

SITC 2019

Gaylord National Hotel
& Convention Center

Nov. 6-10

NATIONAL HARBOR, MARYLAND



Society for Immunotherapy of Cancer



Overexpression of CD200 is a Stem-Cell Specific Mechanism of T Cell Evasion in AML

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SMHerbrich@mdanderson.org



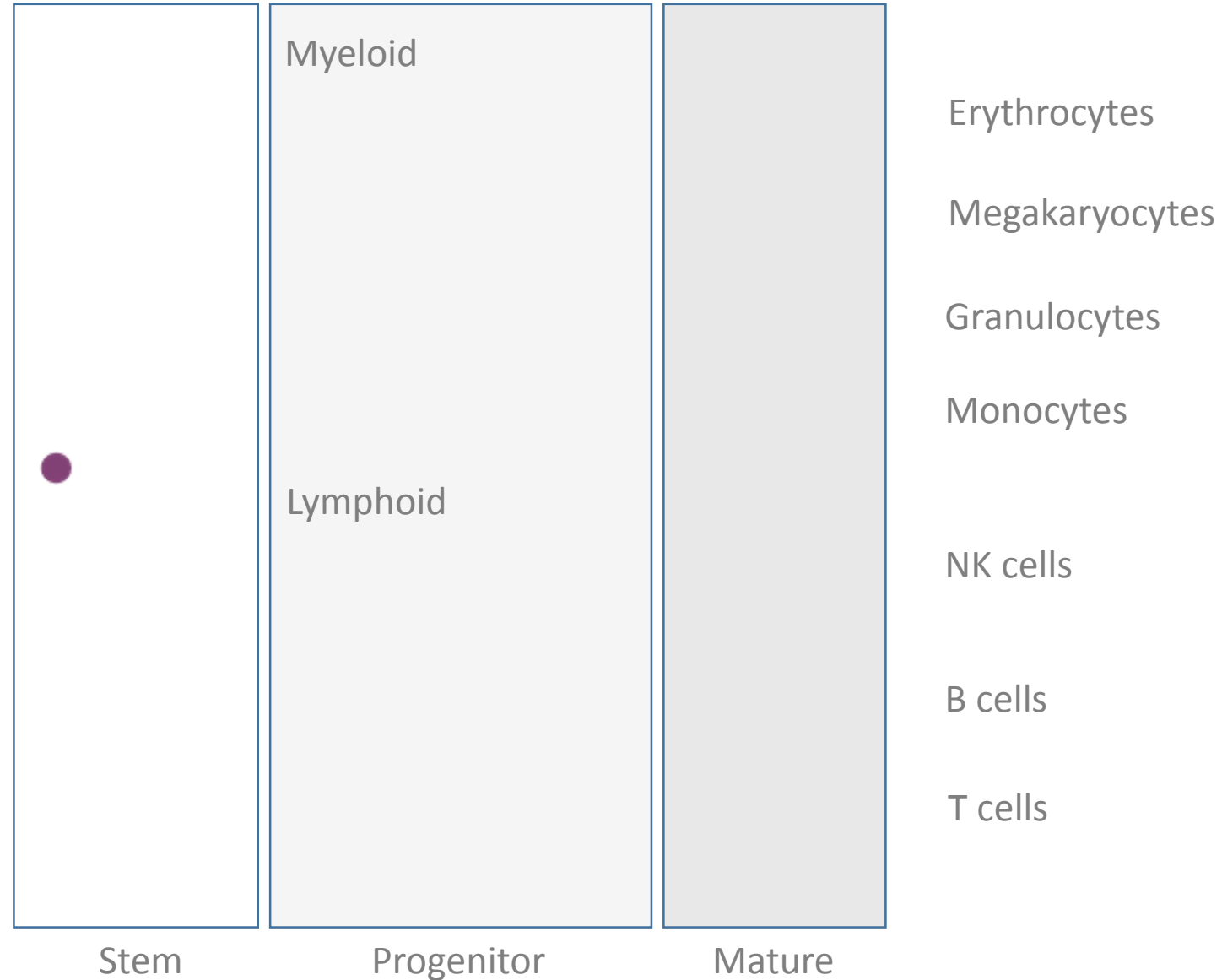
Society for Immunotherapy of Cancer

#SITC2019

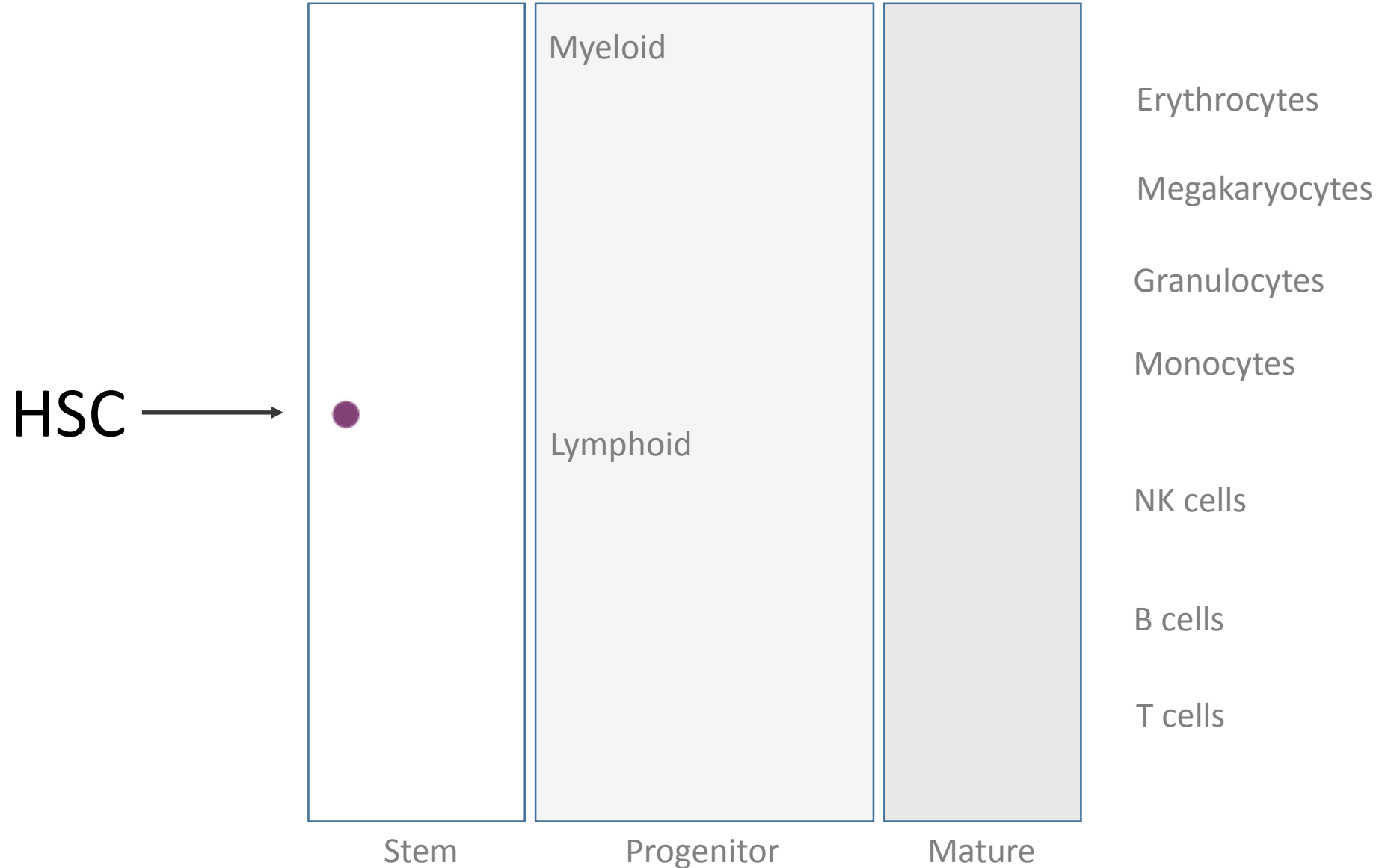
Disclosures

I have no financial disclosure or conflict of interests with the following presented material.

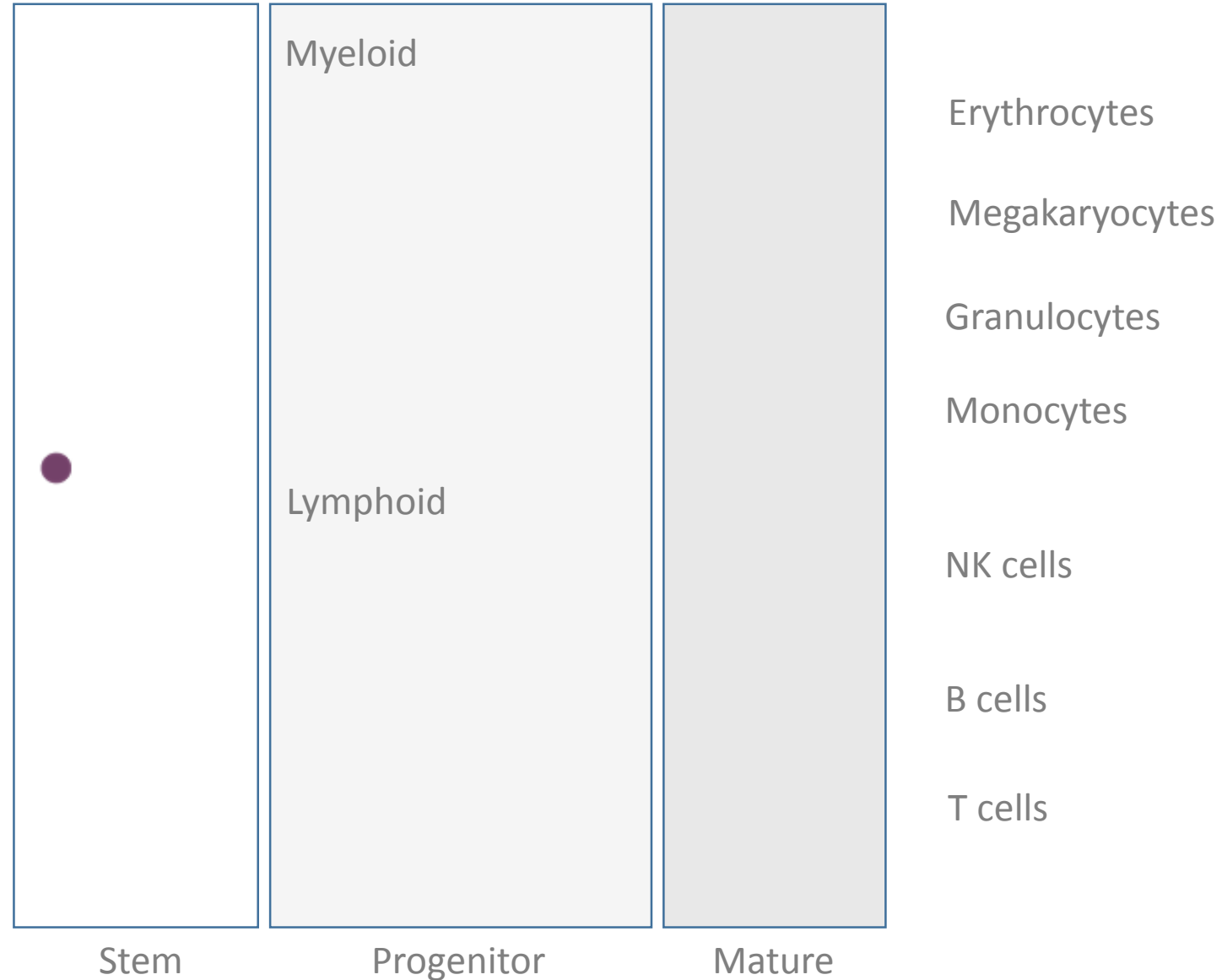
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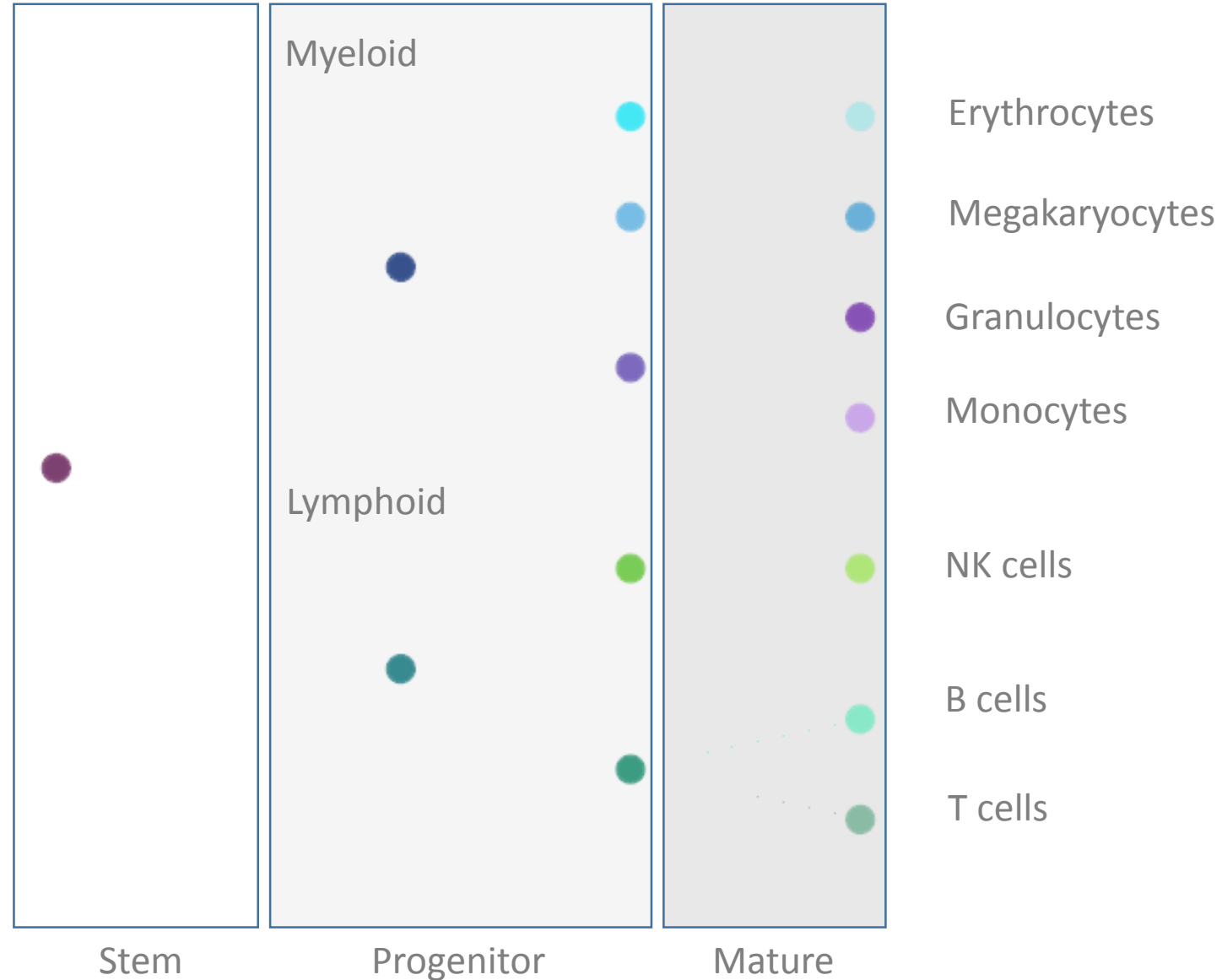
Normal Hematopoiesis



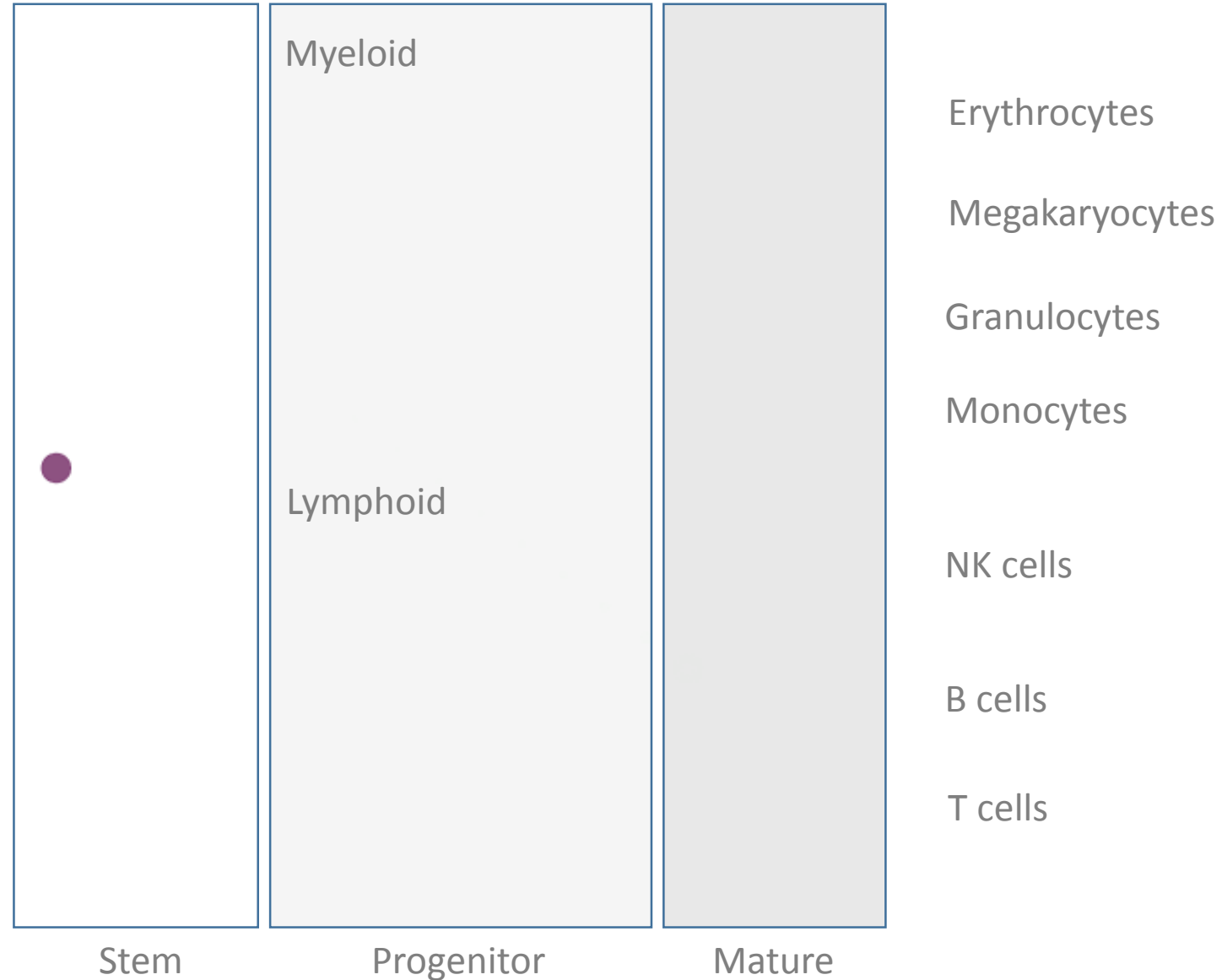
Normal Hematopoiesis



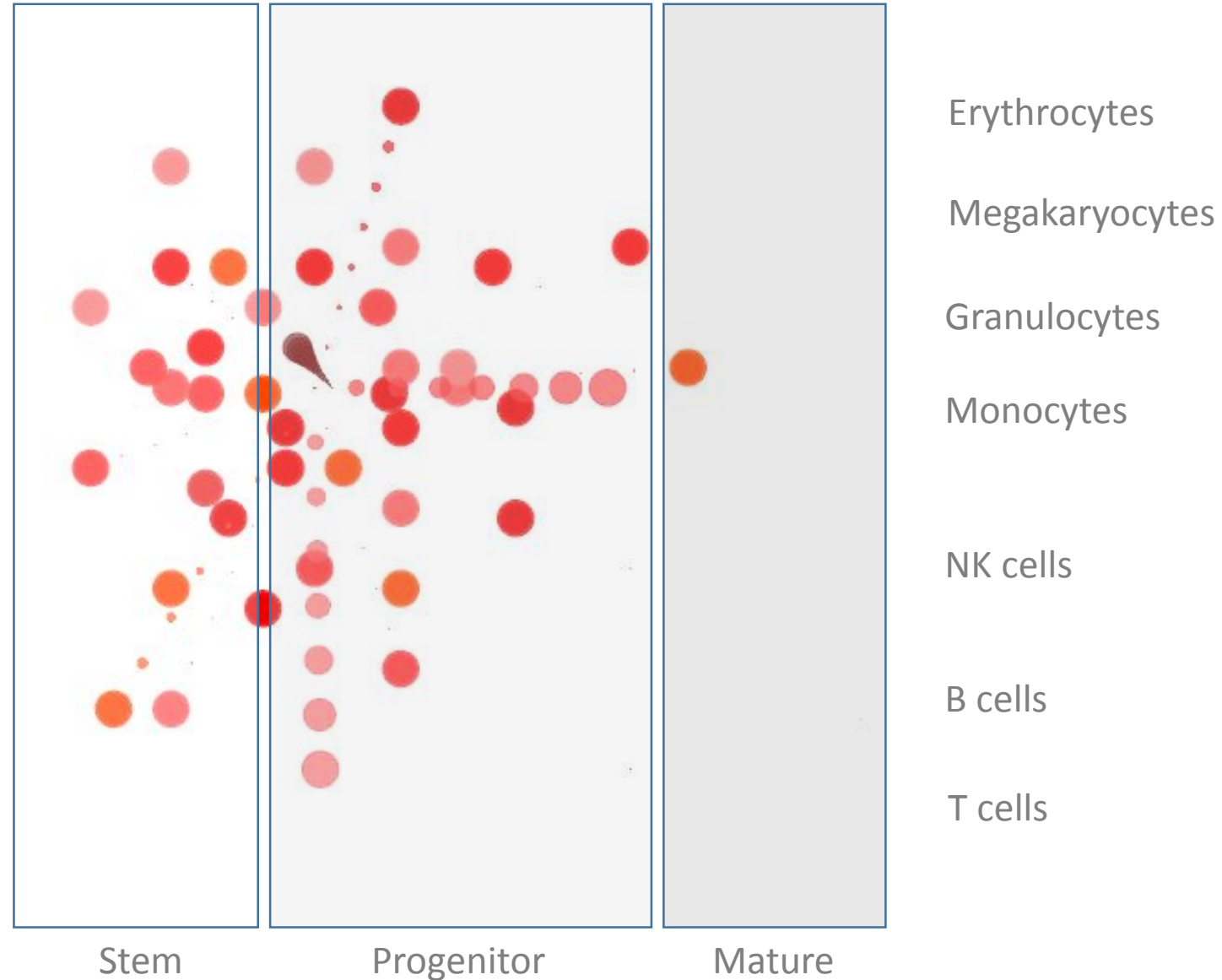
Normal Hematopoiesis



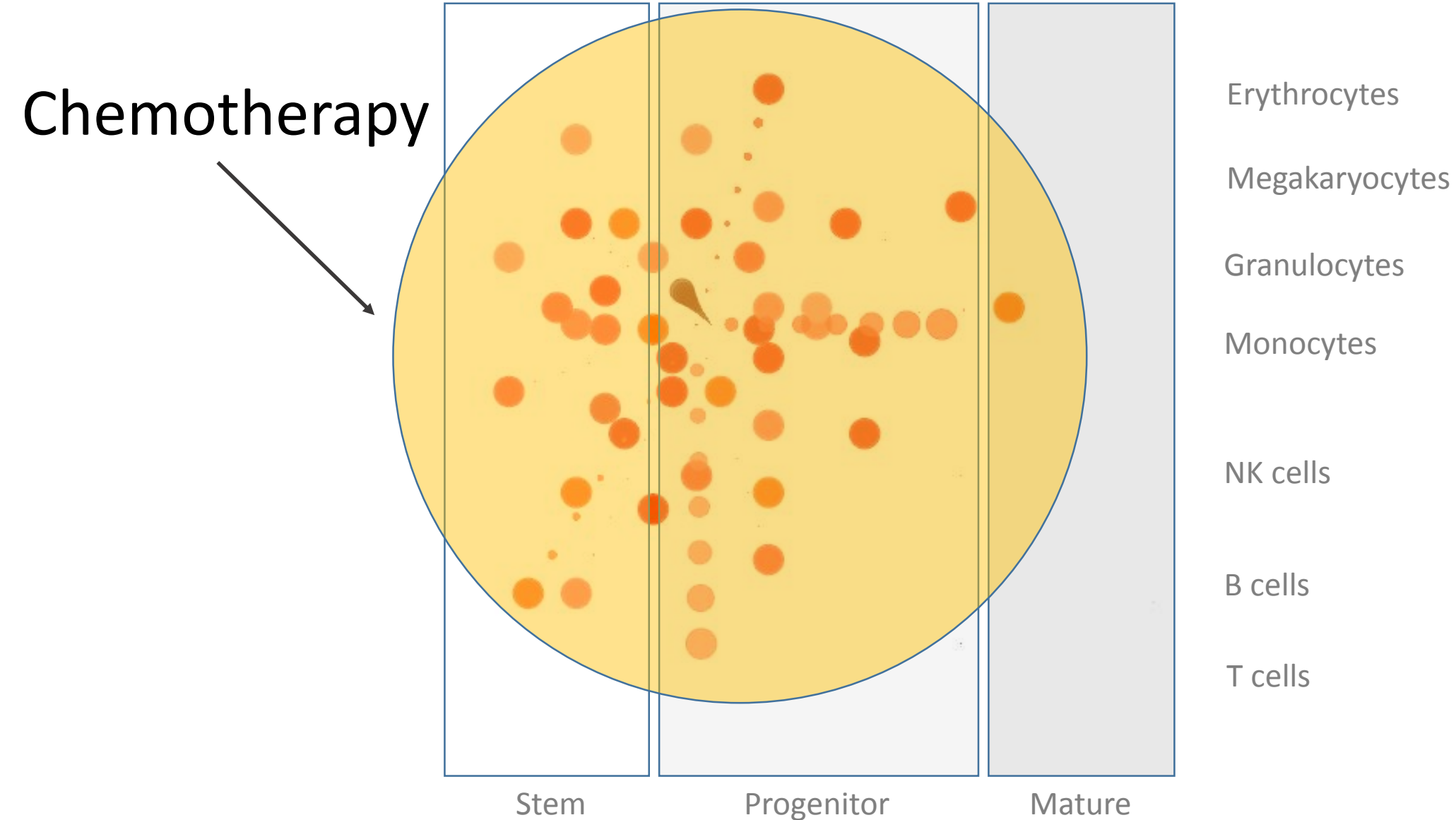
Acute Myeloid Leukemia



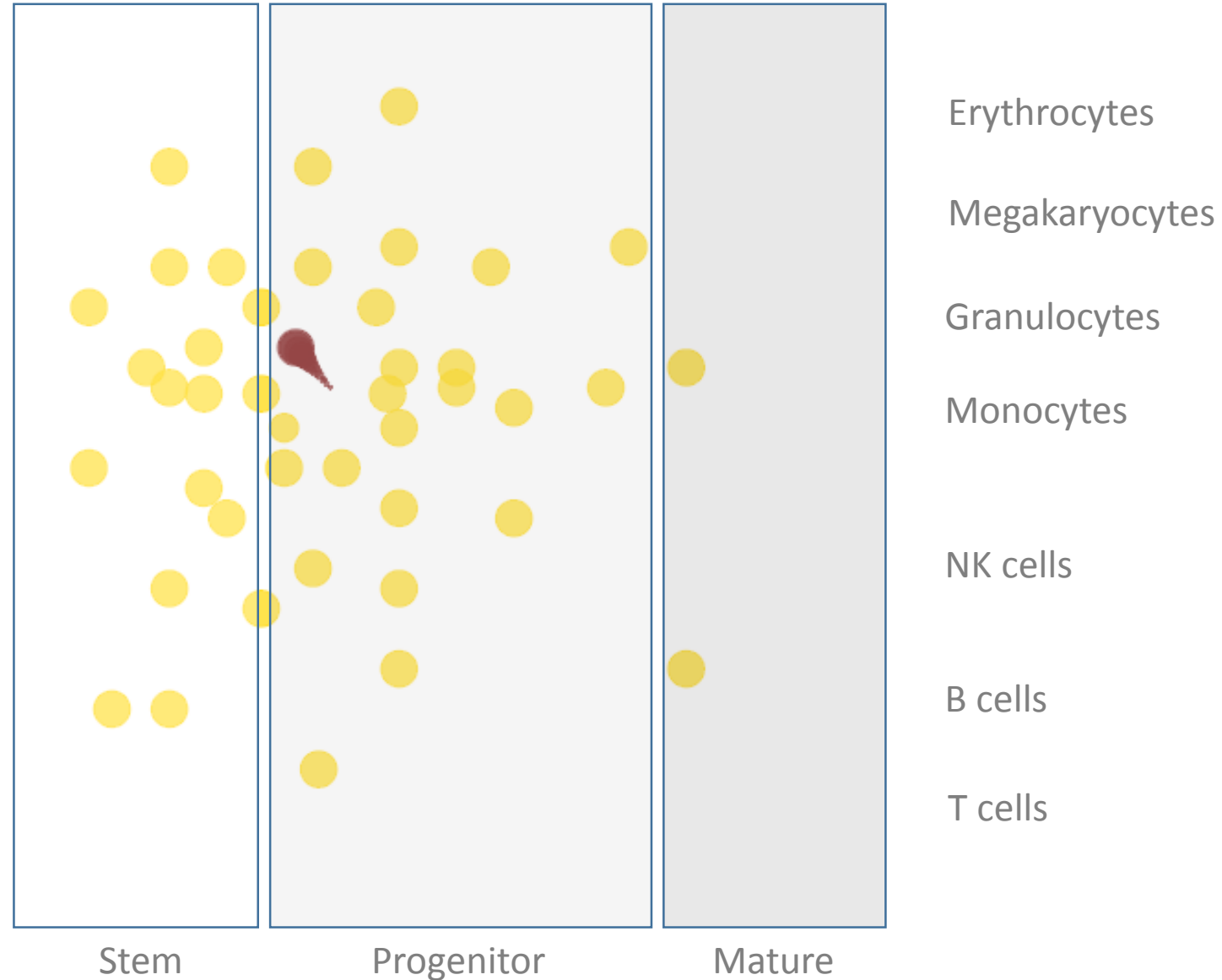
Acute Myeloid Leukemia



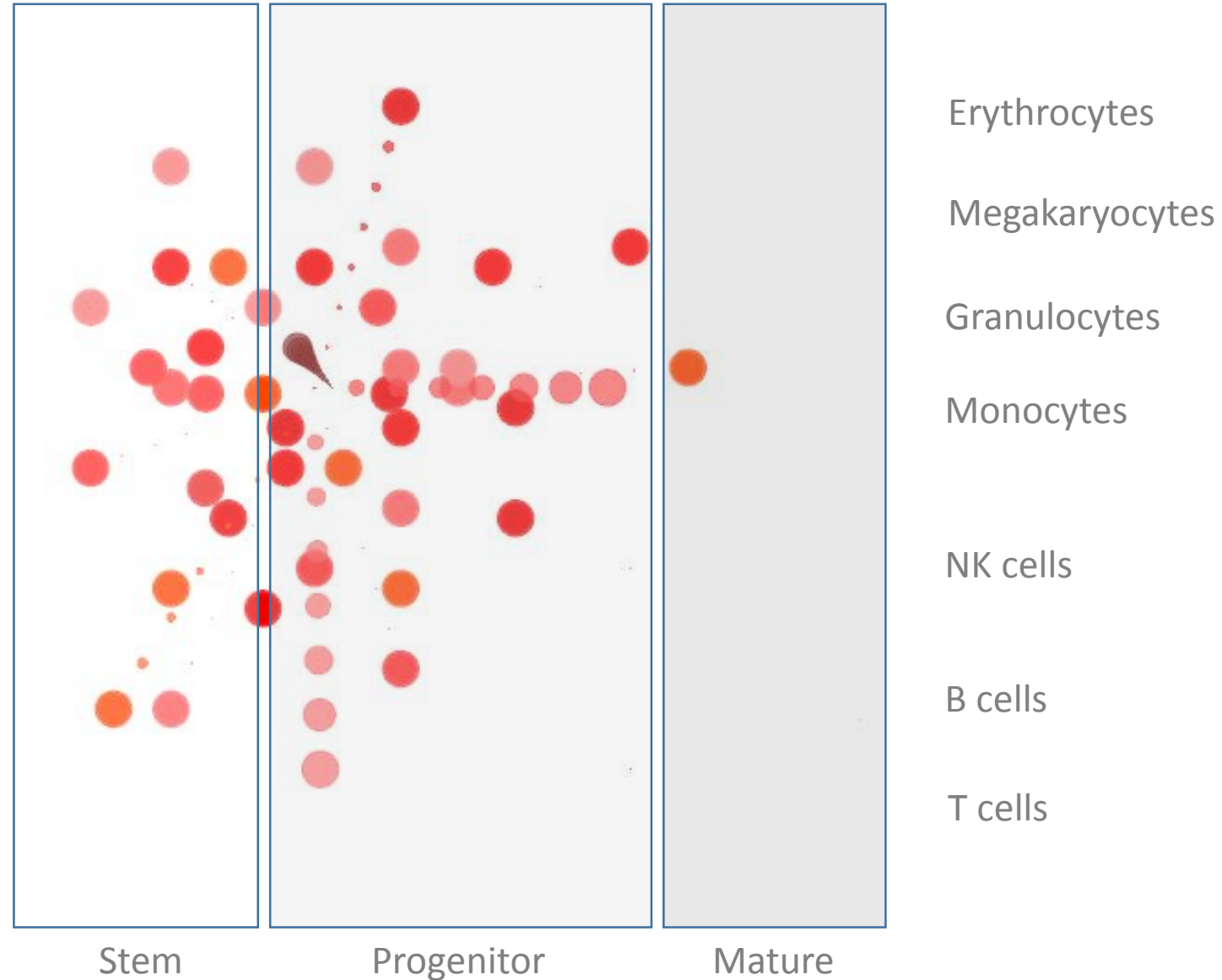
Chemotherapy eliminates blasts



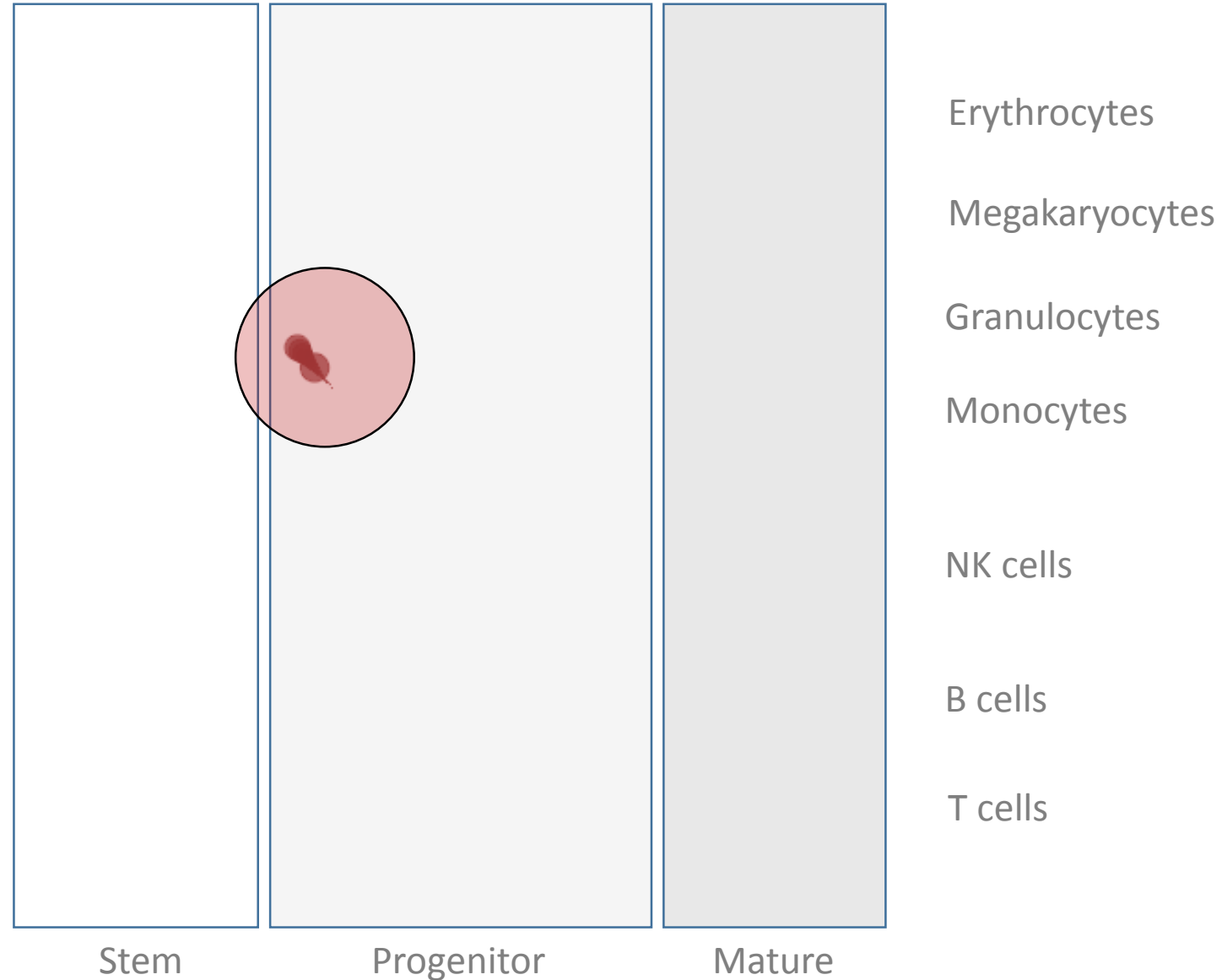
Chemotherapy eliminates blasts



Chemotherapy eliminates blasts



Immunotherapy in AML

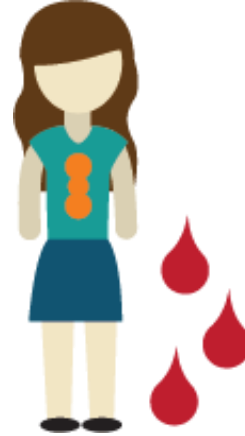


Data mining for AML LSC immune markers

AML



Healthy



1. Collect

Data mining for AML LSC immune markers

1. Collect

AML



Healthy



LSC



blasts



HSC



2. Sort

Data mining for AML LSC immune markers

1. Collect

AML



Healthy



LSC



blasts

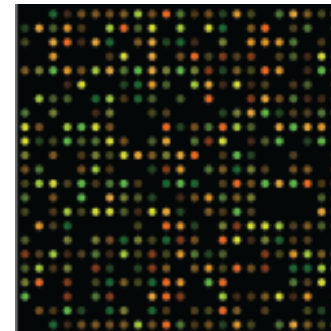
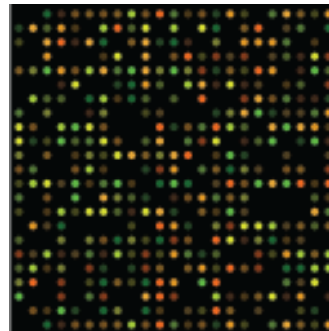
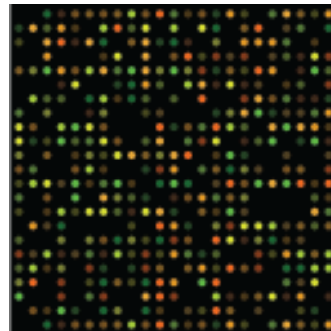


HSC

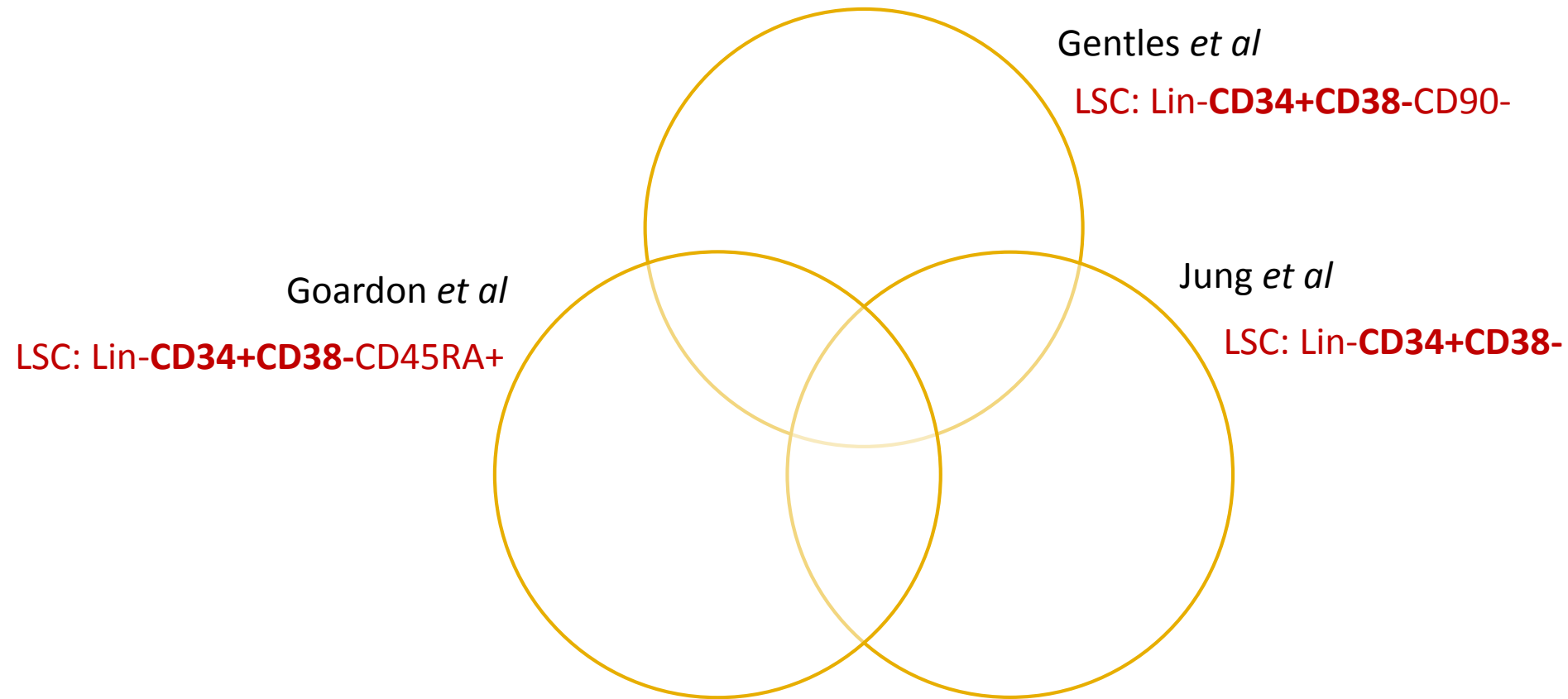


2. Sort

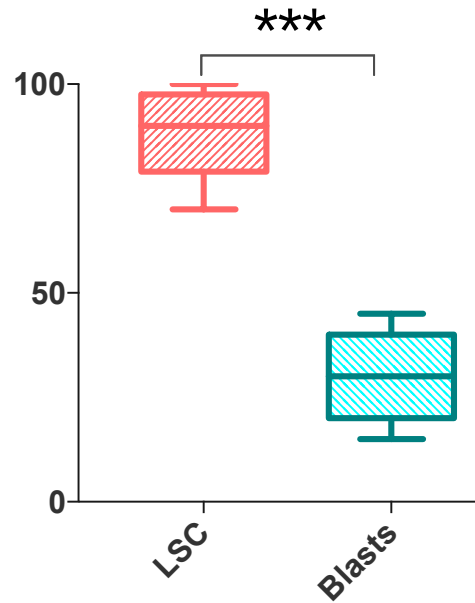
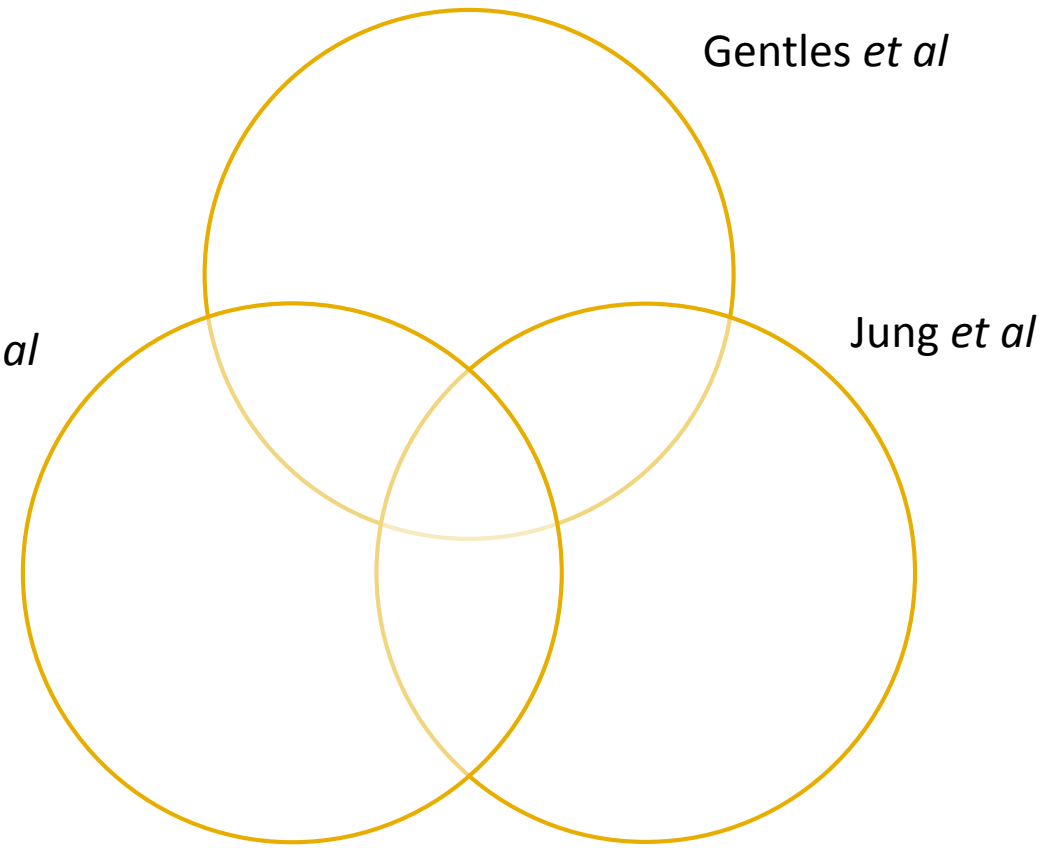
3. Compare



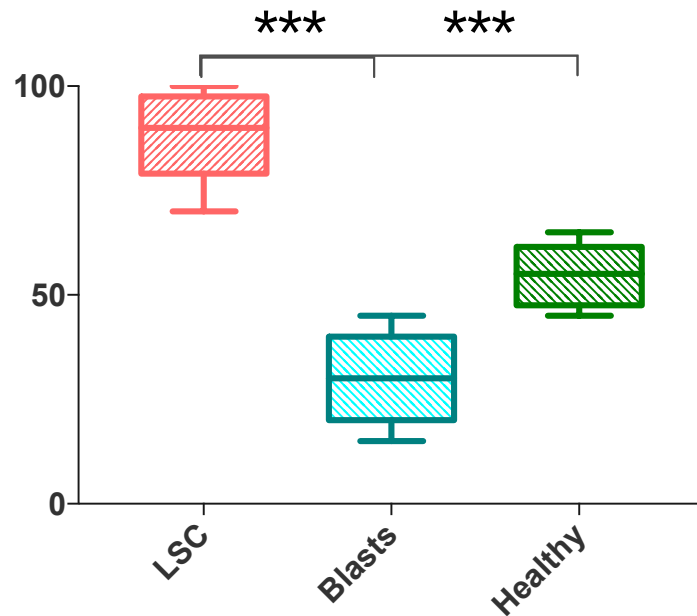
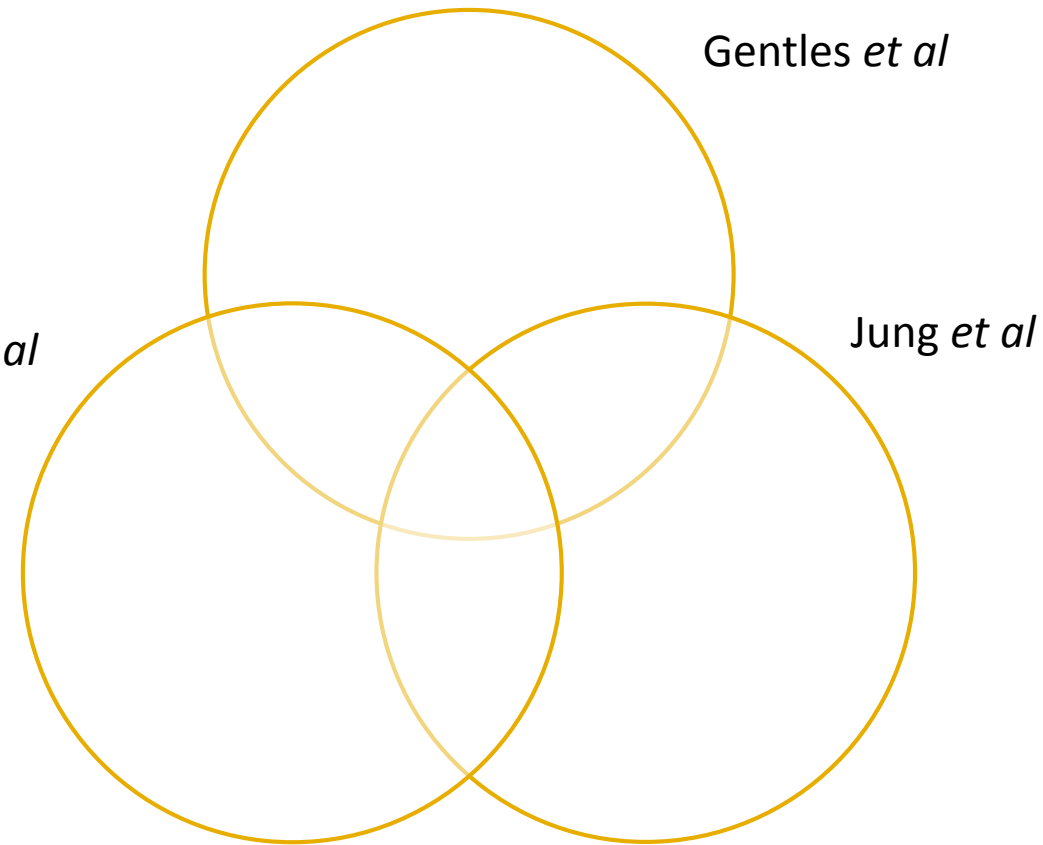
Data mining for AML LSC immune markers



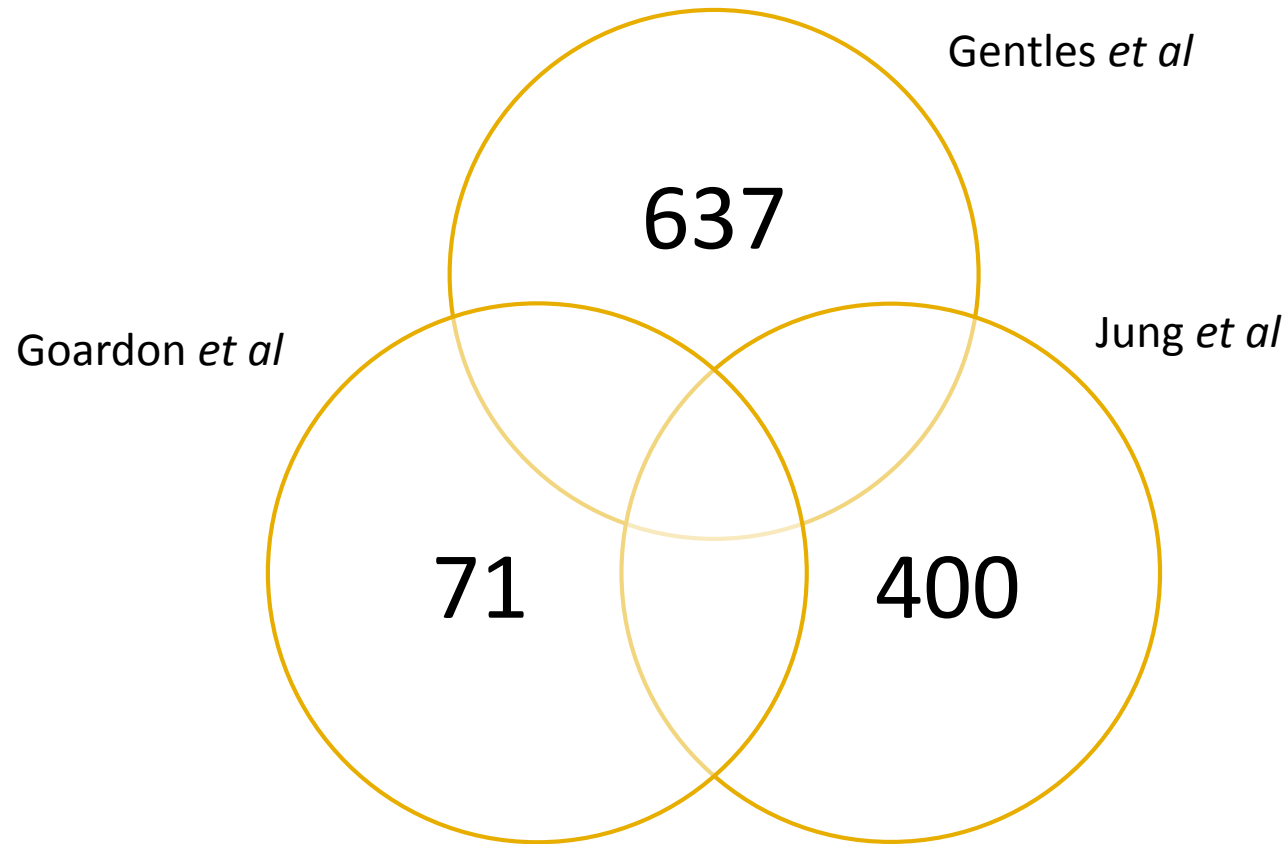
Data mining for AML LSC immune markers



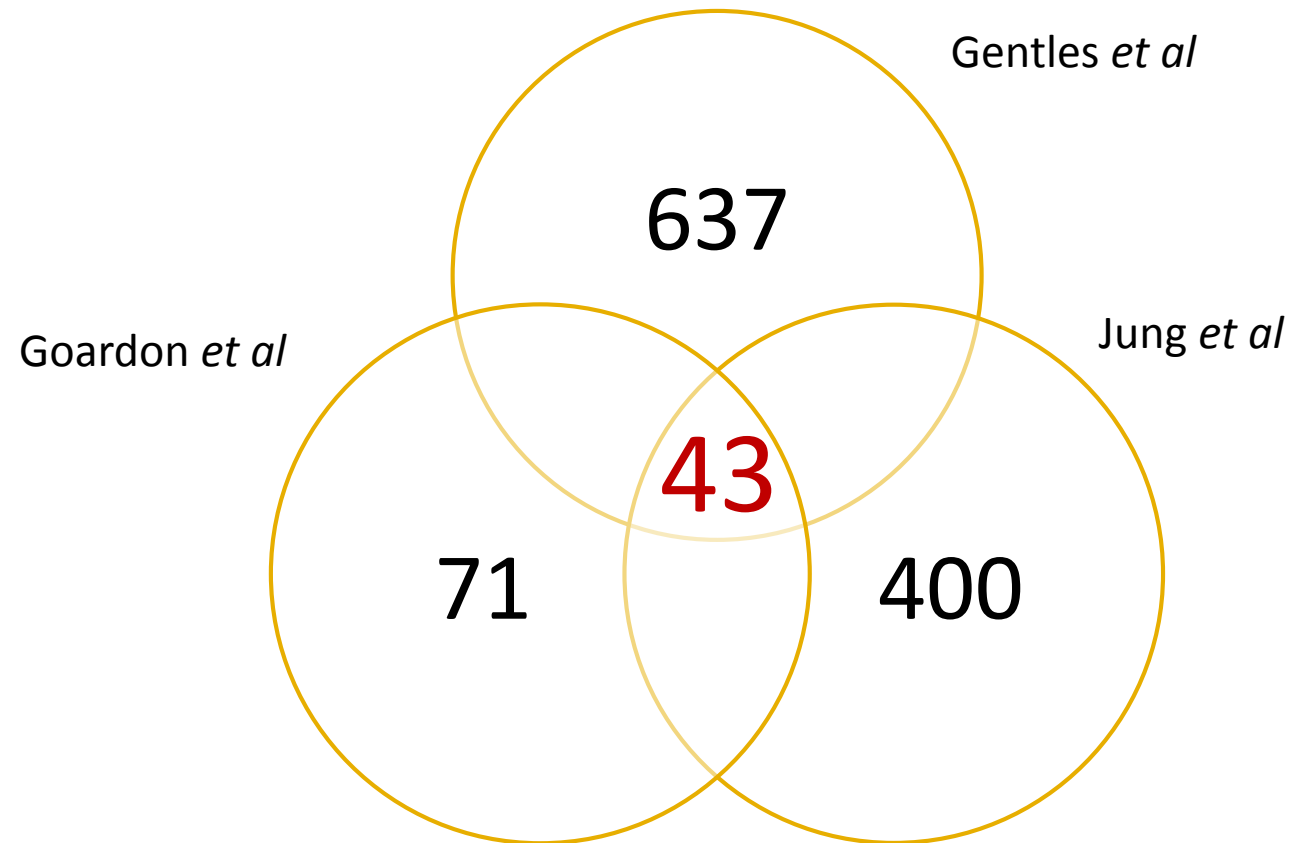
Data mining for AML LSC immune markers



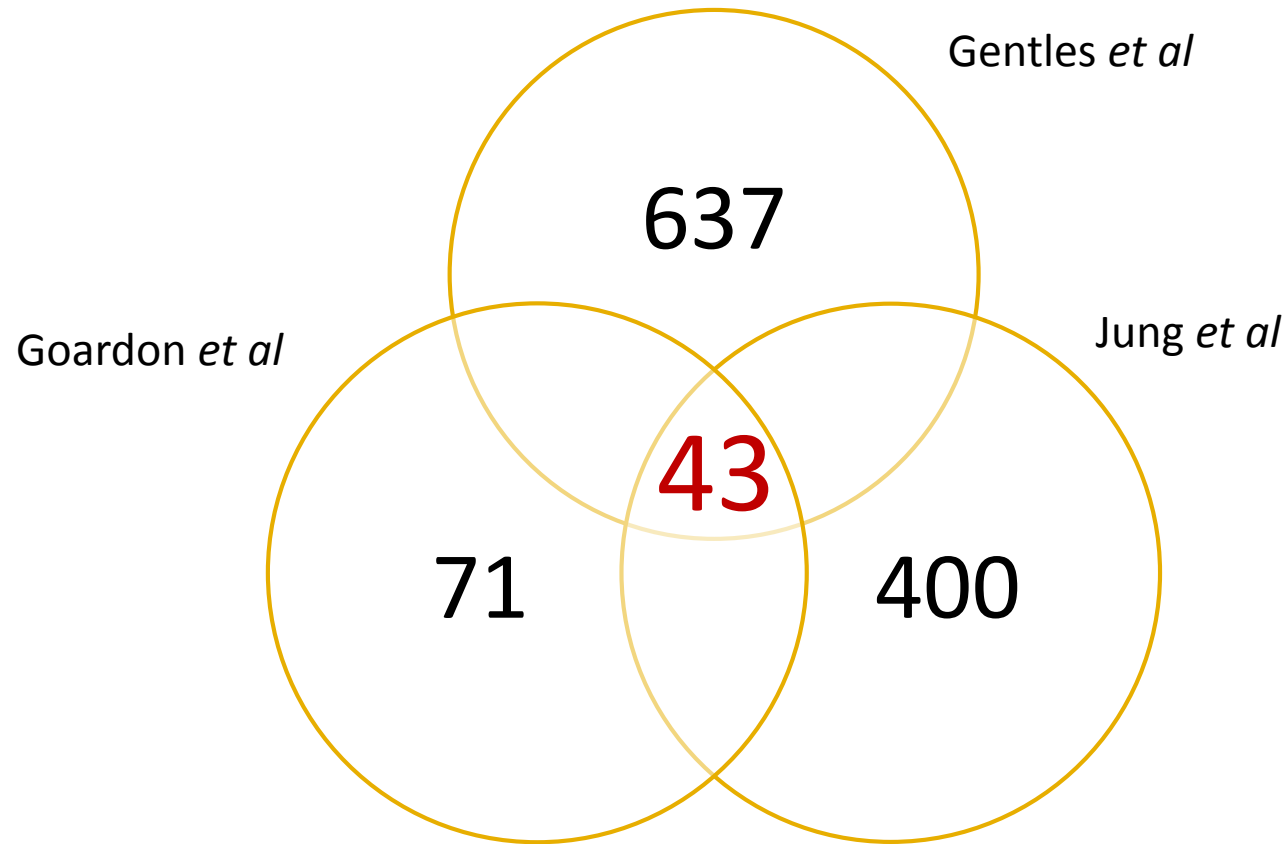
Data mining for AML LSC immune markers



Data mining for AML LSC immune markers

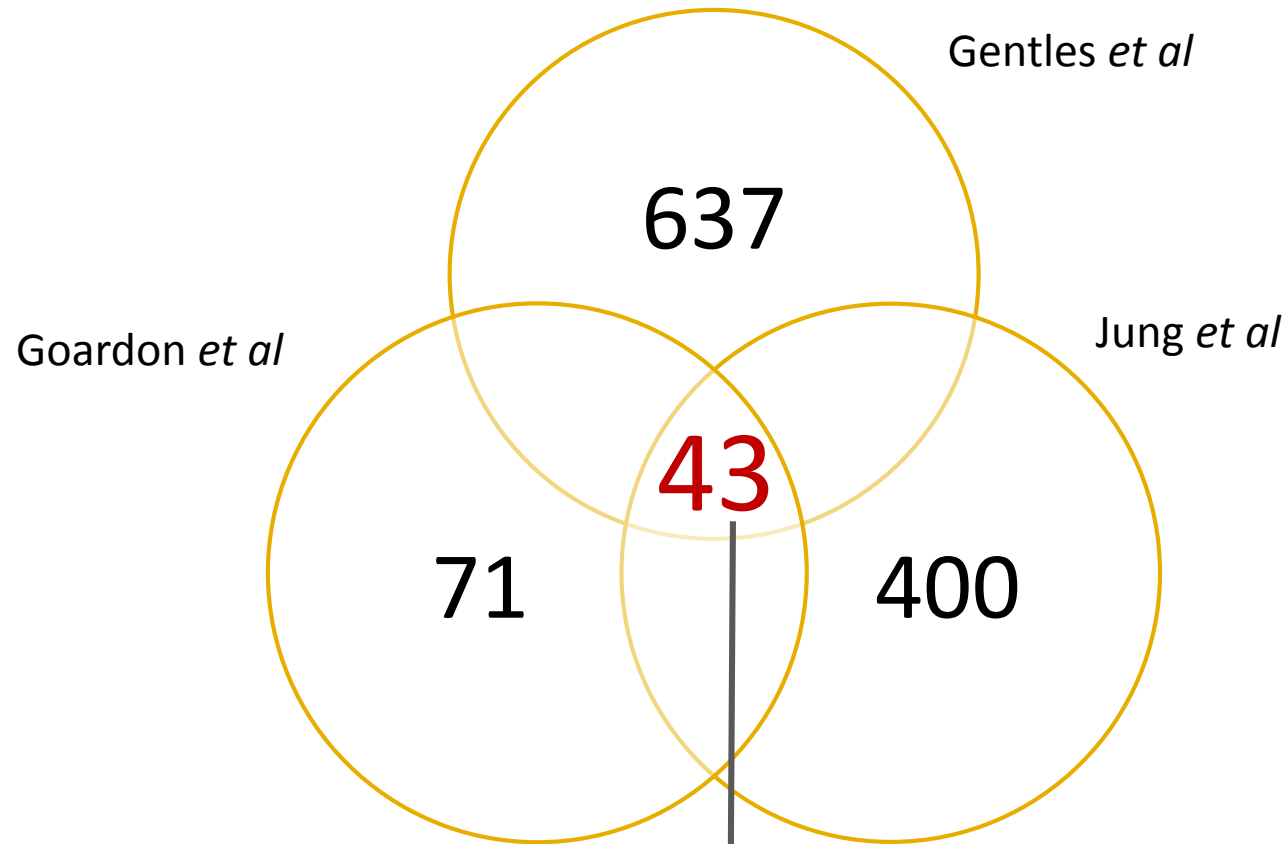


Data mining for AML LSC immune markers



- ✓ Novel in AML
- ✓ Immune regulator
- ✓ Expressed on surface

Data mining for AML LSC immune markers



- ✓ Novel in AML
- ✓ Immune regulator
- ✓ Expressed on surface

CD200

AML

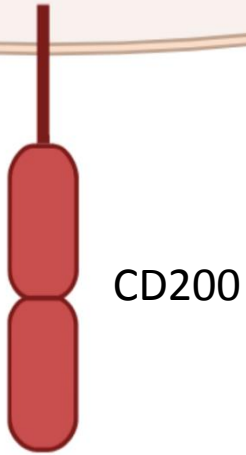


CD200

CD200 background

type-1 transmembrane glycoprotein

AML



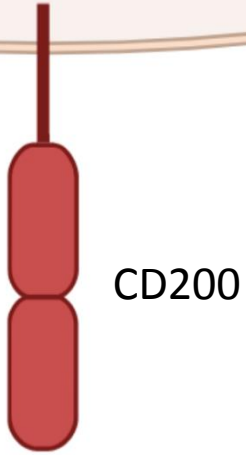
CD200

CD200 background

type-1 transmembrane glycoprotein

no well-established intrinsic function

AML



CD200 background

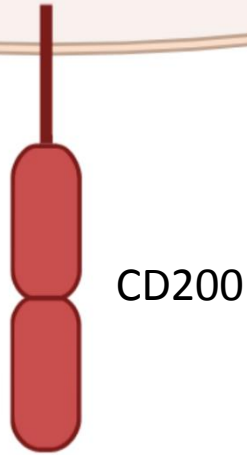
type-1 transmembrane glycoprotein

no well-established intrinsic function

correlates with CD34 in leukemia and epithelial stem cell markers in solid tumors

Kawasaki et al. *Biochem Biophys Res Commun* (2007)

AML



CD200 background

type-1 transmembrane glycoprotein

no well-established intrinsic function

correlates with CD34 in leukemia and epithelial stem cell markers in solid tumors

Kawasaki et al. Biochem Biophys Res Commun (2007)

CD200+ AML patients have significantly reduced overall survival

Damiani et al. Oncotarget (2015)

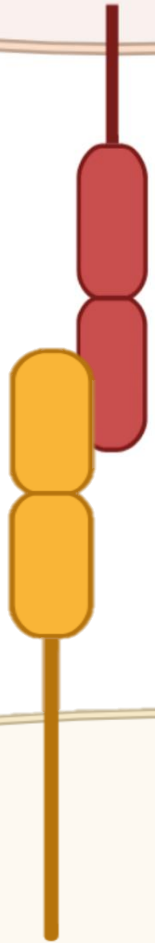
AML

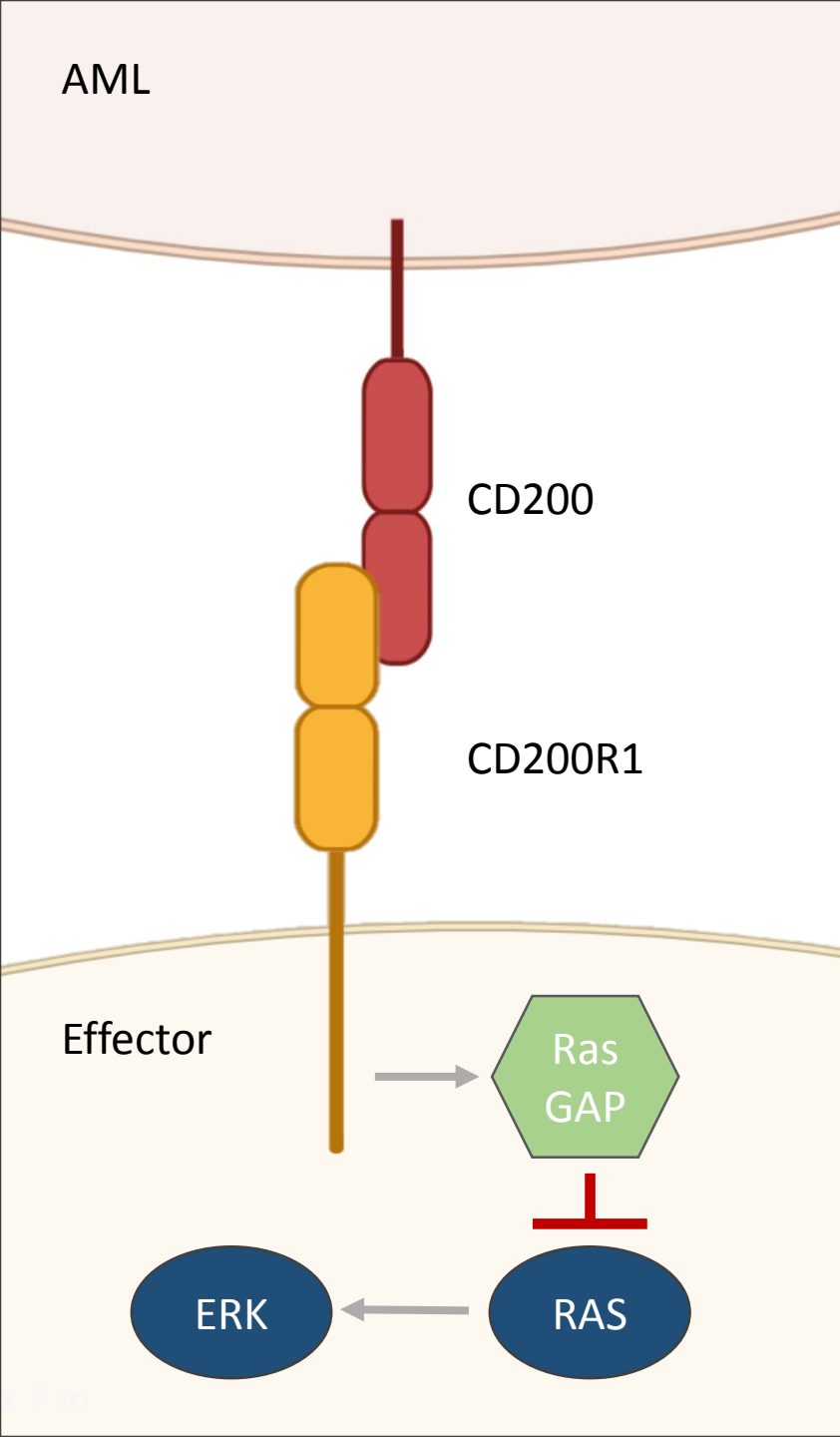
CD200

CD200R1

Effector

CD200 is immunosuppressive

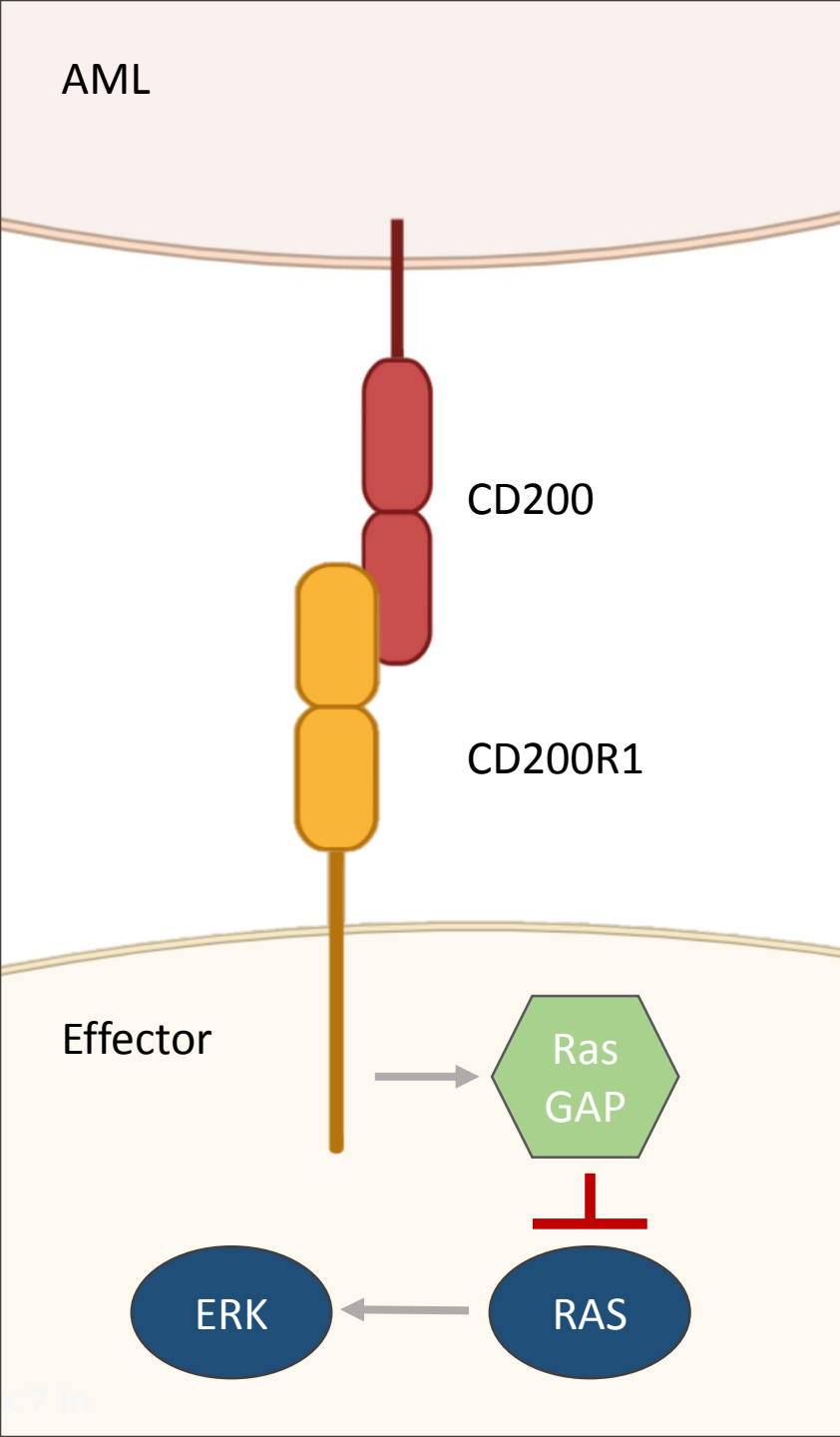




CD200 is immunosuppressive

directly suppresses through CD200R1
expressed on myeloid cells and subsets of NK
and T cells

Hoek et al. *Science* (2000)



CD200 is immunosuppressive

directly suppresses through CD200R1
expressed on myeloid cells and subsets of NK
and T cells

Hoek et al. *Science* (2000)

correlates with accumulation of CD4+FOXP3+
regulatory T cells in AML

Coles et al. *Leukemia* (2012)

AML

CD200

CD200R1

Effector

Ras
GAP

ERK

RAS

CD200 is immunosuppressive

directly suppresses through CD200R1
expressed on myeloid cells and subsets of NK
and T cells

Hoek et al. *Science* (2000)

correlates with accumulation of CD4+FOXP3+
regulatory T cells in AML

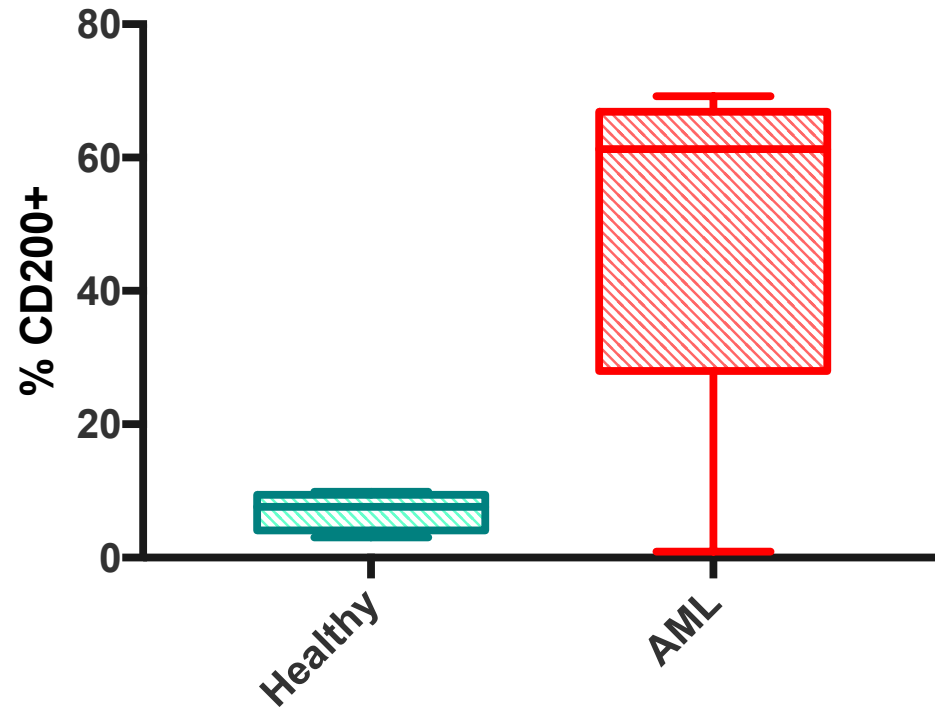
Coles et al. *Leukemia* (2012)

associated with impaired NK and CD4+Th1
function in AML

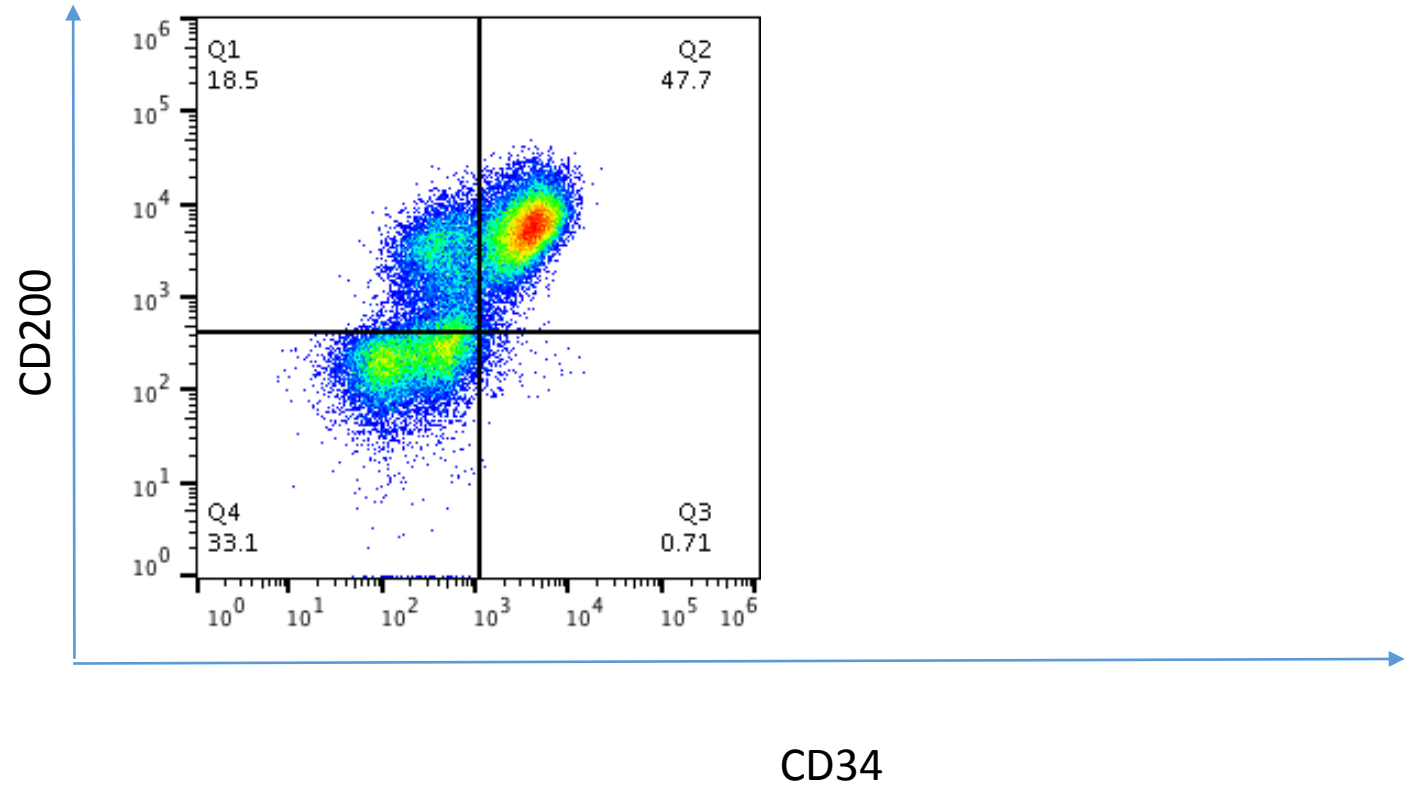
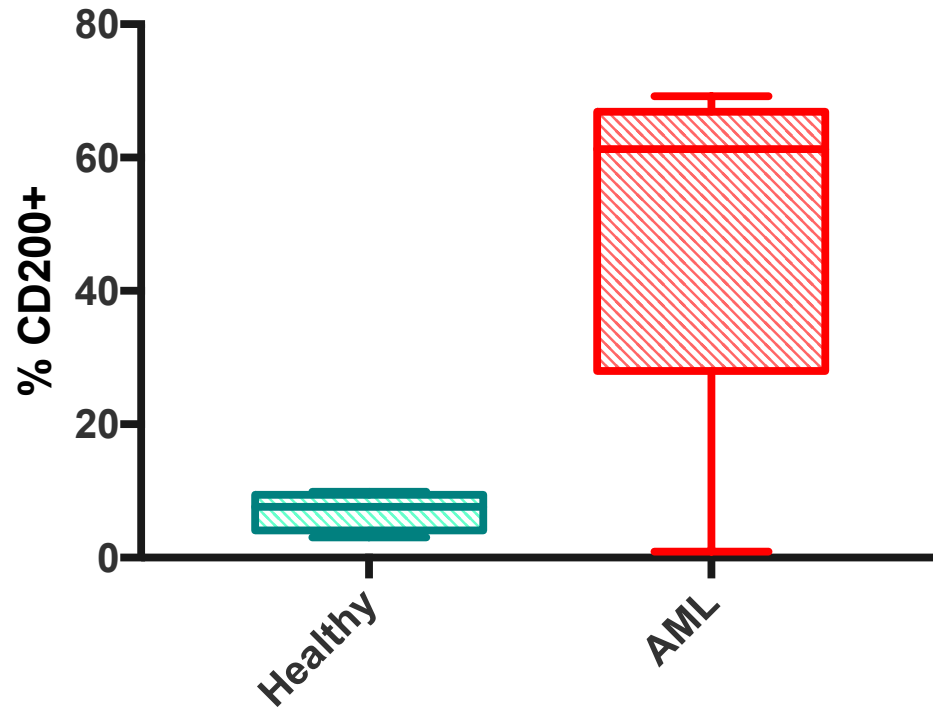
Coles et al. *Leukemia* (2011)

Coles et al. *Leukemia* (2012)

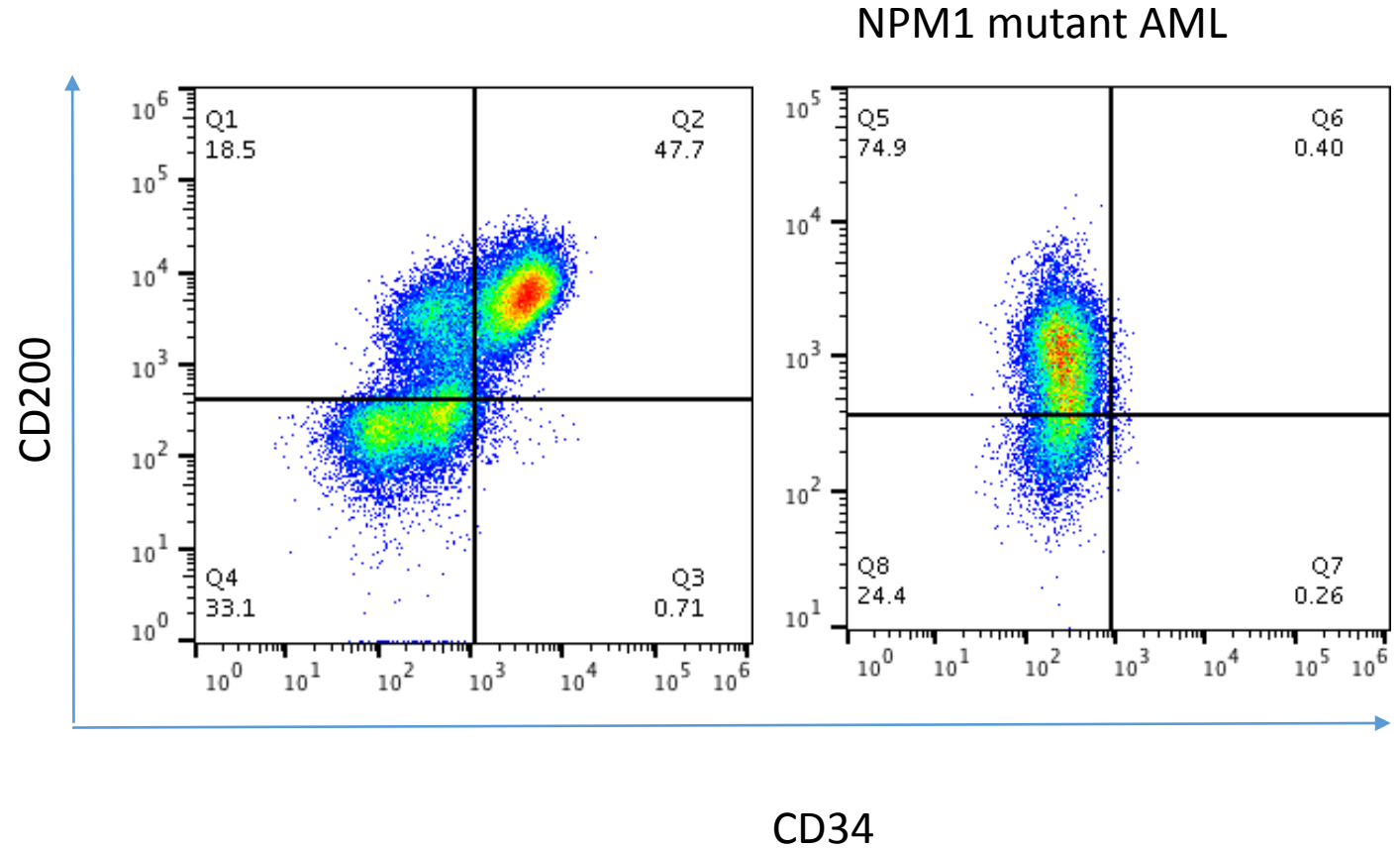
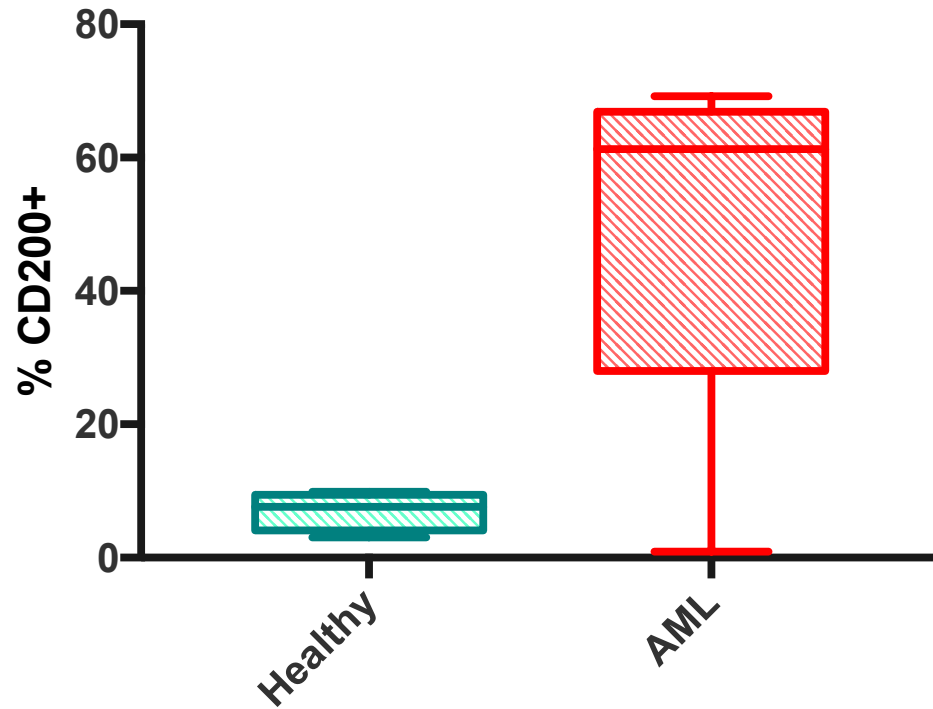
CD200 is expressed in primary AML patients



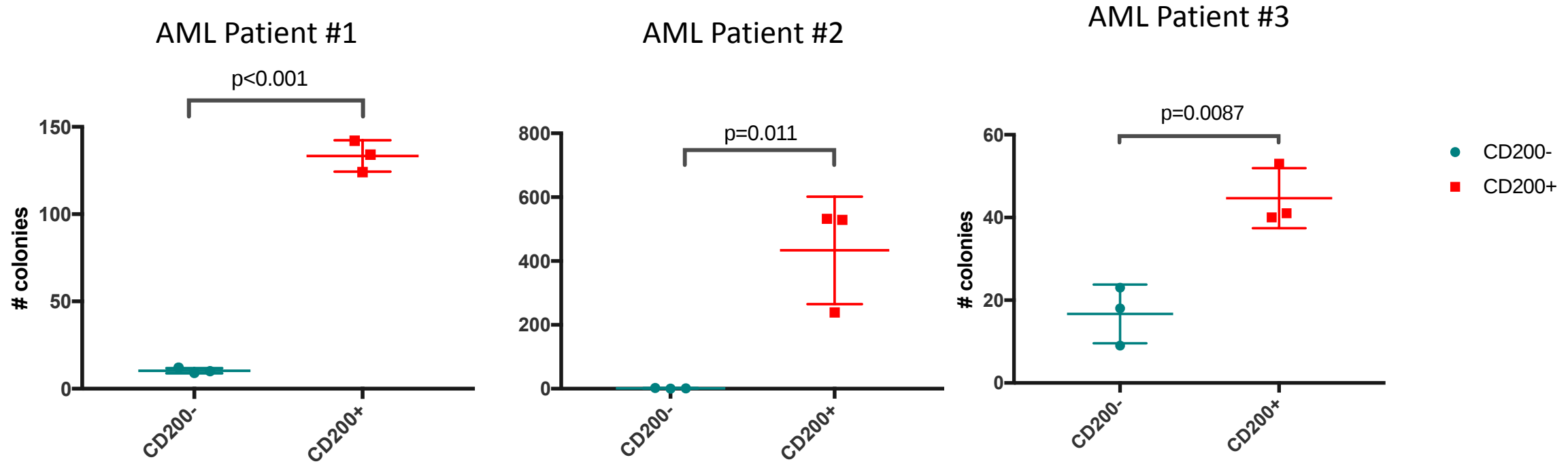
CD200 is expressed in primary AML patients



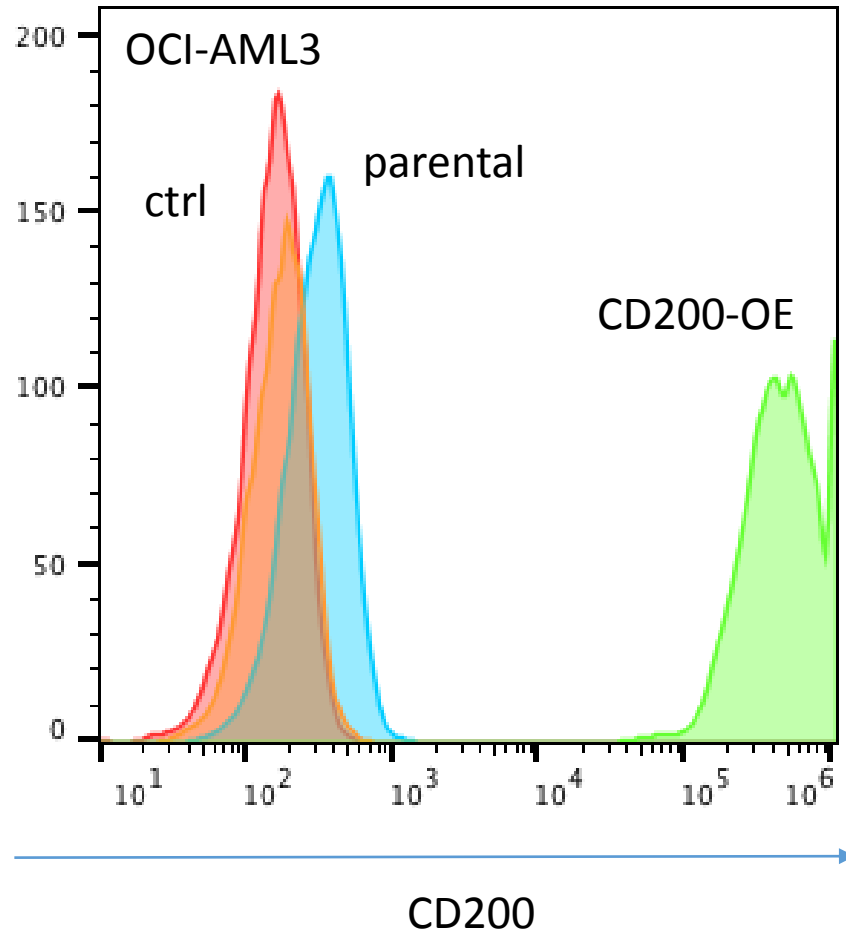
CD200 is expressed in primary AML patients



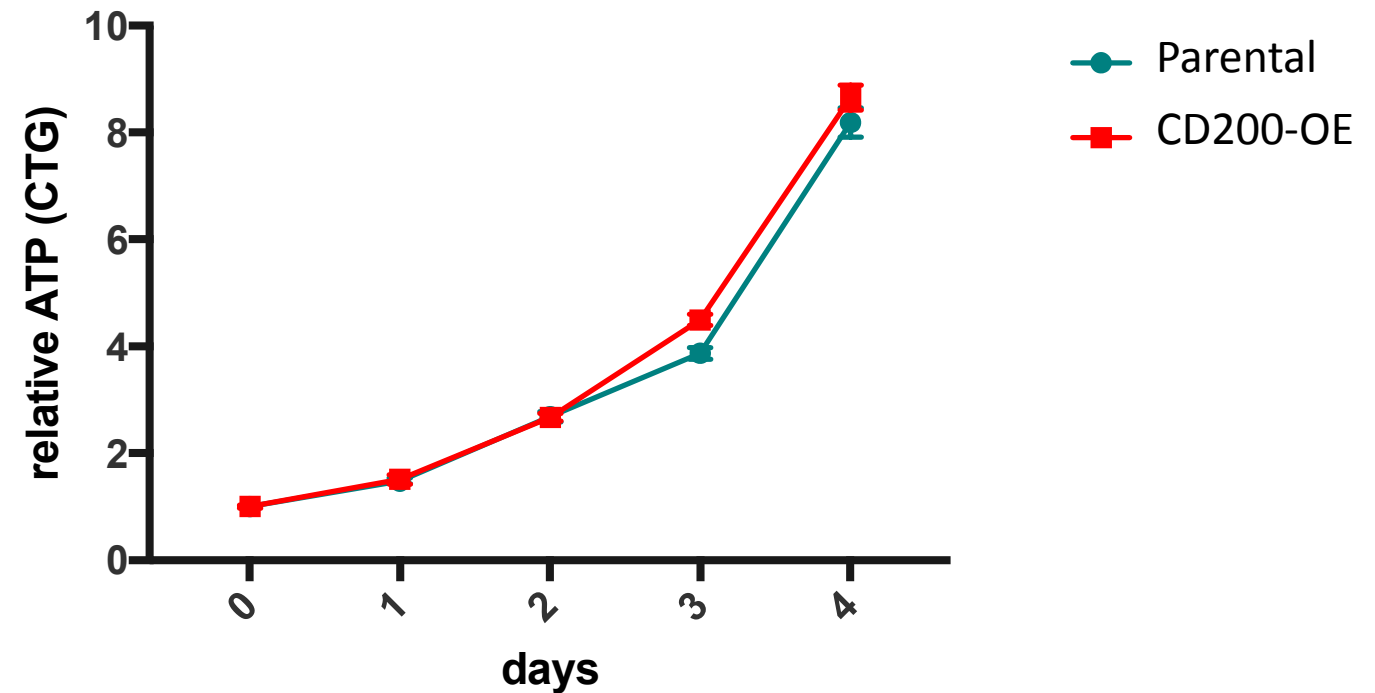
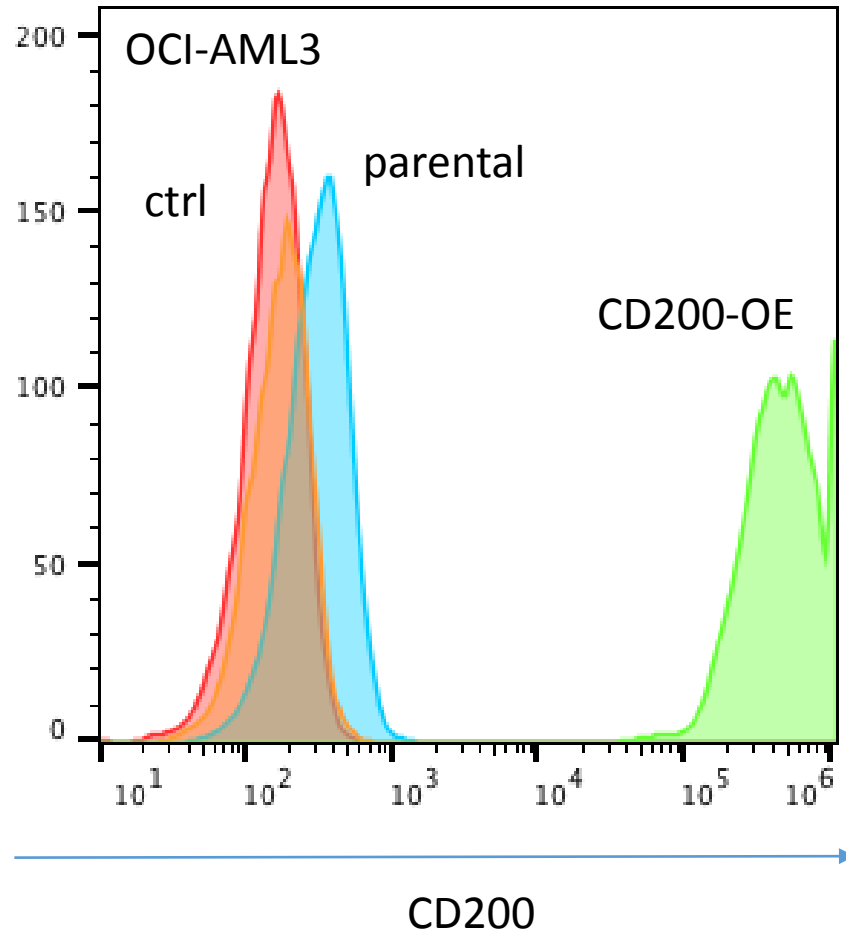
CD200+ AML cells have colony formation potential



CD200 overexpression does not alter proliferation

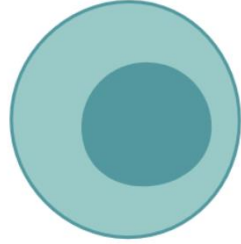
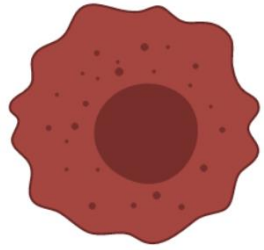


CD200 overexpression does not alter proliferation

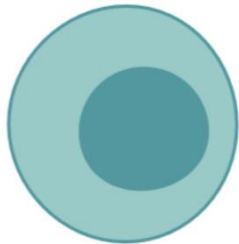
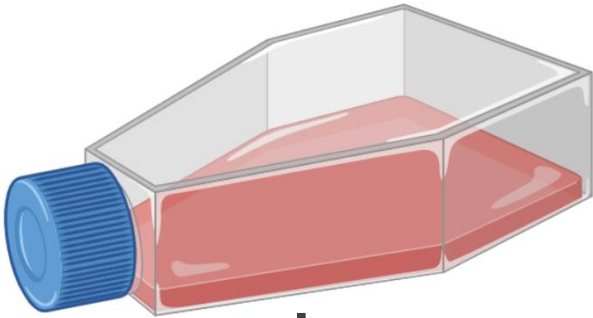


CD200 directly suppresses T cell MAPK signaling

OCI-AML3
Parental
CD200-OE

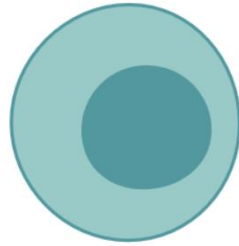
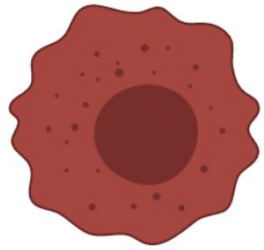


CD3+ T cells

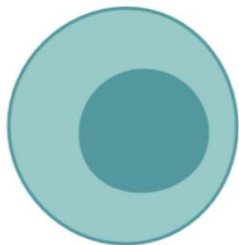
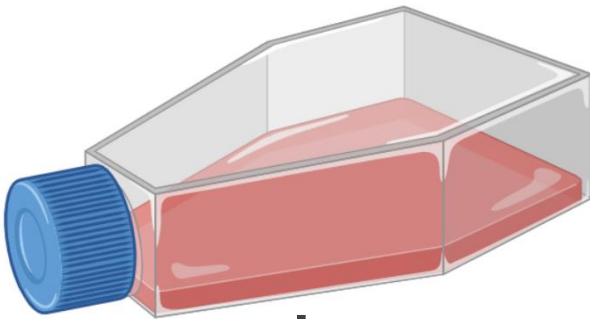


CD200 directly suppresses T cell MAPK signaling

OCI-AML3
Parental
CD200-OE



CD3+ T cells



Sorted T cells

co-cultured with:

control

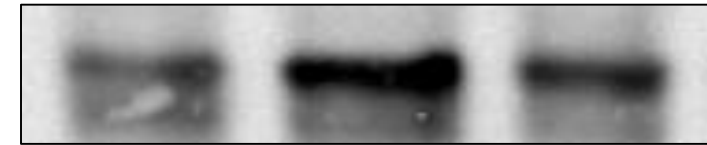
parental

CD200-OE

p-ERK



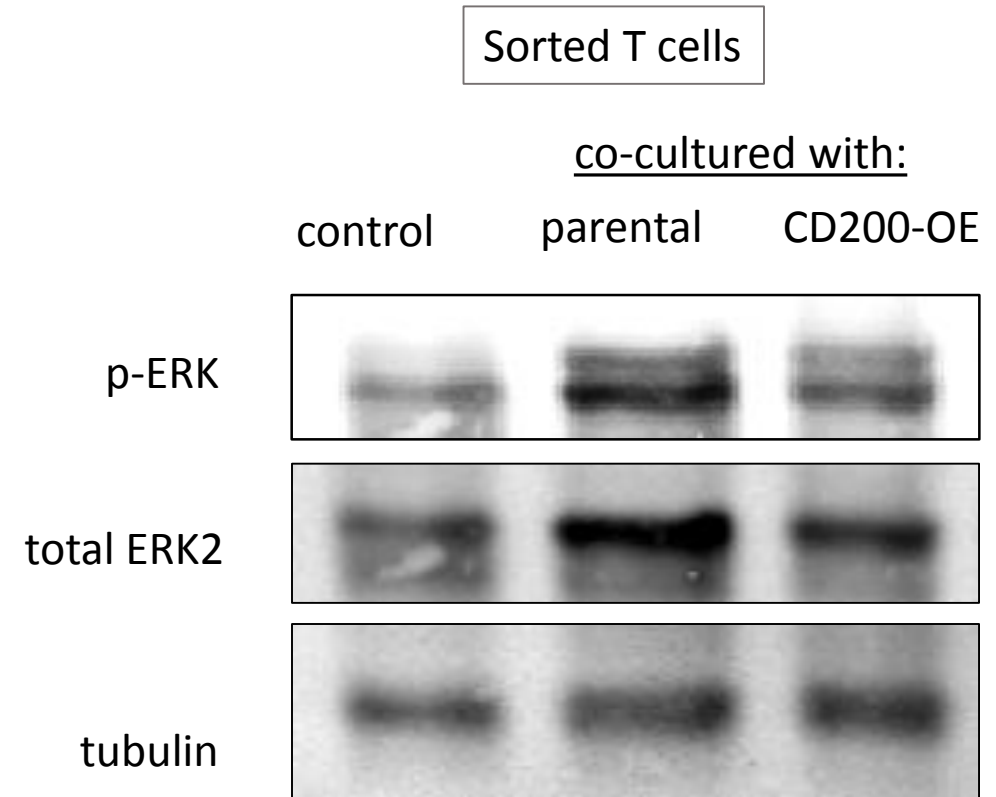
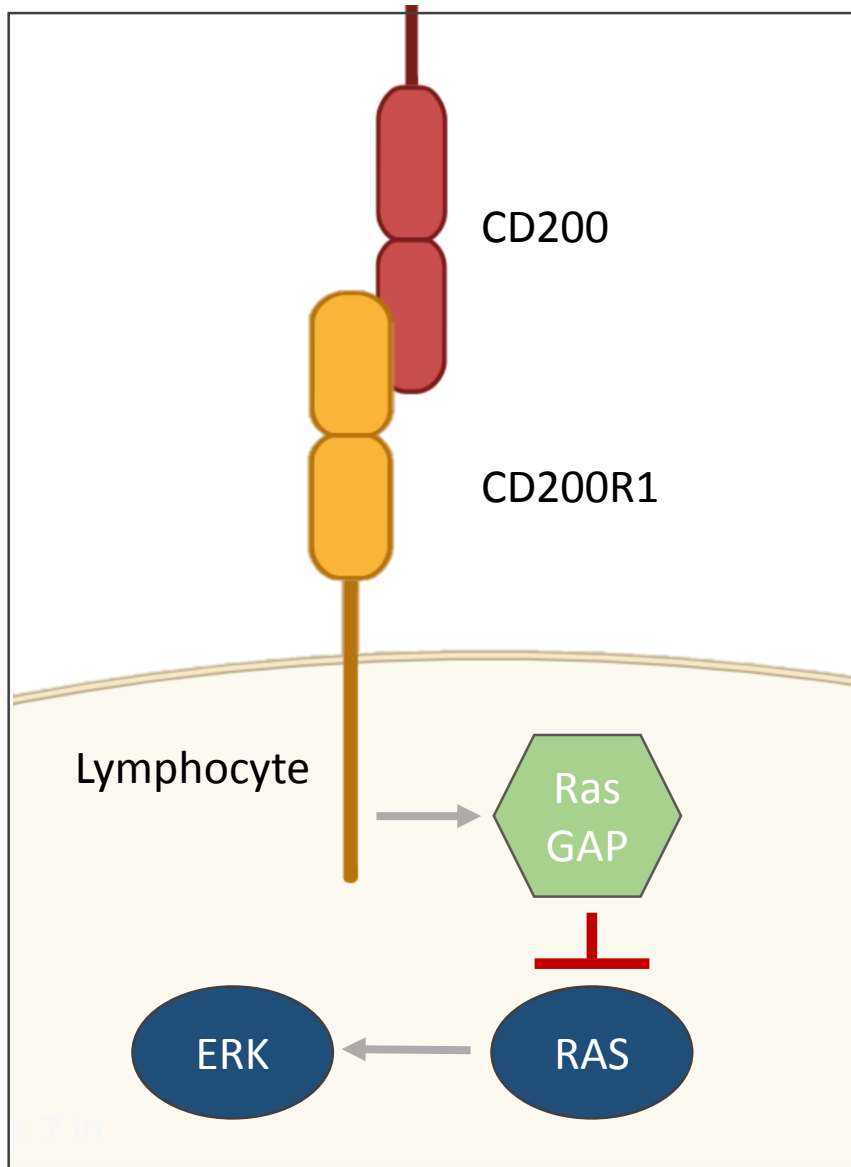
total ERK2



tubulin



CD200 directly suppresses T cell MAPK signaling



Functional consequences of suppression



AML-CD200 does not alter T cell killing *in vitro*

Functional consequences of suppression

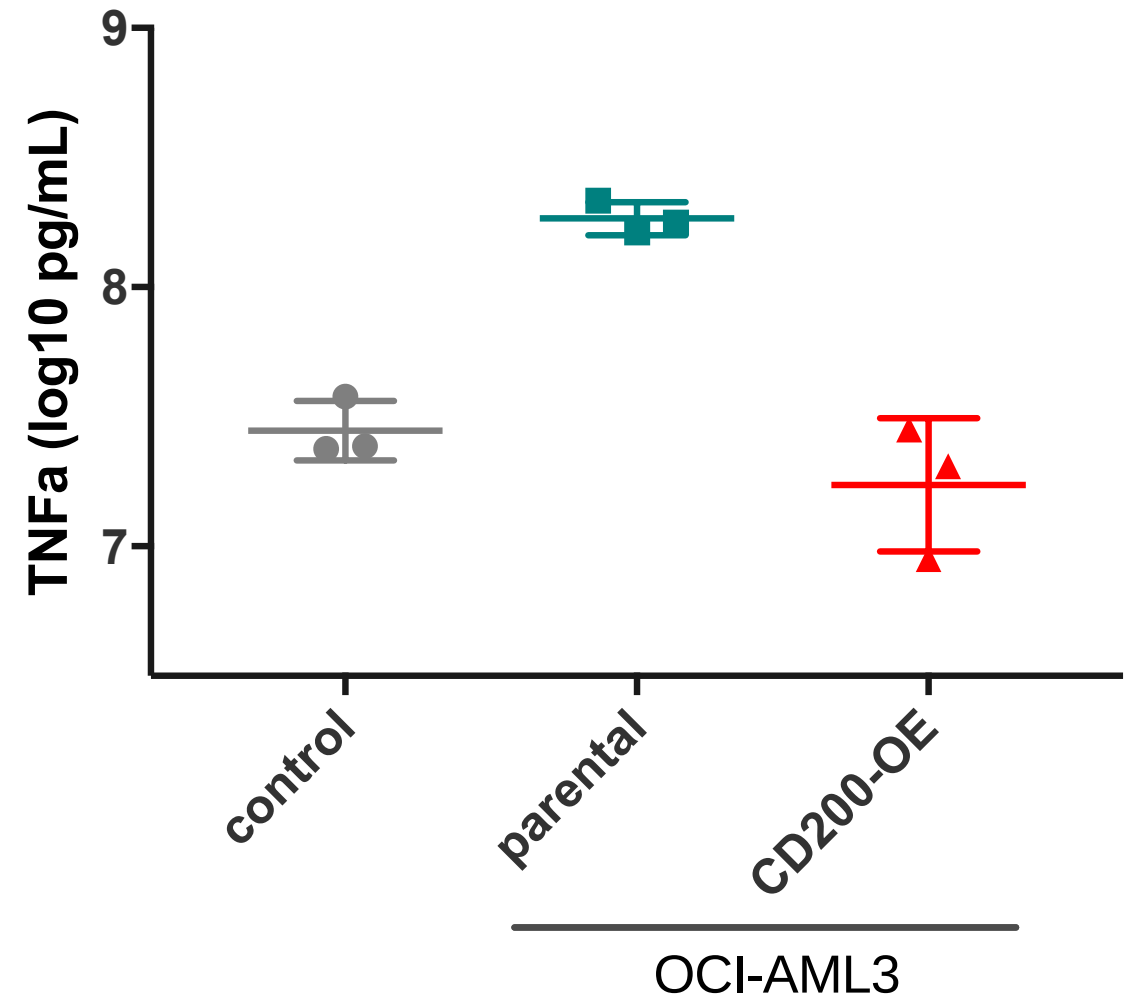
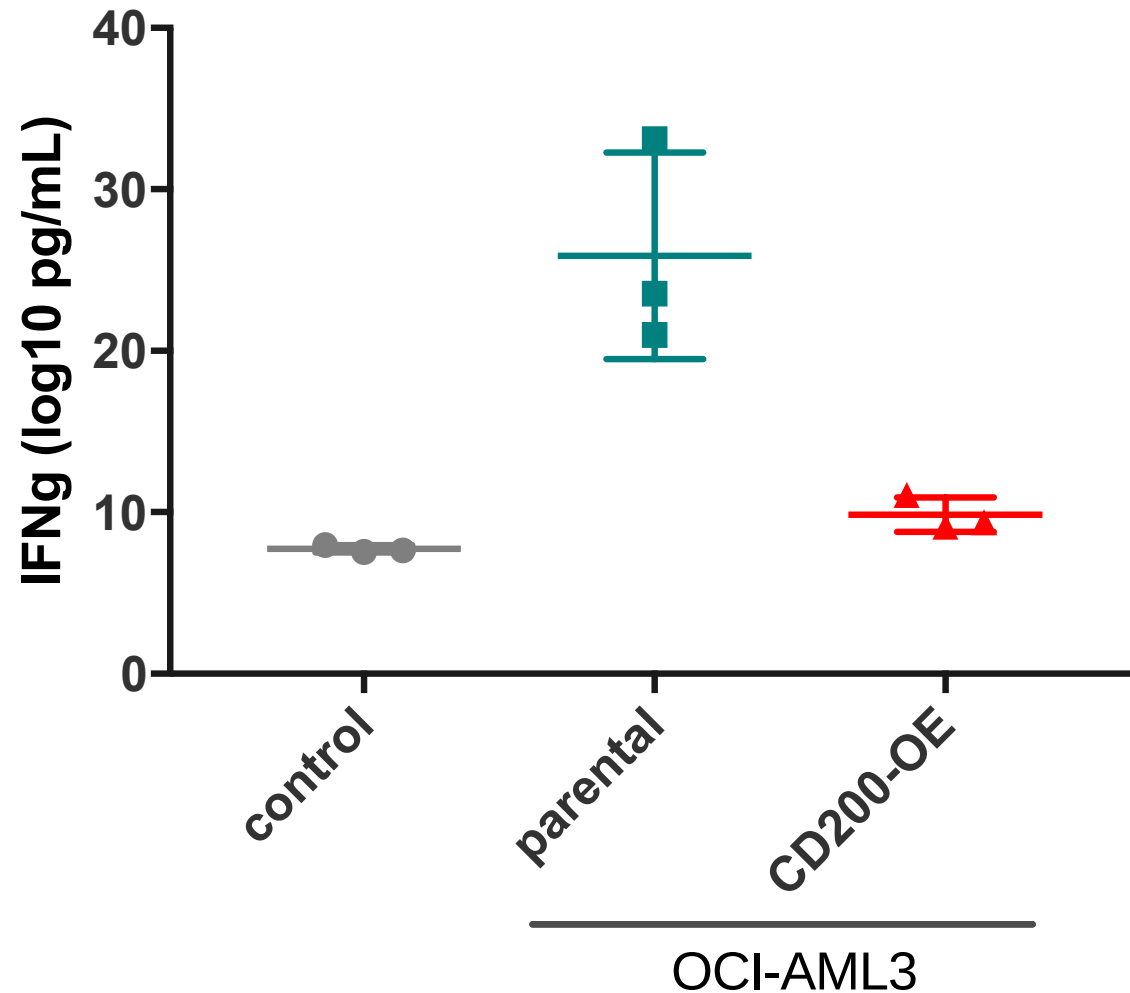


AML-CD200 does not alter T cell killing *in vitro*

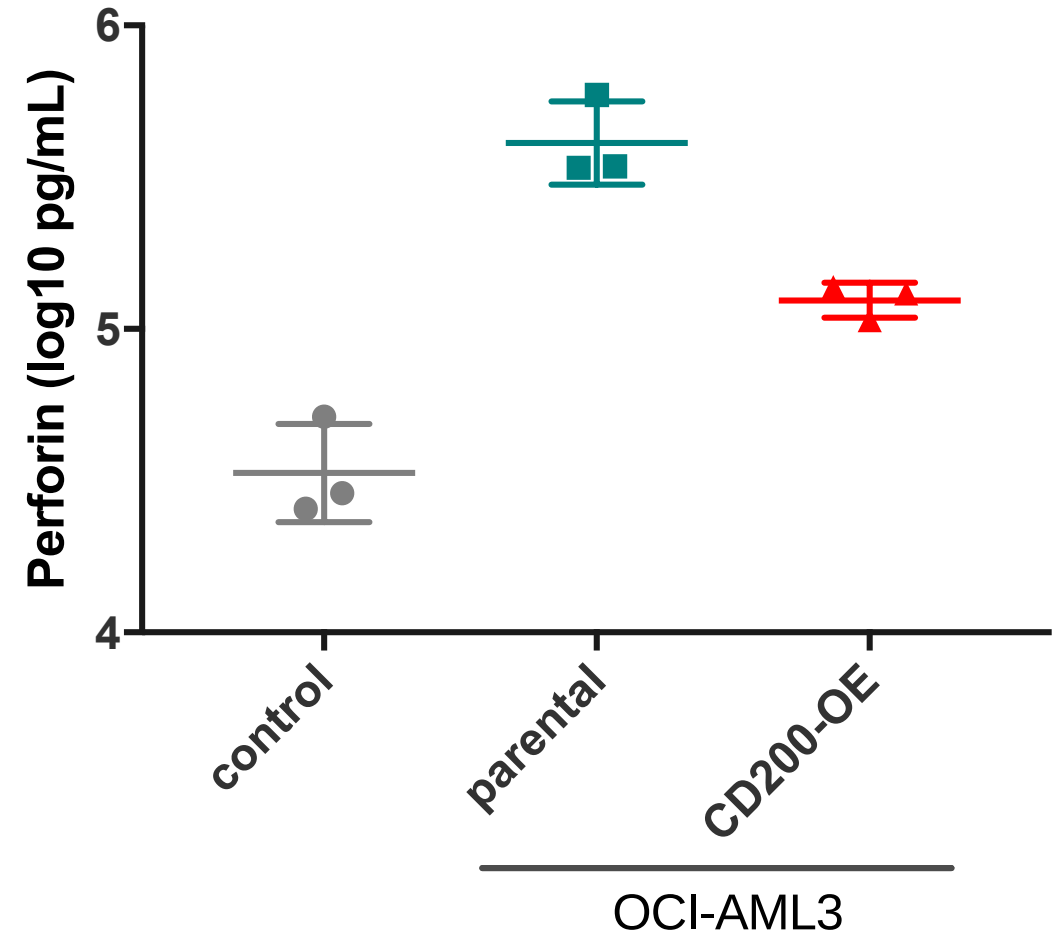
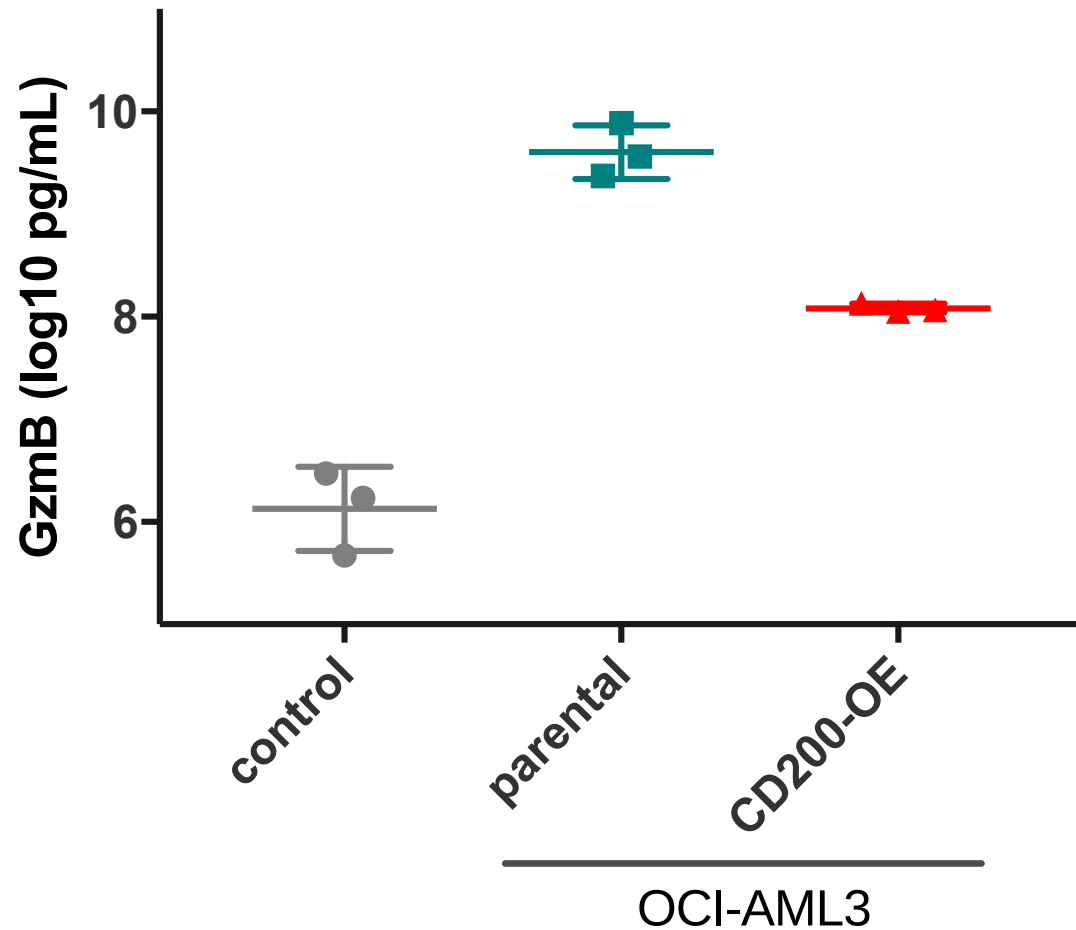


AML-CD200 does not influence CD4 or CD8 T cell proliferation *in vitro*

CD200 suppresses T cell cytokine production



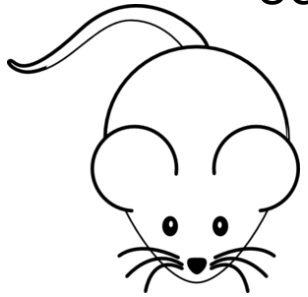
CD200 suppresses T cell cytokine production



In vivo model 1: Immunodeficient

Inject 0.1×10^6
OCI-AML3

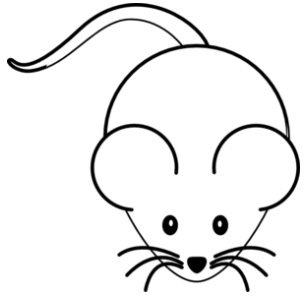
Parental



D0

D7

CD200-OE

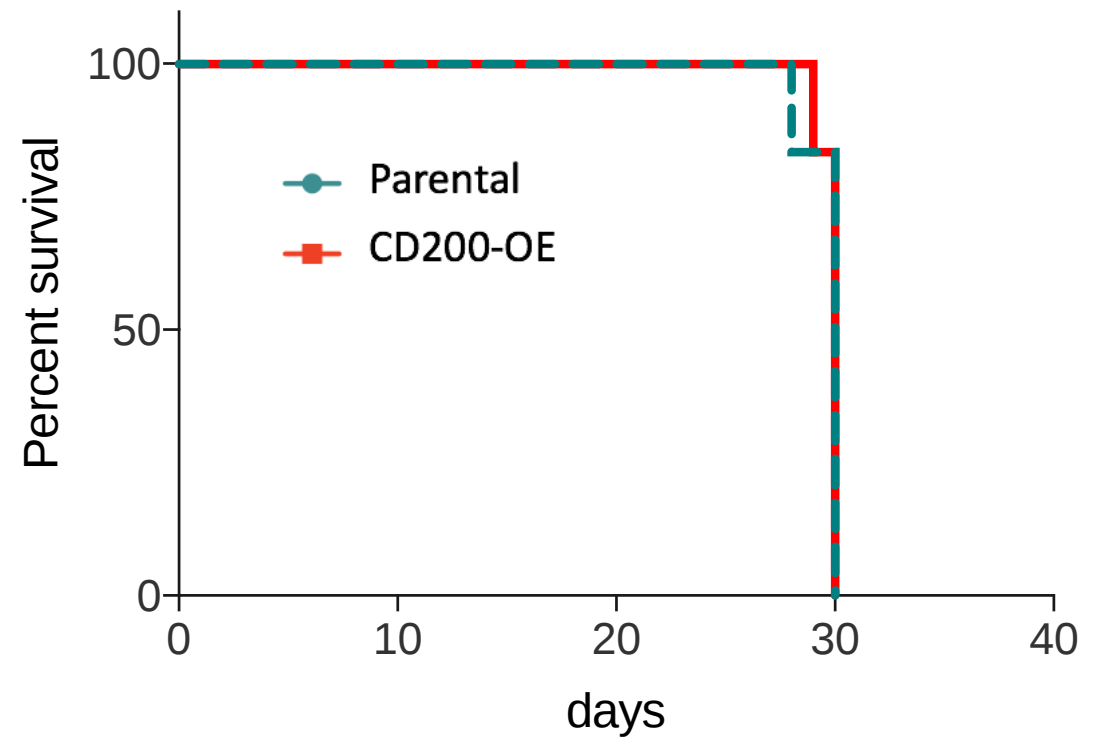
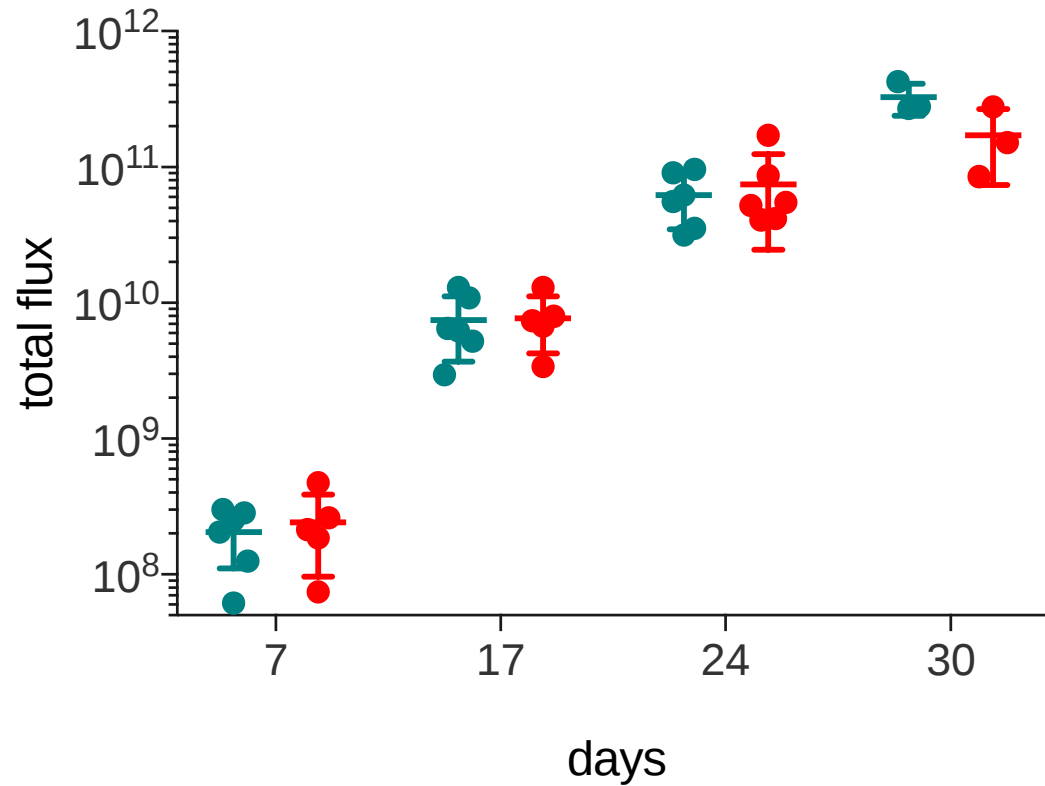


D0

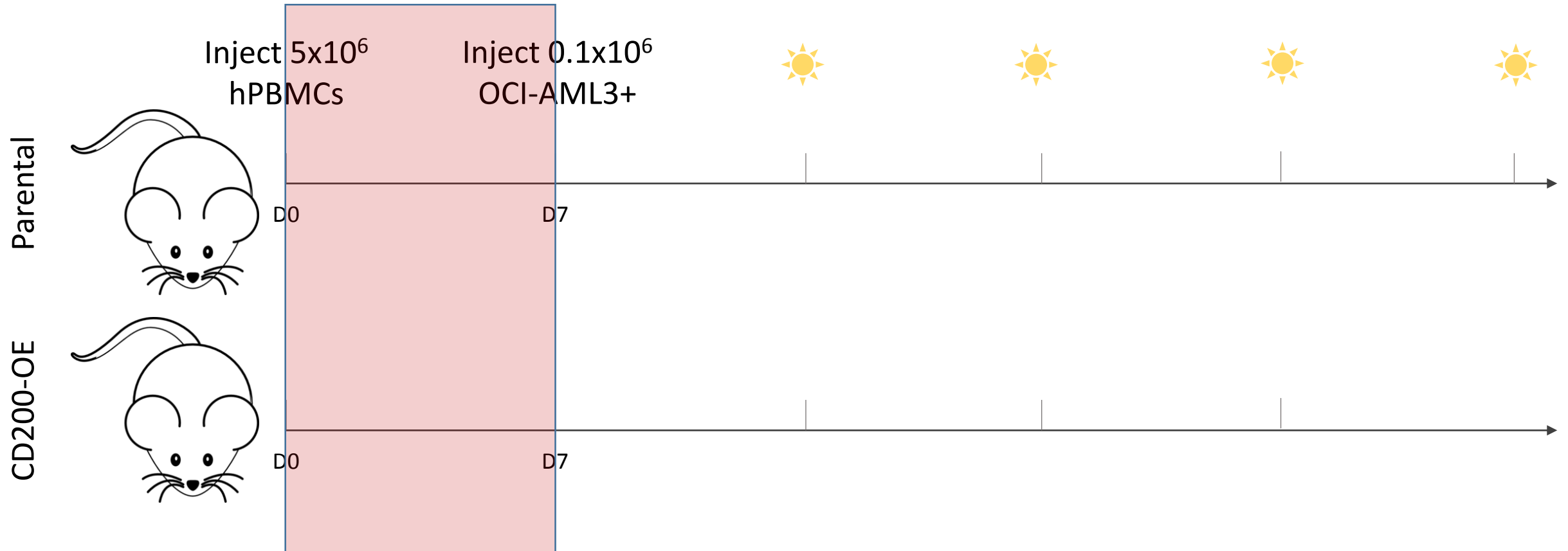
D7



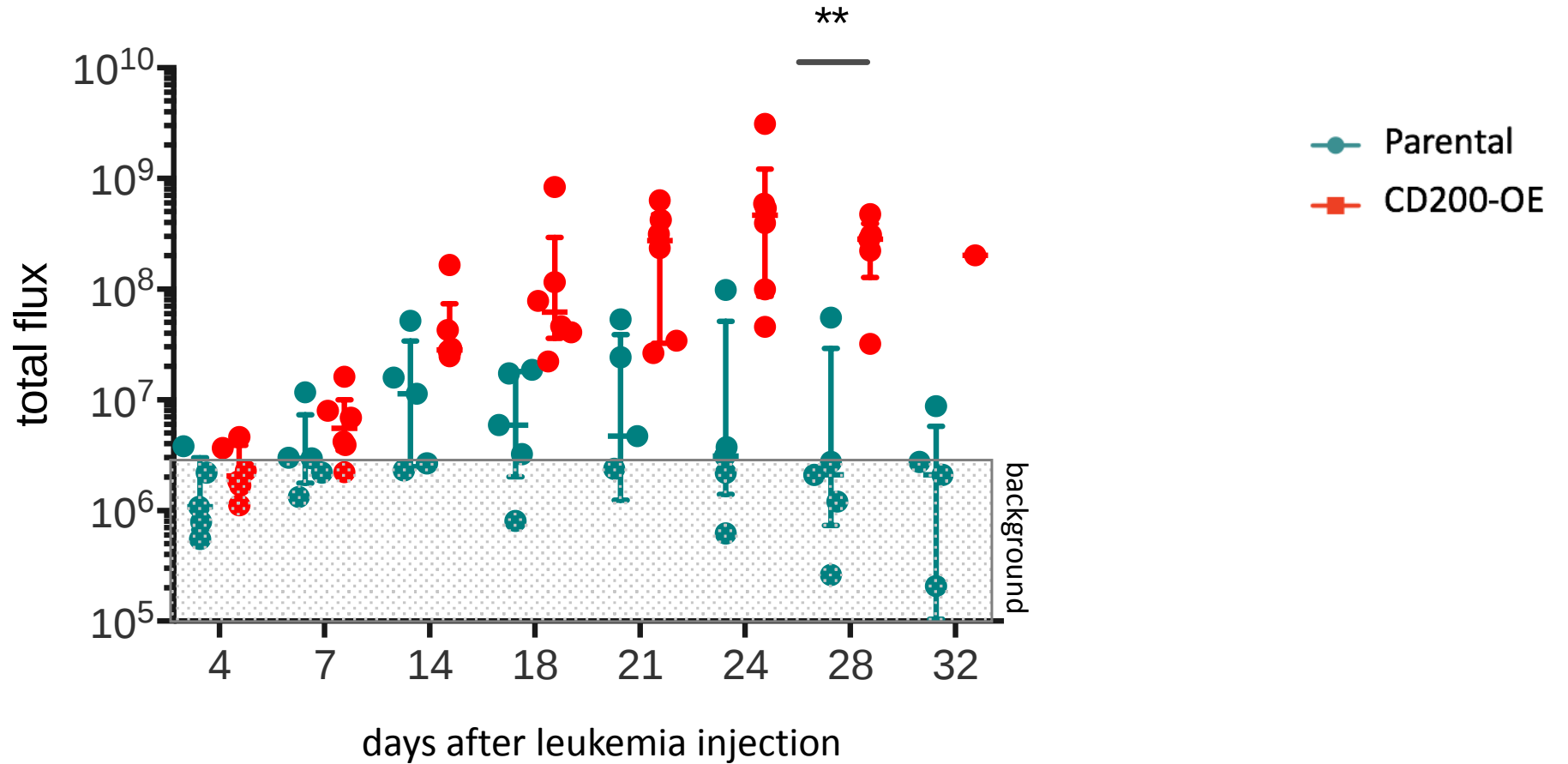
CD200 does not alter leukemic progression in NSG



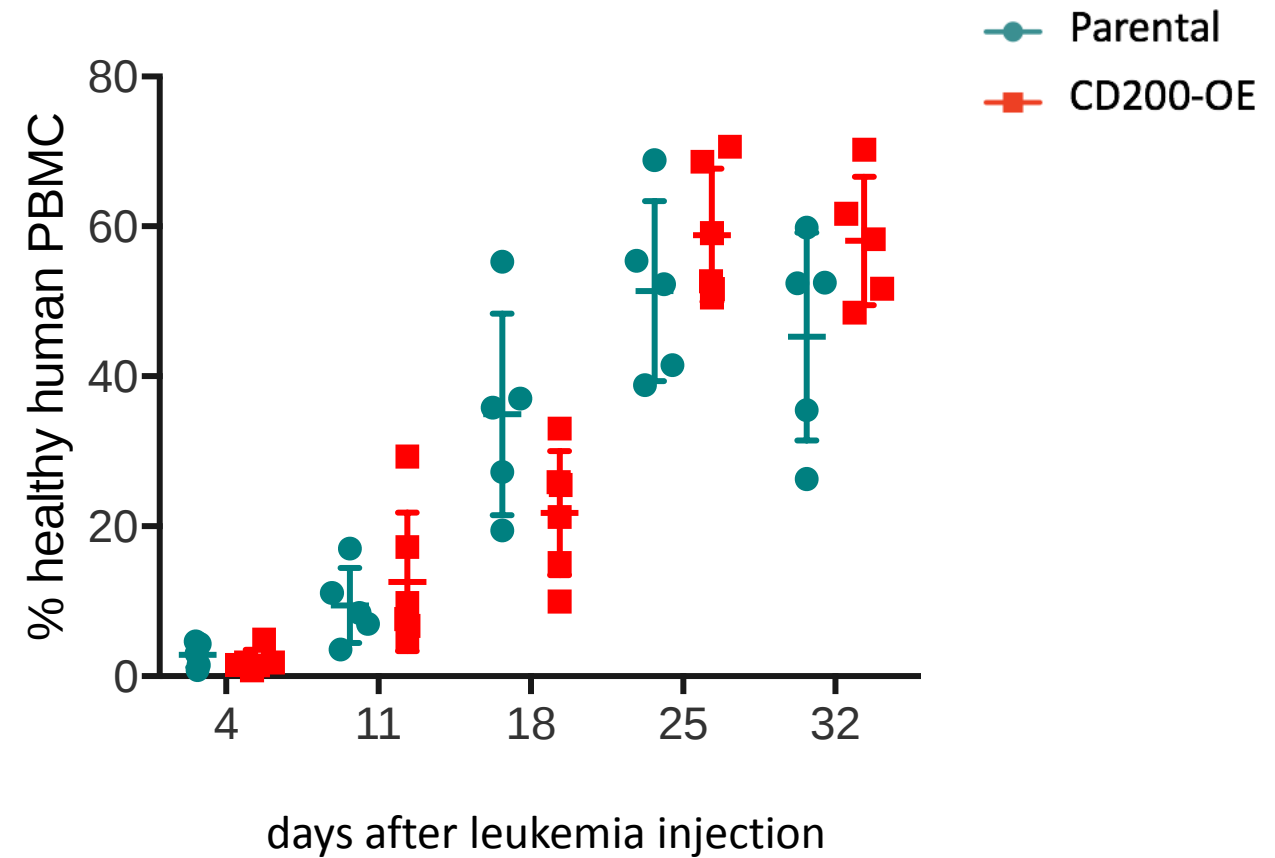
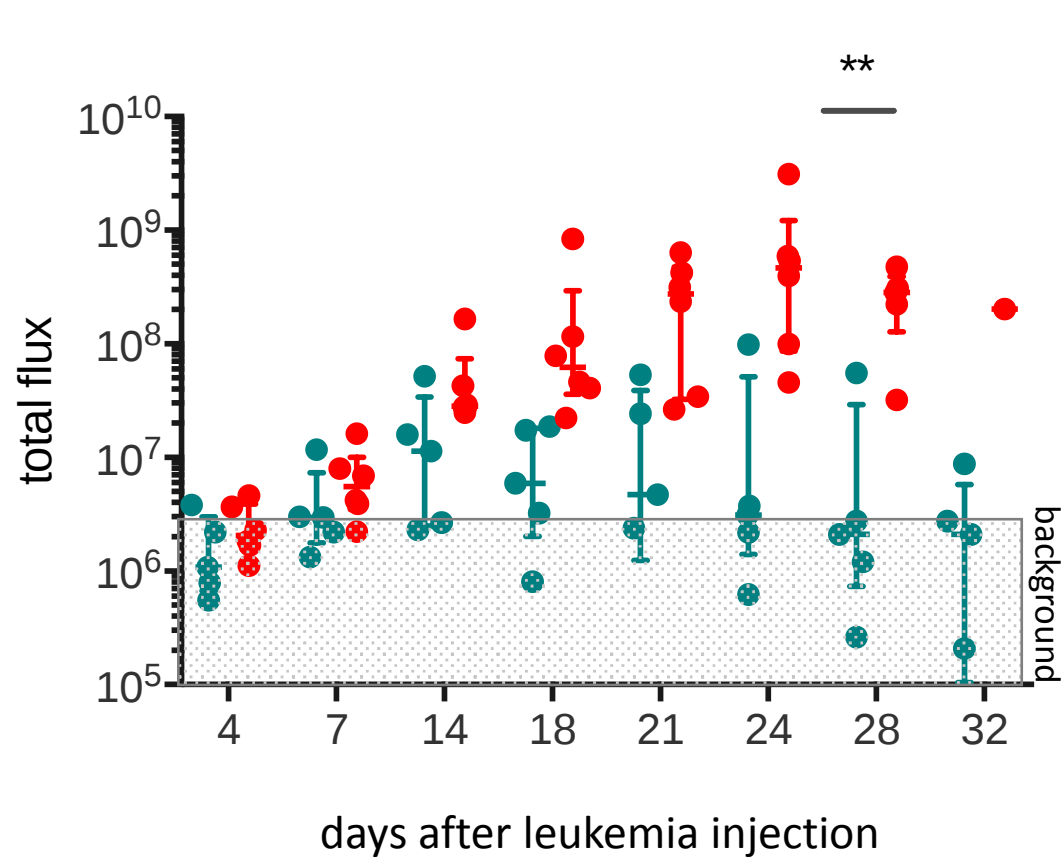
In vivo model 2: PBMC-humanized



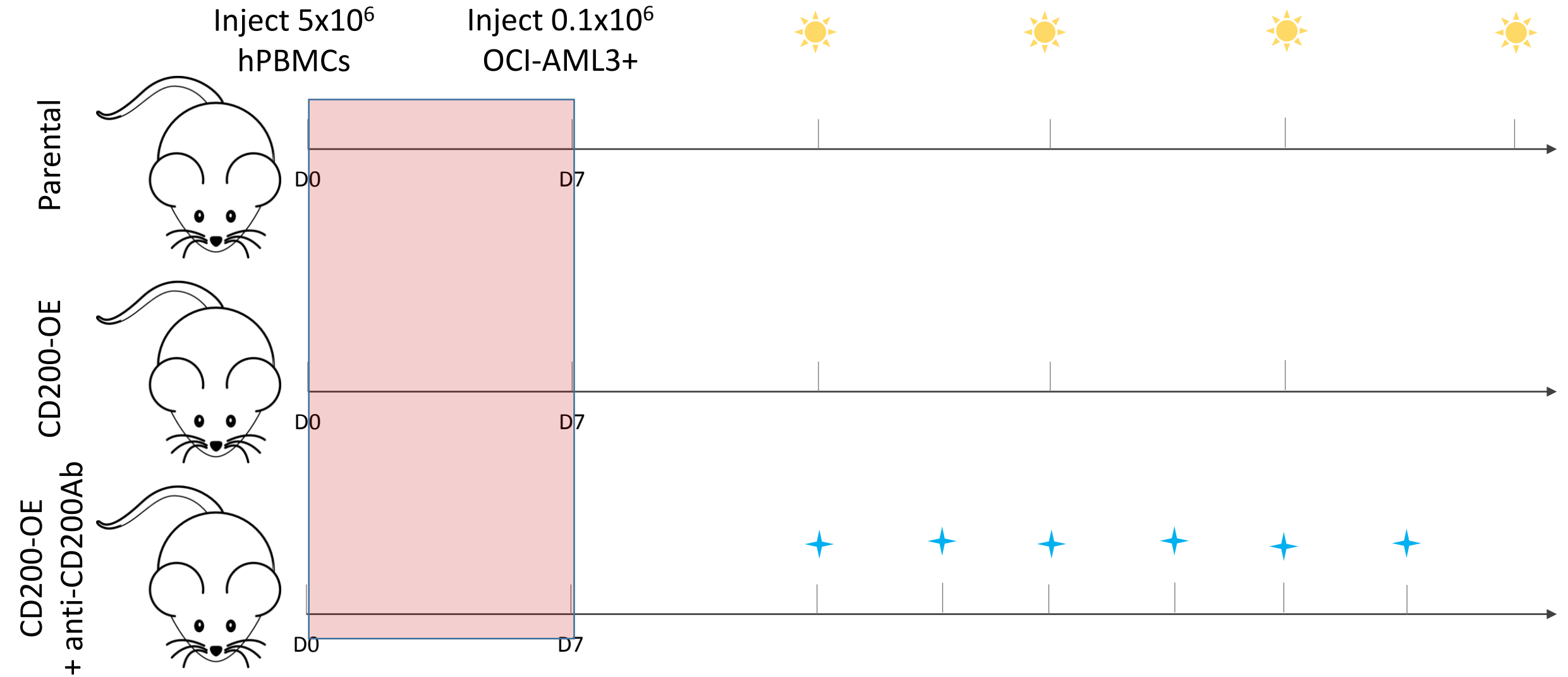
CD200-OE cells persist in humanized mice



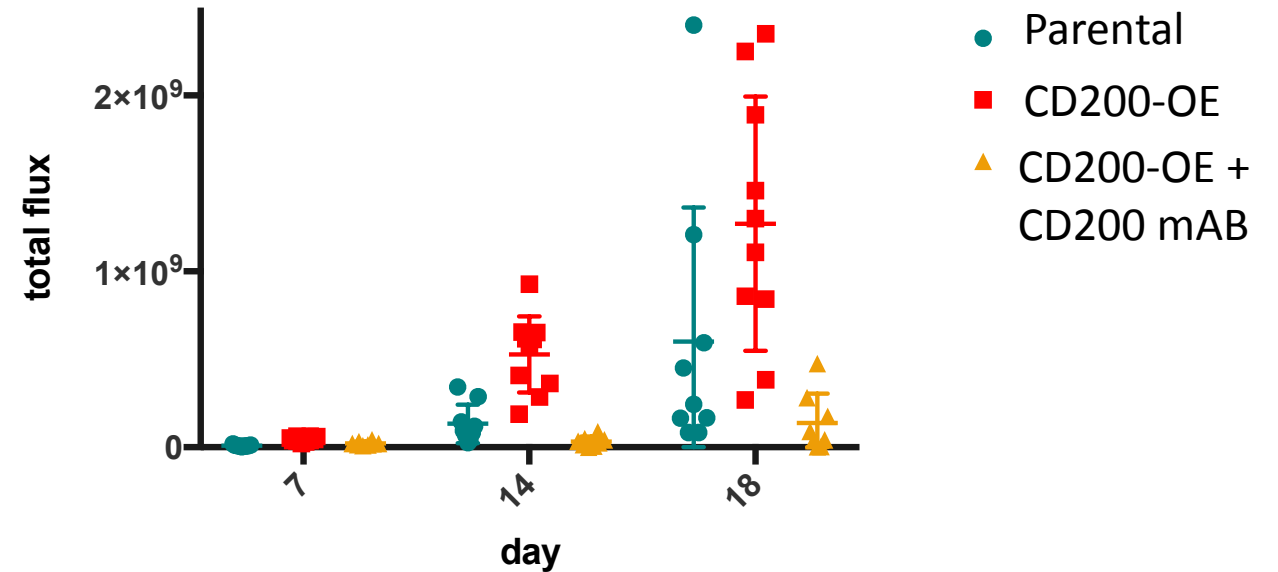
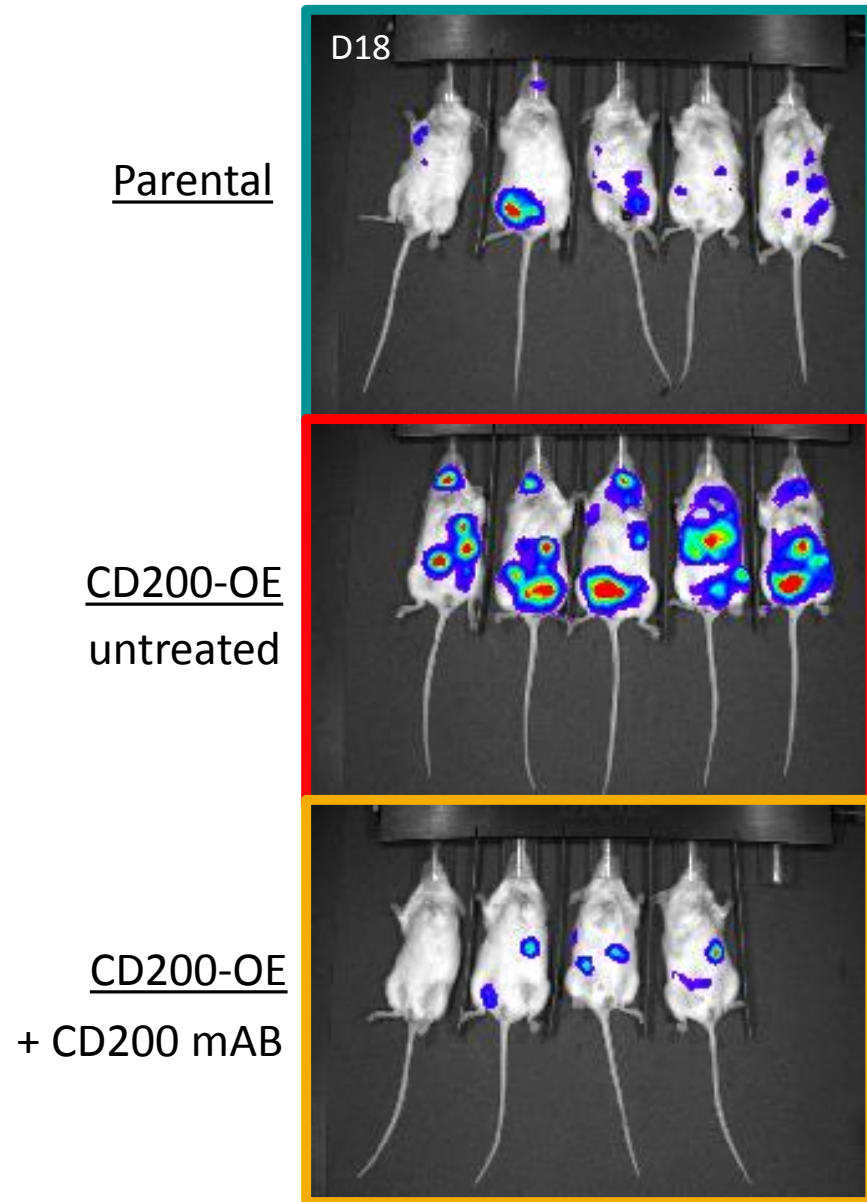
CD200-OE cells persist in humanized mice



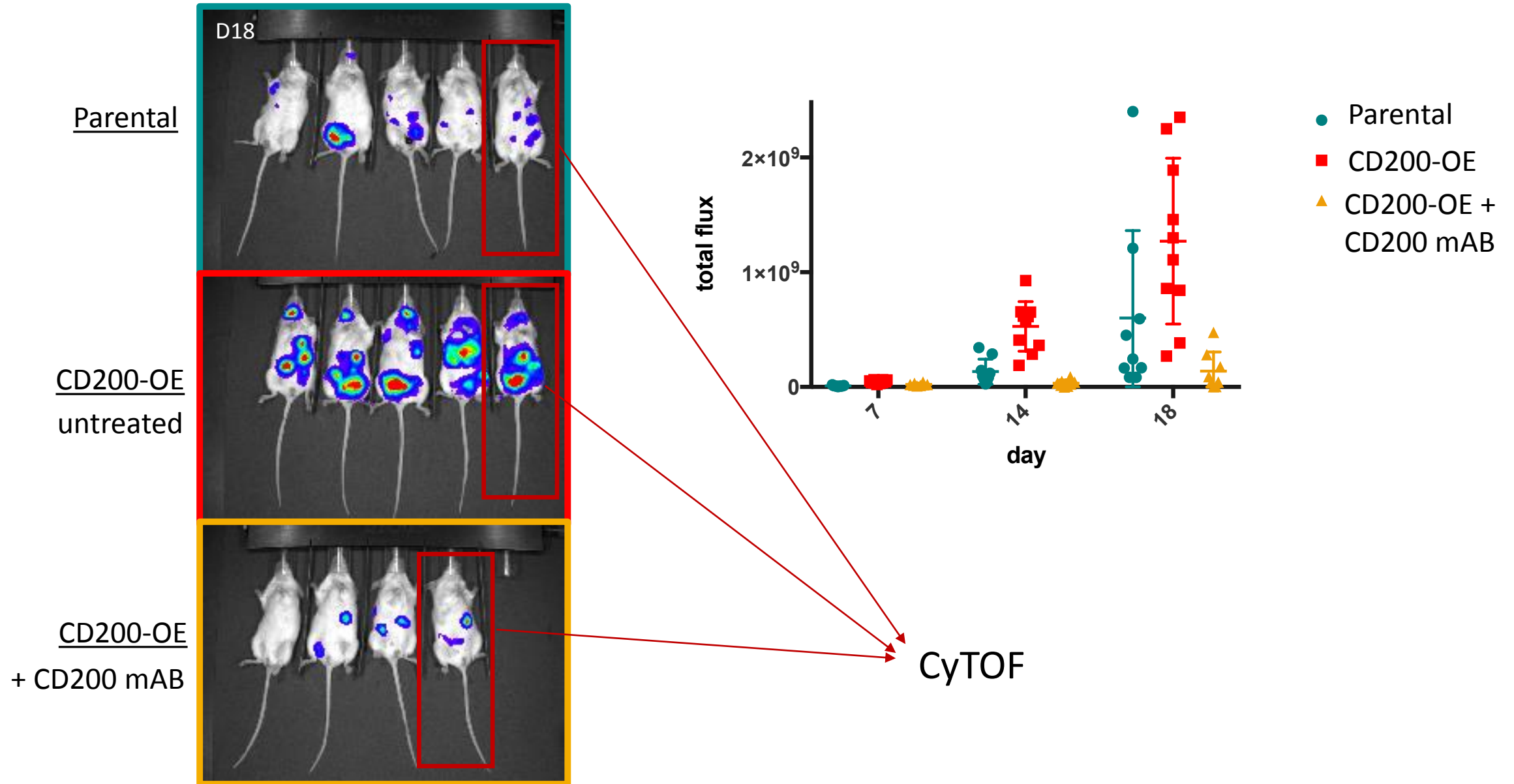
In vivo model 3: PBMC-humanized + antibody



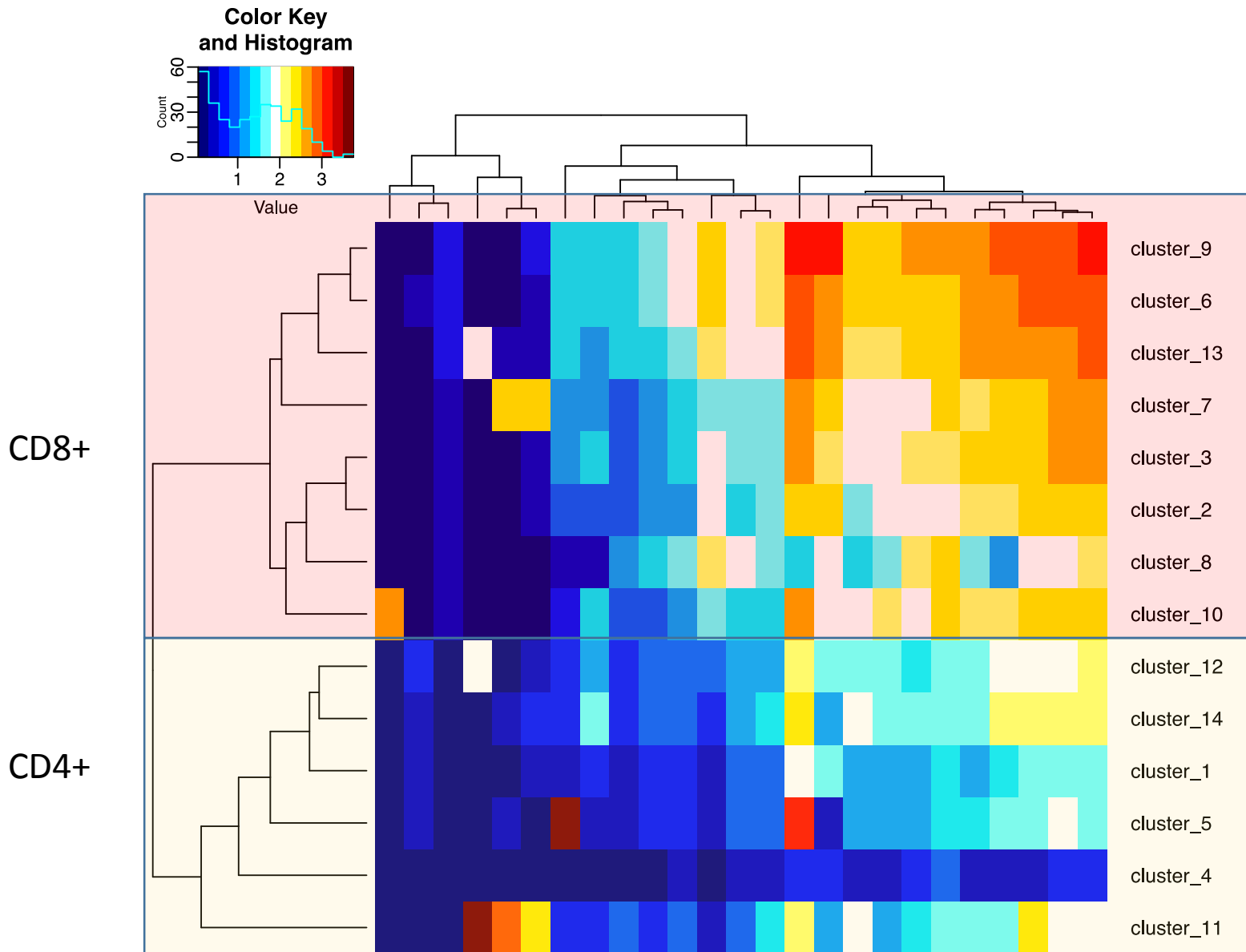
CD200 mAB therapy abrogates leukemia *in vivo*



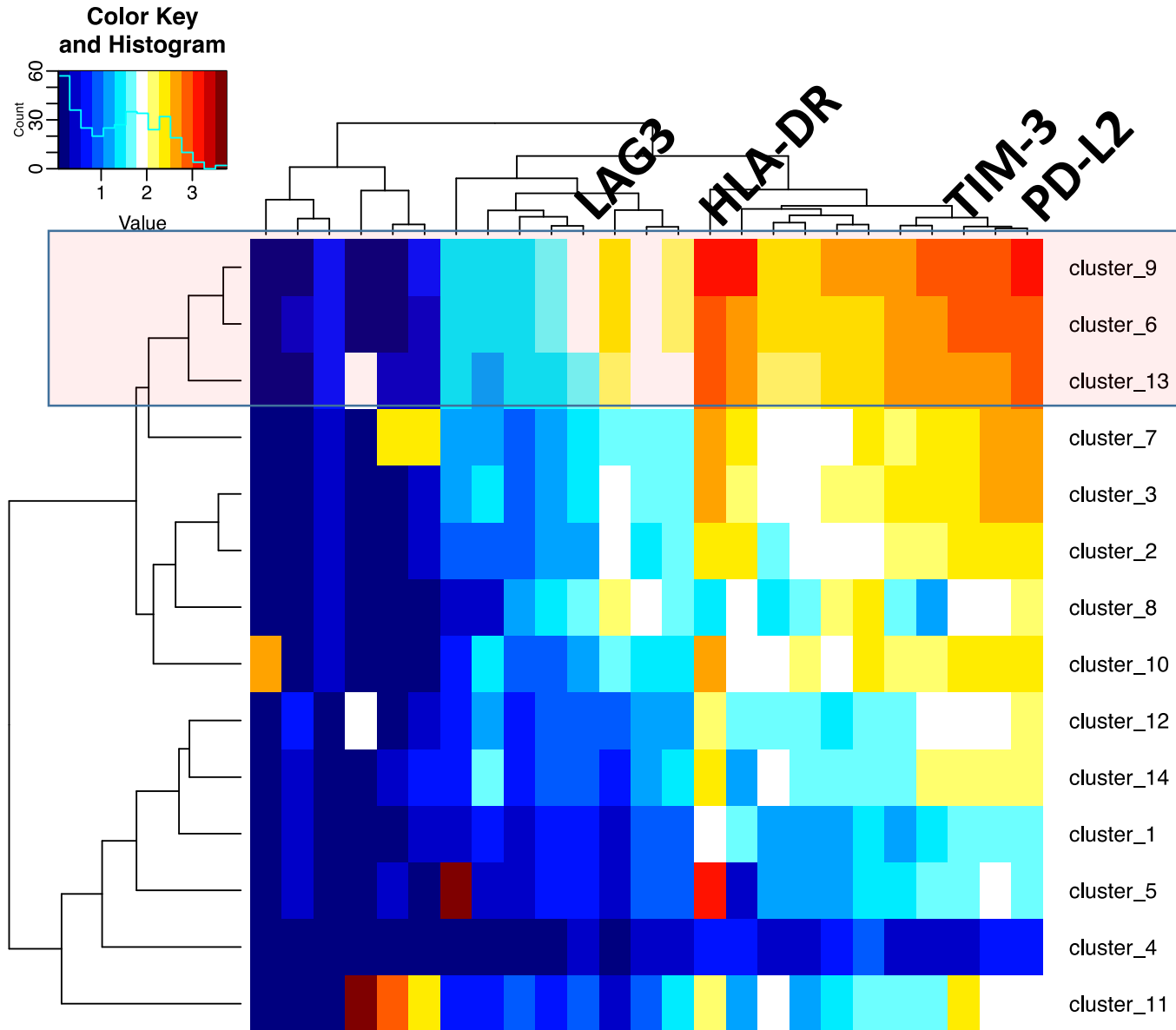
CD200 mAB therapy abrogates leukemia *in vivo*



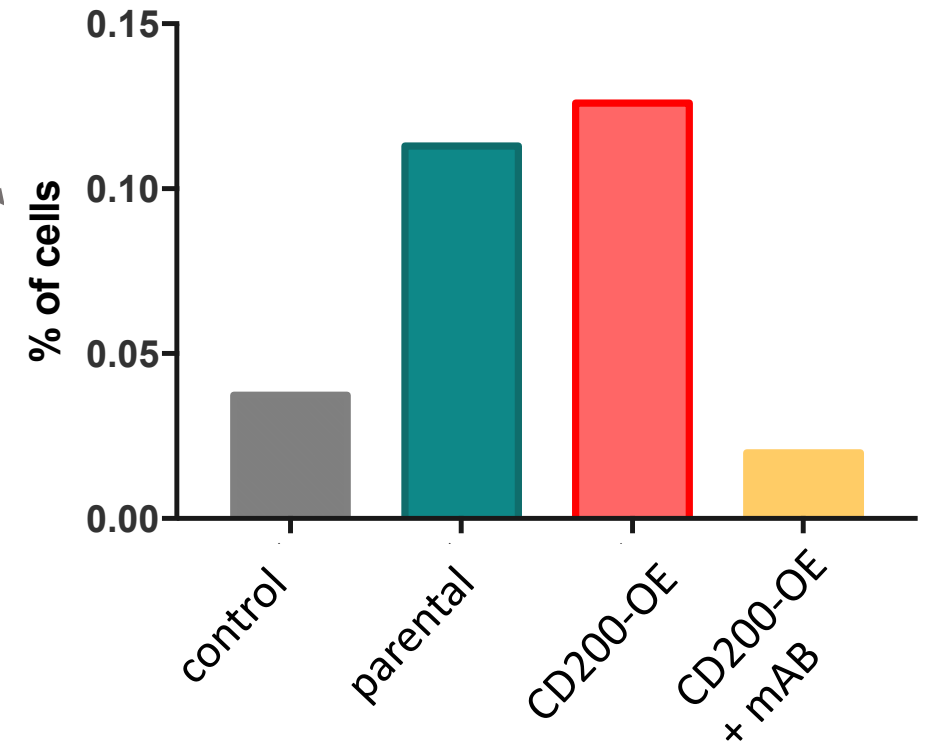
CD200+ AML alters T cell composition



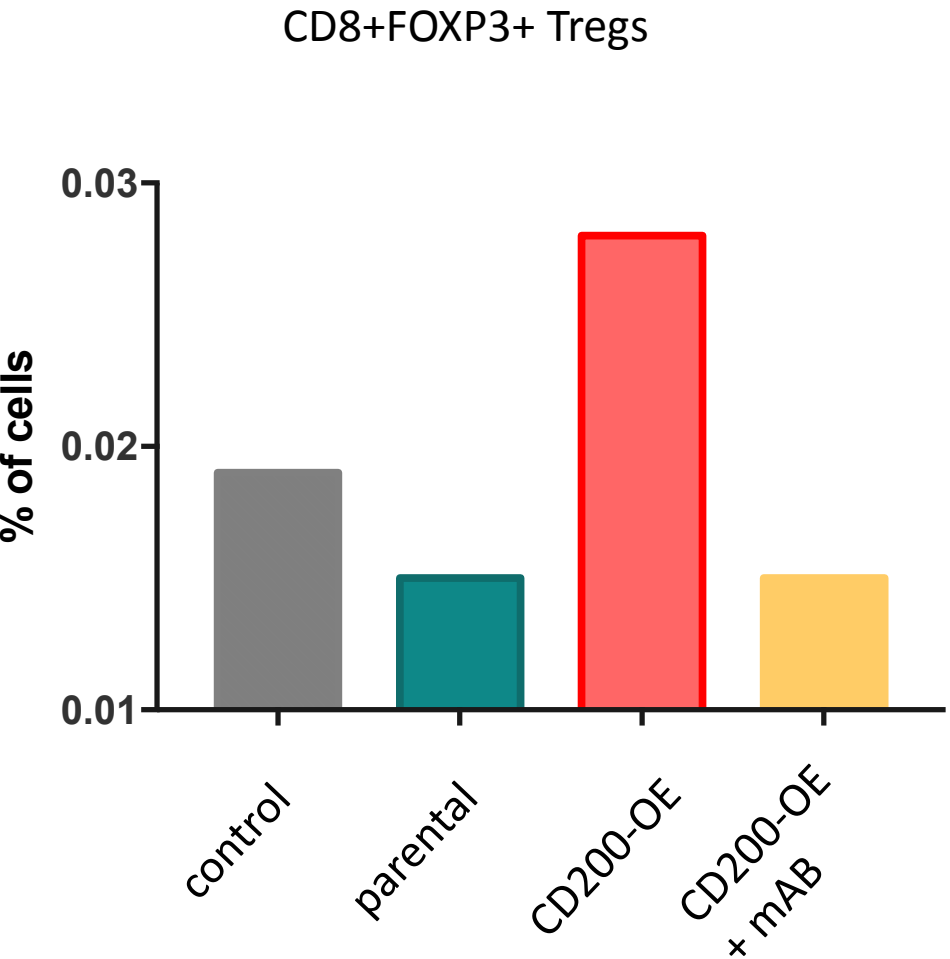
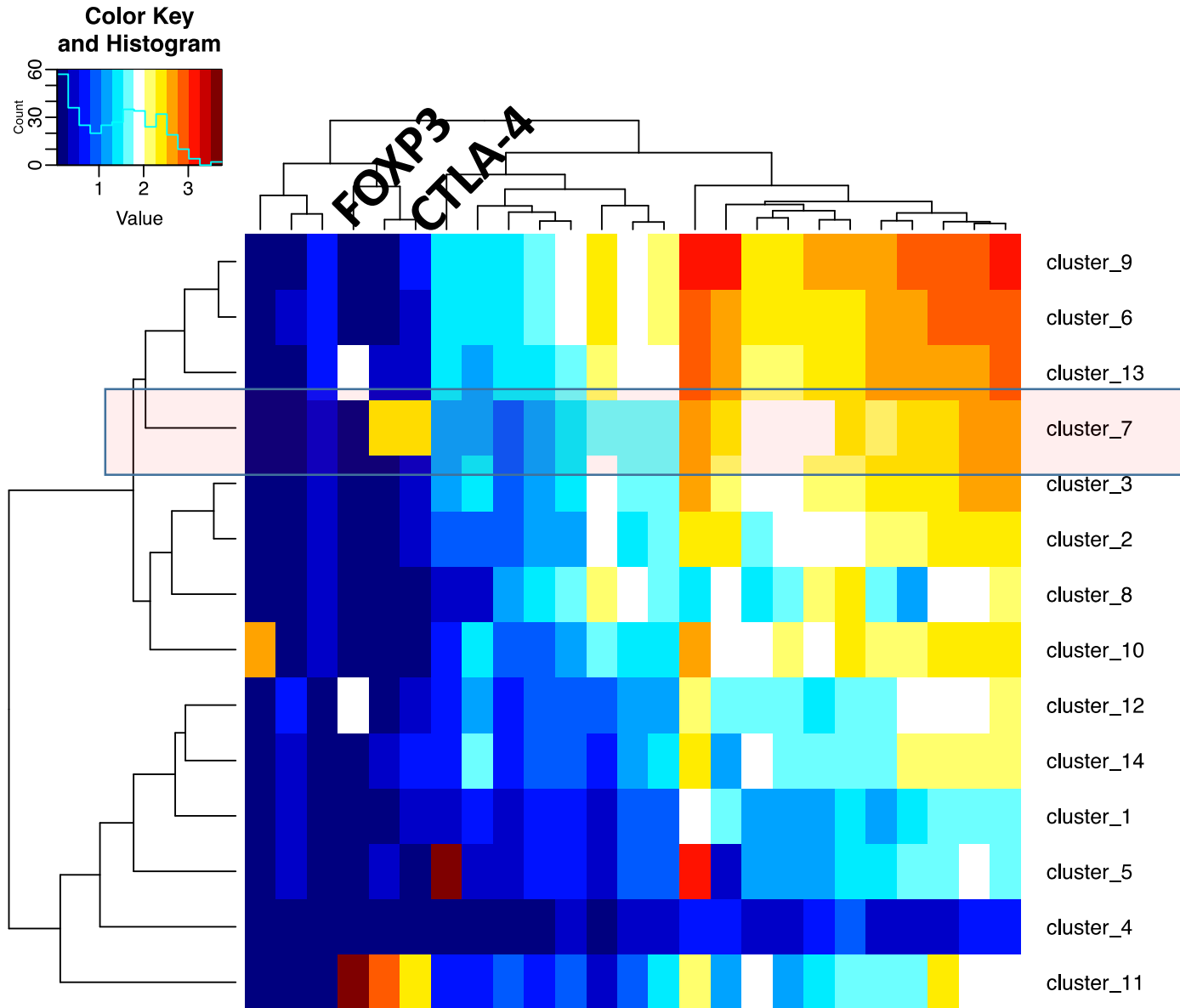
CD200+ AML alters T cell composition



Activated CD8+ T cells

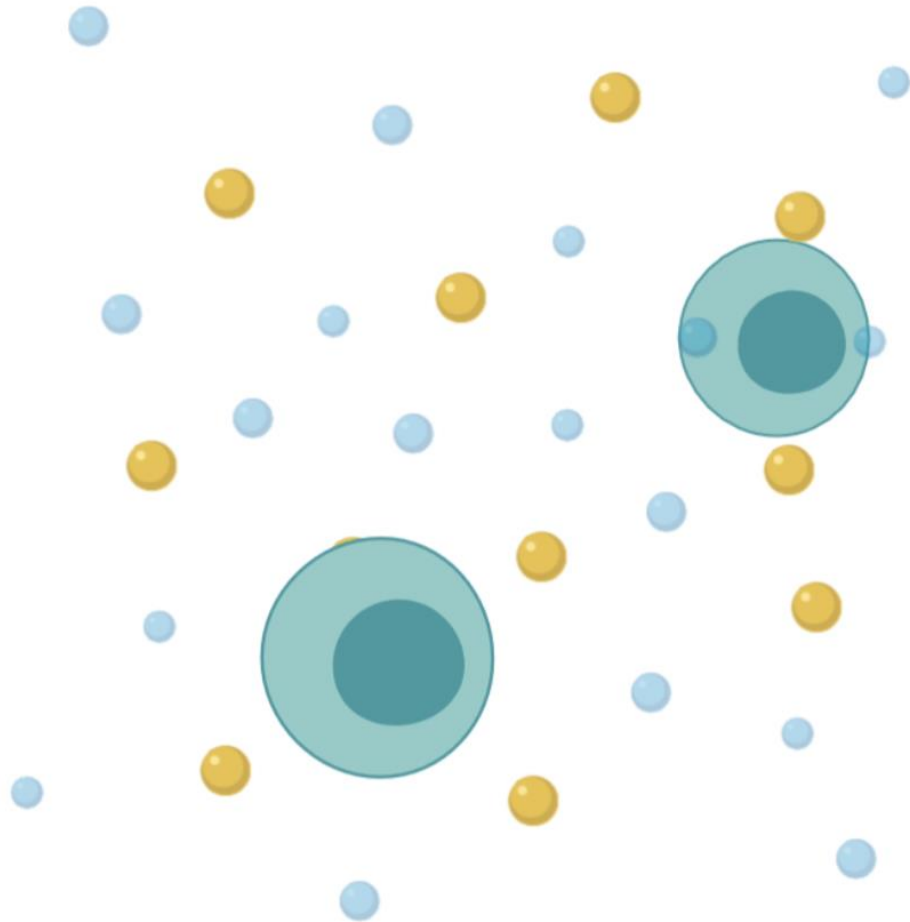


CD200+ AML alters T cell composition

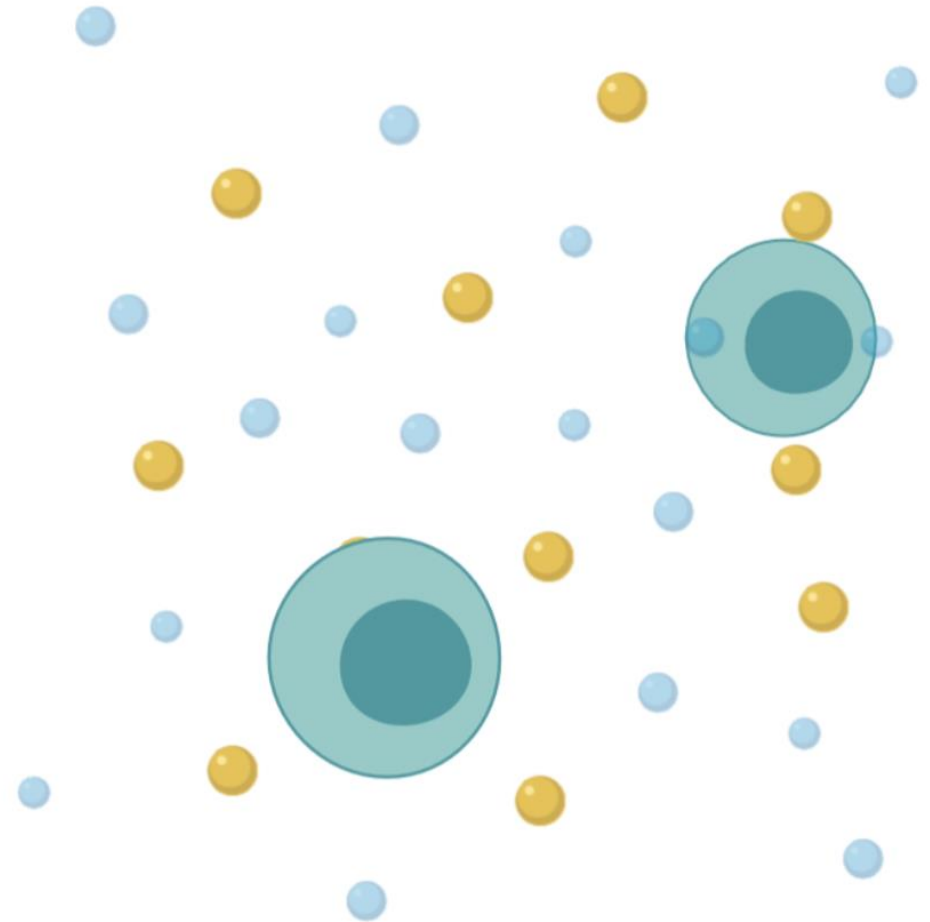


Conclusion

CD200- AML

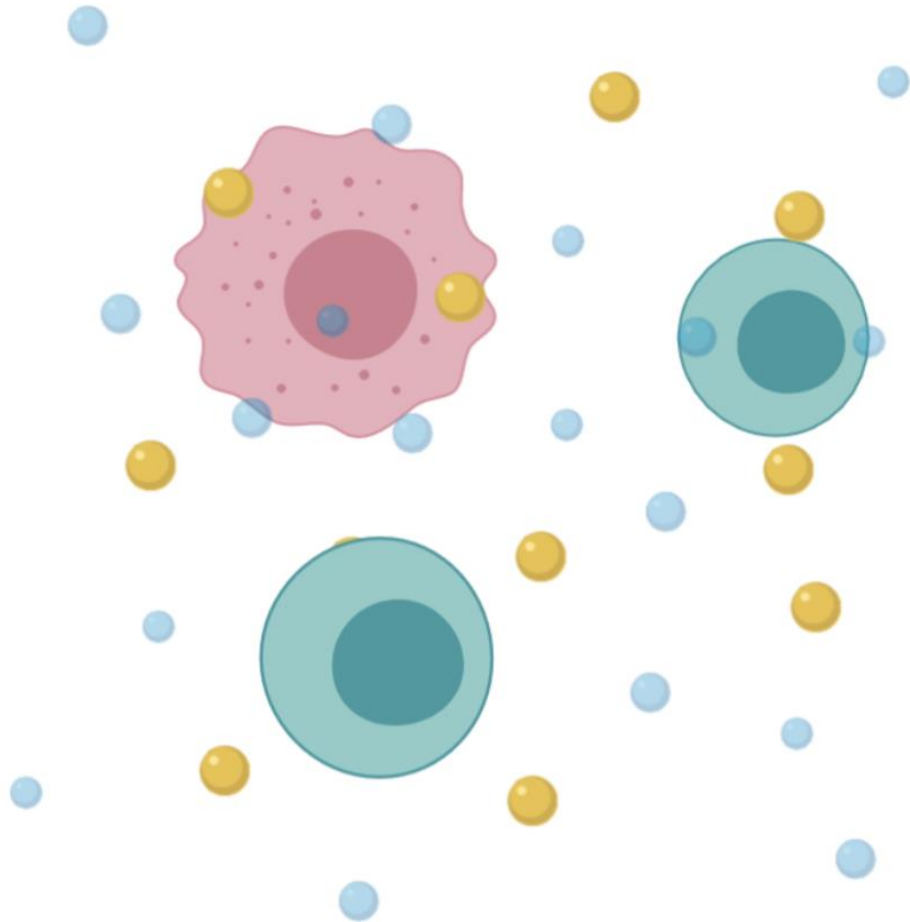


CD200+ AML

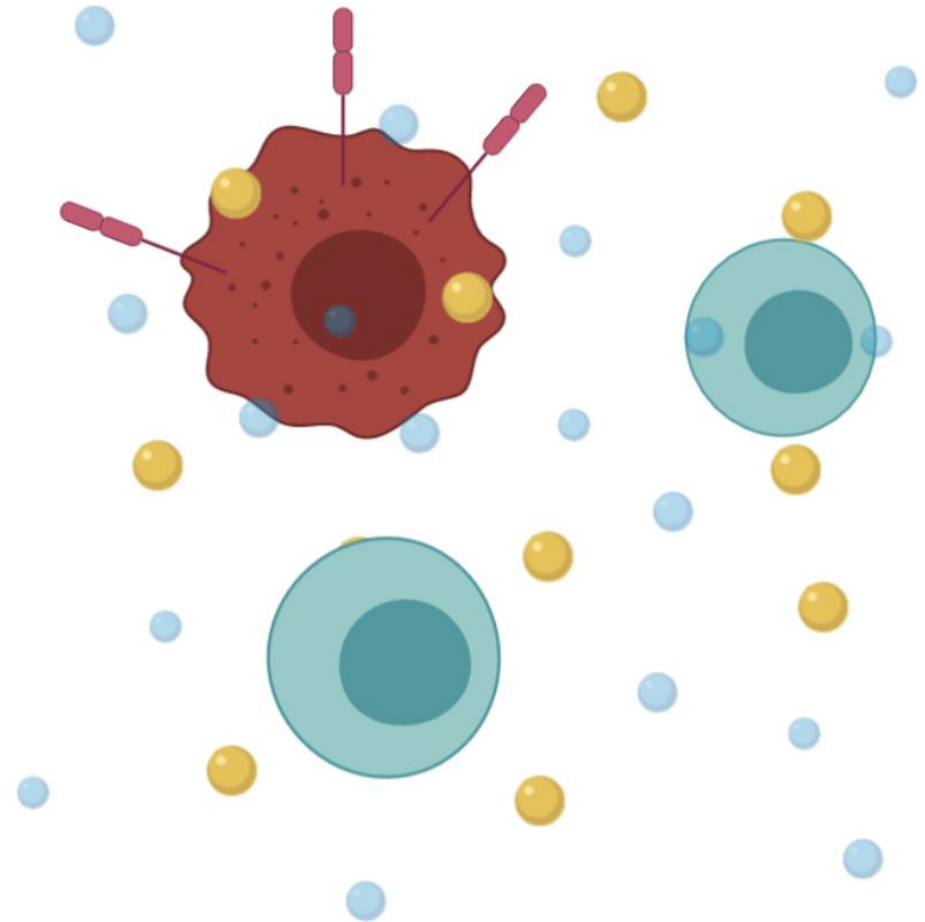


Conclusion

CD200- AML

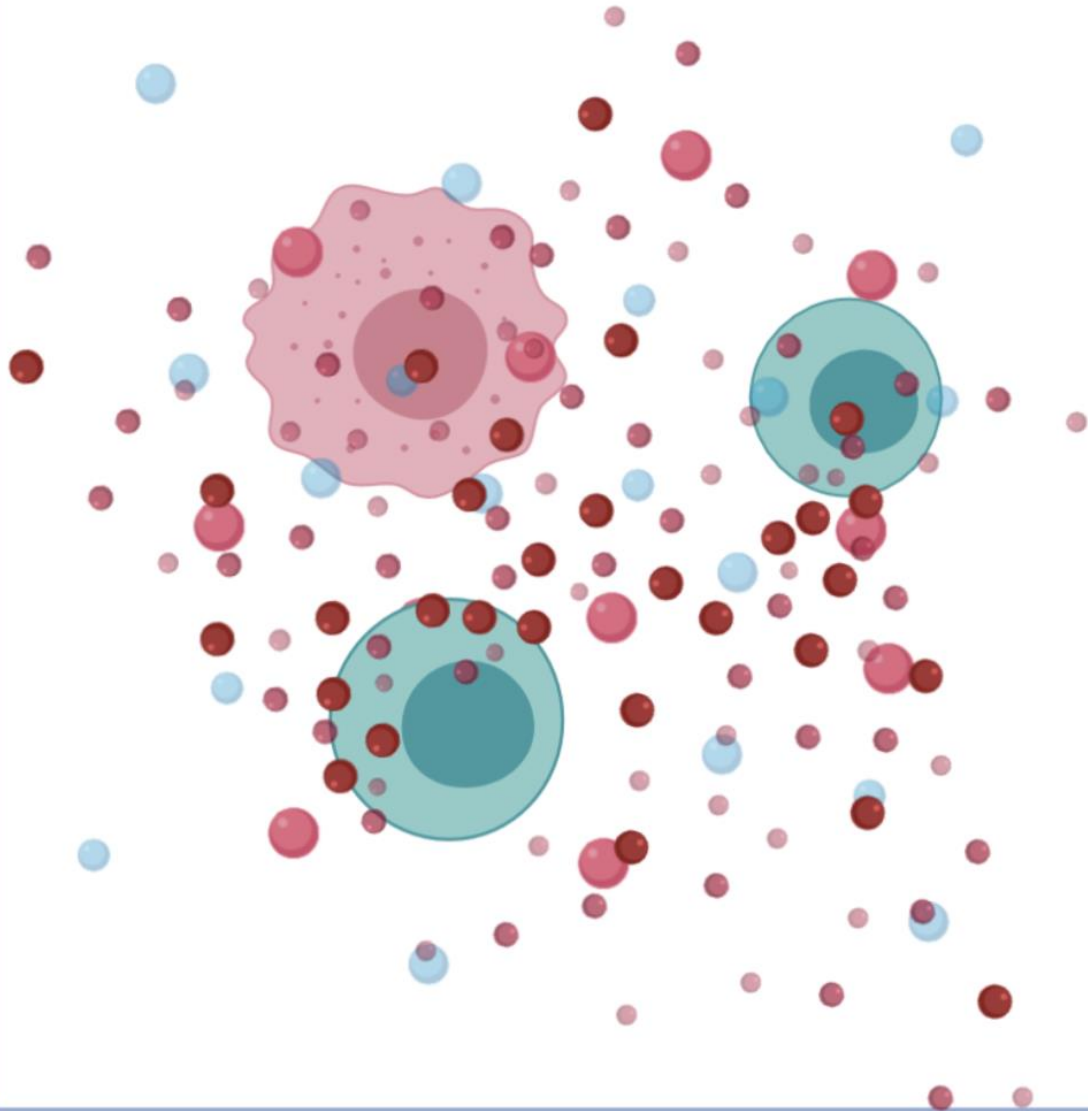


CD200+ AML

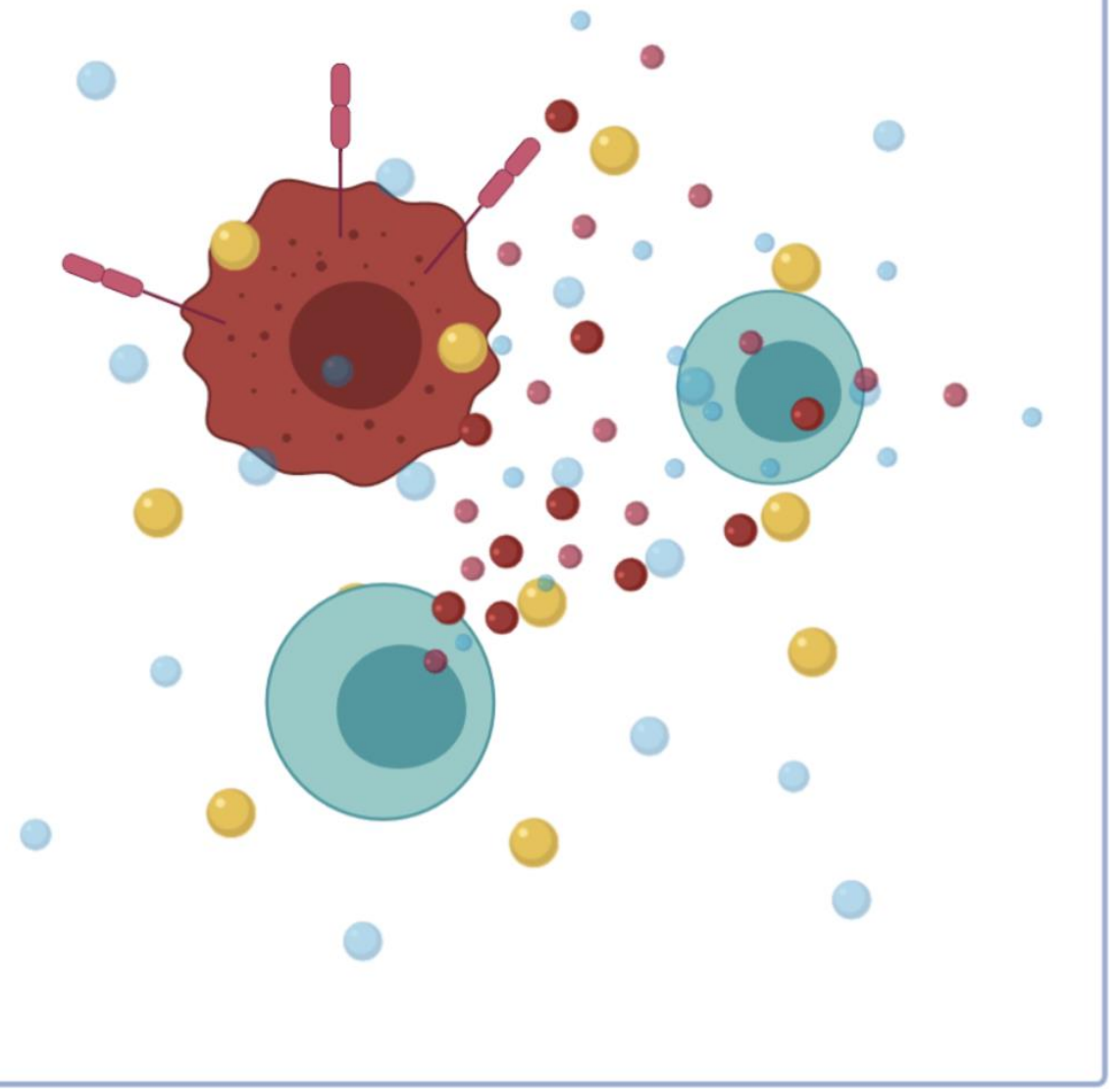


Conclusion

CD200- AML

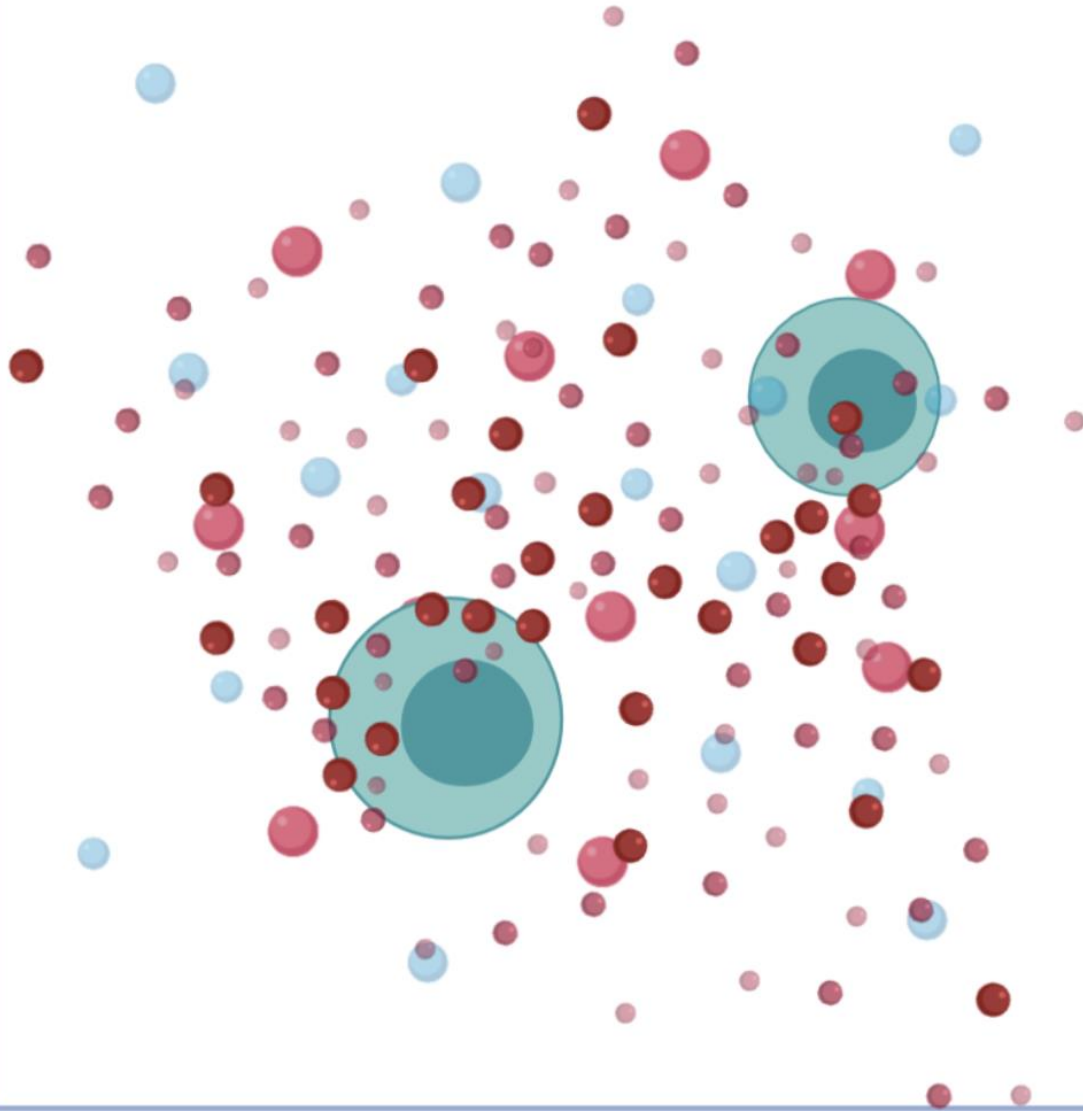


CD200+ AML

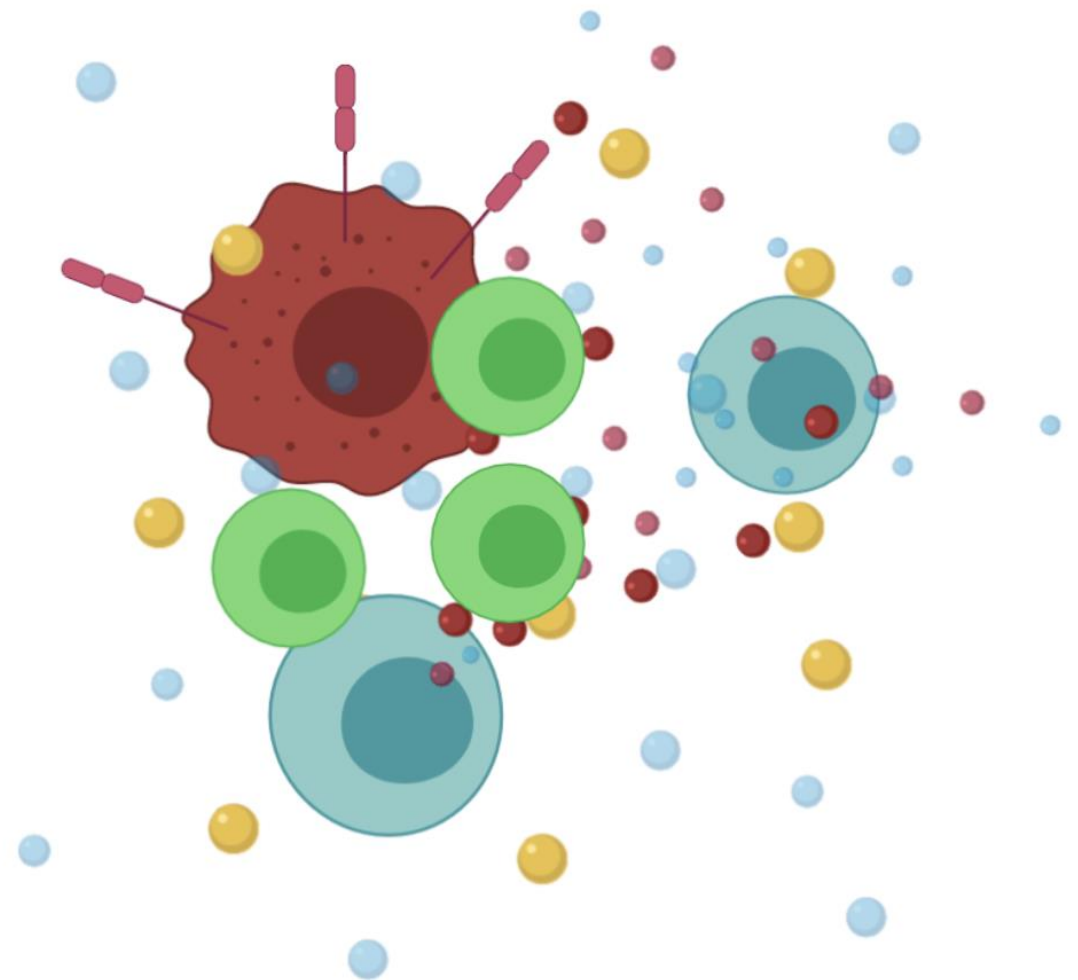


Conclusion

CD200- AML



CD200+ AML



Acknowledgments

Konopleva Lab

Marina Konopleva

Natalia Baran

Tinayu Cai

Post Lab

Sean Post

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