**Supplementary material**

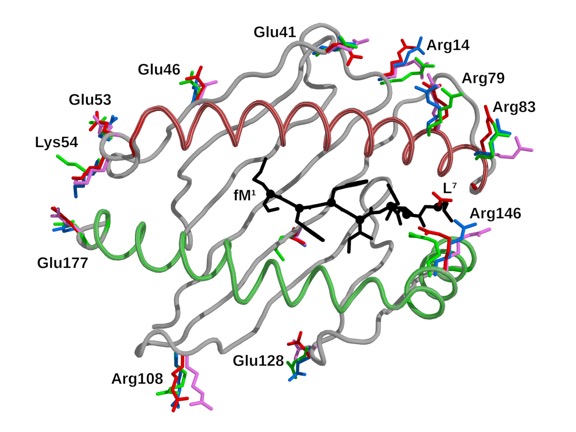
**Table S1. Sequence details for molecular dynamics.** For residues for which there are alternate PDB coordinates (A|B) the A coordinates were used in the simulations. Serine 276 residues wit unmodeled density in pI⁶-M3 and pT⁶-M3 were added using VMD.

|  | Α | β₂m | ligand | alternate coordinates | unmodeled |
| --- | --- | --- | --- | --- | --- |
| pI⁶-M3 | 1-275 | 1-99 | fMFFIN**I**L | α: M98 | α: S276 |
| pV⁶-M3 | 1-276 | 1-99 | fMFFIN**V**L | α: E46, S145, E161 |  |
| pA⁶-M3 | 1-276 | 1-99 | fMFFIN**A**L |  |  |
| pT⁶-M3 | 1-275 | 1-99 | fMFFIN**T**L |  | α: S276 |

**Fig S1**. **Cα-Cα distances of α₁α₂ binding groove residues after backbone alignment of the α₁α₂ domains of crystal complexes p[VAT]⁶-M3 to pI⁶-M3.**



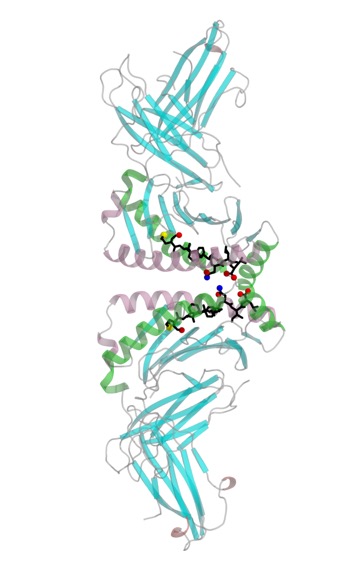
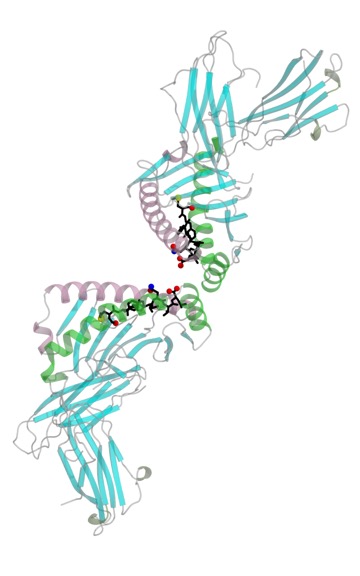
**Fig S2. Side chains of α₁α₂ residues with largest exposed side chain RMSD after backbone fit of α₁α₂ domains.** Side chains in p[IVAT]⁶-M3 complexes are colored red, green, blue, violetrespectively. pI⁶-M3 α₁α₂ helices, floor, peptide and peptide terminal carboxyl are coloredgreen, silver, black and red, respectively



**Fig S3. (A) Complex “a” (chains A,B,C) (lower) and complex “b” (chainsD,E,F) (upper)** **in pI⁶-M3 crystals.** Binding-groove helices α₁ and α₂ are colored red and green, respectively; binding-groove floor and domains α₃ and β₂m are colored cyan. Peptide ligands are shown as black sticks, with sidechain N and O atoms shown as blue and green spheres, respectively.

**(B) Head-to-head orientation of two pV⁶-M3 complexes in C2 crystals.** Colors are the same as in (A), but the peptide is not directly involved in crystal contacts in this crystal, and therefore its bound conformation appears less restricted than in the P1 crystals.

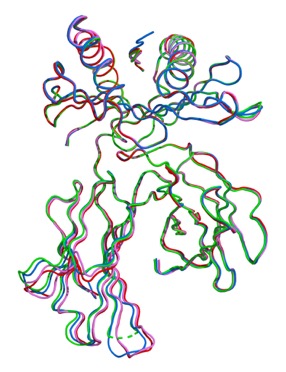
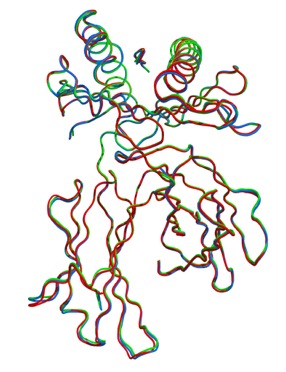
**A** **B**

**Fig S4. P1 complexes after backbone alignment of binding-groove domains α₁α₂.**

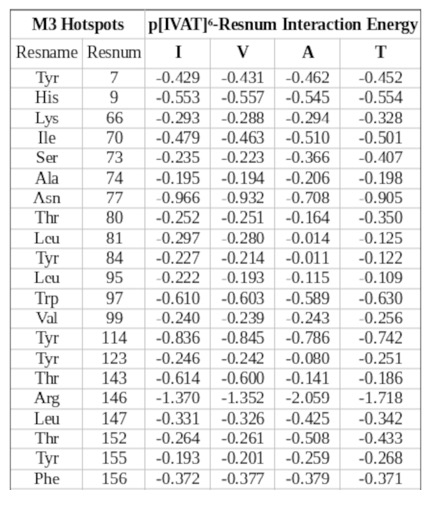
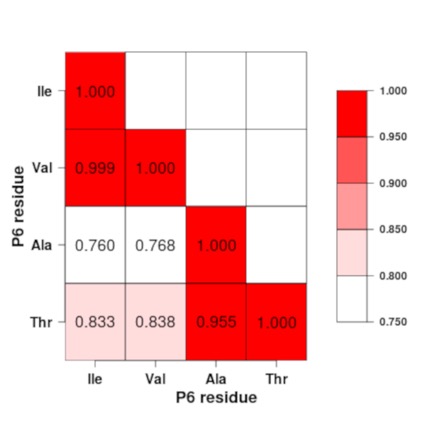
**(A)** p[IVAT]⁶-M3 “a” complexes **(B)** p[IVAT]⁶-M3 “b” complexes. (I,V,A,T complexes are red, green, blue, silver respectively. **(C)** pI⁶-M3 “a” complex (red) and “b” complex (green).

**A B C**



**Fig S5. M3 hot-spot correlations. (A)** Table of p[IVAT]⁶-(M3 hot-spot) MM-GBSA interaction energies **(B)** Correlation coefficients between p[IVAT]⁶-(M3 hot-spot) binding profiles (I,V,A,T columns of (A)).

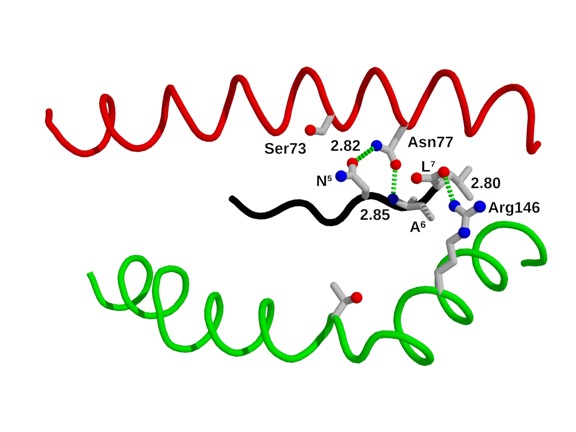
**A B**

  ****

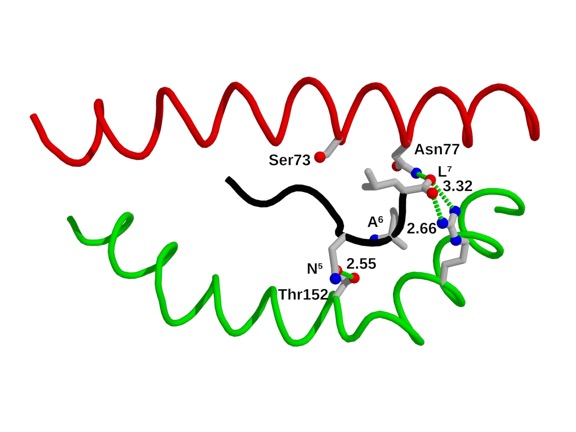
**Fig S6. Interactions between peptide residues N⁵,A⁶, L⁷ and M3 residues Ser73, Asn77,**

**Thr152 and Arg146.** (A) 10 ns (B) 1000 ns

**A**

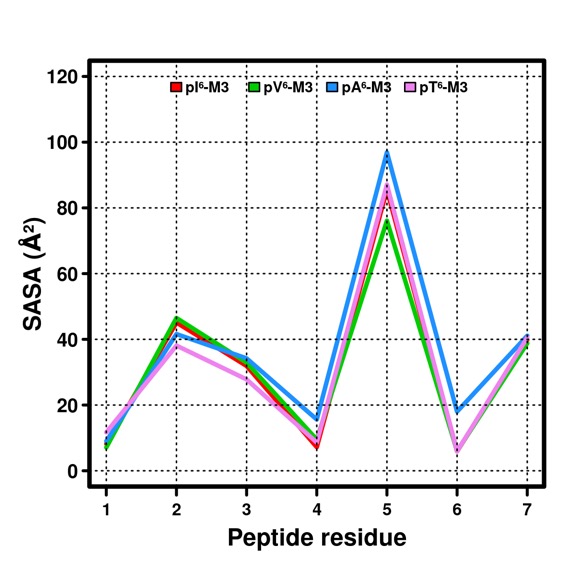


**B**

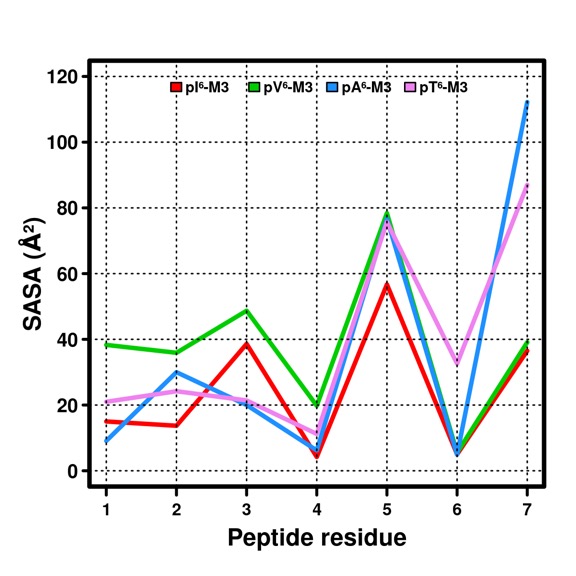


**Fig S7. Peptide exposed side chain SASA. (A)** 0 ns **(B)** 800 ns

**A**



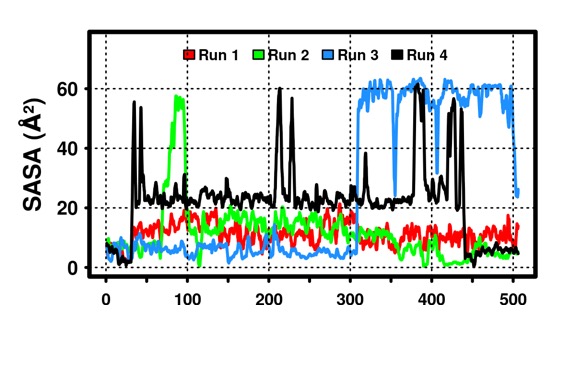
**B**



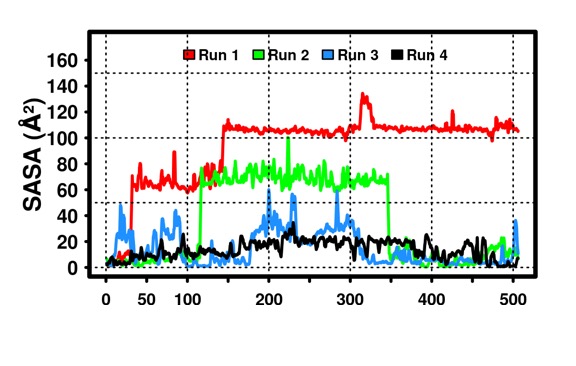
**Fig S8. Exposed side-chain SASA of peptide residues in the 0-500 ns interval of four repeated**

**pA⁶-M3 simulations** (A) A⁶ (B) L⁷

**A**



**B**



**Movies of 1-microsecond simulations of complexes p[IVAT]⁶-M3.** Movies are each 16-second MPEG4 files of 500 consecutive frames spanning the 1-microsecond simulations.

**Movie S1:** pI⁶-M3

**Movie S2:** pV⁶-M3

**Movie S3:** pA⁶-M3

**Movie S4:** pT⁶-M3