

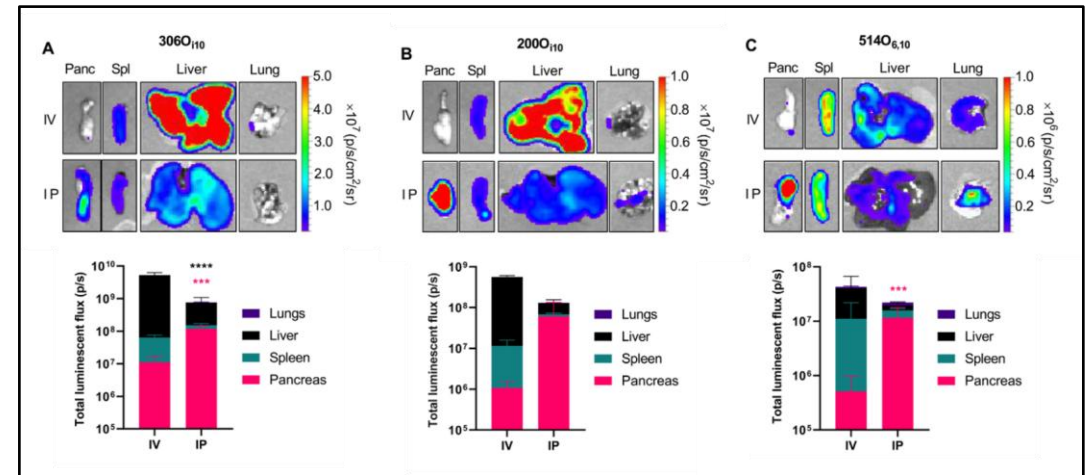
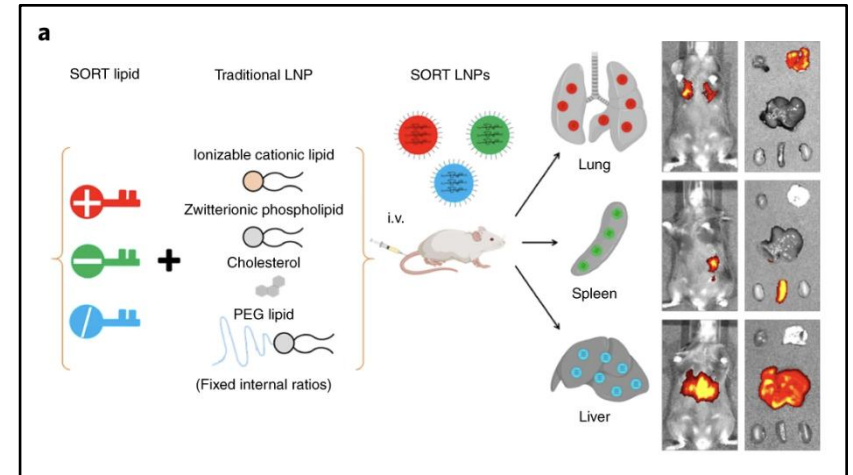
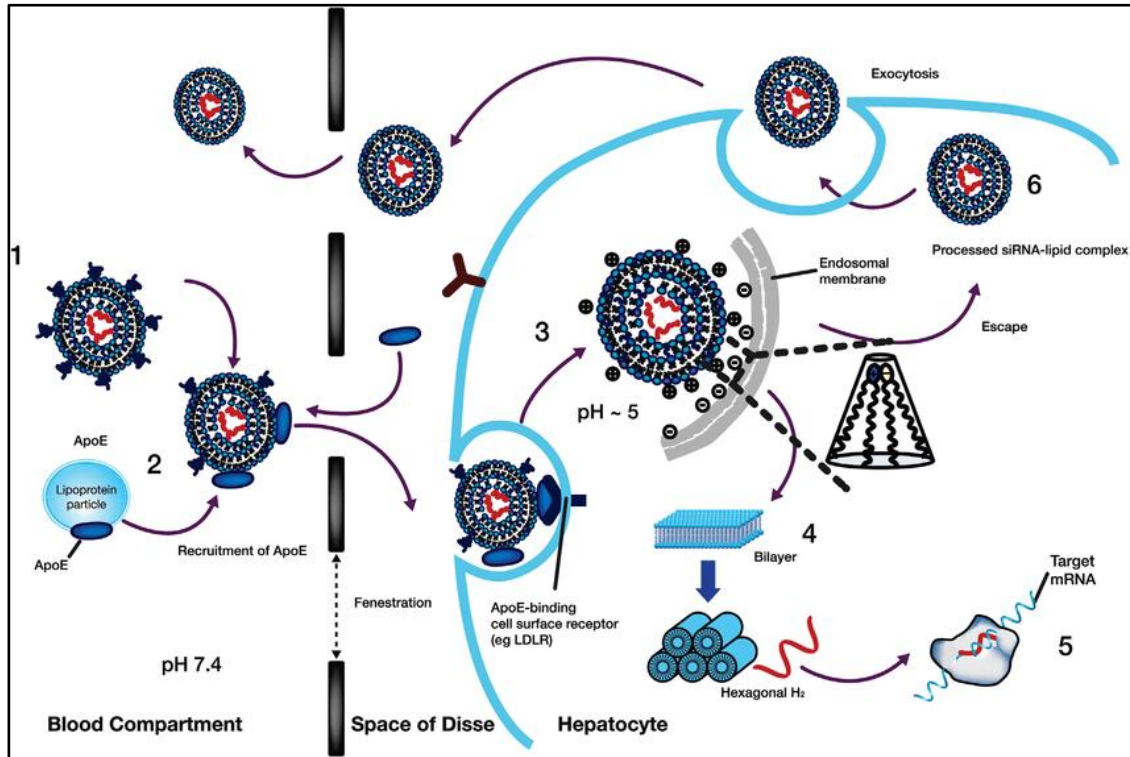
Engineering protein-conjugated lipid nanoparticles for targeted mRNA delivery to the placenta

Hannah Geisler

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Lipid nanoparticles (LNPs) tend to accumulate in the liver

Pharmacokinetics of Onpattro



Zhang, Goel, Robbie. *J Clin. Pharmacol.* 2019

Cheng et al. *Nat. Nanotechnol.* 2020; Melamed et al. *Sci. Adv.* 2023

Active targeting can increase specific LNP delivery

Targeting lipid nanoparticles to the blood-brain barrier to ameliorate acute ischemic stroke

Jia Nong,¹
Raisa Y. K.
Marco E. Z.
Ashley G.
Hamideh

PECAM-1 directed re-targeting of exogenous mRNA providing two orders of magnitude enhancement of vascular delivery and expression in lungs independent of apolipoprotein E-mediated uptake

Hamideh
Raisa Y.
Ying K.
Vladimir

CANCER

CRISPR-Cas9 genome editing using targeted lipid nanoparticles for cancer therapy

Daniel
Nuphar
Zvi R.

Targeted drug delivery to the brain endothelium dominates over passive delivery via vascular leak in experimental intracerebral hemorrhage

Sahily Reyes-Est
Sarah Ohashi^d,
Lauren Sansing^c
Jacob S. Brenne

Targeted lipid nanoparticles for RNA therapeutics and immunomodulation in leukocytes

Nuphar V

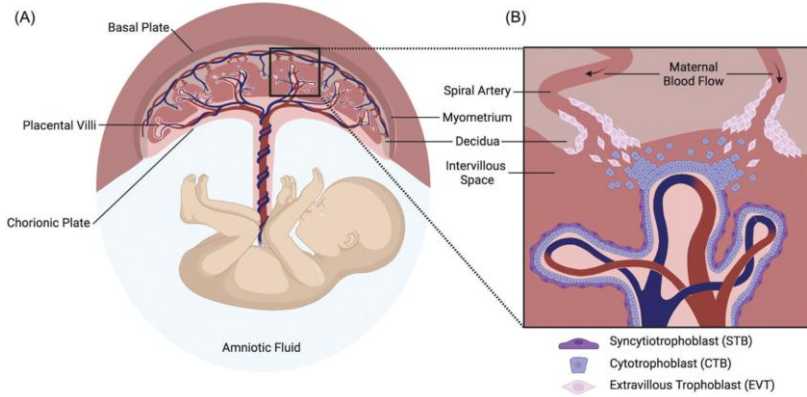
pubs.acs.org/NanoLett

Letter

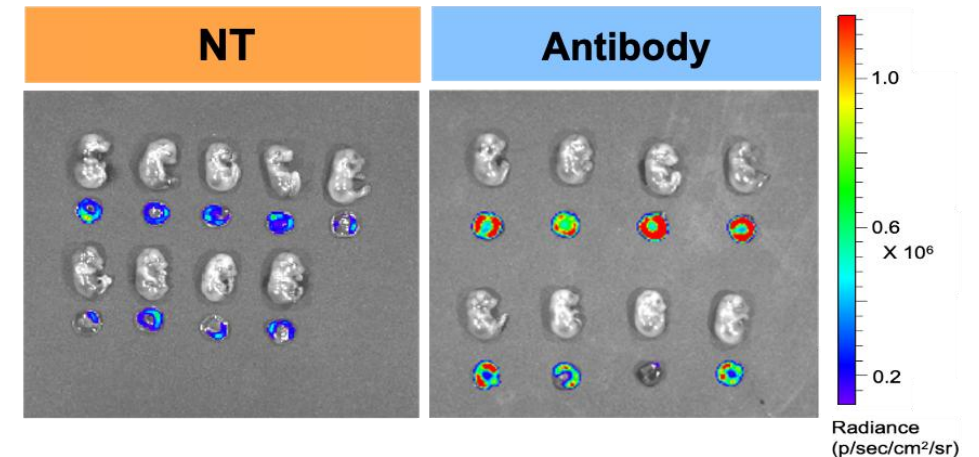
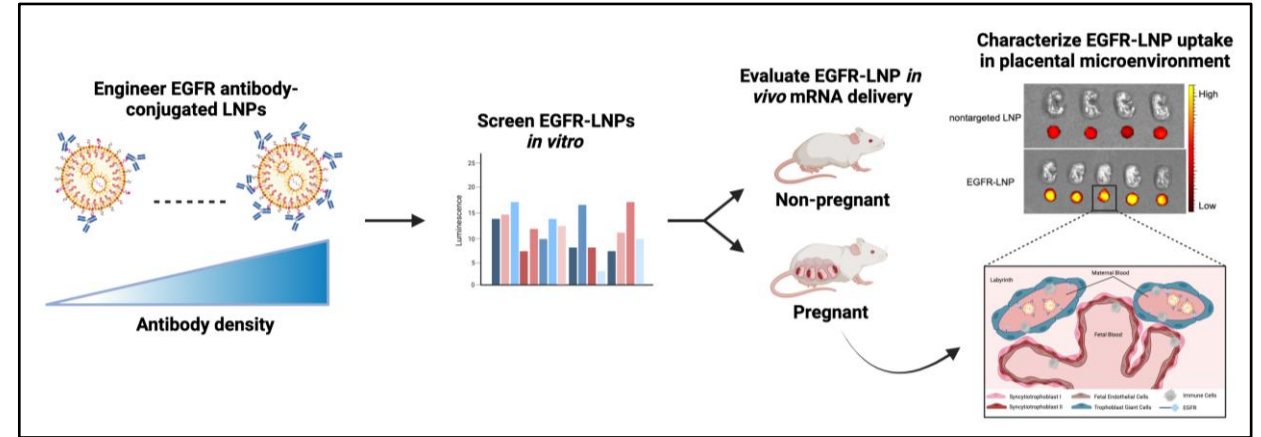
In Vivo RNA Delivery to Hematopoietic Stem and Progenitor Cells via Targeted Lipid Nanoparticles

Dennis Shi, Sho Toyonaga, and Daniel G. Anderson*

Targeted LNPs (tLNPs) for extrahepatic delivery to the placenta

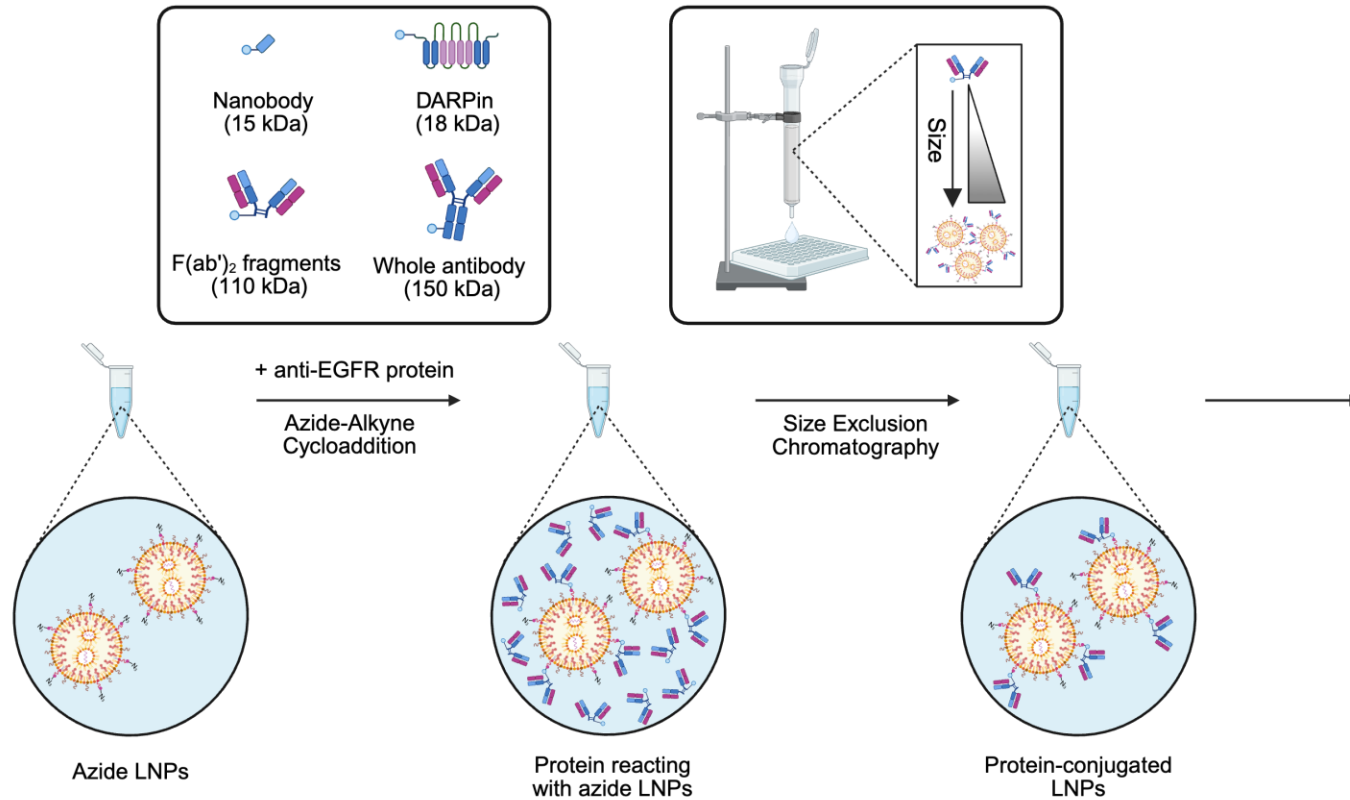


- The placenta develops during pregnancy to support fetal development
- Dysfunctional placental development can lead to obstetric complications
- Delivery platforms needed for extrahepatic placental delivery during pregnancy complications



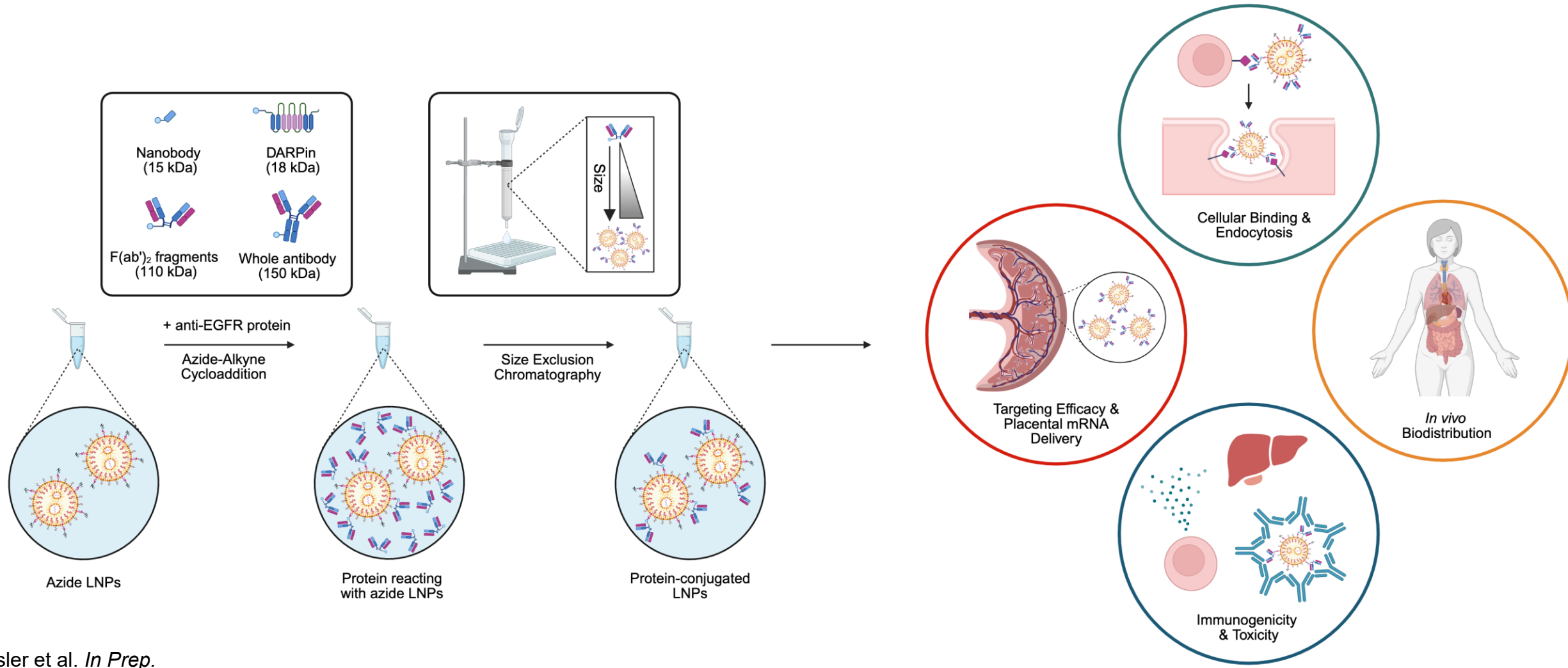
Geisler & Safford. *Small*. 2023; Geisler et al. *JCR*. 2024.

Does protein targeting moiety affect tLNP behavior?



Geisler et al. *In Prep.*

Does protein targeting moiety affect tLNP behavior?



Geisler et al. *In Prep.*

Pregnancy alters LNP biodistribution *in vivo*

Nanobody

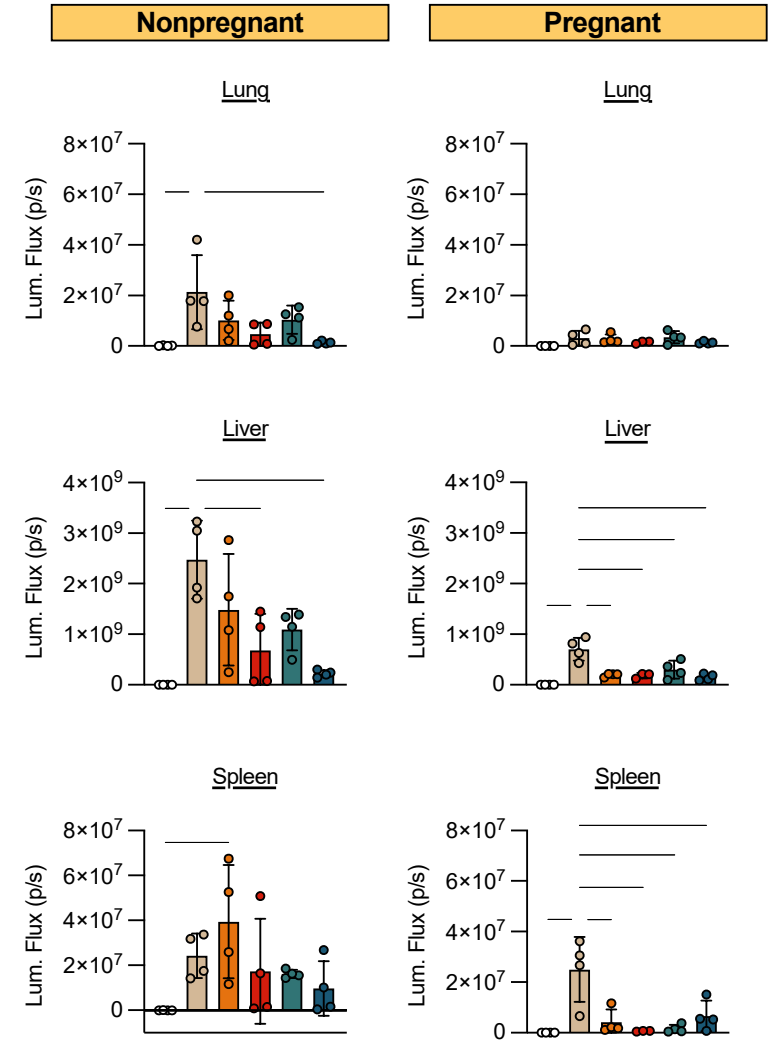
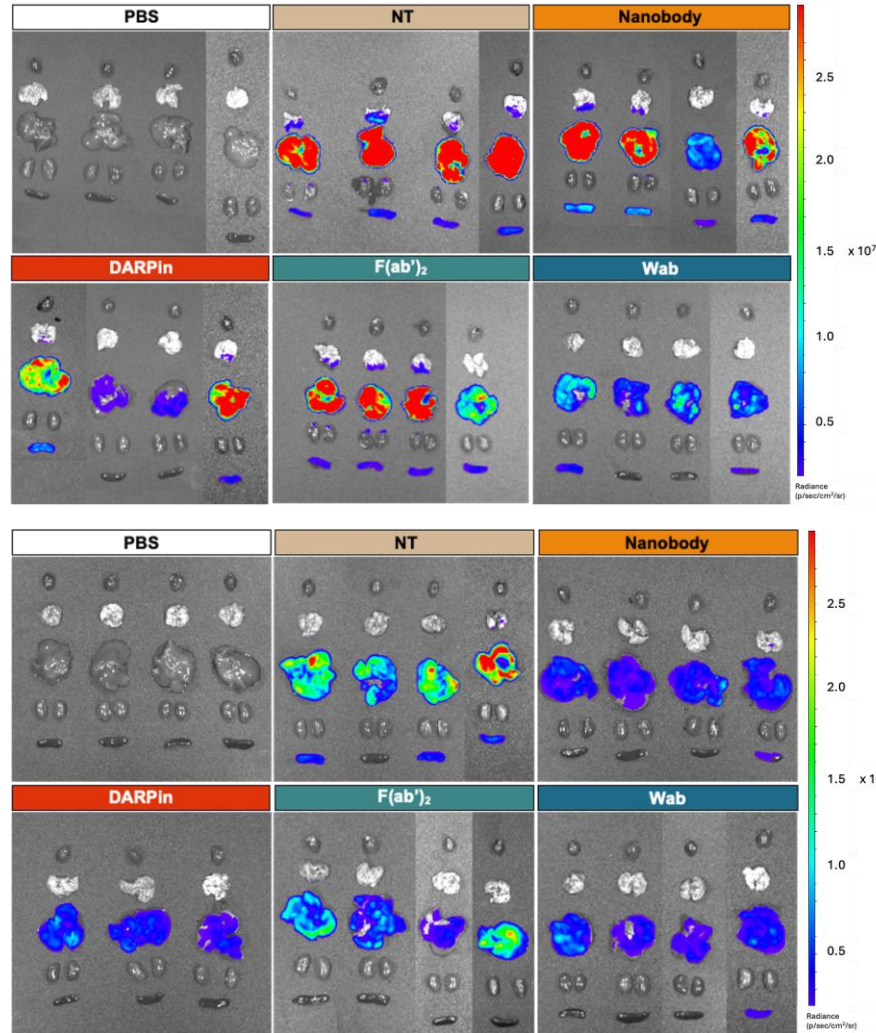
DARPin

F(ab')₂

Wab

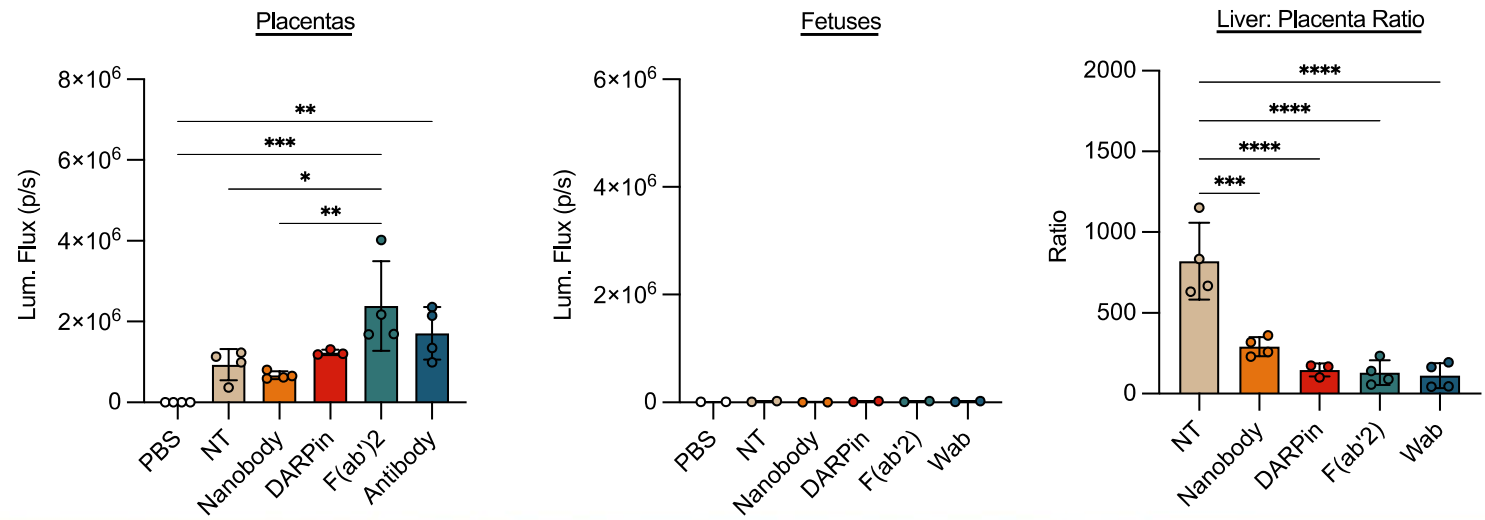
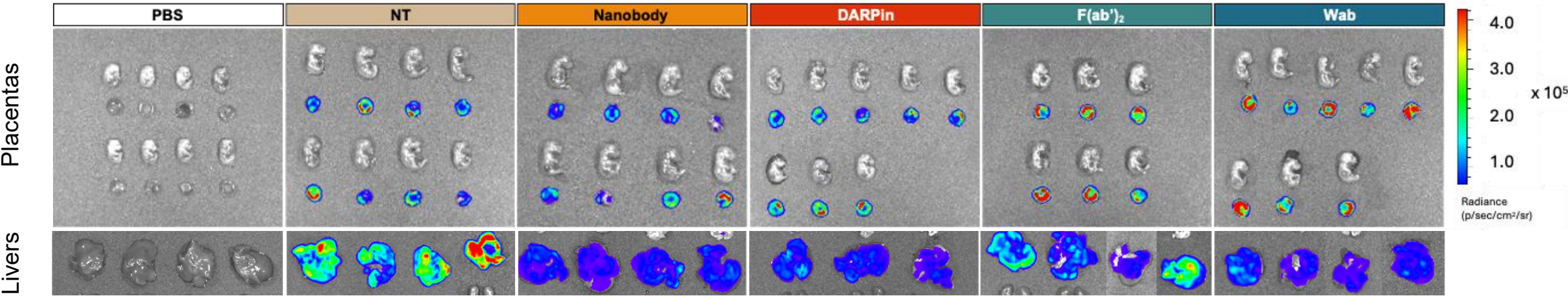
Nonpregnant

Pregnant



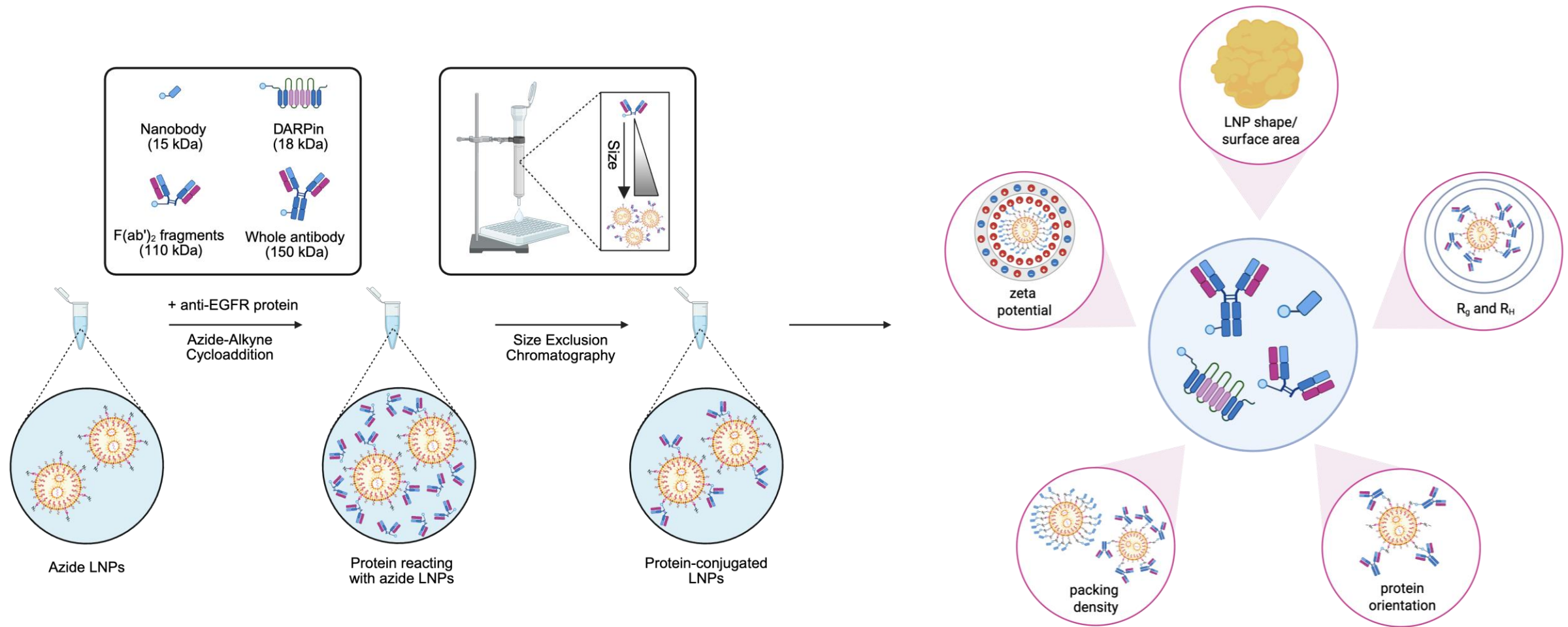
Geisler et al. *In Prep.*

F(ab')₂ tLNPs enhance mRNA delivery to the placenta



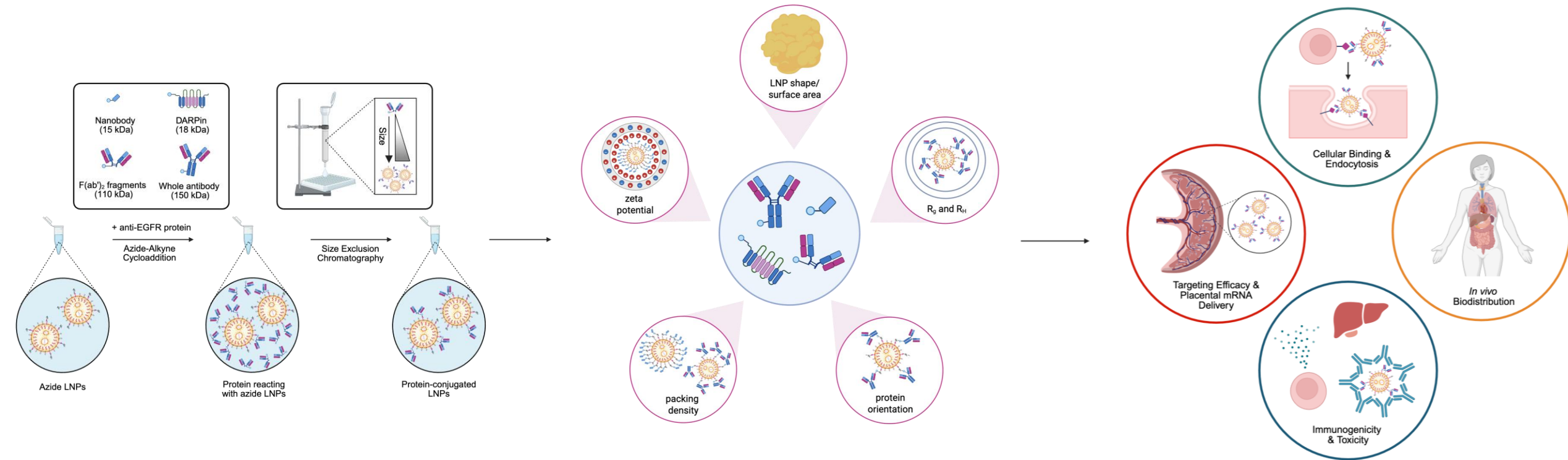
Geisler et al. *In Prep.*

Does protein targeting moiety affect tLNP behavior?



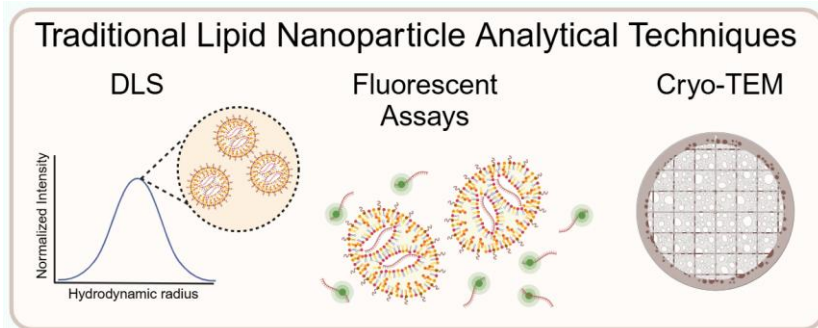
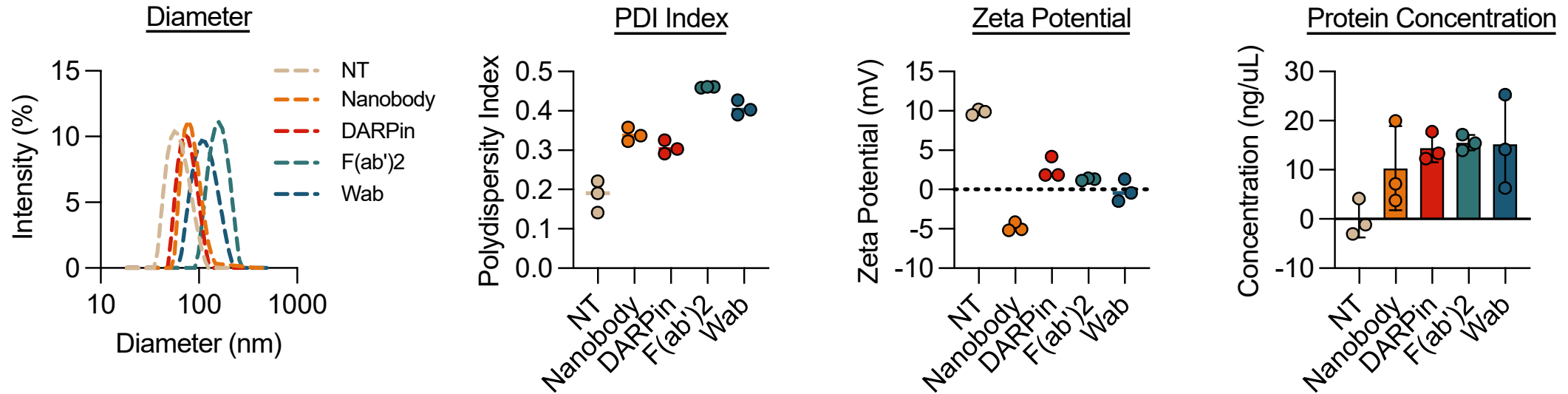
Geisler et al. *In Prep.*

Does protein targeting moiety affect tLNP behavior?



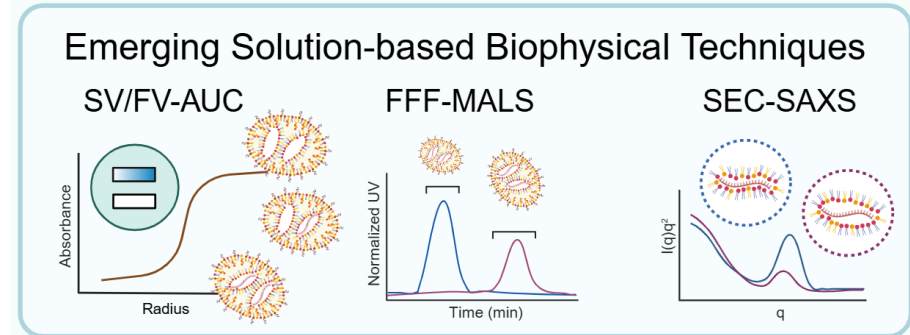
Geisler et al. *In Prep.*

Traditional LNP characterization techniques suggest protein conjugation, but lack resolution



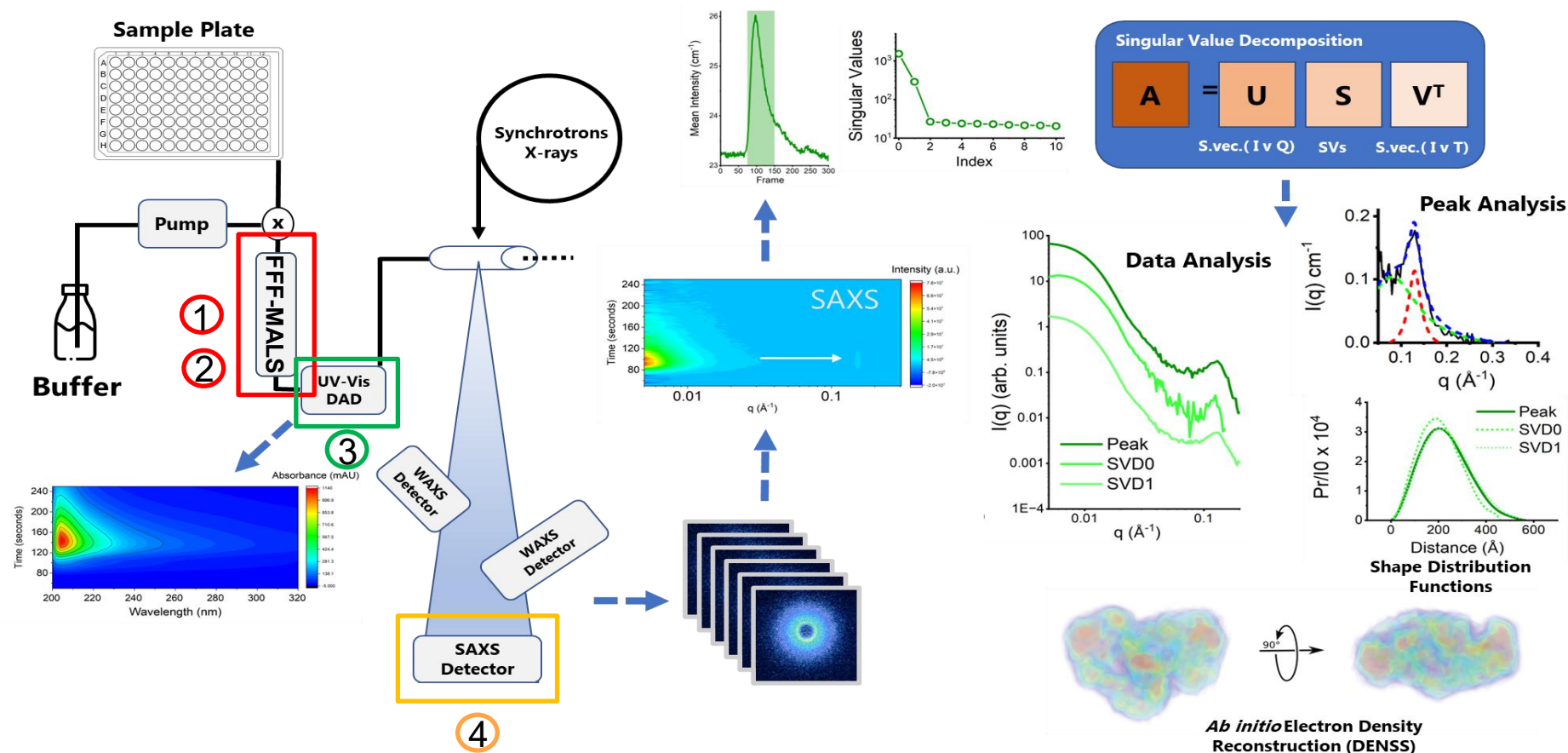
?

≡



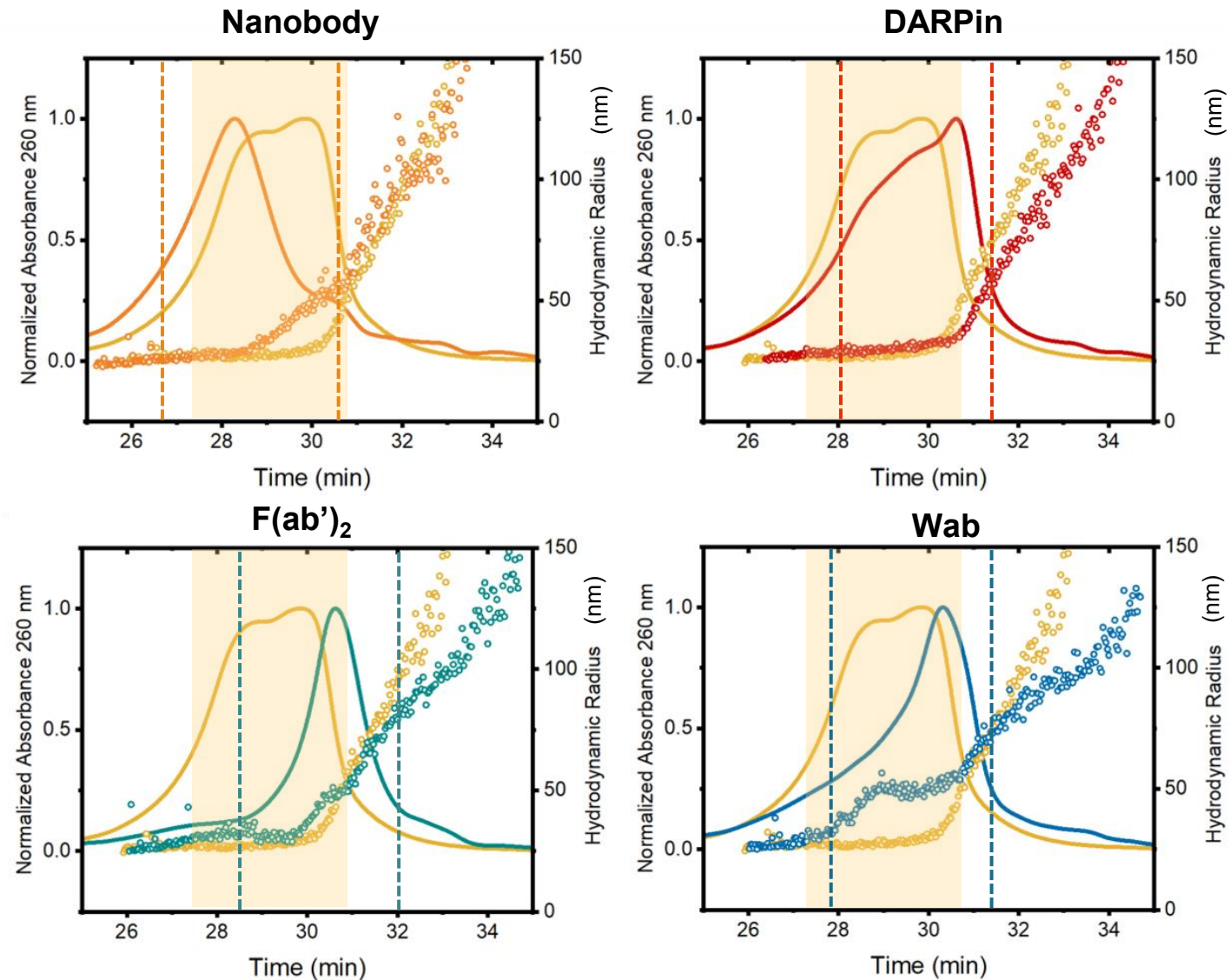
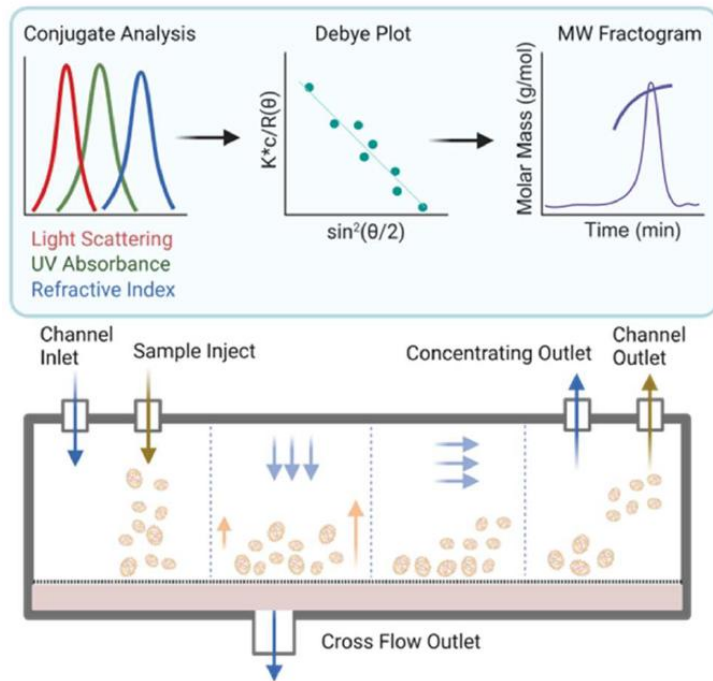
Geisler et al. *In Prep.*

FFF-MALS-SAXS for LNP characterization

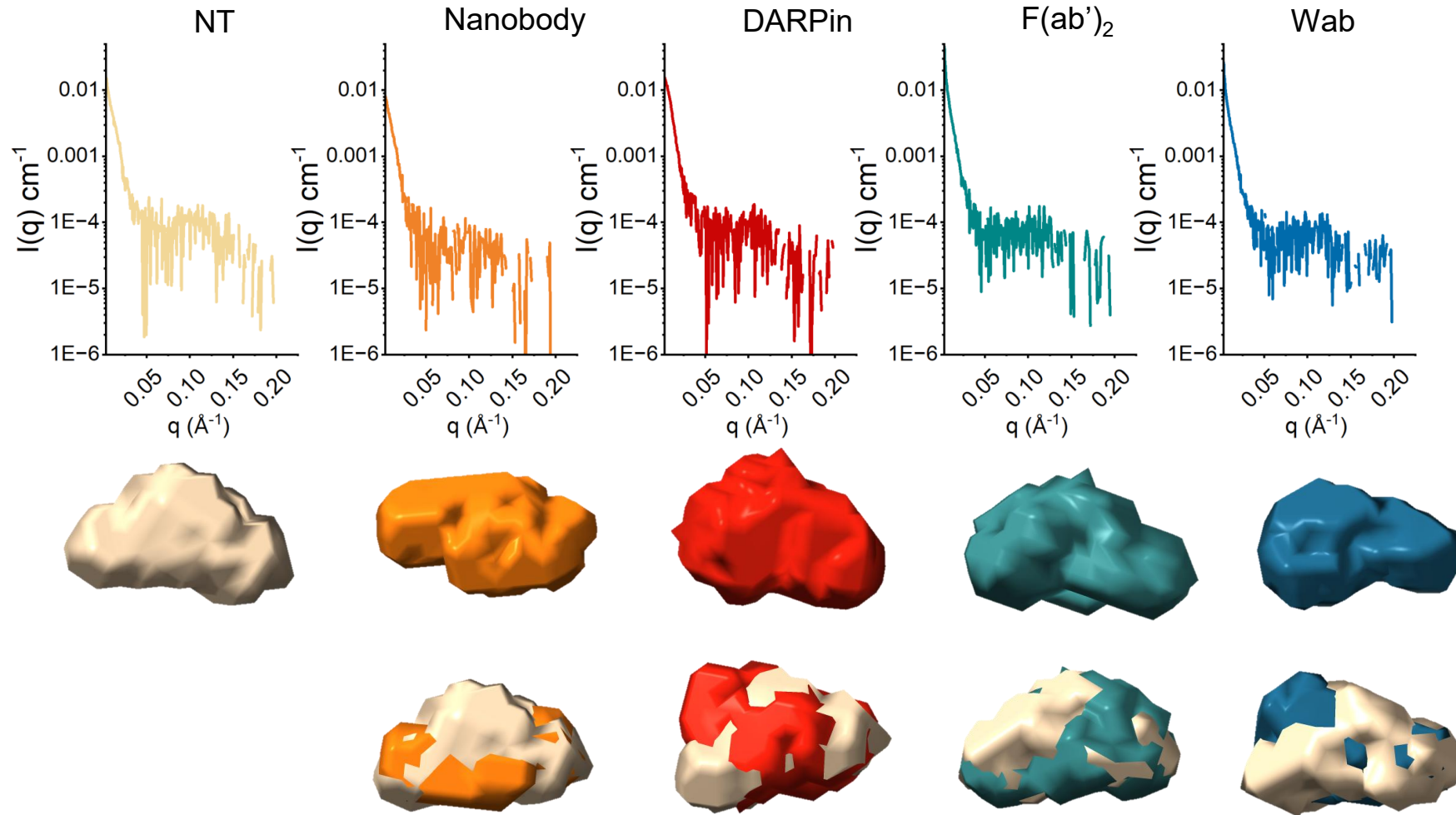


Geisler et al. *In Prep.*

FFF-MALS reveals increase in tLNP size & heterogeneity



SAXS reveals differences in tLNP shape and surface area



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Conclusions

- Pregnancy alters biodistribution of anti-EGFR tLNPs
- F(ab')₂ and Wab enhance placental targeting more than Nanobody and DARPin tLNPs
- FFF-MALS-SAXS reveals that protein moiety influences tLNP physicochemical properties, including tLNP surface area, decoration, and shape

Ongoing work:

- Correlation between determined physicochemical properties & LNP behavior for better predictive safety and efficacious tLNP formulations to treat obstetric disorders

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