TARGETNMDs - A novel and empowered TARGETed gene addition approach at a relevant microglia locus for the treatment of inherited NeuroMetabolic Diseases

Hematopoietic stem cell (HSC) gene therapy based on self-inactivating integrating vectors has proven unprecedented therapeutic potential in inherited neurometabolic diseases (NMDs). However, phenotypic effects are delayed after treatment likely due to the slow replacement of resident microglia by transplant-derived cells that hampers the broad application of this approach. Moreover, unregulated gene expression driven by the in-use promoters could in the long term cause unwanted effects. Finally, recent events suggest that the treated patients might be at risk of developing side effects related to vector integration. Therefore, novel strategies anticipating therapeutic benefit and reducing these potential safety concerns are desirable to address the still unmet medical need of NMD patients.

Our long-term goal is to develop a novel, broadly effective and safe treatment platform for NMDs based on a newly empowered HSC targeted gene addition approach at a newly identified microglia locus. Our central hypothesis is that correcting the gene defect by targeted addition at this locus in HSCs of patients affected by NMDs could generate in a timely manner a microglia-like progeny endowed with unprecedented therapeutic potential. Indeed, based on our recent findings, gene editing and targeted integration at this locus are expected to uniquely favor the timely engraftment and efficient, rapid myeloid/microglia differentiation of transplanted, edited HSCs in the recipients' brain, and to induce robust and regulated expression of the integrated transcript in transplant-derived microglia-like cells. Based on this hypothesis, we aim at developing a targeted gene addition approach at the newly selected microglia locus for correcting the underlying genetic defect in HSCs and obtaining proof of concept of its therapeutic potential in NMDs animal models. Thus, the proposed work could generate the basis for a novel treatment platform for these devastating conditions.

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