Precision systems medicine from leukemia to solid tumors

Most precision cancer medicine efforts are based on the identification of oncogenic driver mutations by genome sequencing. We believe that this will miss therapeutic opportunities and additional profiling technologies as well as cell-based functional testing should be included. This systems approach requires disease-relevant ex vivo cell models, multi-parametric assays, quality metrics, automated analytics pipelines and integration with -omics profiling to enable actionable information to the clinician.

Our studies in leukemia indicate the value of ex vivo drug testing to identify novel, clinically actionable therapeutic opportunities. To pilot this in solid tumors we have developed, by conditional re-programming, patient-derived cells (PDCs) from castration-resistant prostate cancer (CRPC) and renal cell cancer (RCC). PDCs are compared with primary tumor tissue by genomic profiling and then subjected to drug sensitivity profiling with 530 approved and investigational oncology drugs. The drugs are plated in five different concentrations spanning a 10,000-fold concentration range on 384-well plates. So far, cell viability has been the main parameter measured but we are now applying automated high-content imaging of hundreds of phenotypic features from drug treated PDCs. Healthy control cells enable identification of general toxic effects. Intra-patient heterogeneity can be assessed by multiple tumor samplings. High throughput cell-based functional drug testing is conducted in many different ways across laboratories. Hence, harmonization of assay controls and metrics of drug efficacy are needed to enable translation. Correlation of ex vivo and in vivo efficacies need to be demonstrated in large-scale clinical trials in the future.

Acknowledgement

References

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3Saeed et al., Eur Urol, 2017