

# Advances in TARGETED CANCER THERAPIES

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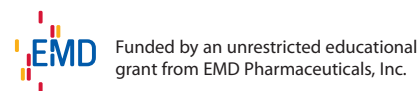
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## DIGEST

Reviewed by Mark A. Socinski, MD

### Targeted Mouse Models May Advance Cancer Drug Development

Olive KP, Tuveson DA. The use of targeted mouse models for preclinical testing of novel cancer therapeutics. *Clin Cancer Res.* 2006;12:5277-5287.

The process by which a candidate compound is investigated in terms of its safety, efficacy, and dosing is arduous and costly, and only a handful of drugs tested go on to become approved therapies. The traditional approach utilizes biochemical assays and cell-based proliferation and cytotoxicity screens to identify those compounds that have reasonable pharmacokinetic properties and should be investigated in an in vivo animal efficacy model. Unfortunately, however, neither cell-based assays nor xenograft models are particularly reliable in predicting drug responses in humans. An NCI analysis of in vitro models and tumor xenografts found poor correlations with activity in phase II clinical trials and suggested that only compounds that are successful in multiple models are likely to be effective in the clinical setting.<sup>1</sup>

Genetically engineered mouse models (GEMs) represent a new and promising alternative to traditional preclinical assays. When appropriately designed, GEMs may overcome many of the shortcomings of cell-based assays and xenografts. They provide in situ tumor development in an immunocompetent animal setting. However, an important caveat is that not all GEMs are relevant for preclinical drug testing.

Early results with GEMs have provided conflicting results. However, most of these early studies were performed on models that did not accurately reflect the physiology of the targeted tumor. The dramatic progress that has occurred in mouse models in recent years is cause for optimism that the newest generation of mouse models will provide a higher standard of predictive utility in the drug development process, according to Kenneth P. Olive, PhD, and David A. Tuveson, MD, PhD, of the University of Cambridge, Cambridge, United Kingdom. Many of these GEMs provide novel platforms for validating new anticancer drugs, assessing therapeutic index, identifying surrogate markers of tumor progression, and defining epigenetic and environmental influences on tumorigenesis. The use of GEMs that develop tumors similar to those found in humans can serve as an initial "filter" to identify molecular targets that, when inhibited, will selectively kill tumor cells. Thus, GEMs may serve as a new strategy for streamlining the overall process of cancer drug development. The 3 areas in which mouse models of cancer may be useful are as:

1. an aid in the investigation of the basic biological principles of cancer
2. an assay for the preclinical development of anticancer agents
3. a tool for discovering new clinical agents and assays.

### Constructing the Model

Human tumors likely develop through the accumulation of multiple mutations that foster increased survival, growth, and dissemination, according to Drs. Olive and Tuveson. These genetic alterations occur spontaneously within somatic cell genomes; in situations in which mutant proteins are produced, they are expressed at physiolog-

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ic levels from endogenous promoters. Although some genes are dramatically upregulated in tumor cells, this process takes place within the constraints of mammalian genetics.

These principles serve as the basis on which an accurate model of cancer can be based. For the purposes of preclinical modeling, the most compelling are those that manipulate the endogenous genome to effect mutations that closely mimic the state of human tumors. These include knockout alleles, in which a gene is deleted, as well as targeted mutant alleles, which harbor subtle mutations in the endogenous locus. Both knockout and targeted mutant alleles are useful for modeling hereditary tumor syndromes that result from the loss of 1 copy of a tumor-suppressor gene. However, many such alleles result in embryonic lethality or background tumor spectra and are not ideal for modeling spontaneous cancers. Thus, conditional alleles have been developed that permit controlled deletion, reactivation, or mutation of endogenous genes.

### **GEMs may serve as a new strategy for streamlining the overall process of cancer drug development.**

Mouse models that are to be used in a preclinical setting must be developed carefully and must always be guided by the human disease. The strenuous evaluation of its potential utility for preclinical studies is outlined in the Table. In particular, the authors suggest a final “credentialing” step aimed at determining the response of a GEM to existing therapies and comparing this to the response of analogous human tumors. By this measure, most xenograft models fail. For example, standard pancreatic cancer xenograft models respond quite readily to treatment with gemcitabine, yet treatment of human pancreatic cancer patients with gemcitabine produces only a nominal extension of overall survival.

As an alternative, Drs. Olive and Tuveson discuss a mouse model of pancreatic ductal adenocarcinoma (PDA) that is based on physiological mutation, in the pancreatic progenitor cells, of 2 endogenous loci: *Kras* and *p53*. These 2 genes are found mutated in 95% and 70% of human pancreatic tumors, respectively. These mice develop advanced PDA with 100% penetrance and most animals develop metastases to the liver or lungs, similar to human PDA patients. Practical issues of working with such a model, such as *in vivo* imaging and trial design, are also discussed in the paper. However, it remains to be seen whether this new model will pass the credentialing criterion proposed in this article.

Drs. Olive and Tuveson go on to suggest that the most predictive mouse models be integrated early in the drug development process—before chemical optimization and toxicity evaluation.

**Table.** Evaluation of Preclinical Mouse Models of Cancer

<b>1</b>	Genetic manipulations should accurately reflect the genetics of the human disease. The ideal model will produce subtle, controlled mutations in relevant endogenous genes in targeted cells while leaving an effective wild-type genotype in nontargeted cells.
<b>2</b>	The histology of the model should closely reflect that of human tumors. This should be accomplished by clinical pathologists with expertise in human pathology and veterinary medicine. Associated pathophysiological conditions (eg, cancer cachexia) should also be assessed.
<b>3</b>	The model should be validated by exploring the tumor phenotype at a molecular level (including an assessment of gene expression, with emphasis on known tumor markers from human studies and analysis of genetic and genomic alterations frequently seen during tumor progression in humans).
<b>4</b>	The model should be “credentialled”—that is, administering to the mice those drugs that have previously been tested in human patients. If a model responds differently than do human patients, its predictive utility for that agent is poor. A positive response to ineffective therapies would suggest the inappropriateness of that model for preclinical investigations.

“Each animal test provides a wealth of related data that should inform and direct future experiments, and less time and effort should be wasted on ineffective compounds and thereby accelerate the overall rate of drug discover for cancer patients,” they wrote. ■

### **Reference**

1. Johnson JI, Decker S, Zaharevitz D, et al. Relationships between drug activity in NCI preclinical *in vitro* and *in vivo* models and early clinical trials. *Br J Cancer*. 2001;84:1424-1431.