Reviewer's report

**Title:** A diagnostic window for the treatment of acute GVHD prior to visible clinical symptoms in a murine model

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**Reviewer:** Ronjon Chakraverty

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Dynamic parameters that predict for the development of acute graft-versus-host disease (GVHD) following allogeneic bone marrow transplantation (BMT) may permit earlier intervention and improved outcomes. Several studies have evaluated the potential for serum or urine biomarkers panels in the clinical setting and some of these are being used to stratify patients for early treatment in clinical trials.

This study describes early changes in peripheral blood donor T cell expression of cell surface homing receptors in the early phase of experimental BMT. The authors demonstrate increases in the frequency of #4#7 (alpha 4 beta 7)+ and P-selectin ligand expressing donor CD4 and CD8 cells before the onset of maximal clinical disease. Intervention with rapamycin at this point ameliorates the ultimate severity of GVHD.

**Major Revisions**

1. Early experimental BMT models from Sprent and co-workers using thoracic duct sampling have already demonstrated the appearance of blasting, alloreactive lymphocytes before the onset of acute GVHD. This work should be cited. In the current study, alloreactive T cells represent a composite of thoracic duct output (early) and effector cells egressing from GVHD target tissues (later).

2. I am not certain that the authors have fully demonstrated the duration of the ‘window’ before the onset of clinical disease, as outlined in Figure 1D. I think that it is important for the authors to delineate in more detail the changes in weight, clinical GVHD score and BLI in syngeneic versus allogeneic BMT recipients that parallel the changes in peripheral blood T cells. Ideally data relating to skin or gut histology or T cell infiltration should be shown at timed intervals. Similar data should be shown for the whole time course for rapamycin-treated recipients.

3. At what time point does intervention with rapamycin cease to prevent GVHD or GVHD-related mortality?

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I have no competing interests