















that the TME can both enhance sensitivity and promote resistance depending on the cell, drug, and TME composition (80). These studies highlight the TME as a missing component in many *in vitro* studies, as well as the large-scale cell line pharmacogenomics studies (3, 4, 8–10). It is worth noting that these large databases were designed to study cell-intrinsic mechanisms of therapeutic response, and models such as those described above will be needed to consider the influence of cell-extrinsic factors on therapeutic response.

**Pharmacogenomic differences between preclinical models.** Several experimental model systems are available to study the molecular underpinnings of cancer, and each has strengths and weaknesses. Here, we describe observed pharmacogenomic differences between several preclinical models, such as xenografts, 3D culturing, and conventional monolayer culturing. Early studies showed differences in morphology and growth between monolayer culturing and xenograft models of cell lines (81), but the pharmacogenomics profiles between preclinical models have been compared only recently.

Alterations in cell lines that are grown in 3D culture (e.g., Matrigel) are similar to those found in cells grown in a monolayer. Kenny and colleagues grew matched cell lines in monolayer or 3D cultures and analyzed differences in gene expression using microarrays. Global changes were found to be minimal, as each cell line clustered with itself, regardless of culturing method. However, there were consistent changes in genes related to signal transduction between the two groups (82). Several other studies have indicated that cells grown in 3D versus monolayer culture have differences in global gene expression, notably increased extracellular matrix genes (83, 84). These differences are likely due to altered environmental signaling and mechanical composition compared with those in conventional monolayer culture.

The cell culture approach itself can also influence sensitivity to therapy. Aljijitwi and colleagues showed leukemia cells were more resistant to chemotherapeutics when cocultured with human bone marrow mesenchymal stem cells in a 3D model versus monolayer (85). In addition, Chambers and colleagues showed that prostate cancer cell lines grown in 3D culture had different responses to docetaxel than those grown in monolayer (86). Other studies have observed pharmacologic differences in 3D culturing (87, 88). Altogether, these observations identify important differences between 3D and monolayer culture, indicating that response to therapy is driven by both the extracellular environment and intrinsic biology.

The genomic differences between xenograft and monolayer models have also been explored. Daniel and colleagues used primary xenografts of human small-cell lung cancer to derive cell lines and then used those cell lines in secondary xenograft experiments (89). The authors were able to identify gene expression differences between primary xenografts and monolayer culturing of the cell lines, suggesting genomic alterations between the two model systems. These genes remained differentially expressed in the secondary xenograft, suggesting stable changes had occurred in monolayer culture.

Ding and colleagues compared mutations between a matched primary breast tumor, a brain metastases, and a patient-derived xenograft model (PDX; ref. 90). While mutations were similar for each type, some mutations were enriched in the metastases and the PDX compared with the primary tumor. This study suggests that many of the genomic aberrations of the primary

tumor are conserved during metastasis and at least early PDX models; however, selection that can have a strong impact on the model under study can occur. Pandita and colleagues used tumor glioblastoma multiforme (GBM) biopsies coupled with serial xenografts and the establishment of cell lines to find that *EGFR* amplifications are conserved *in vivo* but lost *in vitro* (91). Later studies in GBM confirmed that alterations of *EGFR*, *PDGFRA*, *TP53*, *PTEN*, and *CDKN2A* in patient tumors were conserved in flank and intracranial xenografts (92). These studies show that *EGFR* amplifications in GBM are selected against in monolayer culture, but are conserved across xenograft models.

PDX models and xenografts using human cell lines have some similar shortcomings. Immuno-oncology employs various ways to "educate" the immune system to better fight cancer. Because human cells cannot be xenografted into immunocompetent mice, immuno-oncology research most often is performed in mouse models lacking human cells, outlining one area of research where the use of human cancer cell lines is limited. However, the development of humanized mouse models has contributed to the study of immuno-oncology (reviewed by Lodhia and colleagues; ref. 93).

Another issue with these human xenograft models is that important components of the TME are lacking, including cells of the immune system. In addition, not all cancer cell lines are tumorigenic which limits the number of cell lines that are amenable for *in vivo* studies (<http://www.atcc.org>). Xenograft models also display features of species incompatibility. For example, mouse growth factors do not activate human MET, which decreases the effectiveness of *in vivo* models in regards to MET-related studies (94). These disadvantages suggest to some that syngeneic or genetically engineered mouse models may be superior to human xenograft models because of species compatibility and intact immune systems. However, Voskoglou-Nomikos and colleagues have shown that the clinical translatability of murine allograft models was poorer compared with models that contained human cells (95). The different *in vivo* models each offer an array of advantages and disadvantages and their vulnerabilities should be considered before their use [reviewed by Gould and colleagues (96)].

Overall, the studies we described outline the differences that occur in gene expression and pharmacologic profiling of monolayer cultured cells versus other *in vitro* models. To a large degree, these differences are not surprising. The choice of experimental model must be dictated by the question being asked. Cell lines are not perfect models, but have strengths that include ease of use, low cost, and utility in diverse experimental studies. There is evidence in support of xenograft (96) and 3D models (75) more closely resembling tumor biology. However, like conventional cell line studies, these models fail to capture the diversity of microenvironments that tumor cells encounter in patients. In general, the limitations and differences associated with any model system should be considered when assessing the likelihood that observations made from it will be predictive of clinical behavior.

## Discussion

Cell lines have long been used to study the mechanisms underlying biologic processes. Large collections of -omically functionally characterized cell lines are now available as a resource to the biomedical community. These data are now being used to

develop analytic approaches to predict the behavior of complex adaptive systems, and to identify -omic features that provide insights into the mechanisms of therapeutic response. Central to these studies is the availability of well-characterized genomic measurements. Large, publicly available datasets, like the ones listed in Table 1, offer the level of genomic measurement needed to compare cell lines and tumors.

The comparisons of cell line and tumor genomics have offered insights into the relevance of *in vitro* models. In many instances, it is appropriate to use cell line genomics as a model for *in vivo* genomics; however, this is only true if due diligence is performed. Domcke and colleagues showed that the cell lines most commonly used to study HGSOC did not closely model the genomics of the disease, and that less frequently used models show stronger genomic similarities to primary disease (14). In addition, not all tumor subtypes are represented in current panels of cell lines (30–32). This realization has spurred the generation of new cell lines and 3D culturing techniques that more closely reflect the features of the primary tumors from which they were derived.

In all cases, it is important to assess the extent to which cell lines accurately model the aspects of tumor biology being studied. With the advancement of high-throughput data generation techniques, we now have -omic profiles on over 1,000 human cancer cell lines to choose from, and the list is growing (97). These resources offer the data needed to systematically select the appropriate cell line genomic model for studying a primary tumor.

Omic studies have identified molecular features that are common to several different cancer types. These common features are likely related to the epithelial and mesenchymal origins for the tumors and persist in tumor-derived cancer cell lines. This has

been demonstrated in breast and bladder cancers (25, 33). Molecular subtyping can inform patient treatment decisions, but caution must be used when applying molecular subtype signatures to cancer cell lines, as we demonstrated in Fig. 1.

Genomic measurements do not capture all aspects of cellular activity and integrative models provide greater predictive power than individual datasets. We expect that future pharmacogenomics studies will expand in the genomics space by leveraging next-generation sequencing to broaden the spectrum of molecules sampled, namely noncoding RNAs, alternative spliced transcripts, gene fusions, and allele-specific expression. Beyond genomics, we also expect to see an expansion into other -omic data types such as metabolomics and proteomics. From the analysis of data individually or from data integration approaches will come an increasing number of hypotheses to be tested. Cancer cell lines will remain a viable tool in this context and play a central role in cancer biology research into the future.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Grant Support

This study was financially supported by the Denver Chapter of the Golfers Against Cancer, NIH grants 5P30CA069533-16, U54 HG008100, U54 CA 112970, the Prospect Creek Foundation, and the Susan G. Komen Foundation SAC110012.

Received April 27, 2015; revised June 30, 2015; accepted July 29, 2015; published OnlineFirst August 6, 2015.

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*Mol Cancer Res* 2016;14:3-13. Published OnlineFirst August 6, 2015.

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