PATENTS

# The COVID-19 vaccine patent race

The seemingly simple modular technology for making new mRNA vaccines could make vaccine developers a victim of their own success.

COVID-19 has kept the world in its grip for two years and counting. The unfolding of the pandemic came with some remarkable — and in part concerning — developments, including the speed with which the SARS-CoV-2 virus spread across the globe, the rapid development and approval of vaccines, the unexpected vaccine skepticism, and finally the inequitable distribution of the vaccines in different regions of the world.

COVID-19 is also historic in terms of its patent background. Several aspects regarding the patent protection of COVID-19 vaccines have been discussed, including disputes over patent ownership and the role of patents in limiting vaccine access to developing countries[1,2]. Here, we discuss the development of mRNA vaccine technology, the race to the vaccine and the issues surrounding securing patent rights.

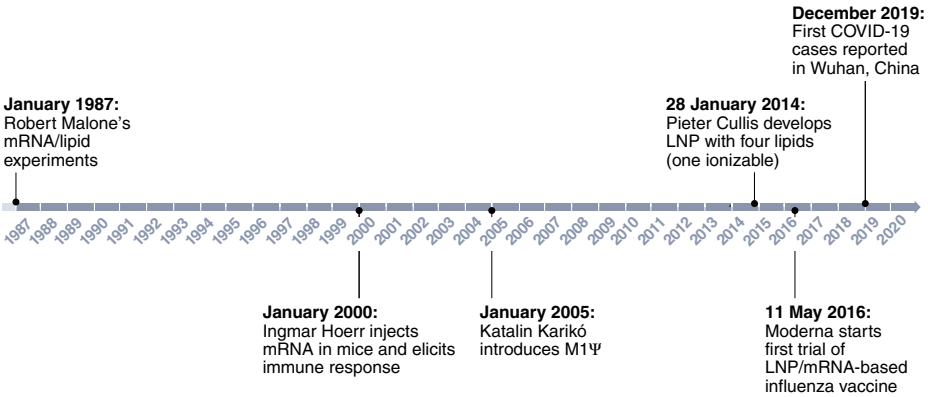


**Fig. 1 | The long road to mRNA vaccines.** As early as 1987, experiments using liposome-mediated mRNA transfection suggested that mRNA could be used as a drug.

## The long road to mRNA vaccines

The rapid development and approval of messenger RNA–based COVID-19 vaccines conceals the fact that the history of mRNA vaccine technology is more than 20 years old, with many pioneers adding incremental advancements to the achievements of others[3]. Key are the following events (Fig. 1):

In 1987, a graduate student at the Salk Institute named Robert Malone mixed mRNA with fat droplets and showed that human cells incubated therein started translating the mRNA and producing proteins[4]. His results suggested that one day mRNA could be used as a drug.

In 2000, Ingmar Hoerr of Tübingen University injected mRNA in mice and was able to elicit immune responses caused by the translated proteins[5]. Hoerr later founded the mRNA company CureVac.

In 2005, Katalin Karikó and Drew Weissman of the University of Pennsylvania showed that mRNA containing pseudouridine (Ψ) had improved translational capacities, increased biological stability and decreased stimulation of innate immunity caused by uridine[6]. A variant thereof, 1-methylpseudouridine (m1Ψ) was later developed by Jason Schrum (but already anticipated in Karikó and Weissman's respective patent US8278036), and is said to exhibit even better protein expression rates and further reduced immunogenicity. Today, m1Ψ is used in Moderna and BioNTech's COVID-19 mRNA vaccines. In contrast, CureVac uses a G+C-enriched open reading frame with a similar goal, namely to reduce the uridine content of the mRNA.

In 2014, Pieter Cullis, who later founded the lipid company Acuitas, and co-workers developed the four-lipid nanoparticles (LNPs) comprising, among other things, a PEGylated lipid and an ionizable lipid that is able to associate with the negatively charged mRNA[7]. These LNPs are used in all mRNA-based COVID-19 vaccines currently on the market.

And in 2016, Moderna began the first clinical trial with an LNP plus mRNA–based vaccine[8]. As a result of these advances, mRNA vaccine technology was fit for purpose when SARS-CoV-2 jumped the species barrier in late 2019. Or, as BioNTech's founders Özlem Türeci and Uğur Şahin recount: "If the pandemic hit a year earlier, we might not have been in the position to respond this fast."[9]

## The *Coronaviridae* foreplay

*Coronaviridae* have accompanied mankind for thousands of years as part of the annual viral winter cocktail, typically causing minor symptoms of a common cold. The virus family came into the spotlight as a consequence of the SARS-CoV and MERS epidemics. Though many research groups started to develop vaccines, these efforts were arrested when the two diseases suddenly disappeared. However, the respective research provided valuable insights that then helped to accelerate the development of vaccines against SARS-CoV-2.

In 2017, scientists at the US National Institutes of Health (NIH), Dartmouth College and Scripps Research Institute led by Barney Graham looked at the MERS-CoV spike protein and found out that, when the spike protein binds to the ACE-2 receptor on a target cell, the two helices and the loop of the spike protein change from their prefusion configuration into one long helix that engages with the target cell, thus allowing the fusion of virus and cell[10]. The researchers realized that blocking that configuration shift could prevent viral fusion, hence extending the time within which the protein, when used as a vaccine, is antigenic and causes immune reactions.

The researchers came up with a mutant MERS-CoV spike protein that comprises two consecutive proline substitutions (the 2P mutation). These substitutions are placed at a junction between heptad repeat 1 (HR1) and the central helix, so as to maintain the spike protein in a prefusion conformation. The group applied this approach to different coronaviruses that were known at that time — including SARS, where the two substitutions are K968P and V969P — and filed a patent application on 25 October 2016

**Table 1 | 2P substitutions in spike proteins of different *Coronaviridae* as suggested by US2020061185A1**

| Coronavirus type | Sequence identifier | Substitutions at | Motif |
|---|---|---|---|
| HKU1 | 9 | N1067P and/or L1068P | SRLDNLEA |
| OC43 | 11 | A1079P and/or L1080P | SRLDALEA |
| HKU9 | 13 | G1018P and/or L1019P | SRLEGLAA |
| WIV1 | 15 | K969P and/or V970P | SRLDKVEA |
| MHV | 17 | A1073P and/or L1074P | SRLDALEA |
| NL63 | 19 | S1052P and/or I1053P | DRLDSIQA |
| 229E | 21 | I869P and/or I870P | DRLDIPQA |
| MERS | 29 | V1060P and/or L1061P | QRLDVLEQ |
| SARS[a] | 30 | K968P and/or V969P | SRLDKVEA |
| PEDV | 39 | I1076P and L1077P | SRLDILSA |
| SDCV | 42 | E855P and V856P | NRLEEVEA |

[a]An almost identical variant of the SARS-CoV spike protein, with slight differences at the C terminus yet also having the motif SRLDKVEA, was released in the SwissProt database under the identifier P59594 on 23 April 2003.

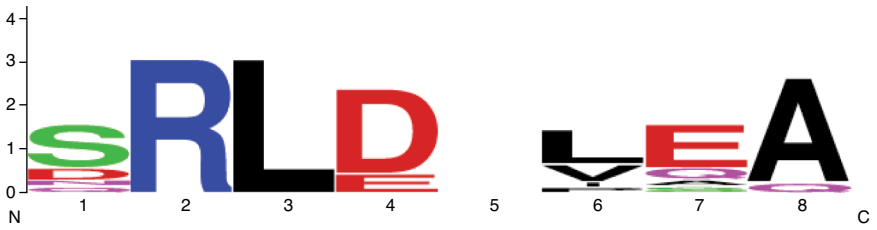


**Fig. 2 | Sequence logo of the sequence motifs shown in Table 1.** The font size of each amino acid correlates to its relative abundance in that motif.

(US2020061185A1 and family members). The disclosure of this patent family is not restricted to MERS-CoV and SARS-CoV spike protein mutants, but also includes spike mutants of quite a few other *Coronaviridae* (Table 1). The motif within which the proline substitutions have been accomplished is well conserved within the spike protein (Table 1). Fig. 2 shows a sequence logo of the sequence motifs from Table 1, with positions 5 and 6 the ones to be substituted by proline, to illustrate the relative abundance of key amino acids in that motif.

The NIH were granted patents in the United States and Europe, among other venues, with claims related to a recombinant coronavirus protein comprising one or two proline substitutions near the junction between HR1 and the central helix. Hence, even though the underlying application was filed before SARS-CoV-2 entered the stage, the claims encompass as well a SARS-CoV-2 vaccine having the 2P mutation in that region.

## Arrival of SARS-CoV-2 and vaccine development

In late December 2019, a series of pneumonia cases occurred in Wuhan, China. It became clear that a new virus was responsible for these new infections, which was soon identified to be a coronavirus — first called 2019 novel coronavirus (2019-nCoV) before virologists settled on the name SARS-CoV-2. On 12 January 2020, Chinese researchers led by Yong-Zhen Zhang of Fudan University uploaded the SARS-CoV-2 genome to GenBank (NCBI reference sequence NC_045512.2)[11].

The genome has a length of 29,903 nucleotides and encodes in reading frame rf 2/direct the 1,273 amino acid peptide sequence of the SARS-CoV-2 spike protein. The translated amino acid sequence of the SARS-CoV-2 spike protein was uploaded to UniProt on 22 February 2020 (UniProt identifier P0DTC2).

The sequences of the SARS-CoV spike protein (UniProt identifier P59594) and that of SARS-CoV-2 turned out to be highly similar (identity 76.4%). In particular, both proteins share the sequence SRLDKVEA at the motif mentioned above — in fact, they have a stretch of 111 identical amino acids in common that surrounds the motif.

The arrival of the new virus did not remain unnoticed in the mRNA vaccine community. Reportedly, Stéphane Bancel of Moderna, who had already worked with the NIH for four years on the development of antiviral mRNA vaccines, contacted Barney Graham on 6 January 2020 (that is, after the first news of the viral outbreak in China came up, but before the genome was published), and Graham told him: "If it's a coronavirus, we know what to do."[12]

BioNTech's Şahin recounts returning from his family's Friday ritual of dinner at a Vietnamese restaurant on 24 January 2020 and checking the latest scientific literature, learning about the rapidly spreading virus in China. By Sunday, he and his team had the respective sequences available, and on Monday, back in the office, they decided to set up vaccine development[9].

Soon after Moderna and BioNTech, CureVac also started to develop an mRNA vaccine. A patent search in the database PatentLens using the 1,273 amino acid spike protein, plus the substitutions K986P and V987P (the latter derived by analogy from the corresponding 2P mutant of the SARS-CoV spike protein as disclosed by the NIH group), revealed that within weeks of the publication of the SARS-CoV-2 genome, several entities filed patent applications disclosing or claiming said SARS-CoV-2 spike protein 2P mutant. Obviously, all applicants — like the author of this article— had gone through the same exercise of combining the sequence of the SARS-CoV-2 spike protein with the findings of the NIH group.

US company Novavax, which is developing the NVX-CoV2373 spike protein vaccine, was the first to receive a receipt stamp from the patent office, securing a filing date of 27 January 2020 — a mere 15 days after the SARS-CoV-2 genome was published. Moderna filed 1 day later. Janssen (a subsidiary of Johnson & Johnson) followed on 31 January 2020, CureVac on 4 February 2020, the NIH on 11 February 2020, and others followed, including BioNTech on 22 April 2020 — all of them claiming an identical 2P mutant protein, or mRNA encoding said same protein (Fig. 3).

None of these early applications comprise experimental data with regard to the claimed vaccine — which is unsurprising, considering the time available for drafting. Moderna's priority application, for instance, comprises mere prophetic examples (example 1: "the instant study is designed to test the immunogenicity of the candidate coronavirus vaccines," "animals are vaccinated," "formulation may include PEG-modified lipid"; example 2: "the instant study is designed to test the efficacy of candidate coronavirus vaccines," "animals are vaccinated," "animals are then challenged

**Table 2 | Key claims of Moderna, CureVac and BioNTech's international patent applications**

| Company/patent application | Priority date | Sequence identifier | m1Ψ claim | G+C enrichment claim | PEGylated lipid | Sterol | Ionizable lipid | Regular lipid |
|---|---|---|---|---|---|---|---|---|
| Moderna/ WO2021154763 | 28 Jan 2020 | 29 | 16. mRNA is modified with m1Ψ | N/A | 20. PEG lipid is PEG2000 DMG | 20. Sterol is cholesterol | 20. Ionizable cationic lipid has the structure of SM102 | 20. Non-cationic lipid is DSPC |
| CureVac/ WO2021156267 | 4 Feb 2020 | 10 | 68. Nucleic acid does not comprise m1Ψ | 35. G/C optimized coding sequence | 95. LNP comprises PEG-lipid ALC-0159 | 95. LNP comprises cholesterol | 95. LNP comprises cationic lipid ALC-0315 | 95. LNP comprises DSPC |
| BioNTech/ WO2021213924 | 22 Apr 2020 | 7 | 12. Modified nucleoside is selected from Ψ, m1Ψ and m5U | 3. G/C content of the coding sequence is increased | 24. LNP particles comprise ALC-0159 | 24. LNP particles comprise cholesterol | 24. LNP particles comprise ALC-0315 | 24. LNP particles comprise DSPC |

m5U, 5-methyluridine; PEG2000 DMG, 1,2-dimyristoyl-*sn*-glycero-3-methoxypolyethylene glycol; DSPC, distearoylphosphatidylcholine.

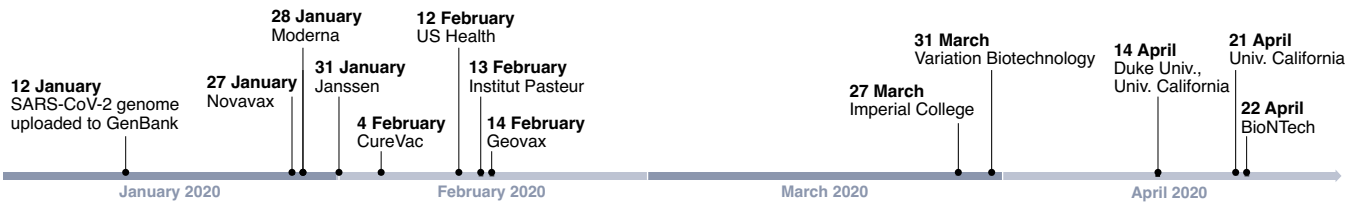


**Fig. 3 | Filing history of patent applications.** Applicants reciting or claiming the SARS-CoV-2 spike protein with the 2P mutant.

with –1 LD90 of coronavirus"), yet no wet-lab results are provided. (Note that in patent literature, the use of the present tense suggests that an experiment was not actually performed, but just hypothesized.)

Remarkably, the overlaps between the different patent filings are not restricted to the sequence of the encoding mRNA or the spike protein, respectively. Moderna, CureVac and BioNTech's mRNA vaccines have even more similarities, which are reflected in their patent claims. Table 2 shows a synopsis of their respective international patent applications, with the sequence identifier of the 1,273 amino acid SARS-CoV-2 spike protein with the 2P mutant, and the claim number and language that refers to similar or identical elements reproduced in abbreviated form. All three applications claim the same sterol and the same conventional lipid, while CureVac and BioNTech also claim the same PEGylated lipid and ionizable lipid. Moderna and BioNTech also claim the use of m1Ψ, while CureVac optionally excludes said variant and prefers G+C enrichment instead (which BioNTech only suggests as an option). In such a situation, where several entities file — almost simultaneously — patents related to essentially the same subject matter, this may inevitably lead to legal conflicts, as we have witnessed in the ongoing CRISPR–Cas9 patent dispute[13].

However, the mRNA vaccine patents may not necessarily follow the same road. All three applications are still in what is called the 18-months long 'international phase' (with one exception for Moderna, described below), and are hence not yet pending in the different destination countries. For all three applications, International Search Reports (ISR) have been issued (prepared by the European Patent Office (EPO) as the International Searching Authority), which come with a preliminary opinion on patentability. In all three cases, the respective examiners came to the conclusion that the claimed subject matter would not be novel or not rely on an inventive step. In all cases, the examiners referred to the prepublished SARS-CoV-2 genome and publications anticipating the 2P mutation in the spike protein of other coronaviruses[14–16]. In the national patent phases, which come after the international phase, most national patent offices rely on (though are not bound to) the opinion of the International Searching Authority. This means that Moderna, CureVac and BioNTech, should they decide to enter the national phases with their cases, will experience considerable headwinds.

Notwithstanding the above, Moderna already has a pending US patent application (US20210228707A1) that received a Notice of Allowance on 27 August 2021. However, on 14 December 2021, the US Patent & Trademark Office delivered an abandonment notice, according to which Moderna failed to pay the issue fee and the publication fee. The application is therefore deemed abandoned. The reason for this step may lie in a smoldering dispute between Moderna and the NIH, who claimed that its inventors have not received credit in Moderna's patent application. Moderna, who before had contested the claim, has backed down and explained on 17 December 2021 that it was in talks with the NIH and payment of the issue fee would be a counterproductive signal[17]. However, to maintain all options, Moderna has filed a continuation application (17/518,542), which is not yet published. In any case, the patent claims as granted, while protecting vaccines that comprise mRNAs encoding the SARS-CoV-2 wild-type spike protein with the 2P mutation included, do not encompass vaccines that comprise only mRNAs for mutated variants. Note, for example, that the Omicron variant has more than

35 mutations in the 1,273 amino acid spike protein, resulting in a sequence identity of only 96.8% with the wild-type protein[18].

In view of the prior art situation, patent claims from the above discussed patent estates, if granted at all, would likely be restricted to the exact SARS-CoV-2 wild-type spike protein with the 2P mutation — which is what happened to Moderna's US patent application. Broader patent claims, wherein the scope is widened by using a homology range of, say, 80%, would bear the risk of also encompassing prior art spike proteins — for example, from the NIH patent publication.

For updated vaccines that mRNA companies are developing[19], such narrow claims are worthless, at least if the updated vaccine is monovalent or does not comprise the wild-type-derived protein. This, combined with the unfavorable findings in the ISRs, could discourage the applicants from further pursuing their respective patent applications, which could result in the unprecedented situation that some of the most successful (and commercially valuable) drugs in history remain without enforceable patent protection, hence dissipating concerns that patents could be the reason for inequitable access to COVID-19 vaccines[2].

## Future developments and conclusions

Ironically, the mRNA vaccine industry could become a victim of its own success. mRNA vaccines have been described as "plug-and-play" tools, with the LNP being a universal vector that can be used to accommodate any conceivable mRNA and shuttle it into a patient[20]. Such a characterization may be oversimplified. For example, CureVac has modified its first-generation anti-COVID mRNA vaccine CVnCoV, which showed disappointing results in clinical testing[21], in the 5′ and 3′ untranslated regions, while the encoding mRNA remained unchanged. It appears that the modified vaccine candidate, CV2CoV, has improved intracellular mRNA stability and translation, which results in improved immunogenicity[22]. Accordingly, there is a likelihood that future vaccines will demand more than just plug and play to be efficacious — and such 'more' can then be the basis for patent protection.

A mere modular approach would make patents protecting the respective vaccines difficult or even impossible to achieve, at least in the case when the mRNA being used is already publicly disclosed. As has already happened in the examples discussed above, patent authorities may consider such new vaccines to be obvious or non-inventive. This will pose serious challenges, for example, to updated variants of the existing COVID-19 mRNA vaccines, where the wild-type-derived spike sequence bearing the 2P mutation has been modified, for example, by the corresponding Omicron sequence.

If it is the case that current mRNA vaccines do not receive patent protection, an essential incentive for researchers and investors to spend time and resources on the still costly development and approval process would vanish. This could lead to something that no one would have expected — namely, that, as a consequence of the seemingly simple modular technology for making new mRNA vaccines, industry will refrain from investing money into research and development, which could lead to a decrease in new vaccines. ❐

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## Competing interests

The author declares no competing interests.