Form 2-4-2

Japan-U.S. Brain Research Cooperation Program
Group Joint Study Project Program FY2015- FY2017: Report

Field: Neurobiology of Disease

1. Principal Researcher
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2. Project Title: Generation and study of a novel ASD model animal by gene manipulation in highly social Prairie vole

3. Japanese Group
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4. U.S. Group
Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
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5. Research Period, from/to (mm/dd/yyyy) and total number of years.
4/1/2015 to 3/31/2018., 3 years

6. Abstract, Results, and Research Significance (300 words):
Among the subsequent project of this collaborative research project, No.1 and No.2 has been successfully achieved, with the establishment of reproductive technology in Prairie Vole species (Horie, K., et al., (2015) *B.B.R.C.463*(4), 907–911), and the development of OXTR(-/-) Prairie Vole, and V1aR(-/-) Prairie Vole (paper in submission). In addition, based on this successful result, the Japanese group (PI, Katsuhiko Nishimori) will receive grant money from NIMH, NIH, US government, as a sub contract of Professor Larry J Young, Emory University, for 5 years.
Moreover, behavioral and physiological study using newly obtained OXTR(-/-) Prairie Vole, showed behavioral impairment in social memory (three chamber test), obsessive behavior (marble burry test), and

allogrooming behavior (empathy consolation behavior), resembled the core symptom-like behaviors observed with Autistic Spectrum Disorders patients. This result strongly suggests that highly social Prairie Vole has a great potential as an experimental resource in the pathophysiological study of ASD, and in the drug discovery to cure core symptom in ASD.
As for subsequent project 3, the humanization of Prairie Vole, by substituting the Oxtr and V1aR genes in Prairie Vole by human Oxtr and V1aR genes, and translational study of pharmacological screening for human Oxtr agonists, using OXTR(-/-) Prairie Vole as behaviorally pharmacological resource, the project is still on going, but hasn't achieved yet, because of limited space for feeding Prairie Vole pairs, and their low-level ability to produce fertilized or unfertilized eggs.
In comparison to mice or rats, Prairie Vole has higher leveled prosocial behaviors, such as higher parental behavior, pair bonding behaviors, empathy•consolation behavior and so on. Newly developed Prairie Vole, harboring genetic mutations such as lacking of Oxtr gene, originally observed as a causal mutation in human ASD patients, may have a great potential for us to study the pathophysiological mechanism of ASD by using those animals. We've already confirmed that OXTR(-/-) Prairie Vole showed serious-leveled impairment in empathy behavior, in comparison with wt. Prairie Vole. This physiological analysis indicates that gene-manipulated Prairie Voles has also great potential for us to develop new anti-ASD drugs and achieve behaviorally pharmacological analysis of those drug candidates. We've successfully achieved the first step to create new anti-ASD drug discovery platform.

7. Other (Research-related concerns, particular points of note):

*Please attach any reference materials as necessary.