1. **No.**

   FP01807099

2. **Title**

   Strategy for Nicotine Analgesia using Spinal Neuroplasticity in Chronic Pain

3. **Period**

   2016-2018

4. **Summary**

Chronic pain, often originating from peripheral nerve injury, has a significant negative impact on life quality and productivity of those who affected as well as the cost of health care. Noradrenergic descending pathway is not only important to endogenous analgesia but also many drugs approved to treat chronic pain, such as noradrenaline-reuptake inhibitors and gabapentinoids, suggesting clinical significance of this pathway. The current study clarified the role of descending noradrenergic inhibition for analgesia from activation of α4β2 nicotinic receptors, by demonstrating that α4β2 nicotinic receptor agonists increases neuronal activity of the locus coeruleus and subsequently induces noradrenaline release in the spinal cord, leading antinociceptive and antihypersensitivity effects in animals with acute and chronic pain. Orally administered novel α4β2 nicotinic receptor agonist Cris-104 produced antihypersensitivity effects within 10 min, much faster than existing drugs which utilize descending noradrenergic inhibition to reduce chronic pain. In addition, the antihypersensitivity effect of Cris-104 can be strongly potentiated by the co-administered cholinesterase inhibitor donepezil, possibly due to noradrenergic-cholinergic neuronal plasticity in the spinal cord after peripheral nerve injury. The combination of Cris-104 and donepezil should be tested as a potential strategy to treat chronic pain.