Table 1 Animal models with bleeding disorders for in vivo target validation

	Weight	Mutation site	Spontaneous bleeding
Genetically engineered models			
Hemophilia A mouse (Bi et al. 1995)	20–30 g	Exon 16 or 17 deletion	Rare
Hemophilia A pig (Kashiwakura et al. 2012)	20–30 kg	Exon 16 deletion	Common and severe
Hemophilia B mouse (Lin et al. 1997)	20–30 g	Promoter to exon 3 deletion	Rare
vWD mouse (Denis et al. 1998)	20–30 g	Exon 4–5 deletion	10% in pups, rare in adults
Larger congenital disease animal models			
Hem A rat (Booth et al. 2010a, b)	200–300 g	Leu176Pro	20%, tarsal joint bleeds
Hem A dog (Giles et al. 1982; Brinkhous and Graham 1950; Graham et al. 1949)	10–30 kg	Intron 22 inversion	Common, joint bleeds
Hem A sheep (Neuenschwander et al. 1992; Porada et al. 2010)	70–75 kg	Exon 14 stop codons	Common, joint bleeds
Hem B dog (Mauser et al. 1996; Evans et al. 1989; Mustard et al. 1960)	15–20 kg	772–776 nucleotide deletion and a C to T transition at 777 (Mauser et al. 1996)	Common, joint bleeds
		G1477A (Evans et al. 1989)	
vWD dog (Haberichter et al. 2005)	8–10 kg	C255 deletion in exon 4	Mucosal surface
vWD Pig (Fass et al. 1979)	60 kg	To be defined, likely point mutation (Bahou et al. 1988)	Mucosal surface

animals (Furth et al. 1994; Kistner et al. 1996). These technologies allow the mouse to develop and mature normally before the gene of interest being ablated.

The first hemophilia A mice with the targeted deletion of coagulation factor VIII was created in 1995 by the disruption of exon 16 or exon 17 (Bi et al. 1995). Hemophilia B mice was created in 1997 by disrupting the promoter through exon 3 region of factor IX (Lin et al. 1997). Similar to the human conditions, the deficiency of factor VIII and factor IX in these mice leads to severe bleeding phenotype upon injury (Table 1). These hemophilia mouse models have been used extensively to validate the PK, PD, and efficacy of hemophilia therapies, including novel therapeutics that could provide extended duration of action (Metzner et al. 2009; Peters et al. 2010; Ostergaard et al. 2011; Dumont et al. 2012; Stennicke et al. 2013; Pastoft et al. 2013; Mei et al. 2010) and enhanced efficacy (Lin et al. 2010; Leong et al. 2015). These mouse models have also enabled gene therapy studies (Crudele et al. 2015; Wang et al. 1997; McIntosh et al. 2013) and different delivery routes (Peng et al. 2010; Brooks et al. 2013).