

The most commonly used vehicle for gene transfer into human target cells is a replication incompetent retroviral vector. The efficiency of gene transfer with this type of vector has proven to be too low to implement effective gene therapy. To date much effort has gone into engineering the genetic and biochemical functionalities of retroviral vectors. Although progress has been achieved, high-efficiency reproducible gene transfer into human cells remains elusive. There are many important physico-chemical and systemic kinetic factors that govern the process of retrovirus-mediated gene transfer. These factors have gone mostly unrecognized to date. The former include the nature of the random Brownian motion of the retrovirus and the physico-chemical forces that determine the binding of the retroviral vector to the target cell. The latter arise from the kinetics of virus binding and entry into the target cell, as well as the kinetic interplay between cell-cycle and retroviral life-cycle events that determine the intracellular fate of the virus. This review describes these processes and how they constrain the efficiency of the gene transfer process.