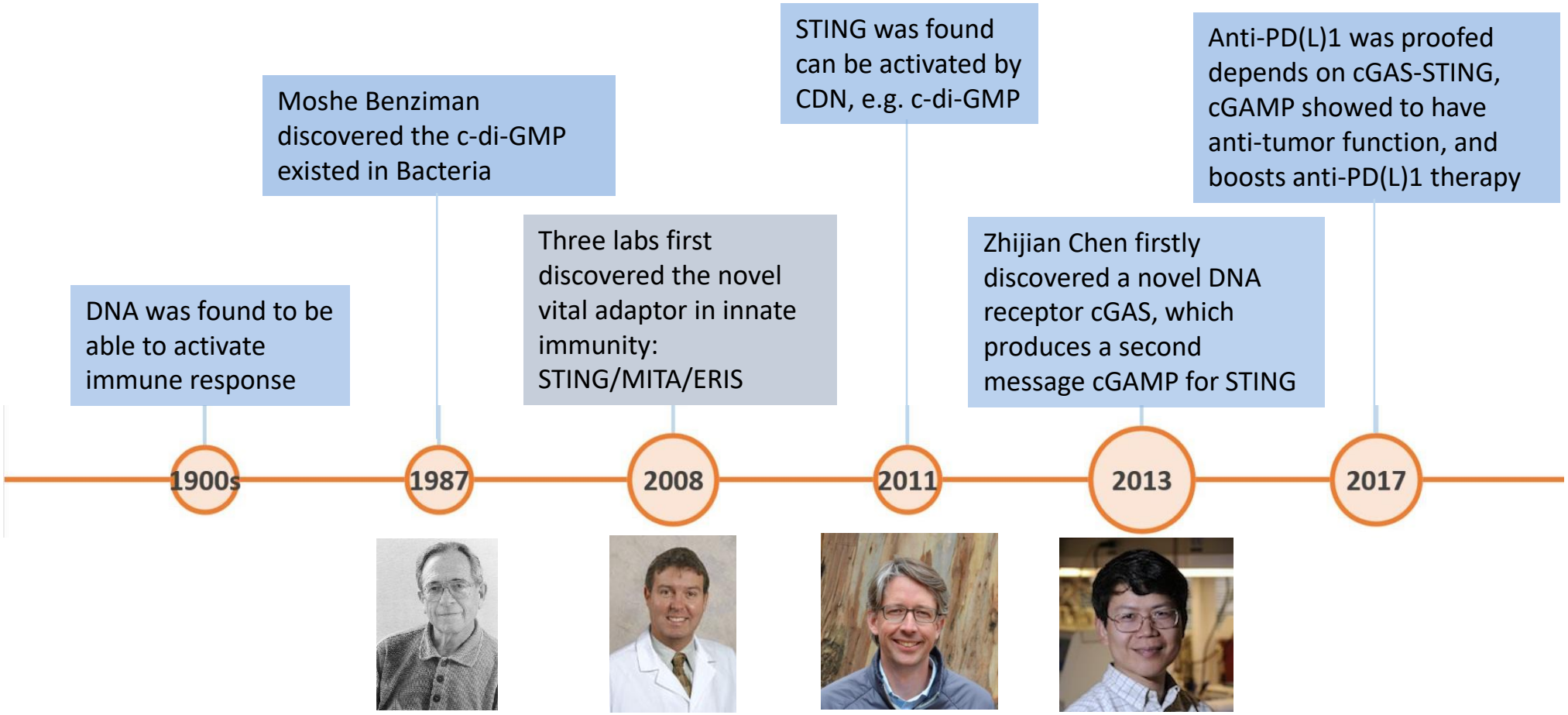
STING Pathway and Cancer Therapy

WuXi AppTec Research Service Division, Oncology & Immunology Unit

2019.09

Outline

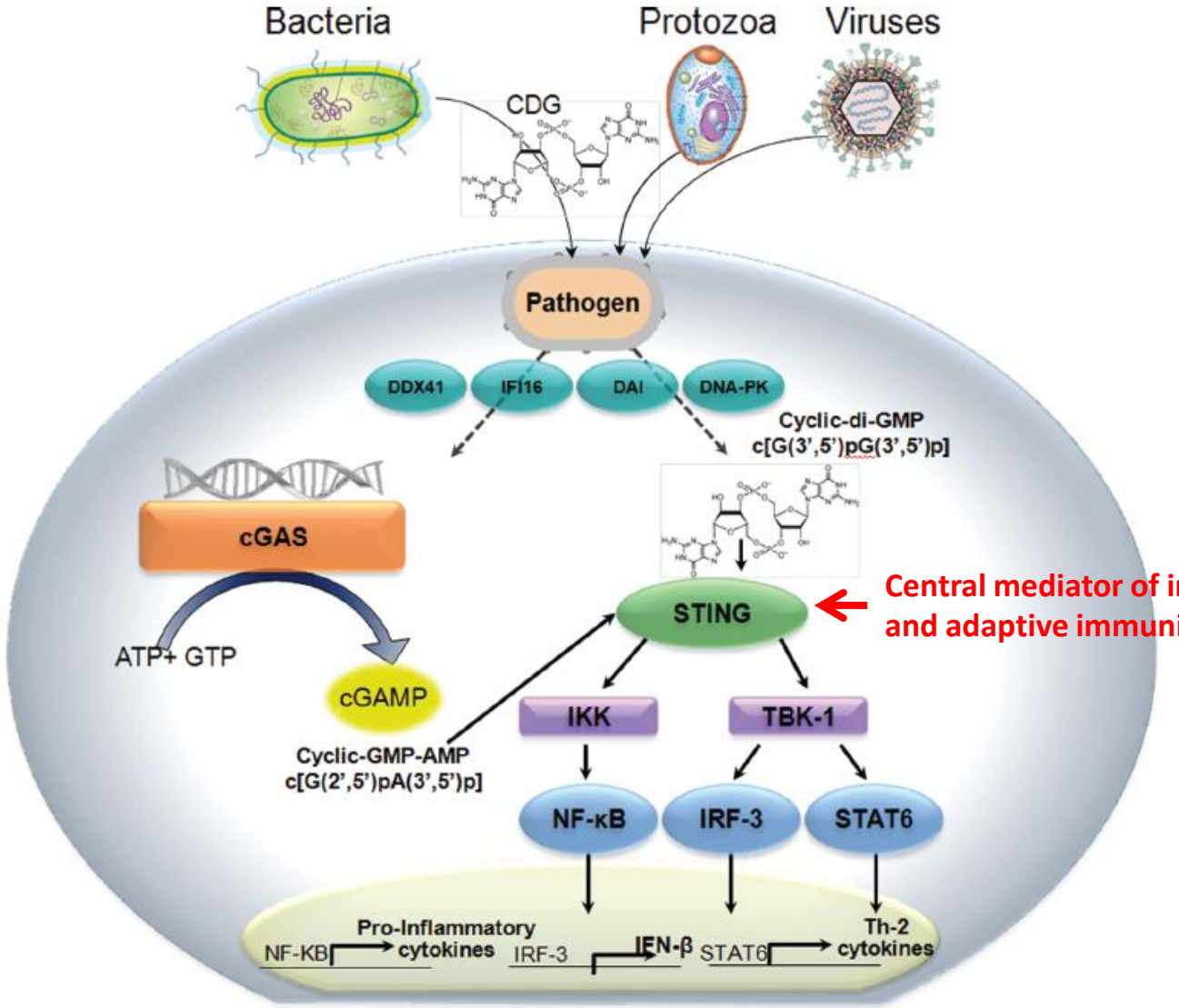
Background: The STING-cGAMP-cGAS chronicle



Background: The STING signaling pathway

- Stimulator of interferon genes (STING) is highly expressed in antigen-presenting cells (APCs), such as macrophages and dendritic cells, as well as plasmacytoid dendritic cells, myeloid-derived suppressor cells, T-cells, and various endothelial or epithelial subtypes.

- The STING pathway is spontaneously activated by cyclic dinucleotides, a product derived from the intracellular enzyme, cyclic GMP-AMP synthase (cGAS), upon invasion by pathogens and exposure to self-DNA, which leads to the production of type I interferons and pro-inflammatory cytokines.

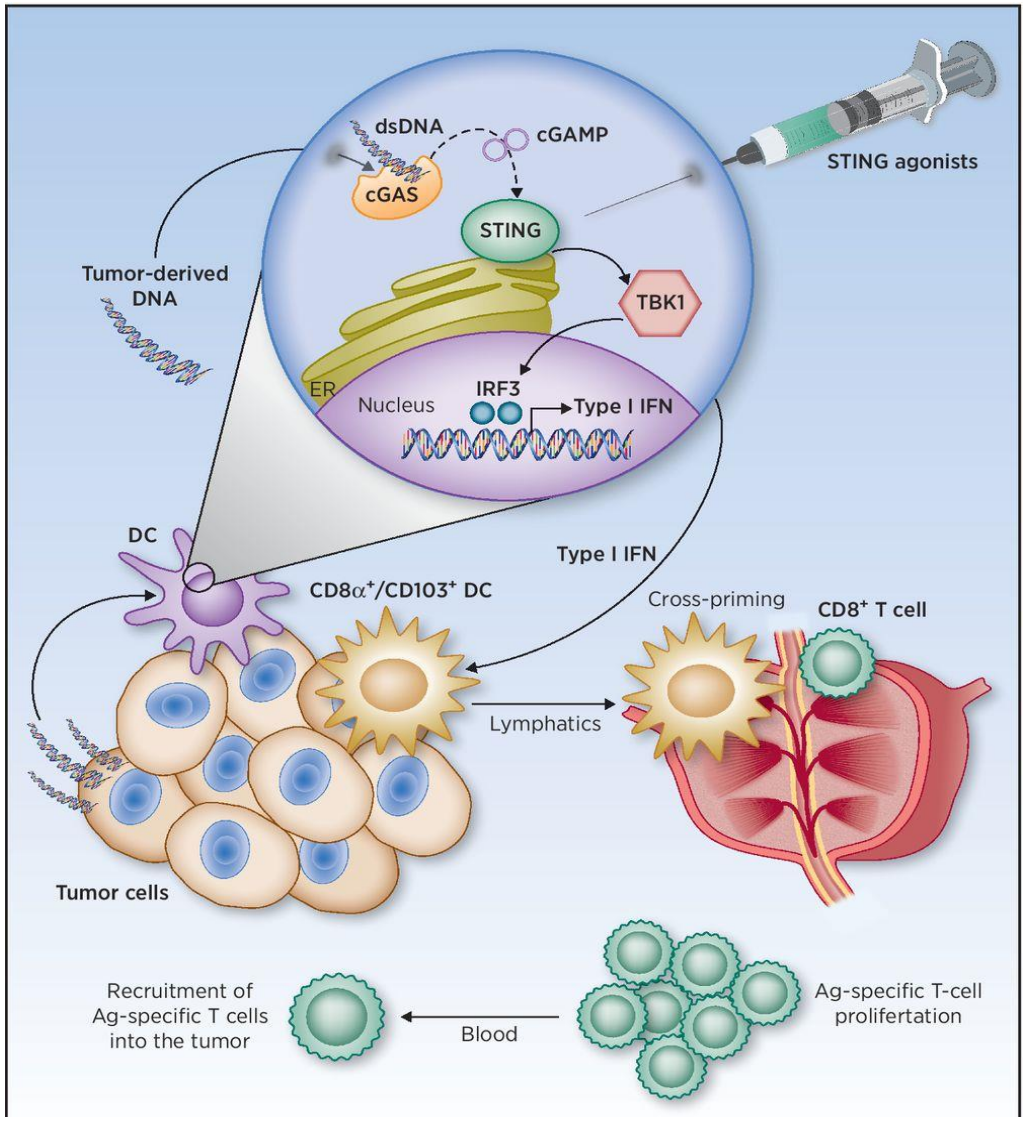


Therapeutic Advances in Vaccines

Background: STING pathway and cancer therapy

- Activation of cGAS-STING signaling pathway can be deliberately stimulated by the use of direct STING agonists, when compounds are therapeutically administrated into the tumor microenvironment.

- *in vivo* studies using gene-targeted mice demonstrated a crucial role of STING-dependent type I IFNs production, and its signaling on BATF3 (basic leucine zipper transcription factor ATF-3) lineage of DCs for spontaneous antitumor T-cell responses *in vivo* and recruitment of effector T cells into the tumor microenvironment.



Leticia, C., et al. (2015). AACR

Background: The current industrial pipelines on STING agonists

Clinical stage

NOVARTIS

ADURO BIOTECH

spring bank pharmaceuticals

Bristol-Myers Squibb

MERCK

IFM THERAPEUTICS

preclinical stage

CURADEV Let science do the talking

MaVu PHARMA

abbvie

VENN THERAPEUTICS

synlogic

VYRIAD

Takeda

Drug discovery stage

NIMBUS THERAPEUTICS

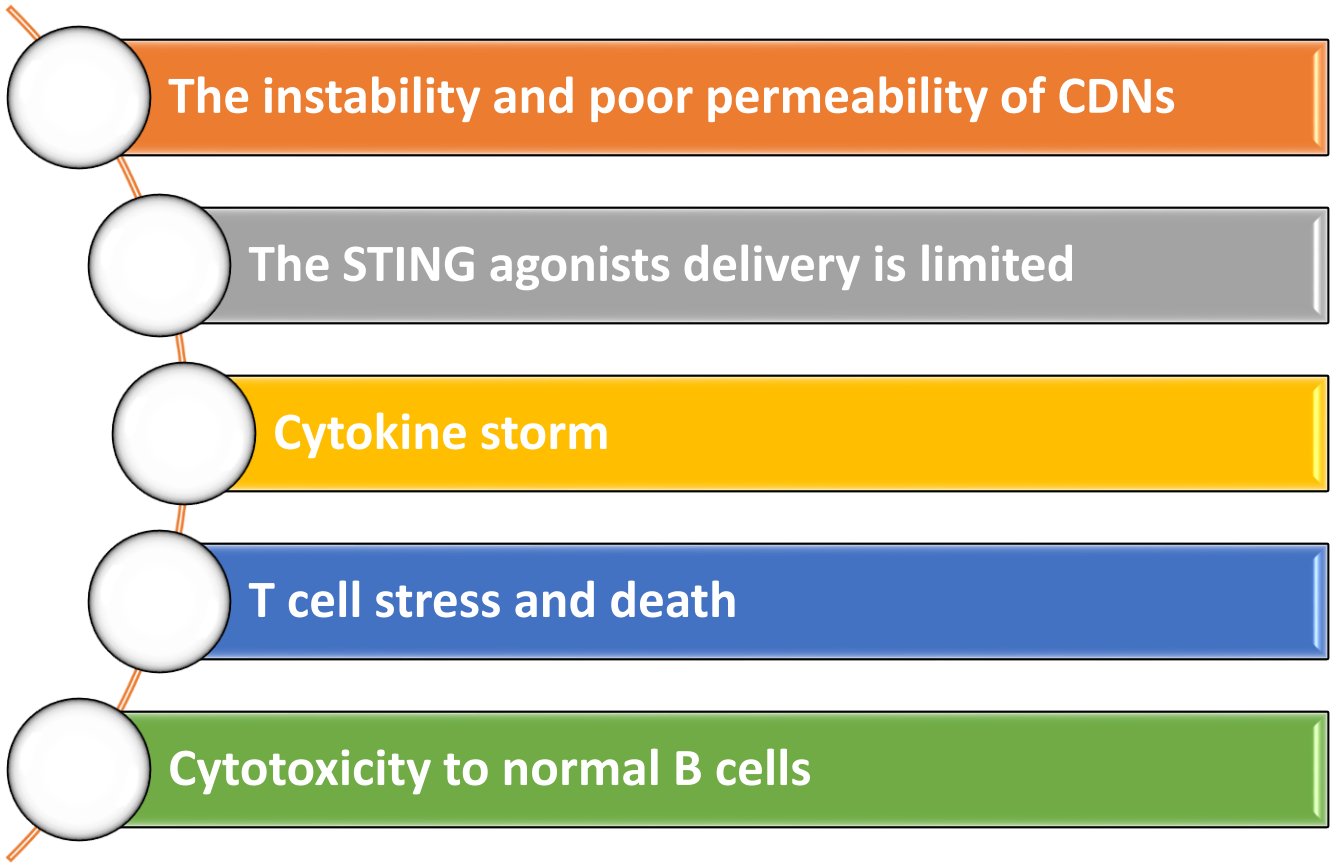
SIRENAS MARINE DISCOVERY

iTeos Therapeutics

Celgene

Cited from Evaluated Pharma database

Background: The limitations and challenges of the STING agonists based therapies



Phosphodiester linkage
Easily digested by RNAase

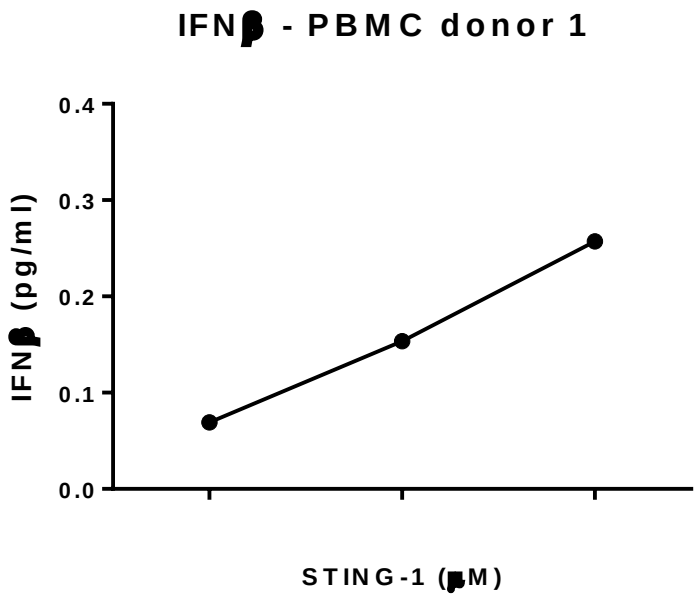
Background: The current strategies to overcome the limitations of the first generation of STING agonists (CDNs)

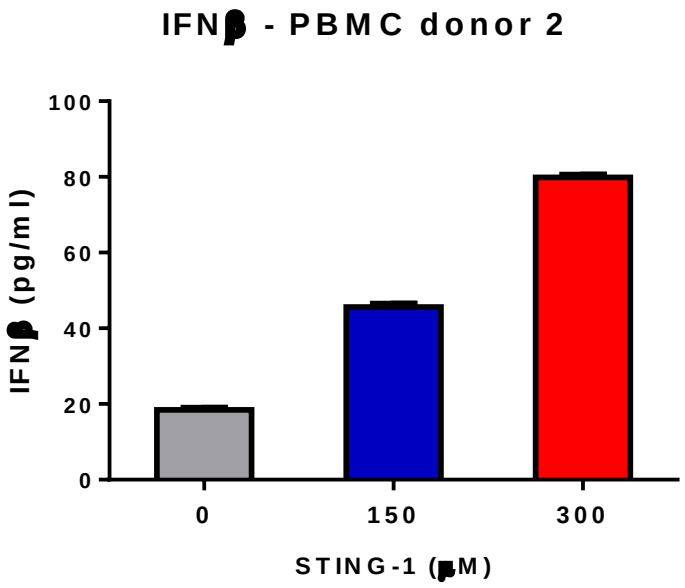
Different formulation of the first generationof STING agonists (CDNs)	• Formulated cancer vaccines: STINGVAX, CT26, SCCFVⅡ, Panc02 Aduro Biotech • Nanostructures+SB11285 Spring Bank, iTeos therapeutics • ADC (Antibody drug conjugated): CRD5500 conjugated with Trastuzumab Curadev SB11285 Spring Bank
The second generation of STING agonists: Non-CDN structure	• GSK: comp3 i.v • Curadev: CRD5500, licensed to Takeda, i.v., s.c.
The STING pathway enhancer	• Mavupharma: MAVU-104 is a first-in-class, orally active, small molecule inhibitor of ENPP1, a phosphodiesterase that negatively regulates the STING (Stimulator of Interferon Genes) pathway.
Injection of viruses/bacteria to produce endogenous c-di-A/GMP	• IT Injection of engineered E. coli specifically engulfed by APCs, SYNB 1891 Synlogic • IT Injection of adenovirus: Venn Therapeutics

In vitro cellular functional STING pathway assay

STING agonist stimulation in PBMC

STING pathway activation readout: the production of IFNβ



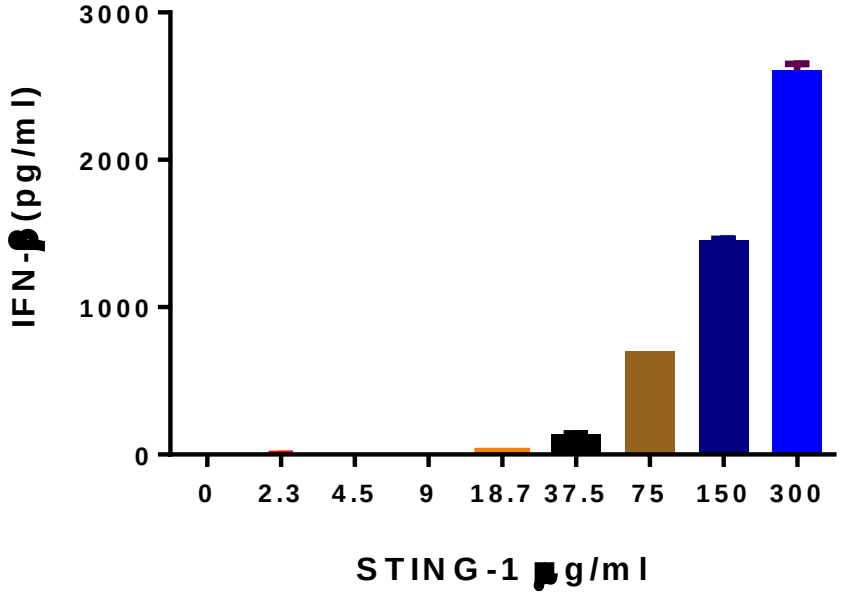


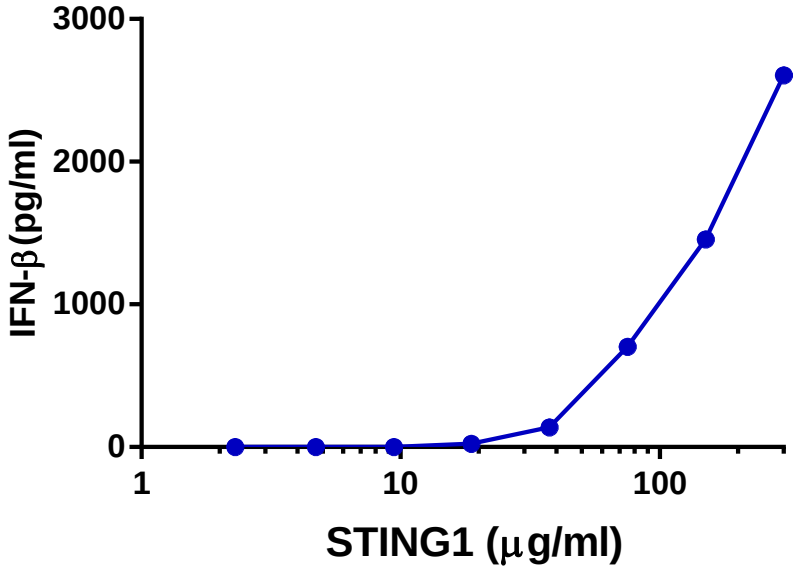
STING activation in fresh human PBMCs in respond to a STING agonist (STING-1)

In vitro cellular functional STING pathway assay

STING agonist stimulation in THP1 cell line

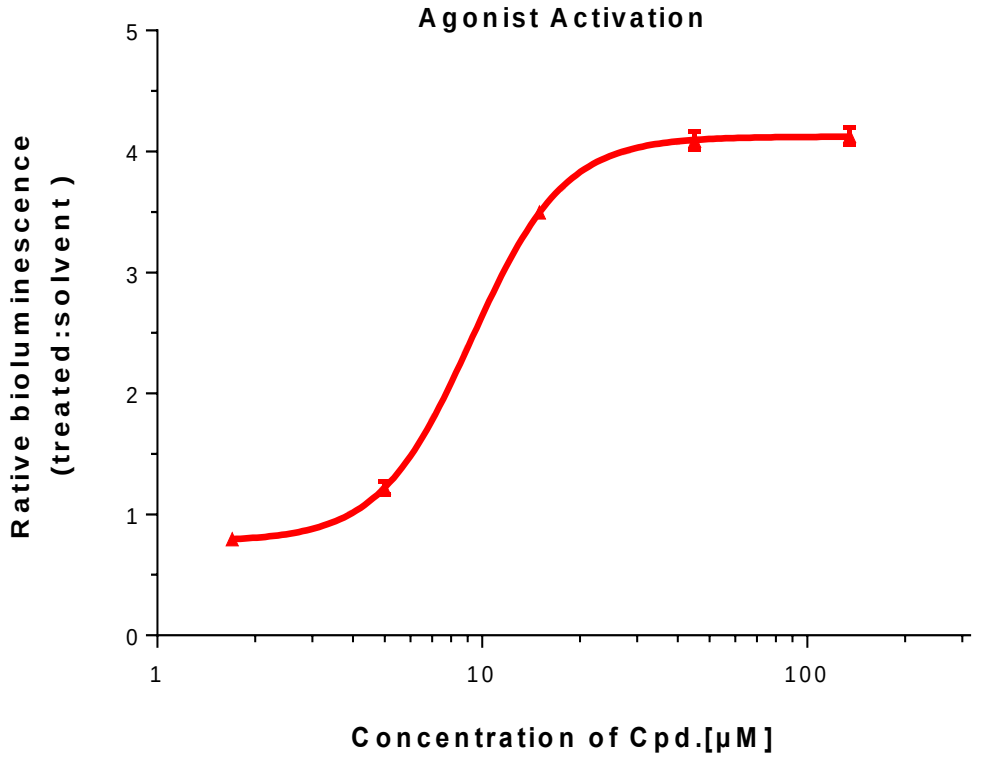
THP-1 (human acute monocytic leukemia)





In vitro cellular functional STING pathway assay

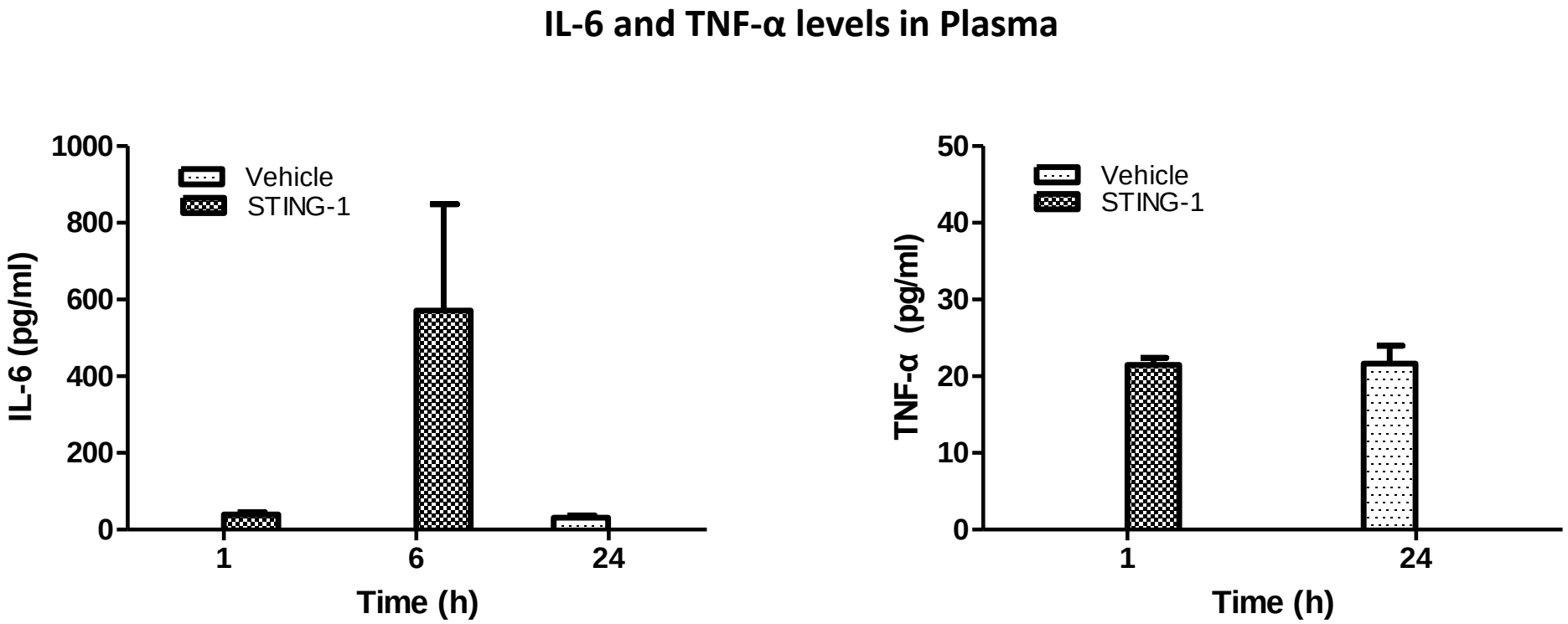
THP1-IFNβ-Luc reporter cell line for STING agonist screening



The reporter cell line was treated with agonist for 18 hours.

Cytokine analysis of B16F10 model post STING-1 treatment (*in vivo*)

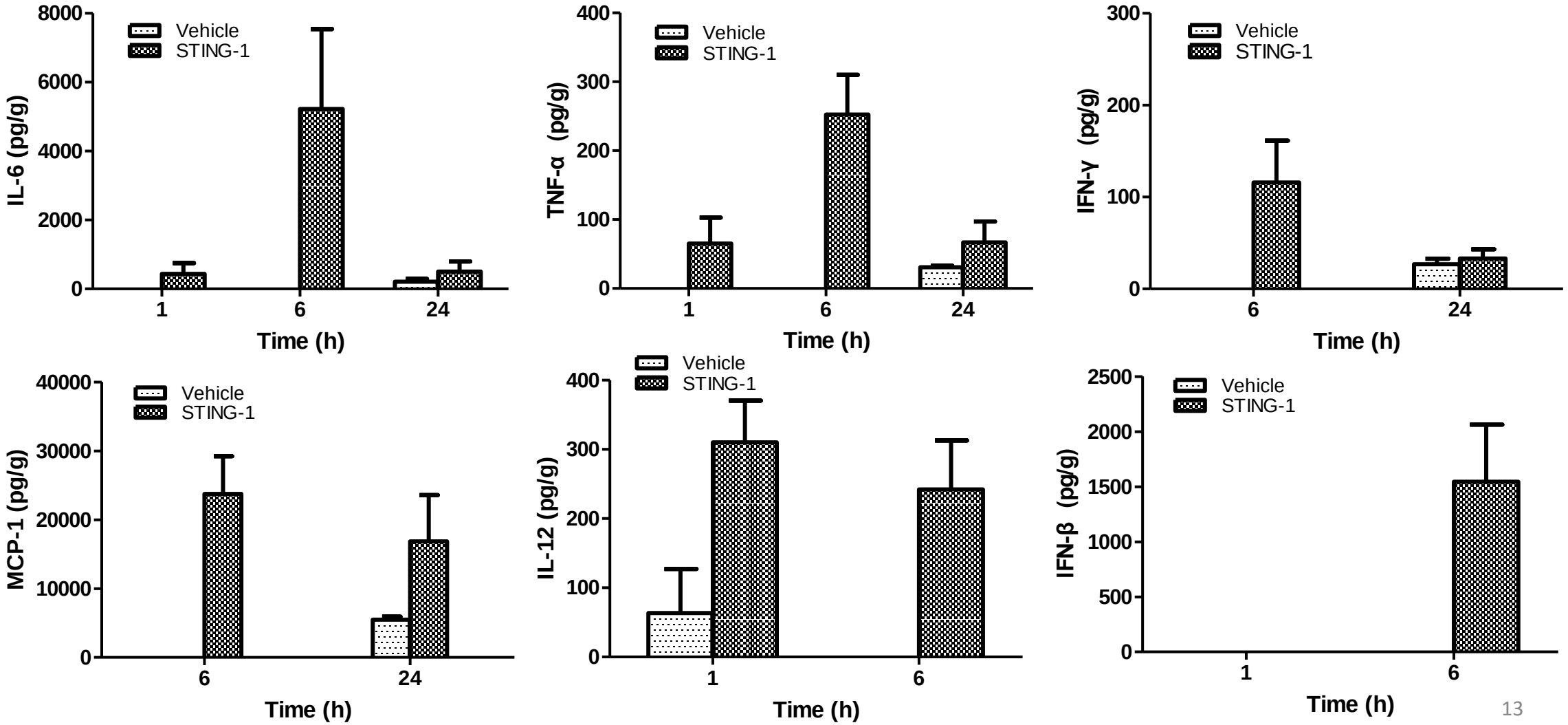
CBA analysis



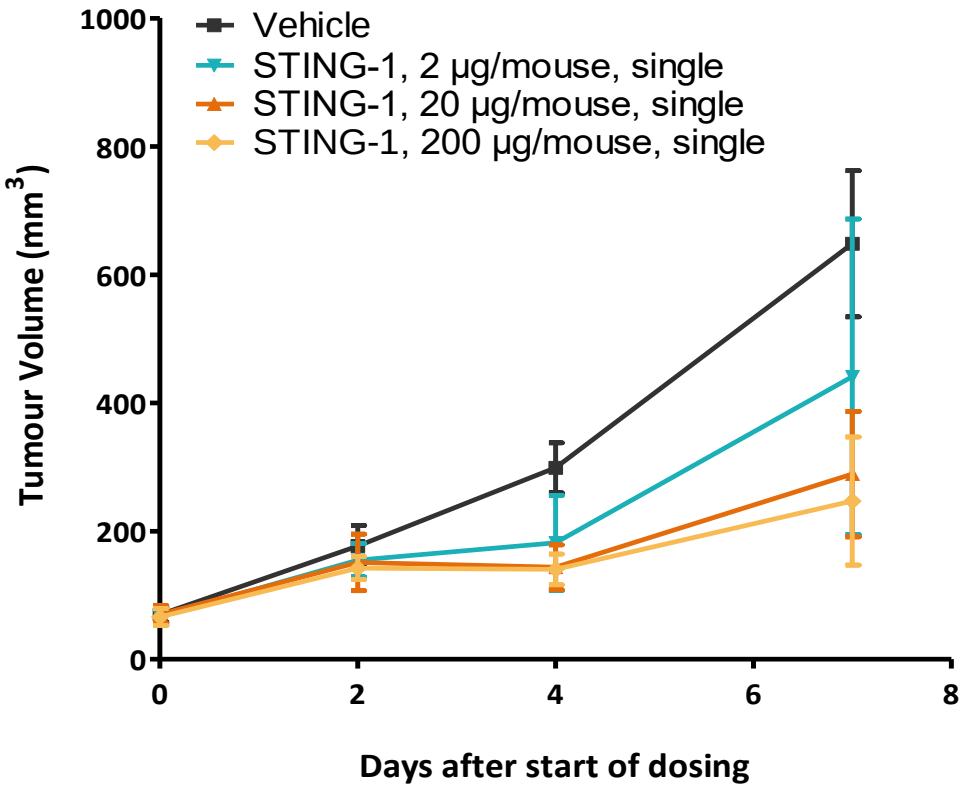
Cytokine analysis of B16F10 model post STING-1 treatment (*in vivo*)

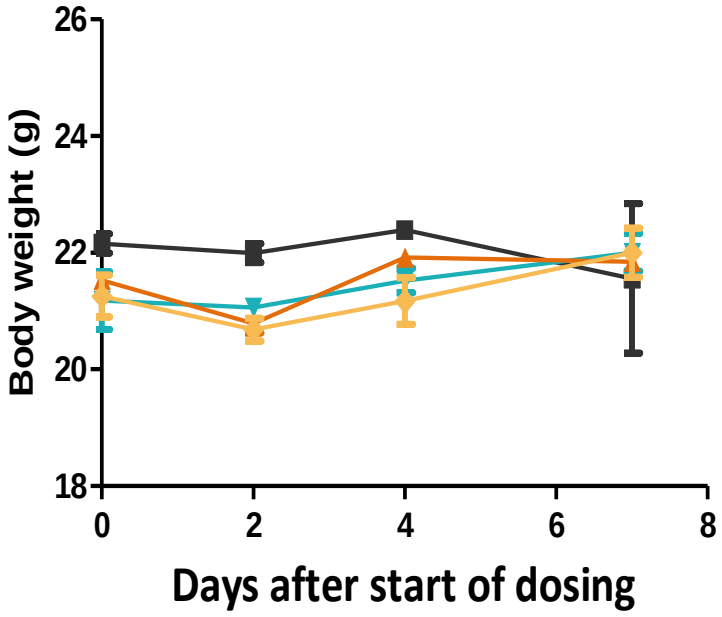
CBA analysis

IL-6, TNF-α, IFN-γ, MCP-1, IL-12 and IFN-β levels in Tumor



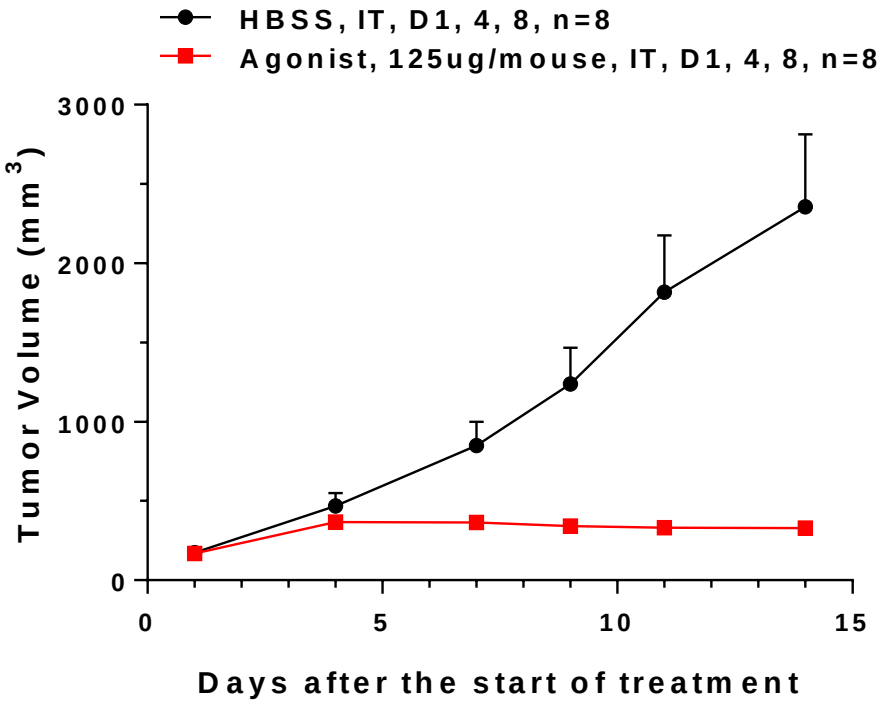
In vivo anti-tumor efficacy study of STING-1 in B16F10 model



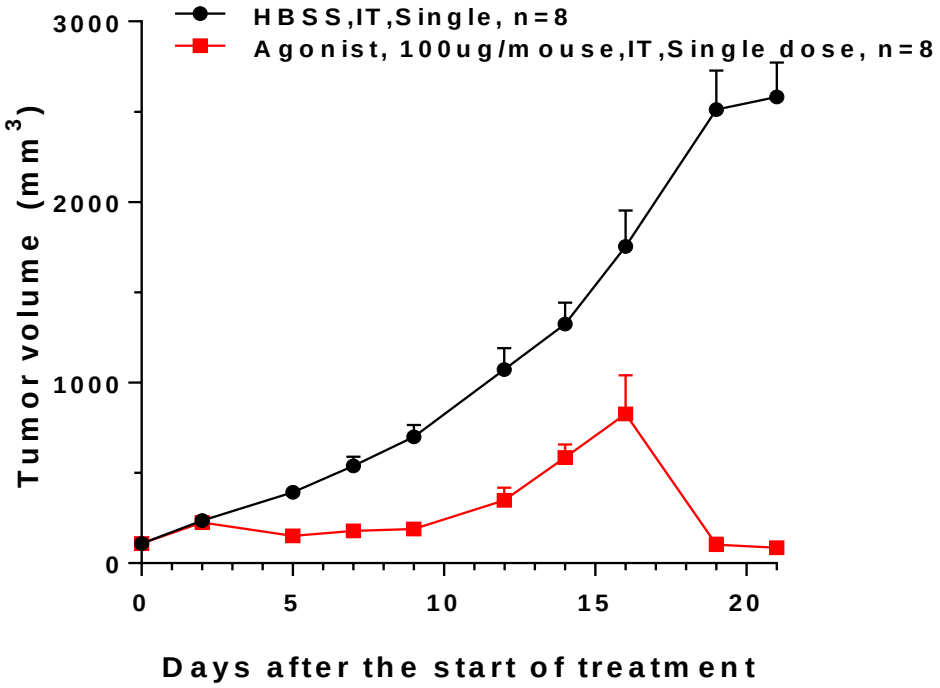


In vivo anti-tumor efficacy study of STING-1 in CT26/4T1 model

CT-26



4T1



Immune cell analysis in B16F10 model post STING-1 treatment

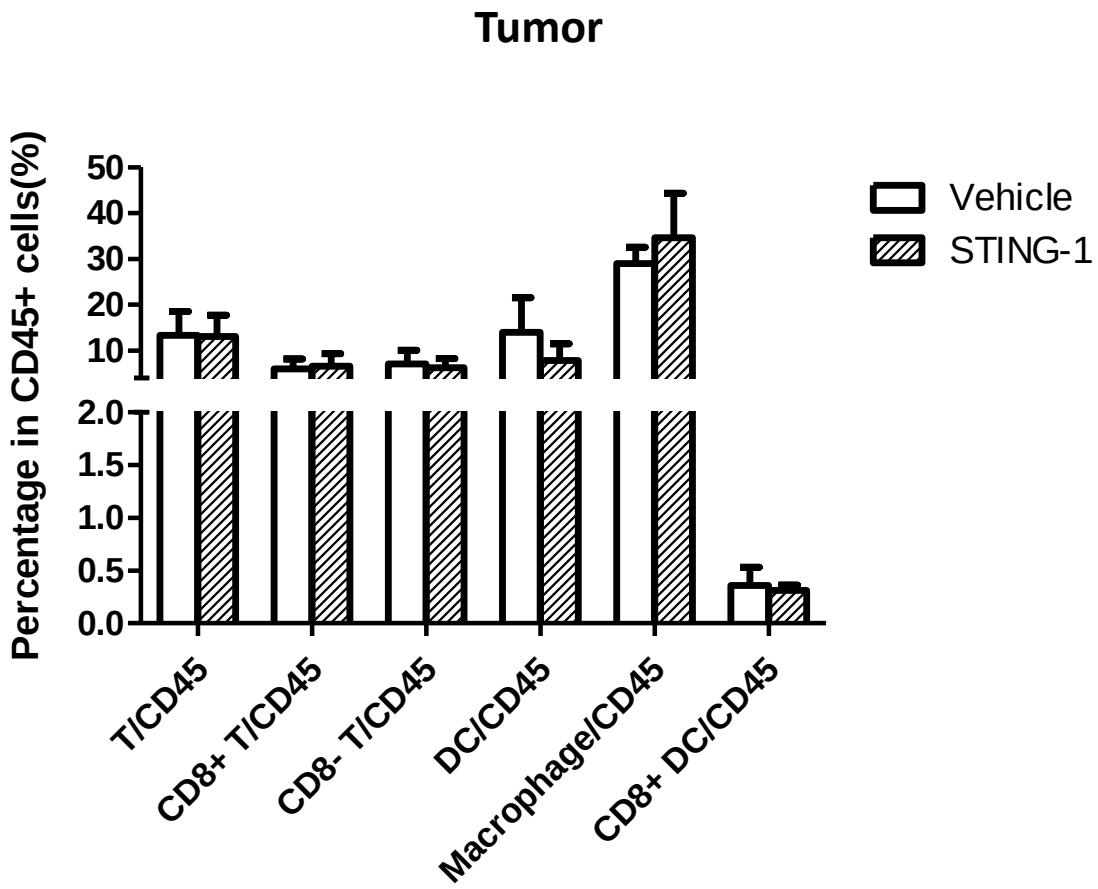
TIL analysis were carried out in B16F10 Melanoma tumors

Model	Cancer Type	Mouse
B16F10	Melanoma	C57BL/6

Panel Design for TIL Analysis:

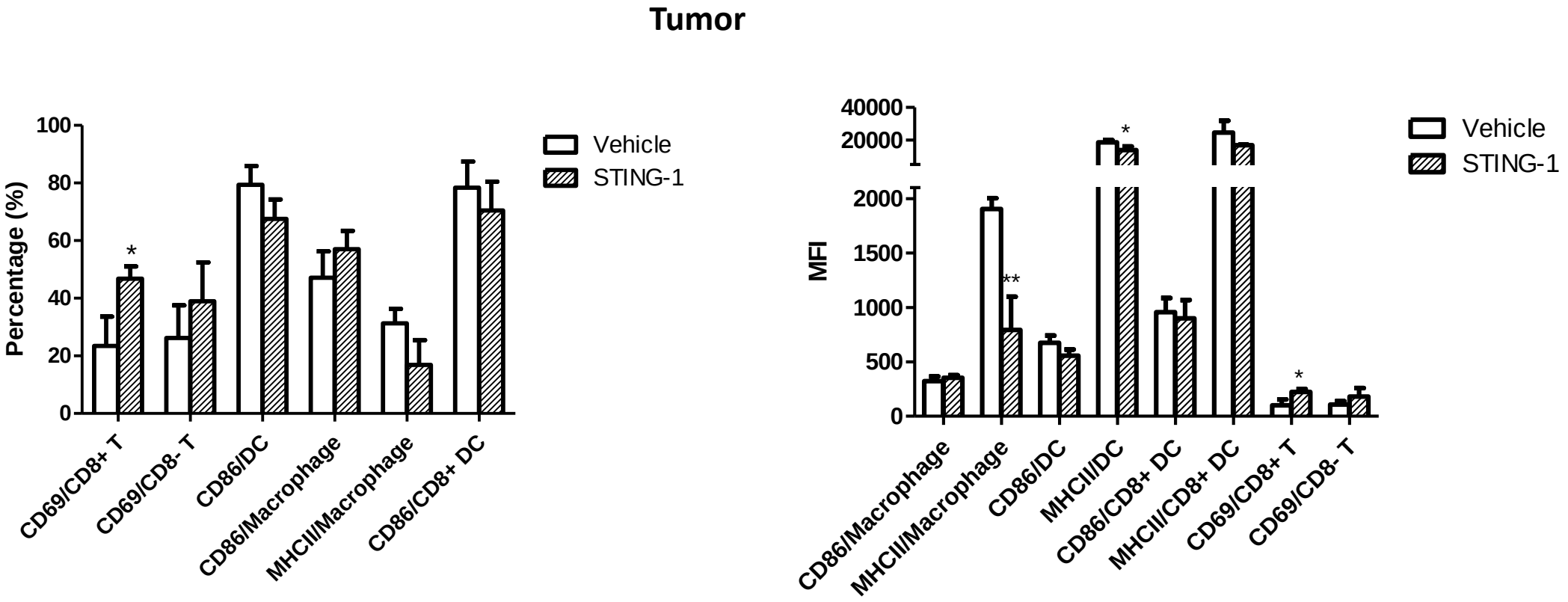
Channel	Fluorescein	Panel 1(Tumor and Spleen)	Panel 2(Blood)
FITC	FITC	F4/80	-
PE	PE	CD69	-
PerCP	PerCP-Cy5.5	CD11c	CD19
APC	APC	CD8	-
APC-R700	AF700	CD45	CD45
APC-Cy7	APC-Cy7	CD3	CD3
V450	BV421	Live/dead	Live/Dead
V500	BV510	CD86	-
BV605	BV605	MHCII	-

Murine Tumor-Infiltrating Leukocytes (TIL) composition in response to STING-1



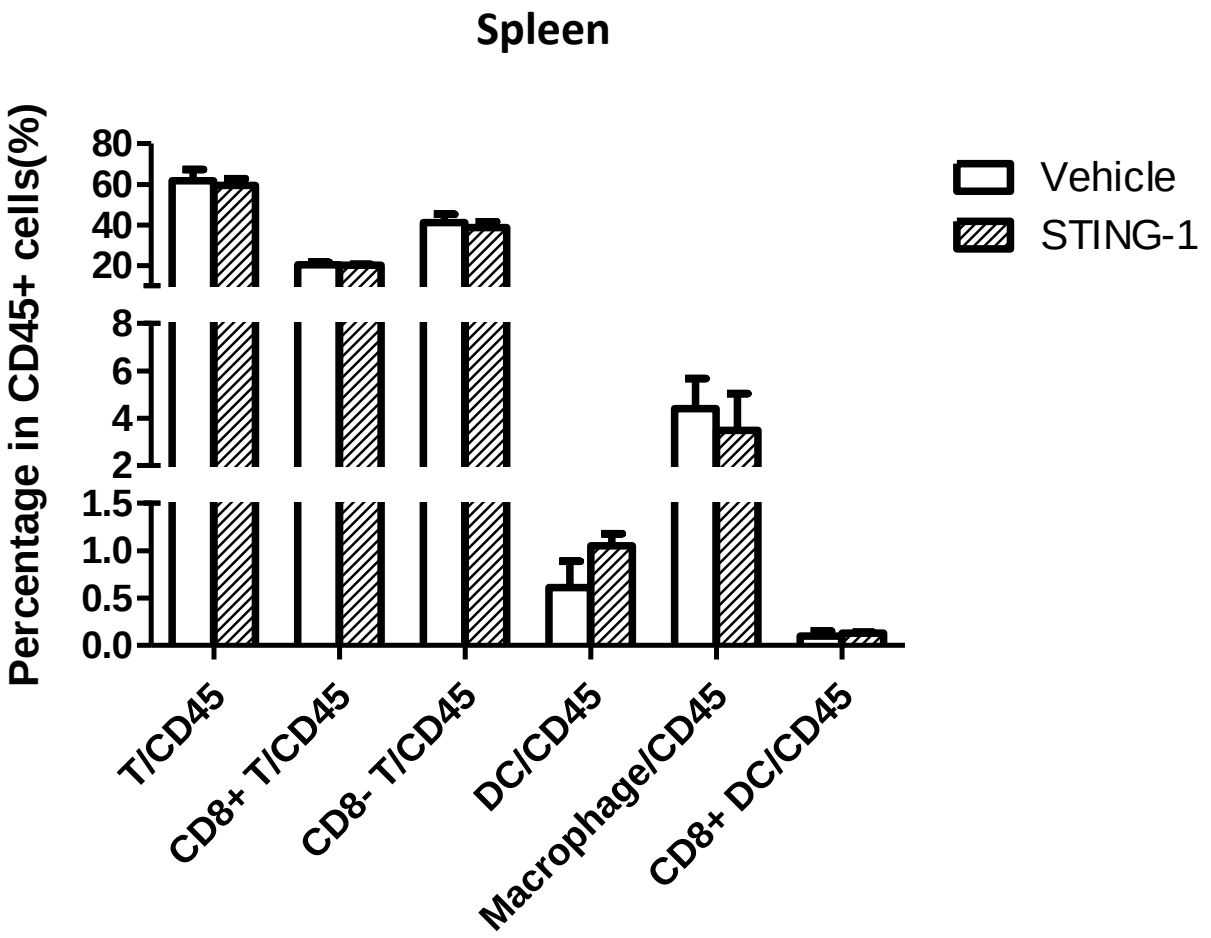
Immune cell activation markers in TILs in respond to STING-1

Expression of CD69, MHCII and CD86

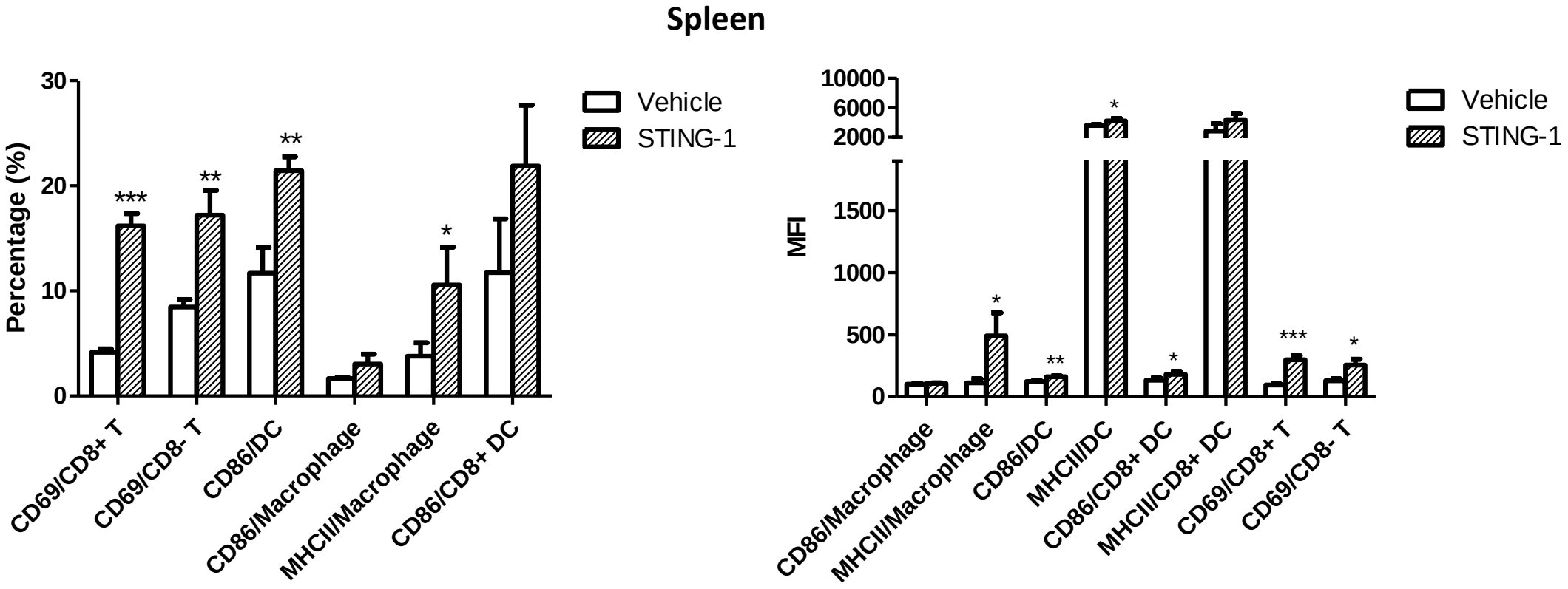


- In STING-1 group, the percentage of CD69 was increased in CD8+ T cells in TILs.
- In STING-1 group, the MFI of CD69 was increased in CD8+ T cells, and the MFI of MHCII was decreased in Macrophage and DC in TILs.

Immune cell subpopulations in spleen in response to STING-1



Immune cell activation markers in T cells, DCs and macrophages in spleen in respond to STING-1



- In STING-1 group, the percentage of CD69 was increased in CD8+ and CD8- T cells, and the percentage of CD86 was increased in DC, meanwhile, the percentage of MHCII was increased in Macrophage in spleen.
- In STING-1 group, the MFI of CD69 was increased in CD8+ and CD8- T cells, and the MFI of CD86 was increased in DC and CD8+ DC, meanwhile, the MFI of MHCII was increased in Macrophage and DC in spleen.

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