The collaboration research for the Dual Graduate School between VNU and JAIST

[Title of collaboration research]: Therapeutic approach for hereditary diseases by genetic modification.

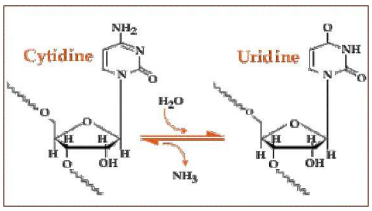
[The members of collaboration research]: Toshifumi Tsukahara

[Reference home-page address]: http://www.jaist.ac.jp/nmcenter/labs/tsukahara-www/

[Other references]: K. Fushimi, N. Osumi, T Tsukahara: NSSRs/TASRs/SRp38s function as splicing modulators via binding to pre-mRNAs. *Genes Cells* (2005) **10**, 531-541.

A. Nagano, R. Koga, M. Ogawa, Y. Kurano, S. Kawada, R. Okada, YK. Hayashi, T. Tsukahara, K. Arahata: Emerin deficiency at the nuclear membrane in patients with Emery-Dreifuss muscular dystrophy. *Nature Genet.* (1996) **12**, 254-259.

[Contents] A number of genetic diseases, called monogenic disorders, are due to the change of a single gene, resulting in an enzyme or other protein not being produced or having altered functionality. The change can be trivial and relatively harmless in its effects. There are little therapeutic approaches except gene therapy in most of genetic diseases. Gene correction, by which a mutated gene is converted to one with the normal (or desired) sequence, is an attractive strategy for gene therapy. The corrected genes should be properly expressed under the control of their natural regulatory elements. Moreover, gain-of-function or predominant mutations, such as activated oncogenes, could be suitable subjects for the gene correction strategy.



Chemical deamination is one of approach for the gene correction. Hydrolytic deamination of cytidine leads to uridine. Therefore, if the deamination could be rationally directed to mutated sequences, genetic diseases caused by certain base substitutions could be treated. We are trying to do site-directed deaminations, on mutated genes by using the template-directed photoligation of oligo-deoxynucleotides (ODNs).

Leigh syndrome is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system, meaning that it gradually loses its ability to function properly. The disorder usually occurs in three stages, the first between eight and 12 months involving vomiting and failure to thrive, the second in infancy, characterized by loss of motor ability, eye problems and respiratory irregularity. The third stage occurs between two and 10 years of age and is characterized by hypotonia and feeding difficulties. Evidence exists that Leigh syndrome may be inherited in some cases from the mother as a DNA mutation inside mitochondria. Mitochondria control the production of cellular energy and carry the genetic code for this process inside their own special DNA. The specific mutation in the ATPase 6 gene; mtDNA8993T→C, is thought to be responsible for some cases of Leigh syndrome. If mutated C could be converted to U by site-specific deamination, the repaired mRNA may work and symptoms of the syndrome may be mitigated.

We have already obtained cells from the patient of Leigh syndrome with mtDNA8993T→C. In this study, we are trying to do the site-specific mutagenesis in mRNA of the ATPase 6 gene *in vivo* by using specific ODN with a photo reactive end group. (Collaboration with Fujimoto,s Lab in JAIST)