【Grant-in-Aid for Specially Promoted Research】

Science and Engineering (Chemistry)

# Title of Project : Chemical Biology Studies on Trinucleotide Repeat Disease using Repeat-Binding Molecules

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Research Area : Chemical Biology
Keyword : In vivo functional expression, chemical probes, hereditary diseases, toxic RNA

## 【Purpose and Background of the Research】

Huntington disease and Fragile X syndrome are classified as neurological disorders so called trinucleotide repeat diseases. Other well-known trinucleotide repeat disease is Myotonic Dystrophy caused by the expansion of d(CTG) repeat. Because these trinucleotide diseases are genetic disorders, there is no way of treatment for complete cure. Thus, it is extremely important to keep or improve the "Quality of Life" of patients. With these molecules specifically bind to the d(CAG)n and d(CGG)n repeats relating neurological disorders in hand, we were eagerly looked for the opportunities of collaborative research with researchers and medical doctors who are studying in the field of neurological disorders in order to make use of our molecules for any possible ways to contribute to keep the QOL of patients.

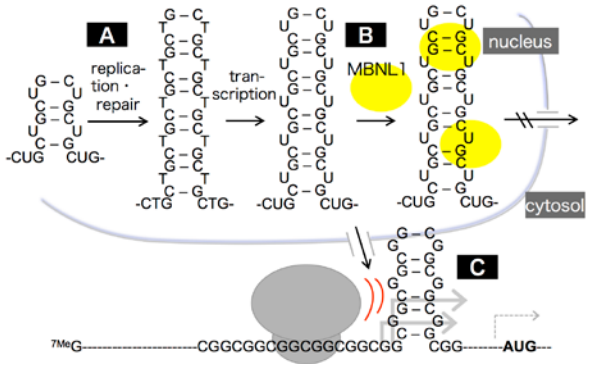


Figure 1. Three stages related the onset of trinucleotide repeat diseases. A) Repeat instability on replication and repair, B) Secretion of nuclear protein by toxic RNA, C) RAN Translation

## 【Research Methods】

Our research methods are as follows: 1) Elucidation of molecular mechanism of repeat instability (expansion and contraction) in cell. We study the structure optimization of probe to minimize the cytotoxic activity, and investigate new molecules specifically binding d(CTG) repeat. 2) Sequestration of toxic RNA. Molecules binding to r(CGG)n and r(CUG)n repeats are expected to sequester these toxic RNA from MBNL1. 3) Elucidation of molecular mechanism and method to modulate RAN (Repeat Associated Non-AUG) translation. Our probe molecules will be useful for the deeper understanding of RAN translation.

## 【Expected Research Achievements and Scientific Significance】

The importance of our proposed research is that the research will provide the deeper understanding of the trinucleotide repeat disorders, which will be indispensable for the more accurate diagnosis and adequate suggestion on the genetic inquiry. In addition, the research may provide with the novel molecules that interfere with the expansion of trinucleotide repeats during aging. For the patients and people before the onset, it is ideal to contract the expanded repeat, which results in preventing aggravation of disease conditions and onset of disease. Thus, molecules effectively suppress the repeat expansion and/or contract the expanded repeat is quite important for the QOL of patients.

## 【Publications Relevant to the Project】

1) Nakatani, K. et al. Small-molecule ligand induces nucleotide flipping in (CAG)n trinucleotide repeats, *Nature Chemical Biology* **2005**, *1*, 39−43.
2) Hagihara, M.; He, H.; Kimura, M.; Nakatani, K. A Small Molecule Regulates Hairpin Structures in d(CGG) Trinucleotide Repeats. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2000-2003.

## 【Term of Project】

FY2014-2018

## 【Budget Allocation】

303,404 Thousand Yen

## 【Homepage Address and Other Contact Information】

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