immunological targets, one needs to take into consideration the Th1/Th2 balance in mice of different genetic background (Hsieh et al. 1995; Stewart et al. 2002).

An example on the mouse strains of different genetic background contributing to differences in hemostasis can be found in the platelets of FVB mice. While the expression of major receptors such as integrin αIIb, integrin β3, glycoprotein (GP) Ibα, or GPVI on platelets from FVB mice is similar to those from C57BL/6, BALB/c, C3H/He, and 129Sv, the expression level of integrin α2 on FVB was approximately 50% lower than as platelets from the other strains. This difference leads to a marked reduction in platelet aggregation and a longer lag phase when activated by collagen (Li et al. 2004).

These examples highlight the importance in performing a thorough literature search on the pathophysiology mechanism in the different strains of mice and selecting the most relevant background strain before in vivo validation. An online tool, Mouse Phenome Database (MPD), which contains database of strain characterization data on the phenotype and genotype of the different mouse strains, is also a valuable tool that could help investigators to identify mouse strains appropriate for their studies (Bogue and Grubb 2004; Grubb et al. 2004, 2014). These readily available literature and data should be consulted and considered as one of the first steps for in vivo target validation using mouse models.

2.1.2 Genetically Engineered Mouse Models

Genetically engineered mouse models (GEMMs) have been a powerful tool for studying human disease and for drug development (Cook et al. 2012; Kucherlapati 2012). GEMMs have not only helped elucidating the pathophysiology of human diseases; these models are also indispensable for in vivo target validation.

When a mouse model is needed within a short period of time, transgenic mice, generated by inserting a bacterial or viral vector into a fertilized mouse egg, can be an option to generate the required genetic model (Gordon et al. 1980). In transgenic animal, the transgene usually integrates into one or more loci. This is a relatively quick approach in establishing a genetically engineered animal, but one needs to be aware of the possible risk that transgene may be inserted into locus with critical functions. As a result, the transgenic mice would develop additional confounding phenotypes. Therefore, it is advisable to evaluate simultaneously several independent lines of mice with the same transgene during the in vivo target validation stage.

Mutagenesis by homologous recombination in embryonic stem (ES) cells (Koller et al. 1989) is a targeted approach for inactivating, overexpressing, and humanizing the genes of interests. Thousands of genetic knockout, knockin, and humanized strains have been generated by this approach. A knockout mouse with targeted gene disruption is used to validate the in vivo function of the gene. Additionally, such a knockout model can be used for evaluating pharmacological agents. While knockout mouse technology is a valuable tool, the disruptions of some genes are developmentally lethal. As a result, some genetically altered embryos cannot develop into adult mice for the purpose of determining a gene's in vivo function after birth. In some instances, a gene may serve a different function in adults than in developing embryos. These problems can be circumvented with technologies developed for generating inducible and tissue-specific knockout