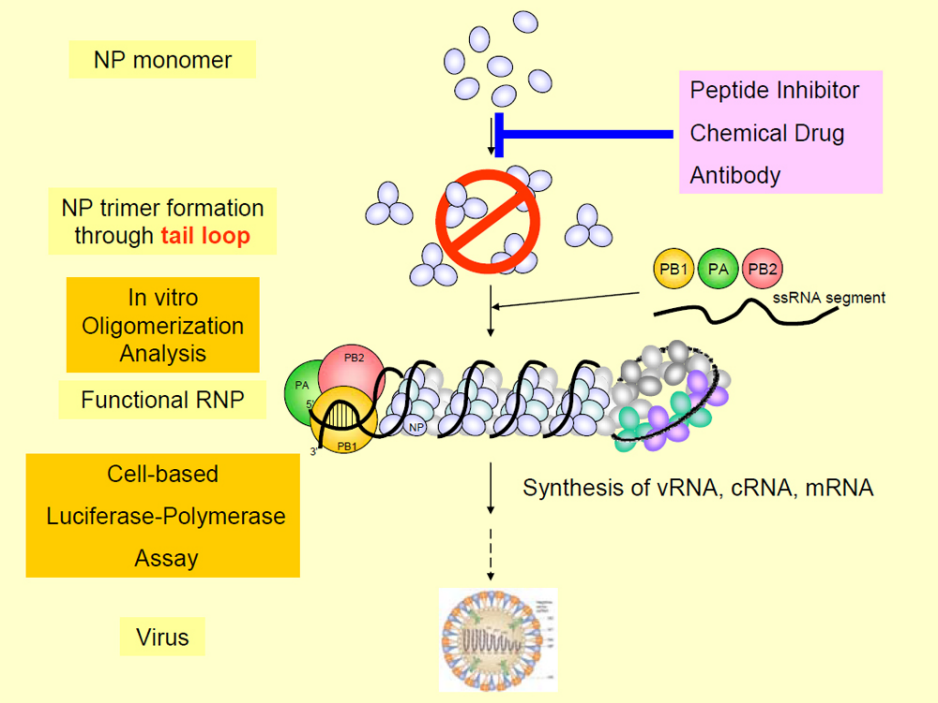
RNA Polymerase Complex of Avian Flu Virus (2006-present). Of only eight viral RNA segments in the flu virus, the longest three encode for RNA-dependent RNA polymerases (RDRP), named PA, PB1, and PB2, and they form a complex and function as a complex biologically. In addition, a fourth protein NP interacts with RDRP and viral RNA (vRNA) during replication. Our goal is to develop therapeutics against the infection of influenza virus based on protein-protein interactions. (Supported by NSC Flu Program)



Recent Results (from paper #2 below):

The nucleoprotein (NP) of the influenza virus exists as trimers, and its tail-loop binding pocket has been suggested as a potential target for antiinfluenza therapeutics. The possibility of NP as a drug target was validated by the recent reports that nucleozin and its analogs can inhibit viral replication by inducing aggregation of NP trimers. However, these inhibitors were identified by random screening, and the binding site and inhibition mechanism are unclear. We report a rational approach to target influenza virus with a new mechanism—disruption of NP–NP interaction. Consistent with recent work, E339A, R416A, and deletion mutant Δ402–428 were unable to support viral replication in the absence of WT NP. However, only E339A and R416A could form hetero complex with WT NP, but the complex was unable to bind the RNA polymerase, leading to inhibition of viral replication. These results

demonstrate the importance of the E339…R416 salt bridge in viral survival and establish the salt bridge as a sensitive antiinfluenza target. To provide further support, we showed that peptides encompassing R416 can disrupt NP–NP interaction and inhibit viral replication. Finally we performed virtual screening to target E339…R416, and some small molecules identified were shown to disrupt the formation of NP trimers and inhibit replication of WT and nucleozinresistant strains. This work provides a new approach to design antiinfluenza drugs.

Publications:

1. “High-throughput identification of compounds targeting influenza RNA-dependent RNA polymerase activity”. Ching-Yao Su , Ting-Jen R. Cheng, Meng-I Lin, Shi-Yun Wang, Wen-I Huang, Shao-Ying Lin-Chu, Yu-Hou Chen, Chung-Yi Wu, Michael M. C. Lai, Wei-Chieh Cheng, Ying-Ta Wu, Ming-Daw Tsai, Yih-Shyun E. Cheng, and Chi-Huey Wong, *Proc. Natl. Acad. Sci. USA, 107*, 19151-6 (2010).

2. “E339…R416 salt bridge of nucleoprotein as a feasible target for influenza virus inhibitors”. Yu-Fang Shen, Yu-Hou Chen, Shao-Ying Chu, Meng-I Lin, Hua-Ting Hsu, Pei-Yu Wu, Chao-Jung Wu, Hui-Wen Liu, Fu-Yang Lin, Gialih Lin, Pang-Hung Hsu, An-Suei Yang, Yih-Shyun E. Cheng, Ying-Ta Wu, Chi-Huey Wong, and Ming-Daw Tsai, *Proc. Natl. Acad. Sci. USA 108,* 16515-16520 (2011).