Determining the mechanism of LINE-1 ribonucleoprotein particle assembly and inhibition by nucleoside reverse transcriptase inhibitors.

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Mobile genetic elements are sequences of DNA capable of altering their genomic location, resulting in host DNA damage and genomic instability. In humans, Long Interspersed Nuclear Element-1 (LINE-1) is the only autonomously replicating element, accounting for 17% of the genome[1]. Age-associated changes in the chromatin landscape and immune function are correlated with the transcriptional derepression of the LINE-1 element during cellular senescence. Two open reading frames produce a chaperone ORF1 protein and a catalytic ORF2 protein which assemble onto its native transcript to form a ribonucleoprotein (RNP) particle. The ORF2 protein consists of endonuclease, reverse transcriptase (RT), and nucleic acid binding domains whose functions are required for successful retrotransposition. After assembly, the LINE-1 RNP particle enters the nucleus and integrates into new genomic locations via a 'copy-and-paste' mechanism using its RNA-intermediate. Through comparative homology modeling[2-3], various constructs isolating the functional LINE-1 RT domain were designed, expressed, and purified from *Escherichia coli.* Nucleoside reverse transcriptase inhibitors (NRTIs) originally developed for treating human immunodeficiency virus (HIV)[4] also inhibit LINE-1 RT activity. Therefore, we are using complementary techniques in biochemistry and structural biology to elucidate both the mechanisms of LINE-1 RNA binding and inhibition by NRTIs to explore the LINE-1 RT as a potential drug target in age-associated diseases.

[1]Lander, ES et al. Initial sequencing and analysis of the human genome. *Nature* 409:860-921 (2001).
[2]Song Y et al. High resolution comparative modeling with RosettaCM. *Structure* (2013).
[3]Xu D et al. FFAS-3D: Improving fold recognition by including optimized structural features and template re-ranking. *Bioinformatics* (2013).
[4]Dia L et al. Effect of reverse transcriptase inhibitors on LINE-1 and Ty1 reverse trancriptase activities and on LINE-1 retrotranposition. *BMC Biochemistry* 12(18):(2011).