

Infectious Disease and Immunity

Biol/Phil 2510
April 9, 2009

Outline

- Viruses- dual use dilemma
- Viruses
- Immune system
 - B cells, T cells
 - Antibodies
 - Monoclonal antibodies
- Treatments
 - Antibiotics
 - Vaccination

Spanish Flu, 1918



- **Origin:**
 - Probably China
 - From avian source

Global Pandemic

- ~20% of world population infected
28% of Americans infected, including President)
- ~50 million dead globally in 2 years (~3% world population).
Victims dead in hours to days; suffocated.
3x total killed in WW1
US average lifespan decreased by 10 years.
- Spread by troops moving in/out of Europe in WW1.
“Spanish” b/c first reported case in Spain.
Severely taxed health system
In US, entered via Boston in Sept. by Oct. 200,000 dead.

Why was 1918 flu so lethal?

- Introduce a novel pathogen into a species with no prior immunity means that species is vulnerable.
- Spanish flu was highly **virulent**:
 - Very effective at infecting an individual;
 - Very effective at spreading between individuals
- Added vulnerability with poor sanitation, international travel, strained health-system, and poor emergency response...

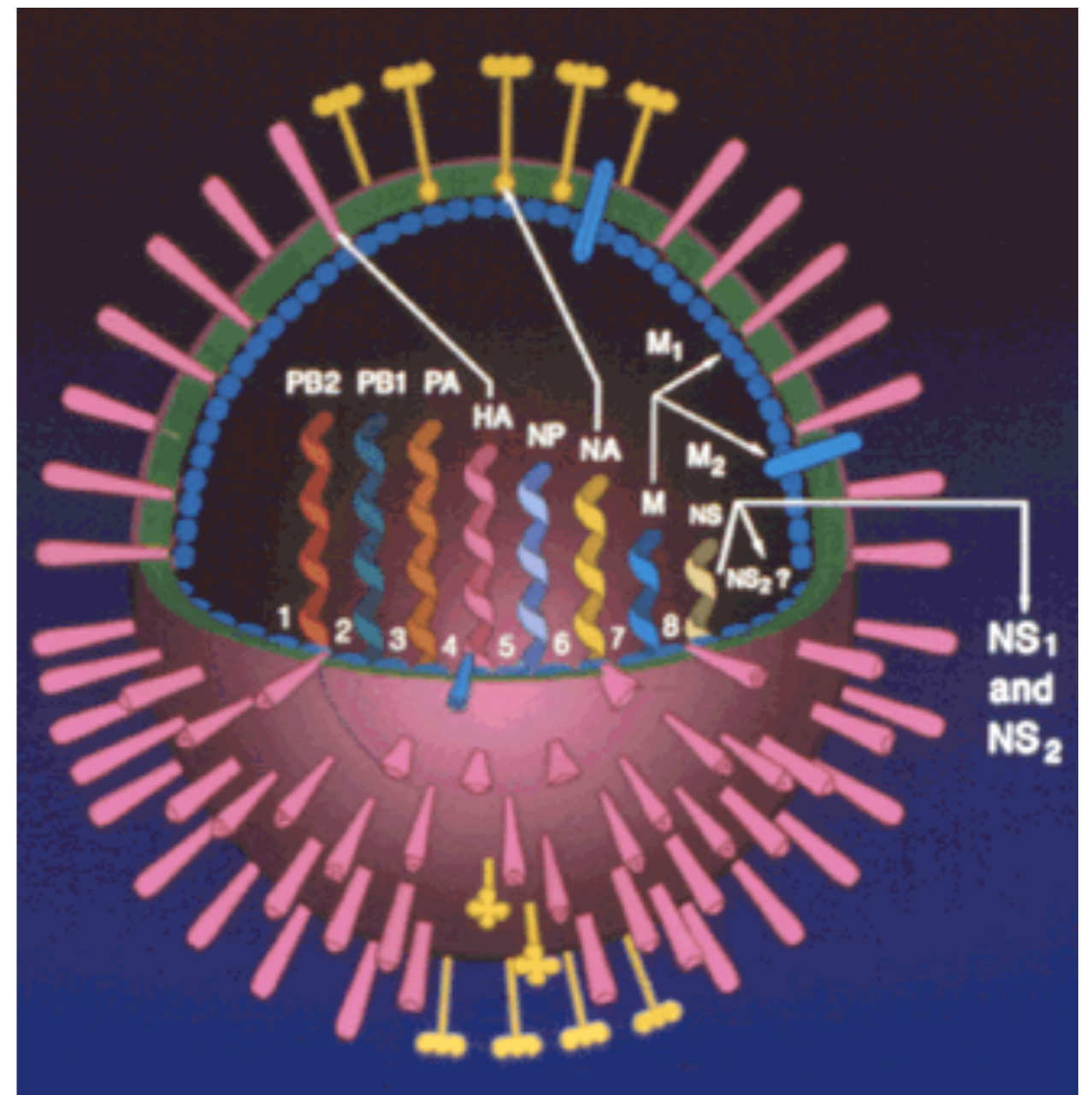
Compare risk associated with xenotransplantation?

Recent Developments

- Severe Acute Respiratory Syndrome (SARS)
 - First detected outbreak in China 2002/2003; mortality rate 10%; human to human spread; first denied, but quarantine measures stopped spread; 8,096 known cases of the disease, and 774 deaths.
- Asian/Avian Flu
 - Detected in “Asia”; 24 cases, 19 deaths in 2008 but some report 100s of deaths; extremely high death rate; limited human to human transmission, so far.

Viruses

- Viruses are just DNA or RNA coated with protein (and sometimes lipid/fat)
- Viruses “dock” onto cells using surface proteins to get into (and out of) cells; keyed to specific receptors on cell surface.



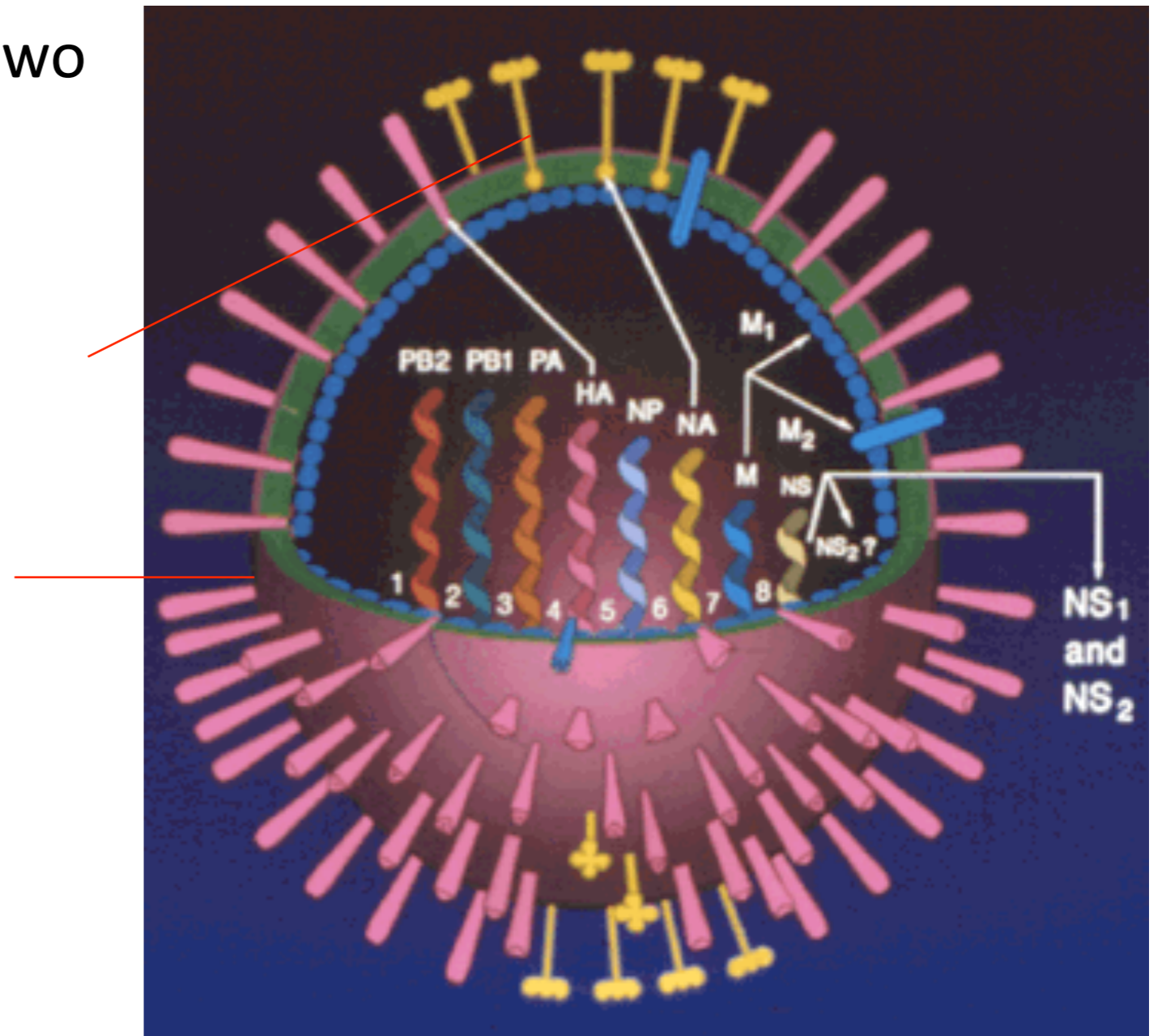
Avian Influenza, Bird Flu

Influenza viruses are named for two proteins on the virus surface:

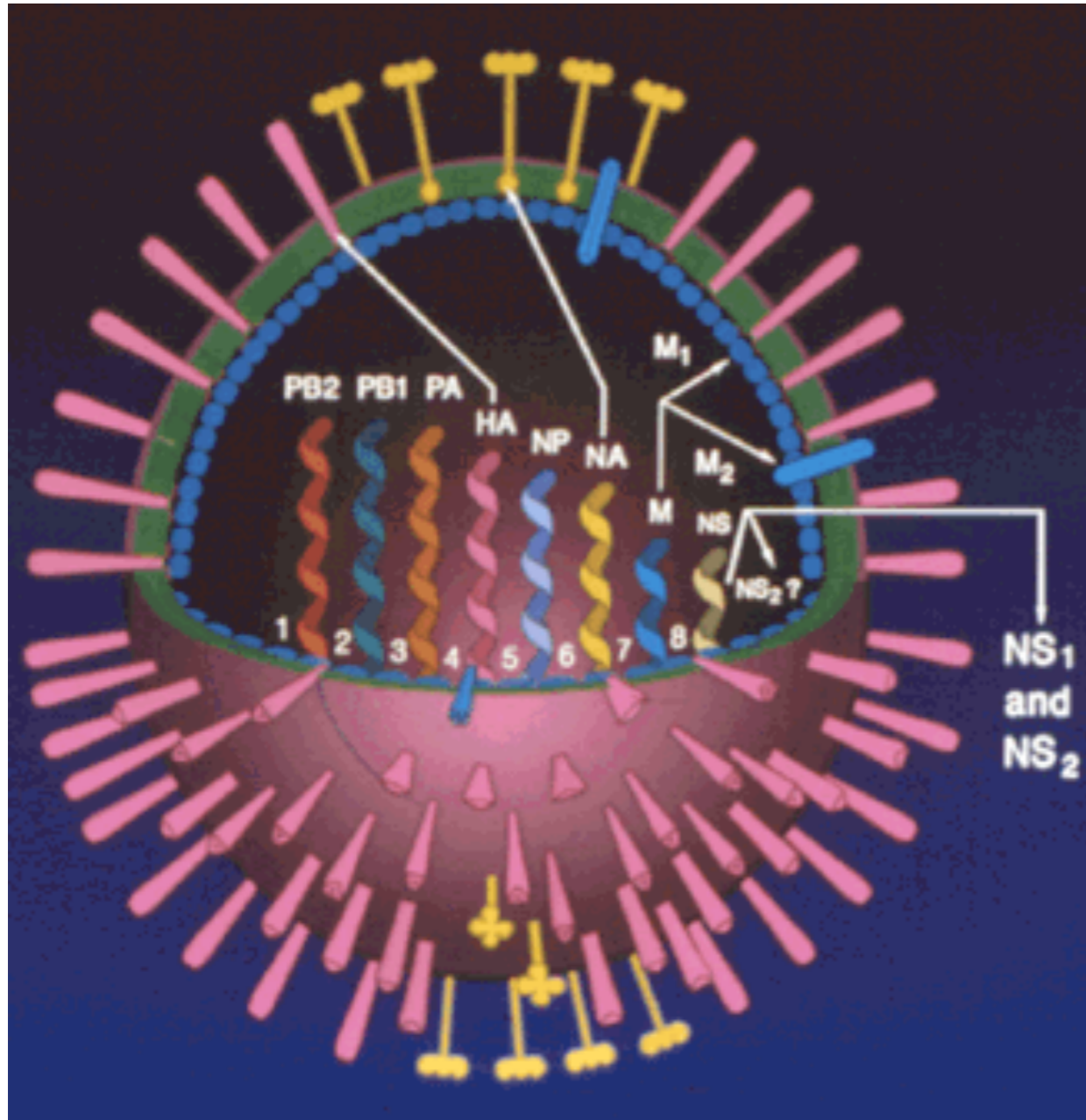
Hemagglutinin (entry into cells)

Neuraminidase (release from infected cells)

- Spanish flu is H1N1
- Avian flu is H5N1



Influenza Evolution



- The virus has 8 separate RNA molecules. If a cell gets infected with two different flu viruses, these can be shuffled into new virus combinations.
- Or random mutations can occur.

For Public Health

- In order to understand how the Avian Flu (H1N1) might become more virulent, such as in the Spanish Flu (H5N1), researchers reconstructed the Spanish Flu virus:
 - No biological sample of the 1918 virus survived, but able to reconstruct the genome, and thus build from scratch a live virus.
 - Moved Spanish H5 into Avian virus: highly virulent!
 - Moved Avian H1 into Spanish virus: reduced virulence!
 - Published findings, including the genome of 1918 virus!
- Raised some questions:

Dual-use Dilemma

- An ethical dilemma that results from the potential uses of a technology, when the same technology can be used for both beneficial and malevolent purposes.
- Questions:
 - How should such technology be “controlled” in order to achieve benefits but reduce risks of abuse?
 - Who has control over technology and the knowledge it is built upon?

1918 Reconstruction Dilemma

Pro

- Provides insight into how virus works, to improve health care-response to potential outbreak.
- Publishing genome and experiment makes it more likely that knowledge will be gained and used for benefit.

Con

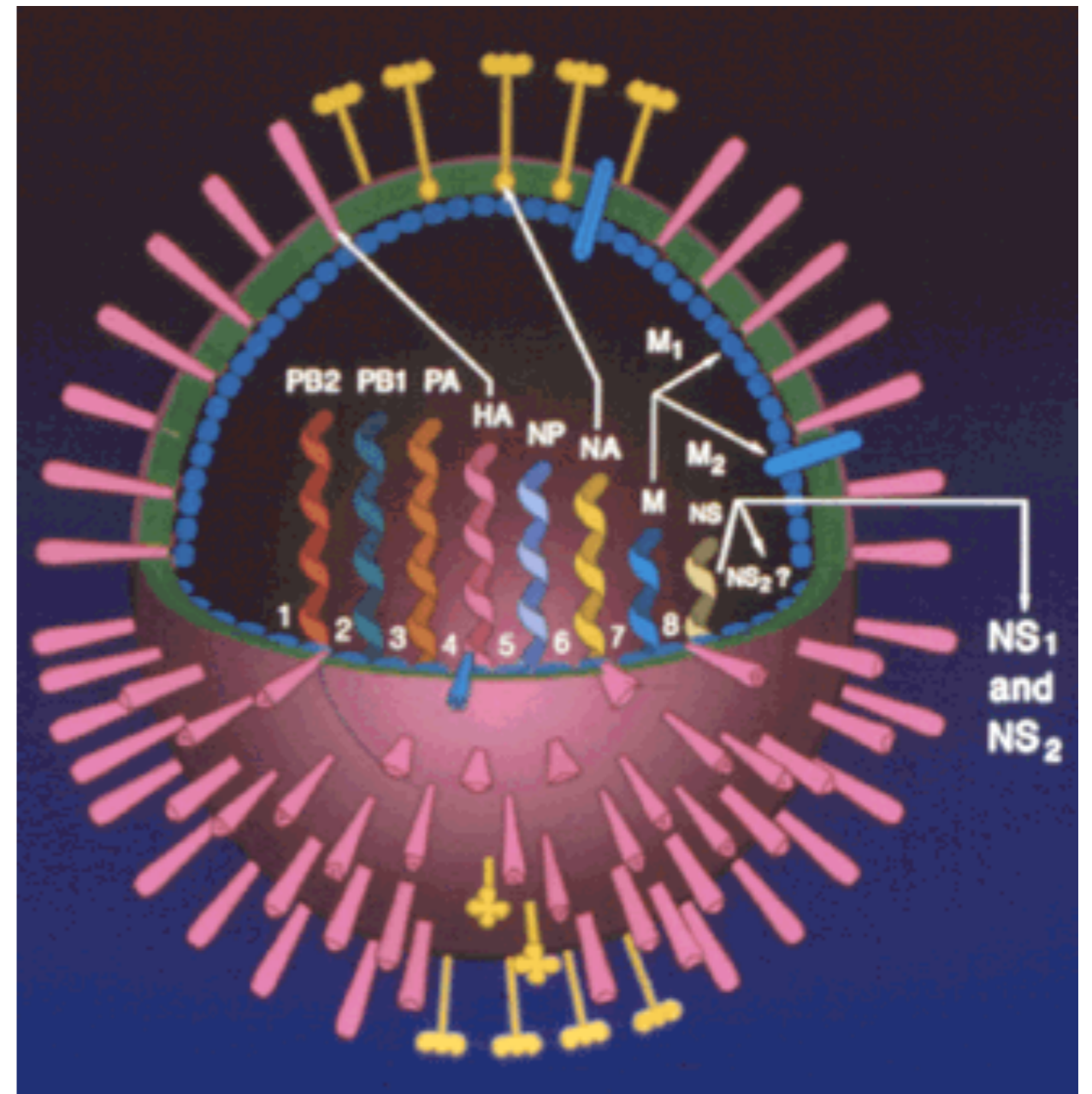
- Publishing genome and experiment makes available information on how to make viruses more virulent; a.k.a., bioweapons.
- Publishing genome and experiment makes technology readily available to people interested in using bioweapons, e.g., bioterrorists.

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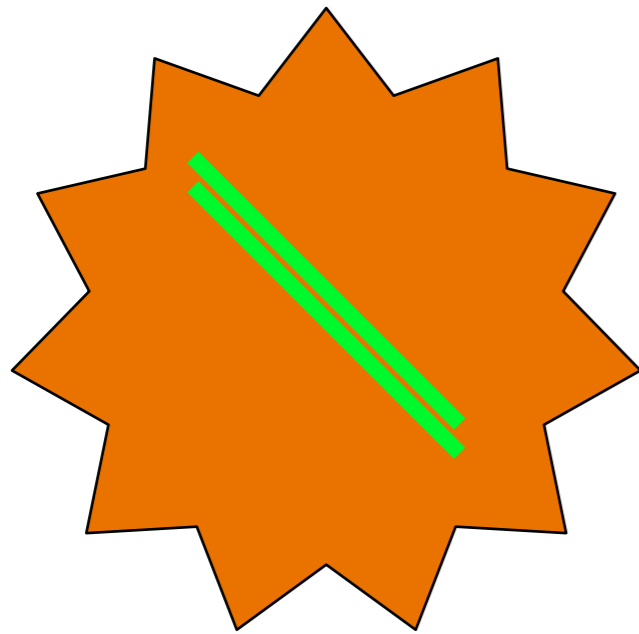
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Viruses

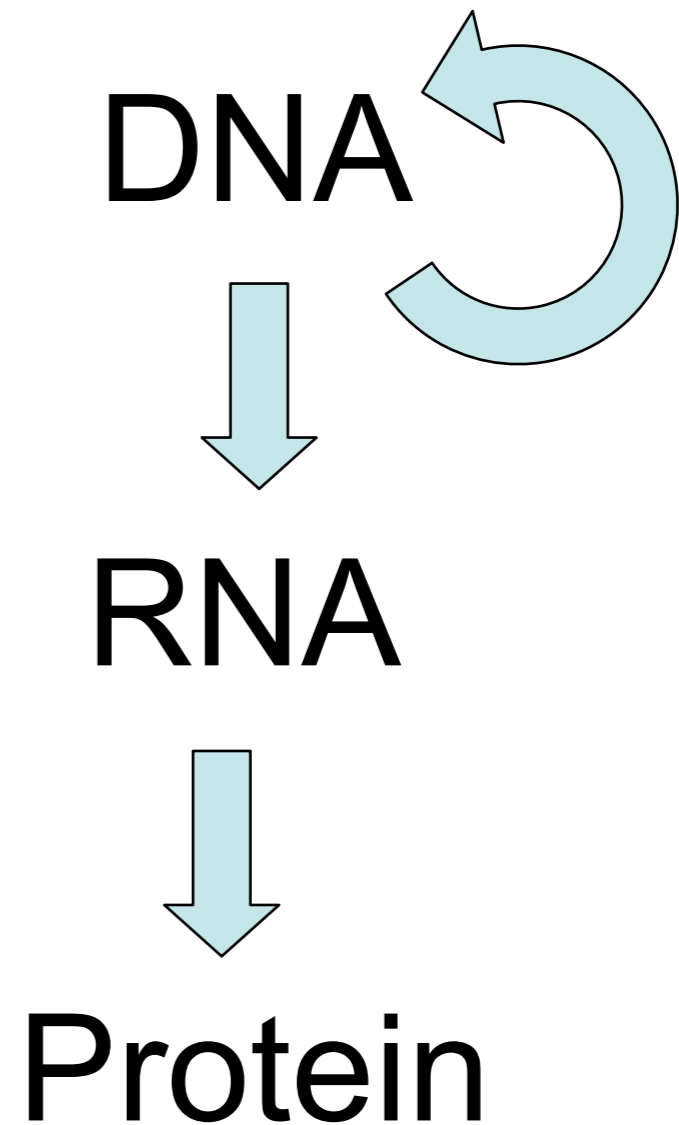
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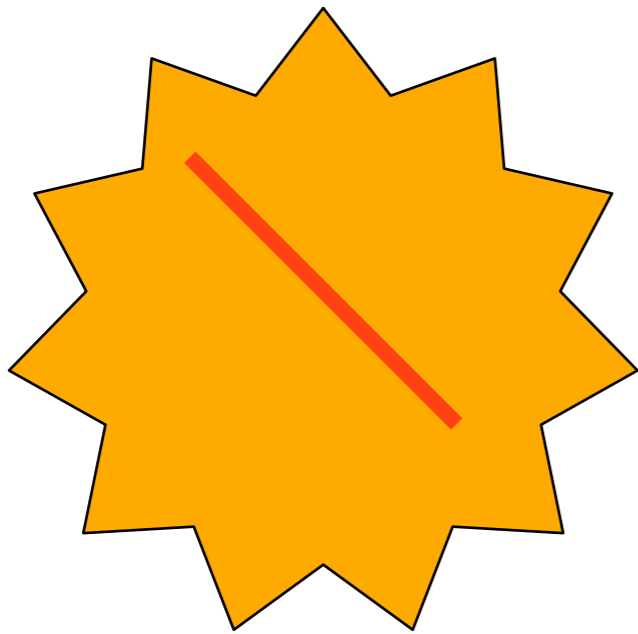
There are many different types of viruses



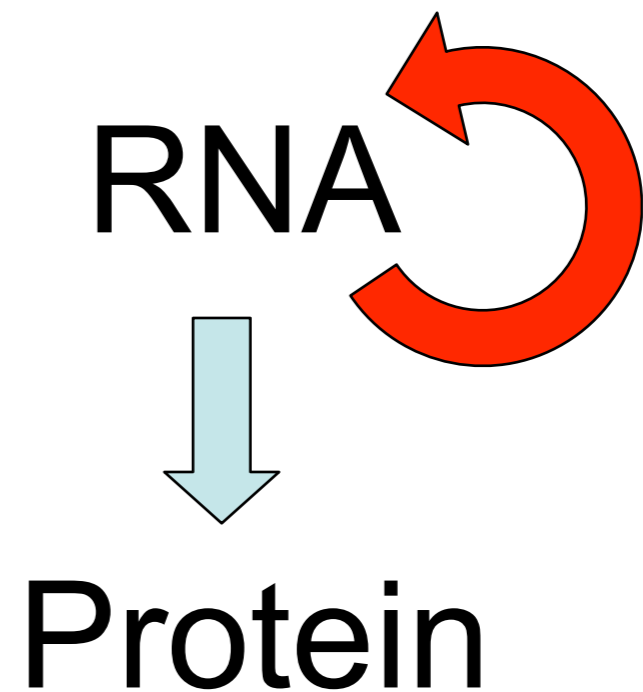
DNA in the infectious particle



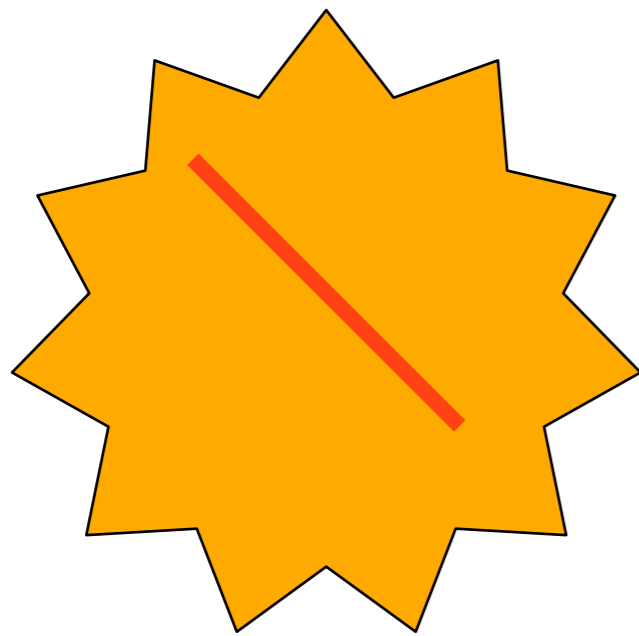
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RNA in the infectious particle

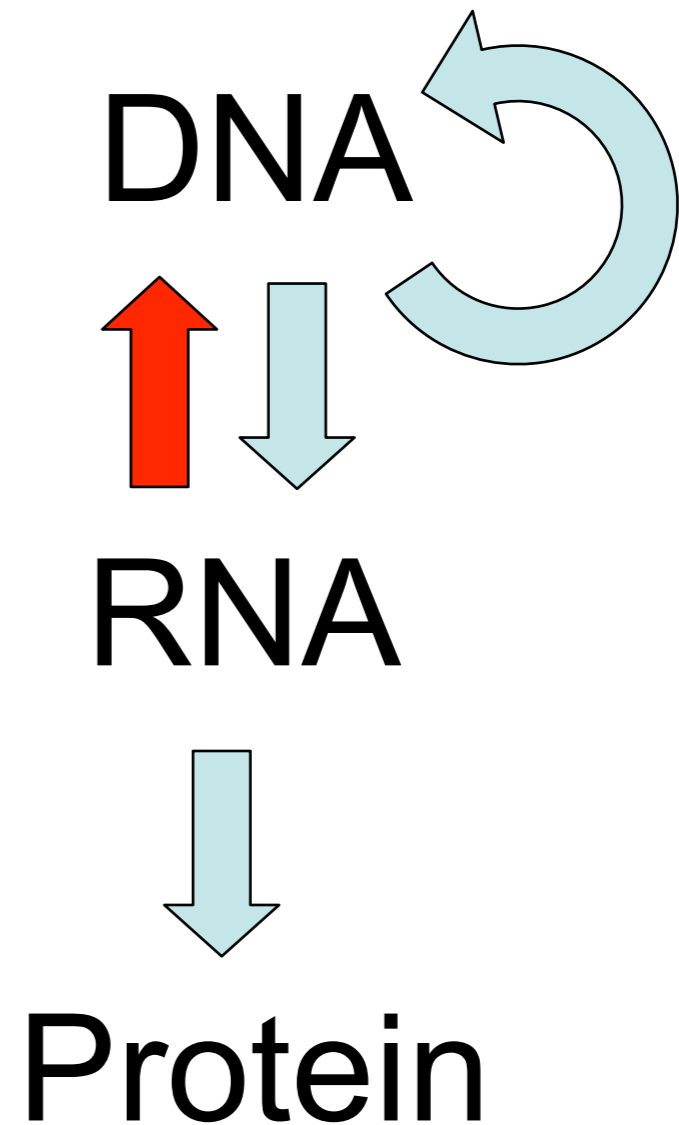


There are many different types of viruses



RNA in the infectious particle

retroviruses



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Two branches of the immune system

- **B-cells**

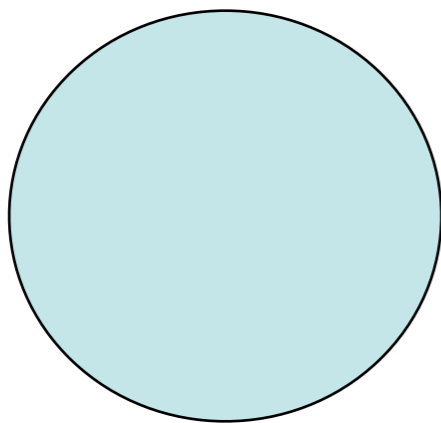
- Make antibodies
- Antibodies recognize and neutralize foreign molecules

- **T-cells**

- Recognize infected or abnormal body cells
- Kill the cells
- Recruit other immune system cells to sites of infection

B cells

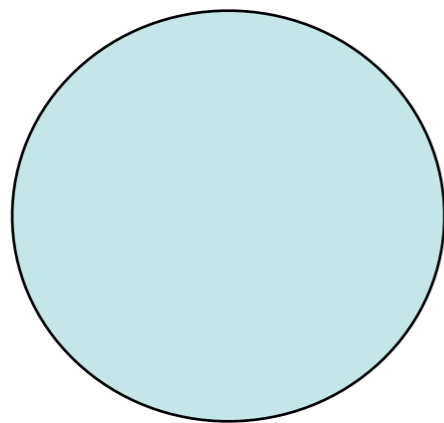
B cells make antibodies



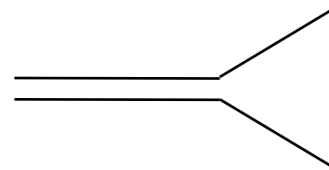
B cell

B cells

B cells make antibodies

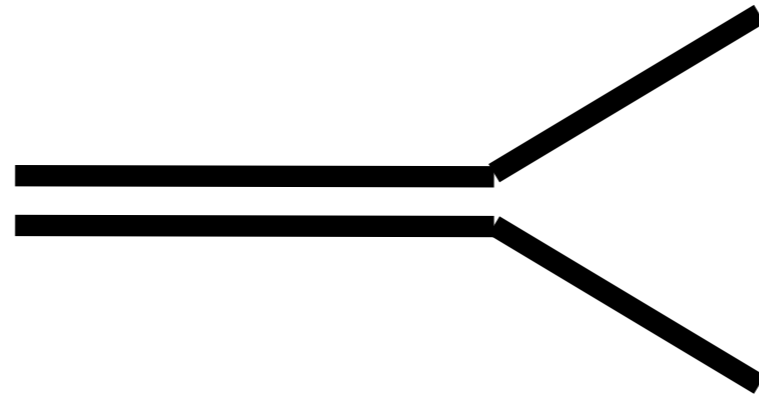


B cell



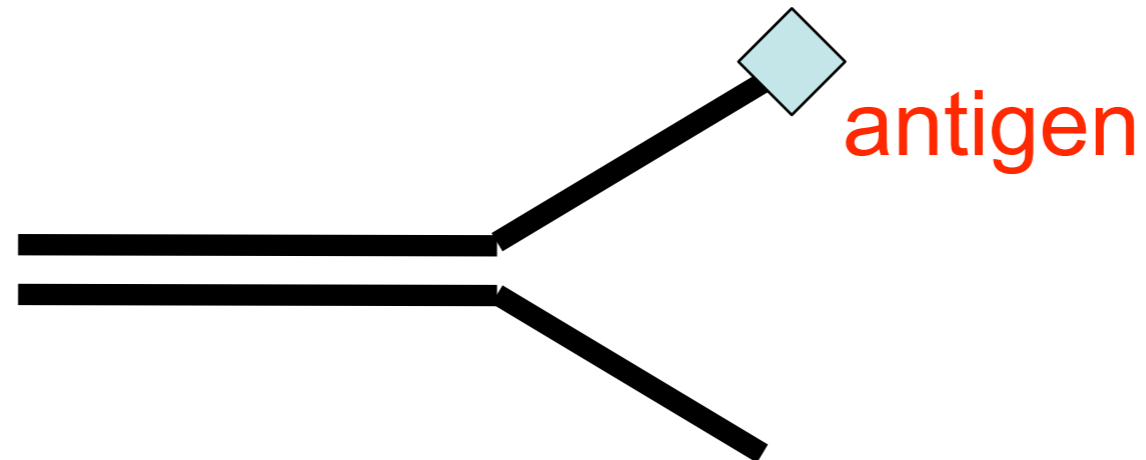
Antibody

Antibodies



Antibodies are proteins that are designed to bind to bind to foreign molecules.

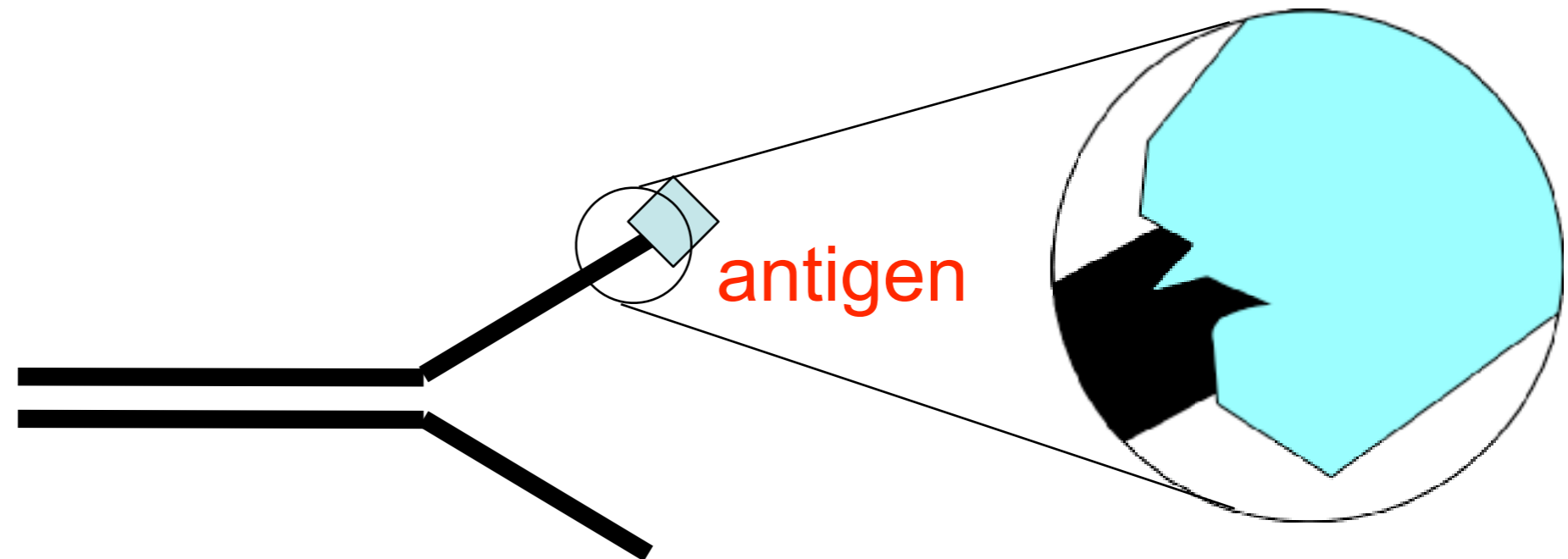
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A molecule that is recognized by an antibody is called an **antigen**.

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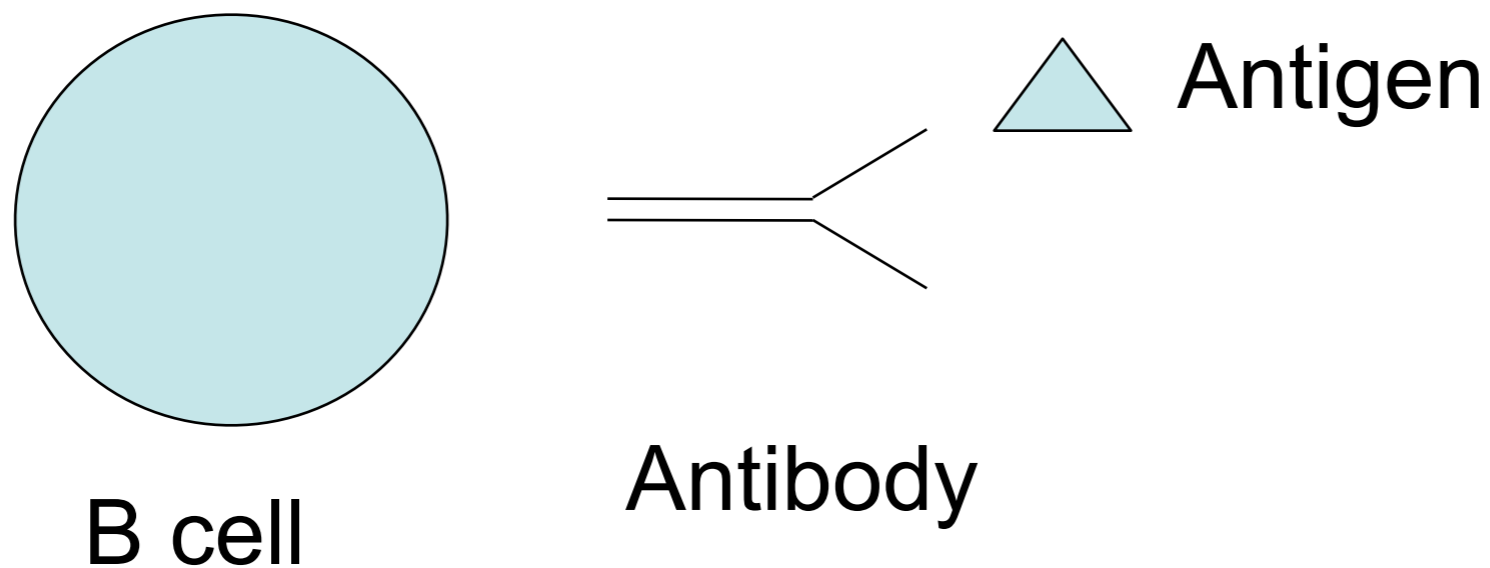
A molecule that is recognized by an antibody is called an **antigen**.

Each antibody has a shape that perfectly fits a site on the antigen like a lock and key

Once an antibody binds an antigen the body destroys the antigen

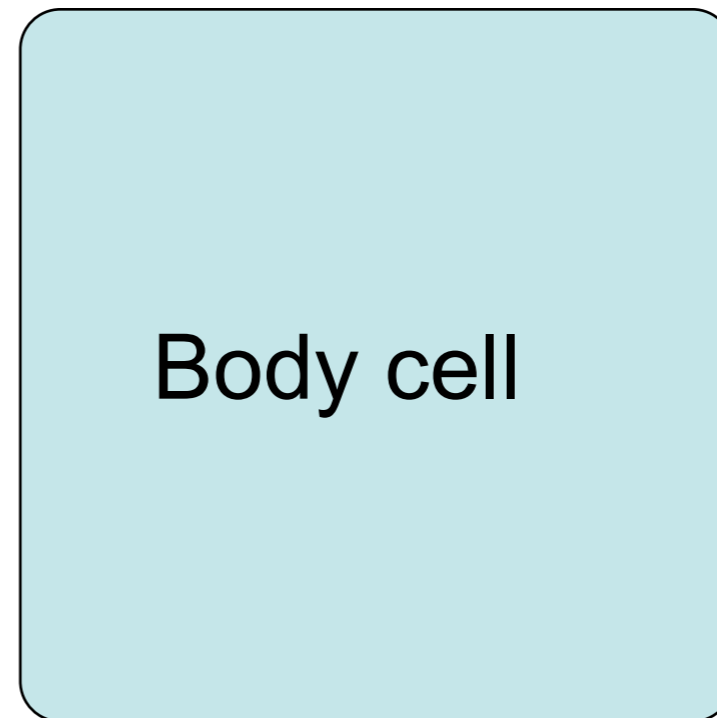
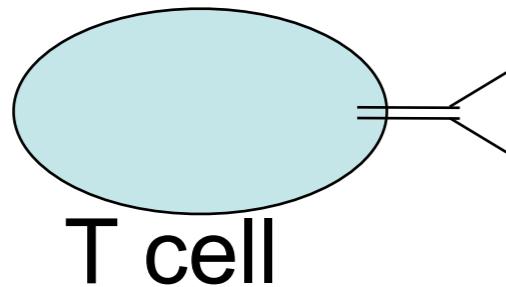
B cells

Each B cell in the blood makes one type of antibody that recognizes one antigen.



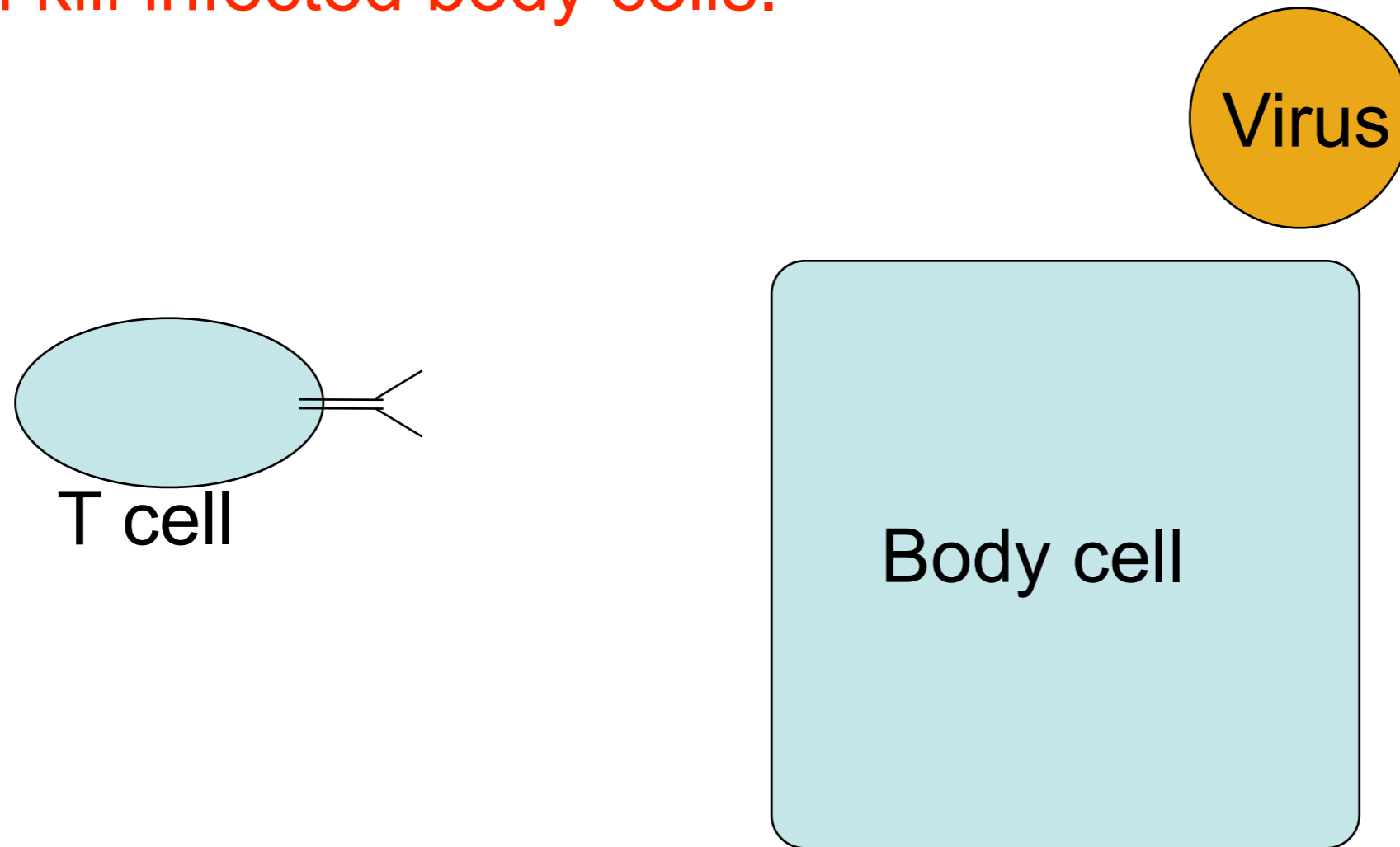
T cells

T cells work the same way, but make a protein T cell receptor that recognizes antigens on cell surfaces then kill infected body cells.



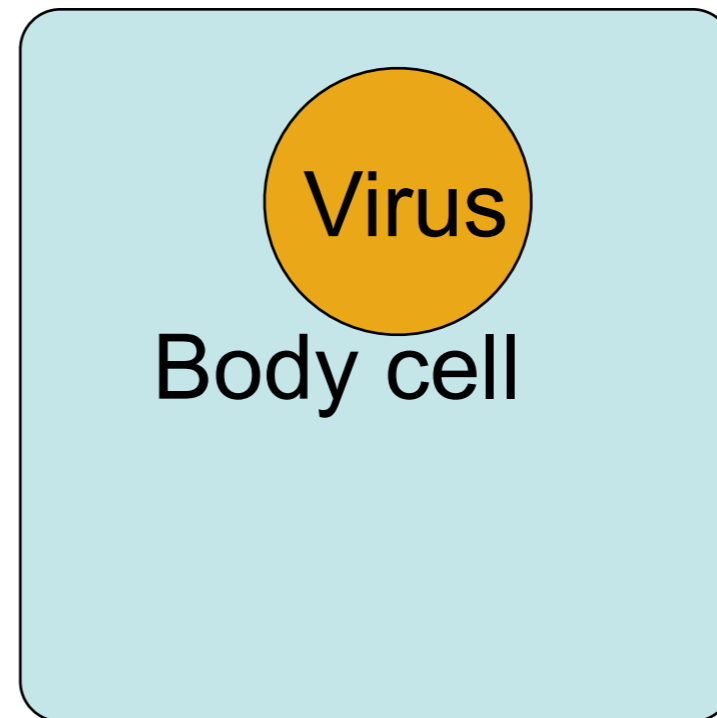
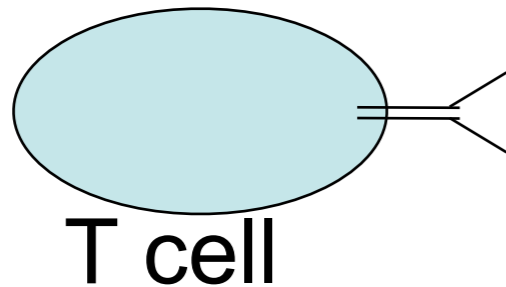
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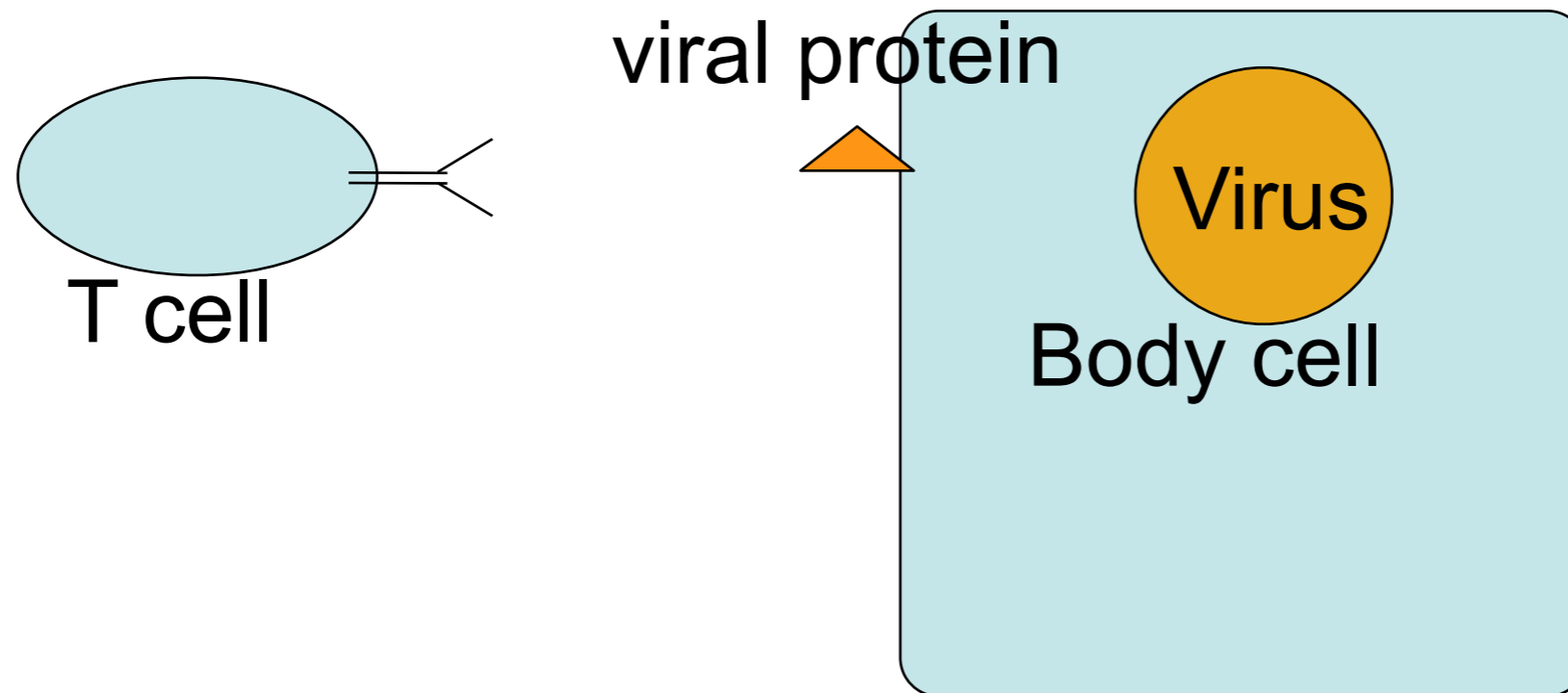
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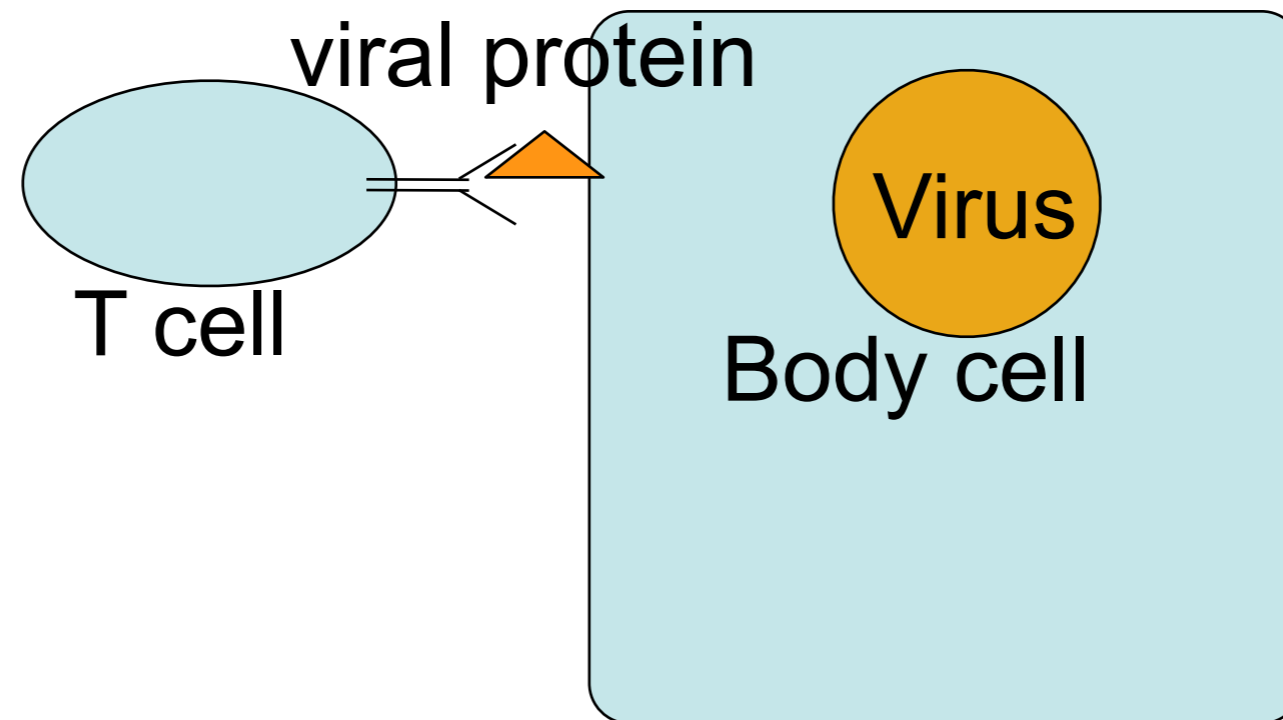
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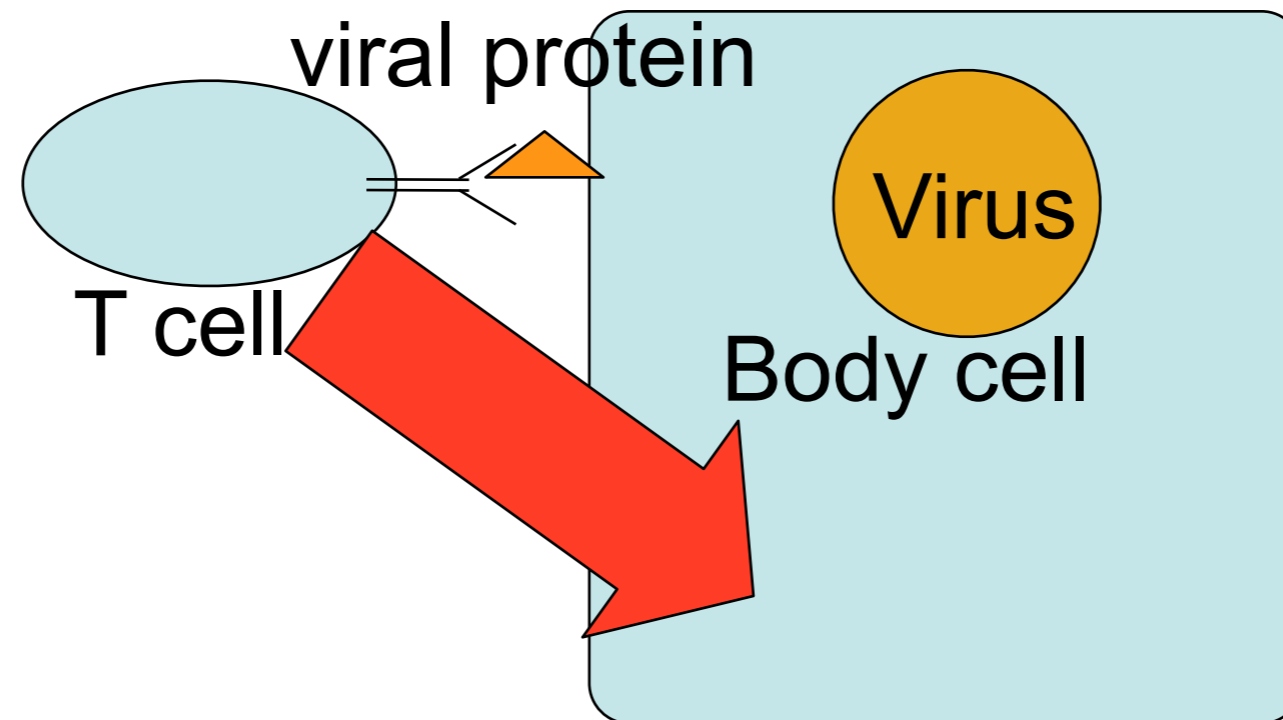
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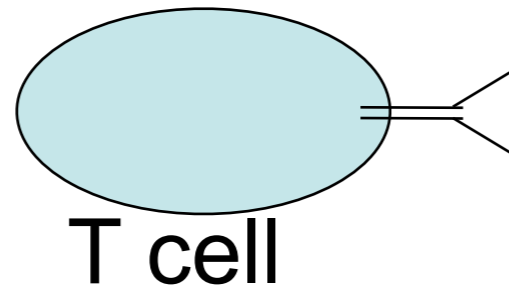
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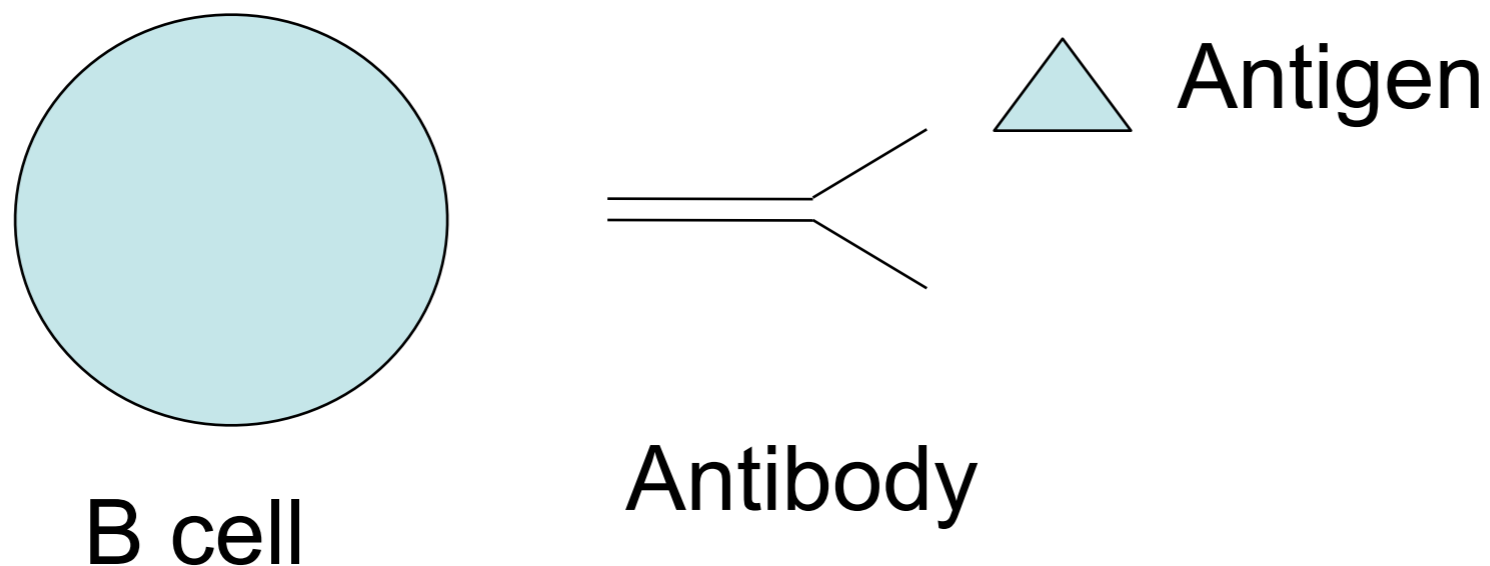
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B cells

Each B cell in the blood makes one type of antibody that recognizes one antigen.

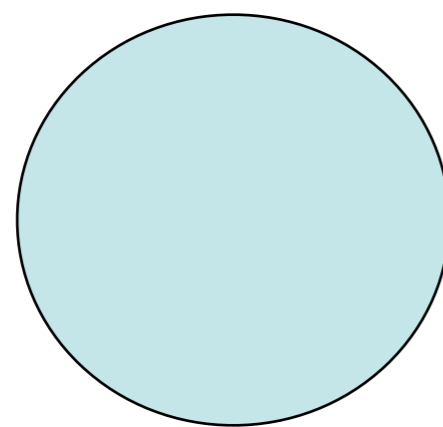
The antibodies are NOT designed to match specific diseases. Their recognition surfaces are RANDOM.



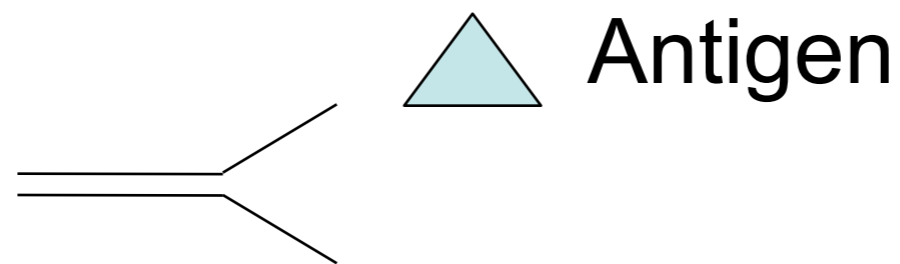
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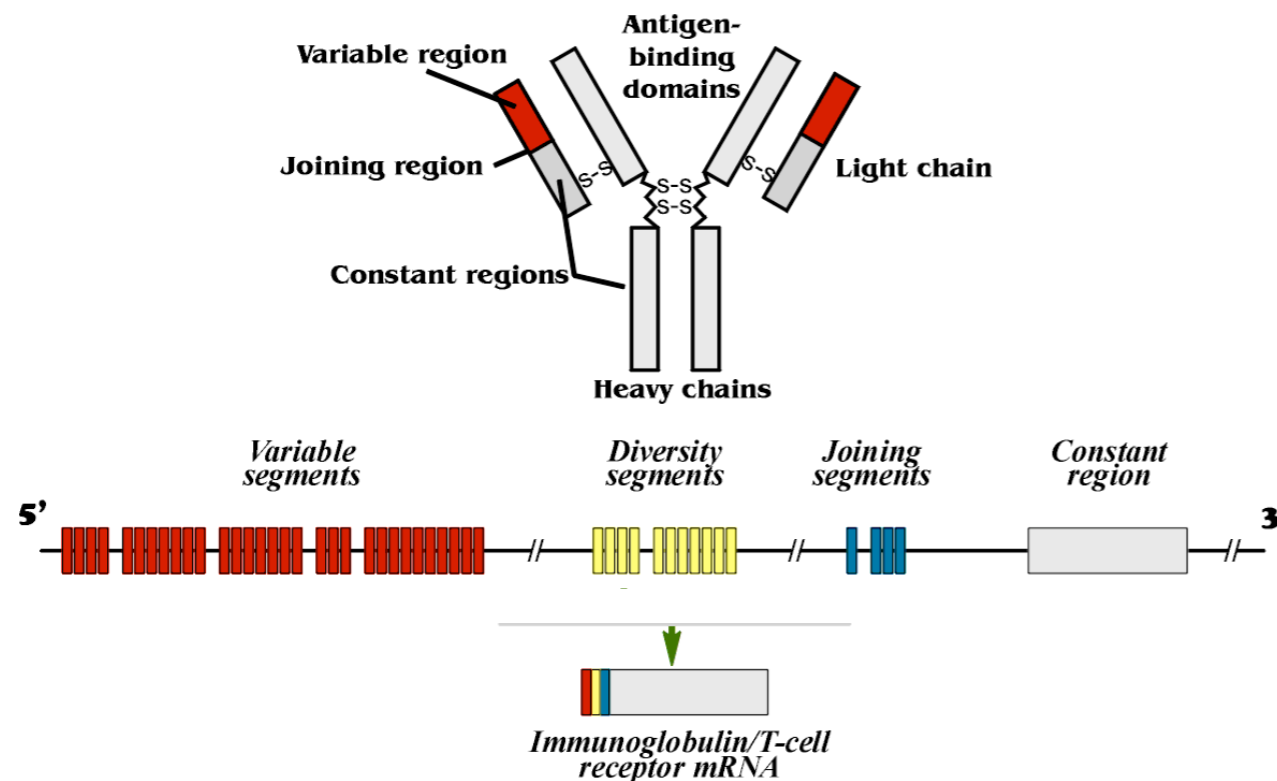
Antibody

Antigen

How do you make billions of random antibody surfaces?

B cells

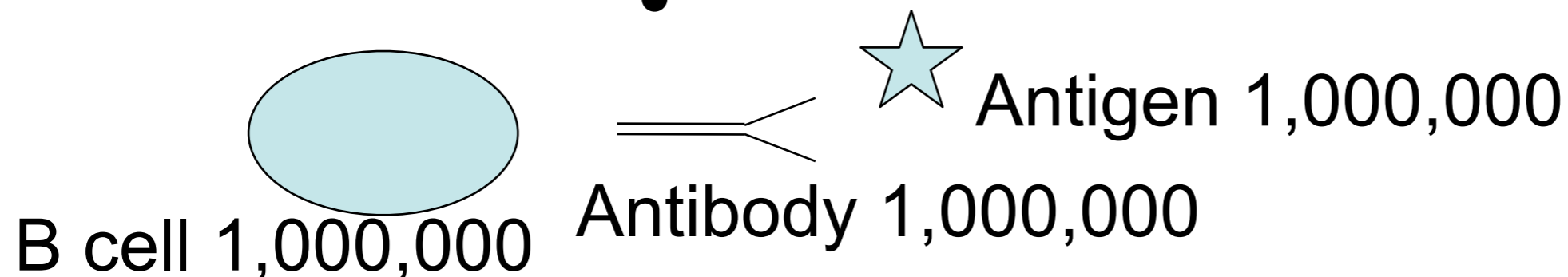
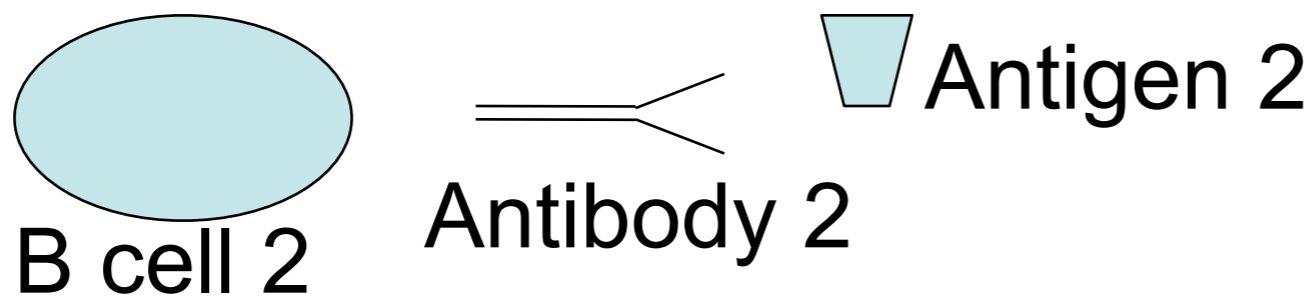
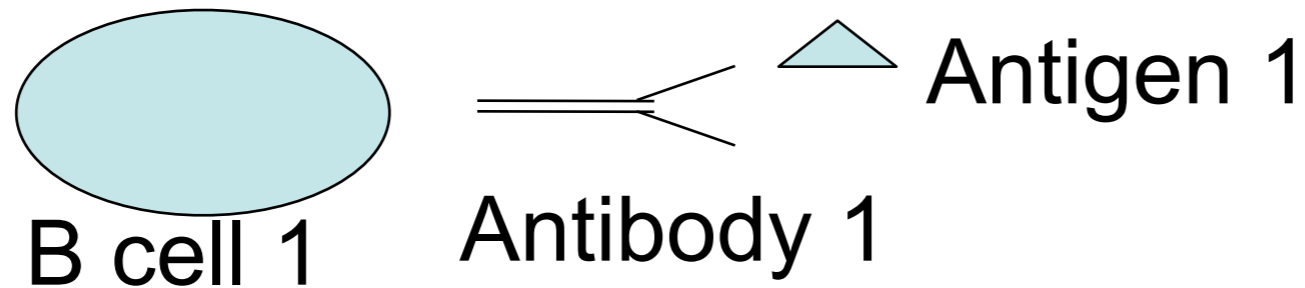
Antibody genes are made by randomly joining gene parts



Once a B cell has made its antibody DNA by recombining parts, it and all of its daughter cells will make the same antibody forever

B cells

Because there are billions of B cells, your body can recognize billions of antigens.



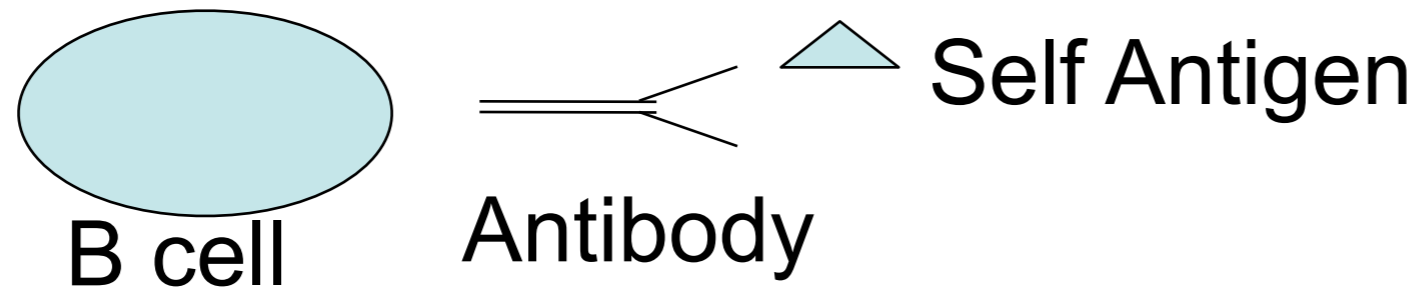
Question

The recombination system is a way to make antibodies that can recognize everything.

So, how does the body not recognize its own proteins?

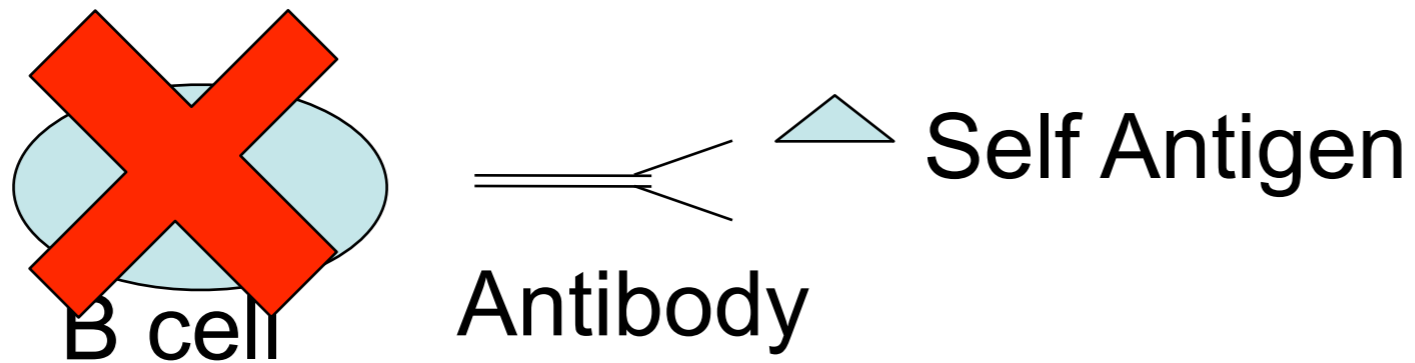
B cells

All B cells that recognize self antigens are killed.



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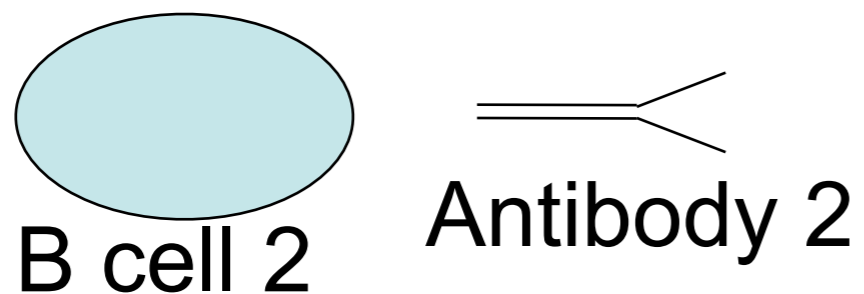
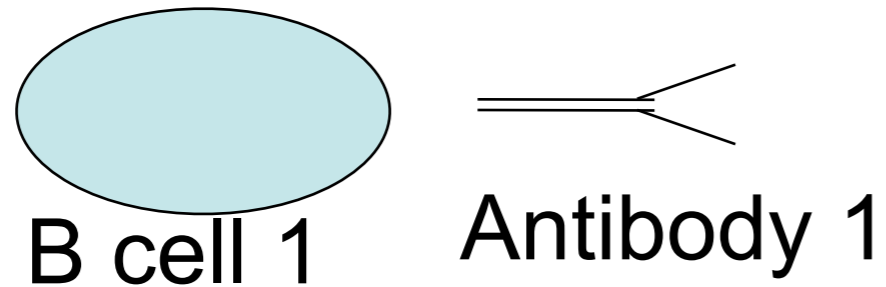
Self/ Non-self distinction

Self/ Non-self distinction

- Seen as Self
 - Chimeras
- Potentially Seen as Non-self
 - Viruses, bacteria and fungi
 - Transgenes
 - Protein drugs
 - Cell transplants
 - Organ transplants

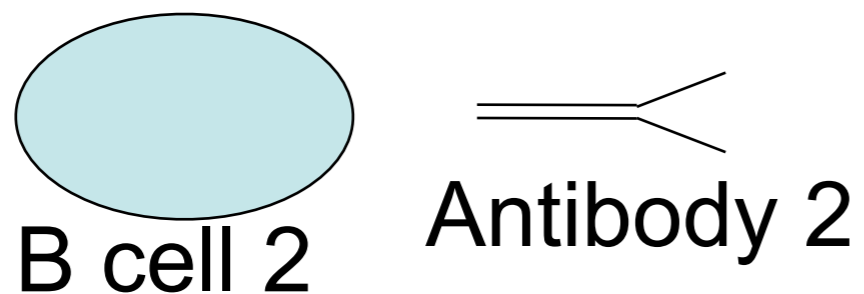
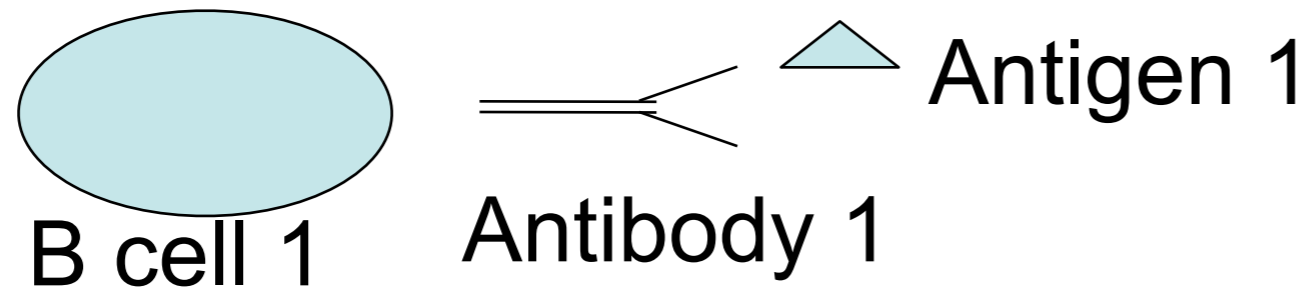
B cells

When a foreign antigen is detected, the B cell that makes that antibody divides rapidly.



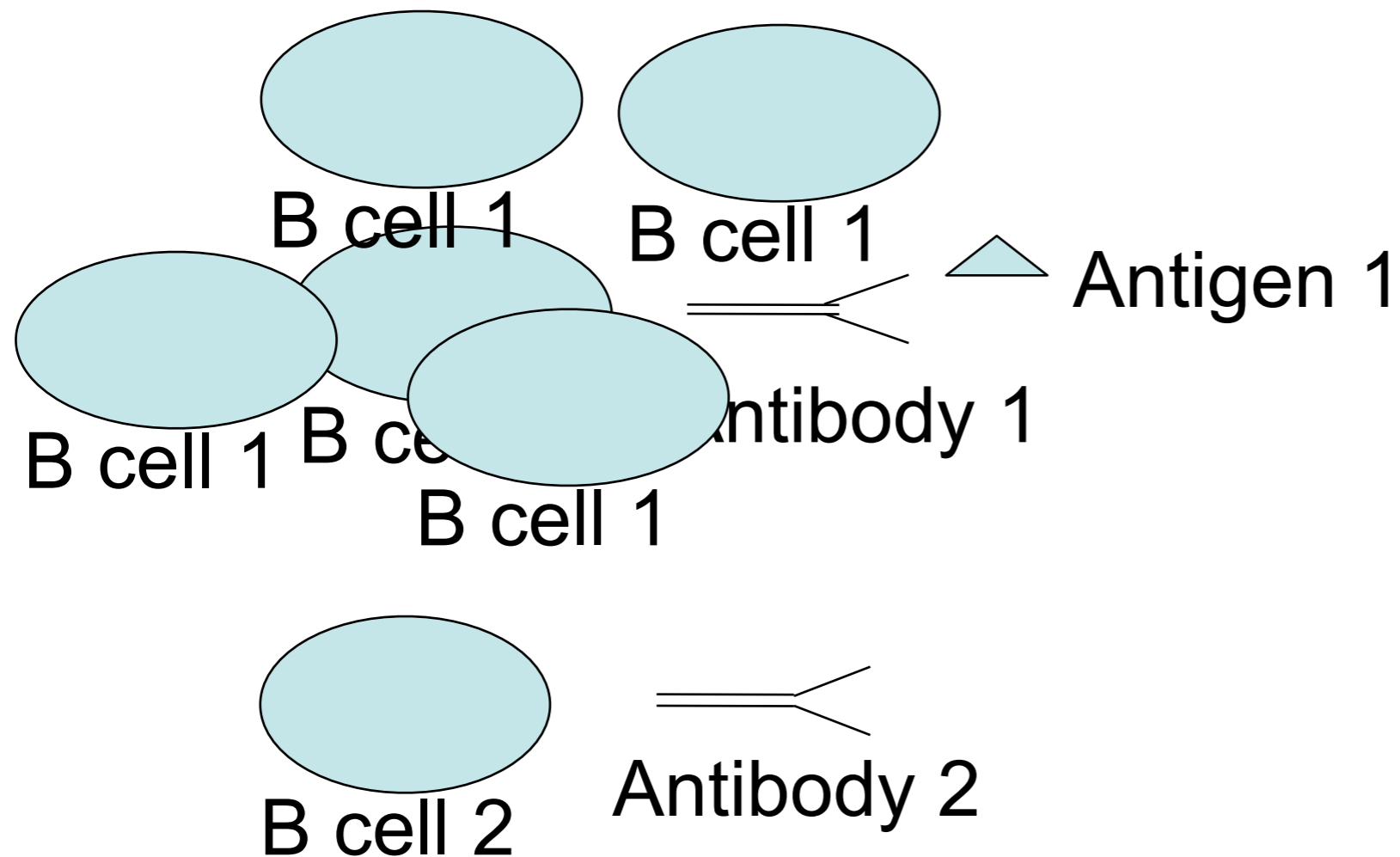
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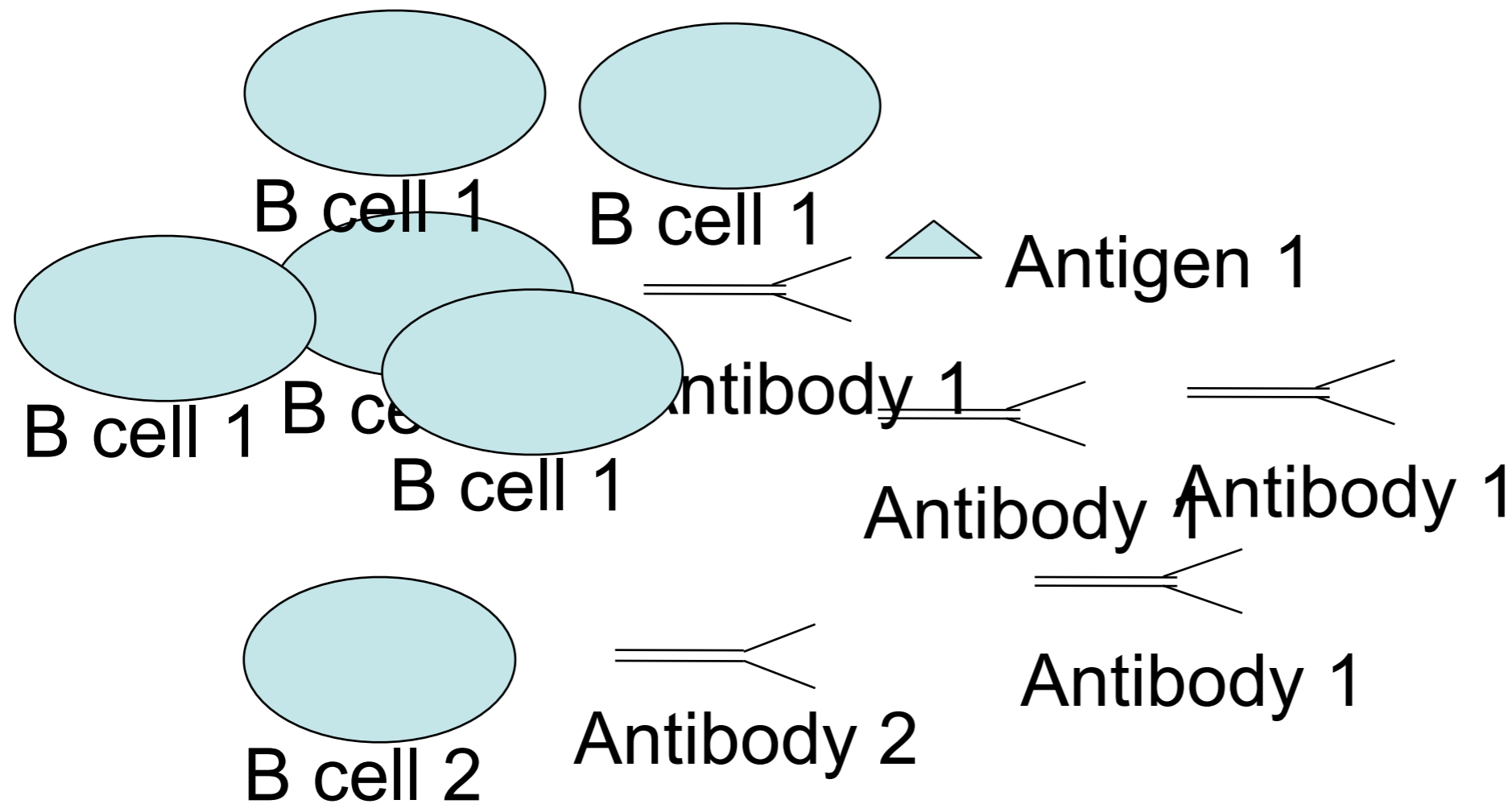
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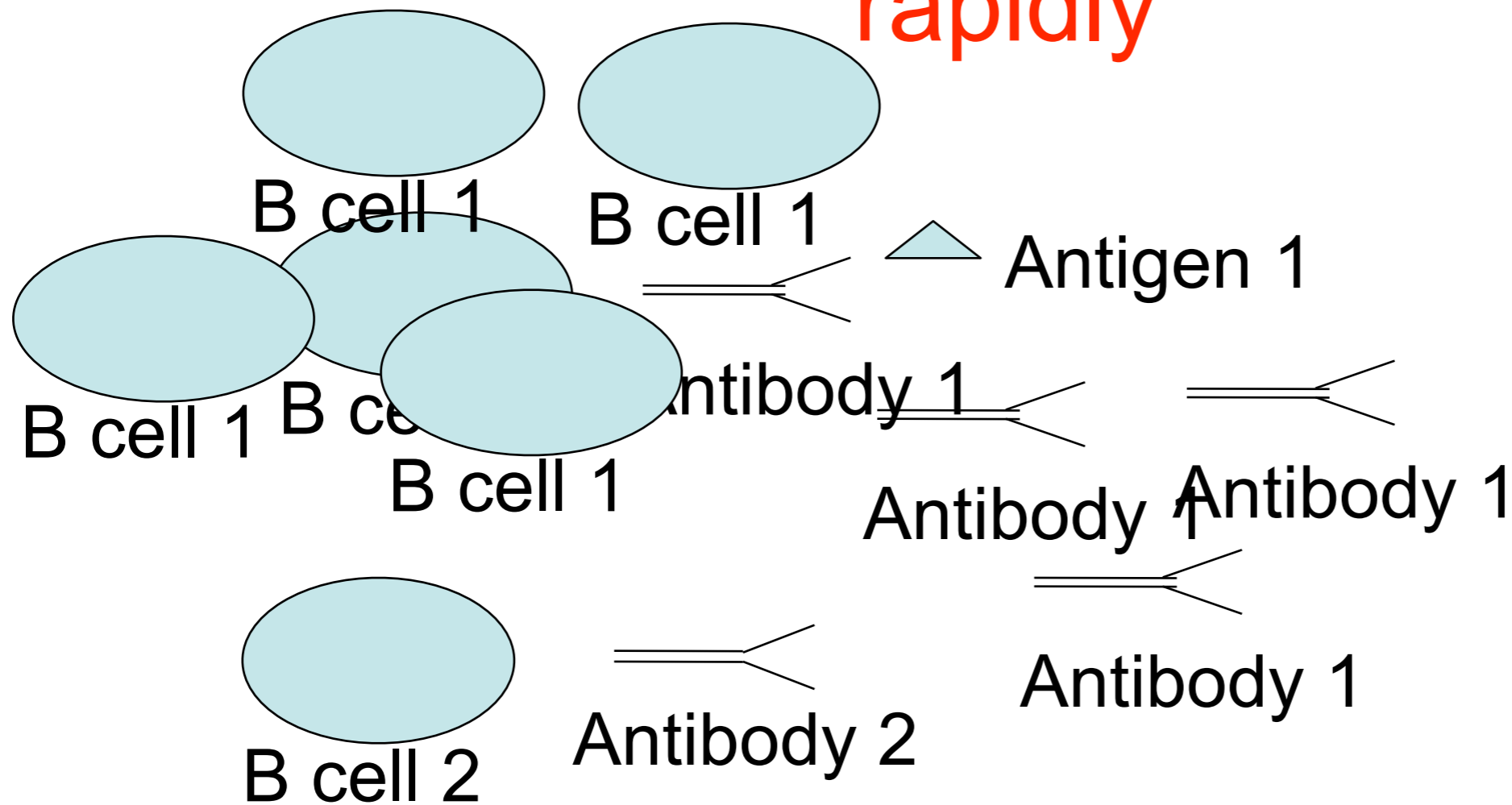
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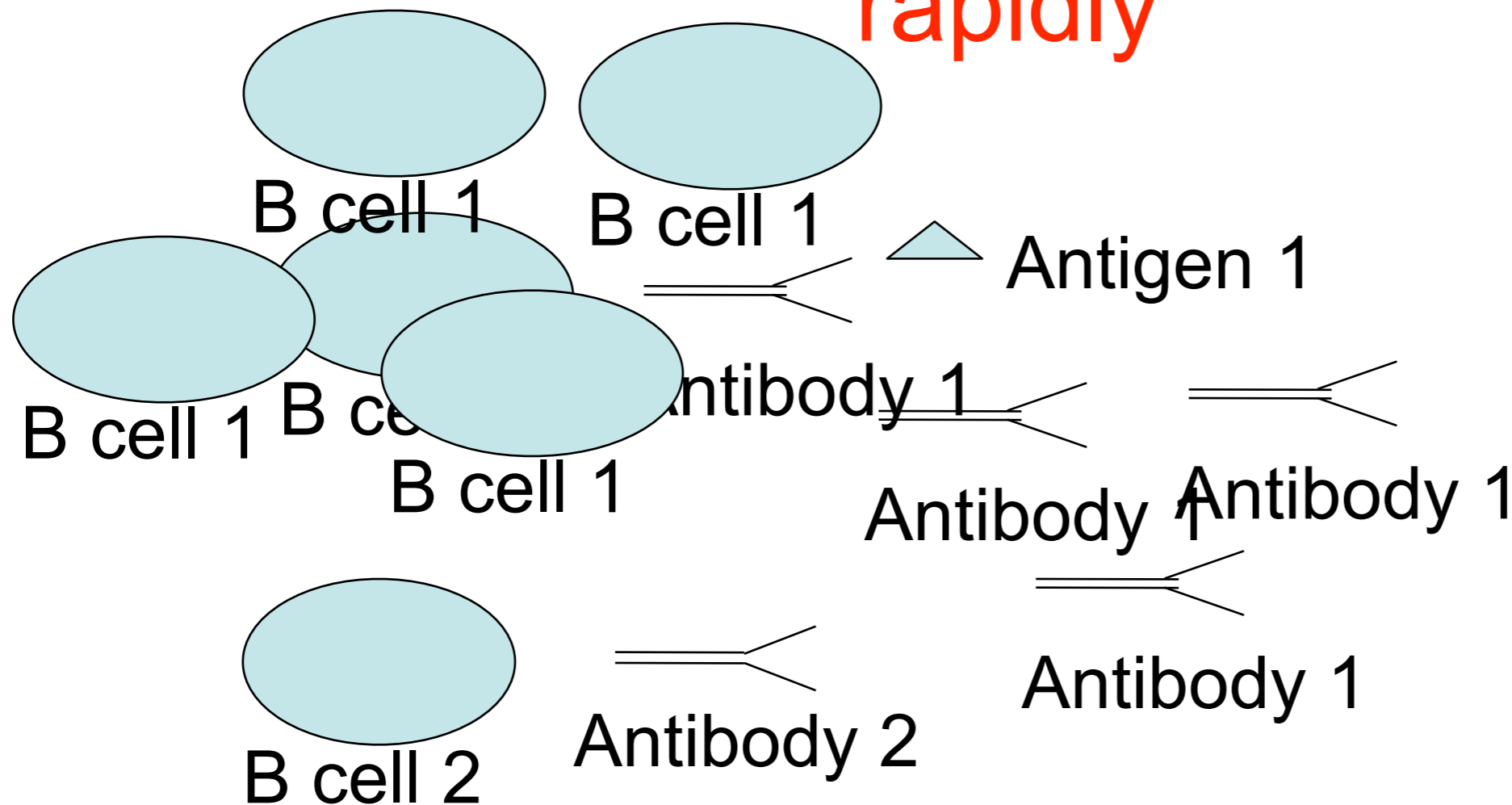
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B cells that have seen antigens before are primed to divide more rapidly



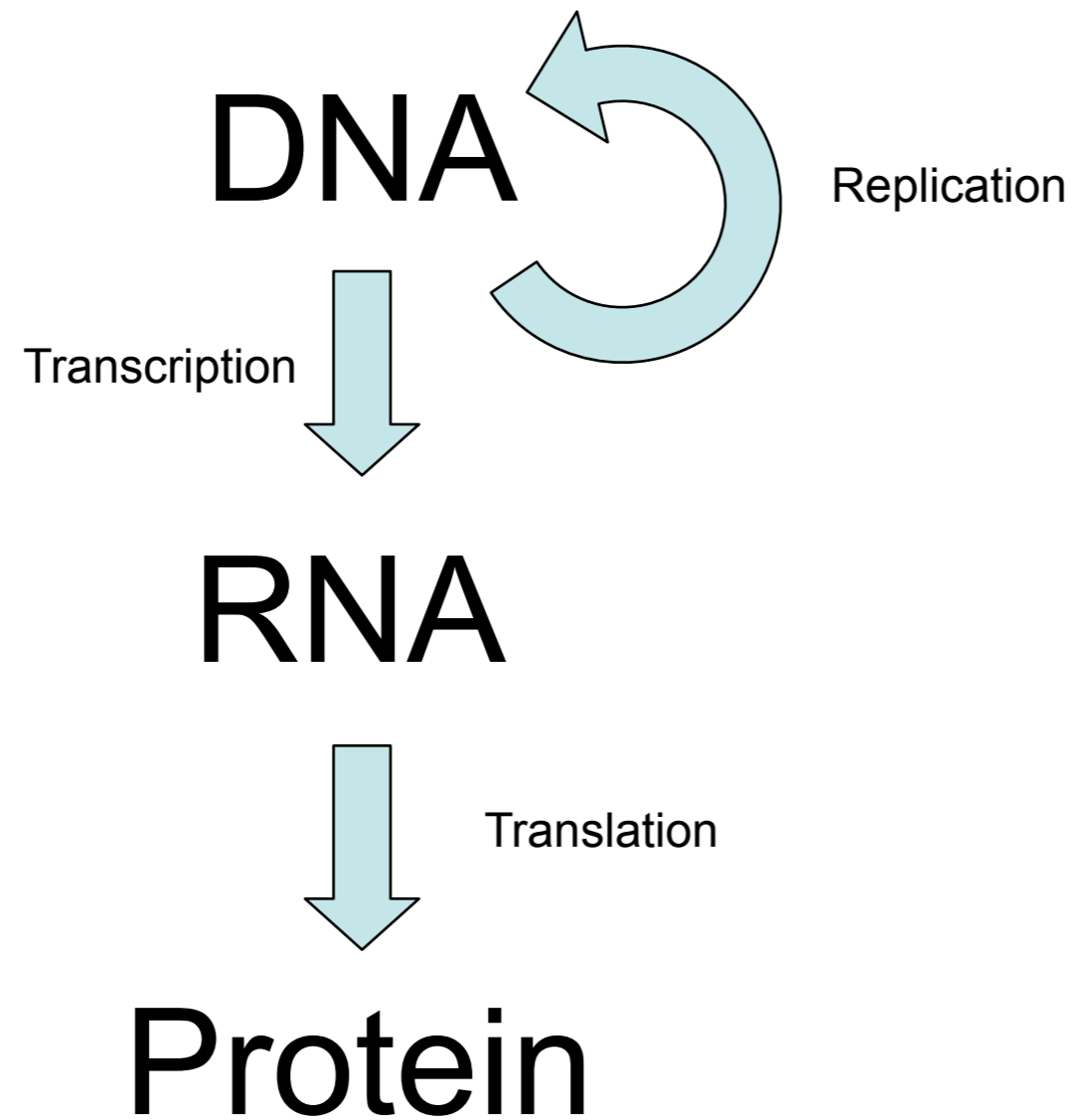
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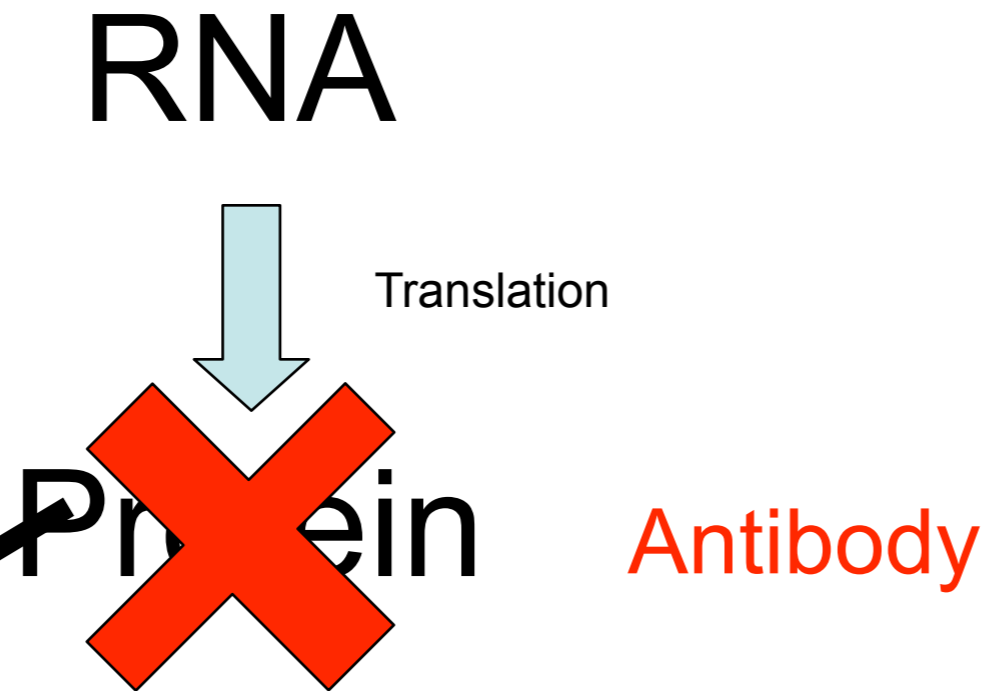
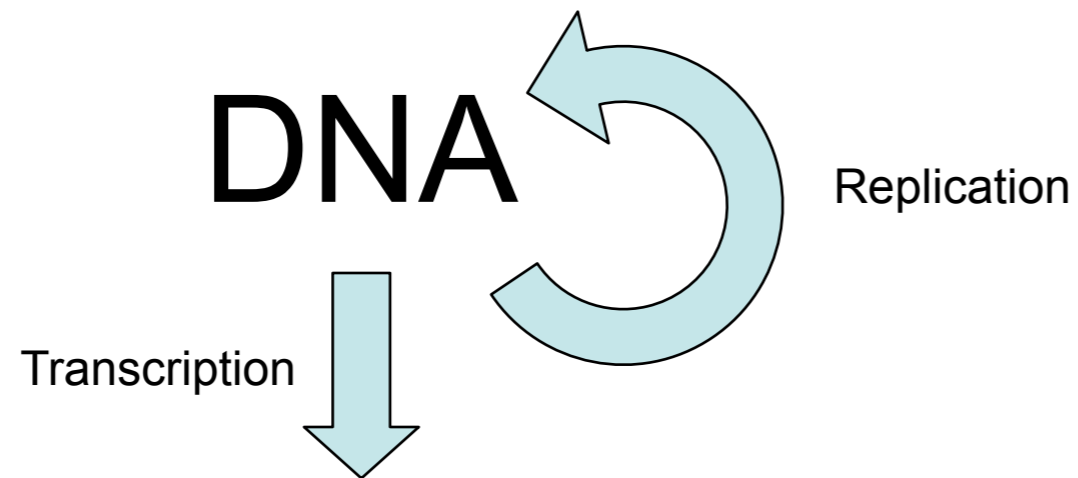


THIS IS HOW
VACCINES
WORK

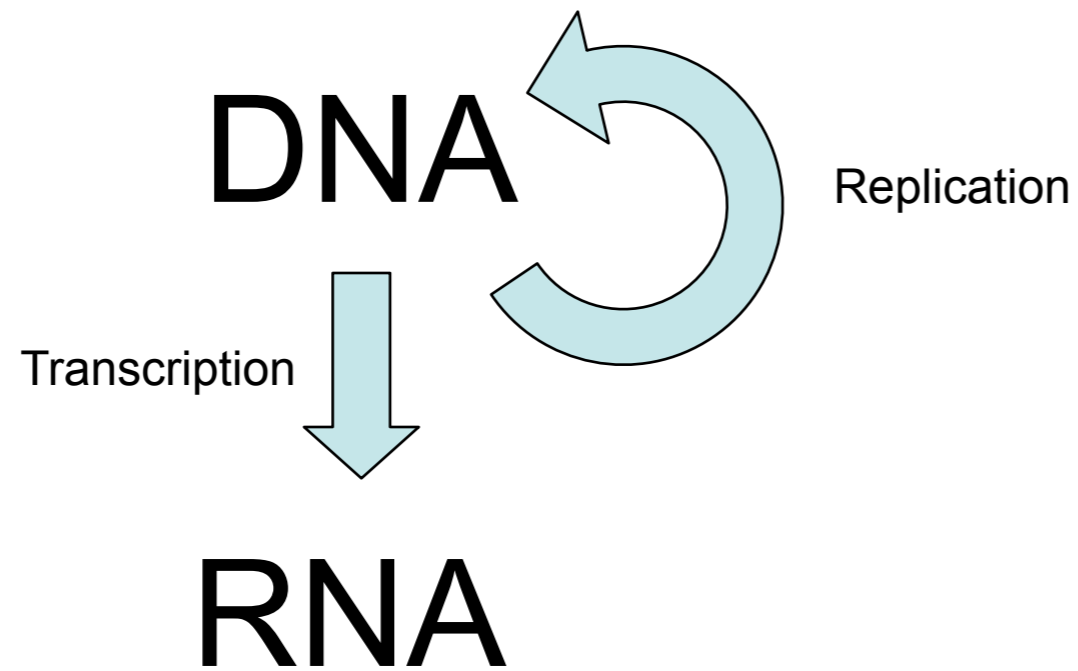
Antibodies can be used as drugs



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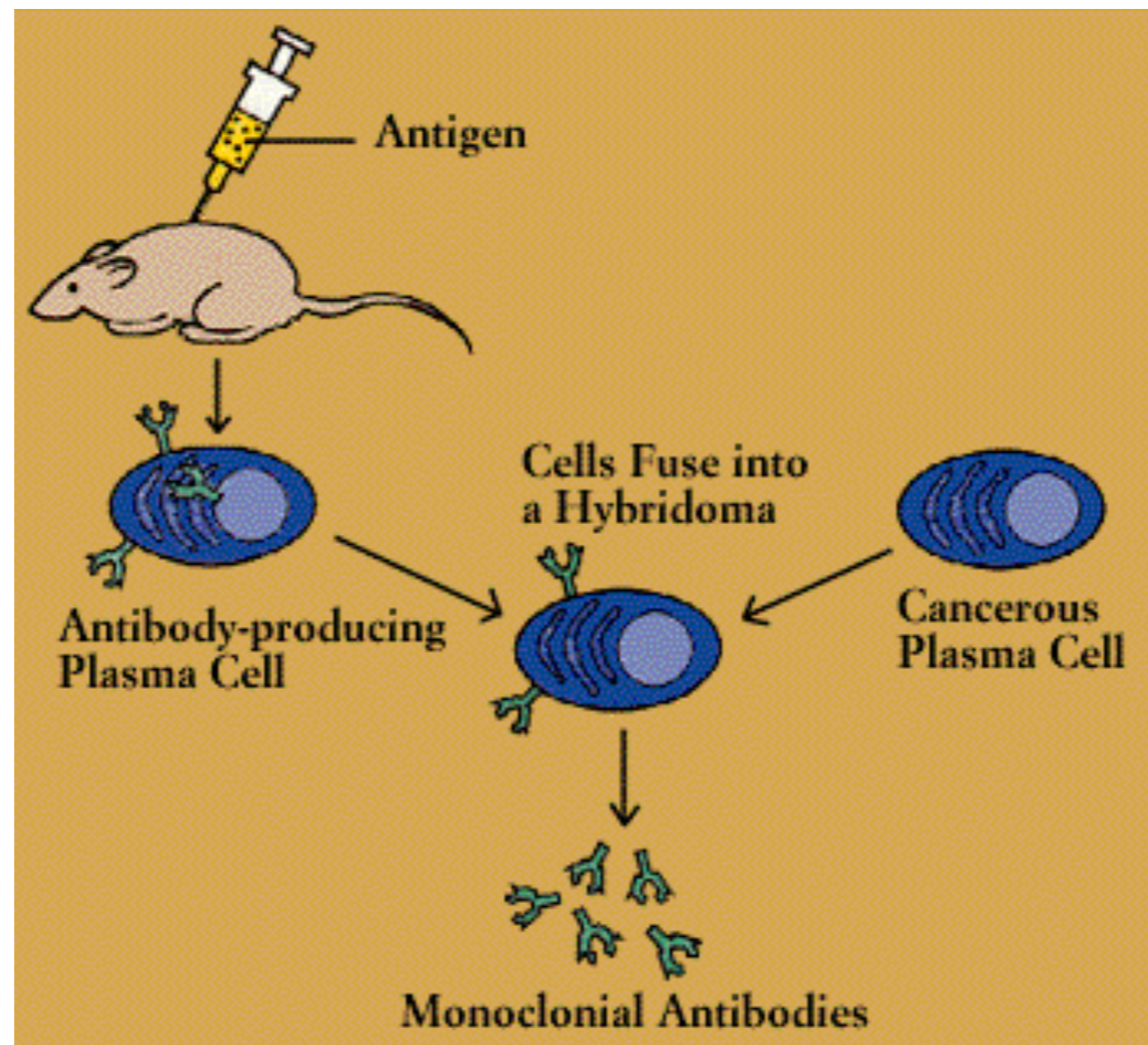


These are not vaccines



We need to get lots of antibody that recognizes a single protein.

Monoclonal antibodies



The hybridoma cell can be grown in a dish forever.
The culture medium contains the antibody (all identical, all against the antigen)

Some monoclonal antibodies in use as drugs

MAB Name	Trade Name	Used to Treat:	Approved in:
Rituximab	Rituxan	Non-Hodgkin lymphoma	1997
Trastuzumab	Herceptin	Breast cancer	1998
Gemtuzumab ozogamicin*	Mylotarg	Acute myelogenous leukemia (AML)	2000
Alemtuzumab	Campath	Chronic lymphocytic leukemia (CLL)	2001
Ibritumomab tiuxetan*	Zevalin	Non-Hodgkin lymphoma	2002
Tositumomab*	Bexxar	Non-Hodgkin lymphoma	2003
Cetuximab	Erbitux	Colorectal cancer Head & neck cancers	2004 2006
Bevacizumab	Avastin	Colorectal cancer	2004

↑
Note that the generic names all end in mab

Humanized mouse

- Kirin (the beer company) has made mice that have human chromosomes containing the human antibody genes.
- The mice have had their antibody genes eliminated.
- These mice (TransChromo Mouse™, TC Mouse™) make fully human antibodies.



Humanized cow

Kirin in collaboration with Hematech, a biotechnology company based in Sioux Falls, South Dakota, is developing a TransChromo™ Cow (the TC Cow™). You can get more antibodies from a cow than a mouse.

South Dakota 2008
business of the year



TM

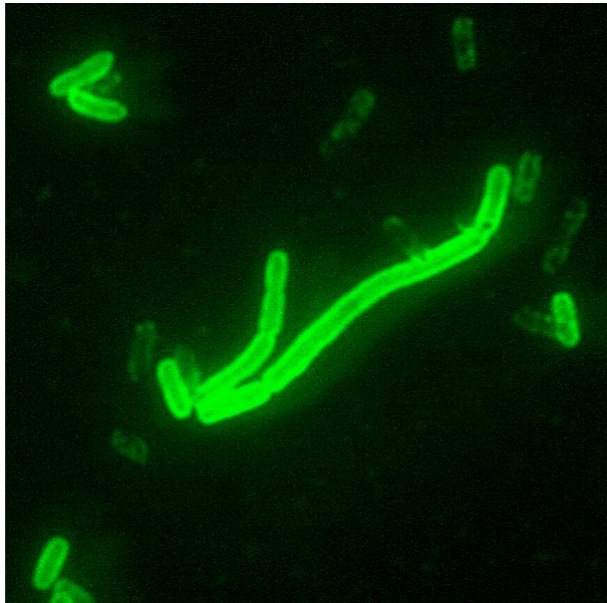
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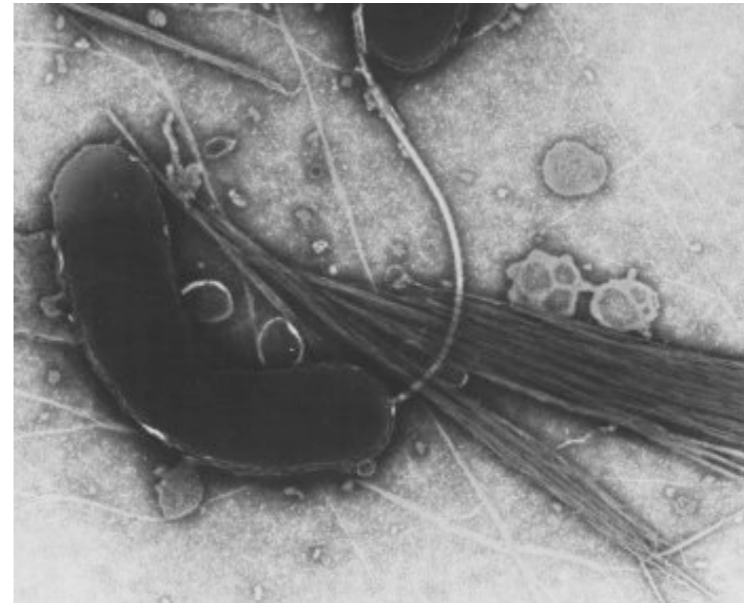
Bacteria vs. virus

Bacteria	Virus
single celled organism	DNA or RNA coated with protein (+other)
can grow outside of cells	has to get into cells to grow
can often infect a wide array of animals	more limited host range
antibiotic treatment	antiviral treatments

Antibiotics have conquered most bacterial diseases



- Plague



- Cholera



- Tuberculosis

- Typhus
- Leprosy

Some bacterial diseases are becoming **resistant** to all available antibiotics

Staph infections are a problem in hospitals (about half of hospital infections), and more are being found to be resistant to antibiotics.

Cases of antibiotic resistant tuberculosis are also a growing health concern

Antiviral drugs

Tamiflu (NOT a flu vaccine), is a chemical inhibitor of neuraminidase. Broad spectrum anti-influenza, not strain specific like a vaccine.

HIV drugs:

Reverse transcriptase inhibitors AZT etc.(1987)

Protease inhibitors (1995)

Fusion inhibitor (2003)

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Immunization has conquered
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Immunization is available for many diseases

- **Viral**
 - Mumps
 - Measles
 - Rubella
 - Hepatitis (A and B)
 - Influenza
 - Meningitis
- **Bacterial**
 - Diphtheria
 - Pertussis
 - Tetanus

Vaccine

- A vaccine exposes your body to the virus so that your body is primed to fight off an infection (more on this later)
- Vaccines can be made from a virus that has been killed or rendered very sick or from proteins on the virus

Smallpox was the first disease completely eliminated



US cases: 102,791 in 1921

15,000 cases annually between 1932 and 1939

Last U.S. case 1949

Routine U.S. vaccination until 1971

Last world case 1977

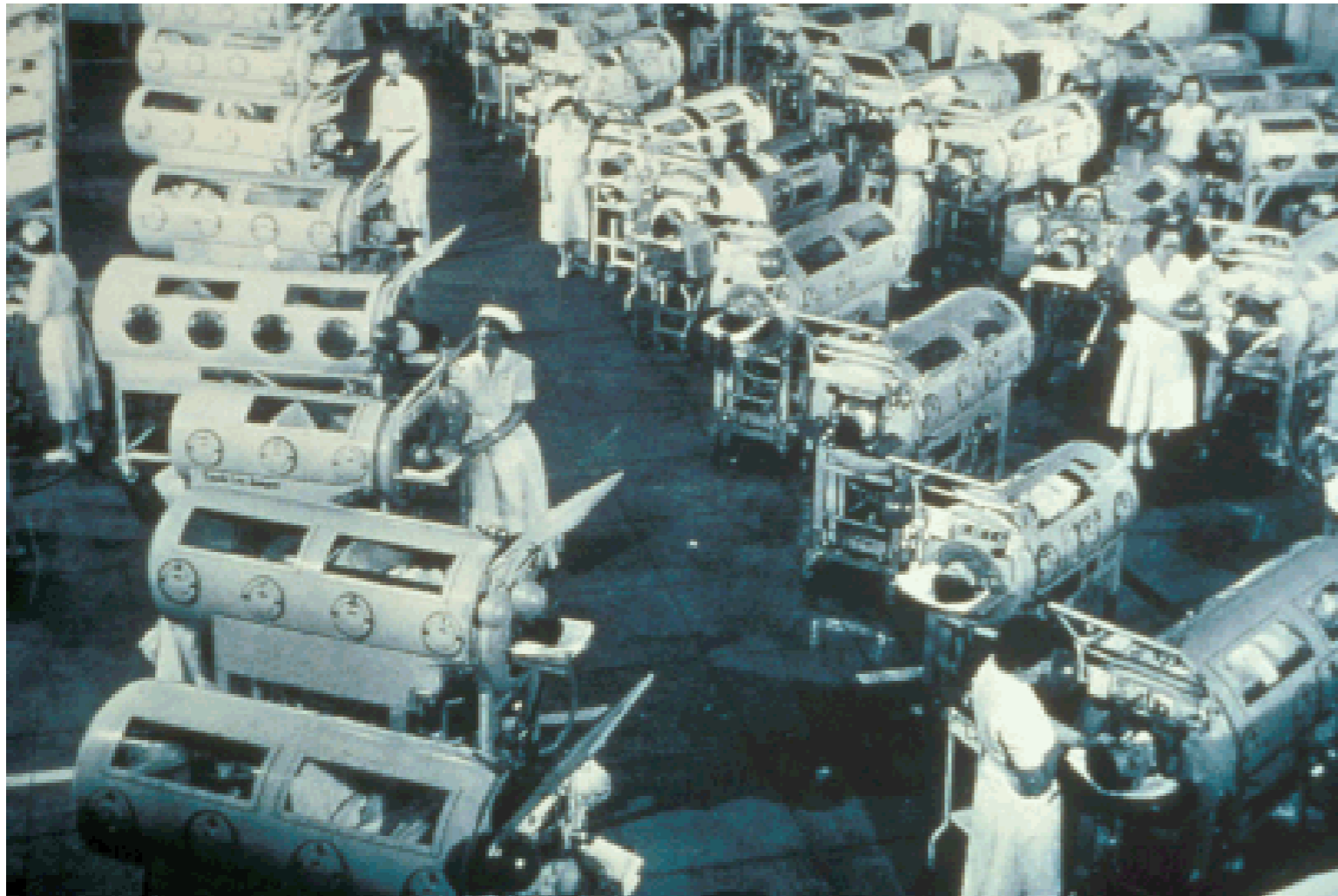
Only isolates are stored at CDC in Atlanta and VECTOR Novosibirsk, Russia

Smallpox aside

The full genome sequence of smallpox is
publicly available

<http://www.ncbi.nlm.nih.gov/nuccore/623595>

Polio



Polio infects nerve cells and causes paralysis.

Iron Lung ward at Rancho Los Amigos Hospital,
Downey, California, ca. 1953

Polio



FDR contracted polio in 1921 at the age of 39.

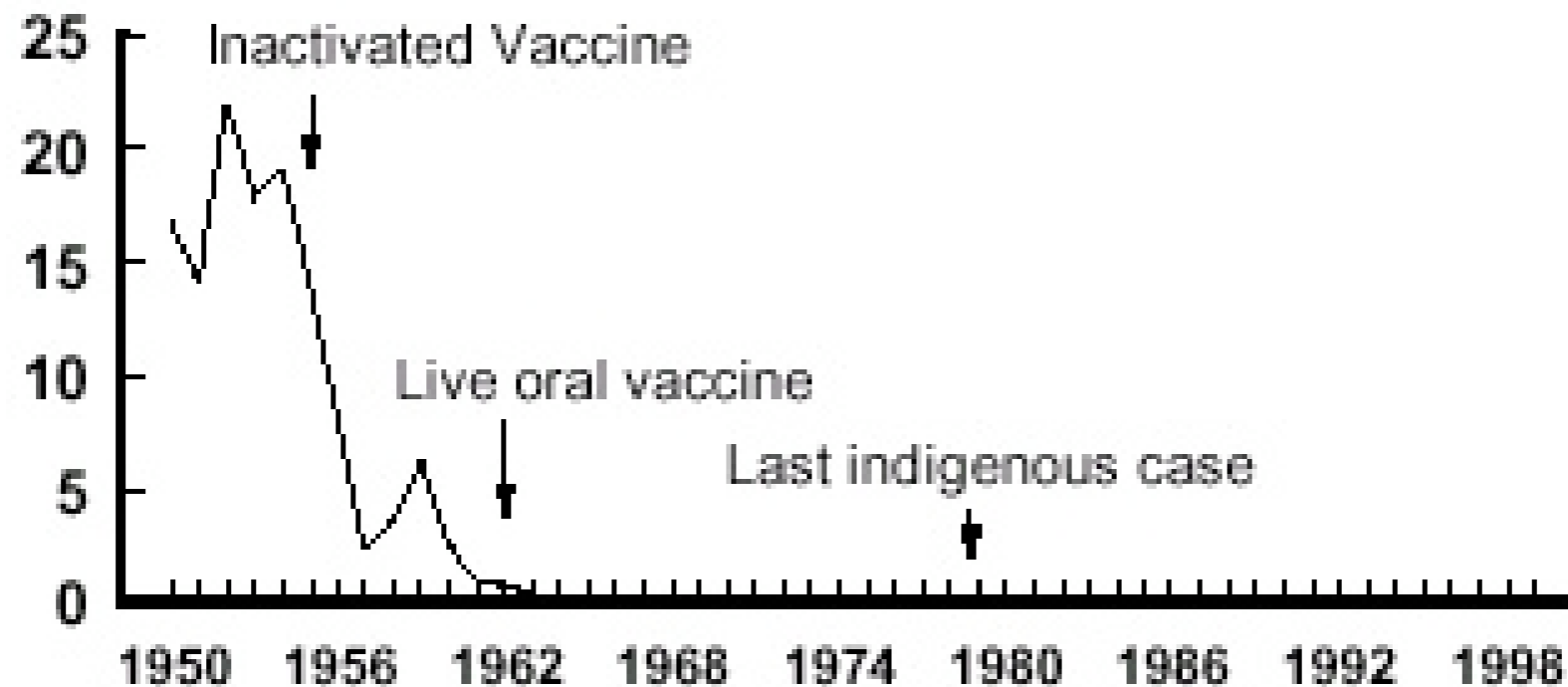
The National Foundation for Infantile Paralysis, later renamed the March of Dimes, was established in 1938 and grew out of the great success of the Birthday Balls for President Franklin Roosevelt.

Polio is on the way out

Poliomyelitis - United States, 1950-1999

Cases

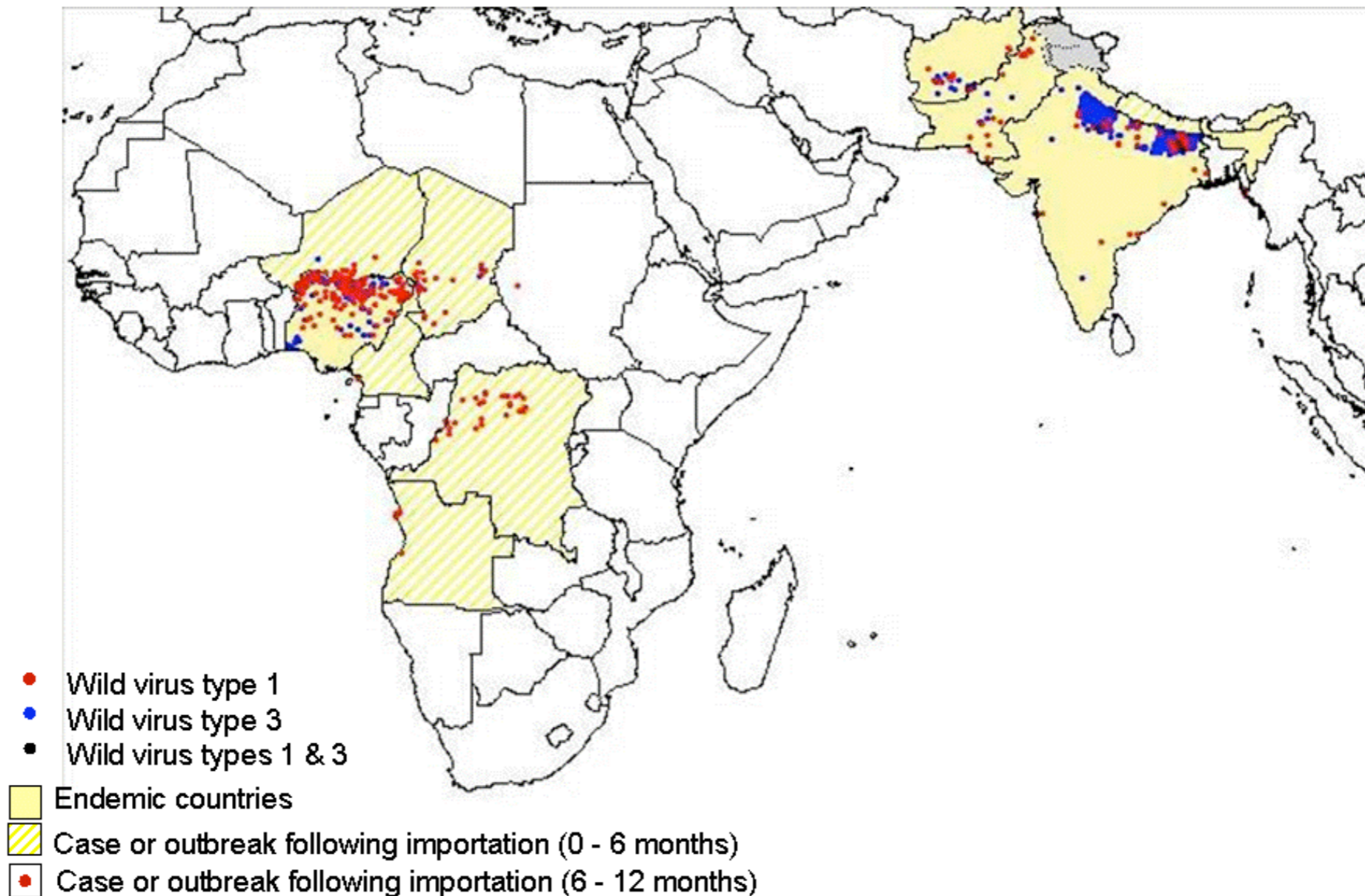
(Thousands)



[HTTP://WWW.BROWN.EDU/COURSES/BIO_160/PROJECTS2000/POLIO/POLIOMYELITIS-US.JPG](http://www.brown.edu/courses/bio_160/projects2000/polio/poliomyelitis-us.jpg)

Polio is on the way out

Wild Poliovirus*, 26 Mar 2007 – 25 Mar 2008



*Excludes viruses detected from environmental surveillance and vaccine derived polio viruses.

Data in WHO HQ as of 25 Mar 2008

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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New vaccines are being introduced

- Chickenpox
- Rotavirus (diarrhea) 600,000 children die from diarrheal disease caused by rotavirus, and another two million are hospitalized. Nearly every child in the world will suffer an episode of diarrhea caused by rotavirus before age five
- Human Papilloma virus

Recombinant vaccines



Current flu vaccines are produced in chicken eggs.

It takes 6 months to produce a complete batch of new vaccine every year.

Techniques using cultured human cells and recombinant viral proteins are being developed to cut the time and costs.

Vaccine Dilemmas

Herd Immunity

Not everyone in a population has to be immunized for a vaccine to be effective.

Herd immunity: If most people are immunized, the ones who aren't are unlikely to come in contact with an infected individual.

If there is a cost (financial, real or perceived risk) from vaccination, this causes a dilemma.

Cultural issues

Polio vaccination programs in Nigeria and India were halted by rumors that the vaccines were a western attempt to harm them.

Only by getting local civic and religious leaders to publicly endorse the program could vaccination resume.

Suspicion of vaccination occurs even in Western countries.

HPV



Worldwide


GARDASIL.
[Quadrivalent Human Papillomavirus
(Types 6, 11, 16, 18) Recombinant Vaccine]

GARDASIL—the only cervical cancer vaccine
For girls and young women ages 9 to 26 years

Key Points About GARDASIL

Who should
receive GARDASIL?

How is GARDASIL given?

Questions to ask
your doctor

Continued screening
is important

HPV and Its Consequences

Cervical cancer and HPV



**YOU COULD BECOME
1 LESS LIFE AFFECTED
BY CERVICAL CANCER.**

Question

What are the potential costs of vaccination?

Should we have mandatory vaccination for everyone?

Outline

- Viruses- dual use dilemma
- Viruses
- Immune system
 - B cells, T cells
 - Antibodies
 - Monoclonal antibodies
- Treatments
 - Antibiotics
 - Vaccination