Use of Computational Methodologies to Identify Small Organic Leads that Recognize and Bind SL3 RNA of the ψ - Recognition Element of HIV-1

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The Ψ-RNA packaging region of HIV-1 virus plays a critical role in the reverse transcription process that is required for viral replication. The Ψ-site has ~120 nucleotides and is composed of four stem-loops numbered 1-4, that are all highly conserved among retroviruses. Of the four stem loops, stem loops 2-4 have apical tetra-loops and are important in the viral replication process. Among the four stem loops, stem loop 3 has been identified as the principal determinant for viral packaging and for specificity. Studies of HIV-1 Ψ-RNA with stem loop 3 (SL3) RNA deleted have shown that packaging is reduced to 10% the efficiency of the wild type.

We are using computational methods to discover small molecules that will inhibit Ψ-RNA–NC protein interactions that are critical to viral replication. Our current computational studies have targeted the junction between the apical tetra loop and the major groove as well as the major groove of SL3 RNA, which are both the sites of interaction with the NC protein. To identify leads for small molecules that can bind to stem loop 3 RNA, we have employed computer-aided drug-discovery techniques that include DOCK, AUTODOCK as well as Molecular Dynamics (MD). Molecules identified using these methodologies are being investigated experimentally to determine their binding affinities and selectivity.