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PROGRESS DEFERRED: LESSONS FROM MRNA VACCINE DEVELOPMENT

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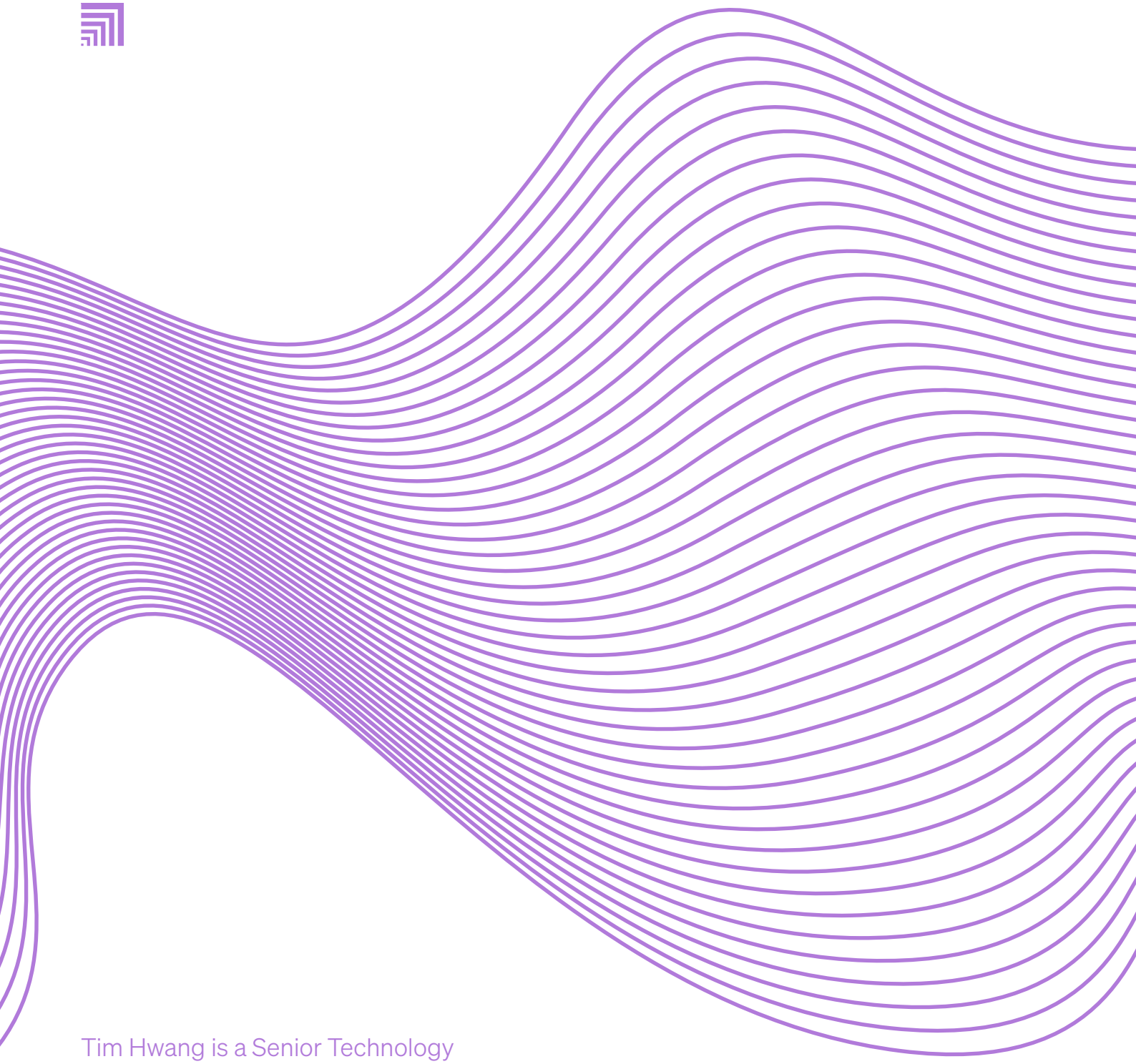

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Introduction

mRNA technologies represent a massive advance in society's ability to combat disease. Since they were used to address the COVID-19 pandemic, mRNA vaccines are now being applied to halt the spread of HIV, MERS, malaria, tuberculosis, and other conditions. mRNA vaccines can also be developed and manufactured at higher speed and lower cost than traditional vaccines, allowing society to more nimbly address biological threats

Global crisis accelerated the development and deployment of mRNA vaccines in 2020. But the concept of mRNA vaccines had been first proposed decades earlier in 1988. A critical discovery by Katalin Karikó and Drew Weissman, that foreign mRNA could be modified to allow it to be introduced into a cell without triggering an immune response from the body, was first published in 2005. Karikó and Weissman's paper was itself based on observations previously made in papers dating to the 1960s.[1]

Much of the fundamental groundwork needed to make mRNA vaccines a practical reality had been available years before it was put to use to fight COVID-19. That Operation Warp Speed was able to quickly resolve many issues of vaccine design and manufacturing within months is indicative. It suggests that the primary limitation to achieving mRNA vaccines was resourcing, rather than fundamental barriers of understanding or technology.

This paper reckons with this incongruity: post hoc, mRNA vaccines were clearly a major breakthrough. But for a long period, investigators like Karikó and Weissman and startups like Moderna and BioNTech languished in relative obscurity. Why were mRNA vaccines not developed and made practical for use significantly earlier?

There are pragmatic reasons for asking this question: if mRNA vaccines had been available as a public health tool before the emergence of a global emergency, they would have saved many lives.[2] Follow-on innovations that are just now taking shape in applying mRNA technologies to address other public health threats would have been available years earlier and made a positive impact. By understanding the structural frictions that slowed development in this case, we may be able to identify broader reforms that allow society to capture the benefits of key breakthrough technologies earlier.

Reviewing the historical progression of mRNA vaccine development suggests three primary frictions significantly delayed the advent of the technology:

- **Perceived Viability of mRNA:** The development of mRNA vaccines took place against the backdrop of a history of disappointing results in adjacent technologies. The poor reputation of DNA vaccines, which had captured the imaginations in the 1990s fight against HIV but had largely not lived up to their promise, shaped perceptions about the viability of mRNA vaccines. mRNA was also widely perceived to be a fragile molecule, difficult to work with, and impractical for mass manufacturing. This perception worked to limit academic interest, funding, and corporate support for pursuing mRNA vaccines and therapeutics as a focus of research and development.

1 Prashant Nair, "QnAs with Kaitlin Karikó," PNAS (Dec 13, 2021).

2 For one estimate of this, *see*, e.g. Markus B. Bjoerkheim and Alex Tabarrok, "Covid in the nursing homes: the US experience," *Oxford Review of Economic Policy* (Dec 14, 2022), (estimating that within nursing homes, "starting vaccinations just 5 weeks earlier could have saved in the order of 14,000 lives and starting them ten weeks earlier could have saved 40,000 lives").

- **Vaccines as an Unprofitable Research Field:** Pharmaceutical companies underwrite and set the agenda for researching the next generation of treatments. mRNA vaccines presented an unattractive business prospect, even if one considered them viable to create. Vaccines as a category tend to be less favored by pharmaceutical companies, since demand for them can be highly unpredictable and margins typically low. This worked to limit the level of industry effort dedicated to translating laboratory findings into applied practices for manufacturing and delivering mRNA vaccines at scale.
- **Specialization in Research vs Entrepreneurship:** The duo of Karikó and Weissman were the first to make some of the major discoveries needed to turn mRNA vaccines into a reality. While both were gifted researchers, both appear to have been less well-suited to the task of popularizing and commercializing their work. This too delayed the development of the technology by limiting awareness of critical knowledge in the broader research community and hindering efforts by Karikó and Weissman themselves to bring their breakthroughs to market.

This paper is organized in three parts. Part I provides a brief overview of the science behind mRNA vaccines, and the timeline of the technology's development. Part II diagnoses the structural frictions that slowed the realization of mRNA vaccines as a practical tool for immunization. Part III will offer policy recommendations that address these frictions. The paper will conclude with some areas for further exploration and argue for applicability of the lessons learned in mRNA vaccines to the more general problem of accelerating development of breakthrough technologies.

Part I – A Brief History of mRNA Vaccine Development

mRNA vaccines should not be understood as a single moment of technological breakthrough. Instead, the technology is the culmination of decades of exploration into how mRNA might be used to improve the body's ability to combat a wide range of threats.

Furthermore, while mRNA vaccines entered public consciousness for their role in combating the 2020-2021 COVID-19 pandemic, much of the development of the underlying technology took place among researchers who did *not* have coronaviruses as their primary target. This specific application was an afterthought, if it was considered at all. The pandemic may have served as a pivotal catalyst in making mRNA vaccines a practical reality at scale, but many of the core discoveries necessary to make it possible had occurred years prior for addressing problems like cancer.

In the extended history of mRNA research, we can see multiple missed opportunities to accelerate the availability of mRNA vaccines. This section provides a capsule history, highlighting pivotal moments and providing context for why and how mRNA vaccines were developed.

The Battle Against HIV

The adaptive immune system is a primary mechanism by which the body combats disease. Complimenting the body's fast "first line" defense system – known as the "innate" system – the adaptive system is responsible for deploying the white blood cells, known as T and B cells, that can recognize major pathogens and deploy antibodies against them. However, this system is relatively slow unless it has had past experience combatting a similar pathogen.

The paradigm of traditional vaccine development relies on triggering this mechanism by introducing weakened versions of a virus to an immune system. The immune system can easily defeat these weakened versions, allowing it to gain the "experience" necessary to rapidly combat the full-strength version of a virus in the future. This basic mechanism guided vaccine development for decades, starting with the work of Edward Jenner and Benjamin Jesty in smallpox vaccination in the late 18th century, and continuing with the work of Jonas Salk and Albert Sabin fighting polio in the 1950s.

But the rise of HIV through the 1980s and 1990s presented a situation that undermined this basic paradigm of vaccine development. For one, HIV severely compromised the immune systems of those infected, raising doubts about whether a patient would be able to combat even a weakened version of a deadly virus. Second, the rapidly mutating state of the HIV virus raised concerns that attempting to cultivate weakened or deactivated versions for vaccine purposes could cause the virus to transform into an even more virulent state.[3]

Synthetic or "recombinant" DNA offered one promising alternative to these challenges. By synthesizing DNA that could produce only harmless, fragmentary portions of the HIV virus, the approach could trigger an appropriate immune system response without the risks associated with injecting the virus itself. These "subunit protein" vaccines rely on inserting selected segments of DNA into a medium like yeast. The yeast produces the desired proteins – in this case, the "envelope" proteins existing on the surface of the HIV virus – which are subsequently introduced into the body of the patient.

However, the subunit protein vaccine approach produced disappointing results from multiple companies through the 1990s, notably Genentech, MicroGeneSys, and Chiron. The constantly changing structure of HIV made it hard to isolate envelope proteins that would teach the immune system to reliably identify and combat the virus in all its potential variants.[4] However, work on these approaches would eventually mature to undergird the vaccines produced by Novovax and GlaxoSmithKline years later during the COVID-19 pandemic.[5]

During this period, Merck – one of the largest and most established companies in the pharmaceuticals industry – also joined the attempt to use DNA as a mechanism for combating HIV. Merck's approach leveraged a common virus type known as an adenovirus to carry the necessary DNA directly into the body's cells. From there, the DNA would produce a set of structural proteins of HIV that would trigger a hypothesized, more robust reaction from the body's T cells. Trials of these "viral vector" vaccines in monkeys in 1998 were promising, with a human trial taking place in 2004.

In 2007, disastrous results from this human trial indicated that Merck's candidate vaccine had no effect. Some evidence suggested that it in fact had worsened infections among some vaccine recipients. Parallel trials run by the National Institutes for Health (NIH) indicated the same.[6] Merck shuttered its trial and its entire HIV vaccine program in response.

3 Gregory Zuckerman, *A Shot To Save The World* (Portfolio, 2021), 9.

4 Id., 28.

5 Id., 26.

6 *See* Enrico Iaccino, et al, "The aftermath of Merck's HIV vaccine trial," *Retrovirology* (Jul 2, 2008), Rafick-Pierre Sekaly, "The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development?," *Journal of Experimental Medicine* (Jan 21, 2008).

Chilling Effects

HIV had motivated decades of work to develop a vaccine. However, the failures and false starts experienced by researchers through the 1990s and early 2000s produced a major chilling effect on funding and continued exploration.

The viral vector approach explored by Merck would later form the basis of the Oxford AstraZeneca and Johnson & Johnson (J&J) COVID-19 vaccines.[7] However, the researchers carrying on this work faced years of skepticism. Researchers Dan Barouch and Jaap Goudsmit continued exploring adenovirus approaches to addressing HIV and the respiratory virus RSV at Crucell (later J&J) through the 2000s. However, negative feedback from Crucell management required Goudsmit to conduct his work while keeping his management in the dark, hiding results in lab notebooks with generic labels like "Assay Validations."[8]

The failures of HIV vaccine development also chilled interest in using mRNA as the basis for a vaccine. In the normal function of the cell, DNA exists within the nucleus of the cell. mRNA functions as a temporary "blueprint" which is copied from DNA and then transmitted outside the nucleus, where it is used by various components of the cell to produce a set of proteins. This feature of mRNA raised the possibility of generating the needed proteins for an immune response without needing to enter the nucleus of a cell, short-circuiting the process relied on by DNA vaccines.[9] The idea of using mRNA as a drug had been proposed as early as 1988 by Salk Institute researcher Robert Malone.[10] Published results by Jon Wolff and several collaborators as early as 1990 demonstrated that mRNA could be directly used to produce proteins.[11]

Despite this, Dan Wattendorf – who led the ADEPT program at DARPA that supported work on mRNA vaccines starting in 2010 – notes that most of the industry experts he consulted with expressed skepticism about his initiative, given their poor experience with viral vector and subunit protein vaccines.[12] It was considered, in the words of one article, "a fool's errand."[13] Matt Winkler, who founded one of the earliest mRNA lab supply companies, stated, "If you had asked me back [then] if you could inject RNA into somebody for a vaccine, I would have laughed in your face."[14]

If DNA was considered an unpromising basis for a vaccine, there was an additional reason to believe that mRNA would have been even less promising. mRNA is highly fragile, prone to degradation in the presence of heat and easily destroyed by a wide range of common enzymes. These features make mRNA challenging to work with in the lab and raise questions about the ability to produce it effectively at scale.

7 *See* Jeffrey Harris, "The repeated setbacks of HIV vaccine development laid the groundwork for SARS-COV-2 vaccines," *Health Policy Technology* (Mar 21, 2022), (reviewing this history in further detail).

8 Zuckerman, 44.

9 Ugur Sahin et al, "mRNA-based therapeutics — developing a new class of drugs," *Nature* (Sept 19, 2014).

10 Elie Dolgin, "The Tangled History of mRNA Vaccines," *Nature* (Sept 16, 2021).

11 Jon Wolff et al, "Direct Gene Transfer into Mouse Muscle in Vivo," *Science* (Mar 23, 1990).

12 Personal Interview with Dan Wattendorf (Aug 15, 2023).

13 Paul Sonne, "How a secretive Pentagon agency seeded the ground for a rapid coronavirus cure," *Washington Post* (Jul 30, 2020),

14 Dolgin.

Nonetheless, several teams of researchers through the 1990s and 2000s pursued the vision of therapeutics based on mRNA. Famously, University of Pennsylvania (Penn) researchers Katalin Karikó and Drew Weissman investigated the use of mRNA as an approach to creating an HIV vaccine. This led to a 2000 publication showing that mRNA could produce the desired proteins of HIV, and another in 2005 showing that modifications of a component called uridine in mRNA allowed it to successfully enter a living cell without rejection.[15] However, funding proposals to the NIH and elsewhere for this work were denied, and their pivotal 2005 paper was summarily rejected from leading journals for representing only an "incremental improvement."[16] Karikó and Weissman were unable to acquire sufficient investment to commercialize their discovery and afford the licensing fees demanded by Penn, and their patents were eventually licensed by the university to Cellscript, a small lab equipment company, for $300,000.[17]

Other teams of researchers pursued mRNA therapeutics in parallel research agendas during this period. Duke University researcher Eli Gilboa published work in 1996 demonstrating that mRNA could be used to treat cancer tumors in mice. Despite these groundbreaking results, further funding from the dean of Duke's medical school was denied in 2005, largely based on the sense that "[b]etting on mRNA seemed a dangerous move at the time…[particularly] given the vexing question of how to stabilize it and deliver the molecule to cells.[18] However, this research inspired the founding of BioNTech by Ugur Sahin and Ozlem Tureci in 2008 to explore mRNA as a strategy for a cancer vaccine, among other approaches.[19] BioNTech would later partner with Pfizer in producing some of the first mRNA vaccines for COVID-19.

Similarly, in 2010, researchers Luigi Warren and Derrick Rossi published results showing that mRNA could be used to program human skin cells to transform into embryonic-like stem cells, a valuable input to various medical treatments. This work would eventually become the basis for the founding of Moderna, which would initially focus on the use of mRNA as a mechanism for programming the body to itself produce a range of potential therapeutics.[20] The company would pivot in 2013 to focus on using these techniques to produce vaccines, and significantly improved the lipid encasement technology that allowed mRNA to be delivered to the cell.[21] It too would deploy an early mRNA vaccine for COVID-19.

Though there were commercial companies actively pursuing mRNA vaccines at the eve of the COVID-19 pandemic, skepticism about the approach persisted. Both BioNTech and Moderna were considered dubious financial propositions. Moderna was widely criticized for a lack of transparency in its claims about its therapeutics, with one Nature Biotechnology article in 2016 comparing CEO Stéphane Bancel and Moderna to Elizabeth Holmes and Theranos.[22] Similarly, by 2019, BioNTech faced a cash crunch, as investors worried about the company's failure to bring any drugs to market after years of operation. The company launched a lackluster IPO for funds in October of that year, raising little over half of their original target.[23]

15 Drew Wessiman et al, "HIV gag mRNA transfection of dendritic cells (DC) delivers encoded antigen to MHC class I and II molecules, causes DC maturation, and induces a potent human in vitro primary immune response," *Journal of Immunology* (Oct 15, 2000), ; Katalin Karikó et al, "Suppression of RNA recognition by Toll-like receptors," *Immunity* (Aug 2005).

16 Nicole Neuman, "Conversations: Persistent Progress," *Cell* (Oct 14, 2021).

17 Katalin Karikó, *Breaking Through* (Crown, 2023), 274.

18 Zuckerman, 62.

19 Dolgin.

20 Zuckerman, 130-31.

21 See Kimberly Hassett et al, "Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines," *Mol. Ther. Nucleic Acids* (Apr 15, 2019).

22 "Research not fit to print," *Nature Biotechnology* (Feb 5, 2016).

23 Rebecca Spalding and Joshua Franklin, "Germany's BioNTech raises $150 million in smaller-than-planning U.S. IPO amid market volatility," *Reuters* (Oct 10, 2019).

The COVID-19 Pandemic

At the advent of the COVID-19 pandemic, mRNA vaccines remained a largely untested concept. While there had been promising results in the laboratory setting and some initial successes applying mRNA vaccines in humans, no mass deployment of the technology had yet occurred.

The COVID-19 pandemic created the urgency ideally suited to make mRNA vaccines an attractive prospect for governments battling the virus. Traditional vaccine development methods are slow, requiring the cultivation of a weakened or deactivated virus over months in large vats of cells. In comparison, mRNA can be quickly synthesized in a few hours from a gene of interest.[24] While untested, mRNA would provide a far faster route to deploying a vaccine.

Even so, mRNA vaccines were not necessarily considered the best candidate for combatting COVID-19 in the initial phases of the pandemic. The viral vector approach taken by the team led by Oxford researchers Sarah Gilbert and Adrian Hill was initially considered more promising, given its relative maturity. In contrast to untested mRNA vaccines, experimental trials done using the Oxford approach for diseases such as MERS, flu, and Zika had previously shown it to be both effective and apparently safe.[25] It was not until clinical trial results raised the possibility of harmful side effects of the Oxford AstraZeneca vaccine and showed lower efficacy than the Moderna/BioNTech vaccines that mRNA was considered the superior option.[26]

mRNA vaccines were therefore just one of a number of speculative bets made to combat the COVID-19 pandemic. The US government's Operation Warp Speed, which allocated $18 billion to accelerating vaccine development and deployment, provided support both to mRNA vaccine development through Moderna, and to alternative approaches like those taken by the Oxford AstraZeneca team.

Operation Warp Speed and similar programs launched by governments globally accelerated the development of mRNA vaccines in two ways. First, upfront commitments to purchase the vaccine and research grants helped underwrite a major expansion in manufacturing capacity. This was particularly critical in the case of startups like Moderna, which lacked the infrastructure to produce its vaccines at massive scale.[27] This funding also helped to accelerate technological progress. Requiring rapid delivery of large numbers of shots of the vaccine necessitated the resolution of the numerous practical challenges in transitioning mRNA research into a practical reality, from managing cooling to ensuring quality control.[28]

Second, Operation Warp Speed allowed the usual clinical trials to be combined and run in parallel. Importantly, it also allowed companies to manufacture vaccine candidates in advance of them being proven to be safe and effective in clinical trials.[29] This cut down on the usual bottlenecks slowing the approval and deployment of vaccines.[30] The unusually accelerated process also helped quickly reduce lingering uncertainty about the viability of different potential solutions to addressing the pandemic. mRNA vaccines, which had been considered an untested and speculative option to combat the pandemic, were identified as the most promising approach in a matter of months.

24 Nair.

25 *See* "Oxford University is leading in the vaccine race," *The Economist* (Jul 2, 2020), (citing the Oxford approach as "the likeliest candidate to produce the world's first vaccine against covid-19").

26 Zuckerman, 299-300.

27 GAO, "Operation Warp Speed: Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges," Feb 11, 2021.

28 Sarah Gilbert and Catherine Green, *Vaxxers* (2021), Ch. 6.

29 *See* Arielle D'Souza, "How to Reuse the Operation Warp Speed Model," Institute for Progress, Feb 7, 2023.

30 *See* Stuart A. Thompson, "How Long Will a Vaccine Really Take?," *New York Times* (Apr 30, 2020), (visualizing the clinical trial acceleration).

In the end, the first American to receive a COVID-19 vaccination outside a clinical trial took place on December 13, 2020, with a Pfizer/BioNTech shot. In the US, approval for the Moderna and J&J vaccines would soon follow. mRNA technologies, now a practical reality, have continued to see widening application in subsequent years, with Moderna announcing in 2022 that it was applying its technology to addressing a wide range of concerning pathogens including malaria, ebola, and dengue.[31] BioNTech has invested its earnings from the COVID-19 vaccine into new programs applying mRNA to make progress on cancer immunotherapies and multiple sclerosis.[32]

Part II – Structural Frictions

The timeline of mRNA vaccine development suggests, tantalizingly, that the technology could have been developed and made practicable many years before the COVID-19 pandemic made it a global necessity. The opportunity to use mRNA as a drug had been recognized as early as 1988, with striking demonstrations showing the practical application of the technology from the mid-2000s onwards.

The fact that foundational advances necessary for mRNA vaccines continued to be made even in the face of considerable skepticism in the larger research community and limited funding from public and private institutions is itself indicative. No fundamental impediments stood in the way of acquiring mRNA vaccines, beyond simple resourcing. Once funding surged through initiatives like Operation Warp Speed, mRNA vaccines rapidly became practicable, and their advantages over other competing alternatives became clear.

What factors, if different, might have allowed mRNA vaccines to become available earlier? This section examines the timeline described in Part I to diagnose the primary frictions that inhibited progress.

Perceived Viability of mRNA

mRNA research progressed slowly during the 2000s and 2010s in part because it was widely perceived to have an extremely low likelihood of success. While this assessment was off the mark, it was arguably a reasonable evaluation, given the facts known at the time. Related approaches to building vaccines for HIV had produced years of lackluster results. mRNA's fragility presented practical challenges at every stage of development. mRNA was hard to work with in the lab, had no obvious pathway to ensure uptake within the body, and would apparently be impractical to manufacture at scale.

One indication of the strength of this skepticism is the degree to which industry experts considered mRNA vaccines a dead end *even at the height of the pandemic*. Economists preparing recommendations to the White House on allocating funds towards different COVID-19 vaccine methodologies received feedback from some corners that investment plans positing a possible role for mRNA were fanciful.[33]

31 Julie Steenhuysen and Michael Erman, "Moderna plots vaccines against 15 pathogens with future pandemic potential," *Reuters* (Mar 7, 2022).

32 *Nature Biotechnology*, "UK, BioNTech test mRNA against cancer," (Feb 15, 2023), Christina Krienke et al, "A noninflammatory mRNA vaccine for treatment of experimental autoimmune encephalomyelitis," *Science* (Jan 8, 2021).

33 *See* Tim Hwang, "The Frontier of Scientific Plausibility," *Macroscience* (Aug 25, 2023).

This view was not shared by all: a minority of researchers continued to push forwards on mRNA technologies throughout the 2000s and 2010s. However, the widespread negative perception of mRNA vaccines likely played a role in slowing progress. Science funders allocated less than they would have, had the true viability of mRNA vaccines been known. Similarly, the research community as a whole did not prioritize exploring and resolving hurdles to the practical development of mRNA vaccines. Companies like Moderna and BioNTech may ultimately have perfected mRNA vaccines and brought them to market, but their relatively fragile financial state on the eve of 2020 suggests that the technology would have taken many more years to become a reality in the absence of a global pandemic.

This low perceived viability of mRNA vaccines also created compounding forms of uncertainty that hindered development. Limited funding and research effort produced a situation where progress on mRNA technologies in general and mRNA vaccines in particular moved relatively slower. This slow pace of development was a constant source of skepticism about the commercial viability of both Moderna and BioNTech. However, as the later period of accelerated progress during the COVID-19 pandemic indicates, this slow progress was a function more of limited resourcing than of inherent flaws in the technology.

Low perceived viability also created a form of epistemological uncertainty: it was simply difficult to get data on whether or not mRNA vaccines worked at all, and how they compared to the alternatives. Slow development meant that clinical trials for mRNA vaccines were scarce, and both Moderna and BioNTech lacked clear evidence for the strength of their approach. Scant data in turn made it difficult to justify the resources for further development. Relatively more proven approaches, like the viral vector method explored by the Oxford AstraZeneca team, were considered more promising during the pandemic. It was not until clinical testing was accelerated through programs like Operation Warp Speed that it became clear that mRNA both worked and was competitive with more fully explored vaccine approaches.

The cumulative impact of widespread negative funder and researcher views on the plausibility of mRNA vaccines was likely significant, though difficult to measure quantitatively. In a counterfactual scenario in which mRNA was generally seen as more promising, funding and effort would have been greater. The end result would have been a speedier resolution of various technical hurdles, and a shorter period of time to reach clinical testing. Both would have served to make mRNA vaccines practical earlier.

Vaccines as an Unprofitable Research Field

It is no accident that the leading companies of mRNA vaccine development – Moderna and BioNTech – were startups, and not established pharmaceutical companies. While Moderna was able to forge an early partnership with AstraZeneca prior to the pandemic and BioNTech partnered with Pfizer to roll out its COVID-19 vaccine, vaccines against infectious disease traditionally have not been a major profit center for leading pharmaceutical companies.

There are a number of reasons for this state of affairs. Vaccines can cost between $200 and $900 million to create, and successful passage through clinical trials only happens 6-11% of the time.[34] Vaccines traditionally take an extremely long time to produce, with the average vaccine requiring a development timeline of 10.71 years.[35] Prior to COVID-19, the fastest vaccine turnaround – a mumps vaccine developed by Merck in 1967 – was four years.[36]

Profits are also highly uncertain. Infectious diseases come and go, leaving a pharmaceutical company with the prospect that it may invest significant resources only for the market for a vaccine to disappear by the time it is available. Many infectious diseases also disproportionately impact poorer nations, creating political pressure for low prices and limiting the size of the

34 Jonathan T. Vu et al, "Financing Vaccines for Global Health Security," NBER Working Paper No. 277212 (May 2020).

35 Esther S. Pronker et al, "Risk in Vaccine Research and Development Quantified," *PLoS One* (Mar 20, 2013).

36 Zuckerman, 259.

profit opportunity.[37] The pandemic produced a unique scenario in which the market for vaccines was guaranteed, both because of the global spread of the virus and because of the willingness of governments to commit to purchasing massive quantities of the vaccine in advance.

These market forces against investment in vaccines are significant. During the early stages of the pandemic, some established pharmaceutical companies were hesitant to invest in vaccine development around COVID-19. Merck ultimately decided against prioritizing a COVID-19 vaccine in part because an earlier, expensive effort around Ebola had won vaccine approval only after the 2014 outbreak had faded. Executives felt that COVID-19 might similarly disappear, making it unwise to shift researchers and financial resources to the problem.[38] Even Moderna and BioNTech did not launch at the outset with the goal of manufacturing vaccines. They initially focused on using mRNA as a method for developing a wide range of therapeutics.[39]

In short, the specific skepticism inhibiting mRNA vaccine development was compounded by broader market forces that disincentivize investment in vaccines generally. Even in a scenario in which researchers and funders had seen mRNA vaccines more favorably, it is likely that the number of companies focused on bringing the technology to market would have remained limited. If a broad research area is perceived as unprofitable, paradigm-changing research may never be commercialized.

Specilization in Research vs Entrepreneurship

The research team of Katalin Karikó and Drew Weissmann has been rightly celebrated for their foundational achievements in demonstrating that mRNA could be successfully implanted within a cell. However, as the record in Part I should make plain, many parallel groups of researchers within academia and private industry were contemporaneously examining similar problems, often with access to more resources than Karikó and Weissman. It is not implausible that another team could have made the discoveries around uridine that resolved one of the key hurdles to mRNA vaccine development.

As it turned out, it was Karikó and Weissman who were first to make this discovery. While the duo were masterful researchers, both appear to have been less well-suited to promoting and fundraising around their work. One close peer described Karikó as "absolutely brilliant, but she challenged people, and that was off-putting to people…Kati was a pain in the ass. She didn't give a shit about getting a gold star from anyone."[40] Weissman "didn't do office gossip, small talk, or chitchat…He rarely smiled, or even grinned, even for photos, adopting a serious mien that could be off-putting."[41] This factor may also have slowed progress towards a workable approach to mRNA vaccines in two ways.

For one, Karikó and Weissman's work failed to become common knowledge even within the community of researchers specifically working on the therapeutic applications of mRNA. Luigi Warren and Derrick Rossi – whose research would become the basis for Moderna – focused on how to use mRNA to reprogram cells at Harvard Medical School in 2007-8. Warren struggled to insert mRNA into a cell without rejection, the same problem Karikó and Weissman had wrestled with and solved years before. Warren was "on the verge of giving up on his project," until a stray reference to Karikó and Weissman's work from an assistant professor at a nearby lab put him on the right track.[42] In the several years following the publication of their 2005 paper, Karikó

37 *See* Zulfigar A. Bhutta et al, "Global burden, distribution, and interventions for infectious diseases of poverty," *Infect Dis. Poverty* (Jul 31, 2014).

38 Zuckerman, 258-60.

39 Joe Miller et al, *The Vaccine* (St. Martin's Press, 2022), 23; Peter Loftus, *The Messenger* (Harvard Business Review Press, 2022), 32-33.

40 Zuckerman, 71.

41 Id., 76.

42 Zuckerman, 95-96

and Weissman only received two invitations to speak about the work.[43] Had the duo been more successful in disseminating their results more prominently, other researchers may have been able to advance progress towards mRNA vaccines faster.

Secondly, Karikó and Weissman were unable to effectively negotiate commercial terms around their intellectual property, stifling the opportunity to commercialize their breakthrough. Penn owned the patents filed by Karikó and Weissman through their research, and ultimately made decisions surrounding the licensing of those patents. Karikó and Weissman negotiated unsuccessfully for years with Penn to obtain a license to their own discoveries for their short-lived startup, RNARx.[44] During this period, RNARx ran through its limited small-business funding from NIH and ultimately shut down in 2009.[45] Cellscript, the company that obtained an exclusive license to the mRNA patents in the end, was introduced to Penn by Karikó herself.[46]

Others did not face such difficulties. Rossi's work in stem cells building in part on Karikó and Weissman's work was declared one of the "top ten medical breakthroughs of 2010" in Time magazine.[47] Moderna launched in 2010, and by 2013 was raising $240 million from AstraZeneca in a drug development partnership.[48]

Progress towards mRNA vaccines was slowed because crucial breakthroughs were made by researchers who did not see success in the entrepreneurial work of popularizing and commercializing their knowledge. Karikó and Weissman were unable to themselves to raise the capital and execute the licensing necessary to commercialize their discoveries immediately. Their publications also took longer to enter the awareness of researchers working on parallel problems. In both cases, a significant advancement failed to be adopted and used by researchers and within industry for years.

How Quickly Can Academic Breakthroughs Diffuse?

Number of new academic citations each year since the publication of key articles. Karikó and Weissman's (K&W) insights in 2000 and 2005 took much longer to diffuse when compared to Rossi's 2010 article.

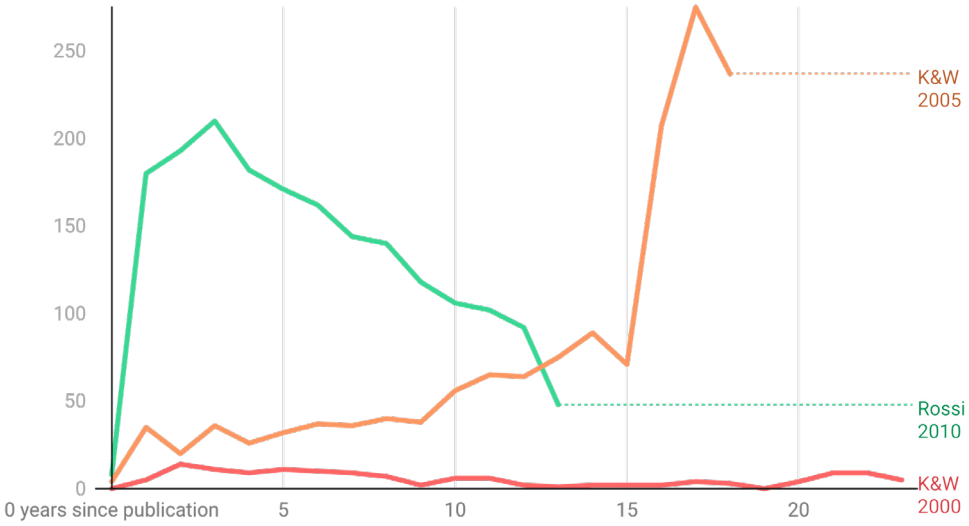

Chart: Matthew Esche, IFP • Source: Web of Science • Created with Datawrapper

43 Karikó, 264.

44 Karikó, 274.

45 Id., 274-5.

46 Karikó, 274.

47 Derrick J. Rossi, Harvard Stem Cell Institute.

48 Andrew Pollack, "AstraZeneca Makes a Bet on an Untested Technique," *New York Times* (Mar 21, 2013).

Part III – Recommendations

The timeline of mRNA vaccine development reveals a number of areas where progress might have been accelerated. Researchers and funders misjudged the true viability of mRNA as a platform for vaccines, underinvesting in experimentation and overcoming technical hurdles. Leading pharmaceutical companies had limited incentives to support vaccine development generally, narrowing the set of firms dedicated to bringing the technology to market. Finally, the scientists that made key breakthroughs enabling mRNA vaccines were brilliant researchers but were less successful in promoting and commercializing their work. This limited broader awareness of critical knowledge and prevented the discoverers themselves from bringing their technology to market.

The result was that society might have benefitted from access to mRNA vaccines and therapeutics years before it ultimately did. If that is so, what might have been done in retrospect to accelerate this timeline?

The complex and multifaceted nature of some of the hurdles evident in the mRNA story mean that there is no single "silver bullet" policy intervention that would have conclusively ensured that the technology was made available earlier. That said, three institutional changes, if implemented, may have raised the chances that mRNA vaccines were developed sooner.

Intervention 1:
Increase the Variance of Research Funding

Grants and other funding allocated to mRNA vaccine research in the 1990s and 2000s were limited in part because of a general sense that the approach was impractical. The fragility of mRNA made it an unlikely candidate as a vaccine platform, and the lackluster history of related approaches in attacking HIV was discouraging.

Skepticism was likely a reasonable scientific assessment given the facts that were known at the time. But, the record suggests that pessimism was grounded more in theoretical considerations and analogies to other approaches rather than conclusive scientific failure. Failure to explore further resulted in a major missed opportunity, given the uniquely high social impact that having mRNA vaccines earlier would have had.

One institutional reform that may have alleviated this issue would be to use mechanisms that encourage funders to make higher variance, heterodox bets against this kind of scientific consensus. This might include "golden ticket" mechanisms that allow reviewers that feel strongly about a research proposal to fund a project even against the consensus of their peers.[49] Similarly, funding programs might be launched to deliberately offer "last shot" funding for potentially high-impact areas that see a period of declining funding and researcher activity.[50] These might counter a natural risk-aversion that leads researchers to abandon problems too early in the face of high-profile failures, as they arguably did in the mRNA case. These mechanisms might have particular applicability in cases parallel to mRNA, where expert judgments are based more on analogies to similar problems and where the technology in question would have a major social impact if viable.

The merit of such an approach is bolstered by examining the funders that unusually did choose to fund mRNA research, even during the period in which it faced major skepticism. These organizations did so in part because they were free to prioritize more speculative, high-risk exploration. The specific reasons for this vary. Dan Wattendorf – who led the DARPA ADEPT program that funded mRNA work in the 2010s – attributes the agency's willingness to support

49 Dalmeet Singh Chawla, "'Golden tickets' on the cards for NSF grant reviewers," *Nature* (Feb 24, 2023).

50 Tim Hwang, "Funding Against The Tide," *Macroscience* (Sept 6, 2023).

mRNA work to an organizational norm of providing managers like himself free rein to direct their programs.[51]

The Bill and Melinda Gates Foundation was also an early supporter of mRNA vaccines, providing a $20M grant to Moderna in 2016[52] and later $55M to BioNTech in 2019.[53] These investments were based in part on the personal interest of Gates in advancing vaccine technologies, and since the foundation prioritized finding promising but overlooked methods in related fields. BioNTech had begun working on mRNA therapeutics to address cancer, but was supported by the "[Gates] foundation [because it] often looked at 'adjacent' scientific disciplines whose innovations might help fight infectious diseases…'We were doing a lot of horizon-scanning to see what the trends were, what was changing, and who were the cutting-edge people,' Stuart [a director at the Gates Foundation] says, 'and BioNTech clearly surfaced.'"[54]

Intervention 2:
Ambition in Addressing Market Failures in the "Scientific Marketplace"

Established pharmaceutical companies were well-positioned to accelerate the development and deployment of mRNA vaccines. These companies possessed the necessary research talent, financial resources, and practical mass production know-how to transform the technology into a workable product.

Despite being well-positioned to lead the way, pharmaceutical companies did not. The high risk of vaccine production and approval, alongside the inconstancy of the market for vaccines, reduced incentives to invest aggressively in commercialization of mRNA approaches. The end result was a delay in the arrival of the technology, only resolved with the vast funding available through Operation Warp Speed.

Of course, it is impractical to require an emergency program on the scale of Operation Warp Speed every time market incentives slow the pace of high-impact scientific innovation. However, the mRNA story suggests policy makers and agencies can effectively focus science policy on encouraging investment in risky areas where companies may underinvest.[55]

There is a wide-ranging literature which proposes interventions for resolving the complex problems inhibiting the larger market for vaccines.[56] However, two interventions are particularly worth highlighting, given their role in making mRNA vaccines a reality.

First, in Operation Warp Speed, the FDA permitted clinical trials to run in parallel and adaptively, with "new treatments entering and inefficacious treatments exiting dynamically as evidence accumulate[d]."[57] This enabled companies and public health officials to understand what treatments were most effective far quicker. This points to the value that the government can provide in architecting common "test beds" that allow companies to quickly experiment with approaches, assess viability, and benchmark themselves against competitors. This may work to reduce the uncertainty – and lower the costs to resolving uncertainty – which lowers investment in a particular research area of interest.

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51 Personal Interview with Dan Wattendorf (Aug 15, 2023).

52 Loftus, 81

53 BioNTech, "BioNTech Announces New Collaboration to Develop HIV and Tuberculosis Programs," (Sept 4, 2019),

54 Miller, 25.

55 *See* Tim Hwang and Caleb Watney, "How DARPA Can Proactively Shape Emerging Technologies," Institute for Progress, Jun 15, 2023, (discussing this strategic approach in further detail).

56 For a small sampling of this literature, *see, e.g.*, Scott Duke Kominers and Alex Tabarrok, "Vaccines and the Covid-19 pandemic: lessons from failure and success," *Oxford Review of Econ Policy* (Dec 14, 2022); Qiwei Claire Xue and Lis Larrimore Ouellette, "Innovation policy and the market for vaccines," *Journal of Law and the Biosciences* (May 18, 2020); Government Accountability Office, "Vaccine Development: Capabilities and Challenges for Addressing Infectious Diseases," Nov 16, 2021; Joshua Monrad et al, "Promoting versatile vaccine development for emerging pandemics," *NPJ Vaccines* (Feb 11, 2021).

57 Kominers and Tabbarok.

Second, the government can choose to "fund the entire portfolio" in high-impact areas, knowing that many of its bets may fail. Operation Warp Speed did not know in advance that mRNA vaccines like those produced by Moderna and BioNTech would produce the best results. Instead, guarantees were made to companies offering four different platform technologies simultaneously in an effort to "[mitigate] the risk of failure due to safety, efficacy, industrial manufacturability, or scheduling factors."[58] This was driven by the urgency of a public health emergency. But such a portfolio approach may have value in situations in which uncertain market demand makes companies particularly prone to controlling their costs by hewing to proven methodologies and failing to explore more experimental approaches.

Intervention 3:
Supporting Research Entrepreneurialism

It is challenging to predict precisely who will make a critical discovery, and the circumstances in which they will make them. One objective of science policy should be to ensure that society can rapidly identify and benefit from a breakthrough, even if the originators of that breakthrough are less well-positioned to promote and commercialize their own work.

The case of Karikó and Weissman is instructive. The two researchers appear to have lacked access to certain entrepreneurial assets, hindering their ability to successfully build a business around their work. The end result was that their critical knowledge had to slowly diffuse to other, more well-positioned researchers at MIT and elsewhere, rather than being exploited immediately. This created a delay in the availability of mRNA vaccines.

This being said, researchers should focus on research. Maximizing scientific and technological progress may mean allowing researchers like Karikó and Weissman to fully dedicate their talents to hard work of discovery. As the frontiers of knowledge continue to move forward, research has documented a trend towards specialization in scientific tasks and larger scientific teams.[59] This phenomenon seems likely to continue, so policymakers should work to find ways of making it easier for important research to flourish even in cases where researchers themselves have little inclination towards the operational tasks of turning a discovery into a business or socializing it with others.

There are two interventions that might be particularly effective in this respect. First, universities and other research institutions should work together in fostering a new class of trained "science operators" who specialize in the promotion of research, fundraising around speculative technology, and the building of businesses around emerging science. These operators would partner with researchers and labs to help accelerate their work, serving in a role akin to a chief operating officer and looking after the practicalities of transforming early research into a sustainable reality. This would expand on strategies being taken by agencies like ARPA-E in establishing dedicated tech-to-market advisors that focus specifically on aiding the movement of technology from the lab into "the real world", and the ARPA-H Project Accelerator Transition Innovation Office (PATIO).[60]

58 Moncef Slaoui and Matthew Hepburn, "Developing Safe and Effective Covid Vaccines–Operation Warp Speed's Strategy and Approach," *New England Journal of Medicine* (Oct 29, 2020); Government Accountability Office, "Operation Warp Speed: Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges," Feb 2021.

59 *See e.g.*, Benjamin F. Jones, "The Burden of Knowledge and the "Death of the Renaissance Man": Is Innovation Getting Harder?," *The Review of Economic Studies*, Volume 76, Issue 1 (Jan 2009), and Stefan Wuchty, Benjamin F. Jones, and Brian Uzz, "The Increasing Dominance of Teams in Production of Knowledge," *Science*, Volume 316, Number 5827 (May 2007).

60 ARPA-E Tech-to-Market Advisors; ARPA-H, Project Accelerator Transition Innovation Office (PATIO); Jassi Pannu et al, "ARPA-H Should Zero In on Pandemic Prevention," *Issues in Science and Technology* (Summer 2023), (discussing the importance of tech transition in the pandemic prevention context).

Second, more flexible university technology transfer processes may be beneficial. One reason for the failure of Karikó and Weissman's startup RNARx appears to have come from Penn rigidly demanding too high of an upfront licensing fee for the company to be viable.[61] This suggests that Penn stifled an important innovation by demanding near-term monetization. Penn's negotiating posture was likely motivated in part by the fact that fewer than 5% of tech transfer offices (TTOs) have net positive returns for a university, and face persistent pressures to "cash out as soon as possible."[62] Greater willingness for TTOs to take risks – and greater flexibility to craft licensing agreements to fit a specific researcher or patent – could play a role in allowing more speculative innovations to come to market.

Conclusion

The last few decades of mRNA vaccine development provide a striking case study of a major technological advancement held back less by fundamental constraints on discovery or development, and more by frictions in the innovation pipeline. While mRNA vaccines ultimately were deployed to great effect, this delay was not costless. Bringing mRNA vaccines to market only after the onset of a global pandemic has a cost that can be measured in lives lost, both in the pandemic and before.

But, the frictions to progress identified in this paper are not unique to the case of mRNA vaccines. Low perceived viability, commercial disincentives, and varied researcher access to entrepreneurial resources appear across fields and industries, though not always precisely in the same form. Neural networks, for instance, offer a highly parallel fact pattern: a major innovation tainted reputationally by high profile disappointments early in its history, only to slowly return to prominence decades later as it produced dramatic breakthroughs in computer vision.[63]

The commonplace nature of these frictions suggests that many other high impact innovations might presently be slowed by the same or similar issues. Further comparative work that looks at the timelines for major innovations across research fields would be valuable in extracting a taxonomy of the most commonly recurring structural issues that slow scientific development.

The commonality of these frictions also suggests that the recommendations identified in this paper may have general applicability. There may be a metascientific "playbook" that offers interventions that can raise the probability that scientific ecosystems are able to capture the benefit from overlooked opportunities, regardless of the field in question.

This analysis provides the seed of such a playbook. Increasing the variance of science funding, using government intervention to address market failures in the scientific marketplace, and supporting research entrepreneurialism all are concrete changes that, in retrospect, would have sped up the development of mRNA vaccines. Making these interventions today may allow us to obtain the next such technology that much sooner.

61 Zuckerman, 82.

62 "As IPO market booms, should universities be managing their equity stakes?," *Technology Transfer Tactics* (September 2015); David Mowery, "Plus ca change: Industrial R&D in the "third industrial revolution," *Industrial and Corporate Change* (Jan 12, 2009); Bhaven N. Sampat, "Patenting and US academic research in the 20th century: The world before and after Bayh-Dole," *Research Policy* (2006), (observing that it "is likely that after taking costs into account, the majority of American research universities are losing money on their patenting and licensing activities").

63 *See* Stuart Russell and Peter Norvig, *Artificial Intelligence: A Modern Approach* (4th ed., Prentice Hall, 2020), 17-26.

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