WEBINAR: Bispecific Antibody Inhalation Therapy for Redirecting Stem Cells from the Lungs to Repair Heart Injury

Questions and answers from the February 24, 2021 webinar titled "Bispecific Antibody Inhalation Therapy for Redirecting Stem Cells from the Lungs to Repair Heart Injury"

This document includes questions we received and answered during the webinar, as well as those that we did not have time to address. Questions have been grouped into relevant categories.

1. **Why do you think inhalation therapy worked better than i.v. injection for delivery of the bispecific antibodies?**
    a. Inhalation offers direct delivery of the antibodies to the lungs, whereas i.v. injection means that the bispecific antibodies enter the bloodstream and can be lost to off-target sites. Delivering the antibodies to the lungs has more binding potential to the hematopoietic stem cells and platelets before entering the bloodstream to the heart.

2. **Did you notice any other side effects after treatment?**
    a. When looking at the major organs, including the lungs, hearts, livers, kidneys and spleen, there were no abnormalities in histology, so we don't expect there was any toxicity.

3. **Did you try fluorescence imaging in vivo to track the movement of the stem cells over time, or simply look at the ex vivo organs at the end stage to observe the location of the signal?**
    a. During this study, only ex vivo fluorescence imaging was performed.

4. **In your cardiac function data, you talked about filling volume, that is the end diastolic volume; while describing the results you mentioned that after treatment the volume showed some increase, but not to the same levels as**

in the untreated group. Can you describe again why this was seen to be a good outcome of the treatment?

a. In myocardial infarction, ventricle dilation is a common observation. As remodeling becomes more advanced the walls often thin and the ventricle dilates, increasing the end diastolic volume. The smaller increase seen in the treated animals would indicate that the therapy was helping to minimize the extent of remodeling, resulting in some increase, but not to the level of the untreated animals.

5. **Similar beneficial results have been found with exogenously delivered hematopoietic stem cells (CD34+). Did you compare homing to the heart with such exogenous CD34+ cells to see if using the bispecific antibody approach is any better?**
    a. This comparison has not been completed at this time.

6. **If your left anterior descending coronary artery was permanently occluded, how do the hematopoietic stem cells home to the downstream infarcted area?**
    a. The surgery was a permanent LAD ligation. In this situation the HSCs would home to the transmural region, or border zone, of the infarct where perfusion is still present. The difference in infarct size between the treated and untreated animals is significant, the presence of the HSCs does provide some protection. The mechanism, and if the cells enter the infarct area itself, is not yet clear and will be further investigated.

7. **What is the PK of the bispecific antibodies between the two routes (inhalation vs i.v. injection)?**
    a. These studies have not yet been completed.