Necker-Enfants Malades Hospital: The gene-ius treating sickle cell disease

Dr Marina Cavazzana is a Professor of Hematology and co-director of research laboratory at *Imagine* Institute on the campus of Necker-Enfants Malades Hospital, Paris. Through her work, she has investigated the potential of gene therapy in treating several genetic diseases that affect children and adolescents. Only two and a half years ago, a teenager affected by sickle cell disease experienced a great clinical benefit thanks to the gene correction of his own hematopoietic stem cells. But, she now hopes to take this further, by targeting other genetic diseases both in France – and beyond.

Almost two and a half centuries ago, back in 1778, the world's first paediatric hospital opened its doors. This was named the Necker Hospital, and was founded by Madame Necker, who remodelled an old monastery building by the hospital in Paris.

Since then, times have drastically changed, but the Necker Hospital's founding principle has always remained the same: to provide help, support and medical treatments to children and adolescents. As of today, the Necker-Enfants Malades Hospital is a teaching hospital in central Paris, affiliated with the University of Paris Descartes.

Working there, Dr Marina Cavazzana has dedicated her time and research to investigating innovative protocol with a particular intervention gene therapy, focusing on sickle cell disease. She recently sat down with us at *Research Features* to discuss her research in more detail, outlining the impact gene therapy could have on the modern world.

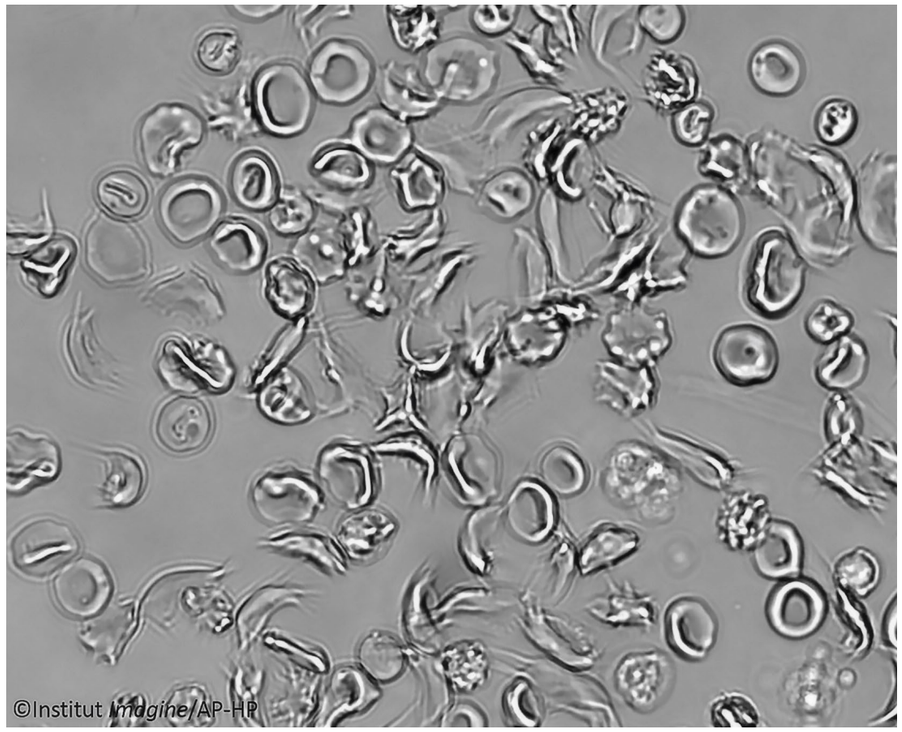
Sickle cell disease often affects people with limited access to information, as well as limited resources, who are difficult to reach, so it really is a worldwide problem

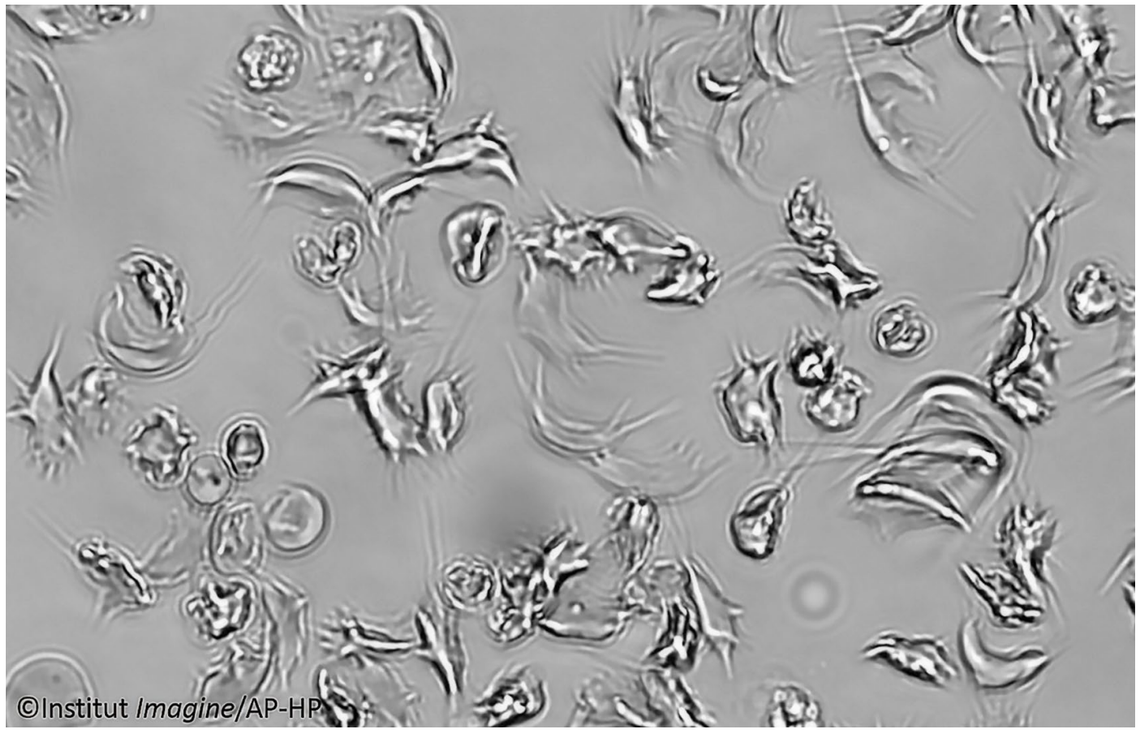
Hi Marina! What first got you interested in researching sickle cell disease?
Sickle cell disease (part of a group of disorders that affects haemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body) is the primary genetic disease in our region, Ile de France. Furthermore, sickle cell disease and thalassemia major occurs when a child inherits two mutated genes, one from each parent. Children born with thalassemia major usually develop the symptoms of severe anaemia within the first year of life. They lack the ability to produce normal, adult haemoglobin and experience chronic fatigue. They may also fail to thrive. Therefore, I thought that by designing a step-by-step approach to sickle cell disease, we could develop a treatment method for patients in potentially difficult situations. Sickle cell disease often affects people with limited access to information, as well as limited resources, who are difficult to reach, so it really is a worldwide problem.

What process did you follow to develop gene therapy research as a method to treat sickle cell disease?
Over twenty years ago, our group started to think about gene therapy as an alternative curative treatment for several genetic diseases. Following our first successful treatment, I thought that we were on a good track to approach a more difficult, red blood cell disease. In 2002, I started working in collaboration with Professor Philippe Leboulch in Boston trying to set up together the best clinical protocol for genetic anaemias. From this, we made a lot of preclinical experiments using *in vitro* and *in vivo* cell and animal models. Although, in 2007, we realised that the vector we were using to treat our first patient was not the best one that we could have been using. But, thankfully due to the collaborative work with Prof Leboulch's lab, our second genetic generation vector was set up, and we initiated a second clinical trial.

Of course, gene therapy is not only a vector matter. For gene therapy to be successful, it is important to put together the expertise that comes from different fields. So, for instance, we need an understanding of how sickle cell anaemia affects patients, expertise on the taking care of these patients, knowledge of bone marrow transplantation, and, of course, we need a long-standing know-how of molecular biology.

When did you first perform gene therapy on a patient with sickle cell disease?
The first patient was a teenager that we treated over two years ago. What was amazing about that was, in the first three months after the transplantation, the therapeutic beta-globin had essentially replaced the transfused one. And then, just six months after transplantation, we acquired proof that the patient had restored a clinical and biological phenotype, very close if not overlapping to that of a heterozygous subject. This was a very important moment for all the contributors to this important advance but it was an especially exciting moment for the family.





Left: Gene corrected sickle cell disease cells under hypoxic conditions

Right: Sickle cell disease cells under hypoxic conditions (not corrected)

What impact has the gene therapy had on that teenager's day-to-day life?
He has recovered a pretty normal life: now he can sustain the same physical and intellectual activity of the friends and students surrounding him, and I think this has had a great impact on his daily life.

How does it feel to have made such a breakthrough?
Obviously, you've got the very personal impact of that first teenager that the therapy worked on, but then there's also the much broader impact of that therapy being a success, that could then be used for so many other people.

Failure pushes you to work harder and be stronger. It forces us to solve the problem that the obstacle creates, to improve on the therapeutical interventions

Rather than my personal feelings, the efforts put into developing and sustaining the clinical research group has been second to none. We now hope to extend the use of this therapeutic approach to a greater number of patients, as there are a huge number of patients affected by this disease in our region.

Has this initial success provided an extra motivation for your work now?
Not really. I am very encouraged by the observation that this patient has recovered, but my motivation is not sustained by this particular success. My motivation is sustained over time, trying to help more patients. Sometimes in the physician's life, failure is more of a challenge than success. Failure pushes us to work harder and be stronger. It forces us to solve the problem that the obstacle creates, to improve on the therapeutic interventions.

When do you hope gene therapy for sickle cell disease will become widely available?
I hope that gene therapy for sickle cell disease will become widely available within the next five years or so at the latest.

And, in terms of cost, is it an expensive therapy to offer patients?
Yes, today it is still very expensive, but this is of less significance – it is more important to take care of patients using the correct treatment. Our aim is to continue to decrease the price of the gene therapy to essentially remove cost as an obstacle for its wide application globally. Besides, the one-off cost of gene therapy is in fact cheaper in the long-run than a lifetime of supportive treatment.

In terms of other applications for the therapy, could you give some examples of how else it could be used, for instance, on other diseases?
Gene therapy can be used to treat a lot of other serious genetic diseases. For example, it could be used to treat patients with: metabolic disease, primary neurodegenerative diseases, and haemophilia but also acquired diseases such as HIV infection or cancer. We are in a world of transition, in terms of the treatments that we can now provide patients who have previously only received partially satisfying treatment. So, this is a really powerful opportunity for a lot of diseases.

Working with genetics must involve several ethical issues. How do you approach those in your work?
Somatic cells are terminal differentiated cells which characterise the body system, and there are no ethical issues with these because there is no modification or impact on any germinal cells. Furthermore, we accurately examine the balance of risks and benefits disease by disease, and we enrol patients without alternative treatments or with more risky treatments. The most important ethical issue we currently have is how we can offer gene therapy treatment to all the people that need it, as well as how we can offer this treatment to more vulnerable populations, while always respecting the patient's rights.

You said that you hope this will be available within the next five years. What other developments do you hope to see within the next five to ten years?
The first important development will be the automation of this technology. If we can set up a process in collaboration with industrial partners building up a machine where we can correct the target cells in a closed system developing a programme that everybody can use, this could produce a method that could make gene therapy easily available.

• *For more information on the Necker-Enfants Malades Hospital's fascinating background, history and research, please check out their website by visiting hopital-necker.aphp.fr.*

Contact

Dr Marina Cavazzana
Hôpital Necker –Enfants Malades
149 Rue de Sèvres
75015 Paris
France

E: m.cavazzana@aphp.fr
T: +33 1 44 49 40 00
W: hopital-necker.aphp.fr

imagine
INSTITUT DES MALADIES GÉNÉTIQUES