Background

- AML has been shown to be highly dependent on the expression BCL protein family
- BCL-2 inhibition has been shown to be a potent modality in AML treatment
- Thrombocytopenia in myelodysplastic syndromes range from 40-65%
- AML has a 30% 5-year prognosis
- 753B is a novel PROTAC bioengineered to degrade the BCL family, specifically BCL2 and BCLXL
- Coincidentally, 753B should have a greater affinity for targeting AML cells specifically over other normal cell types, avoiding thrombocytopenia

Methods

We treated various AML cell lines in vitro to observe the effects of introduction to 753B. We used the BioRad Western Blot system to observe the levels of protein expression degradation as different concentrations (0.37nm, 111nm, 333nm, 1mm) in respective cell lineages. We then utilized a CTG assay to observe rates of apoptosis induction in cell lines exposed to different drugs at identical concentrations. We used ImageStudio and Microsoft Excel for data analysis and visualization.

Results

Aim 1: Prove that 753B is effective in BCL protein degradation

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Aim 2: Indicate the efficacy of 753B in comparison to venetoclax, navitoclax, DT2216

Conclusions

Our experiments indicate that BCLXL is consistently degraded upon exposure to 753B. BCL2 seems to show moderate levels of degradation but tends to not be as significant or consistent as BCLXL. The observed BCL2 resistance may be explained by current research, which suggests that certain cell lines which express higher levels of TP73 show BCL2 inhibition resistance. 753B also induces apoptosis at rates greater than or comparable to current drugs. Due to the specificity of 753B to AML cells, comparable apoptotic induction may prove advantageous clinically, as the drug may avoid side effects, such as thrombocytopenia induction.

References

- Porta et al. Pain Digest Pain 1998;8:346-352
- https://scholar.google.com/scholar?q=aml+treatment+cytopenia+prevalence&hl=en&as_sdt=0&as_vis=1&oi=scholart&d=g_s abs&c=us%23p%3D DakASwHcut_sJ