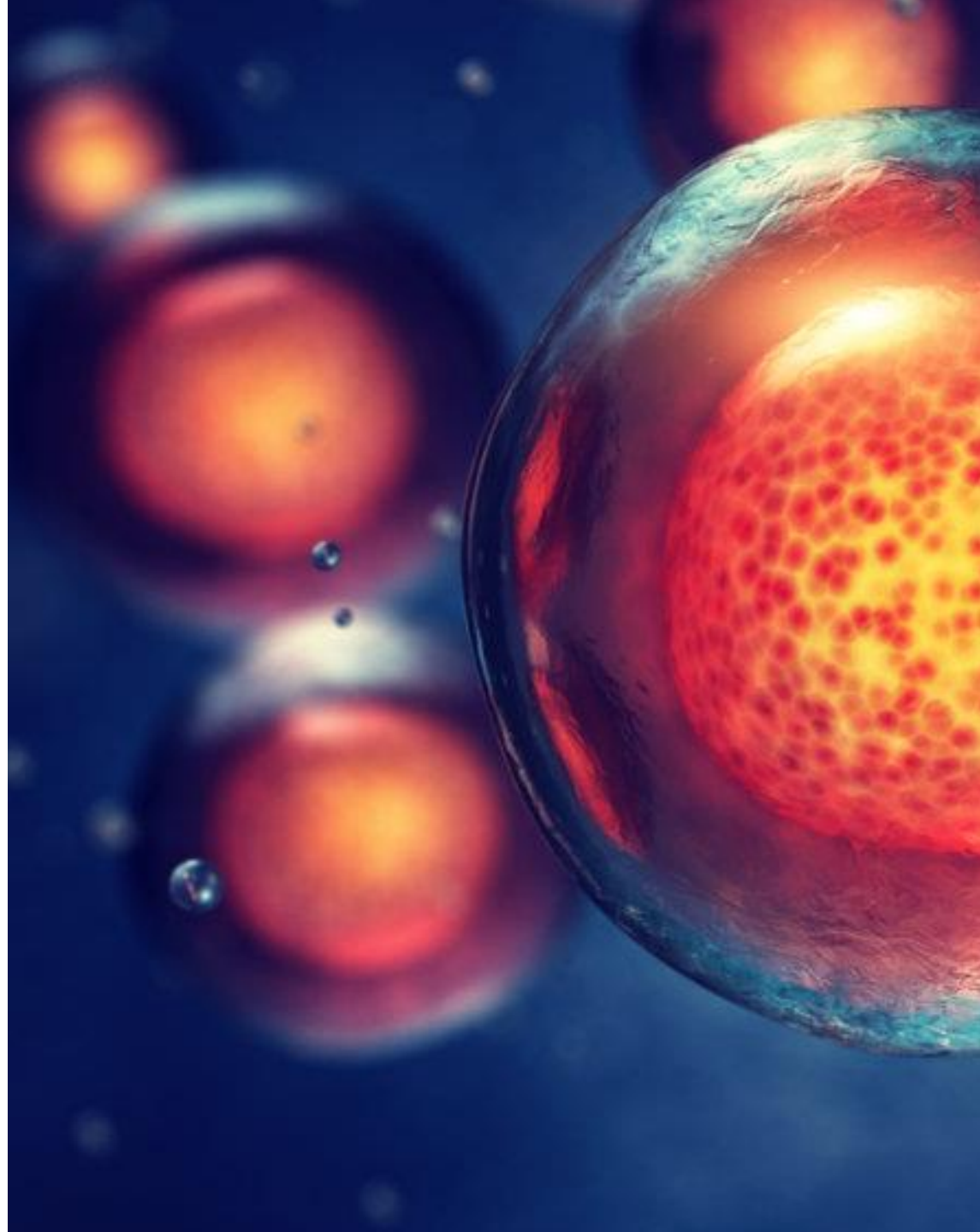


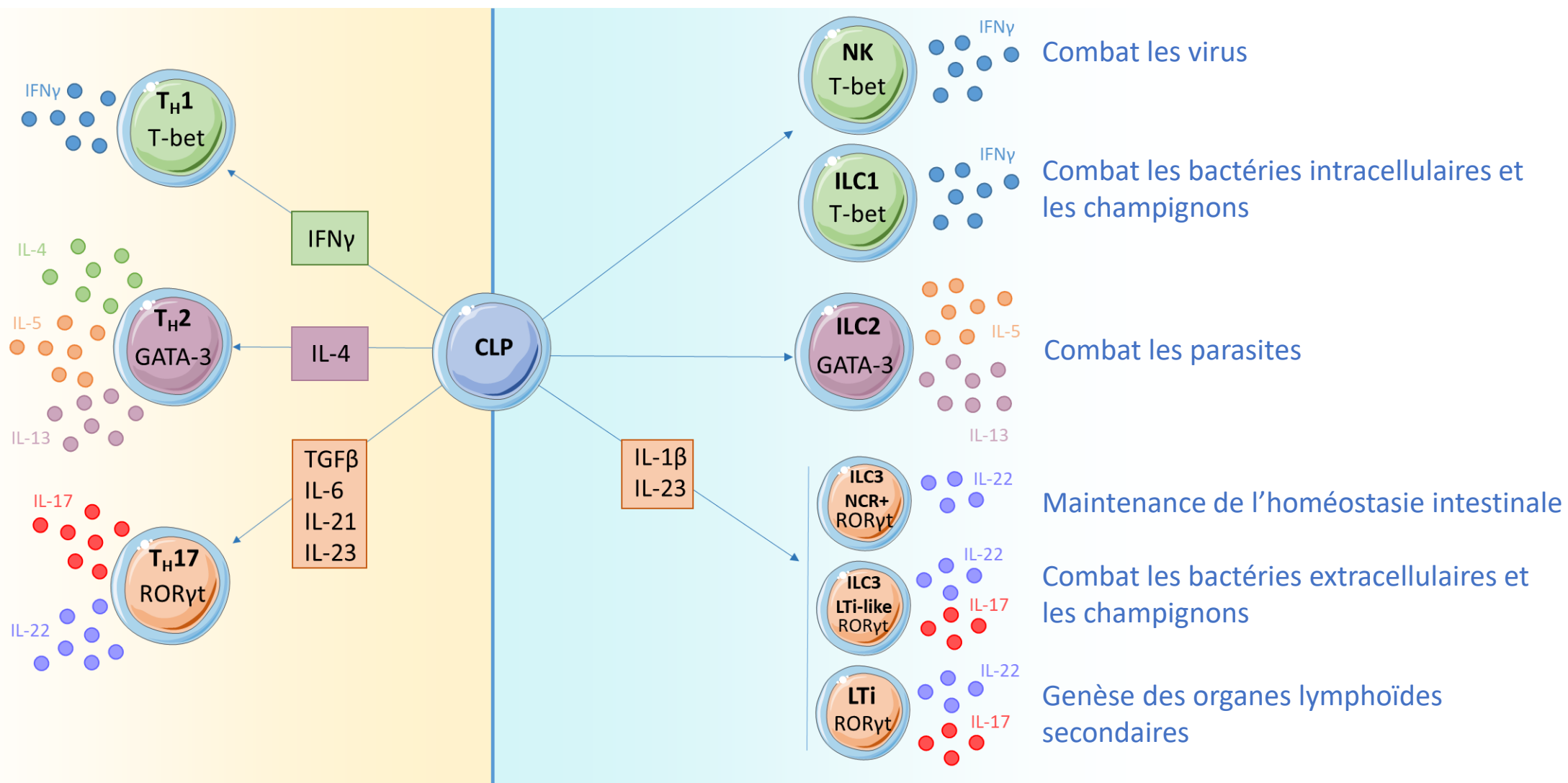
Les ILC3, nouveaux acteurs dans la réponse immunitaire antitumorale

Mélanie Bruchard, PhD

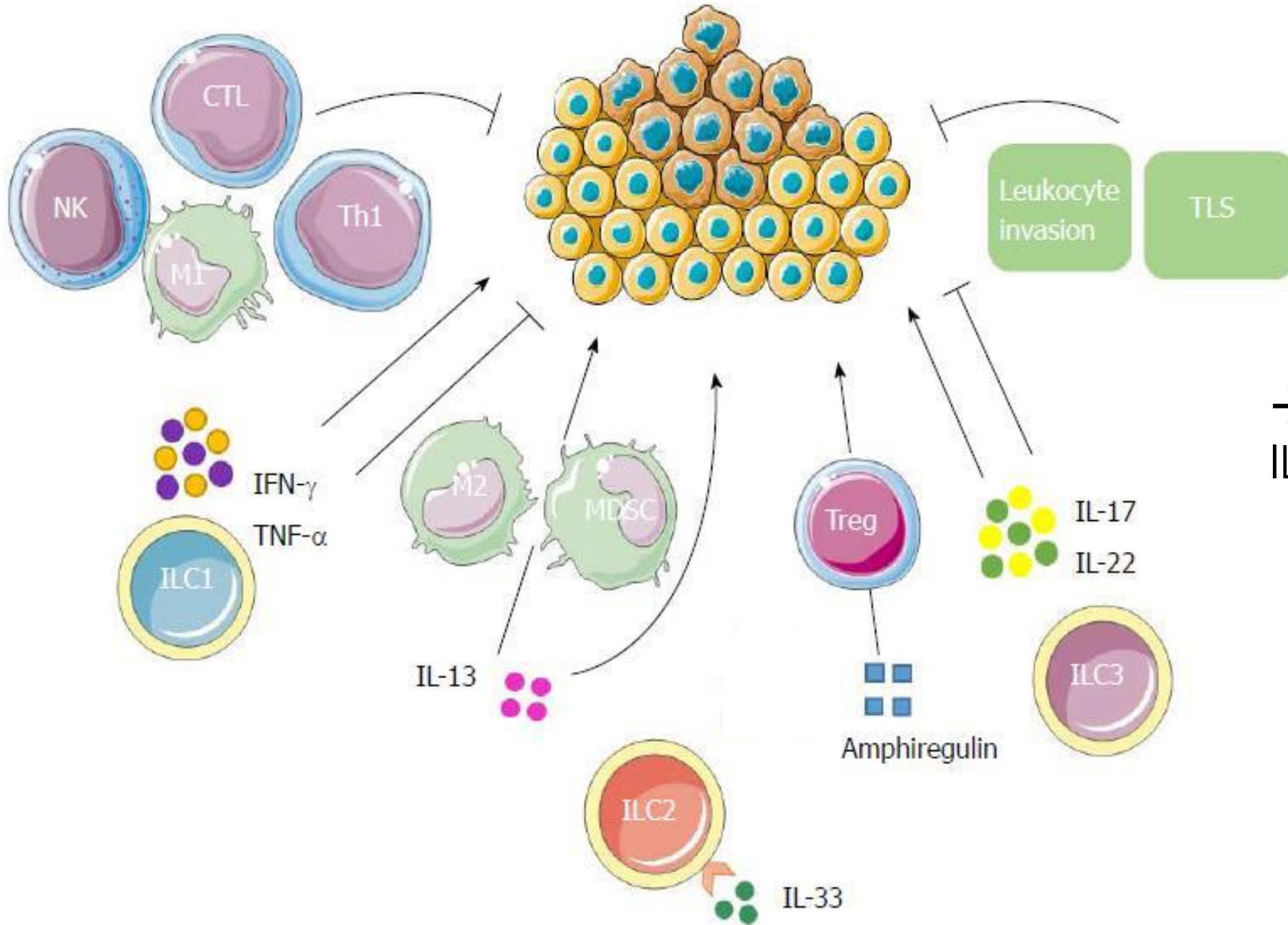
melanie.bruchard@gmail.com



Innate lymphoid cells (ILC) : les nouveaux acteurs de l'immunité innée



ILC et cancer

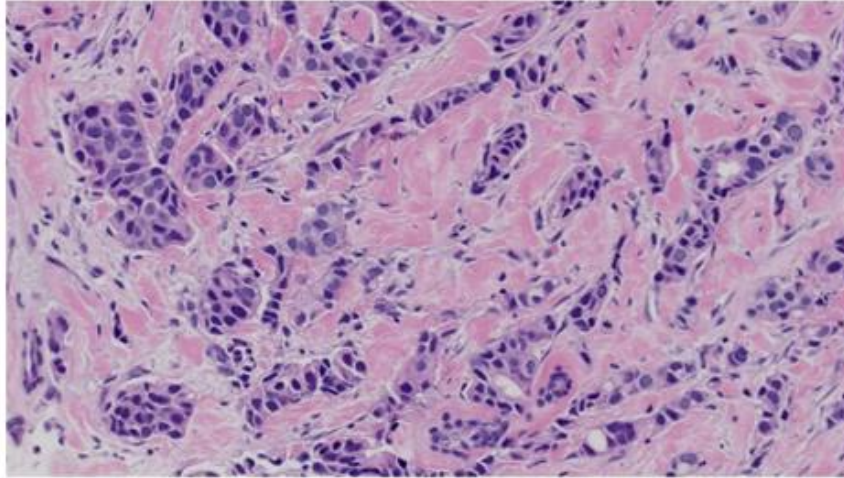


→ Importance des ILCs après traitement?

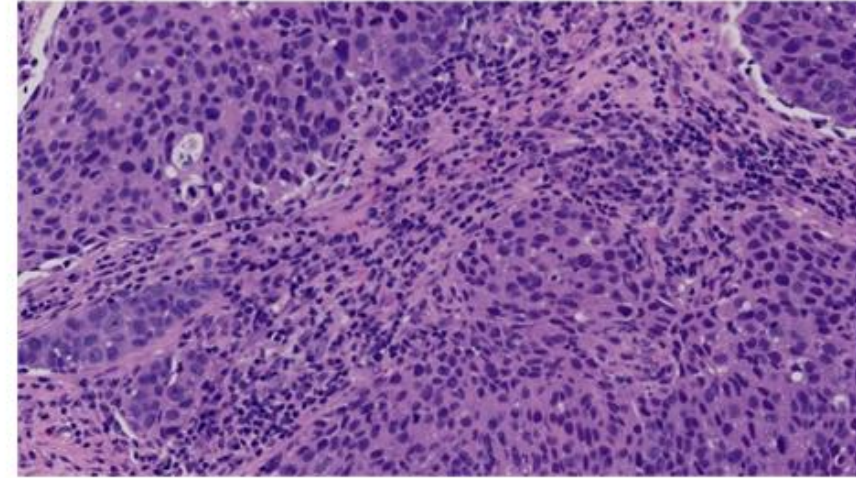
La qualité de l'infiltrat lymphoïde intratumoral est clé dans l'établissement d'une réponse aux traitements

Cancer du sein HER2 +

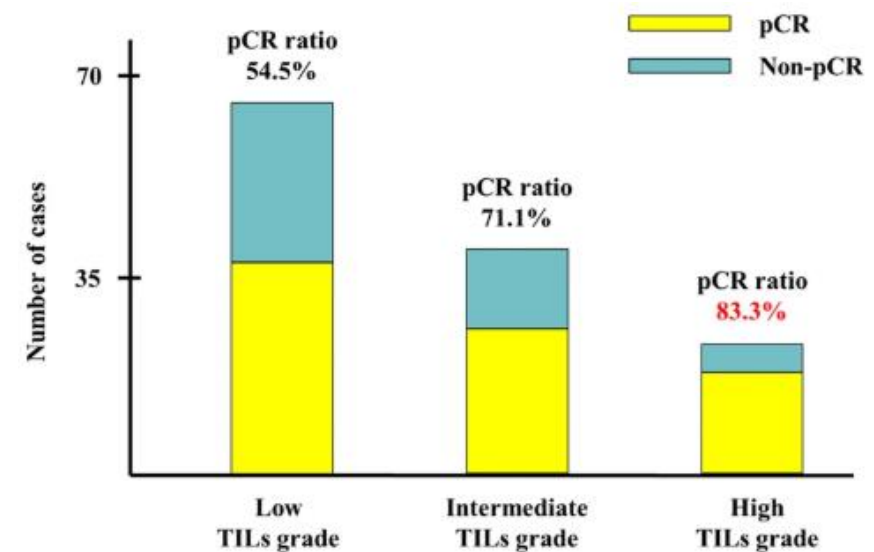
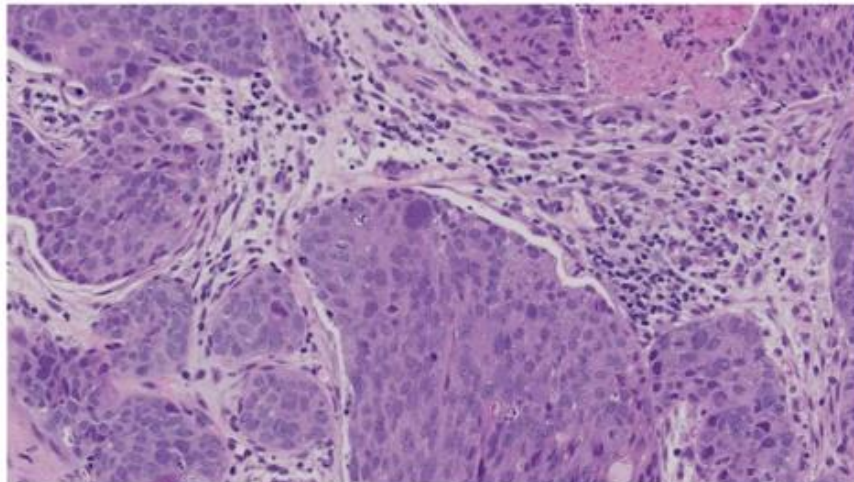
Low grade (TILs, 0% to 10%)



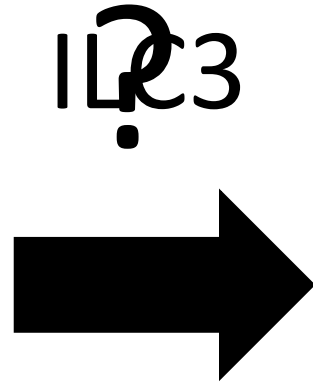
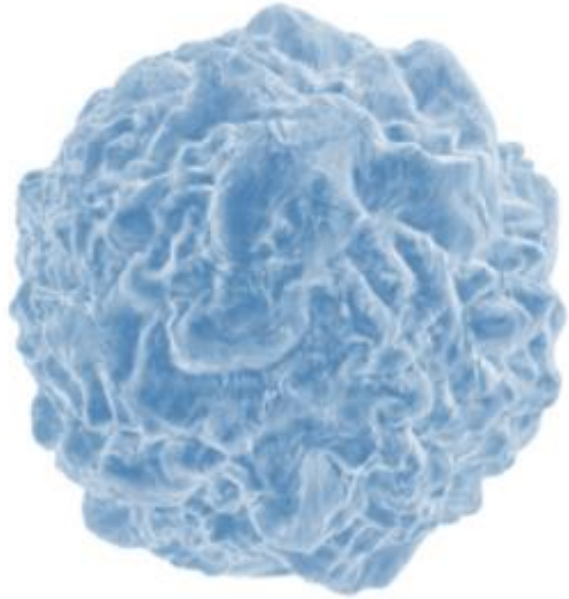
High grade (TILs, 40% to 90%)



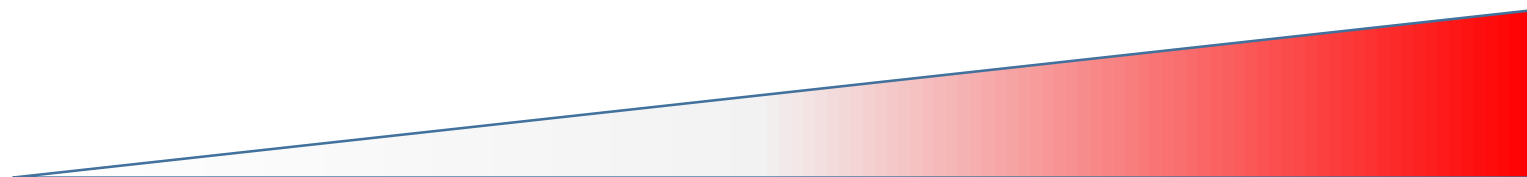
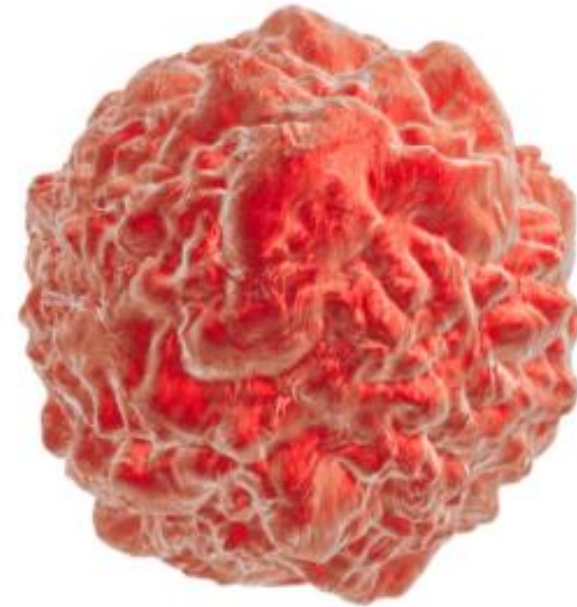
Intermediate grade (TILs, 10% to 40%)



Tumeur froide
Pas ou peu de lymphocytes



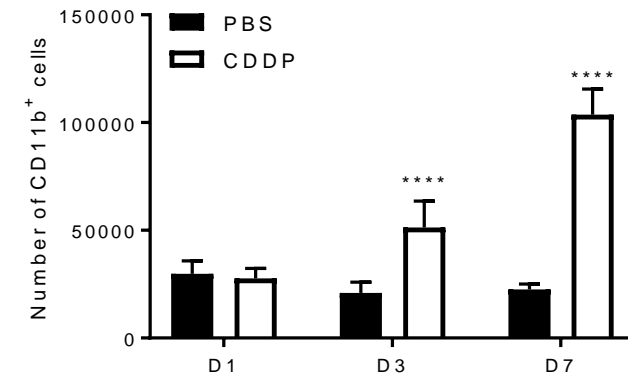
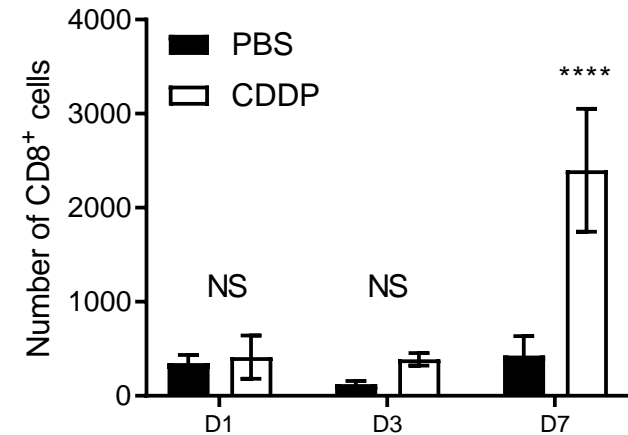
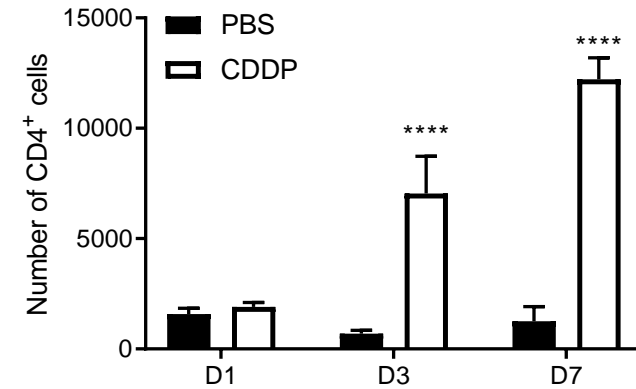
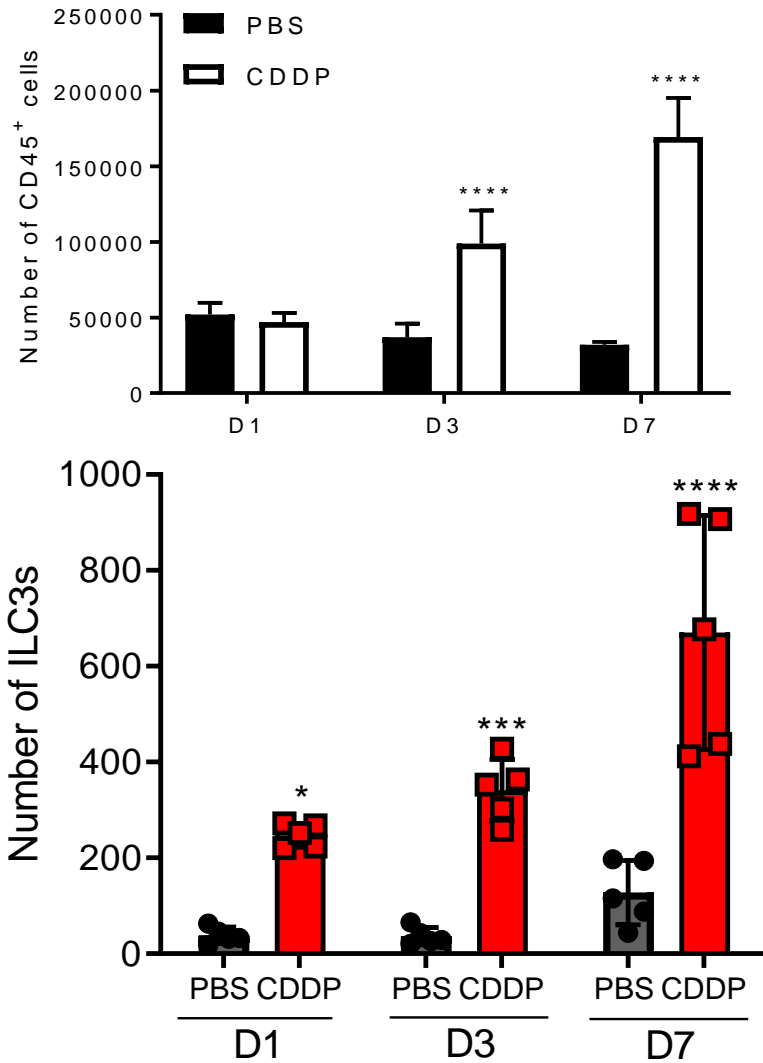
Tumeur chaude
population de lymphocytes importante



Reponse aux traitements

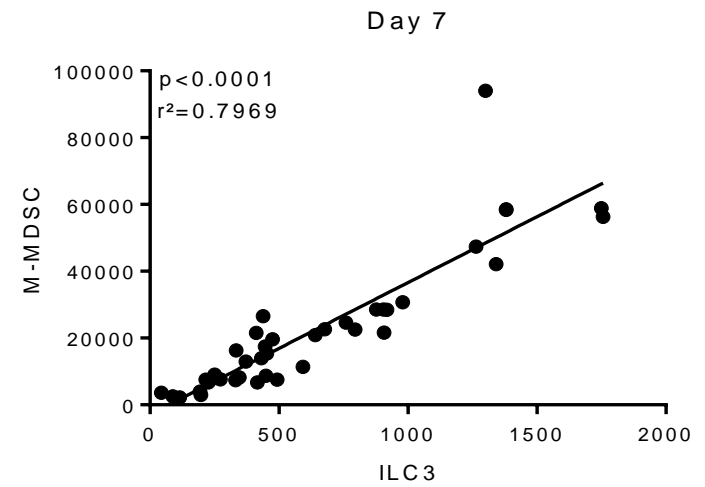
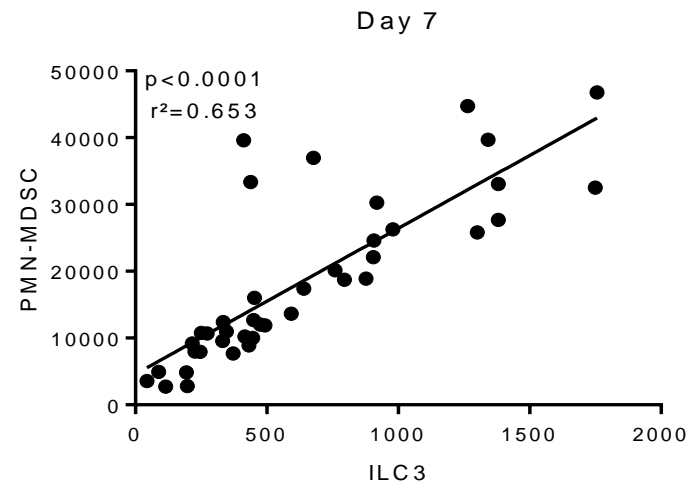
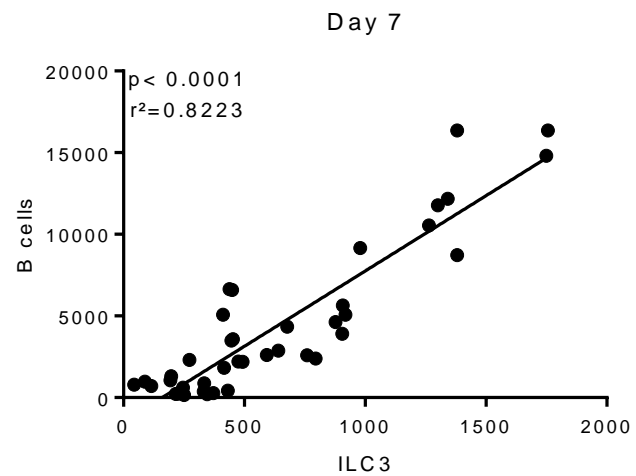
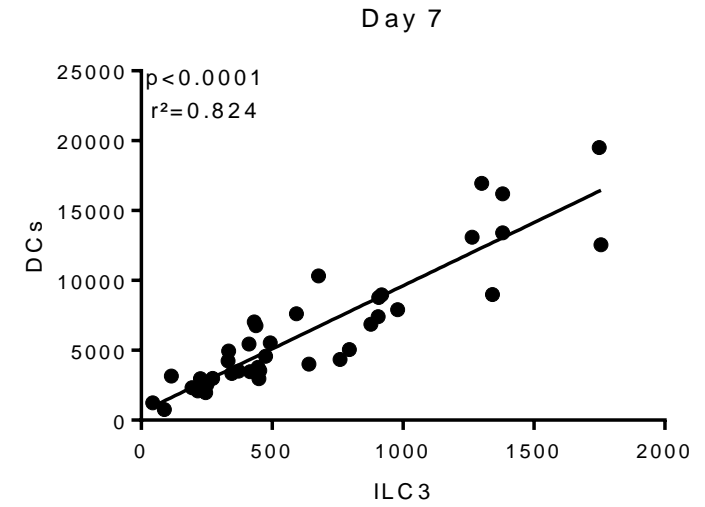
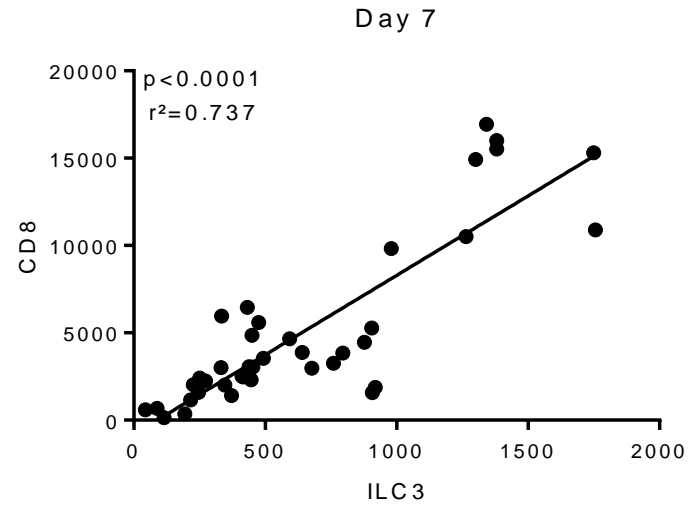
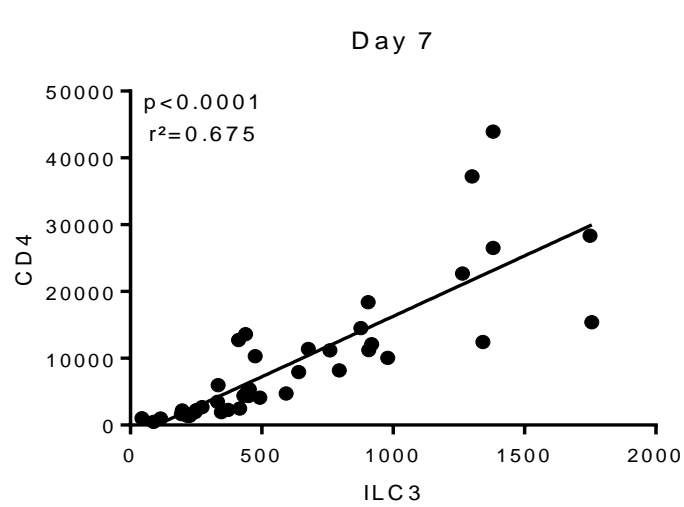
Le cisplatine induit un recrutement immunitaire massif à la tumeur

Cancer du poumon TC-1 traité par cisplatine (CDDP)



→ Les ILC3 sont les seules cellules immunitaires augmentées 1 jour après traitement

Correlation positive entre ILC3 et autres cellules immunitaires dans la tumeur



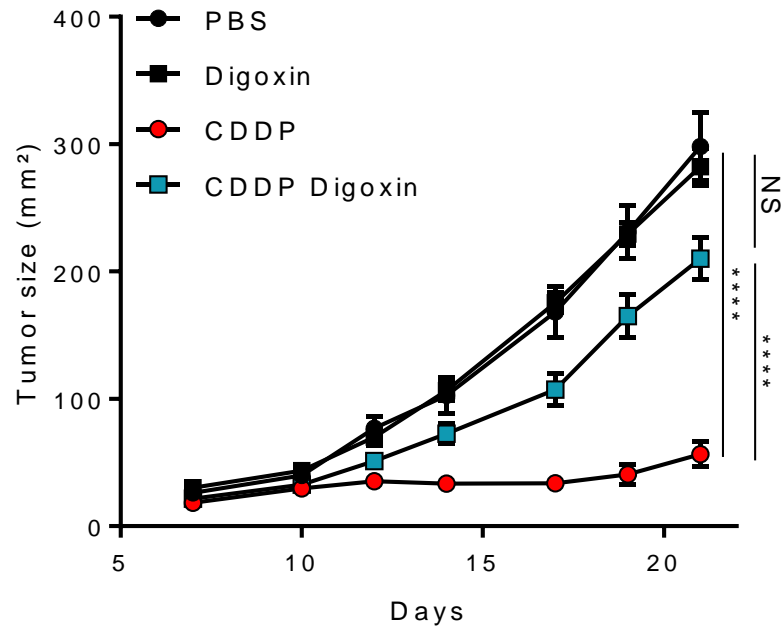
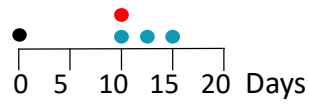
Les ILC3 sont essentielles pour l'efficacité antitumorale du Cisplatine

→ RORγt est un facteur de transcription majeur pour les ILC3 et les Th17

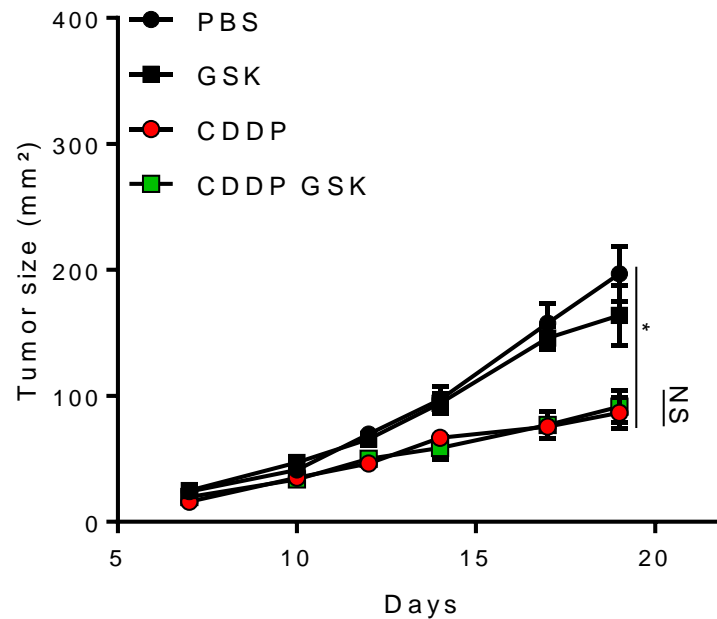
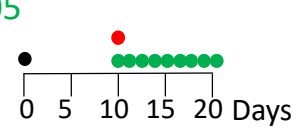
Digoxin : inhibiteur de RORγt → cible les ILC3 et les Th17

GSK805: inhibiteur de RORγt → cible spécifiquement les Th17 sans affecter les ILC3

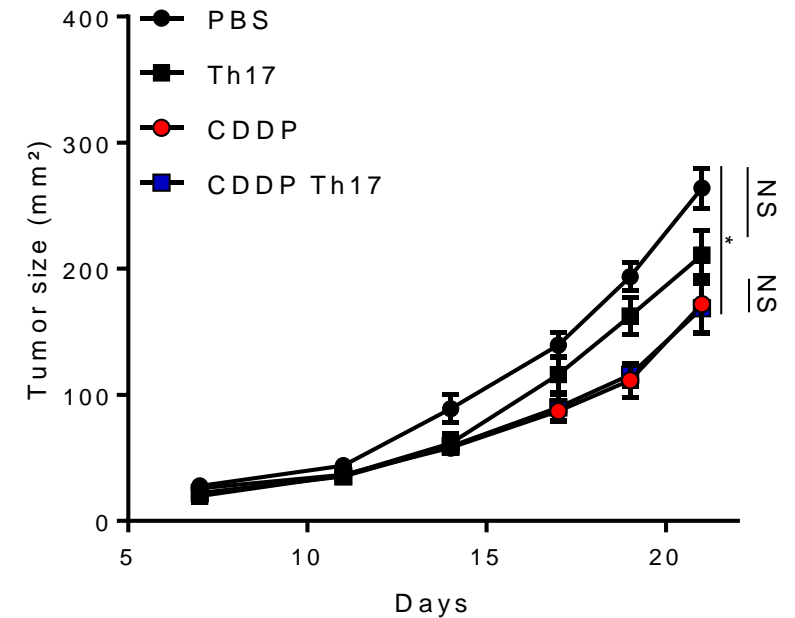
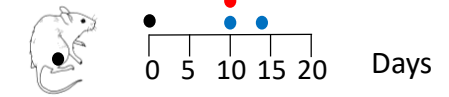
TC-1 CDDP
Control or Digoxin
C57BL/6J mice



TC-1 CDDP
Control or GSK805
C57BL/6J mice



TC-1 CDDP
Th17
RORc^{-/-} mice



→ L'absence d'ILC3 limite l'efficacité du cisplatine.

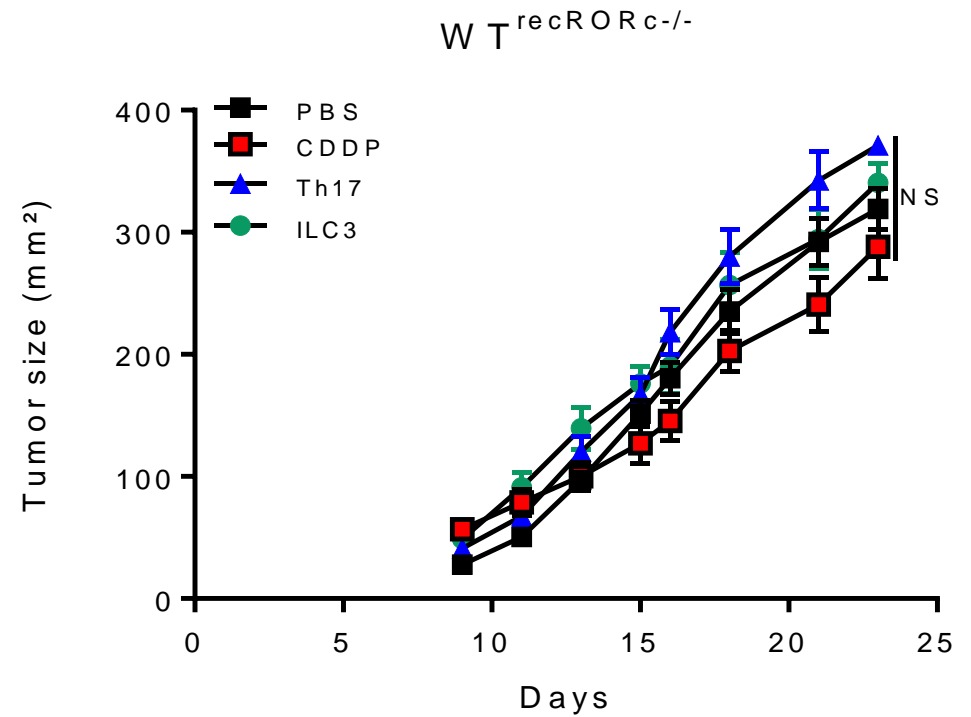
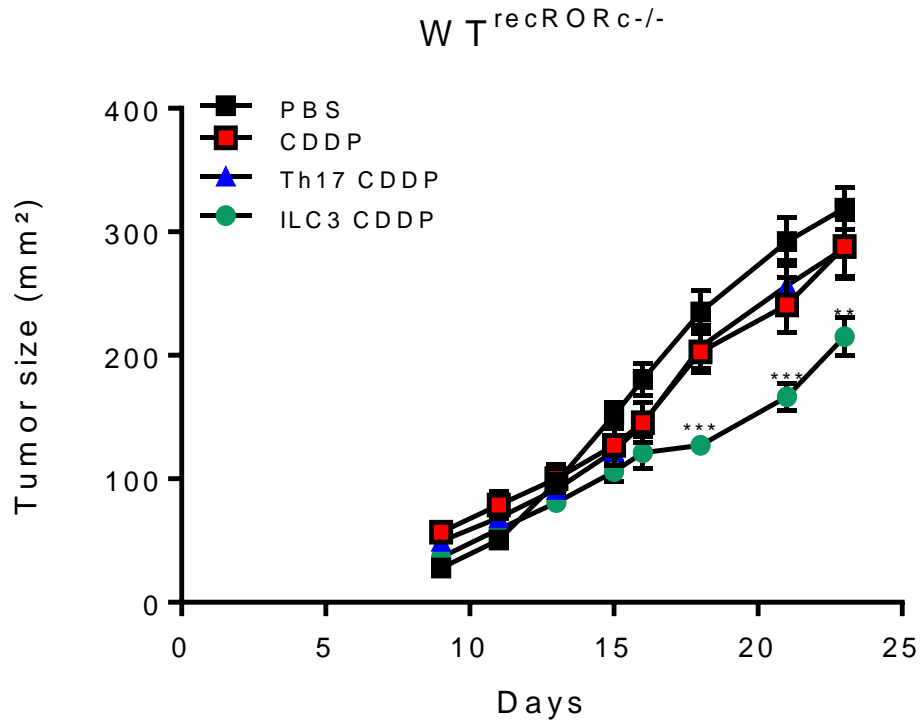
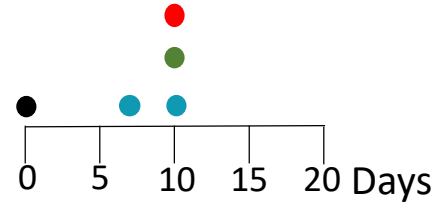
Les ILC3 sont essentielles au fonctionnement du cisplatine contre la tumeur

Souris chimères :
WT irradiées reconstituées
avec MO RORc^{-/-}

TC-1 CDDP

Th17 or ILC3

WT^{recRORc^{-/-}} mice

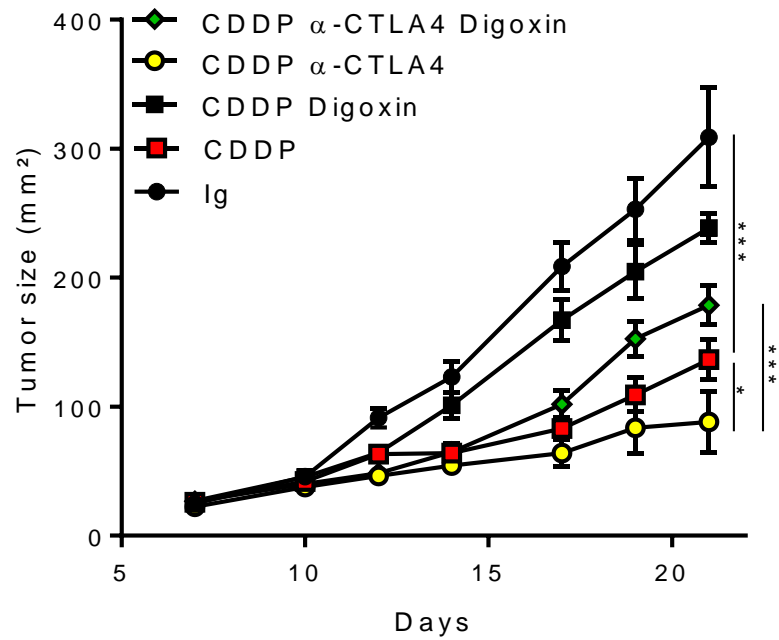
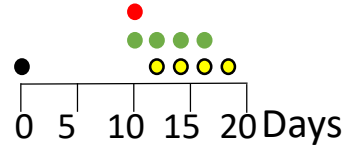


Les ILC3 sont essentielles à la synergie entre CKI et cisplatine

TC-1 CDDP

isotype or anti-CTLA4 and/or control or Digoxin

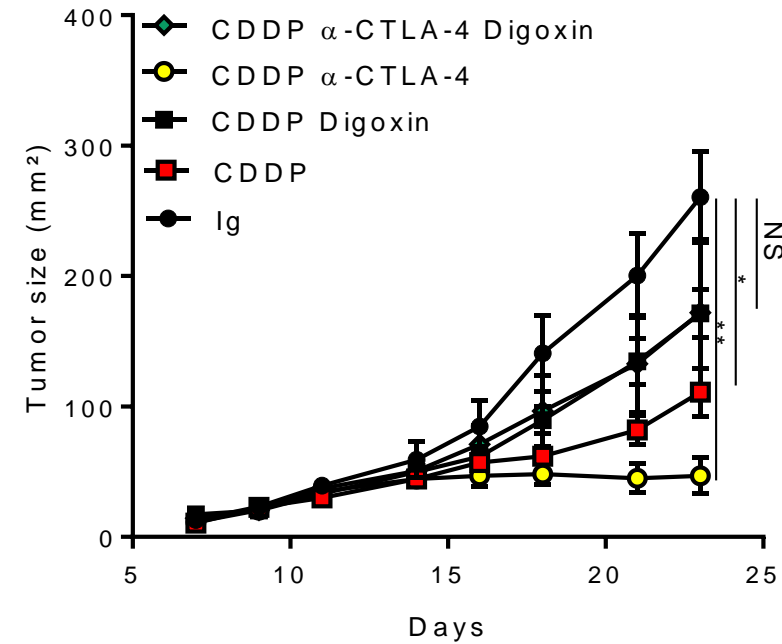
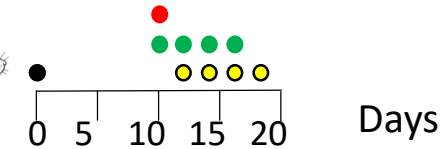
C57BL/6J
mice



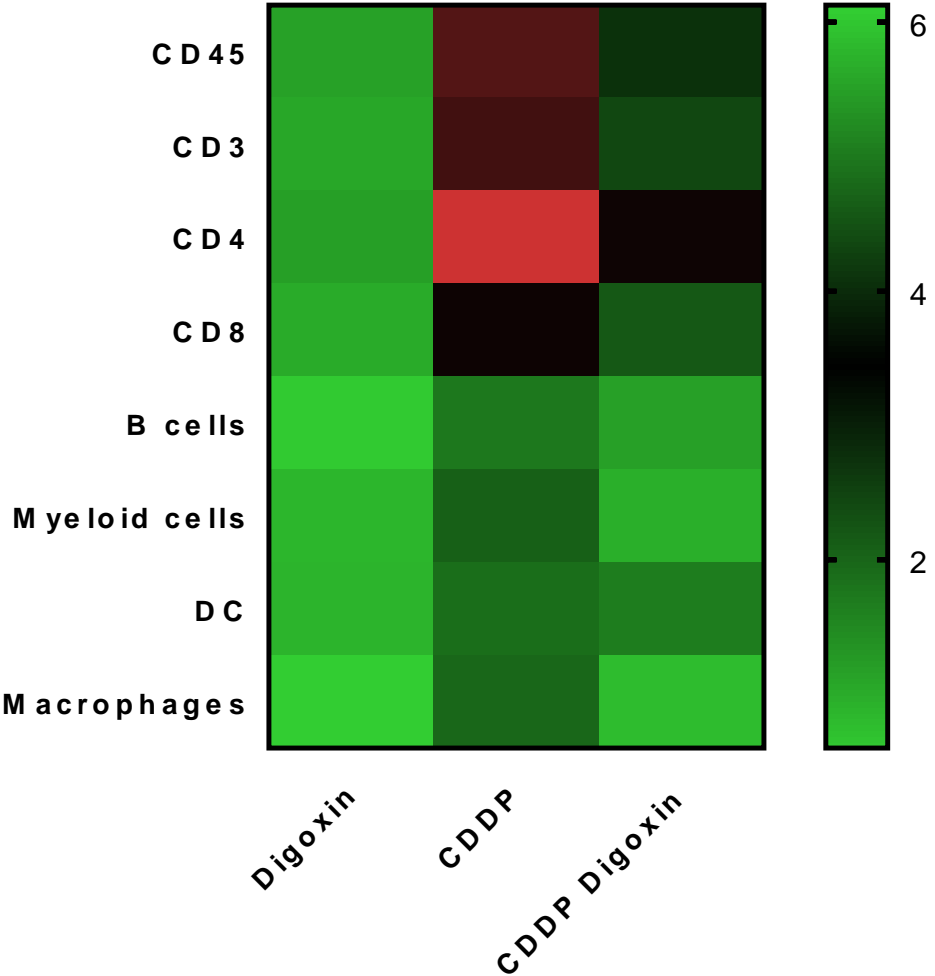
TC-1 CDDP

isotype or anti-CTLA4 and/or control or Digoxin

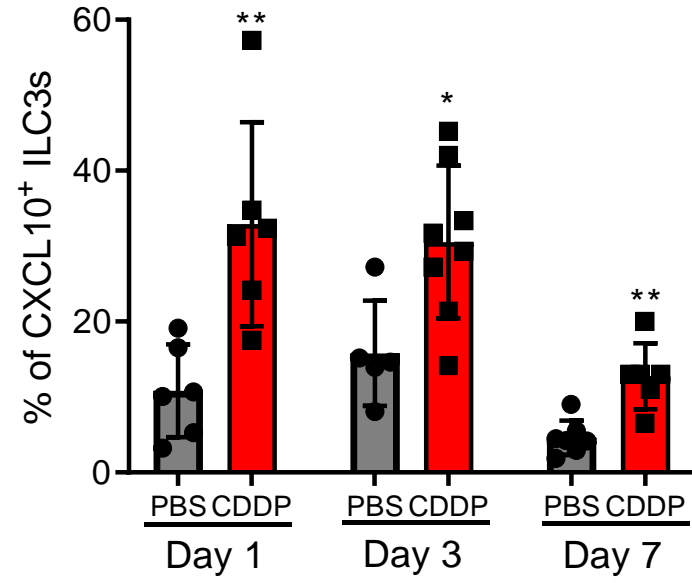
RORc^{fl/fl} CD4^{cre}
mice



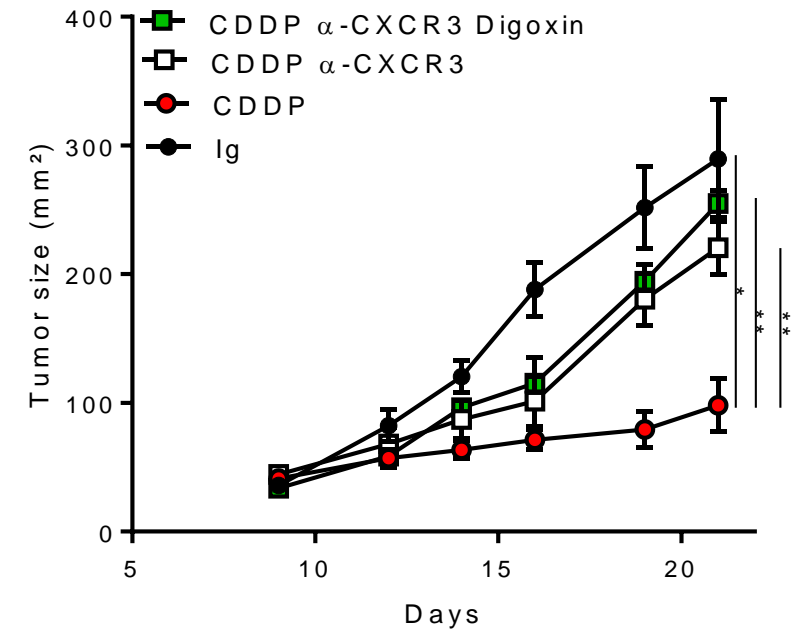
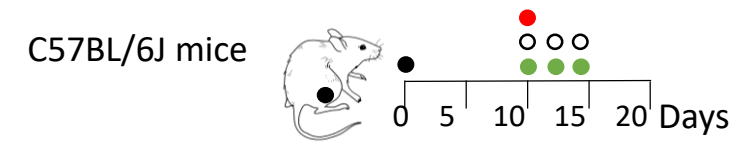
Le recrutement de lymphocytes dans la tumeur induit par le cisplatine est fortement limité en absence de cellules RORyt



Comment les ILC3 recrutent-ils les lymphocytes à la tumeur ?

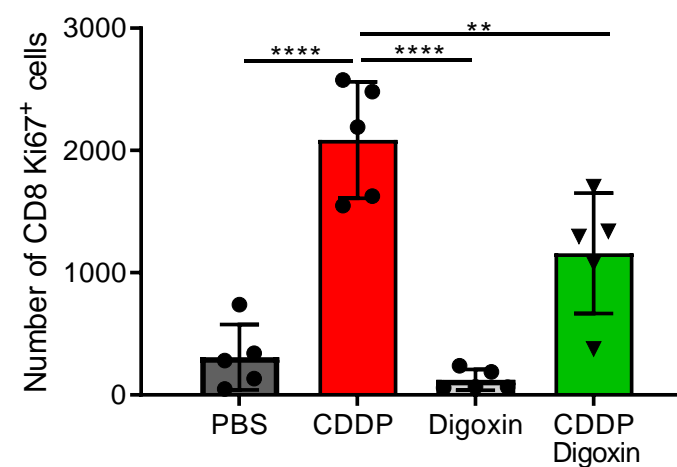
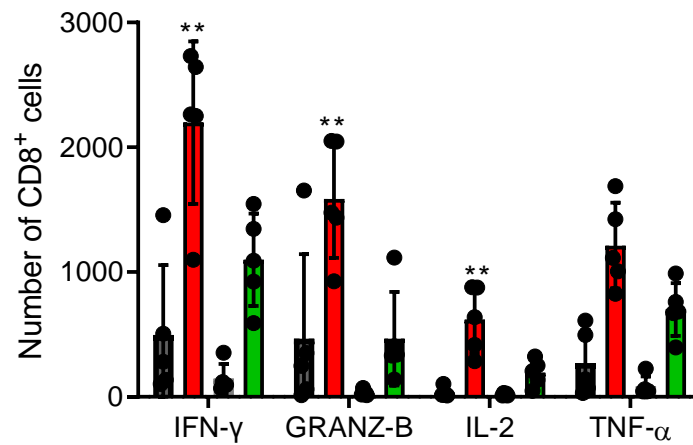
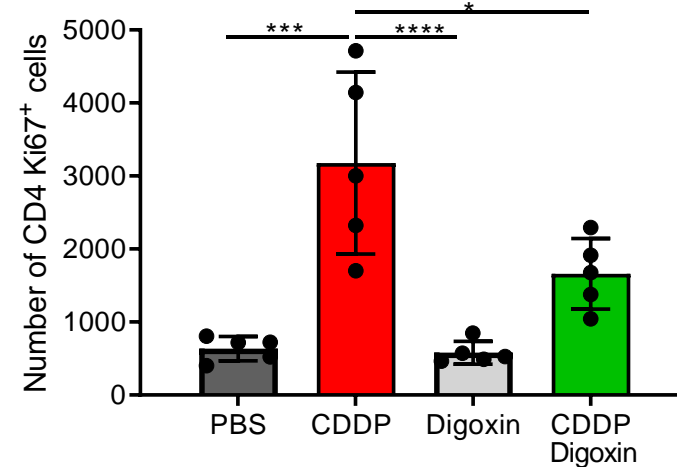
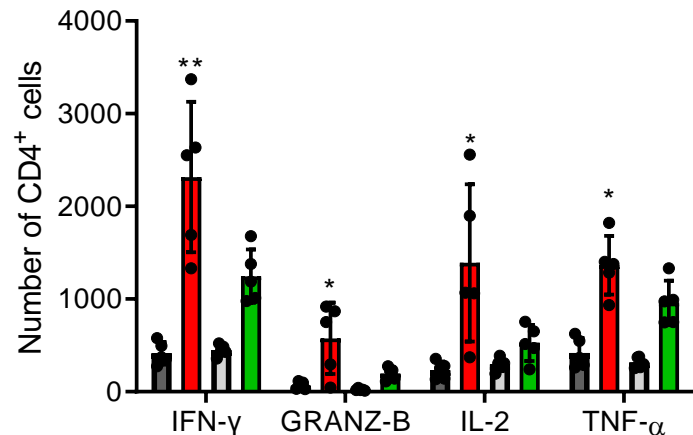
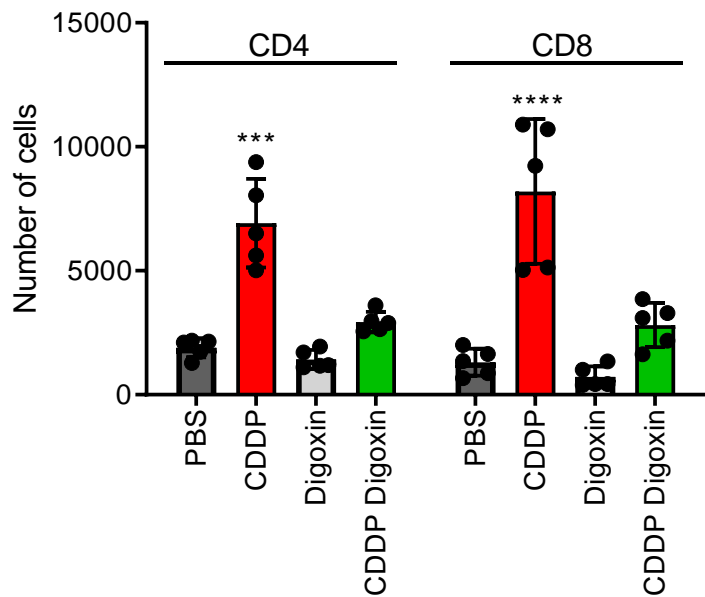


TC-1 CDDP
Control or Digoxin and/or isotype or anti-CXCR3

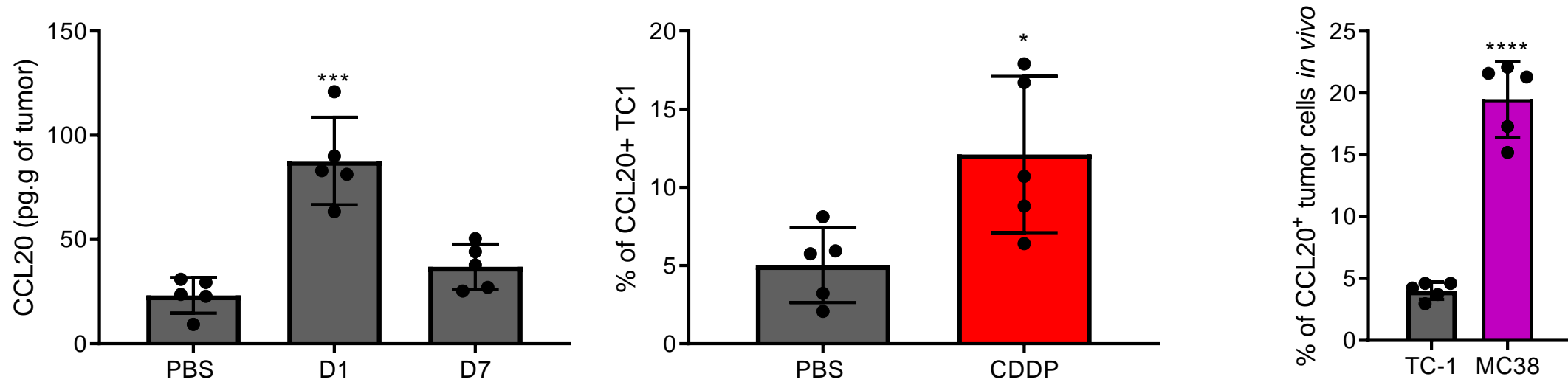


- L'axe CXCL10/CXCR3 est important dans l'efficacité du cisplatine.
- Pas d'effet additionnel de la combinaison α-CXCR3 + Digoxine : suggère qu'ils font partie de la même cascade

Analyse des populations lymphocytaires dans la tumeur

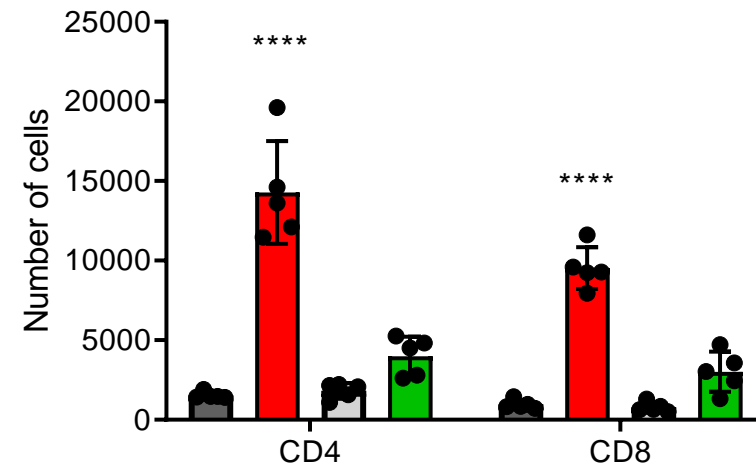
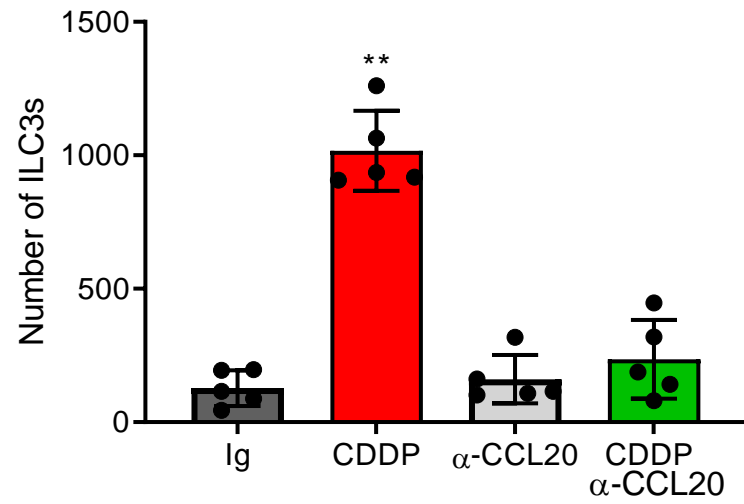


Pourquoi la population d'ILC3 augmente après cisplatine ?

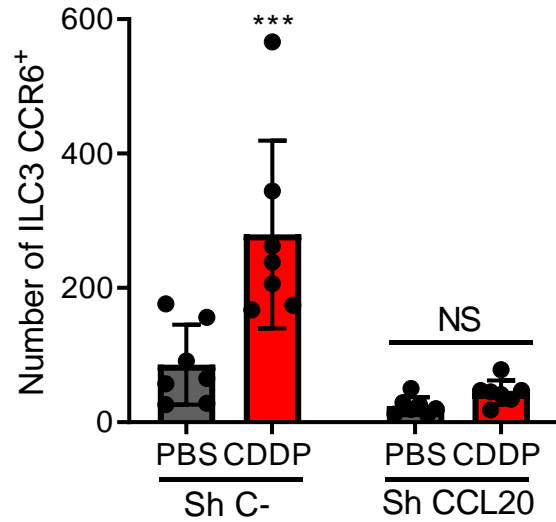


→ Le cisplatine induit la production de CCL20 par les cellules TC-1.

Le CCL20 attire les ILC3 après cisplatine dans la tumeur.



La production de CCL20 est importante pour l'efficacité antitumorale du cisplatine.



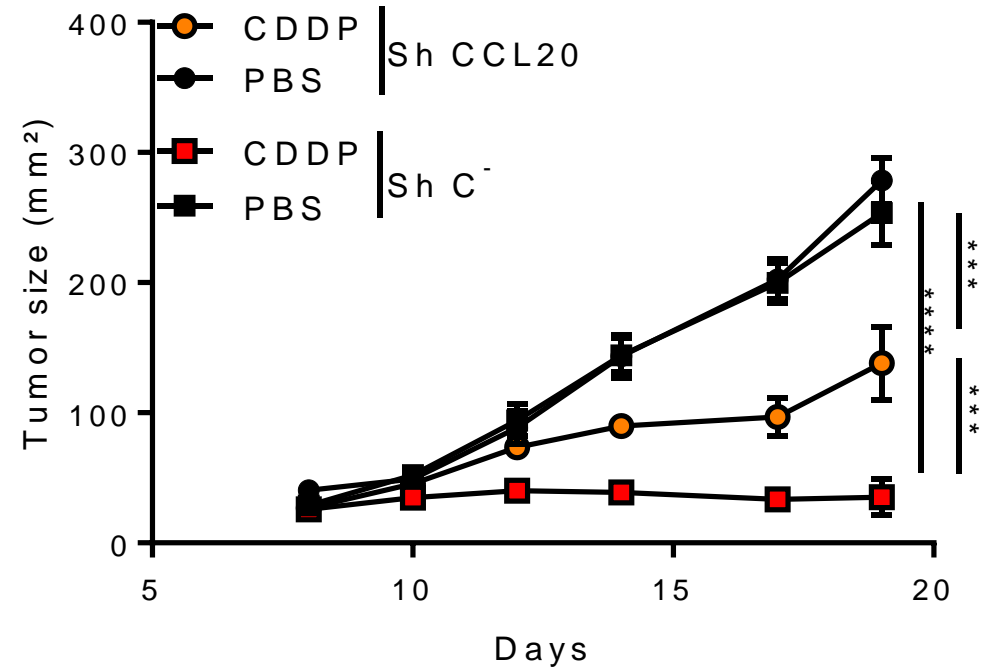
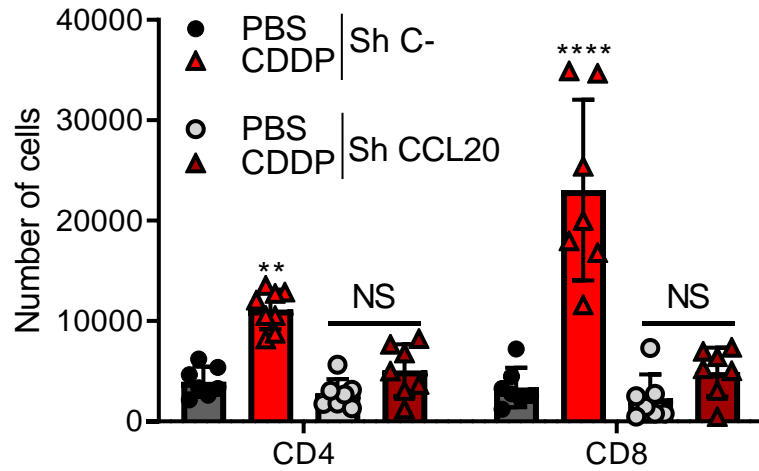
TC-1 Sh C⁻ or Sh CCL20

CDDP

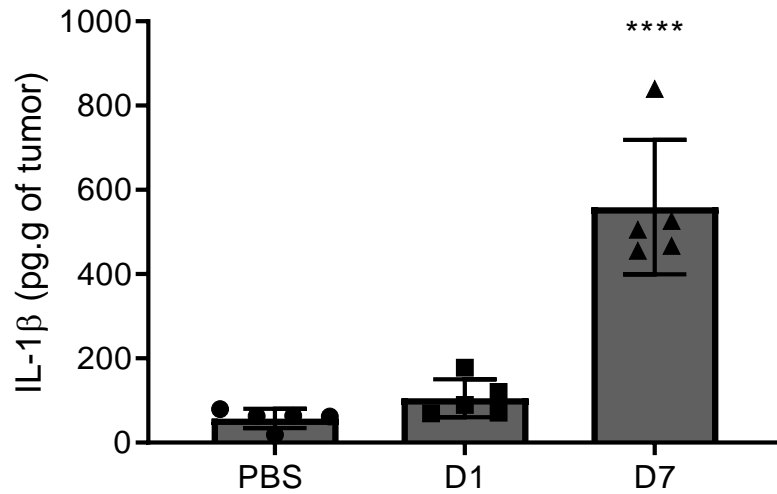
C57BL/6J mice



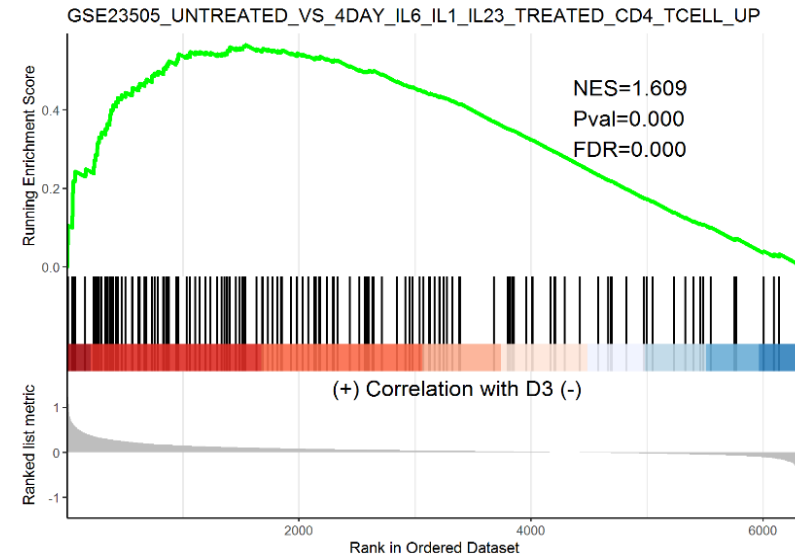
0 5 10 15 20 Days



IL-1 β est produit par la tumeur après cisplatine.



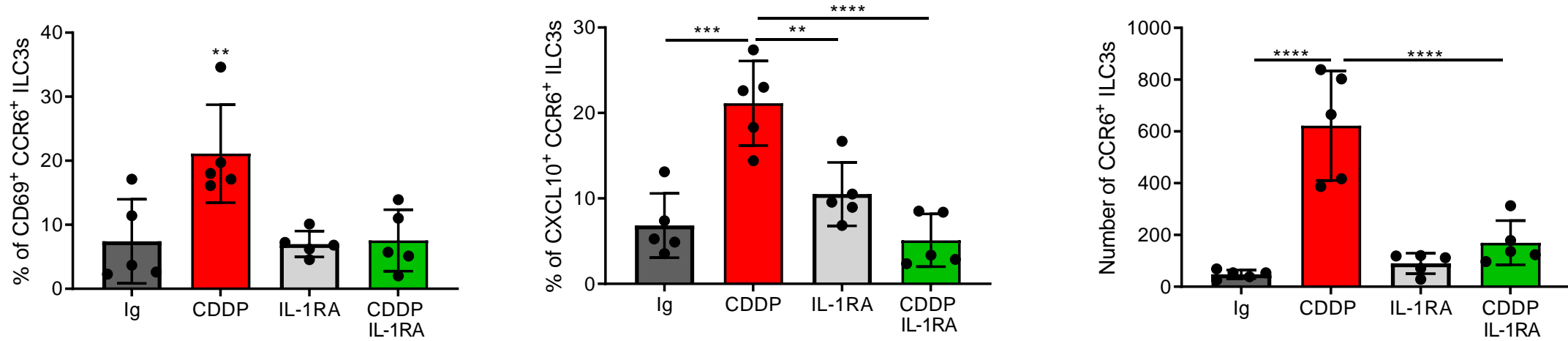
GSEA on single cell RNA seq data ILC from CDDP treated TC-1 tumors



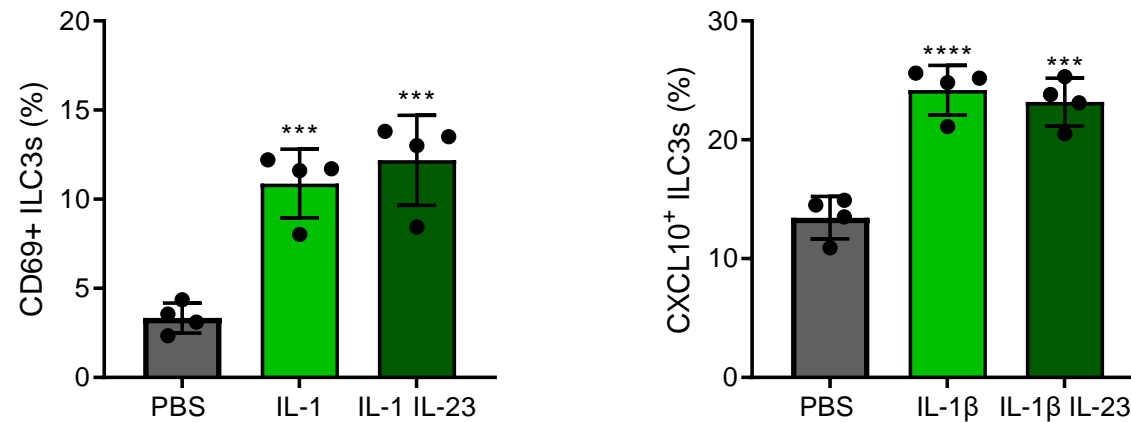
enrichissement du module IL1R dans le cluster d'ILC3 après cisplatine suggérant une activation des ILC3 dépendante de l'IL-1 β

IL-1 β active les ILC3 dans la tumeur

In vivo:

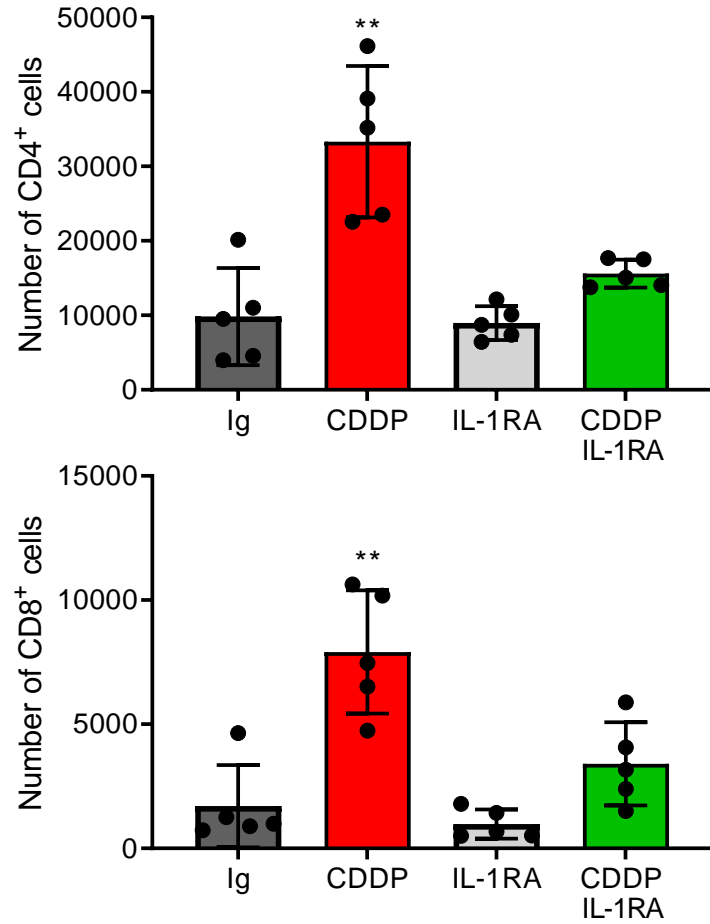


In vitro:



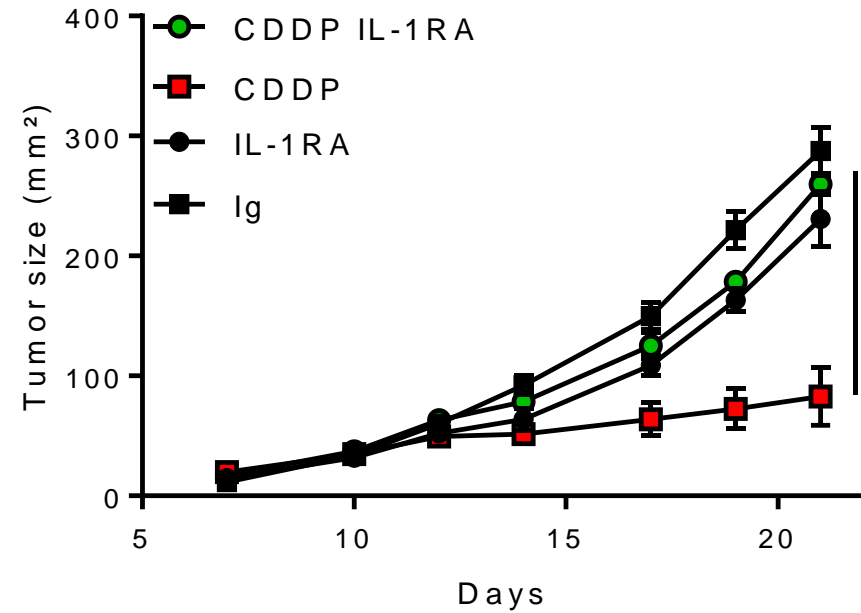
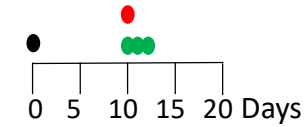
→ IL-1 β augmente l'activation, la production de CXCL10 et la prolifération des ILC3

Les ILC3 activées participent aux effets antitumoraux du cisplatine



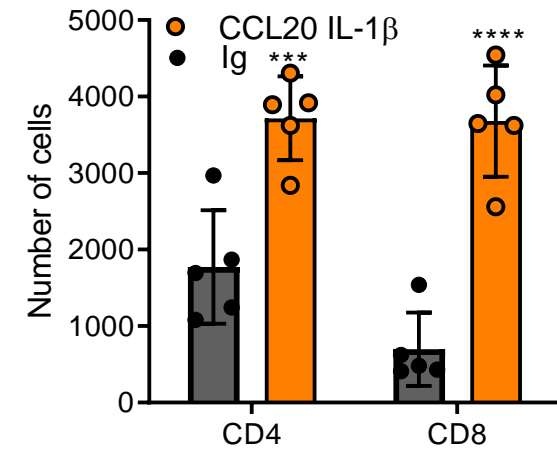
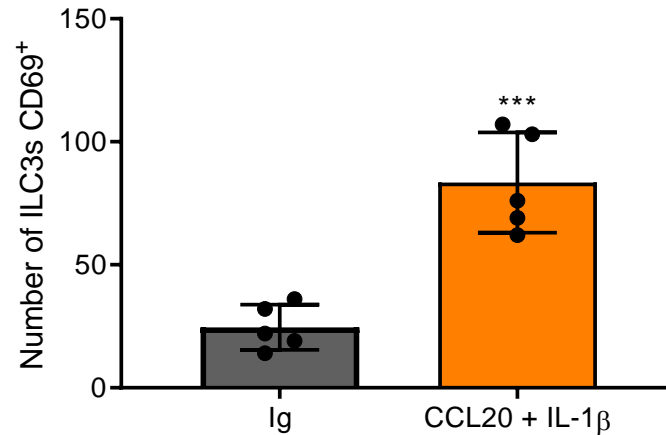
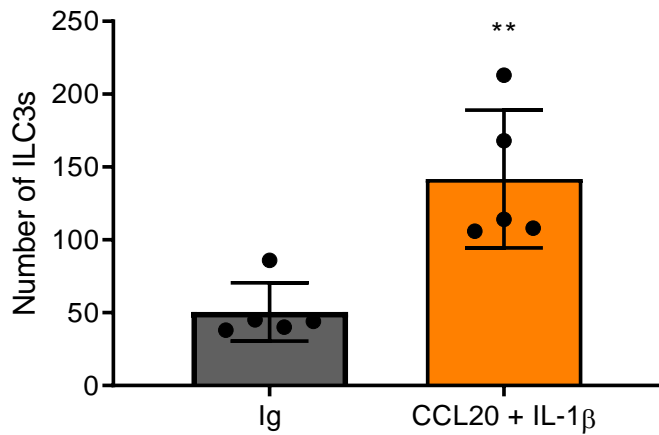
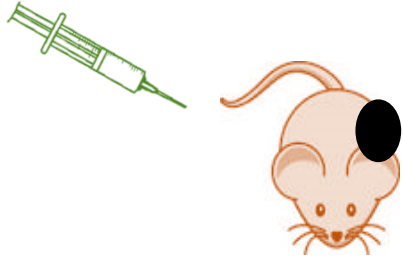
TC-1 CDDP
Isotype or IL-1RA

C57BL/6J
mice



→ L'activation des ILC3 mène à l'augmentation des populations de CD4 et CD8 dans la tumeur.

Le CCL20 et l'IL-1 β suffisent à augmenter l'infiltrat immunitaire dans la tumeur.



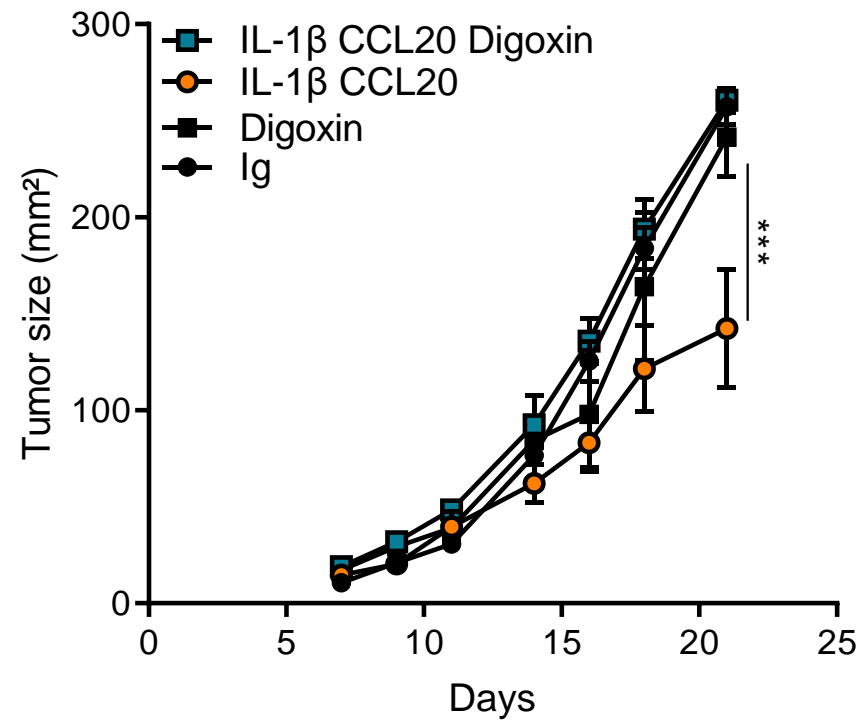
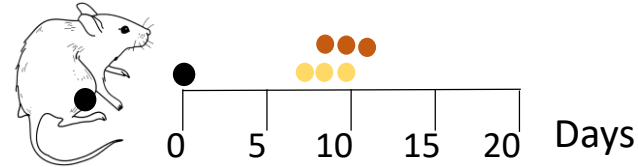
→ Des injections de CCL20 and IL-1 β déclenchent une augmentation et une activation de la population d'ILC3 menant à une augmentation des CD4 et CD8 dans la tumeur.

Le CCL20 et l'IL-1 β ralentissent la croissance tumorale

TC-1

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

C57BL/6J mice

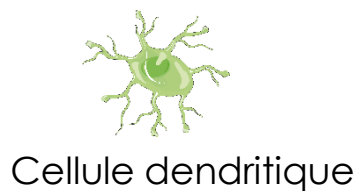


→ Le CCL20 et l'IL-1 β ralentissent la croissance via les ILC3

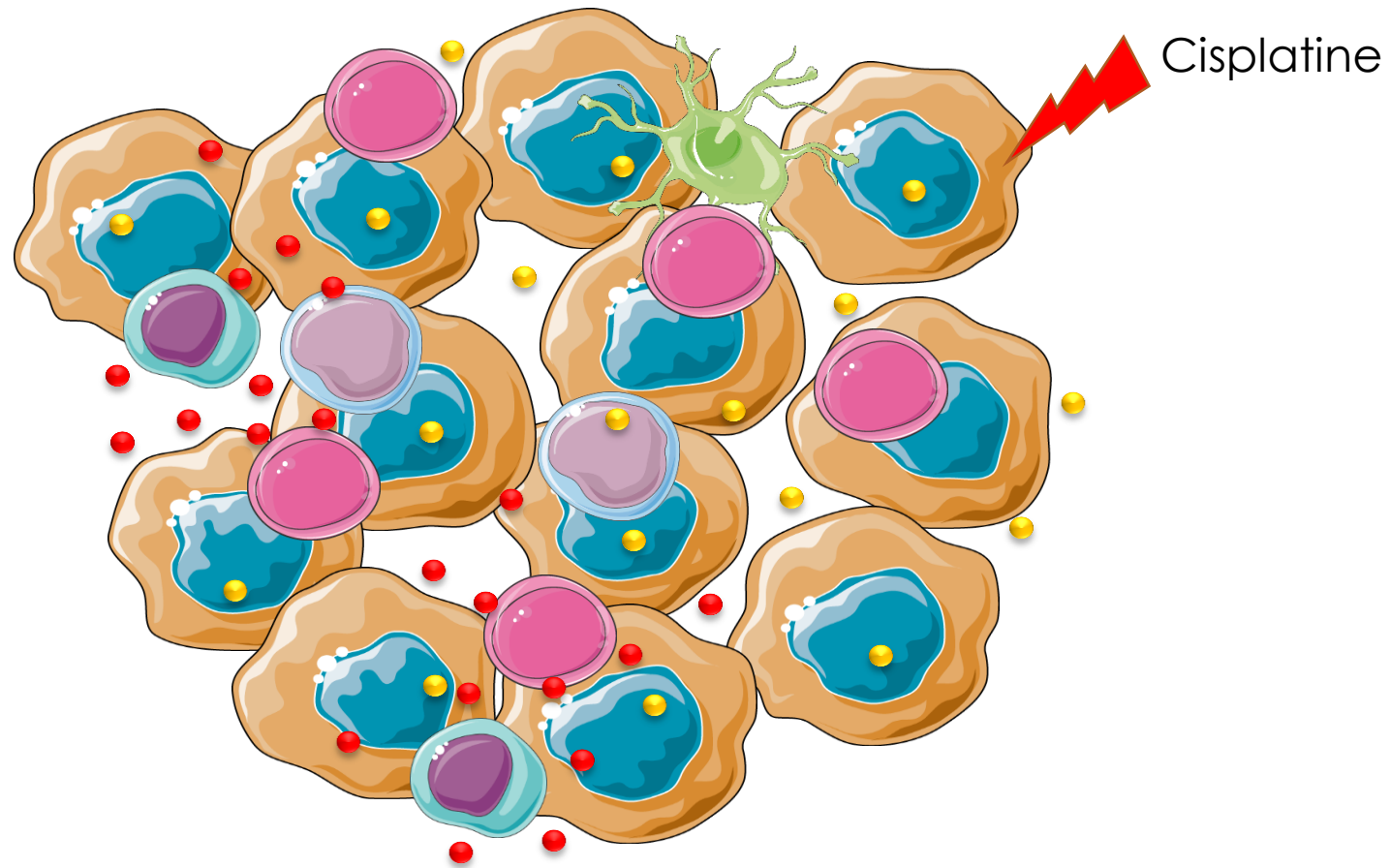
Conclusion



● CCL20



● IL-1 β



ILC3s : rôle crucial

→ première population

→ recrutée et activée par CCL20 et IL-1 β

→ miment les effets immunitaires du cisplatine

Conclusion



Cellule tumorale



Cellule dendritique



lymphocyte



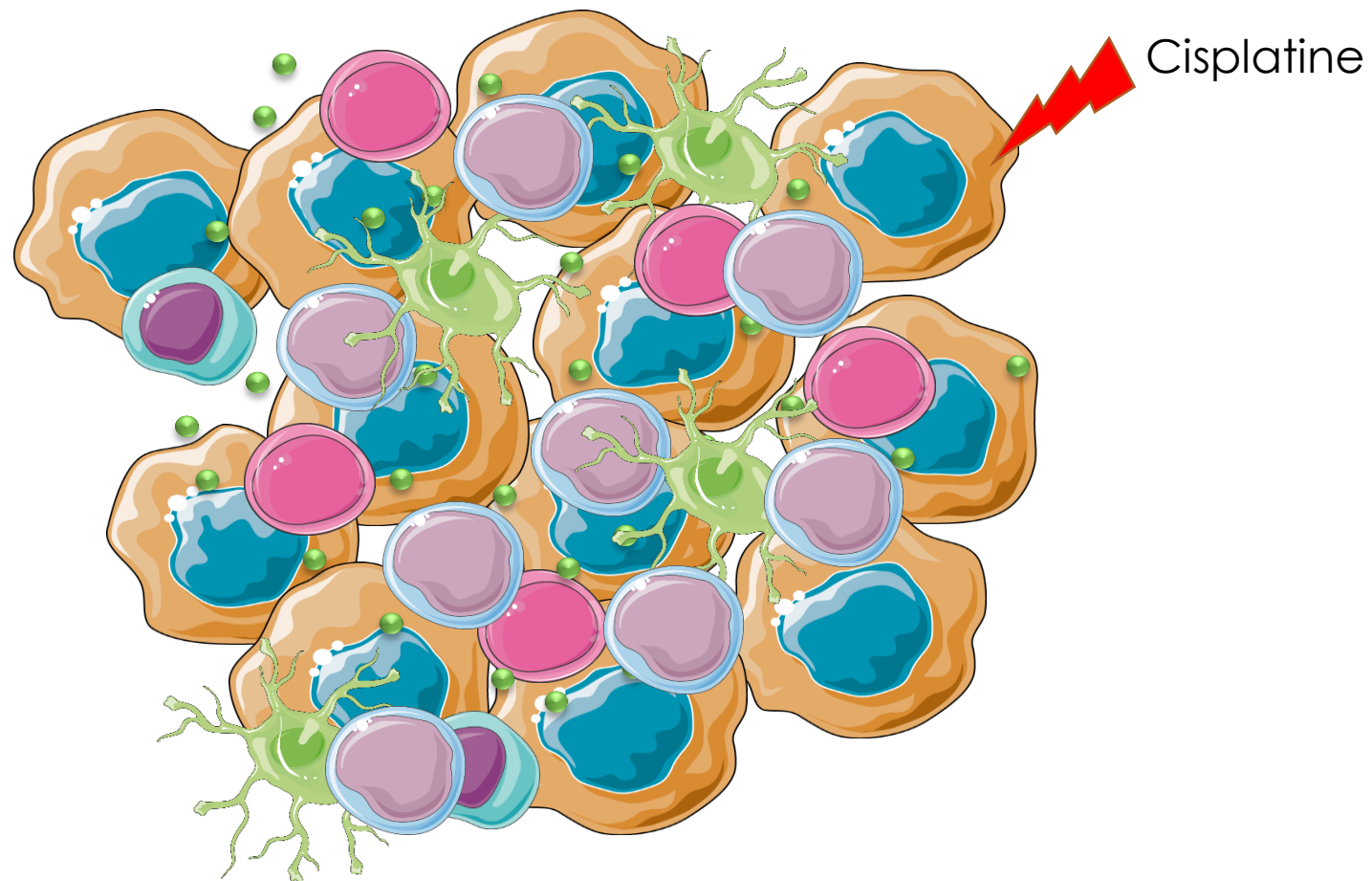
ILC3



CXCL10



Cellule myéloïde

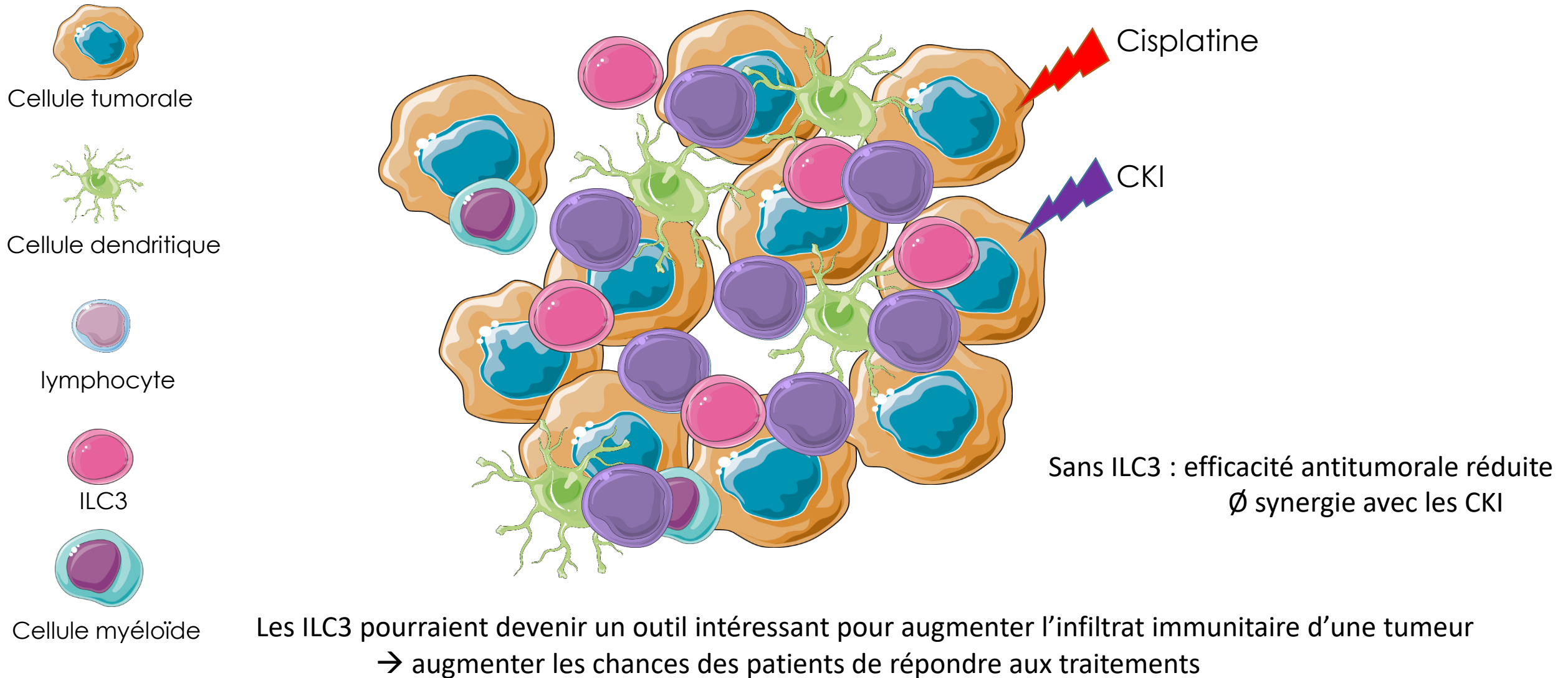


Les ILC3 produisent du CXCL10

→ attire les cellules CXCR3+ (lymphocytes T CD8, Th1, NK...)

Conclusion

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Remerciements

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Emilie Barsac

Centre zootechnologie

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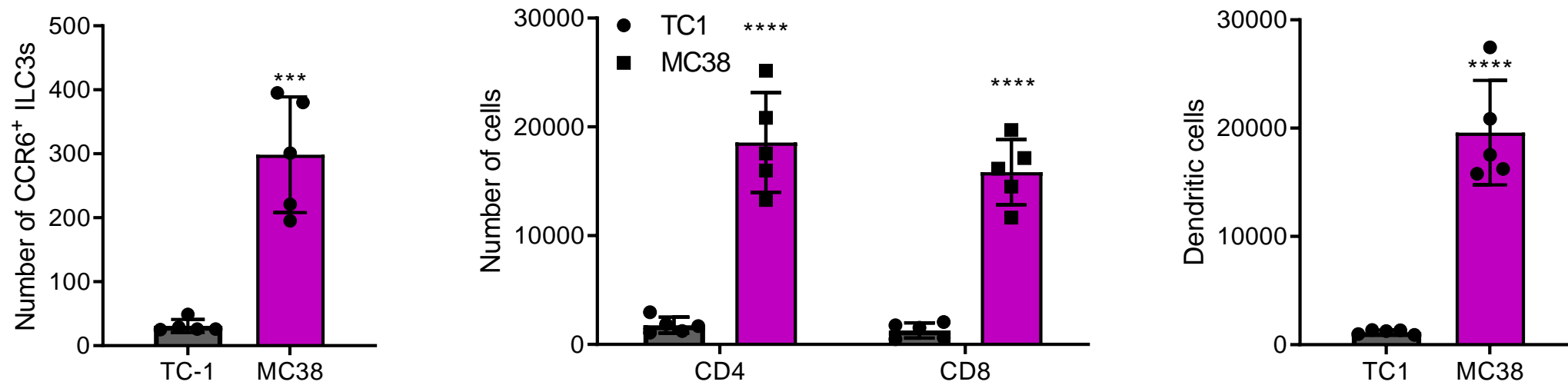


Laboratoire d'excellence



In a hot tumor model, basal levels of ILC3s and lymphocytes are high

MC38: colorectal carcinoma
→ Known hot tumor model

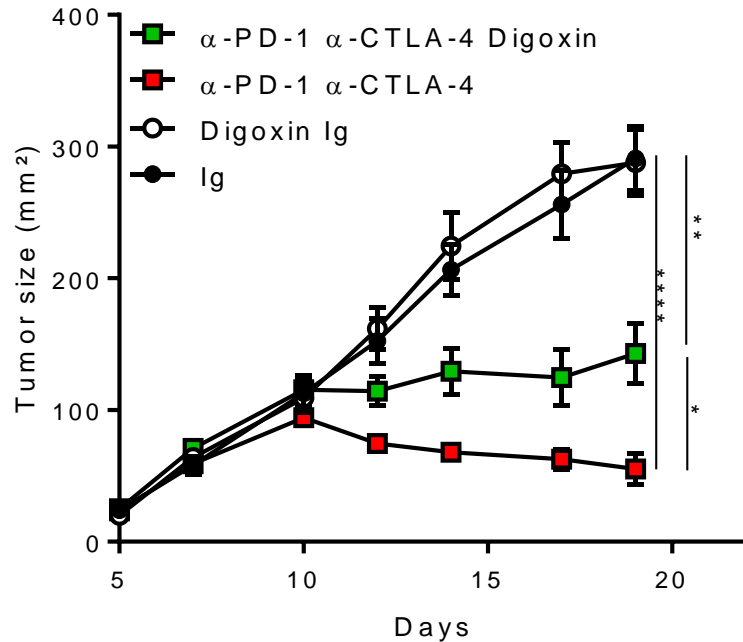
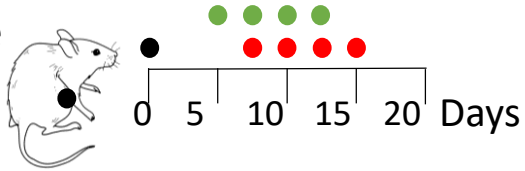


ILC3s are essential for CKI antitumor efficiency

MC38

isotype or α -PD-1 + α -CTLA4 and/or PBS or Digoxin

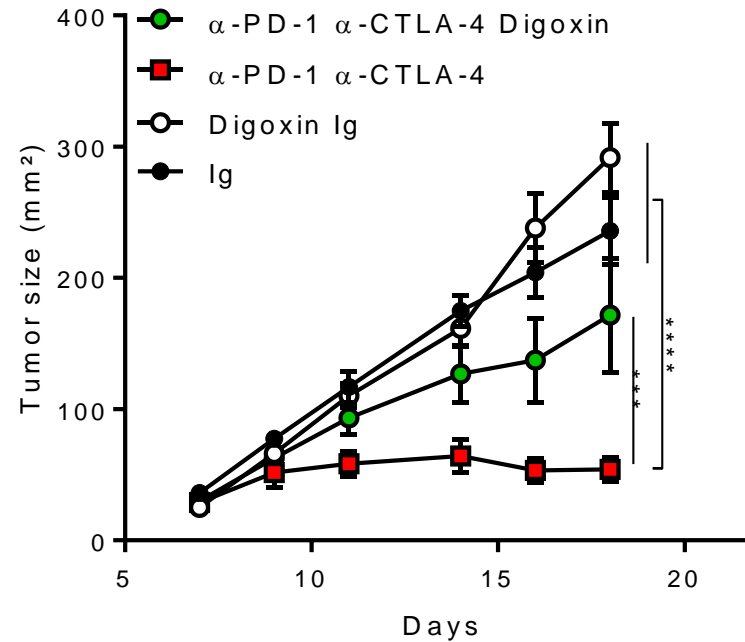
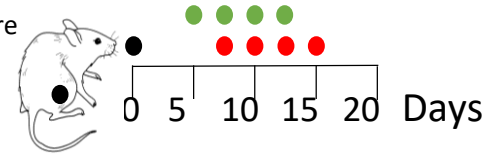
C57BL/6 mice



MC38

isotype or α -PD-1 + α -CTLA4 and/or PBS or Digoxin

Rorc^{fl/fl} CD4^{cre} mice



→ Absence of ILC3 limits CKI anti-tumor efficacy.

Les ILC3 attirent les cellules au lieu de formation des ganglions lymphatiques

