Global Bridges Amsterdam 2019

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The European Diamond-Blackfan anemia symposium
June 10-12, 2019

euro DBA consortium

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10:50 - 12:10
Session VII: Current therapeutic strategies in DBA

Chairs: & Charlotte Niemeyer & Thierry Leblanc

- An Update on Clinical Trials for DBA – Adriana Vlachos, USA (15+5) **page 30**
- Transfusion independence observed in a DBA girl during treatment with Deferasirox and Eltrombopag - Ugo Ramenghi, Italy (15+5) **page 26/27**
- Hematopoietic stem cell transplantation in children and adolescents with DBA: a report from the German DBA registry and French HSCT Registry - Felicia Loewecke, Germany (15+5) **page 20**
- Preclinical studies towards gene therapy of Diamond-Blackfan anemia - Susana Navarro, Spain (15+5) **no abstract**

12:10 - 13:10
Lunch

13:10 - 14:30
Session VIII: Strategies for future therapies

Chairs: Adrianna Vlachos & Stefan Karlsson

- High-throughput screening approaches to identify therapeutic targets for the treatment of DBA – Amee George, Australia (15+5) **page12**
- Novel small molecule therapies for DBA – Johan Flygare, Sweden (15+5) **page 10**
- A clinically applicable Lentiviral vector corrects the anemia and bone marrow failure in a mouse model for DBA – Yang Liu, Sweden (15+5) **page 19**
- The patient perspective: Where to go from here? - Martin Winter, UK (10+5) **no abstract**

14:30 - 14:40
Farewell - Meeting closes

Preclinical Studies towards the Gene Therapy of Diamond-Blackfan Anemia

Authors: Yari Gimenez[1,2], Rebeca Sanchez[1,2], Christiane Zorbas[3], Mariela Villanueva[1,2], Laura Ugalde[1,2], Omaira Alberquilla[1,2], Paula Río[1,2], Eva Gálvez[4], Marion Strullu[5], Jose Carlos Segovia[1,2], Cristina Beléndez[6], Denis L.J. Lafontaine[3], Thierry Leblanc[5], Julián Sevilla[4], Juan Bueren[1,2], Susana Navarro[1, 2]

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Allogenic hematopoietic stem cell transplantation (HSCT) currently represents the unique definitive curative treatment of DBA. Gene therapy (GT) arises as an innovative and safer therapeutic strategy for DBA, based on efficacy of these approaches in several hematopoietic diseases such as primary immunodeficiencies, β-hemoglobinopathies and bone marrow failure (BMF) syndromes such as Fanconi anemia (FA)(FANCOLEN-1/ EudraCT No: 2011-006100-12)

Nevertheless, several questions still require clarification before DBA patients could be treated by GT, including potential limitations in the number and repopulating properties of hematopoietic stem cells and progenitor cells (HSPC) that could be collected from these patients. To answer to these key points we have first characterized the content and functionality of HSPCs from bone marrow samples of DBA patients. In contrast to the very low number of CD34+ and colony forming cells observed in the BM from FA patients, we have observed significantly higher numbers of these progenitor cells in BM samples from DBA patients. Additionally, we have observed evident hematopoietic engraftment in NSG immunodeficient mice transplanted with BM cells from DBA patients, even in the absence of genetic correction.

Aiming at the correcting the phenotype of DBA HSCs, we have constructed two therapeutic lentiviral vectors (LV) carrying a codon-optimized version of the *RPS19* cDNA driven by the PGK or the EF1alpha promoter. Studies carried out in DBA-like cells (K562 transduced with anti-RPS19 shRNA-LVs) and in CD34+ cells from DBA patients showed that transduction of either of these therapeutic LVs, suppressed the pre-rRNA processing phenotype in DBA-like cells, and restored the expression of RPS19 in BM cells from DBA patients, while preserving the repopulating potential of these cells. These studies support that gene therapy may constitute suitable approach for the treatment of the BMF characteristic of DBA patients.