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COMMENTARY

Insider information: Testing cancer drug sensitivity for personalized therapy

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Abstract Cancer death is usually caused by incurable drug-resistant and metastatic cancers. Although tremendous progress has been made in anticancer drug development during the past two decades, cancer medicine still faces unprecedented challenges associated with choosing effective treatments for individual patients. Three recent reports have offered encouraging approaches towards potentially personalized cancer drug selection.

Cancer is a heterogeneous disease, both among affected individuals and within the same affected individual. Despite the significant progress made in the past decade in developing new and/or more specifically-targeted cancer therapeutics, the overall survival rates of many common cancers have been slow to improve. This is largely due to the suboptimal selection of therapeutic agents and/or inevitable development of drug resistance. Thus, there is an urgent need to develop precision and personalized oncology. In three recent reports, investigators developed different technical platforms that may allow the cancer drug sensitivity and efficacy to be tested prior to full-scale clinical treatments.[1–3] If they become widely used, these techniques may facilitate the development and implementation of personalized cancer medicine.

Cancer drug resistance remains a major cause of death of cancer patients.[4] For the past few decades, cancer drug development has moved from empirical approaches that broadly reduce cell proliferation or increase cell death to more focused approaches that target well-defined genetic, epigenetic and environmental drivers of cancer. This progress is highlighted by the dramatic clinical responses seen with drugs targeting the oncogenic BCR-ABL tyrosine kinase fusion protein in chronic myelogenous leukemia (CML) or oncogenic BRAF-V600E mutations in melanoma. However, such molecular-targeted therapies are still associated with drug resistance, just like the classical cytotoxic chemotherapeutics. Thus, there is an urgent need to develop clinically-relevant and novel *in vivo* models and technologies to test and/or predict drug sensitivity and the likelihood of resistance.[4]

For the past few decades, mouse models of cancer development have provided immeasurable translational value for cancer drug discovery.[5] Mouse cancer models can be used to confirm the biological relevance of candidate targets on tumor growth, to establish therapeutic windows, to determine efficacious drug targets, and to identify biomarkers of the tumor response, although mouse models often lack the predictive power for clinical success.[5] In recent years, increasing interest has been focused on the development and characterization of patient-derived

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tumor xenograft (PDX) models for cancer research.[6] PDX models have been shown to retain the main histological and genetic characteristics of the donor tumors, and remain relatively stable across passages. Thus, PDX models may be more predictive of clinical outcomes, and should have great potential for preclinical drug evaluation, biomarker identification, and personalized cancer medicine. However, the generation of PDX models can be time-consuming and investigator-specific. Thus, simple, fast, and effective approaches should be devised to test cancer drugs. Three recent studies may have made significant progress in this regard.

Rubio-Perez et al reported a novel *in silico* analysis to identify potentially effective cancer treatment strategies.[3] This analysis took advantage of cancer genome data generated by high-throughput next-generation sequencing from pan-cancer cohorts that linked approved and experimental therapeutics to specific genetic driver events. Using these large pan-cancer patient cohorts, the investigators developed a three-tier *in silico* prescription strategy by assigning each patient the targeted therapeutic interventions that would be most beneficial based on the identified cancer driver events. By analyzing 6792 tumor samples, the investigators identified 475 driver genes with activating or loss-of-function alterations, such as somatic mutations, copy-number amplifications, and/or gene fusions. The second step involved collecting data on potential anticancer drug treatments targeting driver genes, including FDA-approved compounds and compounds in clinical or preclinical development. Finally, these treatments were prescribed *in silico* to individual patient samples based on the respective driver events.[3] Interestingly, the investigators found that using this strategy, only 5.9% of patients would benefit from FDA-approved therapies. However, the potential benefit of therapeutic intervention could be increased to 40.2% if the tumor type, disease, and off-target repurposing of FDA-approved drugs was considered. This model also predicted that an additional 33.1% of patients may benefit from drugs currently in clinical trials or in pre-clinical development. As expected, combination therapies could provide beneficial effects for 39% of patients whose tumors contained multiple driver events.[3] An additional 80 potentially targetable driver genes were identified in the *in silico* analysis.[3] Thus, such *in silico* approaches may offer a powerful tool for oncologists to link tumor-driving events with clinical treatments towards personalized cancer medicine.

By taking completely different approaches, two independent studies reported the use of newly engineered devices to test drug sensitivity, and hence improve drug selection, by directly injecting drugs into the patient and analyzing the cancer response within the tumor microenvironment *in vivo*.[1,2] Jonas et al engineered a small cylindrical device (820 μm in diameter) containing 16 discrete reservoirs for releasing different drugs.[1] The device was implanted into tumors via a biopsy needle and left *in situ* for 24 h, and then was removed with the tissue-containing coring needle for an immunohistochemical analysis. Combinations of drugs or time-specific drug release can both be achieved using this single device. The investigators showed that there was a correlation between apoptosis and the drug concentration.[1] Of note, the investigators implanted several devices into different areas of each tumor and used replicate wells in each device, usually in the non-necrotic periphery of the tumor, to overcome possible heterogeneity in the drug response. The investigators used doxorubicin in animal models of human melanoma, prostate, and breast cancers, and demonstrated that the device recapitulated the systemic response. Finally, using a mouse model of human triple-negative breast cancer, the investigators showed that the ranking of effective therapies as determined with this device was the same as the whole animal response to the systemically-administered drugs.

Klinghoffer et al developed a different technology platform called CIVO, which contains an array of multiple needles and enables the simultaneous assessment of up to eight drugs or drug combinations within a solid tumor *in vivo*.[2] After drug injection, the needles were withdrawn, leaving a 6-mm "track" containing the drug and tracking dye. After incubation *in situ* for up to 72 h, the tumor tissues were retrieved to assess the drugs' effects on cancer cells. CIVO offers an automated analytical program that assesses the readouts and allows the cellular response to be correlated with distinct microenvironments, offering the opportunity for combinatorial interrogation of drugs.[2] Using human lymphoma xenograft tumors treated with vincristine as a preclinical model, Klinghoffer et al showed that the drug was imaged within a 2-mm limit of distribution beyond the injection epicenter, and the pharmacodynamic effects of vincristine could be monitored using phosphohistone H3 and CC3 assays. The investigators showed that a drug-resistant version of the lymphoma model was unexpectedly responsive to cyclophosphamide, as predicted with the CIVO device, and resistant tumor—bearing animals treated with cyclophosphamide were rendered tumor-free.[2] These findings highlight the importance of in-tumor screening of the drug efficacy, because *in vitro* cell culture-based assays failed to show these cells' responsiveness to cyclophosphamide. The authors further showed that, after testing the sensitivity of the lymphoma models to 97 approved cancer drugs, the resistant cells were most sensitive to a previously unidentified mTOR inhibitor.[2] More importantly, the CIVO platform has been moved forward into clinical testing, and the insertion of the device was shown well-tolerated and safe in the preliminary assessment in a small number of patients.

These *in silico* and/or device-based approaches for cancer drug selection are novel and potentially transformative. However, the *in silico* cancer drug prescription analysis would reply on the availability of large cohorts of genomic data for a given type of tumor. In addition, none of the three approaches can easily overcome the issue of tumor heterogeneity. The reported devices may thus have physical limitations in detecting drug-resistant cells. Moreover, the implantation of these devices may bypass some important factors that limit drug diffusion, such as the elevated interstitial fluid pressure and high concentrations of proteins in the extracellular fluid in tumor tissues. A bigger challenge facing the field of cancer drug development and selection is to identify reliable biomarkers that reflect the drugs' actions and effects *in vivo*. Nonetheless, these investigations offer a promising start towards personalized cancer medication.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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