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| Author(s)           | Kesdangakonwut, Sawang                                                                                                                                                      |
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## 学位論文内容の要旨

博士の専攻分野の名称：博士（獣医学）

氏名：Sawang Kesdangsakonwut

### 学位論文題名

Treatment of rabies by intrathecal immunization and pathogenesis of myocardial necrosis  
in rabid rabbits

(鞘内免疫による狂犬病の治療と狂犬病発症ウサギに見られた心筋症の病理発生)

Rabies is a fatal zoonotic disease for which no effective treatment measures are currently available. However, pre- and post-exposure prophylaxes are empowered to control the rabies. Previously, humoral and cellular immunities are orchestrated in RABV clearance from the CNS and recovery in rabies patients and animal. In addition, we previously described that SC immunization prior to IT immunization induced a more rapid and higher antibody response in the CSF than IT immunization alone. The VNA, which is crucial in RABV clearance, is originated both from serum and de novo locally produced in CNS. We considered that SC immunization prior to IT immunization might be applicable in rabid animal. In this study, we apply SC immunization prior to IT immunization to treat the experimentally induced rabies rabbits and also described the neurogenic cardiomyopathy in rabid rabbits as seen in rabid patients.

In the first experiment, the rabbits exhibited neuromuscular symptoms of rabies within 4-8 dpi of RABV inoculation. All of the rabbits died within 8-12 dpi with the exception of one rabbit in the SC group and all four rabbits in SC/IT group, which recovered and started to respond to external stimuli and eat and drink by hand feeding at 11-18 dpi and survived until the end of the experimental period. RABV was eliminated from the CNS of the surviving rabbits. Humoral and cellular immunities were involved in RABV clearance and recovery. We report here a possible, though still incomplete, therapy for rabies using IT immunization in animal previously received SC immunization. Our protocol may rescue the life of rabid patients and prompt the future development of novel therapies against rabies.

In the second experiment, experimentally induced rabies, which had brain lesions, showed myocardial lesions and the severity of the cardiac lesions was proportional to that of the brain lesions. Rabies virus antigen was not found in the hearts of any rabbits. Neither the frequency nor the cumulative

dose of anesthesia was related to the incidence or the severity of the myocardial lesions. The myocardial lesions were consisted with the neurogenic cardiomyopathy in human being. The rabies- induced brain lesions were most prominent in the brain, which controlled the heart function and autonomic nervous system. Take together, the myocardial lesions were classified as neurogenic cardiomyopathy.

In conclusion, our IT immunization protocol can be applicable to treat rabies animal previously received SC immunization when the rabies signs occurred. However, neuronal complication is still the obstacle for this protocol. Furthermore, neurogenic cardiomyopathy should be considered and treated in rabies patients. Finally, we purposed that our protocol might be rescue the life of rabid patients and prompt the future development of novel therapies against rabies.