Results report

１．Title of Research and Development：.Epigenetics and stemness in human hematopoiesis and leukemia

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４．Results of Research and Development:

Hematopoietic stem cells (HSCs) are the best-studied stem cells and they have been widely used clinically as a form of bone marrow transplantation to treat patients with leukemia, aplastic anemia, immunodeficiency disease and so on. However, lack of HLA-matched donors and graft versus host disease following allogeneic transplantation remain major issues associated with HSC transplantation. Recent discovery of induced pluripotent stem cells (iPSC) technology opened up the way to generate pluripotent stem cells from patient's somatic cells. Thus, if HSCs can be generated from patient-derived iPSCs, above issues associated with allogeneic HSC transplantation will be solved.

Recent advancement in stem cell biology demonstrated the existence of leukemic stem cells (LSCs), which are not susceptible to current cancer therapy. To avoid recurrence of leukemia, development of novel therapy that targets and eliminates LSCs is required.

The overall objectives of our project are, in collaboration with Canadian scientist, to understand how epigenetic modifications govern stemness, differentiation in normal human hematopoiesis,and to use this knowledge to develop the next generation of HSC therapeutics for regenerative medicine and more effective anti- LSC therapeutics. Below is the progress report from the Nakauchi team at the University of Tokyo and the Ogawa team at Kyoto University.

１）Progress made in the Nakauchi team

The system we have developed previously, can generate engraftable HSCs from both human and mouse iPSCs/ESCs via teratoma formation but only in low efficiency. To increase the efficiency of HSC generation, 1) We have generated several transgenic and knock-in mouse lines that are implemented with different type of promoters and suicide genes that are all designed to increase the host bone marrow niche for more efficient engraftment of HSCs generated in teratomas. 2) We also have implemented genetic modification to iPSCs for efficient generation of HSCs in teratoma. The forced expression of several different transcription factors that are known to be related to development of HSCs or of bone marrow niche cells has resulted in generation of variety of blood cells. The system will eventually be applied to more efficient generation of human HSCs. Thus the project to generate mouse and human HSCs via teratoma formation is progressing well.

２）Progress made in the Ogawa team.

Myelodysplastic syndromes (MDS) is a heterogeneous group of chronic myeloid neoplasms, characterized by ineffective hematopoiesis leading to pancytopenia and high propensity to acute myeloid leukemia (AML). In both MDS and AML, frequent genetic alterations involving epigenetic regulators, suggesting that abnormal epigenetic regulation is involved in the pathogenesis of these myeloid malignancies. In the past year, the Ogawa team reported that genetic alterations and abnormal DNA methylation played important roles in exacerbation and progression of MDS/AML. This year, combining the Tet-associated bufulfite seqyencing (TAB-Seq) technology with high throughput genotyping, the group established the platform in which epigenetic alterations in gene promoters/CpG islands and their surrounding regions can be efficiently analyzed in a large number of samples. Using this platform, the group identified candidate genes for abnormal DNA hypomethylation. These represent a substantial and promising progress to achieve the goal of this project, i.e., comprehensive epigenetic mapping of myeloid neoplasms.