# **GENE THERAPY** FOR SEVERE COMBINED IMMUNODEFICIENCY

# RAG-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: RAG-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.

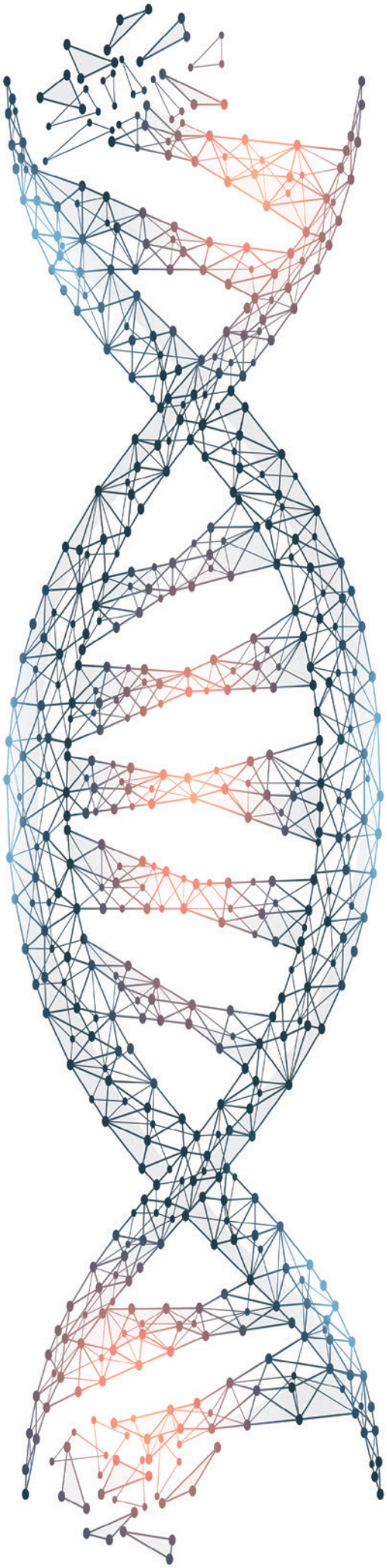
## GENE THERAPY

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 RAG-SCID, **haematopoietic stem cell transplant (HSCT)** has limitations, if a matched donor is not found. 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 RAG-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 means, that families will avoid having to stay long periods of time away from their daily duties at treatment centre, as the treatment will travel not the patient.



# IMPACT OF RECOMB

## SOCIETY AND ECONOMY

### CURRENT STATUS

1) The only currently available treatment for RAG-SCID is allogeneic stem cell transplantation (HSCT) with low survival in mismatched HSCT recipients; Possibilities to develop graft vs. host disease
2) The current treatment can 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 will significantly reduce healthcare costs for the treatment of RAG-SCID in the long term, and potentially many others
3) The Recomb program will make gene therapy a realistic option for ~70% of all 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 treatment requires families to travel and find accommodation at the location of the treatment centre
2) Conditioning is necessary before HSCT transplantation, which is often uncomfortable for the patient
3) Insufficient engagement of patients in research

### EXPECTED IMPACT

1) During gene therapy cells - and not patients - will travel to the site, and genetically modified stem cells will be returned to the clinical centres and transplanted to the patients
2) For some gene therapies, low-dose or no conditioning is sufficient, making the treatment more comfortable for patients
3) 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 research and development of medicinal products to treat rare diseases (orphan diseases) such as SCID are beginning to happen
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 lacking 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 and stimulate interest among industry towards further research and development of orphan medicines
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

geneWERK

BATAVIA biosciences

MHH Hannover Medical School

Great Ormond Street Hospital for Children NHS Foundation Trust

LUMC Leiden University Medical Center

Inserm

Newcastle University

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

SCETIDE

OSPEDALE SAN RAFFAELE

Sheba - Academic Medical Center Hospital

IPOPI

PRZYLĄDEK NADZIEI

UCL

universität ulm

Vall d'Hebron Barcelona Hospital Campus

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