Researcher discusses advances in gene therapy

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After leading successful clinical trials of gene therapy in Milan, Roncarolo hopes to build on that success at Stanford through collaboration with colleagues in the fields of genetics and stem cell science.

Gene therapy, a technique in which doctors attempt to treat a disorder by inserting a gene into a patient's cells is undergoing something of a rebirth. Since the death 16 years ago of a U.S. patient who was in a clinical trial for gene therapy, scientists and physicians have worked to better understand the technique and develop methods for making it safer.

One of the world's experts on gene therapy and stem cell science is Maria Grazia Roncarolo, MD, who joined the School of Medicine faculty in 2014 as a professor of pediatrics and of medicine. She led a couple of successful gene therapy trials in Milan, and hopes to build on those successes at Stanford. She spoke recently with Paul Costello, the school's chief communications officer, during a *1:2:1* podcast about the state of gene therapy. This Q&A has been adapted from their discussion.

Q: The 1999 death of Jesse Gelsinger in a gene therapy trial dramatically changed gene therapy in the United States. Since then, there have been key advances that have changed the science. What were

some significant moments since 1999 where gene therapy became accelerated in its capabilities?

Roncarolo: There is no doubt that the death of Jesse in 1999 was a major setback for gene therapy. It was a tragedy. Also, in 2002 there was a major setback when one of the children in a French trial for severe combined immunodeficiency developed leukemia as a result of the gene therapy. After that, a number of other kids developed leukemia.

These were major setbacks, which were unexpected and unforeseen. The major problem was that we underestimated the complexity that it takes to manipulate the genome and to introduce a healthy gene to fix a genetic disease.

However, from these mistakes and from these tragedies, we learned a lot. We were forced, as doctors, but more importantly, as scientists, to go back to the bench and develop better technology and understand more what was required.

The technology we have today is much more advanced than what we used then. We use better vectors, which are the carriers to introduce the healthy gene. We learned much more about what we have to do to prepare the patients to receive the gene therapy. We also learned that we need to carefully monitor the patients to understand where the genes land in the genome.

Q: Was it a climb out of rubble, in many respects, because a lot of researchers left the field of gene therapy?

Roncarolo: Yes, but a few centers, including the center where I was working in Milan, and many other centers in the United States,

continued to believe and to support the research. If we look today, the landscape is completely changed. Today, we can say that we cured, with gene therapy, a number of genetic diseases that were incurable a few years ago.

Q: Can you talk about those specifics of what diseases have been cured?

Roncarolo: Sure. Let me start with my own personal experience. I had the privilege, in Milan, to be the principal investigator of a trial that is considered a landmark in gene therapy. We used retroviral vectors, which are carriers for the gene. They have limitations, but at that time were the only vector we could use to manipulate the bone marrow cells of a patient with severe combined immunodeficiency. This was a particularly difficult disease because it's a severe combined immunodeficiency due to a defect in an enzyme called adenosine deaminase. The gene therapy in these patients cured them. This was really the first and, I must say today, the only successful trial using the retroviral vector.

I was also the principal investigator of a trial in Wiskott-Aldrich syndrome, which is a complex disease of the blood. There is immunodeficiency, but also there is defect in multiple lineages of the blood, with severe bleeding among these patients. Now we treat these patients successfully with gene therapy.

The other major achievement at my institute in Milan was in metachromatic leukodystrophy. This is a metabolic disease that was incurable before gene therapy. Now we can cure these patients with gene therapy. We can give them an opportunity for life.

There are many other trials in the United States and in Europe that

showed how we can successfully and safely cure patients with a number of genetic diseases such as hemophilia, thalassemia and sickle cell anemia, and diseases of the retina that cause congenital blindness.

Q: You came to Stanford in 2014 from the San Raffaele Scientific Institute in Milan. What drew you here?

Roncarolo: Stanford has a tremendous opportunity to revolutionize the field of stem cell and gene therapy. The basic science is really at the cutting edge of innovation. When we look at the scientists that work in the field of stem cells at Stanford, it's a critical mass of innovation and knowledge that is quite unique.

What I saw is the opportunity to translate this tremendous amount of knowledge, which is now at the level of the bench, to the bedside. When we translate this knowledge to the bedside, we advance medicine. More importantly, we will cure patients who now have incurable diseases.

That's what attracted me here. I saw tremendous potential. Of course, together with the tremendous potential, I saw also a commitment from Stanford to invest in translational research, both in the pediatric and the adult side.

Q: Where do you see as the greatest hope for gene therapy?

Roncarolo: I would make a distinction. The ladder of translational research consists of different steps, from the step of identifying the gene that is defective, in the case of genetic diseases, to the step in identifying the mechanism that caused the disease and to the step of targeting the disease for gene therapy.

When we think about genetic diseases and what we can do at Stanford, one unique opportunity is the possibility of gene therapy using purified stem cells, both blood purified stem cells, but also tissue stem cells. We have at Stanford a very advanced technology of genome editing that we can use to correct these tissue stem cells.

Also, we have a number of novel biological drugs that can help us to prepare the patients to receive these cells in a much less toxic and risky way. These biological drugs would make a huge difference because we could perform the gene therapy without the need of chemotherapy to prepare the patient.

If we adopt these three steps—the genome editing, the use of purified stem cells and the better preparation of the patient—they would revolutionize the field of gene therapy for genetic diseases.

Provided by Stanford University Medical Center

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