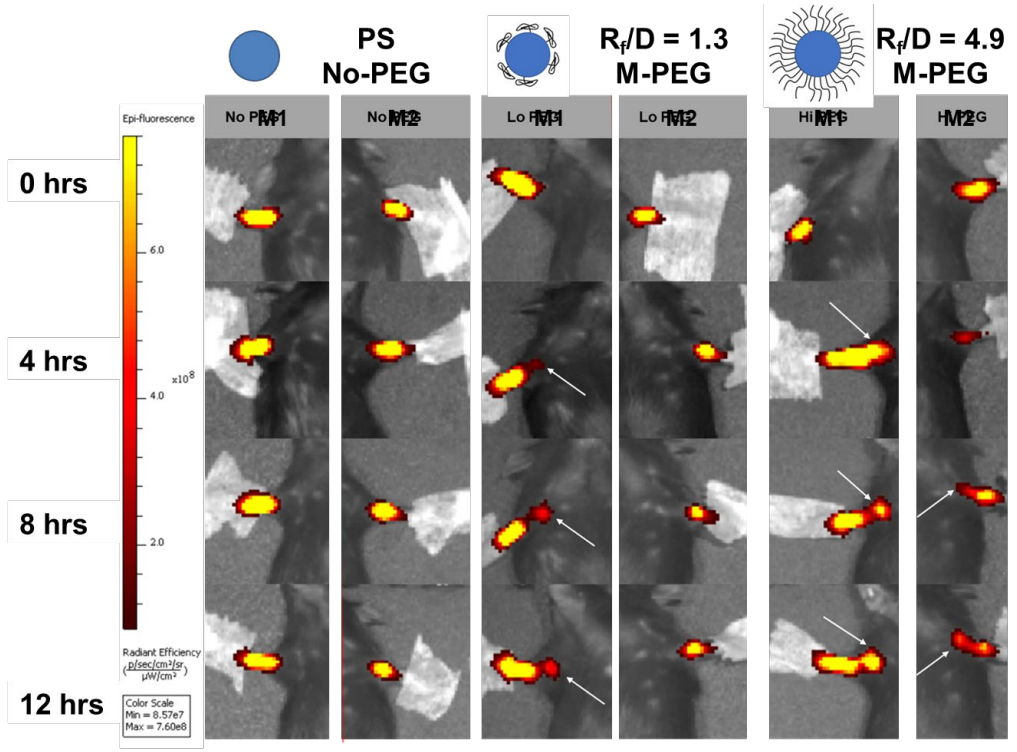
40 nm











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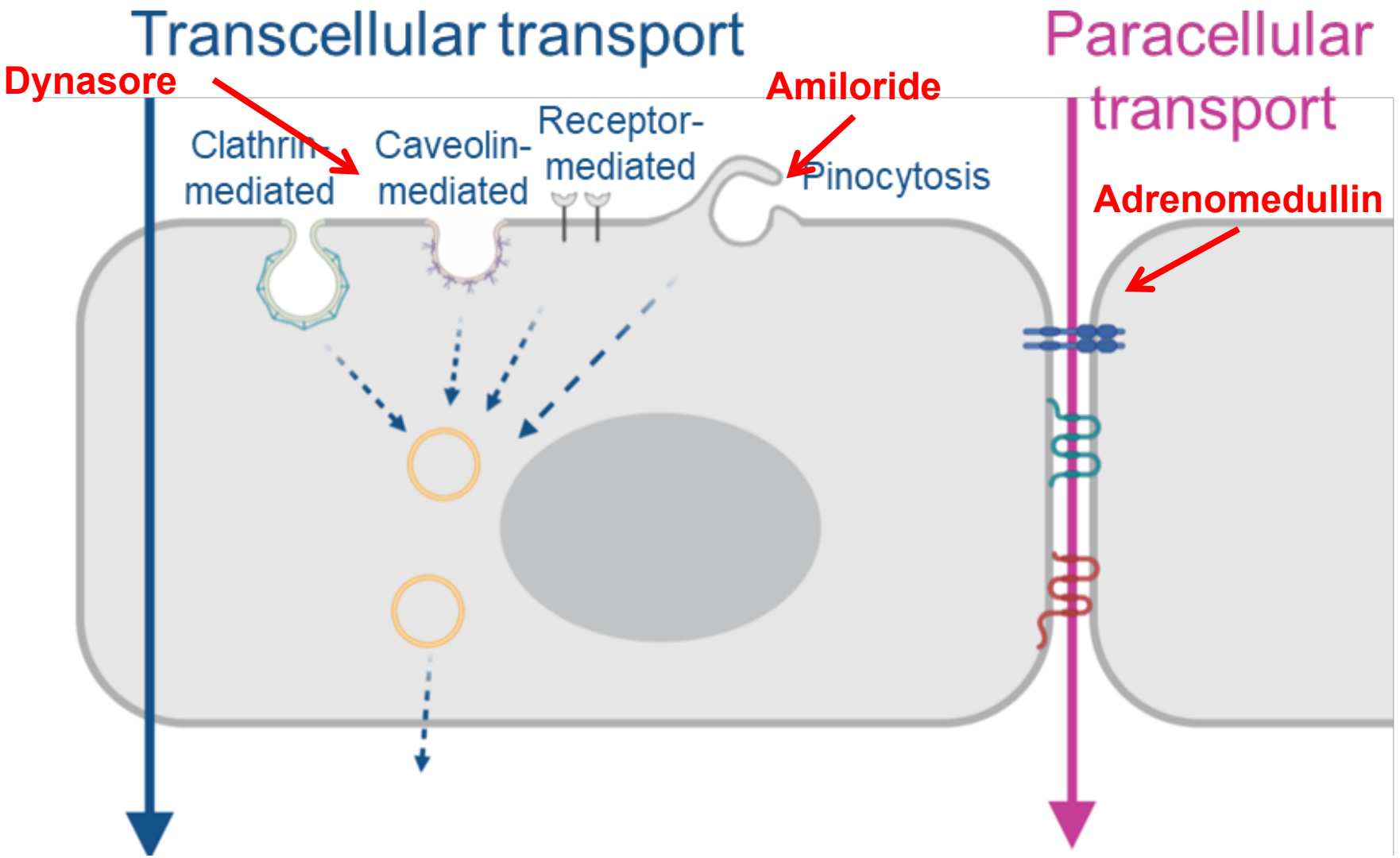
McCright et al. *Acta Biomaterialia 2022*.

Cellular transport mechanisms



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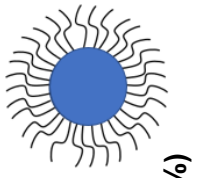
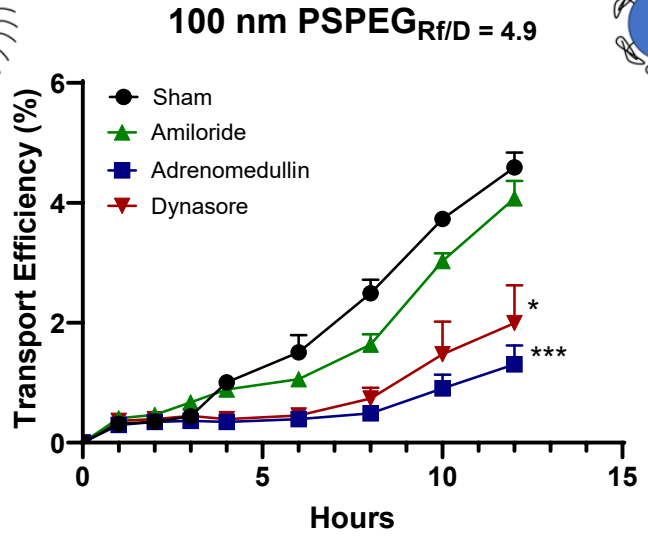
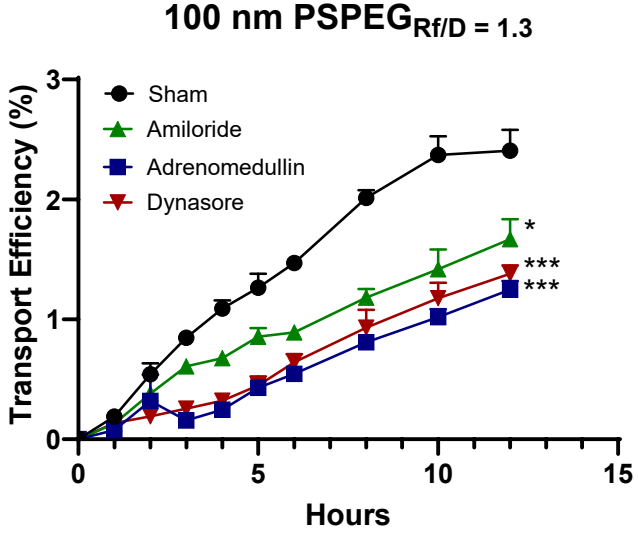
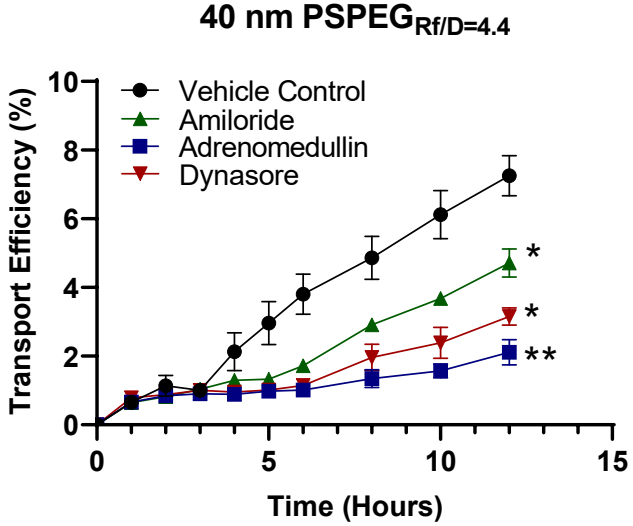
Rennick et al, *Nat Nanotech* 2021

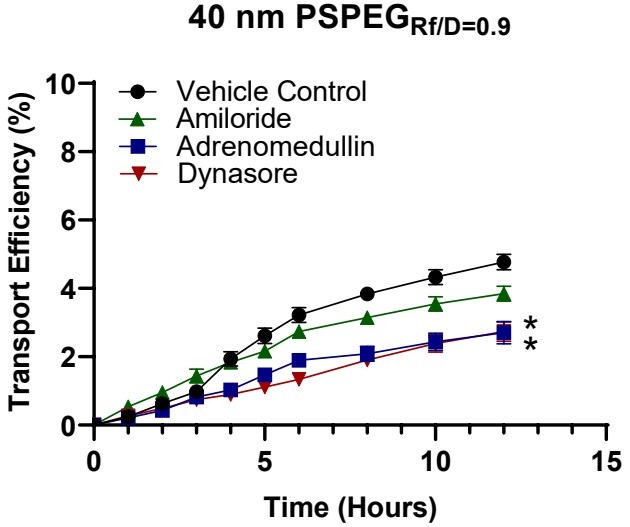
Both paracellular and transcellular mechanisms govern transport of densely PEGylated nanoparticles across lymphatics











Amiloride: Macropinocytosis inhibitor
Adrenomedullin: paracellular transport inhibitors
Dynasore: Dynamin inhibitor

McCright et al. *Acta Biomaterialia 2022*.

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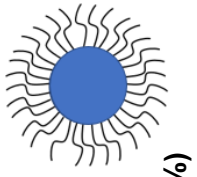

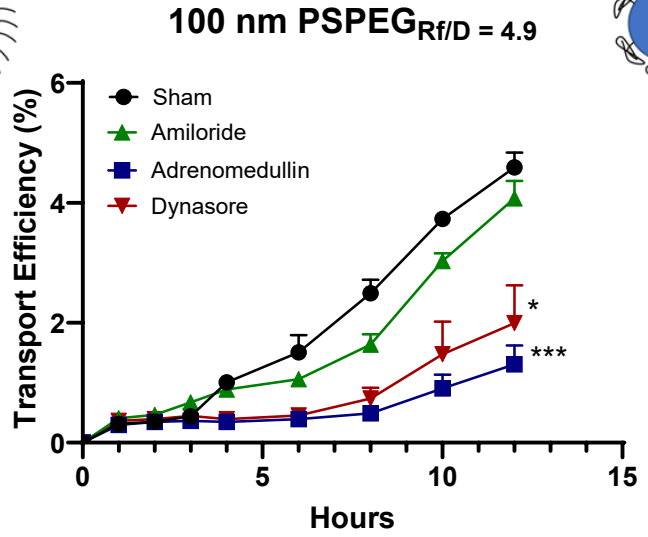

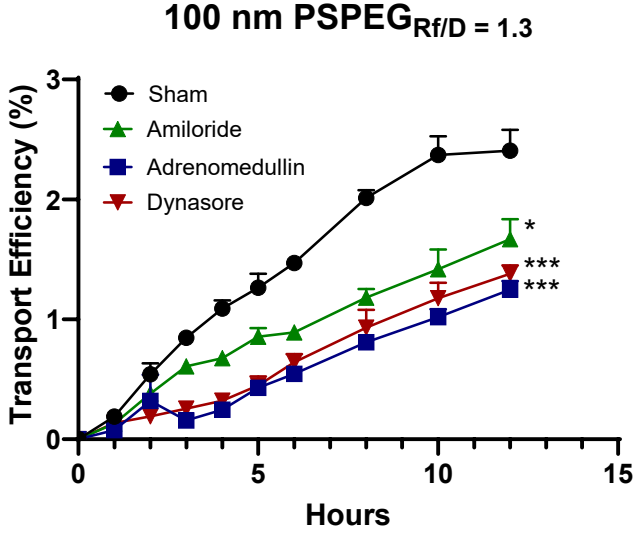

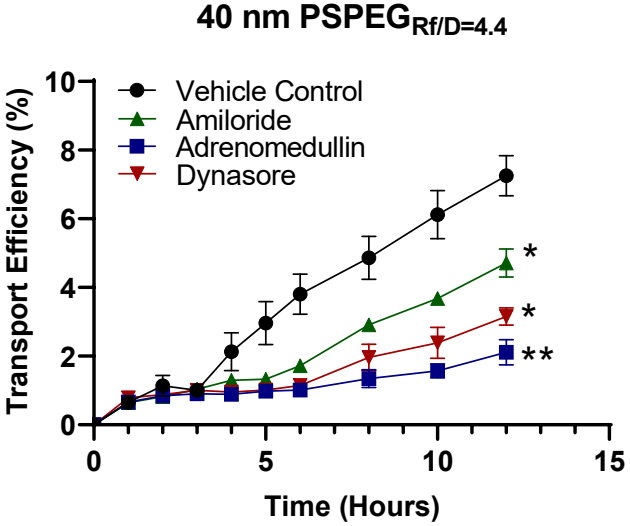

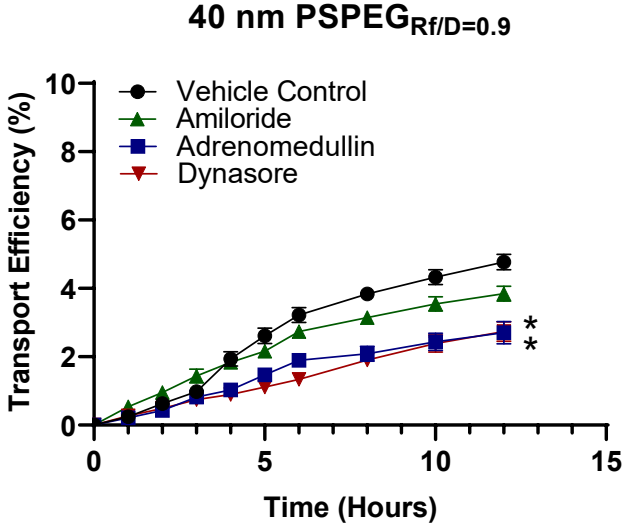

Amiloride: Macropinocytosis inhibitor
Adrenomedullin: paracellular transport inhibitors
Dynasore: Dynamin inhibitor

	high PEG	Low PEG
100 nm	Micropinocytosis Paracellular	Macropinocytosis Micropinocytosis Paracellular
40 nm	Macropinocytosis Micropinocytosis Paracellular	Micropinocytosis Paracellular

McCright et al. *Acta Biomaterialia 2022*.

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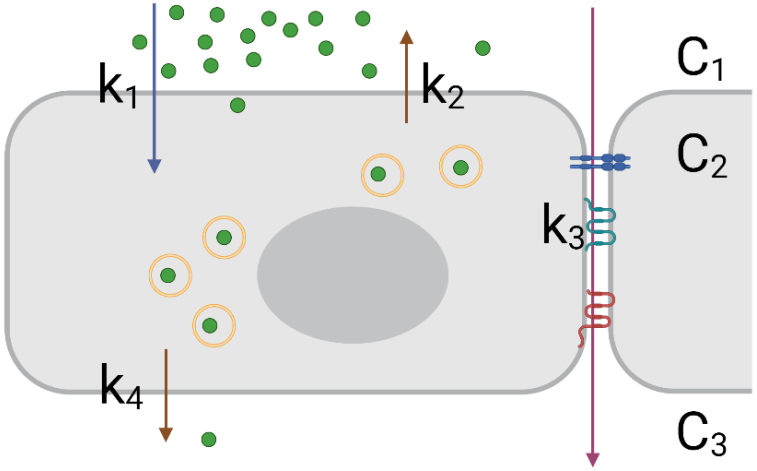

$$\frac{\partial C_1}{\partial t} = -(k_1 + k_3)C_1 + k_2 C_2$$

$$\frac{\partial C_2}{\partial t} = -(k_2 + k_4)C_2 + k_1 C_1$$

$$\frac{\partial C_3}{\partial t} = k_3 C_1 + k_4 C_2$$

Jenny Yarmovsky

McCright et al. *Molecular Pharmaceutics 2024*.

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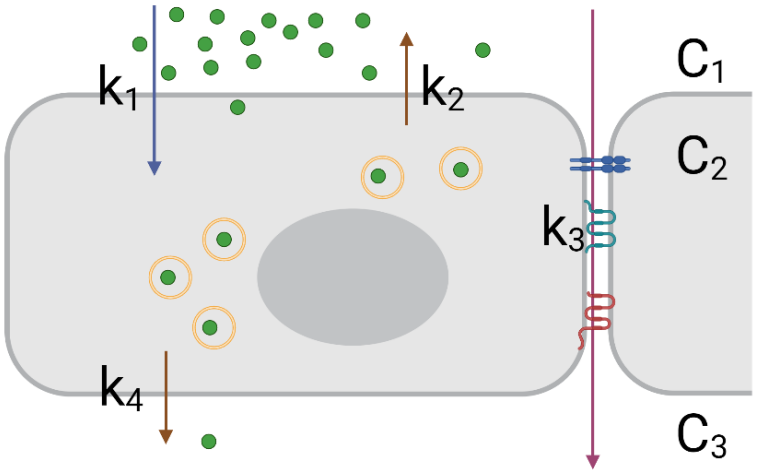

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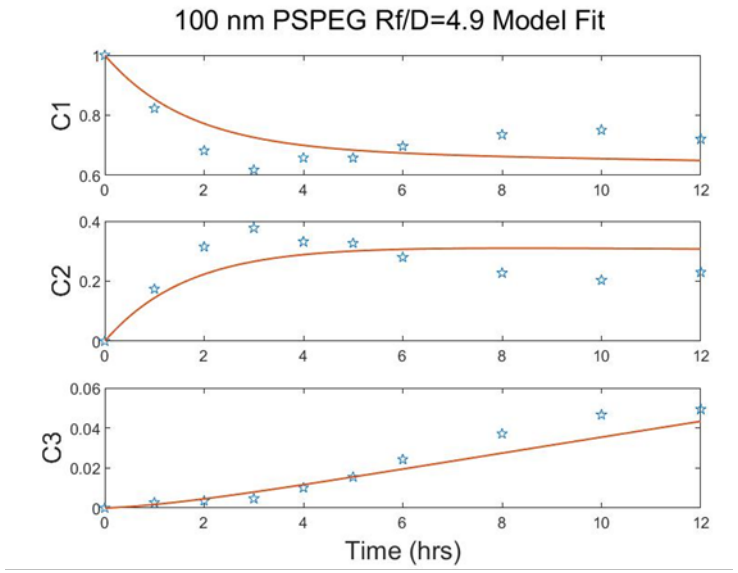


Rate Constants (μg mL^{-1} hr^{-1})	100 nm PSPEG$_{Rf/D=4.9}$	100 nm PSPEG$_{Rf/D=1.3}$	40 nm PSPEG$_{Rf/D=4.7}$	40 nm PSPEG$_{Rf/D=0.8}$
k1	1.9	1.5	1.5	1.2
k2	3.9	3.5	4.0	3.2
k3	0.013	0.012	0.014	0.011
k4	0.13	0.074	0.26	0.21

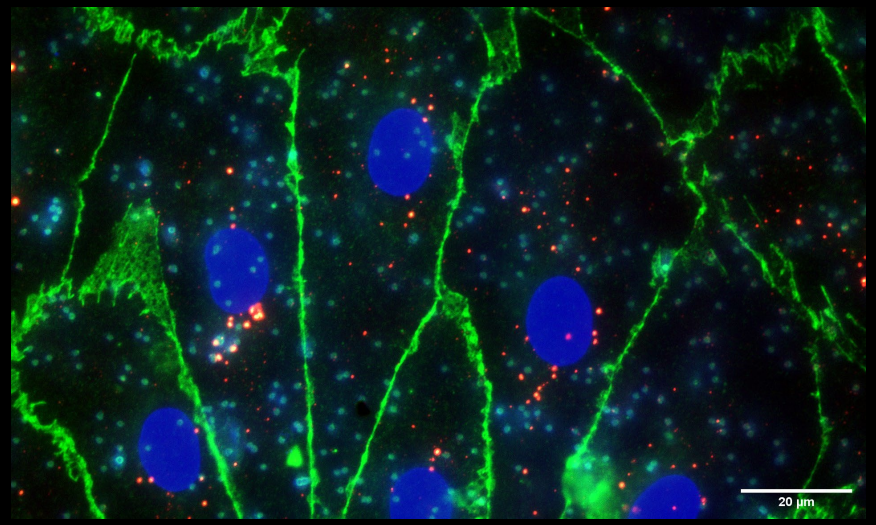
Jenny Yarmovsky

McCright et al. *Molecular Pharmaceutics 2024*.

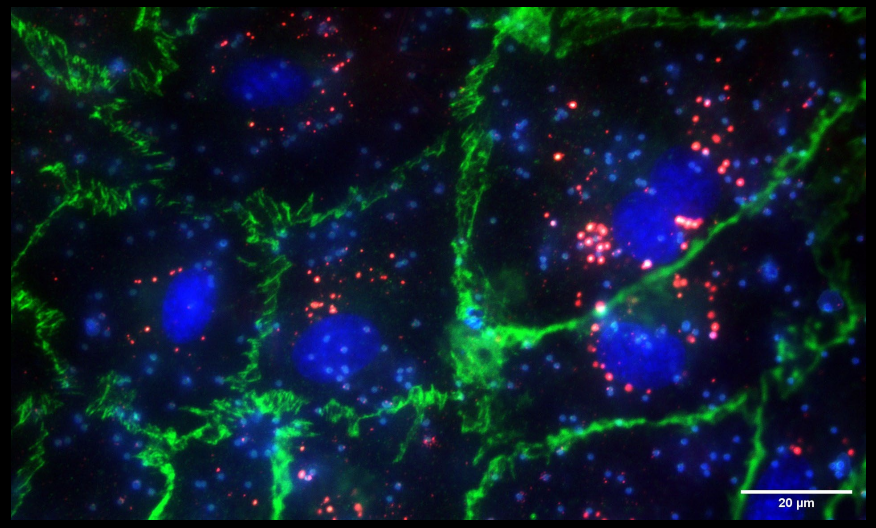
How do the particles get out?

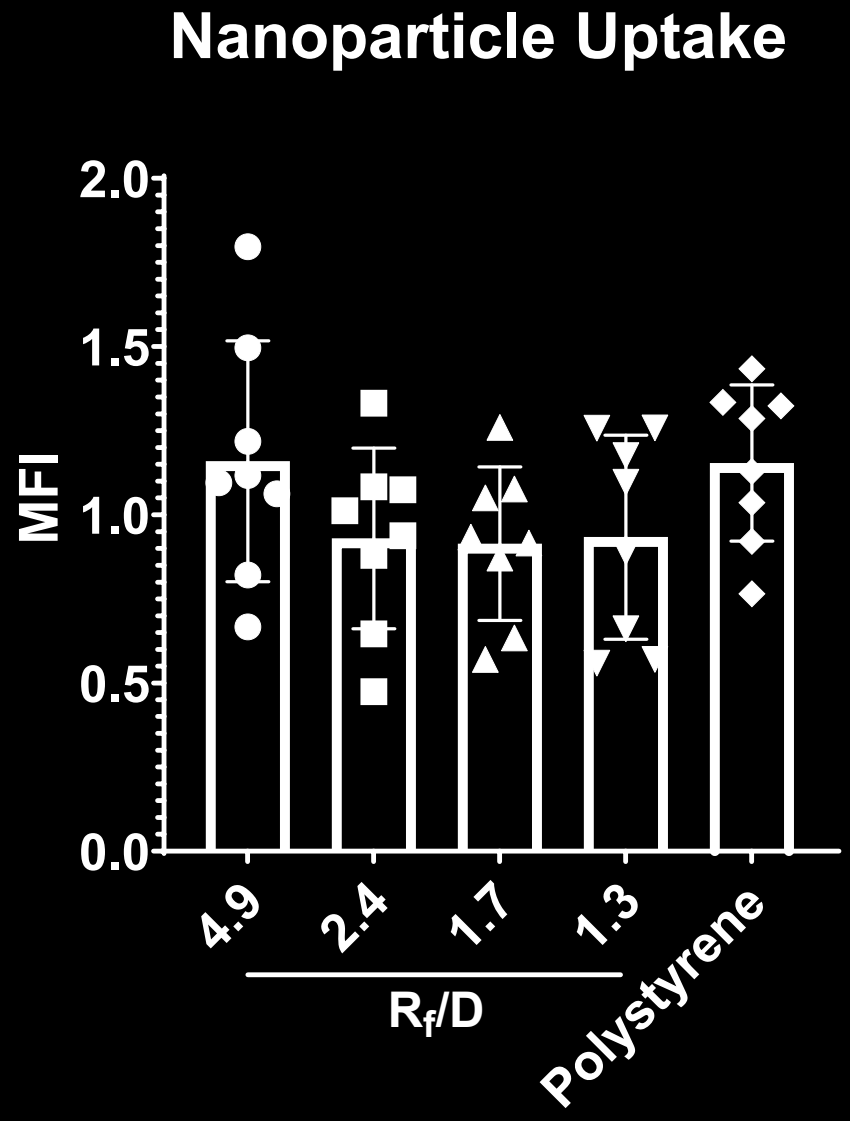
Nanoparticle surface chemistry does not affect uptake by LECs

DAPI PSPEG$_{Rf/D = 4.9}$ VE-Cadherin

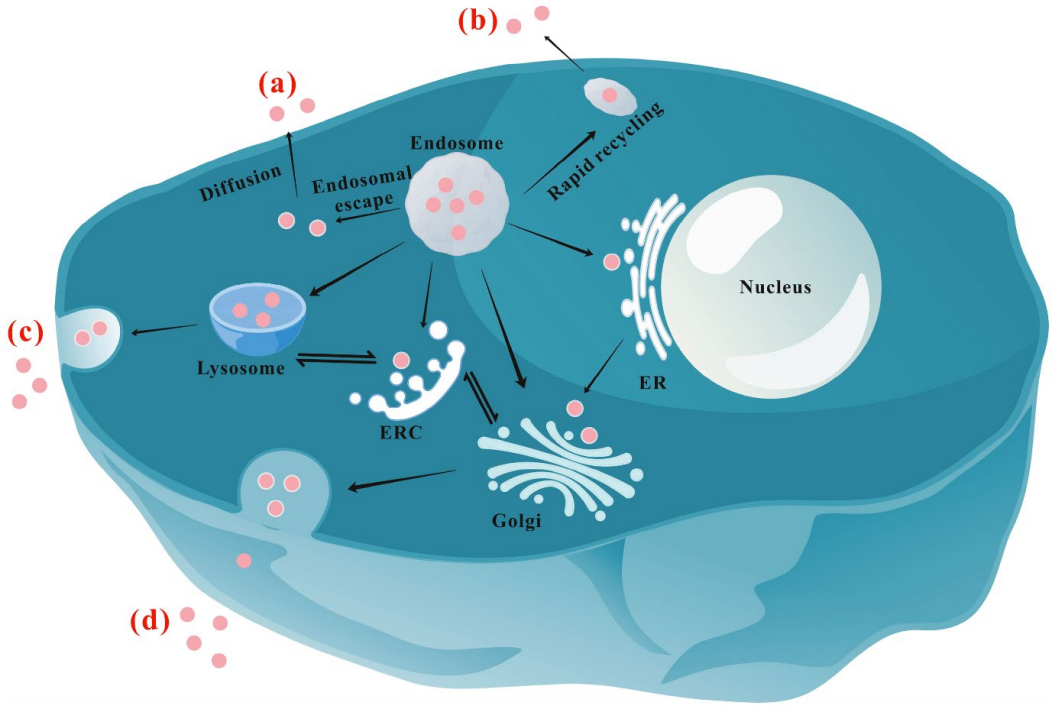


DAPI PS VE-Cadherin





Exocytosis!

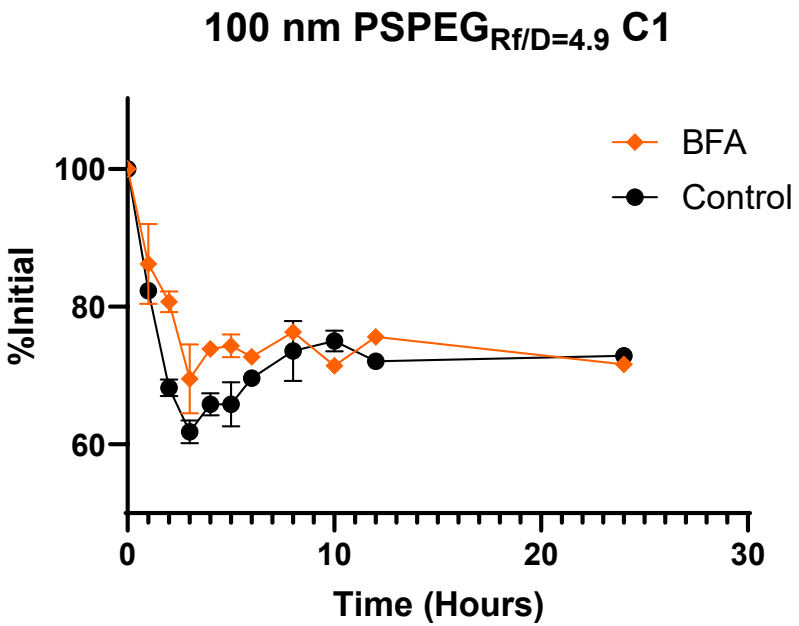


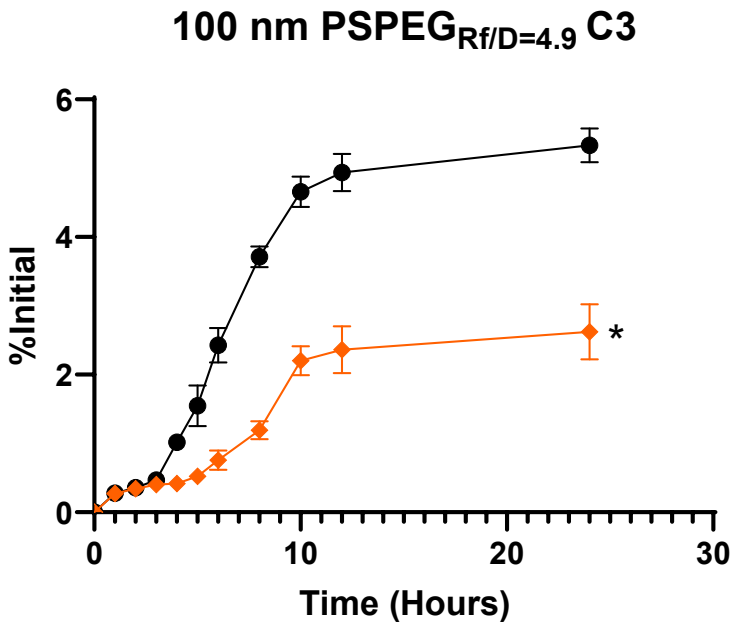
(a) Diffusion

(b) Rapid recycling pathway

(c) Lysosomal pathway

(d) ER/Golgi apparatus pathway

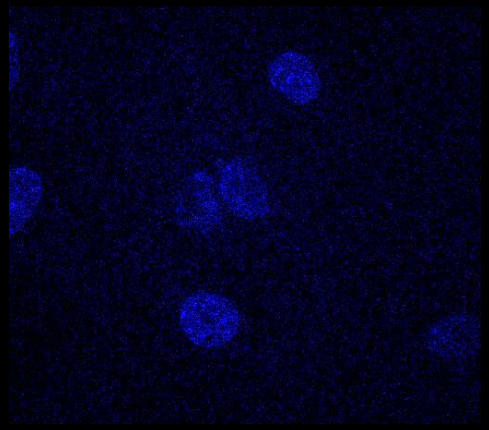




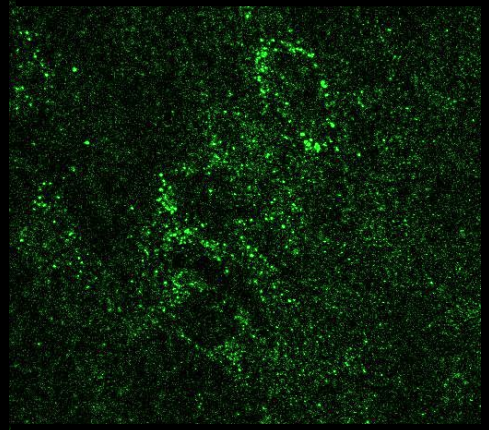
McCright et al. *Molecular Pharmaceutics 2024*.
Liu, J et al. *Nanomaterials* **2023**, *13*, 2215.

Lysosomal exocytosis?

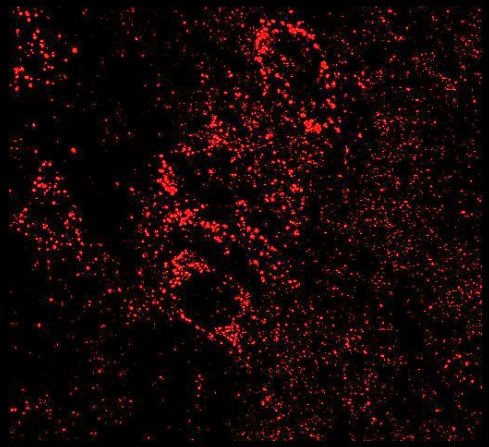
DAPI



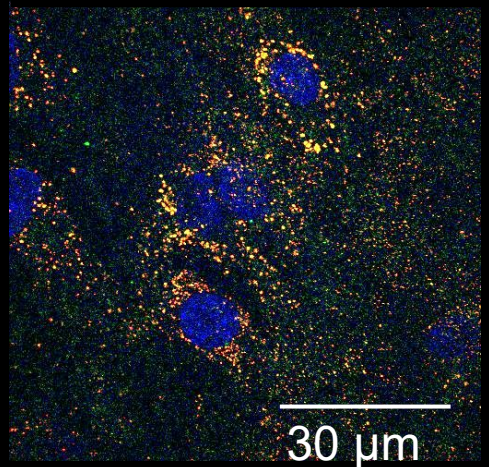
Clathrin



$PSPEG_{hi}$



Overlay

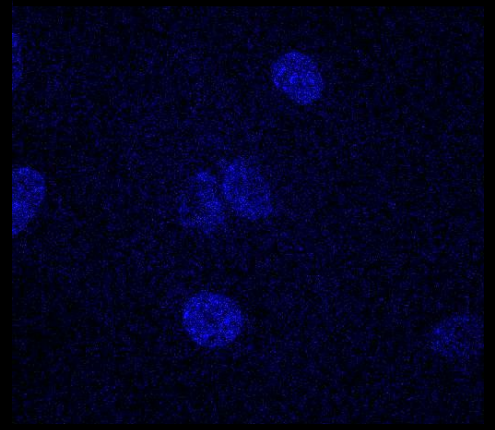


Aisha Abdulkarimu

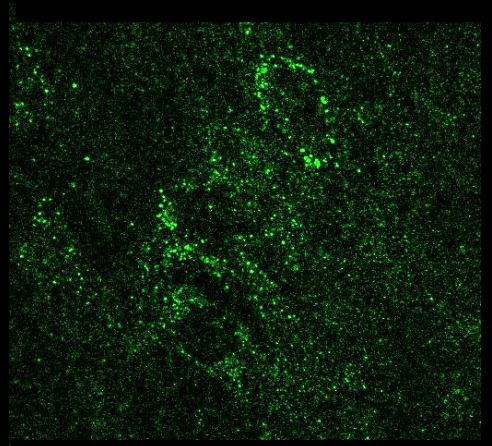
unpublished

Lysosomal exocytosis? Maybe

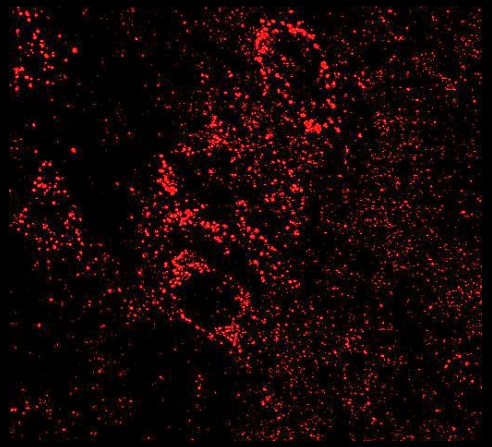
DAPI



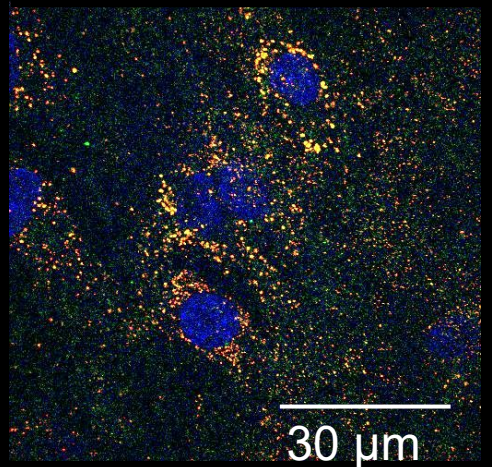
Clathrin



PSPEG$_{hi}$



Overlay



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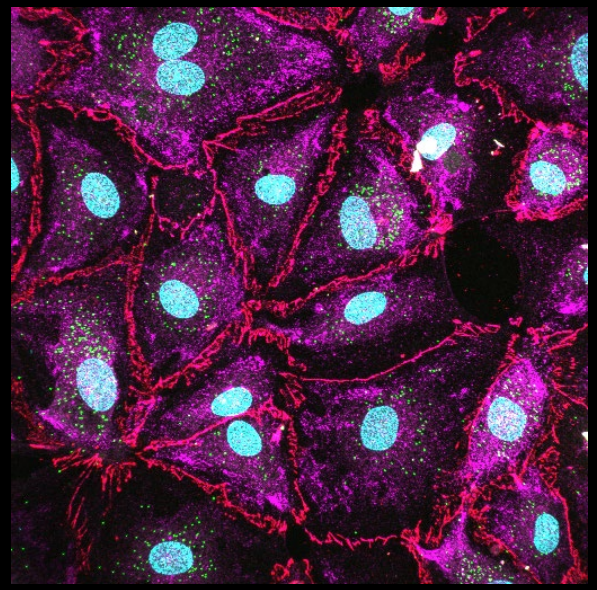

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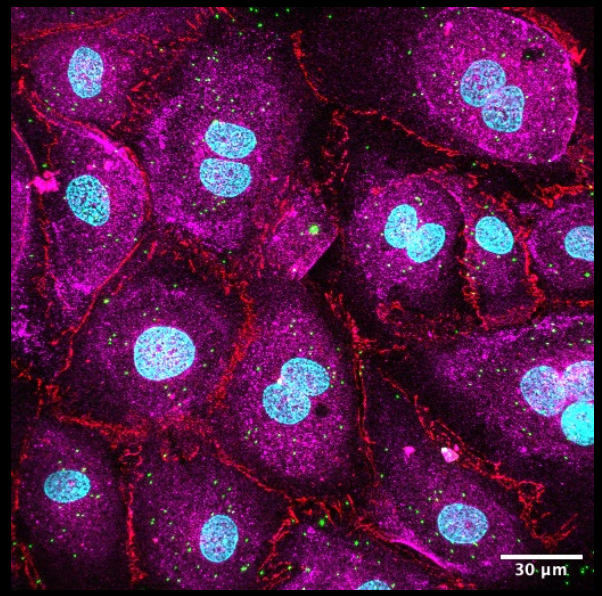
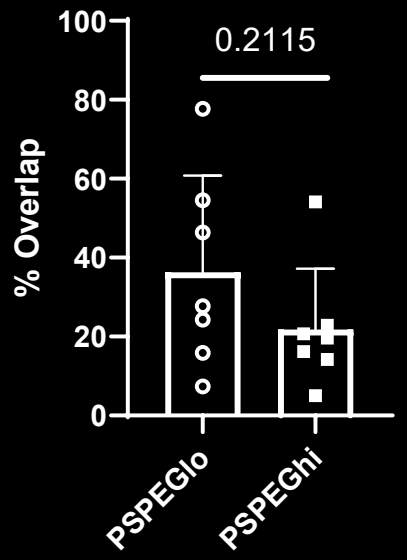




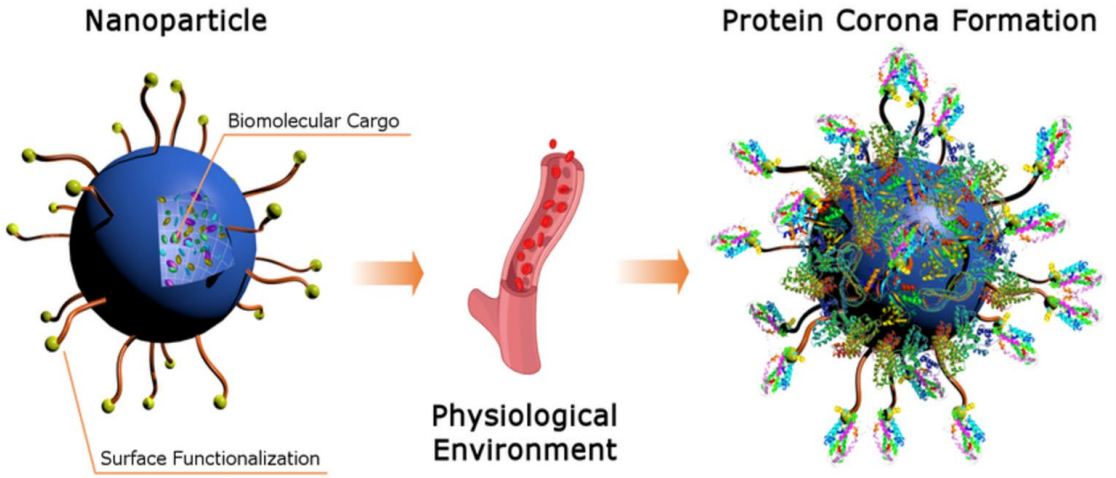
Nanoparticle
VE-cadherin
LAMP1
DAPI

Aisha Abdulkarimu

unpublished

What's causing the differences we see in uptake mechanisms?

PEG density modulates the protein corona on nanoparticles

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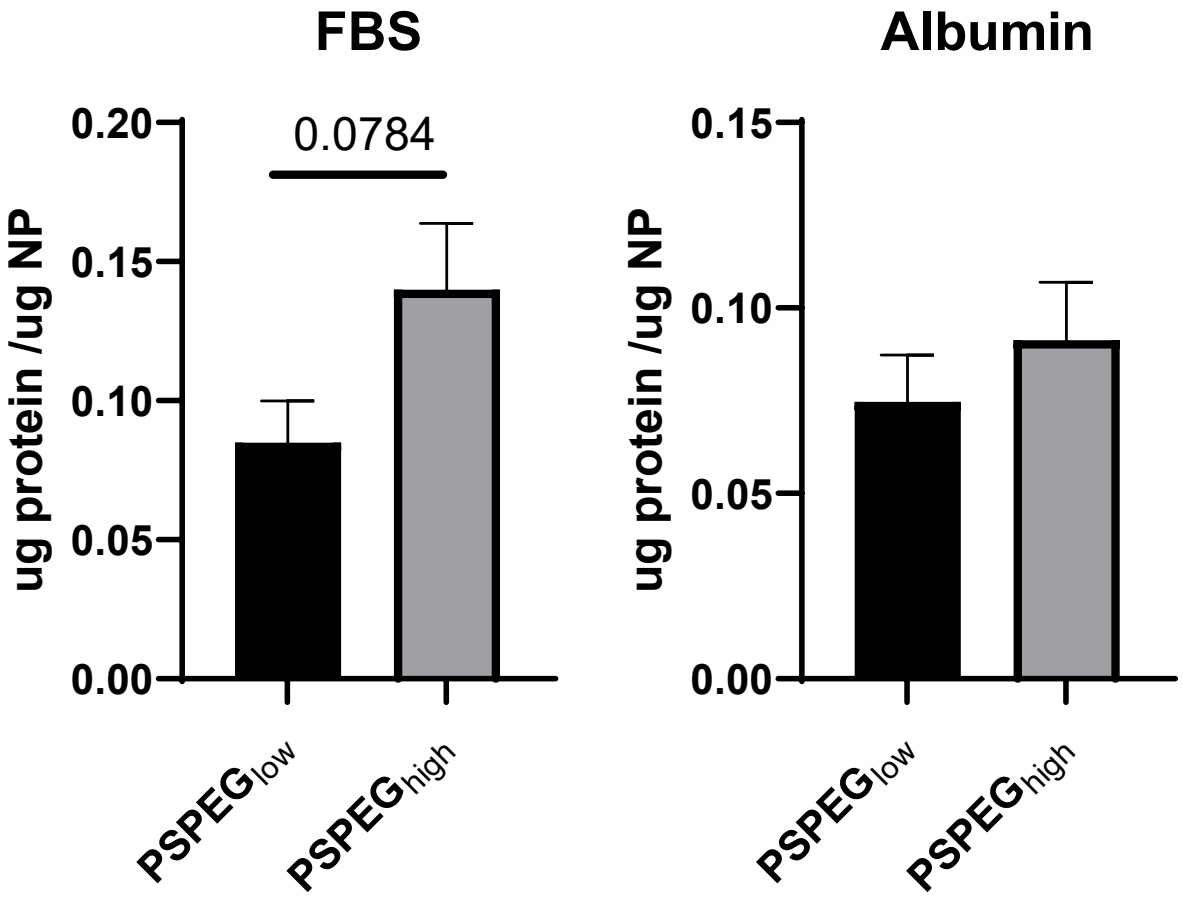
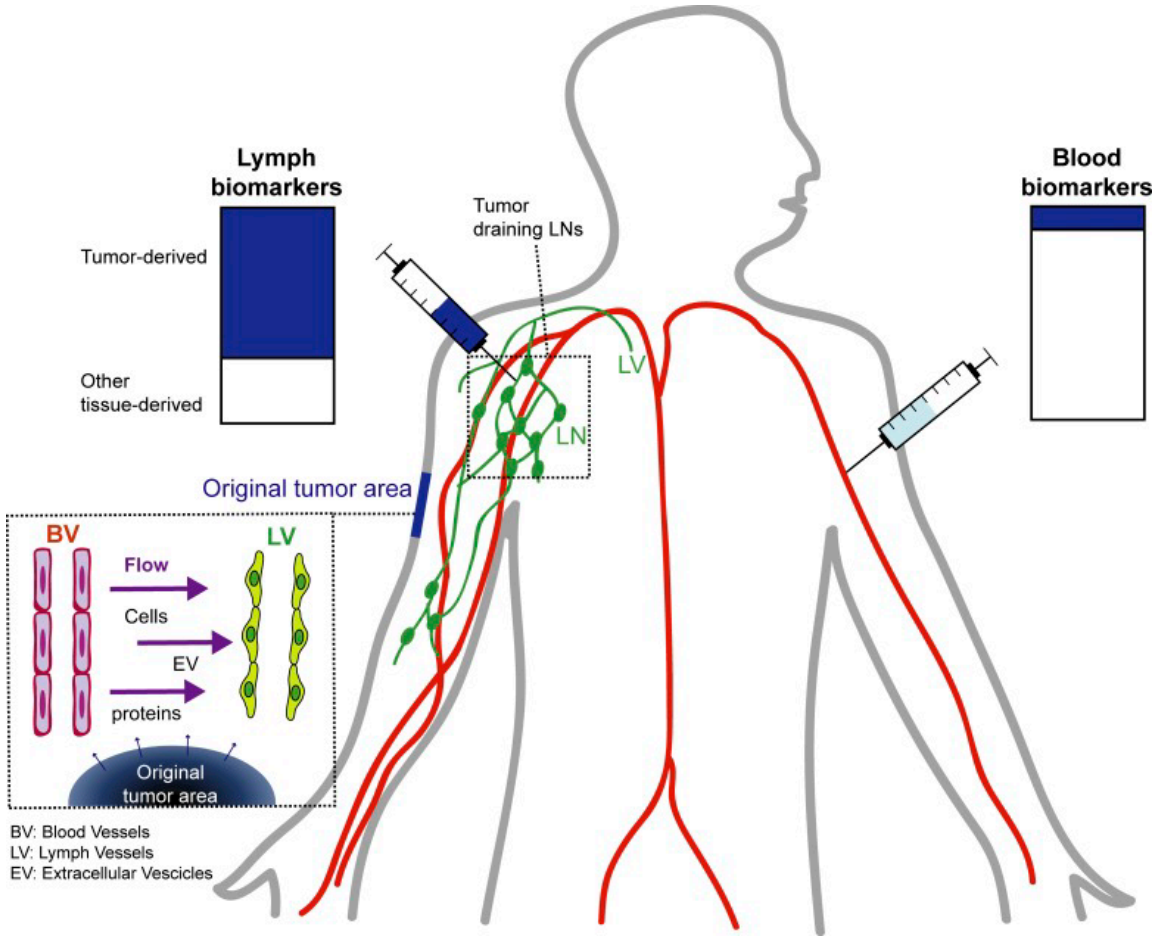
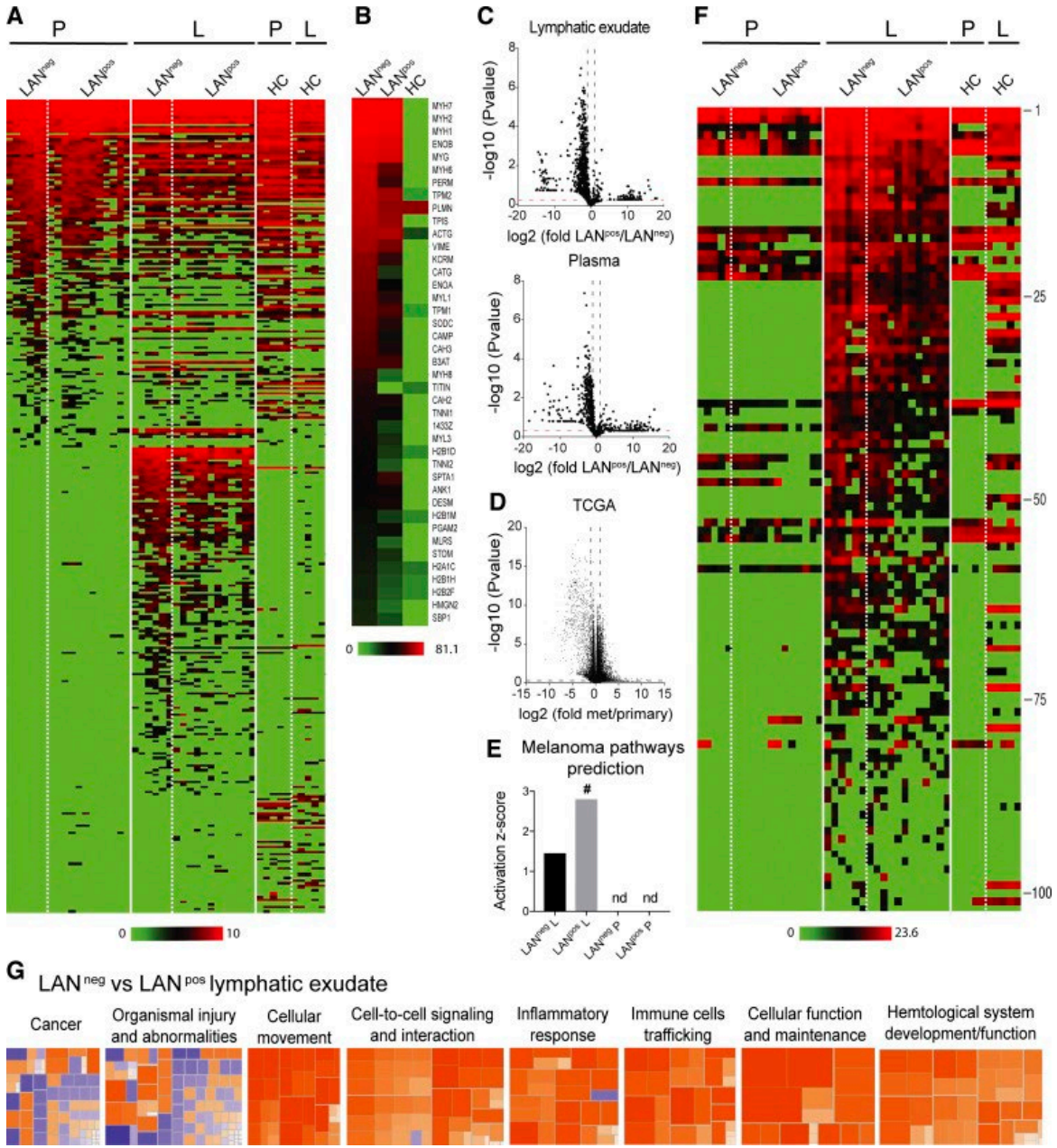


F. Poncin-Epaillard, T. Vrlinic, et al. *J Funct Biomater* (2012).
L Digiacomo, D. Pozzi et al. *WIREs Nanomed Nanobiotechnol.* (2020).

unpublished

Lymphatic exudate has a different composition than plasma





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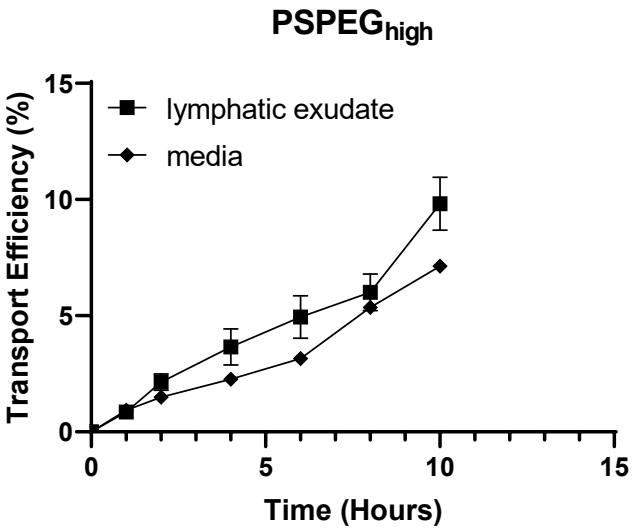
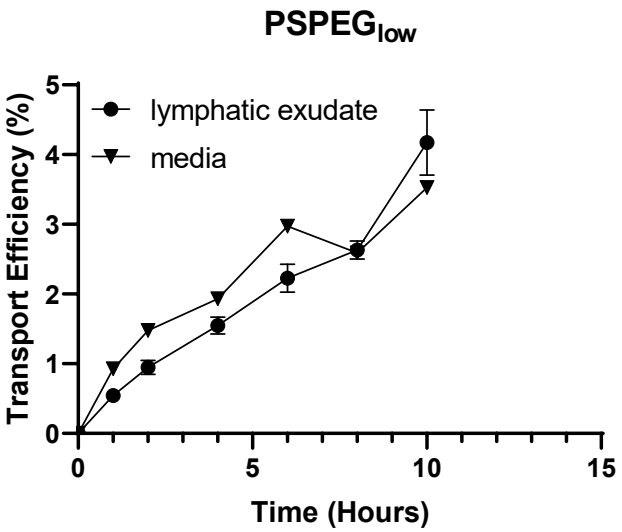
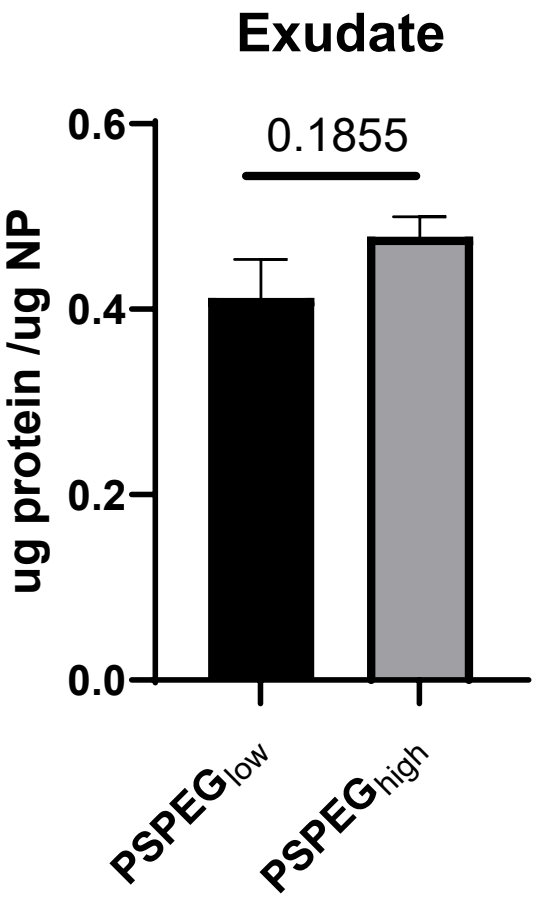
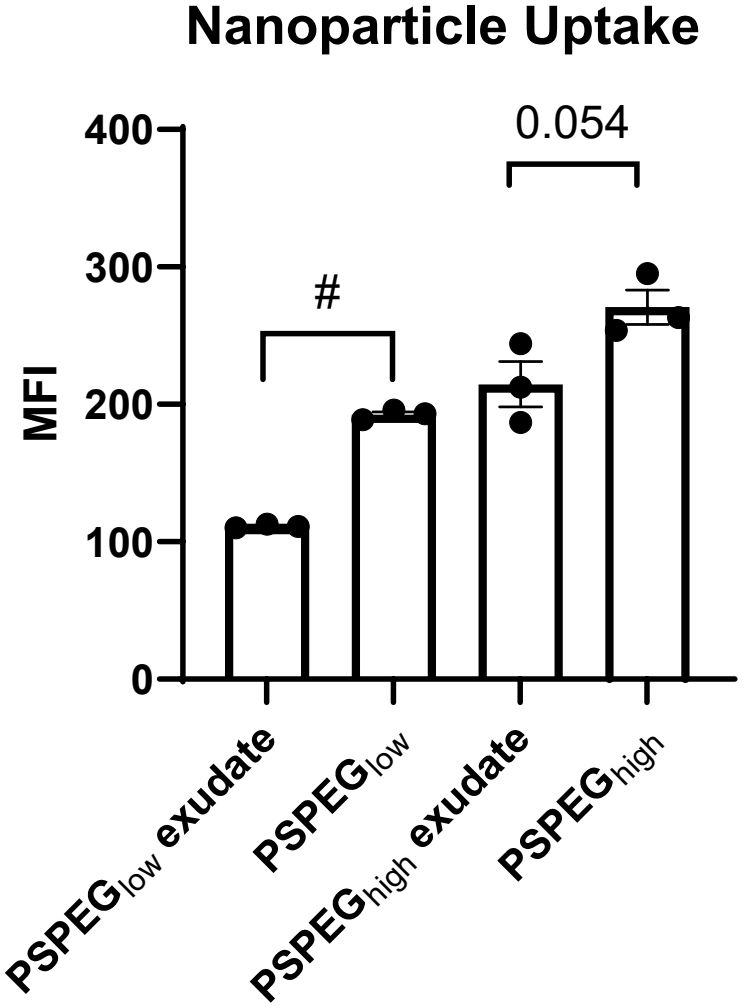
Broggi et al. *J Exp Med*. 2019.

Protein corona from lymphatic exudate affects nanoparticle uptake by LECs









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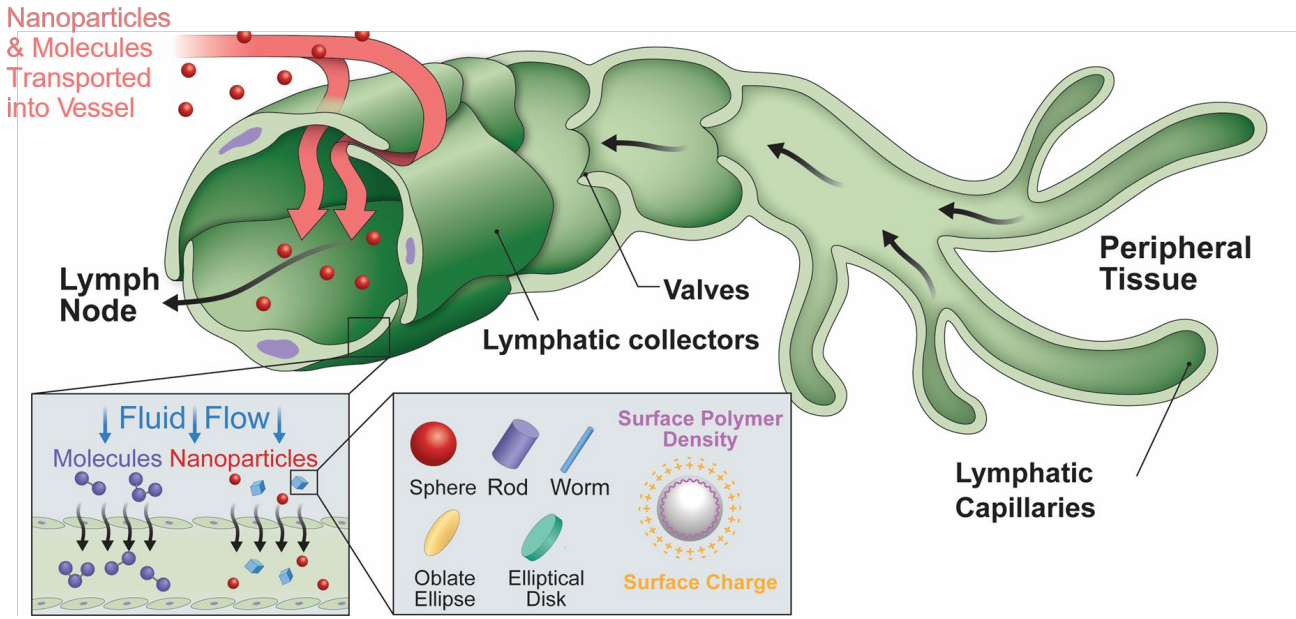
Summary

- Densely PEGylated nanoparticles are most efficiently transported across LECs for nanoparticles 40 – 150 nm
- PEG density modulates nanoparticle transport mechanisms used by LECs
- Transcellular pathways significantly contribute to nanoparticle transport across LECs
- Exocytosis might be driving differences in nanoparticle transport across LECs



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Eric Vaughan
Bennett Yang
Kelly Yeung

Jenny Yarmovsky

Funding

NIH NIGMS
NSF CAREER Award
American Heart Association.
Million Dollar Bike Ride — Raising Money for Rare Disease Research
American Lung Association.
The LAM Foundation — A Breath of Hope
University of Maryland