Structural characterization of the protein-protein interaction between the C-terminal domain of the influenza A polymerase PA subunit and small peptide-based inhibitors

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Influenza RNA-dependent RNA polymerase (RdRp) is a heterotrimeric complex composed of the polymerase acidic (PA), polymerase basic 1 (PB1), and polymerase basic 2 (PB2) subunits. The RdRp has an essential role in the life cycle of the virus as it is responsible for viral replication and transcription. Two subunits, PA and PB1 share an extensive interface. However, their assembly depends on a relatively small hydrophobic cleft formed by the C-terminus of PA (CPA) **(Fig. 1A)**. The PB1 N-terminus binds to the CPA in a form of 3_{10} helix [1, 2]. Disrupting such an important protein-protein interaction appears to be a promising drug target. The first 14 amino acids peptide from the N-terminus of PB1 was identified as a nanomolar inhibitor of the PA-PB1 PPI [3]. Moreover, the peptide array revealed several introduced mutations as advantageous for the peptide binding, though without an X-ray structure [4]. We have structurally and thermodynamically characterized the CPA interacting with optimized minimal peptide-based inhibitors derived from the PB1 N-terminus (**Fig. 1B**). These insights into the PA-PB1 PPI may be considered as a starting point for the rational design of first-in-class anti-influenza inhibitors of the influenza A RdRp.

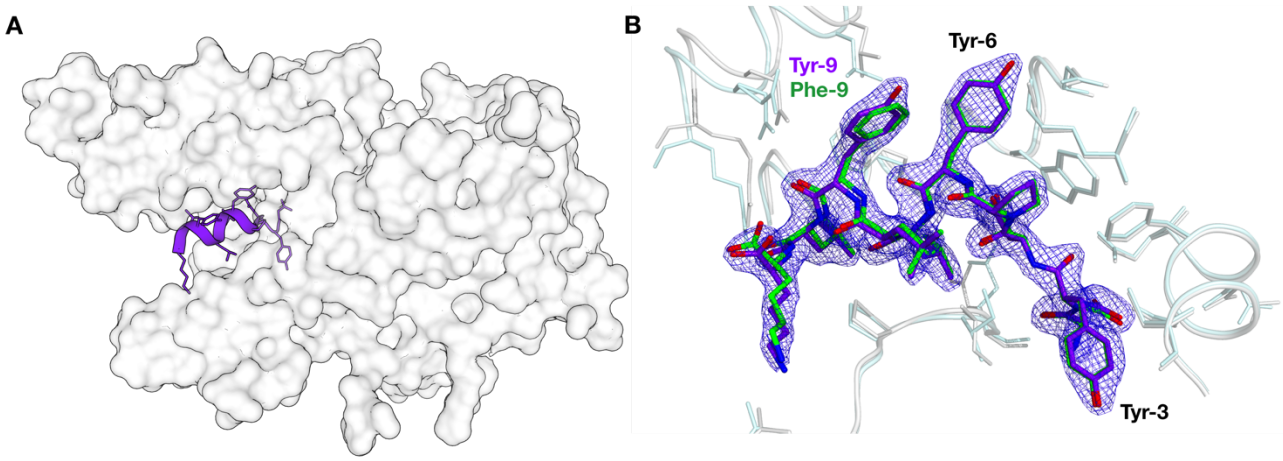

Figure 1. **A)** Overall structure of the PA-PB1 PPI. **B)** Close-up view of the CPA hydrophobic pocket with two peptide-based inhibitors [5, 6].

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