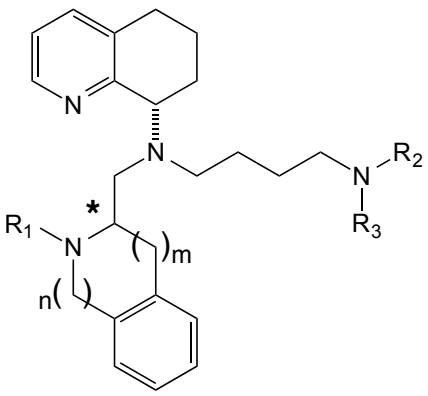
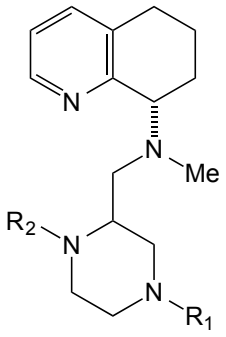
The Role of CXCR4 Modulators in Controlling HIV Entry, Stem Cell Mobilization and Certain Types of Cancer. Dennis Liotta, PhD, DSc, The Emory Institute for Drug Development and the Department of Chemistry, Emory University, Atlanta, GA 30322 USA.

The chemokine receptors, CCR5 and CXCR4, are the primary co-receptors responsible for mediating HIV-1 cell entry. Small molecules that modulate these receptors utilize a fundamentally different approach for controlling viral replication than most other classes of antiretroviral agents in that they act on host factors, rather than viral enzymes. While CCR5 entry inhibitors that demonstrate clinical efficacy against HIV have now become available (Maraviroc), the development of CXCR4 entry inhibitors is currently at a more nascent stage. Due to the ability of HIV to switch between CCR5 and CXCR4 entry co-receptors, the availability of a CXCR4 entry inhibitor that could be used in combination with Maraviroc or other ARVs could prove to be important in prolonging the effectiveness of HIV therapies in patients. Unfortunately, the complexities associated with the multiple CXCR4 signaling pathways (which include, inter alia, expression of survival and proliferation genes, as well as induction of chemotaxis) create a major challenge for identifying efficacious compounds that also possess a safety profile suitable for dosing every day of a patient's life. Alternatively, exploitation of selective aspects of the CXCR4 signaling pathways can be used for other important medical applications, such as hematopoetic stem cell mobilization.





My lab has discovered two series of CXCR4 modulators that, depending on their substitution patterns, exhibit either potent antagonism, suitable for hematopoetic stem cell mobilization or anti-HIV activity with little competitive CXCR4 signaling. In this presentation I will discuss some of the issues and challenges associated with these development opportunities.