Advancing High-Throughput Organoid Drug Screening: Automated Live-Cell Imaging and the Orbits Image and Data Analysis Pipeline

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INTRODUCTION

The dynamic and complex nature of biological systems has sparked a transition away from traditional flat cell cultures toward 3D organoid models. Although organoids better represent in vivo conditions, their high-throughput screening poses challenges, primarily due to intricate morphology and non-homogeneous responses. To address this, we've innovated a protocol for high-throughput drug screening with widefield microscopes, distinguishing cytostatic and cytotoxic responses at the organoid level[1-3].

To overcome the challenges related to high-throughput image and data analysis, we have developed 'Orbits', an innovative platform that integrates label-free AI image analysis with in-house developed drug response metrics tailored to high-throughput organoid drug screening and prediction of patient therapy response.

OBJECTIVES

To test the high-throughput compatibility of our protocol and image and data analysis platform, we have performed a drug screening for Auranofin. The drug was initially approved for rheumatoid arthritis and shows promise as an anti-cancer agent. Auranofin induces oxidative stress and disrupts the redox balance in cancer cells, leading to cell death. In this study we aimed to:

- Identify the best organoid drug response metric.
- Study the selectivity of Auranofin towards cancer cells by including normal epithelial lung organoids.
- Identify the most promising combination strategies based on selectivity and synergy. And overview of the selected compounds is shown in Figure 1.

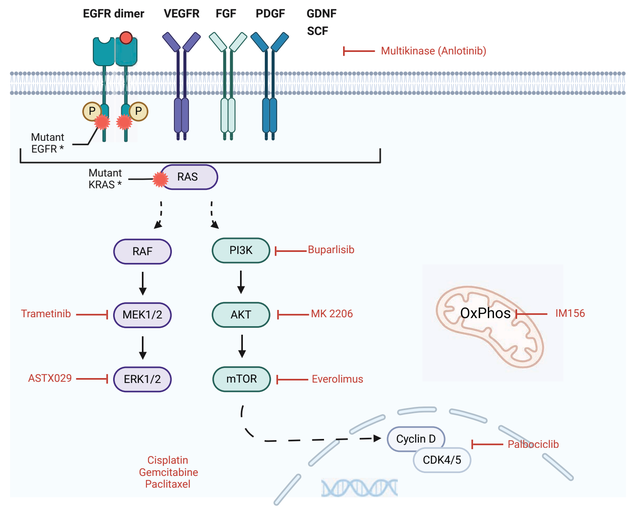

Figure 1: Overview of the compounds that were combined with Auranofin.

METHODS

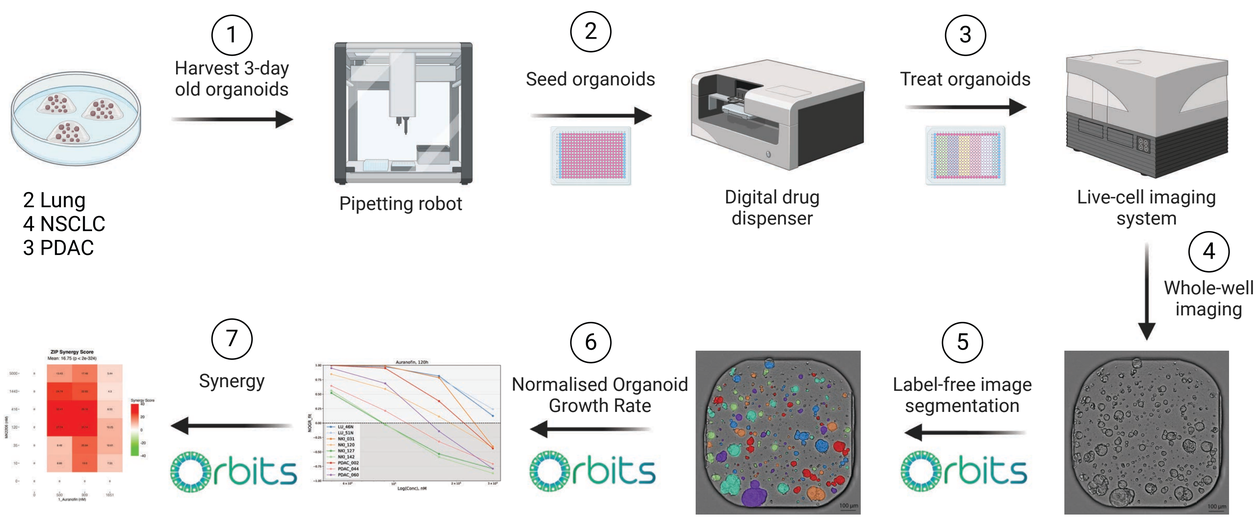

Figure 2: Workflow overview. Le Compte et al., JoVE, 2022.

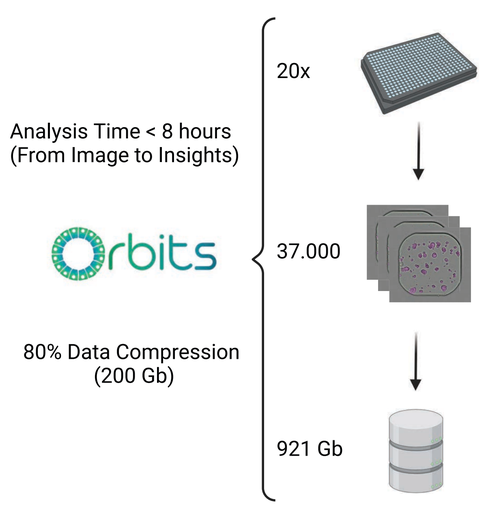

Figure 3: Image and data analysis pipeline.

RESULTS

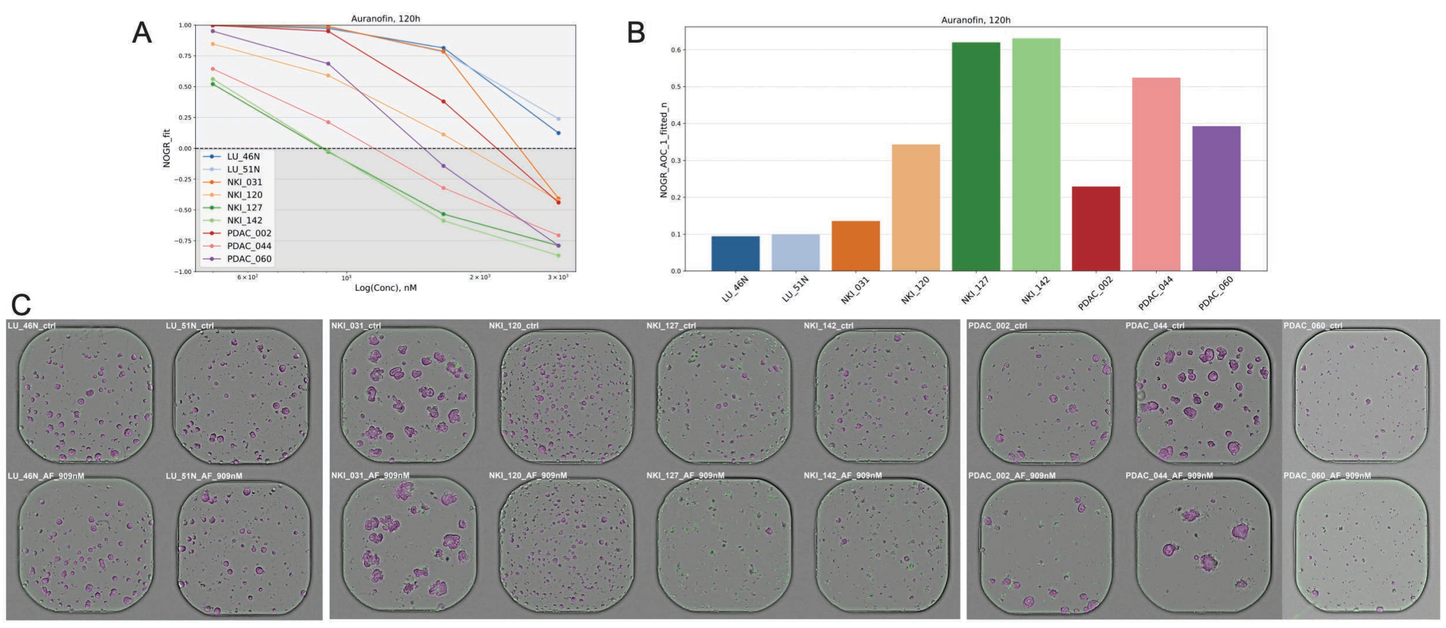

Figure 4. (A) Fitted dose-response curves of the Normalised Organoid Growth Rate (NOGR) for Auranofin monotherapy. (B) Area Over the Curve (AOC) of the fitted dose-response curves. (C) Representative images of organoids treated with vehicle or 909 nM Auranofin for 120h. Magenta shows the label-free image segmentation by Orbits. LU_: normal lung organoids. NKI_: non-small cell lung cancer organoids, kindly provided by E. Voest, Netherlands Cancer Institute. PDAC_: pancreatic ductal adenocarcinoma organoids.

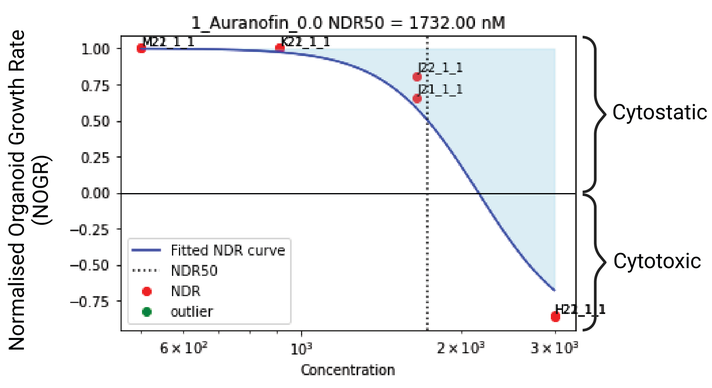

Figure 5: Normalised Organoid Growth Rate (NOGR). Blue area represents the Area Over the Curve (AOC).

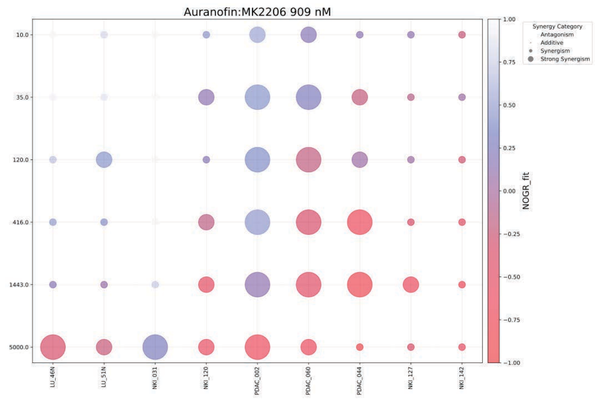

Figure 6: Bubble plot visualizing the ZIP synergy score (bubble size) and NOGR value (colour heatmap) for the combination of Auranofin and MK2206 in all organoid lines.

CONCLUSIONS

Drug Screening Pipeline:

- Established a major advancement in organoid-based drug discovery.
- Offered a robust protocol for high-throughput screening and automated data analysis.
- The Orbits Normalised Organoid Growth Rate (NOGR) significantly improves the identification of organoid drug responses and synergistic interactions from live-cell imaging.

Auranofin:

- Selective towards cancer cells compared to normal epithelial lung cells.
- Highly synergistic with the AKT inhibitor MK2206 in multiple tumor organoid lines.
- Additional organoid dependent synergistic interactions.

CONTACT

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Orbits image and data analysis platform:
www.orbits-oncology.com

Organoid drug screening services:
www.drugvision.ai

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