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POSTER ABSTRACTS

803.EMERGING TOOLS, TECHNIQUES AND ARTIFICIAL INTELLIGENCE IN HEMATOLOGY

Computational Approach Based on Independent Drug Action Identifies Clinically Relevant Combinations for Acute Myeloid Leukemia

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Background
Acute myeloid leukemia (AML) is clinically and genetically heterogenous due to complex co-mutation landscape. Combination therapy has shown effectiveness in overcoming tumor heterogeneity and acquired resistance across multiple cancers including AML. However, the discovery of novel combinations has traditionally relied on cell line-based measurements that often fail clinically due to inter- and intra-tumor heterogeneity of patients. To address this challenge of finding clinically relevant combination therapy for AML, we applied the independent drug action (IDA) principle (Palmer & Sorger, 2017) to computationally predict drug combinations using *ex vivo* monotherapy responses measured in primary AML patient specimens (n > 1000).
Methods
We utilized the *ex vivo* drug sensitivity testing (DST) of primary AML samples from three studies; 1. FPMTB (Malani et al. 2021), 164 patient responses to 515 single agents; 2. Beat-AML (Tyner et al. 2018), 579 patient responses to 166 single agents; 3. Oregon Health & Science University (OSHU), 596 patient responses to 51 single agents and 170 2-drug combinations (Figure 1A). To summarize the multiparametric dose-response relationship into a single metric, drug sensitivity score (DSS) (Yadav et al. 2014) was calculated from the dose-response cell viability data of the samples using the BREEZE pipeline (Potdar et al. 2020) to derive monotherapy efficacy. We modified IDACombo package (Ling & Huang, 2020) to predict the mean combination DSS of every pairwise combination. IDAComboscore was calculated for each predicted combination to determine if it is more efficacious than its constituent monotherapies. The top hits from predicted combinations were selected by filtering for combinations with mean DSS in the top 10 th percentile, and positive IDAComboscore. These combinations were then ranked in descending order of IDAComboscore. For validation, Spearman correlation was applied to compare the predicted DSS against *ex vivo* DST-derived DSS of 170 combinations from the OSHU dataset.
Results
By applying IDA-based prediction on FPMTB and Beat-AML datasets, we identified that the mean combination DSS exceeded monotherapy DSS ($p < 2.2x10^{-6}$, Wilcoxon rank-sum test), suggesting that the predicted combination would outperform monotherapy. After accounting for monotherapies that displayed pan-toxicity across healthy samples and primary AML samples (mean DSS > 95 th percentile), we found venetoclax as the top combination partner of the top 100 most effective predicted combinations (FPMTB, n = 33; Beat-AML, n = 35). We further interrogated the makeup of venetoclax-based combinations and found kinase inhibitors (PI3Ki, MEKi, mTORi), and epigenetic modifiers (BETi, HDACi) as common partners. A total of 8 (FPMTB) and 18 (Beat-AML) out of these 100 combinations were made of FDA-approved drugs (both partners). Next, we investigated the robustness of the predictions across 2 datasets, and we found 1767 overlapping combinations with a strong correlation between their predicted mean DSS (Spearman $\rho = 0.74$, $p < 2.2x10^{-6}$). We finally validated the performance of IDA predictions using *ex vivo* DST data of 170 unique combinations from 596 primary AML samples. We found that the predicted DSS values of the 170 combinations strongly correlated with the actual *ex vivo* DST-derived combination DSS (Spearman $\rho = 0.76$, $p < 2.2x10^{-6}$, Figure 1B). Using 75 th percentile of DSS distribution as effective combination cutoff, the

approach showed an accuracy of 84.7%. We then asked if disease status of patients affected prediction accuracy and found that IDA approach successfully predicted effective combinations for patients at diagnosis as well as at relapse (diagnosis $\rho =$ 0.74 vs relapse $\rho = 0.73$).

Conclusion

We have computationally identified and validated clinically actionable drug combinations for AML using *ex vivo* monotherapy responses from >1000 tumor specimens based on IDA principle. Irrespective of pharmacological interaction, IDA-based combinations are more efficacious than single drugs in AML primary tumors. Our approach enables the major advantage of identifying effective combinations for the entire patient population as an alternative to personalized combinations. Further associations with genetic makeup and transcriptomics signature can be leveraged to identify suitable combinations.

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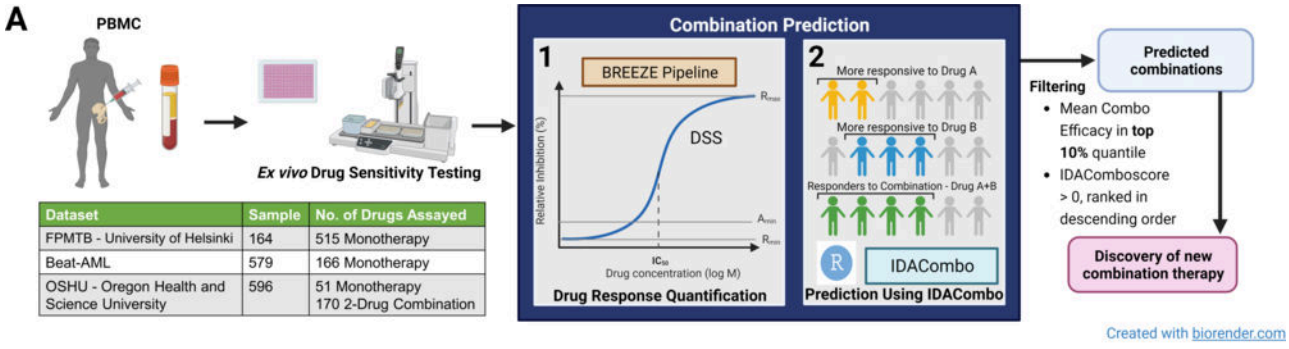

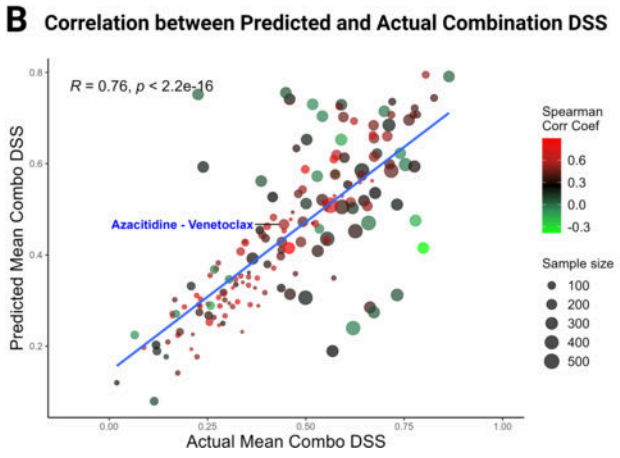

Figure 1

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