

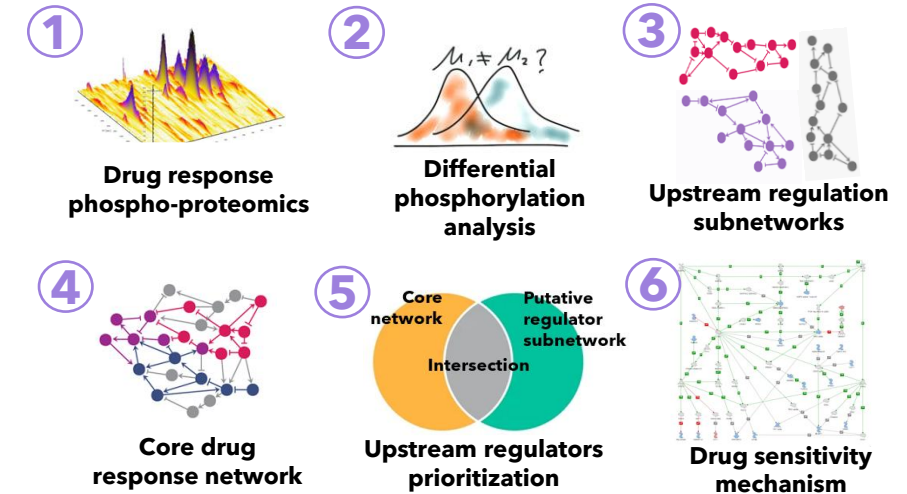
Protein kinase inhibitor sensitivity mechanism reconstruction

Client Background and Objectives:

- Clinical-stage oncology biotech developing a next-generation targeted cancer immunotherapy
- Client wanted to validate the mechanism of action (MoA) of a lead kinase inhibitor and support for combination strategies
- Client wished to identify biomarkers of resistance for patient stratification

Key Business Questions:

- What molecular mechanisms drive response to the kinase inhibitor?
- Which upstream regulators and pathways mediate drug sensitivity and resistance?
- Which biomarkers can support patient stratification and clinical development?



Solution

- Integrated multi-omics analysis of kinase activity, phospho-proteomics, in drug-treated cancer cell lines (1)
- Differential phosphorylation analysis to identify treatment-driven signaling changes (2)
- Causal network reconstruction to map upstream regulators and key pathways (MetaBase™) (3). Integration of subnetworks containing target protein kinases into core drug response network (4)
- Prioritization of regulatory subnetworks and intersection-driven pathway insights (5)
- Reconstruction of drug response and sensitivity mechanisms using the data-driven causal network (6)

Outcomes

- **Integrative model** of pathways affected by treatment
- MetaBase-curated signaling pathways enabled **reconstruction of drug-response subnetworks** linking molecular changes to kinase pathways.
- Our in-silico approach confirmed the primary target of the client's asset as the principal driver of treatment effect, supporting **MoA validation**.
- The integrated regulatory network **identified key regulators** and captured the sensitivity mechanisms, informing **patient stratification strategy** and highlighting **intervention points for combination therapies to overcome resistance** and improve treatment outcomes.