Cancer cells often depend on signals emanating from the proteins encoded by their oncogenes. Consequently, suppression of these signals by cancer drugs can be detrimental to cancer cells. This phenomenon has been dubbed “oncogene addiction” by the late Bernhard Weinstein (1) and has been very successful in developing a range of targeted cancer therapies. Drugs like imatinib mesylate (targeting BCR-ABL) and trastuzumab (targeting ERBB2) are a testimony to the success of this approach. However, the number of “druggable” oncogenes is small, which limits the success of targeted drug development. In addition, the loss of tumor suppressor genes is not easily restored through drug treatment.

How can we expand the pool of highly selective cancer drug targets? A relatively recent strategy to accomplish such an expansion in the cancer genome is based on the notion that every genetic alteration that causes an advantage to the tumor cell is also likely to be associated with an acquired vulnerability that can be exploited therapeutically. This notion of cancer-specific vulnerabilities, referred to as genetic dependencies or synthetic lethal interactions with cancer-specific genetic lesions (2), is both exciting and challenging. The concept is exciting because the genes whose inhibition make cancer cells vulnerable to, for instance, the loss of a tumor suppressor gene may themselves not be mutated or overexpressed in cancer. Such genes may therefore have escaped our attention in drug development to date. Thus, identification of synthetic lethal interactions in cancer cells holds the promise of uncovering a whole new repertoire of both powerful and highly selective drug targets. At the same time, it is challenging to identify the genes that show strong genetic interactions, especially because such genetic dependencies are often context dependent. For instance, in a given breast cancer cell line with a mutation in tumor suppressor gene X, inhibition of gene Y may be detrimental to survival, but in a second X-deficient breast cancer cell line, gene Y inhibition may be without effect because other genetic alterations interfere with the dependency between genes X and Y in the latter cell line. Because of this complication, very few, if any, “hard” (context-independent) synthetic lethal interactions can be used in drug development to date.

In this issue of Cancer Discovery, Brough and colleagues (3), in a brute force approach, take a major step toward finding genotype-specific drug targets for treatment of breast cancer. They used an initial panel of 34 well-characterized breast cancer cell lines. They screened this cell-line panel with an siRNA library targeting all human kinases (the “kinome”) to search for kinases that, upon knockdown, affect cell viability. For each cell line, additional genomic information regarding gene mutation, gene expression, copy-number alterations, and drug sensitivity was also obtained. This procedure allowed the authors to establish statistically significant correlations between breast cancer genotypes and responses to inhibition of specific kinases.

What was found in this massive search for genetic interactions? First, and very gratifyingly, the authors discovered that breast cancers having a mutation in the catalytic subunit of phosphoinositide 3-kinase (PI3-kinase; PIK3CA) are more sensitive to PIK3CA inhibition than are those that do not, thereby validating the oncogene addiction hypothesis mentioned above. Of interest, this subgroup is also more sensitive to AKT2 and AKT3 siRNAs, indicating that pathway components downstream of PI3-kinase are also part of the addiction or dependency. Similarly, they found that ERBB2-amplified tumors were found to depend on ERBB2 expression, as expected. More importantly, Brough and colleagues (3) found that breast cancer cells that had lost the PTEN tumor suppressor gene were highly dependent on the mitotic kinase TTK, thus providing a potentially novel target for treatment in PTEN-deficient breast tumors. Similarly, they identified that only estrogen receptor–positive breast tumors required the kinase ADCK2, a kinase that they subsequently show to be involved in estrogen receptor signaling.

In addition, the authors explored their datasets for dependencies associated with specific genomic alterations and with defined subtypes of breast cancer (e.g., ERBB2, basal and luminal subtypes). In doing so, they identified several candidate dependencies, including ERBB2-CAMK1, ERBB2-MAP2K3, and, for the triple-negative subgroup, the ribosomal kinase RPS6KA3, the protein kinase PRKCL2, and the pyruvate kinase PKLR. Although the identification of these dependencies...
is intriguing and should be explored further, it is also important to extend the number of cell lines with the selected genotypes/phenotypes to firmly establish their dependencies outside the context of the cell-line panel used in this study.

**FUNCTIONAL SUBTYPES VERSUS MOLECULAR SUBTYPES**

Ten years ago, Sorlie and colleagues (4) identified distinct subtypes of breast cancer by analyzing similarity in gene expression patterns. Indeed, these subtypes are distinct in terms of both prognosis and drug responses. Brough and colleagues (3) now add a new dimension to subtyping by introducing a “functional classification” of a large panel of breast cancers based on their patterns of sensitivities to kinase inhibition, which the authors refer to as “functional viability profiles.” Hierarchical clustering of these functional viabilities among the cell-line panel revealed two distinct groups, one characterized by the enrichment for PTEN mutations and another enriched for PIK3CA mutations. Of interest, these groups were distinct from those generated by clustering of genomic data. Although ERBB2-amplified cell lines did not specifically cluster to one group, sensitivity to ERBB2 silencing or the response to the ERBB2 drug lapatinib was contained in one group. These observations imply that clustering of tumors based on functional viability profiling can reveal groups with a dependency on specific signaling networks, which could be explored therapeutically.

The possibilities of this approach are many. As one example, it should be possible to use such breast cancer cell-line panels to identify the breast cancer genotypes that are particularly vulnerable to small-molecule inhibitors of poly(ADP ribose) polymerase (PARP). The recent disappointing results of the PARP inhibitor iniparib in triple-negative breast cancers highlight the need for a better biomarker to identify responders. Brough and colleagues (3) may have the tools to find these response biomarkers.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**REFERENCES**
