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RECRUITMENT AND ACTIVATION OF TYPE 3 INNATE LYMPHOID CELLS PROMOTES ANTI-TUMOR IMMUNE RESPONSES AFTER A CISPLATIN TREATMENT.

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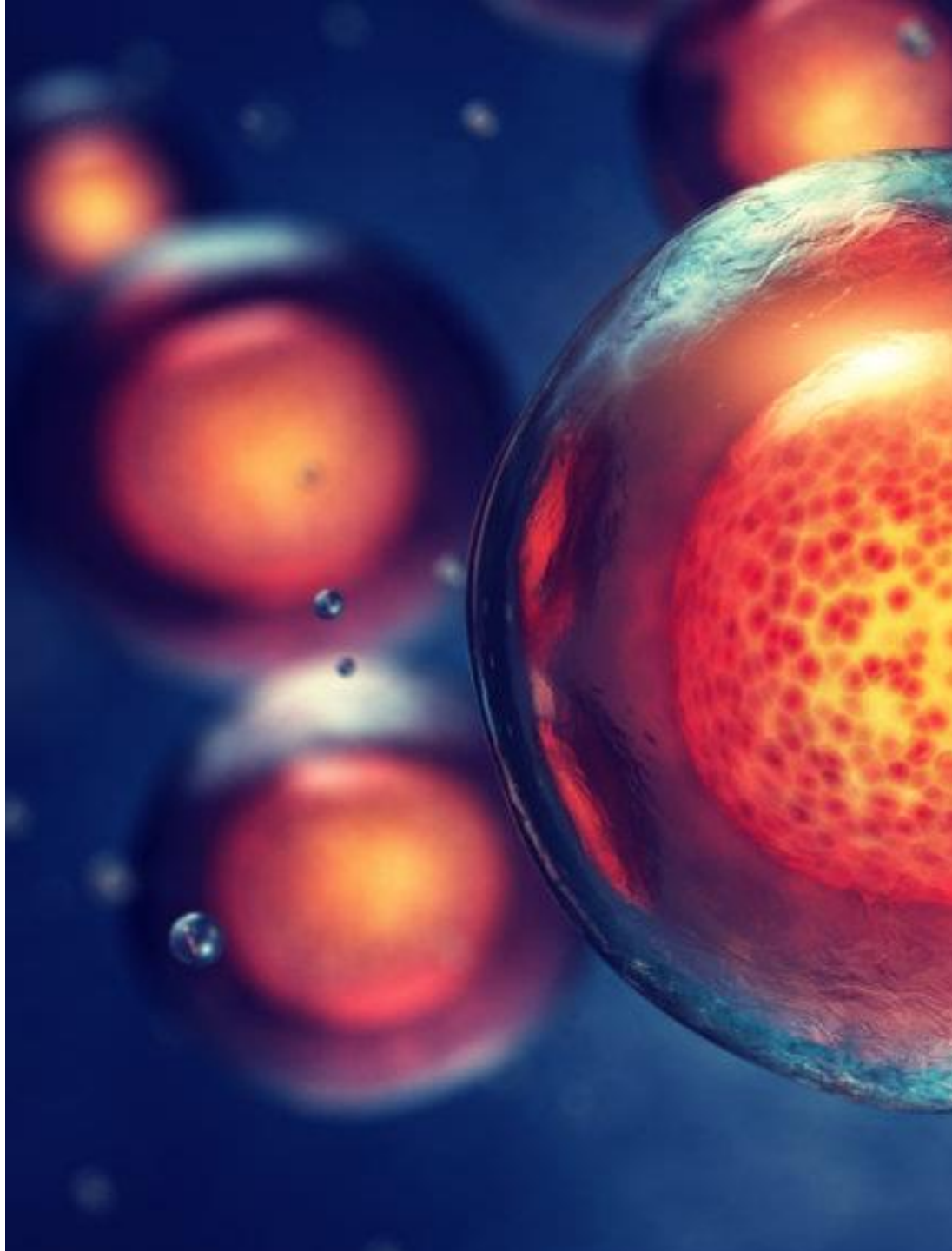
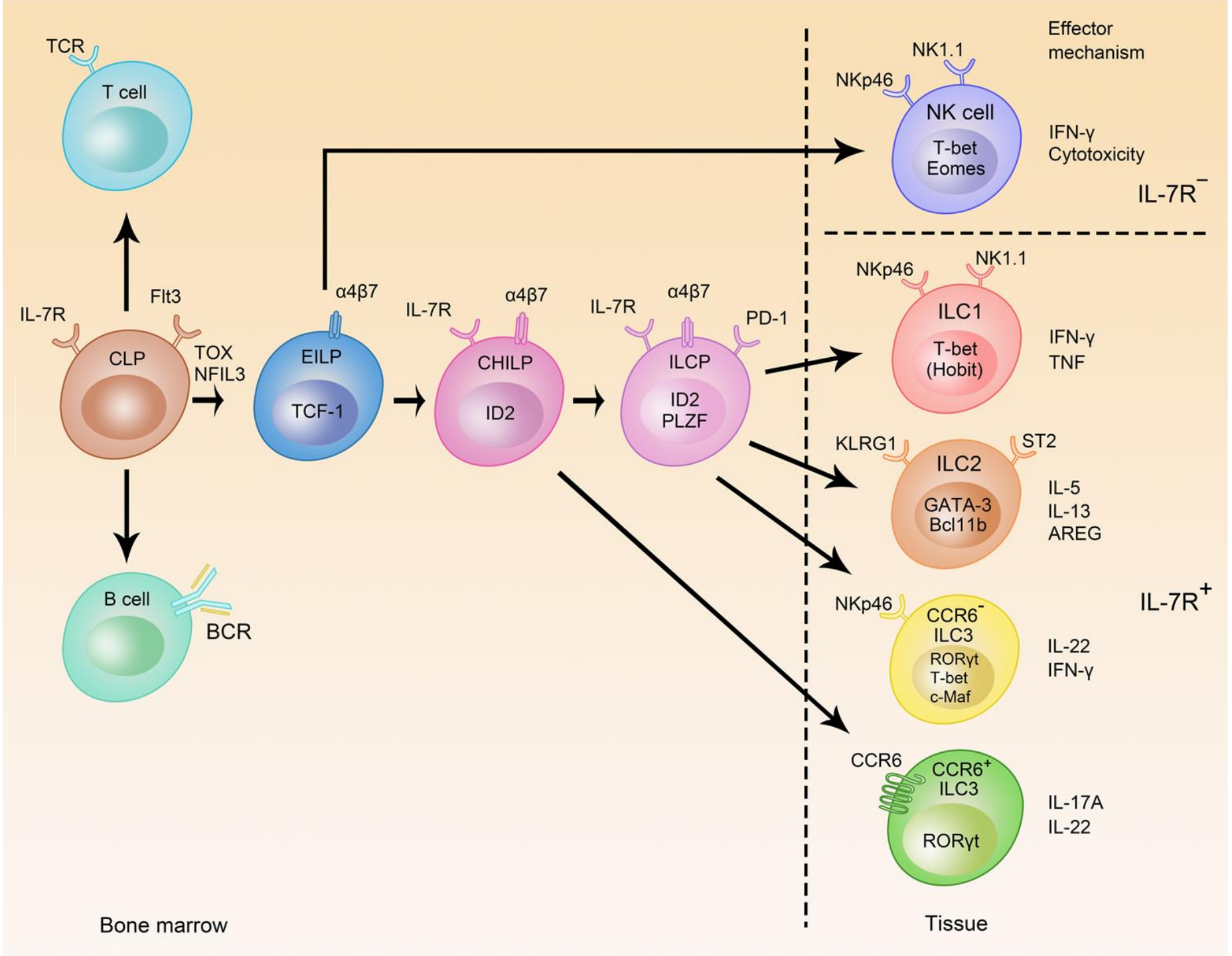
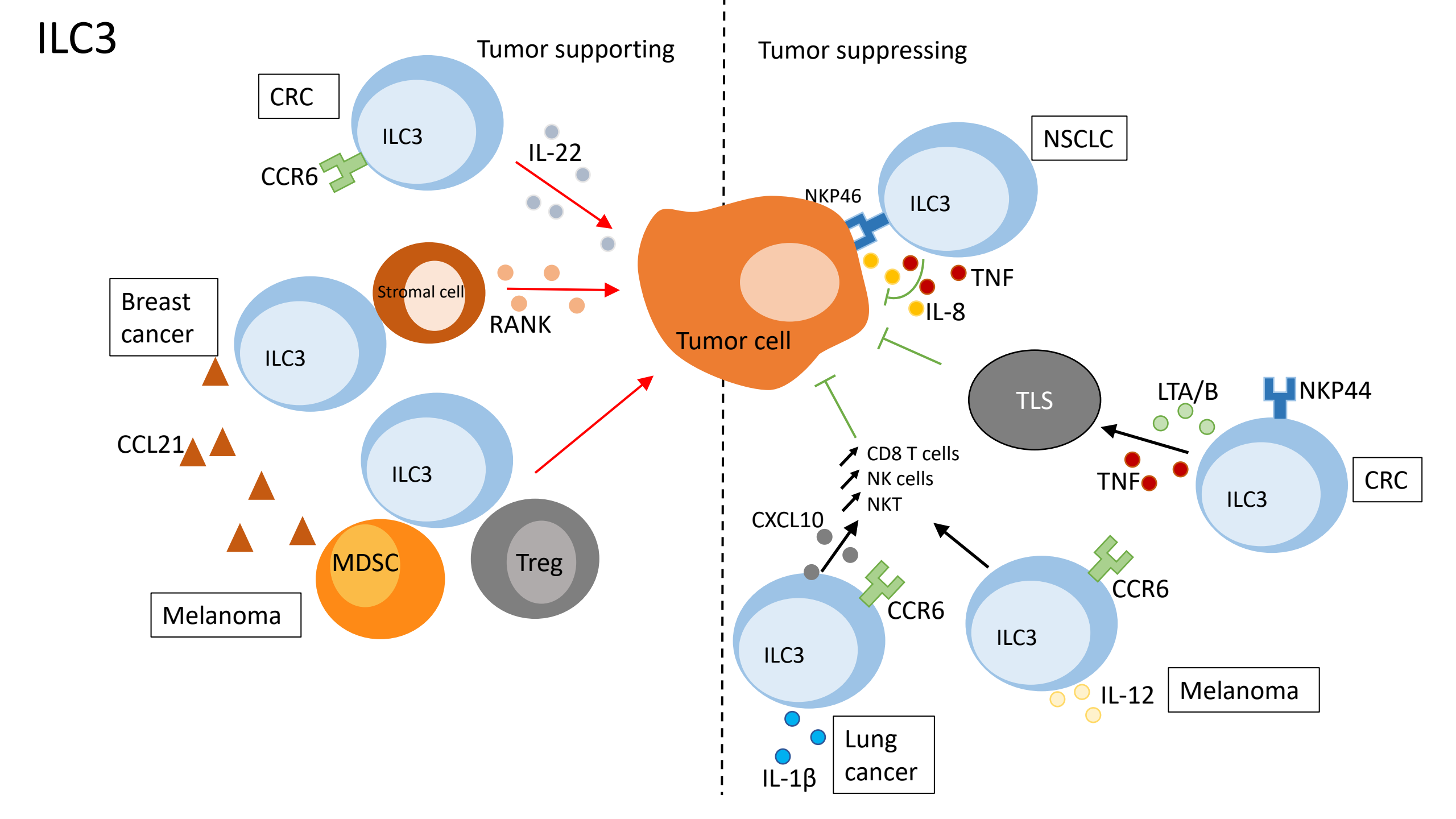
UBFC

CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est





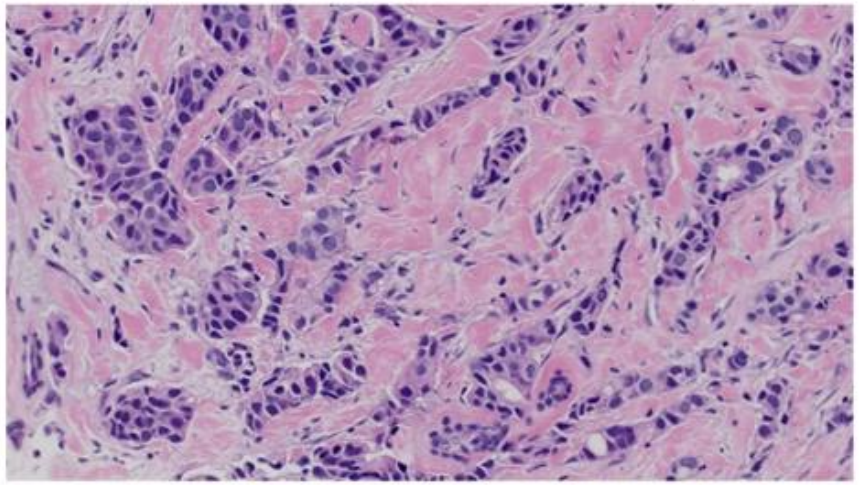
Klose and Artis, 2020


ILC3
Tumor supporting
Tumor suppressing
CRC
ILC3
CCR6
IL-22
Stromal cell
RANK
Breast cancer
ILC3
CCL21
ILC3
MDSC
Treg
Melanoma
Tumor cell
NSCLC
NKP46
ILC3
TNF
IL-8
TLS
LTA/B
NKP44
TNF
ILC3
CRC
CD8 T cells
NK cells
NKT
CXCL10
CCR6
ILC3
ILC3
CCR6
IL-12
Melanoma
IL-1β
Lung cancer

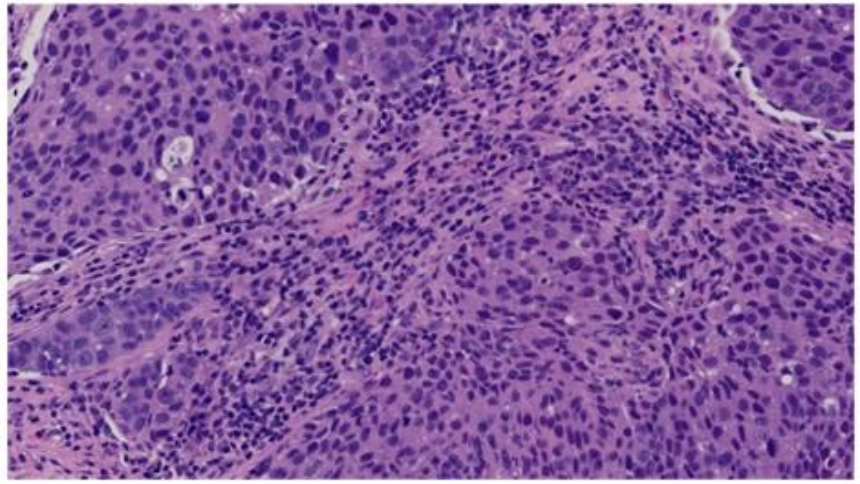
The quality of the lymphoid intratumor population is key for the response to treatments

HER2 + breast cancer : before treatment with chemo and trastuzumab

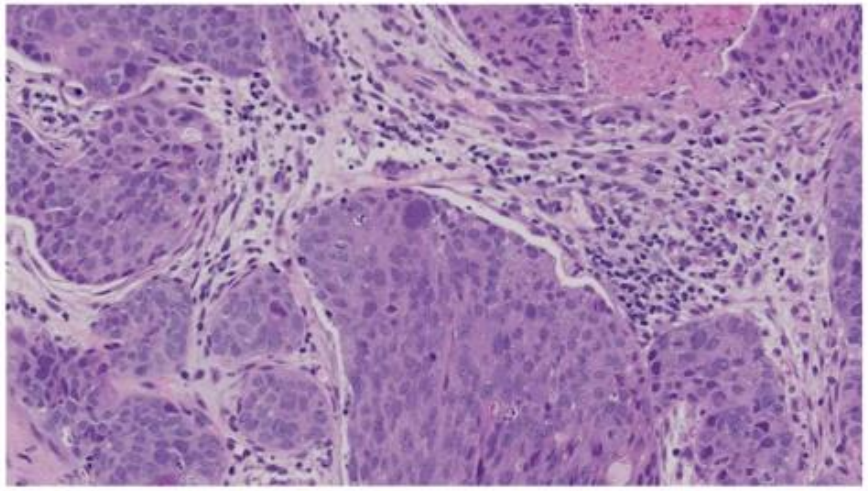
Low grade (TILs, 0% to 10%)

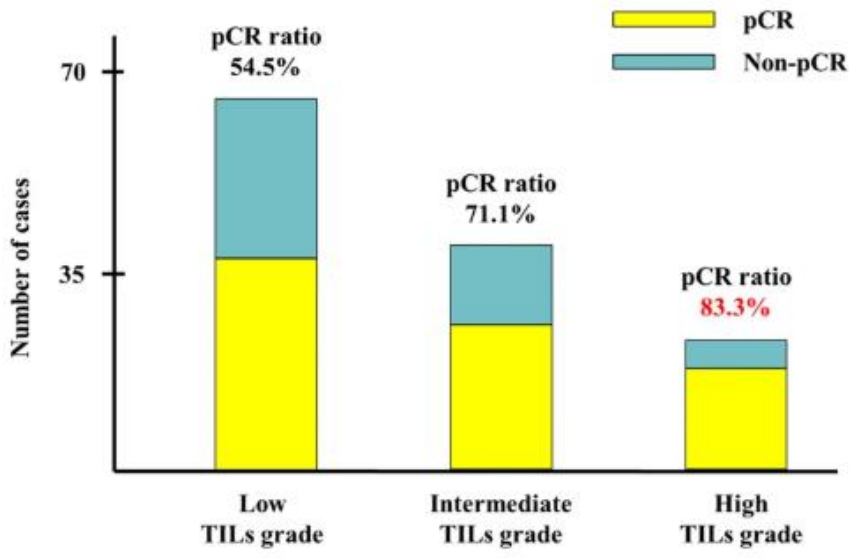


High grade (TILs, 40% to 90%)



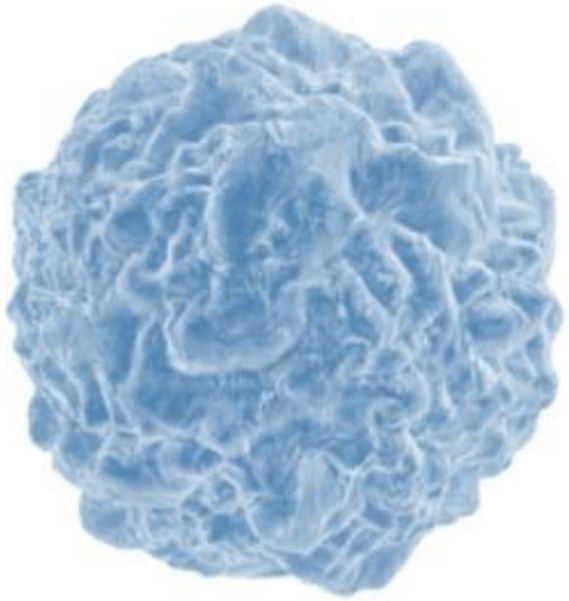
Intermediate grade (TILs, 10% to 40%)





Kurozumi et al, Scientific reports 2019

Cold tumor
Little to no lymphocytes



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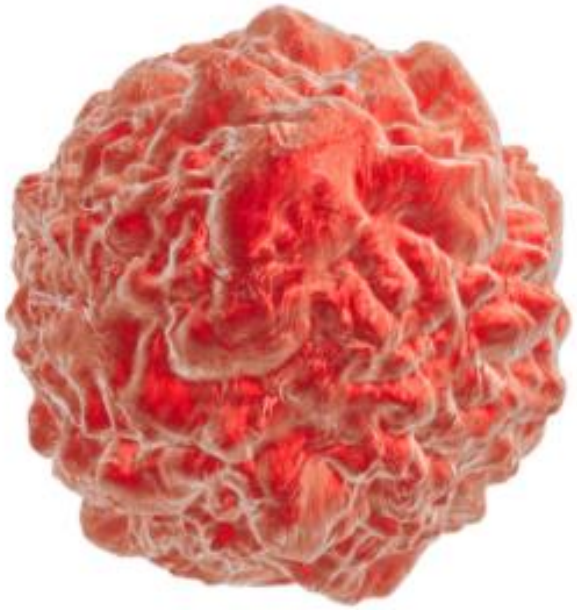
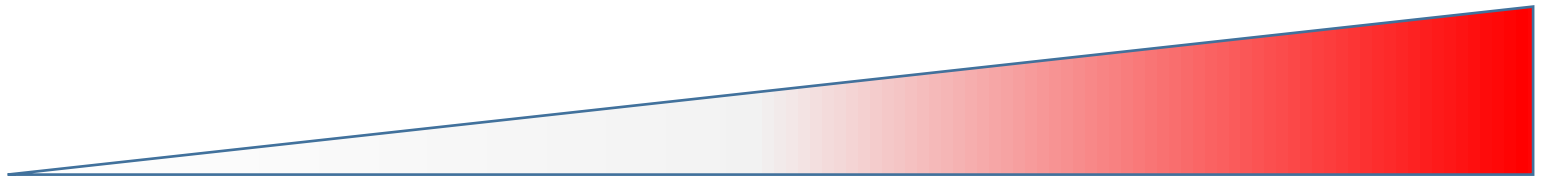
Hot tumor
Strong lymphocytes population

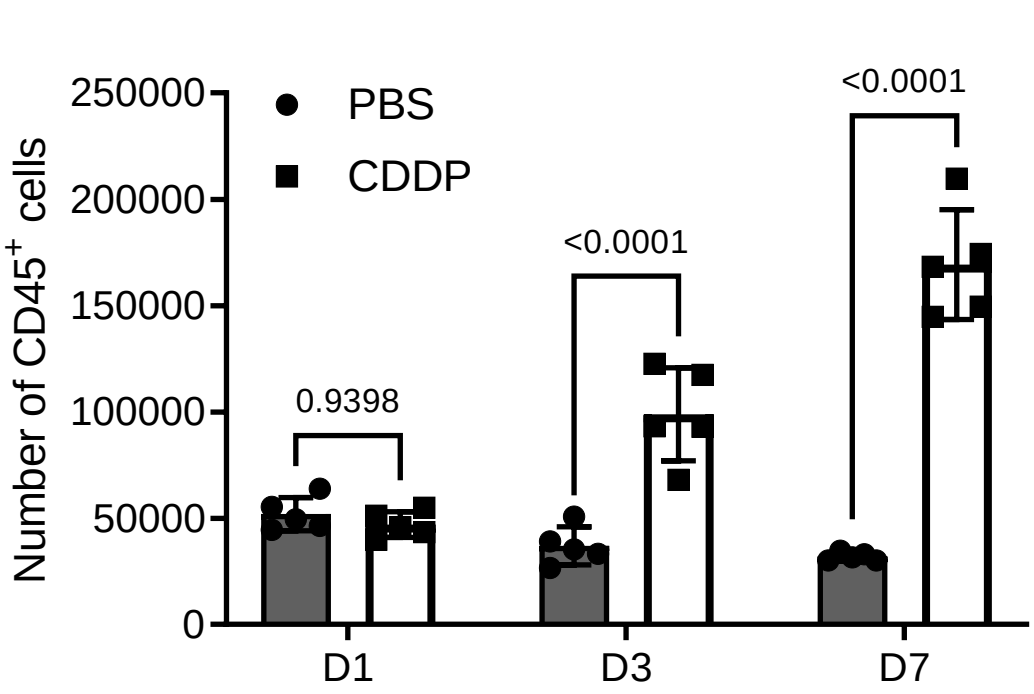


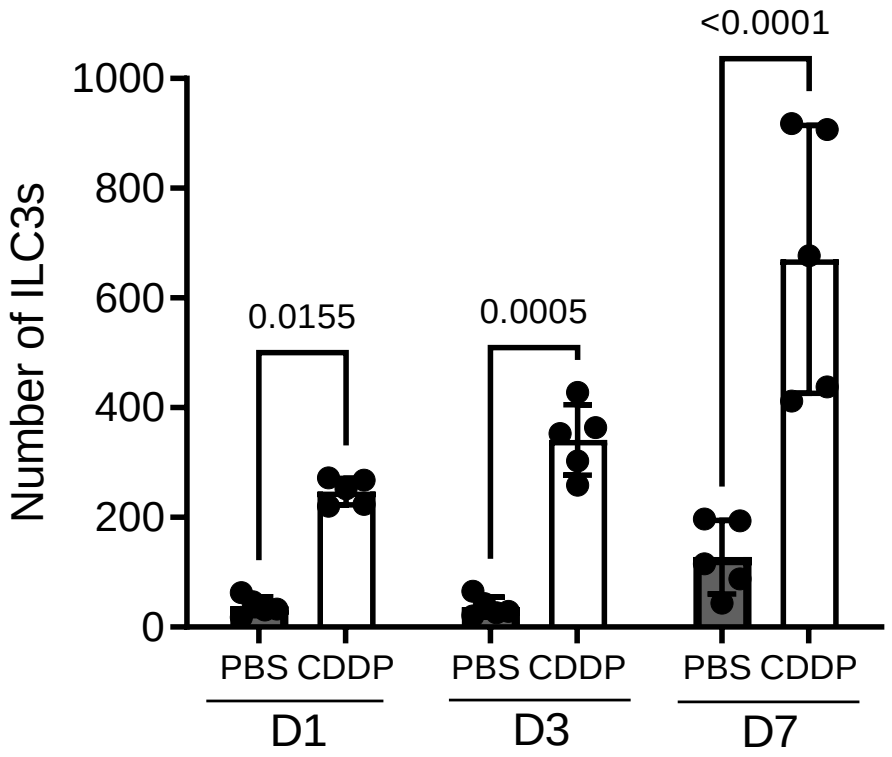


Response to treatments

Cisplatin induces a massive immune recruitment to the tumor

Lung cancer TC-1 treated by cisplatin





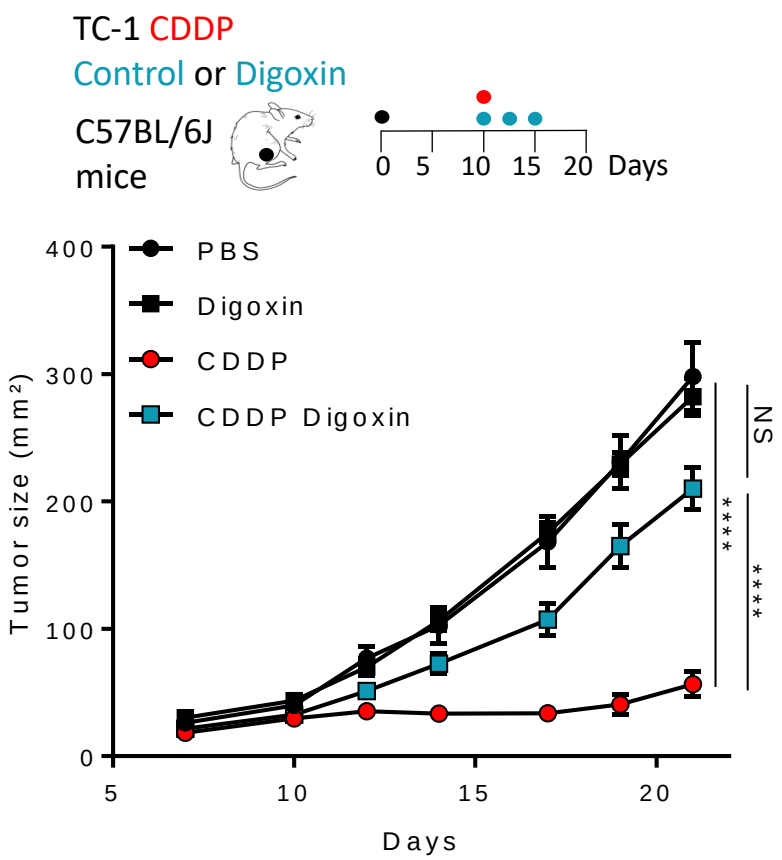
→ ILC3 are the only cell type increased 1 day after CDDP

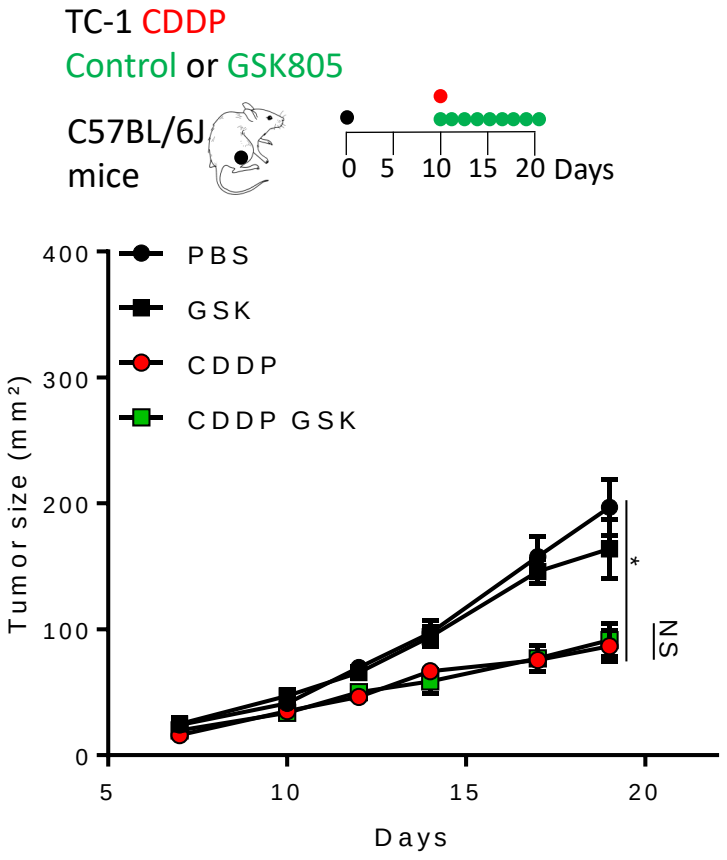
Bruchard M *et al,* Nature Immunology, 2022

ILC3 are essential for CDDP antitumor efficacy

→ RORγt is a major transcription factor for ILC3s and Th17

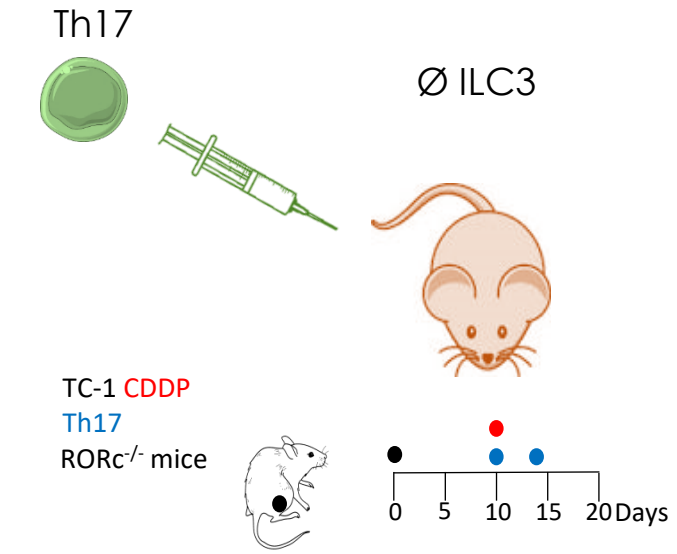
Digoxin : RORγt inhibitor → targets ILC3 and Th17
GSK805: RORγt inhibitor → targets specifically Th17 w/o affecting ILC3 in tumors

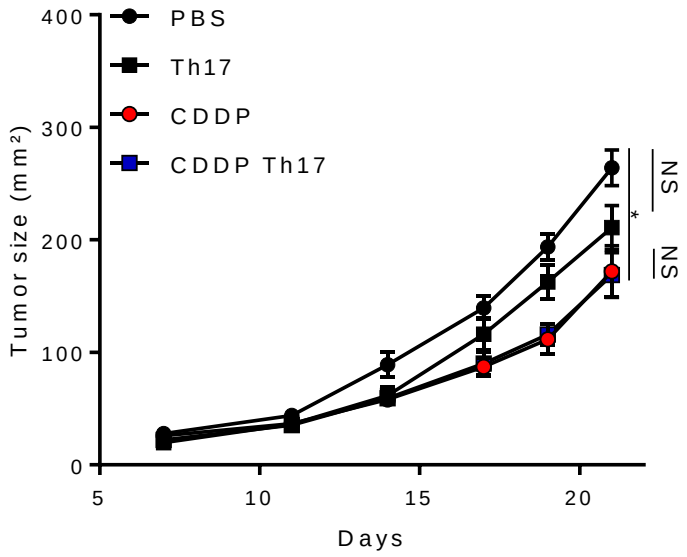


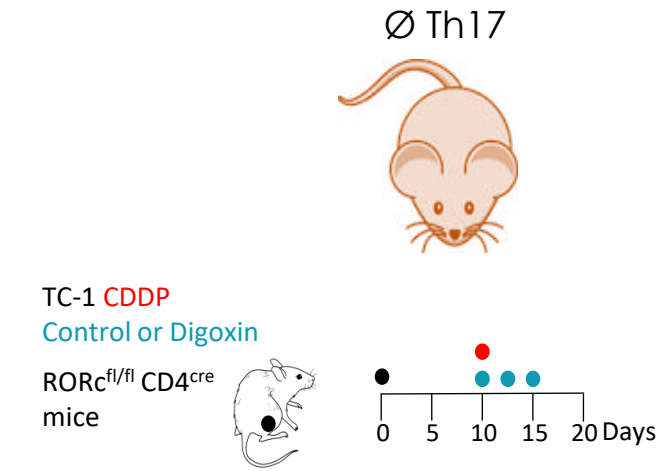


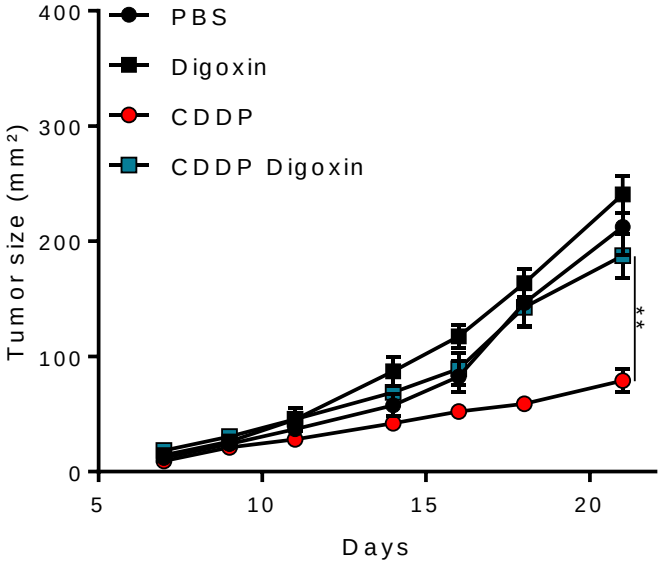
→ Th17 cells are not important for CDDP anti-tumor efficacy.

ILC3 are essential for CDDP antitumor efficacy



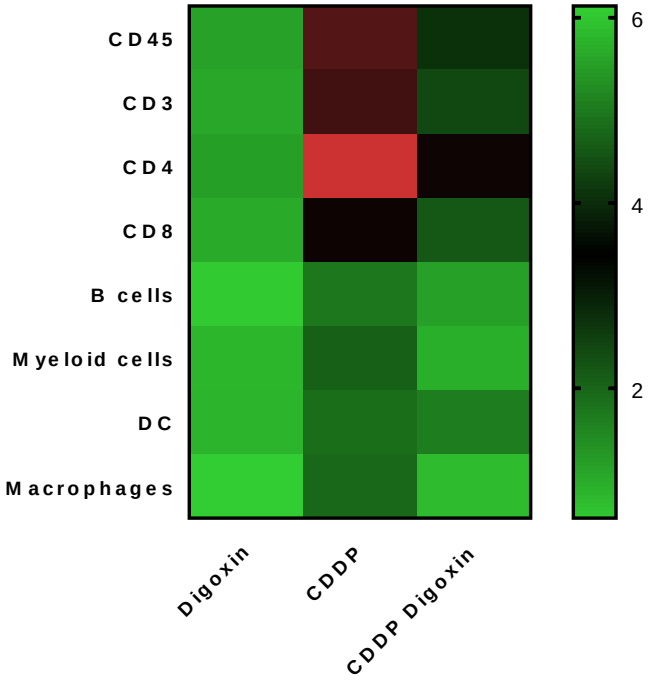


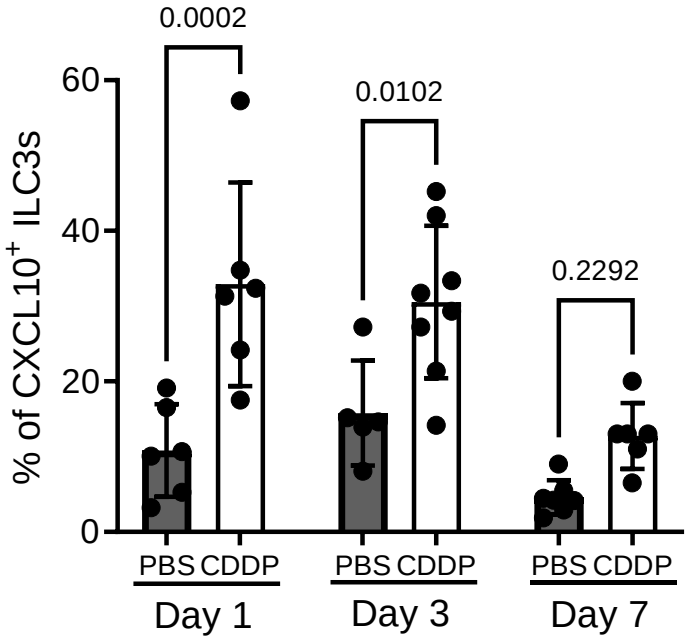




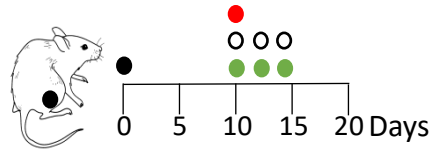
→ Absence of ILC3 limits CDDP anti-tumor efficacy.

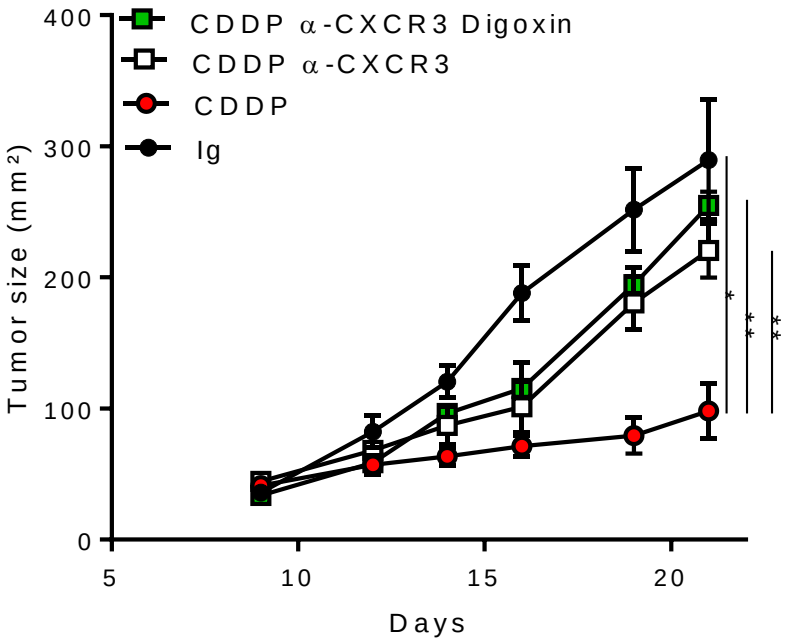
Why are the ILC3 important for Cisplatin's efficacy?





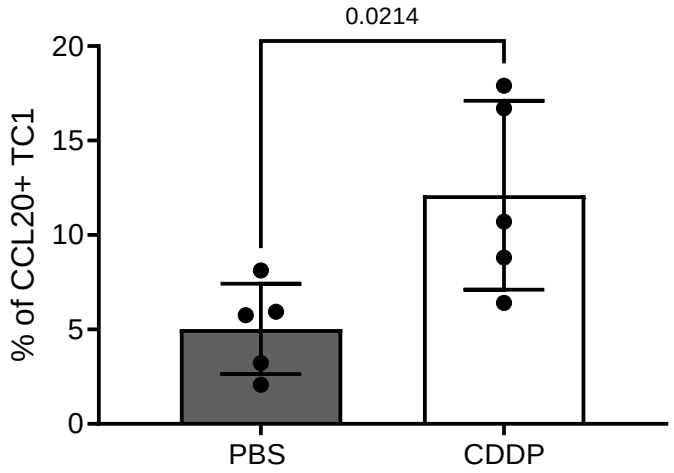
TC-1 CDDP
Control or Digoxin and/or isotype or anti-CXCR3

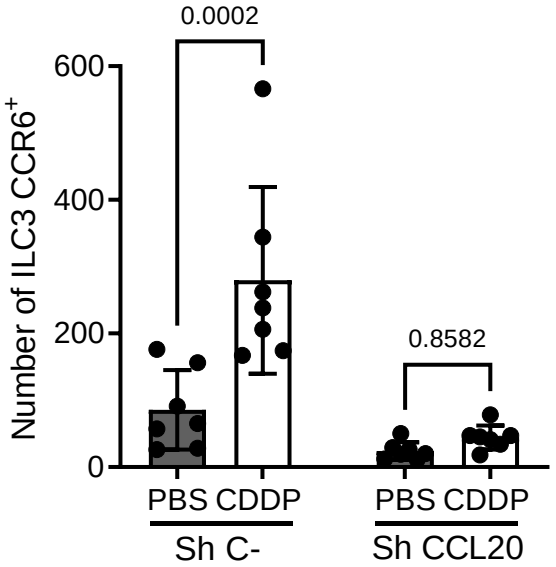


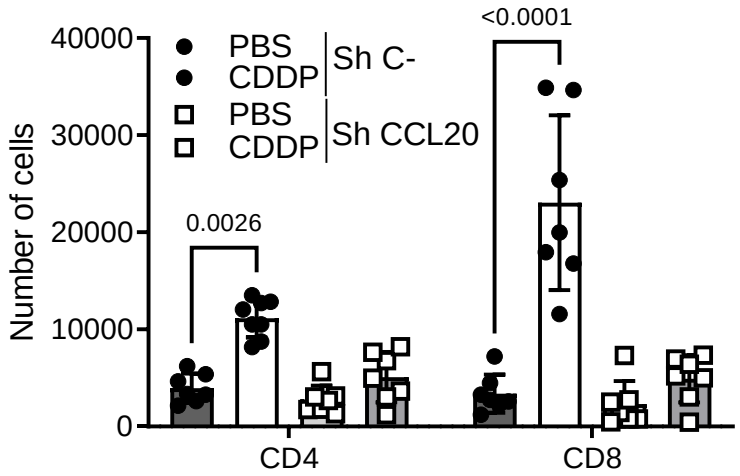


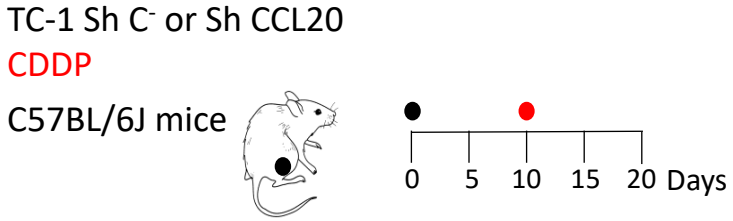
→ The CXCL10/CXCR3 axis is important in CDDP efficiency.
→ No additional effect is observed with combination a CXCR3+ Digoxin : suggest they act in the same cascade of events

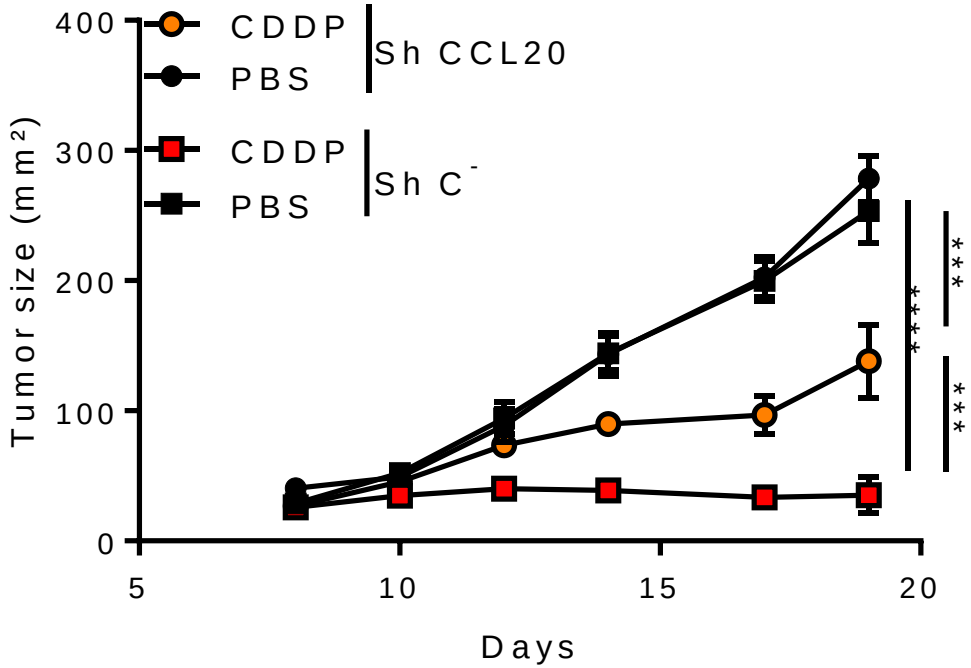
Why are ILC3 increased after CDDP?







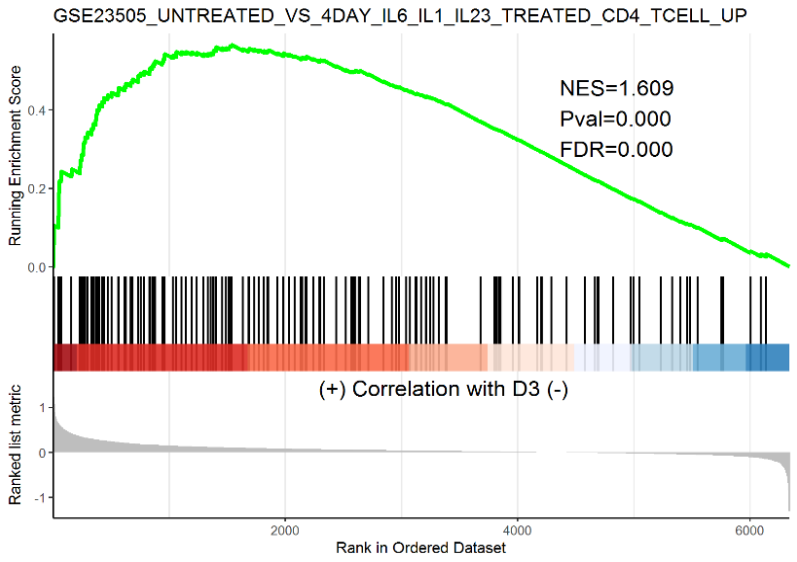




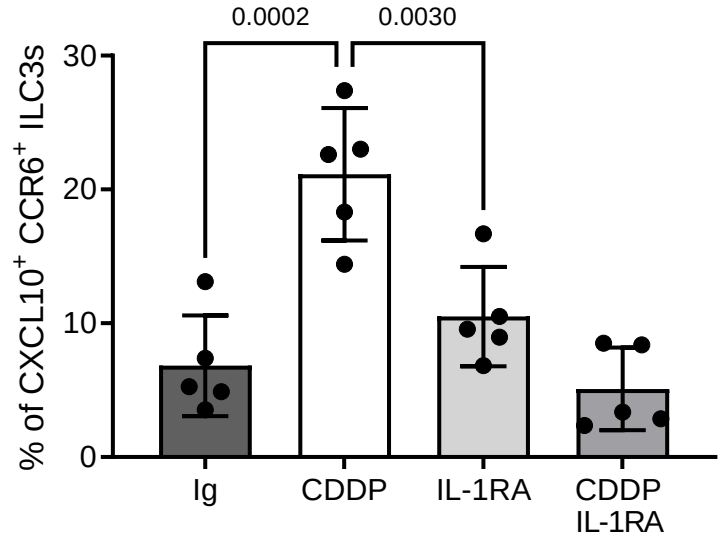
→ CCL20 produced by TC-1 cells attracts ILC3 to the tumor after CDDP

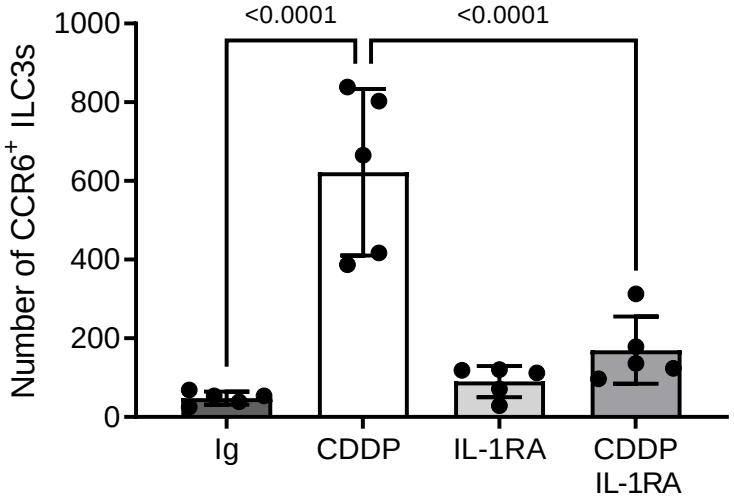
IL-1β activates ILC3 in the tumor

GSEA on single cell RNA seq data
ILC from CDDP treated TC-1 tumors



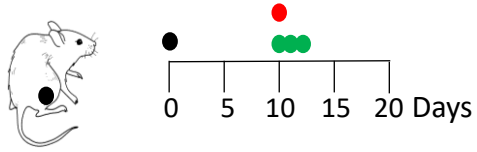
enrichment of the IL1R module in the CCR6⁺ ILC3 cluster

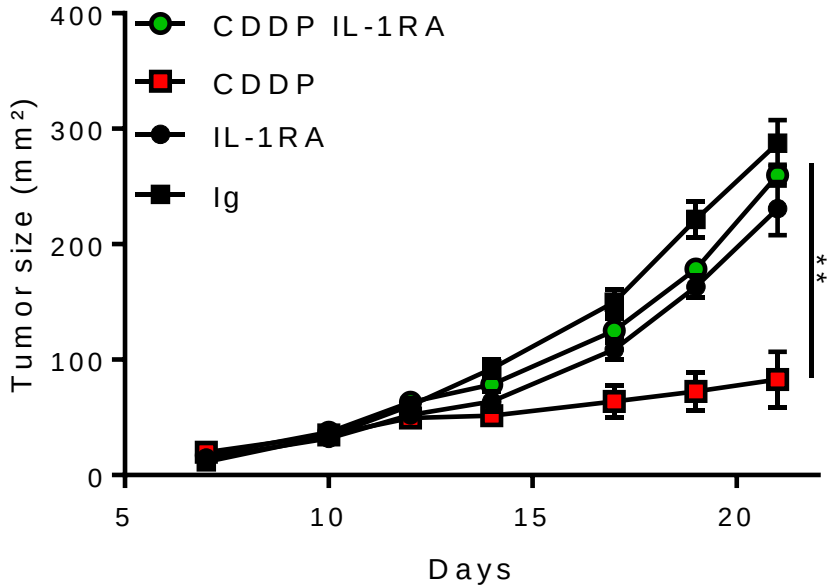




TC-1 CDDP
Isotype or IL-1RA

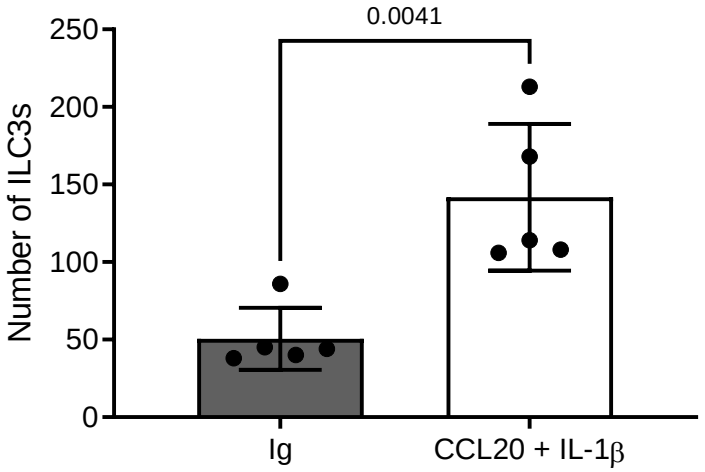
C57BL/6J mice

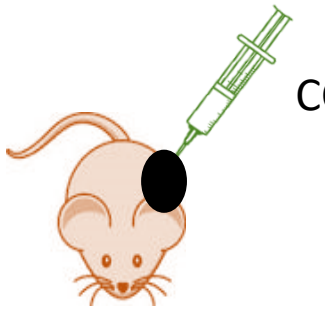




→ IL-1β increases ILC3's activation, production of CXCL10 and proliferation and is essential for the cisplatin's efficacy

CCL20 and IL-1β are sufficient to increase immune infiltration to the tumor

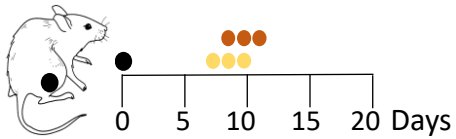


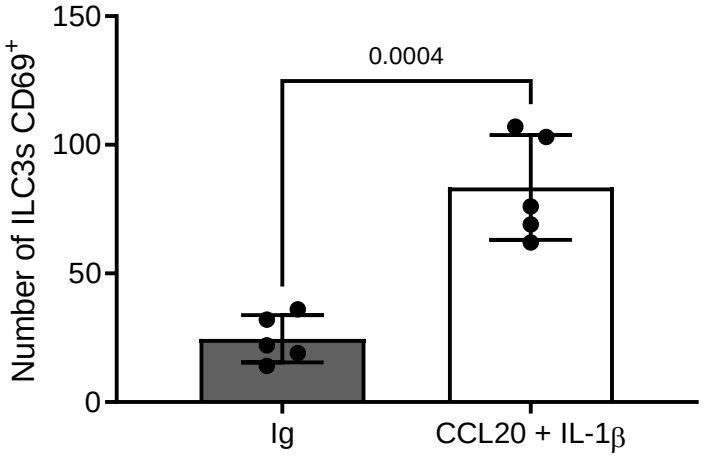


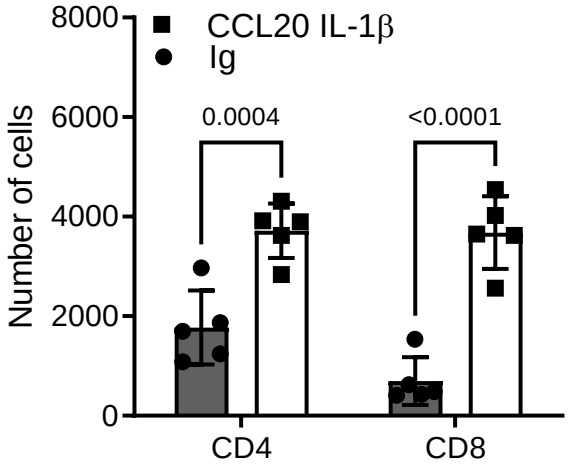
CCL20 + IL-1β

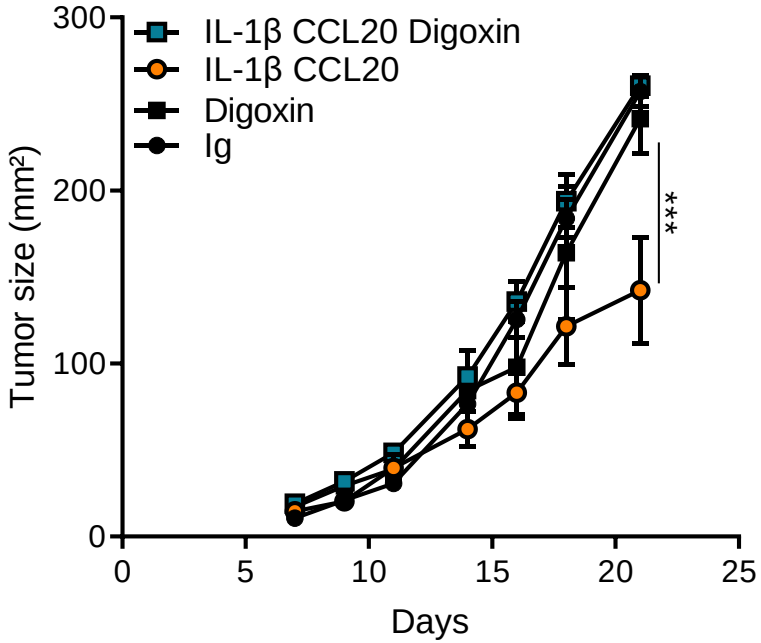
TC-1
isotype or CCL20 and IL-1β and/or Digoxin

C57BL/6J mice



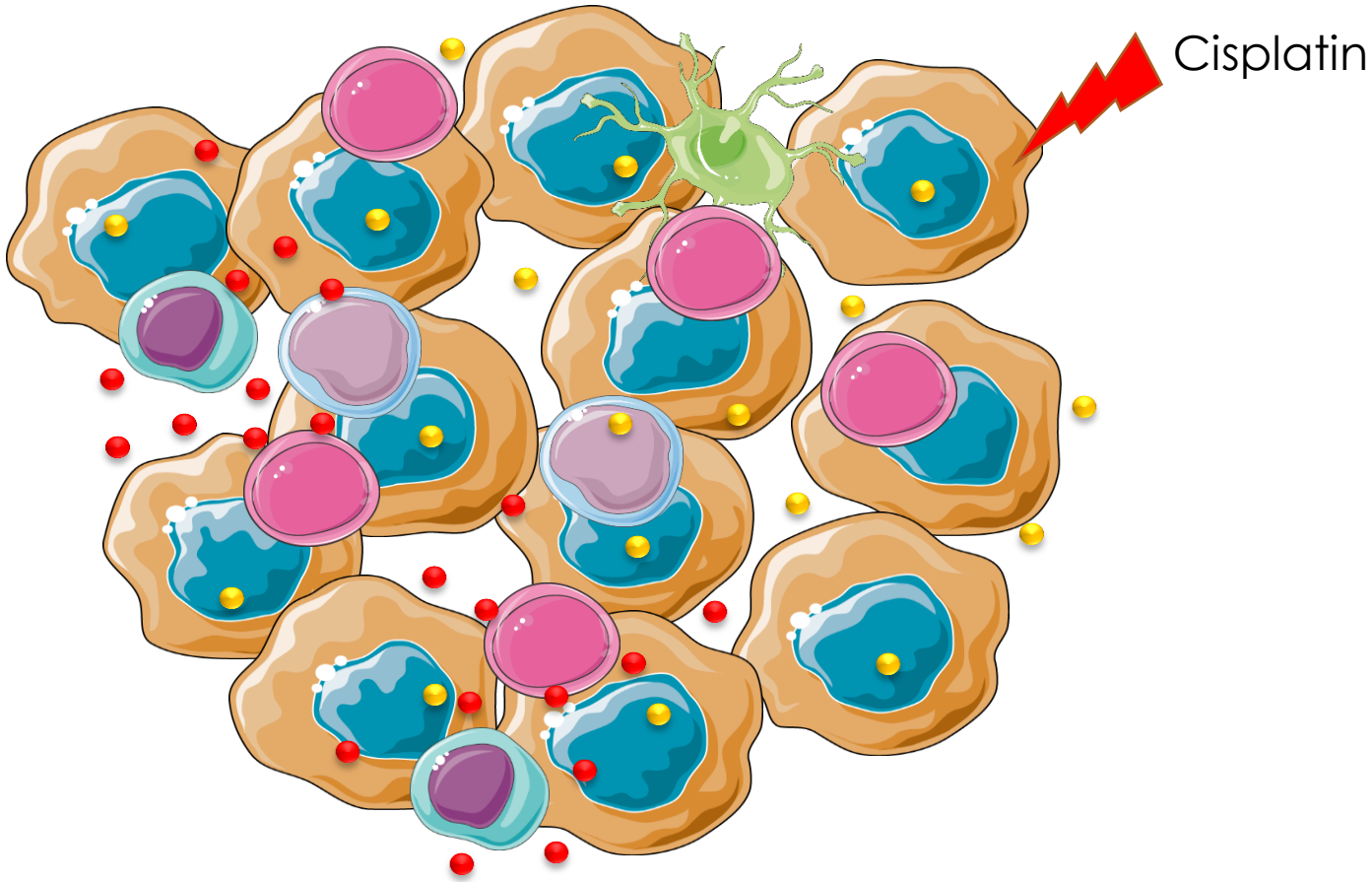






→ CCL20 and IL-1β injections trigger an ILC3 increase and activation leading to reduced tumor growth.

Conclusion



Tumor cell

CCL20

Dendritic cell

Lymphocyte

ILC3

IL-1β

Myeloid cell

ILC3s : crucial role

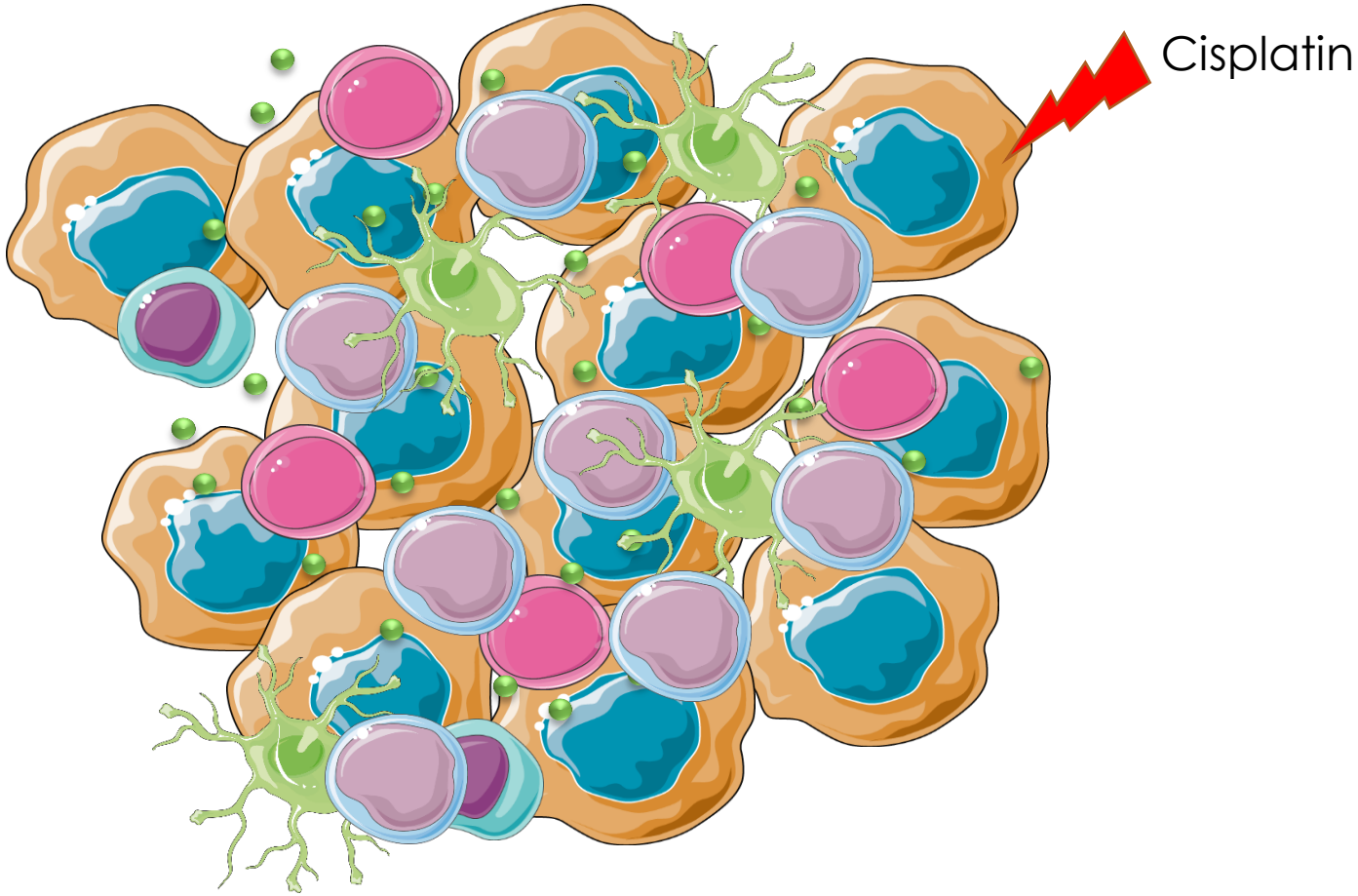
→ first population increased

→ recruited and activated by CCL20 and IL-1β

→ mimic the immune effect of cisplatin

Bruchard M *et al,* Nature Immunology, 2022

Conclusion



Tumor cell

Dendritic cell

Lymphocyte

ILC3

CXCL10

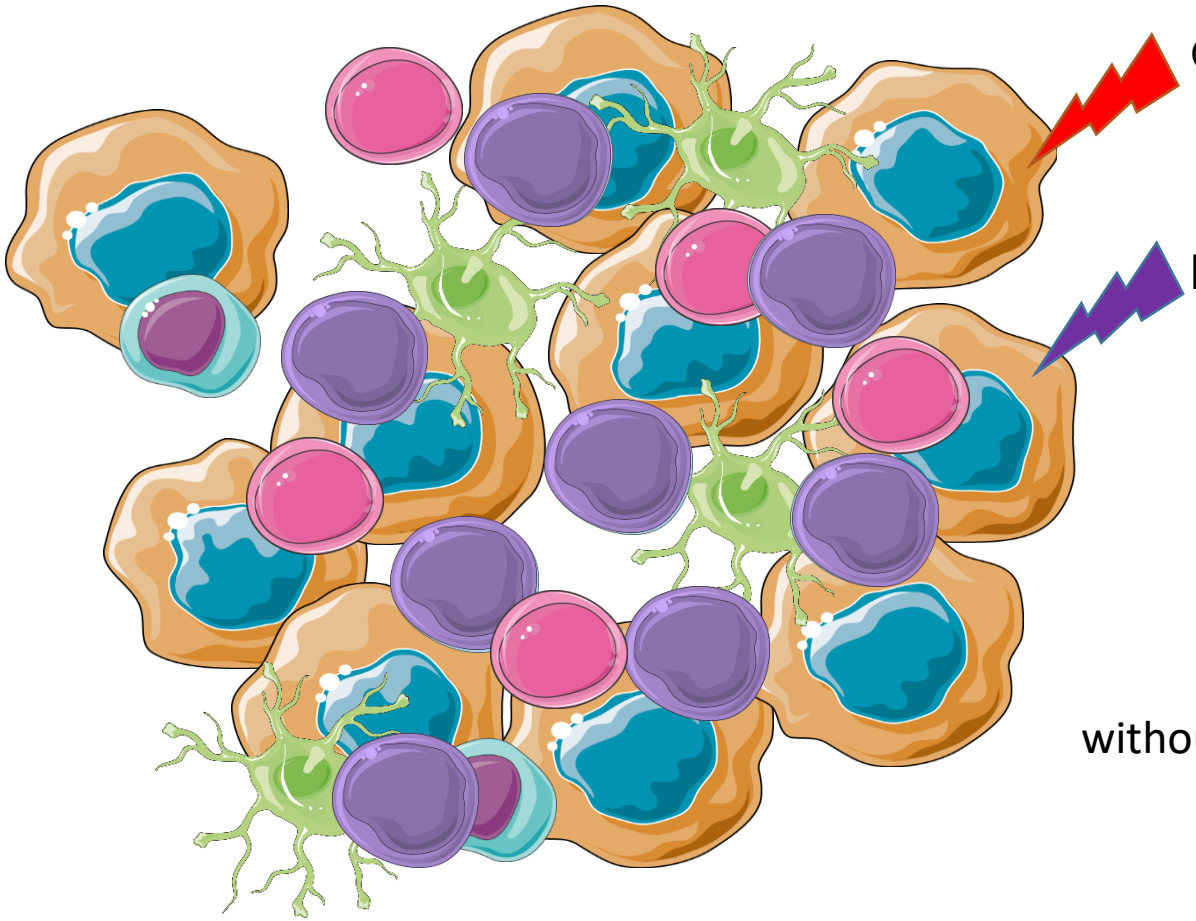
Myeloid cell

ILC3 produce CXCL10

→ attracts CXCR3+ cells (CD8 T lymphocytes, Th1, NK…)

Bruchard M *et al,* Nature Immunology, 2022

Conclusion



Tumor cell

Dendritic cell

Lymphocyte

ILC3

Myeloid cell

without ILC3 : reduced antitumor efficacy
Ø synergy with ICI

ILC3 could become an interesting tool to increase the immune infiltrate of a tumor
→ increase the patients chances to respond to treatments

Bruchard M *et al,* Nature Immunology, 2022

Thanks to

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