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Conditionally Reprogrammed Patient-derived Cells: A Step Forward Towards Personalized Medicine?

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The ability to accurately and efficiently predict systemic therapies that provide the optimal benefit-to-harm ratio for an individual patient before initiation of treatment is a "holy grail" of precision medicine. Over the past several decades, several approaches attempting to achieve this vision for patients with bladder and other cancers have emerged, ranging from the use of genetic and genomic data derived from an individual patient's tumor to harvesting an individual patient's tumor for in vitro or in vivo assays. The latter approach, generating patient-derived xenograft (PDX) models, seems to have particular promise given a growing body of data demonstrating maintenance of genomic and genetic features of the original tumor in the context of a system that includes at least some stromal component and is amenable to a variety of therapeutic manipulations [1]. Unfortunately, high cost, slow growth, variable engraftment, inability to be maintained in culture for prolonged periods of time, and a lack of studies establishing clinical utility to date have challenged the widespread use of PDX models as a tool for individualized drug predictions. The ability to propagate patient-derived cells in culture long term could potentially retain several of the favorable characteristics of PDX models yet overcome some of the limitations.

Conditional reprogramming, which involves co-culture of epithelial cells with fibroblast feeders in the presence of a Rho kinase inhibitor, can successfully achieve sustained expansion of epithelial cancer cells, raising the possibility that such technology could be used to propagate cancer cells in culture for drug sensitivity screening [2,3]. Prior studies have demonstrated the feasibility of this approach [4]. In this issue of *European Urology*, Kettunen et al [5] describe what is, to the best of our knowledge, the first report on conditional reprogramming to generate patient-derived bladder cancer cells to guide an individualized approach to systemic therapy.

The authors used conditional reprogramming technology in an attempt to generate patient-derived cell cultures from six bladder cancers (cystectomy or transuretheral resection of bladder tumors specimens) of various clinical stages. All specimens were urothelial cancer with the exception of one small cell cancer. Among these, cultures could be "established" from four of the specimens including the small cell cancer; established cultures were defined as those that could be cultured for five passages and after cryopreservation could be repropagated for further analyses. Exome sequencing revealed that only two of the cultures retained the majority of mutations found in the corresponding tumors. Drug sensitivity screens revealed some intriguing hits (eg, statins) but the clinical validity of these findings could not be corroborated in the absence of matched patient treatment data.

The development of individualized drug sensitivity assays in oncology is not a new concept and multiple approaches have been described over the past 20–30 yr. The proliferation of such assays, within a regulatory environment historically requiring a lower level of evidence for the development and commercialization of laboratory-based tests than for therapeutics, prompted the American Society of Clinical Oncology (ASCO) to perform a technology assessment of chemotherapy sensitivity and resistance assays in 2004, concluding that a review of the literature could not identify any assays "for which the evidence base is sufficient to support use in oncology practice" [6].

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Acknowledging the rapid development of improved technologies for propagation and characterization of patient-derived tumors, recommendations for future research included the development of assays that (1) yield useful results, (2) are not affected by tumor heterogeneity, (3) guide subsequent systemic therapy, (4) are cost effective, and (5) yield results in a relatively short timeframe.

How does the approach described by Kettunen et al stack up against these ASCO-defined attributes of an ideal assay? To be fair, this is a pilot study seeking to establish the feasibility of this new and exciting technology. While the proportion of specimens from which cultures could be successfully established is somewhat better than prior approaches to generating patient-derived cancer cells in culture, a success rate of 40% (two/five urothelial cancer specimens) would still be troublesome from a clinical standpoint. The poor concordance between the genomic profile of cultured cells and the corresponding tumors raises further pause. Finally, the lack of clinical correlations with drug response predictions precludes an understanding of the potential validity of the approach. The authors are to be congratulated for taking the first steps in the development of a highly novel platform in the search to improve the care of patients with bladder cancer; additional work focused on optimization and refinement followed by clinical validity and utility is required.

From a conceptual standpoint, the use of patient-derived tumor material in the context of in vitro assays to guide treatment decisions for individual patients is attractive. Such an approach is a logical extension of microbial sensitivity assays used for decades to inform antibiotic choice in routine clinical practice. However, there are fundamental differences between tumors and microbes that have historically hindered the development of similar culture-based systems in oncology. Cancer cells probably exhibit much more genomic complexity and clonal heterogeneity than microorganisms. Furthermore, the tumor microenvironment, typically not represented in in vitro culture-based systems, is probably as important or at times perhaps even more important in determining drug sensitivity than cancer cells themselves. Whether model systems that overcome all of these barriers and yet can be deployed within the timeframes required to inform clinical care can realistically be developed is unclear, although the recent pace of progress indicates that such a vision may no longer represent science fiction.

Conflicts of interest: Matthew D. Galsky has served as consultant for BioMotiv, Janssen, Merck, Dendreon, GlaxoSmithKline, Lilly, Astellas, Genentech, BMS, Novartis, Pfizer, EMD Serono, AstraZeneca, Seattle Genetics, Incyte, Aileron Therapeutics, Dracen, Inovio Pharmaceuticals, and NuMab; has received research funding from Janssen, Merck, Dendreon, Novartis, BMS, AstraZeneca, and Genentech/Roche; and owns stock in Rappta Therapeutics, outside the submitted work. Alberto Martini and John P. Sfakianos have nothing to disclose.

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