LP-284 - A Highly Potent Small Molecule Targeting Mantle Cell Lymphoma

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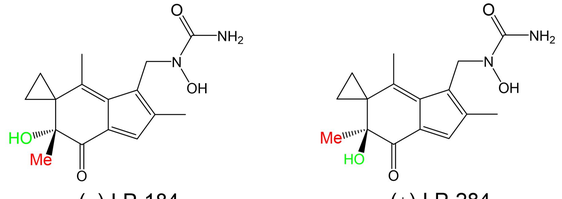
Background

Mantle cell lymphoma (MCL) is a rare and aggressive form of B-cell non-hodgkin lymphoma (NHL). Approximately 40-50% of MCL patients carry inactivating mutations in the gene ataxia telangiectasia mutated (ATM), a core component of the cell's DNA damage response system. MCL cells with mutations in ATM are known to have increased chromosomal imbalance, copy number loss, and hypersensitivity to DNA damaging agents[1,2]. LP-184, a small molecule DNA damaging agent, is known to be synthetically lethal in tumors with DNA repair deficiencies. However, DNA damage by LP-184 is dependent on activation by the oxidoreductase prostaglandin reductase 1 (PTGR1), which is expressed at low levels in many hematological cancers[3]. We synthesized LP-284, an enantiomer of LP-184, which retains synthetic lethality in cancers with impaired DNA damage repair pathway genes, but LP-284's activity is independent of PTGR1 expression.

Primary Objectives

- Test if PTGR1 is required for activating LP-284
- Determine if LP-284 is a potential synthetic lethal drug targeting DNA damage repair (DDR) deficiency
- Evaluate LP-284's tumoricidal activity in NHL cell lines

Chemical Structures



Results

Figure 1. LP-284 doesn't require on PTGR1 for activation and is more potent in hematological cancers than LP-184

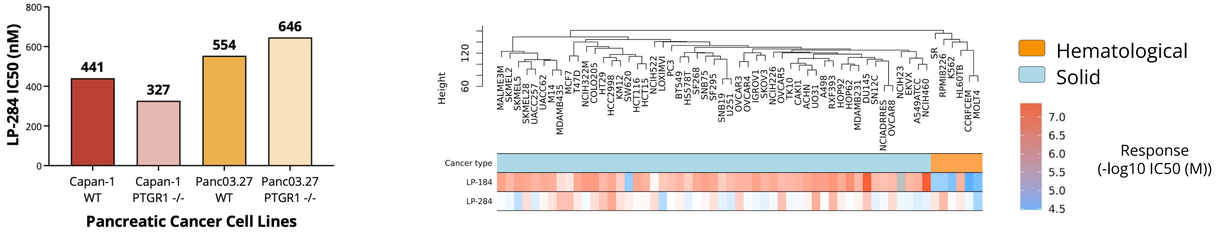


Figure 1 Legend: 1A) Wild type and *PTGR1* CRISPRi Capan-1 and Panc03.27 pancreatic cell lines treated with LP-284. *PTGR1* expression level does not affect the LP-284 IC50 in these cell lines, meaning that LP-284 isn't dependent on *PTGR1* for activation and potency. **1B)** Heatmap representing the IC50 sensitivity of LP-184 and LP-284 across the NCI60 tumor cell lines. LP-284 appeared to have an increased sensitivity to hematological cancers compared to LP-184.

Figure 2. CHO cell lines deficient in nucleotide excision repair are more sensitive to LP-284.

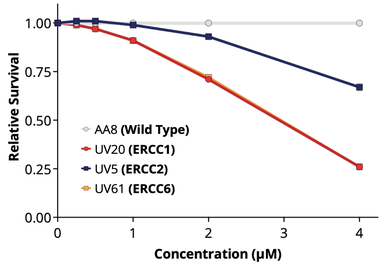


Figure 2 Legend: CHO cells were treated with LP-284. CHO cells carrying nucleotide-excision repair (NER) mutations were up to ~4 fold more sensitive to LP-284 than their parent wild type cells.

Figure 3. Effect of mutations in *ATM* with LP-284 treatment in vitro

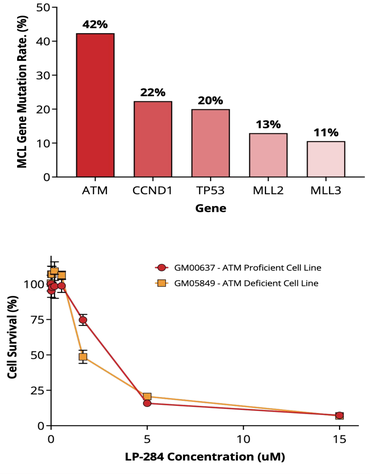


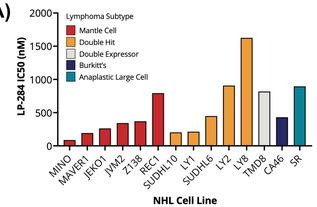
Figure 3 Legend

A) Graph of the 5 most common genes that are mutated in MCL patients. *ATM* is the most frequently mutated gene (42%) in MCL patients, followed by *CCND1*, *TP53*, *MLL2*, *MLL3*[5, 6]

B) Isogenic cell lines GM00637 and GM05849, that are proficient and deficient in *ATM* respectively[4], were treated with LP-284 to determine their IC50 sensitivity. GM05849 cells, which are *ATM* deficient, were ~1.5 fold more sensitive to LP-284 compared to GM00637 cells that were *ATM* proficient.

Results Cont.

A)



B)

MCL Cell Line	Drug Resistance[7-10]	LP-284 IC50 (nM)
MINO	Bortezomib	88
MAVER1	Ibrutinib; Venetoclax	193
JEKO1	Zanubrutinib	263
JVM2	Unknown	343
Z138	Ibrutinib	370
REC1	Bortezomib	794

Figure/Table 4 Legend

A) IC50s of non-Hodgkin Lymphoma cell lines treated with LP-284. All 6 of the MCL cell lines had some of the lowest IC50s tested, which included drug resistant cell lines.

B) Table of the tested MCL cell lines, their known drug resistances, and their IC50 sensitivity to LP-284.

Discussion

- LP-284 is not dependent on PTGR1 for activity.
- LP-284 is a promising preclinical DNA damaging agent that targets DDR deficient cells.
- LP-284 possesses nanomolar-range anti-tumor activities in multiple and diverse MCL cell lines, with the potential to treat MCL patients who are resistant to other therapies.

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