

2.1.3 Larger Disease Animal Models

While GEMM is powerful, it is sometimes limited by the fact that mice are being distantly related to humans. As a result, there could be low homology in some of the drug targets as well as differences in pathophysiology in comparison to patients. Additionally, the small body size of mice also becomes a limitation for sampling of biological specimens, monitoring of vital signs, and performing certain surgical procedures. Therefore, alternative and larger species can be desirable as disease models for target validation.

For the study of bleeding disorders, a collection of larger disease models, most of them congenital, are available for investigators (Table 1). Hemophilia A rat (Booth et al. 2010a, b), hemophilia A dog (Giles et al. 1982; Brinkhous and Graham 1950; Graham et al. 1949), hemophilia B dog (Mauser et al. 1996; Evans et al. 1989; Mustard et al. 1960), hemophilia A sheep (Neuenschwander et al. 1992; Porada et al. 2010), and hemophilia A pig (Kashiwakura et al. 2012) have been described in literature and used for gene and cell therapy studies. Dogs (Haberichter et al. 2005) and pigs (Fass et al. 1979) with von Willebrand's disease bleeding disorders have also been described. Many of these animals are more closely related to humans and may be related better to the clinical situation.

2.2 Nonmammalian Models

For the purpose of in vivo target validation, nonmammalian species could also be attractive options. Due to the short reproductive and life cycles of zebrafish (Spence et al. 2008) and *Caenorhabditis elegans*, these species could be cost-effective models that provide rapid turnaround of data. Additionally, their genomes have been sequenced, and the homology to human equivalent genes has been established for these simple organisms to facilitate in vivo target validation (Howe et al. 2013; *C. elegans* Sequencing Consortium 1998).

2.2.1 Zebrafish

Zebrafish is a small freshwater fish native to Pakistan and India (Spence et al. 2008). It has become an important model organism for studying vertebrate development and gene function.

Transgenic zebrafish has been used as models of cancer (Liu and Leach 2011), cardiovascular diseases (Drummond 2005), and immune diseases (Novoa and Figueras 2012).

2.2.2 *C. elegans*

Caenorhabditis elegans is a small roundworm with 959 somatic cells with a life cycle of 3–5 days (Felix and Braendle 2010). It is the first multicellular organism to have its genome sequenced (*C. elegans* Sequencing Consortium 1998). Human has 74% of its genome sequence matching *C. elegans* and shared a significant number of biological pathways. Transgenic worms have been generated to evaluate the role of specific mutations in human disease pathophysiology. These properties have allowed *C. elegans* to become an attractive model platform for in vivo drug target