لقاحات حمض النووي الريبي:
التكنولوجيا ورؤية جديدة لسوق الدواء

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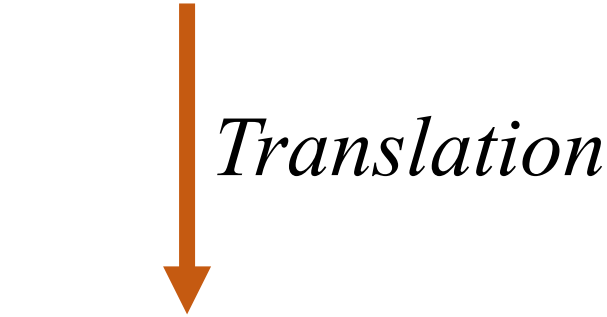
University of Missouri, U.S.A.

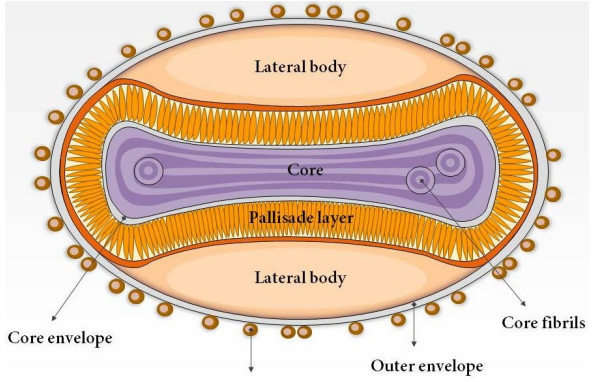
Conference on COVID-19
October 30, 2020

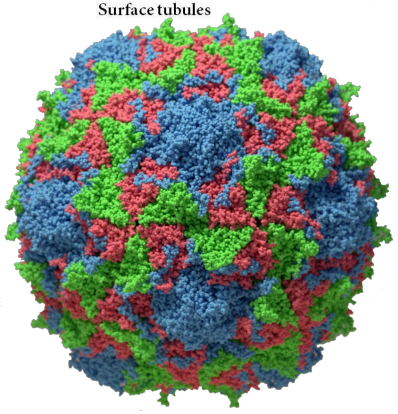
Tunisian Academy of Sciences, Letters, and Arts, with the participation of the Palestine Academy for Science and Technology

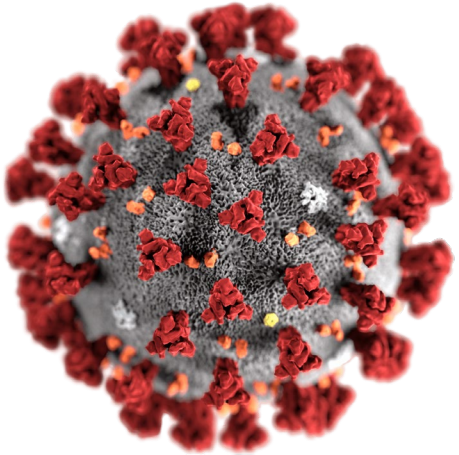


Spike antigen

Pandemics that have been ended by vaccines







Smallpox ~200 years

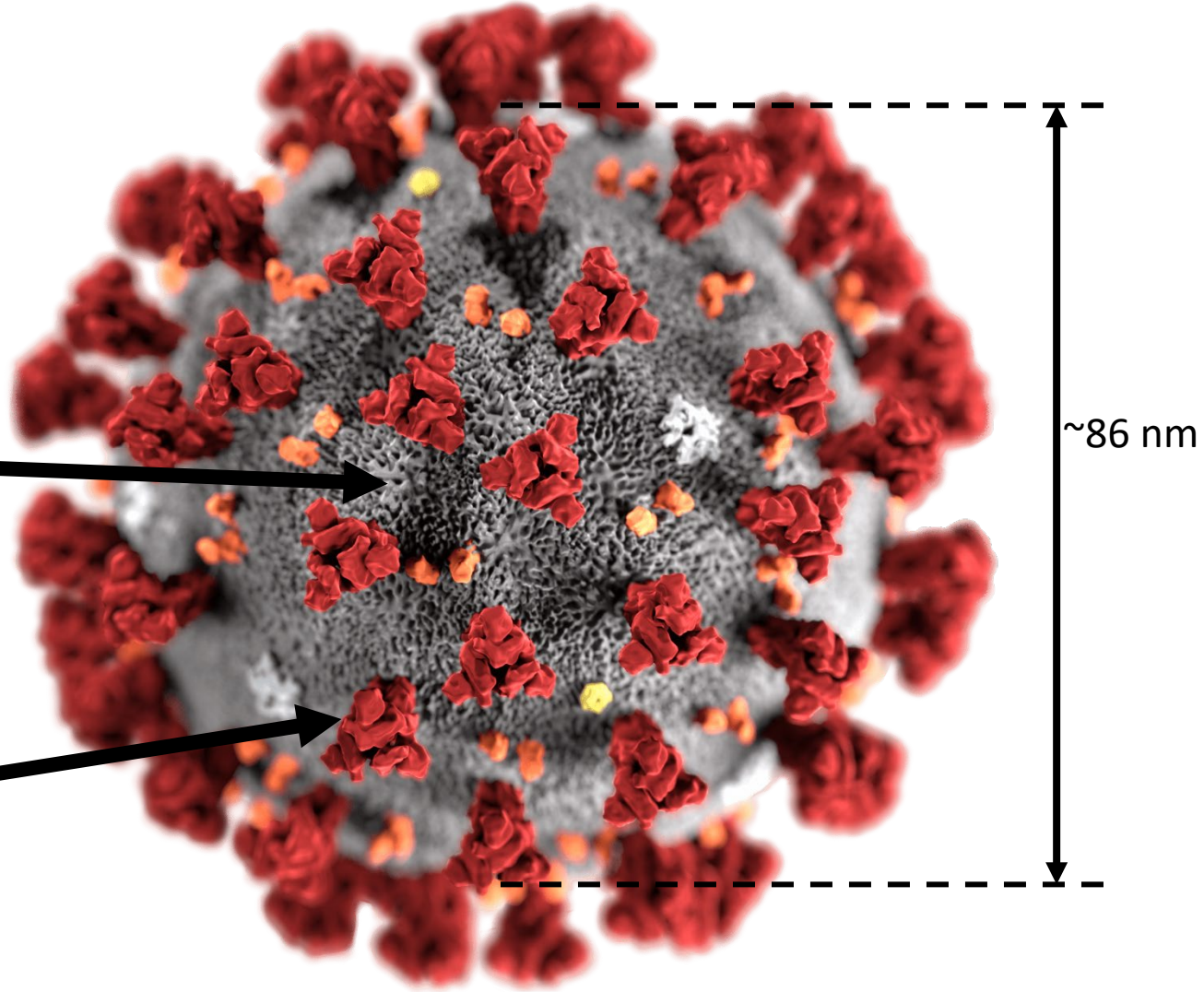
Polio ~50 years

SARS CoV-2 ~2 years???

SARS CoV-2 virion

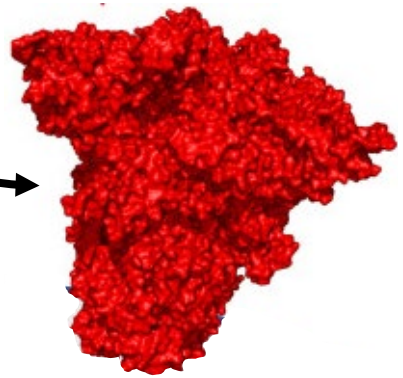
Surrounded by lipid bilayer membrane **envelope**

Spike protein protrudes from membrane, binds ACE 2 on cells to initiate infection; **target of most coronavirus vaccines**



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

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



Spike antigen

Conventional vaccine

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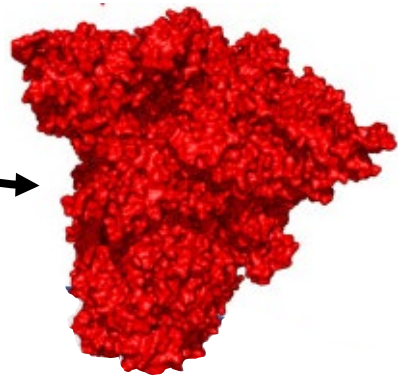
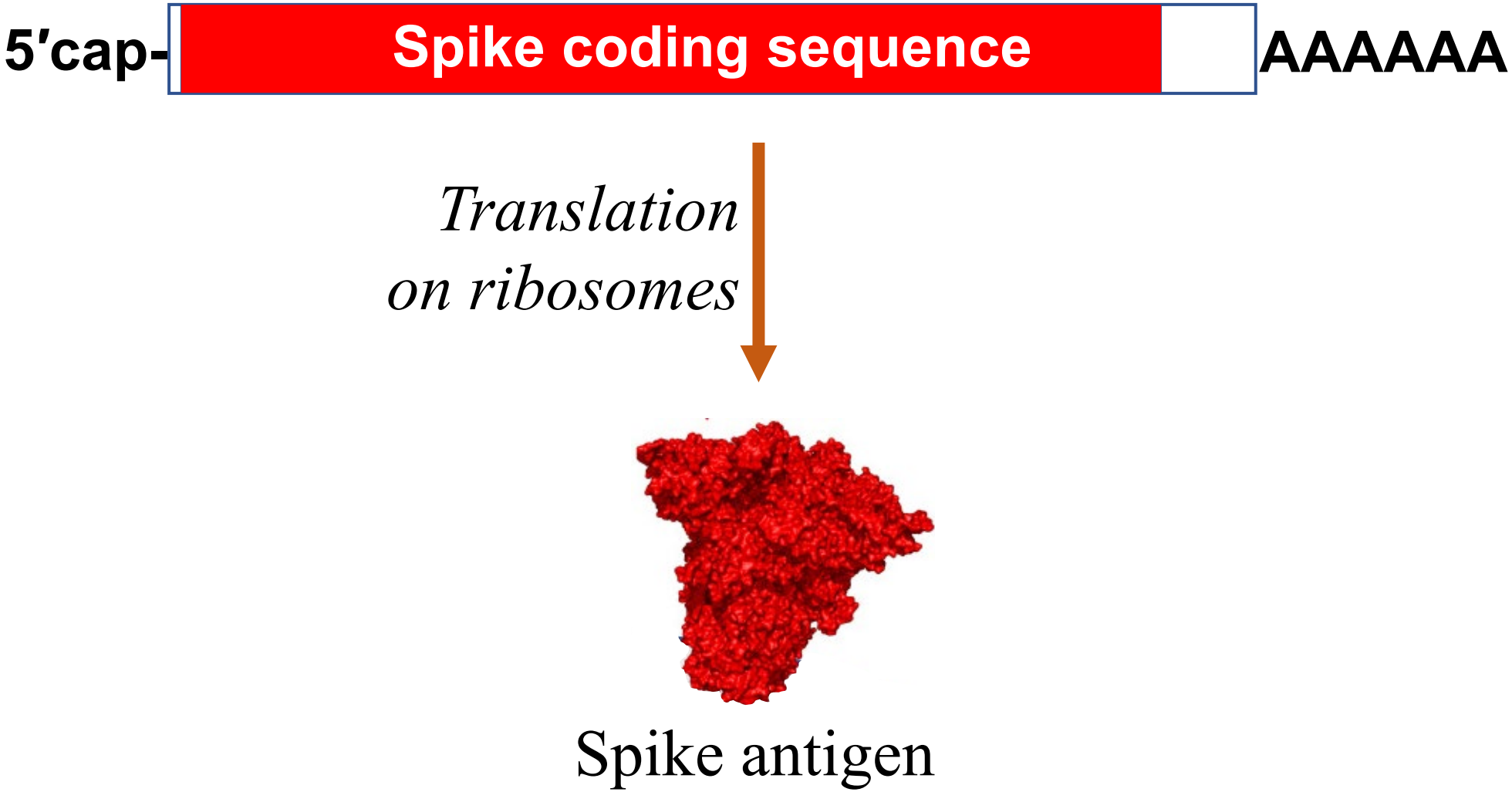


Spike antigen

Messenger RNA (mRNA) vaccine



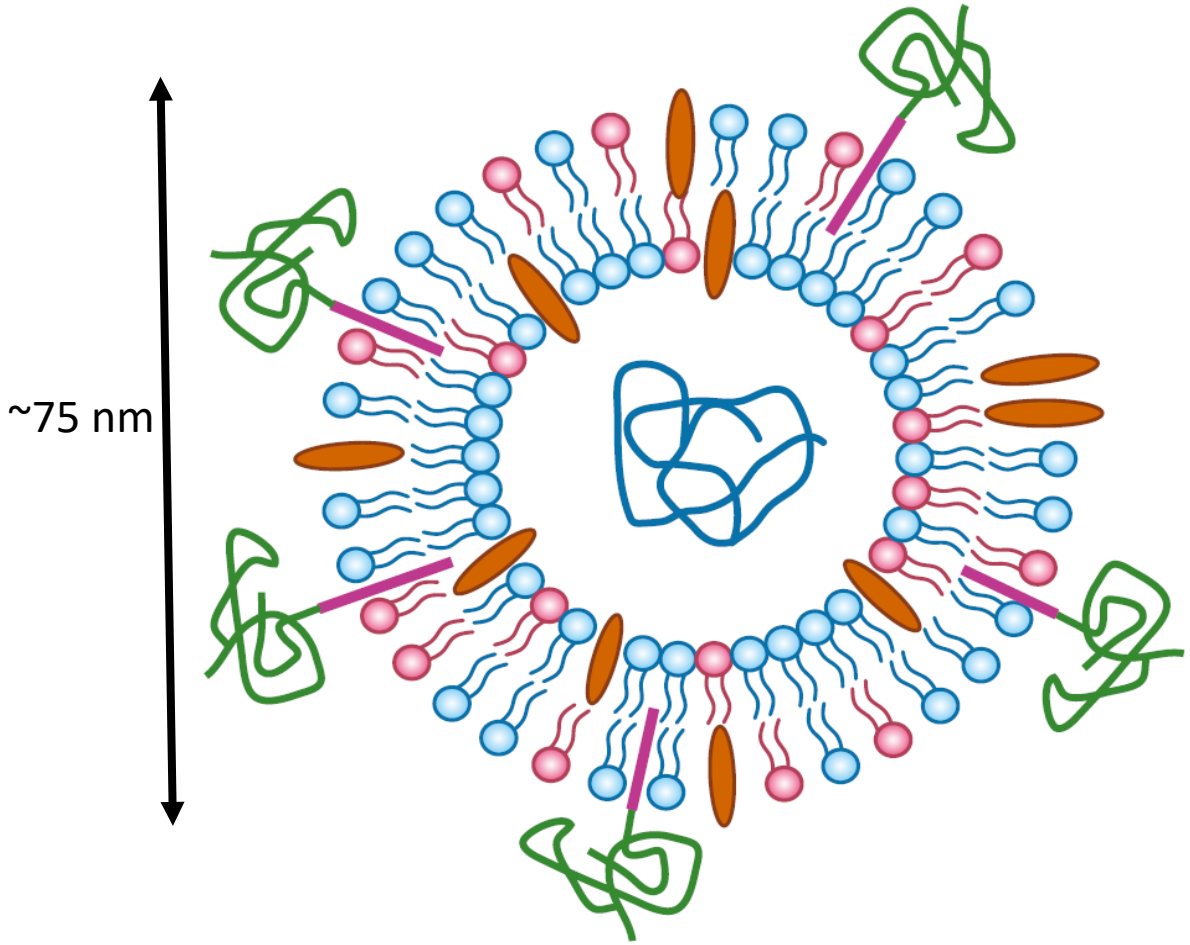
Messenger RNA (mRNA) vaccine

Translation on ribosomes

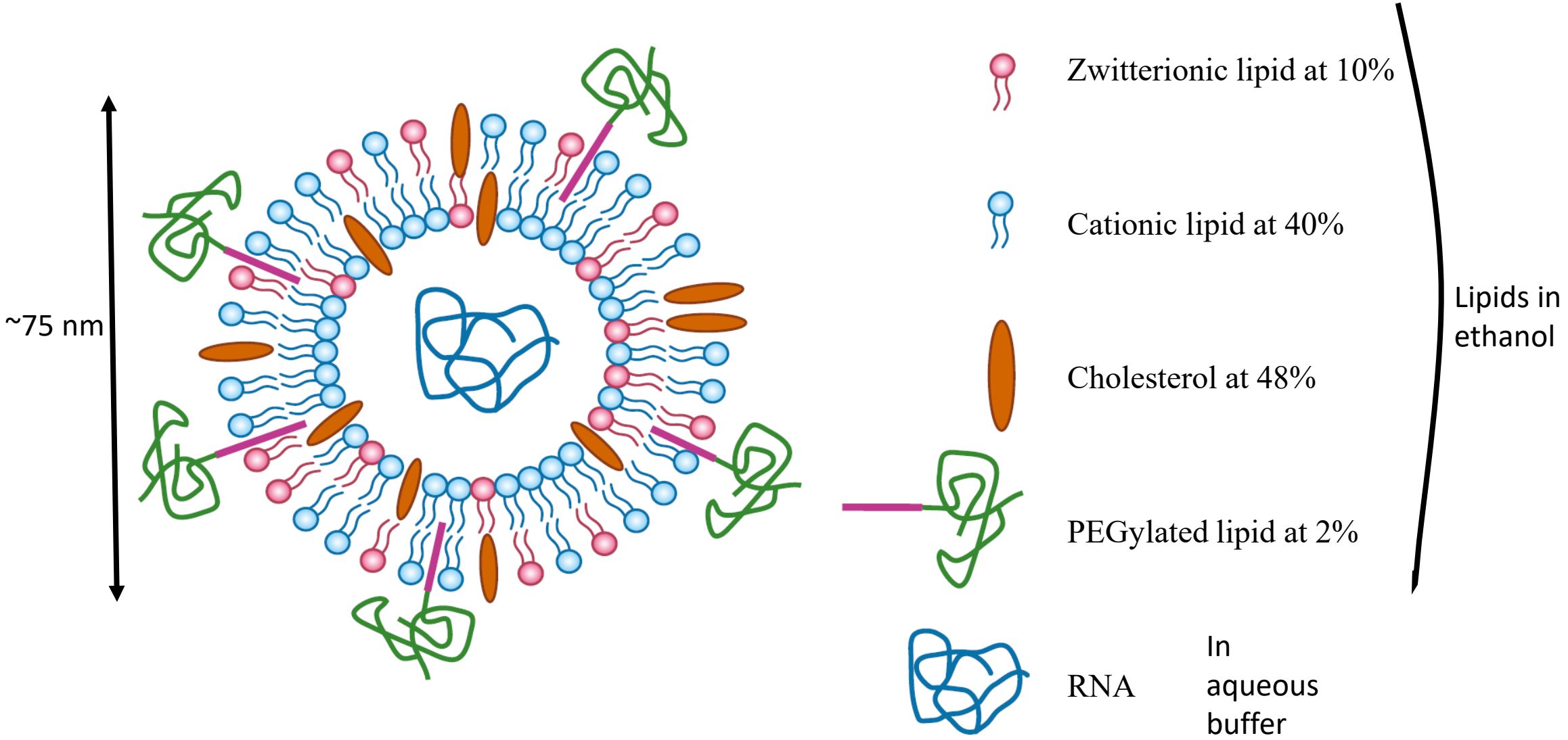
Spike antigen

A few of your cells become factories for producing the antigen!

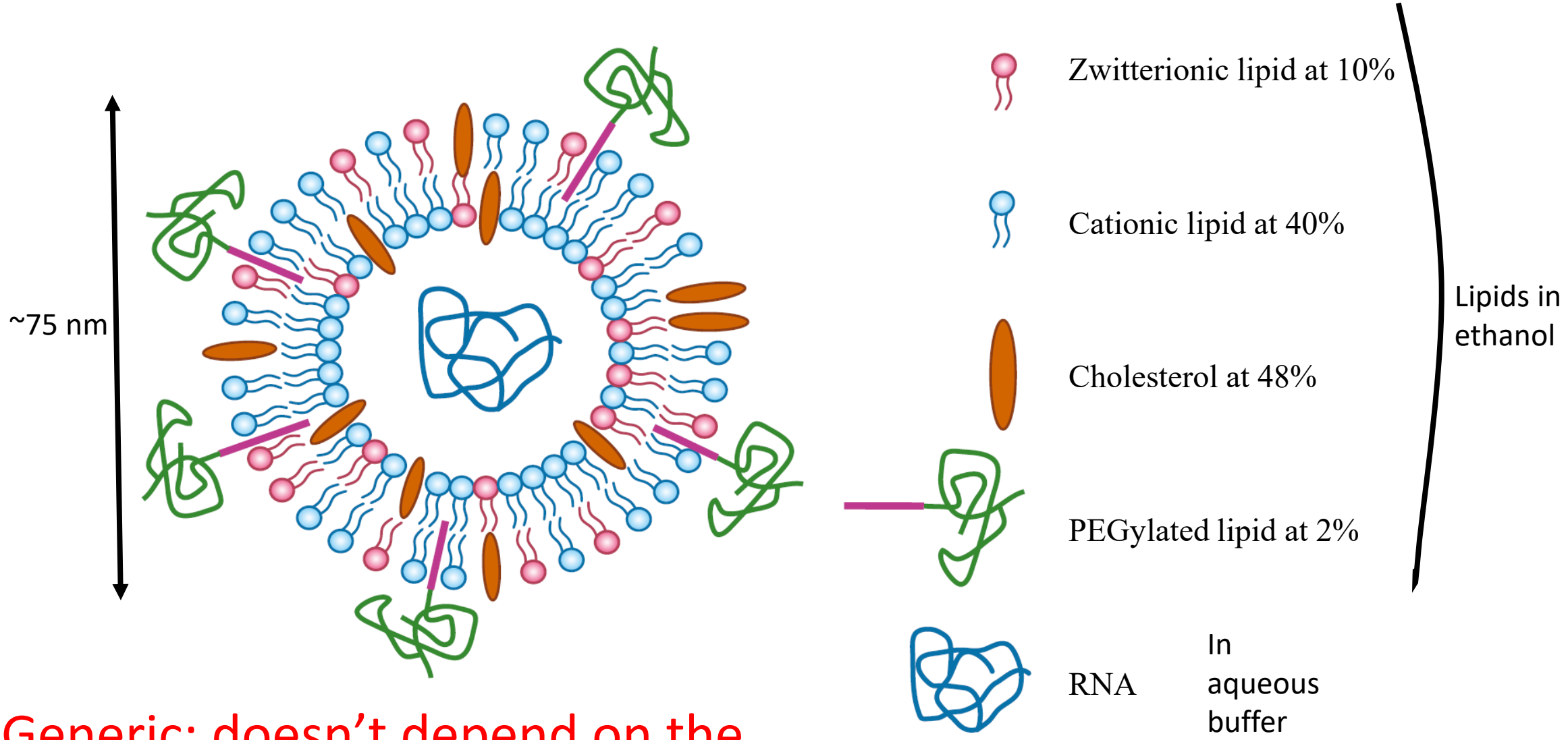
Lipid nanoparticle (LNP)



Lipid nanoparticle (LNP) manufacture

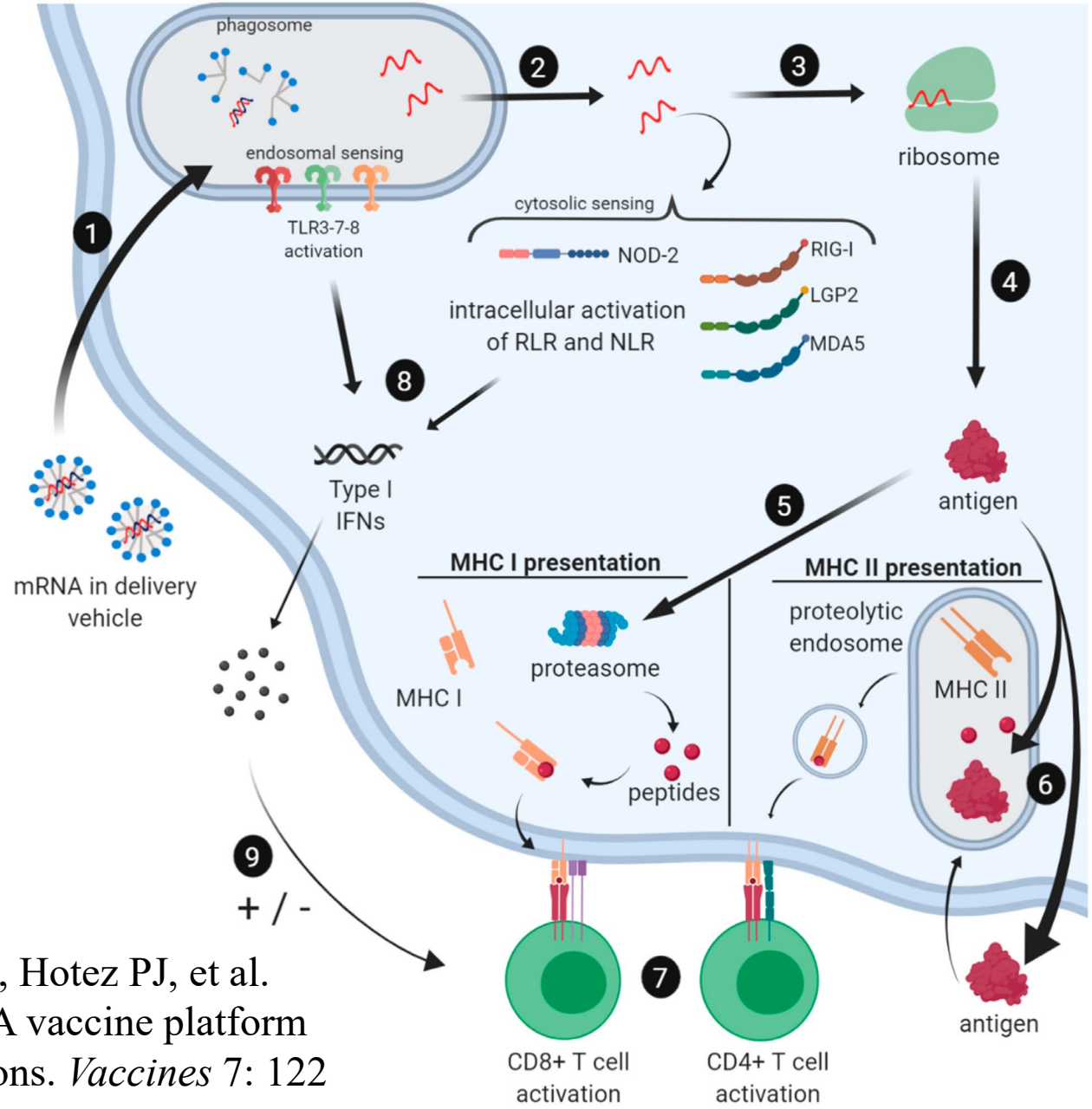


Lipid nanoparticle (LNP) manufacture



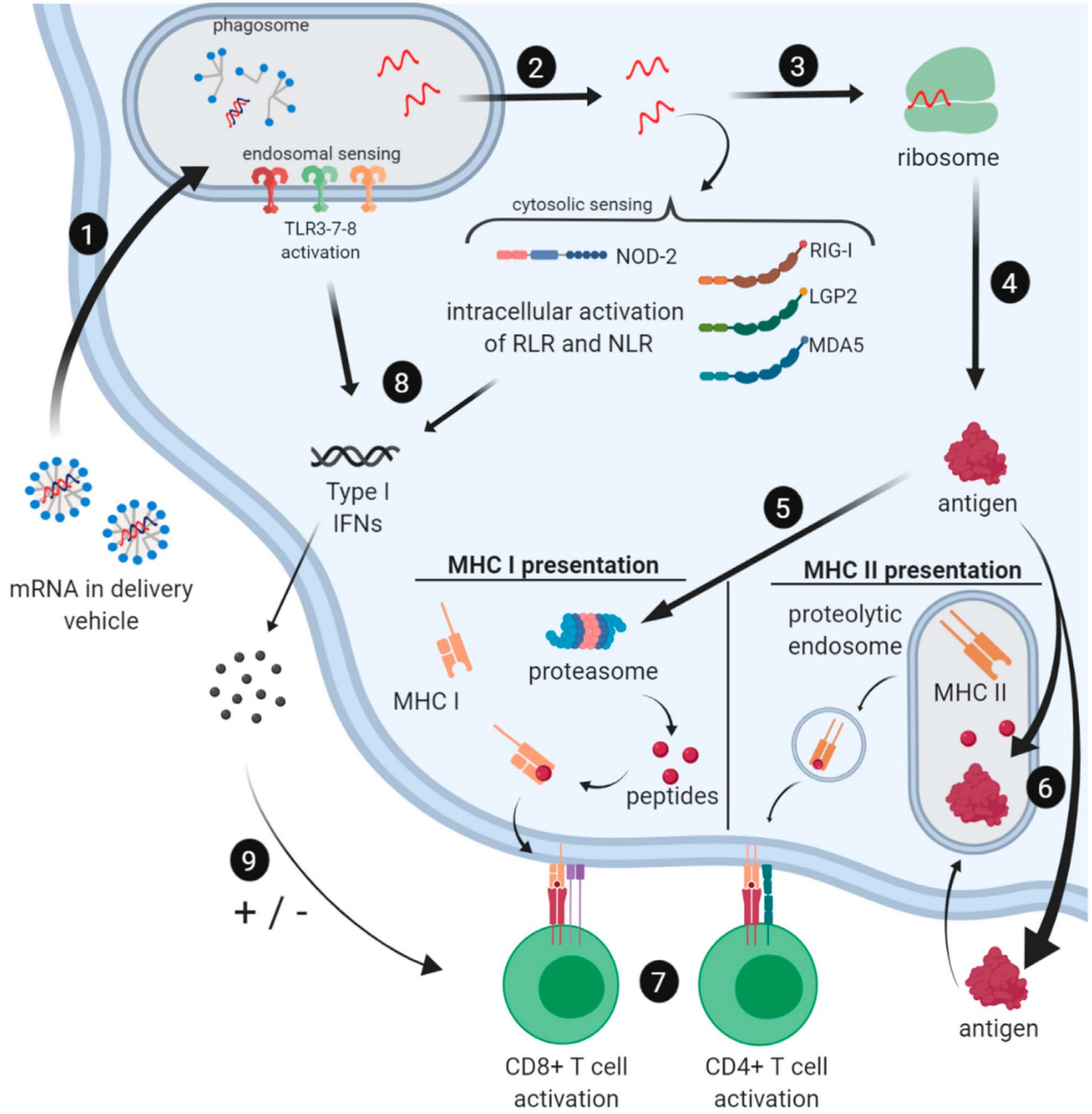
Generic: doesn't depend on the sequence of the RNA

Translation of the protein antigen



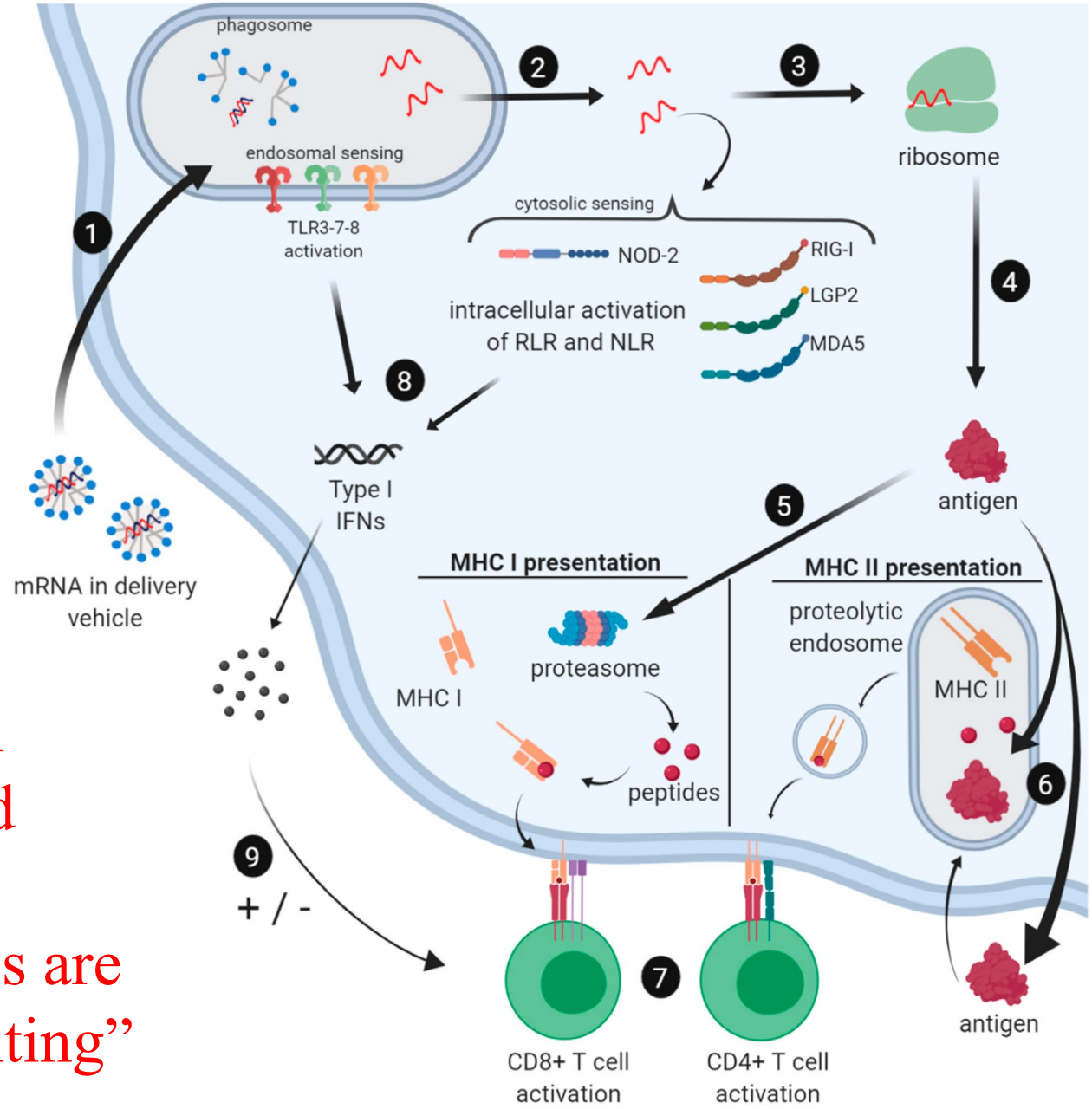
Versteeg L, Almutairi MM, Hotez PJ, et al. (2019) Enlisting the mRNA vaccine platform to combat parasitic infections. *Vaccines* 7: 122

Activation of the innate immune system



- Unlike adaptive immune system, not virus-specific, not induced by antigen
- Recognizes generic pathogen-associated molecular patterns
- Necessary for mobilizing the adaptive immune response

Activation of the innate immune system



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- Recognizes generic pathogen-associated molecular patterns
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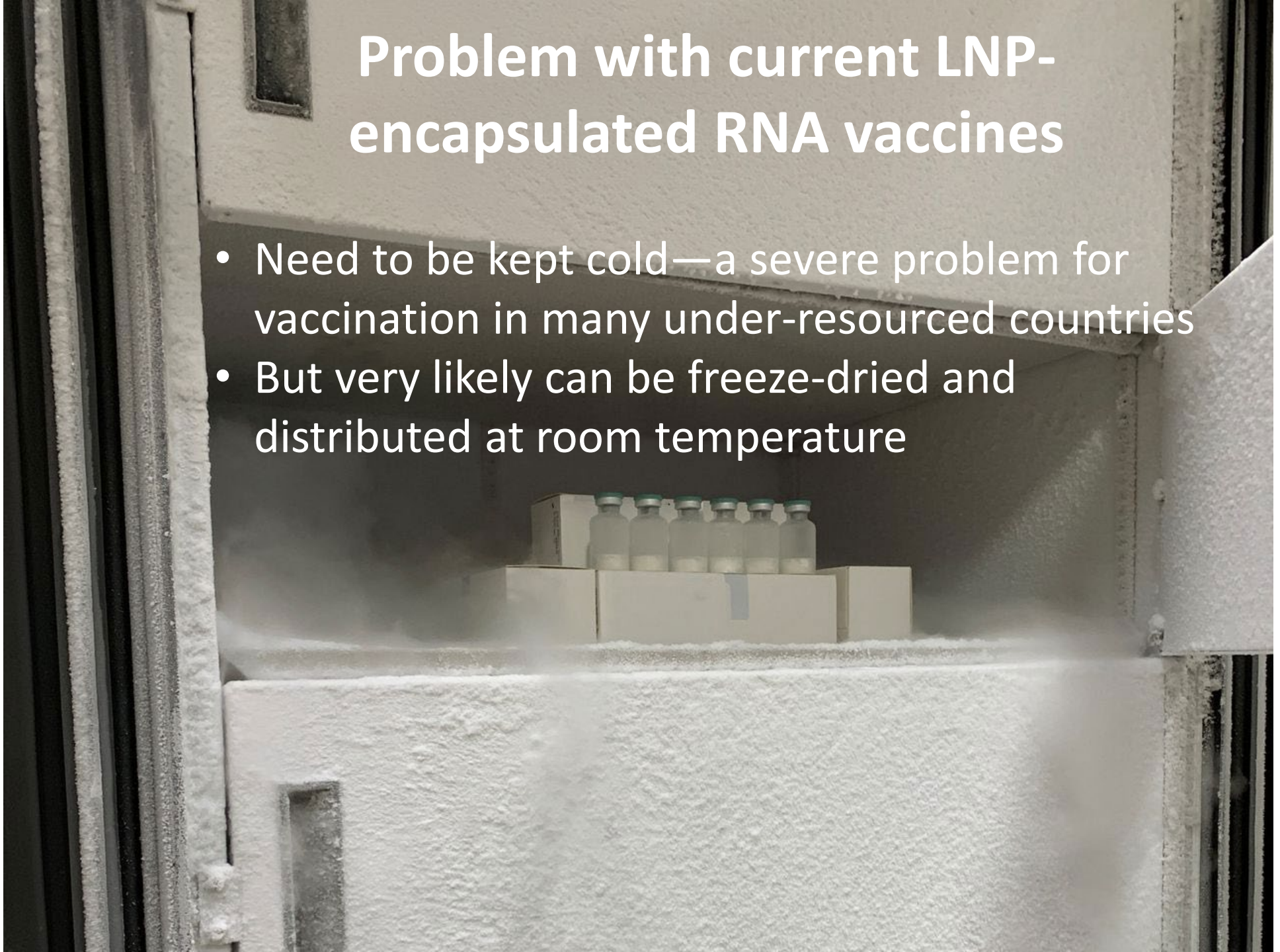
- Conventional vaccines need **adjuvants**
- RNA vaccines are "self-adjuvanting"

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 toxic 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

Problem with current LNP-encapsulated RNA vaccines

- Need to be kept cold—a severe problem for vaccination in many under-resourced countries
- But very likely can be freeze-dried and distributed at room temperature



Self-amplifying RNA vaccines

Alphavirus structural protein gene segments replaced with coronavirus Spike protein gene (untranslated)

Alphavirus replication gene segments (Venezuelan Equine Encephalitis Virus)

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**)

Self-amplifying RNA vaccines

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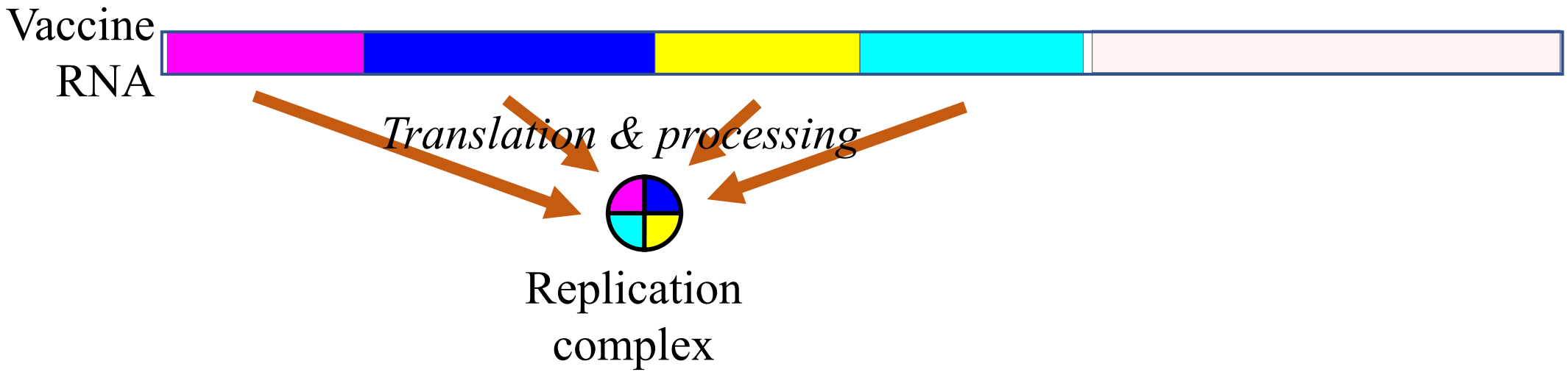

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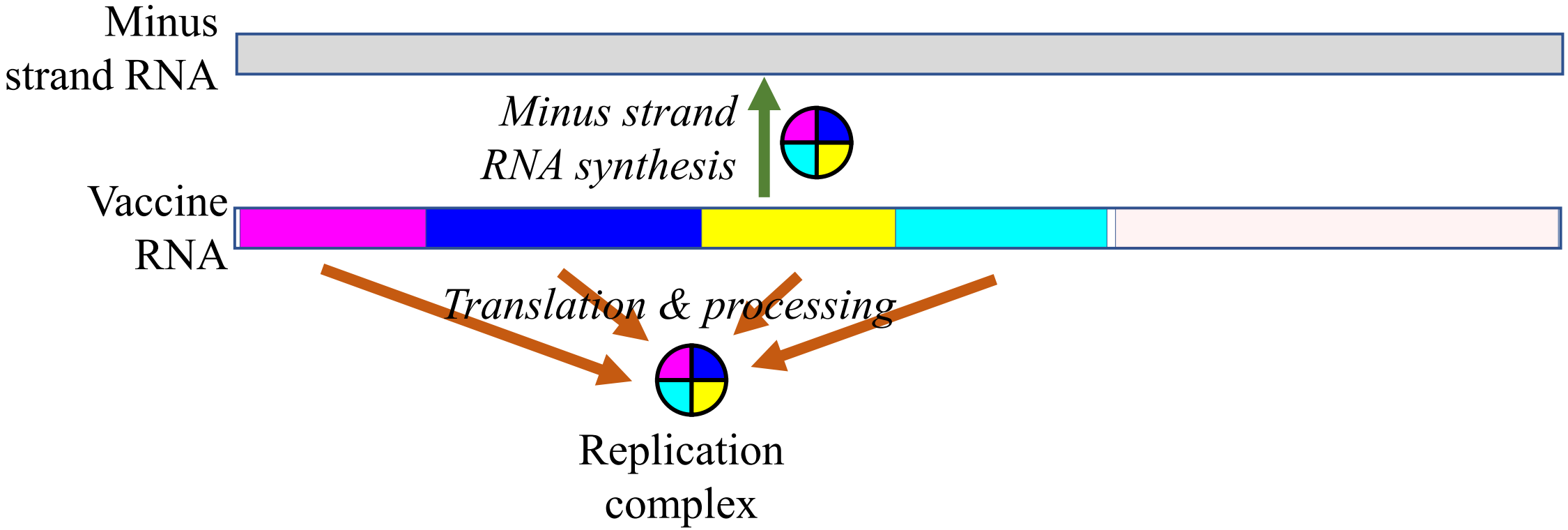

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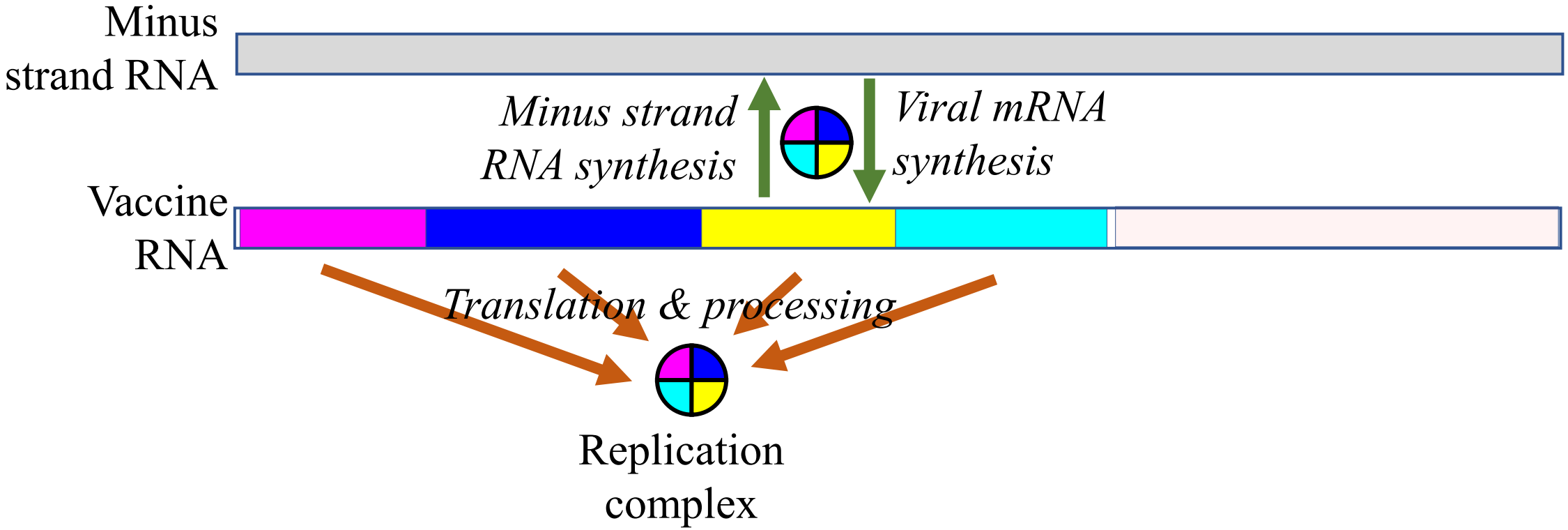

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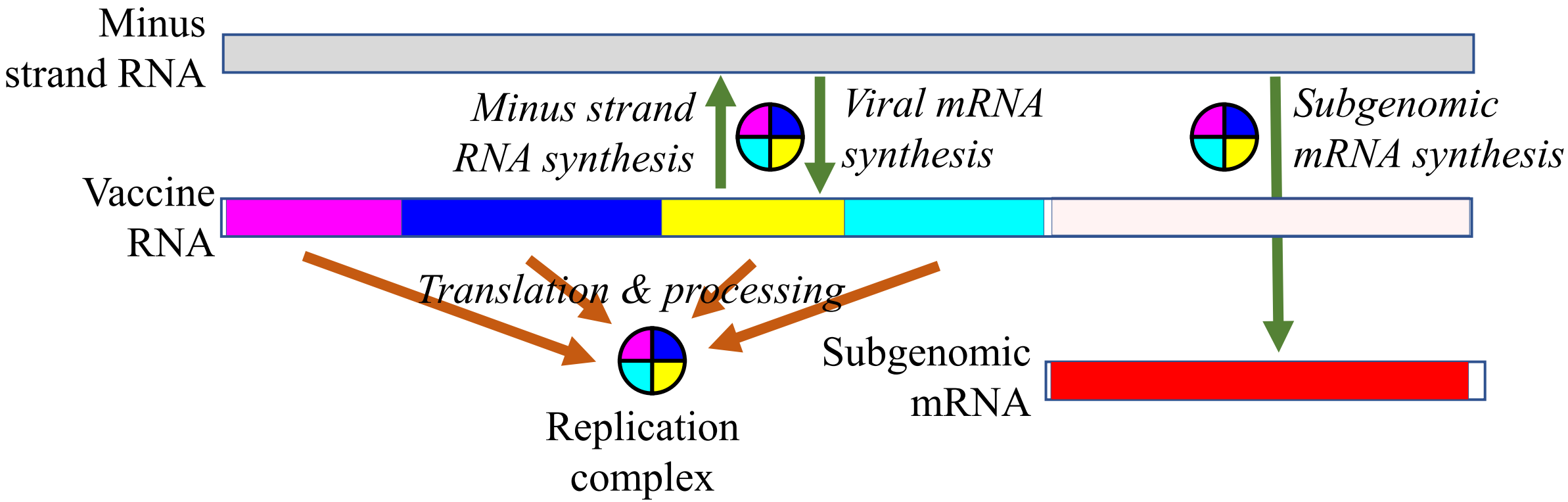

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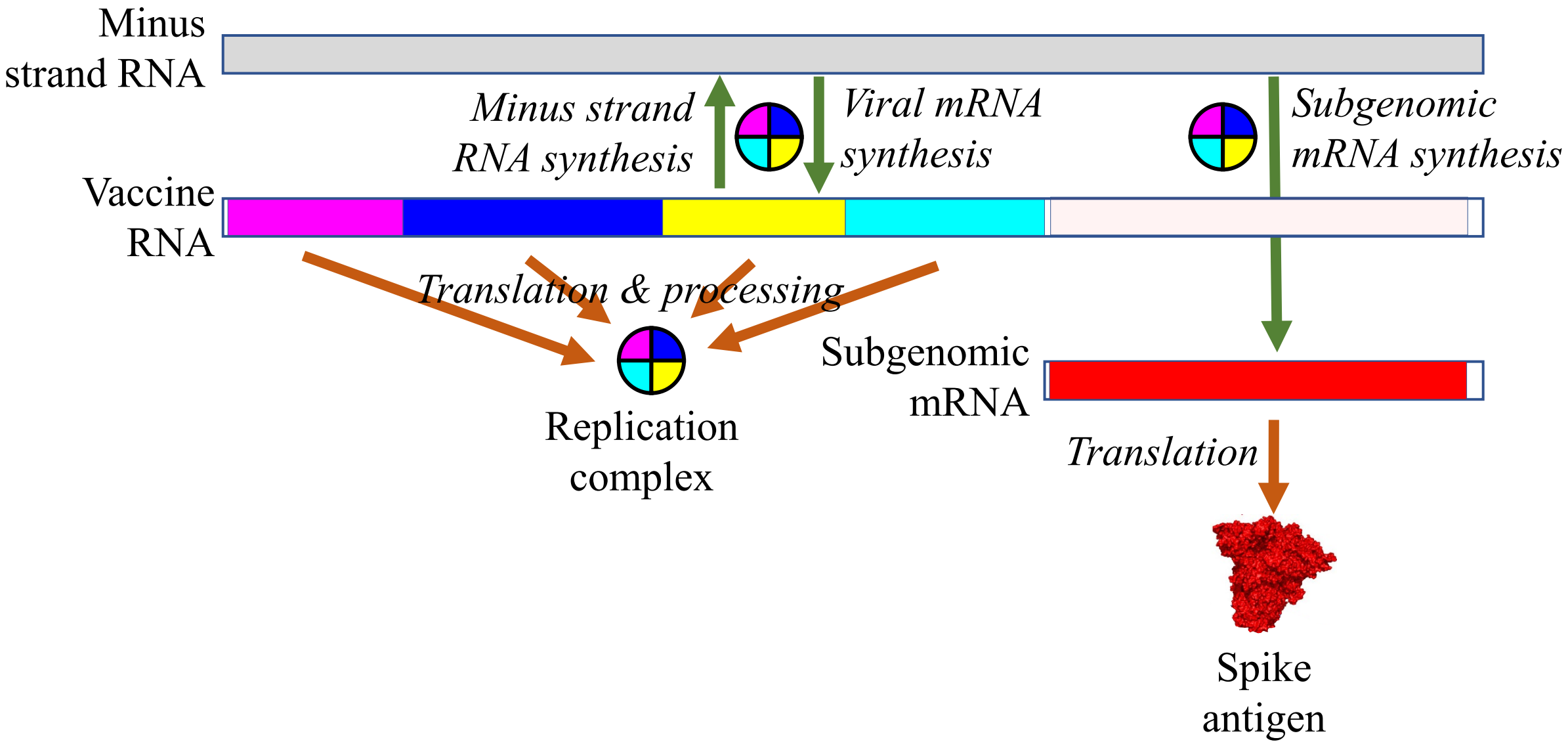

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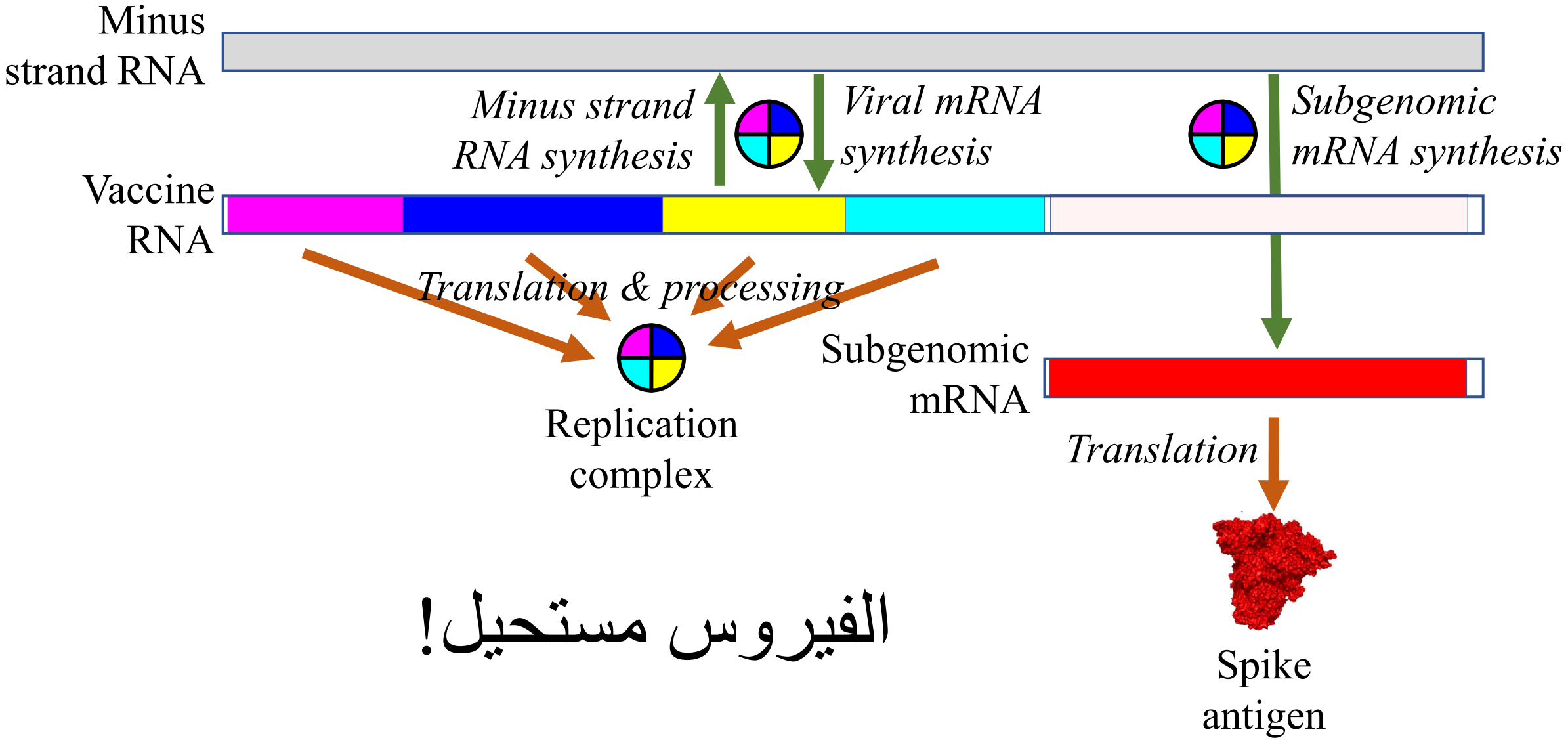
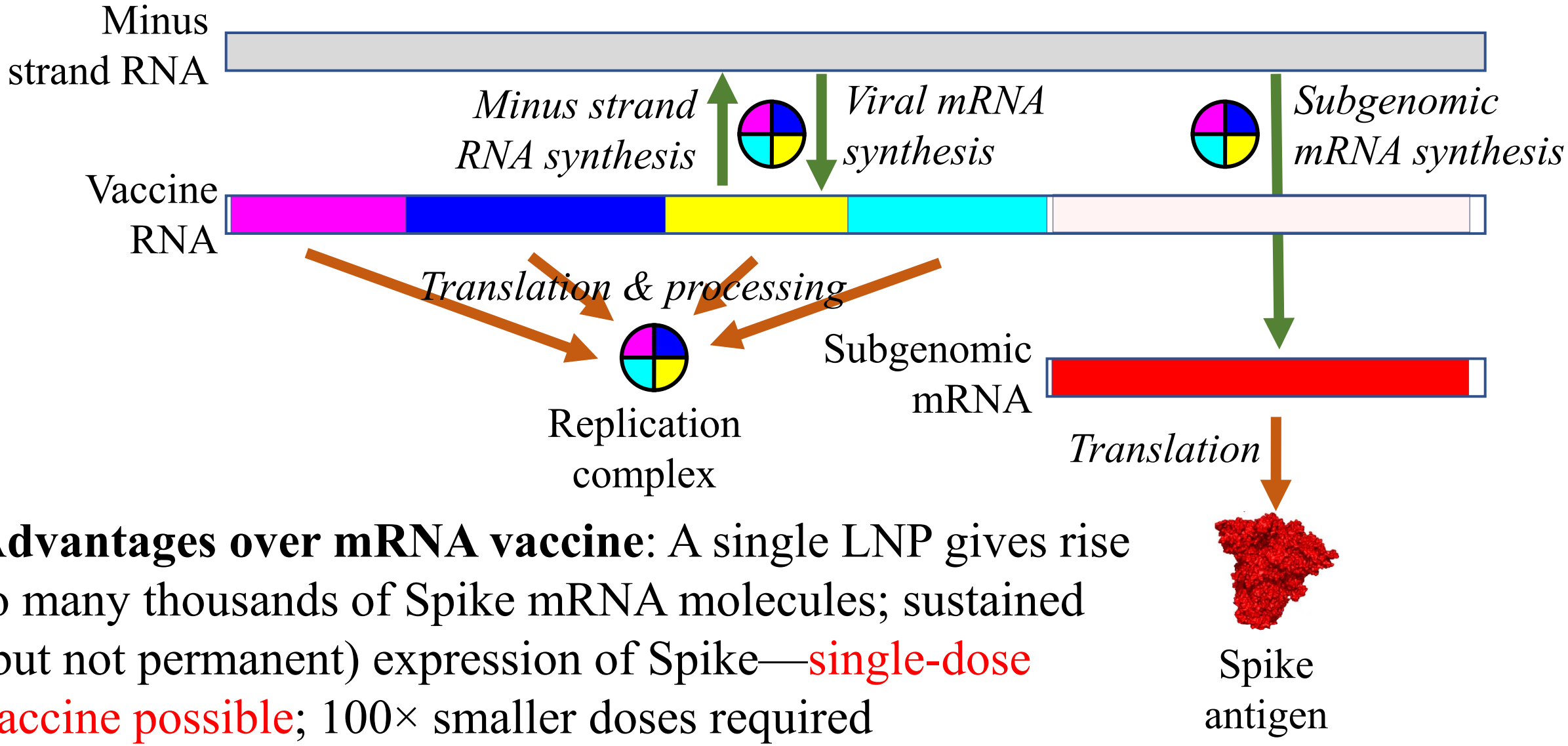


الفيروس مستحيل!

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

Potential problems with self-amplifying RNA vaccines

- Need to develop way to distribute at room temperature—as for non-self-amplifying mRNA vaccines
- Unlike non-self-amplifying RNA vaccines, potential for adaptive immune response against the vaccine itself—may not be indefinitely reusable

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

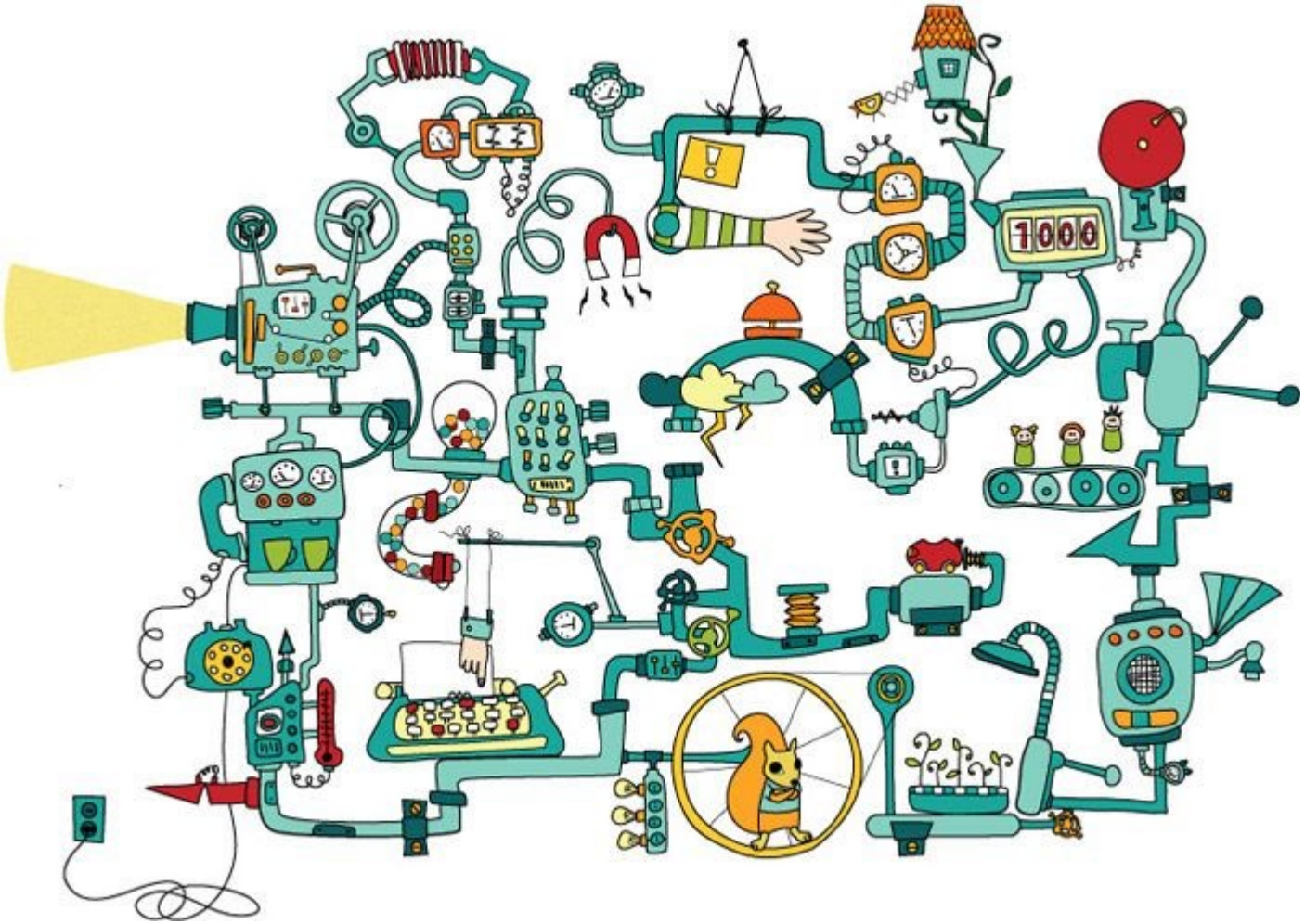
- **Discovery & technological innovation**
  - Exploratory science driven by curiosity & professional ambition
  - Overwhelmingly carried out in academic labs with public funding
  - Innovations (e.g., RNA vaccines) emerge unpredictably from global scientific communities, not individual researchers or research groups
- **Development**
  - Carried out by corporations driven by profit
  - Mostly final optimization and trials, not discovery & innovation
  - Privately financed with promise of government-granted patent monopolies
    - 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

Progress in creation of RNA vaccine for SARS CoV-2

- **Discovery & technological innovation**: (pretty much) finished by ~2000
- **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?
    - Are there generic safety issues?
    - Do they induce vigorous adaptive immunity to the target antigen (antibodies and immune cells)
      - Duration of adaptive immunity?
    - (self-amplifying RNA vaccines only) Does adaptive immunity to vaccine itself limit reusability?
  - SARS CoV-2-specific issues yet to be resolved (in human trials)
    - Are there safety issues for this specific target antigen?
    - Is vaccine-induced adaptive immunity actually protective?

Emergency vaccine development has been a

فوضی!



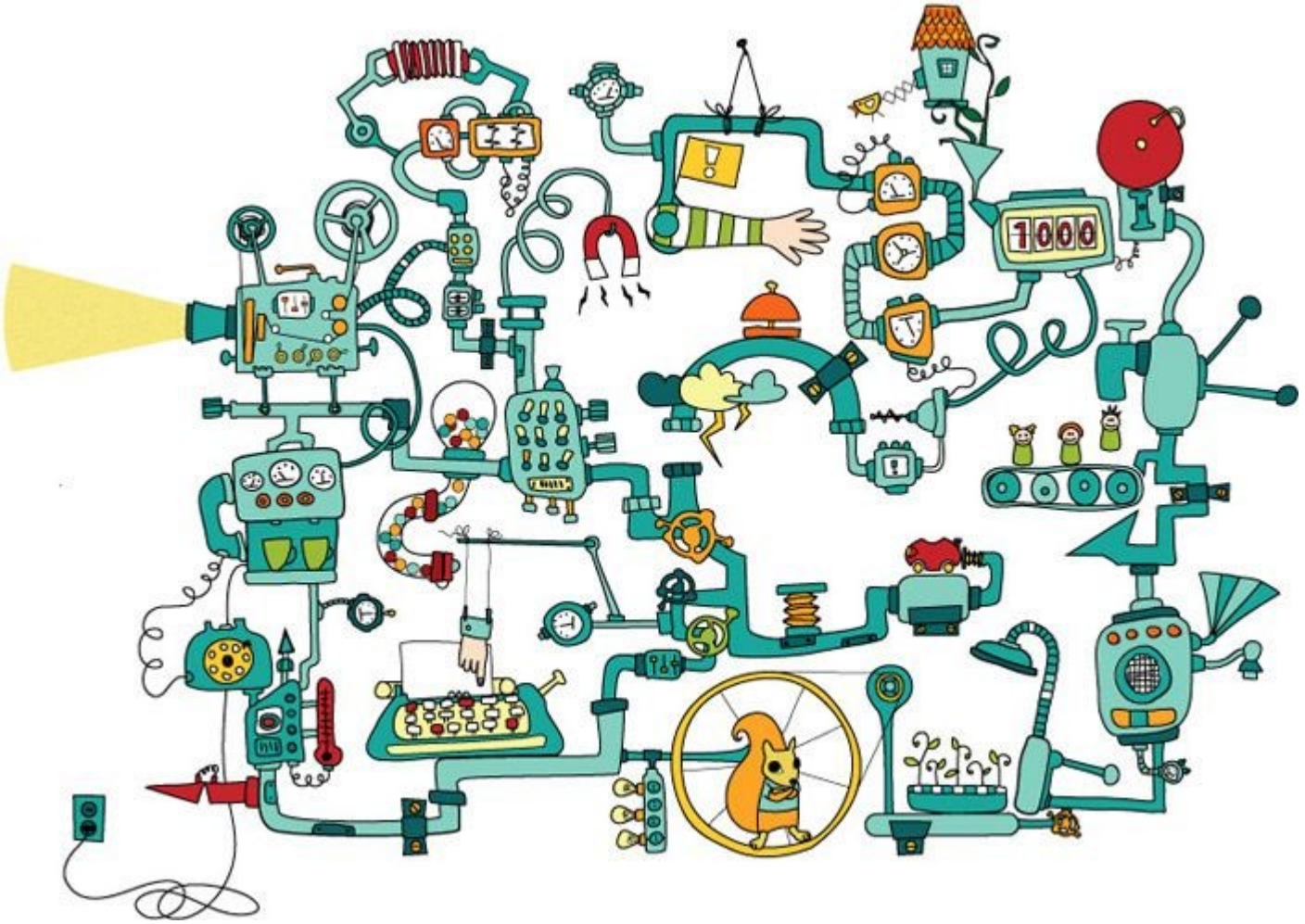
Not this kind of

فوضی!

Emergency vaccine development has been a

فوضی!

- RNA vaccine platforms were ready for development ~20 years ago!
- But no market incentive for generic development of these platforms in preparation for future pandemics
- 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
- Only slightly less chaotic response in other capitalist countries



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

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.

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

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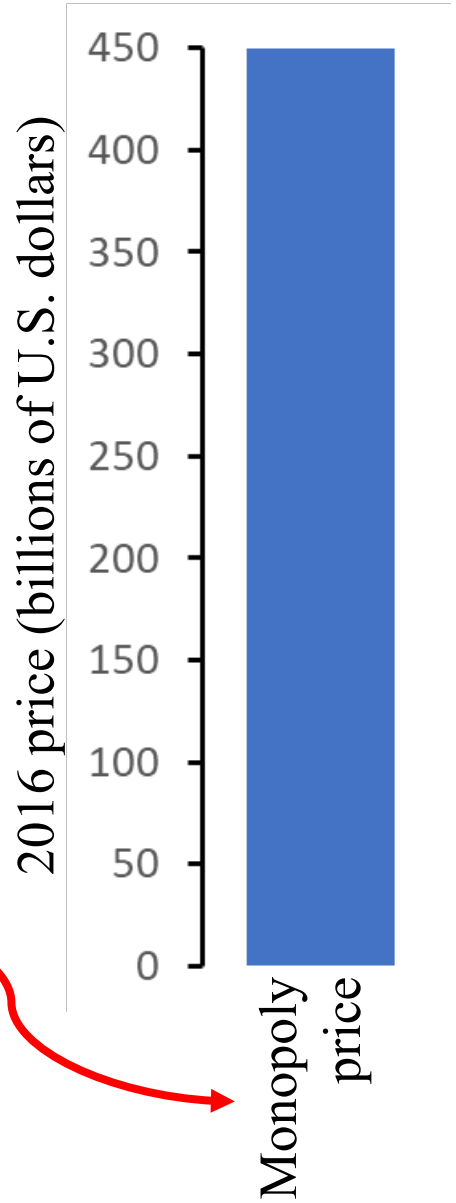

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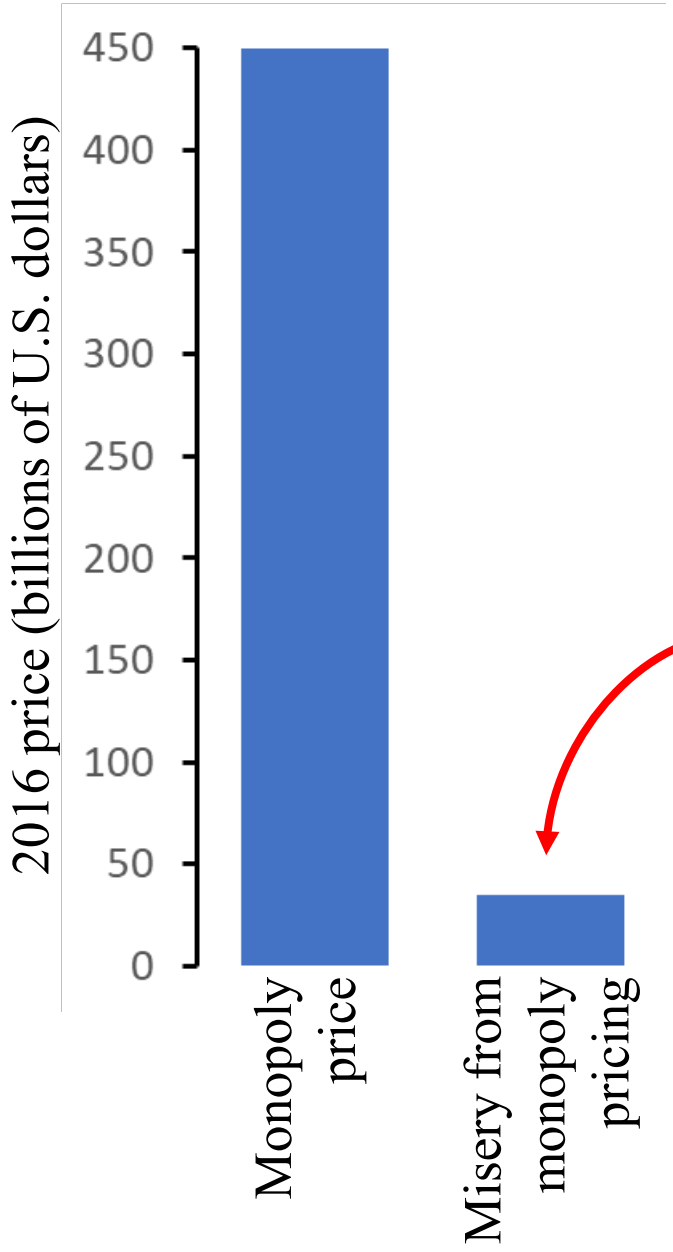
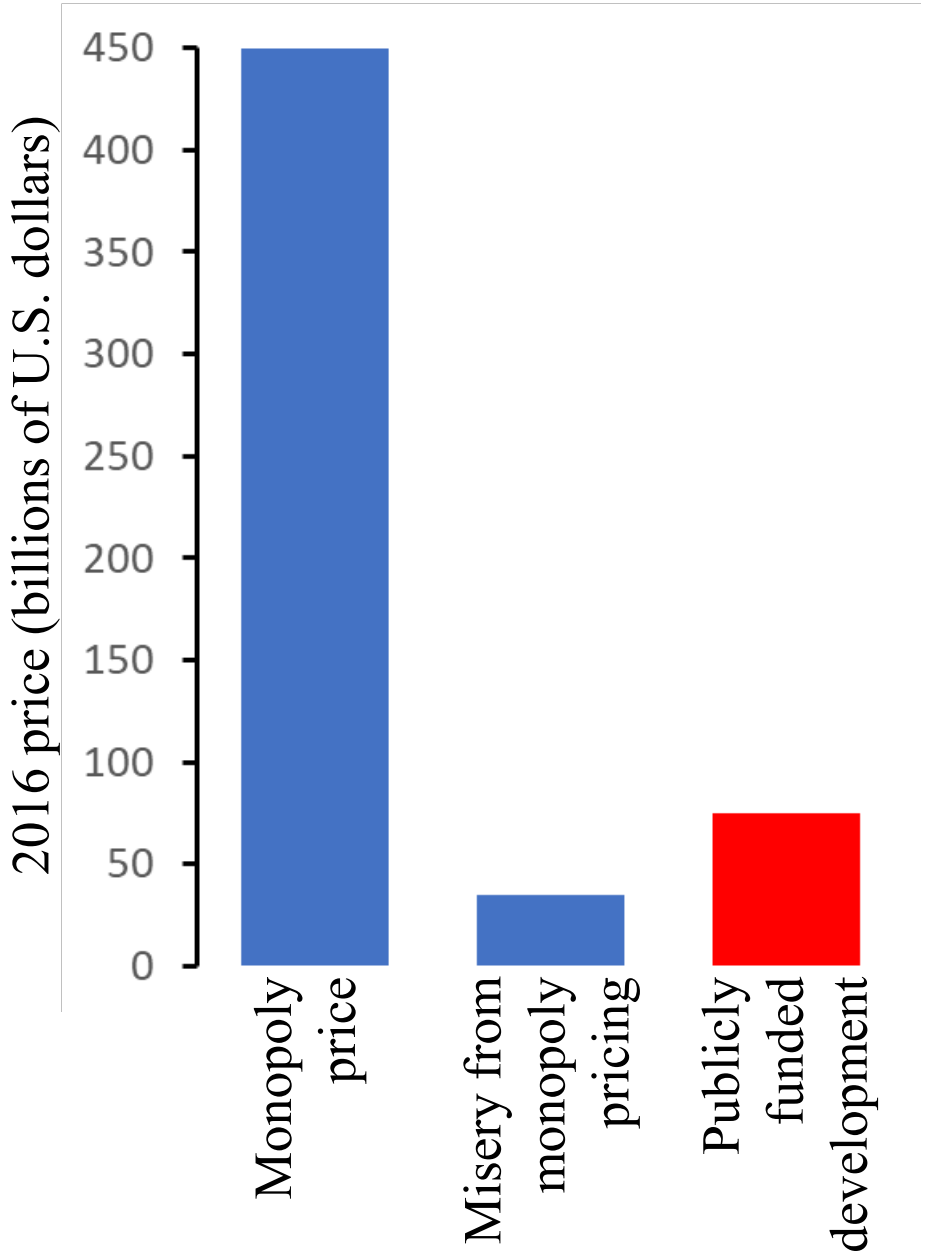


Some people couldn't afford monopoly price for the drugs that they needed, but that society was unwilling to pay for.

Public alternative to monopoly funding of drug development



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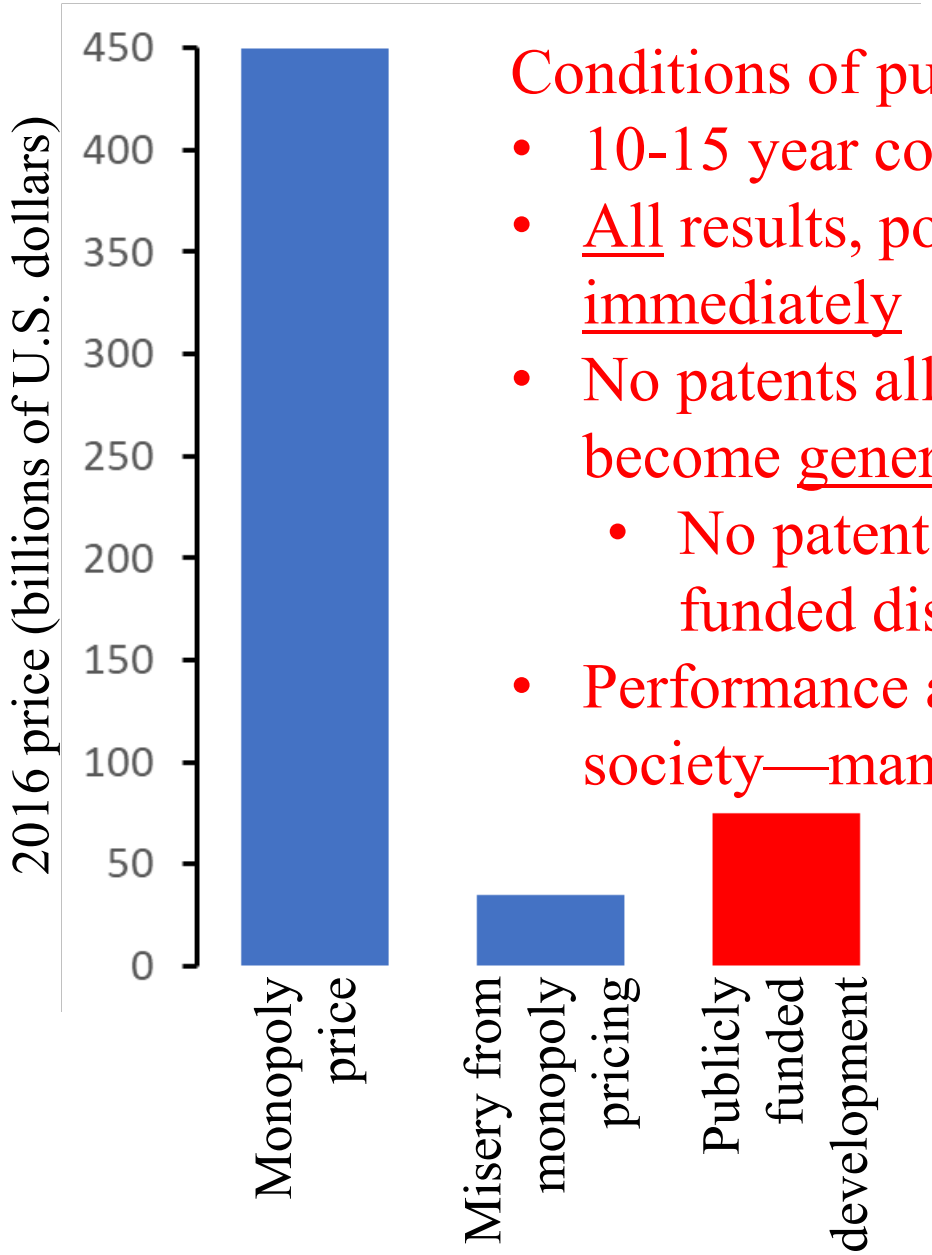
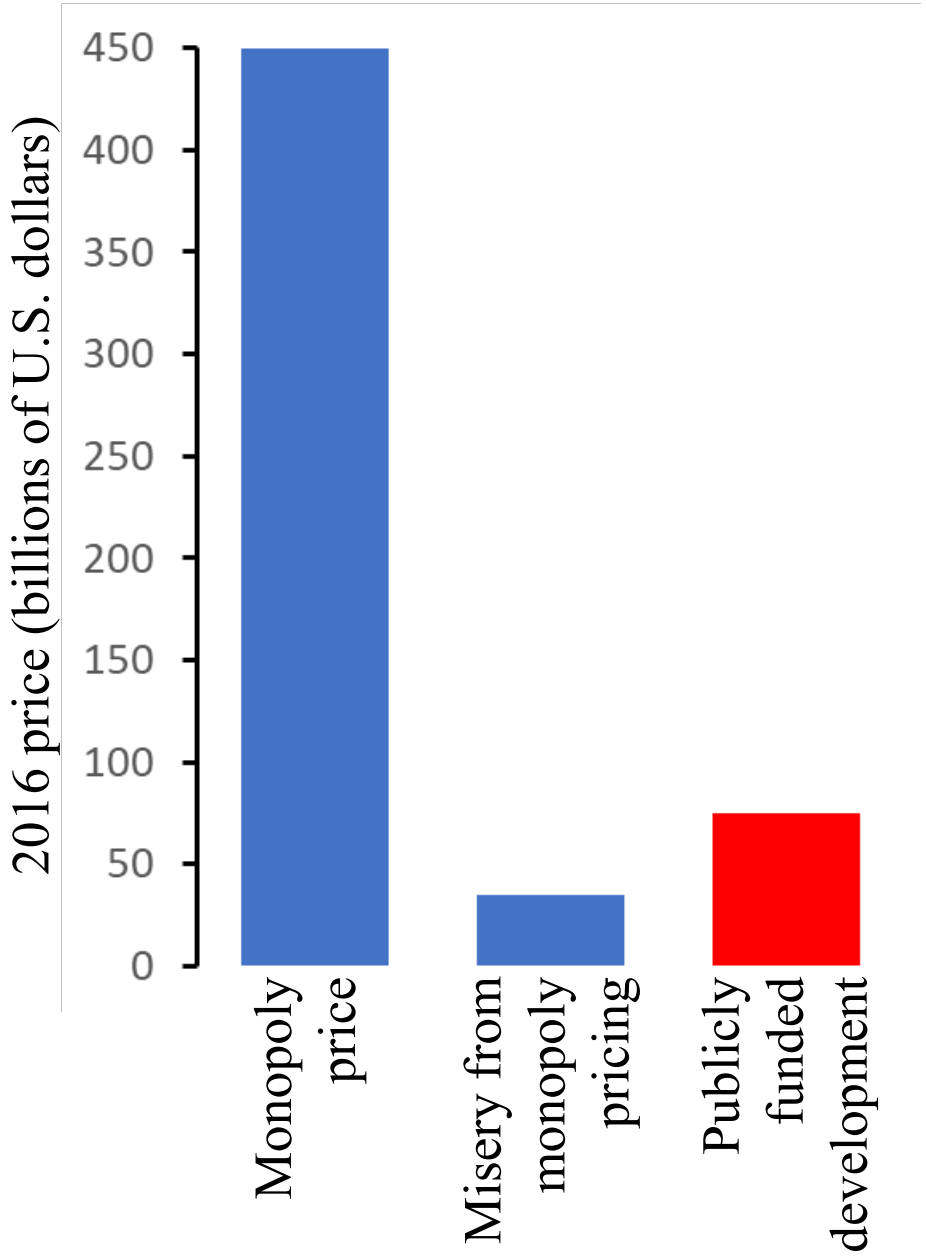


Conditions of public funding

- 10-15 year contracts in broad areas
- All results, positive & negative, 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

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)!

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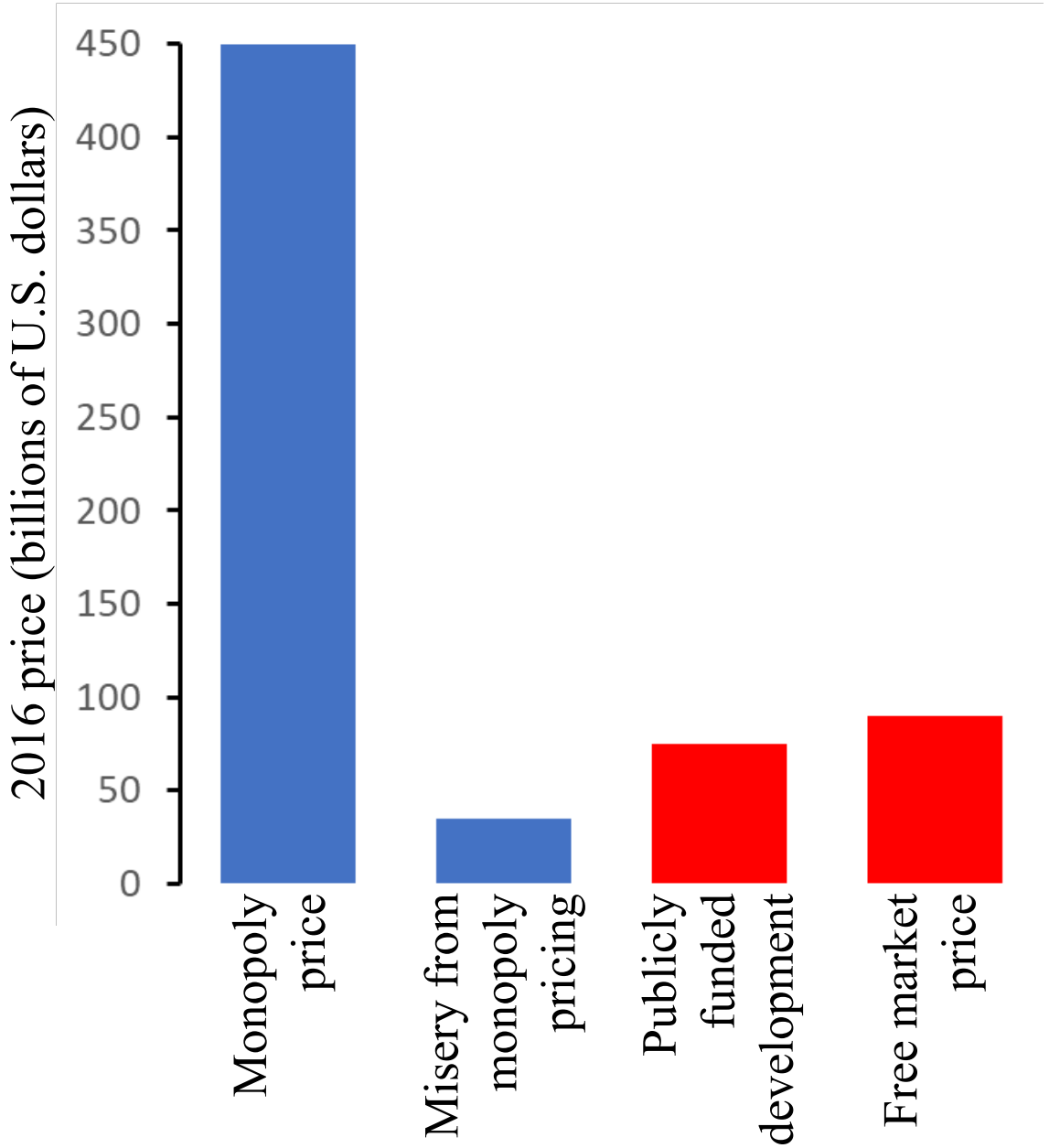

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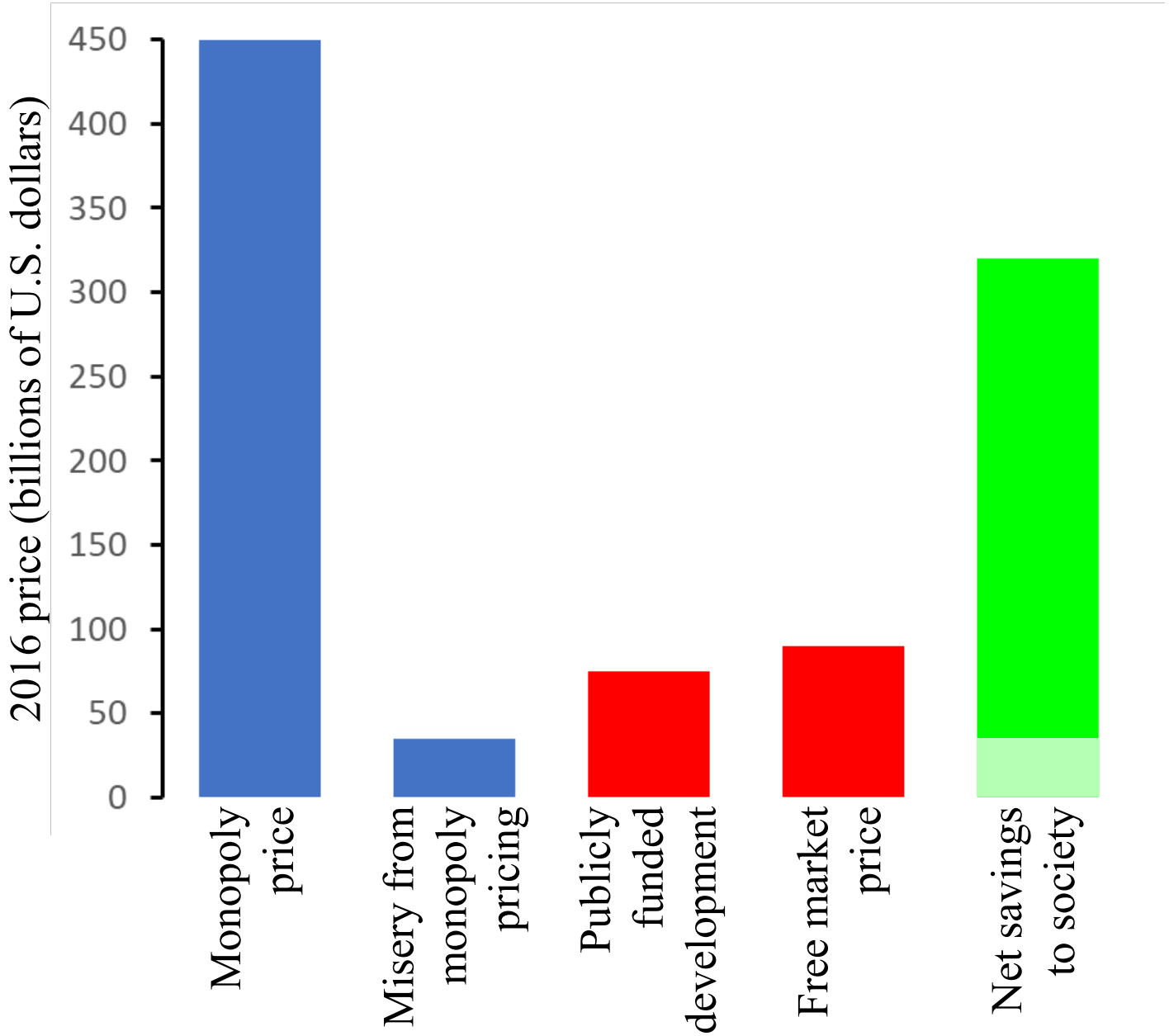

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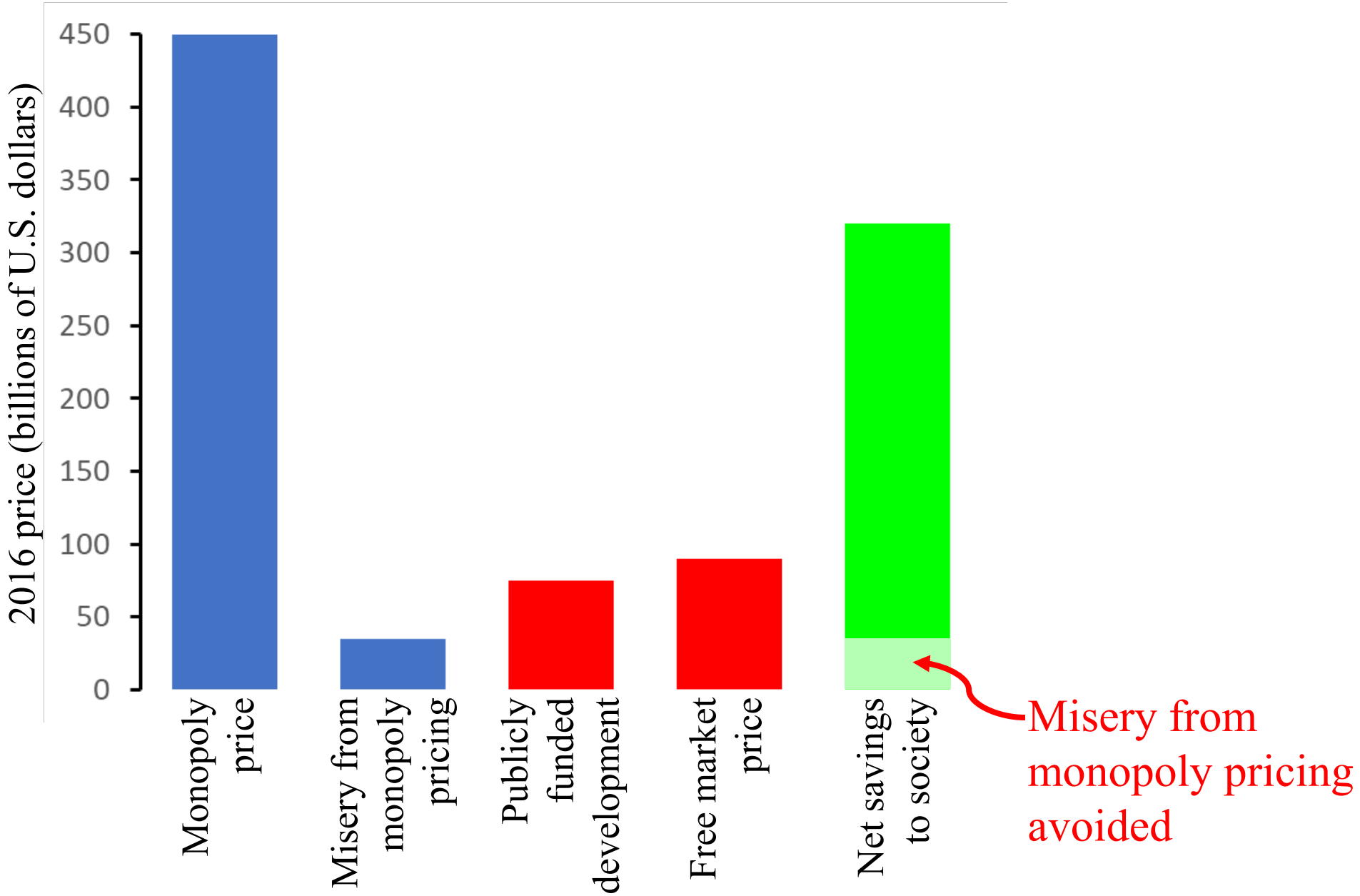

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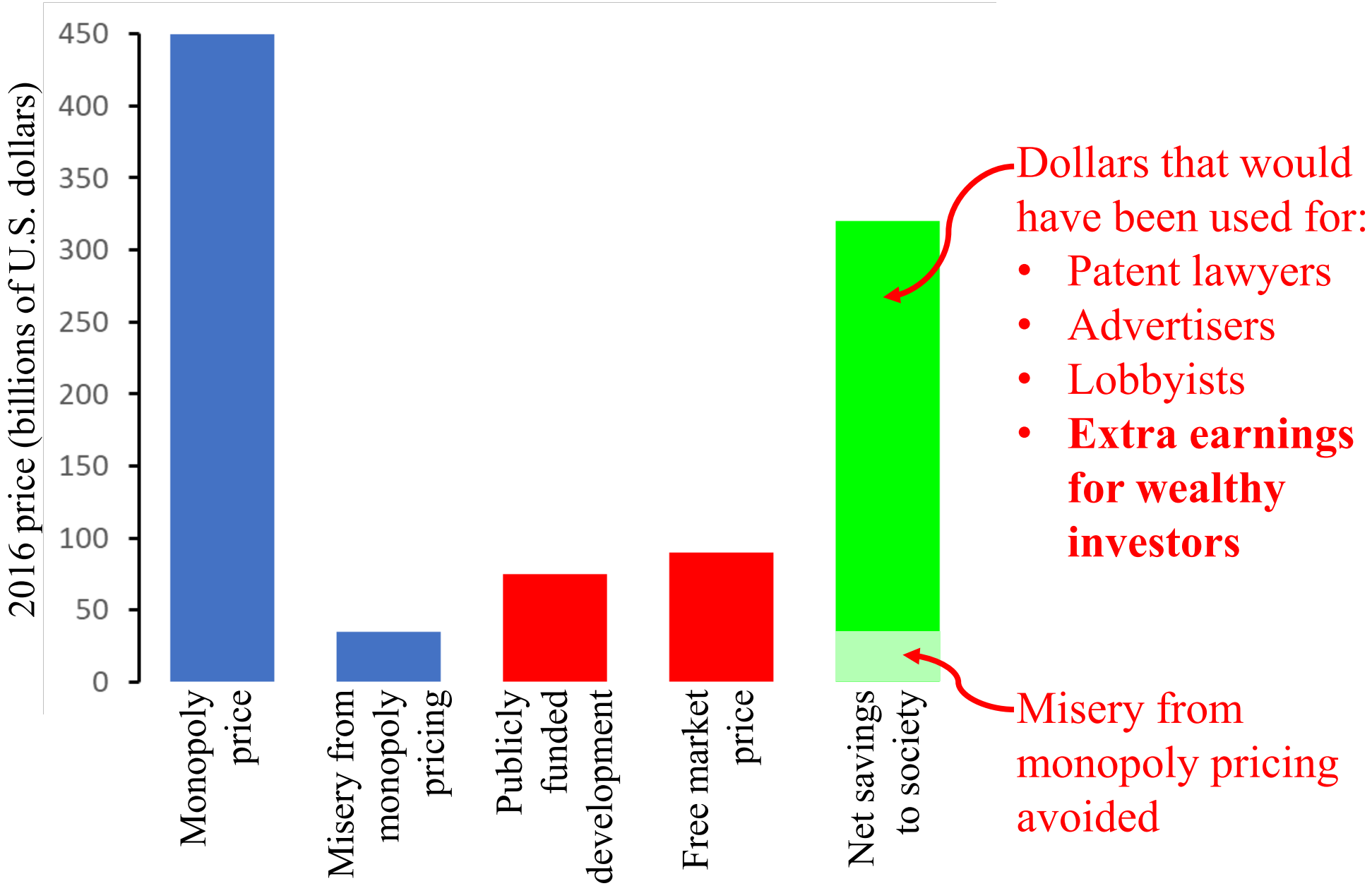

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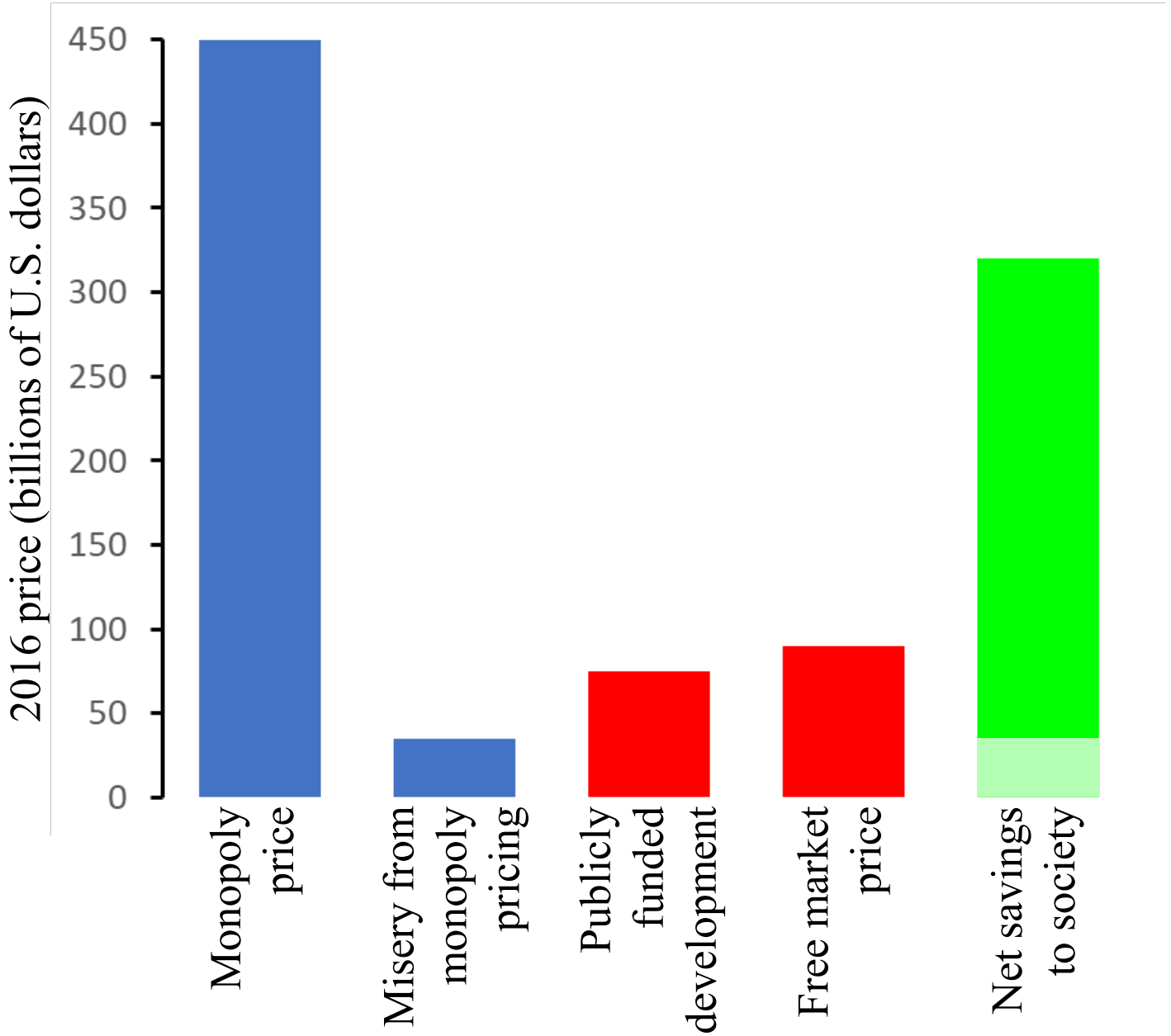

Modified from Dean Baker, Chapter 5 of *Rigged* (it's free)