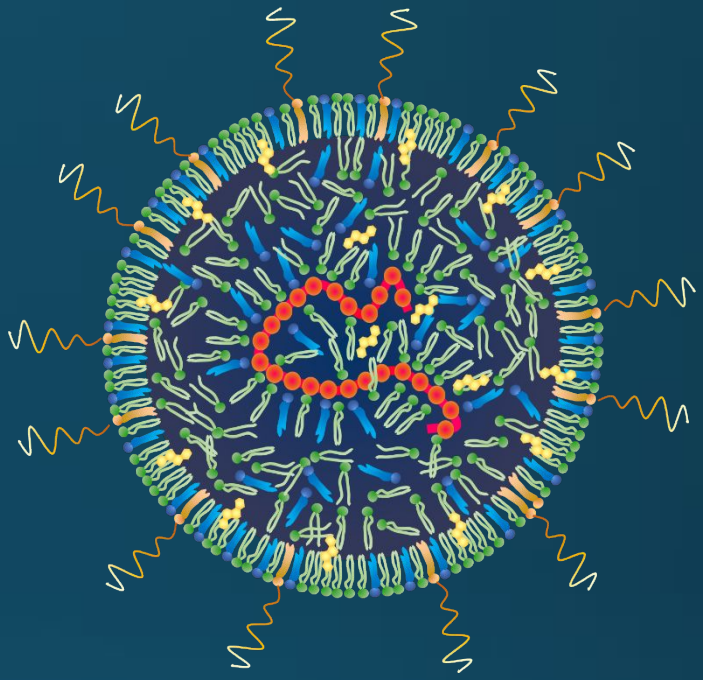
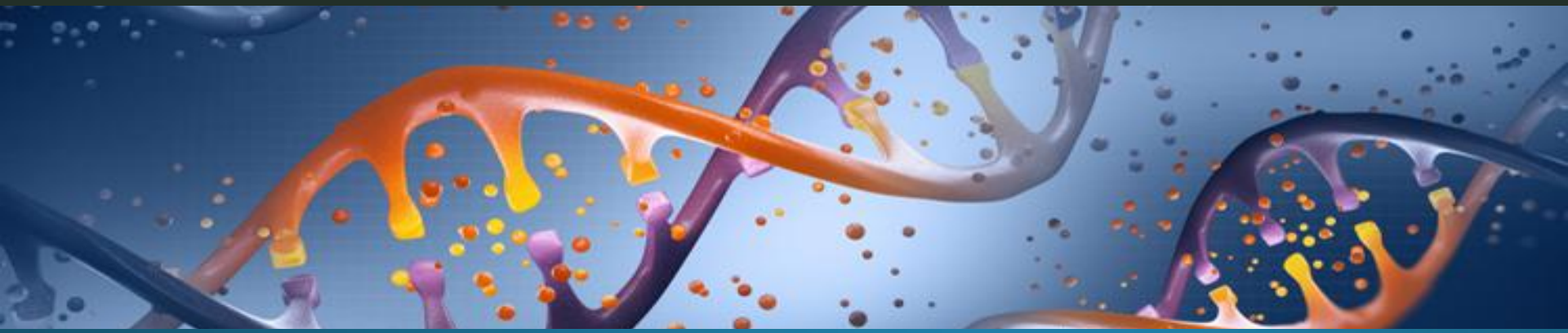
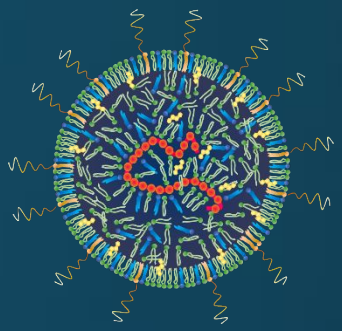


COATSOME® SS Series: Biodegradable Lipid Nanoparticles for Gene Delivery and mRNA Vaccines with Room Temperature Stability

Syed Reza, Drug Delivery Consultant, NOF AMERICA CORPORATION



KEY FEATURES OF COATSOME® SS Series



SS Series are highly biodegradable and this property increases their tolerability and gene delivery activity

Variable Immunogenicty

Highly Stable LNP Drug Product

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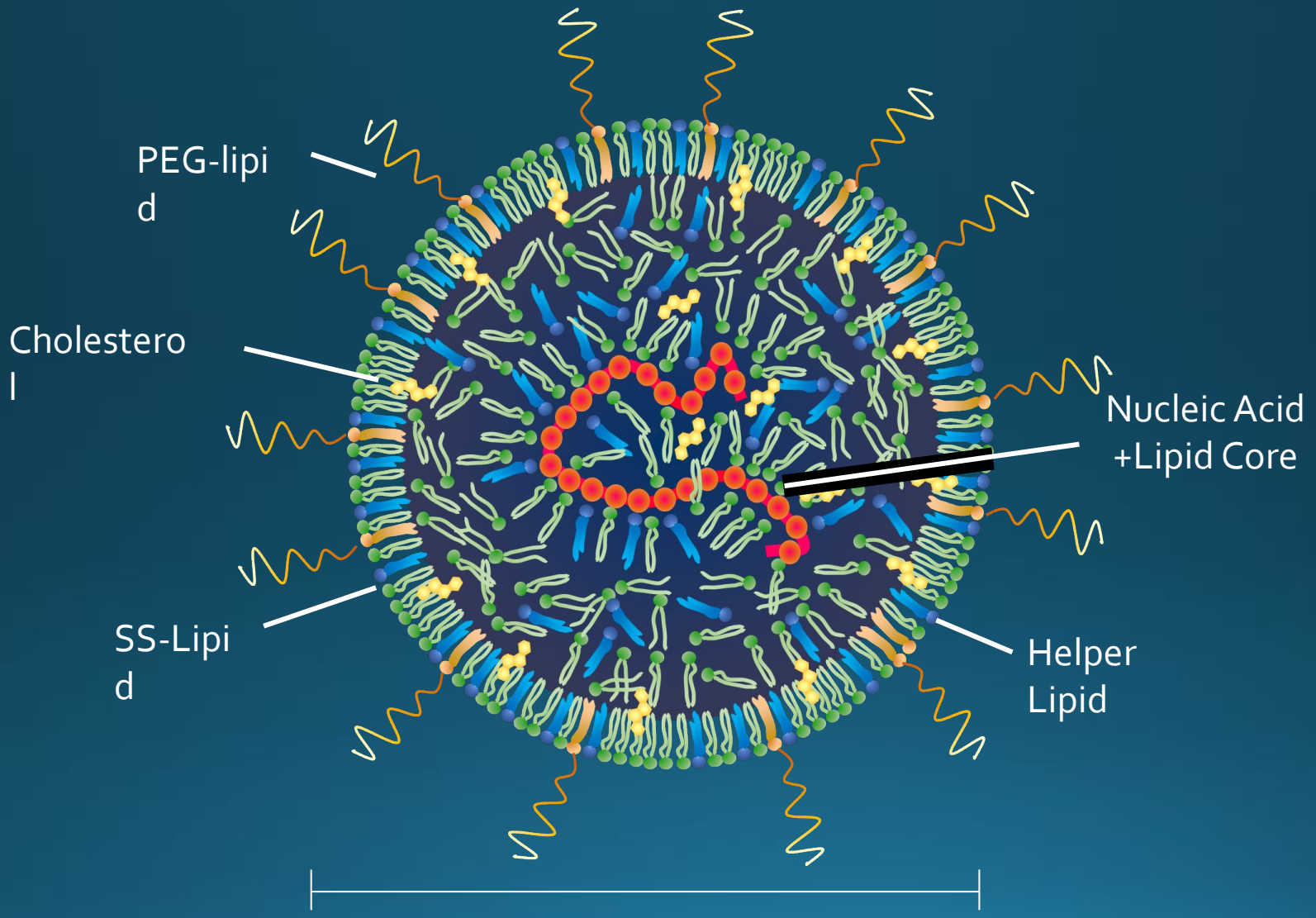
SS-LIPID COATSOME® PARTICLE



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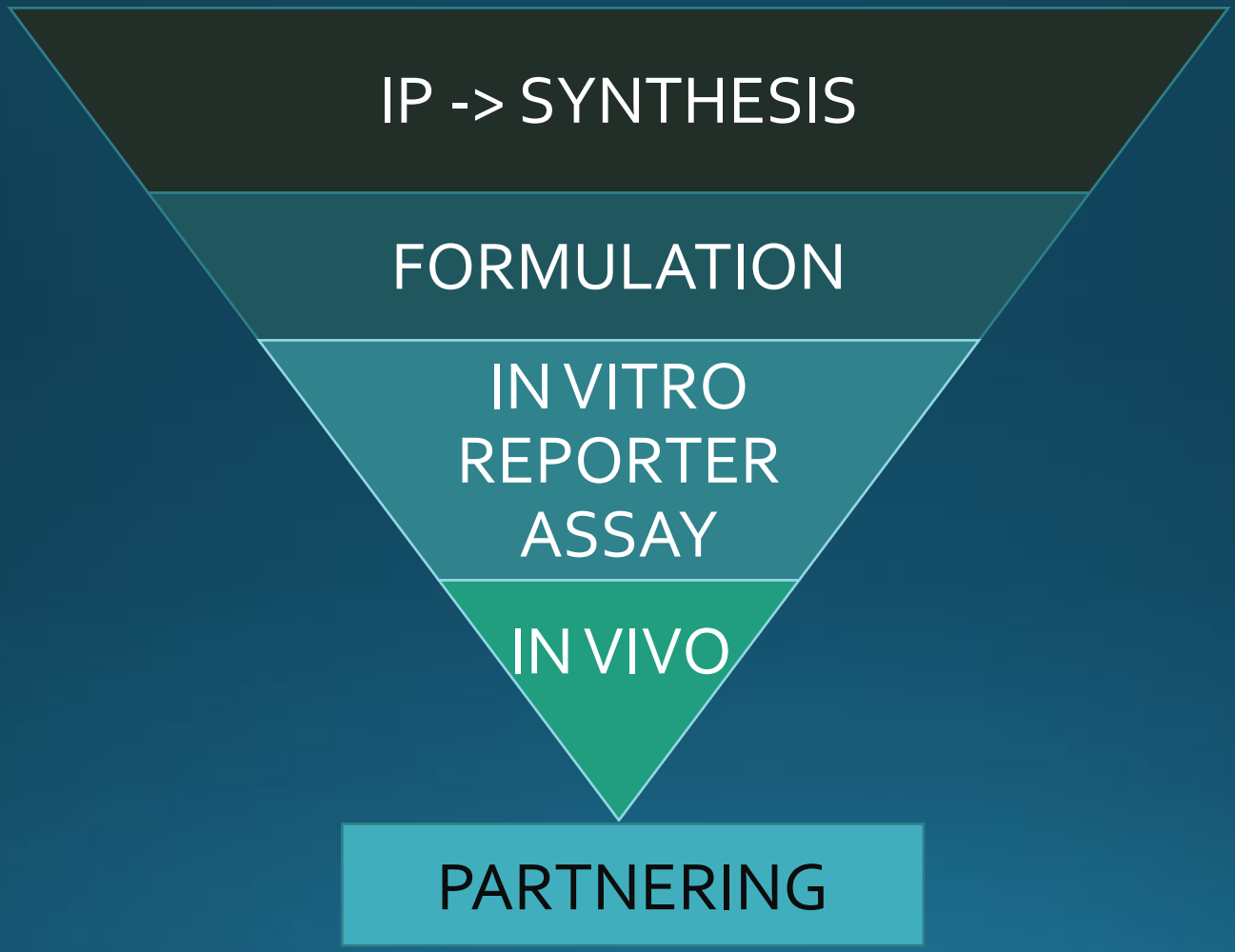
FULLY INTEGRATED DISCOVERY



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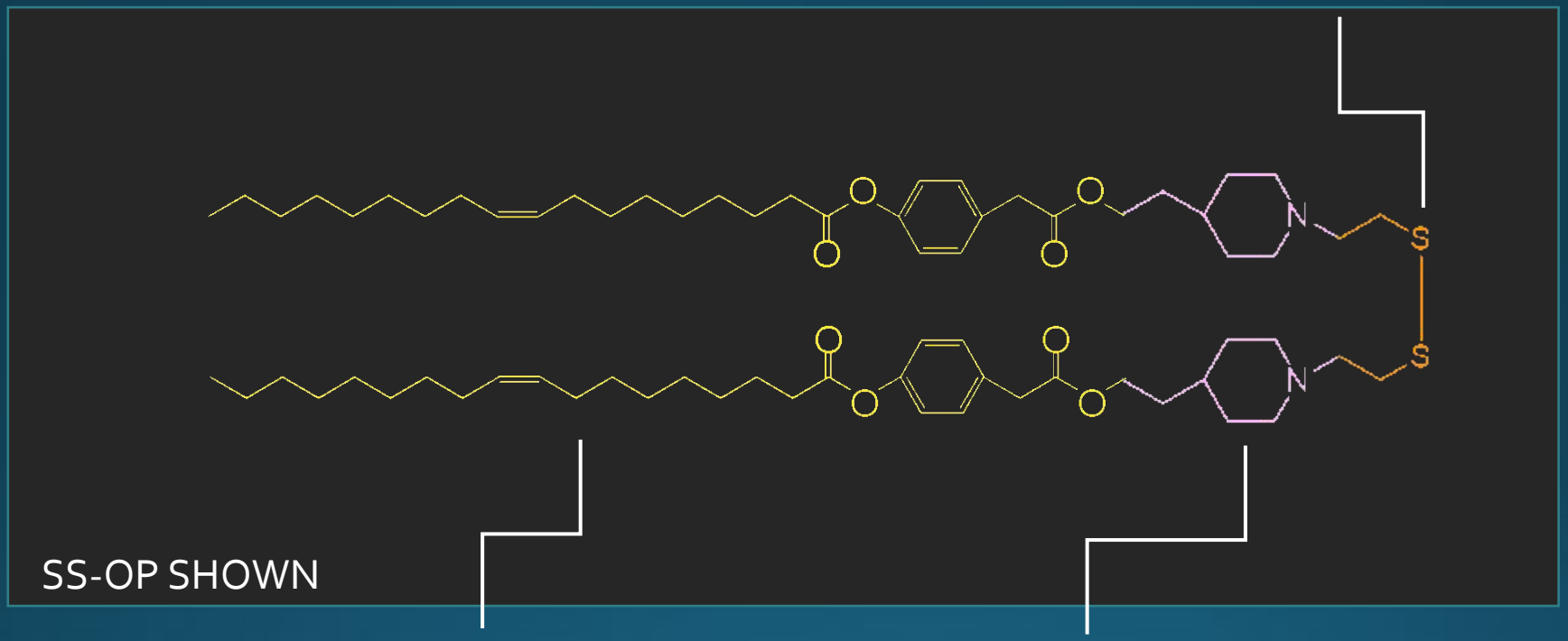
SS-LIPID STRUCTURE

DISULFIDE BOND
(CLEAVABLE)



SS-OP SHOWN

FATTY ACID
(Hydrolyzable)

TERTIARY AMINE
(IONIZABLE)

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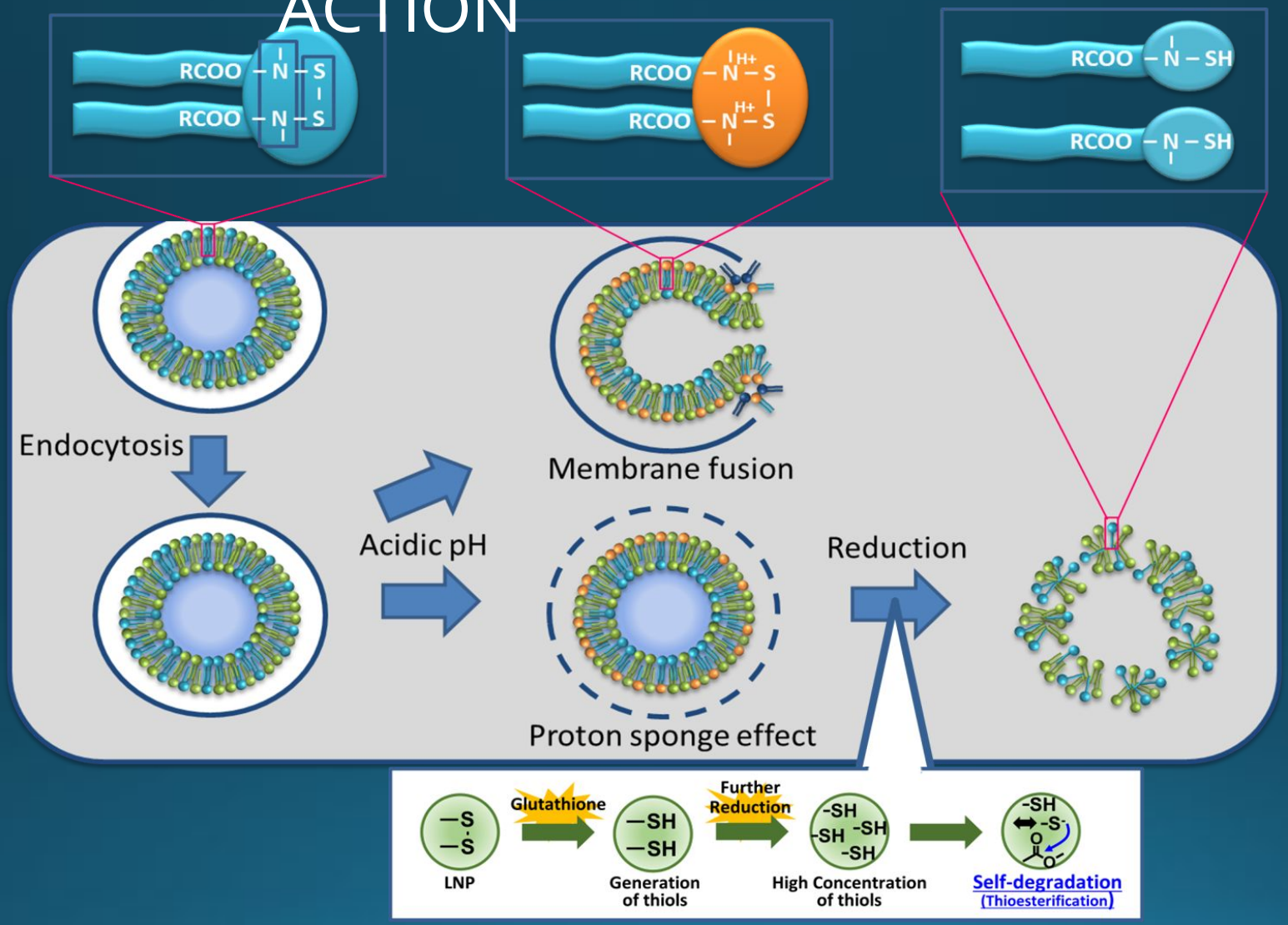
MECHANISM OF ACTION



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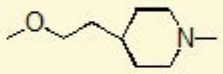
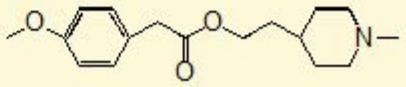
SS-Lipids COATSOME® SS Series PRODUCT RANGE

$$RCOO\text{-}X\text{-}CH_2CH_2\text{-}S$$
$$RCOO\text{-}X\text{-}CH_2CH_2\text{-}S$$

Product name	RCO-	-O-X-	MW
COATSOME® SS-EC	α-D-Tocopherolsuccinoyl		1402.2
COATSOME® SS-OC	Oleoyl		905.5
COATSOME® SS-OP	Oleoyl		1173.8

SS-EC induces immunogenicity

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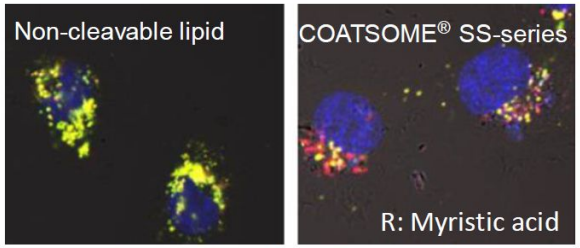
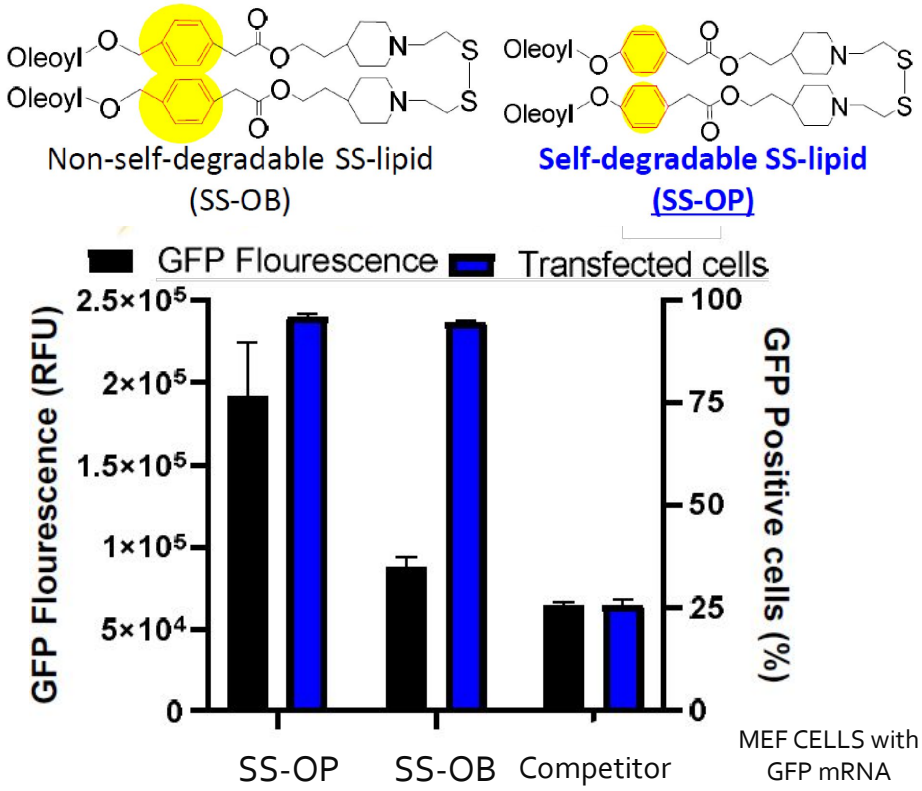
BIODEGRADABILITY = HIGH GENE EXPRESSION

LIPID-CC | SS-M



(L): pDNA in control liposomes remain bound to membrane (yellow)

(R): pDNA (red) delivered by COATSOME dissociates from endosome lipid (green).



NON-BIODEGRADABLE LIPID TRAPS DNA

GENE EXPRESSION OF BIODEGRADABLE SS-OP IS HIGHER THAN MORE STABLE ANALOGS

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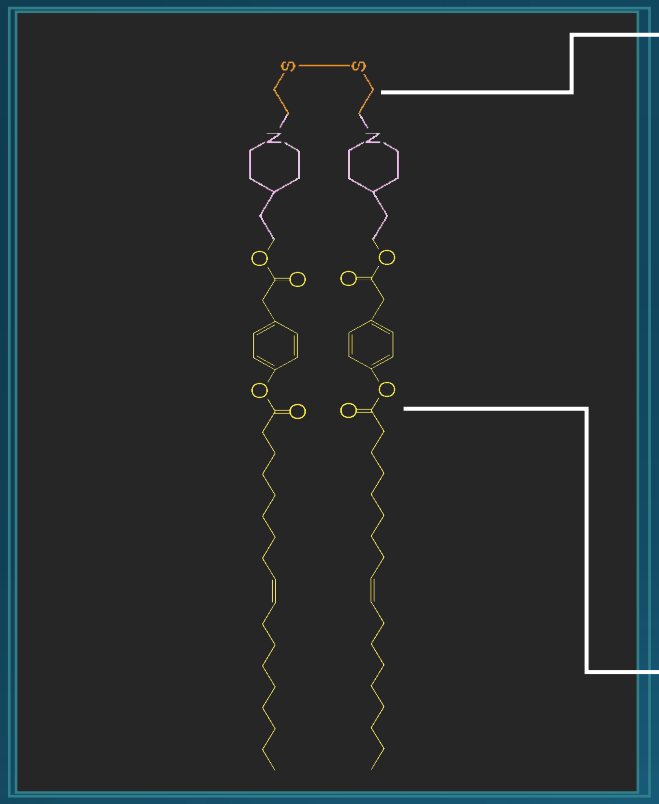
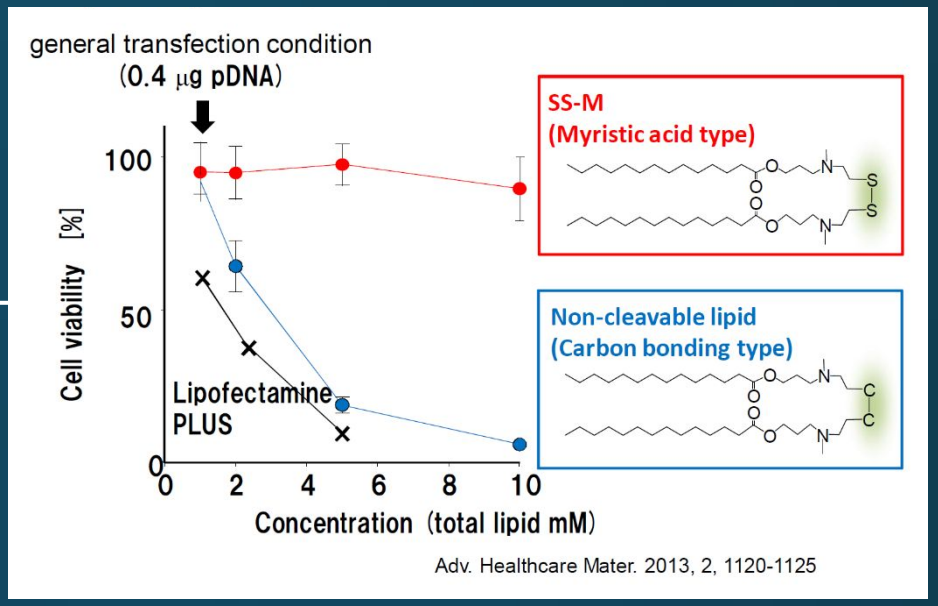
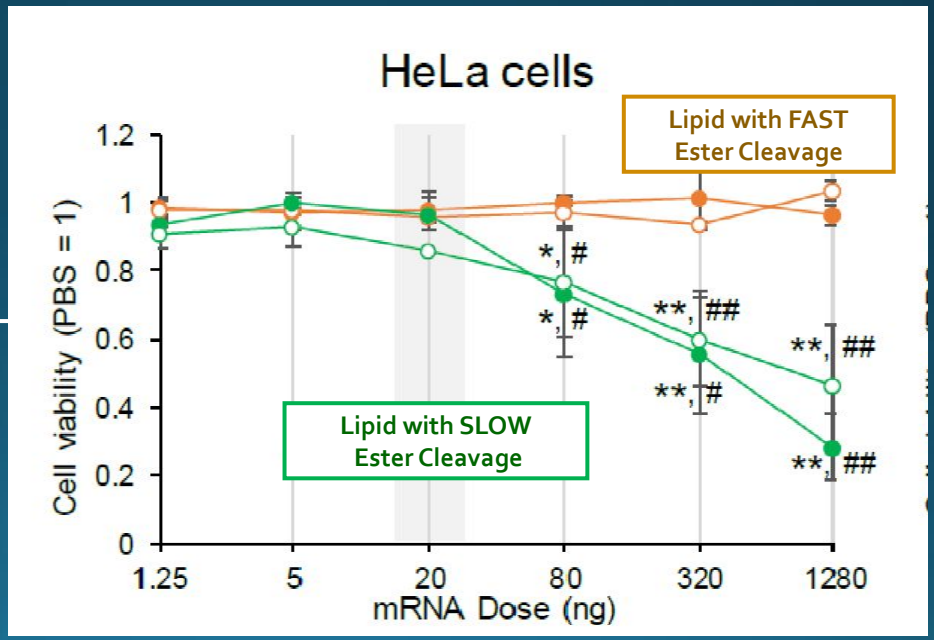
8

BIODEGRADABILITY = LOW TOXICITY





Adv. Healthcare Mater. 2013, 2, 1120-1125



CELL VIABILITY INCREASES WITH IMPROVEMENTS TO DEGRADATION CHEMISTRY

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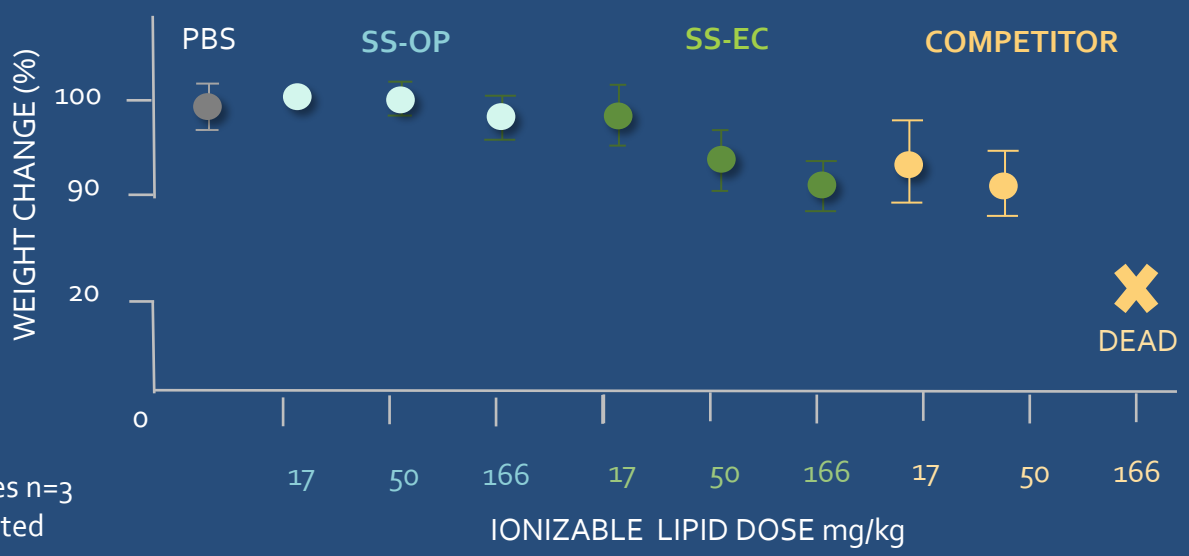
9

SS LIPIDS HAVE LOW SYSTEMIC TOXICITY

LIPID COMPOSITION

70% LIPID
30% CHOL
3% DMG-PEG-2000



MICE

BALB/c 6wk females n=3
200 ul volume injected

SS-Lipids are well tolerated via systemic route

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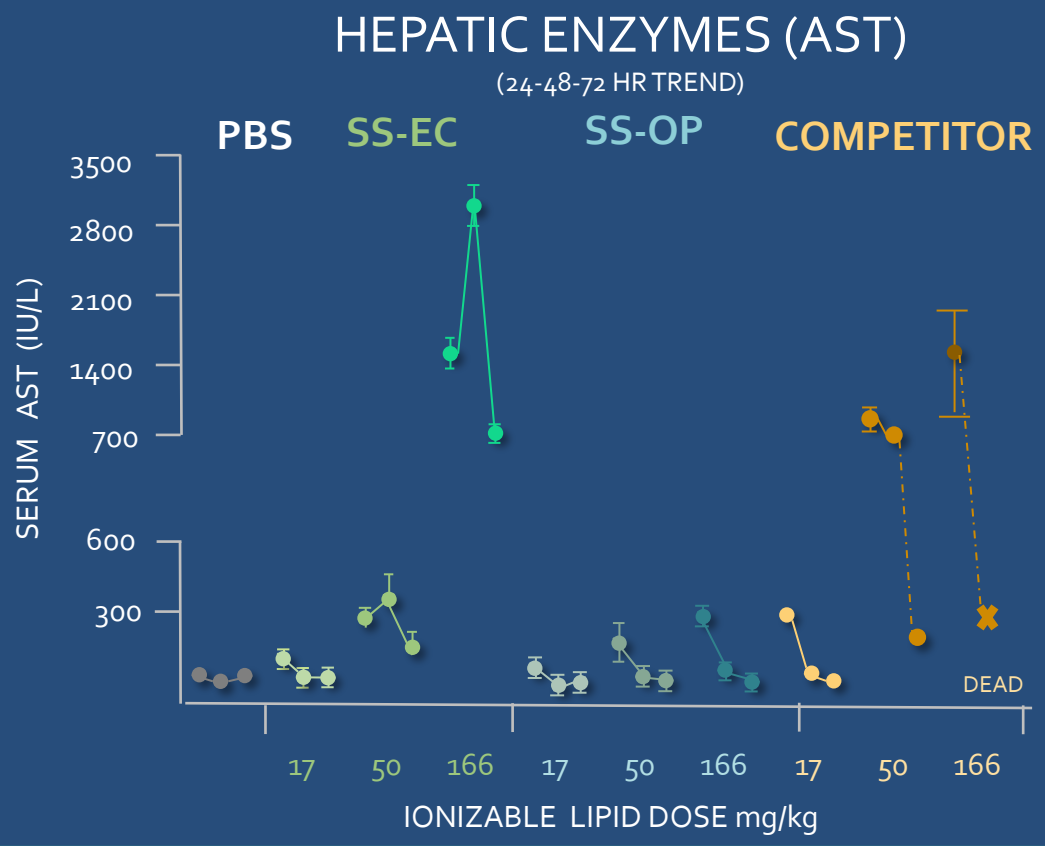
SS LIPIDS HAVE LOW HEPATIC TOXICITY

MICE

Balb/c 6wk females n=3
200 ul volume injected



SS-EC and SS-OP have reduced hepatotoxicity compared to conventional ionizable lipids.

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COATSOME® FORMULATIONS

COATSOME®-HEPATIC

COATSOME®-IVT

COATSOME®-SPLEEN

COATSOME®-VAX

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COATSOME®-HEPATIC

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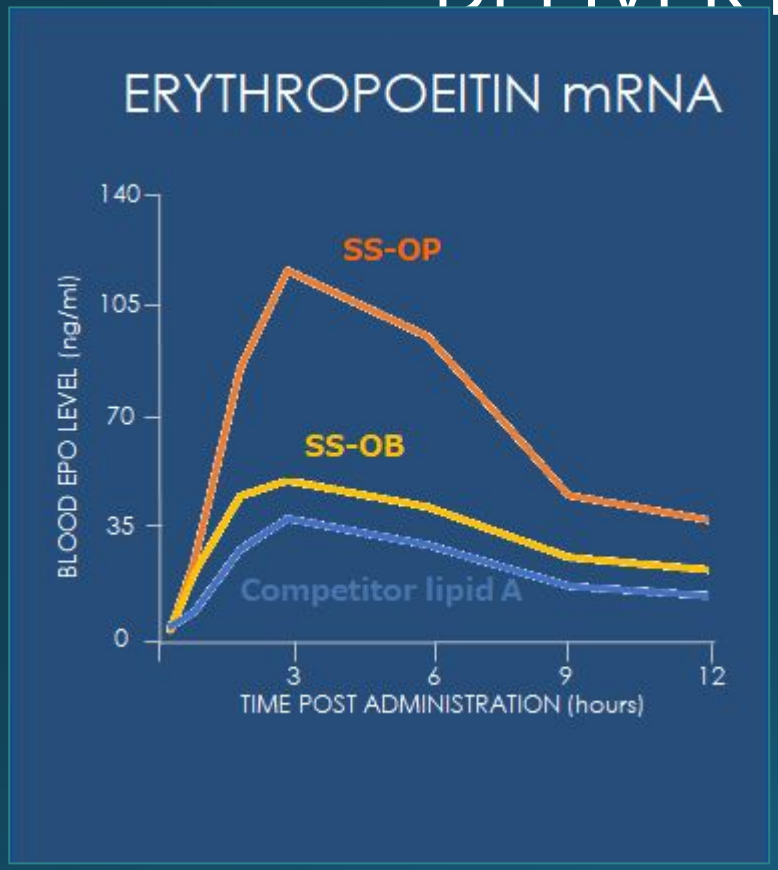
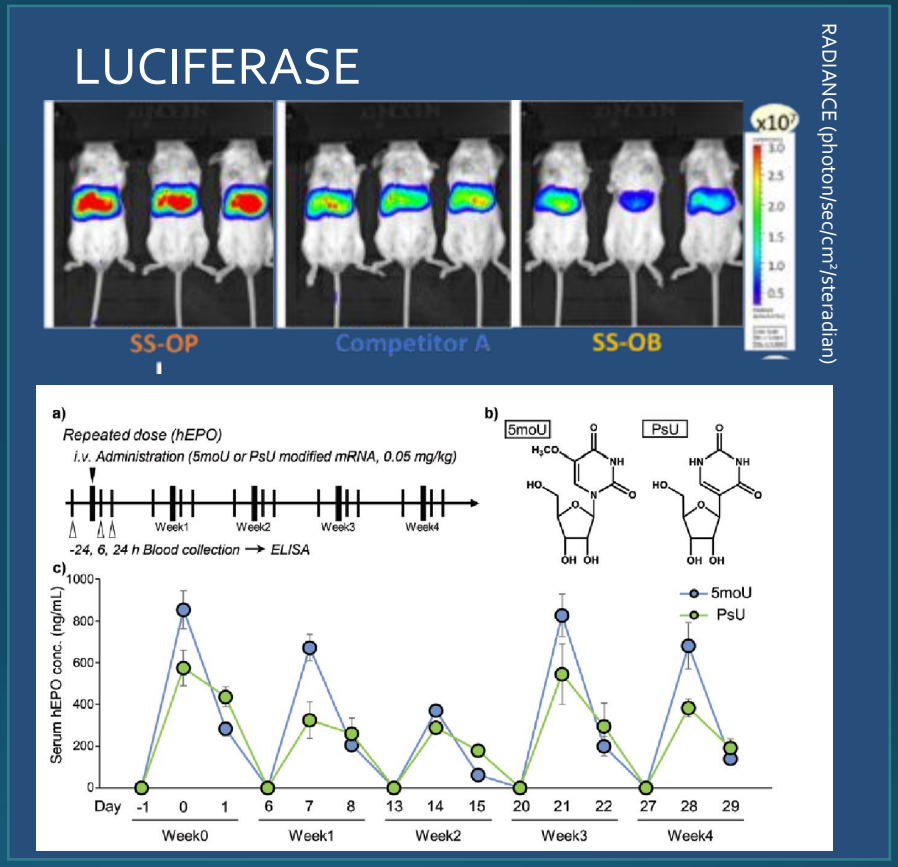
IN VIVO mRNA DELIVERY





Intravenously administered LNPs mainly introduced mRNA to liver. LNPs using SS-OP showed higher transgene activity than LNPs using conventional LNP.

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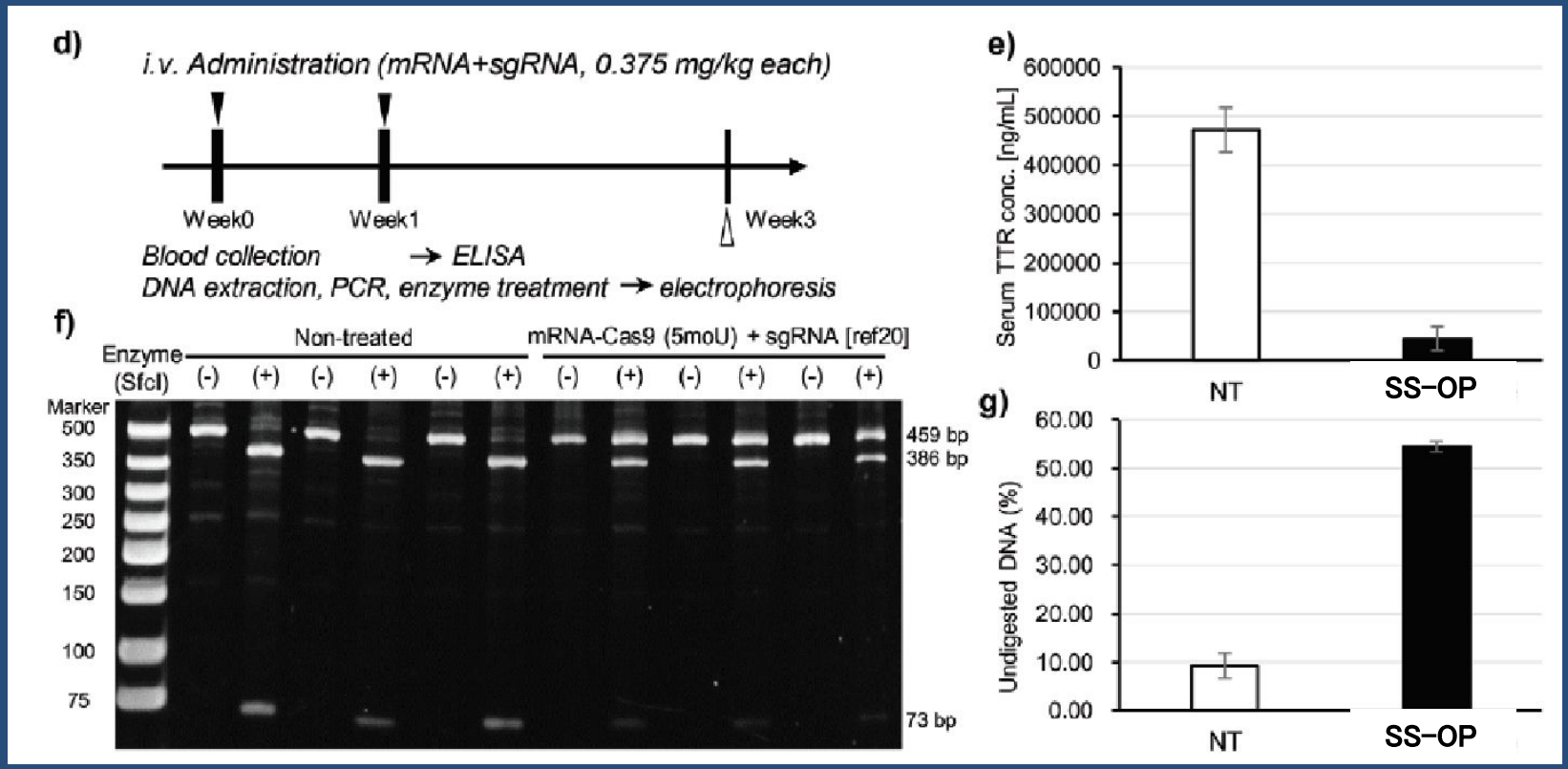
CRISPR-Cas9 GENE EDITING



After two weeks 55% hepatocytes edited, >98% decrease in serum TTR

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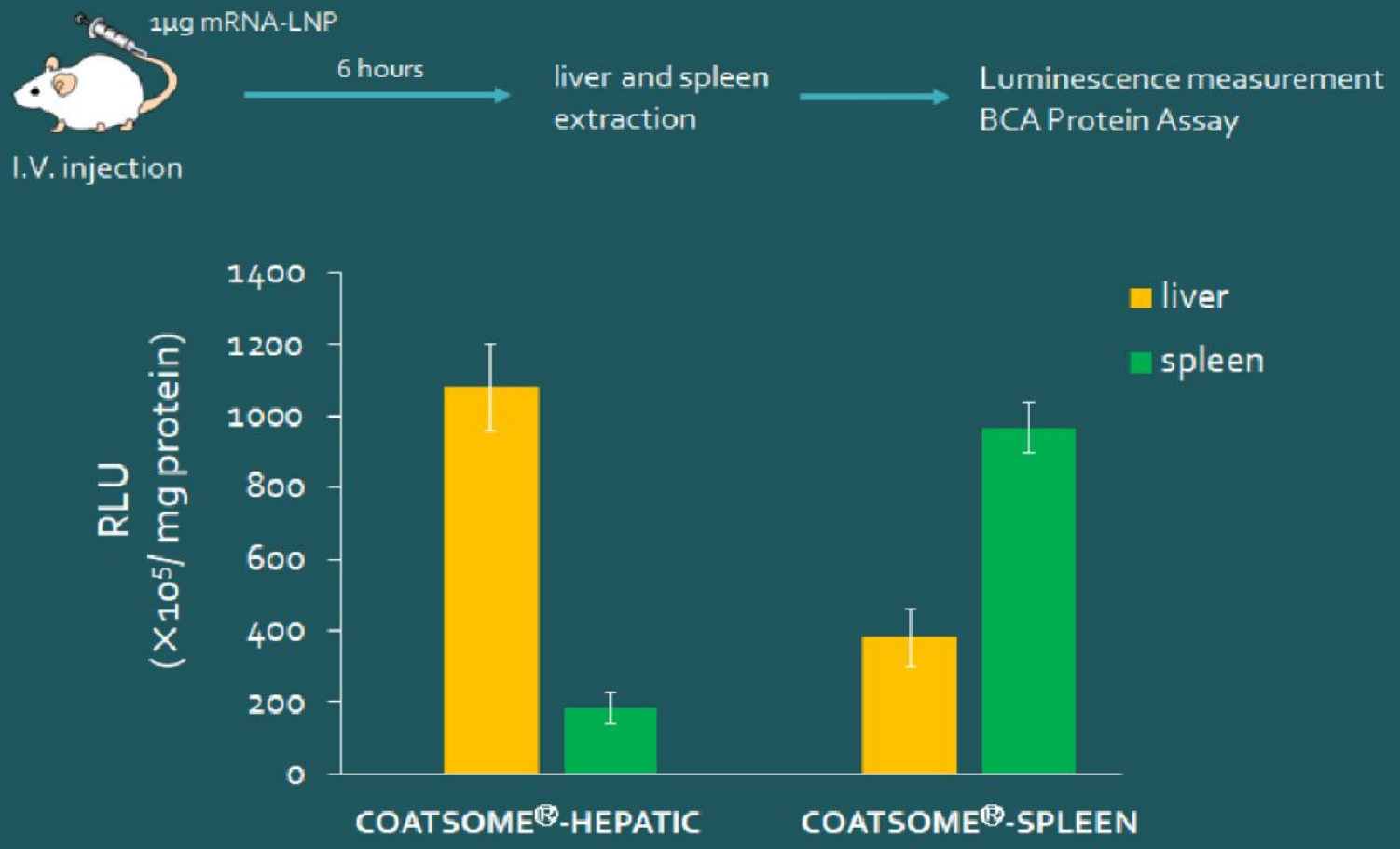
SPLENIC DELIVERY



COATSOME-SPLEEN IS HIGHLY TARGETED

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COATSOME®-VAX

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OUR APPROACH TO IMMUNOGENICITY

PYROGENIC CYTOKINES

TNF-α

IL-6

IL1-β

CELLULAR IMMUNITY

IFN-β

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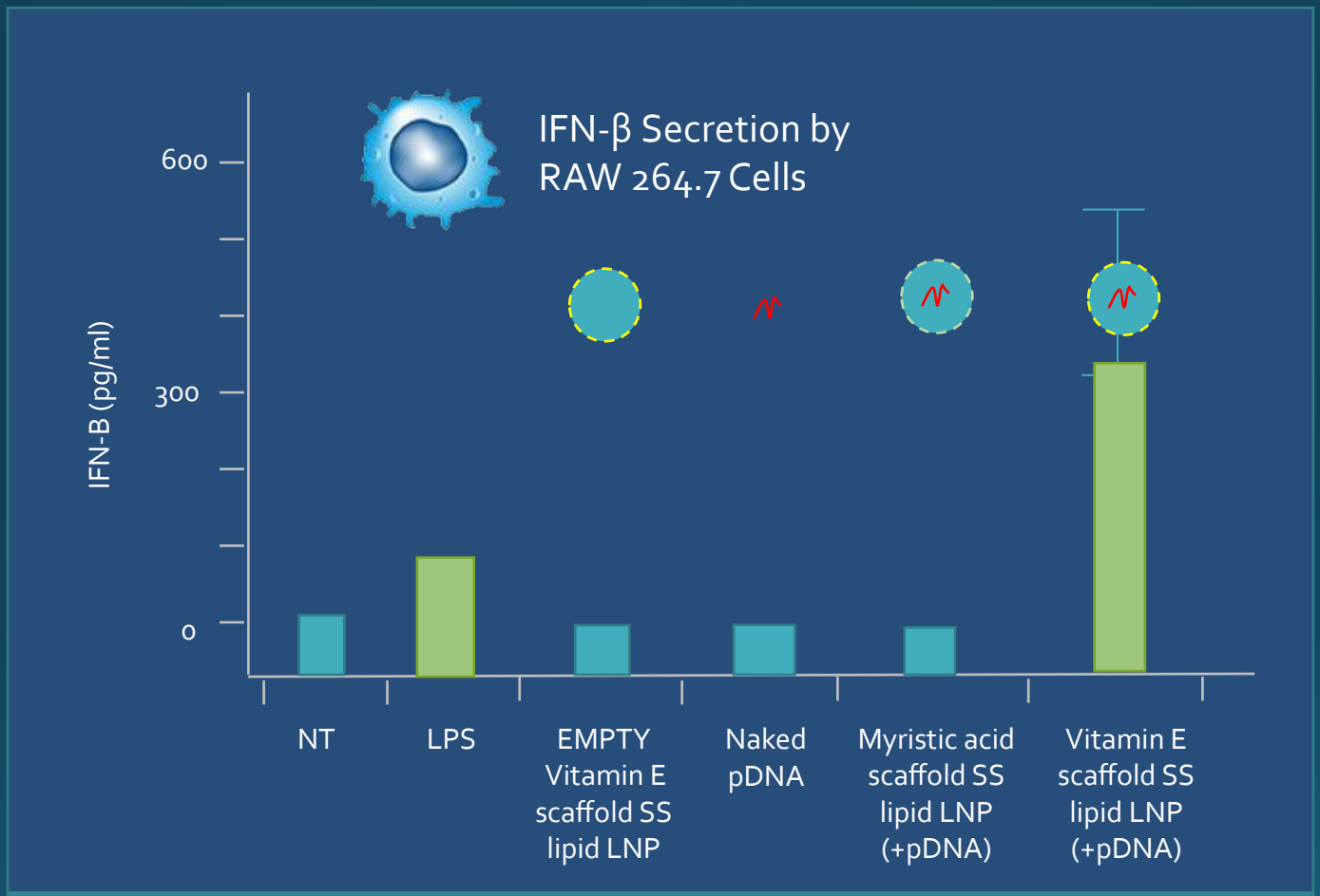
SCREENING OF IMMUNOGENIC LIPIDS



Only combination of Vitamin E scaffold SS lipid and DNA induces macrophage activation

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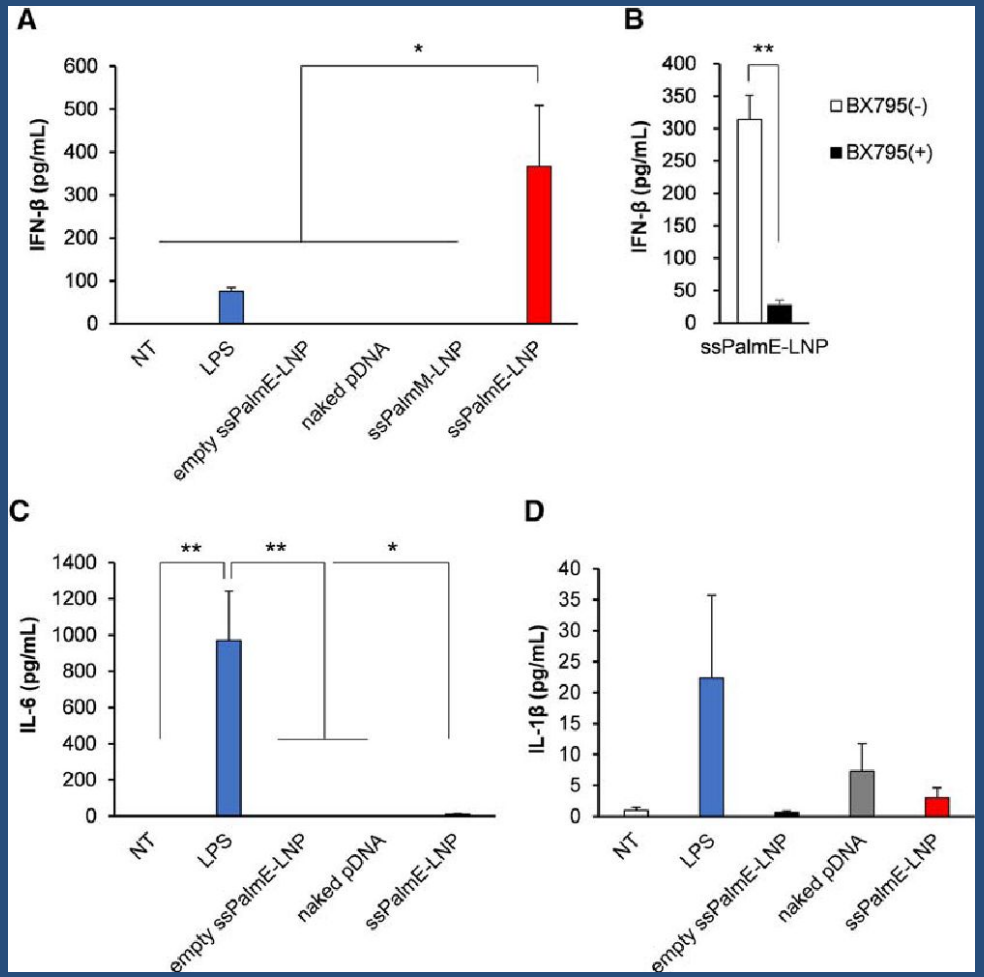
Vitamin E scaffold SS lipid SPECIFICALLY INDUCES IFN-β



Vitamin E scaffold SS lipid induces IFN-B but not other broad inflammatory cytokines.

IFN-B stimulation is blocked by TLR/STING inhibitor.

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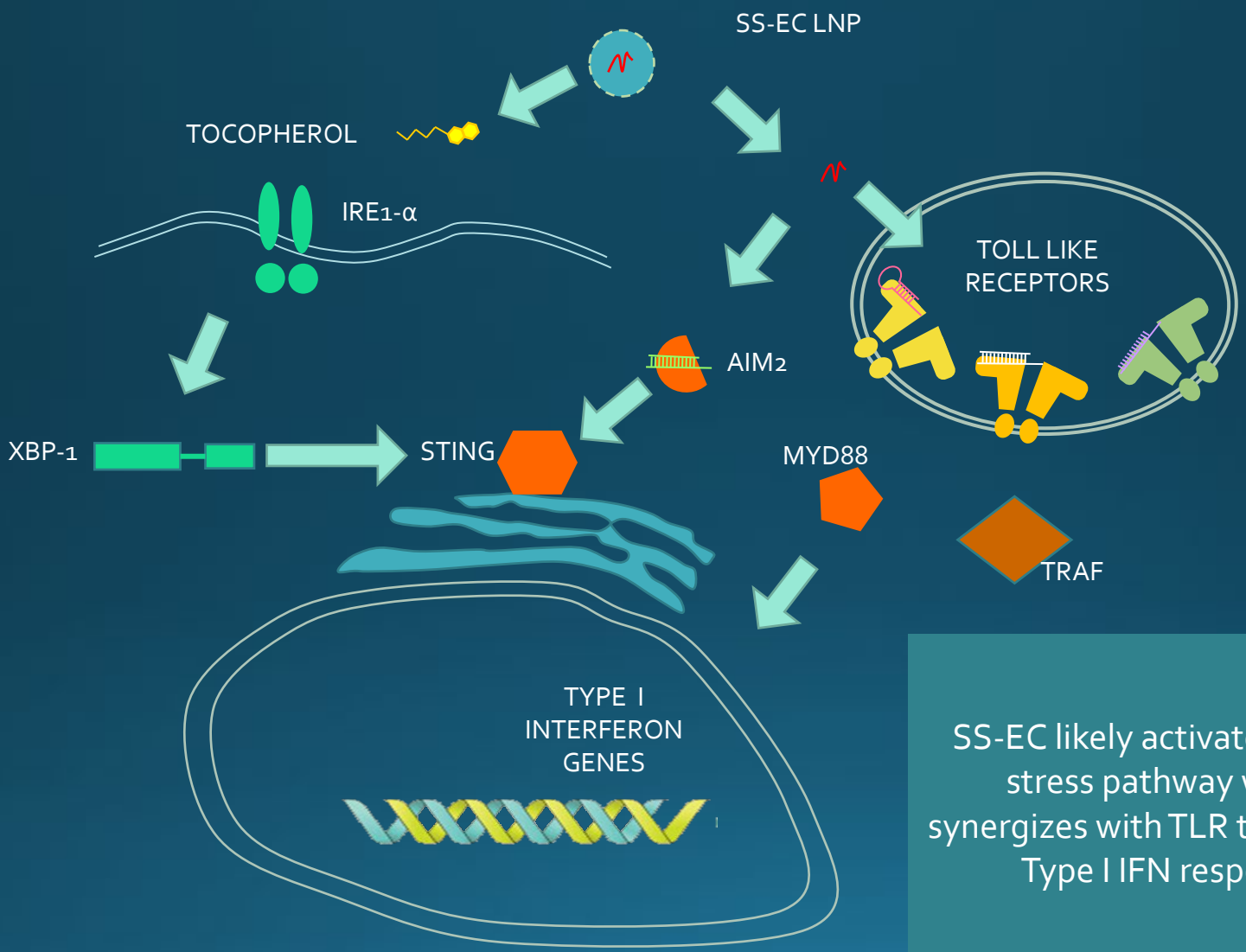
SS-EC LNP MECHANISM OF ACTION



SS-EC likely activates the ER stress pathway which synergizes with TLR to promote Type I IFN response

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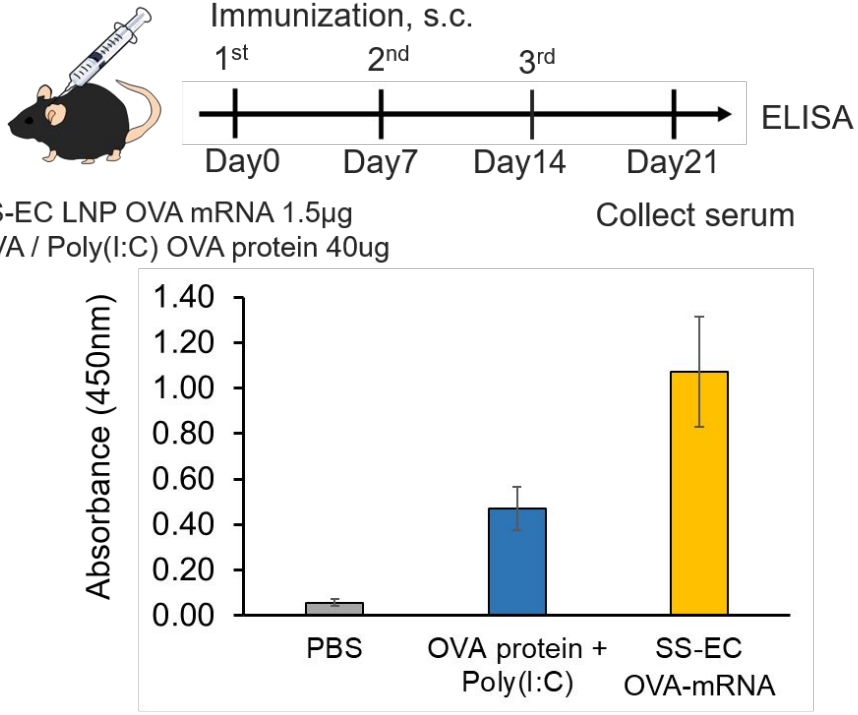
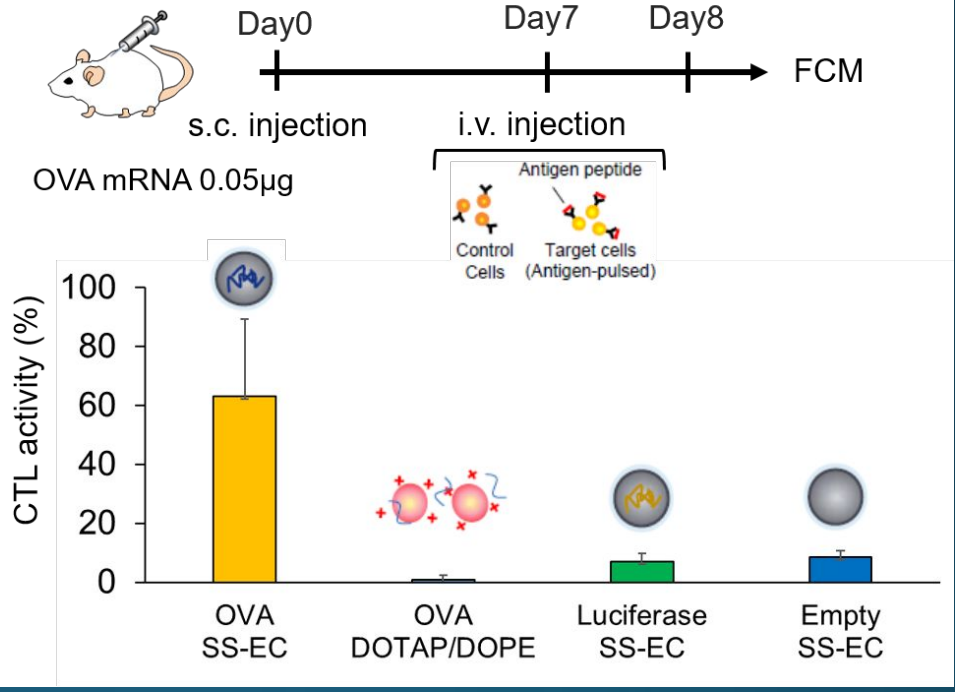
HUMORAL AND CELLULAR IMMUNITY

IgG ASSAY



CTL ASSAY



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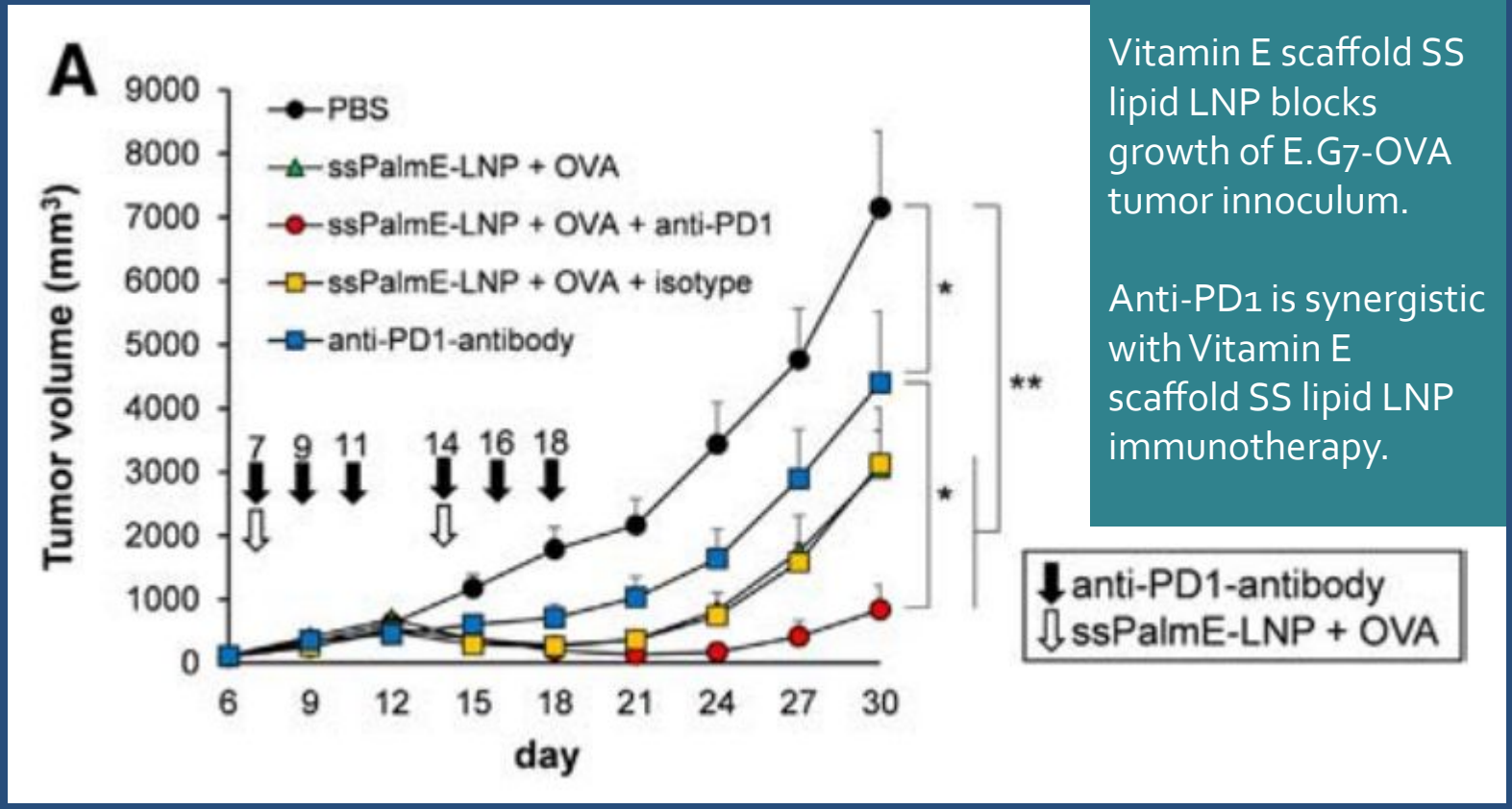
TUMOR VACCINE MODEL



Vitamin E scaffold SS lipid LNP blocks growth of E.G7-OVA tumor innoculum.

Anti-PD1 is synergistic with Vitamin E scaffold SS lipid LNP immunotherapy.

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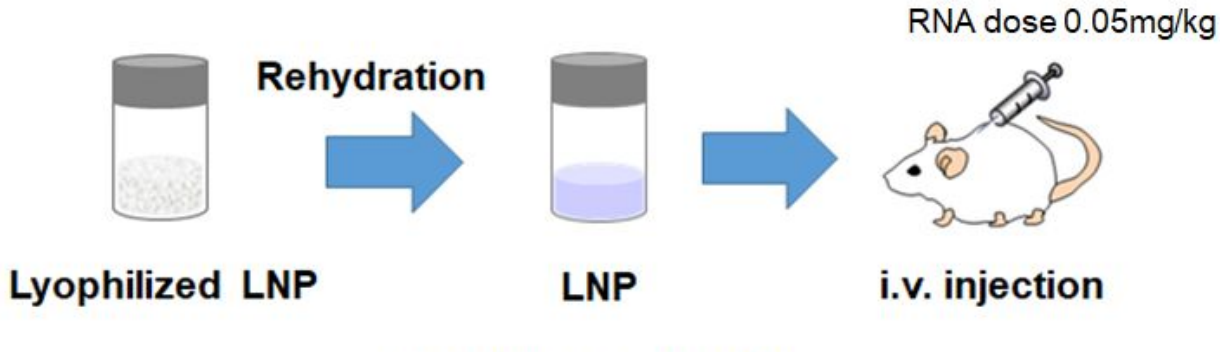
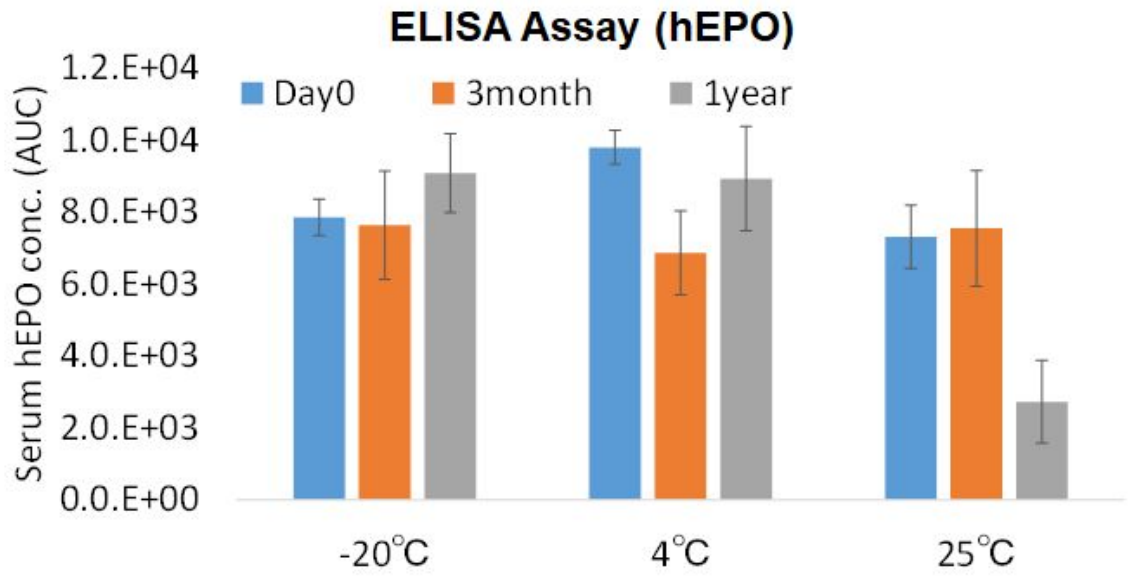
LYOPHILIZED LNP FOR LONG-TERM STRAGE





Lyophilized LNP was stable for 1 year at 4 ℃ and 3 months at room temperature.

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CONCLUSIONS

SS-Lipids are highly biodegradable, ionizable lipids that are well tolerated in vivo.

SS-EC LNP activates macrophages and promotes migration in lymph nodes whereas SS-OP is non-immunogenic.

Properties of SS-Lipids have been optimized for multiple applications.

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WORKING WITH NOF

- Scalable cGMP lipid supply
- CMC package (drug product, analytical methods)
- Regular updates from our preclinical program (metabolism study, anti-drug antibody assays, rodent and NHP studies)
- Strong IP Estate with multiple patents on SS-Lipids

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ACKNOWLEDGEMENTS

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Ms. Yui Kitazawa
Mr. Yuhei Onizuka
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