described that showed clinical efficacy that exceeded what was expected based in their plasma IQ. This was attributed to accumulation of the inhibitor in the liver relative to the plasma compartment.[30] A similar situation may exist for RSV: fusion inhibitors with an accumulation in the lung have been described (see Section 2.5); however, it is not clear if this afforded improved efficacy, mostly because of limitations on the dynamic range of animal models for RSV.

Overall, although very speculative, to set an exposure bar comparable to oseltamivir for the first RSV fusion inhibitor to reach the clinic seems sensible. As a consequence of this goal, very potent inhibitors with a low human plasma shift stand the best chance of success. Targeting highly potent oral inhibitors requiring a low dose has additional benefits such as minimizing DDIs and idiosyncratic toxicities. This could also be achieved by direct pulmonary delivery to reduce systemic exposure; however, technologies for inhalation dosing to neonates and infants less than 2 years of age have not been clinically validated.

Another lesson from HIV, HCV and other viruses is the requirement of pan-genotype coverage for all strains of virus that are in circulation (2.2 Challenges in the development of RSV antivirals). Both RSV subtypes, A and B, typically alternate in prevalence in subsequent winter months and within each A and B strain there are a large number of variants.[31,32] Lastly, in addition to the issue of natural pre-existing resistance, avoiding the development of resistance acquired under drug pressure is essential. This is especially challenging for HIV antivirals, since therapy has to be maintained for life and could be much less of an issue with the self-limiting and relatively short-duration RSV infecton. The few reported cases of resistance towards oseltamivir are believed to be caused by a natural strain and not a result of drug pressure.[33,34] Other antiviral drugs such as amantadine (**2**, Scheme 2.1), however, are known to develop resistance after a few rounds of replication of the flu virus.[35]

The pharmacokinetics and physicochemical properties should also be considered in the target profile. For example, if oral therapy is targeted, good bioavailability is essential and preferably in multiple non-clinical species. Whereas differences in absorption and elimination pathways in adults can be managed, they can create difficulties in predicting doses for infants, for example. Inhaled therapies would avoid these concerns. The physicochemical properties are also important as, for example, high solubility would allow multiple formulations to be considered for all age categories.[35] These factors as they relate to challenges regarding the clinical development are discussed in Section 2.6.

Overall, the target profile is stringent, and appropriate choice of target properties and goals in the discovery and development process can be a significant factor for clinical success.

2.4 RSV Fusion Inhibitors – Biologics

Preventive biological therapies such as palivizumab (Synagis) and motavizumab (Numax) and vaccines are not discussed in detail in this chapter and