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

Biological Sciences (Medicine, dentistry, and pharmacy)

# Title of Project : The elucidation of the carcinogenic mechanism of the Down's syndrome using chromosome engineering technology

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Research Area : Medicine and pharmacy, Clinical internal medicine, Pediatrics
Keyword : Child hematology, Chromosome engineering

## 【Purpose and Background of the Research】

Down's syndrome is a congenital disease caused by trisomy 21, and shows various phenotypes, such as leukemia, a cardiac anomaly, and mental reterdation. Somatic mutations in exon 2 of the transcription factor GATA1 gene have been detected in essentially all Down syndrome megakaryocytic leukemia (AMKL) and transient myeloproliferative disorder (TMD) cases. This is the most specific genetic abnormality other than trisomy 21 in DS-AMKL cases and is likely linked to the estimated 500-fold higher risk of DS children to develop AMKL compared with non-DS-children. N-terminus-deleted protein, GATA1s, is expressed in DS-AMLK patients. Moreover, since GATA1 mutation is not seen in the non-Down syndrome child's AMKL, both of the trisomy 21 and GATA1 mutation are considered to be an essential condition of DS-AMKL development. At present, following questions have not been elucidated "why GATA1 mutation is induced at high frequency by the trisomy 21", and "what is some causative genes on human chromosome 21 which causes DS-AMKL?". Down's syndrome model cells and a model animal are needed to understand the DS-AMKL development and to perform an effective therapy and medicinal development. The purpose of this research is to elucidate the mechanism of DS-AMLK development by using a new Down's syndrome model mouse and a model human embryonic stem cell, which are generated by the unique chromosomal engineering technology.

## 【Research Methods】

In order to solve the mechanism of DS-AMKL development, model animal and cell are produced by the following three steps using mice and human embryonic stem cells. (1) We construct various human chromosome 21 fragments using chromosome engineering technology. (2) We introduce the human chromosomal fragments into normal or GATA1s mice, identify the region on human chromosome 21 related to the phenotype, and identify the genes on the human chromosome 21 via knock out of specific genes on human chromosome 21. (3) We transfer the human chromosome fragments into human ES cells, and identify the genes on the human chromosome 21 using hematopoietic differentiation system.

## 【Expected Research Achievements and Scientific Significance】

Human and mouse artificial chromosomes used in this study have several advantages as gene therapy vectors, including stable episomal maintenance, and the ability to carry large gene inserts. Thus, model mice and cells generated by the chromosomal vectors will be useful tools to overcome the previous problems.

This research gives us the opportunity to understand not only DS-AMKL developmental mechanism, but also an adult cancer developmental mechanism including the rele of chromosome aneuploidy. Thus, it is expected to contribute the drug development of the disease in the future.

## 【Publications Relevant to the Project】

・Takiguchi M, Kazuki Y, Hiramatsu K, Abe S, Iida Y, Takehara S, Nishida T, Ohbayashi T, Wakayama T, Oshimura M. (2012 Nov) A Novel and Stable Mouse Artificial Chromosome Vector. ***ACS Synth. Biol.*** doi.org/10.1021/sb3000723

・ Shinohara T, Tomizuka K, Miyabara S, Takehara S, Kazuki Y, Inoue J, Katoh M, Nakane H, Iino A, Ohguma A, Ikegami S, Inokuchi K, Ishida I, Reeves RH and Oshimura M (2001 May) Mice containing a human chromosome 21 model behavioral impairment and cardiac anomalies of Down syndrome. ***Human Molecular Genetics*** , volume:10, number:11, 1163-1175

## 【Term of Project】 FY2013-2017

## 【Budget Allocation】 161, 800 Thousand Yen

## 【Homepage Address and Other Contact Information】

http://www.med.tottori-u.ac.jp/chromosome/