RADR™ : Development and Clinical Validation of Lantern Pharma's AI engine: Response Algorithm for Drug Positioning and Rescue

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Abstract

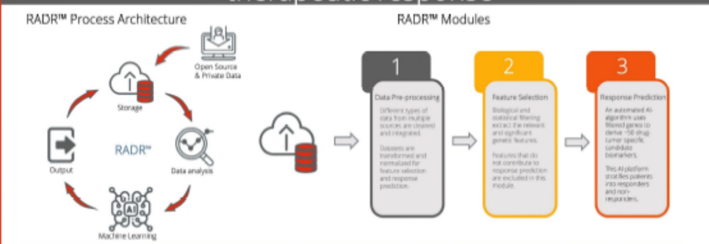
Background:
The Response Algorithm for Drug positioning and Rescue (RADR™) technology is Lantern Pharma's proprietary Artificial Intelligence (AI)-based machine learning approach for biomarker identification and patient stratification. RADR™ is a combination of three automated modules working sequentially to generate drug- and tumor type-specific gene signatures predictive of patient responses to treatment.

Methods:
RADR™ integrates genomic data, drug sensitivity and systems biology inputs with supervised machine learning strategies to generate gene expression-based responder/non-responder profiles for specific tumor indications with high accuracy. In addition, RADR™ identifies new correlations of genetic biomarkers with drug activity. Pre-treatment patient gene expression profiles, along with corresponding treatment outcomes, were used as algorithm inputs. Model training is typically performed using an initial set of genes derived from cancer cell line data, when available, and further applied to patient data for model tuning, cross-validation and final gene signature development. Model testing and performance computation were carried out on patient records held out as blinded datasets. Response prediction accuracy and sensitivity were among the model performance metrics calculated.

Results:
On average, RADR™ achieved a response prediction accuracy of 80% during clinical validation. We present retrospective analyses performed as part of RADR™ validation using independent datasets of patients from selected cancer types treated with approved drugs including chemotherapy, targeted therapy, and immunotherapy agents. For example, retrospective application of the RADR™ program to a Paclitaxel trial in breast cancer patients suggests that the number of patients in the treatment arm could have been reduced from 92 unselected patients to 24 biomarker-selected patients to observe the same number of responders. In addition, we cite published evidence correlating genes from RADR derived biomarkers with increased Paclitaxel sensitivity in breast cancer.

Conclusions:
The enhanced value of the RADR™ platform architecture is derived from its validation through the analysis of approximately 58 million oncology-specific clinical data points and 3541 patient records. By implementing unique biological, statistical, and machine learning workflows, Lantern Pharma's RADR™ technology is capable of deriving robust biomarker panels to pre-selecting true responders for recruitment into clinical trials and thereby improving the success rate of oncology drug approvals.

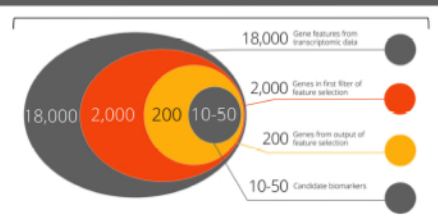
RADR™ is identifying gene signatures correlated with therapeutic response



RADR™'s AI-based machine learning approach for gene signature identification and patient stratification is a combination of three sequential automated modules. These modules include: data pre-processing, feature selection, and response prediction. The RADR™ process architecture illustrates the overview of the engine's workflow.

RADR™ has demonstrated remarkable drug response prediction accuracy in clinical validation and continues to be optimized for improved performance.

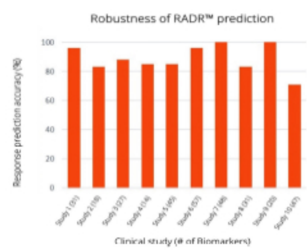
The proprietary RADR™ workflow initially funnels more than 18,000 gene features from whole transcriptomic datasets of each individual into a reduced set of ~2000 features. This step is followed by gene filtering via biological and statistical methodologies yielding ~200 significant genes and ultimately 10-50 candidate gene signatures.



Feature selection ensures that genes that do not contribute to response prediction are excluded from the output dataset. The prediction component subsequently applies an AI-driven reduction algorithm to the previously filtered genes (~ 200), generating a targeted set of typically less than 50 candidate gene signatures predictive of response to a particular drug.

External validation and drug development capabilities of our growing AI engine - RADR™

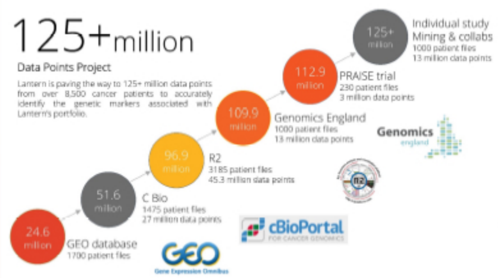
Clinical validation of RADR™ performance using gene signature identification



Study #	Drug(s)	Cancer indication	Ref
1	Paclitaxel	Breast	1
2	Paclitaxel	Breast	2
3	Paclitaxel	Breast	3
4	Paclitaxel	Ovarian	4
5	Paclitaxel + FEC	Breast	5
6	Paclitaxel + FAC	Breast	6
7	Erlotinib	Lung	7
8	Sorafenib	Lung	7
9	Pembrolizumab	Melanoma	8
10	Tamoxifen	Breast	9

- The RADR™ platform was tested on publicly available clinical patient data sets (blind sets) and achieved an average prediction accuracy rate greater than 80% in 10 independent clinical studies.
- Many of the gene signatures derived by RADR™ for different drug-tumor interactions have demonstrated biological significance and are reported to be correlated with enhanced drug sensitivity.

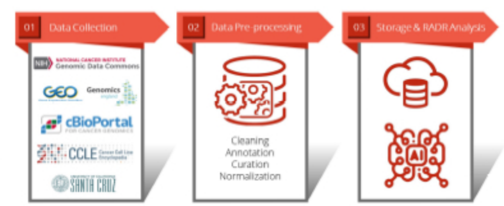
RADR Big Data Roadmap: Designing the RADR™ platform to Optimize Clinical Applications for LP-184


125+million
Data Points Project
Lantern is paving the way to 125+ million data points from over 8,500 cancer patients to accurately identify the genetic markers associated with Lantern's portfolio.
24.6 million
GEO database
1700 patient files
51.6 million
C Bio
1475 patient files
27 million data points
96.9 million
R2
3185 patient files
45.3 million data points
109.9 million
Genomics England
1000 patient files
13 million data points
112.9 million
PRAISE trial
230 patient files
3 million data points
125+ million
Individual study
Mining & collabs
1000 patient files
13 million data points
Genomics england
cBioPortal
FOR CANCER GENOMICS
GEO
Gene Expression Omnibus

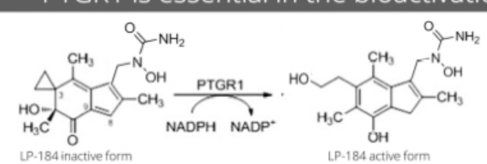
RADR™ 125+M Big Data Roadmap
We are accelerating the robustness of RADR™ by working towards 125+ million data points from real- world patient data by the end of this year. The RADR™ algorithm is written to analyze gene expression data on a large scale and we can validate its identified drug tumor genetic signatures. Over the next few months, RADR™ will analyze 125+ million data points and will identify genetic signatures most common among prostate, lung, ovarian and kidney cancers.

Data collection methodologies

RADR™'s database is built on data from various publicly available sources, in-house generated data and from biopsy samples obtained through collaborations. Data is pre-processed, followed by data storage & RADR™ analysis. Pre-processing includes cleaning, curation, annotation, and normalization of the data by data scientists. Once data is pre-processed, data is stored in a cloud-based database for subsequent RADR™ analysis.



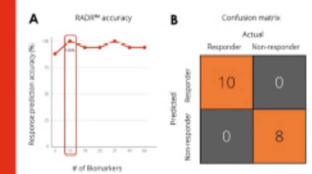
PTGR1 is essential in the bioactivation of the fulvene class of compounds



LP-184, a next-generation analog of the Phase 2 drug LP-100, is a DNA Damage Repair inhibitor being developed primarily as a non-hormone, non-chemotherapy option for the growing indication of taxane- and hormone-resistant metastatic prostate cancer. PTGR1 converts LP-184 to its active form, therefore PTGR1 is essential for LP-184 activity.

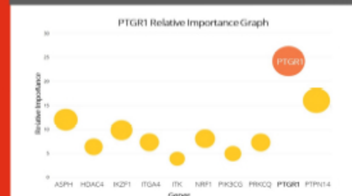
Drug development & clinical trial design using RADR™

To advance LP-184 into clinical stages and achieve accelerated approval, we have employed RADR™ to identify genetic markers unique to solid tumors targeted by LP-184. Using RADR™, a set of 10 genes was identified whose expression levels predict sensitivity to LP-184 with 100% accuracy. Out of these, PTGR1 emerges as a significant gene predictor that is in agreement with the perceived mechanism of action of LP-184.



RADR™ validation for LP-184 sensitivity in preclinical experiments
RADR™ was used to analyze our proprietary preclinical dataset on LP-184 sensitivity to and baseline gene expression profiles of 57 cell lines from the NCI-60 panel. Figure A highlights prediction accuracy across a range of signature numbers. Starting from >18,000 genes, RADR™ identified a 10-gene signature in solid tumors predictive of response to LP-184 treatment with an overall accuracy of 100%. Figure B shows the confusion matrix of the model outcome.

RADR™ is now being used to inform the direction of a targeted clinical trial for our drug candidate LP-184



Relative importance of LP-184 signature genes (plot above)
In this relative variable importance graph, gene weightage analysis was performed using Garson's function to analyze the relative ranking of 10 genes from a set of 66 genes in the LP-184 signature in solid tumors. PTGR1 (Prostaglandin Reductase 1) stands out as the gene with the highest relative importance.

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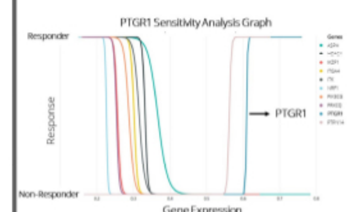
PTGR1 is associated with positive response to LP-184 (graph below)

In this sensitivity analysis graph, the effect of gene expression on the response variable is studied across LP-184 gene signatures using the lekprofile function. High expression of PTGR1 (Prostaglandin Reductase 1) is correlated to positive response to LP-184.



Numerous studies have determined that PTGR1 expression is elevated in several tumor types, including prostate. RADR™ analyses indicate that tumor cells with high PTGR1 expression are more sensitive to the DNA damage drug, LP-184. Independent studies demonstrate that PTGR1 is responsible for converting LP-184 to its active form. These two results provide strong and compelling identification of PTGR1 as the most prominent biomarker for predicting patient responses to LP-184 treatment for multiple indications. RADR™ analyzed a total of 2204 prostate cancer patients from 14 different studies and identified that on average 30% of the patient population showed high PTGR1 expression, and 39% of the patient population showed intermediate PTGR1 expression, representing a group of patients that has the potential to be partial responders to LP-184.

References

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