

**Highly pathogenic Influenza virus A H5N1 Indonesia & Vietnam Hemagglutinin (HA1) contains an urokinase-plasminogen activator explaining the fibrinolysis**

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Avian Influenza is compared to a chicken lethal Ebola for its internal hemorrhagic symptoms. Oseltamivir is inefficient and not recommended in hemorrhagic influenza. In 1996, Zhilinskaia IN (Vopr Virusol) found by computer analysis a similarity between Influenza virus hemagglutinin HA and plasminogen activator (PA), explaining the fibrinolysis. We analysed further these results in Influenza virus A H5N1 Indonesia (83% mortality) and Vietnam HA1. We compared to urokinase (U-PA), tissue PA, TSV-PA, Batroxobin. Results : All the 3 active site residues of serine protease (His, Asp, Ser) were found and the best match was with U-PA :

H5N1 Indonesia/Vietnam

IPKSS-W--S-SH

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U-PA/t-PA active site His ILISScWviSaTH

H5N1 Indonesia/Vietnam G I HHpNDAAEQTK

U-PA/t-PA active site Asp (A,L)HH NDI ALQ IR

H5N1 Vietnam KGDS- - TIMKS(L,E)EYGNCNTKCQTPMGA I

U-PA/t-PA active site Ser QGDSggPLVcS L Q WIRSHTKGEE- NG(A,L)

H5N1 Indonesia/Vietnam 141-YLGKSSF(R,F)N-150

U-PA YLGR-S(L,R)L N

Conversely, Influenza H7 China HA1 has His replaced by Arg, Asp replaced by Ser. The motif His-Phe (HF), in the pocket binding Plasminogen clivage site Arg-Ala-Arg, was present in Influenza H5N1 and U-PA (319-HF-320); but not in Influenza virus H7 China, replaced by Gly-Gly (inactive). Conclusion : The plasminogen activator in avian Influenza virus H5N1 hemagglutinin HA1 ( Zhilinskaia ) was confirmed and may explain fibrinolysis in hemorrhagic Influenza. It seems rationale to use plasminogen inhibitors to block this fibrinolysis. A peptidomimetic drug of the plasminogen Arg-Ala-Arg (RAR) at the cleavage site Arg / Ala can be designed by docking. This strategy was successful in HIV-1 tritherapy, with FP peptidomimetics.