Abstract #546

MLL-Menin inhibition reverses pre-leukemic progenitor self-renewal induced by NPM1 mutations and prevents AML development

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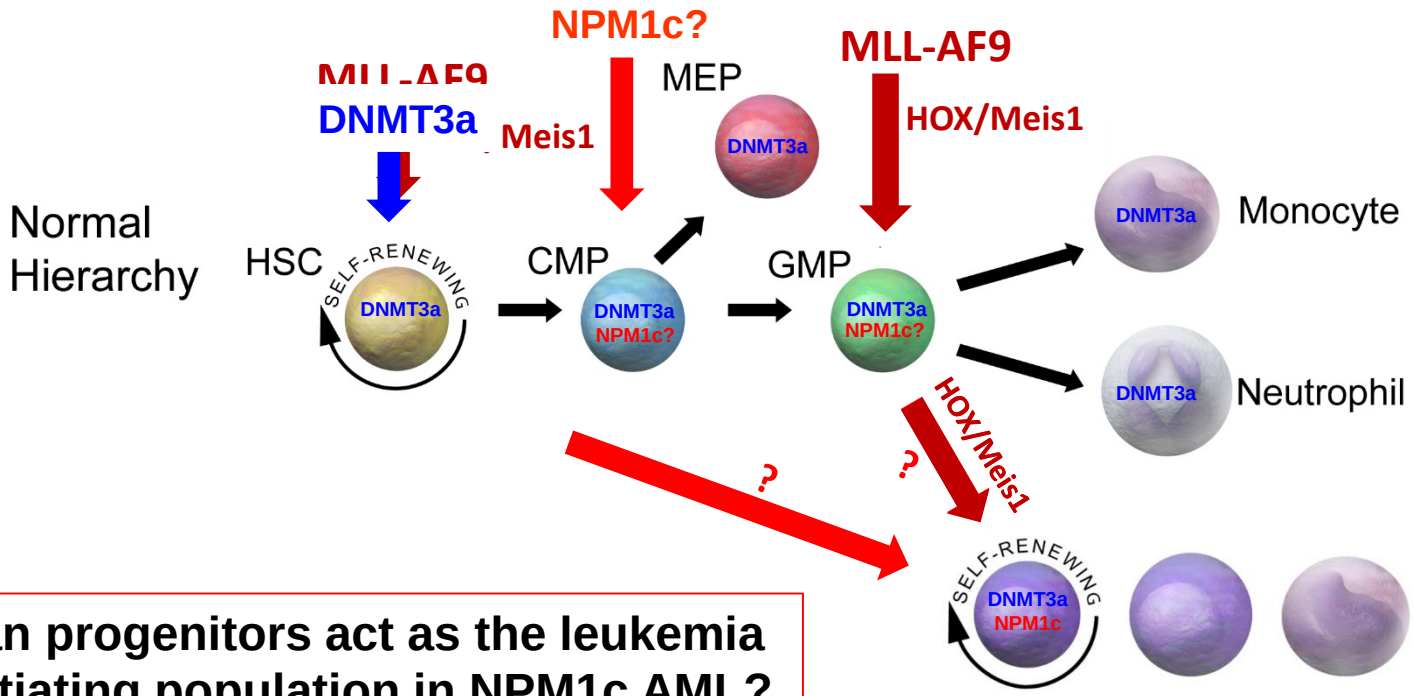
CANCER AND BLOOD DISORDERS CENTER

HARVARD MEDICAL SCHOOL

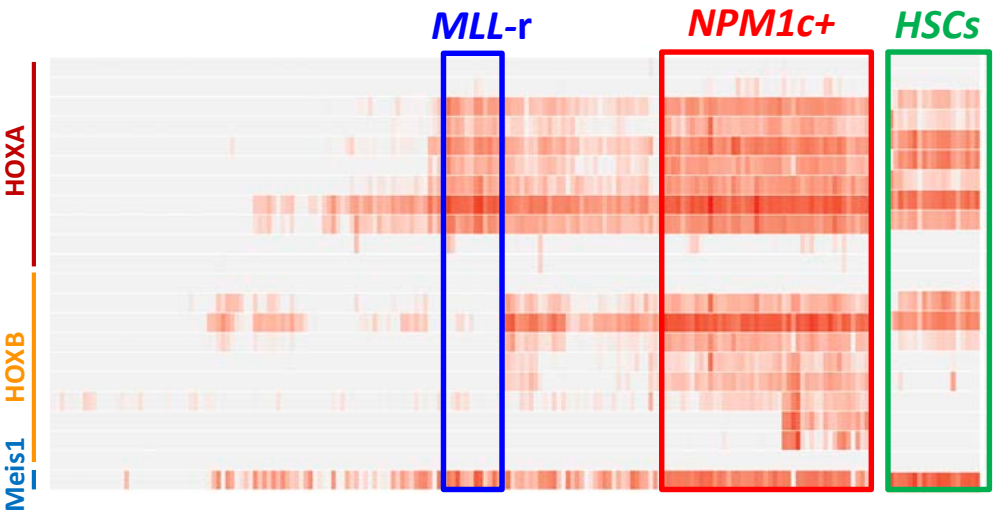
Progression from Stem or Progenitor to Leukemia Stem Cell



Can progenitors act as the leukemia initiating population in NPM1c AML?

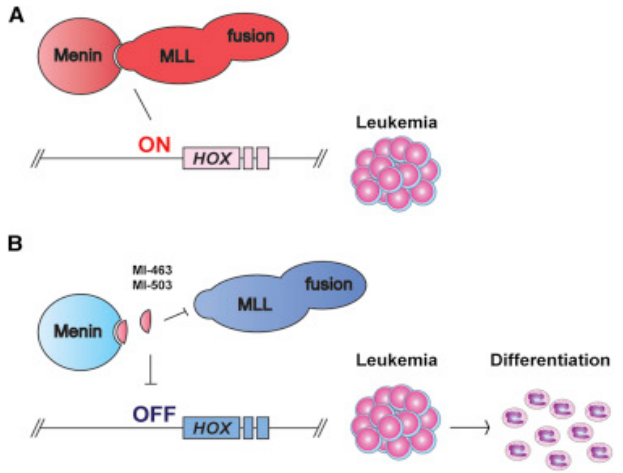
MLL-r and NPM1c AML share common HOX signature and dependencies

HOX expression in AML

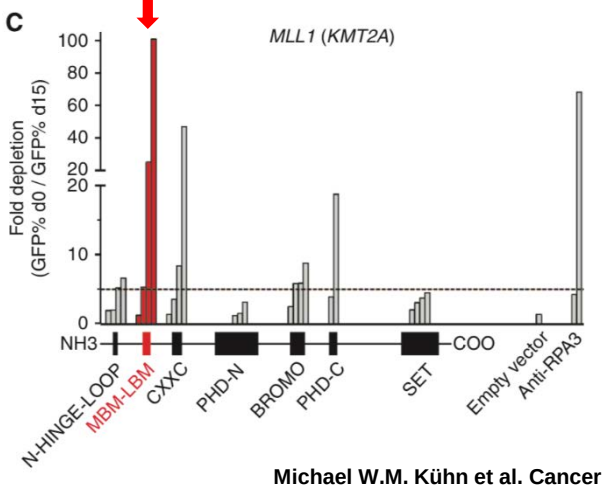


Modified from Spencer et al. Leukemia 2015

Menin-MLL inhibition



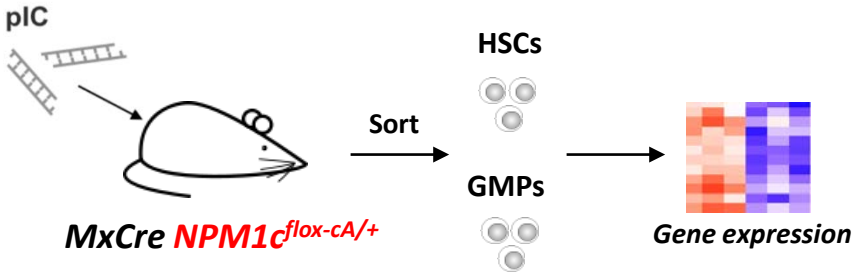
Menin interaction domain



Can MLL-Menin inhibition reverse NPM1c induced self-renewal program?

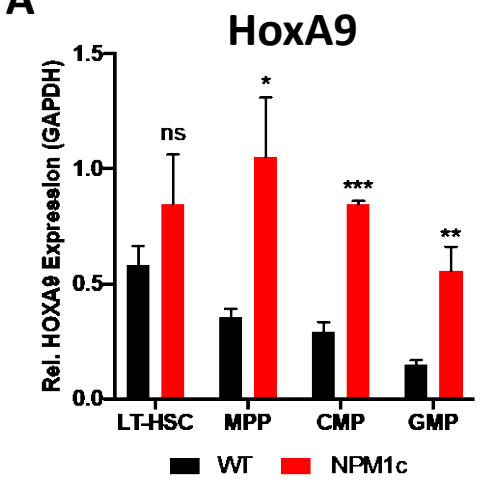
Michael W.M. Kühn et al. Cancer Discov 2016

NPM1c maintains "stem cell program" in committed hematopoietic progenitors.



RNAseq

A



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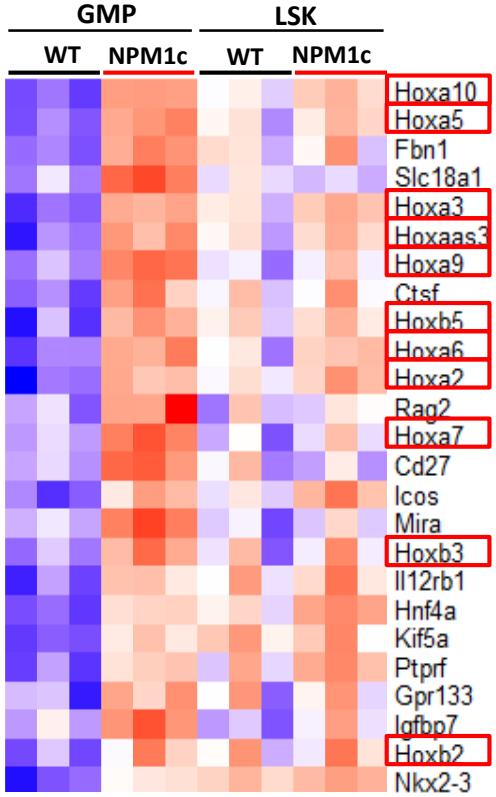
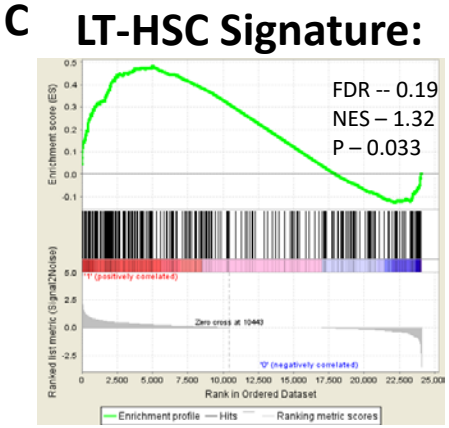
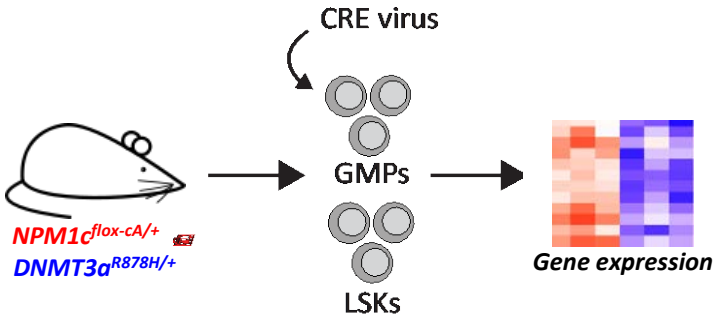


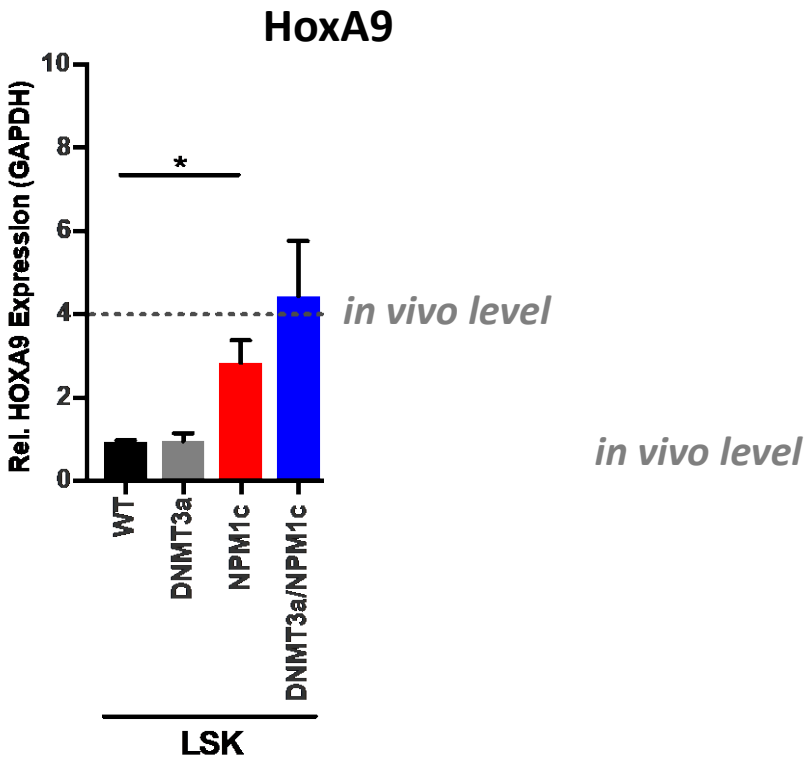
4 weeks post pIC

C



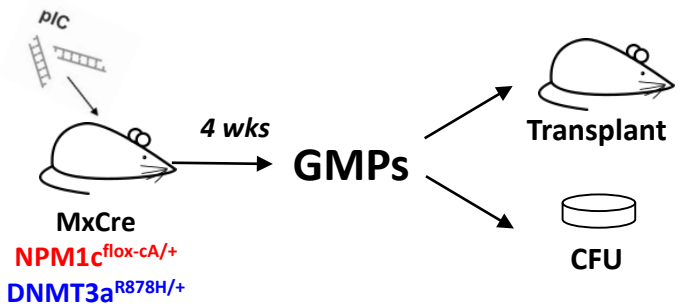
NPM1c induces "stem cell program" in hematopoietic progenitors.

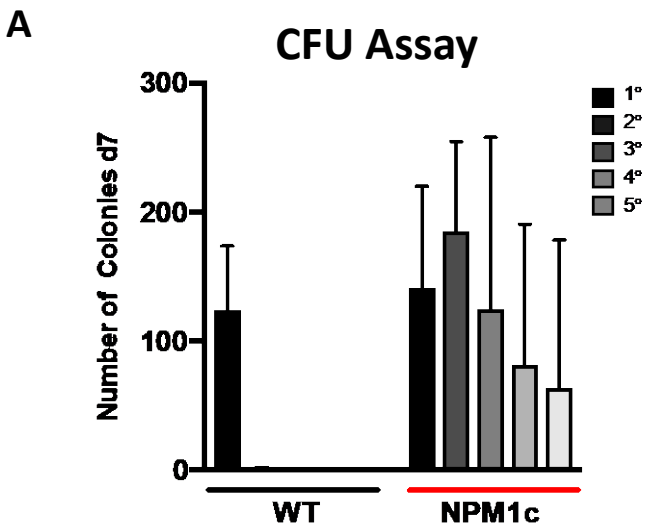


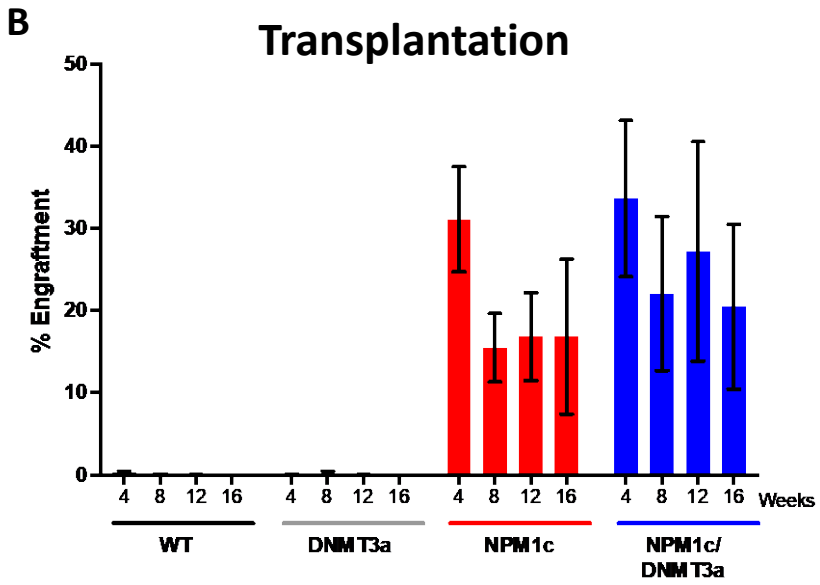


in vivo level

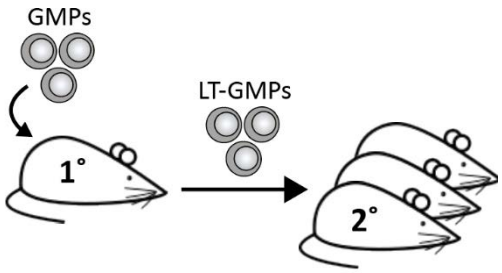
NPM1c expression increases self-renewal of GMPs

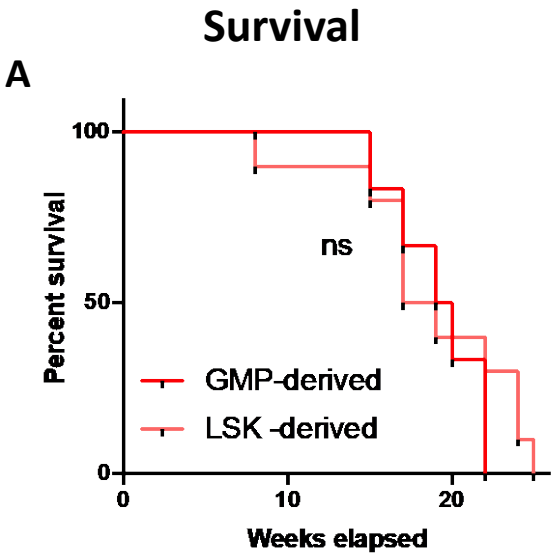


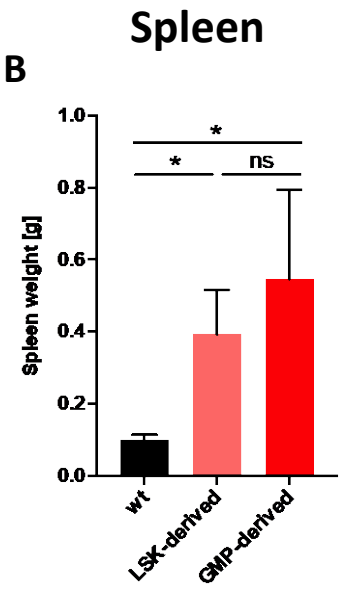




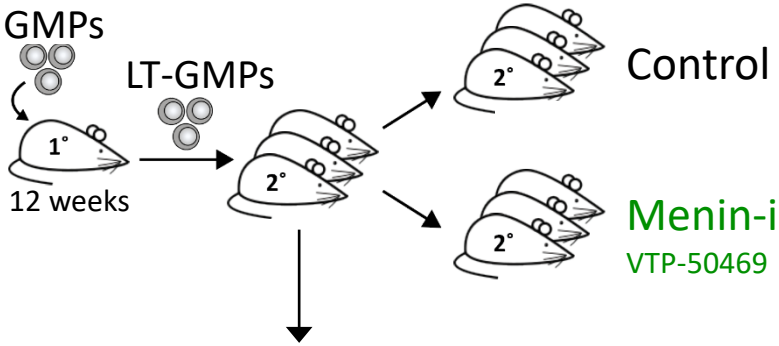
Self-renewing NPM1c+ GMPs are leukemia initiating cells in NPM1c+ AML

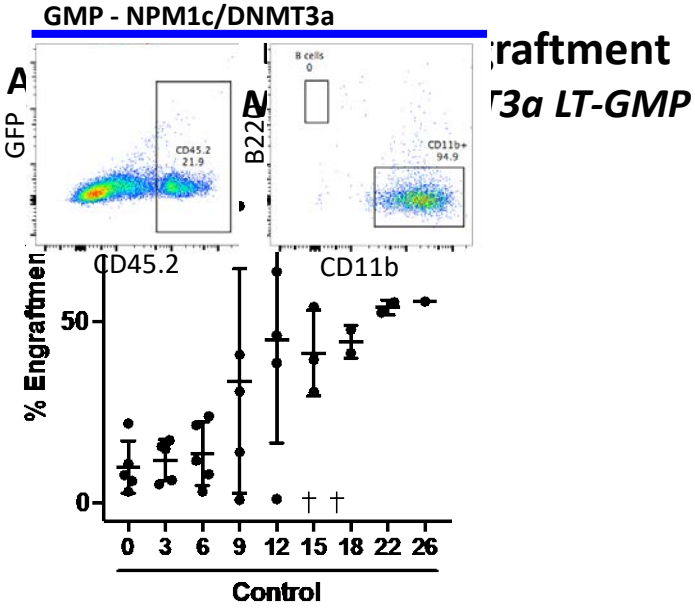


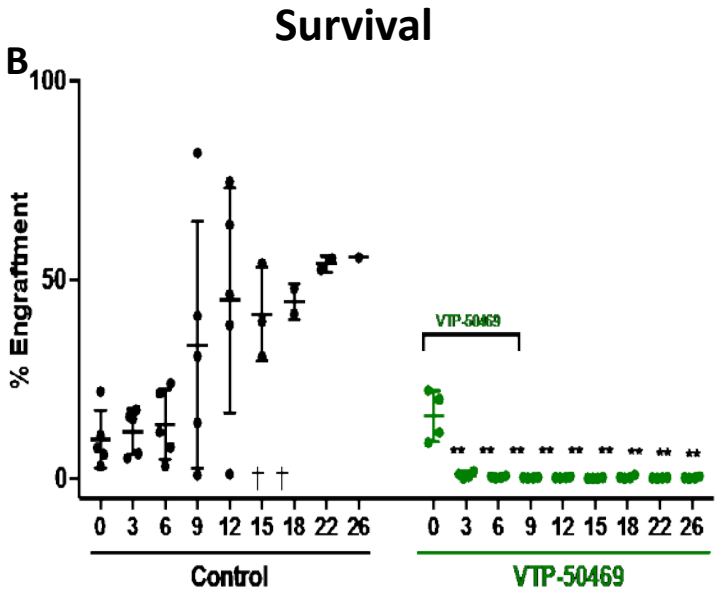




Self-renewing NPM1c^{+} GMPs can be targeted by Menin-i



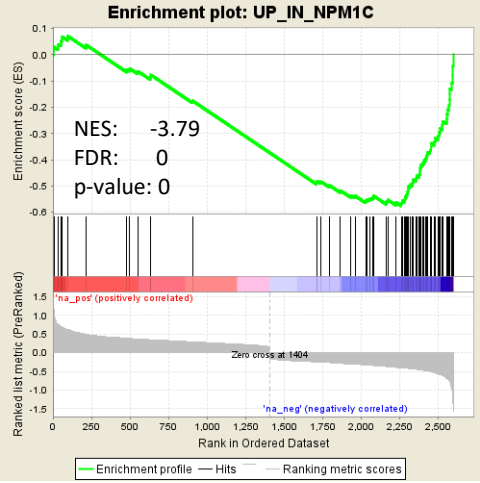




Meis1 is repressed by VTP-50469 in NPM1c mutant cells

NPM1c regulated genes

A



RNAseq

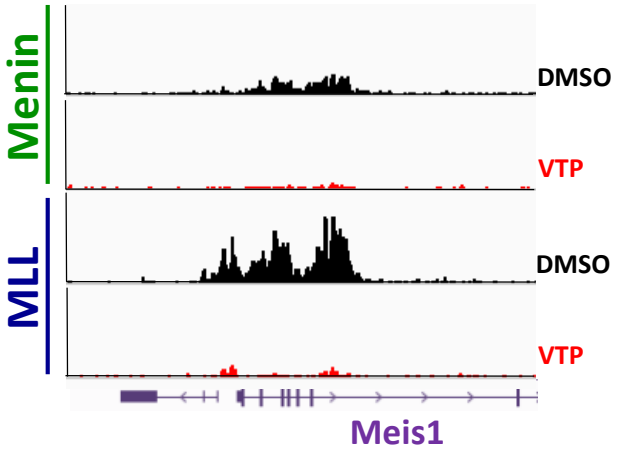
B

Top Ten DOWN VTP:

Symbol	FoldChange (Log2)	p-value
Mecom	-1.57	9.02e-19
Dmrta2	-1.45	3.25e-16
Meis1	-1.36	7.86e-15
Hnf4a	-1.13	7.74e-11
Pcp4l1	-1.12	1.07e-11
Ddx4	-1.10	9.13e-11
Pbx3	-1.07	1.05e-22
Spns2	-1.03	2.75e-09
Kdm5b	-1.00	3.37e-21
Angpt1	-0.99	4.65e-11

C

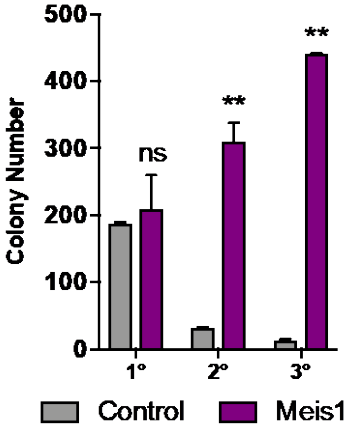
ChIPseq



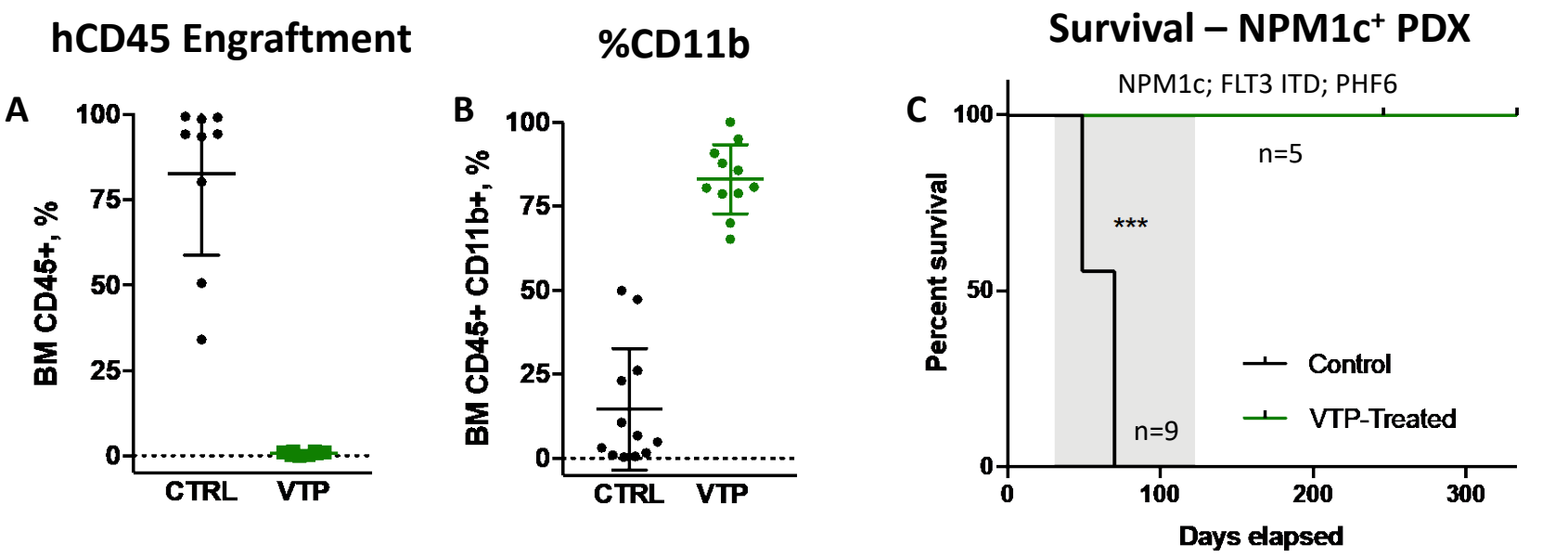
D

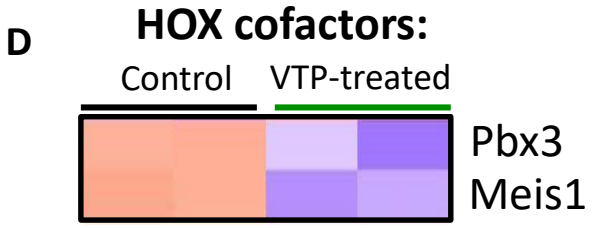
In vitro Rescue

10nM VTP-50469

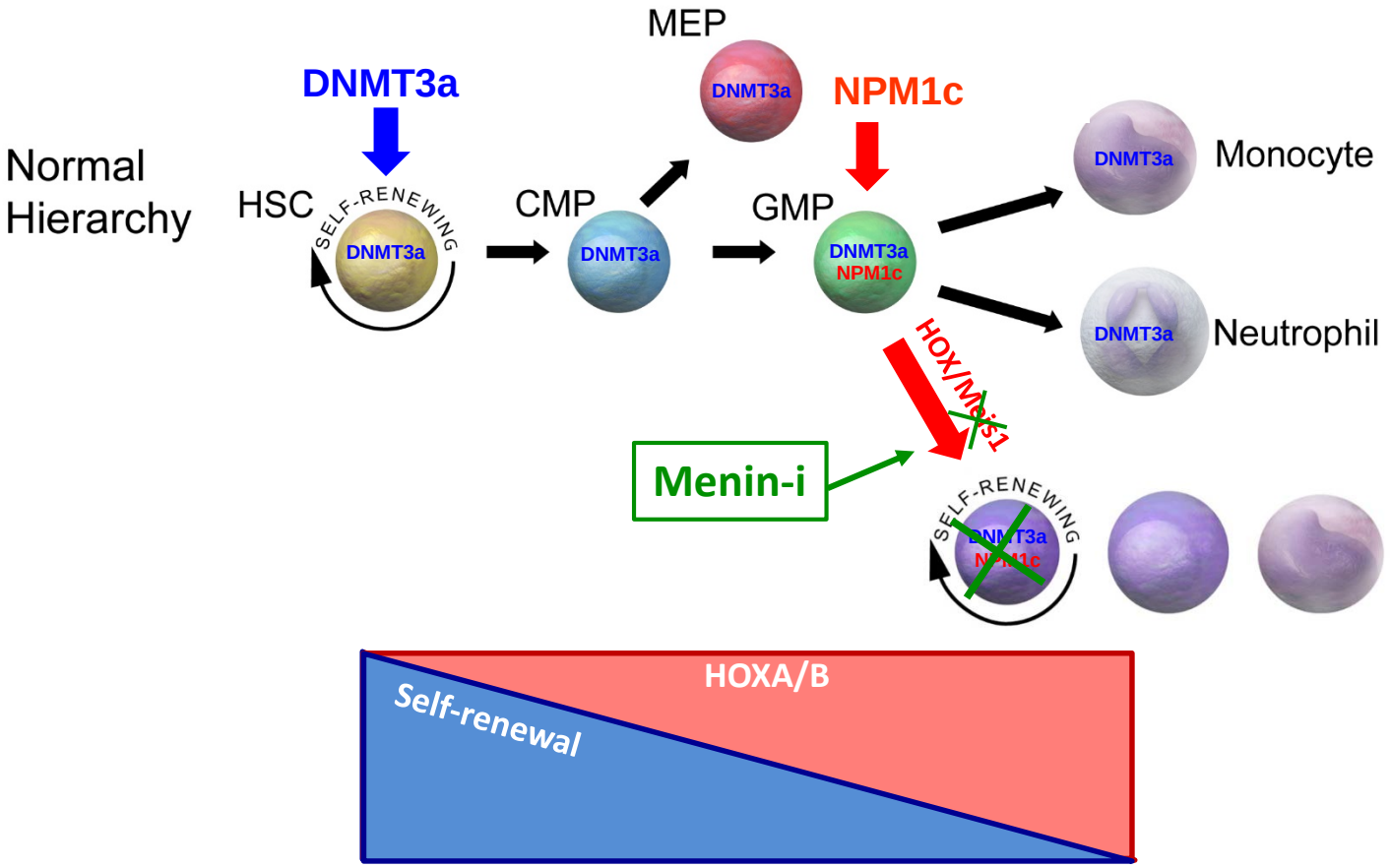


Human NPM1c AML are highly sensitive to VTP-50469 Menin-i treatment





MLL-Menin inhibition reverses progenitor self-renewal induced by NPM1c



Acknowledgements

Armstrong Lab

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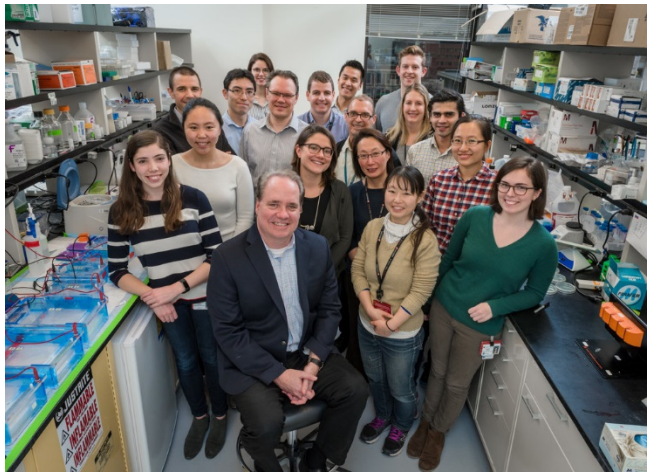
Stephanie Kim
Sayuri Kitajima
Andrei Krivtsov
Chloe Matovina
Naomi Olsen
Sarah Perlee
Florian Perner
Jen Perry
Ken Ross
Franziska Wachter



DFG Deutsche Forschungsgemeinschaft

Vassiliou Lab

NPM1c Knock-in mice

Levine Lab

DNMT3a^{R882} Knock-in mice

Syndax

Menin-i: VTP50469

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