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Introduction

Background:

B-cell lymphomas display heterogeneous responses to kinase inhibitors, reflecting underlying variability in kinase activity and signaling network states. Understanding how baseline kinase activity and broader signaling network patterns relate to drug sensitivity could improve therapeutic stratification and uncover mechanisms of drug response.

Aim of the study:

To determine whether baseline kinase activity and/or signaling network states could predict drug sensitivity in B-cell lymphomas and thereby improve therapeutic stratification.

Method:

Drug sensitivity (IC₅₀) data for B-cell lymphoma cell lines were obtained from CancerRxGene, and kinase activity profiling was performed using PamGene's KinomePro technology. Phosphorylation signatures were integrated with drug response data using Multi-Omics Factor Analysis (MOFA) to identify kinase-drug sensitivity relationships.

PamGene's KinomePro technology

With the advanced PamChip® technology, we can simultaneously measure the activity of over 380 kinases, providing a comprehensive view of kinase signalling pathways in a wide range of cell types and tissues.

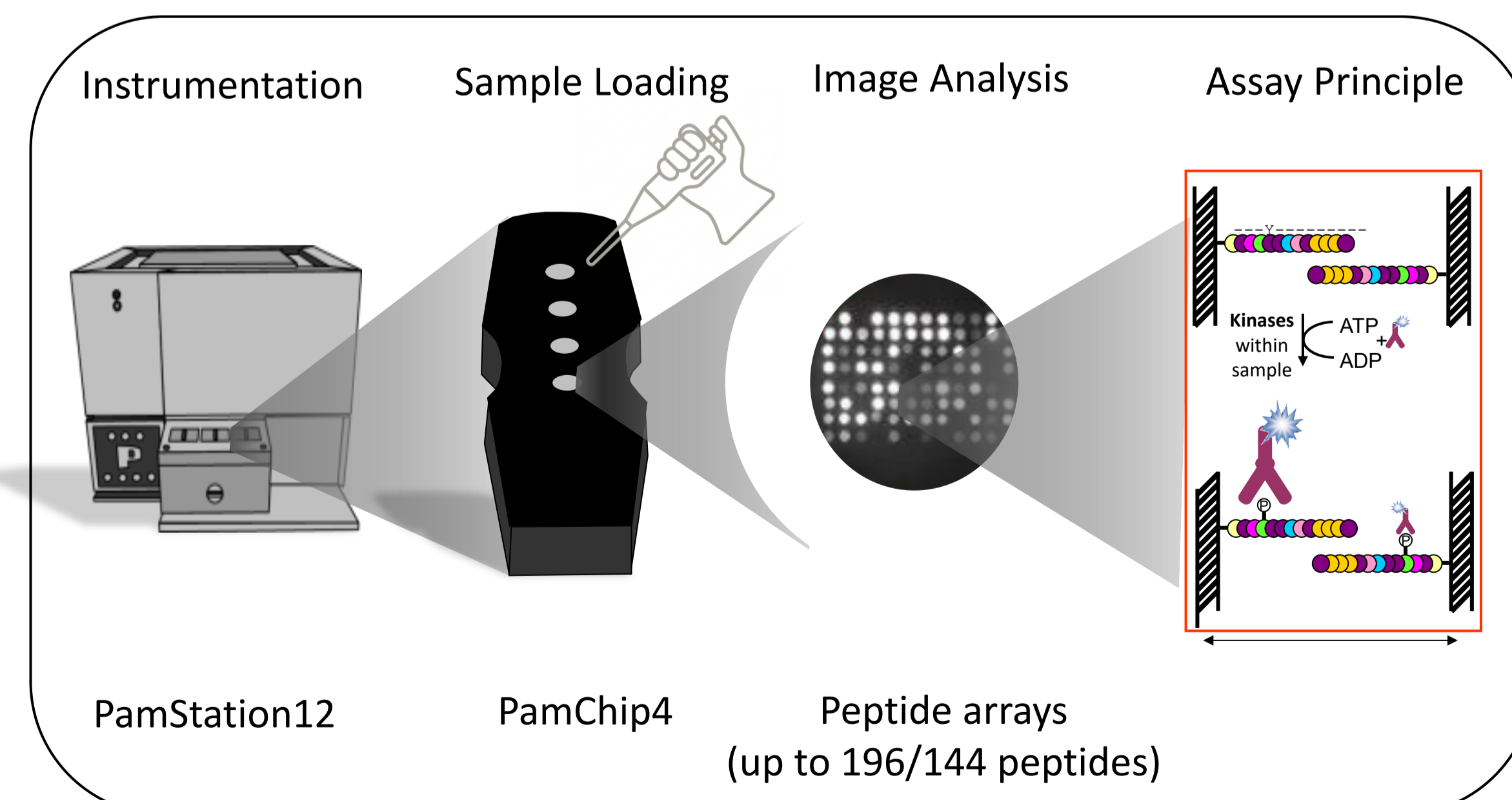


Fig.1. Kinase activity profiling on PamChip® microarrays

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Heterogenous drug sensitivity across B-cell lymphoma lines

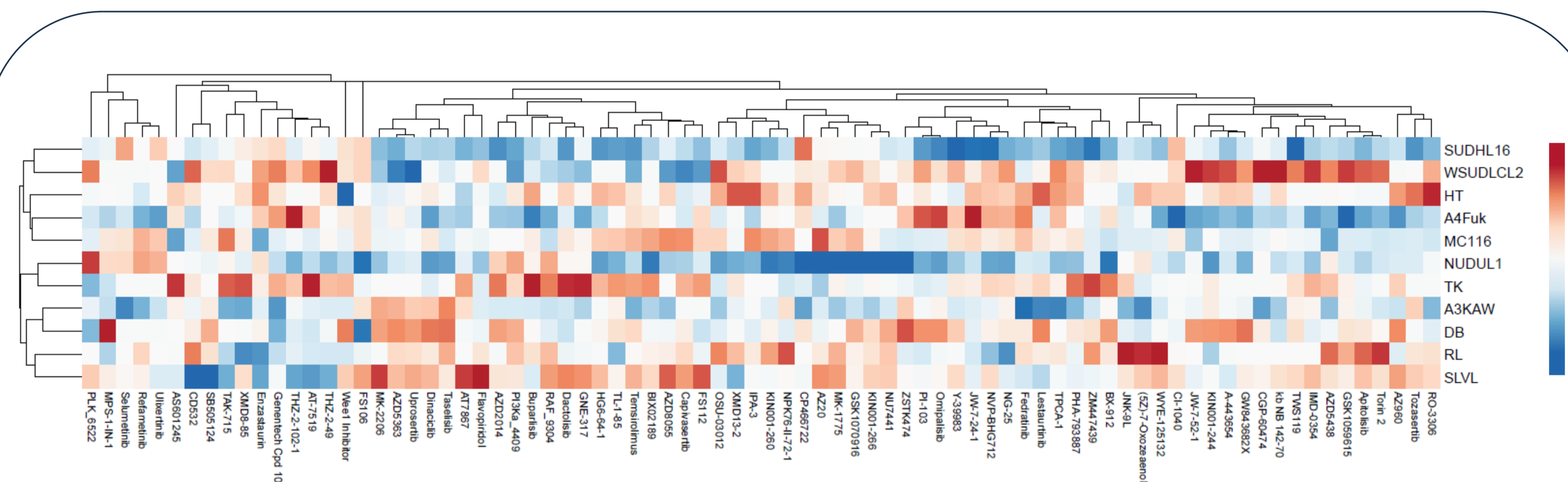


Fig.2. Heatmap depicting drug sensitivity (LN_IC50) of top 80 drugs profiles in ≥ 9 B-cell lymphoma cell lines. Columns are centered; unit variance scaling is applied to columns. Imputation is used for missing value estimation. Both rows and columns are clustered using correlation distance and average linkage.

Conclusion: Drug responses showed substantial heterogeneity across cell lines: 7% of drugs were homogeneous (LN(IC₅₀) SD < 0.5), 41% moderately heterogeneous (SD 0.5-1), and 52% heterogeneous (SD > 1).

Differential Serine/Threonine kinase profiles across B-cell lymphoma lines

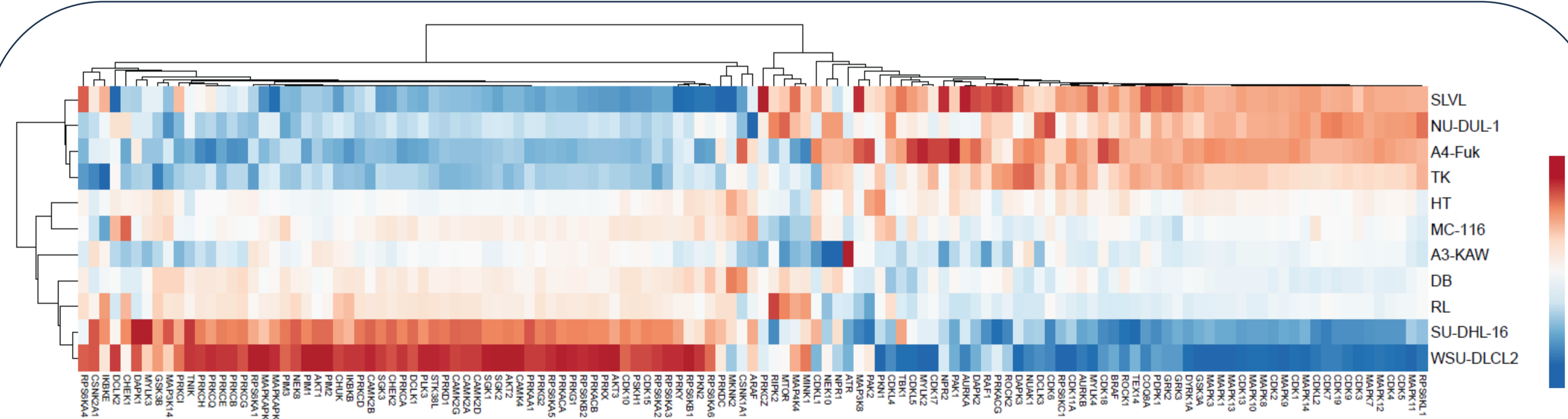


Fig.3. Heatmap depicting fold change kinase activity from 127 serine/threonine kinases in 11 B-cell lymphoma cell lines. Columns are centered; unit variance scaling is applied to columns. Both rows and columns are clustered using correlation distance and average linkage.

Conclusion: KinomePro standard upstream kinase analysis identified distinct clusters: one comprising PI3K/AKT central to cell growth, survival, metabolism, and proliferation; and a second cluster including CDK, ATM/ATR, Wee1, AURKA, and MAPK, central to DNA damage response, cell cycle regulation and checkpoint signaling.

Representative differential kinase activity across B-cell lymphoma lines

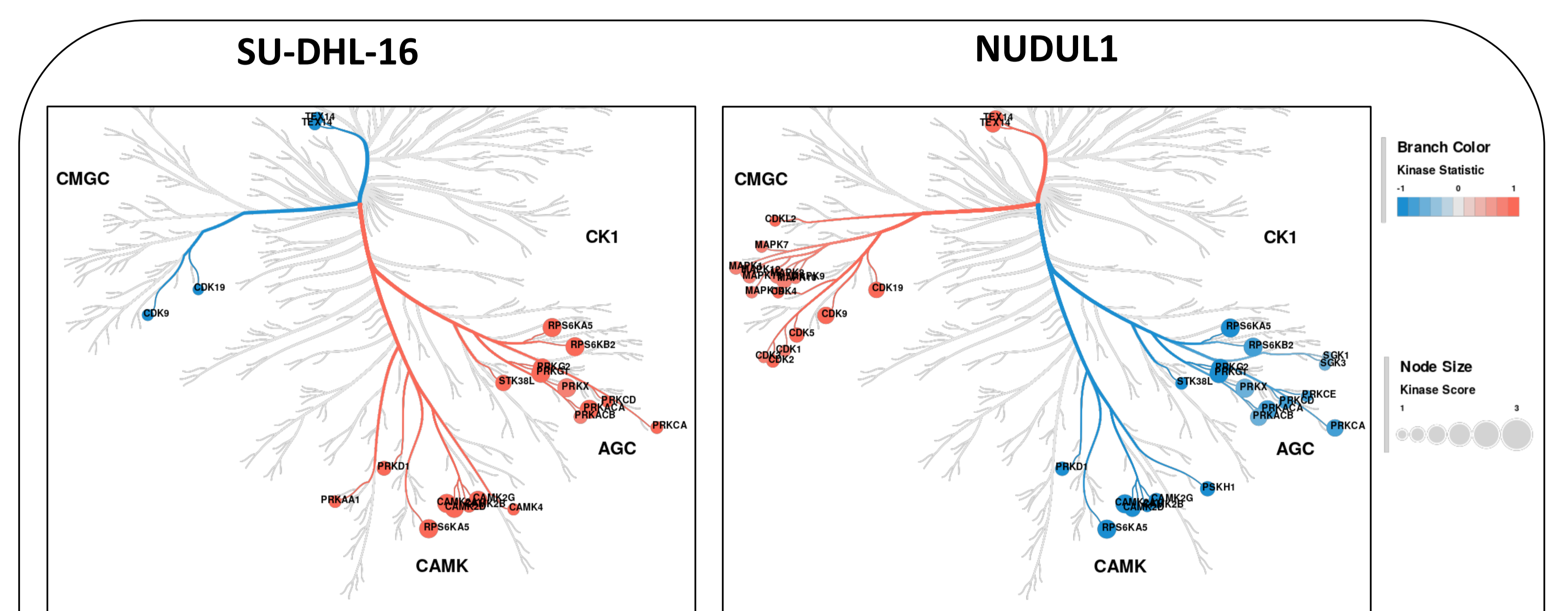


Fig.4. Kinome coral trees depicting most relevant kinases in indicated cell lines. Color specifies direction of change red (upregulated) and blue (downregulated). Size of the circle depicts kinase specificity. Larger the circle more specifically that kinase is affected by treatment. Specificity threshold is set to >1.3.

Network level determinants of drug response

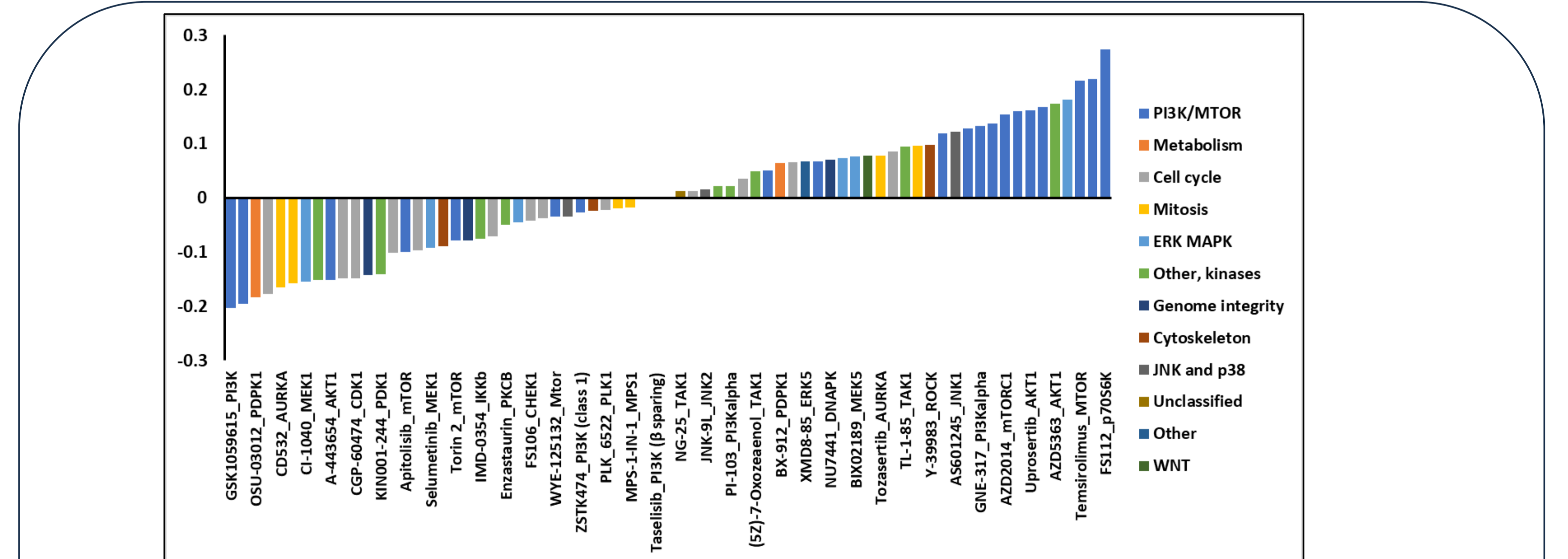


Fig.5. Clustered bar plot depicting pathway targeted by drugs from factor 1 of MOFA analysis. **Conclusion:** MOFA Factor 1 reveals concordance between kinase signaling pathways and drug sensitivity, indicating that B-cell lymphoma response is driven primarily by signaling network architecture rather than individual kinases.

- KinomePro signal-network signatures associated with sensitivity provide mechanistic insight into heterogeneous drug responses.
- These findings lay a foundation for functional validation and the development of combination therapies guided by network-level dependencies.

