RADR®

Response Algorithm for Drug Positioning & Rescue

Precision Oncology Medicine Platform **White Paper**

Lantern Pharma

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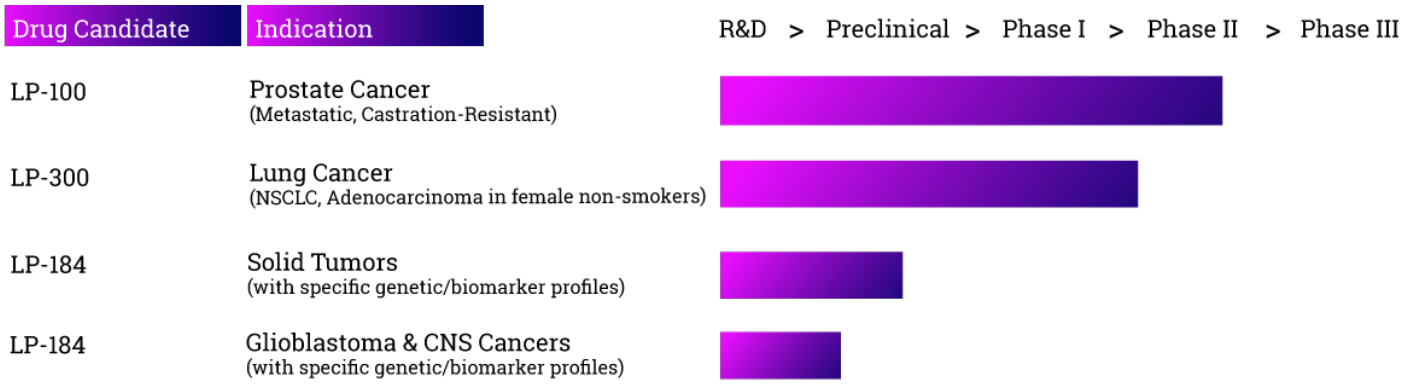
Our A.I.-based platform, RADR® is used in the development of our pipeline of oncology therapies illustrated in the Lantern pipeline below. We use RADR® to assist in key activities that help to compress the cost and time involved in oncology drug development process:

1. understanding and uncovering of potential mechanisms of response between the cancer and our drug candidates,
2. identifying potential combination therapy approaches with approved drugs that should be considered with our pipeline, and
3. accelerating the development of a robust gene or biomarker signature as a CompanionDx for use in identifying patients believed most likely to benefit from our drug in a clinical setting.



Lantern Pharma

WELCOME to Our Platform

Lantern Pharma is a clinical stage biopharmaceutical company innovating the rescue, revitalization and development of precision therapeutics in oncology.

In line with our mission to target the right patients with the right drugs, the compounds in Lantern Pharma's pipeline have been developed using our proprietary platform RADR® that allow us to potentially have a more targeted route to the patient.

Traditional drug development has been plagued with low success rates, long drug development cycles, and exorbitant development costs. Furthermore, many serious cancers with smaller patient populations lack targeted treatments due to limitations of the current drug development paradigm. Recent advances of numerous 'omics' technologies (genomics, transcriptomics, epigenomics, proteomics etc.) and rapid advances in science and medicine are generating exabytes of valuable unexploited knowledge that is widely distributed in multiple big databases with several orders of accessibility, complexity and variety.

Much of this data is not being systematically applied to the development of next-generation therapeutics, thus preventing the optimization of drug development utilizing the understanding of technology, science, medicine, markets and commercial opportunities.

The efficient and intuitive use of big data remains a bottleneck and a challenge to the pharmaceutical industry.

Taken together, these factors underscore the need for fundamental new approaches to drug discovery and development.

We are applying multiple new methods and approaches to developing our own pipeline of small molecule oncology therapeutics.

Our A.I.-based repurposing and development process is the foundation of our precision oncology and drug re-innovation model.

We believe RADR® is a novel method of identifying the most appropriate gene signatures correlated with drug efficacy because it combines the comprehensiveness and efficiency of machine learning and big data analytics with the expertise and intuition of human experience in drug development.

"Today we are able to understand the genomic or biomarker basis of why certain patients respond exquisitely to certain therapies in cancer, while others fail to respond at all.

At the same time, we are now able to access the computing power and algorithms required to more deeply understand the clinical and scientific data that are available to us, and then propose precision focused trials aimed at providing us with a compressed development timeline."

Panna Sharma
President & CEO

Introduction

"RADR® analyzes genetic data using advanced machine learning algorithms to stratify trial patients into responder and non-responder groups. The technology is aimed at enabling more efficient novel drug positioning, existing drug repositioning, and the rescue and repurposing of shelved therapeutic assets."

The costs associated with the development of oncology drugs remain extremely high, and failures during clinical stages remain common, despite significant progress in oncology therapy research and development. The high cost and low success rate hindering oncology drug development and approvals often stem from an ongoing inability to appropriately stratify patient populations prior to clinical trial enrollment, as exemplified in Figure 1 (Wong, Siah, & Lo, 2018). RADR® was designed specifically as an A.I.-enabled platform that leverages machine learning to uncover and predict patient response to specific drugs and drug classes through the deep analysis of genomic and transcriptomic data from both clinical and preclinical studies. We are continually improving RADR® to pinpoint patient groups that can be best treated by our therapies and the therapies of our partners.

Genetic heterogeneity in both cancers and patients makes it difficult to target patients most likely to respond to a drug being evaluated in a clinical trial. This can often result in oncology clinical trial endpoints that are not statistically significant. Accordingly, many oncology drugs fail to demonstrate the clinical benefit required to obtain regulatory market approval. Drugs can fail for many reasons ranging from commercialization to safety to efficacy, but quite often not finding a robust patient group where efficacy and improvement goes beyond the standard of care is a primary reason.

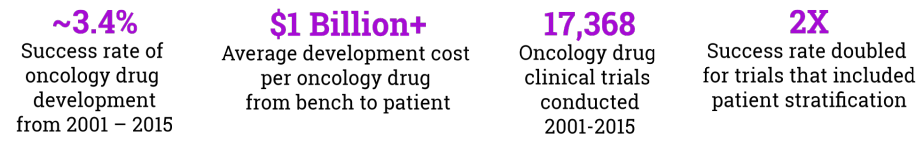


Figure 1. Oncology Drug Development Statistics

We are focused on personalizing cancer therapies for patients and potentially improving the outcome for the patient. Our solution is through the development of a process to stratify patient populations into likely responders and non-responders for a wide variety of oncology therapies, providing the potential to de-risk clinical trials and increase the likelihood of successful FDA approval. Enriching the study with responders results in smaller sample sizes for clinical trials. This potentially leads to reduced research costs, and expediting important new therapies for cancer patients.

Our operational workflow for clinical translation of a drug candidate can be suitably adapted for: 1. early stage drug candidates to help define indications or combinations or targeted effective doses using a high-throughput screening approach; 2. late stage or shelved clinical drug candidates to help define the patient populations believed most likely to respond favorably using a companion diagnostic approach; and, 3. currently marketed drugs or generic drugs for a new or different cancer indication on a defined patient population using the 505(b)(2) pathway.

With the development of a proprietary artificial intelligence (A.I.) platform, RADR® , we have been dedicated to solving the problems associated with poor patient selection since our founding in 2014.

RADR® performs genetic biomarker data analysis using advanced machine learning algorithms. These algorithms stratify patients into likely responder and non-responder groups with the help of identified gene signatures, providing vital information for de-risking and maximizing the success of drug development.

RADR® is focused on improving the placement of novel drugs, repositioning of existing drugs, and rescue and repurposing of shelved assets through application in biomarker-driven oncology clinical trials.

Using A.I., Big Data, Genomics and Computational Biology

"Big-data and A.I.-driven approaches have the potential to change the speed, scale and cost of drug rescue and development, which we believe are perfect problem areas for the application of A.I. ."

Drug development is expensive, challenging and is often beleaguered by protracted timelines. Delays in patient identification and enrollment, lengthy and inconclusive biomarker studies, and challenges in achieving a suitable level of efficacy in later clinical phases in the intended patient population often prevent cancer patients from getting the right therapies and challenge the economic returns for biopharma companies. In cancer drug development, this has led to costs that exceed, on average, over 1 billion USD to develop an approved drug, and a timeline that can range from 10 to 15 years. We believe, that with the significant advances in genomics, biological methods, translational research, and data-driven biology and the simultaneous increase in patient data sharing, genomic data availability, accessibility of large-scale cloud computing and the globalization of cancer research we are entering into a new era of cancer drug development armed with a substantially enhanced understanding of how to treat and manage cancers.

We have been actively developing our RADR® platform through the development, curation and application of data that we believe is integral to the development of molecularly targeted anti-cancer compounds that can be candidates for future therapies. Over the past 18 months our platform has grown from under 10 million data points to over 500 million data points that have been reviewed and organized to provide insights into drug development and drug rescue in oncology. We anticipate, based on our current platform development roadmap, that our RADR® platform will have over 1 Billion data points by the end of 2020. The majority of our data points cover:

- Transcriptome sequencing and gene expression (RNA) studies;
- Drug sensitivity data;
- DNA copy number and mutation data;
- Tumor stage and type data;
- Histology and cancer sub-type data;
- Patient data (age, sex, race/ethnicity) that is de-identified and IRB (Institutional Review Board) compliant; and
- Prior cancer treatment data (drug treatment history, including drug class and treatment response).

As our RADR® platform continues to develop and grow both in data and in feature sets, we have used it in an increasing range of drug development and rescue activities, including:

1. Prediction of potential patient response based on drug sensitivity and machine learning derived biomarker signatures
2. Development of "patient molecular profile avatars," templates that can serve as a guide for both future clinical trials and preclinical studies using patient-derived xenograft (PDX) models and 3D organoid models
3. Creation of insights into potential molecular pathways (genomic, epigenomic, enzymatic and proteomic) that correlate to mechanisms of action or key activity.
4. Identification of potential combination programs with currently approved therapies that have the potential to be additive or synergistic to our portfolio of compounds

RADR® Platform and Workflow

Our business model is focused on in-licensing drugs that have failed, been abandoned or otherwise do not meet clinical endpoints, and then developing a precision oncology approach that clarifies the mechanism of action, potential combination drug usage (if required), and the right, potentially responsive, patient population. We then aim to partner that compound or program to larger pharma and biotech companies. We have validated our business model by successfully out-licensing one drug within 18 months of in-licensing, and have two promising compounds in our pipeline. We are continually improving RADR® to pinpoint patient groups that can be best treated by our therapies and the therapies of our partners. Our approach is schematically represented in Figure 2.

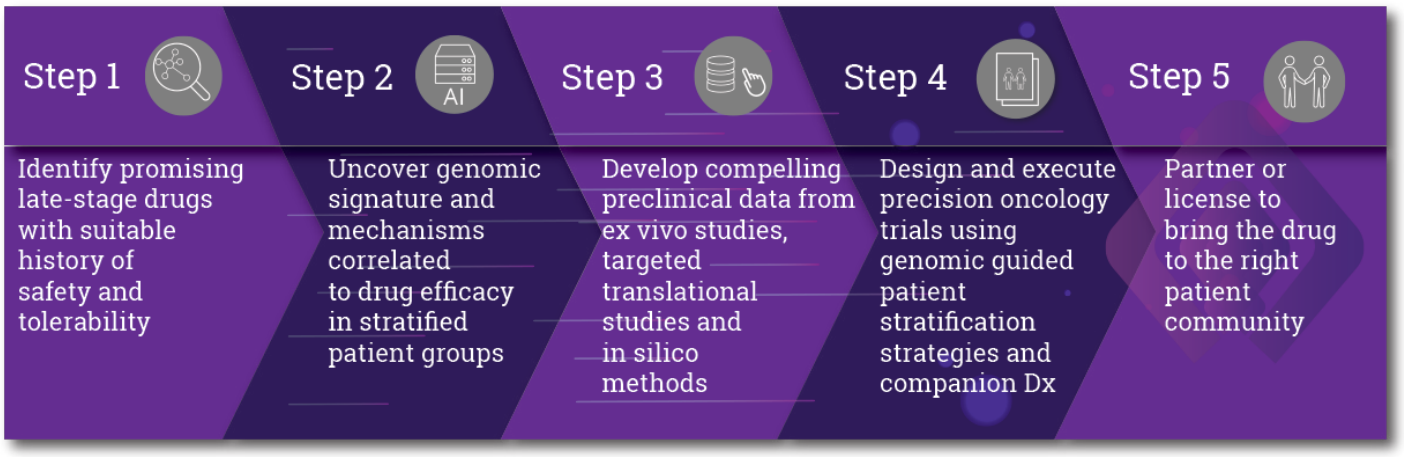


Figure 2. Lantern Pharma's Approach

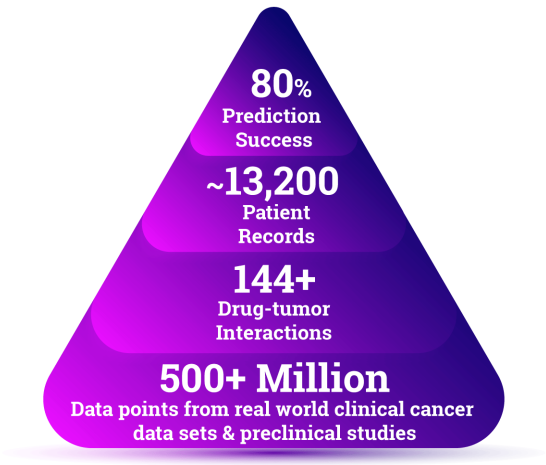
Our A.I. platform incorporates automated supervised machine learning strategies along with big data analytics, statistics and systems biology to facilitate identification of new correlations of genetic biomarkers with drug activity. The value of the platform architecture is derived from its validation through the analysis of over 500+ million oncology-specific clinical and preclinical data points, more than 144 drug-cancer interactions, and over 13,200 patient records (Figure 3). RADR® utilizes cancer cell line gene expression profiles and drug sensitivity data (IC50) as one of its input types. In the case studies described below RADR® has been able to distinguish responders from non-responders with an average historical accuracy of over 80%.

Presently, RADR® has been used to generate genetic signatures believed to have applicability for the majority of FDA approved drug-tumor indications. External validation, through retrospective data analysis of patient datasets from 10 independent clinical studies, achieved an average response prediction accuracy greater than 80%, and internal validation of 144 drug-tumor interactions in cell lines achieved an average accuracy of greater than 85%.

A distinct benefit of the RADR® A.I. platform is its ability to integrate biological knowledge and data-driven feature selection to generate hypothesis-free biomarker signatures. This can then aid in identifying novel targets for predictive screening and drug development.

The RADR® platform is enabled through access to, and analysis of, a number of key datasets: (i) publicly available databases (ii) data from commercial clinical studies and trials and (iii) our proprietary data generated from *ex vivo* 3D tumor models specific to drug-tumor interactions, other preclinical studies and (iv) data generated in collaboration with our research partners.

Figure 3. RADR® Platform Architecture



RADR®'s A.I.-based machine learning approach for hypothesis-free biomarker identification and patient stratification is a combination of thre sequential automated modules: data pre-processing, feature selection, and prediction.

1 

Data pre-processing modules clean, transform, and normalize the raw input data in preparation for downstream analysis. Drug sensitivity and genetic data are processed by standardized methods such as log transformation, median centering and rescaling.

2 

Feature Selection modules select the subset of genes which are most likely to predict drug response. Genes that do not contribute to response prediction are excluded. RADR®'s proprietary workflow performs gene filtering via biological, statistical and machine learning-based methods, yielding a reduced but significant gene list.

3 

Prediction modules use A.I. and machine learning methods to generate a set of candidate predictive biomarkers (typically less than 50) from the intermediate number of filtered genes (approximately 500).

RADR® Modules

The RADR® pipeline computes a gene signature which stratifies patients into responders and non-responders for a particular drug and cancer type. This in silico analysis uses advanced machine learning, artificial intelligence, and the power of the RADR® database to identify a manageable number of biologically focused and statistically meaningful biomarkers. The system is orchestrated by modern bioinformatics workflow systems and optimized to take advantage of the scalability of cloud computing resources.

The data-driven feature selection module uses a combination of biology and statistics, gene expression and drug sensitivity (IC50) values to select the top 500 or so genes from the 20,000 possible genes in the human genome. First, RADR® filters the genes that are highly correlated with drug sensitivity using Pearson correlation function and $p \leq 0.05$ cut-off. These statistically significant genes are further filtered through the biological signaling pathway analysis (using Pathcards database covering 3840 pathways) and gene network analysis (using Pathway commons database covering 1,546,602 interactions) to shortlist biologically relevant genes. Genes that make up this layer are either related to the drug's mechanism of action, heavily interconnected with each other in a gene interaction network, or act as drug-specific response biomarkers. Pathway analysis will filter genes directly or indirectly connected with the drug's target pathway(s). Gene network analysis filters genes based on degree of connections with other genes. Lastly, another inductive learning algorithm, termed the 'Relief algorithm' ranks and assigns weights to these filtered genes based on drug sensitivity (IC50). Highly ranked genes from this feature selection module are used in the subsequent prediction module.

RADR® Machine Learning Platform is developed using Artificial Neural Network (ANN) as the primary predictive algorithm. At the same time, it can also predict using other supervised algorithms such as Support Vector Machine, Random Forest, K-Nearest Neighbors, Logistic Regression and Penalized Multivariate Regression models. Each algorithm is trained with input data to predict drug sensitivity (regressor models) and stratify patients as either responders or non-responders (classifier models). Drug sensitivity value prediction is typically performed using a regression model whereas patient response group prediction is usually performed using a classification model.

Model tuning and optimization is another important aspect of predictive model building. Hyperparameter search algorithm is in place to perform tuning and optimization of models to produce lowest cross validation error. Model is evaluated using performance metrics such as Accuracy, Area under the ROC Curve, Sensitivity, Specificity, Precision (for classifier models), Root Mean Square Error and Mean Absolute Error (for regressor models). Feature reduction algorithm in RADR® helps to reduce the number of predictive genes from ~500 to a signature panel of 10 to 30 genes. This set of genes carries highest coefficient to predict drug sensitivity and highest variable importance to classify responders and non-responders. Genes that do not help in predicting the output variables are eliminated sequentially.

Artificial Neural Network Features and Validity for RADR®

Artificial Neural Network (ANN) provides faster and more accurate predictions than other machine learning algorithms including 1) Random Forest (RF), 2) Support Vector Machine (SVM) - with linear and Gaussian Kernels, 3) KNN - k nearest neighbor, 4) Generalized (penalized) Linear Regression with Elastic Net, 5) Logistic Regression, and 6) Fractional Logistic. We know this from a detailed study using the CCLE database including 35 distinct preclinical drug-tumor datasets, 20 approved cancer drugs and 1000.

cell lines covering 16.97 million data points. Using data and results from large scale comparison of algorithms as represented in figure 4, ANN has the highest average accuracy. We are confident that ANN will be the most effective method as we incorporate more data into RADR® along with multiple enhancements such as hyperparameter tuning using GridSearch, and stepwise elimination. Based on our testing, we report that ANN is the optimal algorithm capable of capturing non-linear relationships as well as providing higher prediction accuracy even for small or limited datasets when compared to other algorithms. We believe that this validation of ANN will translate robustly when scaling to real world clinical data

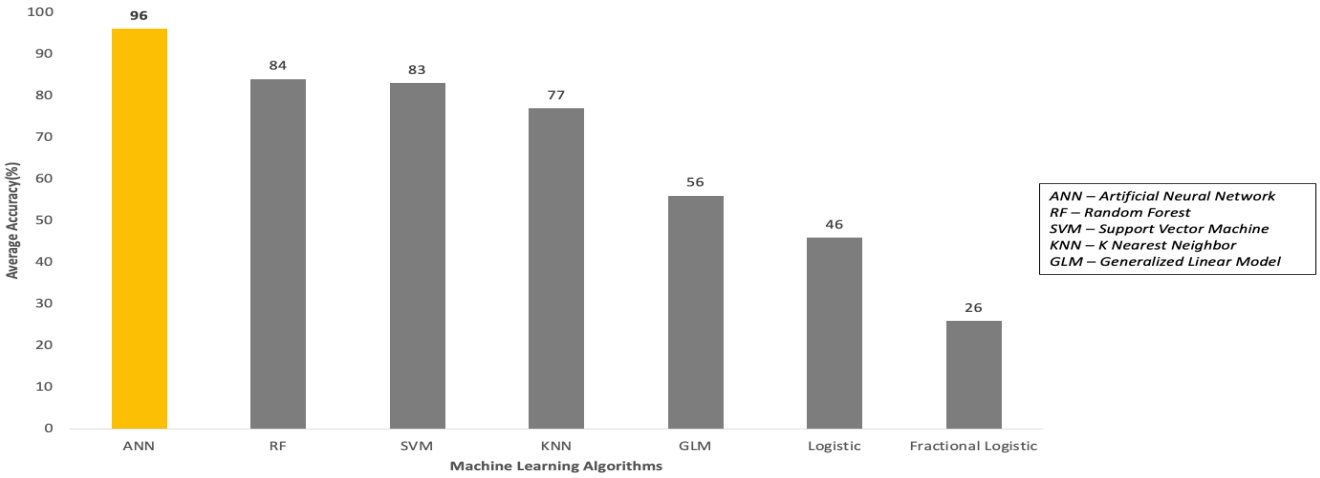


Figure 4. ***Accuracy comparison across different machine learning algorithms on CCLE datasets.***

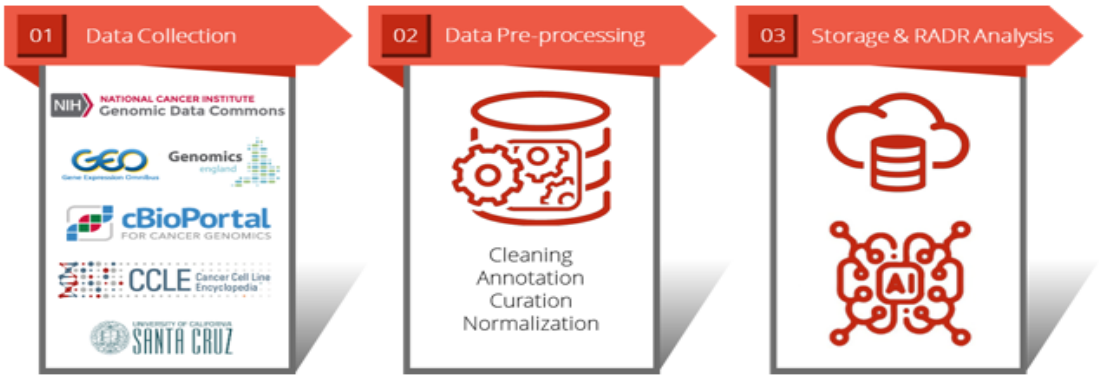


Figure 5. ***Data collection methodologies***

RADR®'s database is being built on data from various publicly available sources, in-house generated data and from tumor biopsy samples obtained through collaborations. Data is pre-processed, followed by data storage & RADR® analysis. Pre-processing includes cleaning, annotation, curation 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. This scheme is outlined in figure 5.

Predictive models are evaluated using multiple performance metrics such as Accuracy, AUC (Area Under the ROC Curve), Sensitivity and Specificity. Findings from RADR® have also been assessed and validated using clinical data. Lantern Pharma's RADR® platform may be applied to oncology research and development to derive robust biomarker panels. Through the use of unique biological, statistical and machine learning workflows, RADR® provides the potential to pre-select true responders for recruitment into clinical trials, which may improve the success rate of oncology drug approvals and has the potential to significantly reduce costs and schedules of cancer drug development.

Roadmap to 1 Billion+ Data Points

Lantern Pharma has developed a roadmap for RADR® to process over 1 Billion+ real-world clinical and preclinical data points. Data point numbers are derived from gene expression values representing whole transcriptome profiles of patient tumor specimens and other data types from cell lines such as drug sensitivity and mutation data. These data points will be specific to the solid tumors being targeted by Lantern Pharma's oncology drug pipeline: prostate, ovarian, lung, liver, kidney, thyroid and pancreatic cancer and glioblastoma..

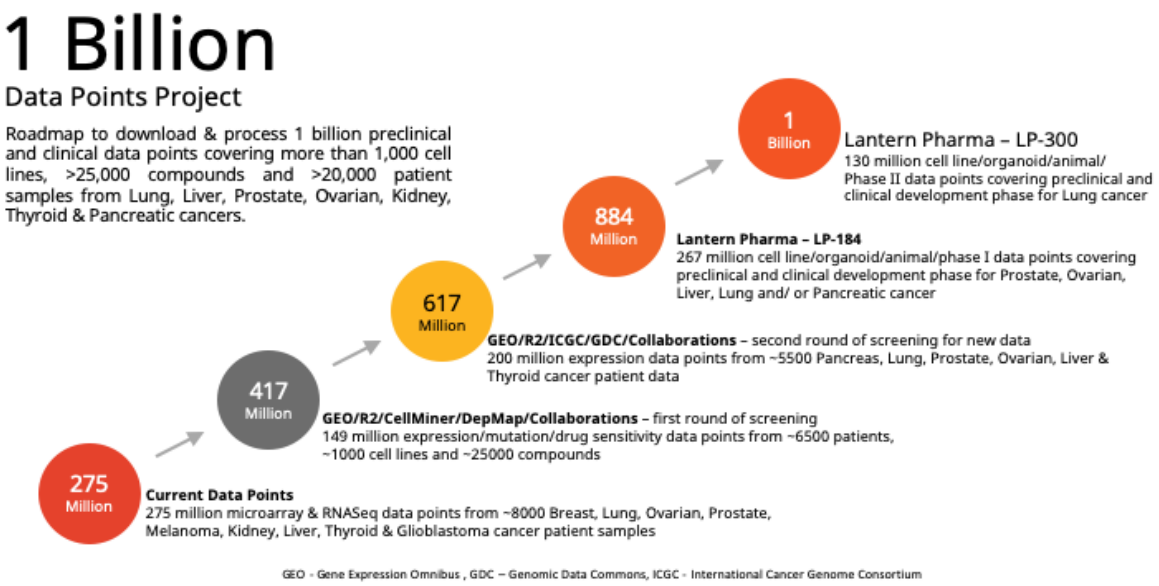


***Figure 6.* RADR® 1 Billion + Big Data Roadmap**

RADR® is being developed to process large data sets that will be funneled down to gene signatures relevant to a drug-tumor inter- action. By designing the RADR® platform to optimize clinical applications for LP-184, Lantern is accelerating the robustness of RADR® by working towards 1 Billion + data points from clinical and preclinical data by end of 2021. The RADR® algorithm is written to analyze gene expression data on a large scale and we can validate its identified drug-tumor specific genetic signatures. In the near future, RADR® will analyze 1 Billion+ data points from proprietary and collaborative data sources as well as from internally curated public databases, thereby facilitating identification of relevant drug and tumor type specific gene signatures.

We leverage various publicly available databases which are incorporated into the RADR® database for performing further analyses and generating insights.

Gene Expression Omnibus is an NCBI repository that includes data on gene expression profiles of patients with different tumor types. It provides raw as well as processed data.

R2 is a Genomics Analysis and Visualization Platform developed by Academic Medical Center (AMC) Amsterdam, Netherlands. It provides processed gene expression data from sources like GEO and TCGA.

CellMiner is a genomic and pharmacologic tool developed by the National Cancer Institute to explore transcript levels and drug activity patterns in the NCI-60 cell line set. It also provides curated and comparable processed expression, mutation, methylation and copy number variation data on the Cancer Cell Line Encyclopedia (CCLE) and Genomics of Drug Sensitivity in Cancer (GDSC) data sets.

GDC/TCGA (Genomic Data Commons) is developed by the National Cancer Institute covering genomic data on ~29 tissue types, covering raw as well as processed data.

cBioportal provides visualization, analysis and download of large-scale cancer genomics data sets representing data form various institutes/projects.

Genotype-Tissue Expression (GTEx) database provides gene expression data of multiple normal tissues types.

RADR® Informing Future Clinical Trials

RADR® is now being used to inform the direction and planning of a targeted clinical trial for our drug candidate 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 our DNA damaging agent, LP-184. Independent studies demonstrate that LP-184 is likely to be transformed into its bioactive form via PTGR1 activity (Yu et al., 2012). These results provide compelling evidence identifying PTGR1 as the most prominent biomarker for predicting patient responses to LP-184 treatment for multiple cancer indications. RADR® has analyzed data on more than 3000 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 at least partial responders to LP-184.

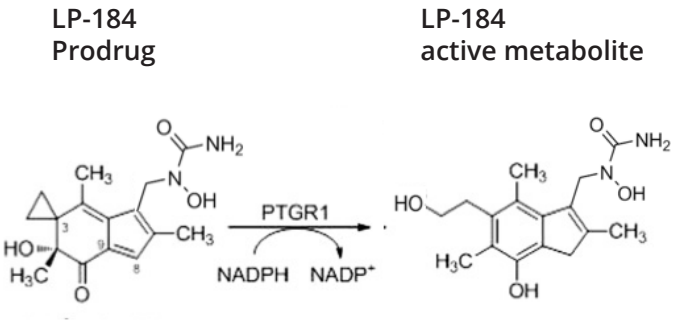


***Figure 7.* PTGR1 is expected to be essential for LP-184 activity.**

PTGR1 (Prostaglandin Reductase 1) stands out as the gene with highest relative importance among genes in the LP-184 response signature.

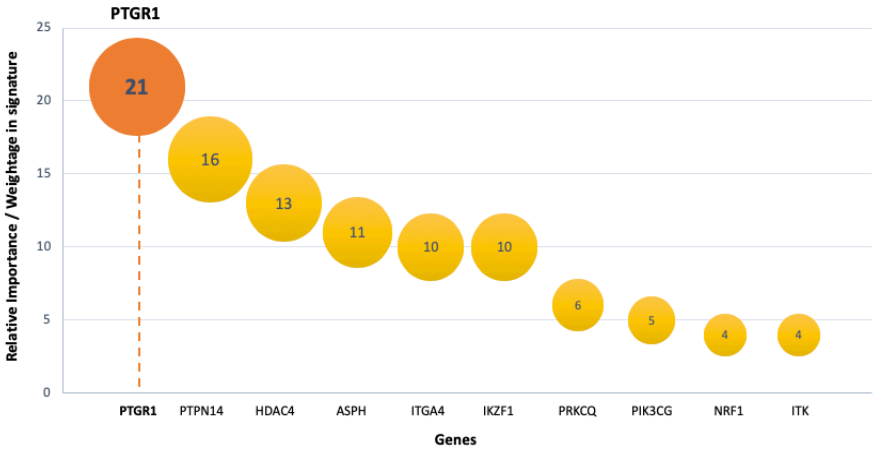
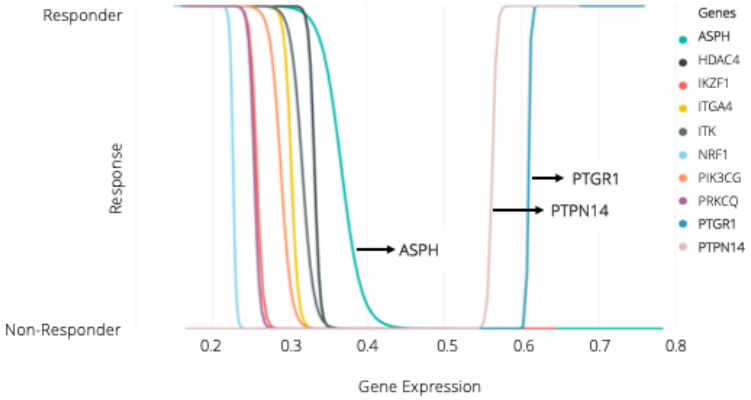


***Figure 8.* Relative importance of LP-184 signature genes**

In this relative variable importance graph, gene weight 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 response gene signature. PTGR1 (Prostaglandin Reductase 1) stands out as the gene with the highest relative importance when we compare an average score over 100 iterations.

***Figure 9.* PTGR1 is associated with positive response to LP-184**

In this sensitivity analysis graph, the effect of gene expression on the response variable is studied across the LP-184 response gene signature using the lekprofile function from neural network. High expression of PTGR1 shifts the profile of response to LP-184 from non-responder to responder.



Illustrative Examples and Case Studies

Case Study 1: Paclitaxel combination treatment in breast cancer patients and prediction of responders using RADR®

Paclitaxel is a standard chemotherapy agent indicated for the treatment of breast cancer. As part of RADR® validation, retrospective analysis of a dataset from 109 patients who had received Paclitaxel treatment followed by 5-Fluorouracil/ Epirubicin/ Cyclophosphamide (FEC) was performed.

Pre-treatment patient tumor gene expression profiles covering more than 16,000 transcripts and corresponding Paclitaxel combination treatment outcomes were obtained from the GEO database entry GSE32646 (Miyake et al., 2012). RADR® extracted the 45 most relevant genes, out of >16,000 identified as correlating to Paclitaxel combination treatment outcomes, that may be used to significantly predict Paclitaxel combination responses.

Model training was performed using an initial set of 90 genes derived from feature selection algorithm of RADR® using panel of 22 breast cancer cell lines, further applied to data from 37 patients for model tuning and final gene signature development. Model testing was conducted using 50 patient records as the blinded hold-out set.

Figure 10A highlights the comparison of response prediction accuracy across a range of biomarker numbers in this historical clinical study. We observed that responder prediction accuracy increased from about 45% with two predictive genes to the maximum achieved 85% with an optimal number of 45 genes.

The historical objective response rate for Paclitaxel clinical trials without biomarker-based pre-screening of patients is highly variable in the range of 20-60%. Out of 50 patients included in the blinded test set who did not undergo biomarker screening, RADR® correctly predicted 17 out of 20 actual responders (85% true positive rare 10B).

Figure 10A. ***Paclitaxel + (FEC) - Breast Cancer***

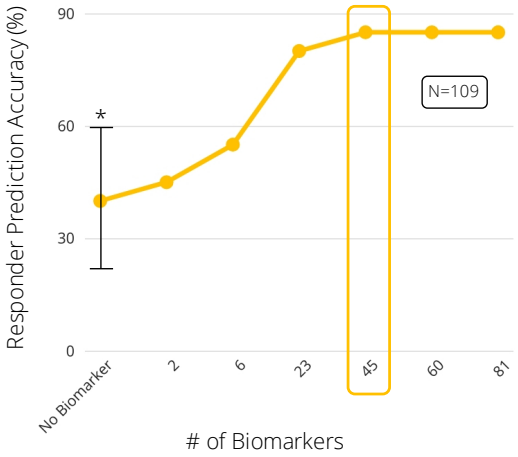


Figure 10B. ***Paclitaxel + (FEC) - Breast Cancer***

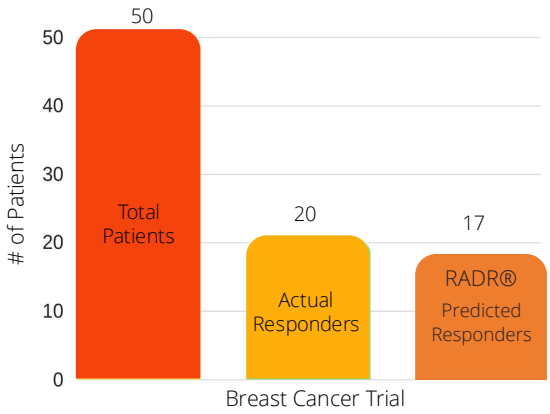


Figure 10A&B. ***RADR® validation by retrospective analysis of Paclitaxel + FEC response in a breast cancer trial***

These data demonstrate the robust predictive capabilities of the RADR® platform. The results indicate the potential value of the RADR® platform if it had been applied to pre-screen patients for this Paclitaxel trial.

Pre-screening could have reduced the number of patients in the treatment arm from 109 unscreened patients down to 50 patients identified to have biomarkers associated with a predicted positive treatment response. Patients not indicated for the trial may have been excluded, rendering a potential 34-40% response rate compared to the observed rate of 17%.

Furthermore, the RADR®-derived list of 45 potential biomarkers includes candidate genes such as PINK1. RADR®-driven extraction of PINK1 as one of the predictive genetic features is supported by published evidence that decreased PINK1 expression correlates with enhanced Paclitaxel sensitivity in breast cancer (MacKeigan, Murphy, & Blenis, 2005).

In retrospective analysis of a Paclitaxel combination trial results in breast cancer, RADR® showed 85% responder prediction accuracy based on 45 candidate signature genes.

Case Study 2: Solid tumor indications exposed to LP-184 in cancer cell lines and prediction of drug sensitivity using RADR®

LP-184 is a DNA damaging agent in our pipeline, being developed in a range of solid tumors. It has shown strong nanomolar potency in vitro and remarkable tumor regression in a xenograft tumor model in vivo (Staake et al., 2016).

As part of RADR® model building, we obtained cell line gene expression profiles covering >18,000 transcripts from the NCI-60 cell line screening database and proprietary LP-184 sensitivity records.

Model training was performed using an initial set of 66 genes derived from feature selection algorithm of RADR® using a panel of 39 solid tumor cell lines that was also used for model tuning and final gene signature development. Model testing was conducted using 18 cell line records as the blinded hold-out set.

Application of the RADR® platform resulted in the identification of 10 genes whose expression level was predictive of response to LP-184 at an overall accuracy of 100%. The trend of response prediction accuracy across a range of potential biomarker numbers is depicted in Figure 11A.

The sensitivity or true positive rate was 100%, since all 10 out of the actual 10 sensitive cell lines were correctly predicted by RADR® (Figure 11B). The RADR® platform thus demonstrated statistical rigor in its hypothesis-free identification of these clinically relevant biomarkers.

Genes from the final 10 predictive list have been shown to be functionally involved in LP-184-specific mechanisms of action, confirming RADR®'s selection.

***Figure 11A.* LP-184 - Solid Tumors**

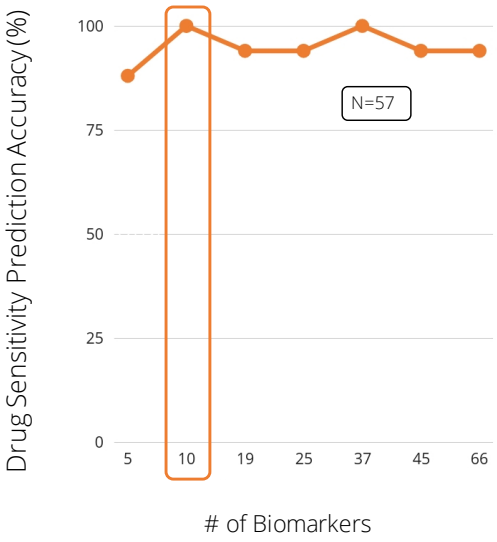


***Figure 11B.* LP-184 - Solid Tumors**

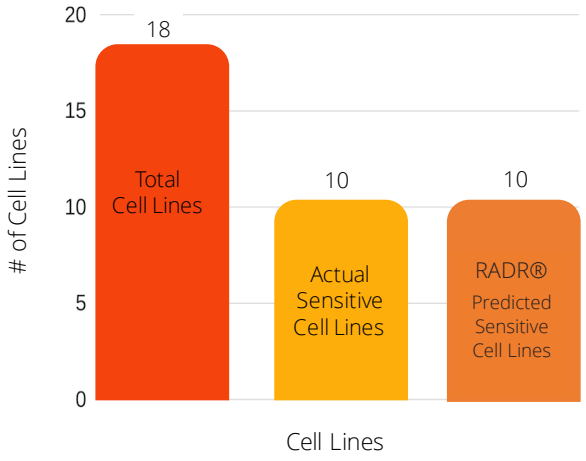


***Figure 11A&B.* RADR® model building via analysis of LP-184 sensitivity in preclinical cell-based assays in solid tumor indications**

As an illustrative example, the enzyme PTGR1 with enone reductase activity is known to be critical for the metabolic activation of Irofulven (Yu et al., 2012), a compound in the same class as LP-184.

The presence of PTGR1 in the top 10 RADR®-derived predictive genes improves confidence in the algorithm's output. Lantern intends to further validate these preliminary biomarker analyses using LP-184 sensitivity and gene expression data derived from fresh tumor biopsy samples.

For our drug LP-184, the RADR®-derived response prediction in terms of sensitivity or true positive rate was 100%, since all 10 out of the actual 10 sensitive cell lines were correctly predicted.

Case Study 3: Lung cancer patients undergoing Erlotinib (Tarceva®) treatment and response prediction using RADR®

Erlotinib is an EGFR-targeted drug used in the treatment of Non-Small Cell Lung Cancer (NSCLC). As part of RADR® validation, retrospective analysis of a dataset from 25 NSCLC patients who had received Erlotinib treatment was performed.

Pre-treatment patient tumor gene expression profiles covering ~16,000 transcripts and corresponding Erlotinib treatment outcomes were obtained from the GEO database entry GSE33072 (Byers et al., 2013). RADR® extracted and identified the 48 biomarkers most relevant to the identification of Erlotinib responders. Model training was performed using an initial set of 90 genes from feature selection algorithm of RADR® using a panel of 46 lung cancer cell lines, further applied to data from 7 patients for model tuning and final gene signature development. Model testing was conducted using 18 patient records as the blinded hold-out set.

After comparing response prediction accuracy across a range of biomarker numbers in this historical clinical study, it was observed that overall response prediction accuracy increases from about 67% with 3 predictive genes to the maximum achieved 100% with an optimal number of 48 genes (Figure 12A).

As shown in Figure 12B, data for a total of 18 patients were included in the testing set and all 5 actual responders were correctly predicted by RADR® with 100% sensitivity.

The RADR®-derived list of 48 potential clinical biomarkers included genes such as SHC1 (Astsaturov et al., 2010), that have been shown to be associated with Erlotinib response in NSCLC patients.

Figure 12A. ***Erlotinib - Lung Cancer***

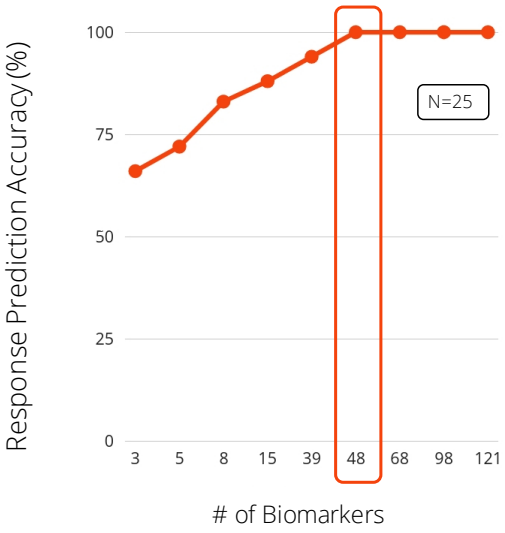


Figure 12B. ***Erlotinib - Lung Cancer***

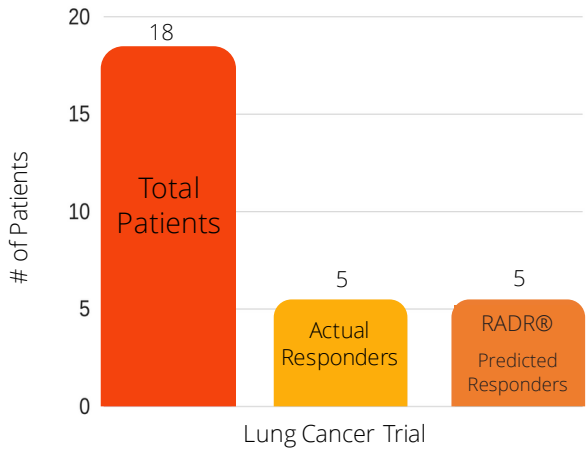


Figure 12A&B. ***RADR ® validation by retrospective analysis of Erlotinib response in a lung cancer trial***

The RADR®-derived list of 48 potential clinical biomarkers included genes that have been shown to be associated with Erlotinib response in NSCLC patients, such as SHC1 (Astsaturov et al., 2010), which is one of the most highly correlated 5 genes predictive of response in this study.

Case Study 4: Melanoma patients undergoing Keytruda® (Pembrolizumab) treatment and response prediction using RADR®

Keytruda® is a PD-1 targeted immuno-oncology agent primarily approved for the treatment of advanced melanoma. As part of RADR® development, retrospective analysis of a dataset from 28 melanoma patients who had received Keytruda® treatment was performed.

Pre-treatment patient tumor gene expression profiles covering ~16,000 transcripts and corresponding Keytruda® treatment outcomes were obtained from the GEO database entry GSE78220 (Hugo et al., 2016).

Model training was performed using an initial set of 20 genes derived from feature selection algorithm of RADR® using 18 patients for model tuning and final gene signature development. Model testing was conducted using 10 patient records as the blinded hold-out set.

RADR® extracted the 9 most significant biomarkers believed capable of stratifying patients as complete responders, partial responders or non-responders.

Application of the RADR® platform resulted in the identification of 9 genes whose expression level was predictive of response to Keytruda® at an overall accuracy of 100%. Figure 13A displays the trend of response prediction accuracy across a range of potential biomarker numbers.

As shown in Figure 13B, a total of 10 patients were included in the testing set. All 5 actual complete responders, 3 actual partial responders and 2 actual non-responders were correctly predicted by RADR® with 100% sensitivity and specificity.

Figure 13A. Keytruda® - Melanoma

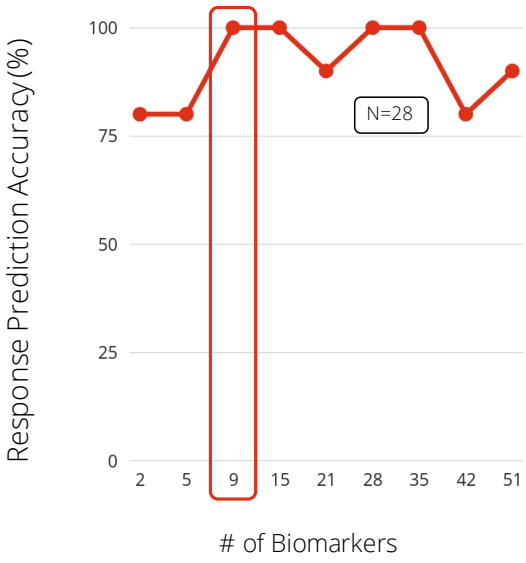


Figure 13B. Keytruda® - Melanoma

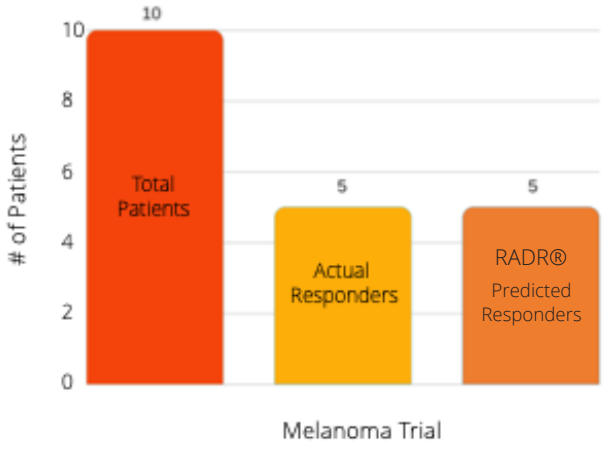


Figure 13A&B. RADR® validation by retrospective analysis of Keytruda® response in a melanoma trial

Disclosure: *Keytruda® is a registered trademark of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

RADR® extracted the 9 most significant biomarkers capable of stratifying Keytruda®-treated melanoma patients as complete responders, partial responders or non-responders.

Case Study 5: NSCLC cell lines exposed to LP-300 and analysis of differentially expressed genes using RADR®

LP-300 is one of our rescue drug candidate in clinical development as a potential combination therapy for non-smoking female NSCLC patients with adenocarcinoma.

To derive mechanistic insights on LP-300 activity, the NSCLC adenocarcinoma cell line HCC827 was treated for 2h with LP-300 alone at concentrations of 1mM and 15 mM and gene expression level changes were measured by whole transcriptome profiling using RNAseq. A control sample with no treatment for the same duration was used as the baseline gene expression level comparator. In vitro studies indicate that the target-specific effects of LP-300 potentially correlate with the covalent modification of accessible cysteine residues important in protein function/structure. These could be involved in disruption/ blocking of cofactor binding sites resulting in blocking of oncoproteins such as ALK, MET and EGFR that are more common in female non-smokers than in any other group. Other potential mechanisms of action of LP-300 could include impact on stress induced oxidoreductases thereby allowing LP-300 to exert its chemoenhancing effects in the presence of chemotherapeutic agents. LP-300 is postulated to potentiate anti-tumor cytotoxicity of standard of care chemotherapy agents such as cisplatin by increasing tumor cell sensitivity to oxidative stress via induction of NRF2/ NFE2L2 and in turn of its target genes. Additionally, NRF2-driven upregulation of the expression of antioxidant proteins that protect against oxidative damage triggered by inflammation is known to protect against chemotherapy-associated toxicity.

Considering the hypothesis that LP-300 exerts part of its effects via the NRF2 pathway (Rojo de la Vega et al., 2018; Namani et al., 2018), differential gene expression analysis of transcriptome data was performed. Using a threshold of fold change > 2 out of a set of 51 curated NRF2 target genes as well as NRF2 itself, we determined the top significantly upregulated genes in response to LP-300 exposure at both the concentrations tested. These genes include NFE2L2, NQO1, PHGDH, HMOX1, SLC7A11, SRXN1, SOX2, GPX2, GPX3, GPX4, GPX7, G6PD, SIRT1, ITGB2 and BCL2. Interaction network of selected genes is shown in figure 14. These genes preferentially map to detoxification of reactive oxygen species, glutathione metabolism and inflammatory response pathways.

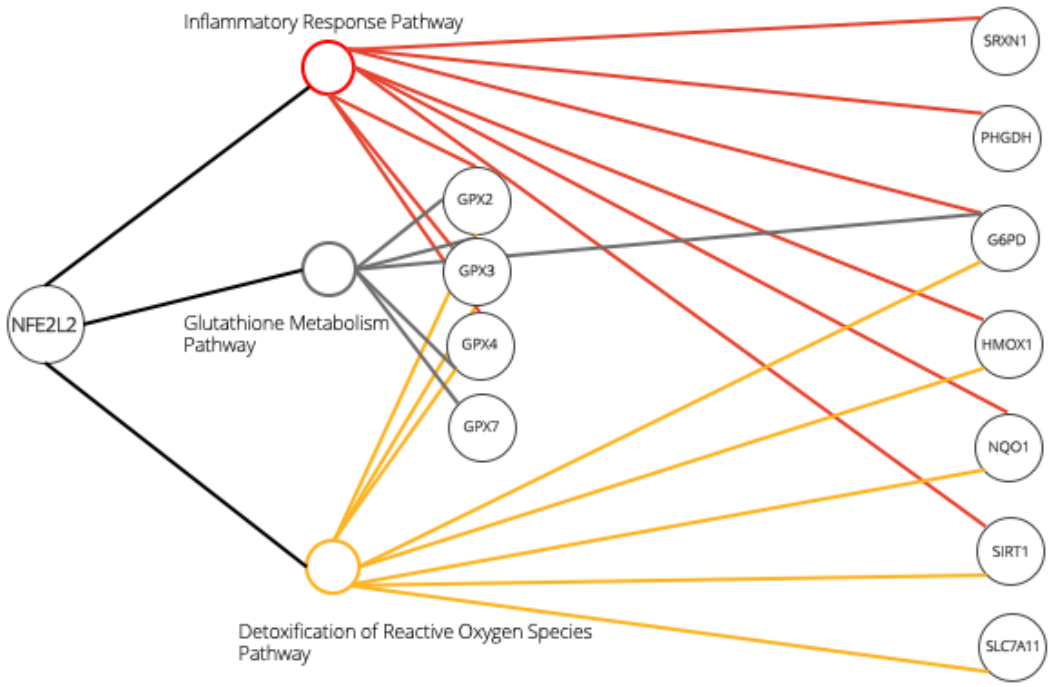


Figure 14. Network of upregulated genes in response to LP-300 treatment in NSCLC cell line.

LP-300 exposure in a selected NSCLC cell line results in an NRF2/NFE2L2 activation signature mapping to genes involved in inflammatory response, glutathione metabolism and detoxification of reactive oxygen species. This supports its chemosensitizing role in potentiating anti-tumor cytotoxicity.

In summary, RADR®- driven drug response predictions are focused on improving potential trial outcomes and reducing contraindicated patient selection. RADR® aims to provide a potent and accelerated in silico approach, complementing in vitro wet laboratory techniques, when determining patient eligibility for a particular therapy.

Outlook

RADR®'s distinguishing characteristics arise from its focus on cancer-specific real world evidence. RADR® incorporates ongoing development of genetic feature selection methodologies that can be game changing in the development of Companion Diagnostics (CDx) for oncology patient management. It generates predictive gene signatures from drug-tumor interaction models applicable in prospective patient stratification in a clinical setting.

The A.I. technology behind RADR® has a cloud-based scalable architecture with automated building blocks that dramatically accelerate parallel data crunching. RADR® leverages leading-edge, multi-layer analyses (biological and statistical), machine learning and big data biomarker management to provide the potential to bring substantially improved efficiency to oncology therapeutic development.

We are engaged in continuous development and validation of its RADR® platform. Enhanced versions of the platform will focus on drug-specific model building and validation for specific histopathological cancer subtypes. Further, it will optimize feature selection in network and pathway analyses by applying filters for gene interaction subtypes and gene ranking, respectively.

These advances are aimed at improving the robustness of the platform by enabling the rediscovery of known mechanistic insights of drugs, and uncovering novel targets for new drug candidates as well as approved therapies. In addition, RADR® aims to incorporate multiomic datasets including preclinical and clinical mutational, proteomic and epigenetic profiles. Lantern is dedicated to designing a next generation process that has the potential to significantly alter oncology drug research and development trends and accelerate the path to personalizing cancer treatment.

Our goal is to rescue and repurpose the extensive library of failed and abandoned oncology drugs by leveraging the power of its RADR® platform and improving the potential to personalize therapies and reduce developmental costs. RADR® will help by providing an additional and significant, state-of-the-art tool aimed at reducing the risks, costs and time that are inherent to today's efforts in oncology drug development and clinical trial development. This has the potential to result in better guidance for clinicians, more effective treatments for patients, and potentially reduced costs for the healthcare system.

Our mission, to personalize cancer therapy by leveraging the latest advancements in A.I. and genomics, can be achieved through collaborative partnerships with pharmaceutical and biotechnology companies, and with leading research institutions and cancer centers.

Lantern Pharma

About Lantern Pharma

Lantern Pharma is a clinical stage biotechnology company focused on innovating the cancer drug development process by rescuing and repositioning drug candidates that others have tried, but failed, and developing new drugs of our own using advanced genomics and artificial intelligence.

Our main focus is to rescue and develop new oncology therapies by targeting specific cancer patient populations and treatment indications identified by leveraging RADR®, our proprietary A.I. enabled engine created and owned by us.

We use our RADR® platform to assess clinical drug candidates together with big data sources of information to both target and evaluate subpopulations and identify new therapeutic indices and gene signatures that will potentially correlate with drug efficacy and favorable patient response to treatment.

Lantern acquires and in-licenses drug assets and then rescues, revitalizes or develops targeted oncology-focused therapies using genomic data, machine learning, and computational biology to identify the patient groups believed most likely to respond to the drug, and to clarify the potential underlying mechanism(s) of action.

We embrace nascent technology

Emerging technologies can help transform the pace and insight of oncology drug development. We currently leverage:

- Artificial Intelligence (A.I.)
- Machine Learning
- Large Scale Genomic Data
- Cloud Computing

These techniques and methods have been robustly tested in many different industries and applying them to healthcare will help solve two of the central problems in cancer therapy:

1. Stratifying patients into responders and non-responders, ultimately providing the potential to de-risk and streamline clinical trials.
2. Clarifying insight into the mechanism of action for drugs, resulting in improved molecular targeting.

Both of these problems have great potential to be improved through the application of A.I., which helps to shorten the drug development timeline and significantly reduce costs.

We are continuously working to advance our precision oncology therapeutics platform through partnerships with cloud computing firms, hospitals, clinical healthcare centers, investigators, other biotechs and pharma companies, and tissue and data banks.

For more information visit www.lanternpharma.com, e-mail us at info@lanternpharma.com or

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