【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Complex Systems)

Title of Project : Therapeutic Drug Discovery and Elucidation of RNA Disease Pathogenesis by Use of CRISPR-Based Disease iPS Cells and Animal Models

Masatoshi Hagiwara
(Kyoto University, Graduate School of Medicine, Professor)

Research Project Number : 15H05721 Researcher Number : 10208423
Research Area : Chemical biology
Keyword : Postgenomic drug discovery, CRISPR, iPS, Splicing

【Purpose and Background of the Research】

RNA is vulnerable to intervention due to its characteristics as a mediator of genetic information. RNA is more extensively and dynamically regulated by modification and processing compared to DNA, where genetic information is stored. Many RNA-binding proteins etc. are involved in RNA processing, and abnormalities in this process cause disease (RNA disease). In this project, we aim to determine the "compound intervening splicing rules" from transcriptome data of cells treated with lead chemical compounds. Using RNA disease model iPS cells and animal models constructed by CRISPR-Cas9, we wish to establish a novel field of chemical biology where postgenomic drugs to RNA disease are generated.

【Research Methods】

In this project, we will follow five steps (Figure 1) to reach our goal. 1) Elucidating "intervening rules" of each splicing intervening compound, 2) Categorizing "abnormal splice codes" of each RNA disease. 3) Matching each RNA disease with appropriate splicing intervening compound and 4) Structure optimization of the compound. We will use a splicing reporter and feedback the information for further optimization of the compound. 5) Using RNA disease model iPS cells and models animals constructed by CRISPR-Cas9, we will verify, secondary screen, and test the efficacy of the compounds to evaluate the effectiveness to RNA disease at whole-body level.

【Expected Research Achievements and Scientific Significance】

This project is completely original from two points of view. First, establishing "intervening rules" of splicing intervening compounds will make it possible to efficiently seek compounds that correct aberrant splicing of RNA diseases with no cure at the moment. Second, using phenotypically relevant RNA disease models of iPS cells and animals constructed by CRISPR/Cas9 in order to verify and optimize structure will help identify compounds closer to clinical application.

We believe this project will develop a new field of chemical biology where genetic diseases are treated by chemical compounds.

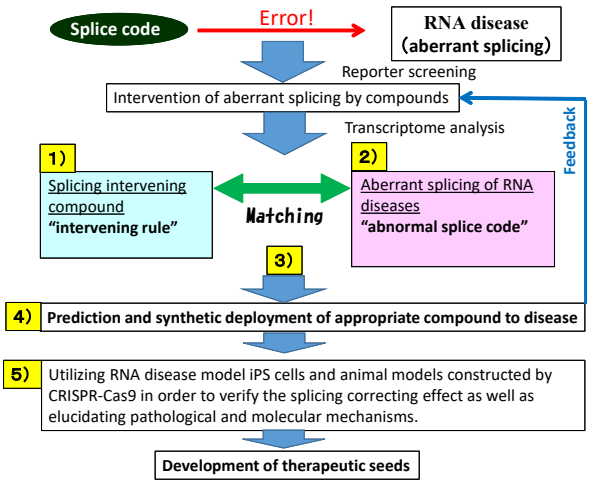

Figure: Matching "splicing intervening compound" and "RNA disease"

【Publications Relevant to the Project】

・Ohe K and Hagiwara M. Modulation of alternative splicing with chemical compounds in new therapeutics for human diseases. ACS Chem. Biol. 10(4):914-924, 2015.

・Yoshida M, Kataoka N, Miyauchi K, Ohe K, Iida K, Yoshida S, Nojima T, Okuno Y, Onogi H, Usui T, Takeuchi A, Hosoya T, Suzuki T, Hagiwara M. Rectifier of aberrant mRNA splicing recovers tRNA modification in familial dysautonomia. Proc Natl Acad Sci U S A. 112(9):2764-2769, 2015.

・Nishida A, Kataoka N, Takeshima Y, Yagi M, Awano, H, Ota, M, Itoh K, Hagiwara M, and Matsuo M. Chemical treatment enhances skipping of a mutated exon in the dystrophin gene. Nature Commun 2, 308, 2011.

【Term of Project】 FY2015-2019

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.anat1dadb.med.kyoto-u.ac.jp/Anat1DADB/TOP.html