Cancer immunotherapy based on image-guided STING activation by nucleotide nanocomplex-decorated ultrasound microbubbles

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Advanced Delivery Science

Conflict of Interest

Scientific Advisory Board
- Innovent Bio
- SpotBiosystems Inc

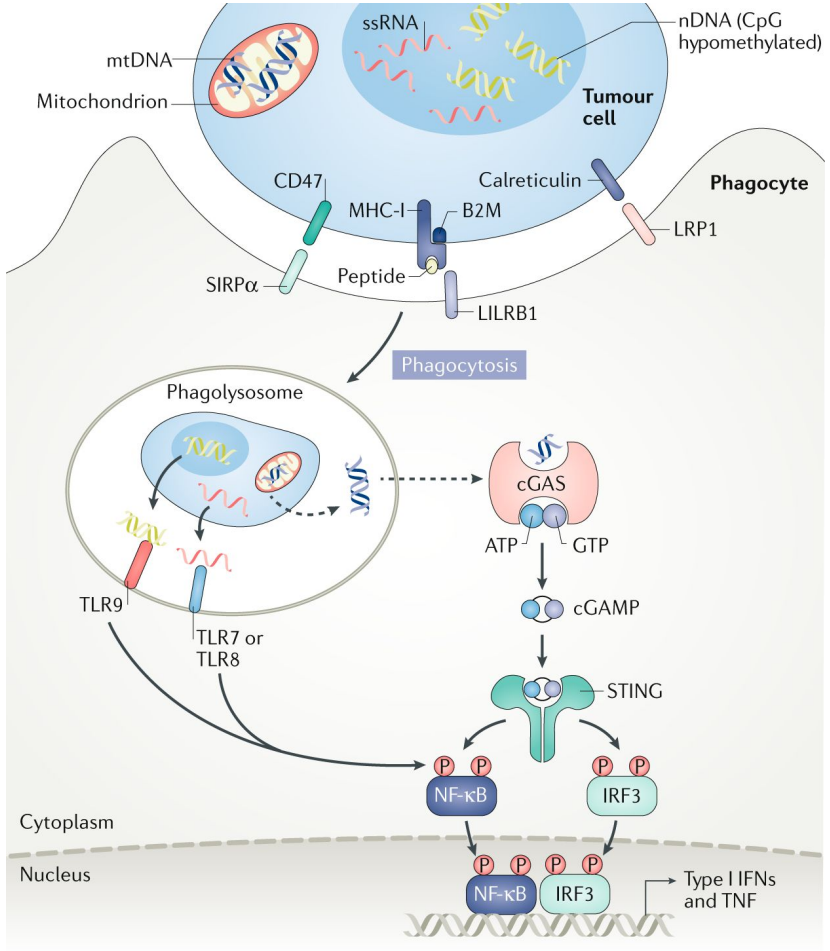
Research Support
- SpotBiosystems Inc
- Neoleukin Therapeutics

Cofounder
- MUSIQ Bio Inc

Bridging innate and adaptive immunities

- Current cancer immunotherapies target adaptive immunity
- Many cancers do not respond to immune checkpoint inhibitors (*e.g.*, anti-PD-L1)
- Activating both innate and adaptive immunity enhances antitumor effect
- Activation of the **innate** immune sensor cyclic GMP–AMP synthase–stimulator of interferon genes (**cGAS-STING**) is necessary for anti-PDL1 efficacy.

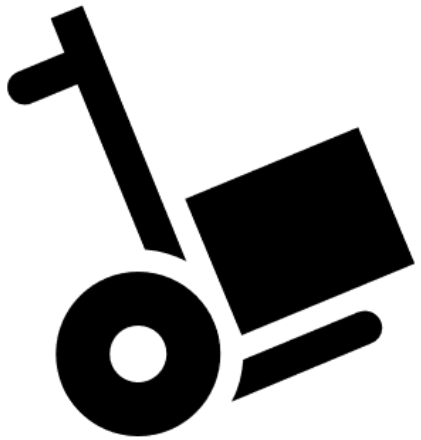
The cGAS-STING pathway



Jiang et al. Nature Rev Cancer, 2019

A successful platform needs

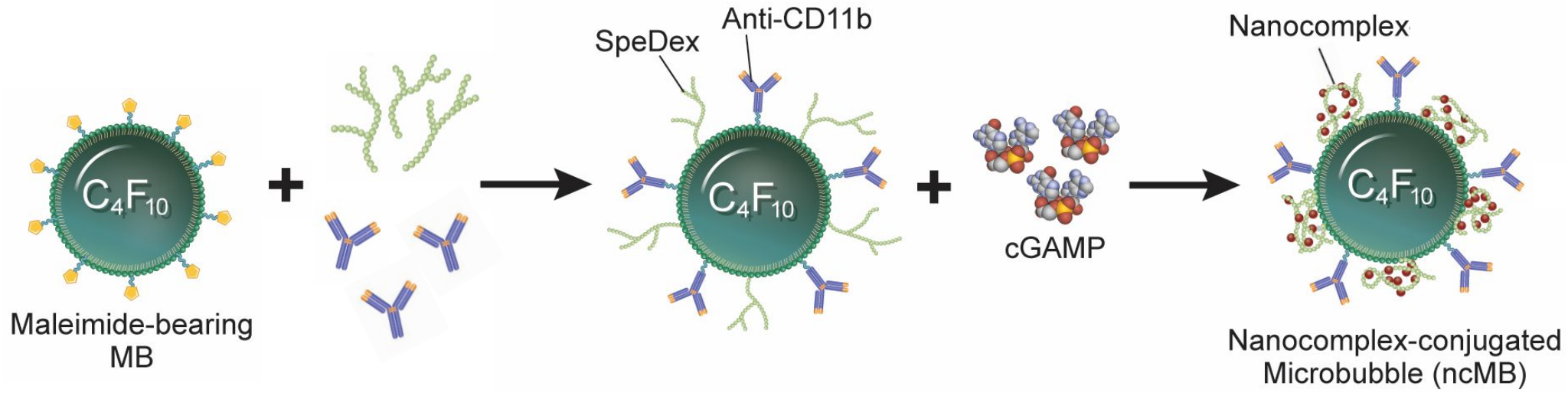
Good loading



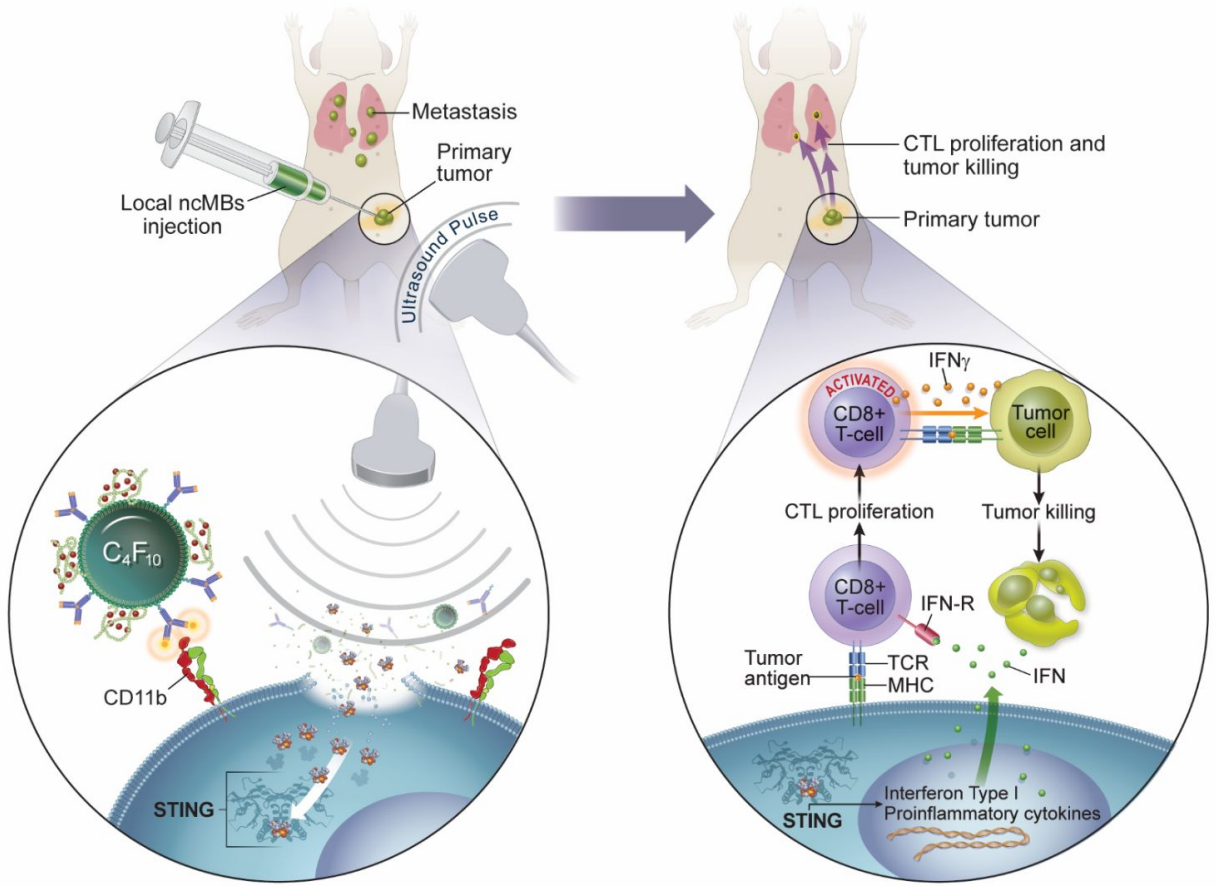
Specific targeting

Efficient cytosolic delivery

Microbubble-assisted UltraSound-guided Immunotherapy of Cancer (MUSIC)

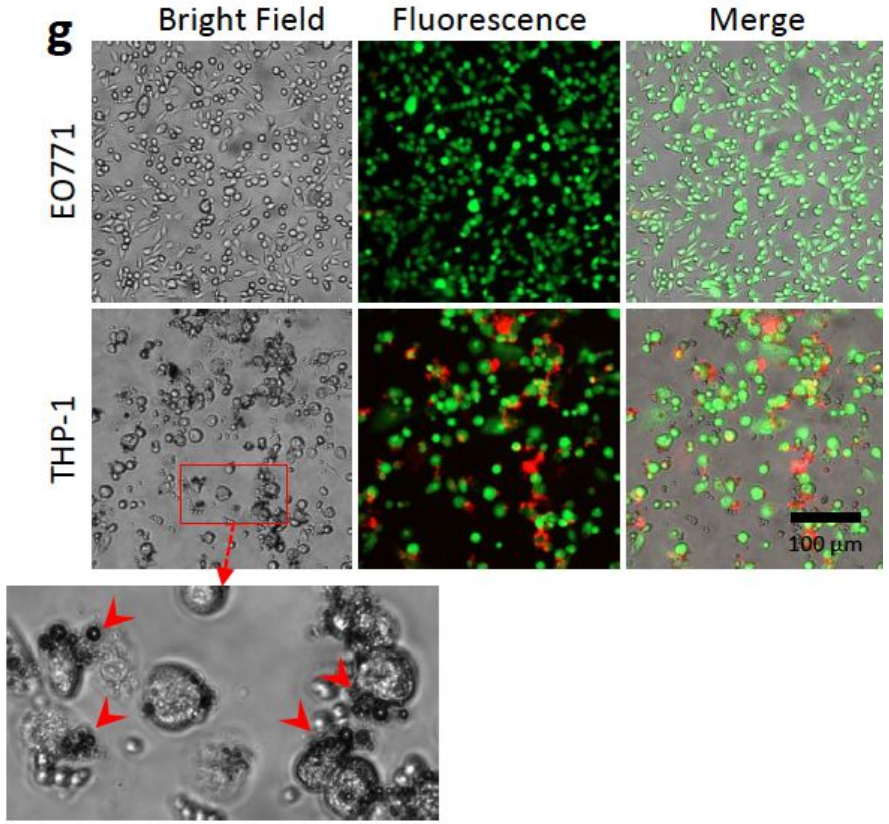


Microbubble-assisted UltraSound-guided Immunotherapy of Cancer (MUSIC)

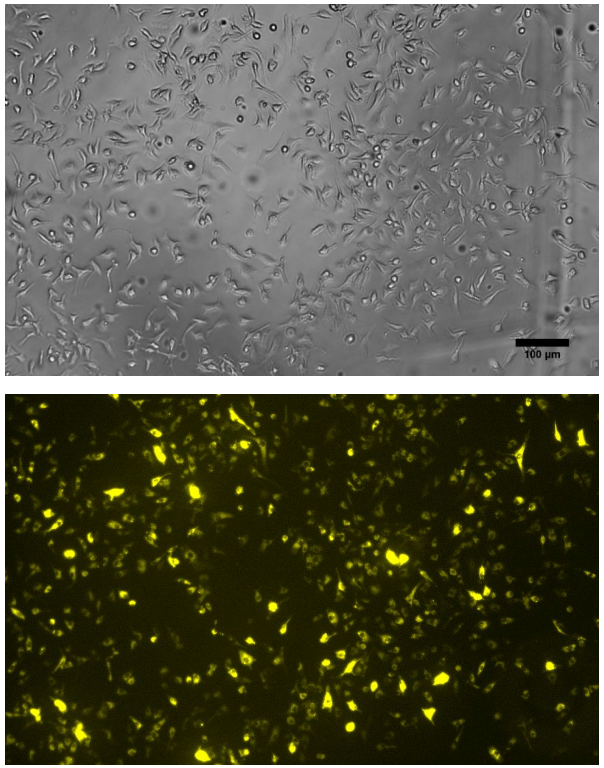


Li et al. Nature Nanotechnol, 2022

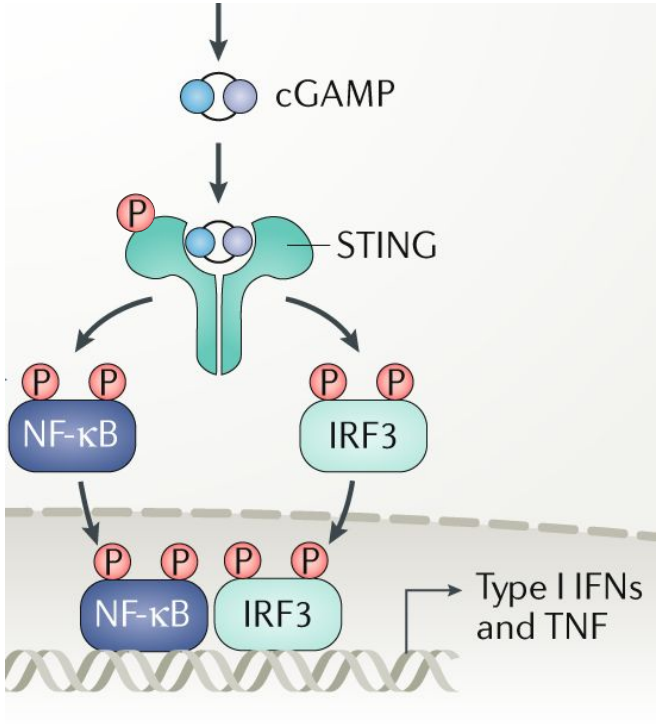
ncMBs show specific targeting and efficient delivery

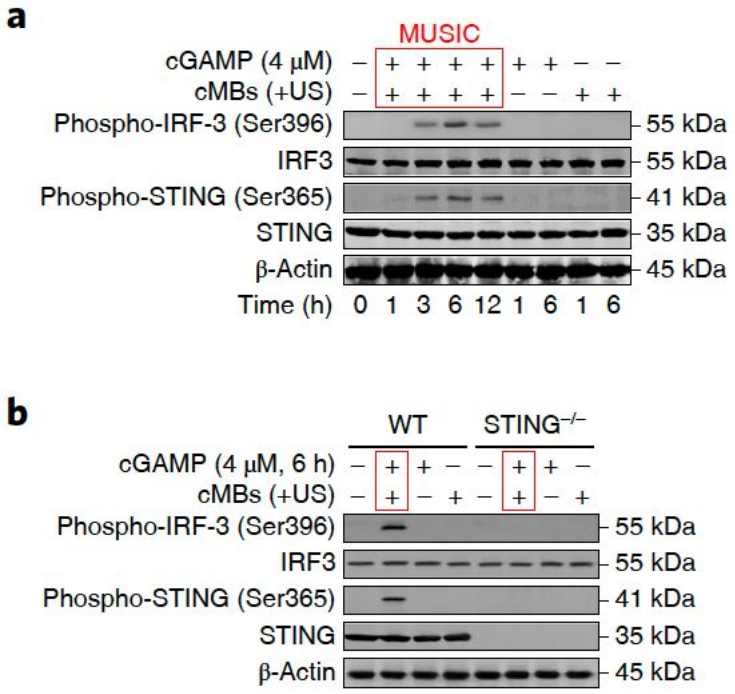


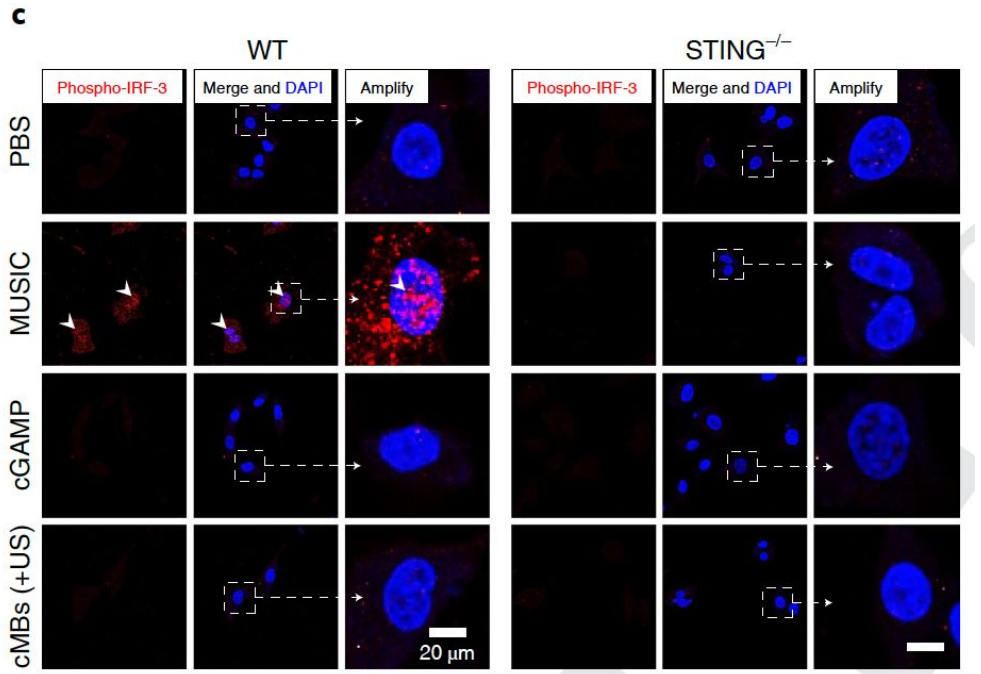
Delivery



MUSIC treatment effectively activates STING pathway in macrophages







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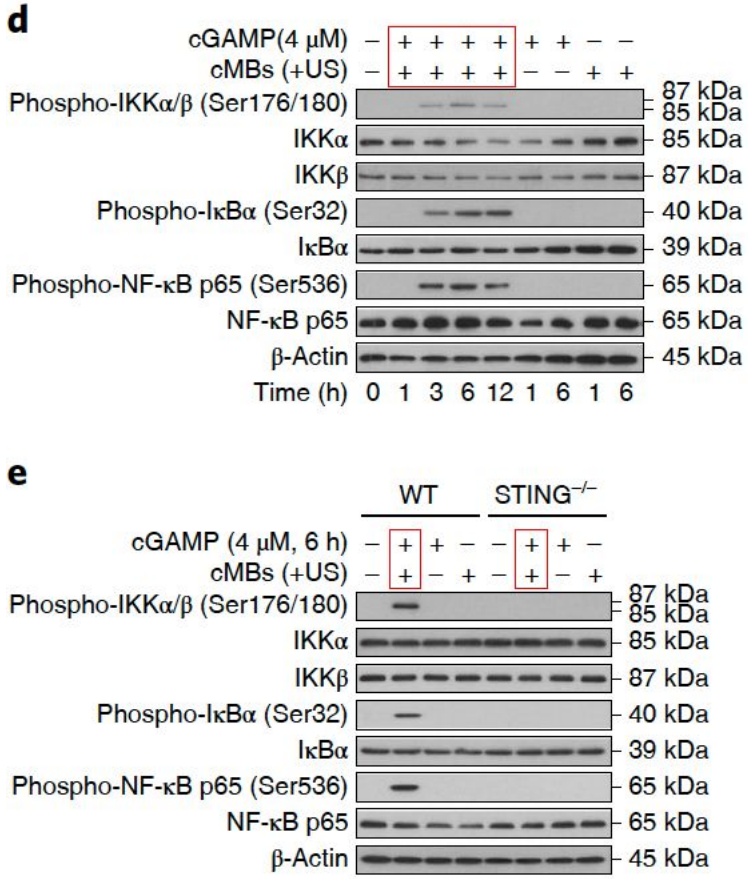
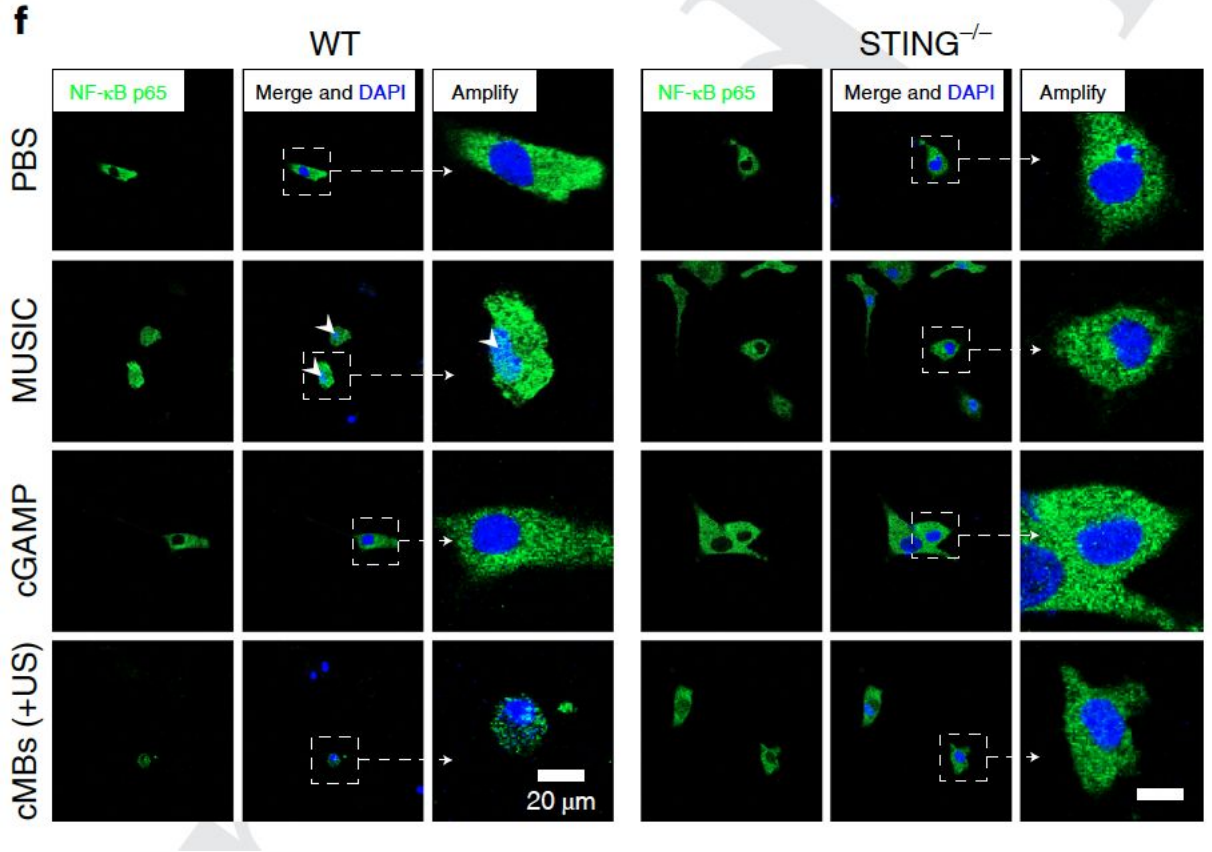
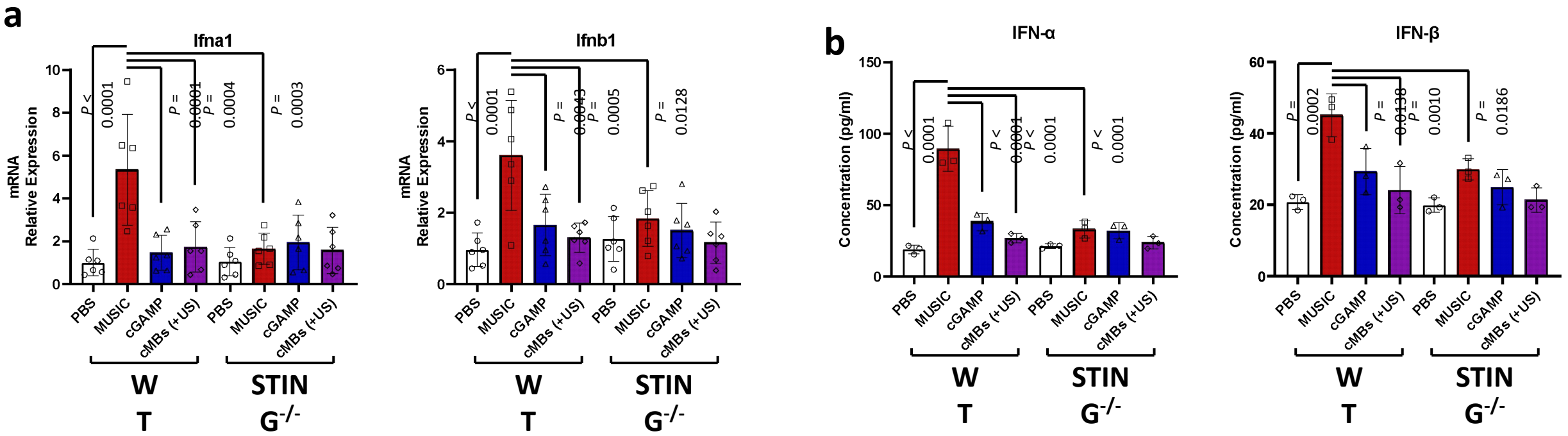
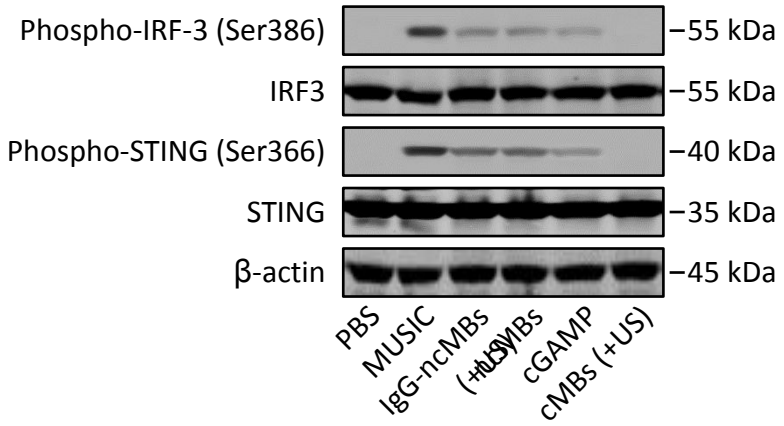


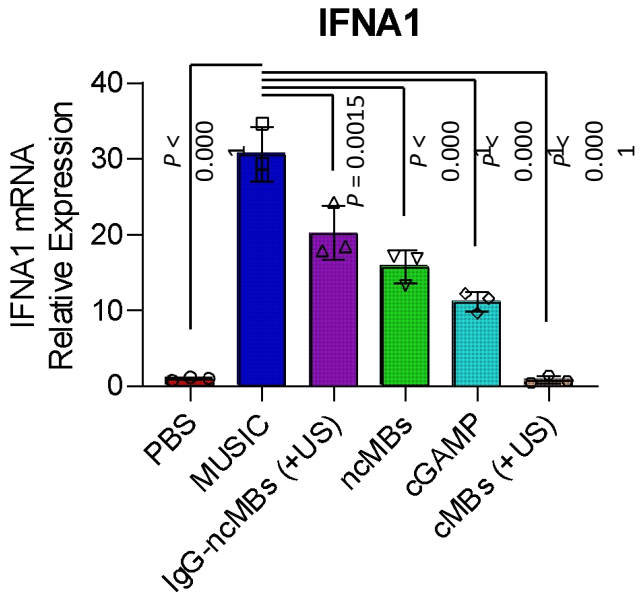


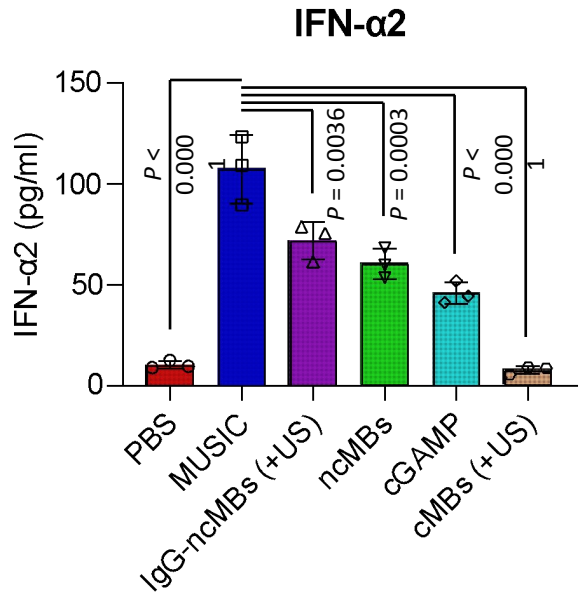
MUSIC enhances type I IFN responses in BM macrophages and DCs



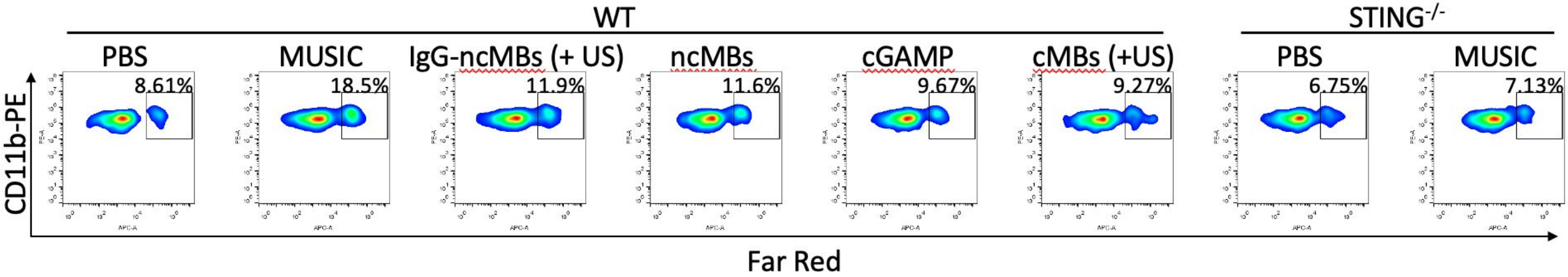
MUSIC activates STING in primary human PBMC-derived macrophages



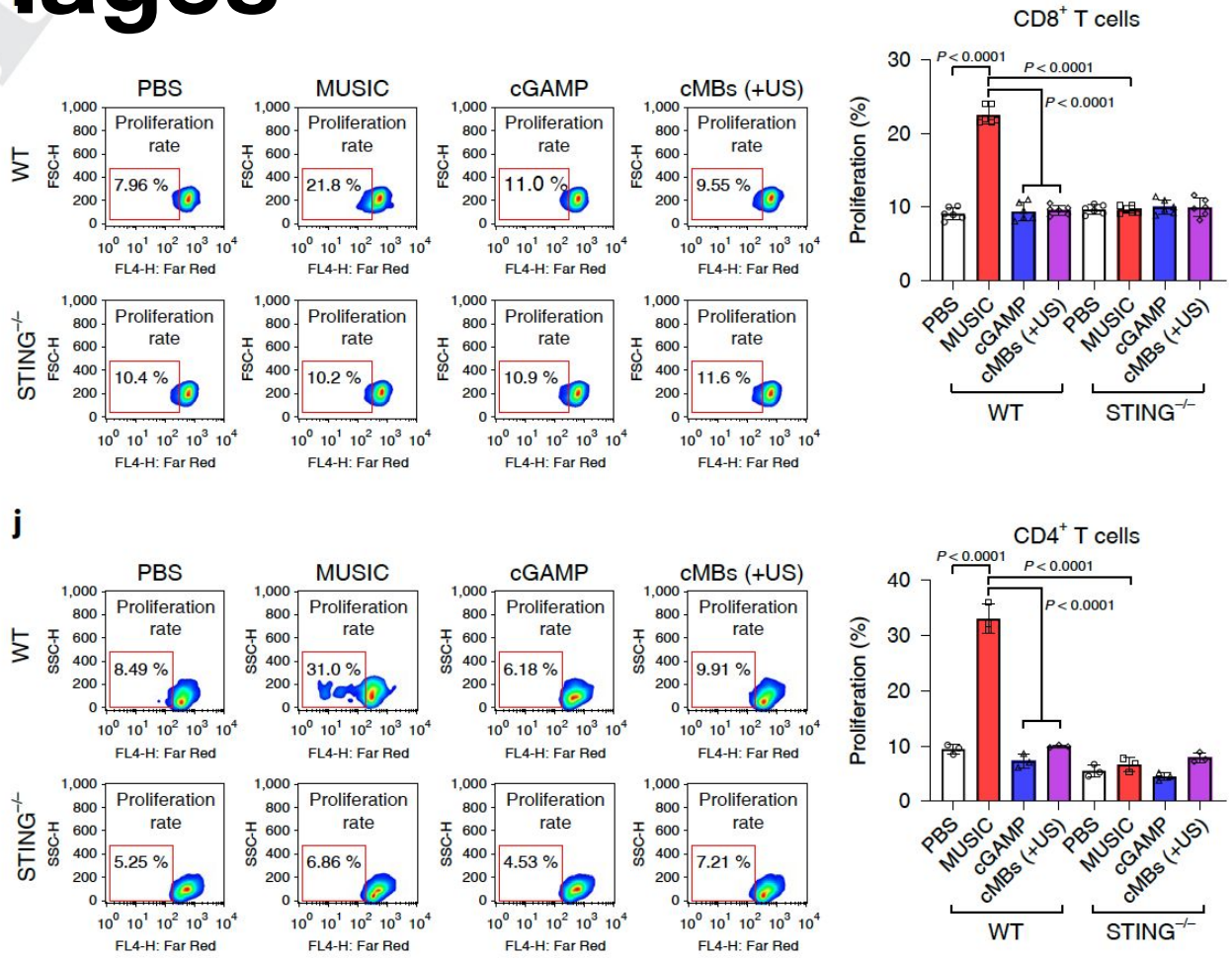




MUSIC treatment improved phagocytosis of E0771 cancer cells by BMDMs

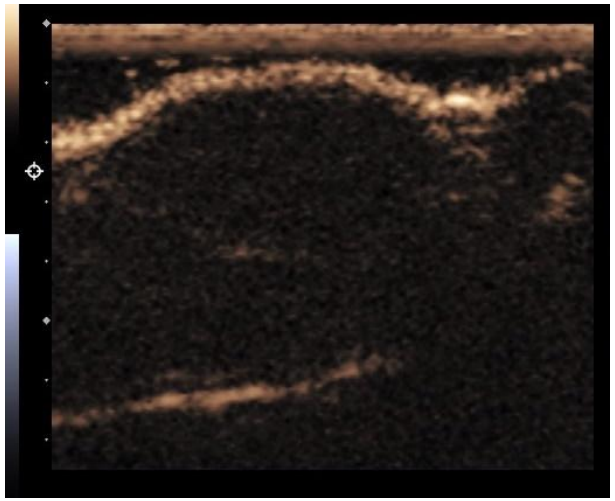


MUSIC enhanced T cell priming by macrophages

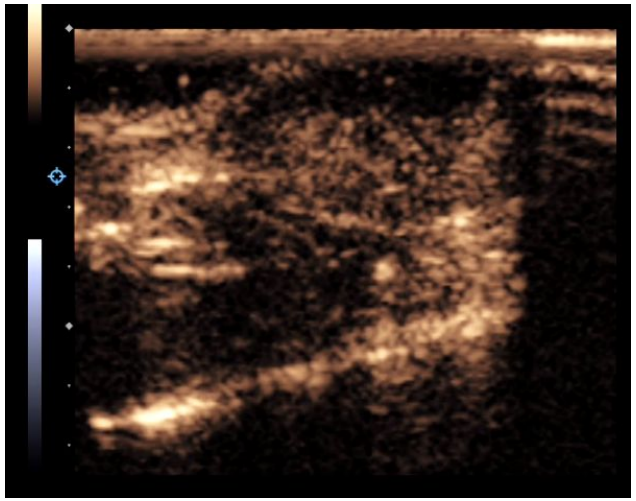


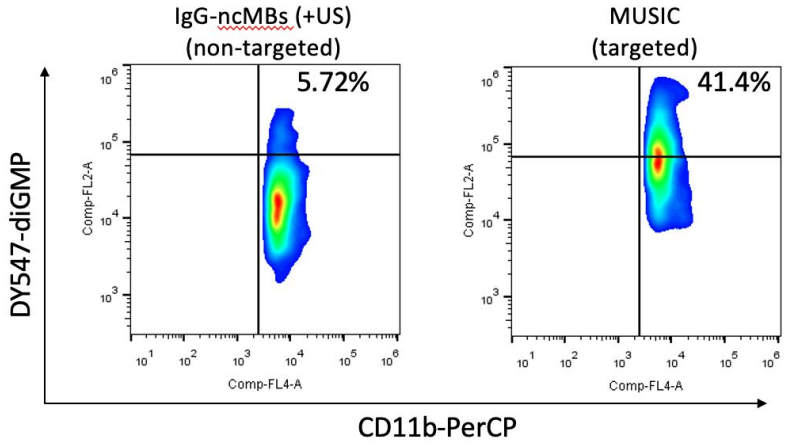
MUSIC enable image-guided activation and improve targeted delivery

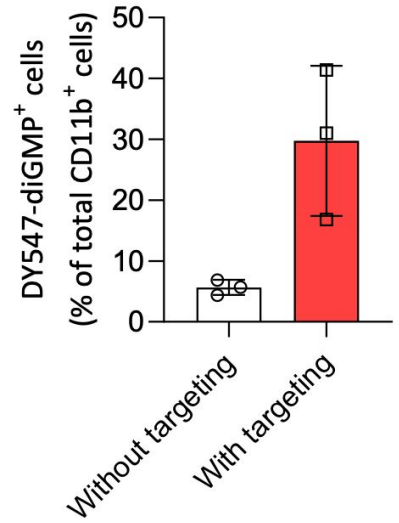
Pre injection



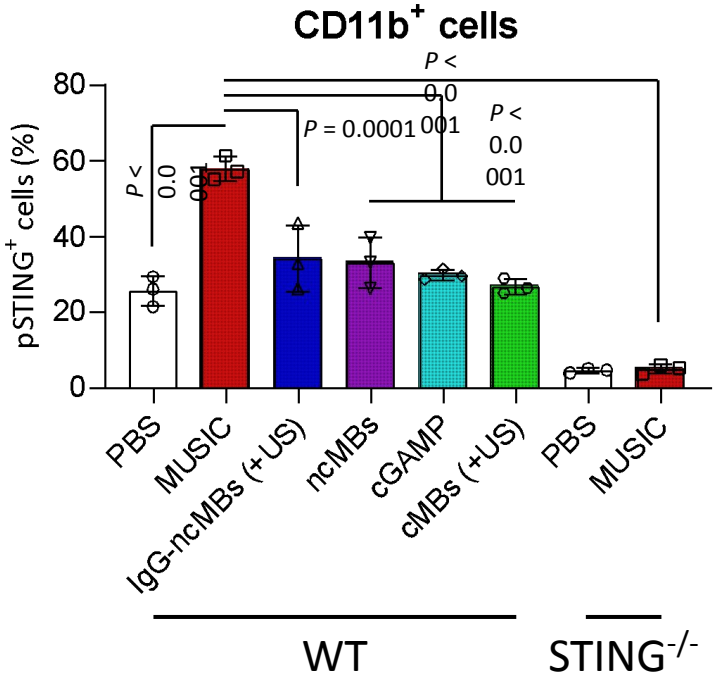
Post injection

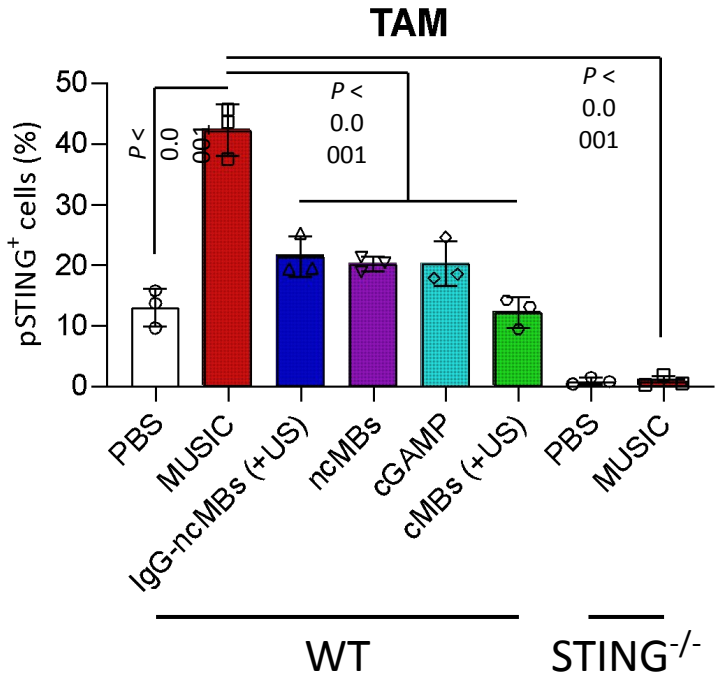




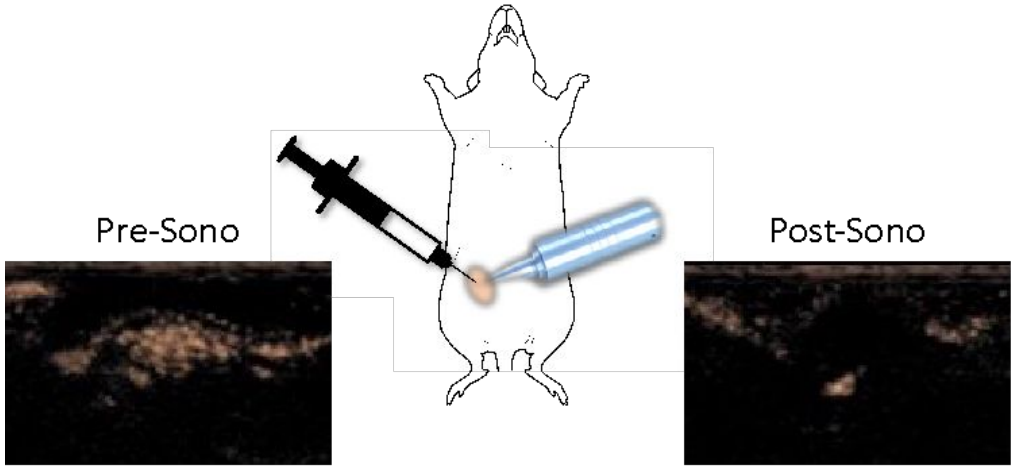


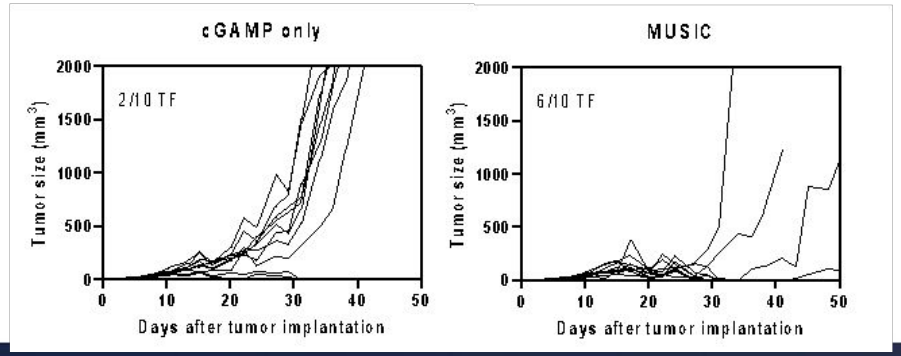
MUSIC activates STING in CD11b+ cells in vivo

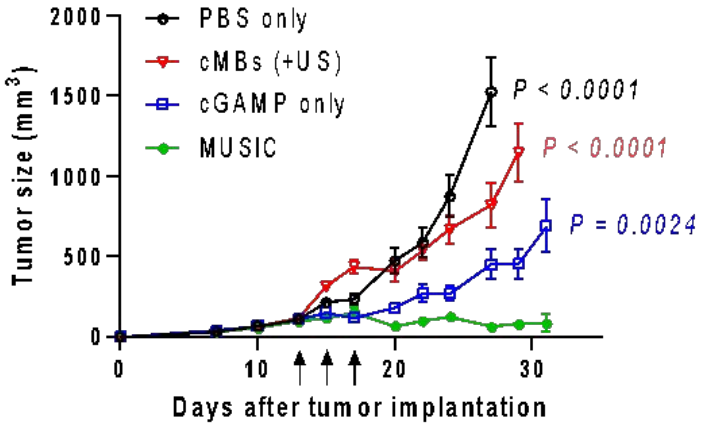


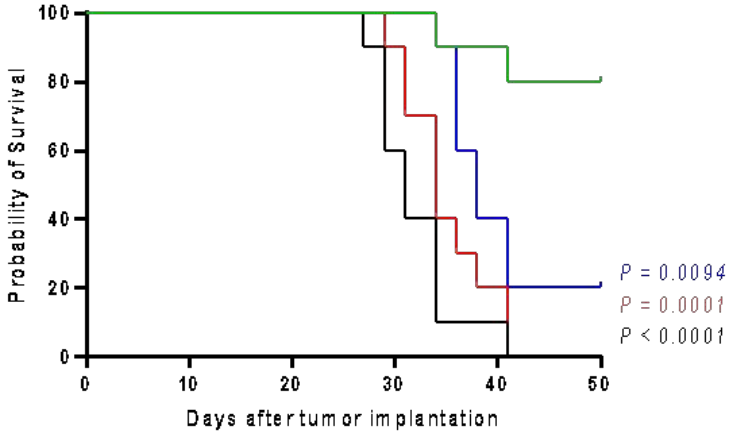


MUSIC treatment effectively inhibits tumor growth in a murine breast cancer model

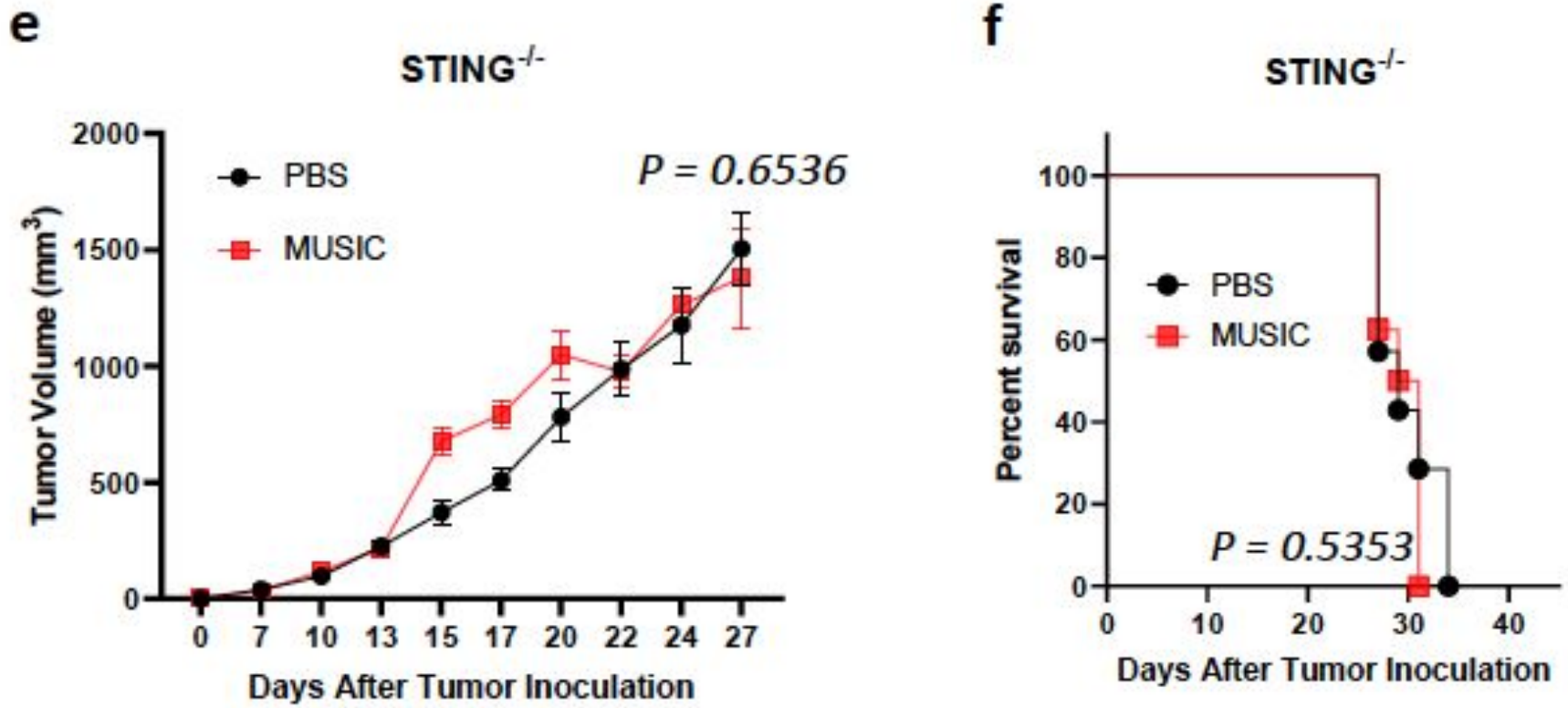




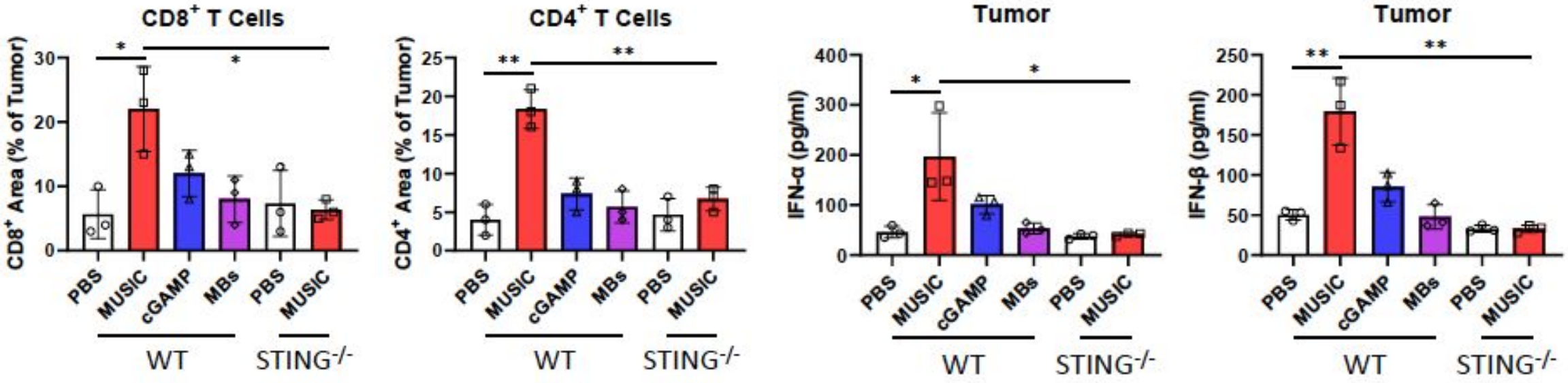




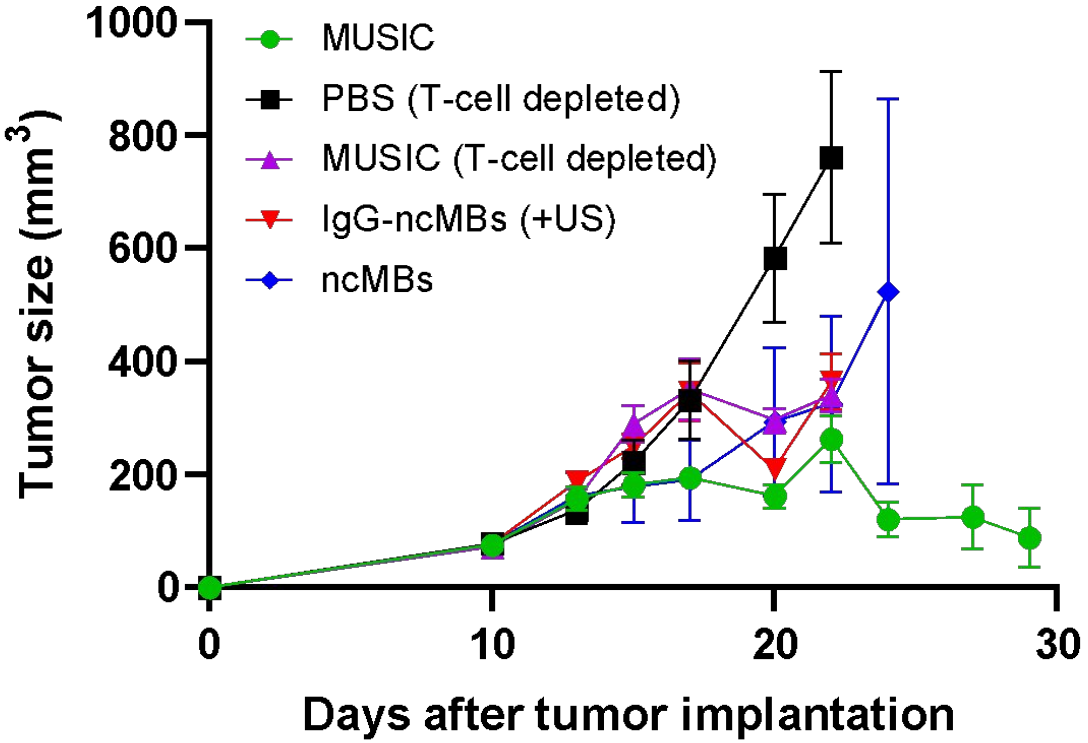
MUSIC's antitumor effect depends on STING

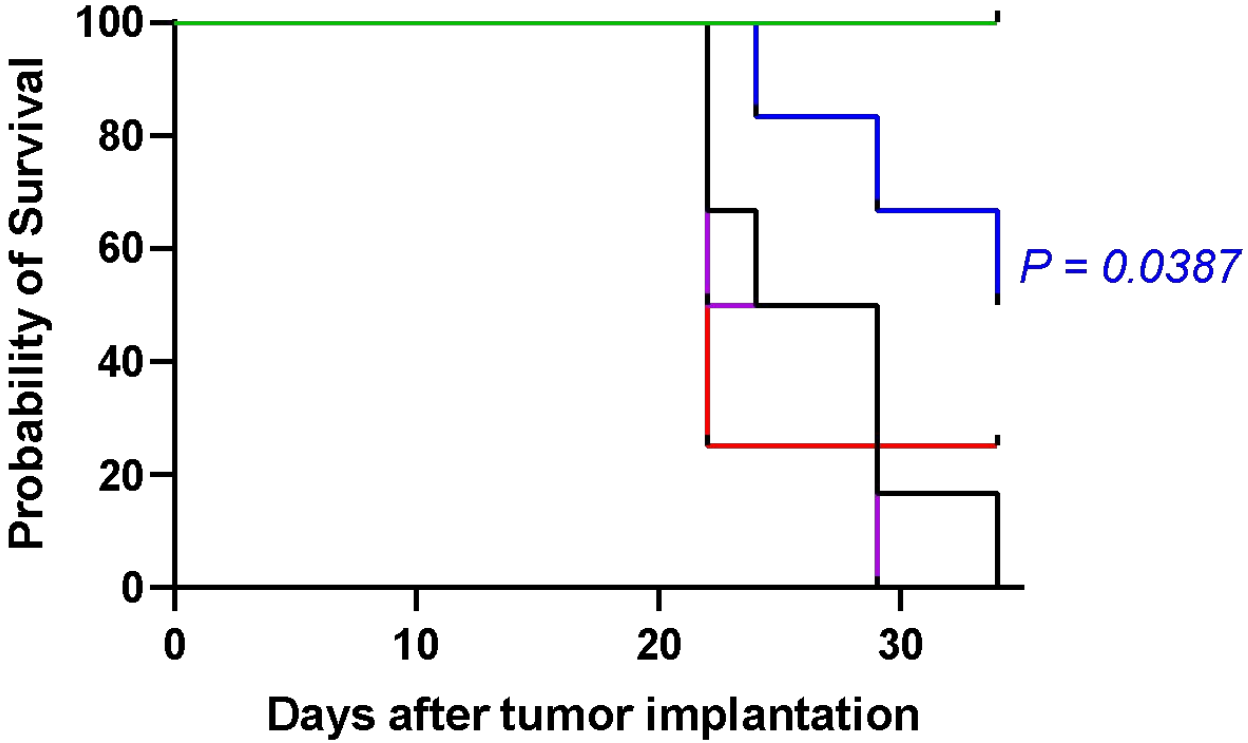


MUSIC enhanced the infiltration of T cells into tumors

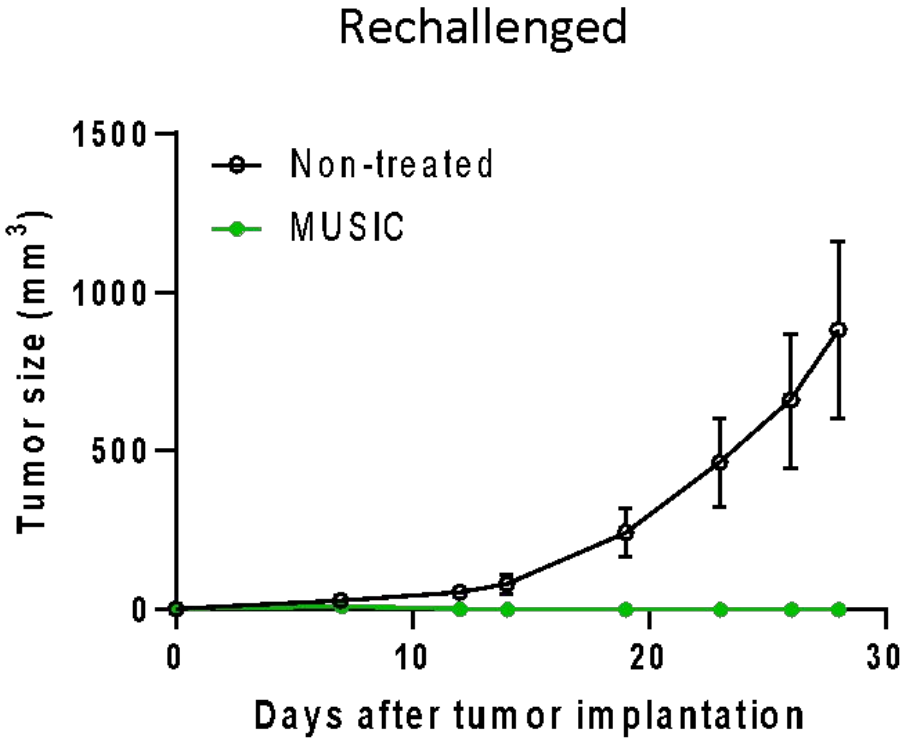


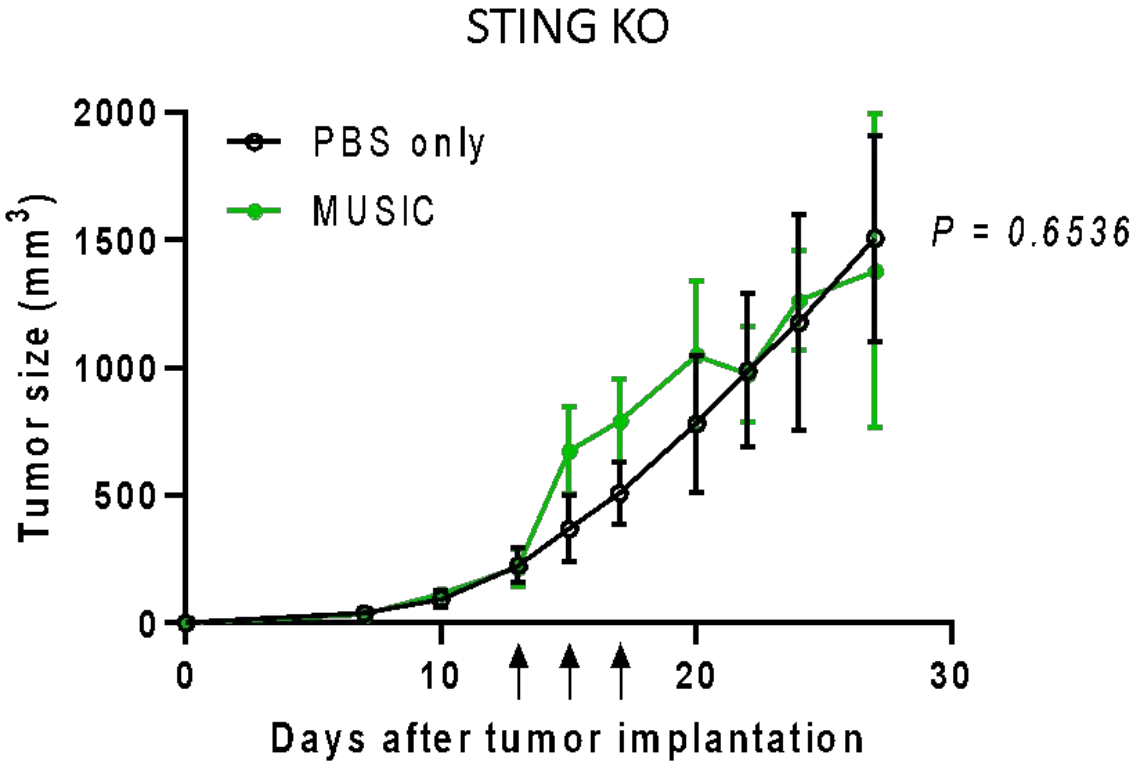
MUSIC efficacy is dependent on T cells





MUSIC-treated mice developed immune memory against E0771 cells





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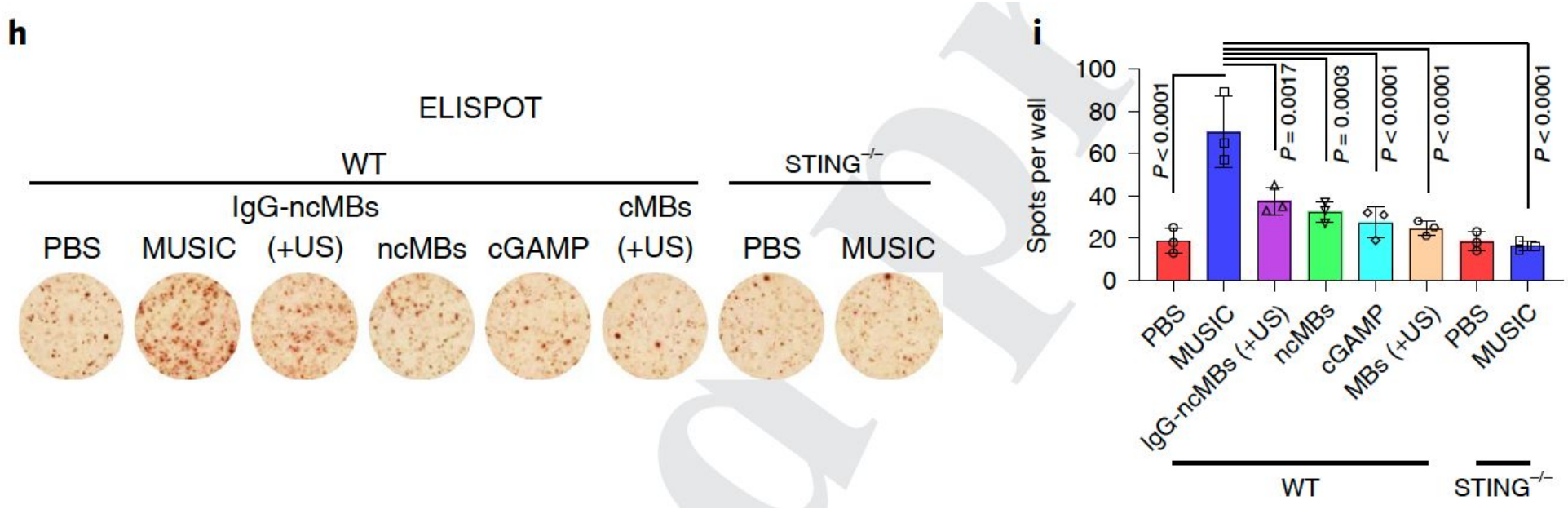
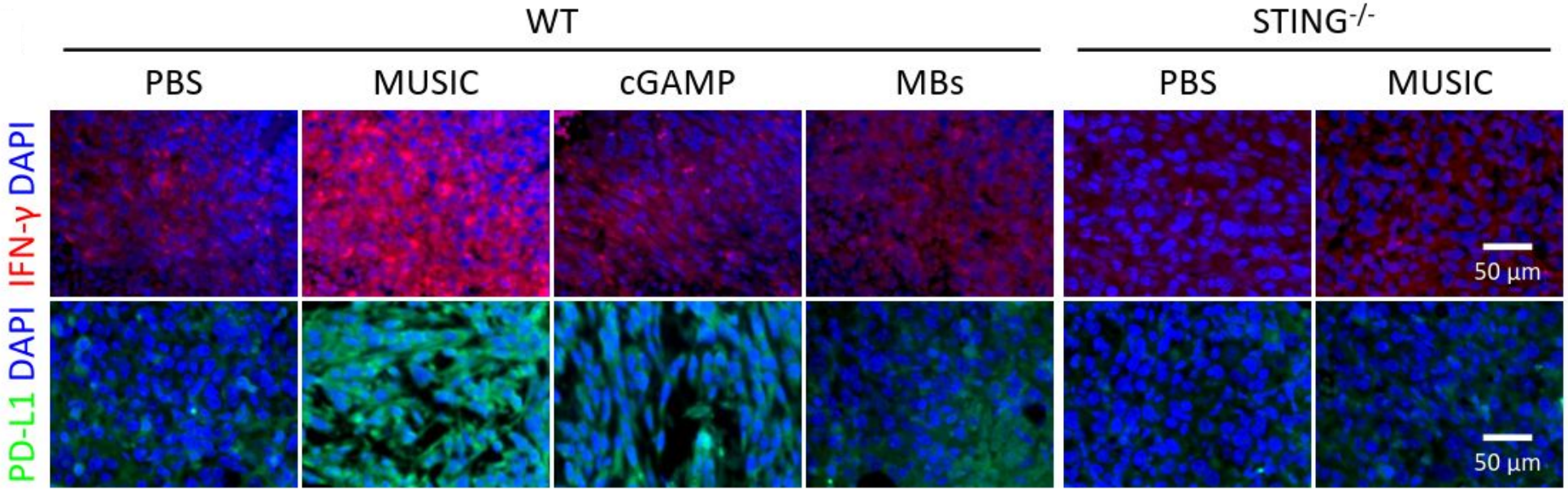
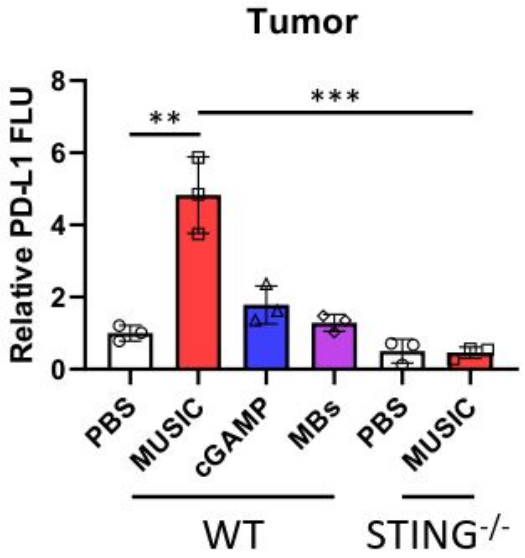
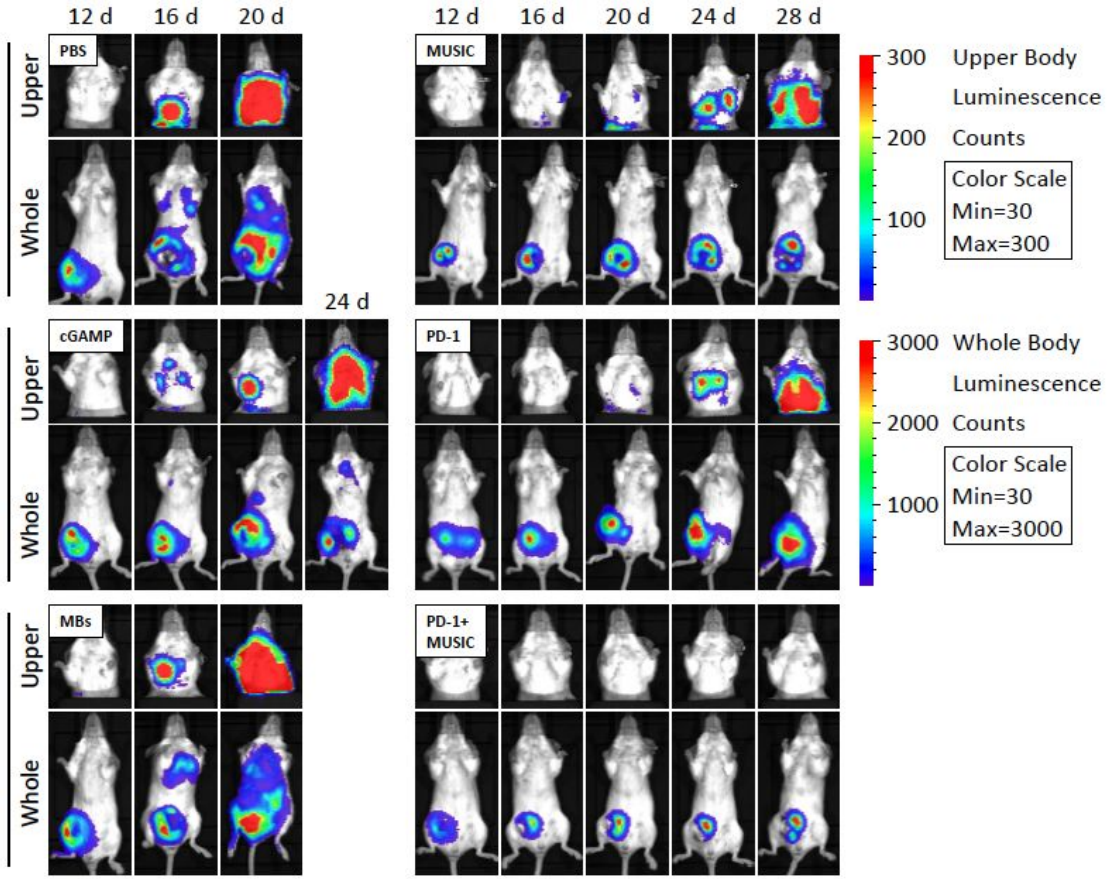


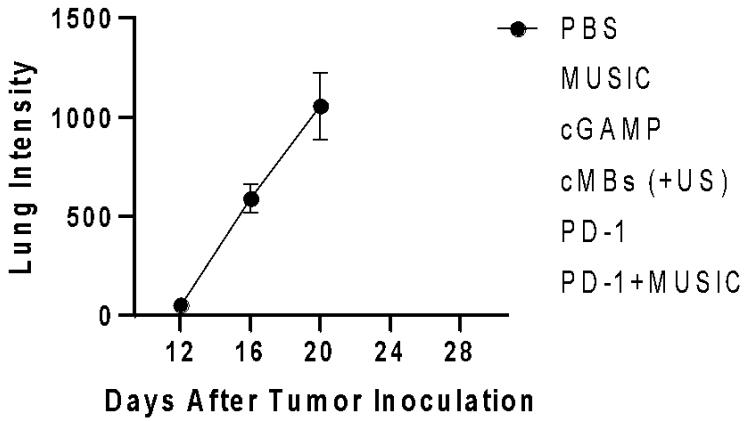
MUSIC-treated mice provide a strong rationale for a MUSIC/anti-PD1 combo

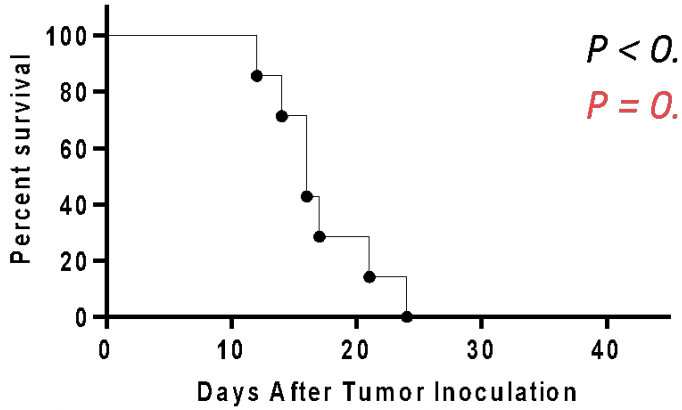




Combo inhibited growth of both primary tumor and metastasis and improved survival







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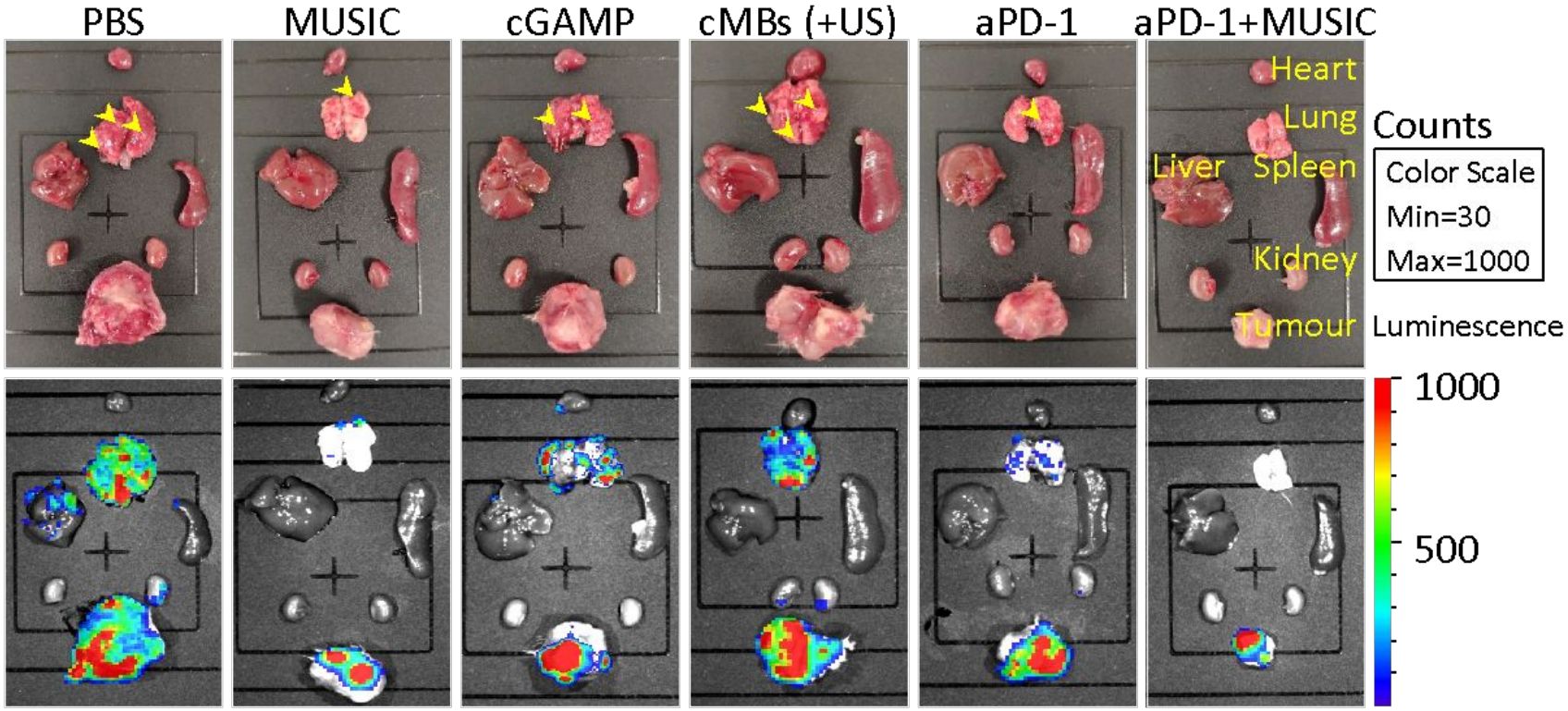
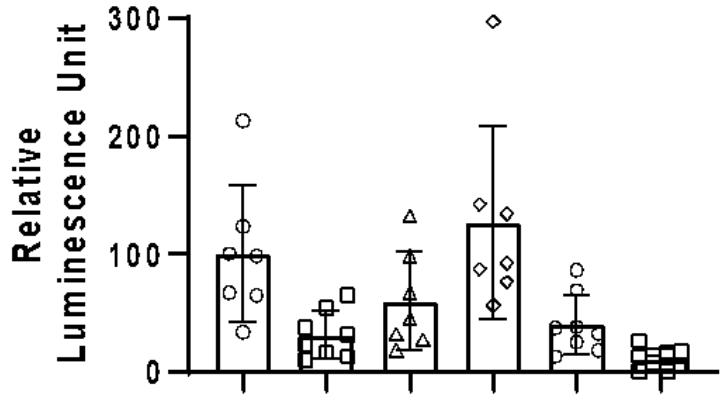
P = 0.007

Combo decreased systemic metastatic burden





Summary

- **MB-assisted sonoporation** enable efficient delivery of cGAMP to activate cytosolic STING
- **Activation of STING** in APCs enhances T cell priming and antitumor immune responses
- **MUSIC** potentiates systemic antitumor immunity of PD-1 blockade to eliminate metastatic breast cancer
- Next step is to expand MUSIC to other tumors including GBM

Acknowledgement

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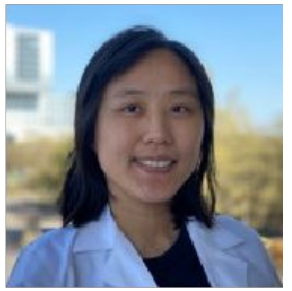
Dr. Benjamin Shrank

Collaborators: Betty Kim Lab, Jacques Lux Lab (UTSW)





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- Neoleukin Inc
- SpotBiosystems Inc