Abstract 1440: Transcriptional reprogramming and survival co-dependencies of chronic lymphocytic leukemia resistant to venetoclax

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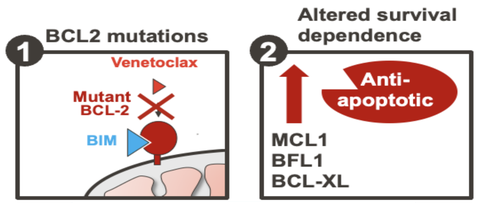
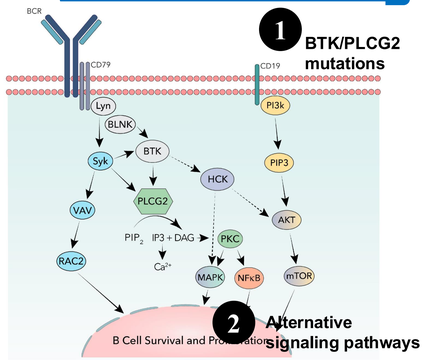
BTKi and venetoclax refractory CLL – An unmet Clinical challenge

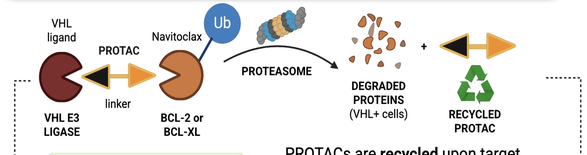
Venetoclax resistance



BTKi resistance



THE PROMISING DESIGN OF PROTEIN DEGRADERS



5 Platelet EC_{50} (48h): Navitoclax > PZ18753b > WH25244 (130 nM, 599 nM, 740 nM)

These **PROTACs** degrade Bcl-xL in cells expressing VHL E3 ligase, which is absent in platelets.

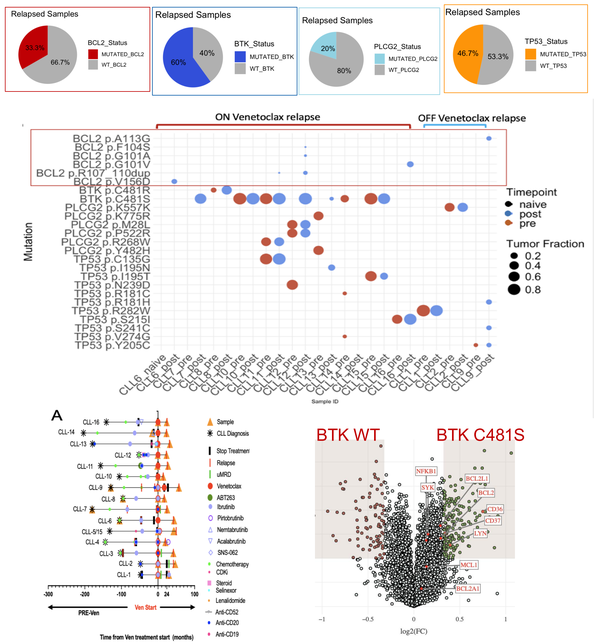
PROTACs are **recycled** upon target degradation and exhibit **catalytic activity**, properties that may enhance their ability to target mutant and post-translationally modified proteins more effectively than traditional small molecule inhibitors. 6

(Dongwen et Al., *Nat Commun*, 2021; Zheng Laboratory, *unpublished*; Rutherford et Al., *Mol Cancer Ther*, 2024)

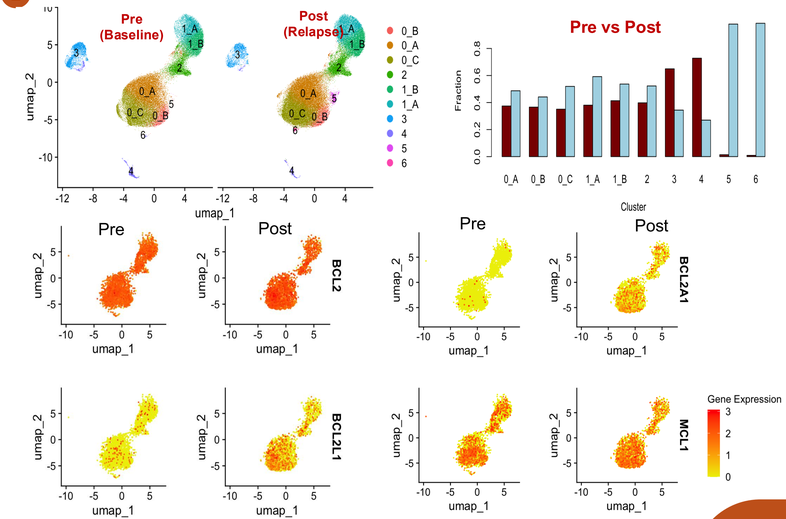
We hypothesized that WH25244 can degrade mutant BCL2, hyperphosphorylated BCL2 and BCL-XL to overcome venetoclax resistance in CLL.

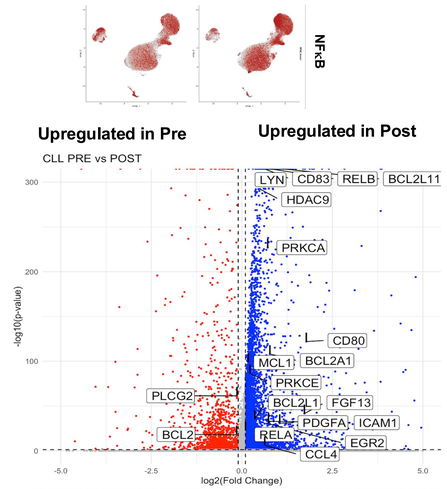
Multiple mechanisms converge on creating a dependence on BCL2 and BCL-xL in CLL relapsed on BTKi and Venetoclax

1 Mutational complexity in BTKi and venetoclax refractory CLL.

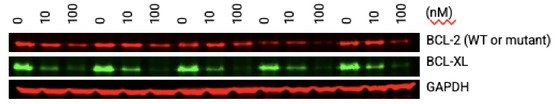


2 Transcriptional reprogramming resulting in abundant BCR and BCL-2 family transcripts at relapse after BTKi and venetoclax

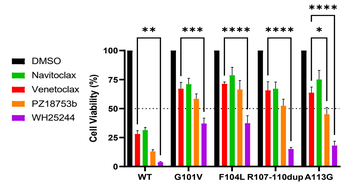




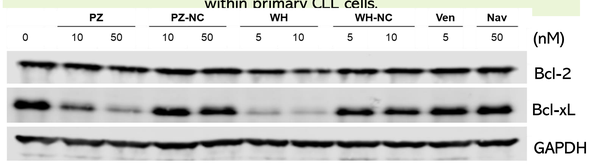
3 WH25244 degrades wildtype and mutant Bcl-2, and Bcl-xL within 24h in OSU-CLL cell lines.



4 WH25244 is superior to venetoclax at killing Bcl-2 mutant OSU-CLL cells (72h, 200 nM).

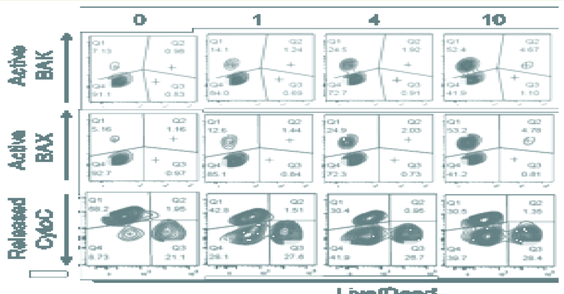


5 PZ18753b and WH25244 recruit the VHL E3 ligase to degrade Bcl-xL within primary CLL cells.



Treatment naïve CLL cells were treated for 14h with PROTACs PZ18753b (PZ), WH25244 (WH) or negative controls (NC) lacking an active VHL ligand (n=5).

6 Treatment with Bcl-2/Bcl-xL PROTACs kills CLL cells via mitochondrial apoptosis (n=4).



KEY FINDINGS

Dual refractory CLL develop a strong co-dependence on BCL2 and BCLxL via multiple mechanism.

1. Recurrent mutations in BTK, PLCG2, or BCL2 that drive upregulation of BCL2, BCLxL, and BCR signaling components.
2. Transcriptional reprogramming that further enhances BCLxL expression and BCR signaling proteins.

WH25244 is a PROTAC-based degrader that has the potential to re-sensitize venetoclax-resistant CLL cells to apoptosis, via degradation of wildtype and mutant Bcl-2, and Bcl-xL, in a VHL-dependent manner.

Its therapeutic index is improved when compared to its precursor, navitoclax, as observed *in vitro* by:

- Increased potency against CLL cells (on-target effect)
- Decreased potency against platelets (on-target toxicity)

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