Immunomodulatory nano in microgel to prevent extrahepatic islet graft rejection in type 1 diabetes

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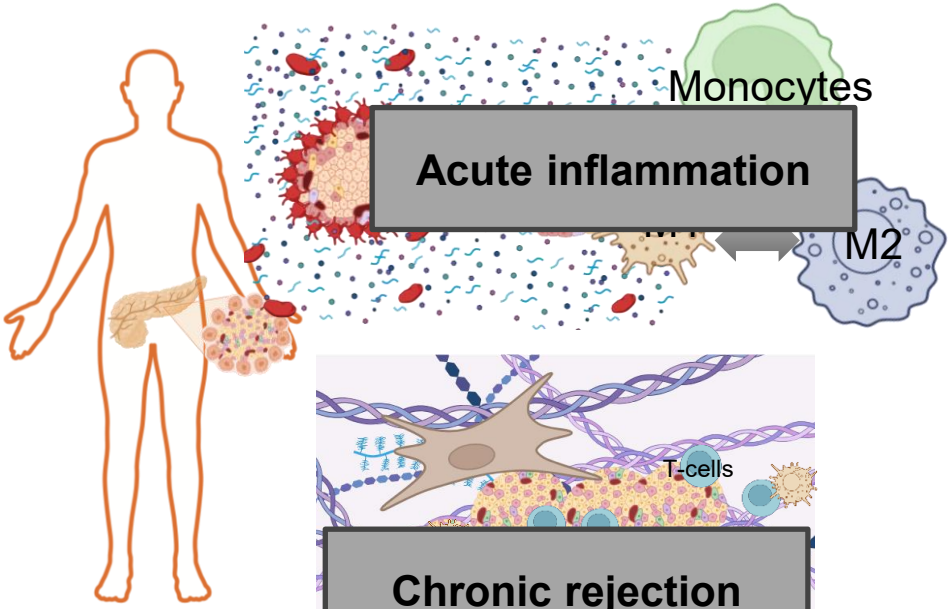
CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

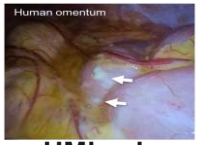
Autoimmune onslaught in type-1 diabetes



Why localized immunomodulation at extrahepatic islet transplant sites?

Extrahepatic transplantation

Omental Pouch | Prevascularized Subcutaneous Sites



UMiami
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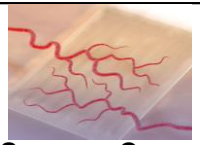
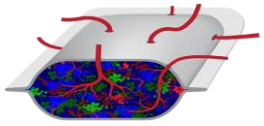
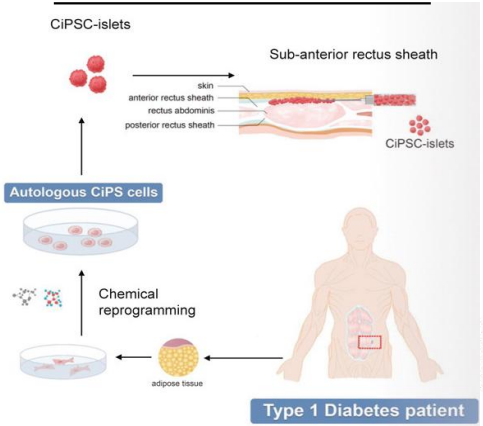


Sernova Corp
NCT03513939



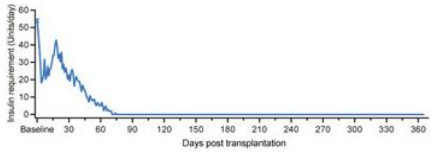
Vertex VC-02
NCT03162926

Sub-anterior rectus sheath

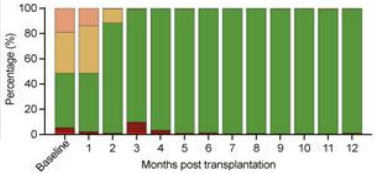


Wang et.al., ***Cell,*** 2024, 187(22):6152-64

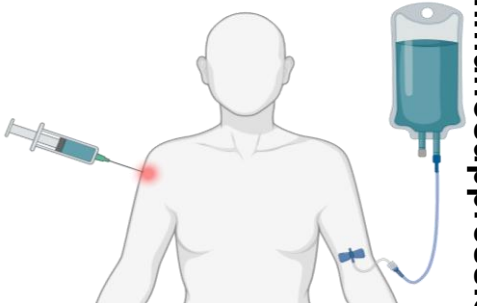
Insulin independence from 75 days post-transplantation



Time-in-target glycemic range > 98%



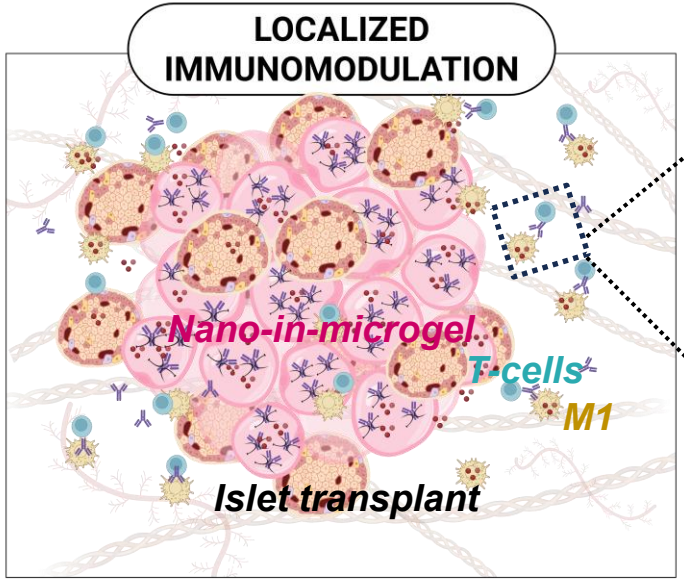
Systemic Immunosuppression

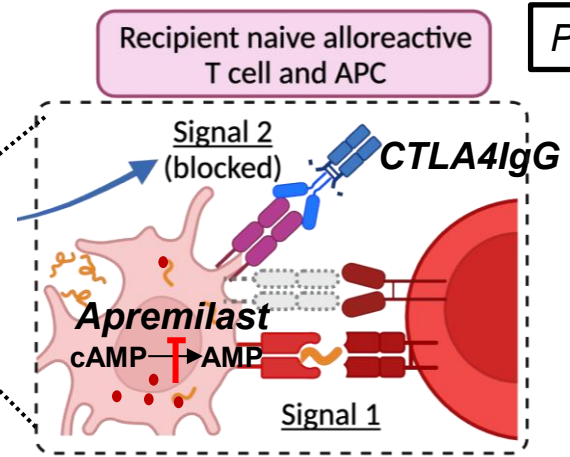


- General immuno-deficiency
- Secondary infections
- Cancer

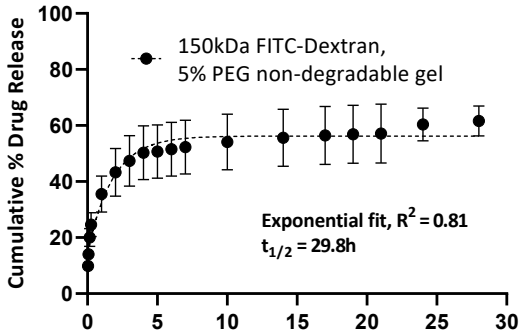
Challenges

How to accomplish effective immunomodulation?

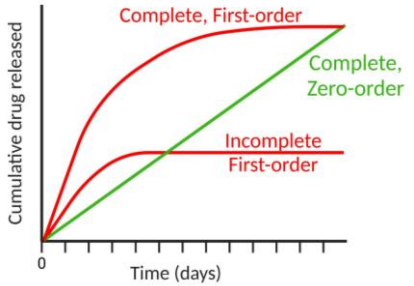




Passive drug loading within microgel



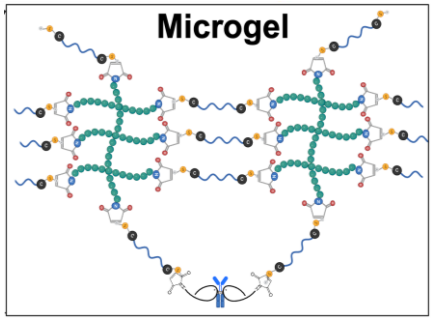
Burst incomplete release of high M.W. molecules from microgels



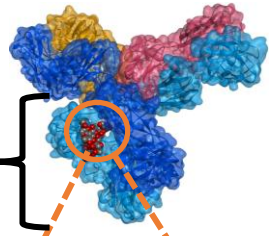
Unpublished (patent pending)

Nano-in-microgel for localized protracted combination delivery

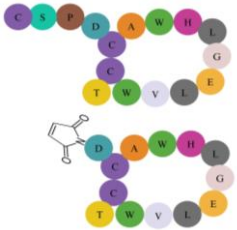
Can we co-deliver IgG-based biological drugs (CTLA4Ig) and hydrophobic islet friendly small molecules (Apremilast; APM) with the same biomaterial platform?



CTLA4IgG and Fc-III peptide complex

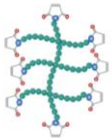


Thiol end-functional modification
CSP Fc-III

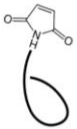


CTLA4Ig
human IgG1

MMP(A)
MMP-degradable crosslinker



PEG-MAL
10kDa 8-arm maleimide-PEG

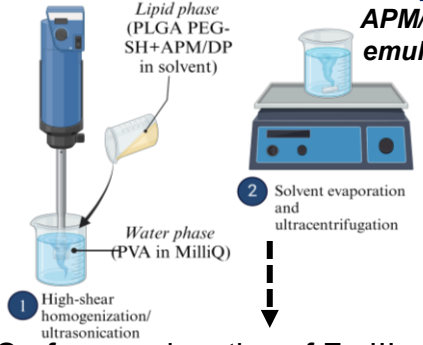


MAL Fc-III
Fc-binding peptide

MAL end-functional modification
MAL Fc-III

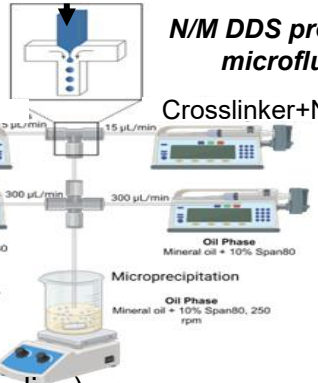
Unpublished (patent pending)

Development of nano in microgel



APM/DP NP preparation using emulsion solvent evaporation method

Surface conjugation of Fc-III peptide and CTLA4IgG on APM/DP loaded nanopellet

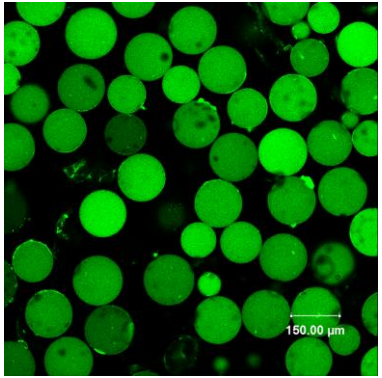


N/M DDS preparation using microfluidic device

PEG Mal+MAL Fc-III

Crosslinker+NP+CTLA4 IgG

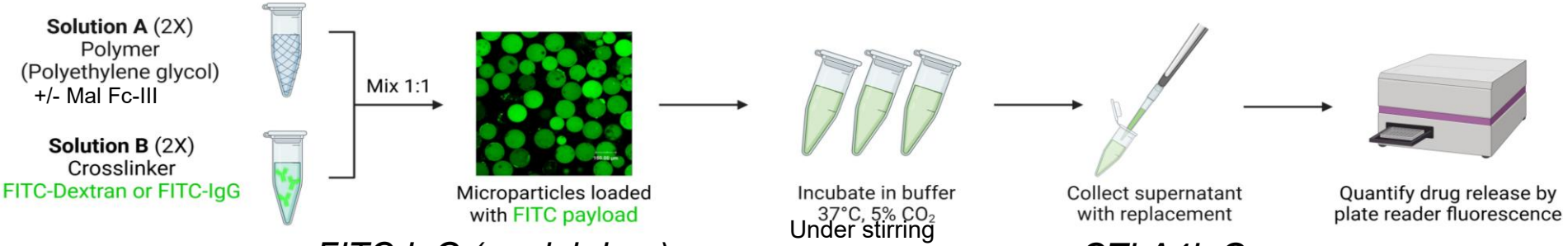
Unpublished (patent pending)



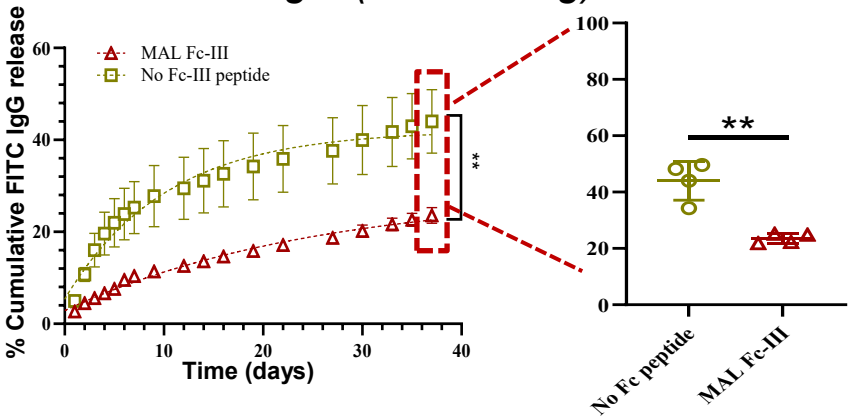
MMP-degradable PEG microparticles loaded with FITC-IgG

Particle size > 10 um & < 200 um to avoid phagocytosis and fibrosis

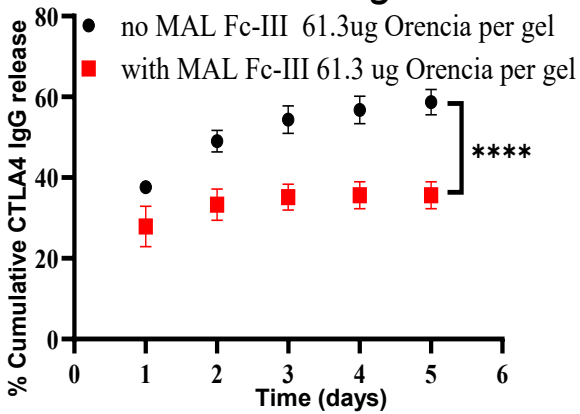
In-vitro drug release studies from microgel



FITC IgG (model drug)



CTLA4IgG

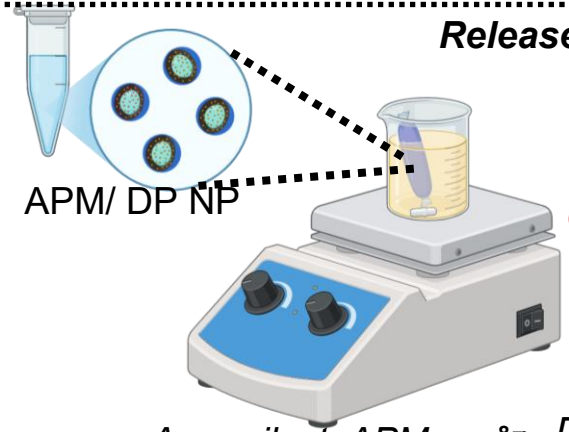


Zero order protracted drug release with Fc-III peptide

Unpublished (patent pending)

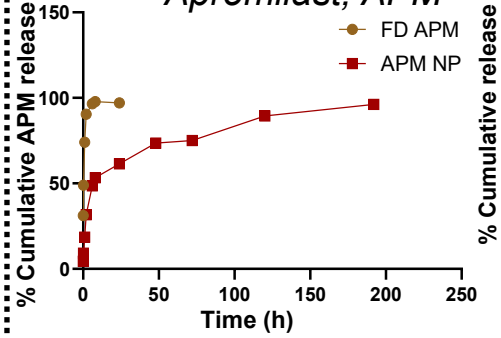
In-vitro characterization of nanoparticles

Release kinetics

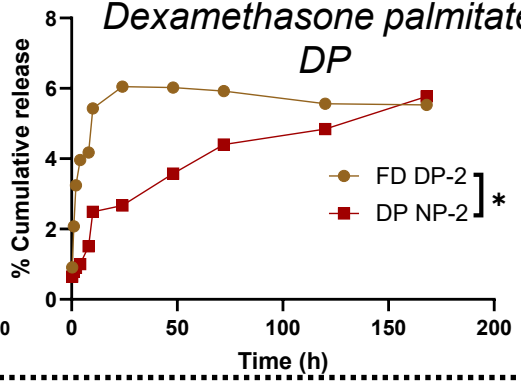


Protracted APM/DP release in non-sink condition (SI: 0.094-0.14)

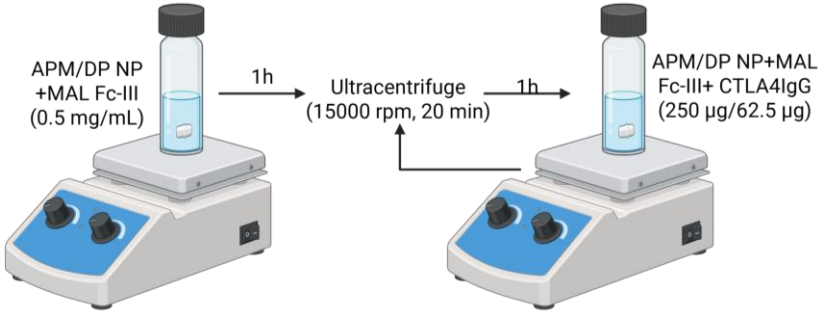
Apremilast; APM

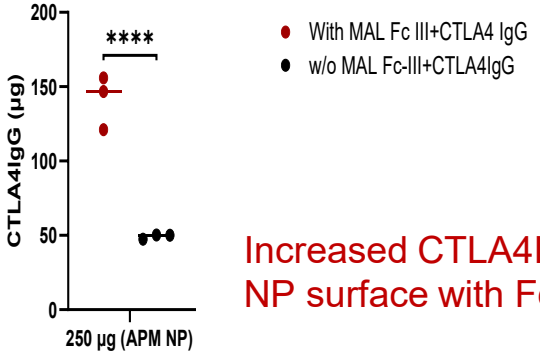


Dexamethasone palmitate; DP



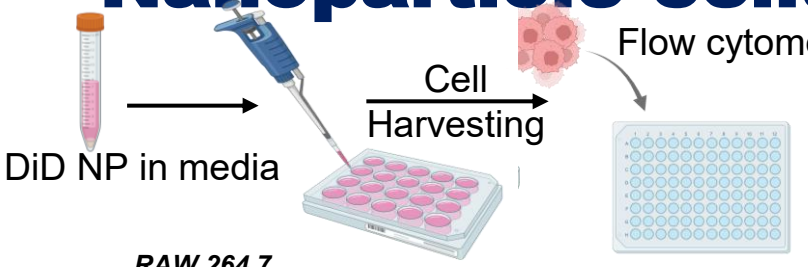
CTLA4IgG surface conjugation

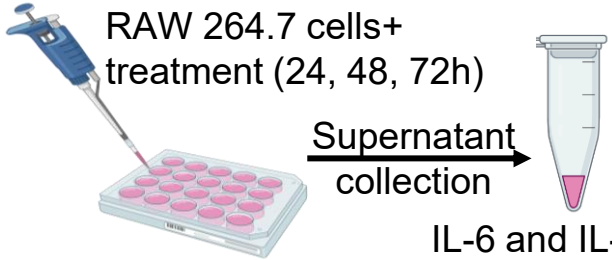


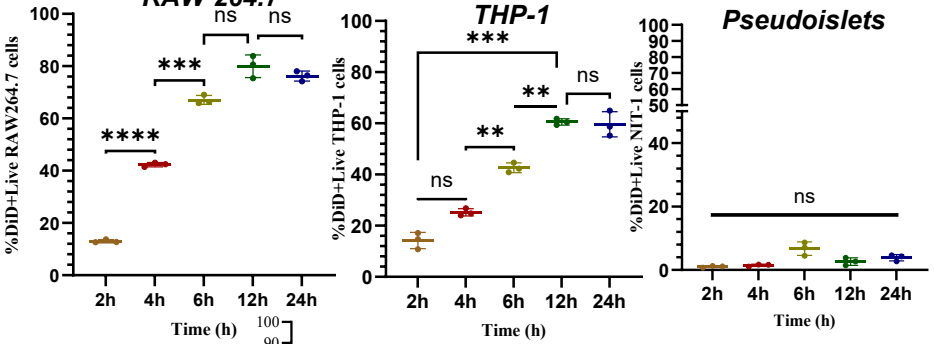


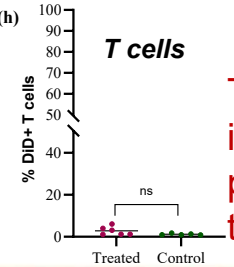
Increased CTLA4IgG loading on NP surface with Fc-III peptide

Nanoparticle cellular uptake and efficacy

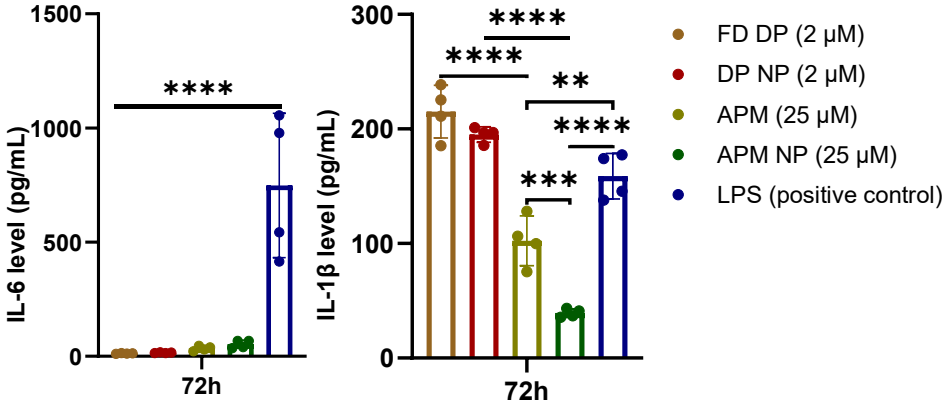








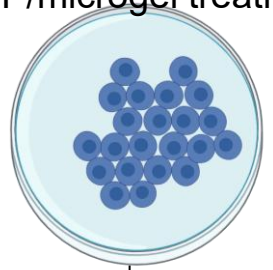
Targeted delivery of NP to innate immune cells versus pseudoislets/ T cells (non target)



Anti-inflammatory potential of APM NP>DP NP

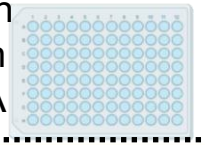
What is the effect of nanoparticles and microgel on islet functionality?

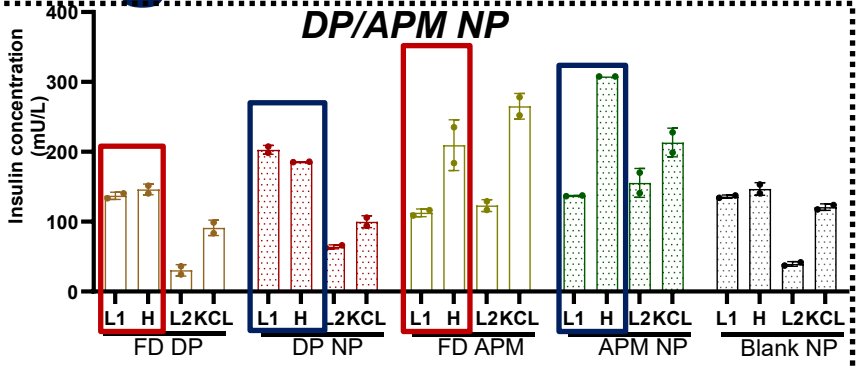
Human Islet+ NP/microgel treatment

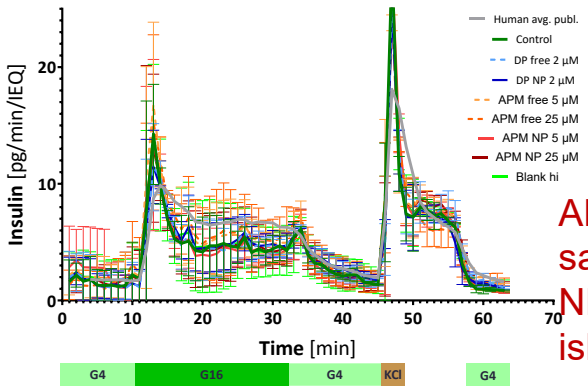


Static GSIS or dynamic perifusion

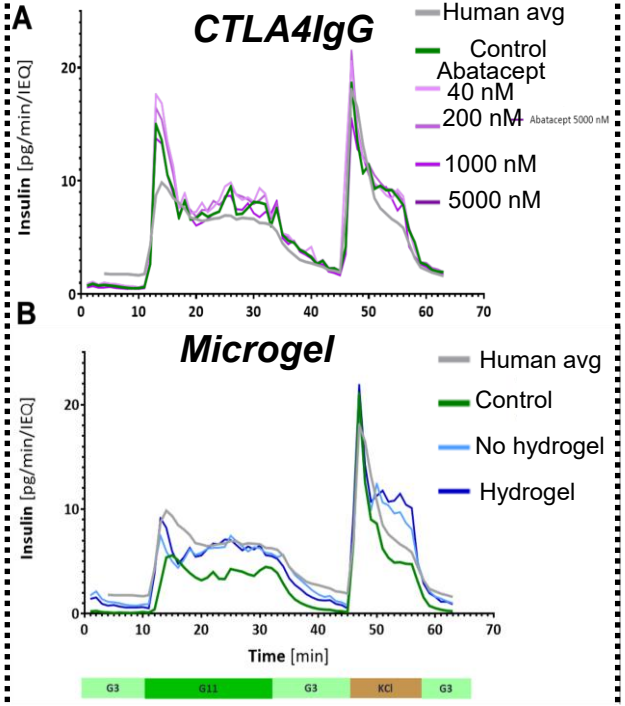
Human insulin ELISA







APM NP were safe than DP NP to human islets

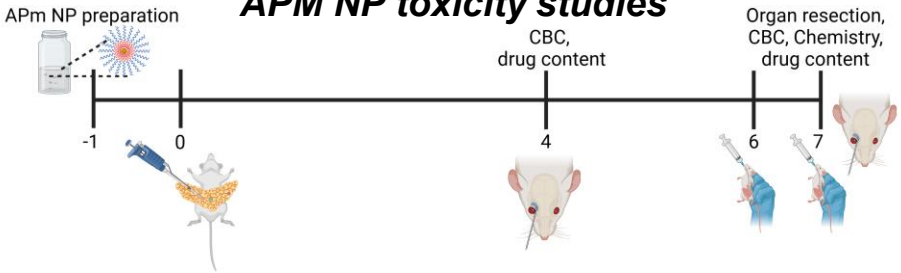


Unpublished (patent pending)

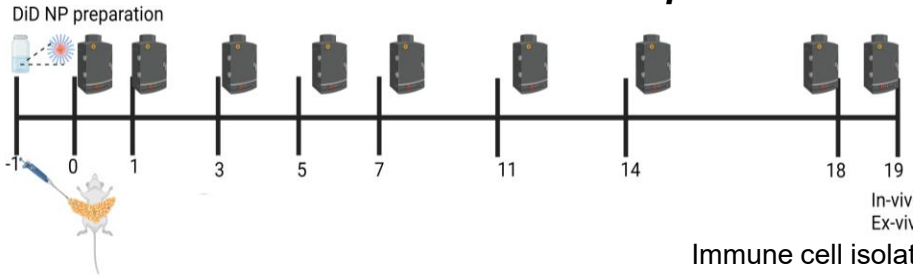
In vivo safety and efficacy of nanoparticles

	APM toxicity studies		DiD NP FP localization studies	
	APM NP	**APM oral control**	**DiD NP**	**Control untreated**
Strain			NOD	
Number of animals			3 per group	
Dose	100 µg	20 µg/ 100 µL	15 µg/30 µL 10µg/ 20 µL	--
Dosing frequency	Day 0	Day 6 (BID), Day 7 (OID)	Day 0	--
Route of administration	FP implantation	Oral gavage	FP implantation	--

APM NP toxicity studies



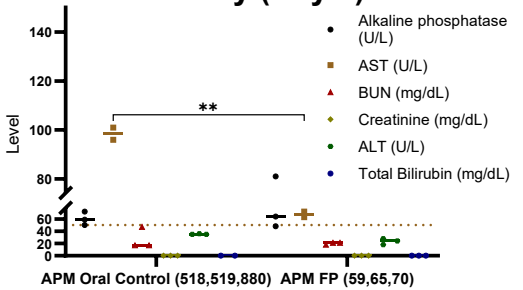
DiD NP localization in fat pad



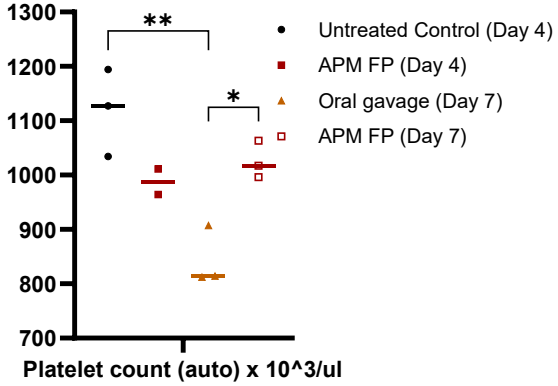
Immune cell isolation & flow cytometry

In vivo safety and efficacy of nanoparticles

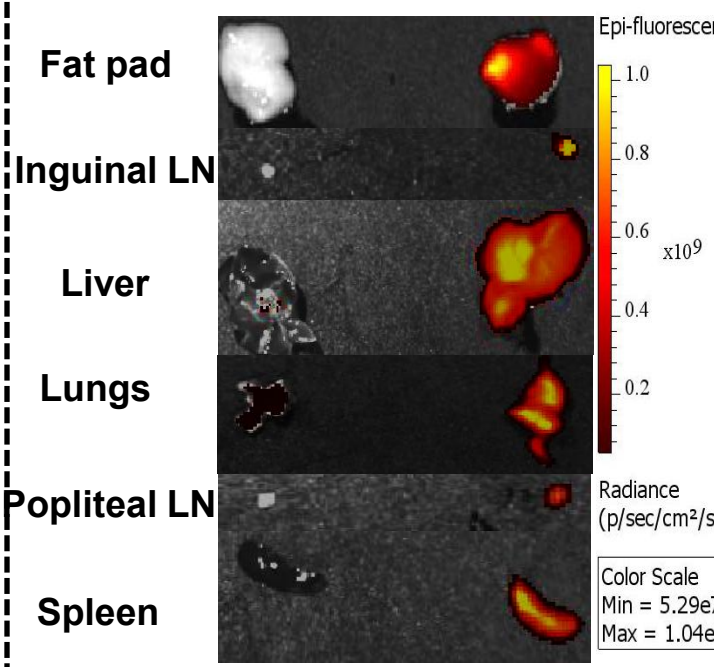
Chemistry (Day 7)



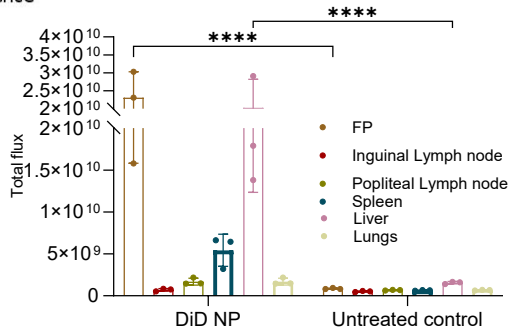
Platelet count



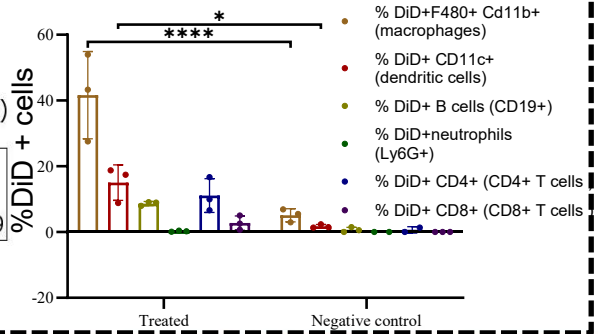
DiD NP localization and biodistribution studies



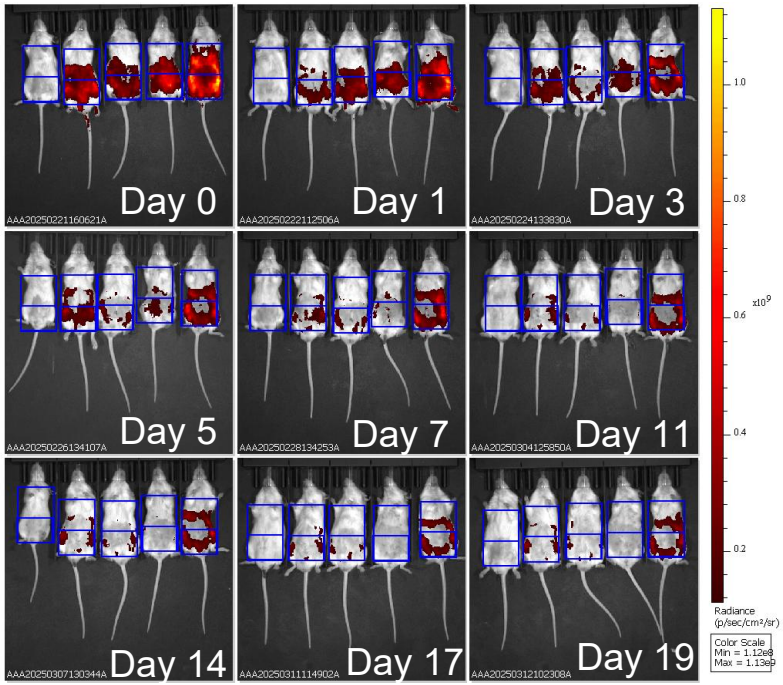
DiD NP biodistribution

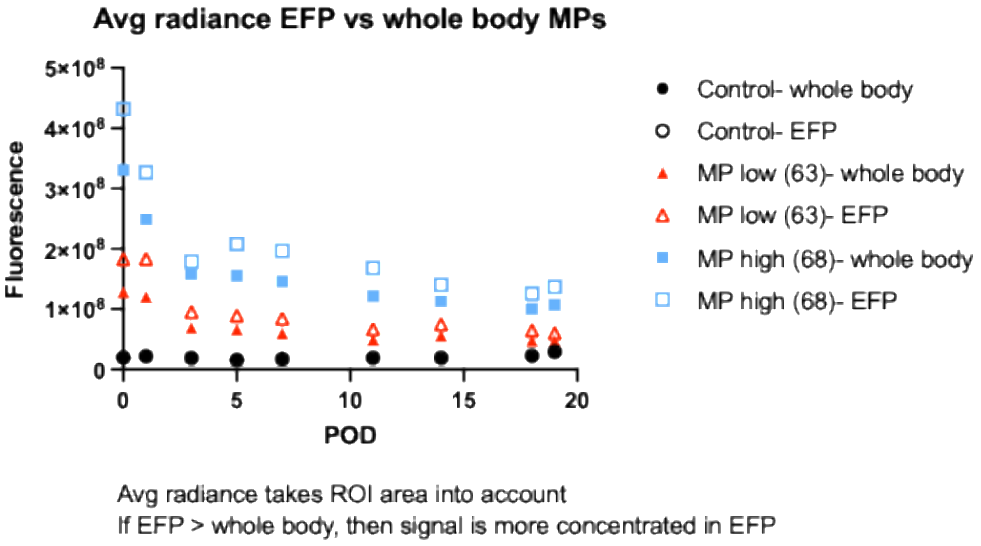


Macrophage targeting



Feasibility of fluorescently labelled CTLA4IgG biodistribution





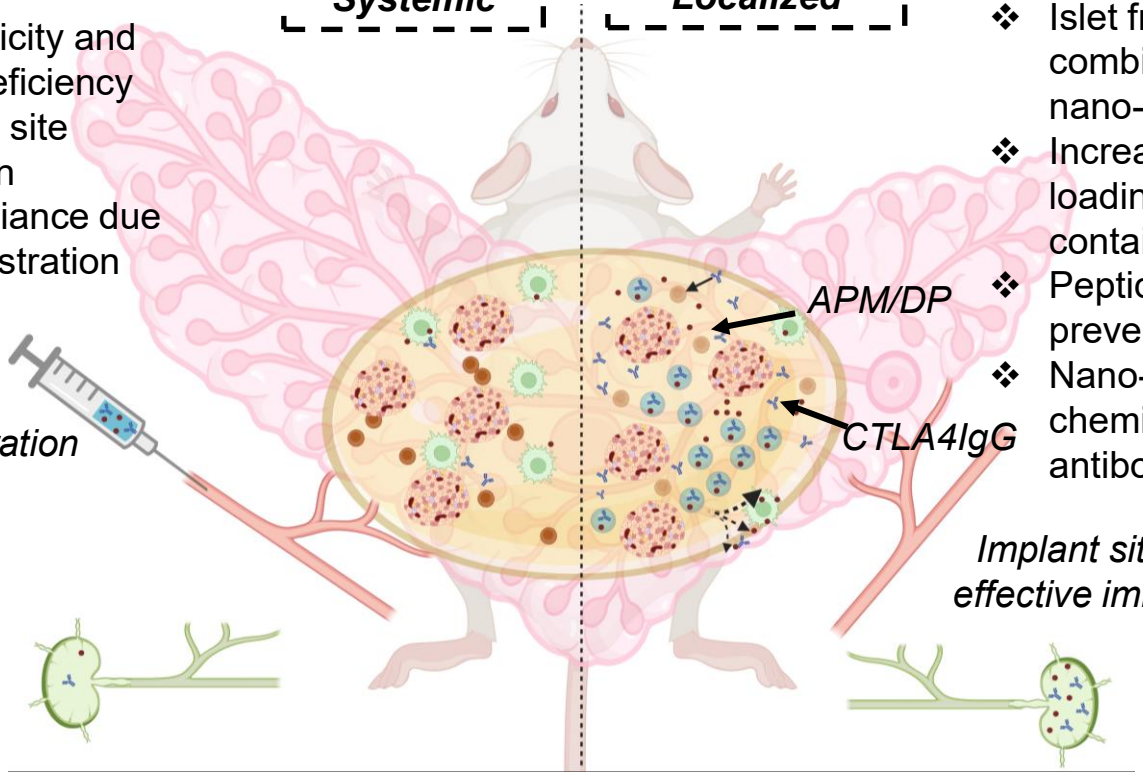
Avg radiance takes ROI area into account
If EFP > whole body, then signal is more concentrated in EFP

Unpublished (patent pending)

Conclusion

- Critical Organ Toxicity and general immunodeficiency
- Ineffective implant site immunomodulation
- Patient non-compliance due to frequent administration

Frequent administration



- Islet friendly drug combination loaded within nano-in-microgel
- Increased CTLA4IgG loading on the NP surface containing hydrophobic APM
- Peptide-protein complex-prevent burst release
- Nano-in-microgel: prevent chemical modification of Fc-antibody

Implant site retention and effective immunomodulation

Acknowledgement

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Ana Hernandez
Grisell Gonzalez

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Dr. Peter Buchwald
Dr. Iga Kucharska

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Imaging Core: Dr. Maria Boulina

Animal Core
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Diagrams made in Biorender

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