The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

803.EMERGING TOOLS, TECHNIQUES AND ARTIFICIAL INTELLIGENCE IN HEMATOLOGY

Geno-Multiomics Strategy Informs Drug Response Profiles in High-Risk Myeloid Neoplasia

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Theclonal diversity of myeloid neoplasia (MN) results from the interplay of genomic entities. While diverse molecular lesions suggest distinct leukemogenic mechanisms, various combinations may lead to similar molecular convergence. Such convergence in the context of clinical heterogeneity may be difficult to discern by classic analytic tools leading to selection based on outcome rather than functional overlaps.

We leveraged the state-of-the-art machine learning (ML) as a new approach to define likelihood of pharmacologic sensitivity/resistance in high-risk MDS/secondary AML (HR-MDS/sAML).

We applied an integrative dimension reduction and subsequent clustering *via* neural networks generating an Encoder-Decoder architecture. Multiple omics were included as input/output to increase the resolution of drug response characterization. Further, drug response data were used to supervise the embedding. Specifically, we generated a deep feed-forward Encoder with 3 layers to embed distinct data modalities and 2 layers for combined embedding generating 100-d latent representation. Drug response measures (IC_{50} values) extracted from The BEAT AML Master Trial[1] was used to supervise the landscape and effectively to generate a non-linear supervised dimension reduction framework.

We previously reported the identification of distinct molecular subclasses in MDS.[2] Unsupervised ML *via* consensus-clustering approach of an autoencoder architecture coupled with GMM resolved clusters according to molecular features, diagnosis, and disease risk. Here, we focus on HR-MDS/sAML (n=1509) clusters. HR-MDS/sAML were grouped in six clusters with mean frequency of 37%. Such clusters, while sharing molecular features were characterized by diverse combinations of genomic features. Therefore, synergistic combination of computational and experimental therapeutics might inform on treatment indications in this group of patients. We noted that treatment response was heterogeneous across the clusters and, in some cases, there was a limited resolution due to molecular heterogeneity. Considering the invariant combinations of dominant and subclonal mutations, we incorporated clonal hierarchy to refine drug response.

By adding a loss function for drug-sensitivity mapping, we generated a multi-omic-phenotype map. Similar joint-dimension reduction (jDR) approaches have been successfully utilized previously as well, specifically in the context of multi-omic single-cell sequencing where majority of the tools are either highly regularized/linear or fully unsupervised.[3] We simulated drug response prediction and show two examples of clusters associated with response profiles using two known drugs (**Fig1A**, HMA, upper 3D surface plot; low plot 3D surface plot: lenalidomide). We identified clusters of patients likely refractory to HMA and responding to lenalidomide (red circles), clusters of patients predicted to respond to HMA and less likely to lenalidomide (black circles) or poorly to both drugs (yellow dots). Since multiple drugs could be assessed simultaneously, clusters of patients sensitive or resistant to drug combination could be also identified (overlapping hills/valleys).

We then applied cluster assignments based on our previous model[2] augmented with VAF and copy number using The Beat AML cohort and characterized drugs with significant difference (ANOVA test). We found significant differences in sensitivity/resistance across the clusters with lower IC_{50} values representing high sensitivity scale against a panel of 120 FDA-approved agents (**Fig1B**). As an example, we generated a 2D embedding. Individual axes show the multi-modal latent-features associated linearly with drug response. Color-coding shows sensitive/resistant IC_{50} profiles for individual samples from The Beat

AML cohort. Four drugs with largest F-statistics are depicted. Interestingly, our prediction show feasibility to simultaneously identify clusters of patients characterized by increased resistance for one drug (*e.g.*, trametinib) and high sensitivity to others (*e.g.*, rapamycin, dasatinib, doramapimod).

In sum, our study suggests that multi-modal genomic configuration increases the power of resolution in HR-MDS/sAML by reducing molecular heterogeneity, which in turn might help resolving therapeutic vulnerabilities.

Disclosures Maciejewski: *Regeneron:* Consultancy, Honoraria; *Alexion:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Speakers Bureau; *Omeros:* Consultancy.

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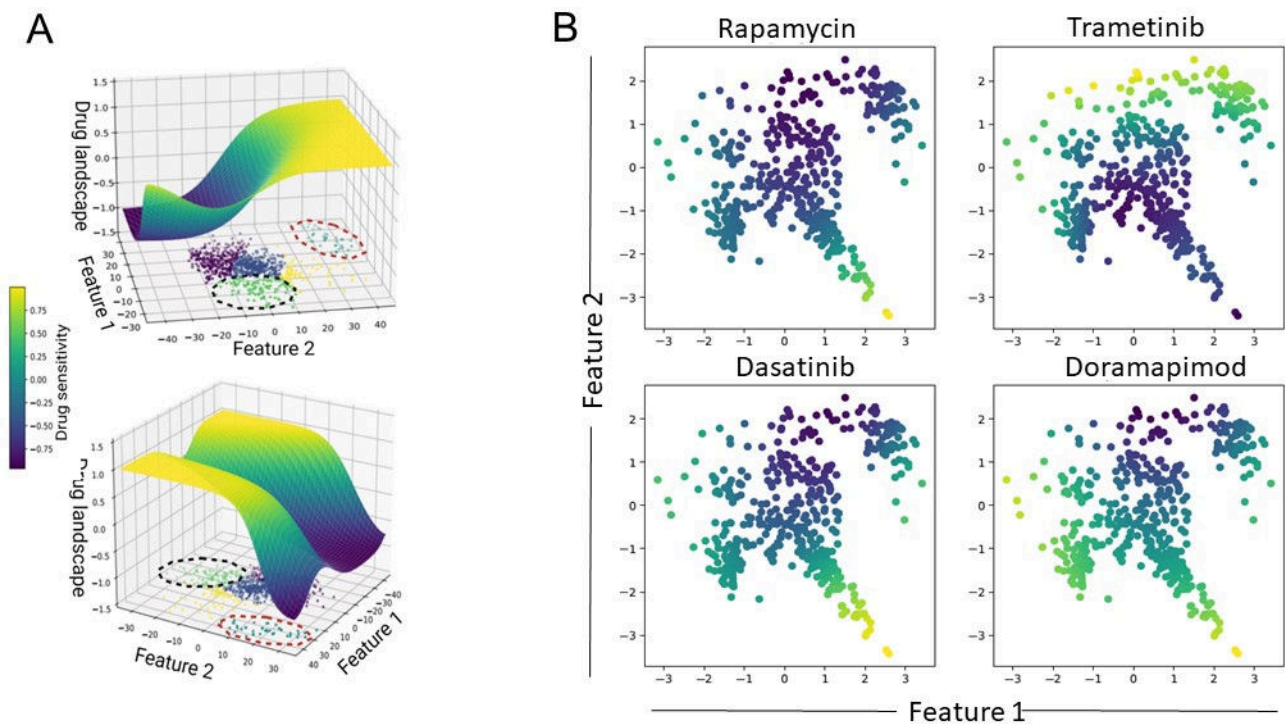
Figure 1. Three dimensional surface plots show predicted drug response of patient clusters. The height (z-axis) indicates the sensitivity/resistance profiles associated with omics features. (**A**, upper) Drug sensitivity is measured by IC50 values (purple, low IC50 = sensitivity; yellow, high IC50 = resistance). (**A**, lower) Overlapping hills/valleys indicate dual sensitivity/resistance. (**B**) Training of our genomic features using available ex vivo drug response from The Beat AML Master Trial. Individual axes show latent-features associated linearly with drug response (IC50 values). Color-coding shows sensitive/resistant IC50 for individual samples.

Figure 1