Interview: Prof. Luigi Naldini – Director, San Raffaele Telethon Institute for Gene Therapy (TIGET), Italy

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Prof. Luigi Naldini, Director of TIGET, discusses the success of the institute and the groundbreaking partnerships it has formed with the pharmaceutical industry, as well as his ambitions for TIGET over the coming years.

Prof. Naldini, the San Raffaele Telethon Institute for Gene Therapy was set up in 1995 as a joint venture between the Telethon Foundation and the SRSI. Could you start off by describing the institute's primary aims and ambitions?

The ambition was to fill a gap in the area of rare diseases where there was little research being conducted and even less opportunities for getting access to a reliable and effective treatment. These orphan diseases are so rare that they become forgotten diseases with forgotten patients. To combat this, a charity was set up and named the Telethon Foundation, with an aim to collect public money in order to fund research.

Today, the organization has become a success story, and I think this can be attributed to the way in which it was managed from the outset, operating through a highly merit-based and peer-reviewed methodology. This is now becoming a gold standard for similar charities across Europe, and we can say that it has been an important driver of scientific research in Italy.

The next big step was creating an institute which combines basic research and clinical activity. It is important to realize that if you want to conduct research and develop a new treatment, it is crucial to speak to a clinician early on in the development process. Scientists need to know if their idea is realistic or not as soon as possible. This was the key idea behind our institute, to bring together a center of excellence in the clinical area, which is San Raffaele, and a team of scientists with a specific mission to develop treatments for rare disease.

How is the institute positioned for gene therapy among the Italian and European scientific communities?

I would say that today we are one of the best known centers for gene therapy in Europe. We have a long track-record of gene therapy research which has yielded very promising results, such as ADA-SCID which is the longest-running and most successful gene therapy program in the world. In that program in particular we have had success with several treated patients without significant adverse effects. Indeed, our successful experience with ADA-SCID gene therapy was the basis for our institute's alliance with GSK, and together we are developing what could become the first ex-vivo gene therapy to be approved anywhere in the world.

The second biggest development for us has been in lentiviral vector technology. This allows for much more efficient and safe gene transfer than previously available tools. Here we have been a leading center, and we have a pipeline of new technology in development, together with dedicated efforts into their clinical translation. We have two trials running in lentiviral gene therapy, one for metachromatic leukodystrophy and another for Wiskott Aldrich syndrome, which are highly advanced with more than 20 and 7 patients treated so far, respectively. Today these are considered by the worldwide scientific community as the most successful ex vivo gene therapy trials in genetic disease. So this is our main expertise. We also have other projects aiming at in-vivo gene therapy, for instance for hemophilia, but these are not yet advanced to the clinical testing.

How was the institute able to build up this world-renowned expertise in clinical trials for gene therapy?

I would say that this was due to the vision of its former directors, who saw at a very early stage that there would be a need to have this expertise available. There was therefore an early recruitment of individuals with the necessary skills and technology, as well as an effort to protect and foster the careers of promising young scientists who would later develop expertise of their own. The third aspect which greatly contributed to our success was the establishment of in-house manufacturing capacity. Early on the SRSI spun off what is now MolMed SPA, a company which still

provides us with the pharmaceutical products needed to conduct our gene therapy trials. Having this capability to manufacture on-site has been key for us.

So in summary it was the combination of excellent clinicians, scientific researchers and advanced gene and cell therapy product manufacturing capabilities, which made it possible for us to excel in this area.

It is clear that here at the institute you have built up a solid eco-system for scientific research and its translation into therapies. Looking at the wider country however, how would you rate Italy's eco-system for conducting research?

That is less encouraging. We have a long tradition of excellence in the early stages of education towards scientific research, which is still present today. However, for a long time we have had serious difficulties in further supporting the career of our young apprentices at home, and providing them with the job opportunities, financial resources and laboratories to conduct their own research. This largely comes down to shortage of funding, pitfalls in the distribution of funding and in the mechanisms of recruitment and advancement in academia. Overall, this means that, although we still produce excellent scientists, they tend to leave the country early on in their career. Until about fifteen years ago there was a trend for scientists to be educated here, then to spend their entire career abroad before returning to Italy for retirement, which is not very effective for breeding our own research community. Slowly however this has been changing as some areas of the country have begun to build up centers of excellence, which provide the opportunity for recruitment of scientists in early and more productive stage of their career.

On the funding side, we are getting a good portion of our funding from the EU, which is highly competitive but can be well rewarding as well. Besides that, the largest portion comes from charities such as Telethon. We also receive funding from the National Ministries of Health and of Scientific Research but this type of funding is unfortunately often delayed from the time of application and given its limited time span and overall budget often makes it difficult to build long-term planning and ambitious research projects on it. In that aspect Italy still has big room for improvement. Unfortunately, the pharmaceutical industry is slow to take up new projects, meaning that the burden of progressing in the early research phases falls almost entirely on the institutes and the EU. Ideally this gap could be filled by small biotech companies, which could support the early steps. This is now starting to happen, and I hope that this trend will continue on. Currently, however we often need to do the early proof of principle in the clinic on our own, before we can attract interest from the pharmaceutical community.

Could you describe the institute's collaboration with the pharmaceutical industry, and GSK in particular?

The alliance with GSK is very interesting because it aims to develop an entirely new form of therapy. In this sense it is groundbreaking in that there is no obvious commercial path to follow. That meant that when GSK started looking at the project, it was completely new for them. Although they liked the science and the early clinical results, they struggled when they started to bring in the manufacturing and regulatory stakeholders. Manufacturing a treatment based on cells harvested from the individual patient is much more challenging than producing an ordinary drug for example. So we are building up a brand new framework here, in many areas, including the regulatory processes for market access.

The effort has certainly been two-sided, with both organizations trying to educate each other. There has been a steep learning curve for GSK and for the institute, but we are certainly making progress. Within the institute I can see that our standards and quality of research have improved as a result. For example, we have established a center for GLP studies to support all pre-clinical trials. For this we had to train some of our people to a new way of working. This is a whole culture with a focus on process quality and accountability, which ordinarily doesn't fit so well with the early, basic research we traditionally conduct, but which becomes essential at later stages of development.

The experience of this institute seems to be emblematic of a shift in culture taking place across the academic and pharmaceutical communities, in which both are recognizing the need to work together more closely in pursuit of a more efficient research model. Is that what you are heading towards?

Yes, I think so, and there are two different ways for doing this. First, when working on early stage projects dealing with new concepts and technologies, such as targeted genome editing, we work better with small biotech's, which have smaller budget but also better understanding and a keen interest in the science and early research. Second, when moving towards the actual clinical deployment of new therapies we need the support of large industry, and the partnerships we have formed are a clear illustration of the progress made here as well.

As director, what are your personal ambitions for the institute?

So far we have been very successful, sometimes even beyond what we had hoped for, in the progress towards development of new treatments for rare genetic diseases. In that process we have contributed to establish an almost entirely new platform and promising strategies for gene

therapy. The biggest challenge now is to bring these models and strategies from gene therapy to oncology as well. The San Raffaele institute has a strong competence in immunology, especially immuno-oncology and we have developed some new ideas for targeting cancer along the way. So this is what we are looking to do now, to create a new focus on bringing our novel strategies to the field of cancer, and that will be another big challenge for all of us.

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