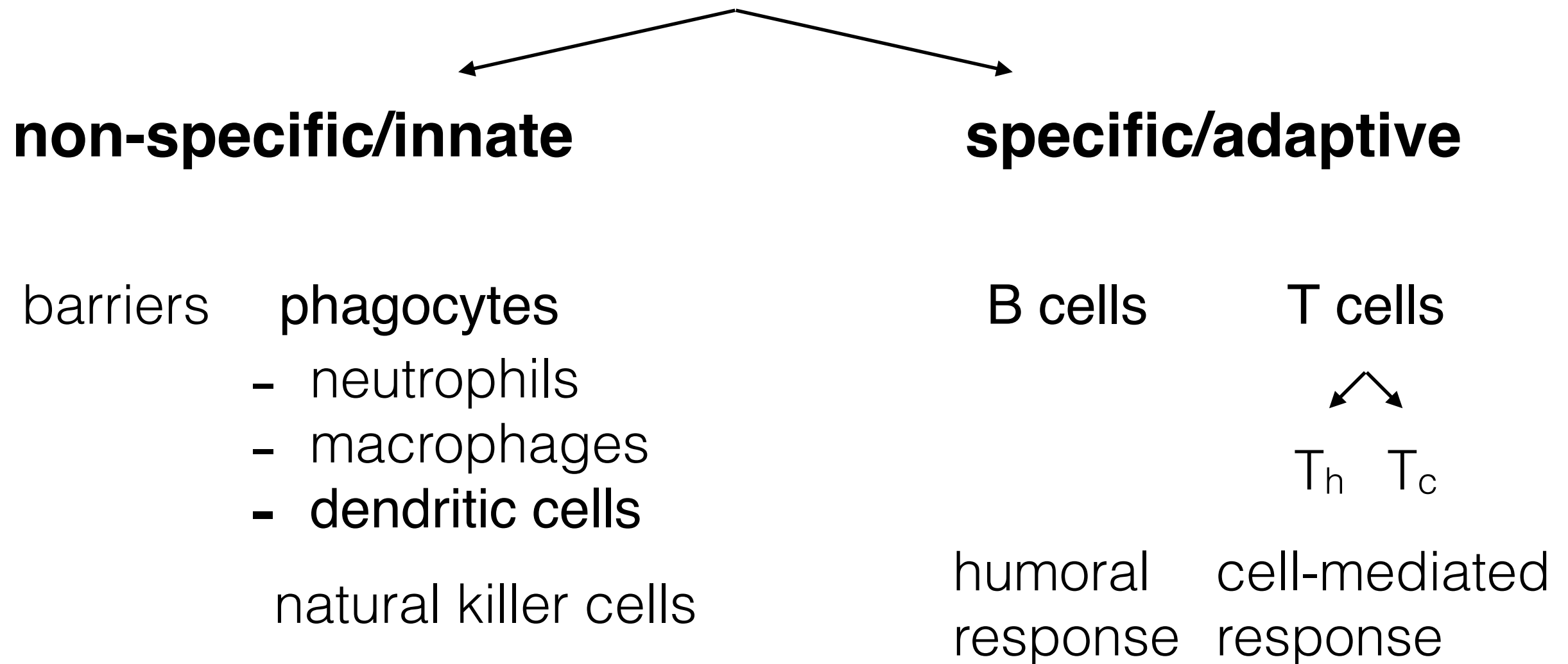


Vaccines and Immunity On Adjuvants, Antibodies, and Herd Immunity

Aliaa Barakat, PhD

October 7, 2020

Innate and Adaptive Immunity





INNATE

ADAPTIVE



Immunology Basics: Essential Information in the Time of COVID-19

<https://www.ildcollaborative.org/covid-19/immunology-primer>

Milestones | 28 September 2020

Nature Milestones in Vaccines

Animation

Vaccines 101: How vaccines work

Vaccines function by safely triggering the kind of immune response that would occur following infection with a pathogen such as a virus or bacterium. This animation takes us through the cellular events that occur from the introduction of the vaccine into the body to the development of immunological memory and the protection that vaccines can offer to the wider population via herd immunity.

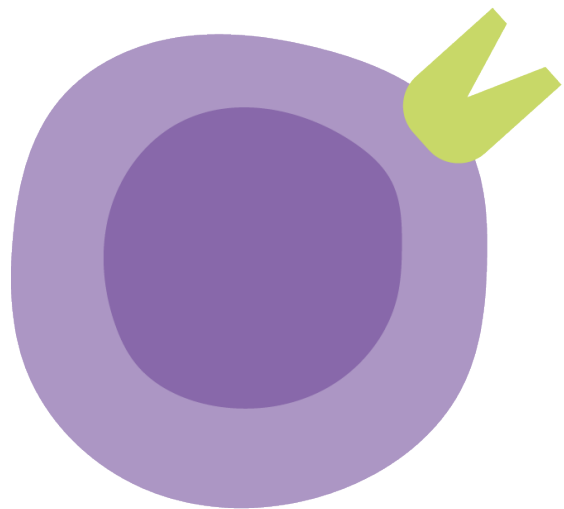
Nature Milestones in Vaccines

<https://www.nature.com/immersive/d42859-020-00005-8>

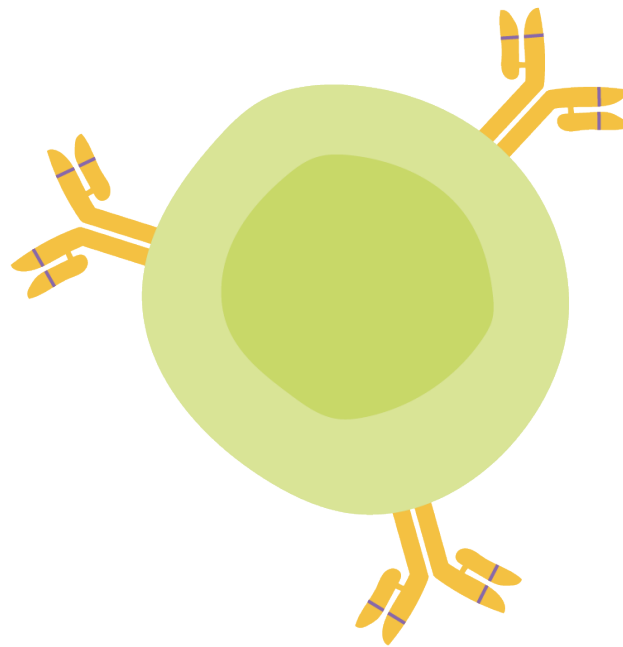
How Vaccines Work



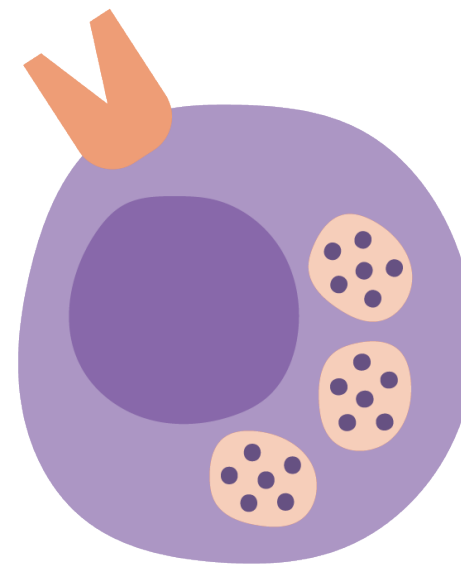
Vaccines train the immune system.



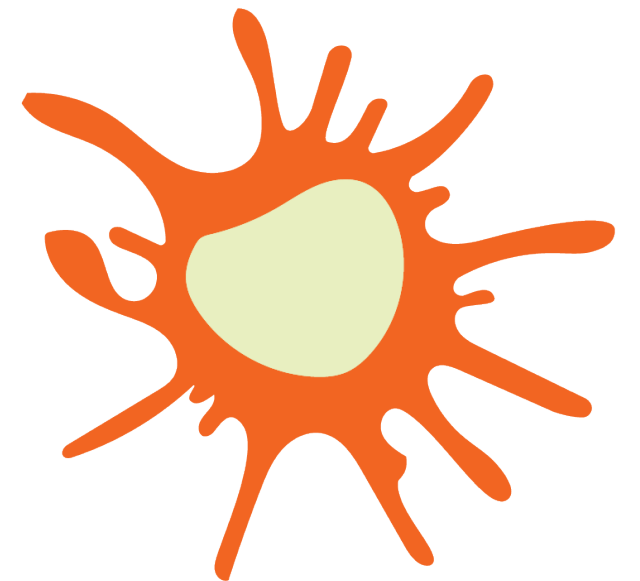
Helper T cell



B cell



Killer T cell

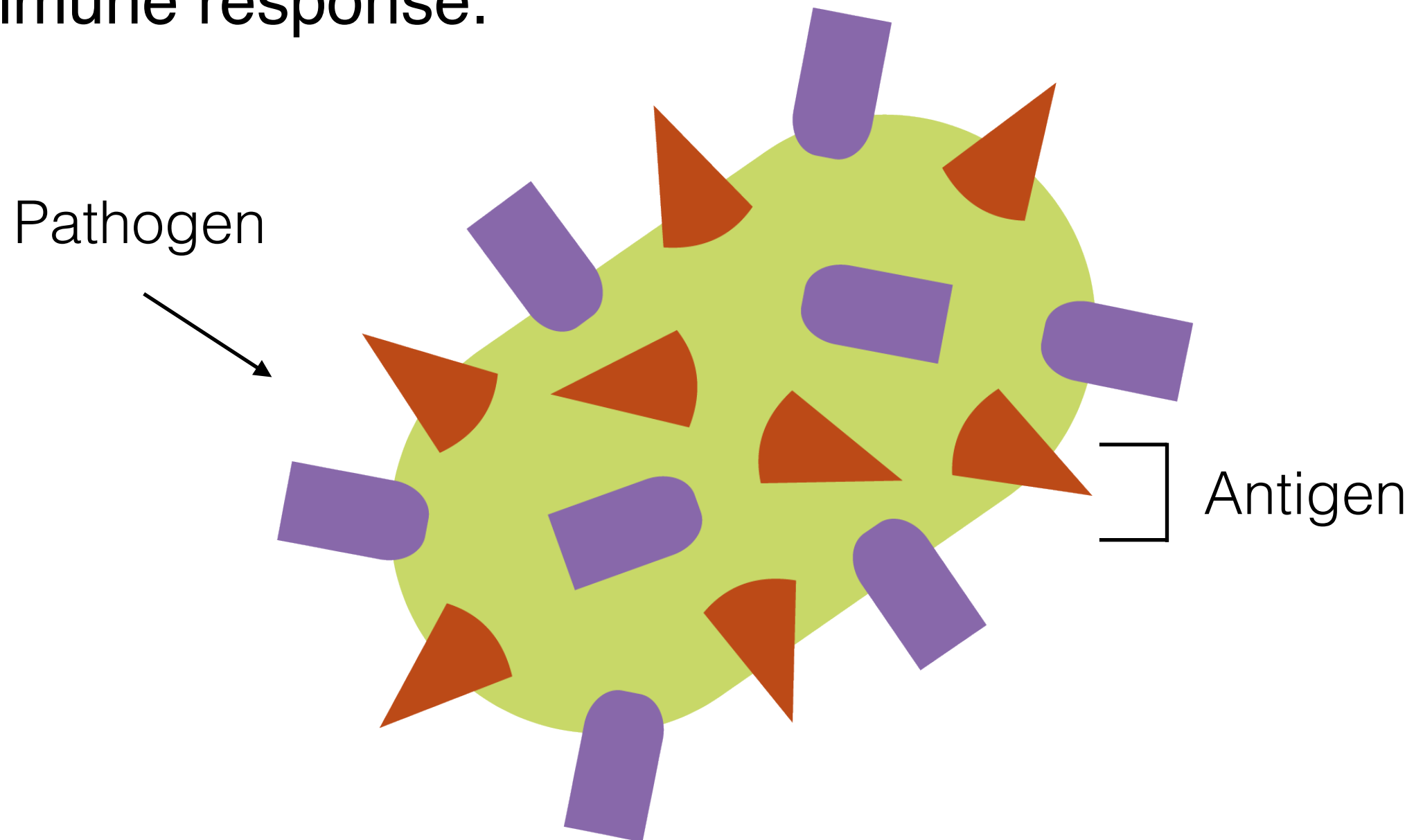


Dendritic cell

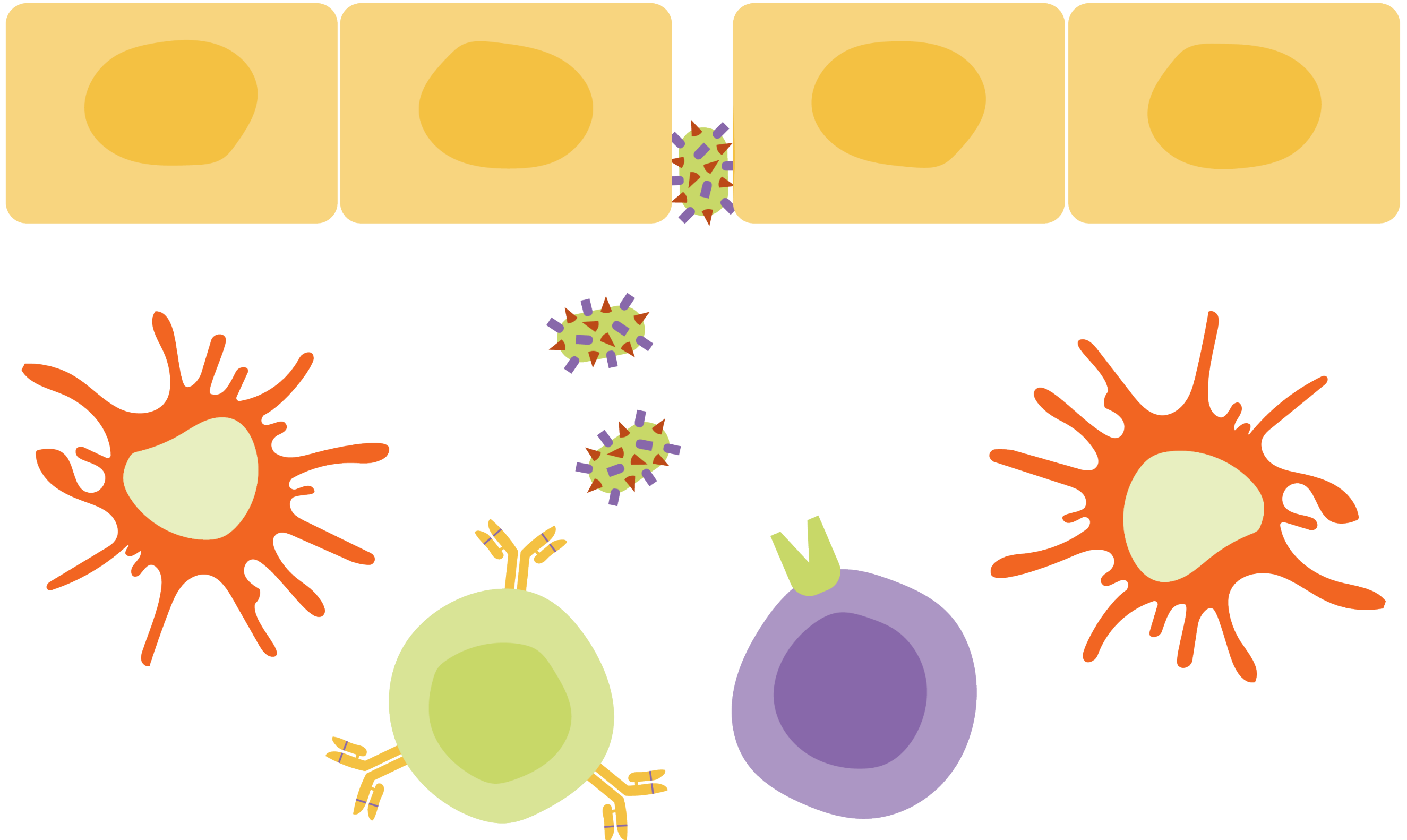
How Vaccines Work



Antigens are molecular markers that can stimulate an immune response.



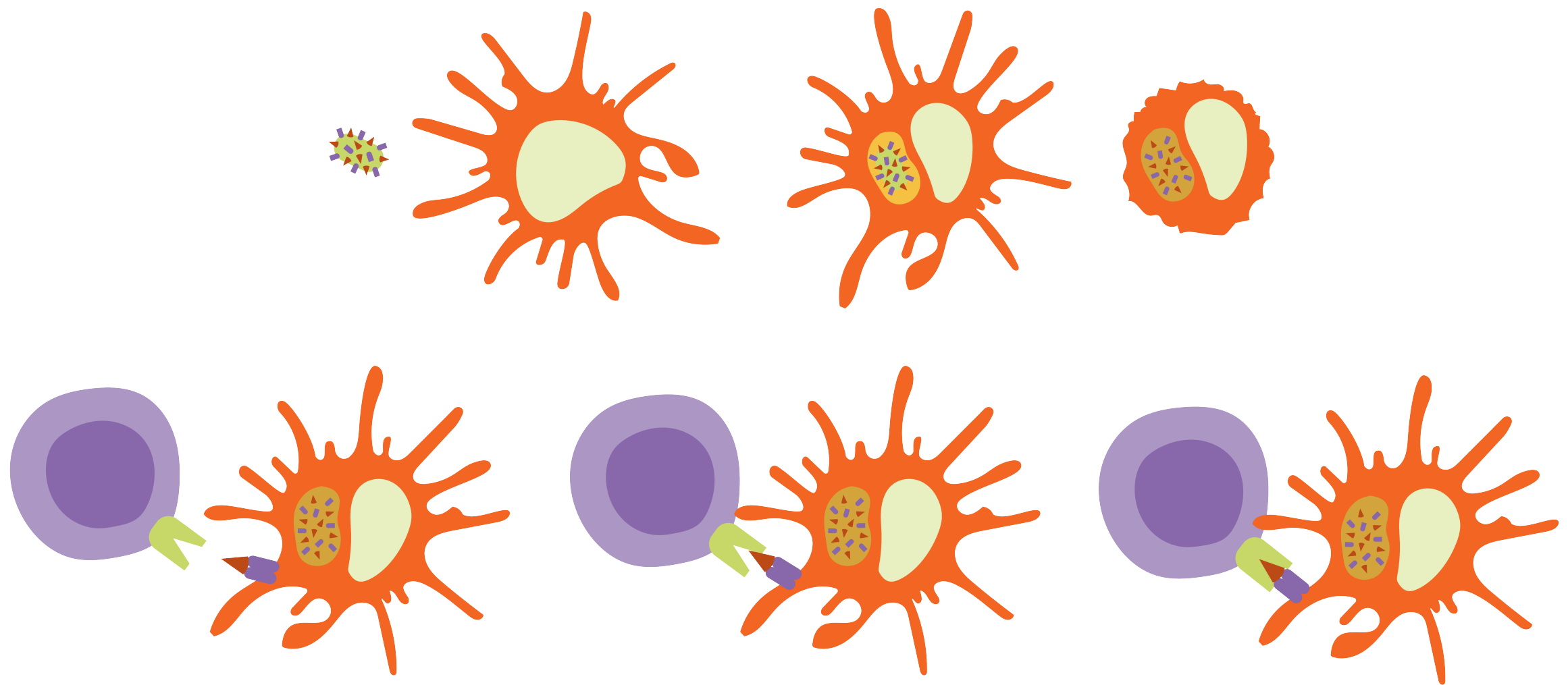
How Vaccines Work



How Vaccines Work



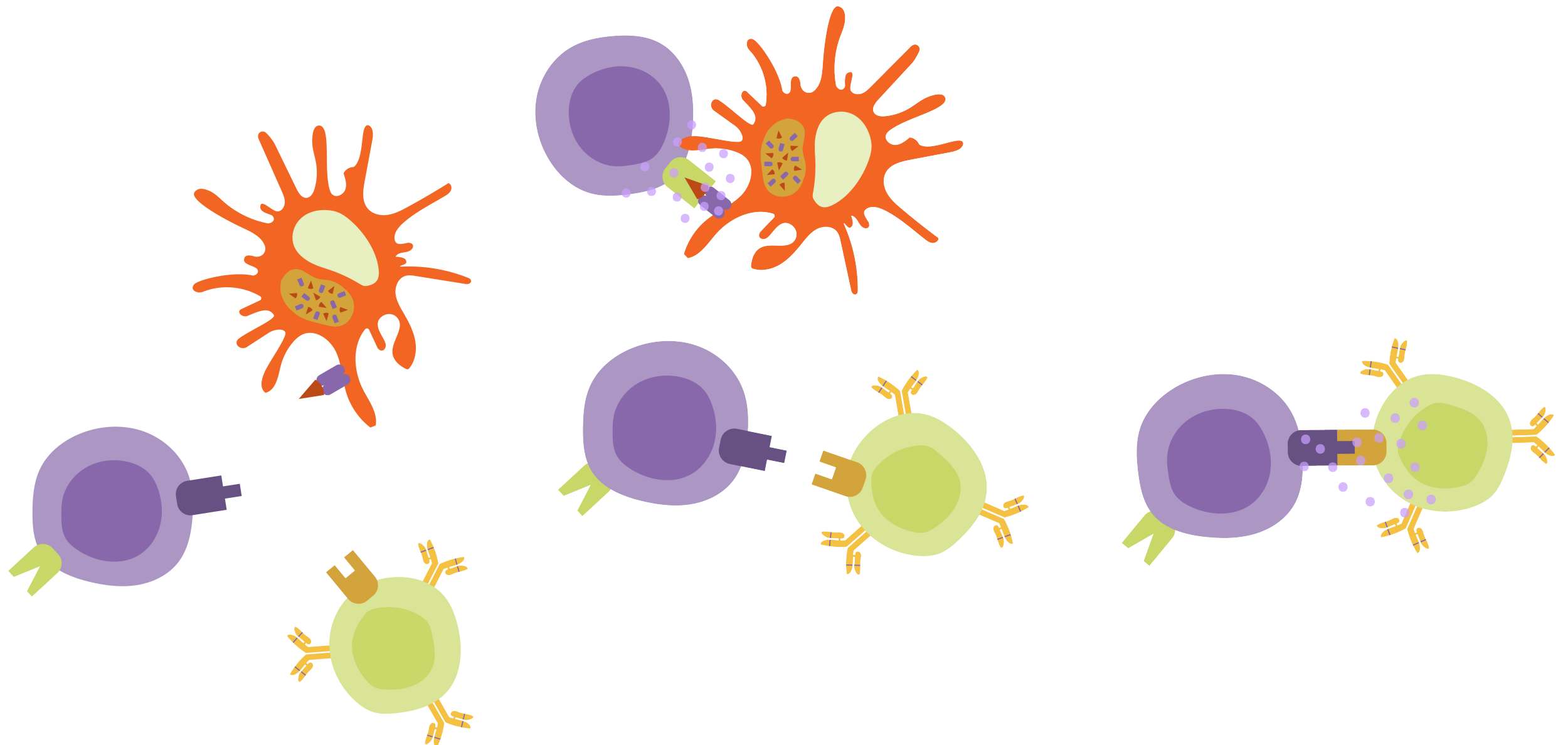
The innate immune system detects the antigen and alarms at the adaptive immune system.



How Vaccines Work



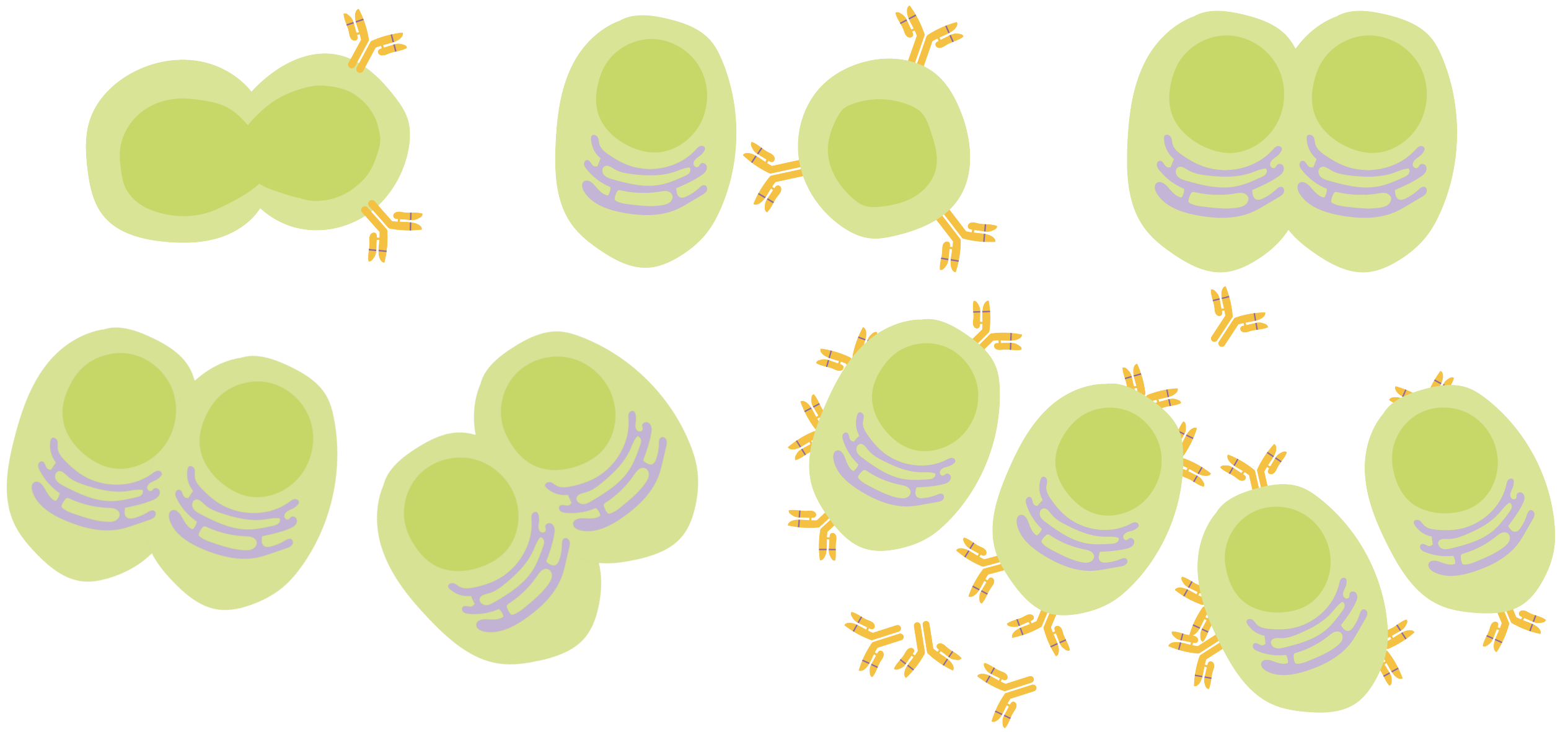
The adaptive immune system starts mounting a bespoke response.



How Vaccines Work



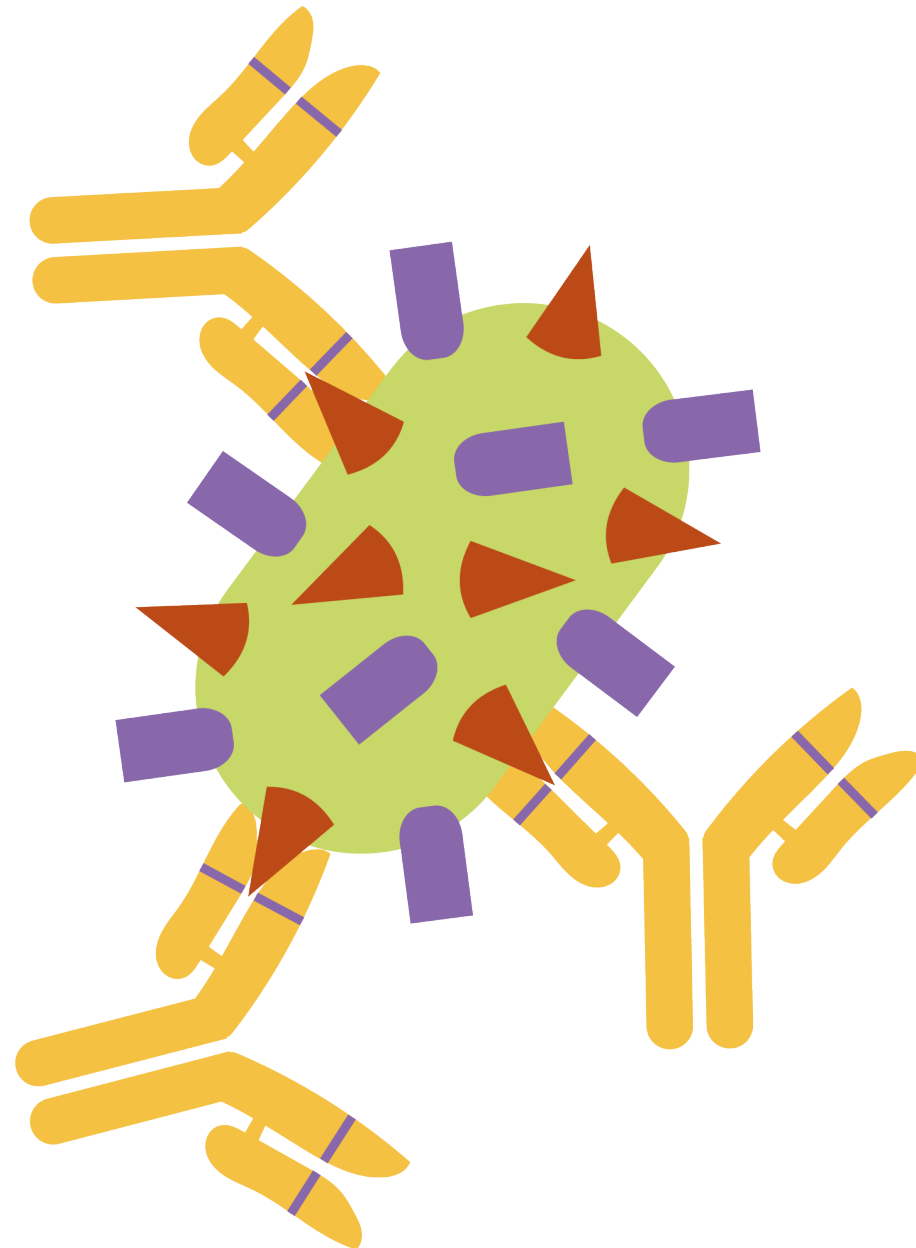
B cells convert to plasma cells, and start creating proteins called antibodies.



How Vaccines Work



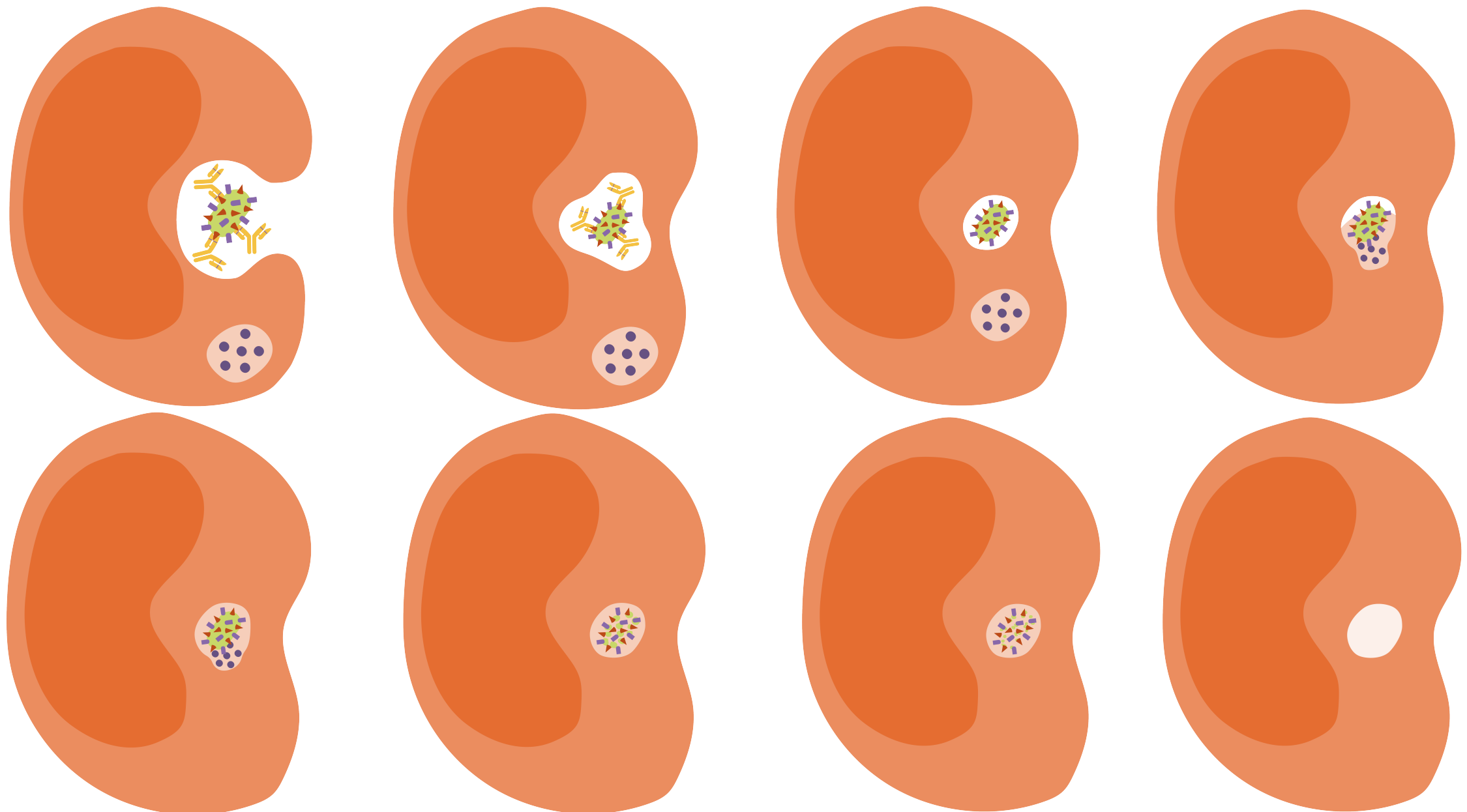
The antibodies bind specifically to the antigen.



How Vaccines Work



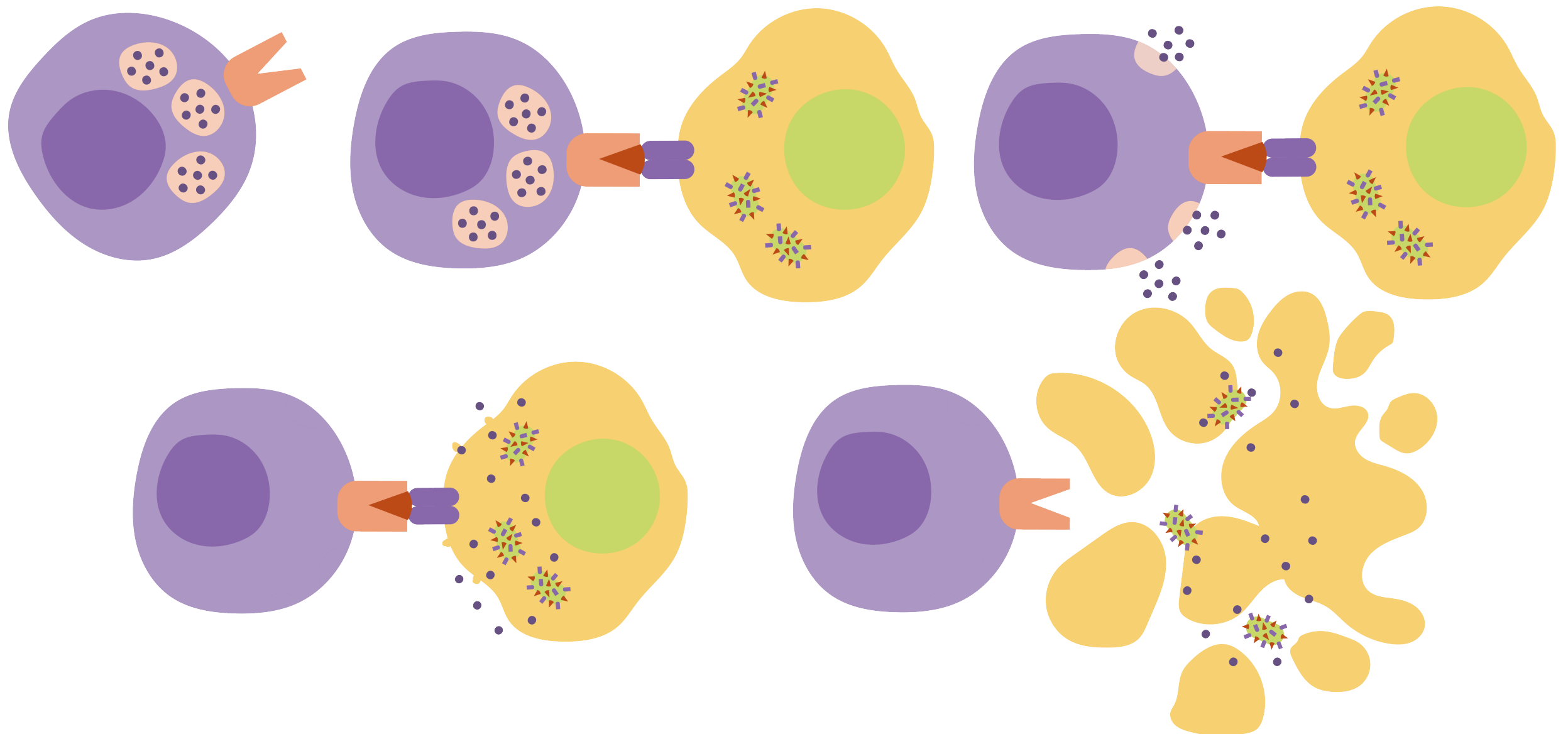
Phagocytes destroy the antibody-bound pathogen.



How Vaccines Work



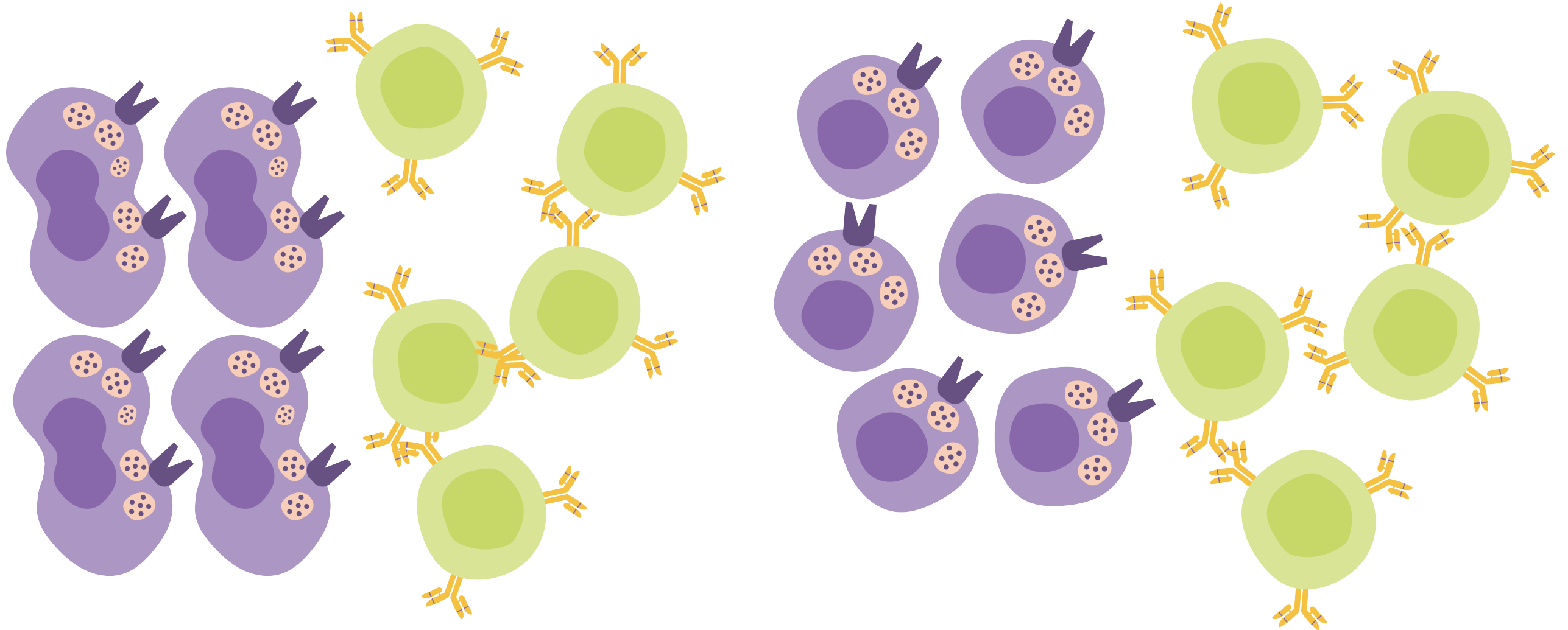
The adaptive immune system also produces killer T cells, which detect and destroy infected cells.



How Vaccines Work



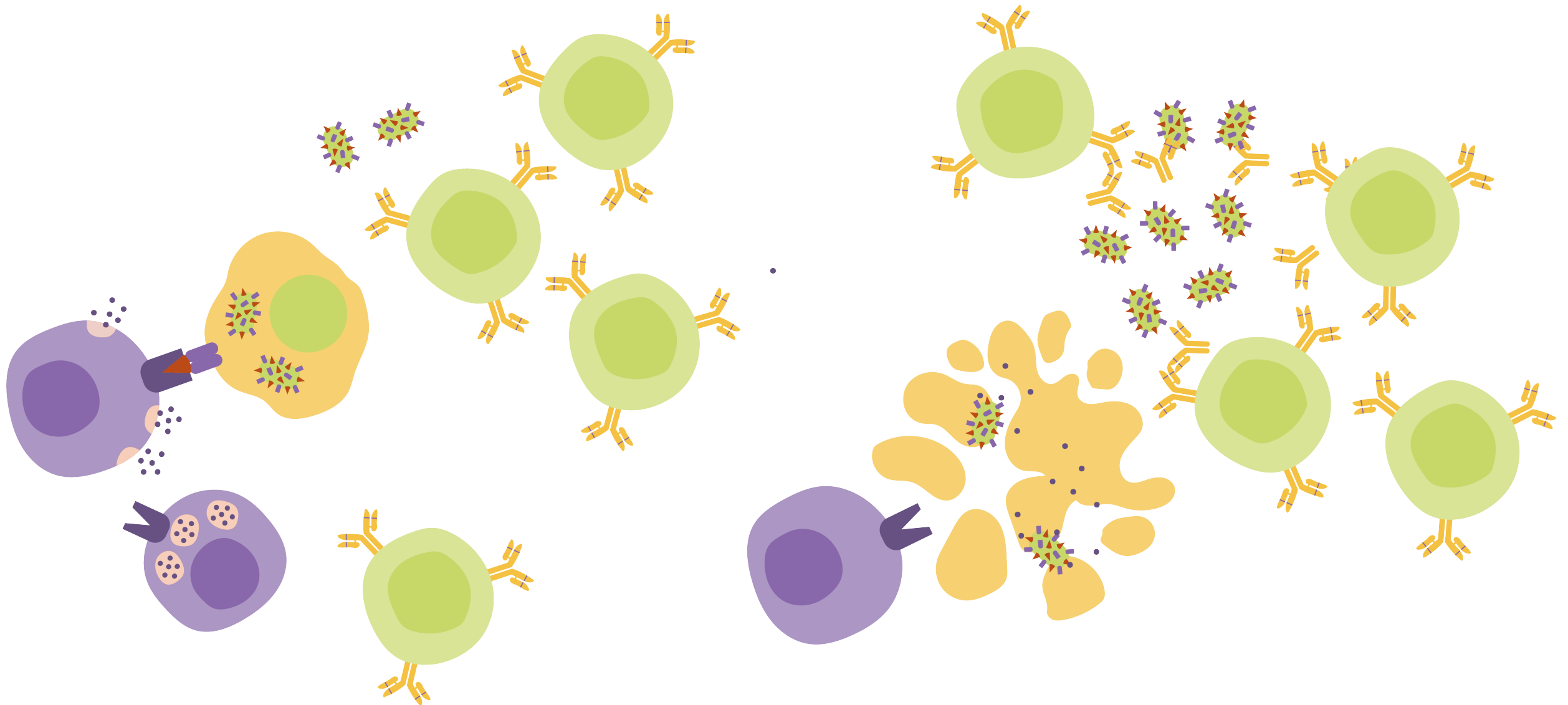
To prevent against future infections, the adaptive immune system produces long-lived memory cells.



How Vaccines Work



Memory cells lie ready to produce the right antibodies and killer T cells if the same pathogen is seen again.



How Vaccines Work



Vaccines present the immune system with a killed, weakened, or partial pathogen so that immune cells will respond and eventually make memory cells. Those memory cells will provide protection if the person is exposed to the actual, active pathogen later in life.

How Vaccines Work



Vaccines 101: How vaccines work



Watch later



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nature



Vaccination: From Alchemy to Science



Variolation

In the beginning was '*variolation*': deliberate 'controlled infection' with smallpox (Variola) puss or blister fluid to provide protection.

It was known that people only ever got smallpox once.

Variolation was practiced in China, India and parts of Africa and Europe since hundreds of years ago. But details varied as to how the procedure should be performed.

Vaccination: From Alchemy to Science



1721: The First 'Clinical Trial' in Immunology

Six prisoners in England were given the choice to either participate with the promise of freedom, or face their judicial execution.

Incisions were made on their legs and arms, and skin and puss from smallpox patient was rubbed in. One participant was instead given the skin and puss up her nose, becoming especially ill.

All participants recovered after about two days of smallpox symptoms and were released from prison.



Vaccination: From Alchemy to Science

Cowpox ‘Vaccination’

By 1760, anecdotes circulated in England and elsewhere that prior cowpox infection afforded milkmaids protection against smallpox.

In 1796, country physician Edward Jenner hypothesized that puss from non-fatal cowpox blisters might be used for inoculation instead of dangerous puss from smallpox patients.

Jenner inoculated an eight year old boy with puss from cowpox infection in a milkmaid. When given puss from a smallpox patient, the boy didn't get ill.

Vaccination: From Alchemy to Science



Cowpox ‘Vaccination’

Jenner had difficulties publishing his experiment in a medical journal at the time, and self-published his work after repeating the experiment on others, including his eleven month old son.

The word ‘vaccine’ was later coined by surgeon Richard Dunning to describe Jenner’s process of inoculation with cowpox to protect against smallpox. *Vacca* is the Latin word for cow.

The wider use of the word vaccine is attributed to Louis Pasteur (1822–95).

Vaccination: From Alchemy to Science



Cowpox ‘Vaccination’

Jenner believed his work would lead to elimination of smallpox, but at the time he had no deep understanding of how vaccination worked.

At his time, it was not even known that cowpox and smallpox were viral diseases, caused by two related viruses.

The discovery that microbes underlay many known diseases of the time was made a century later by Louis Pasteur and Robert Koch (1843–1910).

Vaccination: From Alchemy to Science



Adjuvants and Vaccine Potency

In the 1920s it was discovered that a toxin made by the bacteria which cause diphtheria could be inactivated, and thus potentially used as a safe vaccine against the disease.

However, when injected into animals, the immunity was surprisingly short-lived.

In 1926, Edward Glenny, a London physician, and his research team found that when diphtheria toxoid was purified using aluminum salt, it became an effective vaccine.

Vaccination: From Alchemy to Science



Adjuvants and Vaccine Potency

Later other substances were discovered which when incorporated into vaccines help boost the immune response. Collectively they are called *adjuvants*. Aluminum salt remains the most widely used adjuvant.

Glenny proposed that aluminum salt helped the diphtheria toxoid stay in the body long enough for an immune reaction to develop.

To this day, however, it remains unclear how aluminum salt helps vaccines work.

Vaccination: From Alchemy to Science



Adjuvants and Innate Immunity

It has puzzled Charles Janeway (1943–2003) why the diphtheria toxoid, a protein that is foreign to the body, did not elicit long-term immunity.

Why did puss from cowpox blisters work well as a vaccine, but molecules that are isolated from germs did not?

As we saw last time, Janeway reasoned that the presence of something foreign is not enough for an adaptive immune reaction. There has to be *another signal* that indicates the presence of actual germs.



Adjuvants and Innate Immunity

This other signal comes from innate immune cells that have pattern-recognition receptors (PRRs) on their surfaces, each able to detect a specific type of germ and switch on an immune response appropriate to the particular threat.

It has become clear that adjuvants are important because they switch on the innate immune system.

As a result, instead of using aluminum salt, adjuvants could be tailor-made, using molecules that had been identified as specific targets for PRRs.

Milestones | 28 September 2020

Nature Milestones in Vaccines

Animation

Vaccines 101: How new vaccines are developed

Vaccines are probably the most successful biomedical intervention in history, but why can they be so effective? The initial selection of the target antigens through to the way it is delivered can all impact how well a vaccine works. What goes into a vaccine and how do we test whether it's doing its job properly? This animation answers these questions and more.

Nature Milestones in Vaccines

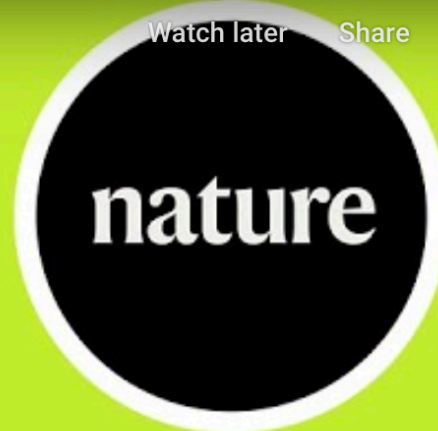
<https://www.nature.com/immersive/d42859-020-00005-8>

How New Vaccines Are Developed



 Vaccines 101: How new vaccines are developed

 Watch later  Share



SARS-CoV-2 Vaccines in Development

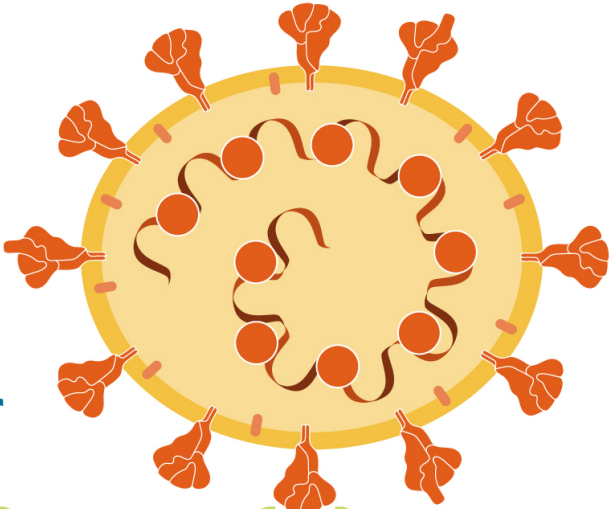


Antigenic Target

Most coronaviruses encode only one large surface protein, the *spike protein*, which is responsible for receptor binding and membrane fusion with the host cell.

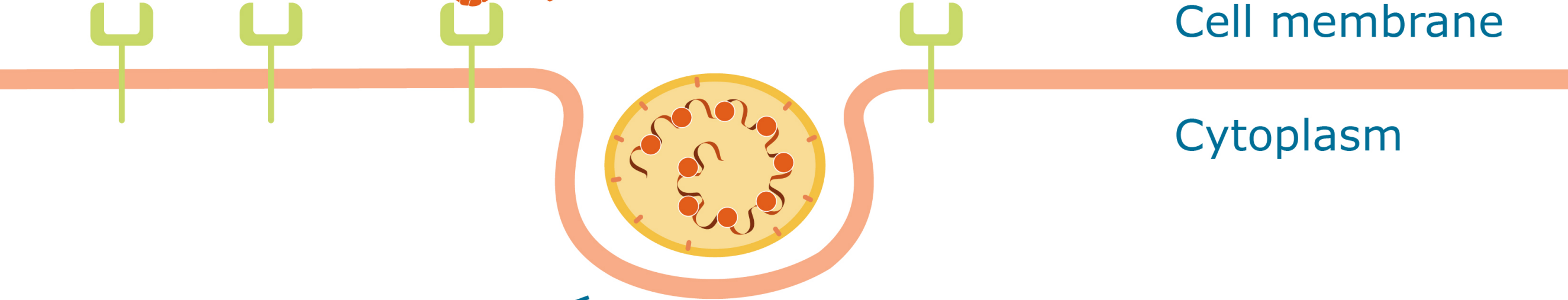
This is followed by release of the viral genome into the cytoplasm.

Human coronavirus



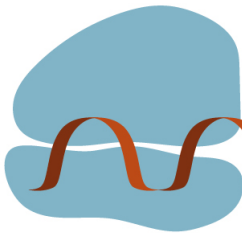
Receptor binding, viral entry, and membrane fusion

Cellular receptor



Cell membrane

Cytoplasm



Vrial RNA release

Genomic RNA



SARS-CoV-2 Vaccines in Development



Antigenic Target

Antibodies that bind to the spike protein, especially to its *receptor-binding domain* (RBD), prevent its attachment to the host cell, and thus neutralize the virus.

The spike protein was identified as an antigenic target for the development of a vaccine against SARS-CoV-2 at a very early stage.

Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses

Jiang S, Hillyer C, Du L.

Trends Immunol. 2020;41(5):355-359.

SARS-CoV-2 Vaccines in Development



Vaccine Platforms

More than 180 vaccine candidates, based on several different platforms are currently in development against SARS-CoV-2.

The World Health Organization (WHO) maintains a working document that includes most of the vaccines in development.

Draft landscape of COVID-19 candidate vaccines

<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

SARS-CoV-2 Vaccines in Development



Vaccine Platforms

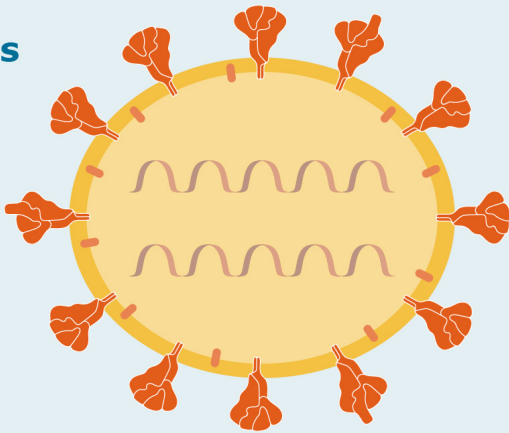
The platforms can be divided into

classical vaccines: these contain actual pathogens or toxins that have been weakened or killed,

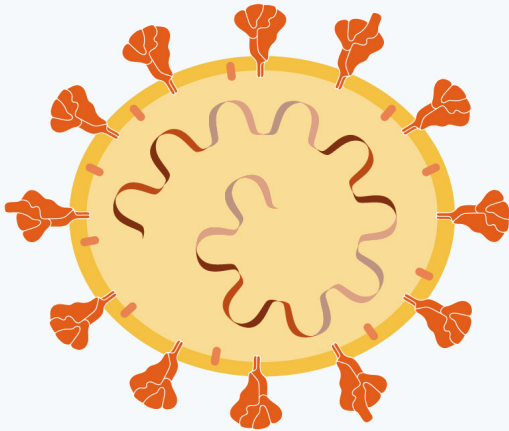
conventional vaccines: these contain antigens that can provoke an immune response, and

next-generation (genetic) vaccines: these use genetic material taken from pathogens that instruct body cells to make antigens.

Whole-inactivated virus
Example: Polio vaccine



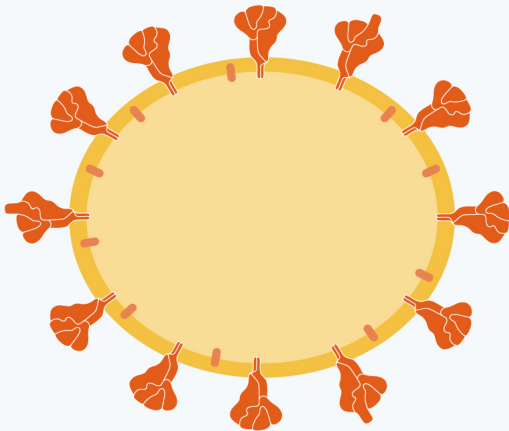
Live-attenuated virus
Example: MMR vaccine



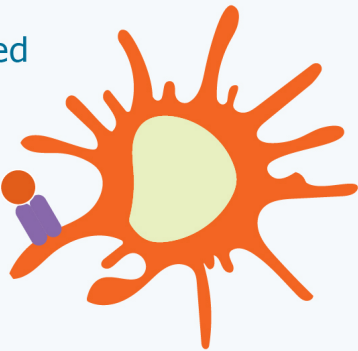
Protein subunit
Example: Seasonal



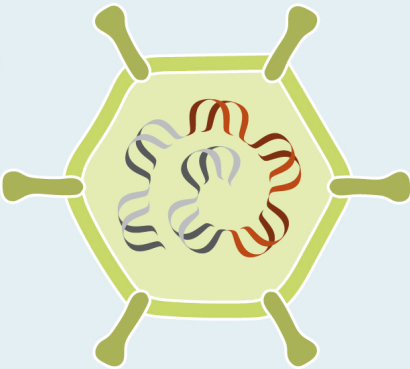
Virus-like particle
Example: Human papillomavirus vaccine



Antigen-presenting cells
Example: Not currently licensed



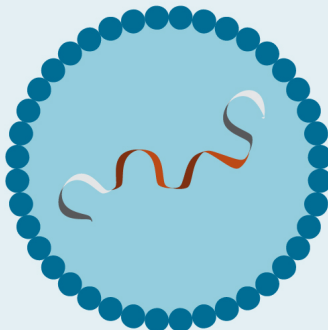
Viral vector
Example: VSV-Ebola vaccine



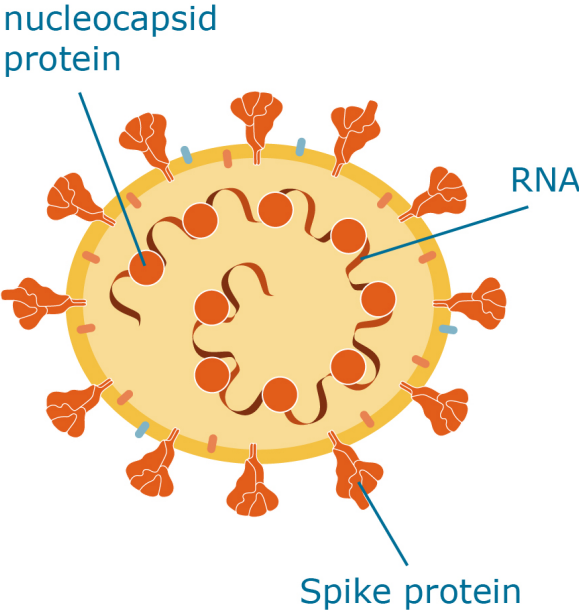
DNA
Example: Not currently licensed



RNA
Example: Not currently licensed



SARS-CoV-2



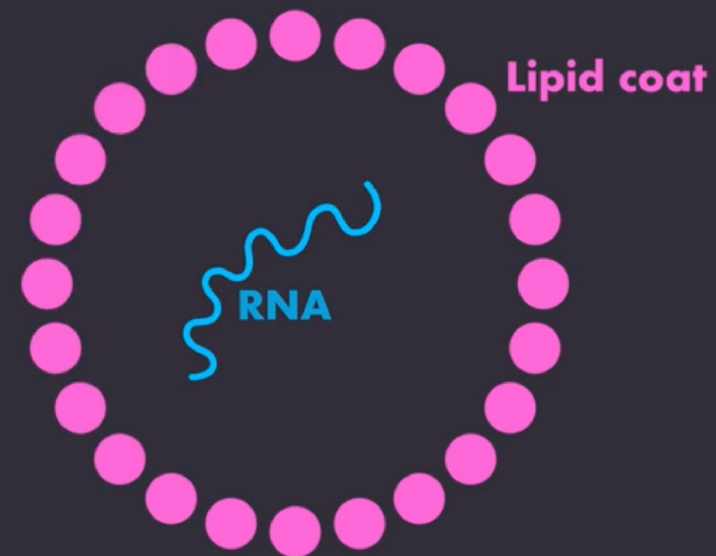
Next-Generation Nucleic Acid Vaccines



 Vaccines 101: How new vaccines are developed

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Nucleic acid



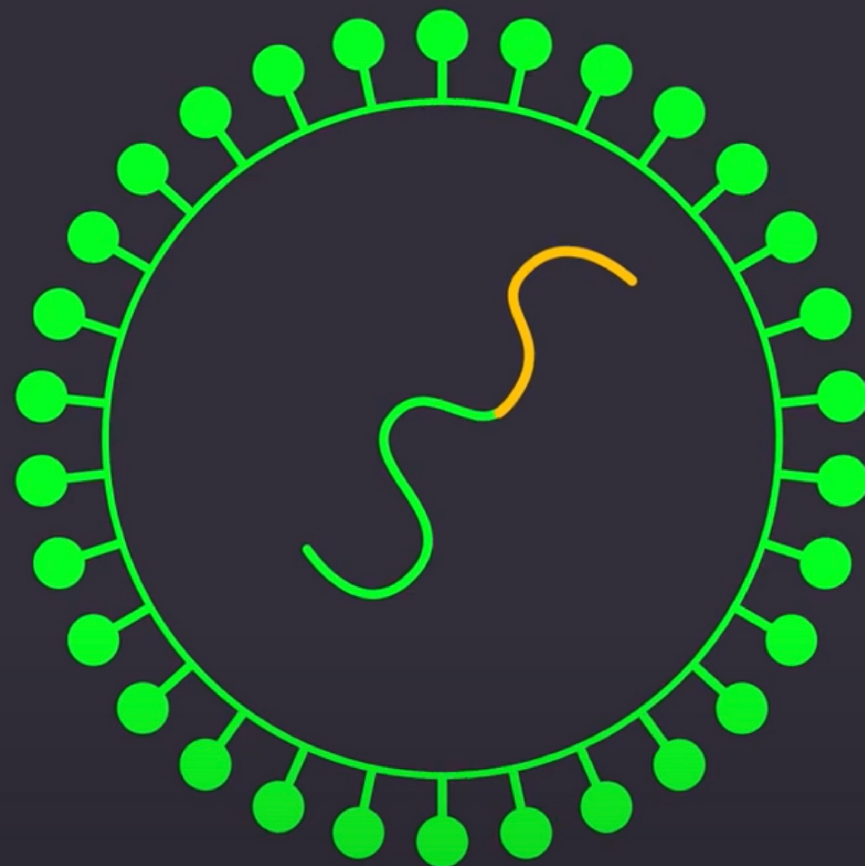
Next-Generation Viral Vector Vaccines



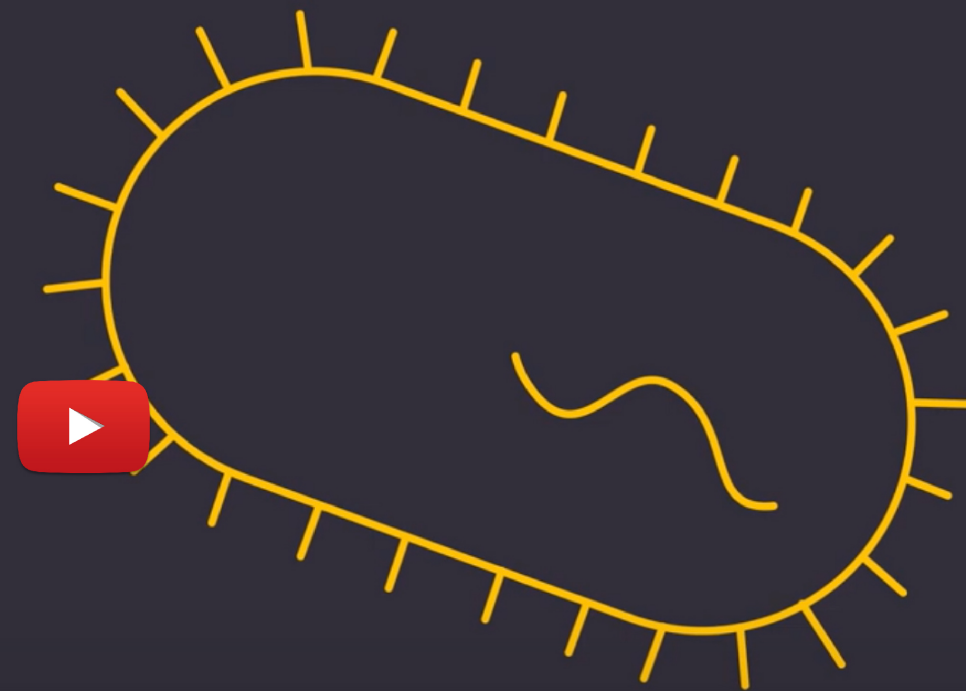
 Vaccines 101: How new vaccines are developed

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Viral vector



Pathogen



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JAMA Network Channel

<https://www.youtube.com/channel/UC4p6bEngiRCN7TyTxZVJ3OQ>

SARS-CoV-2 Vaccines in Development



Coronavirus Vaccines

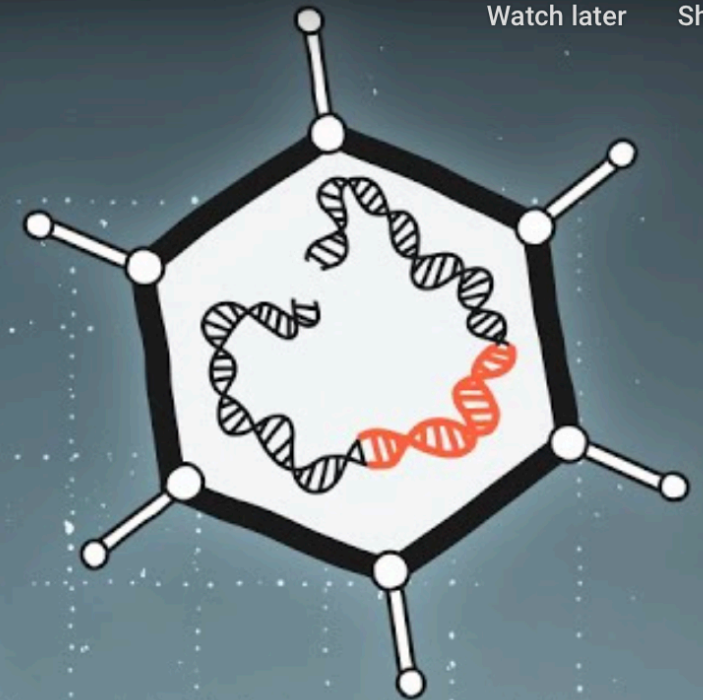
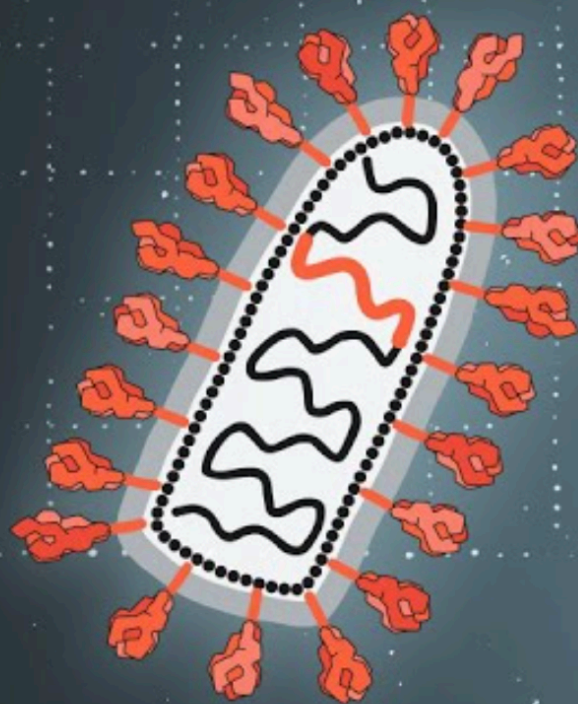


Watch later



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Coronavirus Vaccines



SARS-CoV-2 Vaccines in Development



Current Frontrunners

Pfizer and Moderna both developed RNA vaccines.

AstraZeneca's viral vector vaccine is based on a replication-defective chimpanzee adenovirus expressing a wild-type version of the spike protein.

Combination Prevention/Protection



Current vaccines trials are aiming for approval at roughly 50% efficacy.

Public health measures (distancing, masks, hygiene), and *bridge therapies* (e.g. monoclonal antibodies, antiviral drugs, steroids) will need to complement vaccines.

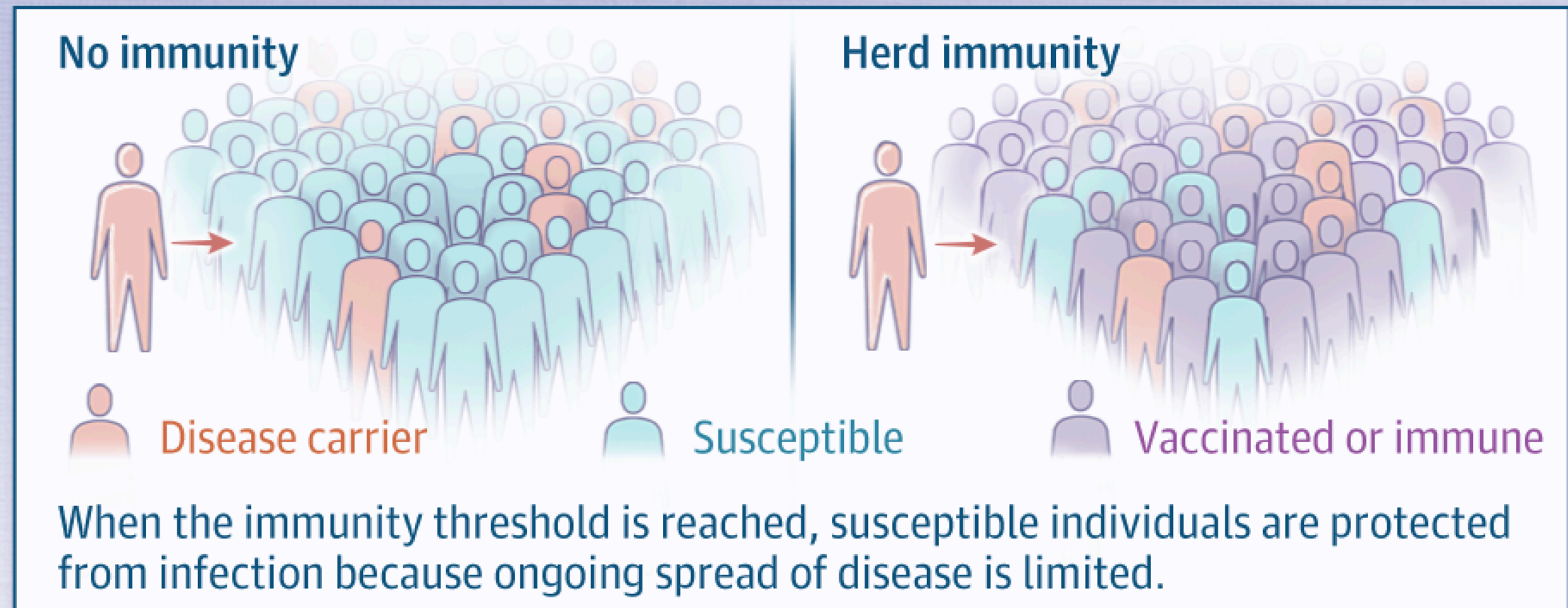
Herd Immunity



Population Level Protection

When “enough”, i.e. a certain percentage of people, acquire immunity, either through direct infection and subsequent recovery, or through vaccination, this can stop the spread of the infection through the population (“herd”).

Herd immunity works to control the spread of disease within a population when a specific amount of that population (threshold) becomes immune to the disease through vaccination or infection and recovery.



What Is Herd Immunity?

<https://jamanetwork.com/journals/jama/fullarticle/2772168>



Population Level Protection

The percentage, or threshold, of acquired immunity that is needed to reach herd immunity depends on R_0 , the *basic reproduction number*, which is an estimate measure of the transmissibility of the new infectious agent. R_0 is estimated when the infectious agent is new and it can be assumed that (almost) everyone in the population is susceptible to infection.

Complexity of the Basic Reproduction Number

Delamater PL, Street EJ, Leslie TF, et al.
Emerging Infectious Diseases. 2019;25(1):1-4.



Population Level Protection

R_0 is an empirical estimation of the average number of people an infected person would infect.

If R_0 is less than 1, the infection will decline in the population, and eventually decay to zero.

If R_0 is equal to 1, the infection will stay alive in the population but does not reach pandemic proportions.

If R_0 is greater than 1, the infection will likely spread *exponentially* in the population, and can lead to a pandemic.

Herd Immunity



Population Level Protection

Factors influencing R_0 are: length of infectious period, contact rate, and mode of transmission.

The higher the R_0 of an infectious agent, the higher the percentage of the population that needs to be immune to achieve herd immunity: $100 \times (1 - 1/R_0)$.

Measles has an average R_0 of 18, and 95% threshold for herd immunity. 1918 flu had an average R_0 of 2, and seasonal flu has an average R_0 of 1.3 (reference).



Population Level Protection

SARS-CoV-2 likely had a median R_0 of 5.7 in the outbreak in Wuhan, China. That's about double an earlier R_0 estimate of 2.2 to 2.7. This raises the threshold for herd immunity to 82%.

High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2

Sanche S, Lin Y, Xu C, et al.

Emerging Infectious Diseases. 2020 Jul;26(7):1470-1477.

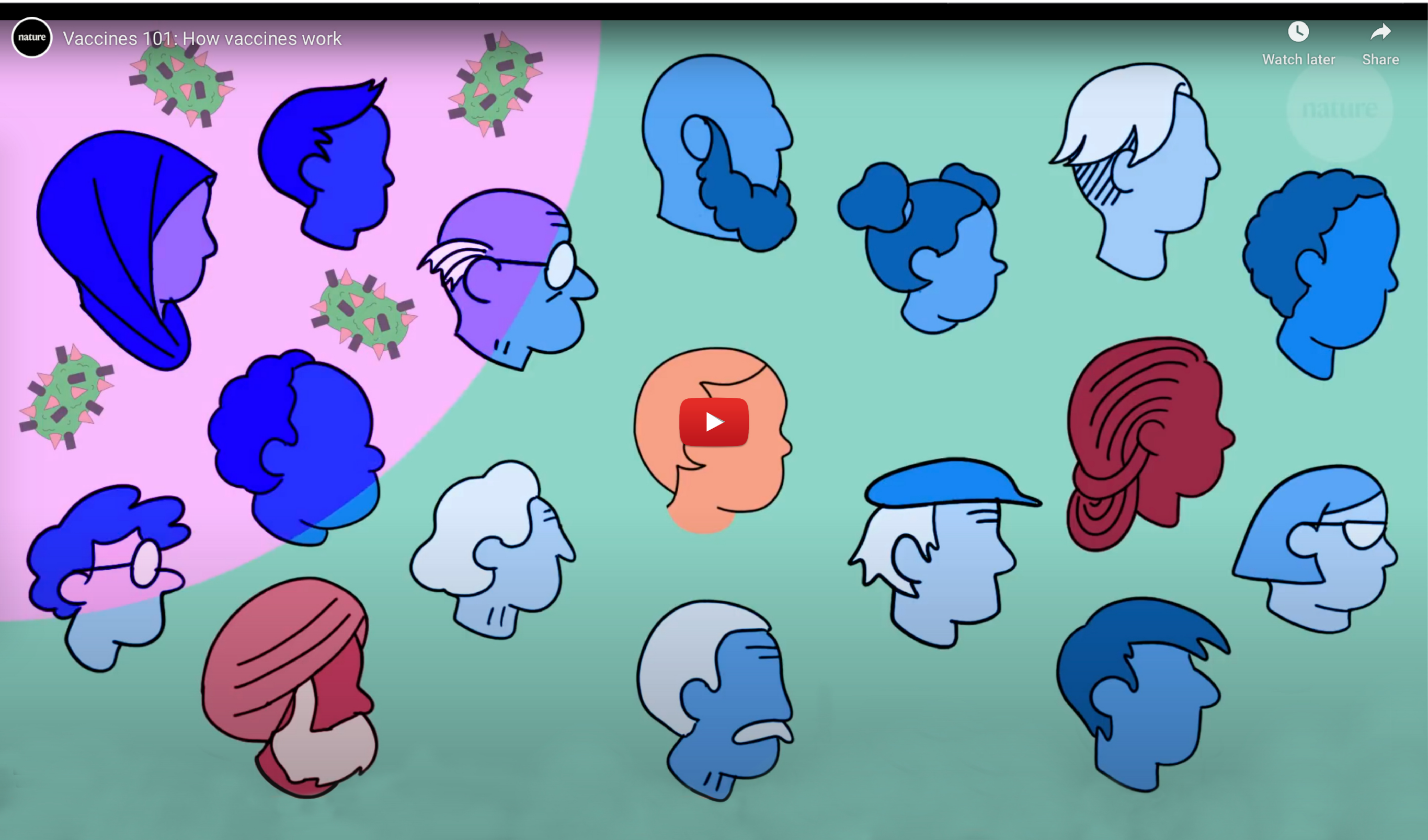
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Nature Milestones in Vaccines

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<https://www.nature.com/immersive/d42859-020-00005-8>

Herd Immunity





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Herd Immunity without Vaccines Is Not a Plan



JN Excess Deaths During the Coronavirus Pandemic

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COVID-19 Excess Deaths



Herd Immunity without Vaccines Is Not a Plan



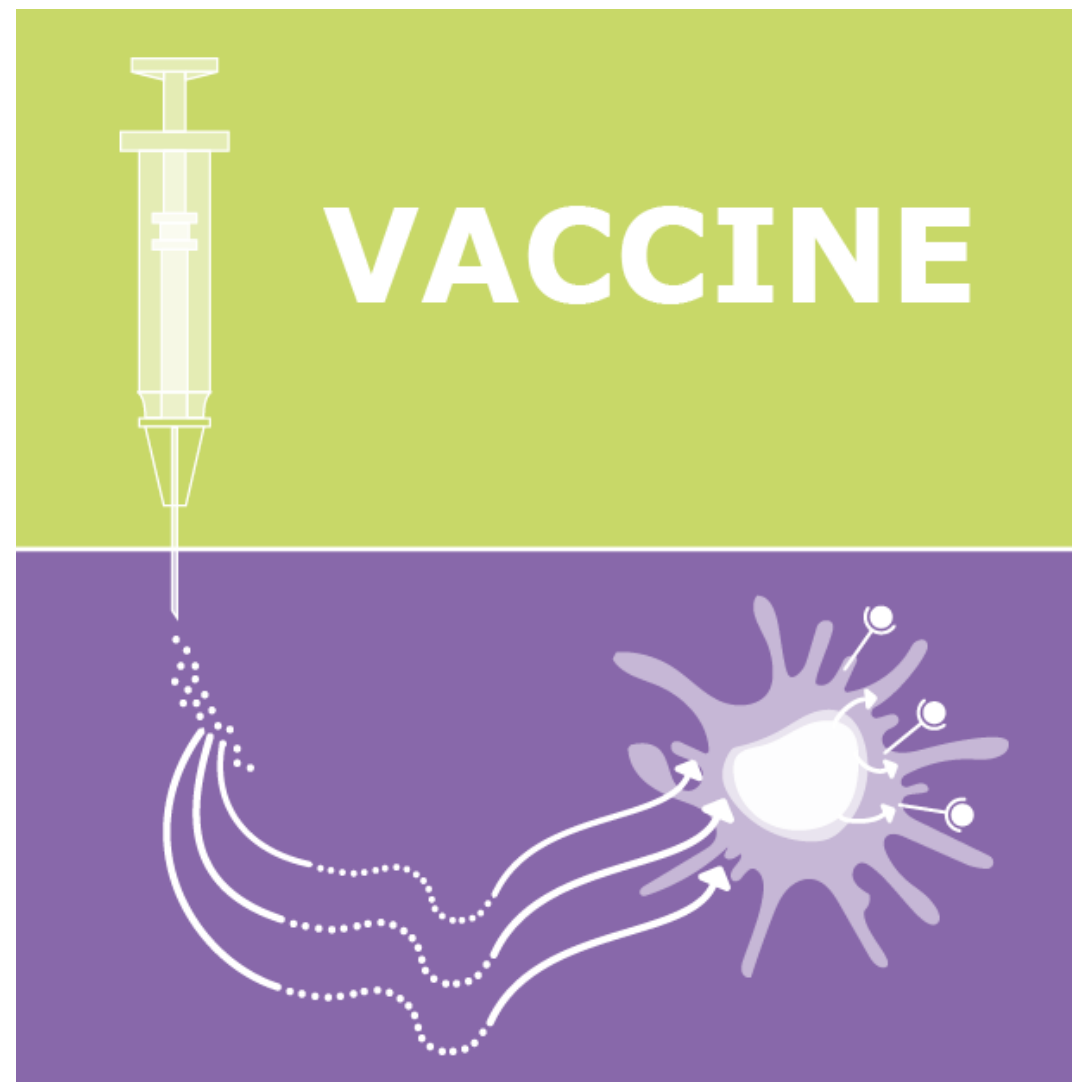
Excess Deaths Associated with COVID-19

CDC Morbidity and Mortality Weekly Report (Oct, 20):

“Overall, an estimated 299,028 excess deaths occurred from late January through October 3, 2020, with 198,081 (66%) excess deaths attributed to COVID-19. The largest percentage increases were seen among adults aged 25–44 years and among Hispanic or Latino persons.”

**Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity
— United States, January 26–October 3, 2020**

https://www.cdc.gov/mmwr/volumes/69/wr/mm6942e2.htm?s_cid=mm6942e2_w



Vaccine Basics Basics: Essential Information in the Time of COVID-19

<https://www.ildcollaborative.org/covid-19/vaccine-primer>