From HIV to SARS-CoV-2: Fusion Inhibitors Based on Dimerization of HR2 Region Peptides

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Biography

Prof Hirokazu Tamamura was graduated from Faculty of Pharmaceutical Sciences, Kyoto University in 1988 (Supervisor: Prof Haruaki Yajima), and his Ph.D. from Kyoto University in 1995. He became an Assistant Professor of Faculty of Pharmaceutical Sciences, Kyoto University in 1989 (Boss: Prof Nobutaka Fujii), and then a Lecturer of Graduate School of Pharmaceutical Sciences, Kyoto University in 1997. He became a Visiting Fellow, National Cancer Institute/NIH, USA in 1999-2000 (Lab. Medicinal Chemistry, Supervisor: Dr Victor E. Marquez). He became an Associate Professor of Graduate School of Pharmaceutical Sciences, Kyoto University in 2005, and then a Full Professor of Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU) in 2005. His research fields extend to peptide & protein chemistry, chemical biology, medicinal chemistry and organic chemistry.

Abstract

The pandemic of COVID-19, which is caused by a positive-strand RNA virus SARS-CoV-2, has been continuing still in 2022. In June 2022, more than 500 million people have been infected with SARS-CoV-2 and more than 6 million people died of the virus-induced diseases. To date, more than 30 vaccines are approved and clinically used in the world to prevent SARS-CoV-2 infection and COVID-19 aggravation. Furthermore, some drugs have been developed and authorized including remdesivir, a repositioning inhibitor of RNA-dependent RNA polymerase (RdRp) from Ebola hemorrhagic fever, molnupiravir, a novel SARS-CoV-2 RdRp targeting inhibitor, and nirmatrelvir, an inhibitor of the main protease (M^{pro}) of SARS-CoV-2. In order to develop drugs with different mechanism of actions for increasing a repertory of drug choice, we focused on fusion inhibitors to inhibit the HR1–HR2 interaction, which plays an important role in membrane fusion step. There are many reports to develop fusion inhibitors based on the SARS-CoV-2 HR2 region. According to the classification of viruses, human immunodeficiency virus type-1 (HIV-1) and SARS-CoV-2 belong to positive-sense single-stranded RNA viruses. These viruses have similar fusion mechanism including the formation of 6-helix bundles (6HBs) by interaction of trimer of HR1 regions with corresponding three HR2 regions. In the past two decades, we have been developing anti-HIV-1 agents including fusion inhibitors, and found that the C-terminal dimer of HIV-1 HR2 region (C34) based peptides demonstrated two orders of magnitude higher potency than the parent monomer peptides [1]. Therefore, we envisioned that this dimerization strategy can be applicable to the development of novel SARS-CoV-2 fusion inhibitors. In this symposium I would like to introduce viral fusion inhibitors based on the dimerization strategy.

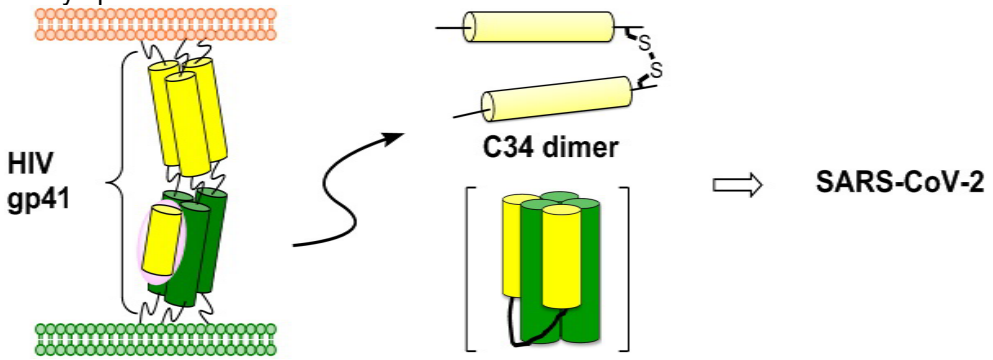

Fig. 1. The dimerization strategy of fusion inhibitors from HIV to SARS-CoV-2.

Reference:

1. Kobayakawa, T.; Ebihara, K.; Honda, Y.; Fujino, M.; Nomura, W.; Yamamoto, N.; Murakami, T.; Tamamura, H. *ChemBioChem: Special Issue dedicated to the 10th IPS in Kyoto* **2019**, *20*, 2101-2108