# **GENE THERAPY** FOR SEVERE COMBINED IMMUNODEFICIENCY

# RAG1-SCID

Recomb gene therapy

www.recomb.eu

## INTRODUCTION

Recomb is a multi-stakeholder research consortium aiming to create **a novel treatment for severe combined immunodeficiency (SCID)** by conducting clinical trials using gene therapy for one of the most common type of SCID: RAG1-SCID. The consortium, started in 2018, brings together clinical and research professionals from 16 European and 1 Israeli institutes with expertise in the management of primary immunodeficiencies, such as SCID. The project received funding from the European Union Horizon 2020 programme.

SCID comprises a group of rare diseases in which cells in the adaptive immune system fail to develop properly. The specific SCID phenotype depends on the underlying genetic defect, and more than 20 SCID-associated genes have been identified to date. SCID affects around 1:35,000 infants, with approximately 145 affected babies born each year in the EU.

These infants are born without a functional immune system, thus typically experience a wide range of serious, eventually life-threatening infections, including pneumonia, meningitis, and sepsis, **and die within the first year of life** unless effective treatment is given.

## GENE THERAPY

Gene therapy is a novel type of treatment for genetic conditions that involves correcting the faulty gene in the patient's stem cells. Members of our research consortium have successfully conducted clinical trials using gene therapy for treating two of the other major categories of SCID (X-linked SCID and ADA-SCID).

In gene therapy, working copies of the missing gene are inserted into the patient's DNA using a vector. Vectors are "vehicles" for delivering genetic material, such as DNA, into a cell. A vector is often a bacterium or a virus that has been inactivated, so that it no longer causes a disease.

Currently, the only treatment for RAG1-SCID, haematopoietic stem cell transplant (HSCT) has limitations, particularly in case an HLA-matched donor is unavailable. In gene therapy, a stem cell donor is not necessary because the patient's own stem cells are used and modified in the process.

Recomb aims to develop autologous haematopoietic stem cell-based gene therapy for RAG1-SCID whereby the patients' own blood-forming stem cells will be collected and sent to the transduction site at Leiden University (LUMC) in the Netherlands. Then, the genetically modified stem cells will be returned to the participating clinical centres and transplanted to the patients. This implicates that families will be able to avoid traveling across borders with their new born child and having to stay several months at a foreign treatment center, away from their daily social life and duties.

NOVEMBER 2023 **UPDATE**

## PHASE I/II CLINICAL TRIAL FOR STEM CELL GENE THERAPY IN RAG1-SCID IS NOW OPEN

We are proud to announce that, after 15 years of research, the stem cell gene therapy developed for RAG1-SCID patients is now being used in the clinic and can offer a solution for patients across Europe and potentially other areas of the world.

This study is a prospective, non-randomized, open-label, two-centre phase I/II intervention study designed to treat children up to 24 months of age with RAG1-deficient SCID with an indication for allogeneic hematopoietic stem cell transplantation but lacking an HLA-matched donor. The study involves infusion of autologous CD34+ cells transduced with the RAG1 lentivirus in patients with RAG1-deficient SCID. The study has already recruited two patients with a successful follow-up of up to two years.

Currently, we are recruiting at Leiden University Medical Center (LUMC) in the Netherlands and the recently added Recomb sites Vall d'Hebron in Barcelona, Spain and Wroclaw Medical Center in Poland as well as the affiliated centre Erciyes University Kayseri in Turkey. Soon additional Recomb and affiliated clinical sites are expected to be ready for recruitment, including:

- Great Ormond Street Hospital for Children (UK)
- University Medical Center Ulm (Germany)
- Ludwig-Maximilians-University Munich (Germany)
- Newcastle Institute of Cellular Medicine (UK)
- Ospedale Pediatrico Bambino Gesù (Italy)
- SHEBA Medical Centre (Israel)
- Royal Children's Hospital Melbourne (Australia)

Clinical centres outside RECOMB may refer their patients to LUMC.

For more details, please contact the LUMC team (Prof. Staal and Prof. Lankester) via **rag1trial@lumc.nl**

# IMPACT OF RECOMB

## SOCIETY AND ECONOMY

### CURRENT STATUS

1) The only currently available treatment for RAG-SCID is allogeneic stem cell transplantation (HSCT) with less favorable survival in mismatched HSCT recipients; Graft vs. host disease regularly affects HSCT recipients, especially with mismatched donors.
2) The current treatment is suboptimal and can therefore be expensive
3) Significant increase in the number of RAG-SCID patients on the horizon with newborn screening for SCID
4) Current healthcare for SCID and other severe forms of PID is orientated around HSCT as the definitive treatment option

### EXPECTED IMPACT

1) Provide a curative treatment with gene therapy using autologous HSCs, which will: Increase survival; Eliminate risk of graft vs. host disease. High level of safety and efficacy
2) Gene therapy has the potential to significantly reduce healthcare costs for the treatment of (RAG) SCID in the long term, and potentially many others
3) The Recomb program will contribute to make gene therapy a realistic option for the majority of SCID patients
4) A new model including highly specialized centres with the expertise to receive, transduce and return cells to remote clinical units in the EU, will likely become a global standard

## PATIENTS AND FAMILY

### CURRENT STATUS

1) Current gene therapy treatment requires families to travel and find accommodation at the location of the treatment centre
2) Insufficient engagement of patients in research

### EXPECTED IMPACT

1) In the Recomb trial, cells - and not patients - will travel to the coordinating study center, and genetically modified stem cells will be returned to the participating and expert clinical centres and transplanted to the patients
2) Patients are actively involved due to the participation of The International Patient Organisation for Primary Immunodeficiencies (IPOPI)

## SCIENCE AND CLINICAL PRACTICE

### CURRENT STATUS

1) Europe is the global leader in developing stem cell-based gene therapy due to SCID programmes granted by EU, but still over 50% of SCID patients do not have access to gene therapy as a treatment option
2) Industry investments in gene therapy to treat rare diseases (orphan diseases) such as SCID are sparse and there have been notable setbacks in recent years
3) Current knowledge base regarding lymphoid development in humans is incomplete
4) Lack of EU-wide guidelines in assessing efficacy of treatments
5) Many other diseases lack safe and efficient (curative) therapies

### EXPECTED IMPACT

1) Recomb building on these projects will reinforce this leading role by delivering gene therapy as treatment for more patients
2) Recomb will engage with industry towards further research and development of orphan medicines and may stimulate public-private partnerships
3) Recomb will provide new scientific insights regarding haematopoiesis and lymphocyte development in humans
4) Recomb will develop harmonised and highly standardised protocols and tools for monitoring the short and long-term effects of gene therapy
5) The knowledge and expertise obtained during the Recomb program can also be applied to other diseases that can be treated with autologous HSC gene therapy, i.e. other SCIDs, immune disorders, lysosomal storage diseases and hemoglobinopathies, such as β-thalassemia and sickle cell anaemia

## RECOMB

### DEVELOP

Develop an autologous haematopoietic stem cell–based gene therapy within a multinational, multicentre clinical trial for treating RAG1-SCID.

### TREAT

Treat the patients with the developed RAG1-SCID gene therapy eliminating complications and increasing survival.

### IMPACT

Make gene therapy a realistic option for > 70% of all SCID patients in Europe with reduced healthcare costs.

## RECOMB PARTNERS

Bambino Gesù Istituto per la Salute

ProtaGene Analytical Excellence

BATAVIA biosciences

MHH Hannover Medical School

IPOPI

Great Ormond Street Hospital for Children NHS Foundation Trust

LUMC Leiden University Medical Center

Inserm

Newcastle University

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

SCETIDE

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

OSPEDALE SAN RAFFAELE

Sheba - Academic Medical Center Hospital

PRZYLĄDEK NADZIEI

UCL

universität ulm

Vall d'Hebron Barcelona Hospital Campus

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