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PMedIC SEMINAR SERIES

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Mapping the Proteogenomic Landscape of Acute Myeloid Leukemia to Enable Prediction of Drug Response

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Acute Myeloid Leukemia (AML) affects thousands of patients in the US annually with a five-year survival rate of approximately 25%. Although some biomarkers possess clinical utility, they generally do not translate to a therapeutic benefit across all patients, likely due to the heterogenous molecular landscape of AML patients. This landscape, comprising distinct mutational, transcriptomic, proteomic, and metabolic markers, represents a multidimensional view of the patient tumor and, therefore, provides a more in-depth summary of factors that give rise to individual drug response. Toward this end, the Beat AML research program prospectively collected genomic and transcriptomic data from over 1000 AML patient specimens and carried out ex vivo drug sensitivity assays to identify genomic and transcriptomic signatures that could predict patient-specific drug responses. As a member of the Clinical Proteomic Tumor Analysis Consortium, we extended the proteogenomic characterization of this cohort by characterizing the proteome and phosphoproteome of 210 of these patient samples to evaluate the impact that signaling activity has on drug response. We leveraged the proteogenomic data to cluster the Beat AML patient samples into four distinct subtypes that capture the gene and protein expression changes that occur across patients. We then built a classifier of these subtypes based on proteomics data alone that was able to predict drug response in patient samples and cell lines. Using this classification, we identified complementary drug response profiles with both synergistic and antagonistic effects of drugs combinations. Finally, we applied ours models to quizartinib exposes cell lines and predicted trajectories across the subtype-based landscape, allowing us to predict the changes in response to two drugs with distinct mechanism of action. This work demonstrates the utility of AML subtypes and how one can control its trajectory to sensitize it to known therapeutics.

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