LP-184, a molecule with nanomolar potency, exhibits strong activity in prostate cancers with DNA damage repair defects

A Kulkarni[1], C Schimke[1], P Banerjee[2], U Kathad[1], K Bhatia[1], P Sharma[1]

[1]Lantern Pharma Inc., Dallas TX; [2]Georgetown University, Washington DC

Permanent Abstract #1249

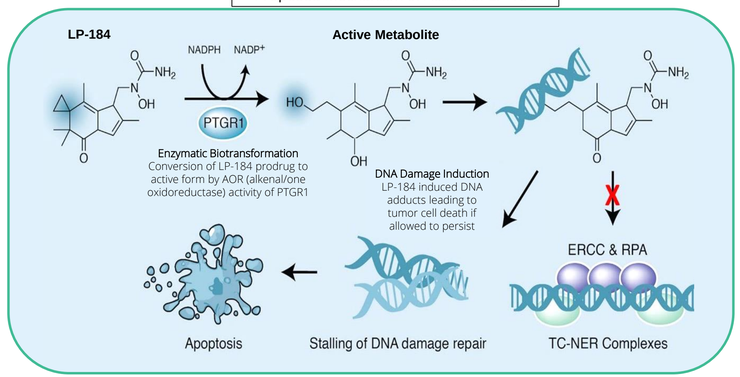
Introduction

- The 5-year survival rate for localized Prostate Cancer (CaP) over 99%, yet that drops to only 30% in patients with distant metastases making it the second leading cause of cancer related deaths in men which is also responsible for ~33,000 deaths/year in the US alone [1]
- Advances in androgen/androgen receptor related treatment options will inevitably be hindered by emergence of metastatic Castration Resistant Prostate Cancer (mCRPC)
- LP-184, an acylfulvene (AF) class novel alkylating agent, is currently in preclinical development after exhibiting nanomolar potency (20 – 350 nM) against widely used CaP cell lines in 2D culture as well as in 3D organoid models cultured from patient-derived xenografts
  - Equipotency with standard chemotherapeutic Docetaxel and between 100 and 9000 times more potent than Cisplatin and Olaparib in vitro
- Frequent mutations of prominent DNA Damage Repair Genes (DDRGs) including BRCA2, ATM, ERCC2/3 are suspected to influence the efficacy of LP-184 in various CaP models
- Additionally, truncation of a crucial transcription coupled nucleotide excision repair (TC-NER) gene, ERCC3 resulted in enhanced LP-184 sensitivity.
- Connectivity Map (CMAP) analysis of full transcriptome profiling data identified potential drug classes synergistic with LP-184

Rationale & Hypothesis

The activity of LP-184, a next generation acylfulvene derivative, is dependent upon the expression of Prostaglandin Reductase 1 (PTGR1). LP-184 is expected to be transformed into its bioactive form by the oxidoreductase activity of PTGR1 [2]. LP-184 induced DNA adducts are thought to be selectively repaired by TC-NER.

Proposed Mechanism of Action of LP-184



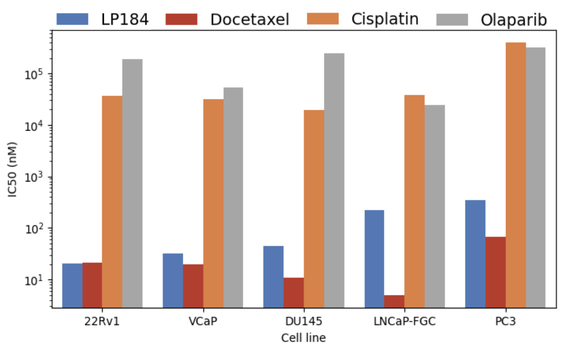
We hypothesize that

- LP-184 would exhibit potent growth inhibitory effects on lethal prostate cancer cells through a compromised DNA repair milieu of mCRPC due to recurrent DDRG mutations such as in BRCA2/ ATM/ ERCC complex components.

Objectives

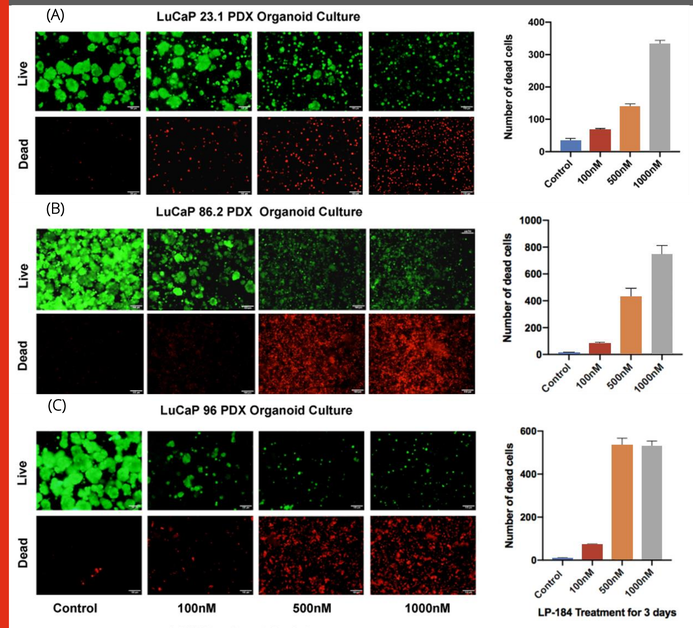
- Establish the therapeutic efficacy of LP184 in lethal CaP/mCRPC using established in vitro (2D and 3D)
- Identify genomic alterations associated with DNA repair deficits by which LP-184 can inhibit mCRPC growth in parental or engineered tumor cell lines and PDX models

LP-184 matches *in vitro* performance of standard cancer drugs at similar or improved potency



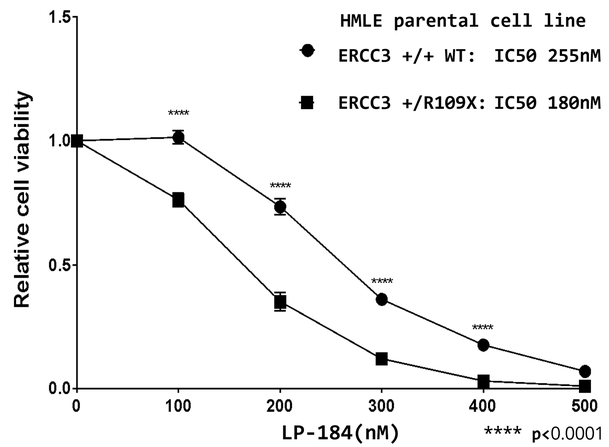
Cell line	DDRGs mutated (SNP or DEL)	Damaging mutations	LP-184 IC50 (nM)
22RV1	ATM, BRCA2, PALB2	BRCA2	20.5
VCAP	CCND1		32.2
DU145	BRCA1, BRCA2, BRIP1, ERCC6, FANCI, MLH1, MSH2, MSH6	ERCC6, FANCI	44.9
LNCAP CLONE FGC	ATM, ATR, CHEK2, ERCC1/3/5/8, FANCA, MLH1	ATM, ERCC3	219
PC3	MMS19	None reported	384.8

LP-184 shows dose-dependent cell kill in the nanomolar range in several prostate cancer organoid models

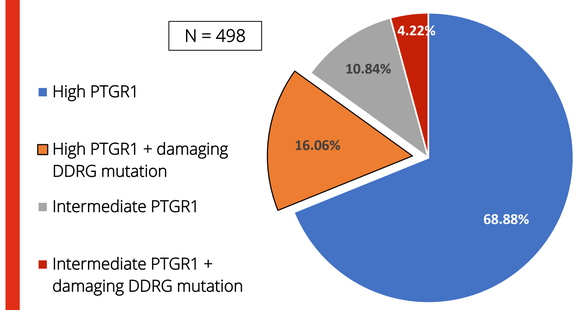


- LuCaP 23. 1 (A), 86.2 (B), and 96 (C), cell clusters were treated with vehicle control (0.01% ethanol), or various doses of LP-184 for three days and organoid formation was evaluated by staining with Calcine AM (for live cells) and Ethd III (for dead cells).
- Quantitative results were calculated from three replicates. P< 0.0001 and plotted for each dosage level against the number of dead cells observed.
- LuCaP 86.2 is BRCA2+/- [3] and shows the highest relative dose dependent cell kill among the LuCaP models tested under these conditions

Preliminary data suggests deficiency in TC-NER machinery genes such as ERCC3 increases sensitivity to LP-184

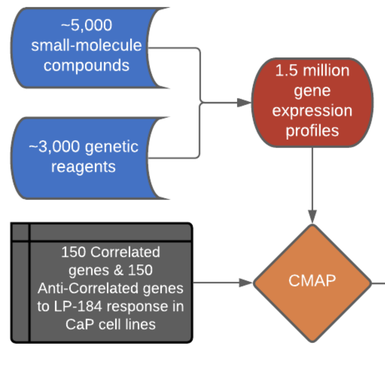


Analysis of primary prostate cancer clinical data from TCGA revealed that ~16% of patients have elevated PTGR1 and harbor damaging mutations across a panel of 121 DDRGs



Selected DDRG	Mutation frequency in TCGA (out of 498)
ATM	19
BRCA2	8
ERCC2	3
CDS1	3
ATR	2
ERCC3	1
ERCC6	1
BRCA1	1

Connectivity Map (CMAP) [4] analysis has identified potential synergistic drug classes being considered for LP-184 combination treatment



Overlapping/Hypersensitizing		
Drug Class	Inhibitor	CMAP Score
Topoisomerase inhibitors	Irinotecan	99.3
Proteasome inhibitors	Ixazomib	86.8

Orthogonal/Synthetic Lethal		
Drug Class	Inhibitor	CMAP Score
PARP inhibitors	Rucaparib	-60
MTOR inhibitors	Deforolimus	-76.4

Key findings and future directions

Key findings

- LP-184 is as effective as or better than other approved prostate cancer drugs in terms of *in vitro* potency
- LP-184 has the potential to target tumors with high PTGR1 regardless of presence of other co-occurring mutations but is especially found to be effective in tumor models with mutations in DNA damage repair pathway components including in genes involved in homologous recombination and TC-NER

Future directions

- Determine the therapeutic efficacy of LP184 on various CaP xenograft models *in vivo*
- Evaluate the synergistic effects of LP184 with antineoplastic agents currently used in the treatment of mCRPC in selected models.

References

[1] Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, & Cronin KA. (2019). SEER Cancer Statistics Review, 1975-2016. In National Cancer Institute.

[2] Yu, X., Erzinger, M. M., Pietsch, K. E., Cervoni-Curet, F. N., Whang, J., Niederhuber, J., & Sturla, S. J. (2012). Up-regulation of human prostaglandin reductase 1 improves the efficacy of hydroxymethylacylfulvene, an antitumor chemotherapeutic agent. Journal of Pharmacology and Experimental Therapeutics. https://doi.org/10.1124/jpet.112.195768

[3] Beshiri, M. L., Tice, C. M., Tran, C., Nguyen, H. M., Sowalsky, A. G., Agarwal, S., Jansson, K. H., Yang, Q., McGowen, K. M., Yin, J. J., Aillin, A. N., Karzai, F. H., Dahut, W. L., Corey, E., & Kelly, K. (2018). A PDX/Organoid biobank of advanced prostate cancers captures genomic and phenotypic heterogeneity for disease modeling and therapeutic screening. Clinical Cancer Research. https://doi.org/10.1158/1078-0432.CCR-18-0409

[4] Subramanian A, et al. A Next Generation Connectivity Map: L1000 Platform And The First 1,000,000 Profiles. Cell. 2017/12/1. 171(6):1437–1452

Contact

Aditya Kulkarni, PhD
Senior Research Scientist

aditya@lanternpharma.com