Bioengineering IV

Enhancing nano-immunotherapy efficacy in mouse sarcoma models through tumor microenvironment reprogramming

Antonia Charalambous, PhD
Cancer Biophysics Laboratory
University of Cyprus

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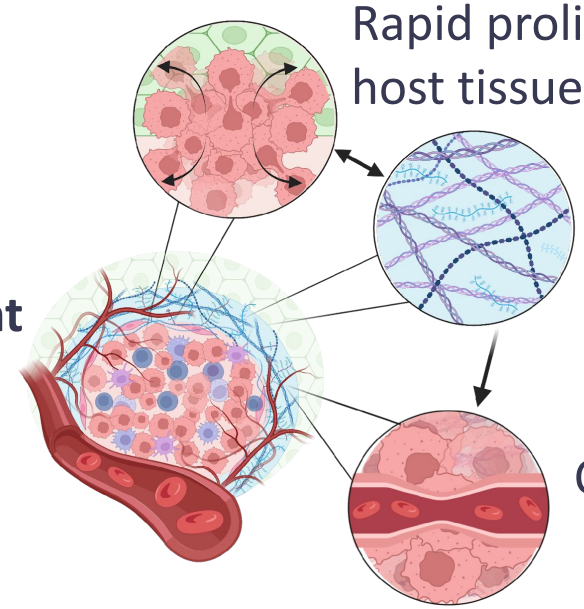
Tumor Microenvironment Abnormalities: Barriers to Effective Drug Delivery

Despite significant advancements in cancer therapeutics, in particular Nanomedicine & Immunotherapy, the efficacy of these treatments is often hindered

Tumor Microenvironment (TME) Abnormalities



Rapid proliferation of cancer cells in the confined. Space of the host tissue generates **mechanical forces**

Dense ECM (composed of mainly collagen fibers & hyaluronan) leads to **tumor stiffening**

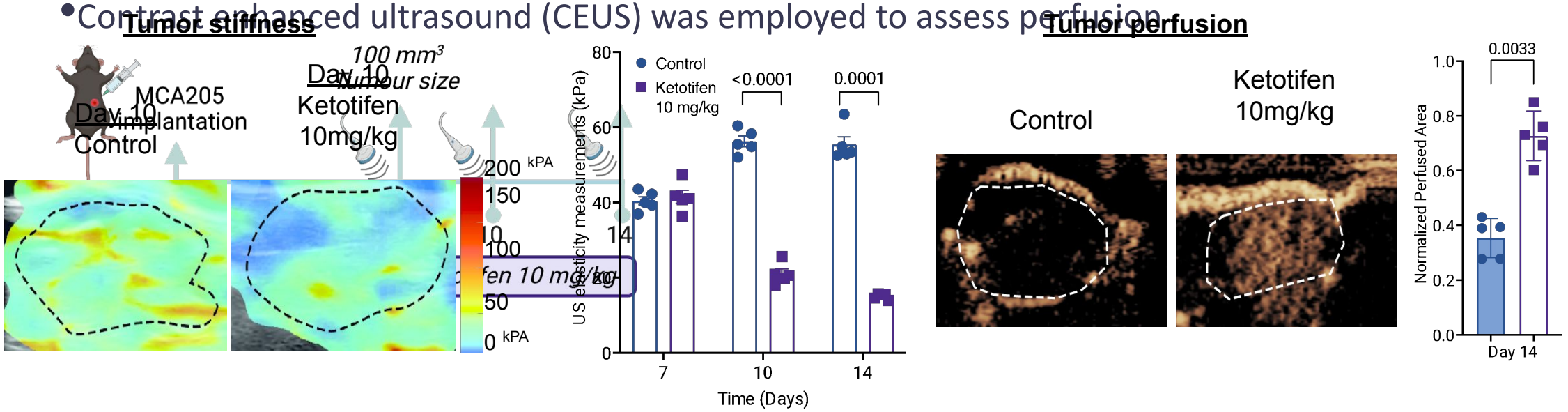
Compressed tumor blood vessels cause **hypo-perfusion**

Utilizing Mechanotherapeutics to Overcome Tumor Microenvironment Abnormalities

- Mechanotherapeutics are specialized drugs with tissue reprogramming capabilities
- Conventional drugs that are used in other diseases (e.g. anti-hypertensive, losartan)
- They function as TME normalizing agents, targeting the mechanical environment of a tumor such as stiffness with the aim to improve perfusion
- **Ketotifen**, originally recognized for its anti-histamine properties, has now emerged as a mechanotherapeutic agent

Ketotifen reduces tumor stiffness and increases tumor perfusion

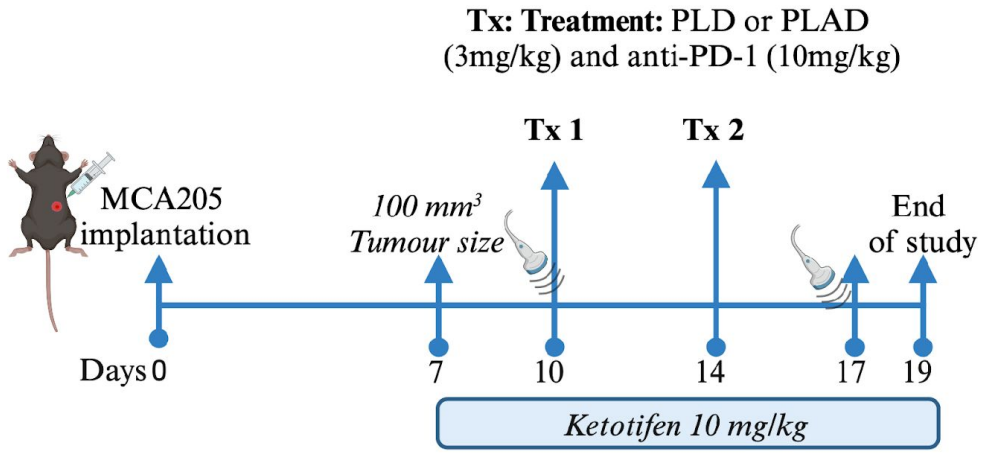
- Utilized a mouse model of fibrosarcoma, to investigate the effects of ketotifen on the TME
- Shear wave elastography (SWE) was used to quantify tumor stiffness
- Contrast enhanced ultrasound (CEUS) was employed to assess perfusion



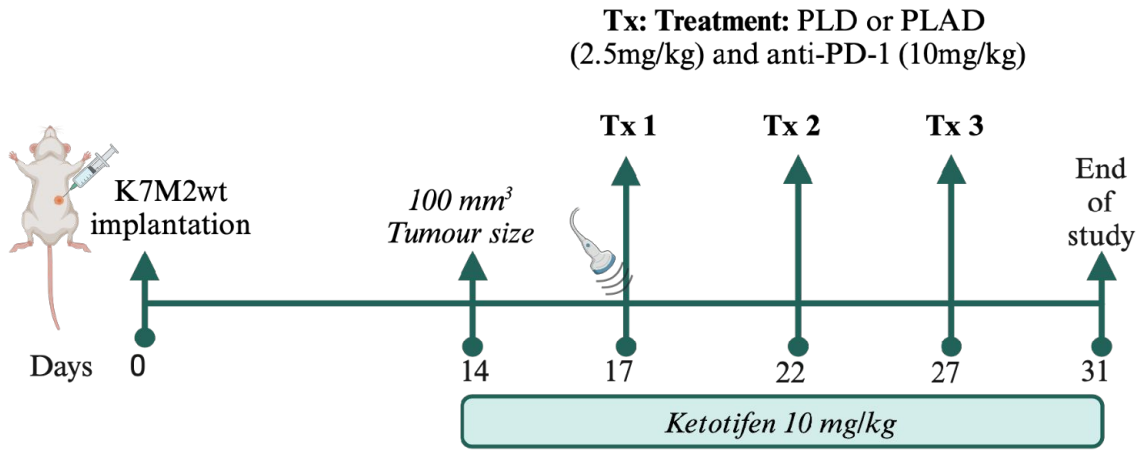
Panagi, M et al. Clinical Cancer Research. 2024

Evaluating Ketotifen's Impact on Enhancing Nano-immunotherapy in Sarcoma Models

Fibrosarcoma model



Osteosarcoma model



PLD: Pegylated Liposomal-Doxorubicin (Doxil)
- Chemotherapy
- Disrupts DNA replication and induces cell death in cancer cells

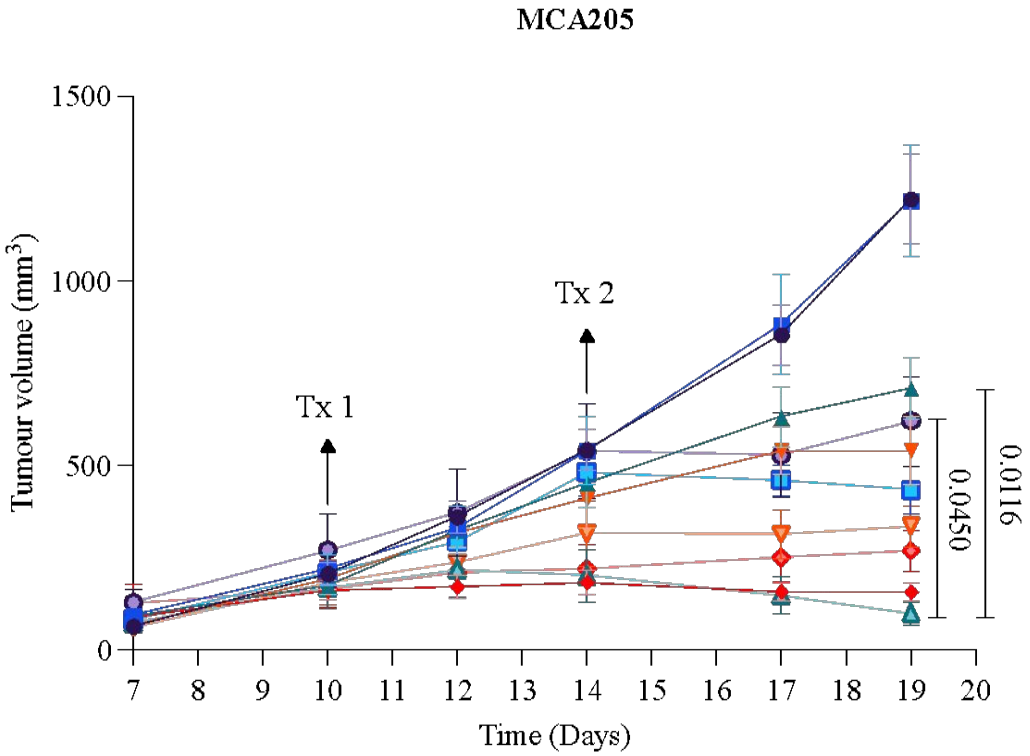
or

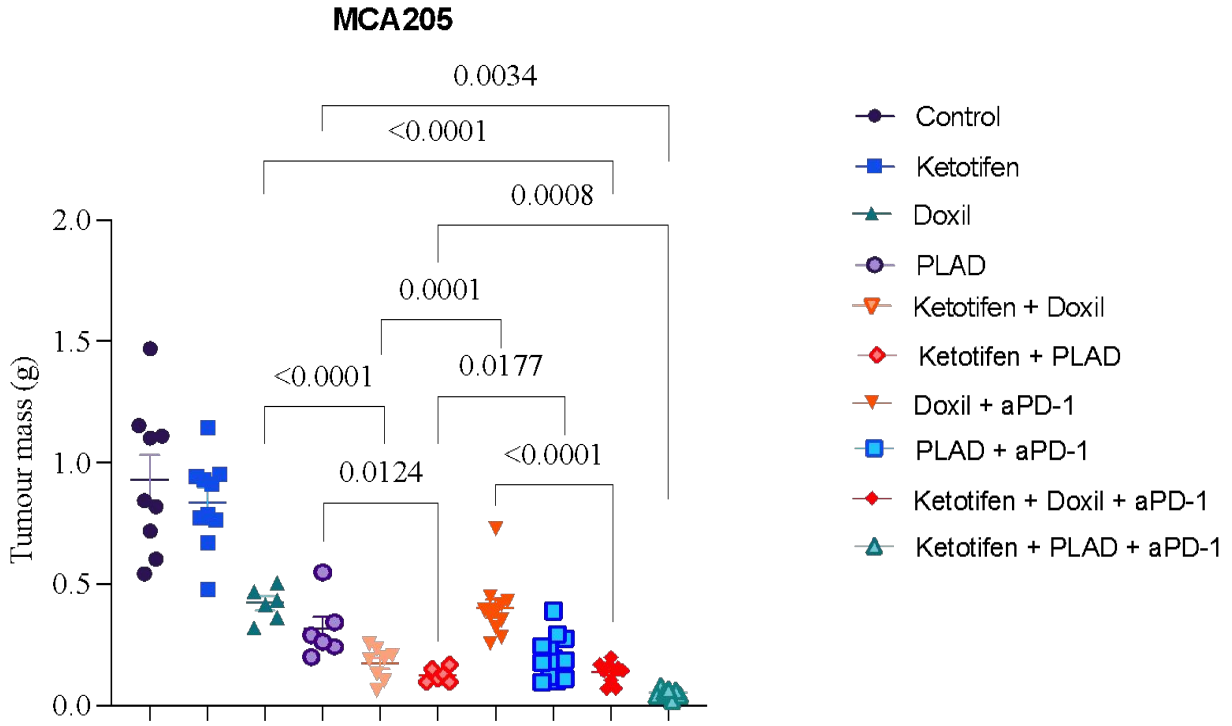
PLAD: Pegylated Liposomal Alendronate/Doxorubicin
- Alendronate: Amino-bisphosphonate
- Modulates the immune response

Anti-PD-1:
- Immune checkpoint inhibitor
- Enhances immune attack on cancer cells

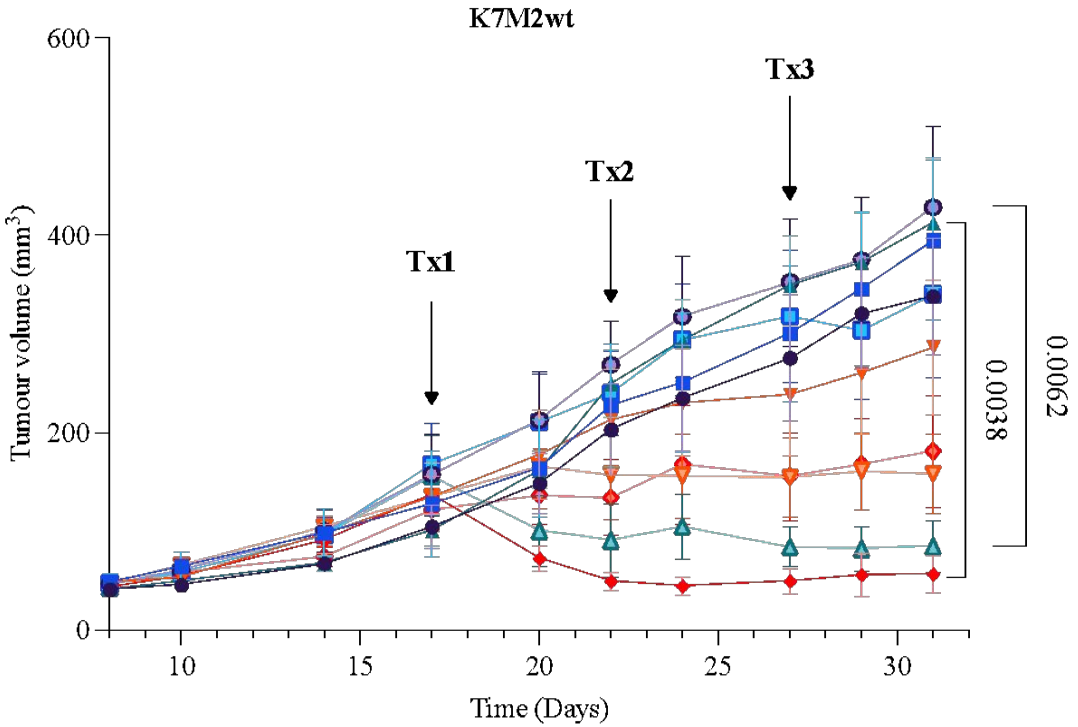
Charalambous, A et al. Molecular Cancer Therapeutics. Accepted

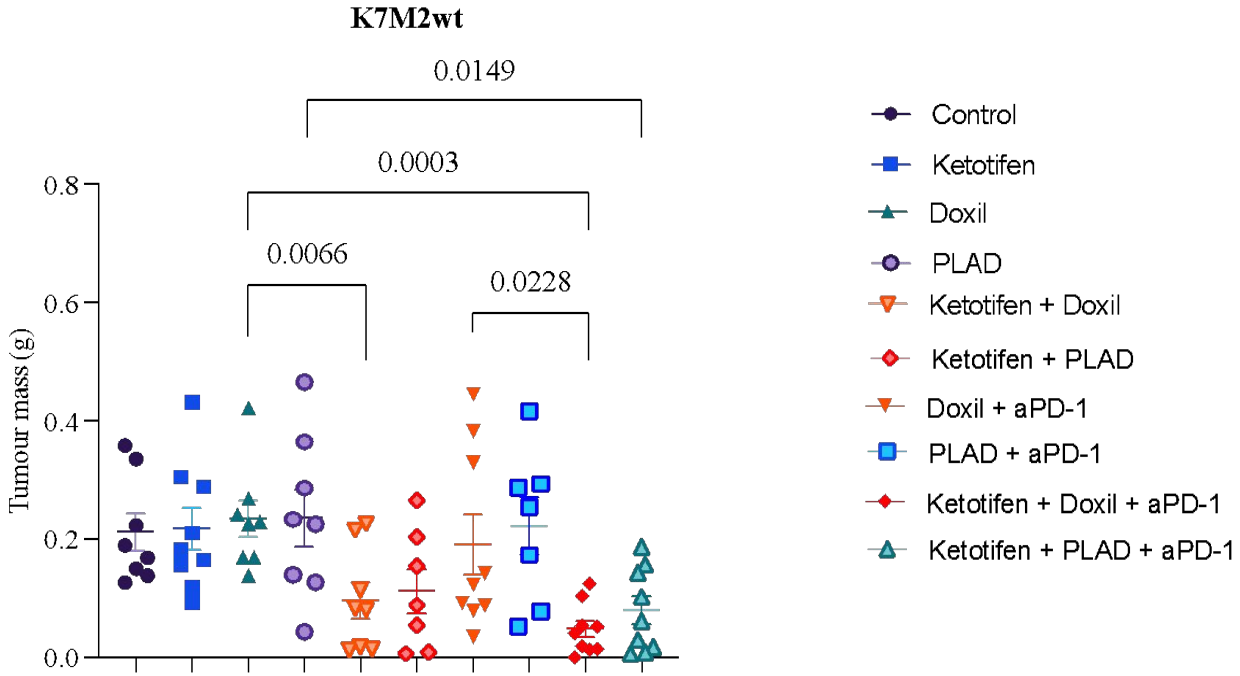
Ketotifen-induced TME Reprogramming Enhanced Nano-Immunotherapy Efficacy: Fibrosarcoma model





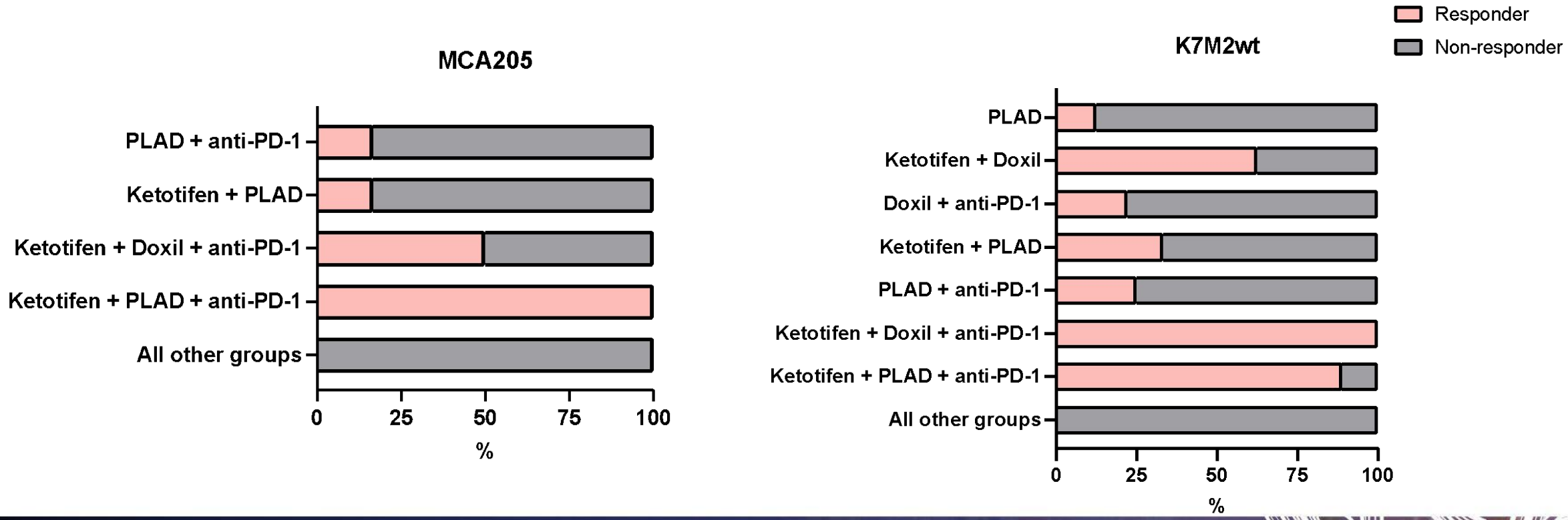
Ketotifen-induced TME Reprogramming Enhanced Nano-Immunotherapy Efficacy: Osteosarcoma model





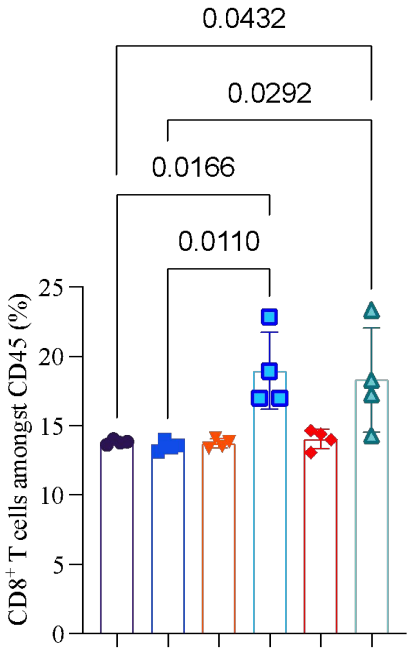
Examining Treatment Outcomes: Responders vs Non-Responders

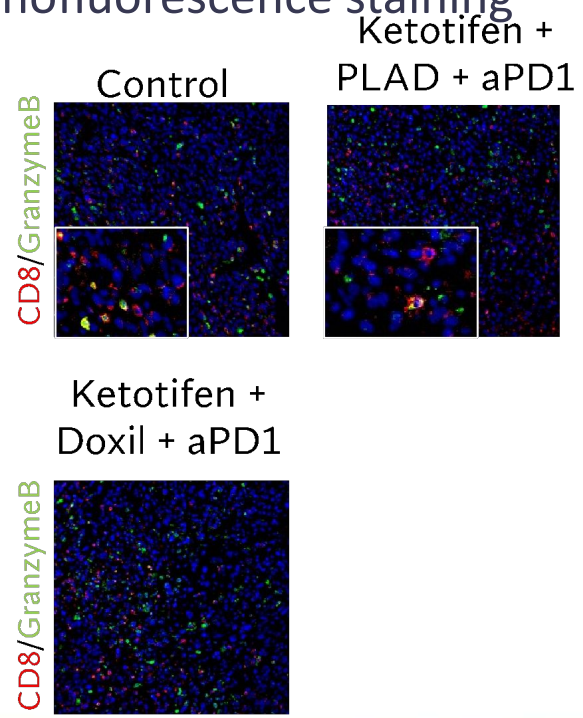
Responder: defined as a subject whose tumor volume was smaller on the day of treatment completion compared to the day of treatment initiation

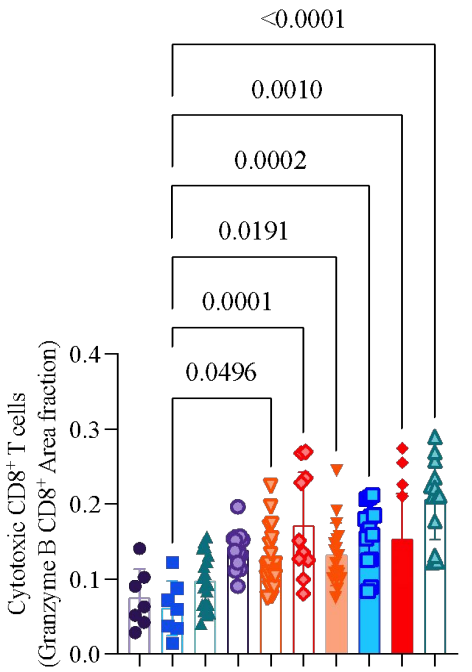


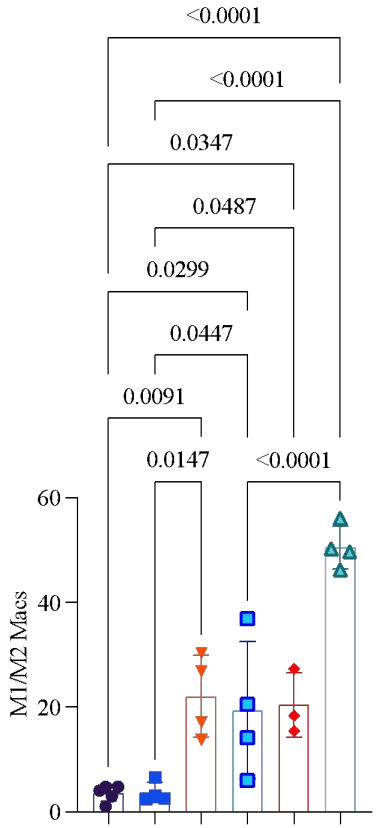
Ketotifen-Induced TME Reprogramming Enhanced Nano-Immunotherapy Efficacy by Enhancing the Cytotoxic Immune Response: Fibrosarcoma model

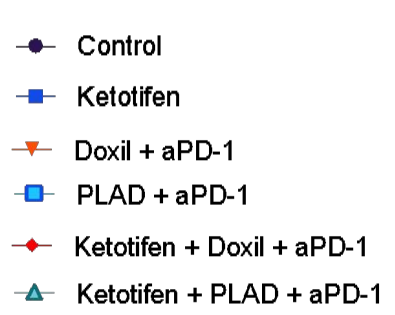
- Utilized flow cytometry to characterize immune cell populations
- Performed immunofluorescence staining





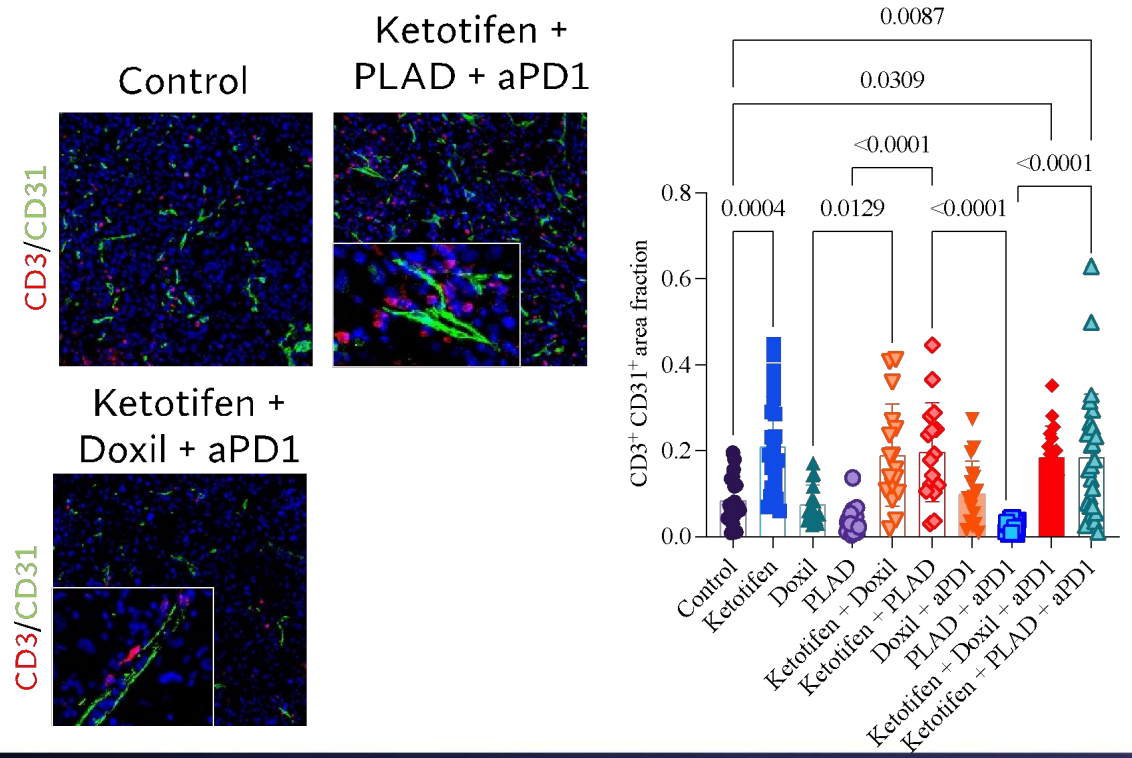




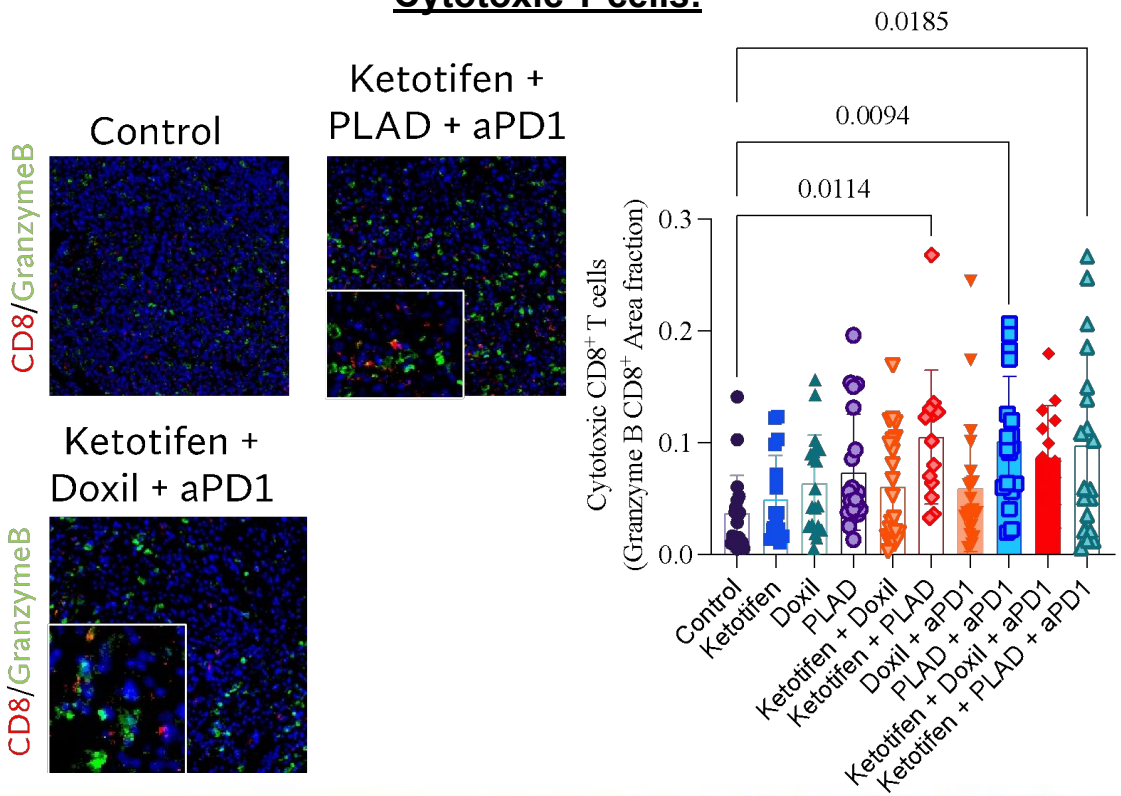


Ketotifen-Induced TME Reprogramming Enhanced Nano-Immunotherapy Efficacy by Enhancing the Cytotoxic Immune Response: Osteosarcoma model

Tumor T cell infiltration via CD3-CD31 co-localization:



Cytotoxic T cells:



Conclusions

- Overcoming TME barriers such as tumor stiffness and poor perfusion is critical for improving drug delivery and therapeutic efficacy

- TME reprogramming with ketotifen, significantly enhances nano-immunotherapy in two sarcoma models

Acknowledgements

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