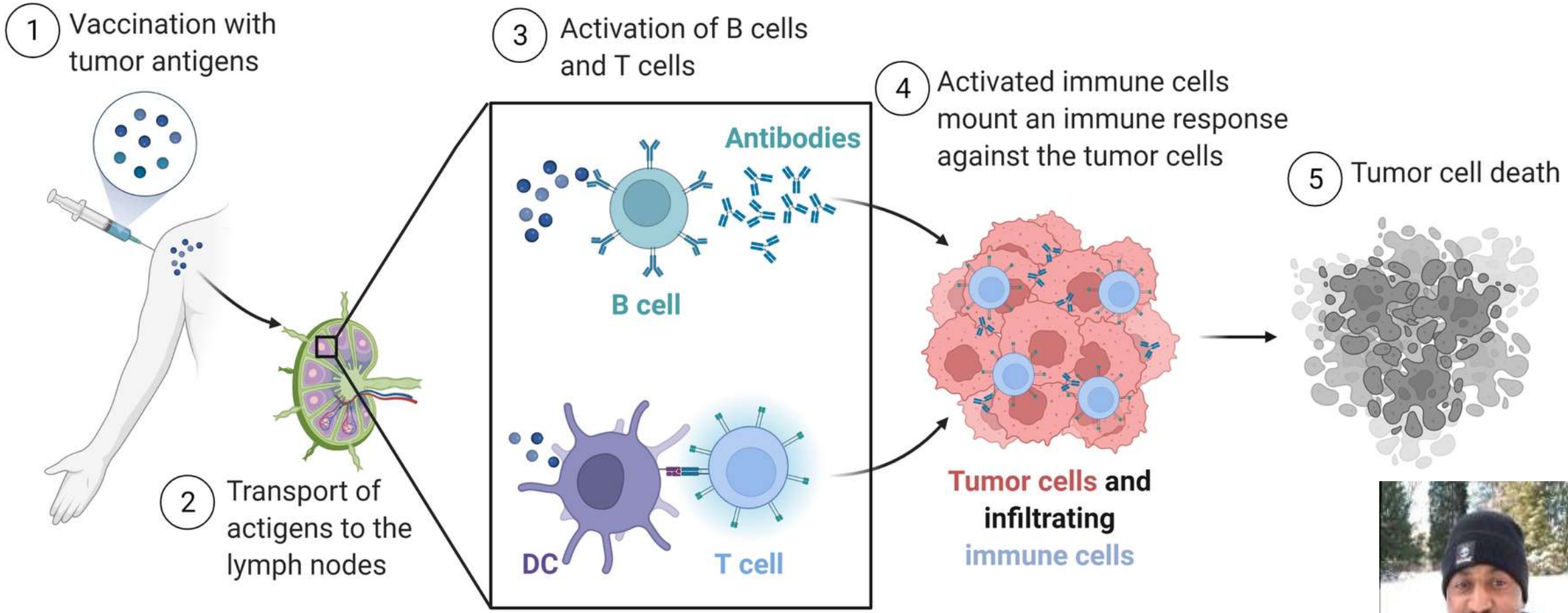
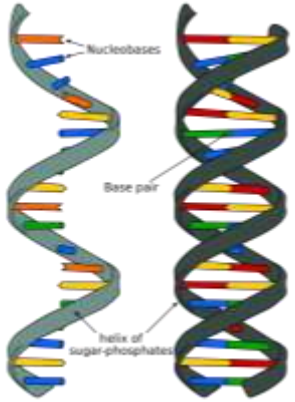
Engineering Polymeric Prodrugs for Immune-Therapies

Immune Therapy Based On Inducing Antigen-Specific Tumor Response



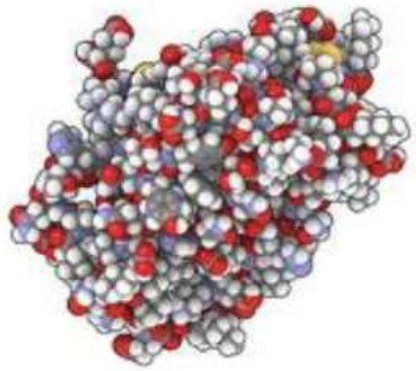
Dr. Simba Jokonya

Antigen Platforms For Generating Anti-Tumor Responses

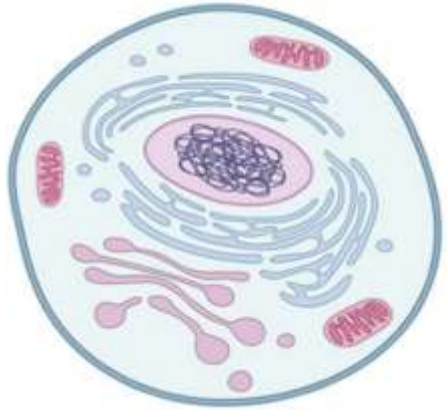


DNA and RNA

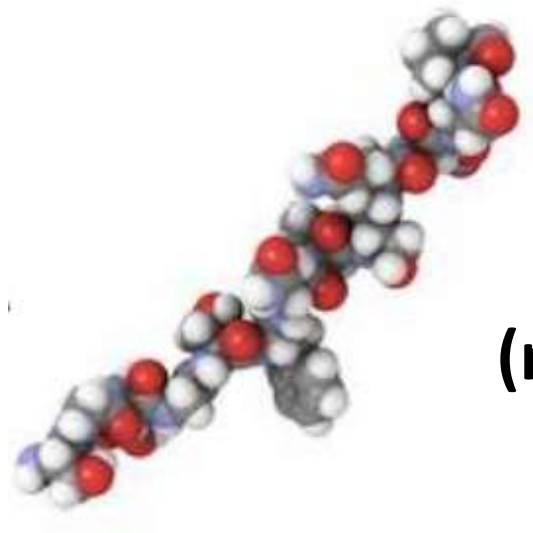
Peptides



Proteins



Tumor Cell/Lysate



Peptide Neo-Antigens
(more than one needed)

Pros

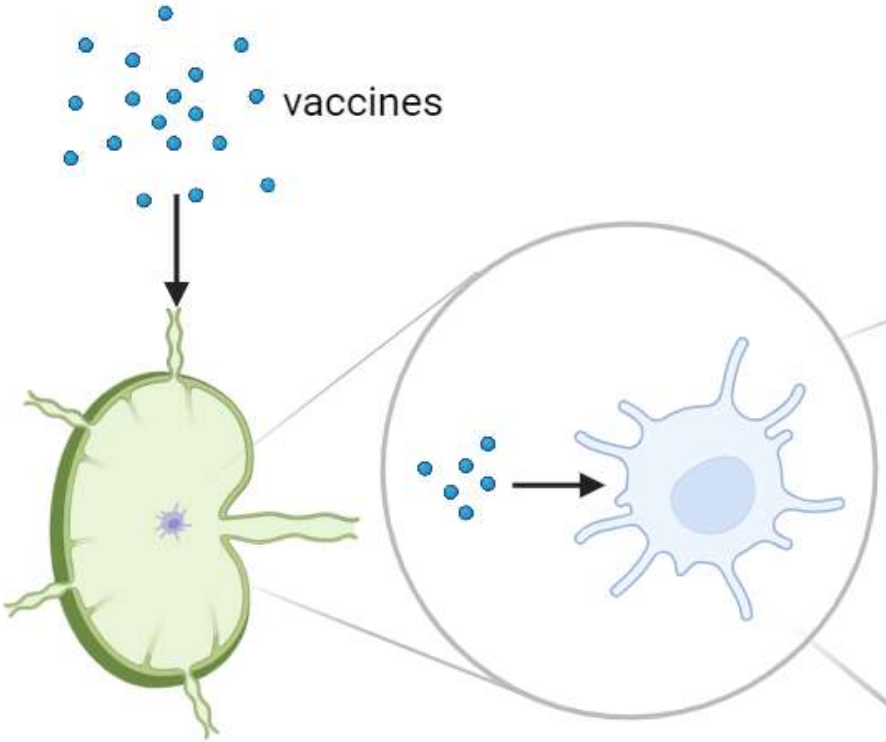
Easy to manufacture
Low cost
Storage stability
Directly serve as T cell epitopes

Cons

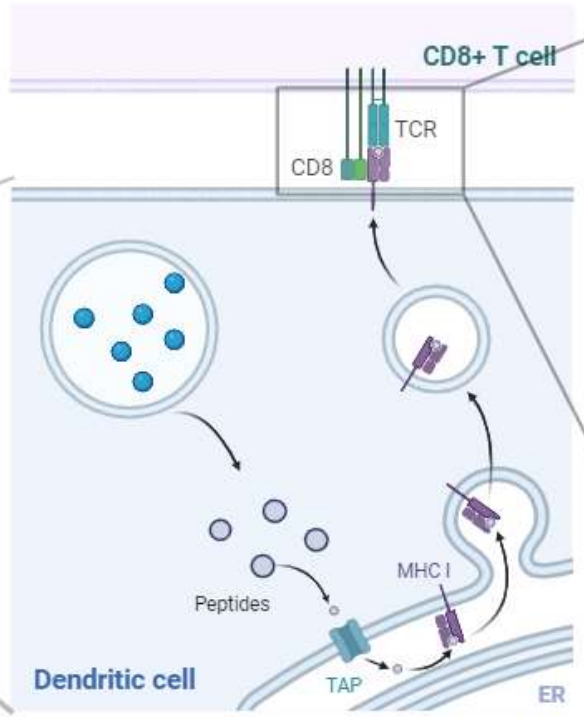
Fast clearance
Inefficient delivery to lymph nodes (LNs)
Low dendritic cell (DC) uptake
Low immunogenicity

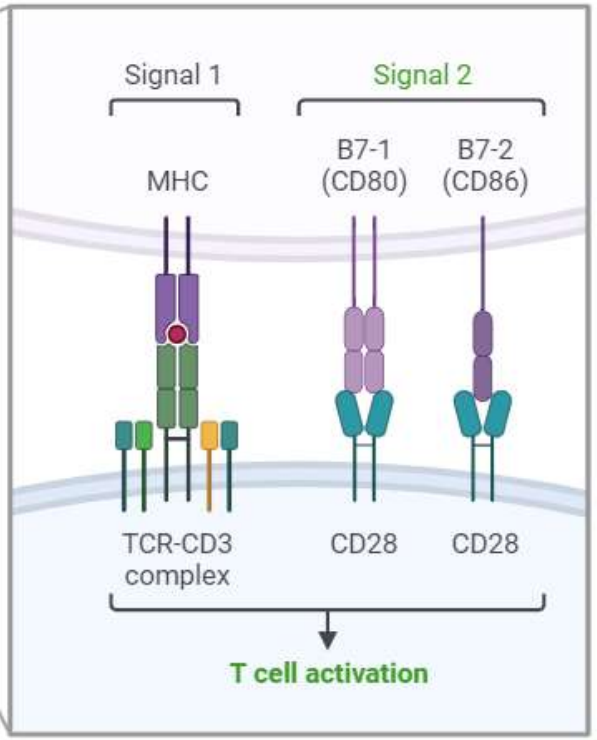
Improving Peptide Neo-Antigen Based Immune Therapy Polymeric Carriers Can Aid at Two Levels:

1. LN Trafficking and DC Targeting

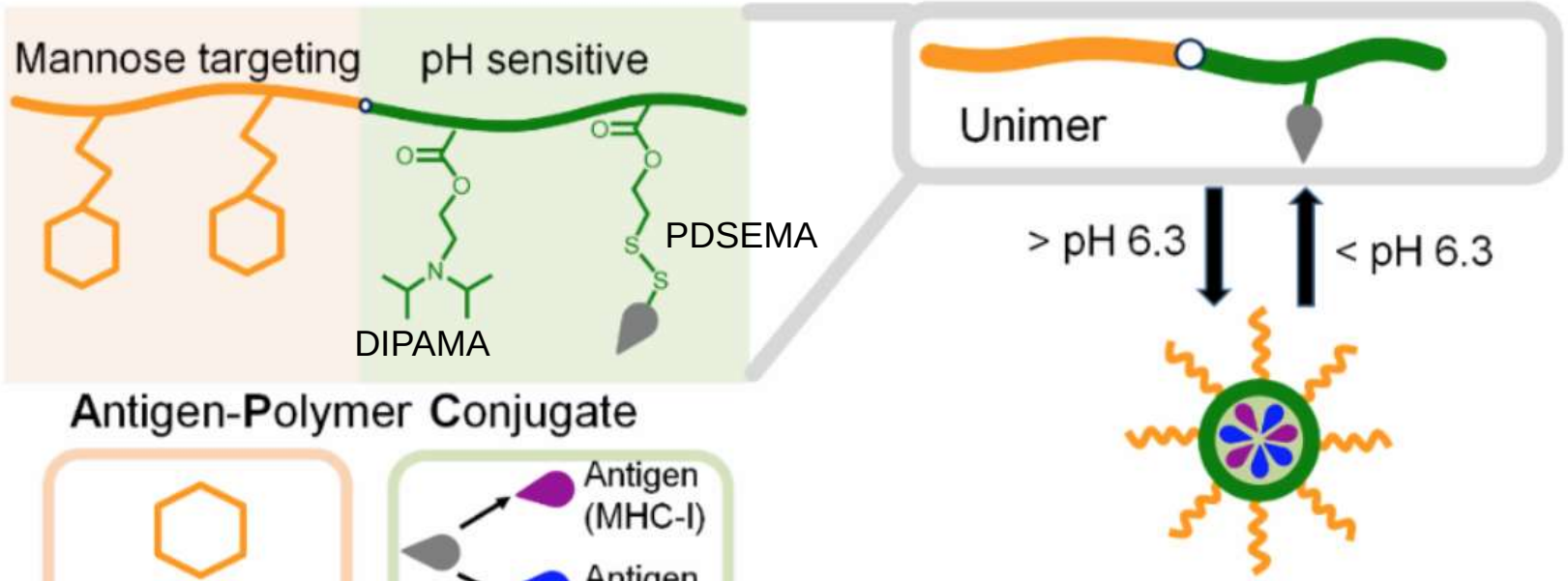


2. Cross-Presentation & Co-Stimulation

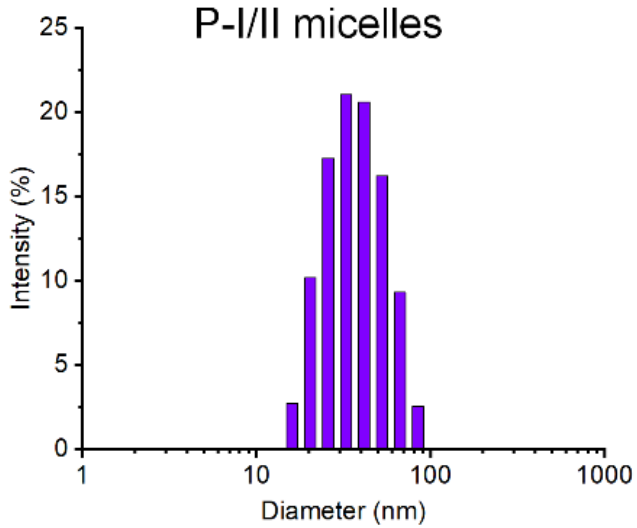




Mannosylated Polymeric Carriers to Target DCs in LNs



P-I/II micelles



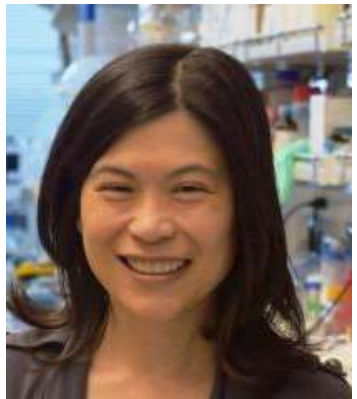
40 nm diameter

LN Delivery

Target mannose receptors on DCs

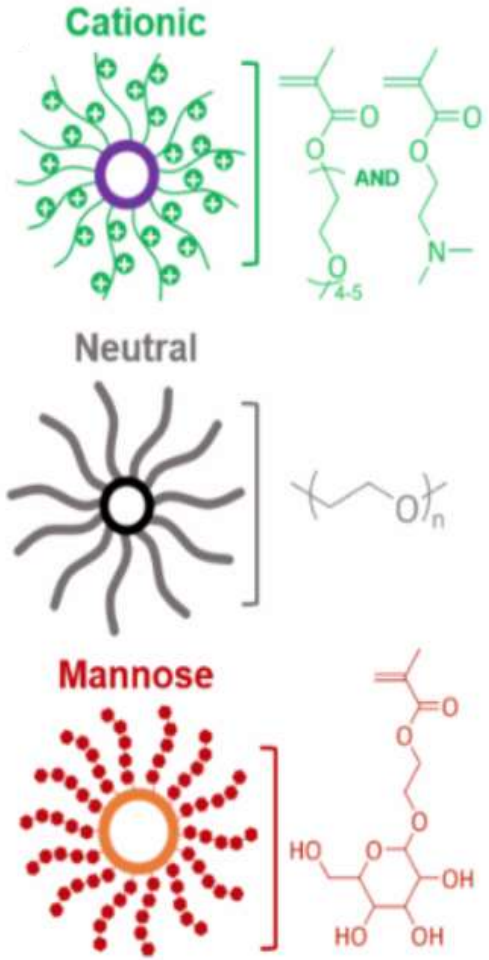
Song K, Nguyen DC, et al.
J Control Release. 2023 356:232
Bioconjug Chem. 2009 20, 241
Bioconj. Chem. 2010 21, 2205

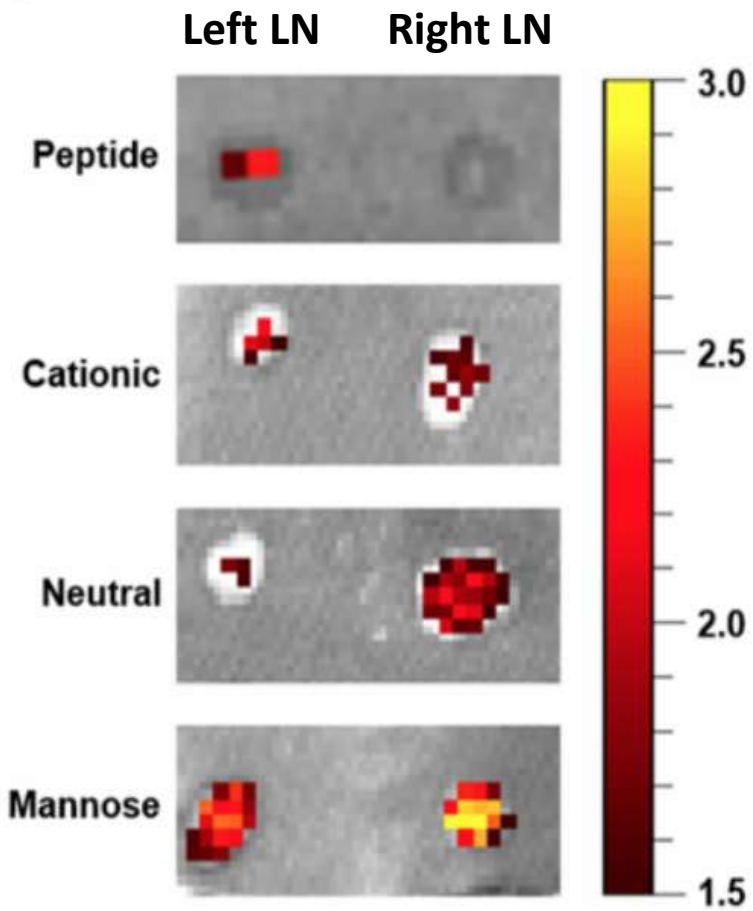
Suzie Pun

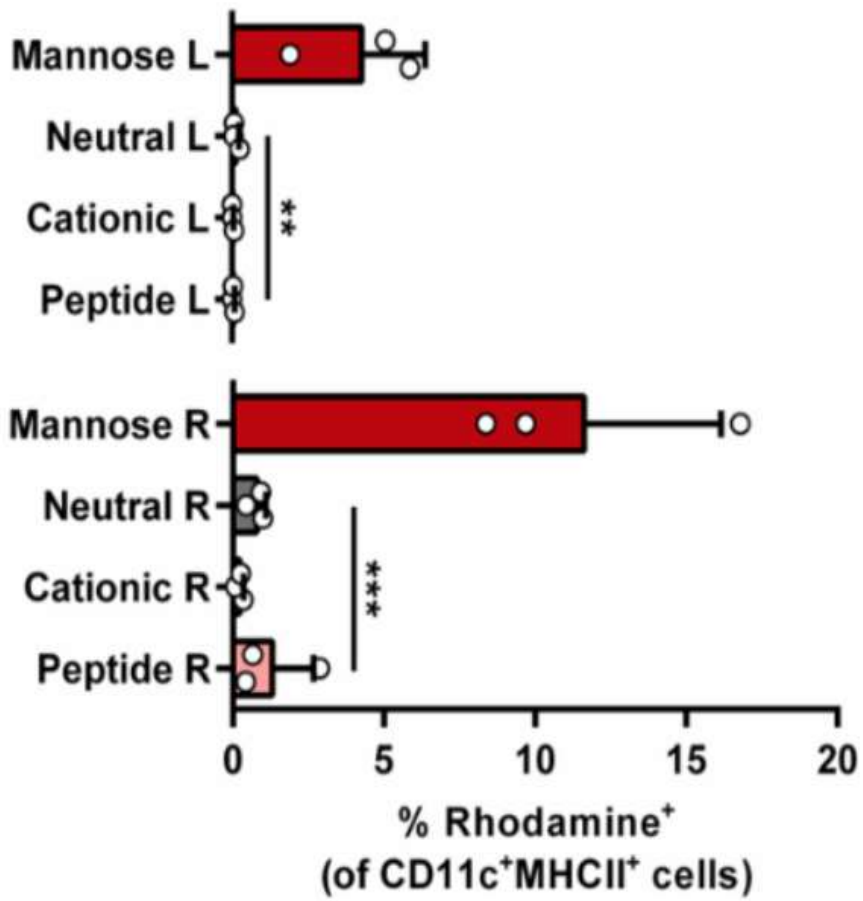


Ben Nguyen

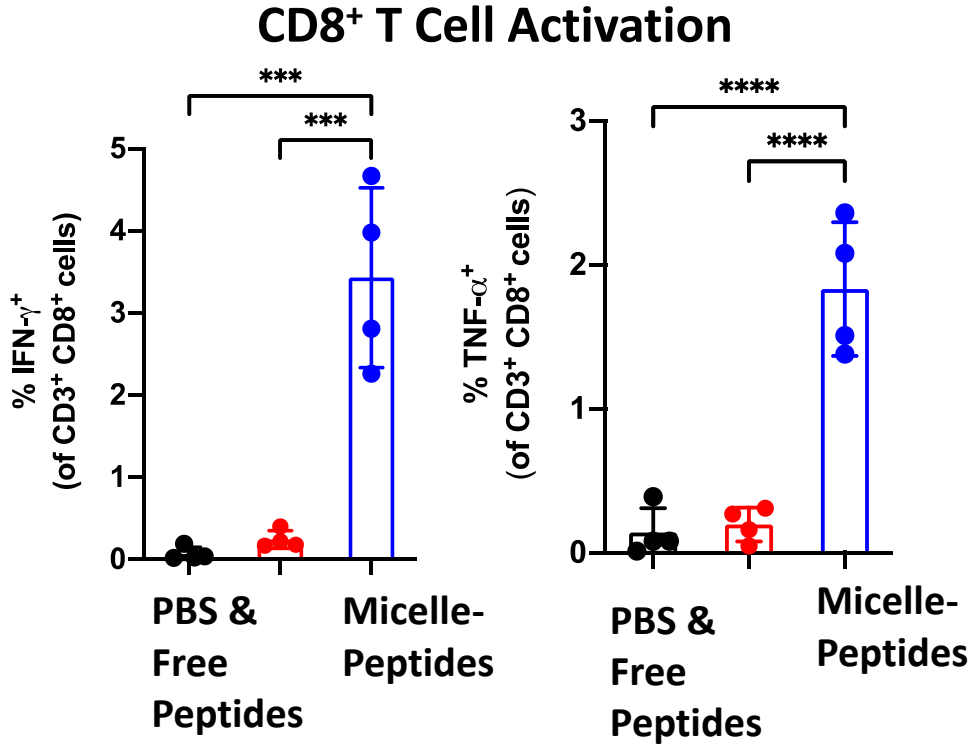
Mannosylated Micelles Improve LN Trafficking & DC uptake of Peptide Antigens

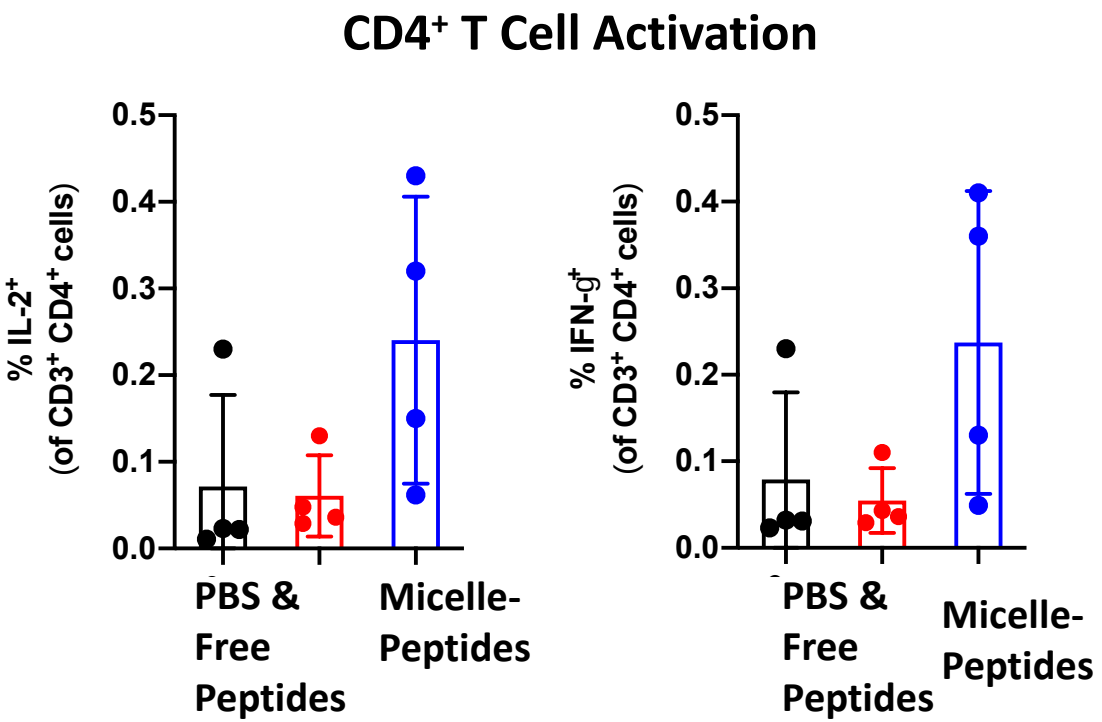






Mannosylated Polymeric Micelles Enhance T-Cell Responses



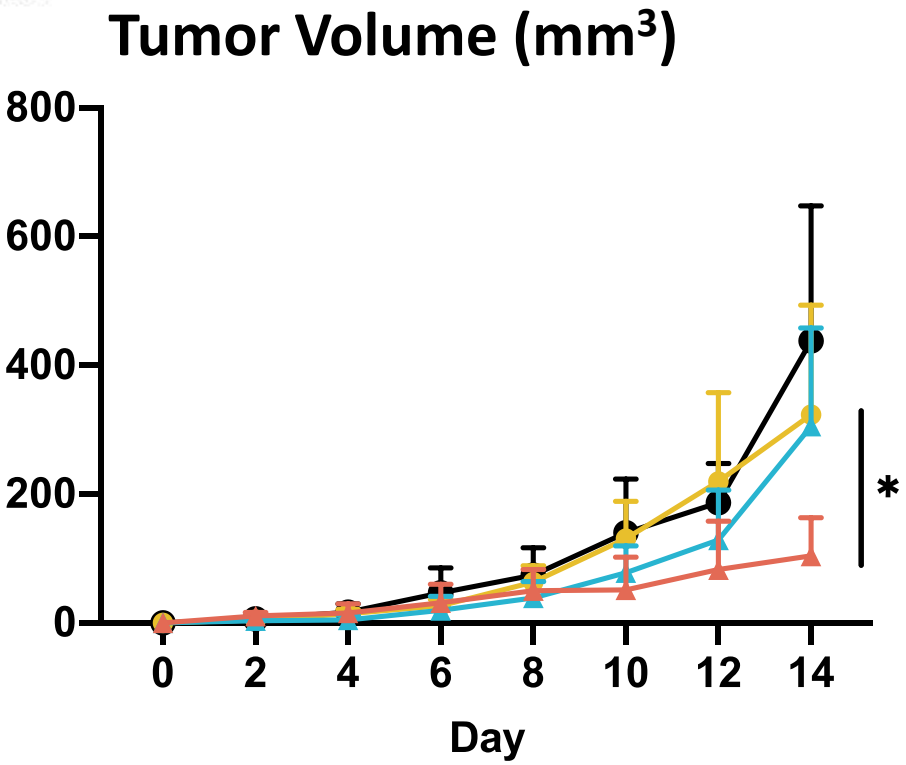


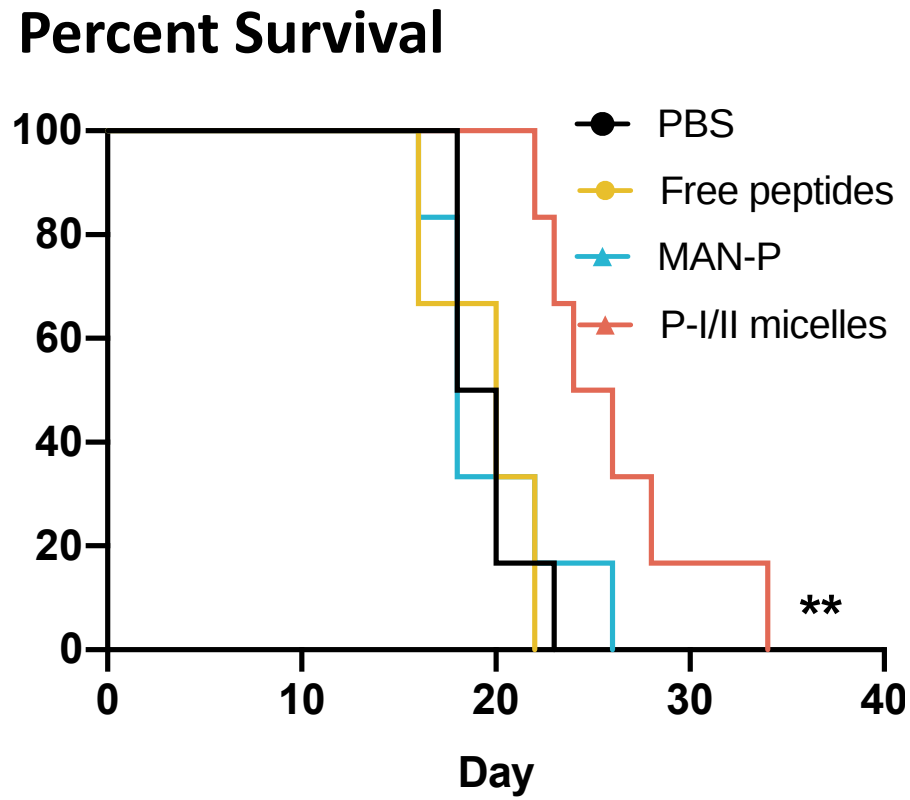
Kefan Song

Song K, Nguyen DC, et al.
J Control Release. 2023 356:232

Mannosylated Micelles Delay Tumor Growth and Prolong Survival But Responses Need Improvement

Day
-4 B16F10-OVA Tumor Inoculation
0 Prime
1 ICB
7 Boost
8 ICB
14 Boost
15 ICB

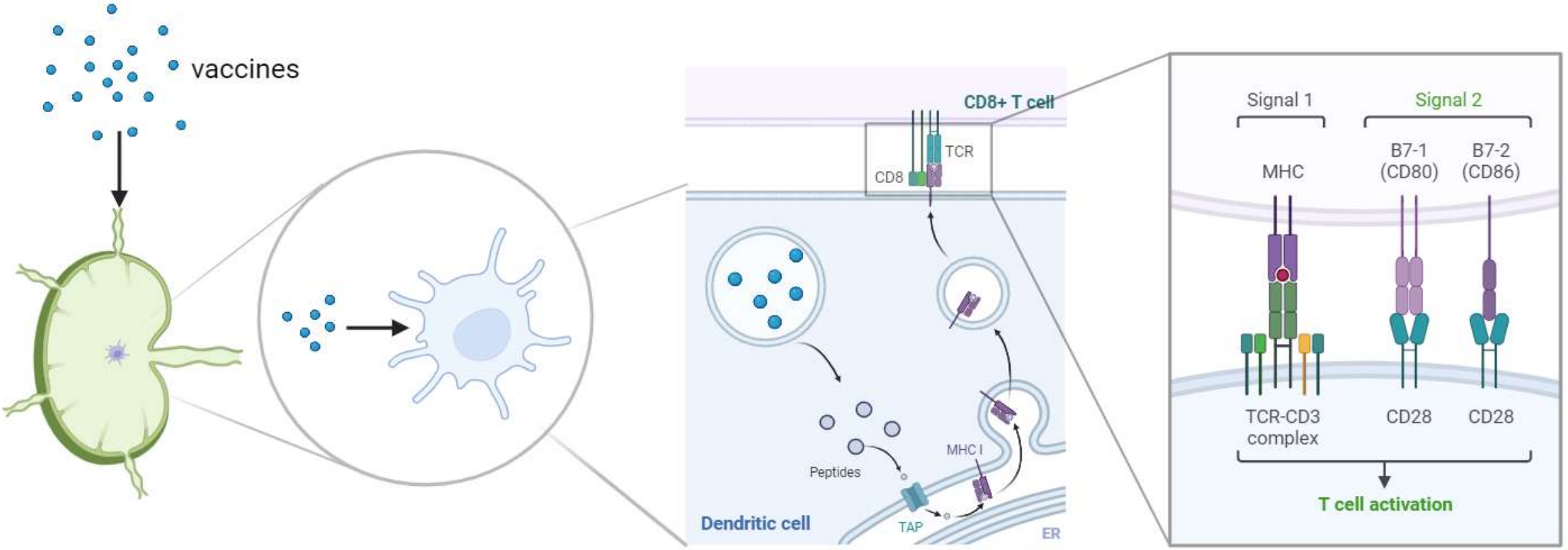




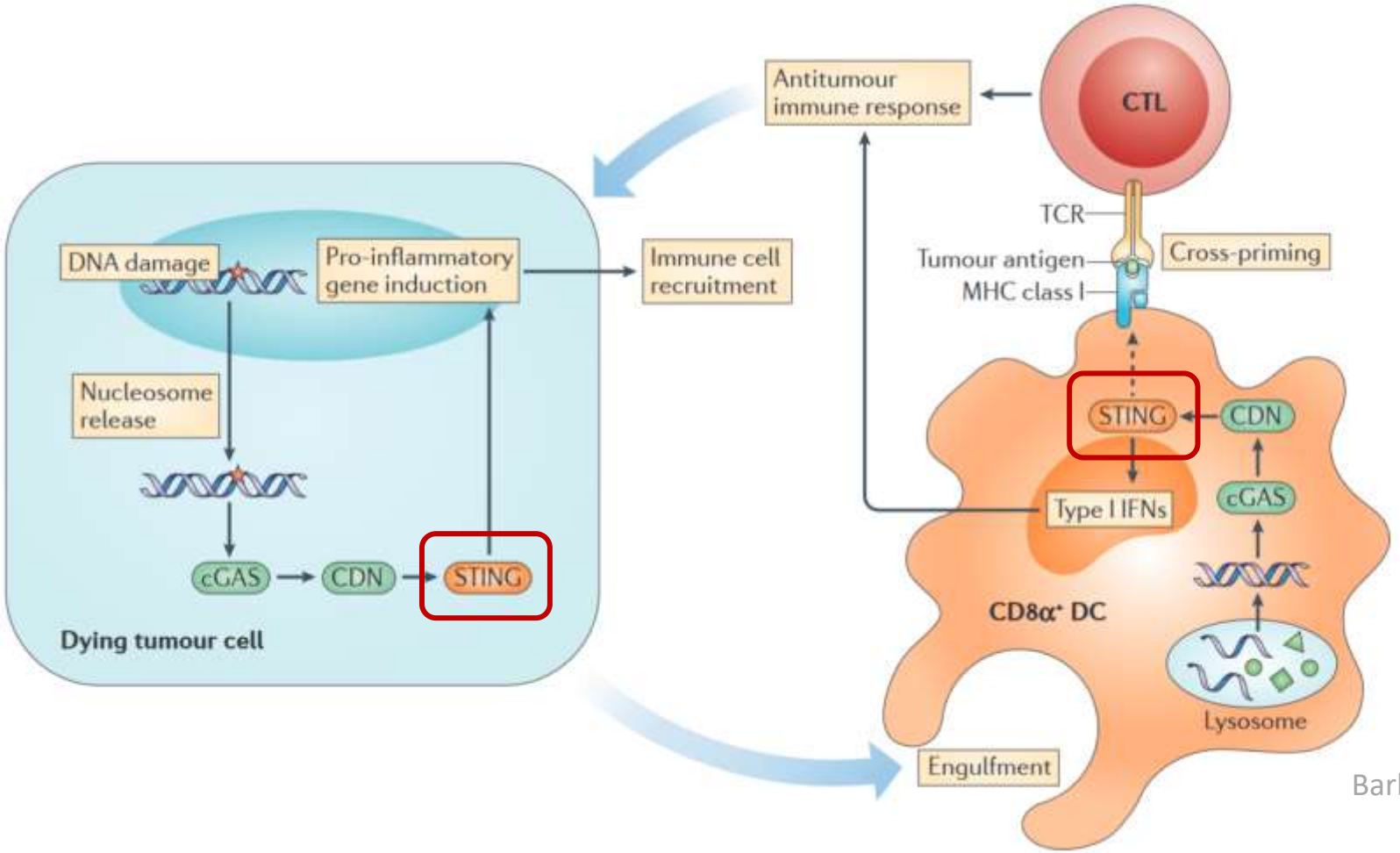
Improving Peptide Neo-Antigen Based Immune Therapy

1. LN Trafficking and DC Targeting

2. Cross-Presentation & Co-Stimulation



STING Agonists Can Stimulate Cross-Presentation and Priming



STING activation in DC:

Type I IFN production

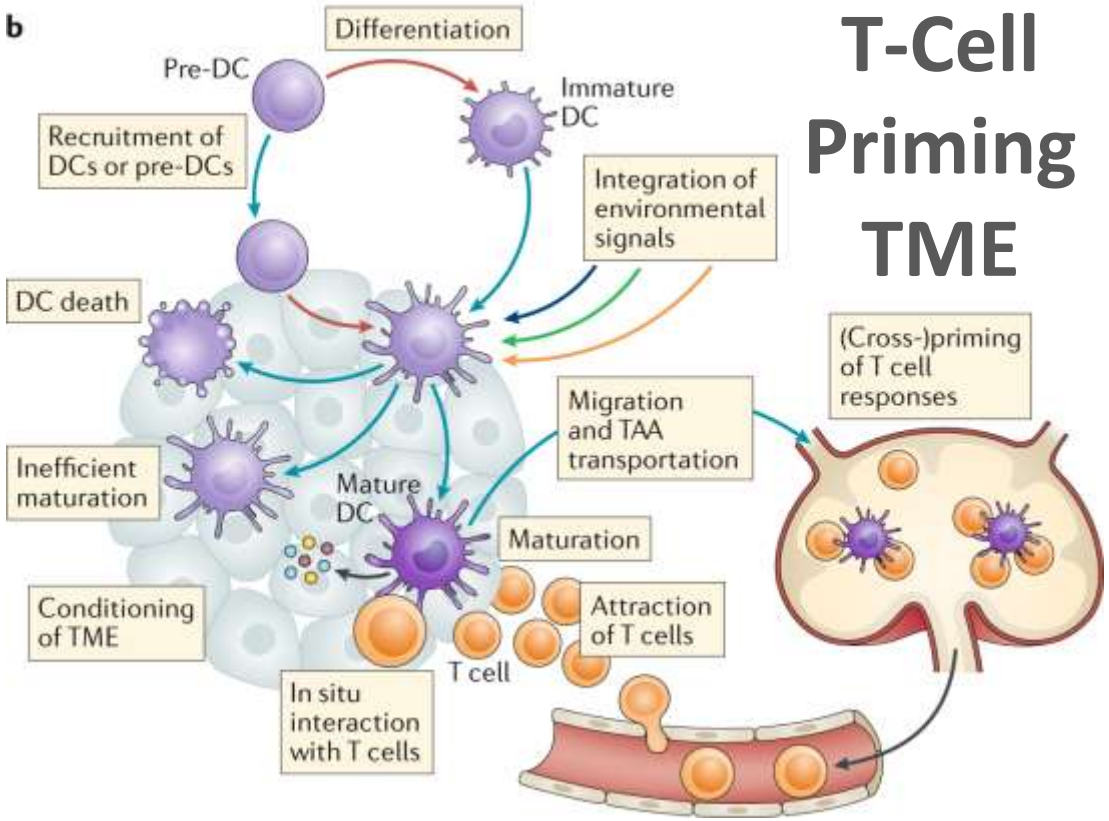
DC maturation

Cross-presentation

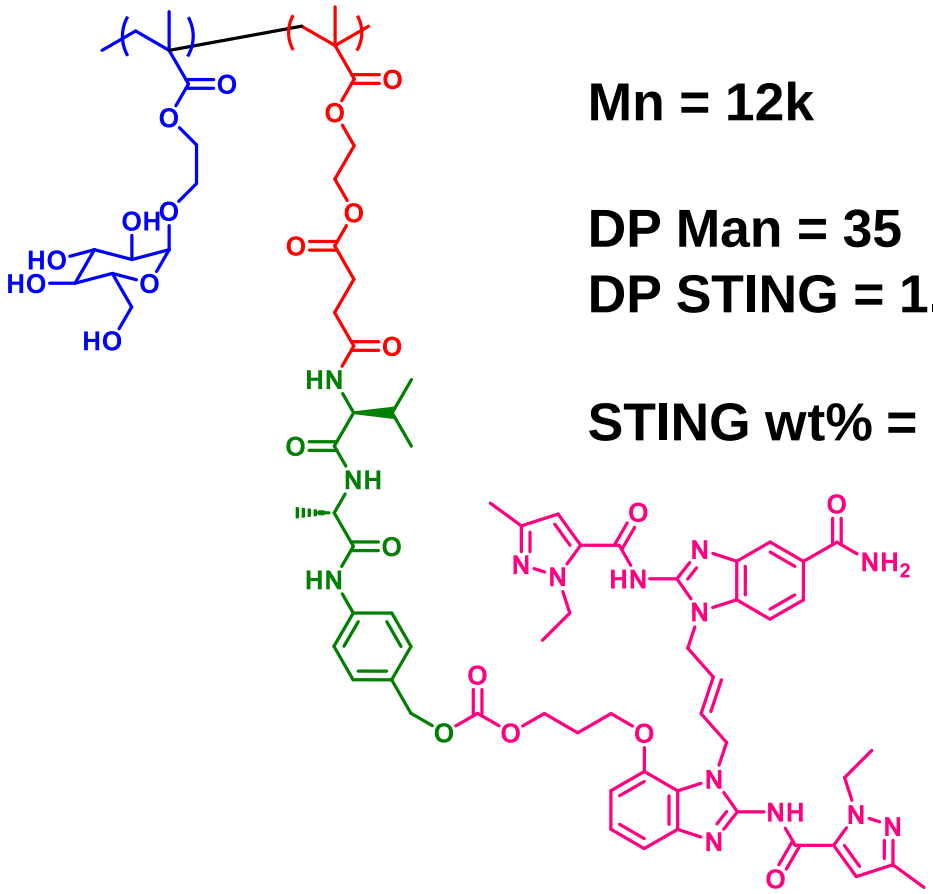
Priming $CD8^+$ T cells

Barber et al. Nature reviews. Immunology 2015

Soluble CD206-Targeted STING Polymeric Prodrug for Direct Tumor Microenvironment Reprogramming



T-Cell Priming TME



Mn = 12k

DP Man = 35
DP STING = 1.2

STING wt% = 8.0%

Wculek et al. (2020). *Nature reviews. Immunology*, *20*(1), 7–24.

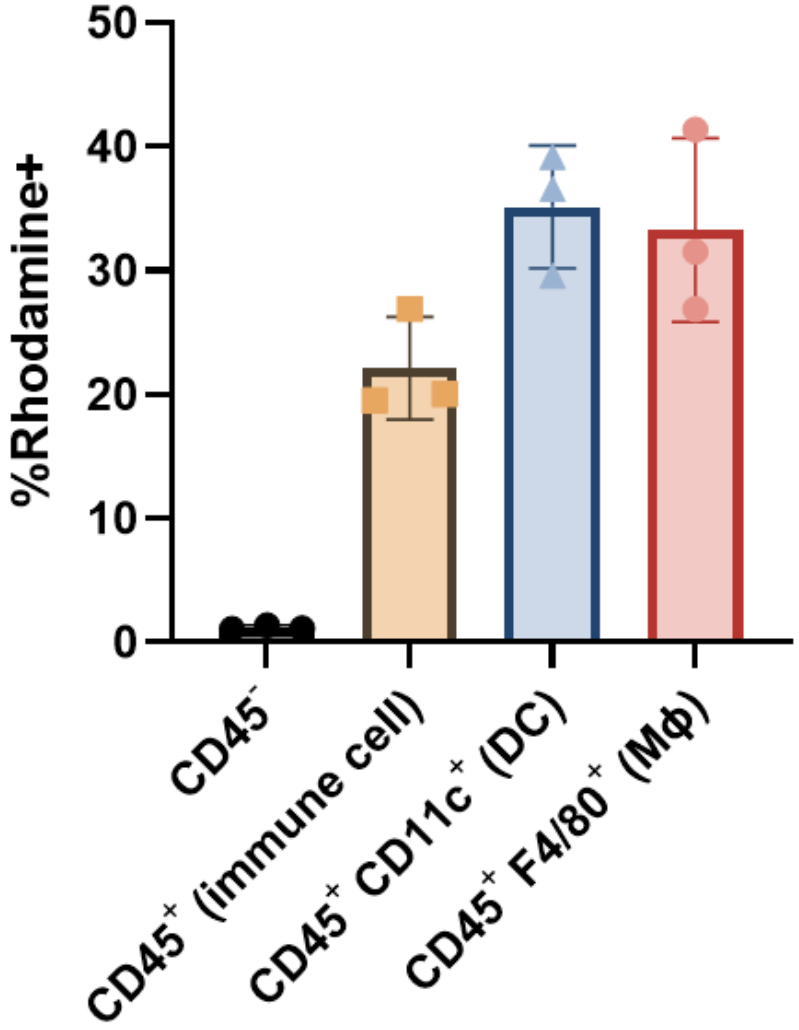
PolySTING Targets Immune Cells in the TME

Inoculate B16F10

Tumor grows to
100-200 mm^3

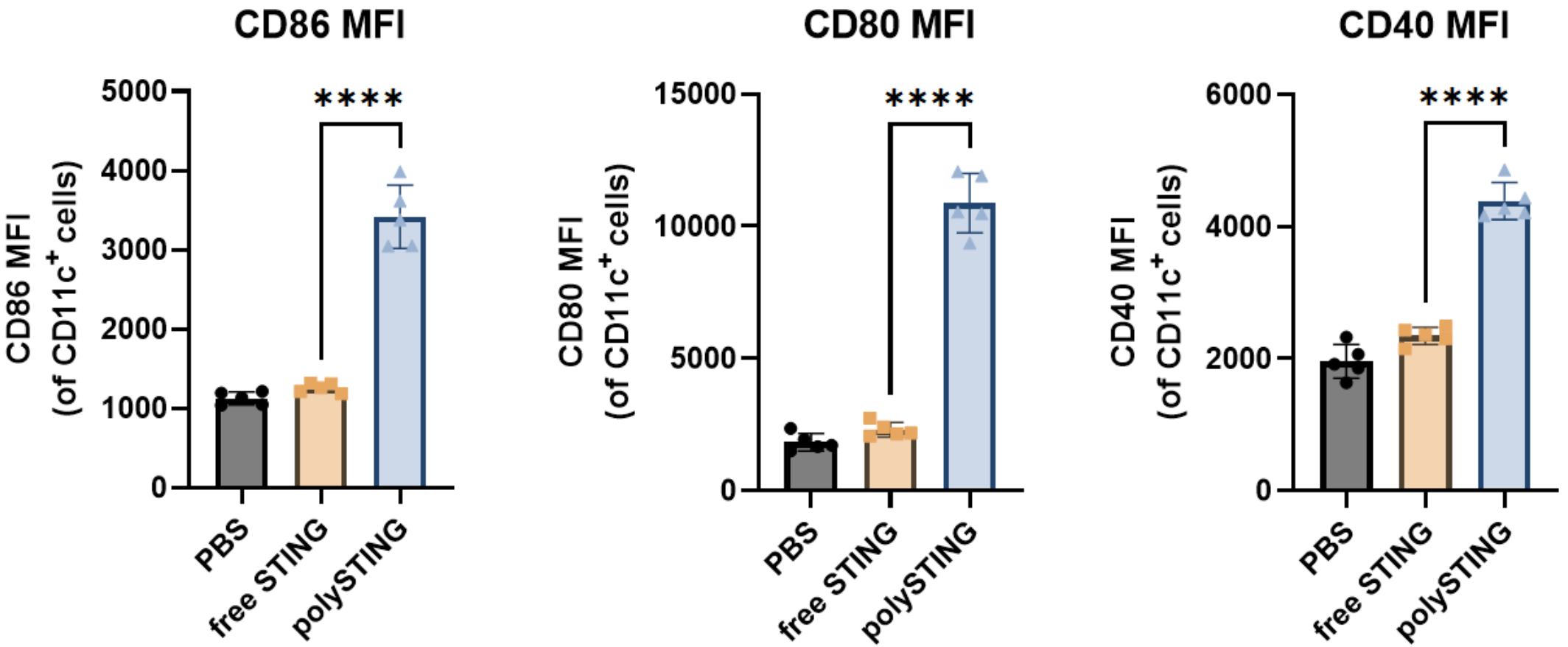
Inject rhodamine-labeled polySTING

Harvest tumors
30 min later



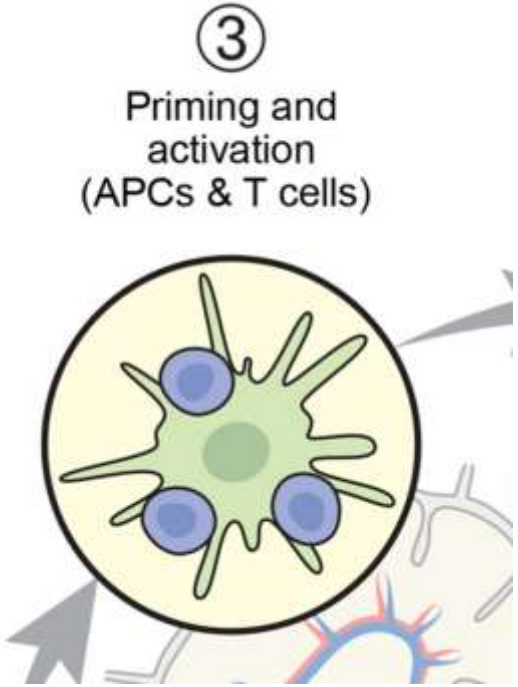
ACS Central Science,2024 in press

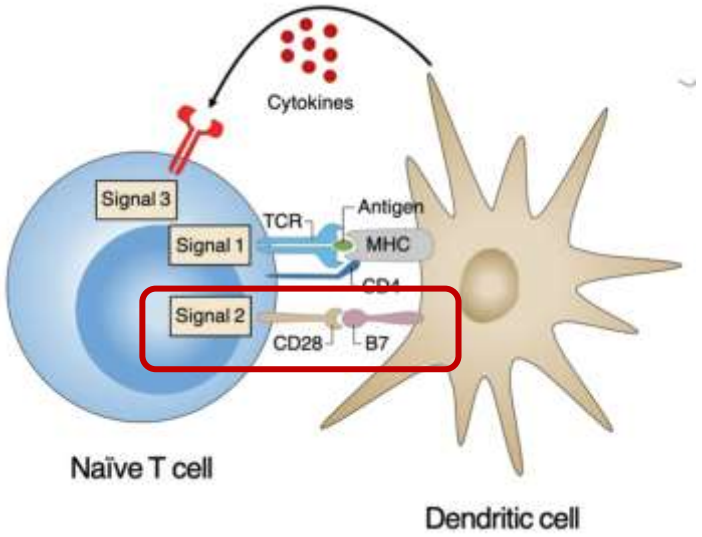
polySTING Induces DC Maturation in TDLN

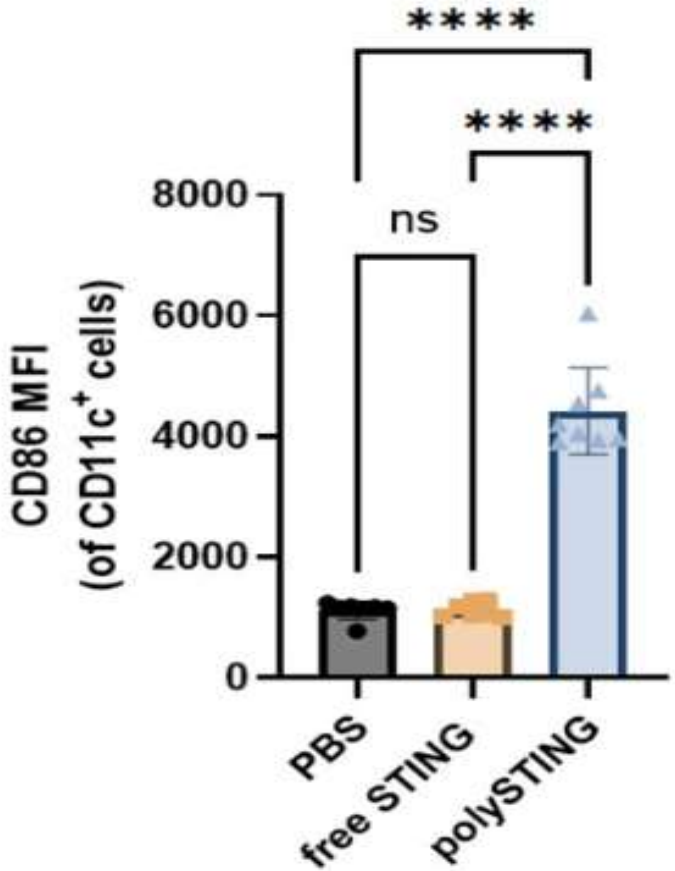


TDLN: inguinal LN on the same side with the tumor

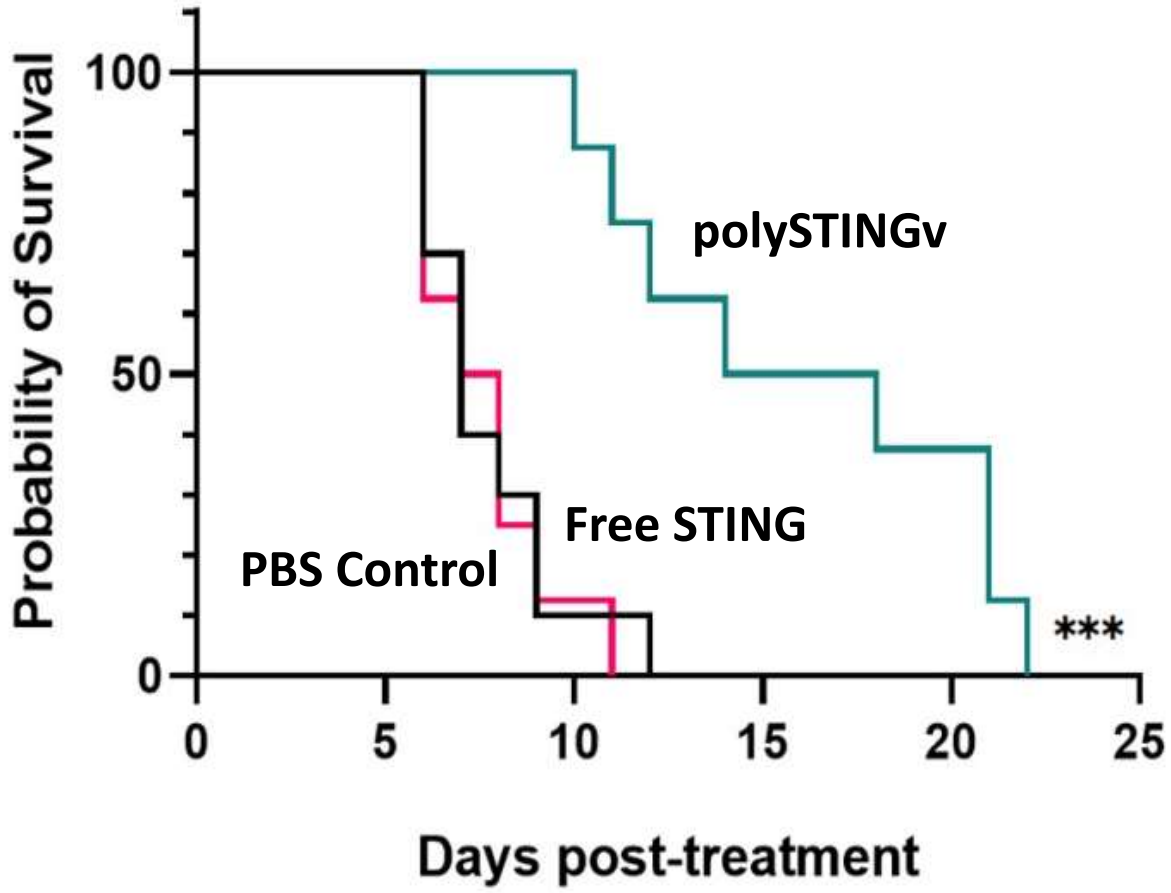
PolySTING induces DC maturation and proliferation in tumor-draining lymph node

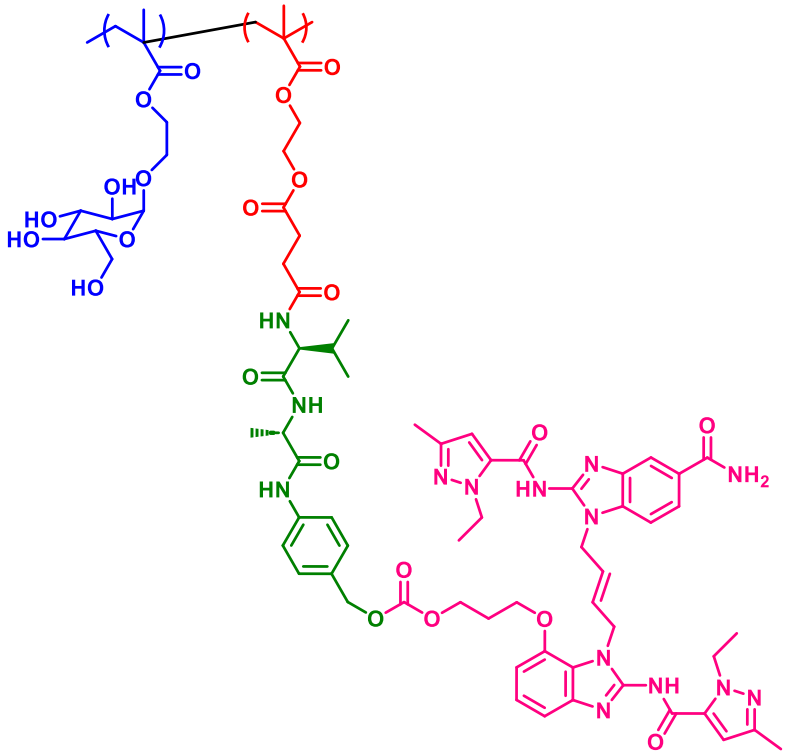






Mannose-Targeted STING Polymer Prodrug Prolongs Survival in B16F10 Melanoma Tumor Model





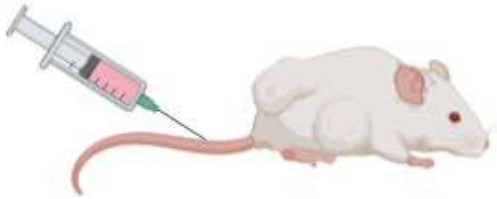
ACS Central Science,2024 in press

Thank you to our collaborators at UW, Melbourne CSIRO, Seattle Children's Research Institute, Dana Farber Cancer Institute, Fred Hutchinson Cancer Research Center!

Work funded by DTRA, NIH, Bill & Melinda Gates Foundation, Washington Life Sciences Discovery Fund, UW Center for Commercialization, Australian SIEF Program

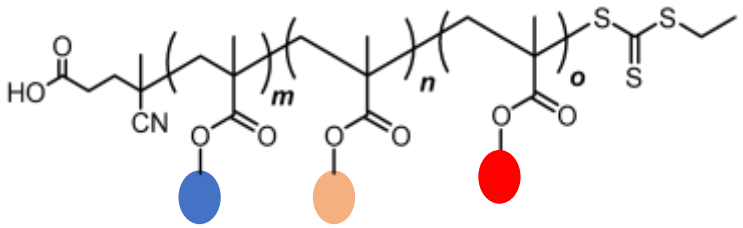
POLYSTING TARGETS APCS IN THE TME AND ACTIVATES STING?

- B16-F10 tumor-bearing mice



	Measured Concentration	
Sample Type (unit)	**Free STING/diABZI**	**PolySTING**
Plasma (ng/mL)	**1.57**	**130.41**
Tumor (ng/g)	**103.15**	**2978.72**

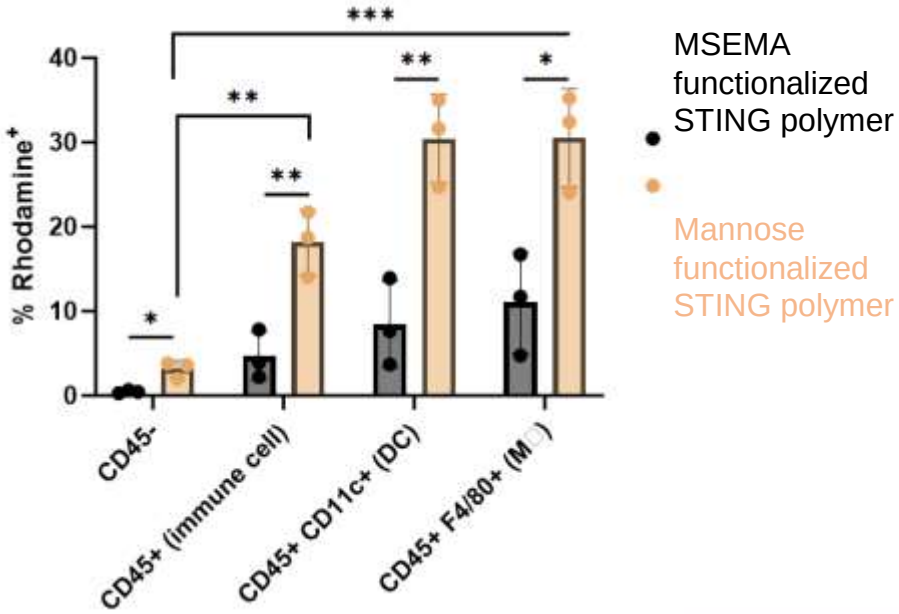
MSEMA: 2-methylsulfinyl ethyl methacrylate



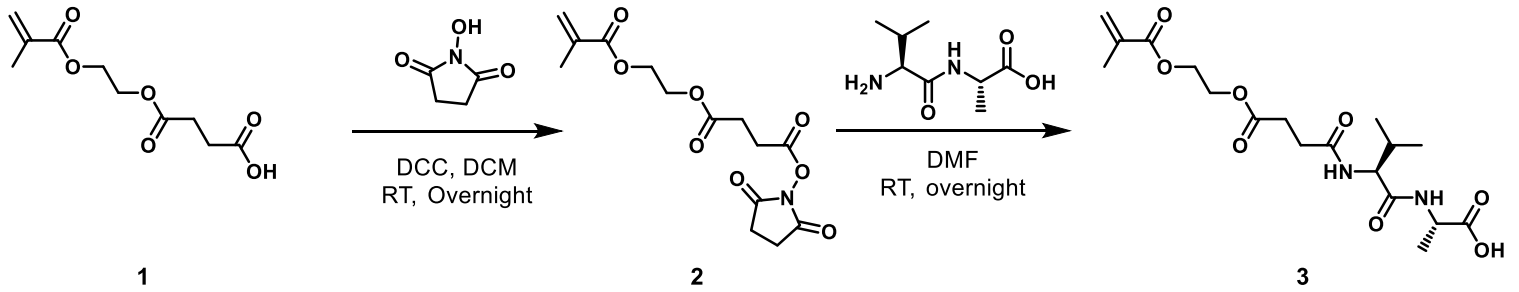
STING agonist

Mannose MSEMA

Rhodamine



PRODRUG MONOMER SYNTHESIS



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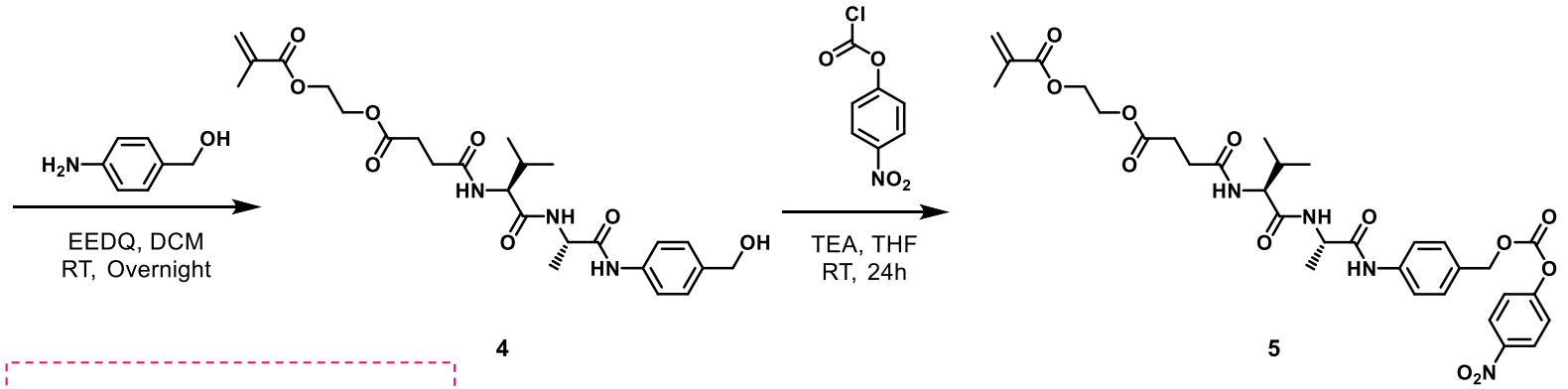
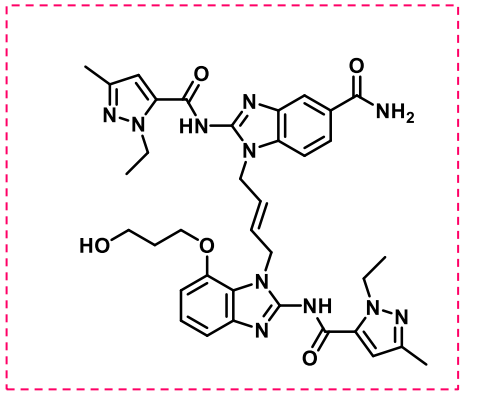
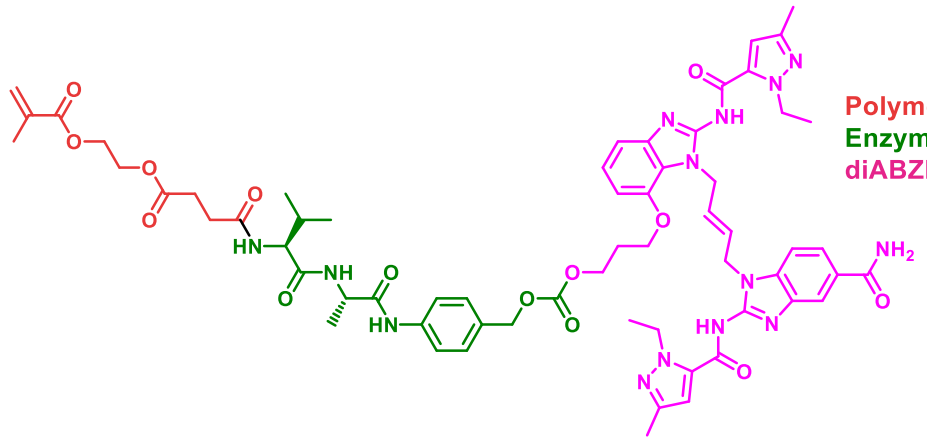


4 5

"STING Agonist-3"





Polymerizable methacrylate
Enzyme-cleavable, self-immolative Val-Ala Linker
diABZI STING Agonist

6