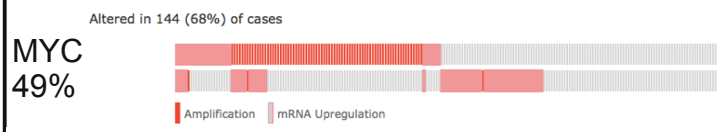
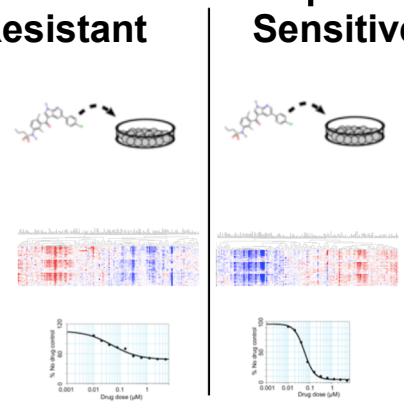
Box 2. Pathway analysis of proteomic response to BET bromodoain inhibition in ovarian Cancer

Either c-MYC or BRD4 is upregulated in 68% of ovarian cancers either in copy number or mRNA expression level (26). Inhibition of BRD4 or c-Myc may be therapeutically effective in ovarian cancer. We treated four ovarian cancer cells with BET bromodomain inhibitor, JQ1. JQ1 directly targets the bromodomain protein BRD4, which marks select genes including c-Myc on mitotic chromatin and reduces the mRNA transcript of c-Myc and other genes in different cancers. We performed a pathway analysis to address three questions; 1) is JQ1 effective in ovarian cancer cell lines? 2) which pathways are associated with response (up/down regulated) and resistance to JQ1. 3) can we nominate drug combinations to overcome the BET bromodomain inhibition resistance in ovarian cancer cell lines.



1. Perturbation and profiling experiments



2. Statistical filters

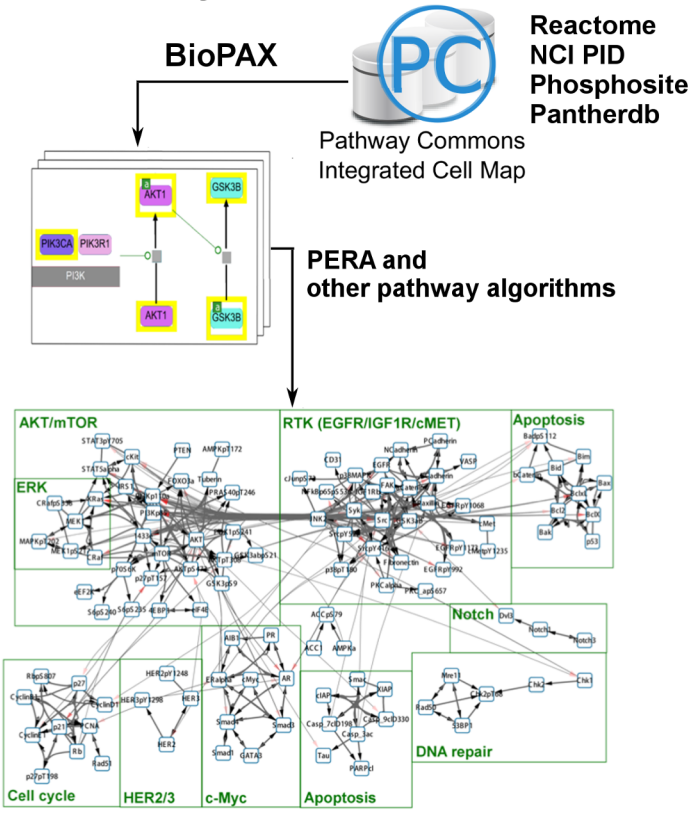
Select proteomic entities with
-Significant response

-Dose dependent response

- Correlation to cellular response

-Differential response in diverse samples

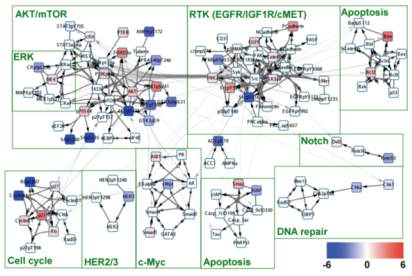
3. Pathway extraction



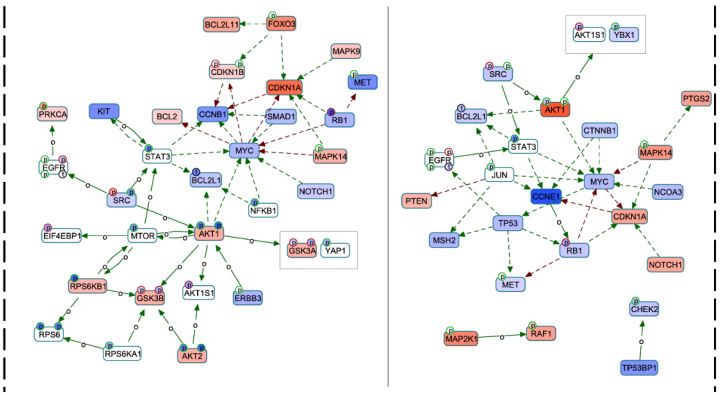
DATA **PATHWAY**

4. Pathway analysis of response to perturbations

Map response to pathways

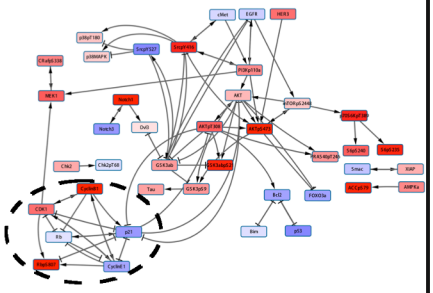


Compare diverse samples

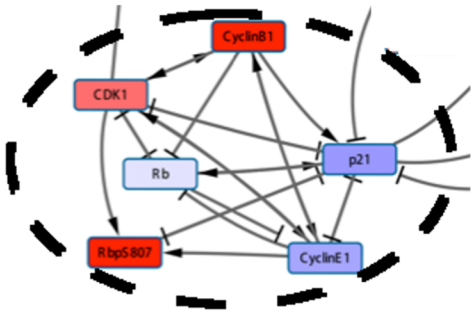


Map differential response

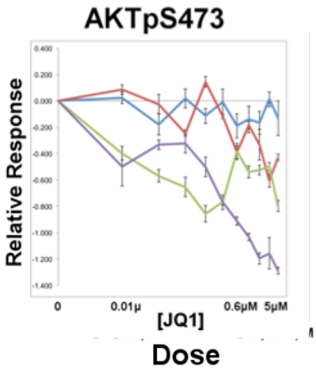
<resistant-sensitive>



Characterize responding modules



Identify hub responders



Test promising drug combination