Moderna’s Mysterious Coronavirus Vaccine Delivery System

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Moderna Therapeutics headquarters in Cambridge, Massachusetts, on May 18, 2020.
Boston Globe via Getty Images

On Monday, Vice President Mike Pence helped launch the big late-stage trial of Moderna Therapeutics’ Covid-19 vaccine. “It is remarkable to think that Moderna—that will be initiating this phase 3 clinical trial—actually entered phase 1 back in March,” Pence said.

Moderna has moved lightning fast and is doing work based on bleeding-edge messenger RNA technology that could result in a viable vaccine. There is widespread hope Moderna’s vaccine will play an important role in combating the pandemic. To aid the effort, Moderna has secured $955 million of commitments from the federal government’s Biomedical Advanced Research and Development Authority (BARDA).

Wall Street also has high expectations for the vaccine, and Moderna’s stock has quadrupled this year to a market valuation of $30 billion, allowing Moderna to raise $1.3 billion in a May stock offering. Moderna insiders have sold some $250 million of shares as the stock has soared.

With the stakes incredibly high, the mystery around a key technological component of Moderna's coronavirus vaccine has only become deeper. Last week, the U.S. Patent Trial and Appeal Board rejected Moderna's challenge to a patent owned by Arbutus Biopharma ABUS -3% related to the lipid nanoparticle (LNP) technology that is crucial to Moderna's mRNA medicines.

For a decade, Moderna has been working to develop mRNA technology that could turn the body's cells into drug factories. In order for the approach to work, Moderna needs to safely deliver the mRNA to the body's cells without the payload breaking down in the bloodstream. As a result, any mRNA vaccine or therapeutic consists of two components, the actual sequence mRNA and the delivery mechanism. Moderna has clearly engineered the first component, but there remain questions about the second. No mRNA vaccine or medicine has ever been approved by U.S. or European regulators.

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Even though Moderna took the trouble to try to invalidate the patent owned by Arbutus, a small Canadian biotechnology company, Moderna said after it lost its patent challenge that its LNP technology had advanced well beyond the technology described in the Arbutus patent. Moderna claimed the LNP used to make mRNA-1273, its Covid-19 vaccine candidate, is not covered by the Arbutus patent. "Moderna is not aware of any significant intellectual property impediments for any products we intend to commercialize, including mRNA-1273," the company said.

In June, researchers from the NIH and Moderna made a manuscript preprint of preclinical data for mRNA-1273 available on bioRxiv, an open-access preprint repository. The preprint described Moderna's coronavirus vaccine candidate as using delivery technology that appears to be covered in the Arbutus patent that was upheld last week. The preprint of the study that tested the vaccine in mice described the mRNA for mRNA-1273 as being encapsulated into LNP "at molar ratio of 50:10:38.5:1.5 (ionizable lipid:DSPC:cholesterol:PEG-lipid)."

The first claim of the upheld Arbutus patent describes "a cationic lipid comprising from

50 mol % to 65 mol % of the total lipid present in the particle;" a non-cationic lipid comprising a mixture of phospholipid and cholesterol, where the "phospholipid comprises from 4 mol % to 10 mol %" and the cholesterol comprises "30 mol % to 40 mol %;" and a conjugated lipid "comprising from 0.5 mol % to 2 mol %."

In a statement to *Forbes*, Ray Jordan, Moderna's chief corporate affairs officer, said the June preprint describes data generated using a preclinical research formulation of a SARS-CoV-2 vaccine that is not the same as the vaccine itself.

"While the authors of the preprint used the term 'mRNA-1273' for convenience of the reader, the preprint does not describe the cGMP process by which we make our messenger RNA and LNP or the final drug product composition in our commercial candidate (mRNA-1273)," Jordan wrote in a statement.

When asked if Moderna would provide the molar ratios at which mRNA-1273 encapsulates its LNP, Jordan said, "Nope, we are not disclosing our proprietary ratios at this time."

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In a different preclinical study testing Moderna's vaccine in non-human primates that was published in *The New England Journal of Medicine* on Monday, the authors wrote mRNA-1273 is encapsulated in LNP as described in a 2019 paper, which said the mRNA was encapsulated at the same molar ratios as in the mouse study.

The description of the phase 1 study of Moderna's coronavirus vaccine registered with the federal government shows the LNP for mRNA-1273 is composed of an ionizable (cationic) lipid; cholesterol; DSPC (phospholipid) and PEG2000-DMG (conjugated anti-aggregation lipid). The percentages of the four components in the formulation of mRNA-1273 were not disclosed in the clinical trial registration or the July publication of an interim analysis of the Phase 1 study of mRNA-1273 in *The New England Journal of Medicine*. The appendix of the interim analysis redacts information associated with LNP.

For years, Stephane Bancel, the billionaire CEO of Moderna, has said the company had moved beyond the delivery technology owned by Arbutus. "We knew it was not very good," he told Forbes in 2016. "It was just okay." He said Moderna was producing its own nanoparticle lipids, N1GEL, for example, and licensing another from Merck MRK -0.4%. He added that Moderna only used the Arbutus technology initially and had stopped using it for new drugs back in 2016.

When Moderna was first getting off the ground, Bancel turned to a tiny company called Acuitas to get access to a delivery technology for his mRNA vision. Acuitas was headquartered in the Vancouver, British Columbia, home of Thomas Madden, who founded it in 2009. Madden had been involved in a lawsuit with Tekmira Pharmaceuticals, which had merged with a company Madden had worked for and

eliminated his position. Through the litigation, Madden secured a license for the LNP technology he had helped develop. Bancel decided to get a license for the LNP technology from Acuitas and not Tekmira, which later changed its name to Arbutus.

In 2016, Arbutus terminated Acuitas' license to the LNP technology, causing Acuitas to sue Arbutus in British Columbia court. Arbutus countersued, claiming Acuitas had no right to sublicense the LNP technology to Moderna. A B.C. judge issued a temporary 2017 injunction stopping Acuitas from further sublicensing the LNP technology.

A year later, in 2018, Arbutus reached a settlement with Madden that terminated Acuitas' license and stipulated Moderna could only use the technology in four vaccines that targeted viruses that had already been identified.

The Arbutus patents have since been taken over by Genevant Sciences, a subsidiary of Roivant Sciences, which is Arbutus' biggest shareholder and run by Vivek Ramaswamy. Arbutus retains a stake in Genevant and a right to a portion of the economics of the patents. Genevant declined to comment.

In the years since the Acuitas settlement, other vaccine candidates developed by Moderna have been described in publications with LNP technology comprised of the four components listed in the Arbutus patent with formulated percentages that seem to run through the patent. For example, publication of a study of an HIV vaccine listed on Moderna's website in July describes mRNA as being encapsulated by LNP "at molar ratio of 50:10:38.5:1.5 (ionizable lipid:DSPC:cholesterol:PEG-lipid)."

Moderna has challenged three of the Arbutus patents at the adjudicative body within the U.S. Patent and Trademark Office. One of its challenges was successful, another partially successful, and the challenge against the third patent was lost last week. There are three other relevant Arbutus patents that Moderna has not tried to challenge.

Whatever happens on the intellectual property front, it is highly unlikely that a patent issue will get in the way of the development or distribution of a Covid-19 vaccine. But shareholders of Moderna's hot stock were broadly warned in a May securities filing that the company had instituted *inter-partes* review proceedings against issued U.S. patents related to mRNA delivery and the unsuccessful invalidation of those patents might lead to the kind of litigation that could result in substantial damages.

Taxpayers also might have an interest in knowing the ownership of the delivery technologies used by an mRNA vaccine backed by nearly $1 billion of federal government funds. When asked about the delivery technologies, a spokesperson for the Department of Health and Human Services, which houses BARDA, said that intellectual property is assessed for any company submitting a proposal to BARDA, as part of the proposal evaluation process.

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