

transplanted tissues such as human tumors. Both primary and metastatic tumors of human origin can be grown and studied in the nude mouse. As such, they were rapidly accepted as a major model for the study of cancer progression and therapeutic intervention. The nude mouse also facilitated the study of infectious disease, as it became possible to study pathogen progression and potential therapies in the absence of a full immune response.

### **The SCID Mouse**

The development of immune compromised models was further advanced in 1983 with the introduction of the severe combined immune deficient (SCID) mouse.<sup>25</sup> An autosomal recessive mutation in mice was identified at the Fox Chase Cancer Center that, when homozygous, leads to animals that are severely deficient in B- and T-lymphocytes. This leaves them highly susceptible to infectious disease, irrespective of the nature of the pathogen, and, similar to nude mice, unable to reject transplanted tissues. The introduction of the SCID mouse model, and the variations that were developed as a result of its identification, provided an additional platform for the study of cancer and infectious disease that was previously unavailable to the research community.

### ***Transgenic Animal Models***

Up until 1974, the ability to develop new animal models was limited to selective breeding and depended on the natural occurrence of mutations, such as the nude mouse, to provide improved models for research. Direct manipulation of an animal's genetic codes was not possible. This changed, however, with the introduction of transgenic science. The initial breakthrough in this area was provided by Rudolf Jaenisch, who successfully inserted simian virus 40 DNA sequences into mice.<sup>26</sup> Although the genes were not passed onto offspring, these efforts marked the first successful transfer of foreign DNA into an animal suitable for drug discovery research. Subsequent efforts by Frank Ruddle (Yale),<sup>27</sup> Frank Constantini (Oxford), and Elizabeth Lacy (Oxford)<sup>28</sup> demonstrated that the addition of foreign DNA to single cell mouse embryos provided incorporation of the foreign DNA, and the new genes were passed on to subsequent generations (Figure 2.9). These efforts marked the beginning of a new era in both animal modeling and drug discovery. It was now possible to insert disease-related genes into animals that did not normally demonstrate the pathology in question. Mouse models of Alzheimer's disease, for example, were created by inserting DNA that induced the production of A $\beta$ 42 plaques, a hallmark of this disease, providing a new platform for the study of this important malady.<sup>29</sup> Similarly, models of human obesity have been generated in mice through the transgenic methods, providing significant insight into the mechanism of obesity.<sup>30</sup> The pathogenesis of viral infections such as HIV, hepatitis (B and C), polio, and measles