

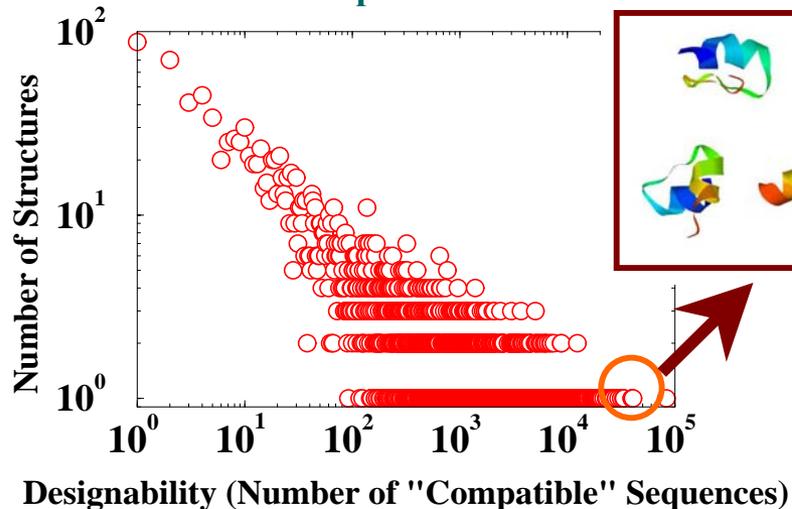
Computational Peptide/Protein Modeling and Design

Chen Zeng, The George Washington University, DMR-0094176, 0313129

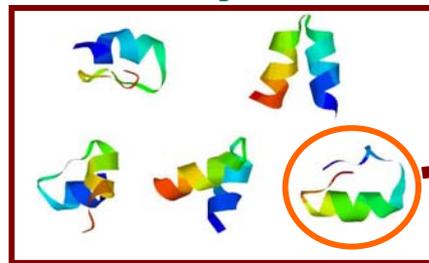
Design Novel Protein Folds (Collaborators: C. Tang & N. Wingreen, NEC; L. Lai, PKU)

It is observed that nature uses about 1000 folds to make proteins. What are the physical characteristics for a stable protein fold? The principle of designability formulated from recent theoretical studies states that structures can differ vastly in their designability (i.e., the number of “compatible” sequences) and high designability entails other protein-like properties. Our goal is to turn this concept into a computationally practical scheme to design novel folds. To this end, we carried out computations on a model system whose top designable folds are popular motifs occurred in nature, albeit only as small parts of much larger protein structures. Our current efforts center on designing a small $\beta\alpha\beta$ motif that is stable by itself. We have designed sequences that are expected to adopt this fold. Although its CD spectrum is consistent with the designed structure, much remains to be done in probing the extent of the folding that can be further characterized via NMR measurements.

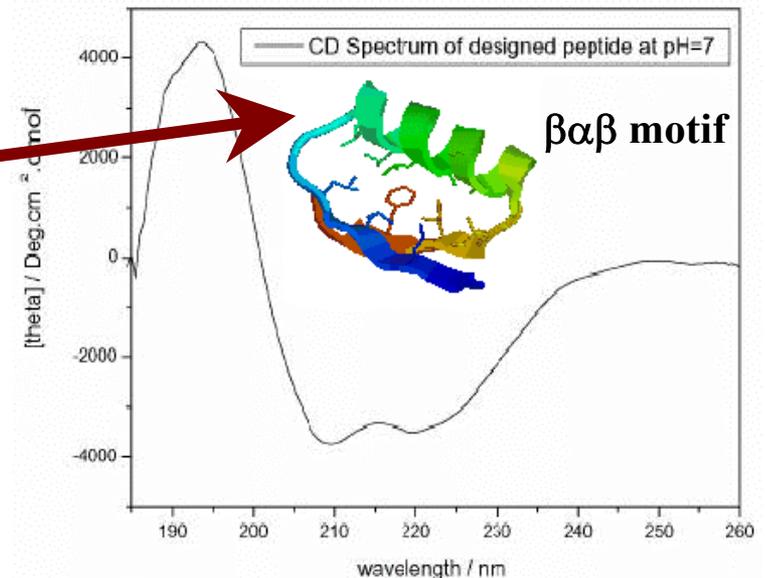
I. Model Computation



II. Pick Top Folds



III. Sequence Design and Verification



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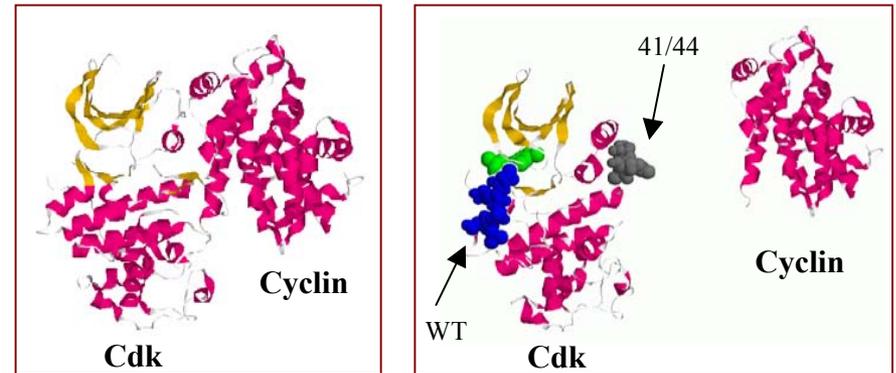
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Design HIV-1 Tat Inhibitor

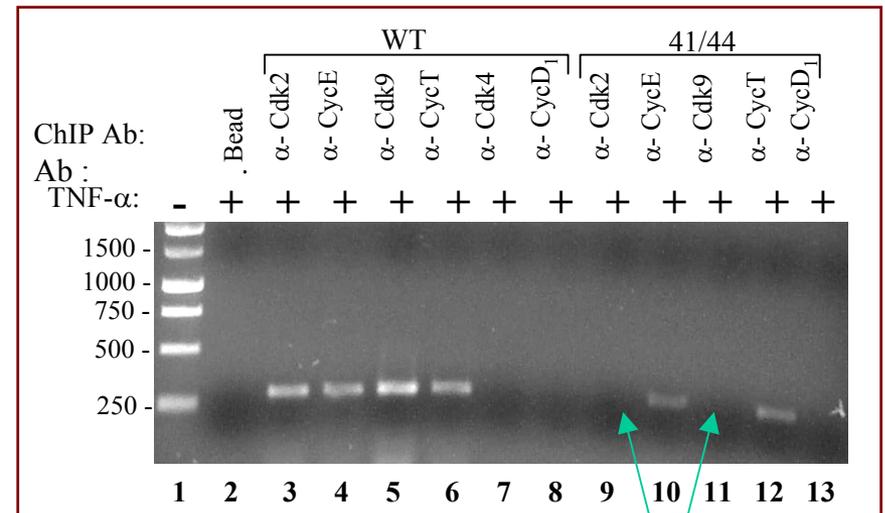
(Collaborator: F. Kashanchi, Medical School, GWU)

HIV-1 viral protein Tat, among other things, recruits a CyclinE-Cdk2 complex to elongate the transcription needed for HIV replication. Unlike a wild-type Tat analog and several Cdk inhibitor drugs (green) that bind to the ATP-binding site, a 5-mer peptide mutant, Tat-41/44, is found to dock at the interface of the complex that blocks its formation. The disassociation of the complex inactivates the kinase activity of Cdk and thus greatly suppresses the HIV replication. This computational finding is supported by a very recent Chromatin Immunoprecipitation (ChIP) experiment where only Cyclins but not Cdks are found on HIV promoter in the presence of Tat-41/44.

Our current efforts focus on detailed characterization of the binding site to facilitate direct experimental verification. We also plan to improve the algorithm so that an efficient computational screening can be systematically carried out to search for shorter and/or stronger peptide inhibitors as well as small molecule analogs as a more suitable drug.



Blocking of Cyclin-Cdk Complex by Peptide 41/44



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