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## Neutron Reflectometry and Integrative Modeling Reveal HIV-1 Nef Homodimer Formation on Model Lipid Membranes

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Neutron reflectometry (NR) is intrinsically a low-resolution structural technique, yielding one-dimensional scattering length density profiles that are often inadequate for detailed structural biology applications. However, NR stands out as one of the few methods capable of characterizing membrane-bound proteins and protein assemblies in a biomimetic, solvent-immersed, and thermodynamically relevant state, making it invaluable for biophysical studies. Integrating NR with complementary experimental data and molecular simulations can overcome its resolution limitations and obtain detailed three-dimensional structural information.

In this presentation, I will discuss our recent advancements in applying this integrative approach to study the homodimer formation of HIV-1 Nef at the lipid membrane. HIV-1 Nef is crucial for viral infectivity, high-titer replication in vivo, and immune evasion in HIV-infected cells. Nef functions not through intrinsic biochemical activity but through interactions with various host cell signaling proteins and intracellular trafficking pathways. Previous studies have underscored the importance of Nef homodimer formation at the plasma membrane for its functions.

In collaboration with the Smithgall group at the University of Pennsylvania School of Medicine, we combine NR of full-length myristoylated Nef bound to model lipid membranes with molecular simulations of high-resolution Nef monomer and homodimer structures [1]. This integrated approach provides direct evidence that Nef associates with the membrane as a homodimer, with its structured core region positioned away from the membrane to engage partner proteins. Additionally, studies on a dimerization-defective mutant, Nef-L112D, reveal that the helical dimerization interface seen in previous crystal structures is crucial for stabilizing the membrane-bound dimer.

[1] Heinrich F., Thomas E. C., Alvarado J. J., Eells R., Thomas A., Doucet M., Whitlach K. N., Aryal M., Lösche M., Smithgall T. E., Neutron Reflectometry and Molecular Simulations Demonstrate HIV-1 Nef Homodimer Formation on Model Lipid Bilayers. *Journal of Molecular Biology* 435(8):168009 (2023), DOI: 10.1016/j.jmb.2023.168009

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