

Prodrug-Tethered Lipid Nanoparticles for Synergistic mRNA Cancer Immunotherapy

Qiangqiang Shi, Ningqiang Gong, Jinjin Wang, Rohan Palanki, Mohamad-Gabriel Alameh, Jilian Melamed, Junchao Xu, Christian G. Figueroa-Espada, Lulu Xue, Ye Zeng, Xuexiang Han, Qinyuan Chen, Hannah Yamagata, Rakan El-Mayta, Il-Chul Yoon, Drew Weissman, and **Michael J. Mitchell**

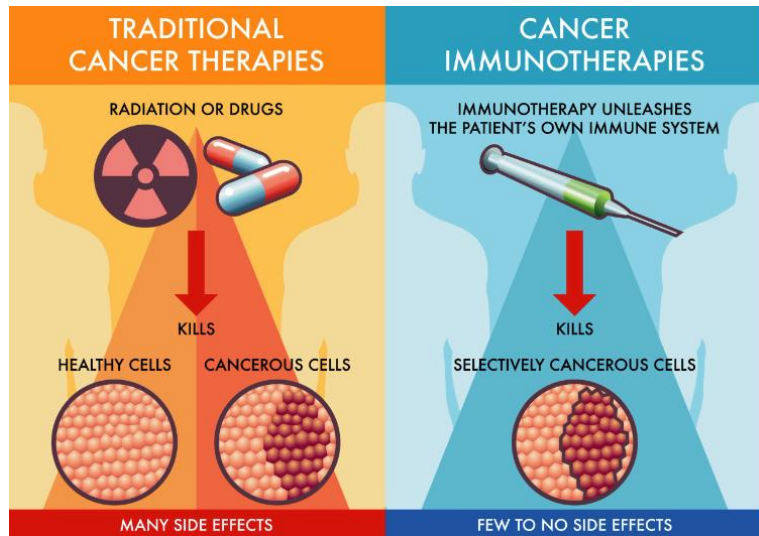
Qiangqiang Shi, PhD
Postdoc in Mitchell lab
University of Pennsylvania



PHILADELPHIA, PA
JULY 13-18, 2025

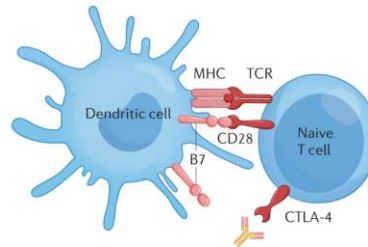
**NEXT-GENERATION
DELIVERY INNOVATIONS**

Cancer Immunotherapy: Low Response Rate and T Cell Exhaustion

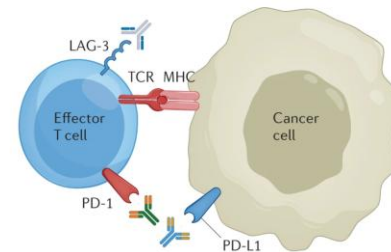


Immune checkpoint blockade (ICB)

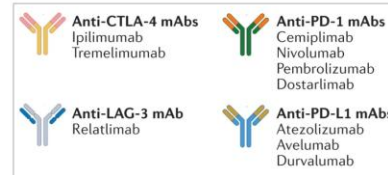
a Lymphoid organs



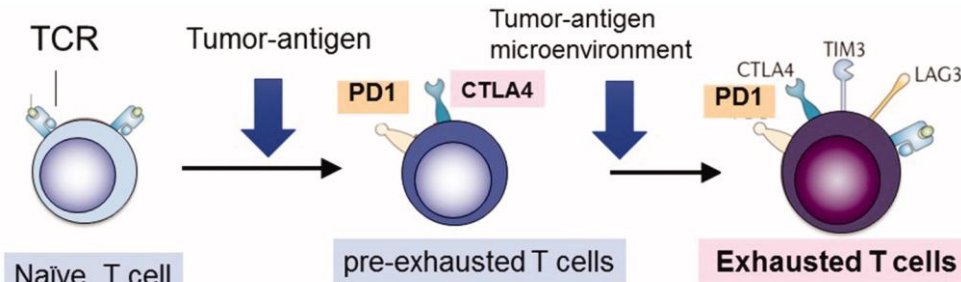
b Target tissues



c

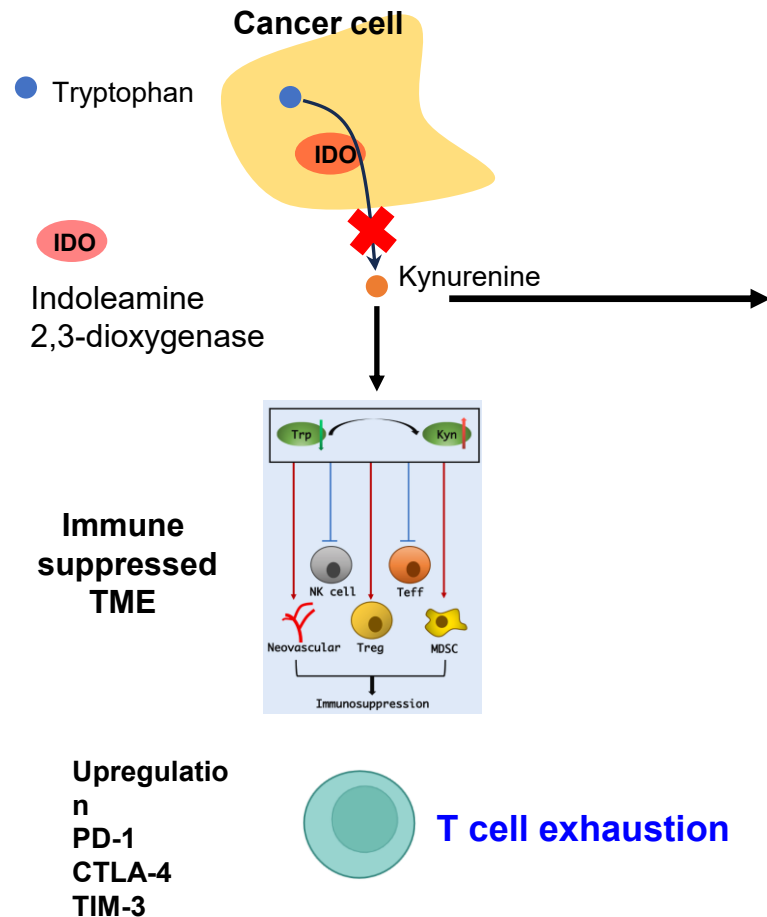


Low response rate

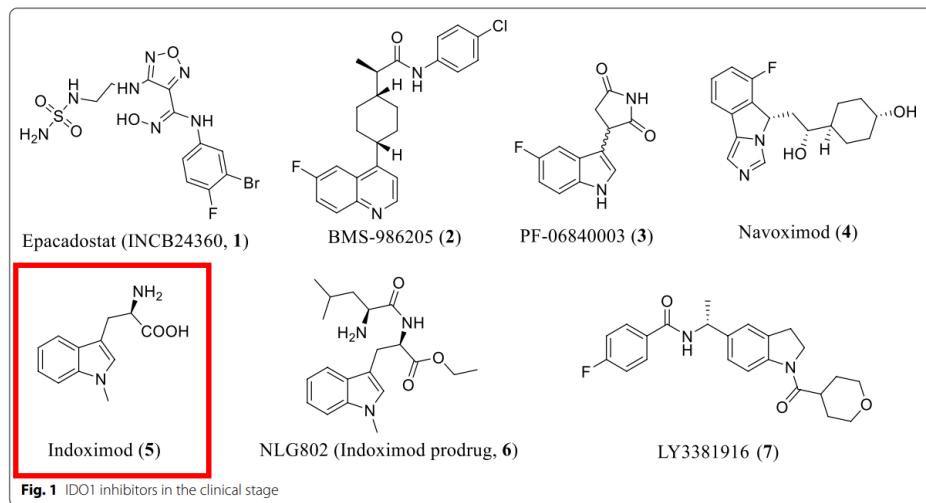


Regulation of T cells between **activated** and **exhausted** stages in tumor microenvironment is also important and remains a significant challenge

IDO Inhibitor for Preventing T Cell Exhaustion



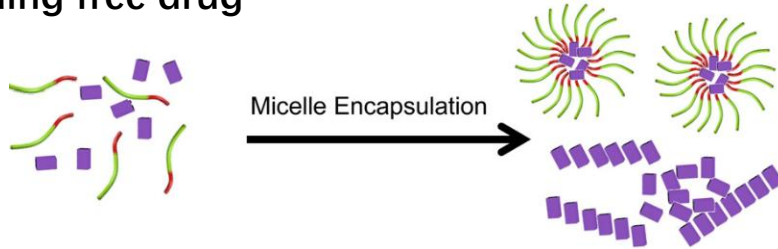
IDO inhibitors in clinical stage



How to delivery small molecule?

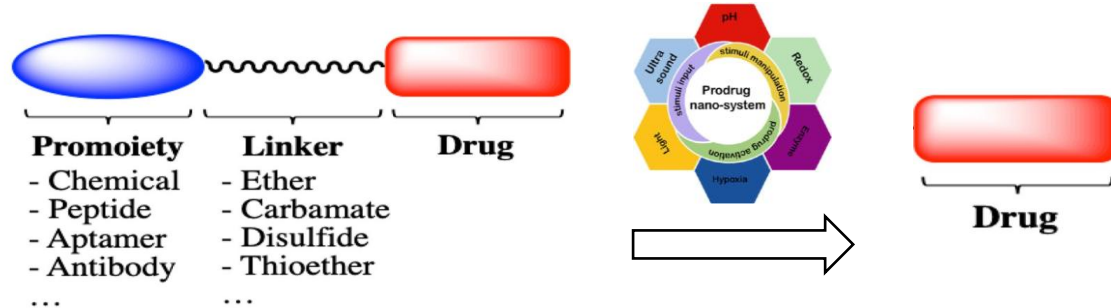
Free Drug Loading and Prodrug Strategy

Loading free drug



- ◆ Low loading efficiency
- ◆ Drug leakage in vivo
- ◆ Hydrophobic drug only

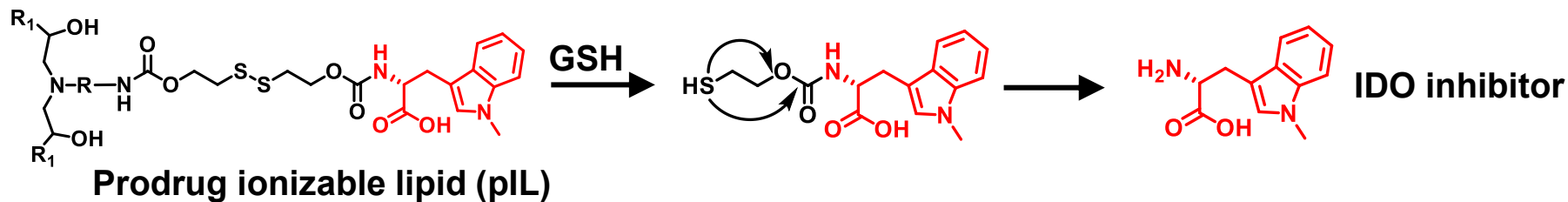
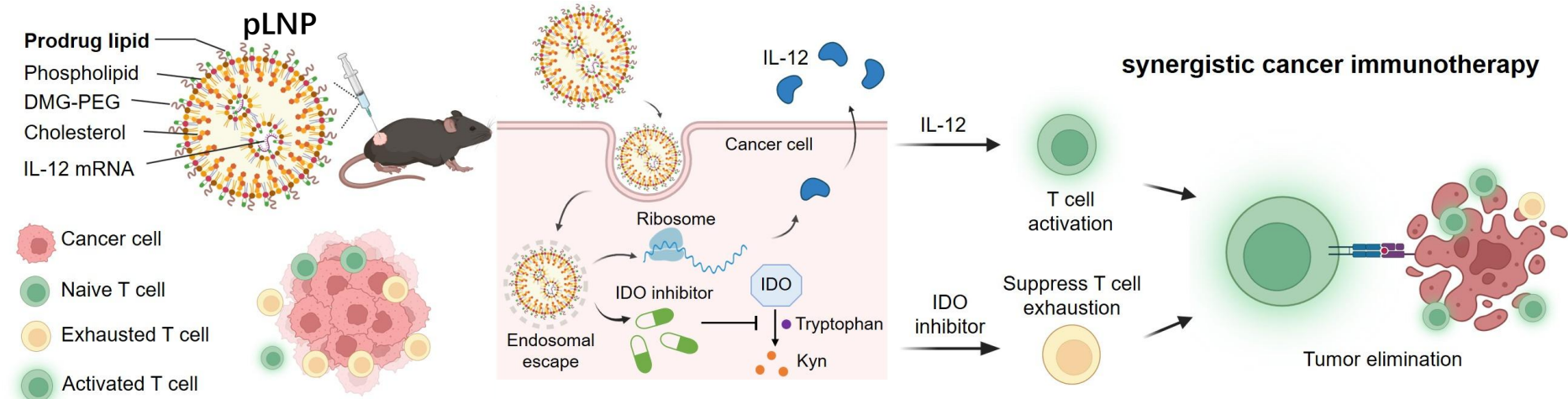
Prodrug system



Drug delivery to specific lesion or cells

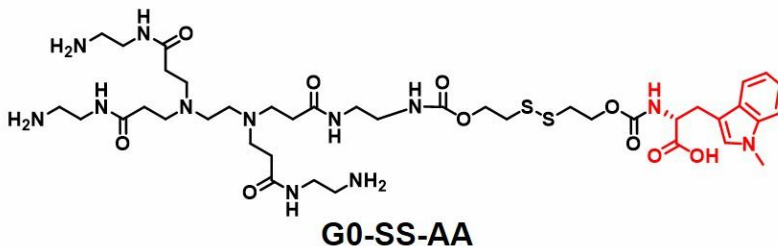
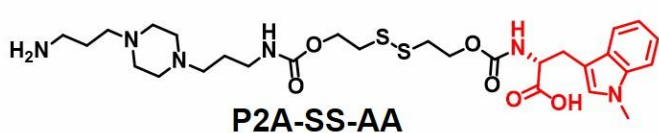
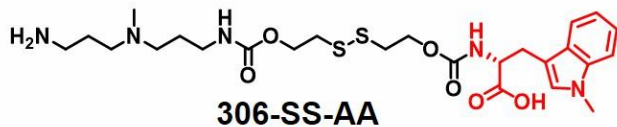
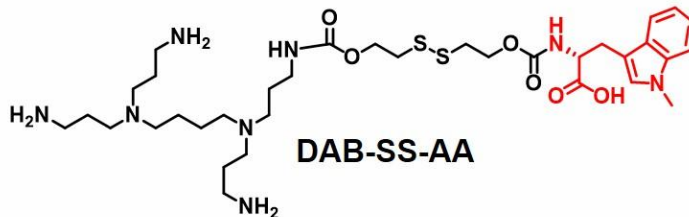
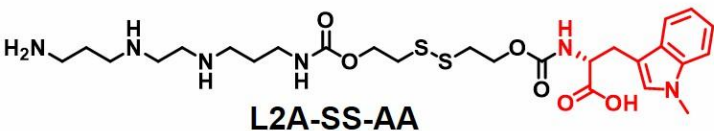
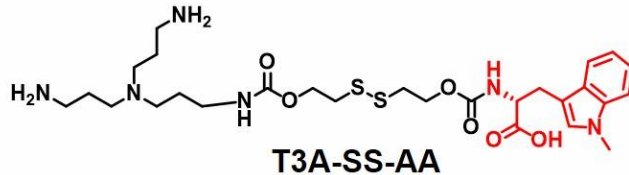
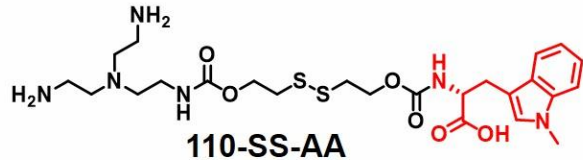
Prodrug could be a promising strategy for specific drug delivery

Prodrug-tethered Lipid Nanoparticles for Synergistic mRNA Cancer Immunotherapy

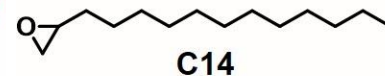
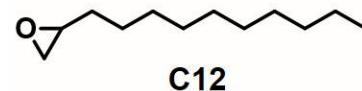
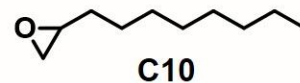


Synthesis of Prodrug Ionizable Lipids (pILs)

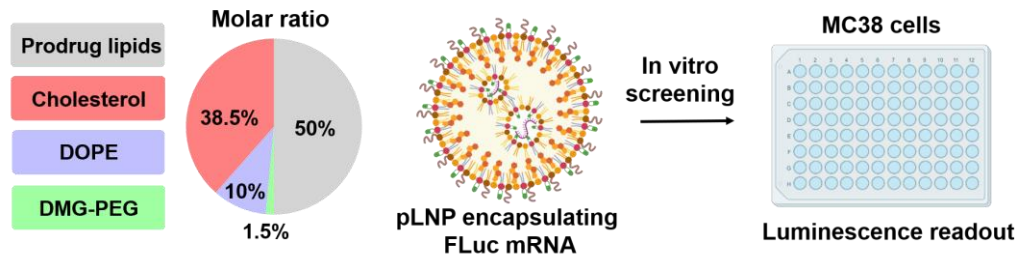
Prodrug amine heads



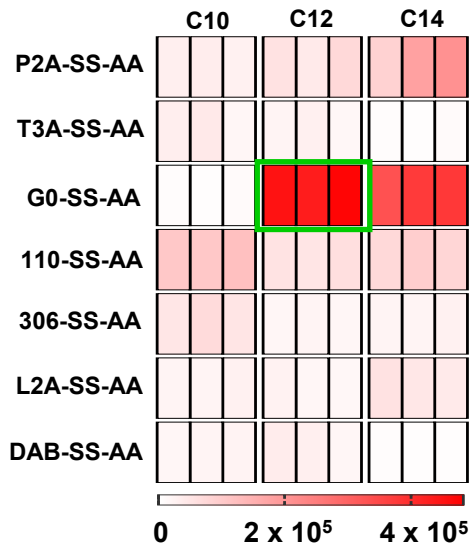
Tails



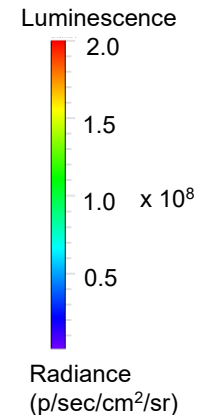
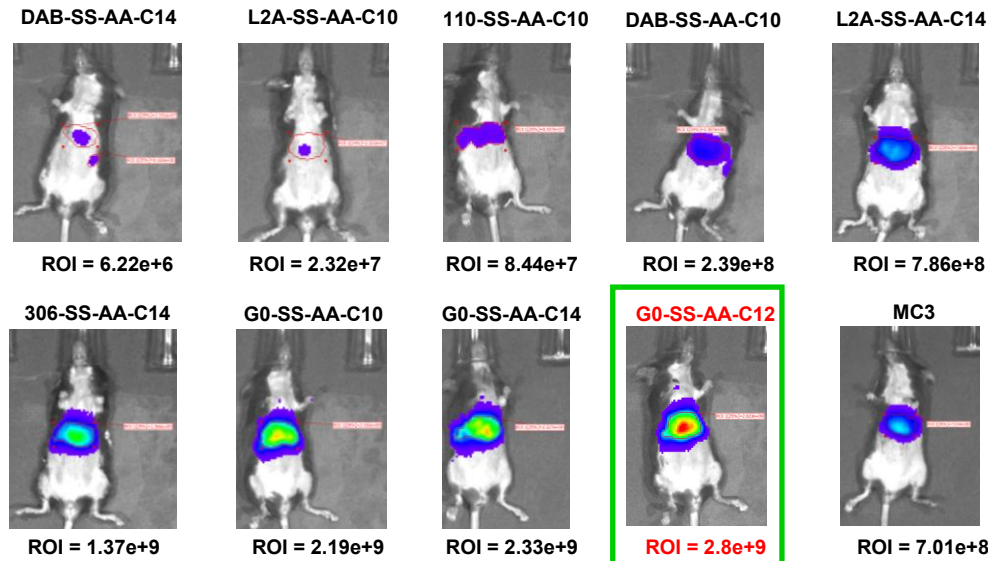
Screening of pLNP Library in Vitro and in Vivo



In vitro

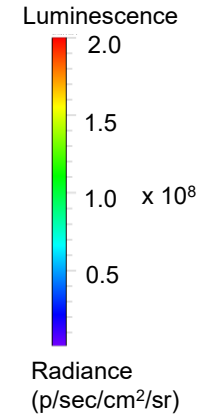
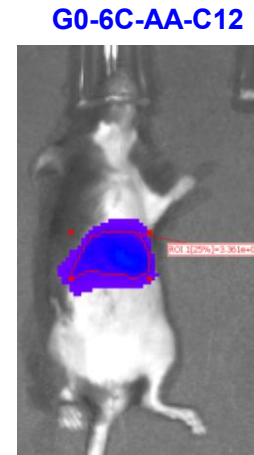
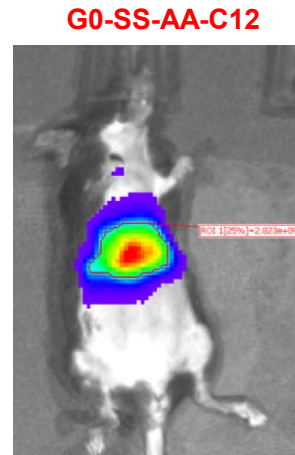
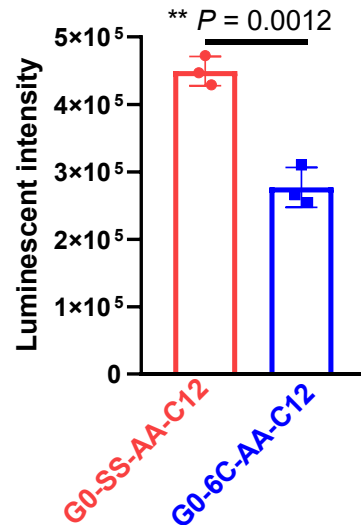
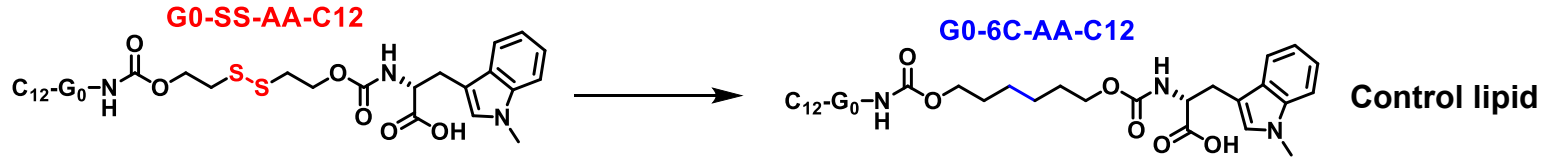


In vivo

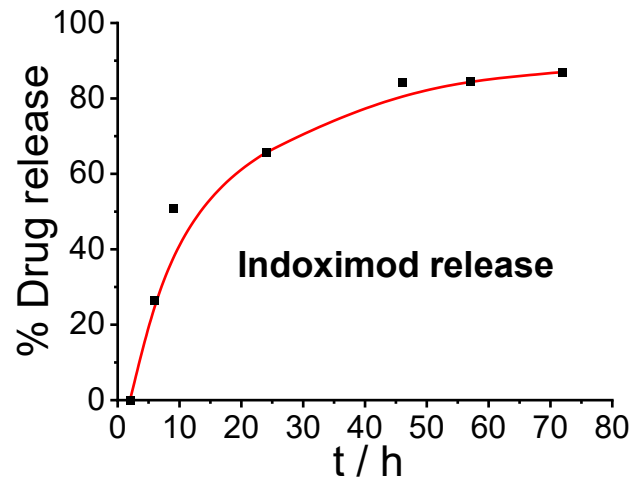
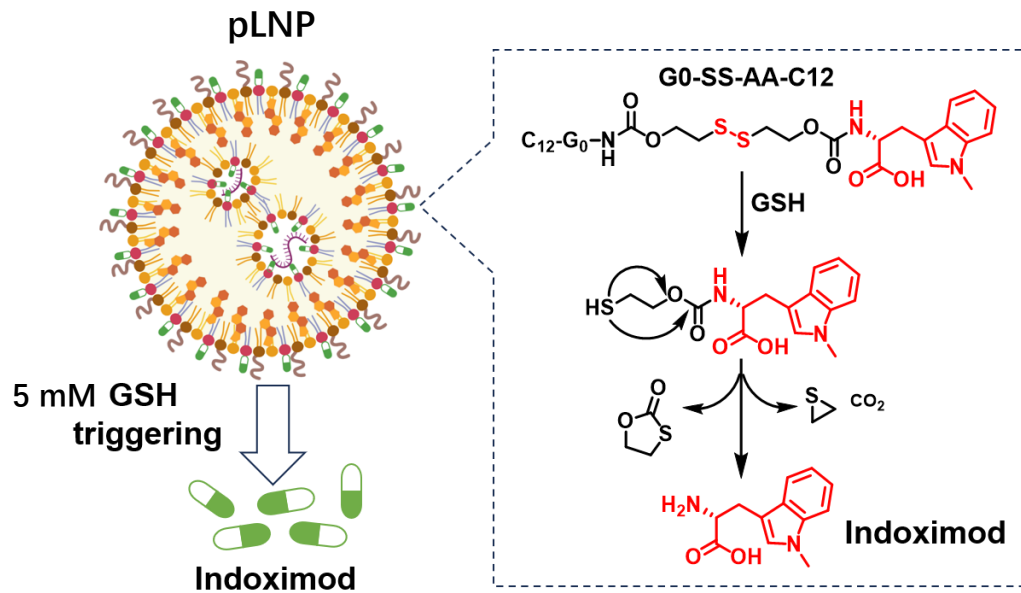


Disulfate Linkage Enhances mRNA Transfection

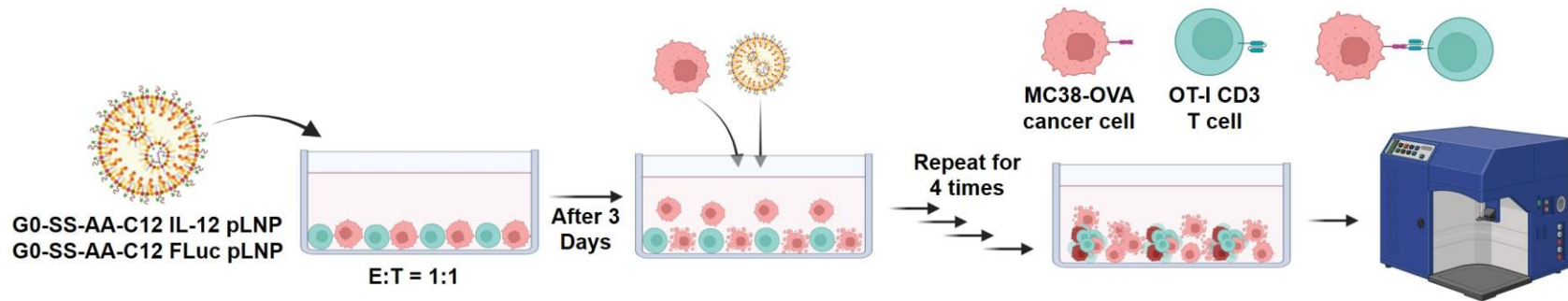
Replaced disulfate linkage with C-C linkage



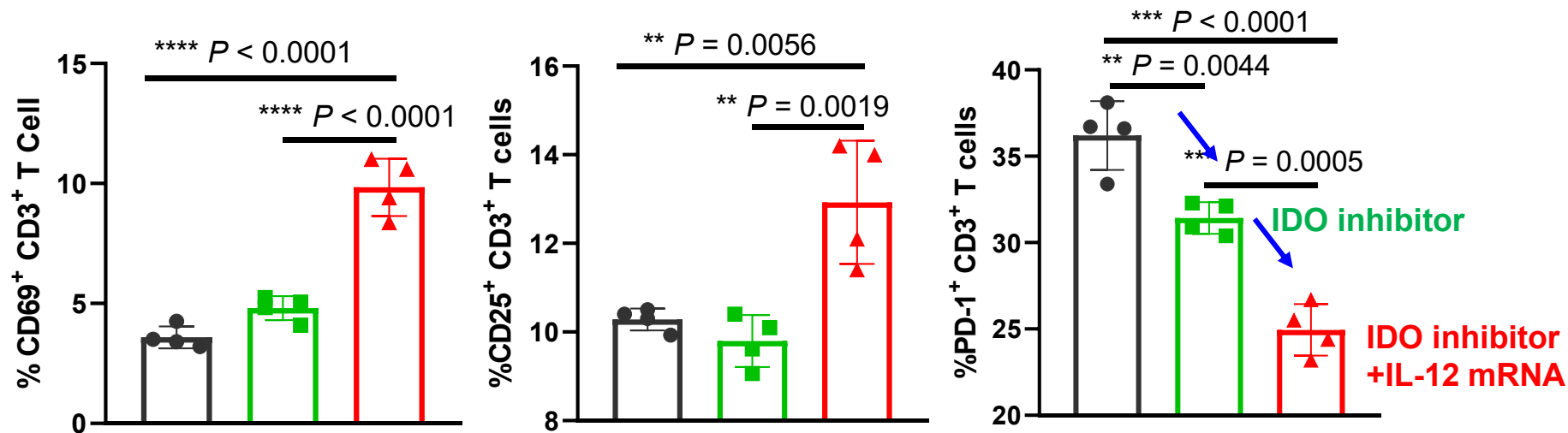
Drug Release from pLNP after Triggering



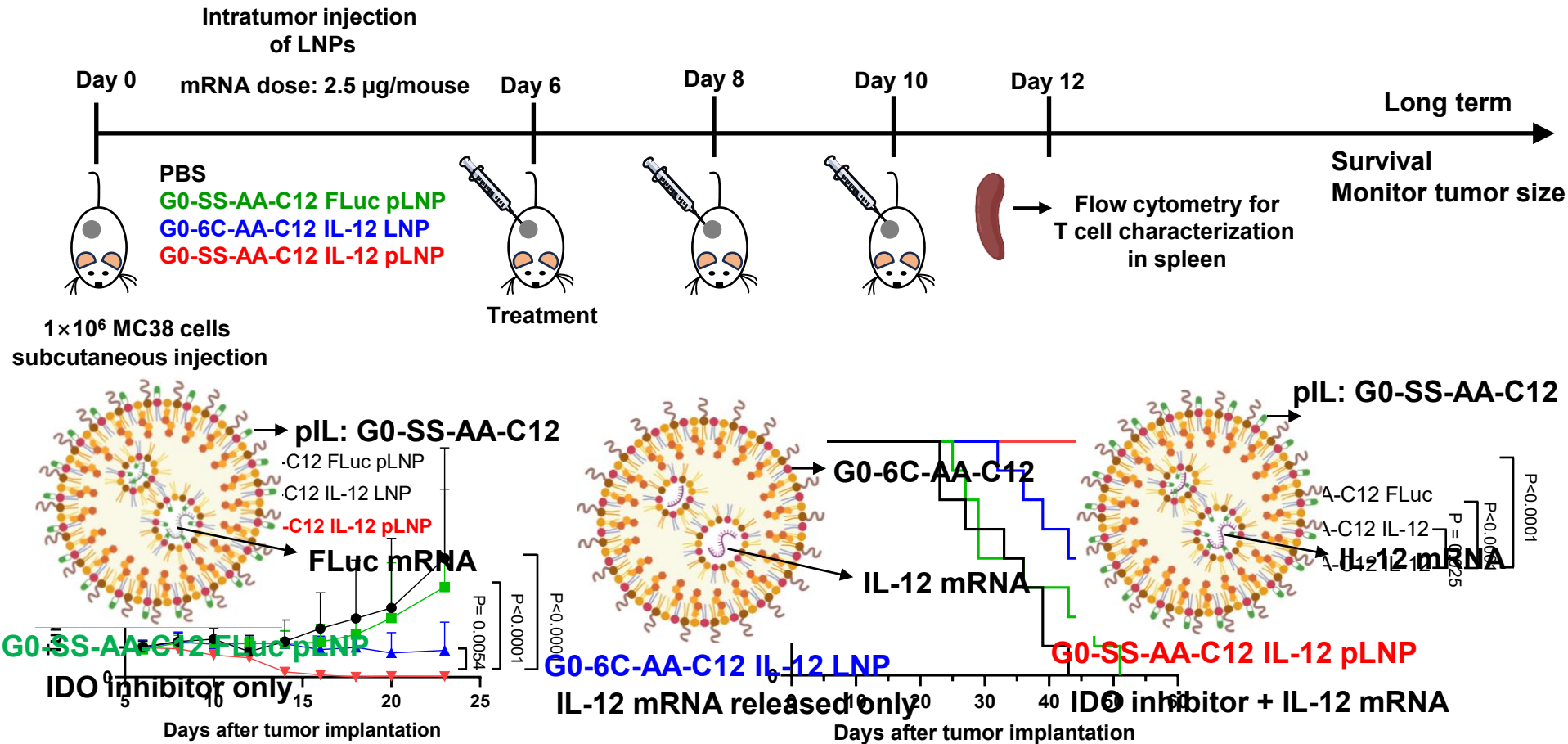
pLNP Mediates T Cell Activation and Suppresses T Cell Exhaustion



● PBS ■ G0-SS-AA-C12 FLuc pLNP ▼ G0-SS-AA-C12 IL-12 pLNP

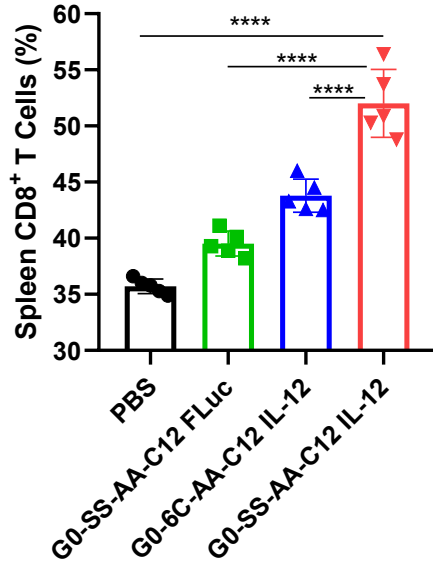


Immunotherapy Evaluation of pLNP in MC38 Tumor Model

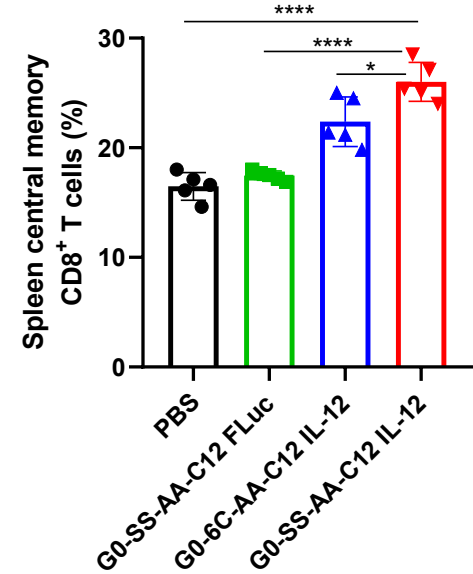
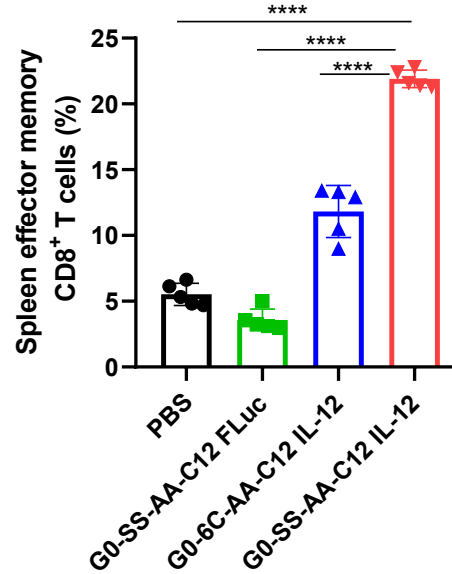


pLNP System Elicits Immune Response in Mice

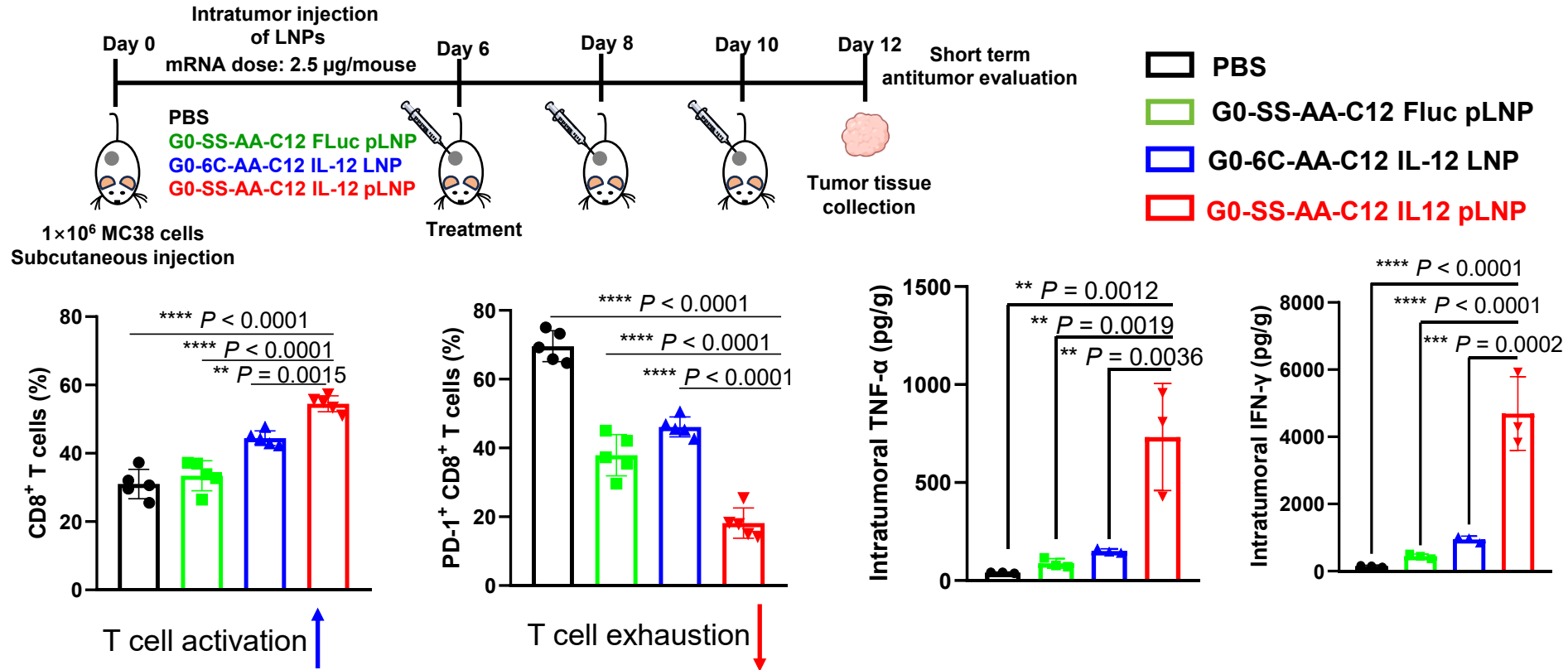
The CD8 T cell changes in Spleen



Memory CD8 T cells



T Cell Infiltration in Tumor Microenvironment



Conclusion

- 1. In summary, we have developed a novel pLNP platform combining IDO inhibitor with IL-12 mRNA.**
- 2. In a MC38 mouse tumor model, pLNP system effectively shrunk tumors and generated systemic immunologic memory.**
- 3. These results highlight pLNPs as a promising delivery system for synergistic, locally-activated cancer immunotherapy.**

Acknowledgement

Michael Mitchell
Briyanna Hymms
Lulu Xue
Junchao Xu
Marshall Padilla
Jinjin Wang
Ye Zeng
Dongyoon Kim
Adele Ricciardi
Melgious Ang
Soyeon Yoo
Zhangyi Luo
Jingcheng Zhu
Rohan Palanki
Kelsey Swingle
Alex Hamilton
Ann Metzloff
Hannah Safford
Hannah Geisler

Ajay Thatte
Emily Han
Hannah Yamagata
Amanda Murray
Andrew Hanna
Shuran Zhang
Katlin Mrksich
Jacqueline Li
Ryann Joseph
Sridatta Teerdhala
Ben Nachod
Cecilia Shuler
Sophia Tang
Rachel Ou
Sophia Cheng



Michael Mitchell



Drew Weissman

