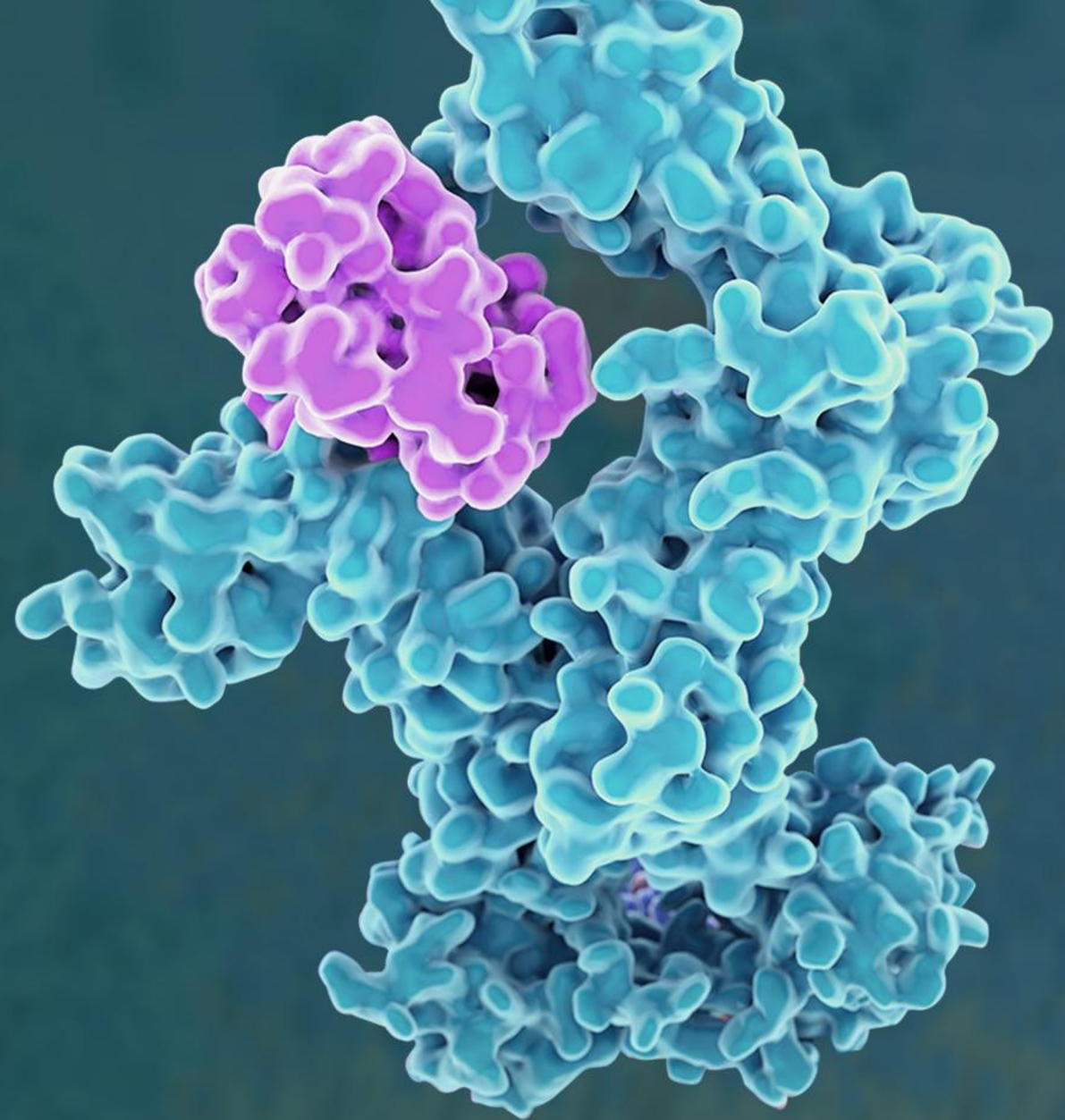


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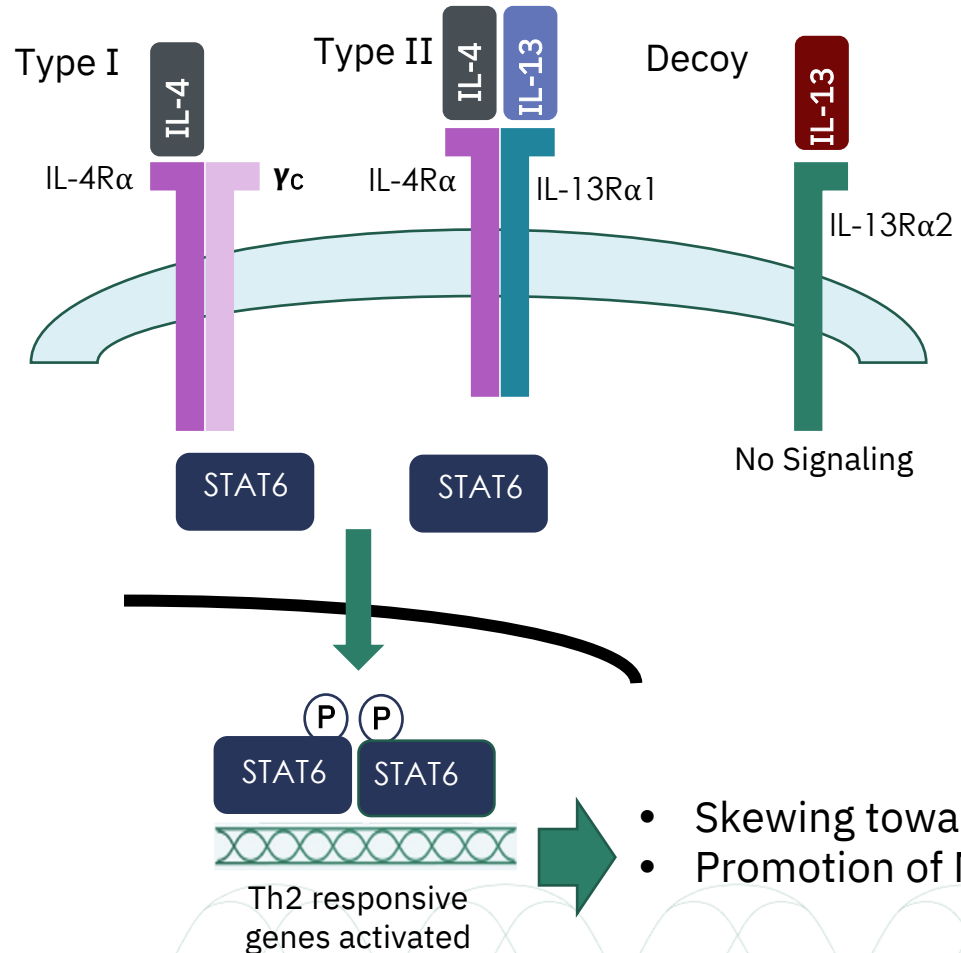
# Characterization of a Long-Acting IL-13 Super-Antagonist Engineered to Target Tumor Associated Macrophages and Myeloid Cells

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# Overview of IL-4/IL-13 Signaling

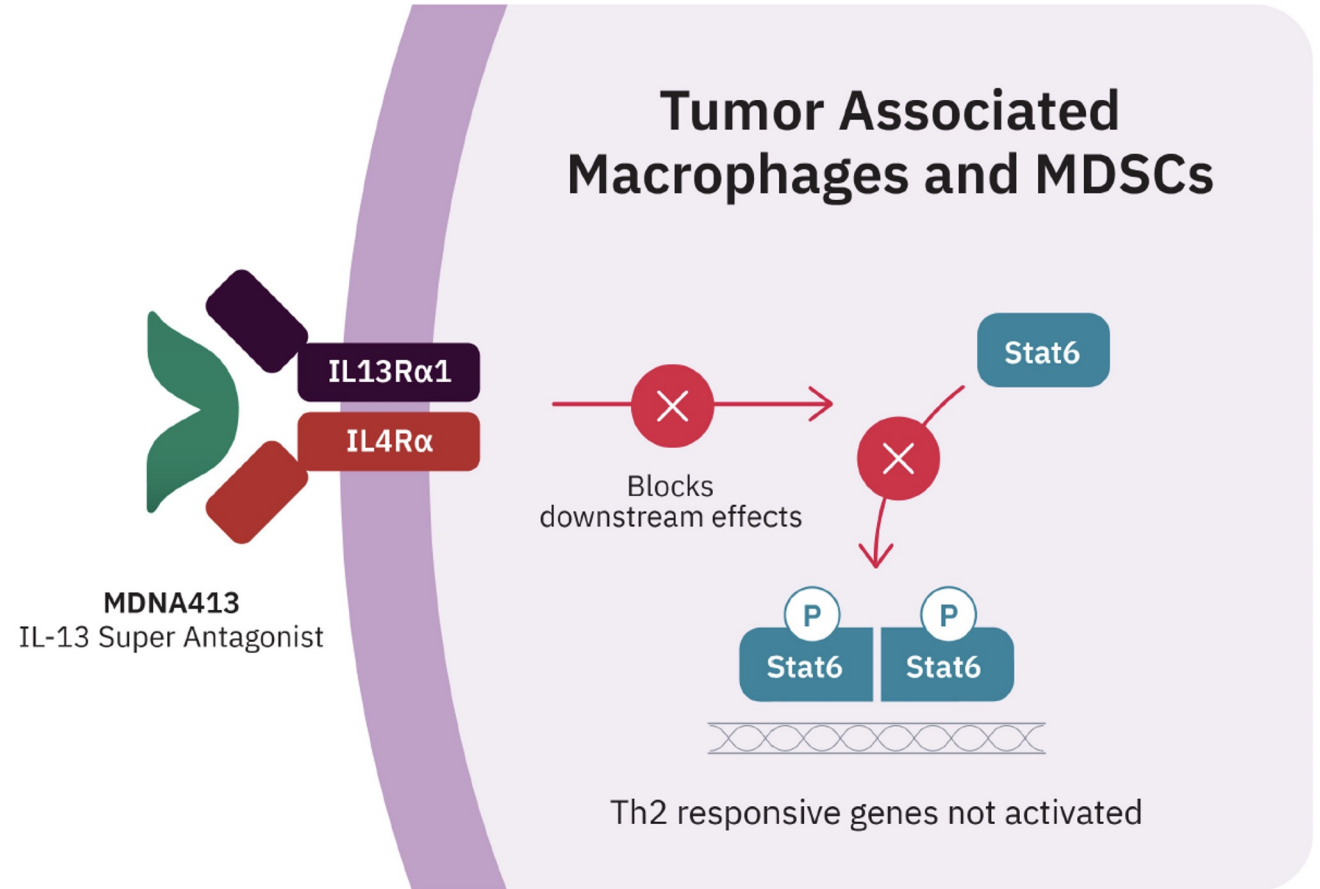
- ❑ M2 Tumor Associated Macrophages (TAMs) and Myeloid Derived Suppressor Cells (MDSCs) promote an immune suppressive tumor microenvironment (TME)
- ❑ IL-4/IL-13 pathway promotes M2 TAMs and MDSC, therefore limiting immune effector cells (i.e., immunologic cold tumors) to support tumor growth and progression
- ❑ Inhibition of IL-4/IL-13 signaling invigorates effector immune cells and enhances anti-tumor immunity



# Fc-MDNA413: Proposed Mechanism of Action

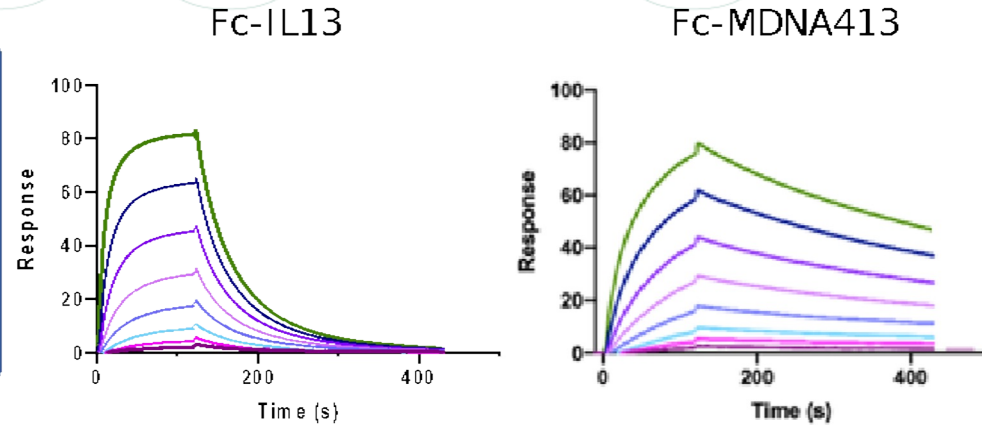
MDNA413 binds and blocks signaling from Type II (IL-4 $\alpha$ /IL-13R $\alpha$ 2) receptor, leading to:

- ❑ Blockade of polarization of TAM to M2a lineage.
- ❑ Inhibition of MDSC expansion and immune suppressive capabilities.
- ❑ Potential Inhibition of tumor growth and progression by directly acting on tumor cells.

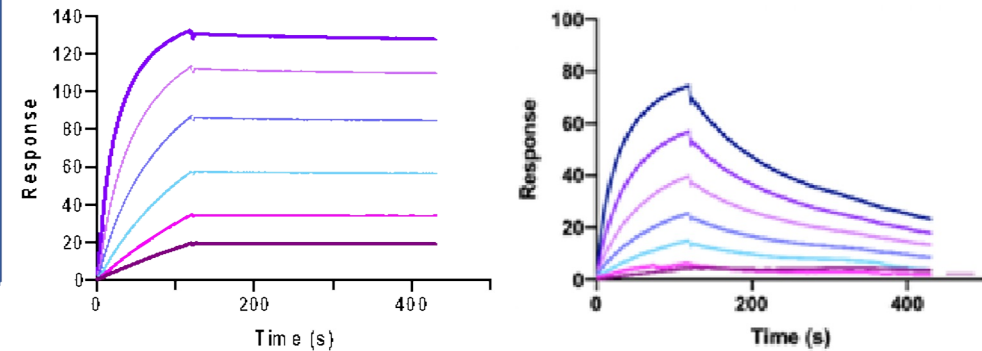


# Selectivity Towards IL-13R $\alpha$ 1 With Reduced Affinity to IL-13R $\alpha$ 2

IL-13R $\alpha$ 1



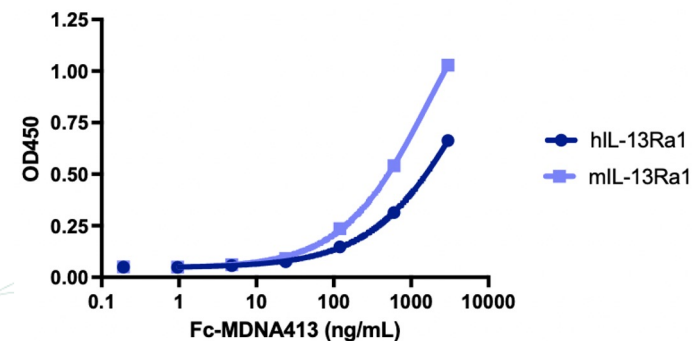
IL-13R $\alpha$ 2



$K_D$ (nM)	Fc-IL13	Fc-MDNA413
IL-13R $\alpha$ 1	202	18.1
IL-13R $\alpha$ 2	0.69	19.6

SPR performed on immobilized ligands with receptors as flow analytes using MCK

MDNA413 Binds Human & Mouse IL-13R $\alpha$ 1.



ELISA analysis of binding to coated human (h) and mouse (m) IL-13R $\alpha$ 1



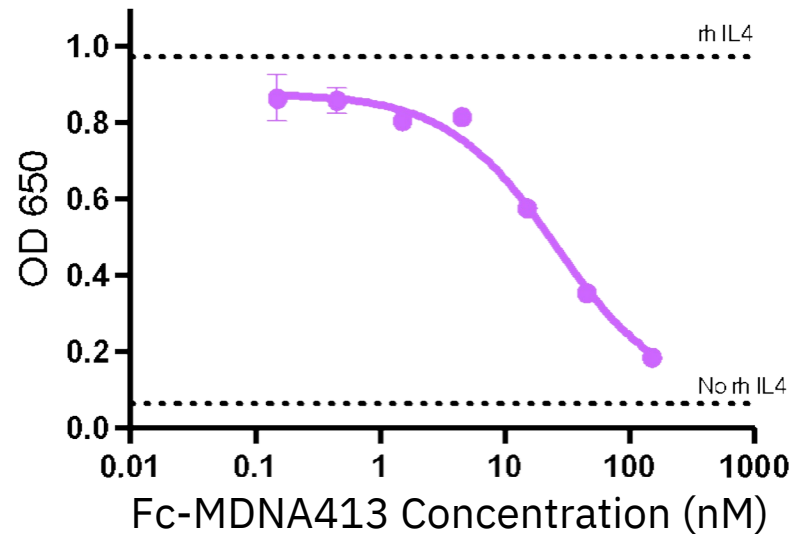
AACR Annual Meeting April 8<sup>TH</sup>- 13<sup>TH</sup> 2022

Characterization of a Long-Acting IL-13 Super-Antagonist Engineered to Target Tumor Associated Macrophages and Myeloid Cells.

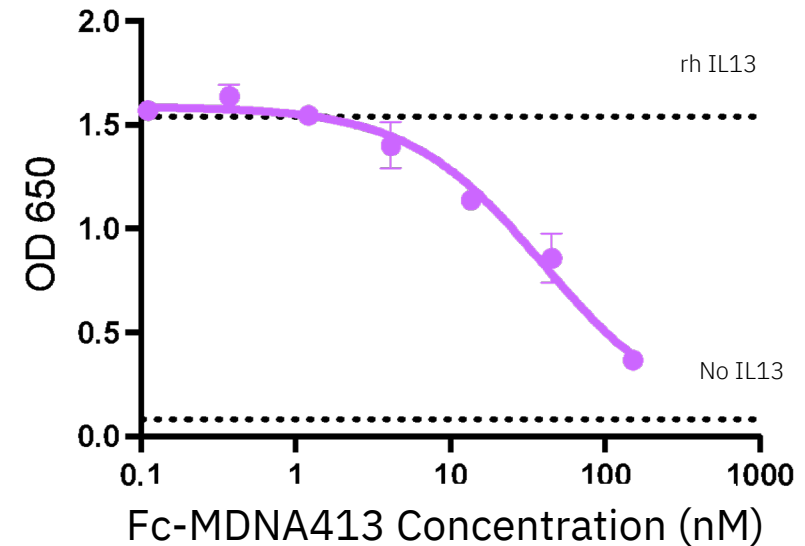


# Fc-MDNA413 Inhibits IL-4 and IL-13 Induced Signaling

## Inhibition of IL-4 Induced Signaling



## Inhibition of IL-13 Induced Signaling

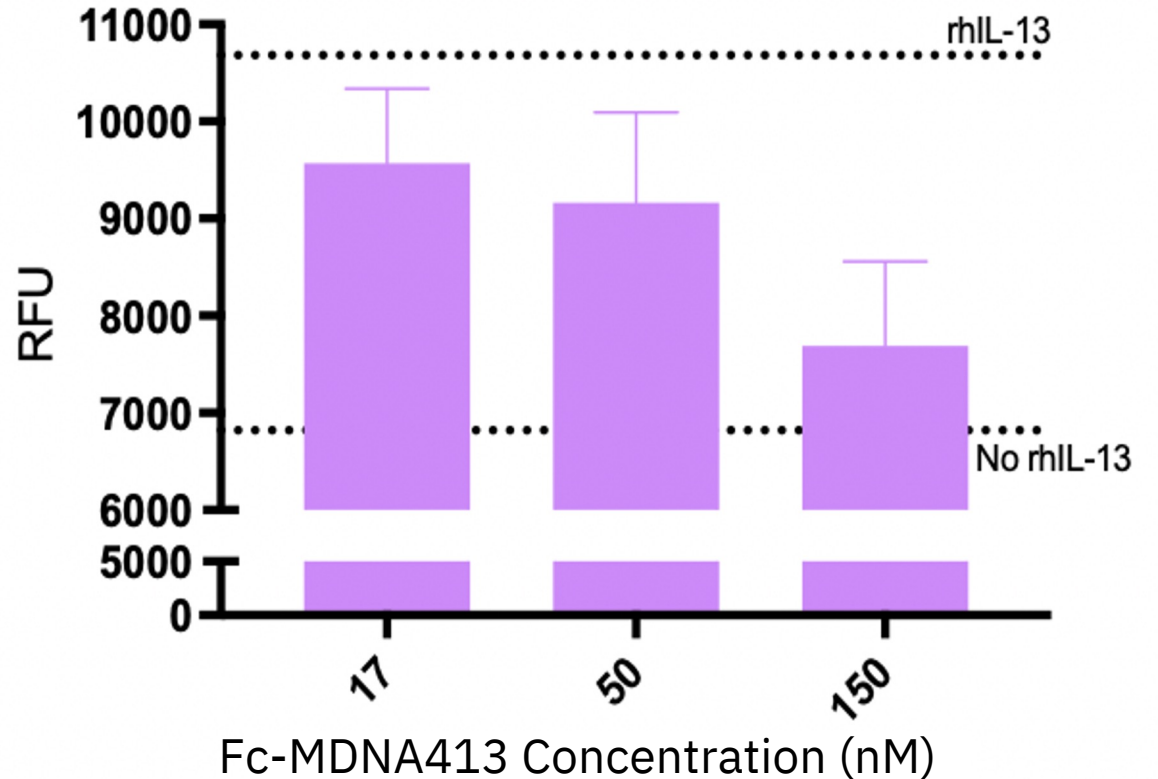


IC <sub>50</sub> (nM)	Fc-MDNA413
IL-4 Signaling	26.4
IL-13 Signaling	39

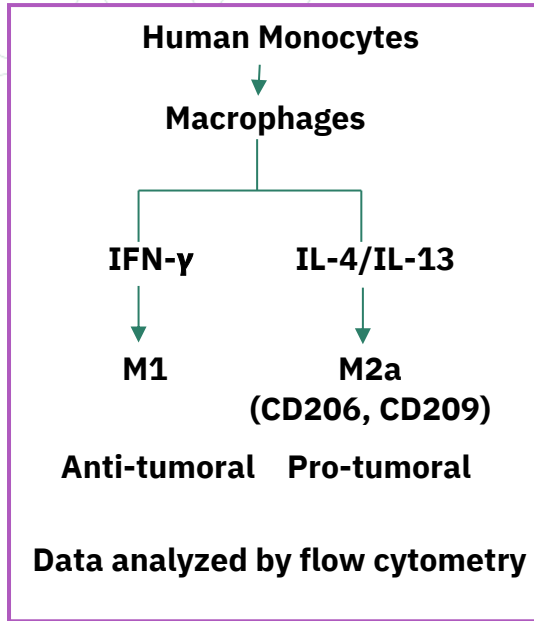
Assay performed in HEK Blue IL-4/IL-13 reporter cells (InvivoGen); Measurement of pSTAT6 activity. 0.1 nM of rh IL-4 and 0.8 nM of rh IL-13 was used in the competition assay format

# Fc-MDNA413 Inhibits IL-13 Induced TF-1 Proliferation

- TF-1 is a human erythro-leukemia cell line that is highly dependent on IL-4/IL-13 for proliferation.
- Inhibition of IL-13 Induced TF-1 Proliferation.

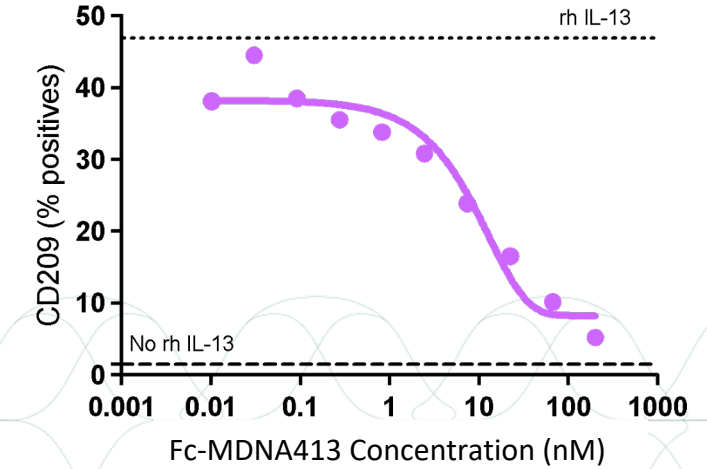
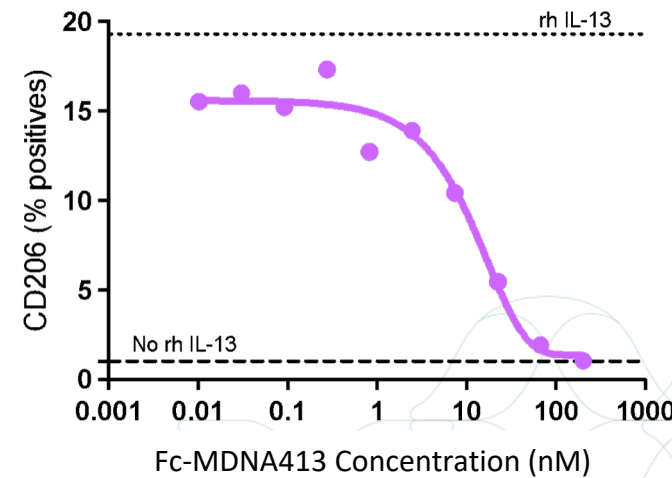
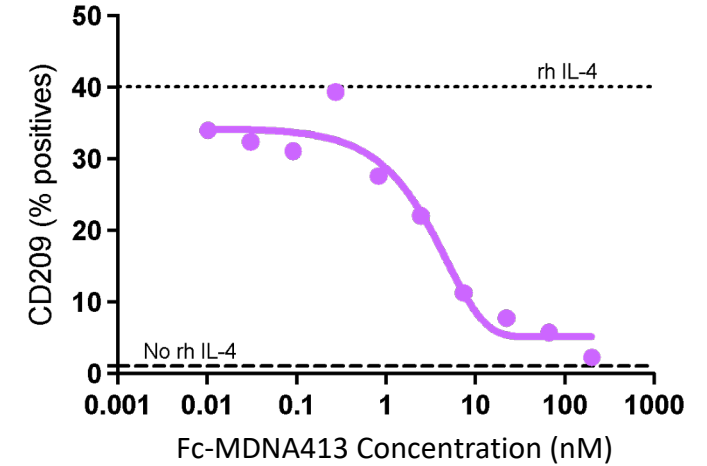
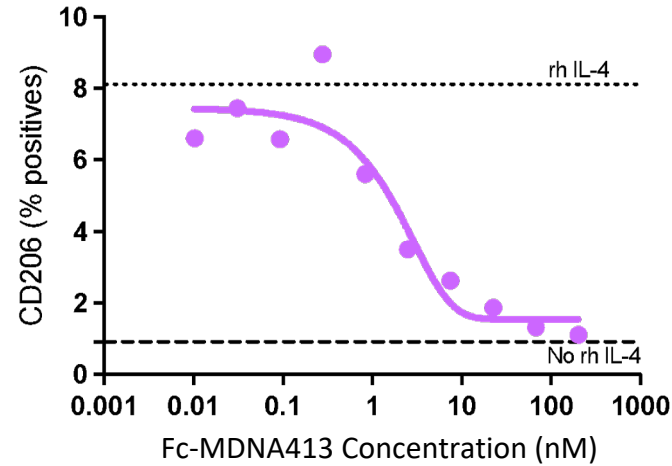


# Fc-MDNA413 Inhibits IL-4 and IL-13 Induced M2a Polarization



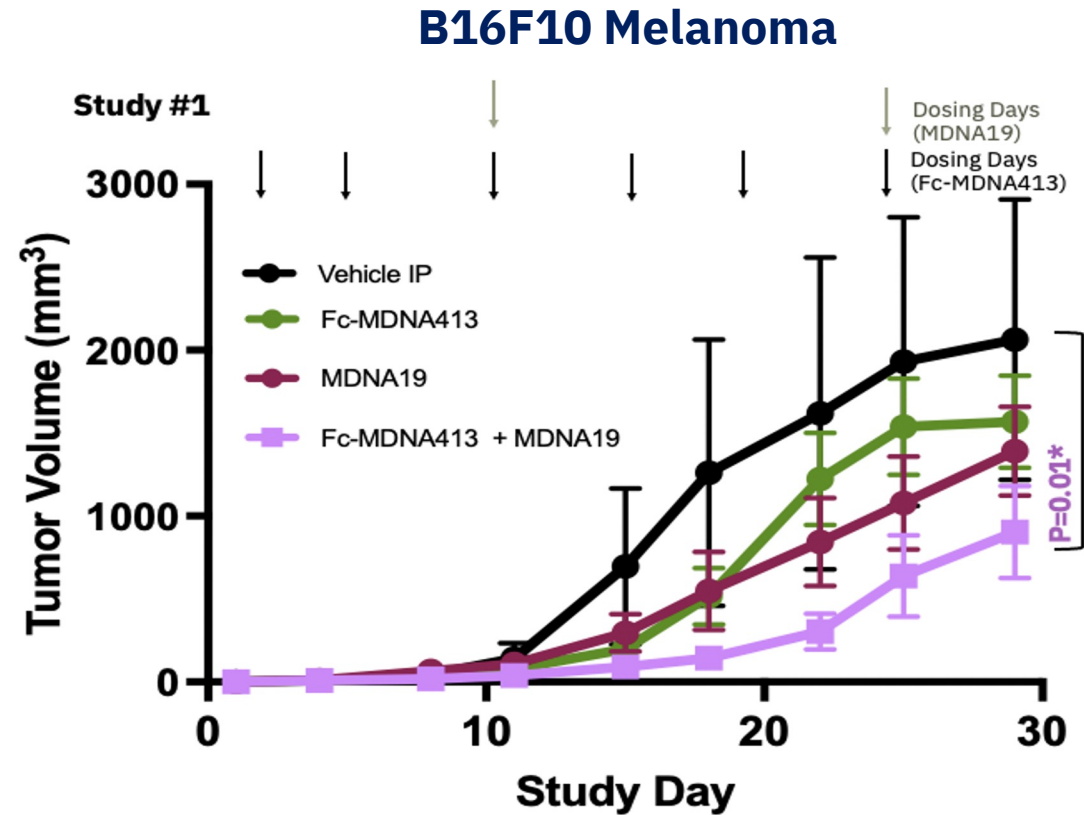
Fc-MDNA413	CD206 IC <sub>50</sub> (nM)	CD209 IC <sub>50</sub> (nM)
IL-4 mediated M2 polarization	1.76	3.2
IL-13 mediated M2 polarization	12.7	11.9

## Surface Expression of M2a markers, CD206 and CD209



# Fc-MDNA413 Inhibits Tumor Growth As Monotherapy and Acts Synergistically With a Long-Acting IL-2 Super-Agonist (MDNA19)

- B16F10 is an aggressive melanoma model with low mutation burden (i.e., poorly immunogenic) and infiltration of TAMs and MDSC.
- Combination treatment suppresses M2a TAMs and MDSC (i.e., Fc-MDNA413) while promoting immune effectors cells (i.e., MDNA19) to promote a potent anti-tumor response.

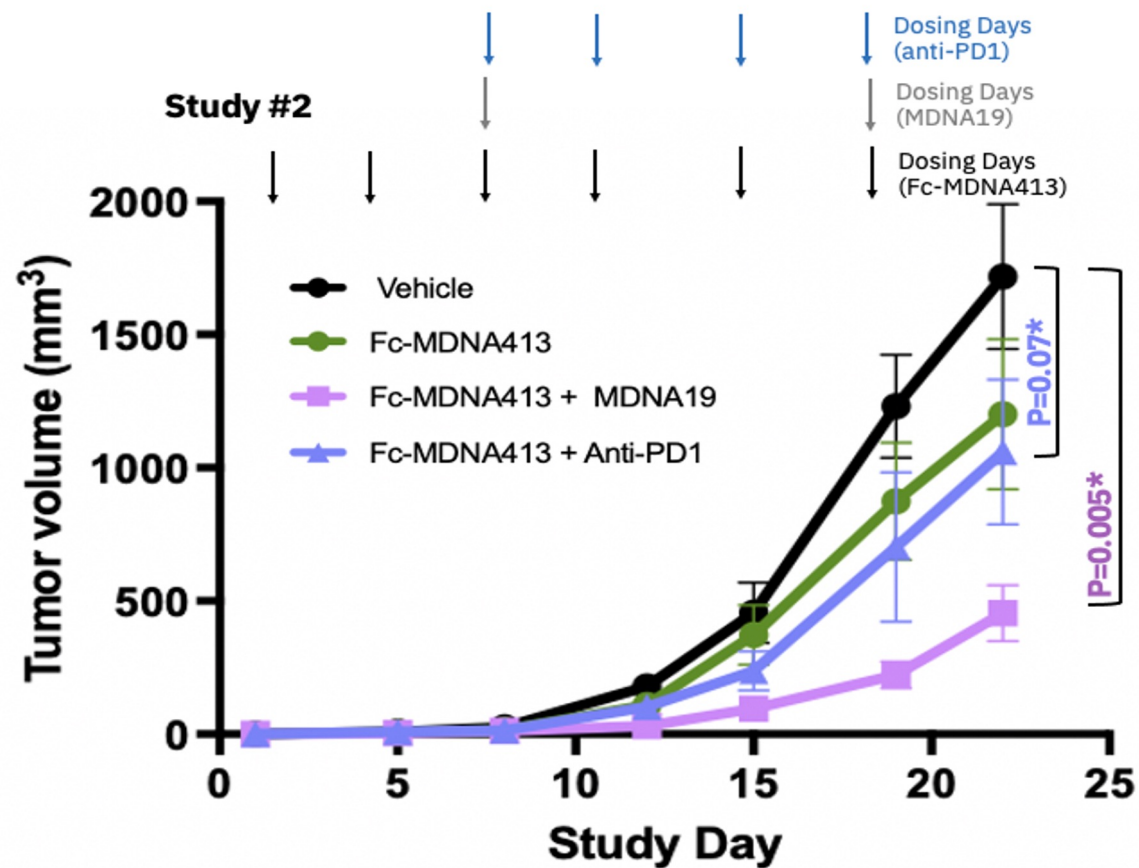


Tumor bearing mice were treated with either Fc-MDNA413 30 mg/kg twice weekly x 3 post 3 days of cell implantation or MDNA19 5 mg/kg once weekly X 2 IP, a week after Fc-MDNA413 dosing.





# Fc-MDNA413 Exhibits Synergy with MDNA19 but not Anti-PD1 in B16F10 Model



Tumor bearing mice were treated with either Fc-MDNA413 30 mg/kg twice weekly x 3 post 3 days of cell implantation or MDNA19 5 mg/kg once weekly X 2 IP, a week after Fc-MDNA413 dosing, or anti-PD1 10 mg/kg twice weekly x 2 IP, a week after Fc-MDNA413 dosing



# Key Summary

- ❑ **IL-13 Super-Antagonist, Fc-MDNA413 Superkine shows:**
  - ❑ Selectivity towards IL-13R $\alpha$ 1 and blocks IL-4 / IL-13 mediated function (pSTAT6 signaling, TF-1 proliferation and M2a polarization of macrophages).
- ❑ **Fc-MDNA413 synergizes with an IL-2 agonist (MDNA19) to inhibit *in vivo* tumor growth**
  - ❑ Fc-MDNA413 suppresses the Th2 immune response while MDNA19 enhances the Th1 immune response to act in conjunction resulting in enhanced efficacy.
- ❑ **These data highlight the potential synergy of co-targeting suppressive and effector immune cells within otherwise ‘immunologically cold’ TME to achieve effective therapeutic efficacy.**

