

The ability to replicate specific genetic abnormalities known to produce tumors in humans also provides an opportunity to study specific tumor development pathways with the appropriately designed GEM model.

GEM models of cancer are, of course, not without their disadvantages. As with most genetically engineered animal model, developing a GEM model is a costly and time-consuming process and can require several years to validate. There are commercially available GEM models that can be used if they are appropriate for the cancer to be studied. It is also important to keep in mind that GEM model tumors are not necessarily comparable to actual human tumors. Unlike GEM tumors which are typically the result of limited alteration of the mouse genome, human tumors are heterogeneous in nature. Multiple mutations may be present in a clinical setting, and GEM models do not adequately recapitulate this aspect of disease progression. Finally, and perhaps the most importantly, tumors that develop in GEM models are mouse tumors, not human tumors. As a result, efficacy in a GEM model is not necessarily predictive of what will happen in a clinical setting.⁵⁵

Selecting an appropriate animal model is a key aspect of a drug discovery program. Choosing the wrong animal model can lead to termination of viable programs based on erroneous data, or worse the progression of a compound into clinical trials based on results that are not truly correlated to the human condition. In many cases, discovery programs will employ multiple animal models in order to develop a more comprehensive understanding of potential clinical candidates. Additional animal models may be utilized to assess potential safety and toxicity risks. The animal models discussed in this chapter are just a small fraction of those available for the identification of novel therapeutics. Transgenic and knockout animal models have greatly enhanced the development of novel animal models, and it is likely that the number of viable animal models will continue to increase over time.

QUESTIONS

1. What is the definition of the term therapeutic index?
2. What is a homologous animal model?
3. What is an isomorphic animal model?
4. What is a predictive animal model?
5. Why is it necessary to use more than a single animal in an *in vivo* experiment?
6. A mouse treated with a candidate compound spends more time in the open arms of an elevated plus maze as compared to an untreated mouse. What does this suggest about the candidate compound?