Combined targeting of distinct c-Myc and JunB transcriptional programs induces synergistic anti-myeloma activity
<table>
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<th>Disclosures</th>
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<td>1. Employment or Leadership Position</td>
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Background

Transcription Factors in MM

- Proliferation
- Drug-resistance
- Survival
- Secretion

Angiogenic factors

Secretion
- IL-6
- SDF-1α, HGF, TNF-β, TNF-α, TGF-β...

Angiogenesis
- EC migration
- Tubuli formation

Adhesion

JunB target genes

ERK JNK NFkB

JunB

Podar K, Chauhan D, Anderson KC. Leukemia. 2009; 23:10–24
Atsaves V, et al. Cancers 2019, 11, 1037
Q1: Anti-MM effects of c-Myc inhibition?

Q2: Anti-MM effects of c-Myc inhibition on JunB?

Q3: Anti-MM effects of JunB inhibition on c-Myc?

Q4: Anti-MM effects of combined inhibition of c-Myc and JunB?
Importance of Transcription Factors in MM

**Background**

- **cMyc**: Gene expression suggesting potential regulatory roles in MM.

**Aims**

- **CoMMpass** (n=908)
  - cMyc mRNA level vs. JunB mRNA level
  - BRD4 mRNA level vs. JunB mRNA level

**Results**

- **CoMMpass** (n=908)
  - cMyc mRNA level (10^3)
  - JunB mRNA level (10^3)

- **NDMM** (n=73)
  - cMyc mRNA level (10^3)
  - JunB mRNA level (10^3)

- **GSE2658** (n=559)
  - cMyc mRNA level (10^3)
  - JunB mRNA level (10^3)

**Conclusion**

- MAAP2K2 transcription factor levels in MM context.
- CoMMpass dataset analysis indicates significant correlations.
- GSE2658 dataset further validates the findings.

*Images depict scatter plots and linear regression analyses for gene expression patterns in MM.*
Independent expression of c-Myc and JunB

**Results**

**A**

- **qPCR:**
  - Rel. mRNA levels
  - JunB (fold change)
  - siMyc: - - + +
  - IL-6: - + - +

- **Bolt:**
  - c-Myc
  - JunB
  - ERK2
  - siMyc: - - + +
  - IL-6: - + - +

**B**

- **qPCR:**
  - Rel. mRNA levels
  - c-Myc (fold change)
  - Dox: - - + +
  - IL-6: - + - +

- **Bolt:**
  - c-Myc
  - JunB
  - ERK2
  - Dox: - - + +
  - IL-6: - + - +
No impact of c-Myc inhibition on JunB levels by MZ-1

Aims

Results

Conclusion

Background

Aims

Results

Conclusion
Knockdown of JunB has no effect on c-Myc levels
Anti-MM effects of combined c-Myc/JunB inhibition

A

TetshJunB/MM.1S

- Dox+IL-6
+ Dox+IL-6

Cell proliferation [% of untreated control]

MZ-1[nM] 0 40 80 120
Control 100 250

B

Dox
NCI H929
U266

150
100
50
0

Cell viability [% of untreated control]

IL-6 + + + + + + +
siJunB − + − + − + +
MZ-1 − − + − + + +
No impact on c-Myc levels by MEK-Inhibitor-Trametinib

**Background**
- mRNA expression JunB
- IC50 Trametinib [µM]

**Aims**

**Results**
- No impact on c-Myc levels by MEK-Inhibitor-Trametinib

**Conclusion**
- Trametinib
- Combi
- Dox or Tra

**Images**

- A: Graph showing mRNA expression JunB
  - MM.1S
  - U266
  - NCI H929
  - OPM-2

- B: Bar chart showing relative luciferase activity
  - TetshJunB/MM.1S
  - IL-6
  - IL-6 + TRA
  - IL-6 + TRA + MZ-1
  - IL-6 + MZ-1

- C: Bar chart showing relative luciferase activity
  - TetshJunB/MM.1S
  - IL-6
  - IL-6 + TRA
  - IL-6 + TRA + MZ-1
  - IL-6 + MZ-1

- D: Scatter plots for different cell lines

- E: Diagram showing treatment combinations
Distinct c-Myc and JunB transcriptional programs: Rationale for combined targeting of TF in MM
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