challenge strain is approved for use in healthy adult volunteers by the European Medical Agencies. Exposure of adult volunteers to 3.0–5.4$\log_{10}$PFU mL^{-1} virus produces an infectivity rate ranging from 71 to 86%. Furthermore, the onset of infection measured by viral culture or qt-PCR coincided with the onset of upper respiratory tract disease symptoms such as mucous weight. The challenge virus in healthy adults does not progress to a lower respiratory tract disease, so the study does not provide a means for following progression of upper to lower respiratory tract disease. However, shortly after approval of the challenge strain, the siRNA compound ALN RSV-01 was studied in the experimental model.[74] In this study, ALN RSV-01 or placebo was delivered daily by nasal spray for 5 days starting 2 days before inoculation with virus. The direct impact on viral production was assessed through regular sampling of the nasal cavity using twice daily nasal washes during the study. Infection rate, determined by culture of the nasal wash samples, was reduced by 38% in the treated group ($N = 19$ infected on drug *versus* 30 infected on placebo). A reduction in peak viral load of $\sim$1.0$\log_{10}$PFU mL^{-1} and also reduction in viral load area under the curve (AUC) was observed for the treated group, although the study was not powered for statistical significance. As such, the study provided a POC for evaluation of an RSV replication inhibitor targeting the N-protein when administered prophylactically. Prophylactic administration of an RSV fusion inhibitor would also be expected to result in antiviral and symptomatic responses. However, it has not been proven whether treatment-based therapy, for example, treatment upon detection of virus or symptoms, would be effective, in terms reduction of viral load, in this model. In this respect, the fact that disease remains in the upper respiratory tract should be borne in mind since this is a key difference to the natural setting where progression to the lower respiratory tract is the goal of antiviral intervention. Nevertheless, the model provides a significant advance in the ability to test RSV antivirals early in clinical development and avoids some of the hurdles associated with naturally infected patients. Furthermore, demonstration of even a modest antiviral effect in the experimental model may be sufficient to justify a potential benefit for infants and allow initiation of trials in infants infected with RSV.

2.7 Conclusion and Outlook

Significant efforts by BMS, J&J, AstraZeneca, Biota, Wyeth, Viropharma, MicroDose, Gilead and others have afforded potent small-molecule RSV fusion inhibitors with a surprisingly high structurally diversity. Some of these compounds have reached clinical development, but the road to late-stage clinical trials for RSV has been too demanding and to date no Phase 2 study demonstrating efficacy in a therapeutic setting for a fusion inhibitor has been reported. This is not surprising in the light of the challenges both in the preclinical setting for optimization and in the clinical setting for development: unclear MOA of fusion inhibitors, lack of structural information that would guide inhibitor design, development of resistance, pan-genotype potency, lack