Engineering the STING protein for a peptide cancer vaccine

Celestine Hong

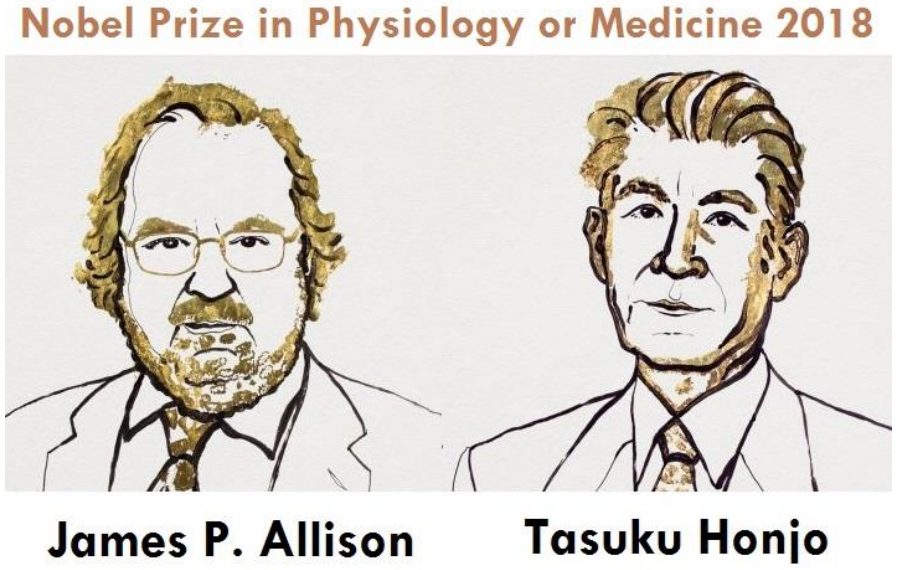
Hammond Lab
Massachusetts Institute of Technology
July 13th, 2022

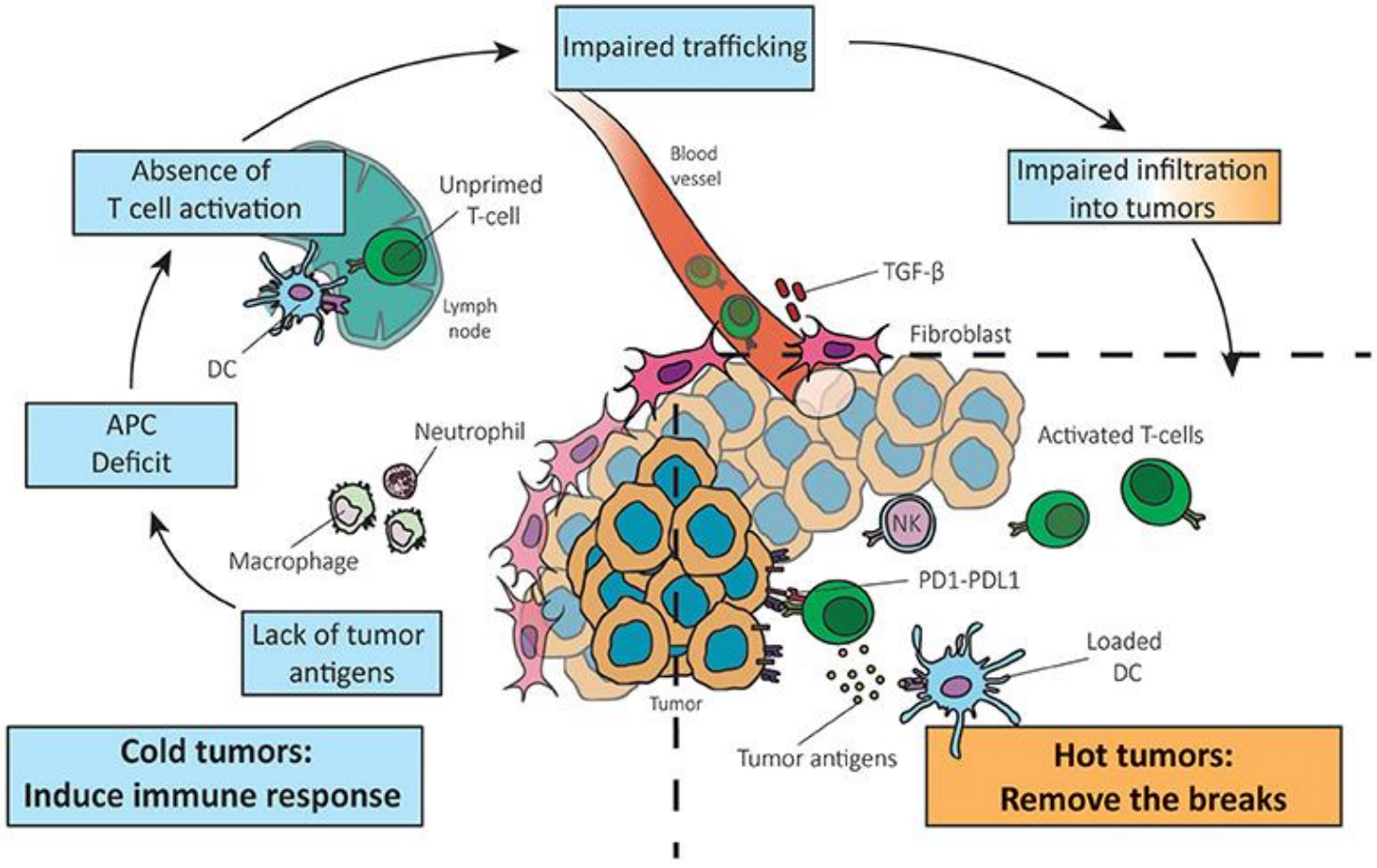
MARBLE CENTER FOR CANCER NANOMEDICINE

INSTITUTE FOR SOLDIER NANOTECHNOLOGIES

KOCH INSTITUTE for Integrative Cancer Research at MIT

Cancer immunotherapy and peptide cancer vaccines





Cancer Immunotherapy: to treat cancer patients that involves or uses components of the immune system.

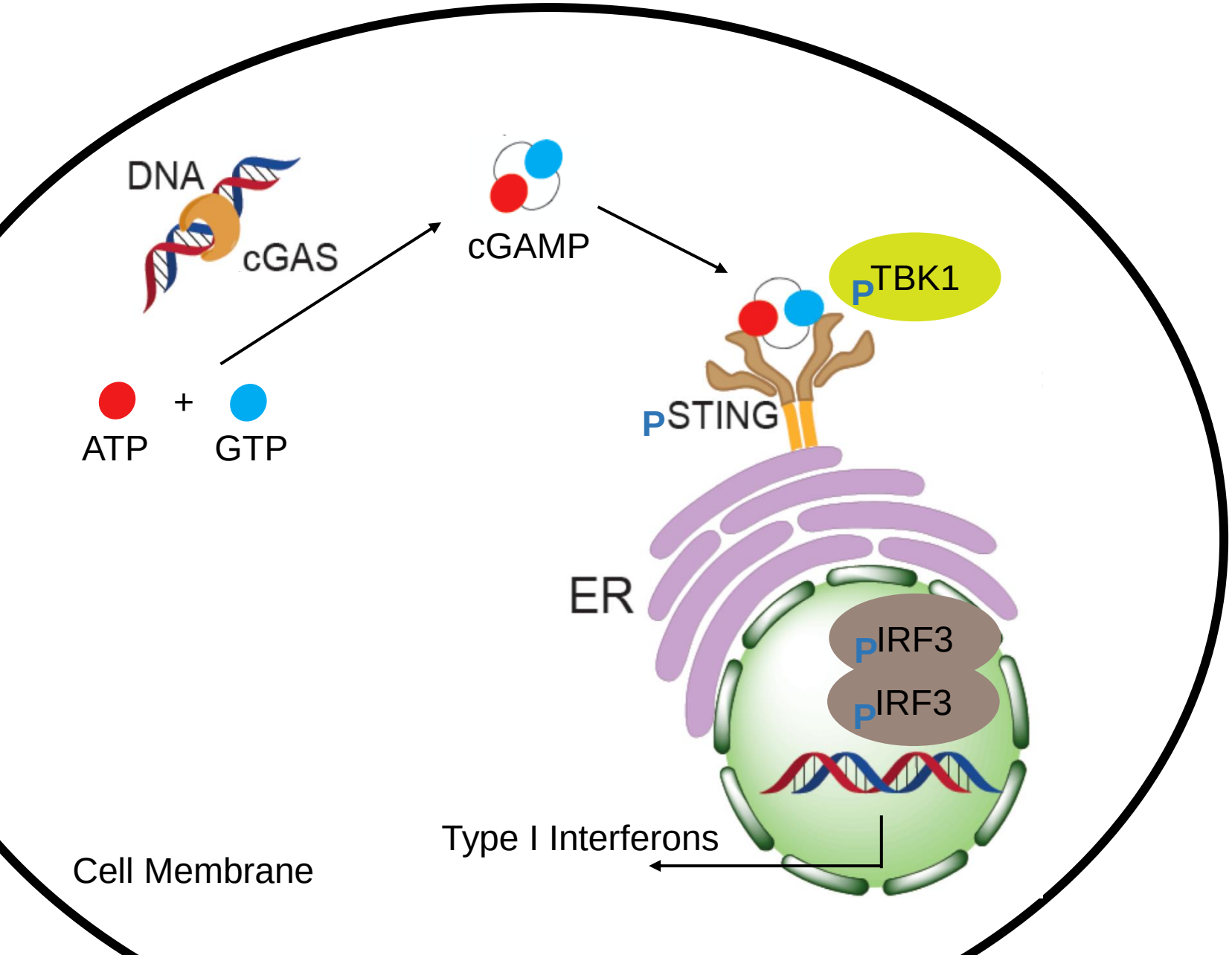
Prize motivation: "for their discovery of cancer therapy by inhibition of negative immune regulation."

Peptide cancer vaccines: Vaccines targeted towards epitope peptides found on cancer cells, though “the poor lymphatic drainage and short in vivo half-life of linear peptides likely contribute to the low potency of peptide vaccines”.

(Bonaventura, P. et al., 2019)

(Moynihan, K.D. et al., 2018)

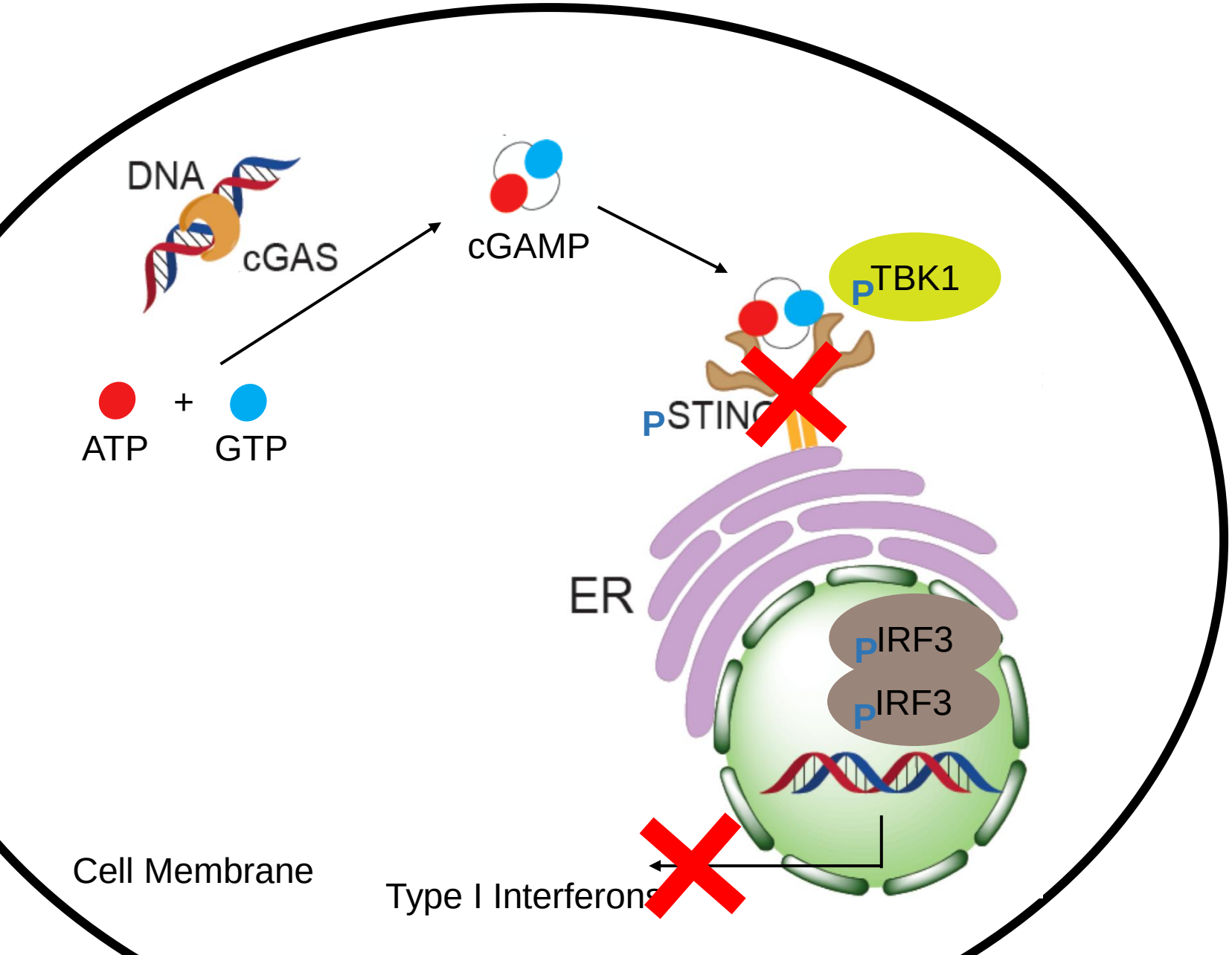
The STING (stimulator of interferon genes) Pathway



1. cGAS binds double-stranded DNA in cytosol
2. cGAS synthesizes cGAMP
3. cGAMP binds STING
4. STING recruits TBK1
5. STING and TBK1 phosphorylate each other
6. The complex recruits, phosphorylates and dimerizes IRF3
7. $(pIRF3)_2$ is the transcription factor for interferons

cGAMP = cyclic GMP AMP
cGAS = cGAMP Synthase
STING = Stimulator of Interferon Genes

Cancer cells can silence STING for immune escape



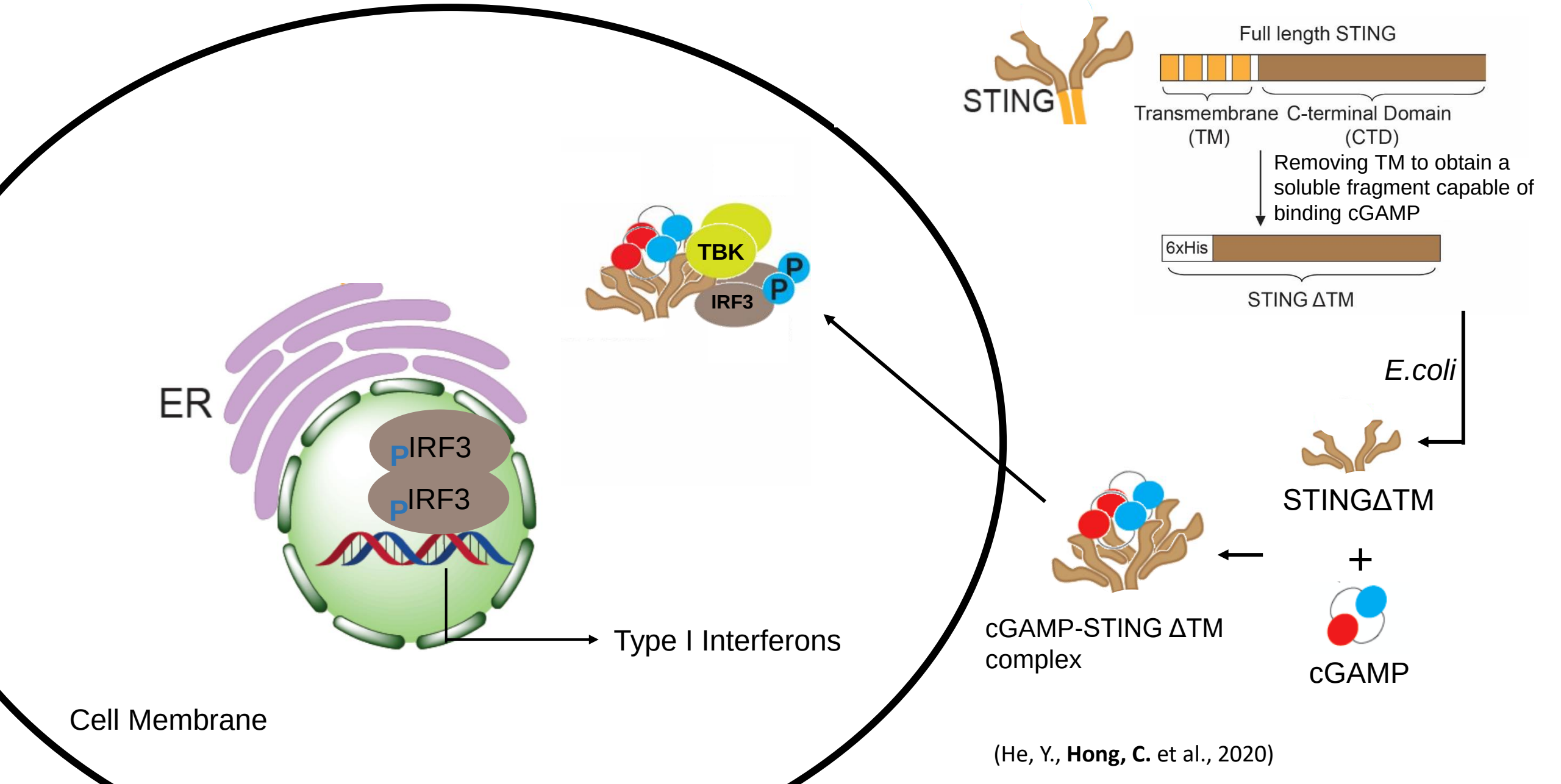
"cGAS and/or STING expression was absent in ~54% of colon cancers examined and ~54% of melanomas examined."

"Greater silencing of cGAS and/or STING expression was observed in the late stages of both cancers relative to their respective earlier stages."

"Activation of the intracellular STING protein triggers the production of a multifaceted array of immunostimulatory molecules."

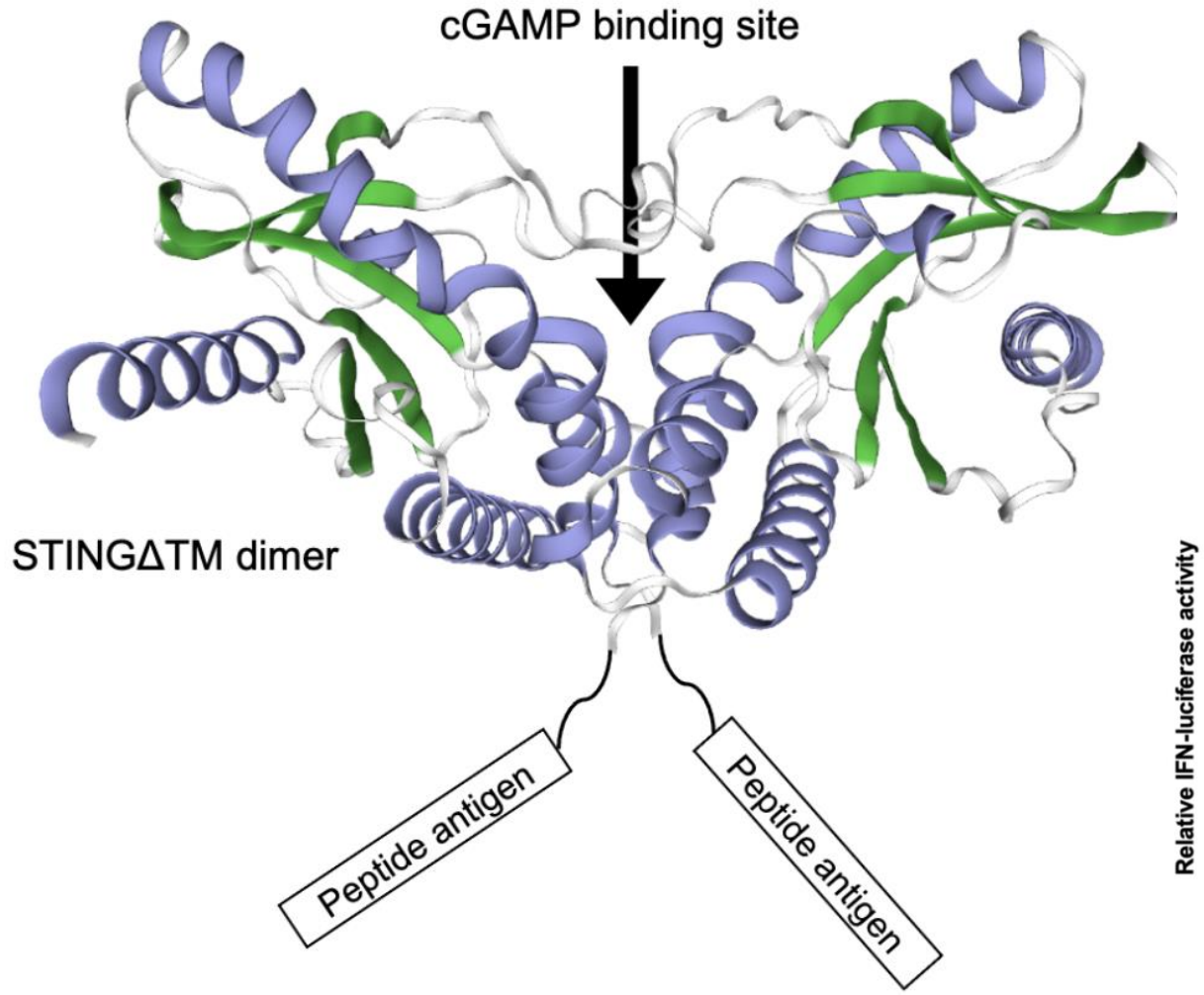
(Garland, K.M. et al. , 2022)
(Xia, T. et al. , 2016)
(Ahn, J. et al., 2015)

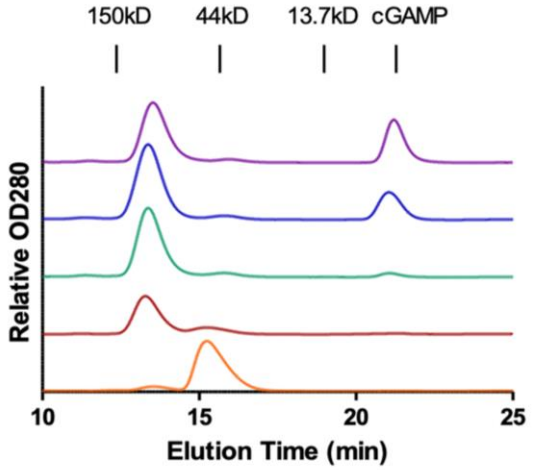
Our approach: STINGΔTM as a functional cGAMP carrier

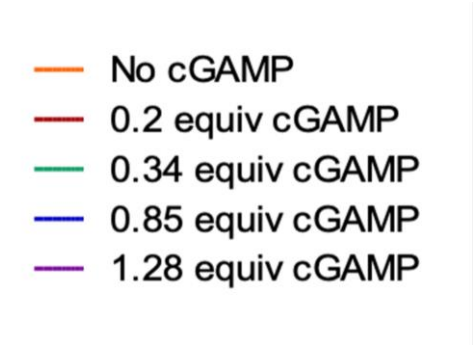


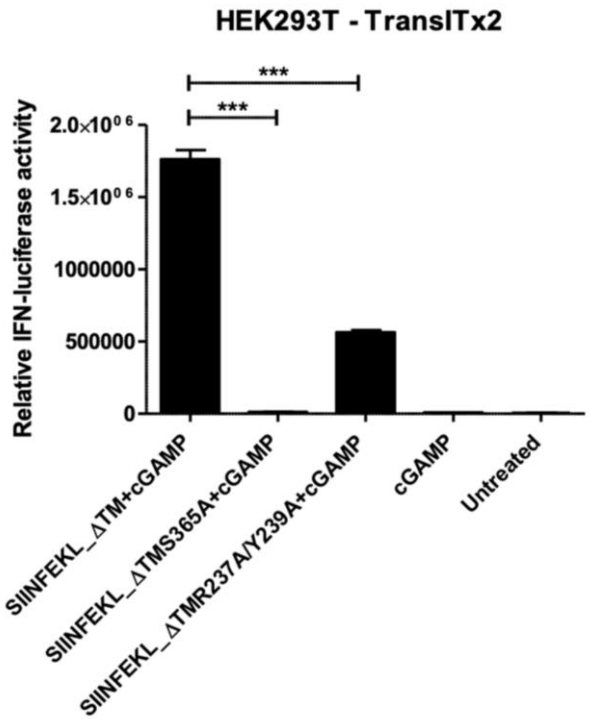
(He, Y., **Hong, C.** et al., 2020)

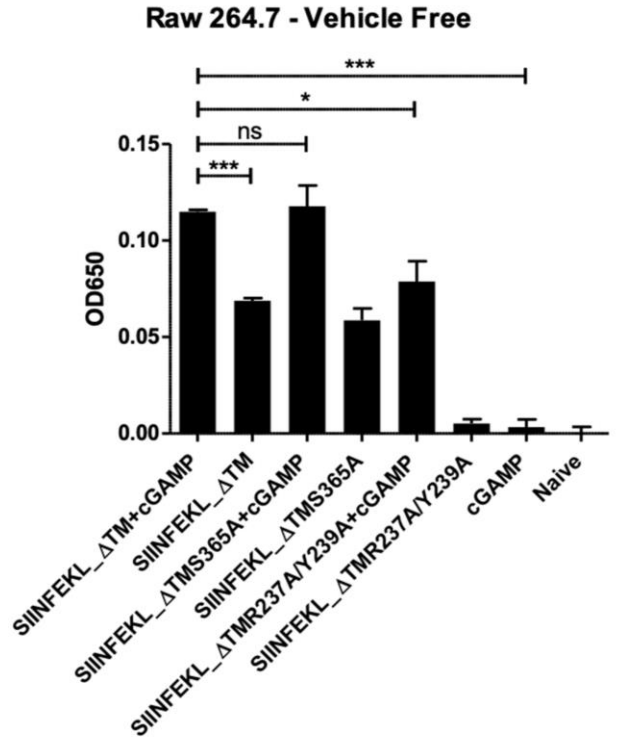
Peptide-STINGΔTM for peptide-based vaccine





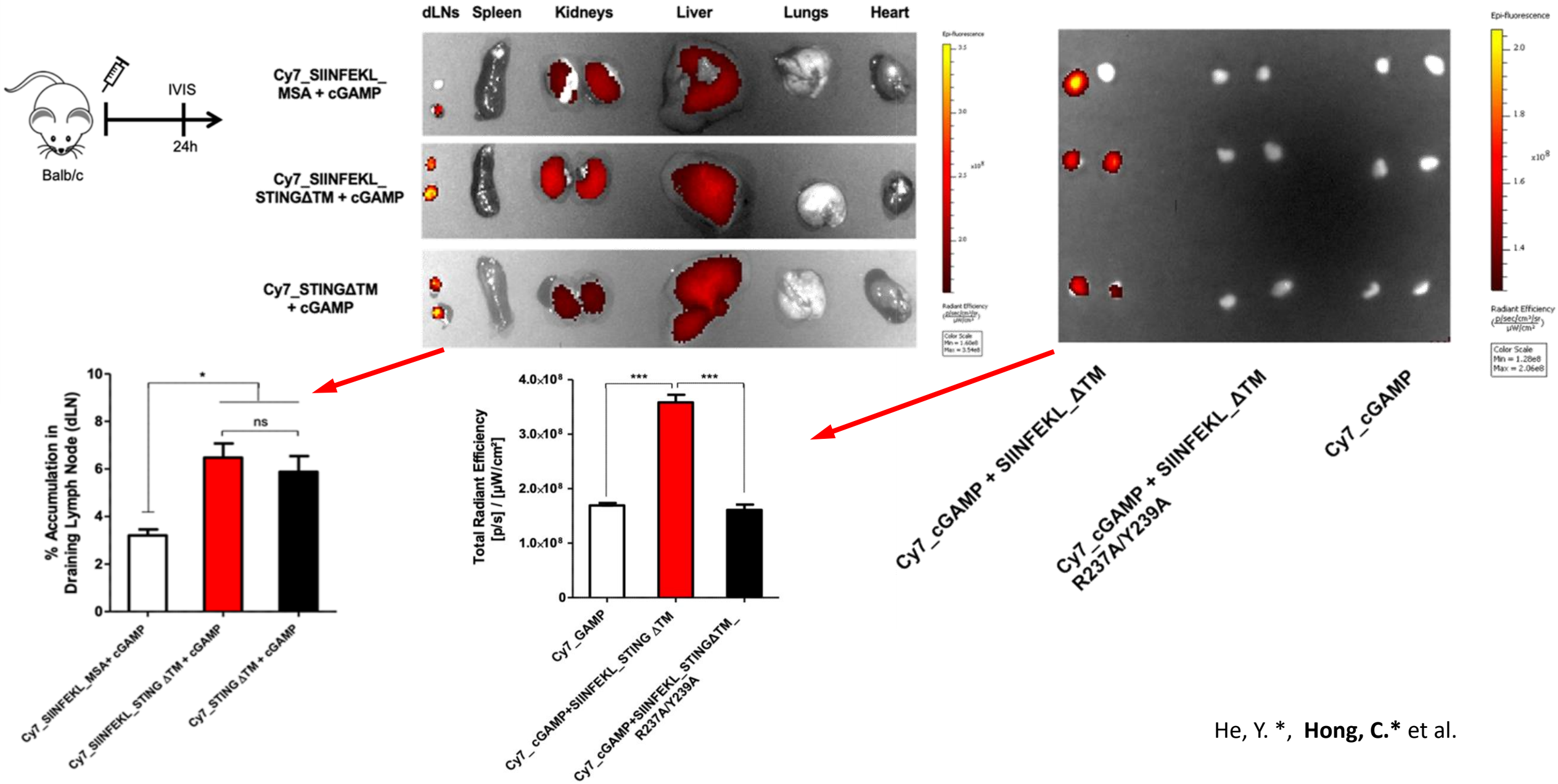






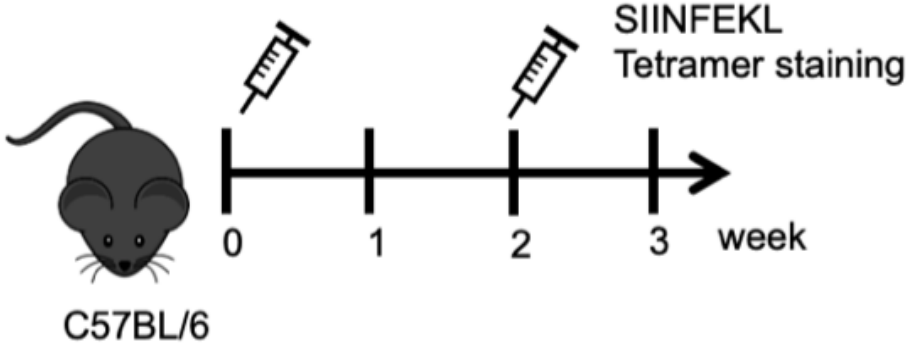
He, Y. *, **Hong, C.*** et al.

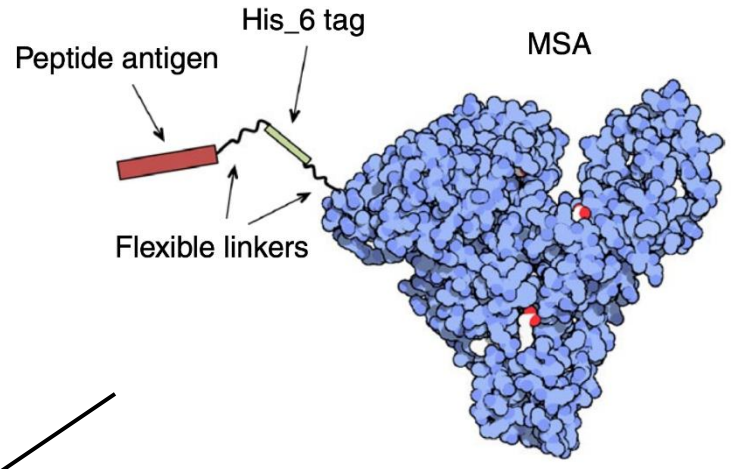
Peptide-STINGΔTM displays efficient lymphatic trafficking



He, Y. *, **Hong, C.*** et al.

Peptide-STINGΔTM induces antigen-specific T cell response

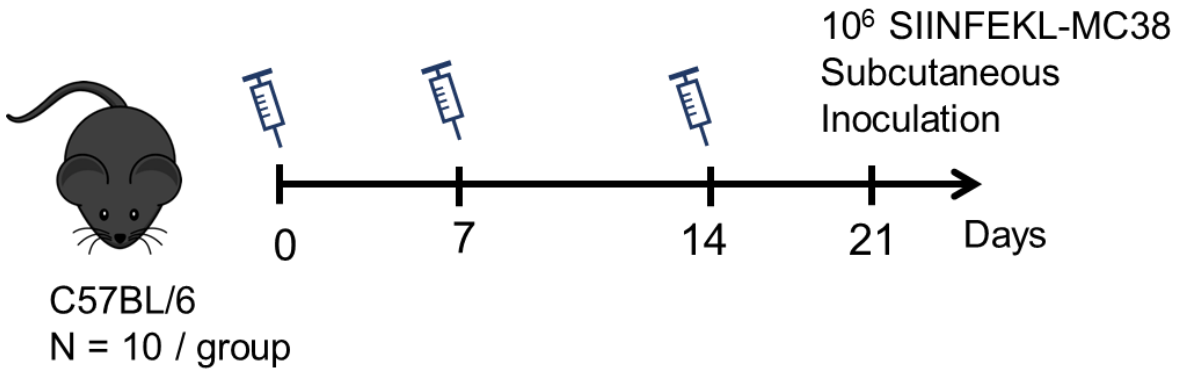


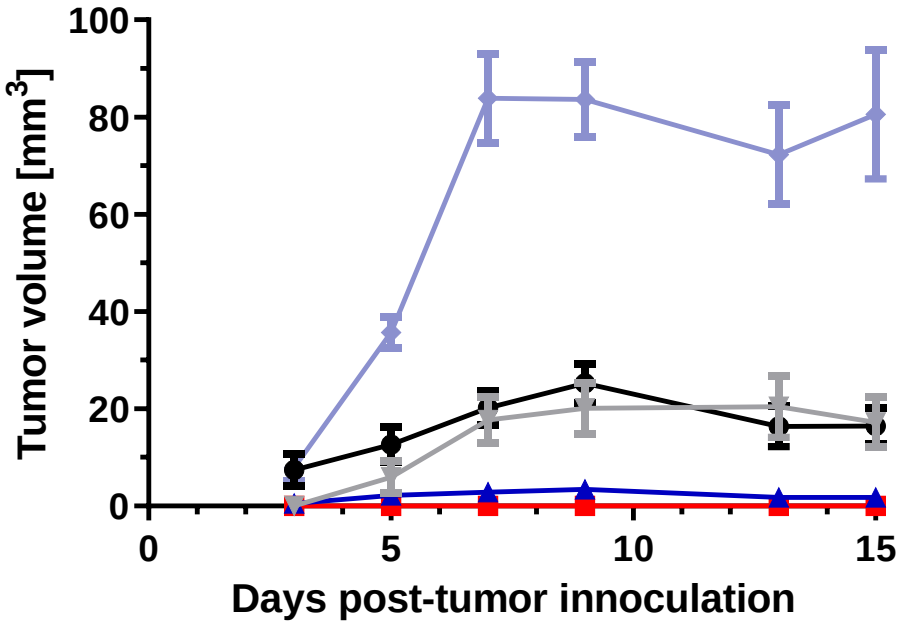


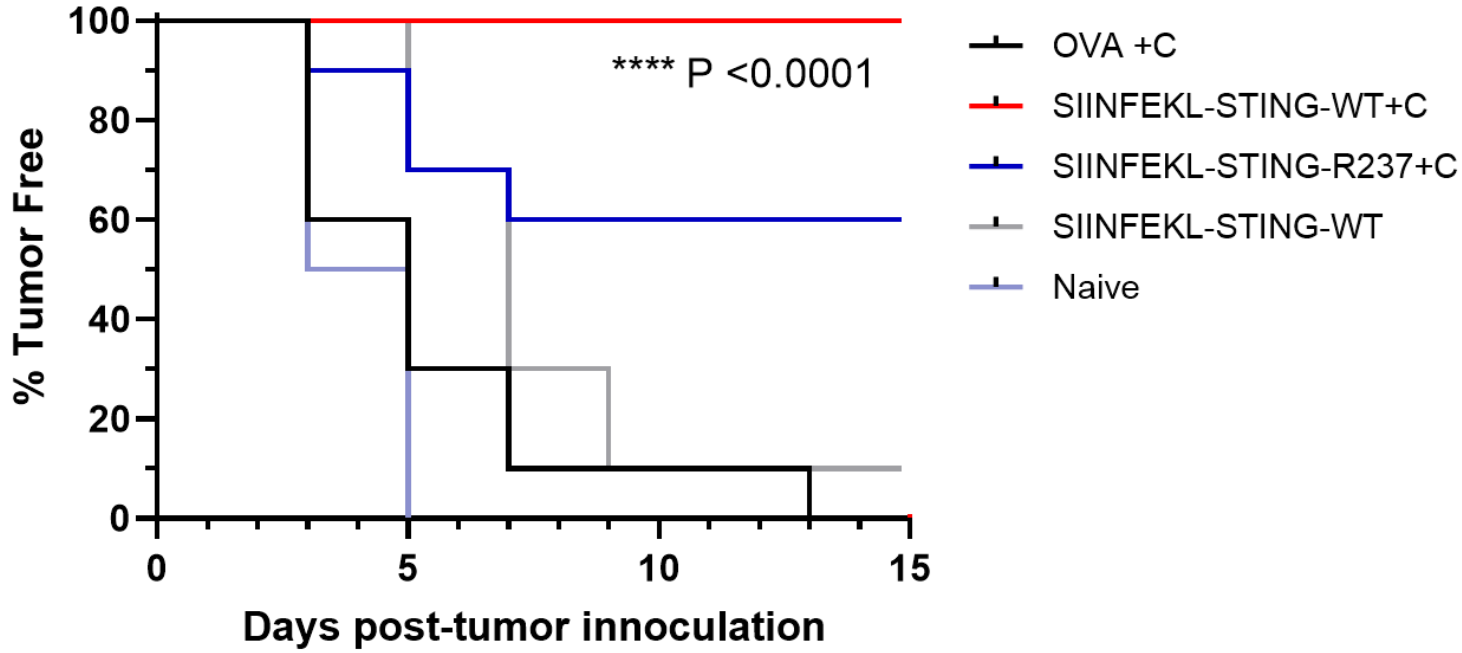
Mehta, N, et al. *Nature BME (2020)*

He, Y. *, **Hong, C.*** et al.

Peptide-STINGΔTM as cancer vaccine





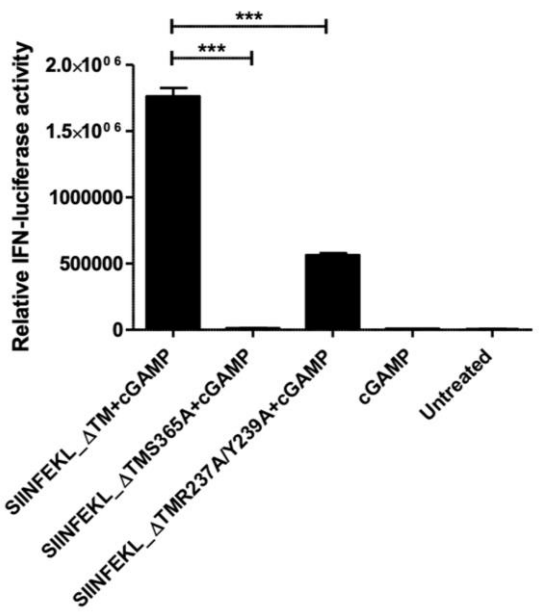


He, Y. *, **Hong, C.*** et al.

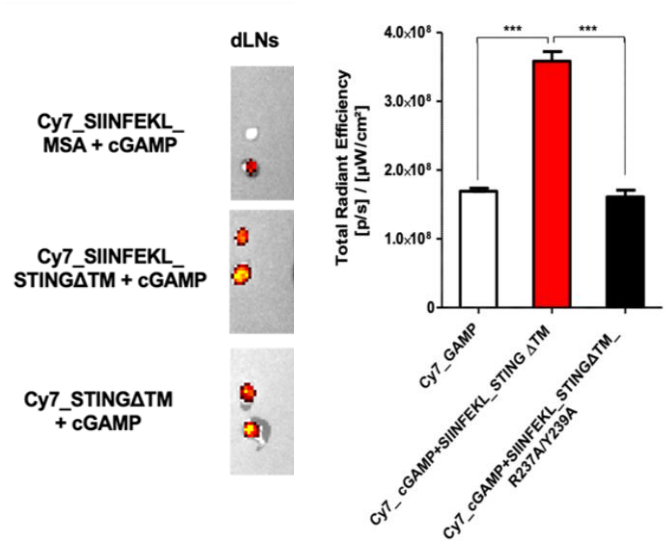
Conclusions

Challenges in peptide vaccine delivery: **low lymphatic trafficking** and **immunogenicity**

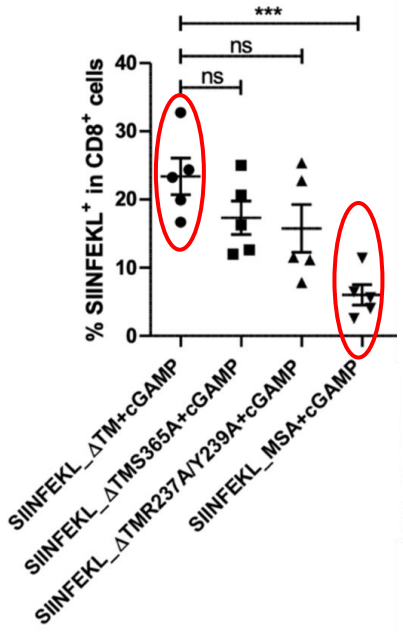
The **peptide-STINGΔTM** platform results in:



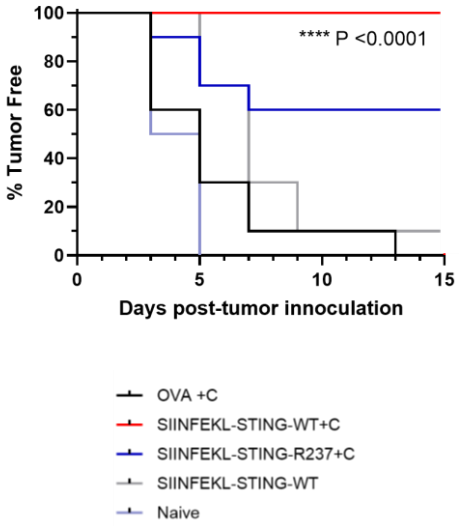
Recovery of STING signaling in cells lacking endogenous STING



Efficient lymphatic trafficking of both peptide and adjuvant



High levels of antigen-specific T-cell responses compared to state-of-the-art



Robust antitumor response

Acknowledgement

Prof. Paula Hammond

Hammond lab (MIT)
Dr. Yanpu He
Samantha Fletcher
Emily Yan

Prof. Darrell Irvine

Irvine lab (MIT)
Dr. Yingzhong Li

Prof. Jiahe Li

Li lab (NEU)
Ge Zhu
Mengdi Yang
Dr. Xin Sun

Prof. Angela Belcher

Belcher lab (MIT)
Dr. Shengnan Huang

Koch Institute's Joseph C. Jefferds, Jr. Research Travel Award

MARBLE CENTER FOR CANCER NANOMEDICINE

KOCH INSTITUTE for Integrative Cancer Research at MIT

INSTITUTE FOR SOLDIER NANOTECHNOLOGIES