Investigation of Adaptive Responses To Targeted Therapy In BRAF Inhibitor-Resistant Melanoma Cells

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Adaptive Resistance

- Despite major breakthroughs in treatment development procedures, there is still no long-term solution to the problem of drug resistance.
- This resistance occurs through rapid rewiring of cancer cell signaling as a result of targeting specific genomic aberrations.
- Collective changes in pathway activities are better predictors of resistance and mitigation strategies than abundances of individual molecules.

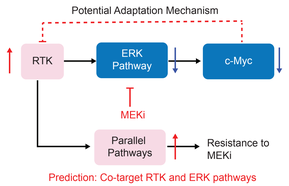


Figure 1: Adaptive resistance concept. Drug perturbations can lead to the immediate impact of the down-regulation of target pathways (e.g., inhibition of ERK phosphorylation by MEK inhibitor) and upregulation of compensatory responses that lead to adaptation of tumor cells and subsequent resistance to therapy (e.g., upregulation of RTK expression by MEK inhibitor via a feedback loop).

Target Score (TS)

- The TS quantifies the adaptive pathway responses to a perturbation as a sum of the response from each individual protein and its pathway neighborhood.
- This method reveals pathways involved in drug activity and adaptive resistance.
- High TS: identifies proteins involved in adaptive responses
- Low TS: immediate impact of the drug

$$TS_i^d = fs_i\left(\frac{\Delta x_i^d}{\sigma_{\Delta xi}} + \sum_j 2^{-p_{ij}} \frac{\Delta x_j^d}{\sigma_{\Delta xj}} W_{ij}\right)$$

$$\Delta x_i = \log\left(\frac{x_i}{x_i^u}\right)$$

$$fs_i = \begin{cases} 1, & if\ oncogene \\ 0, & if\ dual/unknown \\ -1, & if\ tumor\ suppressor \end{cases}$$

$$W_{ij} = \begin{cases} 1, & if\ phosphorylation/upregulation \\ -1, & if\ dephosphorylation/downregulation \end{cases}$$

Equation 1. Target Score. fs_i represents the functional score; Δx_i is the proteomic response; $\sigma_{\Delta xi}$ is the standard deviation; p_{ij} is the pathway distance between the nodes i and j; and W_{ij} represents the signaling interaction between nodes i and j.

Technique

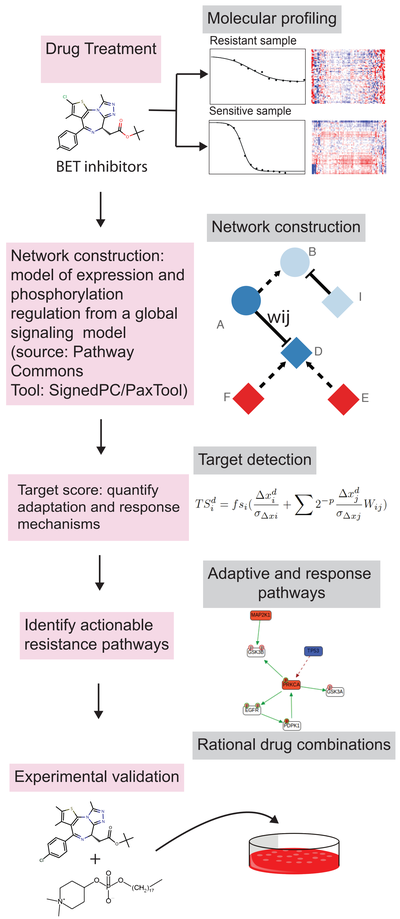


Figure 2: Protocol for identification of adaptive resistance pathways and the nomination of effective drug combinations. An important step involves calculating the target score (TS). A high TS identifies proteins involved in an adaptive response (e.g., upregulation of RTK expression by MEK inhibitor via a feedback loop) and a low TS corresponds to the immediate impact of the drug (e.g., inhibition of ERK phosphorylation by MEK inhibitor).

Data

- BRAF inhibitor-resistant melanoma cell line
- Proteomic (RPPA) data
- Normalized with respect to pretreatment levels
- 12 targeted therapeutic agents
- 89 perturbations
- 138 protein responses

MEK inhibitor	PKC inhibitor
AKT inhibitor	SRC inhibitor
HDAC inhibitor	STAT3 inhibitor
Nutlin (MDM2 inhibitor)	mTOR inhibitor
JAK inhibitor	PI3K inhibitor
BRAF inhibitor	CDK4 inhibitor

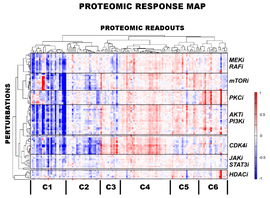


Figure 3: Data. The table (above) lists the 12 targeted therapeutic agents. The heatmap (below the table) represents proteomic expression under the various conditions.

Network Model

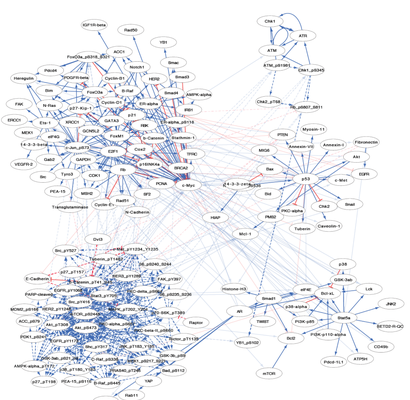
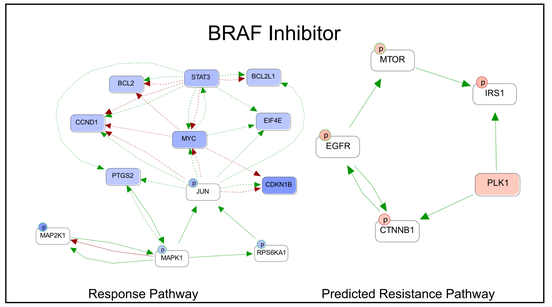
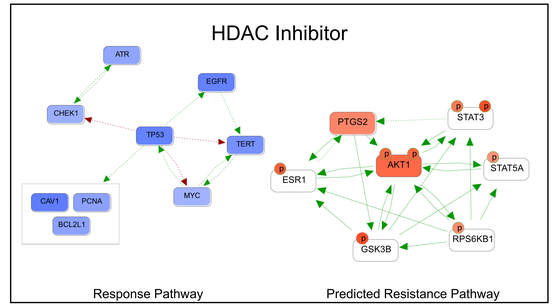
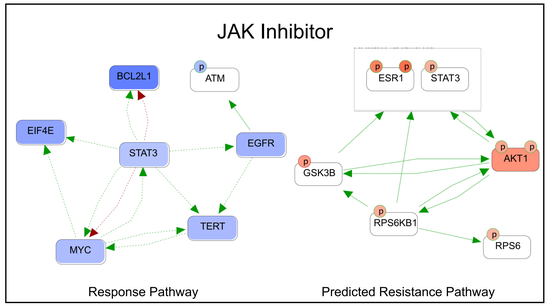


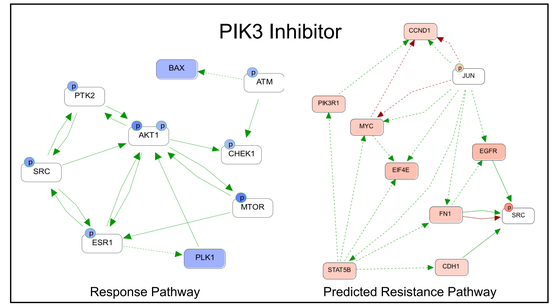
Figure 4: Network model construction. Network models are constructed using the signaling data stored in the Pathway Commons (PC) database and manual curation/correction by experts. Both the network and the data are used in calculating the TS.

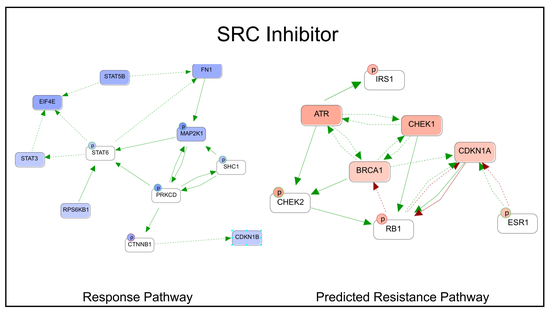
Results











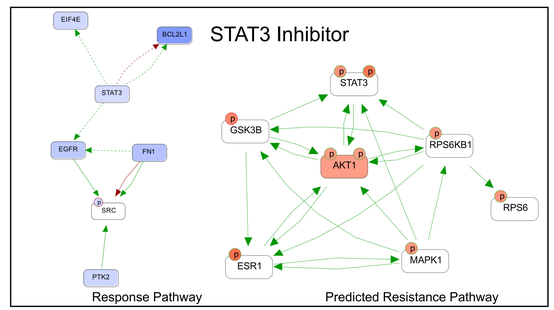


Figure 5. Target score and adaptive resistance pathways in BRAF inhibitor-resistant melanoma. The response pathway (blue) and adaptive resistance pathway (red) are shown for each perturbation listed. The highest and lowest 12 TS values are ranked. The top (red to pink) and lowest (pale blue to blue) are shown.

phosphorylates
dephosphorylates
upregulates expression
downregulates expression

Conclusion

Using Figure 5, the high target score values and the resistance pathways (red) inform drug combination trials, while low target scores and the response pathways (blue) demonstrate how drug activity impacts cell signaling. These combinations can be used in future trials to validate the accuracy of this technique. This method can be applied to patient biopsy samples. By analyzing the resistance pathways of samples before and after treatment, we can suggest improved treatments.