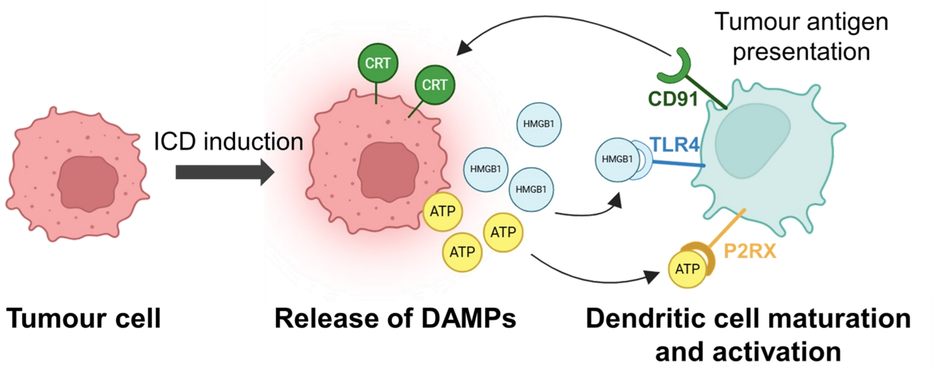
Immunogenic cell death in glioblastoma via lipid nanoparticle co-delivery of chemotherapy and siRNA

Pratistha Panday[1], Osama Hassuneh[1,2], Victor M. Moreno-Zafra[1], Alaa Zam[1], Hend Abdelbar[1], Nadia Rouatbi[1], Julie Tzu-Wen Wang[1], Adam Walters[1], Khuloud T Al-Jamal[1,2]

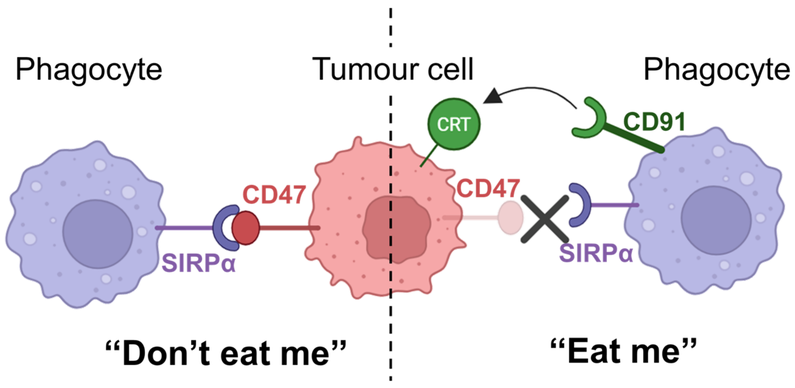
[1]King's College London, London, UK; [2]The University of Hong Kong, HKSAR, China

Introduction

- Glioblastoma (GBM) is highly aggressive brain tumour with poor prognosis and limited therapeutic options [1,2].
- Immunotherapy efficacy is hindered by the immunosuppressive brain tumour microenvironment [3,4].



Immunogenic cell death (ICD) can convert tumours into *in situ* vaccines by releasing danger-associated molecular patterns (DAMPs). Key DAMPs include extracellular ATP, HMGB1 release, and calreticulin (CRT) exposure, which promote anti-tumour T-cell responses [5].

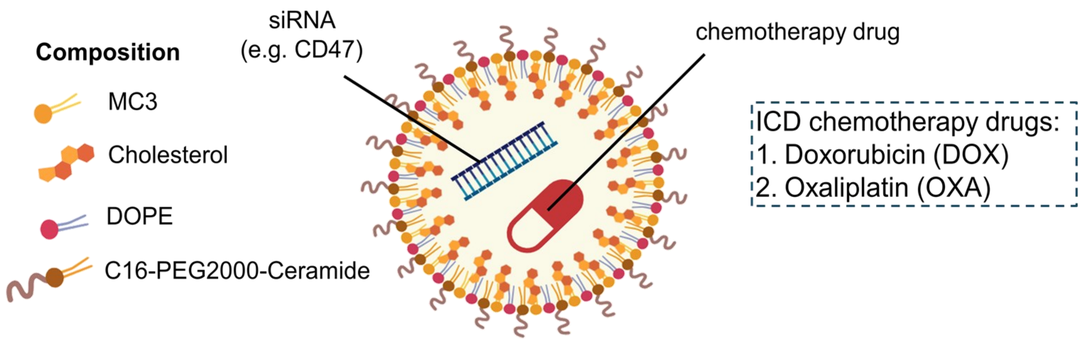


GBM evades immunity via CD47, which binds SIRPα to deliver a "don't eat me" signal, reducing phagocytosis and opposing "eat me" signals.

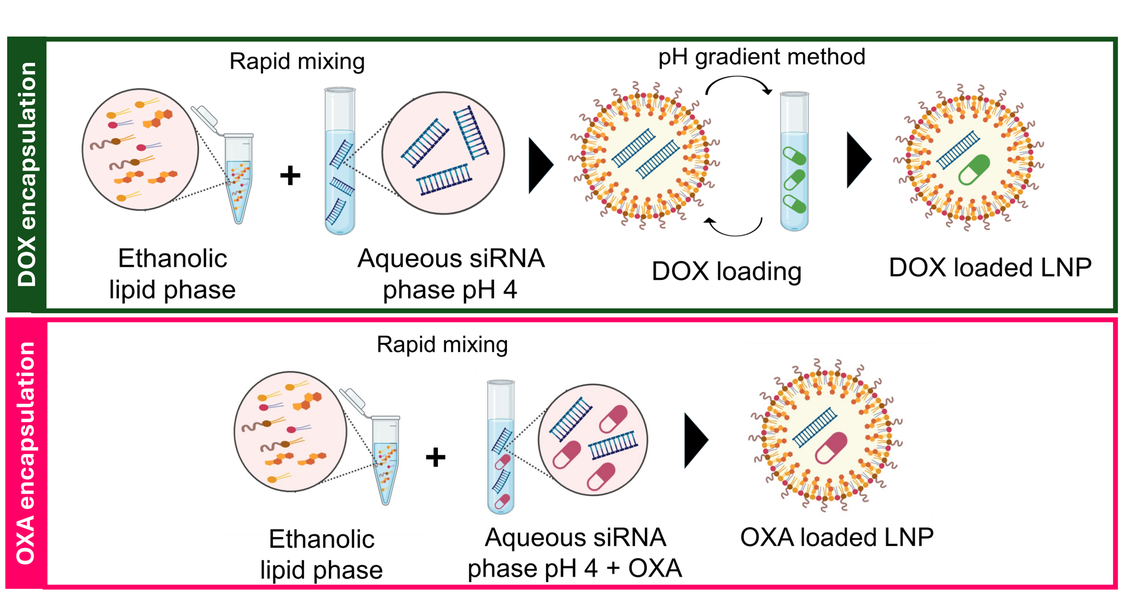
Objective: Investigate ICD induction in GBM and its immunological consequences using LNP-based co-delivery of chemotherapy and CD47-targeting siRNA.

Methods

Formulation of Lipid nanoparticles

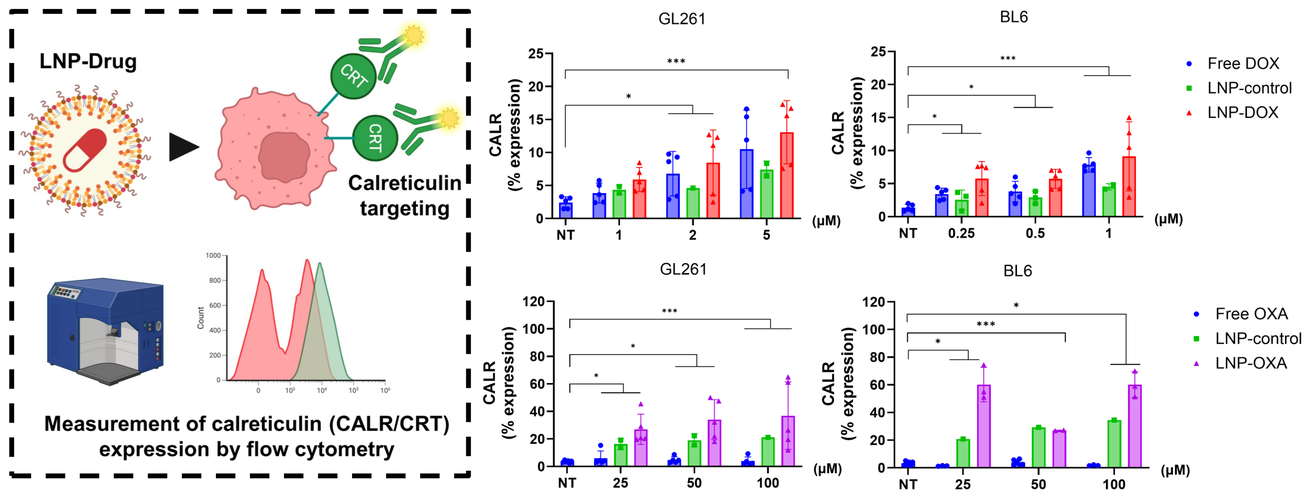


ICD chemotherapy drugs:
1. Doxorubicin (DOX)
2. Oxaliplatin (OXA)



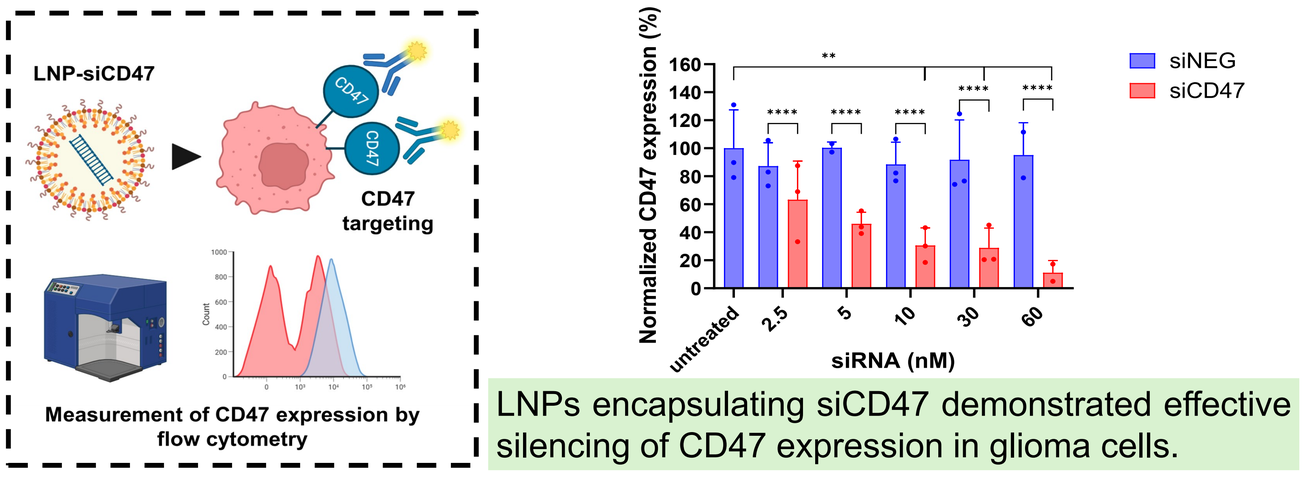
Results

LNP-drug increased CALR expression in GL261 and BL6 glioma cells.



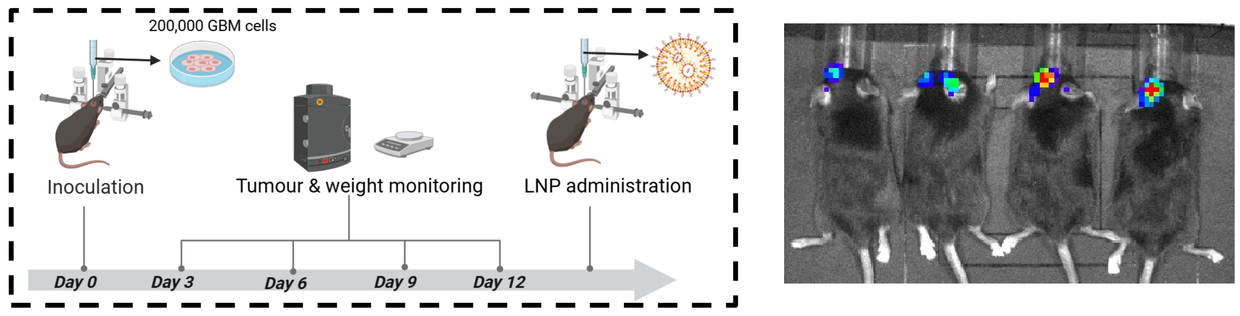
LNP encapsulating DOX or OXA induced ICD in GL261 and BL6 glioma cells as demonstrated by an increase in CALR expression.

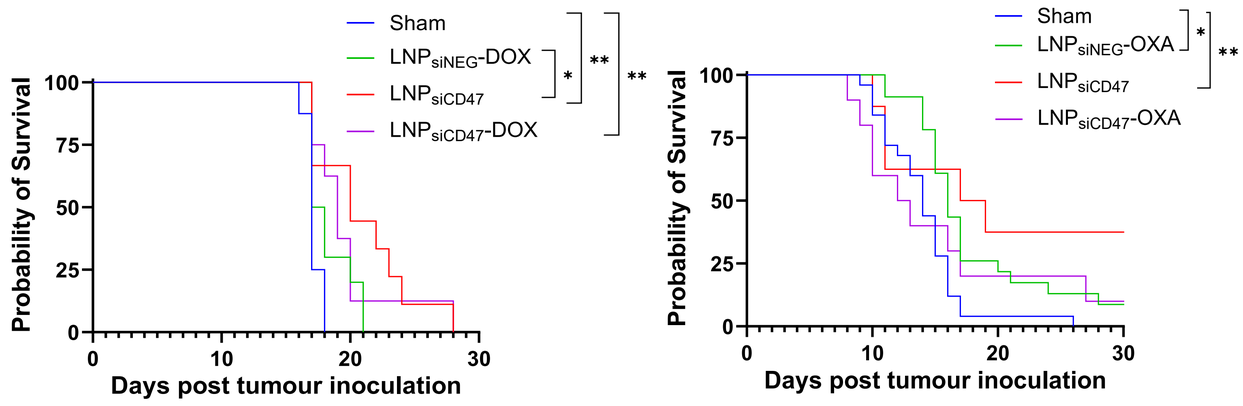
LNP-siCD47 demonstrated effective CD47 silencing.



LNPs encapsulating siCD47 demonstrated effective silencing of CD47 expression in glioma cells.

LNP-siCD47+drug significantly prolonged survival





LNP-siCD47 or LNP-siCD47+DOX significantly prolonged survival. LNP-DOX alone had no effect.

LNP-OXA monotherapy improved survival, but co-delivery with siCD47 did not enhance outcomes.

Conclusion

- ✓ LNPs effectively promoted ICD in GBM models *in vitro*.
- ✓ LNPs encapsulating siCD47 significantly improved survival in GBM mice models
- ✓ Dual-payload LNPs combining siCD47 and DOX significantly improved survival in GBM mice models
- ✓ LNP-OXA alone improved survival but co-delivery with siCD47 offered no additional benefit.

Acknowledgements

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References

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Contact details

Dr Pratistha Panday
Postdoctoral Associate
Institute of Pharmaceutical Science
King's College London
pratistha.panday@kcl.ac.uk