Therapeutic impact of BET inhibition on immune cell death checkpoints in MPN

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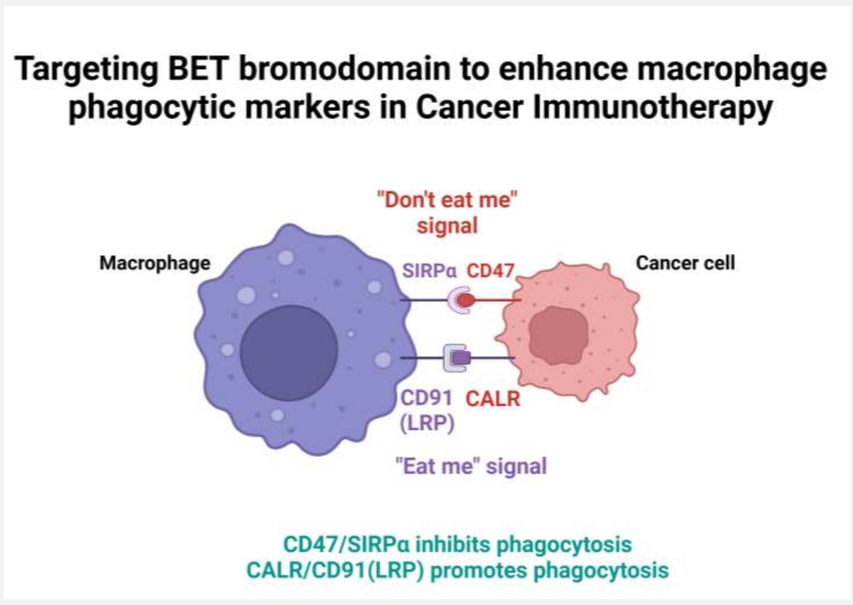
Current Challenges in MPN & Targeting CD47 to Enhance Treatment Outcomes

- Myeloproliferative neoplasms (MPNs) are hematological cancers involving excessive bone marrow cells proliferation, with the potential to progress into acute myeloid leukemia (AML).
- Current treatments like Azacytidine & Ruxolitinib offer varied success rates, underscoring the need for better therapies, particularly targeting immune evasion mechanisms such as the CD47/CALR pathway.
- CD47 expressed on cancer cells acts as a "don't eat me" signal & inhibits macrophage-mediated phagocytosis. In contrast, Calreticulin (CALR) functions as an "eat me" signal that promotes programmed cell of cancerous cells via phagocytosis.

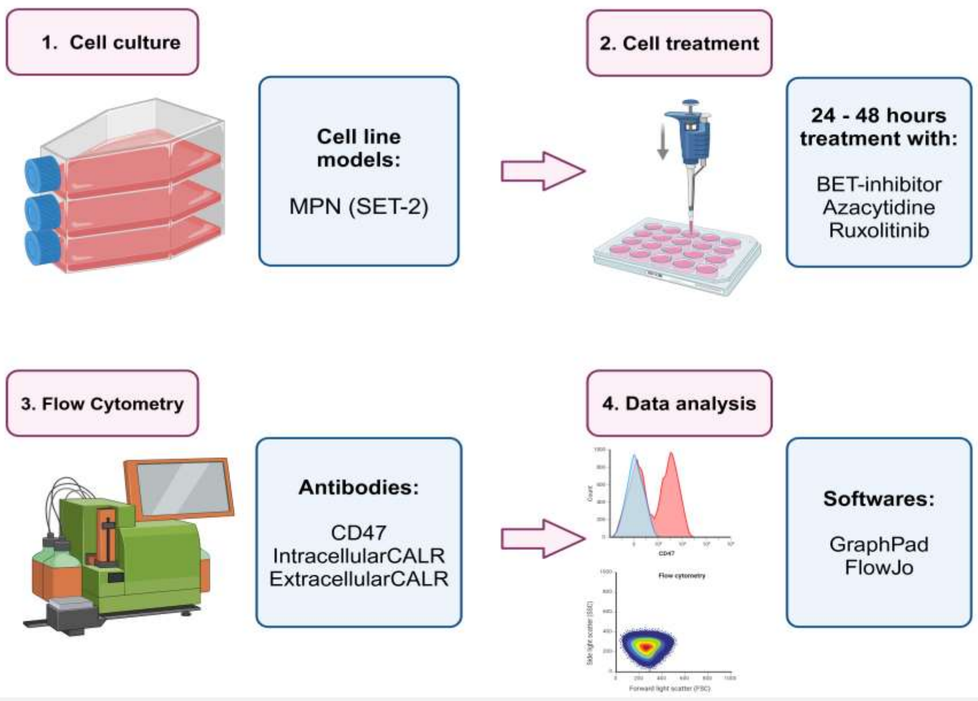


- Emerging therapies, such as Bromodomain & extra terminal (BET) inhibitors, focus on targeting cancer proliferation and immune surveillance pathways (e.g., CD47/CALR), offer promising new directions in cancer immunotherapy.

Aim

To determining the impact of BET inhibitors, by themselves, or in combination with standard therapies on CD47/CALR signalling and cellular death in a cell line models of MPN

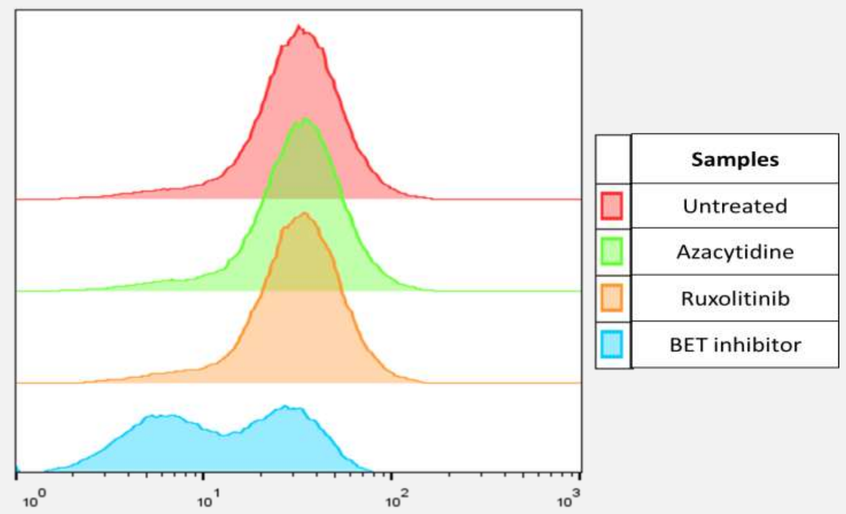
Methods



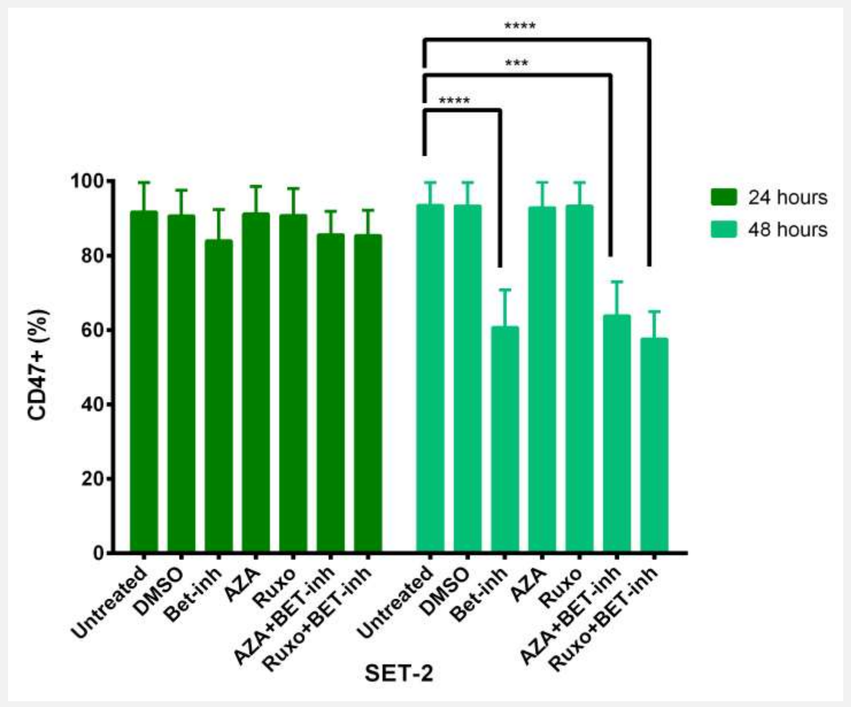
References
1- Weiskopf K. European journal of cancer. 2017;76:100-9.
2- Chao MP.; Ash A. Alizadeh; Chad Tang. Cancer Research. 2011;71(4):1374-84.
3- Cencini E.; Alberto Fabbri; Anna Sicuranza. Cancers. 2021;13(14):3597.

Anti-phagocytic CD47 expression decreases in presence of BET Inhibition

- Presence of BET inhibitor alone reduced CD47 expression on SET-2 cells from 94% in untreated samples to 61% after 48 hours treatment ($p<0.0001$).

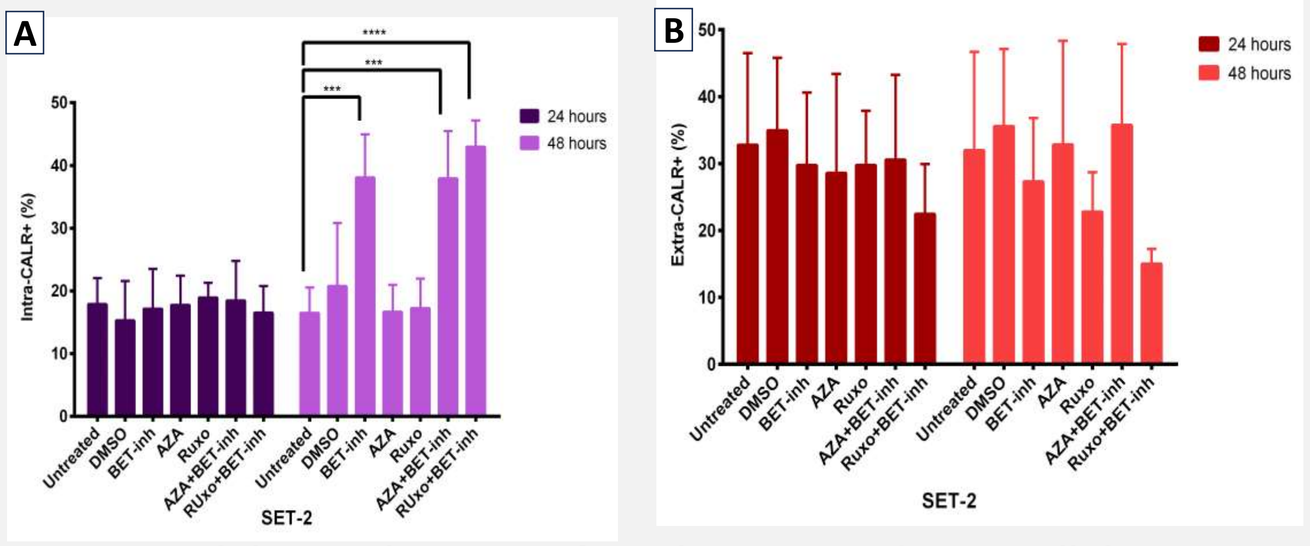


- Combination treatment with BET inhibitors & Ruxolitinib decreased CD47 expression from 94% to 58% on the SET-2 cell line ($p<0.0001$).



* $p<0.05$, ** $p<0.01$, ***$p<0.001$, ****$p<0.0001$. Data from n=3 experiments.

BET Inhibition leads to increased Intracellular CALR expression in MPN



- BET inhibitor alone significantly increased intracellular CALR levels from 17% to 38% ($p<0.001$) on SET-2. The combination of BET inhibitors with Ruxolitinib further elevated CALR levels to 43% ($p<0.0001$)(Figure A).
- In contrast, BET inhibitor monotherapy slightly reduced extracellular CALR levels from 32% in untreated control to 27% after 48 hours. Combination with Ruxolitinib further decreased CALR to 15%, however none of these decreases were statistically significant ($p=0.09$-0.06, respectively).

Discussion

- BET inhibitors significantly impact immune surveillance in MPN cells by decreasing anti-phagocytic CD47 levels.
- This suggests BET inhibitors have potential as a therapeutic strategy for MPN immunotherapy.
- Future studies will assess cancer cell phagocytosis markers in the presence of macrophages to explore BET inhibitors' role in boosting anti-cancer immune responses.