Thomas D. Madden – CEO, Acuitas Therapeutics

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Dr Thomas D. Madden, CEO and founder of Acuitas Therapeutics, shares the story behind their involvement in Pfizer and BioNTech's COVID-19 vaccine, the numerous applications of the company's proprietary lipid nanoparticle (LNP) delivery technology, as well as the growth strategy of the Canadian company.

Thomas, congratulations on the successful collaboration with Pfizer and BioNTech's COVID-19 vaccine, which has since been approved for emergency use in the UK, and with pending applications in the US and the EU. This messenger RNA (mRNA) vaccine uses Acuitas Therapeutics' proprietary lipid nanoparticle (LNP) delivery technology. Could you give us a quick overview of this?

Acuitas was established in 2009 and this LNP technology came out of the research conducted by Professor Pieter Cullis at the University of British Columbia in Vancouver. We have developed an LNP delivery technology to enable our partners to be able to move new classes of drugs – drugs that are essentially based on biological molecules or systems – into the clinic and the marketplace. These are nucleic acid drugs, including RNA interference (RNAi) or soluble RNA (sRNA) drugs intended to inhibit the production of particular proteins. One of our first partners was Alnylam Pharmaceuticals. We provided the LNP delivery technology for their product Onpattro™, which became the first approved RNAi drug in 2018.

More recently, we have focused on working with partners, developing mRNA therapeutics. Our delivery system is critical here for two reasons. Firstly, the mRNA itself is very rapidly broken down within the body, so it needs to be protected within a carrier system. Secondly, the mRNA also needs to enter cells within the body in order to be active but it is too big to enter on its own. Our LNP technology protects the drug after it has been administered and also delivers it into the cell cytoplasm so that it can start expressing proteins.

Our work with mRNA really began around 2011, when I read an article about mRNA that outlined the concept of using it as a therapeutic. mRNA is a natural biological molecule and all of our proteins are made through it, so it is an extremely powerful tool. This article was the first to propose that it could be used as a therapeutic – for instance, in individuals with a genetic disease that prevents them from producing a functional form of a protein. Using mRNA, a synthetic message can be delivered to help the cell produce that protein, which would then address the genetic disease. That was when I realized that our delivery technology was ideally suited to enable mRNA therapeutics to move into the clinic.

We undertook research internally to demonstrate the feasibility of this approach, and we also began talking with companies that, at that point, were just beginning to look at the potential of mRNA as a therapeutic. We also worked on feasibility studies with these companies so that they could evaluate our technology. Over the years, we have built a number of different partnerships, including with BioNTech – one that has culminated in our technology being used in the development of COVID-19 vaccines.

Could you share a little more regarding this successful collaboration with Pfizer and BioNTech on the COVID-19 vaccine?

We had already been working with BioNTech prior to this COVID-19 vaccine, so when the pandemic hit, they recognized that our technology could be used to help them develop a vaccine. We began discussions with them in January, and then we flew to Germany in early February to meet the German regulatory authorities, as well as BioNTech, to map out the clinical program necessary to support a COVID-19 vaccine candidate.

Throughout the process, we have been working extremely closely with BioNTech and Pfizer to support selection of the vaccine candidate, since a number of different mRNA constructs expressing different proteins were being looked at.

We have also supported the work necessary for the manufacturing scale-up so that our partners are able to provide as many doses as possible. Pfizer and BioNTech are projecting to manufacture 1.3 billion doses in 2021, which requires a huge commitment. The Acuitas model is that we transfer our process technology through specialized cGMP organizations, as we do not do manufacturing, and so we have also worked closely with these organizations to improve the manufacturing scale. We helped them see how they could produce much larger batches – and much more quickly – which required some development work to be undertaken internally and subsequently transferred.

The other challenge is related to the lipid nanoparticles used in our systems, since these are proprietary lipids. We had to work with our lipids manufacturers to increase the scale of *their* manufacturing vastly as well.

Prior to this COVID-19 vaccine, mRNA technology had never been used to develop an approved product. How do you think this achievement might boost the mRNA market?

Indeed, this COVID-19 vaccine would be the first approved mRNA product, and it looks like the second vaccine approved might also be an mRNA product. There had previously been mRNA vaccines in development. For instance, one of our other partners is CureVac, who did a very interesting Phase 1 study on a rabies mRNA vaccine.

When COVID-19 emerged, we quickly recognized that the mRNA vaccine approach was potentially ideally suited for the rapid development of a vaccine to address COVID-19. Compared to conventional approaches taken, where killed or attenuated viruses – or adenoviral vectors – are used, mRNA vaccines are inherently a much more precise and elegant approach. Rather than using an entire virus, we are simply providing the instructions to allow the body to construct a single component found in the virus that would trigger an immune response. I think there are potential safety and potency advantages with this approach.

We have also shown that this technology is capable of developing a vaccine more rapidly. Therefore, I think this will generate a lot of interest in other vaccine opportunities, as well as in the investment of an infrastructure that would allow us to respond much more rapidly, should a new viral threat come along. No one who has lived through COVID-19 wants to live through a COVID-20 or a COVID-21.

mRNA is still a very new technology. Do you think existing players are likely to also start exploring this new platform?

Personally, I think Big Pharma can sometimes feel trapped by the scale of investments they have made. If a company has invested USD 5 billion in manufacturing plants based on a particular technology, it would potentially be political suicide to suggest that they move away from that technology. That is a challenge Big Pharma faces, so it is a difficult sell to suggest that they think about adopting a new technology.

But I think we should always be open to evaluating new ideas and to accepting that better approaches may exist out there, as opposed to saying that, well, we have always done it this way, so we will continue to do it this way.

The good news is that companies do seem open to collaboration. There are three major mRNA companies today: CureVac, BioNTech and Moderna. Obviously, BioNTech has partnered with Pfizer, and CureVac recently announced a major collaboration with GSK, so there are opportunities to work together to gain expertise and technology from major players in this new field.

What do you hope to see from a regulatory perspective?

In addition to the inherent benefits of mRNA technology for vaccine development, another exciting area in which we are working on with our partners is gene editing. We have many partners using our technology to deliver gene-editing proteins or base-editing proteins, and we are seeing very exciting data in this field. But this is also a very challenging field, from a regulatory point of view, because it is about changing the genetic information of patients – so there are ethical and safety considerations. We would be very interested in understanding the regulatory considerations that would allow for the clinical development of these products.

Partnership is clearly a critical strategy for Acuitas. What has been instrumental in developing successful collaborations?

Our business model is a little unusual for a biotechnology company, since we are a pure technology provider. We do not develop products internally in competition with our partners; our model is to provide our technology to partners to enable them to develop products through the clinic and into the marketplace.

For us, our values are transparency, honesty, collegial interactions, and respect for our partners. These have greatly facilitated effective and efficient international collaborations. The groundwork we have put in place in our partnerships allows us to move very rapidly. For instance, with BioNTech, I know the CEO on a personal level, we enjoy working together, and we have built up trust. These personal relationships really facilitate rapid mobilization. If you have built up trust in a partner, then you are willing to take risks with that partner, and they are committed to supporting you when it is needed.

Acuitas is working in a niche area and has established a market leadership position. How do you evaluate the current competitive landscape, and what do you see as Acuitas' main advantages?

Firstly, we have a large IP portfolio with around a hundred patents, which is pretty significant for a small company. I think the key consideration is that people want to use our technology because it is the best, and we do believe we have the best technology in this area, and the best-tolerated LNP compositions. That is one of the primary reasons people should work with us.

Secondly, we are good partners. We try to ensure that we are as supportive and as collegial as possible, so that we can provide a positive environment for collaboration.

Another advantage is that we have worked with a lot of companies developing mRNA therapeutics. We are known globally and work with companies globally. Of course, the information we generate with each company for their products is maintained strictly confidential and we would never disclose information about one partner to another. However, with all of these collaborations, we have learnt about areas with potential and areas that are nonproductive. We have experience regarding which is a good path to go down and which is not. Therefore, we are able to provide this perspective to any potential partner, along with our experience and guidance – again, without ever disclosing anything confidential about a single partner's projects. Being able to see the big picture – the entire mRNA landscape – is a major advantage we can provide.

In addition, we have also established a global alliance of academic collaborators with whom we work. That gives us insight into a lot of leading-edge research that has not been translated into commercial activities yet, so we also have an understanding of what people are exploring in terms of this technology.

Many platform technology companies eventually move on to develop their own portfolio of products. Will Acuitas also move in this direction?

When companies have been very successful in developing a technology and then they want to do something different, for me, I have to ask, why? Acuitas is not going to become a product development company. That is not our business model. I think product development distracts from the research. As soon as a company starts developing products, all of its resources need to be directed towards that. The market only cares about how the products perform, and having worked in companies with product development models, I think that is a huge limitation.

As a biotech company, we are also unusual because we have always been profitable, so we have always reinvested revenues in technology development. We want to continue to invest heavily in our technology so that we can stay ahead of the field. We want to continue to be the global leader.

We also try to stay in front of our partners and to anticipate what they might need so that we can undertake research in those areas so that we can support them.

We have seen a lot of success over the last two or three years, and certainly, the COVID-19 vaccine development is a seminal event for us, but our business model is not going to change substantially. We have always wanted to increase the number of partners we work with, and we have grown to ensure that we have the resources and people to support these collaborations, so we will continue to do that. We are also open to collaborations with non-government entities like the Coalition for Epidemic Preparedness Innovations (CEPI) and the Bill and Melinda Gates Foundation.

Given the niche area you play in, how have you developed the talent pipeline necessary for Acuitas' continued growth?

We have been extremely fortunate in being able to bring together a fantastic team. I have worked in this space for many decades, and many of the people on our team are people I have worked with previously who subsequently decided to join or return to Acuitas. There are many excellent people in the industry but the experience and expertise we require is very specific, so we are very targeted in our approach to recruiting talent.

However, we do also bring in young individuals who are looking for a challenge and want to learn a new technology. That has also been very successful, and we ensure that we provide a really supportive, respectful and considerate learning environment so that people without a background in LNP can feel comfortable joining the company, making mistakes, and ultimately excelling.

2020 has been a challenging and uncertain year for many. What goals have you set for 2021?

We go through very comprehensive planning every year to define objectives for the next. This process is conducted with the entire team. What does the company need to ensure that we are fully supporting our partners – from the scientific, technological and business perspectives? The management team then defines corporate goals, and then the teams work together to identify the resources and funding necessary to achieve them.

While we have enjoyed incredible success with vaccines this year, many of our partners are looking at other opportunities. For instance, we also have a focus on intravenously administered products that are intended to affect protein expression in the liver, and we have devoted a lot of our core research programs to understand how our carrier systems could work in this area. We have fairly defined goals in terms of what we want to be able to demonstrate in these programs in 2021.

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