HOKKAIDO UNIVERSITY

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The titles of thesis and other information are as follows:

Studies on the pathogenicity and vaccine development of H5N1 highly pathogenic avian influenza virus strains.

Norikazu Isoda

Laboratory of Microbiology, Department of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan

Since 1997, outbreaks of highly pathogenic avian influenza caused by H5N1 viruses have occurred. In the present study, pathogenicity of two H5N1 HPAI virus strains, A/chicken/Yamaguchi/7/2004 (H5N1) (Ck/Yamaguchi/04), which was isolated from a dead chicken during the first outbreak in Japan, and A/whooper swan/Mongolia/3/2005 (H5N1) (Swan/Mongolia/05), which was isolated from a dead whooper swan which had found at the lake Erhel nuur, Mongolia, was assessed in avian species and mammalians by experimental infection study.

Ck/Yamaguchi/04 (H5N1) was highly pathogenic to the birds and cause systemic infection, including the brain. On the other hand, mice were susceptible to infection with Ck/Yamaguchi/04 (H5 N1) but with a mild pathogenicity. In contrast, miniature pigs were not susceptible to Ck/Yamaguchi/04 (H5N1). Swan/Mongolia/03 (H5N1) was highly pathogenic to ducklings and mice and infected to miniature pigs. These results indicated that the pathogenicity of Swan/Mongolia/05 (H5N1) was higher than that of Ck/Yamaguchi/04 (H5N1) in avian species and mammalians. The susceptibility of pigs to Swan/Mongolia/03 (H5N1) was confirmed, indicating that the possibility of genetic reassortments with this strain in pigs is a concern.

Inactivated avian influenza vaccine with high efficacy prepared from a non-pathogenic H5N1 virus was developed and potency of it was evaluated by animal experiments. Although, "stamping-out" is the basic measure for the control of HPAI, vaccination may be an optional measure in cases where the disease spread widely. In the present study, a non-pathogenic H5N1 reassortant influenza virus with high proliferation in embryonated chicken eggs was generated between A/duck/Mongolia/54/01 (H5N2) and A/duck/Mongolia/47/01 (H7N1) strains which were isolated from the migratory ducks in Asia. High titers of antibody were induced in the chickens injected with inactivated vaccine prepared from A/duck/Hokkaido/Vac-1/2004 (H5N1) three weeks post vaccination and then all the vaccinated chickens survived without showing any disease signs after challenge either with Ck/Yamaguchi/04 (H5N1) or with Swan/Mongolia/05 (H5N1). All 3 chickens challenged on 6 days post vaccination, died, whereas 3 chickens challenged on 8 days post vaccination survived. These results indicate that the present vaccine confers clinical protection and reduction of virus shedding against highly pathogenic avian influenza virus challenges and should be useful as an optional tool in the emergency case.

Original Papers of this thesis appeared in *Arch. Virol.,* **151**: 1267-1279 (2006) and *Arch. Virol.,* **153**: 1685-1692 (2008).