Computational models of synergy contribute to efficient combination screening

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Introduction

- Combination of anticancer drugs is essential to improve response rates and prevent the emergence of drug resistance.
- The efficiency of combination screening can be improved by incorporating knowledge of a compound's biological mechanism [1-4].
- We constructed three models to predict synergy based on the profiling of single agents in a cancer cell line panel.
- The model predictions for niraparib are compared to the outcome of a large and unbiased combination screen.

Experimental approach

- Oncolines™ is a panel of 102 cell lines in which antiproliferative IC_{50}s are determined in parallel in 9-point duplicate dose response curves (Figure 1).
- We have profiled more than 150 anti-cancer agents, including FDA-approved drugs, in the Oncolines™ panel (Figure 2). [1]
- Gene expression and mutation data for all cell lines were downloaded from the Depmap and CCLE databases. [1]
- Based on analysis of cancer drivers (Figure 3), synthetic lethal interactions (Figure 4) and resistance mechanisms (Figure 5), we constructed three models that predicted synergistic partners of niraparib. [2-5]
- Results were compared to a large SynergyScreen™ study, where we investigated the ability of niraparib to shift the dose-response curves of 150 different anti-cancer agents (Figure 6).

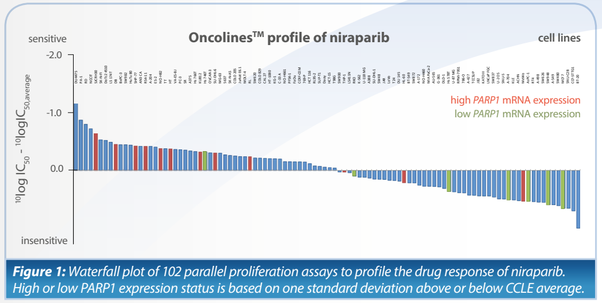

Figure 1: *Waterfall plot of 102 parallel proliferation assays to profile the drug response of niraparib. High or low PARP1 expression status is based on one standard deviation above or below CCLE average.*

Oncolines™ drug response library

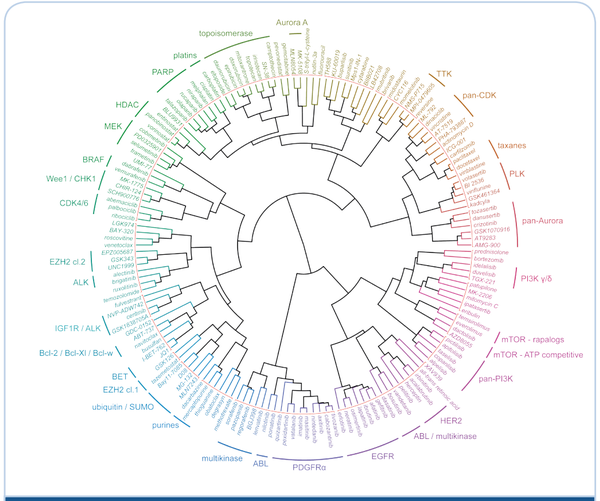

Figure 2: *Cluster dendrogram of the response of more than 150 anticancer agents in the Oncolines™ cancer cell line panel.*

Model 1: targeted synergy

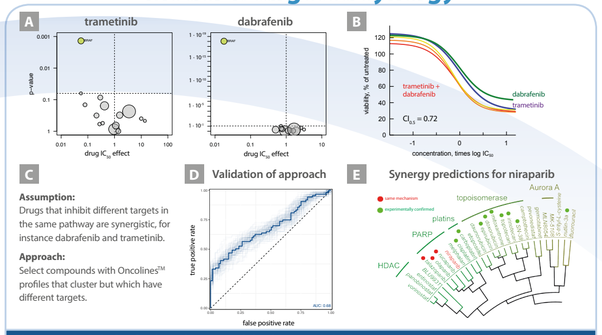

Figure 3. A-C*: Dabrafenib and trametinib both target B-RAF mutant cancer and work synergistically.* ***D****: Predicting the O'Neil [6] synergy data set with model 1.* ***E****: Candidates for the niraparib case study.*

Model 2: synthetic lethality

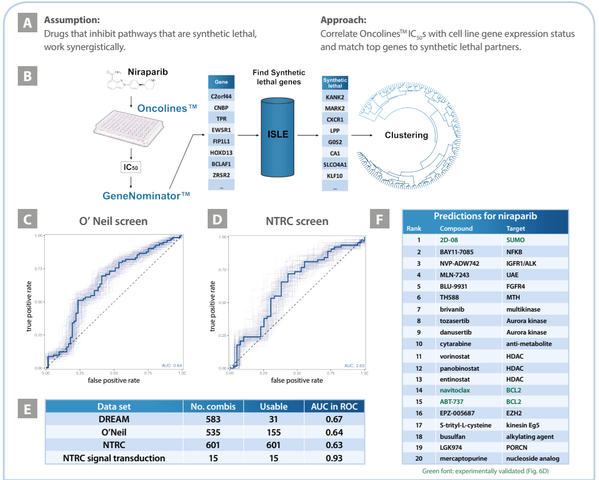

Figure 4. A-B*: The synergy prediction algorithm based on synthetic lethality [4].* ***C-D****: ROC with 100-fold cross validation of the O'Neil [6] and internal NTRC data set [7].* ***E****: Validation statistics including DREAM set [8].* ***F****: Predictions based on the niraparib Oncolines™ profile (66 cell lines).*

Model 3: minimal cross resistance

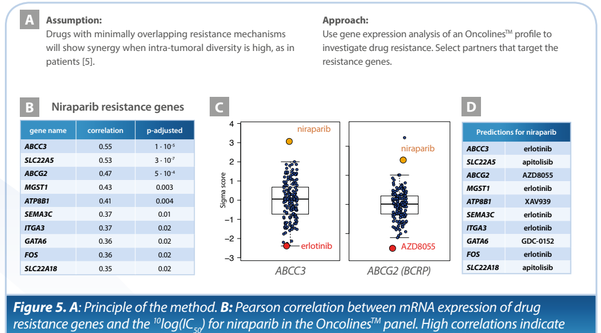

Figure 5. A*: Principle of the method.* ***B****: Pearson correlation between mRNA expression of drug resistance genes and the $^{10}log(IC_{50})$ for niraparib in the Oncolines™ panel. High correlations indicate involvement in resistance.* ***C****: Scores of niraparib compared to other compounds for two genes.* ***D****: Compounds with lowest scores per gene: erlotinib and apitolisib are the best synergy candidates.*

Niraparib full library SynergyScreen™

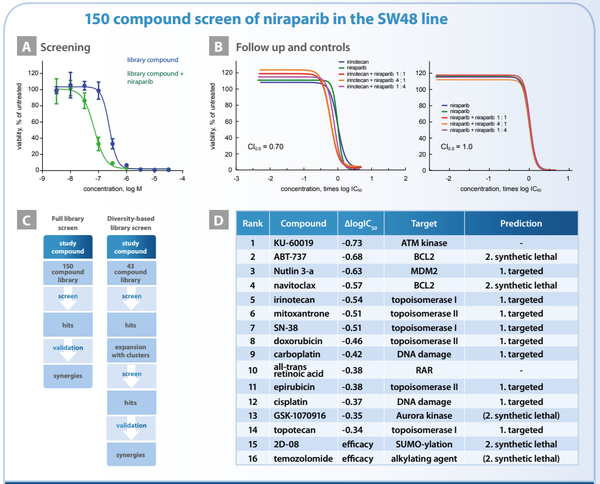

Figure 6: *A: Example curve of the 150-compound library screening [7].* ***B:*** *Follow up by curve shift in multiple ratios.* ***C:*** *Overview of workflow with a (not used) diversity-based alternative.* ***D:*** *Results compared to the predictions from models 1-3. Bracketing means only compound class was predicted.*

Conclusion

- NTRC has developed three models to predict synergy based on a single agent's response in Oncolines™.
- The minimal cross resistance model suggests combination of niraparib with EGFR or PI3K/mTOR inhibitors. However, this cannot be validated on a single cell line.
- Models 1 and 3 predicted 12 out of 16 validated synergistic partners for niraparib, with the targeted synergy model being most successful.
- *A priori* selection of compounds can help in reducing size and cost of synergy screening experiments, but not replace them.

References
[1] Uitdehaag *et al.* (2019) Mol. Cancer Therap. 18, 470-481. [2] Seashore-Ludlow *et al.* (2015) Cancer Discovery 5, 1210-1223. [3] Uitdehaag *et al.* (2015) PLoS ONE 10(5): e0125021. [4] Lee *et al.* (2018) Nature Communications 9: 2546. [5] Palmer and Sorger (2017) Cell 171: 1678-1691. [6] O'Neil *et al.* (2016) Mol. Cancer Therap. 15: 1155-1162. [7] Prinsen *et al.* (2018) Mol. Cancer Therap. 17, Abstract A153. [8] Menden *et al.* (2017) BioRXiv. DOI: 10.1101/200451.