لقاحات حمض النووي الريبي:
التكنولوجيا ورؤية جديدة لسوق الدواء

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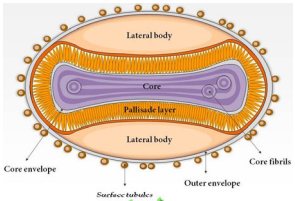
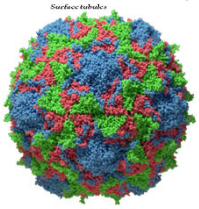
Spike antigen

Hello, bonjour, salaam. I would like to thank the Tunisian Academy of Sciences, Letters, and Arts, along with the Palestinian Academy for Science and Technology, for the privilege of talking with you today. Special thanks to Ahmed Abbes for arranging this address.

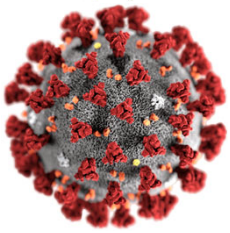
Pandemics that have been ended by vaccines



Smallpox ~200 years



Polio ~50 years



SARS CoV-2 ~2 years???

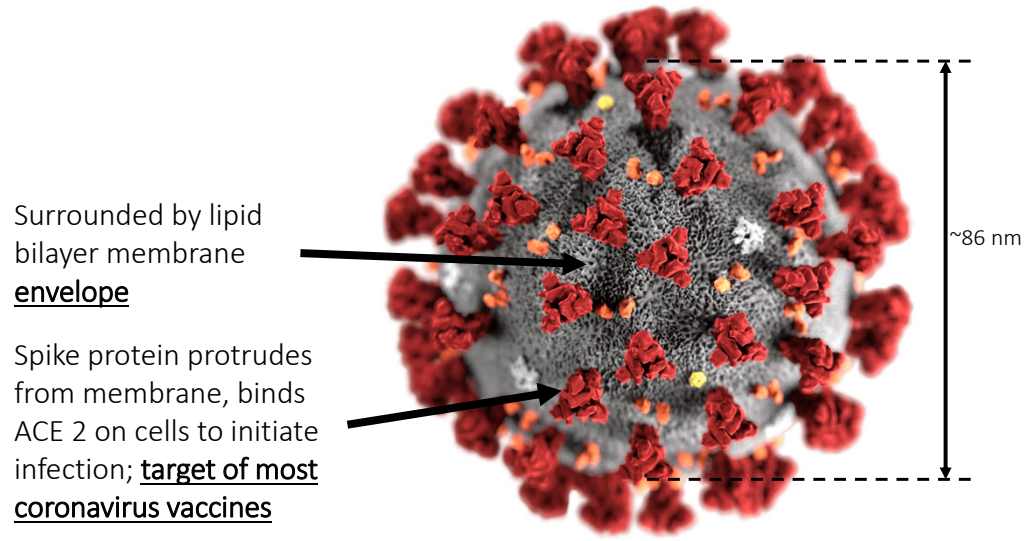
Let's start by considering pandemics that have been brought to an end by vaccines. There's the smallpox pandemic, which was ended by the first modern vaccine. That's a process that took about 200 years. There's the polio vaccine, which was brought nearly to an end in about 50 years. Now we're talking about the possibility of ending the current pandemic in about 2 years—truly warp speed! Is that even possible?

I'm going to describe a vaccine technology—RNA vaccines—that has every prospect of being rolled out at this pace—at least in the U.S. and other rich countries (it will undoubtedly take much longer for most of the world to be vaccinated). But I must emphasize that I'm not making false claims. I'm not pretending to give a critical review of all vaccine technologies at play today. It would be foolish to predict that this, or any other, type of vaccine will actually be effective against the viral disease. Even if it is effective, it's by no means clear that it will be a major factor in ending the pandemic.

Nevertheless, I think it is worthwhile giving serious consideration to RNA vaccine technology, whether or not in turns out to be decisive in the current emergency. That's because it's a generic vaccine platform that has many extremely attractive features, and that can be adapted without change to any new emerging infectious

disease threat.

SARS CoV-2 virion (virus particle)



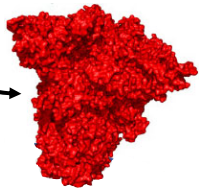
Here's the culprit: the SARS CoV-2 "virion" (virus particle). It's a typical animal virus, with an average diameter of 86 nm. It's surrounded by a lipid bilayer membrane, called the envelope, that's very similar to the membrane that surrounds our cells—indeed, the envelope is derived from cell membrane.

Protruding from the envelope are 50–100 copies of the Spike protein, shown here in red. Spike is absolutely required for the infection process. The first step in infection is the binding of Spike to angiotensin converting enzyme 2 (ACE 2) on the surface of virus-susceptible cells. Spike plays additional key functional roles in the infection process subsequent to binding.

Spike is the target of most coronavirus vaccine projects.

As a foreign protein it induces virus-specific **adaptive immunity**:

- neutralizing antibodies that block infection
- cellular immunity that kills infected cells



Spike antigen

When Spike enters the body, either as a result of virus infection or as a result of artificial vaccination, it acts as an antigen: a foreign protein that induces a Spike-specific adaptive immune response. Adaptive immunity is a powerful defense against infectious diseases like COVID-19. Adaptive immunity is inducible—that is, adaptive immunity to a foreign antigen isn't present until the immune system actually encounters that foreign antigen. It's also highly specific for the inducing foreign antigen. The adaptive immune response to Spike doesn't react with other antigens—for example, the non-foreign proteins in our own bodies. It doesn't even cross-react with the Spike protein from most other coronaviruses.

Adaptive immunity has two arms. There's humoral immunity, which is mediated by antibody proteins circulating in body fluids. Some Spike-specific antibodies bind to Spike on the surface of virions and block those virions' ability to infect cells. Such antibodies are called neutralizing. Neutralizing antibodies are one important way that adaptive immunity—whether induced naturally in response to a previous infection or artificially in response to a vaccine—helps protect against viral disease.

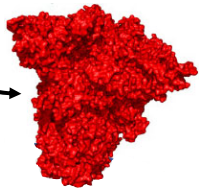
The second arm of the adaptive immune response is cellular immunity, which is mediated by whole immune cells, called T cells, rather than by circulating protein

molecules. Among these immune T cells are cells that specifically recognize other body cells that harbor the Spike protein—for example, because they're infected by the virus. Some of these T cells, called cytotoxic T cells, are equipped to kill the cells they recognize. That's another important way that the adaptive immune response protects against viral disease.

Conventional vaccine

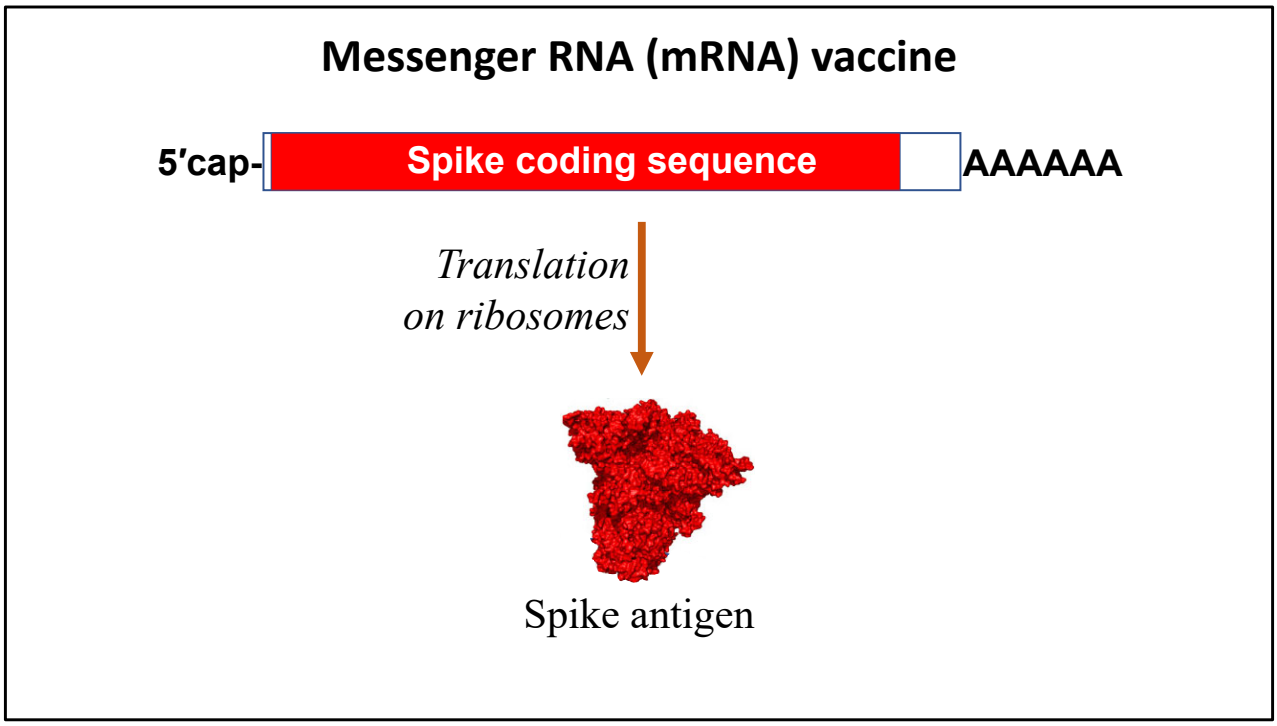
As a foreign protein it induces virus-specific **adaptive immunity**:

- neutralizing antibodies that block infection
- cellular immunity that kills infected cells



Spike antigen

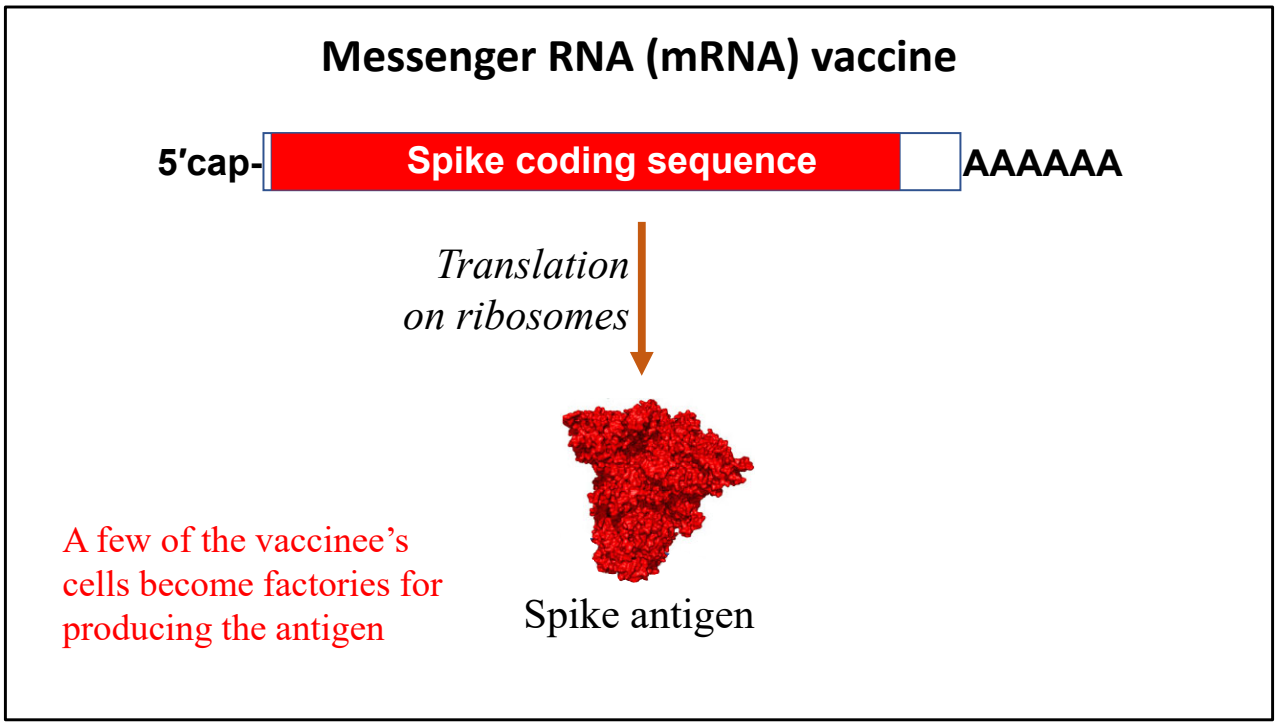
Conventional vaccines introduce a pathogen-derived protein such as Spike, harmless on its own, into the body to induce a specific adaptive immune response that will protect the vaccinee against a subsequent encounter with pathogen itself.



But here I will describe another vaccine design, in which it is not the Spike antigen itself that it introduced, but rather an artificial messenger RNA (mRNA) that encodes Spike. The artificial mRNA looks just like the tens of thousands of natural mRNAs that are in any of our bodies' cells. It has a special structure called the cap at one end, and at the other end a string of ~100 adenylic acids (A's)—just like natural mRNAs. In between is the coding sequence for Spike: the sequence of nucleotide triplets (codons) that specify the sequence of amino acids in the Spike polypeptide (chain of amino acids in a specific order).

When the artificial mRNA enters a cell's cytoplasm, components of the protein synthesis apparatus, including the ribosome, assemble at the beginning of the coding sequence. The mRNA is threaded codon-by-codon through the ribosome; at each step, the amino acid specified by the current codon is added to the end of the growing polypeptide chain. Protein synthesis is called translation because the information in the sequence of mRNA nucleotides is "translated" into a sequence of polypeptide amino acids. When the polypeptide is complete, the complex comes apart, releasing the mRNA, the polypeptide, and the components of the protein synthesis apparatus (including the ribosome). The Spike polypeptide folds spontaneously into its natural three-dimensional form. Meanwhile, the other

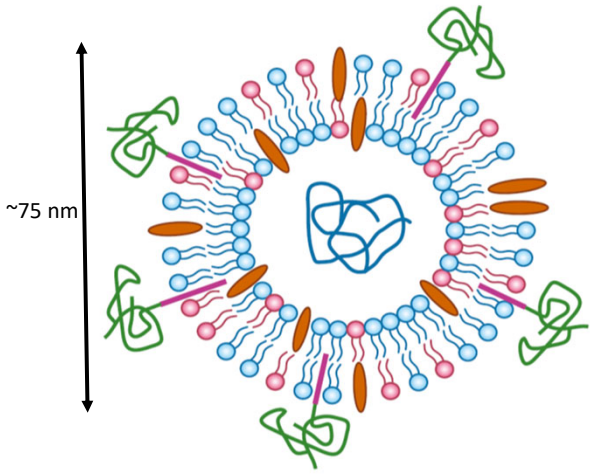
components, including the mRNA, are recycled to make additional Spike polypeptides. Over time, a single Spike mRNA can be translated into hundreds or thousands of Spike molecules.



In effect, a few of the vaccinee's cells become factories for production of the Spike antigen.

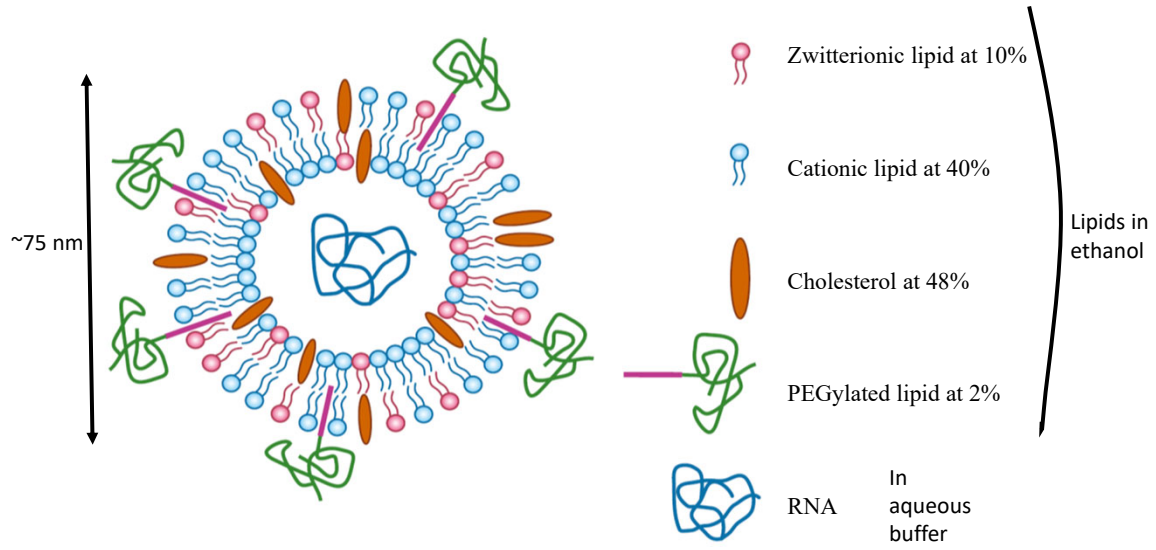
Administering naked mRNA is a very inefficient way to get mRNA molecules into cells. That's because unprotected RNA is rapidly degraded by ubiquitous RNA-degrading enzymes, and because even RNA molecules that aren't degraded have a low probability of successfully entering cells.

Lipid nanoparticle (LNP)



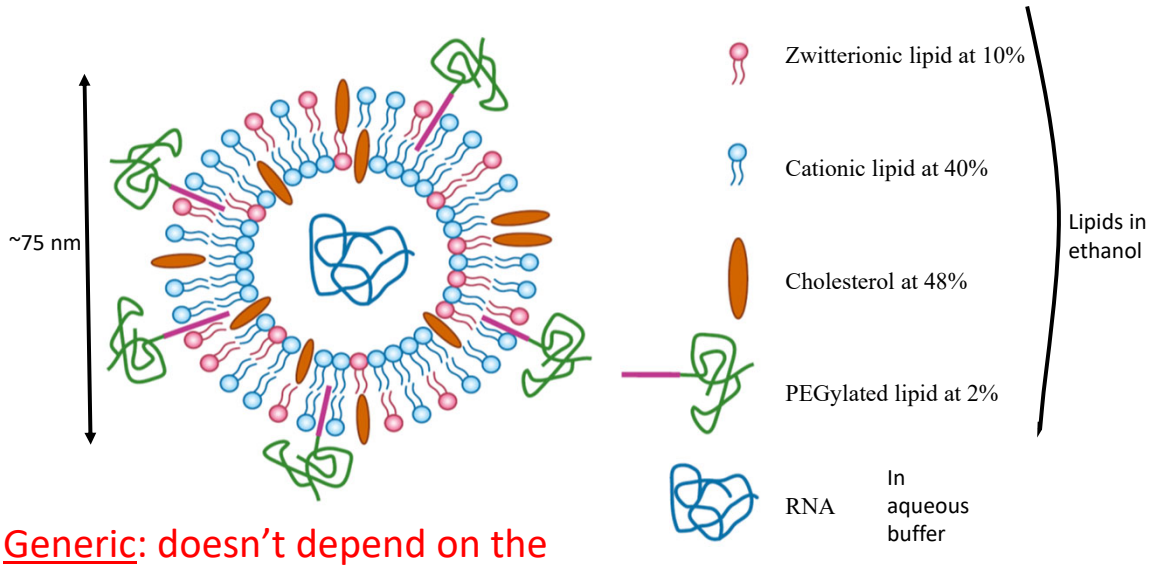
Instead, the vaccine mRNA is formulated to protect it against enzymatic degradation and facilitate its entry into cells. Here's the formulation: lipid nanoparticles (LNPs). An LNP is about the same size as the virion, and like the virion is surrounded by a lipid bilayer membrane—an artificial membrane in this case. Inside the membrane is one or a few copies of the mRNA.

Lipid nanoparticle (LNP) manufacture



LNP-encapsulated mRNAs are manufactured from five highly purified components: four purified lipids dissolved in ethanol, and highly purified mRNA dissolved in aqueous buffer. The RNA is not extracted from whole cells; instead, it's synthesized in vitro with a highly purified enzyme and purified nucleotide precursors, and purified after synthesis to remove extraneous substances. When these two liquids are mixed in a certain way, the LNPs self-assemble reproducibly in massive numbers.

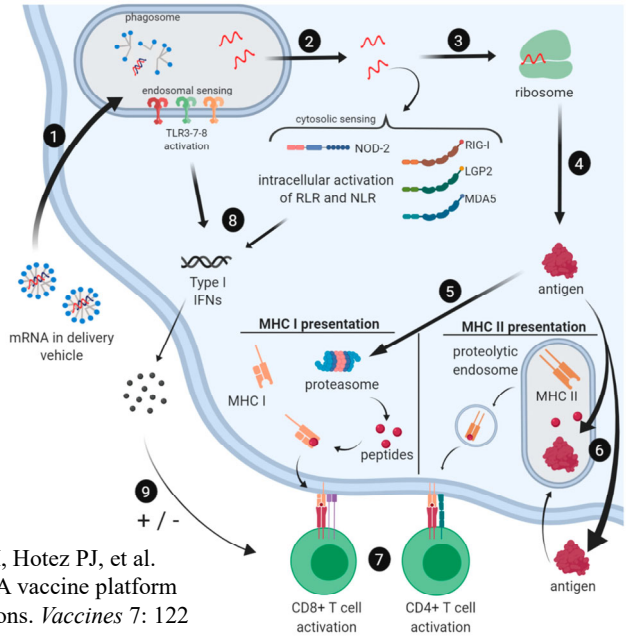
Lipid nanoparticle (LNP) manufacture



Generic: doesn't depend on the sequence of the RNA

The manufacturing process is completely generic: it's independent of the nucleotide sequence of the mRNA, and thus of the antigen protein. Precisely the same manufacturing process, with precisely the same equipment, serves for any mRNA vaccine targeting any pathogen.

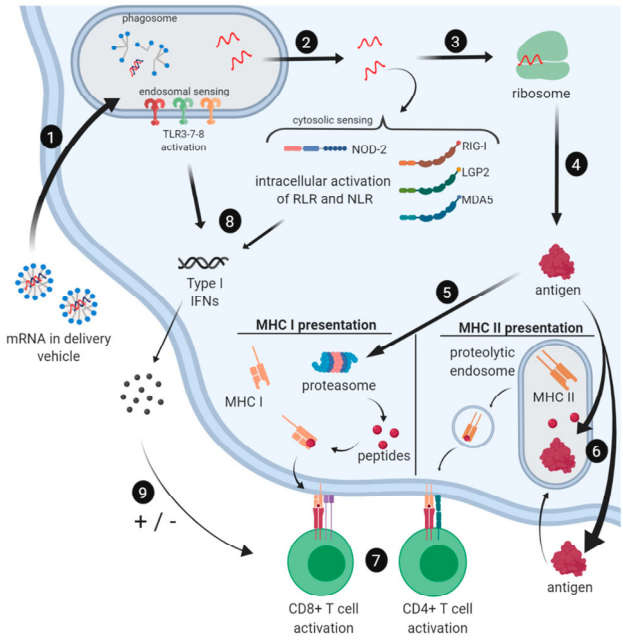
Translation of the protein antigen



Versteeg L, Almutairi MM, Hotez PJ, et al. (2019) Enlisting the mRNA vaccine platform to combat parasitic infections. *Vaccines* 7: 122

What happens when these LNPs are administered to the body? They enter cells (step 1 in the diagram) by a process (not pictured) that's similar to the process by which the virion itself enters, ending up in membrane-bound vesicles within the cell's cytoplasm. Inside the vesicle, the mRNA molecules—the red squiggles in the diagram—exit from the LNPs and then from the vesicles into the cytoplasm (step 2), where they're recognized by ribosomes (step 3). There, the cells' protein synthesis (translation) apparatus synthesizes many copies of the Spike antigen (step 4), using the mRNA's coding sequence as template as I've just described. That's how the Spike protein appears as a result of vaccination with LNP-encapsulated mRNAs.

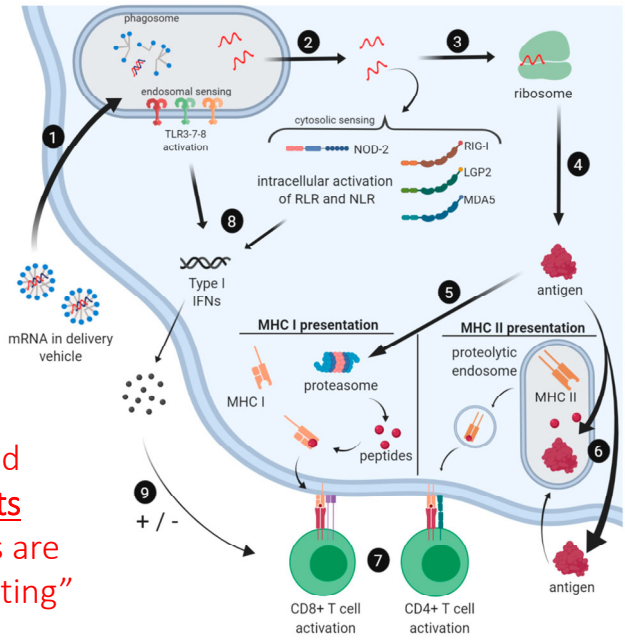
Activation of the innate immune system



- Constitutive, not induced by antigen
- Not antigen-specific
- Sensors recognize generic pathogen-associated molecular patterns (PAMPs)
- Necessary for mobilizing the adaptive immune response

But synthesis of the antigen is not all that happens when an LNP bearing an mRNA enters the cell. It also activates the innate immune system. Unlike the adaptive immune system, which is inducible (absent until induced by the antigen), the innate immune system is constitutive: that is, it's present all the time, not requiring induction by an antigen. It's also not specific for the antigen. Instead, it consists of sensor molecules that recognize generic molecular patterns that are characteristic of broad classes of pathogen. An RNA in a membrane-bound vesicle is an example of one of these pathogen-associated molecular patterns (PAMPs). In a healthy cell, there shouldn't be RNAs in membrane-bound vesicles. In a cell infected by an RNA virus, however, there's every reason to expect RNAs in vesicles. The innate immune system includes sensors—TLR3, TLR7, and TLR8—that surveil the insides of vesicles for RNA. When an RNA, such as an mRNA just delivered by an LNP, engages one of these RNA-specific sensors, the cell is triggered to synthesize Type I interferons (step 8 in the diagram). The interferons are signaling proteins that are secreted from the cell and recruit other elements of the innate and adaptive immune systems to the site. This activation of the innate immune system is necessary for initiation of a prompt, vigorous adaptive immune response.

Activation of the innate immune system



- Conventional vaccines supplemented with adjuvants
- RNA vaccines are "self-adjuvanting"

- Constitutive, not induced by antigen
- Not antigen-specific
- Sensors recognize generic pathogen-associated molecular patterns (PAMPs)
- Necessary for mobilizing the adaptive immune response

Conventional protein vaccines don't activate the innate immune system. They are generally supplemented with extra substances called adjuvants that independently activate the innate immune system at the site of vaccination. This is not necessary for RNA vaccines: they're "self-adjuvanting."

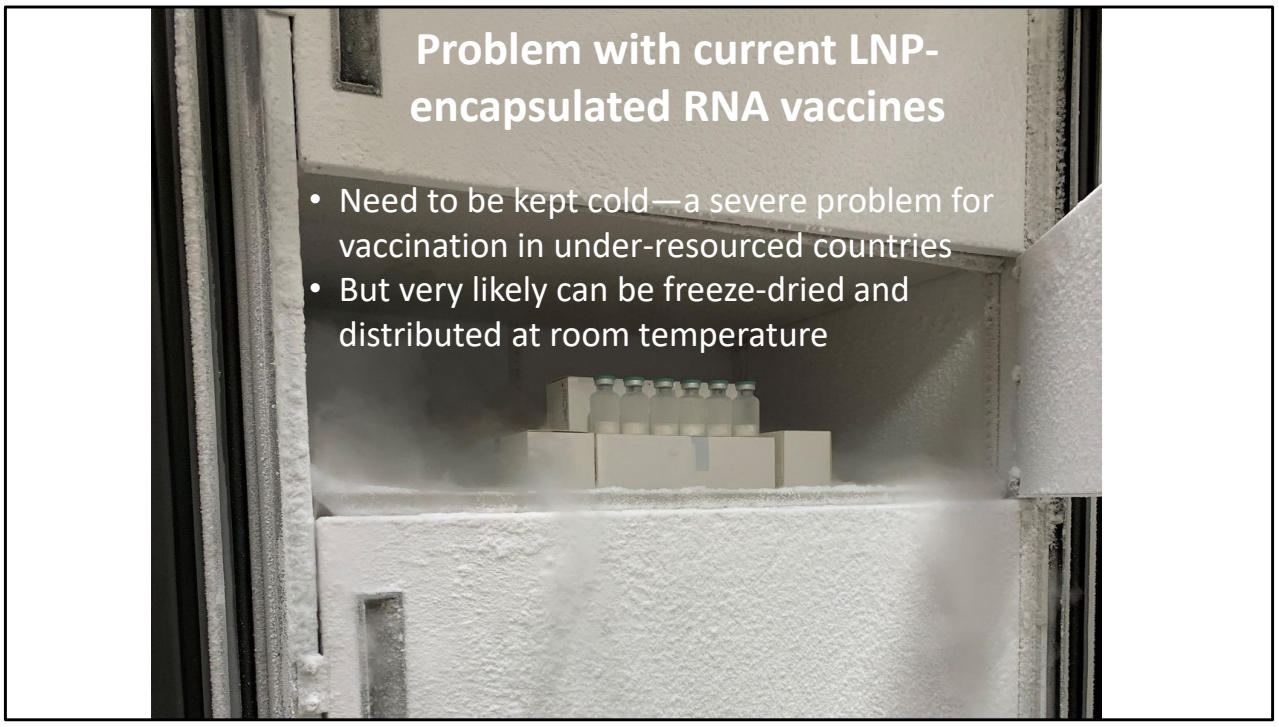
Theoretical advantages of LNP-encapsulated RNA vaccines

- Simple generic good manufacturing practice (GMP) process from 5 highly-purified components: 4 lipids plus RNA synthesized *in vitro*
  - No potentially toxic components or contaminants
  - Very short manufacturing time scale
  - Easy scale-up
  - Manufacturing infrastructure immediately usable for future pandemics
- No adaptive immune response to the vaccine itself—reusable for other target antigens
- Self-adjuvanting—no adjuvants needed
- RNA never enters nucleus & is not reverse-transcribed into DNA—no possibility of oncogenic heritable alterations to chromosomes
- Generic, reusable "platform" immediately adaptable to new vaccine targets

Let's review the theoretical advantages of LNP-encapsulated RNA vaccines.

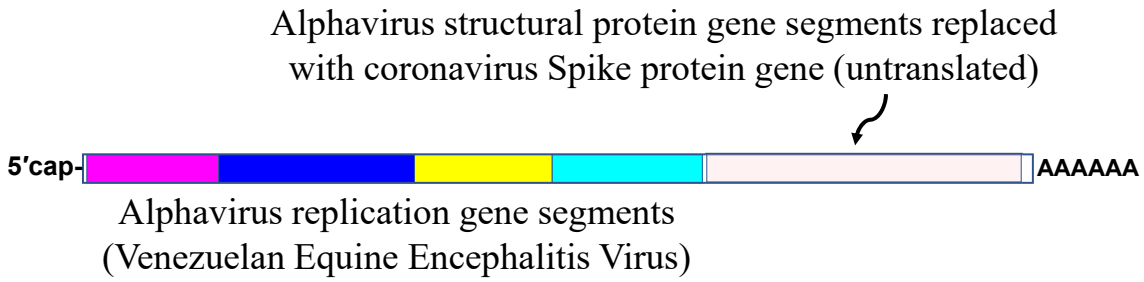
- First, they're made by a simple generic good manufacturing practice (GMP) process from five highly purified components: the four lipids and the RNA. There are no potentially toxic components or contaminants. The manufacturing time-scale is very short, and scale-up is straightforward. Any infrastructure put in place for one RNA vaccine is immediately resuable for another RNA vaccine, encoding another antigen.
- Second, there's no adaptive immune response to the vaccine itself. That means that the LNP-encapsulated mRNA platform is indefinitely reusable for future vaccine targets. If there were an adaptive immune response to the vaccine itself, that response might prevent antigen production following a second use of the platform from completing its full course.
- Third, RNA vaccines are self-adjuvanting, as we've just seen, thus avoiding the need for added adjuvants.
- Fourth, the RNA never enters the cell's nucleus and is not reverse-transcribed into DNA. That means there's no possibility of rare heritable oncogenic alterations to chromosomes that might result in cancers in some vaccinees.

In sum, LNP-encapsulated mRNA is a generic, safe, reusable platform that's immediately adaptable to new vaccine targets.



There is an important problem with current LNP-encapsulated RNA vaccines: they have to be kept cold. Even in rich countries, that will complicate a mass vaccination program. In poor countries, it will make mass vaccination nearly impossible. Many researchers believe this is a solvable problem: there should be a way to freeze-dry the vaccine so it can be distributed at room temperature and reconstituted on site just before use. But this aspect of development of these vaccines has not yet been accomplished.

Self-amplifying RNA vaccines



Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing antibody titers in mice. Paul F. McKay, Kai Hu, Anna K. Blakney, Karnyart Samnuan, Jonathan C. Brown, Rebecca Penn, Jie Zhou, Clément R. Bouton, Paul Rogers, Krunal Polra, Paulo J. C. Lin, Christopher Barbosa, Ying K. Tam, Wendy S. Barclay and Robin J. Shattock, *Nature Communications* 11, 3523 (2020) (**University College London**)

Before I leave the subject of RNA vaccines, I'd like to describe a variation on the theme, called self-amplifying RNA vaccines. These vaccines are based on the RNA chromosome of alphaviruses, a type of RNA virus, like coronaviruses.

The alphavirus chromosome is an mRNA with two long coding sequences. The first coding sequence, corresponding to the four brightly colored segments, is translated into a long polypeptide that is cleaved into four segments, which then assemble into the alphavirus replication complex.

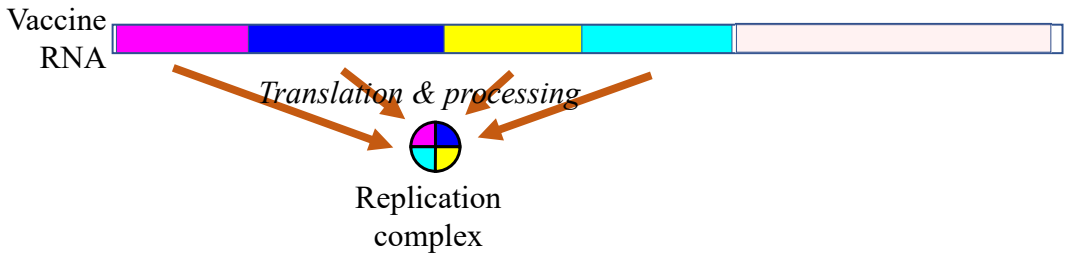
The second coding sequence is translated into another long polypeptide that is cleaved into five segments, which are the five so-called structural proteins. The structural proteins are necessary for assembly of the alphavirus virion, and are incorporated into the virion.

In a self-amplifying RNA vaccine, the second coding sequence (for the alphavirus structural proteins) is replaced with the coding sequence of the target antigen—the Spike protein in this case. I've colored this coding sequence pale red in the diagram, because it can't be translated. With few exceptions, only the first coding sequence in a eukaryotic mRNA can be translated. That's not a problem, as we'll see.

Self-amplifying RNA vaccines

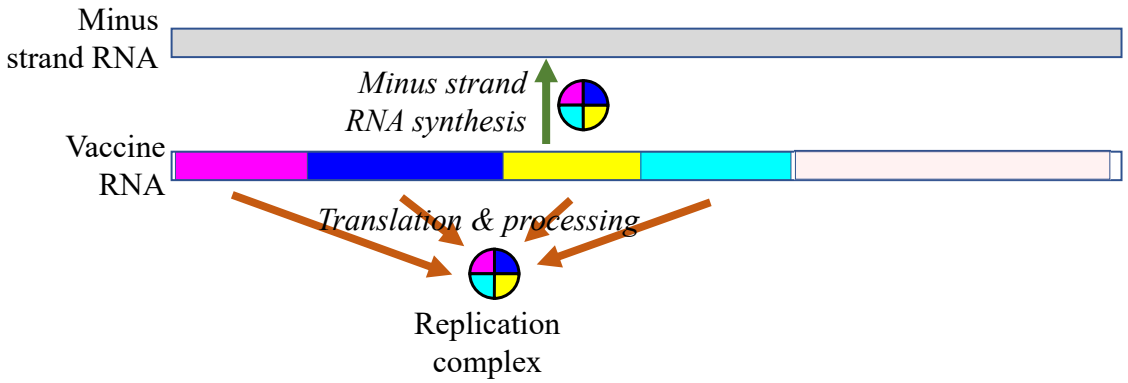
Let's follow what happens when one of these RNAs, formulated in an LNP, enters the cytoplasm of a cell.

Self-amplifying RNA vaccines



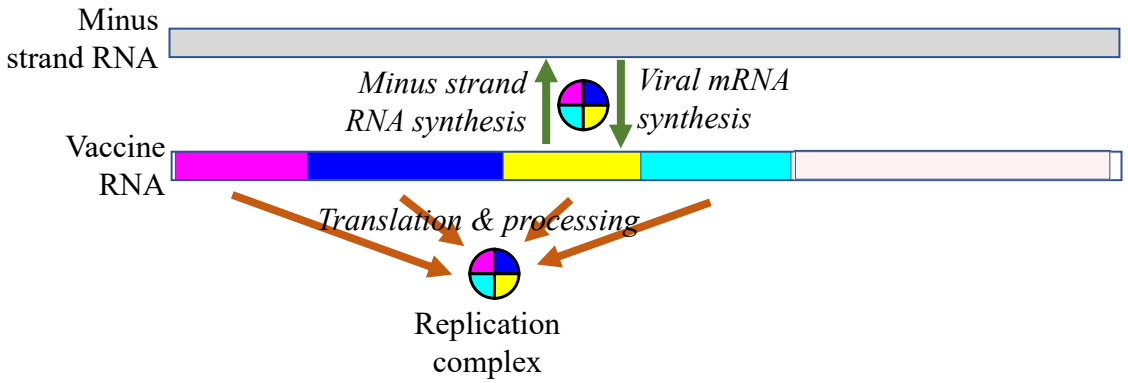
The first step is translation of the first coding sequence to make multiple copies of a long polypeptide. That chain is cleaved into four component proteins, which assemble into the alphavirus replication complex.

Self-amplifying RNA vaccines

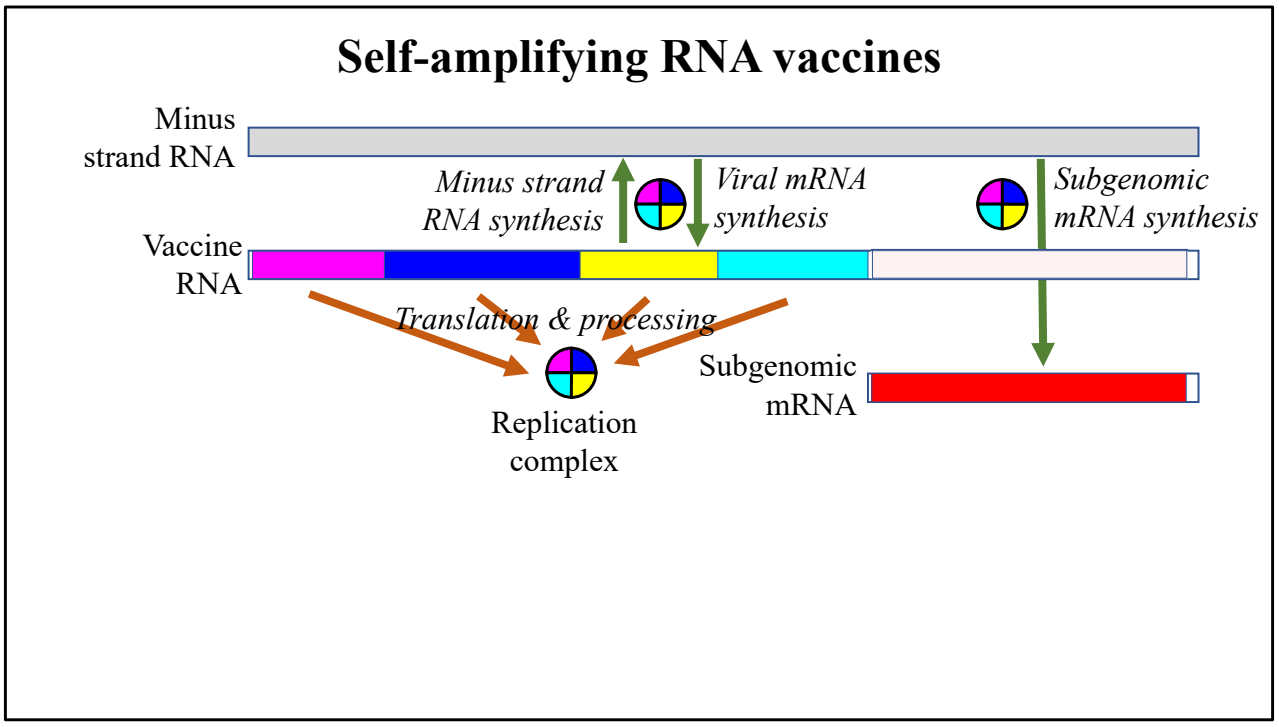


The replication complex uses the RNA as a template to make complementary minus strand RNAs.

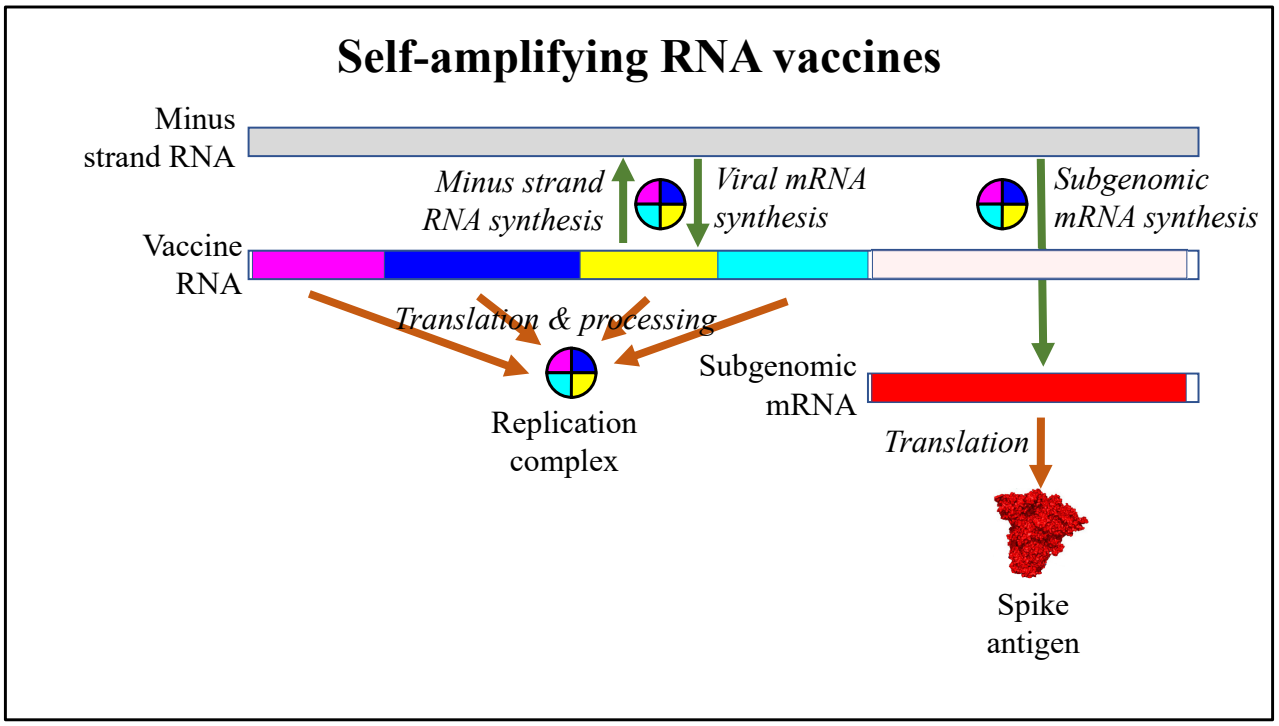
Self-amplifying RNA vaccines



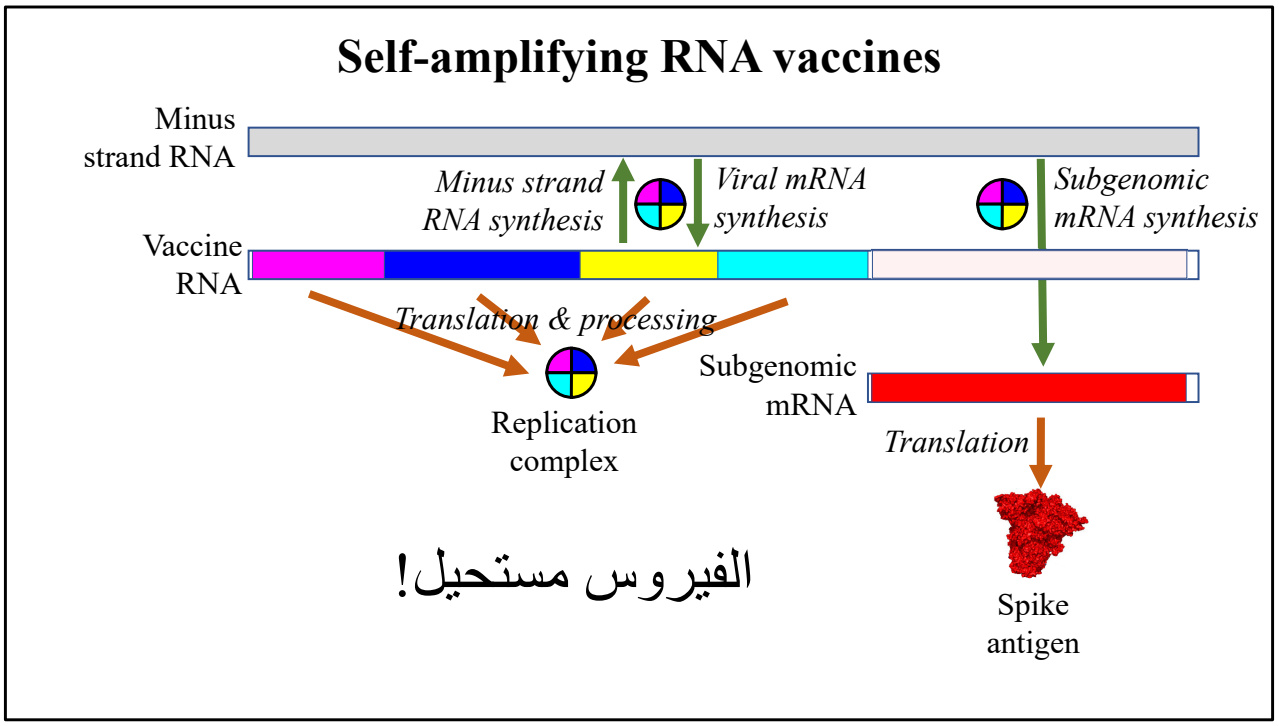
The replication complex in turn uses the minus strand RNAs as templates to make many more copies of the original RNA.



At the same time, the replication complex uses the last third of the minus strand as template to make many copies of a shorter complementary RNA: a subgenomic mRNA, in which the Spike coding sequence is first in line.

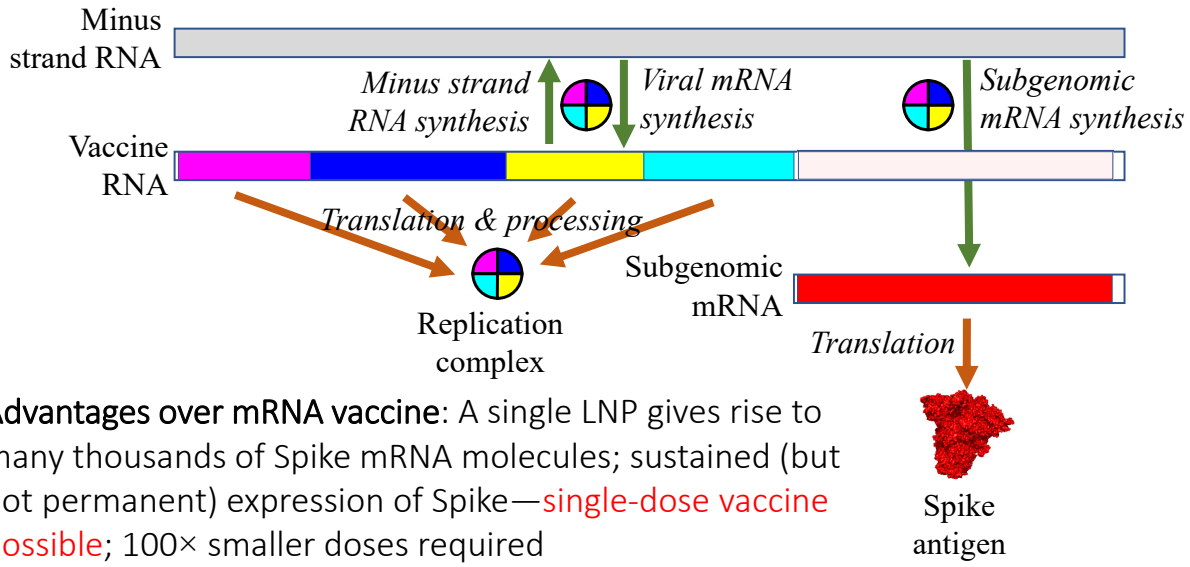


Each subgenomic mRNA is translated many times on a ribosome to make many copies of the Spike antigen. That's how the Spike protein appears after vaccination with a self-amplifying RNA vaccine.



No infective virions are possible in this system. That's because the genes for the structural proteins required for virion formation are missing.

Self-amplifying RNA vaccines



Advantages over mRNA vaccine: A single LNP gives rise to many thousands of Spike mRNA molecules; sustained (but not permanent) expression of Spike—single-dose vaccine possible; 100× smaller doses required

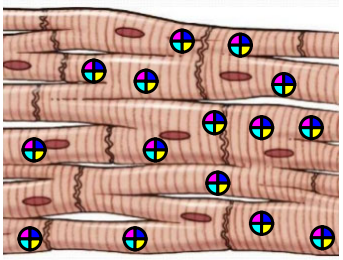
This design has dramatic potential advantages over non-self-amplifying mRNA vaccines. A single LNP, delivering a single RNA molecule into the cell, gives rise after a few days to thousands of subgenomic Spike mRNA molecules. Synthesis of the Spike antigen is sustained for weeks (but eventually dies out). This holds out the possibility of a single-dose vaccine, while other vaccines require two doses—a primary dose and a booster—to achieve protective immunity. Much smaller doses—about 100 times smaller—are required, greatly simplifying production.

Potential problems specific to self-amplifying RNA vaccines

Potential for adaptive immune response to the alphavirus replication complex—the platform may not be indefinitely reusable (unlike non-self-amplifying mRNA vaccines)

The alphavirus replication complex is a foreign antigen

Potential for uncontrolled spread that's not mediated by virion infection—e.g., diffusion through multinucleate muscle cell syncytia



There are potential problems with self-amplifying RNA vaccines. First, these vaccines can induce an adaptive immune response to the alphavirus replication complex proteins. If a person who has previously been vaccinated with a self-amplifying RNA vaccine for one infectious disease is subsequently vaccinated with a self-amplifying vaccine for another infectious disease, adaptive immunity against the replication complex proteins may attack the antigen-producing cells and bring the desired pathogen-specific adaptive immune response to a premature halt. Unlike non-self-amplifying RNA vaccines, therefore, this vaccine platform may not be indefinitely reusable, or reusable at all. This problem might be circumvented by using a different alphavirus, with different replication complex proteins, as the basis of the second vaccine.

A second reservation about self-amplifying RNA vaccines is that the replicating RNA may be able to spread widely even in the absence of infection. The vaccine is administered to skeletal muscle, and skeletal muscle cells are very large multinucleate syncytia with cytoplasms that span hundreds or thousands of micrometers. Viral replication centers could potentially diffuse widely through these syncytial cytoplasms without ever having to cross a cell membrane. No evidence of such uncontrolled spread has emerged from limited studies so far, but it's not yet

clear that this is not a safety concern.

Two phases in genesis of a new vaccine (or other drug)

- Discovery & technological innovation
  - Exploratory science driven by curiosity & professional ambition
  - Overwhelmingly carried out in academic labs with public funding
  - Innovations (e.g., RNA vaccines) emerge unpredictably from global scientific communities, not individual researchers or research groups
- Development
  - Carried out by corporations driven by profit
  - Mostly final optimization, manufacture, and trials
  - Privately financed with promise of government-granted patent monopolies when successful drugs result
    - Key patent rights mostly purchased from public institutions or associated start-ups
    - Governments permit researchers to pursue patent rights to discoveries & innovations arising from publicly-funded research

Before I continue, I would like to define two phases in the genesis of a new vaccine, or any other new pharmaceutical. These are overlapping phases with no sharp boundary, but I think they're useful in thinking about how new drugs, including new vaccines, come into being today.

- The first phase is what I'll call discovery and technological innovation. This is the province of exploratory science driven by curiosity and professional ambition. It is overwhelmingly carried out in academic labs with public funding. The technologies that result—what the pharmaceutical industry calls "leads"—emerge from vast global scientific communities, almost always—and certainly in the case of RNA vaccines—depending on hundreds of scientific discoveries and technological innovations from hundreds of research groups all over the globe. No one individual researcher or research group can plausibly be identified as the true inventor of such an advance.
- The second phase is what I'll call development. This is largely the province of corporations driven by profit. It is primarily responsible for final optimization of drug leads, for development of efficient and safe manufacturing procedures, and for the animal and human trials that are required for regulatory approval. Development is mostly privately financed with the promise of government-granted

patent monopolies when successful drugs result. This means that the corporations must acquire key patent rights, which they often purchase from public institutions or associated start-ups. To facilitate this system, governments now permit researchers and their institutions to pursue patent rights to discoveries and innovations arising from publicly-funded research.

Progress in creation of RNA vaccine for SARS CoV-2

- Discovery & technological innovation: (pretty much) finished years ago
- Development: (pretty much) not yet started when pandemic hit
  - Generic issues yet to be resolved
    - Can they be freeze-dried and distributed at room temperature?
    - Do they induce vigorous, durable adaptive immunity to the target antigen (antibodies and immune cells)?
    - Are there unanticipated generic safety issues?

    Self-amplifying RNA vaccines only:
    - Does adaptive immunity to vaccine platform limit reusability?
    - Unchecked proliferation without mediation by virion infection?
  - SARS CoV-2-specific issues yet to be resolved
    - Are there safety issues for this specific target antigen?
    - Is vaccine-induced adaptive immunity actually protective?

Let's review these two phases in the particular case of RNA vaccines for the SARS CoV-2 pandemic.

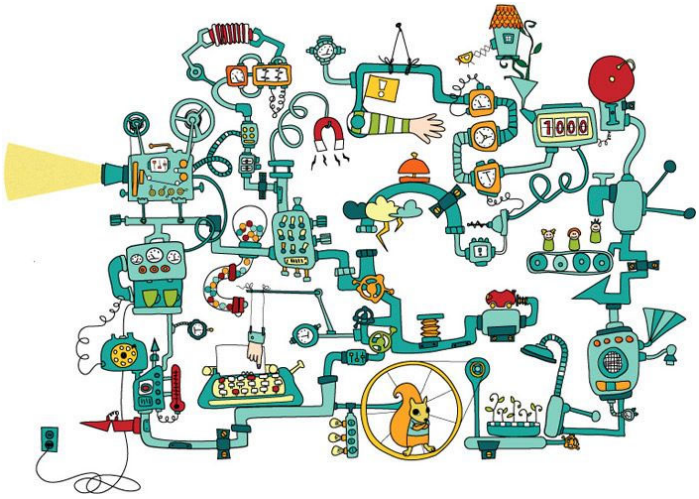
- The discovery and technological innovation phase was essentially complete years before this pandemic hit. The scientific literature abounds in publications about RNA vaccine technology, which is why vaccines with this design are leading contenders for pandemic vaccine programs today.
- In contrast, the development phase had pretty much not started when the pandemic hit. Of course development steps that are specific to this particular pandemic couldn't have been started before the pandemic actually began. But I've already discussed a number of key generic issues with this vaccine design that could have been addressed ahead of time:
  - Can they be freeze-dried and distributed at room temperature?
  - Do they induce vigorous, durable adaptive immunity—both antibodies and immune cells—to the antigens they encode?
  - Are there unanticipated generic safety issues?
  - Generic issues for self-amplifying RNA vaccines in particular:
    - Does adaptive immunity to the alphavirus replication complex limit reusability?

- Is unchecked proliferation not mediated by infection a safety issue?

It’s not surprising that these generic development issues were not addressed in advance. That would have been a very risky investment for a profit-driven corporation.

Emergency vaccine development has been a

فوضی!



The result is that governments, including our own, were faced with the necessity of massive public investment in vaccine development, including both generic and pandemic-specific development, with no careful advance planning or prior experience to guide them. It's not surprising that this investment has been chaotic.

Not this kind of

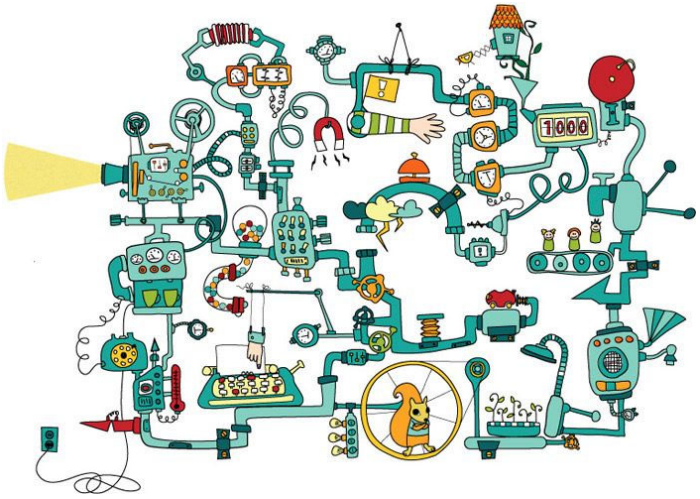
فوضى!

To my Palestinian colleagues, I should explain that I don't mean this kind of fauda!

Emergency vaccine development has been a

فوضی!

- RNA vaccine platforms ready for development years ago
- Patent-funded development failed to address generic questions that could have been answered before pandemic hit
- Example: U.S.'s hasty investment in Moderna's RNA vaccine
  - $1 billion for development
  - Will buy 100 million doses at inflated price ($15.25 versus ~$4 production cost); option for 400 million additional doses
  - Commercial secrecy permitted!
  - Available to U.S. citizens only
- Barrier to cooperation



The U.S. federal government's hasty investment in Moderna, a leading developer of RNA vaccines, well illustrates this chaos. The government invested almost $1 billion in development of the company's RNA vaccine. It also promised to buy 100 million doses at inflated prices ($15.25—much higher than production costs), with an option to buy 400 million additional doses at the same price. Despite this massive public investment, Moderna is permitted to patent the developmental advances that result.

Emergency public investment in other capitalist countries has been only slightly less chaotic.

Commercial privatization of vaccine development also imposes a huge barrier to global cooperation of the sort that is essential to discovery and technological innovation in publicly funded exploratory biomedical research. For example, several corporations today are independently trying to formulate LNPs so they can be distributed at room temperature; they'd undoubtedly make much faster progress if they could benefit from one another's work.

A number of economists argue that we can do better—for developing vaccines specifically and developing drugs in general

Can we do better than this? A number of economists argue that we can do much better—and not just for developing pandemic vaccines in particular, but for developing drugs in general. I'll spend the remaining minutes of this address summarizing their argument.

Monopoly funding of drug development

Tax-averse governments prefer to stimulate drug development by promise of government-granted patent monopolies rather than by direct government spending.

Most governments today, including the U.S. federal government, are extremely averse to taxing their citizens. That's why they prefer to stimulate drug development by the promise of government-granted patent monopolies rather than by direct government spending.

Monopoly funding of drug development

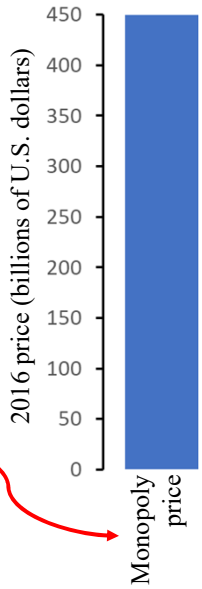
Tax-averse governments prefer to stimulate drug development by promise of government-granted patent monopolies rather than by direct government spending.

Street demonstrations against austerity measures imposed by International Monetary Fund, Tunis January 2018

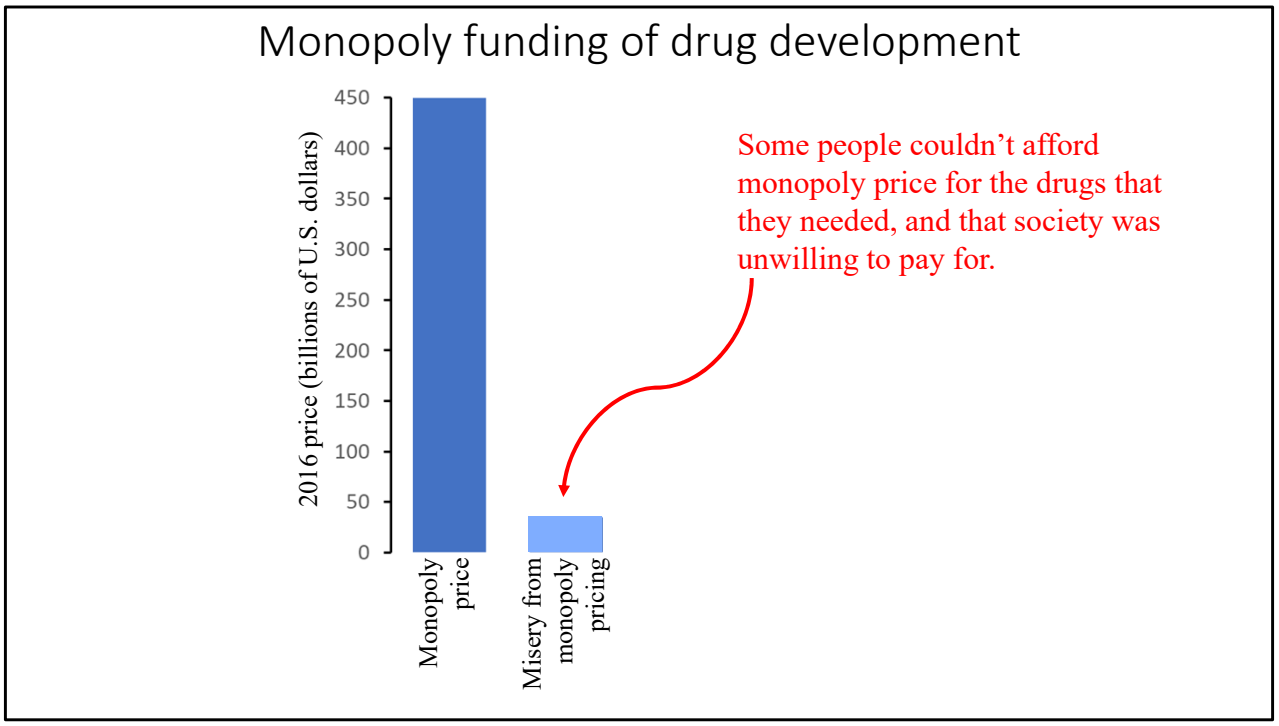
Austerity funding is forced on many governments in poorer countries by the International Monetary Fund as a conditional for IMF loans.

Monopoly funding of drug development

Tax-averse governments prefer to stimulate drug development by promise of government-granted patent monopolies rather than by direct government spending.

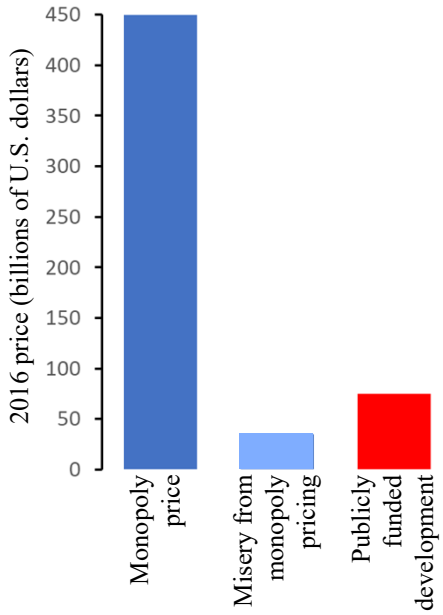


The result is that we pay extremely high prices for drugs. The U.S. paid $450 billion for drugs in 2016—more than $1,300 for every person in the country. The World Trade Organization compels other countries to recognize patent and other intellectual property rights as well. So these countries, including many poor countries, are forced to pay monopoly prices as well.



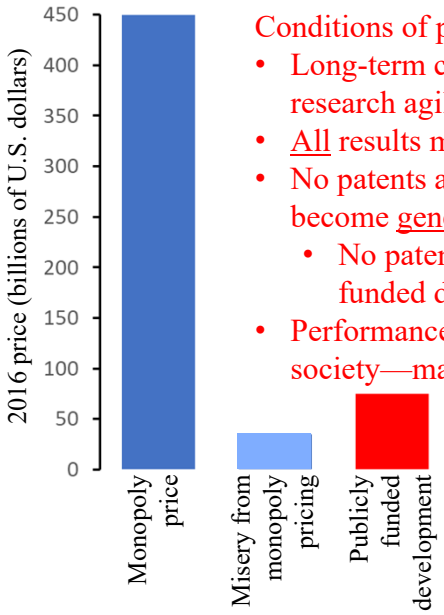
There's an additional cost to monopoly pricing, represented by the second blue bar. This represents the misery some people suffer because they can't afford the monopoly prices for the drugs they need, and because their insurance (if any) is unwilling to pay for the drugs either. I've colored this bar a fainter shade of blue to signal that these are virtual dollars. They represent economists' attempt to attach a monetary value to this monopoly-caused misery in the U.S. I don't think we should take the monetary value very seriously, but there's no denying that it stands for a real cost to society. Some people die each year because they can't get the drugs they need. These virtual dollars also serve to remind us that drugs are not just a commodity like TVs or new running shoes; they're also a public good. And their effective development is not just a matter of commercial prosperity; it's also a matter of social justice.

Public alternative to monopoly funding of drug development



So let's consider a public alternative to private drug development. Looking at the red bar, you may be surprised to learn that funding drug development publicly wouldn't cost very much. That's because drug companies do not spend very much of their money for actual drug development—only about $75 billion for the U.S. in 2016.

Public alternative to monopoly funding of drug development

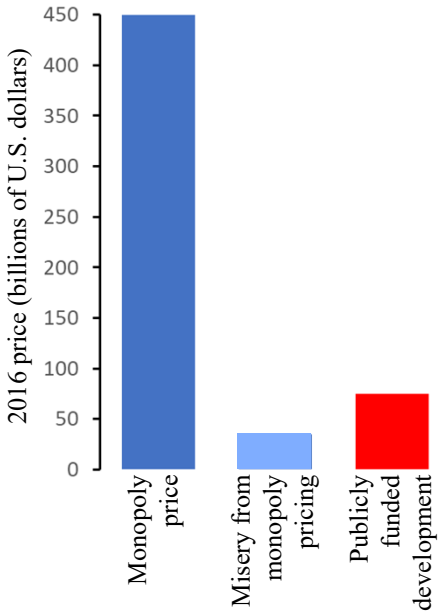


Conditions of public funding

- Long-term contracts in broad areas to preserve research agility
- All results made public immediately
- No patents allowed on resulting drugs, which become generic
  - No patents allowed on results of publicly funded discoveries & innovations either
- Performance assessed based on usefulness to society—many perverse incentives avoided

Publicly funded drug development would be patterned on the exploratory biomedical research that is already funded by government agencies such as the U.S. National Institutes of Health. In order to preserve research agility, funding would probably be predominantly in the form of long-term contracts (e.g., 10 to 15 years) in broad areas of concern. All results would have to be made public immediately, so that other contractors and research groups can take advantage of them. No patents would be permitted on the resulting drugs, which would immediately become generic. As a corollary, patents would no longer be permitted for results of publicly funded exploratory biomedical research either. A contractor's performance, and its chance of contract renewal, would be assessed based on the usefulness of its work to society. In this way, many perverse incentives would be avoided.

Public alternative to monopoly funding of drug development

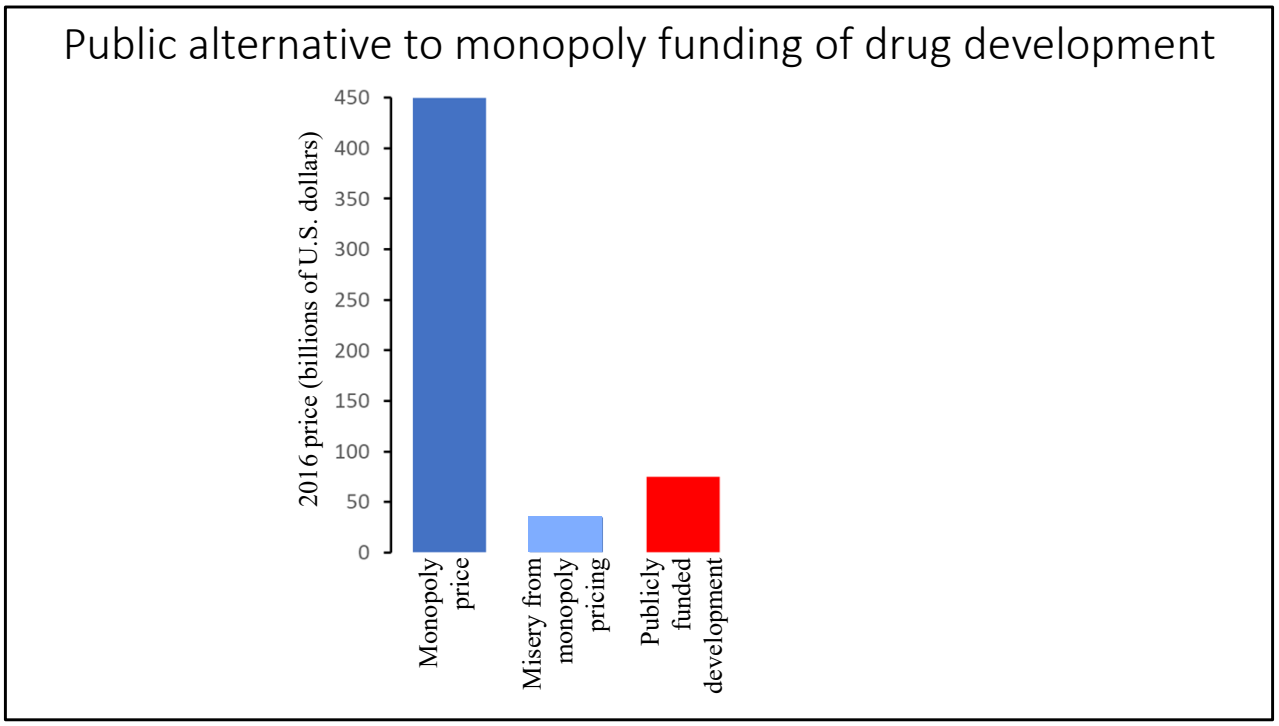


perverse incentives

- Don't develop cures or vaccines!
- Capture market share with me-too drugs with no benefit to society!
- Don't prepare for future challenges!
- Hide your results (especially negative results)!

Let's enumerate some of the perverse incentives of patent-funded development:

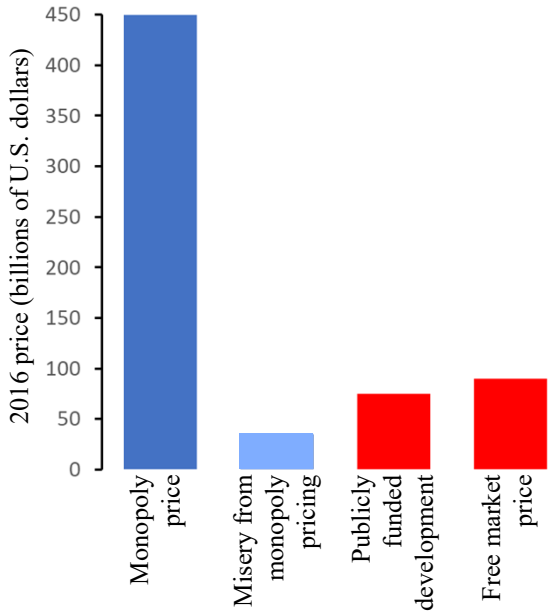
- If you're a corporation driven by profit, don't develop cures or vaccines! Focus on lifetime treatments, ensuring a steady revenue stream.
- If you're a corporation driven by profit, it's a good idea to capture market share from your competitors with me-too drugs with no benefit to society, thus augmenting the steady revenue stream.
- If you're a corporation driven by profit, don't prepare for future challenges like pandemics! That's way too risky an investment.
- If you're a corporation driven by profit, hide your results! Hide them from your competitors! When feasible, hide your negative results from regulators.



Would this modest level of government-controlled funding suffice to sustain the entrepreneurial spirit that has resulted in stunning achievements in the drug industry—immunotherapies for cancers and autoimmune diseases for example—that are justly celebrated today? I think so. When we talk about scientific and engineering entrepreneurship, which is what would matter for publicly-funded drug development, there is no shortage of that in publicly-funded discovery and technological innovation, whose workforce enjoy comfortable but modest incomes. Why wouldn't that also be the case for publicly-funded development, in which there would be no corporate secrecy to thwart professional ambition?

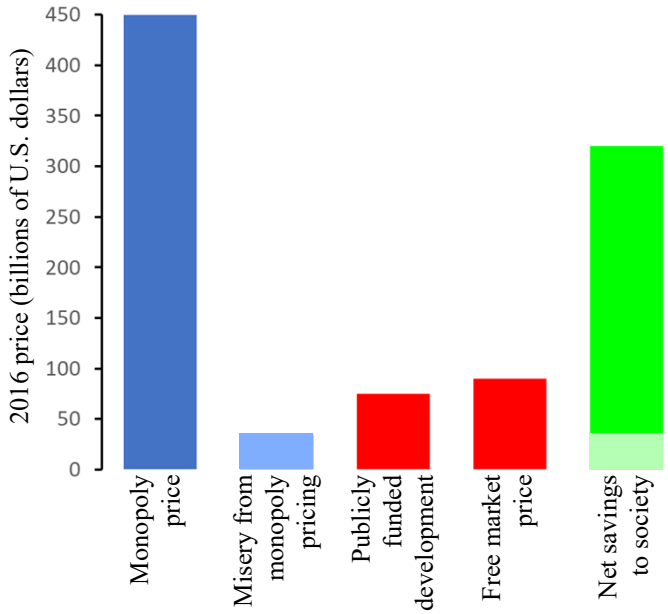
It's true that a handful of technological superstars in successful pharmaceutical corporations enjoy extravagant remuneration in the form of stock options and so on. I doubt that such people would be any less driven if they had to settle for the salaries of their academic superstar counterparts.

Public alternative to monopoly funding of drug development

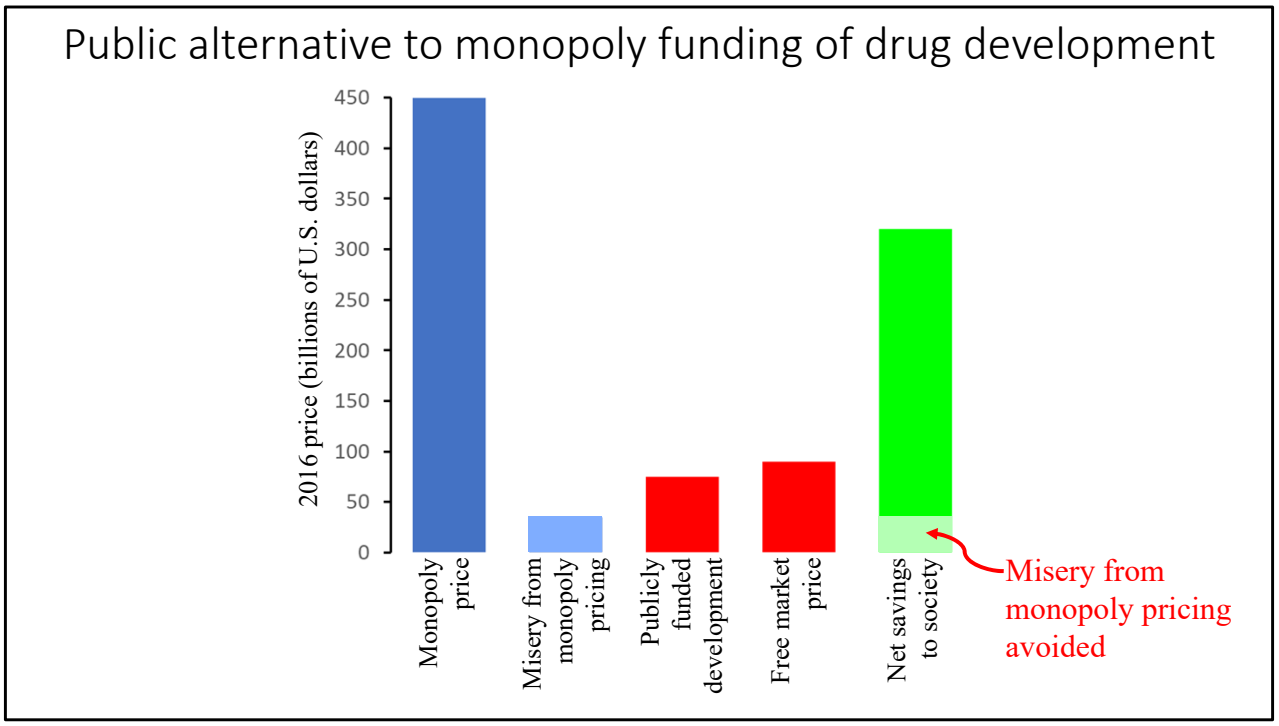


Of course we'd still have to pay for drugs. But we (or our insurance) would pay generic drug prices, not monopoly prices. That's because any company would be free to enter the competitive market to manufacture and sell the drugs. A plausible estimate is that the U.S. would have paid about $90 billion for drugs in 2016 if all drugs had been generic—1/5 of the amount we actually paid in that year. That's the amount shown on the second red bar.

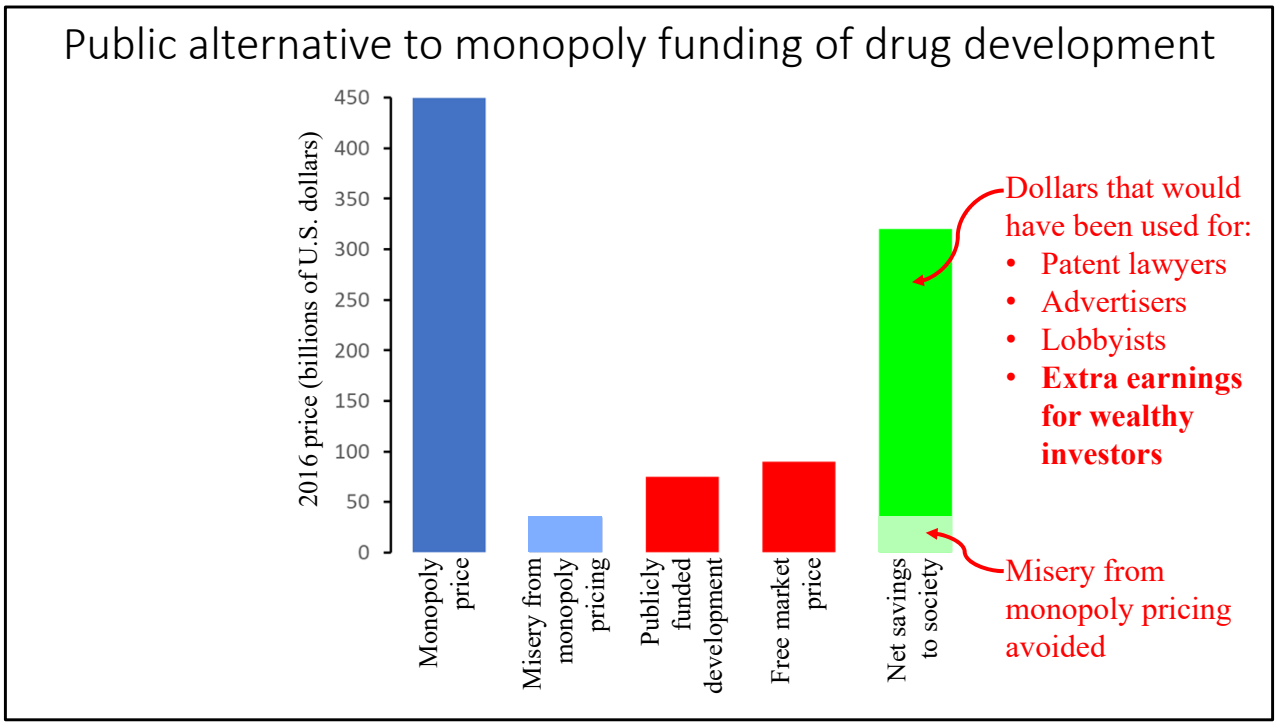
Public alternative to monopoly funding of drug development



If we subtract the red expenses from the blue expenses, we get an estimate of the net savings that would have resulted for the U.S. in 2016 if public funding of drug development had been in place in that year. Those projected savings are shown in the green fifth bar.

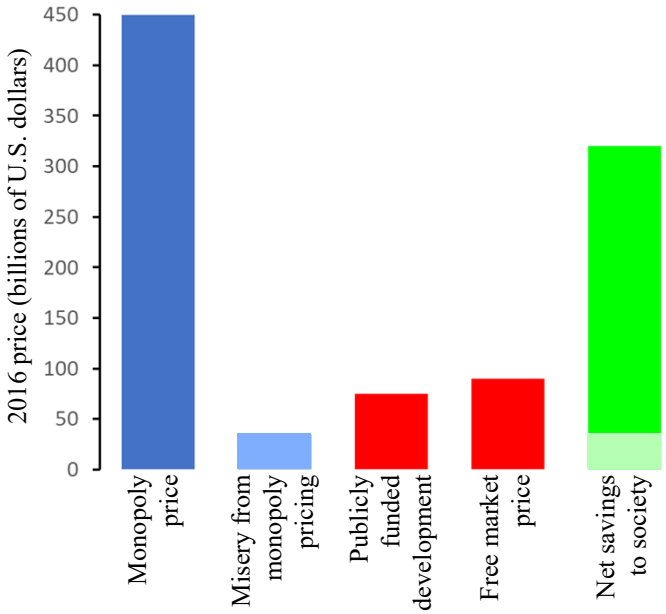


The lower part of the fifth bar, in the lighter shade of green, is numerically equal to the light blue bar. It corresponds to the virtual dollar value of the misery that would be avoided by replacing monopoly with generic pricing. Again, I don't think we should take the numerical value very seriously. But certainly avoiding this misery is a real economic gain to society.



The upper part of the fifth bar, in the brighter green, is an estimate of real dollars that would have been saved if drugs had been developed with public funding in 2016. These are dollars that went to patent lawyers, advertisers, corporate lobbyists, and especially to wealthy investors. The first three are genuine economic losses. Those patent lawyers, those advertisers, those corporate lobbyists would lose their jobs and have to find other work. But that last item—those extra earnings that would no longer go to wealthy investors? I find it hard to think of this as an economic loss. Maybe it should be considered an economic gain instead. Patent monopolies—in general, not just in the pharmaceutical industry—are a significant factor in the upward mobility of wealth. Reducing them would be a step in reversing the obscene wealth inequality that characterizes our economies today.

Public alternative to monopoly funding of drug development



Modified from Dean Baker, Chapter 5 of *Rigged* (it's free)

OK, that's it. That's these economists' vision of how patent-funded drug development could be replaced by a more effective public system. I don't think these ideas are really very "visionary." They build in a pretty straightforward way on the public system that already sustains exploratory biomedical research in the U.S. today—a system embodied in the National Institutes of Health, the National Science Foundation, and other public entities that are the envy of the scientific world. And it's a system that would align better than the current patent-funded system with widely-held notions of social and economic justice.