



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • [www.citizen.org](http://www.citizen.org)

## **Leading COVID-19 Vaccine Candidates Depend on NIH Technology**

Coronavirus spike proteins are notorious for changing shape. The spike proteins—which give coronaviruses their name for their crown-like appearance—play a critical role in viral infection, helping the virus fuse with human cells by attaching to cellular receptors.<sup>1</sup> Developing antibodies to the *prefusion* spike protein is considered critical for vaccines, but natural spike proteins in isolation are inherently unstable and do not retain the prefusion shape.<sup>2</sup> This presents a significant challenge for coronavirus vaccine development.

Long before this pandemic, NIH scientists working with academic researchers came up with a solution. They engineered a new way of “freezing” coronavirus spike proteins in the prefusion shape. The prefusion spike protein for an earlier coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), produced a stronger antibody response at lower doses than the naturally occurring protein in mice.<sup>3</sup> The approach required substituting two amino acids with prolines near the central helix and heptad repeat 1 (“the 2P approach”). The scientists filed a patent application covering this approach.<sup>4</sup>

When severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, the scientists realized the same approach could work for the new virus. They filed another patent application.<sup>5</sup> **Now, most of the leading first-generation COVID-19 vaccine candidates—including those by Pfizer/BioNTech, J&J, Novavax, CureVac and Moderna—are using the publicly developed 2P approach. Years of public investment have fueled the rapid advancement of COVID-19 vaccine candidates.**<sup>6</sup>

Table 1: COVID-19 Vaccine Candidates Using 2P Approach<sup>7</sup>

| Corporation         | Candidate Description   |
|---------------------|---|
| Pfizer/BioNTech     | “BNT162b2, encodes the SARS-CoV-2 full-length spike, <b>modified by two proline mutations</b> to lock it in the prefusion conformation.” <sup>8</sup>   |
| Johnson and Johnson | “We produced seven Ad26 vectors that expressed SARS-CoV-2 S variants that reflected different leader sequences, antigen forms and stabilization mutations . . . wild-type leader sequence with full-length S and mutation of the furin cleavage site and <b>proline-stabilizing mutations</b> .” <sup>9</sup> |

<sup>1</sup> Daniel Wrapp et al., Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, *Science*, (Mar. 13, 2020), <https://science.sciencemag.org/content/367/6483/1260> (“2019-nCoV makes use of a densely glycosylated spike (S) protein to gain entry into host cells. The S protein is a trimeric class I fusion protein that exists in a metastable prefusion conformation that undergoes a substantial structural rearrangement to fuse the viral membrane with the host cell membrane.”)

<sup>2</sup> Ryan Cross, What will it take to make an effective vaccine for COVID-19 (July 17, 2020), *Chemical & Engineering News*, <https://tinyurl.com/yv3kirb7> (“Many researchers believe it is crucial to show your immune cells this so-called prefusion form of the spike protein in order to make antibodies that prevent infection. In contrast, if the vaccine teaches the immune system to make antibodies to the postfusion form, the shape the spike protein takes after binding to a cell, those antibodies will bind to the spike too late to prevent infection, says Andrew Ward, a structural biologist at Scripps Research who co-led the study.”)

<sup>3</sup> Pallesen et al., Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen, *PNAS* (2017), <https://www.pnas.org/content/114/35/E7348> (“These data demonstrate that retaining MERS-CoV S in its prefusion conformation increases the breadth and potency of the neutralizing activity elicited by vaccination.”)

<sup>4</sup> U.S. Application No. 16/344,774. <https://www.ott.nih.gov/technology/e-234-2016>.

<sup>5</sup> U.S. Application No. 62/972,886. Chris Rowland, A coronavirus vaccine rooted in a government partnership is fueling financial rewards for company executives, *The Washington Post* (July 2, 2020), <https://tinyurl.com/y5ex9z6s>

<sup>6</sup> Public Citizen, Blind Spot: How the COVID-19 Outbreak Shows the Limits of Pharma’s Monopoly Model, <https://www.citizen.org/article/blind-spot/>

<sup>7</sup> This is not an exhaustive list. The Imperial College and Medigen candidates, for example, also rely on proline substitutions.

<sup>8</sup> Edward Walsh et al., Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates, *NEJM* (2020), <https://www.nejm.org/doi/full/10.1056/NEJMoa2027906>

<sup>9</sup> The protein with the proline-stabilizing substitutions was ultimately selected. Noe Marcado et al., Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques, *Nature* (2020), <https://www.nature.com/articles/s41586-020-2607-z>.

|         |   |
|---------|---|
| Novavax | "rSARS-CoV-2 is generated with 682-QQAQ-685 mutations at the S1/S2 cleavage sites to confer protease resistance and <b>two proline substitutions</b> at residues K986P and V987P at the top of the heptad repeat 1/central helix in the S2 subunit to stabilize the construct in a prefusion conformation." <sup>10</sup> |
| CureVac | "CVnCoV is comprised of lipid nanoparticle (LNP)-formulated, non-chemically modified, sequence engineered mRNA encoding full length S protein <b>with two proline mutations</b> (S-2P)." <sup>11</sup>  |
| Moderna | "The mRNA-1273 vaccine candidate, manufactured by Moderna, encodes the S-2P antigen . . . S-2P is stabilized in its prefusion conformation <b>by two consecutive proline substitutions</b> at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit." <sup>12</sup>                         |

One vaccine scientist noted that we were “very lucky, actually” that scientists had developed the 2P approach earlier.<sup>13</sup> “It wouldn’t be possible to go so fast with the Moderna vaccine otherwise,” he said.<sup>14</sup> Moderna is one of many beneficiaries.<sup>15</sup> In fact, Pfizer and J&J actually tried to test other vaccine proteins, but selected a 2P protein because it showed early superiority in clinical trials.<sup>16</sup> In the Pfizer Phase 2 trial, for example, the 2P protein seemed to produce fewer side effects, particularly in older adults.<sup>17</sup> Pfizer then selected the vaccine candidate based on the 2P protein for Phase 3 trials.<sup>18</sup>

Our analysis is limited by a lack of transparency. There remains some ambiguity about the scope of the patent applications—one of them remains unpublished—and whether they will ultimately be granted. The precise nature of the licensing agreements between the federal government and the corporations also remains unclear. As of early August, the NIH, the academics and the corporations involved were still discussing details around licensing and royalty arrangements.<sup>19</sup>

But it is clear that the federal government’s early investment in coronavirus research laid the foundation for the rapid response to COVID-19, helping accelerate the development of many leading vaccine candidates. These candidates then received billions of dollars in additional funding from the U.S. government among others.<sup>20</sup>

The U.S. government should require the corporations that benefit from public funding and public science to act in the public interest. This should include conditions on reasonable pricing and expanding manufacturing. Indeed, while there remains some uncertainty about the immunity provided by potential vaccines, many analysts expect annual vaccines will be required, with some projecting that the vaccine market in the U.S. could be worth \$10 billion a year alone.<sup>21</sup> Taxpayers should not have to repeatedly pay for the technologies they helped develop. In line with its commitment to ensure “consumers are not price gouged as new drugs and therapies come to market,” the Biden Administration should require reasonable pricing.<sup>22</sup> It should also require corporations to share technology and know-how to scale up supply around the world. That is the only way to bring a rapid end to the pandemic.

<sup>10</sup> Cheryl Keech et al., Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine, NEJM (2020), <https://www.nejm.org/doi/full/10.1056/NEJMoa2026920>

<sup>11</sup> Susanne Rauch et al., mRNA based SARS-CoV-2 vaccine candidate CVnCoV induces high levels of virus neutralizing antibodies and mediates protection in rodents, bioRxiv (2020) (preprint), <https://www.biorxiv.org/content/10.1101/2020.10.23.351775v1>.

<sup>12</sup> Lisa Jackson et al., An mRNA Vaccine against SARS-CoV-2 — Preliminary Report, NEJM (2020), <https://tinyurl.com/y2ve7nsf>.

<sup>13</sup> Ryan Cross, The tiny tweak behind COVID-19 vaccines (Sept 29, 2020), Chemical & Engineering News, <https://tinyurl.com/yxoj472x>

<sup>14</sup> *Id.*

<sup>15</sup> Bob Herman, The NIH claims joint ownership of Moderna’s coronavirus vaccine, Axios (June 25 2020).

<sup>16</sup> Edward Walsh et al., Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates, NEJM (2020) and Noe Marcado et al., Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques, Nature (2020).

<sup>17</sup> Edward Walsh et al., Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates, NEJM (2020), (“BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults”).

<sup>18</sup> *Id.*

<sup>19</sup> A coronavirus vaccine is on the horizon, thanks to a key discovery by UT researchers, New Statesman (Aug. 10 2020), <https://tinyurl.com/y4gas4i7>

<sup>20</sup> <https://www.citizen.org/article/barda-funding-tracker/>. The German government also significantly supported BioNTech.

<sup>21</sup> Covid-19 vaccine market worth \$10bn a year, analysts say, Financial Times (Nov 5, 2020), <https://tinyurl.com/yxmredyb>.

<sup>22</sup> The Biden-Harris Plan to Beat COVID-19, <https://buildbackbetter.com/priorities/covid-19/>