1 Ideal Animal Disease Model for Target Validation

An ideal animal disease model for target validation would be a model that recapitulates the disease phenotype, shares the same pathophysiology as human, and responds to existing human therapies in a manner similar to patients. Animal models that faithfully resemble the disease pathophysiology are invaluable for the characterization of the mechanism of action, pharmacokinetics, pharmacodynamics, biomarkers, safety, and toxicity of future therapies. Such animal models could also help to predict the human dose prediction for clinical trials. While these principles are obvious, the available animal models often have limitations and do not meet these ideals or mimic closely enough the human diseases. Far too often, molecules that provided impressive efficacy in preclinical models fail in clinical trials. This could be due to the preclinical disease model species being only distantly related to human. It could also be due to that inappropriate endpoints have been used for target and efficacy evaluation in the chosen models. Another possibility for the failed translatability from experimental models to the clinic could also be flawed clinical trial designs. Regardless of these potential hindsights, in vivo target validation with predictive animal models is a crucial part of the drug development process. If performed well, with careful consideration to minimize obtaining misleading information, in vivo disease models represent significant value for discovery and development of new treatment options for patients.

To initiate in vivo target validation, the first decision to be made is to select a validation approach. In this chapter, we will focus on (1) in vivo animal models and (2) pharmacological tools for target validation.

2 In Vivo Models for Target Validation

2.1 Mammalian Models

2.1.1 Wild-Type Mice

Wild-type mouse strains are indispensable tools for medical research and drug development. Disease phenotypes can be induced in these mice by genetic, pharmacological, or surgical means. C57BL/6, FVB/N, BALB/c, C3H/He, and 129Sv are some of the commonly used wild-type mouse strains. However, it is important to recognize there could be differences among these different strains that could affect one's target validation effort.

For example, special attention should be paid when selecting mouse strains for studying Th1 and Th2 responses. C57BL/6 and BALB/c mice are, respectively, regarded as Th1- and Th2-dominant mouse strains. T cells from C57BL/6 mice preferentially produce Th1 cytokine with high interferon-γ (IFNγ) and low interleukin (IL)-4. In contrast, BALB/c mice produce Th2 cytokine production with low IFNγ and high IL-4 (Mills et al. 2000). Similar T-cell responses were observed when these mouse strains were evaluated in Leishmania major infection studies (Heinzel et al. 1989; Scott et al. 1988). Therefore, for the purpose of validating