human variant of a compound's intended macromolecular target may allow it to perform the desired function in mice, but not in humans. As a result of this issue, allograft models are less utilized than the xenograft models in cancer drug discovery programs.

Genetically Engineered Mouse Models of Cancer

Although xenograft and allograft animal models are staples of cancer drug discovery and have provided a wealth of information on cancer progression, they are far from perfect models. Both of these models require the introduction of tumorigenic material into an animal from cultured cells. This has provided scientist with a means of improving their understanding of tumor growth and the various factors that effect tumor growth, but they have limitations. The microenvironment of naturally occurring tumors is very different from the artificial conditions required to grow tumor cells for implantation in the xenograft and allograft models. Factors that would influence natural tumor cell growth and tumor formation are simply not present in these models. As a result, these models cannot be relied upon to predict the role of a tumor's microenvironment on cancer progression.

The genetically engineered mouse (GEM) model of cancer is an alternative model that has gained in popularity since its introduction. In GEM models, genes that are suspected of participating in the transformation of normal cell into malignant cells and tumors are targeted for mutation, overexpression, or deletion. The resulting mice can then be studied to determine the impact of the genetic alteration on their propensity to develop tumors over time (Figure 7.19). In addition, it is possible to study the various stages

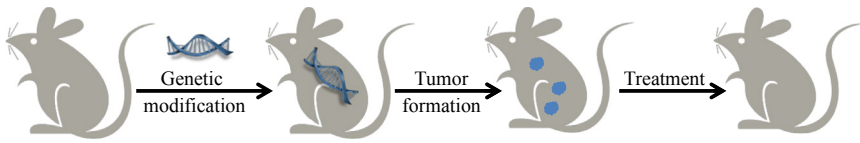

FIGURE 7.19 Genetically engineered mice are created using transgenic techniques. In one method, genes that promote spontaneous tumor formation are inserted into otherwise normal mice. Candidate compounds with *in vivo* antitumor properties will cause the tumors to shrink and/or decreased in number.

of tumor progression and determine the impact of therapeutic agents at each of these stages. Also, unlike xenograft models, GEM models are developed in mice with a fully intact immune system (the mice are immunocompetent). As a result, it has been postulated that the tumor microenvironment of GEM models more closely mimics natural cancer progression.