117. Liver-targeting tolerogenic Nanoparticles

(University of California-Los Angeles)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Nanoparticle
Disease Area	Inflammatory Disease
Indication	Autoimmune Disease
Current Stage	Lead Optimization
Target	Scavenger and mannose receptors on specialized tolerogenic liver sinusoidal endothelial cells (LSECs)
MoA	• NP^{OVA} induced abundant TFG-β, IL-4, and IL-10 production, which was further increased by surface ligands. • NP^{OVA} suppressed anti-OVA IgE responses, airway eosinophilia and TH2 cytokine production in the bronchoalveolar lavage fluid.
Brief Description	• Antigen specific interventions for allergies and autoimmune disorders—two groups of disorders characterized by patients' hyperactive immune response against non-pathogenic bodies—are limited in number and efficacy • UCLA inventors present a novel nanoparticle based therapeutic platform that induces immune tolerance towards a predetermined antigen in animal models. Through targeting of tolerogenic antigen presenting cells in the liver, researchers demonstrated, as a proof of principle, that administration of nanoparticles to mouse models of asthma and anaphylaxis can reduce these potentially fatal systemic allergic disorders. • There is also preliminary evidence that the same is true in animal models for rheumatoid arthritis, lupus, and type I diabetes. Importantly, the tolerogenic effect can be obtained by using intact, antigens or representative epitopes in these disease models, thereby avoiding the need for nonspecific immunosuppression or immune modulatory therapies. The tolerogenic nanoparticle platform is earmarked for treatment of a wide range of allergic disorders and autoimmune diseases.
Intellectual Property	WO2021096972A1
Publication	Use of Polymeric Nanoparticle Platform Targeting the Liver To Induce Treg-Mediated Antigen-Specific Immune Tolerance in a Pulmonary Allergen Sensitization Model. ACS Nano. (2019)
Inventors	Andre E. Nel, Tian Xia, Qi Liu

Highlights

- Treats cause rather than symptoms for allergies/autoimmune diseases.
- Targets a novel cell type in the liver that exert widespread control over systemic immune responses.
- Can be designed for intact allergens as well as specific epitopes.
- Can treat a wide variety of diseases characterized by overactive, misguided immunity.

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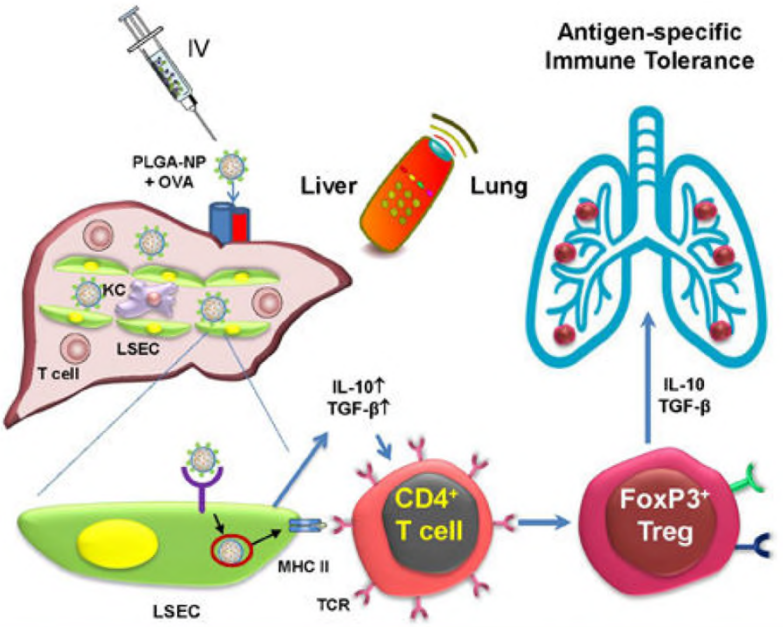
Key Data

Graphical Abstract



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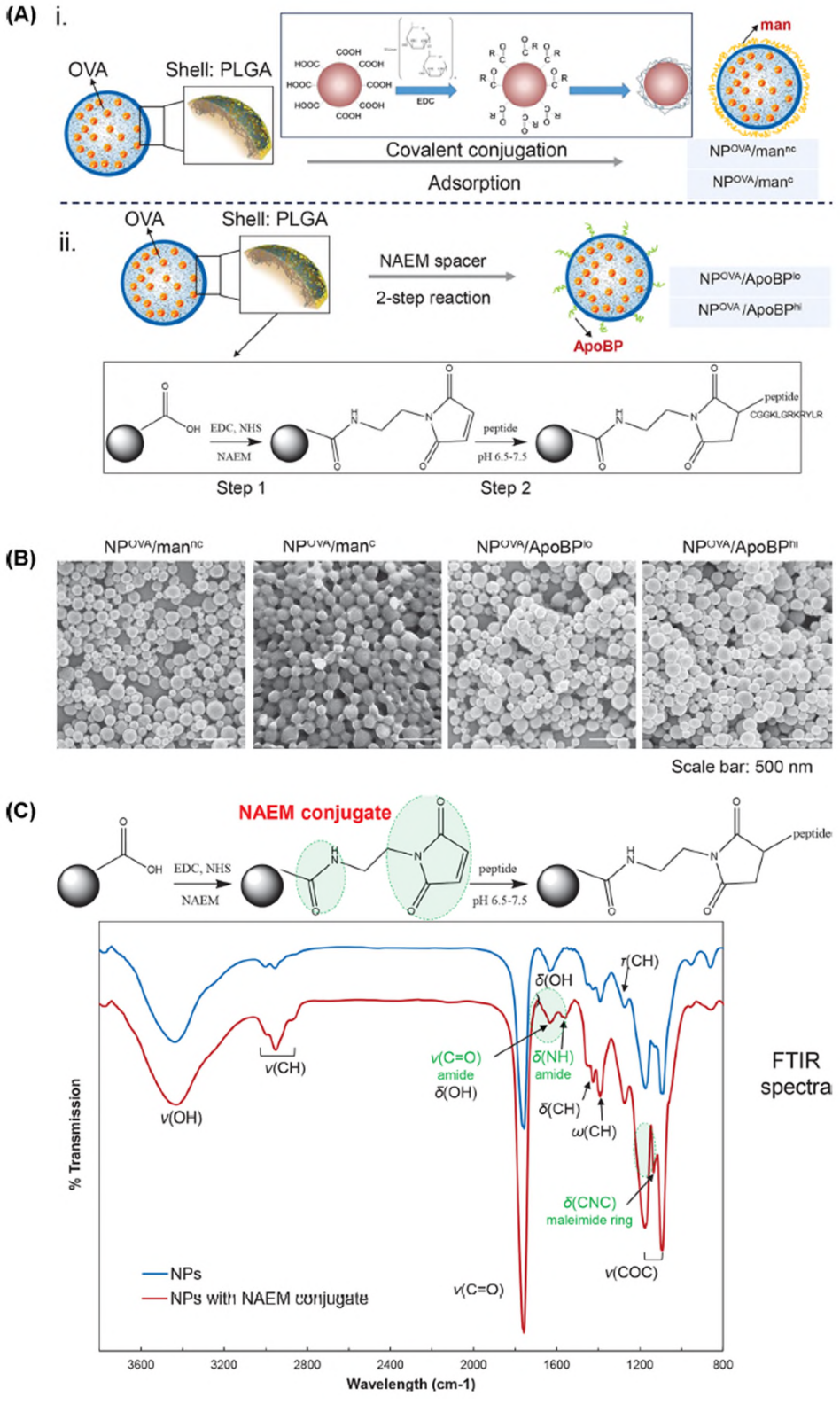
Synthesis and characterization of the LSEC-targeting PLGA NP platform for OVA delivery.



To be continued

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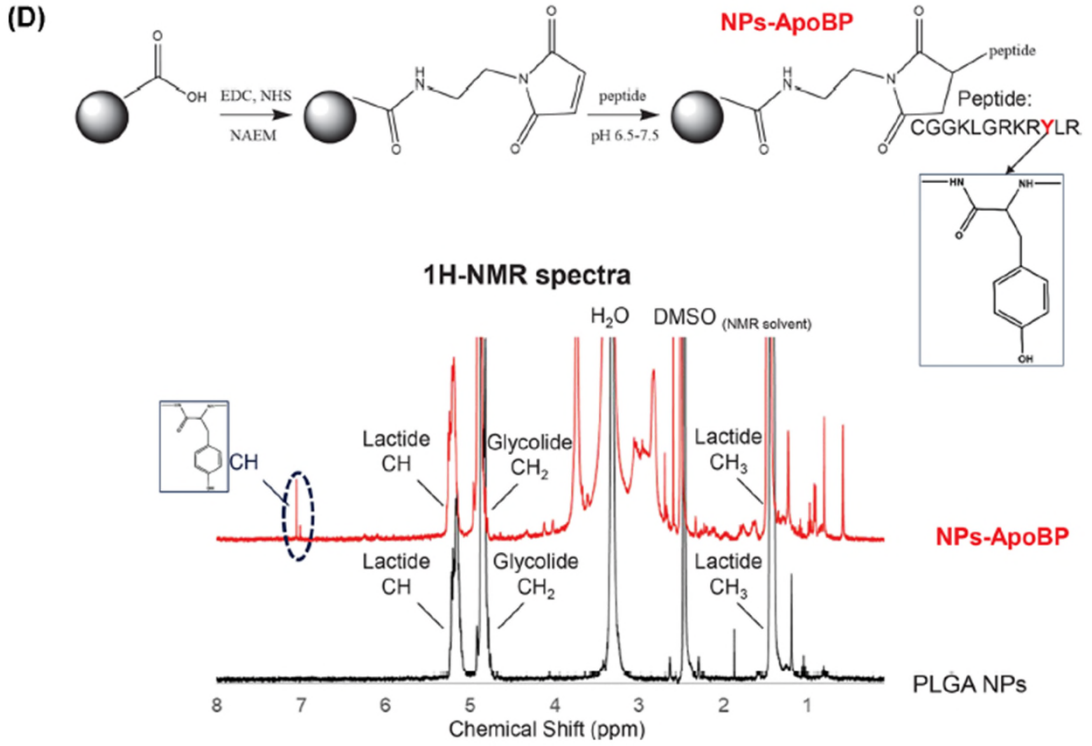

(A) Schematic showing particle surface decoration with mannan and ApoBP: (i) mannan (man) was either physically adsorbed to the particle surface or its hydroxyl-terminus used for covalent conjugation to the PGLA COOH-terminal groups; (ii) ApoBP was linked to the NP surface by a NAEM spacer, using a two-step conjugation process between the ApoBP cysteine tag and the NAEM maleimide group. (B) Scanning electron microscopy pictures to show NP morphology, in the presence of attached ligands. (C) Fourier transform infrared spectra of the NAEM-conjugated NPs. (D) 1H NMR spectra of the synthesized particles with and without the ApoBP attachment, showing the appearance of the newly conjugated peptide at 7 ppm.

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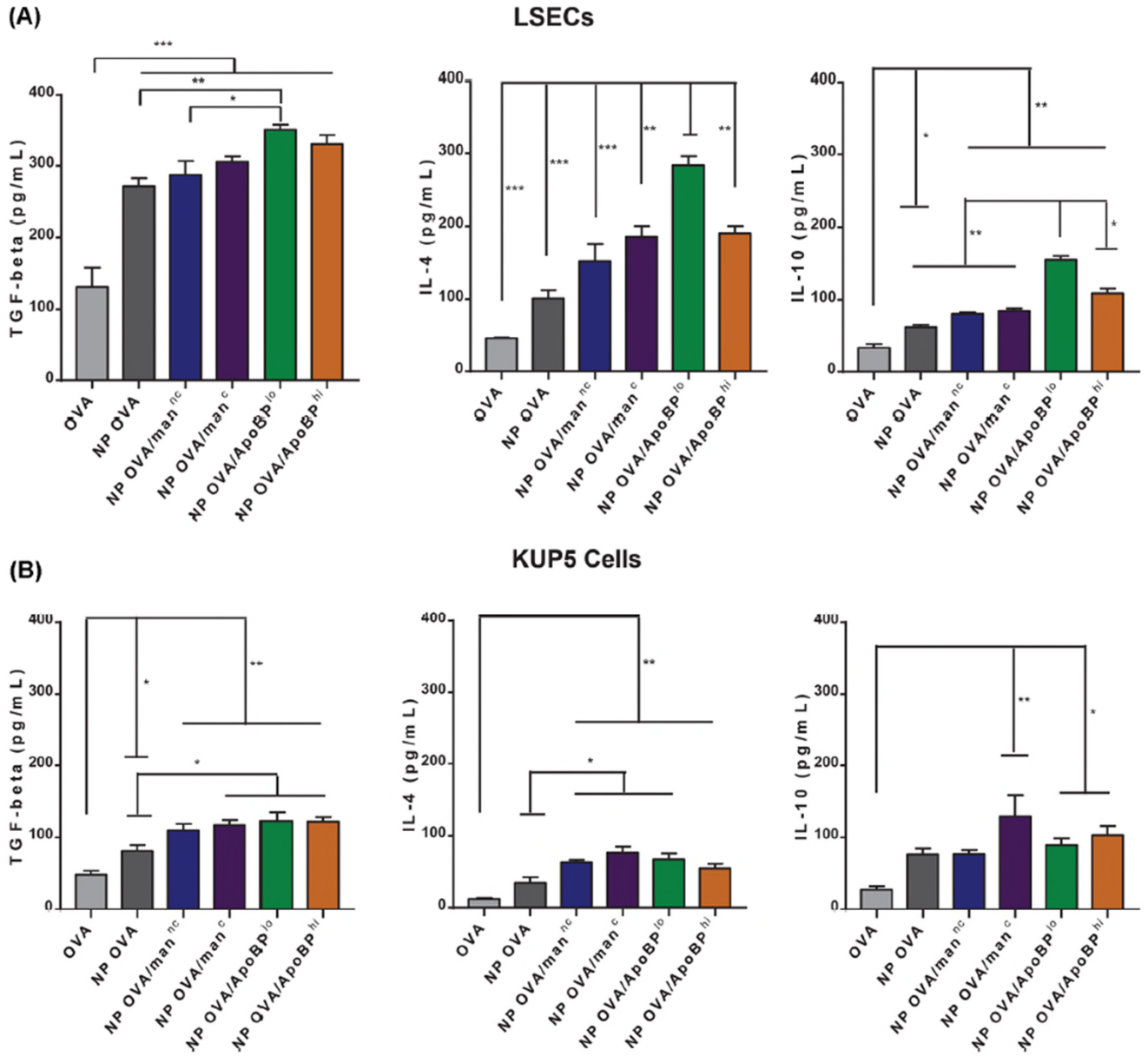
Assessment of the effect of NPs on tolerogenic cytokine production, including TGF-β, IL-4, IL-6, and IL-10 in LSECs



(A) and KUP5 cells (B). These cells were treated with NPs for 24 h, before removal of supernatants and assessment of cytokine content, using ELISA kits according to the manufacturer's instructions. Data are expressed as the mean ± SEM (n = 6); *p < 0.05; **p < 0.01; ***p < 0.00 (one-way ANOVA followed by Tukey's test).

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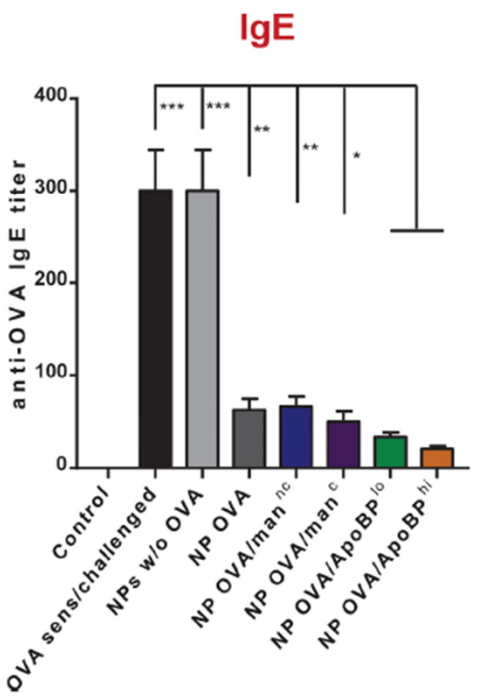
NP pretreatment interferes in OVA-induced antibody responses in an OVA sensitization model.

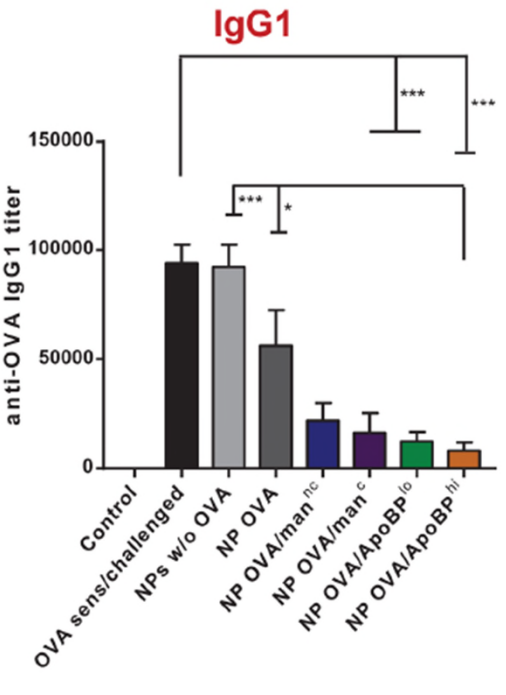
(A)

C57BL/6
6 mice/group

STEP		GROUP	OVA	Nanoparticles	PBS	
1 & 2 Treatment	1	Control	0	0	0	Control
	2	OVA sens/challenged (No NPs)	0	0	0	No treatmer
	3	NPs w/o OVA	0	500 μg	100 μL	
i.v. injection	4	NP^{OVA}	25 μg	500 μg	100 μL	
	5	NP^{OVA}/man^{nc}				
	6	NP^{OVA}/man^{c}				
	7	$NP^{OVA}/ApoBP^{lo}$				
	8	$NP^{OVA}/ApoBP^{hi}$				Pre-treatment
STEP 3&4 Sens		OVA i.p. injection10 μg/mouse				
STEP 5 challenge		Aerosolized OVA 10 mg/mL, 20 min				

(B)





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NP pretreatment interferes in OVA-induced antibody responses in an OVA sensitization model.

(A) Outline of the experimental animal protocol. Six to 8 week old C57/BL6 mice received IV injection of NPOVA to deliver 25 μg OVA in 500 μg particles per mouse on days 0 and 7. The animals were subsequently sensitized by two IP doses of OVA (10 μg/mouse) on days 14 and 21, prior to being exposed to aerosolized OVA inhalation (10 mg/mL) for 20 min on days 35−37. Animals were sacrificed for tissue harvesting and BALF on day 40. The treatment groups (n = 6) in the experiment included (1) a control group without NP pretreatment, sensitization, or challenge; (2) no pretreatment before sensitization and challenge; (3) pretreatment with NPs w/o OVA before sensitization and challenge; or pretreatment with (4) NPOVA, (5) NPOVA/mannc, (6) NPOVA/manc, (7) NPOVA/ApoBPlo, (8) NPOVA/ApoBPhi before sensitization and challenge. (B) Serum anti-OVA IgE and IgG1 antibody titers were determined by ELISA. Data are expressed as the mean ± SEM; *p < 0.05; **p < 0.01; ***p < 0.00 (one-way ANOVA followed by Tukey's test).