CONFIDENTIAL

LP-184, a tumor site activated small molecule synthetic lethal therapeutic, is effective in central nervous system cancers

Aditya Kulkarni[1], Bachchu Lal[2], John Laterra[2,3], Rana Rais[3], Barbara Slusher[3], Jean-Philippe Richard[4], Rama Modali[4], Joseph McDermott[1], Caleb Schimke[1], Panna Sharma[1], Kishor Bhatia[1]

1: Lantern Pharma, 1920 McKinney Ave, 7th floor, Dallas TX 75201
2: The Kennedy Krieger Institute, 707 N. Broadway, Baltimore MD 21205
3: Johns Hopkins School of Medicine, 600 N. Wolfe St., Baltimore, MD 21287
4: Reprocell USA, 9000 Virginia Manor Road, Suite 207, Beltsville, MD 20705

Permanent Abstract Number: 5442

AACR Annual Meeting 2022

Introduction

- **Disease background:** Glioblastoma multiforme (GBM) and atypical teratoid/rhabdoid tumors (ATRT). These represent 2 extremely aggressive and lethal types of CNS malignancies sharing a median overall survival of 12-18 months and 5-year survival rate of 5 to 30% in the US [1].
- **Unmet need:** Blood-brain barrier (BBB) permeable agents effective against recurrent, chemotherapy-resistant central nervous system (CNS) malignancies are urgently needed.
- **Proposed solution:** Lantern Pharma is advancing LP-184 (hydroxyurea-methylacylfulvene), a tumor site activated small molecule drug candidate belonging to the acylfulvene (AF) class. LP-184 is believed to be activated to a highly labile metabolite by the enzyme Prostaglandin Reductase 1 (PTGR1). FDA has granted orphan drug designation (ODD) for the use of LP-184 in the treatment of both malignant glioma and ATRT, and rare pediatric disease designation (RPDD) for the use of LP-184 in the treatment of ATRT.

Hypothesis & Rationale

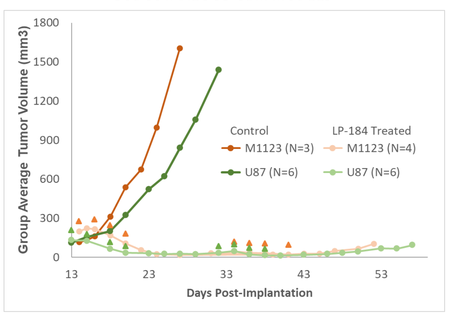
- We hypothesize that LP-184 may be a potent therapeutic as a single agent for CNS cancers expressing elevated PTGR1.
- The rationale for this is that the activity of LP-184 is dependent upon the expression of PTGR1. LP-184 is expected to be transformed into its bioactive form by the oxidoreductase activity of PTGR1 [2].
- Belonging to the AF class of compounds, LP-184 is believed to create DNA adducts at N3 of adenine base [3] whereas Temozolomide (TMZ, the standard of care agent for GBM) methylates O6 of guanine base [4]. The repair enzyme MGMT removes the primary TMZ-induced cytotoxic lesion, O6-methylguanine but not LP-184-induced DNA alkylation.
- LP-184-induced DNA damage is likely repaired preferentially via ERCC-dependent transcription couples nucleotide excision repair (TC-NER) [5].

Objectives

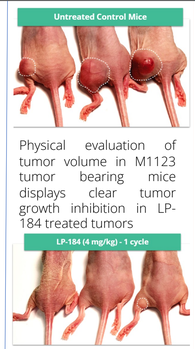
- Establish the therapeutic efficacy of LP-184 in GBM, ATRT and brain metastases using *in vitro* and *in vivo* models
- Determine the effect of LP-184 + Spironolactone combination treatment on GBM cell viability
- Determine the in vivo bioavailability of intravenously administered LP-184 in normal and tumor brain tissue

Intravenous LP-184 induced complete and durable regression of pre-established subcutaneous U87 and M1123 GBM xenografts and prolonged survival of mice bearing orthotopic U87 and M1123 xenografts

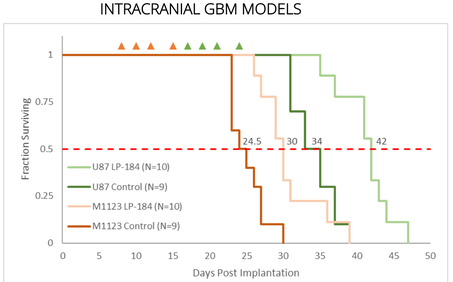
SUBCUTANEOUS GBM MODELS

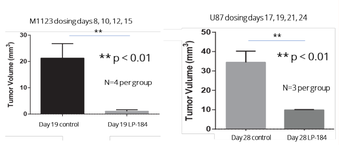


- Colored triangles signify days of intravenous dosing with 4 mg/kg LP-184 or vehicle control
- Tumor Growth Inhibition (TGI) by LP-184 was 107% for both the M1123 and U87 models
- 3/10 LP-184 treated U87 tumor bearing mice were entirely tumor-free from day 38 onwards until study termination
- 3/4 LP-184 treated M1123 tumor bearing mice were entirely tumor-free from day 29 onwards until study termination.



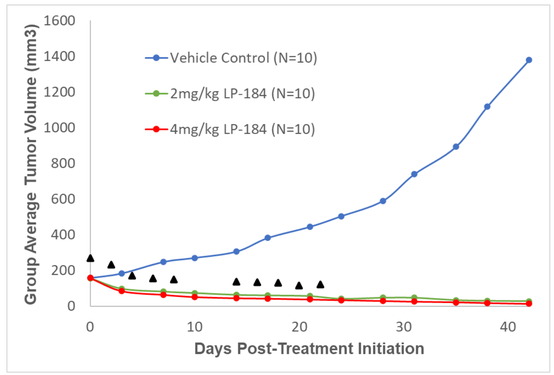
INTRACRANIAL GBM MODELS

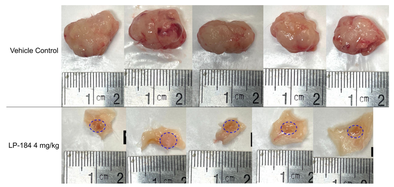




- Dosing regimen consisted of one cycle of four every other day doses of 4 mg/kg LP-184 as intravenous injection
- Median survival in days is shown at the intersection of each group with the dotted red line

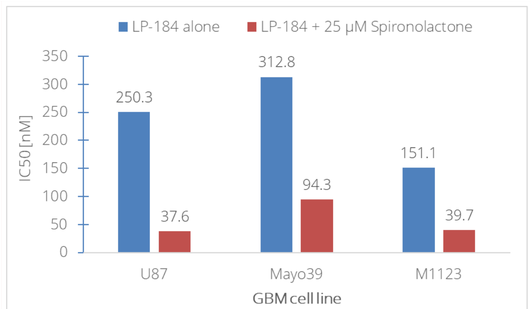
LP-184 treatment showed near complete tumor regression in A subcutaneous ATRT xenograft model



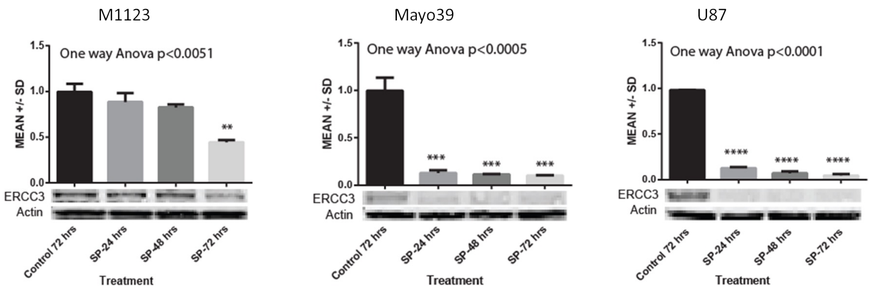


- Analysis of genes associated with LP-184 sensitivity in solid tumor cell lines revealed that expression of SMARCB1 is significantly anti-correlated to LP-184 sensitivity, suggesting that LP-184 will be effective in ATRTs and other tumors with SMARCB1 loss.
- Intravenous LP-184 administration induced tumor regression in mice implanted with SMARCB1 deficient CHLA06 ATRT subcutaneous xenografts, with 2 of 10 treated mice being virtually tumor-free after 2 cycles. Timing of doses are marked by black triangles on days 0, 2, 4, 6, 8, 14, 16, 18, 20, 22.

There is clear cooperativity between LP-184 and Spironolactone in GBM models in vitro



- LP-184 response is influenced by tumor DNA repair status, and acylfulvene-induced damage is mainly repaired by the transcription-coupled nucleotide-excision repair (TC-NER) pathway.
- Spironolactone, an FDA approved, blood-brain-barrier permeable diuretic, induces degradation of ERCC3 protein, a key TC-NER component.
- Co-treatment with Spironolactone resulted in a 3-6 fold decrease in LP-184 IC50s assayed at 72 hrs in M1123, Mayo39, and U87 cultures.
- Spironolactone alone did not affect cell viability at the concentrations tested and resulted in ERCC3 degradation as assayed by western blotting.

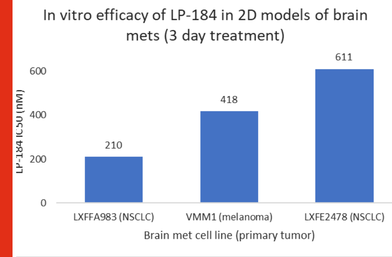


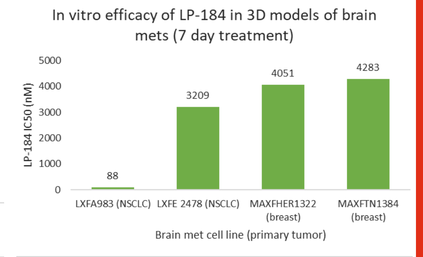
LP-184 CNS bioavailability and pharmacokinetics *in vivo*

Measured Analyte & Dose	Matrix	Dosing Route	Pharmacokinetic Data (Mean ± SEM)						
			C_{max} (ng/g or ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/g or ng.h/mL)	Half-Life (h)	C_{max} (nM)	AUC (nM)	Brain Tissue/ Plasma Ratio
LP-184 4 mg/kg	Plasma	IV	3438 ± 125	0.0833	1592 ± 28.7	0.236	11296 ± 410	5231 ± 160	-
	Peritumoral Normal Brain		279 ± 20.2	0.25	165 ± 11.6	0.383	916 ± 66	542 ± 38	0.103 ± 0.10
	Contralateral Normal Brain		223 ± 50.6	0.25	123 ± 15.9	0.444	732 ± 166	404 ± 52	0.077 ± 0.12
	Brain Tumor		773 ± 58.6	0.0833	319 ± 26.4	0.281	2539 ± 193	1048 ± 120	0.200 ± 0.029

- Pharmacokinetic analyses in SCID mice following a single LP-184 infusion (4 mg/kg, i.v.) showed favorable CNS bioavailability with normal brain/plasma ratio 0.1 (C_{max} = 916 nM) and brain tumor/plasma ratio 0.2 (C_{max} = 2539 nM).
- LP-184 BBB permeability is comparable to TMZ and brain C_{max} achieved (equivalent to ~800 nM) after a single i.v. infusion is greater than IC_{50} for sensitive GBM cell models.

LP-184 showed activity against in vitro models of brain metastases from primary lung, breast, and skin cancers





Key findings and future directions

Key findings

- Subcutaneous xenograft models of both GBM and ATRT showed rapid and near complete tumor regression with durable responses after 2 treatment cycles of 2 mg/kg or 4 mg/kg LP-184.
- Orthotopic xenografts models of GBM treated with LP-184 showed statistically significant survival benefit after a single treatment cycle.
- Co-treatment of several GBM cell lines with LP-184 and Spironolactone, an ERCC3 inhibitor, results in 3-6X increased anti-tumor activity.
- LP-184 has favorable blood brain barrier (BBB) penetration with a brain tumor:plasma ratio of 0.2
- While one of the most common TMZ resistance pathways in GBM is thought to be associated with unmethylated MGMT promoters, LP-184 is predicted to be agnostic to MGMT promoter methylation status.
- Efficacy of LP-184 may extend beyond primary brain cancers to other solid tumors that have metastasized to the brain as evidenced by in vitro efficacy in brain met cell lines.

Future directions

- Phase 0/1 dose finding and toxicity studies to prepare for a phase 2 trial

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Contact

Lantern Pharma.
Aditya Kulkarni, PhD
Senior Research Scientist
aditya@lanternpharma.com