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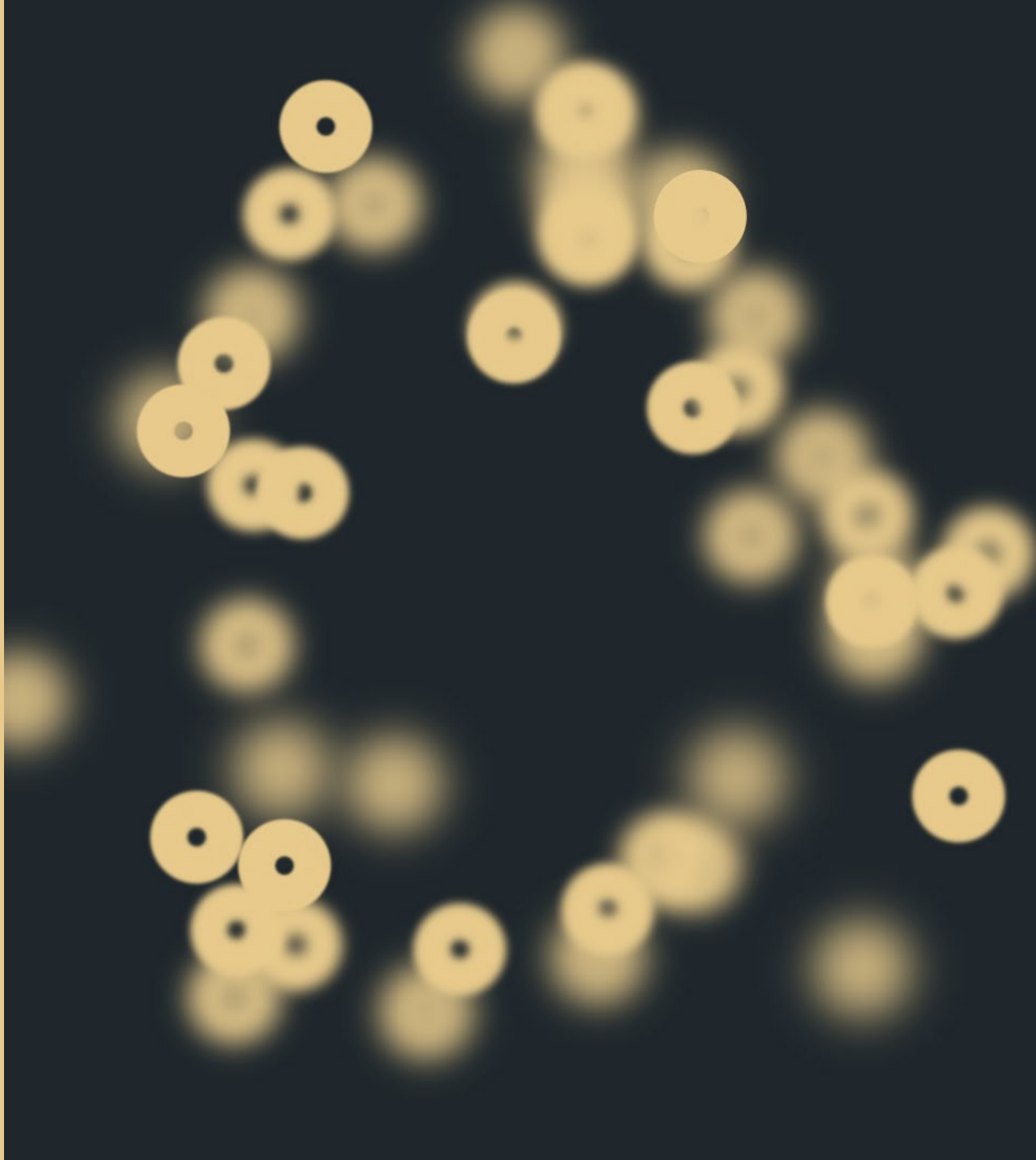
EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
April 25-26, 2025



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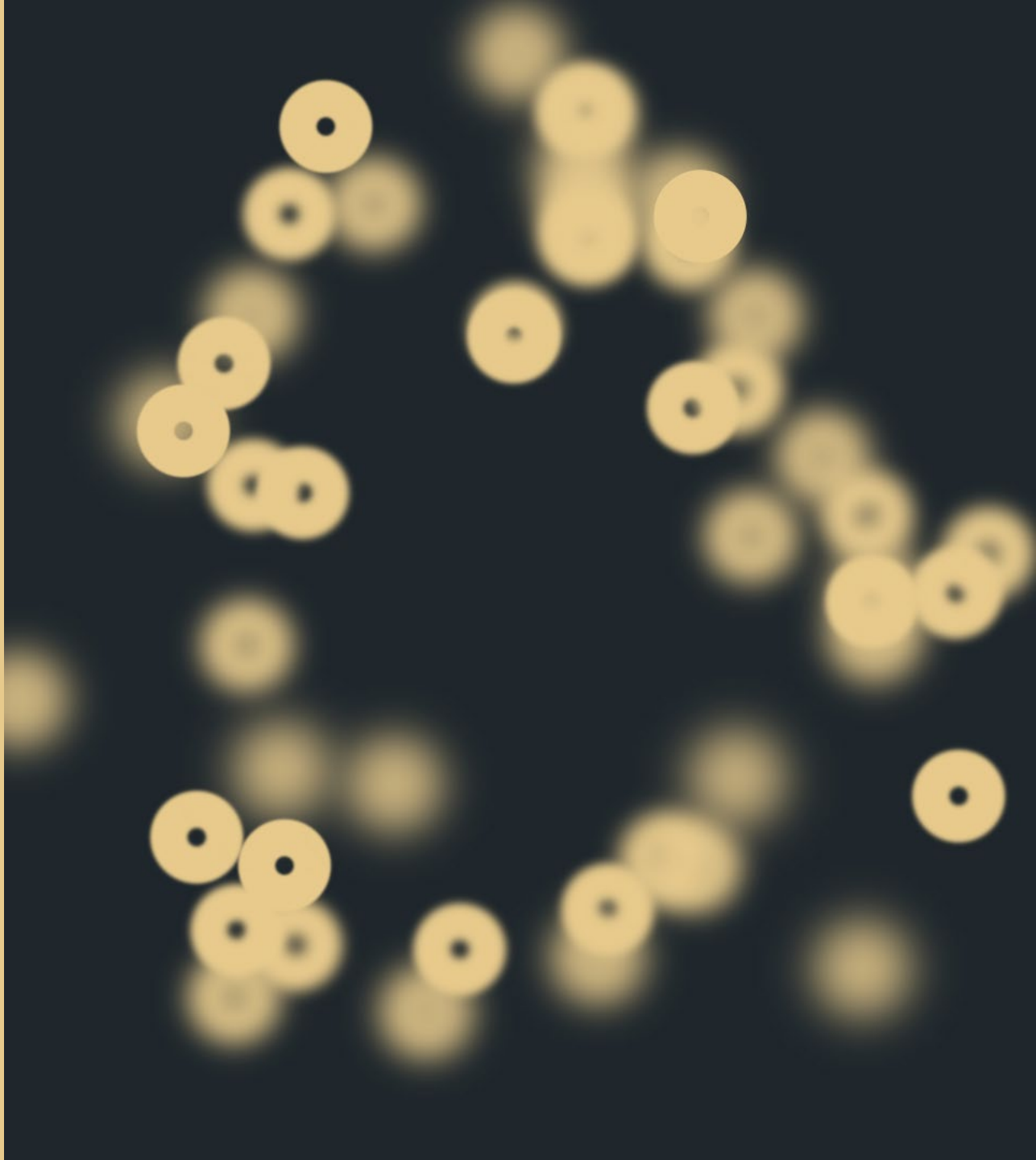
Phylogenetics of MDS-to-AML Progression at Single-Cell Resolution: A Genetic and Epigenetic Approach to Unravel Clones Resistant to Hypomethylating Agents



April 26, 2025

Ignacio Campillo Marcos, PhD

Contents

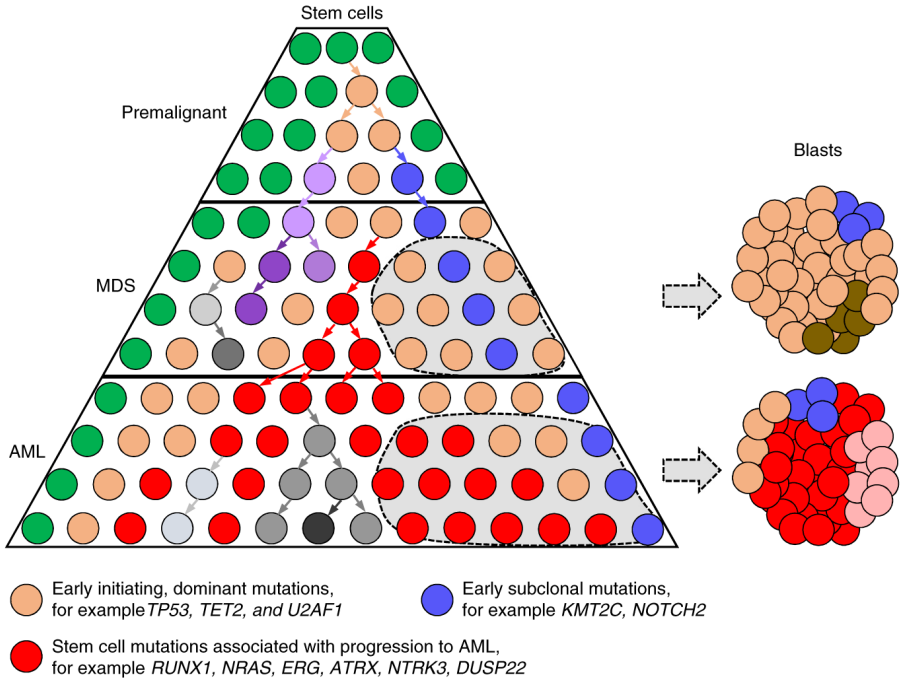
Introduction

Myelodysplastic syndromes/neoplasms (MDS) are characterized by:

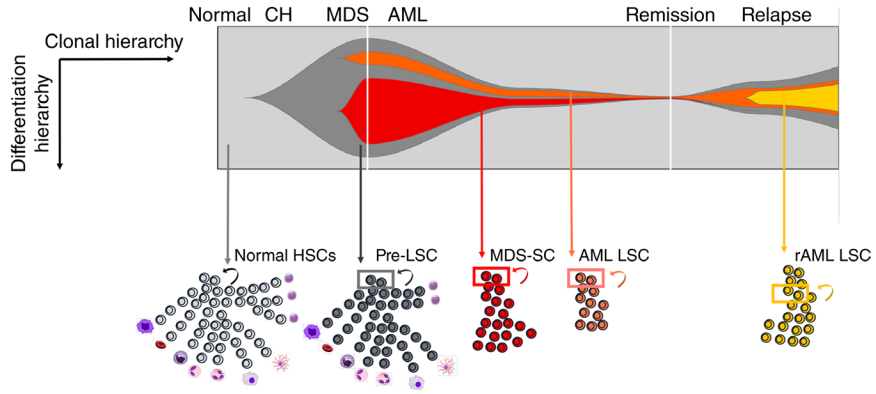
- The **accumulation** of **somatic mutations**
- **Chromosomal abnormalities**
- The **disruption of epigenetic marks**

Hypomethylating agents (HMAs) such as **azacitidine (AZA) or decitabine** remain the **standard of care** for patients with **high risk MDS**.

However, **nearly 50% of these patients fail to respond to HMAs**, substantially **increasing** the **risk** of progression to **acute myeloid leukemia** (AML).

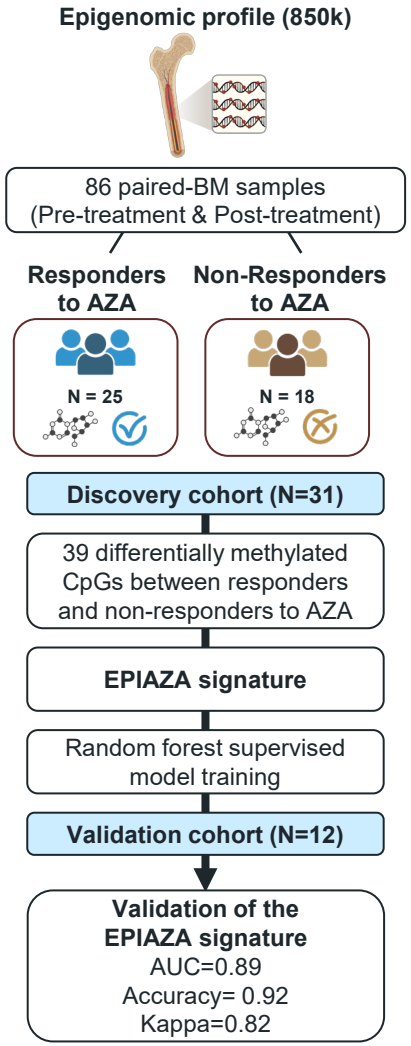


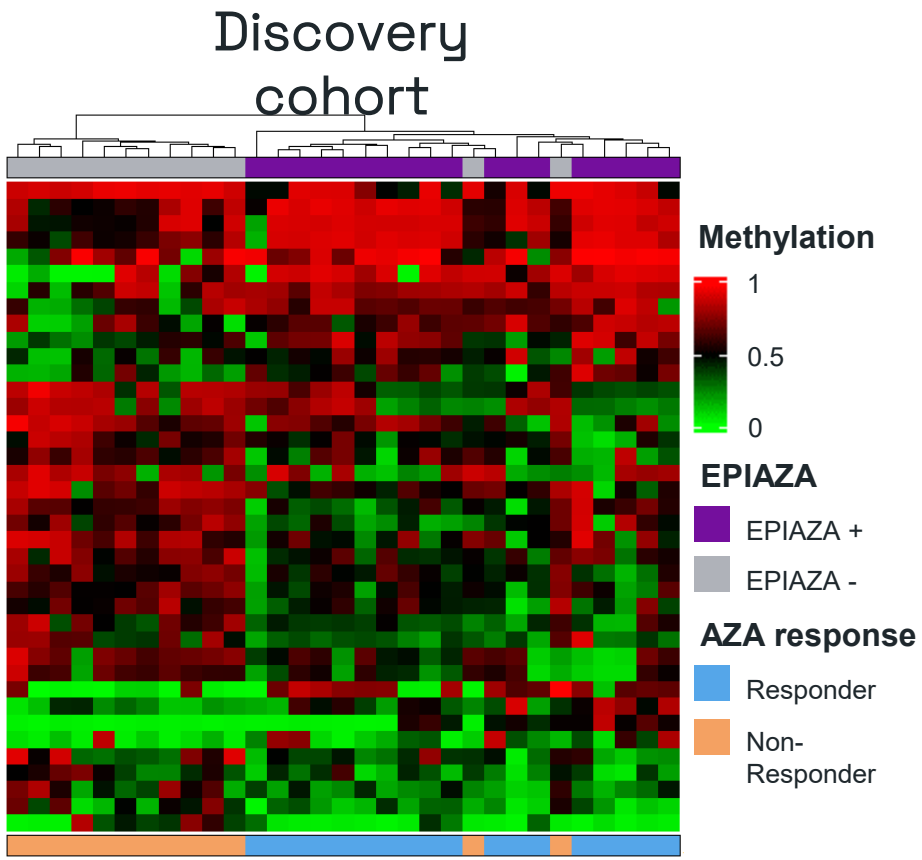
Chen et al. *Nature Genetics* (2019)

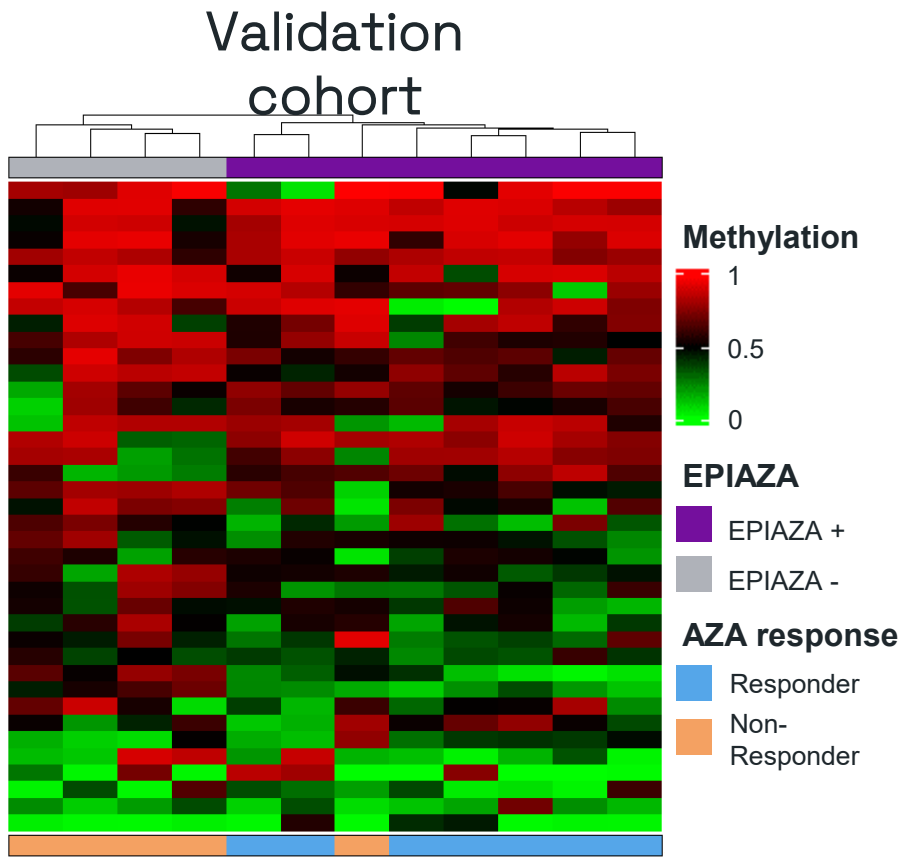


Sturgeon et al. *Blood Cancer Discovery* (2019)

Epigenetic profiling in MDS



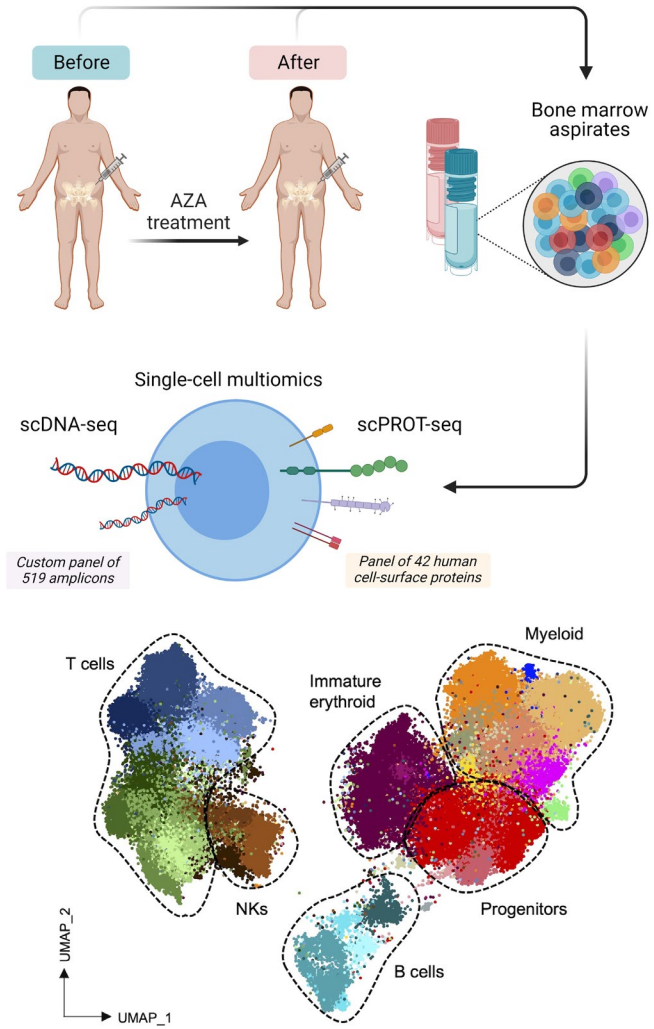


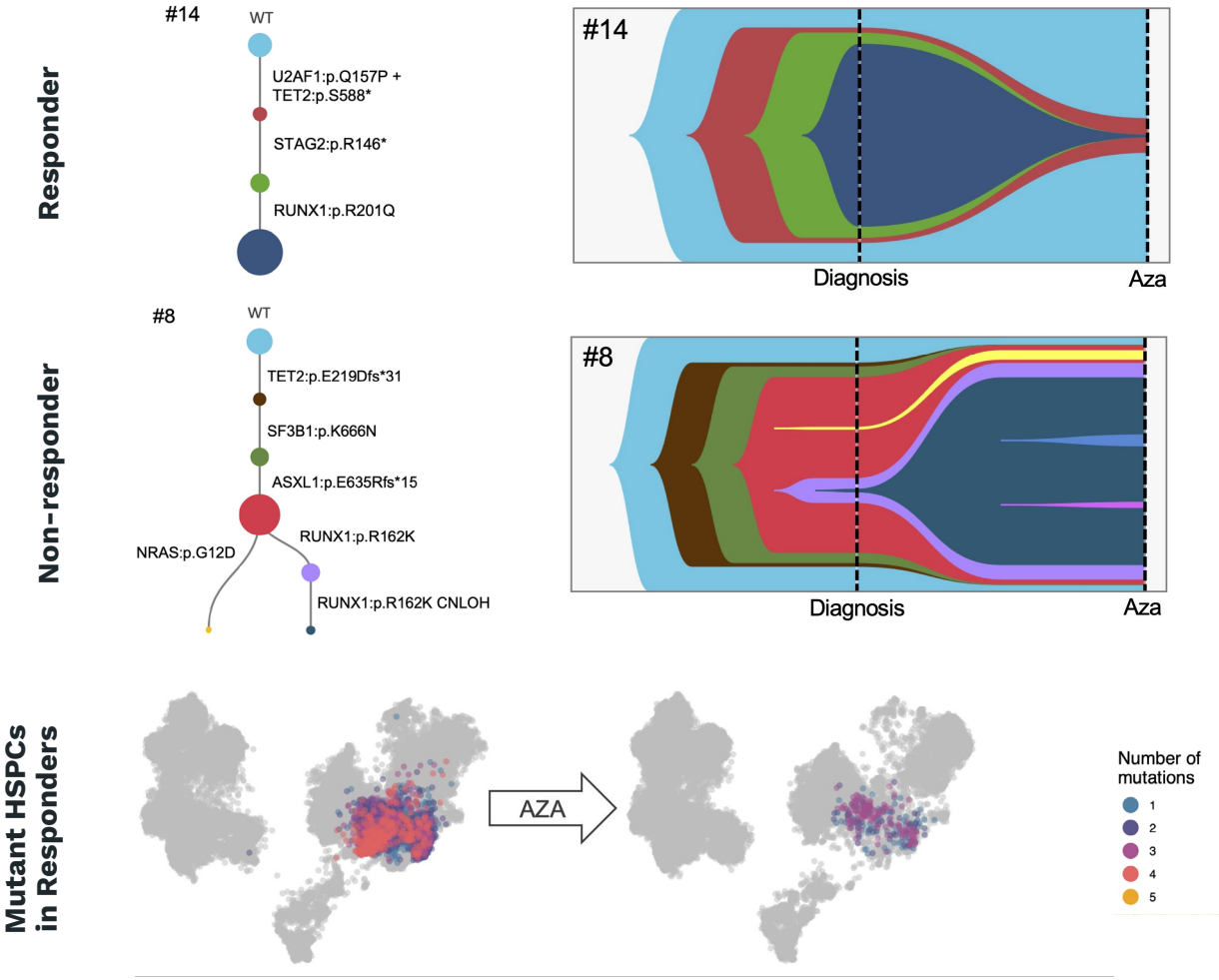


Noguera-Castells et al. *British Journal of Haematology* (2024)

Phylogenetics of MDS-to-AML Progression at Single-Cell Resolution: A Genetic and Epigenetic Approach to Unravel Clones Resistant to Hypomethylating Agents > Preliminary data

Single-cell proteogenomics in MDS





Campillo-Marcos et al. *Cancer Research Communications* (2024)

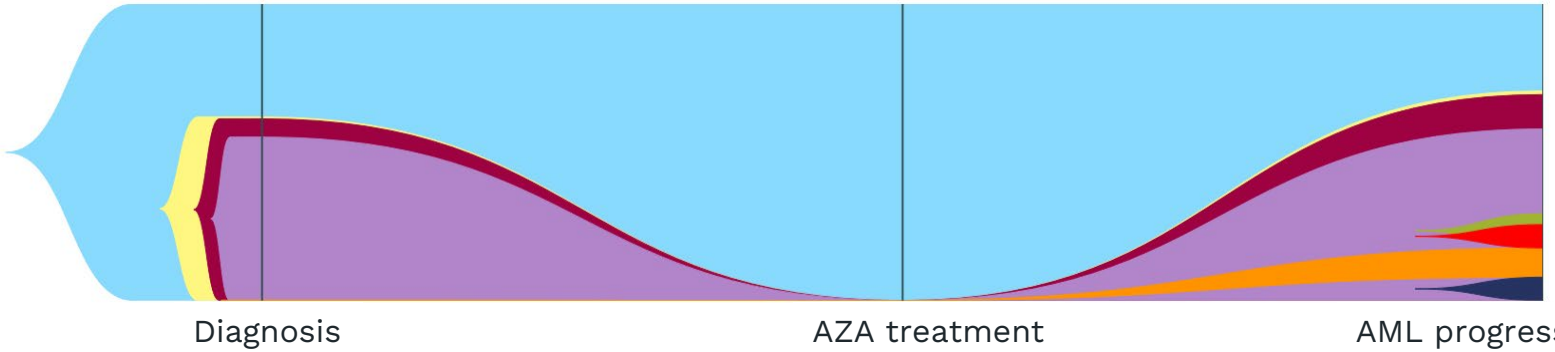
Hypothesis and objectives

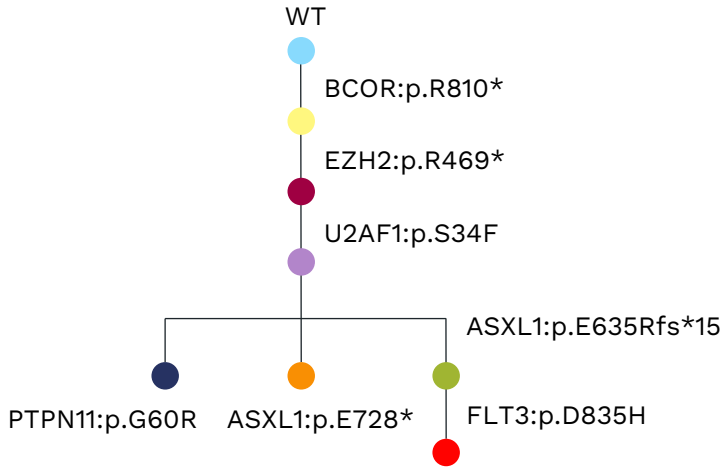
To date, there are **no reliable prognostic markers to predict the efficacy of AZA or the risk of transformation to AML**, largely due to the poorly understood clonal heterogeneity driving disease progression.

To investigate the **genetic, transcriptomic and epigenetic dynamics underlying MDS-to-AML transformation** using **single-cell multi-omics approaches.**

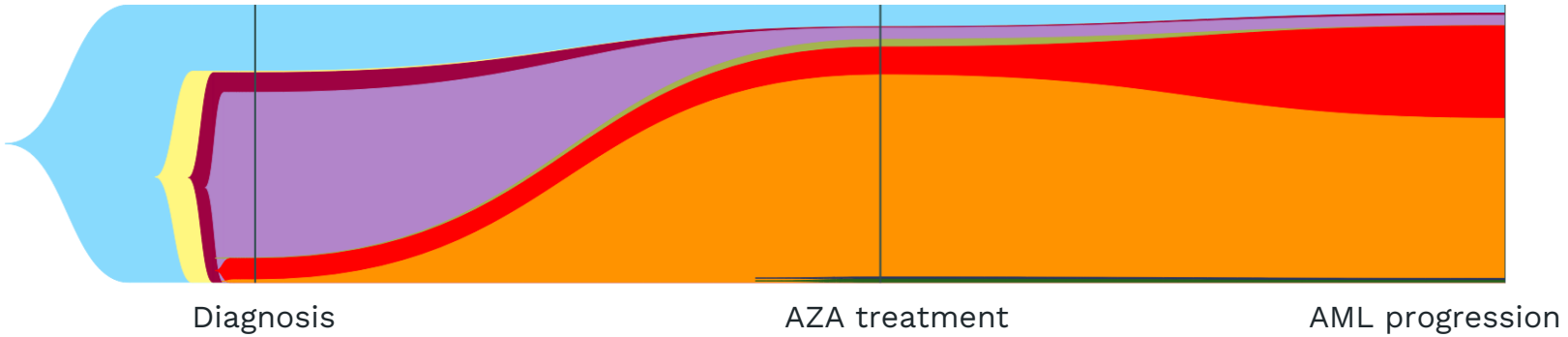
Clonal evolution from MDS to AML

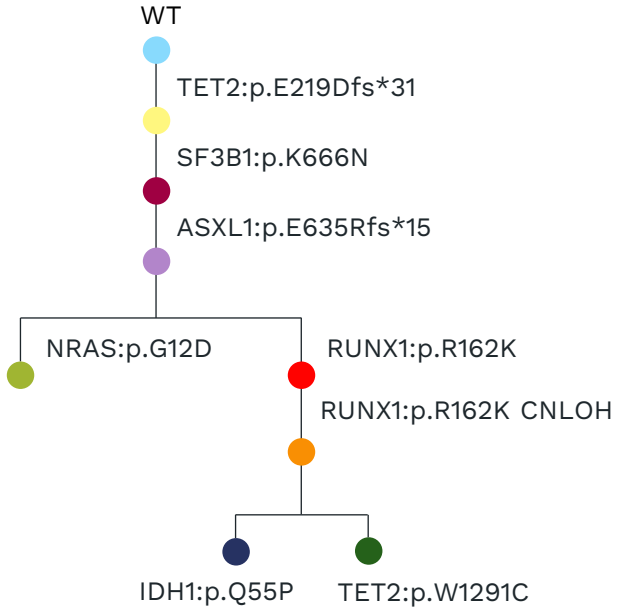
Responder



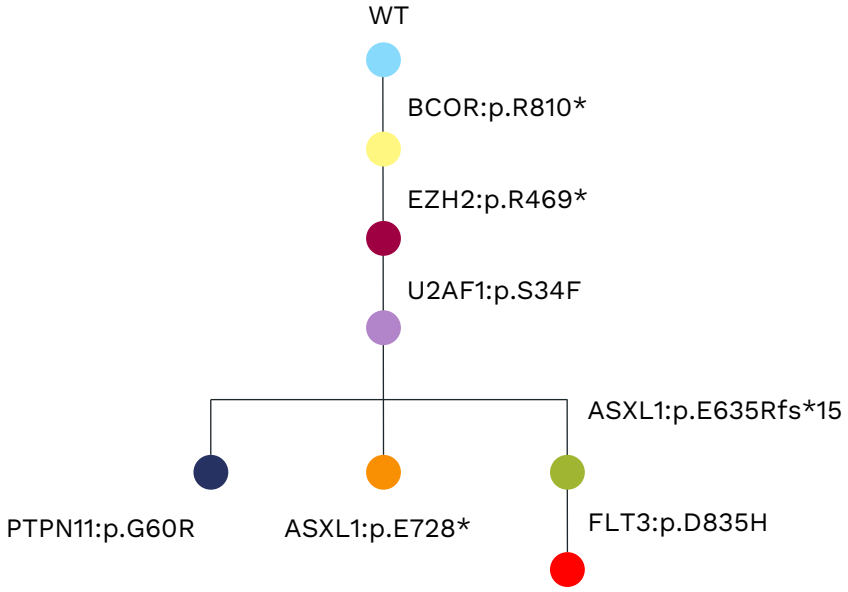


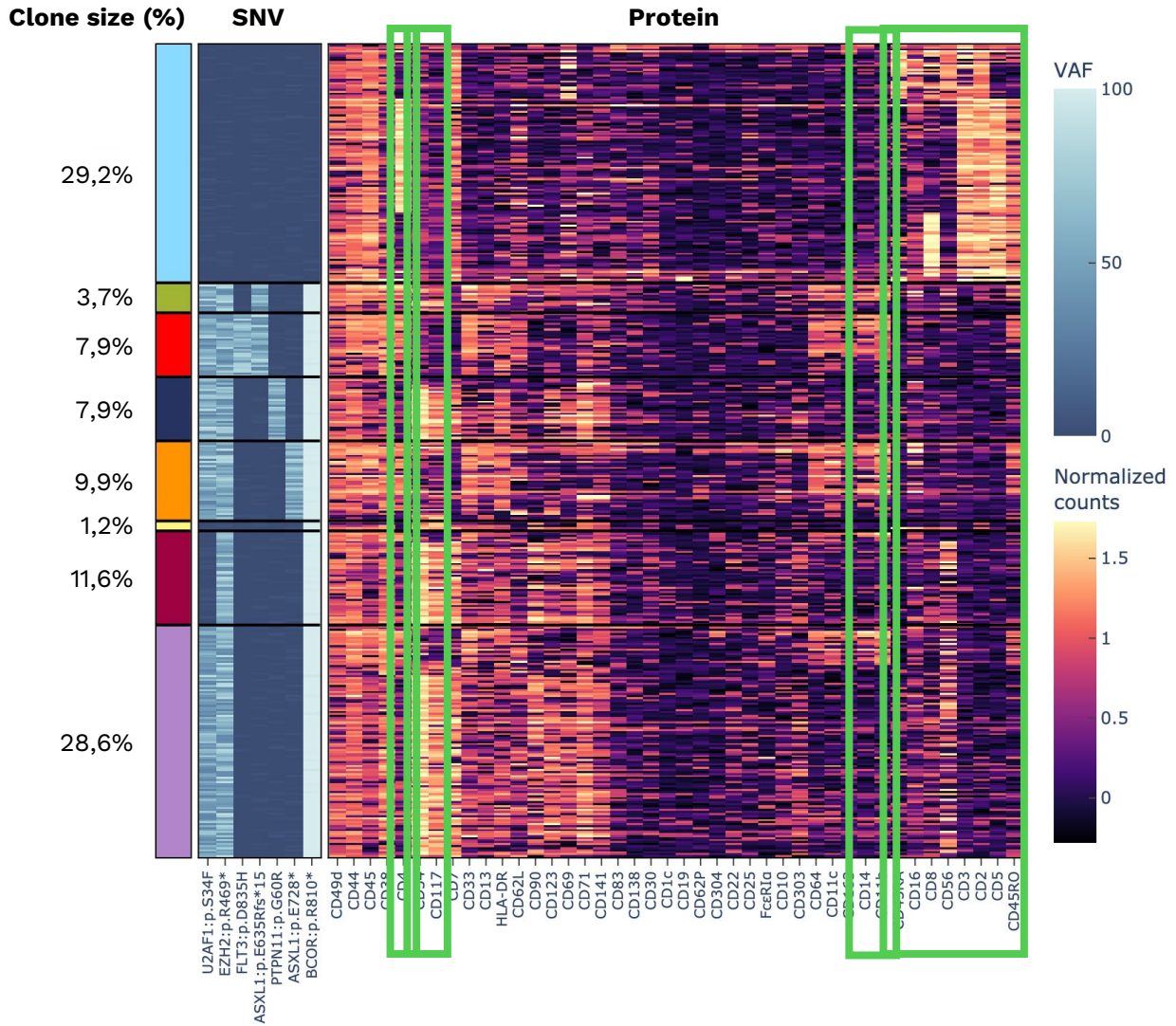
Non-responder





Clones & immunophenotypes in MDS/AML





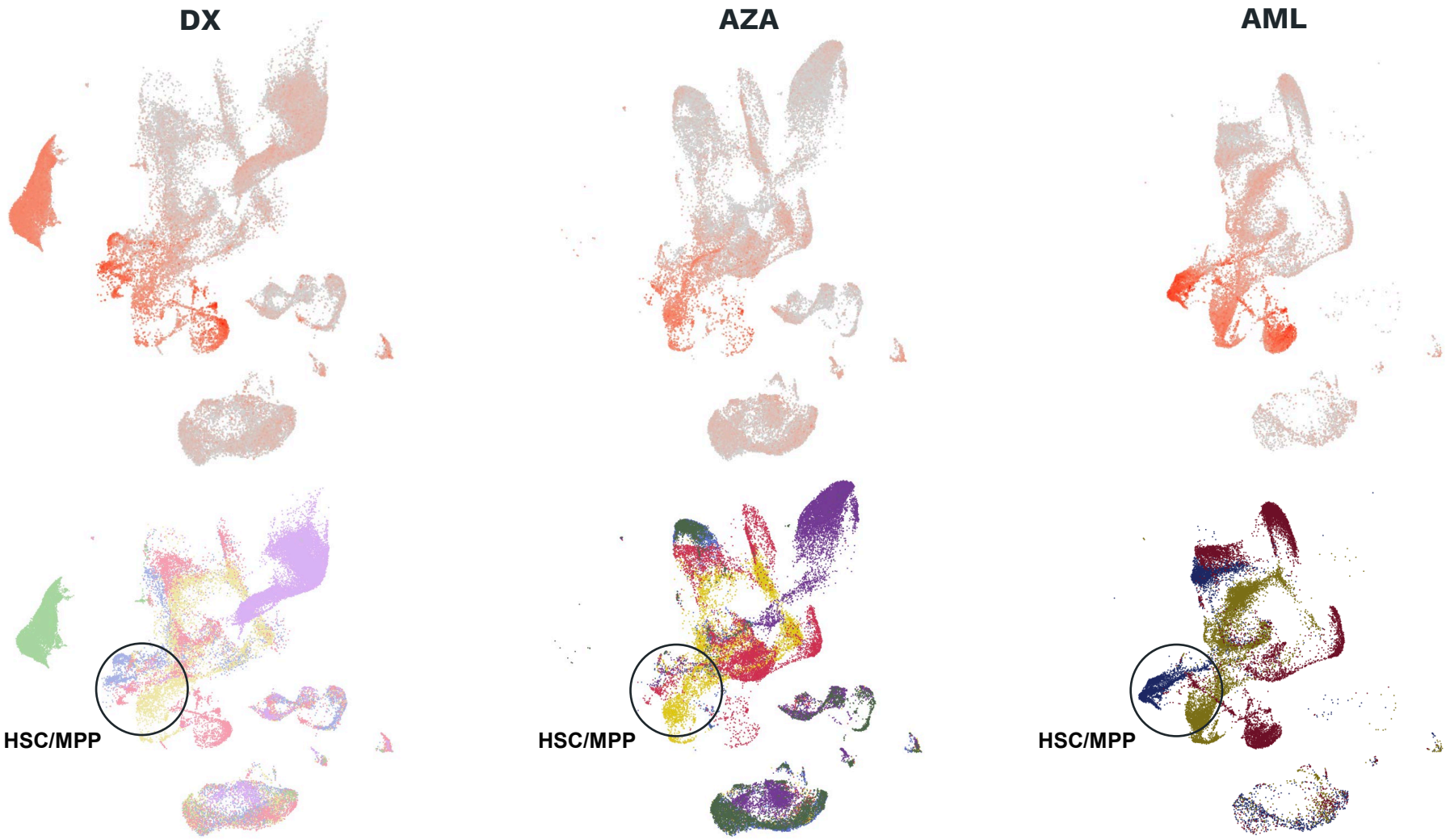
Phylogenetics of MDS-to-AML Progression at Single-Cell Resolution: A Genetic and Epigenetic Approach to Unravel Clones Resistant to Hypomethylating Agents > Results

BM populations defined by scRNA-seq

***CellTypist* annotation**

- HSC or MPP
- CMP
- GMP
- Megakaryocyte precursor
- Early MK
- Early erythroid
- Mid erythroid
- Late erythroid
- Promyelocytes
- Neutrophil–myeloid progenitor
- Classical monocytes
- Non–classical monocytes
- Erythrophagocytic macrophages
- DC precursor
- DC2
- pDC
- Mast cells
- MAIT cells
- CRTAM+ gamma–delta T cells
- CD16+ NK cells
- CD16– NK cells
- ETP
- Regulatory T cells
- Tcm or Naive helper T cells
- Tem or Effector helper T cells
- Tcm or Naive cytotoxic T cells
- Tem or Temra cytotoxic T cells
- Tem or Trm cytotoxic T cells
- Double–negative thymocytes
- ILC3
- Pro–B cells
- Naive B cells
- Memory B cells
- Plasma cells
- Fibroblasts

AML-risk signature: from MDS to AML



RNA signature

Shiozawa et al. *Blood* (2017)

0.6
0.4
0.2
0.0

Patient sample

- P1_DX
- P1_AZA
- P1_AML
- P2_DX
- P2_AZA
- P2_AML
- P3_DX
- P3_AZA
- P3_AML
- P4_DX
- P4_AZA
- P5_DX
- P5_AZA

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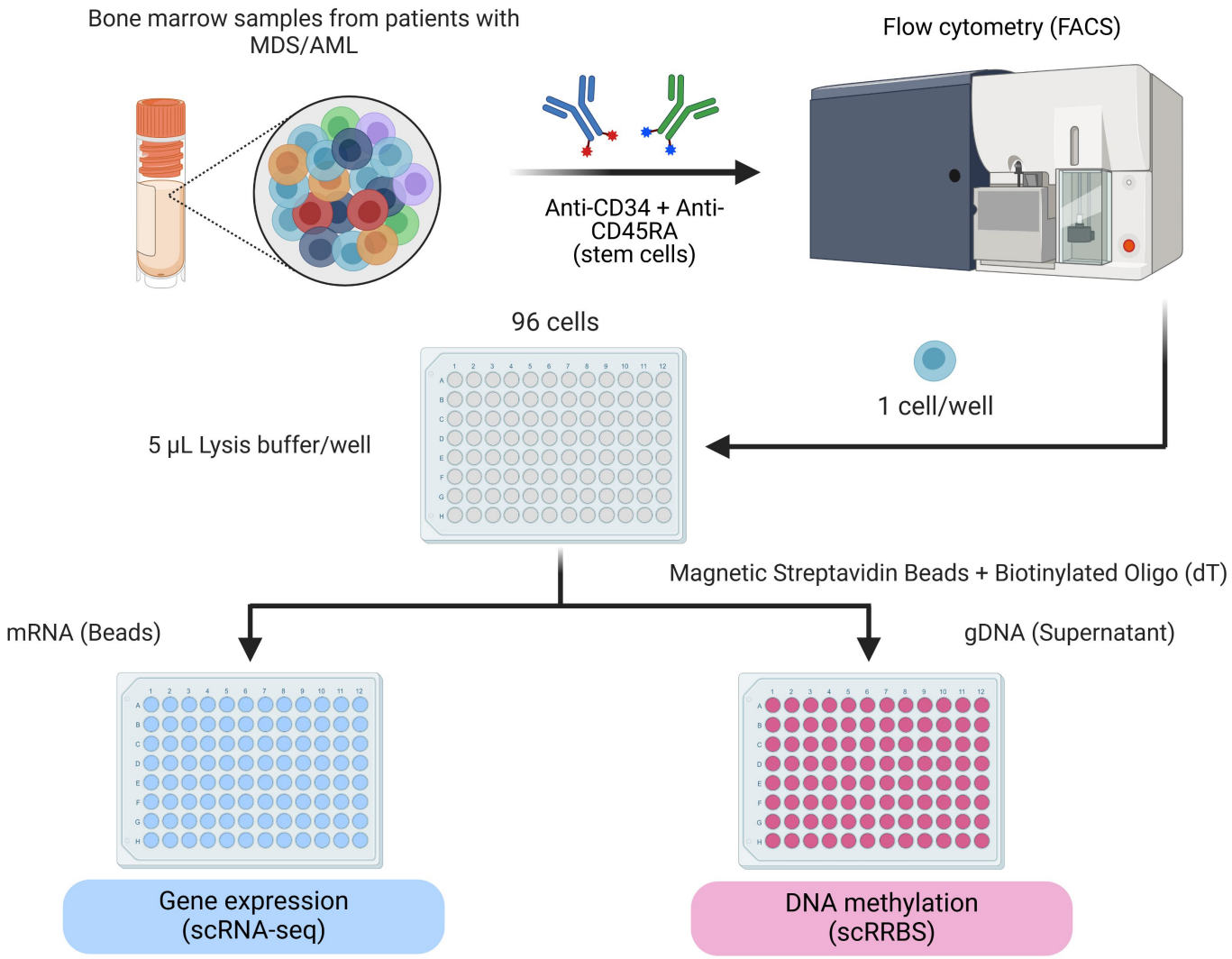
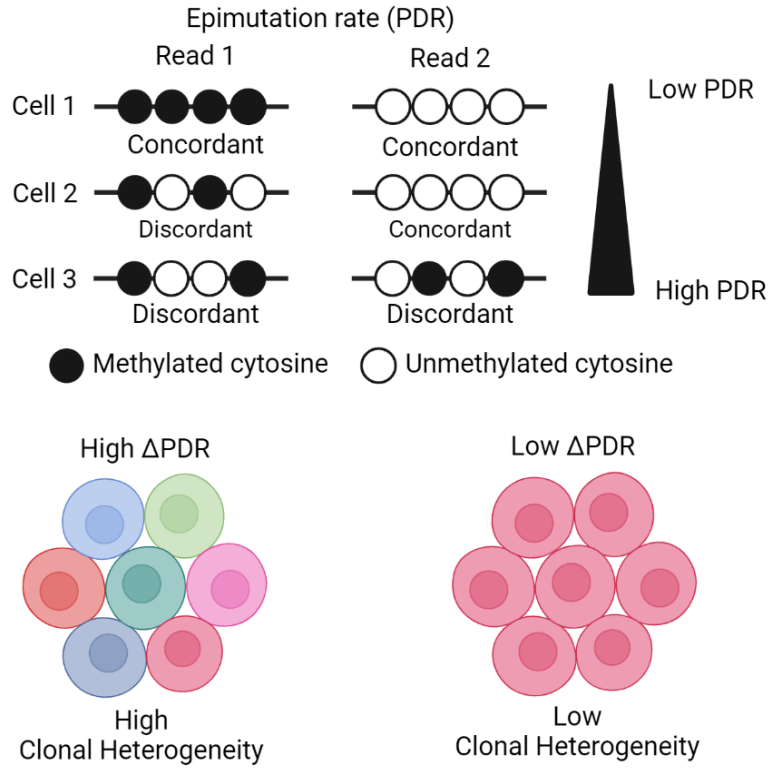
Single-cell DNA methylation in LSCs

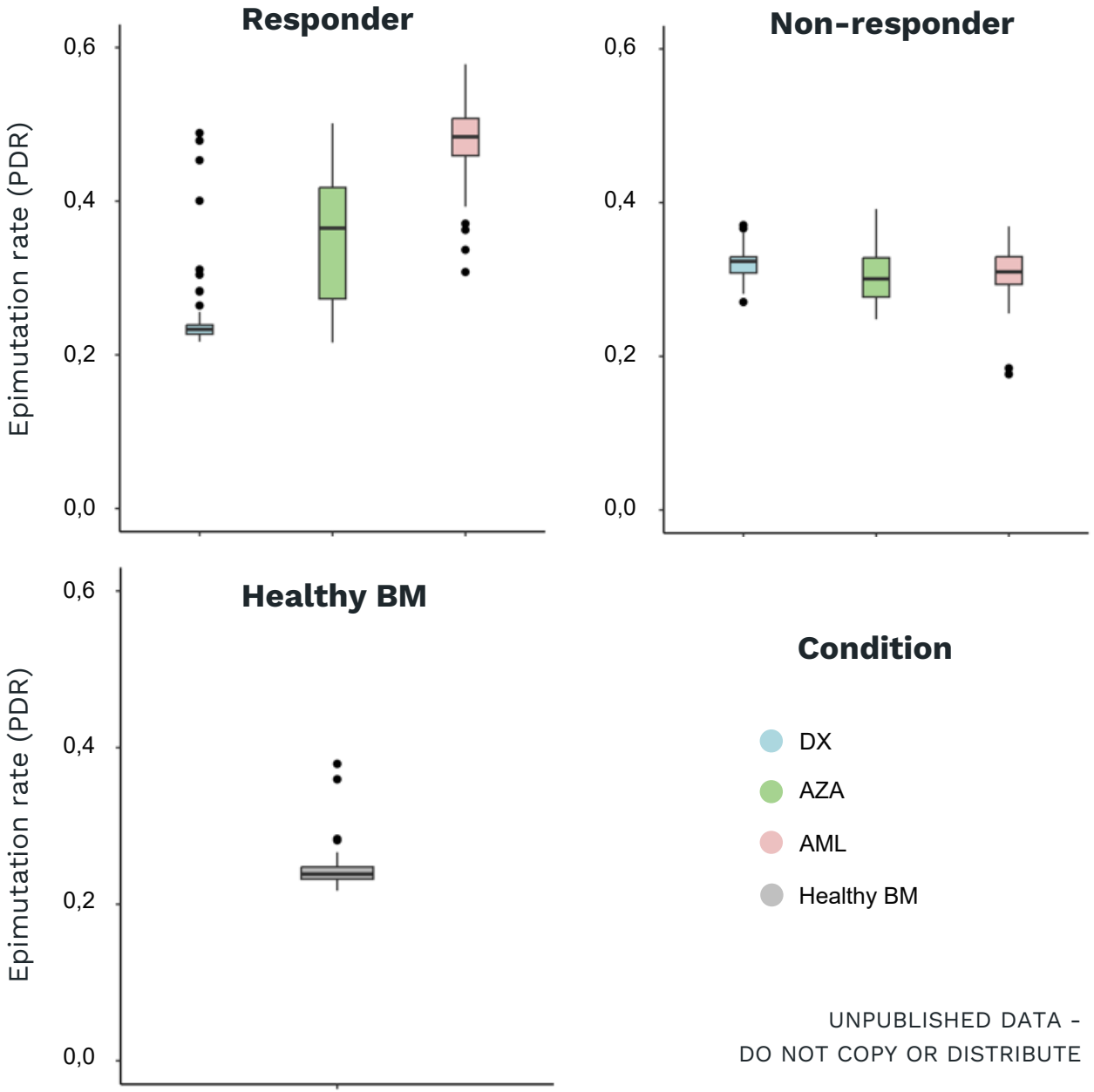


Protocol adapted from Gu et al. *Nature protocols* (2021)

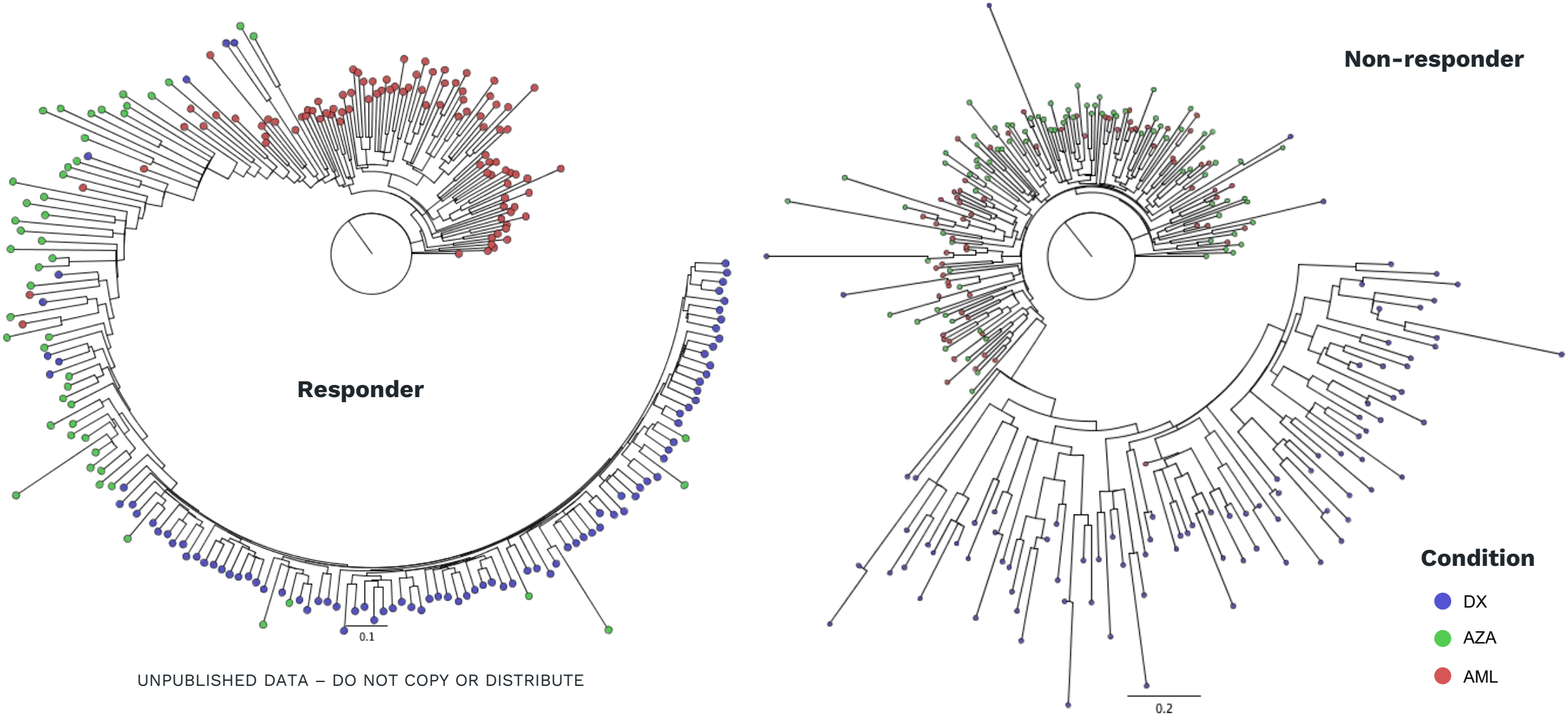
Epimutation rate in MDS & AML



Adapted from Gaiti et al. *Nature* (2019)



Epiphylogenetics in MDS-to-AML transition



Take-home messages

- The **expansion of initially minor clones at MDS diagnosis and the emergence of new ones drive the progression from MDS to AML**, despite the significant reduction of the clonal size in responders after HMA treatment.
- **Patient-specific clusters associated with** both **stem and myeloid compartments** of the BM **reveal distinct trajectories** of **MDS-to-AML transformation**.
- The **AML-risk signature** is **preferentially found in HSPCs** at **both** the **MDS and AML stages** and also appears in patient-specific clusters.
- Focusing on LSCs, **two distinct trends** are uncovered **based on the initial response to AZA**: in most responders, pre-AZA, post-AZA and AML stem cells form different clusters, whereas in non-responders, post-AZA and AML stem cells cluster together, distinct from pre-AZA.

Acknowledgements

Cancer Epigenetics group (IJC, Spain)

Myelodysplastic syndromes group (IJC, Spain)
Francesc Solé

Myeloid neoplasms group (IJC, Spain) **and Department of Hematology** (ICO-IJC-HGTiP, Spain)
Lurdes Zamora

Single Cell Unit (IJC, Spain)

Leukemia Unit (Humanitas Cancer Center; Milan, Italy)
Matteo G. Della Porta

Cancer Genomics & Evolutionary Dynamics (WCM/NYGC; New York, USA)
Dan Landau

Josep Carreras LEUKAEMIA Research Institute
Instituto de Salud Carlos III
ciber | ONC CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED Cáncer
MINISTERIO DE CIENCIA E INNOVACIÓN
UNIÓN EUROPEA
FONDO EUROPEO DE DESARROLLO REGIONAL "Una manera de hacer Europa"
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