# Research Center for Medical Sciences
# Core Research Facilities for Basic Science
# (Division of Molecular Genetics)

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## General Summary

We can now analyze a person's whole genome. These technological developments have started a new era of medicine. The etiology and therapy of disease will be studied on the basis of genetics. As physicians of today, our research fields are the epigenetic control of cancers and neurodegenerative disorders. Gene therapy has become an attractive procedure to cure diseases. We contribute to gene therapy through the development of regulation of gene-expression and genome editing.
Our division plays a role in supporting various research studies. We served more than 8,000 sequence analysis. The management of the cell sorter and the next-generation sequencer were satisfactory.

## Research Activities

*Molecular pharmacology of anticancer agents*
Ample evidences indicate that epigenetic dysfunctions play an important role in leukemogenesis. We previously showed that targeting bromodomain and extra-terminal (BET) family proteins had shown therapeutic efficacy in diverse hematologic malignancies and solid cancers. However, treatment with BET inhibitors induces various resistance responses, the resistance mechanism remains poorly understood. We established I-BET151-resistant U937 cells (U937R) and compared the characterization of these cells. Treatment with I-BET151 induced a growth inhibition and apoptosis in U937 cells, but not in U937R cells. The drug sensitivity test showed that IKK inhibitor VII had significant higher sensitivity in U937R cells than in U937 cells. BRD2, BRD4, and nuclear NFkapperB were higher expressions in U937R cells. These findings suggested resistance for I-BET151 in U937R cells might be related to the constitutive activation of NFkapperB signaling pathway via increased expressions of both BRD2 and BRD4. Targeting the NFkapperB signaling pathway could be effective therapeutic strategy to restore the sensitivity.

*Development of the adenovirus vector systems*
Because the adenovirus vector (AdV) is an attractive tool for gene expression and for the regulation of gene expression, it is applied to many areas of research. It is well known that the AdV is useful tool to transduce the purpose gene in hepatocytes. We develop a protocol for cure of hepatitis B virus (HBV) using AdV. In culture cells, the efficiency of HBV genome replication is poor. Therefore, we established the efficient genome replica-

tion of HBV applying AdVs (HBV103-AdV system). The HBV103-AdV-mediated HBV replication was easy and detected the replicated HBV genome in primary hepatocytes as well as in HepG2 cells. And also we were able to show that this system was useful for high-throughput screening of new anti-HBV drugs. Now we develop the completely HBV genome exclusion protocol using genome editing.

We also researched the efficient differentiation and enrichment methods to neural cells from induced pluripotent stem cells. We constructed 22 AdVs for this purpose. These AdV systems may contribute to the analysis of the cause of the neurologic disease.

## Publications

***Shinagawa S, Kobayashi N, Nagata T, Kusaka A, Yamada H, Kondo K, Nakayama K.*** DNA methylation in the NCAPH2/LMF2 promoter region is associated with hippocampal atrophy in Alzheimer's disease and amnesic mild cognitive impairment patients. *Neurosci Lett.* 2016 Aug 26; **629:** 33-7.

***Suzuki A[1], Shibata N[1], Kasanuki K[1], Nagata T, Shinagawa S, Kobayashi N, Ohnuma T[1], Takeshita Y[1], Kawai E[1], Takayama T[1], Nishioka K[1], Motoi Y[1], Hattori N[1], Nakayama K, Yamada H, Arai H[1] ([1]Juntendo Univ).*** Genetic Association between Presenilin 2 Polymorphisms and Alzheimer's Disease and Dementia of Lewy Body Type in a Japanese Population. *Dement Geriatr Cogn Dis Extra.* 2016 Mar 16; **6:** 90-7.

***Suzuki K[1], Yamamoto K[1], Arakawa Y, Yamada H, Aiba K, Kitagawa M[1] ([1]Juntendo Univ).*** Anti-myeloma activity of bromodomain inhibitors on the human myeloma cell line U266 by downregulation of MYCL. *Anticancer Drugs.* 2016 Sep; **27:** 756-65.

***Takeshita Y[1], Shibata N[1], Kasanuki K[1], Nagata T, Shinagawa S, Kobayashi N, Ohnuma T[1], Suzuki A[1], Kawai E[1], Takayama T[1], Nishioka K[1], Motoi Y[1], Hattori N[1], Nakayama K, Yamada H, Arai H[1] ([1]Juntendo Univ).*** Genetic association between RAGE polymorphisms and Alzheimer's disease and Lewy body dementias in a Japanese cohort: a case-control study. *Int J Geriatr Psychiatr.* Epub 2016 Oct 4.

***Kobayashi N, Shinagawa S, Nagata T, Shimada K, Shibata N[1], Ohnuma T[1], Kasanuki K[1], Arai H[1] ([1]Juntendo Univ), Yamada H, Nakayama K, Kondo K.*** Usefulness of DNA Methylation Levels in COASY and SPINT1 Gene Promoter Regions as Biomarkers in Diagnosis of Alzheimer's Disease and Amnestic Mild Cognitive Impairment. *PLoS One.* 2016 Dec 19; **11:** e0168816.

***Suzuki M[1], Kondo S[1], Yamasaki M[2], Matsuda N[2], Nomoto A[2], Suzuki T[3], Saito I[1], Kanegae Y ([1]Tokyo Univ) ([2]Institute of Microbial Chemistry) ([3]Hamamatsu University School of Medicine).*** Efficient genome replication of hepatitis B virus using adenovirus vector: a compact pregenomic RNA-expression unit. *Sci Rep.* 2017; **7:** 41851.