**Annoncer:** The Bio*World Insider Podcast*.

**Lynn Yoffee:** This is the Bio*World Insider Podcast*, and I'm Lynn Yoffee. The rapid development of COVID-19 vaccines in many of the world's richest nations has brought global attention to the messenger RNA-based technology behind them, also known as mRNA, but another potentially transformative technology has advanced too. There are vaccines that use DNA to prime the immune system. Emergency use authorization for Zydus Cadila’s DNA-based COVID vaccine called ZyCoV-D made headlines recently in India. It was a global first that we shared with *BioWorld* readers in late August.

Today, we'll take a closer look at this type of vaccine with our guest, Lucio Rovati. He's the CEO and Chief Scientific Officer at Rottapharm Biotech, which is headquartered in Italy. Just recently, his firm announced early results from a Phase 1 study of Covid-eVax. It's the first DNA vaccine candidate against COVID-19 to enter clinical development in Europe. Rottapharm is developing it with Takis BioTech, another Italian firm. We're glad to welcome Lucio as our guest to talk about the early clinical results with BioWorld Managing Editor, Michael Fitzhugh. Over to you, Michael.

**Michael Fitzhugh:** Thanks Lynn, and thanks for being with us today, Lucio.

**Lucio Rovati:** Thank you, Michael. Thank you, Lynn, for the kind invitation.

**Michael Fitzhugh:** I'm really excited to talk to you about Covid-eVax and DNA vaccines more broadly, but before we get there, could you tell us a bit about the backstory of how and why you founded Rotterpharm BioTech?

**Lucio Rovati:** Sure, with pleasure. Well, the history of Rotterpharm goes back to some 60 years ago. The company was founded by my father who was a physician and a pharmacologist as well. He left the university in order to found his own private drug discovery laboratory. Actually, he was able to create a company out of that became one of the largest pharmaceutical companies in Italy, with a global presence throughout the world. It was probably the fourth or fifth largest pharmaceutical company in Italy, when, in 2014, we decided to merge the commercial activity into another larger company. Today, our franchise is with the American company Mylan, and now Viatris, actually, and we retained for us only the R&D activities, as this was the founding basis of the company.

**Michael Fitzhugh:** The R&D activities, tell me a little bit about why you retained that piece and a little bit about your background because I understood, reading about it, why you would gravitate toward that. Tell our listeners a little bit about that.

**Lucio Rovati:** Sure, with pleasure. I'm a physician as well, and a clinical pharmacologist. I've always been the scientific background of the company over the past 30 years. I directed the R&D activities and the medical activities and the medical marketing activities. I wanted to continue to do that, and I was very happy not to deal any longer with the commercial activity, which may be, for a scientist sometimes, it may be frustrating as you may understand. I was very happy to do that and concentrate 100% on research together with my scientists. We formed a great group.

Actually, it was the group that promoted the scientific activity of the Rottapharm through time. We could now finally devote it only to R&D activities for new innovative medications. That's the only thing that we want to do, and we do it according to a pure biotech model, that is we discover, we develop, we partner our compounds, or we get compounds from outside, try to develop them as much as possible, and then find partners in proper pharmaceutical companies that can eventually complete the development and bring them to market.

**Michael Fitzhugh:** Now, before COVID-19, you'd started weed programs that Rottapharm Biotech in areas where there is still tremendous need and room for innovative products, osteoarthritis, rheumatoid arthritis, and even cancer. In June 2020, just a month after Italians appeared from what was then the world's longest nationwide COVID-19 lockdown, you announced a collaboration with Rome-based Takis to develop a DNA-based vaccine against Sars-Cov-2. The world was really at that point focused a lot on late-stage mRNA vaccines. What drew you to this program with Takis?

**Lucio Rovati:** Well, thank you very much for this question, Michael. Actually, as you can understand, I'm an entrepreneur, a physician, and a pharmacologist. Immediately, in March 2020, I asked myself what could I do? What could my company do with that, and what could my scientists do with that? We looked around, we found this potential partnership with Takis. They had this tremendous technology of DNA vaccines. We knew that, of course, mRNA vaccines were along the development as viral vector-based vaccines, but this was a different platform.

We wanted to see if this platform could add something to vaccines that were under development at that time, and on the other end, on which we didn't know much in April when we actually started the development together with Takis. We started with enthusiasm. Although we were-- never been involved in vaccine development, but we believed we could do something with that. Especially we have this new technology and we wanted to see how the technologies could compare and how one could be better than the other, and in which aspects.

Immediately we started that, and honestly, I'm very proud of my team because in six months, which is a record time for us, probably others did better, but for us, it's a record time to arrive to Phase 1 clinical trial, to the submission of the request for Phase 1 clinical trials. Actually, we did a very good Phase 1 and we are now dealing with some very good results.

**Michael Fitzhugh:** It is really remarkable, the speed at which all programs in this area has moved. I think that there seems to be a motivation electricity running through the industry that's really driving people to Excel.

**Lucio Rovati:** Absolutely. This was great. As you said, it's probably the first time that pharmaceutical companies, independent scientists, academic scientists, they work together. Data are available on a real-time basis and anybody can benefit from it. That's why probably we had four vaccines approved in less than nine months, and several others are coming. This is extremely important because we still do not know which one is the best platform, what is the best combination? What is the best antigen? What is the best way of administration? It's great and it can benefit R&D in several other areas besides vaccines against the Sars-COVID-2.

**Michael Fitzhugh:** In that discovery mode, just going back to what you were saying earlier about how your team had curiosity around which platform might offer what. Tell us a little bit about how mRNA and DNA vaccines differ in their approach to building immunity.

**Lucio Rovati:** Well, the approach is pretty similar. These are genetic vaccines that includes also the viral vector vaccine. The basis is pretty common. On the other end, DNA as, of course, you know is the genetic information which is on top of messenger RNA information. We believed, from the very beginning, that there might have been differences and advantages in using DNA. For example, since the information stays on the top of the genetic information, compared to messenger RNA vaccines.

We believe that it may give a longer duration of the immunological response because the production of the protein, of which we administered the information, is longer. This is one of the potential advantages. Then it does not relate to the platform, but it relates exactly to our vaccine. We didn't use the full-length spike protein as most of the vaccines available today. We used only the RBD segment of the spike protein, which is very conserved among variants. Actually, we have laboratory data showing that the immunologic or response induced by our vaccines in animals so far, is not influenced by the variant. The efficacy seems to be more or less the same independently of the variant. There are potential advantages with the technology and potential advantages with our approach as an antigen.

**Michael Fitzhugh:** I understand that there may be some other differences too in terms of-- You've mentioned administration obviously, but manufacturer and transport. Can you tell me a little bit about those elements?

**Lucio Rovati:** This is a very important point, of course. Manufacturing, first of all, because manufacturing of DNA is fast and cheap, definitely faster and cheaper than messenger RNA, as long as they work, of course. Transportation is also a key point. You know that RNA vaccines are subject to the coal chain for transportation and storage, while DNA is a very stable molecule. You do not need a cold chain, so it can be transported, it can be stored at room temperature, most likely. This makes the life of everybody easier. There is a drawback, which is, as you correctly mentioned in your last part of your question, the administration.

DNA is a bulky molecule, bulkier than RNA, and therefore, in order to enter the cell, you have to do something. Either you have to use a complex formulation, as on the other end is the case for RNA, or you do something different. For example, we use electroporation. Electroporation is a very small electrical field applied to the muscle when you administer intramuscular-related vaccine, the electrical current opens up some pores in the membrane of the muscle cells and the DNA can enter. It is very safe. There is no problem from this point of view, but on the other end, it's a complication. It's easier manufacturing, transporting, and storing, it's a bit more complicated to administer DNA vaccines.

**Michael Fitzhugh:** In the case of COVID-eVax, you and Takis, I think have a partnership with an electroporation technology provider. I can't recall the name, sorry.

**Lucio Rovati:** Absolutely. It's another Italian company, it's called IGEA. It's in the center of Italy. It's one of the most important companies in Italy for developing this kind of medical device and, and other medical devices as well. It's a great Italian collaboration, which is not easy. I believe it's one of the most important things that we're doing right now.

**Michael Fitzhugh:** Why is it not easy to have a great Italian collaboration?

**Lucio Rovati:** The world has become global. Whenever you have a collaboration with other companies, it's usually a global collaboration. You collaborate either with an American company and then with a German company, and perhaps with a French one or with a Chinese one. It's very difficult to find collaboration in the same countries, which, especially in the case of a pandemic, might stimulate the interest of the country itself, which is very good, I believe in this period.

**Michael Fitzhugh:** Very interesting. Let's talk about COVID-eVax itself in this trial. It's early days obviously Phase 1. Tell me a little bit about the potential that you've seen showing through from that Phase 1 trial and how the efficacy appears so far.

**Lucio Rovati:** Absolutely. Let me, first of all, say that as in any Phase 1 study, the main objective was safety and safety was great, despite electroporation. We confirmed that electroporation may be a bit cumbersome, but it's a small complication, but it is very safe. There are no problems from this point of view. We, of course, analyzed the immunological response, which was pretty good. The surprising thing was that the cellular immunity that apparently we induced is better than the humoral, or antibody immunity. This was a bit surprising because we expected more or less the same effect, the same efficacy on humoral antibody or cellular immunity.

Actually, we saw that the cellular immunity was really outstanding. This opens several perspectives in order to understand the efficacy on the disease. Actually, if you have a good cellular immunity, and you can therefore attack cells, our cells, human cells that are eventually infected by the virus, you could probably stop the disease, avoid the disease, and have a very good efficacy from this point of view. The other question is how these will, in some way, go together, go along with the immunity induced by other vaccines.

For example, when you do a third dose or a fourth dose after an RNA vaccine, can the DNA vaccine, with this huge cellular response, improve or call back a different immunity compared to the RNA and therefore obtain even longer, better, safer protection? This is the question that we have to answer right now.

**Michael Fitzhugh:** I think that leads to something that you talked a little bit about in the press release that maybe it would be difficult to carry out a Phase 2 study as it was originally planned, but that maybe there, if I'm recalling correctly, there was some opportunity to look at that booster that synergistic space. Can you tell me more about what you're thinking about that element now?

**Lucio Rovati:** Yes, absolutely. In Italy, for example, we have our Phase 2 approved in Italy, but in Italy we have right now 80% of the population, which is fully vaccinated, and it will be probably 90% in the next one or two months. It's impossible to run clinical trials here. It's virtually impossible to do it also in the rest of Europe where the situation is pretty similar, perhaps they are not at 80%, but we are over 60 and close to 70 or 75%. The same applies also to major countries in the Eastern world and in the US, of course. If we want to develop a new vaccine, we have to look at something different.

Actually, what we should look at is a third dose or a further dose from now on, and see, as I was saying before, whether the different responses that we observe can in some way potentiate the previous administration of a different platform of vaccines. This is extremely important, I believe, and also, it's important to confer that such a heterologous administration vaccination induces a higher immunity. This has already been shown. Several people have been vaccinated with the first dose of a viral vector vaccine, and then a second dose of the messenger RNA vaccine. The immunity seems to be better when you combine these two platforms.

We believe that there is a chance that combining this third platform with DNA might further improve and differentiate the immunological response, so there is a huge potential. The second thing, of course, and probably I should have mentioned it before, this huge cellular response opens up a lot of perspectives with other indications of DNA vaccine. A cellular response is probably the most important immunological response when you go against cell. Therefore, it is a tremendous weapon that we have to test against tumors in oncology indications.

**Michael Fitzhugh:** Does that suggest that oncology is an arena in which DNA vaccines are maybe more likely to stand on their own?

**Lucio Rovati:** I definitely think that. Actually, there are DNA vaccines approved in animals in the veterinary space for oncology indications. I believe this should pursued also in humans. DNA vaccines have had problems in the past in that we knew that they were potent immunological weapons, but it was difficult to translate from the animal to humans. Now with this first Phase 1 data, we are showing that actually it can be translated to humans, perhaps not as good as with animals, but in a sufficient way. Therefore we should plan for these indications, but also for other indications, and oncology stands up as the favorite, I would say.

Let me also add that, as you cited in the very beginning, there is a DNA vaccine, which has been very recently approved, which is the vaccine of Zydus Cadila in India. Although this seems to be less effective than other vaccines, such as the RNA vaccines, I'm not that this is the case because anything about 60% on the symptomatic disease is great. Where if we had bet on that, that would've been great, of course. Second, don't forget the DNA vaccine was develop in India under the pressure of the Delta variant. That 67% probably cannot be compared directly with vaccines that have run their Phase 3 earlier than the Delta variant, and probably the efficacy is pretty close.

**Michael Fitzhugh:** That is really interesting context, I have not considered that in thinking about that result. Thanks for bringing that up. According to Clarivate Cortellis, there are now more than 20 DNA vaccines for COVID-19 in development. How do you think that market might develop and how do you think COVID-eVax might ultimately fit into that?

**Lucio Rovati:** First of all, you see, we have to understand, the scientific community has to understand which is the role of DNA vaccines compared to the other genetic vaccines. I was mentioning some of the possible advantages and disadvantages. We have to see which one is the best platform, which one is the best combination, and also which one is the best antigen because these 20 or so DNA vaccines are probably using different antigens, either the full-length spike, or the RBD, or different combinations of viral proteins. The other thing is that not all DNA vaccines are administered in the same way.

As I mentioned, we are administering it with electroporation. Someone else, such as Zydus Cadila, for example, they are employing needle-free injection, and we have to understand which are the differences. Someone else again is employing complex formulations. These 20 DNA vaccines are not at all the same. We have to understand which one performs better and which one may combine better with other genetic vaccine as third dose or further boost.

**Michael Fitzhugh:** Got it. Obviously, as this program develops, Rottapharm Biotech is developing other programs, you're working on other goals. Can you tell us a little bit about where you envision the company being in the year?

**Lucio Rovati:** Absolutely. As you correctly mentioned at the beginning of this talk, our traditional field of discovery and research is not vaccine. We have been very active in the rheumatological space, for example. I tell you, we have to find a drug, a treatment for osteoarthritis. This is something that we've been pursuing for the last decades. We developed some very interesting compounds. You may know that Rottapharm was the company that developed glucosamine sulfate for osteoarthritis, which is now a very famous medication in OTC used everywhere, but it is not exactly what we want. We really want a treatment for osteoarthritis.

We are dealing with the disease phenotypes. We believe we could be in the clinic soon with something for the different osteoarthritis phenotypes. Having said that, we've moved in recent years also to the oncology field. We have a Phase 2 program running in immune-oncology. We have a Phase 1 clinical trial in preparation with a small molecule in glioblastoma. We are widening our collaboration on advanced therapy in oncology, including especially cellular therapy. I believe that we are in a very good phase and in a very good mood, and in a year from now, we should have very good results in order to progress the company.

**Michael Fitzhugh:** Excellent. Lucio, thank you so much for sharing your time with us today. I really appreciate you joining us.

**Lucio Rovati:** It was my pleasure. Thank you for the invitation.

**Lynn Yoffee:** Thank you, Lucio and Michael. Given the tsunami of issues around boosters related to the current mRNA vaccines, a new DNA vaccine that extends immunity might certainly offer a stronger option. As always, *BioWorld* will continue to keep you informed of all the most important scientific, clinical, and business updates in the field. That's our show for today. If you need to track the development of drugs, turn to *bioworld.com*. Follow us on Twitter or email us at *newsdeskatbioworld.com*. Also, if you're enjoying the podcast, don't forget to subscribe. Thank you for joining us.

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