Computer-Aided Search for Novel HIV-1 Entry Inhibitors Based on a Broadly Neutralizing Antibody Against the Envelope gp120 V3 Loop

A. M. Andrianov[1]

[1]*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus,*

Kuprevich Street, 5/2, 220141 Minsk, Republic of Belarus, andrianov@iboch.bas-net.by

I.A. Kashyn[2]

[2]*United Institute of Informatics Problems, National Academy of Sciences of Belarus,*

Surganov Street 6, 220012 Minsk, Republic of Belarus, lighkia@gmail.com

A.V.Tuzikov[2]

[2]*United Institute of Informatics Problems, National Academy of Sciences of Belarus,*

Surganov Street 6, 220012 Minsk, Republic of Belarus, tuzikov@newman.bas-net.by

Computer-aided search for novel anti-HIV-1 agents that are able to mimic the pharmacophore properties of the antigen-binding site of a broadly neutralizing monoclonal antibody (mAb) 3074 against the envelope gp120 V3 loop was carried out followed by evaluation of their potential inhibitory activity by molecular modeling. In doing so, the following problems were solved: (i) the mAb 3074 amino acid residues responsible for specific binding to the HIV-1 V3 loop were identified from the X-ray structures of this antibody Fab in complexes with the MN, UR29 and VI191 V3 peptides [1]; (ii) using these data, 2039 possible mAb 3074 peptidomimetics were found by pepMMsMIMIC presenting a public, web-oriented virtual screening platform [2]; (iii) the complexes of these compounds with the above V3 peptides were built by molecular docking and, based on their analysis, the four molecules exhibiting a high affinity to V3 in the *in silico* studies were selected as the most probable peptidomimetics of mAb 3074, and (iv) stability of the complexes of these molecules with the MN, UR29 and VI191 V3 peptides was estimated by molecular dynamics and free binding energy simulations.

As a result, a key role in specific binding of the selected compounds to the V3 loop was shown to belong to π-π interactions between their aromatic rings and the conserved Phe20 and/or Tyr21 of the V3 immunogenic crown. Similarly to mAb 3074, these compounds were found to block the tip of the V3 loop forming its invariant structural motif, which contains residues critical for cell tropism [3, 4]. In addition, the complexes of interest do not undergo significant changes within the molecular dynamics calculations, exhibiting the low values of free energy of their formation. In this context, the compounds found by pepMMsMIMIC [2] in the MMsINC database [5] are considered as the promising basic structures for the design of novel, potent and broad anti-HIV-1 drugs.

This study was supported by grant from the Belarusian Foundation for Basic Research (project X12-022).

References

1. X. Jiang, V. Burke, M. Totrov et al. (2010) Conserved structural elements in the V3 crown of HIV-1 gp120, *Nat. Struct. Mol. Biol.*, **17:** 955–961.

2. M. Floris, J. Masciocchi, M. Fanton, S. Moro (2011) Swimming into peptidomimetic chemical space using pepMMsMIMIC, *Nucl. Acids Res.,* **39:** 261–269.

3. A.M. Andrianov, I.V. Anishchenko, A.V. Tuzikov (2011) Discovery of novel promising targets for anti-AIDS drug developments by computer modeling: application to the HIV-1 gp120 V3 loop, *J. Chem. Inf. Model.*, **51:** 2760–2767.

4. A.M. Andrianov, Yu.V. Kornoushenko, I.V. Anishchenko et al. (2012) Structural analysis of the envelope gp120 V3 loop for some HIV-1 variants circulating in the countries of Eastern Europe, *J Biomol Struct Dynam,* **doi:10.1080/07391102.2012.706455:**1–19.

5. J. Masciocchi, G. Frau, M. Fanton et al. (2009) MMsINC: a large-scale chemoinformatics database, *Nucl. Acids Res.* **37:** D284–D290.