EMBARGOED UNTIL 11PM ON 01/03/2017 H

Press release

==== Press release embargoed until 11pm CET on 1 March 2017 ====

Remission of symptoms in the first sickle-cell anemia patient in the world treated with gene therapy

A 13 year-old patient with severe sickle-cell anemia received gene therapy in October 2014. The team led by Professor Marina Cavazzana administered the therapy in October 2014 in Necker-Enfants Malades and the *Imagine* Institute (AP-HP/INSERM/Université Paris Descartes) as part of a phase I/II clinical trial. The team worked with Professor Philippe Leboulch (French Alternative Energies and Atomic Energy Commission (CEA)/Faculty of Medicine in Paris-Sud and Harvard University), who developed the vector used in the treatment and directed the preclinical trials. The results of the novel treatment were full remission of clinical symptoms and correction of biological signs. Published in the New England Journal of Medicine on 2 March 2017 the results confirm the effectiveness of this therapeutic breakthrough.

Sickle-cell anemia is a serious form of inherited chronic anemia. Patients have a mutation in the gene that codes for β-globine that causes the production of abnormal hemoglobin and sickle shaped (falciform) red blood cells. Problems faced by sufferers include attacks of sudden very severe pain caused by vaso-occlusive crises. Other consequences are lesions on all vital organs, much increased susceptibility to infection, iron overload in the blood and endocrine disorders. 7% of the world's population are estimated to be affected by hemoglobinopathies. Of these, sickle-cell anemia is considered to be the most common with 50 million people who are either carriers of the mutation – with the risk of passing on the disease – or sufferers. β-globin, sickle-cell anemia and β-thalassemia anomalies are the most common inherited diseases in the world, and occur more frequently than all other genetic diseases combined.

The clinical trial coordinated by Prof. Marina Cavazzana* took place at the AP-HP Necker-Enfants Malades hospital and *Imagine* Institute.

During phase I, hematopoietic stem cells (HSC) responsible for the production of all the cell lines were harvested from the patient's bone marrow. A gene therapy viral vector[1], or lentiviral vector, developed by Prof. Philippe Leboulch** to treat ß-thalassemia was then transduced into the cells to correct the mutation. The vector can carry complex long DNA segments and is being produced on a large scale by US firm bluebird bio[2].

The treated cells were then reinjected into the young patient intravenously in October 2014. In-patient treatment took place in the Pediatric Immunohematology Department of Necker-Enfants Malades hospital, working closely with Professor Stéphane Blanche and Dr. Jean-Antoine Ribeil.

[1] A vector is a DNA or RNA self-replicating molecule (plasmid, cosmid, viral DNA) in which the foreign DNA is introduced. It is then used to transduce this DNA into a target cell.

[2] Bluebird bio, the company founded by Professor Philippe Leboulch, is running the clinical trial.

Fifteen months after receiving the corrected cell graft, the patient is transfusion-independent, free of vaso-occlusive crises and has completely resumed normal physical activities and schooling. "*We also note that the therapeutic protein expression from the vector, which is a powerful inhibitor of the pathological falciformation, is remarkably high and effective,*" said Prof. Philippe Leboulch.

"*We want to develop new clinical trials with this gene therapy model and enroll a large cohort of patients with sickle-cell anemia from the Greater Paris area and France as a whole*", added Prof. Marina Cavazzana

***Professor Marina Cavazzana** - M.D., Ph.D. Professor of Hematology at Université Paris Descartes, Research Director at the Center for Clinical Research in Biotherapy, Necker-Enfants Malades hospital, AP-HP, Paris Necker Hospital, Paris, and joint Director of the Inserm Human Lymphohematopoietic research group at the *Imagine* Institute for Genetic Diseases, Paris, France.

****Professor Phillipe Leboulch**, Professor of Medicine at Université Paris-Sud Faculty of Medicine, Senior Advisor in medical innovation to the CEA and International Scientific Director of the François Jacob Biology Institute, discovered the therapeutic vector used in the trial (paper published in *Science* in 2001) and directed the preclinical trials with colleague Dr. Emmanuel Payen (Inserm, CEA).

References: ***Gene Therapy in a Patient with Sickle Cell Disease*** *(+link) NEJM 1/3/2017 authors + affiliations*

About the AP-HP: *Assistance Publique-Hôpitaux de Paris (AP-HP) is a world-renowned European university hospital. AP-HP treats 7 million patients every year at its 39 hospitals. We care for patients across the healthcare spectrum providing medical consultations, emergency care, planned in-patient care, as well as home hospitalization. AP-HP is proud to fulfill its mission of providing 24-hour public health services for all. The hospital group is the leading employer in the Greater Paris region, with 100,000 people on staff, including physicians, researchers, paramedics, administrative and other personnel.* www.aphp.fr

About the Imagine Institute: *One of the leading European centers for research, care and teaching in genetic diseases, the Imagine Institute's primary aim is to understand and cure. The Institute's staff includes 850 of the best physicians, researchers and healthcare professionals housed in an innovative new building designed to generate synergy. This unprecedented continuum of expertise available in close proximity to patients allows Imagine to make discoveries for patients.*
The approximately 9,000 genetic diseases inventoried affect 35 million patients in Europe and 3 million in France, where 30,000 new cases are recorded every year. Close to 60% of children are undiagnosed following consultation for a genetic condition. Curative treatments have yet to be discovered for 90% of genetic diseases. The challenge of this major public health issue is twofold: diagnose and cure. www.institutimagine.org

About the CEA*: The CEA is a public research body active in four main areas: defense and security, nuclear and renewable energies, technological research for industry, and fundamental research.*
Drawing on its widely acknowledged expertise, the CEA actively participates in collaborative projects with a large number of academic and industrial partners. 16,000 researchers and staff form the backbone of the CEA. The Commission is a key player in European research and is increasingly taking a major role on the European stage. For more information: www.cea.fr

Press contacts:
AP-HP Media Relations: Anne-Cécile Bard & Marine Leroy - +33 (0)1 40 27 37 22 - service.presse@aphp.fr

Imagine Media Relations: 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 Media Relations: 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

Joint Director of the Human Lymphohematopoietic research group at the *Imagine* Institute, Marina Cavazzana is a pediatrician by training. Born in Italy, she graduated with a Doctor of Medicine degree in 1983, completed her qualifications as a pediatrician in 1987 and was awarded a PhD in Life Sciences in 1993.
She has held the position of Professor of Hematology since 2000 and is also Head of the Department of Biotherapy at Necker-Enfants Malades hospital, AP-HP, and Director of the Center for Clinical Research in Biotherapy, Inserm/Hôpitaux Universitaires Paris Ouest AP-HP.
Her research work on the development of the immune system and genetic diseases of the haematopoietic system to improve clinical outcomes has been rewarded by a number of distinguished societies, including the American Society of Hematology and the European Society of Cell and Gene Therapy.
Prof. Marina Cavazzana, Prof. Alain Fischer and Prof. Salima Hacein-Bey take credit for the first successful gene therapy for "bubble babies" with severe combined immunodeficiencies (SCID).
Marina Cavazzana received the title of Officier de l'Ordre National de la Légion d'Honneur (French Legion of Honor) and was awarded the 2012 Irène Joliot Curie Woman Scientist of the Year prize, presented by the French Académie des Sciences and the French Ministry for Education, Higher Education and Research. In December 2016, she was honored with the Prix National de l'Académie de Médecine in recognition of all her work.

Prof. Philippe Leboulch

Prof. Leboulch has a Doctor of Medicine degree from University Paris 12 and is a former intern at Hôpitaux de Paris (1985-1988). After a postdoctoral fellowship at Massachusetts Institute of Technology (1989-1993) he was appointed to the medical faculty at Harvard Medical School where he was a professor 1993 to 2007. He remains a Visiting (full) professor / Lecturer at Harvard.
Professor of Medicine and Hospital Consultant (PU-PH) at Paris-Sud Faculty of Medicine, Professor Philippe Leboulch founded and heads up the CEA's Institute of Emerging Diseases and Innovative Therapies (iMETI). In 2017, he was appointed Senior Advisor in medical innovation to the CEA and International Scientific Director of the new François Jacob Biology Institute, part of the CEA's Fundamental Sciences Division. He is also Visiting Professor at the Ramathibodi Faculty of Medicine, Mahidol University, Bangkok, Thailand.
Prof. Leboulch is a gene therapy pioneer and his work has been honored with many awards, including major grants from the National Institutes of Health (NIH) in the United States, as well as the Excellence Chair and Industrial Chair at the French National Research Agency (ANR). He served on the editorial board of *Blood* and on many international panels, including as Chairman of the *"Strategic review and recommendation panel for the 21st century"* subcommittee of the NIH National Heart Lung and Blood Institute (NHLBI). He was awarded the Grand Prix Etancelin from the French Académie des Sciences and the Ordre National de la Légion d'Honneur (French Legion of Honor). He is founder and co-chairman of the Scientific Advisory Board of bluebird bio, the US firm running this trial.