# Combination Therapies Against the Apoptosis Sensitizing Target OPA1 for Overcoming Therapy Resistance in Acute Myeloid Leukemia

**Innovative, efficacious, and novel treatment strategy for overcoming resistance to BH3 mimetics in Acute Myeloid Leukemia (AML) and myelodysplastic syndrome (MDS)**

### Technology

NYU investigators have developed a novel therapeutic strategy for overcoming first-line therapy resistance in acute myeloid leukemia (AML) by targeting the mitochondrial adaptations that contribute to drug resistance. Using advanced microscopy and genome-wide CRISPRi screens, as described in *Chen et al Cancer Discovery 2019* and in recent unpublished studies, the investigators identified Optic Atrophy 1 (OPA1) as a critical mediator of resistance to BH3 mimetic Venetoclax, the frontline treatment for AML. Resistant AML cells were found to upregulate the cristae-shaping protein OPA1 to modify their mitochondrial architecture and evade apoptosis, offering a promising therapeutic target with limited on-target toxicity. Indeed, two OPA1 inhibitors, including the tool compound MYLS22 and an undisclosed next-generation derivative, both promoted apoptotic cristae remodeling and cytochrome c release, resulting in a synergism with Venetoclax treatment in AML cells and in AML patient-derived xenografts *ex vivo* and *in vivo*. For example, concomitant administration of MYLS22 and Venetoclax in xenograft mice transplanted with AML cell lines and patient-derived xenografts (PDX) significantly prolonged the maximum survival time post transplantation, compared to Venetoclax alone. Of note, MYLS22 showed no detectable adverse effects on hematopoiesis when administered intraperitoneally in mice, and its synergism with Venetoclax was independent of the mutational landscape of AML. Very recent in vitro data suggest that OPA1 inhibition can also synergize with Venetoclax treatment in a pre-leukemic condition called MDS. Overall, these findings suggest that targeting OPA1-mediated mitochondrial adaptations could provide a novel and effective strategy for overcoming resistance to Venetoclax, in acute leukemia and MDS.

### Background

AML is the most common and lethal form of leukemia in adults, with a five-year overall survival rate of only 30%. Current treatments, including the frontline BH3 mimetic Venetoclax, which triggers cancer cell apoptosis, are often met with resistance, leading to treatment failure. BH3 mimetics initiate apoptosis, independent of upstream initiators such as p53, by binding and inhibiting select antiapoptotic BCL-2 family members. The investigators have identified OPA1 as a critical mediator of drug resistance in AML. OPA1 upregulation in AML cells leads to mitochondrial adaptations that confer resistance to BH3 mimetics. By inhibiting OPA1, these mitochondrial adaptations can be reversed, thereby overcoming resistance to BH3 mimetics and leading to increased programmed cell death in AML cells.

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More recent data suggest that OPA1 loss synergizes with Venetoclax treatment in MDS. MDS is a group of bone marrow disorders where the bone marrow doesn't produce enough healthy blood cells, with approximately 15,000 new cases diagnosed annually in the US. MDS often leads to low blood cell counts, potentially causing symptoms like fatigue and frequent infections. The five-year survival rate for newly diagnosed MDS patients is approximately 40%, with most of the MDS patients transforming into AML. The FDA has granted a Breakthrough Therapy Designation to Venetoclax in 2021 for the treatment of MDS patients.

### Development Stage

The investigators have demonstrated efficacy and preliminary safety for therapeutically targeting OPA1 *in vivo*. NYU TOV is seeking a commercial partner to support clinical development.

### Applications

For the treatment of:

- **AML**, particularly in patients who have developed resistance to Venetoclax.
- **MDS**, particularly in patients who have developed resistance to Venetoclax.
- **Other cancers**, where apoptosis-inducing agents (or BH3 mimetics) are used.

### Advantages

- **Innovative combination approach:** A BCL2 and OPA1 inhibitor cocktail provides a potential first-in-class and best-in-class therapeutic strategy for treating AML.
- **Overcomes resistance:** Effectively reverses cancer cell resistance to frontline BH3 mimetics in AML cells.
- **Broad applicability:** Effective in AML cells with diverse mutational backgrounds, including p53 mutant AML.
- **Low toxicity:** OPA1- targeting small molecule MYLS22 has a favorable safety profile in animals, and OPA1-targeting therapeutics are in Phase 1 for other indications.

### Intellectual Property

NYU has a pending U.S. non-provisional patent application covering compositions and methods for sensitizing cancer cells to drug-induced apoptosis

### References

1. Chen, Xufeng et al. , https://pubmed.ncbi.nlm.nih.gov/31048321/