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学位論文内容の要旨
Abstract of the dissertation

博士の専攻分野の名称：博士（感染症学）

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学位論文題名
The title of the doctoral dissertation

Seroepidemiological study for bat- and shrew-borne hantaviruses and analysis of renal pathology in hantavirus-infected mouse model simulating hemorrhagic fever with renal syndrome

（コウモリおよびトガリネズミ由来ハンタウイルスの血清疫学および腎症候性出血熱マウスモデルの腎病理学的解析）

Hantavirus was first isolated in 1976 and reported in 1977 by Lee, Ho Wang, et al, 1982 as a causative agent of rodent-borne zoonoses, causing hemorrhagic fever with renal syndrome (HFRS). HFRS and Hantavirus Pulmonary Syndrome (HPS) are the two main known diseases associated with hantaviruses. Apart from the classical disease-causing rodent-borne hantaviruses such as Hantaan and Sin Nombre viruses, numerous species of hantaviruses of shrews and bats have also been reported. The infectivity and pathogenicity of these viruses in humans are unknown. This thesis examines the seroepidemiology of bat- and shrew-borne hantaviruses and investigates the renal pathology of hantavirus infections using a mouse model that simulates hemorrhagic fever with renal syndrome (HFRS). The study is divided into three interconnected chapters, each addressing critical gaps in understanding these emerging zoonotic pathogens.

A novel seroepidemiological tool was developed to detect antibodies against five bat-borne (Brno virus; BRNV, Dakrong virus; DKGV, Quezon virus; QZNV, Robina virus; ROBV, Xuan Son virus; XSV) and six shrew-borne (Asama virus; ASAV, Altai virus; ALTV, Cao Bang virus; CBNV, Nava virus; NVAV, Seewis virus; SWSV, Thottapalayam virus; TPMV) hantaviruses. The tool demonstrated minimal cross-reactivity, except between phylogenetically related viruses like QZNV and ROBV. Screening 1,764 bat serum samples from Zambia revealed seropositivity rates of 11.4% for bat-borne and 17.4% for shrew-borne hantaviruses, with fruit bats (*Eidolon helvum*, *Rousettus aegyptiacus*) showing the highest exposure. In fruit bats, the antibody prevalence was high for multiple antigens, including BRNV, QZNV, ASAV, ALTV, and TPMV, but no positivity was observed for NVAV or SWSV antigens. These findings suggest cross-species transmission or unidentified reservoir hosts in Africa.

The serological tool was used to analyze human sera from Sri Lanka to detect antibodies against bat- and shrew-borne hantaviruses in febrile patients (n=168) and healthy individuals (n=168). Notably, 31 sera were positive for shrew-borne viruses, while 12 reacted to bat-borne antigens, with higher seropositivity in febrile individuals compared to healthy controls. Analysis using individual antigens revealed high

antibody prevalence to QZNV, ASAV, and CBNV antigens, whereas no positivity was observed to BRNV, DKGV, or NVAV antigens. The presence of antibodies to these viruses suggests zoonotic transmission, warranting further investigation into their pathogenicity and reservoir hosts.

The renal pathology of HFRS was examined using a mouse model infected with the Hantaan virus strain, Korean hemorrhagic fever virus clone 5 (KHFV). The study documented weight loss, oliguria, hematuria, and albuminuria, peaking at 7 days post-infection (dpi). Prophylactic and therapeutic administration of the neutralizing monoclonal antibody HCO2 significantly reduced disease severity, viral load, and histopathological damage, highlighting its potential for HFRS treatment.

Collectively, this research advances the understanding of hantavirus ecology, pathogenesis, and zoonotic potential, providing essential tools for surveillance and therapeutic development. The findings underscore the need for expanded studies on emerging hantaviruses to mitigate their public health risks.