Naringenin Conjugated Precision Polyester Nanosystems for Folate Receptor-Mediated Oral Delivery of Insulin

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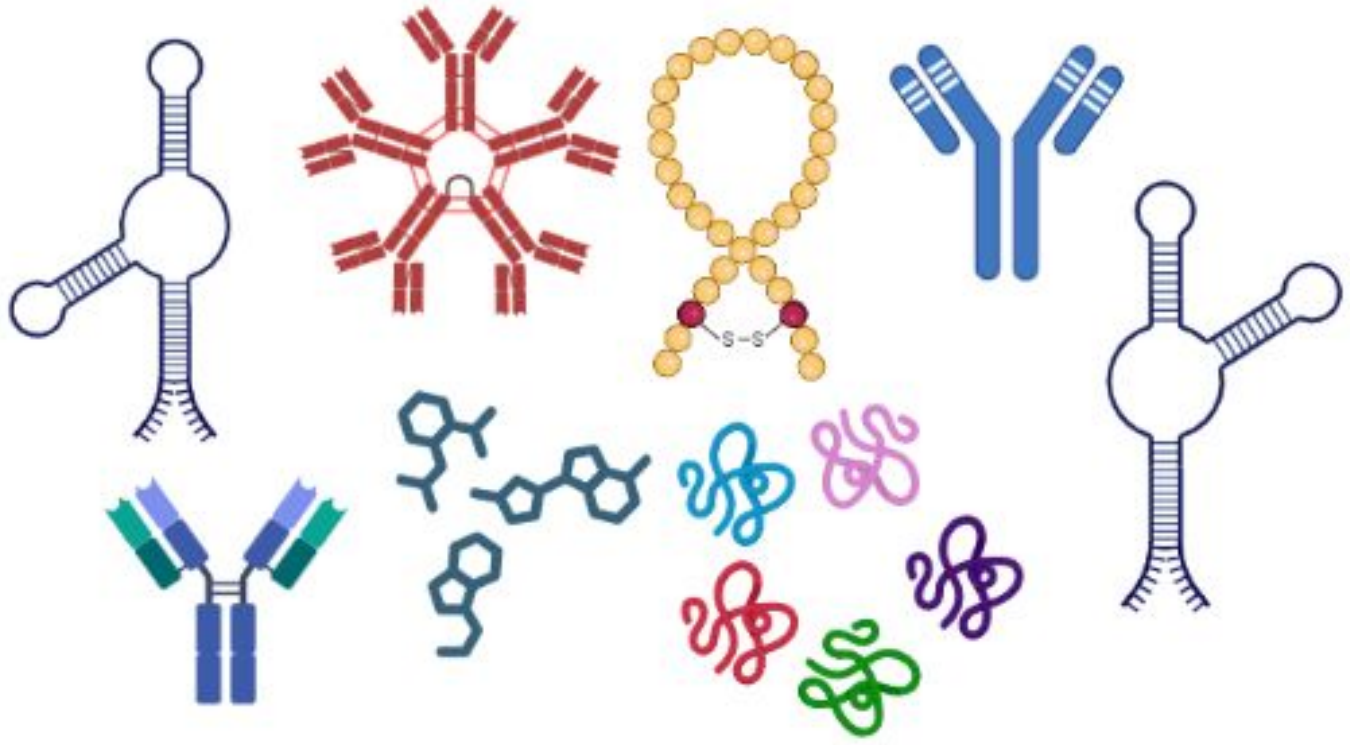
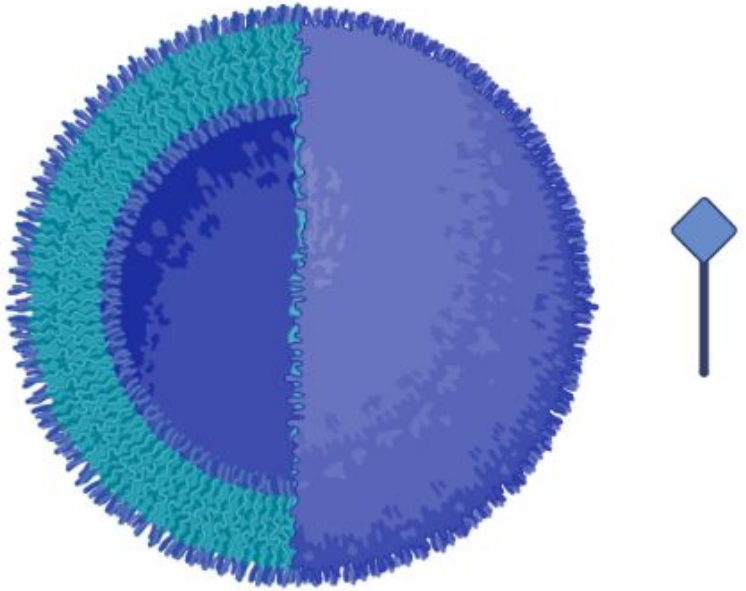
Receptor-mediated drug delivery: Choice of ligands and ligand-receptor stoichiometry





Receptor-ligand stoichiometry

Saw, et al., *Protein & Cell*, **2019**
Yan, et al., *ACS Applied Materials & Interfaces*, **2021**
Nanna, et al., *Nature communications*, **2017**
Ganugula, et al., *Journal of American Chemical Society*, **2017**

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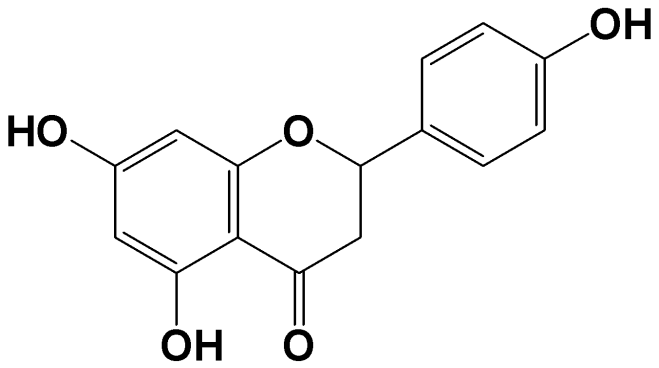
Our choice, a natural small molecule flavonoid

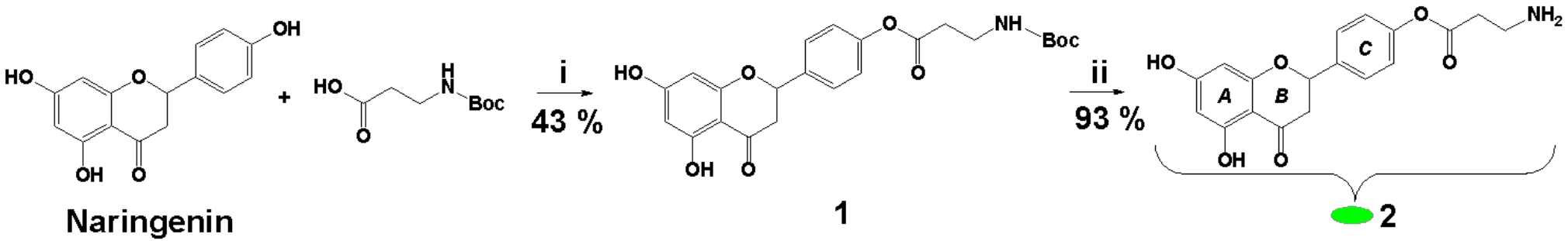


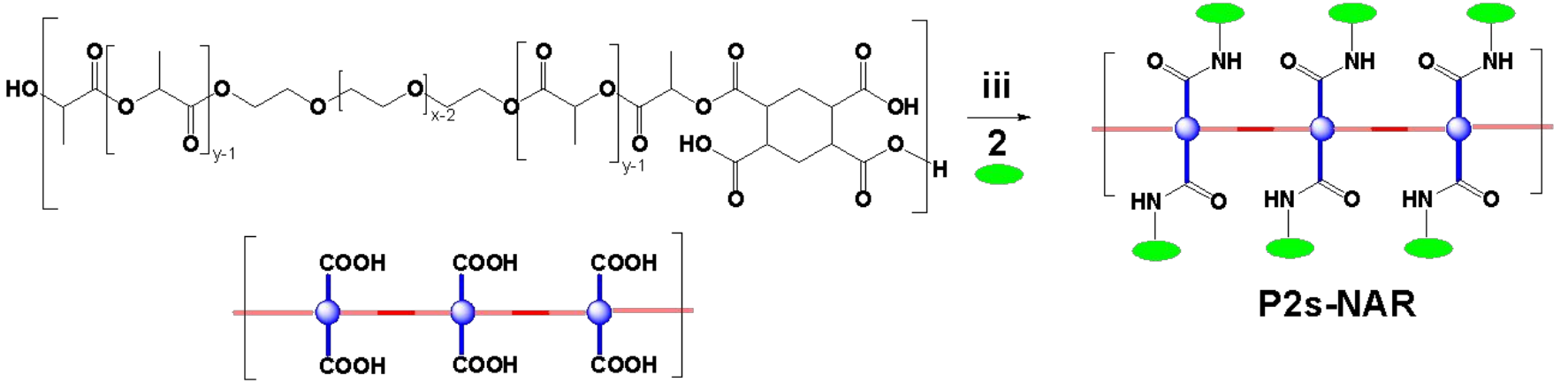
Ligand	Docking Score
Folic Acid **Customary for FR-targeting*	-11.96
MTHFA	-11.00
NAR	-11.44

FA in larger doses is associated with adverse side-effects including toxicity to humans

Selhub, et al., *Biochimie* **2016**
Devnath, et al., *Journal of forensic sciences,* **2017**
Sawaengsri, et al., *The Journal of nutritional biochemistry,* **2016**

Synthesis Strategy

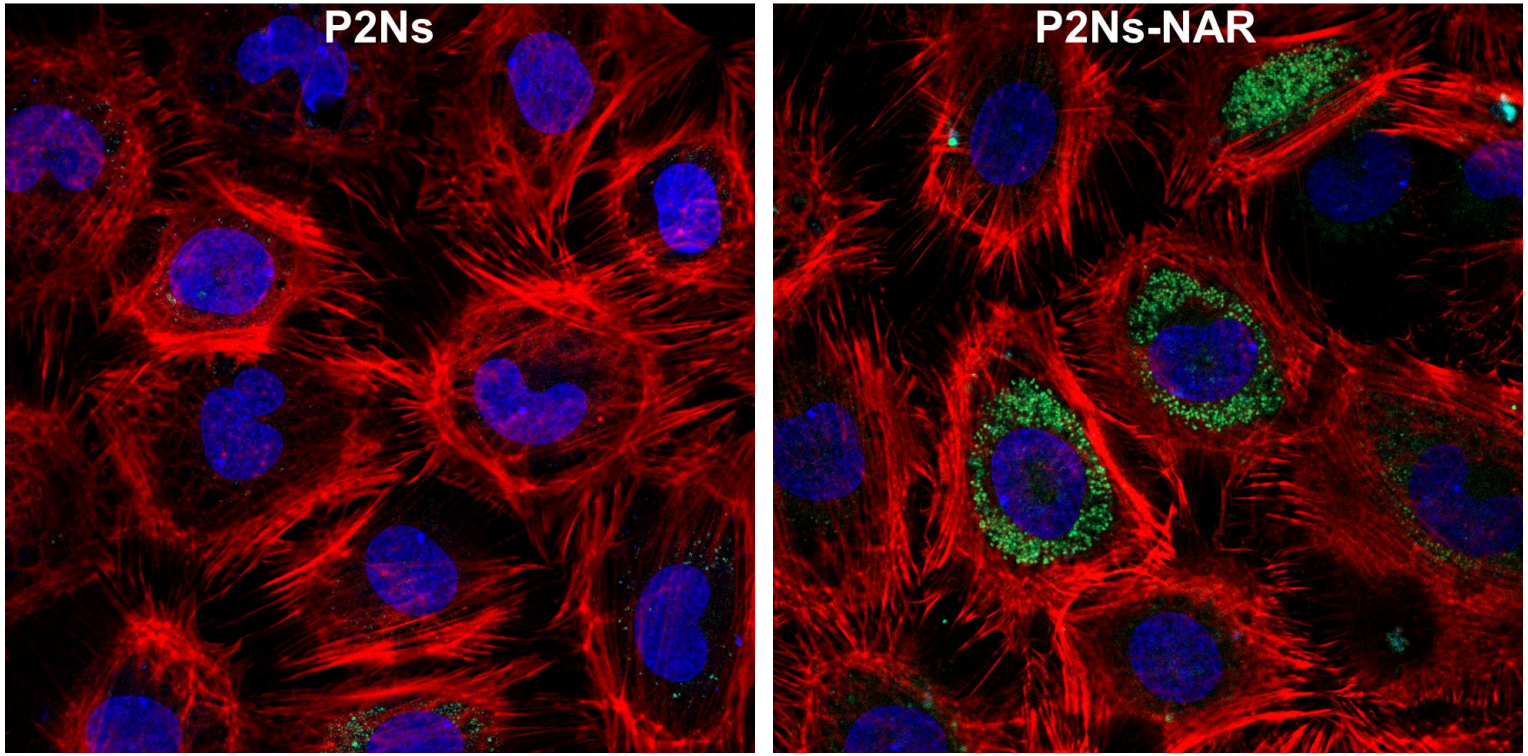


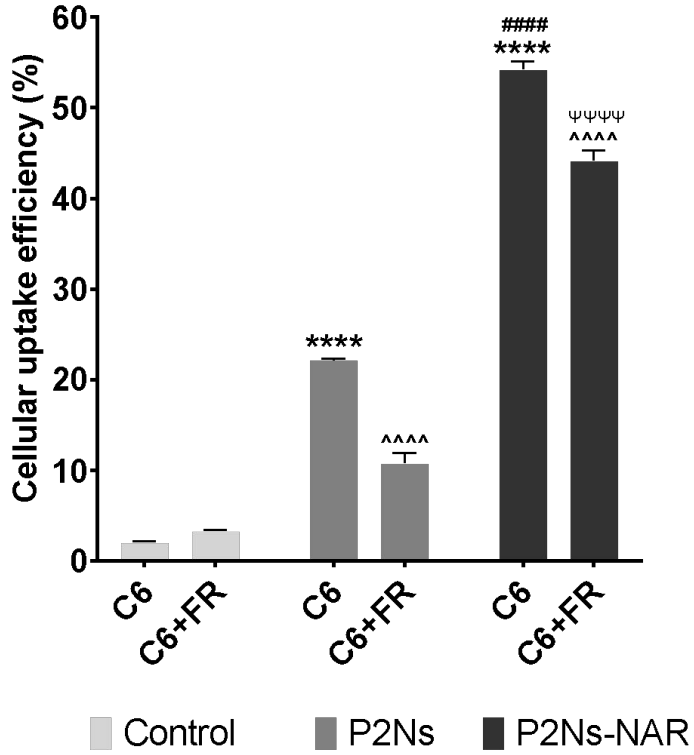


Ganugula, et al., *Journal of American Chemical Society*, **2017**

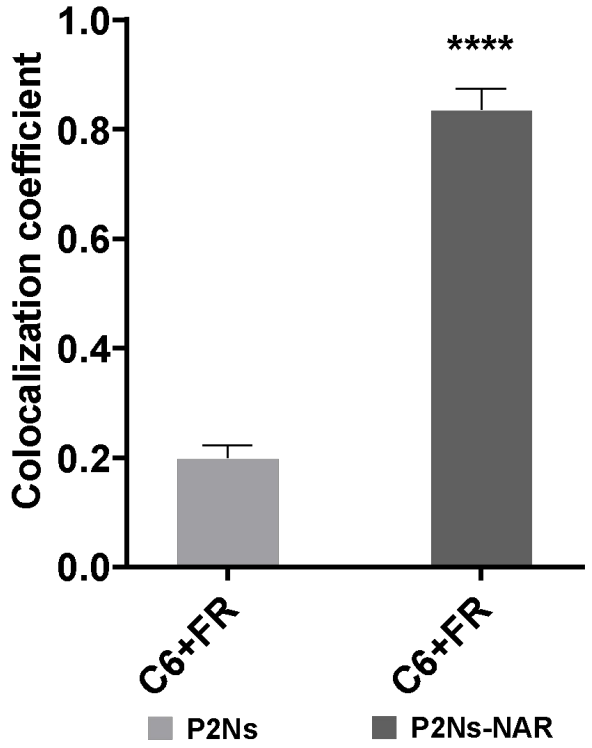
Synthesis of P2s-NAR: i) EDC.HCl, DMAP, dimethylformamide, 0 °C to r.t.; ii) trifluoroacetic acid, methanol, dichloromethane, 0 °C; iii) EDC.HCl, DIEA, dimethylformamide, dichloromethane, 0 °C to r.t.

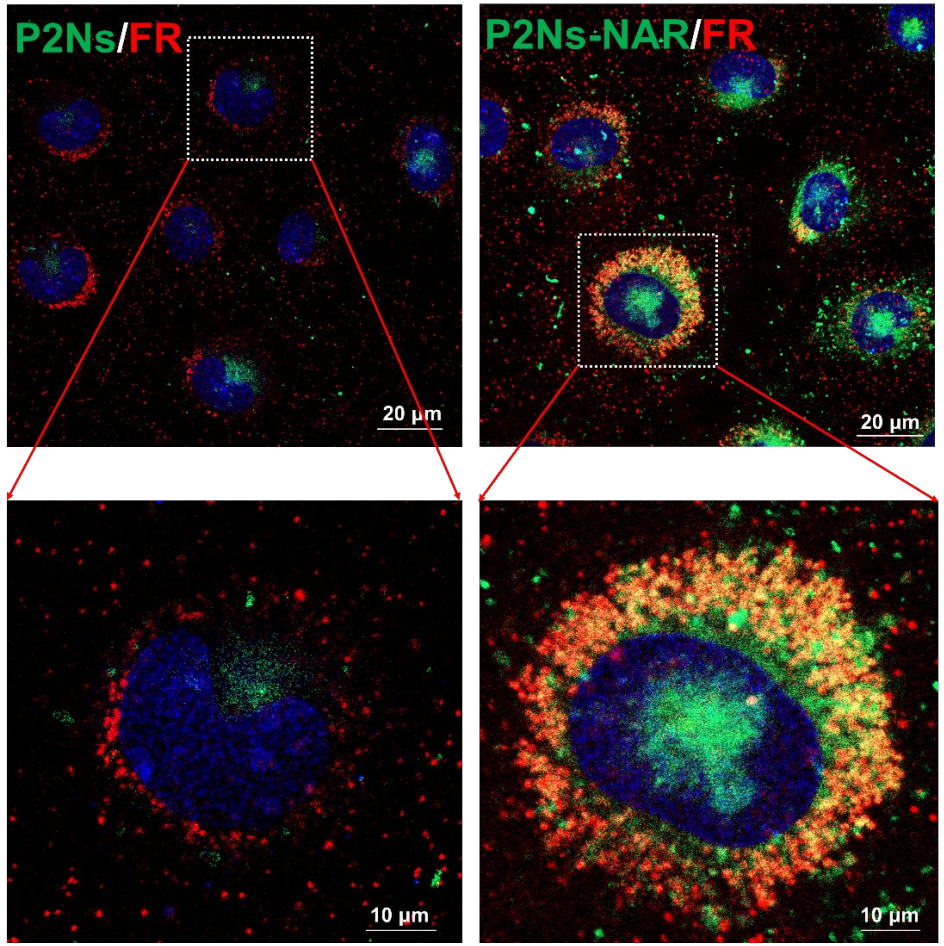
Folate Receptor-Mediated Endocytosis *In Vitro*



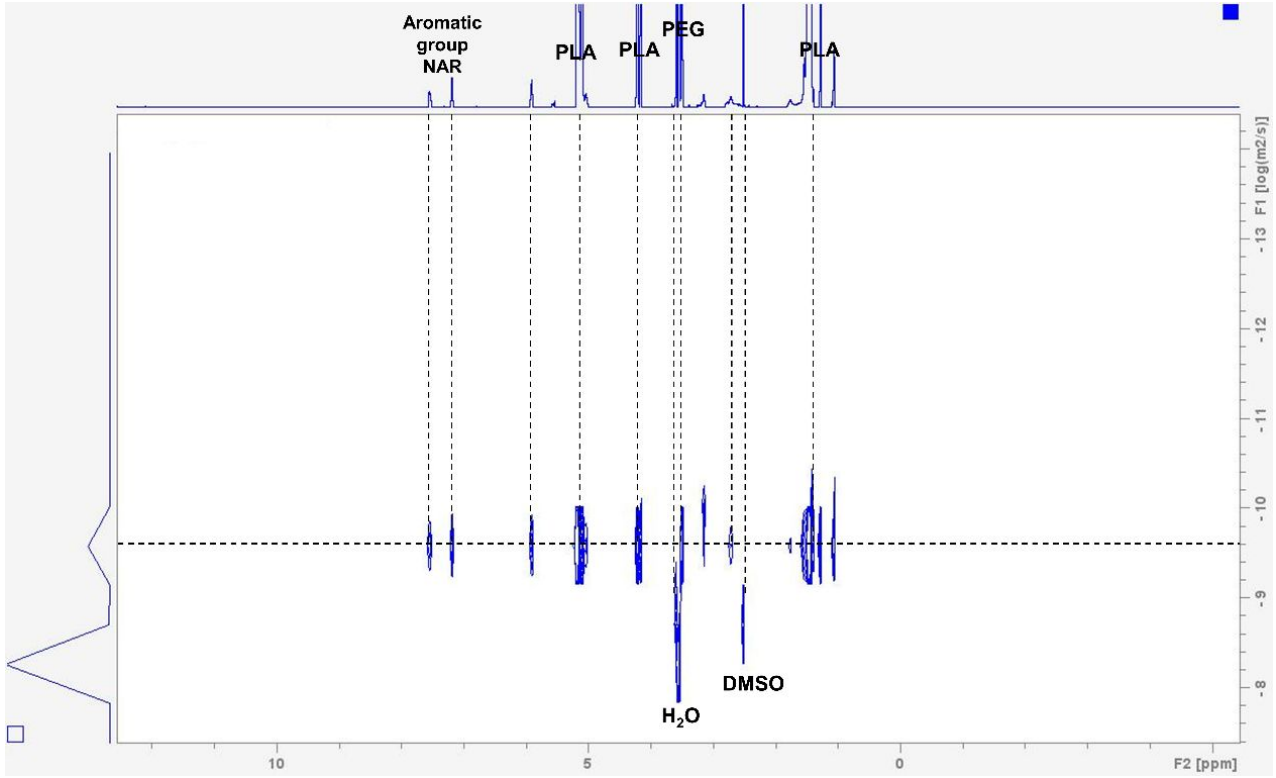


Folate Receptor-Mediated Colocalization Studies *In Vitro*

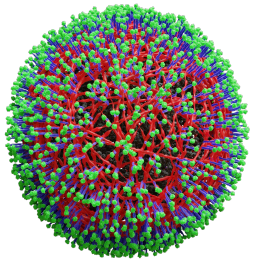




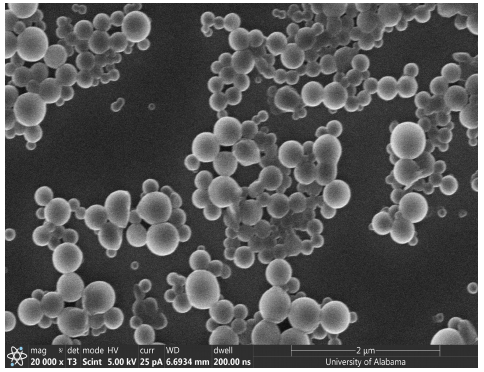
Insulin as a model compound, formulation & pharmacokinetics



Nanoparticles	P2Ns (INS-laden)	P2Ns-NAR (INS-laden)
Size (nm)	289 ± 12	220 ± 22
EE (%)	77.0 ± 10.4	75.0 ± 12.1
Zeta Potential (mV)	-16.3 ± 0.1	13.9 ± 1.4



INS-laden P2Ns-NAR



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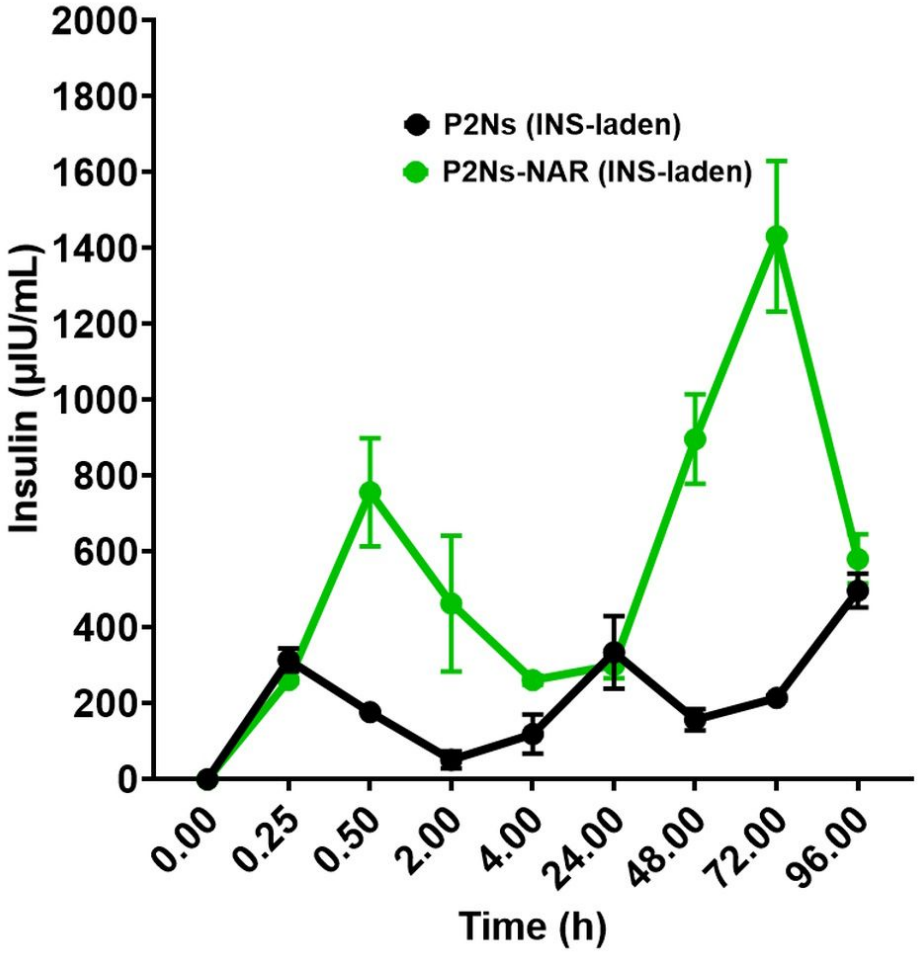
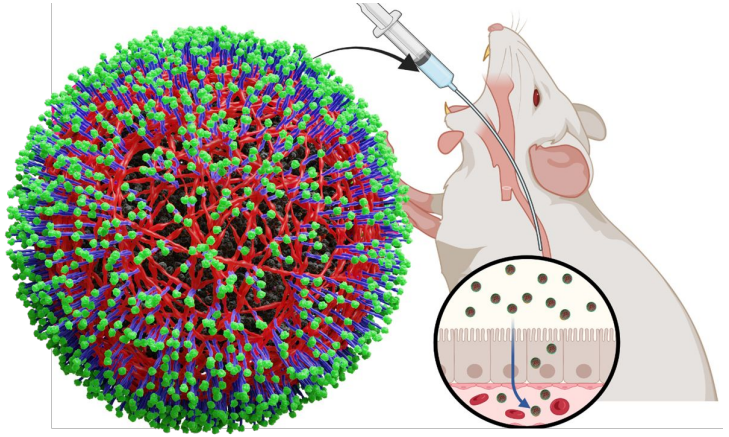
In Vivo



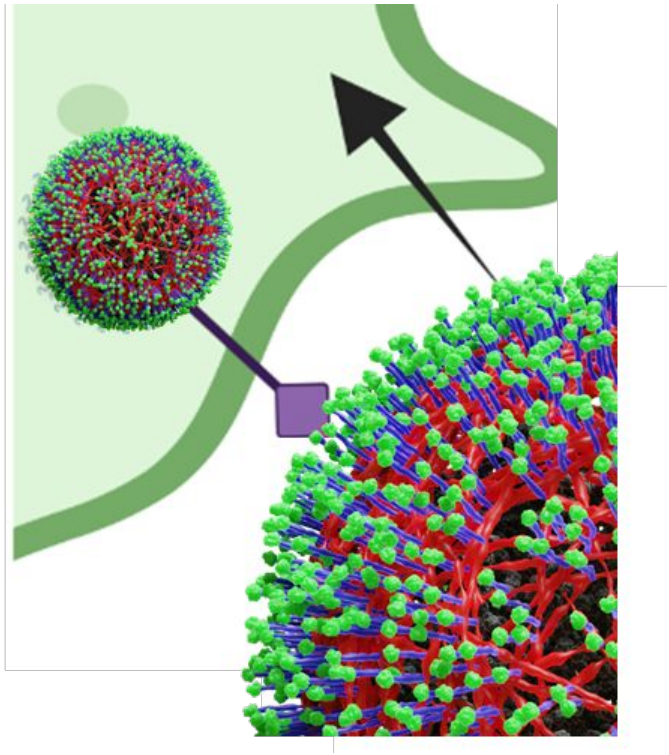
INS-laden
40 IU/kg



PK parameters	P2Ns (INS-laden)	P2Ns-NAR (INS-laden)
AUC (μIU/h/mL)	22,920	73,910
C_{max} (μIU/mL)	315/301	757/1432
T_{max} (h)	0.25/24	0.5/72

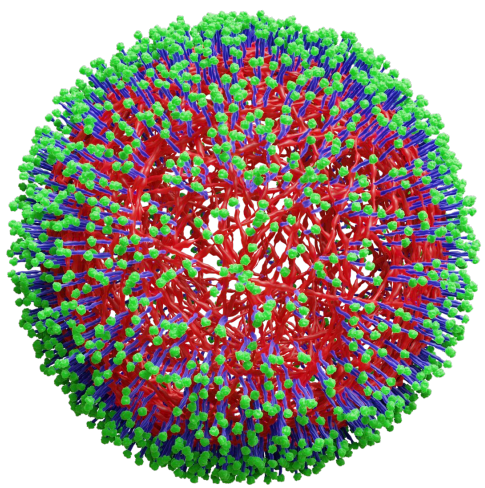
Summary

- Optimized ligand-receptor stoichiometry
- High hydrophilic therapeutic cargo entrapment
- Increased cellular uptake and FR colocalization
- Increased bioavailability

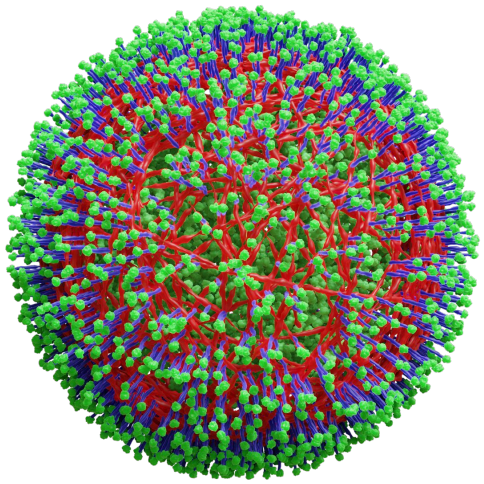


Future Perspectives

- Evaluating the therapeutic efficacy in type diabetes models
- Assessing formulation compatibility with other therapeutic proteins and peptides
- Extending to hydrophobic polyphenolic-laden nanoparticles
- We have observed self-therapeutic properties of particles, we plan to conduct therapeutic effects of void P2Ns-NAR in suitable models



Void P2Ns-NAR



NAR-laden P2Ns-NAR

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