

virus causes lethal infection in >95% of animals.³³ Mice are inoculated with ectromelia virus either by footpad scarification, which is similar to the natural route of infection, or intranasal delivery.³⁹ The virus multiplies in the lymphatic endothelial cells, macrophages and lymphocytes within the regional node over a period of 2–4 days. By day 4 post-inoculation, animals appear ill, with hunched posture, ruffled coat and increased respiration. Viral replication in liver and spleen and other internal organs causes death in the infected animal between days 6 and 10 post-inoculation.³⁹ Like the vaccinia virus and cowpox models, antiviral efficacy is measured by decreased mortality, inhibition of virus-induced weight loss and reduction in viral titers in liver, spleen and other tissues.

4.3.2.3 *Rabbitpox Virus Model*

Rabbitpox virus is genetically related to vaccinia virus but highly adapted to replicate in rabbits, and as little as 15 PFU can establish productive infection in most rabbit species.⁴³ Rabbits are inoculated with rabbitpox virus in the footpad by intradermal injection or the nasal cavity by aerosol spray. Virus replicates in the mucosa or local lymph tissue to produce a primary viremia which lasts 2–4 days.⁴⁴ Animals develop fever within the first few days of infection and focal lesions appear on the ear by day 3 post-infection and can be visualized as small red spots near blood vessels visualized by backlighting.⁴⁴ The virus spreads through the lymph to the blood, ultimately seeding lung, liver, spleen and other internal organs. Virus replication at these sites often results in multi-organ failure and fatal disease.⁴³ Rabbits that survive infection of internal organs develop a secondary viremia where high levels of circulating virus seed the endothelial cells that line the dermal blood vessels to produce a rash on the skin that appears by day 6 post-inoculation. Vertical transmission of virus to susceptible rabbits has been observed, allowing for potential assessment of drug effects on virus spread within a population.⁴³

To establish a lethal infection, rabbits are inoculated with 100 PFU of rabbitpox virus by dermal abrasion or intranasal administration through aerosol delivery to the respiratory tract. Dermal lesions appear near blood vessels in the ears between days 3 and 5 post-infection and can be visualized by backlighting. The appearance of these lesions provides a therapeutic trigger for initiation of antiviral treatment. By day 6 post-inoculation, animals develop fever, listlessness and purulent discharges from the eyes and nose.⁴⁴ Most animals experience respiratory distress by this time in the infection. A rash develops between days 6 and 8 post-inoculation; however, skin lesions range from a few scattered lesions to confluency. Most animals die without developing a rash and death is accompanied by a fall in body temperature to below normal levels. Thus, quantifying lesion number or severity of the rash is a subjective measure of systemic virus spread and may not be possible in all cases. Since rabbits can tolerate more frequent and larger volume blood draws, blood chemistries can be measured to correlate changes in hematological status with disease progression. To quantify the level of virus spread, animals are sacrificed