Settima edizione di

# AIEOP...

## ...in Lab

G.d.L. Biologia Cellulare Molecolare

AIEOP

ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

**Studio multiomico a singola cellula della leucemia mielomonocitica giovanile**

*Alberto Peloso*

Milano, 22 e 23 maggio 2026

# Disclosures of Alberto Peloso

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
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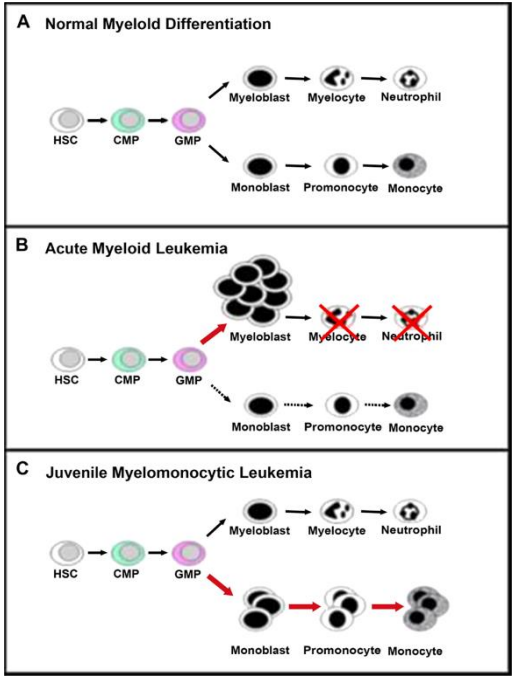
# Juvenile myelomonocytic leukemia

- JMML is a rare **myeloproliferative/myelodysplastic** neoplasm of early childhood
- HSCT is the only curative treatment, but ~50% of patients experience disease progression and relapse
- Hyperproliferation of **monocytic** and **granulocytic** cells in both BM and PB




Chan RJ et al. *Leuk Res.* 2009

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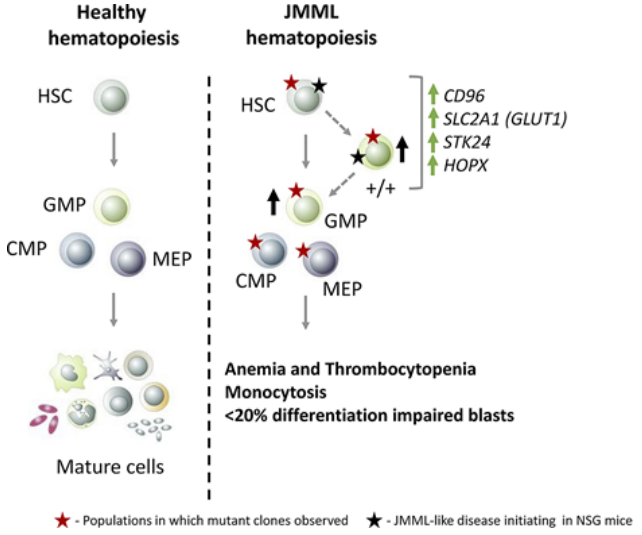
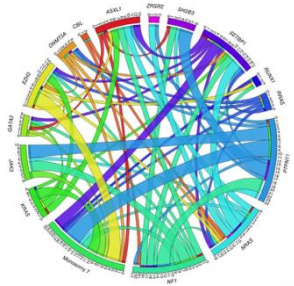
- It is driven by mutations in **RAS pathway** genes: *PTPN11*, *NRAS*, *KRAS*, *CBL* and *NF1*



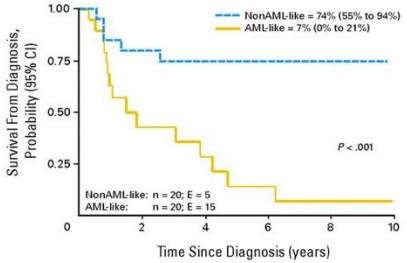

Adapted from: Sundaravel S et al. *J Exp Med*. 2021

# Juvenile myelomonocytic leukemia

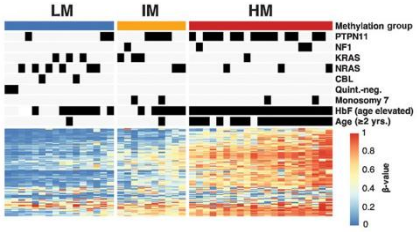


Stieglitz E et al. *Nat Genet*. 2016

- Genomic, transcriptomic and epigenomic profiling enhanced the knowledge of **molecular mechanism** driving JMML
- Methylation classification is used to guide clinical decisions, while also transcriptomics and genomics stratify patients
- JMML **heterogeneity** in clinical trajectories and outcomes suggests that **additional layers** of biological regulation are still unexplored

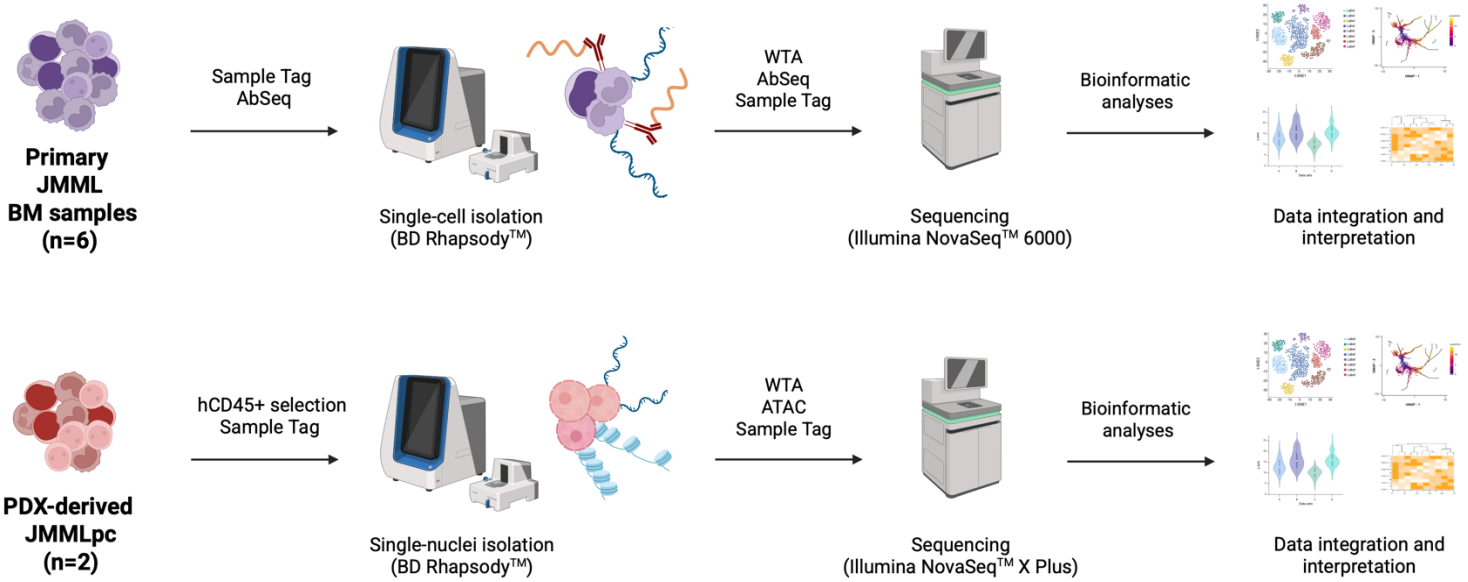



Bresolin S et al. *J Clin Oncol*. 2010




Schönung M et al. *Clin Cancer Res*. 2021

# A multimodal single cell strategy to dissect JMML heterogeneity

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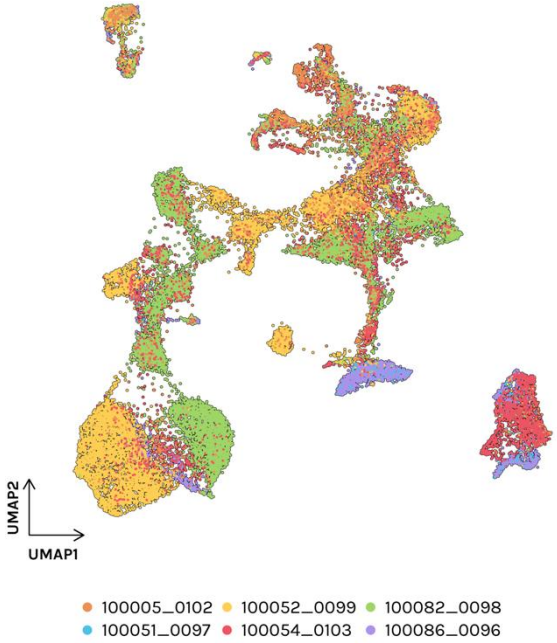
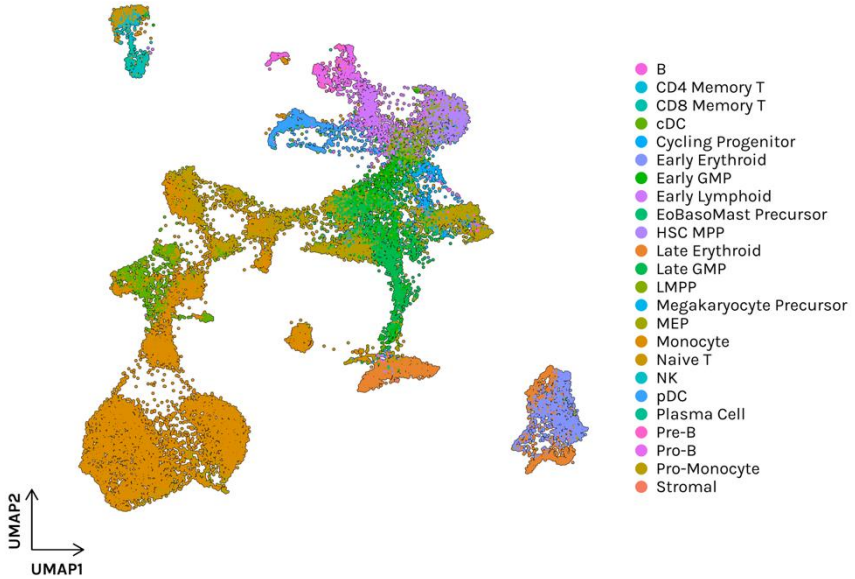
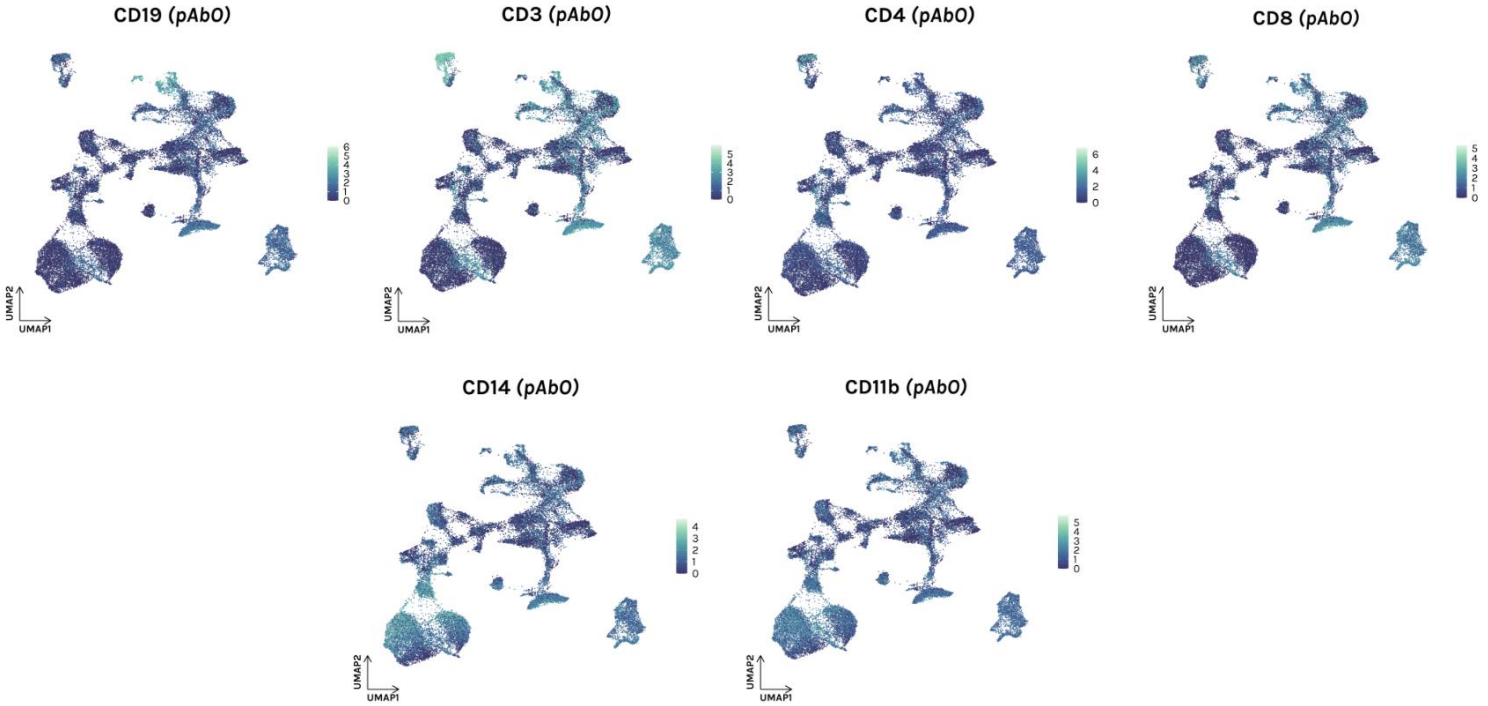
# JMML cells are broadly distributed among BM subpopulations, but patients show differential abundances in immature and myeloid/ery compartments

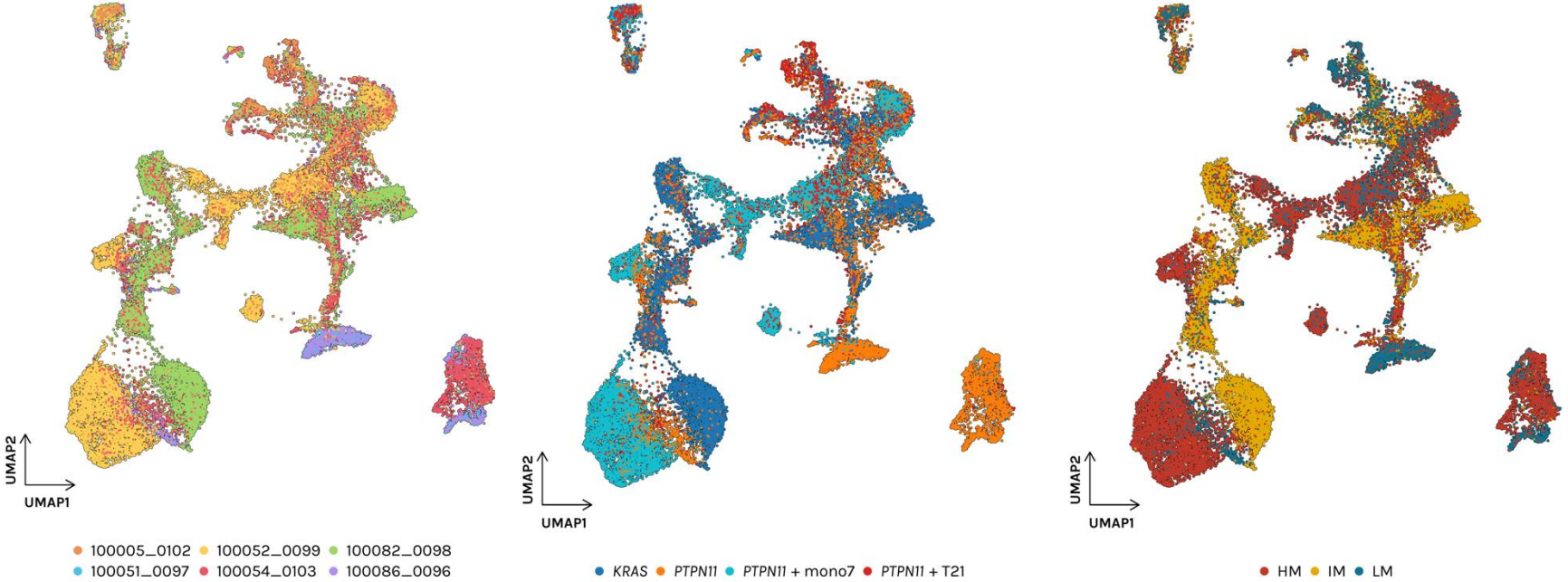


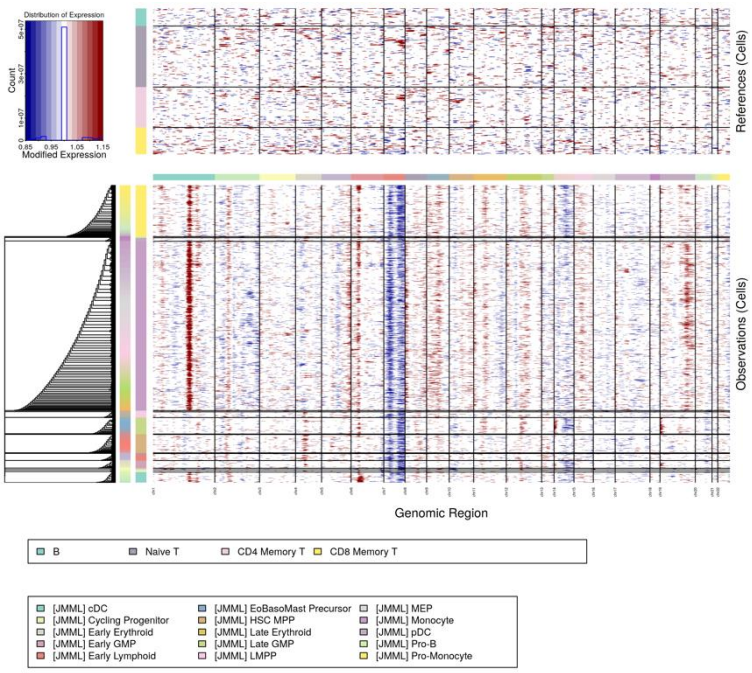
# Surface markers confirm that all the hematopoietic lineages are represented, with an abundance of mature myeloid cells

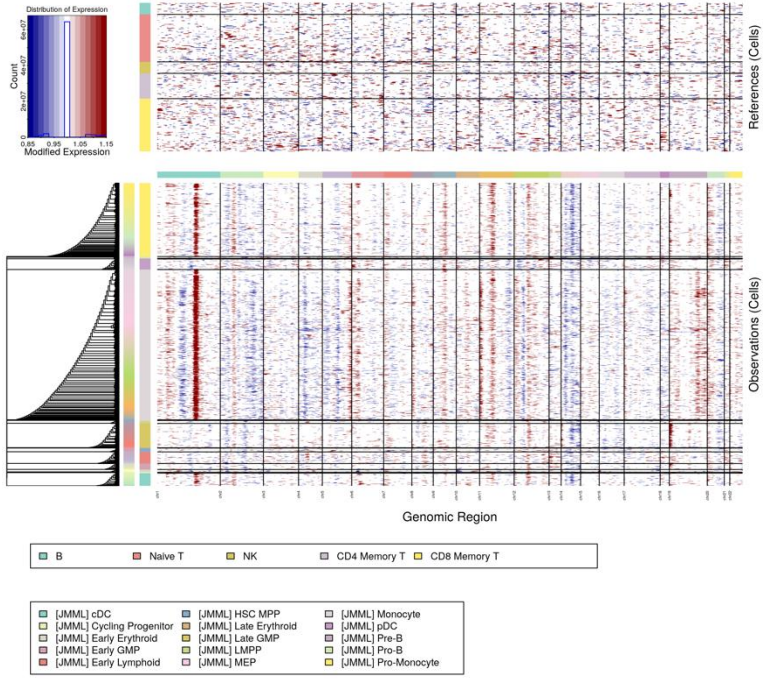


# Canonical driver mutation and methylation profile do not fully resolve JMML heterogeneity at the single-cell level

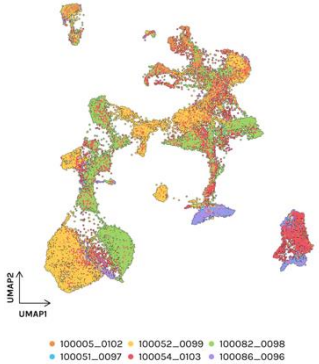


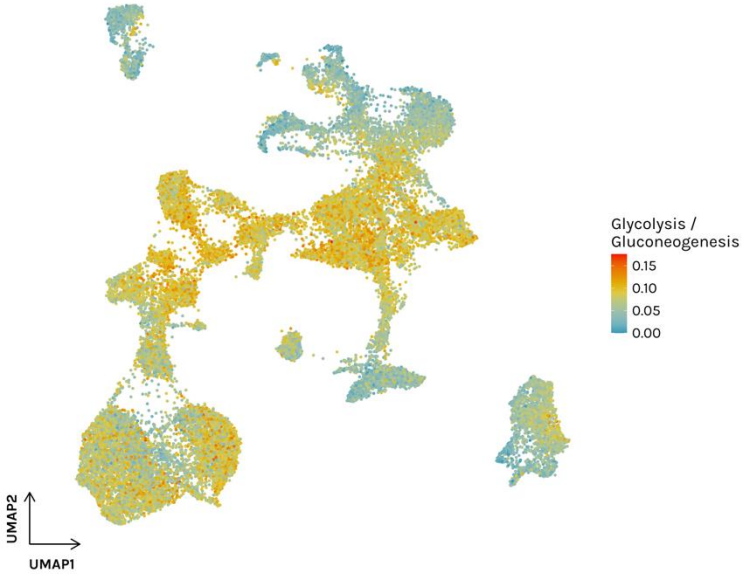
# inferCNV confirms known JMML chromosomic aberrations and suggest novel altered regions

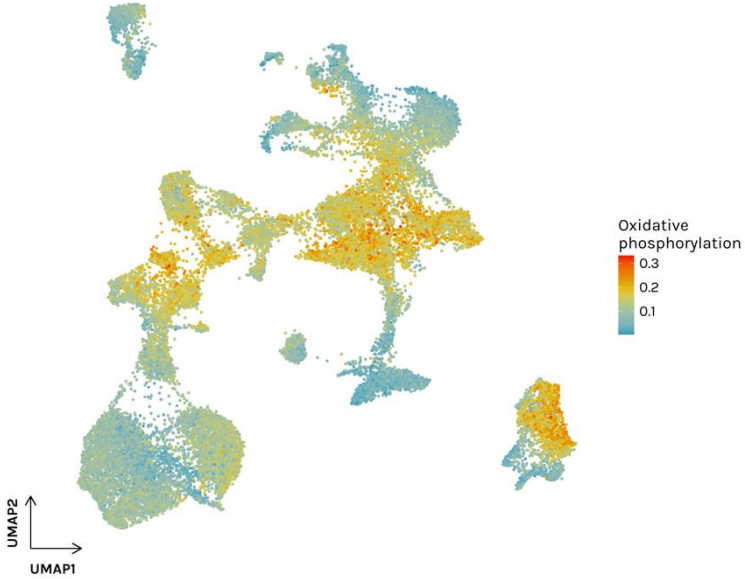


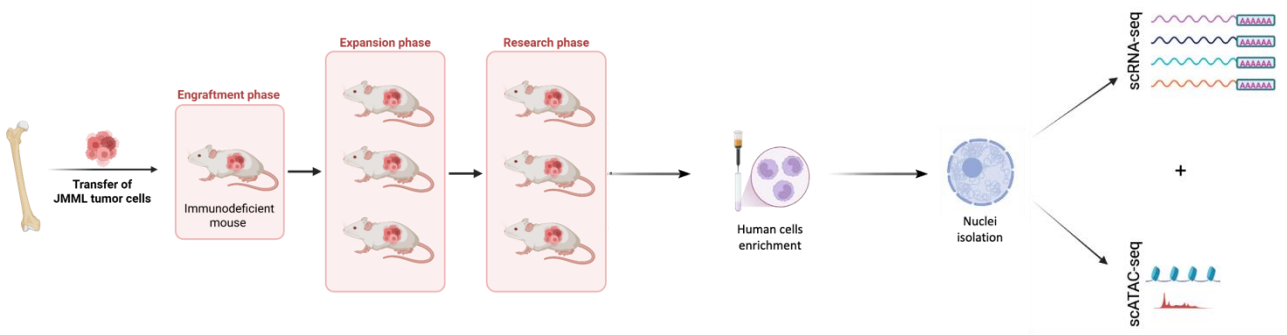
# Clusters show patient-specific pattern, but converge on shared biological programs and metabolic signatures

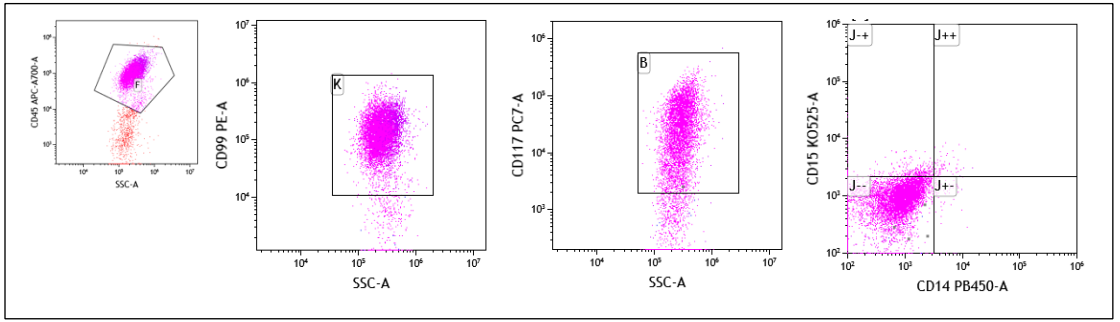


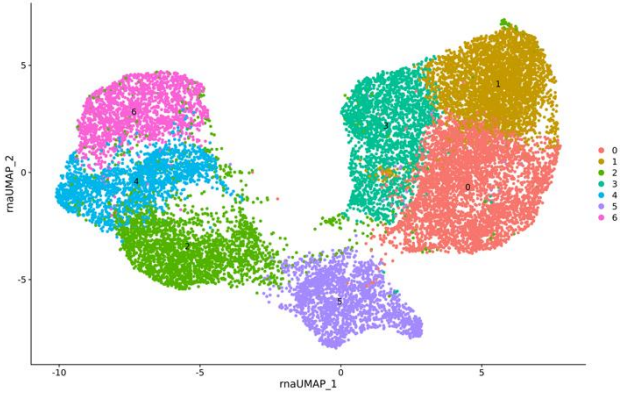
# PDXs generation as a platform for the dissection of JMML propagating cells



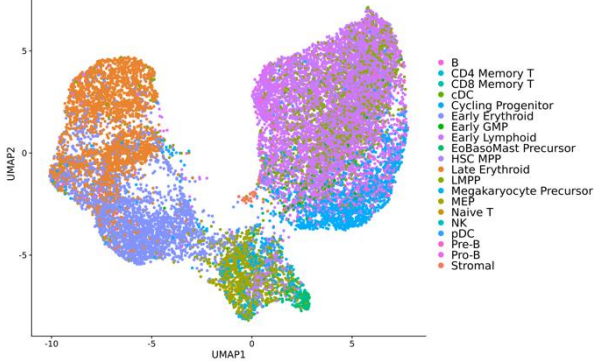




in collaboration with Prof Martina Pigazzi and Ambra Da Ros

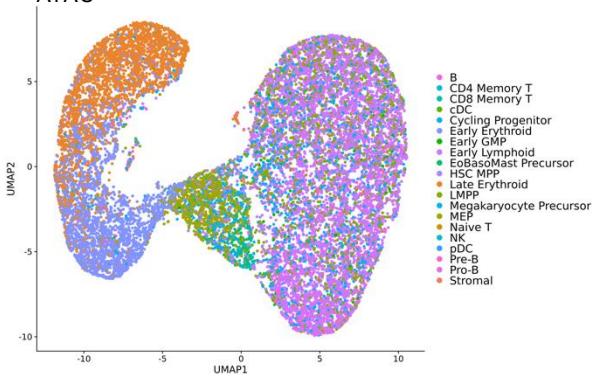
# snRNA-seq and snATAC-seq identifies hidden cell states in JMMLpc




RNA




ATAC



# Conclusions

- JMML cells are mapping onto the whole BM development, but patients show differential abundances in **immature** and **erythroid** compartments
- Driver mutations and methylation are not fully recapitulating the heterogeneity at a single-cell level, while **copy number alternations** and **metabolic signatures** suggest the contribution of different regulatory layers
- **JMML PDXs** provide a powerful platform to identify and expand JMML propagating cells, enabling the investigation of their biological properties and contribution to the disease
- The study of **chromatin state** at a single-cell level shows that different cell states might be hidden by immmunophenotypically homogeneous cell population, suggesting a role of chromatin organization in JMML initiation and progression

# Acknowledgments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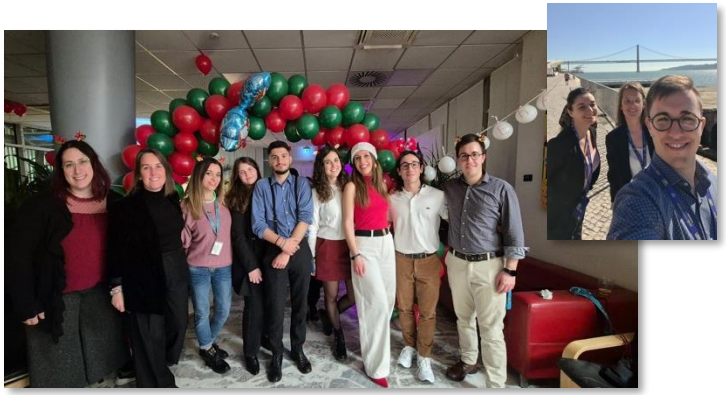


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**Italian Working Group on MDS and JMML**

Coordinator Prof Riccardo Masetti

EWOG-MDS

**European Working Group on MDS (EWOG-MDS)**

Chairwoman Prof Charlotte Niemeyer

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**AIRC Foundation for Cancer Research in Italy**

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