Reviewer's report

Title: Targeting insulin resistance in type 2 diabetes via immune modulation of cord blood-derived multipotent stem cells (CB-SCs) in stem cell educator therapy: phase I/II clinical trial

Version: 2 Date: 5 April 2013

Reviewer: Anne Joerns

Reviewer's report:

In the manuscript beneficial, functional changes of C-peptide concentration and HbA1C in long-standing T2D patients, divided in three groups, were described after one treatment with the Stem Cell Educator therapy with the autologous mononuclear cells after 4, 12 and 56 weeks. The three analysed groups of 12 persons showed functional benefits with a decrease of inflammation parameters and a beneficial function of the beta cells.

Major Compulsary Revisions

1. Introduction:
   a) Type 2 diabetes starts with a dysfunction and later leads to a loss of pancreatic beta cells. Please clarify this in the introduction as well as in the discussion sections.

2. Materials and Methods:
   Please introduce all methods used for the present study, especially the in vitro studies with mononuclear cells using, for example, Western Blots and ELISA for the patient groups.

3. Results:
   a) Please make statements about the importance of the different cytokines. The cytokine, IL-17A is very important for the ongoing autoimmune process in T1DM as well as in other autoimmune diseases. IL-12 is important for IFN-gamma production. These cytokines are primarily not involved in T2DM.
   b) The analysed panel of cytokines is not a biomarker panel for T2DM which uses more TNF-alpha, IL-6 and others.
   c) The in vitro analyses with the co-culture needs longer exposure than performed in the in vivo situation. This is a barrier for a comparative view.

4. Discussion:
   a) The description of the pathogenesis of diabetes is more about type 1 than type 2 regarding the different T cell subtypes. This issue has to be clarified.
   b) It is a low inflammation in the pancreas with mostly macrophages and adipokines in the circulation. This issue has to be clarified.
   c) Macrophages are antigen-presenting cells, but with much lower capacity than dendritic cells. The co-stimulatory molecules are only important to identify the
subpopulation of the educated immune cell type.

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests.