Lyophilized Lymph Nodes for Improved Delivery of CAR T Cells

Jiaqi Shi
College of Pharmaceutical Sciences
Zhejiang University

July 11th, 2024

CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
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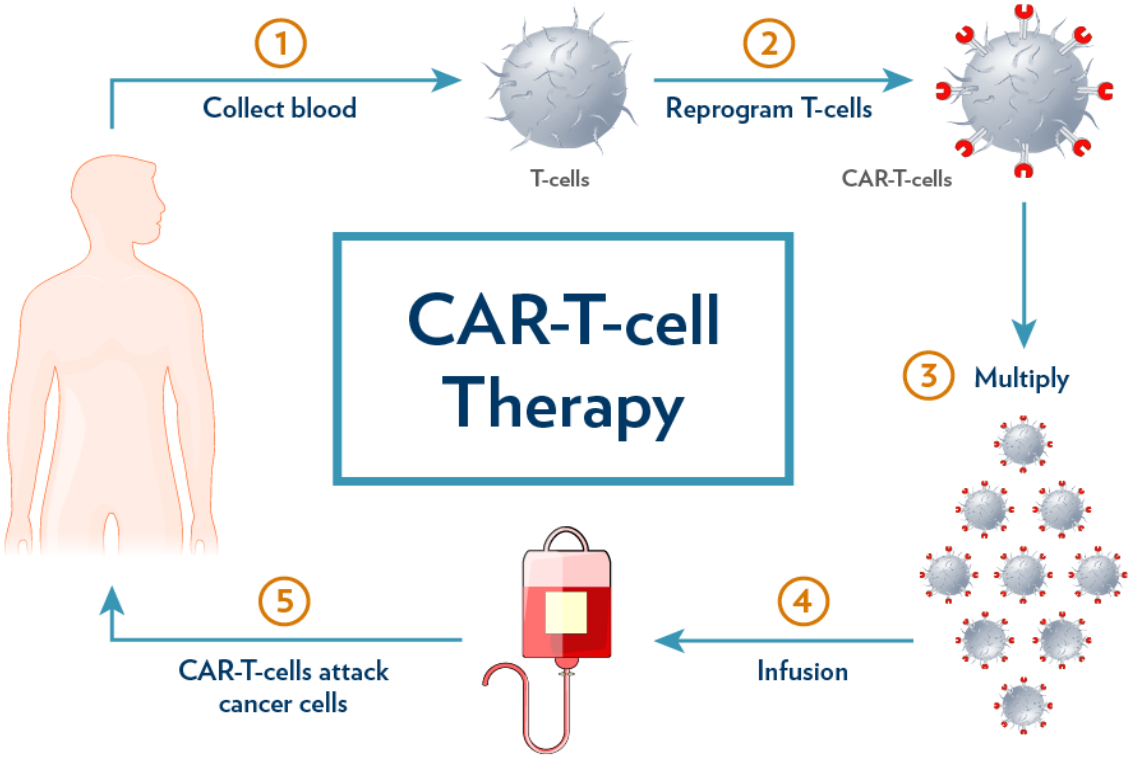
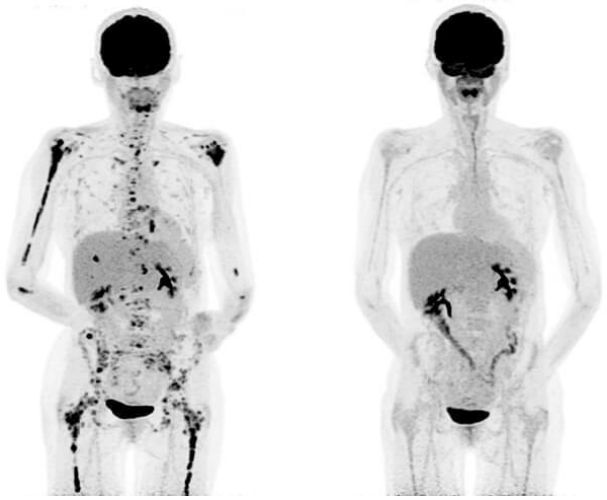
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

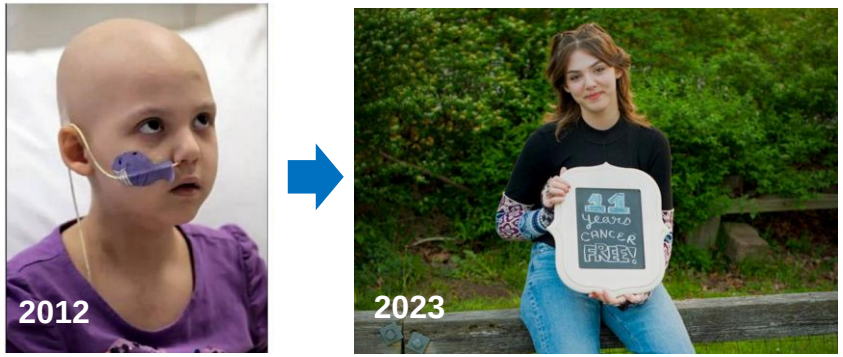
CAR T cell therapy: breakthrough in cancer treatment

- In haematologic malignancies, CAR T cell therapy has achieved **complete response rates** of up to **70–90%**.



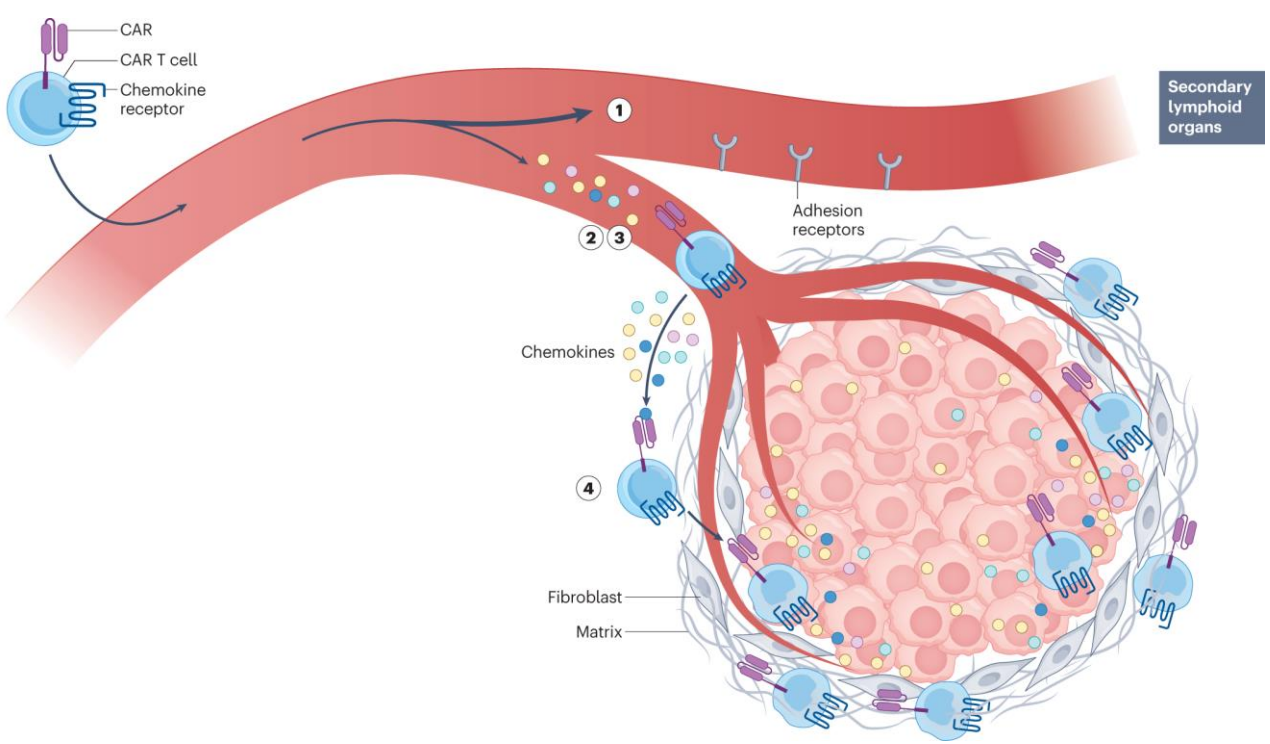
Dartmouth Cancer Center, Emily Whitehead Foundation, National Cancer Institute

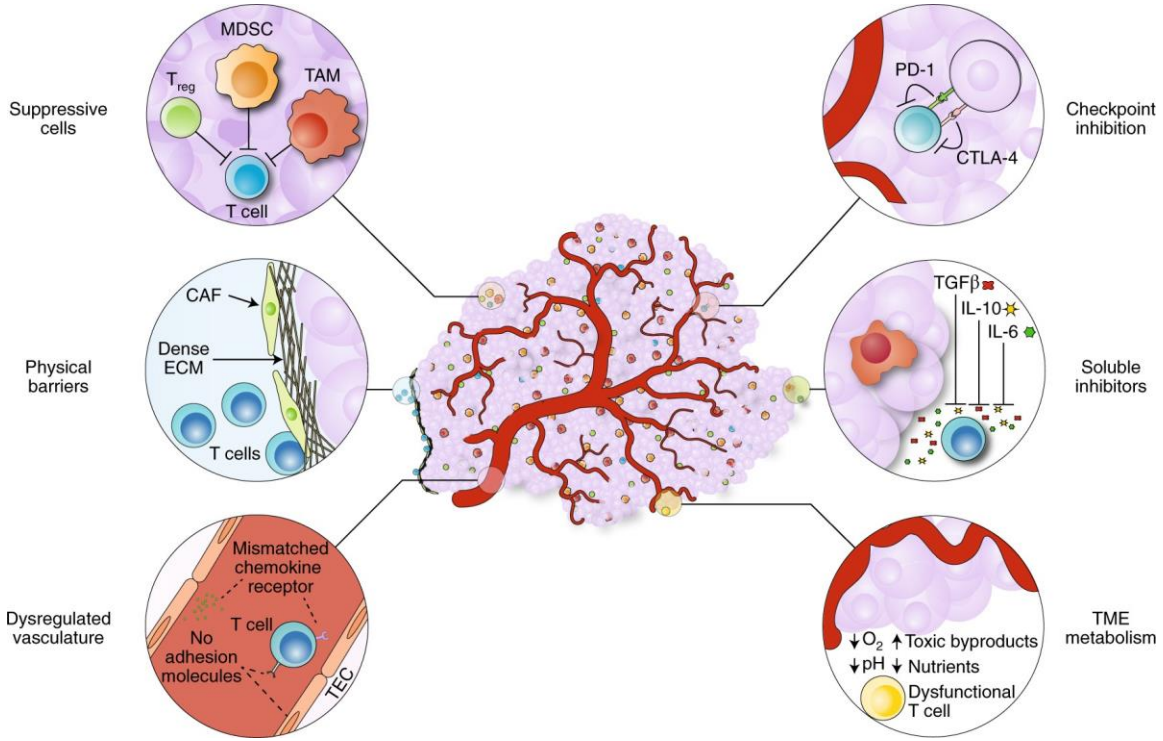




Barriers to the activity of CAR T cells against solid tumours

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

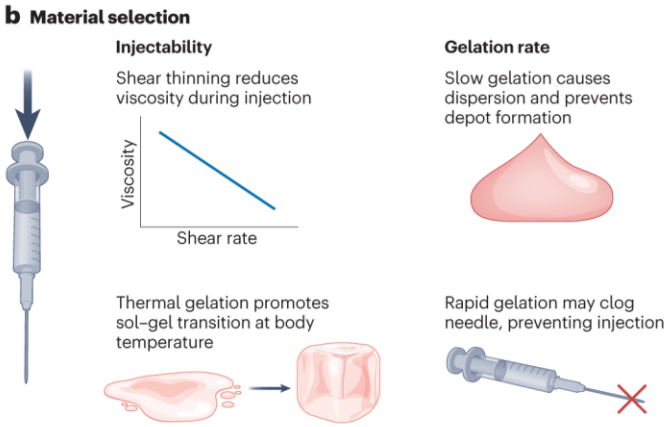


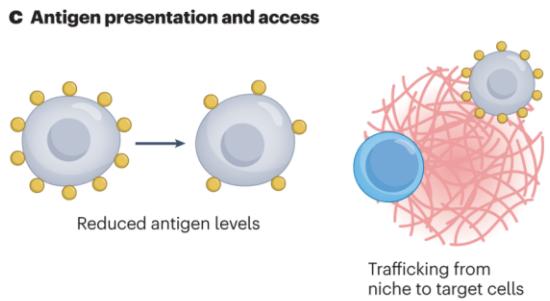


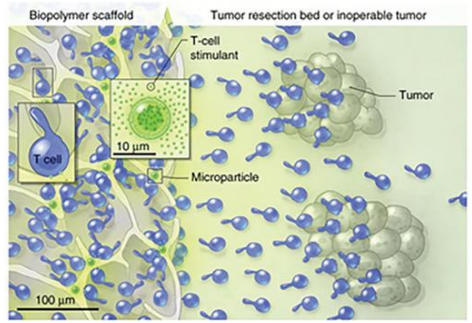
Nat Rev Clin Oncol, 2024, 21, 47–66; *Nat Biomed Eng*, 2018, 2, 377–391

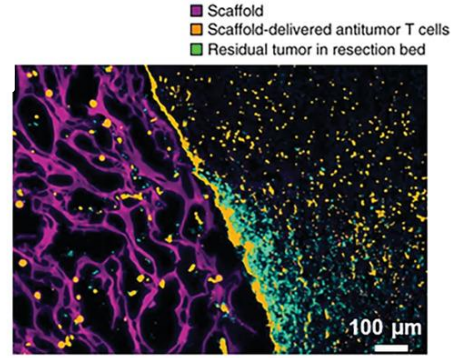
Biomaterials to enhance CAR T cell therapy

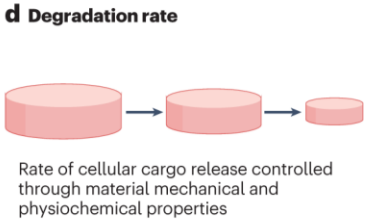
- **Synthetic biomaterials** loaded with CAR T cells and T cell-supporting factors are being studied to **concentrate**, **invigorate** and **controlled release** CAR T cells.

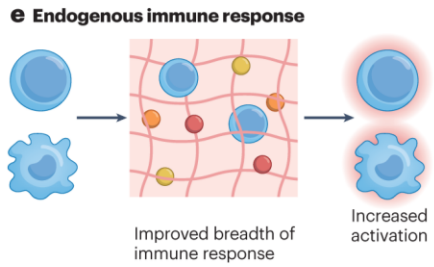


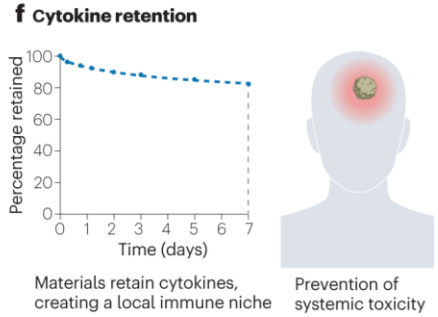












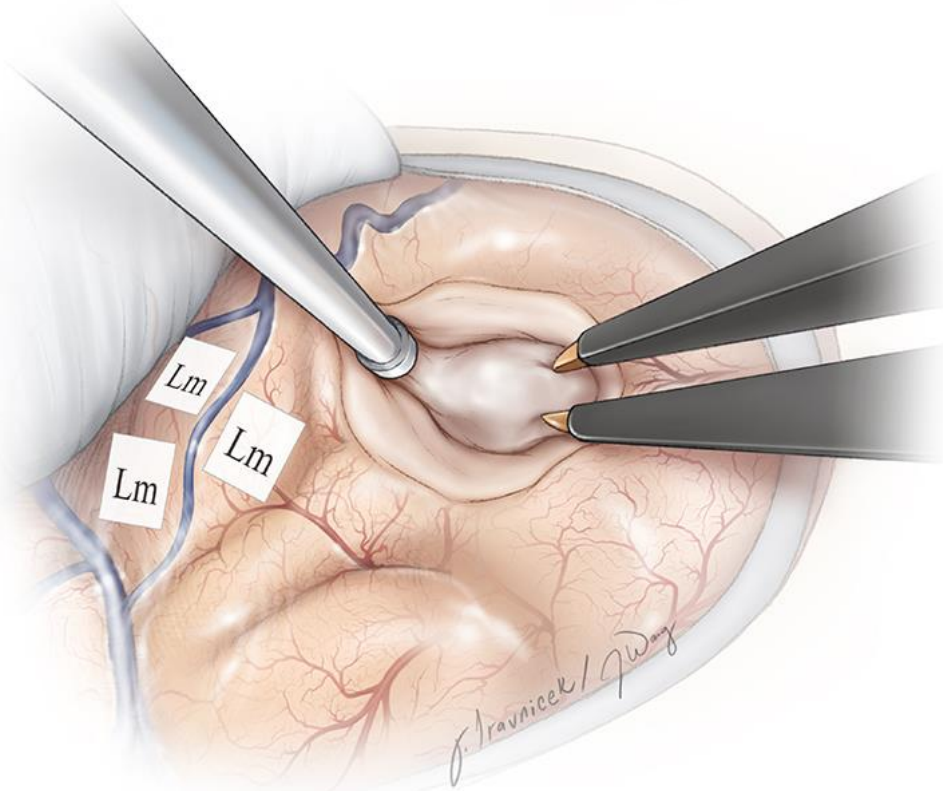
Limitations of artificial biomaterials

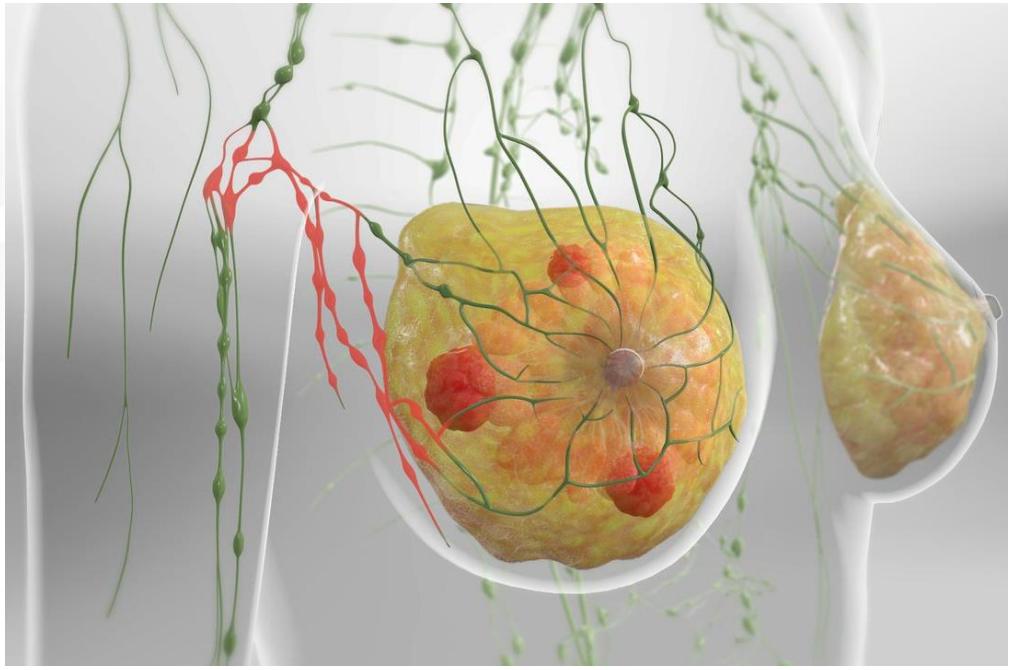
- **No physiological activity**
  (supplemented with IL2, IL15, anti-CD3 antibodies et al.)
- **High cost for clinical translation**
  (GMP manufacturing)
- **Limited biocompatibility**

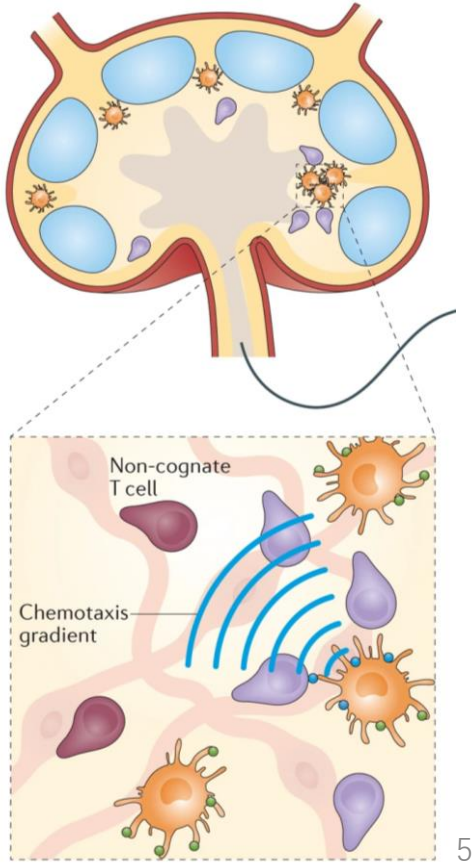
Nat Rev Bioeng, 2024, 2, 408–424; *Nat Biotechnol*, 2015, 33, 97–101

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.







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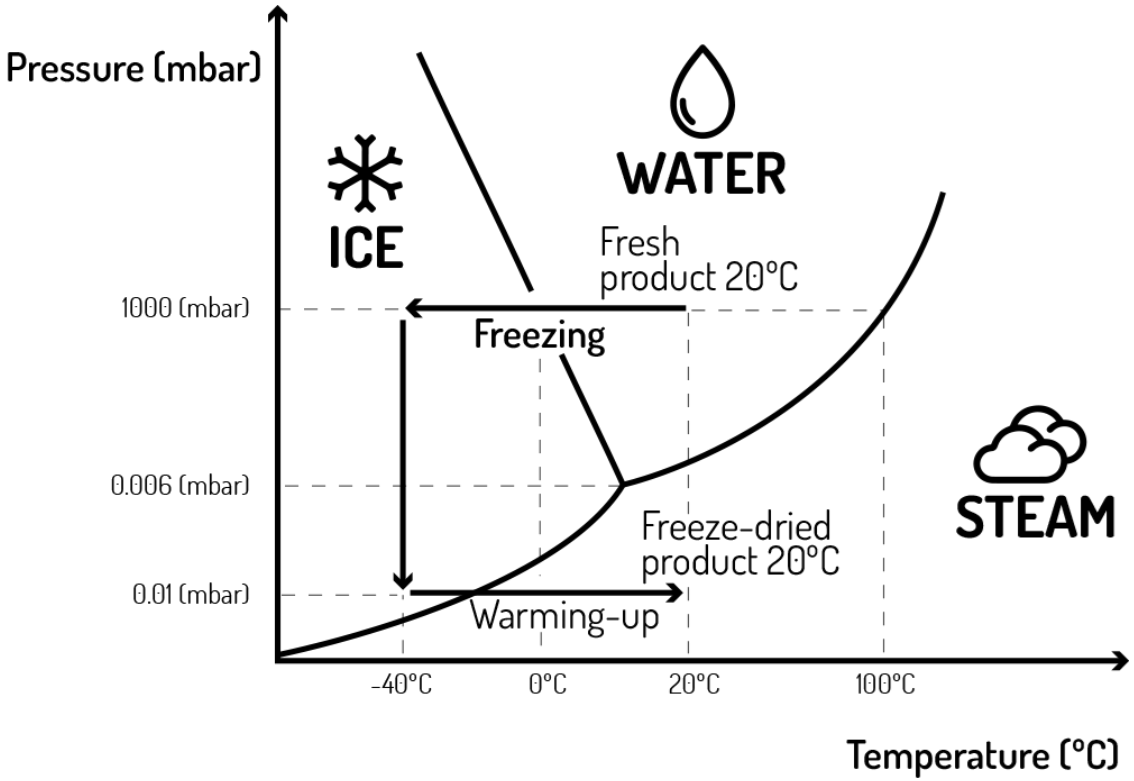
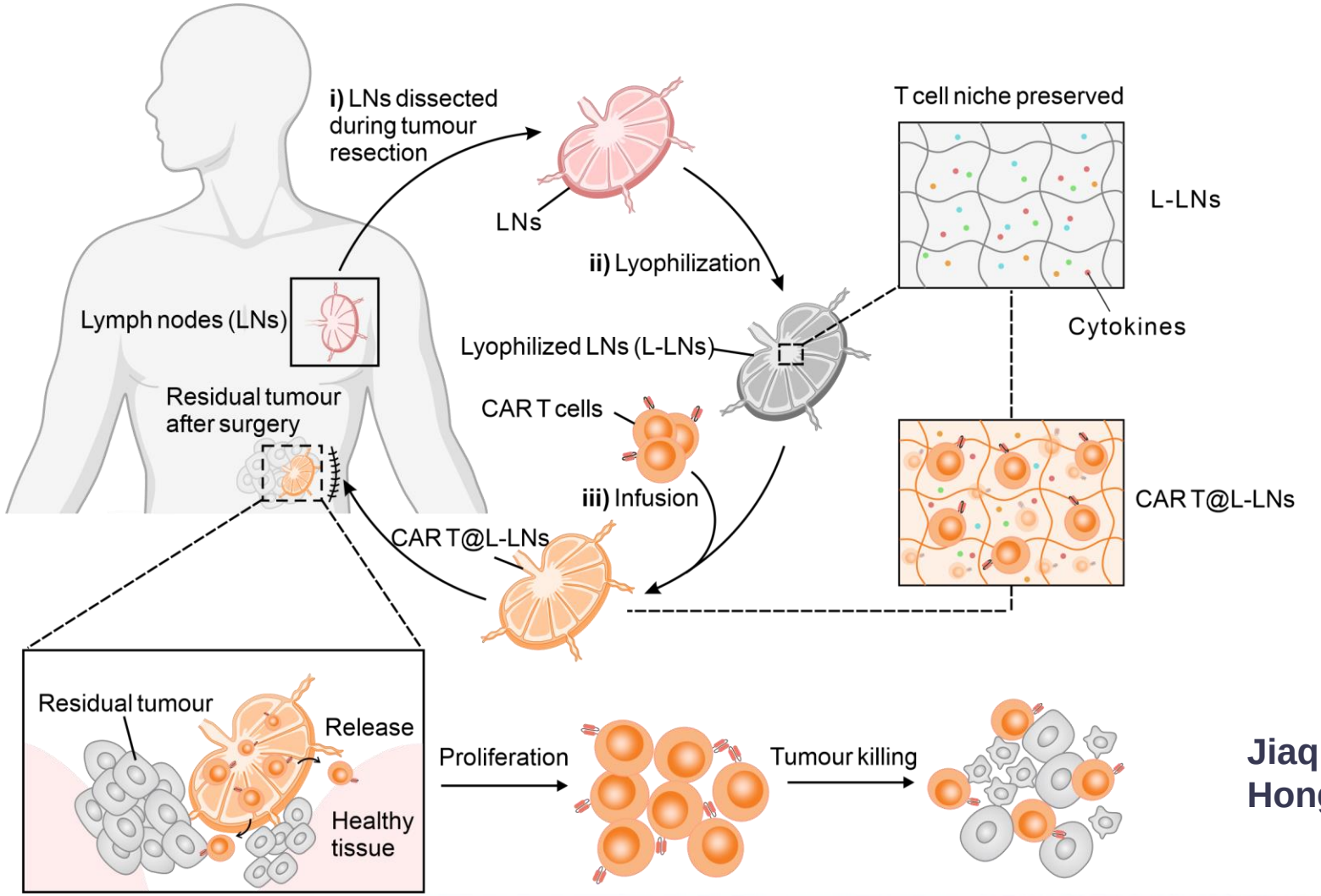
Nature Reviews Immunology, 2016, 16, 193–201

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

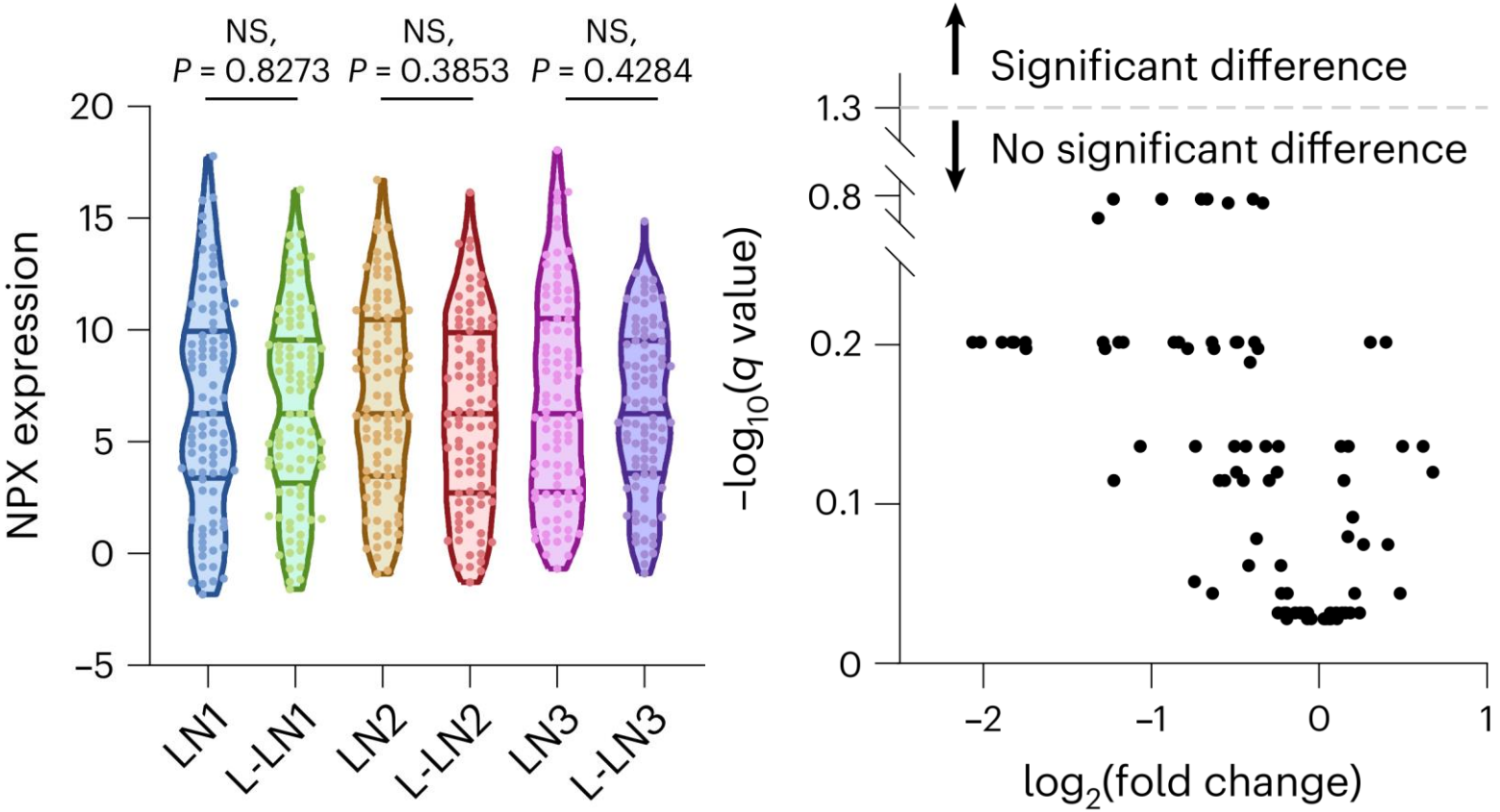


- **Lyophilization** maintained the stromal **framework** and the content of **cytokines** and **chemokines** of **LNs.**
- **Lyophilized LNs (L-LNs)** restored **a native home** for optimal T cell survival and function.
- **Autologous materials** possessed superior **biocompatibility**.

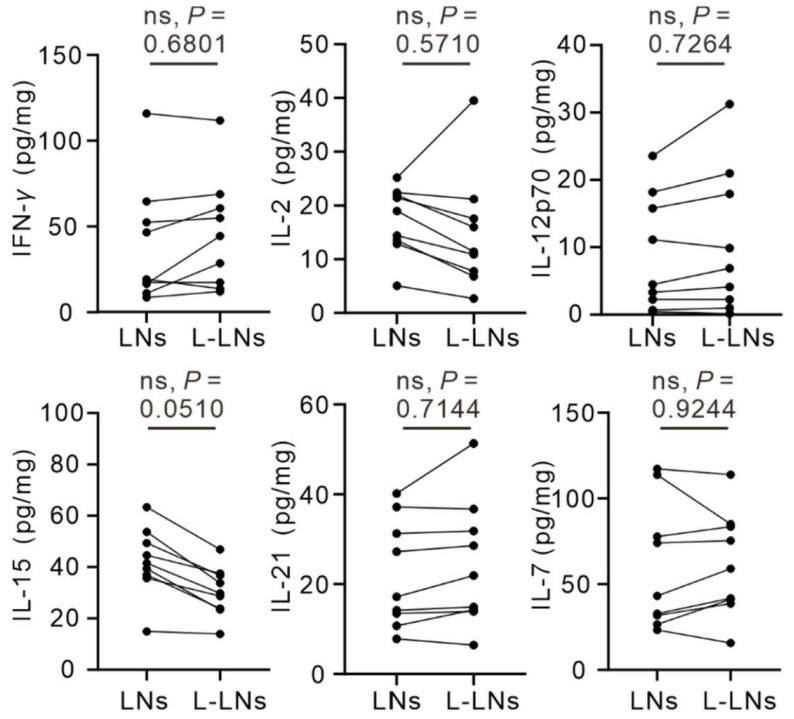
Jiaqi Shi, **Wei Wu**, **Dong Chen**,..., **Peng Zhao**, **Hongjun Li**, **Zhen Gu**. ***Nat Mater,*** 2024, 23, 844–853

Lyophilization preserved key components in LNs.

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

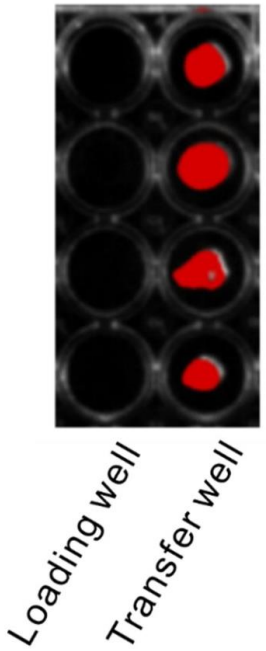


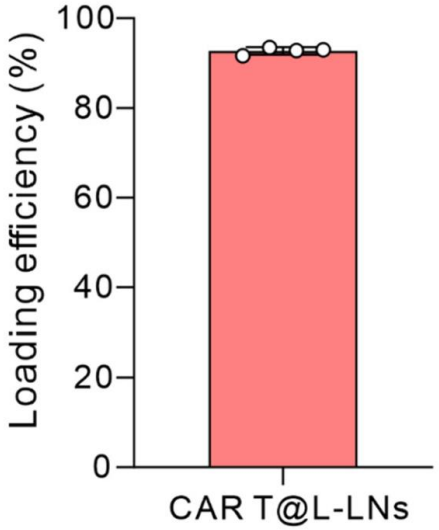
- Lyophilization preserves the **T cell-supporting cytokines** of native LNs.

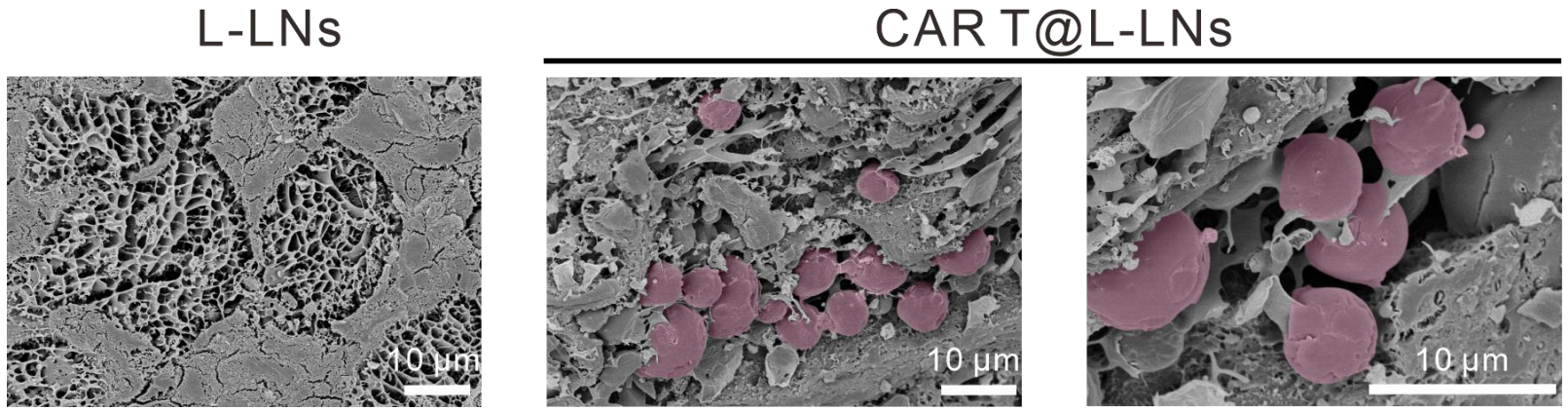


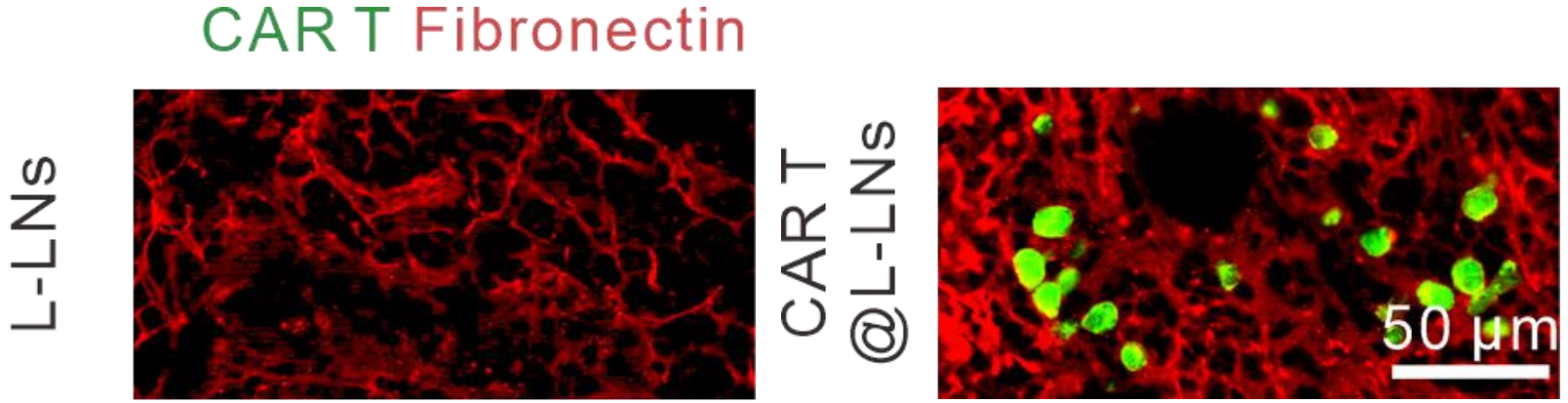
CAR T cells were loaded into L-LNs (CAR T@L-LNs).

- Loading efficiency of CAR T cells reached 93%.



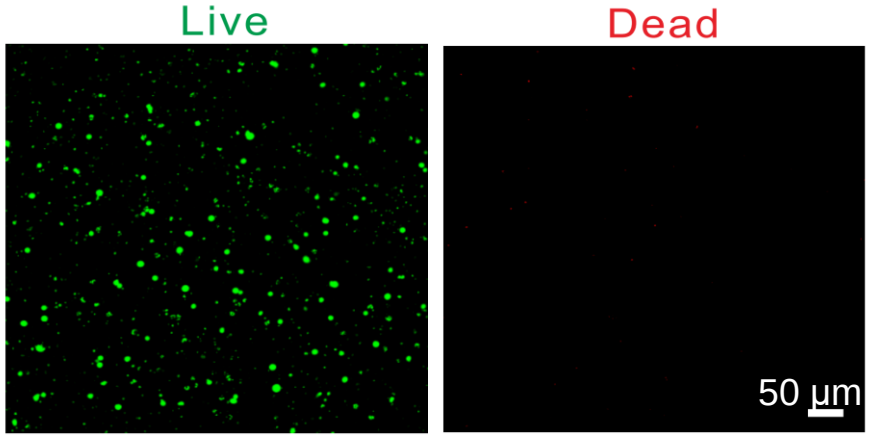


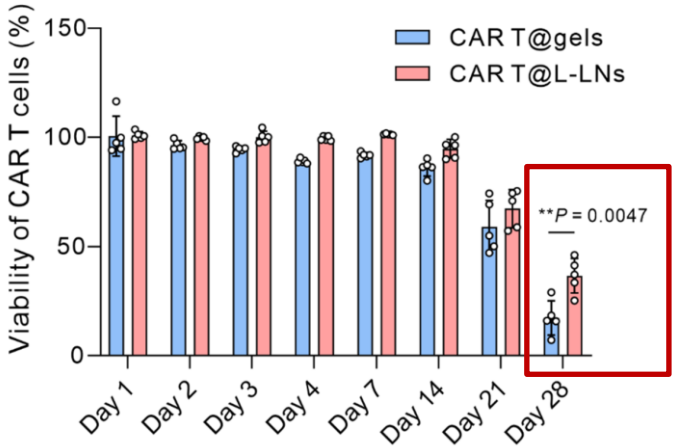


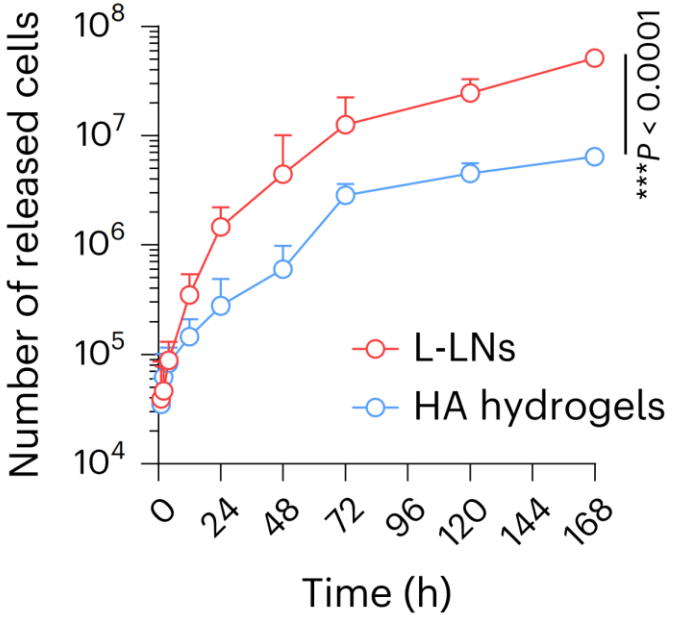


CAR T cells were loaded into L-LNs (CAR T@L-LNs).

- 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.

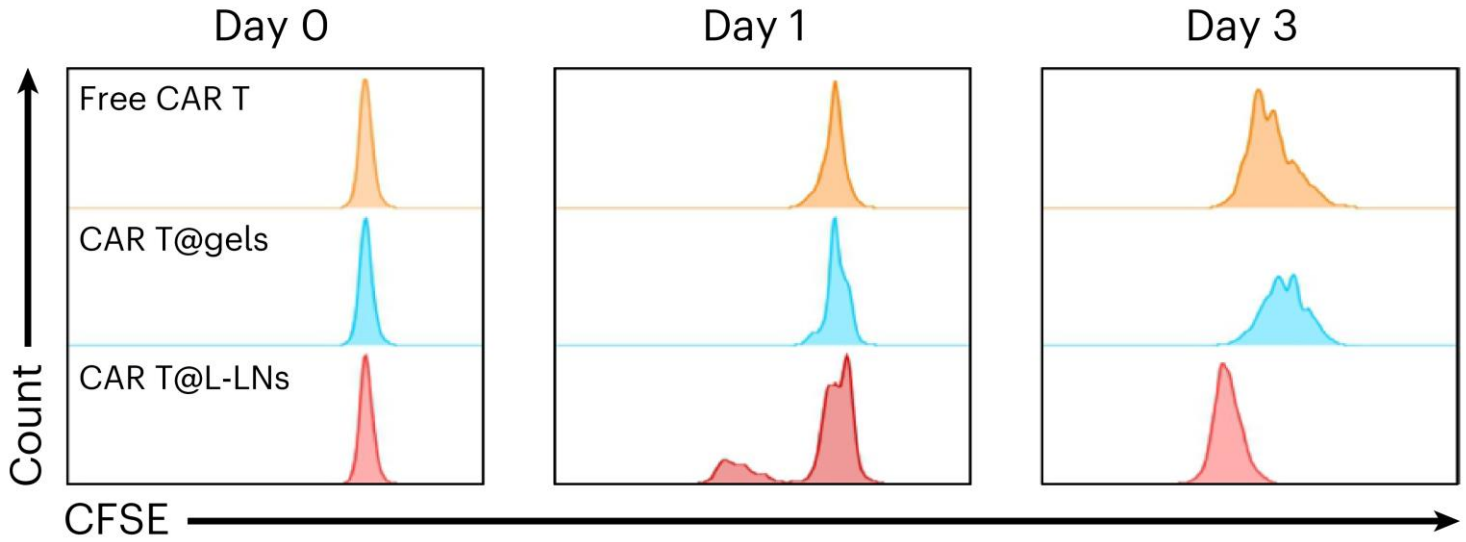


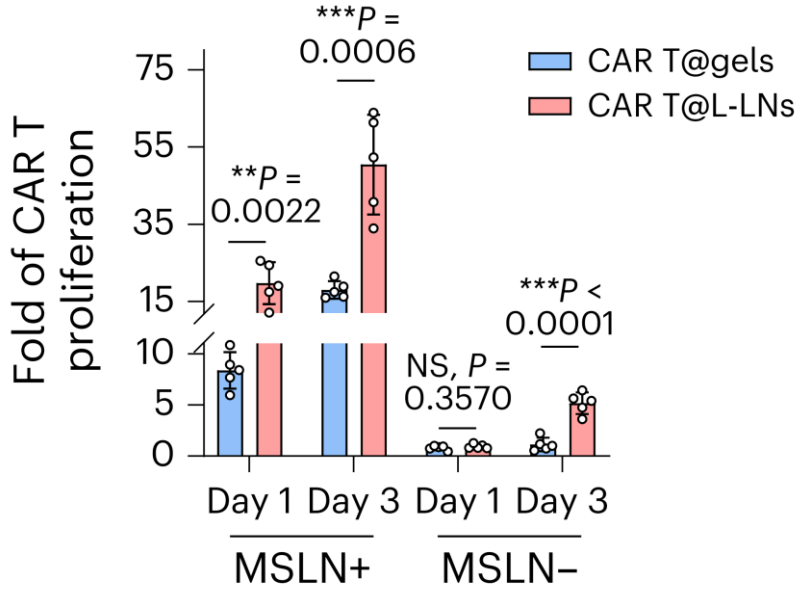




L-LNs enhanced CAR T cell expansion.

- 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.



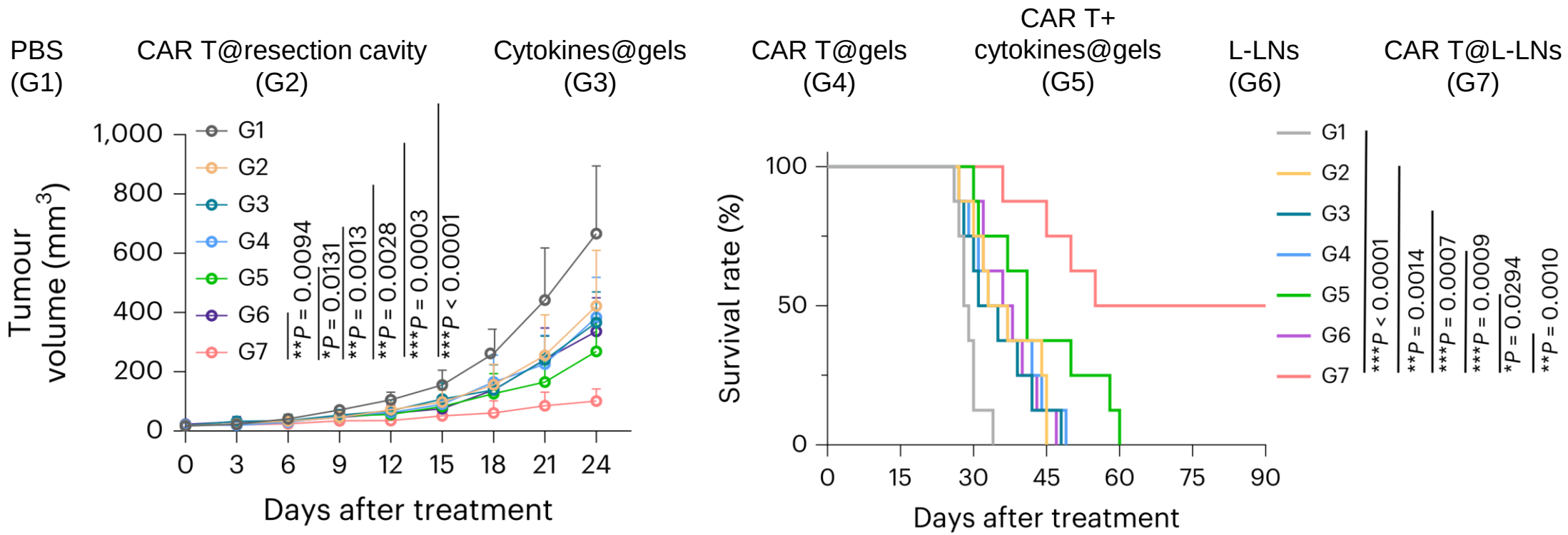


CAR T@gels: CAR T cells loaded in hyaluronic acid hydrogels supplemented with critical cytokines (IL-2, IL-7, IL-15 and IFNγ)

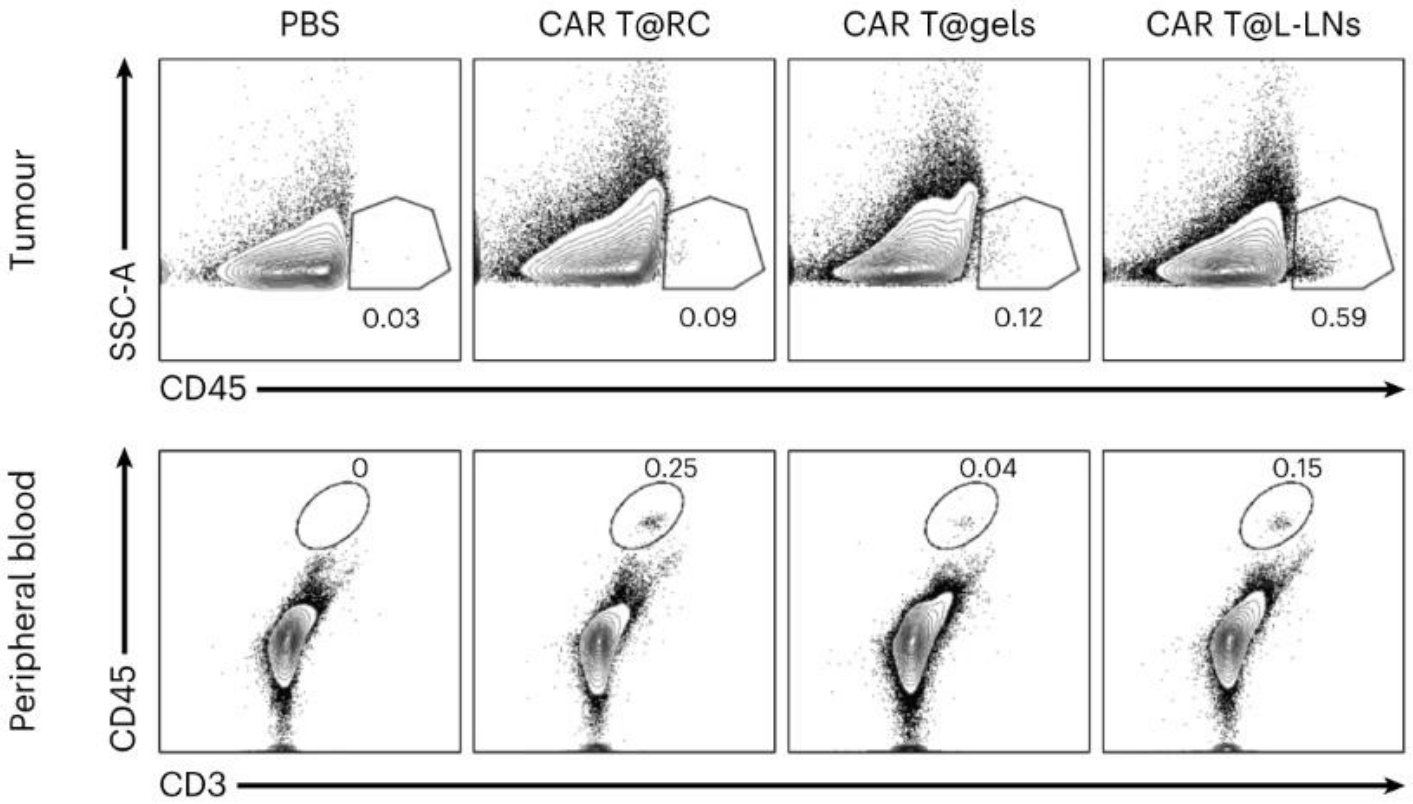
MSLN: mesothelin

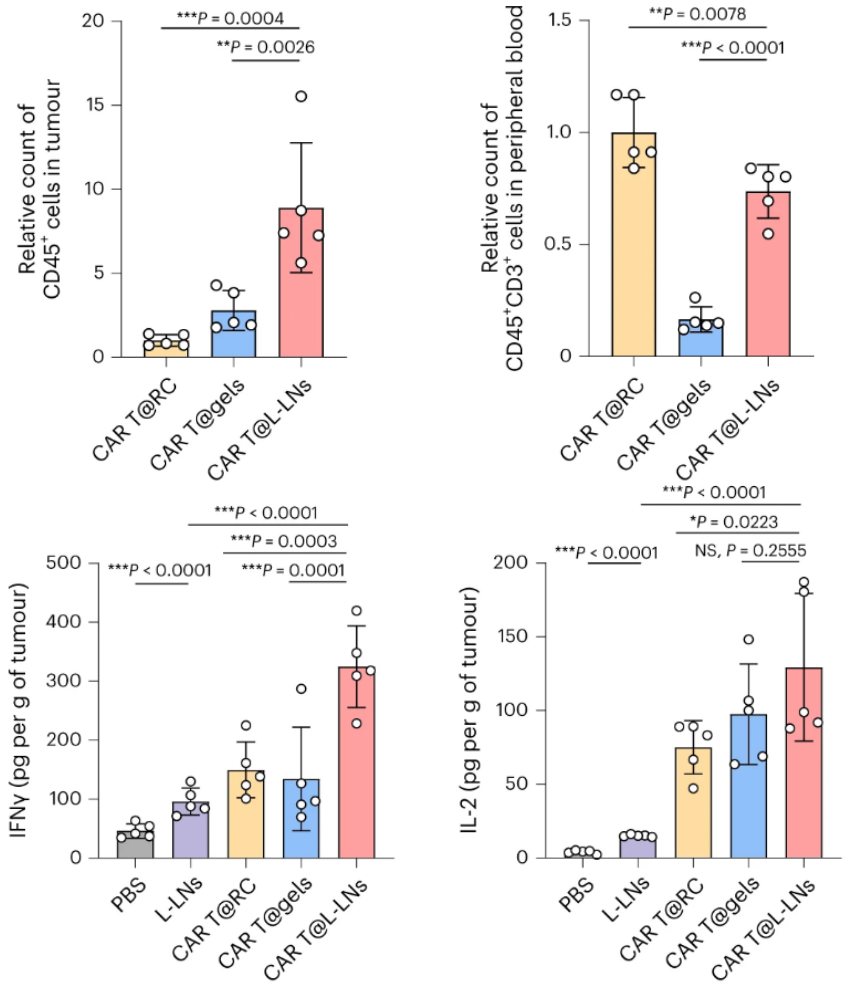
CAR T@L-LNs: superior antitumour effect in a HeLa tumour resection mouse model

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



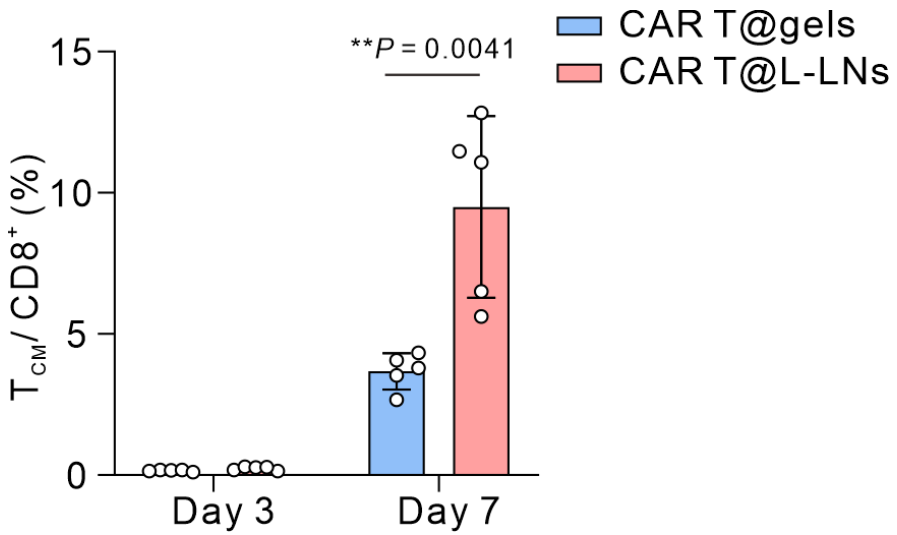
CAR T cell infiltration and intratumoural IL-2 and IFN-γ levels were elevated.

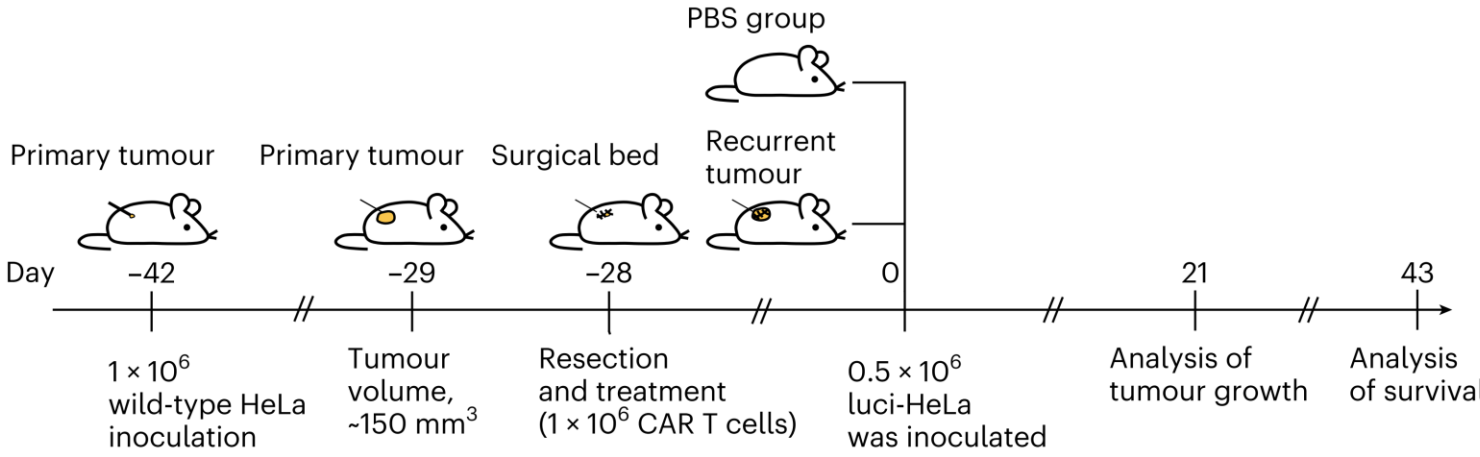


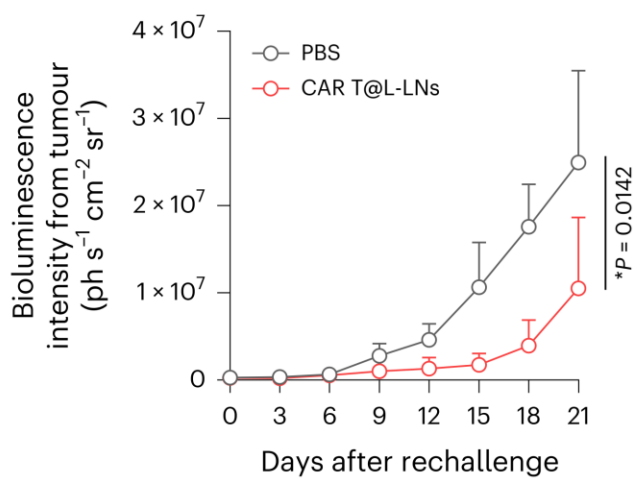


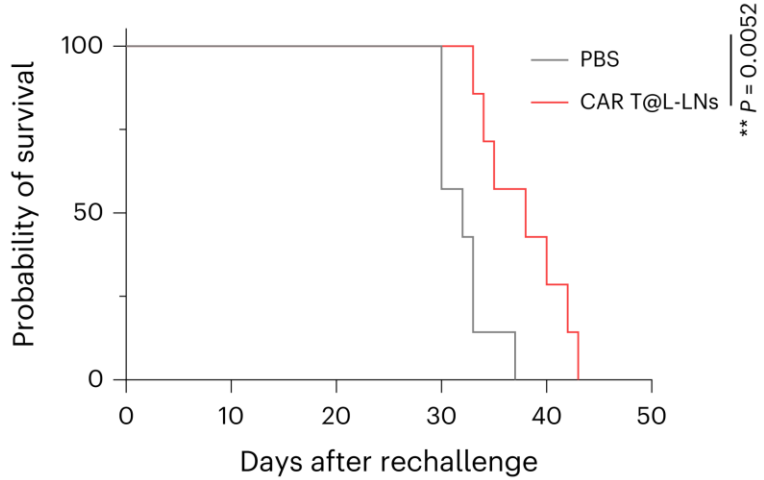
CAR T@L-LNs showed persistent antitumour activity.

- 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.

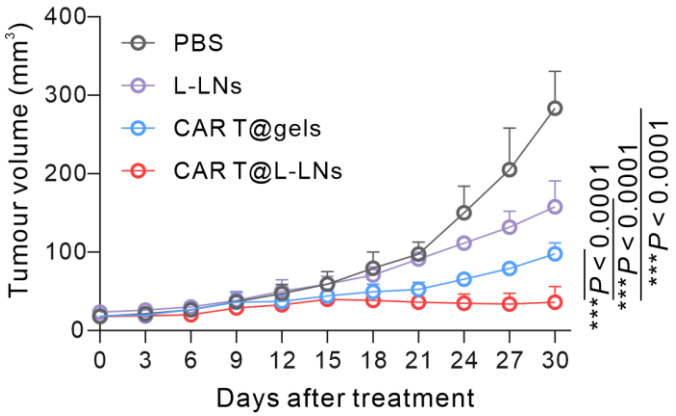


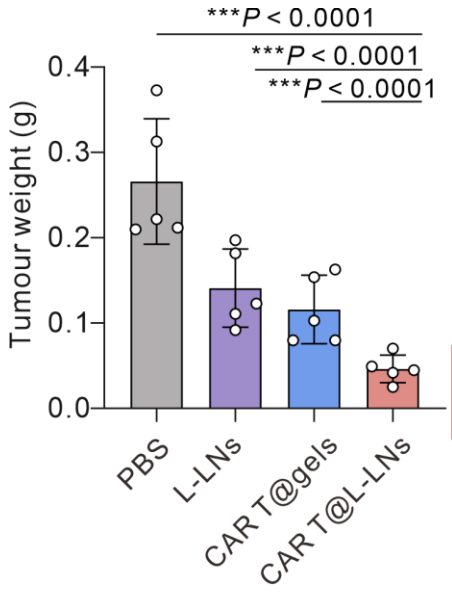


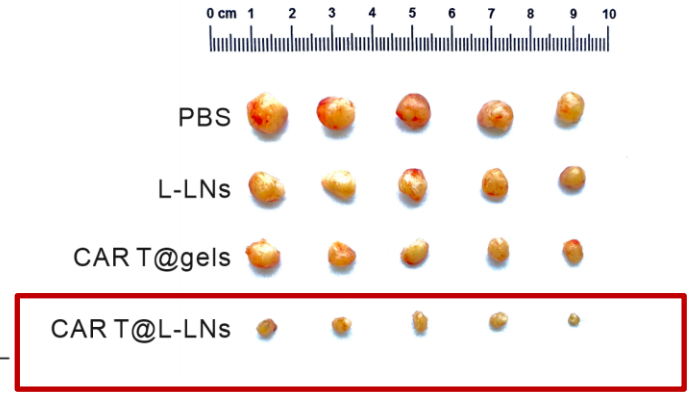


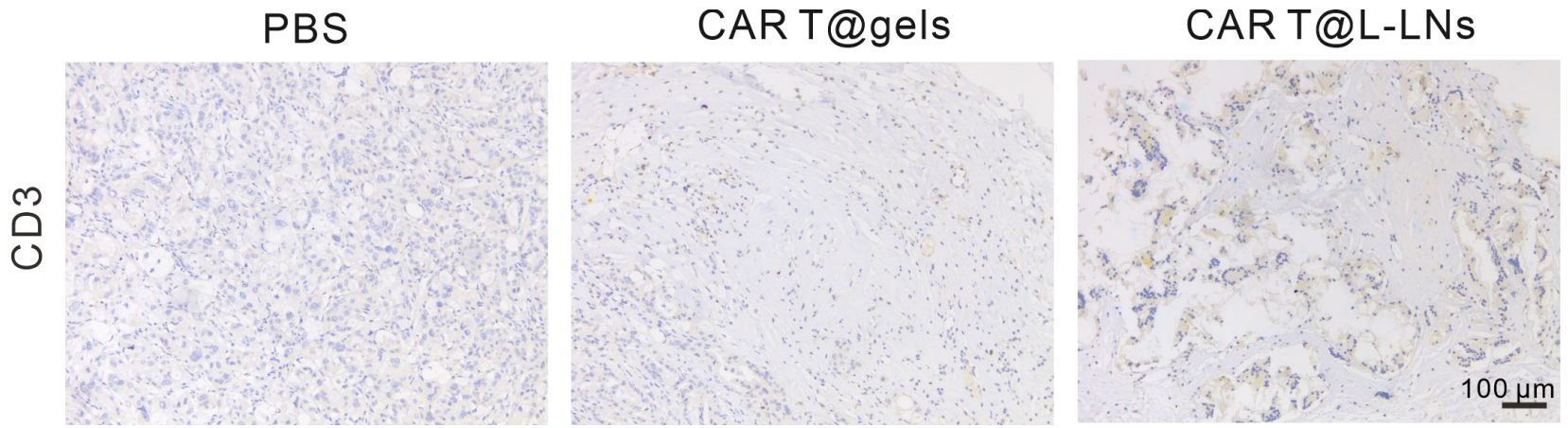


Anticancer effect of CAR T@L-LNs was assessed in a patient-derived xenograft (PDX) tumour model



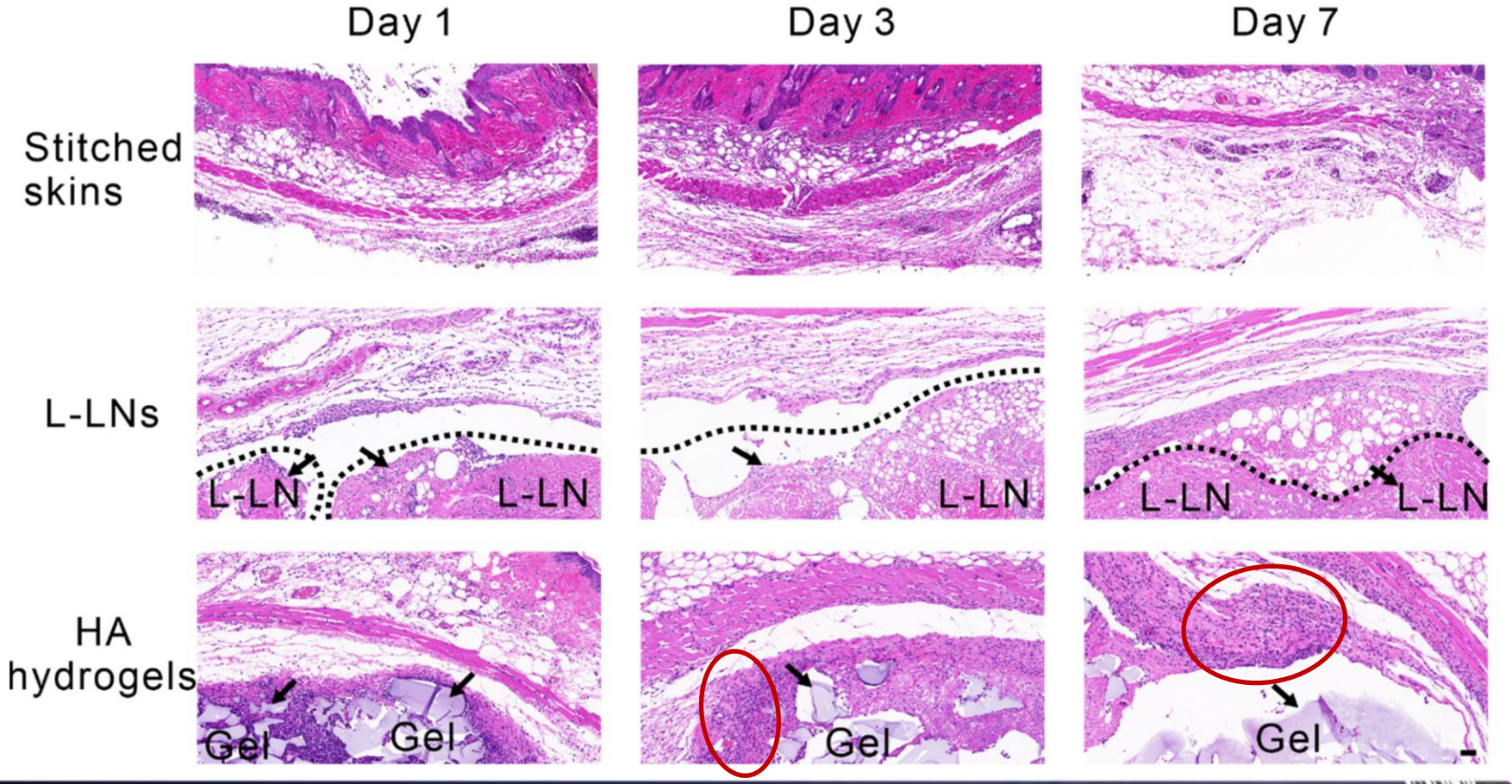






L-LNs were well biocompatible.

- 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.



Acknowledgments

Advisers:

Prof. Zhen Gu

Prof. Hongjun Li

Collaborators:

Prof. Peng Zhao

Prof. Dong Chen

Prof. Weijia Fang

Prof. Xiao Liang

Prof. Jie Sun

Prof. Gianpietro Dotti

Prof. Weilin Wang

Prof. Yuan Ding

Prof. Zhengwei Mao

Lab members:

Wei Wu

Ziyan Liao

Tao Sheng

Yanfang Wang

Yuejun Yao

Qing Wu

Feng Liu

Ruyi Zhou

Chaojie Zhu

Xinyuan Shen

中华人民共和国科学技术部
Ministry of Science and Technology of the People's Republic of China

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浙江大学 ZHEJIANG UNIVERSITY 1897

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Thank you!