# 学位論文の要約

題目　Genetic Knowledge-based Artificial Control over Neurogenesis in Human Cells Using Synthetic Transcription Factor Mimics

（転写因子を模倣した合成分子による、遺伝子塩基配列情報に基づく神経発生制御に関する研究）

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序論

Epigenetic mechanism control gene expression without alteration in DNA sequence. Chromatin structure changes the histone affinity to the related DNA, and also change the accessibility of transcription factors and RNA polymerase packages to chromatin. Through this 3-D structure modification, gene transcription can be changed in activation or repression.

The mainly epigenetic control mechanism is as the following 4 methods in the organism, that is DNA methylation, histone modification by methylation or acylation, chromatin remodeling and non-conding RNAs. Epigenetic function in neural genesis, especially the histone modification in neural differentiation's function has also been well clarified. HAT and HDAC have played important roles in this processes, therefore, controlling the specific gene acylation or deacylacation in neural processes may contribute to the neural differentiation. Our gene switcher small moleculars SAHA-L and PIP-RBPJ-1, have the function of rebuilding transcription factor by inhibiting HDAC or blocking transcription factor in the target gene promotor or enhancer region, therefore have the ability in editing gene epigenetic situation and controlling cell differentiation in neural systems. Besides, recently years, neuroepigenetics have begun to have impact in neural disease. ATRX is a disease by gene mutation of the ATPase related SNF2 chromatin remodeling in H3.3. The studying about this rare genetic disorders give us more knowledge about the chromatin remodeler disease.

１．　SAHA-L could manuscript therapeutically Significant Nervous system Genes and enhance neural induction from iPS cells

An integrated multi-target small molecule capable of altering dynamic epigenetic and transcription programs associated with the brain and nervous system has versatile applications

in the regulation of therapeutic and cell fate genes. We identified a DNA-based epigenetic ON switch termed SAHA-L as the first-ever multi-target small molecule capable of inducing transcription programs associated with the human neural system and brain synapses networks in BJ human foreskin fibroblasts and 201B7-iPS cells. Ingenuity pathway analysis showed that SAHA-L activates the signaling of synaptic receptors like glutamate, γ-aminobutyric acid, which are key components of autism spectrum disorders. The long-term incubation of SAHA-L in 201B7-iPS cells induced morphology changes and promoted a neural progenitor state.

２. A Synthetic DNA-binding inhibitor of HES1 alters the Notch signaling pathway and induces neuronal differentiation

Synthetic DNA-binding inhibitors capable of gaining precise control over neurogenesis factors could obviate the current clinical barriers associated with the use of small molecules in regenerative medicine. Here, we report the design and bioefficacy of the synthetic ligand PIP-RBPJ-1, which caused promoter-specific suppression of neurogenesis-associated HES1 and its downstream genes. Furthermore, PIP-RBPJ-1 alone altered the neural-system-associated Notch signaling factors and remarkably induced neurogenesis with an efficiency that was comparable to that of a conventional approach.

３. ATRX patient HDF cell derived iPS have different character in the neuron differentiation

ATRX gene encoding chromatin-remodeling proteins, however, the role of ATRX protein in normal neurogenesis in vitro is unknown. Here, we used an ATRX patient derived iPS cell line A196, and A197 to clarify the mutation gene related neural characters in vitro. Mutation of ATRX patient derived protein caused widespread difference in the following stage. In the neural induction stage, Atrx patient iPS generate fewer neural stem cells; in the differentiation stage, ATRX patient derived cells have more rate of glia cells fate than neurons. In the mature stage, ATRX neurons cannot generate electrical functional neuron and GABA were less compared with the normal neurons, which can also been proved by microarray analysis, and PCP signaling increasing contribute a lot to these difference. Taken together, our results indicate that the increased neuronal loss may contribute to the severe mental retardation observed in human ATRX patients. This in vitro disease modal may give biological insight and combining the basic research to the clinical research.