Immunotherapy with 4-1BBL-expressing iPS cell−derived myeloid lines

Haruka Kuriyama[1], Satoshi Fukushima[1], Toshihiro Kimura[1] , Mina Kadohisa-Tsuruta[1], Yosuke Kubo[1], Satoshi Nakahara[1], Aki Tokuzumi[1], Azusa Miyashita[1], Hirotake Tsukamoto[2], Takashi Inozume[5], Rong Zhang[6], Yasushi Uemura[6], Yasuharu Nishimura[3,4] , Satoru Senju[3],and Hironobu Ihn[1]

[1]Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto, Japan.
[2]Department of Immunology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.
[3]Department of Immunogenetics, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.
[4]Nishimura Project Laboratory, Institute of Resource Development and Analysis, Kumamoto University, Kumamoto, Japan.
[5]Department of Dermatology, University of Yamanashi, Yamanashi Japan

Background

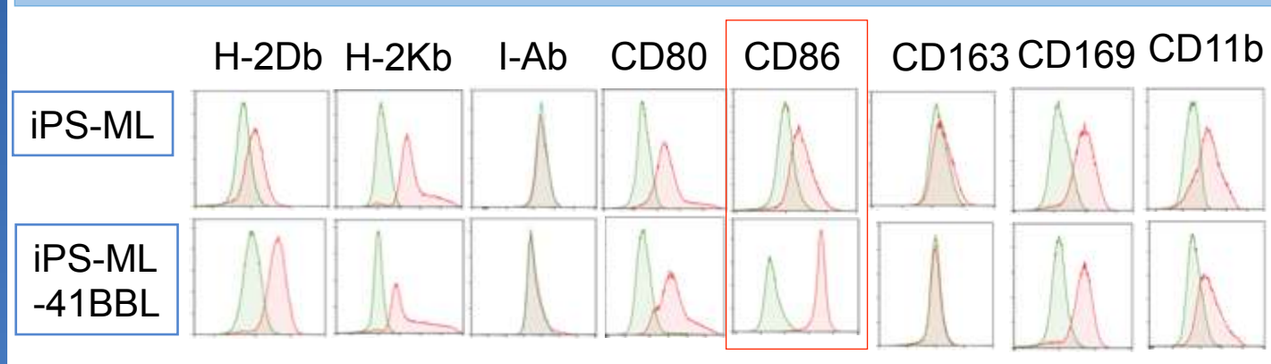
Only 30–40% of malignant melanoma patients respond to the treatment with immune checkpoint inhibitors. Thus, we more effective methods for treating malignant melanoma are required. The benefits of using induced pluripotent stem−cell−derived myeloid (iPS−ML) cell lines are that they have an infinite proliferative capacity and are easy to genetically modify. The interaction between the receptor 4-1BB and its ligand 4-1BBL provides co-stimulatory signals for T-cell activation. We introduced the 4-1BBL gene into an iPS-ML to obtain the iPS-ML-41BBL.

Purpose

To investigate the possibility that iPS-ML-41BBL has the therapeutic potential to suppress malignant melanoma.

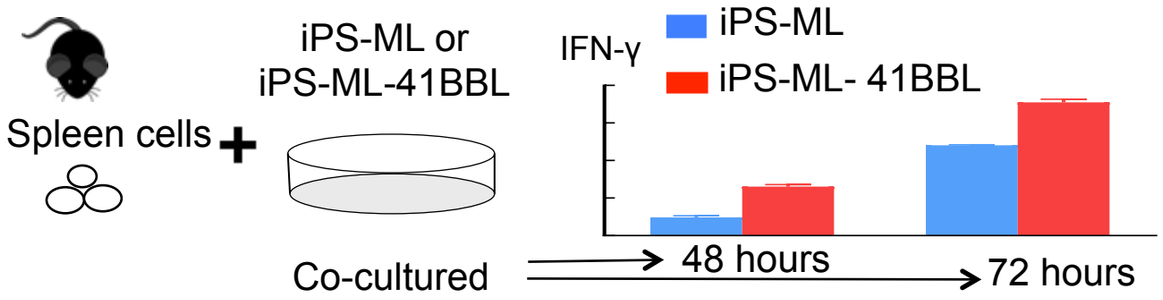
Result

Flow cytometry analysis for the expression of the cell-surface molecules



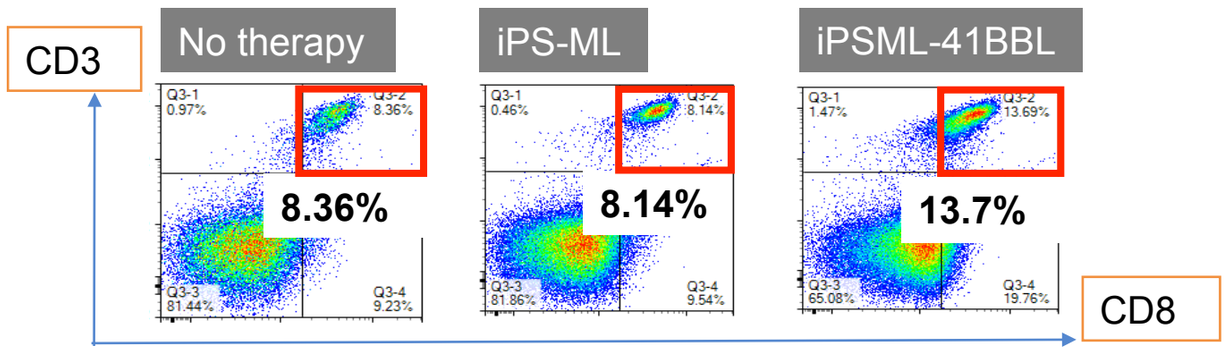
The expression of CD86 was upregulated in the iPS-ML-41BBL.

iPS-ML vs iPS-ML-41BBL (ELISA for IFN-γ)

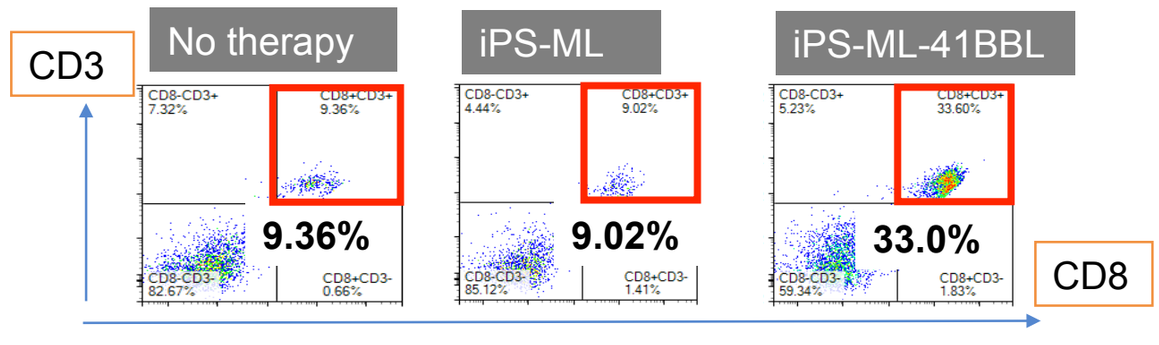


The INF-γ levels were upregulated in the culture supernatants of the iPS-ML-41BBL.

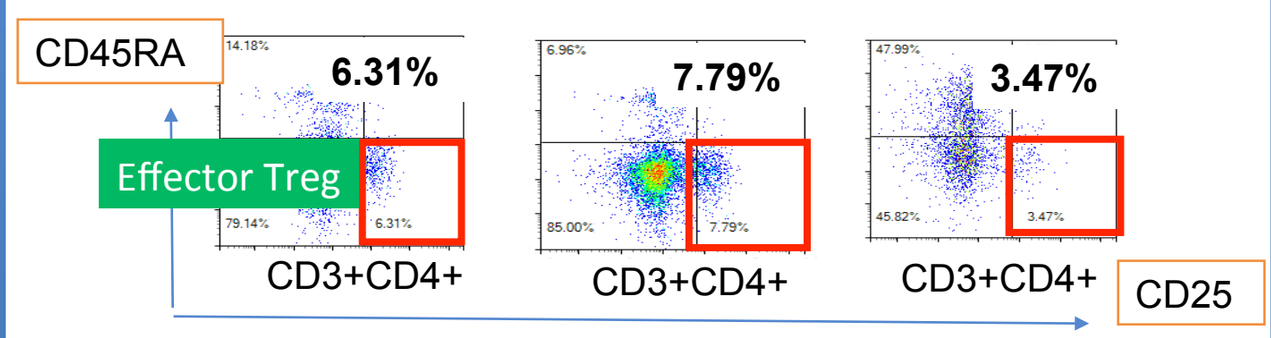
Flow cytometry analysis of the dissociated cells obtained from spleen



Flow cytometry analysis of the dissociated cells obtained from tumor

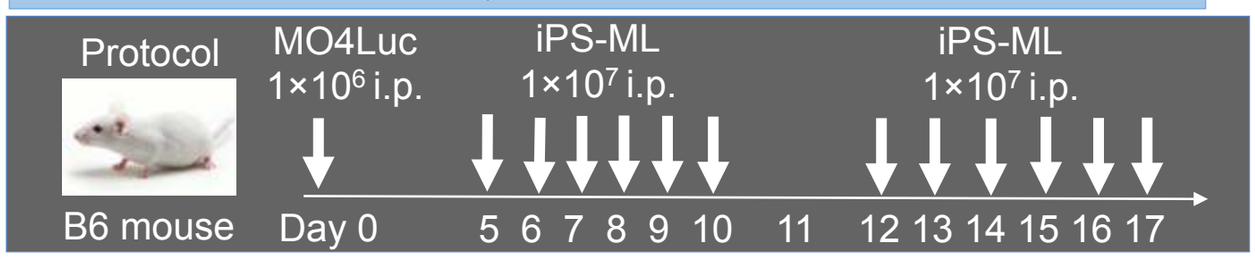


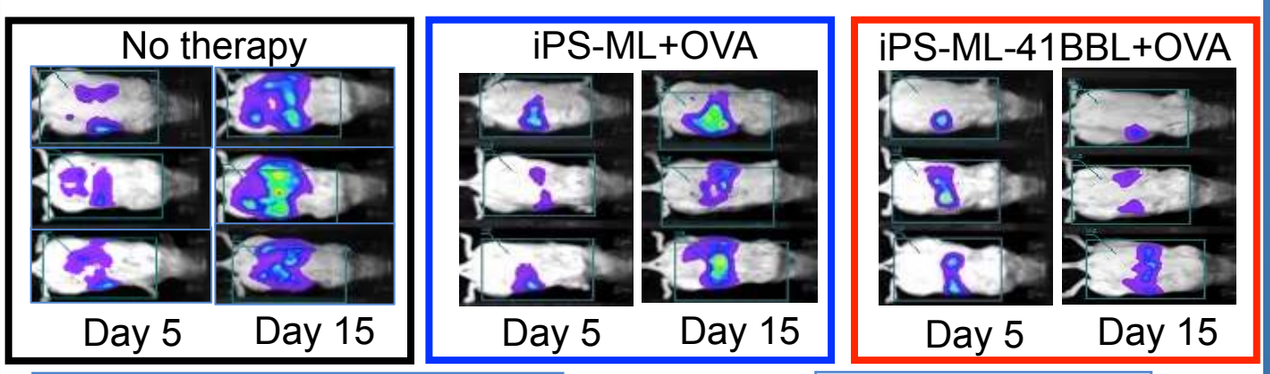
The proportion of CD8⁺ T cells in spleen and tumor following treatment with OVA epitope peptide-pulsed iPS-ML-41BBL increased.

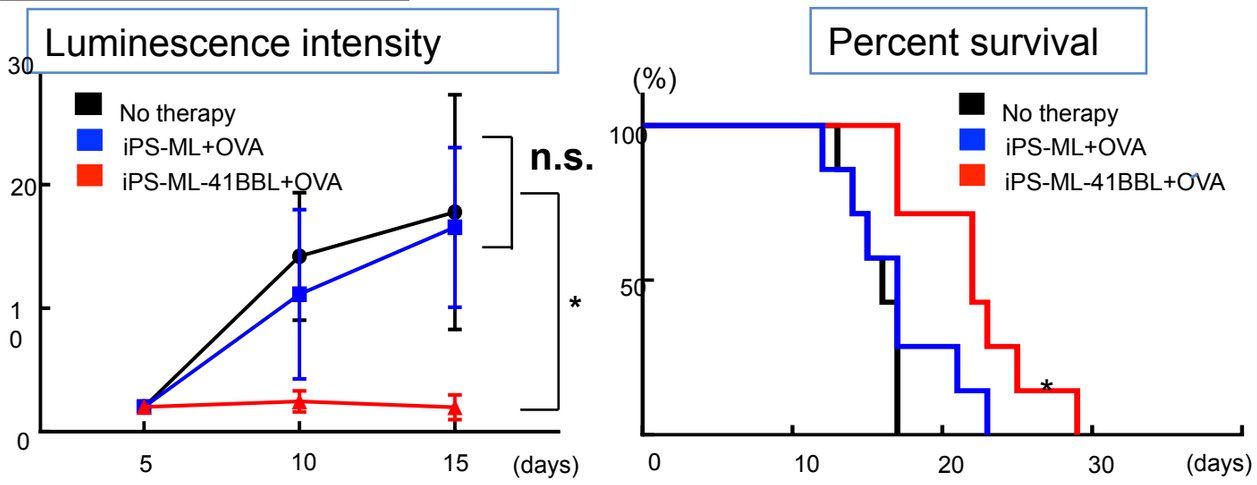


The proportion of effector Treg cells in tumor following treatment with OVA epitope peptide-pulsed iPS-ML-41BBL increased.

Effects of iPS-ML-41BBL against MO4 melanoma *in vivo*

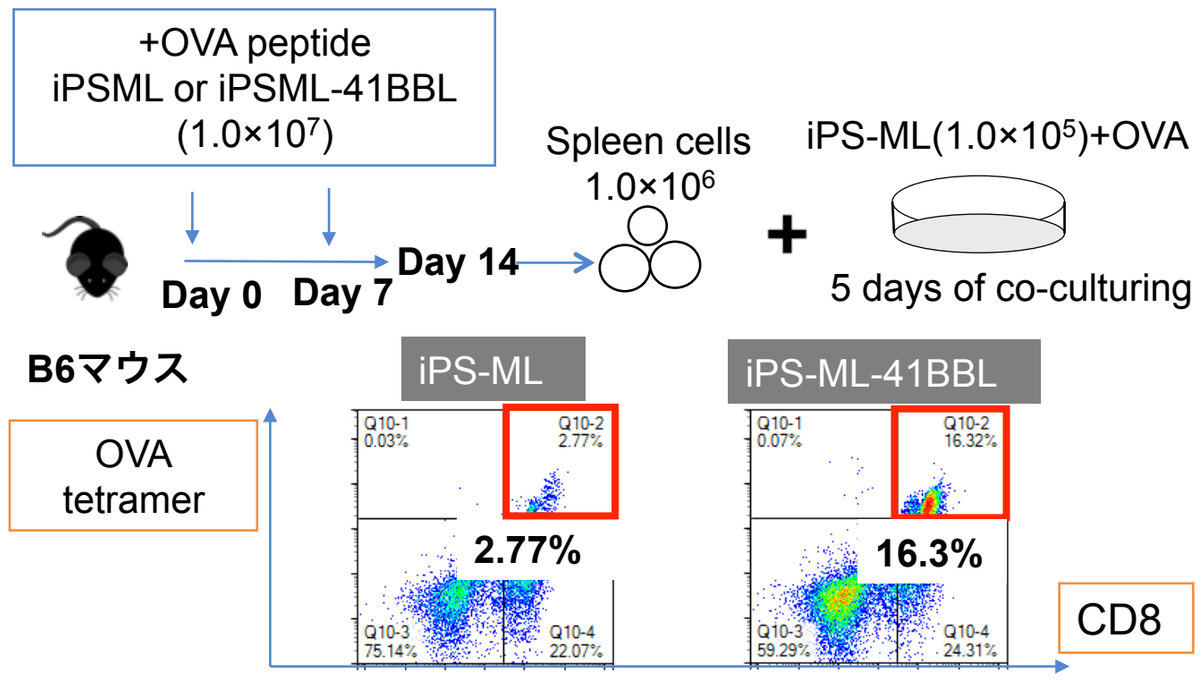






Peritoneal injections of iPS-ML-41BBL _reduced the tumor growth and prolonged the survival of the mice.

Flow cytometry analysis of OVA-specific CD8+T cells



The proportion of OVA-specific CD8⁺ T cells among the iPS-ML-41BBL increased.

Conclusion

The iPS-ML-41BBL could activate antigen-specific T cells, and may thus, be a candidate for immune cell therapies utilizing iPS cells.