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Harnessing Multiplexed Mass Cytometry to Dissect Acute Myeloid Leukemia Heterogeneity

Dr. Muftuoglu is an instructor in the Department of Leukemia at the UT MD Anderson Cancer Center. He received his Doctor of Medicine degree, with distinction, from the University of Istanbul, Cerrahpasa School of Medicine and completed his residency in internal medicine at the University of Istanbul, Istanbul School of Medicine. He joined the Department of Stem Cell Transplantation and Cellular Therapy at the University of Texas MD Anderson Cancer Center in December 2012 as a postdoctoral fellow. During his postdoctoral fellowship, his research was mainly focused on T-cell immunology, adoptive immunotherapy and utilization of single-cell approaches to dissect complex biological systems. Dr. Muftuoglu has established several adoptive immunotherapy approaches for the treatment of viral infections and leveraged highly multiplexed single-cell proteomic approaches to investigate T-cell dysfunction in hematological malignancies. In his current research at the Department of Leukemia , he utilized single-cell proteomic approaches , particularly CYTOF and spectral flow cytometry , to dissect heterogenous acute myeloid leukemia (AML) at the single-cell level, identify novel therapeutic targets and mechanism of resistance, and discover proteomic correlates informing clinical outcomes. One of his main interests is to develop novel computation tools in collaboration for data integration across different single-cell platforms and we have developed a novel computational tool, SCMER, which will allow us to integrate single-cell proteomics and single-cell DNA sequencing platforms and identify the association between mutation profiles and proteomic landscape in AML. To further expand the utility of CyTOF to study AML biology he developed novel probes and sample multiplexing approaches which enable them to interrogate hundreds of parameters across numerous multiplexed samples. This allowed them to decipher the heterogenous proteomic landscape of myeloid leukemias. Their aims are to identify proteomic correlates informing on clinical outcomes, decipher the relationship between AML mutation profiles and proteomic landscape, and discover novel targetable molecules and pathways to guide the clinical decision-making and improve the patient care.

Abstract: Acute myeloid leukemia (AML) is a biologically and clinically heterogenous disorder characterized by accumulation of myeloid blasts. Insights into the

clinico-genetic heterogeneity in patients with AML significantly improved clinical outcomes and paved the way for the development of targeted therapeutic approaches, thereby advancing the field of AML treatment. Taking aim at biological dependencies using targeted therapies, utilization of chimeric antigen receptor (CAR) T-cells against abundantly expressed antigens on leukemic cells and use of immune checkpoint (IC) inhibitors to reinvigorate anti-tumor response stand out as potential therapeutic approaches to tackle AML. To overcome these limitations and decipher the heterogenous leukemia compartment we leverage multiplexed mass cytometry, enabling us to concomitantly assess phenotypic traits, signaling pathways, metabolic alterations, epigenetic modifications and apoptotic networks. To overcome technical variations and increase sample throughput we have developed a unique CD45-based barcoding technique which allowed us to pool 45 samples, which are measured concomitantly, thus avoiding variabilities in staining and instrument performance. We tailored our barcoding approach for AML by utilizing antibodies against three surface antigens, namely CD45, CD298 and beta-2-microglobulin. For leukemia and immune assessment, we have established and validated five different panels with more than 200 antibodies, all of them can be linked by utilizing backbone markers shared among these panels. We utilized this customized single-cell proteomics approach in multiple different scenarios and identified distinct leukemia associated phenotypic traits, metabolic profiles and signaling pathways. This approach also allowed us to map how leukemia cells adapt and evolve under therapy pressure and reveal resistance mechanisms.