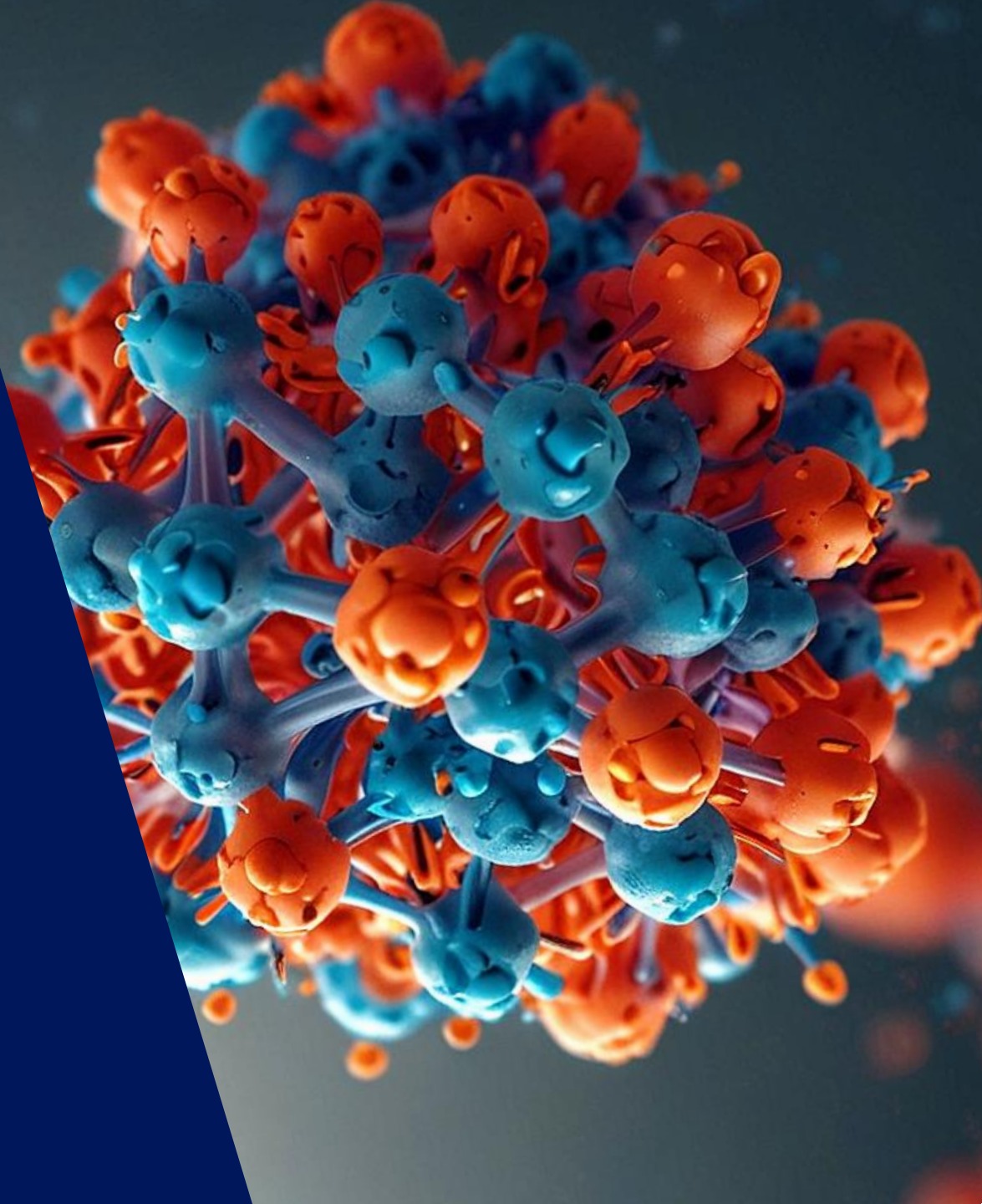
Localized antitumor therapy via mitochondrial apoptosis with siRNA-loaded metallo-alginate hydrogels

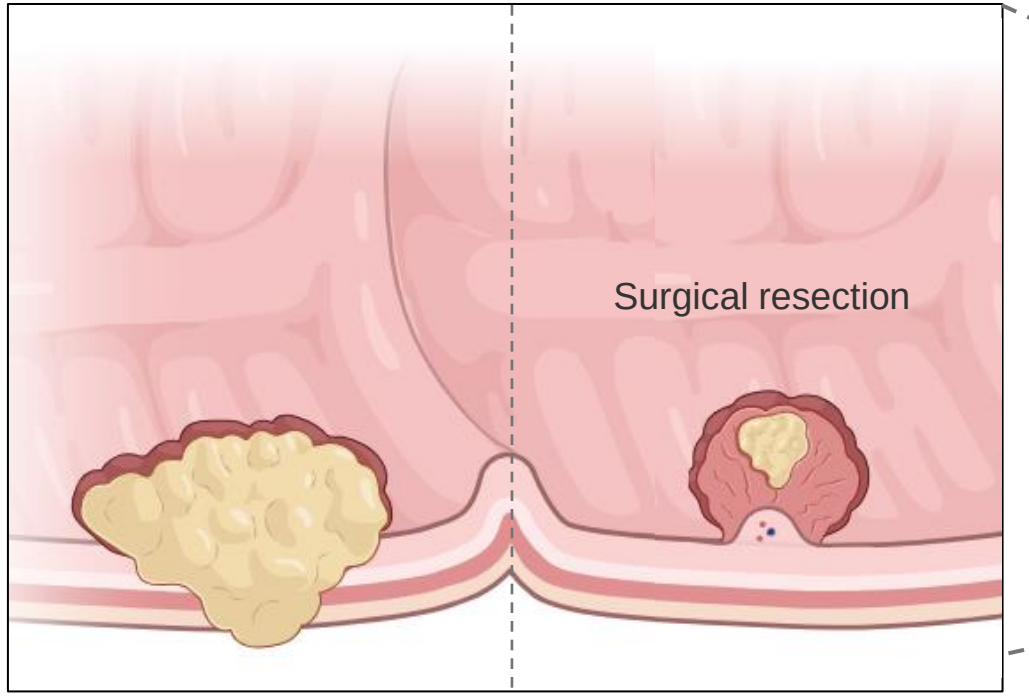
Jennifer Fernández Alarcón
Grup d'enginyeria dels materials (GEMAT)
15th of July 2025



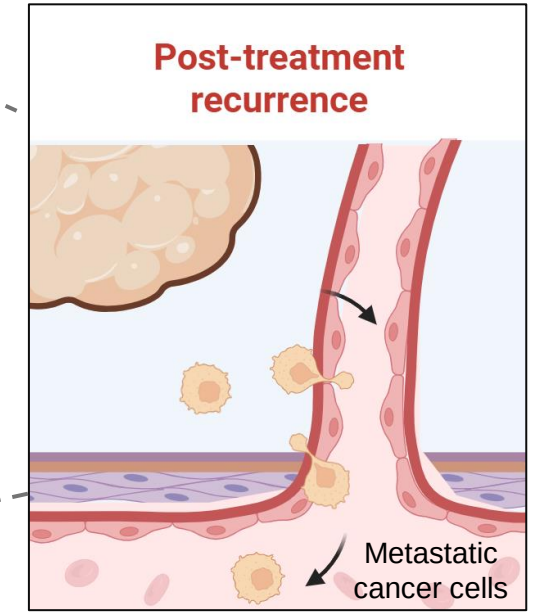
Introduction

Tumor surgical resection

Tumor complete surgical resection, although usually being the standard of care, is hindered due to the complicated anatomy of the diseased tissue.



Patients suffer recurrence and metastasis due to an incomplete surgical resection.



Therefore, there is a clinical need to develop adjuvant biomaterials to potentiate the death of remaining cancer cells preventing tumor recurrence or metastasis.

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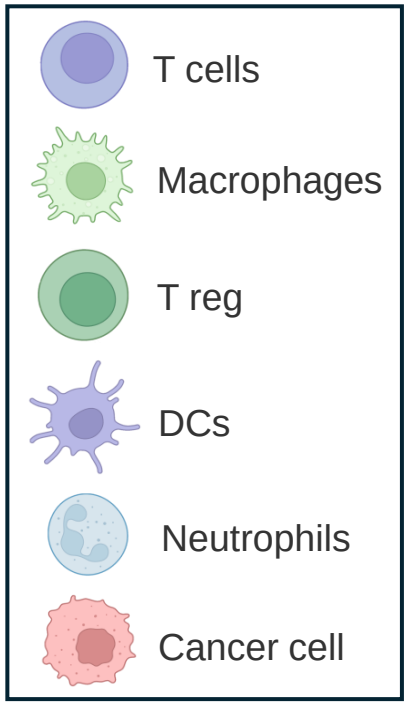
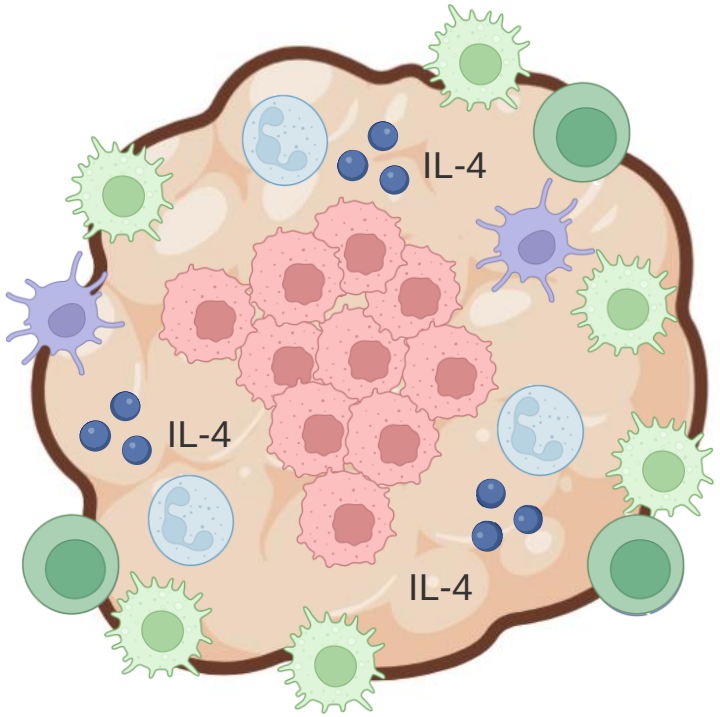
Introduction

Tumor multidrug resistance

Residual cancer cells often respond poorly to systemic therapy do to an immunosuppressive immune system surrounding the TME.





Increase in anti-inflammatory cytokines.

Insufficient tumor-infiltrating lymphocytes.

High tumor-promoting macrophages.

Presence of regulatory T cells.

Multidrug resistance frequently arises as the key obstacle, and tumors present at least one mutation in the PI3K/AKT metabolic pathway.

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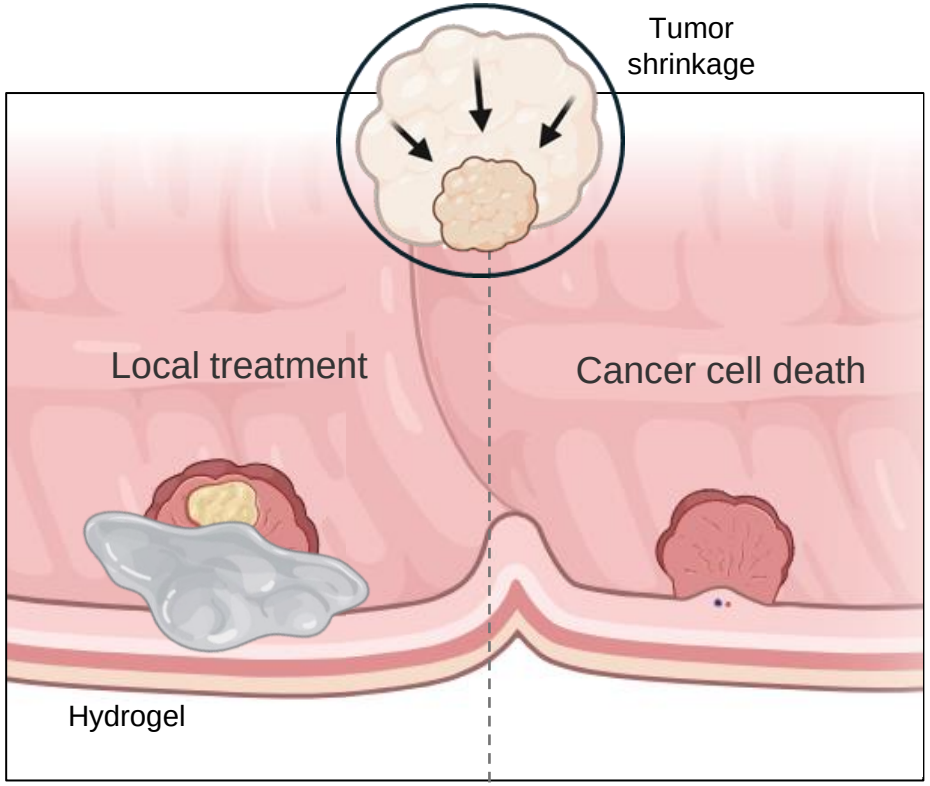
Introduction

Synergistic biomaterials

Some biomaterials are able to reprogram the immune response by modulating ROS levels through macrophage polarization and neutrophil aggregation.



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Introduction

Synergistic biomaterials

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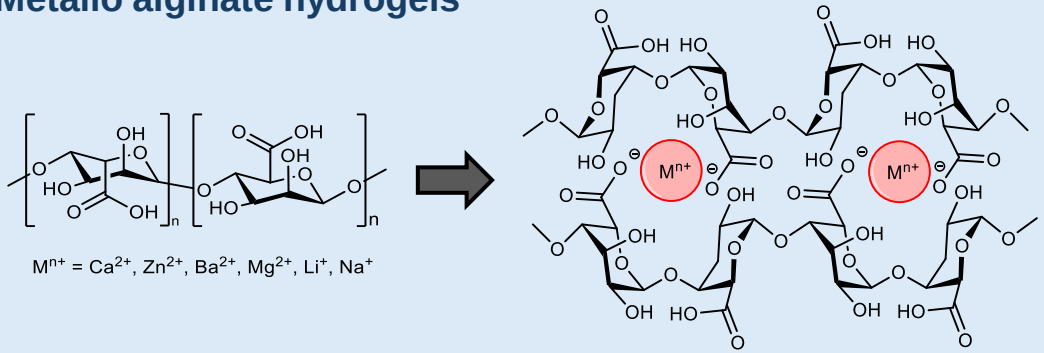
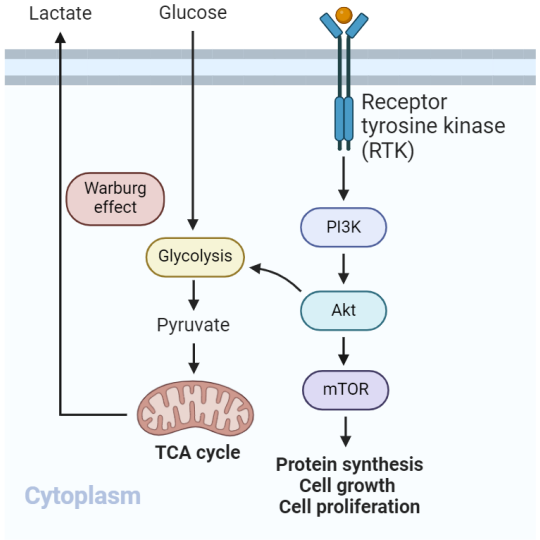
Metallo alginate hydrogels



- Natural anionic polymer
- Biocompatible and biodegradable

Poly beta(amino esters) NPs for mTOR siRNA delivery



Combinatory treatment has the potential to eliminate residual cancer cells and enhance antitumor immunity.

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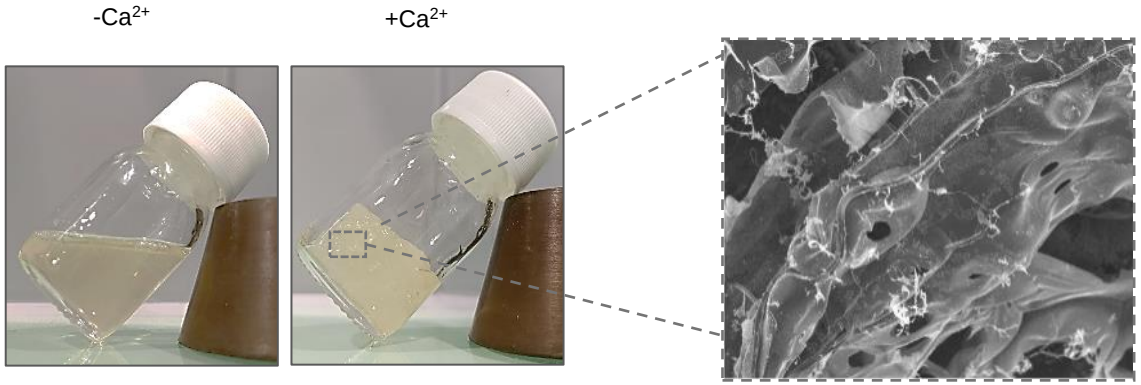
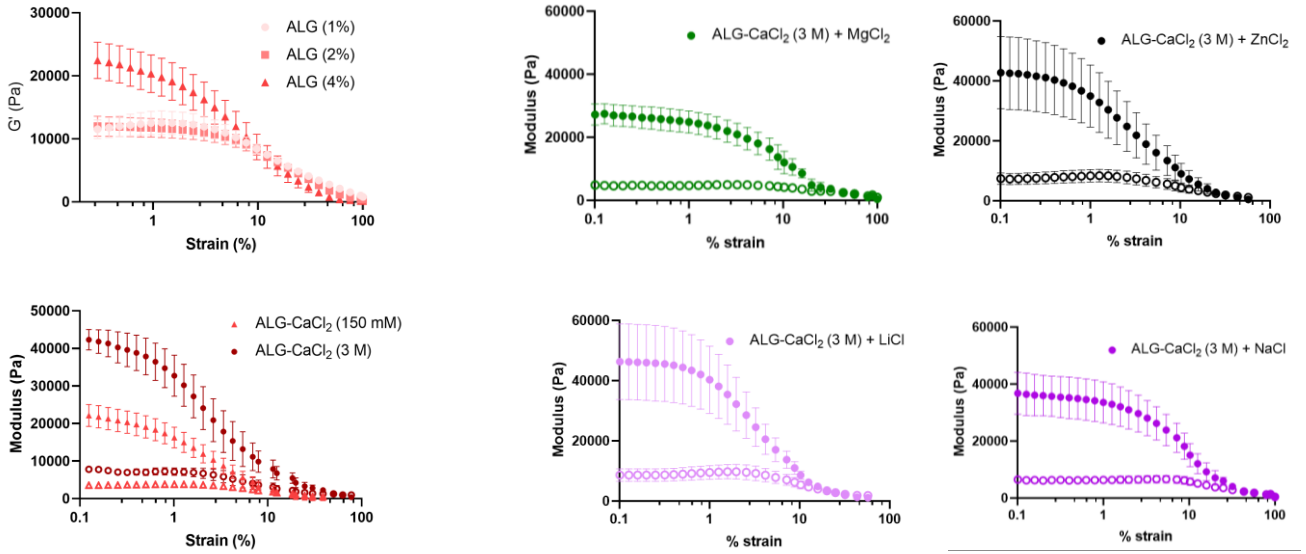
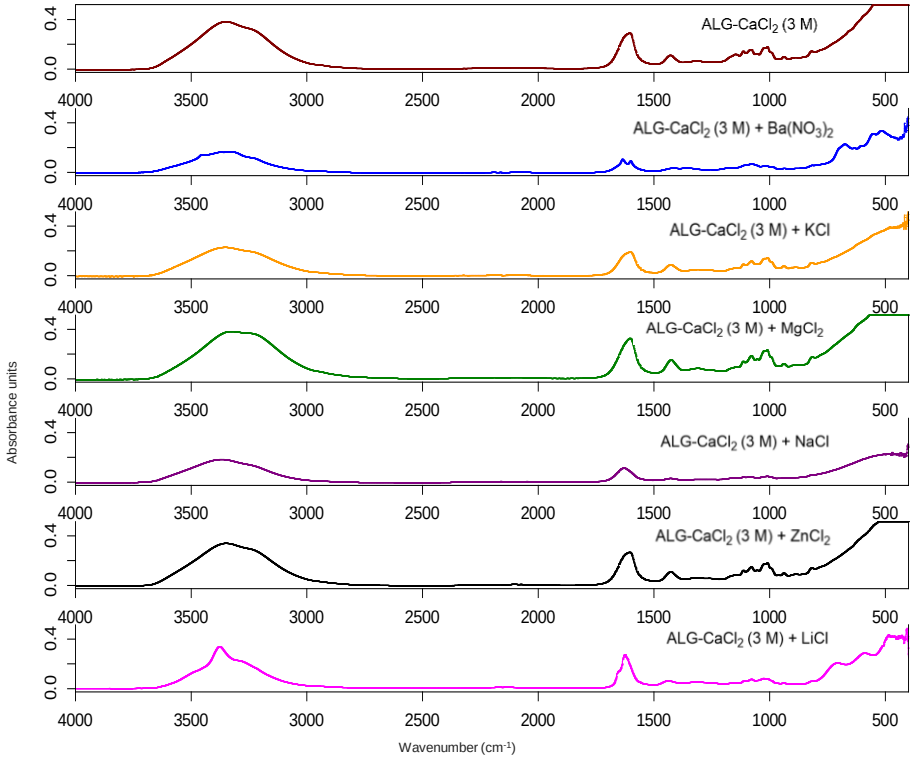
Metallo-alginate hydrogels

Synthesis and characterization







Bivalent cations of Ca^{2+} were mixed with another metallic ions. Even by rheological properties they do not present significant differences, the *in vitro* behavior will vary significantly.

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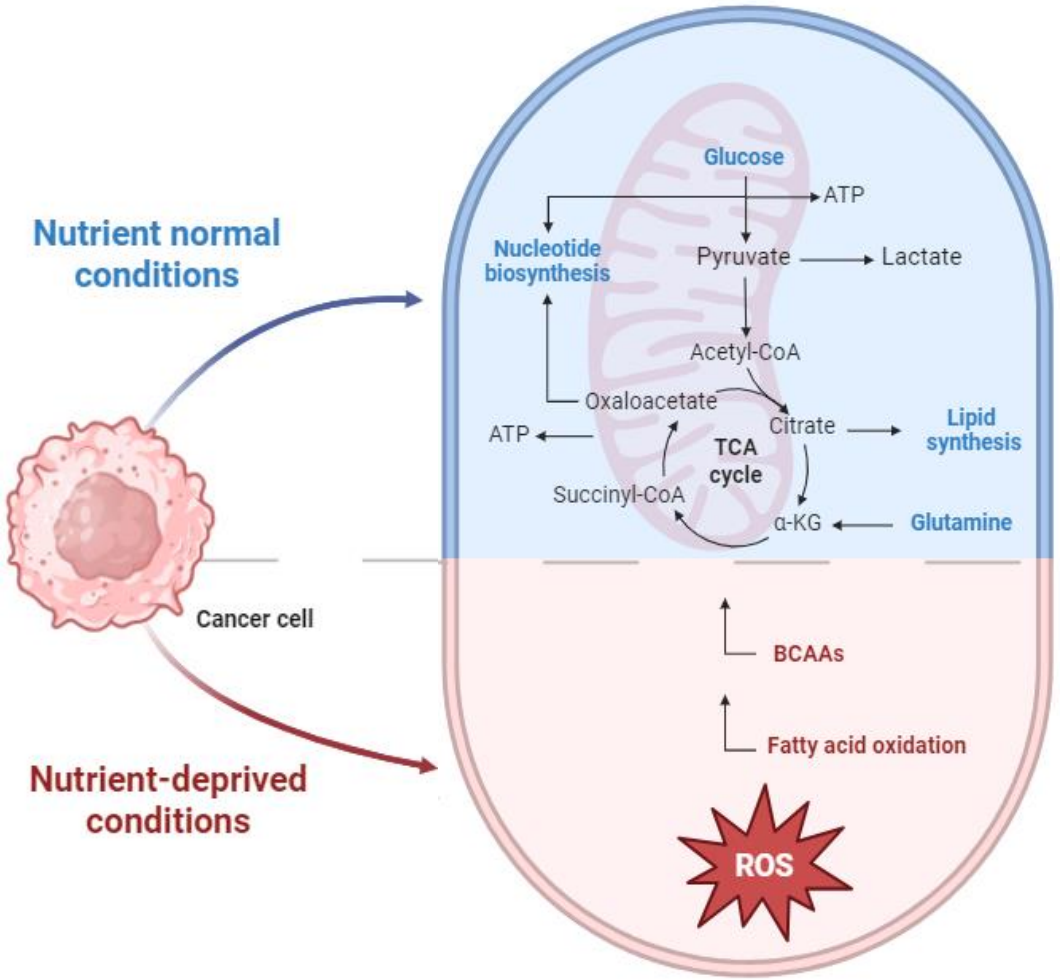
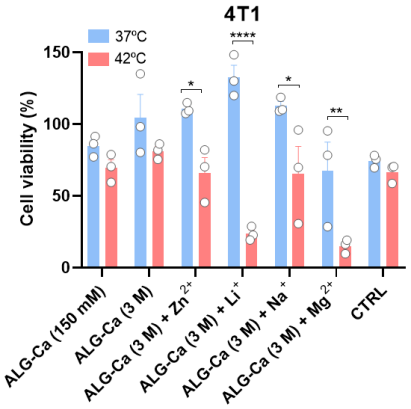
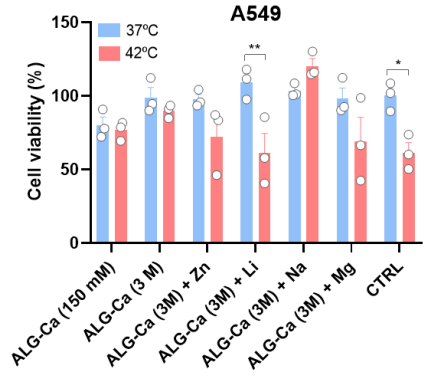
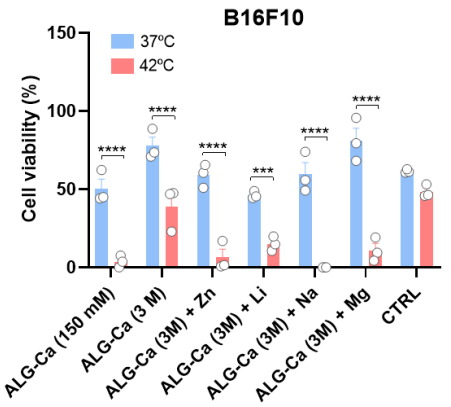
In vitro experiments

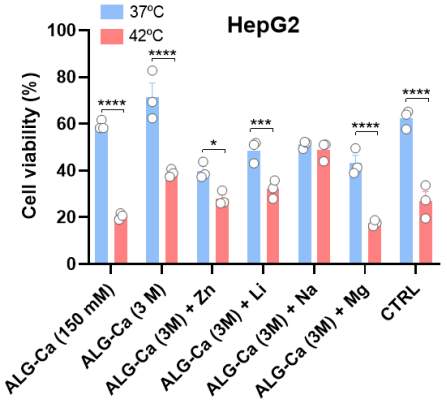
MTT assay

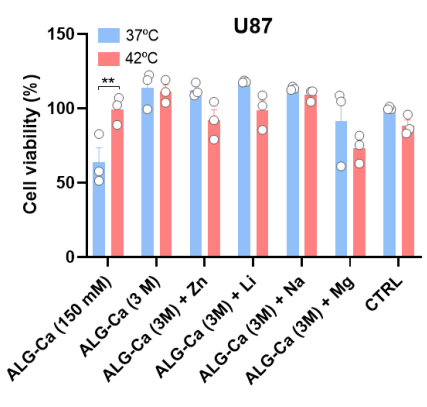












Disruption of intracellular Ca^{2+} hemostasis enhanced localized hyperthermia by causing cancer cell death via mitochondrion disruption.

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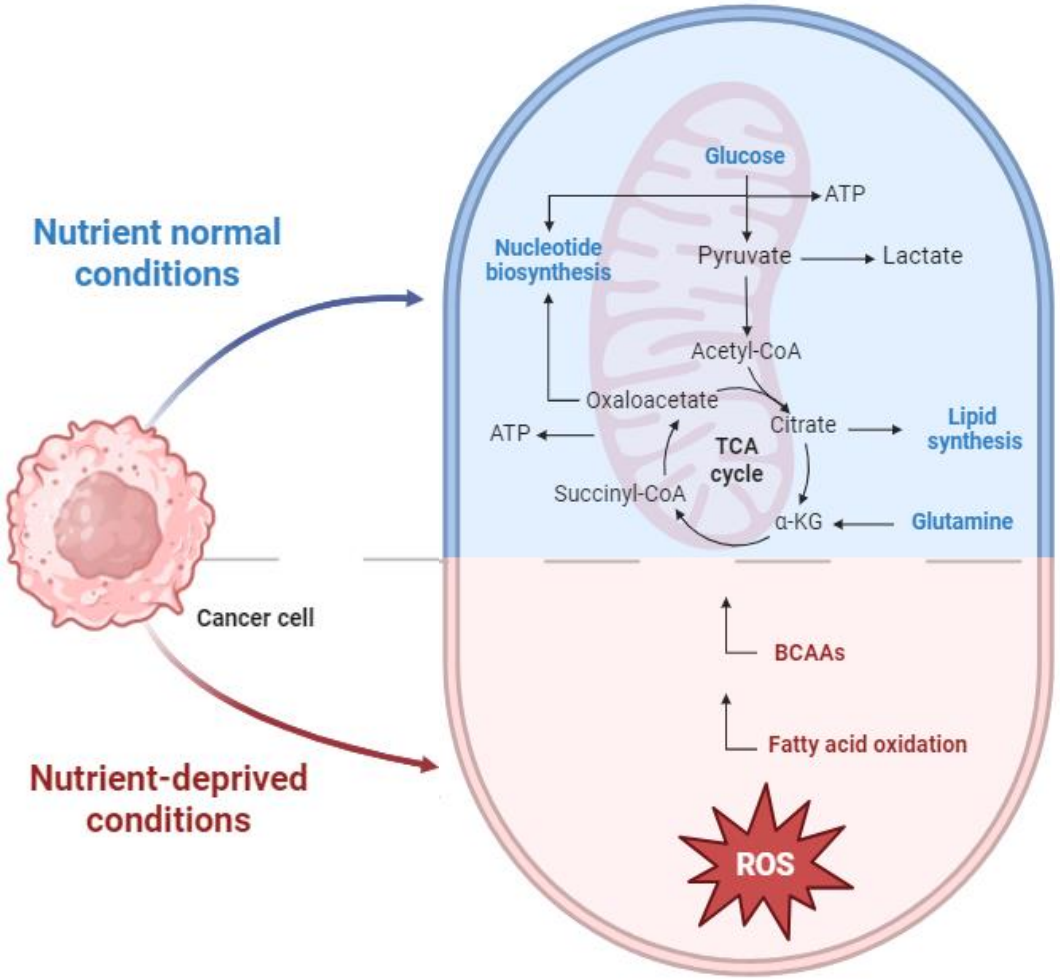
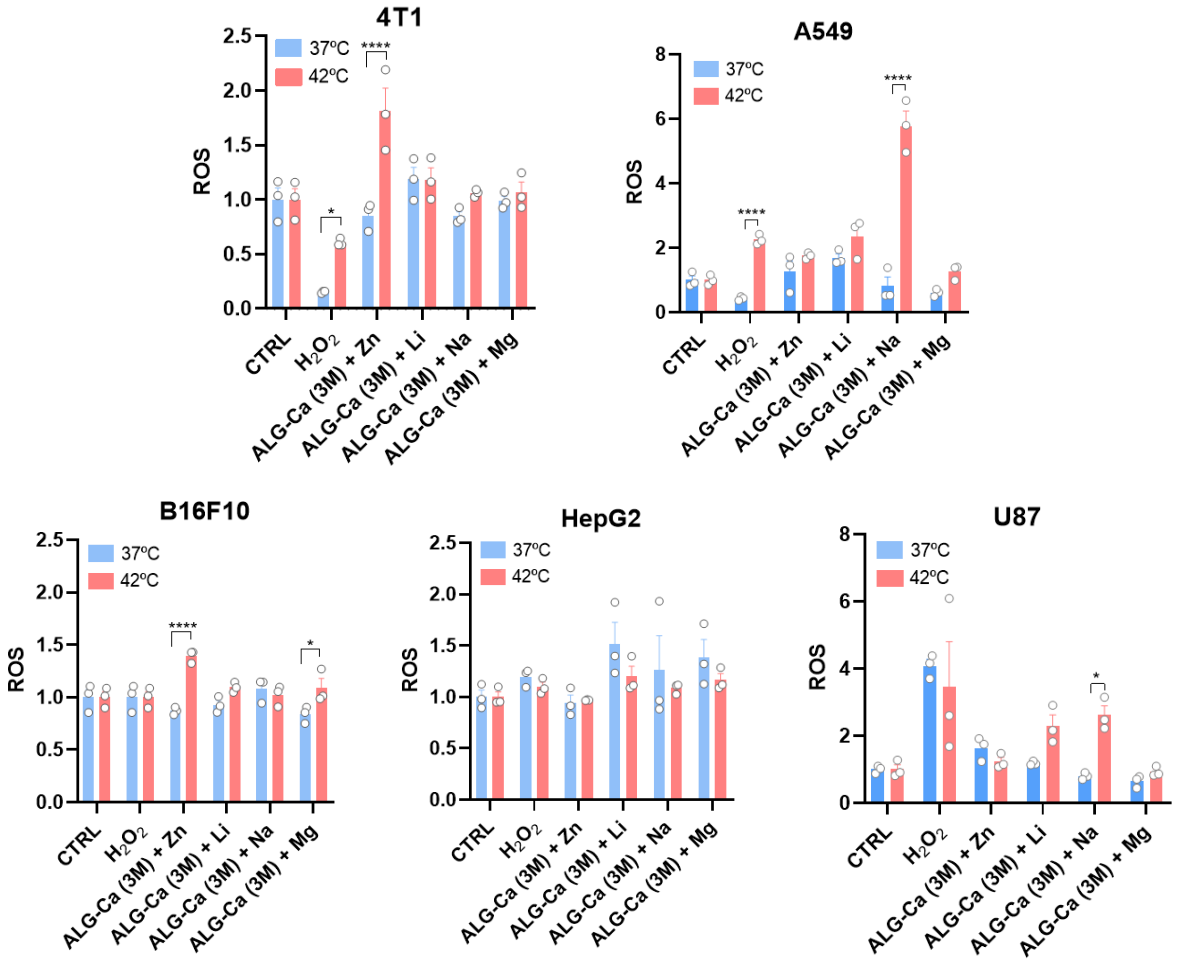
In vitro experiments

ROS generation





ROS generated by the release of the metallic ions can kill tumor cells and also stimulate pro-inflammatory effects, enhancing the activation of the immune response.

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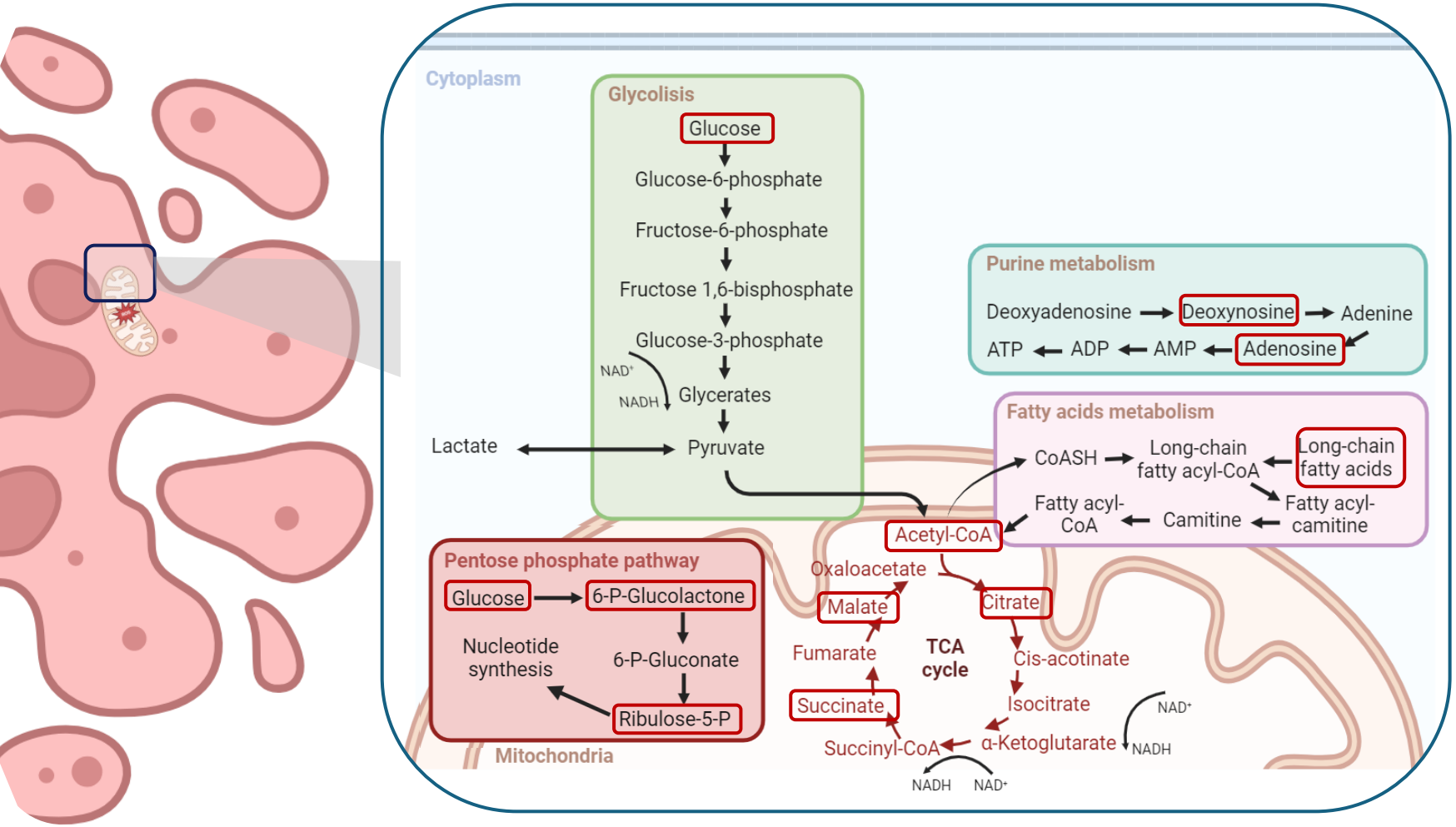
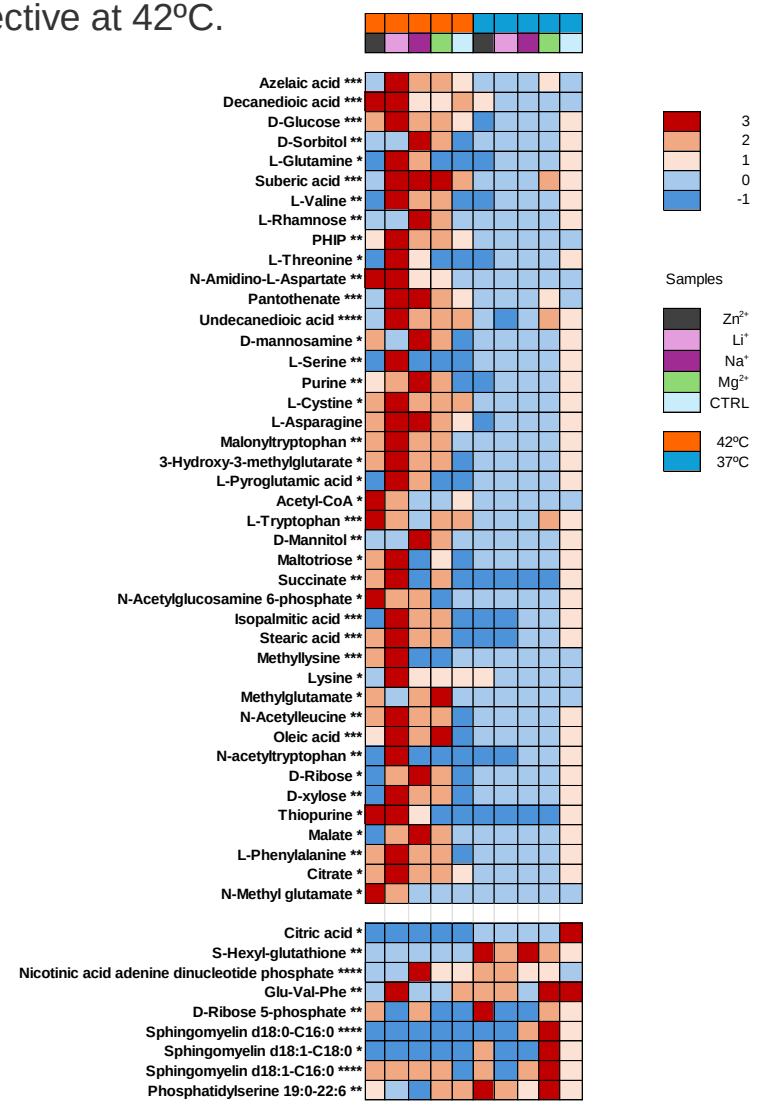
In vitro experiments

Metabolomics

The hydrogels containing Zn^{2+} and Li^{+} seemed to be the most effective at 42ºC.

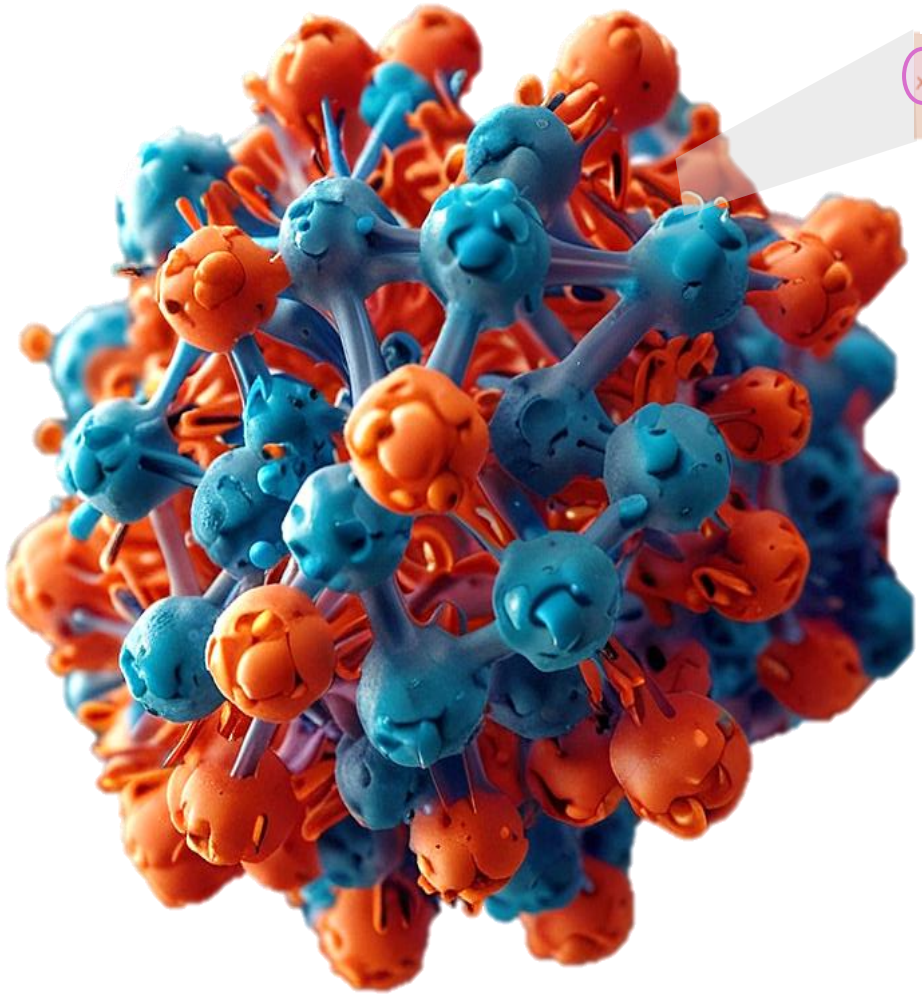


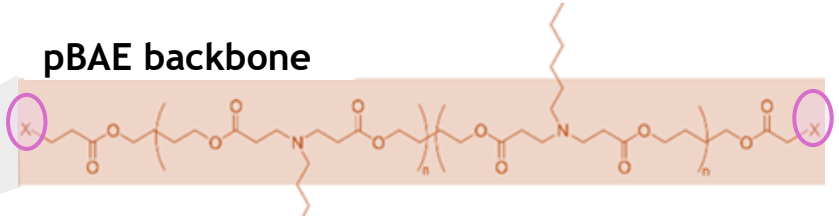


TCA cycle, pentose phosphate pathway and fatty acids metabolism were the main pathways affected.

In vitro experiments

mTOR siRNA pBAE NPs





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In vitro experiments

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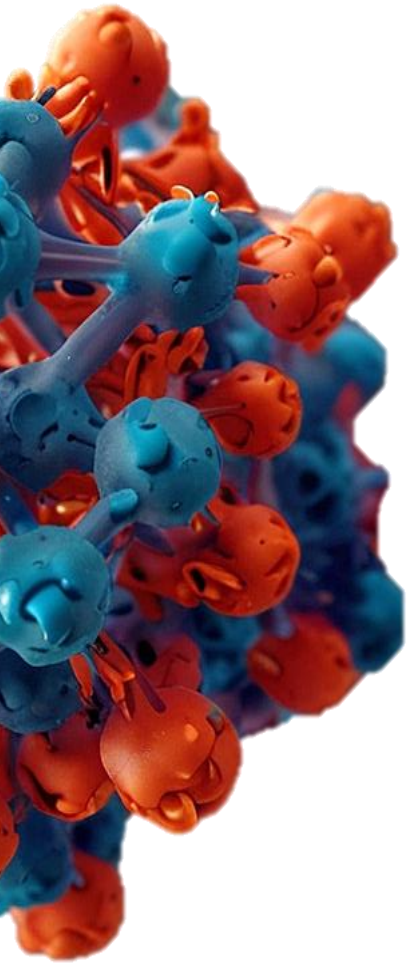
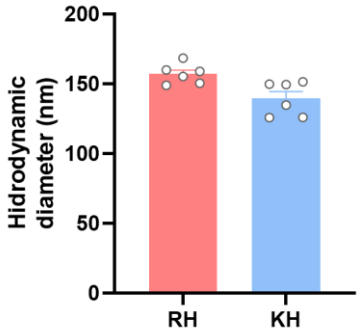
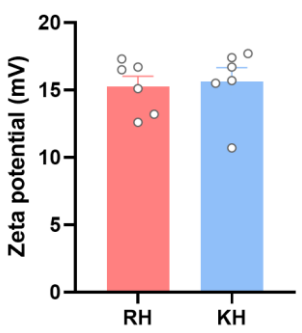
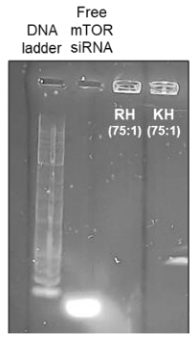
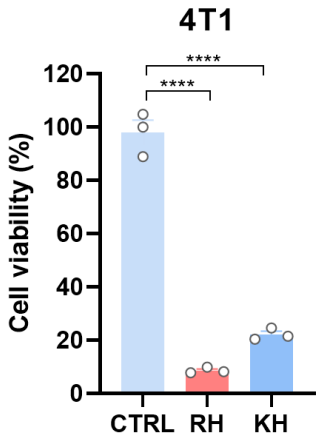


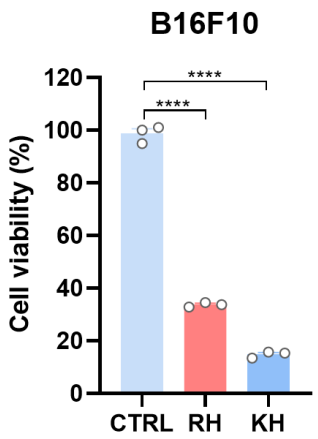


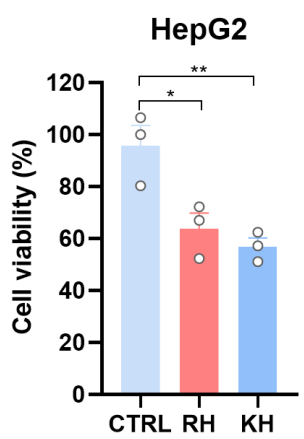


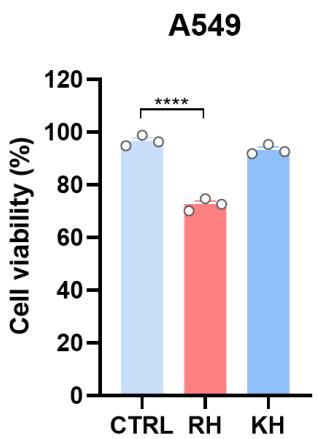


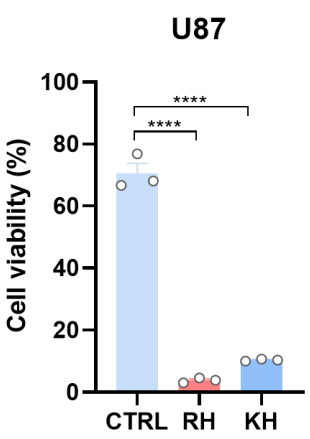
pBAE NPs with siRNA ratio 75:1











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In vitro experiments

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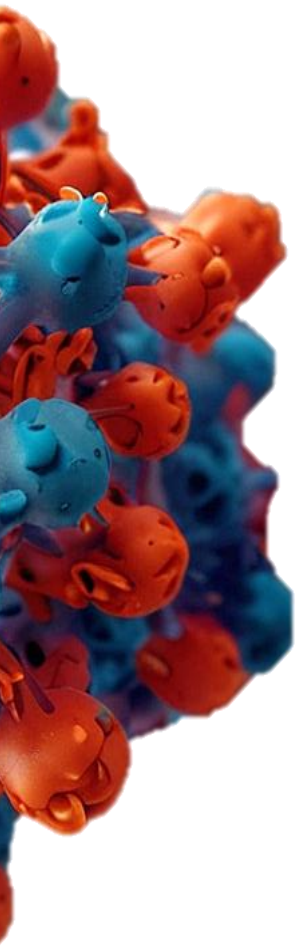
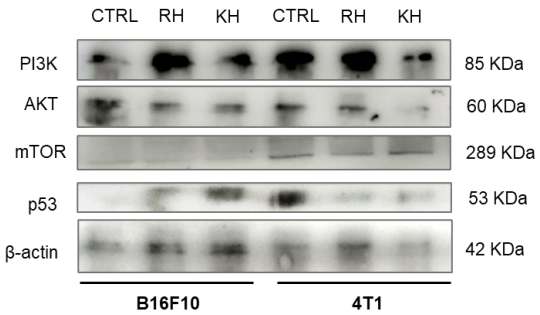
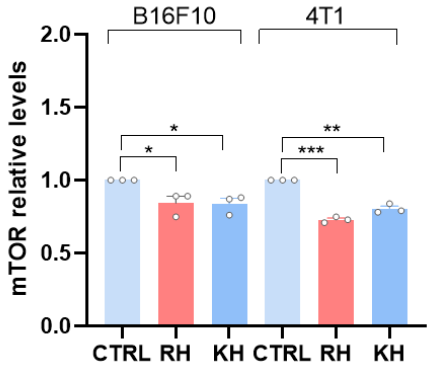
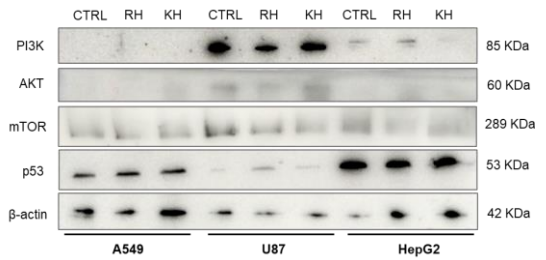
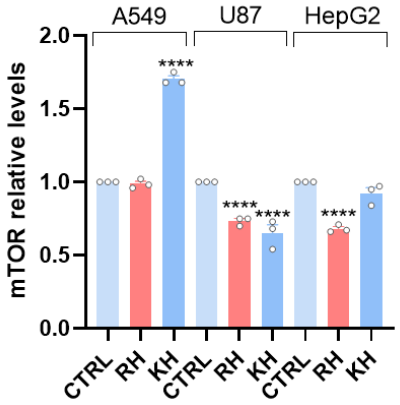


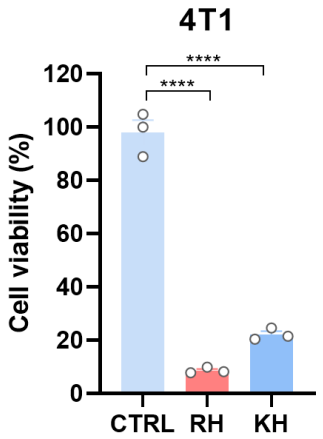


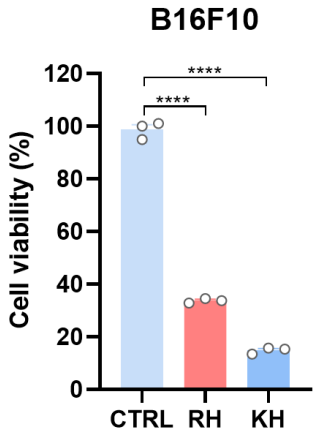


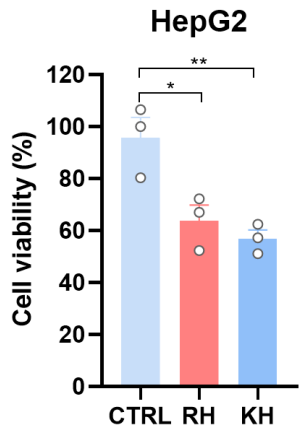


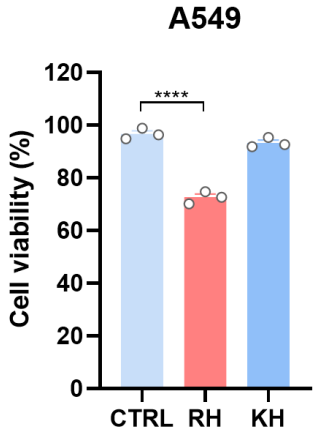


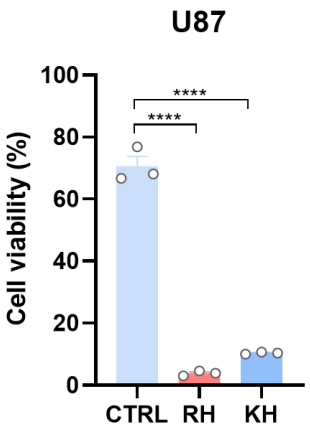
Silencing of mTOR protein expression











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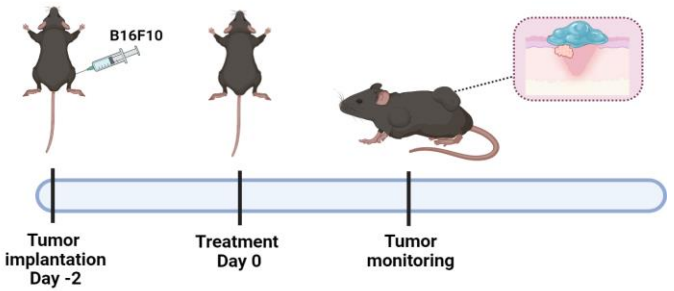
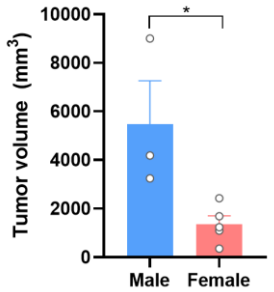
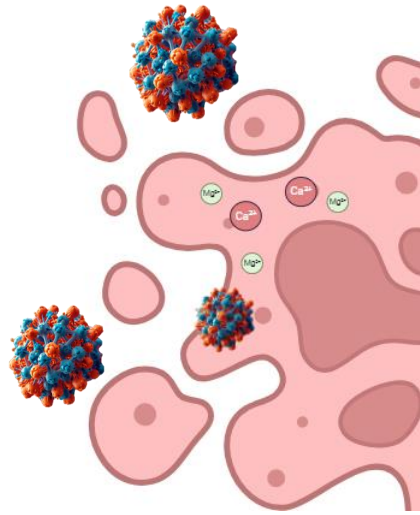
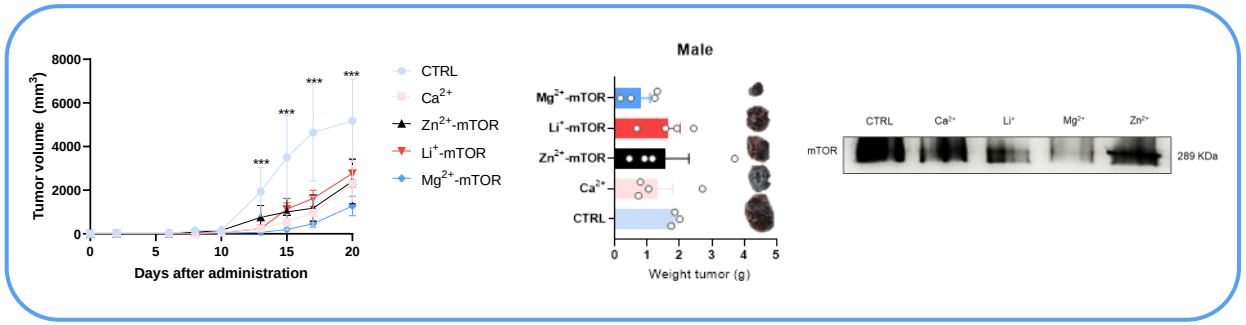
In vivo experiments

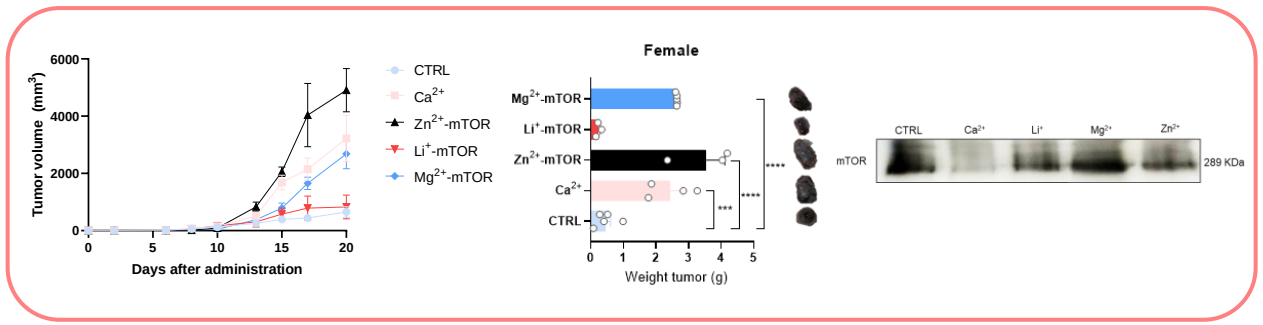
Synergistic therapy

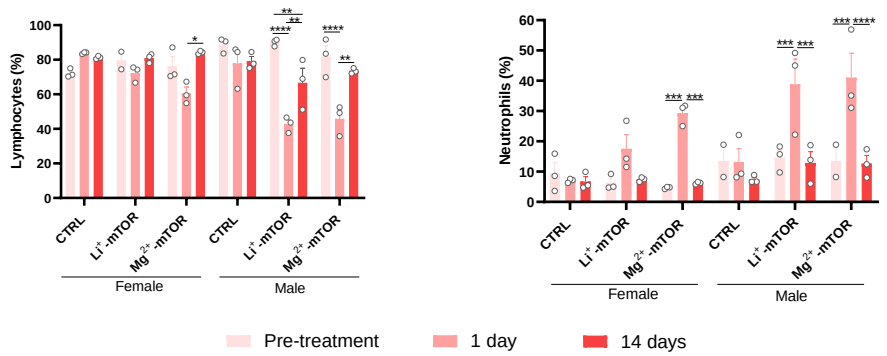












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