Thromboxane A2-Prostanoid Receptor (TPR) Blockade with Ifetroban Disrupts Platelet-Tumor Cell Interactions to Reduce Metastasis in Triple-Negative Breast Cancer

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BACKGROUND

- Platelets drive multiple steps of metastasis, including:
  Circulating tumor cell (CTC) survival
  Vascular arrest and adhesion
  Extravasation and niche formation
- Thromboxane A_2 (TXA_2) is a key platelet activator functioning via the Thromboxane–prostanoid receptor (TPR)
- Ifetroban, a selective TPR antagonist, is FDA-orphan designated and clinically safe

Rationale: Blocking platelet–tumor interactions may reduce metastasis in TNBC.

OBJECTIVE

- Evaluate the effect of TPR inhibition with ifetroban on:

1. Platelet activation and tumor-cell interactions
2. Metastasis in zebrafish, 4T1, and MDA-MB-231 TNBC models
3. Tumor burden and immune-related effects

METHODS

In vitro assays



Platelet activation (flow cytometry)

Platelet–tumor cell binding

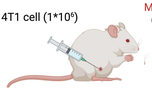
In vivo models



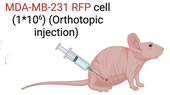
72-96 hpf
Injection of human cancer cells in the yolk.

1. Zebrafish xenograft (MDA-MB-231-RFP)
   - Platelet recruitment (CD41⁺)
   - Metastatic dissemination

2. BALB/C
4T1 cell (1*10⁶)



3. Athymic nude mice
MDA-MB-231 RFP cell (1*10⁶) (Orthotopic injection)



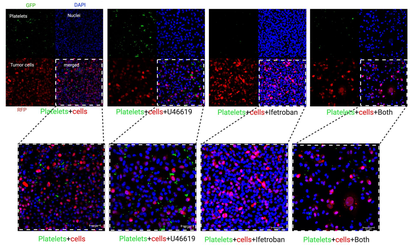
Ifetroban treatment: 50 mg/kg, oral, starting 2 weeks pretreatment, continued till end

Analyses

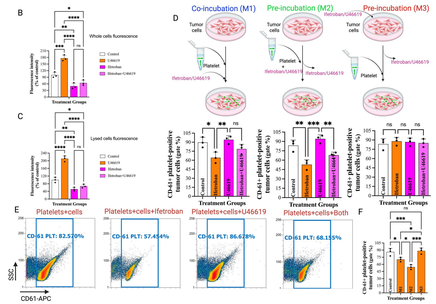
- IVIS imaging
- Histopathology(H&E lung, liver)
- Circulating TXB_2 quantification
- Tumor volume/weight
- Safety and cytotoxicity (up to 500 µM in vitro)

RESULTS

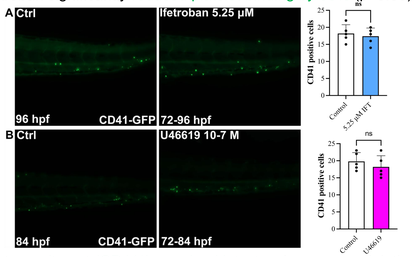
Ex-vivo platelet-tumor cell adhesion



Ifetroban significantly reduced platelet activation ($p<0.05$)

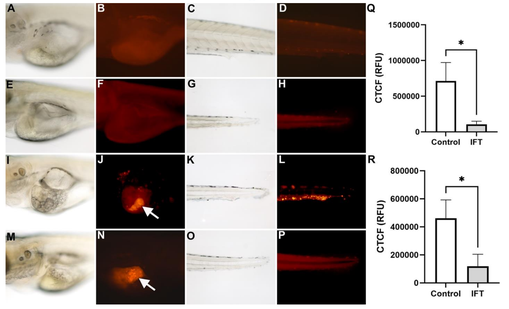


Ifetroban significantly reduced platelet binding by 65% ($p<0.05$)



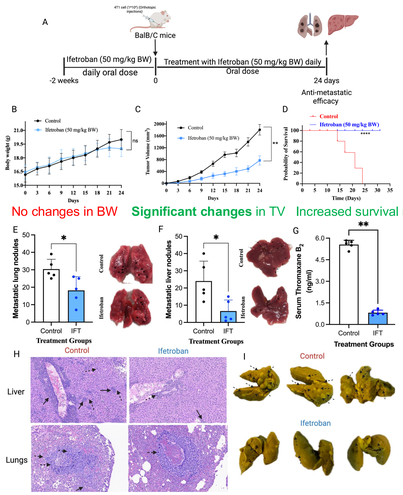
Platelet recruitment (CD41⁺) remained intact → immune modulation without platelet depletion

Zebrafish xenograft model



Ifetroban reduced metastatic dissemination of MDA-MB-231-RFP cells.

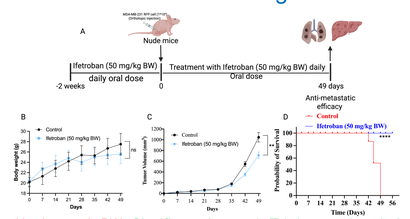
4T1 Syngeneic TNBC model



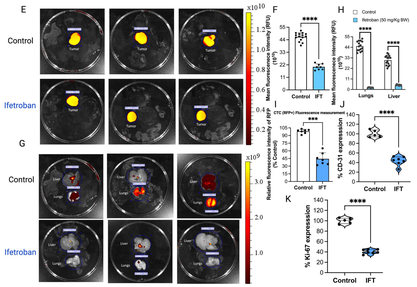
No changes in BW **Significant changes** in TV Increased survival rate

Ifetroban significantly reduced metastatic foci ($p<0.05$) in lungs & liver

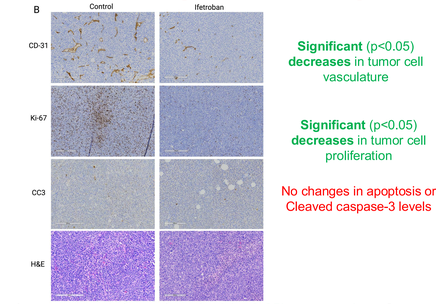
MDA-MB-231-RFP Xenograft model



No changes in BW **Significant changes** in TV Increased survival rate



Ifetroban treatment showed marked ($p<0.05$) suppression of CTCs metastasis to liver/lungs, tumor volume and weight



Significant ($p<0.05$) **decreases** in tumor cell vasculature

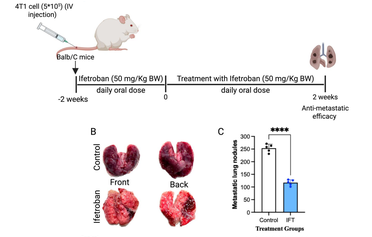
Significant ($p<0.05$) **decreases** in tumor cell proliferation

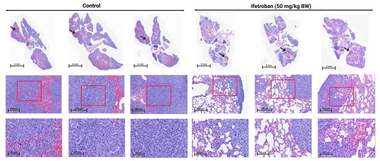
No changes in apoptosis or Cleaved caspase-3 levels

Ifetroban treatment showed marked ($p<0.05$) suppression of tumor growth modulating immune system

RESULTS

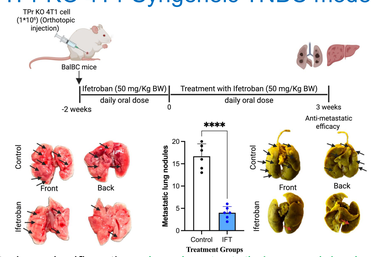
4T1 experimental metastatic model





Ifetroban significantly reduced lungs metastatic ($p<0.05$) in the absence of a primary tumor

TPr KO 4T1 Syngeneic TNBC model



Ifetroban significantly reduced metastatic lung nodules by 72%

CONCLUSION

- Ifetroban disrupts platelet–tumor interactions in TNBC.
- Significantly reduces metastasis in three independent model systems.
- Demonstrates broad anti-metastatic efficacy without direct tumor toxicity.
- Supports repurposing ifetroban as an adjuvant anti-metastatic therapy.

Curious about our work?
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