Engineering Polymer-Protein Interactions to Control the Polymersome Protein Corona

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Center for
NANOTHERAPEUTIC STRATEGIES IN THE CENTRAL NERVOUS SYSTEM
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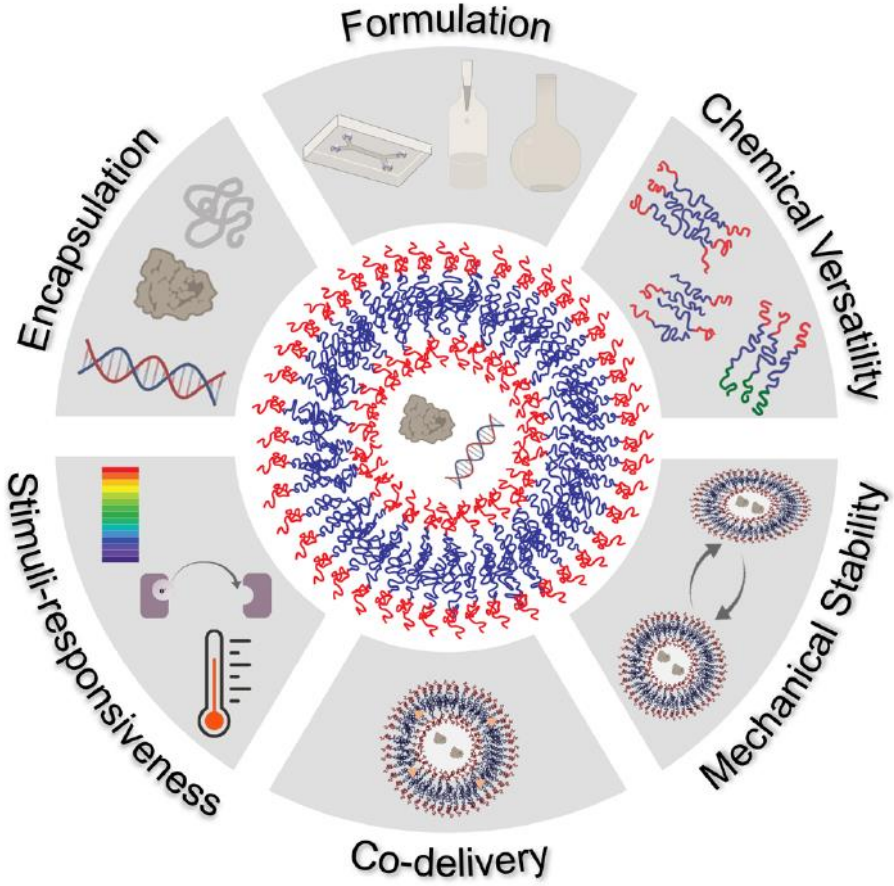
Polymersomes are versatile drug delivery vehicles

Polymersomes are nanoparticle vesicles developed from the formation of amphiphilic block copolymers

+ Self assemble into vesicles under with hydrophilic fraction between 25 and 45%
+ Clinically approved polymers
+ Tunable properties
+ High MW payloads or multiple payloads



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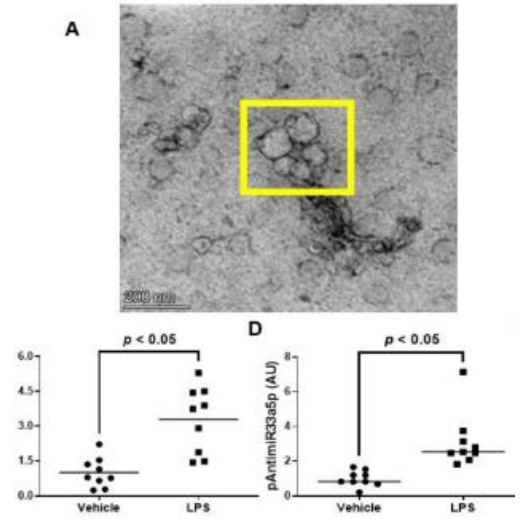
Iqbal, S.; Blenner, M.; Alexander-Bryant, A.; **Larsen, J.** ACS Biomaterials Science and Engineering. 2020. DOI: 10.1021/acs.biomac.9b01754

Polymersomes are versatile drug delivery vehicles



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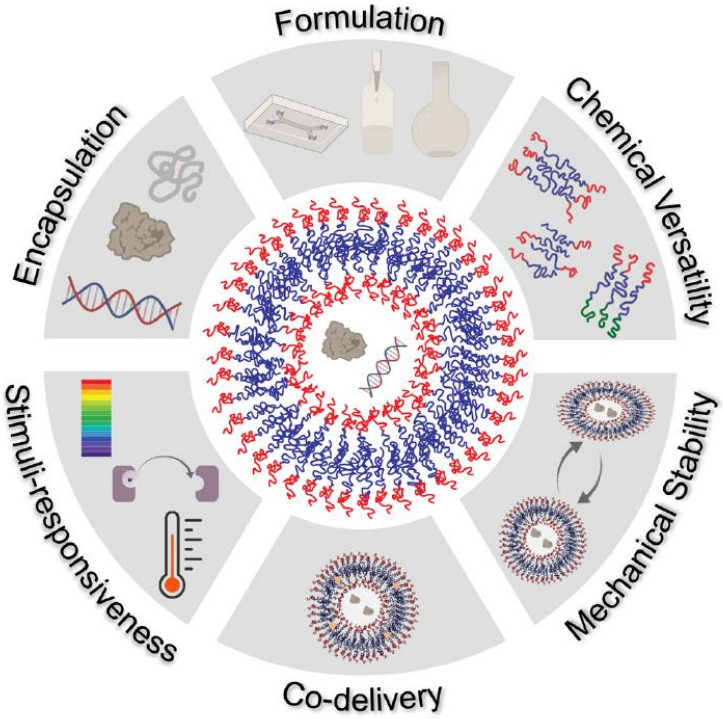

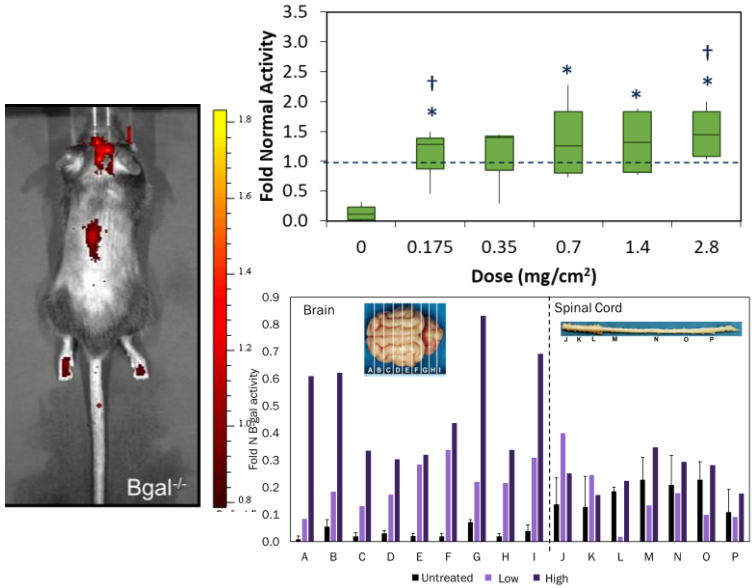

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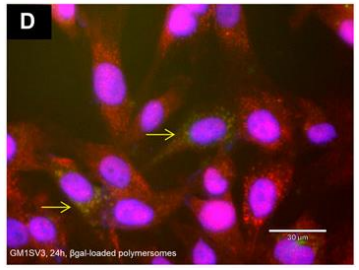
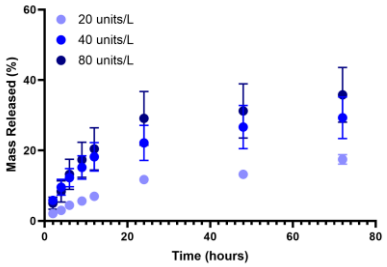
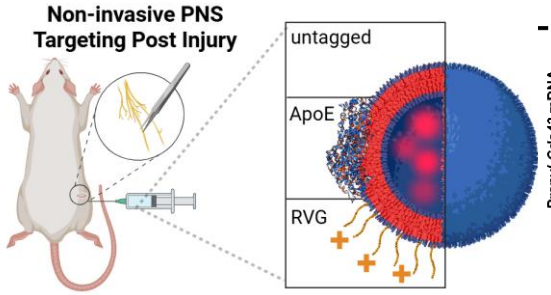
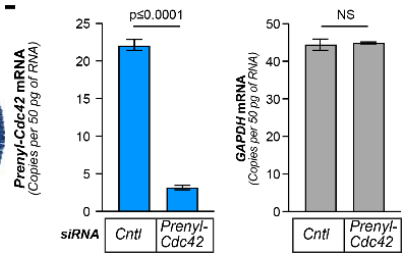




10.3389/fceng.2022.997607
10.2217/nnm-2023-0300





10.1021/acs.bioconjchem.5c00072
10.1101/2025.02.06.636857
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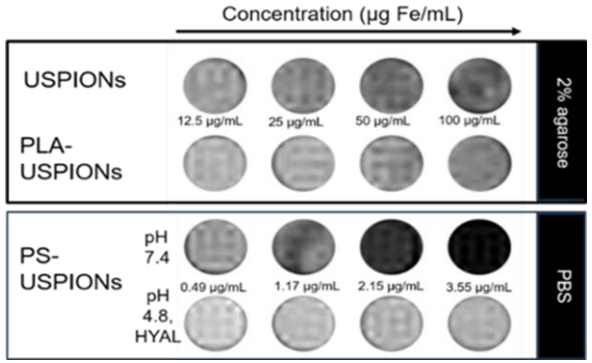
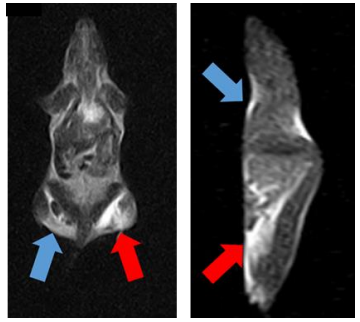
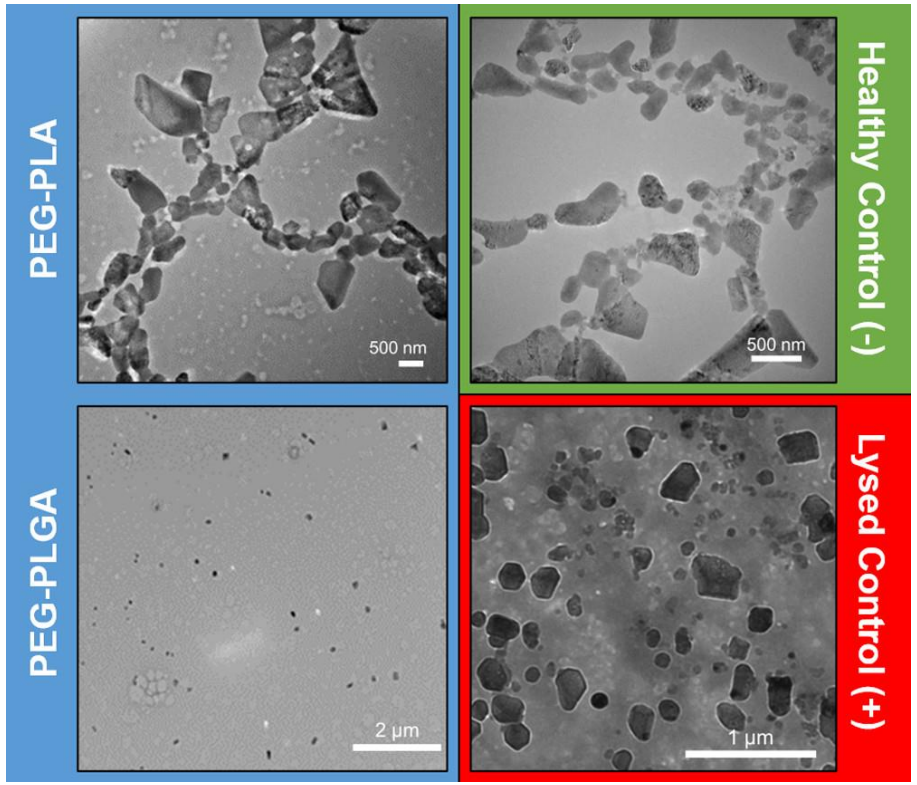
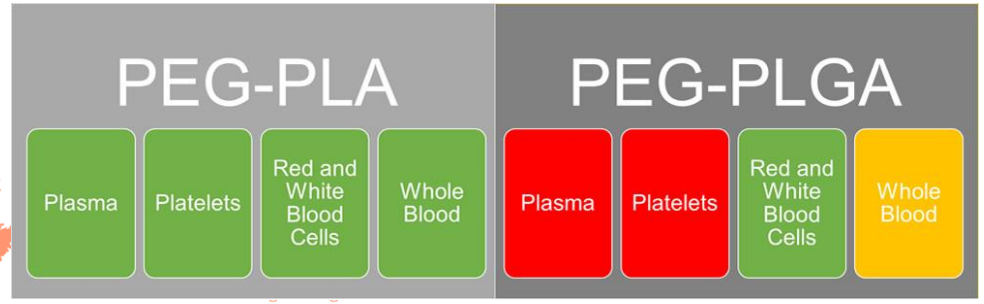


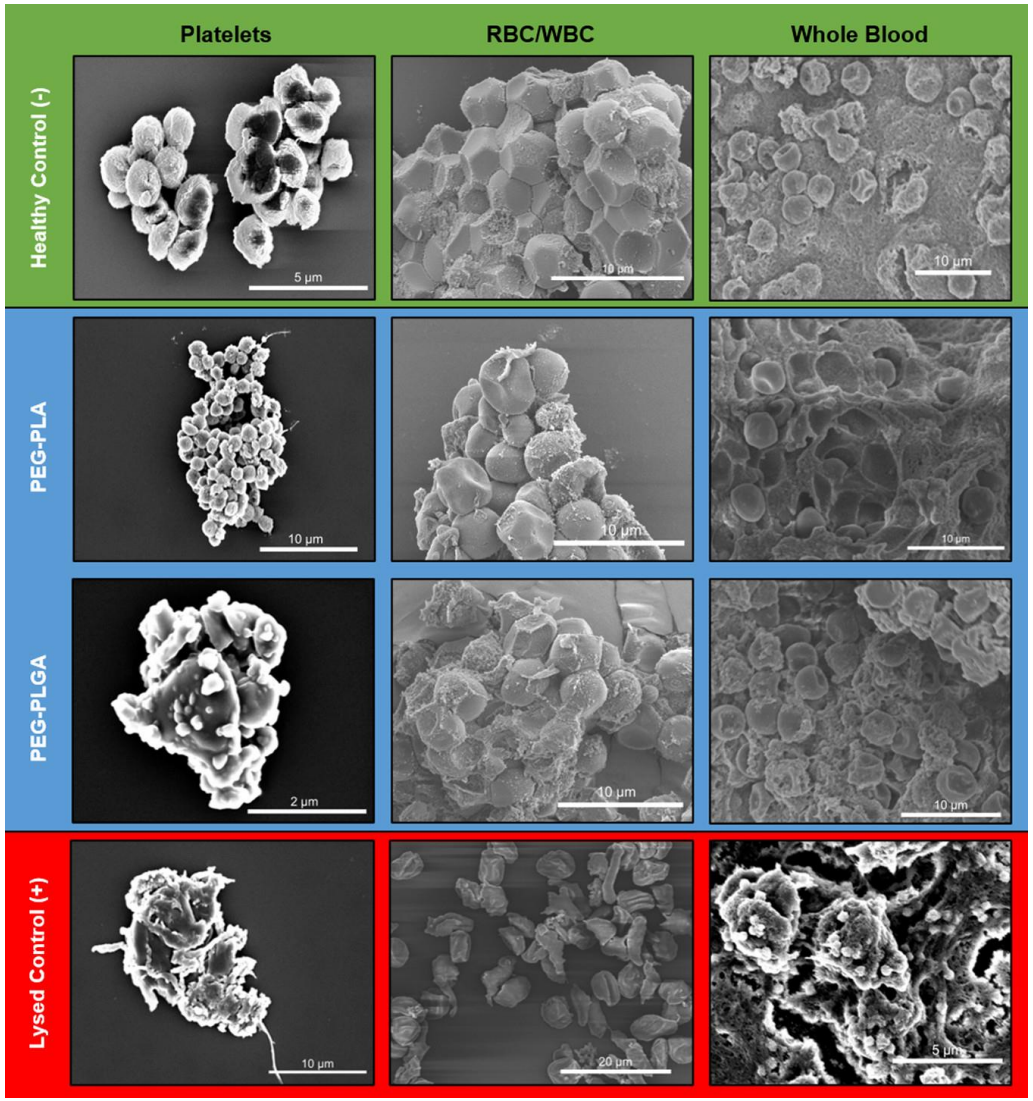


10.1039/D4BM01583E

Polymersomes can be effective but are also synthetic.

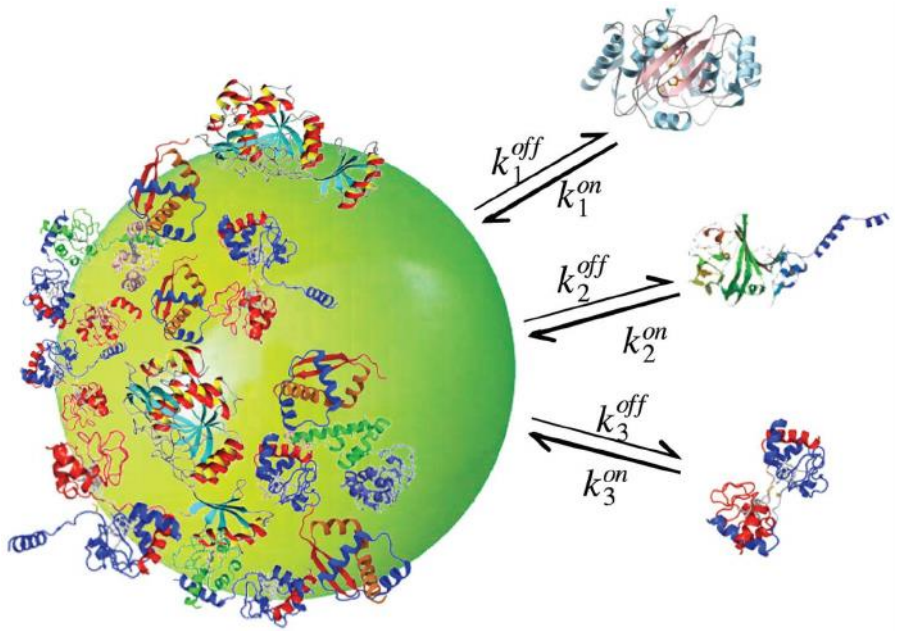






Maghak, L.; **Larsen, J.** ACS Biomaterials Science and Engineering. 2020. DOI: 10.1021/acsbiomaterials.0c00680

A protein corona forms around polymersomes upon injection.



Biomolecular identity of nanoparticles changes upon injection, which impacts the cellular interactions.

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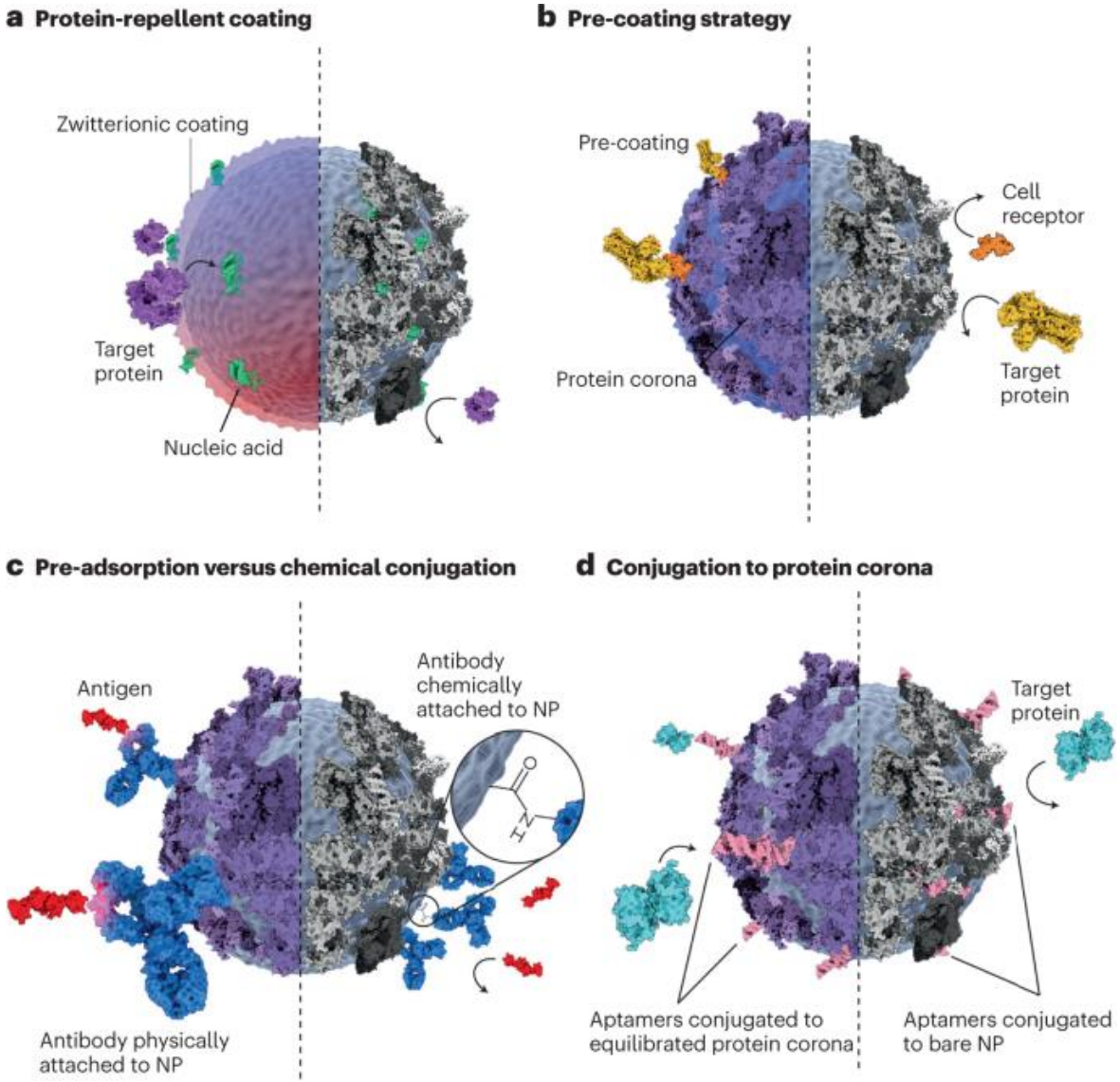
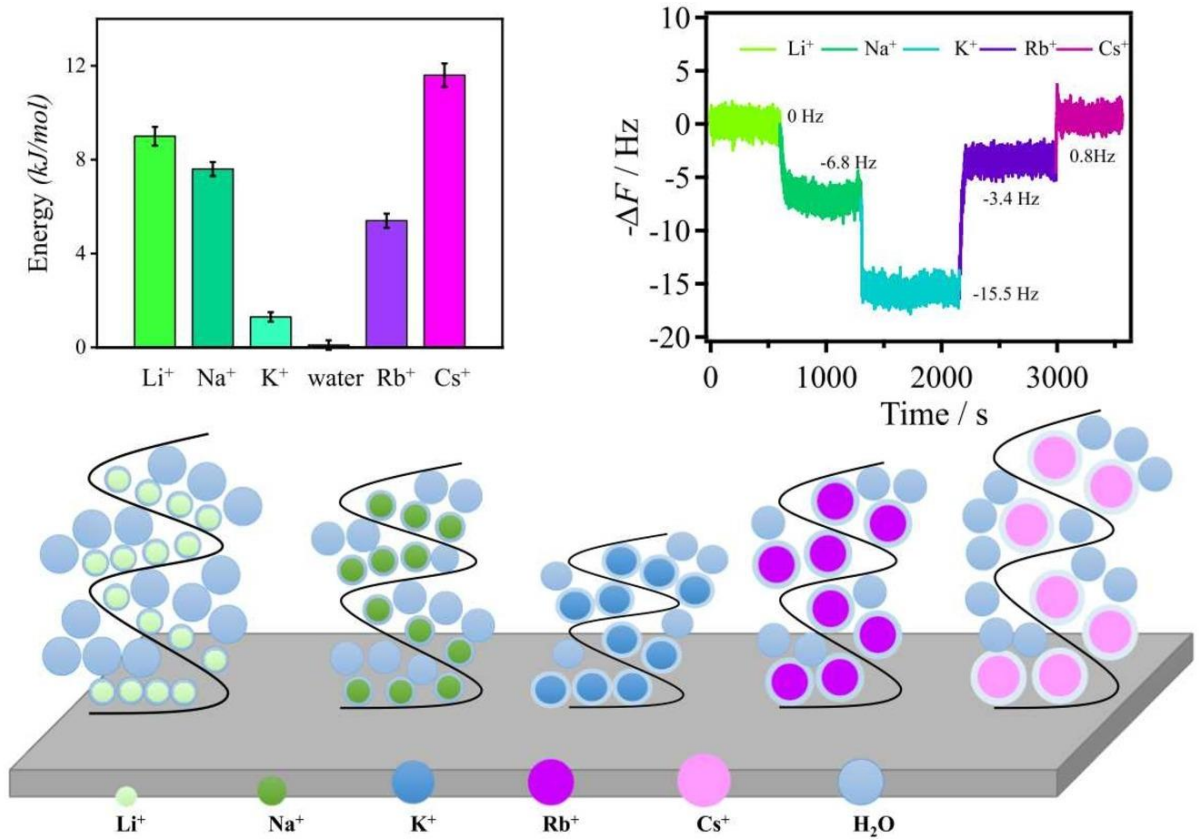
Sahneh, F., et. al. *PLoS One* (2013).

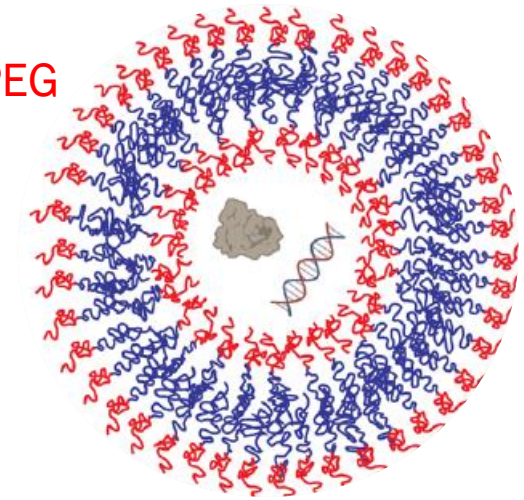


Mahmoudi, M., et. al. *Nat Rev Mater* (2023).

Cations impact polyethylene glycol conformation and hydration.



Yu, et al. Colloids and Surfaces A, 2024.



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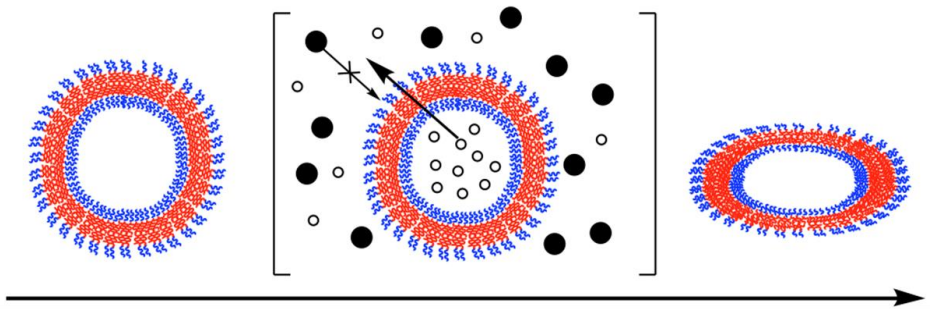
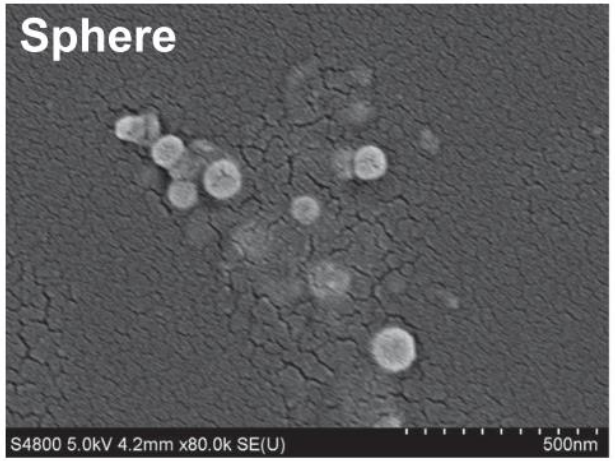
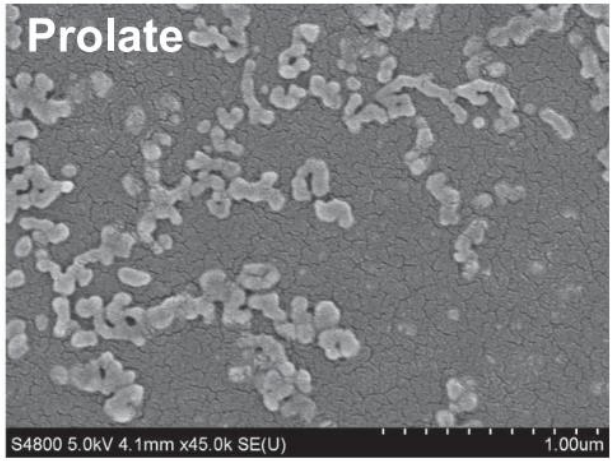
PEGPLA Polymersomes are Modulated using Osmotic Pressure

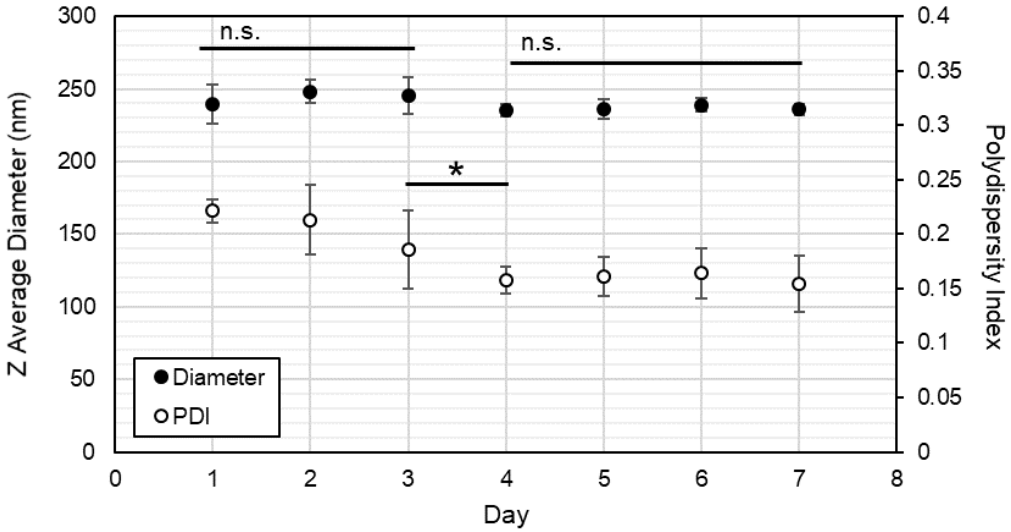








NaCl	Diameter ± SD (nm)	Zeta Potential ± SD (mV)	PDI ± SD
-	145.5 ± 6.1	-41.6 ± 1.7	0.05 ± 0.02
+	190.9 ± 1.3	-19.3 ± 1.6	0.12 ± 0.01



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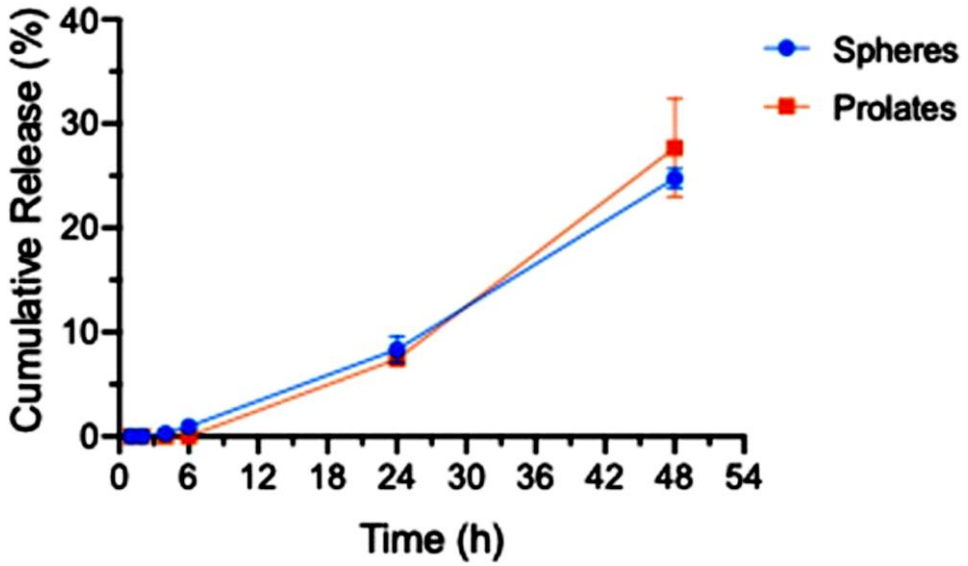
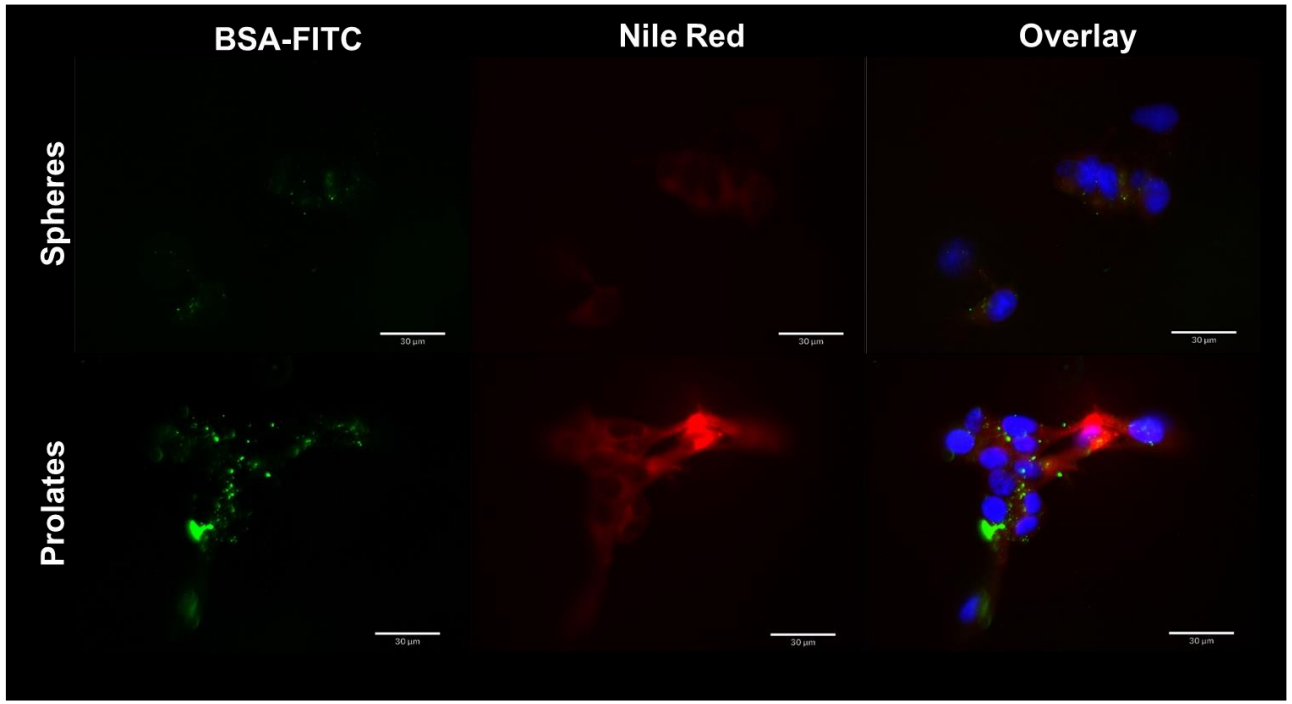
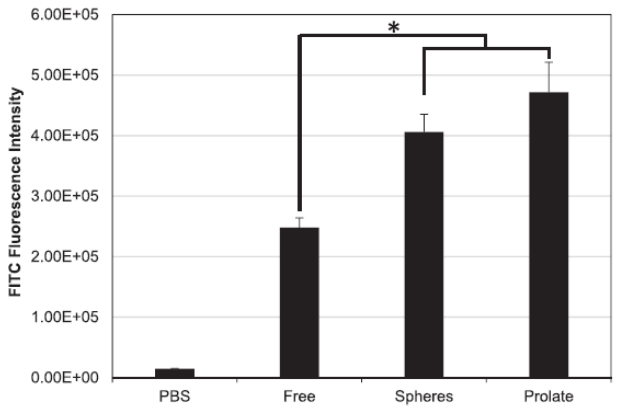
L'Amoreaux, N.; Ali, A.; Iqbal, S.. **Larsen, J.** Nanotechnology. 2020. doi: 10.1088/1361-6528/ab6bf1

Prolates encapsulate and deliver more payloads to cells.





NaCl	Shape	Nile Red		BSA-Fluorescein	
		EE ± SD (%)	Loading Content (μg dye/mg polymer)	EE ± SD (%)	Loading Content (μg dye/mg polymer)
-	Sphere	5.2 ± 0.4	1.7 ± 0.004	13.9 ± 1.2	46.5 ± 4.0
+	Prolate	10.9 ± 0.3	3.6 ± 0.1	23.6 ± 9.4	78.5 ± 31.4



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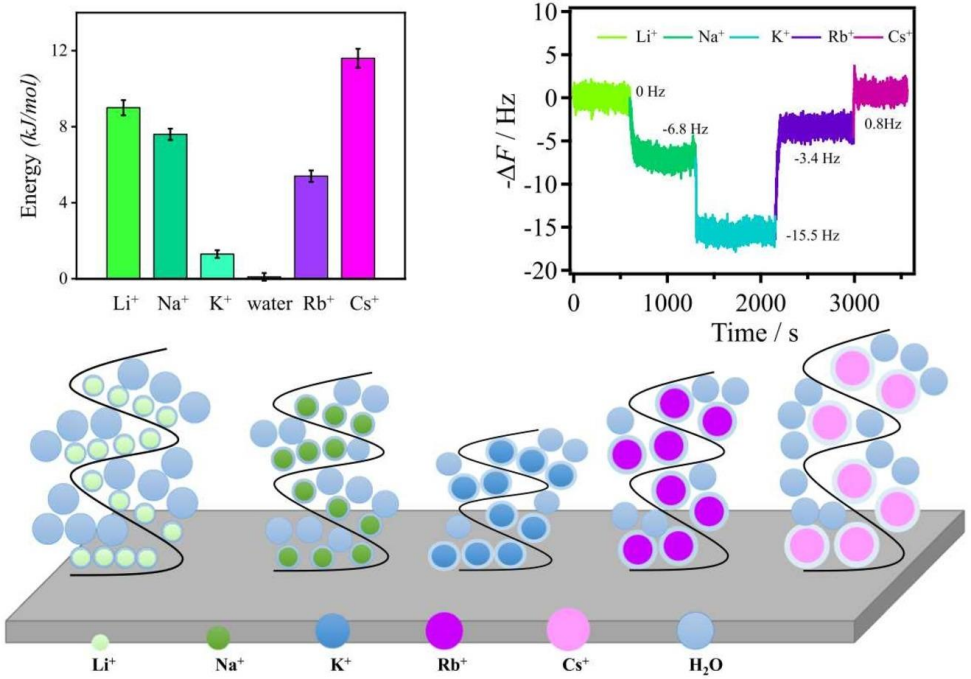
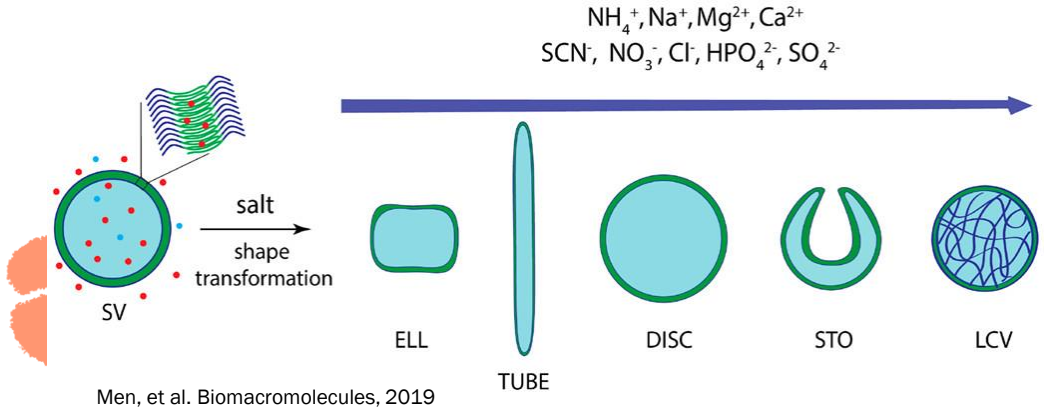
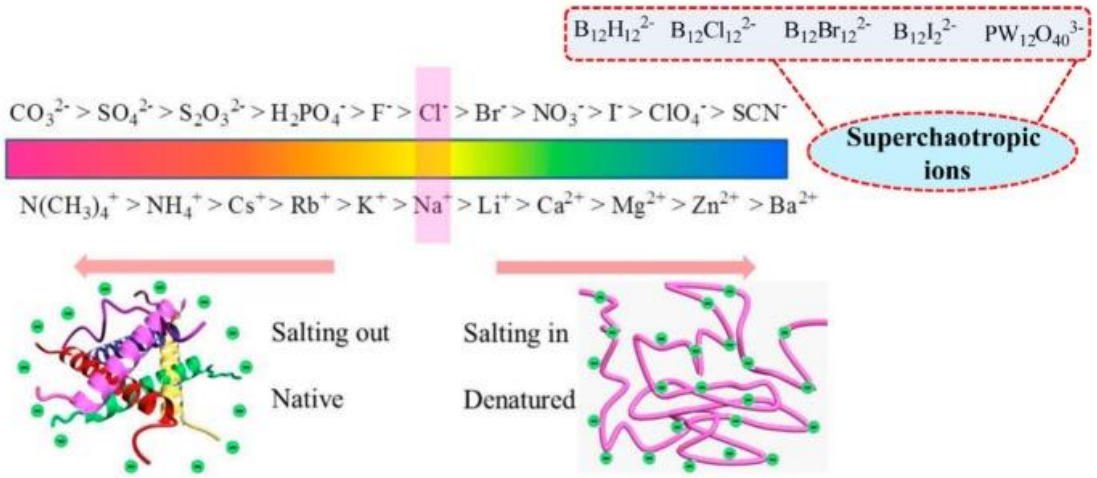
Chaotropic salts impact PEG and protein conformation.



Yu, et al. Colloids and Surfaces A, 2024.



Men, et al. Biomacromolecules, 2019

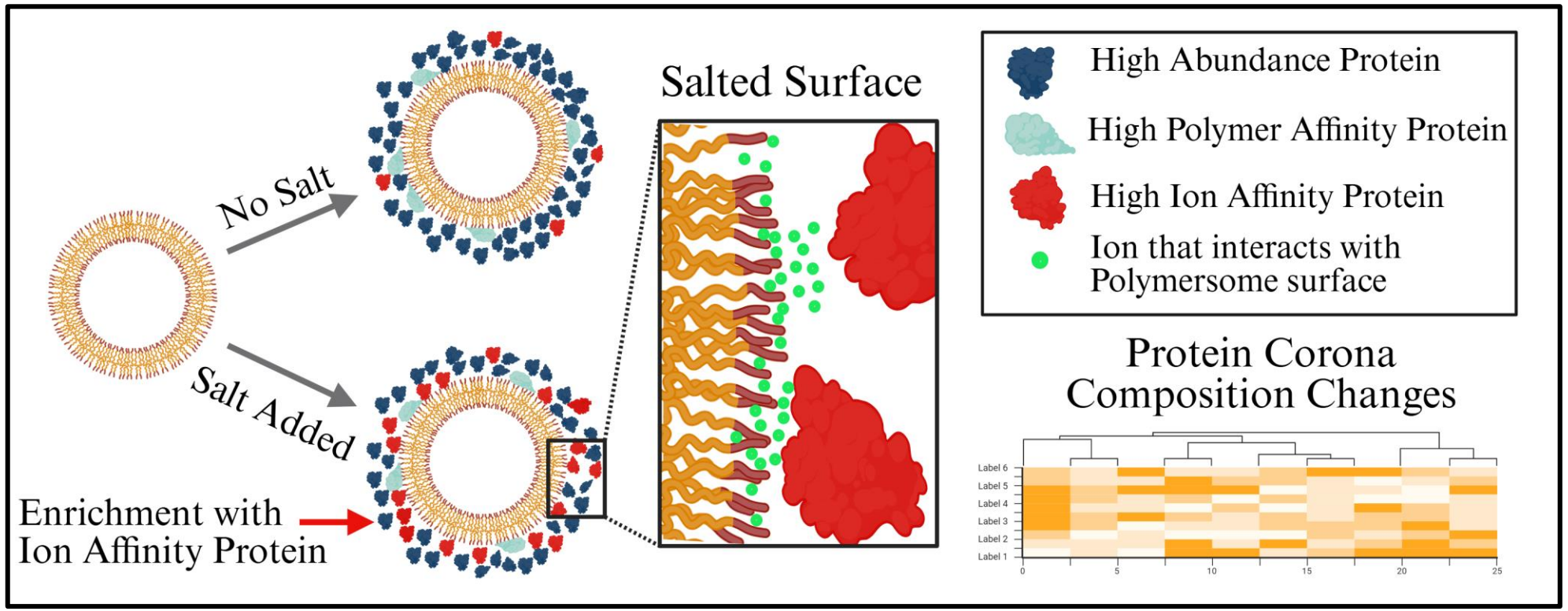


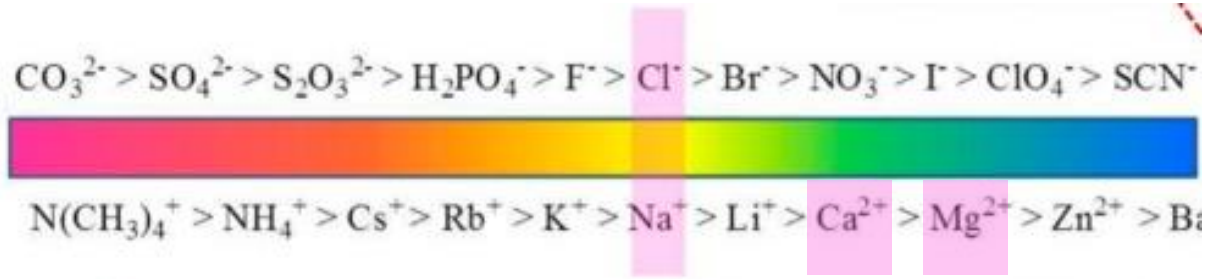
Kang, et al. ACS Omega. 2020

Hofmeister series salts change protein **and** PEG conformation.

Was the shape change improving uptake or was uptake improved due to an **altered protein corona?**

Chaotropic salts impact PEG and protein conformation.





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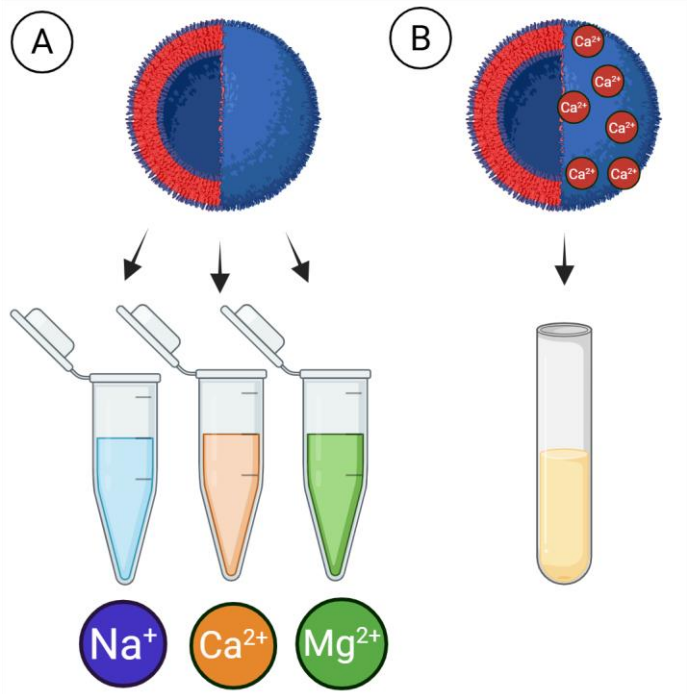
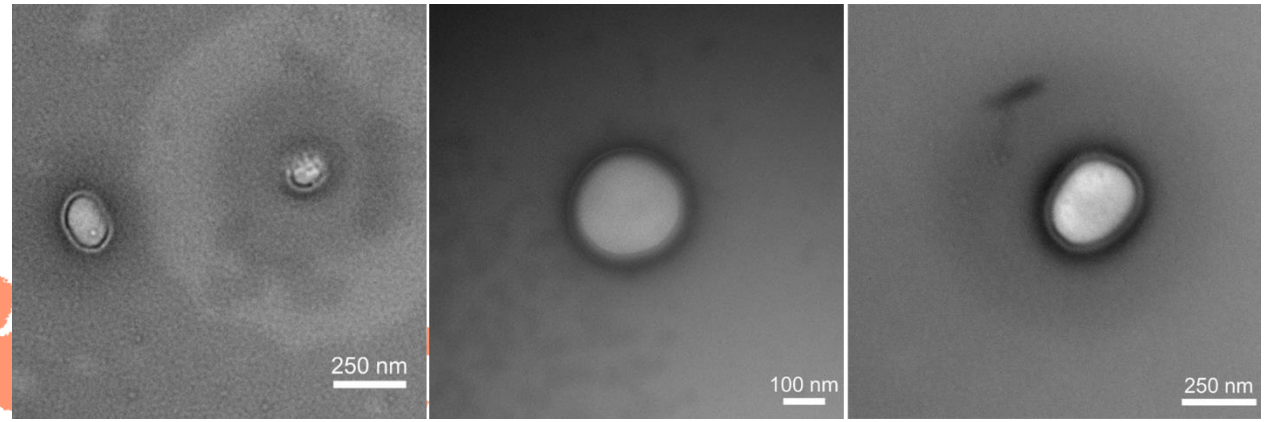
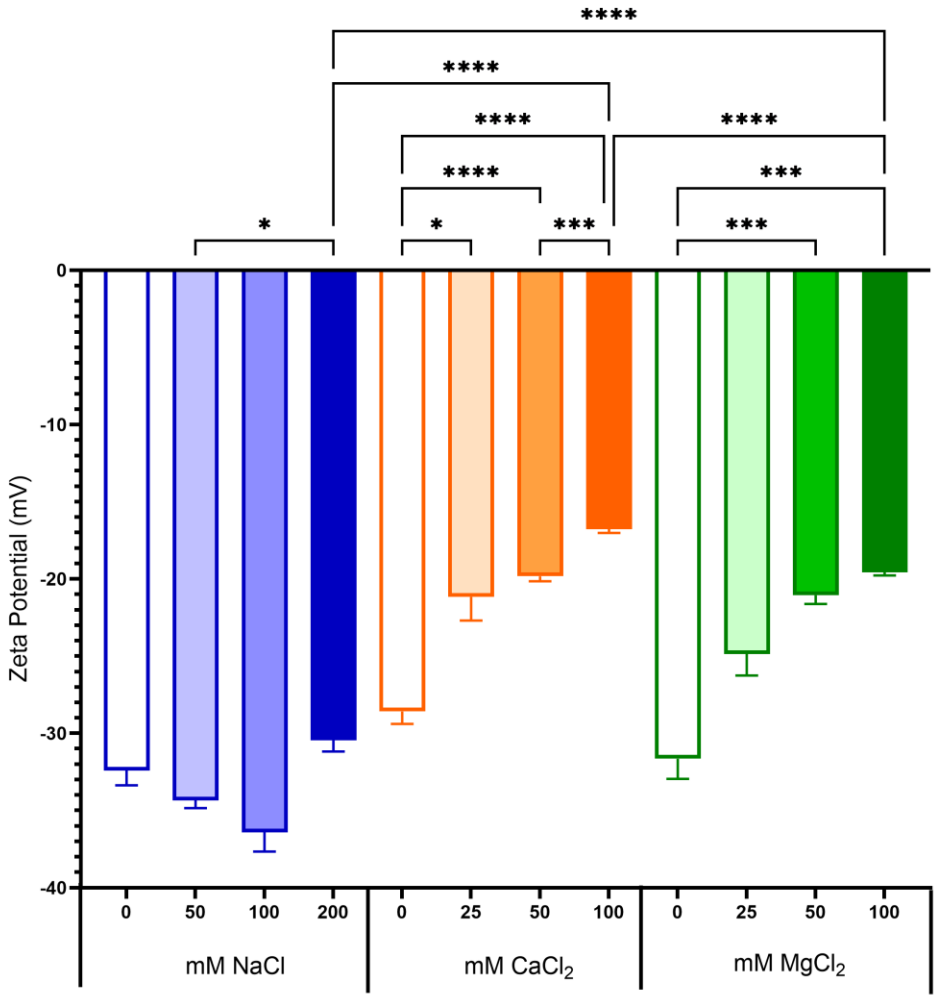
Tabah, O.; Nichols, D.; Blake, A.; Witt, G. **Larsen, J.** Journal of Colloid and Interface Science. 2025.

Different salts had varying affinities for PEG-b-PLA polymersomes.



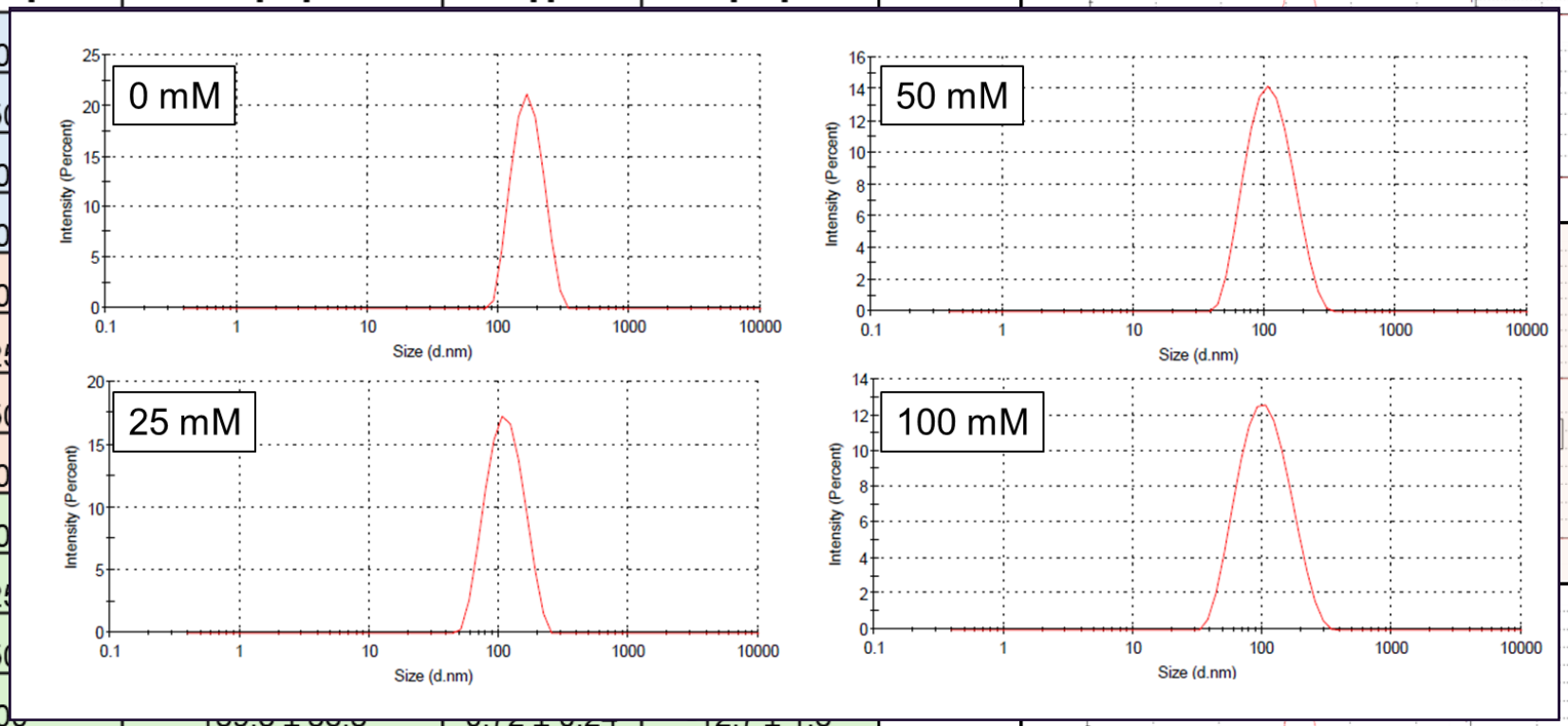


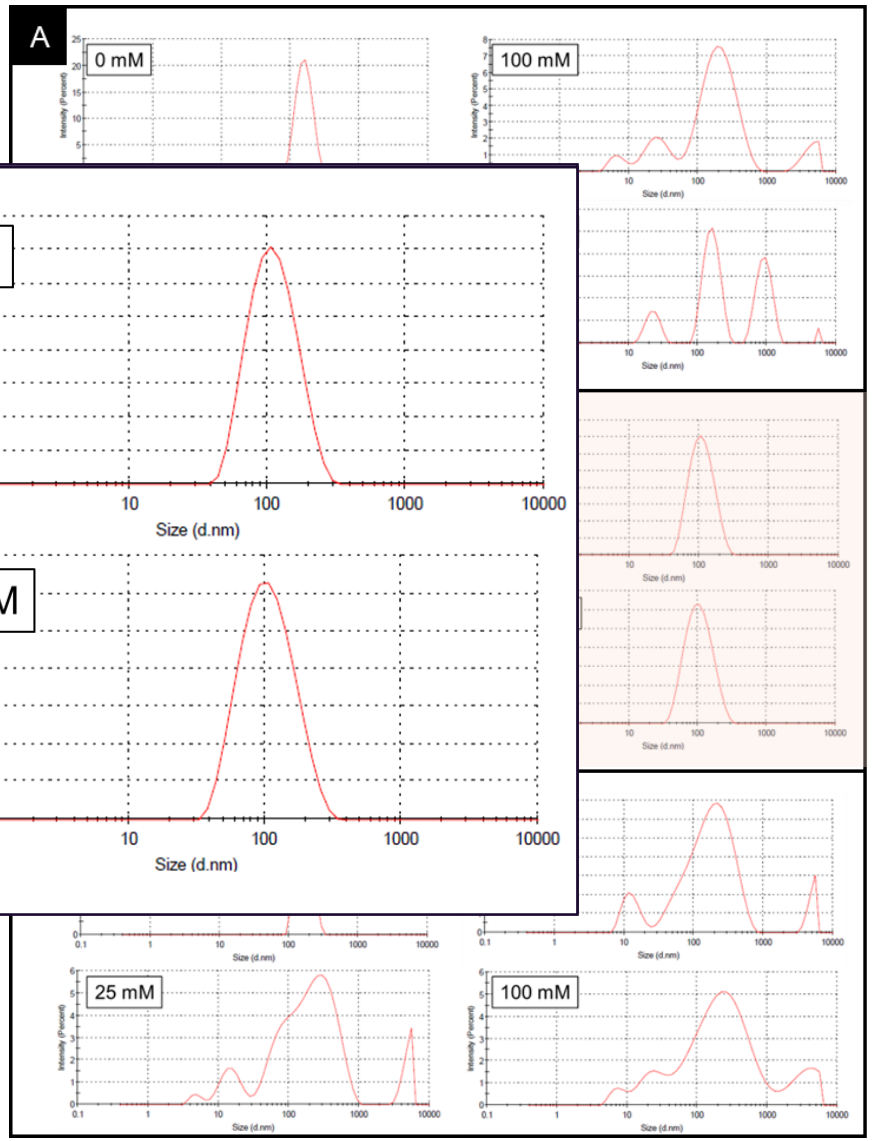


Tabah, O.; Nichols, D.; Blake, A.; Witt, G. **Larsen, J.** Journal of Colloid and Interface Science. 2025.

Only Ca^{2+} formed a predominantly hard protein corona.

Salt	Concentration [mM]	Post Serum Incubation: Z-average Diameter [nm]	PDI [-]	Zeta Potential [mV]
NaCl	0			
	50			
	100			
	200			
$CaCl_2$	0			
	25			
	50			
	100			
$MgCl_2$	0			
	25			
	50			
	100			





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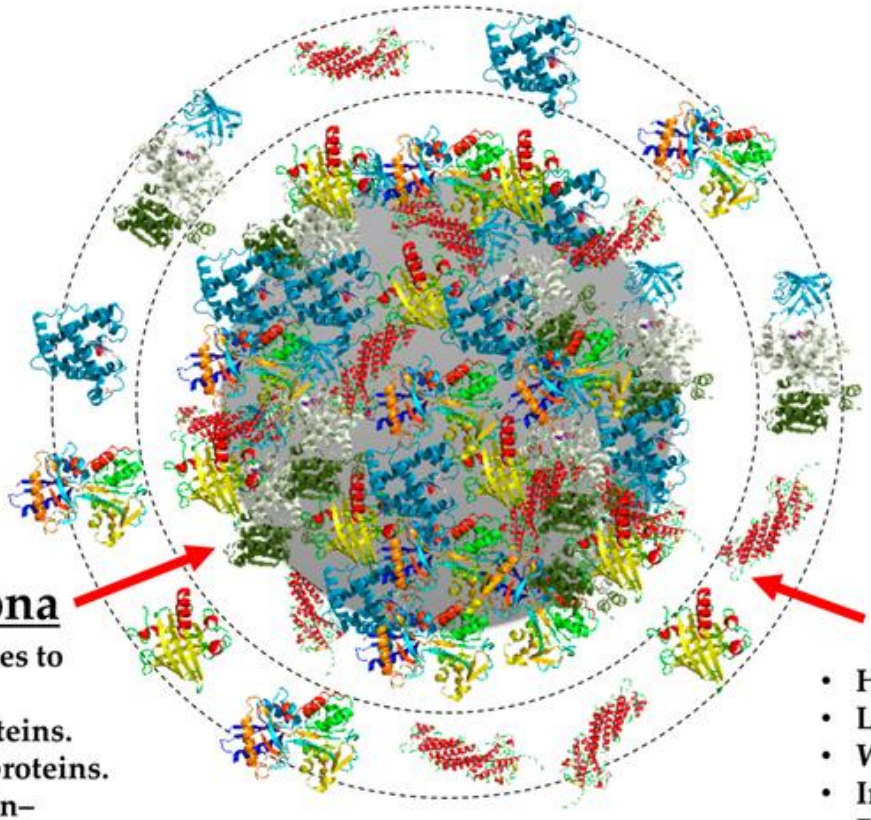

Hard Corona

- Seconds to minutes to form.
- High affinity proteins.
- Strongly bound proteins.
- Interaction Protein–Nanoparticle.
- Low dissociation constant.

Soft Corona

- Hours to form.
- Low affinity proteins.
- Weakly bound proteins.
- Interaction Protein–Protein.
- High dissociation constant.

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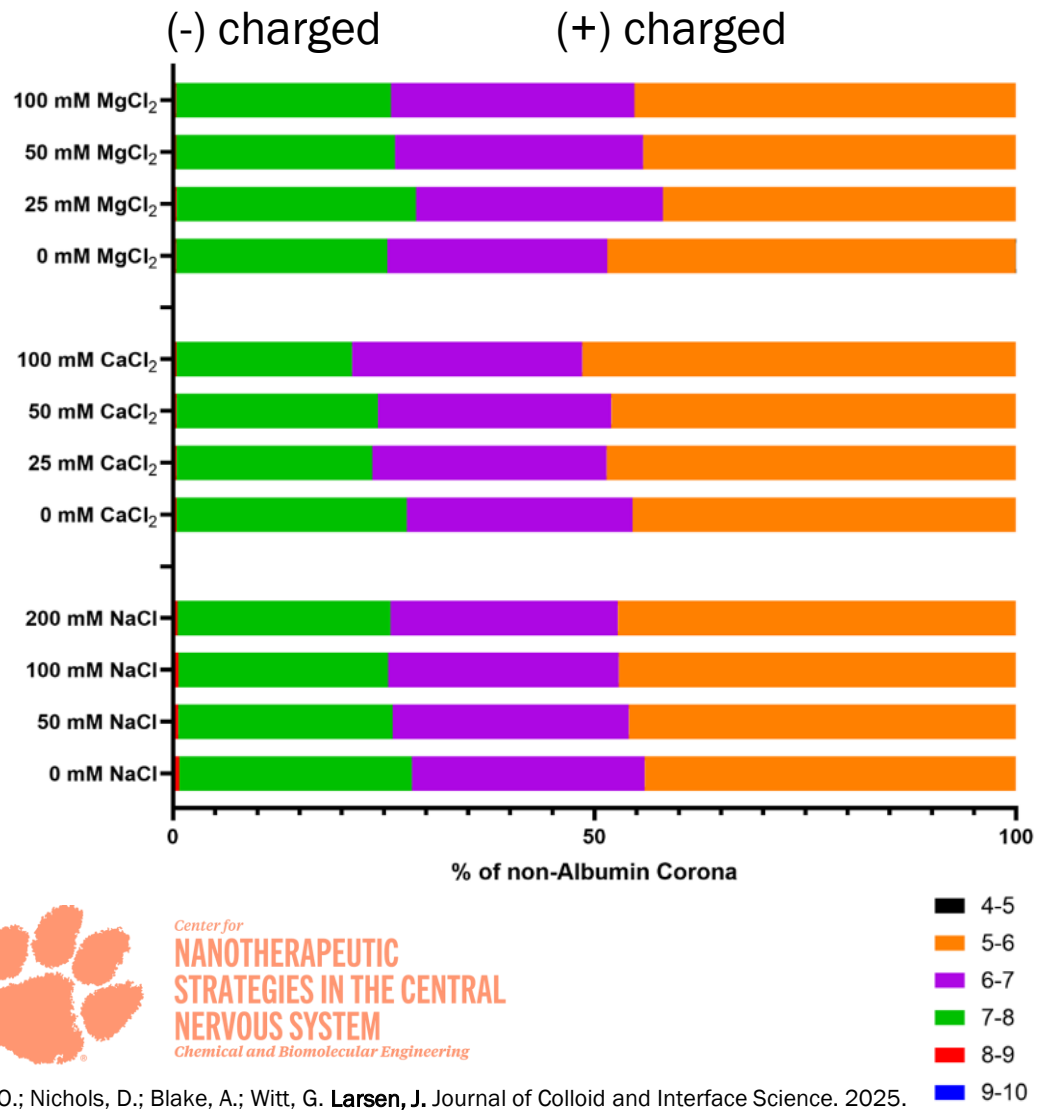
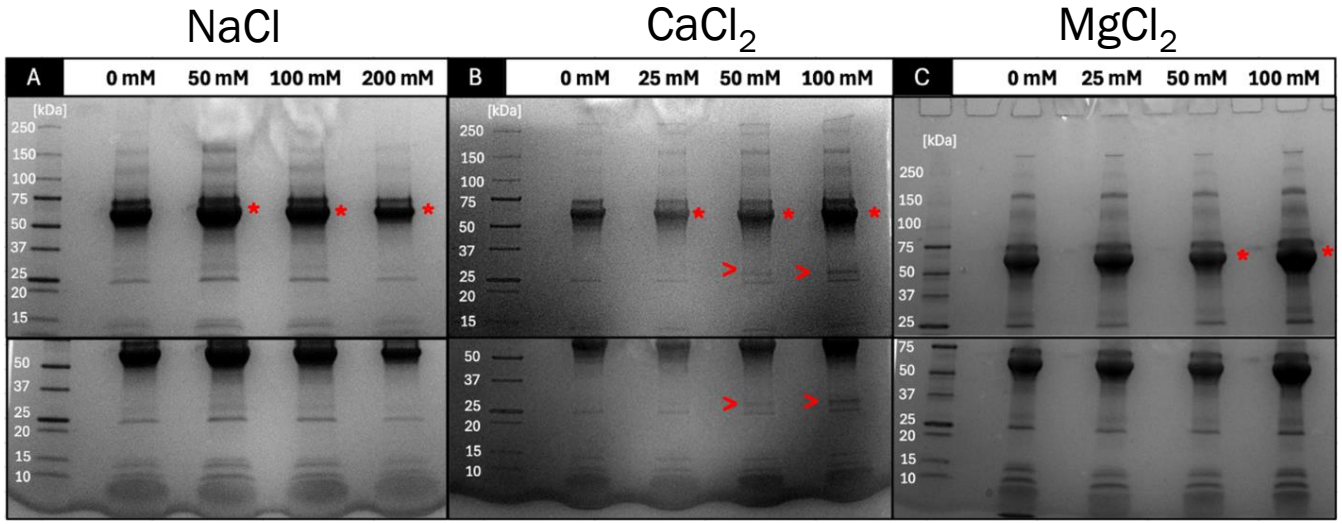
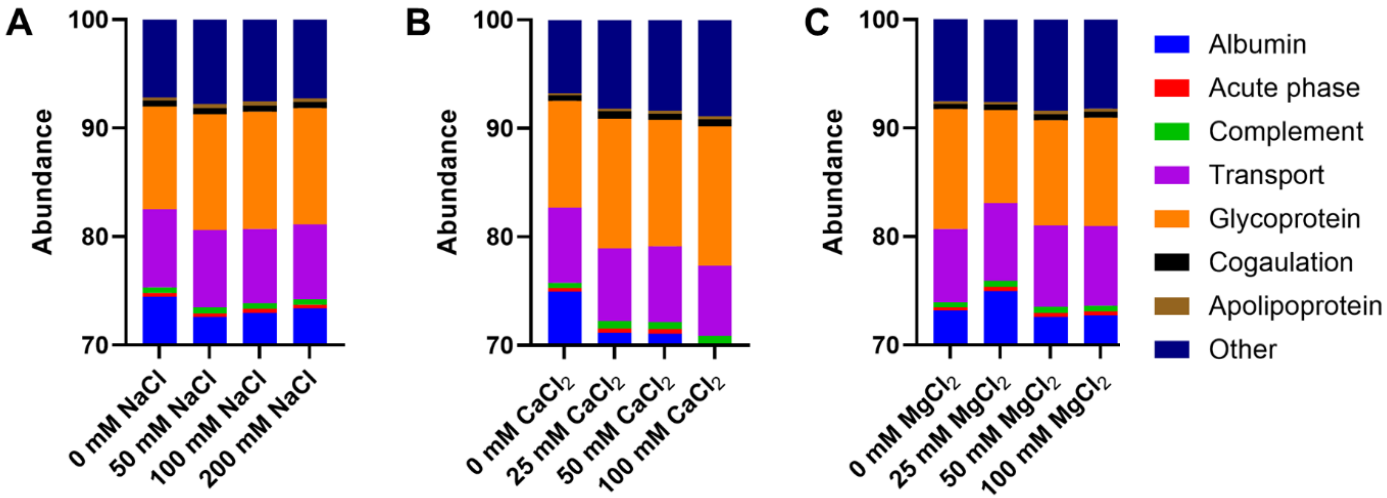
Strongly bound cations had a dramatic impact on composition.







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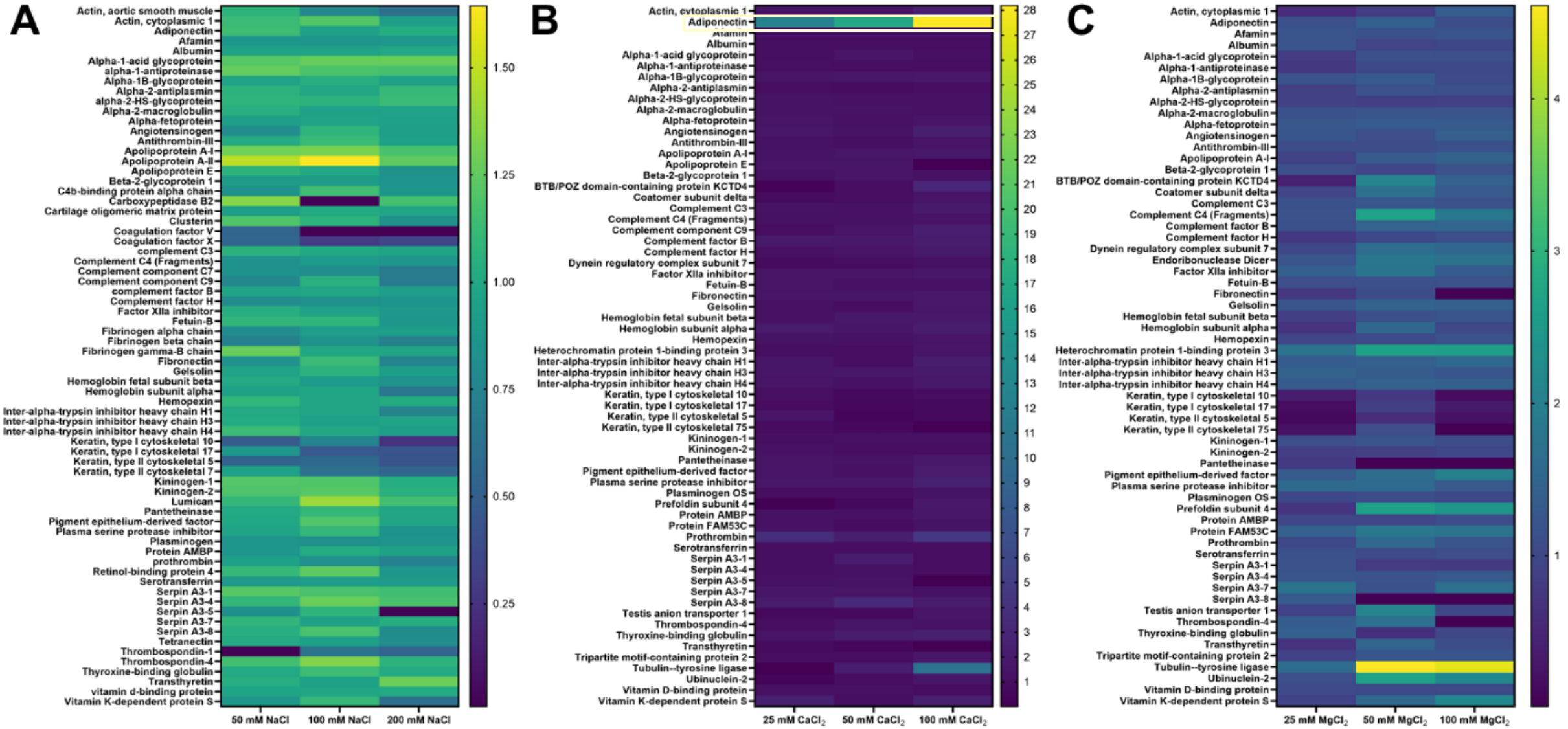
Protein corona composition changed amongst salts.



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20 most abundant proteins changed after incubation with $CaCl_2$.

Protein Rank	0mM $CaCl_2$	25mM $CaCl_2$	50mM $CaCl_2$	100mM $CaCl_2$
1	Albumin OS	Albumin OS	Albumin OS	Albumin OS
2	Alpha-2-HS-glycoprotein OS	Alpha-2-HS-glycoprotein OS	Alpha-2-HS-glycoprotein OS	Alpha-2-HS-glycoprotein OS
3	Serotransferrin OS	Serotransferrin OS	Serotransferrin OS	Serotransferrin OS
4	Alpha-1-antiproteinase OS	Alpha-1-antiproteinase OS	Alpha-1-antiproteinase OS	Alpha-1-antiproteinase OS
5	Alpha-2-macroglobulin OS	Alpha-2-macroglobulin OS	Alpha-2-macroglobulin OS	Alpha-2-macroglobulin OS
6	Alpha-fetoprotein OS	Alpha-fetoprotein OS	Alpha-fetoprotein OS	Alpha-fetoprotein OS
7	Vitamin D-binding protein OS	Fetuin-B OS	Vitamin D-binding protein OS	Complement C3 OS
8	Fetuin-B OS	Complement C3 OS	Fetuin-B OS	Vitamin D-binding protein OS
9	Complement C3 OS	Vitamin D-binding protein OS	Complement C3 OS	**Adiponectin OS**
10	Serpin A3-1 OS	Serpin A3-1 OS	Serpin A3-1 OS	Serpin A3-1 OS
11	Apolipoprotein A-I OS	Inter-alpha-trypsin inhibitor heavy chain H4 OS	Apolipoprotein A-I OS	Apolipoprotein A-I OS
12	Inter-alpha-trypsin inhibitor heavy chain H4 OS	Apolipoprotein A-I OS	Inter-alpha-trypsin inhibitor heavy chain H3 OS	Inter-alpha-trypsin inhibitor heavy chain H4 OS
13	Antithrombin-III OS	**Adiponectin OS**	**Adiponectin OS**	Prothrombin OS
14	Plasminogen OS	**Prothrombin OS**	Alpha-1B-glycoprotein OS	Alpha-1B-glycoprotein OS
15	Alpha-2-antiplasmin OS	Antithrombin-III OS	Antithrombin-III OS	**Angiotensinogen OS**
16	Kininogen-2 OS	Plasminogen OS	Plasminogen OS	Antithrombin-III OS
17	Hemopexin OS	Alpha-1B-glycoprotein OS	Hemopexin OS	Plasminogen OS
18	Alpha-1B-glycoprotein OS	Hemopexin OS	Kininogen-2 OS	Hemopexin OS
19	Protein AMBP OS	**Kininogen-1 OS**	**Angiotensinogen OS**	Protein AMBP OS
20	Alpha-1-acid glycoprotein OS	**Angiotensinogen OS**	Alpha-2-antiplasmin OS	Alpha-2-antiplasmin OS

Adiponectin: Ca^{2+} binding motif
Angiotensinogen: Ca^{2+} in renin-angiotensin system

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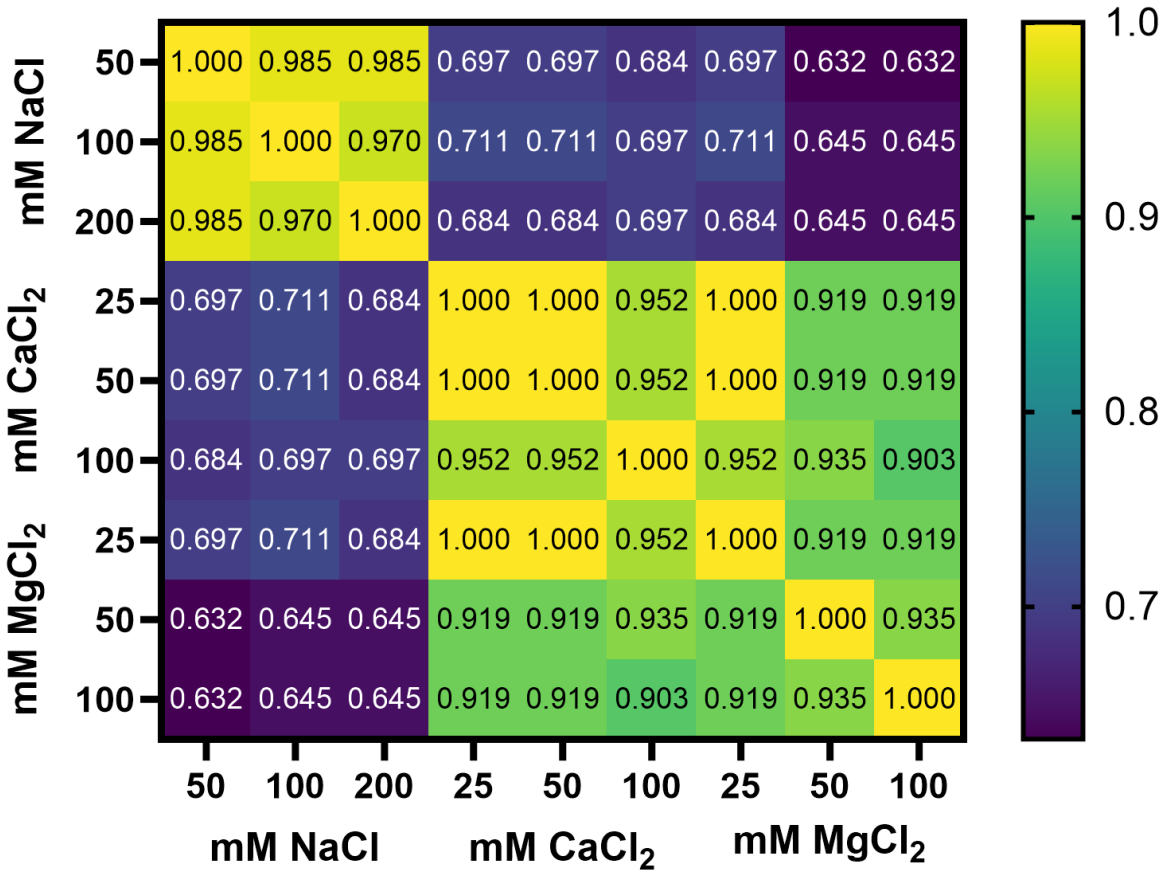
Conclusions

- **Salt ions can change the shape of polymersomes** while maintaining their properties.
- **Divalent chaotropic salts bind more tightly to PEG**, impacting the isoelectric point of proteins found in the protein corona.
- **Calcium** incubation leads to the most **biologically specific** protein corona changes.

Protein corona composition can be engineered on the surface of PEG-b-PLA polymersomes.



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SC EPSCoR/IDeA

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Thank you for your time and attention!

Graduates

Nick L'Amoreaux
Aon Ali
Dr. Shoaib Iqbal
Daniel Nichols
Owen Tabah

Postdoctoral Fellows

Dr. Apoorvi Chaudhri

Graduate Students

Vida Nazar
Joey Lavalla
David Forsman
Elijah Barnes
Chloe Forenzo
Seoyoung Lee
Noah Arnold
Kati Lorenz (MS)

Undergraduate Students

Vanessa Maharens
Amelia Weber
Ava McKee
Grace Witt
Ashley Blake
Isabella Stamato
Quintin Martin
Sierra Niskanen
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Current Funding:
NIH NINDS R21NS133477
NSF CAREER 2047697
NIH NIGMS P20GM146584
NSF AMBIC 2100800CAR (x2)
NTSAD
NSF STRIDE STRP
NIH NINDS R01NS142877