Novel combinations to target *NPM1* mutated acute myeloid leukemia

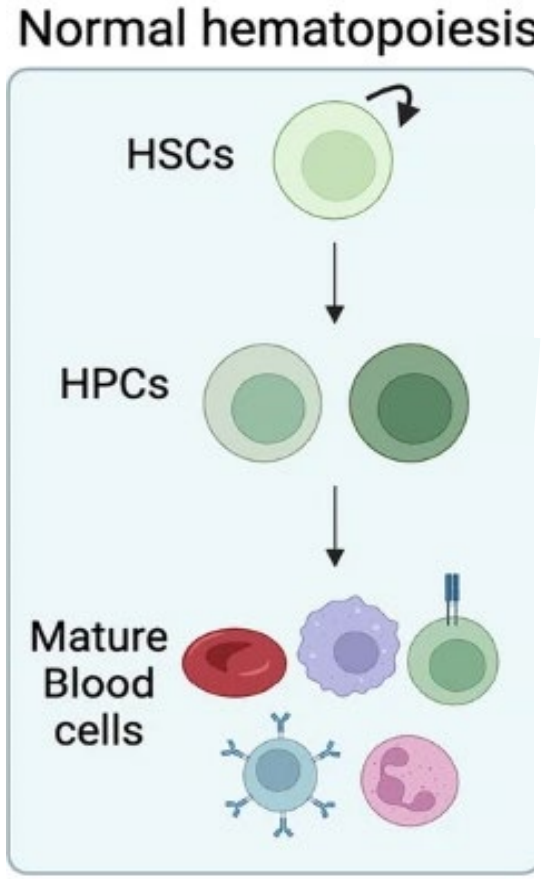
Daniela Mendoza-Ortiz

26.09.2024

Disclosures

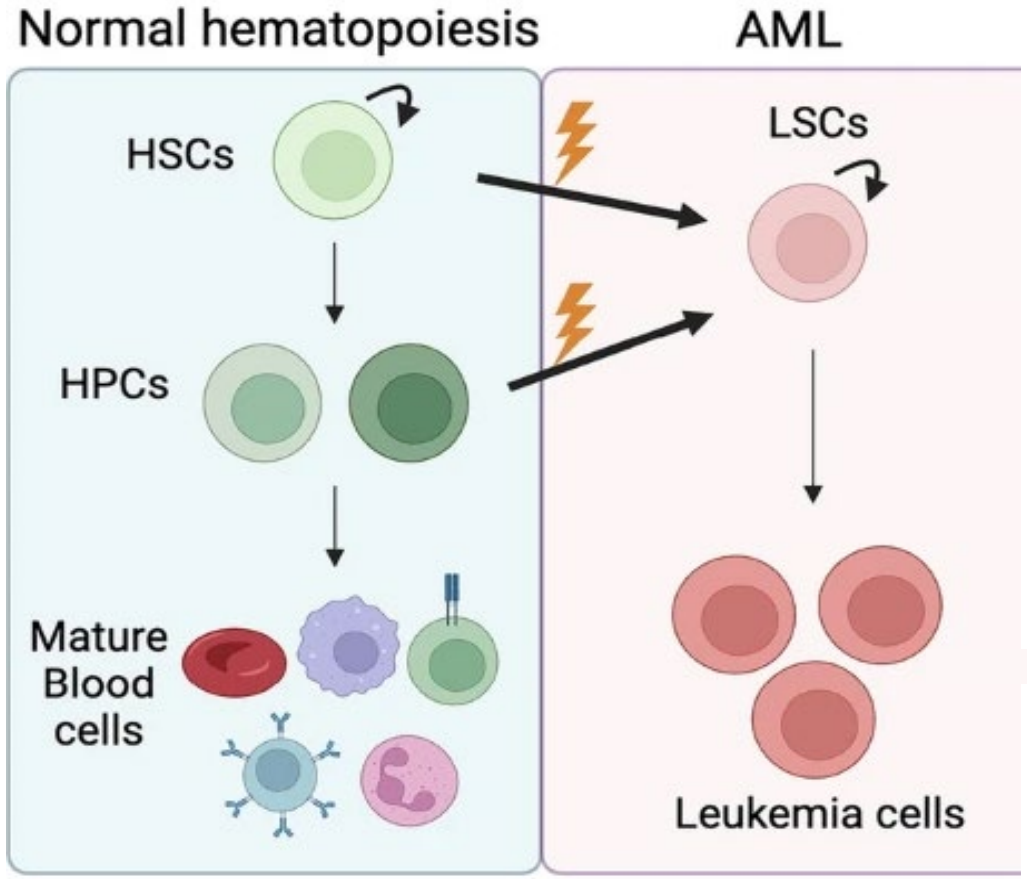
Nothing to disclose

Acute myeloid leukemia (AML)



Modified from Shi et al. 2024.

Acute myeloid leukemia (AML)



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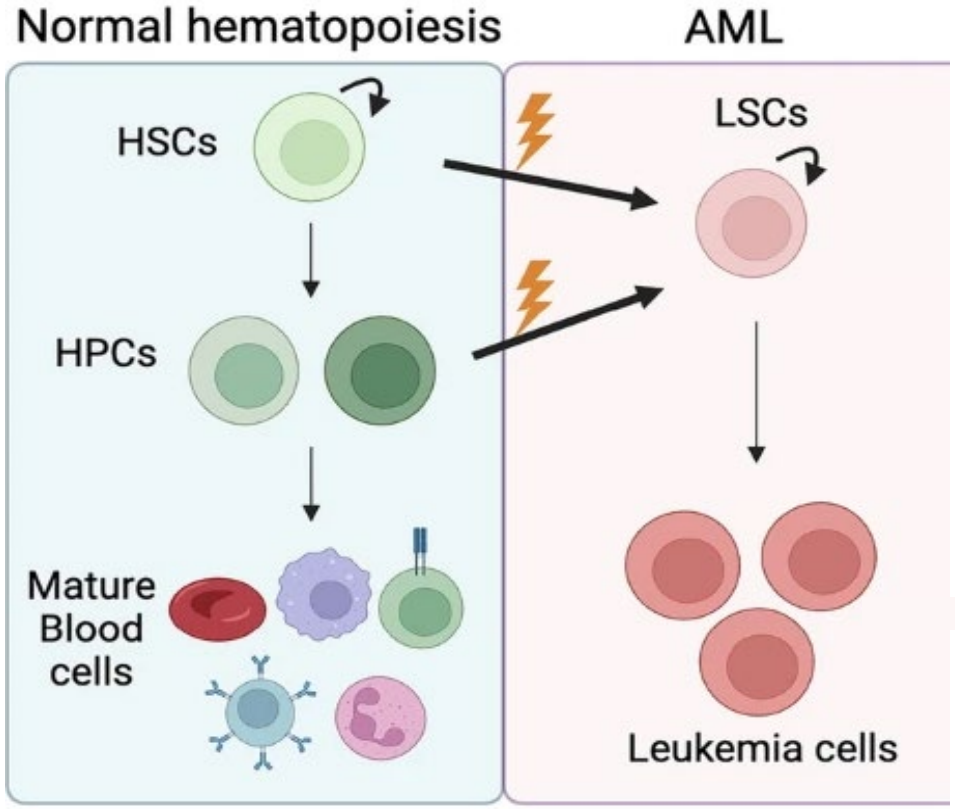
Acute myeloid leukemia (AML)

- Cancer of the blood and bone marrow (BM)



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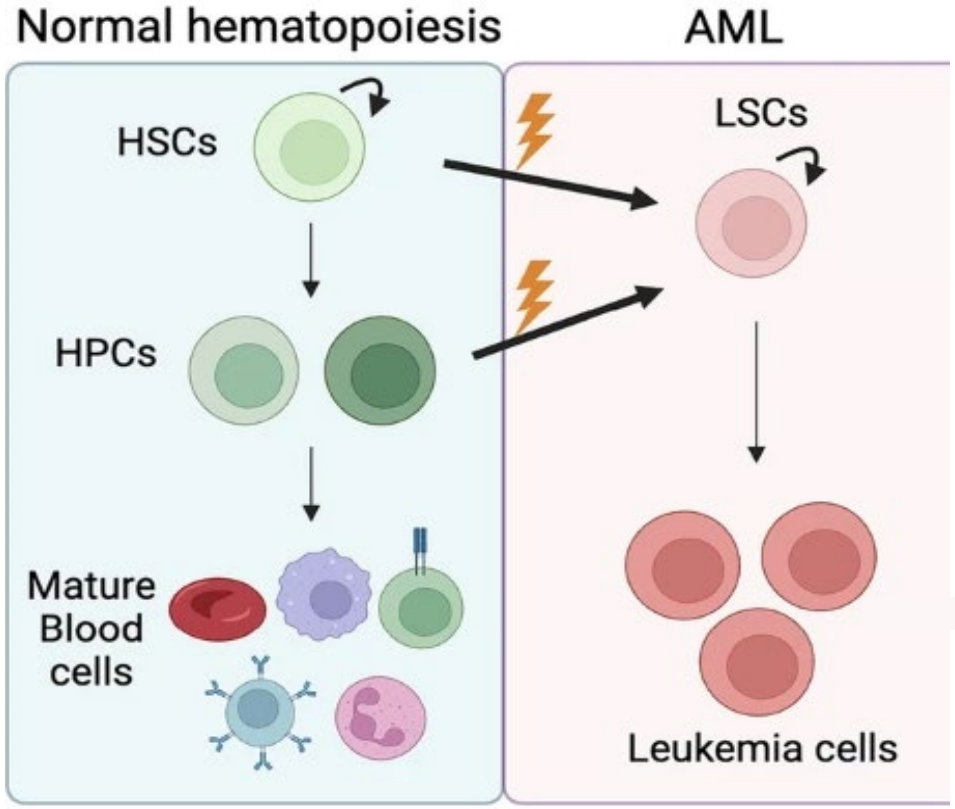
Acute myeloid leukemia (AML)

- Cancer of the blood and bone marrow (BM)
- Most common form of leukemia



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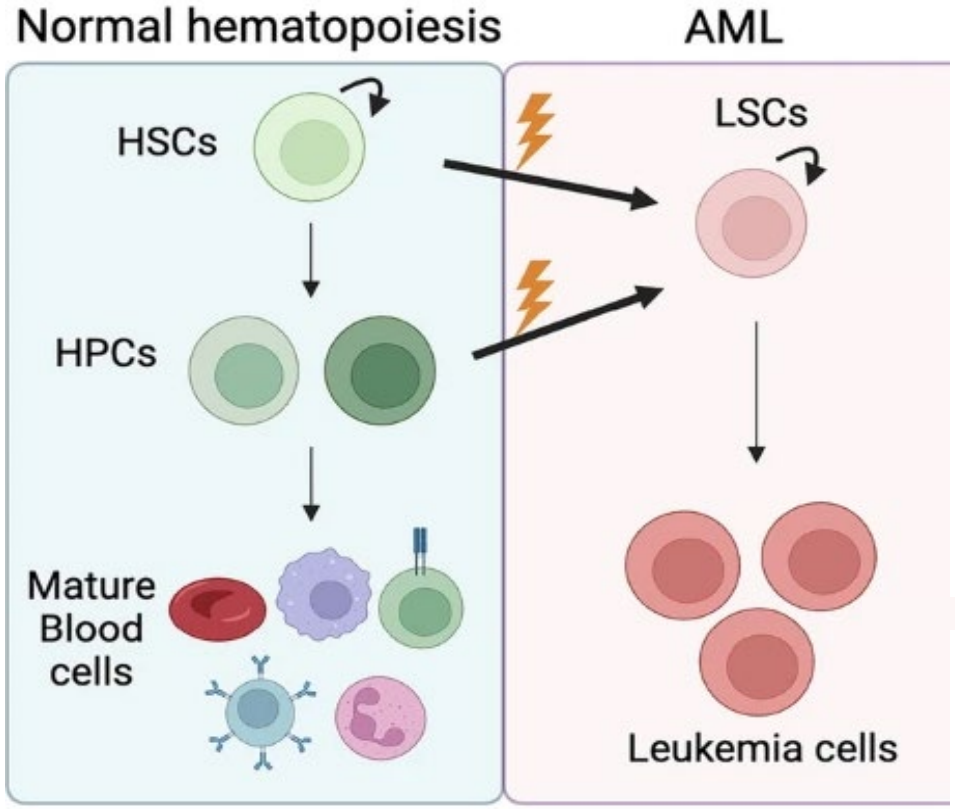
Acute myeloid leukemia (AML)

- Cancer of the blood and bone marrow (BM)
- Most common form of leukemia
- Treatment options
  - Standard treatment
    - “7 + 3” chemotherapy
    - Hypomethylating agents
  - Targeted treatments → Venetoclax
  - BM transplant



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Acute myeloid leukemia (AML)

- Cancer of the blood and bone marrow (BM)
- Most common form of leukemia
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- The European Leukemia Net (ELN) 2022

  NPM1 mutation as critical marker for risk stratification and guiding treatment decisions.

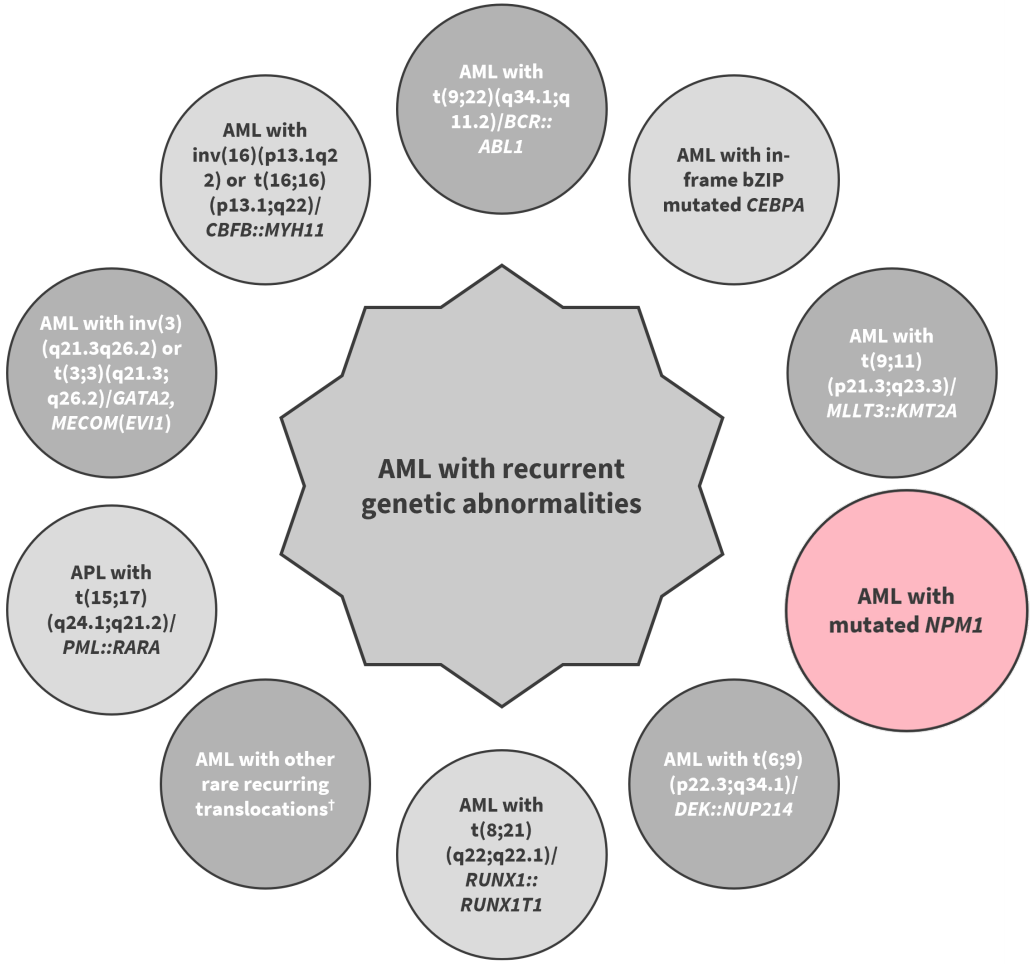
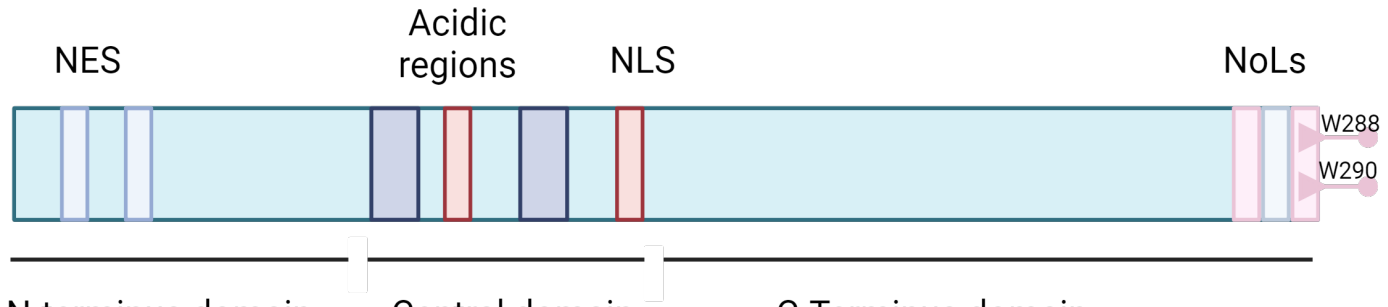


Image Source: AML Hub, 2022. Retrieved from AML Hub.

Nucleophosmin 1 (NPM1)

- Nucleus-cytoplasmic shuttling protein
  - Nucleolar localization



Modified from Zarka et al., 2020.
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Nucleophosmin 1 (NPM1)

- Nucleus-cytoplasmic shuttling protein
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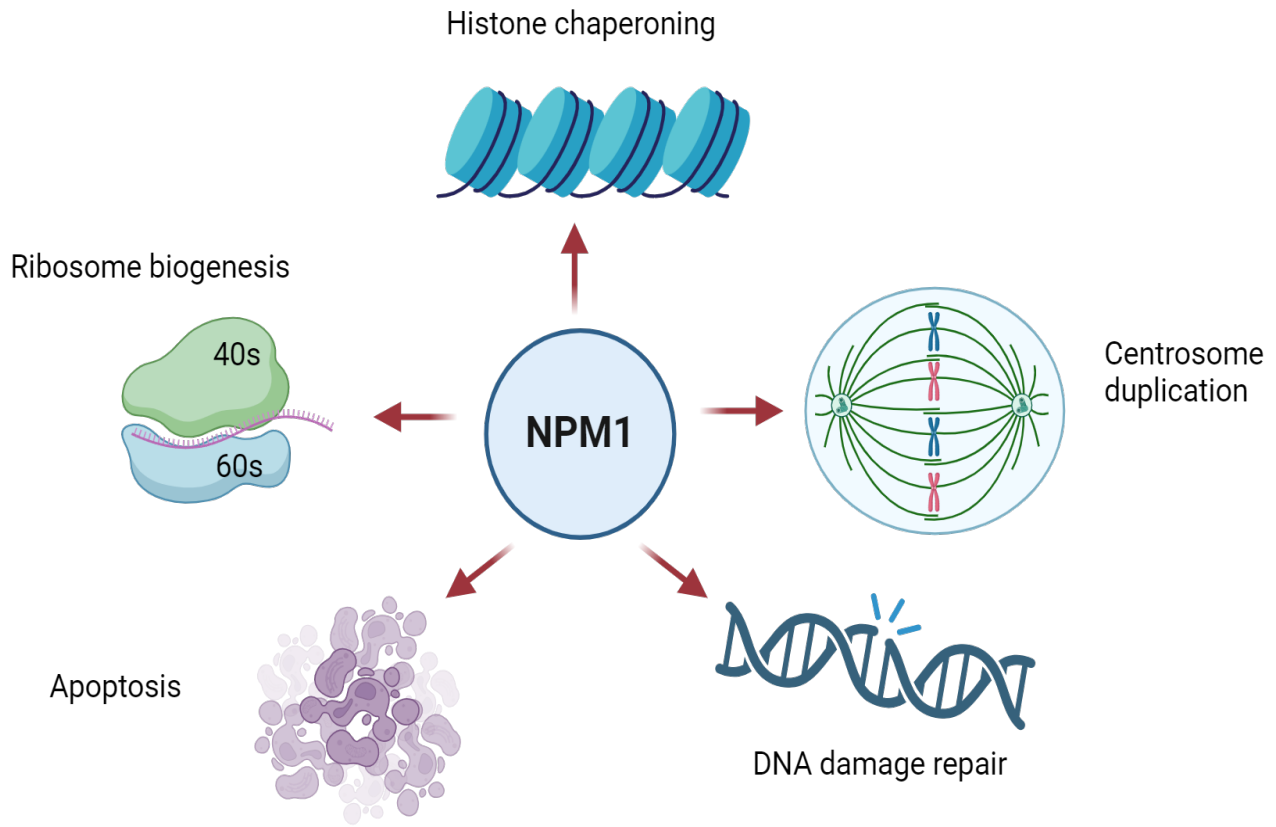
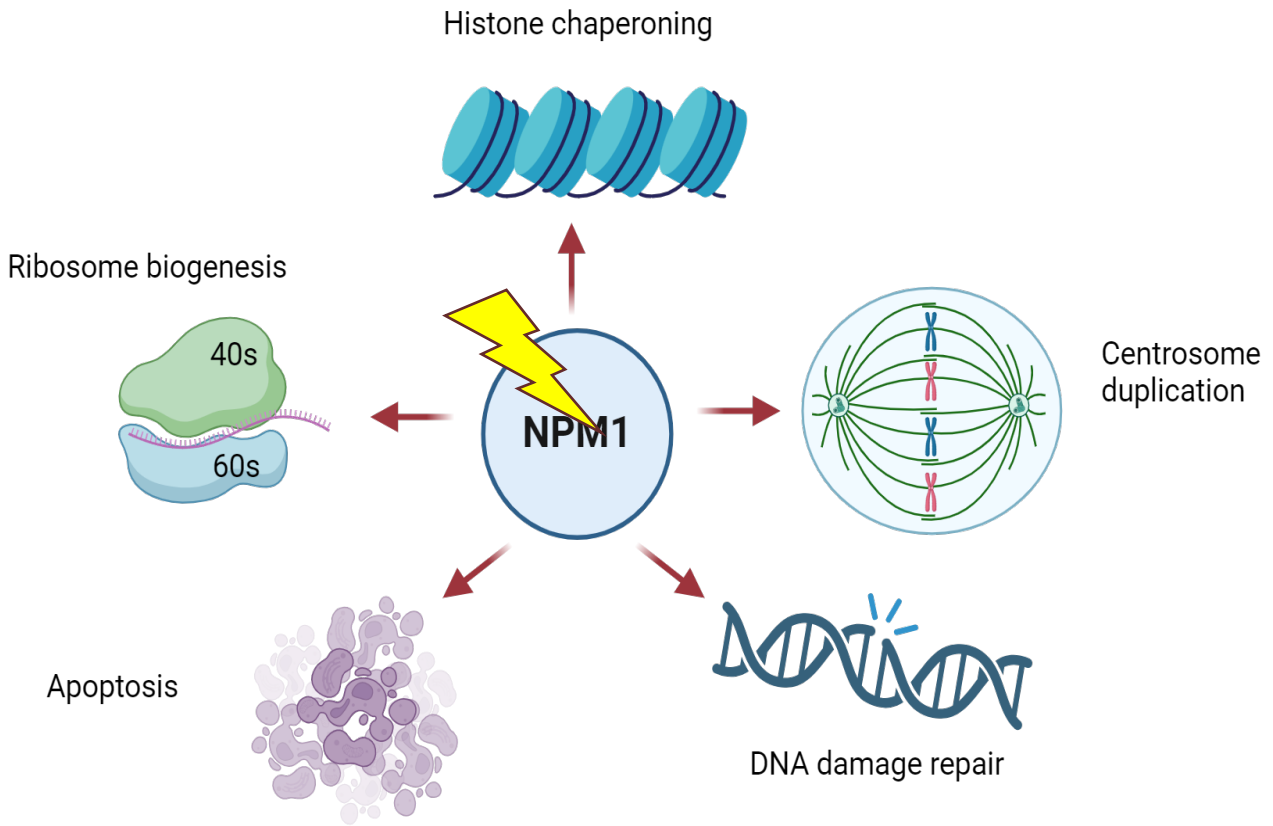
- Multifunctional protein with critical roles for normal cell proliferation and survival



Modified from Brunetti et al., 2019.
Created with BioRender

Nucleophosmin 1 (NPM1)

- Nucleus-cytoplasmic shuttling protein
  - Nucleolar localization
- Multifunctional protein with critical roles for normal cell proliferation and survival
- Dysregulation can contribute to cancer development



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NPM1 in AML (*NPM1* mut)

- Most common AML genetic alteration

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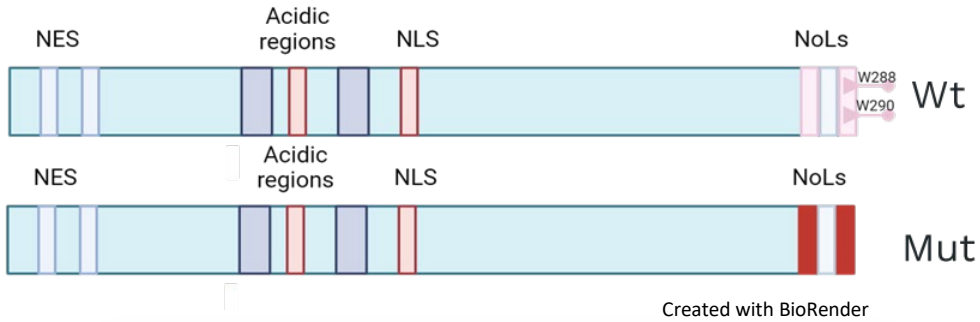

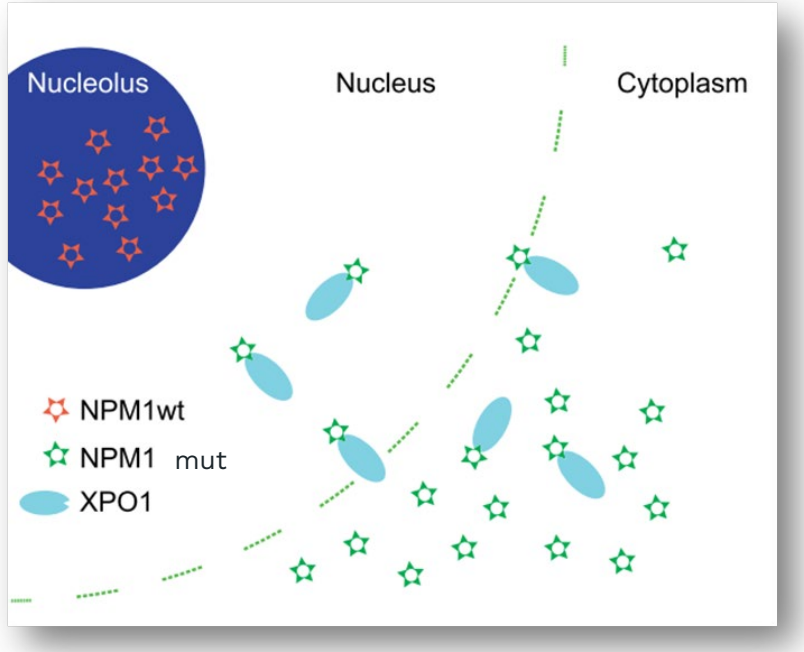

Modified from Brunetti et al., 2019.

eha Sf(PM)

NPM1 in AML (*NPM1* mut)

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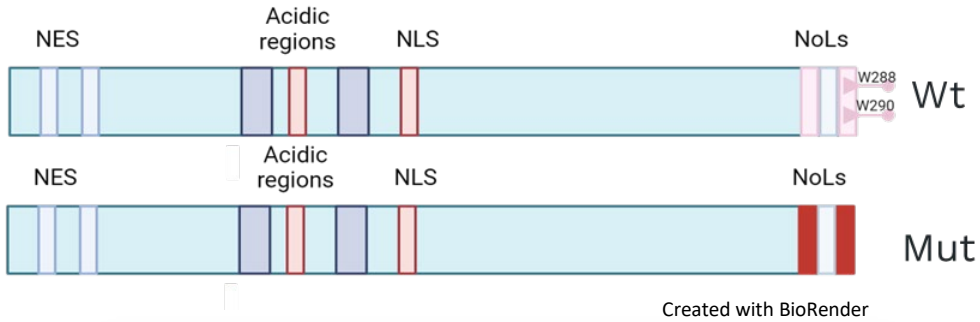
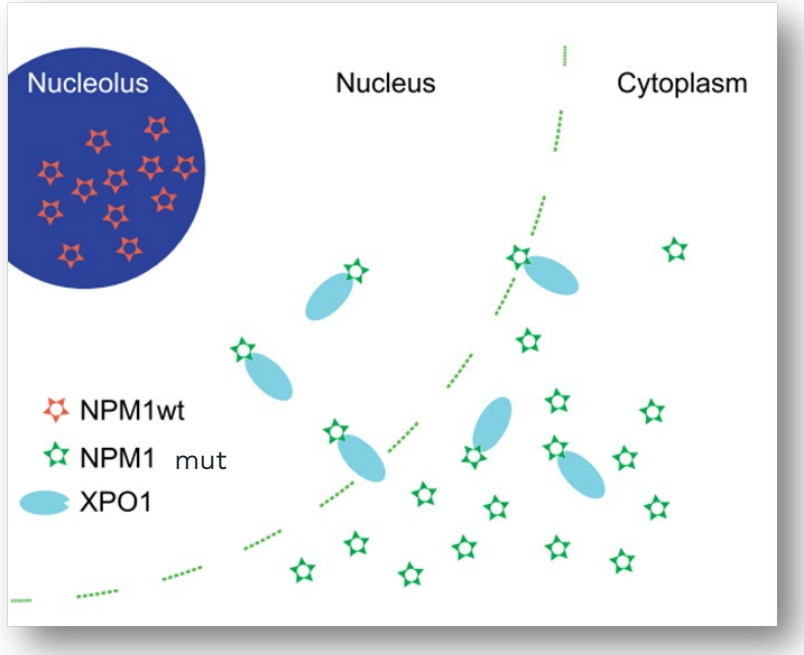
- Frameshift mutation at the C-terminus domain
  - Aberrant cytoplasmatic localization



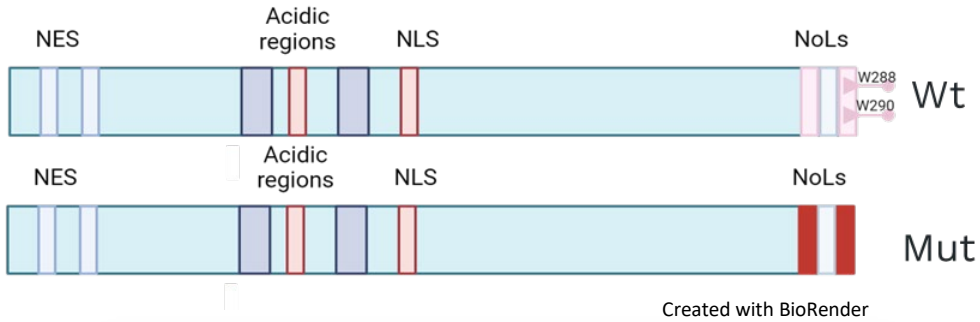


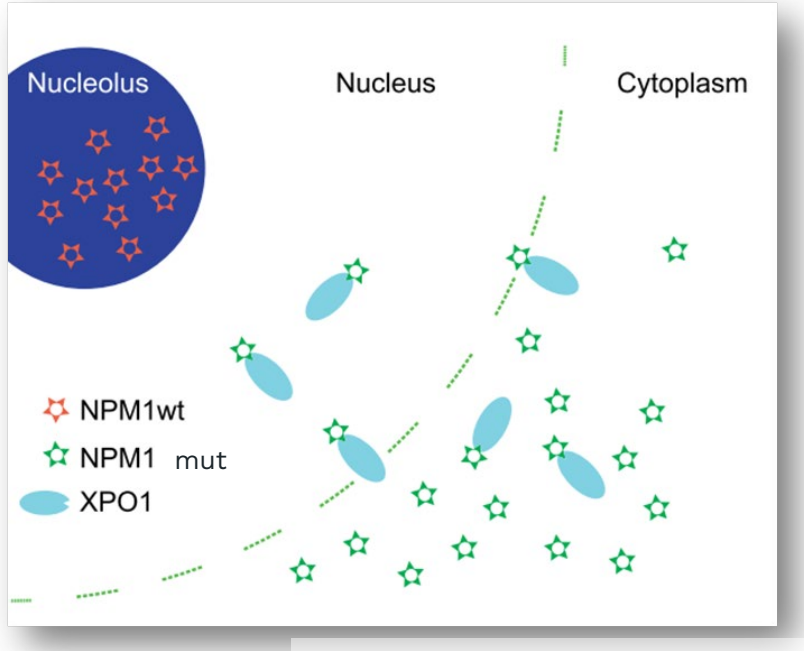
Modified from Brunetti et al., 2019.

eha Sf(PM)

NPM1 in AML (*NPM1* mut)

- Most common AML genetic alteration
- Frameshift mutation at the C-terminus domain
  - Aberrant cytoplasmic localization
- Associated with increased *HOX* genes expression





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eha Sf(PM)

NPM1 in AML (*NPM1* mut)

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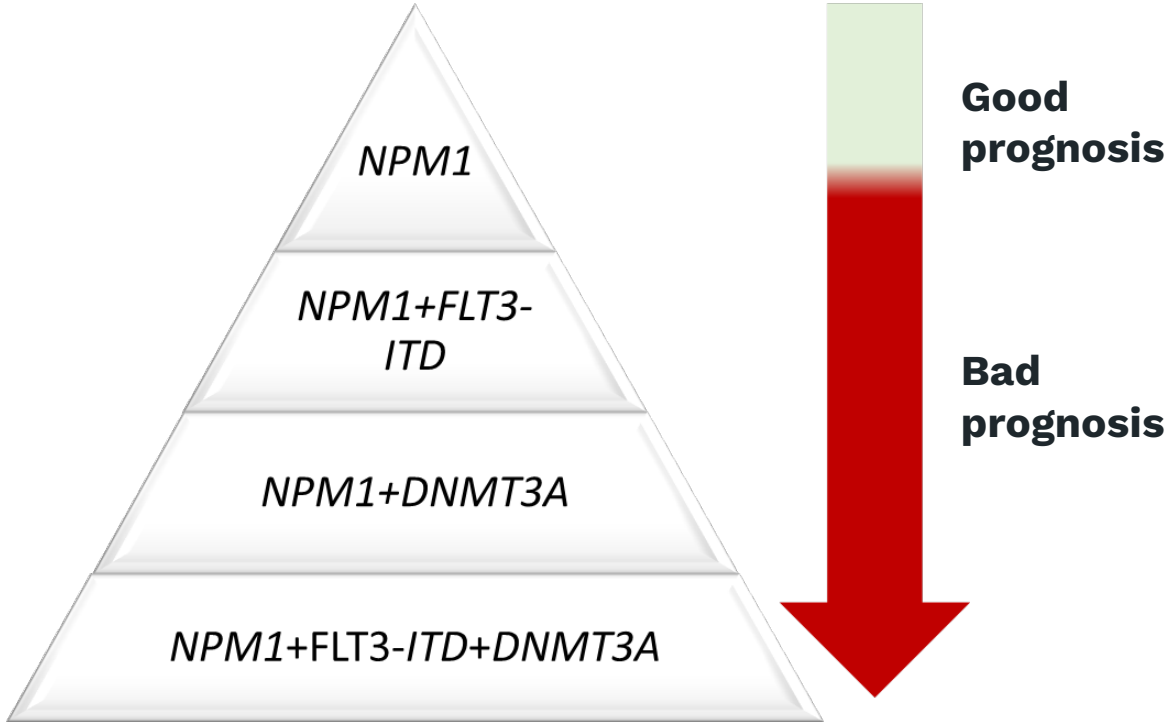
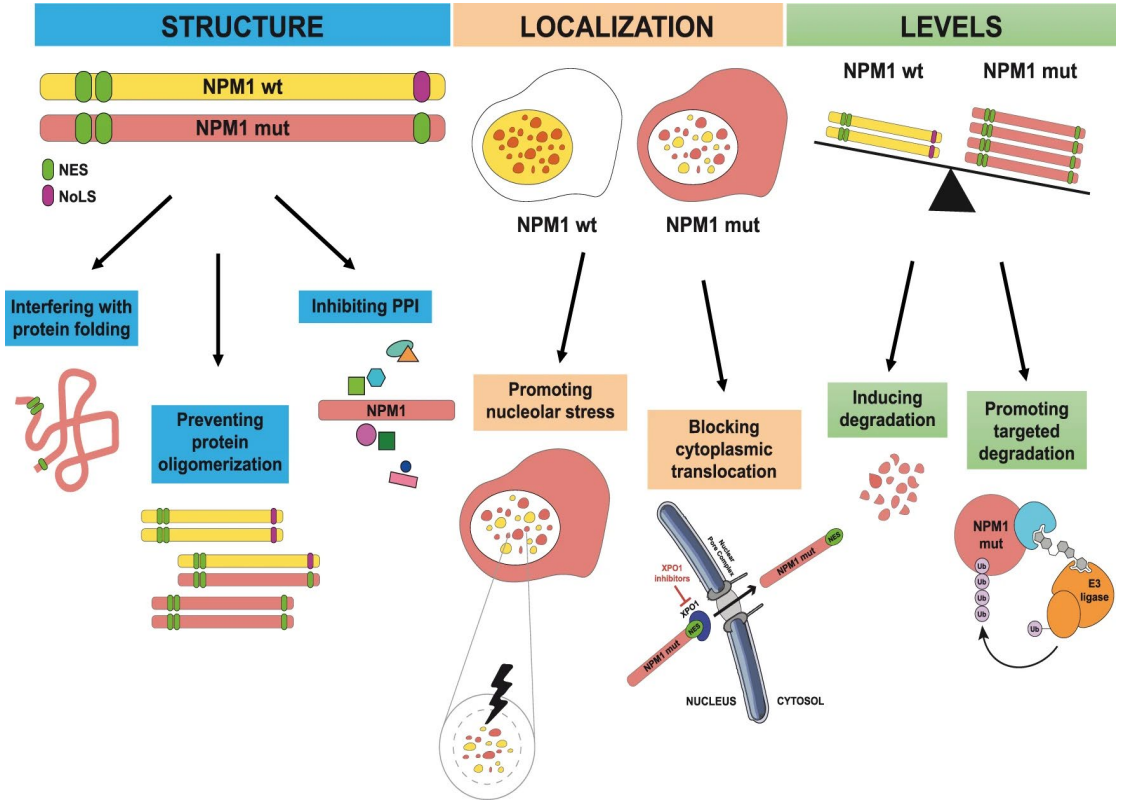
- Often co-mutated with *FLT3-ITD* and/or *DNMT3A*



NPM1 in AML (*NPM1* mut)

- Most common AML genetic alteration
- Frameshift mutation at the C-terminus domain:
  - Aberrant cytoplasmatic localization
- Associated with increased *HOX* genes expression
- Often co-mutated with *FLT3-ITD* and/or *DNMT3A*
- Treatment:
  - Standard therapy → High relapse rates
  - The heterogeneity of *NPM1* mut confers different treatment strategies



Ranieri et al., 2020.

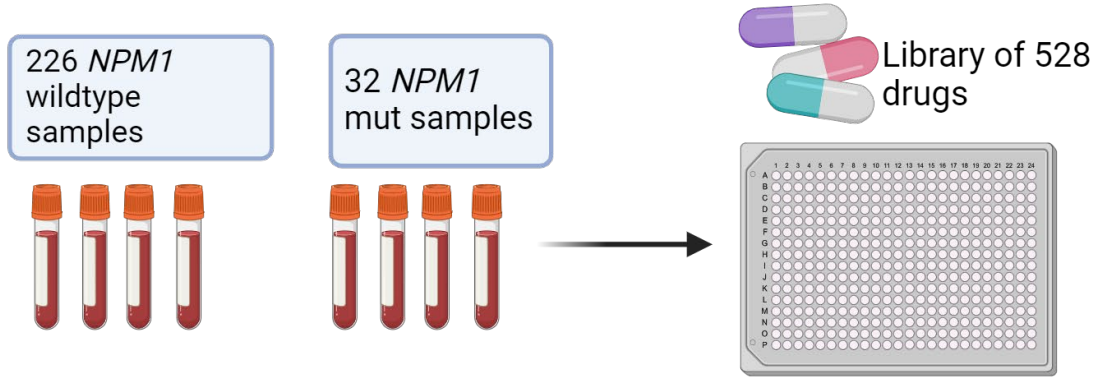
Project background

226 *NPM1* wildtype samples

32 *NPM1* mut samples

Peripheral blood/Bone marrow samples from patients

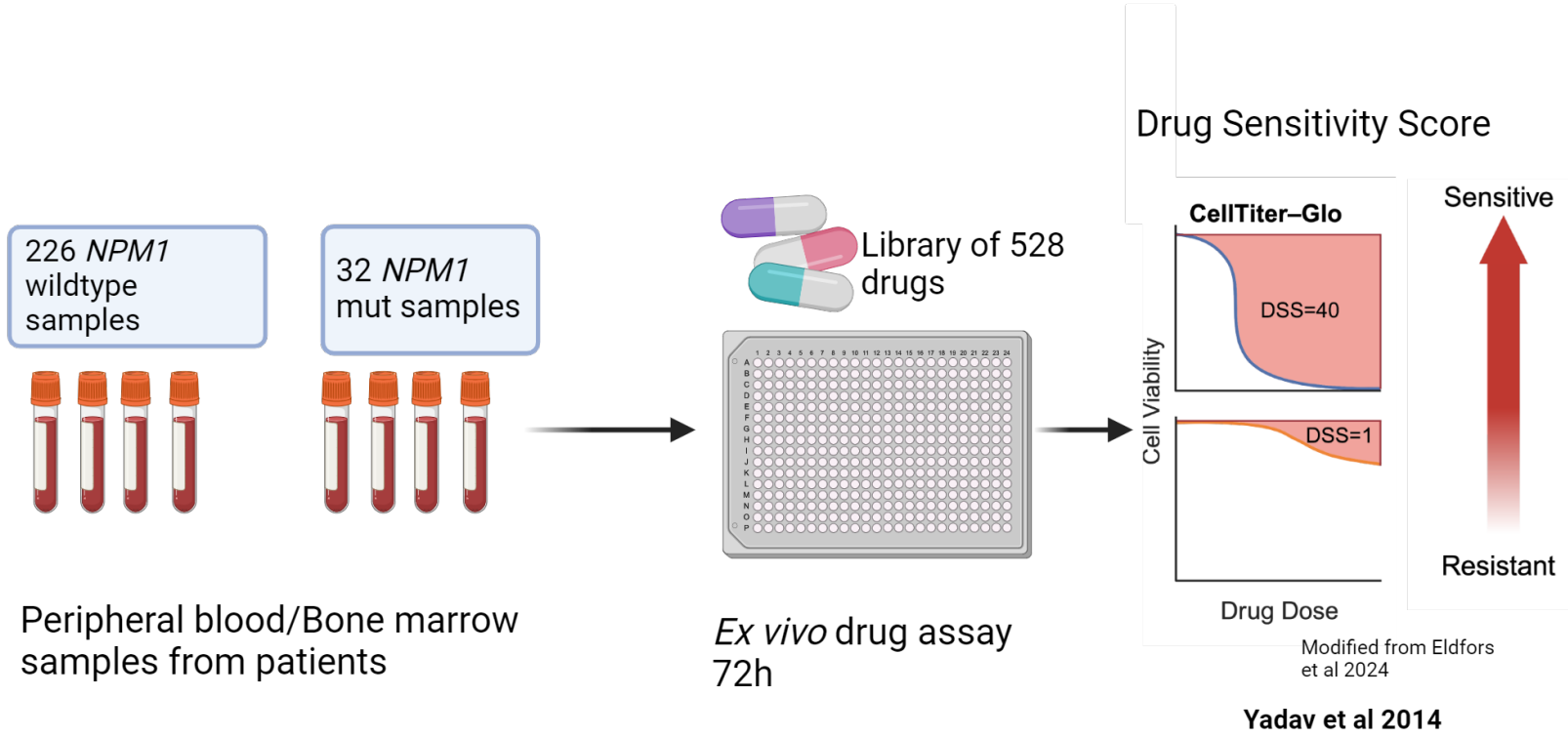
Project background



Peripheral blood/Bone marrow samples from patients

Ex vivo drug assay 72h

Project background



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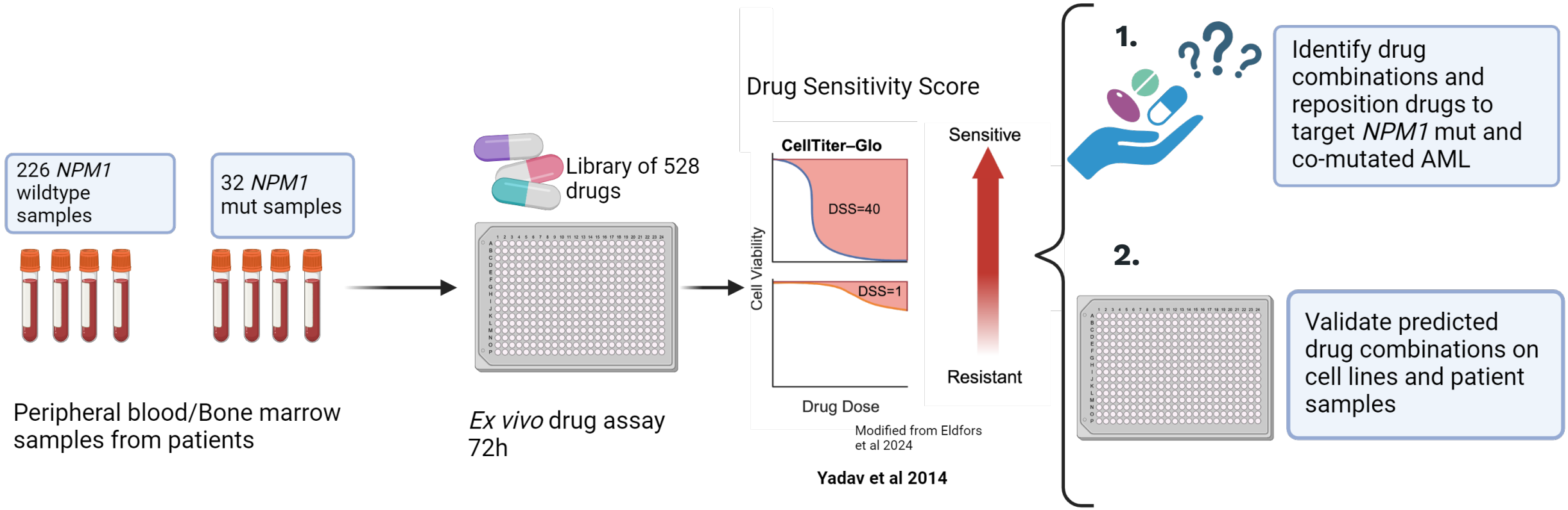
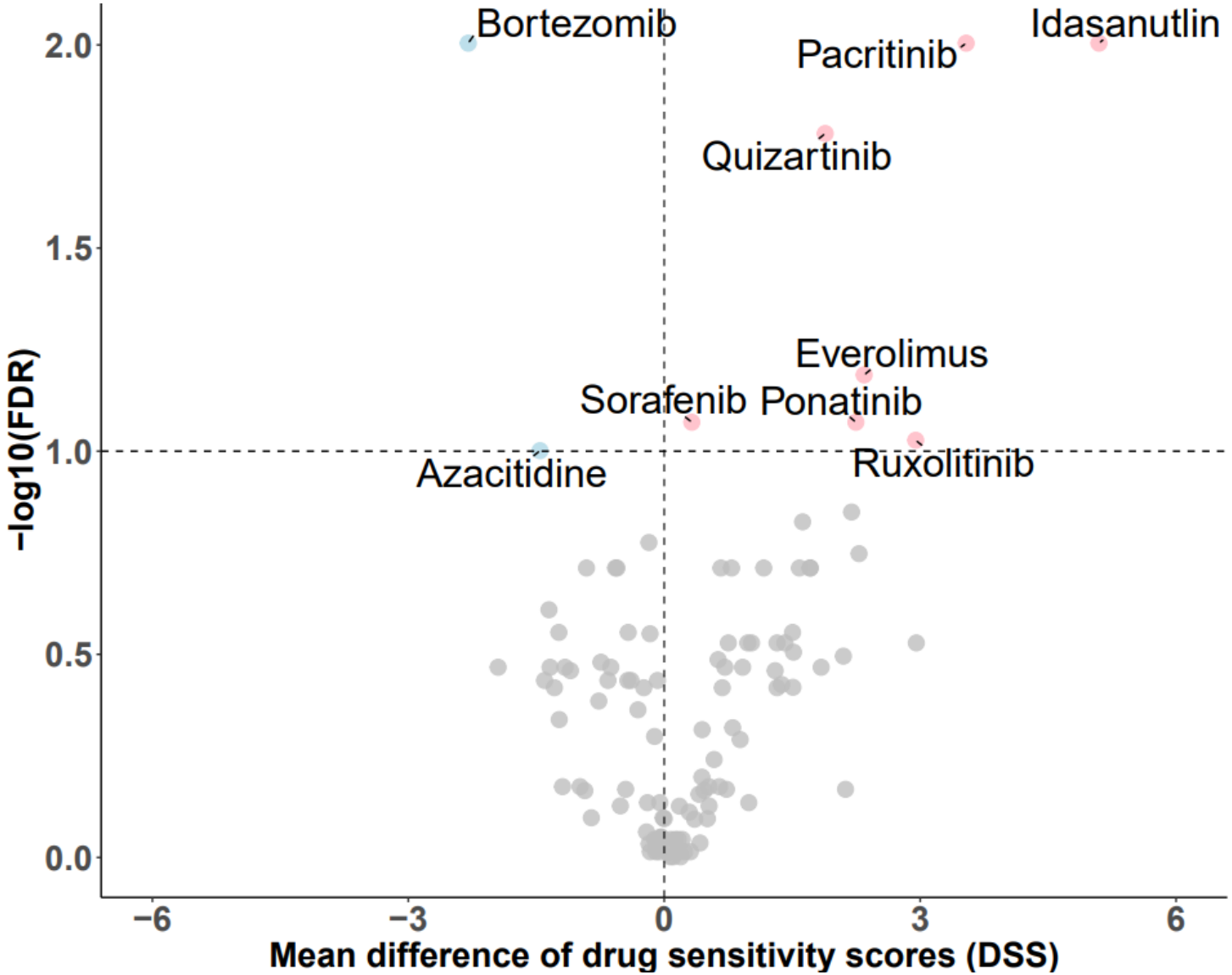


NPM1 mut samples exhibited increased sensitivity to pacritinib

Less sensitive in *NPM1* mut samples ← → More sensitive in *NPM1* mut samples



Unpublished data. Do not post

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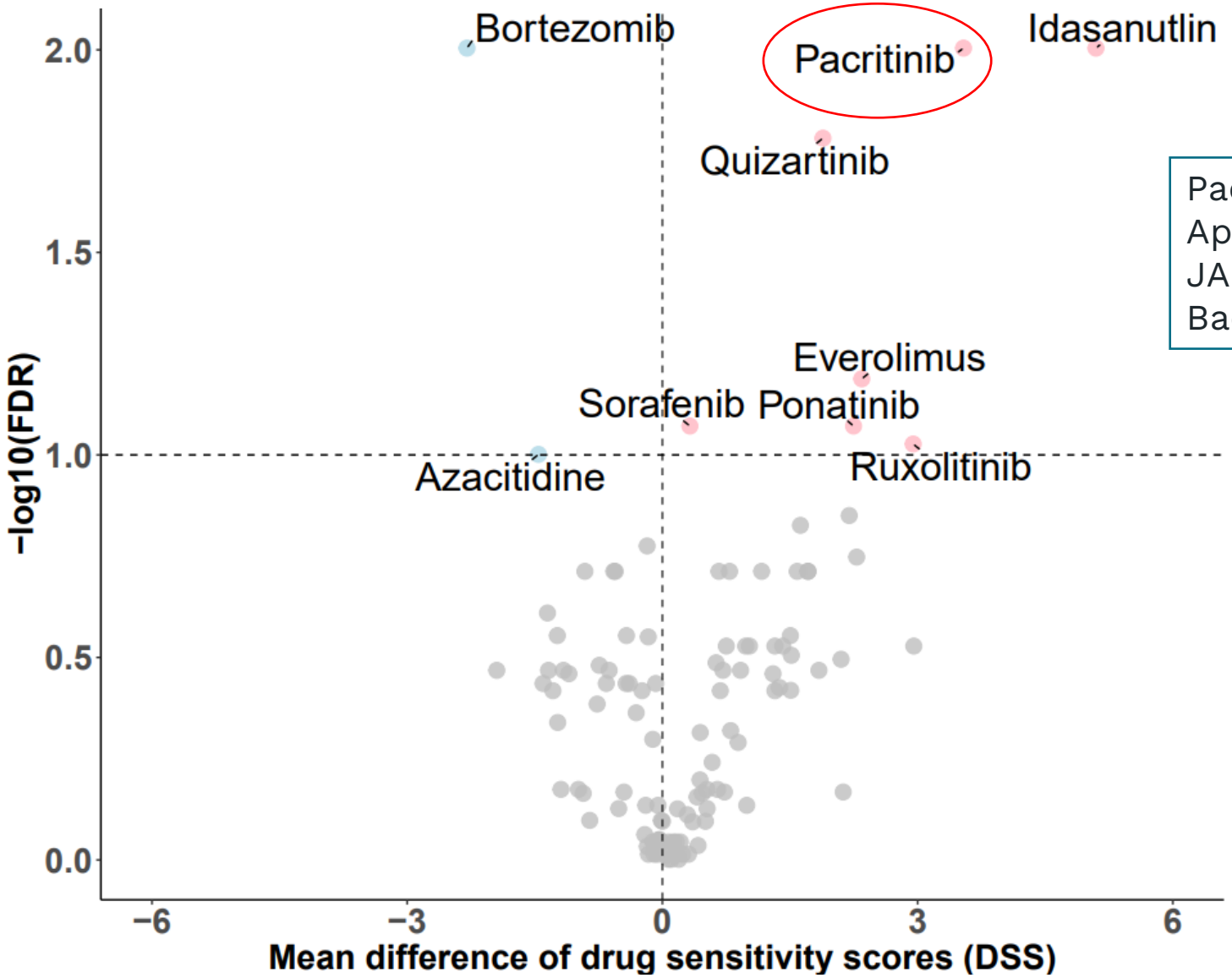
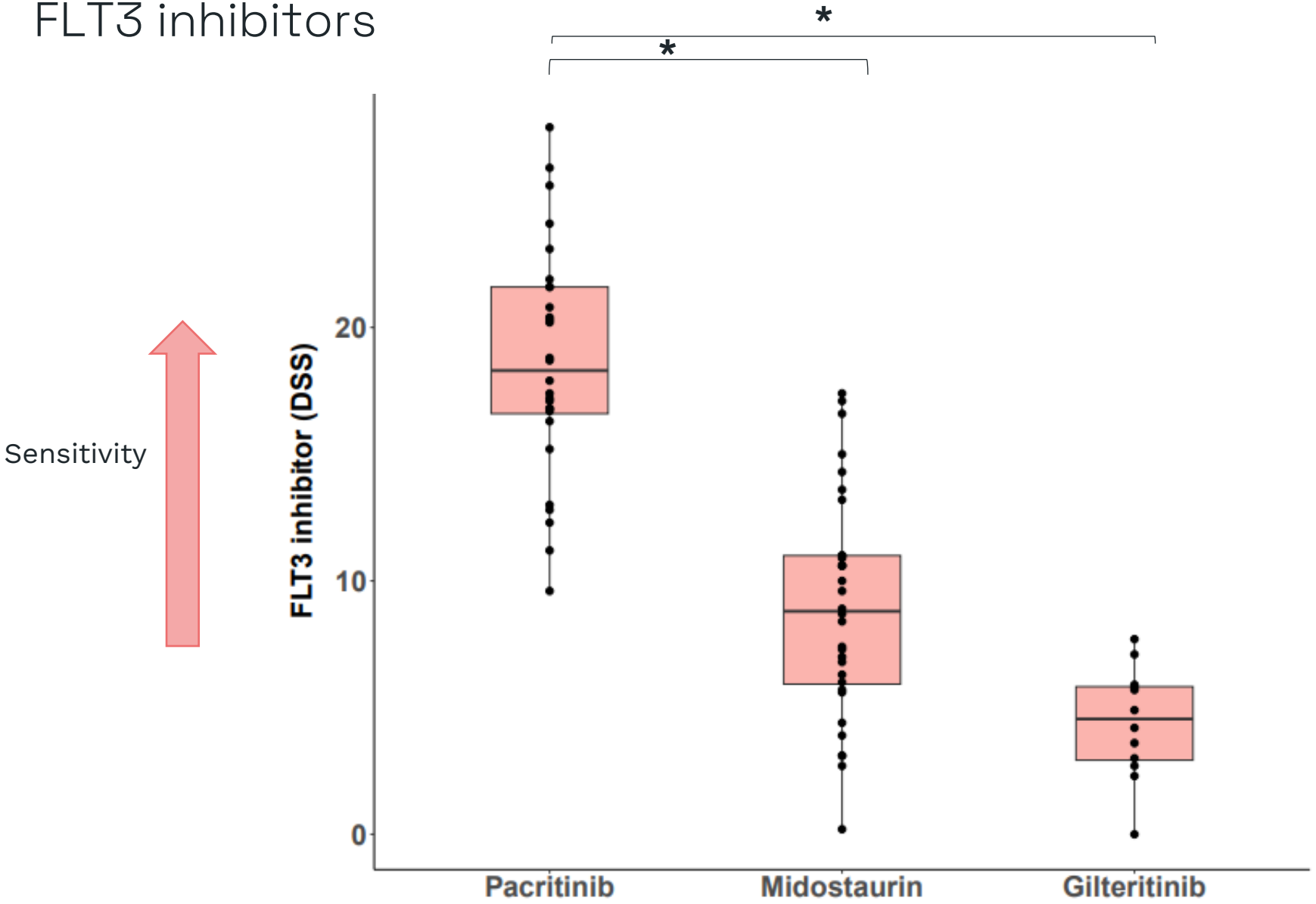


Pacritinib:
Approved for myelofibrosis
JAK2 and FLT3 inhibitor
Background in *FLT3* mutated AML

Unpublished data. Do not post

Pacritinib showed higher efficacy in *NPM1* mut samples than conventional FLT3 inhibitors

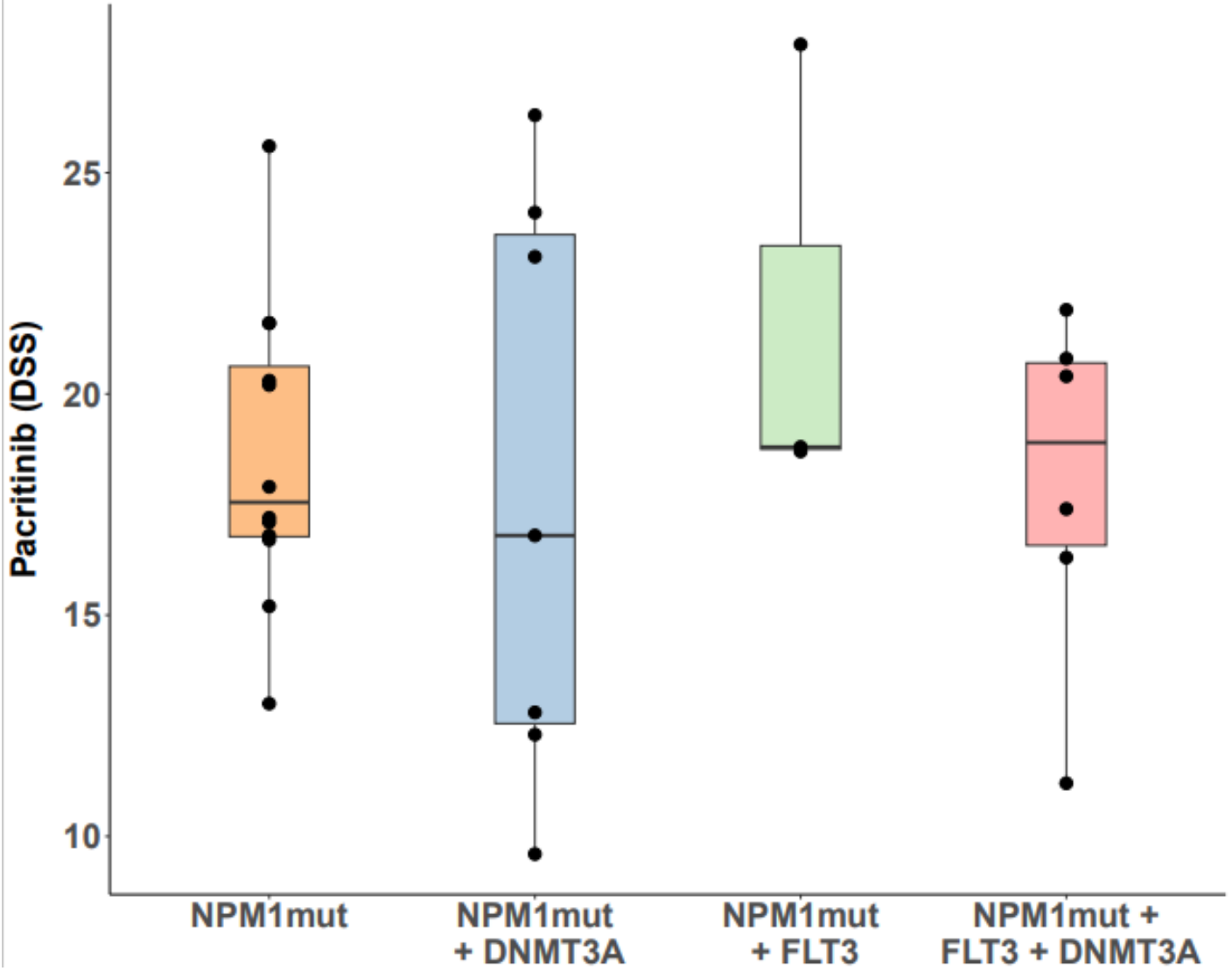


FIMM cohort → 32 samples with *NPM1* mut
ANOVA p ≤ 0.05

Unpublished data. Do not post

The efficacy of pacritinib did not yield any significance among *NPM1* co-mutated samples.

Sensitivity



FIMM cohort → 32 samples with *NPM1* mut
ANOVA p > 0.05

Unpublished data. Do not post

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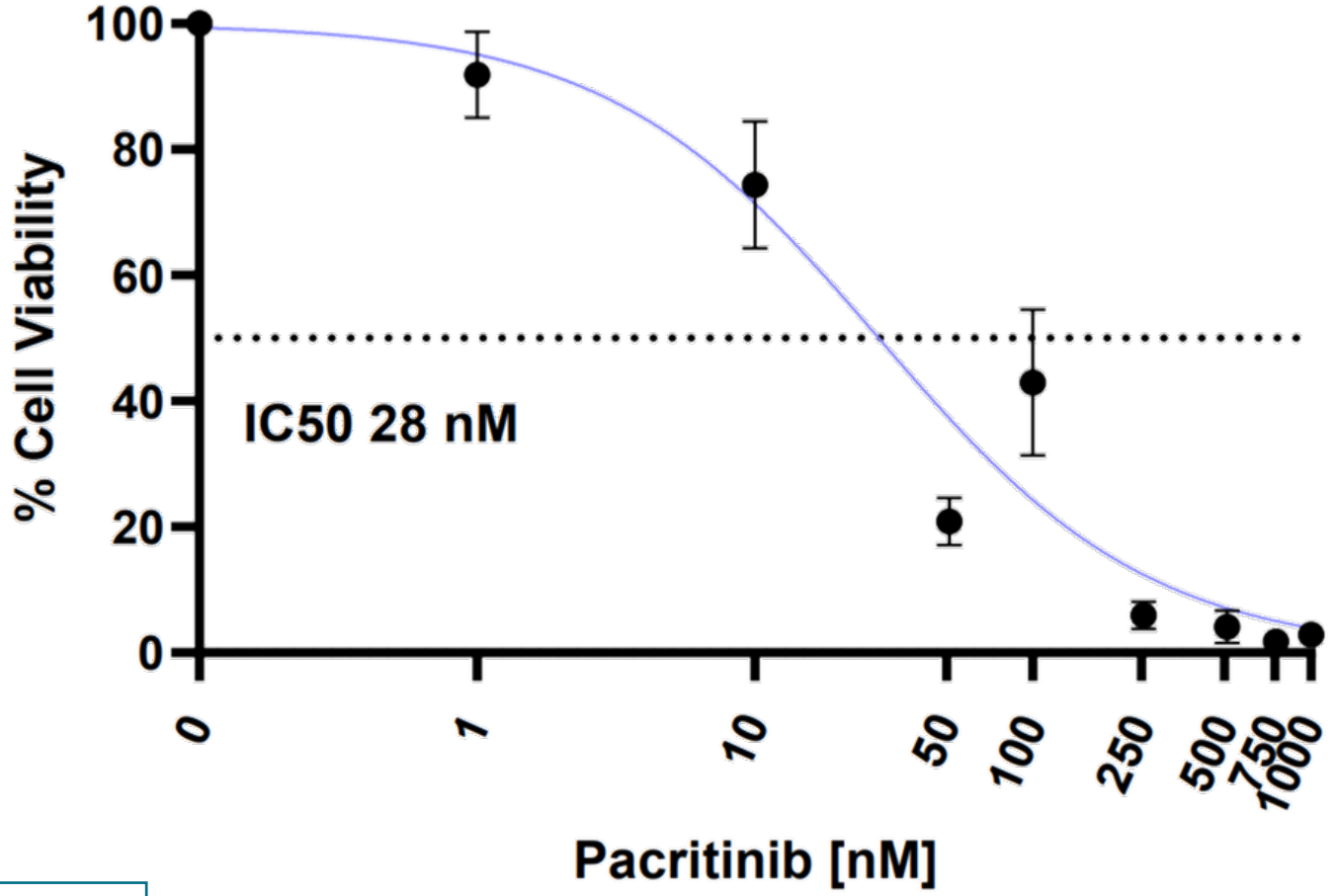
AML *NPM1* mut+ *FLT3-ITD*+ *DNMT3A* mouse cell line is sensitive to pacritinib



N = 4

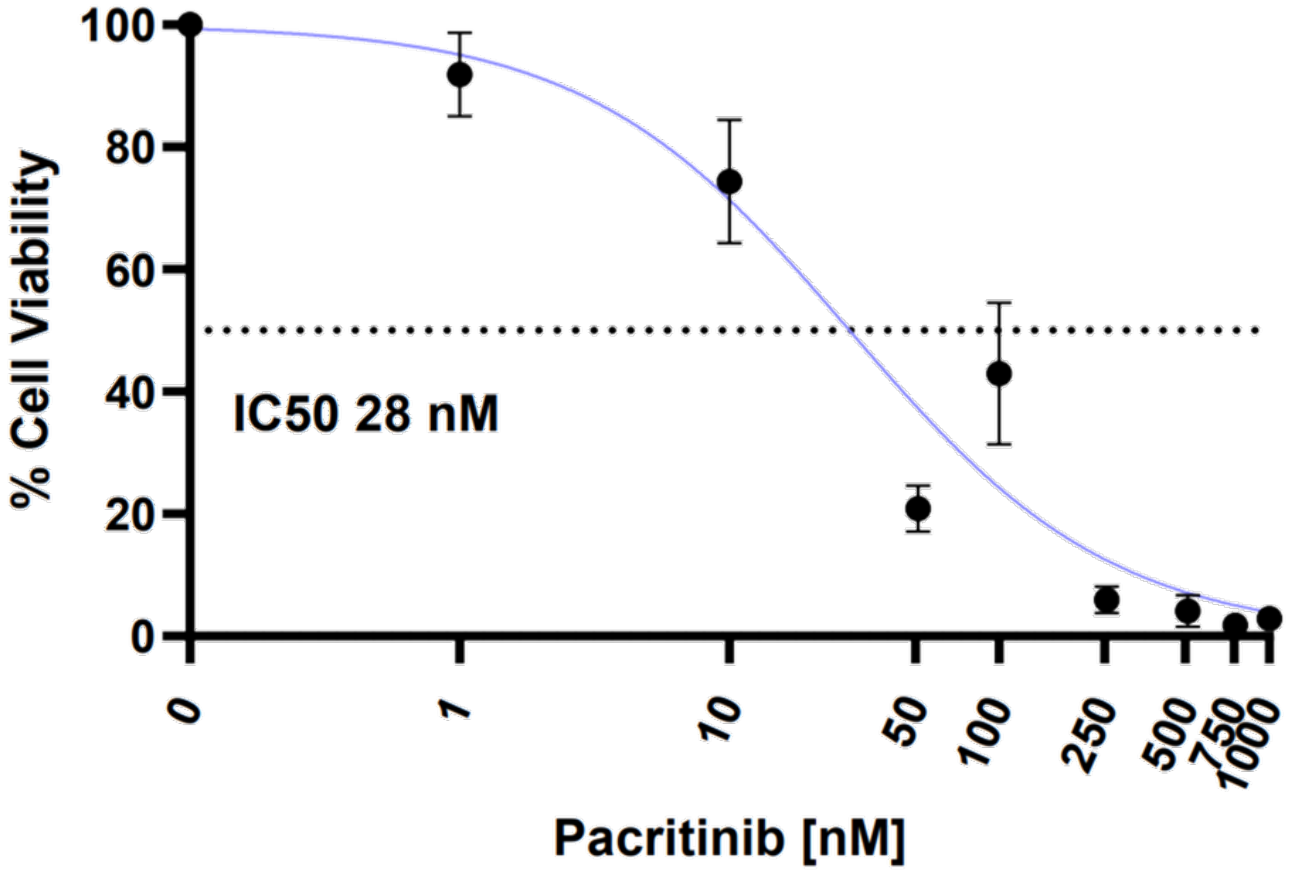
Dr. Kasper Rasmussen

AML mouse model with humanized mutations in *NPM1, FLT3* and *DNMT3A*.

Unpublished data. Do not post

Pacritinib + venetoclax synergizes to induce cell death at low concentrations in AML

NPM1 mut+ *FLT3-ITD*+ *DNMT3A*



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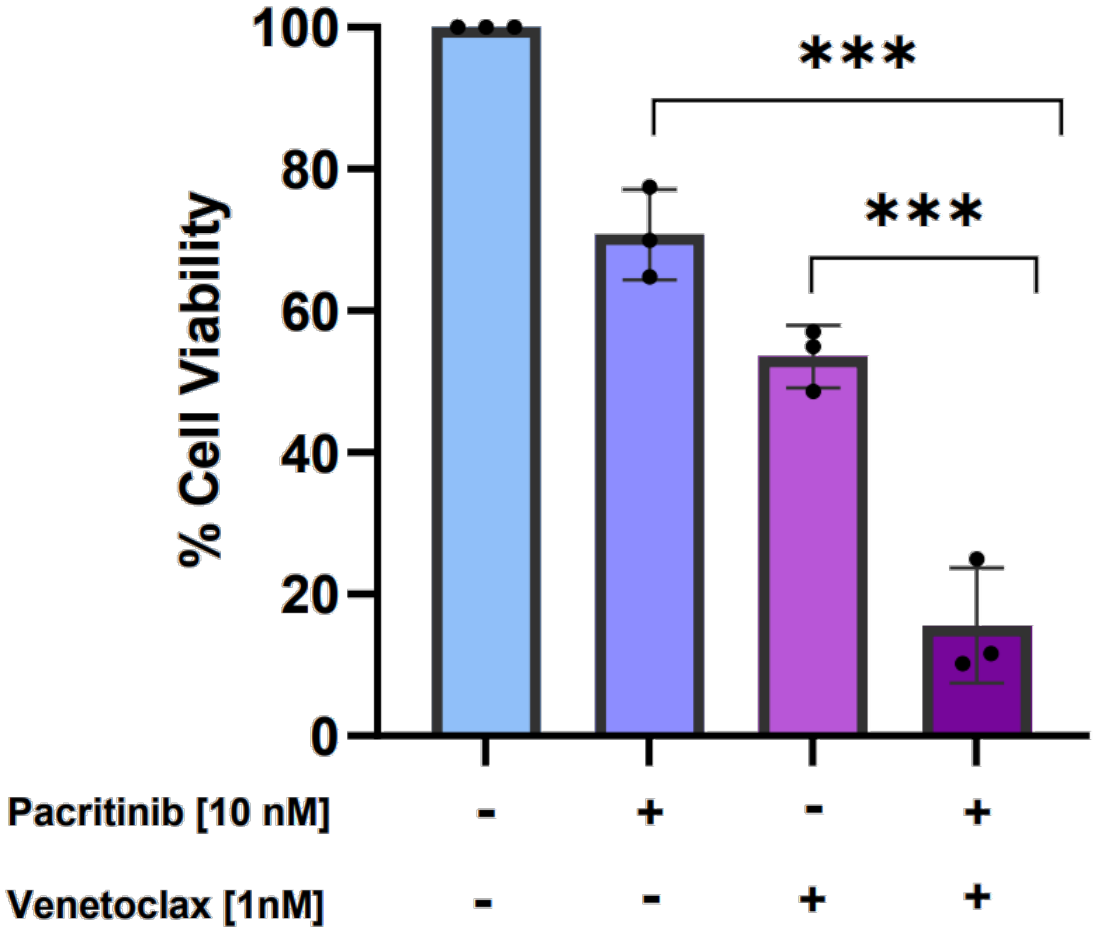


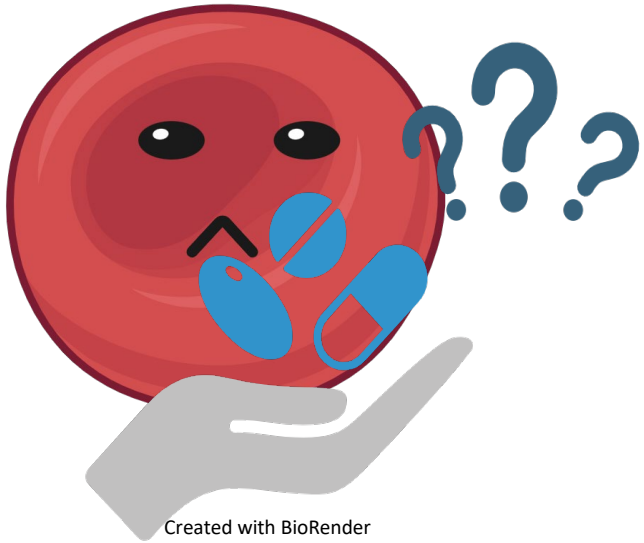
N = 3

ANOVA p ≤ 0.05

Unpublished data. Do not post

Conclusions and future perspectives

- Pacritinib shows superior activity in *NPM1* mut AML samples comparted to other FLT3 inhibitors, with efficacy independent of the co-mutations.
- It effectively induces cell death in *NPM1* triple mutant (*FLT3-ITD* + *DNMT3A*) at a relatively low doses
- The combination of pacritinib with venetoclax enhances its therapeutic effect
- Currently validating the results on *NPM1* mut + *FLT3-ITD*
- Further validation on patients' samples



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Nordic EMBL Partnership for Molecular Medicine
HiLIFE UNIT

UNIVERSITY OF HELSINKI

iCAN Digital Precision Cancer Medicine

Research Council of Finland

Syöpäsäätiö
Cancer Foundation Finland

Juselius Sigrid Stiftelse

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