LEXOGEN
The RNA Experts

BigOmics® Analytics

Advancing Cancer Drug Discovery and Boosting Therapy Efficacy with Complete End-to-end Omics Solution

A Combined Case Study of Lexogen and BigOmics Analytics

Lexogen, a leader in NGS services and RNA-Seq expertise, has partnered with BigOmics Analytics, provider of the collaborative Omics Playground for advanced RNA-Seq and proteomics data analysis. Together, they deliver a **seamless, end-to-end omics solution designed to accelerate the advances of cancer drug discovery and to transform cancer therapeutics**. This case study showcases the power of their combined offering to accurately reveal common drug mode-of-action mechanisms and identify novel combinatorial therapies for solid tumors based on the recent publication by Raghuwanshi *et al.*, 2024.

Introduction & Summary

Forkhead box protein M1 (FOXM1) is a transcription factor involved in the gene regulation of proliferation, cell cycle, migration, and apoptosis and as such is often dysregulated in various cancers, including ovarian, colorectal, breast, esophageal, and prostate cancers. Overexpression and cytoplasmic relocation of FOXM1 confers resistance to chemotherapy and is associated with poor prognosis. **FOXM1 is therefore a promising target to sensitize therapy-resistant solid cancers**[1]. The authors highlight the anticancer potential of STL001, first-generation modification drug of a previously identified FOXM1 inhibitor. STL001 is highly selective and effectively downregulates FOXM1 expression leading to a reduced expression of FOXM1 target genes involved in cell proliferation, survival, and drug resistance. Further, treatment with STL001 significantly increased the sensitivity of cancer cells to various chemotherapeutic agents, including cisplatin, paclitaxel, and doxorubicin, across multiple cancer types suggesting its potential in targeting chemotherapy-resistance solid tumors. The combination of STL001 with chemotherapy leads to increased cancer cell apoptosis and increased drug efficacy.

Methods & Benefits

Whole transcriptome sequencing (WTS) is commonly used to reveal underlying pathways in cancer etiology and progression for therapeutic purposes. Here, it confirmed **the mechanism of action (MoA) for STL001** by comparison with the predecessor compound and a FOXM1 knock-down on the **transcriptome-wide level in multiple cancer systems**[1]. The authors identified known FOXM1 targeted pathways as well as new activities using Lexogen's WTS solution and demonstrated the potential of STL001 for clinical translation as combination therapy.

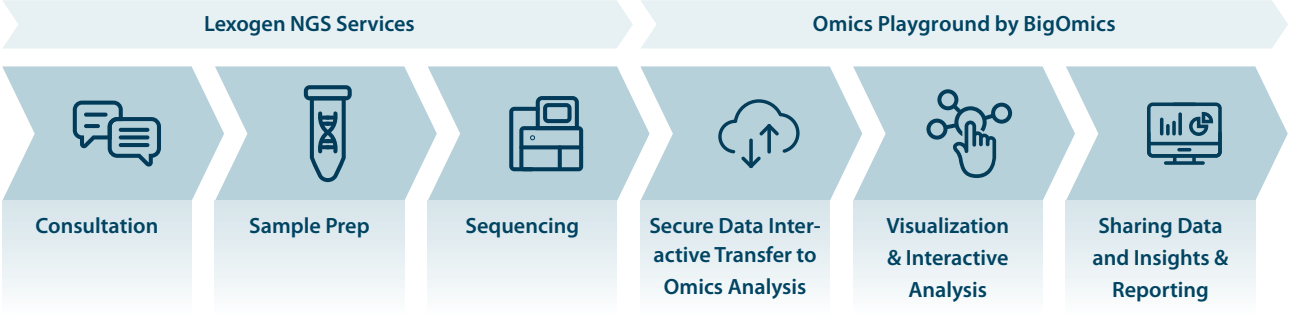
Lexogen's WTS Service Offers:

- ✓ High-quality results from low-input/rare samples
- ✓ Maximized consistency in streamlined manner
- ✓ Customizable solution for rapid output
- ✓ Deliverables include primary and secondary data analysis for seamless integration into Omics Playground

Omics Playground Differentiates through:

- ✓ Interactive, fast, and simple tertiary analysis for non-bioinformaticians
- ✓ Standardized analytics workflow and reporting
- ✓ Highly maintained, state-of-the-art algorithms
- ✓ Ideal for drug discovery studies

Streamlined Workflow of Lexogen NGS Services and BigOmics' Advanced Data Analysis



Results

Identification of Mode-of-action

Omics Playground identified a strong correlation between the expression profiles of STL001 and mTOR/PI3K inhibitors (Fig. 1), suggesting a shared influence on cell growth, proliferation, and survival. This overlap is attributed to common pathway interactions and shared downstream targets involved in mitotic checkpoints and DNA repair. The combined action of STL001 and mTOR inhibitors also enhances apoptosis, presenting a promising avenue for synergistic anticancer therapies.

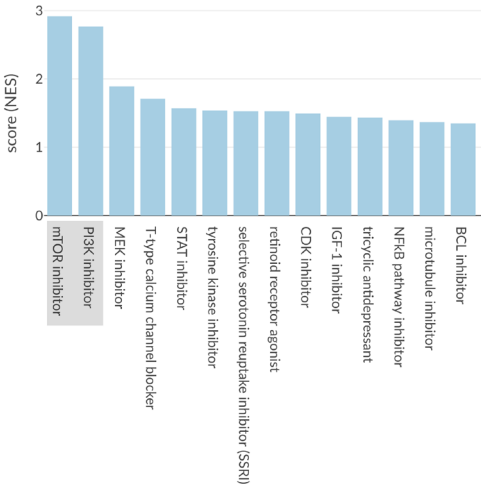


Figure 1 | Correlation in expression profiles between STL001 and mTOR/PI3K inhibitors, as highlighted using the L1000 Drug connectivity map meta-analysis implemented in Omics Playground.

Overcoming Chemoresistance with Combination Strategies

STL001 enhances the efficacy of several cancer treatments by acting as a cell cycle inhibitor, an apoptosis enhancer, and a DNA damage repair inhibitor[1]. This multifaceted mechanism allows STL001 to synergize with drugs like paclitaxel, doxorubicin, cisplatin, irinotecan, and 5-FU, intensifying their cytotoxic effects on cancer cells as also confirmed with Omics Playground (Fig. 2).

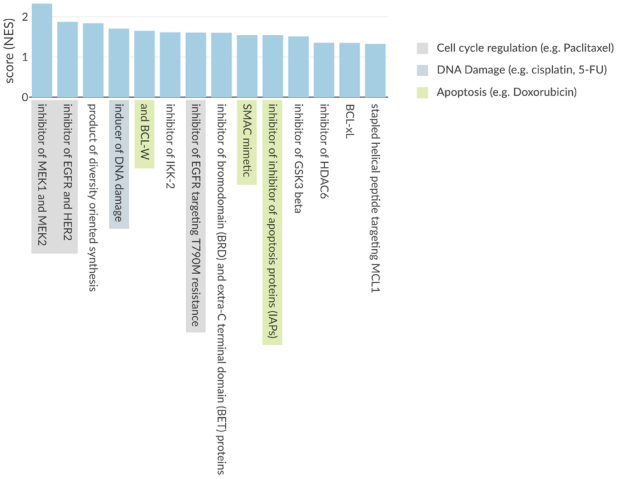


Figure 2 | Using the CTRP (v2) database developed by the Broad institute Omics Playground performed a meta-analysis based on the mechanisms of actions of the tested small molecules to identify mechanisms enhanced by exposure to STL001.

Discussion & Summary

RNA-Seq has emerged as a cornerstone of cancer research and drug discovery, providing crucial insights for the development of novel therapies, such as elucidating MoA and identifying mechanisms of drug resistance. Lexogen's tailored RNA-Seq solutions and services enable comprehensive drug discovery using Whole Transcriptome Sequencing, high-throughput screening, single-cell sequencing, and more.

By including public data sets, an extended gene set enrichment analysis was conducted on the Omics Playground. Tetrandrine was revealed as further synergistic therapeutics based on similar expression profiles for potential drug resistance reversal in combination therapy (Fig. 3).

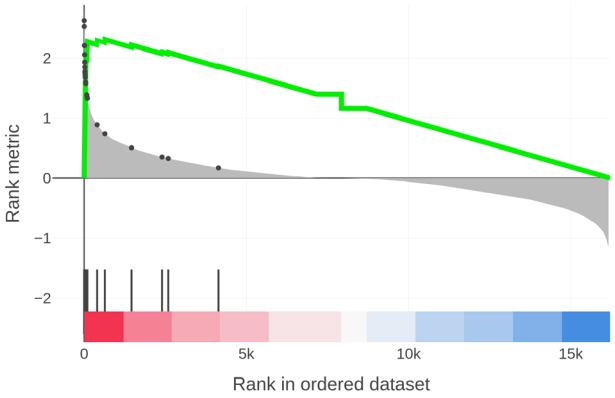


Figure 3 | Gene set enrichment analysis against the Drug database contained in the Omics Playground platform indicates a strong correlation in gene expression profiles between STL001 and Tetrandrine.

Lexogen is a leading provider of reagents and NGS services, specialized in RNA sequencing. Project-tailored services and rigorous quality control ensure accurate and reliable results even for the most demanding applications. **BigOmics Analytics** is a Swiss company that expedites tertiary analysis, by providing a centralized platform solution for scientists to efficiently scale their omics data analysis and obtain reproducible results.

The collaboration of Lexogen and BigOmics Analytics **significantly accelerates accurate MoA identification and prediction of most effective cancer therapies in patients**, and thus unlocks new potential in cancer drug discovery.

References

[1] Raghuwanshi *et al.*, 2024: Novel FOXM1 inhibitor STL001 sensitizes human cancers to a broad-spectrum of cancer therapies. Cell Death Discov. 10, 211. DOI: 10.1038/s41420-024-01929-0

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