Target Deconvolution Analysis

Target deconvolution analysis was performed as previously described ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib1)). Briefly, cell-based activities, expressed as DSS ([Yadav et al., 2014](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib29)) ([Table S5](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "mmc5)), were used to stratify compounds into one of two classes: hits (DSS ≥ 5) and non-hits (DSS ≤ 0.5). Kinase activity profiles for the stratified compounds were acquired from previously published datasets ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1), [Anastassiadis et al., 2011](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib2), [Arrowsmith et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib3), [Davis et al., 2011](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib6), [Drewry et al., 2014](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib8), [Drewry et al., 2017](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "bib7)), and integrated with additional activity data obtained from PubChem and ChEMBL (<https://doi.org/10.6019/CHEMBL1961873>). In total, 200 non-mutant kinases were included in the analysis. The mutual information for each kinase within the compound classes was calculated and used to prioritize a subset of potentially relevant target kinases for each cell line (maximum relevance algorithm, MR, ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1))) A rule-based selection algorithm using vector machine (SVM) was then used to identify the smallest number of kinases that can predict the hit class of compounds (maximum information set, MAXIS, ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1))). This analysis was performed 100 times, each time using a different combination of hits and non-hits as the starting set (90% of total, randomly selected, with hits to non-hits ratios preserved). The overall scheme is abbreviated as MR-SVM. In the end, each kinase received a MAXIS score ranging between 0 and 100, reflective of how many times it was selected by the algorithm into MAXIS over the 100 runs. The inhibition bias of each kinase (Bk) by the hits or the non-hits was also quantified using the metric previously described in ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1)). A positive Bk (more inhibition by hits) value suggests that the kinase is a target (inhibition results in the cell viability inhibition), while a negative Bk (more inhibition by non-hits) suggests that the kinase is an anti-target (inhibition results in cell proliferation). The product of MAXIS score and Bk constituted the combined score for every kinase for each cell line. A scaling function was used to adjust combined kinase scores to a range of [-100, +100] and to de-emphasize the scores for low inhibition bias (i.e. to emphasize kinases whose inhibition shows high correlation with cellular outcome). Finally, kinases that have high likelihood of being co-inhibited by the same compounds were grouped into pharmacologically linked groups as previously described ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1)). The MAXIS score and Bk for the groups were calculated as the means of the MAXIS scores and Bks ([Table S7](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub" \l "mmc7)) of the individual kinase members, respectively. The combined MAXIS\*Bk scores were then used to [rank order](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/ordo) the groups. The whole process is termed idTRAX (Identification of [Drug TaRgets](https://www.sciencedirect.com/topics/chemistry/drug-target) and Anti-targets by Cellular and Molecular Cross-referencing). A high positive MAXIS\*Bk score indicates that a group contains one or more targets, while a low negative score indicates that a group contains one or more anti-targets. In this study, we used an implementation of idTRAX generated by Truvitech LLC through a collaboration with the company, though the method can also be recreated from the methods described in [Al Ali et al. (2015)](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1) ([Al-Ali et al., 2015](https://www.sciencedirect.com/science/article/pii/S2451945619301072?via%3Dihub#bib1)).