Emerging Ex-vivo Drug Sensitivity Platforms

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In acute myeloid leukemia (AML), increasingly refined genomic and transcriptomic stratification still leaves a critical gap: real-world treatment response is shaped by profound intra-patient heterogeneity, clonal evolution, and context-dependent resistance that are not fully captured by static biomarkers. Functional ex-vivo drug sensitivity testing is therefore emerging as a practical precision-oncology layer that directly measures a patient's leukemia vulnerability in primary cells under standardized conditions. This talk focuses on two complementary platforms for AML: (1) a multidrug test platform that simultaneously quantifies sensitivity across a curated panel of clinically relevant agents and rational combinations, and (2) a quantitative venetoclax (VEN) responsiveness assay that reports VEN vulnerability as a continuous metric rather than a binary label. In the multidrug platform, diagnostic or on-therapy (response, relapse, secondary resistance) AML samples are exposed to single agents and selected combinations over clinically anchored concentration ranges; readouts generate dose–response curves and ranked sensitivity profiles using summary indices, while combination effects are interpreted within additivity/synergy frameworks. The quantitative VEN responsiveness platform quantifies responsiveness by directly measuring VEN-modulated protein-protein interactions(PPIs) involving the VEN target complex—capturing how effectively VEN disrupts pro-survival BCL-2–centered interactions and/or reshapes binding competition with BH3-only proteins and effectors—thereby yielding a continuous, quantitative susceptibility metric that can distinguish deep sensitivity, intermediate vulnerability, and functional resistance even when bulk viability differences are subtle. Taken together, these platforms can inform upfront regimen selection by functionally prioritizing the most effective agents and rational combinations for an individual AML sample, while also enabling rapid therapeutic triage in relapsed/refractory or medically unfit AML where options are limited. Beyond patient-level decision support, cohort-scale analyses can construct cross-sensitivity maps that connect VEN resistance states to actionable alternative backbones and add-on partners, providing an empirical basis for prospective trial designs that incorporate ex-vivo response metrics for regimen optimization, enrichment, or stratification. Key challenges remain—sample quality and time-to-assay, incomplete microenvironment recapitulation, and inter-laboratory reproducibility—making strict quality control, standardized operating procedures, transparent reporting of performance metrics, and prospective clinical validation essential steps to move DST from promising decision-support to clinically trustworthy infrastructure.