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Murine Model to Predict Viral Rebound in HIV+ Allotransplanted Subjects

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for the IciStem Consotium

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Background: The IciStem Consortium

To date, Berlin patient's case provides the only evidence of long-term HIV-1 control after allogeneic stem cell transplantation (SCT), potentially due to the CCR5Δ32/Δ32 donor genotype. The case of the two Boston patients, without resulting in HIV cure, showed that the SCT procedure itself involves a tremendous reduction of the viral reservoir. The reason why this happened is unraveled yet.

IciStem is a collaborative project to guide and investigate the potential for HIV cure in HIV-infected patients requiring allogeneic stem cell transplantation for hematological disorders.
The EPISTEM consortium is composed of an expert panel of hematologists with experience in allogeneic SCT procedures along with infectious disease specialists, virologist and immunologists with expertise in the field of HIV-1, reservoirs and cure (Figure 1).

Figure 1. IciStem Consortium



Principal **achievements of the IciStem Consortium**:

1. **IciStem is the largest international cohort** of allogeneic SCT recipients with HIV-1 infection currently including **14 transplanted patients** (Figure 2), 4 of them with CCR5Δ 32/Δ32 donor .

2. **Longitudinal samples from peripheral blood (phlebotomy and leukapheresis), gut biopsy, cerebrospinal fluid (CSF), lymph node and bone marrow** have been collected and analyzed.

3. In parallel, **30000 cord blood units have been tested for** CCR5Δ32/Δ32 mutation in Europe. **200 mutated units** have been identified and are available for new transplantations

4. Preliminary analysis of the cohort suggests that **allogeneic stem cell transplantation resulted in a decay of the latent reservoir** in all analyzed cases. (Figure 3).

Figure 2. IciStem Patients

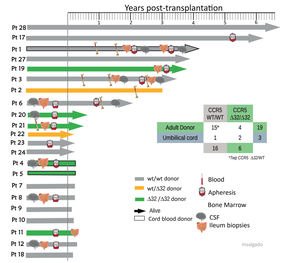
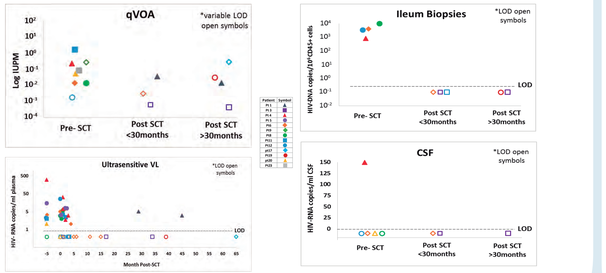


Figure 3. HIV reservoir after SCT (*open symbols mean undetectable measurement)



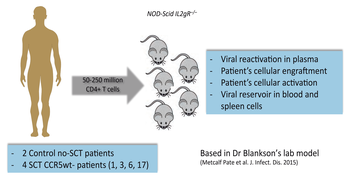
Findings

Herein, we explore the mice viral outgrowth approach (mVOA) as a potential tool to predict early viral rebound after cART discontinuation needed to evaluate the success of any eradication strategy.

Methods

Blood leukapheresis was collected from 4 subjects that had undergone SCT within the IciStem cohort (Pt 1, Pt 3, Pt 6 and Pt 17); and 2 "control" HIV-infected subjects who did not receive allotransplants, all of them on cART. Purified CD4+ T cells were transferred to 3 to 5 immunosupressed NSG mice per patient. Mouse health condition as well as human cell engraftment, T-cell subpopulation and T-cell activation were monitored. We quantified HIV RNA in mouse plasma, as well as total HIV-DNA on peripheral blood cells during the follow up and in spleen upon animal euthanasia. All procedures performed were reviewed and approved by the correspondent Ethical Committees and according to the national and European legislations.

Figure 4. mice qVOA approach



Results

We transferred 10-50 million CD4+ T cells per mouse. A total of five mice were used per study subject, 76% of them completing the follow up. Just one week post-infusion, we detected up to 104 HIV RNA copies/mL in the plasma of mice to which cells from control subjects had been transferred. Total HIV DNA was also detected in peripheral blood cells between weeks 1 and 3 (105 copies/million cells). Conversely, after 13 weeks of follow up, no HIV RNA or DNA was detected in either plasma or peripheral blood cells of mice to which CD4 T cells from transplanted subjects had been transferred. These mice achieved a human lymphocyte engraftment over 40%, with human CD4+ T cells activation levels over 50% in all cases. Finally, total HIV DNA was detected in all spleens of mice from "control" cases (106 copies per million cells), but not in the ones infused with cells from allotransplanted cases

Figure 5. Results of HIV plasma viremia, human lymphocyte engraftment, human CD4 population and activation in infused mice

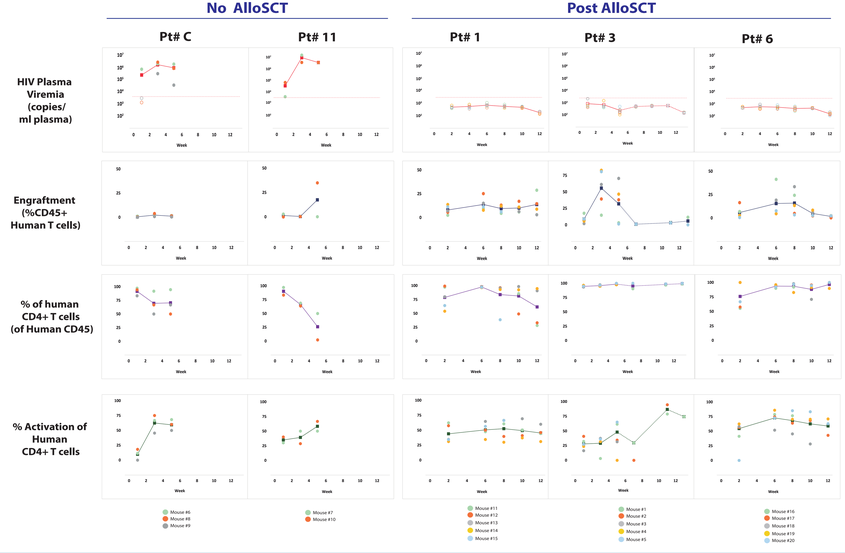


Figure 6. HIV-DNA infection in blood from mice infused with patient's cells

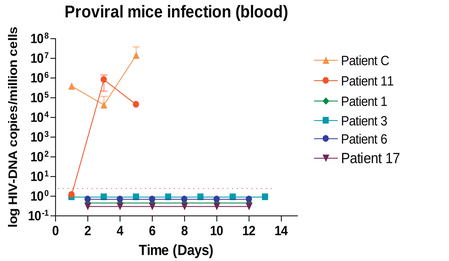
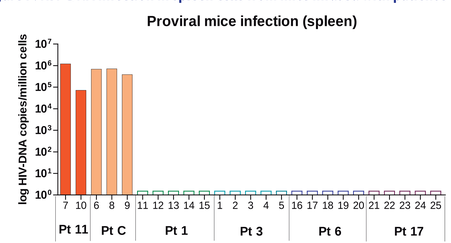


Figure 7. HIV-DNA infection in spleen cells from mice infused with patient's cells



Conclusions

Mice qVOA might become a feasible tool to anticipate in vivo viral rebound dynamics after a substantial reduction of the HIV latent reservoir in eradication strategies, such as allogeneic stem cell transplantation. Compared with other assays, mVOA might reflect more physiological conditions of viral reactivation.

Acknowledgements

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