4 Challenges in Target Validation and Clinical Translatability of Preclinical Model

While a variety of tools are available to enable in vivo target validation, it remains a challenging process as evidenced by the number of failed clinical trials (Hay et al. 2014). This is because animal models often do not fully recapitulate the disease phenotype or share the same pathophysiology as patients. The targets in the animal models may have a different tissue expression and distribution than in humans. Also, the pathophysiological pathways in patients could be evolutionarily diverged from the animal models and serve a different mechanism of action. Therefore, it is most desirable to validate a target in at least two species with different approaches to gain further confidence in clinical translatability before entering the resource-intensive clinical development phase of drug development.

4.1 Translatability of Preclinical Animal Models: Hemophilia Mice as Examples

Hemophilias A and B are characterized by the deficiency of coagulation factors VIII and FIX, respectively, in patients. The deficiency in these coagulation factors leads to complications such as joint bleeds, intramuscular bleeds, and sometimes intracranial bleeds. Bleeding into joints eventually leads to inflammation. Overtime, patients develop joint arthropathy and severe limitation to mobility. In hemophilia clinical trials, the annualized bleed rate in patients is used as the efficacy endpoint to evaluate the efficacy of a therapy. Genetically engineered hemophilia mouse models have been invaluable for hemophilia research and drug development. Coagulation factor VIII (FVIII) and factor IX (FIX) have been deleted in mice to generate hemophilia A and hemophilia B models, respectively. Both mouse models suffer from severe bleeding upon injury. All new drugs developed for hemophilia are tested in these models. While these hemophilia mice provided successful clinical translatability in patients, there are significant differences between clinical observations in patients and the actual disease phenotype in mice. Unlike patients, hemophilia mice very rarely develop spontaneous joint or soft tissue bleeds (Bi et al. 1995). This observation is likely due to the small size of mice exerting significantly lower load-bearing stress to the joints. Therefore, an acute bleeding model induced by tail amputation has been used as a surrogate model to assess impact of the therapy on bleeding. The acute tail amputation is a relative simple model for evaluating the efficacy of a coagulation factor (Mei et al. 2010; Elm et al. 2012). However, it is rather insensitive, needing $\geq$50% FVIII to correct bleeding phenotype, a level significantly higher than the 1% FVIII threshold accepted to be required for prophylaxis in humans. Also, the acute tail cut model also does not evaluate efficacy for recurrent rebleeds. Therefore, for a more faithful recapitulation of human physiology, more sensitive injury model such as the tail vein transection model and the saphenous vein injury model has been developed. In comparison to acute tail amputation model, only a vein is injured