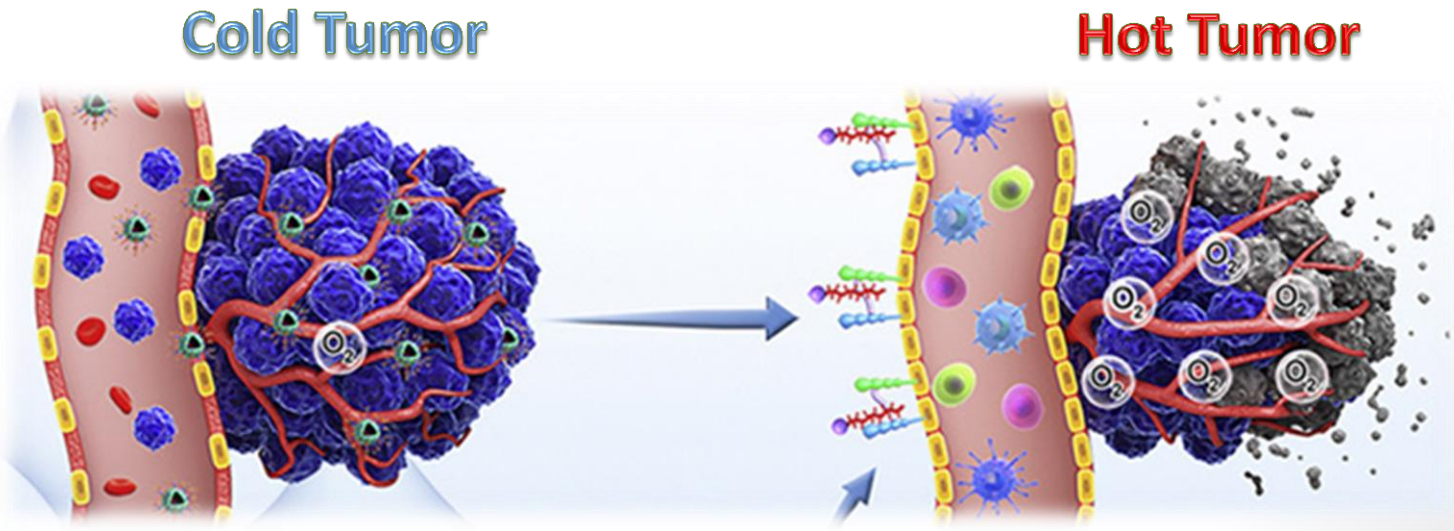
Immunotherapy Strategies For Turning Cold Tumors Into Hot Tumors

Presented By Zahra Asadi Samani

Master Student Of Medical Immunology

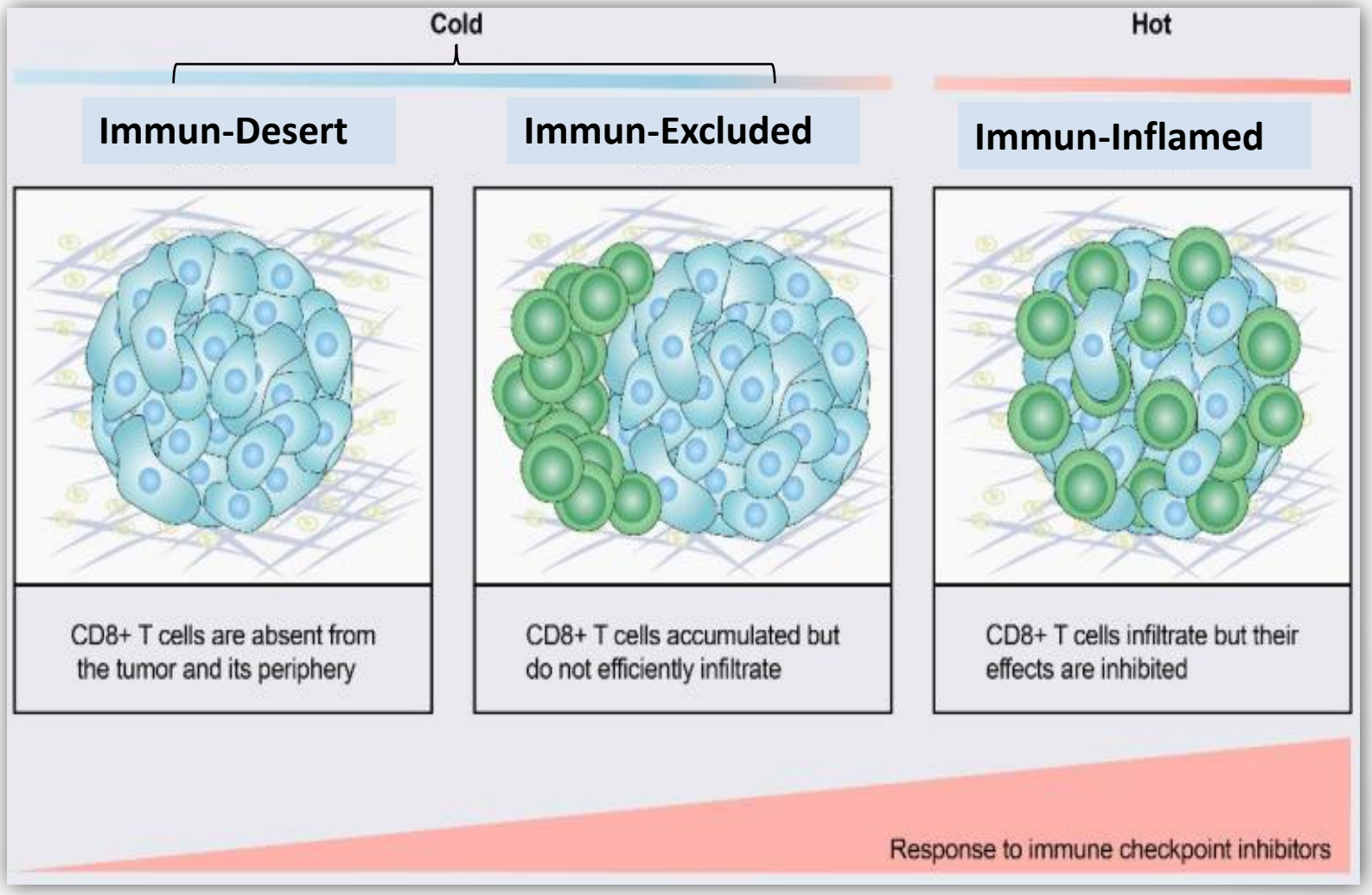
Introduction

- Immune checkpoint inhibitors (ICIs) as a immunotherapy resulting in long-lasting tumor suppression and regression.
- Promoting the conversion of “cold” tumors to “hot” tumors is currently a key challenge in tumor immunotherapy.



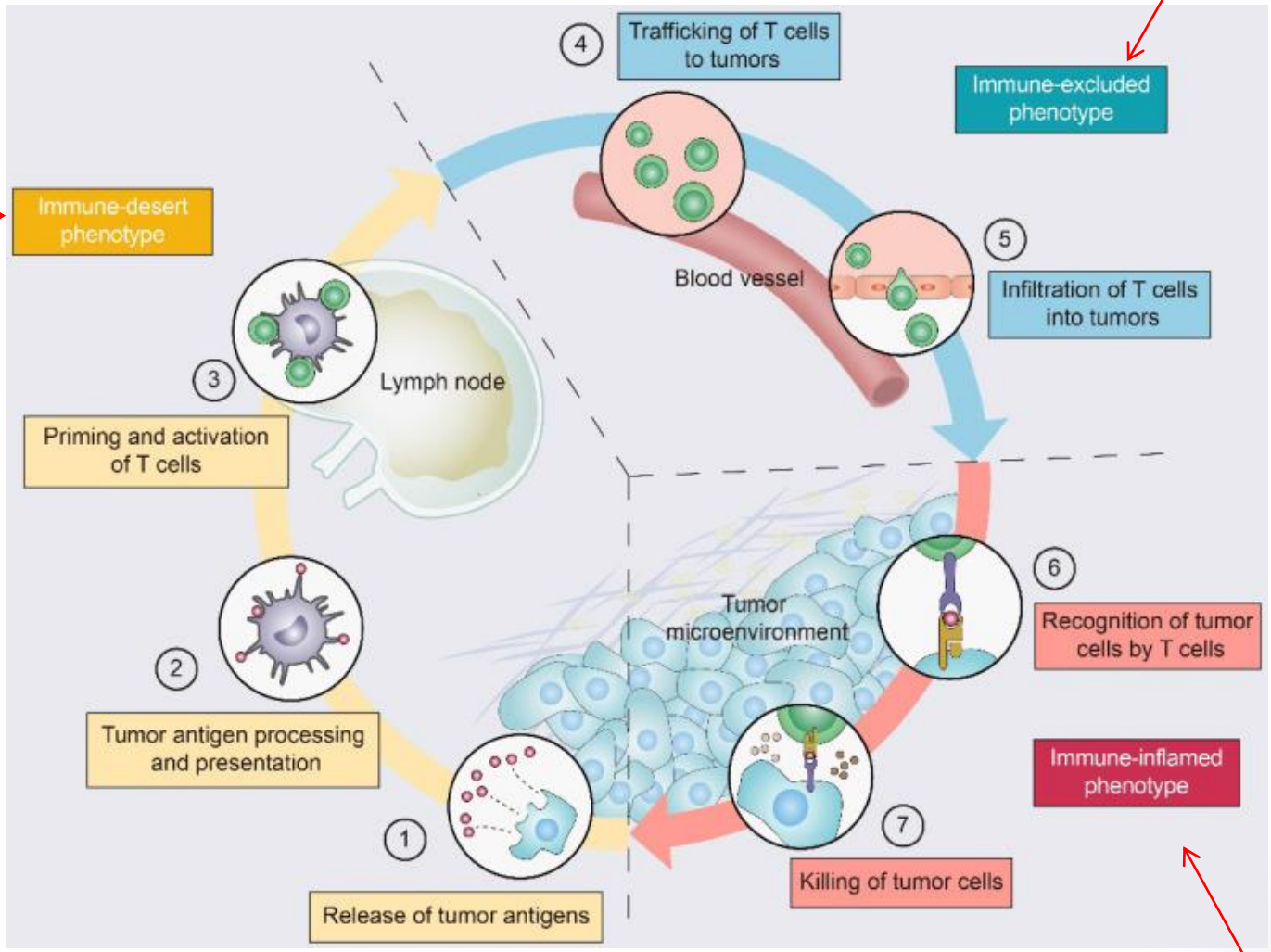
YI, Yunfei, et al.Matter, 2022

Tumor Immunophenotypes



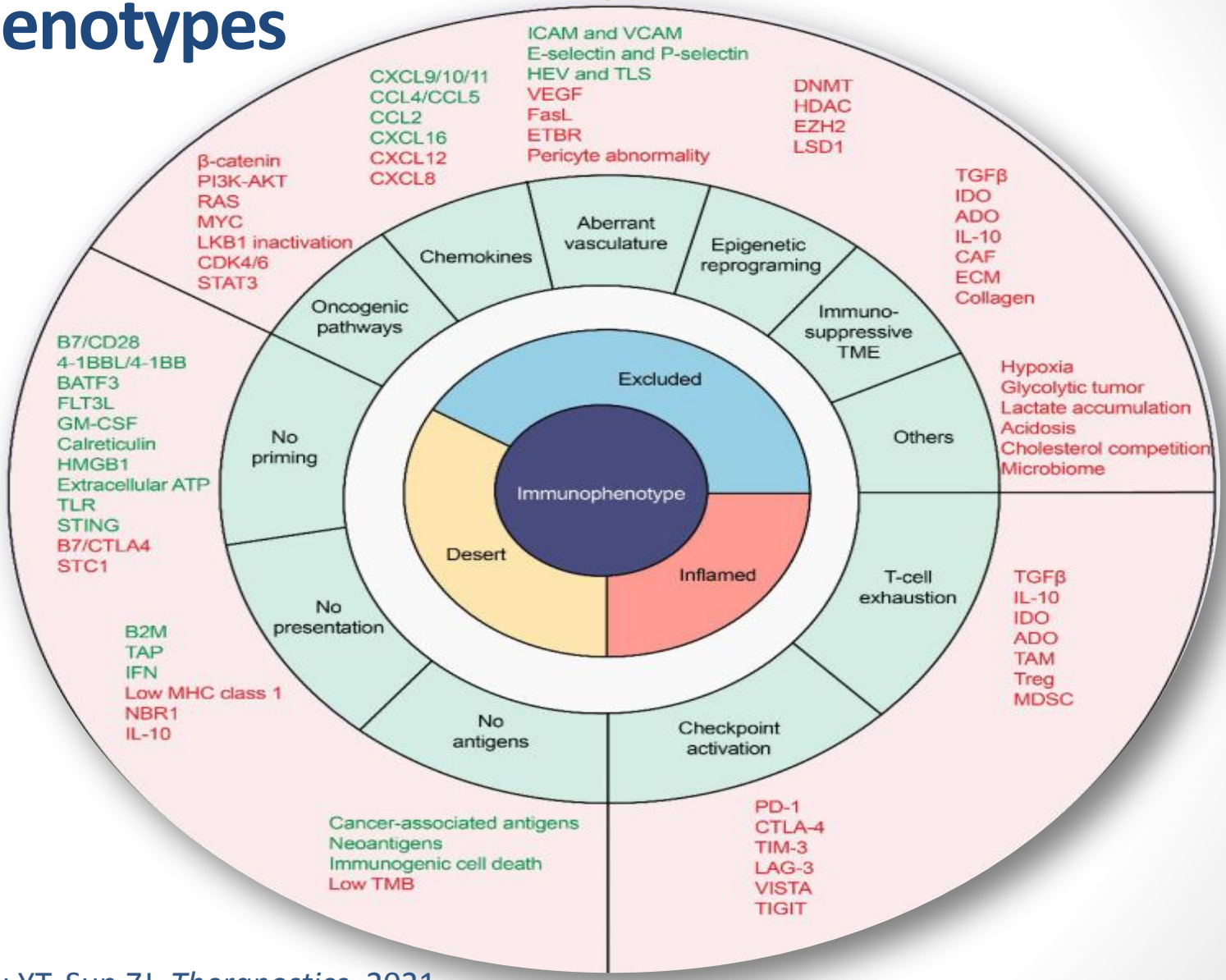
- Liu YT, Sun ZJ. *Theranostics*. 2021

The Tumor-immunity Cycle And Three Immunophenotypes



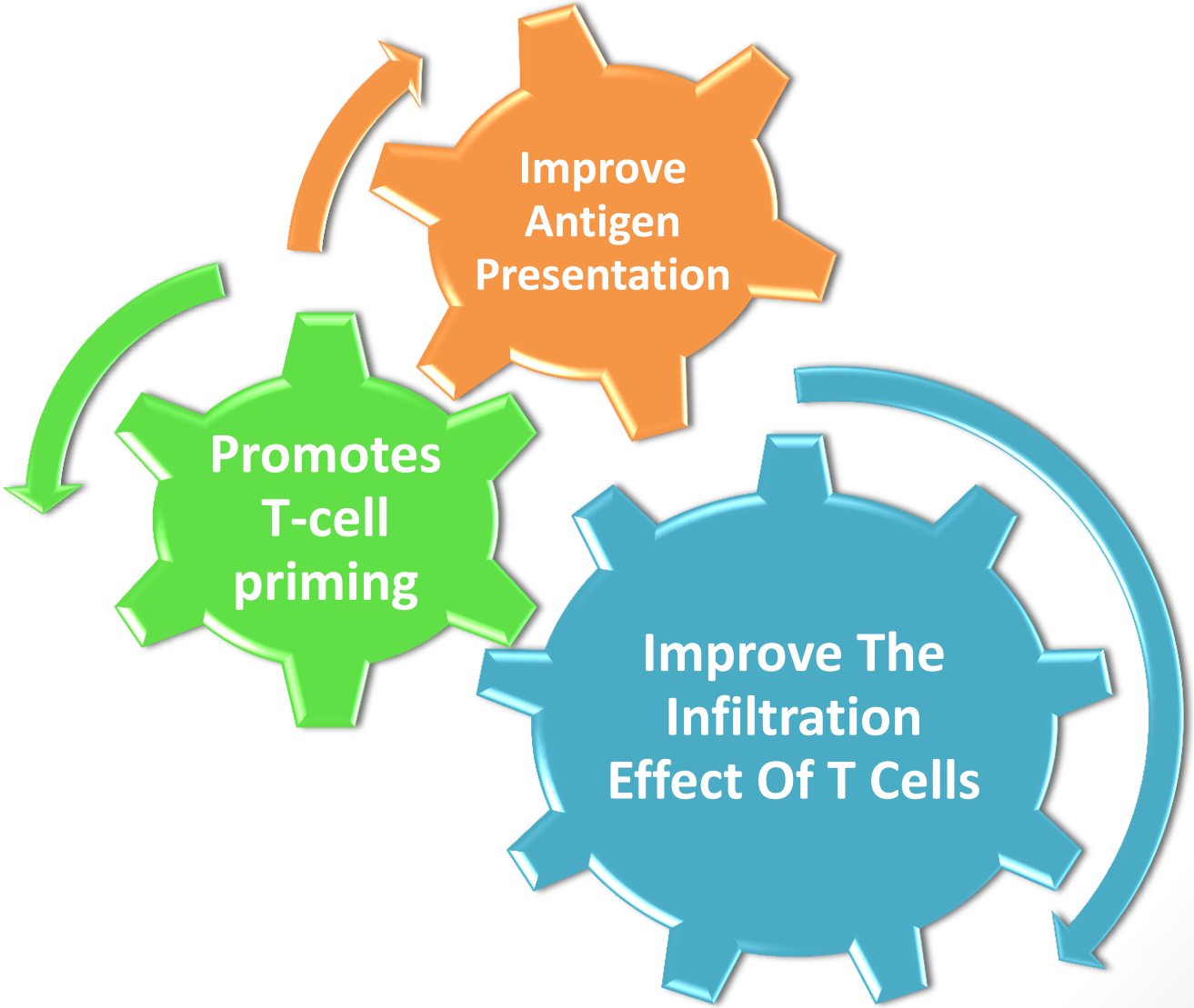
- Liu YT, Sun ZJ. *Theranostics*. 2021

Mechanisms of three distinct tumor phenotypes



- Liu YT, Sun ZJ. *Theranostics*. 2021

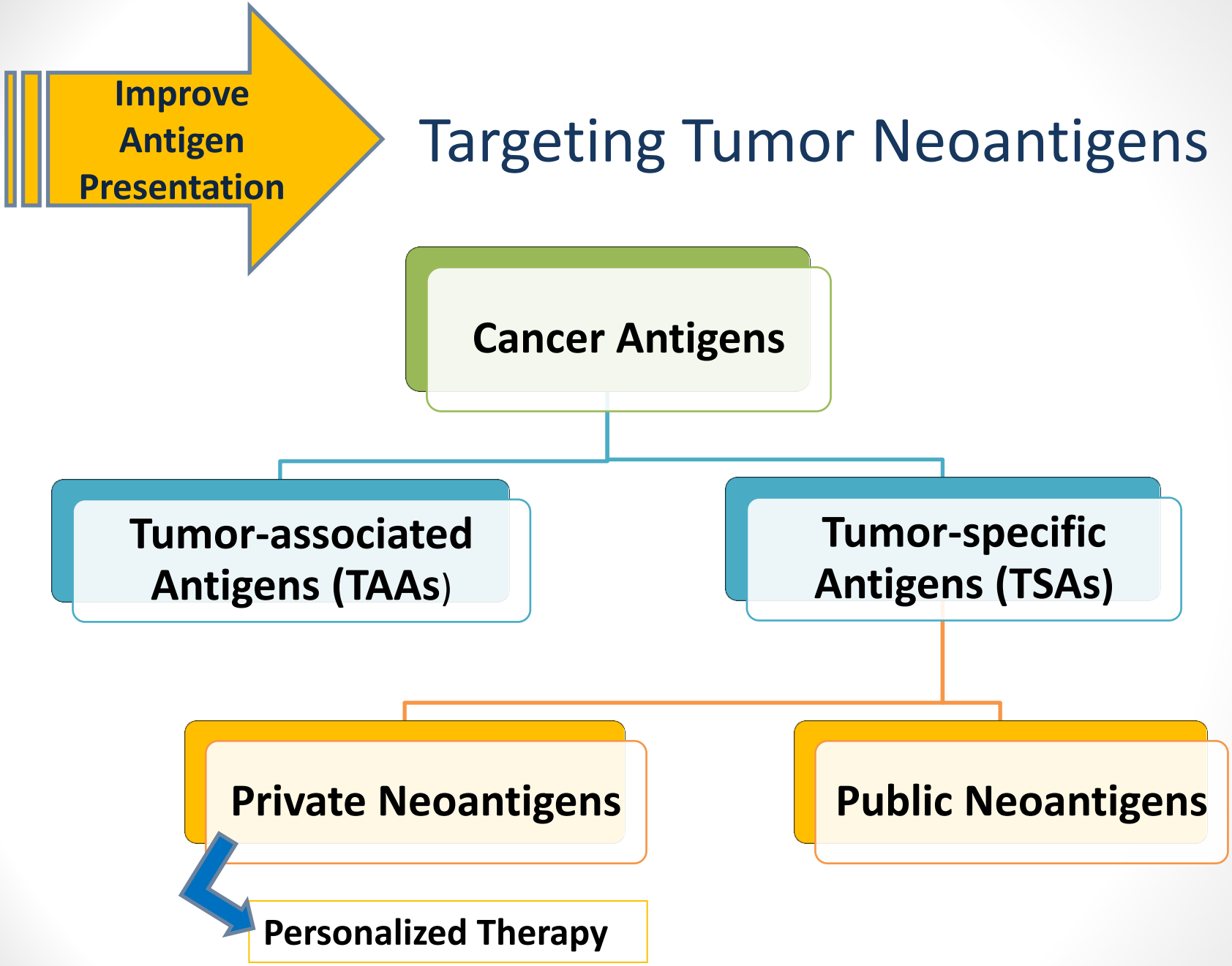
PURPOSES OF IMMUNOTHERAPY



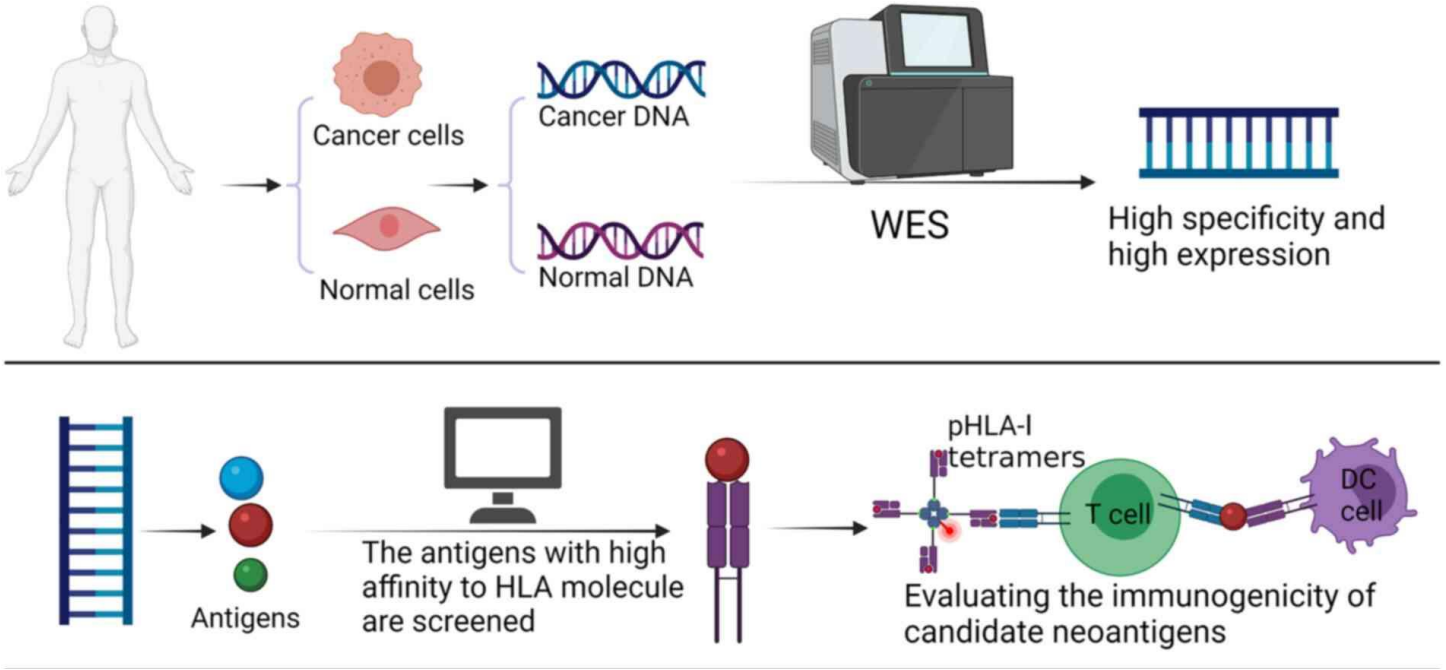
Improve Antigen Presentation

- Targeting Tumor Neoantigens
- Cancer Vaccine
- CD40 Agonist
- Regulate Gut Flora
- Adoptive cellular therapy (TILs, CAR-T cells)

Targeting Tumor Neoantigens



Targeting Tumor Neoantigens



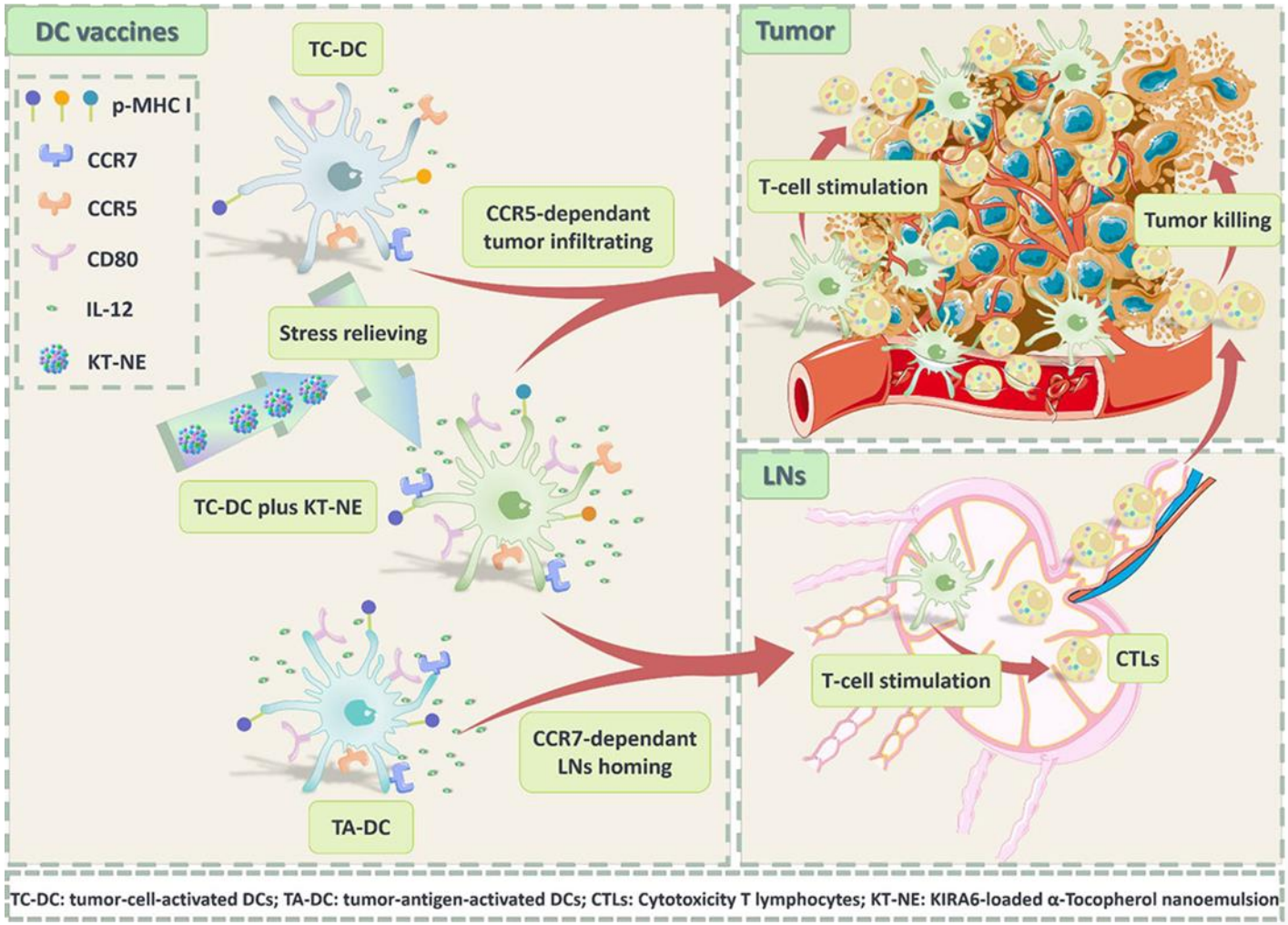
- Protein/peptide vaccines
- Autologous DCs vaccines
- DNA and RNA vaccines

➢ FANG, Xianzhu, et al. *Oncology Letters*, 2022

Improve Antigen Presentation

Cancer Vaccines

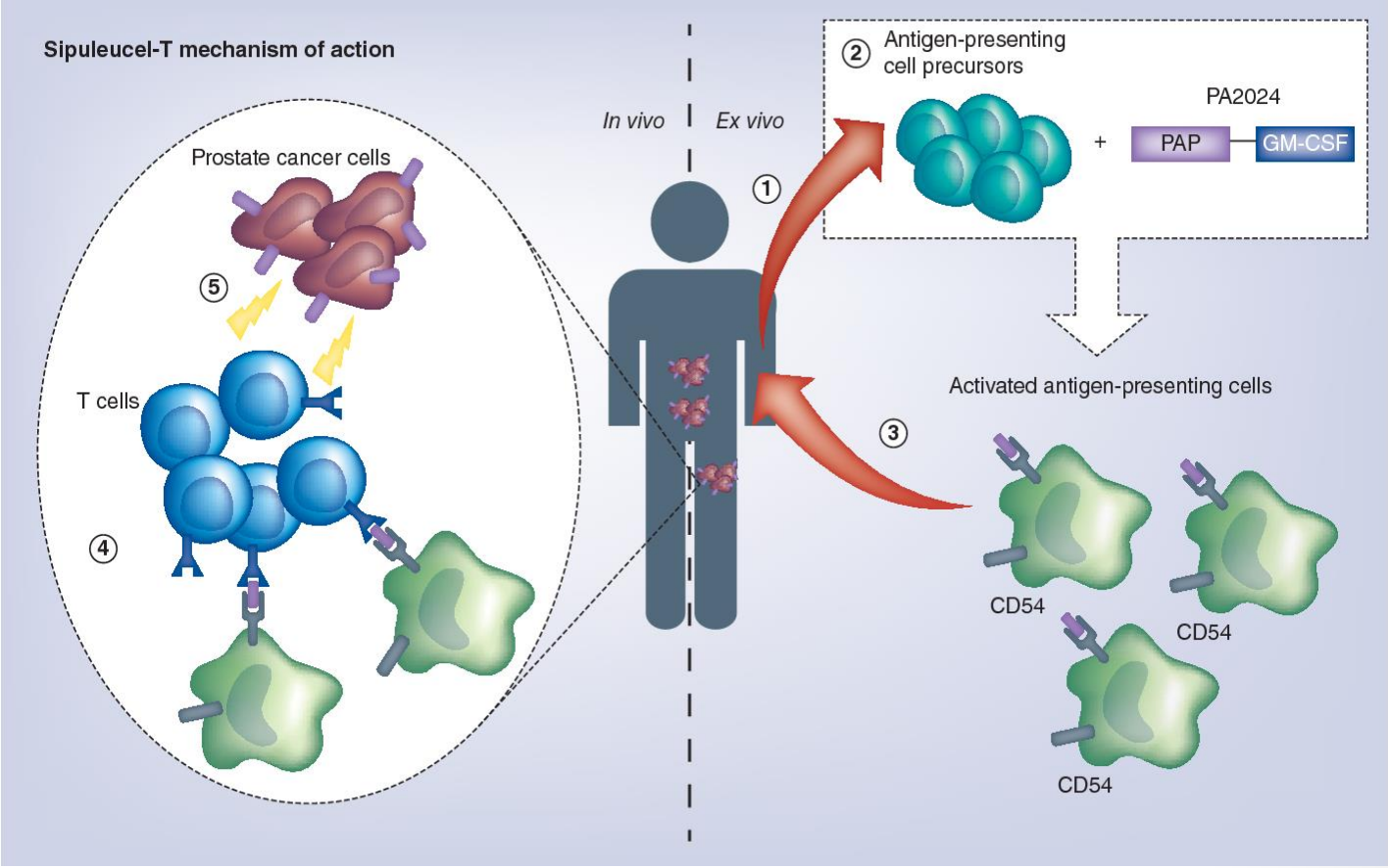
DC Vaccines



- LU, Yichao, et al. *Journal of Controlled Release*, 2022

Improve Antigen Presentation → Cancer Vaccines → DC Vaccines

Sipuleucel-T(Provenge)



- Catherine E. Handy and Emmanuel S. Antonarakis .Future oncology.2018

Improve Antigen Presentation → Cancer Vaccines → DC Vaccines

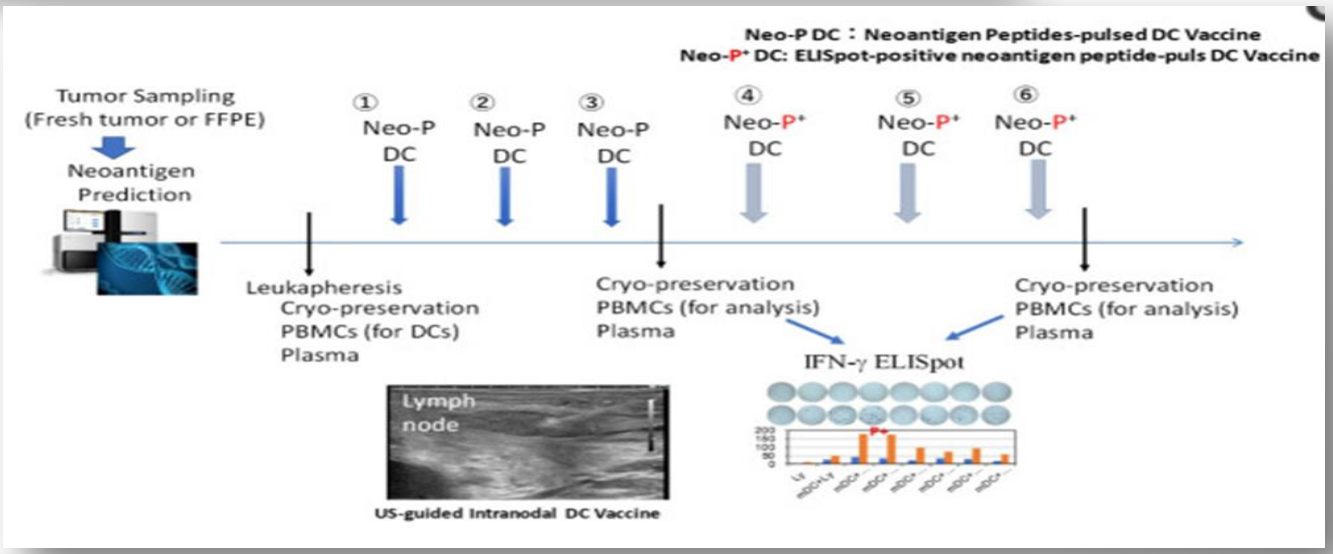
frontiers in Immunology

Front Immunol. 2023; 14: 1223331.
Published online 2023 Oct 10. doi: 10.3389/fimmu.2023.1223331

PMCID: PMC10595142
PMID: 37881436

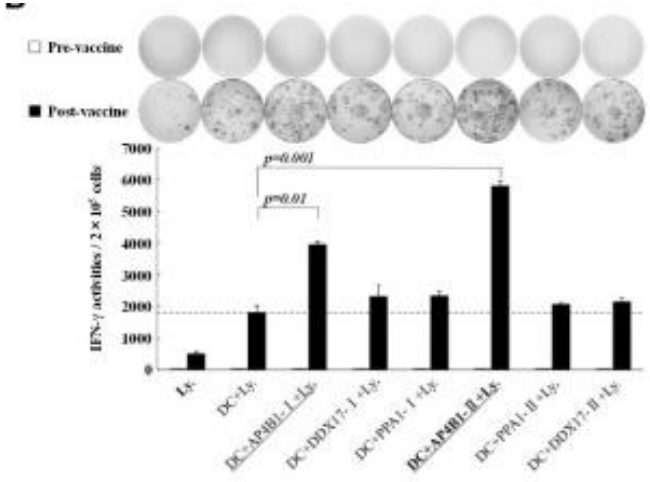
Immunological analysis of hybrid neoantigen peptide encompassing class I/II neoepitope-pulsed dendritic cell vaccine

Shinji Morisaki, [1,2,3] Hideya Onishi,[✉2,*] Takafumi Morisaki, [4] Makoto Kubo, [4] Masayo Umebayashi, [1] Hiroto Tanaka, [1] Norihiro Koya, [1] Shinichiro Nakagawa, [1] Kenta Tsujimura, [1] Sachiko Yoshimura, [5] Poh Yin Yew, [5] Kazuma Kiyotani, [7] Yusuke Nakamura, [7] Masafumi Nakamura, [4] Takanari Kitazono, [3] and Takashi Morisaki [1]



Immune responses after intranodal neoantigen peptide-pulsed DC vaccine administration

1



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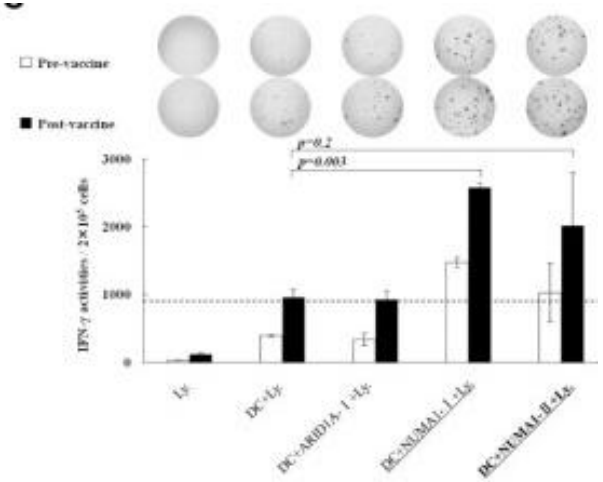

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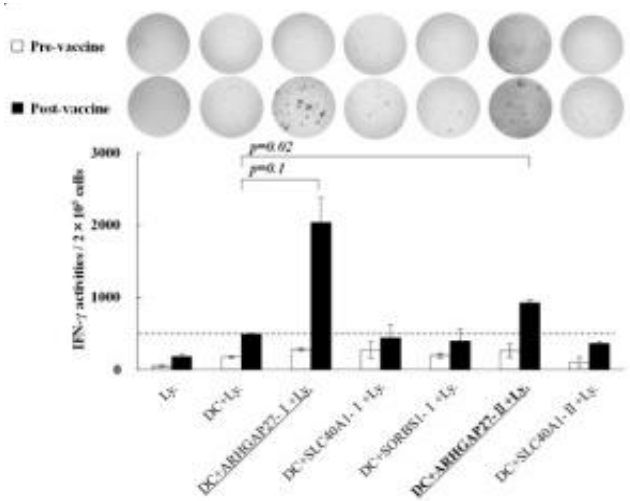

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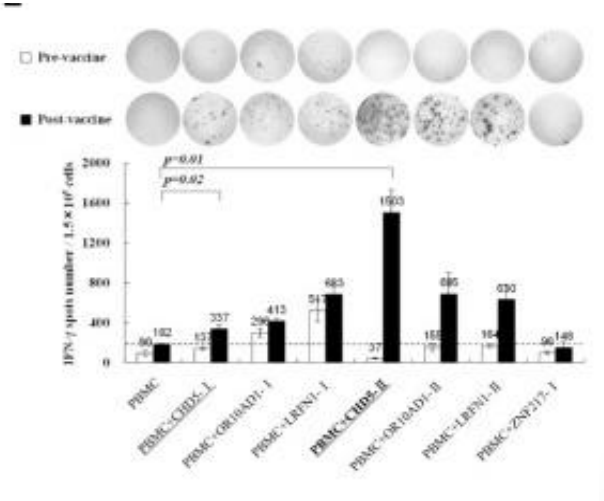
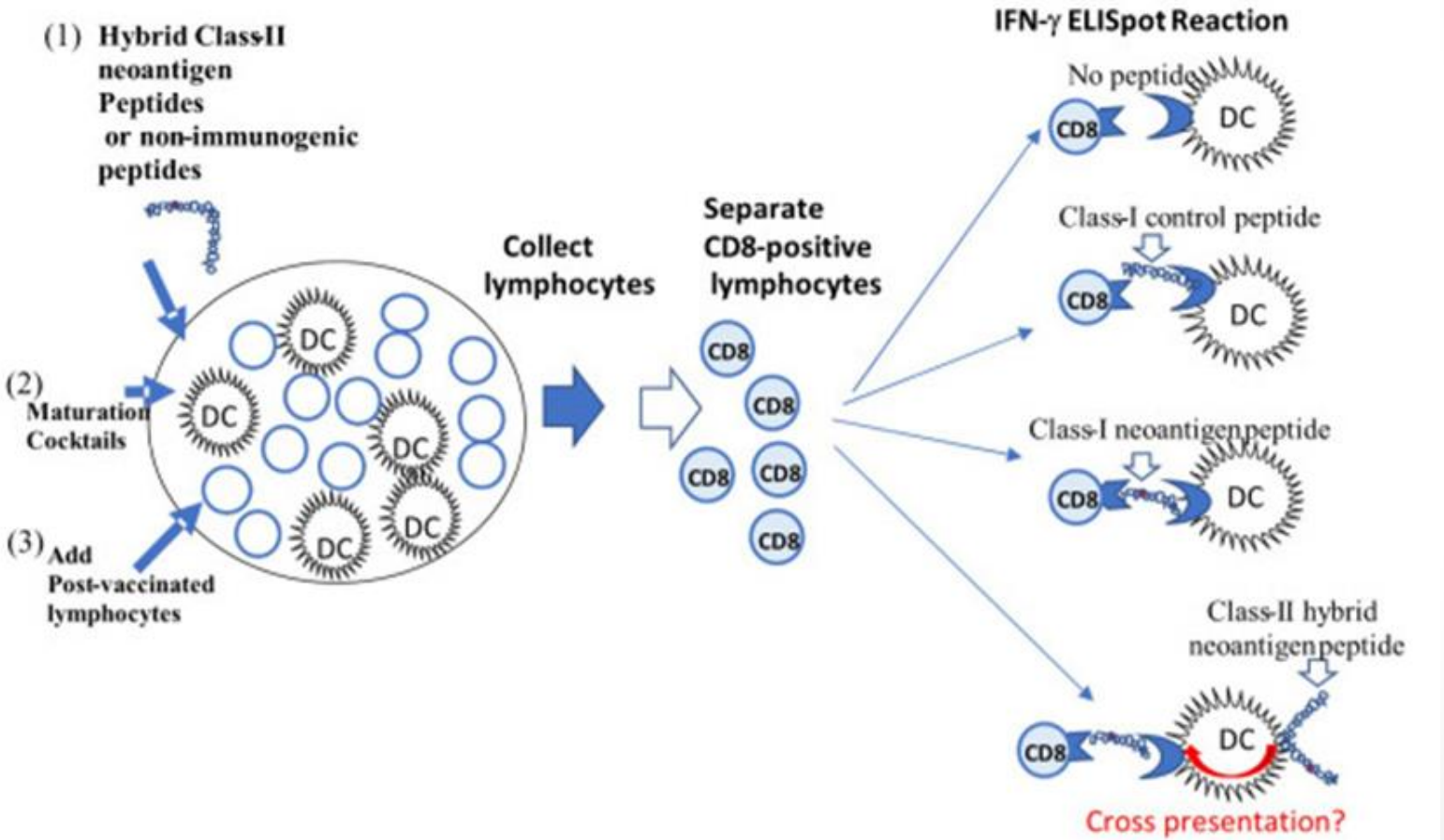


➢MORISAKI, Shinji, et al. *Frontiers in Immunology*, 2023

Hybrid class II long peptide-pulsed DCs can cross-present class-I neoepitopes



➢ MORISAKI, Shinji, et al. *Frontiers in Immunology*, 2023

➢MORISAKI, Shinji, et al. *Frontiers in Immunology*, 2023

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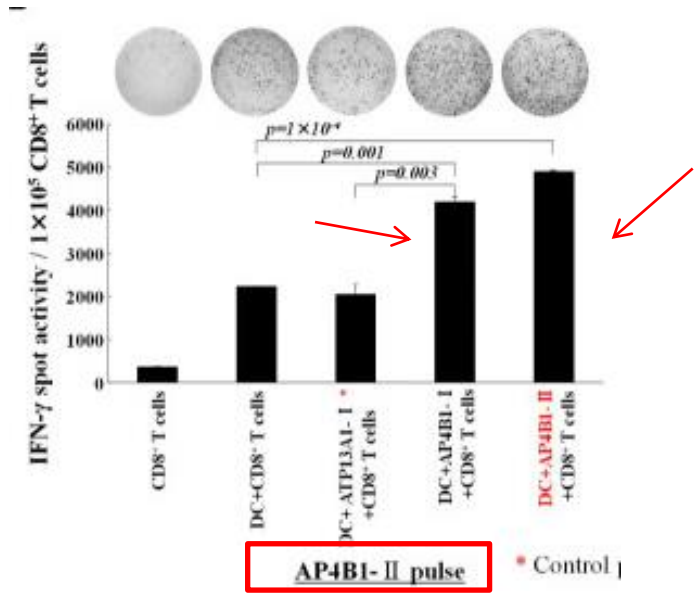

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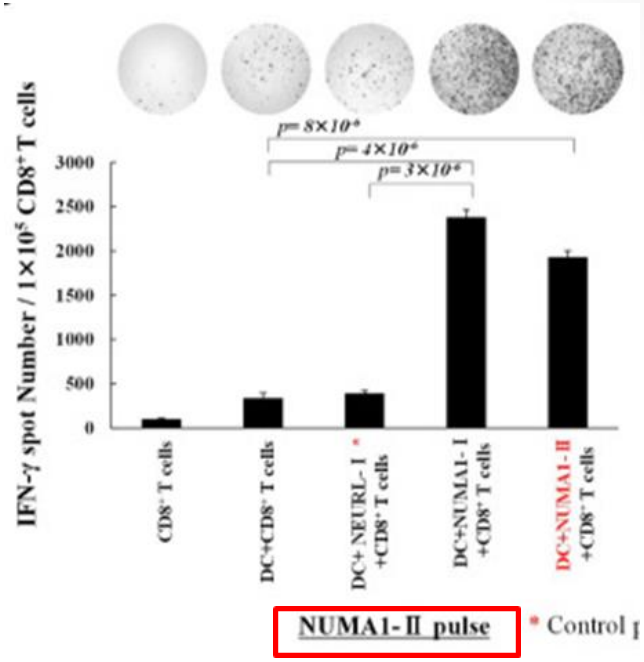

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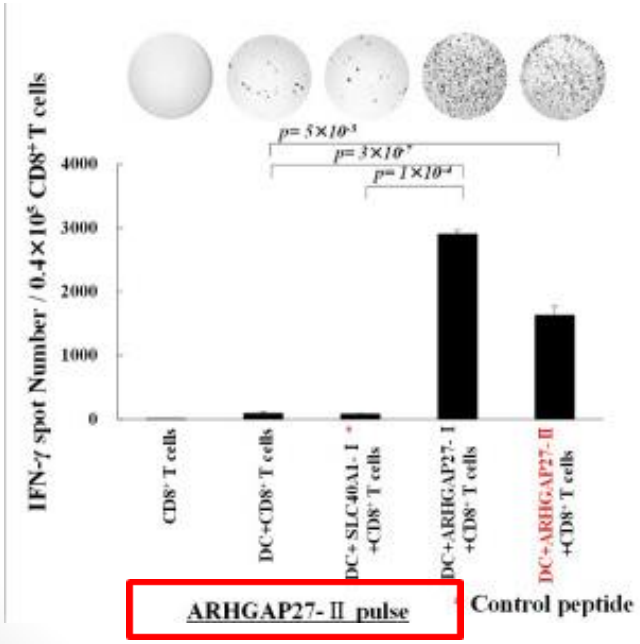

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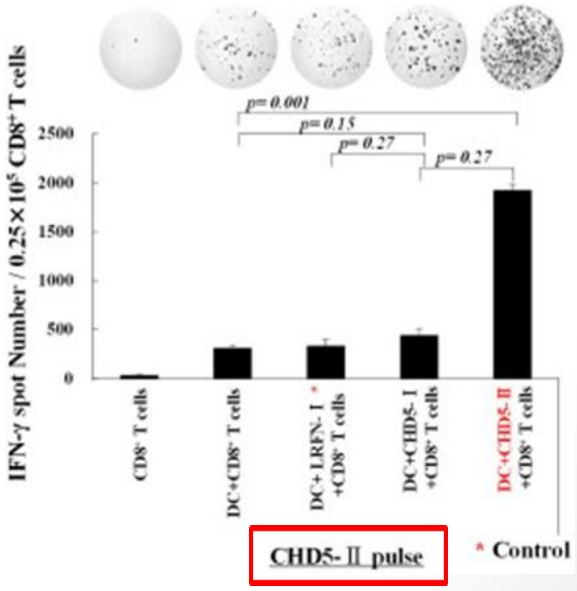
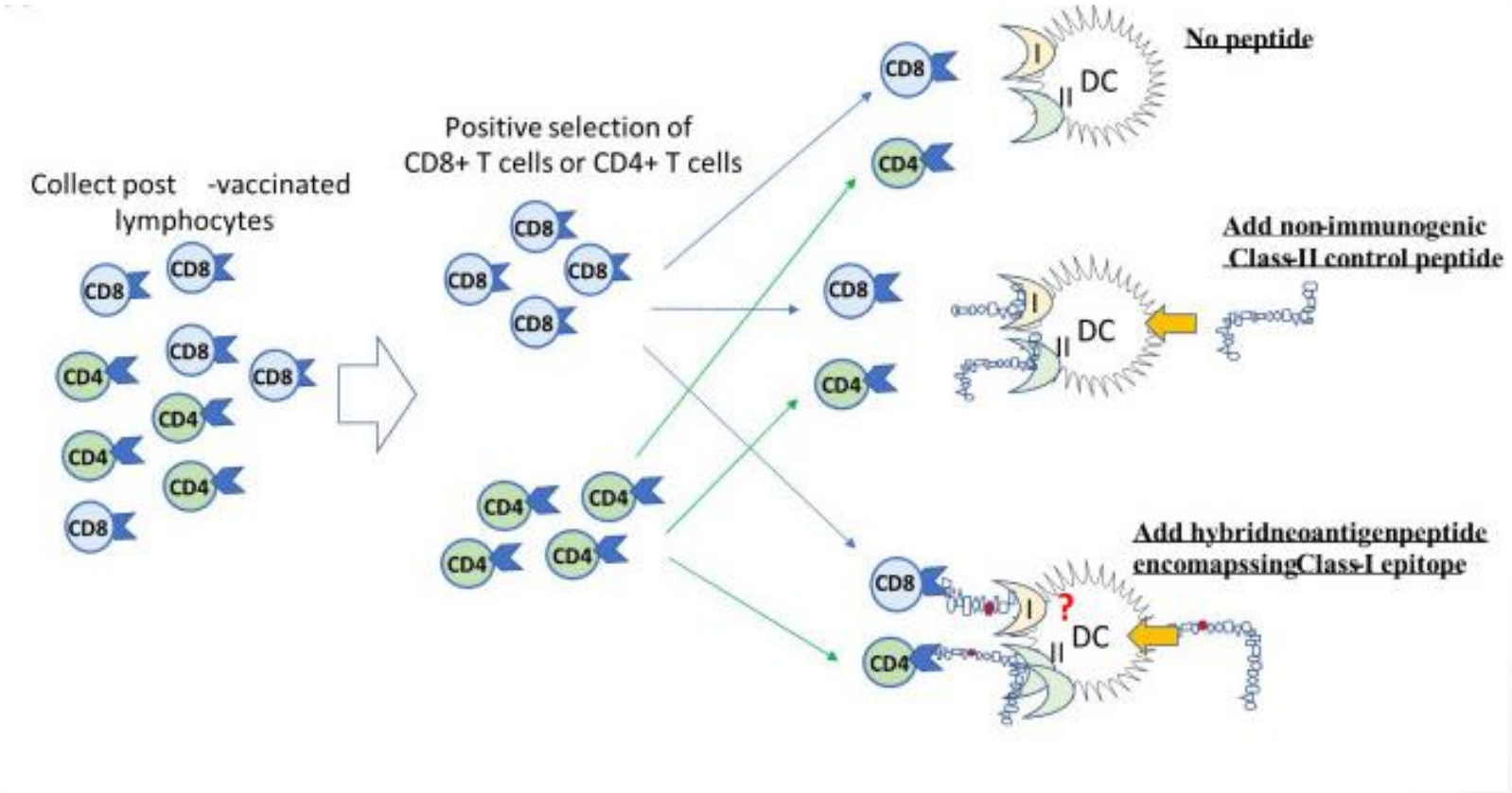


Both CD8+ T cells and CD4+ T cells responded to DCs pulsed with class II-binding mutant peptide



➢ MORISAKI, Shinji, et al. *Frontiers in Immunology*, 2023

Both CD8⁺ T cells and CD4⁺ T cells responded to DCs pulsed with class II-binding mutant peptide

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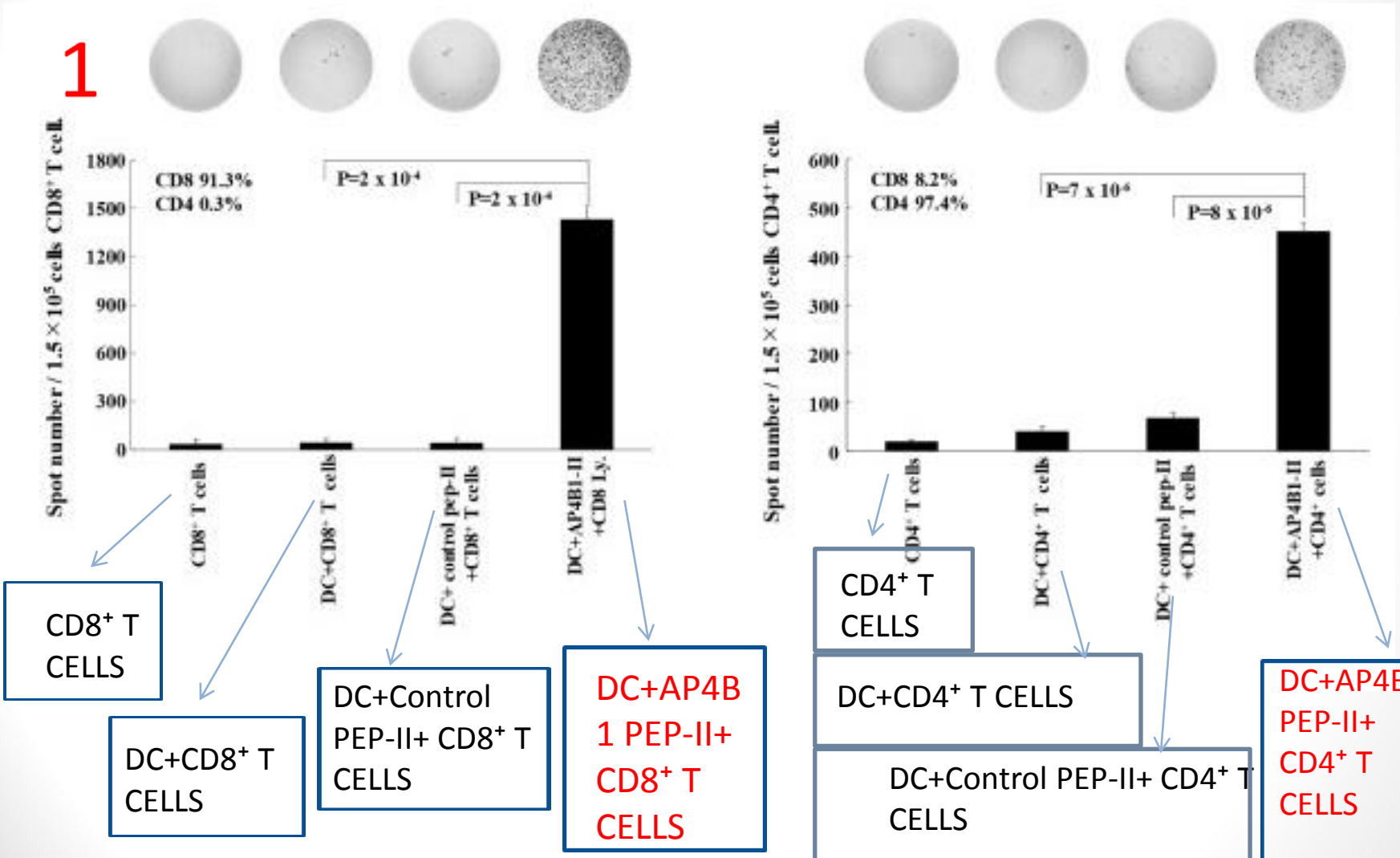


CD8⁺ T CELLS

DC+CD8⁺ T CELLS

DC+Control PEP-II+ CD8⁺ T CELLS

DC+AP4B 1 PEP-II+ CD8⁺ T CELLS

CD4⁺ T CELLS

DC+CD4⁺ T CELLS

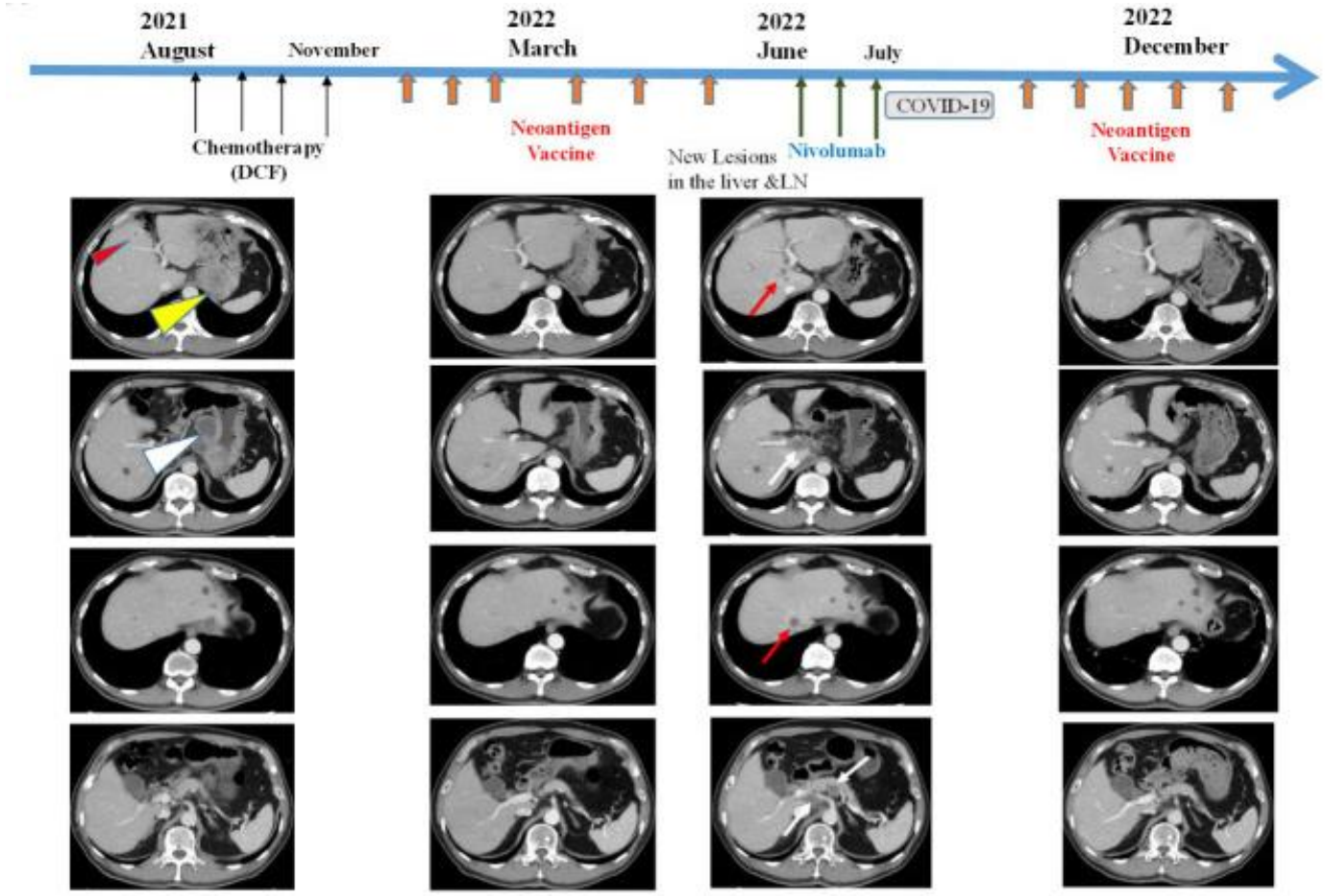
DC+Control PEP-II+ CD4⁺ T CELLS

DC+AP4B1 PEP-II+ CD4⁺ T CELLS

➢ MORISAKI, Shinji, et al. *Frontiers in Immunology*, 2023

❖ The immunological analysis of all four patients showed no vaccine-related immunological adverse events

1

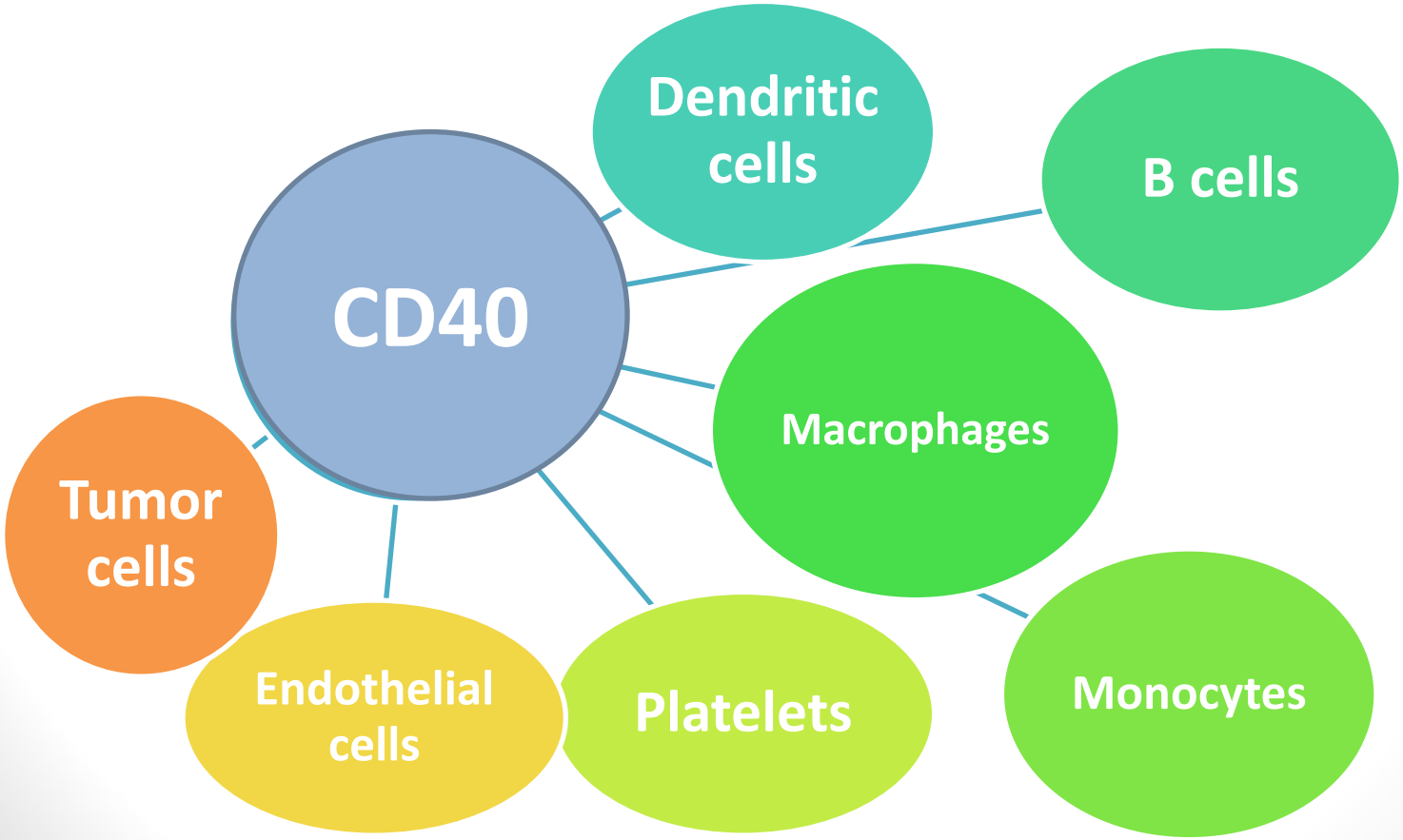


➢ MORISAKI, Shinji, et al. *Frontiers in Immunology*, 2023

Improve Antigen Presentation

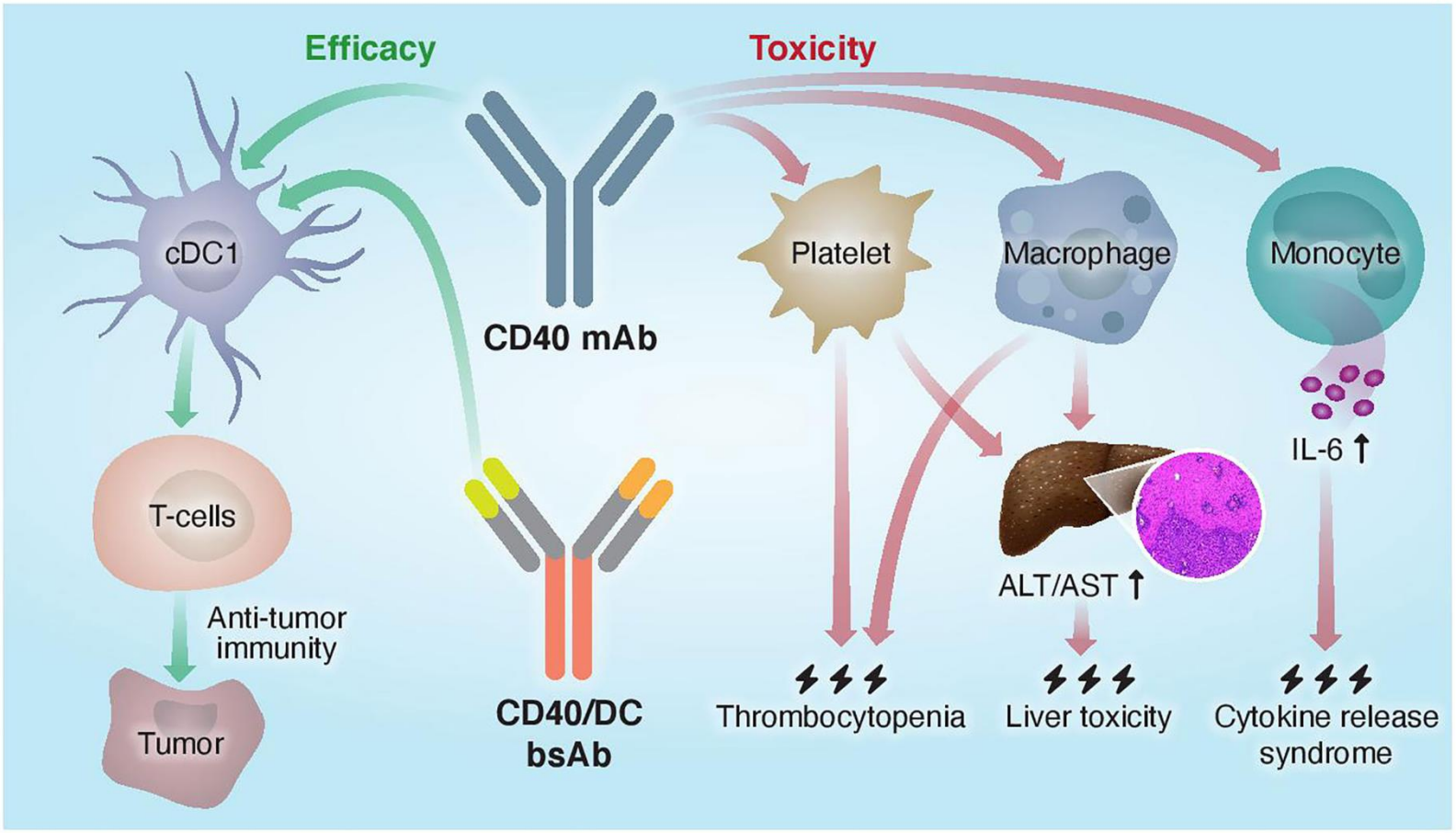
CD40 Agonists

- CD40 is a tumor necrosis factor receptor (TNFR) superfamily member.



Improve Antigen Presentation

CD40 Agonists



- SALOMON, Ran; DAHAN, Rony.. *Frontiers in Immunology*, 2022

Improve Antigen Presentation

CD40 Agonists

Journal for ImmunoTherapy of Cancer

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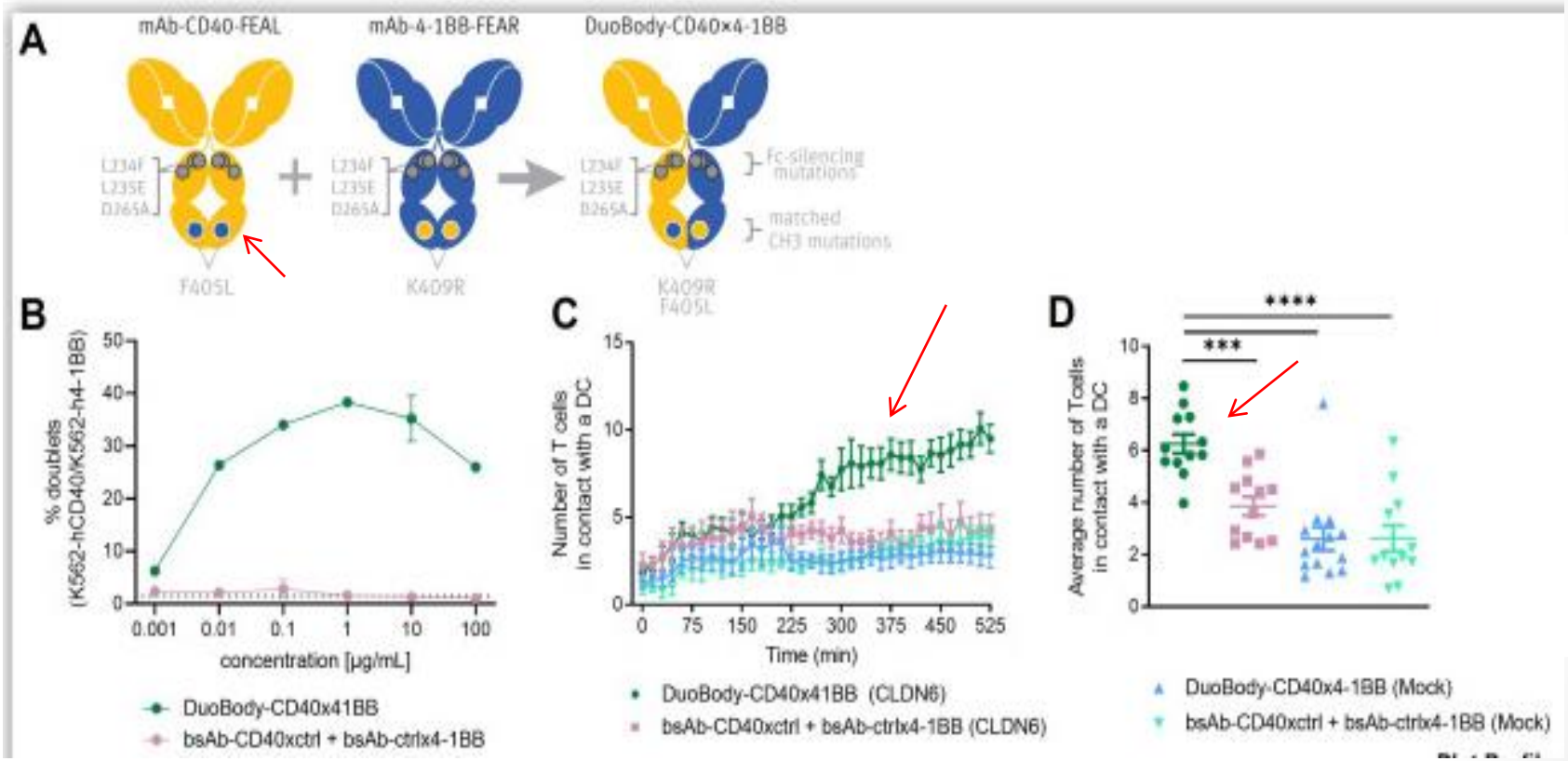
J Immunother Cancer. 2022; 10(6): e004322.
Published online 2022 Jun 10. doi: 10.1136/jitc-2021-004322
PMCID: PMC9189854
PMID: 35688554

Original research

DuoBody-CD40x4-1BB induces dendritic-cell maturation and enhances T-cell activation through conditional CD40 and 4-1BB agonist activity

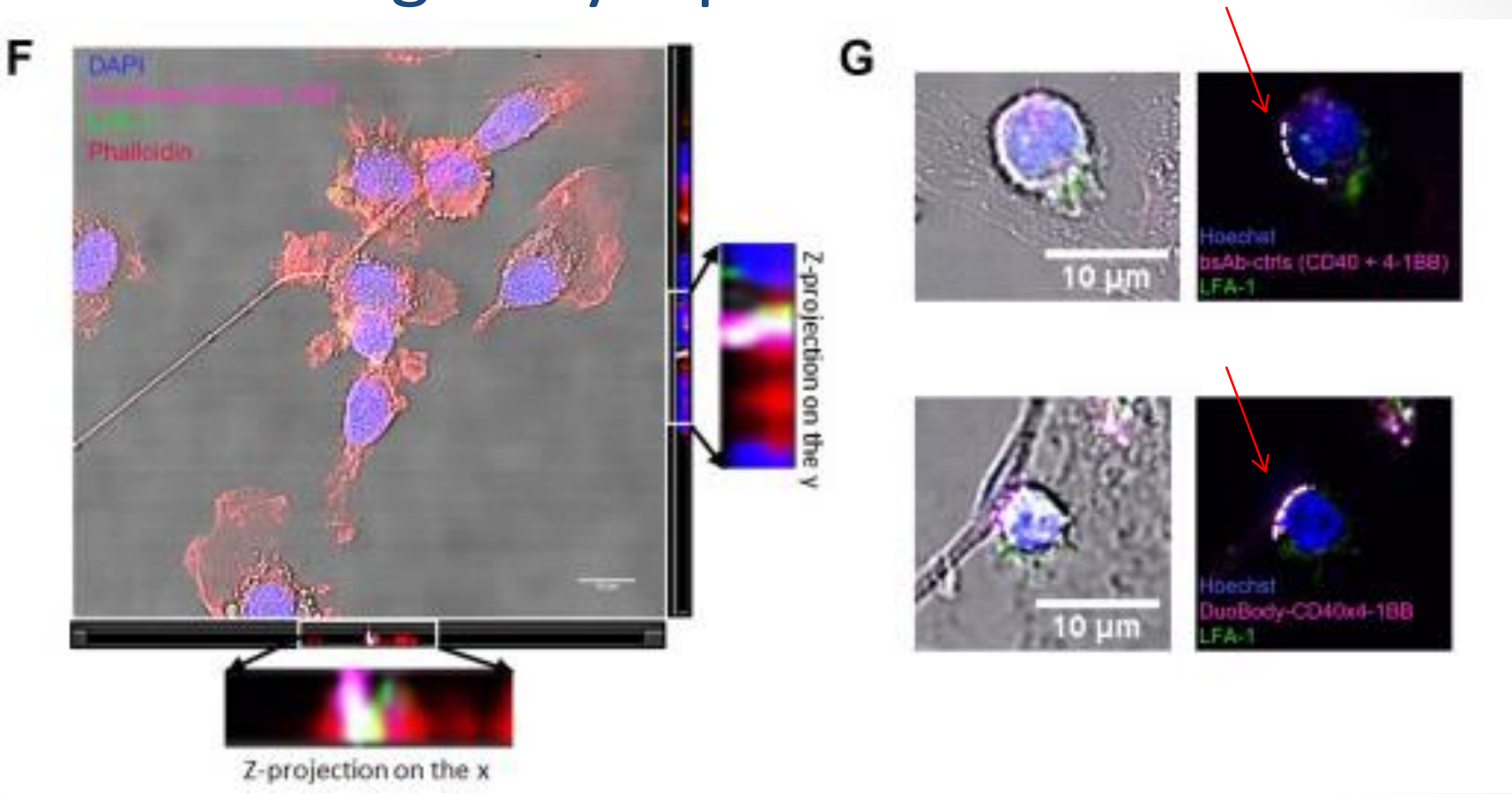
Alexander Muik,[1] Homer C Adams, 3rd,[2] Friederike Gieseke,[1] Isil Altintas,[3] Kristina B Schoedel,[1] Jordan M Blum,[2] Bianca Sänger,[1] Saskia M Burm,[3] Eliana Stanganello,[4] Dennis Verzijl,[3] Vanessa M Spires,[2] Fulvia Vascotto,[4] Aras Toker,[1]

DuoBody-CD40x4-1BB reinforces the immunological synapse



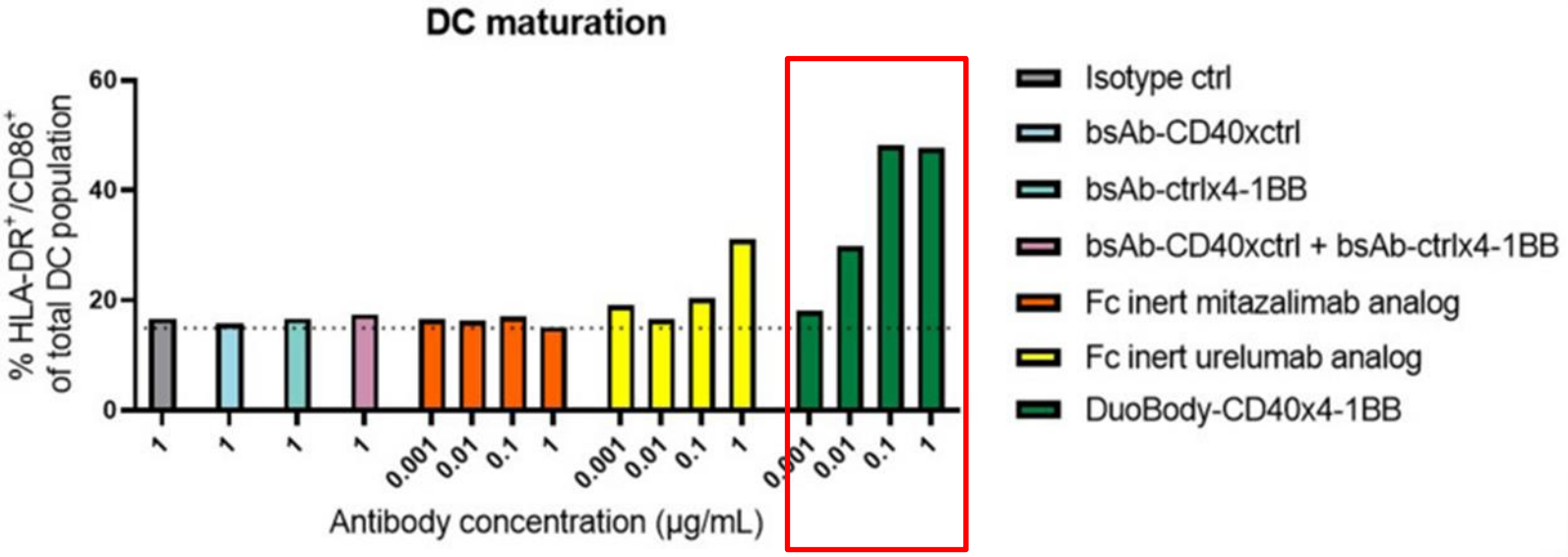
- Muik, Alexander et al .*Journal for immunotherapy of cancer* .2022

DuoBody-CD40x4-1BB reinforces the immunological synapse



- Muik, Alexander et al .*Journal for immunotherapy of cancer* .2022

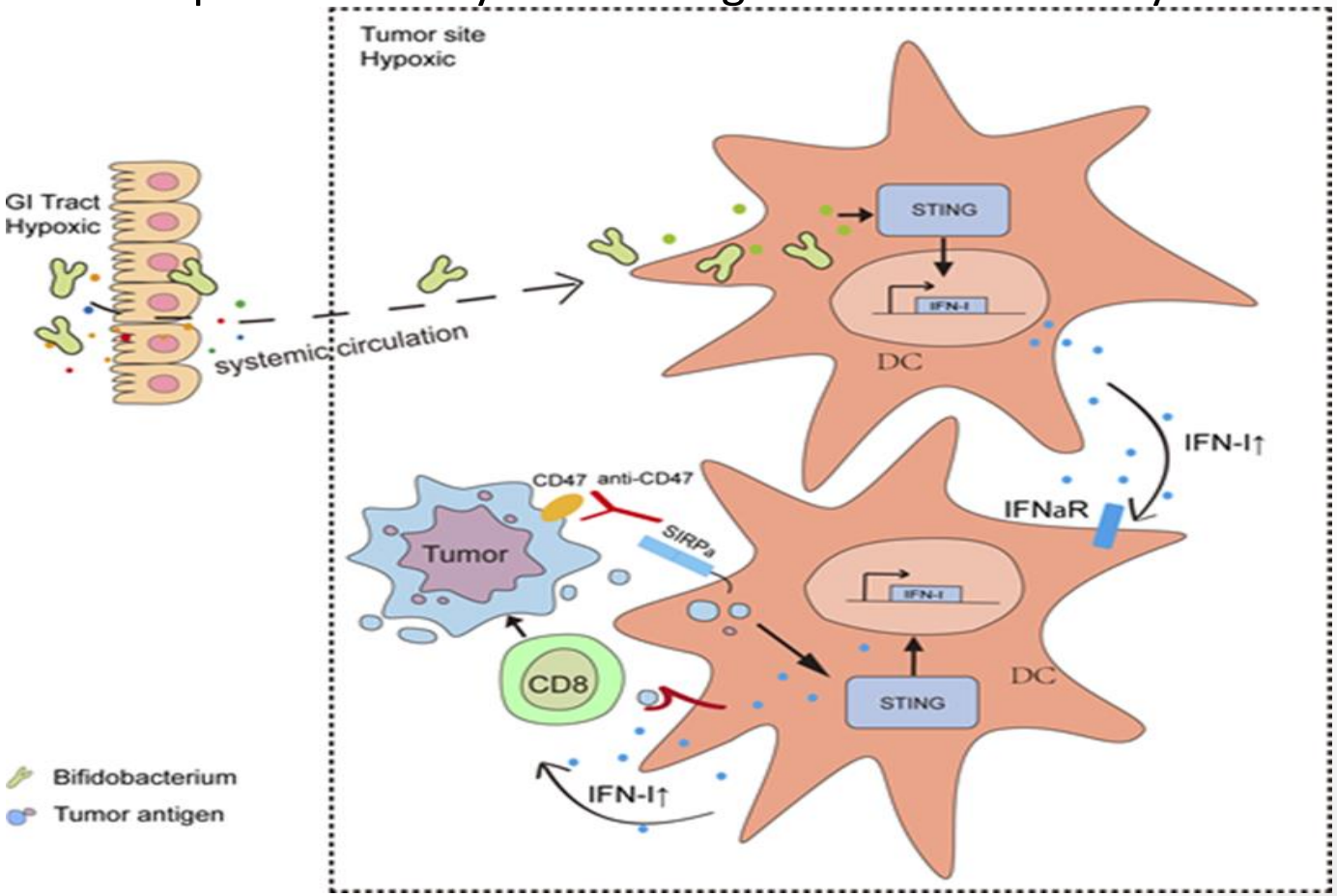
DuoBody-CD40x4-1BB induces DC maturation in vitro



- Muik, Alexander et al *.Journal for immunotherapy of cancer* .2022

Improve Antigen Presentation → **Regulate Gut Flora** → **Bifidobacteria**

- There are approximately 1000 microorganisms present in the human gut that can reshape the TME by modulating the host immune system



➢ QIU, Qin, et al. *Frontiers in immunology*, 2021

Promotes T-cell priming

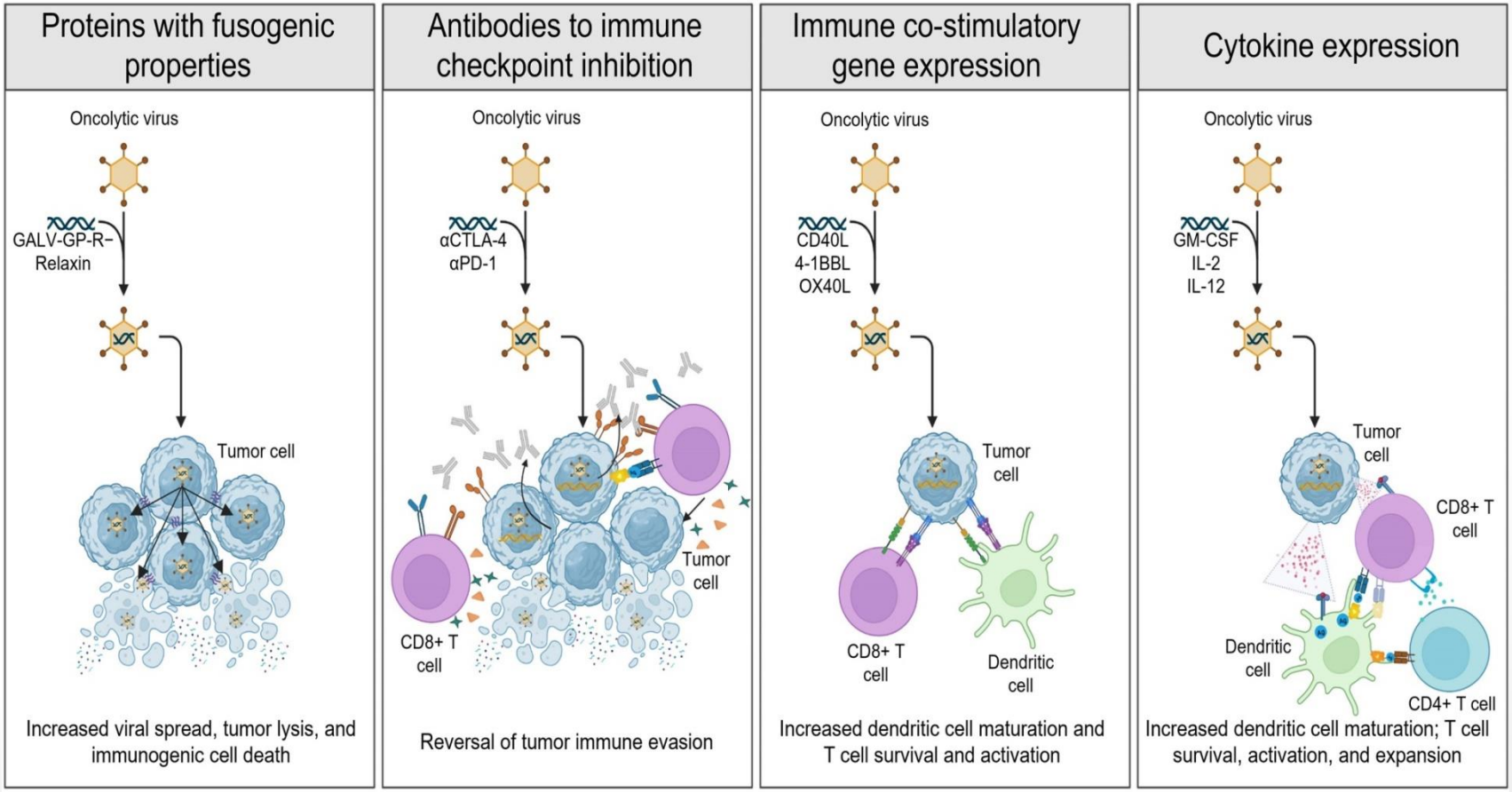
- **Oncolytic Immunotherapies**
- Immune adjuvants
- Epigenetic modification inhibitors
- Metabolic intervention
- Local thermal ablation therapy
- Photothermal therapy
- Photodynamic therapy
- Magnetic hyperthermia
- High-intensity focused ultrasound

Promotes T-cell priming

Oncolytic Immunotherapies (OIs)

- Oncolytic viruses are natural or recombinant viruses designed to target and kill tumor cells
- The TAA, DAMPs and PAMPs are then recognized by DC
- The oncolytic virus attacks tumor stromal cells to disrupt the complex tumor architecture
- The oncolytic virus stimulates the production of CXCL9 and CXCL10

Genetic Engineering Approaches To Improve OI Efficacy



- Khushalani, Nikhil I., et al.. *Molecular Therapy-Oncolytics* 2023

Limiting virulence and toxicity

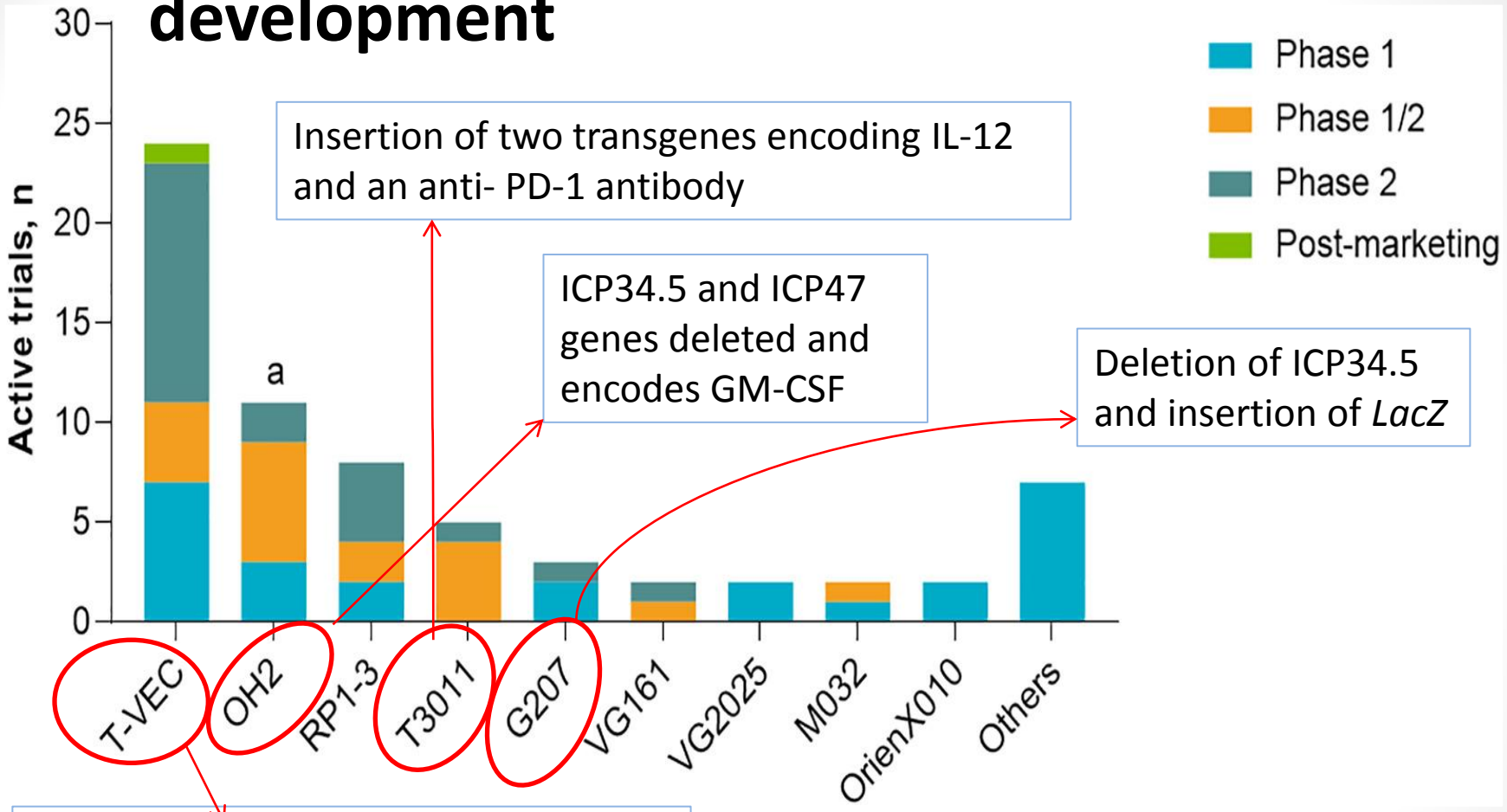
- Tumor selectivity of OIs relies on several biological characteristics of tumors, including :

  - Expression of viral entry receptors
  - Dysregulation of IFN signaling
  - The rapid rate of cellular division
  - High metabolic activity of tumors

- Using tumor tissue-specific promoters for expression of viral genes

- Using deletions or miRNA-mediated suppression of virulence factors

Example HSV-based OIs in clinical development



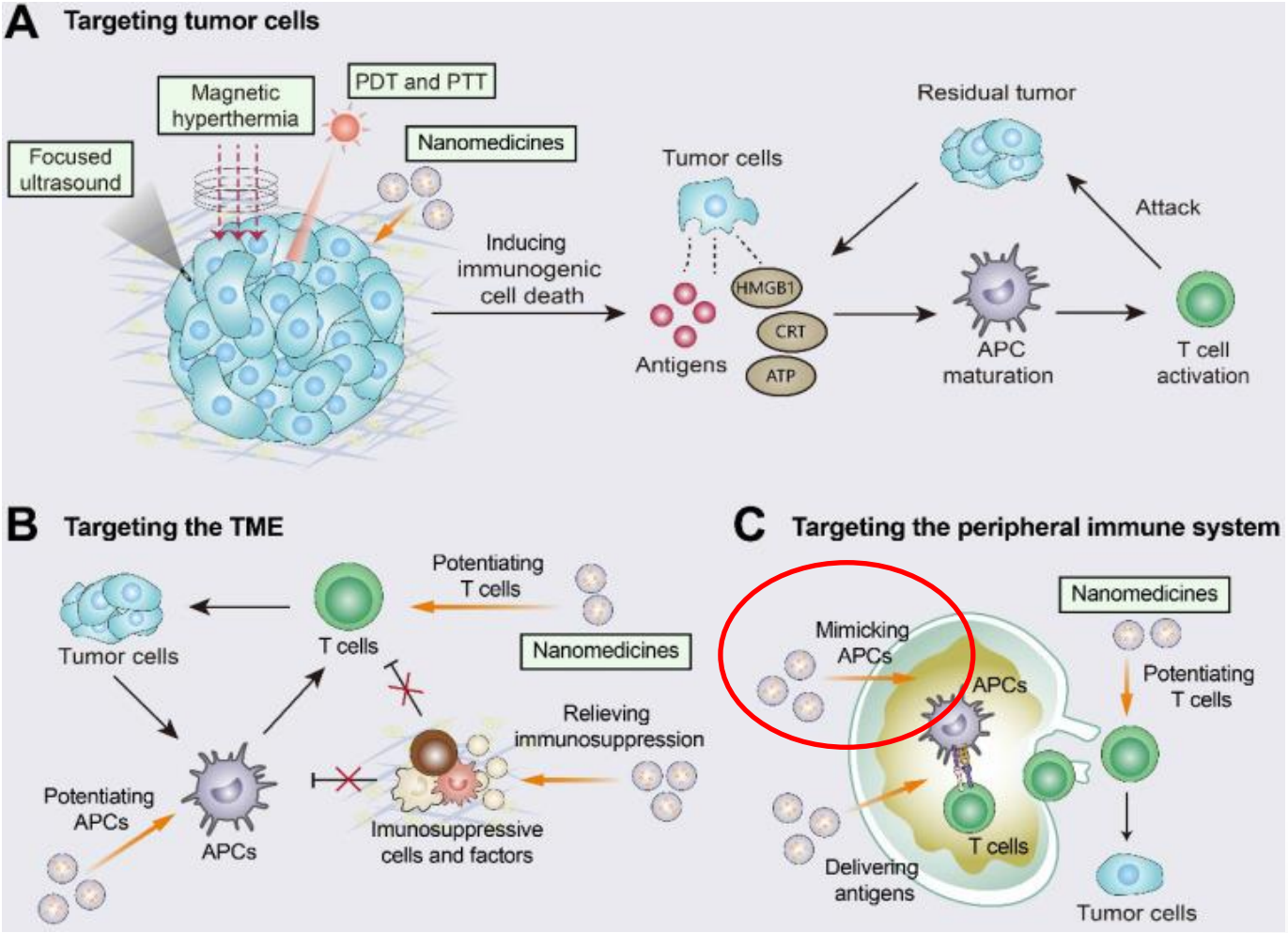
Talimogene laherparepvec (T-VEC)
Deleted for ICP34.5 and ICP47 and expressing GM-CSF

- Khushalani, Nikhil I., et al.. *Molecular Therapy-Oncolytics* 2023

Improve The Infiltration Effect Of T Cells

- **Nanomedicine**
- Oncogenic pathway inhibitors
- Epigenetic modification inhibitors
- MDSC Inhibitors
- TGF-β Inhibitors
- Antiangiogenic Therapy (Anti-VEGF)
- CXCR4 antagonists

Improve The Infiltration Effect Of T Cells → **Nanomedicine** → Artificial antigen presenting cells (aAPCs)



- Liu YT, Sun ZJ. *Theranostics*. 2021

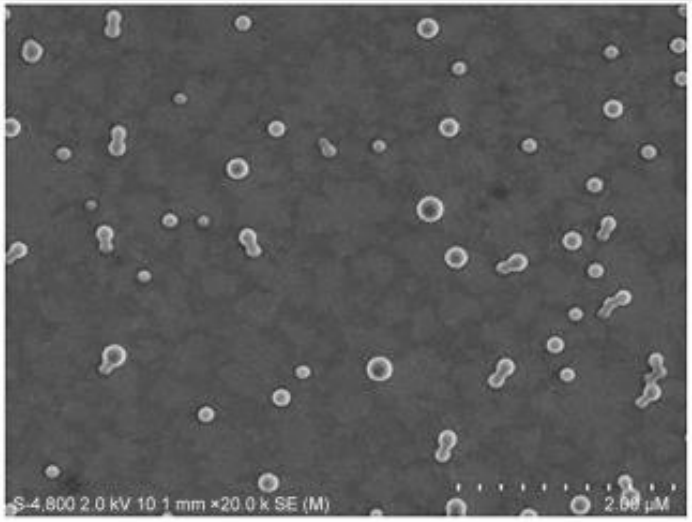
Improve The Infiltration Effect Of T Cells → **Nanomedicine** → Artificial antigen presenting cells (aAPCs)

Original Research

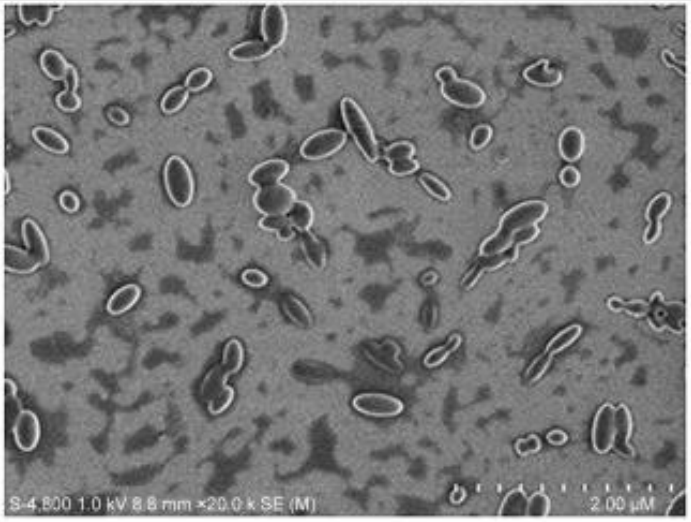
PEGylated and CD47-conjugated nanoellipsoidal artificial antigen-presenting cells minimize phagocytosis and augment anti-tumor T-cell responses

Shilong Song, Xiaoxiao Jin, Lei Zhang, Chen Zhao, Yan Ding, Qianqian Ang, ...show all

Pages 2465-2483 | Published online: 08 Apr 2019

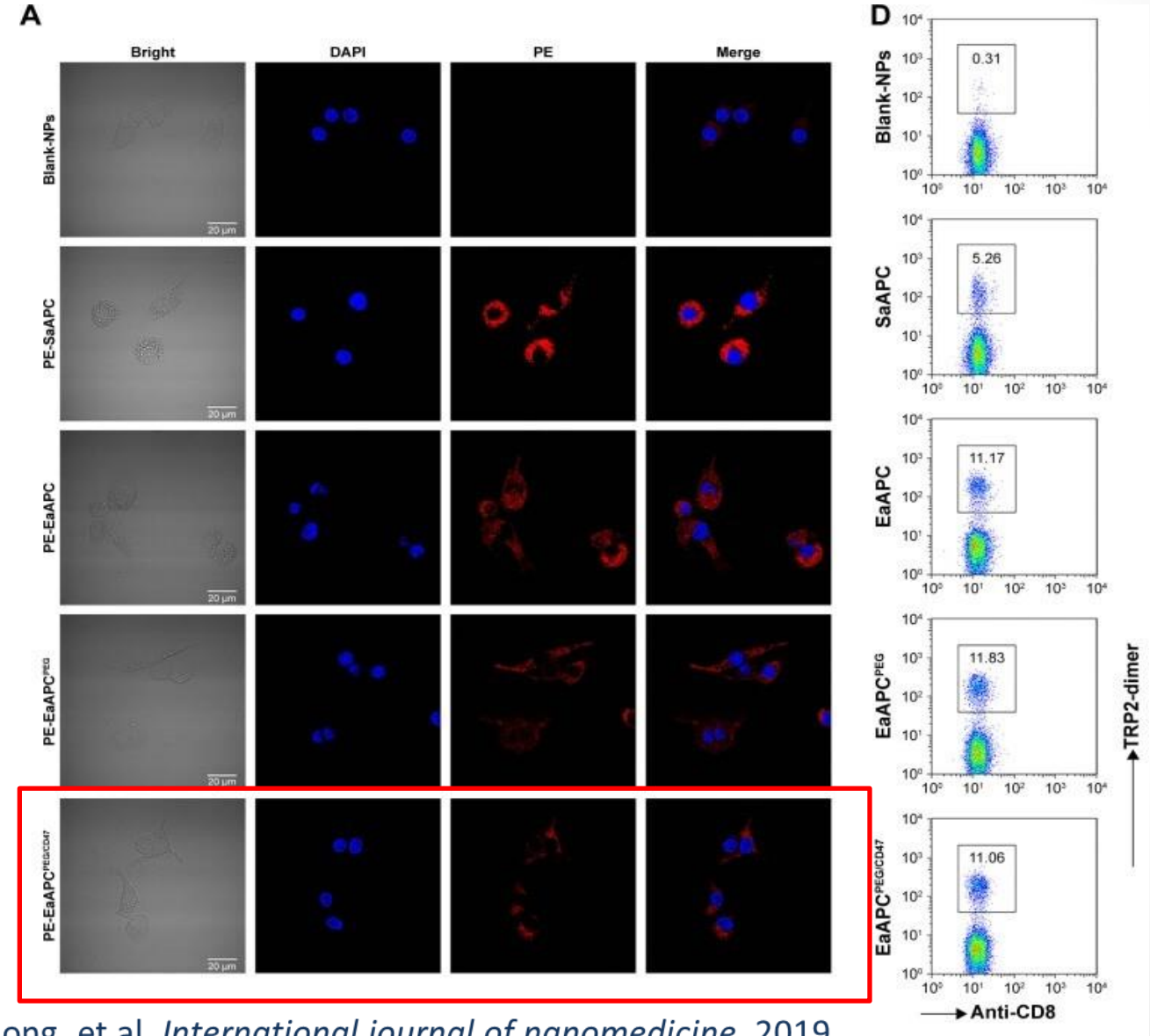


Spherical PLGA-NPs



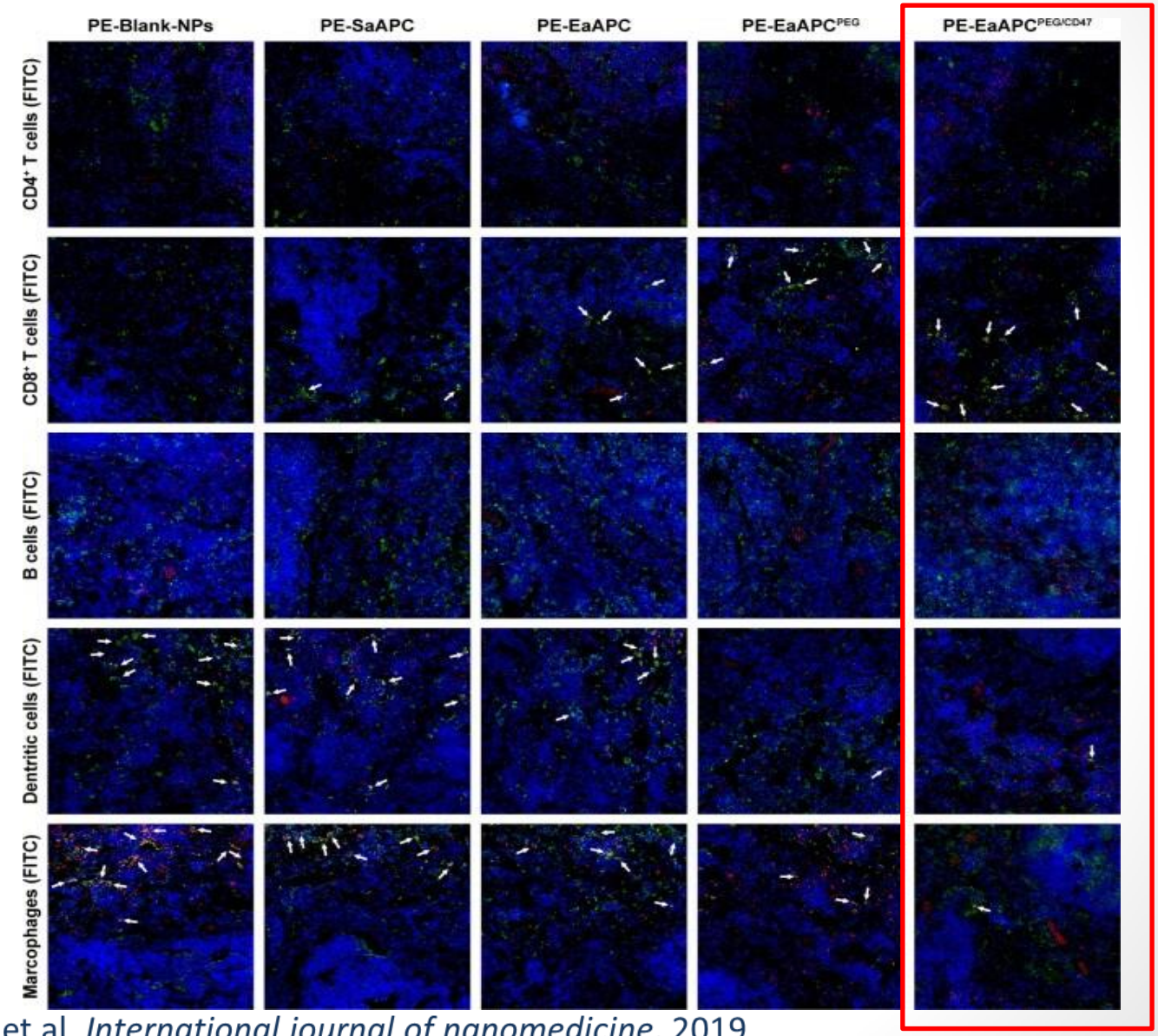
Twofold ellipsoidal PLGA-NPs

EaAPC$^{PEG/CD47}$ Markedly Reduced Cellular Uptake By Macrophage In Vitro



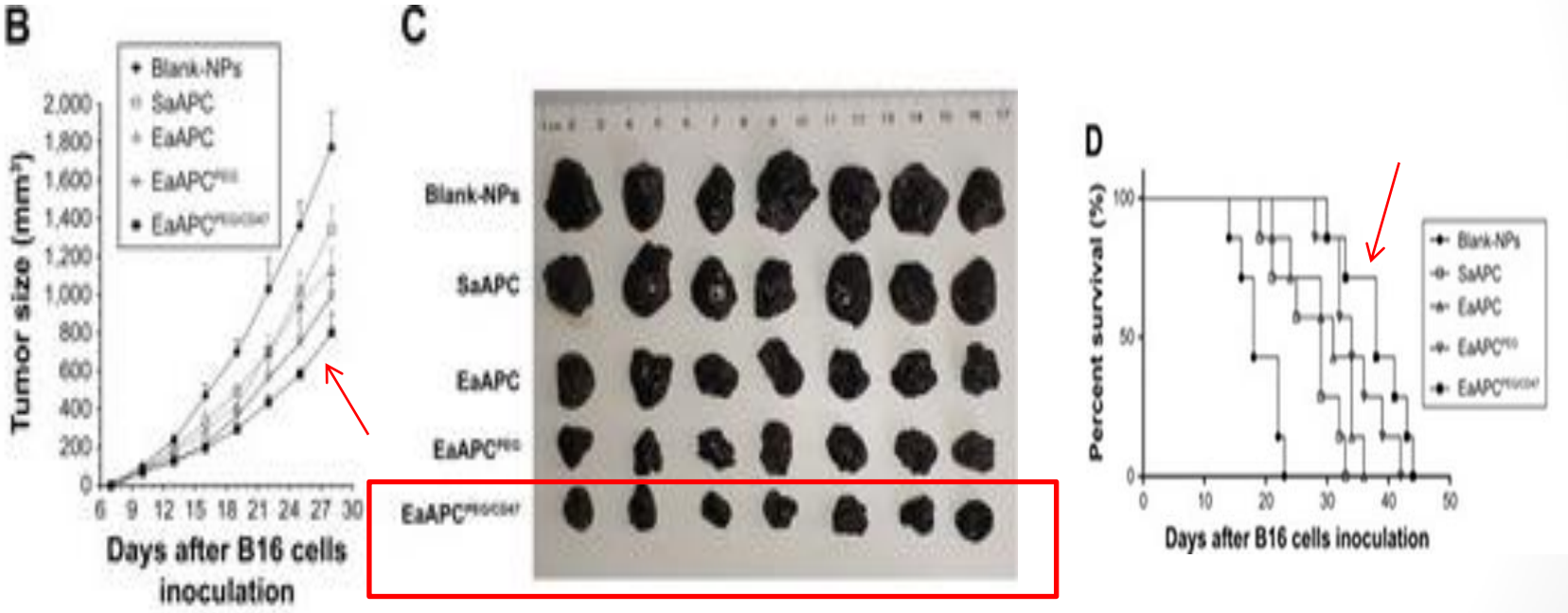
- SONG, Shilong, et al. *International journal of nanomedicine*, 2019

EaAPC$^{PEG/CD47}$ Markedly Reduced Co-localizations With Phagocytes And Increased Contacts With CD8^{+} T Cells In Vivo



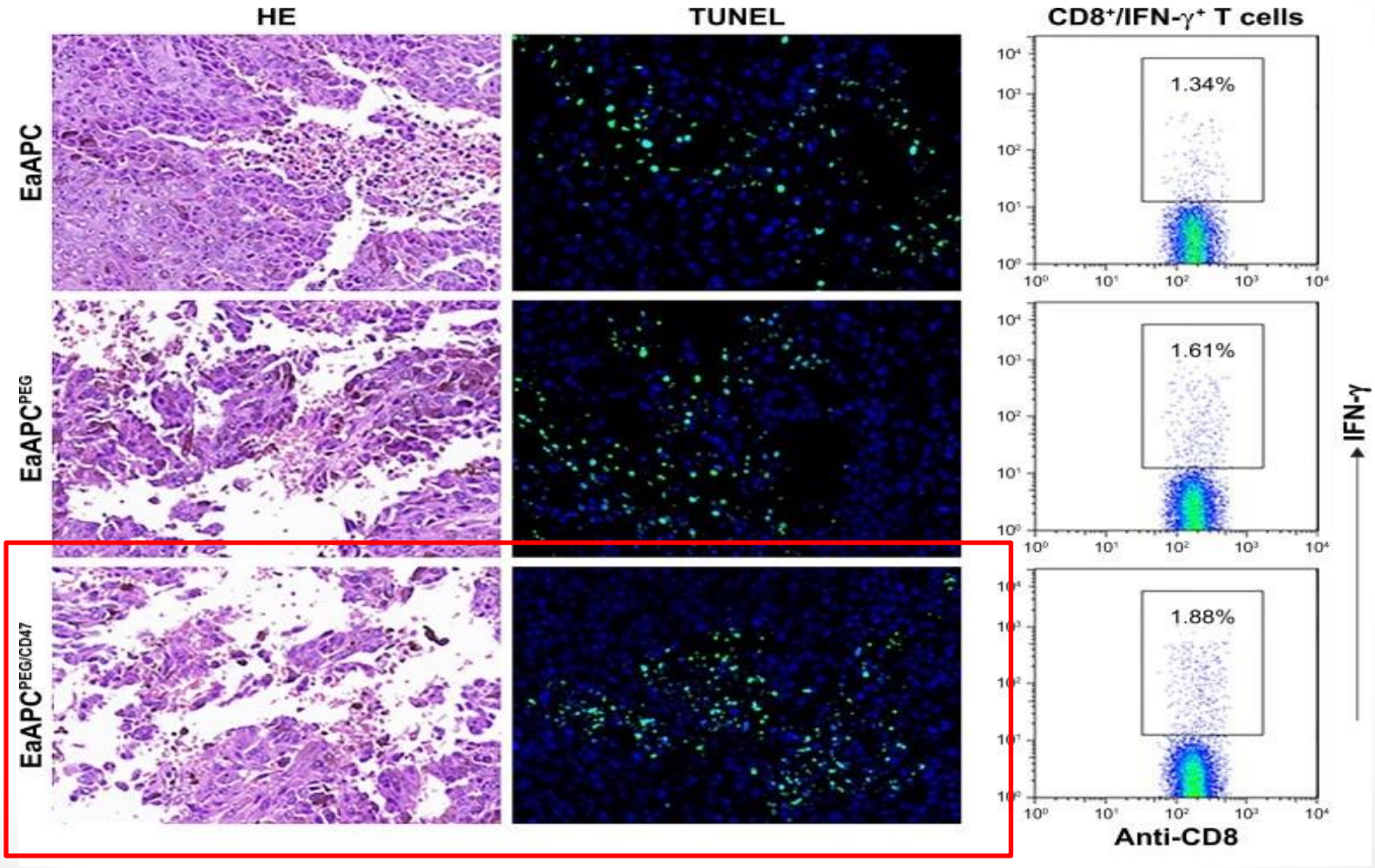
- SONG, Shilong, et al. *International journal of nanomedicine*, 2019

EaAPC$^{PEG/CD47}$ Markedly Inhibited Melanoma Growth



- SONG, Shilong, et al. *International journal of nanomedicine*, 2019

EaAPC$^{PEG/CD47}$ Caused Extensive Necrosis And Apoptosis In Melanoma Tissues



- SONG, Shilong, et al. *International journal of nanomedicine*, 2019

Conclusions

- we then discuss a variety of therapeutic measures to improve T-cell infiltration.

- The combination of ICIs with these therapies reverses T-cell exhaustion, enhances the “abscopal effects” of therapy, and demonstrates incremental clinical efficacy.

- However, the optimal dose and sequence of administration of combination therapy needs to be further evaluated to optimize T-cell function, promote T-cell memory, and avoid overactivation .

Conclusions

- In addition, some issues still need to be addressed, such as the nonspecific distribution of drugs, and the treatment-induced systemic adverse effects
- With the development of nanotechnology offers new opportunities for the future.
- The use of nanomedicines improves drug precision and bioavailability, reduces immunotherapy-induced side effects, and enables selective accumulation of drugs in tumors.

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- THANK YOU FOR YOUR ATTENTION