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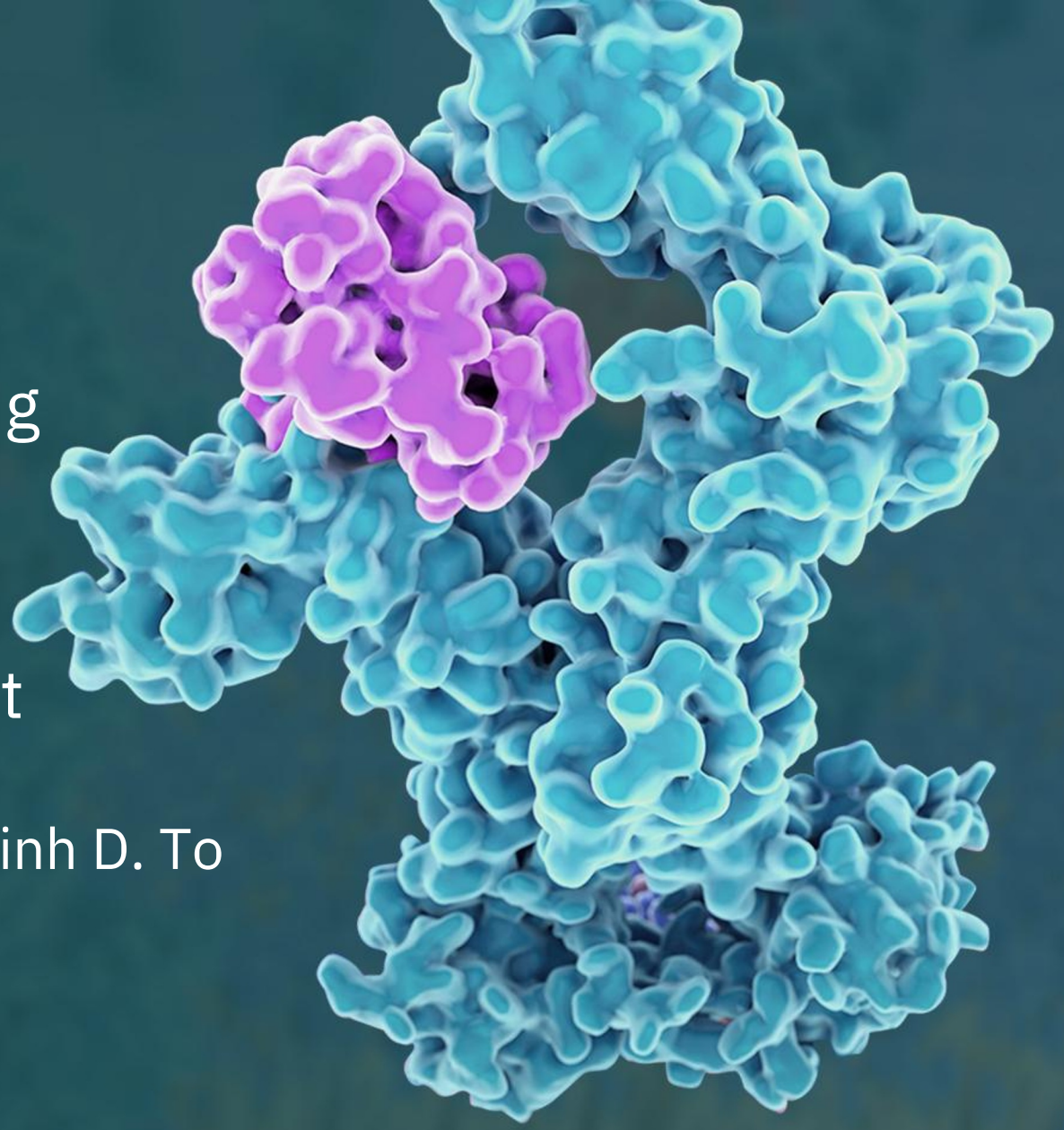
Fc-MDNA413 is a novel Long-Acting IL-4/IL-13 Super-Antagonist that Suppresses M2aTAM Skewing and *In Vivo* Tumor Growth Including Synergy with an IL-2 Super-Agonist



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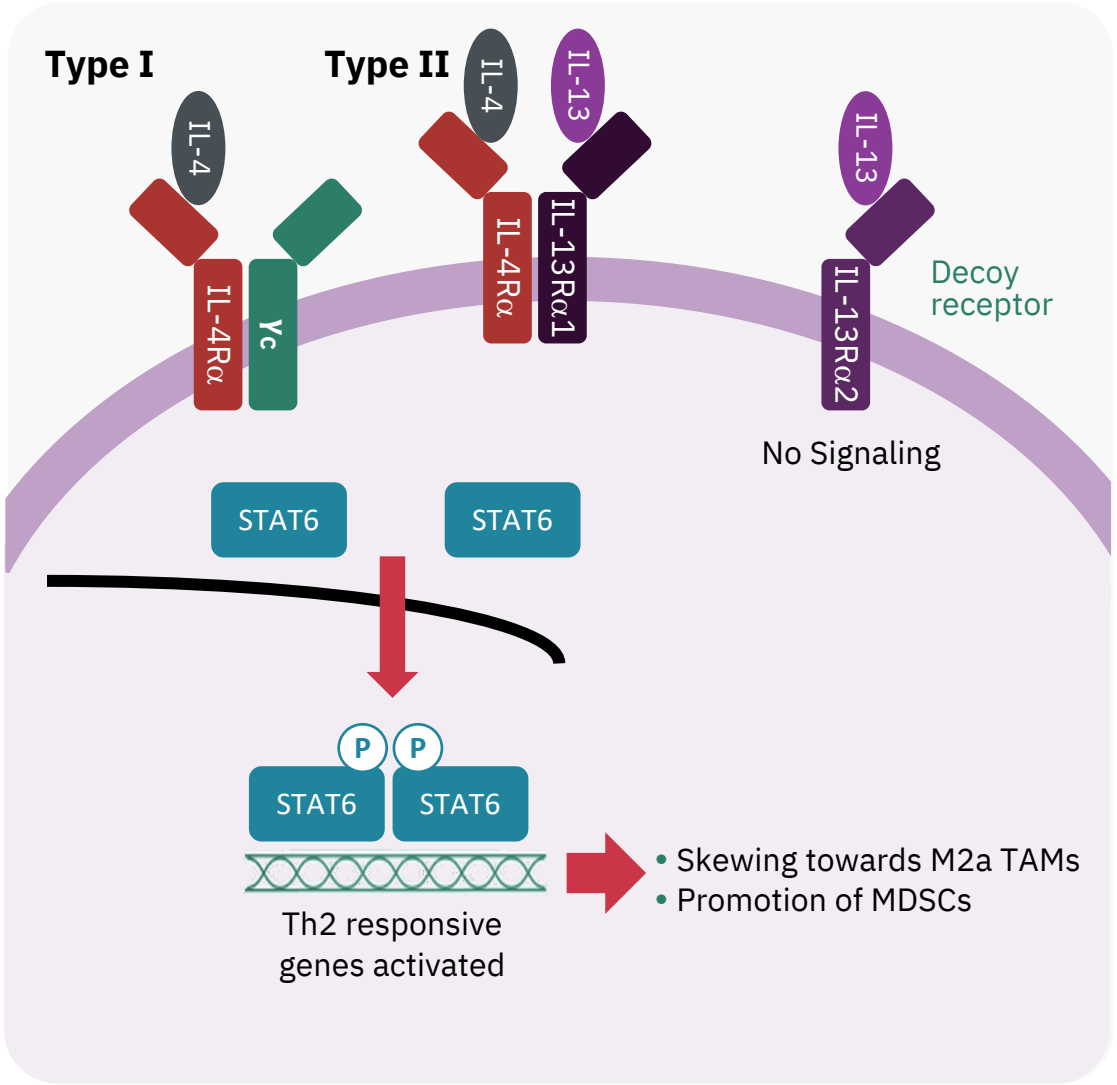
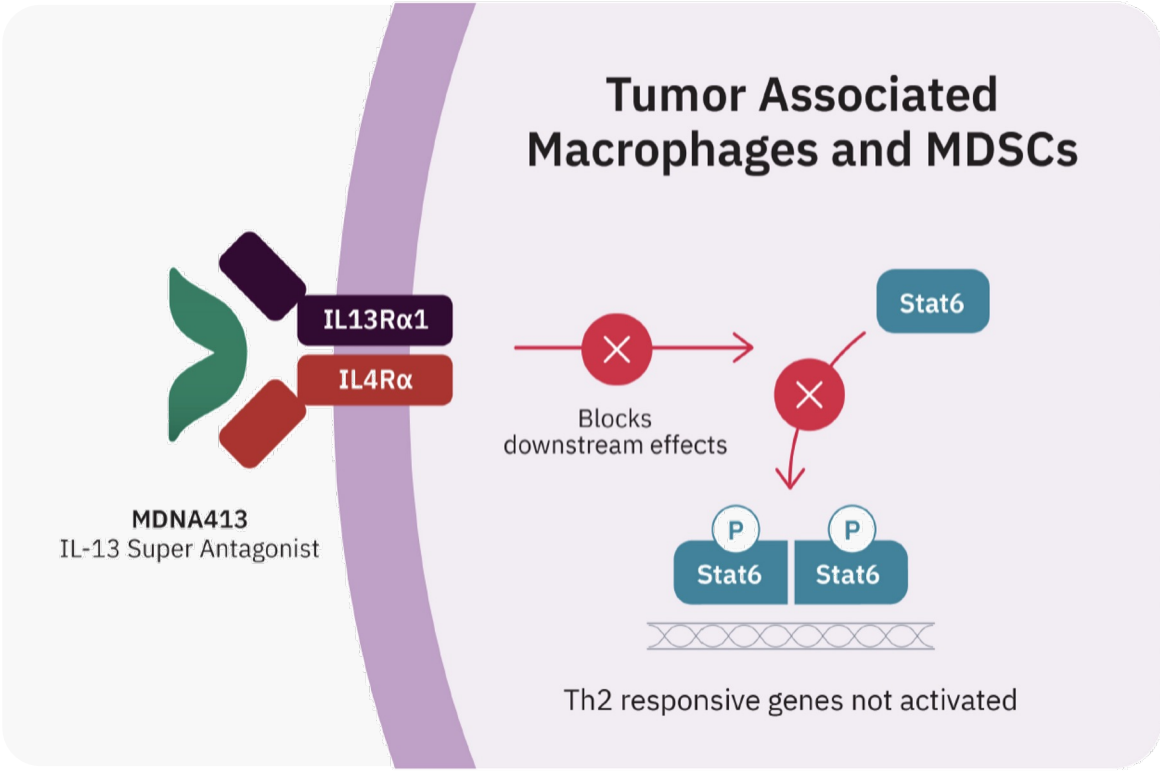
Overview of IL-4/IL-13 Pathway in Cancer

- IL-4/IL-13 signals through Type I (IL-4Rα/γc) and/or Type II (IL-4Rα/ IL-13Rα1) receptors to induce p-STAT6, triggering M2a skewing of Tumor Associated Macrophages (TAMs) and promoting Myeloid Derived Suppressor Cells (MDSCs)
- M2a TAMs and MDSCs foster an immune suppressive tumor microenvironment (TME) to support tumor growth by hindering anti-tumor immune effector cells
- IL-4/IL-13 can act autonomously on cancer cells to promote tumor growth and progression



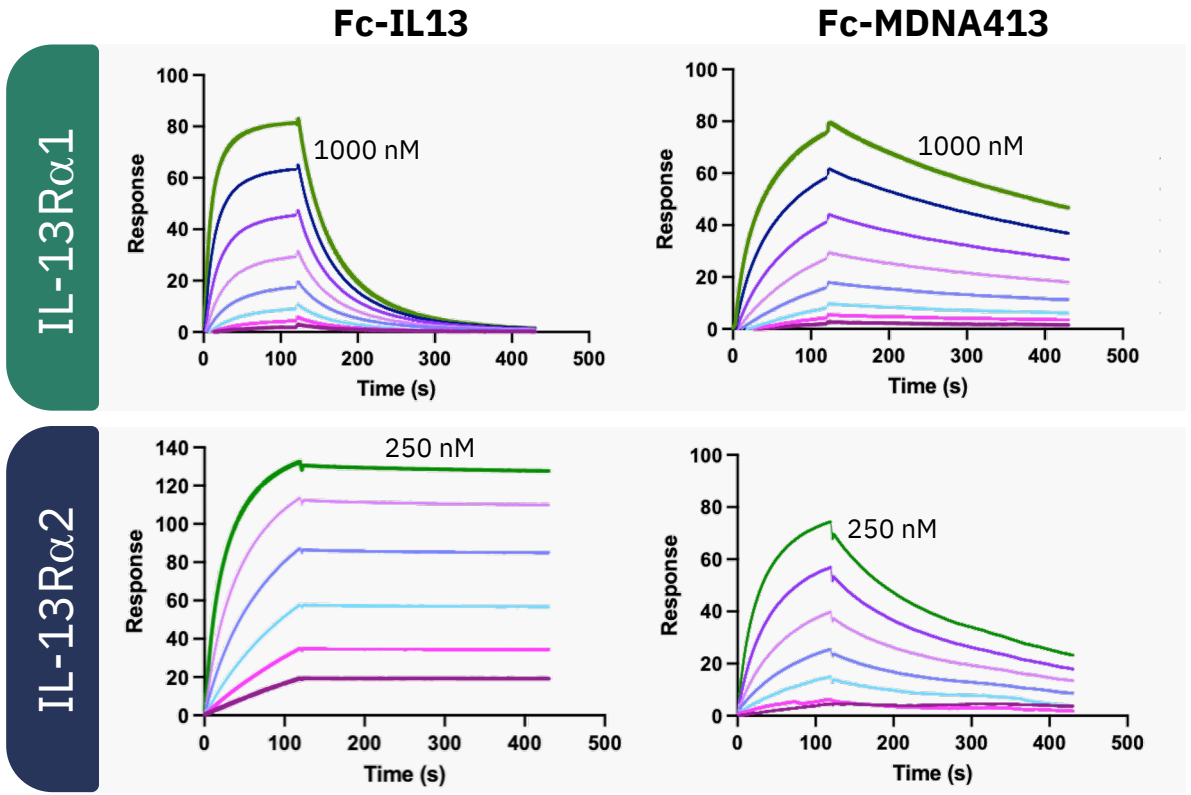
Proposed MOA of Fc-MDNA413, an IL-4/IL-13 Pathway Super-Antagonist

- MDNA413 is an IL-13 superkine that outcompetes wild-type IL-13 for binding to Type II (IL-4Rα/IL-13Rα1) receptor and blocks downstream signaling
- Fusion of MDNA413 with human IgG Fc* is designed to increase half—life for cancer immunotherapy by:
  - Blockade of M2a TAM skewing and MDSC expansion to reverse the immune suppressive TME and invigorate immune effector cells
  - Potentially block the direct effect of IL-4/IL-13 on tumor cells

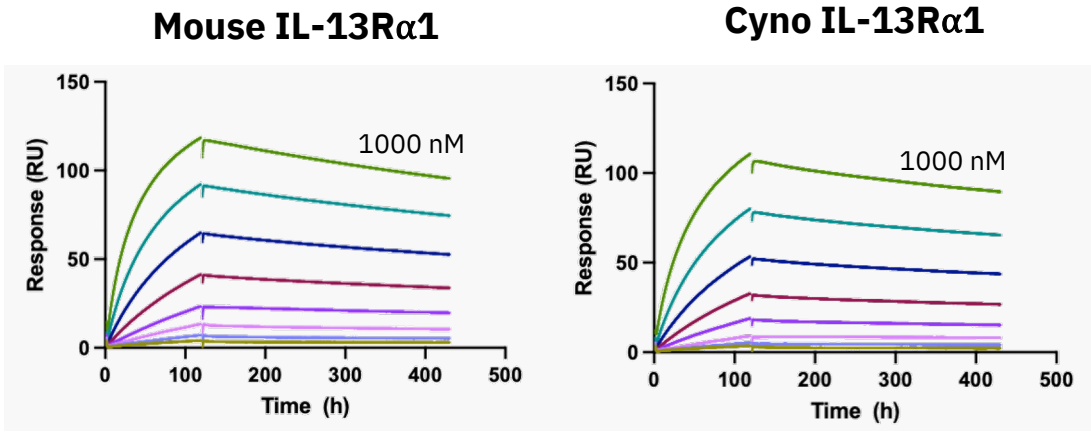


* Effector function silenced

Fc-MDNA413 is Highly Selective Towards IL-13Rα1 With Reduced Affinity for IL-13Rα2



- IL-13 is highly selective for IL-13Rα2 over IL-13Rα1
- Fc-MDNA413 shows enhanced selectivity for IL-13Rα1 over IL-13Rα2 by >300 fold



K_D (nM)	Fc-IL13	Fc-MDNA413	Fold change in Affinity
IL-13Rα1	202	18.1	11.1 ↑
IL-13Rα2	0.69	19.6	28.4 ↓

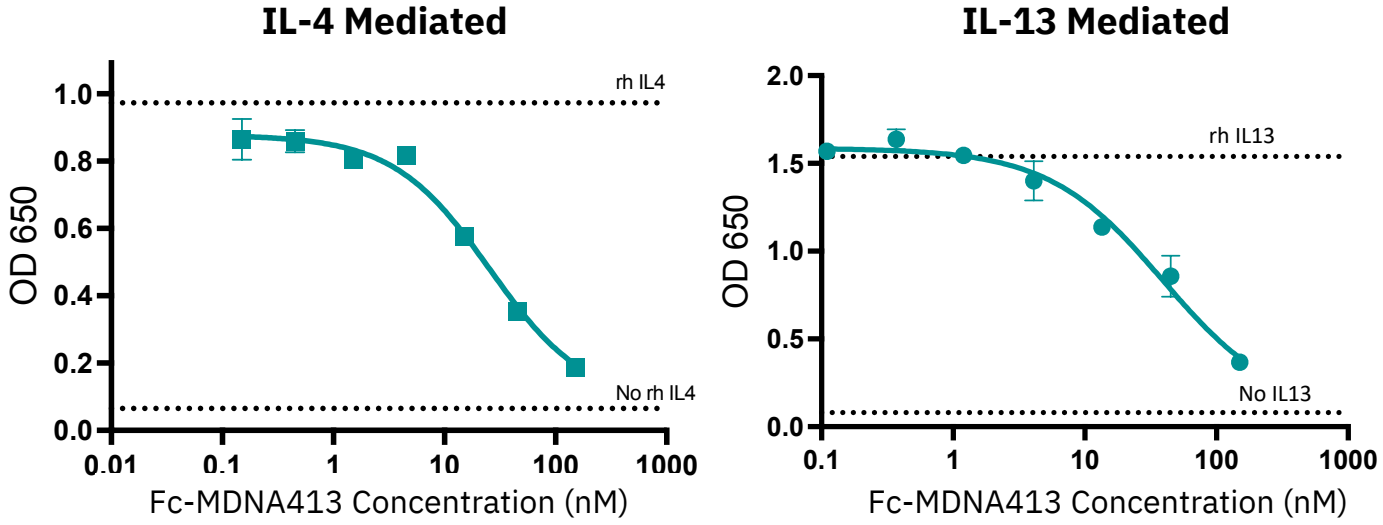
SPR performed on immobilized ligands with receptors as flow analytes using MCK

Fc-MDNA413	K_D (nM)
Human IL-13Rα1	18.1
Mouse IL-13Rα1	25.5
Cyno IL-13Rα1	65.5

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

Fc-MDNA413 Inhibits Downstream Signaling and Function

Inhibition of pSTAT6 Signaling in HEK Blue IL-4/IL-13 Reporter Assay System

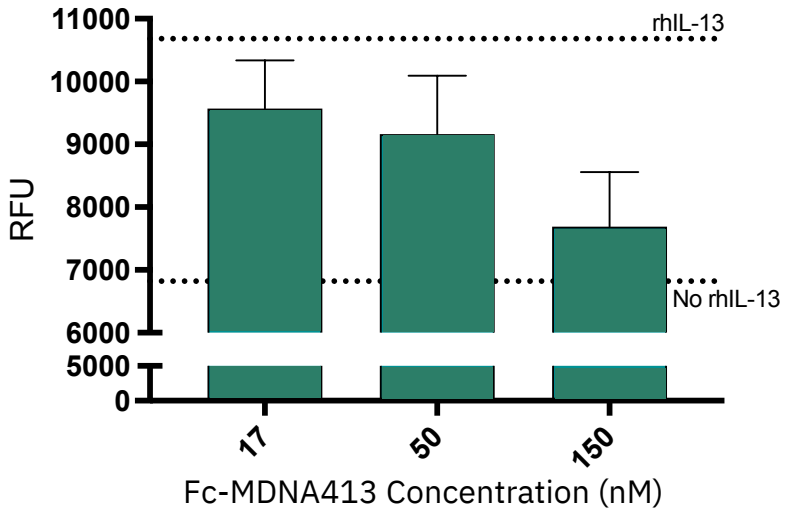


Fc-MDNA413	IC_{50} (nM)
IL-4 Signaling	26.4
IL-13 Signaling	39

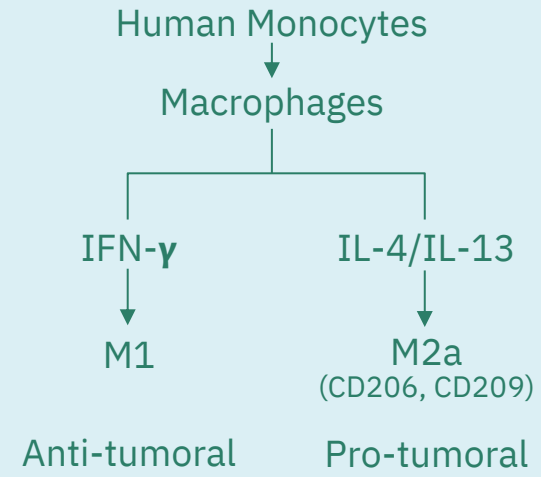
Assay performed in HEK Blue IL-4/IL-13 reporter cells (InvivoGen); Measurement of pSTAT6 activity. 0.1 nM of rh IL-4 and 0.8 nM of rh IL-13 was used in the competition assay format

Inhibition of 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.



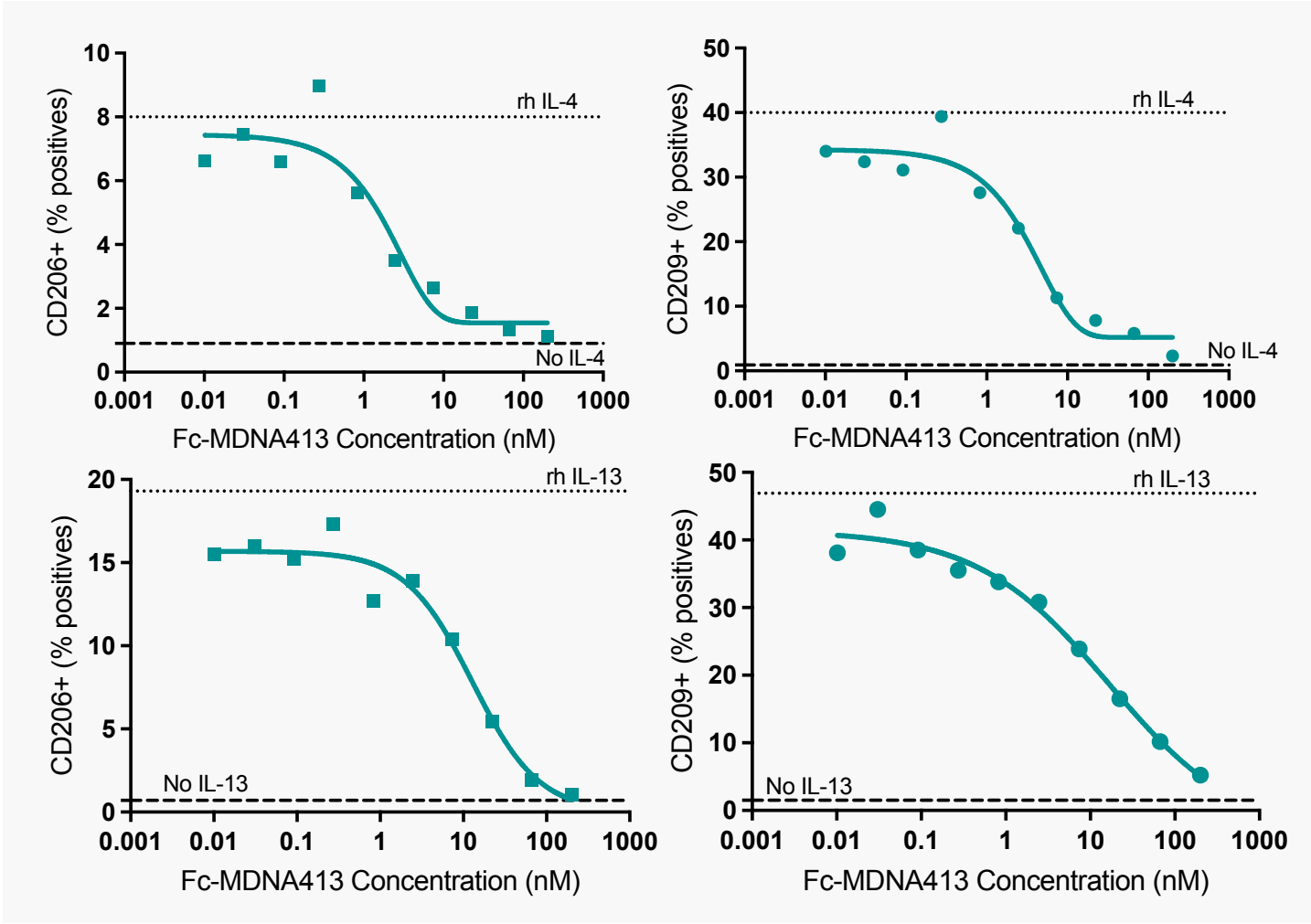
Fc-MDNA413 Inhibits IL-4 and IL-13 Mediated M2a Polarization



Data analyzed by flow cytometry

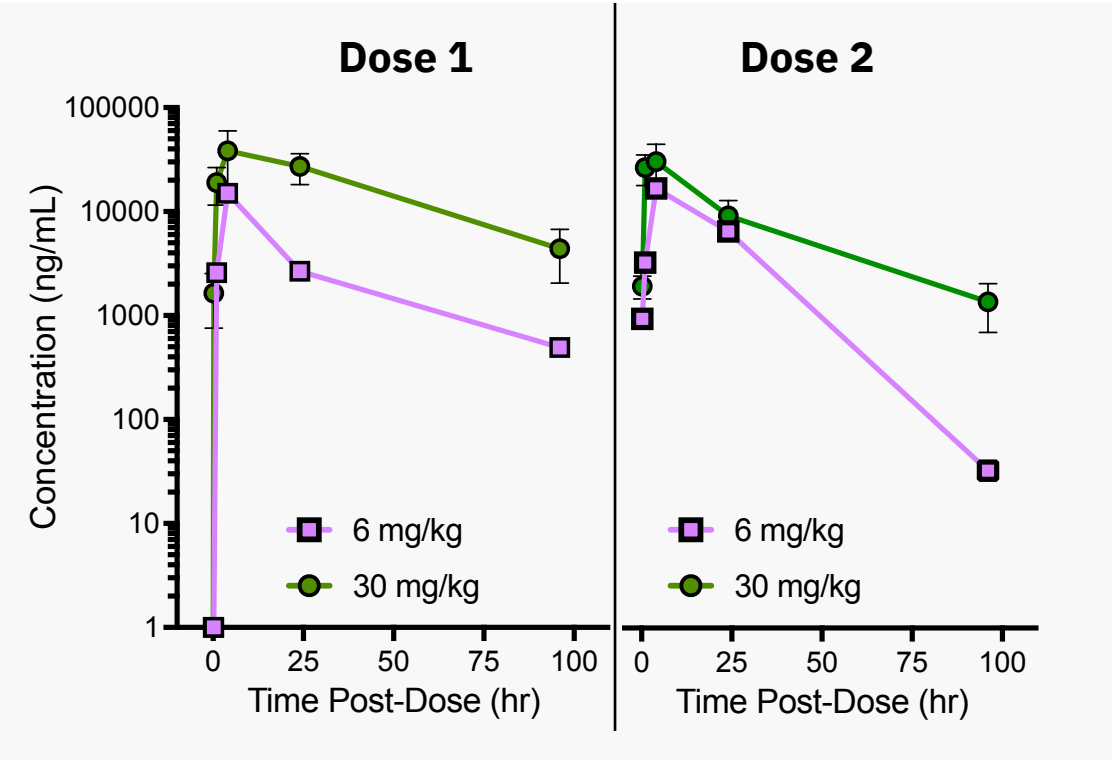
Fc-MDNA413	CD206 IC_{50} (nM)	CD209 IC_{50} (nM)
IL-4 mediated M2 polarization	1.76	3.2
IL-13 mediated M2 polarization	12.7	11.9

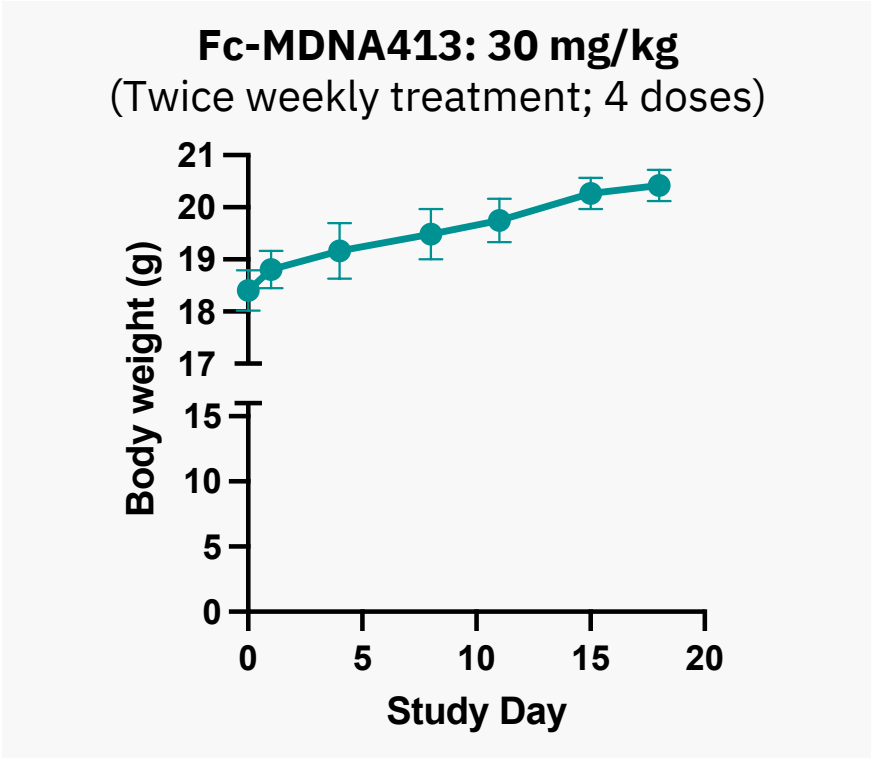
Reduction in Surface Expression of M2a markers, CD206 and CD209



PK Profile in Mice Shows Sustainable Serum Exposure on Repeat Dosing

- Dose-dependent increase in exposure
- Serum exposure maintained > 1000 ng/mL on a twice weekly IP dosing schedule at 30 mg/kg
- Treatment well tolerated; mice showed steady weight gain

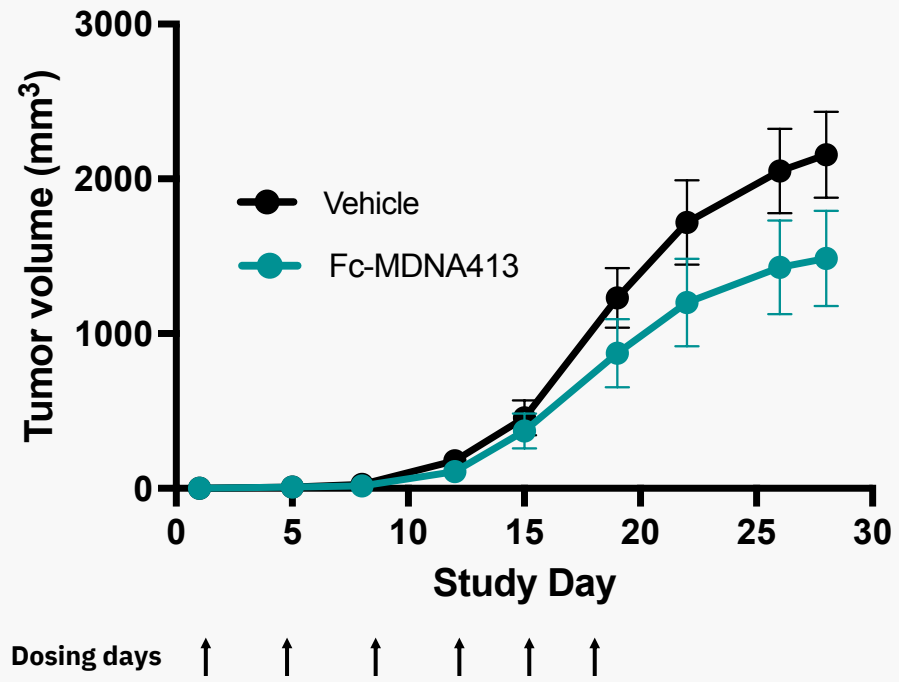




Fc-MDNA413 Demonstrates Single-Agent Efficacy in Syngeneic Tumor Models

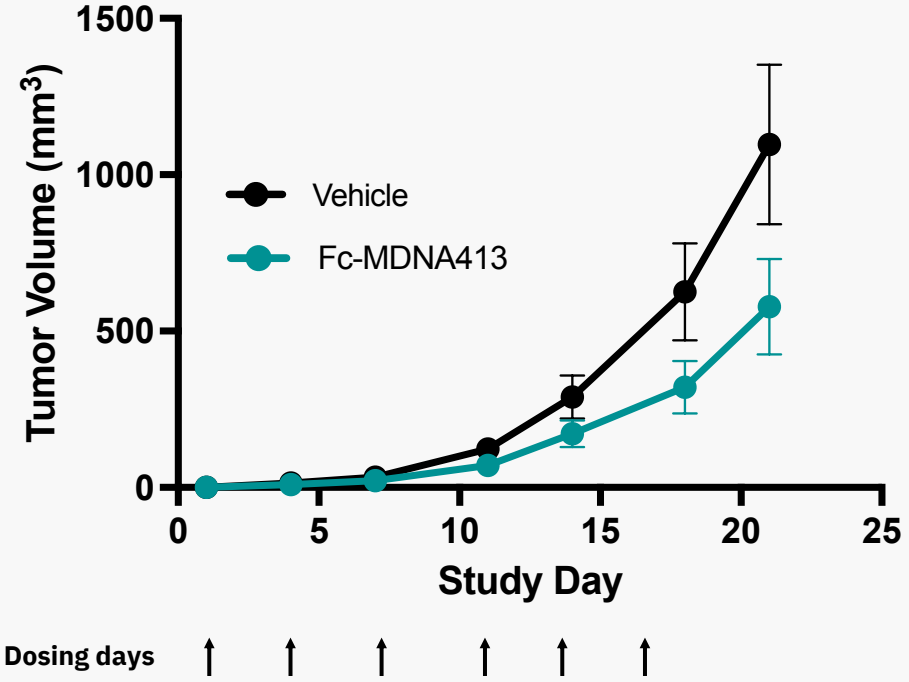
B16F10

Aggressive melanoma model with low mutation burden (poorly immunogenic) and high infiltration of TAMs and MDSC



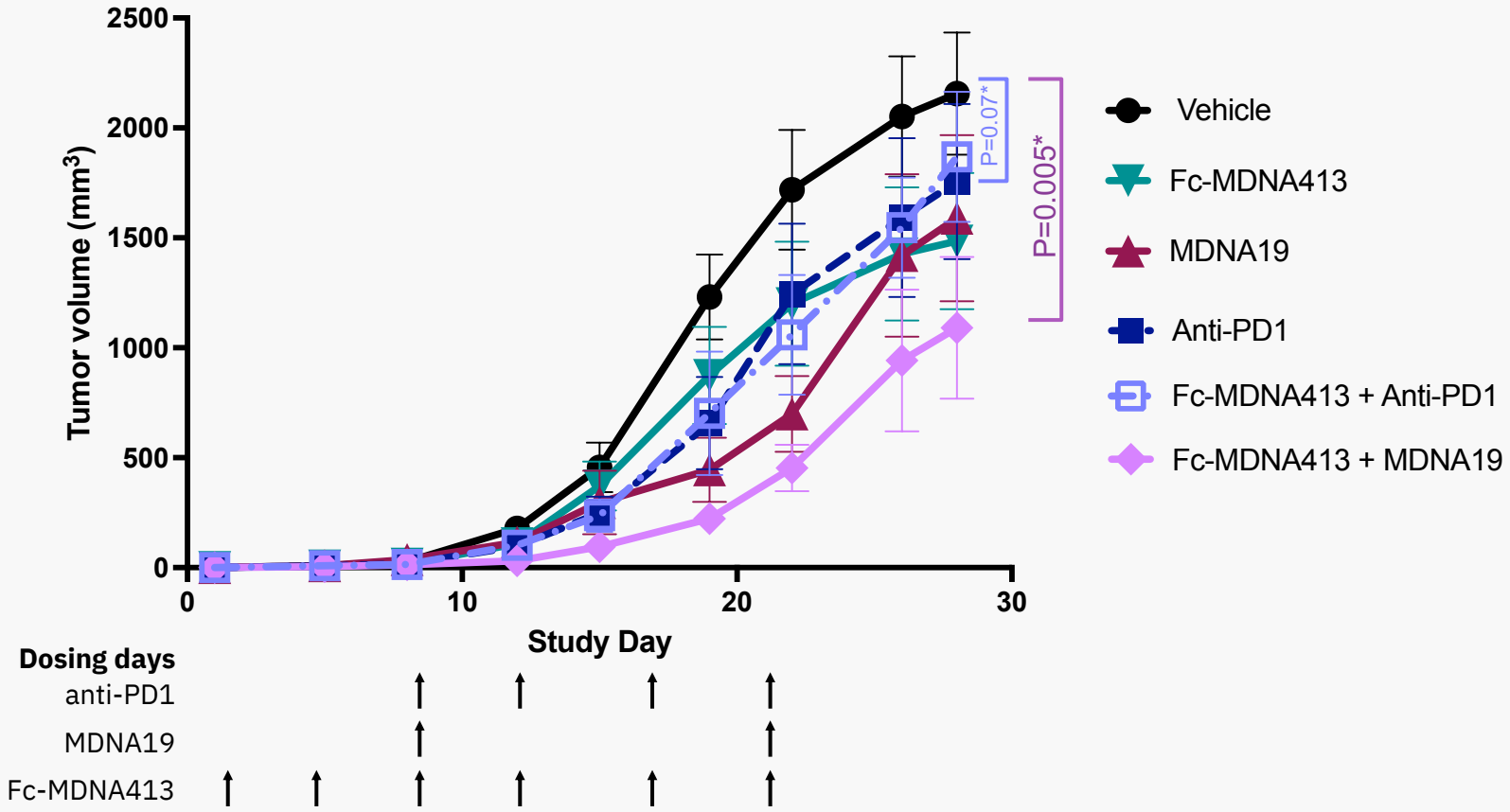
CT26

Immunogenic colon carcinoma model infiltrated with TAMs and MDSC



Tumor bearing mice were treated with either Fc-MDNA413 30 mg/kg twice weekly x 3 post 3 days of cell implantation

Fc-MDNA413 Shows Synergy With a Long-Acting IL-2 Super-Agonist (MDNA19) in B16F10 Melanoma Model



- Fc-MDNA413: Inhibits M2a TAMs and MDSCs
- MDNA19: Potentiates immune effector cells ($CD8^+$ T and NK cells)

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

Summary

- **IL-13 Super-Antagonist, Fc-MDNA413 Superkine shows:**
  - Selectivity towards IL-13Rα1 across species and blocks IL-4 / IL-13 mediated function (pSTAT6 signaling, TF-1 proliferation and M2a polarization of macrophages).
- **PK profile demonstrates sustainable serum exposure at a dose that is well tolerated.**
- **Fc-MDNA413 exhibits tumor growth inhibition in B16F10 melanoma and CT26 colon carcinoma model**
- **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.**

Thank you

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