

Moving cancer immunotherapy towards earlier stages of disease

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Moving cancer immunotherapy towards earlier stages of disease

Reminders

coreceptors

Stimulatory and inhibitory coreceptors

Antigen
presenting cell
or
Tumor cell

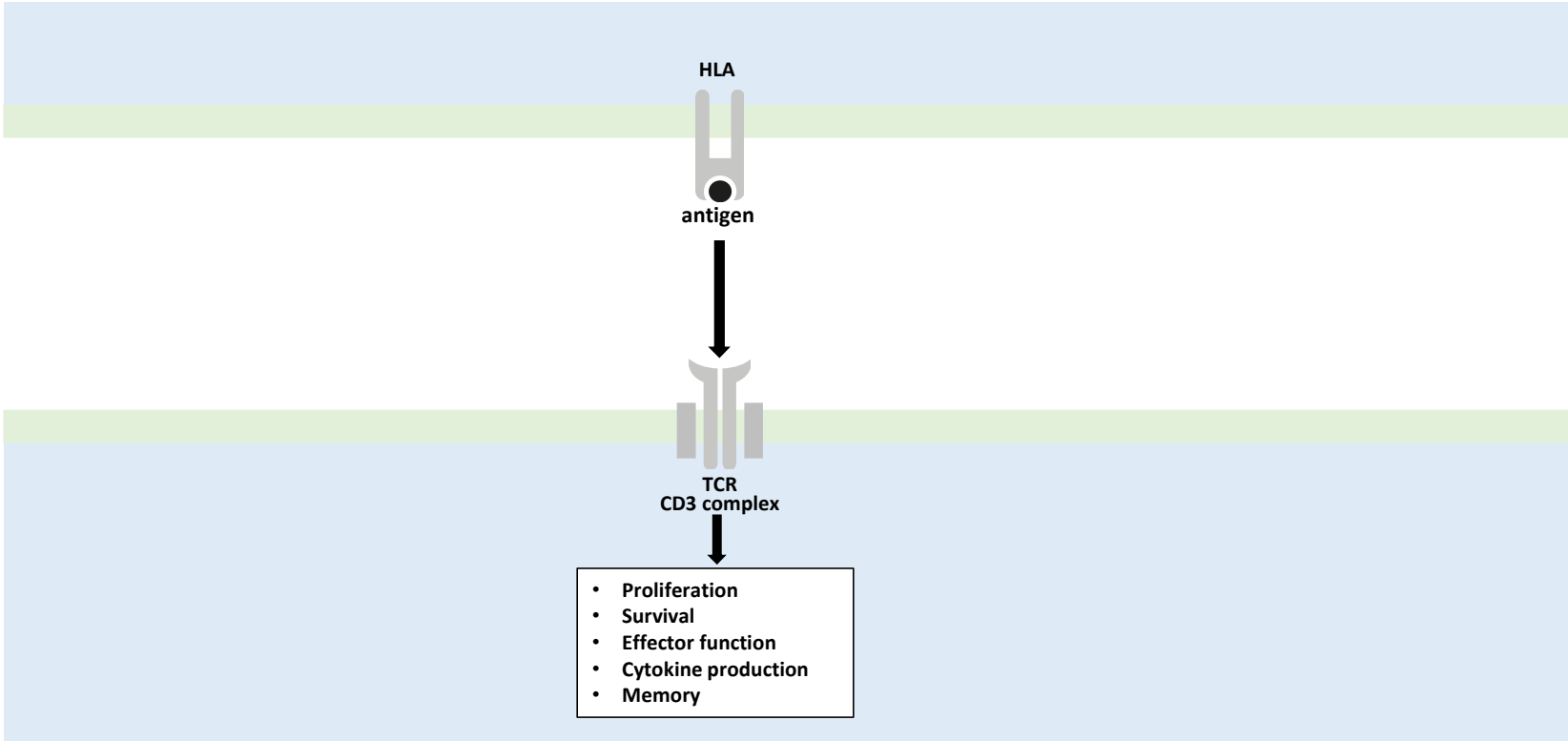
HLA

antigen

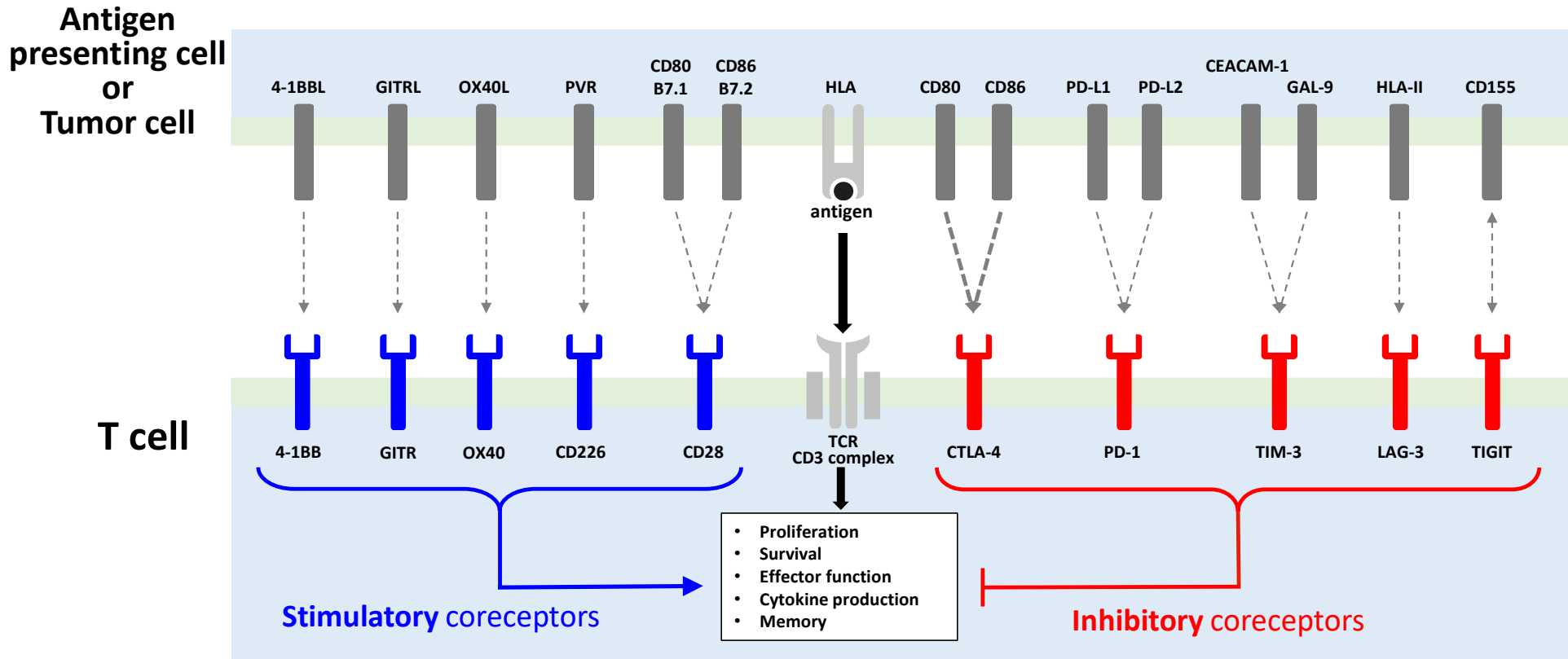
T cell

TCR
CD3 complex

- Proliferation
- Survival
- Effector function
- Cytokine production
- Memory



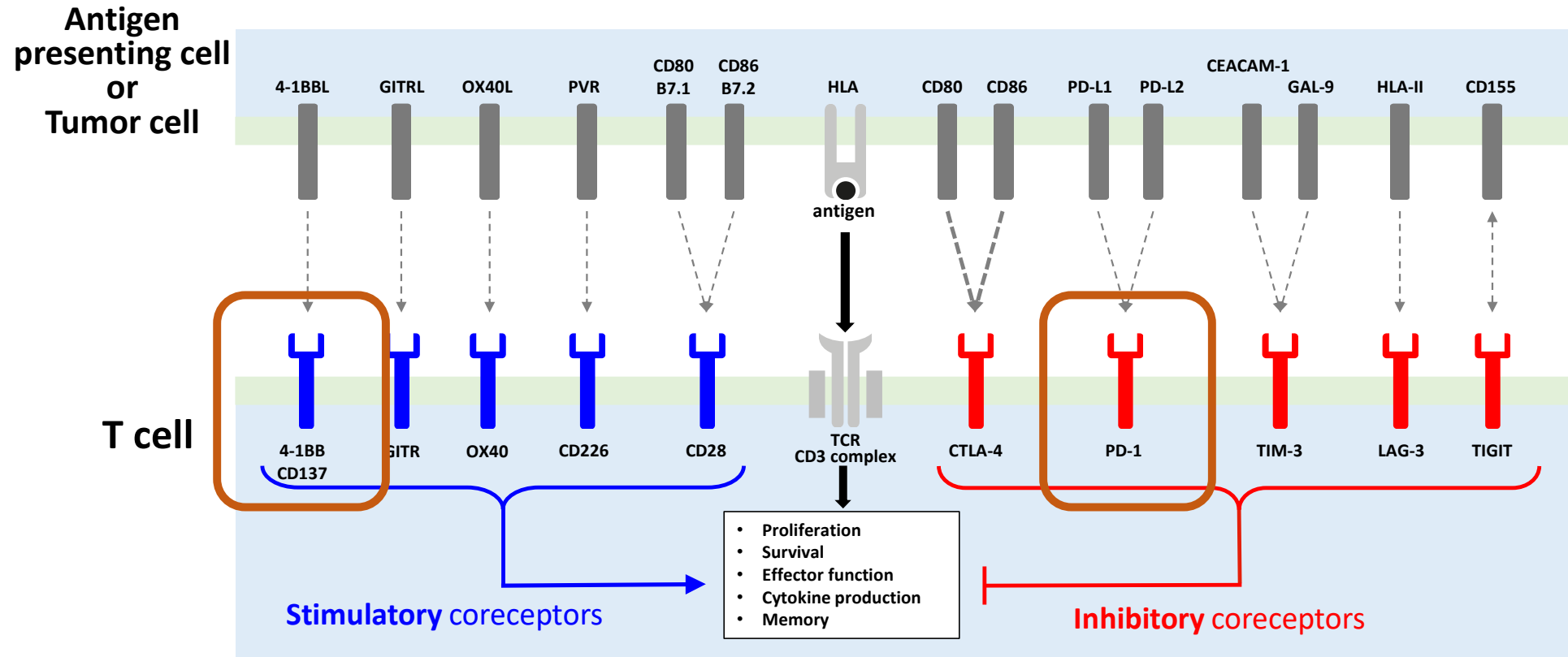
Stimulatory and inhibitory coreceptors



Function: fine-tuning of T-cell activation in time and space

Stimulatory and inhibitory coreceptors

Involved in anti-CTLA-4 or PD-(L)1 blockades



CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-(L)1; programmed death-(ligand) 1.

Reminders

PD-1 (or CTLA-4 or CD137) is a coreceptor, i.e. it exerts its immunomodulatory effect on T cells simultaneously activated by their T cell receptor recognizing an antigen.

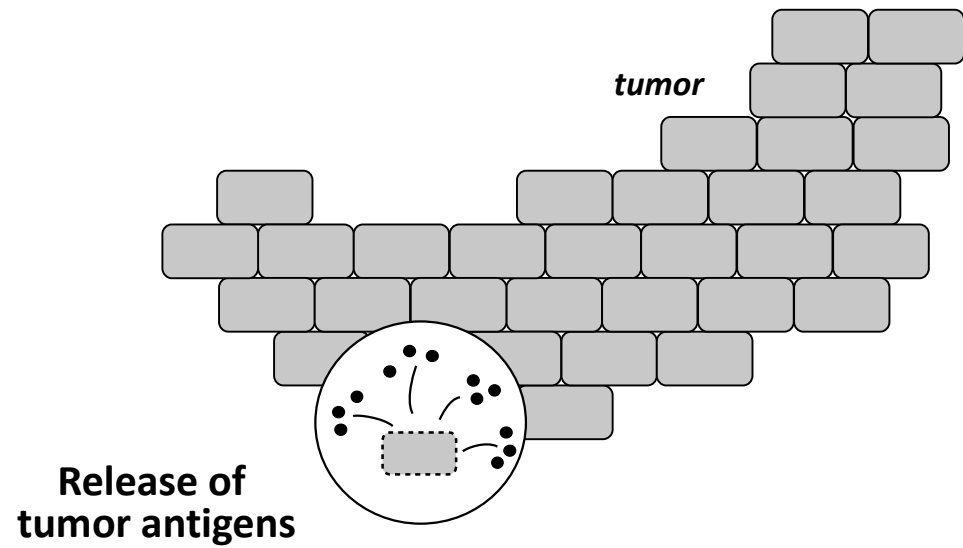
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Reminders

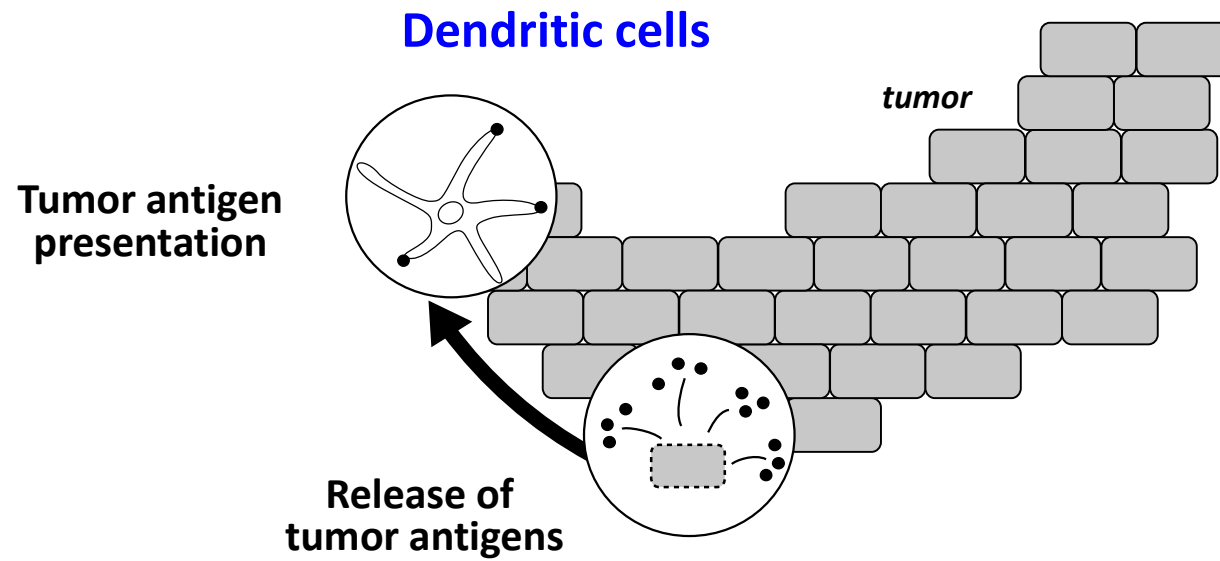
coreceptors

PD-1 / PD-L1 inhibition: not only with PD-L1 on tumor cells

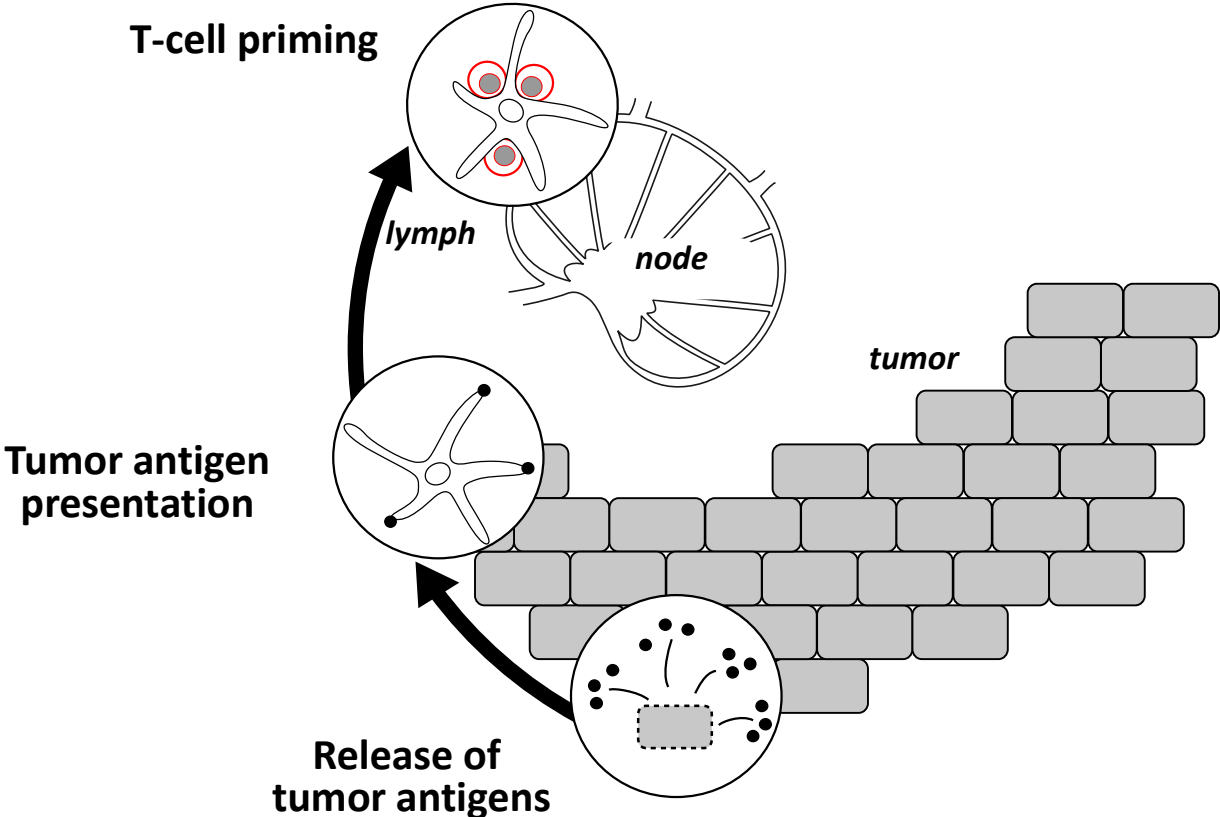
Mounting an antitumor T-cell response



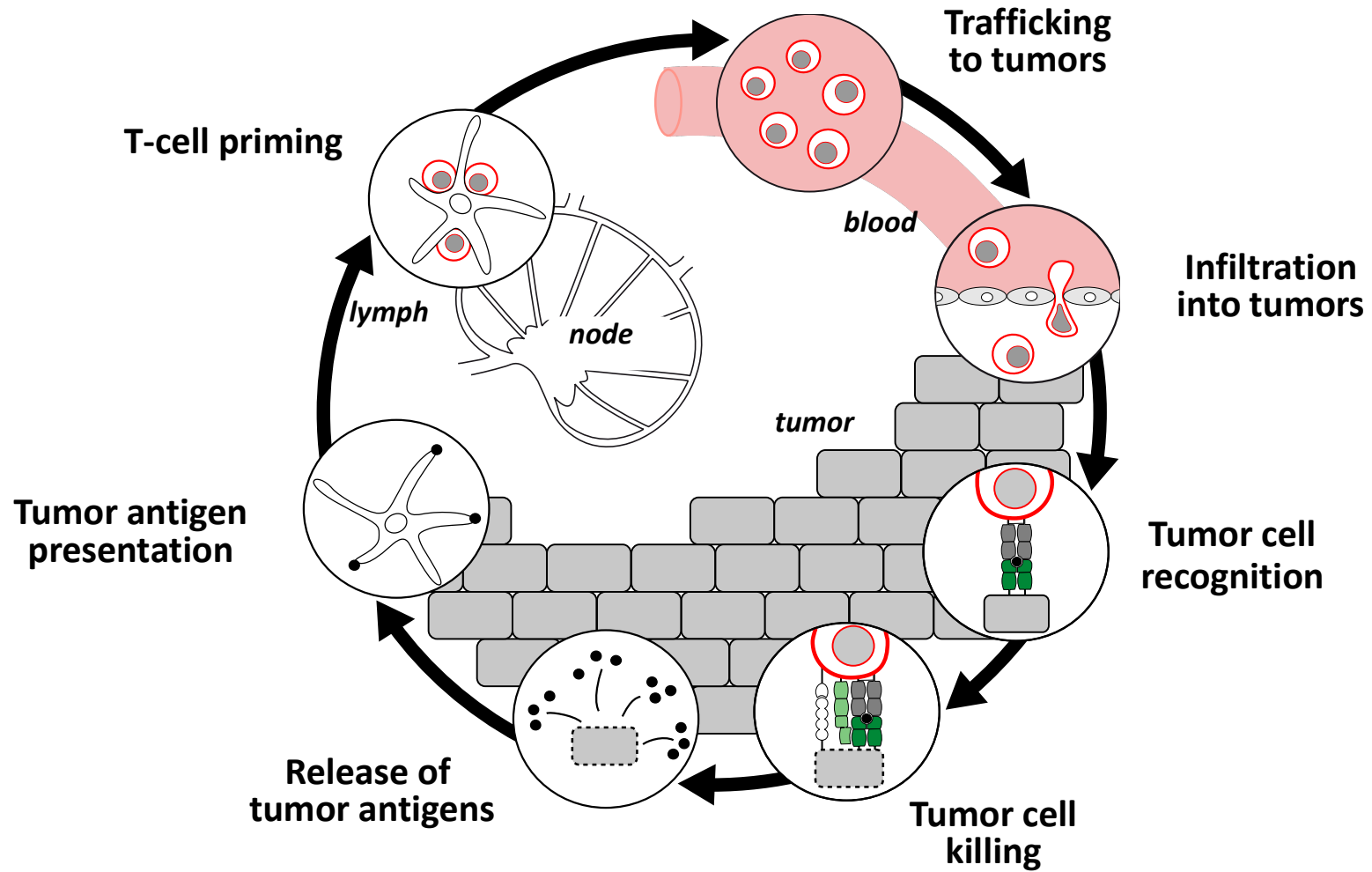
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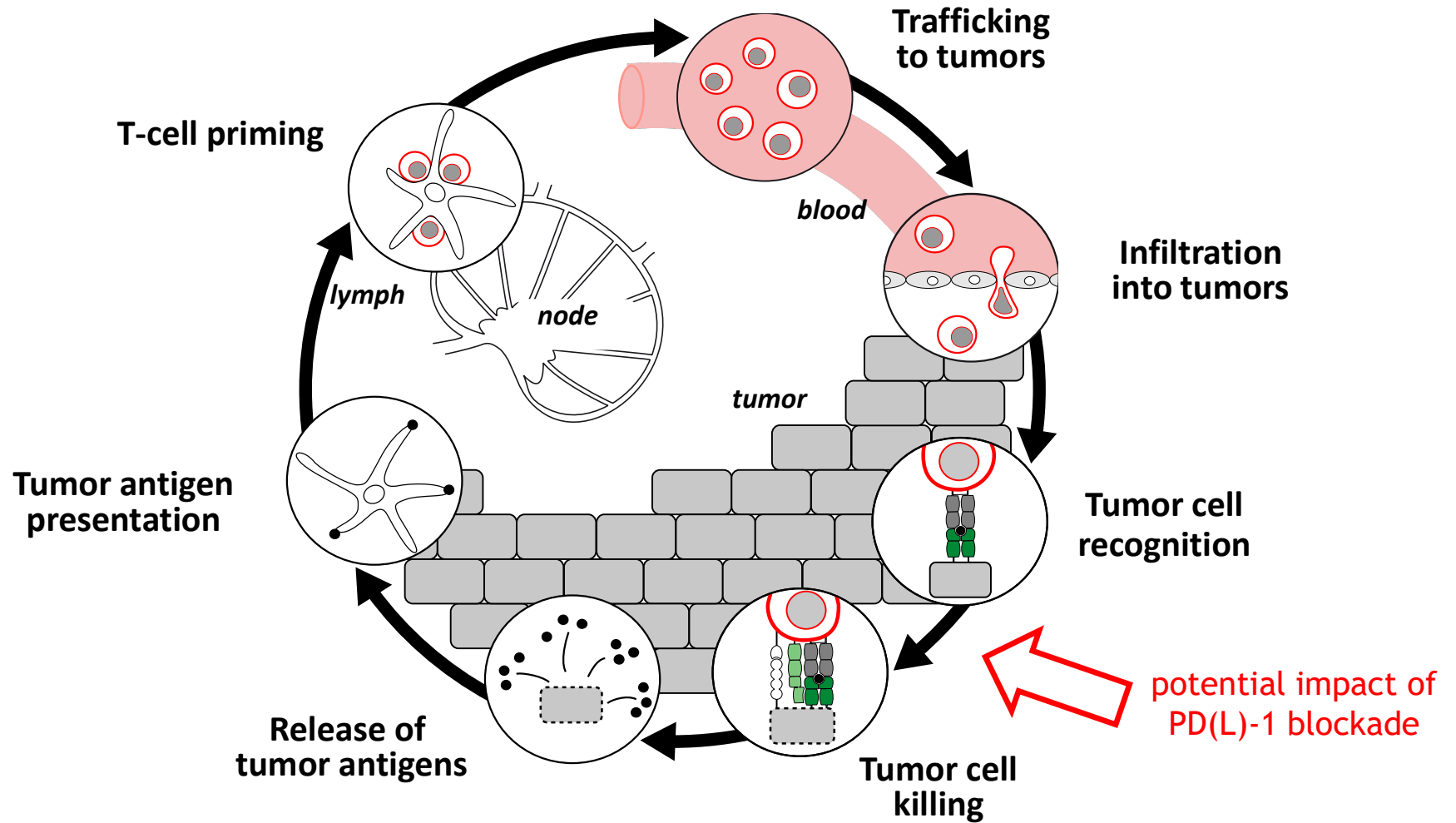


Mounting an antitumor T-cell response

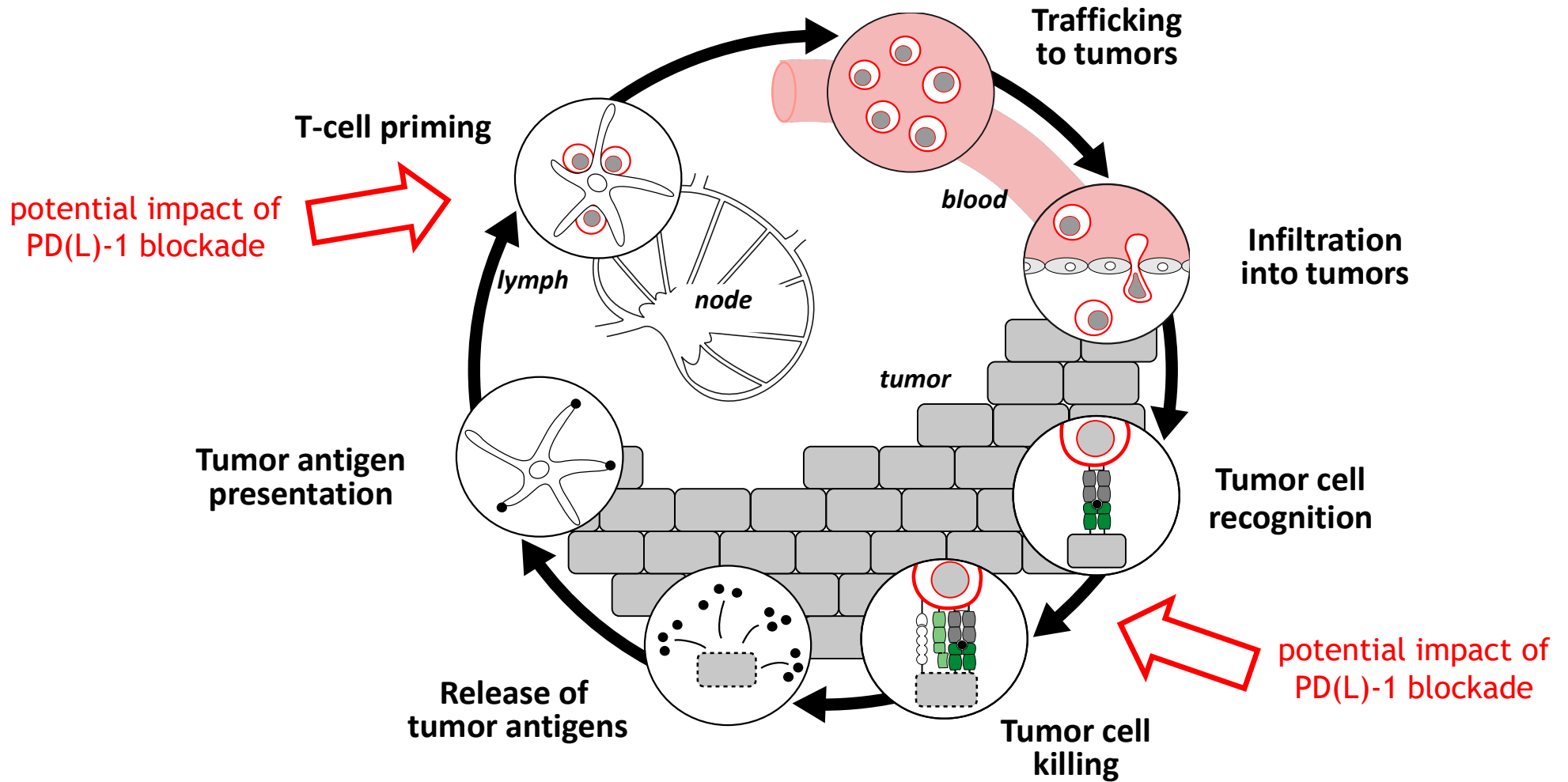


Adapted from Chen & Mellman (2013) *Immunity* 39(1):1-10.

Mounting an antitumor T-cell response

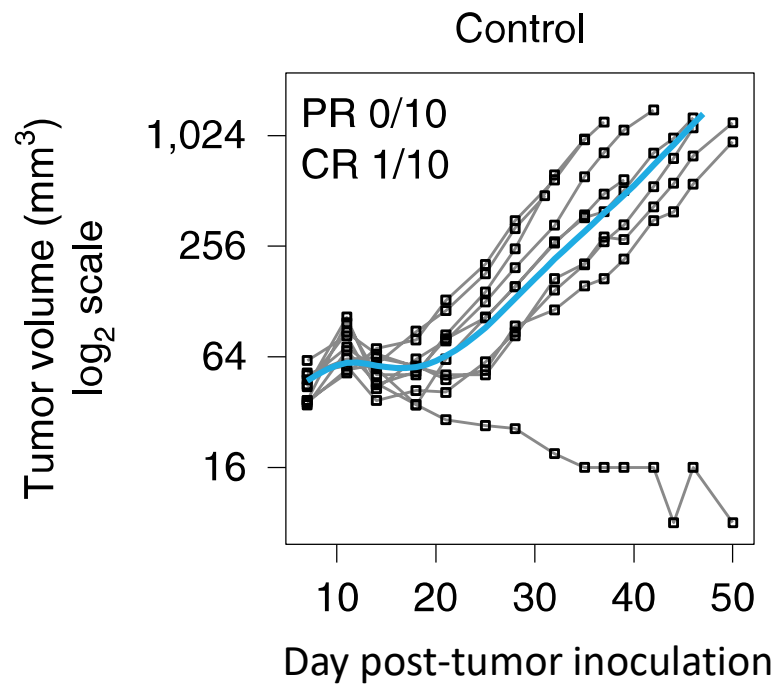


Mounting an antitumor T-cell response



PD-L1 on dendritic cells is a critical regulator of antitumor T-cell immunity

Growth of PD-L1 KO MC38 sarcoma cells:

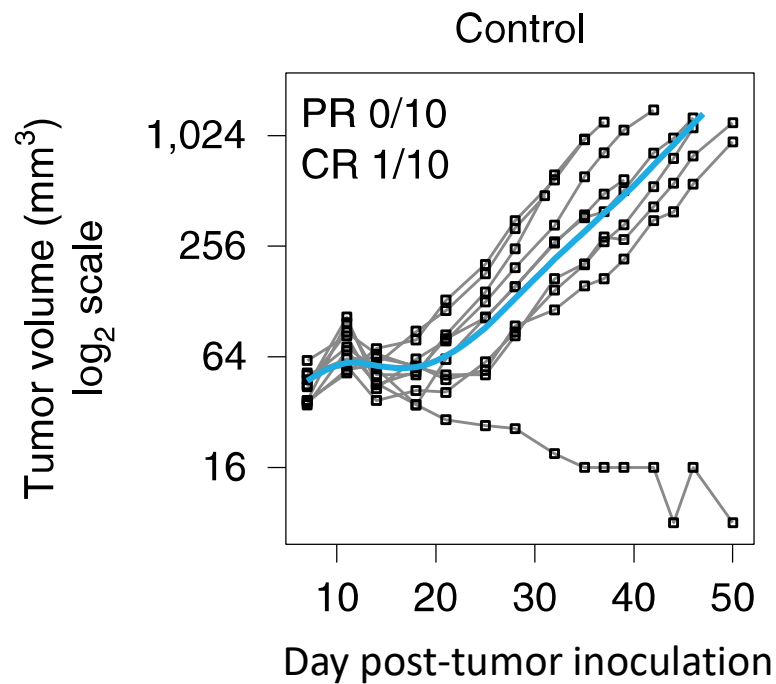


— Individual group fit

CR, complete response; DC, dendritic cell; KO, knockout;
PD-(L)1; programmed death-(ligand) 1; PR, partial response.
Oh et al. *Nature Cancer* 2020 1:681.

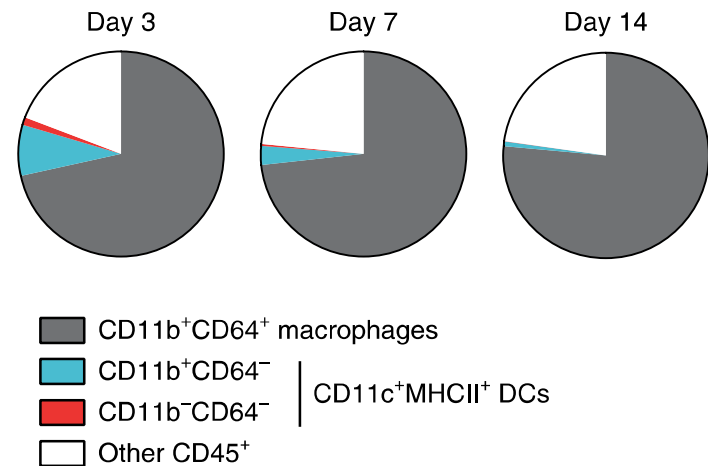
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Growth of PD-L1 KO MC38 sarcoma cells:



Tumors are infiltrated by PD-L1⁺ cells, most of which are macrophages. A small proportion are dendritic cells.

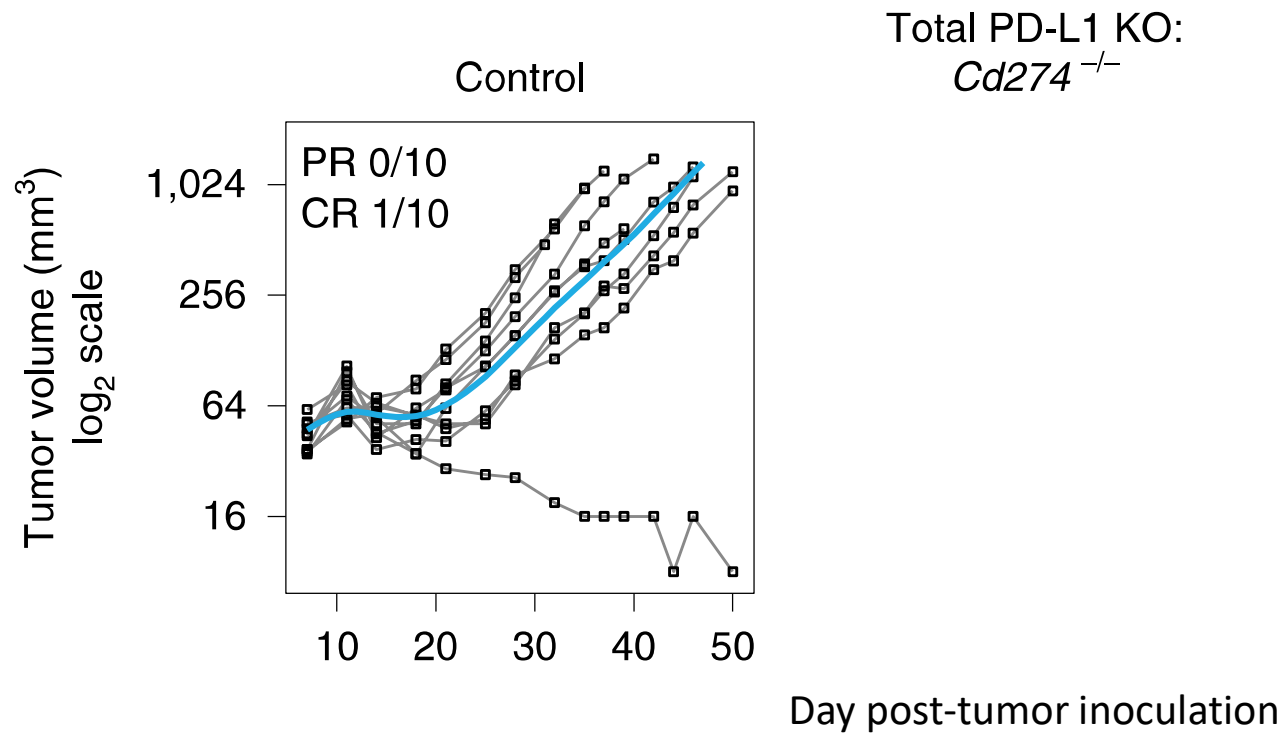
Fraction of all tumor-infiltrating CD45⁺ PD-L1⁺ cells:



— Individual group fit

PD-L1 on dendritic cells is a critical regulator of antitumor T-cell immunity

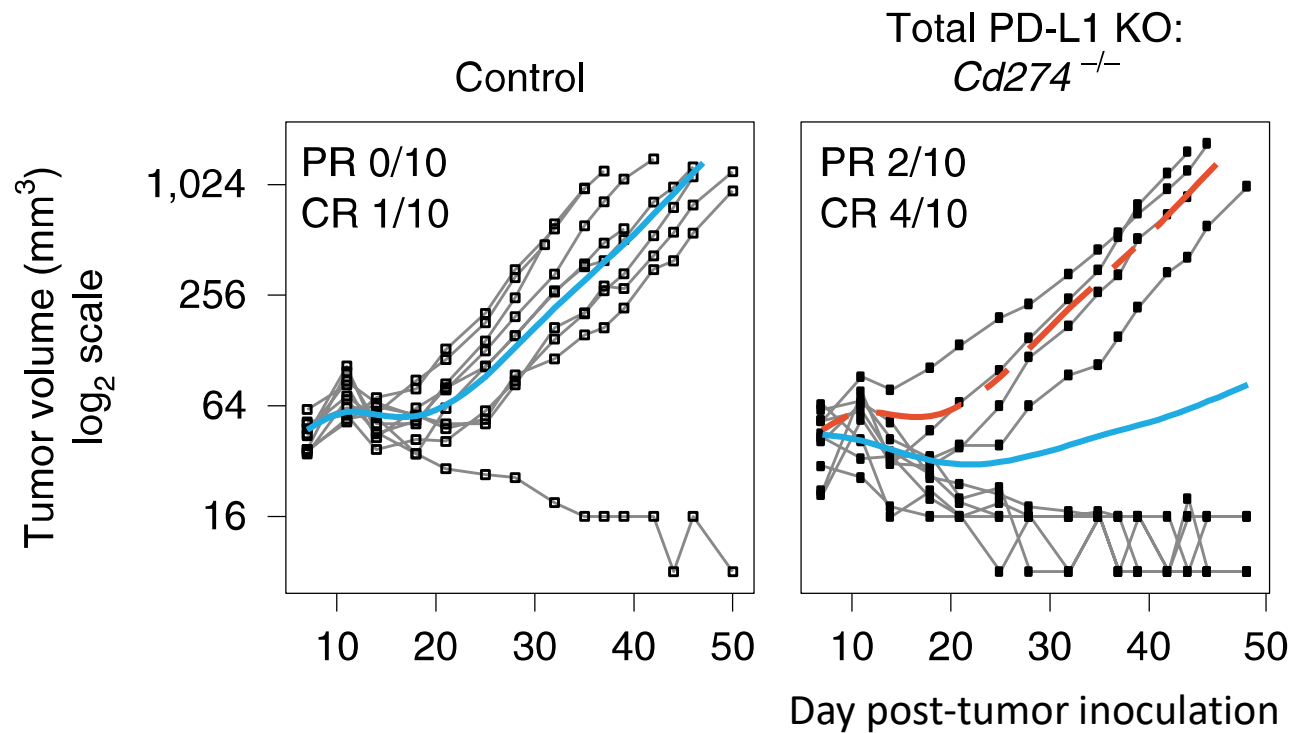
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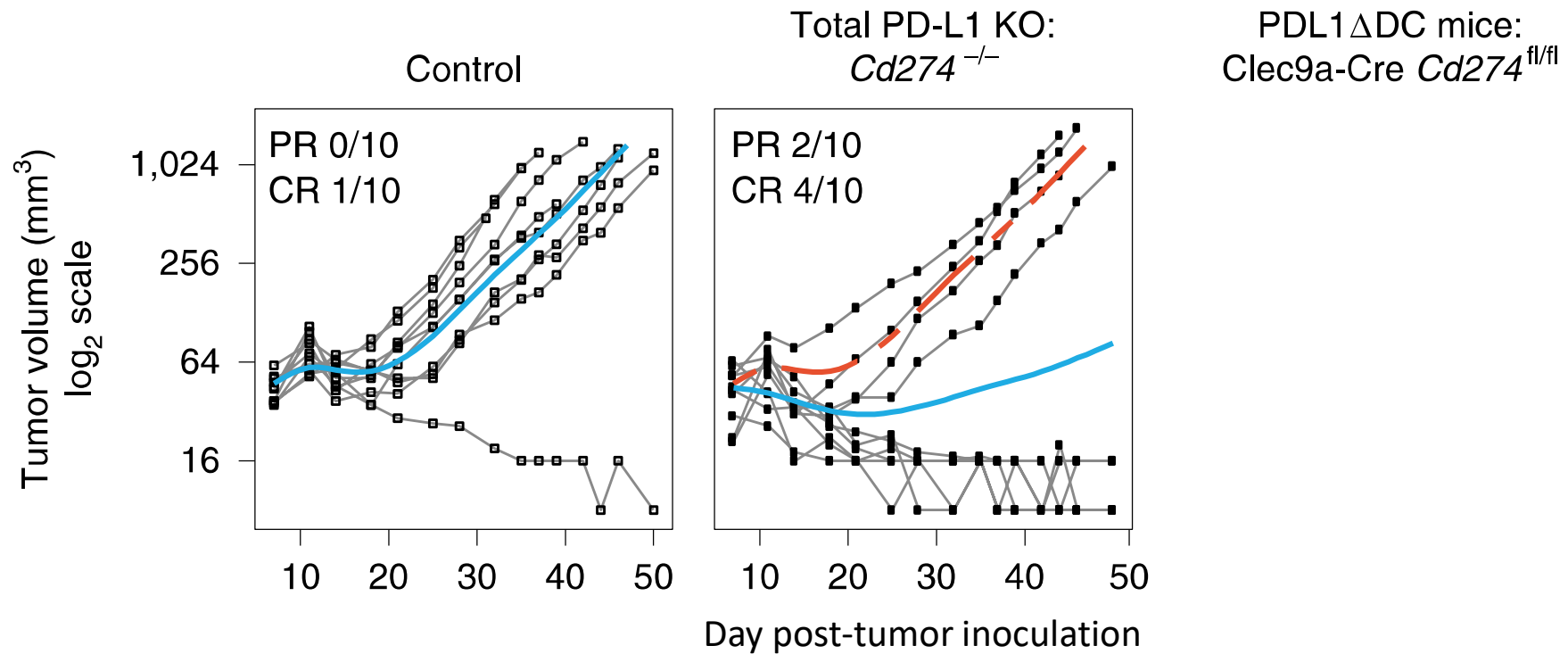


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for control group
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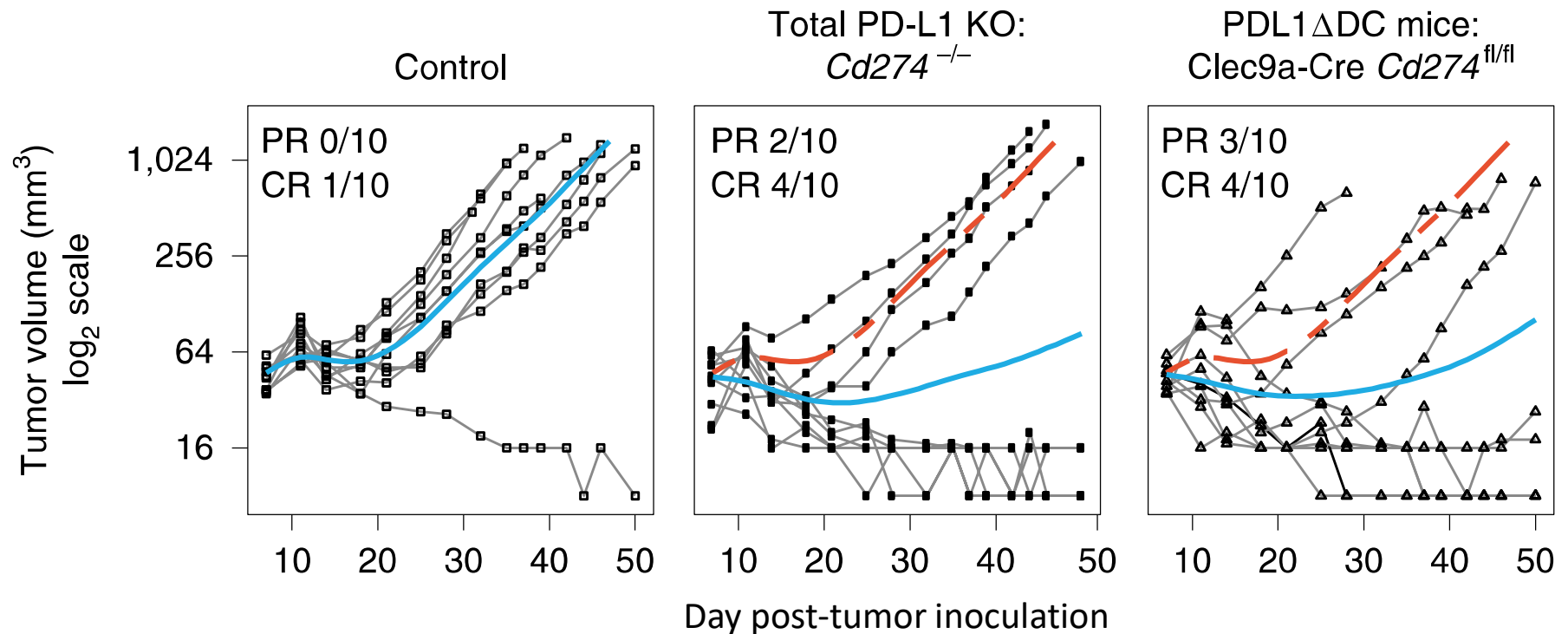
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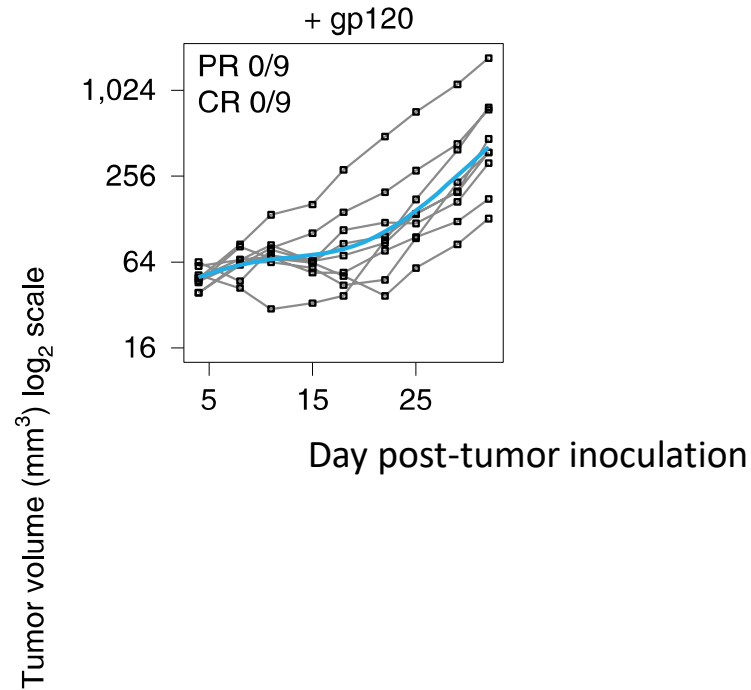


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PD-L1 on dendritic cells is a critical regulator of antitumor T-cell immunity

Growth of
PD-L1 KO
MC38 sarcoma cells:



Control mice

- Reference fit for control group
- Individual group fit

CR, complete response; DC, dendritic cell; KO, knockout;
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Day post-tumor inoculation

Reminders

PD-1 (or CTLA-4 or CD137) is a **coreceptor**, i.e. it exerts its immunomodulatory effect on T cells simultaneously activated by their T cell receptor recognizing an antigen.

T cells are inhibited by PD-L1 present on other immune cells, including dendritic cells. Through dendritic cells, PD-(L)1 blockade can increase T cell priming.
(CTLA-4 blockade also increases T cell priming)

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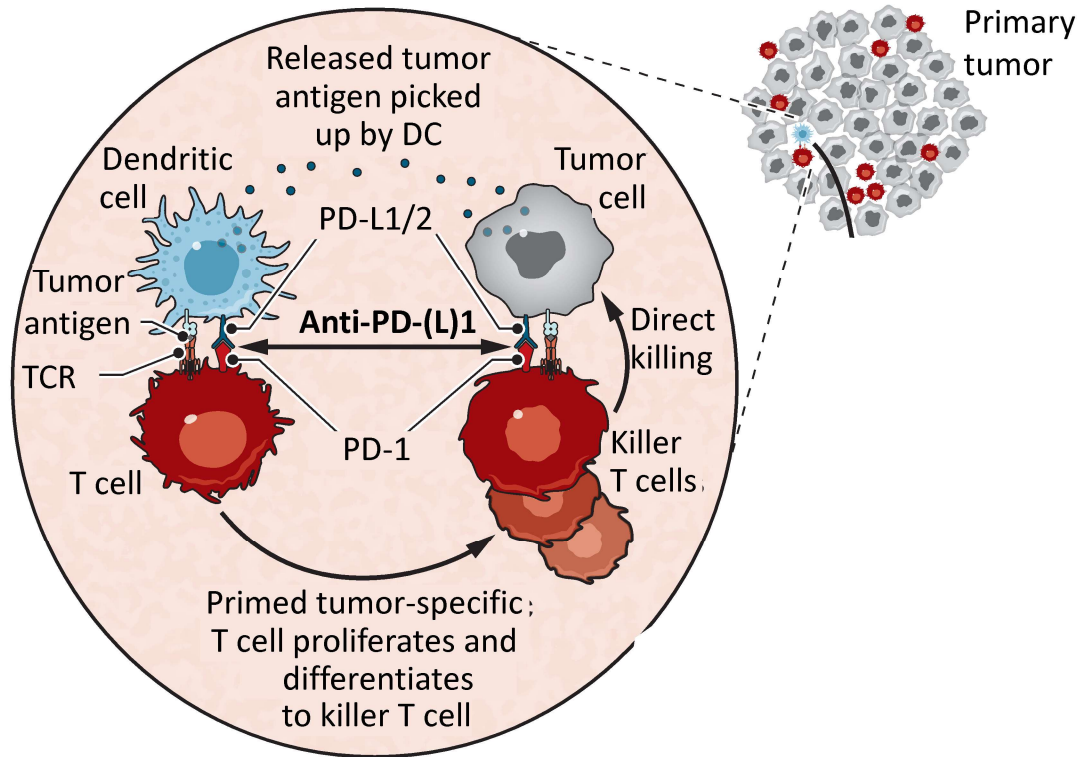
Reminders

coreceptors

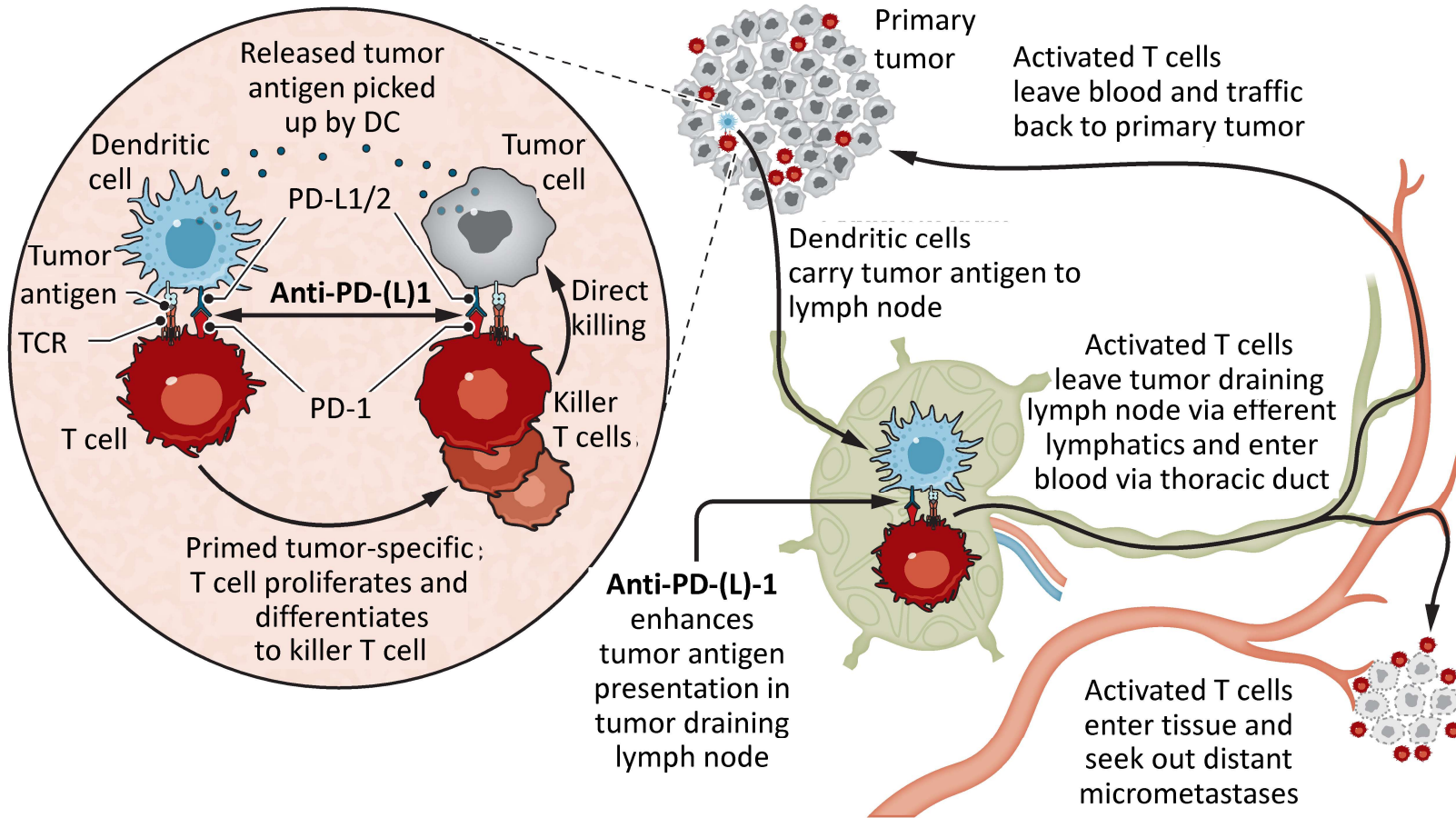
PD-1 / PD-L1 inhibition: not only with PD-L1 on tumor cells

PD-1 / PD-L1 inhibition: not only in tumors

PD(L)-1 blockade



PD(L)-1 blockade



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T cells are inhibited by PD-L1 present on other immune cells, including **dendritic** cells. Through dendritic cells, PD-(L)1 blockade can increase T cell priming.
(CTLA-4 blockade also increases T cell priming)

PD-1 blockade increases T cell activity not only in tumors (including tertiary lymphoid structures) **but also in draining lymph nodes.**

Moving cancer immunotherapy towards earlier stages of disease

Reminders

coreceptors

PD-1 / PD-L1 inhibition: not only with PD-L1 on tumor cells

PD-1 / PD-L1 inhibition: not only in tumors

Adjuvant or neoadjuvant PD-(L)1 blockade: what is 'immunologically' better?

Neoadjuvant immunotherapy is more attractive, since the primary tumor may be an antigen source for expansion and activation of tumor-specific T cells and systemic surveillance of micrometastases.

Preclinical testing of adjuvant or neoadjuvant immunotherapy

Cancer Discov 2016 6:1382-1399

Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease

J. Liu , S. Blake , M. Yong , H. Harjunpää , S. Ngiew , K. Takeda , A. Young , J. O'Donnell , S. Allen , M. Smyth , M. Teng

- triple-negative breast cancer cell lines 4T2.1 and E0771
- orthotopic inoculation (mammary fat pad)
- mice spontaneously develop lethal metastases in several organs prior to extensive primary tumor growth
- previously used to test adjuvant therapies after surgery

Preclinical testing of adjuvant or neoadjuvant immunotherapy

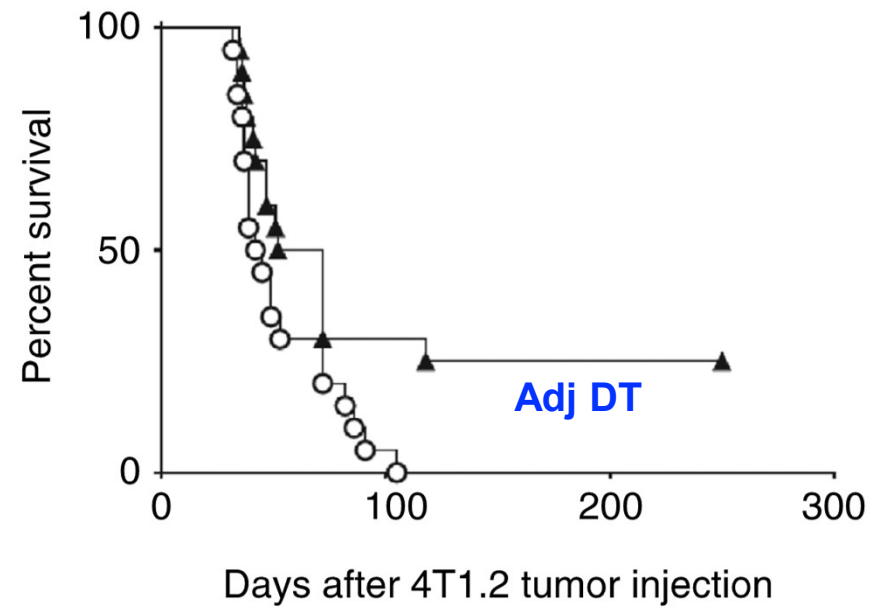
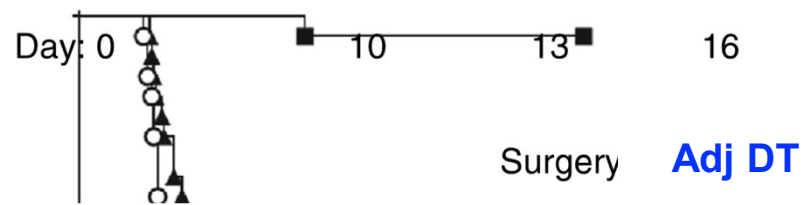
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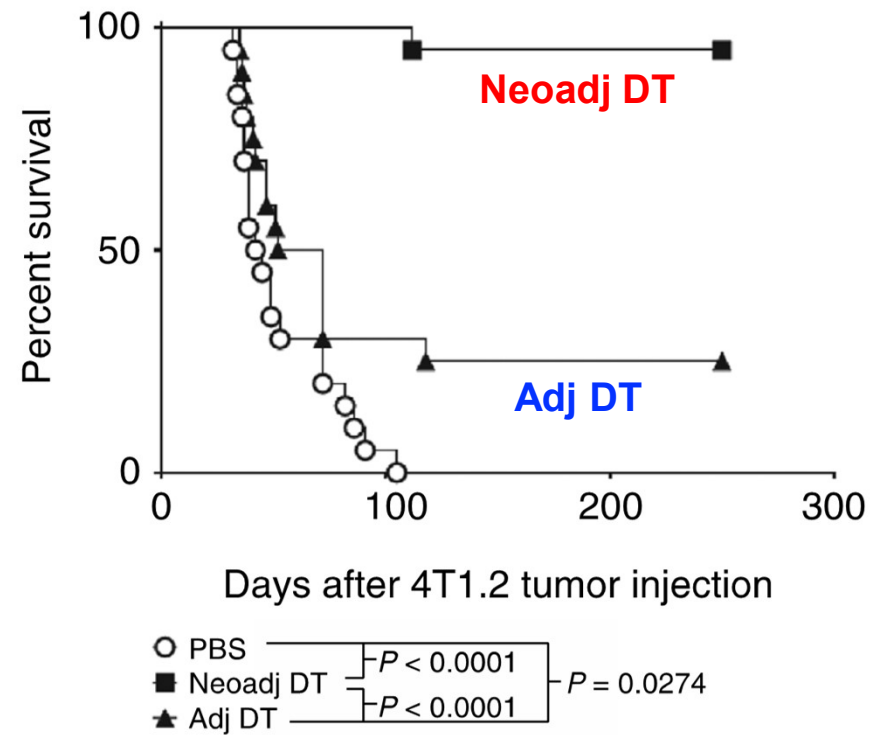
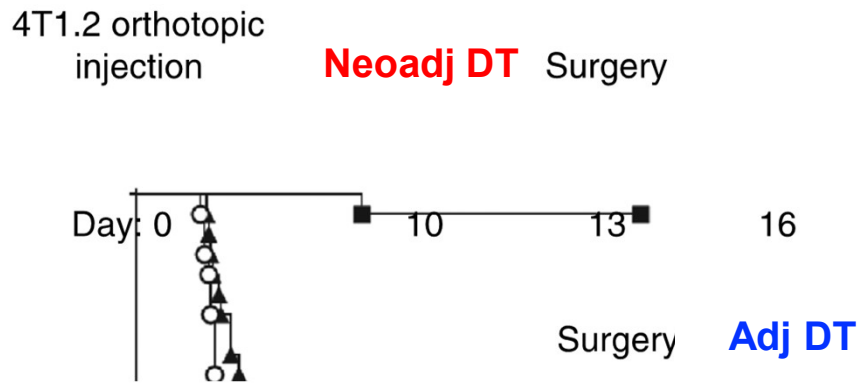
- triple-negative breast cancer cell lines 4T2.1 and E0771
- orthotopic inoculation (mammary fat pad)
- mice spontaneously develop lethal metastases in several organs prior to extensive primary tumor growth
- previously used to test adjuvant therapies after surgery
- here several immunotherapies are tested to eradicate metastases:
 - Treg depletion with diphtheria toxin (DT) in *FOXP3-DTR* transgenic mice
 - Treg depletion with depleting anti-CD25 monoclonal antibody
 - anti-PD-1
 - anti-PD-1 and anti-CD137

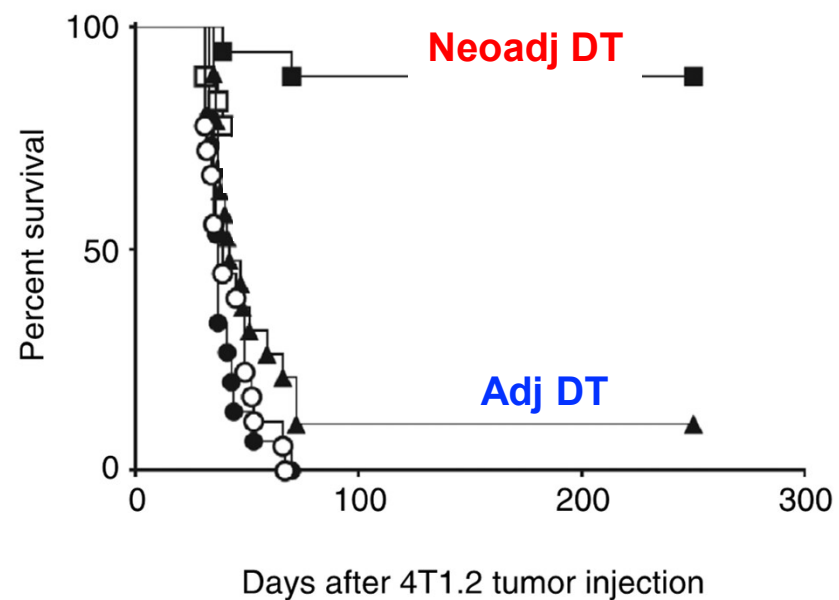
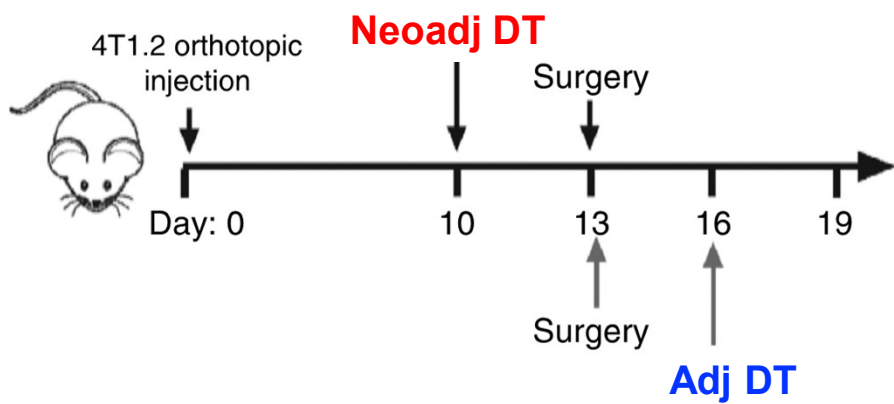
4T1.2 orthotopic injection

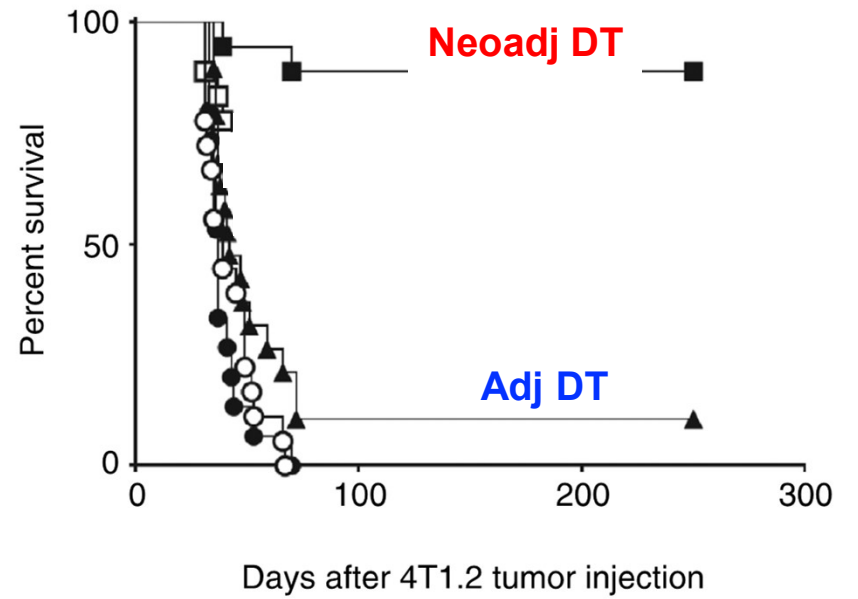
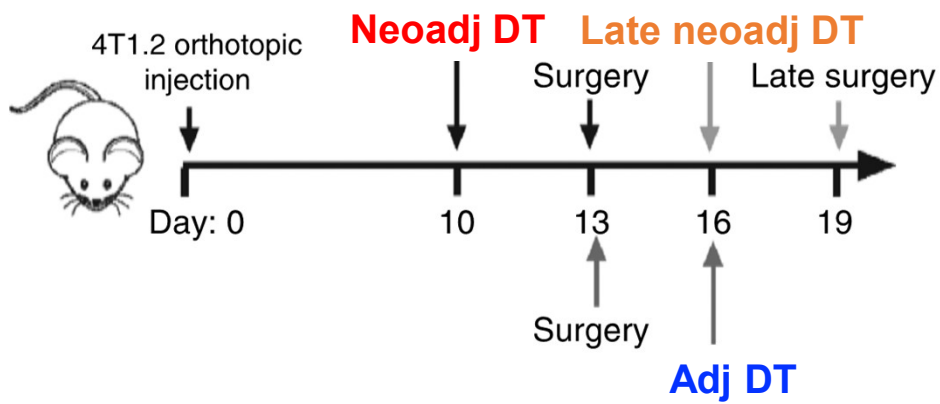


Adj, adjuvant; DT, diphtheria toxin.

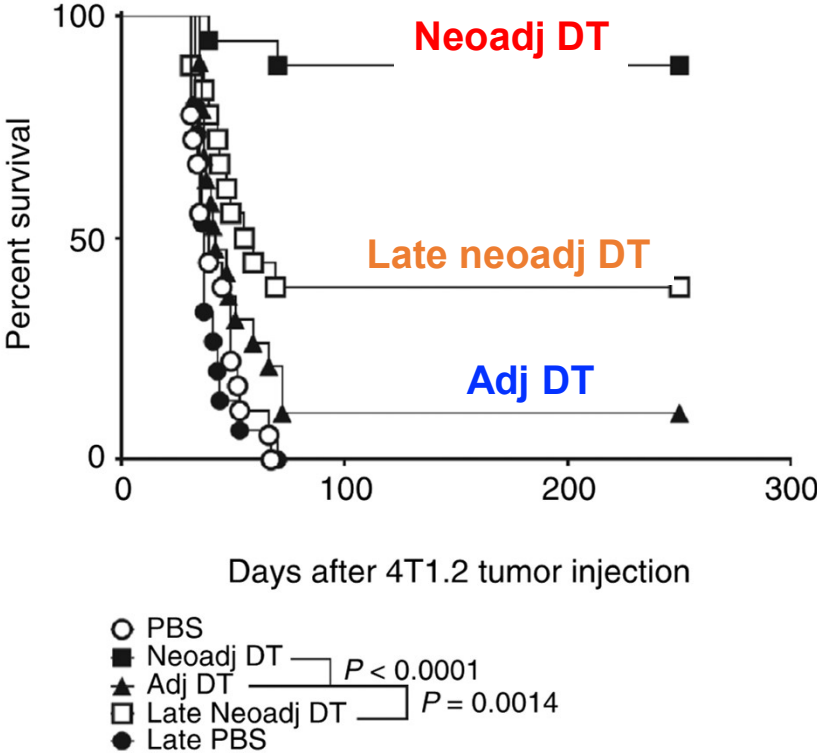
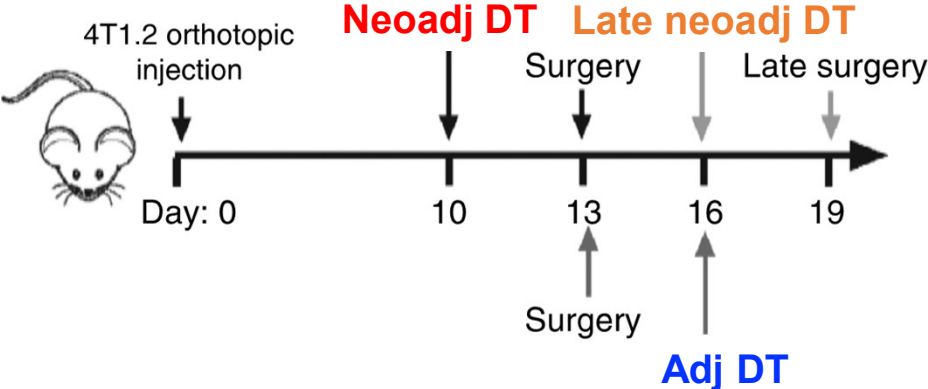
Neoadjuvant superior to adjuvant complete Treg depletion



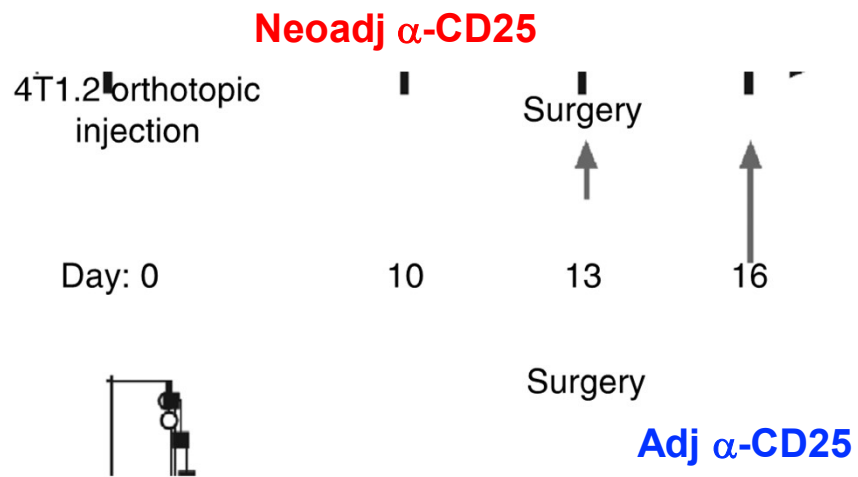




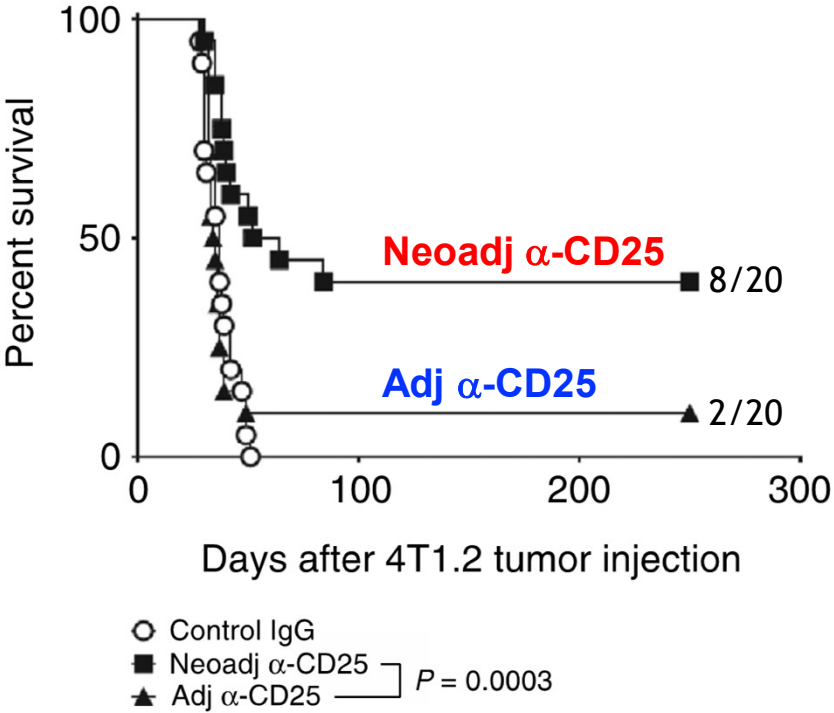
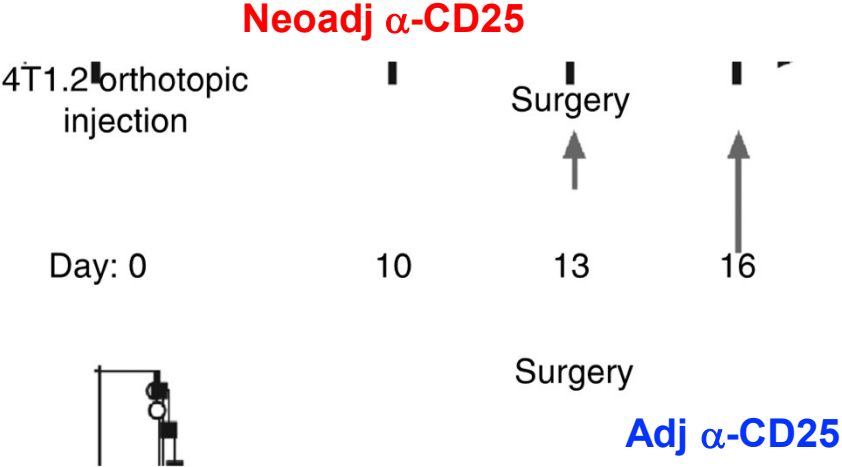
Improved neoadj efficacy is not due to differences in metastatic burden



Adj, adjuvant; DT, diptheria toxin; neoadj, neoadjuvant; PBS, phosphate-buffered saline.

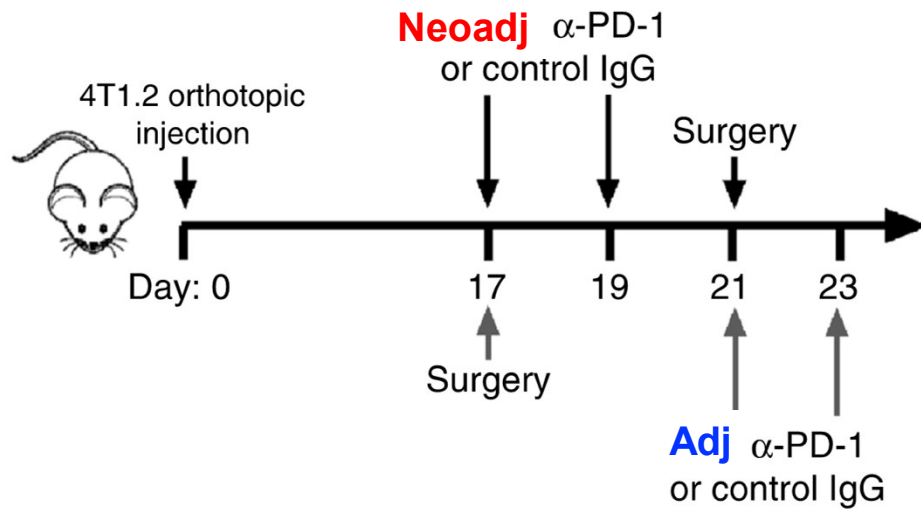


Neoadjuvant superior to adjuvant Treg depletion (not complete)

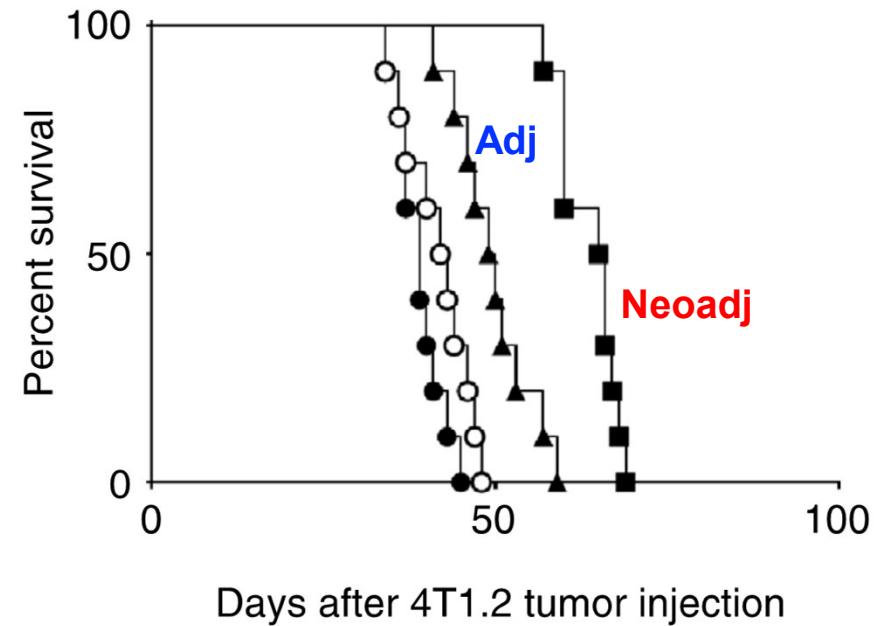
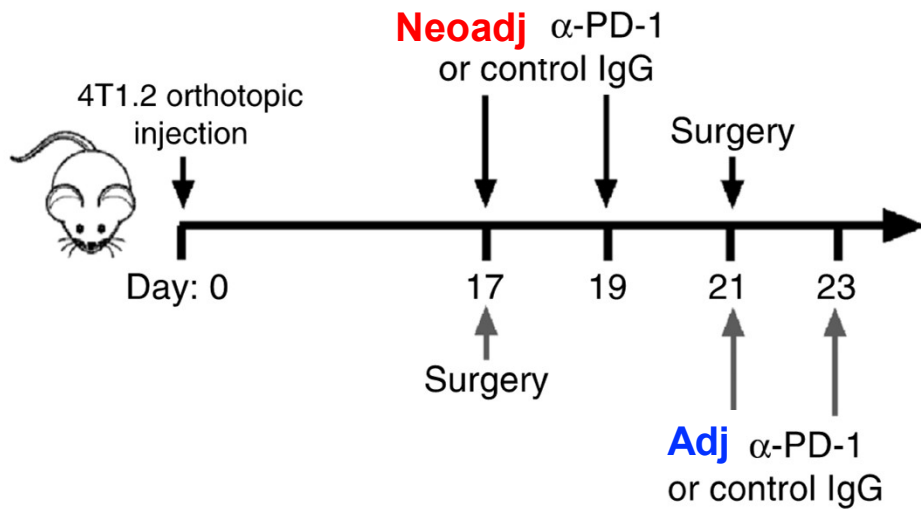


Adj, adjuvant; CD, cluster of differentiation; IgG, immunoglobulin G; neoadj, neoadjuvant; Treg, regulatory T cells.

Neoadjuvant α -PD-1 compared with adjuvant α -PD-1



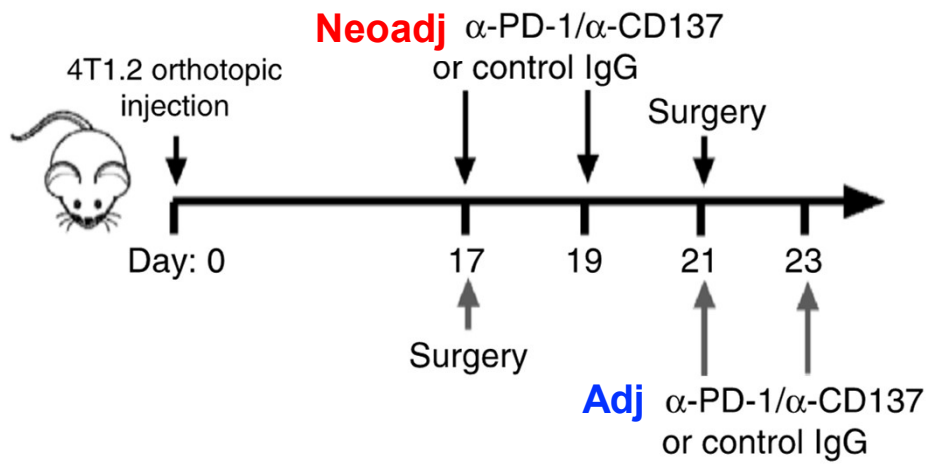
Neoadjuvant compared with adjuvant α -PD-1



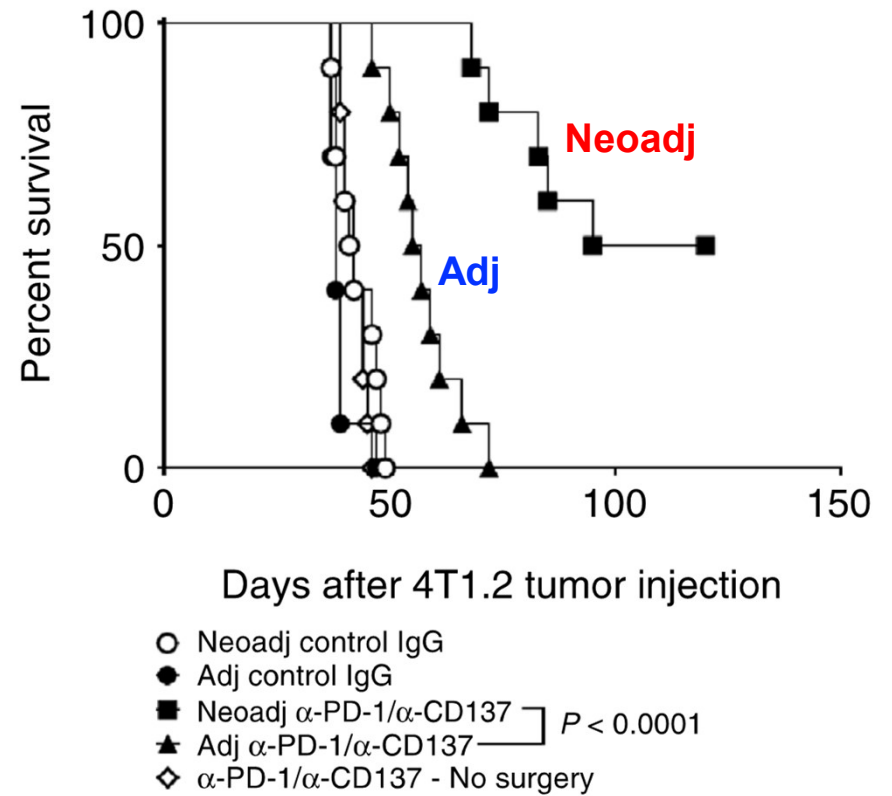
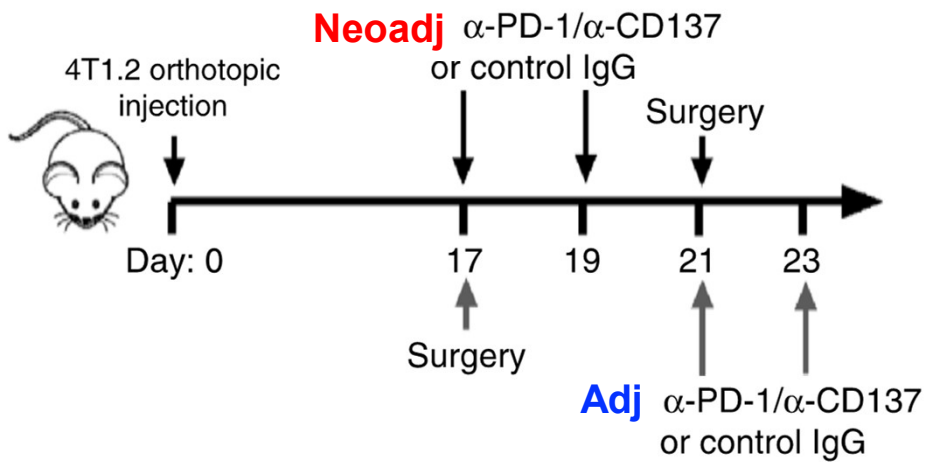
longer survival with neoadj but
no mice survived long term: poor efficacy of PD-1 blockade alone in this model

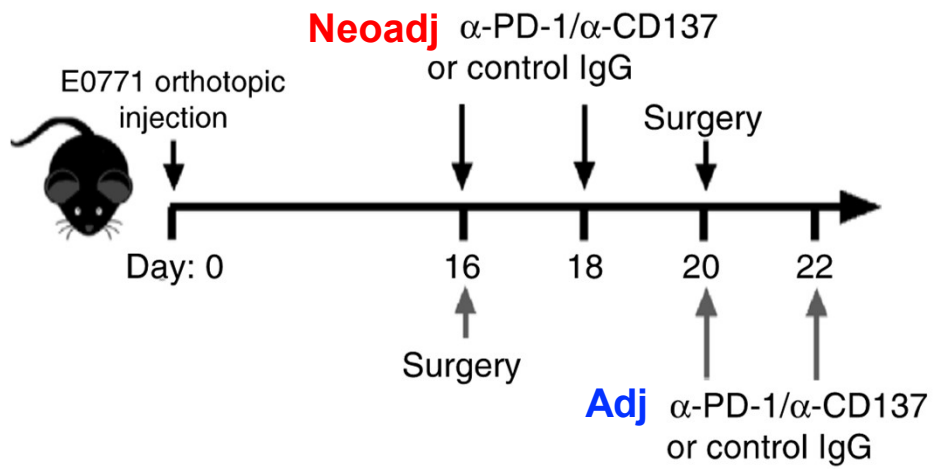
Adj, adjuvant; IgG, immunoglobulin G; neoadj, neoadjuvant; PD-1, programmed death-1.

Liu et al - Cancer Discov - 2016 - 6:1382



Neoadjuvant superior to adjuvant [α -PD-1 + α -CD137]

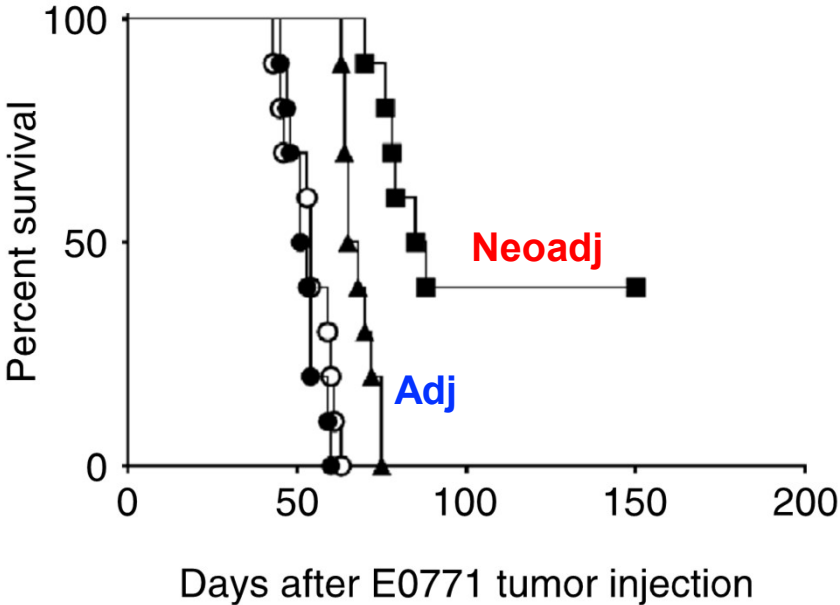
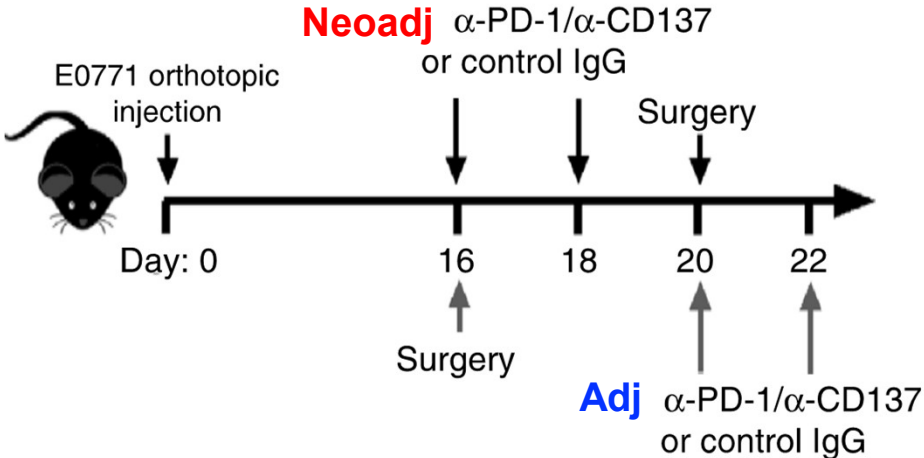




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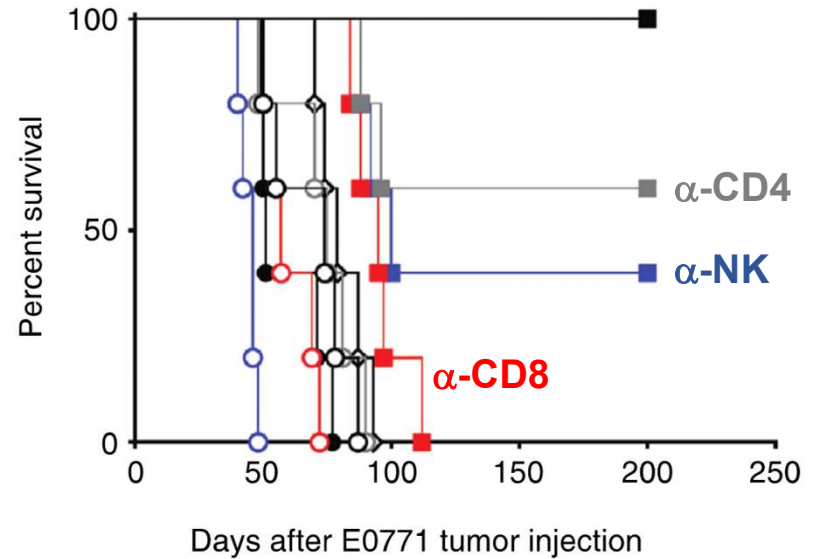
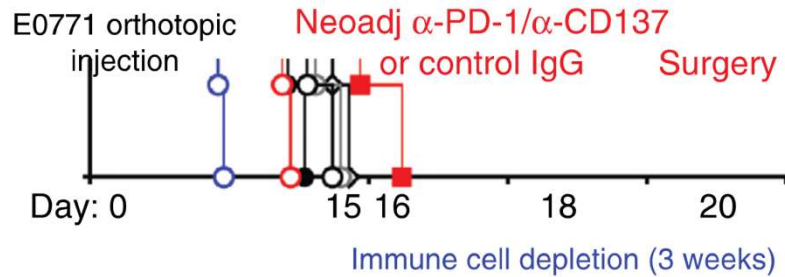
Neoadjuvant superior to adjuvant [α -PD-1 + α -CD137]



- Neoadj control IgG
 - Adj control IgG
 - Neoadj α -PD-1/ α -CD137
 - ▲ Adj α -PD-1/ α -CD137
- $P < 0.0001$

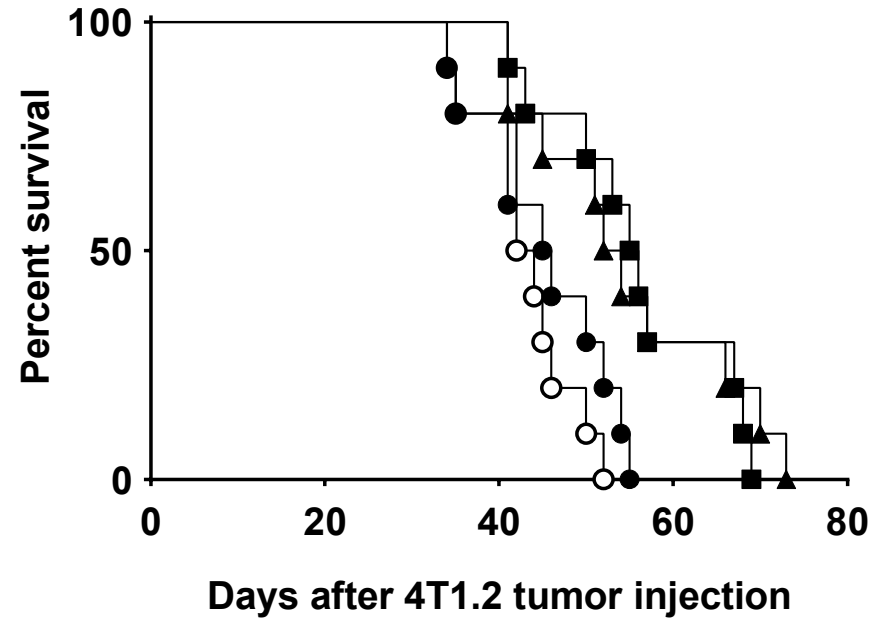
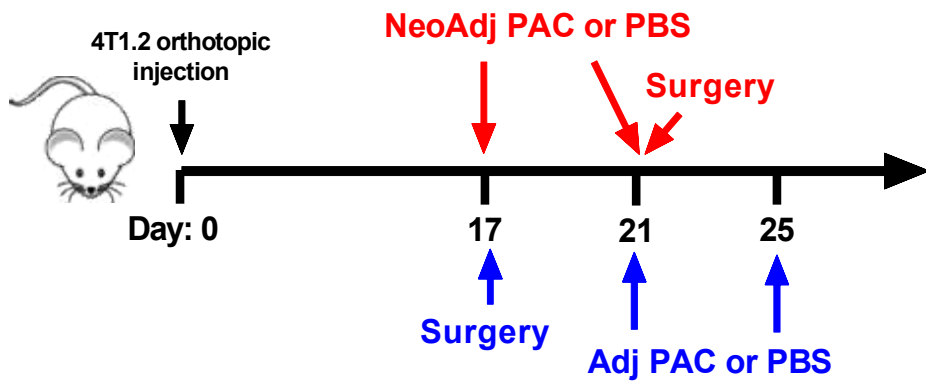
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Neoadjuvant immunotherapy efficacy depends on CD8 T cells



- Neoadj control IgG
- Neoadj control IgG + α -asGM1
- Neoadj control IgG + α -CD8 β
- Neoadj control IgG + α -CD4
- Neoadj control IgG + α -CD4/CD8 β
- Neoadj α -PD-1/ α -CD137 + control IgG
- Neoadj α -PD-1/ α -CD137 + α -asGM1 $P = 0.0494$
- Neoadj α -PD-1/ α -CD137 + α -CD8 β $P = 0.0018$
- Neoadj α -PD-1/ α -CD137 + α -CD4 $P = 0.1343$
- ◇ Neoadj α -PD-1/ α -CD137 + α -CD4/CD8 β

Neoadjuvant compared with adjuvant chemotherapy



- NeoAdj PBS
 - Adj PBS
 - NeoAdj PAC
 - ▲ Adj PAC
- p = 0.7422

Different advantages of neoadjuvant and adjuvant PD-(L)1 blockade

Neoadjuvant

- prime or restimulate T cells recognizing all tumor antigens present in the tumor
- opportunities: pathologic response, tumor material for biomarkers

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Adjuvant

- prime or restimulate T cells recognizing tumor antigens that were not expressed in the tumor (antigenic heterogeneity)
- could be more efficient than neoadjuvant if the tumor was strongly immunosuppressive
- maintain a sufficiently strong antitumoral immune response
- associated with vaccination as most anti-tumor T cells, previously in the tumor and its draining lymph nodes, are lost and the amount of tumor antigens is too low for efficient priming or restimulation

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→ Complementarity

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PD-1 / PD-L1 inhibition: not only in tumors

Adjuvant or neoadjuvant PD-(L)1 blockade: what is 'immunologically' better?

Surgery combined with adjuvant **and neoadjuvant PD-(L)1 blockades:
'Perioperative immunotherapy'**