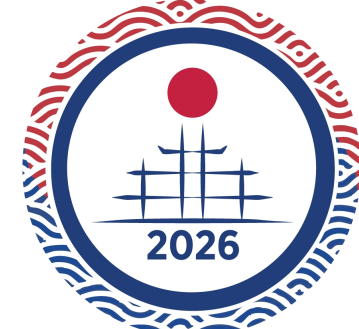




INTRODUCTION

Extensive-stage small cell lung cancer (ES-SCLC) is a highly aggressive malignant tumor with a 5-year overall survival rate of only 7%. Although first-line chemotherapy with the etoposide plus cisplatin (EP) regimen achieves a high initial response rate, acquired chemoresistance remains the major barrier limiting the long-term survival of patients. Gut microbiota and its metabolites have been well documented to modulate the progression and therapeutic efficacy of multiple malignancies, while their role in ES-SCLC chemoresistance remains largely uncharacterized.

METHODS

A total of 60 pathologically confirmed ES-SCLC patients treated with first-line EP chemotherapy were enrolled in this study, and stratified into the chemoresistant group (Re group, n=24) and non-chemoresistant group (NRe group, n=36) according to progression-free survival (PFS). Baseline fecal samples were collected from all enrolled patients for untargeted metabolomic profiling. In vitro, CCK-8 assay and Transwell migration assay were performed to verify the regulatory effect of β -ionone on the chemosensitivity of human SCLC parental H69 cells and chemoresistant H69AR cells.

ACKNOWLEDGEMENTS

Artificial Intelligence (AI) Use Disclaimer

No artificial intelligence (AI) tools were utilized in the development, creation, or drafting of this educational content. All material was produced exclusively by human subject matter experts with relevant clinical and scientific expertise.

RESULTS

There were no statistically significant differences in baseline clinical characteristics between the two groups, including age, gender, smoking history, drinking history, and family history of cancer. Untargeted metabolomic profiling identified β -ionone as the key differential metabolite, with a significantly higher abundance in the NRe group. Receiver operating characteristic (ROC) curve analysis showed that β -ionone yielded an area under the curve (AUC) of 0.696 for predicting chemoresistance. Preliminary in vitro functional assays confirmed that β -ionone significantly enhanced the sensitivity of H69AR cells to cisplatin and etoposide, inhibited tumor cell proliferation, and reversed the chemoresistant phenotype.

Figure 1. (A) Distribution of baseline clinical characteristics of enrolled ES-SCLC patients. (B) Bar plot of fold change of differential intestinal metabolites between Group Re and Group NRe. Red bars indicate metabolites significantly upregulated in Group NRe, and green bars indicate downregulated metabolites. (C) ROC curve of β -ionone for predicting chemotherapy resistance in ES-SCLC patients (AUC = 0.696), and comparison of β -ionone abundance between Group Re and Group NRe. (D) Feature importance ranking of differential metabolites via random forest model, identifying β -ionone as the core candidate biomarker for predicting chemotherapy resistance. (E,F) CCK-8 assay detecting the inhibitory effect of chemotherapy alone and the combination of β -ionone and chemotherapy on the proliferation of H69AR/H69 cells. (G) Transwell migration assay validating that β -ionone enhances the chemosensitivity of H69AR cells. (H) Colony formation assay validating that β -ionone enhances the chemosensitivity of H69AR cells.

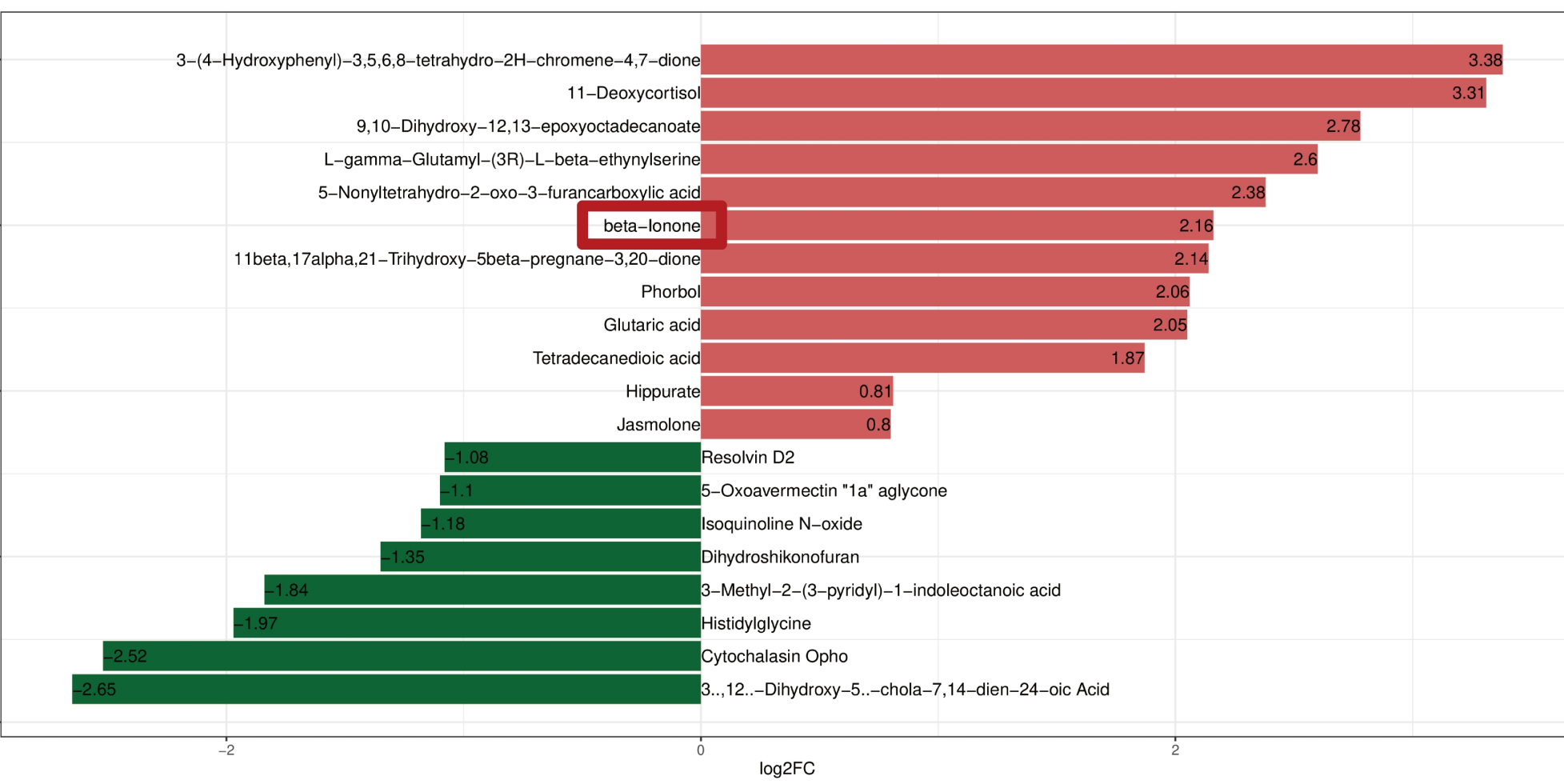
DISCUSSION AND CONCLUSION

Gut metabolite β -ionone is a promising predictive biomarker for the response to EP chemotherapy in ES-SCLC patients, and it can effectively enhance the chemosensitivity of SCLC cells.

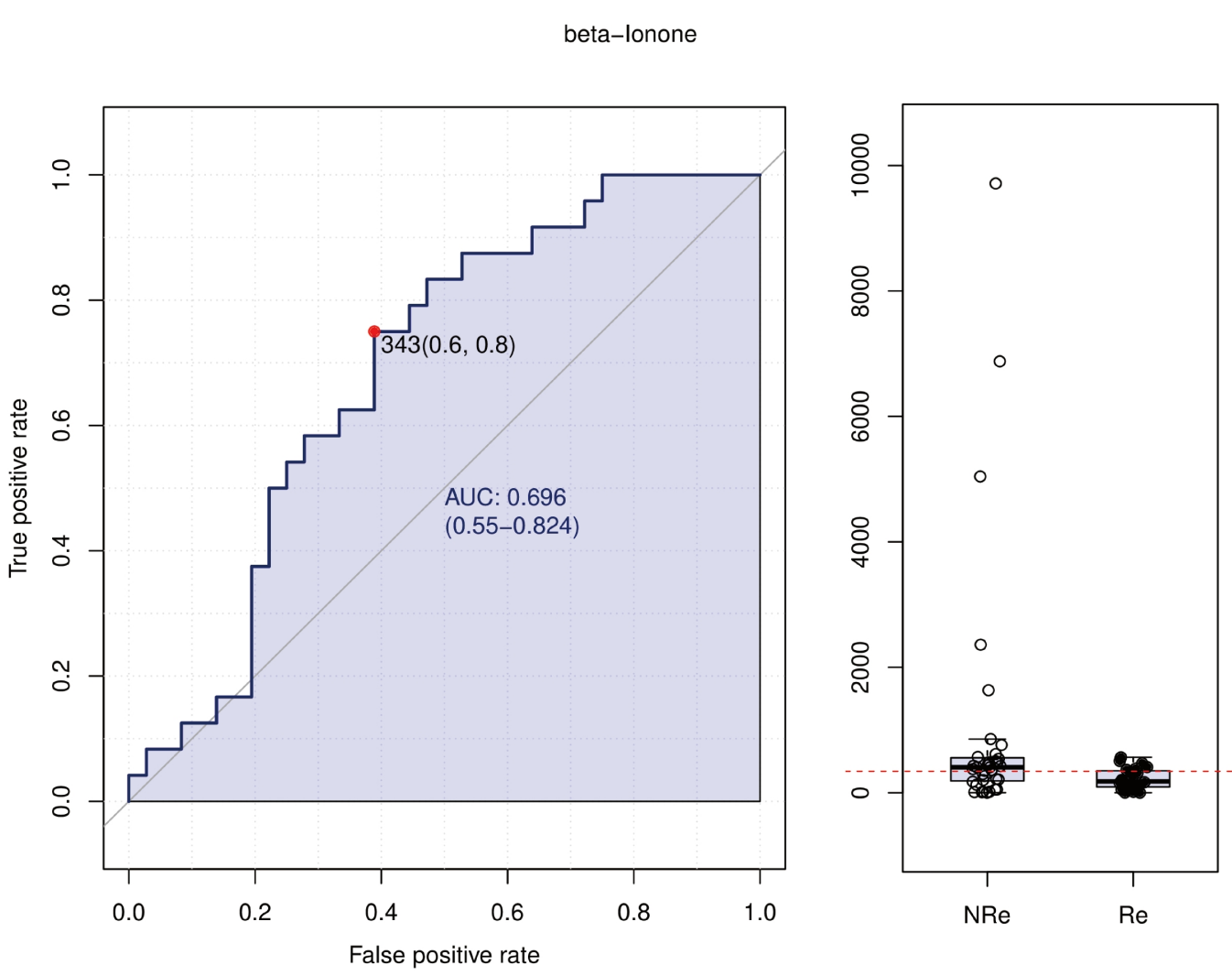
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Distribution of Baseline Clinical Characteristics in Enrolled Patients			
Clinical Characteristics	Group Re (n=24)	Group NRe (n=36)	P value
Age (x̄±s, years)	64.5±7.45	65±9.62	0.776
Gender, n(%)			
Male	16 (66.7%)	25 (69.4%)	0.434
Female	8 (33.3%)	11 (30.6%)	
Smoking History, n (%)			
Current Smoker	6 (25.0%)	6 (16.7%)	0.747
Former Smoker	6 (25.0%)	12 (33.3%)	
Never Smoked	12 (50.0%)	18 (50%)	
Drinking history, n (%)			
Current Drinker	2 (8.3%)	7 (19.5%)	0.728
Former Drinker	4 (16.7%)	4 (11.1%)	
Never Drunk	18 (75.0%)	25 (69.4%)	
Family history of cancer, n (%)			
None	20 (83.3%)	23 (63.9%)	0.392
Lung Cancer	4 (16.7%)	8 (22.2%)	
Other Cancers	0 (0%)	5 (13.9%)	

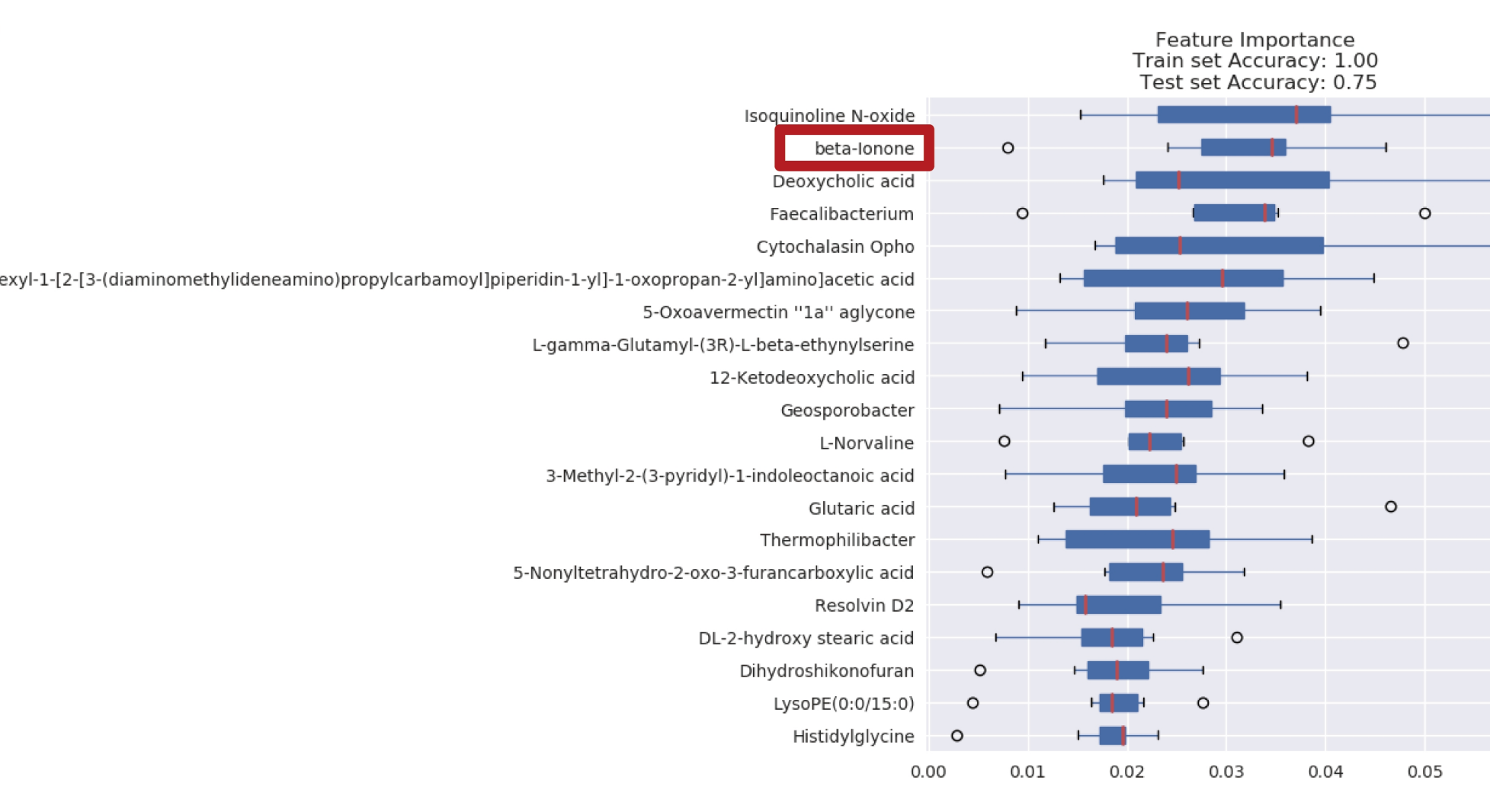
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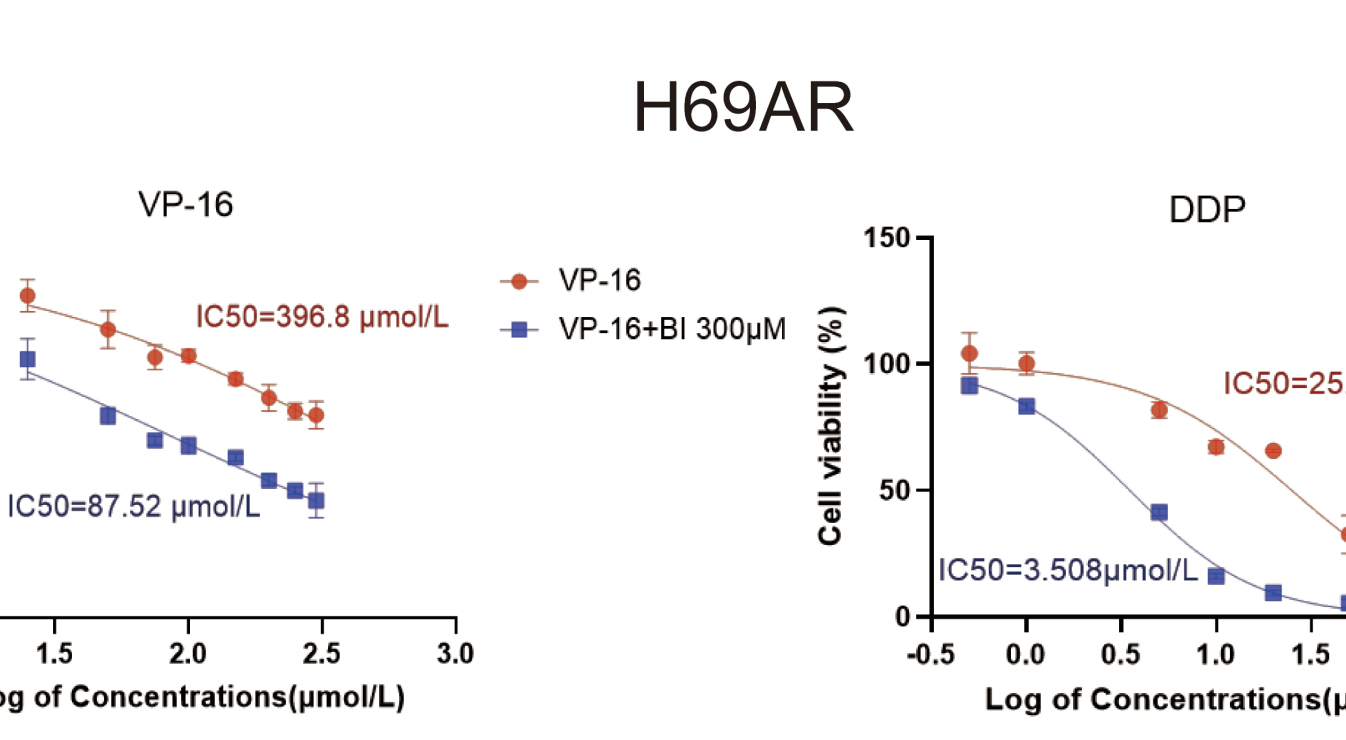
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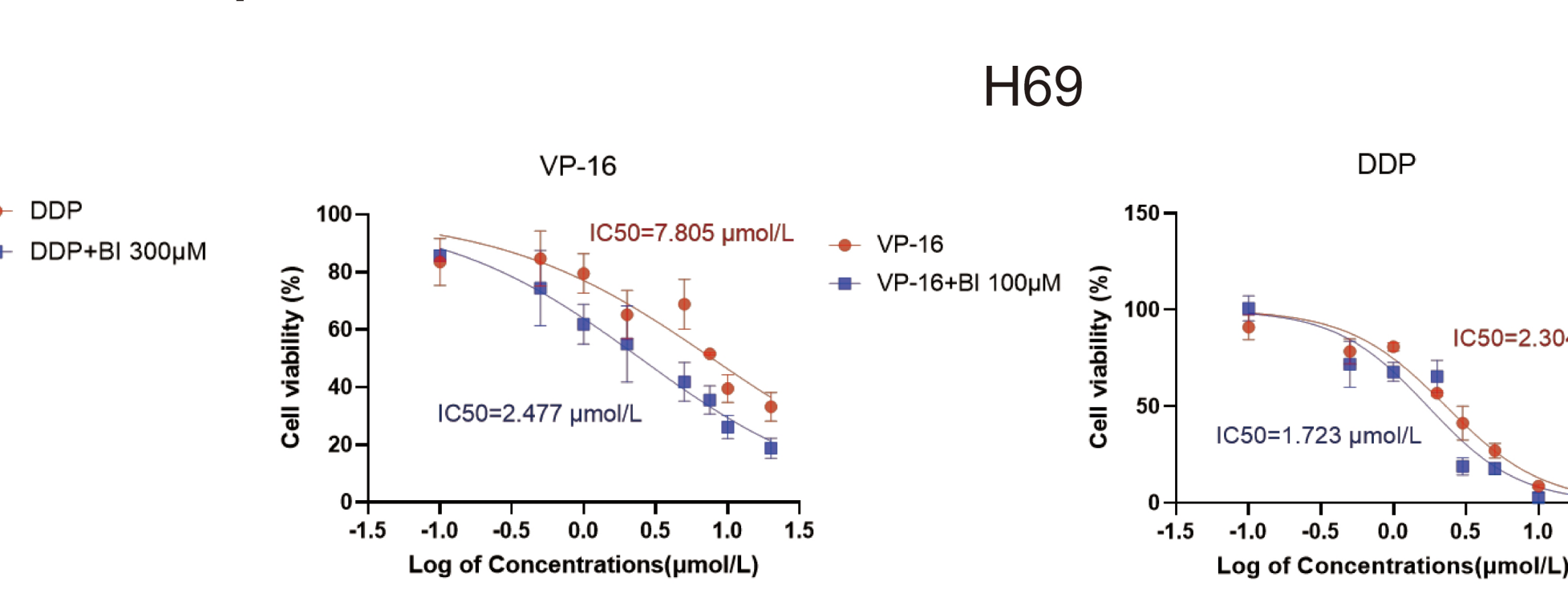
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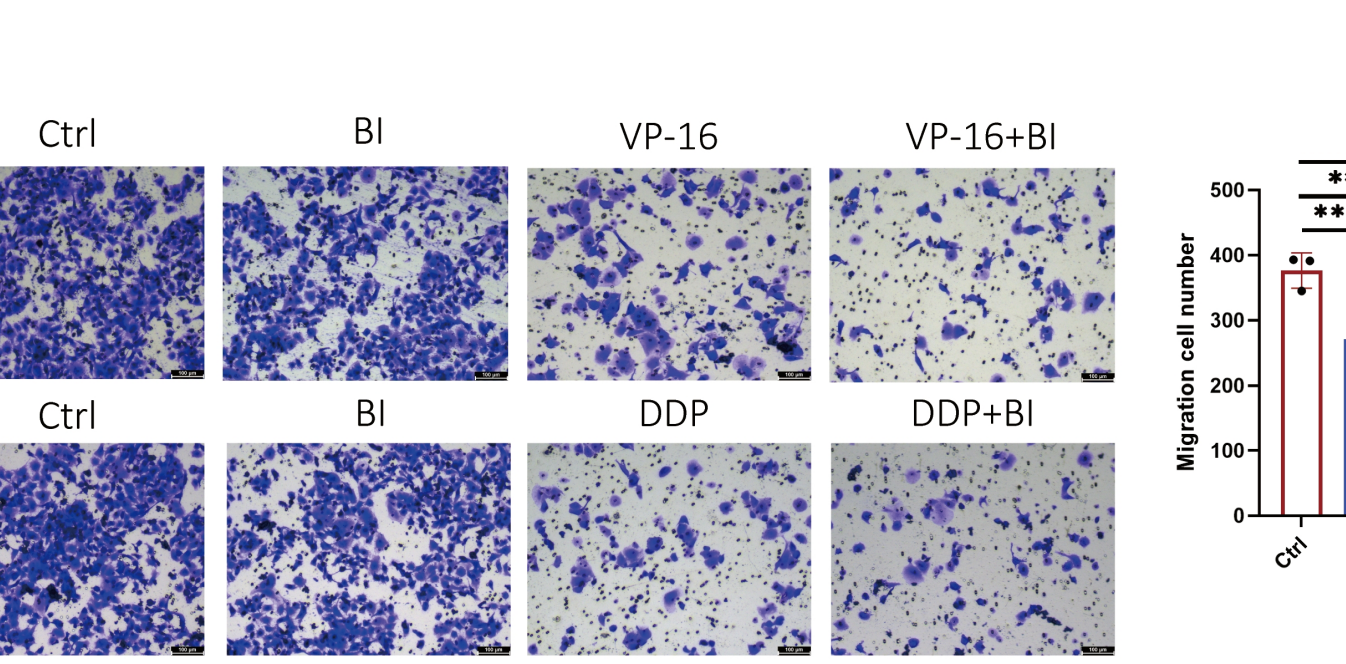
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