Comirnaty®

Pfizer-BioNTech's COVID-19 Vaccine, mRNA

The joint efforts of inventors from the National Institute of Allergy and Infectious Diseases (NIAID), their collaborators, and NIAID's Technology Transfer and Intellectual Property Office (TTIPO) positioned BioNTech/Pfizer to quickly develop a COVID-19 vaccine and bring it to market.

Context/Background

On December 31, 2019, China informed the World Health Organization (WHO) of cases of "pneumonia of unknown etiology," which was later found to be the result of a novel coronavirus outbreak.[1] The novel coronavirus spread outside China incrementally, including to the United States. By March 2020, confirmed U.S. cases totaled 60, and worldwide cases totaled more than 118,000 in 114 countries with 4,291 deaths. WHO subsequently declared the coronavirus disease outbreak a pandemic. As of September 2022, the United States documented 94.1 million cases of the disease, now known as coronavirus disease of 2019 (COVID-19), which is caused by infection with severe acute respiratory coronavirus 2 (SARS-CoV-2). Over 1 million deaths have been associated with COVID-19 in the United States.[2]

The pathway to develop a safe and effective vaccine against COVID-19 was anything but linear. In the words of Dr. Barney Graham, former deputy director of the Vaccine Research Center (VRC) at NIAID, National Institutes of Health (NIH), "It wasn't just innovation, it was providence."[3] Building on break-through innovations in respiratory syncytial virus (RSV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and other coronaviruses, NIAID scientists and collaborators were well-positioned to rapidly develop the antigen technology needed for COVID-19 vaccines. Protecting these innovations through patents and facilitating development through partnerships, the efforts of TTIPO would eventually enable vaccine developers to access the antigen technology needed to quickly develop safe and effective vaccines against COVID-19.

The Discovery of the Technology (inventor story)

In 1999, Dr. Graham was a professor at the Vanderbilt University School of Medicine studying RSV and conducting clinical studies on HIV vaccines when he was recruited to be one of the first investigators at VRC. At the time, VRC was a new center within NIH that was established to develop a vaccine to combat HIV. In 2000, Dr. Graham joined VRC to lead a research laboratory focused on respiratory viruses and to direct the VRC's clinical trials program.

While working on HIV vaccines, Dr. Graham realized that the envelope protein engineering techniques used in HIV vaccine research and development could be applied to create potent neutralizing antibodies in patients with RSV.[4] The unsuccessful attempt to develop an RSV vaccine in the 1960s focused on the postfusion form of the RSV fusion (F) protein, a protein with a flexible, dynamic structure that "docks" the virus to its target cell during the infection process. Dr. Graham and his team hypothesized that a

[1] World Health Organization. "COVID-19 – China." Last modified January 5, 2020. https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON229

[2] World Health Organization. "United States of America: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data." Accessed September 16, 2022. https://covid19.who.int/region/amro/country/us.

[3] Lawrence Tabak, "Pfizer/BioNTech Vaccine: How COVID-19 Immunity Holds Up Over Time." NIH Director's Blog. Last modified March 1, 2022. https://directorsblog.nih.gov/tag/pfizer-biontech-vaccine/.

[4] Michael Blanding, "Shot in the Arm: Groundbreaking COVID-19 Vaccine Research by Alumnus Dr. Barney Graham Began at Vanderbilt Decades Ago." Vanderbilt University. Last modified March 17, 2021. https://news.vanderbilt.edu/2021/03/17/shot-in-the-arm-groundbreaking-covid-19-vaccine-research-by-alumnus-dr-barney-graham-began-at-vanderbilt-decades-ago/.

successful RSV vaccine would need to lock the RSV F protein in its prefusion form, so the immune system can prevent the virus from connecting with the target cell. Despite this hypothesis, one challenge remained: No one knew what the prefusion form of the F protein looked like.[5]

Dr. Graham enlisted the help of his VRC colleagues, Dr. Peter Kwong and Dr. Jason McLellan from the Structural Biology Section of the Laboratory of Virology. The team determined the structure of the prefusion form of the F protein using X-ray crystallography. Knowledge of the RSV F protein's prefusion form allowed the team to devise a way to engineer the protein to stabilize it in its prefusion form. The hypothesis was validated when this RSV prefusion F protein was tested in humans and elicited a protective immune response.[6] This success revolutionized techniques for protein engineering in vaccine development for RSV and other enveloped viruses with fusion proteins of similar structure, including influenza and other respiratory viruses.

Following the discovery of MERS-CoV in 2012, the team tried to engineer the MERS-CoV spike (S) protein to lock it into the prefusion form but was impeded by their inability to determine the structure of the S protein due to its flexibility. These struggles, compounded by fears of potential infection from this highly contagious virus, led the team to seek a less-virulent coronavirus to study. Unsure about where to turn, the team got inspiration from an unexpected source—a colleague in Dr. Graham's laboratory who had returned from a trip to the Middle East with symptoms similar to MERS, only to be diagnosed with human coronavirus HKU1 infection. This serendipitous finding motivated the team to quickly pivot and work with HKU1, a human coronavirus known to cause symptoms of common cold with only moderate clinical impact. Using cryogenic electron microscopy, the team, which included Dr. McLellan (who had moved to Dartmouth College) and Dr. Andrew Ward at The Scripps Research Institute, determined the structure of HKU1 S proteins in their prefusion forms. The team used this structure to guide their work to engineer the S protein with the goal of stabilizing the spike in its prefusion conformation. They discovered that adding two prolines, which are rigid amino acids, to a specific location in HKU1's S protein would stabilize the protein in its prefusion form, unable to morph into its postfusion form. The team called this the "2P" mutation and the entire mutated S protein, "S2P." This finding suggested that the 2P mutation could stabilize the S protein of any coronavirus.[7]

"Using the tools that we had to work on HIV allowed us to solve an RSV problem, which contributed to the development of a vaccine for SARS-CoV-2."
—Dr. Barney Graham

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[5] Jillian Kramer, "They Spent 12 Years Solving a Puzzle. It Yielded the First COVID-19 Vaccines." *National Geographic.* December 2021. https://www.nationalgeographic.com/science/article/these-scientists-spent-twelve-years-solving-puzzle-yielded-coronavirus-vaccines

[6] Michael Blanding, "Shot in the Arm: Groundbreaking COVID-19 Vaccine Research by Alumnus Dr. Barney Graham Began at Vanderbilt Decades Ago." Vanderbilt University. Last modified March 17, 2021. https://news.vanderbilt.edu/2021/03/17/shot-in-the-arm-groundbreaking-covid-19-vaccine-research-by-alumnus-dr-barney-graham-began-at-vanderbilt-decades-ago/.

[7] Geddes, Linda, "Taming the spike: How Jason McLellan helped turn the tide of the pandemic." May 16, 2022. https://www.gavi.org/vaccineswork/taming-spike-how-jason-mclellan-helped-turn-tide-pandemic

Role of NIAID's Technology Transfer and Intellectual Property Office (Tech Transfer Story)

Notwithstanding their profound discovery, Dr. Graham and his colleagues struggled to get their research published, receiving rejections from five scientific journals before their research was published in the *Proceedings of the National Academy of Sciences* in 2017.[8,9] Despite little commercial interest in coronaviruses during this time, the VRC team was adamant that coronaviruses would continue to be a public health threat and thus were committed to protecting this invention with a patent. The VRC team had the steadfast support of TTIPO, which worked with them throughout the patenting process. The team first approached TTIPO when they had crystallized the S protein of HKU1. TTIPO recognized that a patent application describing the HKU1 S protein structure would have limited utility but encouraged the VRC team to report its progress in applying their protein engineering expertise to modify the S protein and improve its usefulness in a vaccine. After stabilizing the S proteins for HKU1 and MERS using the 2P mutation, the inventors reported the invention to TTIPO. In October 2016, TTIPO filed a patent application (US Application 62/412,703) titled Prefusion Coronavirus Spike Proteins and Their Use.[10] This technology employs protein engineering techniques to stabilize S proteins in coronaviruses in their prefusion state, preventing structural rearrangement. By 2017, when TTIPO filed a follow-on application under the Patent Cooperation Treaty (PCT Application US2017/058370), the team had used the same approach in multiple coronaviruses. TTIPO hypothesized that, because the approach worked in each of the 11 coronaviruses the VRC team tried, it should be possible to obtain patent claims for the use of the 2P mutation to stabilize any coronavirus. And so, they did. The patent describes its technology as applicable to all coronaviruses.[11]

Recognizing the potentially devastating threat that coronaviruses pose to public health, Dr. Graham's laboratory collaborated with a commercial partner to design an experimental messenger RNA (mRNA) vaccine for MERS.[12] TTIPO helped memorialize the partnership in a research collaboration agreement. The commercial partner and Graham's lab had worked together previously to combat Zika virus as part of NIAID's prototype pathogen approach for pandemic preparedness. NIAID's prototype pathogen approach for pandemic preparedness entailed studying the characteristics of a prototypical member of a viral family—in this case MERS—to inform the development of vaccines for viruses from the same family, that is, betacoronaviruses.[13] The collaboration on the MERS vaccine was successful in animal models, creating a "portfolio of data" that researchers and scientists could leverage and apply to new coronaviruses.[14] This partnership, forged by TTIPO and the VRC team, highlights the importance of collaboration between NIH and commercial entities in preparing for future pandemics. Moreover, the

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[8] Michael Blanding, "Shot in the Arm: Groundbreaking COVID-19 Vaccine Research by Alumnus Dr. Barney Graham Began at Vanderbilt Decades Ago." Vanderbilt University. Last modified March 17, 2021. https://news.vanderbilt.edu/2021/03/17/shot-in-the-arm-groundbreaking-covid-19-vaccine-research-by-alumnus-dr-barney-graham-began-at-vanderbilt-decades-ago/.

[9] Jesper Pallesen, Nianshuang Wang, Kizzmekia S. Corbett, Daniel Wrapp, Robert N. Kirchdoerfer, Hannah L. Turner, Christopher A. Cottrell, Michelle M. Becker, Lingshu Wang, Wei Shi, Wing-Pui Kong, Erica L. Andres, Arminja N. Kettenbach, Mark R. Denison, James D. Chappell, Barney S. Graham, Andrew B. Ward, and Jason S. McLellan, "Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen." *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*, vol. 114, no. 35, August 14, 2017, pp. E7348–E7357. https://doi.org/10.1073/pnas.1707304114

[10] The USPTO issued the patent in March 2021.

[11] Graham, B., McLellan, J., Ward, A., Kirchdoerfer, R., Cottrell, C., Joyce, M.G., Kanekiyo, M., Wang, N., Pallesen, J., Yassine, H., Turner, H., Corbett, K. *Prefusion Coronavirus Spike Proteins and Their Use*. US Application 62/412,703, United States Patent and Trademark Office, Filed on 25 October 2016.

[12] Jillian Kramer, "They Spent 12 Years Solving a Puzzle. It Yielded the First COVID-19 Vaccines." *National Geographic.* December 2021. https://www.nationalgeographic.com/science/article/these-scientists-spent-twelve-years-solving-puzzle-yielded-coronavirus-vaccines

[13] Barney S. Graham, and Kizzmekia S. Corbett, "Prototype Pathogen Approach for Pandemic Preparedness: World on Fire." *Journal of Clinical Investigation,* vol. 130, no. 7, July 2020, pp. 3348–3349. https://doi.org/10.1172/JCI139601

[14] Jillian Kramer. "They Spent 12 Years Solving a Puzzle. It Yielded the First COVID-19 Vaccines." *National Geographic.* December 31, 2020. https://www.nationalgeographic.com/science/article/these-scientists-spent-twelve-years-solving-puzzle-yielded-coronavirus-vaccines

collaboration helped the commercial partner establish a proof of concept of their platform, which ultimately enabled the rapid development of a COVID-19 vaccine.

TTIPO began marketing the S2P technology in April 2018, [15] but the emergence of SARS-CoV-2 in 2020 triggered a flood of interest in this invention. With a torrent of commercial interest and a pandemic surging, the VRC team and their commercial partner shifted focus to SARS-CoV-2. By February 2020, TTIPO had filed a patent application (U.S. Application 17/798,021) that specifically applied the 2P mutation of the 2016 invention to SARS-CoV-2. TTIPO swiftly made the strategic decision to adopt a nonexclusive licensing approach to ensure the availability of this foundational invention to as many vaccine developers as possible. Federal technology transfer legislation requires non-exclusive licensing, unless exclusivity can be justified, to incentivize commercial development to ensure the broadest dissemination of inventions resulting from federal research. Moreover, because the prefusion spike stabilization technique was broadly applicable to vaccines, there was uncertainty about which vaccine platform would ultimately be successful. This approach enabled NIAID to cast a wide net and license to many companies, accelerating the development and commercialization of a sorely needed vaccine. With huge market potential and a flood of commercial interest, TTIPO managed relationships with dozens of commercial partners. By October 2022, TTIPO had received 47 license applications for the technology, and ultimately 15 companies (10 vaccine developers; 5 diagnostic developers) licensed the technology for commercial development.

"Comirnaty wouldn't be possible without the support of NIAID'S Technology Transfer and Intellectual Property Office. They really had to work hard to bring it all together."
- Dr. Barney Graham

Role of Licensee (commercialization story)

NIH granted a nonexclusive license to BioNTech, a German biotechnology company focused on mRNA delivery of immunogens and therapeutic proteins. BioNTech partnered with Pfizer to jointly develop a COVID-19 vaccine. The partnership between Pfizer and BioNTech dates back to 2018 when the two companies agreed to develop an influenza vaccine using mRNA. Their co-developed influenza vaccine was due for human trials in 2020, but they pivoted after the emergence of SARS-CoV-2 in January.[16] With NIH license in hand, the BioNTech-Pfizer partnership developed, tested, and gained Emergency Use Authorization for its SARS-CoV-2 vaccine—all in less than 12 months, and by December 15, 2020, the first doses were being administered. In August 2021, the Pfizer-BioNTech vaccine became the first FDA-approved COVID-19 vaccine and was given the brand name Comirnaty® .[17]

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[15] Federal Register, "Government-Owned Inventions; Availability for Licensing." April 16, 2018. https://www.federalregister.gov/documents/2018/04/16/2018-07822/government-owned-inventions-availability-for-licensing

[16] Bojan Pancesvski, and Jared S. Hopkins, "How Pfizer Partner BioNTech Became a Leader in Coronavirus Vaccine Race." *The Wall Street Journal*, October 22, 2020. https://www.wsj.com/articles/how-pfizer-partner-biontech-became-a-leader-in-coronavirus-vaccine-race-11603359015

[17] U.S. Food and Drug Administration, "FDA Approves First COVID-19 Vaccine." U.S. Food and Drug Administration. Last modified August 23, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine.

Impact

Availability of the NIH-developed prefusion S protein technology, has

- Contributed to the development of a COVID-19 vaccine in less than 12 months, the fastest on record[18] and subsequently the first FDA-approved and most widely administered COVID-19 vaccine;
- Enabled the development of the four vaccines available in the United States;
- Helped boost the global supply of vaccines through WHO's COVID-19 Technology Access Pool; and
- Spurred innovation in vaccine research and development for other viruses.

The novel discovery by Dr. Graham and his colleagues had a profound impact on the rapid development of safe and effective COVID-19 vaccines. The vaccine was a remarkable scientific achievement: scientists were able to identify the pathogen, characterize an immune response, and develop and test a safe and effective vaccine, all in under 12 months—the fastest vaccine in history.[19] Over 15 companies licensed the coronavirus S2P technology, and as of November 2022, the four vaccines available in the United States use the NIH-developed S2P mutation.[20] BioNTech and Pfizer's Comirnaty vaccine was the first FDA-approved vaccine and is the most widely administered vaccine in the United States, with over 370 million doses of the vaccine being administered as of October 5, 2022.[21]

NIH has also worked to ensure that the critical technology is broadly available to vaccine developers by contributing it to WHO's COVID-19 Technology Access Pool under standard terms.

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[18] Sandy Cohen, "The Fastest Vaccine in History." UCLA Health. Last modified December 10, 2020. https://connect.uclahealth.org/2020/12/10/the-fastest-vaccine-in-history/

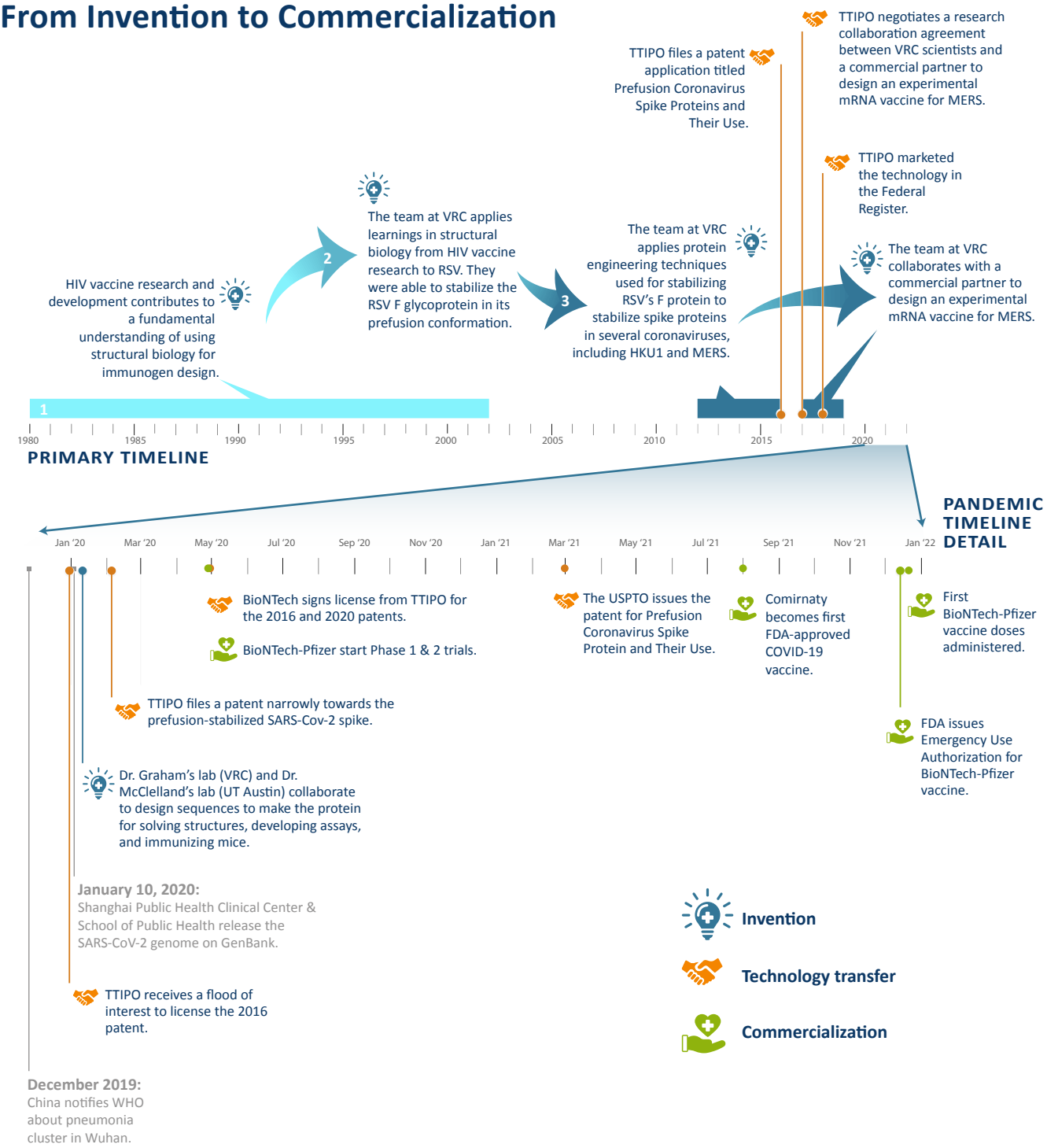
[19] Sandy Cohen, "The Fastest Vaccine in History." UCLA Health. Last modified December 10, 2020. https://connect.uclahealth.org/2020/12/10/the-fastest-vaccine-in-history/

[20] Zain Rizvi, "Leading COVID-19 Vaccine Candidates Depend on NIH Technology." *Public Citizen*, November 10, 2020. https://www.citizen.org/article/leading-covid-19-vaccines-depend-on-nih-technology/

[21] Our World in Data. (September 2022). *COVID-19 vaccine doses administered by manufacturer, United States.* Retrieved from https://ourworldindata.org/grapher/covid-vaccine-doses-by-manufacturer

Comirnaty Timeline

From Invention to Commercialization



THE INVENTION STORY:

1

Research on the development of HIV vaccines contributed to foundational learnings on structural biology that ultimately played a role in the development of Comirnaty.

2

Scientists translated learnings from HIV vaccine research to RSV and were able to capture the crystal structure of the prefusion form of RSV's F protein using x-ray crystallography and stabilize the shape to determine its structure.

3

The protein-engineering techniques used on RSV revolutionized vaccines development and were applied to coronaviruses.