Neutrophil-Targeted Nanoparticles For Antibiotic Delivery to Remediate Lung Injury in Sepsis

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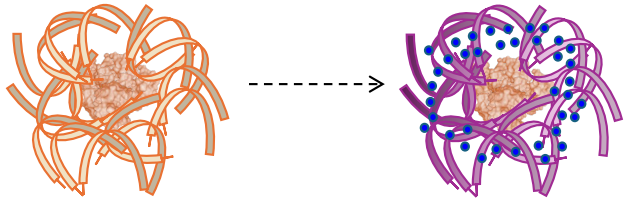
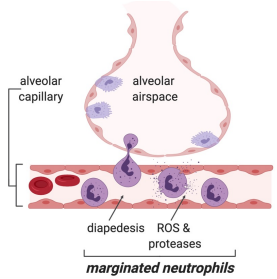
Outline

1) Designing neutrophil targeting by controlling nanoparticle structure

2) Redesigning a neutrophil targeting nanoparticle for antibiotic delivery

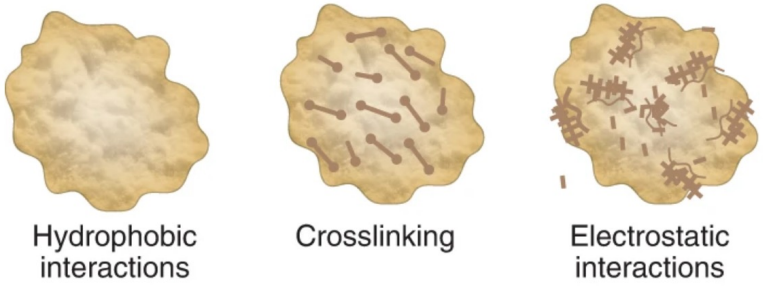


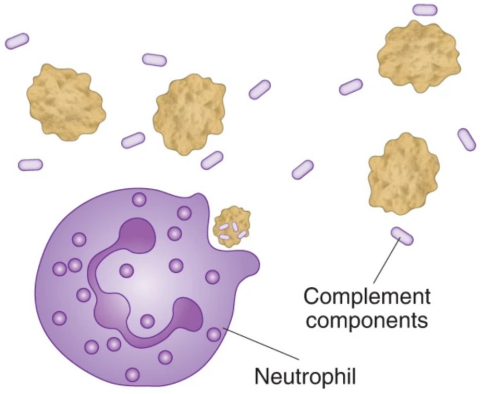
3) Targeting neutrophils in sepsis: Mitigating acute lung injury with antimicrobials



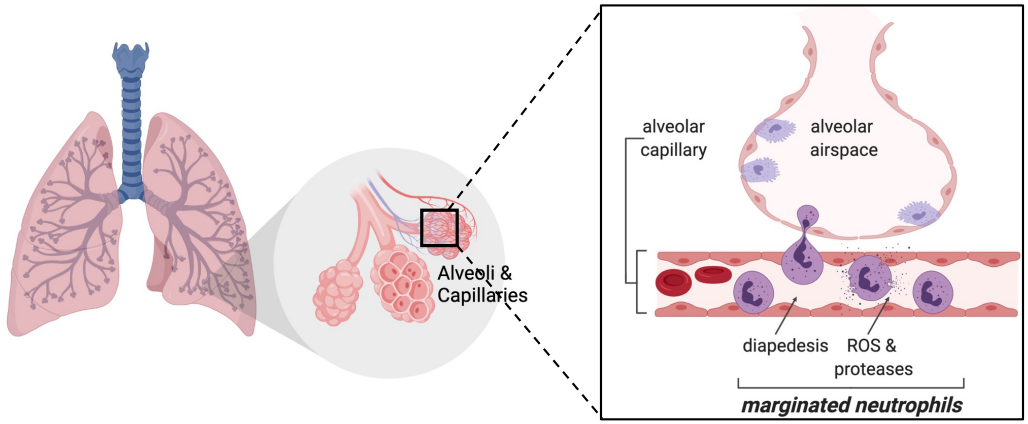
Nanoparticle design for neutrophil targeting

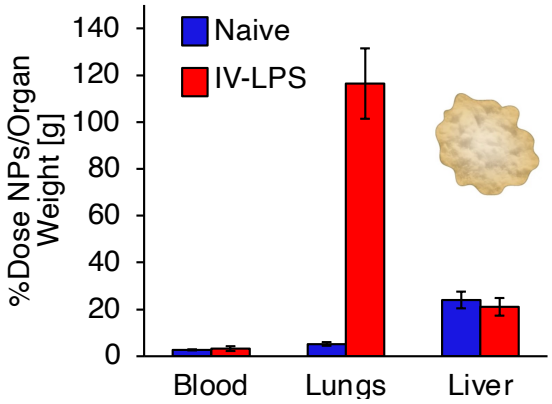
Motifs in arrangement of protein in nanoparticle structures predict serum protein-mediated uptake in neutrophils

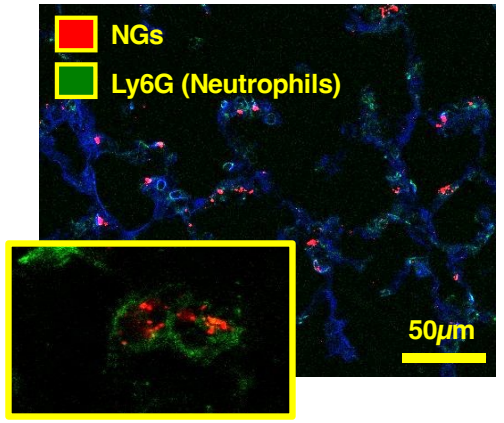




Neutrophil-targeting nanoparticle designs efficiently accumulate in inflamed lungs

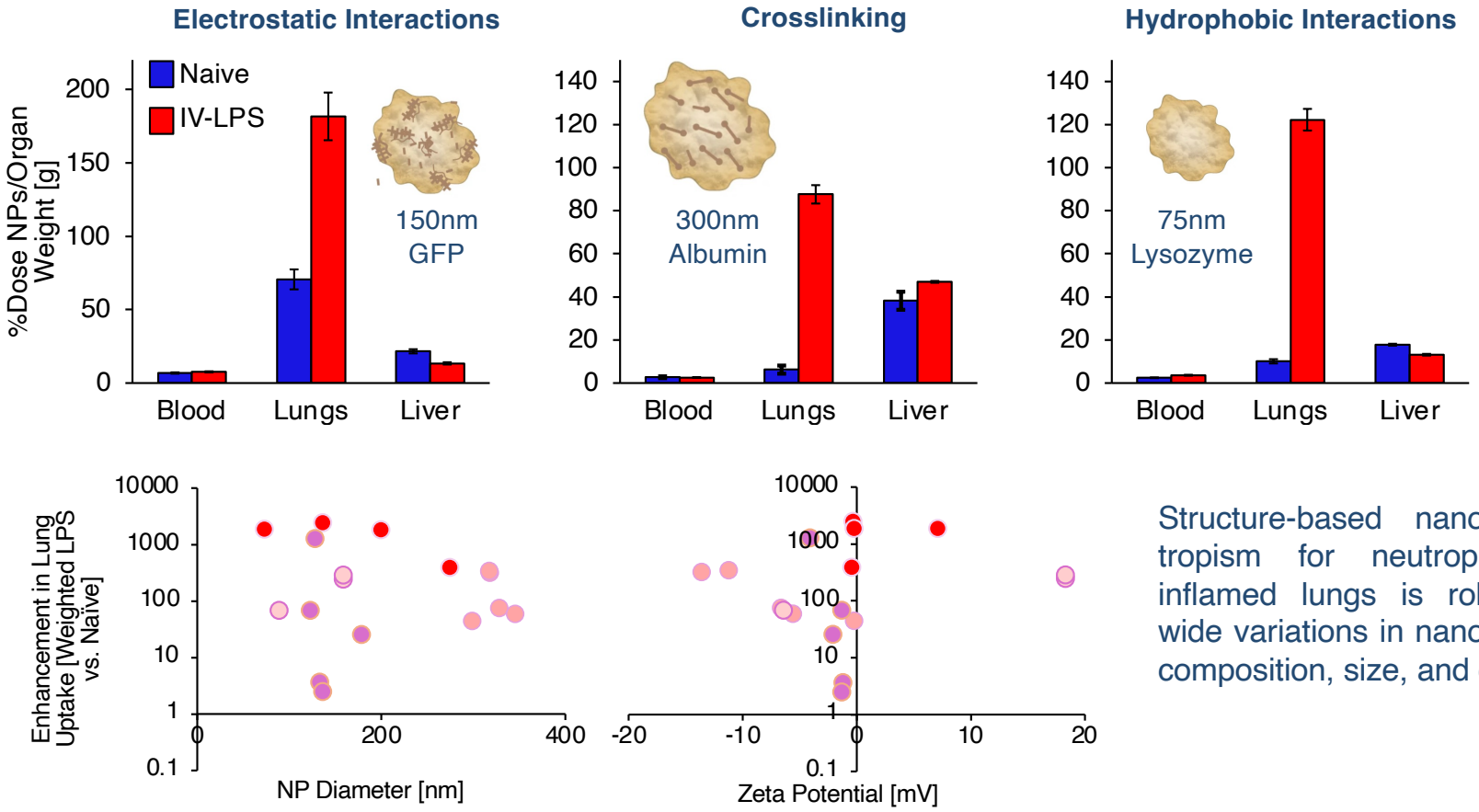






Myerson, Nature Nanotech 2022

Options for structure-based neutrophil targeting



Structure-based nanoparticle tropism for neutrophils in inflamed lungs is robust to wide variations in nanoparticle composition, size, and charge

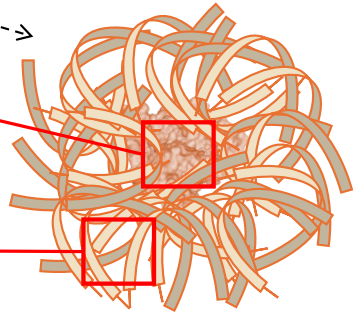
Myerson, Nature Nanotech 2022

Neutrophil targeting protein core-saccharide shell nanogels

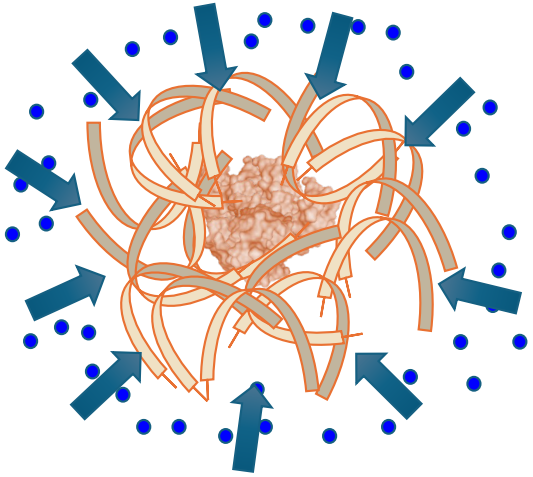
A prototype “hydrophobic interactions” neutrophil-tropic nanoparticle with adaptable structure/composition

Agglutinated lysozyme core
(gelation/hydrophobic interactions)

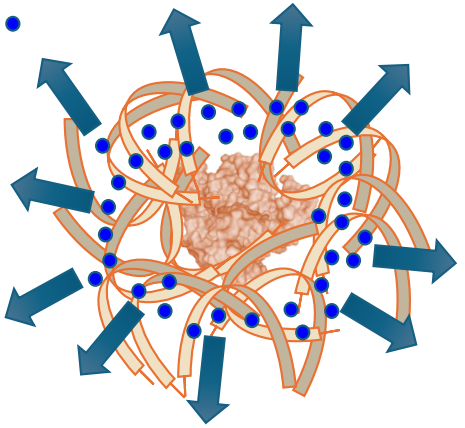
Diffuse dextran shell

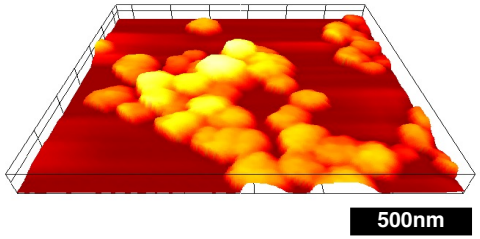


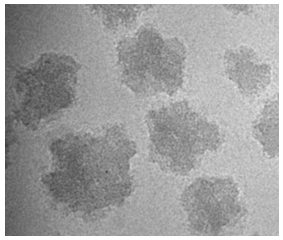
Osmotic Drug Loading in Drug Solution



Osmotic Drug Release in Drug-Free Solution



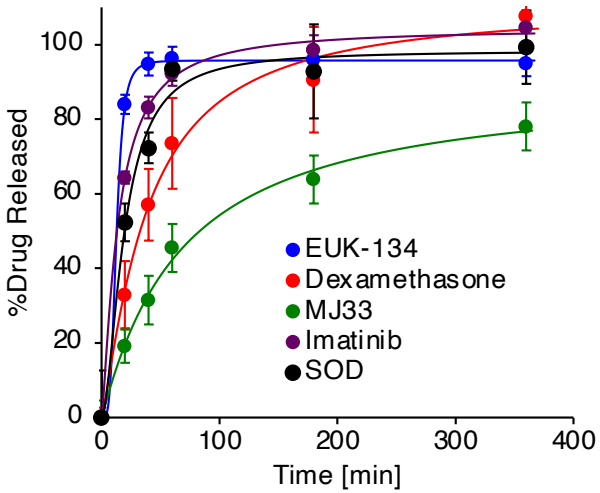




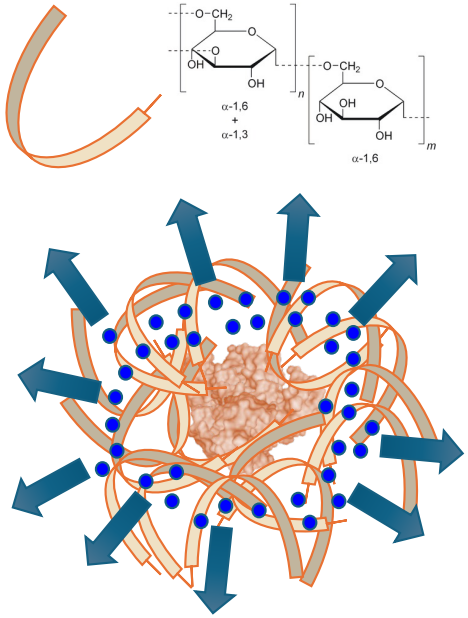
The dextran shell provides a permeable volume for loading and controlled release of various drugs

Changing the saccharide shell to change drug loading and release profiles

Burst release of drug loaded in the dextran shell

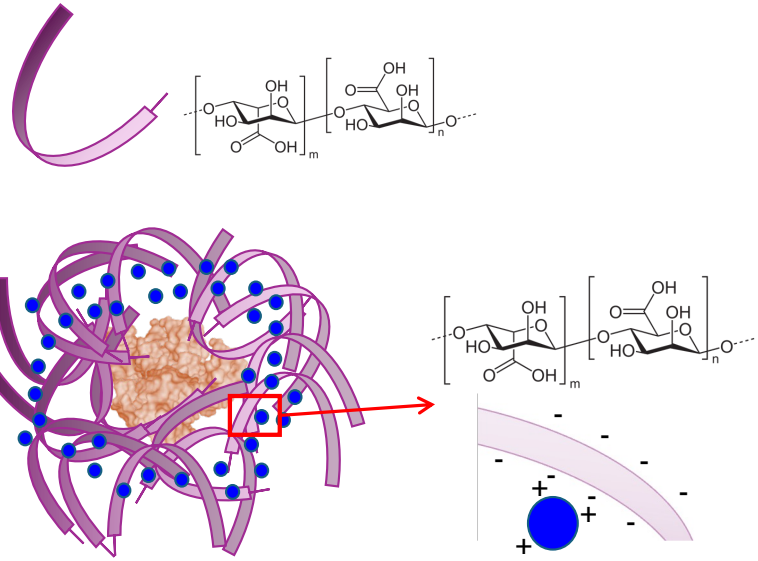


Dextran



Replacement of dextran with charged or functional polymers for stable drug loading

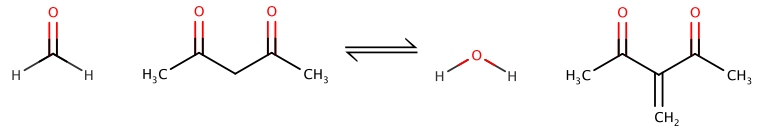
Alginate



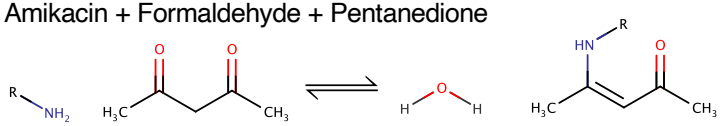
Loading aminoglycoside antibiotics in modified nanogels

Derivatization and quantification of Amikacin loading in alginate-lysozyme nanogels: ~50% drug loading by mass, stability in particles over 1 week storage

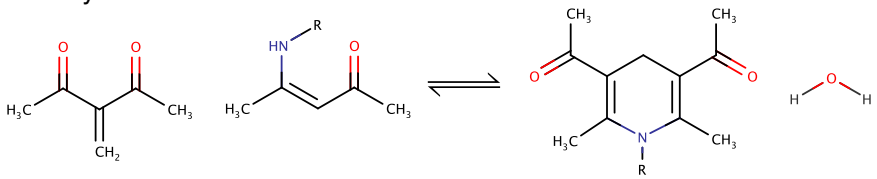
Formaldehyde + Pentanedione

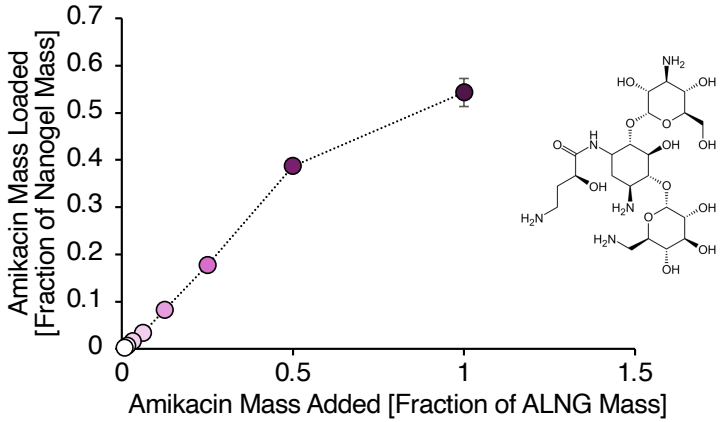


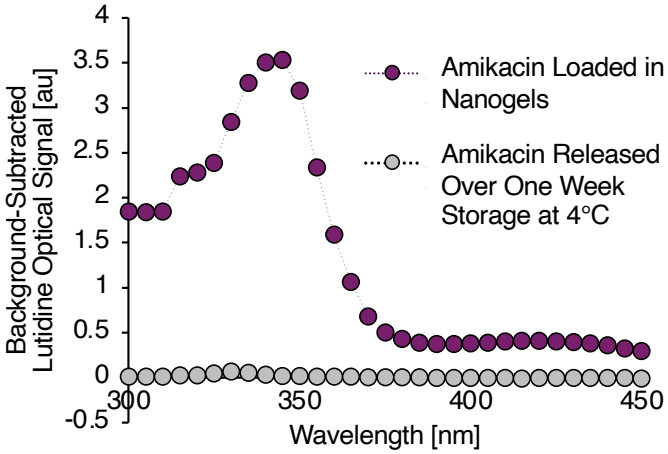
Amikacin + Formaldehyde + Pentanedione



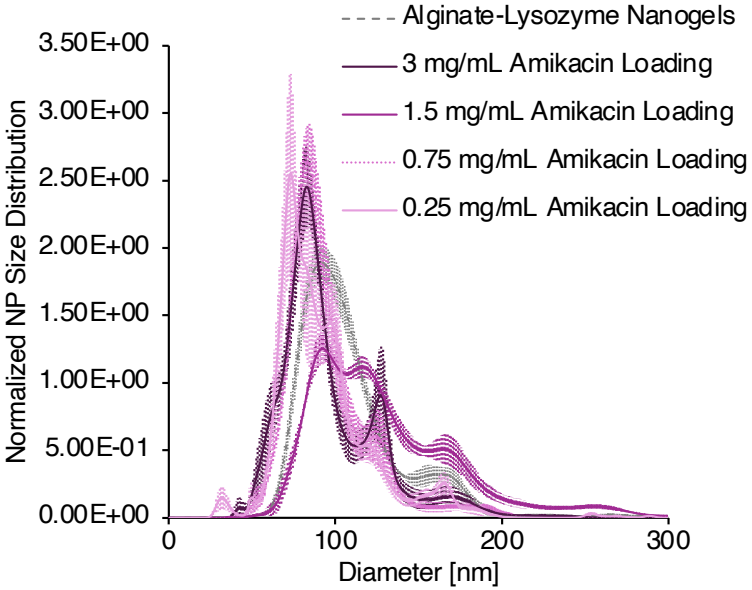
Dihydrolutidine derivative

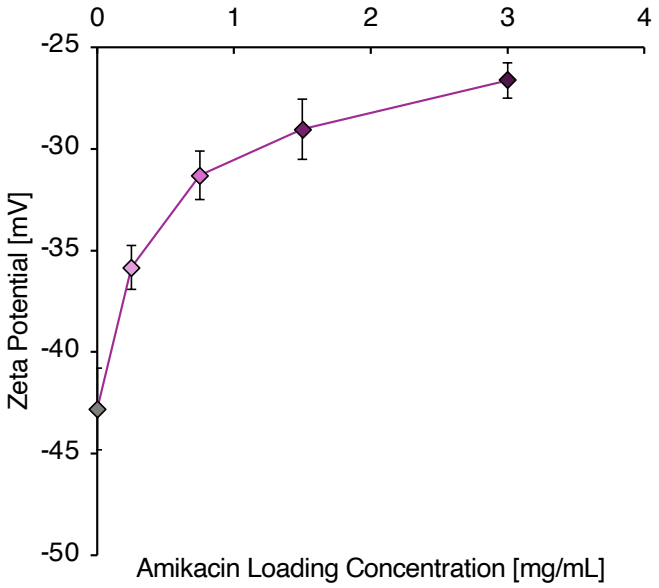


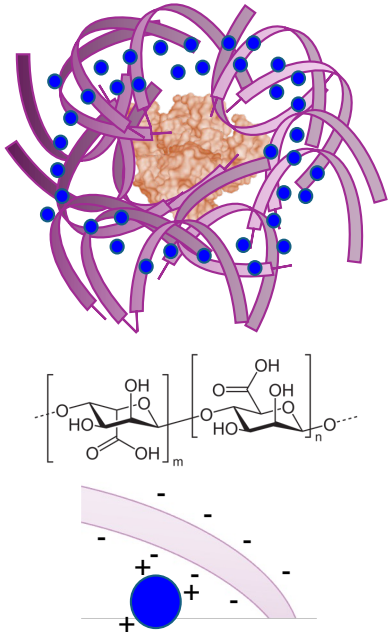




Loading aminoglycoside antibiotics in modified nanogels

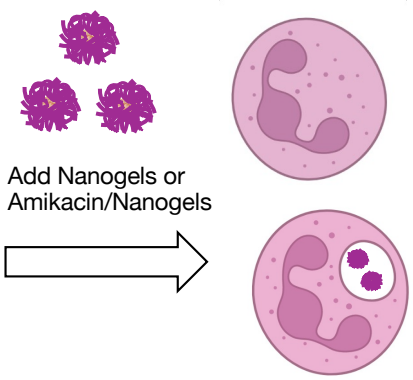


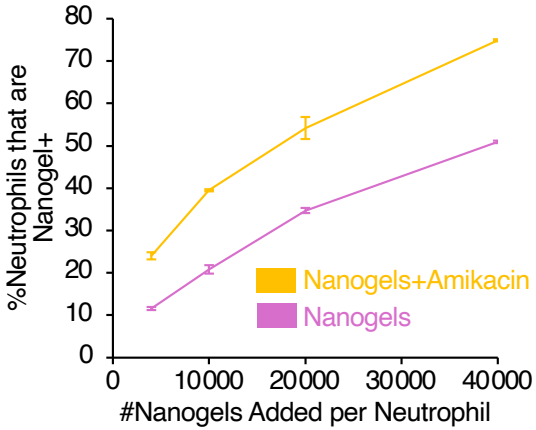


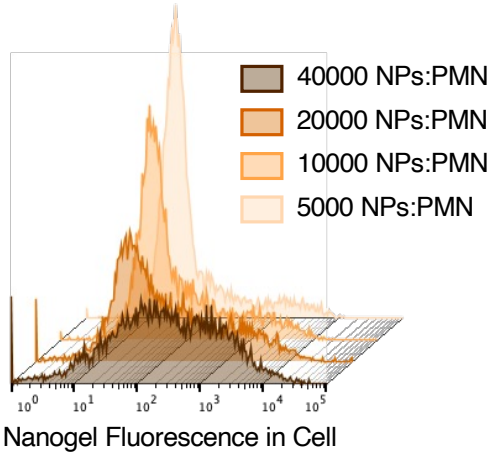


Amikacin loading causes no significant changes to nanoparticle size/concentration
Zeta potential shift reflects shielding of negatively charged alginate shell

Neutrophil targeting with modified nanogels + antibiotic

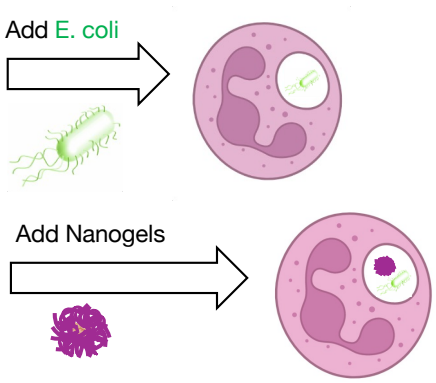


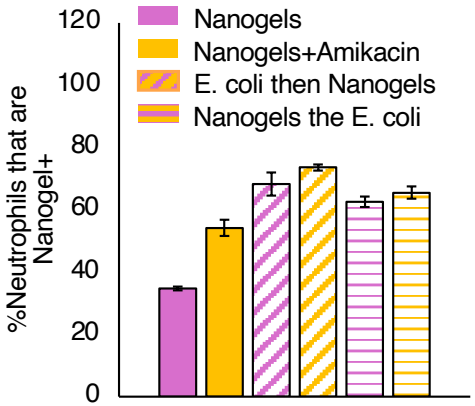


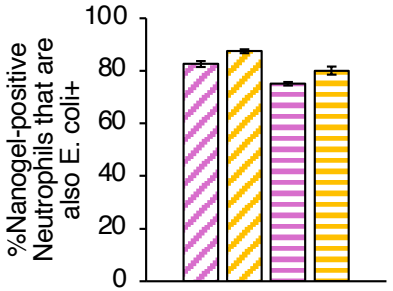


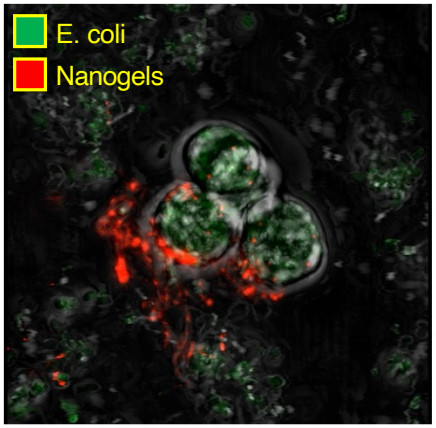
Nanogels+amikacin are taken up by neutrophils more avidly than ALNGs alone

Nanogels+amikacin effectively target neutrophils taking up E. coli, indicating potential delivery to sites of infections



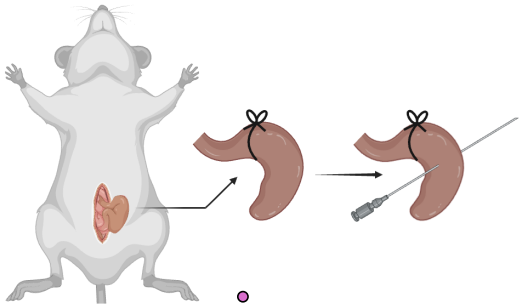


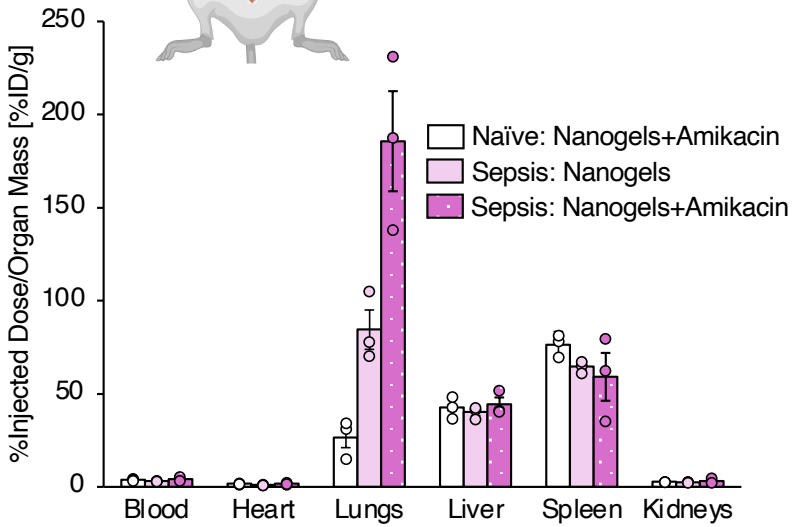


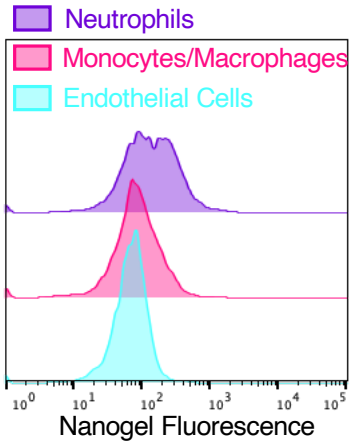


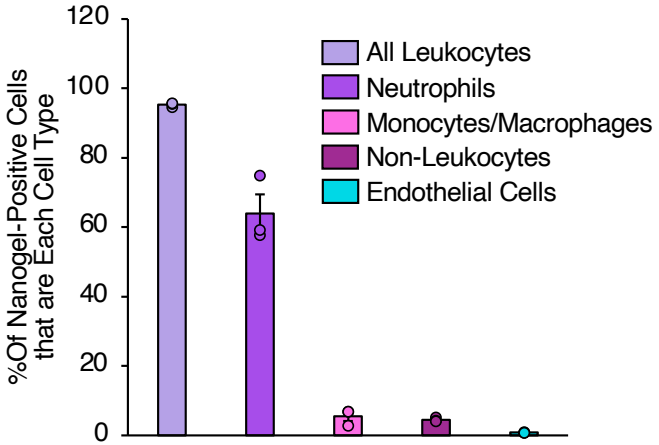
Targeting neutrophils in septic lungs with modified nanogels + antibiotic

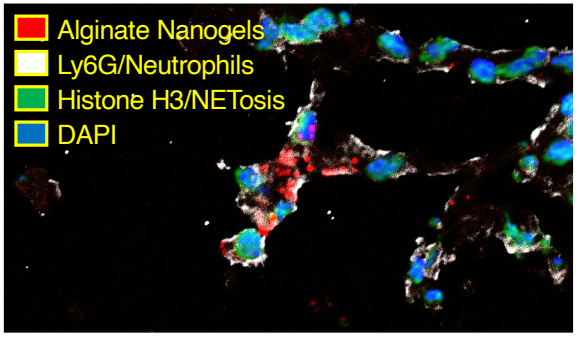
Peritoneal sepsis significantly increases lung uptake of nanogels+amikacin





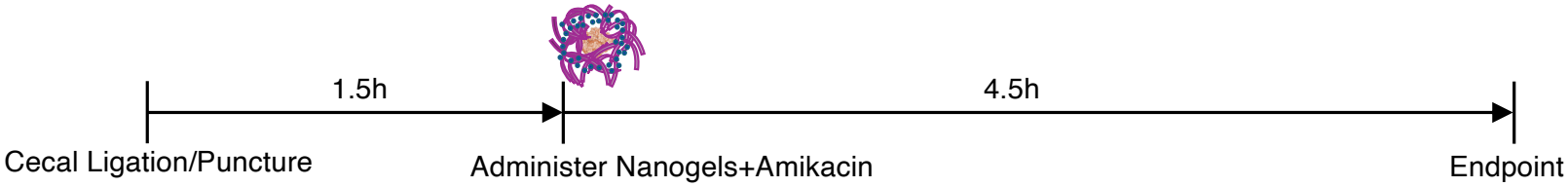


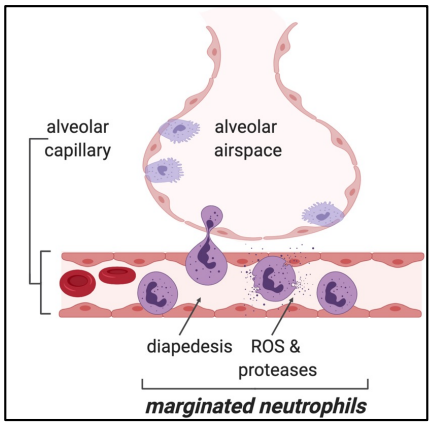


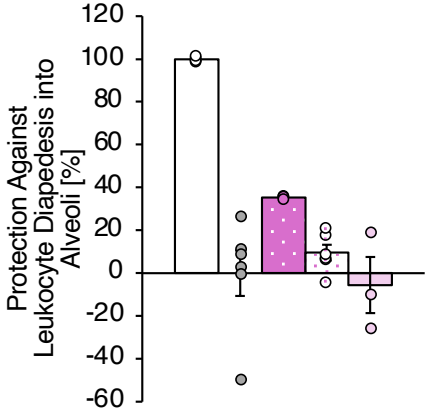


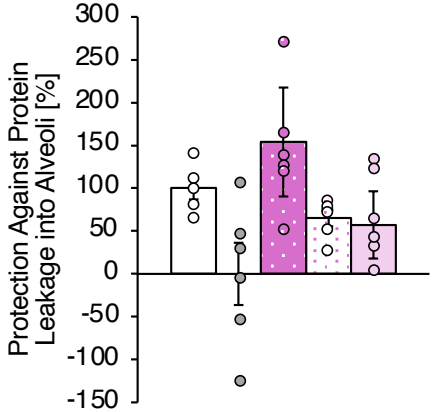
Neutrophils are the primary target for uptake of nanogels+amikacin in septic lungs

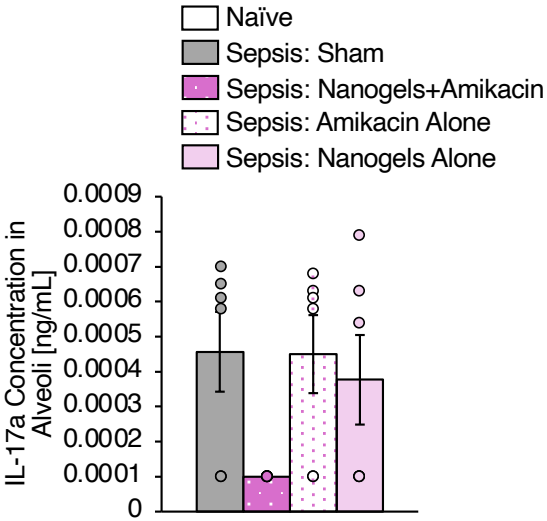
Therapeutic effects of nanogels + antibiotic in sepsis-induced acute lung injury











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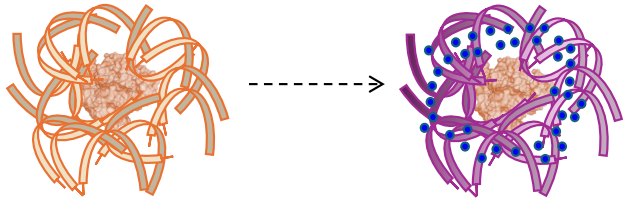
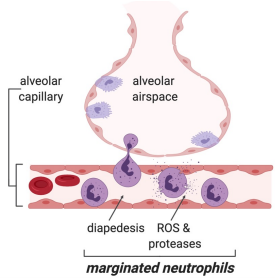


3) Targeting neutrophils in sepsis: Mitigating acute lung injury with antimicrobials



*Myerson
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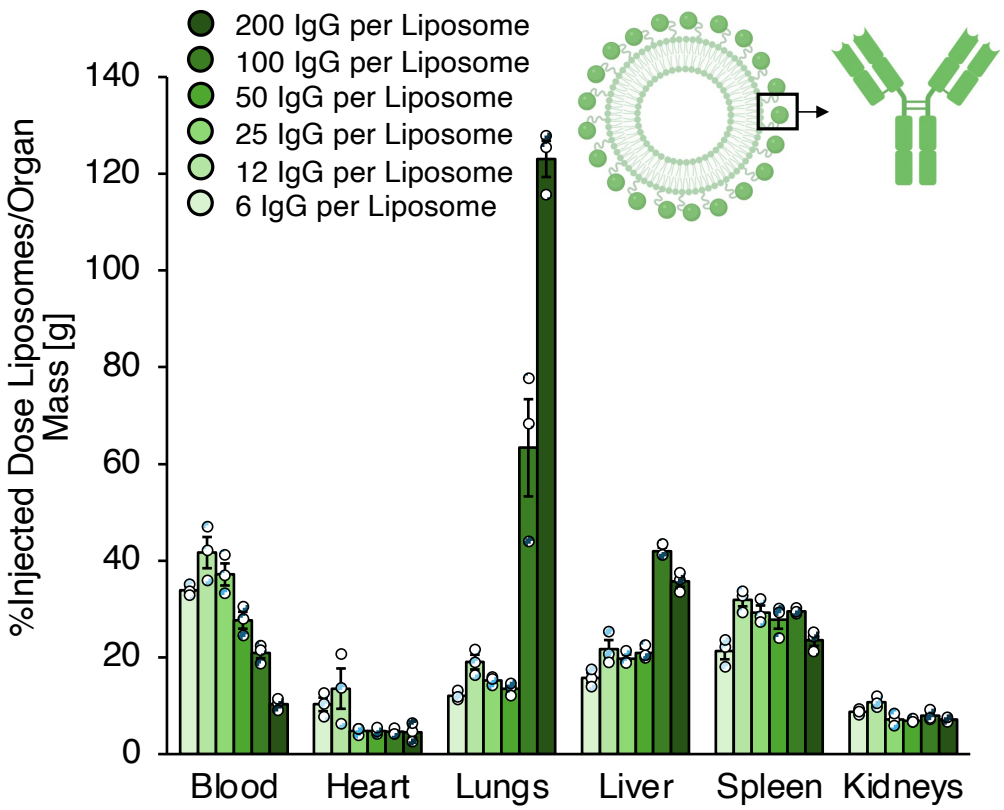
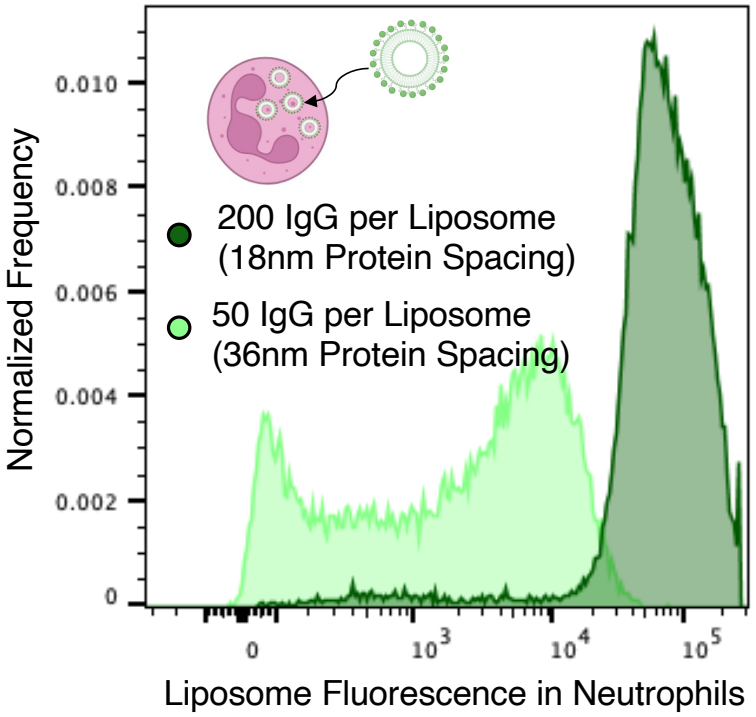
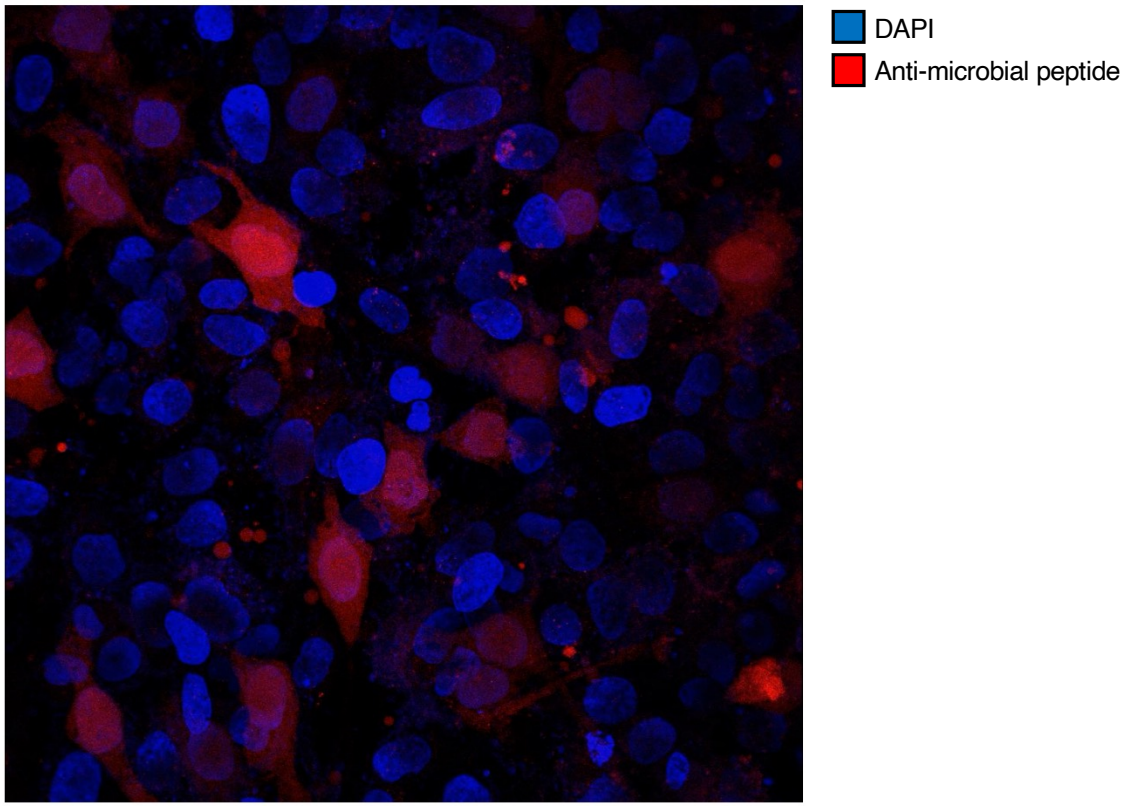
NCATS/NIH UL1TR001878

Backup Slides


200 IgG per Liposome
100 IgG per Liposome
50 IgG per Liposome
25 IgG per Liposome
12 IgG per Liposome
6 IgG per Liposome
%Injected Dose Liposomes/Organ
Mass [g]
140
120
100
80
60
40
20
0
Blood
Heart
Lungs
Liver
Spleen
Kidneys


Normalized Frequency
0.010
0.008
0.006
0.004
0.002
0
200 IgG per Liposome
(18nm Protein Spacing)
50 IgG per Liposome
(36nm Protein Spacing)
0
10^3
10^4
10^5
Liposome Fluorescence in Neutrophils


DAPI
Anti-microbial peptide