validation and compound screening for drug discovery in indications such as neurological diseases (Alzheimer's, Parkinson's, and Huntington's diseases) (Li and Le 2013), and cancer (Kirienko et al. 2010).

3 Biological Tools for Target Validation

3.1 Biologic Approaches

Monoclonal antibodies and recombinant proteins are important biologic tools for in vivo target validation. Depending on the targets, antagonistic or agonistic monoclonal antibodies could be used for target validation. Recombinant proteins could also have activating or inactivating properties depending on the specific targets or pathways being interrogated.

Validation by biologics is possible of targets, which reside in a physiological location accessible by the administered biologics, for example, soluble targets in systemic circulation, cell surface receptors, and extracellular tissue compartment targets. To validate a soluble target, the plasma concentration of the target and the affinity of the biologics towards the target need to be determined beforehand in order to ensure that the validation study is performed with a dose that saturates the target in question. For the validation of cell surface target, attention should be paid on whether the surface target becomes released into circulation as part of the physiological or disease process or gets internalized. The soluble form of the target can act as a sink and reduce the amount of biologics available for engaging the target on cell surface.

The pharmacological properties of the biologics need to be determined before the initiation of in vivo target validation study. The plasma threshold concentrations of biologics should be obtained with in vitro binding and potency studies to predict the level, which can provide efficacy. Additional pharmacokinetic studies will help to design and establish the plasma concentration needs to be attained for in vivo studies. Furthermore, the clearance rate and duration of action of the biologics should also be characterized with the help of these pharmacokinetic and pharmacodynamics studies. These information will guide the decision of the dosage and dosing regimen of the biologics in animals for in vivo target validation study.

While the use of biologics is a valuable approach for in vivo target validation, this process is sometime hampered by the development of immunogenicity against the biologics. This is especially true for longer-term validation studies in which animals receive multiple doses of the biologics. This could lead to the development of antibodies which could neutralize the activity and the efficacy of the biologics. Therefore, the monitoring of antibody development towards the biologics during the validation is necessary, especially in studies where no efficacy was observed. One way to reduce the risk of immunogenicity development is to use species-matching biologics, e.g., mouse monoclonal antibody in a mouse model but not a rat model.

Another potential hurdle of using biologics for target validation is the lack of existing tool molecules of high quality and high specificity to the target of interest.