

Developing Novel STING-activating Immunotherapy



Xiaoqi (Kevin) Sun
July 13, 2022



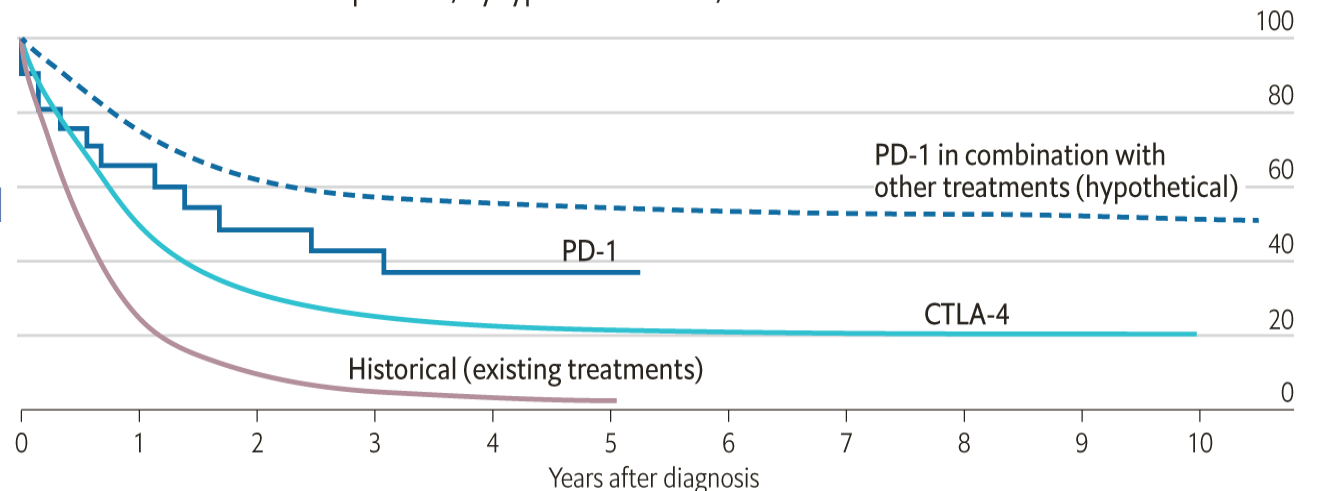
MOON Laboratory
ImmunoEngineering

Increase therapeutic response of cancer immunotherapy

Current immunotherapy:

- Potential long-term survival
- limited response rate

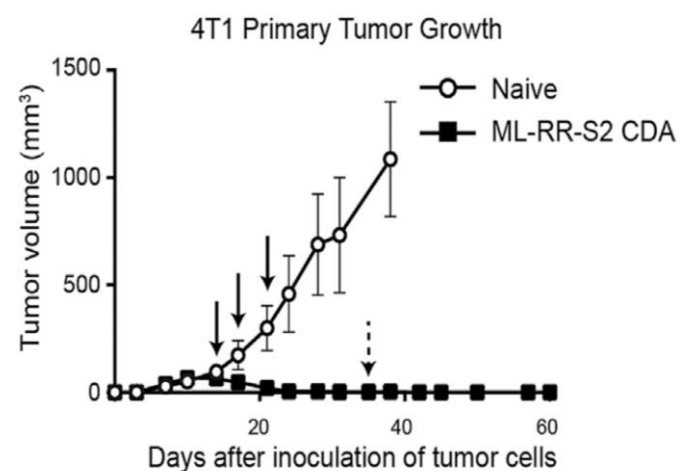
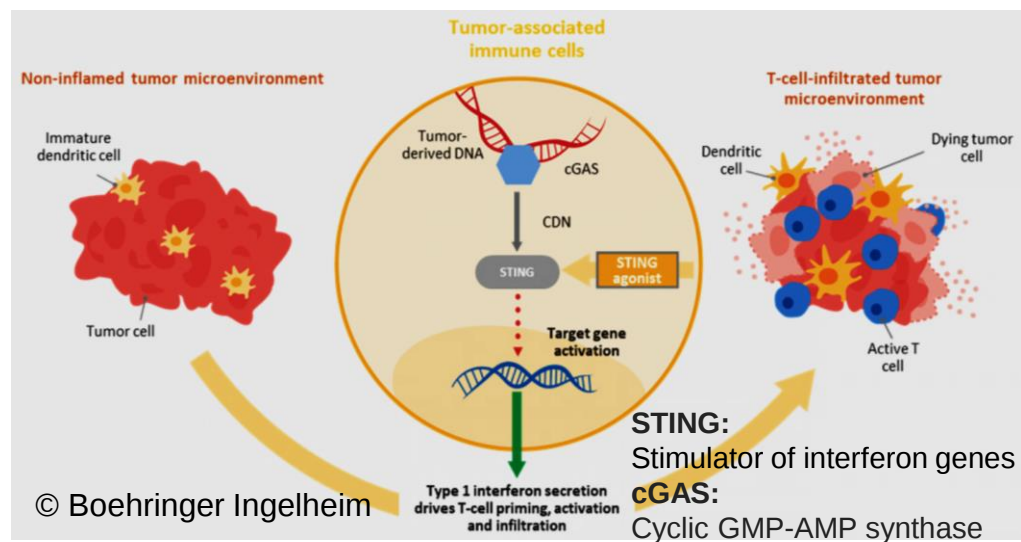
Survival rates of melanoma patients, by type of treatment, %



Sources: AACR 2016; J Clin Oncol

Challenge: how to increase the responding rate among different patients

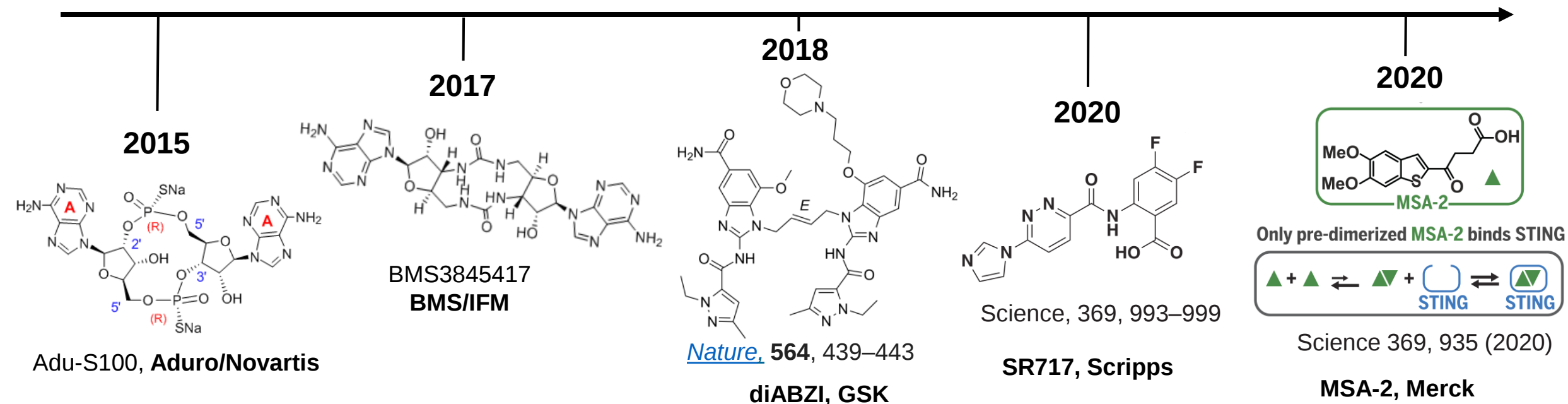
cGAS-STING pathway: orchestrator of innate and adaptive immunity



Cell Reports, 2015

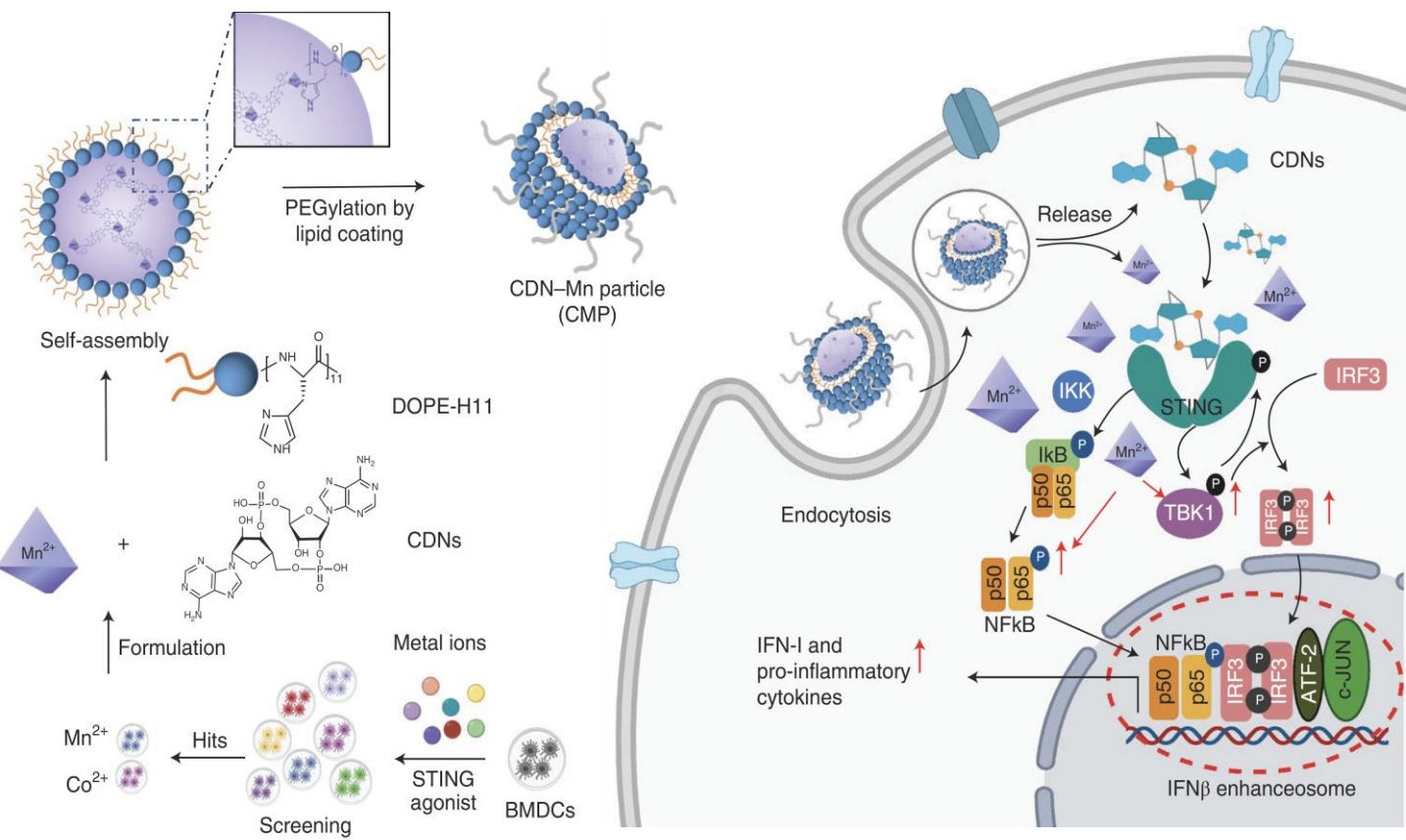
Improve drug-like properties of STING agonist

- Limited therapeutic effect after systemic administration
- Low serum stability, short half life (<20 mins)
- Low cellular permeability
- Fast clearance in the tumor after IT injection



Preview: Novel delivery system for STING agonist

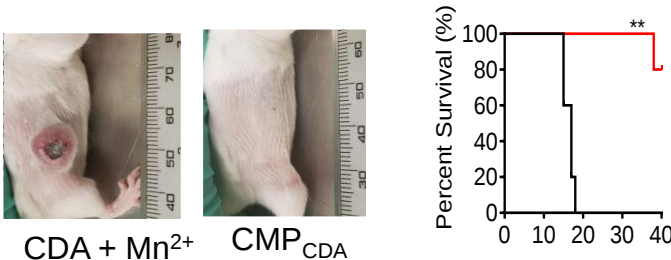
Amplifying STING activation by Cyclic Dinucleotide-Mn Particles (CMP)



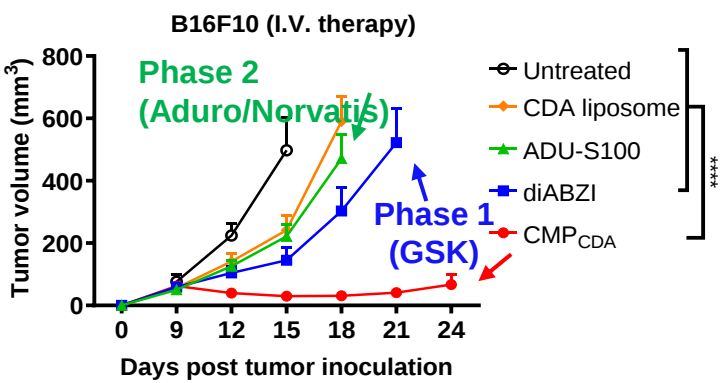
X Sun, et.al. Nature Nanotechnology 2021

Systemic injection, durable immune response

Tumors after treatment Re-challenged on Day 145



Performed best in benchmark studies

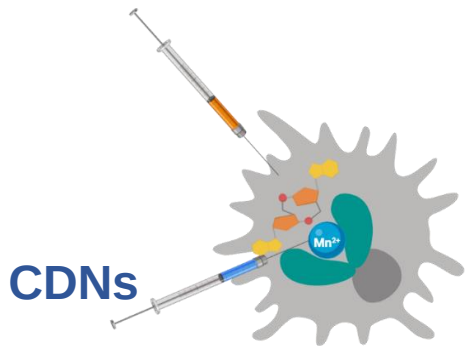


Eradicated CBI-resistant tumors



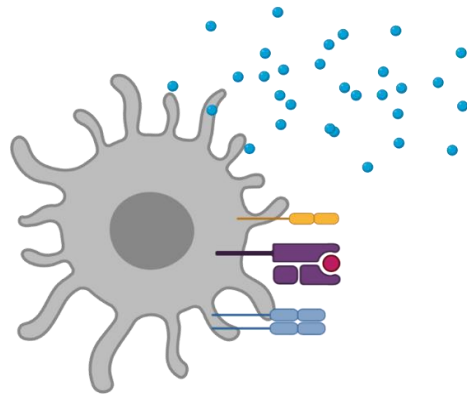
Mn²⁺ and Co²⁺ amplify CDNs induced STING activation

Serial amounts of
nutritional metal ions



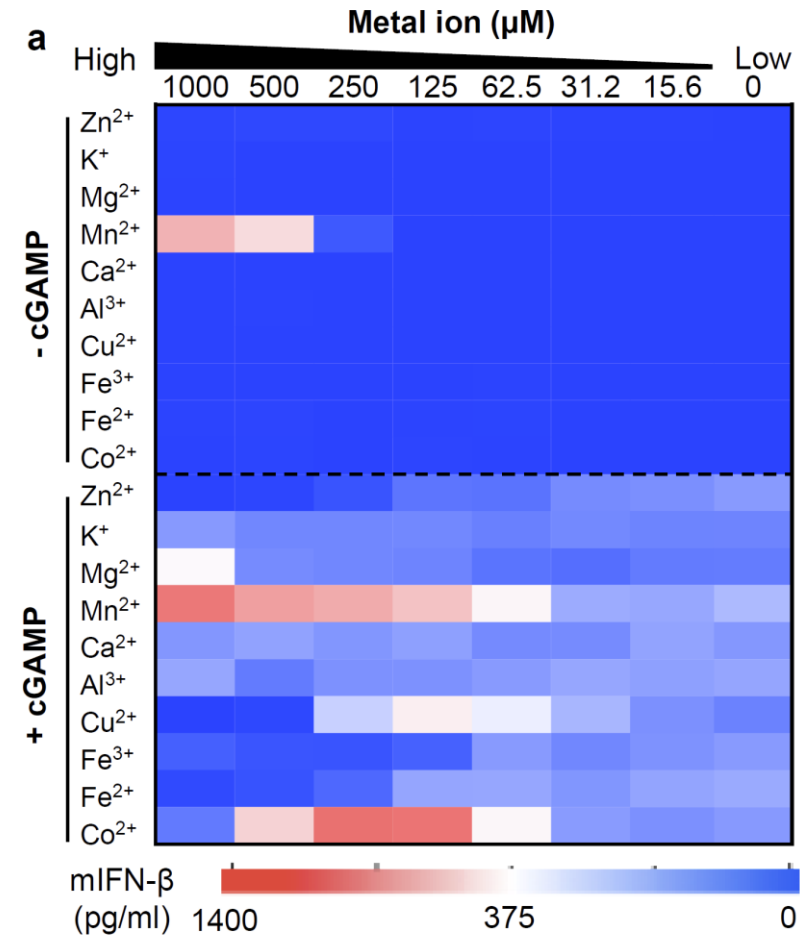
Immature BMDC

Type-I IFNs

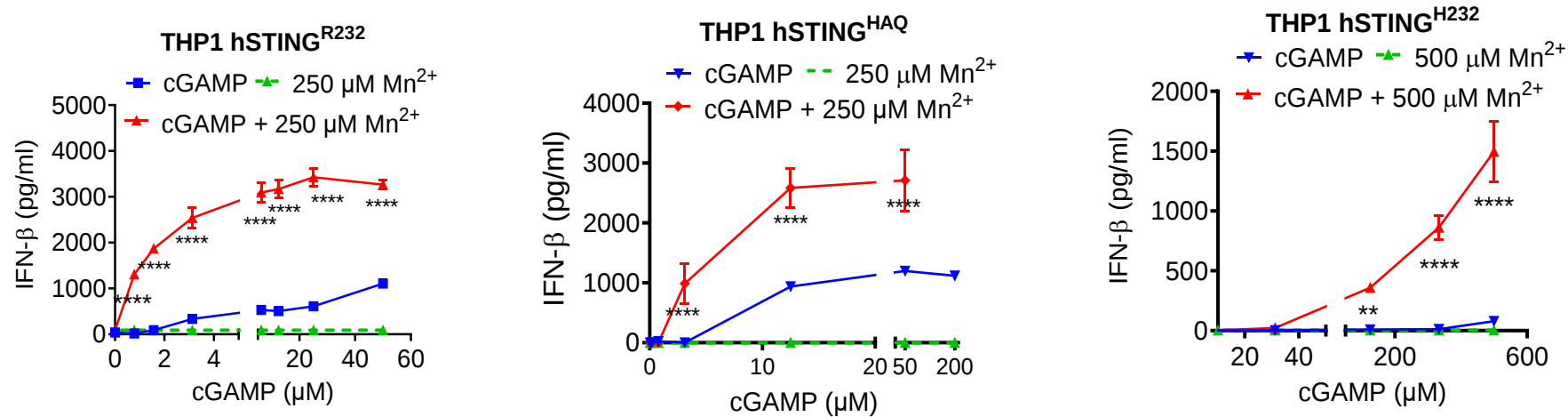


Mature BMDC

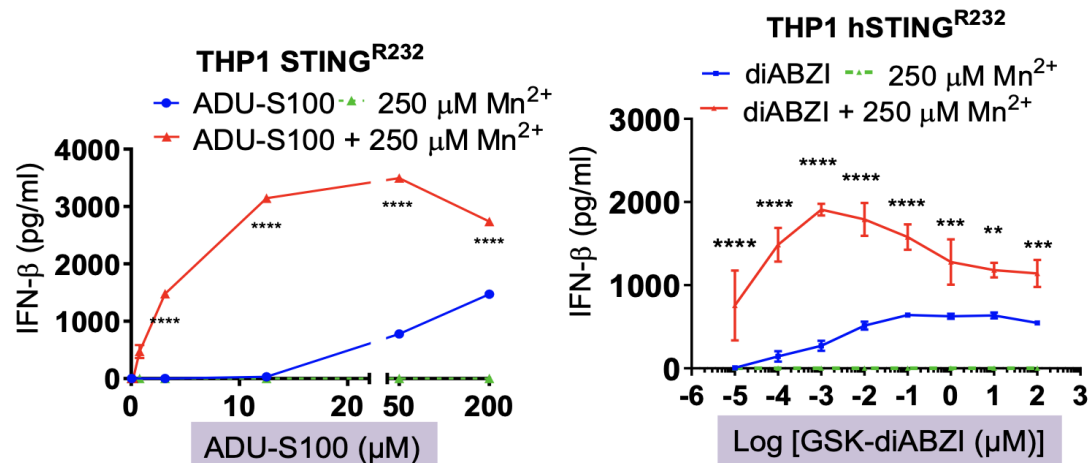
Type-I Interferon response in BMDCs



Mn²⁺ amplifies Type-1 IFN Activation of STING agonists



Validated in hSTING^{R232}, ^{H232}, and ^{HAQ}, covering ~92% of human STING variants



How dose Mn^{2+} synergize with STING agonist?



Jiaqian Li
Dr. Yu Leo Lei

Immunity Article

Manganese Increases the Sensitivity of the cGAS-STING Pathway for Double-Stranded DNA and Is Required for the Host Defense against DNA Viruses

Chenguang Wang,^{1,2,3,7} Yukun Guan,^{1,2,3,7} Mengze Lv,^{1,2,3} Rui Zhang,^{1,2,3} Zhaoying Guo,^{1,2,3} Xiaoming Wei,^{1,2,3} Xiaoxia Du,² Jing Yang,^{1,2,3} Tong Li,⁴ Yi Wan,⁴ Xiaodong Su,² Xiaojun Huang,^{3,5} and Zhengfan Jiang^{1,2,3,6,*}

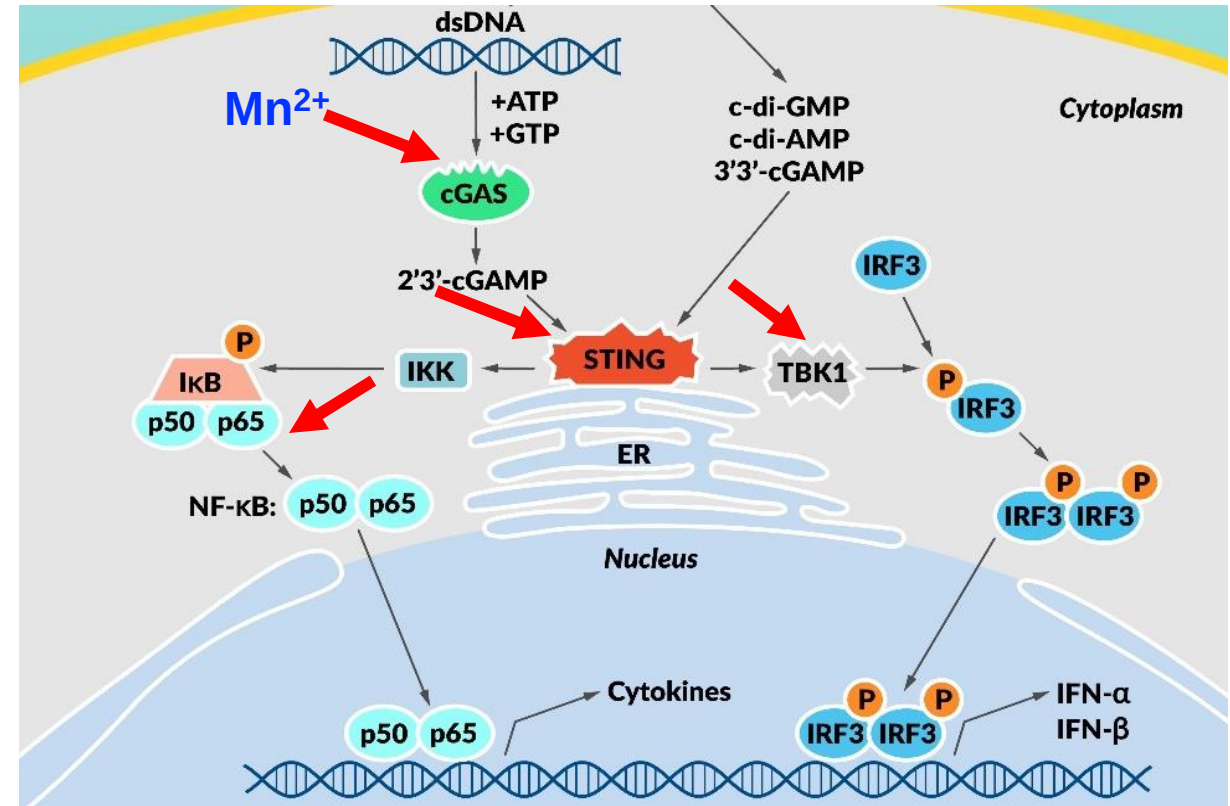
(Immunity, 48, 675–687, 2018)

Cell Reports

Mn^{2+} Directly Activates cGAS and Structural Analysis Suggests Mn^{2+} Induces a Noncanonical Catalytic Synthesis of 2'3'-cGAMP

(Cell Reports, 32, 7, 108053, 2020)

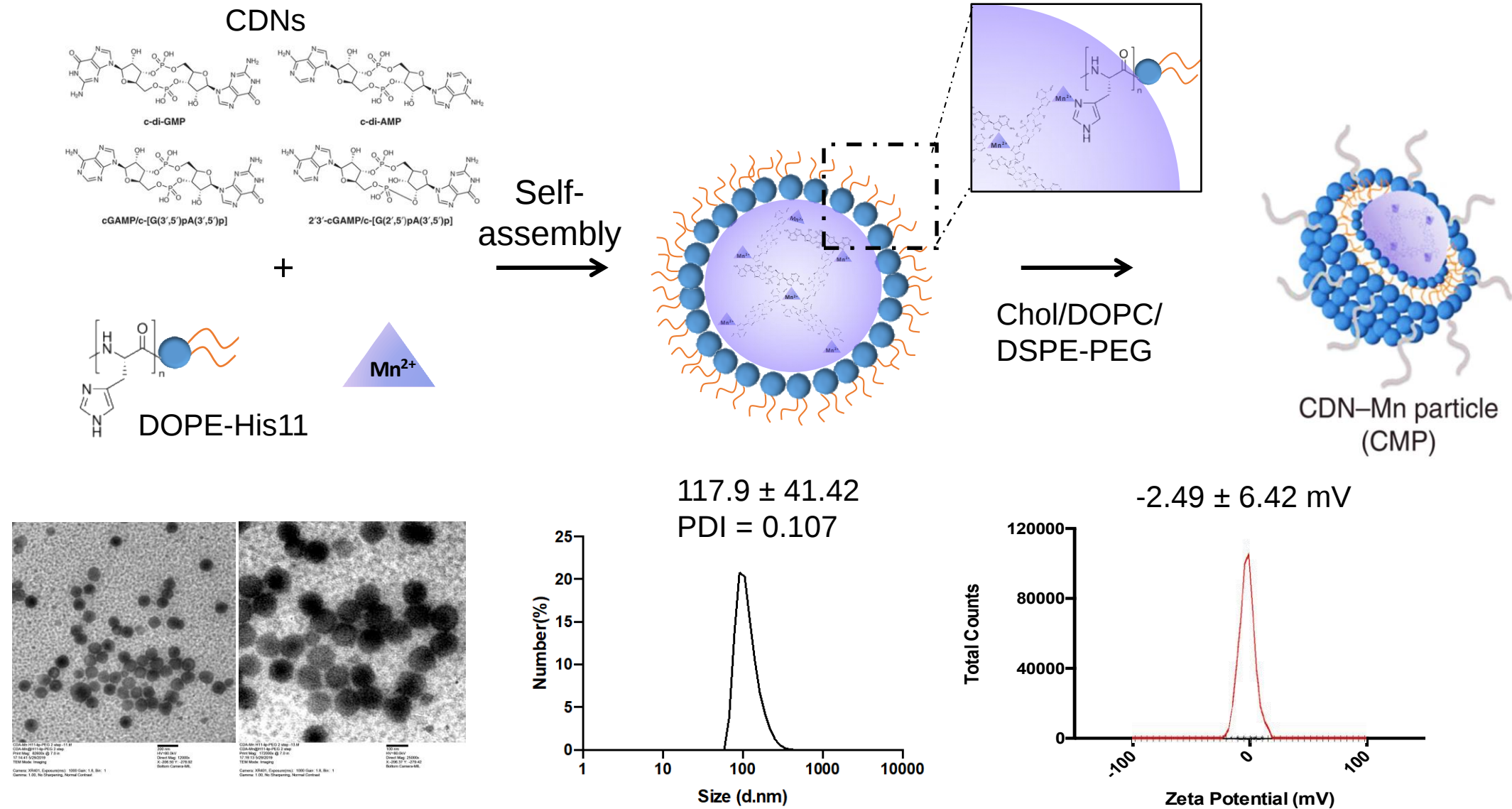
Article



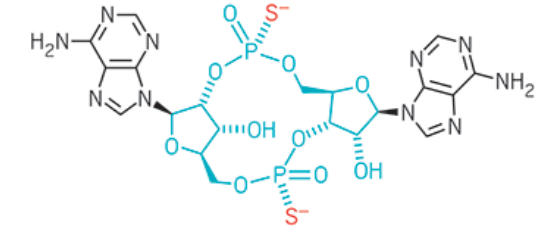
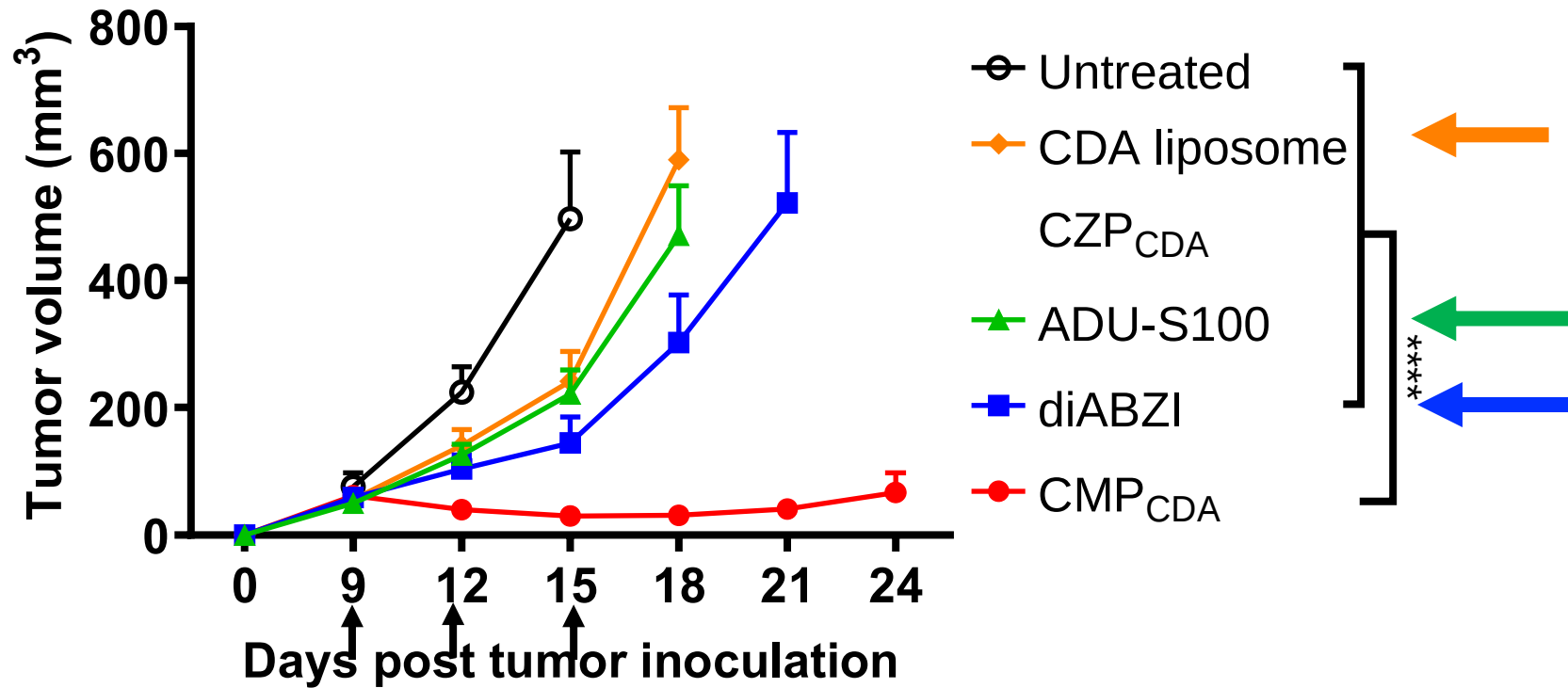
Thus, Mn^{2+} approach may address the dysregulated STING pathway observed in some cancer patients.

GOAL: A pharmaceutical formulation for systemic immunotherapy with STING agonist and Mn^{2+}

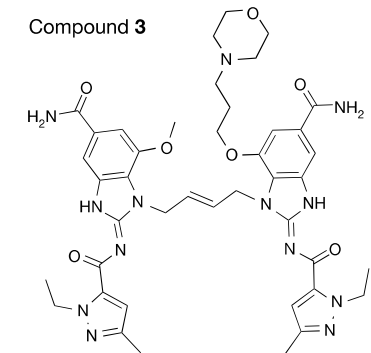
CDN-Mn Particle (CMP) for effective codelivery of CDA and Mn



CMP IV therapy in established B16F10 melanoma model



Aduro Biotech's ADU-S100



GSK's diABZI STING agonist
currently in a Phase I trial.

Ramanjulu et al., *Nature* 2018

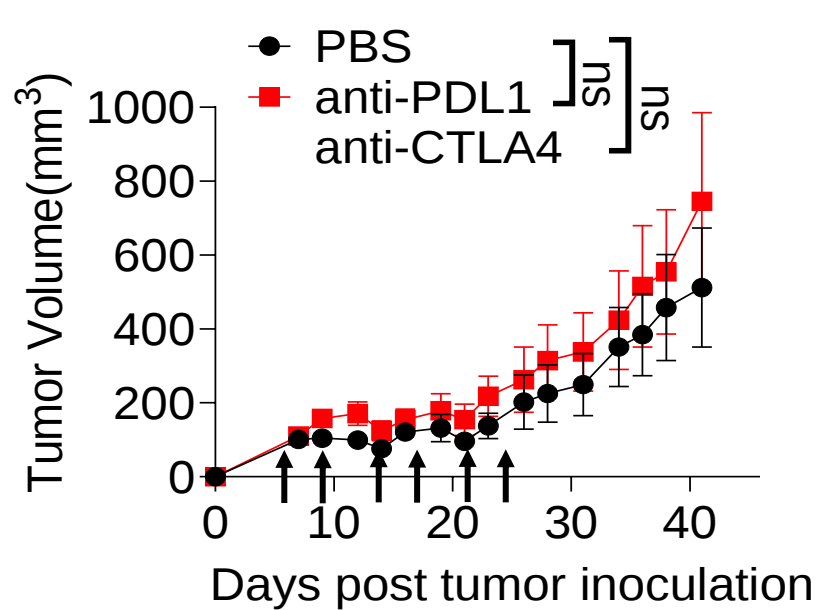
ADU-S100: the first-in-class CDN STING agonist in clinical trials, IT injection
diABZI: the first-in-class non-CDN STING agonist in clinical trials, IV injection

CMP treat ICB-resistant NOOC1 head and neck cancer model

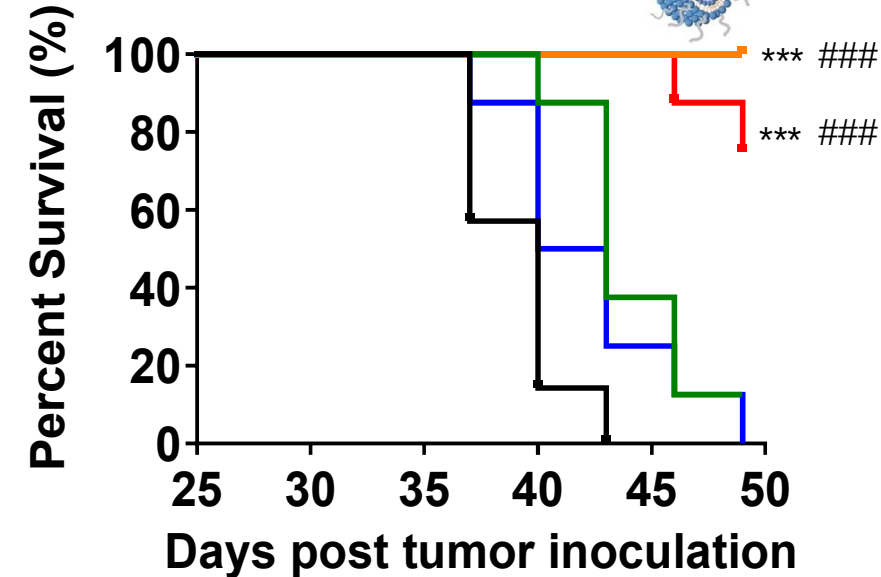
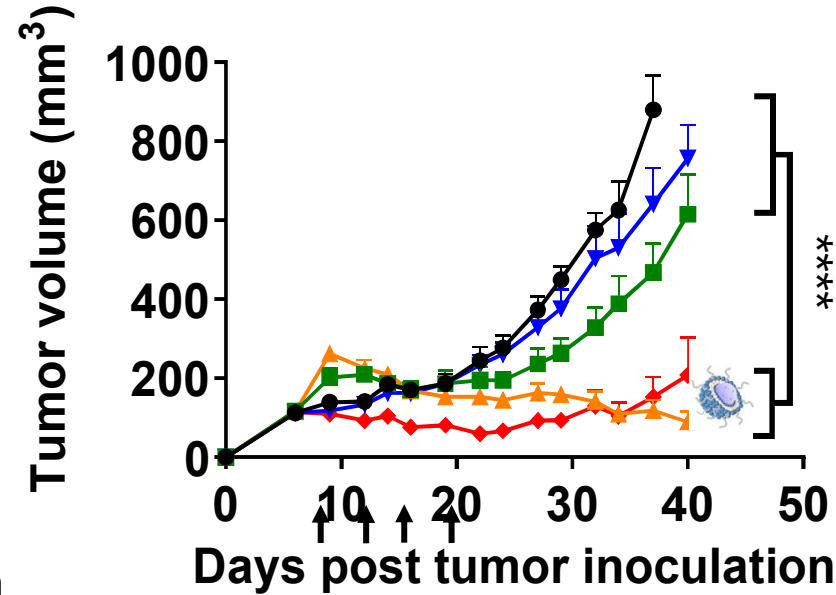


Jiaqian Li
Dr. Yu Leo Lei

NOOC1 tumors are resistant to 6 cycles of 200 μ g ICB therapy.

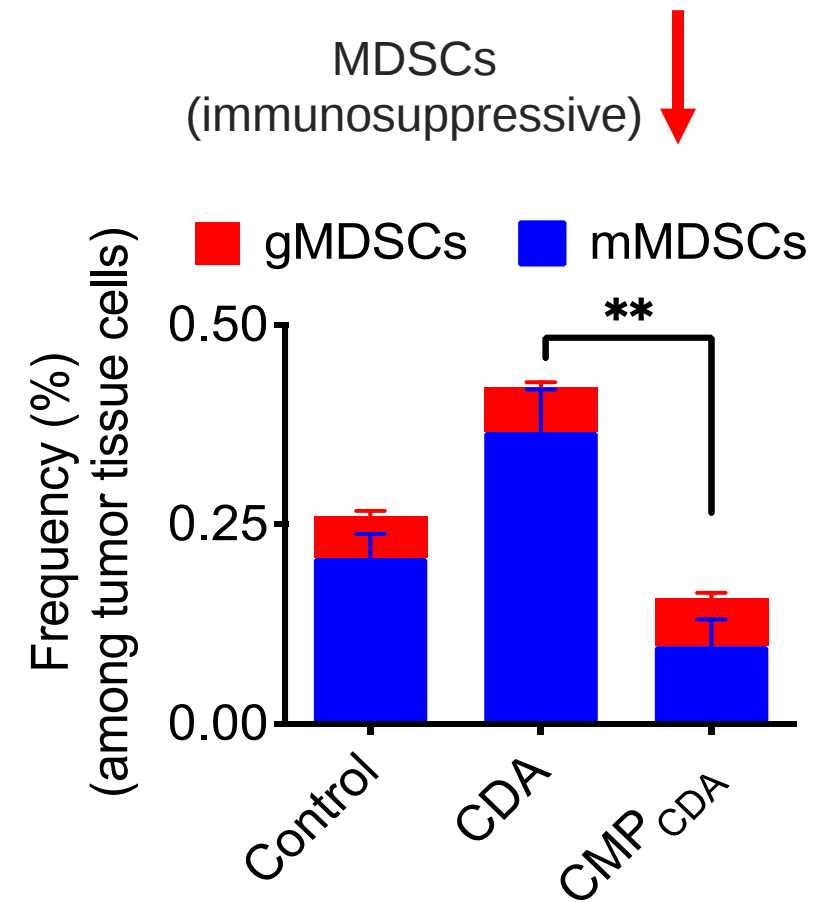
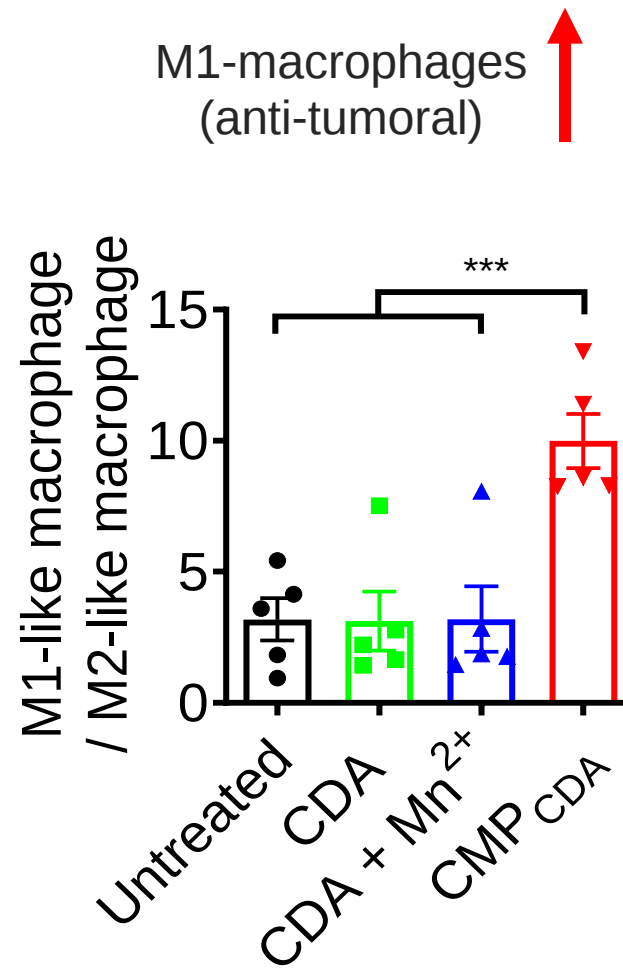
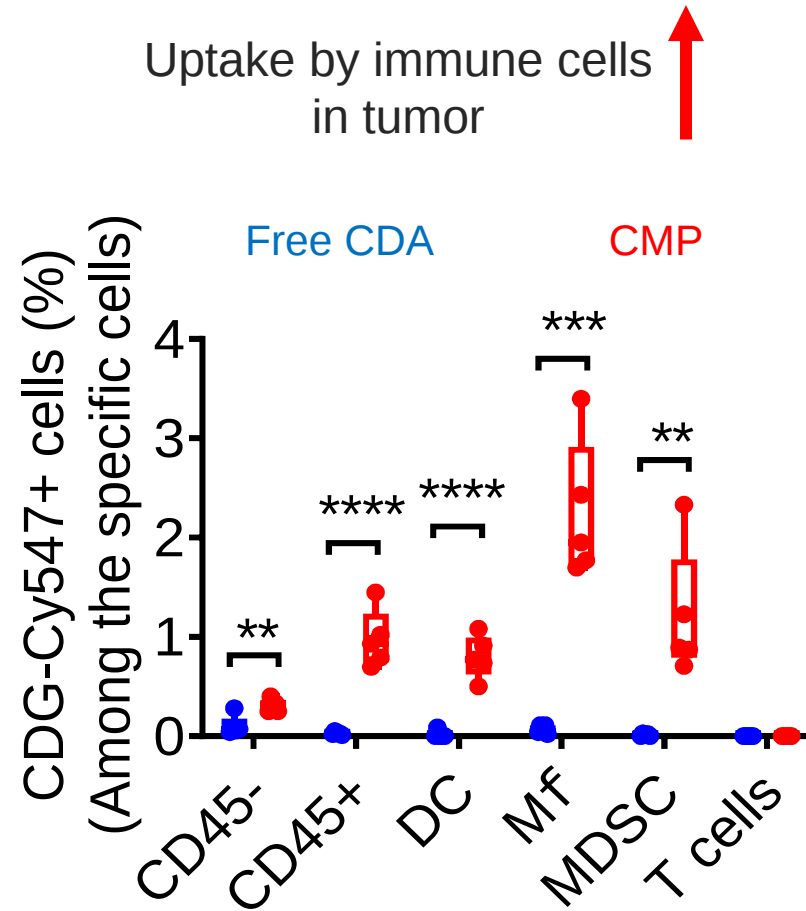


4 cycles of IV therapy eliminates NOOC1 tumor



● PBS ■ CDA, I.T. ▲ CDA, I.V. ▲ CMP_{CDA} , I.T. ◆ CMP_{CDA} , I.V.

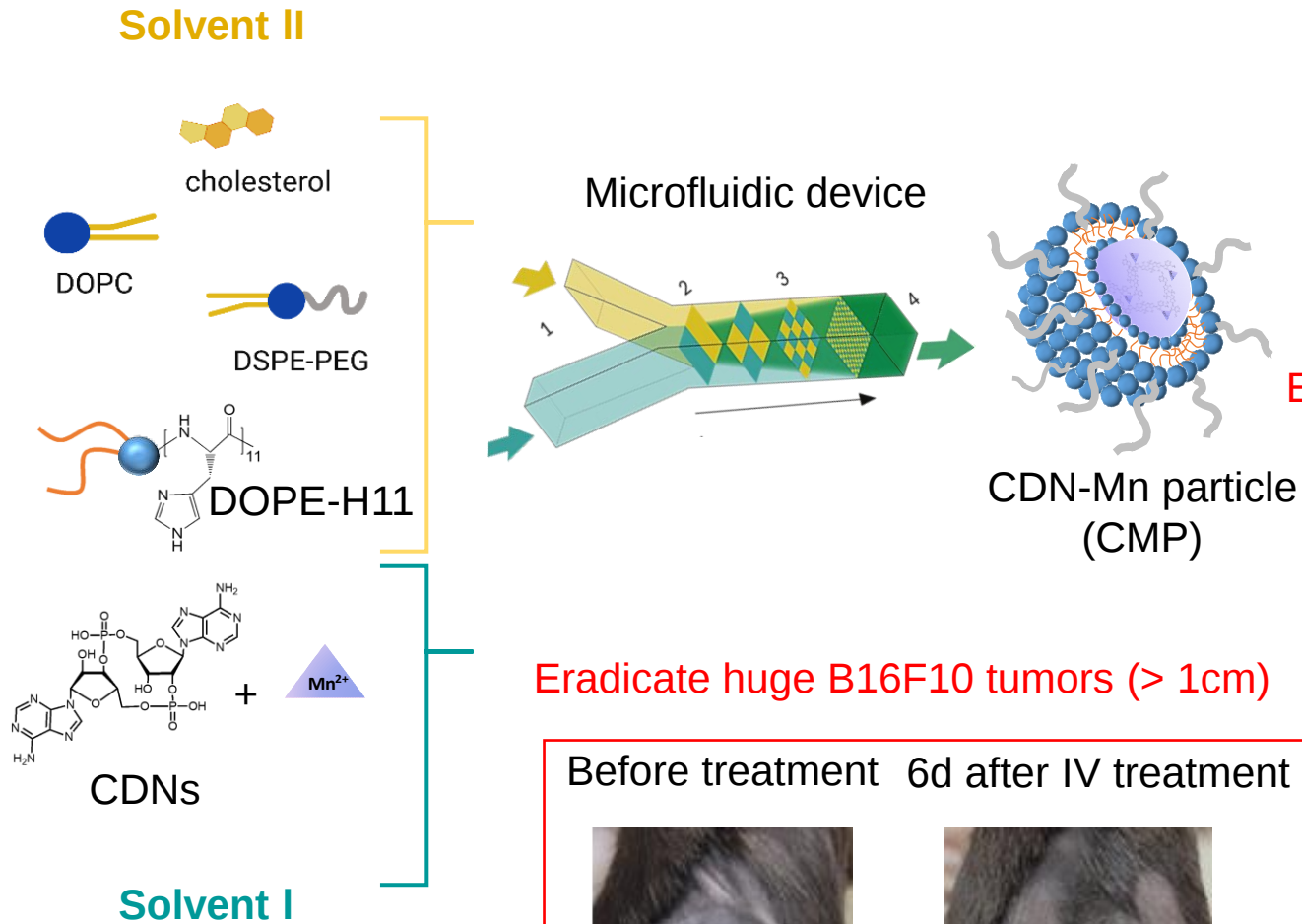
CMP elicits strong immune activation in tumor



Further optimization-- scalable synthesis of CMP



Xingwu Zhou



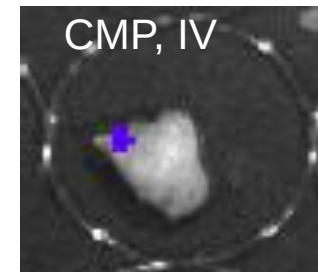
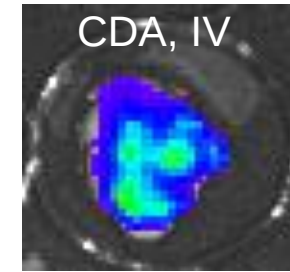
Unpublished data

Eradicate huge B16F10 tumors (> 1cm)

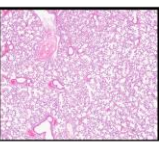
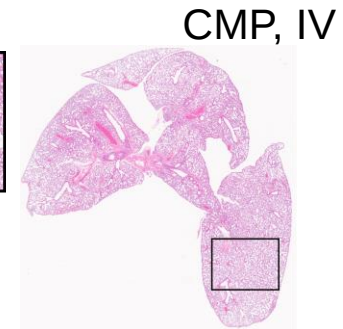
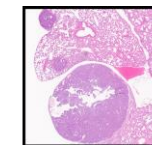
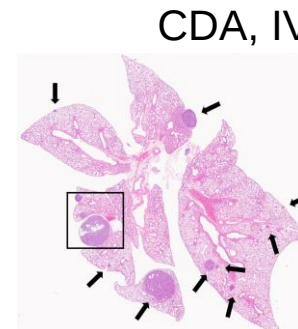
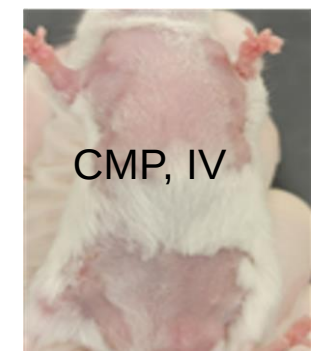
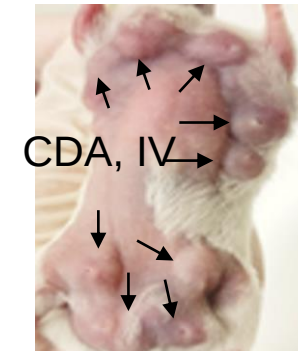
Before treatment 6d after IV treatment



Eradicates orthotopic pancreatic tumor



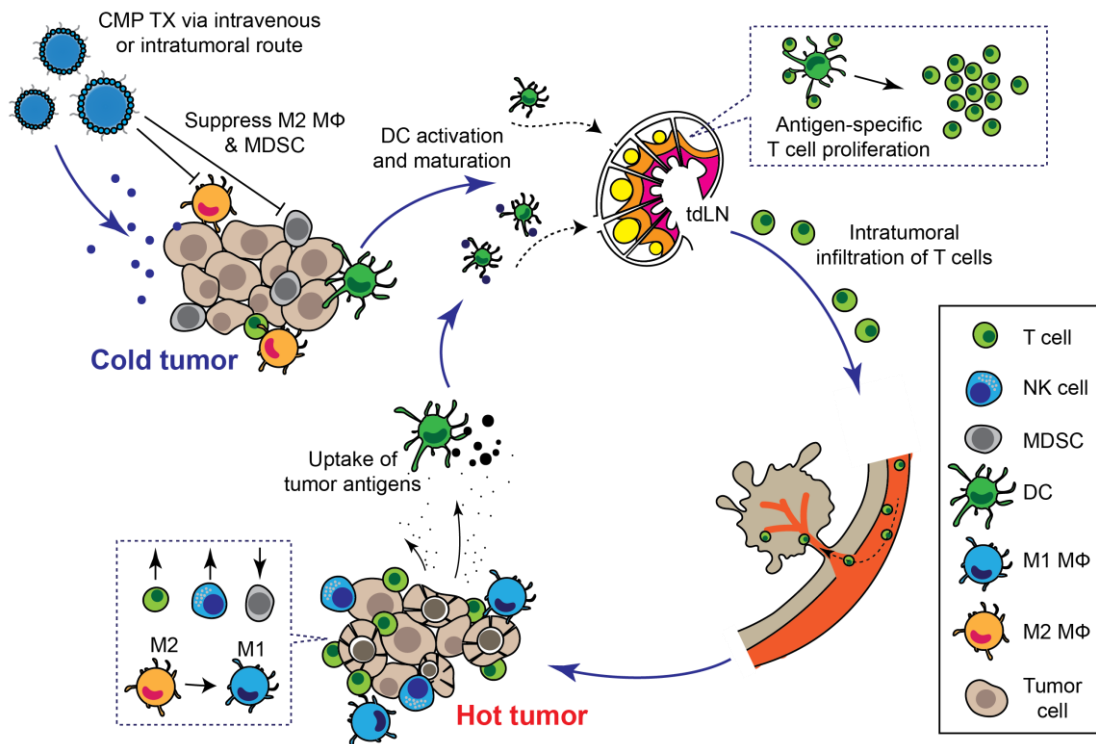
Eradicates spontaneous breast tumor and lung metastasis



Summary

Amplifying STING activation by cyclic dinucleotide-manganese particles for local and systemic cancer metalloimmunotherapy

Xiaoqi Sun^{1,2}, Yu Zhang¹, Jiaqian Li³, Kyung Soo Park^{2,4}, Kai Han^{1,2}, Xingwu Zhou^{1,2}, Yao Xu^{1,2}, Jutaeek Nam^{1,2,5}, Jin Xu^{1,2}, Xiaoyue Shi^{1,2}, Lei Wei³, Yu Leo Lei^{6,7,8} and James J. Moon^{1,2,4,8}✉



- LNP-based coordination nanomedicine
- Potent STING activation across human STING variants
- Strong efficacy in multiple murine tumor models
- Ongoing studies: testing in large animals (rabbits, dogs)

Acknowledgement

Committee:

Dr. James Moon,
Dr. Duxin Sun,
Dr. Pete Tessier,
Dr. Leo Yu Lei,
Dr. David Sherman



MOON Laboratory ImmunoEngineering

Xingwu Zhou	Marisa Aikins
Yu Zhang	Cheng Xu
Charles Park	Jin Xu
Kai Han	Sejin Son
Jutaek Nam	Emeka Okeke
Yao Xu	Lindsay Scheetz
Rui Kuai	Ali Hassani
Xiaoyue Shi	Dylan
Xuehui Huang	and other lab members



Collaborators:

Jiaqian Li
Dr. Leo Yu Lei
Dr. Ashu Tripathi (Natural Drug Discovery Core)
Dr. Osama Mohamed (Natural Drug Discovery Core)

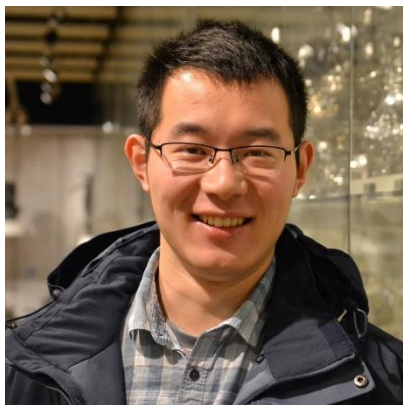
Core facility:

Immunology core (Joel Whitfield)
Center for Chemical Genomics (Steve Roest)
Flow Cytometry core (Mark)
Microscope core (Binyamin Jacobovitz)

Grants:

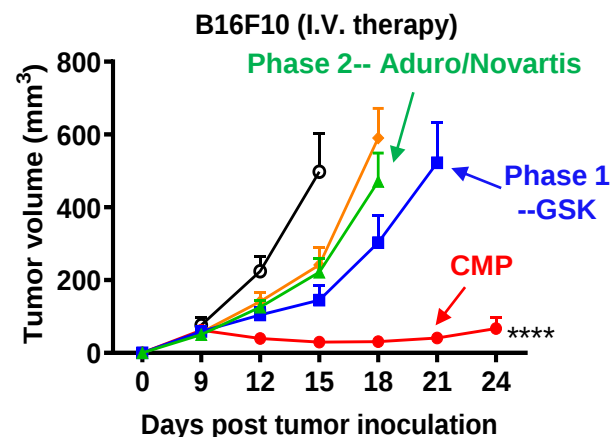
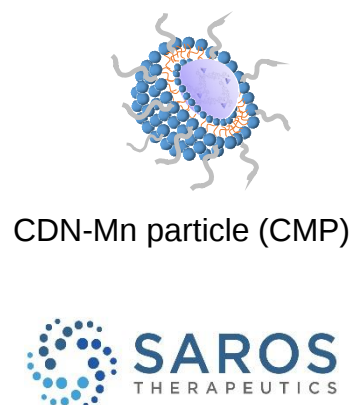
Michigan Drug Discovery Grant
Rackham Pre-doctoral Fellowship
Rackham Int. Student Fellowship
Rackham Research Grant

Representative scientific works



Dr. Xiaoqi (Kevin) Sun

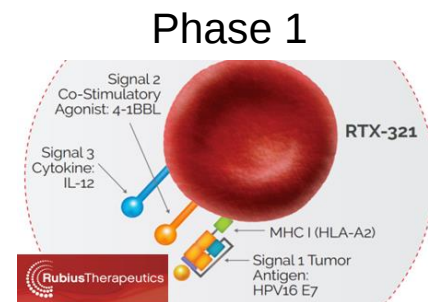
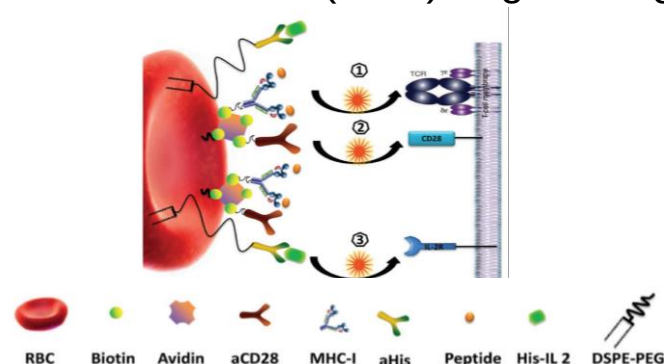
I. STING-activating Immunotherapy



Representative publications:

- X Sun, et.al. *Nature Nanotechnology*. 16, 1260–1270 (2021)
- X Sun, et.al. Under preparation for *Nat. Biomed. Eng.*
- K Park[#], X Sun[#], M Aikins[#], *Adv. Drug Deliv. Rev.* 169, 137-151 (2020) (**Co-first author**)

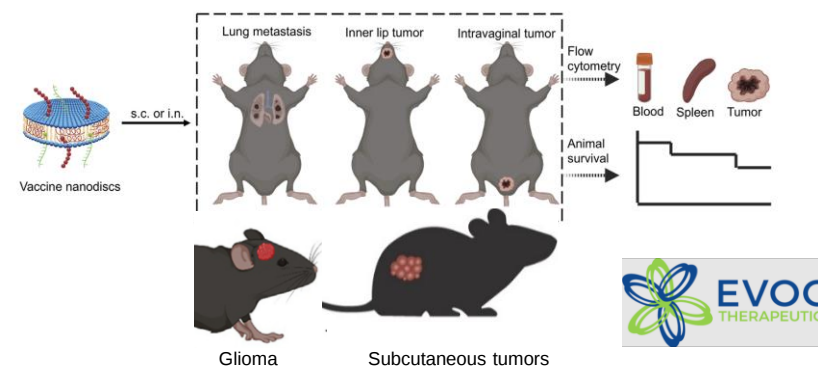
II. Red blood cell (RBC) engineering



Representative publications:

- X Sun, et.al. *Adv. Funct. Mater.* 25, 2386–2394. (2015). (Back Cover Story)
- X Sun[#], X Han[#], et.al. *Small* 13 (40), 1701864 (2017). (**the first RBC artificial antigen presenting cell, adopted by Rubius Therapeutics for RTX-321**)

III. Personalized cancer neoantigen vaccine



Representative Publications:

- R Kuai[#], X Sun[#], et.al. *Bioconjugate chemistry* 29 (3), 771-775 (2018). (**Co-first author**)
- R Kuai, X Sun, et.al. *Journal of controlled release* 282, 131-139 (2018).
- R Kuai[#], P Singh[#], X Sun[#], et.al. *Advanced Therapeutics* 3 (9), 2000094 (2020). (**Co-first author**)
- L Scheetz[#], P Kadiyala[#], X Sun[#], et.al. *Clinical Cancer Research* (2020). (**Co-first author**)



Thank you!

Video Message from Xiaoqi (Kevin) Sun

