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PRECISION SYSTEMS MEDICINE IN UROLOGICAL TUMORS – MOLECULAR PROFILING AND FUNCTIONAL TESTING

Khalid Saeed
University of Helsinki, Finland

Background: Most precision cancer medicine efforts are based on the identification of oncogenic driver mutations by genome sequencing. We believe and have emerging evidence that this will miss therapeutic opportunities and additional technologies, such as cell-based functional testing should be included. Pioneering studies in leukemia indicate the value of ex vivo drug testing to identify novel, clinically actionable therapeutic opportunities.

Methods: Using conditional re-programming technology, we established patient-derived cells (PDCs) from castration-resistant prostate cancer (CRPC) and renal cell cancer (RCC) to pilot precision systems medicine in solid tumors. The PDCs were compared with primary tumor tissue by genomic profiling and then subjected to drug sensitivity testing with >306 approved and investigational oncology drugs.

Results: Here, we generated both benign and malignant PDCs from prostate tissue, including six benign PDCs that were androgen receptor (AR)-negative, basal/transit-amplifying phenotype, but could re-express AR in 3D-culture. The PDCs from a CRPC patient displayed multiple CNAs, some of which were shared with the parental tumor. The cancer-selective drug profile for these PDCs showed sensitivity to taxanes, navitoclax, bexarotene, tretinoin, oxaliplatin and mepacrine. RCC displays extensive intra-tumor heterogeneity and clonal evolution. There is, however, very little information on how much this impacts drug sensitivities. Therefore, we generated several PDCs from each RCC patient across multiple tumor regions. We verified their clonal relationship with the uncultured tumor tissue by NGS and performed drug sensitivity profiling. The PDCs retained CNAs and driver mutations in e.g., VHL, PBRM1, PIK3C2A, KMD5C, TSC2 genes present in the original tumor tissue. Drug testing with 461 oncology drugs identified shared vulnerability among the multiple PDCs to pazopanib and temsirolimus that inhibit well-established renal cancer pathways VEGFR/PDGFR/FGFR and mTOR. Importantly, however, the individual PDC from different regions in one patient also showed distinct drug response profiles, confirming that genomic heterogeneity leads to variability in drug responses.

Conclusions: Our aim is to generate molecular profiles and drug testing data using representative PDCs from each patient to help clinicians in treatment decision and to facilitate the early selection of the best drug candidates for clinical development. We believe this approach will help to personalize treatment, prioritize drugs for clinical testing, provide for intelligent selection of drug combinations and improve treatment outcomes.