Gene therapy of β-hemoglobinopathies: trials and trends

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Presenter Author
Carsten Werner Lederer

Affiliation
Department of Molecular Genetics Thalassaemia, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus & Cyprus School of Molecular Medicine, Nicosia, Cyprus

E-mail
lederer@cing.ac.cy

Mobile
0035796664521

Postal Address
Carsten W. Lederer, Department of Molecular Genetics Thalassaemia, The Cyprus Institute of Neurology and Genetics & Cyprus School of Molecular Medicine, 6 International Airport Avenue, P.O. Box 23462, 1683 Nicosia, Cyprus

Author
Carsten Werner Lederer
Molecular Genetics Thalassaemia Department, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus & Cyprus School of Molecular Medicine, Nicosia, Cyprus

Abstract
This presentation will summarise the current state of play in the clinical translation of gene therapy for the major β-haemoglobinopathies, sickle cell anaemia and β-thalassaemia.
As severe monogenic diseases of the haematopoietic system, sickle cell disease and β-thalassaemia are ideal target for gene therapy. In preclinical research, substantial success has been achieved in the correction of critical disease parameters by three principal therapeutic approaches of (i) gene addition of β-globin-like transgenes, (ii) repair of the primary mutation by genome editing and (iii) functional correction of β-globin deficiency by re-activation of the primarily fetal γ-globin chain. Gene addition is the longest-established of these approaches and is the only one as yet applied in the clinic and informing future development of improved therapies. Second, repair of the primary mutation is still hampered by low efficiencies in primary cells but is based on nascent genome and base editing technology with substantial scope for improvement. Finally, an array of strategies dedicated to the activation of fetal

hemoglobin has led to the registration of clinical trials based on genome editing and shRNA-mediated knockout, respectively.
Accumulating data for clinical trials based on gene addition indicate significant therapeutic benefits but also a high level of variability in treatment outcomes for β-haemoglobinopathies. This talk will extrapolate how the approach might be improved based on the current state of knowledge and technology development, and where gene correction and activation of fetal hemoglobin might offer superior performance in future clinical trials and, eventually, in routine curative treatment of patients.

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Carsten Werner Lederer, PhD
Laboratory Scientific Officer & Assistant Professor
Molecular Genetics Thalassaemia Department
The Cyprus Institute of Neurology and Genetics & The Cyprus School of Molecular Medicine