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論文審査の要旨

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Identification of dihydroorotate dehydrogenase inhibitor, vidofludimus, as a potent and novel inhibitor for influenza virus

（ジヒドロオロト酸デヒドロゲナーゼ阻害剤 vidofludimus をインフルエンザウイルスに対する強力かつ新規な阻害剤として同定した）

Influenza A viruses (IAV) and B (IBV) viruses are mainly seasonal epidemics disease viruses. Two IAV subtypes, subtypes H5 and H7, possess high pathogenicity with the potential to cause severe disease and high mortality in infected animals. Although the IAV H5N1 is poorly transmissible from avian-human and human-human, an uncommon mutation (T271A) of the viral RNA-dependent RNA polymerase (RdRp) subunit PB2 gene was reported to increase the viral infectivity and, infection of avian IAV H5N1 among mammals are reported in mink farm. Baloxavir marboxil has been approved by the U.S. Food and Drug Administration (FDA) as an antiviral drug for influenza. Whereas the recent clinical studies found that IAV carrying an I38T mutation in the viral RdRp subunit PA showed resistance to baloxavir marboxil. The degree applicant has therefore screened a Phase II Drop compound library by using a RdRp assay system derived from H5N1 IAV including a drug-resistant PA mutant (I38T) and a viral polymerase activity enhancing PB2 mutant (T271A) to explore potential antiviral compounds.

As a result, the following findings were identified in this study:

1) Vidofludimus was identified as a potent inhibitor of the influenza virus by screening of compound library using an RdRp assay system.
2) Vidofludimus could maintain high antiviral activity even when the RdRp carried both mutations (PA I38T, PB2 T271A).
3) Vidofludimus prevented IAV replication/transcription by inhibition of dihydroorotate dehydrogenase (DHODH).
4) The RdRp assay system could reflect the results of antiviral activities evaluated by the natural infection of IAV H1N1.
5) Vidofludimus also showed antiviral activity against another type of influenza virus, B/Yamagata/16/1988 (IBV).

The antiviral activity of vidofludimus shown in this study for IAV H1N1, H5N1 and IBV might also be employed for the other types/subtypes of influenza viruses and other RNA viruses.

In the present study, the degree applicant constructed a plasmid-mediated cell-based assay system for IAV H5N1 vRNA replication/transcription inhibitors. Using this RdRp assay system, he found a potential antiviral, vidofludimus, for influenza virus wild-type and mutation-type. The study is therefore judged to be of sufficient value as a dissertation.