Research Article

The COVID 19 vaccine patent race

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COVID 19 has kept the world in its grip over the last 2 years already. It came with some remarkable - and in part concerning - developments, including the speed with which the virus, SARS CoV 2, spread over the globe, the fast vaccine development and approaval, the unexpected vaccine skepticism, and finally the inquitable distribution of the vaccines in different regions of the world. COVID 19 is also historic in terms of its patent background. The author has discussed different aspects thereof already.[1][2] In this article, the race to the vaccine, and its patents, will be discussed in detail.

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Phase 1: The long road to mRNA vaccines

The phenomenon that mRNA based COVID 19 vaccines were developed and approved so quickly may conceal 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. Key events are presented in the following, as well as in Figure 1, yet a more detailed account of the tangled history of mRNA vaccines is given in Dolgin 2021.[3]

In 1987, Robert Malone, a graduate student at the Salk Institute in La Jolla, mixed mRNA with fat droplets and showed that human cells incubated therein started translating the mRNA and produced proteins.[4] He realized that his results could suggest that one day mRNA could be used as a drug.

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

In 2005, Katalin Kariko and Drew Weissmann of University of Pennsylvania showed that mRNA containing pseudouridine ("Ψ") has improved translational capacities, increased biological stability,

and decreased stimulation of innate immunity caused by uridine.[5]

A variant thereof, 1-methyl pseudouridine ("m1Ψ") was later developed by Jason Schrum (but already anticipated in Kariko's and Weissmann's respective patent US8278036), and is said to exhibit even better protein expression rates and further reduced immunogenicity. m1Ψ is today being used in Moderna's and BioNtech's anti COVID 19 mRNA vaccines. Contrary thereto, Curevac uses a GC-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 coworkers developed the 4-lipid nanoparticles comprising, *inter alia*, a PEGylated lipid, and an ionizable lipid that is able to associate with the negatively charged mRNA.[6] These LNPs are being used in all mRNA based COVID 19 vaccines currenty on the market.

And in 2016, Moderna started a first clinical trial with an LNP/mRNA based vaccine.[7]

As a result, luckily, mRNA vaccine technology was fit for purpose when SARS CoV 2 jumped over the species barrier in late 2019. Or, as BioNTech's founders Özlem Türici and Ugur Sahin recount: "If the pandemic hit a year earlier, we might not have been in the position to respond this fast."[8]

Phase 2: 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 1 and MERS epidemics. Though many research groups started to develop vaccines, these efforts came to an arrest when the two diseases suddenly disappeared. However, the respective research provided valuable insights which then helped to accelerate the development of vaccines against SARS CoV 2.

In 2017, scientists at NIH, Dartmouth College and Scripps Research Institute, led by Barney Graham, looked into 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, and thus allows fusion of the virus therewith.[9]

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 in place at a junction between a heptad repeat 1 (HR1) and a central helix, so as to maintain the spike protein in a prefusion conformation.

The group applied this approach to different coronavirus which were known at that time, including SARS, where the two substitutions are K968P and V969P, and filed a patent application on 25.10.2016 (US20200611185A1 and family members). The disclosure of this patent family is not restricted to MERS CoV and SARS CoV spike protein mutants, yet also discloses spike mutants of quite a few other *Coronaviridae*, as shown in table 1.

Therein, It can be seen that the motif within which the proline substitutions have been accomplished is quite conserved within the spike protein. Figure 2 shows a sequence logo of the sequence motifs shown in table 1, with positions 5 and 6 the ones to be substituted by proline (P), to illustrate the relative abundance of key amino acids in that motif.

NIH received granted patents *inter alia* in the US and Europe, with claims related to a recombinant coronavirus protein comprising one or two proline substitutions near a junction between HRl and a central helix. Hence, even though the underlying application was filed before SARS CoV 2 entered the stage, the claims encompass also a SARS CoV 2 vaccines having the 2P mutation in that region.

Phase 3: 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, then called 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).[10]

The genome has a length of 29903 nucleotides and encodes in reading frame rf 2/direct the 1273 AA long peptide sequence of the SARS CoV 2 spike protein. The translated amino acid sequence of the SARS CoV 2 spike protein was later uploaded to UniProt on 22.04.2020 (UniProt identifier: P0DTC2).

It turned out that the sequences of the SARS CoV 1 spike protein (UniProt identifier: P59594) and that of SARS CoV 2 are highly similar (Identity: 76.4 %). In particular, both proteins share the above identified motif SRLDKVEA – in fact, they have a stretch of 111 identical amino acids in common that surrounds the above motif.

The arrival of the new virus did not remain unnoticed in the mRNA vaccine community. Reportedly, Steve 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 (i.e., 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."[11]

On 24 January 2020, BioNTech's Ugur Sahin recounts to have returned from his family's Friday ritual, their weekly dinner at a Vietnamese restaurant, checking the newest scientific literature, only to learn about the rapid spreading of the Virus in China. On Sunday, he and his team had the respective sequences available, and on Monday, back in the office, they decided to set up vaccine development.[8]

Next to Moderna and BioNTech, also CureVac started to develop an mRNA vaccine. What then happened is quite unique: A patent search[12] using the 1273 amino acid long 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 after the publication of the SARS CoV 2 genome, companies filed patent applications disclosing or claiming said SARS CoV2 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 – who is making the NVX-CoV2373 spike protein vaccine – was the first to receive an receipt stamp from the patent office, and secured a filing date of 27 January 2020 – i.e., merely 15 days after the SARS CoV 2 genome was published. Moderna came one day later. Janssen (a subsidiary of Johnson and Johnson) followed on 31 January 2020, CureVac on 4 February 2020, the NIH on 11 February 2020, and, with others in between, BioNTech followed on 22 April 2020 – all of them claiming the 100% identical 2P mutant protein, or an mRNA encoding for said same protein. Figure 3 gives an overview of these events.

None of these early applications comprise experimental data with regard to the claimed vaccine – which is not surprising, considering the time budget that was available for drafting. Moderna's priority application, for instance, comprises only 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 with -1 LD90 of coronavirus"), yet no wet 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 only restricted to the sequence of the encoding mRNA or the spike protein, respectively. Moderna's, CureVac's 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 SEQ ID NO of the 1273 aa long 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:

As can be seen, all three applications claim the same sterol and the same "regular" lipid, while CureVac and BioNTech also claim the same PEG lipid and ionizable lipid. Moderna and BioNTech also claim the use of m1Ψ, while CureVac optionally excludes said variant and prefers GC enrichment instead (which BioNTech only suggests as an option).

A situation like this, where several entities file, almost simultaneously, patents related to essentially the same subject matter, may inevitably lead into legal conflicts - as we have witnessed in the year long CRISPR Cas 9 patent dispute.[13]

However, in the present case, it may not come so far. All three applications are still in what is called the 18-months long "international phase" (with one exception for Moderna, see below), and are hence not yet pending in the different destination countries. For all three applications, International Search Reports (ISR) have issued, prepared by the European Patent Office (EPO) as International Searching Authority (ISA), which reports come with a preliminary opinion on patentability.

In all three cases, though, the respective examiners came to the conclusion that the claimed subject matter would not be novel/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 Coronavirus.[9][14][15] In the national patent phases, which come after the international phase, most national patent offices, though not bound to, rely on the opinion of the ISA. This means that Moderna, CureVac and BioNTech, should they decide to enter the national phases with their cases, would experience considerable headwind.

Notwithstanding the above, Moderna has already a pending US patent application (US20210228707A1) which received a Notice of Allowance on 27 August 2021. However, on 14 December 2021, the USPTO delivered an abandonment notice, according to which Moderna failed to pay the issue fee and the

publication fee. The application is therefore deemed abandoned (Moderna has filed a continuation application (17/518,542), which is not yet published though).

The reason for this step may be that the patent claims as granted, while protecting vaccines that comprise mRNAs encoding for the SARS CoV 2 wildtype spike protein with the 2P mutation factored in, 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 1273 AA long spike protein, resulting in a sequence identity of only 96.8 % with the wildtype protein.[16] However, in view of the prior art situation, patent claims from the above discussed patent estates, if granted at all, would be likely restricted to the exact SARS CoV 2 wildtype 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 e.g. 80 %, would bear the risk to also encompass prior art spike proteins e.g. from the NIH patent publication. For updated vaccines that mRNA companies are about to develop, [17] such narrow claims are worthless at least if the updated vaccine is monovalent, or does not comprise the wildtype-derived protein.This, combined with the unfavourable findings made in the International Search Reports (ISR), could discourage the applicants to further pursue their respective patent applications. This might result in the unprecedented situation that some of the most successful (and commercially valuable) drugs of these times remain without enforceable patent protection - hence, dissipating concerns that patents could be the reason of inequitable access to COVID 19 vaccines.[2]

Future developments and conclusions

Ironically, in some aspect, the mRNA vaccine industry may eventually 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. [18] Such characterization may be a bit oversimplified. For example, CureVac has modified its 1st generation anti COVID mRNA vaccine CVnCoV, which showed disappointing results in the clinical testing,[19] in its 5' and 3' untranslated regions (UTRs), while the encoding mRNA remained unchanged It appears that the modified variant, CV2CoV, has improved intracellular mRNA stability and translation, which results in improved immunogenicity.[20] Accordingly, there is a likelihood that future vaccines will demand more than just "plug and play" to be efficacious – and that "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 case the mRNA that is used is already publicly disclosed. As already happened in the three 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 mRNA vaccines, where the wildtype derived spike sequence bearing the 2P mutation has been modified, e.g., by the corresponding omicron sequence. In case there is no chance to receive patent protection for such vaccine, an essential incentive for researchers and investors to spend time and resources into the still costly development and approval process would break away. 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 therein - and that might lead to a decrease in numbers of new vaccines.

Figures and Tables

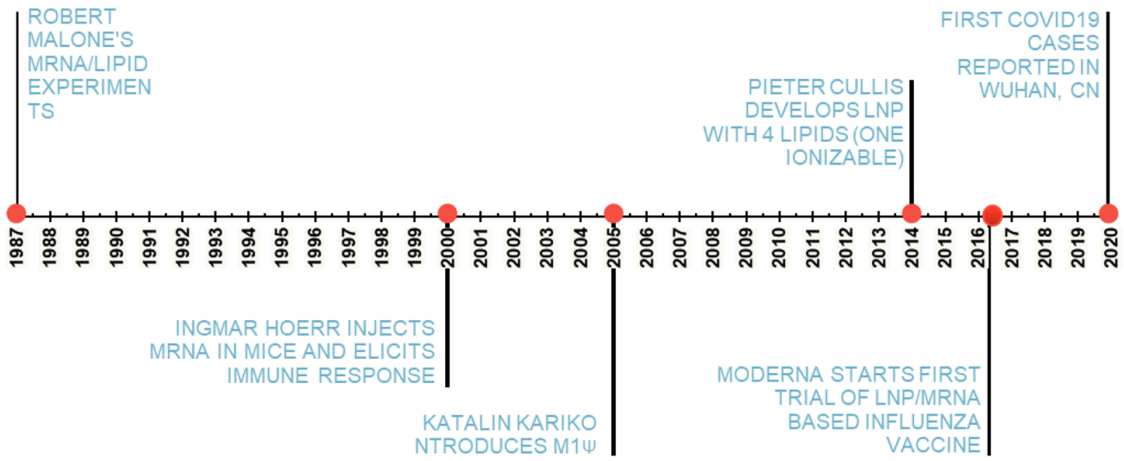

Figure 1: The long road to mRNA vaccines

doi.org/10.32388/8QZ8K1

Coronavirus type	SEQ ID NO	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[1]	30	K968P and/or V969P	SRLDKVEA
PEDV	39	I1076P and L1077P	SRLDILSA
SDCV	42	E855P and V856P	NRLEEVEA

Table 1

[1] An almost identical variant of the SARS CoV 1 spike protein with slight differences at the C-terminus, yet also having the motif SRLDKVEA, was released in the SwissProt database under the indentifier P59594 on 23.04.2003.

Figure 2: Sequence logo of the sequence motifs shown in table 1

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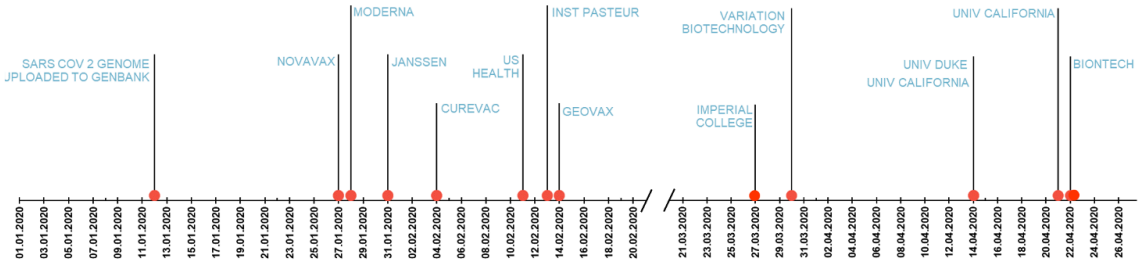

Figure 3: Filing history of patent applications reciting or claiming the SARS CoV 2 spike protein with the 2P mutant

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Company	Priority date	SEQ ID	m1Ψ claim	GC enrich-ment claim	PEG Lipid	Sterol	Ionizable Lipid	Regular Lipid
Moderna/ WO2021154763	28.01.20	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	04.02.20	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	22.04.20	7	12. Modified nucleoside is selected from ψ, m1Ψ and m5U	3. Coding sequence the G/C content is increased	24. LNP particles comprise ALC-0159	24. LNP particles comprise cholesterol	24. LNP particles comprise ALC-0315	24. LNP particles comprise DSPC

Table 2: Key claims of Moderna's, Curevac's and BioNTech's international patent applications

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