



# 2<sup>nd</sup> BOLOGNA WORKSHOP

## on IMMUNOTHERAPY FOR ACUTE MYELOID LEUKEMIA

Bologna, Royal Hotel Carlton  
September 29-30, 2026

**Menin inhibition: immunological effects and implications for future immunotherapies**

- **NPM1 and immune microenvironment**

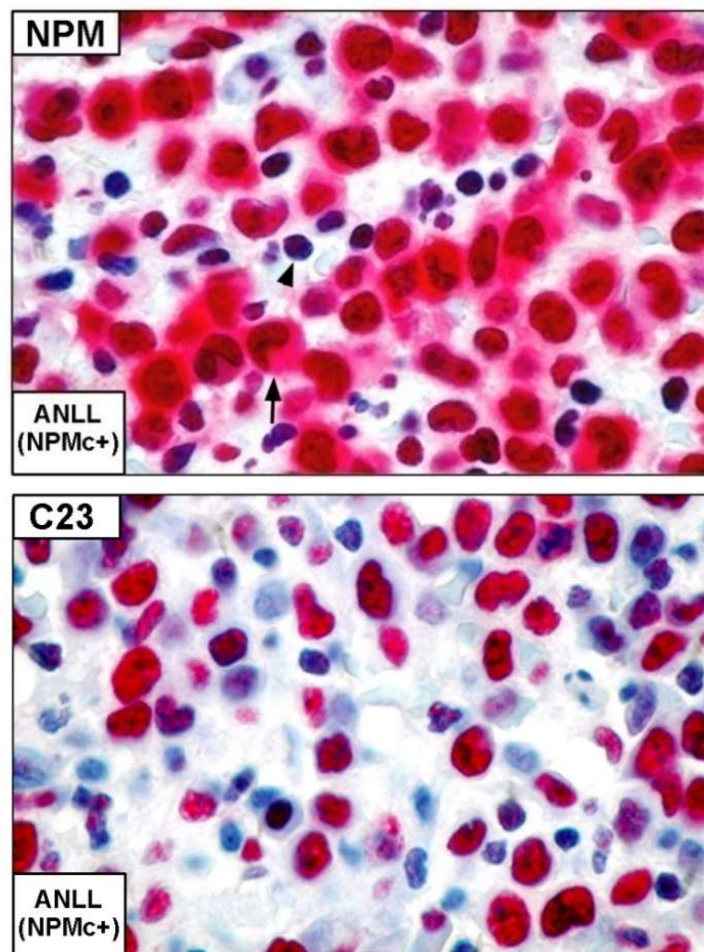
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**MARIA PAOLA MARTELLI**

| Company name         | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|----------------------|------------------|----------|------------|-------------|-----------------|----------------|-------|
| AbbVie               |                  |          | X          |             | X               | X              |       |
| Amgen                |                  |          |            |             | X               | X              |       |
| BMS                  |                  |          |            |             | X               | X              |       |
| Delbert              |                  |          | X          |             |                 |                |       |
| Gilead               |                  |          |            |             |                 | X              |       |
| Incyte               |                  |          |            |             |                 | X              |       |
| Janssen              |                  |          |            |             | X               | X              |       |
| Jazz Pharmaceuticals |                  |          |            |             | X               | X              |       |
| Novartis             |                  |          |            |             | X               | X              |       |
| Otsuka               |                  |          |            |             | X               | X              |       |
| Pfizer               |                  |          | X          |             | X               | X              |       |
| Roche                |                  |          |            |             |                 | X              |       |
| Servier              |                  |          |            |             | X               | X              |       |

✓ 2005



*The* NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

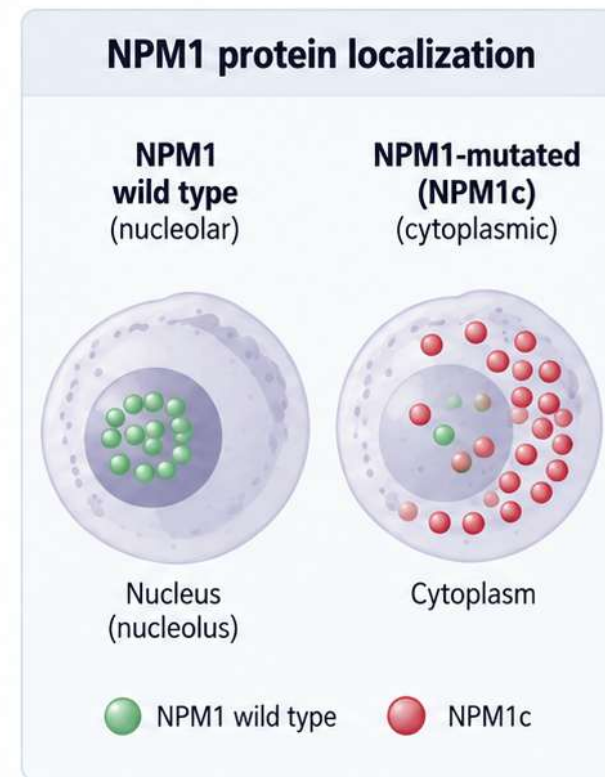
## Cytoplasmic Nucleophosmin in Acute Myelogenous Leukemia with a Normal Karyotype

Brunangelo Falini, M.D., Cristina Mecucci, M.D., Ph.D., Enrico Tiacci, M.D., Myriam Alcalay, M.D., Ph.D., Roberto Rosati, Ph.D., Laura Pasqualucci, M.D., Roberta La Starza, M.D., Ph.D., Daniela Diverio, M.D., Emanuela Colombo, Ph.D., Antonella Santucci, M.D., Barbara Bigerna, Roberta Pacini, Alessandra Pucciarini, Ph.D., Arcangelo Liso, M.D., Marco Vignetti, M.D., Paola Fazi, M.D., Natalia Meani, Ph.D., Valentina Pettrossi, Ph.D., Giuseppe Saglio, M.D., Franco Mandelli, M.D., Francesco Lo-Coco, M.D., Pier-Giuseppe Pelicci, M.D., Ph.D., and Massimo F. Martelli, M.D., for the GIMEMA Acute Leukemia Working Party\*

N ENGL J MED 352;3 WWW.NEJM.ORG JANUARY 20, 2005

## *NPM1*-mutated AML: a distinct biological and clinical entity

|   |                                                                                     |                                         |                                                                                                                                                                                                   |
|---|-------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 |    | <b>Frequency and clinical setting</b>   | <ul style="list-style-type: none"> <li>• ~30–35% of adult AML</li> <li>• Predominantly <i>de novo</i> AML</li> <li>• ~60% of AML with normal karyotype</li> </ul>                                 |
| 2 |    | <b>Distinctive phenotype</b>            | <ul style="list-style-type: none"> <li>• CD34 and CD133 low or negative</li> <li>• Wide morphological spectrum (often M4/M5)</li> <li>• Multilineage involvement</li> </ul>                       |
| 3 |    | <b>Distinct transcriptional program</b> | <ul style="list-style-type: none"> <li>• Up-regulation of <i>HOX</i> genes (GE profile)</li> </ul>                                                                                                |
| 4 |    | <b>Genetic context</b>                  | <ul style="list-style-type: none"> <li>• Frequent <i>FLT3</i> co-mutation (especially <i>FLT3</i>-ITD)</li> <li>• Mutually exclusive with other recurrent AML-defining genetic lesions</li> </ul> |
| 5 |  | <b>Stability of the lesion</b>          | <ul style="list-style-type: none"> <li>• <i>NPM1</i> mutation is generally maintained throughout disease evolution</li> </ul>                                                                     |
| 6 |  | <b>Clinical relevance</b>               | <ul style="list-style-type: none"> <li>• High sensitivity to induction therapy</li> <li>• Outcome influenced by cooperating mutations and by measurable residual disease (MRD)</li> </ul>         |





TO THE EDITOR: M. Nakagawa, Y. Kameoka, R. Suzuki

| Mutation         | Predicted Protein in C-Terminal Region |   |   |   |   |   |   |   |   |   |   |     |
|------------------|----------------------------------------|---|---|---|---|---|---|---|---|---|---|-----|
| None (wild type) | -D                                     | L | W | Q | W | R | K | S | L |   |   |     |
| Mutation A       | -D                                     | L | C | L | A | V | E | E | V | S | L | R K |
| Mutation B       | -D                                     | L | C | M | A | V | E | E | V | S | L | R K |
| Mutation C       | -D                                     | L | C | V | A | V | E | E | V | S | L | R K |
| Mutation D       | -D                                     | L | C | L | A | V | E | E | V | S | L | R K |
| Mutation E       | -D                                     | L | W | Q | S | L | A | Q | V | S | L | R K |
| Mutation F       | -D                                     | L | W | Q | S | L | E | K | V | S | L | R K |

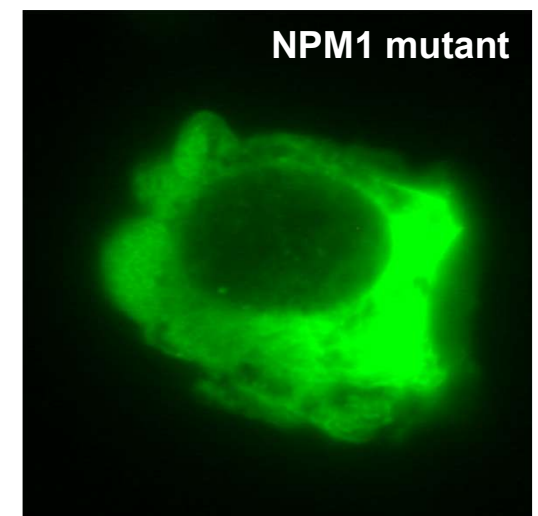
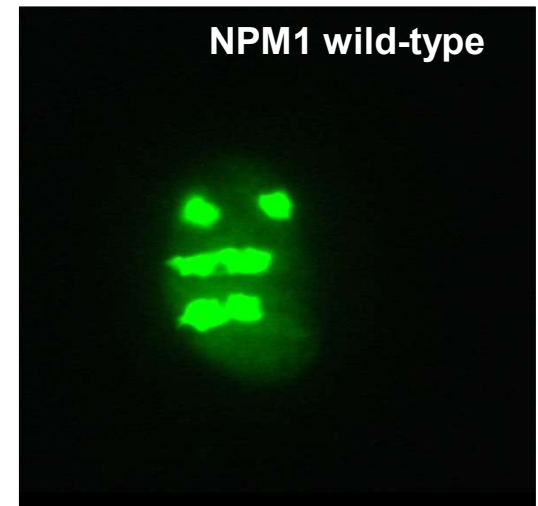
NES consensus sequence: Lx(1-3)Lx(2-3)LxL

**Figure 1. Nuclear-Export-Signal (NES) Motif in the C-Terminal of Nucleophosmin (NPM) Mutants.**

A short and hydrophobic motif, like a consensus sequence of NES, is found in the C-terminal of all the NPM mutants. Putative residues of an NES are shaded.



- NES-mediated cytoplasmic localization (CRM1/XPO1-mediated)



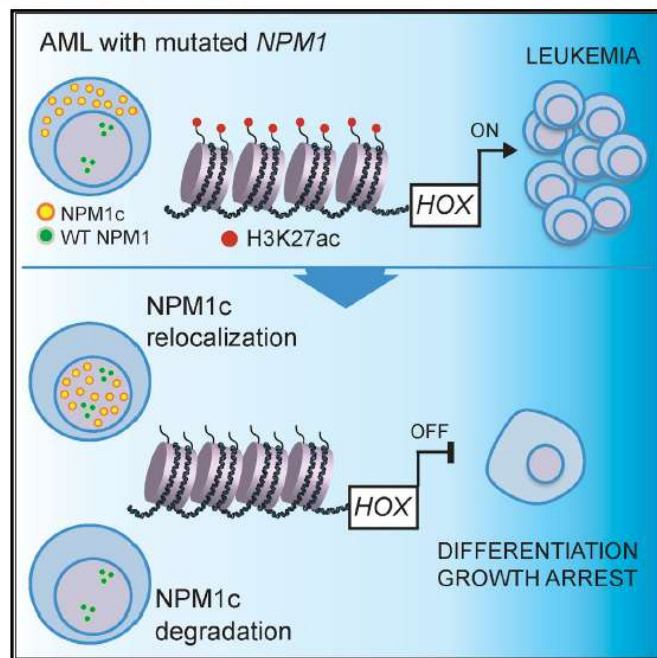
Falini B et al., Blood 107:4514, 2006

## NPM1c sustains the leukemic program

### Cancer Cell

#### Mutant NPM1 Maintains the Leukemic State through HOX Expression

##### Graphical Abstract



##### Authors

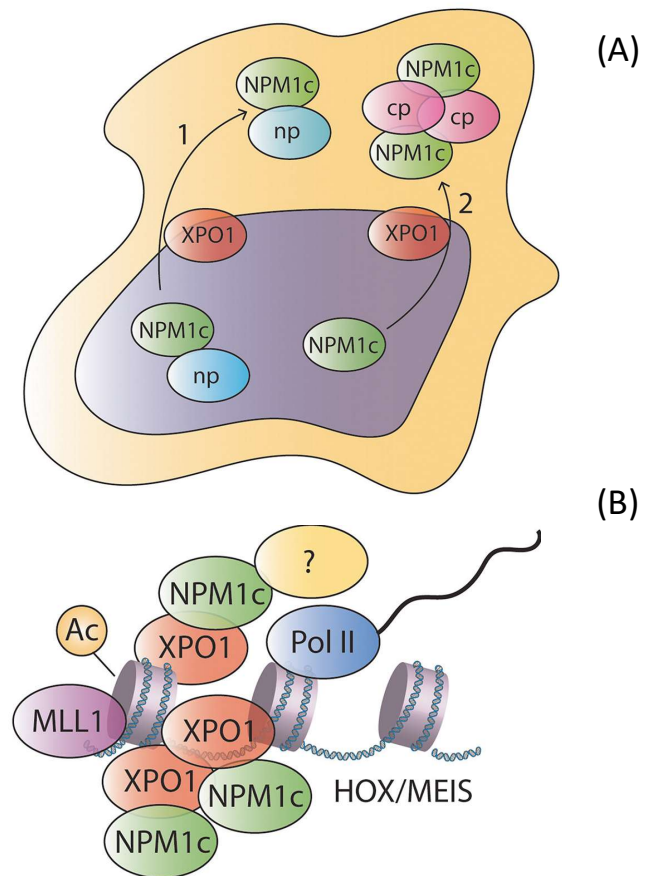
Lorenzo Brunetti, Michael C. Gundry, Daniele Sorcini, ..., Maria Paola Martelli, Brunangelo Falini, Margaret A. Goodell

##### Correspondence

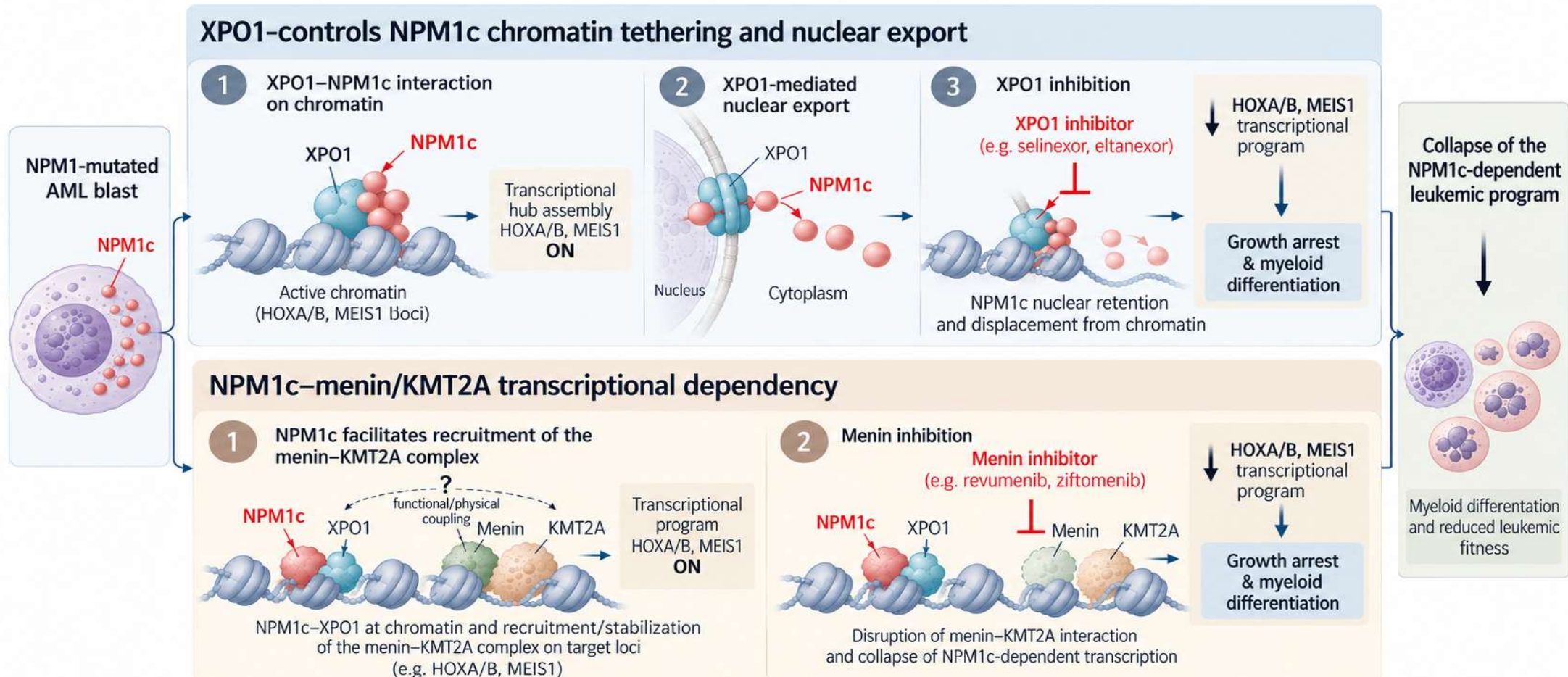
goodell@bcm.edu

##### In Brief

Brunetti et al. show that specific loss of NPM1c from the cytoplasm leads to downregulation of HOX genes and differentiation in *NPM1* mutant AML. Blocking NPM1c nuclear export by XPO1 inhibition reduces cytoplasmic NPM1c, promotes AML differentiation, and prolongs the survival of a mouse model of NPM1c<sup>+</sup> AML.



# XPO1 and menin inhibition converge on the NPM1c leukemic program

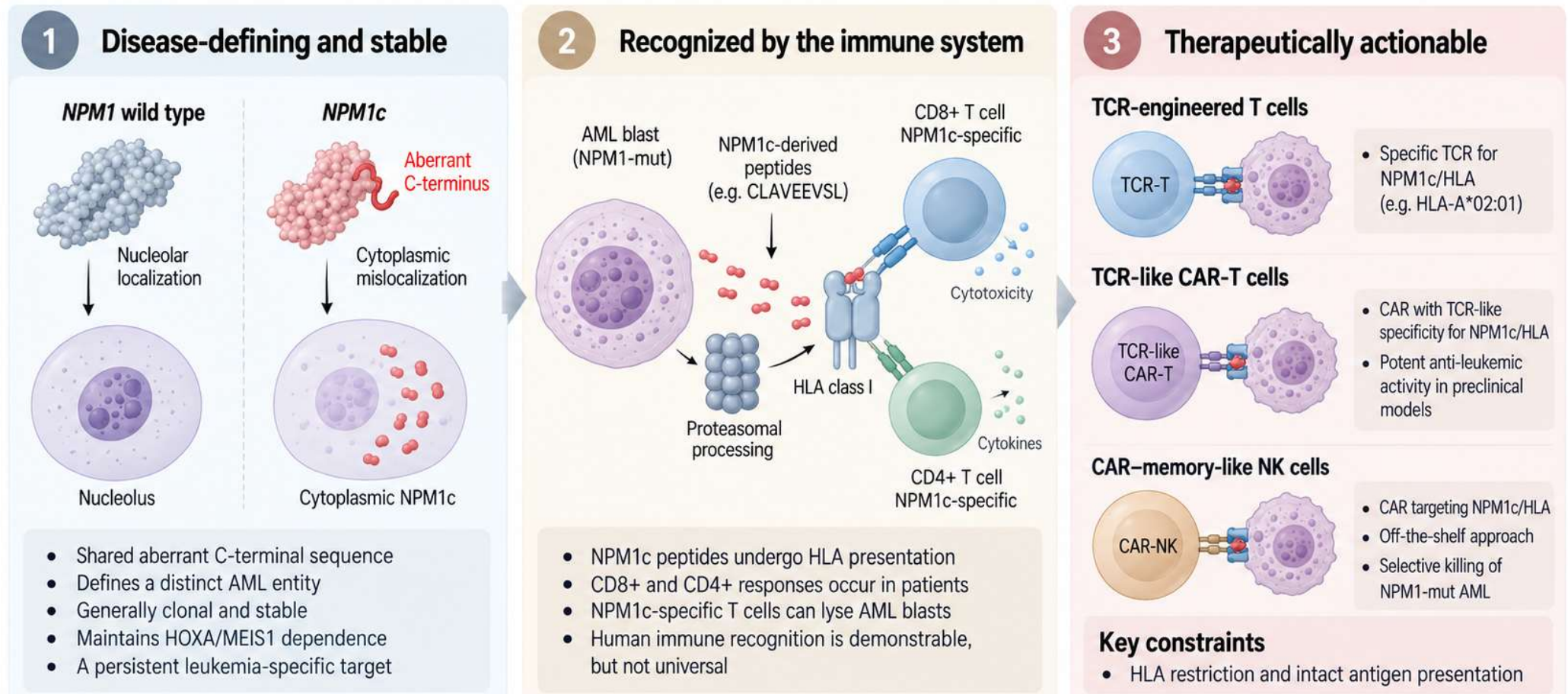


Author-designed, graphical rendering assisted by ChatGPT (OpenAI)

Brunetti L et al. Cancer Cell 2018; Wang XQD et al. Cancer Discov 2023; Uckelmann HJ et al. Cancer Discov 2023.

# NPM1c: a leukemia-specific immunogenic sequence generating HLA-binding peptide

graphical rendering assisted by ChatGPT (OpenAI)



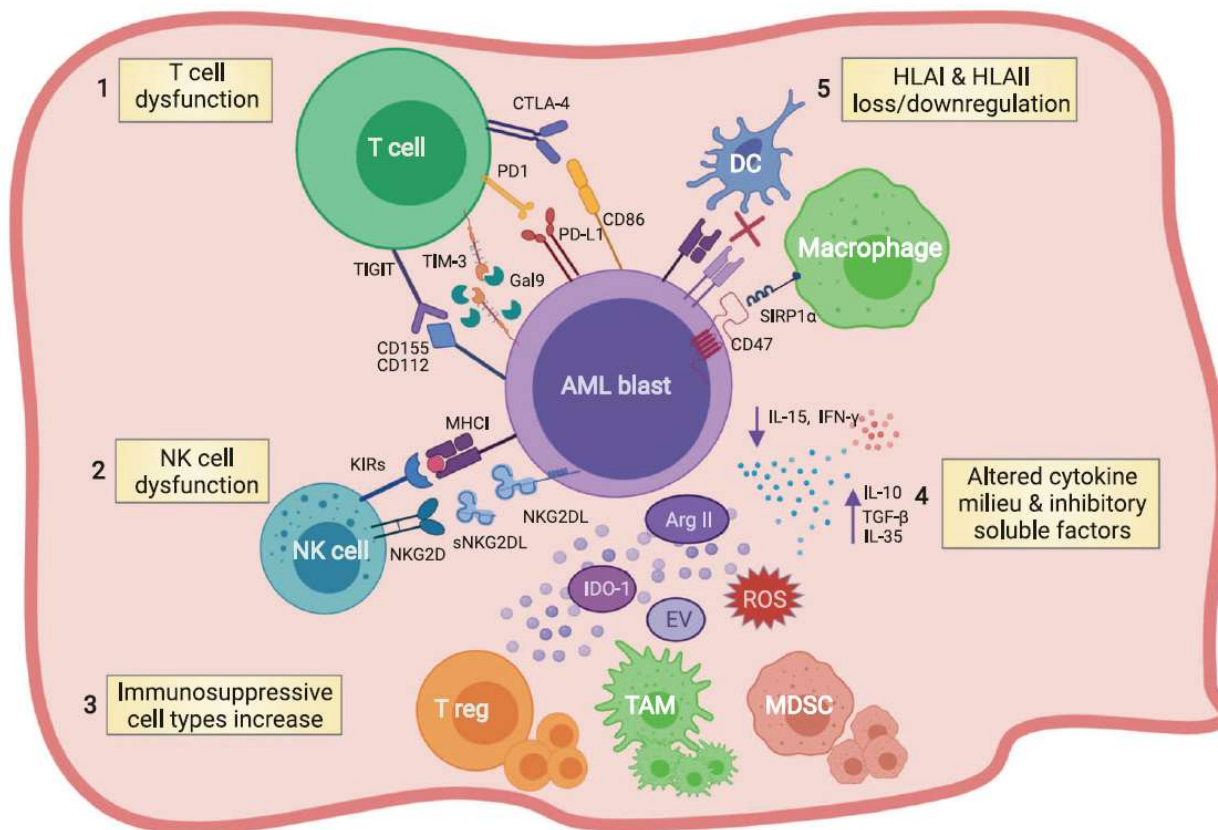
Falini B et al., NEJM. 2005  
Martelli MP, et al. Leukemia. 2008  
Brunetti L et al, Cancer Cell. 2018

Liso A, et al. Leukemia. 2008  
Greiner J, et al. Blood. 2013.  
Rücker-Braun E, et al. Front Immunol. 2025

van der Lee DI, et al. J Clin Invest. 2019  
Xie G, et al. Nat Biomed Eng. 2021  
Dong H, et al. Proc Natl Acad Sci USA. 2022

## Antigen presentation and immune escape in AML

Leukemia visibility is determined by antigen processing, HLA presentation and the bone-marrow immune context



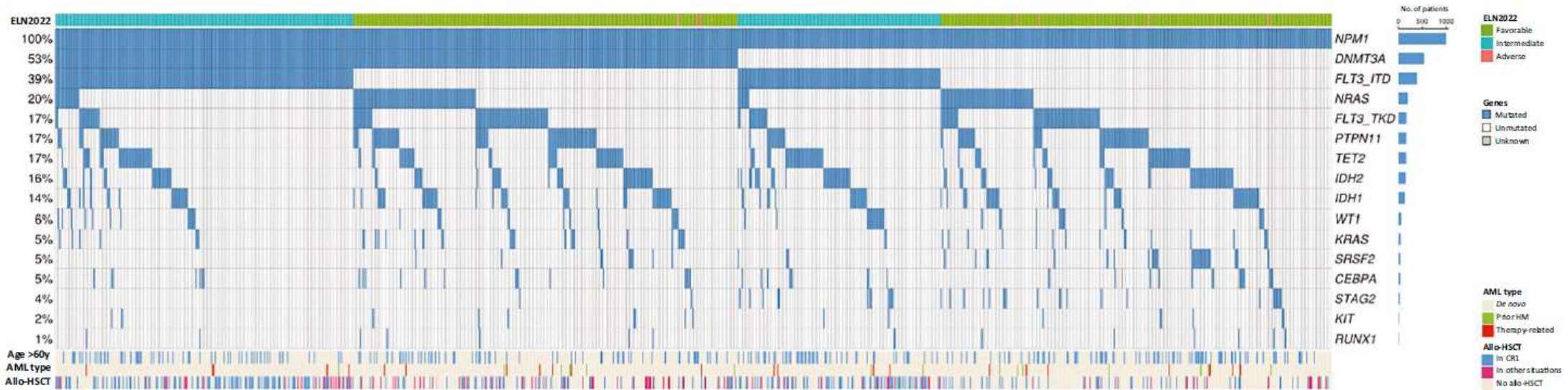
- ❖ **Reduced antigen presentation** limits leukemic blast recognition by immune effectors.
- ❖ **Inhibitory checkpoint signaling** promotes T- and NK-cell dysfunction and exhaustion.
- ❖ **Immunosuppressive cells and soluble factors** sustain a permissive bone-marrow microenvironment.
- ❖ **Multiple escape mechanisms cooperate**, progressively reducing effective anti-leukemic immunity.

↓ Leukemia visibility + ↓ immune effector fitness

→ immune evasion → persistence / relapse

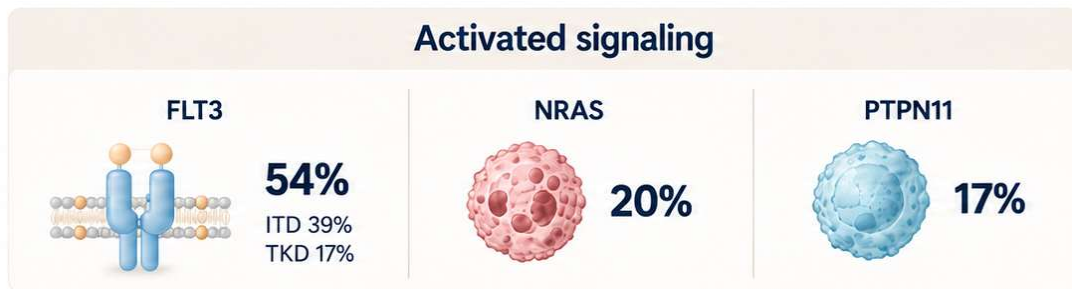
***Key question: is the immune context in which NPM1c is presented the same in every *NPM1*-mutated AML?***

## One disease-defining mutation, multiple genetic contexts

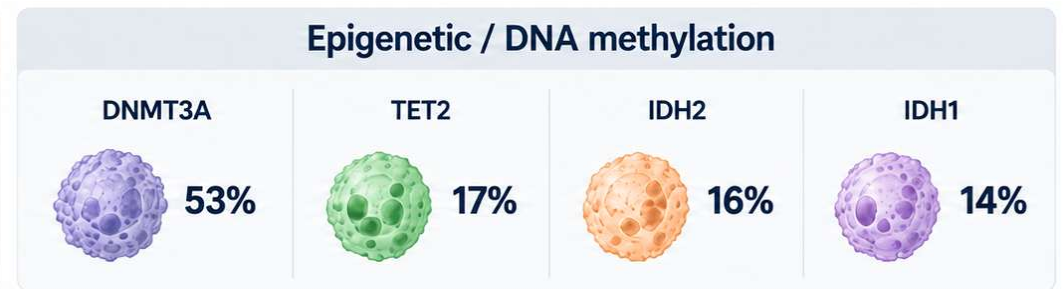


Mutational landscape of *NPM1*-mut adult AML (HARMONY study)

### Activated signaling



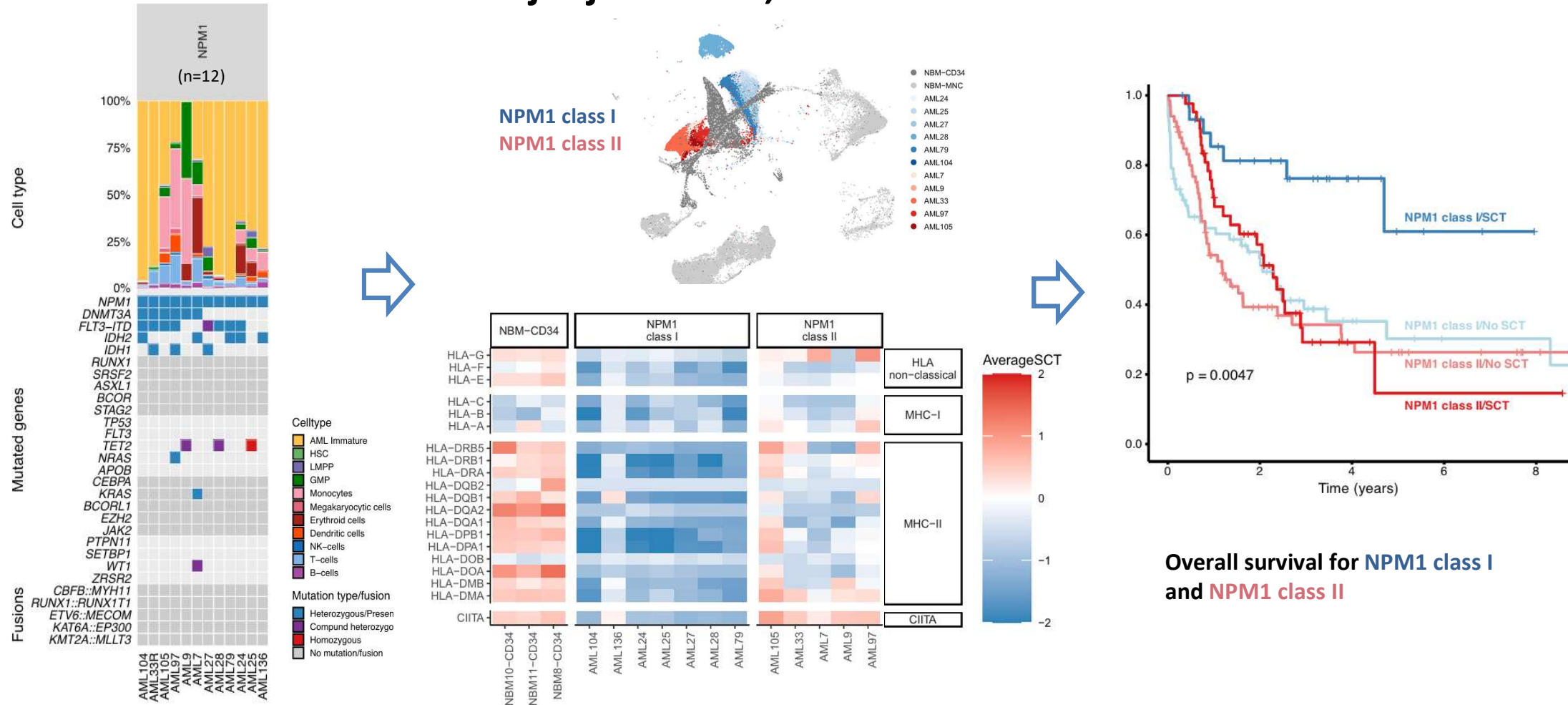
### Epigenetic / DNA methylation



graphical rendering assisted by ChatGPT (OpenAI)

Hernández-Sánchez et al., Leukemia. 2026

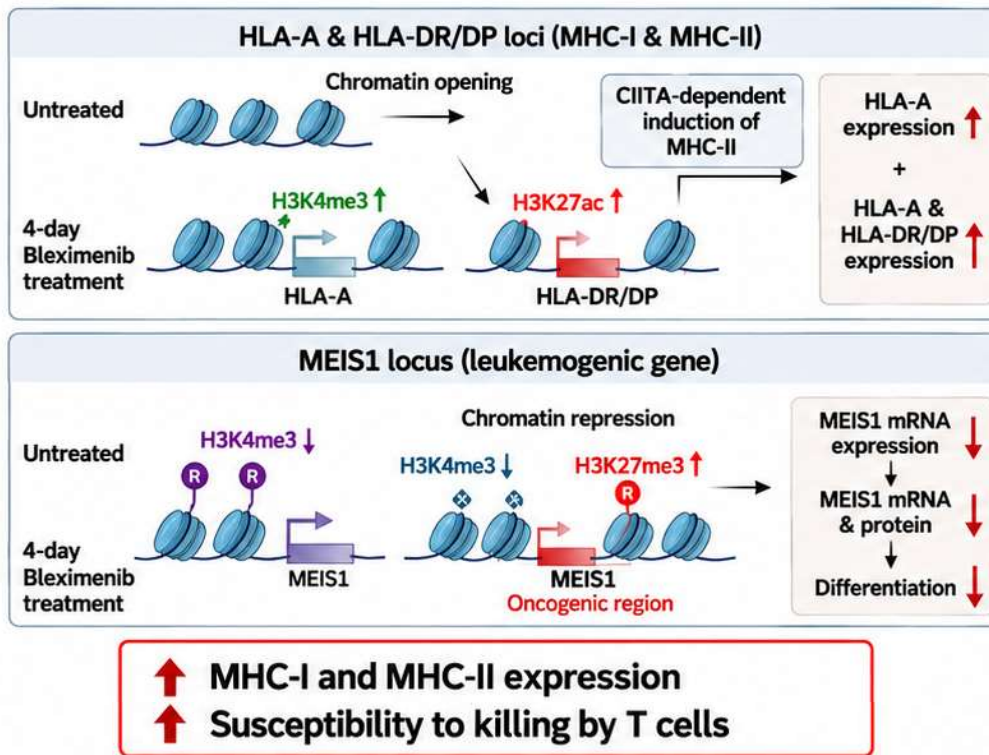
# Single cell RNA-seq analyses of NPM1-mutated AML from Lilljebjorn et al., Nat Comm. 2025



# Menin inhibition can reprogram leukemic cells and enhance immune recognition

## 1. EPIGENETIC REMODELING BY MENIN INHIBITION

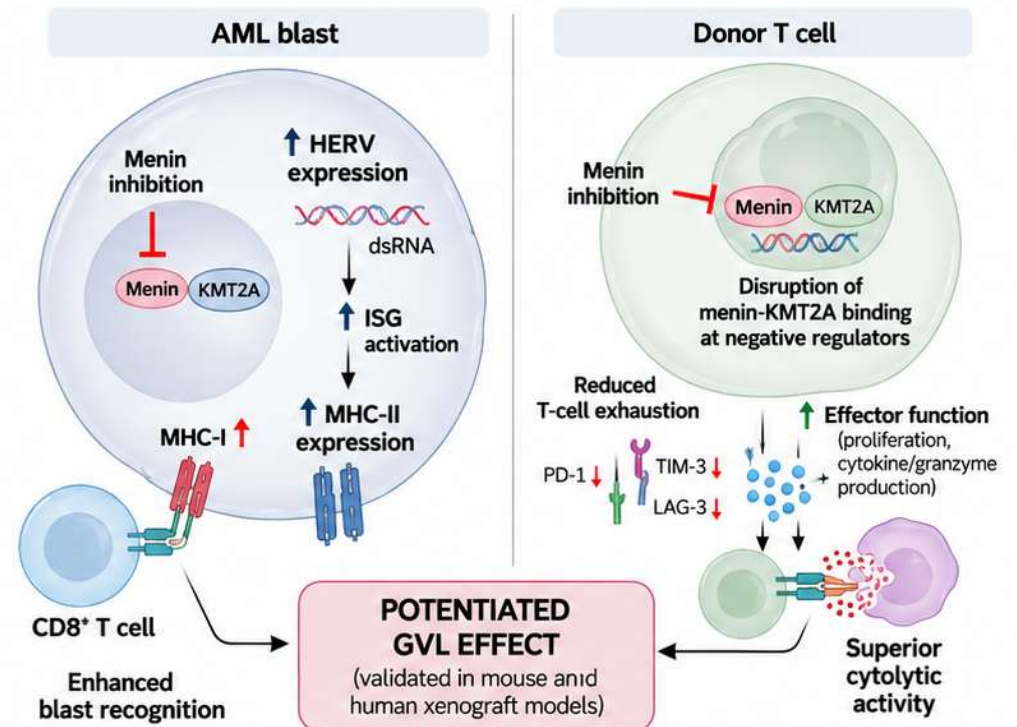
Bleximenib in primary AML cells



Hogeling et al. Bleximenib, the novel menin-KMT2A inhibitor JNJ-75276617, impairs long-term proliferation and immune evasion in acute myeloid leukemia. Haematologica, 2025

## 2. MENIN INHIBITION ENHANCES GRAFT-VERSUS-LEUKEMIA EFFECT BY IMMUNE ACTIVATION

Preclinical models



Fetsch et al. Menin inhibition enhances graft-versus-leukemia effects by T-cell activation and endogenous retrovirus induction in AML. Blood, 2026

## Take-home messages

- ❖ NPM1c provides a shared leukemia-specific target, but ***NPM1*-mutated AML does not represent a single immune state.**
- ❖ Distinct transcriptional states are associated with **coordinated differences in immune visibility**, across antigen presentation, IFN signaling and inflammatory immune programs.
- ❖ The FLT3like state shows reduced immune-visibility programs and co-mutational context further contributes to immune heterogeneity.
- ❖ **Menin inhibition can modify the leukemia–immune interface**, raising the possibility that its immunological effects may depend on the pre-existing immune state.

**Could the baseline immune state influence how effectively menin inhibition re-opens leukemia visibility, and help guide future immunotherapy combinations?**

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Bologna, Royal Hotel Carlton • September 29-30, 2026



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