LP-184, an acylfulvene class small molecule therapeutic, is synthetically lethal in DNA damage repair deficient cancers

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Background

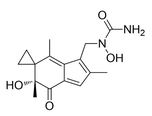
- **Approximately 30% of solid tumors** (ovarian, breast, pancreatic, prostate cancers) harbor deficiency in some DNA Damage Repair (DDR) pathways, making them selectively vulnerable to DDR inhibitors [1].
- LP-184 is a next-generation acylfulvene prodrug that is metabolized to an active compound by prostaglandin reductase 1 (PTGR1) that is commonly elevated in multiple solid tumor types [2, 3].
- LP-184-induces DNA lesions are likely repaired by the Nucleotide Excision Repair (NER) and Homologous Repair (HR) pathways.
- Reduced activity of multiple DDR-related pathways in solid tumor models is strongly correlated with increased sensitivity to LP-184.
- **LP-184 is synthetically lethal in tumors deficient in NER/HR pathways** and expressing a threshold level of PTGR1 resulting from its ability to cause unresolvable DNA damage.
- The concept of synthetic lethality has been successfully applied to develop strategies to treat subsets of DDR-deficient tumors [4]. Clinically, PARP inhibitors (PARPi) have been successful in treating Homologous Recombination Deficiency (HRD) cancers.
- BRCA1/2 are typically involved in HR and ERCC1/2/3/6 underlie NER processes [5].
- **Lantern is anticipating an IND filing with the FDA and Phase 1A trial launch for LP-184 in Q2 2023**.

Objectives

1. Evaluate the anti-tumor efficacy profile of LP-184 in HR/NER deficient in vitro and in vivo tumor models.
2. Compare LP-184 potency with standard-of-care PARP inhibitors across preclinical tumor models.
3. Identify drug combinations that are potentially synergistic with LP-184.

LP-184 Drug Profile

- **LP-184** (hydroxyurea methylacylfulvene) is a prodrug belonging to the acylfulvene class of naturally derived small molecule therapeutics [6, 7].
- The FDA has granted LP-184 **orphan drug designations (ODD)** for the treatment of pancreatic cancer, malignant gliomas, and atypical teratoid rhabdoid tumors (ATRT).



Patient PTGR1 & DDR Gene Profiles

Table 1. Analysis of TCGA Patient Data# for Cancers with High PTGR1 Expression and Deleterious DDR Gene Mutation Status Considering a Panel of 135 curated commonly recognized DDR genes

Cancer type	Patient (%) with High PTGR1 Expression	Transcript levels of PTGR1 High Patients*	Patient (%) with Elevated PTGR1 and Del. DDR Mutations
Pancreatic (N = 179)	40.8	9.7 - 11.9	29.1
Prostate (N = 498)	84.9	9.7 - 13.9	26.7
NSCLC (N = 517)	35.6	9.7 - 14.5	26.7
Breast (N = 1100)	38.2	9.7 - 12.0	15.6
Ovarian (N = 307)	45.3	9.7 - 12.0	28.3
Bladder (N = 408)	57.1	9.6 - 14.7	46.3
Gastric (N = 415)	21.2	9.7 - 11.9	13.2
Head and neck (N = 522)	52.5	9.7 - 14.7	41.8
Renal Clear Cell (N = 534)	81.3	9.7 - 13.4	22.8

*Microarray
The results shown here are in whole or part based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga

Results

CHO Cells with NER Mutations (ERCC1/2/6) are 4-6 Fold More Sensitive to LP-184 Relative to Isogenic Parental Cells

Fig. 1

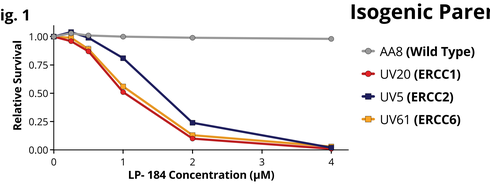


Fig. 1) Chinese Hamster Ovary (CHO) cells harboring NER mutations ERCC1, ERCC2, or ERCC6 were treated with LP-184 in a concentration range of 250 nM – 4 μM over 3 days. Cell viability was evaluated using CellTiter Glo reagent and compared to wild type cells.

BRCA2 Depletion Enhances LP-184 Sensitivity 8X in a Metastatic Prostate Cancer Cell Line

Fig. 2

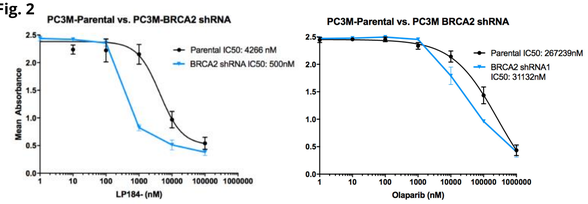


Fig. 2) Metastatic prostate cancer cell line, PC3M (parental or shRNA mediated BRCA2 knockdown) were treated with LP-184 in a concentration range of 1 nM – 100 μM or with the PARP inhibitor Olaparib in a concentration range of 1 nM – 1 mM over 3 days. Cell viability was evaluated using CellTiter Glo reagent and IC50 values computed in GraphPad Prism.

LP-184 Showed 120 Fold Higher Potency than Olaparib in a Prostate Cancer Organoid Model LuCaP 96 Harboring BRCA2/ CHEK2 Inactivating Mutations

Fig. 3

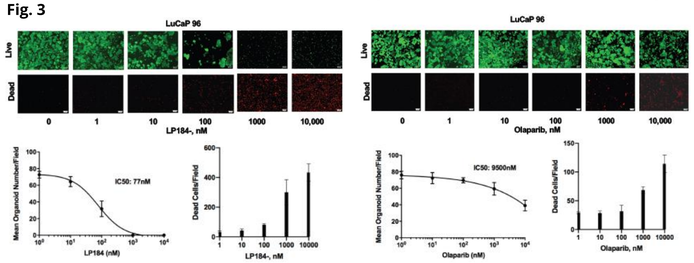


Fig. 3) LuCaP 96 organoids [8] were plated with growth factor reduced Matrigel in DMEM/10% FBS growth media and treated with either LP-184 [1 nM – 10 μM] or Olaparib [1-nM – 10 μM] over 5 days. Organoid spheres were stained with Calcein AM, a fluorescent viability stain, photographed by light microscopy and counted using ImageJ.

LP-184 Showed Strong ex vivo Nanomolar Potency Across 14 Patient-Derived Tumor Models Harboring a Variety of HR Mutations

Table 2. Comparison of LP-184 and Olaparib in HR Deficient Patient-Derived Tumor Models

Tumor Type	Model ID	LP-184 IC_{50} (nM)	Max Inhibition (%)	Olaparib IC_{50} (nM)	Max Inhibition (%)	HR Genes Mutated
Non-small Cell Lung Cancer	CTG-1194	31	91	ND	52	ATM
	CTG-2532	54	99	17000	81	CHEK1, FANCA, NBN, RAD50
	CTG-0166	57	97	720	77	ATM, FANCD2, NBN
	CTG-1680	140	99	48000	88	PARP2
	CTG-0192	200	88	2900	73	BRCA1, RAD54L
Pancreatic Cancer	CTG-1522	45	97	7900	81	ATR, BRIP1, PARP1
	CTG-1643	57	77	ND	65	BRCA1, BRIP1
	CTG-0302	110	91	ND	46	BRCA2, ATM, BLM, FANCA
	CTG-0314	270	82	1700	80	BRCA2, CDK12, PALB2
Prostate Cancer	CTG-2440	31	95	ND	59	PMS2
	CTG-3167	54	97	4200	48	BRCA2, ATM, FANCA, FANCI, FANCM
	CTG-3537	54	98	ND	29	BRCA2, CDK12, FANCI, RAD54L
	CTG-2429	92	92	18000	68	ATM, ATR, PALB2
	CTG-3337	230	99	3700	73	RAD51C

LP-184 and Olaparib Have Strong in vitro Synergy in HRD/NERD Ovarian Cancer Cells

Fig. 4

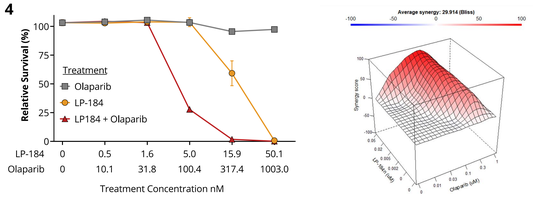


Fig. 4) Ovarian cancer cells, OVCAR3, were treated with LP-184 [0.5–50 nM], Olaparib [10–1000nM], or a combination of LP-184 and Olaparib over 10 days. Cell viability was determined using CellTiter Glo reagent. LP-184's IC50 was 13 nM, Olaparib's IC50 was 145 nM, and their combination Bliss Synergy Score was 29, indicating strong synergy between LP-184 and Olaparib. Bliss Scores > 10 reflect synergy.

Results Cont.

LP-184 Treatment Resulted in Complete Tumor Regression in HRD and Standard of Care Resistant Triple Negative Breast Cancer (TNBC) Models

Fig. 5A

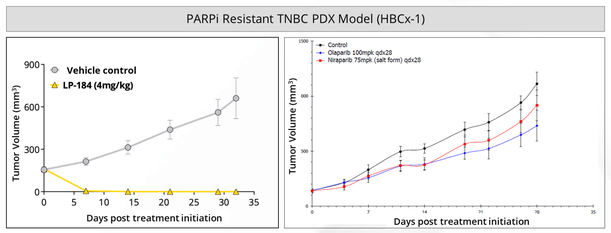


Fig. 5B

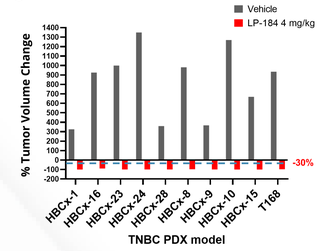


Fig. 5A) Average tumor volumes (mm^3) over days post treatment initiation in HBCx-1 subcutaneous PDX tumor model as a representative example treated with vehicle control (N = 3) and LP-184 (4 mg/kg i.v.) (N = 3). Error bars represent SEM. LP-184 dosing on days 0, 2, 4, 6, 8, 16, 18, 20, 22, 24. Historical Olaparib/ Niraparib treatment data from the same model. **B)** LP-184 treatment resulted in complete tumor regression (107-141% TGI) in 10/10 HR Deficient (BRCA1 LOH) TNBC PDX models of which 7/10 were resistant to Olaparib/ Niraparib and to Doxorubicin/ Cyclophosphamide.

LP-184 Treatment Resulted in Complete Tumor Regression in HR Deficient Pancreatic Cancer PDX Models

Fig. 6A

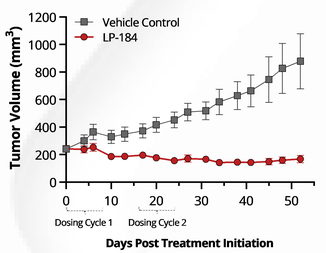


Fig. 6B

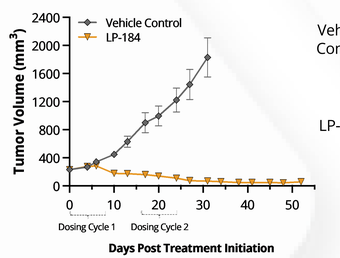
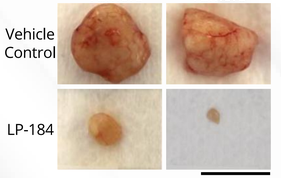


Fig. 6C



PDX Model	HRD Mutation	%TGI
CTG-1522	ATR 1774fs	140
CTG-1643	BRCA1 Q1460fs	112

Fig. 6A-B) Average tumor volumes (mm^3) over days post treatment initiation in CTG-1522 and CTG-1643 subcutaneous PDX tumor models treated with vehicle control (N = 6) and LP-184 (4 mg/kg i.v.) (N = 6). Error bars represent SEM. LP-184 dosing on days 0, 2, 4, 6, 8, 16, 18, 20, 22, 24. **C)** Excised terminal tumors. Mice bearing either CTG-1522 or CTG-1643 PDX tumors were treated with either vehicle control or LP-184 (4mg/kg i.v.). Scale bar represents 1.0 cm.

Summary

1. Approximately 50% of clinical solid tumor samples represented in TCGA express elevated PTGR1 of which about 28% on average have some pathogenic DDR gene mutation. These subsets are highly likely to benefit from LP-184 based therapy.
2. In vitro and in vivo cancer models carrying a broad spectrum of DNA repair pathway mutations are highly sensitive to LP-184.
3. LP-184 is synthetically lethal in multiple contexts when combined with genetic DDR pathway aberrations.
4. LP-184 shows potential to extend therapeutic opportunities for a large subset of cancer patients with synergistic combination approaches likely with PARP inhibitors.

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