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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. Alijitwi 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

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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.

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References

1. Sharma SV, Haber DA, Settleman J. Cell line-based platforms to evaluate the therapeutic efficacy of candidate anticancer agents. Nat Rev Cancer 2010;10:241–53.
2. The Cancer Genome Atlas Research Network Weinstein JN, Collisson EA, Mills GB, Shaw KRM, Ozenberger BA, et al. The cancer genome atlas pan-cancer analysis project. Nat Genet 2013;45:1113–20.
3. Shoemaker RH. The NCI60 human tumour cell line anticancer drug screen. Nat Rev Cancer 2006;6:813–23.
4. Shankavaram UT, Varma S, Kane D, Sunshine M, Chary KK, Reinhold WC, et al. CellMiner: a relational database and query tool for the NCI-60 cancer cell lines. BMC Genomics 2009;10:277.
5. Heiser LM, Sadanandam A, Kuo W-L, Benz SC, Goldstein TC, Ng S, et al. Subtype and pathway specific responses to anticancer compounds in breast cancer. Proc Natl Acad Sci 2012;109:2724–9.
6. Daemen A, Griffith OL, Heiser LM, Wang NJ, Enache OM, Sanborn Z, et al. Modeling precision treatment of breast cancer. Genome Biol 2013;14:R110.
7. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, et al. The connectivity map: using gene-expression signatures to connect small molecules, genes, and disease. Science 2006;313:1929–35.
8. Yang W, Soares J, Greninger P, Edelman EJ, Lightfoot H, Forbes S, et al. Genomics of drug sensitivity in cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. Nucleic Acids Res 2013;41:D955–61.
9. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, Kim S, et al. The cancer cell line encyclopedia enables predictive modelling of anticancer drug sensitivity. Nature 2012;483:603–7.
10. Basu A, Bodycombe NE, Cheah JH, Price EV, Liu K, Schaefer GI, et al. An interactive resource to identify cancer genetic and lineage dependencies targeted by small molecules. Cell 2013;154:1151–61.
11. Ross DT, Perou CM. A comparison of gene expression signatures from breast tumors and breast tissue derived cell lines. Dis Markers 2001;17:99–109.
12. Ross DT, Scherf U, Eisen MB, Perou CM, Rees C, Spellman P, et al. Systematic variation in gene expression patterns in human cancer cell lines. Nat Genet 2000;24:227–35.
13. Neve RM, Chin K, Fridlyand J, Yeh J, Baehner FL, Fevr T, et al. A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes. Cancer Cell 2006;10:515–27.
14. Domcke S, Sinha R, Levine DA, Sander C, Schultz N. Evaluating cell lines as tumour models by comparison of genomic profiles. Nat Commun 2013;4:2126.
15. Li H, Wawrose JS, Gooding WE, Garraway LA, Lui VWY, Peyser ND, et al. Genomic analysis of head and neck squamous cell carcinoma cell lines and human tumors: a rational approach to preclinical model selection. Mol Cancer Res 2014;12:571–82.
16. Mouradov D, Sloggett C, Jorissen RN, Love CG, Li S, Burgess AW, et al. Colorectal cancer cell lines are representative models of the main molecular subtypes of primary cancer. Cancer Res 2014;74:3238–47.
17. Lin WM, Baker AC, Beroukhim R, Winckler W, Feng W, Marmion JM, et al. Modeling genomic diversity and tumor dependency in malignant melanoma. Cancer Res 2008;68:664–73.
18. Sos ML, Michel K, Zander T, Weiss J, Frommolt P, Peifer M, et al. Predicting drug susceptibility of non–small cell lung cancers based on genetic lesions. J Clin Invest 2009;119:1727–40.
19. Paz MF, Fraga MF, Avila S, Guo M, Pollan M, Herman JG, et al. A Systematic profile of DNA methylation in human cancer cell lines. Cancer Res 2003;63:1114–21.
20. Cope LM, Fackler MJ, Lopez-Bujanda Z, Wolff AC, Visvanathan K, Gray JW, et al. Do breast cancer cell lines provide a relevant model of the patient tumor methylome? PLoS ONE 2014;9:e105545.
21. Varley KE, Gertz J, Bowling KM, Parker SL, Reddy TE, Pauli-Behn F, et al. Dynamic DNA methylation across diverse human cell lines and tissues. Genome Res 2013;23:555–67.

22. Perou CM, Jeffrey SS, van de Rijn M, Rees CA, Eisen MB, Ross DT, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc Natl Acad Sci U S A 1999;96:9212–7.
23. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 1999;286:531–7.
24. Cho Y-J, Tsherniak A, Tamayo P, Santagata S, Ligon A, Greulich H, et al. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol 2011;29:1424–30.
25. Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 2014;25:152–65.
26. Prat A, Bianchini G, Thomas M, Belousov A, Cheang MCU, Koehler A, et al. Research-based PAM50 subtype predictor identifies higher responses and improved survival outcomes in HER2-positive breast cancer in the NOAH Study. Clin Cancer Res 2014;20:511–21.
27. Sadanandam A, Lyssiotis CA, Homicsko K, Collisson EA, Gibb WJ, Wullschleger S, et al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. Nat Med 2013;19:619–25.
28. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci 2001;98:10869–74.
29. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609–15.
30. Virtanen C, Ishikawa Y, Honjoh D, Kimura M, Shimane M, Miyoshi T, et al. Integrated classification of lung tumors and cell lines by expression profiling. Proc Natl Acad Sci 2002;99:12357–62.
31. Kao J, Salari K, Bocanegra M, Choi Y-L, Girard L, Gandhi J, et al. Molecular profiling of breast cancer cell lines defines relevant tumor models and provides a resource for cancer gene discovery. PLoS ONE 2009;4:e6146.
32. Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. Nat Med 2011;17:500–3.
33. Damrauer JS, Hoadley KA, Chism DD, Fan C, Tiganelli CJ, Wobker SE, et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. Proc Natl Acad Sci 2014;111:3110–5.
34. Parker JS, Mullins M, Cheang MCU, Leung S, Voduc D, Vickery T, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009;27:1160–7.
35. Lee JK, Havaleshko DM, Cho H, Weinstein JN, Kaldjian EP, Karpovich J, et al. A strategy for predicting the chemosensitivity of human cancers and its application to drug discovery. Proc Natl Acad Sci 2007;104:13086–91.
36. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.
37. Chan KS, Espinosa I, Chao M, Wong D, Ailles L, Diehn M, et al. Identification, molecular characterization, clinical prognosis, and therapeutic targeting of human bladder tumor-initiating cells. Proc Natl Acad Sci 2009;106:14016–21.
38. Isella C, Terrasi A, Bellomo SE, Petti C, Galatola G, Muratore A, et al. Stromal contribution to the colorectal cancer transcriptome. Nat Genet 2015;47:312–9.
39. Alsner J, Yilmaz M, Guldberg P, Hansen LL, Overgaard J. Heterogeneity in the clinical phenotype of TP53 mutations in breast cancer patients. Breast Cancer Res 2000;2:P4.04.
40. Maley CC, Galipeau PC, Finley JC, Wongsurawat VJ, Li X, Sanchez CA, et al. Genetic clonal diversity predicts progression to esophageal adenocarcinoma. Nat Genet 2006;38:468–73.
41. Landau DA, Carter SL, Stojanov P, McKenna A, Stevenson K, Lawrence MS, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell 2013;152:714–26.
42. Roschke AV, Tonon G, Gehlhaus KS, McTyre N, Bussey KJ, Lababidi S, et al. Karyotypic complexity of the NCI-60 drug-screening panel. Cancer Res 2003;63:8634–47.
43. Nagai Y, Miyazawa H, Huqun, Tanaka T, Udagawa K, Kato M, et al. Genetic heterogeneity of the epidermal growth factor receptor in non–small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. Cancer Res 2005;65:7276–82.
44. Charafe-Jauffret E, Ginestier C, Iovino F, Wicinski J, Cervera N, Finetti P, et al. Breast cancer cell lines contain functional cancer stem cells with metastatic capacity and a distinct molecular signature. Cancer Res 2009;69:1302–13.
45. Kondo T, Setoguchi T, Taga T. Persistence of a small subpopulation of cancer stem-like cells in the C6 glioma cell line. Proc Natl Acad Sci U S A 2004;101:781–6.
46. Harper LJ, Piper K, Common J, Fortune F, Mackenzie IC. Stem cell patterns in cell lines derived from head and neck squamous cell carcinoma. J Oral Pathol Med 2007;36:594–603.
47. Lee J, Kotliarova S, Kotliarov Y, Li A, Su Q, Donin NM, et al. Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. Cancer Cell 2006;9:391–403.
48. Paull KD, Shoemaker RH, Hodes L, Monks A, Scudiero DA, Rubinstein L, et al. Display and analysis of patterns of differential activity of drugs against human tumor cell lines: development of mean graph and COMPARE algorithm. J Natl Cancer Inst 1989;81:1088–92.
49. Scherf U, Ross DT, Waltham M, Smith LH, Lee JK, Tanabe L, et al. A gene expression database for the molecular pharmacology of cancer. Nat Genet 2000;24:236–44.
50. Bhatla T, Wang J, Morrison DJ, Raetz EA, Burke MJ, Brown P, et al. Epigenetic reprogramming reverses the relapse-specific gene expression signature and restores chemosensitivity in childhood B-lymphoblastic leukemia. Blood 2012;119:5201–10.
51. Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 1996;14:737–44.
52. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639–2639.
53. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031–7.
54. Yu M, Selvaraj SK, Liang-Chu MMY, Aghajani S, Busse M, Yuan J, et al. A resource for cell line authentication, annotation and quality control. Nature 2015;520:307–11.
55. Haibe-Kains B, El-Hachem N, Birkbak NJ, Jin AC, Beck AH, Aerts HJWL, et al. Inconsistency in large pharmacogenomic studies. Nature 2013;504:389–93.
56. Weinstein JN, Lorenzi PL. Cancer: discrepancies in drug sensitivity. Nature 2013;504:381–3.
57. McDermott U, Sharma SV, Dowell L, Greninger P, Montagut C, Lamb J, et al. Identification of genotype-correlated sensitivity to selective kinase inhibitors by using high-throughput tumor cell line profiling. Proc Natl Acad Sci U S A 2007;104:19936–41.
58. Costello JC, Heiser LM, Georgii E, Gönen M, Menden MP, Wang NJ, et al. A community effort to assess and improve drug sensitivity prediction algorithms. Nat Biotechnol 2014;32:1202–12.
59. Vaske CJ, Benz SC, Sanborn JZ, Earl D, Szeto C, Zhu J, et al. Inference of patient-specific pathway activities from multi-dimensional cancer genomics data using PARADIGM. Bioinformatics 2010;26:i237–45.
60. Consortium TEP. The ENCODE (ENCyclopedia Of DNA Elements) Project. Science 2004;306:636–40.
61. ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature 2012;489:57–74.
62. Bansal M, Yang J, Karan C, Menden MP, Costello JC, Tang H, et al. A community computational challenge to predict the activity of pairs of compounds. Nat Biotechnol 2014;32:1213–22.
63. Griner LAM, Guha R, Shinn P, Young RM, Keller JM, Liu D, et al. High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell–like diffuse large B-cell lymphoma cells. Proc Natl Acad Sci 2014;111:2349–54.
64. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039–43.
65. Bean J, Brennan C, Shih J-Y, Riely G, Viale A, Wang L, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A 2007;104:20932–7.

66. Parisot JP, Hu XF, DeLuise M, Zalcberg JR. Altered expression of the IGF-1 receptor in a tamoxifen-resistant human breast cancer cell line. Br J Cancer 1999;79:693–700.
67. Massarweh S, Osborne CK, Creighton CJ, Qin L, Tsimelzon A, Huang S, et al. Tamoxifen resistance in breast tumors is driven by growth factor receptor signaling with repression of classic estrogen receptor genomic function. Cancer Res 2008;68:826–33.
68. Drury SC, Detre S, Leary A, Salter J, Reis-Filho J, Barbashina V, et al. Changes in breast cancer biomarkers in the IGF1R/PI3K pathway in recurrent breast cancer after tamoxifen treatment. Endocr Relat Cancer 2011;18:565–77.
69. Cowley GS, Weir BA, Vazquez F, Tamayo P, Scott JA, Rusin S, et al. Parallel genome-scale loss of function screens in 216 cancer cell lines for the identification of context-specific genetic dependencies. Sci Data 2014;1: 140035.
70. Hartwell LH, Szankasi P, Roberts CJ, Murray AW, Friend SH. Integrating genetic approaches into the discovery of anticancer drugs. Science 1997;278:1064–8.
71. Jerby-Arnon L, Pfetzer N, Waldman YY, McGarry L, James D, Shanks E, et al. Predicting cancer-specific vulnerability via data-driven detection of synthetic lethality. Cell 2014;158:1199–209.
72. Sullivan KD, Padilla-Just N, Henry RE, Porter CC, Kim J, Tentler JJ, et al. ATM and MET kinases are synthetic lethal with non-genotoxic activation of p53. Nat Chem Biol 2012;8:646–54.
73. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, Zecchin D, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature 2012;483:100–3.
74. Trédan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 2007;99:1441–54.
75. Weigelt B, Ghajar CM, Bissell MJ. The need for complex 3D culture models to unravel novel pathways and identify accurate biomarkers in breast cancer. Adv Drug Deliv Rev 2014;69-70:42–51.
76. Hanahan D, Weinberg RA. Hallmarks of Cancer: the next generation. Cell 2011;144:646–74.
77. Winslow S, Leandersson K, Edsjö A, Larsson C. Prognostic stromal gene signatures in breast cancer. Breast Cancer Res 2015;17:23.
78. Rajski M, Vogel B, Baty F, Rochlitz C, Buess M. Global gene expression analysis of the interaction between cancer cells and osteoblasts to predict bone metastasis in breast cancer. PLoS ONE 2012;7:e29743.
79. Reynolds TY, Rockwell S, Glazer PM. Genetic instability induced by the tumor microenvironment. Cancer Res 1996;56:5754–7.
80. McMillin DW, Delmore J, Weisberg E, Negri JM, Geer DC, Klippel S, et al. Tumor cell-specific bioluminescence platform to identify stroma-induced changes to anticancer drug activity. Nat Med 2010;16:483–9.
81. Tveit KM, Pihl A. Do cell lines in vitro reflect the properties of the tumours of origin? A study of lines derived from human melanoma xenografts. Br J Cancer 1981;44:775–86.
82. Kenny PA, Lee GY, Myers CA, Neve RM, Semeiks JR, Spellman PT, et al. The morphologies of breast cancer cell lines in three-dimensional assays correlate with their profiles of gene expression. Mol Oncol 2007; 1:84–96.
83. Hong H, Stegemann JP. 2D and 3D collagen and fibrin biopolymers promote specific ECM and integrin gene expression by vascular smooth muscle cells. J Biomater Sci Polym Ed 2008;19:1279–93.
84. Liu H, Lin J, Roy K. Effect of 3D scaffold and dynamic culture condition on the global gene expression profile of mouse embryonic stem cells. Biomaterials 2006;27:5978–89.
85. Aljitawi OS, Li D, Xiao Y, Zhang D, Ramachandran K, Stehno-Bittel L, et al. A novel three-dimensional stromal-based model for in vitro chemotherapy sensitivity testing of leukemia cells. Leuk Lymphoma 2014;55:378–91.
86. Chambers KF, Mosaad EMO, Russell PJ, Clements JA, Doran MR 3D cultures of prostate cancer cells cultured in a novel high-throughput culture platform are more resistant to chemotherapeutics compared to cells cultured in monolayer. PLoS ONE 2014;9:e111029.
87. Fischbach C, Chen R, Matsumoto T, Schmelzle T, Brugge JS, Polverini PJ, et al. Engineering tumors with 3D scaffolds. Nat Methods 2007;4:855–60.
88. Muranen T, Selfors LM, Worster DT, Iwanicki MP, Song L, Morales FC, et al. Inhibition of PI3K/mTOR leads to adaptive resistance in matrix-attached cancer cells. Cancer Cell 2012;21:227–39.
89. Daniel VC, Marchionni L, Hierman JS, Rhodes JT, Devereux WL, Rudin CM, et al. A primary xenograft model of small-cell lung cancer reveals irreversible changes in gene expression imposed by culture *in vitro*. Cancer Res 2009;69:3364–73.
90. Ding L, Ellis MJ, Li S, Larson DE, Chen K, Wallis JW, et al. Genome remodelling in a basal-like breast cancer metastasis and xenograft. Nature 2010;464:999–1005.
91. Pandita A, Aldape KD, Zadeh G, Guha A, James CD. Contrasting *in vivo* and *in vitro* fates of glioblastoma cell subpopulations with amplified EGFR. Genes Chromosomes Cancer 2004;39:29–36.
92. Giannini C, Sarkaria JN, Saito A, Uhm JH, Galanis E, Carlson BL, et al. Patient tumor EGFR and PDGFRA gene amplifications retained in an invasive intracranial xenograft model of glioblastoma multiforme. Neuro-Oncol 2005;7:164–76.
93. Lodhia KA, Hadley AM, Haluska P, Scott CL. Prioritizing therapeutic targets using patient-derived xenograft models. Biochim Biophys Acta 2015;1855: 223–34.
94. Wilson TR, Fridlyand J, Yan Y, Penuel E, Burton L, Chan E, et al. Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. Nature 2012;487:505–9.
95. Voskoglou-Nomikos T, Pater JL, Seymour L. Clinical predictive value of the *in vitro* cell line, human xenograft, and mouse allograft preclinical cancer models. Clin Cancer Res 2003;9:4227–39.
96. Gould SE, Junttila MR, de Sauvage FJ. Translational value of mouse models in oncology drug development. Nat Med 2015;21:431–9.
97. Klijn C, Durinck S, Stawiski EW, Haverty PM, Jiang Z, Liu H, et al. A comprehensive transcriptional portrait of human cancer cell lines. Nat Biotechnol 2015;33:306–12.

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