Therapeutic Potential of an Anti-High Mobility Group Box 1 Monoclonal Antibody in Epilepsy

Junli Zhao¹, Yi Wang¹, Cenglin Xu¹, Keyue Liu², Ying Wang¹, Liying Chen¹, Xiaohua Wu³, Feng Gao³, Yi Guo³, Junming Zhu³, Shuang Wang³, Masahiro Nishibori² and Zhong Chen¹,³*

¹Department of Pharmacology, Key Laboratory of Medical Neurobiology of the Ministry of Health of China, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China.

²Department of Pharmacology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

³Epilepsy Center, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

*Corresponding author: Professor Zhong Chen
E-mail address: chenzhong@zju.edu.cn (Z. Chen)

Abstract: Objective Brain inflammation is a major factor in epilepsy, and the high mobility group box-1 (HMGB1) protein is known to contribute significantly to the generation of seizures. Here, we investigated the therapeutic potential of an anti-HMGB1 monoclonal antibody (mAb) in epilepsy. Methods Anti-HMGB1 mAb or control mAb was injected intraperitoneally and their anti-epileptic effect was tested in different kinds of mouse epilepsy models and human epilepsy sample. The anti-epileptic effect of mAb was also evaluated in TLR4 mutant mice. Results Anti-HMGB1 mAb attenuated both acute seizure models (maximal electroshock seizure pentylenetetrazole-induced and kindling-induced), and chronic epilepsy model (kainic acid-induced) in a dose-dependent manner. Meanwhile, the anti-HMGB1 mAb also attenuated seizure activities of human brain slices obtained from surgical resection from drug-resistant epilepsy patients. The mAb showed an anti-seizure effect with a long-term manner and appeared to be minimal side effects at even very high dose (no disrupted physical EEG rhythm and no impaired basic physical functions, such as body growth rate and thermoregulation). This anti-seizure effect of mAb results from its inhibition of translocated HMGB1 from nuclei following seizures, and the anti-seizure effect was absent in toll-like receptor 4 knockout (TLR4⁻/⁻) mice. Interestingly, the anti-HMGB1 mAb also showed a disease-modifying anti-epileptogenic effect on epileptogenesis after status epileptics, which is indicated by reducing seizure
frequency and improving the impaired cognitive function. **Conclusion** These results indicate that the anti-HMGB1 mAb should be viewed as a very promising approach for the development of novel therapies to treat refractory epilepsy.

**Keywords:** Epilepsy; Monoclonal Antibody; HMGB1