

A Patient-Derived Pharmacogenomic Platform Reveals Therapeutic Trajectories and Context-Specific Vulnerabilities in Refractory Lung Cancer

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Abstract

Background: Immediate monitoring and tailored drug prediction according to therapeutic progression remain major challenges in overcoming tumor resistance. Although tumor organoids can recapitulate certain aspects of patient tumors, they may undergo genetic, phenotypic, and compositional alterations during culture. Conventional cancer cell lines are further limited by extensive adaptation to long-term in vitro conditions, resulting in substantial divergence from the cellular heterogeneity and tumor microenvironment (TME) of the original patient tumors. We employed patient-derived cells (PDCs) maintained under short-term culture conditions to better preserve the molecular and phenotypic characteristics of patient tumors.

Methods: PDCs from refractory lung cancer patients were screened against 62 compounds. We integrated matched targeted/RNA sequencing with drug response data. To further interpret drug responses, we inferred the mechanisms of action (MOA) of individual drugs using a sparse neural network structured along a pathway hierarchy architecture.

Results: Multi-omics profiling revealed TP53- and EGFR-dominant molecular features and enabled the classification of non-small cell lung cancer into three therapeutic progression states: T1 (epithelial-to-mesenchymal transition-associated), T2 (immune-active), and T3 (less progressed). Based on mutational context and therapeutic progression states, potential therapeutic candidates were identified. PDCs derived from tumors previously treated with EGFR tyrosine kinase inhibitors (TKIs) exhibited reduced TKI sensitivity, reflecting tumor heterogeneity and the influence of TME-associated cellular components. Subtype C4 (the endpoint of T1) showed sensitivity to CDK9 inhibitor AT-7519, suggesting its potential to prevent disease progression. In contrast, subtype C3 (the endpoint of T2) was predicted to benefit from ruxolitinib-based combination therapy to enhance immunotherapy responsiveness. Meanwhile, small cell lung cancer samples formed a distinct molecular group characterized predominantly by sensitivity to cell-cycle inhibitors.

Notably, the pharmacogenomic platform using PDCs captured clinically relevant molecular features and enabled prediction of drug responses together with their associated mechanisms of action. The inferred therapeutic progression states were consistent with real-world patient treatment trajectories, supporting the biological and clinical relevance of the model. Furthermore, the therapeutic candidates predicted for the immune-active T2 subtype were consistent with outcomes reported in clinical trials investigating combination immunotherapy strategies.

Conclusion: These findings demonstrate that the PDC-based pharmacogenomic platform can capture dynamic therapeutic trajectories, reveal context-specific drug vulnerabilities, and provide a practical framework for precision therapeutic prediction in refractory lung cancer.

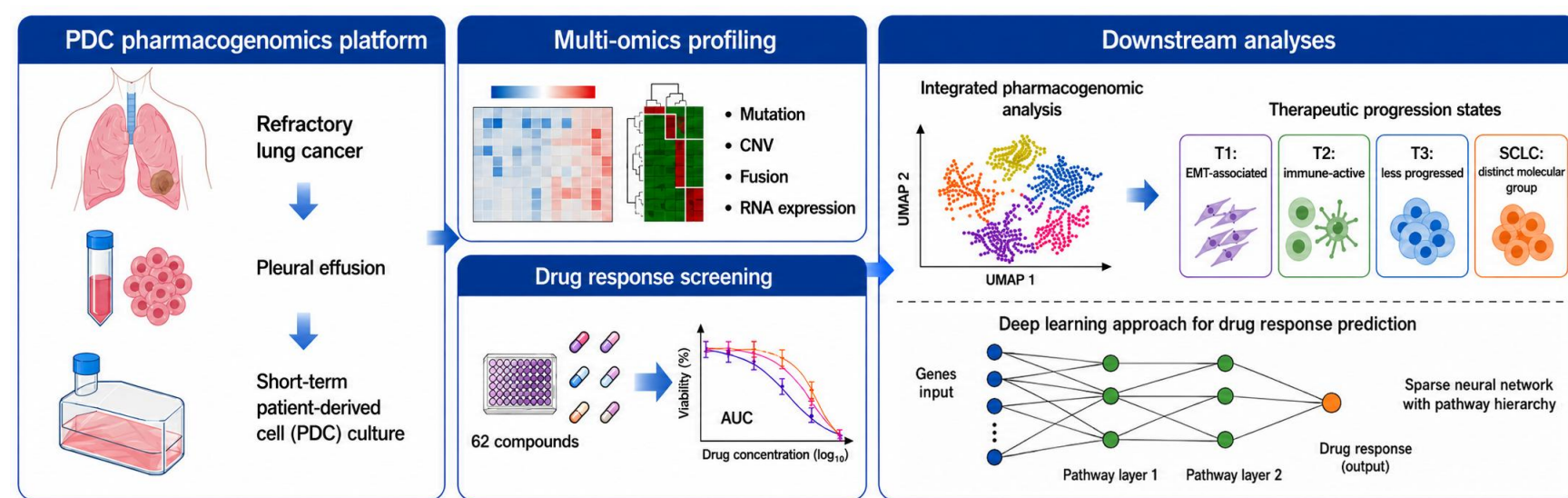
Acknowledgement

Data availability: Next-generation sequencing files of refractory lung cancer patient PDC samples have been deposited in the National Center for Biotechnology Information GEO (GSE165611, GSE229535) and SRA (PRJNA694788).

Fund: This work was funded by the National Cancer Center Research Grant (NCC-2510843 to JYH, and CP); National Research Foundation of Korea (NRF-2023R1A2C2003565 to JYH).

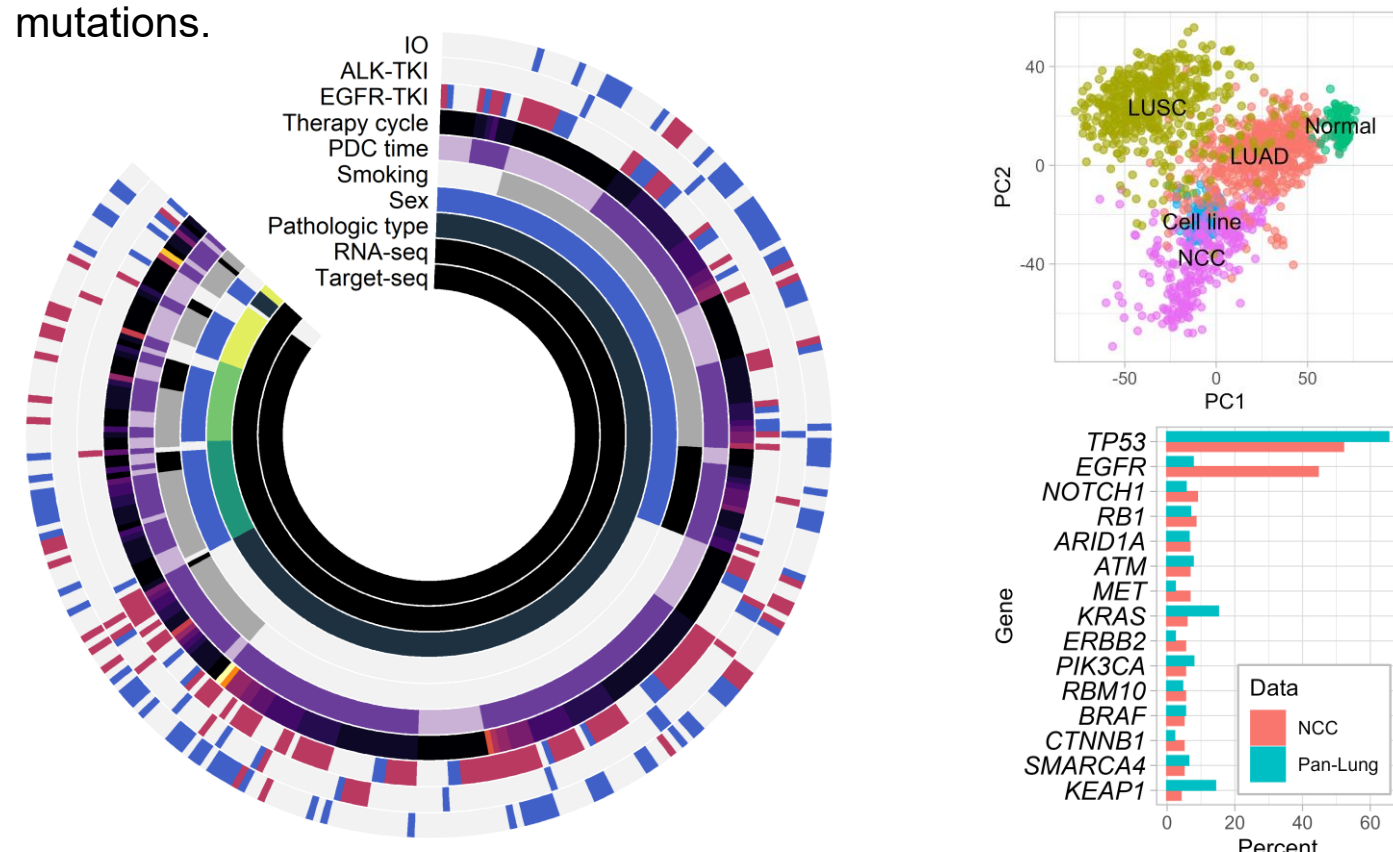
Pharmacogenomics Platform Establishment

Schematic overview of the PDC-based pharmacogenomic platform for refractory lung cancer



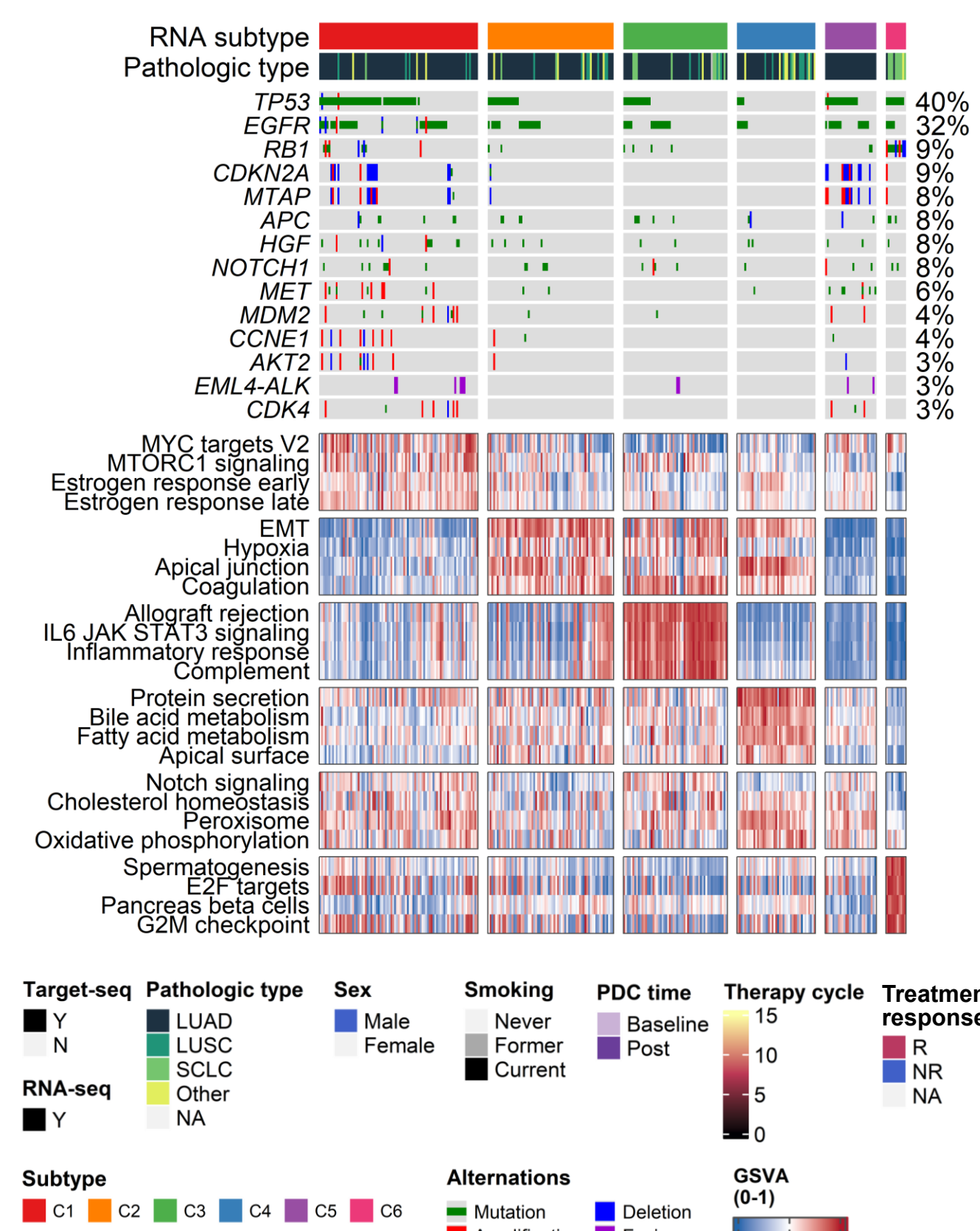
Clinical and Molecular Landscape of the NCC PDC Cohort

- Integrated genomic, transcriptomic, and clinical profiling across NCC PDC cohort
- To compare with TCGA pan-Lung datasets
 - NCC transcriptomics exhibits solid tumor-level heterogeneity.
 - Genomic profile shows East Asian cohort characteristics, with highly recurrent EGFR mutations.



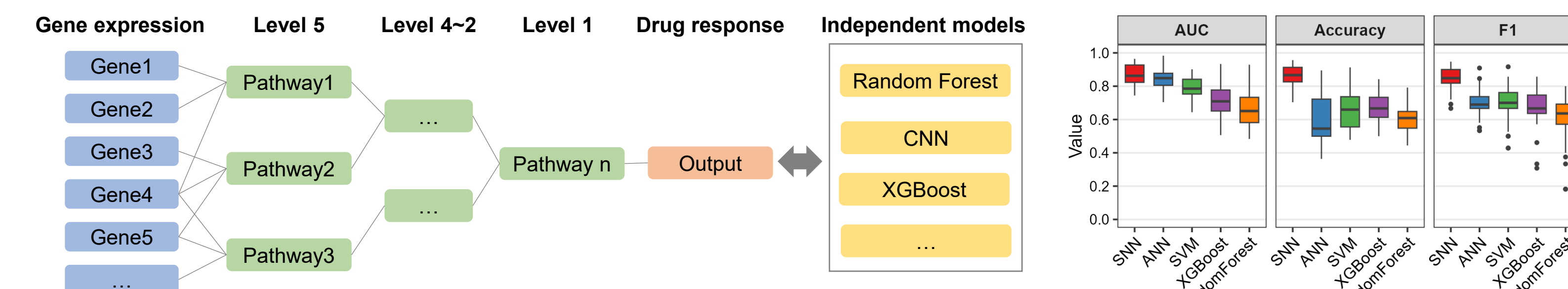
Molecular Features of Transcriptomic Subtypes

- Six RNA subtypes exhibit distinct genomic alterations and pathway programs involving EMT, immune signaling, and metabolism



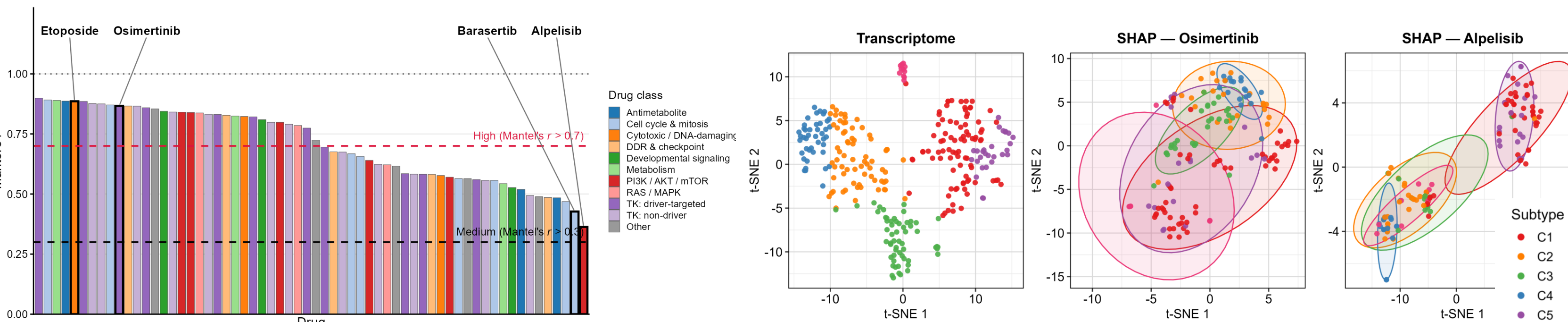
Deep-Learning Approach for Drug Response Prediction

Pathway-Informed Sparse Neural Network Improves Drug Response Prediction



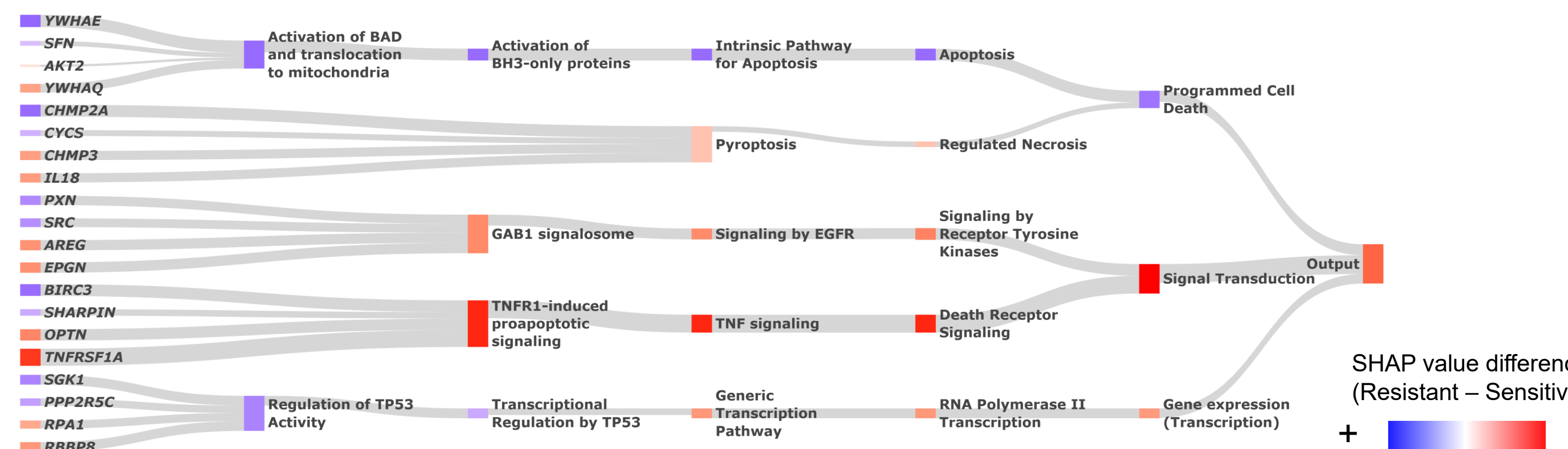
Distance Correlation Between SHAP Values and Transcriptome Profile Across Drugs

- Machine learning-derived SHAP profiles recapitulated transcriptome-defined sample characteristics, suggesting that the learned pathways capture the molecular features of the PDC300 cohort relevant to drug response.



Pathway-Hierarchical Interpretation of Etoposide Response

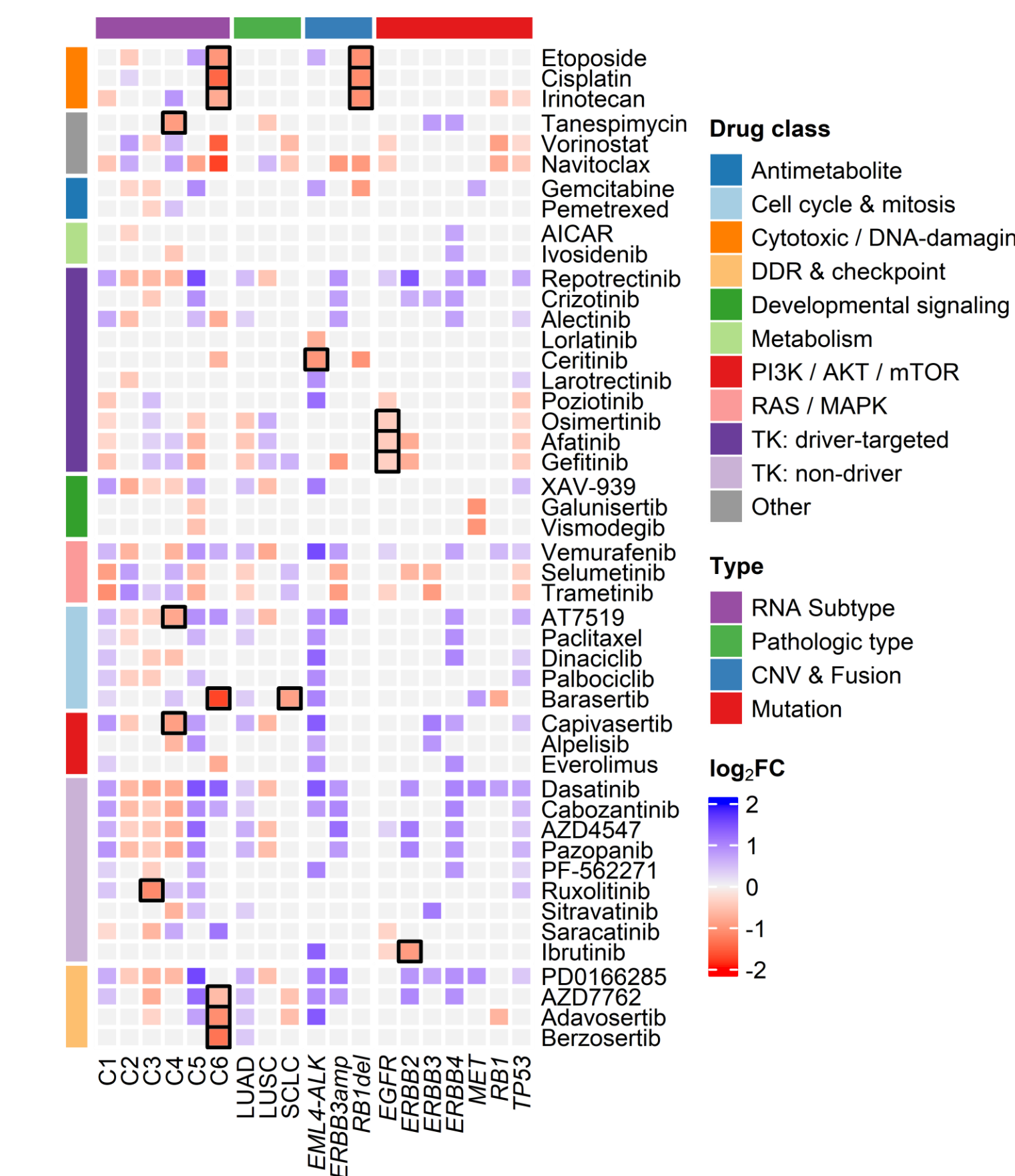
- SNN uncovered the hierarchical mechanisms of Etoposide: TP53 activity, programmed cell death, and TNF signal.



Drug Responses Across Molecular and Therapeutic States

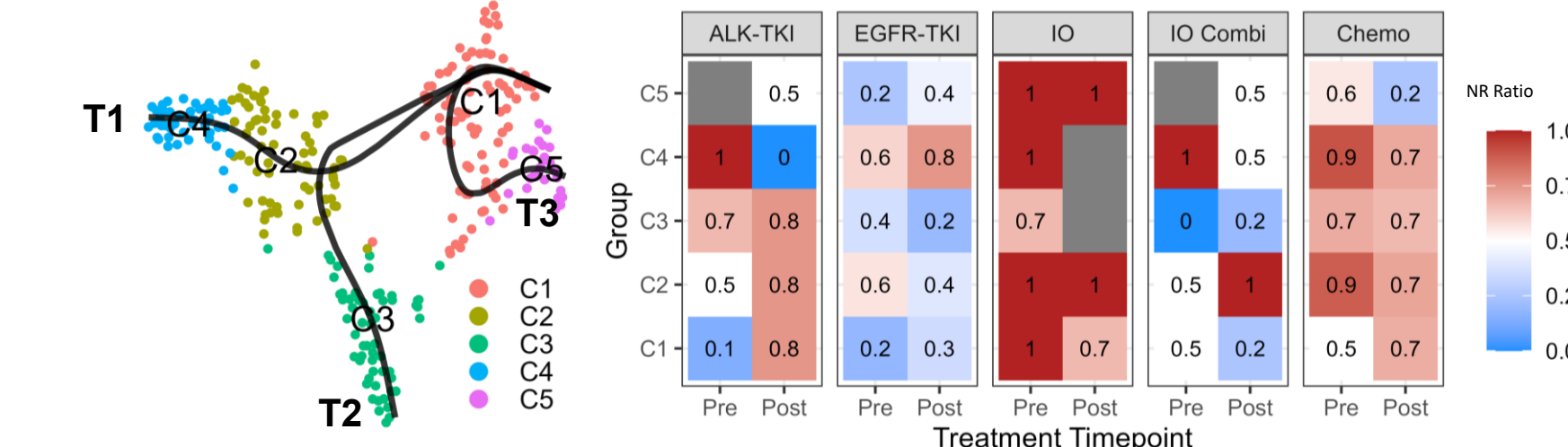
Molecular Feature-Specific Drug Response Landscape

- Drug responses show heterogeneous, drug-specific associations with RNA subtype, pathologic type, CNV/fusion, and mutation features



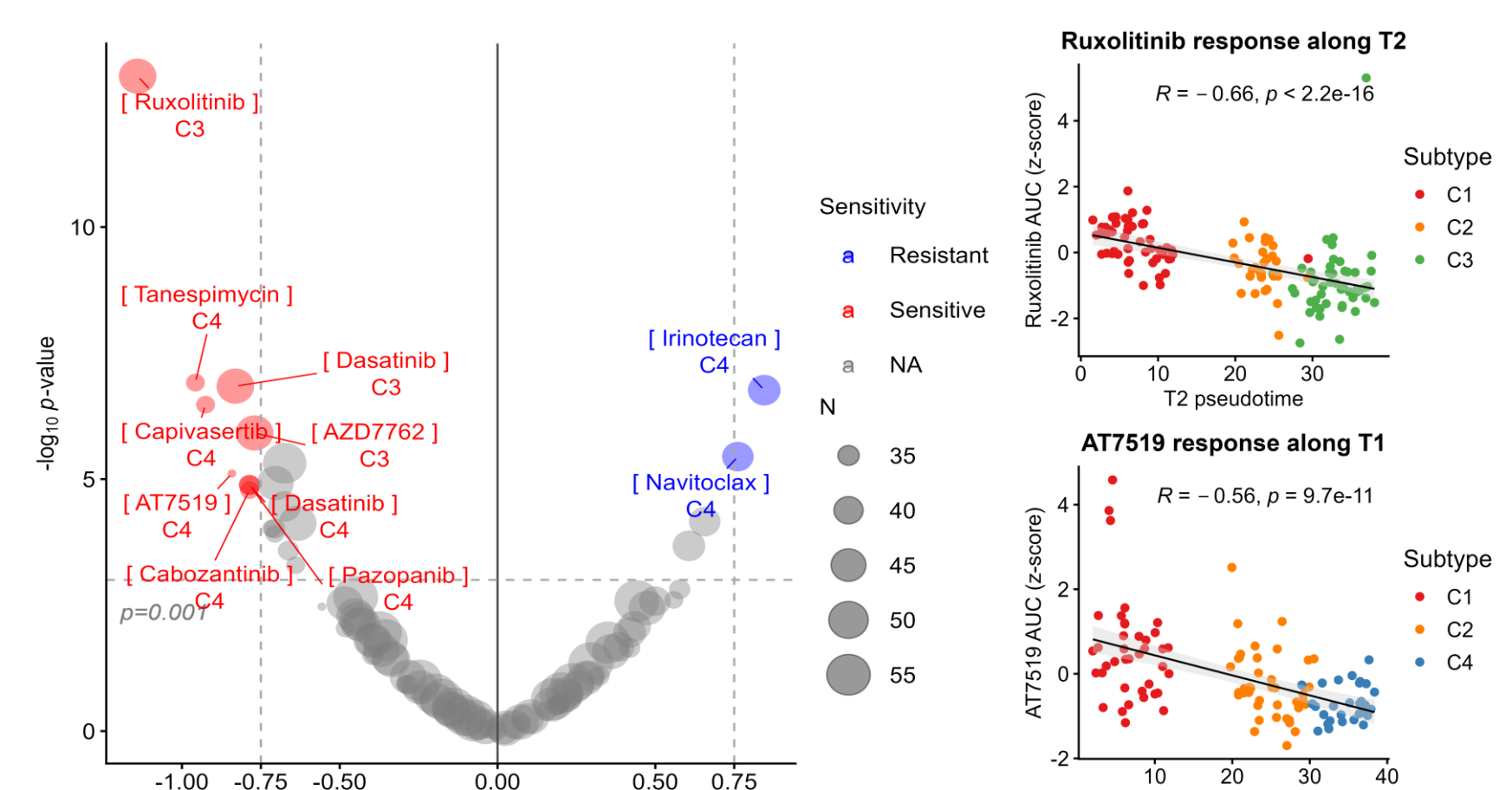
Treatment Response Dynamics Across Therapeutic Progression States

- Three therapeutic trajectories were identified: EMT progression (T1), immune activation (T2), and a less-progressed state (T3)
- Treatment response varies across therapeutic states, with marked pre-post changes in IO-based treatments



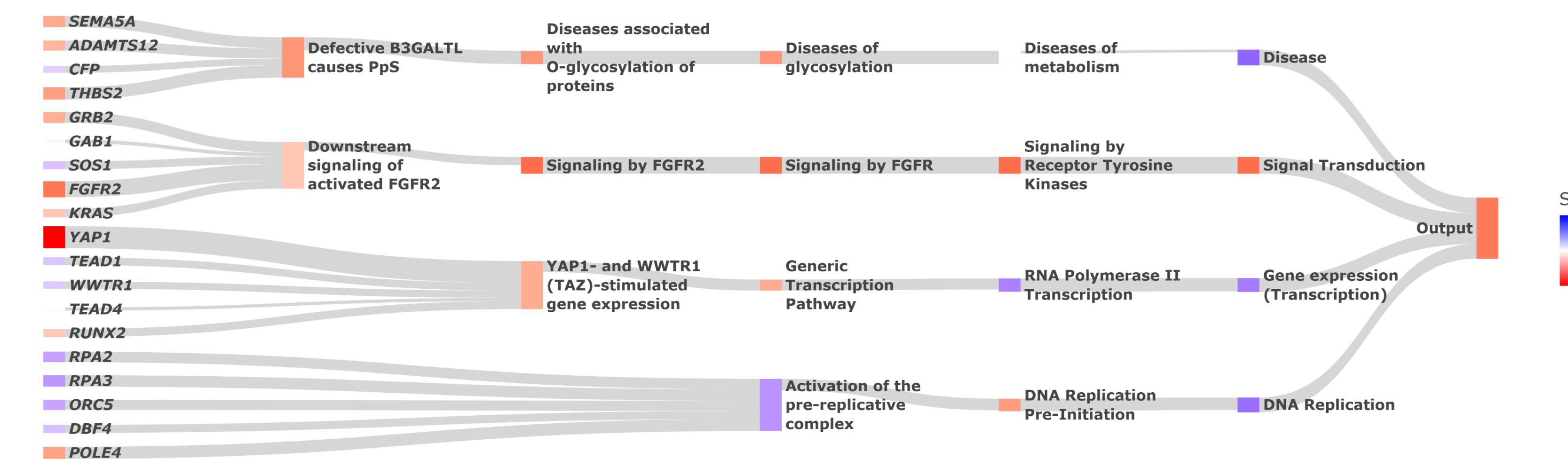
Therapeutic Progression-Associated Drug Response Patterns

- Comparison of the T1 and T2 trajectory endpoints revealed distinct drug-specific responses, including ruxolitinib sensitivity in C3 and AT7519 sensitivity in C4.



Hierarchical SHAP Interpretation of C4-Specific AT7519 Response

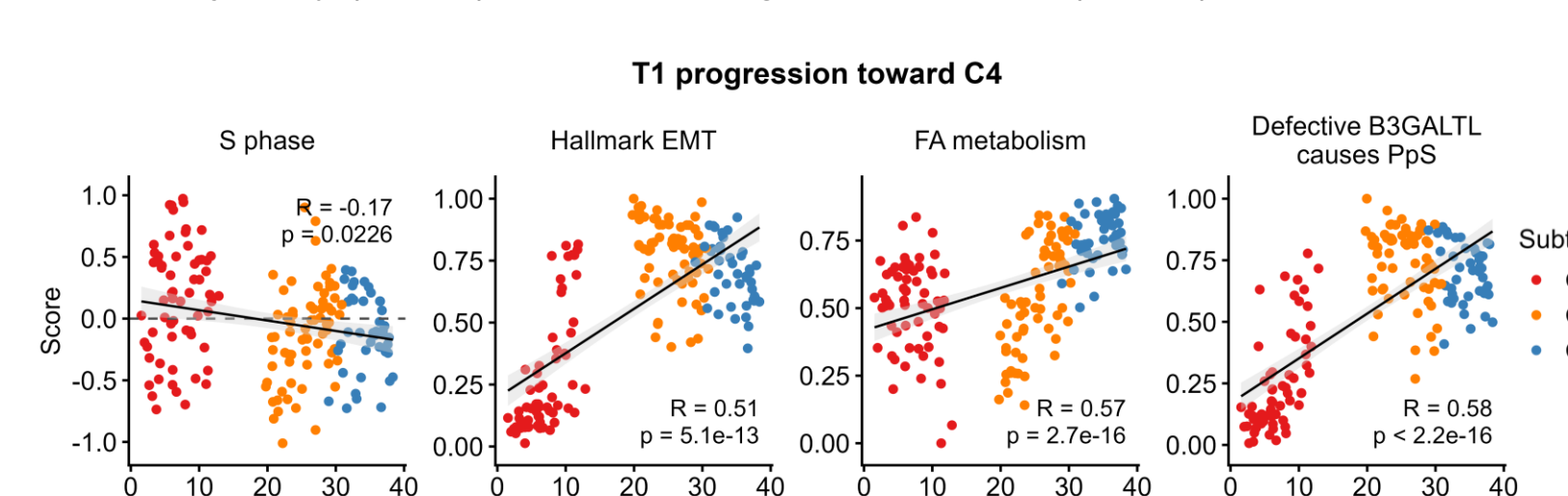
- AT7519 sensitivity associated with DNA replication, FGFR2 signaling and glycosylation-related pathways



Therapeutic Progression of NSCLC

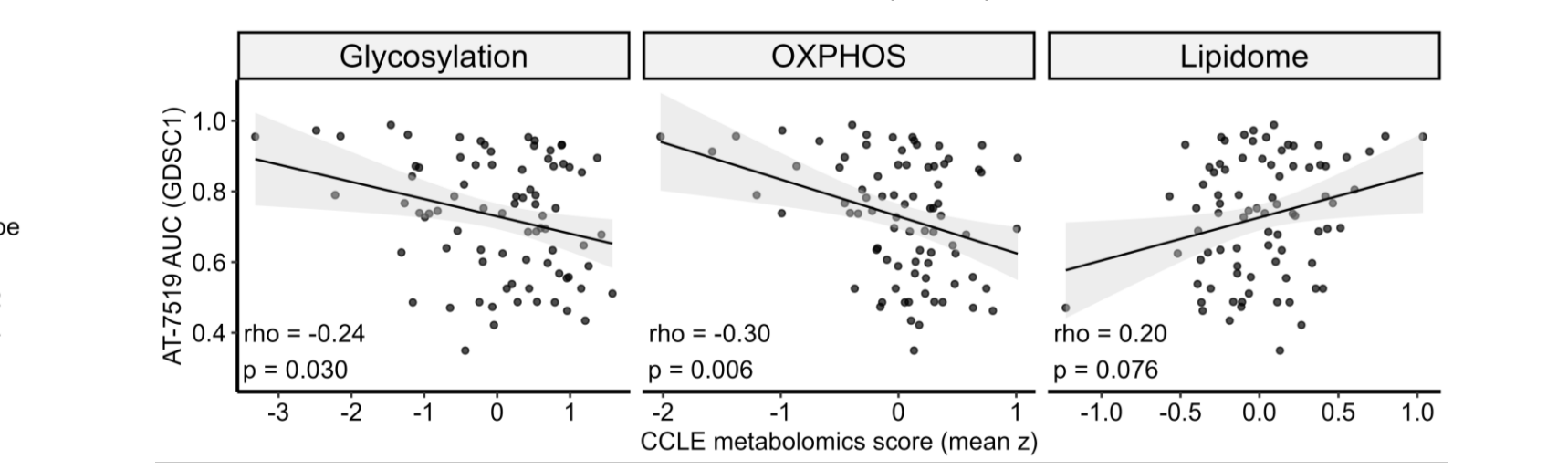
C4-signature defines mesenchymal metabolic state

- The C4 program captures a mesenchymal, metabolically remodeled state in PDC T1 trajectory (n=174) and CCLE lung cancer models (n=206).

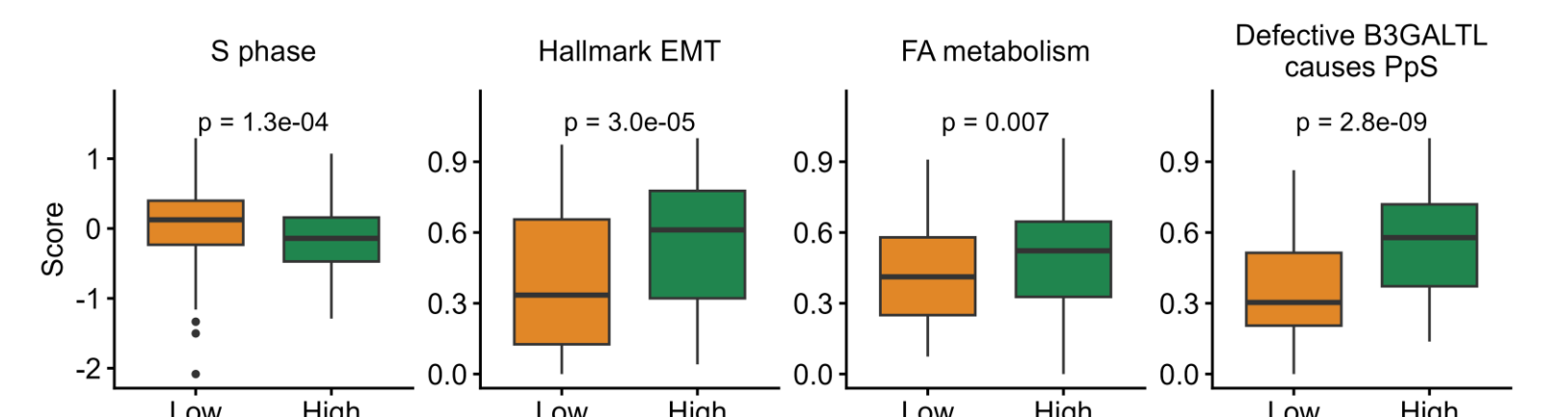


Metabolic features associated with AT-7519 sensitivity

- Higher glycosylation and OXPHOS scores correlated with greater AT-7519 sensitivity in matched CCLE-GDSC1 NSCLC cell lines (n=85).

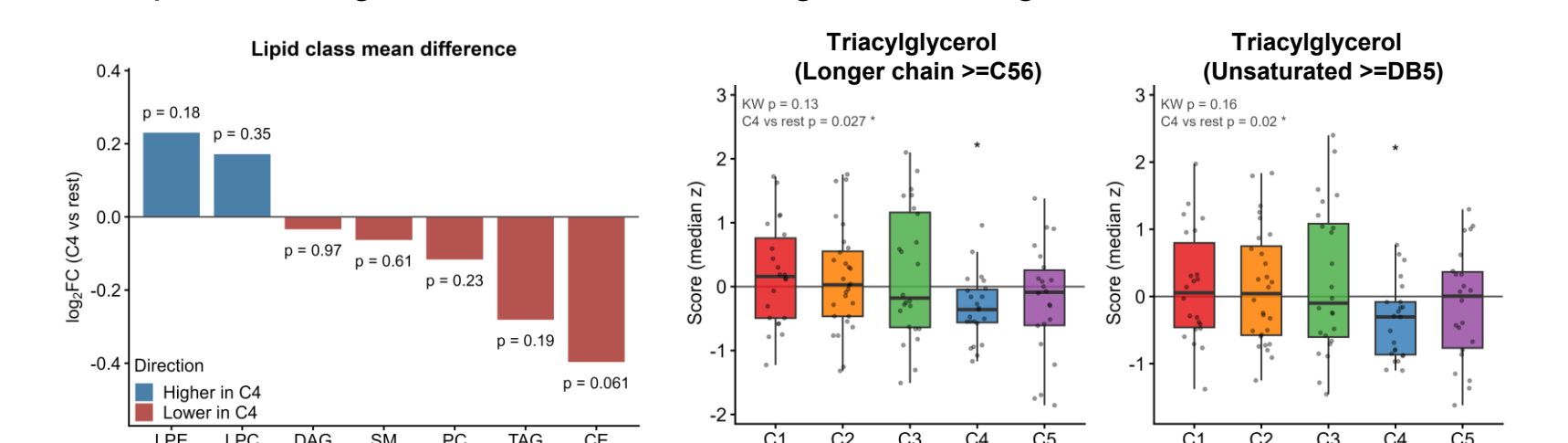


CCLE validation of the C4-like EMT and metabolic phenotype



C4-associated lipid remodeling

- C4 shows reduced cholesteryl ester (CE) and (triacylglycerol) TAG, with greater TAG depletion at higher unsaturation and longer chain length.



Fatty acid oxidation (FAO) activation was enriched in C4. Consistently, cell lines exhibiting a comparable FAO-high phenotype showed reduced triacylglycerol (TAG) abundance, suggesting enhanced lipid mobilization and a metabolic shift from lipid storage toward fatty-acid utilization.