
Promoting Healing and Overcoming ELANE Neutropenia with ex vivo CRISPR

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In the PHOENIX (Promoting Healing and Overcoming ELANE Neutropenia with ex vivo CRISPR) project, we aim to advance the clinical development of the MILESTONE gene therapy approach for congenital neutropenia in collaboration with the University Hospitals of Tübingen (UKT) and Freiburg (UKF), and the Hannover Medical School (MHH). This recently patented and published method is an innovative procedure for inactivating disease-causing genes. In the case of congenital neutropenia, we use this method to inactivate the non-essential ELANE gene. Mutations in this gene are the cause of the disease in half of all patients with congenital neutropenia.

To this end, we will adapt the Good Manufacturing Practice (GMP)-compliant ex vivo gene editing process established in Tübingen for the MILESTONE approach. For the first time, we will test the gene editing of large quantities of blood stem cells using the MILESTONE method and examine its effectiveness and safety.

The gene-edited blood stem cells will be analyzed using state-of-the-art methods. The efficiency of gene editing will be measured via digital droplet PCR and next-generation sequencing, and the stem cells will be characterized using flow cytometry. The function of the stem cells will be assessed through in vitro and in vivo assays. Finally, the integrity of the genome will be determined using CAST-Seq and optical genome mapping.

In parallel, we are developing a synopsis for the first clinical trial and preparing the necessary documents for the application of an Investigational Medicinal Product Dossier (IMPD). Moreover, an active patient participation in the process is included by structured patient interviews and presentation of the study results in patient organizations. Based on these results, we will seek scientific advice from the Paul-Ehrlich-Institute to define the final preclinical work packages required for approval to conduct a clinical study.
