decay is not the only mechanism underlying acquired oncogene dependence, and engaging these other mechanisms may require longer-term drug exposure (Figure 1Bc). Hence, it remains to be seen whether a "short, sharp shock" or "staying the course" proves the best strategy for drug delivery.

More generally, the important and fascinating observations of Sharma et al. underscore once again (as if this were even necessary) the critical importance of identifying which of the legion of mutations in human cancers is responsible for maintenance of the established tumor. Tumors accumulate much mutational clutter—bottlenecks that once passed are thenceforth irrelevant for further tumor maintenance, collateral havoc borne of telomere erosion, background noise that clones out with the tumor, bystanders swept up by neighboring amplifications or deletions, and weakly advantageous traits contingent upon the platform of oncogenic engines that buttress tumor maintenance. The real trick is to work out who is pulling the levers and pressing the buttons that keep the established tumor going and not get sidetracked into endless cataloging of epiphenomena. Sharma et al. show that evolution has handed us a great gift for cancer treatment—so long as we stay on target.

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mILC-ing the mouse mammary gland: A model for invasive lobular carcinoma

Mouse models that faithfully recapitulate human cancers are indispensable tools for studying the molecular mechanisms of tumorigenesis and testing potential anticancer therapies. In this issue of *Cancer Cell*, Derksen et al. describe a new mouse model that mimics multiple features of invasive lobular carcinoma of the breast (ILC), a histological subtype of human breast cancer for which no mouse model currently exists. This model further reveals an important causal link between E-cadherin loss and tumor initiation and metastasis and, in doing so, provides a valuable entrée into the tumor-suppressive functions of E-cadherin as well as the molecular underpinnings of ILC.

Over the past two decades, the development of improved mouse models for human cancers has made important contributions to our understanding of this set of diseases. By engineering mice to contain specific genetic lesions found in human cancers, it has been possible to address the causal relationship between individual genes and the disease phenotype. Furthermore, mice that develop malignancies that faithfully recapitulate their human counterparts provide—at least in theory—more appropriate physiological systems in which to test candidate antineoplastic drugs. Indeed, an array of mouse models now exists in which the modulation of one or more genes altered in a particular human cancer gives rise to a malignancy in mice that resembles that cancer at both the histological and molecular levels (Holland, 2004). Moreover, as a first step toward fulfilling their promise, these models are now being utilized for the validation and testing of therapies (Sharpless and Depinho, 2006).

Given the success of genetically engineered mouse models to date, an important next step will be the creation of refined models that accurately reflect the diverse pathologies of human cancers. In breast cancer, for instance, the majority of patients present with invasive ductal carcinoma (IDC), whereas ~10% of patients present with a histologically distinct form of the disease, termed invasive lobular carcinoma (ILC). Beyond their morphologic distinctions, these tumor types also differ at the molecular level. One particularly prominent difference is that ILCs typically lose expression of the cell adhesion molecule E-cadherin, whereas IDCs retain its expression. ILC and IDC also exhibit differences in their biological behavior, including their patterns of metastatic spread. To date, however, there has been no mouse model that recapitulates the unique features of ILC, a fact that has impeded research into this disease.

A study by Derksen et al. in this issue now addresses this shortcom-

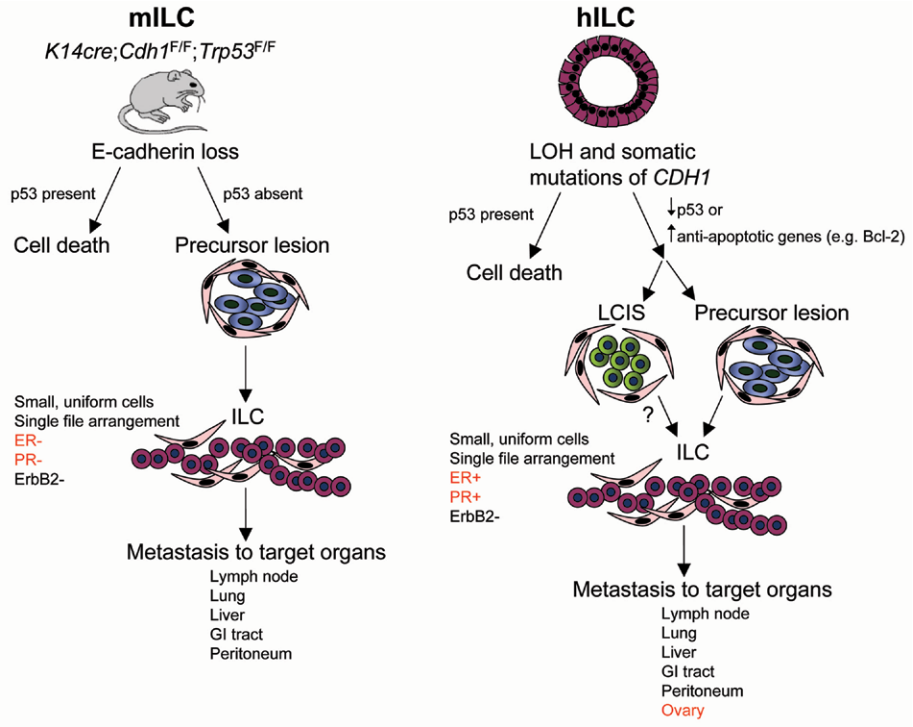

Figure 1. Similarities between a mouse model for invasive lobular carcinoma, mILC, and its human counterpart, hILC

mILC: Conditional deletion of *E-cadherin* alone in the mammary epithelium is thought to lead to p53-dependent cell death, whereas conditional deletion of both *E-cadherin* and *p53* leads to invasive lobular carcinoma (ILC). The morphological characteristics of precursor lesions are unknown. mILCs have an increased incidence of metastasis compared to tumors lacking p53 alone. hILC: Loss of *E-cadherin*—thought to occur through somatic mutation or LOH—is found in both LCIS and ILC, though it is unclear whether LCIS is a precursor of ILC. The pattern of metastasis in ILC differs significantly from IDC, with metastases to the GI tract and ovary occurring more frequently in ILC compared to IDC. The majority of human ILCs are thought to express wild-type p53, though some tumors may lose the *p53* locus. In the presence of functional p53, increased expression of antiapoptotic genes may suppress cell death downstream of E-cadherin loss. Differences between mILC and hILC are shown in red.

ing while simultaneously supporting a causal link between E-cadherin loss and the development of ILC (Derksen et al., 2006). In this study, the authors have created a mouse model for breast cancer driven by the conditional deletion of floxed *p53* and/or *E-cadherin* alleles in the mammary gland and skin via expression of Cre recombinase under the control of the Keratin 14 (K14) promoter. While mice whose mammary epithelial cells lacked p53 alone developed mammary carcinomas, the latency was long (330 days), and tumors exhibited a low frequency of metastasis. Given the documented role of E-cadherin in tumor cell invasion, the authors next tested the effect of adding *E-cadherin* deletion to *p53* deletion on tumor formation and metastasis. Interestingly, they found that mice lacking both p53 and E-cadherin developed mammary tumors significantly faster than mice lacking p53 alone. In addition, loss of E-cadherin appeared to be selected for early in the course of tumorigenesis. Together, their findings suggest that E-cadherin loss may contribute to both tumor initiation and progression.

However, the most notable finding of this study was that tumors forming in mice whose mammary epithelial cells lacked both E-cadherin and p53 had a histological appearance highly reminiscent of human ILC. Specifically, cells from these tumors were small and uniform, were oriented in a characteristic "single file" arrangement, and had invaded the surrounding stroma. Notably, tumors lacking both p53 and E-cadherin metastasized more frequently than those lacking p53 alone. From these data, the authors conclude that mammary tumors arising in mice in the context of p53 and E-cadherin loss frequently mimic the cellular and histological features of human ILC, and term their model "mouse ILC" (mILC).

How well does this new model recapitulate human ILC? In several respects—including histological pattern, cellular morphology, lack of E-cadherin expression, and Her2/neu negativity—this model is a dead ringer for its human counterpart. In addition, mILC metastasizes to analogous sites as seen in women, including the lymphatics, lungs, liver, gastrointestinal tract, and peritoneum (Figure 1). Nevertheless, mILC differs from human ILC in several important ways. First, mammary tumors arising in mice due to loss of p53 and E-cadherin are estrogen receptor (ER) and progesterone receptor (PR) negative, whereas the vast majority of human ILCs are ER and PR positive. However, as most mammary tumors induced in mice are ER and PR negative, this may reflect a general shortcoming of the mouse as a model for ER-positive human breast cancer rather than a specific problem with this model. The metastatic behavior of these tumors also reveals differences between the mouse model and human disease. Whereas the overall incidence of metastasis is similar between ILC and IDC in humans (Arpino et al., 2004), mILC tumors have a markedly higher metastatic potential than tumors wild-type for *E-cadherin*.

On other points, the jury is out. For example, the formation of mILC in the mouse requires loss of both E-cadherin and p53, a potential concern given that *p53* mutation is reportedly less common in human ILC than IDC (Arpino et al., 2004). Nevertheless, up to 25% of hILC may express mutant p53, and more recent studies suggest that a substantial fraction of human ILCs may harbor chromosomal losses encompassing the *p53* locus (Mohsin et al., 2005; Stange et al., 2006). One intriguing possibility is that the mouse model presented by Derksen et al. recapitulates that subset of human ILCs that have lost p53 function, either through mutation or chromosomal loss, whereas other subsets of hILC may exist that retain p53 function. If this is the case, it is possible that this latter subset of tumors may contain genetic alterations more commonly found in human ILC, such as bcl-2 overexpression, that substitute for p53 loss in synergizing with the loss of E-cadherin (Papadimitriou et al., 1997). Gaining a clearer understanding of the status of p53 in human ILC will be critical for resolving whether the mouse model falls short—or provides novel insights—on these points.

Importantly, the findings of Derksen et al. constitute the first demonstration in mice of a causal link between E-cadherin loss and tumor formation. Given the wealth of data from cell culture studies and human patient samples implicating E-cadherin in tumor progression, this is a central finding that establishes E-cadherin as a bona fide tumor suppressor. Notably, while E-cadherin loss is thought to be a critical step in the process of epithelial-to-mesenchymal transition (EMT), the extent to which EMT per se is involved in tumor progression remains unclear. For example, the transcriptional repressor Snail has been shown to downregulate *E-cadherin* as well as promote both EMT and tumor progression in a conditional mouse model for HER2/neu-induced breast cancer (Moody et al., 2005). In contrast, E-cadherin loss in the model described by Derksen et al. does not by itself lead to a frank mesenchymal phenotype. This suggests that, at least in this context, E-cadherin loss can promote tumorigenesis independently of its contribution to EMT.

Another puzzling feature of this disease has been the uncertain relationship between ILC and lobular carcinoma in situ (LCIS). Women with LCIS are at substantially increased risk for developing breast cancer both in the same breast in which the LCIS was identified and in the opposite breast. As such, whether LCIS represents a precursor lesion to ILC, or merely a marker of increased risk, continues to be a matter of debate. It is notable, therefore, that despite the markedly increased risk of mILC in mice in which E-cadherin and p53 have been deleted in the mammary epithelium, classic LCIS lesions are not found. This raises the important possibility that LCIS is not a precursor lesion for ILC, or that mILC models a form of ILC that does not pass through an LCIS phase.

Finally, beyond its important mechanistic implications, this study by Derksen et al. is equally significant for its establishment of a faithful model for human ILC where none existed before. This accomplishment represents a significant step forward in the effort to accurately model human cancers in mice. As they constitute only 10%–15% of all breast cancers, lobular carcinomas are likely to differ from ductal carcinomas with respect to their etiology, biology, and response to therapy. As such, the availability of this model holds significant promise for improving our ability to understand and treat this type of breast cancer. Undoubtedly, it will be important to continue refining this model to more precisely incorporate the molecular alterations found in human ILC, as these become elucidated. Ultimately, such models should prove useful for testing therapeutic regimens targeted specifically against ILC and in that manner improve the clinical management of this disease. This hope, if realized, would constitute the most meaningful validation of all for this—or any—mouse model.

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Accelerating drug discovery: Open source cancer cell biology?

The possibility that experimental data from diverse cell biology experiments might shed light on other experiments has been generally outside the realm of cancer biologists. Recent experiments suggest that core RNA expression profiles distilled from experiments using a set of known members with related attributes may be used as query tools to probe expression profiles from other unrelated experiments. The potential benefit arises from the possibility to share findings without fully reconstructing the exact initial conditions. The limitations will be framed by the robustness of the hypotheses so generated.

As one looks back over past decades, or for that matter, past centuries, scientific progress, though remarkable, has been limited by tools and the ways insights have been shared. Three recent papers by the Golub and Armstrong groups (Lamb et al., 2006; Hieronymus et al., 2006; Wei et al., 2006) describe a process, a tool, and even better, examples of how that tool functions that suggest an opportunity which, if fully implemented, has the potential to truly change the speed and efficiency of drug discovery.

One of the rather hidden inadequacies of cancer biology and drug discovery is the full extent to which we fly blind. From the size of textbooks and the complexity of pathway diagrams it is hard to recognize that for virtually all cancer processes we do not have confidence in the complete "parts list" of components