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Orna goes into orbit on $3.65B Merck megadeal, $221M series B round

By Cormac Sheridan, Staff Writer

Orna Therapeutics Inc., which is pioneering a novel circular RNA (circRNA) protein expression technology in several therapeutic areas, has achieved lift-off. The Cambridge, Mass.-based company has closed a broadly based alliance in infectious disease and oncology with Merck & Co. Inc., under which it is getting $150 million up front and up to $3.5 billion in development, regulatory and sales-based milestones. In addition, Merck, of Rahway, N.J., is investing another $100 million in Orna's equity, as part of its $221 million series B round, which the company also disclosed on Aug. 16.

The cash injection will propel the early stage company into the clinic and alert the wider biopharmaceutical industry to an RNA-based technology that could offer significant levels of improvement over current manufacturing approaches. Although the COVID-19 pandemic has rapidly transformed mRNA into the biotech industry's hottest modality, it still has significant shortcomings, foremost among them being a limited half-life. That may be less of an issue for vaccines than it is for therapeutics addressing chronic conditions, which need to be administered on an ongoing basis. But Orna is also focusing heavily on vaccines, given its simpler and cheaper approach to production.

Ansbert Gadicke, chairman, Orna Therapeutics and managing partner MPM Capital, Bioimpact Capital

"This is the largest deal in the history of the biotechnology industry for an early stage preclinical company," claimed Orna's chairman, Ansbert Gadicke, who is managing partner of its founding investors MPM Capital and Bioimpact Capital. There are, of course, many ways of defining any deal category, but what makes the transaction "particularly special," he told *BioWorld*, is that Orna is retaining full ownership and control over its technology – Merck is getting access to it for a defined number of programs.

The main focus is on vaccine development, but oncology forms a second strand of the alliance. "We've had preliminary discussions about what we'll do together," Orna CEO Thomas Barnes told *BioWorld*. Further details have not been disclosed as yet, but one area they plan to explore is whether the immune response to a given vaccine can be shaped through appropriate vaccine design.

Thomas Barnes, CEO, Orna Therapeutics

Orna is retaining full ownership of what Gadicke described as "the crown jewel" within the company, its CD19-directed in-situ chimeric antigen receptor (isCAR) program, which is in development for B-cell lymphomas. In preclinical studies in a mouse model of a B-cell malignancy, the circRNA-encoded CAR, which is delivered by lipid nanoparticle (LNP), attained complete eradication of the tumor after five injections. "If that holds true in the clinic, it will make the current CAR T technology obsolete," he said. Repeated dosing may bypass the problem with T-cell exhaustion seen with current therapies, he said. "Each injection drives a new wave of CAR T cells."

The isCAR therapy is delivered by injection and, unlike current CAR T-cell therapies, does not require risky and expensive lymphodepletion protocols. "It's a much better patient experience," Barnes said. Obtaining equivalent or near equivalent efficacy to CAR T therapies would mark a significant step, given the limited access and high costs associated with existing CAR T therapies. A first-in-human trial is penciled in for the first half of 2024.

LNP technology 'just as important'

The company has explicitly avoided including the letter "T" in the isCAR name, as it is experimenting with several "immunotrophic" LNPs that can deliver genetic payloads to T cells, natural killer cells or macrophages. Conceivably, a therapy could address more than one immune effector cell type. The LNP delivery technology "is just as important" as the circRNA platform, Gadicke said. It is pursuing LNP research in-house and through a joint venture with Cambridge-based Renagade Therapeutics Inc., an RNA delivery specialist.

Orna's technology originated in the lab of Daniel Anderson at the Massachusetts Institute of Technology. Anderson and his former PhD student Alexander Wesselhoeft – now director of molecular biology at Orna – developed methods for circularizing linear mRNA molecules by introducing self-splicing introns to improve their stability by making them more resistant to endonuclease degradation.

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Orna has moved fast since it was established about three years ago. "What makes it a compelling technology is several things we discovered subsequently," Barnes said. Protein production efficiency is also boosted by the inclusion of internal ribosome entry sites – or IRES – sequences, which facilitate translational initiation in the absence of the 5' methyl guanine cap that is added to synthetic linear mRNA molecules.

Circularization occurs spontaneously, at high efficiency, immediately after in vitro transcription of the linear mRNA molecule. Both steps are performed in a single reaction vessel, which introduces significant efficiencies when compared with linear mRNA manufacturing, in which synthesis, capping and tailing are carried out in successive steps. The inclusion of modified nucleotides, a key step in reducing activation of the innate immune system with conventional mRNA molecules – is not needed with circRNA. All of these elements add up to significant cost savings. "You drop your cost by a factor of 10," Barnes said.

The efficiency of packaging circRNA into LNPs is about two times higher than that associated with linear mRNA, Barnes said, which can allow either for increased dose strength or reduced toxicity. With conventional linear mRNA, the LNP component is about 40 times heavier than its payload; with circRNA, it's about 20 times heavier.

Orna's third focus area is on genetic disease, and it has an active research program in Duchenne muscular dystrophy. The company is experimenting with transferring circRNA's encoding full-length dystrophin genes as well as truncated versions that have been the focus of several gene therapy developers employing adeno-associated virus (AAV) vectors that can only carry limited payloads.

In addition to Merck, MPM Capital, its affiliate Biompact Capital, and other investors participated in the series B round. The Merck portion of the series B investment is subject to closing conditions.