



HAL
open science

Graft versus host disease in humanized mice is differentially controlled by CD28 and CD80/86 antagonists

Nicolas Poirier, Nahzli Dilek, Caroline Mary, Bernard Vanhove

► To cite this version:

Nicolas Poirier, Nahzli Dilek, Caroline Mary, Bernard Vanhove. Graft versus host disease in humanized mice is differentially controlled by CD28 and CD80/86 antagonists. 7th European Workshop on Immune-Mediated Inflammatory Diseases, Nov 2012, Netherlands. pp.O2. inserm-00758217

HAL Id: inserm-00758217

<https://inserm.hal.science/inserm-00758217>

Submitted on 28 Nov 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



ORAL PRESENTATION

Open Access

Graft versus host disease in humanized mice is differentially controlled by CD28 and CD80/86 antagonists

Nicolas Poirier^{1,2}, Nahzli Dilek^{1,2}, Caroline Mary^{1,2}, Bernard Vanhove^{1,2*}

From 7th European Workshop on Immune-Mediated Inflammatory Diseases
Noordwijk aan Zee, the Netherlands. 28-30 November 2012

Background

Antagonist anti-CD28 antibodies prevent T-cell costimulation and functionally differentiate from CTLA4Ig since they cannot block CTLA-4 and PDL-1-mediated coinhibitory signals. They demonstrated efficacy in suppressing effector T cells while enhancing regulatory T cells function after organ transplantation.

Methods and results

Here we evaluated FR104, a novel antagonist pegylated Fab' anti-CD28 monovalent antibody, in xenogeneic graft-versus-host disease (GVHD) induced in NOD/SCID mice infused with human PBMC and compared efficacy with CTLA4Ig molecules. *In vitro*, FR104 and CTLA4-Ig (LEA29Y) dose-dependently prevented human T cell proliferation to a similar extent in mixed lymphocytes reactions with EC50 at 0.16 and 0.18 micrograms/ml, respectively. IL-2 secretion after stimulation with SEE superantigens was also inhibited in a similar manner.

NOD/SCID mice adoptively transferred with human PBMC presented > 80% engraftment after a week and developed a florid GVHD in the third week due to the proliferation of xenogeneic human T cells and their infiltration into the liver, gut, lung and skin, eventually leading to weight loss and sacrifice. Treatment of recipient mice with 5 mg/Kg FR104 biweekly from day 0 to day 25 reduced target organs infiltration by human T cells and completely prevented weight loss and mortality ($p < 0.0001$). Mice continued gaining weight and did not succumb even a month after treatment withdrawal. Flow cytometry analysis 2 month post engraftment revealed

that FR104 treated mice displayed low level of human cells engraftment (<10%), indicating that targeting the CD28/B7 pathway protected from acute GVHD by inhibiting donor T cell expansion. The therapeutic effect of FR104 was dependent on CTLA-4, since co-administration of FR104 with blocking anti-CTLA4 antibodies completely abrogated FR104-mediated protection. This might be explained by the fact that CTLA-4 signals attenuate T cell responses independently of CD28. In Contrast, biweekly administrations of CTLA4-Ig (LEA29Y or Abatacept), which reduces CD28-CD80/86 costimulation as well as CTLA-4-CD80/86 coinhibition, was ineffective to protect mice from severe GVHD, whereas a less intensive protocol of administration (once a week) was partially effective.

Conclusion

Our data suggests that antagonist anti-CD28 monovalent antibodies might lead to higher therapeutic indexes, by sparing CTLA-4, as compared to CD80/CD86 antagonists, to dampen T cell activation in transplantation.

Author details

¹Institute of Transplantation Urology Nephrology, University of Nantes, INSERM UMR 643, Nantes, France. ²Effimune, Nantes, France.

Published: 28 November 2012

doi:10.1186/1479-5876-10-S3-O2

Cite this article as: Poirier et al.: Graft versus host disease in humanized mice is differentially controlled by CD28 and CD80/86 antagonists. *Journal of Translational Medicine* 2012 **10**(Suppl 3):O2.

¹Institute of Transplantation Urology Nephrology, University of Nantes, INSERM UMR 643, Nantes, France

Full list of author information is available at the end of the article