# LP-184, a molecule with nanomolar potency, exhibits strong activity in lung cancers with KEAP1 mutations

A Kulkarni[1], JP Richard[2], U Kathad[1], M Seddon[2], T Lehman[2], R Modali[2], P Sharma[1]

[1]Lantern Pharma Inc. , [2]Reprocell USA

Permanent Abstract Number: 4185

## Challenges

- For > 40% of Non-Small Cell Lung Cancer (NSCLC) patients, there are no druggable driver genes identified. Commonly altered genes in these patients include TP53, KRAS, CDKN2A, STK11, KEAP1, KMT2D, ARID1A for which no effective therapy options are available, or are linked to high first line treatment failure. [1].
- Alterations in KEAP1 account for >12% of NSCLC patients for which there is no specific approved therapy option or available chemotherapies, and alternate therapies are weakly to moderately effective [2].

## Hypothesis & Rationale

Lantern Pharma's preclinical small molecule drug candidate, LP-184, is efficacious in lung cancers with KEAP1 mutations.

- 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.

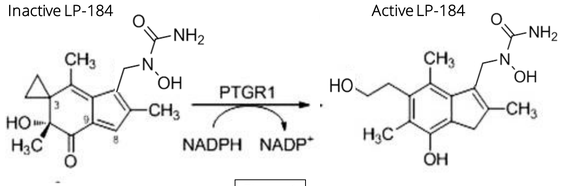


Figure 1

- PTGR1 is upregulated in tumors with deregulated NRF2, including tumors with mutations in KEAP1. KEAP1 mutations are predictive of chemotherapy resistance in NSCLC patients. Decreased KEAP1 activity in cancer cells induces greater nuclear accumulation of NRF2, causing enhanced transcriptional induction of antioxidants, xenobiotic metabolism enzymes, and drug efflux pumps. KEAP1-NRF2 pathway provides an explanation for poor clinical outcomes observed in NSCLC [3, 4].

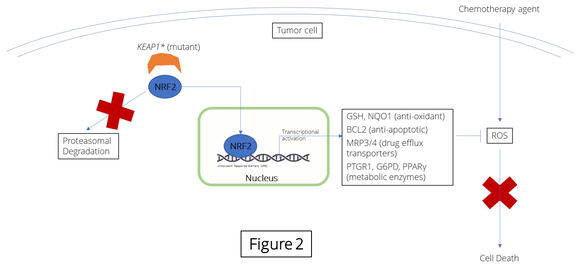


Figure 2

- 4 of top 10 cancer cell lines sensitive to LP-184 from the NCI-60 panel are NSCLC.

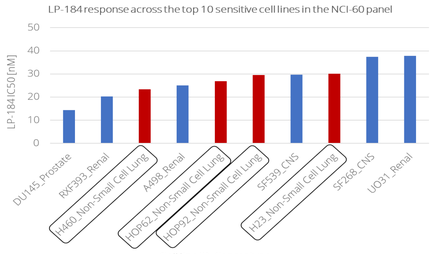


Figure 3

## Objectives

1. Assess LP-184 activity in a panel of selected NSCLC adenocarcinoma cell lines
2. Compare LP-184 cell line response profile with that of approved chemotherapy agents
3. Predict LP-184 sensitivity in an independent set of NSCLC cell lines from the CCLE database

## KEAP1 mutant NSCLC cell lines are highly sensitive to LP-184

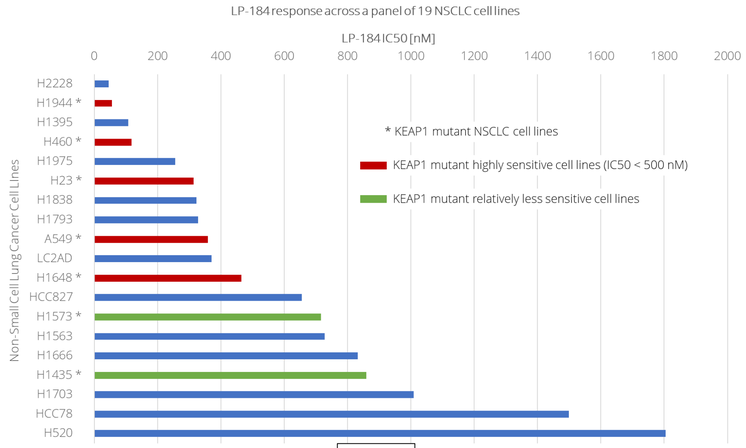


Figure 4

Indicated NSCLC cell lines were seeded in 96 well plates at recommended cell densities in 100 uL media. 24 hours post plating, media were replaced with LP-184 final concentrations of 14 nM, 41nM, 123 nM, 370 nM, 1.11 uM, 3.33 uM, and 10 uM. 72 hours post drug addition, cell viability was measured using Promega's CellTiter-Fluor assay, and IC50 generated from dose response curves using GraphPad Prism.

Table 1

| NSCLC Cell Line | KEAP1 mutation |
|---|---|
| H1944 | R272L* |
| H460 | D236H |
| H23 | Q193H |
| A549 | G333C* |
| H1648 | G364C, G430C |
| H1573 | A143P |
| H1435 | R413L* |

* Clinically prevalent KEAP1 mutations in NSCLC, according to AACR Project Genie data. Alterations in KEAP1 including amplification, loss, missense mutations, splice site mutations or deleterious truncations account for >12% of NSCLC cases on average [5].

AACR American Association for Cancer Research
PROJECT GENIE

## PTGR1 expression is significantly higher among LP-184 sensitive as well as KEAP1 mutant NSCLC cell lines

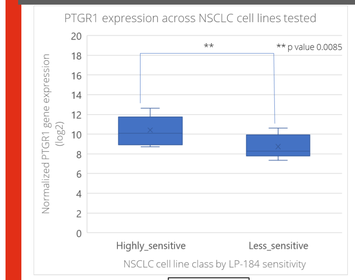


Figure 5A

PTGR1 expression was compared among two groups of NSCLC cell lines tested: 11 cell lines with LP-184 IC50 < 500 nM and 8 cell lines with IC50 > 500 nM. The t-test value comparing these groups is 2.6471.

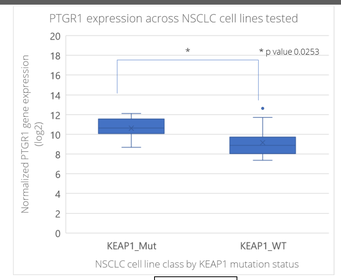


Figure 5B

PTGR1 expression was compared among two groups of NSCLC cell lines tested: 7 cell lines with KEAP1 mutation and 12 cell lines without KEAP1 mutation. The t-test value comparing these groups is 2.1028.

## LP-184 is 10-3800 times more potent than Cisplatin in a panel of NSCLC cell lines

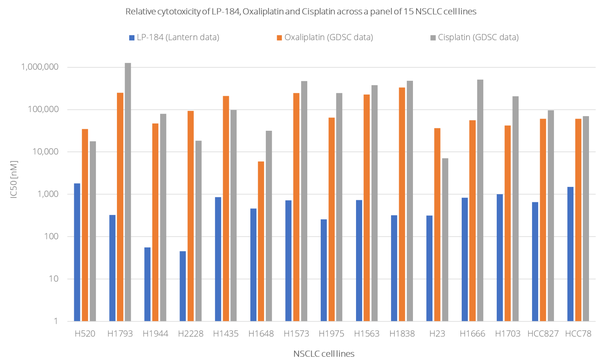


Figure 6

Table 2

| Alkylating agents anti-correlated with LP-184 drug activity pattern according to the NCI CellMinerCDB | Correlation coefficient (p value < 0.05) |
|---|---|
| Oxaliplatin | -0.621 |
| Ifosfamide | -0.603 |
| Carmustine | -0.524 |
| Lomustine | -0.512 |
| Estramustine | -0.502 |
| Dacarbazine | -0.45 |
| Cyclophosphamide | -0.347 |
| Bendamustine | -0.338 |
| Melphalan | -0.314 |

## Machine learning derived gene signature predicts nanomolar potency of LP-184 in several NSCLC cell lines upon extrapolation to CCLE database

Table 3

| LP-184 response parameter observed across 19 NSCLC cell lines tested | Outcome |
|---|---|
| Nanomolar potency observed | 11 of 19 cell lines (58%) with IC50 < 500 nM |
| Median IC50 | 371 nM |
| Mean IC50 | 570 nM |
| KEAP1 mutant highly sensitive cell lines | 5 of 7 with IC50 < 500 nM |

Table 4

| LP-184 response parameter predicted across 129 NSCLC cell lines from the CCLE database | Outcome |
|---|---|
| Nanomolar potency predicted using a 9 gene signature (details in poster # 3305) | 118 of 129 cell lines (91%) with IC50 < 500 nM |
| Median IC50 | 391 nM |
| Mean IC50 | 408 nM |
| KEAP1 mutant highly sensitive predicted cell lines | 26 of 28 cell lines with IC50 < 500 nM |

## LP-184 is likely to benefit NSCLC patients with clinically significant co-occurrence of KEAP1 mutation and PTGR1 elevation

In an analysis of 533 NSCLC adenocarcinoma patient records from TCGA portal, significant co-occurrence of KEAP1 mutation with PTGR1 elevation was observed. In the plot below, the value adjacent to highly mutated gene is the permutation test p-value of PTGR1 relative gene expression between driver mutated (red) and not-mutated (gray) samples. This result is most significant for KEAP1, with PTGR1 being highly expressed in KEAP1 mutated samples [6].

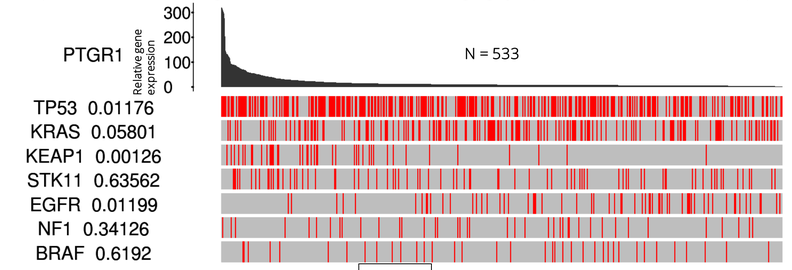


Figure 7

## Key findings and future directions

Key findings

- LP-184 demonstrates nanomolar potency in several NSCLC cell lines, and is more potent than certain approved alkylating chemotherapy agents.
- 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 the background of KEAP1 mutations.

Future directions

- Testing of LP-184 in model systems such as organoids and xenografts to support clinical translation
- Identifying tumor types by primary site, histopathology and/or biomarker signature for optimal positioning of LP-184
- Determining synergistic combination agents to address current unmet needs of reducing drug resistance and dose-dependent adverse events in multiple cancers

## References

[1] Testa, Ugo et al. "Lung Cancers: Molecular Characterization, Clonal Heterogeneity and Evolution, and Cancer Stem Cells." Cancers vol. 10,8 248. 27 Jul. 2018, doi:10.3390/cancers10080248

[2] Frank, Rieke et al. "Clinical and Pathological Characteristics of KEAP1- and NFE2L2-Mutated Non-Small Cell Lung Carcinoma (NSCLC)." Clinical cancer research : an official journal of the American Association for Cancer Research vol. 24,13 (2018): 3087-3096. doi:10.1158/1078-0432.CCR-17-3416

[3] Namani, Akhles/twar et al. "NRF2-regulated metabolic gene signature as a prognostic biomarker in non-small cell lung cancer." Oncotarget vol. 8,41 69847-69862. 18 Jul. 2017, doi:10.18632/oncotarget.19349

[4] Barrera-Rodríguez, Raúl. "Importance of the Keap1-Nrf2 pathway in NSCLC: Is it a possible biomarker?." Biomedical reports vol. 9,5 (2018): 375-382. doi:10.3892/br.2018.1143

[5] The AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discovery. 2017;7(8):818-831

[6] http://tcgaportal.org/TCGA/Lung_TCGA_LUAD

## Contact

Aditya Kulkarni, PhD
Senior Research Scientist

aditya@lanternpharma.com