Lymph node-inspired biomaterials for CAR T cell therapy

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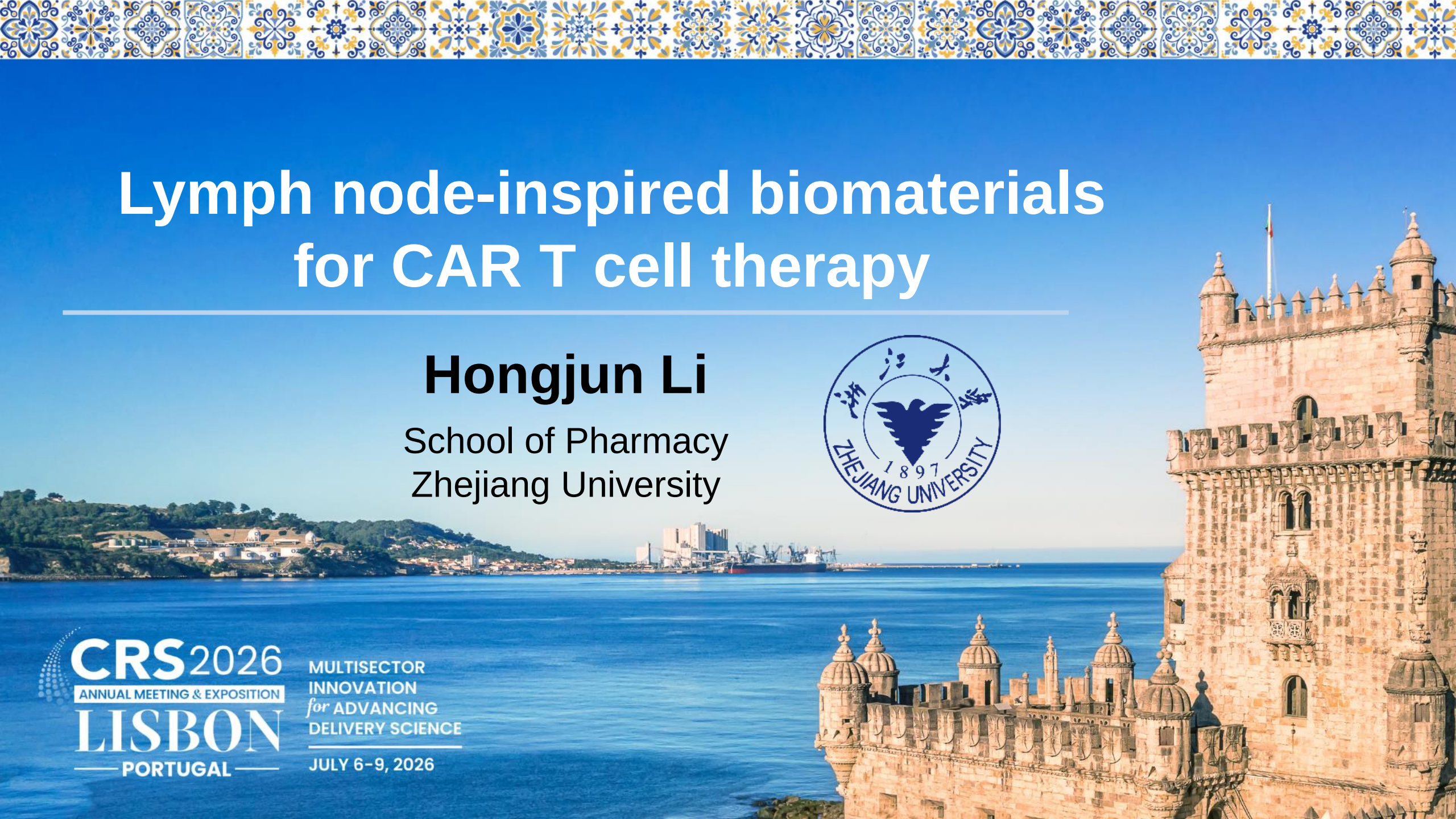
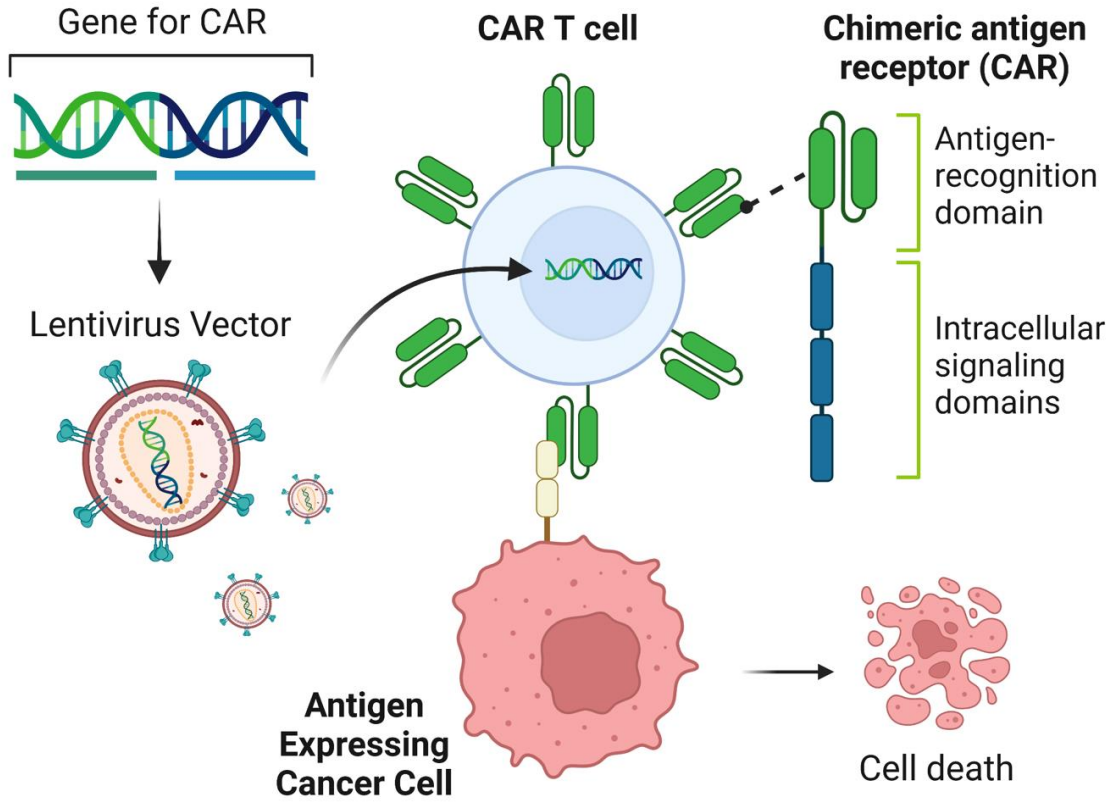


CAR T cell therapy: breakthrough in cancer treatment

CAR-T cell therapy



Ref.: BPS Bioscience, Inc.

Approved CAR-T products

Brand Name	Target Antigen	Targeted Disease
Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)
		B-cell non-Hodgkin lymphoma (NHL)
Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)
		Follicular lymphoma
Tecartus	CD19	Mantle cell lymphoma (MCL)
		B-cell acute lymphoblastic leukemia (ALL)
Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)
Abecma	BCMA	Multiple myeloma
Carvykti	BCMA	Multiple myeloma
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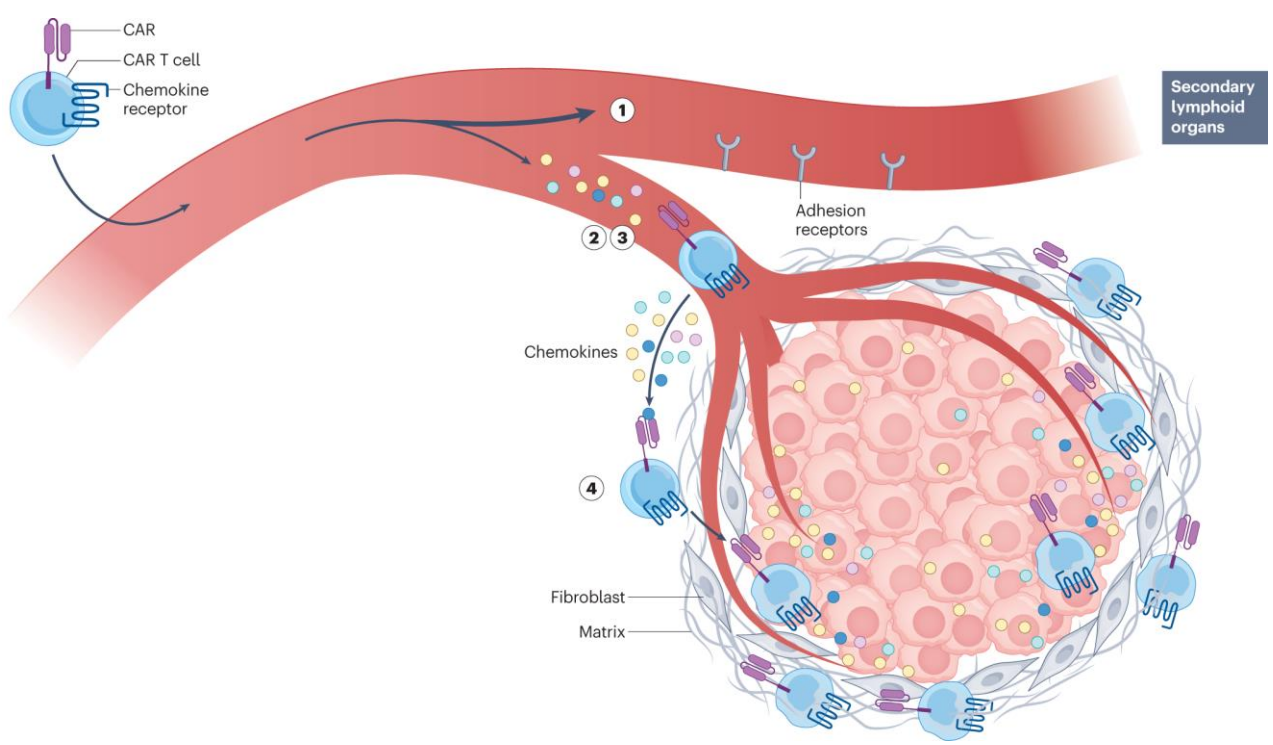
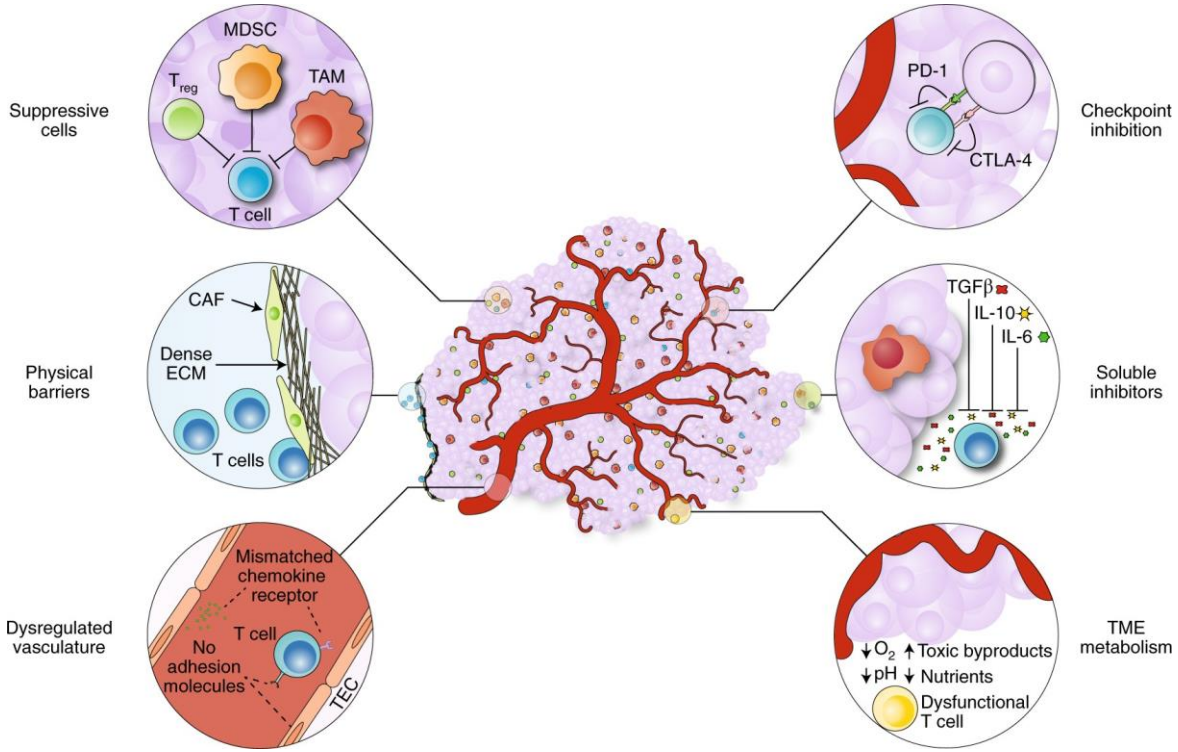
Barriers to the activity of CAR T cells against solid tumours

Poor infiltration of immune cells and **immunosuppressive microenvironment of tumours** are two key mechanisms limiting CAR T cell effectiveness in solid cancers.





Nat Rev Clin Oncol, 2024, 21, 47–66; *Nat Biomed Eng*, 2018, 2, 377–391

Biomaterials to enhance CAR T cell therapy

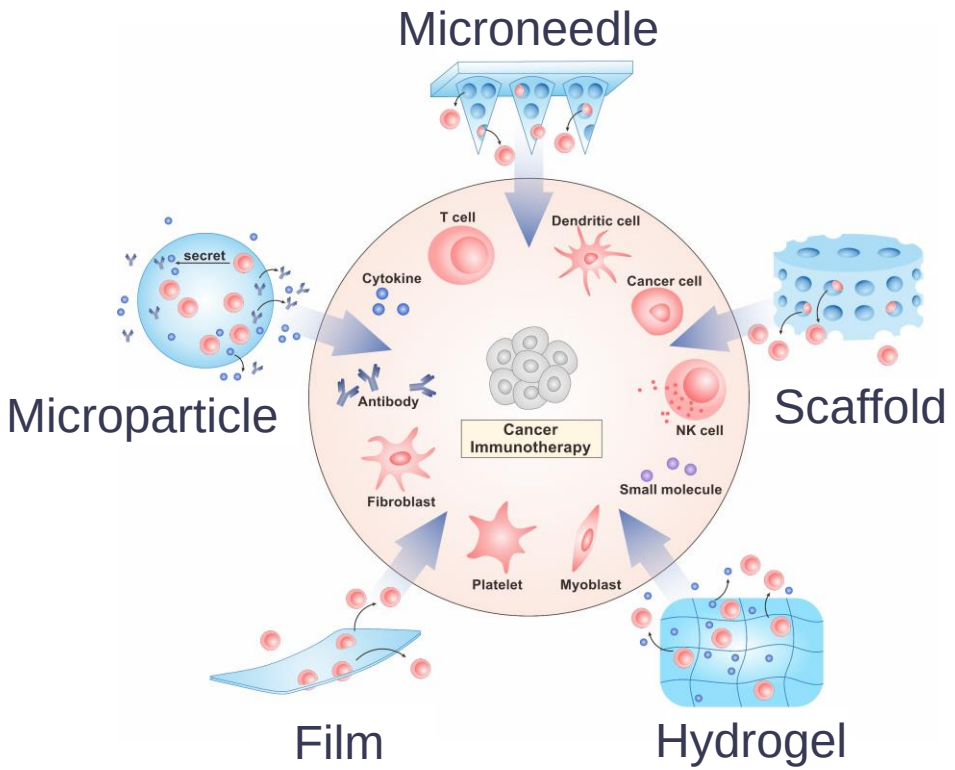
Materials

Organic materials:

- Polymeric materials
- Lipid-based materials

Inorganic materials:

- Mesoporous silica
- Metal composites



Function

- Enhanced accumulation at disease sites
- Sustained and controlled release of CAR T cells
- Maintenance of cell viability
- Modulation of the tumor microenvironment

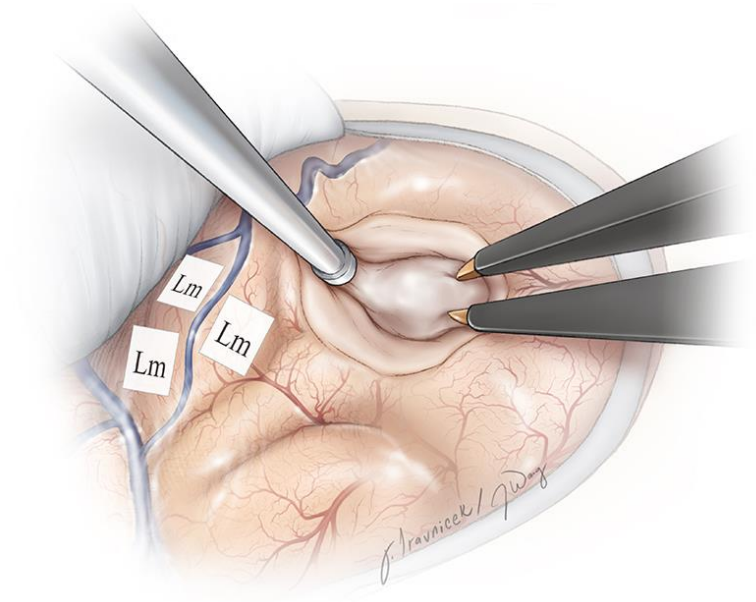
Limitations of artificial biomaterials

- **No physiological activity** (supplemented with IL2, IL15, anti-CD3 antibodies, etc.)
- **High cost for clinical translation** (GMP manufacturing)
- **Limited biocompatibility**

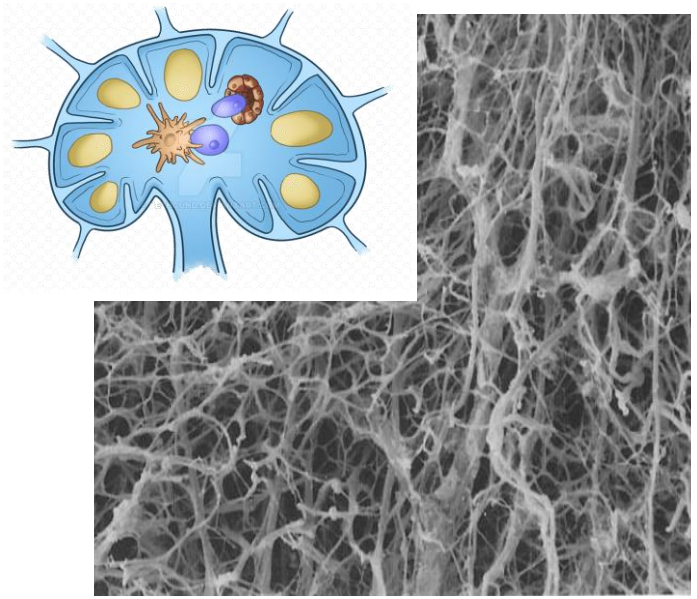
Lymph nodes (LNs): crucial for T cell priming, activation and tolerance

- LNs provide a **natural T cell-supporting microenvironment**.
- LNs are routinely removed during tumour dissection for prognostic information.

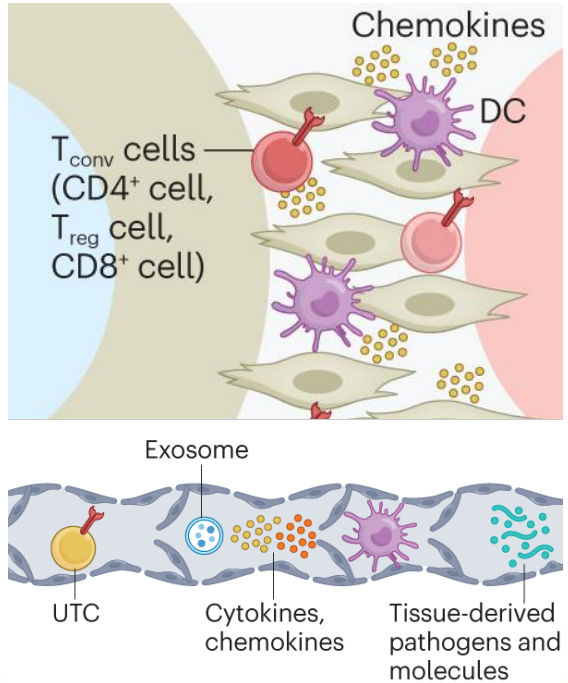
Native structure and function:



Porous structure of lymph nodes: Provides space for cellular interactions and mechanical support



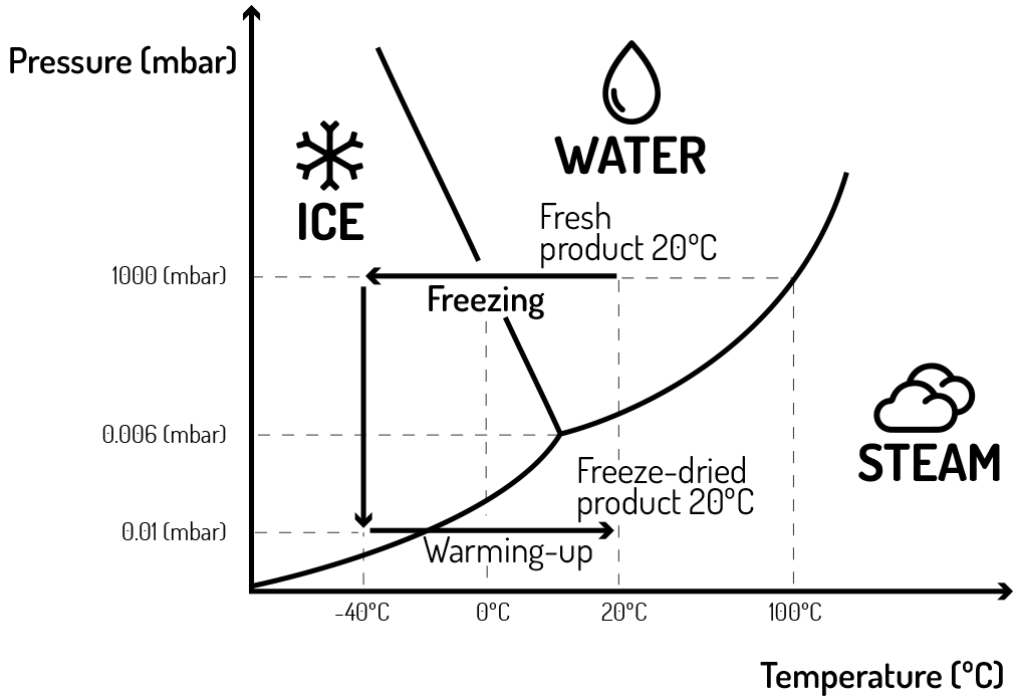
Diverse nutrients and molecules: Promotes T-cell recruitment, activation, and proliferation



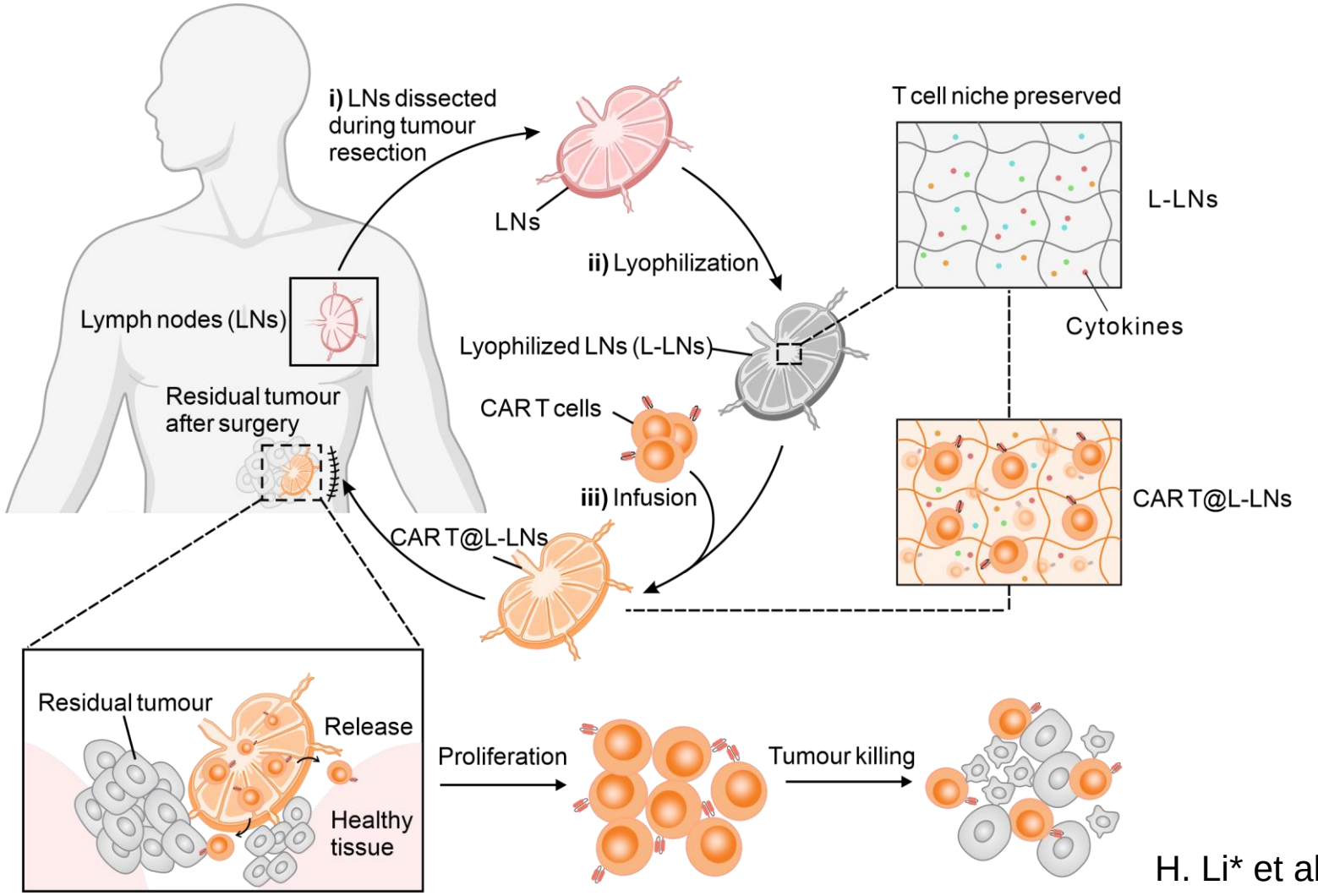
 Nat Rev Immunol, 2024, 24, 358–374

Lyophilization: wide application in food and pharmaceutical industry

Lyophilization **removes water** from a sample to **stabilize** a drug, vaccine, or biological sample **without changing characteristics** of the product.



Scheme

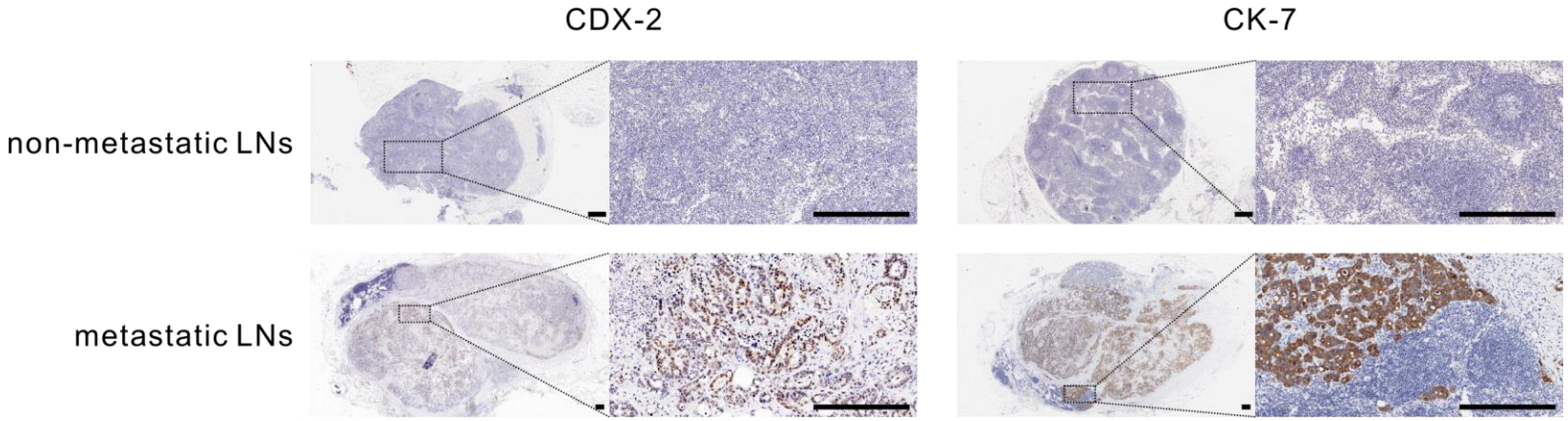


- **Lyophilization** maintained the stromal **framework** and the content of **cytokines** and **chemokines** of **LNs.**
- **Lyophilized LNs (L-LNs)** restored **a native home** for optimal T cell survival and function.
- **Autologous materials** possessed superior **biocompatibility**.

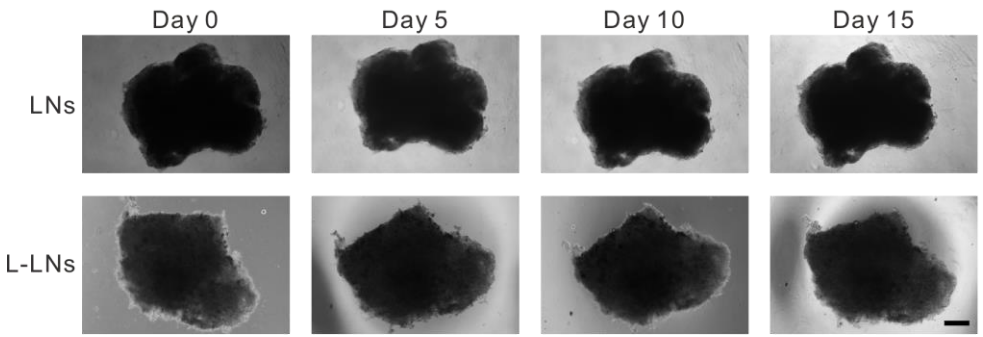
H. Li* et al., **Nature Materials**, 2024, 23, 844-853

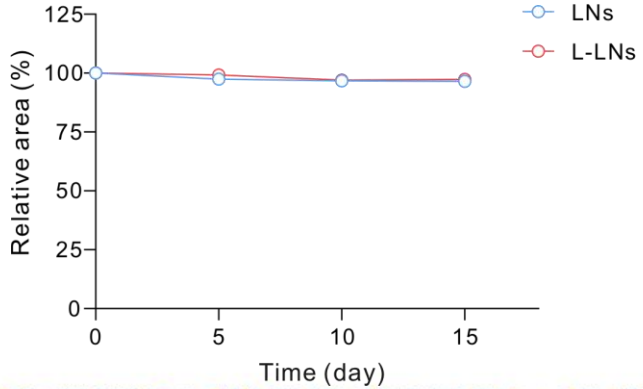
Collection of patient-derived lymph nodes

- Pathologically confirmed tumor-free lymph nodes were selected for subsequent experiments.



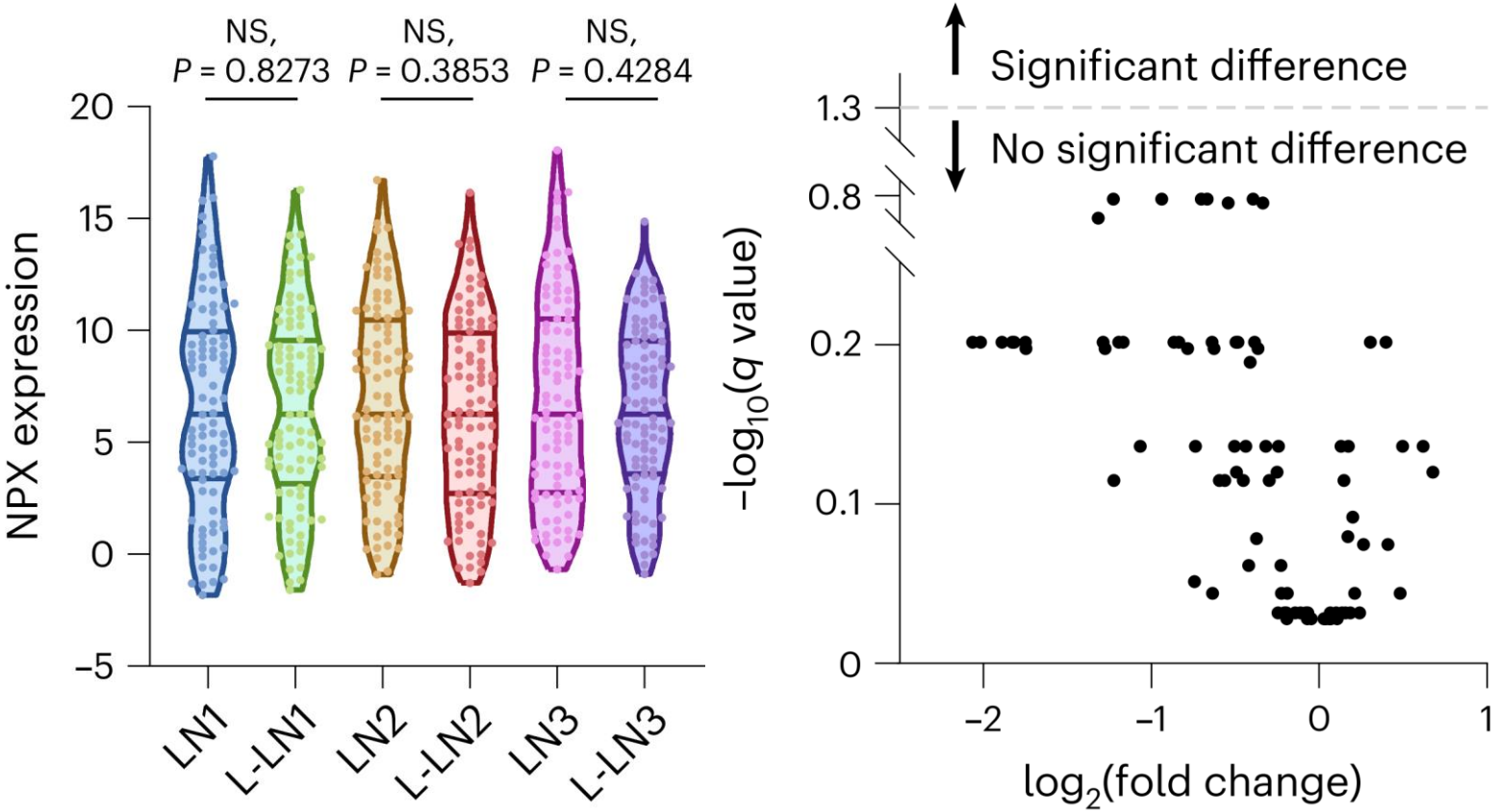
- No tumor cell cluster escape or abnormal tissue overgrowth was observed in screened fresh or lyophilized lymph nodes during long-term *in vitro* culture.



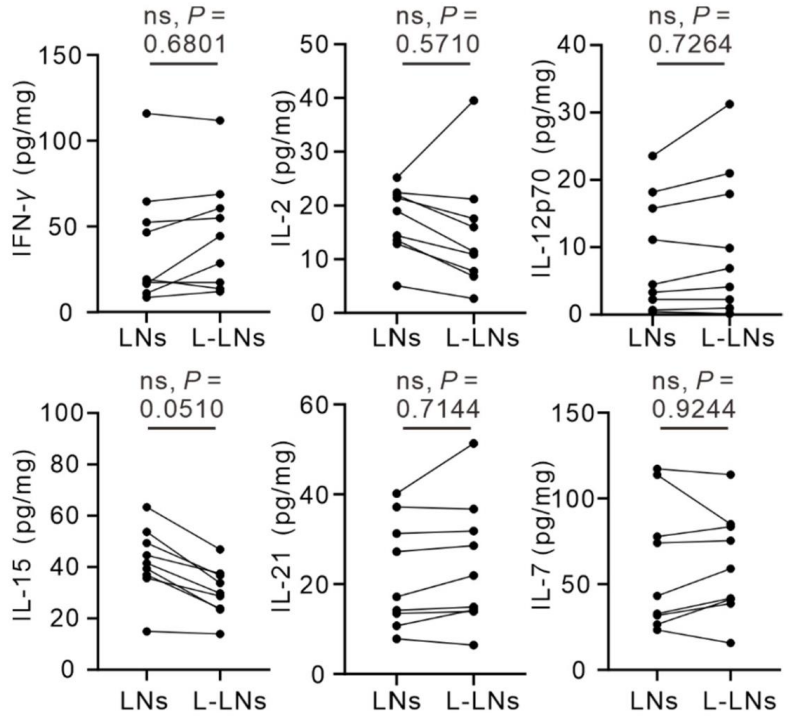


Lyophilization preserved key components in LNs

- Tissue proteomic analysis showed there was **no notable variance** in the protein context between LNs and L-LNs.

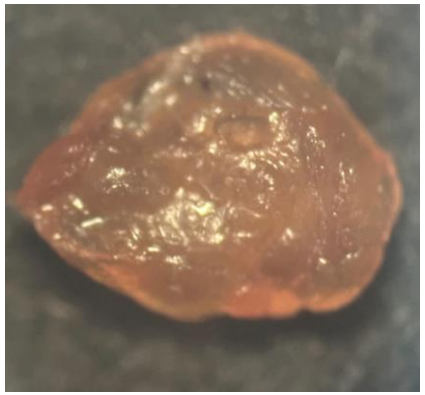


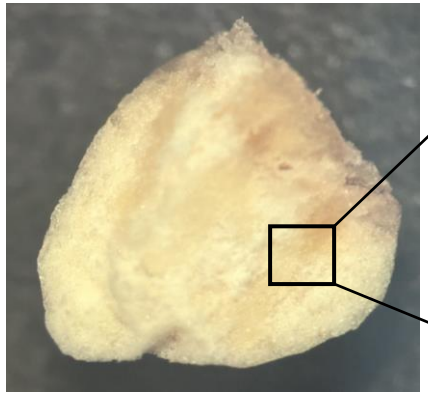
- Lyophilization preserves the **T cell-supporting cytokines** of native LNs.

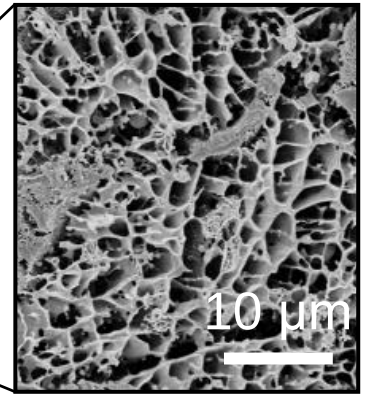


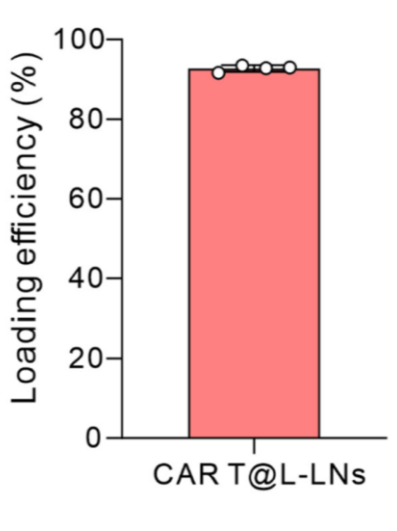
CAR T cells were loaded into L-LNs (CAR T@L-LNs)

Loading efficiency of CAR T cells reached 93%.



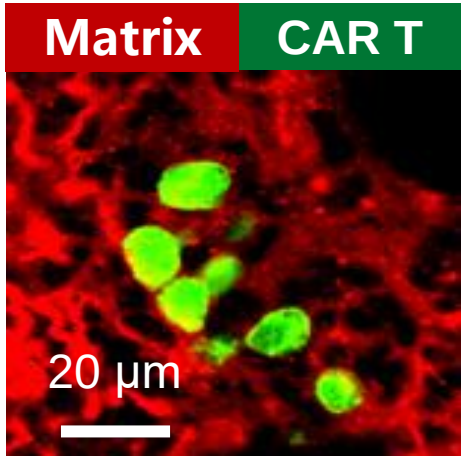


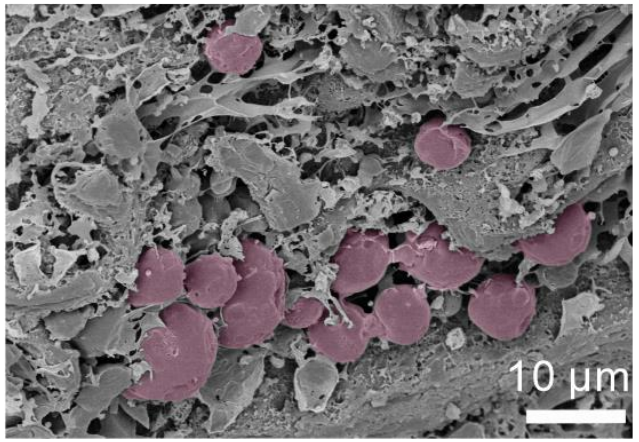


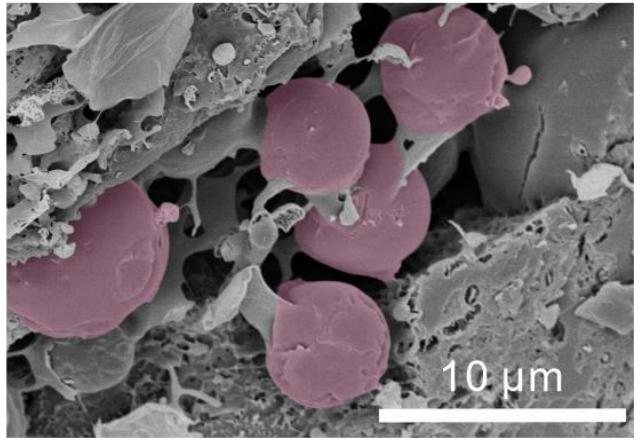


Fresh lymph nodes

Lyophilized lymph nodes

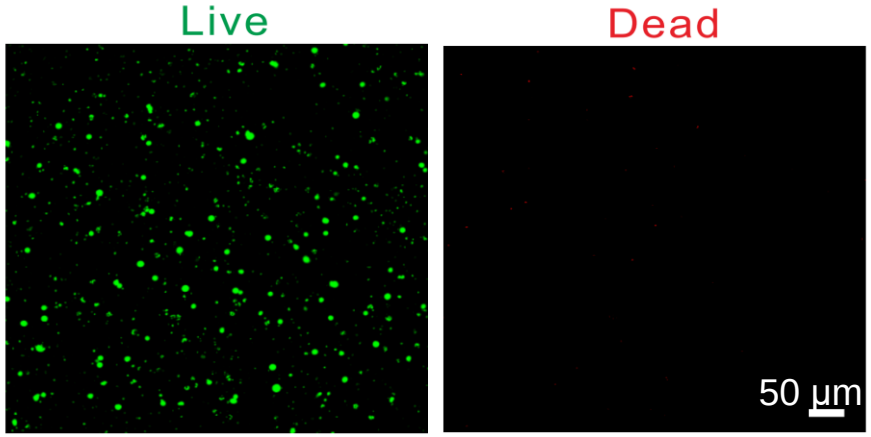


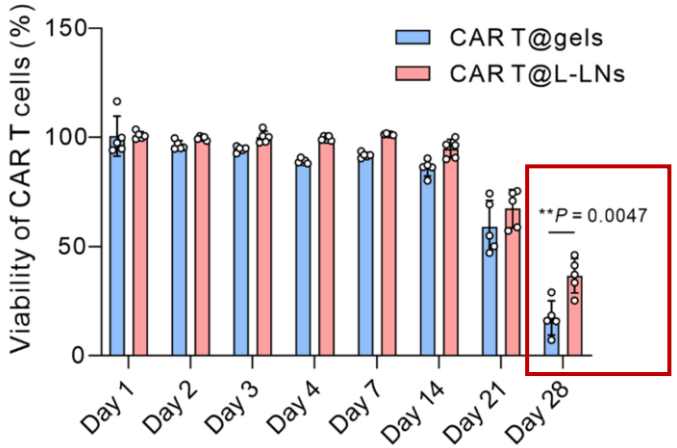


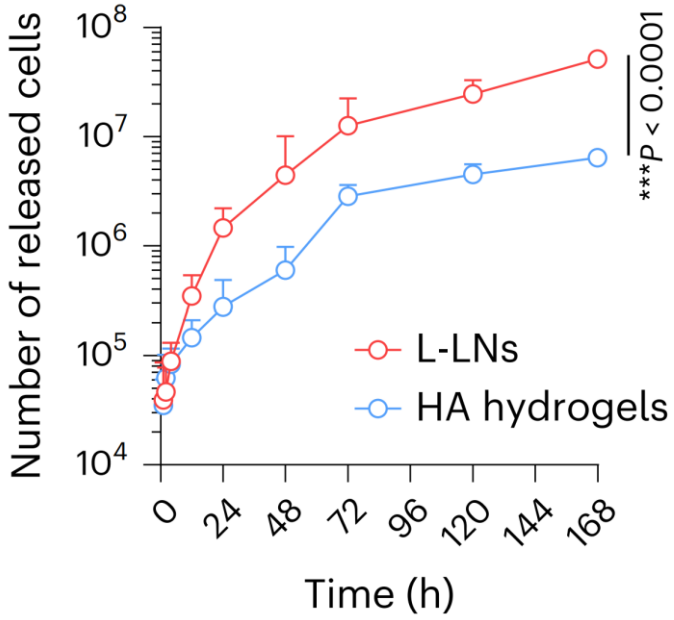


CAR T cells were loaded into L-LNs (CAR T@L-LNs)

- L-LNs did not cause obvious toxicity.
- CAR T cells in L-LNs maintained better activity than those in artificial scaffolds.
- L-LNs sustainedly released a higher number of CAR T cells than hyaluronic acid (HA) hydrogels over 7 days.

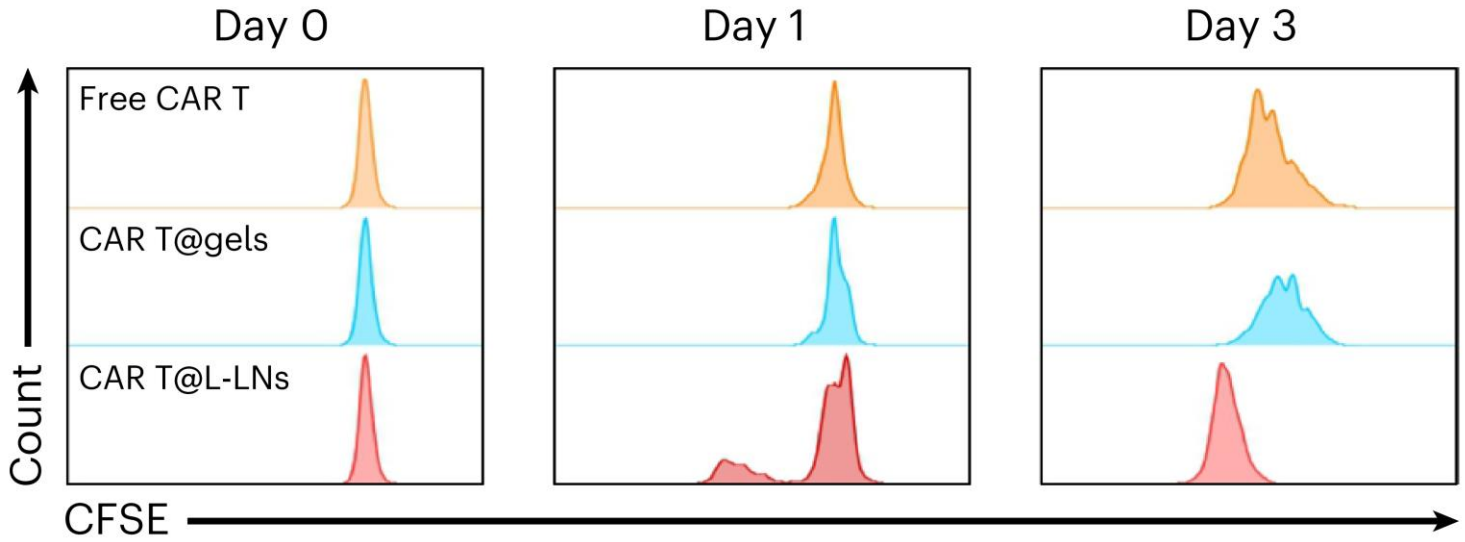


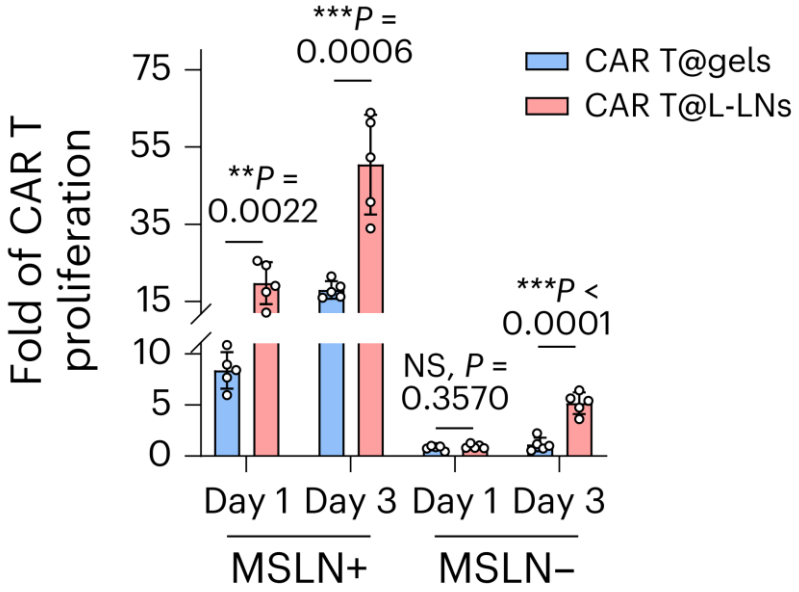




L-LNs enhanced CAR T cell expansion

- Without tumour antigen stimulation, CAR T cells from L-LNs reproduced 5 times at Day 3.
- With tumour antigen stimulation, CAR T cells from L-LNs reproduced 50 times at Day 3.





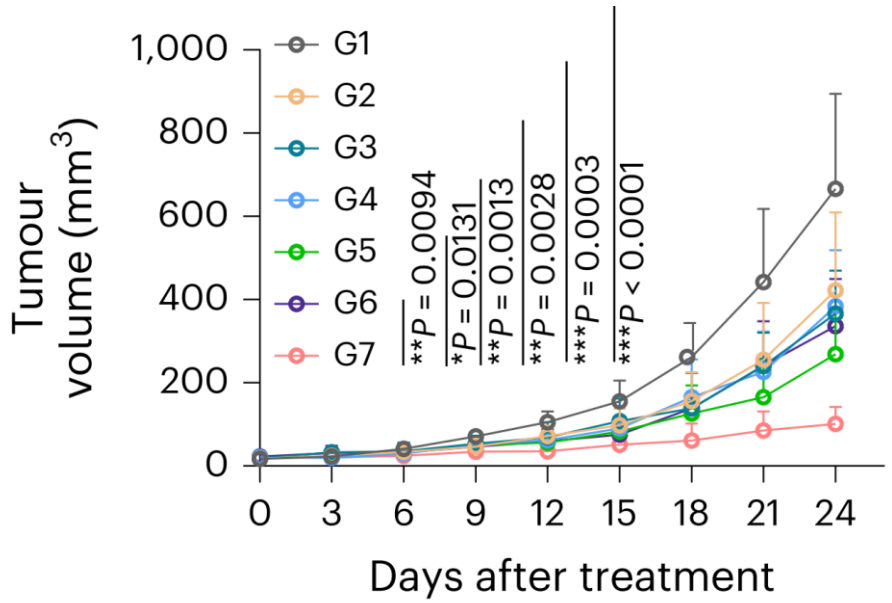
CAR T@gels: CAR T cells loaded in hyaluronic acid hydrogels supplemented with critical cytokines (IL-2, IL-7, IL-15 and IFN-γ)

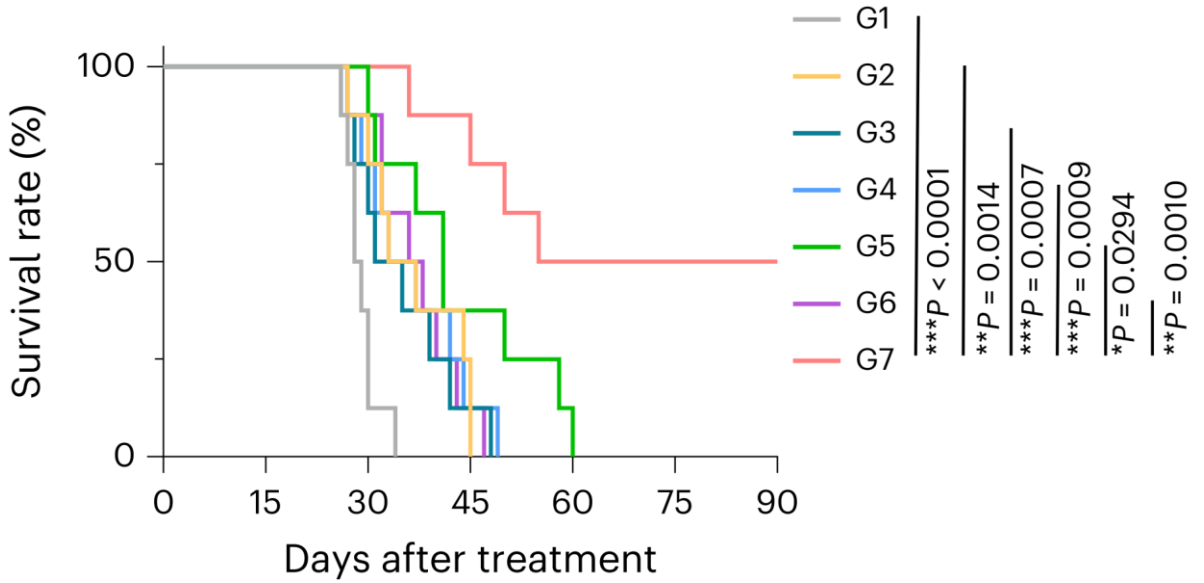
MSLN: mesothelin

CAR T@L-LNs: superior antitumour effect in a HeLa tumour resection mouse model

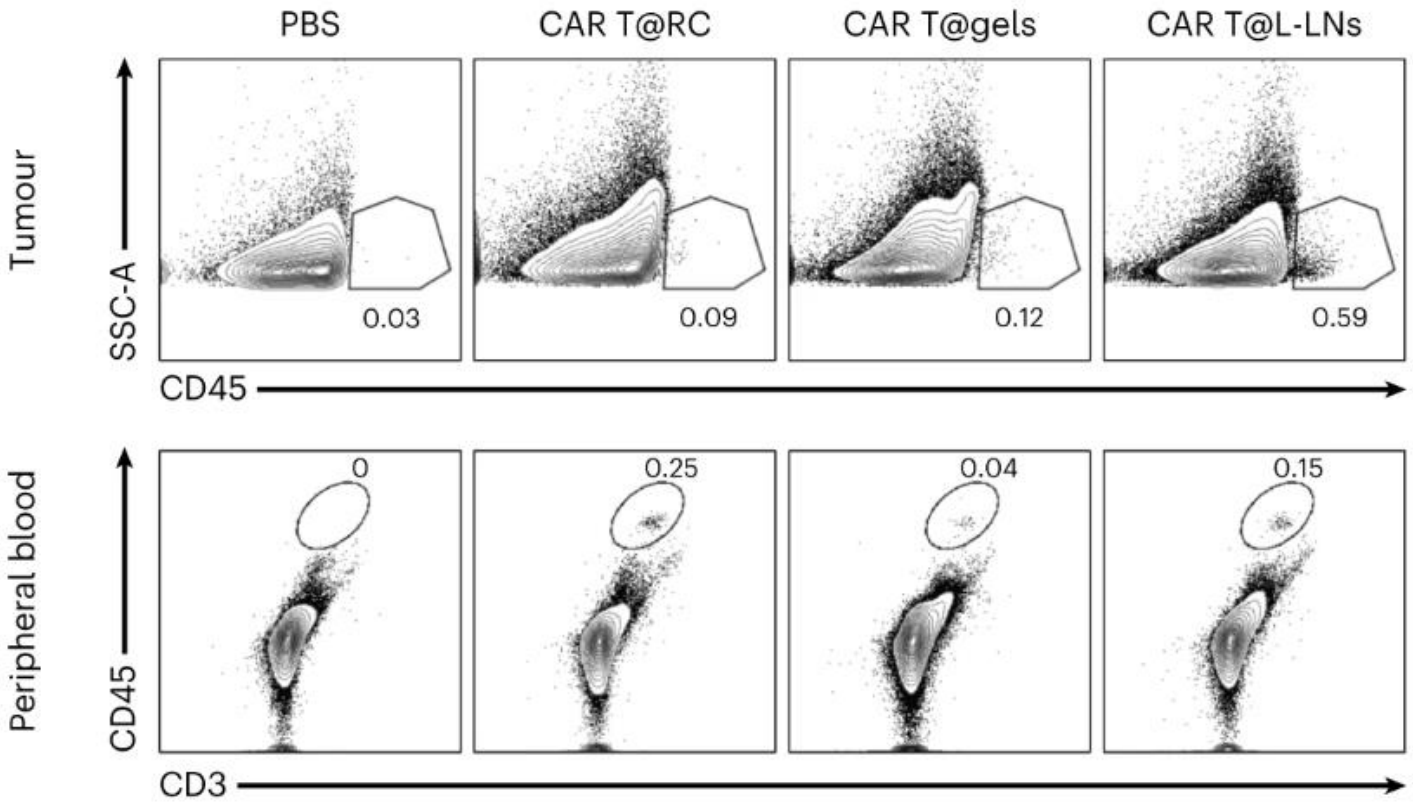
CAR T@L-LNs achieved 50% survival over 90 days versus around 60 days survival for cytokine-supplemented synthetic hydrogels.

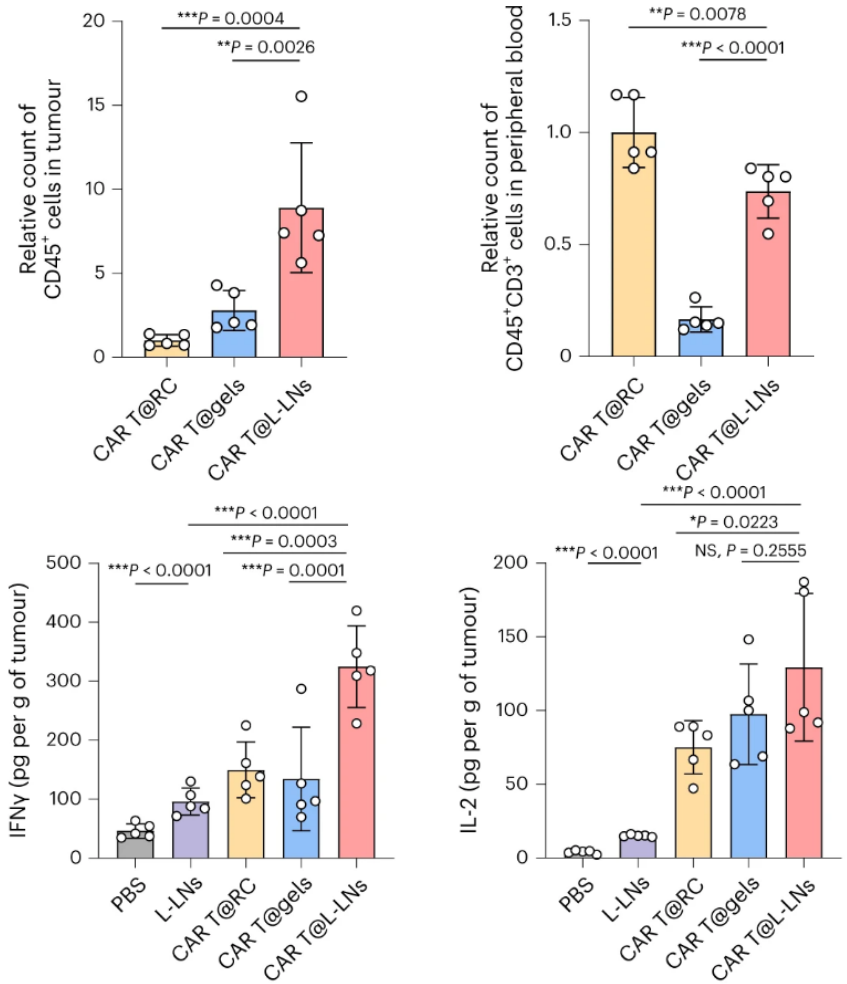
PBS (G1)
CAR T@resection cavity (G2)
Cytokines@gels (G3)
CAR T@gels (G4)
CAR T+ cytokines@gels (G5)
L-LNs (G6)
CAR T@L-LNs (G7)





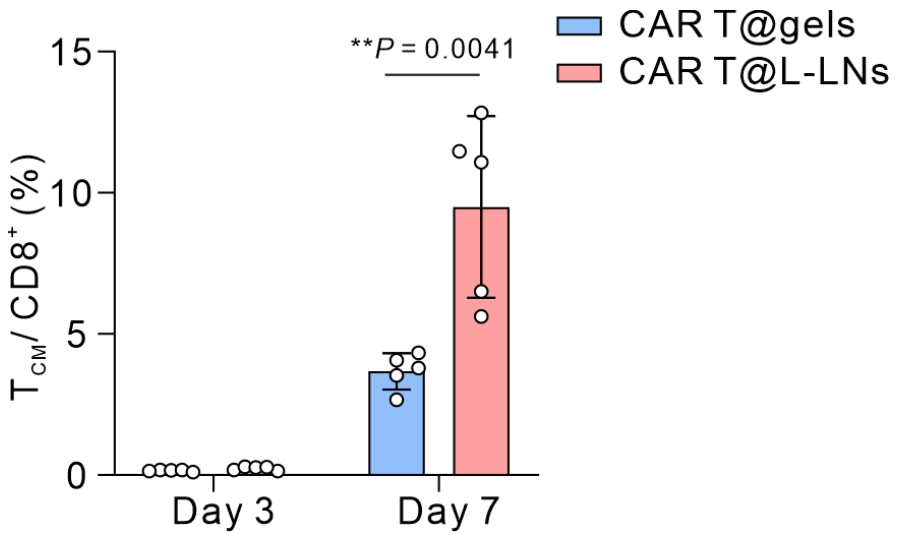
CAR T cell infiltration and intratumoural IL-2 and IFN-γ levels

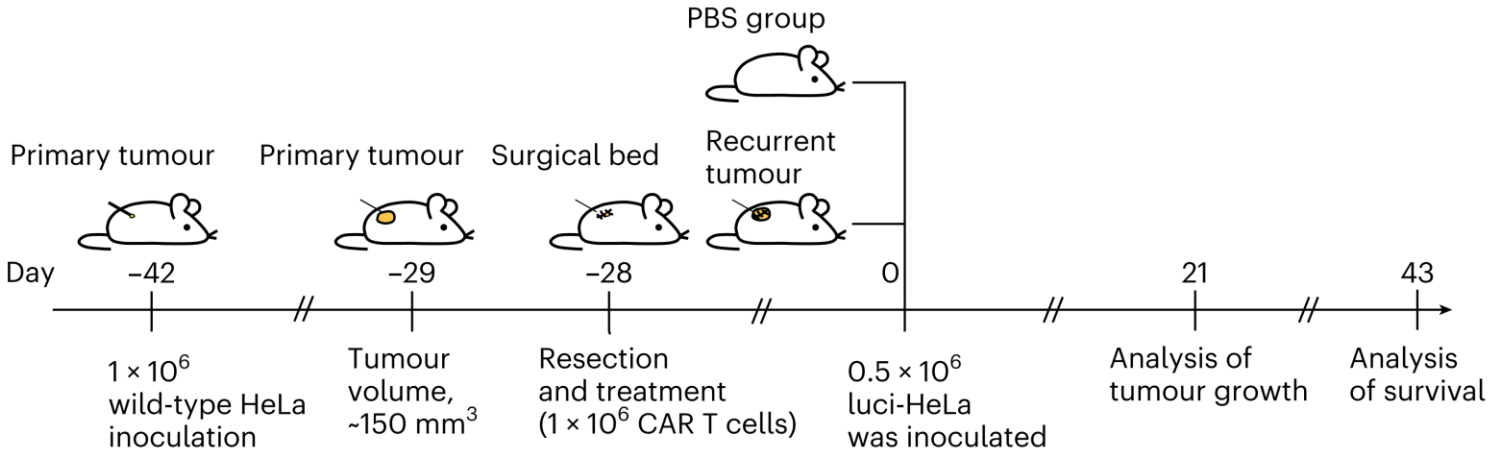


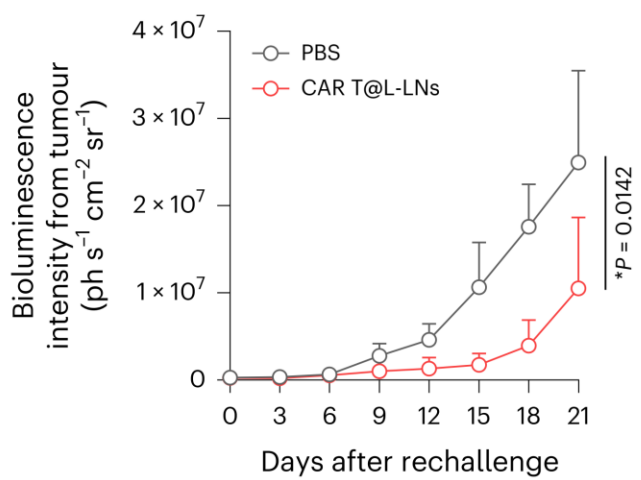


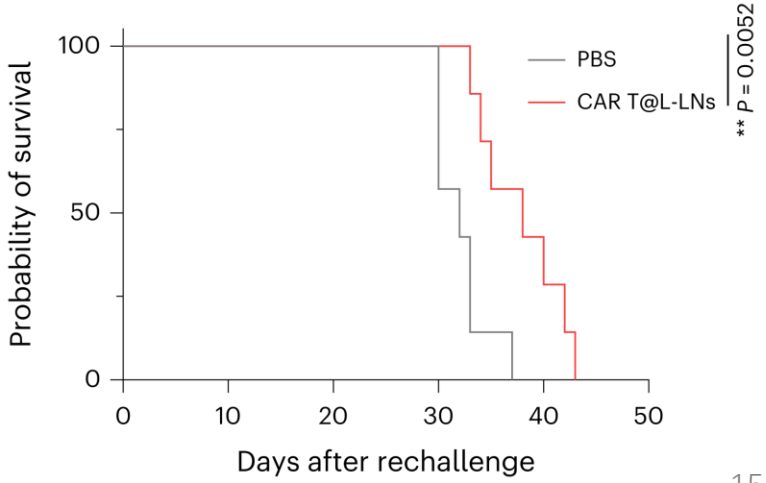
CAR T@L-LNs showed persistent antitumour activity

- L-LNs induced a skewed differentiation of CAR T cells into central memory phenotypes (Tcm).
- In a tumour rechallenge model, mice in CAR T@L-LNs group survived longer.

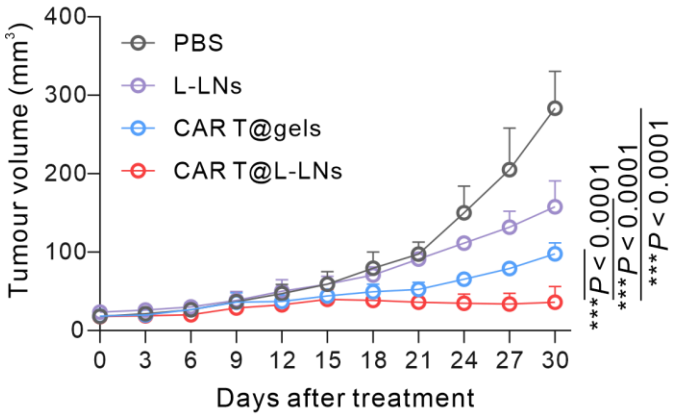


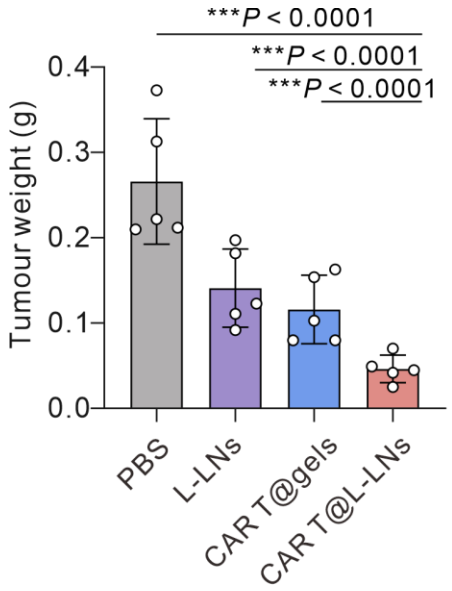


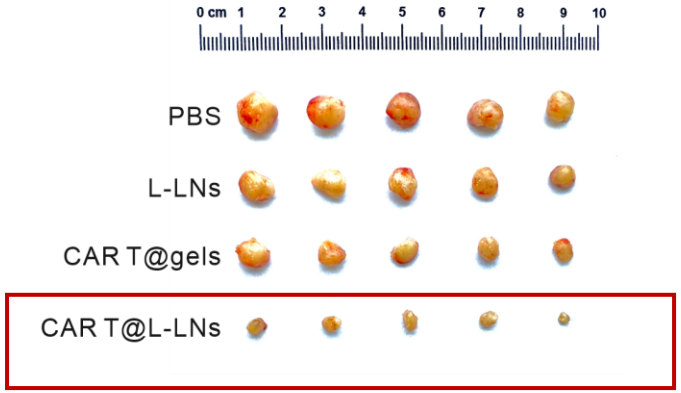


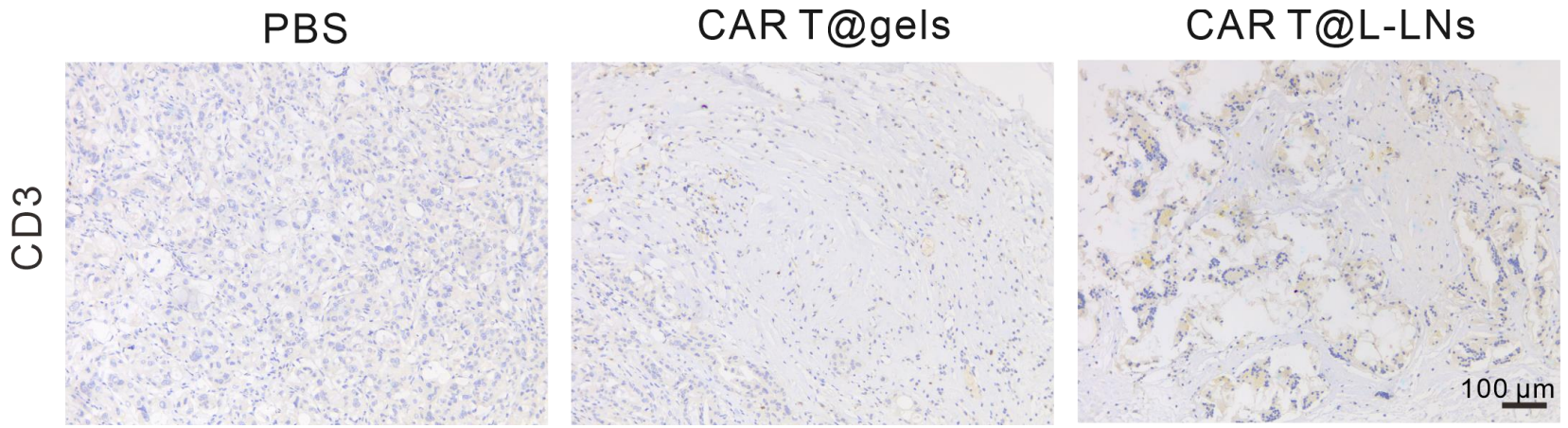


Anticancer effect in a patient-derived xenograft (PDX) tumour model



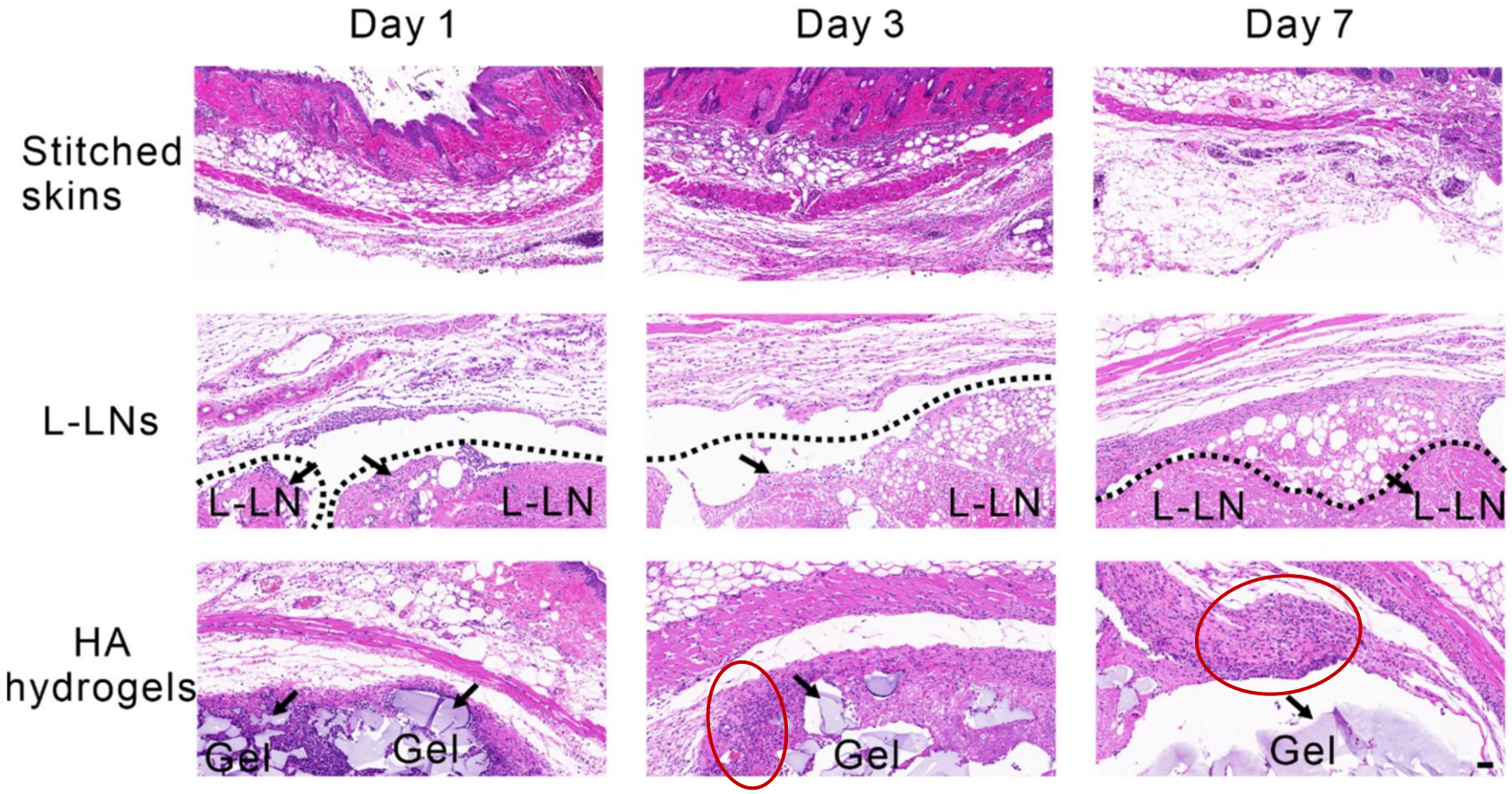




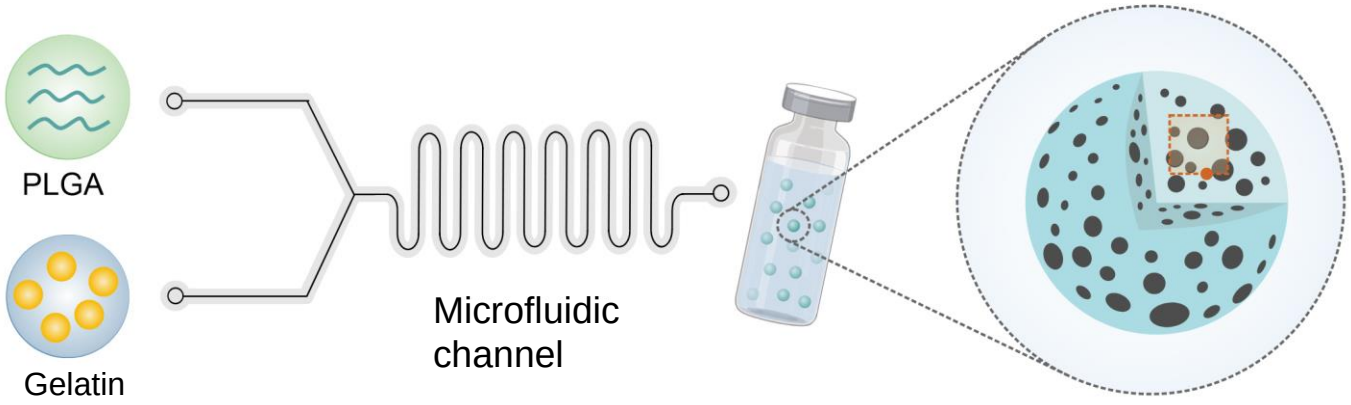


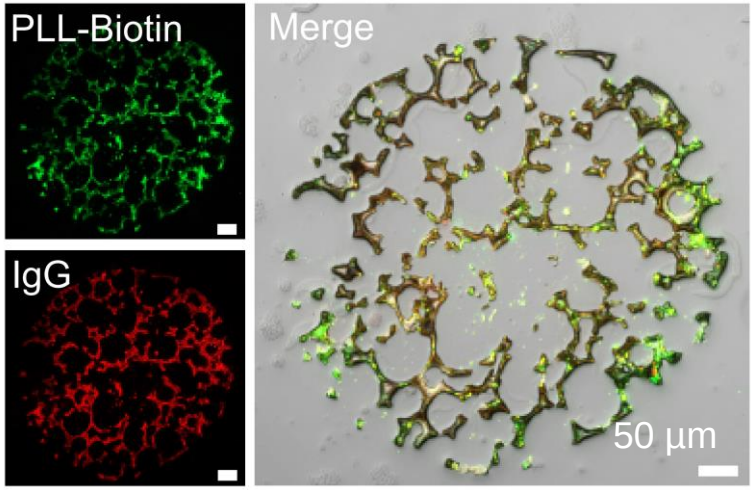
L-LNs were well biocompatible

- The inflammation in L-LNs group receded at day 3 and generally faded away at day 7.
- The implanted hydrogels exhibited an obvious inflammatory response throughout 7 days of implatation.

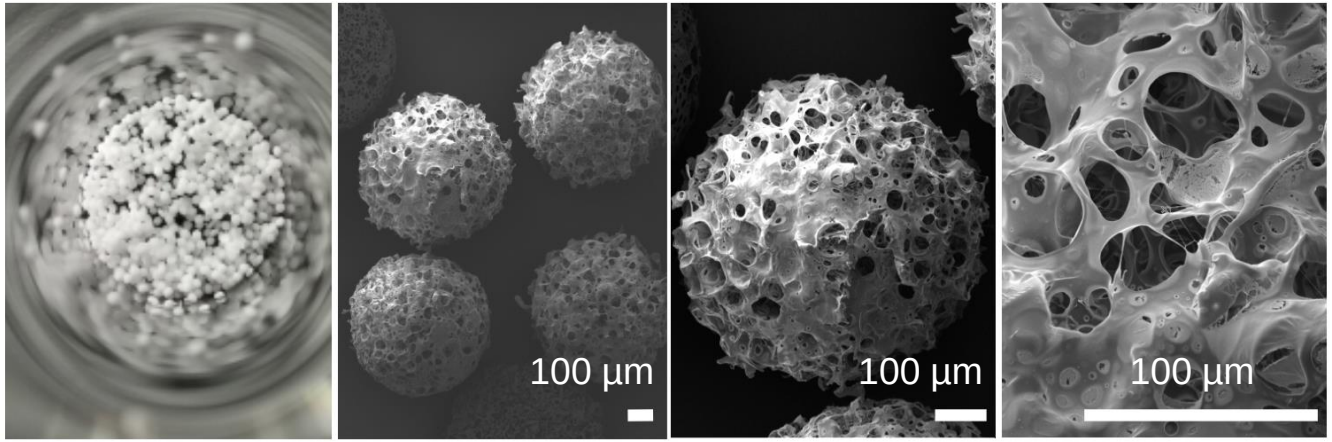


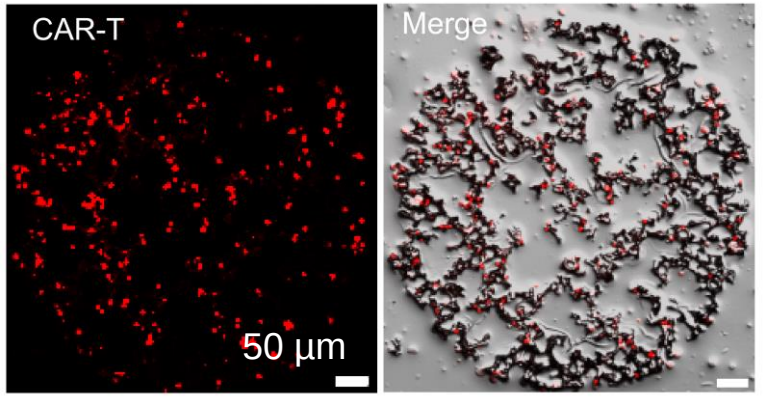
Artificial LNs for CAR-T cell delivery





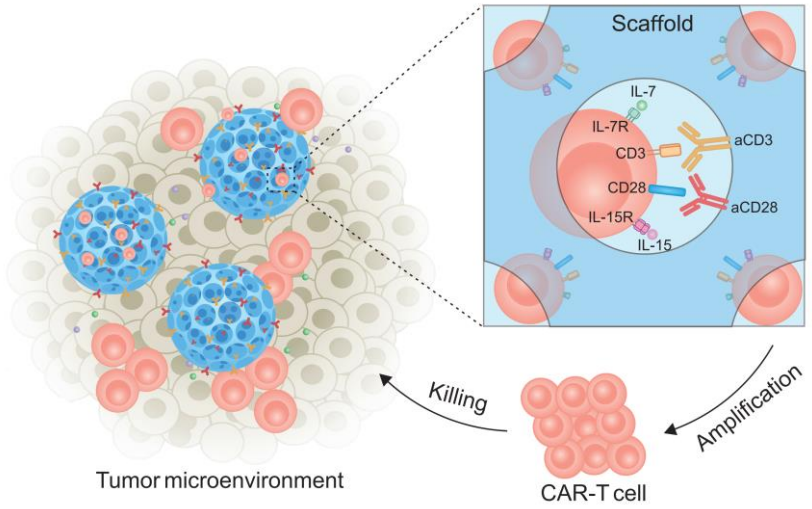
Diameter: 550 μm，pore size: 20 μm

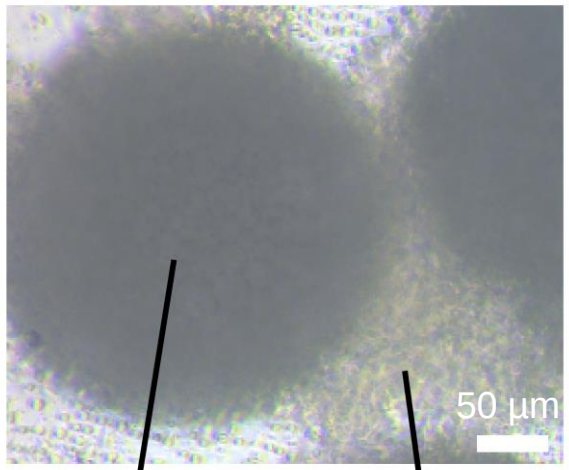


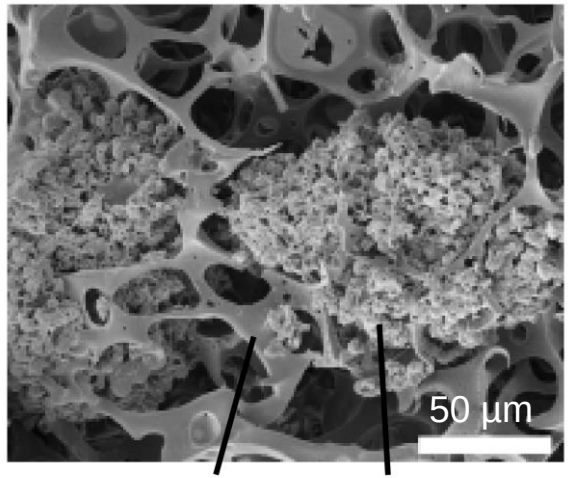


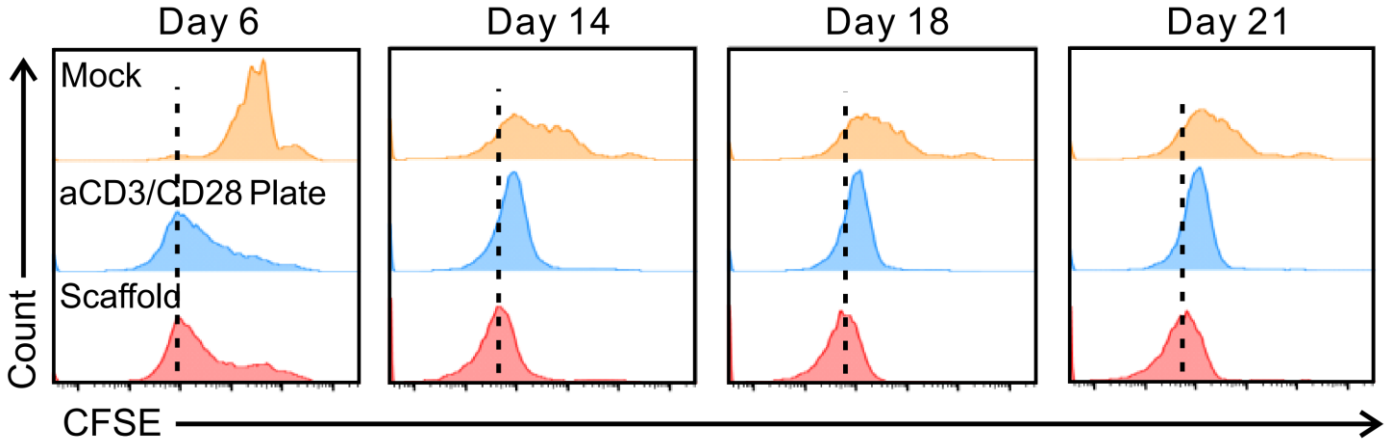
H. Li* et al., **National Science Review**, 2024, 11, nwae018

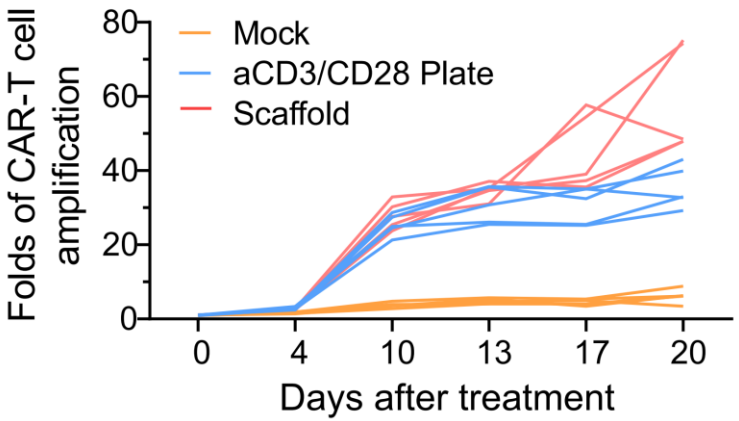
Artificial LNs for CAR-T cell delivery



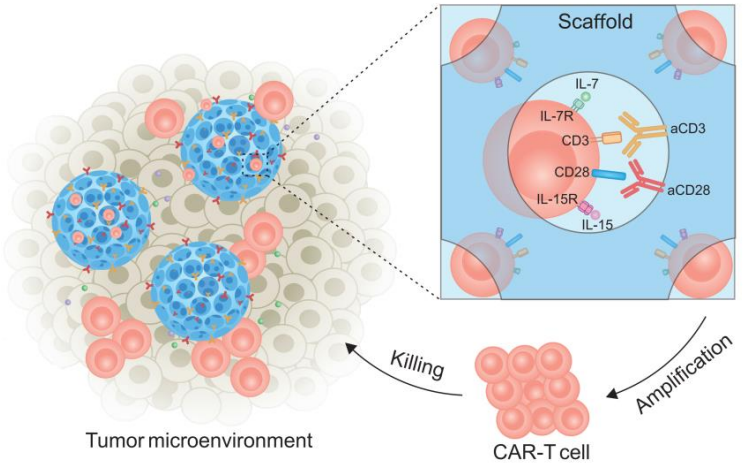


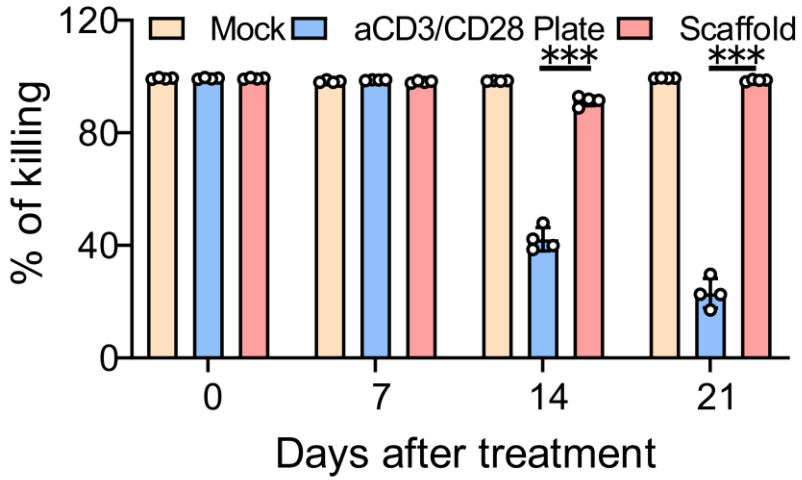






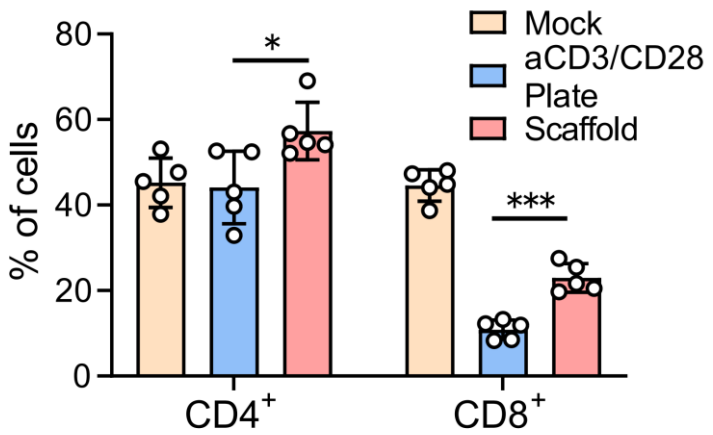
Artificial LNs for CAR-T cell delivery

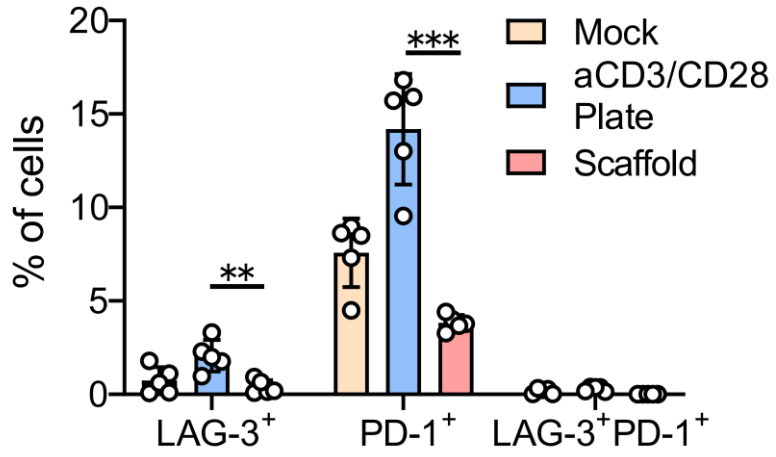




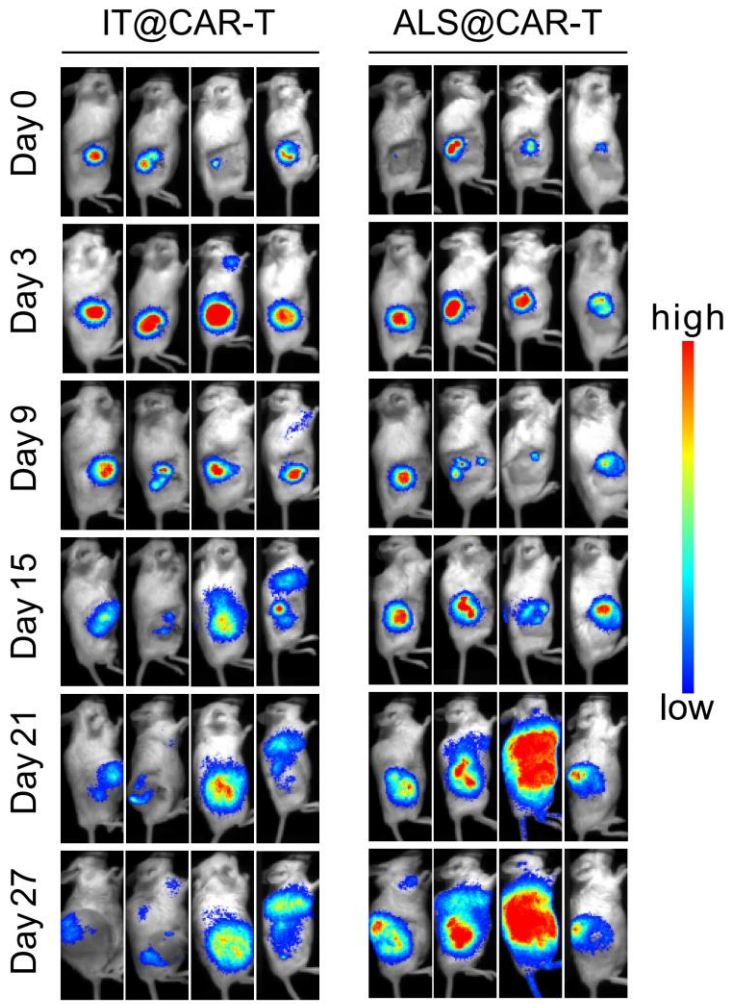
Persistence and killing ability

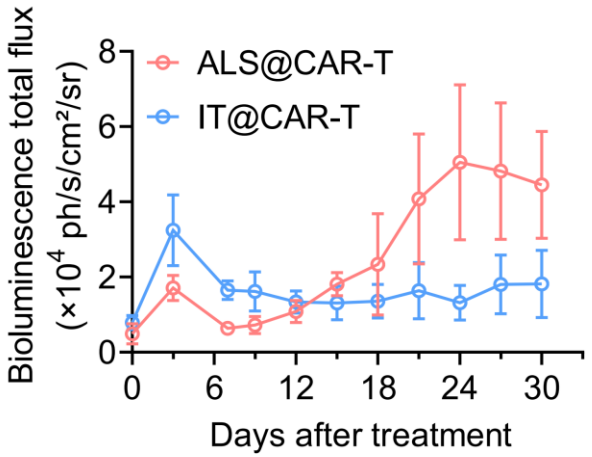
10 days after stimulation

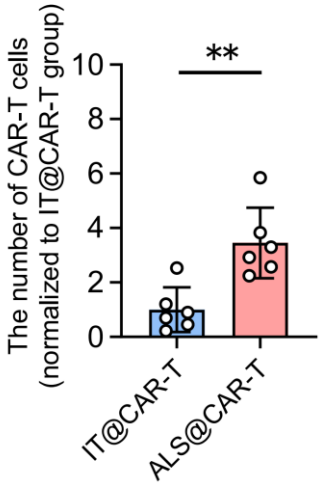


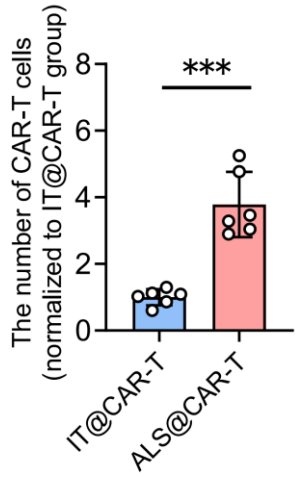


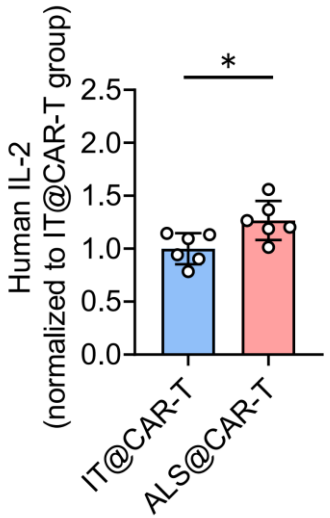
Artificial LNs for CAR-T cell delivery

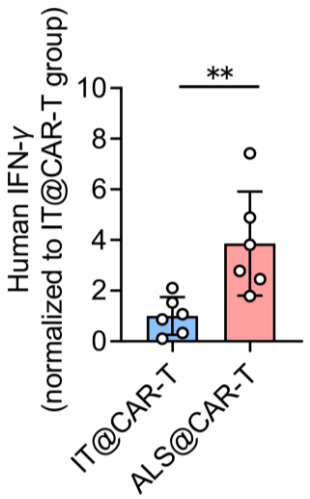


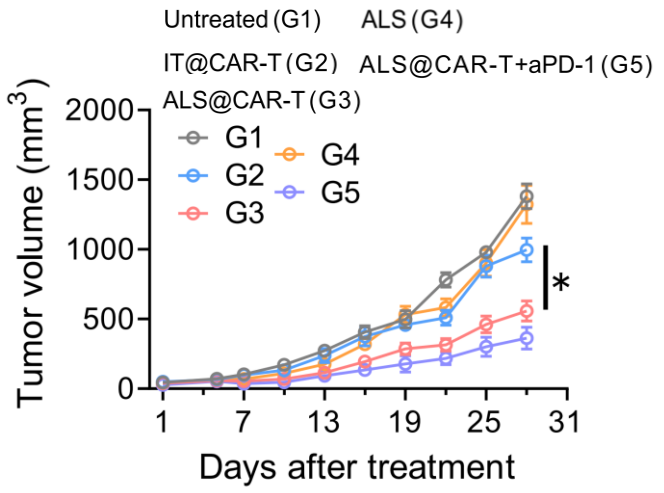












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Thank you!