EUROPEAN HEMATOLOGY ASSOCIATION

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SCIENTIFIC WORKING GROUPS

PROGRAM BOOK

EHA-SWG Scientific Meeting on Granulocytes and Constitutional Marrow Failure Disorders and Leukemia Predisposing Genes

October 10-12, 2019 | Prague, Czech Republic

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FRIDAY, OCTOBER 11

08:45 - 10:15 SESSION 3: SPECIFIC DISEASES - TELOMERE DISEASES AND FANCONI ANEMIA

Chair: C Dufour (G Gaslini Children's Hospital, Genova, Italy)

Telomere disease: Molecular pathogenesis & clinical phenotype
I Dokal (Barts and the London School of Medicine and Dentistry, London, United Kingdom)

Gene therapy in Fanconi anemia (FA)
J Bueren (CIEMAT, Madrid, Spain)

Non classical Constitutional Marrow Failure Syndromes
M Miano (IRCCS G Gaslini, Genova, Italy)

New Frontiers in Diagnosis and Treatment of Gaucher's Disease
M Machaczka (Södersjukhuset, Stockholm, Sweden)

10:15 - 10:45 Coffee break

10:45 - 11:45 SESSION 4: SPECIFIC DISEASES - RIBOSOMAL DISORDERS

Chairs: K de Keersmaecker (KU Leuven, Belgium) & A Warren (University of Cambridge, United Kingdom)

Shwachman-Diamond Syndrome and the quality control of Ribosome assembly
A Warren (University of Cambridge, United Kingdom)

Zebrafish models and hematologic Ribosome diseases
E Payne (UCL Cancer Institute, London, United Kingdom)

Disruption of pre-rRNA maturation in DBA
PE Gleizes (Center for Integrative Biology, Toulouse, France)

11:45 - 12:15 SESSION 5: PRESENTATION AND DISCUSSION OF RARE AND UNUSUAL CASES

Chairs: C Mecucci (University of Perugia, Italy) & B Schlegelberger (Department of Human Genetics, Hannover Medical School, Germany)

Presentation and discussion of rare and unusual cases
C Mecucci (University of Perugia, Italy),
C Niemeyer (Children's Hospital Freiburg, Germany),
T Ripperger (Department of Human Genetics, Hannover Medical School, Germany),
B Schlegelberger (Department of Human Genetics, Hannover, Germany)

12:15 - 13:15 Lunch

Further reading list

1. Heiss NS, Knight SW, Vulliamy TJ, Klauck SM, Wiemann S, Mason PJ, et al. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. Nature Genetics 1998; 19: 32-38.
2. Knight SW, Heiss NS, Vulliamy TJ, Aalfs CM, McMahon C, Richmond P, et al. Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. British Journal of Haematology 1999; 107: 335-339.
3. Vulliamy T, Marrone A, Goldman F, Dearlove A, Bessler M, Mason PJ, et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature 2001; 413: 432-435.
4. Vulliamy T, Marrone A, Dokal I, Mason PJ. Association between aplastic anaemia and mutations in telomerase RNA. Lancet 2002; 359: 2168-2170.
5. Yamaguchi H, Baerlocher GM, Lansdorp PM, Chanock SJ, Nunez O, Sloand E, et al. Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. Blood 2003; 102: 916-918.
6. Yamaguchi H, Calado RT, Ly H, Kajigaya S, Baerlocher GM, Chanock SJ, et al. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. New England Journal of Medicine 2005; 352: 1413-1424.
7. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. New England Journal of Medicine 2007; 356: 1317-1326.
8. Alter BP, Baerlocher GM, Savage SA, Chanock SJ, Weksler BB, Willner JP, et al. Very short telomere length by flow fluorescence in situ hybridization identifies patients with dyskeratosis congenita. Blood 2007; 110: 1439-1447.
9. Kirwan M, Vulliamy T, Marrone A, Walne AJ, Beswick B, Hillmen P, et al. Defining the pathogenic role of telomerase mutations in myelodysplastic syndrome and acute myeloid leukaemia. Human Mutation 2009, 30: 1567-1573.
10. Calado RT, Regal JA, Kleiner DE, Schrump DS, Peterson NR, Pons V, et al. A spectrum of severe familial liver disorders associate with telomerase mutations. PLoS One 2009; 4(11): e7926.
11. Islam A, Rafiq S, Kirwan M, Walne A, Cavenagh J, Vulliamy T, et al. Haematological recovery in dyskeratosis congenita patients treated with danazol. British Journal of Haematology 2013; 62: 854-856.
12. Townsley DM, Dumitriu B, Liu D, Biancotto A, Weinstein B, Chen C, et al. Danazol Treatment for Telomere Diseases. New England Journal of Medicine 2016; 374: 1922-3191.
13. Fioredda F, Iacobelli S, Korthof ET, Knol C, van Biezen A, Bresters D, et al. Outcome of haematopoietic stem cell transplantation in dyskeratosis congenita. British Journal of Haematology 2018; 183: 110-118.

SESSION 3: SPECIFIC DISEASES - TELOMERE DISEASES AND FANCONI ANEMIA

Friday, October 11, 08:45 - 10:15

Gene therapy in Fanconi anemia (FA)

Author: Juan Bueren (CIEMAT, Madrid, Spain)

Disclosures: CIEMAT (Speaker's bureau)

Learning objectives:

After attending this presentation, you will be able to:

1. introduce the state of the art of gene therapy, and
2. update the results of a gene therapy trial in Fanconi anemia patients.

Hematopoietic gene therapy is currently showing excellent clinical results in a variety of monogenic diseases affecting the hematopoietic system. Nevertheless, no positive results have been reported so far in bone marrow failures syndromes. We are currently developing a gene therapy trial in patients with Fanconi anemia, subtype A (FA-A) using autologous CD34+ cells that were mobilized to peripheral blood (PB) with G-CSF and plerixafor and transduced a therapeutic lentiviral vector. Nine patients with ages between 2-6 years old have been infused with either cryopreserved or fresh gene-corrected CD34+ cells, at cell doses ranging from 50,000 to 1.600,000 corrected CD34+ cells/kg. To avoid any side effect, no conditioning was used in this clinical trial. In this presentation I will summarize the results of the first four patients after a follow-up of 2-3 years. In no instance severe adverse events related to the infusion of transduced cells

were observed. Corrected PB cells were detected in all these patients after six months post-infusion. Progressive increases of gene marking were observed thereafter in all these patients until the more recent visit at 24 to 36 months post-infusion. The highest levels of gene marking were observed in the patient that was infused with the highest number of corrected CD34+ cells, at 3 years post-infusion. In this patient the percentage of gene marked cells in BM and PB was above 50%. Analyses of the lentiviral vector insertion sites demonstrated the engraftment of multipotent HSCs and did not reveal risks associated with insertional mutagenesis. Functional studies showed progressive increases in the resistance of BM progenitor cells to mitomycin-C over time, correlating with the enhanced proportion of the therapeutic vector in BM progenitors. Similarly, the in vitro challenge of PB T cells to diepoxybutane, showed significant decreases in the proportion of PB T-cells with chromosomal breaks. Finally, the study of the hematological parameters in these patients suggests the stabilization of the bone marrow failure in patients with higher levels of gene corrected cells. Our results provide first evidence of efficacy of gene therapy in patients with FA.

Further reading list

1. Successful Engraftment of Gene Corrected Hematopoietic Stem Cells in Non-conditioned Fanconi Anemia Patients. Rio et al. Nature Medicine. Accepted. In press
2. Rio, P., et al. Engraftment and in vivo proliferation advantage of gene corrected mobilized CD34(+) cells from Fanconi anemia patients. Blood 409 130, 1535-1542 (2017).
3. Adair JE, et al. Lessons Learned from Two Decades of Clinical Trial Experience in Gene Therapy for Fanconi Anemia. Curr Gene Ther. 2017.
4. Liu JM, et al. Engraftment of hematopoietic progenitor cells transduced with the Fanconi anemia group C gene (FANCC). Hum Gene Ther. 1999;10(14):2337-2346.
5. Kelly PF et al. Stem cell collection and gene transfer in Fanconi anemia. Mol Ther. 2007;15(1):211-219.

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Friday, October 11, 08:45 - 10:15

Non classical Constitutional Marrow Failure Syndromes
Author: Maurizio Miano (IRCCS Istituto Giannina Gaslini, Genova, Italy)
Disclosures: No affiliations

Summary unavailable

SESSION 3: SPECIFIC DISEASES - TELOMERE DISEASES AND FANCONI ANEMIA
Friday, October 11, 08:45 - 10:15

New Frontiers in Diagnosis and Treatment of Gaucher Disease
Author: Maciej Machaczka (Rzeszow University, Poland and Södersjukhuset, Stockholm, Sweden)
Disclosures: Sanofi Genzyme (Speaker's bureau)

Learning objectives:
After attending this presentation, you will be able to:
1. describe phenotypic heterogeneity in a single gene GBA disorder
2. identify and appropriately diagnose patients with Gaucher disease
3. have learned about the new available treatments for Gaucher disease

FACULTY & DISCLOSURE INDEX

EHA would like to thank the following people for their contribution to the EHA-SWG Scientific Meeting on Granulocytes and Constitutional Marrow Failure Disorders & Leukemia Predisposing Genes as speakers and chairs in the invited speaker program.

Bueren, Juan
CIEMAT, Madrid, Spain
Disclosures: CIEMAT (Speaker's bureau)

Dalle, Jean Hugues
University of Paris & Robert-Debre Hospital - APHP, France
Disclosures: X4 pharma (Advisory board)

de Keersmaecker, Kim
KU Leuven, Belgium
Disclosures: No affiliations

Dietrich, Ralph
Deutsche Fanconi-Anämie-Hilfe e.V., Unna, Germany
Disclosures: No affiliations

Dokal, Inderjeet
Barts and the London School of Medicine and Dentistry, United Kingdom
Disclosures: No affiliations

Donadieu, Jean
Hôpital Trousseau APHP, Paris, France
Disclosures: X4 pharma (Advisory board)

Dufour, Carlo
G Gaslini Children's Hospital, Genova, Italy
Disclosures: Novartis (Advisory board, sponsored meeting)

Fioredda, Francesca
IRCCS Giannina Gaslini Hospital, Genova, Italy
Disclosures: No affiliations

Gleizes, Pierre-Emmanuel
Center for Integrative Biology, Toulouse, France
Disclosures: No affiliations

Leblanc, Thierry
Hôpital Robert-Debré - Assistance publique Hôpitaux de Paris, France
Disclosures: No affiliations

Machaczka, Maciej
Södersjukhuset, Stockholm, Sweden
Disclosures: Sanofi Genzyme (Speaker's bureau)

Mecucci, Cristina
University of Perugia, Italy
Disclosures: Celgene (Advisory board)

Miano, Maurizio
IRCCS Istituto Giannina Gaslini, Genova, Italy
Disclosures: No affiliations

Niemeyer, Charlotte
Childrens Hospital Freiburg, Germany
Disclosures: No affiliations

Palmblad, Jan
Karolinska Institutet, Stockholm, Sweden
Disclosures: ApoPharma Ltd (Advisory board, consultant); CampusPharma Ltd (Consultant)

Papadaki, Helen
University of Crete, Heraklion, Greece
Disclosures: Genesis Pharma (Research grant); Gilead (Research grant, advisory board)

Payne, Elspeth
UCL Cancer Institute, London, United Kingdom
Disclosures: Novartis (Speaker honoraria, advisory board); Celgene (Speaker honoraria, advisory board)

Ripperger, Tim
Department of Human Genetics, Hannover Medical School, Germany
Disclosures: No affiliations

Schlegelberger, Brigitte
Department of Human Genetics, Hannover, Germany
Disclosures: No affiliations

Skokova, Yulia
University Hospital Tuebingen, Germany
Disclosures: No affiliations

Touw, Ivo
Erasmus MC, Rotterdam, The Netherlands
Disclosures: No affiliations

Warren, Alan
University of Cambridge, United Kingdom
Disclosures: No affiliations

Welte, Karl
University Children Hospital Tuebingen, Germany
Disclosures: No affiliations