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Quantitative assessment of the dynamics of soluble form of DNAM-1 (CD226) in human serum explains the mechanism of acute Graft Versus Host Disease (GVHD).

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Acute graft-versus-host disease (aGVHD) is the major complication of Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT). A lot of previous studies showed that the importance of DNAM-1(CD226) which is expressed on CD4+ T cells, CD8+ T cells, natural killer (NK) cells, and monocytes Therefore, DNAM-1 has been considered as essential molecule of developing aGVHD *in vitro* and *vivo* [1], [2]. But understanding the mechanism of aGVHD in human body is not understood well since few clinical trials related to the mechanism of aGVHD were performed. Recently, Kanaya *et al.* [3] focused on the soluble form of DNAM-1 (sDNAM-1) and collected the data which were from the subjects who recieved the transplantation. A form of the data set is time course therefore each subject has several observations by each time point. Despite of the time course data set, they just focus on the maximum value of the observation i.e. they didn't assess the dynamics of soluble DNAM-1. Therefore, they couldn't explain the connection between the dynamics of sDNAM-1 and developing aGVHD well. So then, we analyzed this data set by considering the dynamics of sDNAM-1. In our research, we made the hypothesis of mechanism of aGVHD and proved it by applying mathematical model and computational simulation to this data set. These results suggest that there exist 3 types of DNAM-1 after transplantation in the subject's body. The 1st type of DNAM-1 is released temporally and the 2nd types of DNAM-1 is released constantly. Those are from donor cells. On the other hand, 3rd types of DNAM-1 is residual one in the recipient body which is released from recipient cells. In addition, we proved quantitatively that the more 1st type of DNAM-1 exist in the human body after transplantation, the more the subjects tend to develop aGVHD. From the several previous researches and this research, we conclude that those cells which release DNAM-1 temporarlly can be considered as allo reactive T cells. Therefore, allo reactive T cells which expresses DNAM-1 can be treatment target for aGVHD.

[1] T. Nabekura *et al.*, "Critical role of DNAX accessory molecule-1 (DNAM-1) in the development of acute graft-versus-host disease in mice.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 107, no. 43, pp. 18593–8, Oct. 2010.
[2] M. Koyama *et al.*, "Promoting regulation via the inhibition of DNAM-1 after transplantation.," *Blood*, vol. 121, no. 17, pp. 3511–20, Apr. 2013.
[3] M. Kanaya et al., "Soluble DNAM-1, as a predictive biomarker for acute Graft-Versus-Host disease," *PLoS One*, vol. 11, no. 6, pp. 1–12, 2016.

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