Press release

Sickle cell disease: remission of disease symptoms in the world's first patient treated using gene therapy

A team led by Prof. Marina Cavazzana, working at Necker Hospital for Sick Children, AP-HP, and the Imagine Institute (AP-HP/Inserm/Paris Descartes University) performed gene therapy on a 13-year-old patient with severe sickle cell anaemia in October 2014 as part of a phase I/II clinical trial. Conducted in collaboration with Prof. Philippe Leboulch (CEA/Faculties of Medicine at Paris-Sud and Harvard Universities), who developed the vector used, and supervised the preclinical studies, this innovative treatment provided complete remission from the clinical signs of the disease, and the correction of biological signs. Results (15-month follow up after transplantation) are published in the New England Journal of Medicine on 2 March 2017 and confirm the efficacy of this new therapy of the future.

Sickle cell disease, a serious form of chronic anaemia of genetic origin, is characterised by the production of abnormal haemoglobin and deformed (falciform or sickle-shaped) red blood cells, due to a mutation in the gene encoding β-globin. This disease is associated with very serious episodes of pain caused by vaso-occlusive crises. It also causes lesions in all the vital organs, great sensitivity to infection, iron overload and endocrine disorders. Haemoglobinopathies affect an estimated 7% of the world's population. Among them, sickle cell disease is considered the most common, with 50 million people carrying the mutation, i.e. who are at risk of transmitting the disease or actually have it. Abnormalities in the β-globin gene, i.e. sickle cell disease and β-thalassaemia, are the most widely distributed inherited diseases in the world, more common than all other genetic diseases combined.

The clinical trial, coordinated by Prof. Marina Cavazzana*, was conducted at Necker Hospital for Sick Children, AP-HP, and the Imagine Institute.

The first phase involved taking haematopoietic stem cells, the source of all blood cell lineages, from the patient's bone marrow. A viral vector[1] carrying a therapeutic gene, previously developed to treat ß-thalassaemia, was then introduced into these cells in order to correct them. This lentiviral vector, capable of carrying long complex segments of DNA, was developed by Prof. Philippe Leboulch**, and is produced on a large scale by the American company bluebird bio[2].

The treated cells were then reinjected intravenously into the young patient in October 2014. During his subsequent period in hospital, the adolescent then received care in the Paediatric Immunohaematology Unit at Necker Hospital for Sick Children, in collaboration with Prof. Stéphane Blanche and Dr Jean-Antoine Ribeil.

Fifteen months after transplantation with the corrected cells, the patient no longer requires blood transfusions, no longer suffers from vaso-occlusive crises, and has fully resumed his physical and academic activities. "*We also note that the therapeutic protein from the vector, which strongly inhibits pathological sickling, is remarkably highly expressed and effective,*" explains Prof. Philippe Leboulch.

[1] A vector is a self-replicating molecule of DNA or RNA (plasmid, cosmid, viral DNA) into which foreign DNA is inserted, and which is then used to enable this DNA to enter a target cell.

[2] A company founded by Prof. Philippe Leboulch, and sponsor of the clinical trial.

"With this gene therapy approach, we hope to develop future clinical trials and enrol a high number of patients with sickle cell disease, in Île de France and throughout the national territory," says Prof. Marina Cavazzana.

***Prof. Marina Cavazzana** - M.D., Ph.D., Professor of Haematology at Paris-Descartes University, Head of the Biotherapy Department and of the Clinical Investigation Centre – Biotherapy (CIC-BT) at Necker Hospital for Sick Children, AP-HP and Co-Director of the Inserm Laboratory of Human Lymphohematopoiesis at the Imagine Institute for Genetic Diseases, Paris, France.

****Prof. Philippe Leboulch**, Professor of Medicine at the Paris-Sud University Faculty of Medicine, Senior Advisor to the CEA on medical innovation and International Scientific Director of the François Jacob Biology Institute, developed the therapeutic vector used (published in the journal *Science* in 2001), and supervised the preclinical studies with his collaborator Dr Emmanuel Payen (Inserm, CEA).

Reference: ***Gene Therapy in a Patient with Sickle Cell Disease*** *NEJM 1/3/2017*

About AP-HP: *AP-HP is an internationally renowned university hospital system with a European dimension. Its 39 hospitals receive 8 million patients a year, in clinics, emergency departments, and through planned hospital admissions or home hospitalisation. It provides a public health service for all, on a 24-hour basis, which for AP-HP is a matter of both duty and pride. AP-HP is the biggest employer in Île de France: 100,000 people – physicians, researchers, allied medical staff, administrative staff and other employees – work there. www.aphp.fr*

About the Imagine Institute: *One of the leading centres in European for research, care and education on genetic diseases, the Imagine Institute's mission is to understand and treat these conditions. The Institute brings together 850 of the best physicians, researchers and other healthcare staff in a structure that creates synergy. This unique continuum of expertise, combined with closeness to patients, allows Imagine to make discoveries for the benefit of patients.*
There are some 9,000 genetic diseases, affecting 35 million patients in Europe, and nearly 3 million in France, where approximately 30,000 new cases are diagnosed each year. Nearly 60% of the children seen in clinics leave without a genetic diagnosis, and 90% of genetic diseases are still without curative treatment. Given this major public health problem, the challenge is two-fold: to diagnose and to treat. www.institutimagine.org

About the French Alternative Energies and Atomic Energy Commission (CEA)*: The CEA is a public research body involved in four areas: defence and security, nuclear and renewable energy, technological research for industry and basic research.*
Using its recognised expertise, the CEA is involved in establishing collaborative projects with many academic and industrial partners. With 16,000 researchers and staff, it is a major player in the European research area, and has a growing international presence. To find out more: www.cea.fr

Press contacts:
AP-HP Press Office: Anne-Cécile Bard and Marine Leroy – +33 (0)1 40 27 37 22 – service.presse@aphp.fr
Imagine Press Office: Pauline Rodrigue-Moriconi - +33 (0)6 77 23 71 19 - pauline.rodrigue@institutimagine.org or Béatrice Parinello-Froment: +33 (0)6 63 72 16 06 beatriceparrinello@bpfconseil.com
CEA Press Office: Tuline Laeser tuline.laeser@cea.fr +33 (0)1 64 50 20 97 or Guillaume Milot guillaume.milot@cea.fr +33 (0)1 64 50 14 88

Prof. Marina Cavazzana

Co-director of the Laboratory of Human Lymphohematopoiesis at the Imagine Institute, Marina Cavazzana is a paediatrician by training. A native of Italy, she graduated in Medicine in 1983, received certification in Paediatrics in 1987, and was awarded a doctorate in Life Sciences in 1993.
Professor of Haematology since 2000, she is also Head of Unit at the Department of Biotherapy at Necker Hospital for Sick Children, AP-HP, and Director of the Inserm/ Paris West University Hospitals (AP-HP) Clinical Investigation Centre – Biotherapy (CIC-BT).
Her research on the development of the immune system and genetic diseases of the haematopoietic system, aimed at improving their therapeutic management, has been rewarded by different learned societies such as the American Society of Hematology, and the European Society of Cell and Gene Therapy.
Prof. Marina Cavazzana, together with Prof. Alain Fischer and Prof. Salima Hacein-Bey, is credited with the first successful gene therapy for "bubble babies," who are born with severe combined immunodeficiencies (SCID).
Marina Cavazzana received the title of Officer of the National Order of the Legion of Honour in 2011, and the Joliot Curie prize for "Woman Scientist of the Year" in 2012, awarded by the French Academy of Sciences and the French Ministry of Higher Education and Research. In December 2016, she was awarded the Prix National of the French National Academy of Medicine for her entire body of work.

Prof. Philippe Leboulch

Prof. Leboulch is a graduate in Medicine from Paris 12 University (now Paris-Est Créteil Val-de-Marne University), and an *Ancien Interne* of the Paris Hospitals (1985-1988). He was a postdoctoral fellow at Massachusetts Institute of Technology (1989-1993) before joining the staff at Harvard Medical School from 1993 to 2007, where he remains a Visiting (full) Professor/Lecturer.
He is a University Professor and Hospital Practitioner (PU-PH) at the Paris-Sud Faculty of Medicine, and he founded and has directed the CEA's Institute of Emerging Diseases and Innovative Therapies (iMETI). Since 2017, he is Senior Advisor for medical innovation at the CEA, and International Scientific Director of the new François Jacob Biology Institute, Division of Basic Sciences, CEA. He is also a Visiting Professor at Ramathibodi Faculty of Medicine at Mahidol University, Bangkok, Thailand.
Prof. Leboulch is a pioneer of gene therapy, and has obtained many awards for his work, including major grants from the National Institutes of Health (NIH), and a Chair of Excellence and Chair of Industry from the French National Research Agency (ANR). He has been a member of the Editorial Board of the journal *Blood* and of many international panels, including subcommittee Chairman of the *"Strategic review and recommendation panel for the 21st century"* of the National Heart Lung and Blood Institute (NHLBI) at the NIH. He is a recipient of the Grand Prix Etancelin from the French Academy of Sciences, and of a decoration from the National Order of the Legion of Honour. He is founder and co-chairman of the Scientific Advisory Board of the US company bluebird bio, which sponsored the present trial.