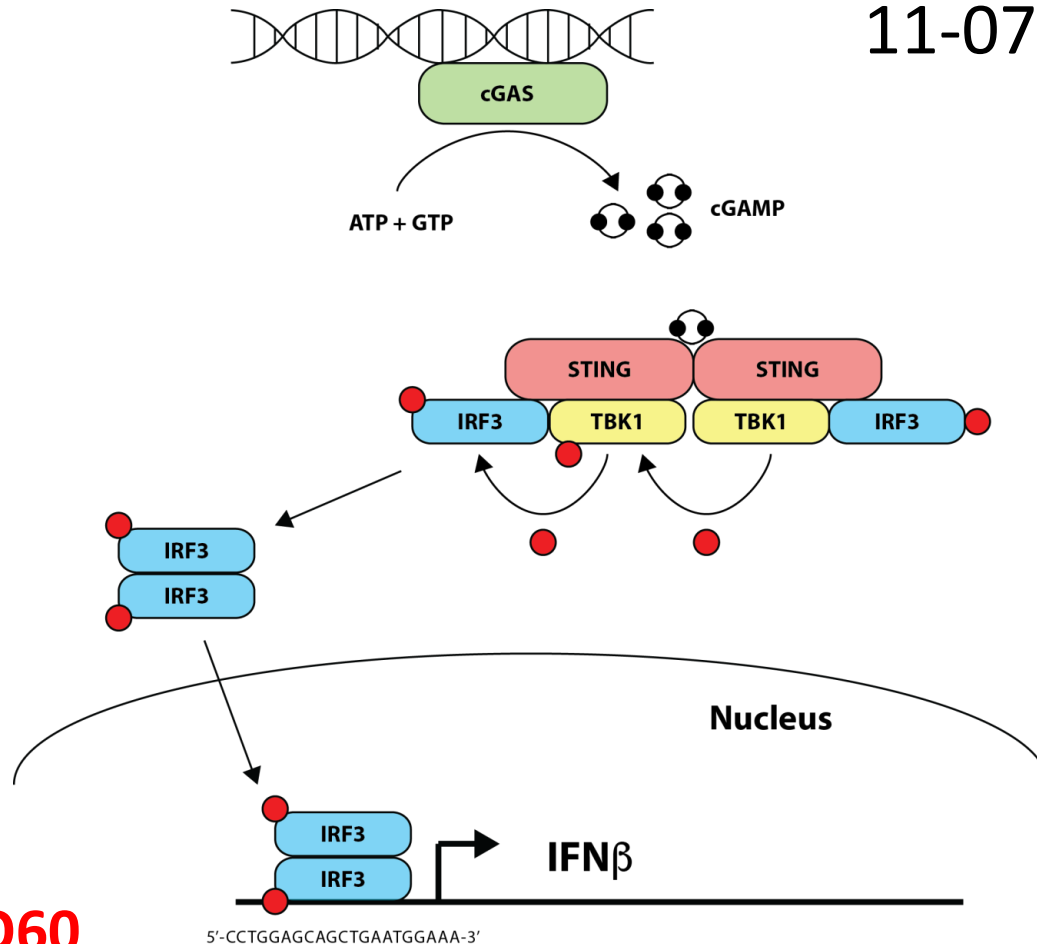


Tumor Cell-Intrinsic Defects in STING Pathway Signaling

11-07-2019



Blake Flood

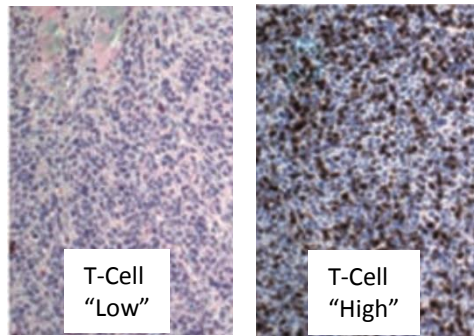
Thomas Gajewski Lab
University of Chicago

Financial Disclosures

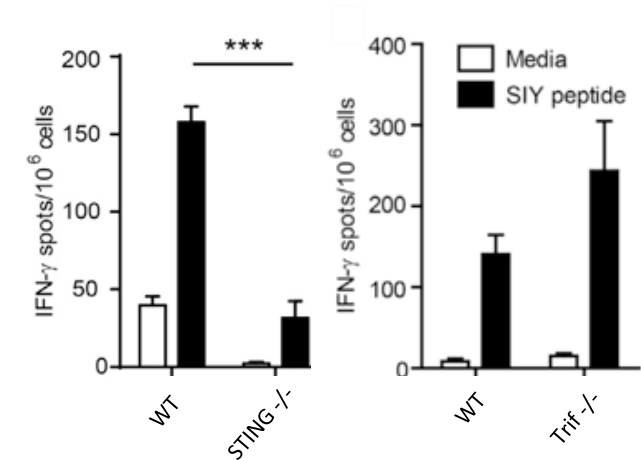
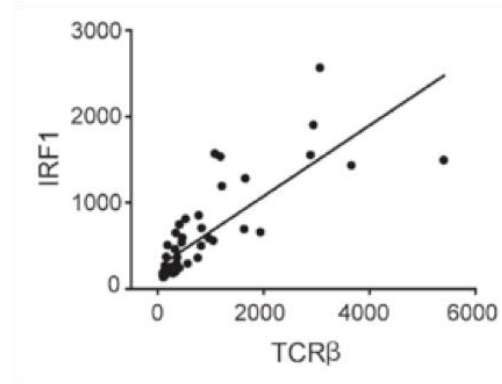
I have nothing to disclose.

STING activation and subsequent type I IFN signaling are essential for optimal priming of anti-tumor T cells

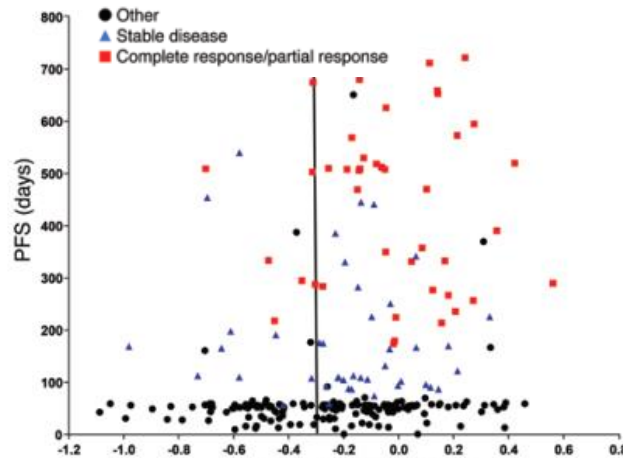
CD8 Staining



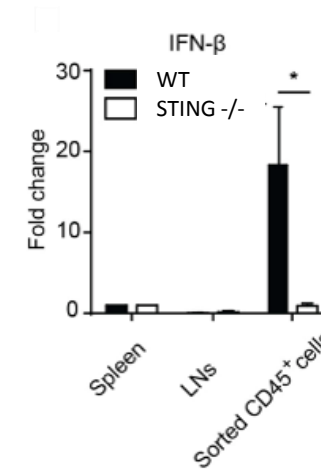
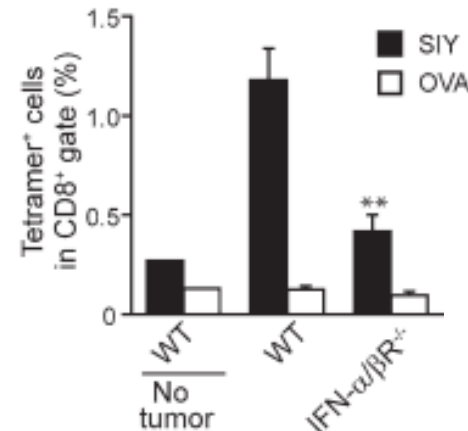
Harlin et al, 2009



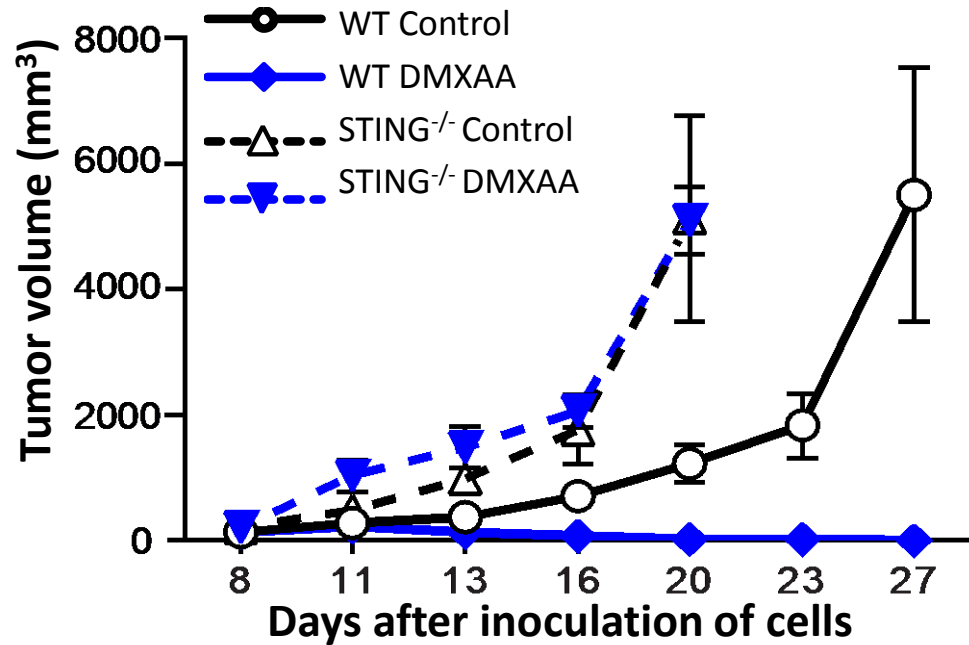
Also: MAVS, TLR4, TLR9, P2RX7



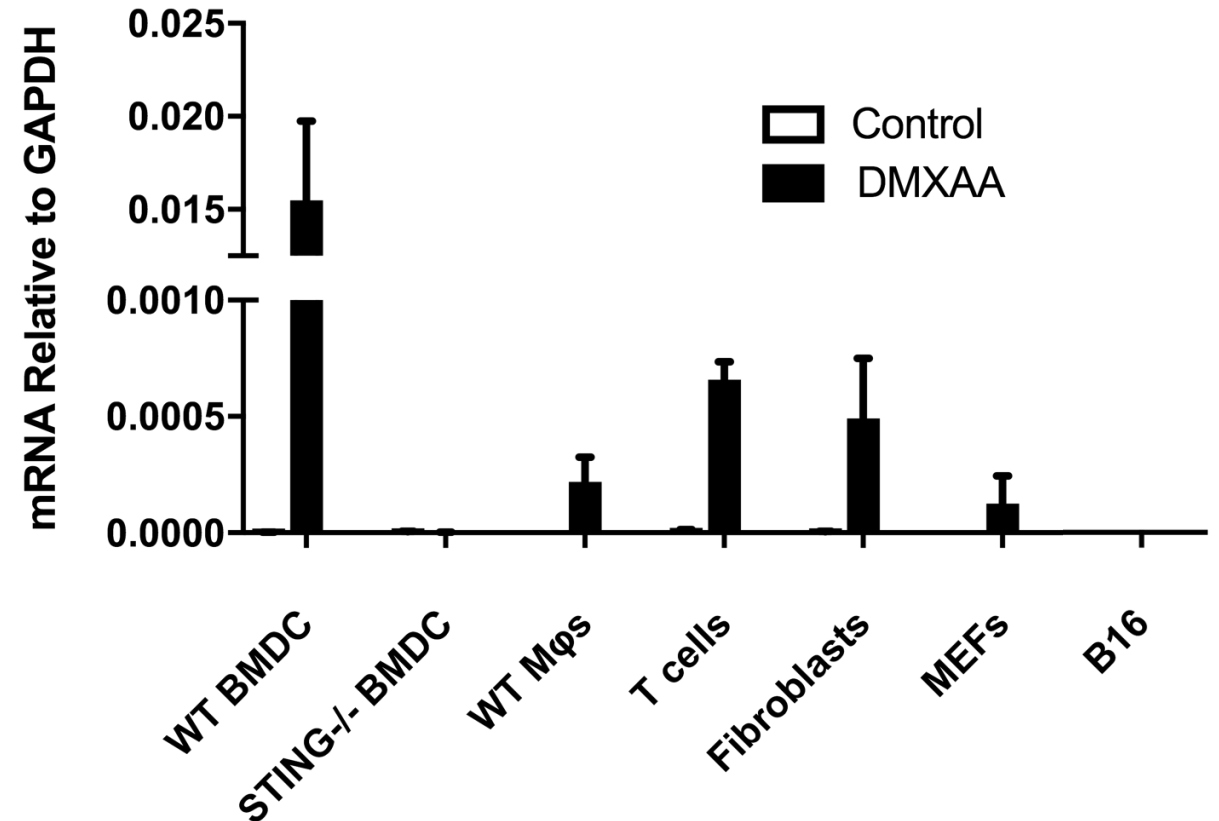
T-Cell Inflamed GEP Score



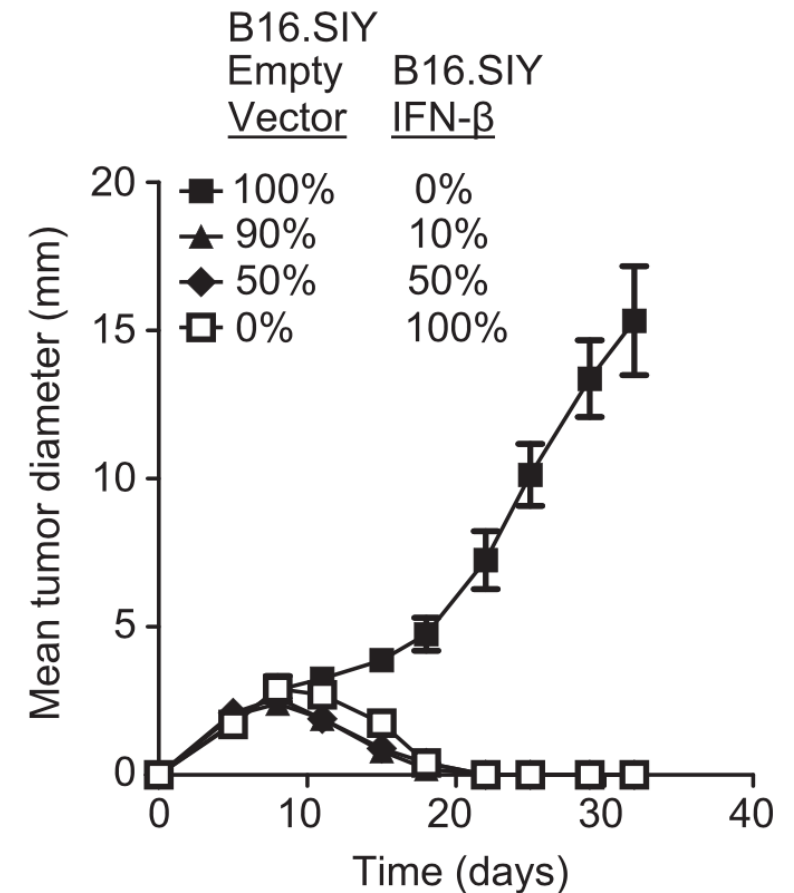
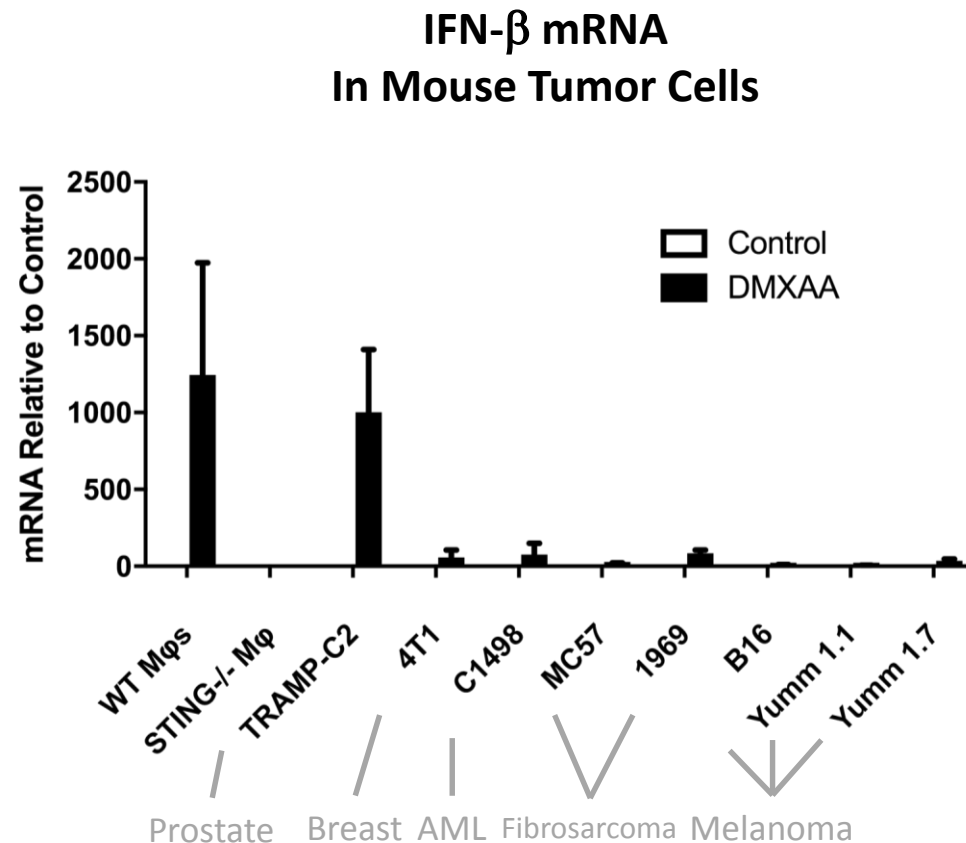
Of the cell types in the TME, only tumor cells failed to make IFN- β following STING agonist injection



IFN- β mRNA expression



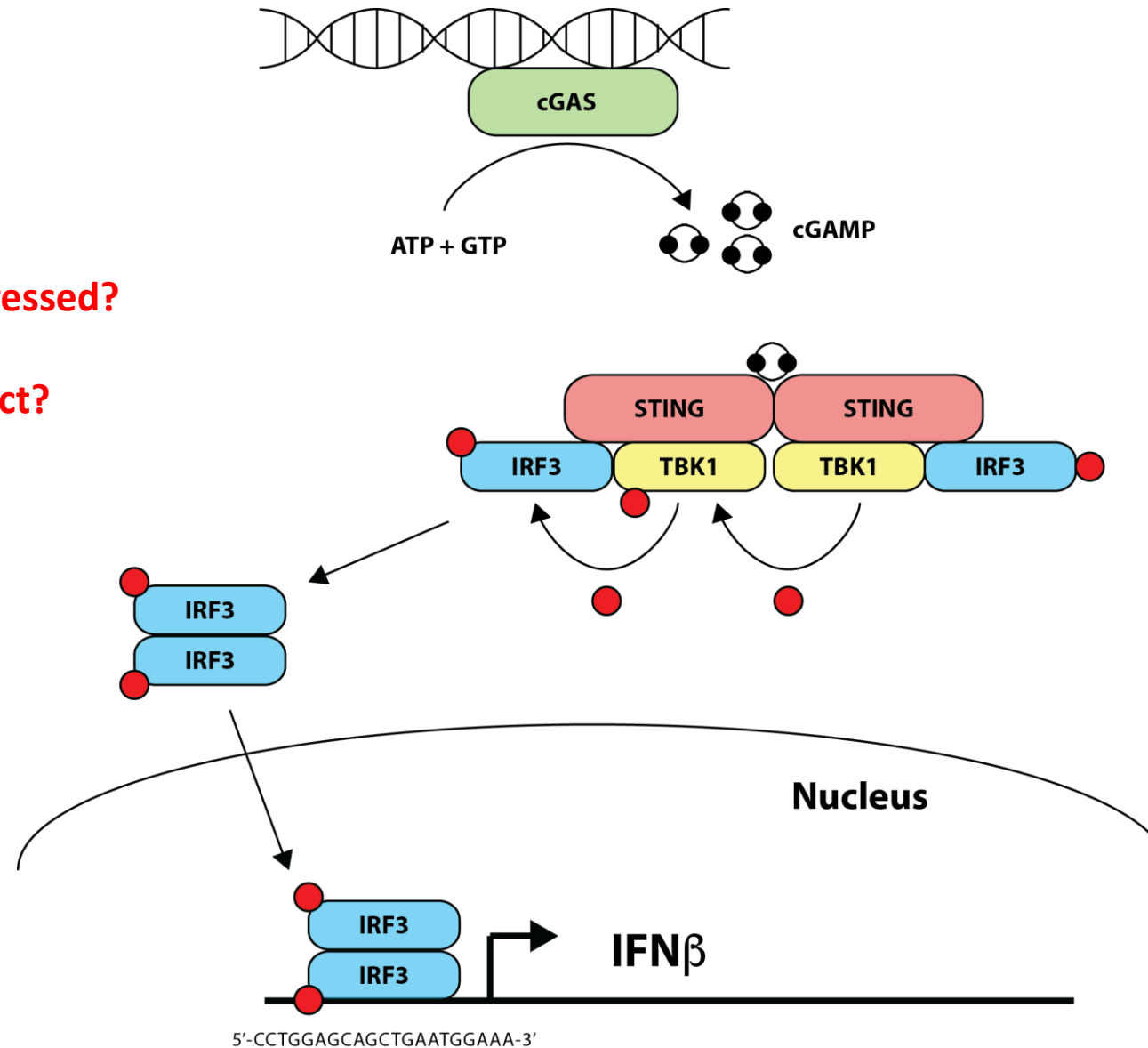
STING pathway activation fails to elicit IFN- β from the vast majority of tumor cells, suggesting selective pressure against STING signaling



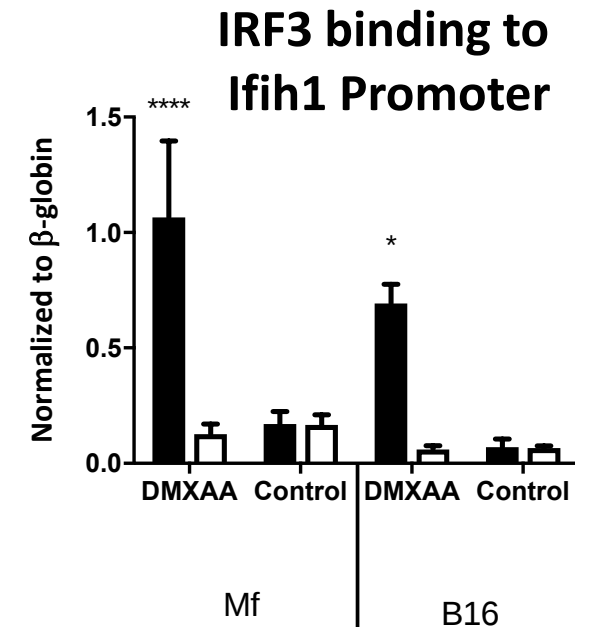
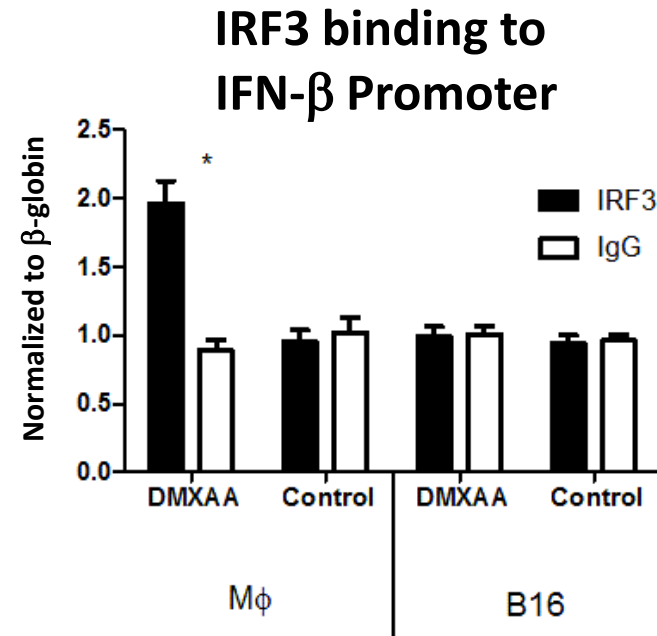
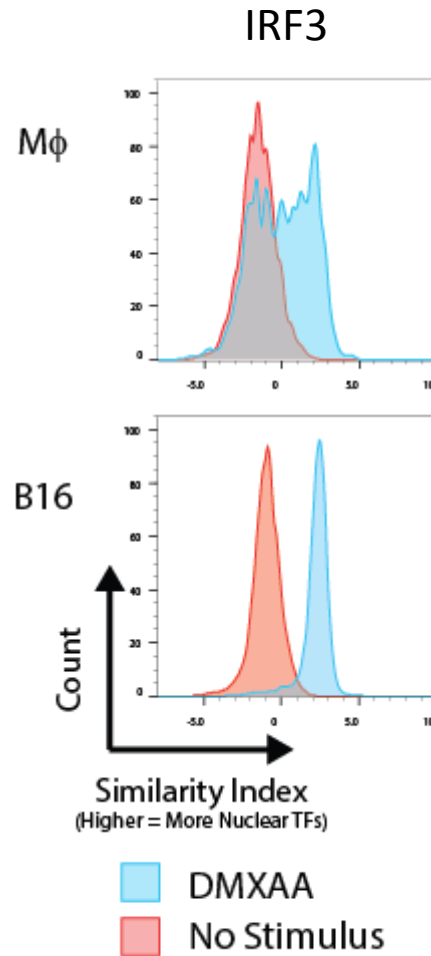
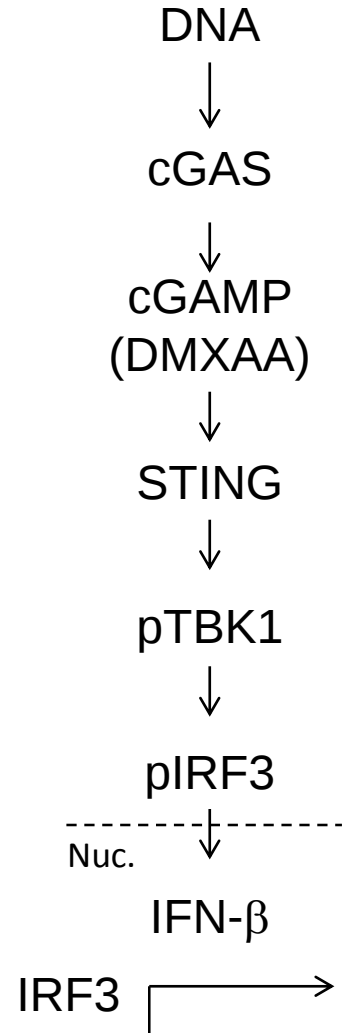
The STING pathway & type I IFN transcription

Pathway expressed?

Signaling intact?

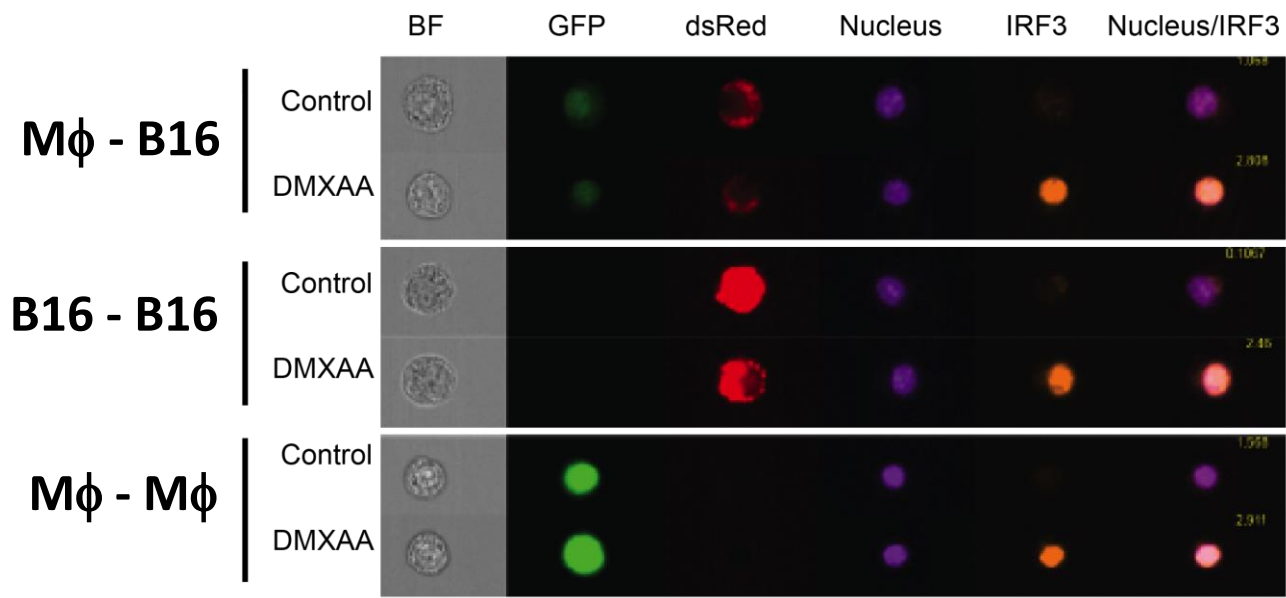
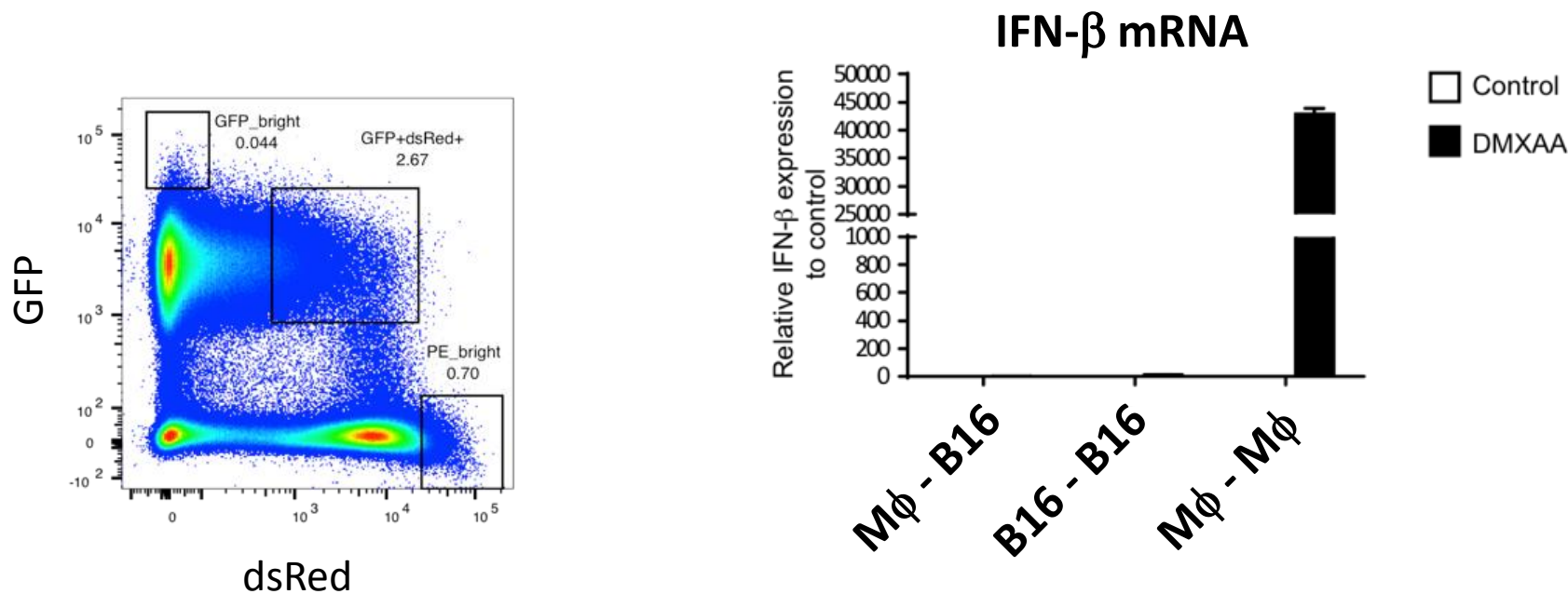


Following STING activation, IRF3 translocates to the nucleus of B16 tumor cells but fails to bind the IFN- β promoter

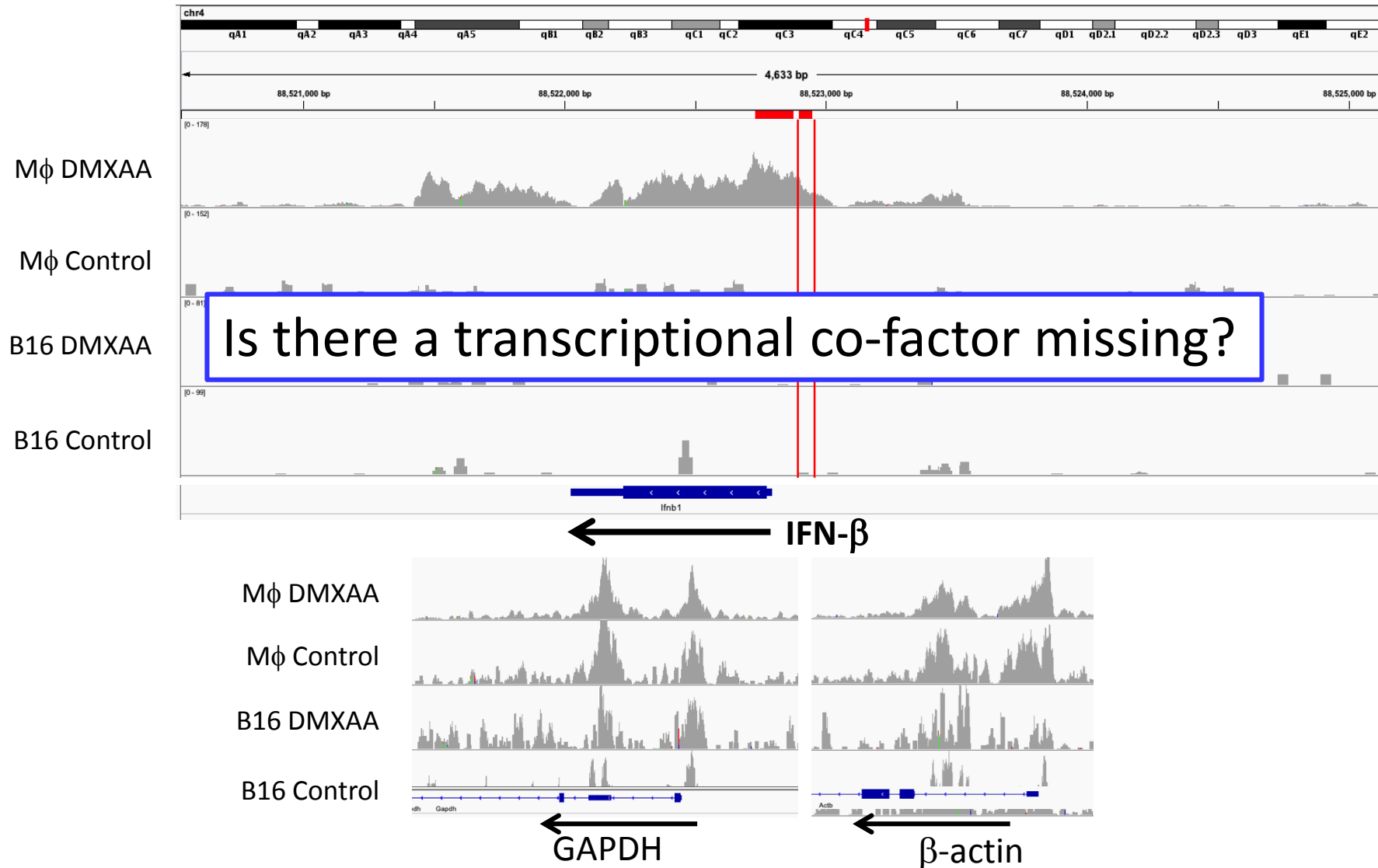


Is this a dominant or recessive phenotype?

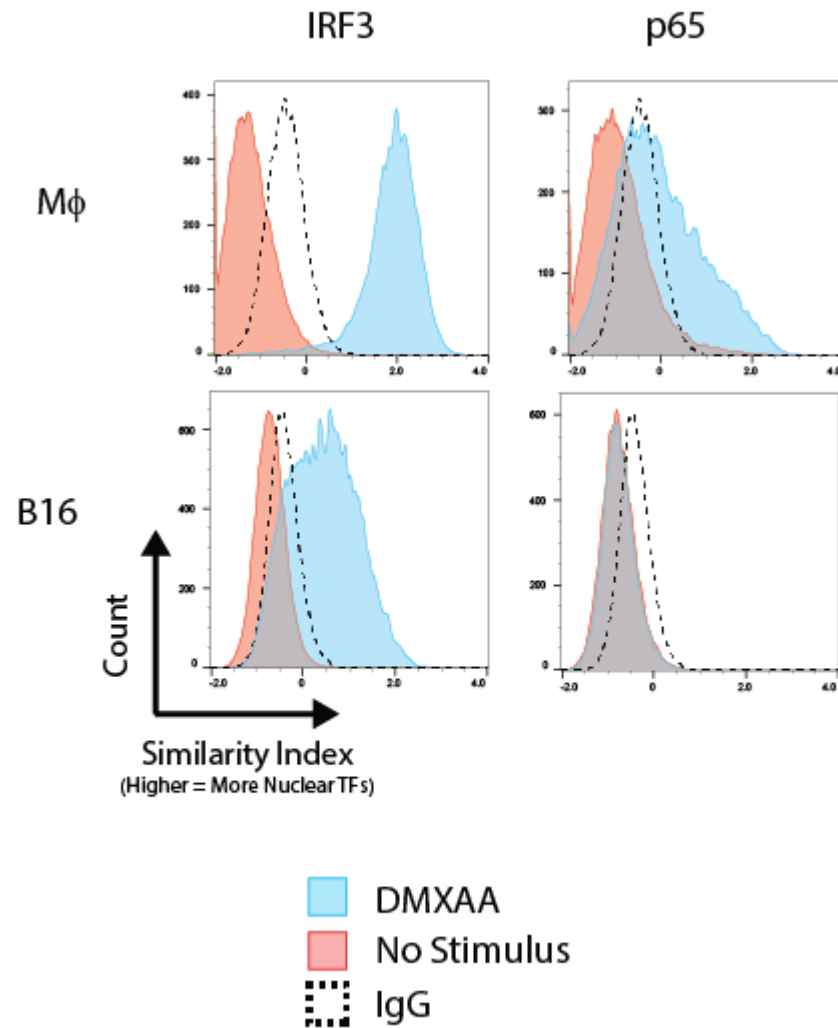
DMXAA stimulation fails to elicit IFN-β From B16 – Mφ hybrids



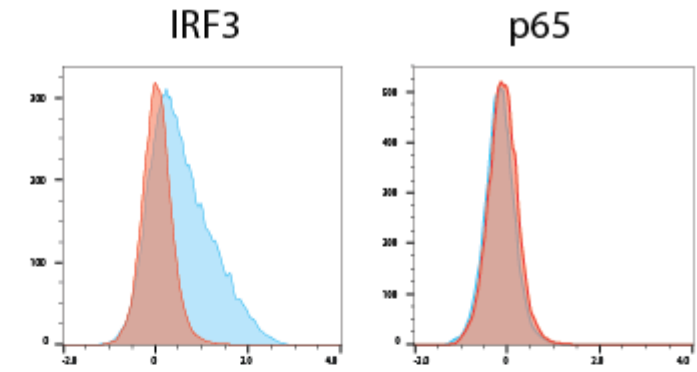
The IFN- β locus is largely inaccessible at baseline but opens up following STING activation in M ϕ but not B16 tumor cells



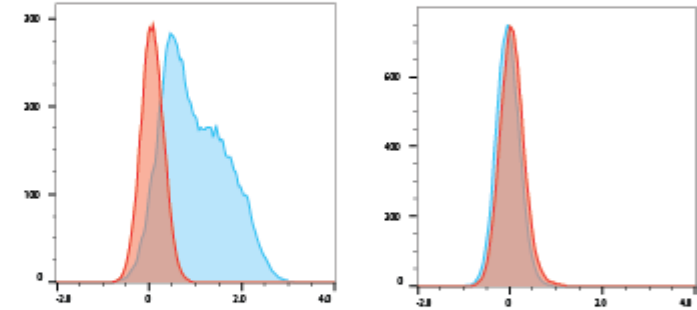
B16-macrophage hybrid cells fail to activate NF- κ B p65 after STING activation, indicating a dominant negative phenotype



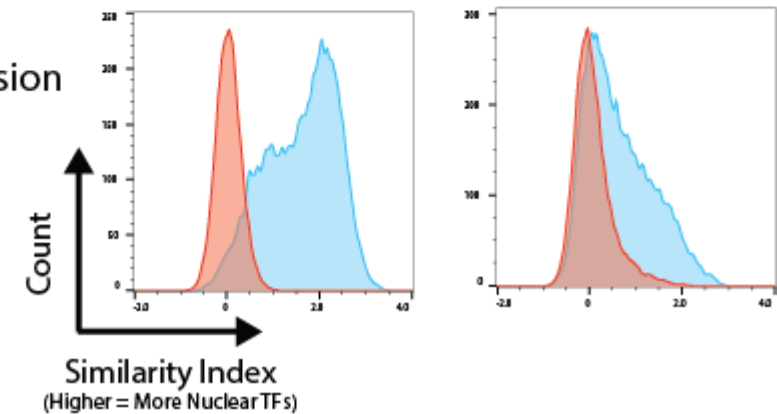
B16-B16 Fusion



B16- M ϕ Fusion

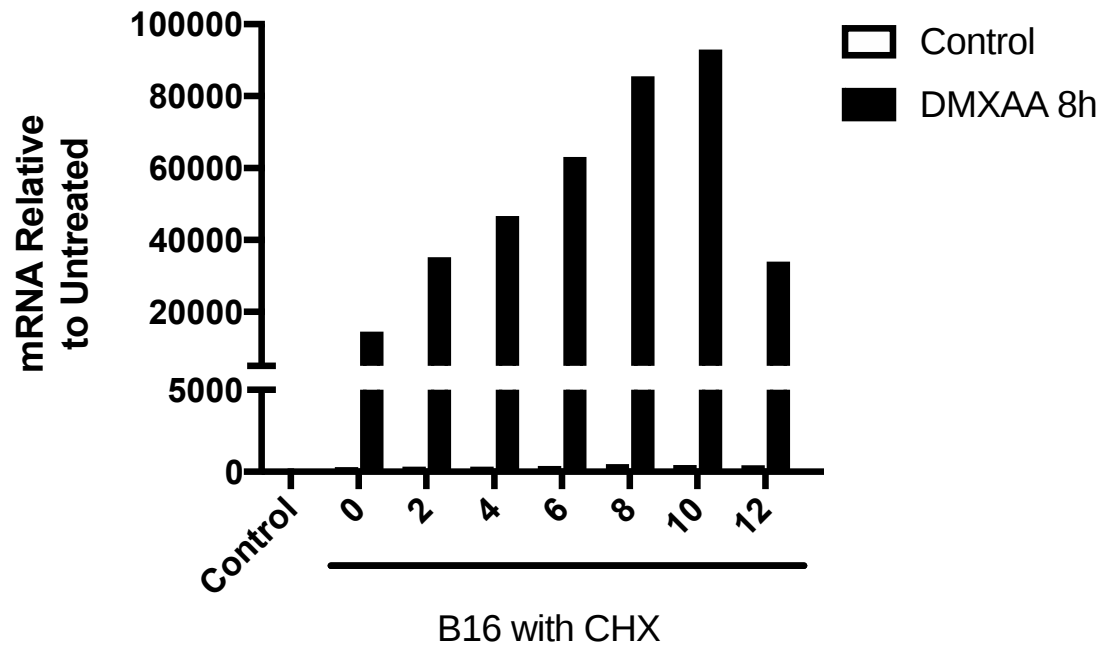


M ϕ -M ϕ Fusion

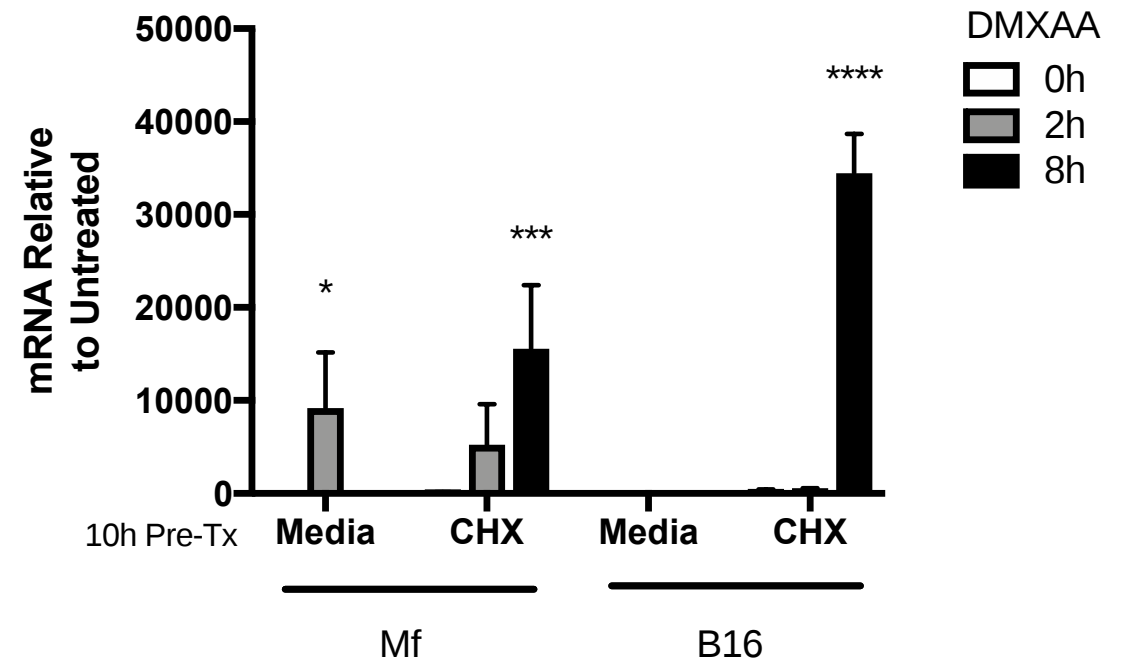


Cycloheximide treatment enables tumor cell-intrinsic IFN- β expression, likely due to degradation of an inhibitory factor

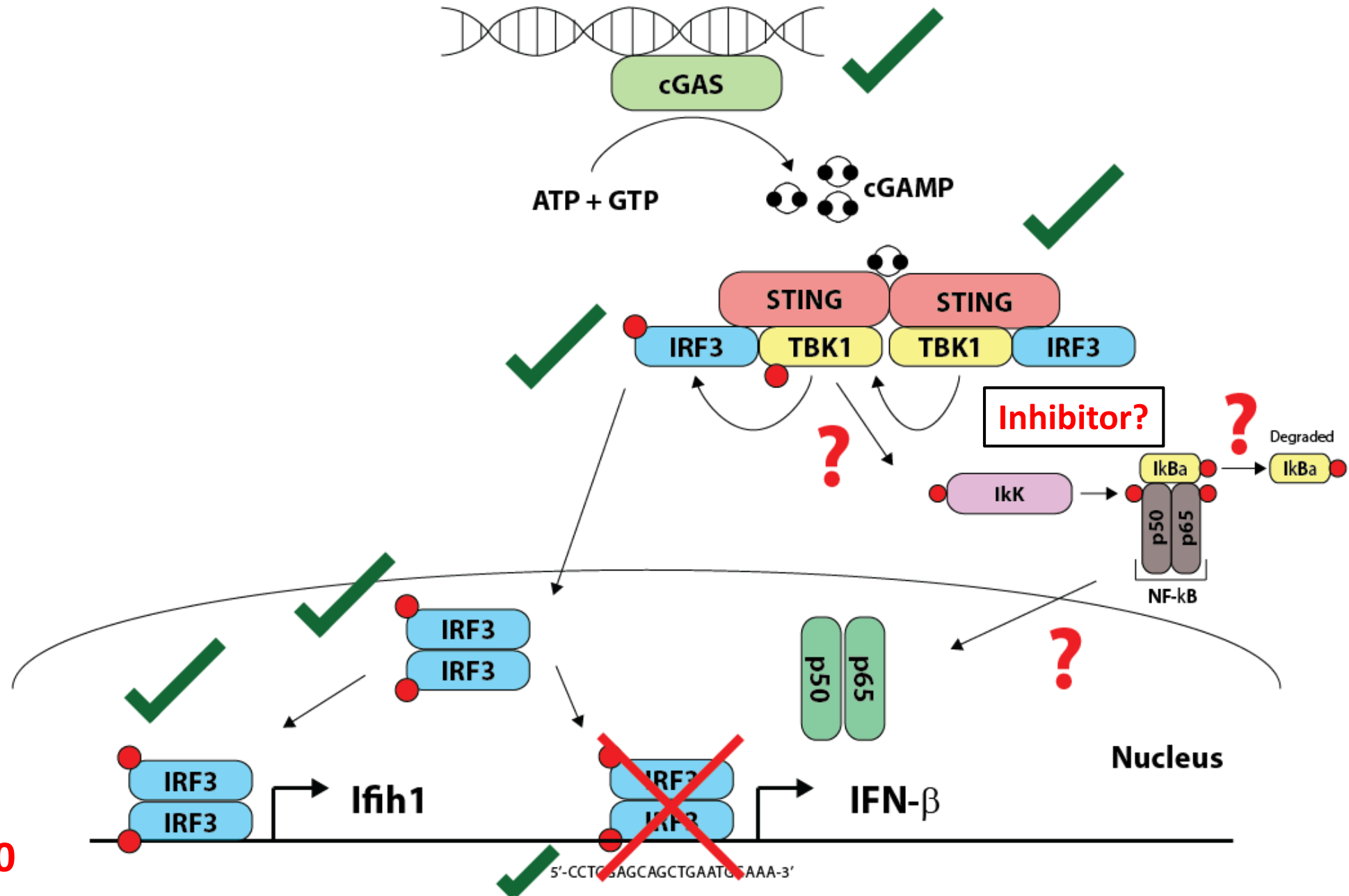
IFN- β mRNA after CHX Timecourse



IFN- β mRNA after CHX



Summary and Future Directions



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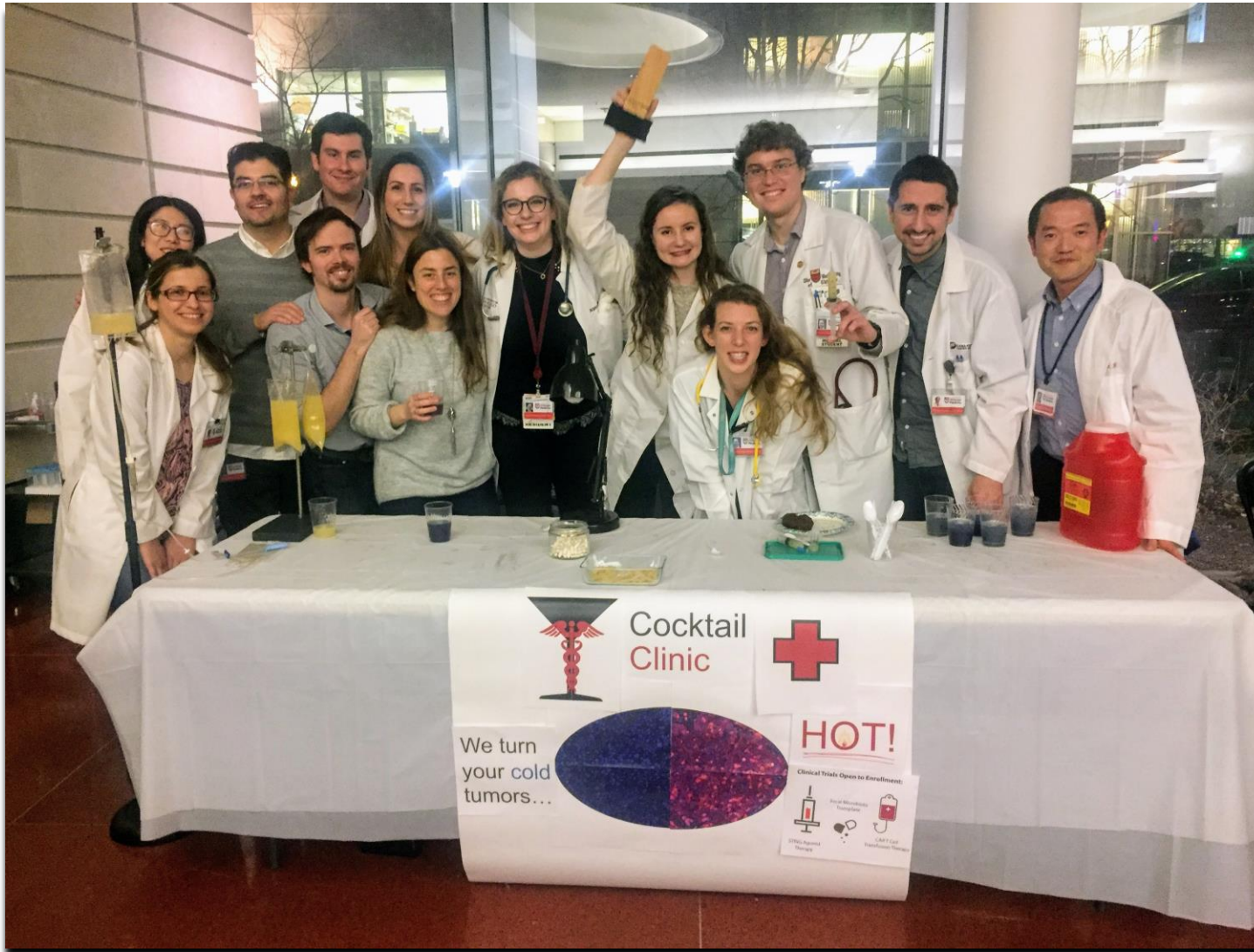
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Committee on Immunology

University of Chicago MSTP

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Poster O60