



Use of polymeric CXCR4 inhibitors as siRNA delivery vehicles for the treatment of acute myeloid leukemia

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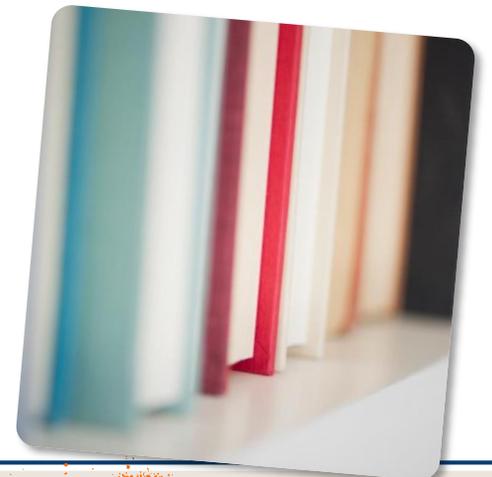
ARTICLE



Use of polymeric CXCR4 inhibitors as siRNA delivery vehicles for the treatment of acute myeloid leukemia

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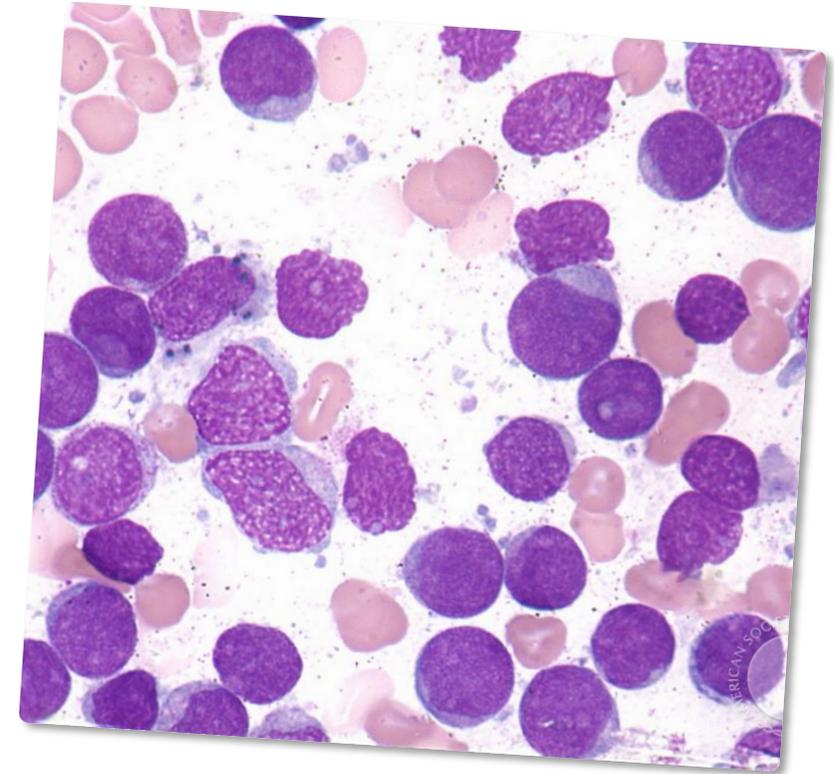




Introduction

- ❖ AML is a heterogeneous clonal disorder
- ❖ Accumulation of immature myeloid cells in the bone marrow
- ❖ Many AML mutations involve transcription factors, for example RUNX1

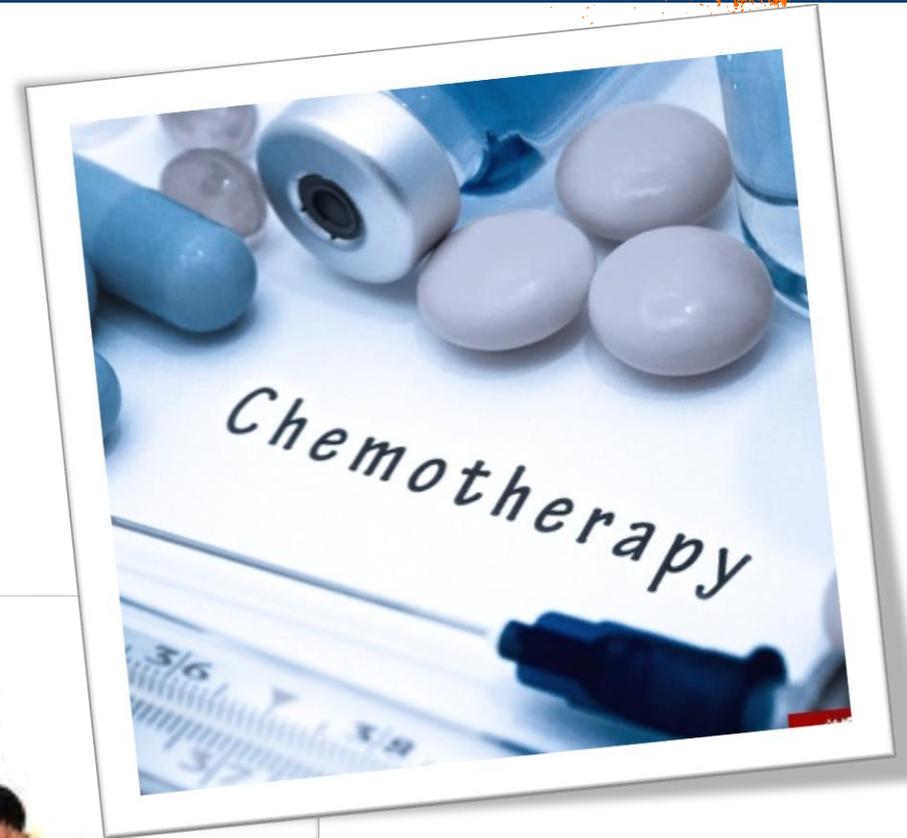
Acute myeloblastic leukemia



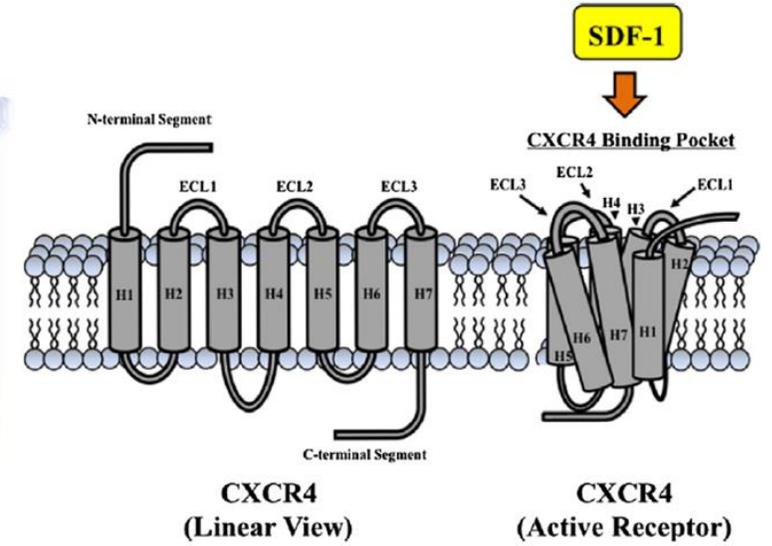
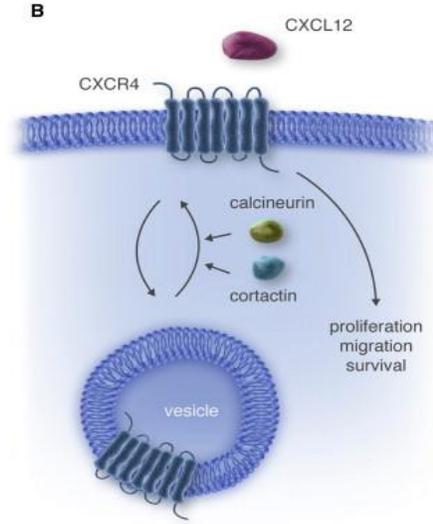
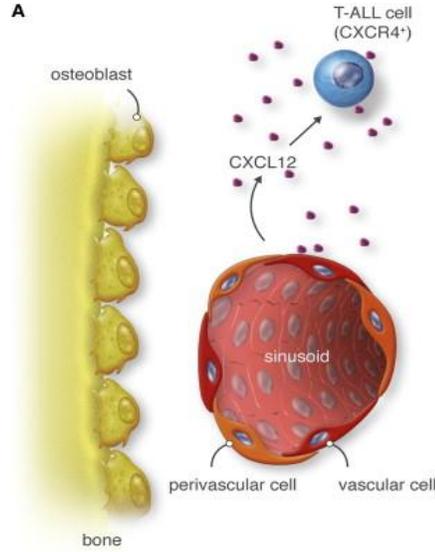
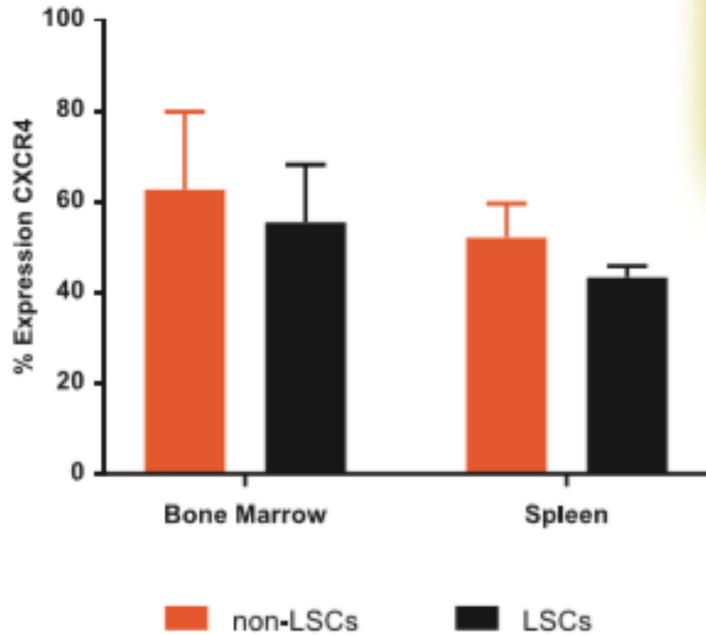


Treatments

- **Chemotherapy**
- **Radiation therapy**
- **Stem cell transplantation**
- **siRNA-based therapeutics targeting**



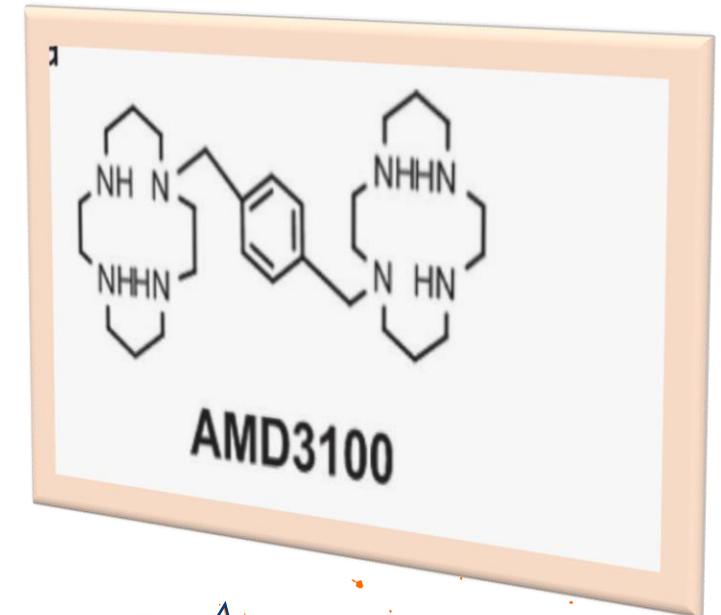
CXCR4





Inhibitors of CXCR4

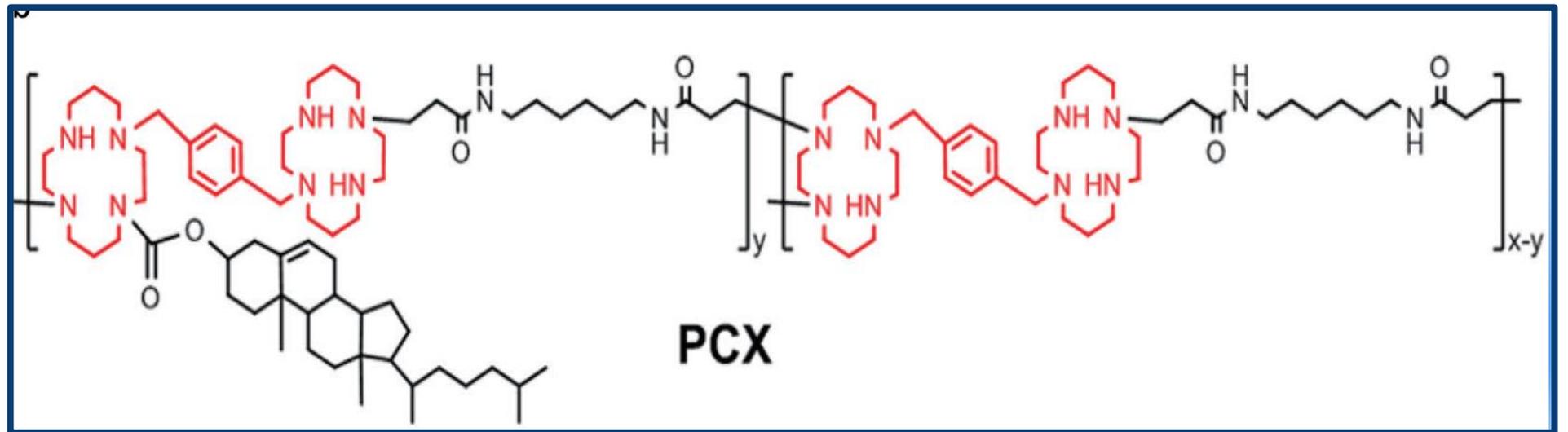
- ✓ small molecule inhibitor ➔ **AMD3100 (plerixafor)**
- ✓ peptide CXCR4 inhibitors ➔ **BKT140 / LY2510924**
- ✓ polymeric CXCR4 inhibitor ➔ **PCX**





pcx

- ❑ Inhibition of CXCR4
- ❑ Delivery of siRNAs against critical genes.
- ❑ Induces leukemia cell differentiation
- ❑ Mobilization from bone marrow
- ❑ Increased sensitivity to chemotherapy
- ❑ Decreases leukemic burden





Anti-leukemic effects of PCX

Humanized anti-CXCR4 antibodies

Ulocuplumab and **PF-0674714**

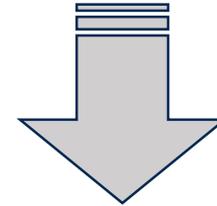
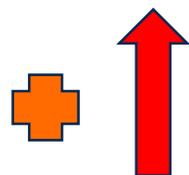


exhibit anti-leukemic activity both **in vitro** and **in vivo**



PCX with novel anti-leukemia activities

cells from 3 independent
Cbfb-MYH11+, Mx1-Cre+ mice



(PCX)



Viability

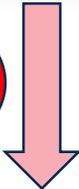
BKT140

LY2510924

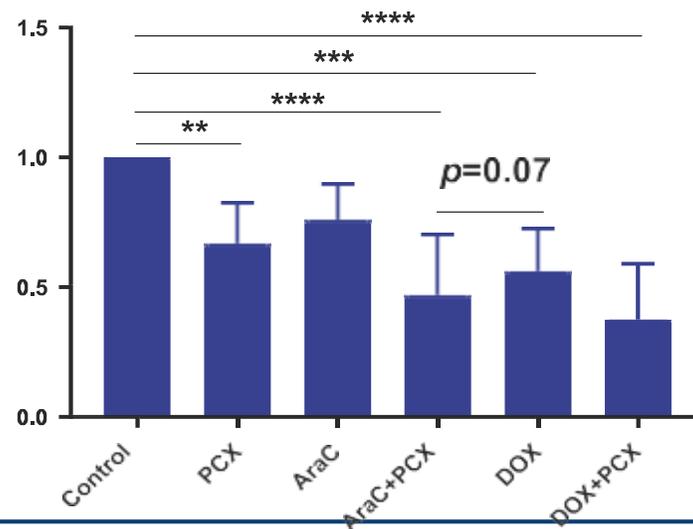


CXCR4

Effects of PCX ,doxorubicin (DOX) , cytarabine (AraC)on each other

PCX ➡   viability caused by either AraC or DOX alone

PCX **does not block** the activity of frontline chemotherapeutic agents.

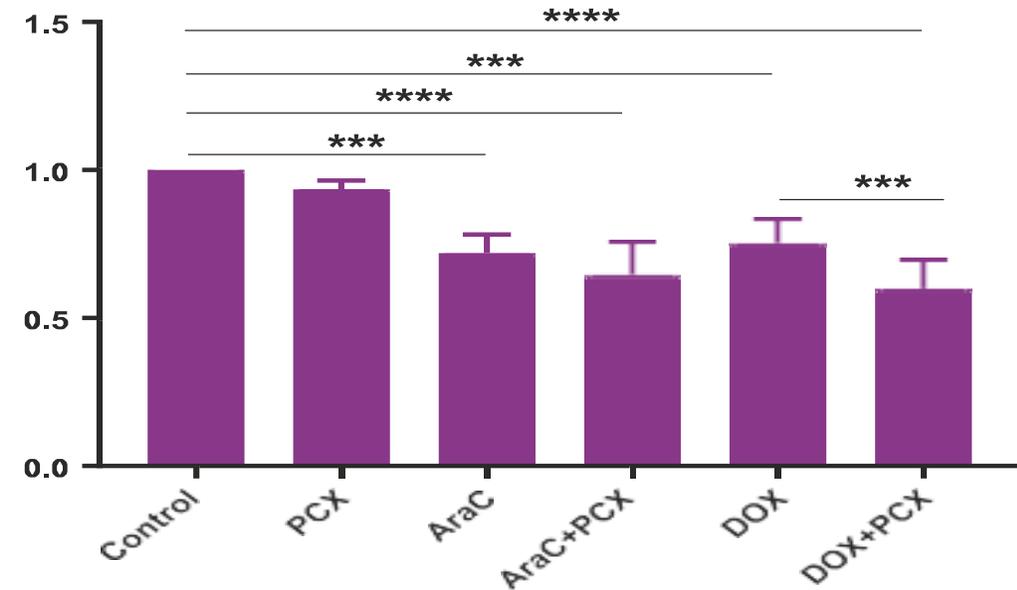




Effects of PCX on human cancer cells

Kasumi -1 → t(8;21)

ME -1 → Inv(16)



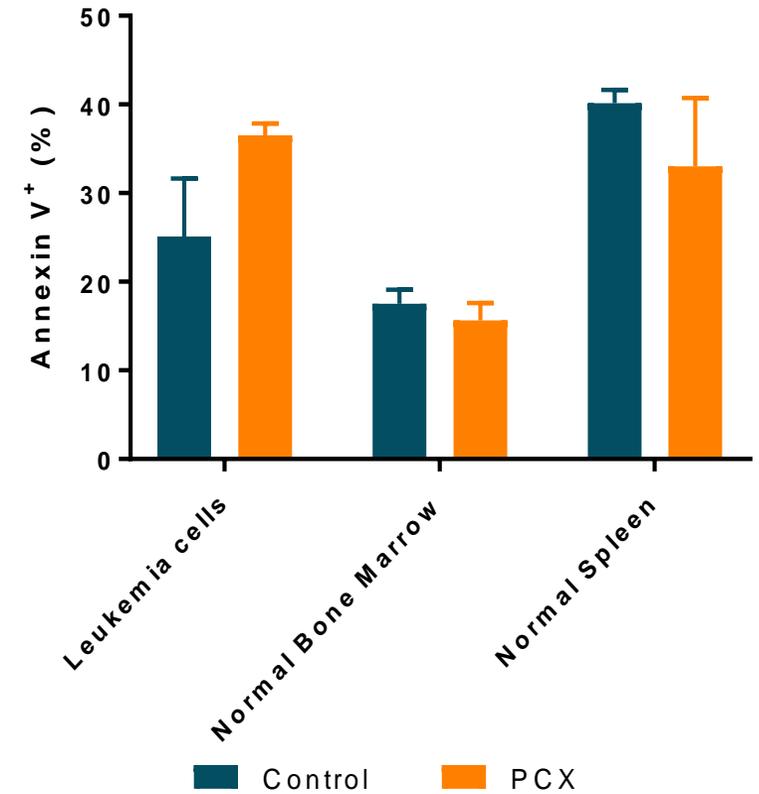
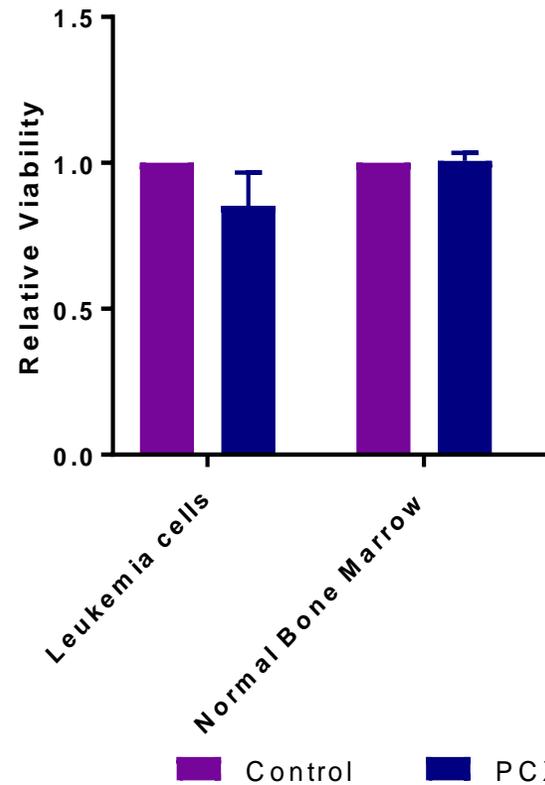
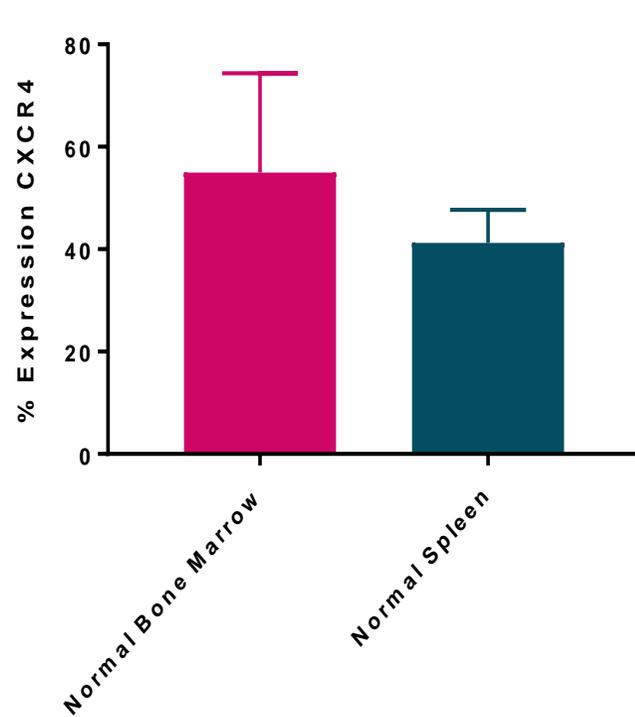
PCX + DOX → ↓↓↓↓ Viability



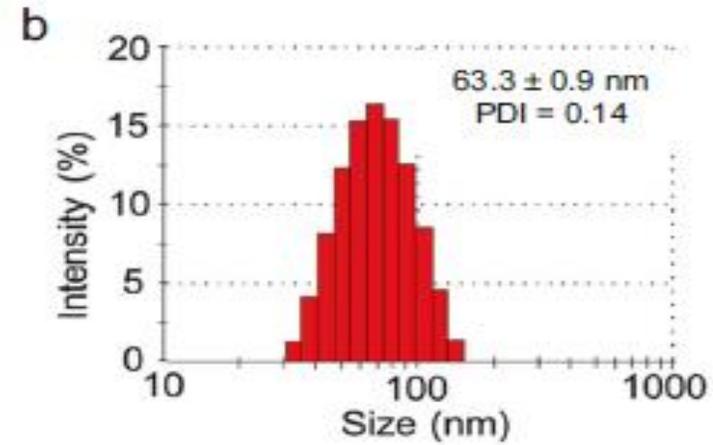
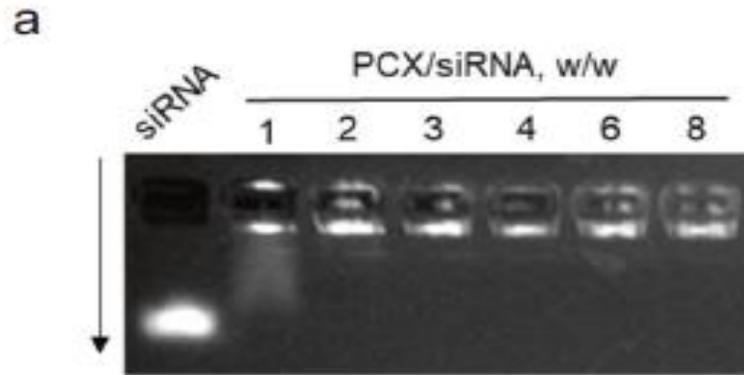
Viability ↓↓↓ ← DOX



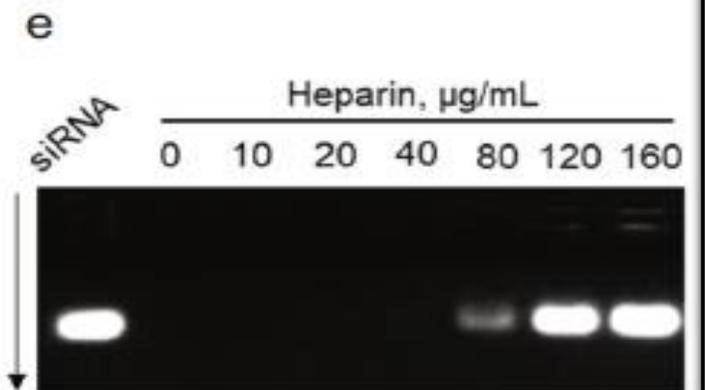
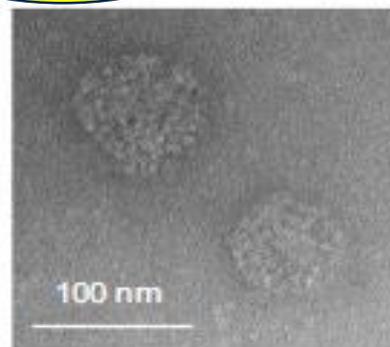
PCX affect in normal cells



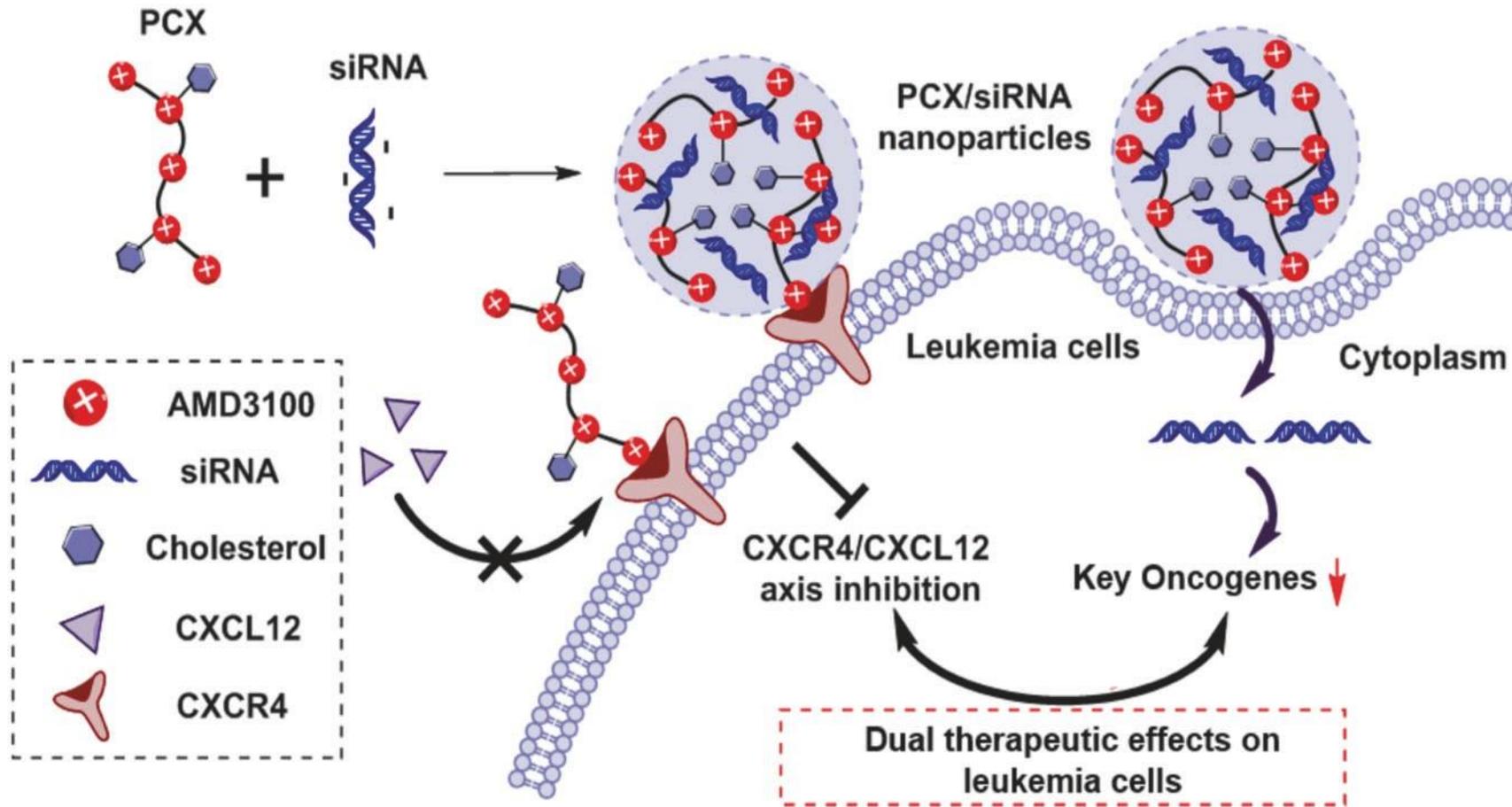
PCX/siRNA nanoparticles



TEM



mechanism of action of **PCX/siRNA nanoparticles** for treatment of AML





PCX / siRUNX1

inversion [16] [inv(16)]  Cbfb-MYH11+

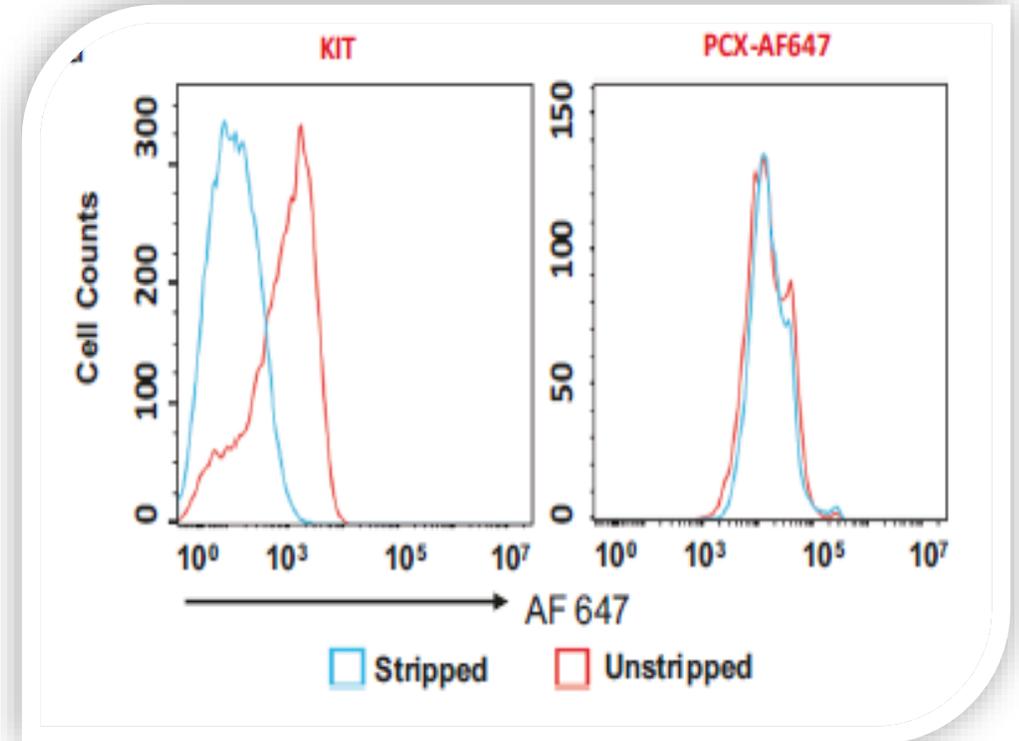
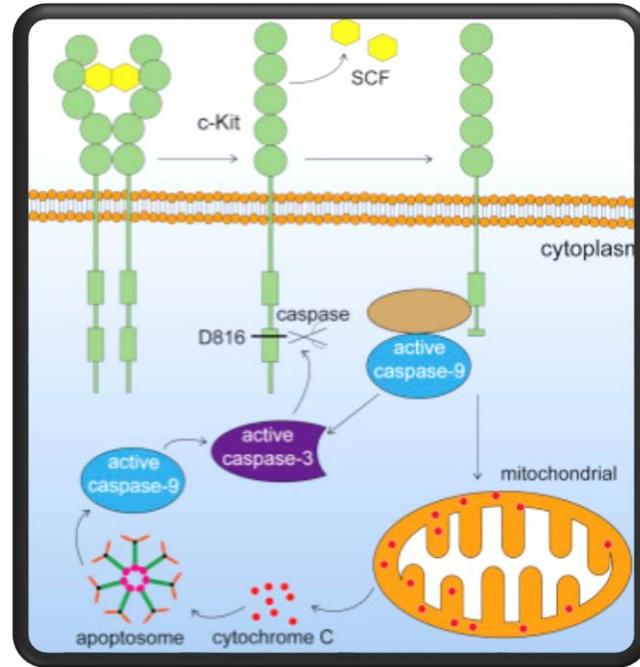
- both sexes
- at least 6 weeks of age



Runx1 knockdown **increased** apoptosis and **decreased** colony-forming ability in Cbfb-MYH11+ leukemia cells

Testing the ability to deliver siRNA by PCX

(AF647-PCX)



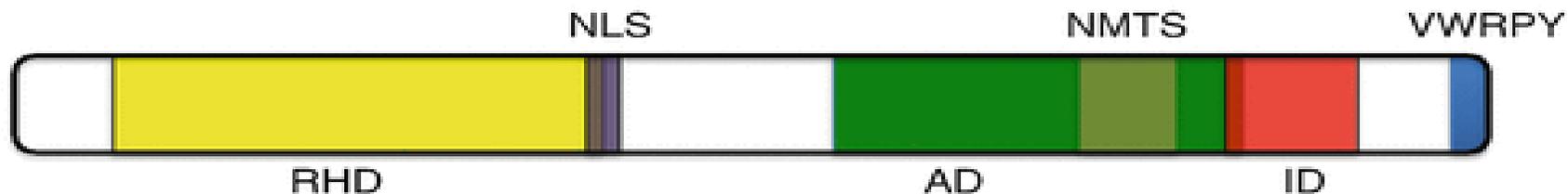
Target



RUNX1

Transcription Factors

ETS1 PU.1 FLI1 ERG GATA1 GATA2 C/EBP α SCL/TAL1 LMO2/LDB1



RUNX1

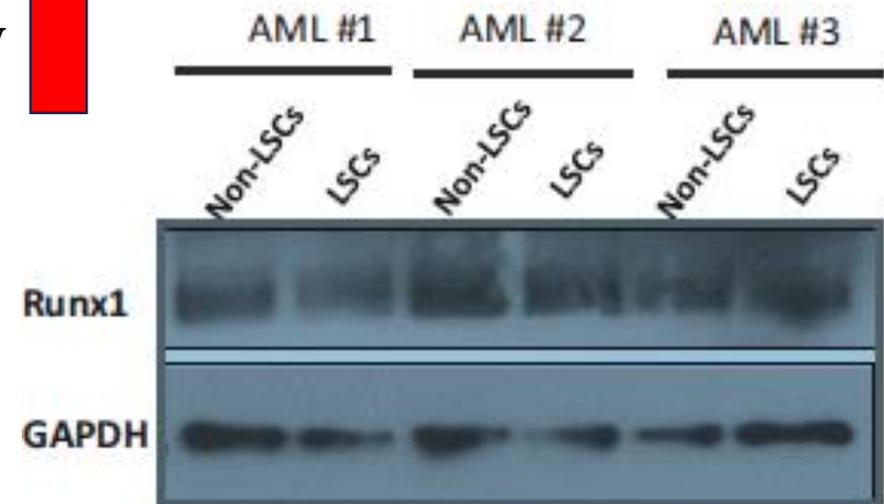
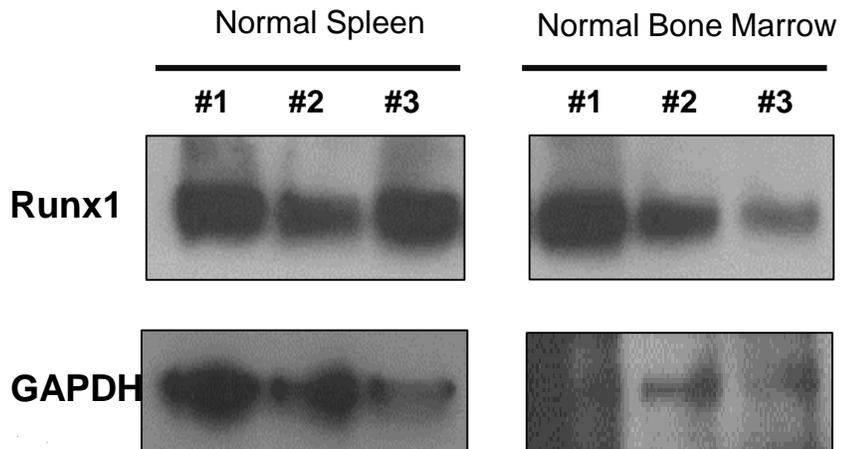
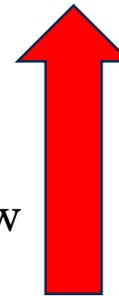
MOZ/CBP/p300 SIN3A BRG1/INI MLL HDAC1/3 TLE PcG

Epigenetic Regulatory Machinery



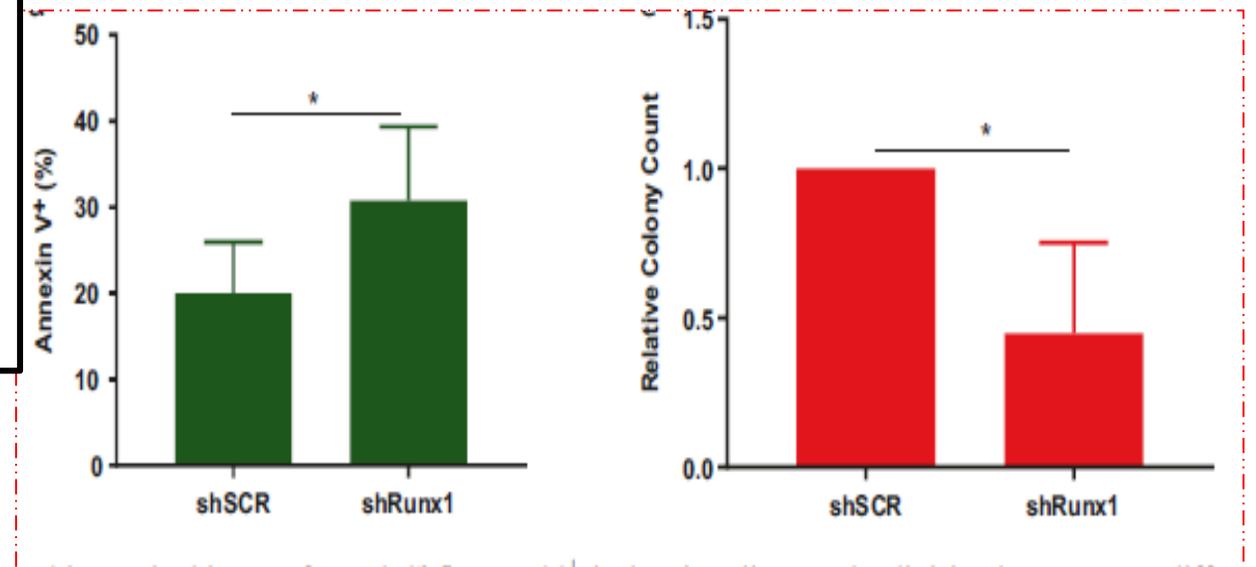
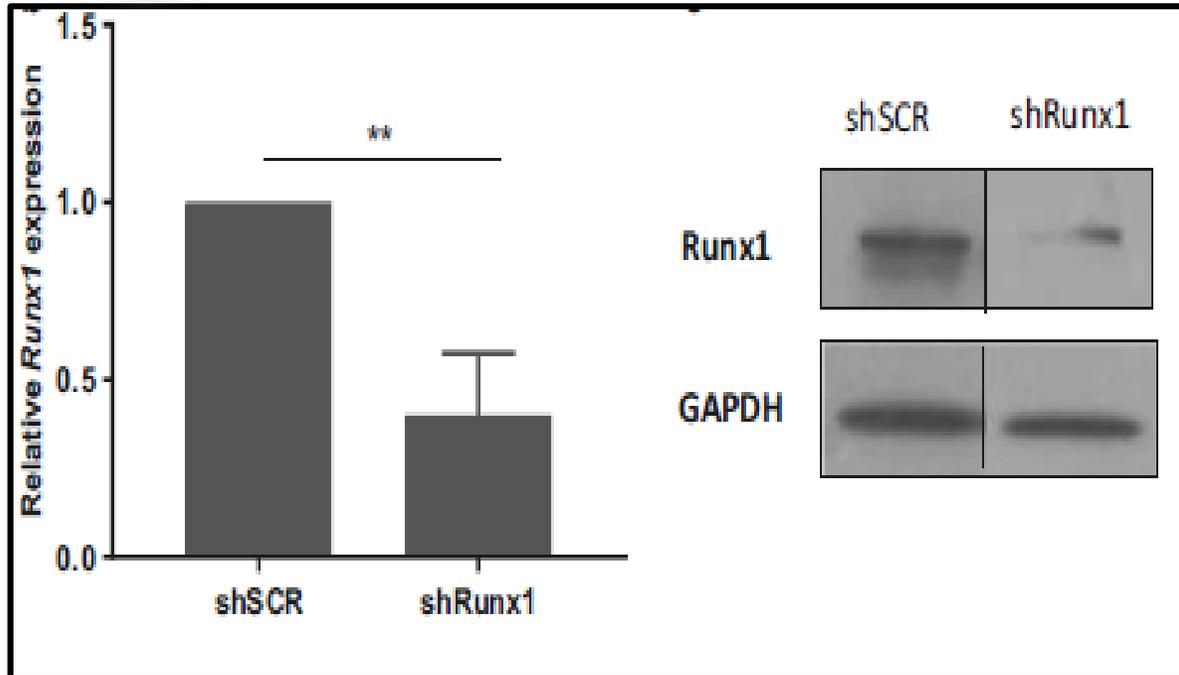
Runx1 protein and mRNA expression levels

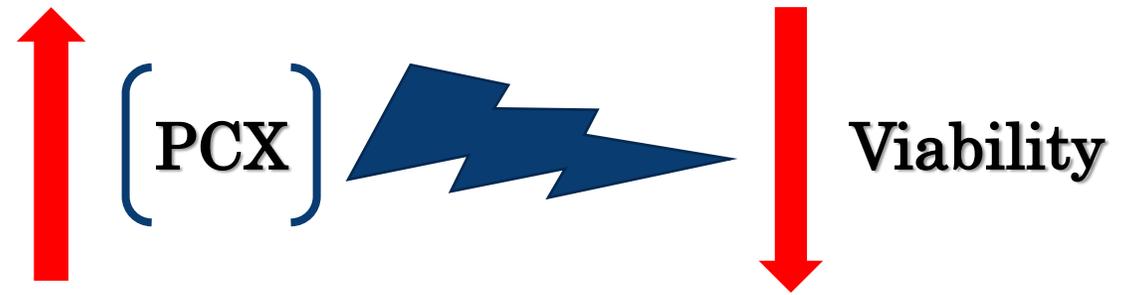
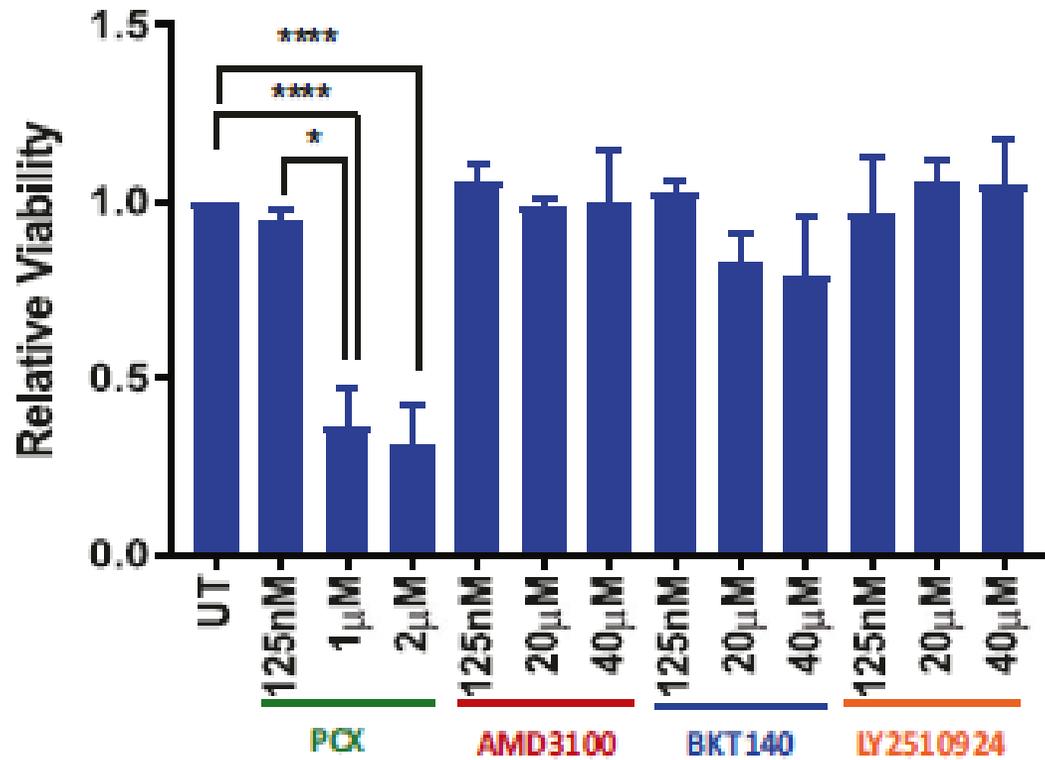
- Normal bone marrow and spleen cells
- LSCs and non-LSCs harvested from both the bone marrow and spleen of leukemic Cbfb-MYH11+ mice



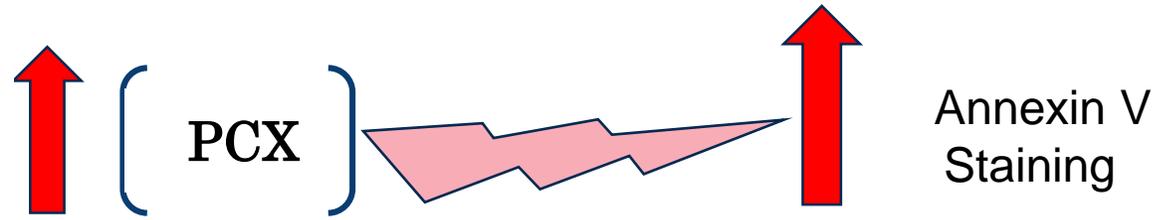
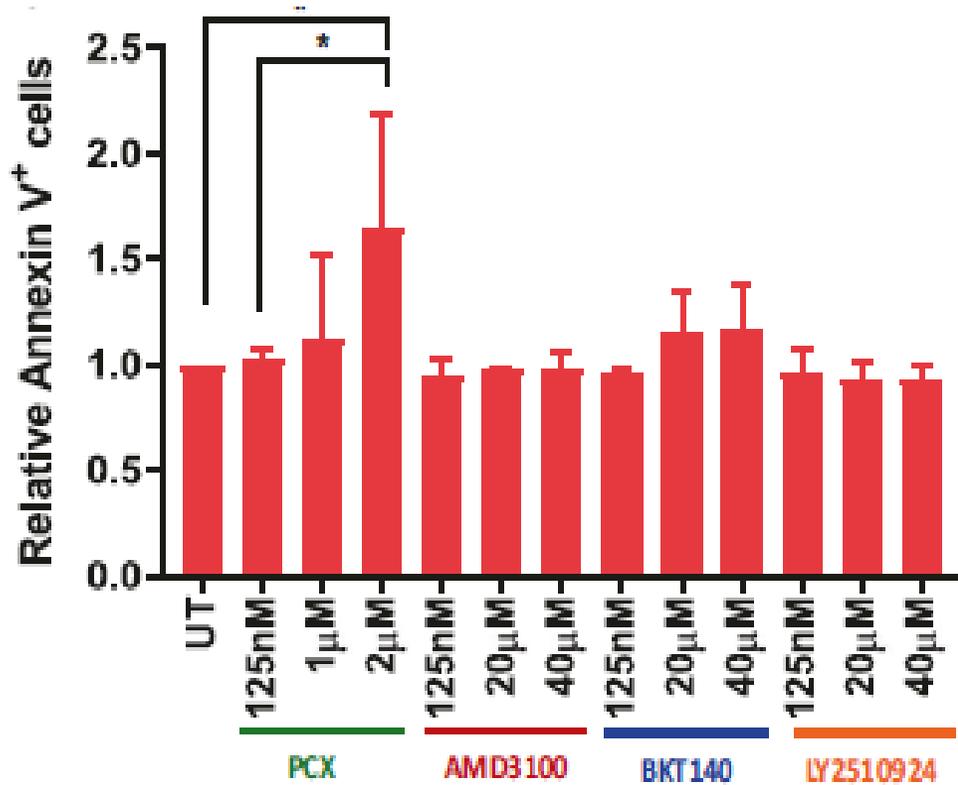


Runx1 knockdown increased apoptosis and decreased colony-forming ability in Cbfb-MYH11+ leukemia cells





PCX caused decreased viability via apoptosis in leukemia cells





PCX cytotoxicity



increased differentiation

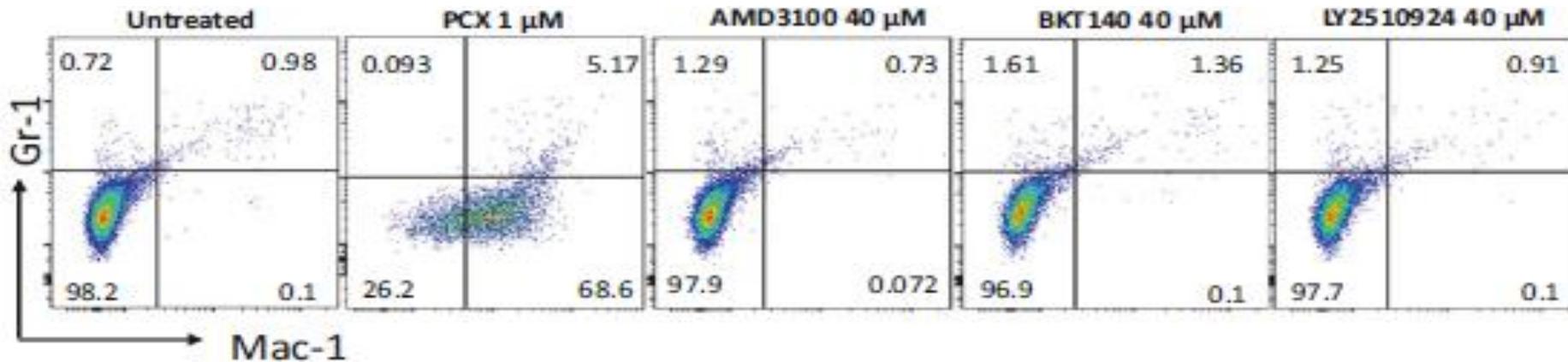
markers of mature myeloid cells

Mac-1

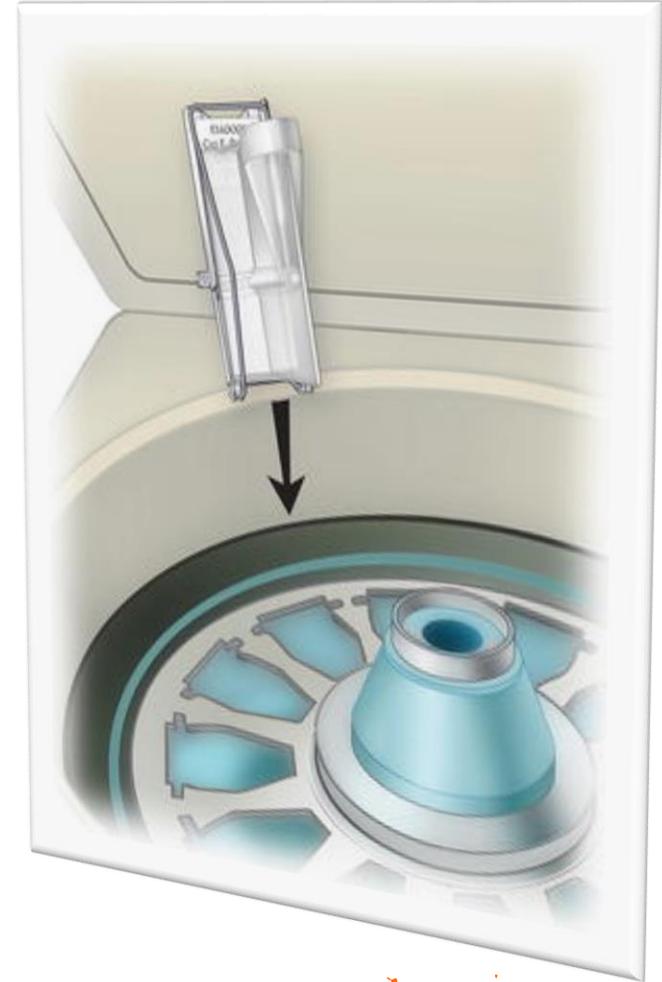
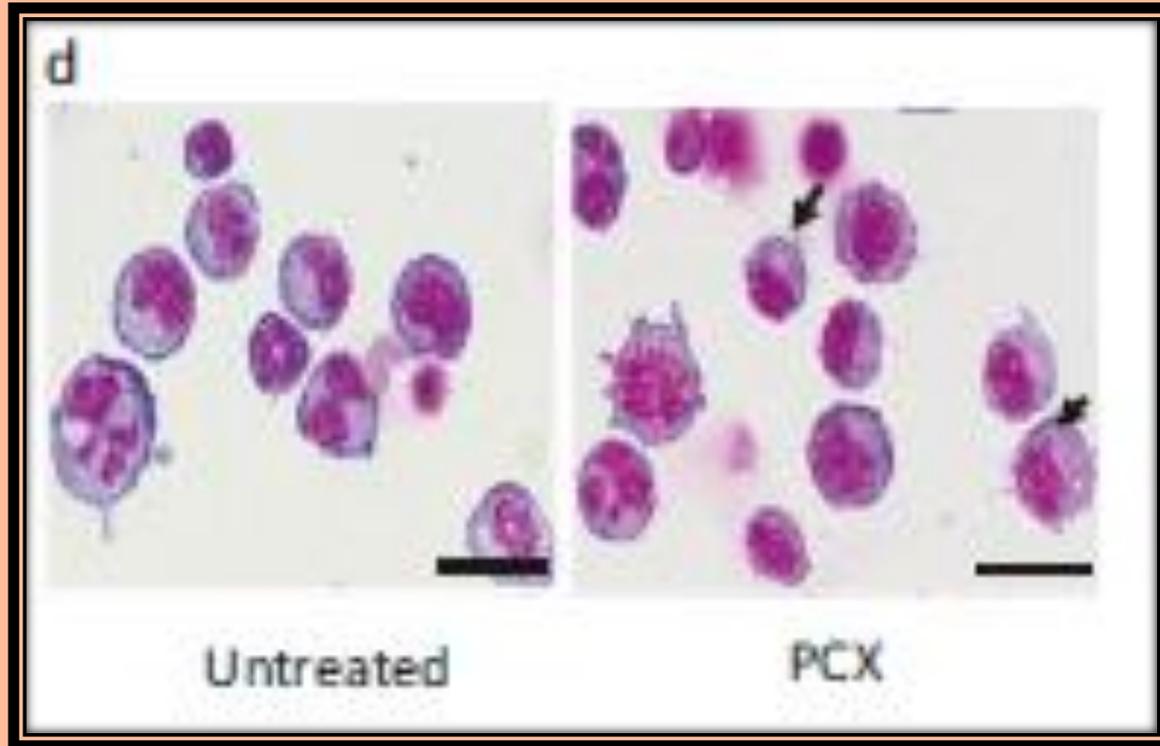


expression in treated cells

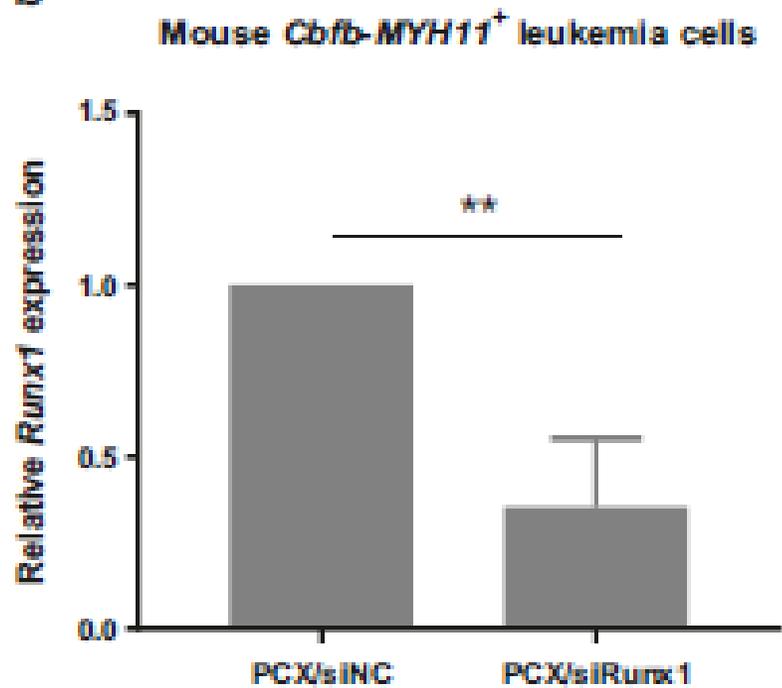
Gr-1



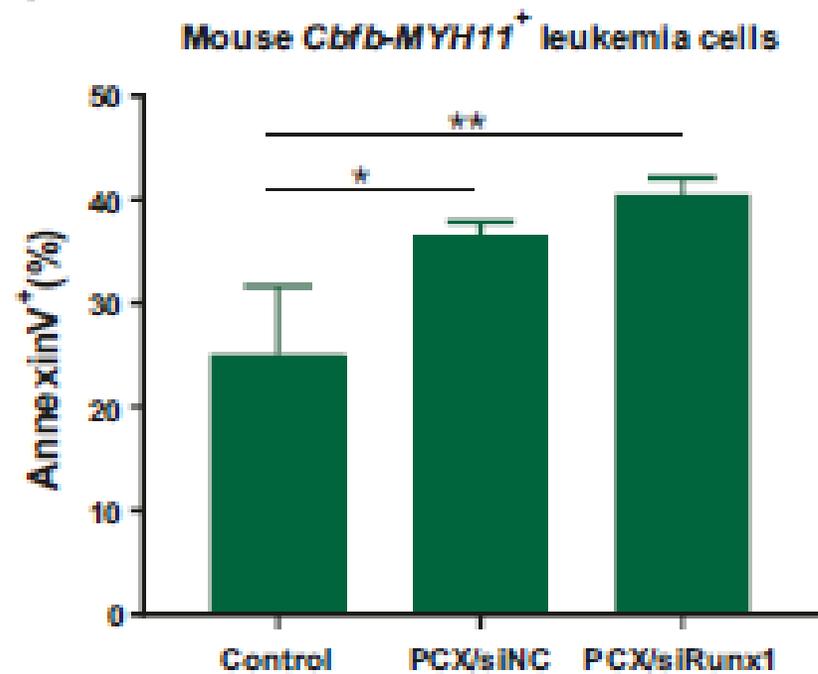
differentiation with PCX treated cells



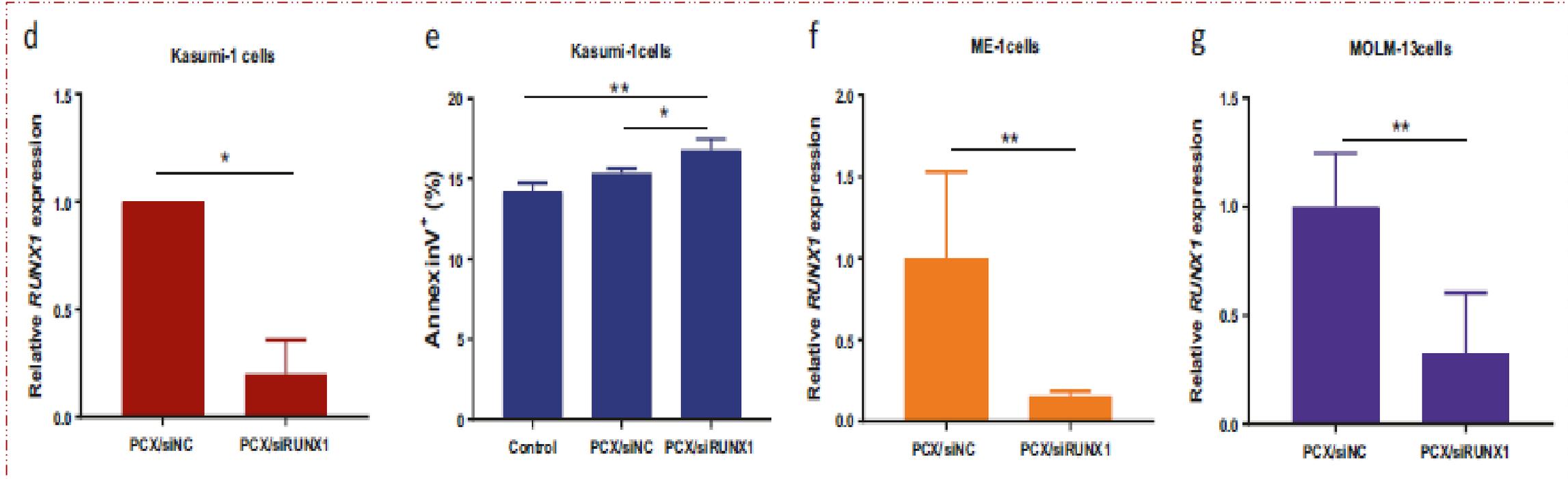
b



c



Testing the ability to deliver siRUNX1 to human AML cells, by PCX





Cell culture medium table :

Cells	Media	FBS	Amine acid (L. Glutamine)	Antibiotic (penicillin– streptomycin)
Kasumi-1	RPMI1640	20%	2 mM	1%
MOLM-13	RPMI1640	20%	2 mM	1%
Mice leukemic cells	RPMI1640	20%	2 mM	1%
HEK293T	DMEM	10%	2 mM	1%



**THANKS
FOR YOUR
ATTENTION**

Is There a question that I will
gladly answer ?

