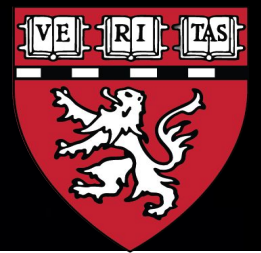
Engineering Immunity Using Biomaterials

Natalie Artzi

July 3rd, 2022

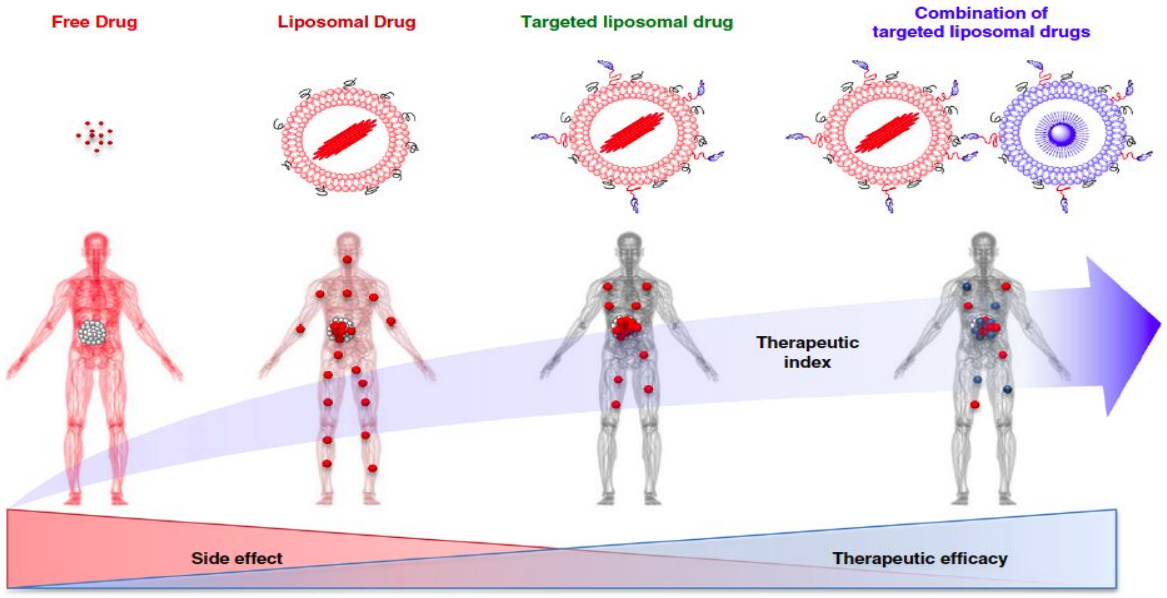


Immunotherapy delivery: Rethinking the target site

Chemotherapy

Targeting Cancer Cells

Reaching the Target Site(s)

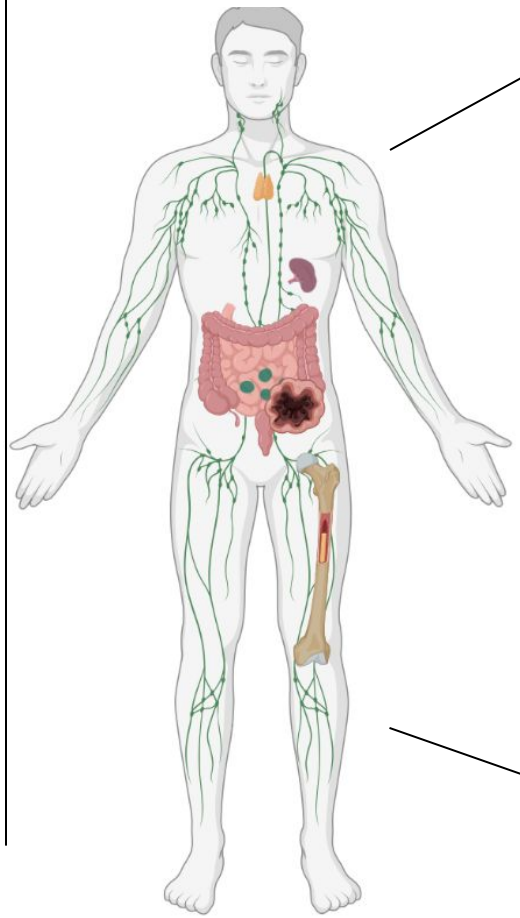


Wu et al. Journal of Biomedical Science (2016)

Immunotherapy

Targeting immune cells

Reaching the Lymphatic Tissues

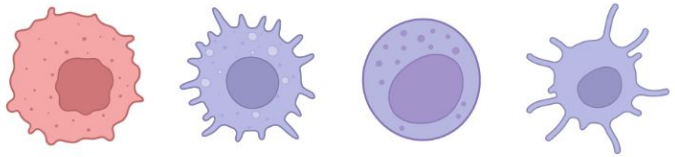


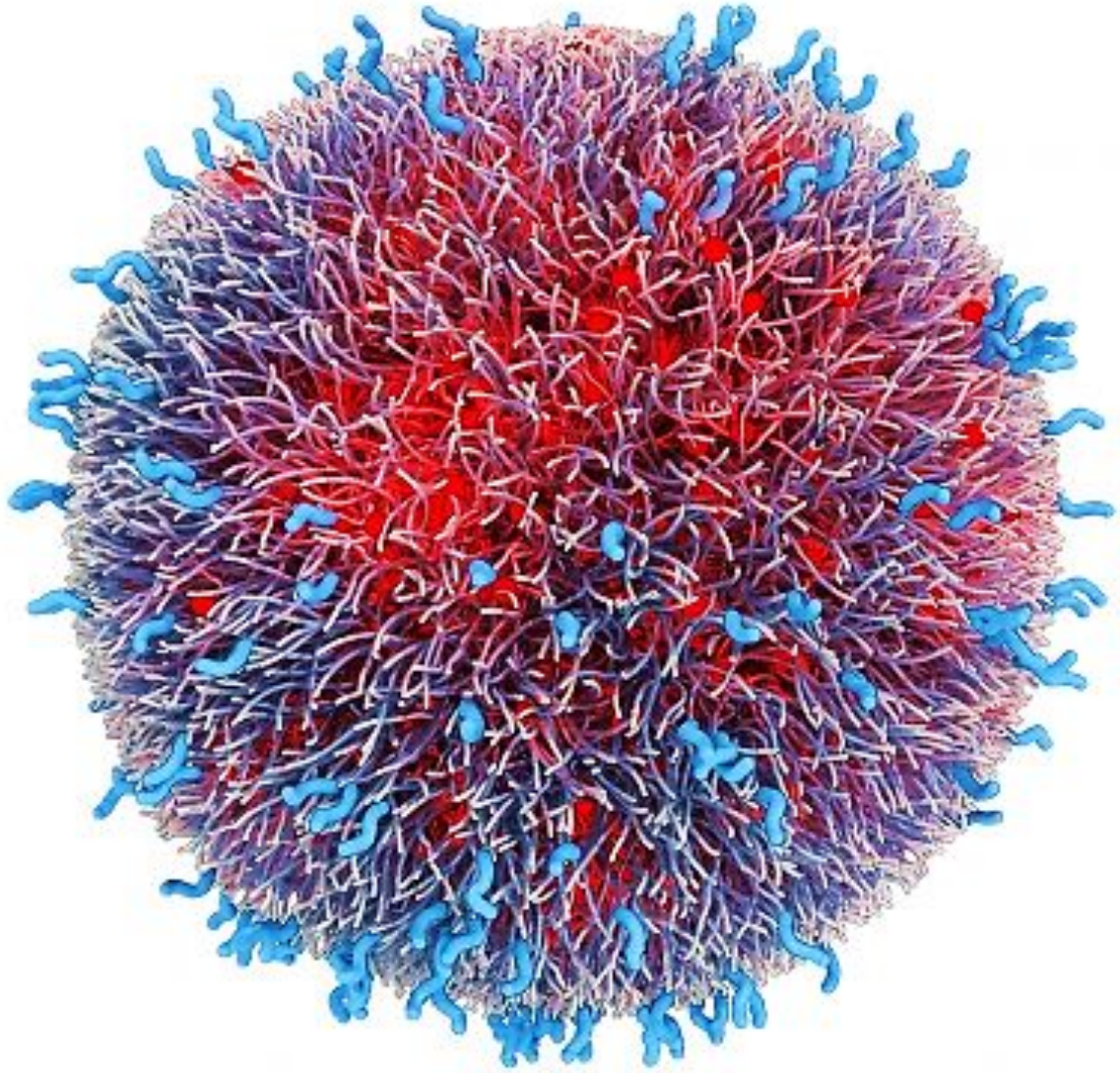
Tissues

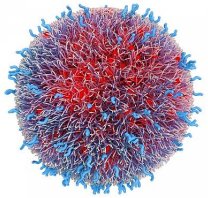
Tumor Spleen tdLN

Cells

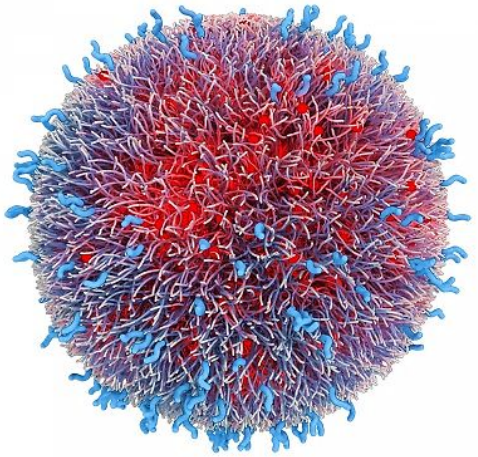
Cancer Mφ NK DCs







THE NANO vs CANCER



Artzi et al, Nat Mat, 2016

Artzi et al, PNAS, 2015

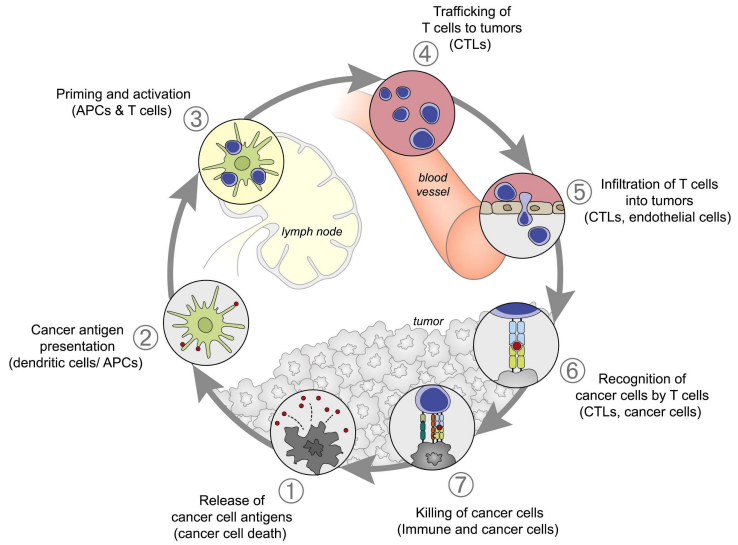
Artzi et al, Adv Func Mat, 2021

Artzi et al, Adv Mat, 2019

Artzi et al, Nat Comm, 2016

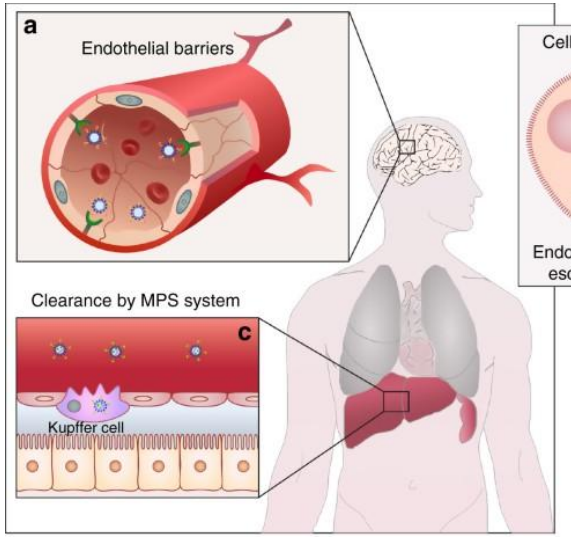
Immunotherapy Delivery: Old Challenges, New Opportunities

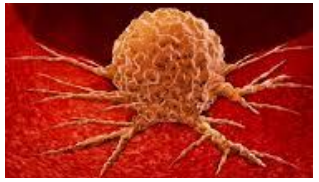
Enabling & Enhancing Therapeutic Activity

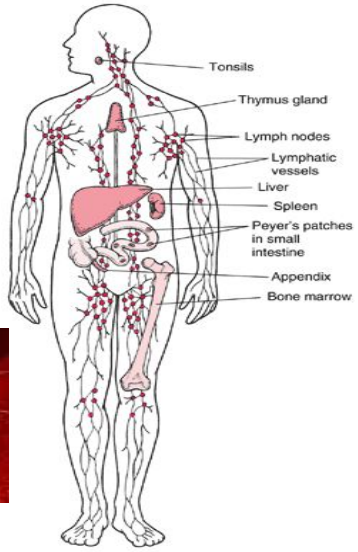


Chen & Mellman, *Immunity*, 2013

Reaching the Target Site(s)

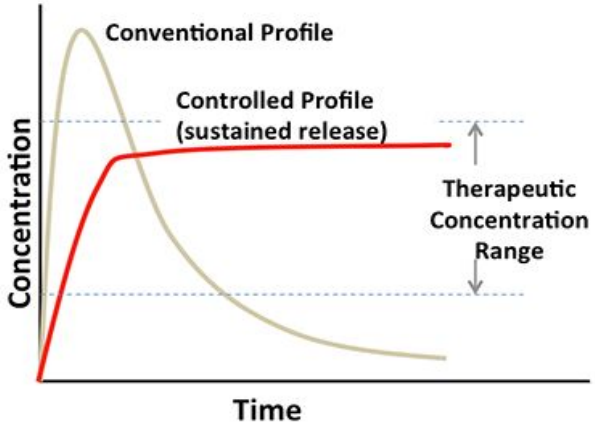


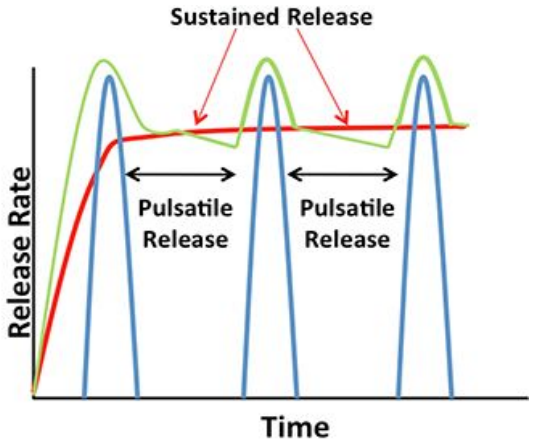




Rosenblum et al. *Nat Commun* 2018

Achieving Defined Spatiotemporal Delivery Profiles

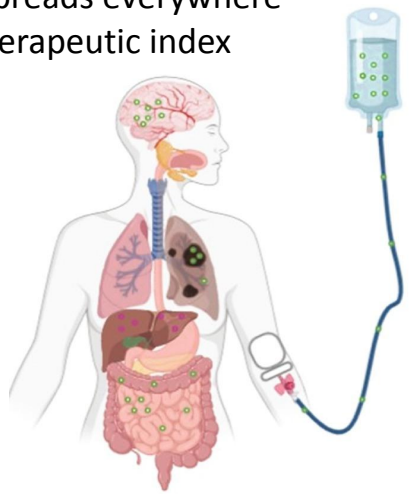




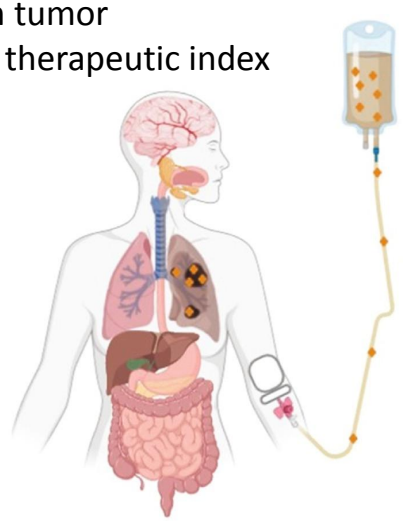
Elman, *Curr Pharma Biotechnol*, 2010

Reducing Toxicity

Drug spreads everywhere
Low therapeutic index

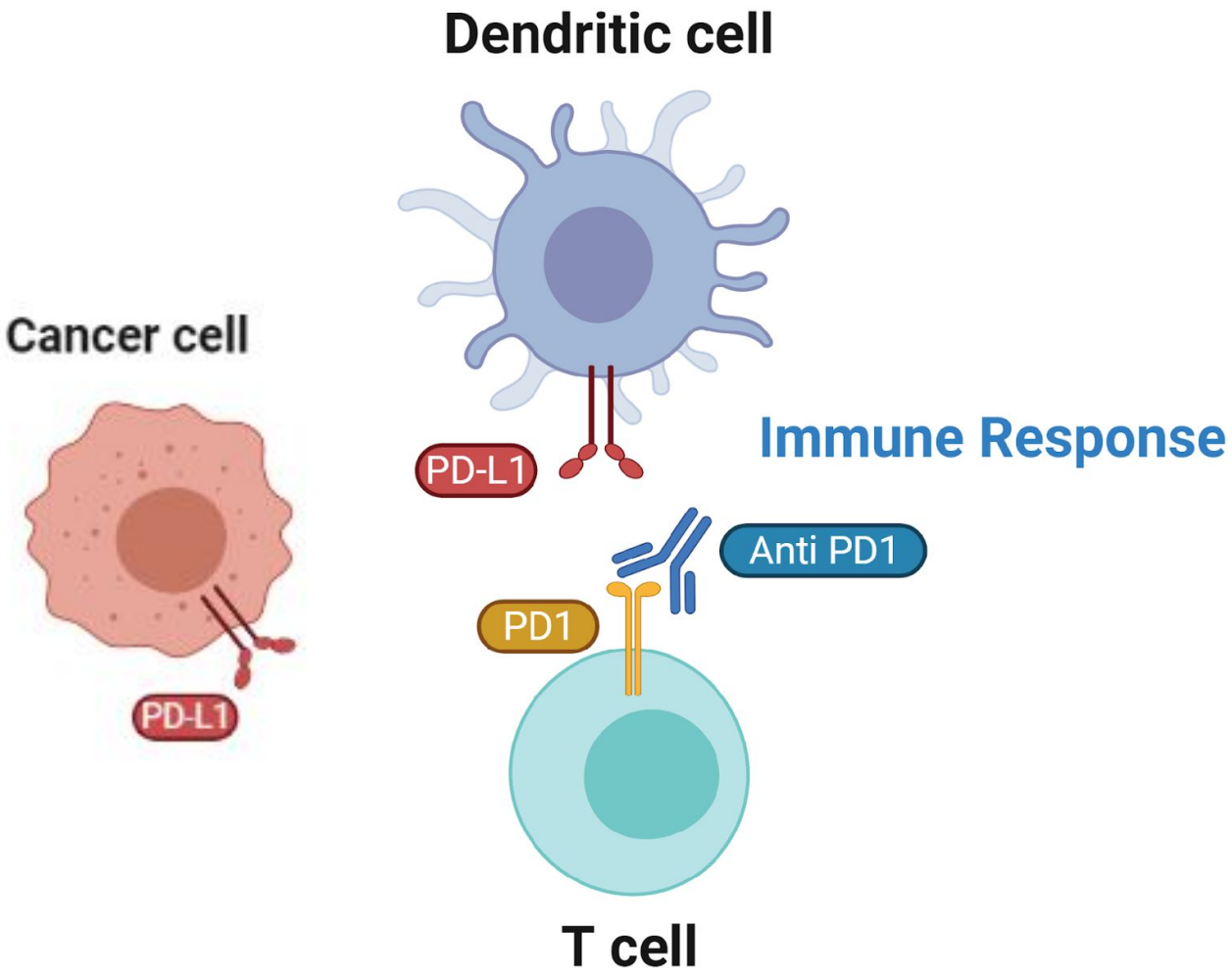


Drug in tumor
Higher therapeutic index

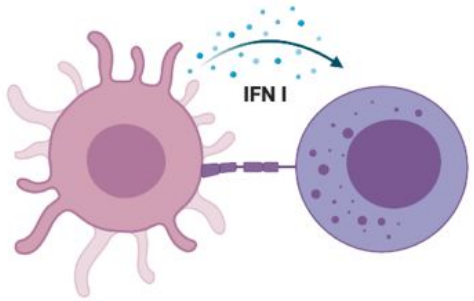


Cavalcanti and Soares, Advances in Cancer Treatment 2021.

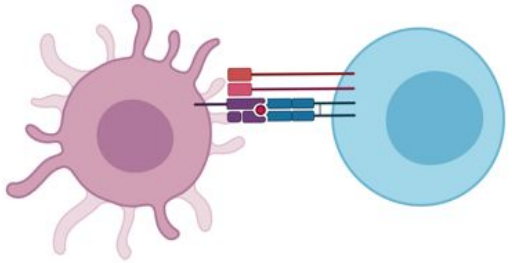
The cGAS-STING pathway



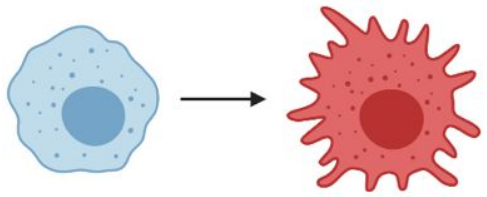
Enhanced priming of T cells



Stimulation of NK cell

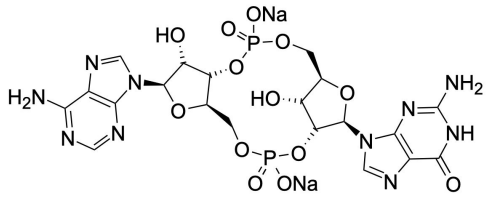


Polarization of macrophages



Polymeric-based nanoparticles allow the delivery of different types of nucleic acids

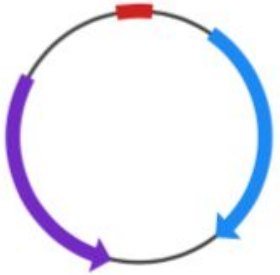
Nucleic Acids Based Drugs



STING Agonist

RNAi

mRNA

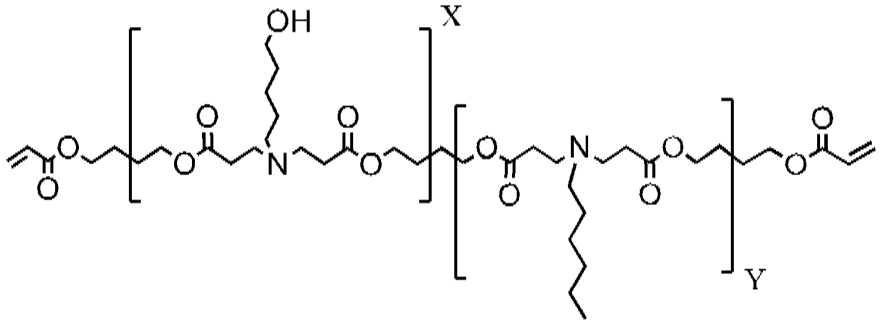


Plasmids

X Rapid clearance upon systemic administration

X Negative charge limits its ability to cross the cell membrane

Electrostatic Interaction



poly(beta-amino ester)s (pBAE)

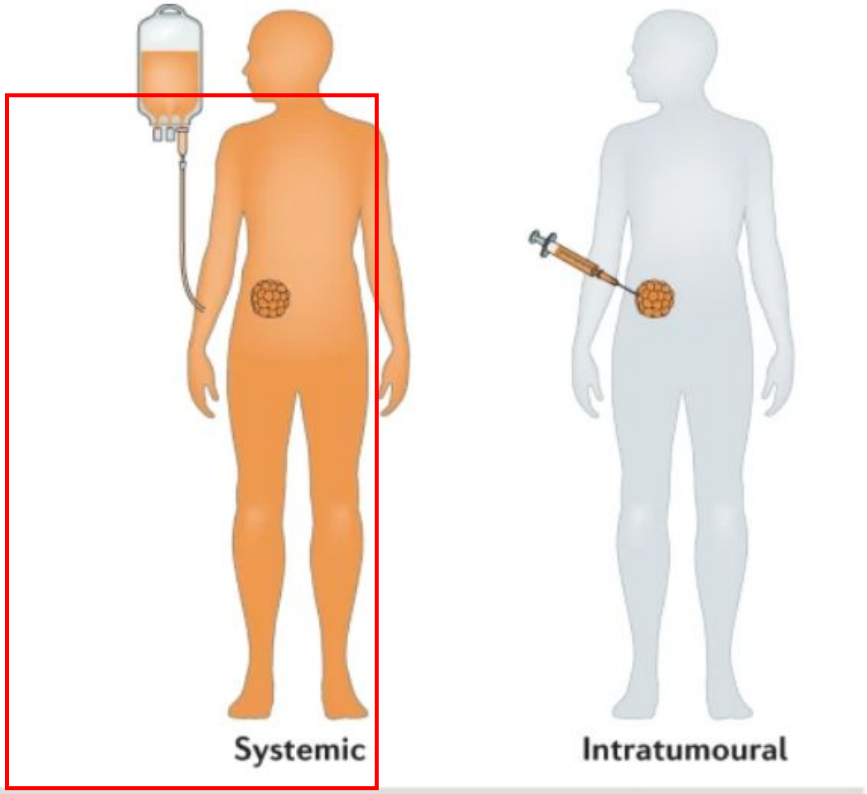
✔ High biodegradability → **Low toxicity**

✔ Nucleic acids encapsulation → **Amine groups**

✔ High endosomal escape → **Good buffering capacity**

Considerations for a systemic STING agonist NP formulation

a



Advantages	Practical	• High therapeutic index • Low toxicity
Disadvantages	• Low therapeutic index • High toxicity	Technical

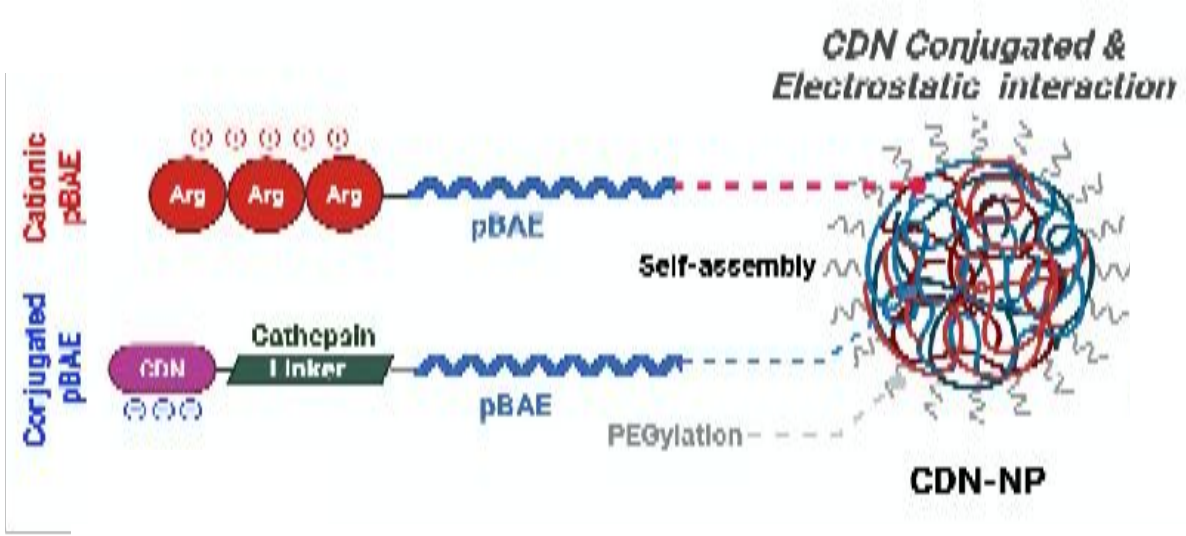
Requirements of a nucleic acid NP formulation for <u>systemic delivery</u>:

- Good serum stability (protection of cargo)
- Circulatory half-life (not immediately cleared)
- Potent transfection of cells (internalization and endosomal escape)
- Biodegradable (non-toxic)
- Facile synthesis (potential for scale-up)

How do we enlist these criteria in a STING agonist NP formulation?

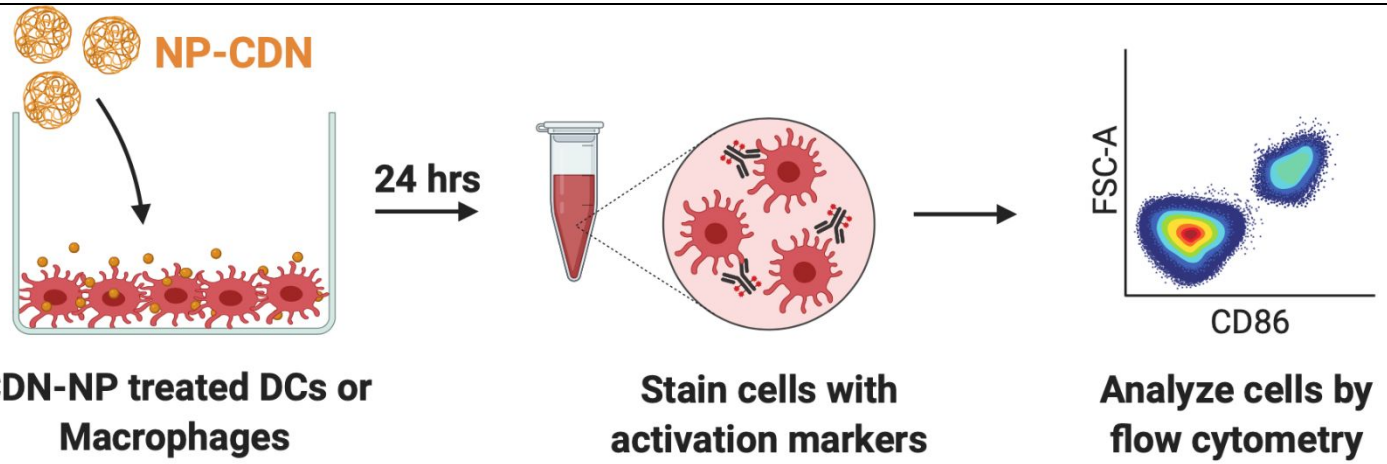
Paunovska *et al.,* 2022. Nat. Rev. Gen.

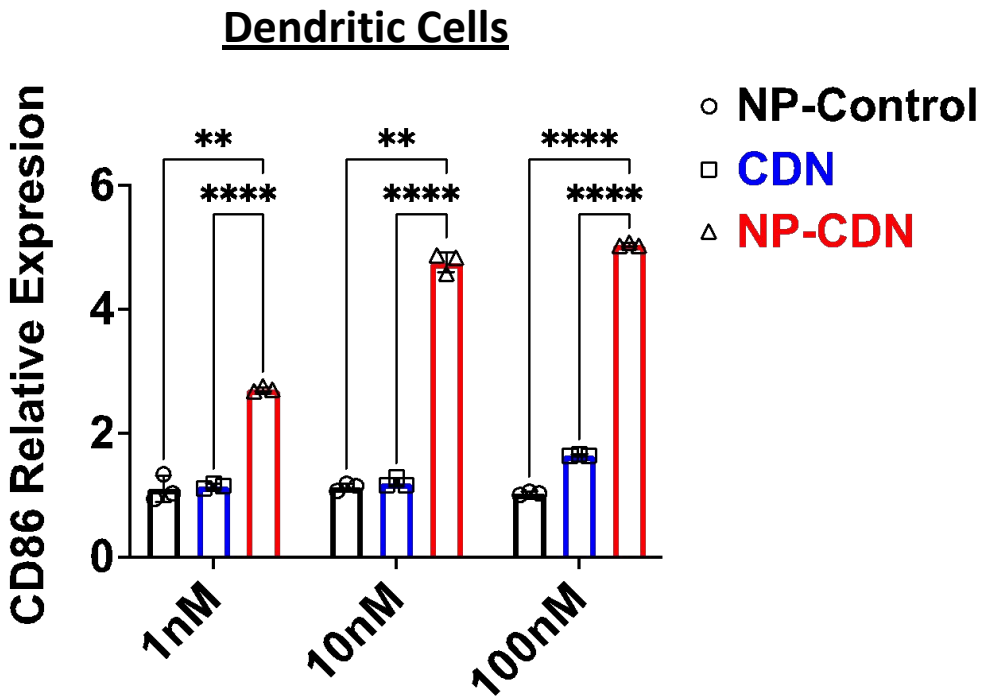
Design of conjugated STING agonist nanoparticles

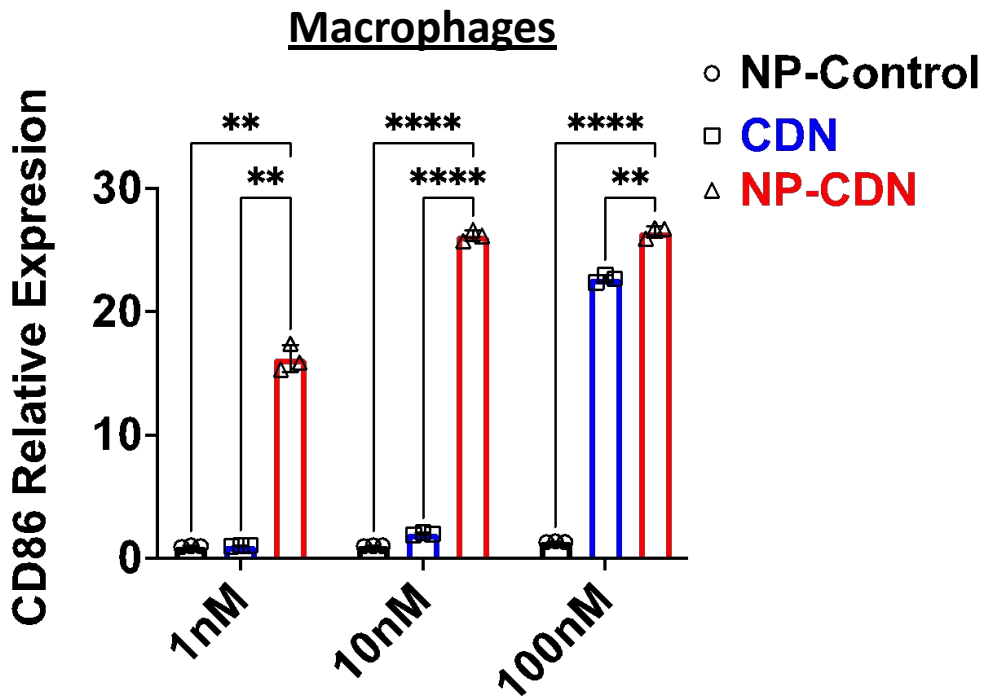


P. Dosta et. al. **Nature Nanotechnology**, under review

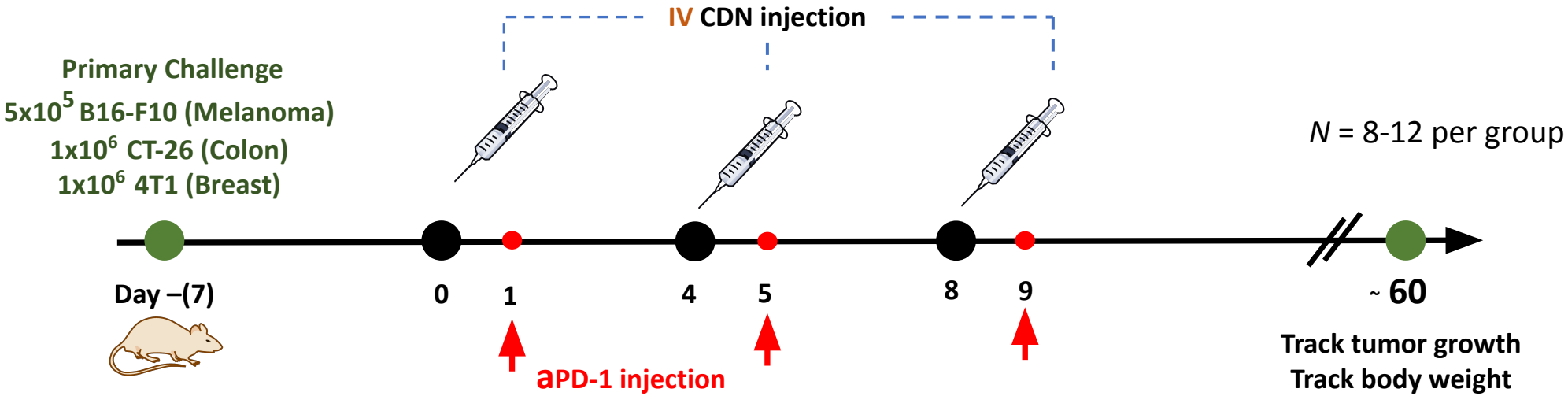
CDN-NPs stimulate dendritic cells and macrophages





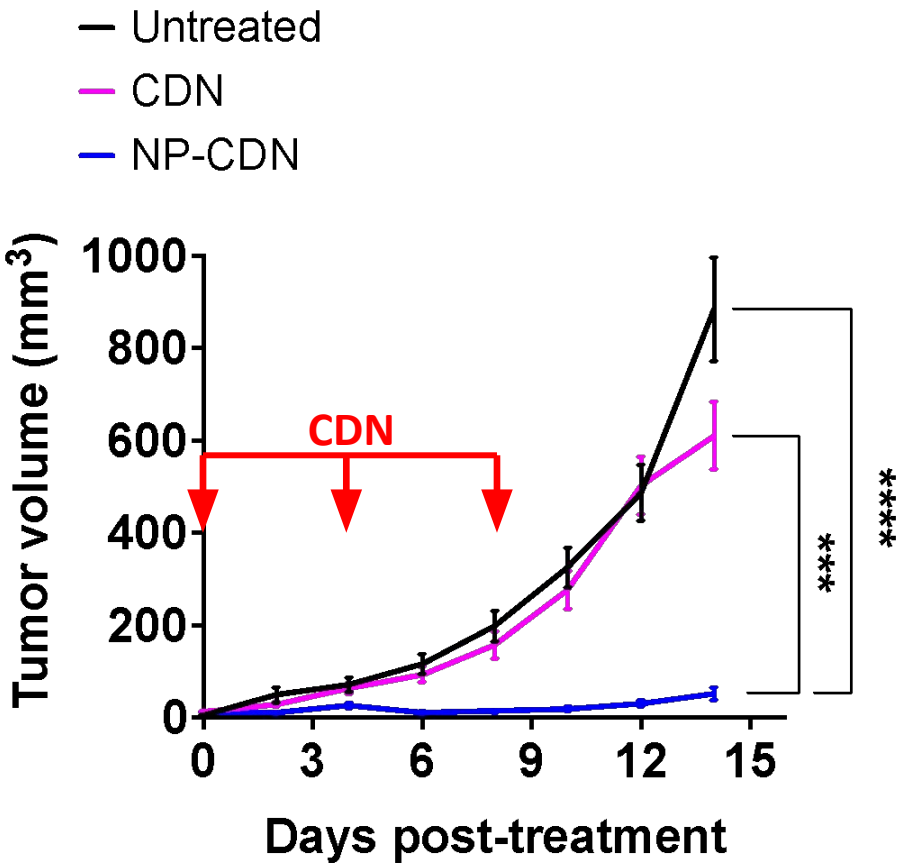


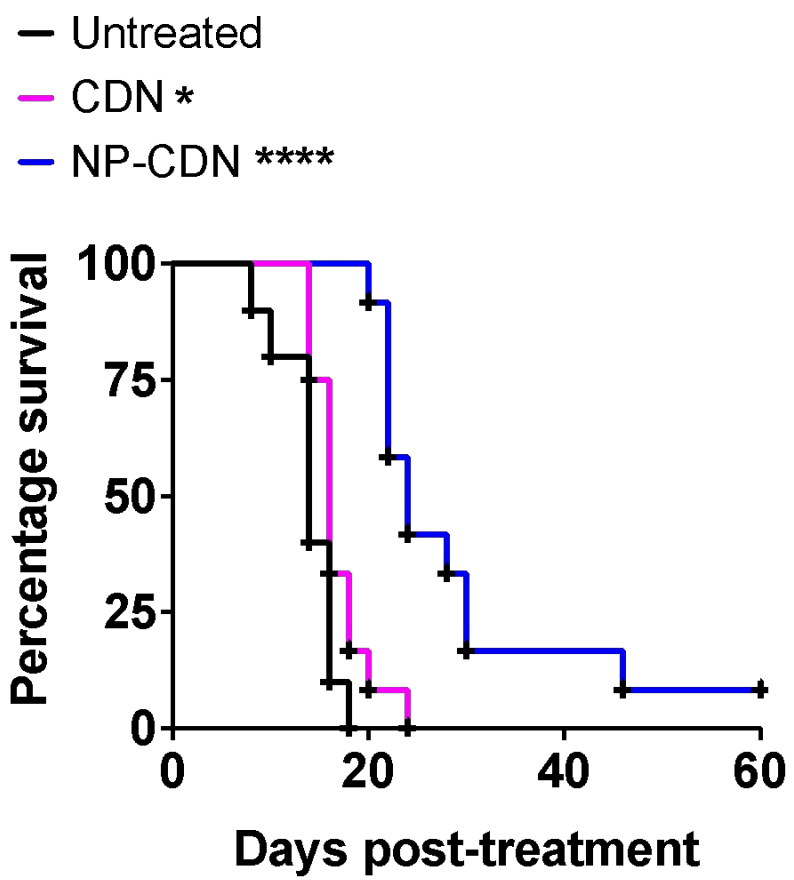
Intravenous delivery of CDN-NPs in multiple syngeneic tumor models



Dose: 0.5 ug CDN-NP/mouse
0.5 ug CDN/mouse
100 ug aPD-1 mAb

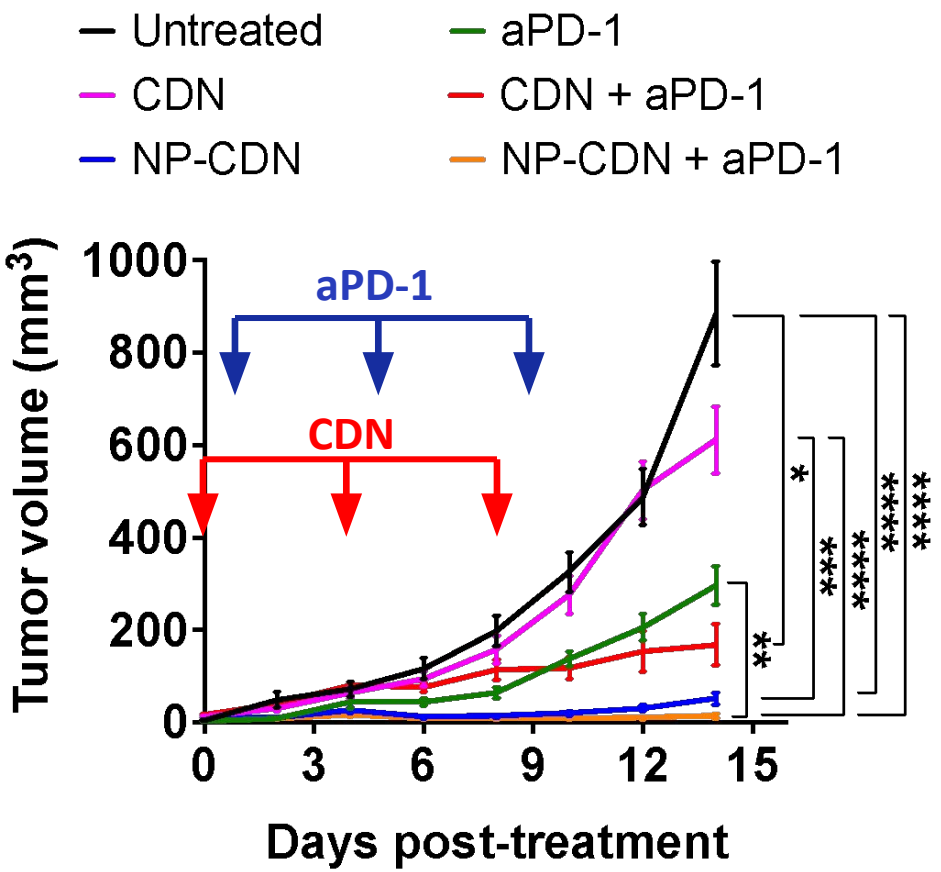
Reduced tumor burden and increased survival in mice treated with CDN-NPs and aPD-1 in a B16-F10 Melanoma Model

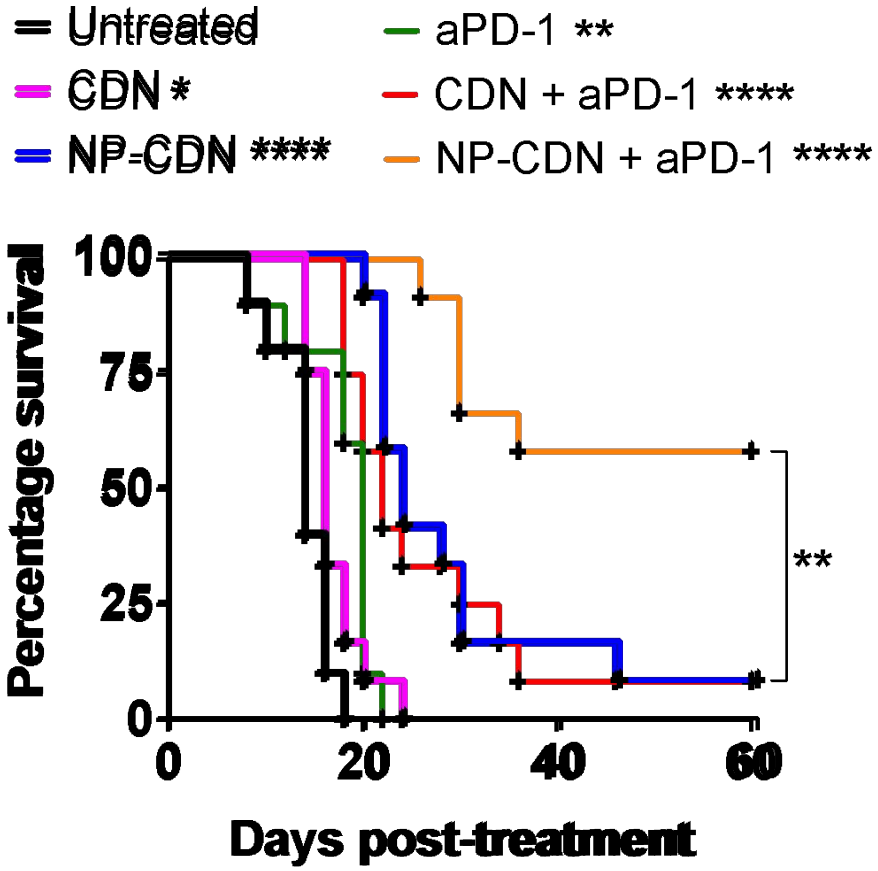




CDN □ 3 doses, every 4 days; Dose : 0.5 µg

Reduced tumor burden and increased survival in mice treated with CDN-NPs and aPD-1 in a B16-F10 Melanoma Model



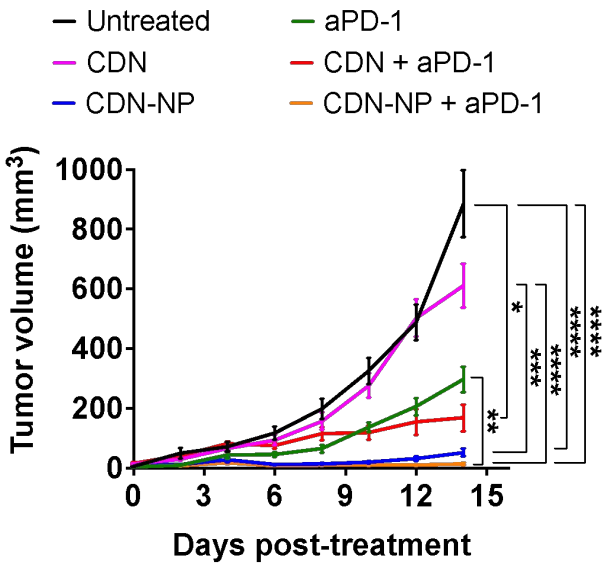


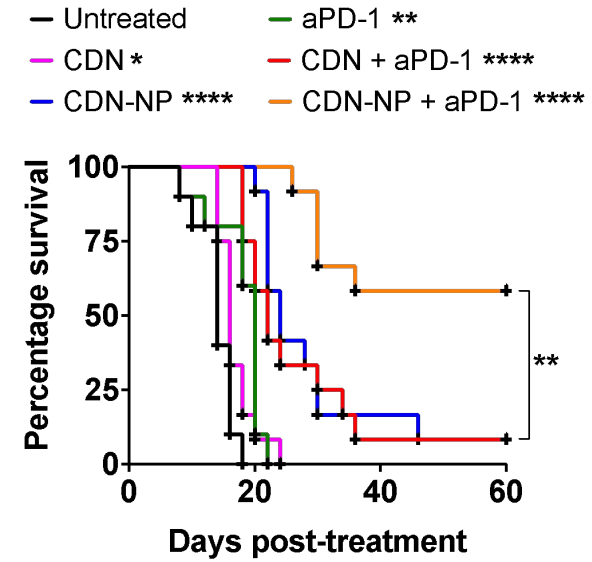
CDN □ 3 doses, every 4 days; Dose : 0.5 µg

aPD-1 □ 3 doses, 24h after CDN therapy; Dose : 100 µg

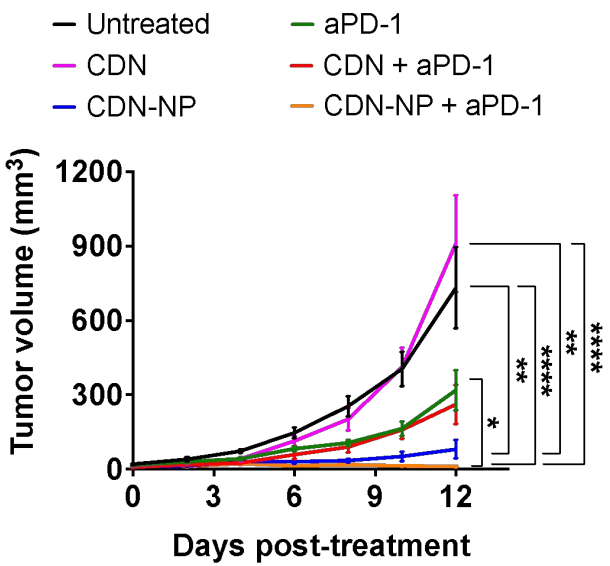
CDN-NP improve therapeutic outcome of CDN and synergize with immune checkpoint blockade (aPD-1 mAb)

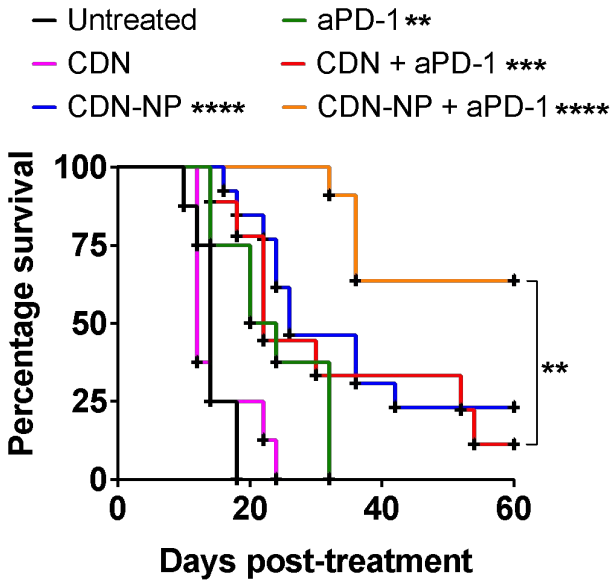
Melanoma



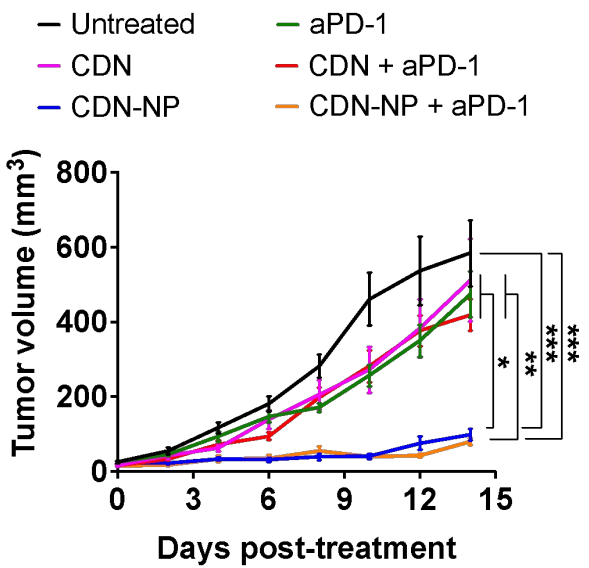


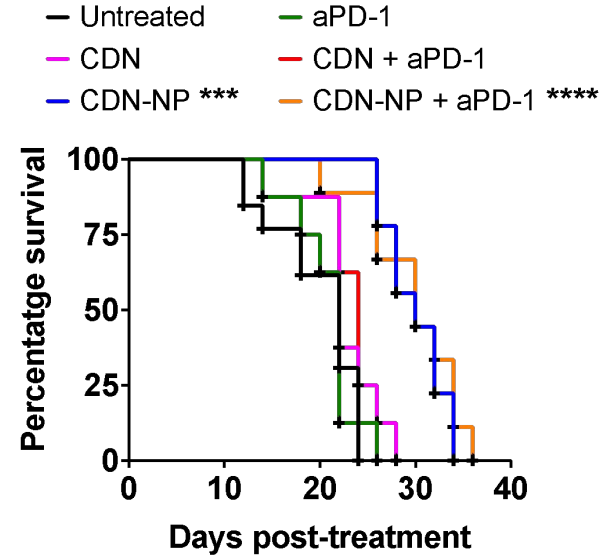
Colon cancer



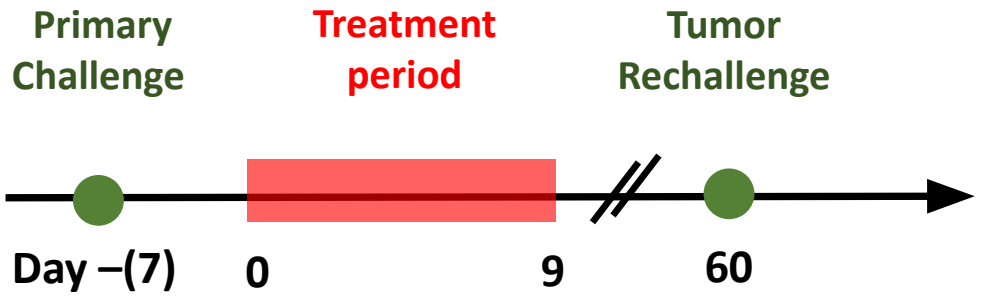


Breast cancer

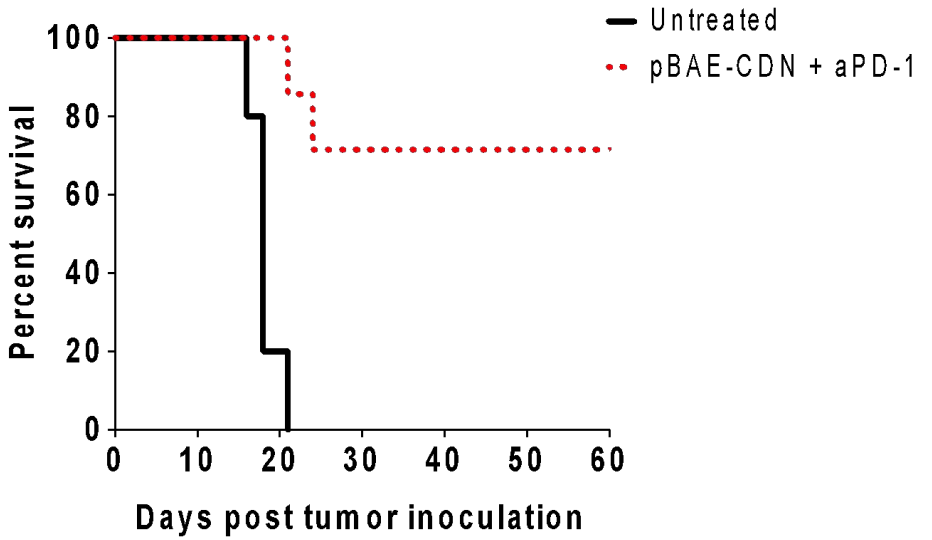




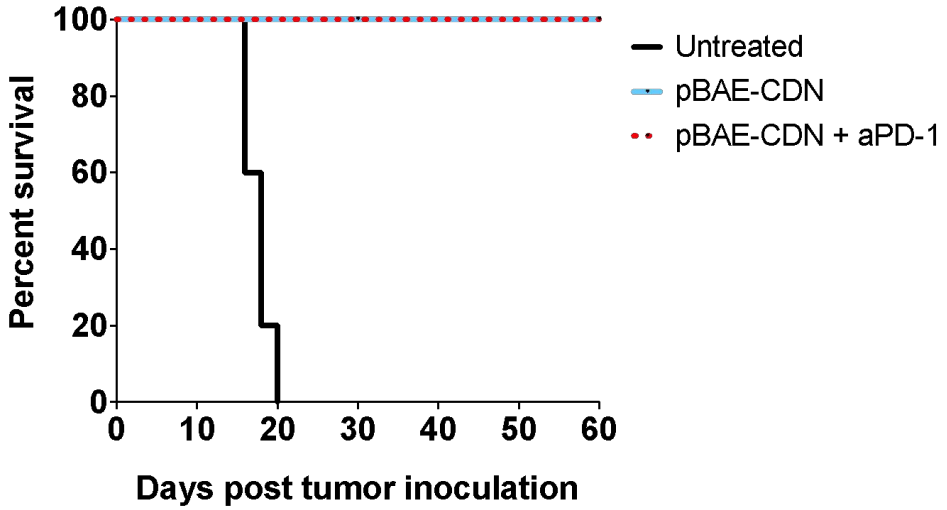
Cured mice treated with CDN-NPs reject tumors upon rechallenge



B16-F10 melanoma model

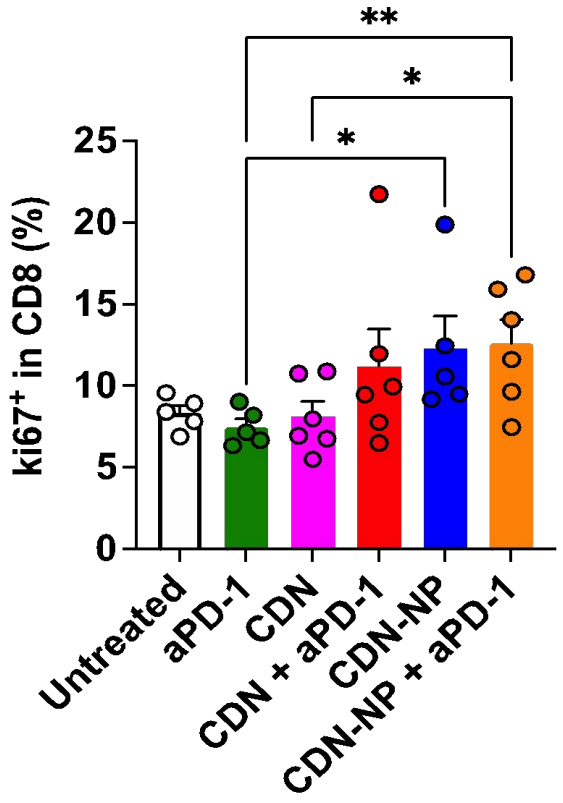


CT-26 colon cancer model

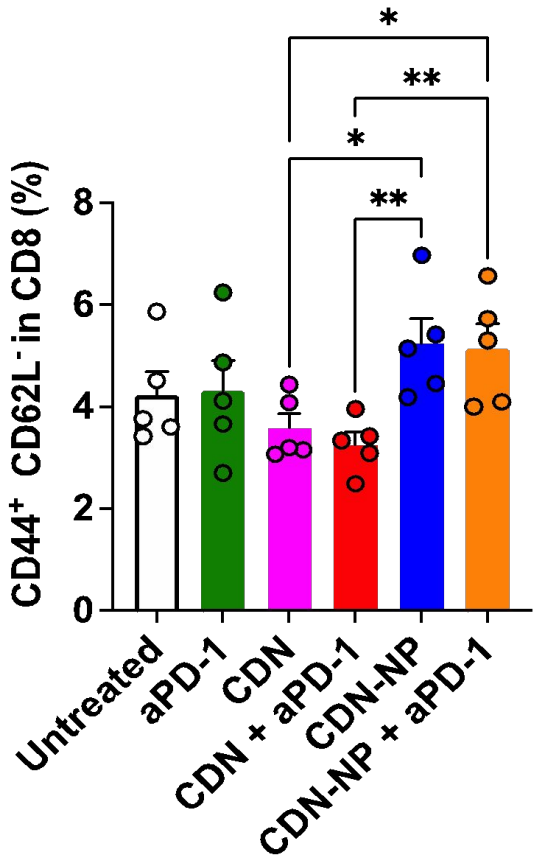


CDN-NPs promote the generation of immune memory

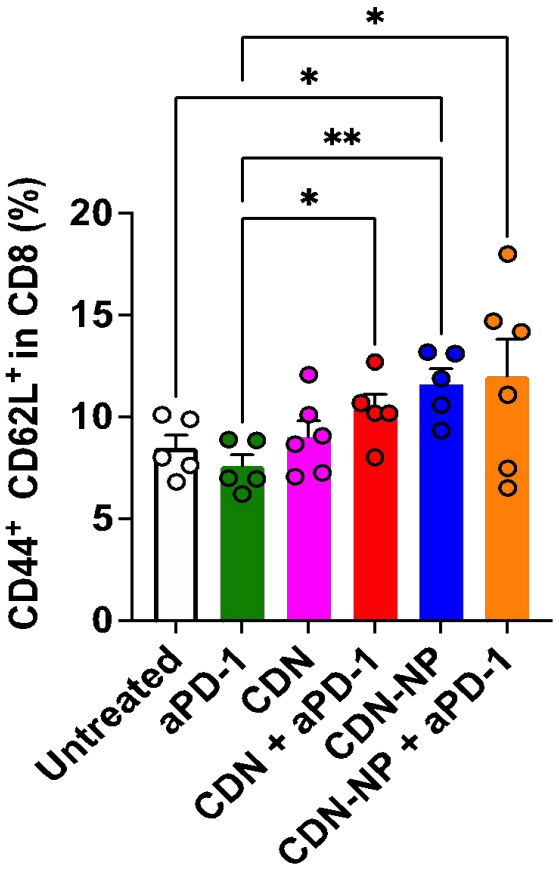
CD8 Cell Proliferation



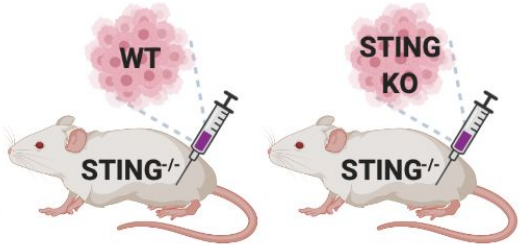
Effector CD8+ Cell Memory

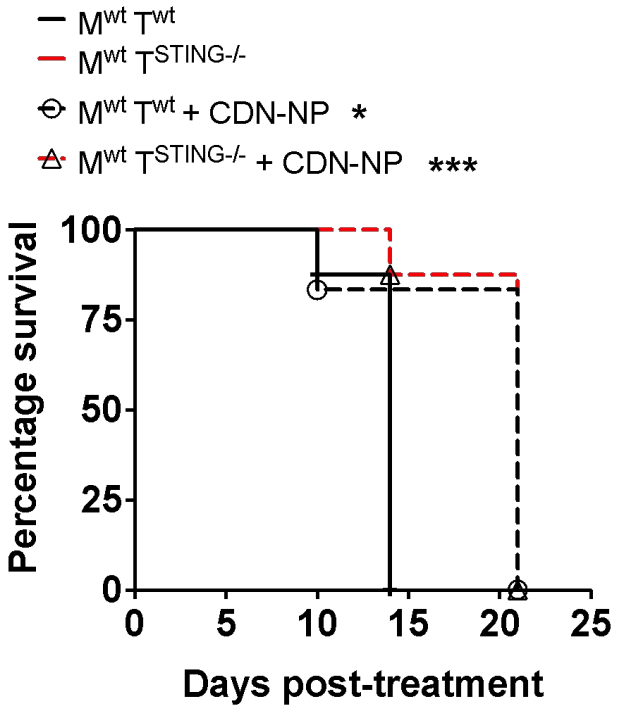


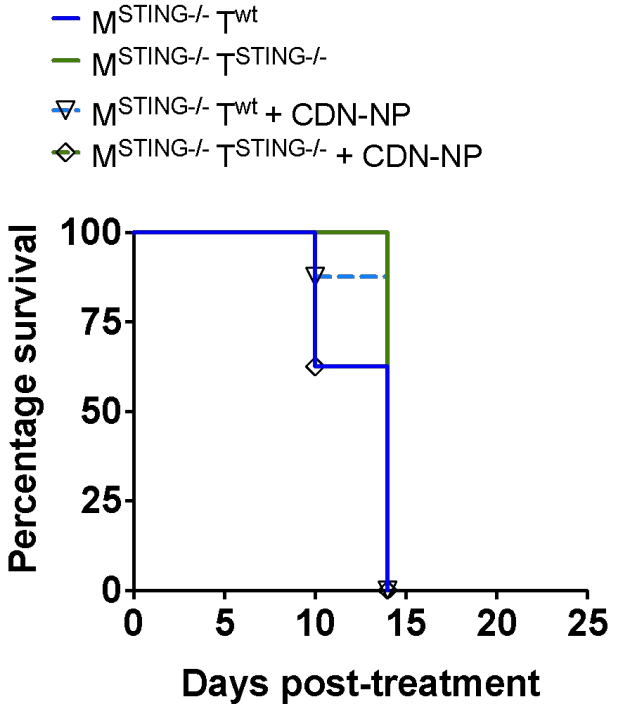
Central CD8+ Cell Memory

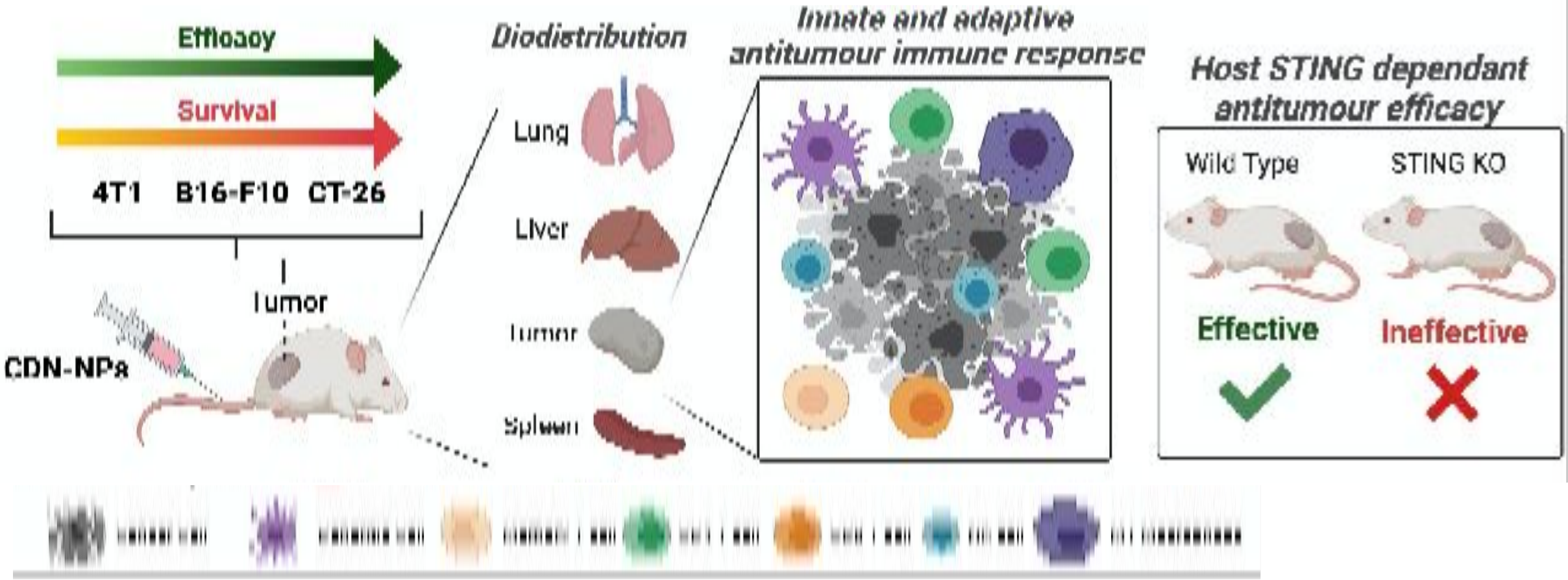


STING activation within host cells is sufficient to promote anti-tumor immunity in the B16-F10 melanoma model



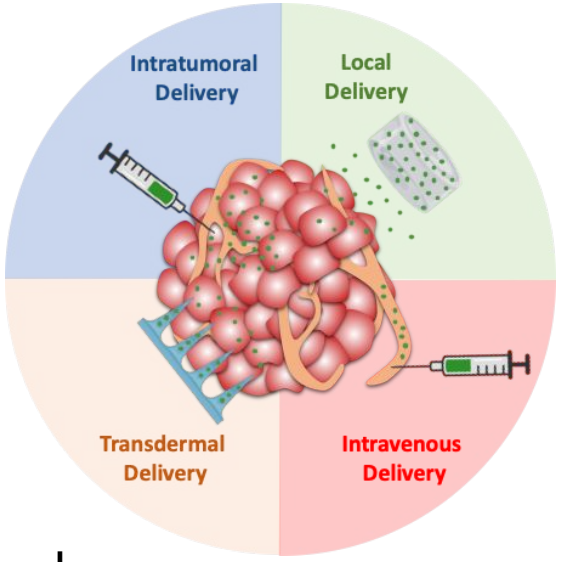


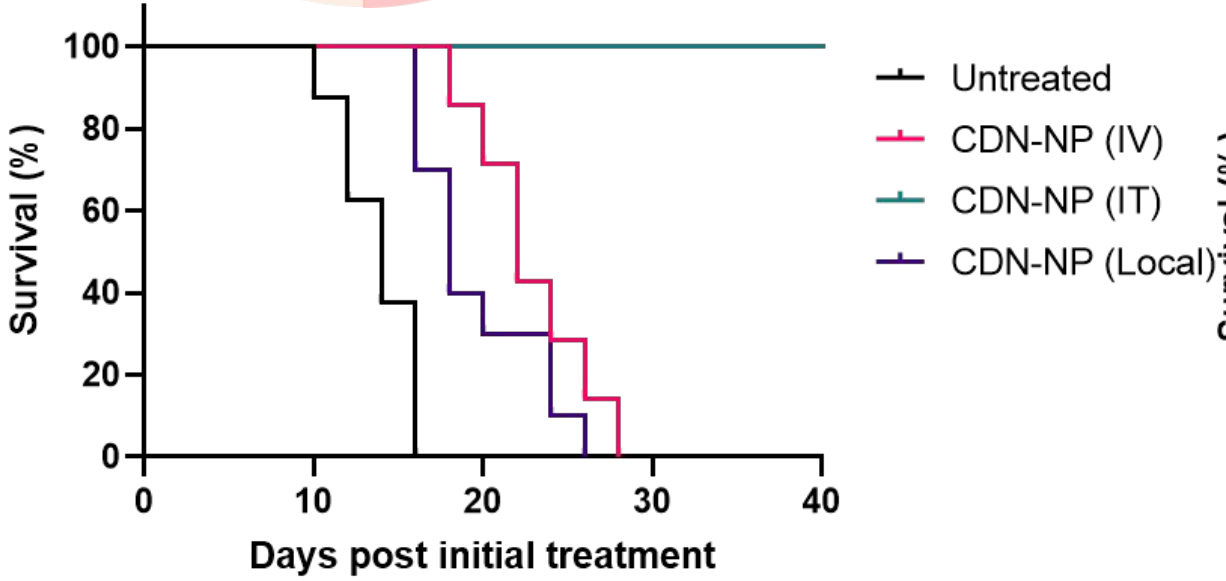



Efficacy
Survival
4T1 B16-F10 CT-26
Tumor
CDN-NPs
Biodistribution
Lung
Liver
Tumor
Spleen
Innate and adaptive antitumour immune response
Host STING dependant antitumour efficacy
Wild Type
STING KO
Effective
Ineffective

Ongoing work

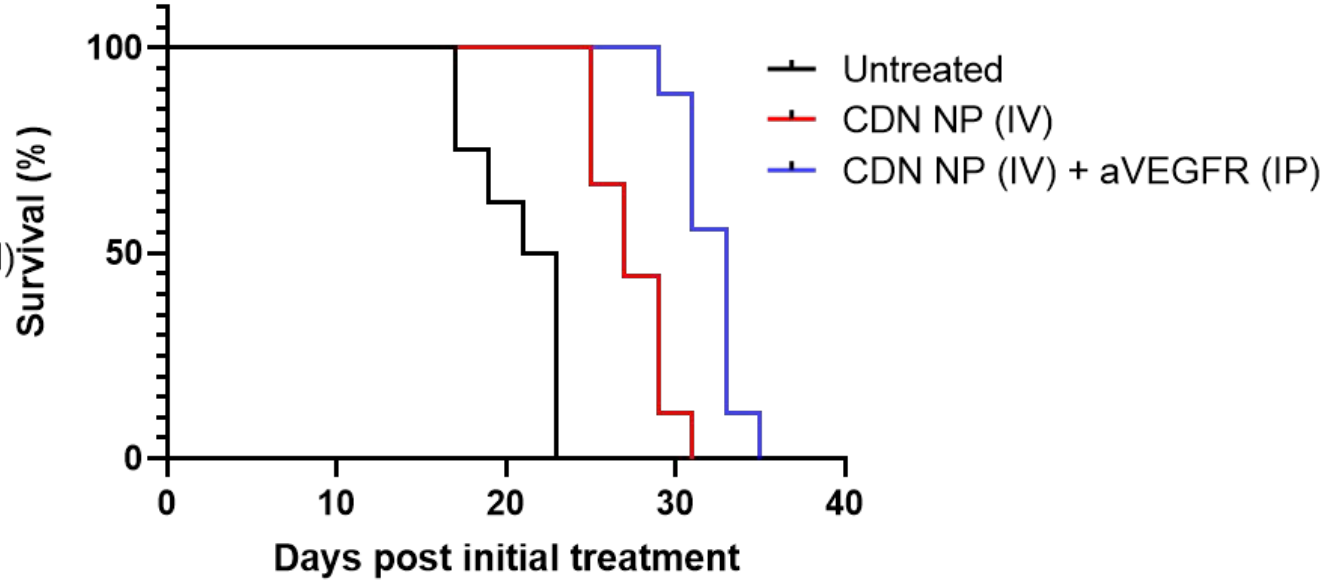
Can delivery route affect therapeutic efficacy?



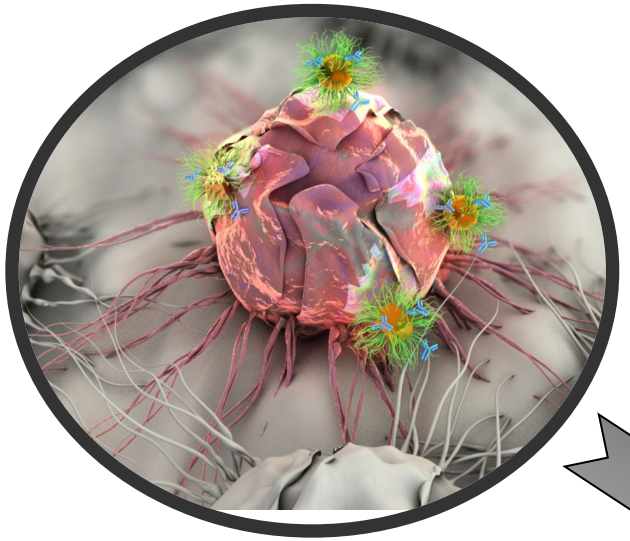


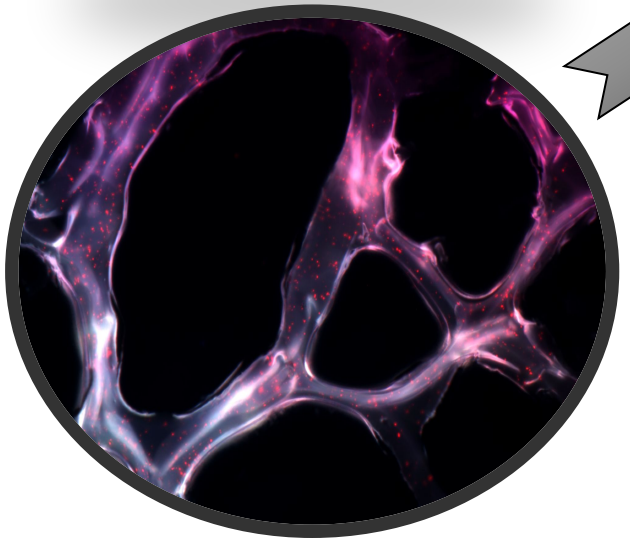
Can clinical therapies synergize with STING agonism?

- Vascular-normalizing therapies
- Chemotherapy
- Radiotherapy

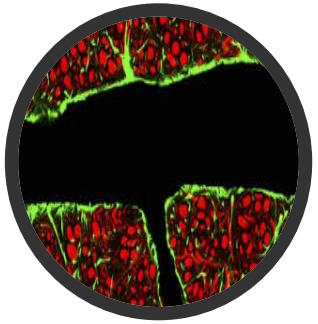


Synergizing immunology and pharmacology using materials to enhance therapeutic efficacy and safety



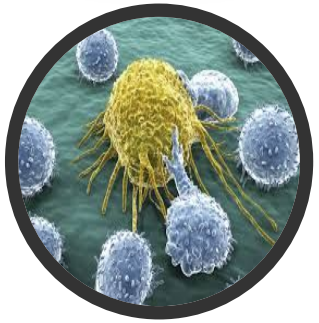


Overcome delivery barriers

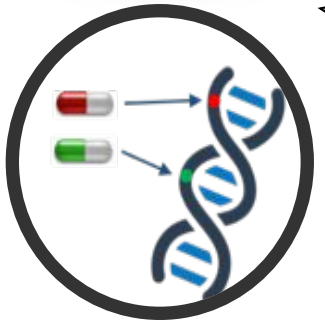


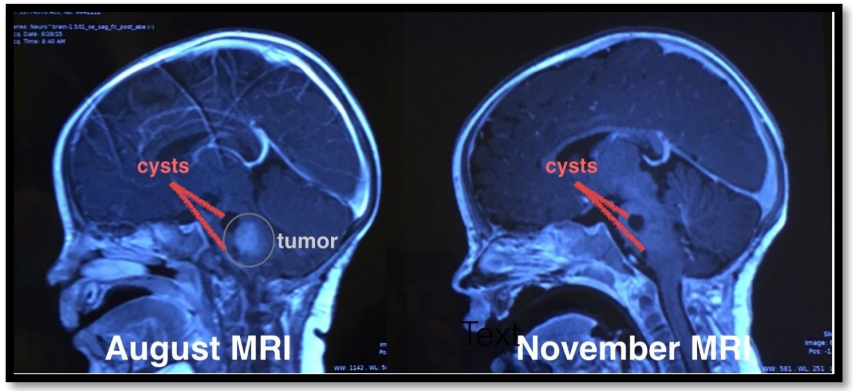
Monitor disease status

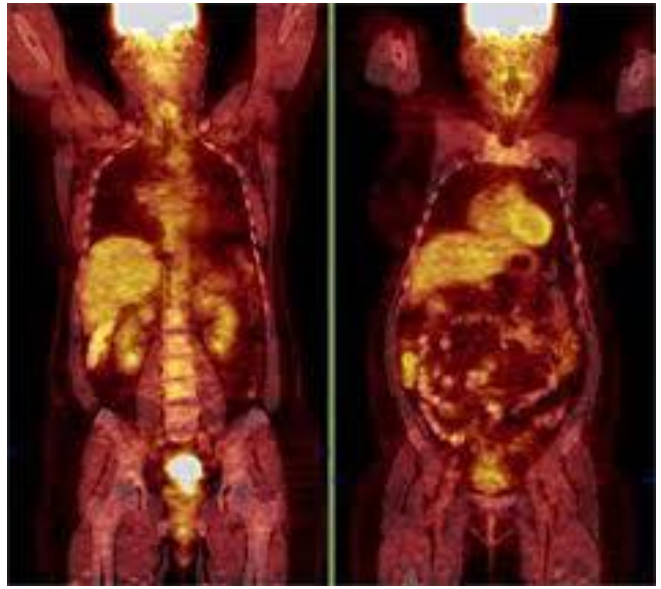
Modulate therapeutic immunity



Synergize combination therapy







Acknowledgements

Artzi Lab

Pere Dosta

Alexander Cryer

Núria Puigmal

Michelle Dion

Santhosh Kalash

Shiran Ferber

Michaela Prado

Alma L. Rodriguez

Takeda Pharmaceuticals

Adnan Abu-Yousif

Steve Langston

Tsubasa Shiraishi

Sean Harrison

David Lok

Michelle Ganno-Sherwood

Tiquella Hatten

Angel Maldonado Lopez