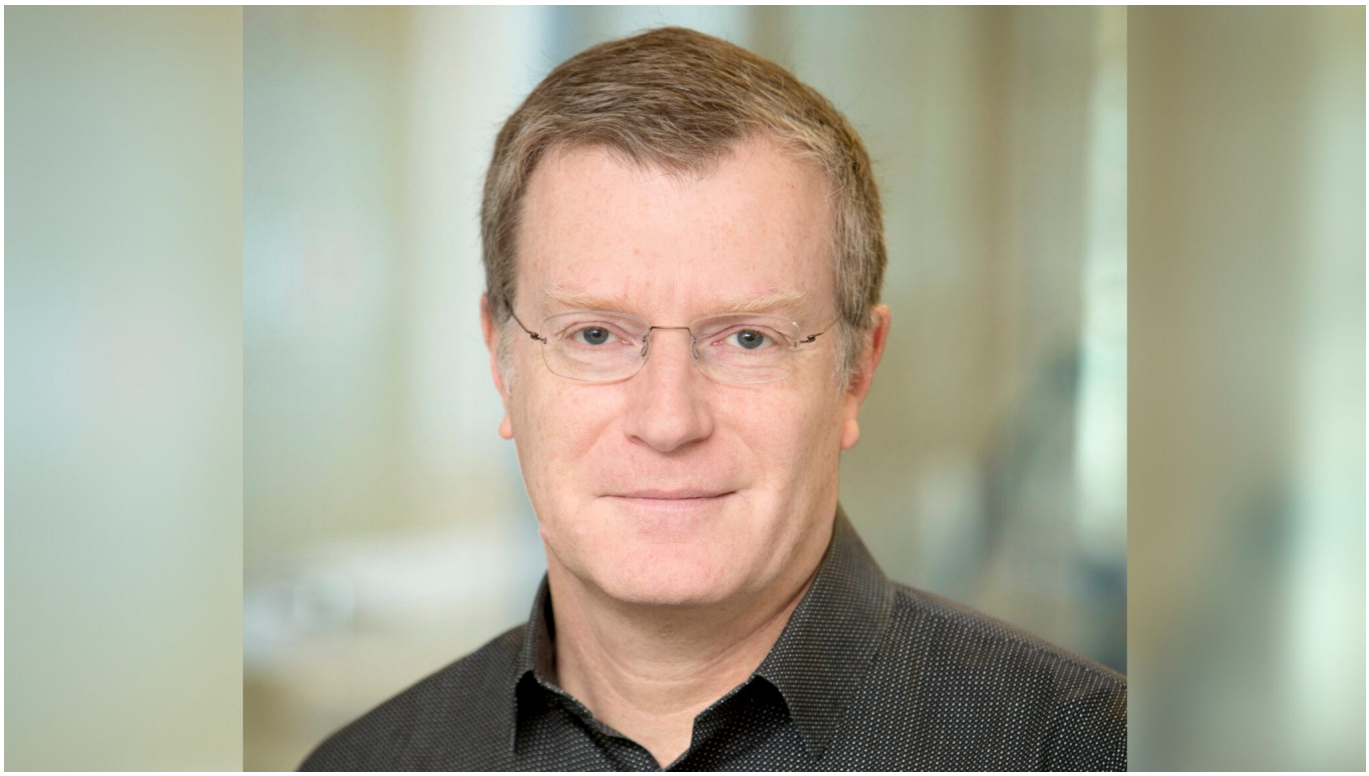
ENDPOINTS NEWS

The mRNA era is here. MPM believes the future belongs to oRNA — and Big Pharma wants a seat at the table

by **Amber Tong** on February 24th, 2021



If the ultra-fast clinical development of Covid-19 vaccines opened the world's eyes to the promises of messenger RNA, the subsequent delays in supply offered a crash course on the ultra-complex process of producing them. Even before the formulation and fill-finish steps, mRNA is the precious end product from an arduous journey involving enzyme-aided transcription, modification and purification.

For Bristol Myers Squibb, Novartis Institutes for Biomedical Research, Gilead's Kite and Astellas, it's time to rethink the way therapeutic RNA is engineered.

The Big Pharma names are among a Series A syndicate backing Orna Therapeutics, an MPM-seeded biotech startup now armed with $80 million to steer the lead programs toward the clinic — with some unexpected applications.

It all started, CEO Tom Barnes told *Endpoints News*, as an academic project.

Alex Wesselhoeft, then a PhD student at Dan Anderson's MIT lab, wanted to know if it's possible to make synthetic compounds that could have a longer half-life than mRNA. Like endogenous circular RNA, or circRNA, they would look like a circle; but compared to the natural counterpart, their invention — which would eventually be christened oRNA — would have better protein-coding potential.

Here's how they did it, from a Nature Communications article in July 2018:


Dan Anderson

> First, we engineer a self-splicing intron to efficiently circularize a wide range of RNAs up to 5▉kb in length in vitro by rationally designing ubiquitous accessory sequences that aid in splicing. We maximize translation of functional protein from these circRNAs in eukaryotic cells, and we find that engineered circRNA purified by high performance liquid chromatography displays exceptional protein production qualities in terms of both quantity of protein produced and stability of production.

In a follow-up paper almost a year later, the group reported that not only did the circularization extend translation duration in mice, it also appeared to diminish immunogenicity — waiving any need for extra steps that are traditionally required to boost the persistence and expression or minimize immune reaction of long RNA.


Raffaella Squilloni

By then, Wasselhoeft, Anderson and co-founder/director of business development Raffaella Squilloni had already spun out Orna and received $10 million in seed cash from MPM. Barnes, who'd left the CSO post at gene editing shop Intellia in early 2019, was tapped as the CEO — admittedly with no prior knowledge of the technology.

"I was a little amazed as to how efficiently it happens and the more I dug in, certainly the data we have to date has revealed to us that circles are just better than lines, as we call them, in every way we've looked," Barnes said. "There's no cap, there's no tail, there's no post-transcriptional production processing, so we essentially run the transcription reaction, purify. That's it. [...] If the world could make long RNA like we do, they wouldn't make it any other way."

The oRNA would be packaged in a lipid nanoparticle, a research field that he believes is experiencing a bit of a renaissance thanks to successes of pioneers like Moderna and BioNTech.


Ansbert Gadicke

"We believe that oRNA is the future," said Ansbert Gadicke, co-founder and managing director at MPM. He's also chairing Orna's board.

Having spent the past year testing the idea and growing the team to the mid-20s, Barnes adds that the $80 million, co-led by MPM Capital, Taiho Ventures and F2 Ventures with participation from the PAGS Group, will bankroll multiple programs aimed at delivering the oRNA to different sites. There are ones targeted at the liver — a well-studied route — on one hand, and in situ CAR on the other, where they'd be looking at delivering chimeric antigen receptors directly to immune cells.

That strategy, which fits snugly into MPM's long-running focus on oncology, would put them shoulder-to-shoulder to Umoja and Ixaka, which are developing a lentiviral vector and nanoparticle that can help patients make their own cancer-fighting CAR-T cells (MPM also invested in Umoja).


Greg Motz

Orna goes broader by exploring the full immune repertoire, eyeing not just T cells but also NK cells and macrophages, noted Greg Motz, head of biology.

"Even in the earliest days, I think many of us in our imaginations were wanting to sort of do an in vivo CAR, but the technology wasn't really there," Motz, whose cell therapy résumé features stints at Penn, Novartis and Unum, said.

The dream here is to come up with a redosable biologic that can be infused in an outpatient setting, an approach that would dramatically bring down the toll, both physical and financial, that CAR-T therapies currently bring to patients.

"We're certainly thinking of our technology as like coding RNA version 2.0. So these sorts of concepts are bandied about very often and I myself am guilty of having done that in prior lives," Barnes said. "But I think in this case very much this is the better way of making long RNA and it's very distinct technology; it's not a micro tweak, it's done in a completely different way."

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