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Vantage Point – The messenger comes calling

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About 15 years ago a PhD student named Ingmar Hoerr hit a brick wall in his research into gene therapies. His work had convinced him that plasmids were the wrong tool for getting a cell to generate proteins, but he had a better idea: why not use the body's own messenger, mRNA?

Fast-forward to 2013, and a biotech company founded on the promise of mRNA therapeutics signs a huge deal with AstraZeneca, at a stroke marking this approach as one of the industry's hottest. Yet that company was not Curevac, of which Mr Hoerr was by now chief executive, but its relatively young US rival, Moderna Therapeutics.

True, Curevac has had its own successes, including a tie-up with Boehringer Ingelheim and recent $76m private financing. Still, given Moderna's record-breaking $450m venture capital round, $240m up front from Astra and additional deals with Merck & Co and Alexion, there is little doubt which of the two has been more commercially successful.

The ideal tool

Both groups were founded on the promise of mRNA as an ideal therapeutic tool; getting a therapeutic into a cell has long been a stumbling block, yet mRNA offered a natural way to get proteins to be expressed intracellularly.

But that was just theory, since in practice mRNA was thought to be extremely unstable. "That instability is only one of the issues," Moderna's chief financial officer, Lorence Kim, tells *EP Vantage*. "The other big step was to dodge the innate immunity that occurs when cells sense single strands of RNA, which tend to look like [those of] a virus."

This goes to the heart of the work that has propelled Moderna to the forefront. "Some of [our technology] has to do with modification of the base pairs, some with the various types of formulations or encapsulation. Some has to do with other engineering that we can do around the mRNA sequences themselves," says Mr Kim.

"Instability and degradation of mRNA was thought to be the problem. It is something that we've solved."

Remarkably, however, while Moderna has put its faith in mRNA with modified bases, Curevac's bet is on unmodified – or virtually unmodified – and non-encapsulated, so-called naked mRNA. And Mr Kim's views are at odds with Mr Hoerr's findings.

"Everybody claims RNA is unstable, which is not true. RNA is chemically a completely stable molecule," the Curevac chief exec tells *EP Vantage*. "I initially thought: 'Naked mRNA is unstable, it will be degraded'. But I found that it was the best."

In his initial mouse studies he tried liposomal encapsulation to protect the mRNA as much as possible, and only included naked mRNA administration as a "negative control. But I got the highest T-cell responses [with naked mRNA]."

This was echoed in later studies. "We thought, 'Let's improve mRNA stability in the cytosol, to get a long-lasting expression,' so we worked on sequence modifications, and also on chemistry; we modified a lot of the backbone, modified a lot of the bases. But in most cases when we did this the RNA was barely transcribed.

"So then we thought, 'Why make it complicated?'" Mr Hoerr says Curevac was able to get away with only minor changes to the mRNA, for instance adding enhancing or stabilising elements to non-translated regions, and stresses the importance of the buffer composition and a strict clean room to avoid contamination with RNAses.

Diametrically opposed

These structural differences aside, both groups agree that there are two fundamental applications of mRNA at present: using it to generate therapeutic proteins intracellularly on the one hand, and causing it to stimulate an immune response, and thus act as a vaccine, on the other. Both companies are looking at both of these approaches.

Moderna says that conceptually these applications are diametrically opposed: “The issue of evading innate immunity has to do with the therapeutic application; with the vaccine you want to stimulate adaptive immunity,” says Mr Kim.

“One can [stimulate the immune system] by encoding for antigens that the immune system would recognise. The mRNA codes for expression of a protein antigen … In the case of an infectious disease vaccine that antigen would be something recognisable on a virus, for instance.”

This split is also reflected in Moderna’s deals: AstraZeneca and Alexion have bought into therapeutic approaches against cardiovascular/oncology and rare disease targets respectively, whereas Merck’s interest lies in mRNA vaccines against infectious diseases.

For Curevac, meanwhile, vaccines were a logical initial target. Mr Hoerr says: “We were aware that we could express proteins in tissue, but we’ve chosen the vaccine approach because in our hands it’s the ideal target to reach the market as soon as possible. We are driven to have the first product on the market.”

One advantage is that only very small amounts of antigen in the cell are necessary to trigger a strong immune response – assuming that the mRNA is coding for the right antigen, of course.

First to the clinic

The split reveals that, in clinical development at least, it is not Moderna but Curevac that is out in front. The German group has already studied its mRNA technologies in over 300 subjects, though this has all involved the vaccine approach.

In phase I this showed no serious side effects, says Mr Hoerr, while in phase IIa immune responses were seen versus each of four antigens in 79% of patients. Owing largely to the availability of patients the first target indication is prostate cancer, though given the wide array of available treatments this only represents what the chief exec calls “the proof of a platform technology”.

For its part Moderna is still roughly a year away from human trials. “We are going to be entering the clinic with multiple candidates between the end of this year and the end of next year,” says Mr Kim. “That would include both therapeutic and vaccine approaches, but we haven’t broken out the split – they’re both important to us.”

In the meantime, the US biotech is pumping $100m a year into its core technology, including automating production. “We’ve been preparing for going into the clinic, with our own GMP-scale manufacturing. But we’ve also made extensive investments in automation … we’ve got a facility dedicated to making hundreds and thousands of unique mRNA constructs.”

Given the estimated $1bn that Moderna has raised in equity and up-front fees, it can well afford such a luxury.

But it might come as a surprise that production is not prohibitively expensive. It has complexity, says Mr Kim, “but it’s actually fairly low-cost. Given where we are on the technology curve, as it’s scaled up we think it’s going to be very low-cost.”

The same goes for the clinical study burden, which he thinks will not differ much from a typical small-molecule or antibody programme. “[This involves] transient induction of protein expression, so we look more like your classic pharmaceutical product than a gene therapy product that may have various permanent effects and may attract additional scrutiny.

“Remember, we’re not gene therapy.”

Two-horse race?

While this looks like a clash between two titans it would be unfair to characterise mRNA as a two-horse race, and there have been several new entrants recently.

For instance, Arcturus, a private Californian company, recently moved into this field. The French company Eukarys, meanwhile, is looking at an mRNA production system that it says is an easy, one-step process, and results in increased yields. And, just as Curevac once flirted with RNAi and antisense, at least one current RNAi player – Tekmira – has also looked at mRNA.

Another group, Acuitas, had been in dispute with Tekmira, but this was settled in a 2013 cross-licensing agreement. Acuitas recently collaborated with Curevac on a large-animal study showing that sequence-optimised but chemically unmodified mRNAs – Curevac’s sweet spot – resulted in protein expression without unwanted immune reactions, and even hinted at advantages versus modified mRNAs.

And about five years ago another German competitor, BioNTech, entered the fray, though it seems to be pursuing multiple therapy approaches, including diagnostics, bispecific immunostimulatory antibodies and even CAR-T technology.

In a recent interview BioNTech’s chief operating officer, Sean Marett, told *EP Vantage* that his group was

testing both naked mRNA and mRNA delivered in a proprietary lipid nanoparticle formulation, adding: “It’s just a question of which one will drive efficacy the furthest. We’re exploring both at the moment to see which we will take forward.”

Development aside, BioNTech appeared to strike a major coup two years ago with the hiring of Professor Katalin Karikó, of the University of Pennsylvania medical school. Dr Karikó is an expert in mRNA base modification, suggesting that this will be the way BioNTech will head.

Patent estates

One of the problems with all this is the threat of overlaps with Moderna’s patent estate. The US group’s chief executive, Stephane Bancel, has previously touted its significant patent position, which coupled with Moderna’s financial clout would make it a truly formidable opponent in a legal action.

Understandably Mr Kim becomes cagey on the subject of IP, but insists that there are lots of technology aspects, as well as manufacturing knowhow, that are important. “A good chunk of our IP does relate to modified nucleotides, but there are many other components to the technology that we’ve been patenting. It’s not about modified versus unmodified.”

And Mr Hoerr insists that, in any case, Curevac got there first, having been founded in 2000 – or 11 years before Moderna was incubated by Flagship Ventures.

“We have a really nice patent situation covering unmodified bases,” says Mr Hoerr. “We got IP when there was nobody out there. It was beautiful – we could patent whatever we wanted, there was never any opposition ... until 2010, and then BioNTech appeared.”

That said, one gets the sense that each company has a quiet admiration for the other, and Mr Hoerr freely accepts that Moderna has been much more successful in venture fund raising and partnering. “But if you look at the technology – there’s no doubt about this – we are the leaders,” he insists.

Mr Kim is more pragmatic, stating that Curevac has “been around and is in the clinic. But we’re not actually competing with them in specific indications at this point. I don’t know how much there is to glean from ... technological comparisons between vastly different products. They have a different technology.”

One similarity is that they both effectively operated in stealth mode until quite recently, Moderna perfecting technology derived from Dr Derrick Rossi’s work at Harvard Stem Cell Institute, and Curevac focusing on Mr Hoerr’s own research at Tübingen University.

Curevac, too, has noteworthy venture capital backers, including the German software billionaire Dietmar Hopp and the Bill & Melinda Gates Foundation. But Mr Hoerr says Curevac “never had the pressure to present ourselves – maybe that’s the reason why this technology was hidden for such a long time. We are not really vision-driven... I don’t know, maybe it’s more of a German attitude.”

Clearly all the players here agree that mRNA represents a real revolution, though “I was saying that already in my PhD thesis”, says Mr Hoerr. As such, the fact Moderna has raised so much more cash than Curevac might simply be a reflection of the craze for US biotech and the fact that appetite is still so much higher among US investors than on the opposite side of the Atlantic.

Where the two leaders part company is in the uniqueness of their offerings. “There’s no way you always have to go after base modification, and there’s no way ... that if you want to work in RNA you have to ask Moderna because Moderna has all the patents and technologies,” insists the Curevac chief exec.

“That’s not true: you can also ask in Tübingen.”

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