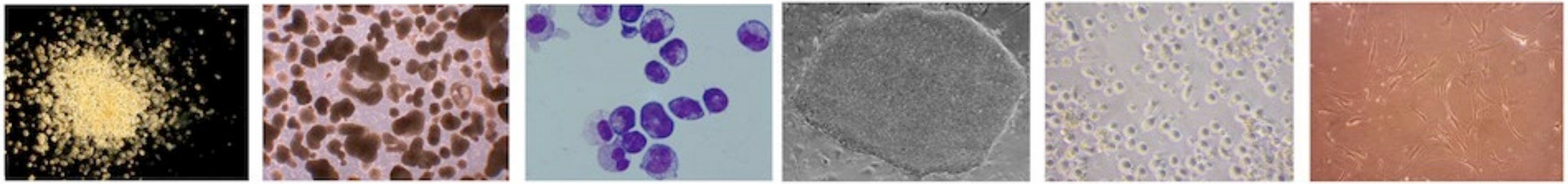
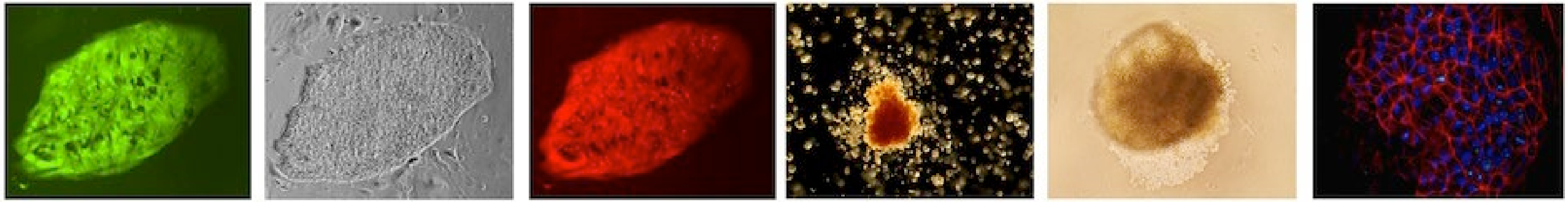


Modelling secondary AML using human induced pluripotent stem cells

Eirini Papapetrou, MD, PhD

Icahn School of Medicine at Mount Sinai

Center for Advancement of Blood Cancer Therapies

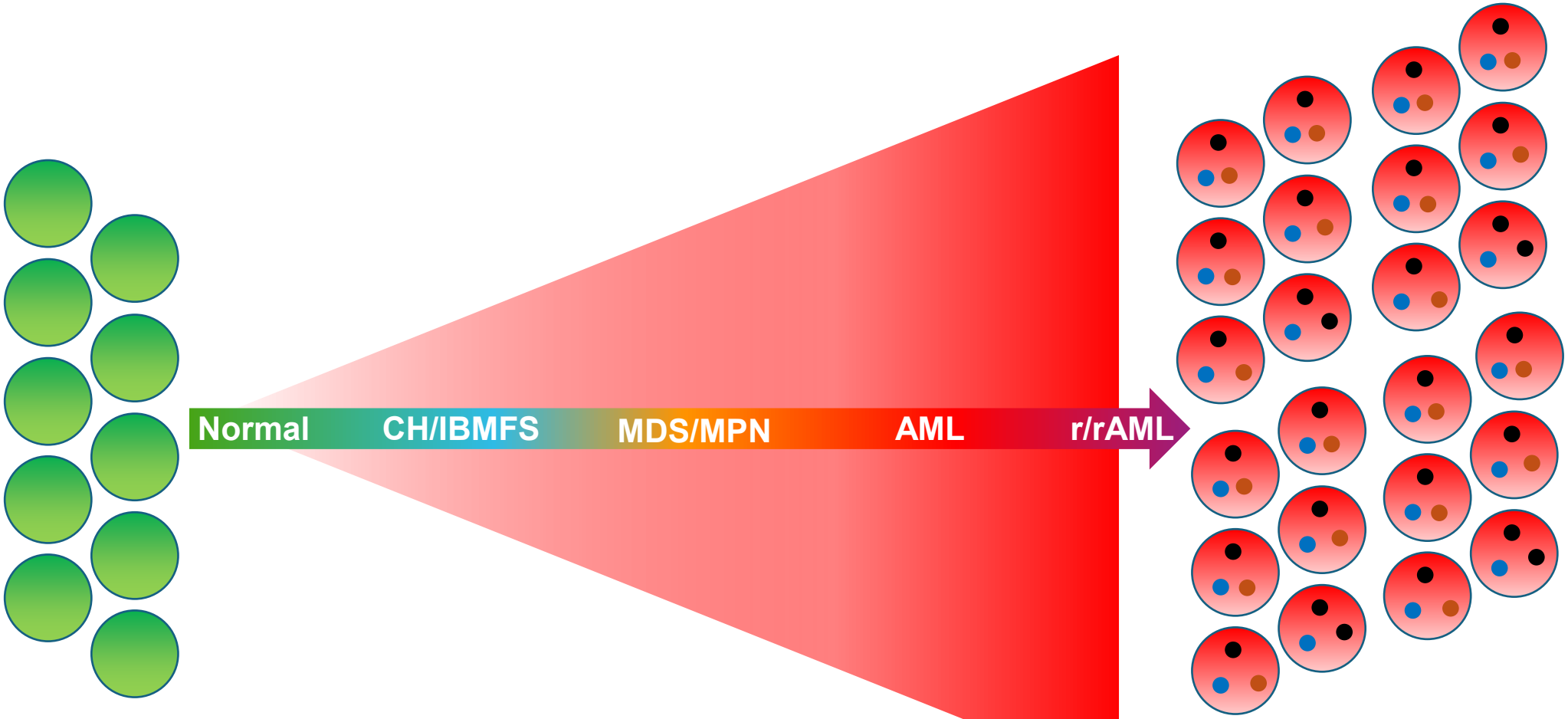


How does a normal HSPC turn bad?

Normal hematopoietic
stem/progenitor cells (HSPCs)

Leukemia
stem cells (LSCs)

How does a normal HSPC turn bad?



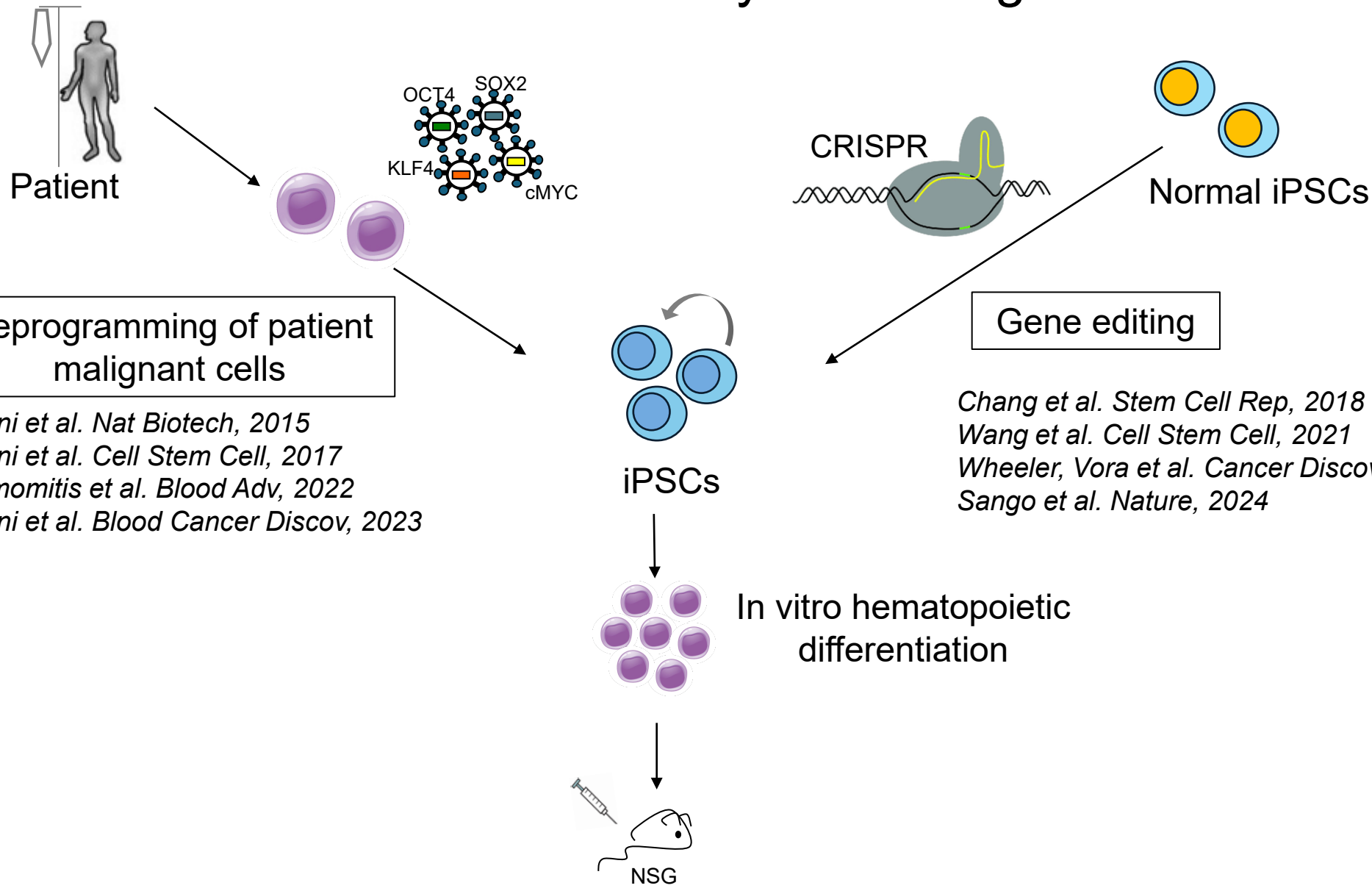
Normal hematopoietic stem/progenitor cells (HSPCs)

Leukemia stem cells (LSCs)

Richard Feynman
1918-1988

"*What I cannot create I do not understand*"

Human iPSC models of myeloid malignancies



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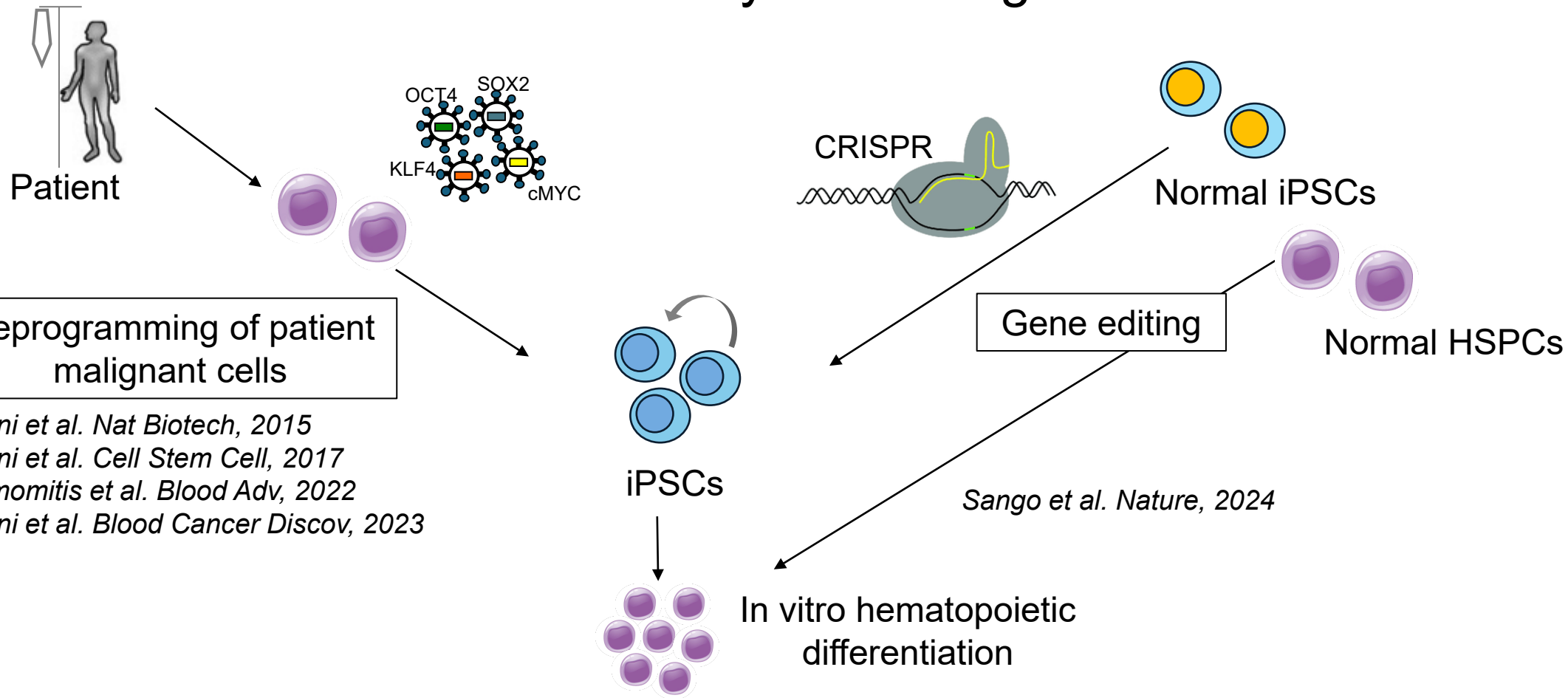


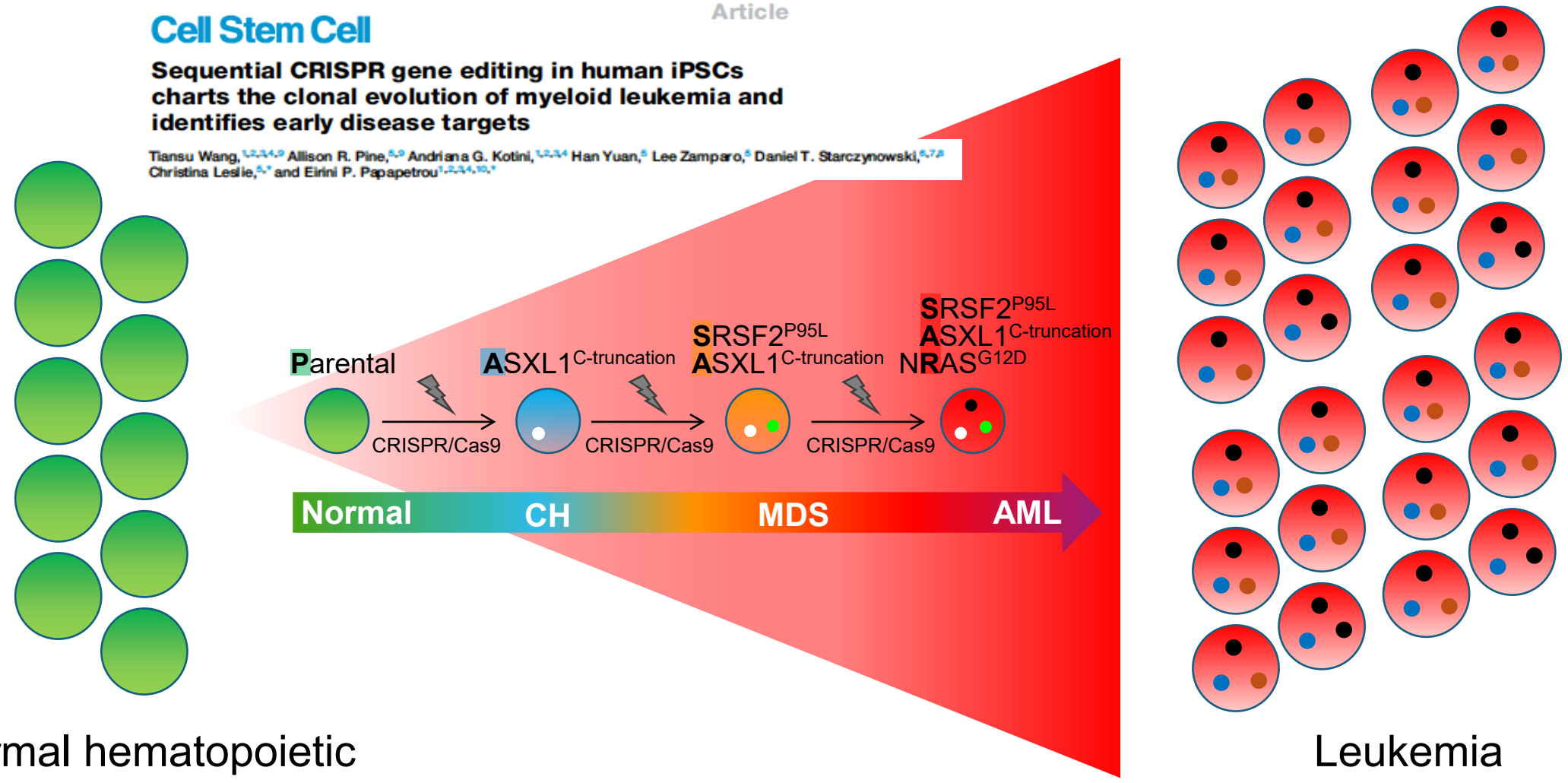
Kotini et al. Nat Biotech, 2015
Kotini et al. Cell Stem Cell, 2017
Asimomitis et al. Blood Adv, 2022
Kotini et al. Blood Cancer Discov, 2023

Sango et al. Nature, 2024

Key advantages:

- Human
- Genetically faithful models
- Isogenic
- Unlimited cell numbers, high throughput
- Functional studies

A synthetic model of CH-MDS-sAML progression



Normal hematopoietic stem/progenitor cells (HSPCs)

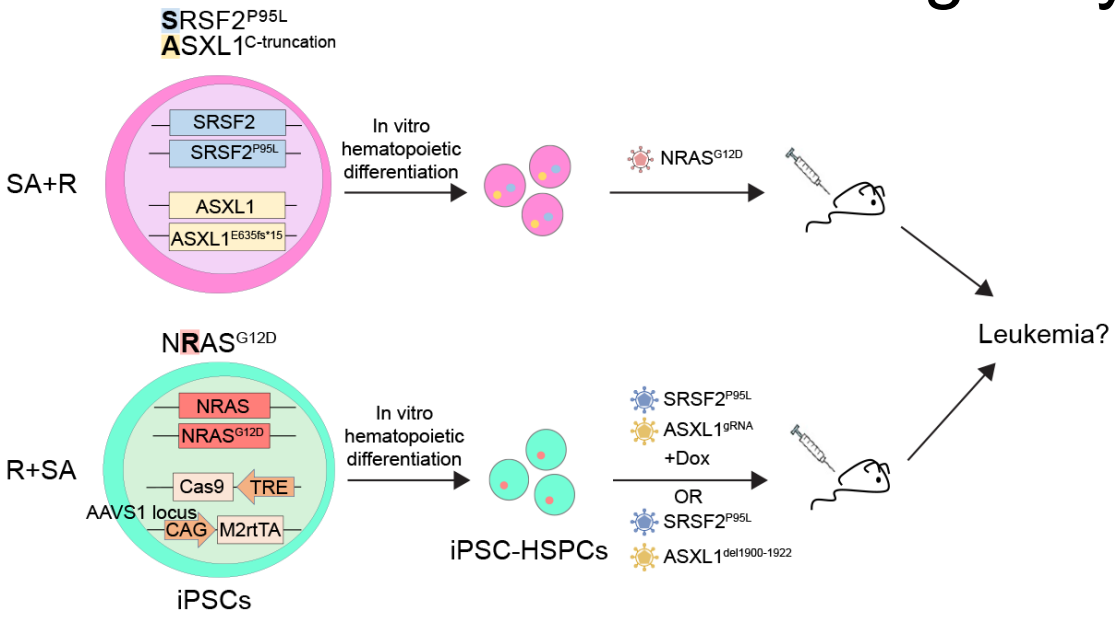
Leukemia stem cells (LSCs)

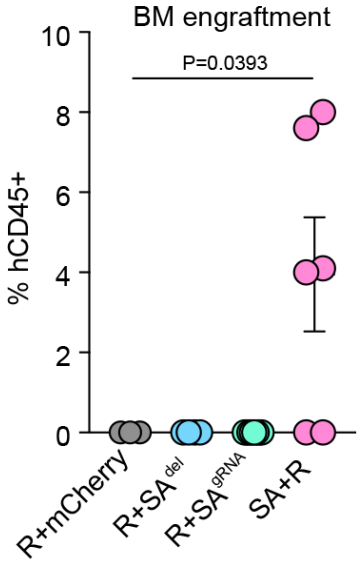
Why are RAS mutations always late in AML?

N/KRAS mutations:

- are present in up to 30% of AML patients
- are almost always subclonal
- are often acquired upon relapse
- are often acquired during progression from MDS to sAML
- are, in contrast, early truncal events in epithelial cancers

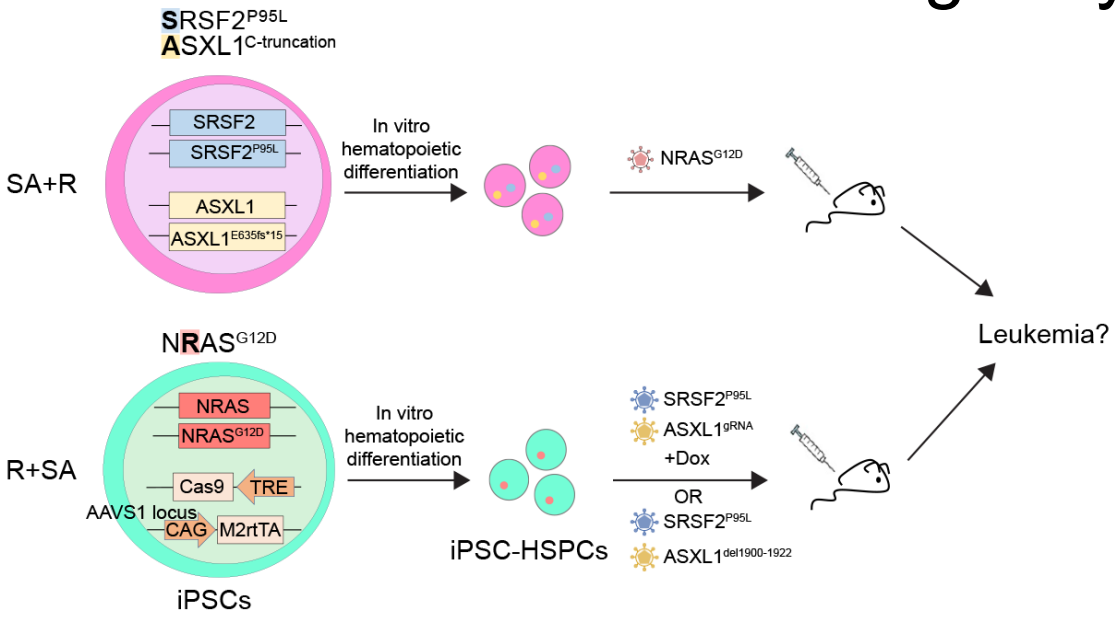
$NRAS^{G12D}$ is an obligatory late mutation

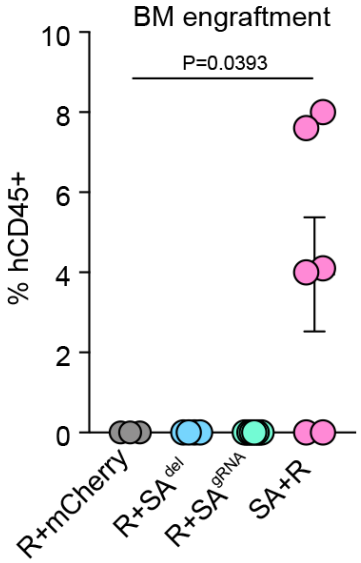




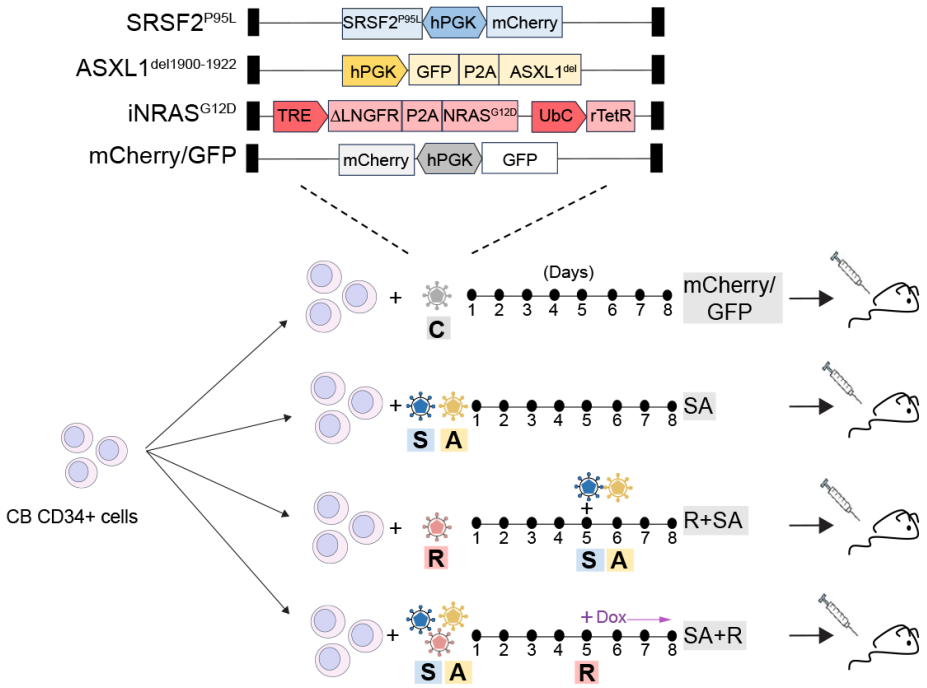
Junya Sango

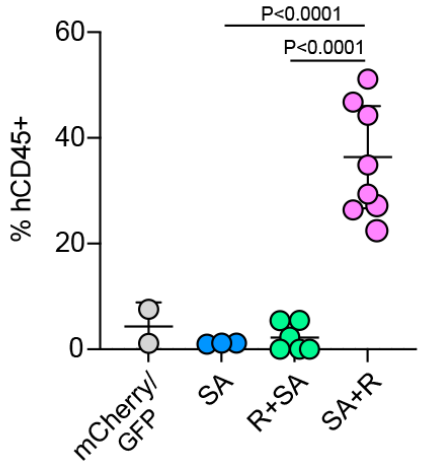
NRAS^{G12D} is an obligatory late mutation

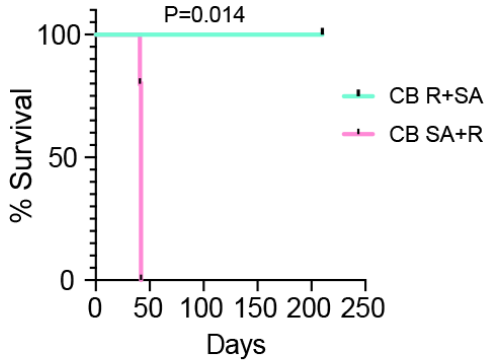




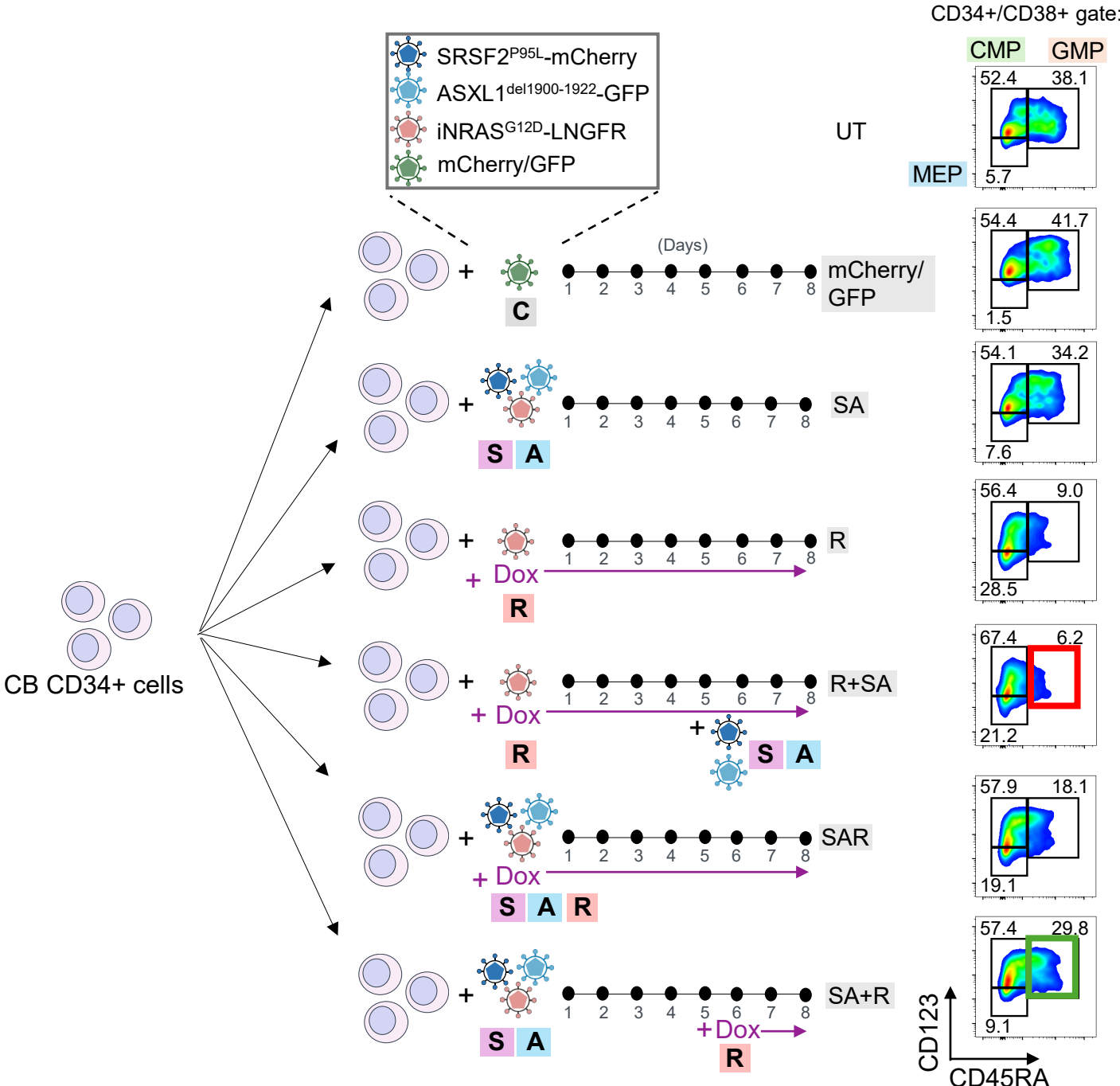
Junya Sango







RAS mutations transform GMPs harboring preexisting mutations



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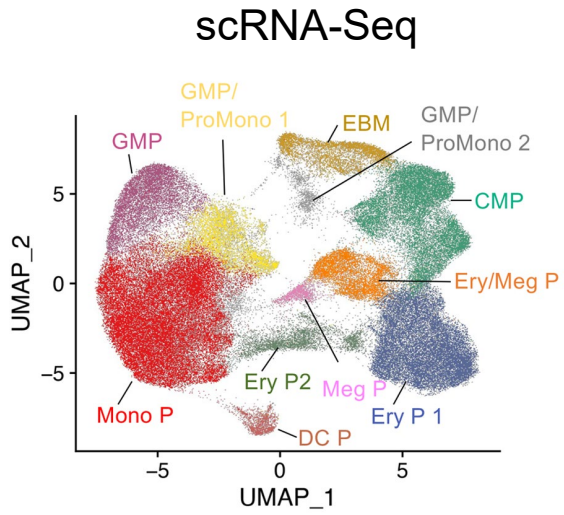
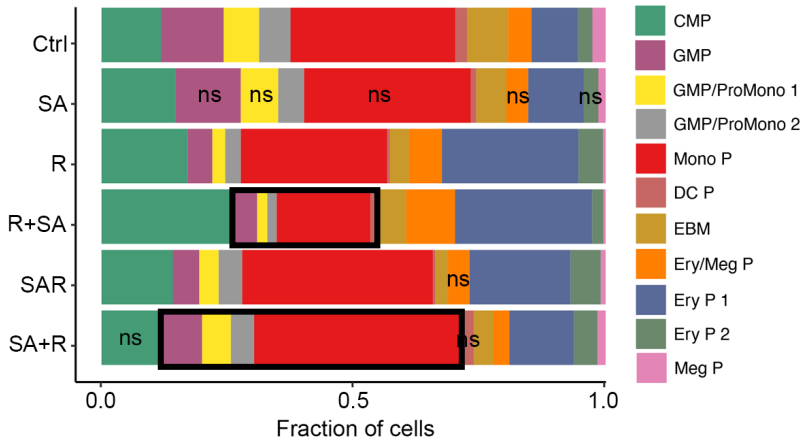
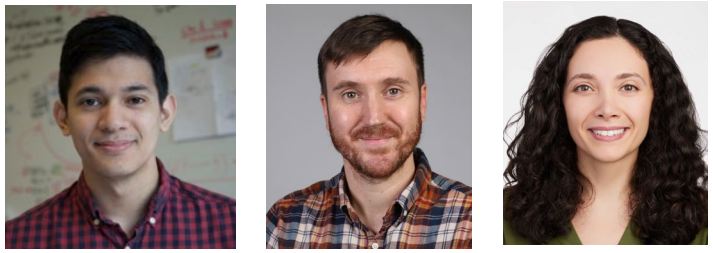
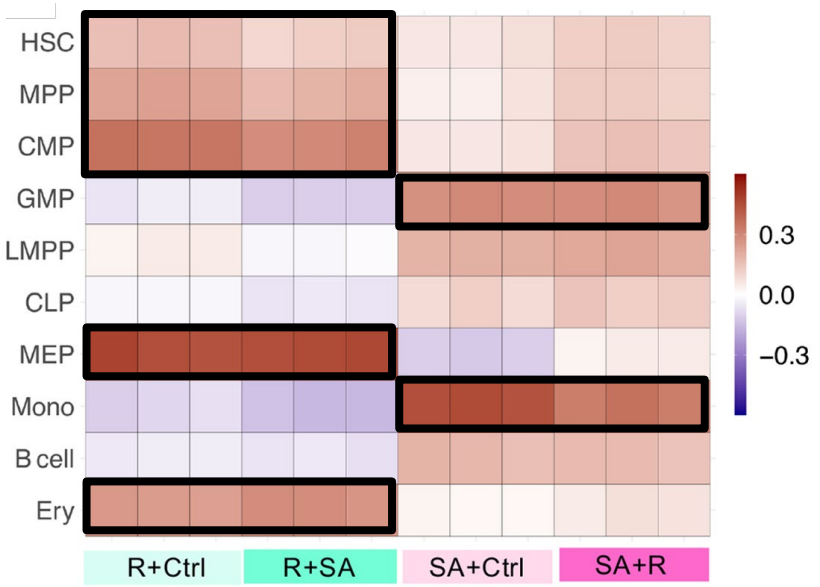


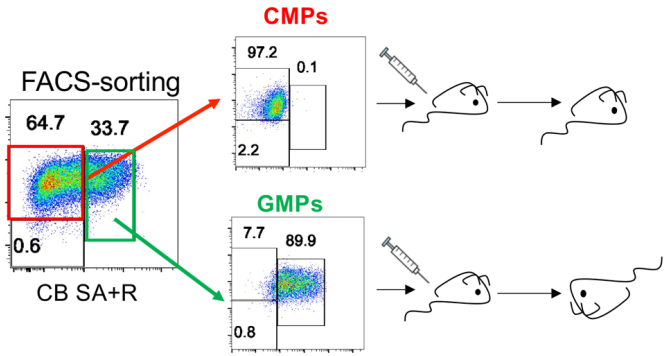




Saul Carcamo Lewis Tomalin Gulay Ulukaya

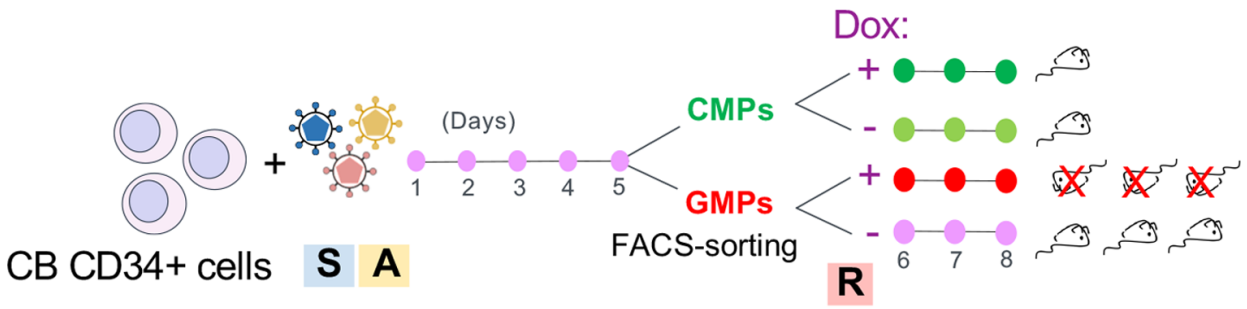


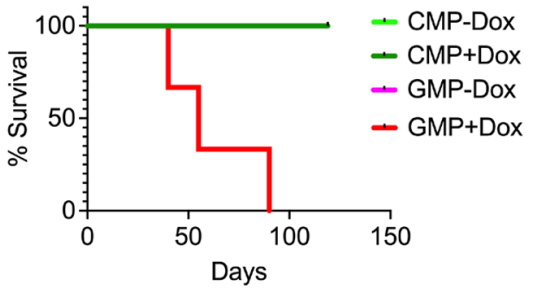
RAS mutations transform GMPs harboring preexisting mutations



- **SA+R GMPs are the leukemia initiating cells**

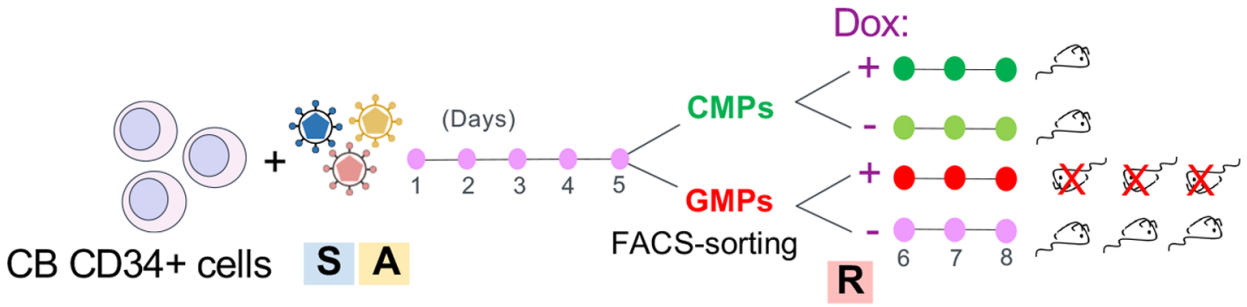
RAS mutations transform GMPs harboring preexisting mutations

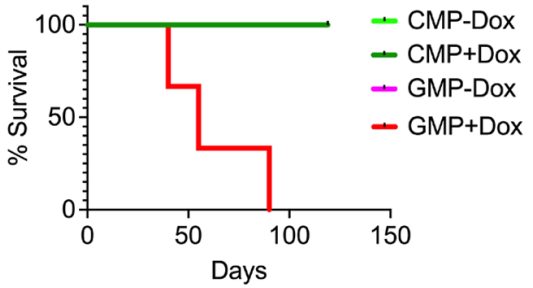




- **SA GMPs are the target cells of transformation by RAS mutations**

RAS mutations transform GMPs harboring preexisting mutations





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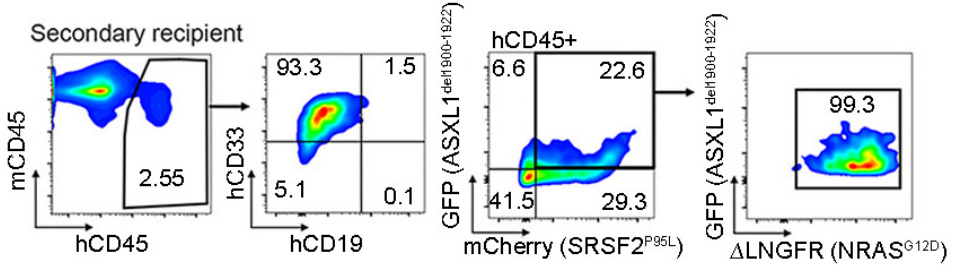

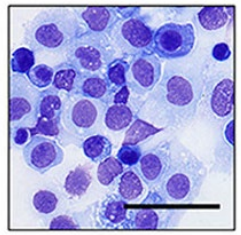

- **SA+R GMPs are leukemia stem cells**

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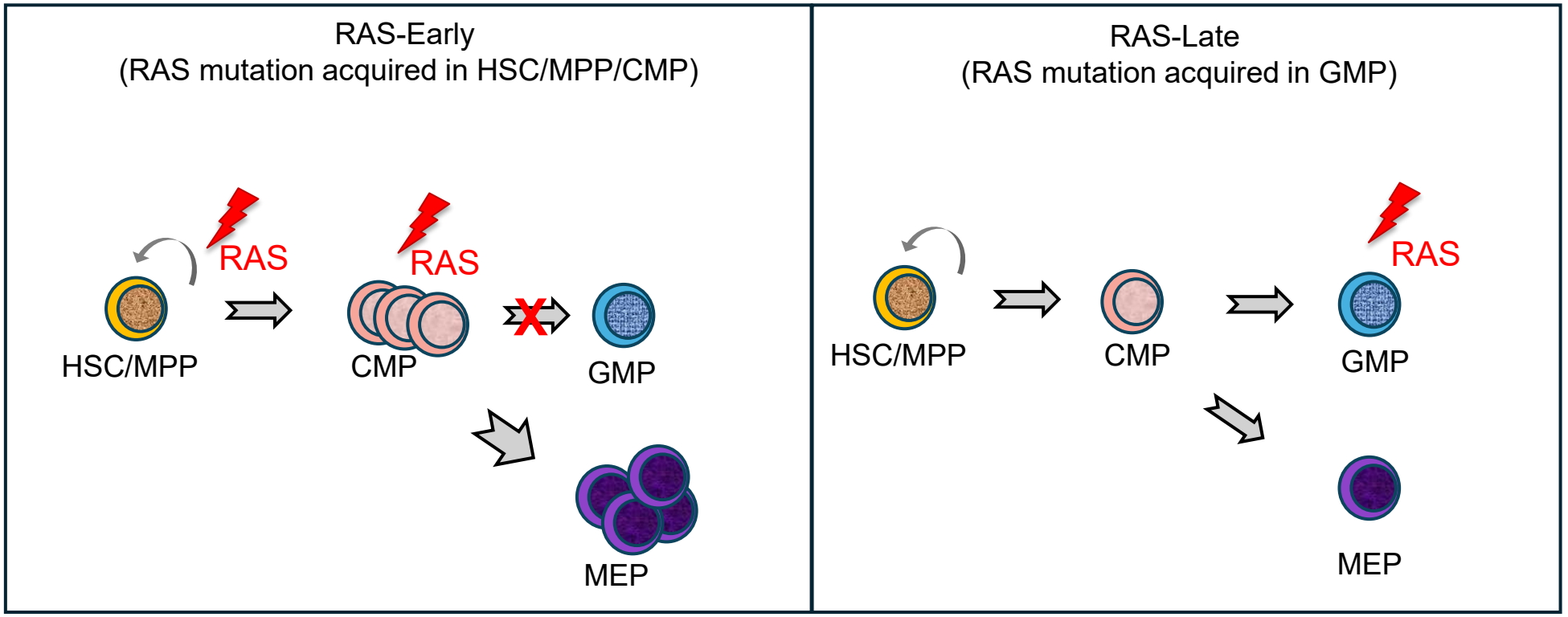
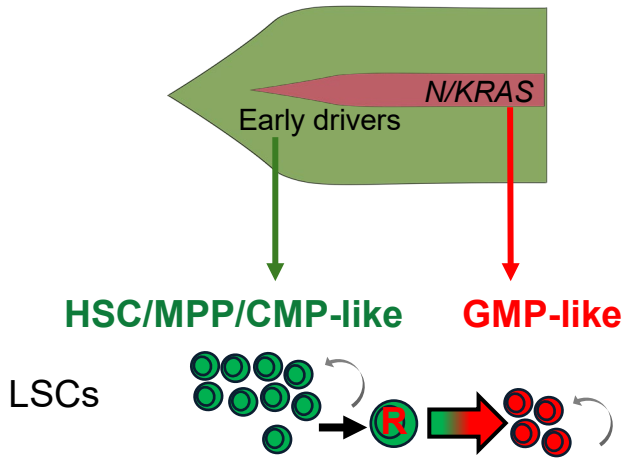
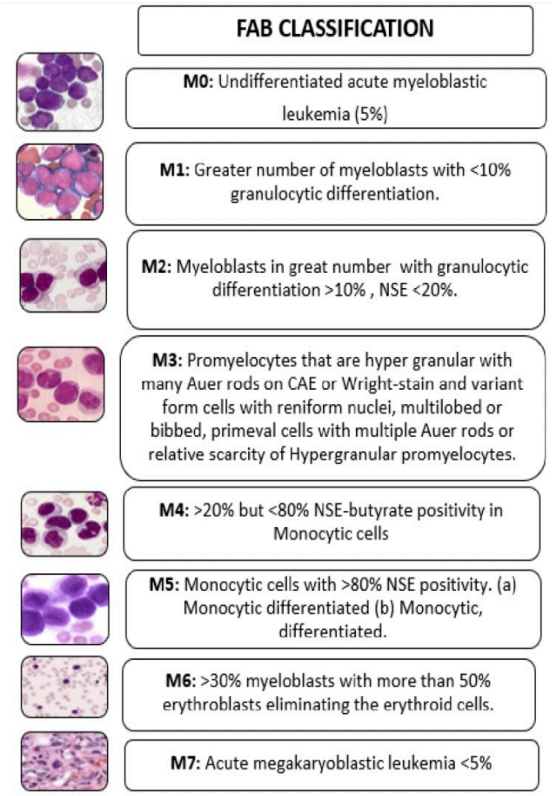


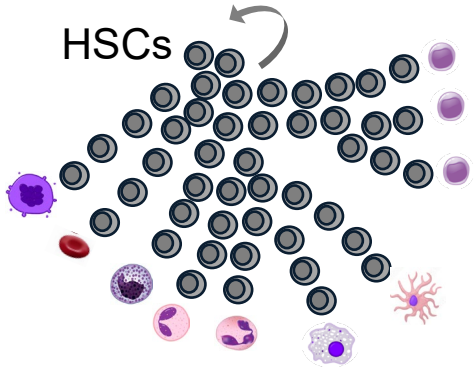
- RAS mutations transform progenitors committed to the myelomonocytic lineage (GMPs) that have previously acquired driver mutations, i.e. are descendants of an ancestral clone originating from a more primitive (HSC/MPP/CMP) cell



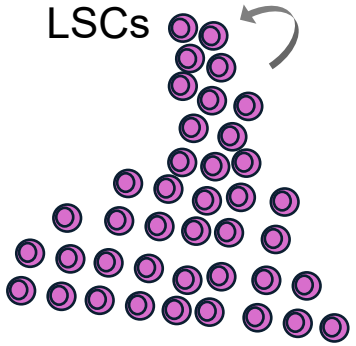
AML hierarchies and phenotype



Normal hematopoiesis



AML with deep hierarchy



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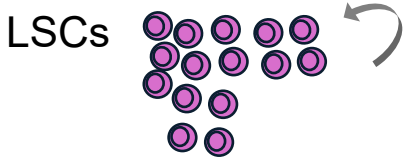

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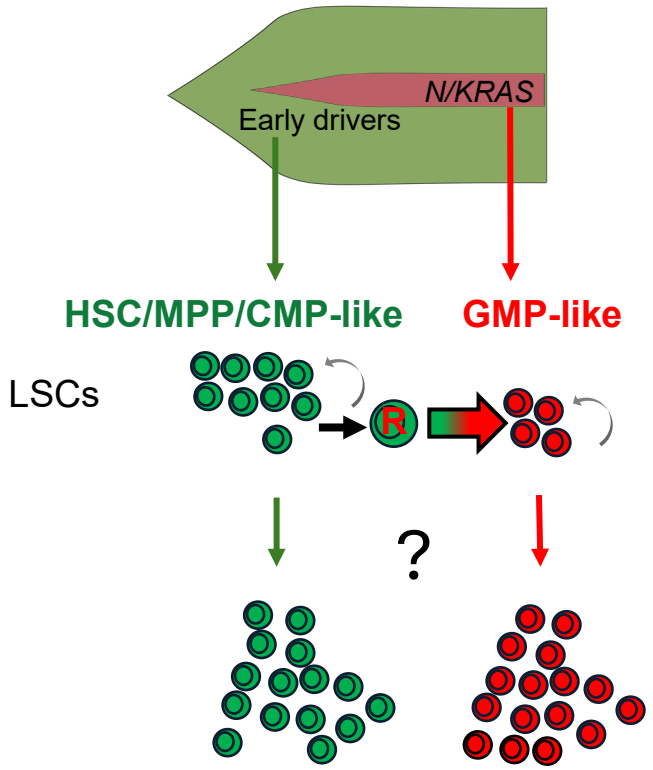
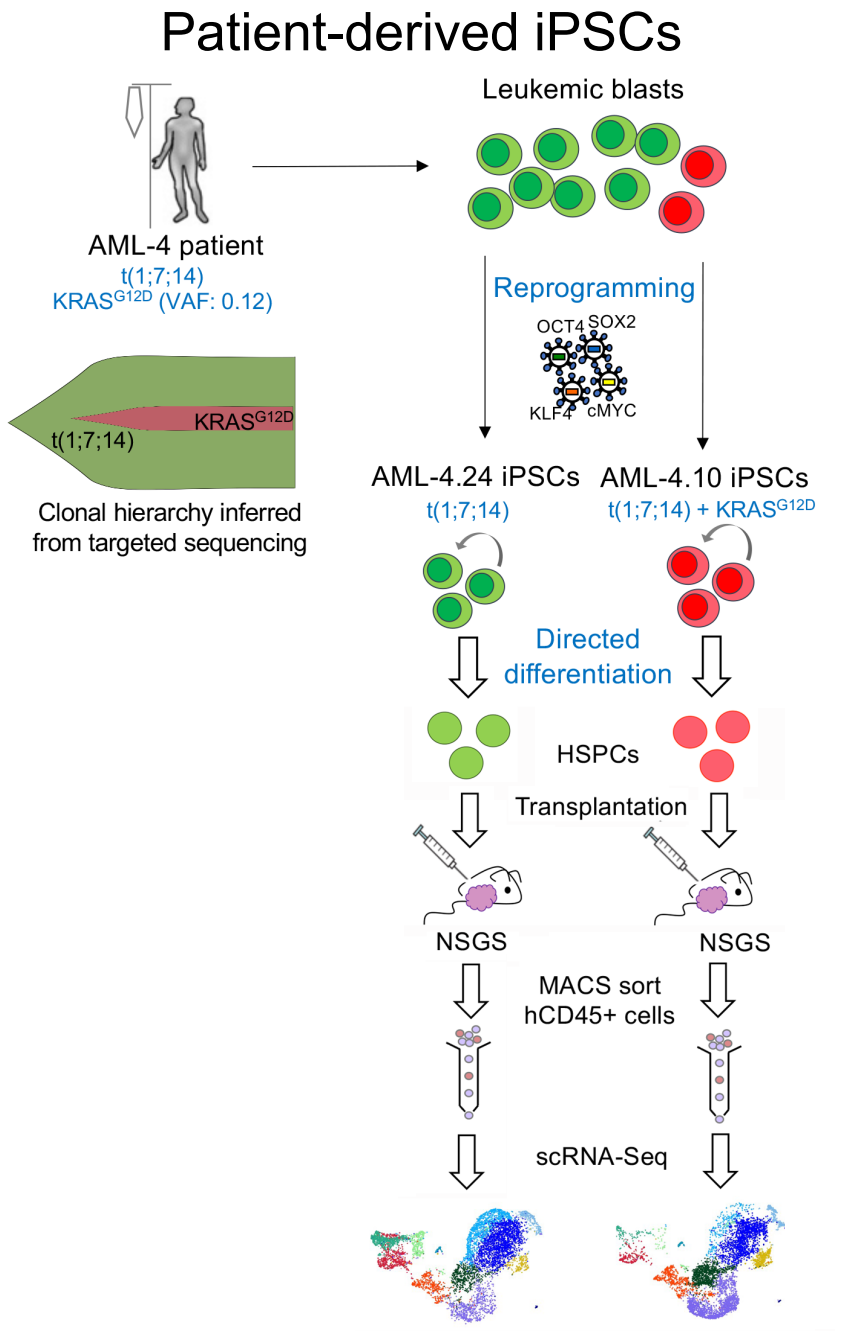


Comparison of RAS-MT and RAS-WT cells within the same AML patient



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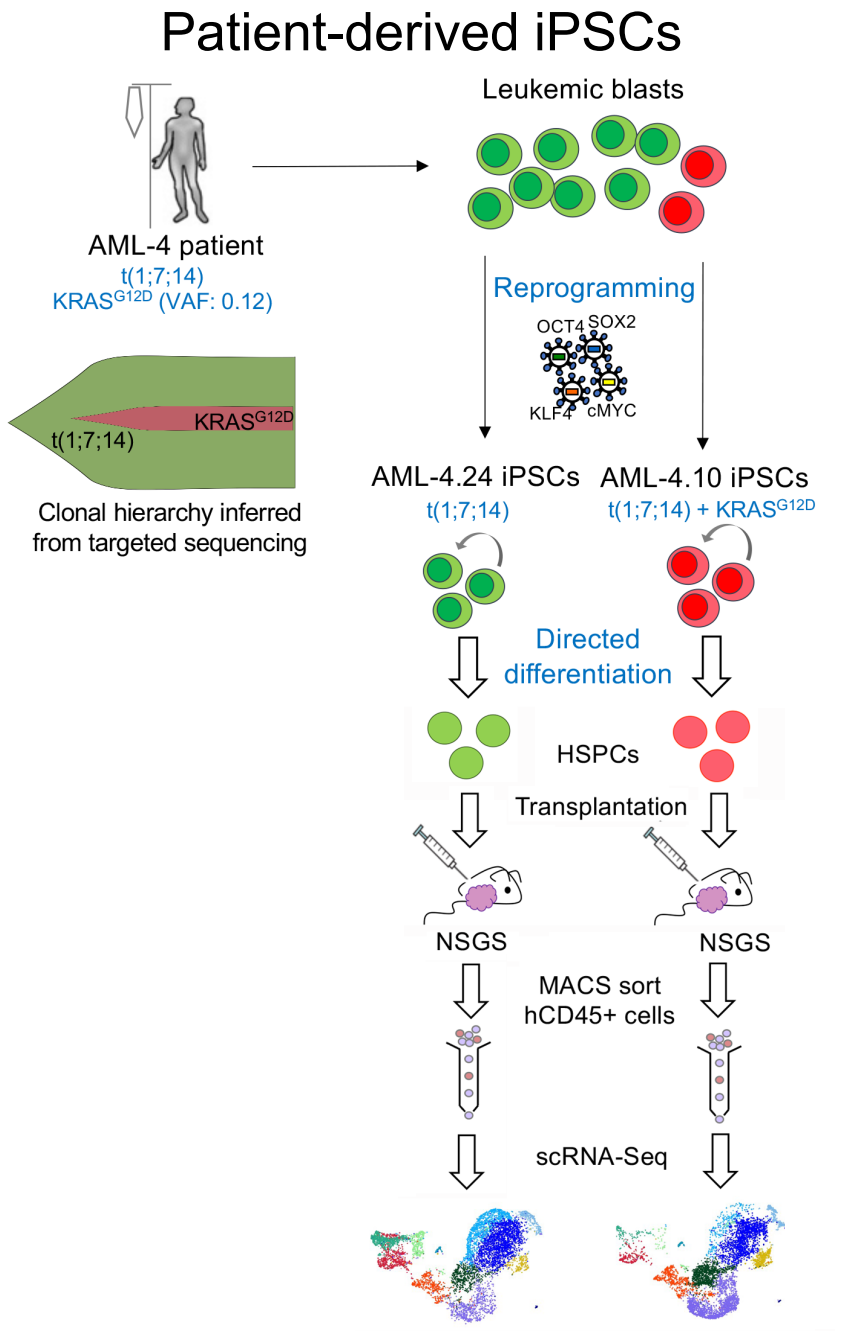
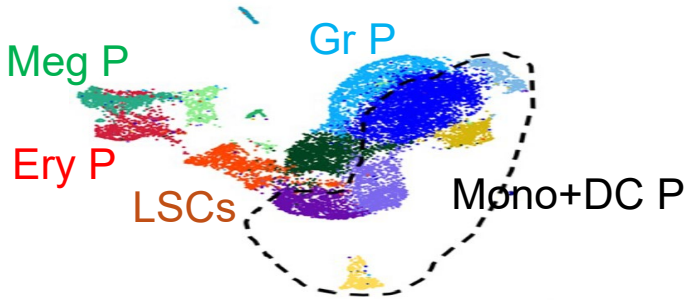
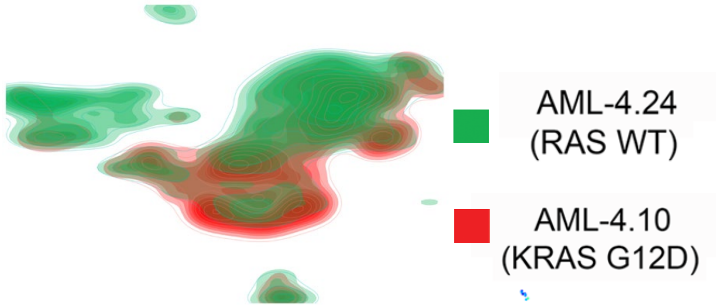
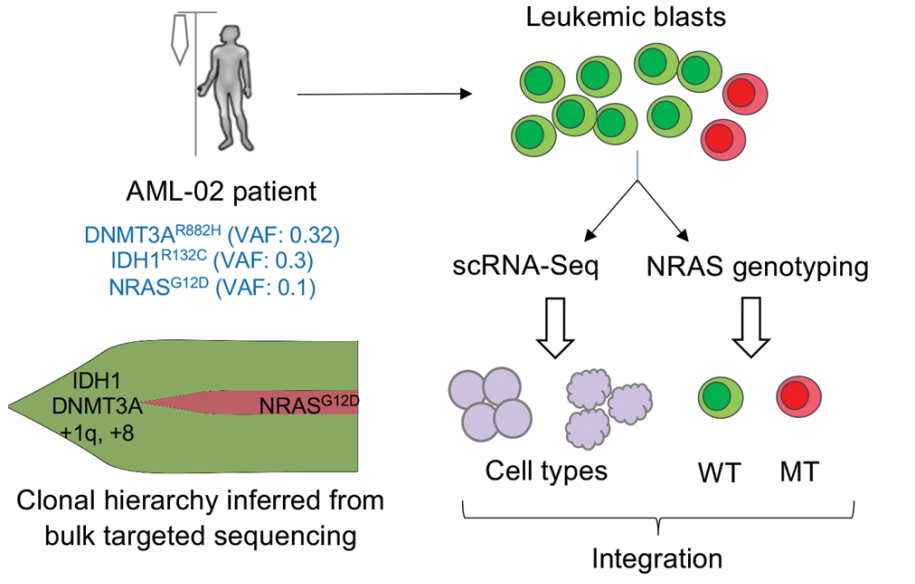






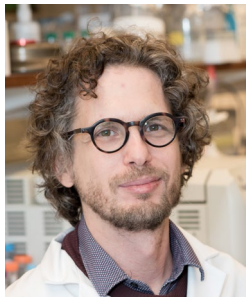
Comparison of RAS-MT and RAS-WT cells within the same AML patient

Genotyping of Transcriptomes (GoT)




Maria Sirenko


Elli Papaemmanuil


Dan Landau

Comparison of RAS-MT and RAS-WT cells within the same AML patient

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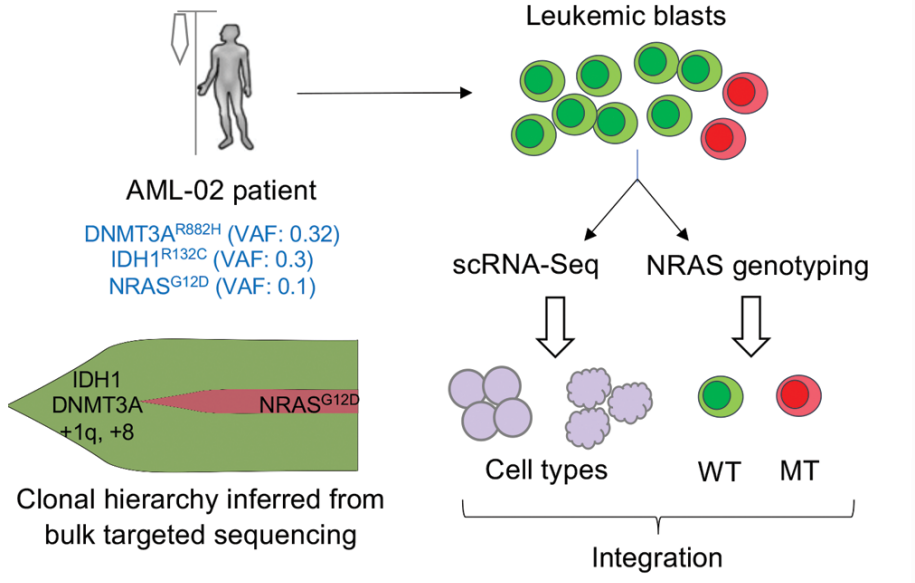
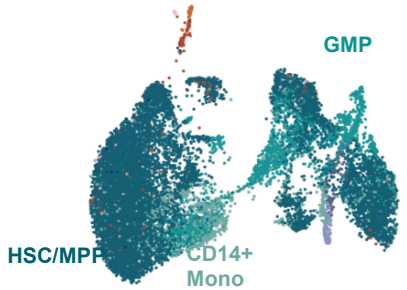
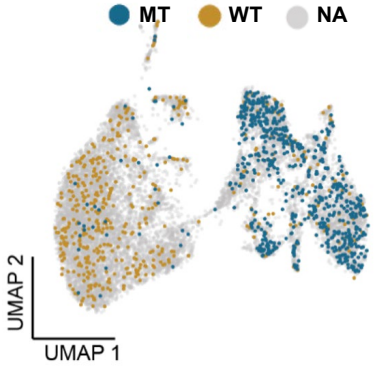


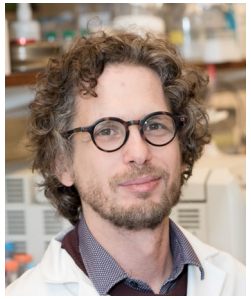


NRAS (n= 1184 cells genotyped)



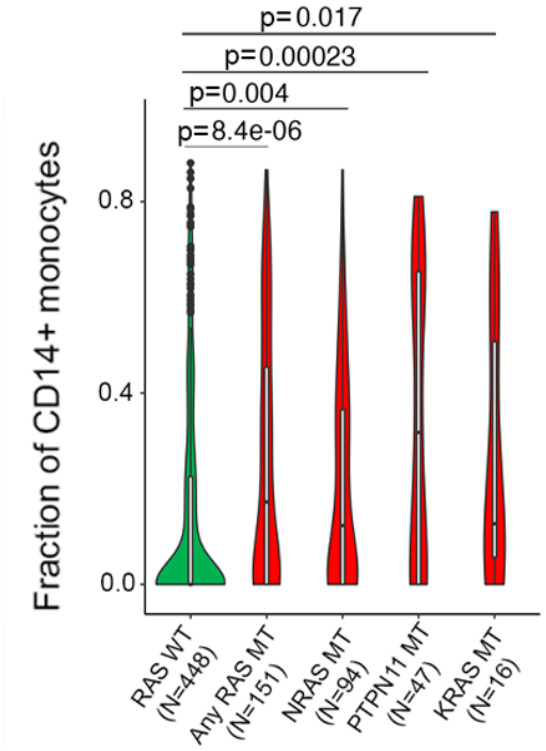
Maria Sirenko

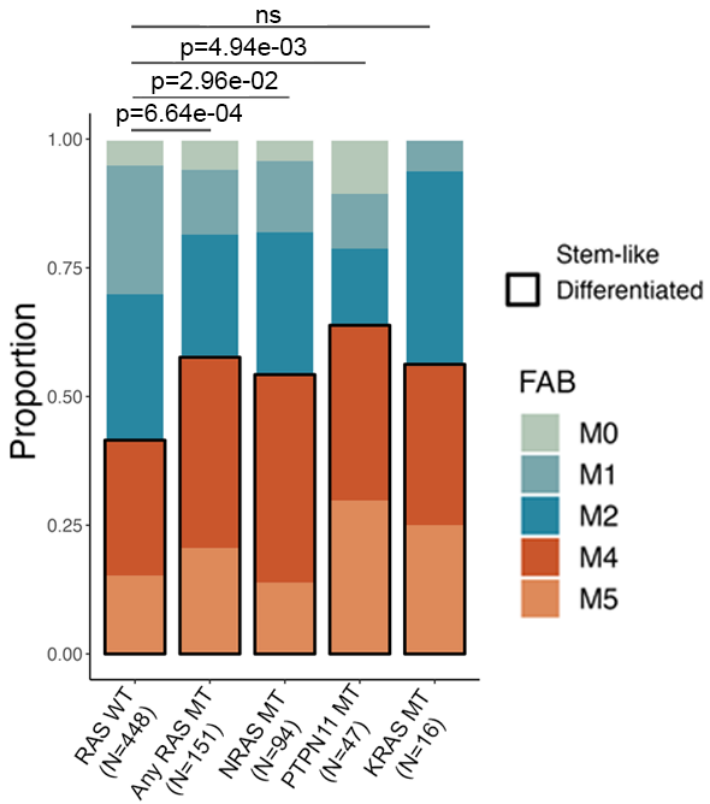
Elli Papaemmanuil



Dan Landau

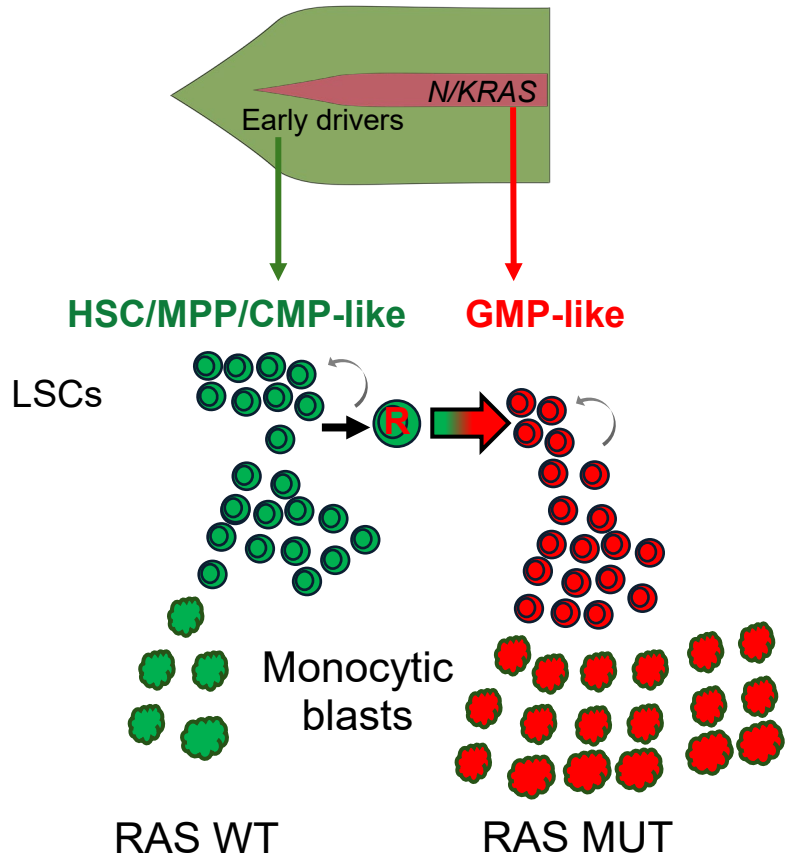
RAS-MT AML is monocytic





Maria Sirenko
Ann-Kathrin Eisfeld
Bettina Nadorp

- RAS-mutant LSCs give rise to AML blasts with monocytic differentiation, whereas ancestral LSCs generate primitive AML blasts



Venetoclax (VEN) resistance in AML

? Determinants of relapse/resistance

- VEN resistance/relapse associated with monocytic AML.
- VEN resistance/relapse associated with RAS pathway mutations.

➢RAS pathway mutations cause monocytic AML.

Venetoclax (VEN) resistance in AML

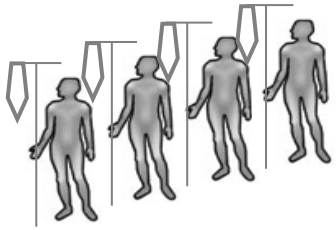
? Determinants of relapse/resistance

- VEN resistance/relapse associated with monocytic AML.
- VEN resistance/relapse associated with RAS pathway mutations.

➢RAS pathway mutations cause monocytic AML.

➢ Is it the monocytic differentiation stage or the RAS mutational status that is the cause of VEN resistance?

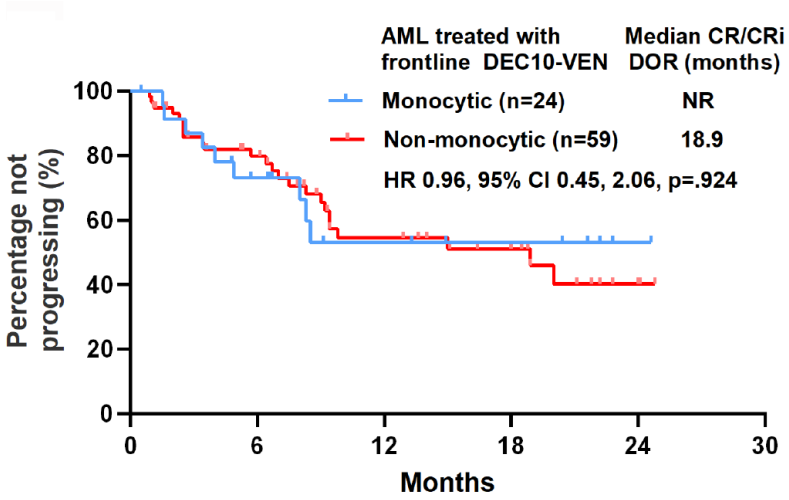
N/KRAS mutation, but not monocytic stage, is associated with poor outcomes in AML patients in a prospective clinical trial of VEN+DEC

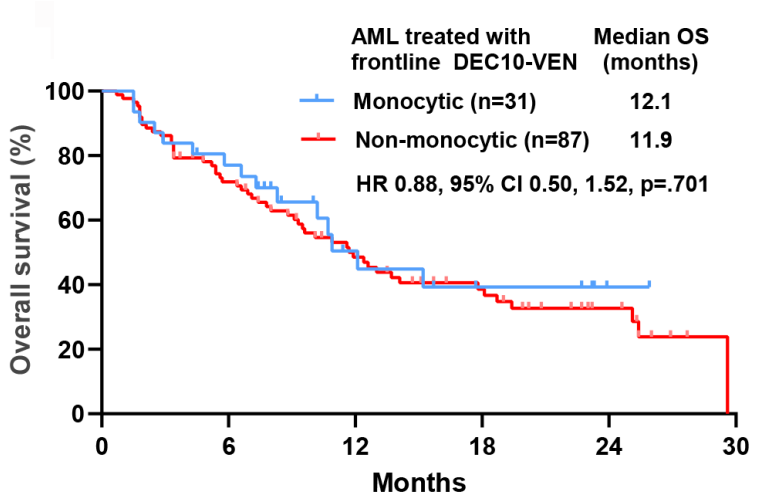


VEN + DEC

Older/unfit patients with newly diagnosed AML

NCT03404193

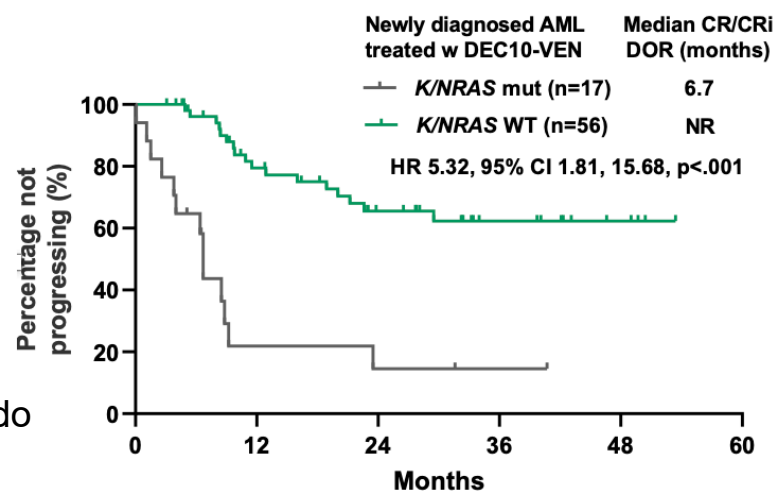


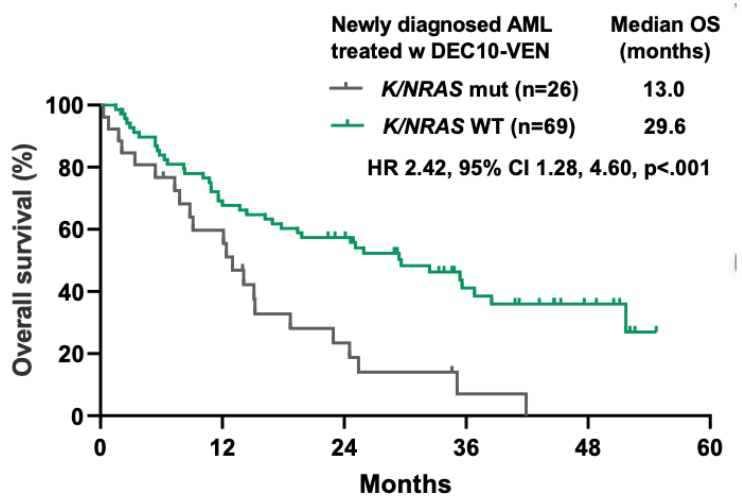


Marina Konopleva

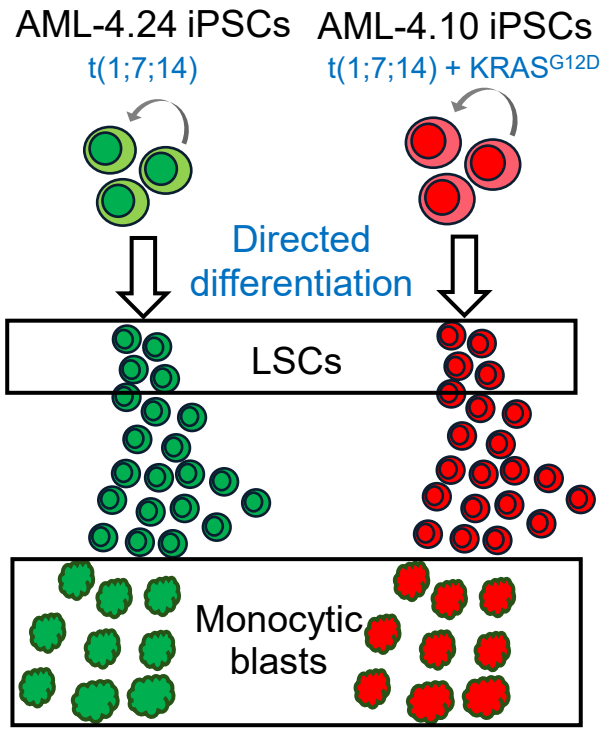
Abhi Maiti

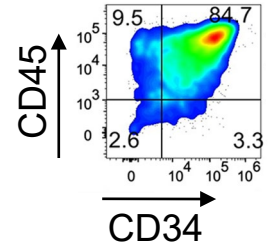
Courtney DiNardo

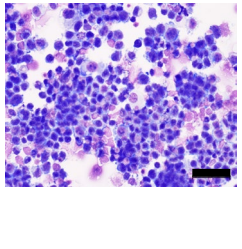




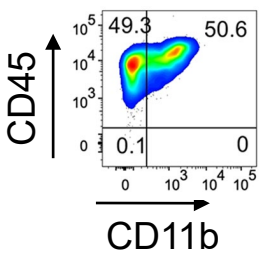
Separating the impact of differentiation state vs mutational status

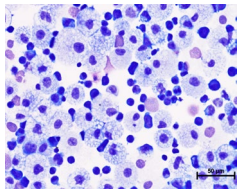






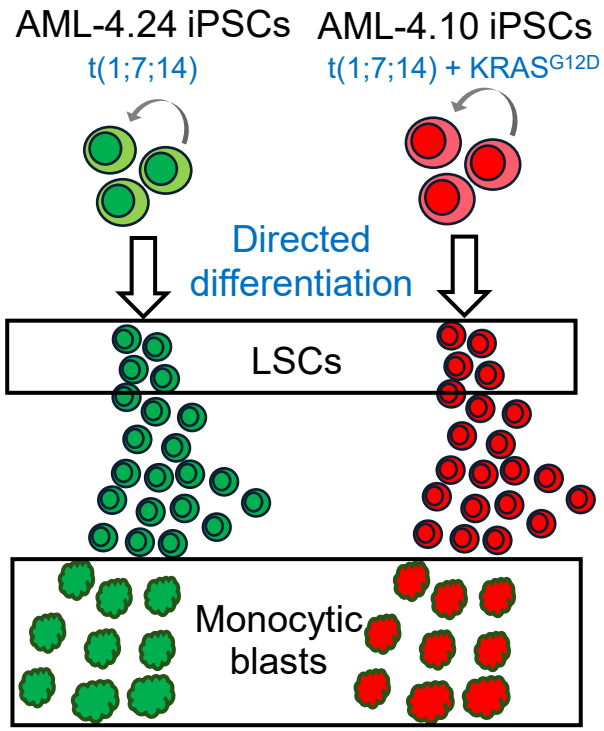
+Ven

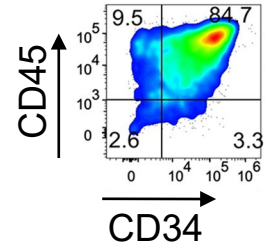


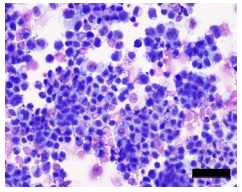


+Ven

RAS-WT LSCs are sensitive to VEN, but RAS-MT LSCs are resistant







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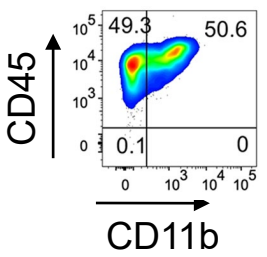

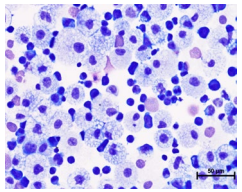

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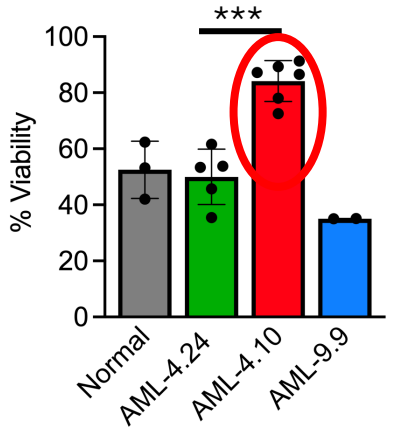
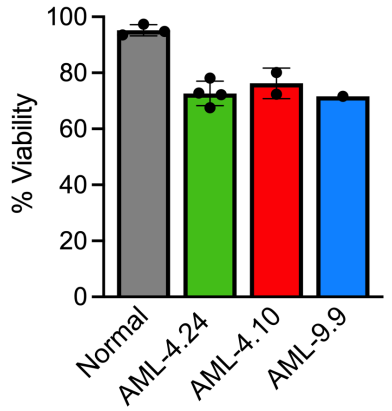
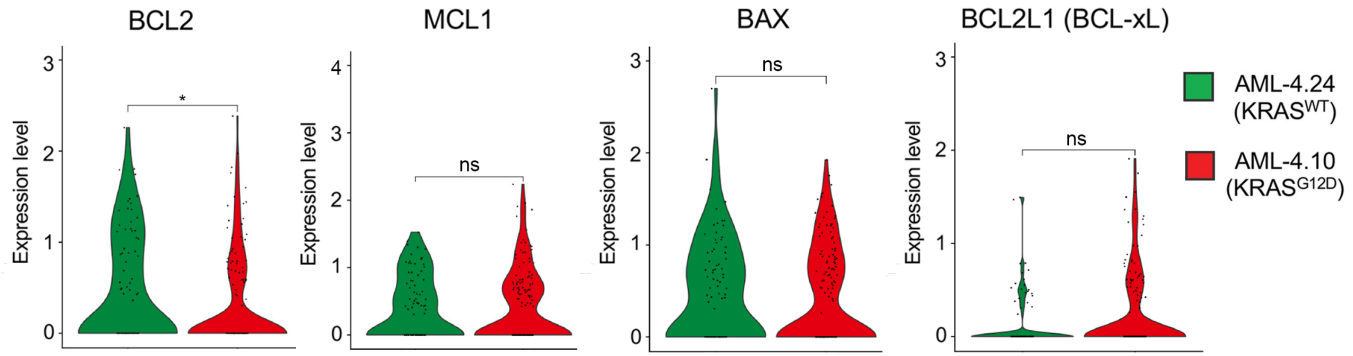


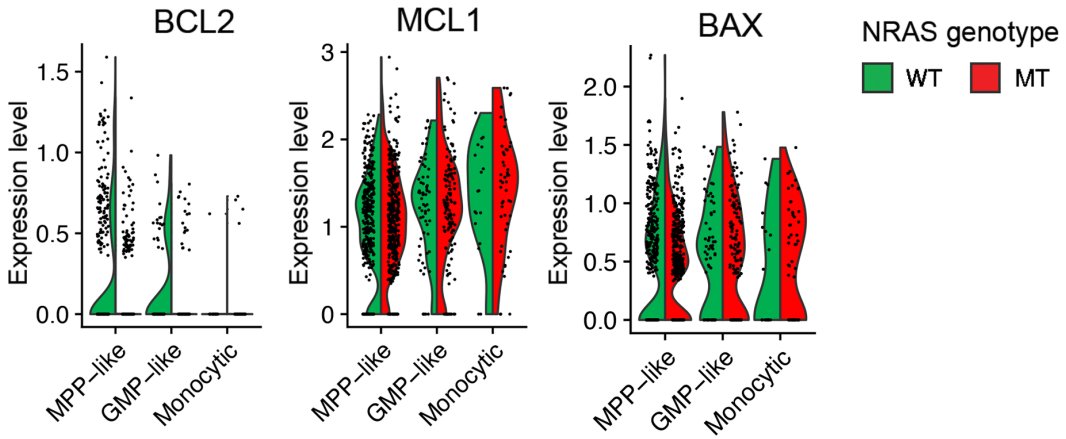


RAS mutations and not the GMP state confer VEN resistance to LSCs

Patient-derived AML-iPSC xenografts

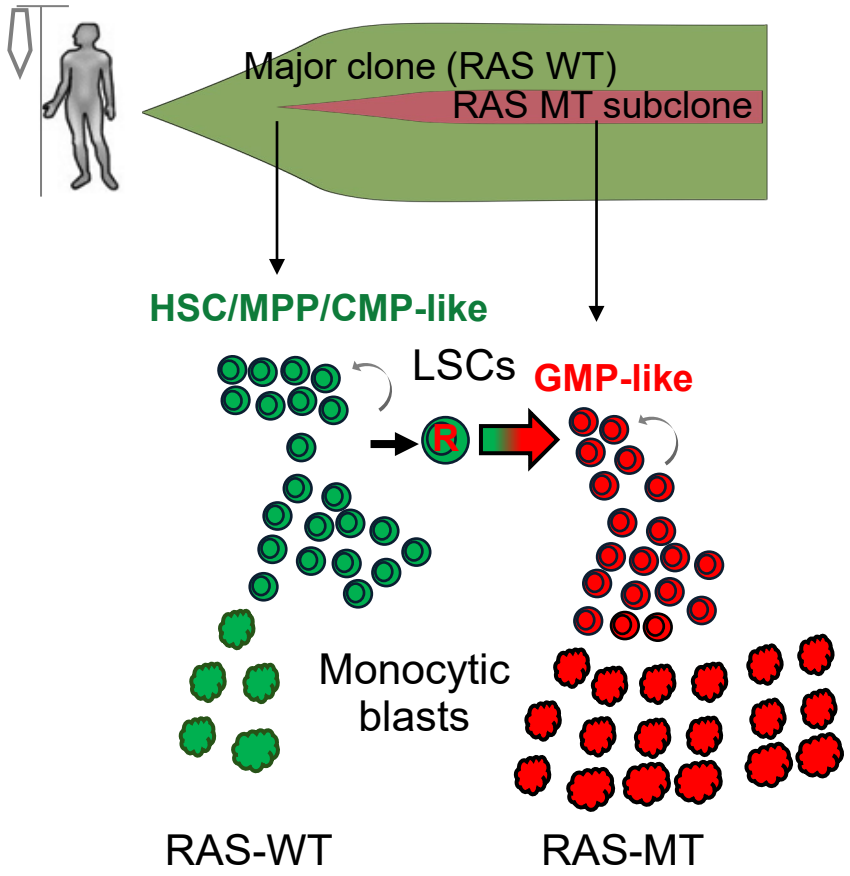


Genotyping of Transcriptomes (GoT)

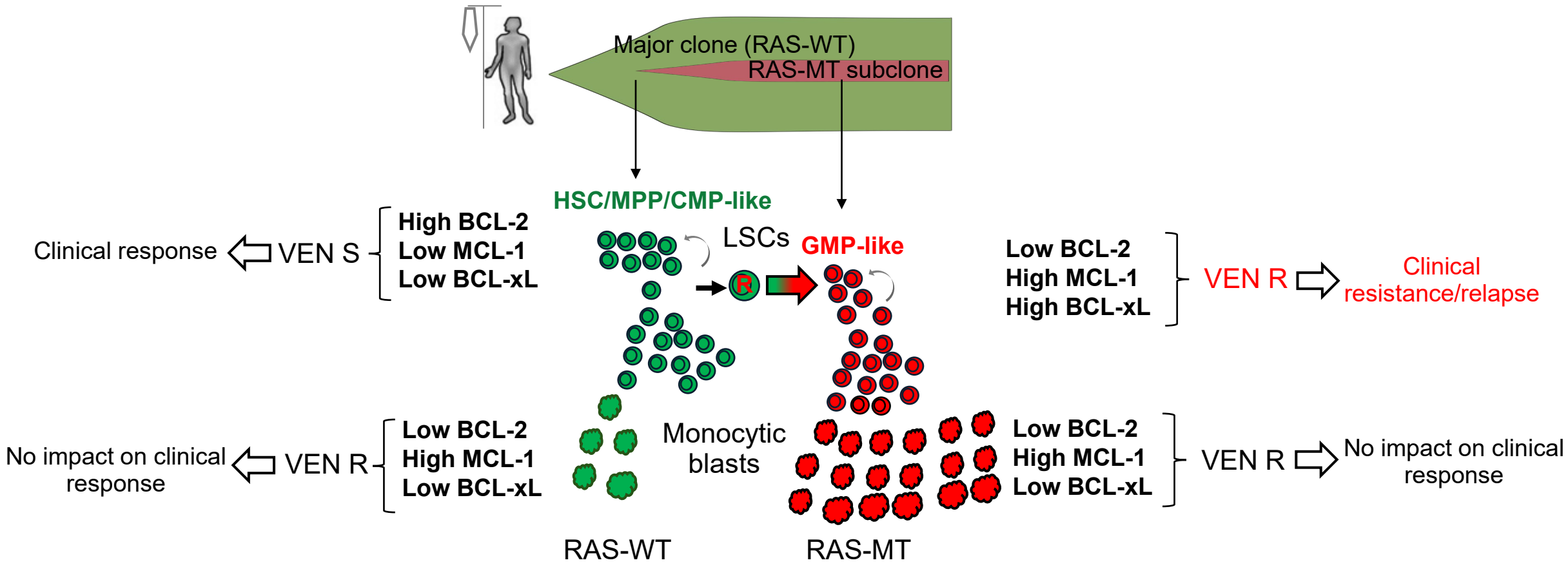


RAS-MT LSCs have ↓ BCL2 and ↑ MCL1 and ↑ BCL-xL

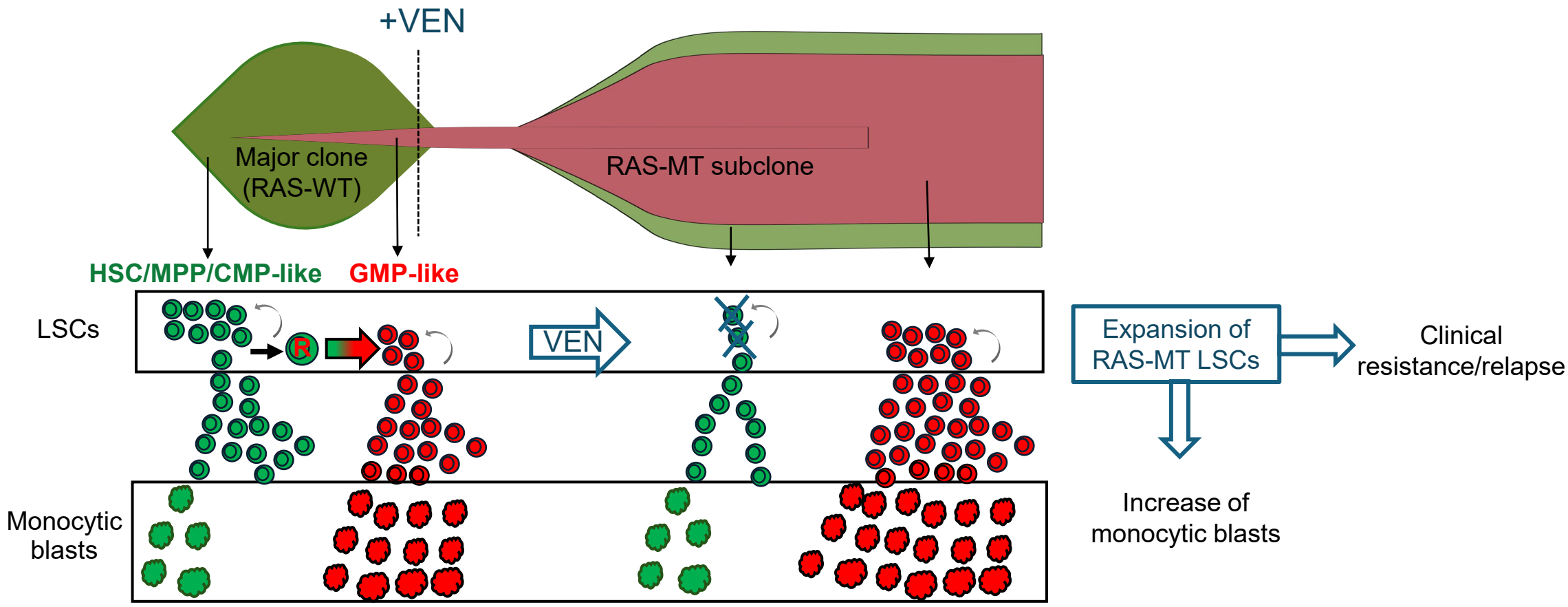
Unified model of VEN resistance



Unified model of VEN resistance



Unified model of VEN resistance



Article

RAS-mutant leukaemia stem cells drive clinical resistance to venetoclax

Junya Sango[1,2,3,4,5,22], Saul Carcamo[1,2,3,4,5,6,22], Maria Sirenko[7,8,22], Abhishek Maiti[9,22], Hager Mansour[1,2,3,4,5], Gulay Ulukaya[1,2,3,4,5,6], Lewis E. Tomalin[2,3,4,5,6], Nataly Cruz-Rodriguez[1,2,3,4,5], Tiansu Wang[1,2,3,4,5], Malgorzata Olszewska[1,2,3,4,5], Emmanuel Olivier[1,2,3,4,5], Manon Jaud[1,2,3,4,5], Bettina Nadorp[10,11], Benjamin Kroger[12,13], Feng Hu[14], Lewis Silverman[2,4,5], Stephen S. Chung[12,15], Elvin Wagenblast[1,2,3,5], Ronan Chaligne[16,17], Ann-Kathrin Eisfeld[18], Deniz Demircioglu[1,2,5,6], Dan A. Landau[16,17], Piro Lito[14], Elli Papaemmanuil[7], Courtney D. DiNardo[9], Dan Hasson[1,2,3,5,6], Marina Konopleva[19,20,21] & Eirini P. Papapetrou[1,2,3,4,5]✉

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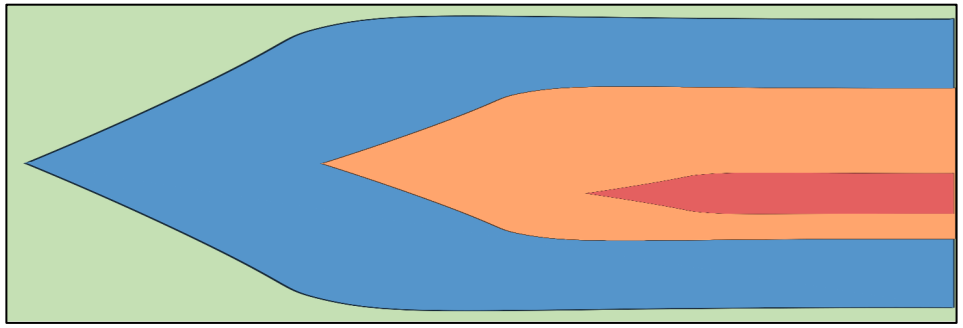
LSCs in two dimensions

Clonal evolution

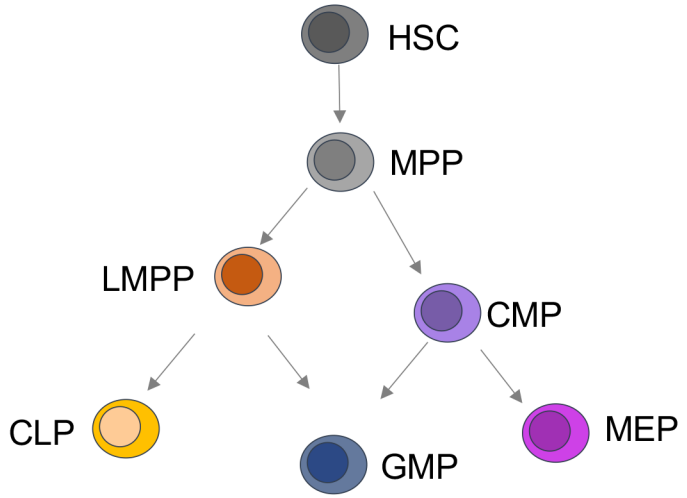
Differentiation hierarchy

Clonal heterogeneity (genetic)

Normal CH (MDS or AML) AML

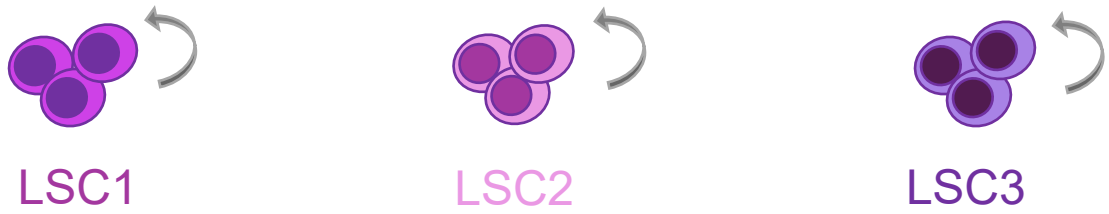


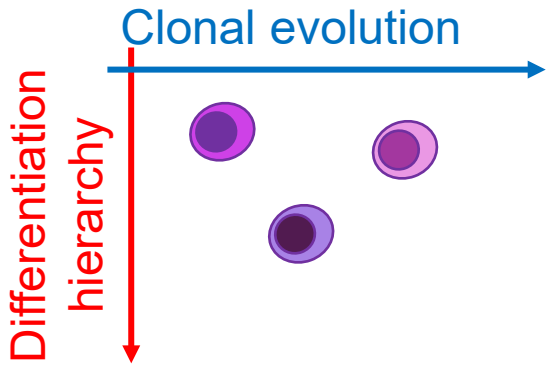
Cell state heterogeneity (non-genetic)



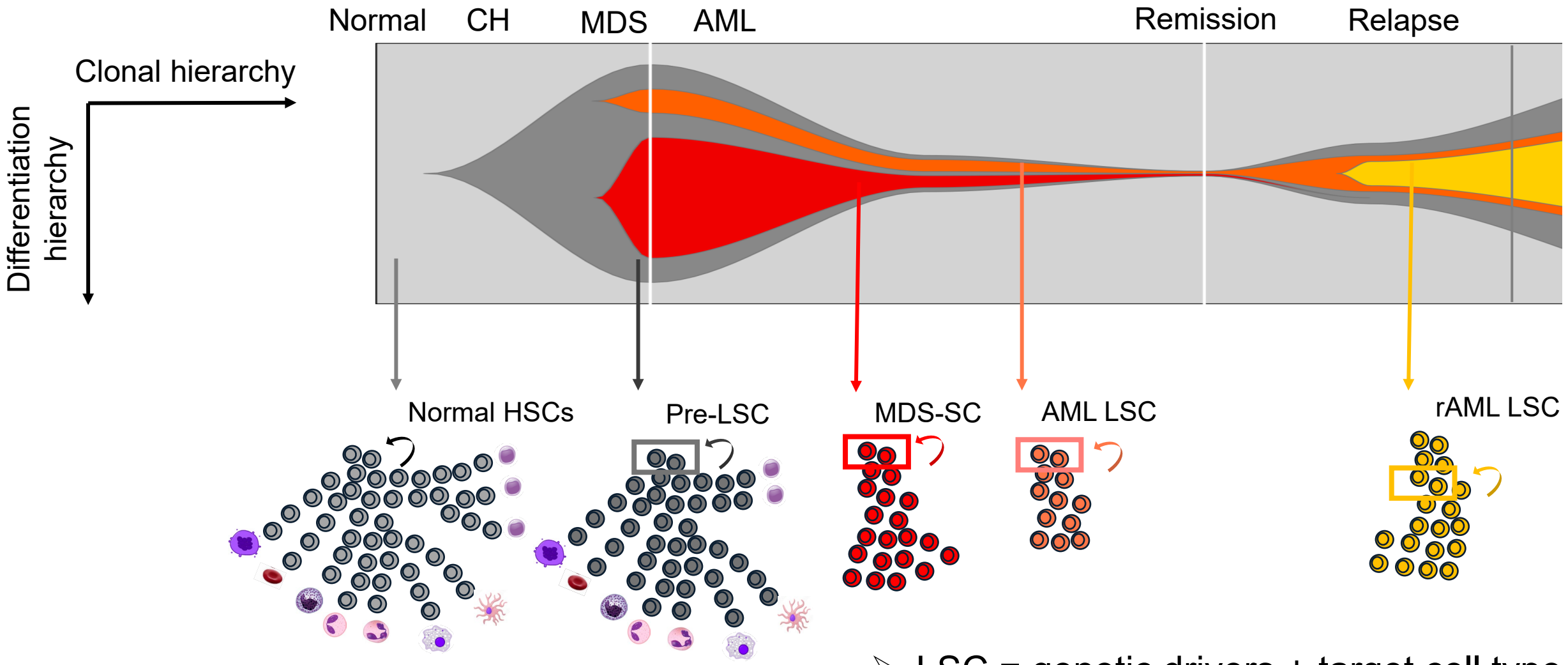
LSCs in two dimensions

LSCs in two dimensions





A revised LSC model

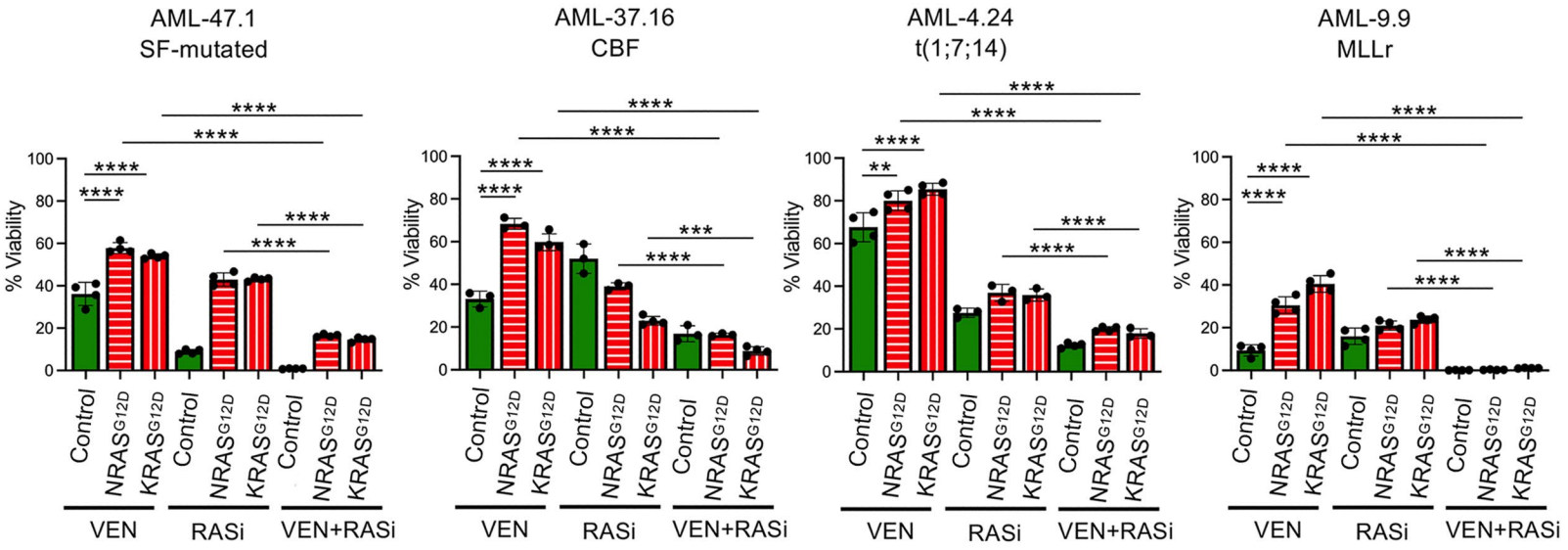


- LSC = genetic drivers + target cell type
- PreL SC ≠ MDS-SC ≠ AML LSC ≠ rAML LSC

- How can we overcome VEN resistance in RAS-MT AML?

N/KRAS mutations confer VEN resistance to AML LSCs

RMC-7977
active state-selective RAS multi-inhibitor

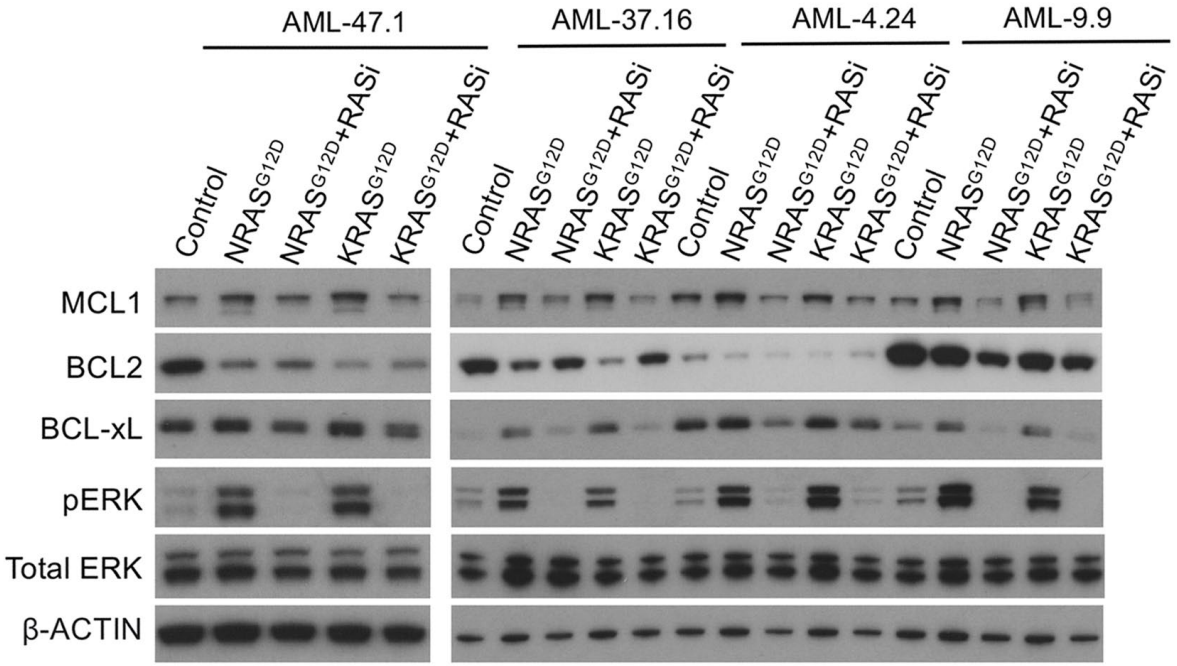


Article

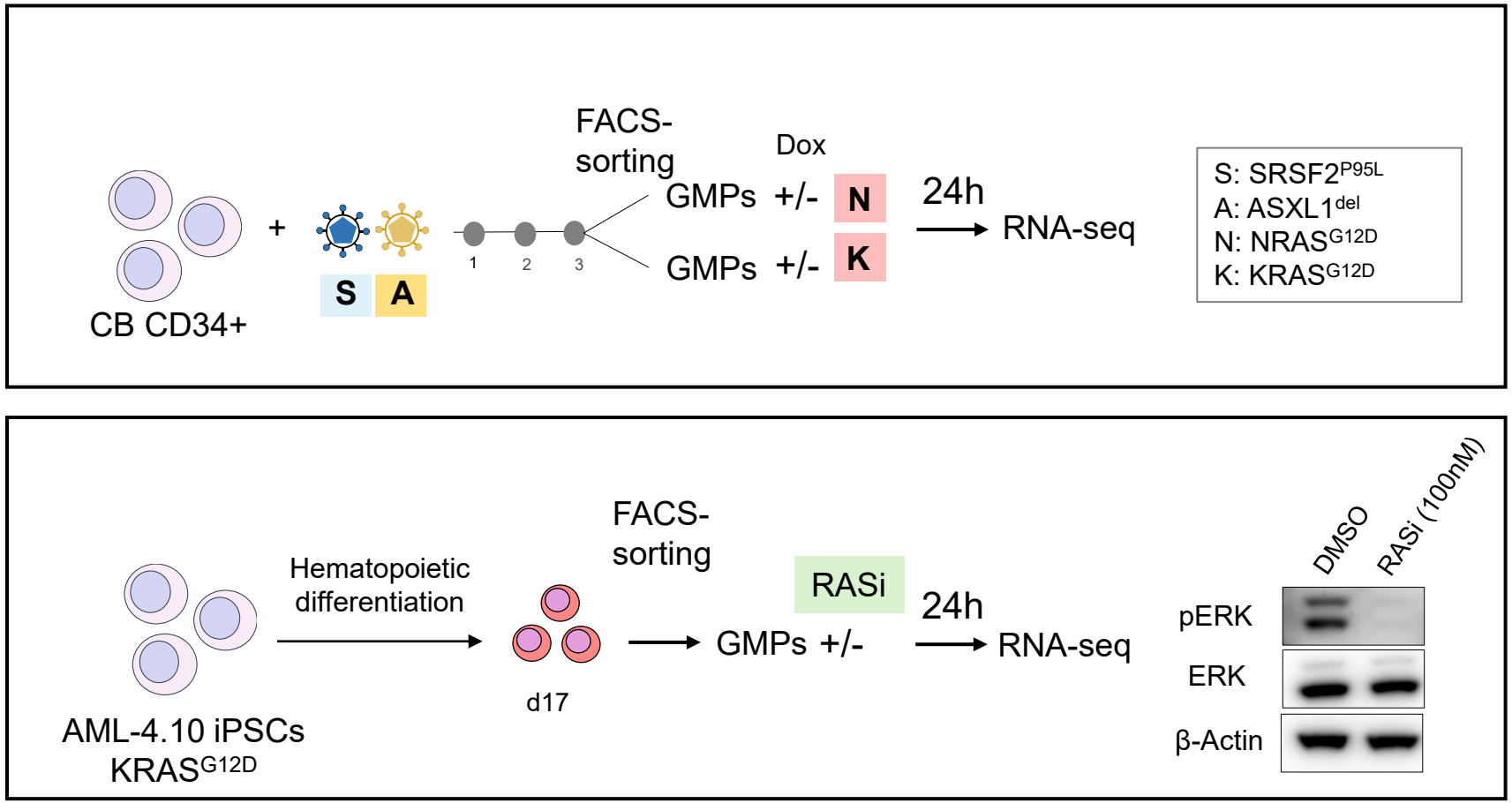
Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy

Matthew Holderfield[1], Bianca J. Lee[1], Jingjing Jiang[1], Aidan Tomlinson[1], Kyle J. Seamon[1], Alessia Mira[2], Enrico Patrucco[2], Grace Goodhart[3], Julien Dilly[4], Yevgeniy Gindin[1], Nuntana Dinglasan[1], Yingyun Wang[1], Lick Pui Lai[1], Shurui Cai[1], Lingyan Jiang[1], Nicole Nasholm[1], Nataliya Shifrin[1], Cristina Blaj[1], Harshit Shah[1], James W. Evans[1], Nilufar Montazer[1], Oliver Lai[1], Jade Shi[1], Ethan Ahler[1], Elsa Quintana[1], Stephanie Chang[1], Anthony Salvador[1], Abby Marquez[1], Jim Cregg[1], Yang Liu[1], Anthony Milin[1], Anqi Chen[1], Tamar Bar Ziv[1], Dylan Parsons[1], John E. Knox[1], Jennifer E. Klomp[5], Jennifer Roth[6], Matthew Rees[6], Melissa Ronan[6], Antonio Cuevas-Navarro[7], Feng Hu[7], Piro Lito[7,8], David Santamaria[9], Andrew J. Aguirre[4,6,10,11], Andrew M. Waters[3,5,12,13], Channing J. Der[5,12], Chiara Ambrogio[2], Zhengping Wang[1], Adrian L. Gill[1], Elena S. Koltun[1], Jacqueline A. M. Smith[1]✉, David Wildes[1]✉ & Mallika Singh[1]✉

Nature | Vol 629 | 23 May 2024 |



A GMP LSC-specific RAS activation gene signature



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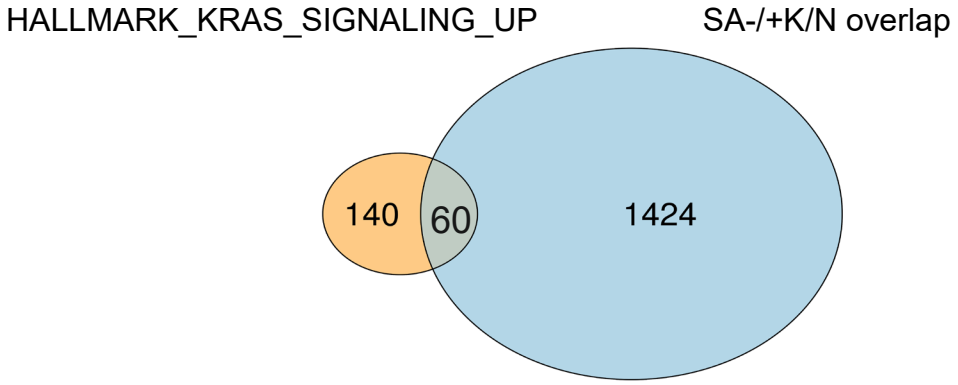

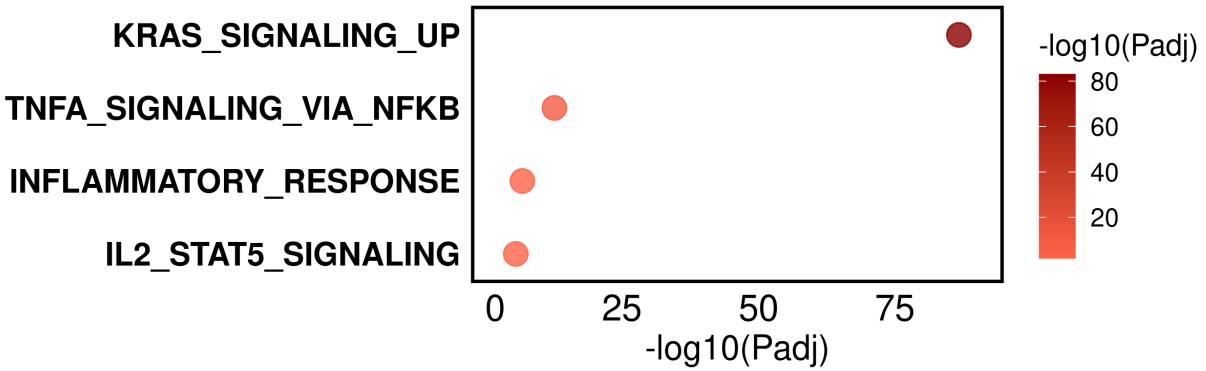

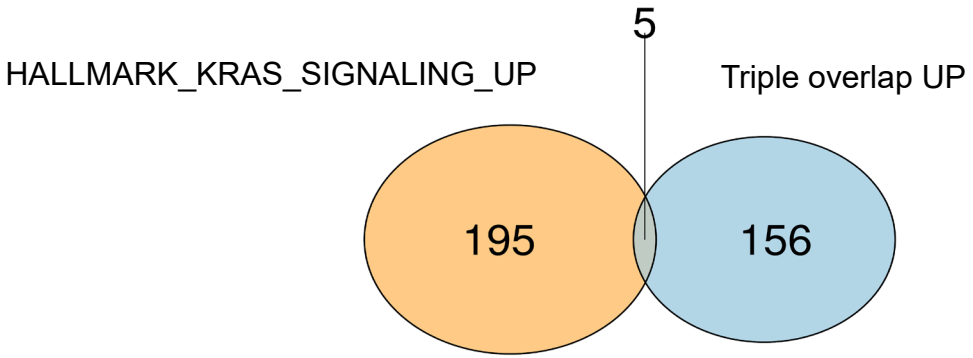

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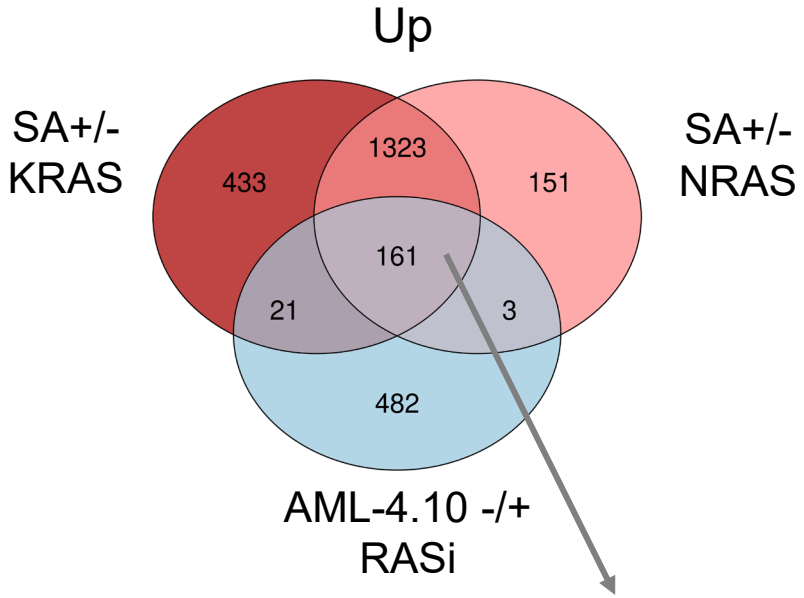

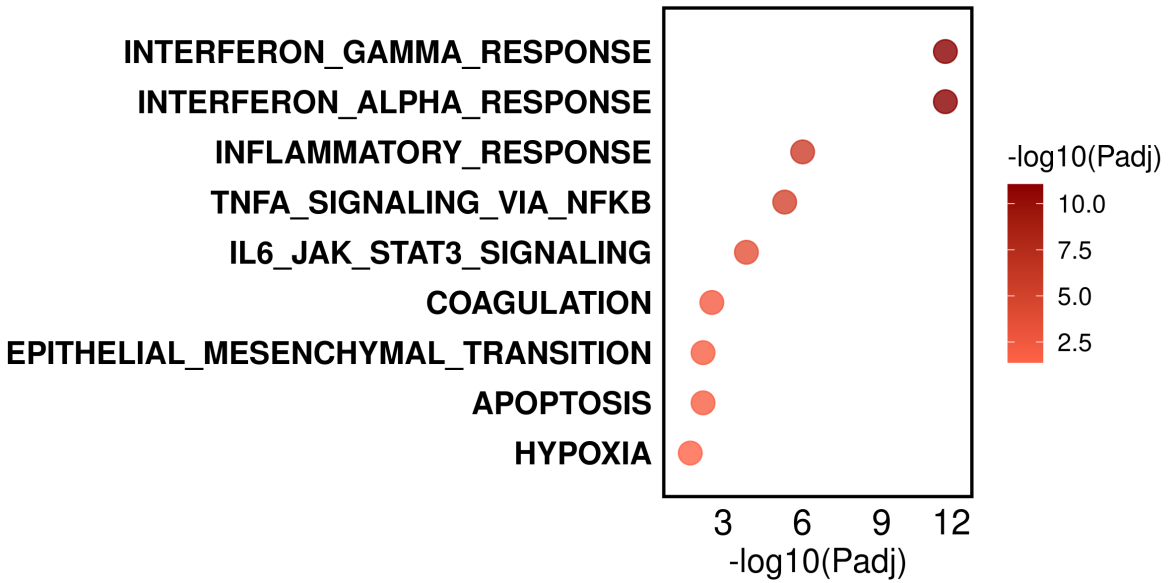

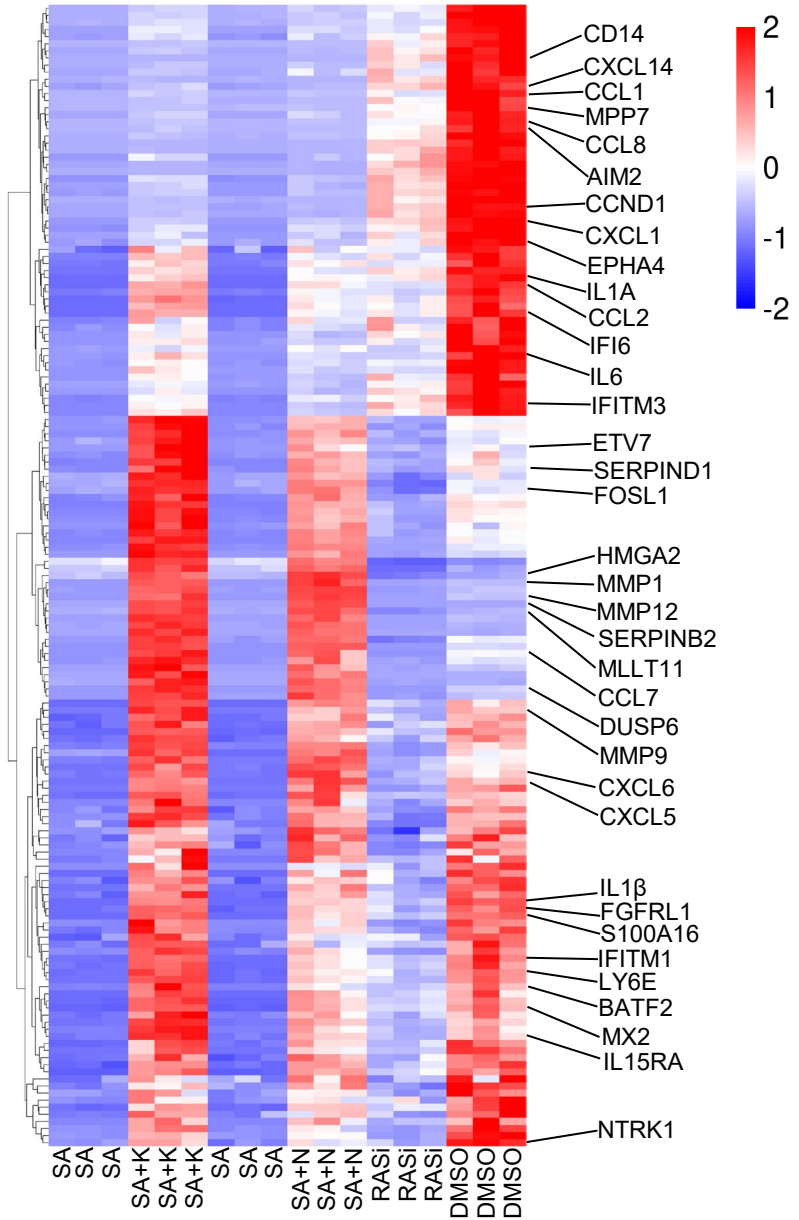

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National Cancer Institute

Leukemia & Lymphoma Society® fighting blood cancers

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AACR American Association for Cancer Research® FINDING CURES TOGETHER®

BiNGS Bioinformatics for Next Generation Sequencing

Gabrielle's Angel Foundation for Cancer Research

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