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EOS-215, a first-in-class TREM2 antagonist, designed to reprogram the tumor microenvironment and overcome resistance.

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iTEOS THERAPEUTICS

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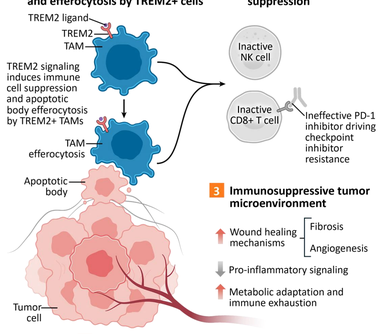
Introduction

TREM2 (triggering receptor expressed on myeloid cells 2) is a lipid sensor and a central regulator of macrophages involved in wound healing, the resolution of inflammation and the formation of lipid associated macrophages across pathologies.

TREM2⁺ macrophages comprise a critical immunosuppressive population that plays a detrimental role in established tumors:

- Their immediate proximity to tumor cells, their wound healing promoting activities (e.g. efferocytosis) and their regulation of lipid metabolism are crucial in fueling tumor progression.
- They shield tumor cells from the immune system, causing both immune cell exclusion and T cell exhaustion leading to resistance to checkpoint inhibitor therapy such as anti-PD-1.
- They have been described as key actors in the establishment of metastases in the lungs, liver, bones and brain across multiple solid tumor types.

Given this wealth of evidence, targeting TREM2 with an antagonist antibody to selectively rewire this pro-tumoral macrophage population is a promising path in oncology.

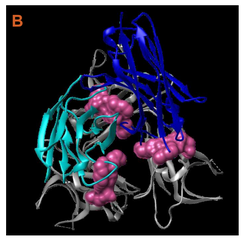


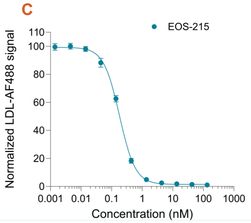
Molgora et al. Cell. 2020; Katzenelenbogen et al. Cell. 2020; Jaitin et al. Cell. 2019; Katzenelenbogen et al. Cell. 2020; Binnewies et al. Cell Rep. 2021; Mulder et al. Immunity 2021; Obradovic et al. Cell. 2021; Sun et al. Sci. Adv. 2023; Yofe et al. Cancer Discov. 2023; Park et al. Nat Immunol. 2023; Ramos-et al., Cell. 2022; Kirschenbaum et al. Cell. 2024; Sun et al. Nat Commun. 2024; Ning et al. Cell Rep Med. 2024; Zhang et al. Cell Metab. 2022; Guimaraes et al. Nat Commun. 2024; Polonia et al. Immunity 2024 ; Gan et al. Cancer Cell. 2024; Mei et al Genome Med. 2024 ; Bizimar et al. Nat Med. 2024; Keshari et al. Cell Reports. 2024; Scortegagna et al. Cancer Res. 2025 ; Wisniewski et al. Cell Rep. 2025 ; Ramirez and Akkari Trends Cancer. 2025

EOS-215, a first-in-class TREM2 antagonist

EOS-215 is a potent, high affinity and cross-reactive TREM2 antagonist

A Cell	K_d (nM)	EC_{50} (nM)
Human monocyte derived macrophages	0.41	0.33
Mouse bone marrow derived macrophages	0.11	0.13
CHO-K1 overexpressing **cynomolgus** TREM2	0.29	0.50





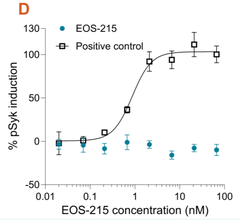
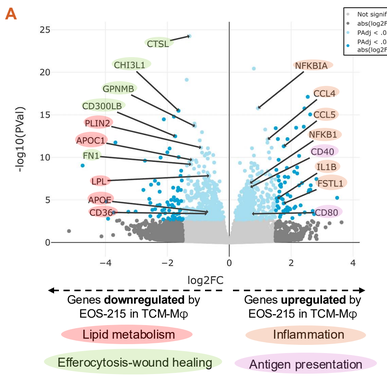
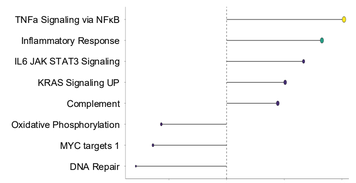


Fig. 1. A. EOS-215 binding affinity for human, mouse and cynomolgus TREM2 measured by flow cytometry **B.** *In silico* predicted complex between human TREM2 (grey) and EOS-215 (blue) or phosphatidylserine (PS) (pink). EOS-215 binds to an epitope that has a crucial role in multimerization as well as PS binding. **C.** EOS-215 competition with human low-density lipoprotein (LDL) measured by flow cytometry. **D**. SYK phosphorylation assay measured by αLISA.

EOS-215 profoundly impacts macrophage identity

EOS-215 shifts macrophage pro-tumoral programming…





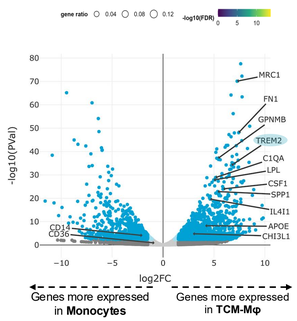
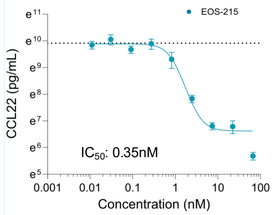
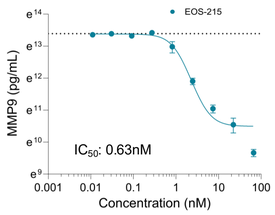


Fig. 3. Macrophages were differentiated from monocytes exposed to tumor conditioned media from a TNBC cell line (MDA-MB-231) and IL-4 (TCM-Mφ) in presence of EOS-215 over 6 days. **A.** Transcriptome comparison between control and EOS-215 treated conditions reveals that the expression of more than 1000 genes was significantly modified. **B.** Hallmark gene set enrichment analysis (GSEA) revealed a significant enrichment in genes related to metabolism and regulation of the immune response in EOS-215 treated condition compared with isotype control. **C.** Transcriptome comparison between freshly isolated monocyte and TCM-Mφ demonstrates that this differentiation protocol leads to an upregulation of TREM2 and associated gene signature.

In vitro models using tumor conditioned media have emerged as an alternative to represent the complex biology of tumor-associated macrophages, complementing the cytokine-derived models (Cassetta et al. Cancer Cell. 2019, Benner et al. J Immunother Cancer. 2019).

...all the way to inhibiting their release of pro-tumoral factors



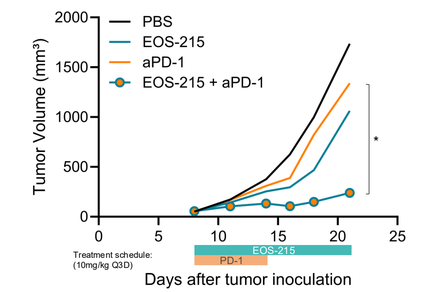


MMP9 is involved in multiple pro-tumoral processes, including angiogenesis, regulation of inflammation and metastatic niche formation (Kassenbrock et al. Cell. 2010). **CCL22** is a chemokine essential for Treg infiltration leading to the inhibition of anti-tumoral response in multiple cancer indications (Röhrle et al. Adv Exp Mel Bio. 2020).

Fig. 4. M2a macrophages were generated in presence of EOS-215 and then stimulated overnight with LPS at 100 ng/mL. CCL22 and MMP9 concentrations were measured by MSD. In this model, EOS-215 exhibits a sub-nanomolar potency to inhibit the secretion of pro-tumoral factors.

EOS-215 unlocks anti-PD-1 resistance

EOS-215 in combination with anti-PD-1 significantly reduces CT26 tumor growth and reprograms macrophages *in vivo*



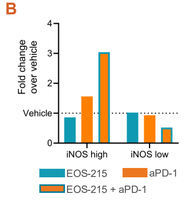


Fig. 6. A. Median growth curves of CT26 s.c. partially resistant to anti-PD-1 therapy showing significantly reduced tumor growth treated with a combination of anti-PD-1 and EOS-215. **B.** Reprogramming of tumor associated macrophages towards a pro-inflammatory phenotype following combination treatment in the CT26 model, illustrated by the Fold Changes (% of macrophages over vehicle) of iNOS high and low macrophage subpopulations identified by t-SNE analysis (flow cytometry).

TREM2 blockade overcomes primary therapy resistance in a PDAC mouse model

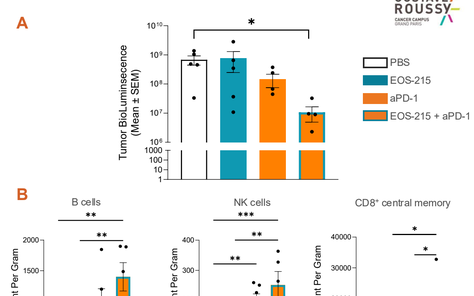
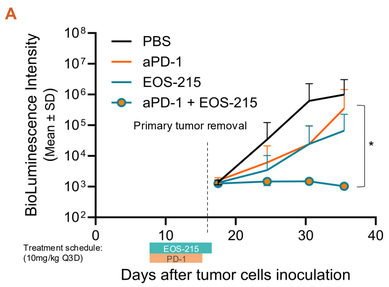


Fig. 7. A. Mean bioluminescence intensity from an orthotopic PDAC mouse model (KPC) showing significantly lower tumor burden in mice treated with a combination of anti-PD-1 and EOS-215, 21 days post inoculation. Treatment started on day 12, EOS-215 and aPD-1 were administered IP at 10 mg/kg, Q3D. **B.** Increased B cells, NK cells and CD8⁺ T_{cm} infiltration following combination treatment observed in the TME by flow cytometry analysis 35 days post inoculation (endpoint).

EOS-215 synergizes with a-PD-1 to prevent spontaneous lung metastases in a TNBC mouse model



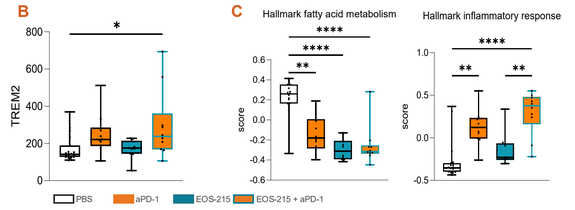
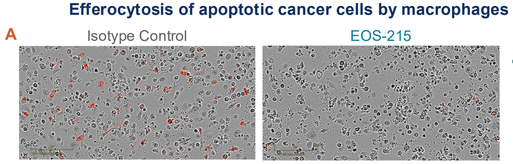
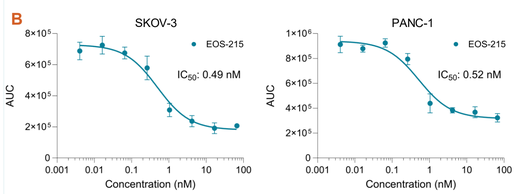


Fig. 8. A. Mean bioluminescence intensity curves of lung metastases from a 4T1 TNBC model showing significant prevention of metastasis burden in mice treated with a combination of anti-PD-1 and EOS-215 in neoadjuvant settings. **B.** Anti-PD-1 treatment increases *TREM2* expression levels (bulk RNA sequencing analysis from 4T1 tumors). **C.** Mechanistically, bulk RNA sequencing analysis demonstrates that anti-PD-1 increases inflammatory response while EOS-215 impairs lipid metabolism related signatures and that there is synergy when both drugs are combined.

EOS-215 shuts down pro-tumoral wound healing

Efferocytosis of apoptotic cancer cells by macrophages is inhibited by EOS-215



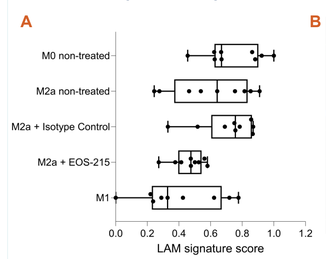


Efferocytosis, the clearance of cellular debris and apoptotic cells, promotes pro-resolving signaling in macrophages, essential for wound healing and pro-tumoral functions (Park et al. Nat Immunol. 2023)

Fig. 2. A. Representative images from an efferocytosis assay. M2a macrophages were cocultured in presence of apoptotic SKOV-3 or PANC-1 tumor cells labelled with pH-rodo. Red fluorescence represents efferocytosis events. **B.** The data represent the area under the curve (AUC) of pH-rodo associated fluorescence measured with LIPSI system.

EOS-215 disrupts macrophage lipid management capacity

EOS-215 prevents Lipid-Associated Macrophages (LAMs) programming and function



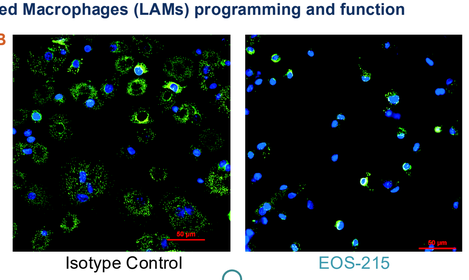
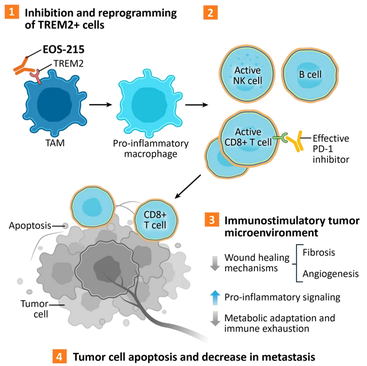


Fig. 5. A. Monocyte derived macrophage transcriptome was measured by mRNA sequencing. LAM signature (Ma et al., 2022) was applied to the dataset. **B.** M2a macrophages were differentiated in presence of EOS-215 or isotype control. Then, macrophages were treated with fatty acid labelled with bodipy for 24 hours and lipid content was analyzed by fluorescence imaging.

LAMs play a major role in cancer initiation and progression (Taranto et al. Nat Rev Cancer 2024)

Conclusions & perspectives



- ► EOS-215 is the first selective and highly potent TREM2 antagonist designed to reverse the tumor-promoting functions of macrophages.
- ► EOS-215 exhibits high potency to inhibit tolerogenic processes such as LAM formation and efferocytosis.
- ► Multiple mode-of-actions translated to *in vivo* efficacy in relevant models of primary tumors and metastases where EOS-215 strongly synergizes with anti-PD1.
- ► EOS-215 is currently being investigated in a First-in-Human Phase I/Ib Dose Escalation and Expansion Cohort Study as Monotherapy and in Combination with Pembrolizumab in Participants with Advanced Solid Tumors (NCT06877533).

EOS-215 ability to reverse the many pro-tumoral roles of TREM2⁺ macrophages driving therapy resistance opens the opportunity for promising combinations with standard-of-care therapies.

For more information, visit iTeos Therapeutics at ***booth #3240***

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