Thomas Madden – CEO, Acuitas Therapeutics

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Thomas Madden is the CEO of Acuitas Therapeutics, the lipid nanoparticle delivery technology company whose platforms underpinned some of the most significant advances in mRNA medicine, such as the COVID-19 vaccines. In this interview, Madden shares how the company is evolving beyond COVID. He discusses the company's preformed vesicle technology and its potential to make personalized genetic medicines shelf-ready, the clinical and infrastructure challenges facing n-of-1 therapies, and his view of where LNP technology is headed over the next five years.

How has the success of the mRNA vaccines shaped Acuitas's position and the direction of its partner programs today?

We very much benefited from the excitement triggered by the success of the mRNA vaccines. It really expanded the network of partners we work with and cemented our global leadership in the LNP delivery space. At the moment, roughly half of our partners are working on vaccine-related programs and half on gene editing. There is also a lot of emerging interest in *in vivo* CAR T, which is a gene editing application, but we tend to separate it out because the technology is distinctly different.

We are really fortunate that many of those partners are now in the clinic. We have supported 33 programs moving into the clinic in the last two years, and we are now getting clinical data that is helping to support our core research program. We are able to understand how these LNP are

working in people, getting a picture of the safety profile and the efficacy profile, and that is very much informing the work we are doing to further improve our technology.

The gene therapy and epigenetic editing space has also been very hot recently. The success of Baby KJ sparked a lot of interest in the treatment of rare diseases, and that is an area where we continue to be heavily engaged, both with biotech and pharma partners, but also with major hospitals that want to put in place programs for newborns with rare genetic diseases. We are now working with them to look at how we can enable them to offer these kinds of therapeutics more broadly to patients in need.

As genetic medicines move into the clinical setting, what are the manufacturing and access challenges, and how does Acuitas's preformed vesicle technology address them?

Like in the case of Baby KJ, many gene therapies are used for the treatment of rare diseases, which are by definition, rare. In some cases a therapeutic needs to be designed for a single patient with a unique genetic disorder, or for a very small population sharing the same disease category. The conventional manufacturing model, producing large-scale batches to support clinical programs and commercialization, is incredibly inefficient at that scale.

To address this, we developed a technology we call preformed vesicles (PFV), where the payload is loaded into the LNP immediately prior to patient administration. Vials of the LNP sit ready on the shelf. Once the payload has been designed and synthesized for that individual patient, the two are simply mixed and administered. The time saving and cost saving are extraordinary.

Access is central to this. There have been a number of approved gene therapies that were discontinued simply because the sticker price made them unaffordable. It does not make sense to continue investing in this technology without ensuring there is a clear pathway to patient access. The PFV model directly addresses that by removing a significant portion of the manufacturing cost and complexity.

The approach also aligns well with where the FDA is heading. The agency is actively looking at platform technologies and how to enable a basket of related therapeutics to be approved and deployed across a patient population. A single LNP formulation, pre-released and sitting in a vial ready for administration, fits that regulatory vision and supports the goal of reducing the cost barriers that have historically impeded access to advanced genetic medicines.

How prepared are hospitals and clinical centers today to deliver n-of-1 genetic therapies, and where do the gaps in infrastructure and expertise lie?

We were familiar with the program put in place at the Children's Hospital of Philadelphia, involving UPenn and CHOP, in preparation for a treatment like Baby KJ. They had invested a great deal of time, money, and effort building the laboratory infrastructure needed, and had essentially performed dry runs to test their ability to diagnose the condition, analyze the genetic information, and then design and synthesize a therapeutic. That preparation is what allowed them to execute so successfully when Baby KJ was identified as a potential recipient.

Other centers see that success and the timeframe it was achieved in, but there may not be a full appreciation of how many years of groundwork it took to get there. They want to offer similar services and are in the process of gearing up, but they are at very different stages of maturity.

One of the things I find really exciting is the question of how much of the diagnosis and design process can be automated. It is still a laborious process and involves a large number of people working hands-on in the lab to support the Baby KJ program. To what extent can we take advantage of AI, machine learning, and automation to reduce time to treatment and bring costs down further?

Beyond platform-based approaches, what do you see as the most exciting area of innovation in the cell and gene therapy space right now?

Probably the most exciting space we are engaged in at the moment is *in vivo* CAR T. We are working with a large number of partners who want to take advantage of the versatility of mRNA LNP approaches to deliver these types of therapeutics. It is interesting because for years, targeting LNP to specific cells was the goal – the silver bullet. It is only recently that we have truly been able to realize that vision.

We published earlier work in Nature and Science on *in vivo* delivery to T cells for both autoimmune and oncology applications. That research used antibodies to target the T cells, but we found that attaching an antibody to the surface of an LNP created real stability challenges. The product could not be frozen and needed to be prepared fresh. We moved instead to DARPin technology, which are essentially antibody mimetics. Their structure allows you to attach the DARPin at a precise location on the LNP, and critically, they are stable when frozen. That really revolutionized our ability to support partners advancing *in vivo* CAR T therapies.

Our partners have recently published non-human primate data showing very profound suppression of B cells, both circulating and tissue B cells. The drive now is to take that into the clinic, initially for autoimmune diseases and then for oncology indications.

This is also an area with significant cost implications for patients. Current CAR T applications for lupus and other autoimmune diseases are expensive because they involve depleting cells from the body and repopulating with modified T cells. Delivering CAR constructs directly to T cells *in vivo* saves a huge amount of time and reduces the cost very substantially.

How engaged is Acuitas in the cancer vaccine space, and do you see it as the next frontier in oncology?

Cancer vaccines are, I think, the next step in oncology therapy, and we have already seen promising results in that space. We have developed LNP systems that we believe are superior to the delivery technologies currently in the clinic for cancer vaccines, and we are actively engaged with companies bringing expertise around neoantigen selection for personalized cancer vaccines.

A personalized cancer vaccine is also very well suited to the PFV approach, where you load the vaccine payload into the preformed LNP immediately prior to patient administration. The time and cost savings are significant. It is very much an area we are actively pursuing with partners with neoantigen design expertise who have a need for a delivery technology.

Looking at recent news for the company, can you explain the rationale behind Acuitas taking a majority ownership stake in RNA Technologies & Therapeutics, and what it means for the business going forward?

We work with companies around the world developing mRNA therapeutics, from large pharma to small startups. One challenge we and others have observed is the significant variability in mRNA payload quality. Some partners achieve strong efficacy against particular targets; others, their payload simply is not as active. The expertise around mRNA design and synthesis is not easy to come by and can take years to develop.

We had been working with Dr. Mohamed Alameh at UPenn initially and then at CHOP. We knew him and his colleagues who went on to form RNA Technologies & Therapeutics (RNA T&T) very well, and we were familiar with his expertise around mRNA design and synthesis. When they formed the

company, we sourced mRNA from them and were impressed by the quality and consistency. That is something we had struggled to access before. There are suppliers out there offering mRNA, and sometimes it is good and sometimes it is not. RNA T&T really had a handle on quality for both the design and the synthesis.

We recognized a strong fit between their payload expertise and our delivery technology, and were able to put together an agreement to take a majority ownership position in RNA T&T. Our intention is that they continue to focus on what they do well while we continue to focus on LNP expertise. We have already connected RNA T&T to a number of our partners interested in accessing their payloads, and the early collaboration has matched our expectations.

As a company that doesn't develop its own therapies but rather has a partner-centric business model, how do you balance the different needs of your collaborators from large pharma to early-stage biotech?

One of the things we try to ensure is that we do not play favorites. We want to provide the same high level of support to all of our partners, but we also recognize that no two companies have the same personality or the same way of wanting to engage with us. We work with each of them to understand what their needs are and what type of support they are looking for.

Over the last few years, US-based biotech partners in particular have faced real challenges around financing and market sentiment. In some cases we have needed to be sensitive to their financial situation and work with them to ensure they can keep moving forward. We are not looking for transactional relationships. We want to be working with people on a long-term basis, and we do what we can to evolve our agreement structures to remain relevant to what their needs are.

Looking ahead five years, where do you see LNP technology taking personalized cell and gene therapies?

The focus is on convenience. The most pressing question is how do we make this technology doctor-friendly, pharmacist-friendly, patient-friendly, and bring the cost down so that it is accessible? I can anticipate a future, for example in the rare disease area and the personalized cancer vaccine space, where pharmacies simply have vials of Acuitas LNP sitting on the shelf for different applications. When a patient with a rare genetic disease is identified, the pharmacist matches the payload and the guide to that patient, takes a vial of PFV, loads the payload, and

administers.

People sometimes talk about commoditizing the technology as though that is a negative. In some applications, I see it as a positive. It means clinicians can have confidence in the delivery technology and match it to the payload as and when the patient needs it.

What is the legacy you want Acuitas to leave in the field of nucleic acid-based medicines?

The one thing I would continue to emphasize is the value of collaboration. We do not do any of this on our own. We collaborate with our partners, with clinicians, with researchers. When companies try to hold on to everything themselves and bring all the expertise in-house, I do not think that lends itself to innovation or advancement.

To some extent, the Acuitas legacy should be a demonstration of the value of that collaboration: being willing to work with others, to rely on others, to provide expertise and support toward a common goal. The power of that is really quite impressive.

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