

How Vaccines Work

Professor Katie Flanagan

Quiz

Vaccines Work

Smallpox

Eradicated 1979 due to vaccine campaign

Polio

99% reduction in cases since 1988, estimated 1.5 million lives saved

Measles

Estimated 60 million deaths prevented between 2000 and 2023

Tetanus

96% drop in neonatal tetanus cases

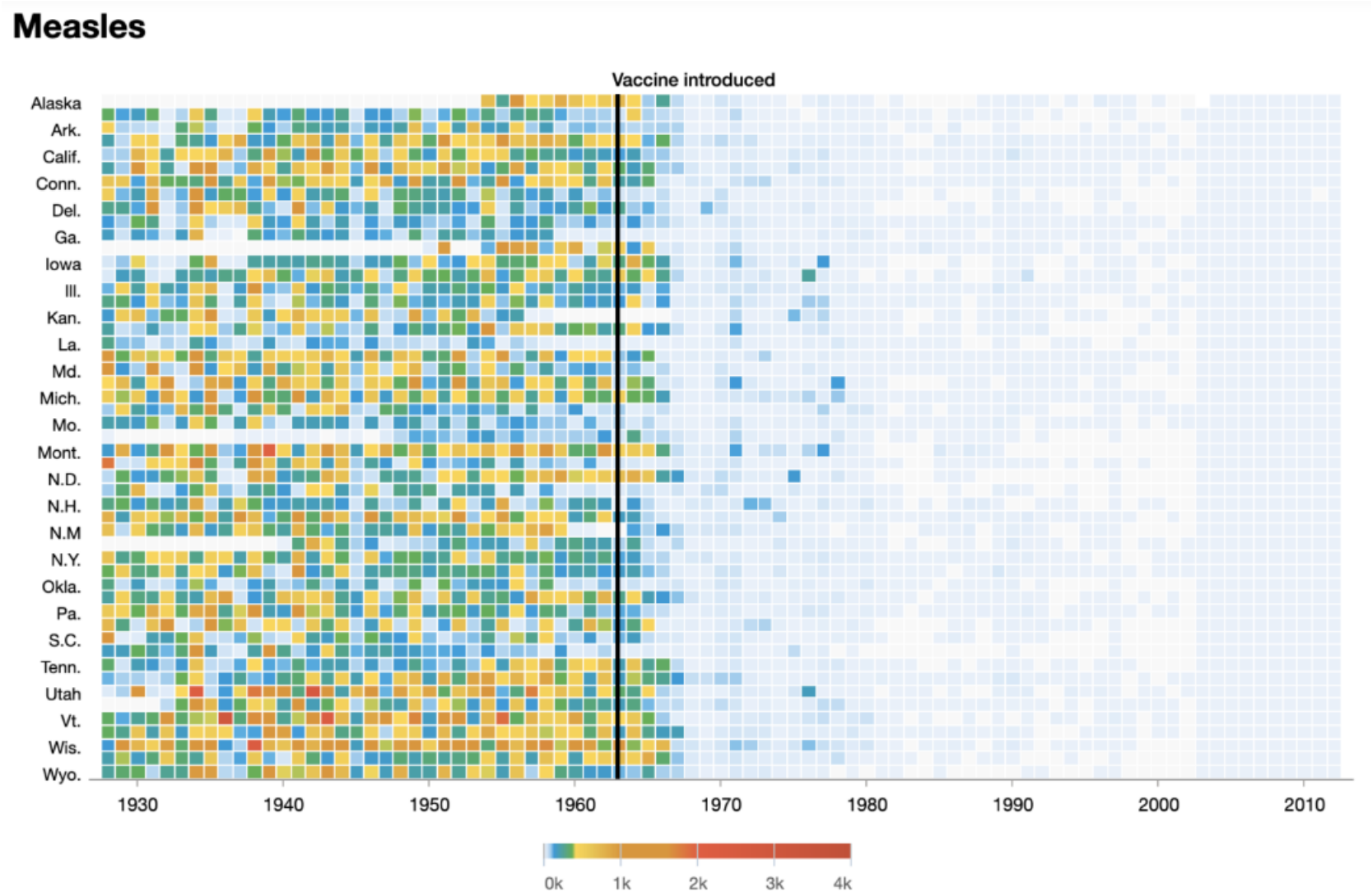
Meningitis

Over 41 million lives saved in low- and middle-income countries between 2000 and 2023 due to vaccines preventing meningitis

Hepatitis B

Global reduction in hep B cases with millions of cases of cirrhosis and liver cancer averted.

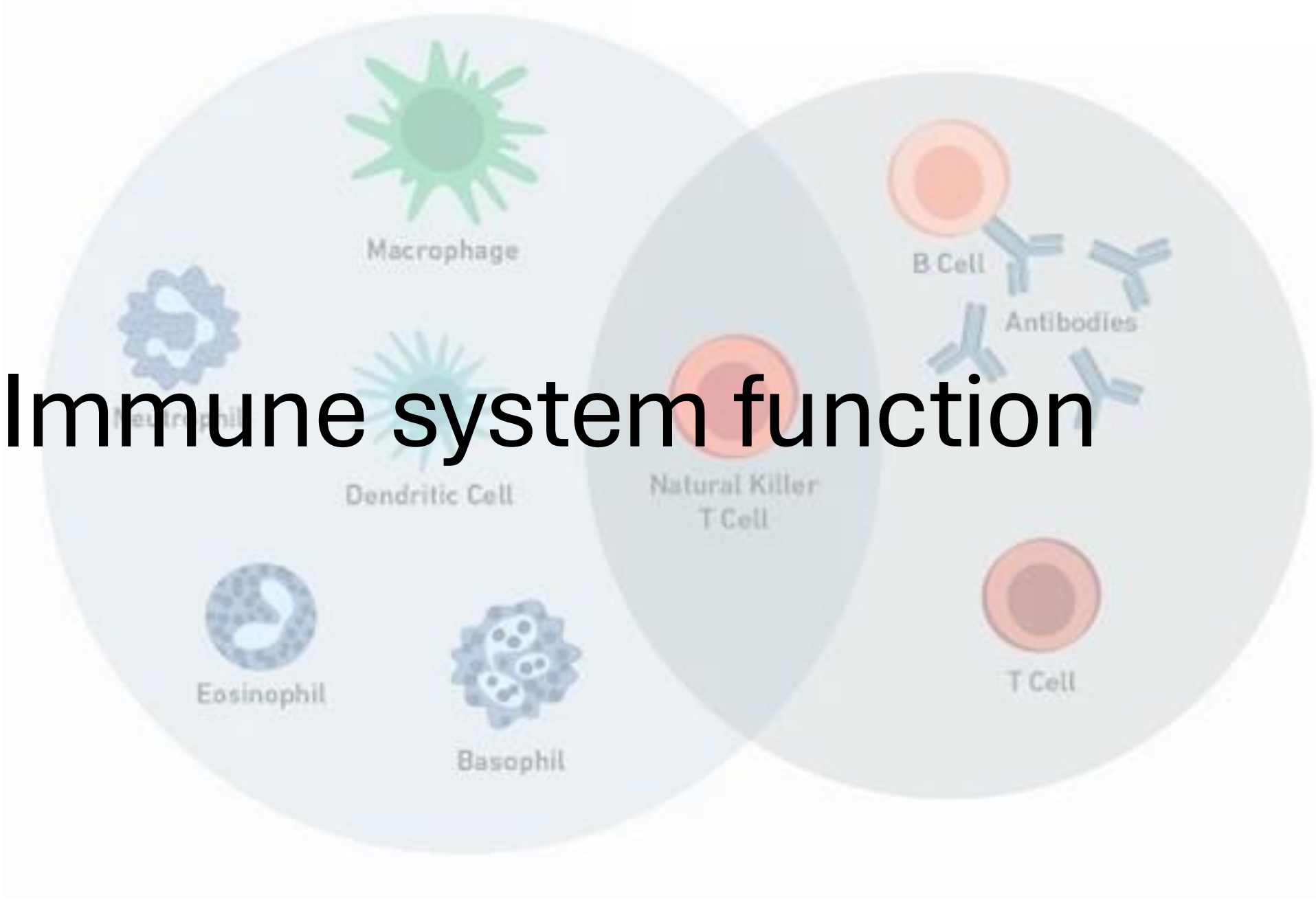
Vaccines Work



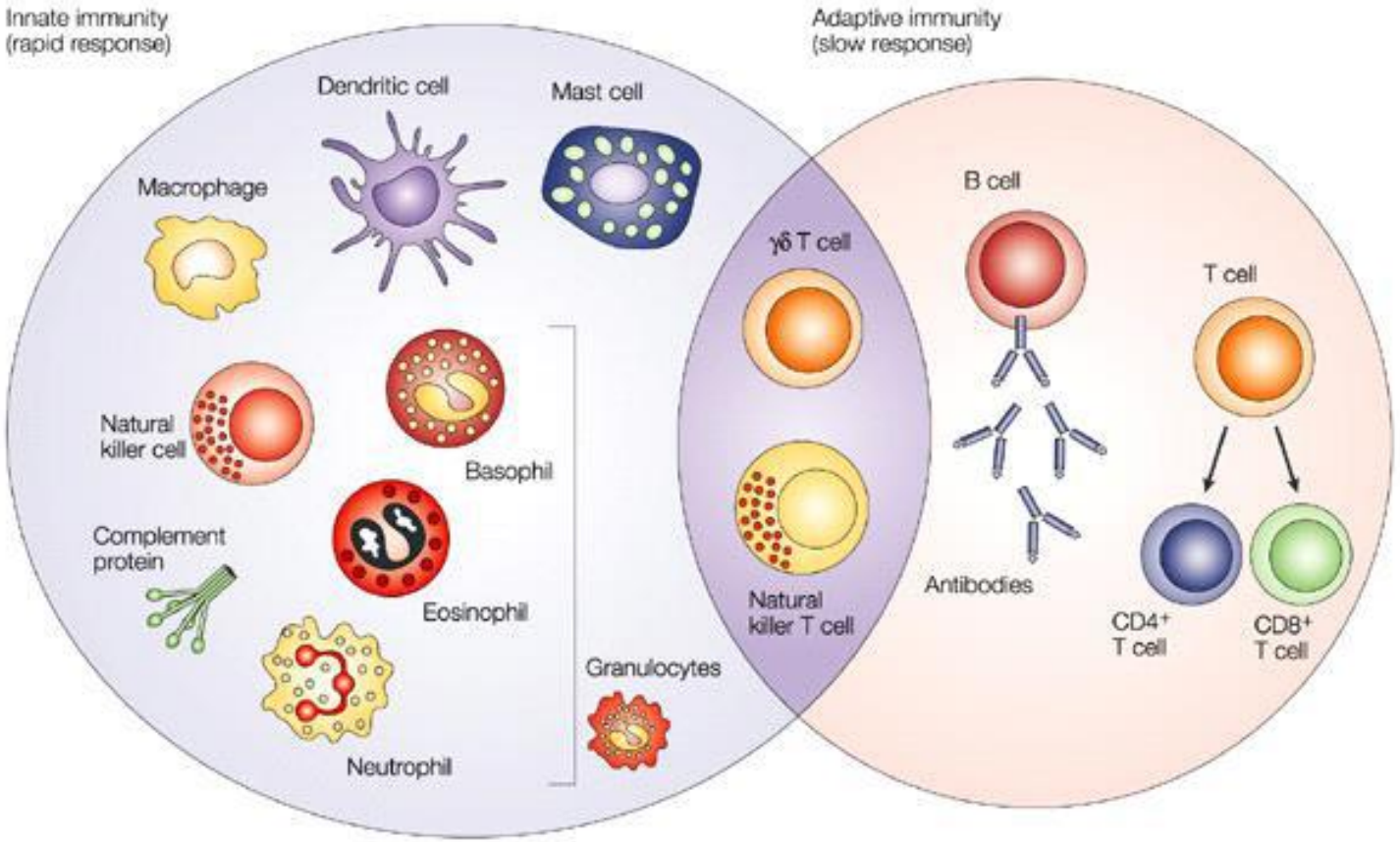
Impressive impact of introducing a new vaccine

(No. of cases per 100,000 people across 50 US States over approx. 70 years).

Immune system function



Innate & Adaptive Immunity

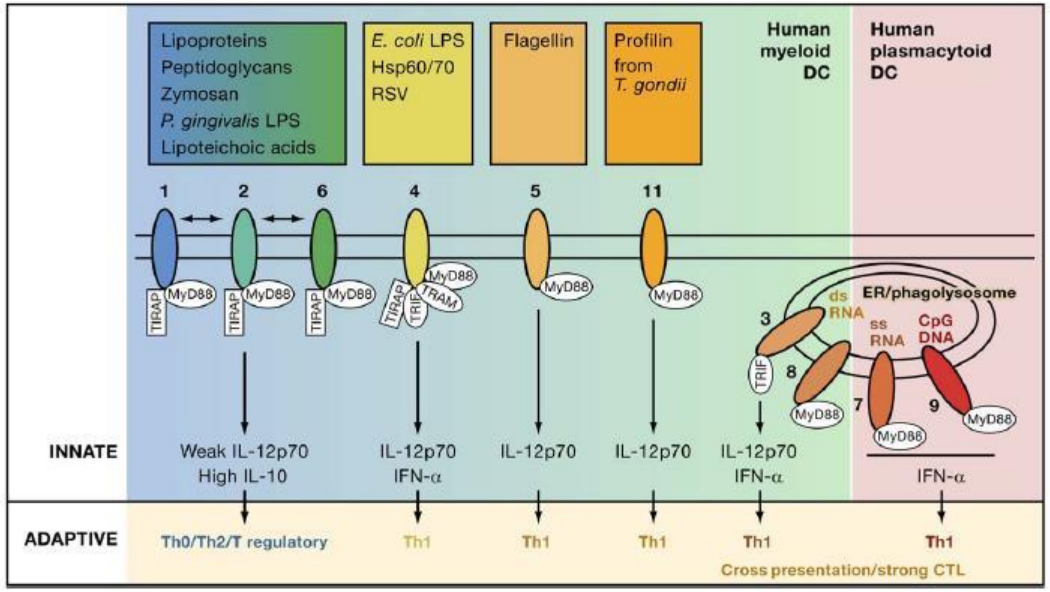


- Two major arms of the immune system – Innate Immunity and Adaptive Immunity
- Innate is rapid and non-specific i.e. multiple immune cells activated by the same pathogen or danger signal
- Adaptive immunity is slower, highly specific and leads to the establishment of long-term immune memory

Innate Immunity

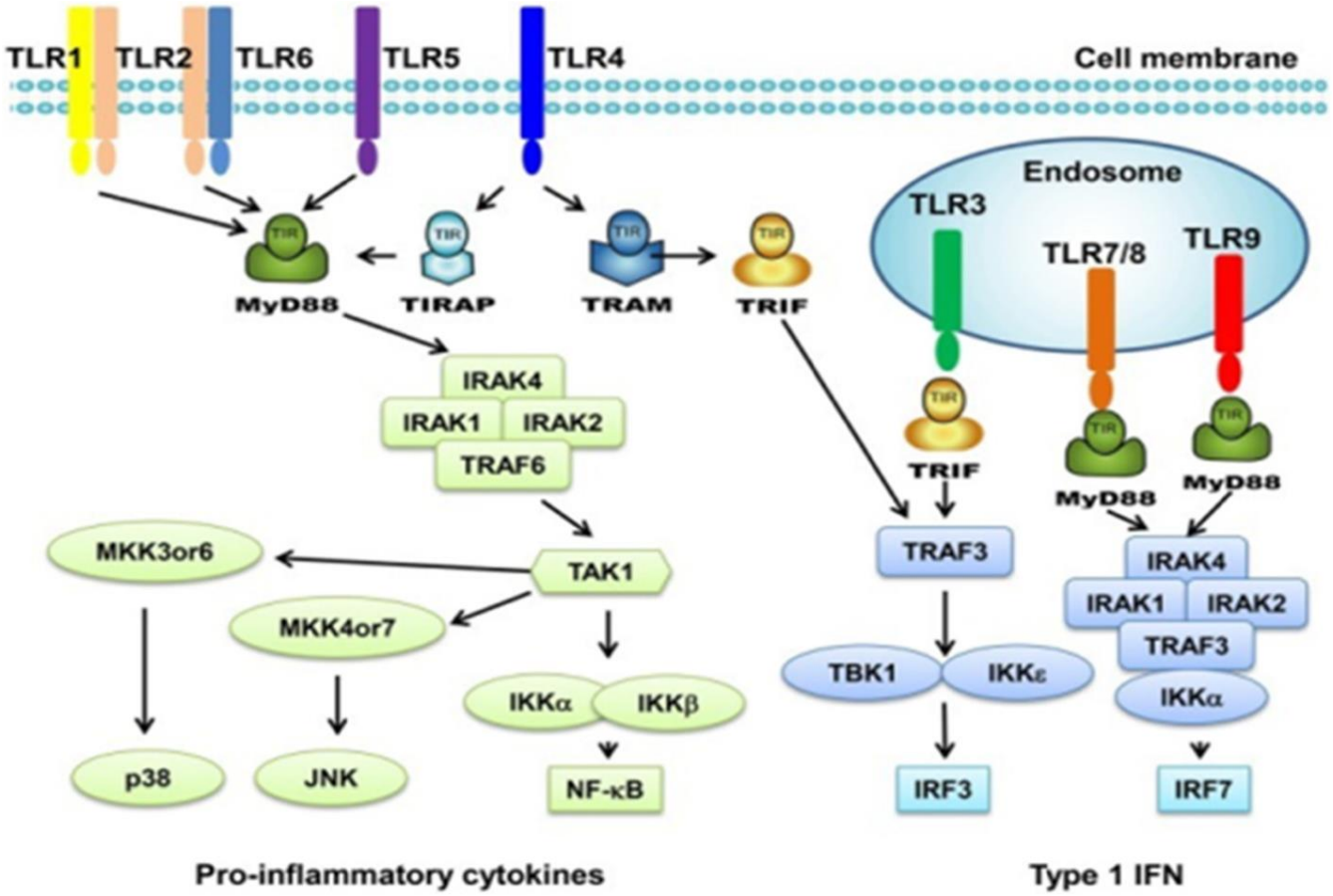
Innate Immunity

- First line of defence
- Pattern associated molecular patterns (**PAMPs**) of microbes stimulate innate response via pattern recognition receptors (**PRRs**)
- PRRs include Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I-like receptors (RLRs) (stimulatory or inhibitory)

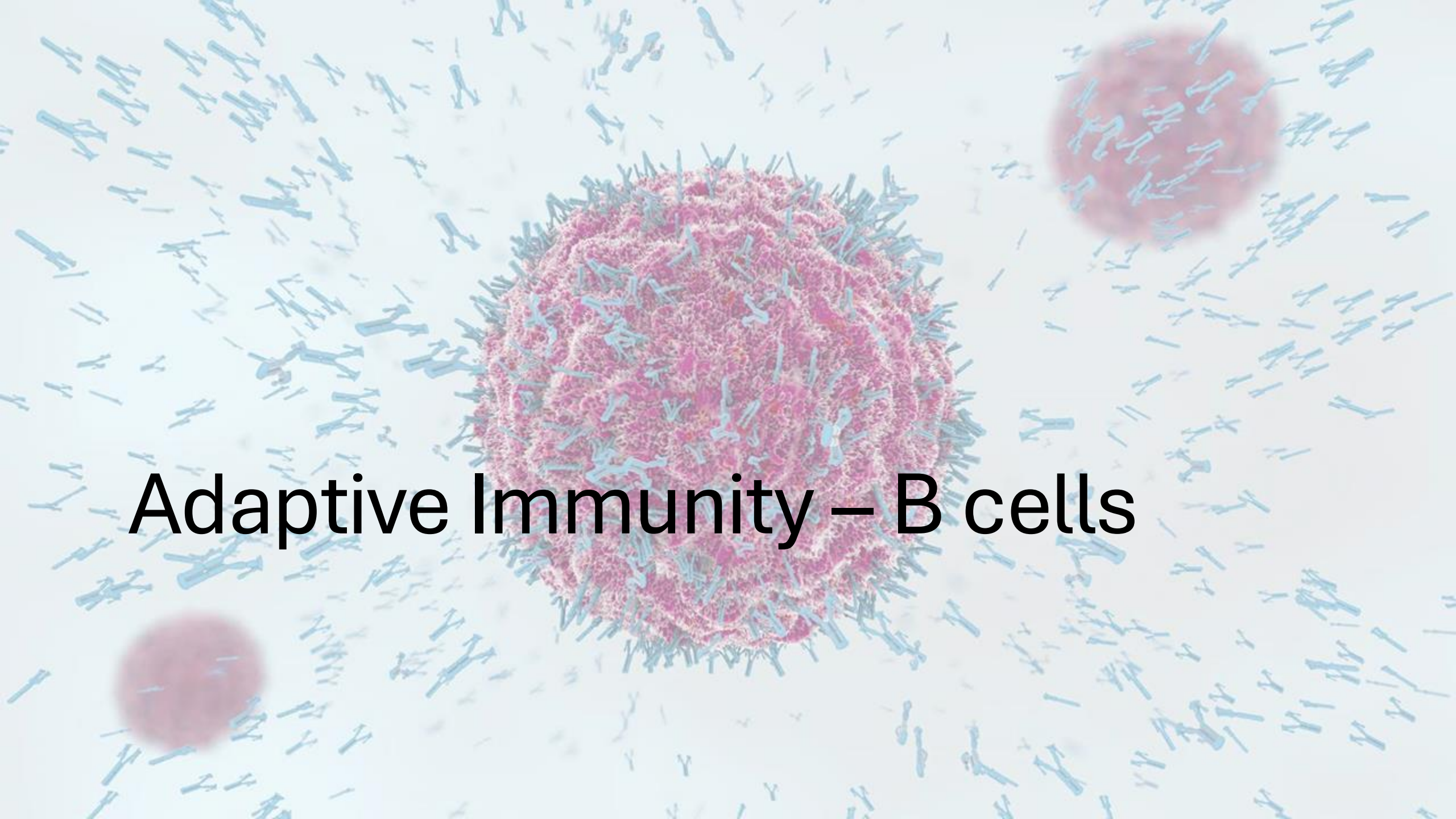


- Some on surface of cells and others (viral sensors) are intracellular
- Mainly expressed by innate cells including dendritic cells, macrophages, monocytes, neutrophils, mast cells, basophils, eosinophils
- Also expressed by epithelial /endothelial cells, CD4 and CD8 T cells, Tregs and γδ T cells

Innate Immunity

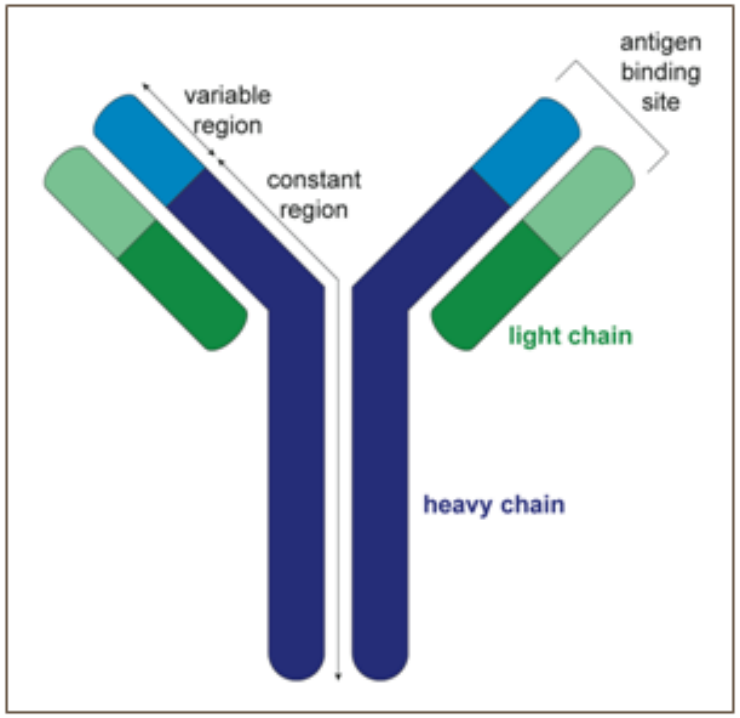


- Occurs rapidly – minutes to hours
- When activated, the PRRs (e.g TLRs) signal intracellularly leading to the production of transcription factors such as IRF7, NF-κB which enter the nucleus, bind to chromosomes and lead to the expression of genes for type 1 IFNs and pro-inflammatory cytokines



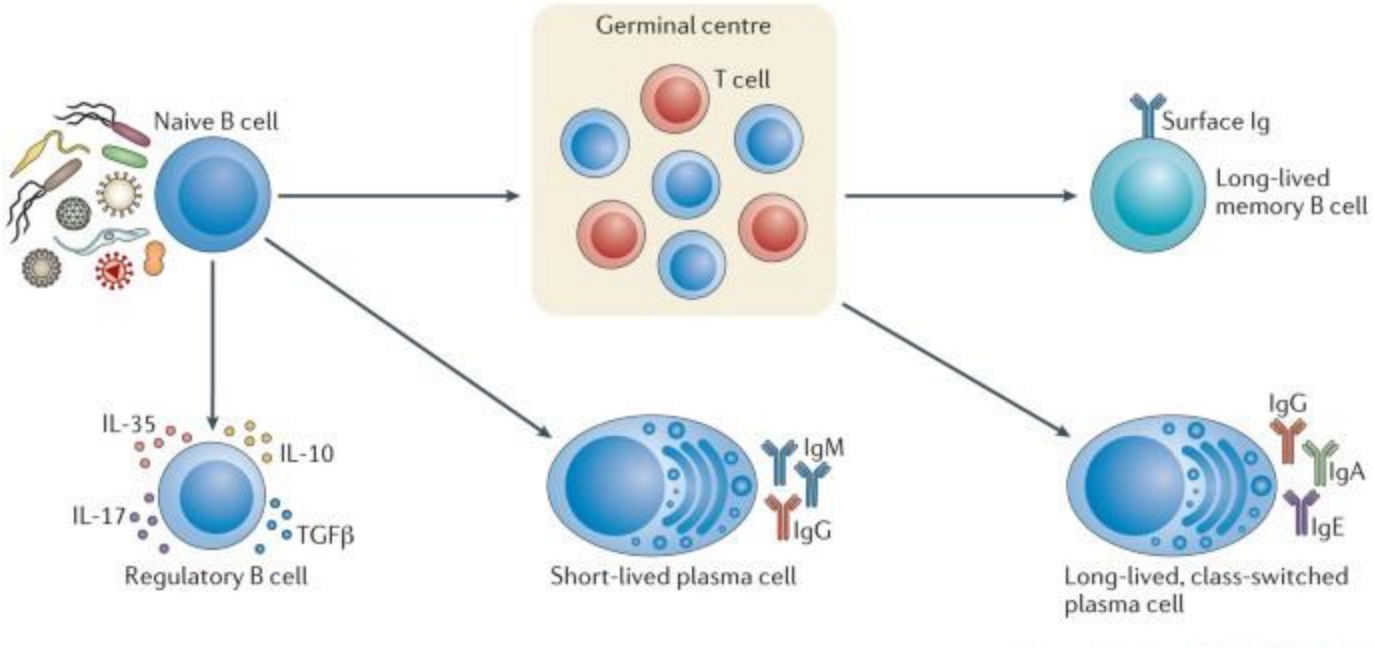
Adaptive Immunity – B cells

B Cell Diversity



- B cells are bone marrow derived
- The B cell receptor (BCR) is identical in structure to an antibody
- The BCR is membrane bound a protrudes from the surface of naïve B cells ready to recognise the antigen for which it is specific
- Various antigens can bind to BCRs including viruses, bacteria, toxins and allergens
- Humans are thought to have $10^{11} – 10^{12}$ B cells with unique antigen receptors – called the B cell repertoire
- Allows humans to recognize and respond to a wide range of pathogens and antigens

B Cell Differentiation

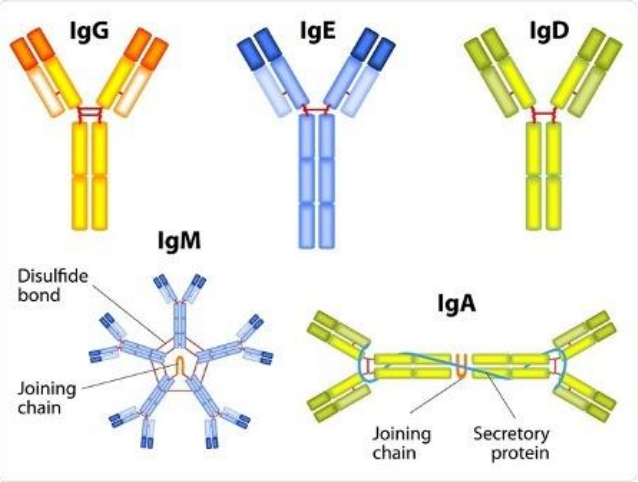


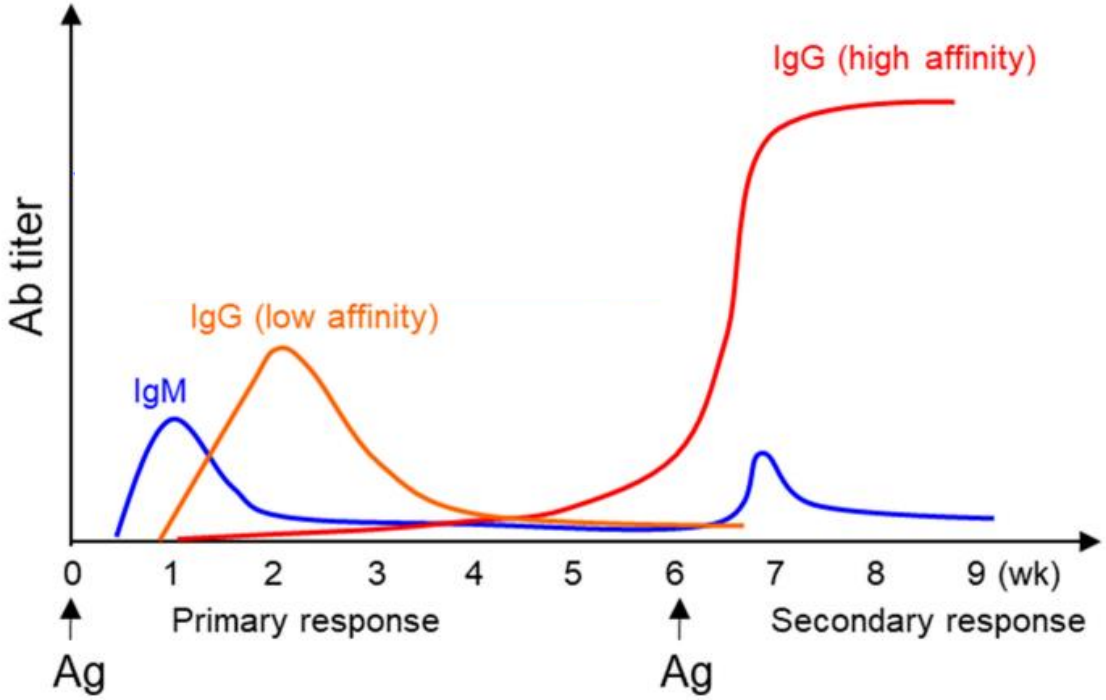
- Antigen-BCR complexes are internalised, processed and peptide fragments presented on B cell surface bound to MHC class II molecules.
- This allows B cells to interact with helper T cells which further activate the B cell and allows differentiation to **short-lived antibody-producing plasma cells** in the periphery.
- In the germinal centre of the lymph node naïve B cells can become **long-term memory B cells** or **long-lived class-switched plasma cells**.
- Long-lived B cells recognise and rapidly produce antibodies to the specific antigen when next encountered.

Types of Antibodies

There are 5 types of antibodies

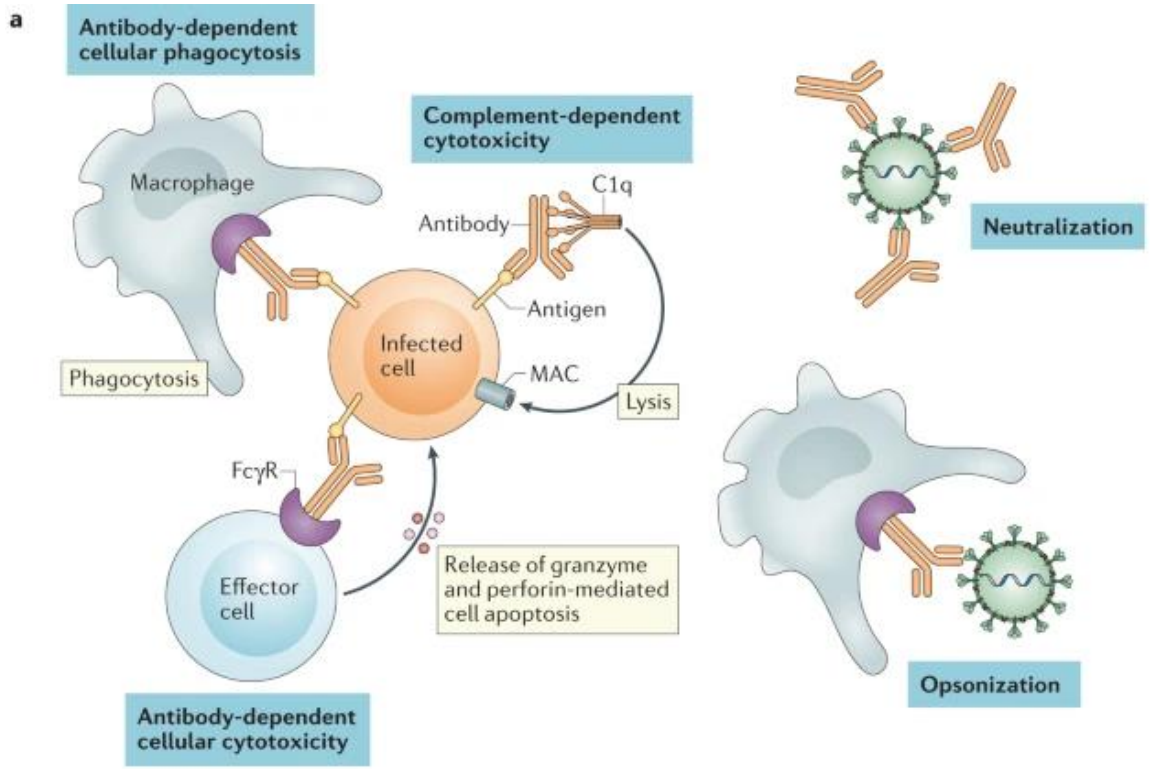
- Naïve B cells express IgG and IgD
- IgM is a pentamer and is produced early in infection
- IgG (a monomer) is then produced later during an immune response
- IgA (a dimer) is stimulated by mucosal pathogens and provides mucosal protection
- IgE is involved in allergic reactions





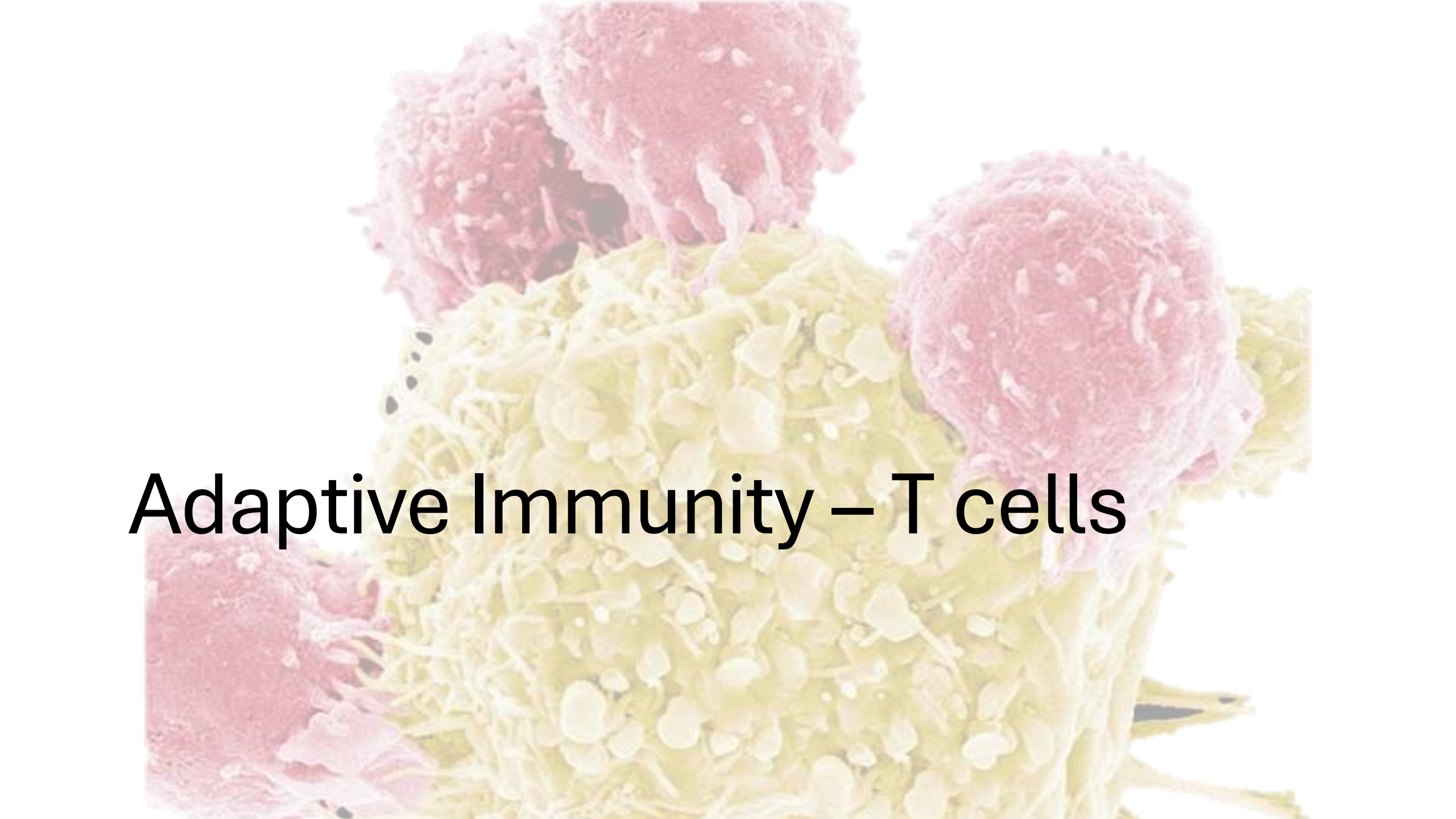
- Secondary Ab response is more robust than the primary response
- During primary infection the IgG is low affinity but in subsequent infections it becomes high affinity and more efficient

How Antibodies Work



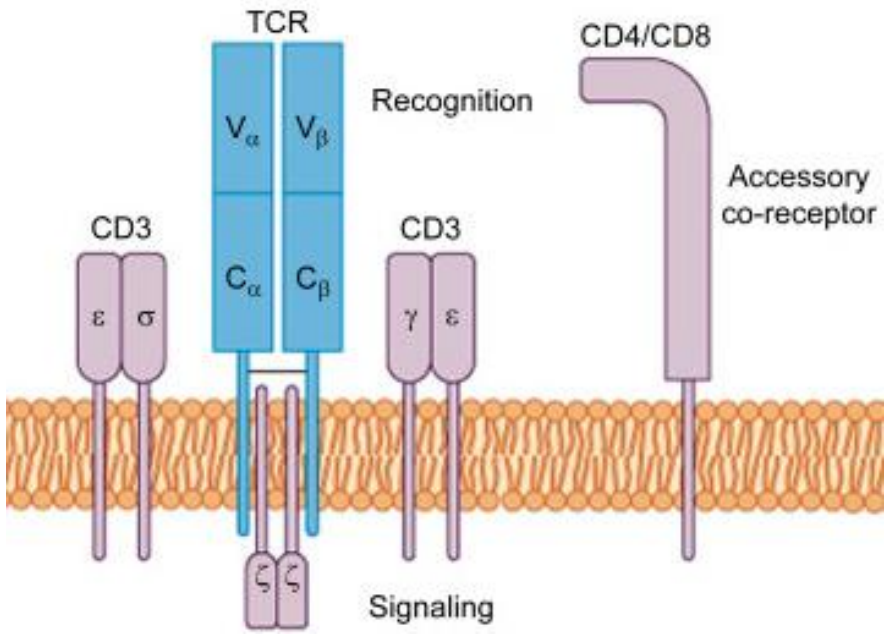
Taylor et al. Nat Rev Immunol 2021; 21: 382

- Antibodies target pathogens via several mechanisms leading to either neutralisation or opsonization of circulating pathogen or killing of pathogen-infected cells via ADCC, ADCP and complement-dependent cytotoxicity



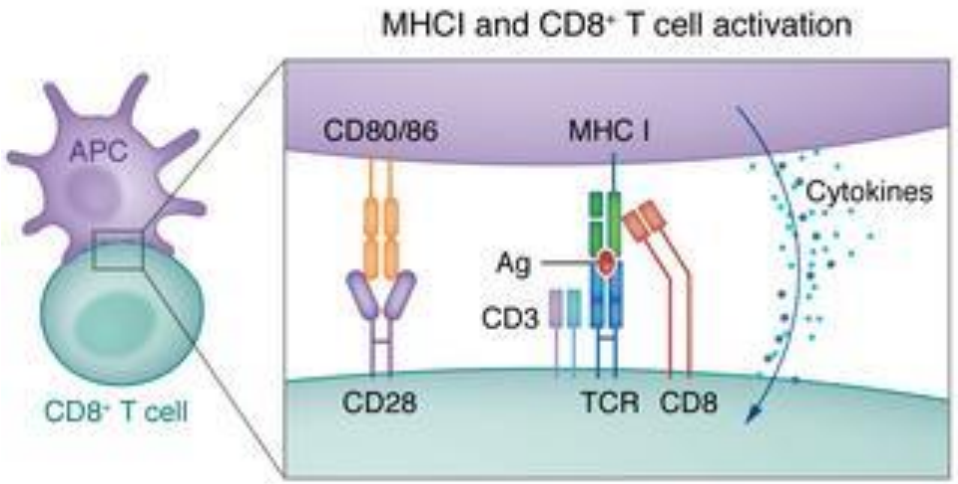
Adaptive Immunity – T cells

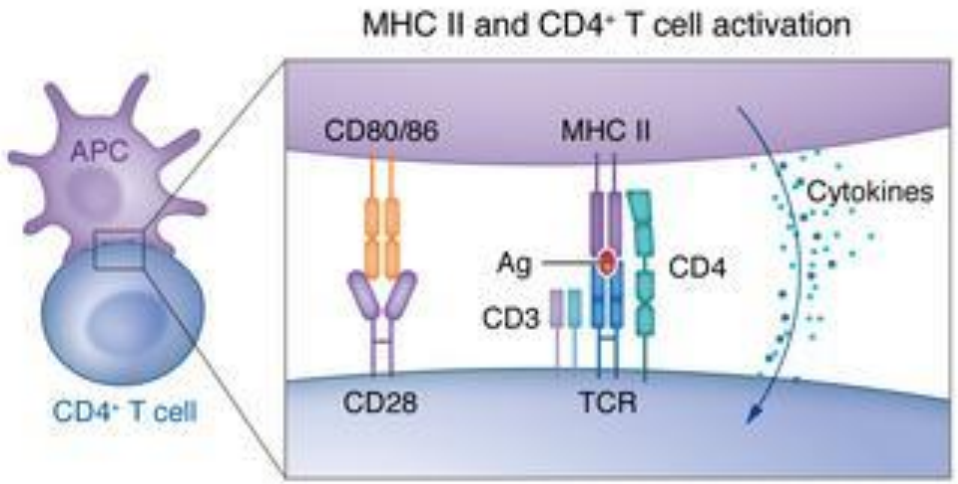
T Cell Receptor



- T cells are thymus derived
- TCR has a transmembrane constant region and the external α and β variable regions
- Combined with CD3 (expressed by all T cells) and CD4 or CD8
- T cells recognise antigen presented by antigen presenting cells (APCs) e.g. dendritic cells
- The antigen binds to the terminal variable region of the TCR
- T cells only recognise fragments of proteins, so the pathogen needs to be processed, and the antigens chopped up and presented to the T cell

CD4 and CD8 T Cell Activation



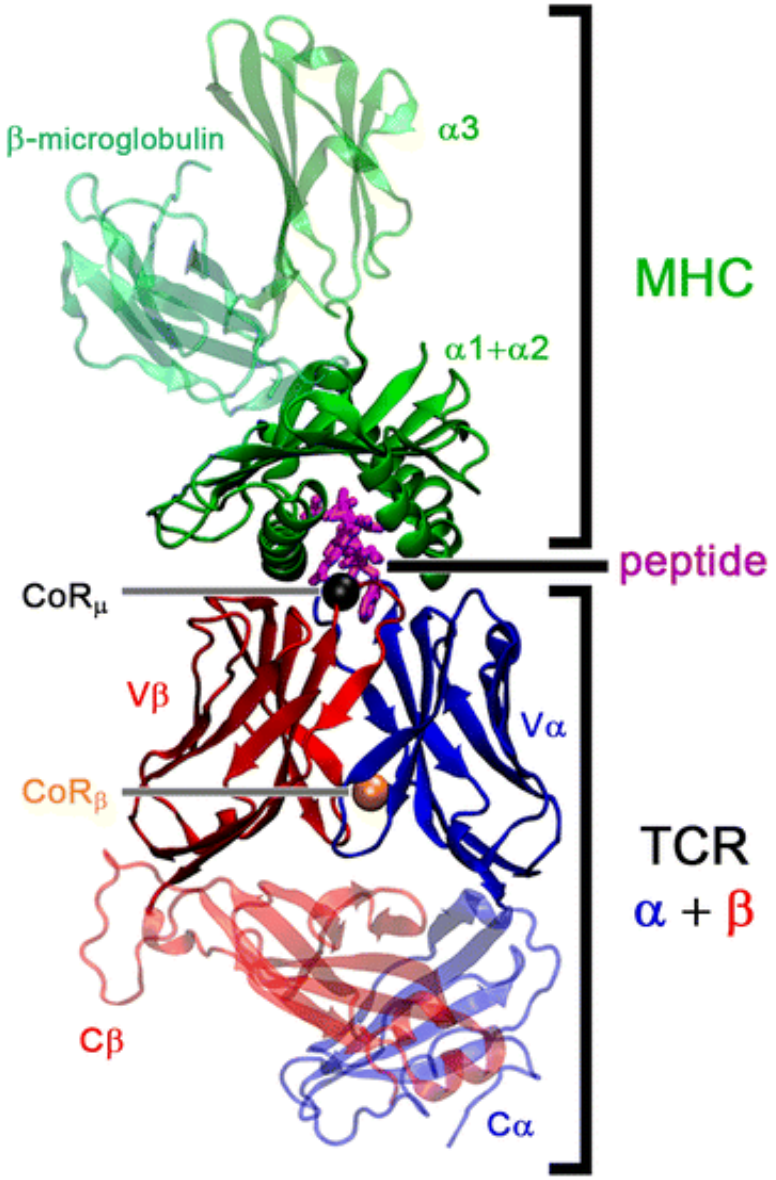


CD8+ T cells recognise short peptides of 8-11 amino acids presented with MHC class I on surface of APC

CD4+ T cells recognise longer peptides of 12-25 amino acids presented with MHC class II

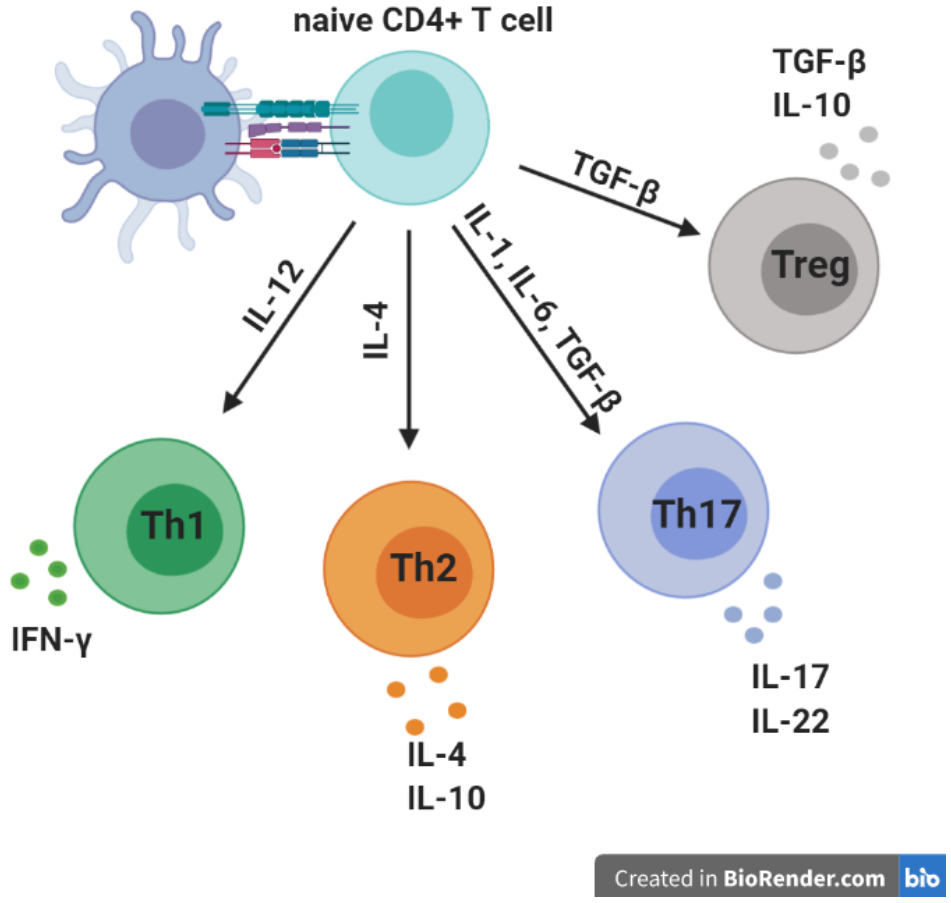
The human Major Histocompatibility Complex (MHC) is Human Leukocyte Antigen (HLA)

3-D Structure of TCR / HLA / Peptide Interaction

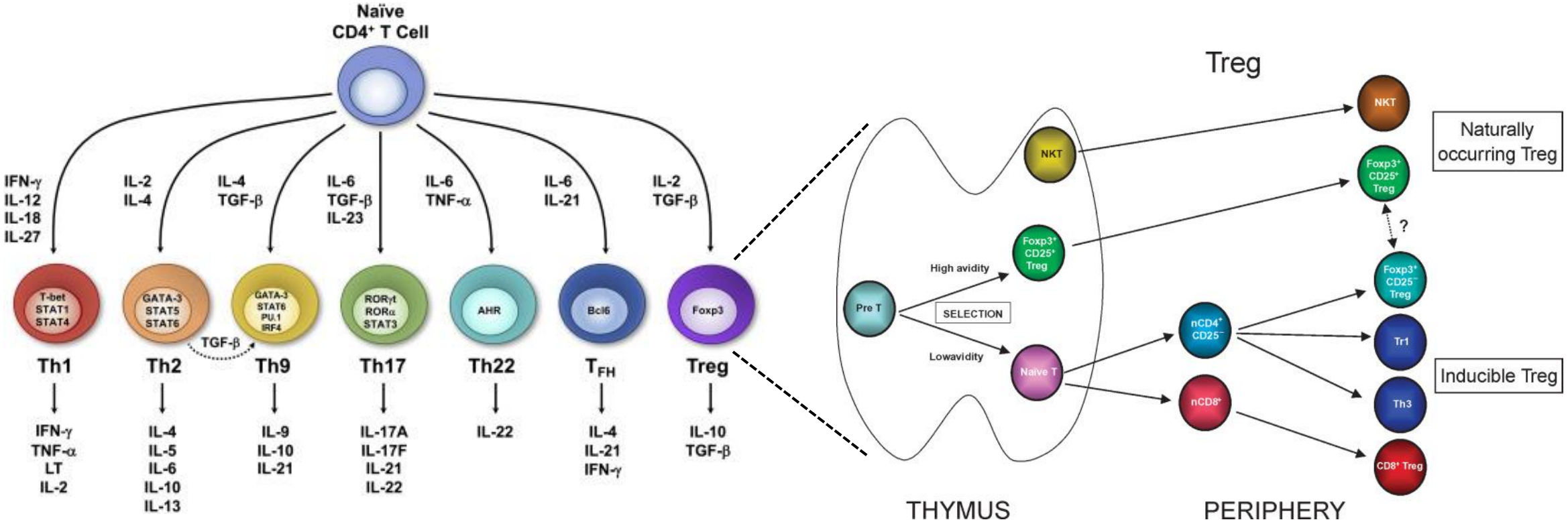


CD4+ T Helper Cells

- There are multiple subsets of CD4+ T cells
- They develop according to the type of antigen encountered and the cytokine milieu:
  - Many viruses stimulate Th1 pro-inflammatory responses
  - Helminths often induce Th2 type responses
- They express different transcription factors which determine their lineage
  - Th1 – T-bet
  - Th2 – GATA3
  - Th17 - RORγt
  - Tregs – FOXP3
- They have different cytokine profiles which determine their functions
- One function is providing help for Ab production – Th2 and T_{FH}
- There is overlap between them e.g. Th2, Th9 and Tregs all express IL-10

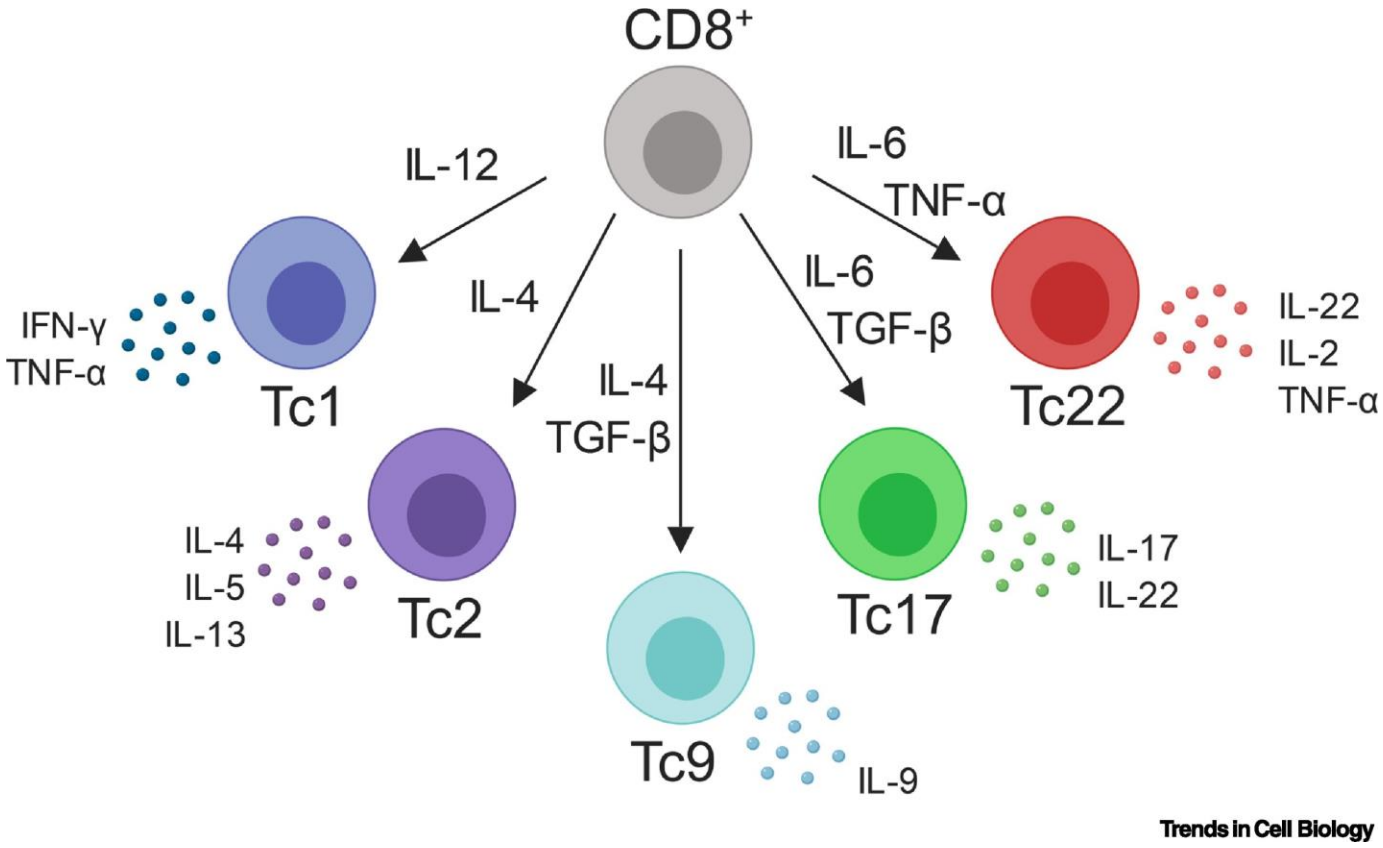


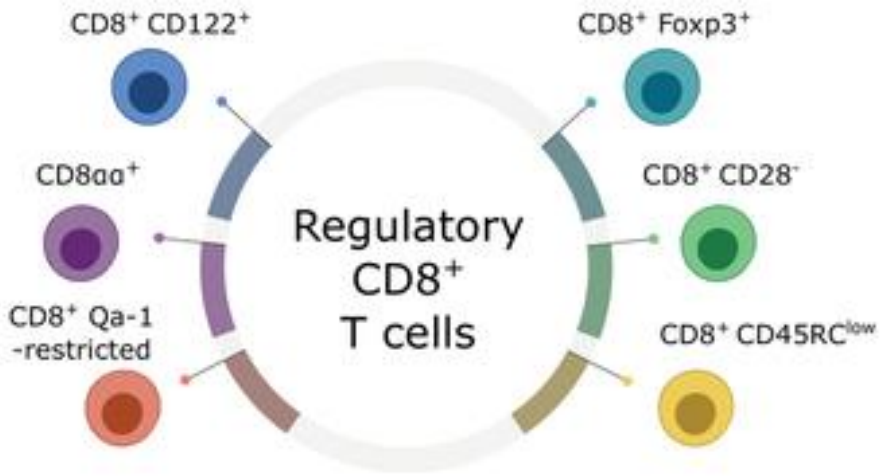
Multiple Subsets of CD4⁺ T Cells



CD8+ Cytotoxic T Cells

- Parallel subsets exist in the CD8+ T cell compartment



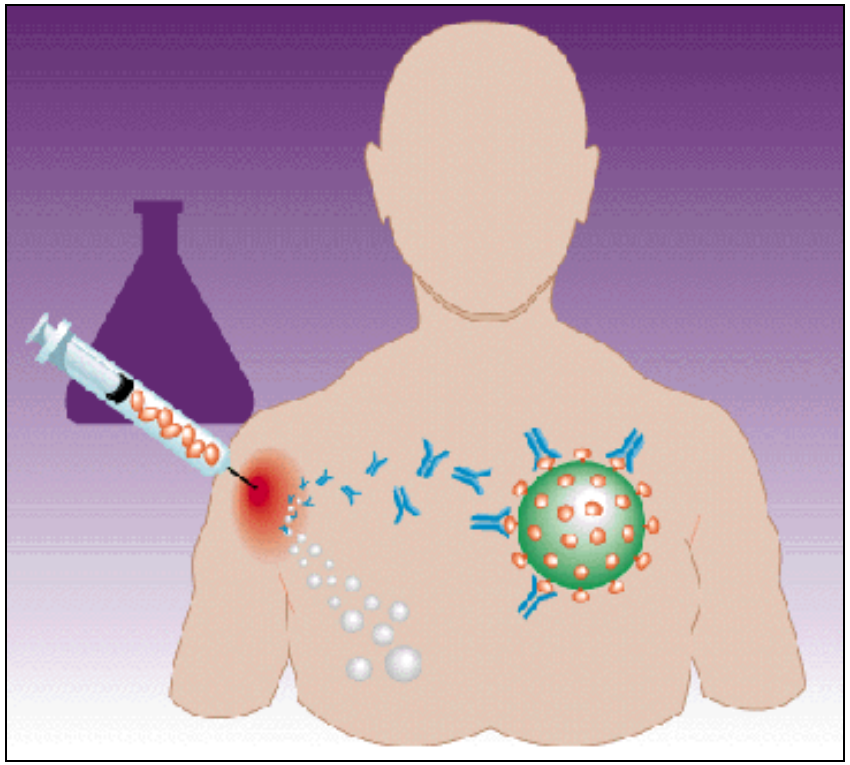


- There are also a series of CD8+ Tregs

How vaccines induce protection

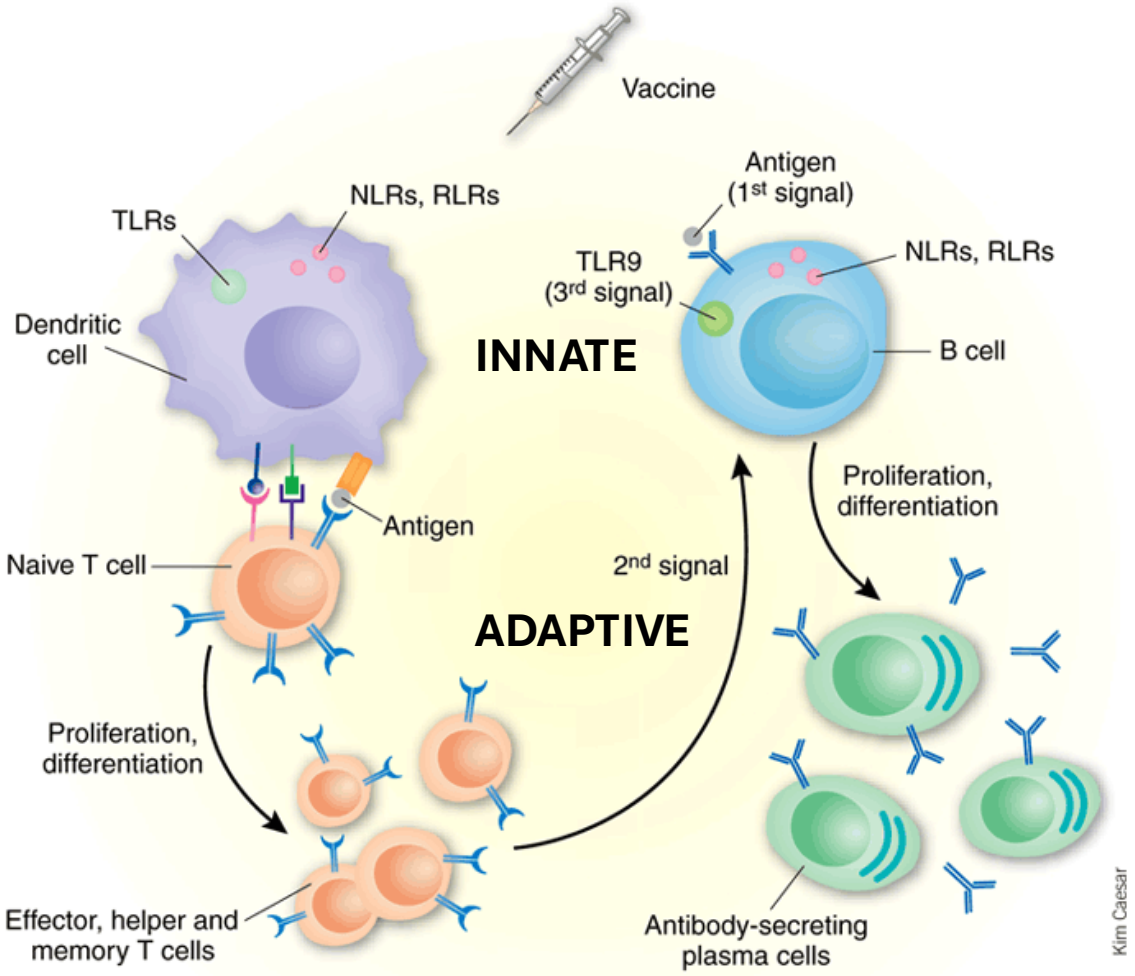
How Vaccines Work

• A vaccine is a substance introduced into the body to stimulate an immune response against the vaccine-targeted disease.



- Made of dead or inactive microbes / bits of microbes / genetic sequences which stimulate the immune system to make antibodies and T cell responses which inactivate the organism and / or prevent the disease.
- The resulting immune memory will be rapidly reactivated when the person is next exposed to the vaccine-targeted infection thus preventing the person from becoming infected and / or ill.
- Vaccine-induced true sterilizing immunity is rare and immunity wanes over time.

Immune Response to Vaccination



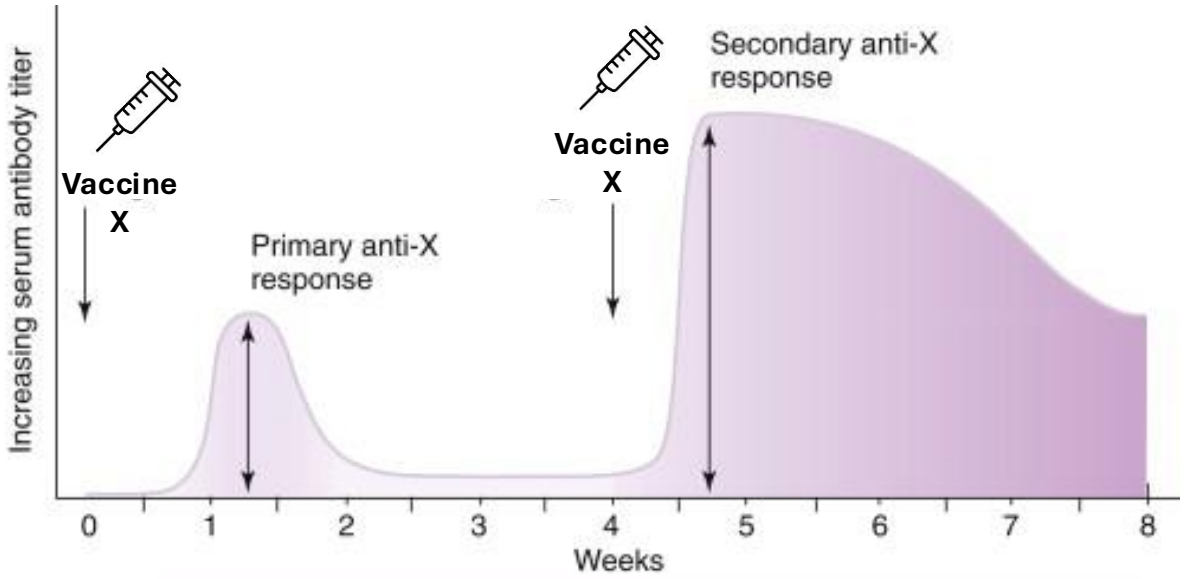
Innate Response

- Produces an immediate non-specific inflammatory response.

Adaptive Responses

- Antigen-specific antibodies and T cells.
- Takes several days and often peaks several weeks after vaccination
- Many vaccines were developed empirically, and we don't understand exactly how many commonly used vaccines work (e.g. BCG, yellow fever
- We often don't have good correlates of protection (except antibodies).
- We don't understand the broader effects of vaccination on the immune system

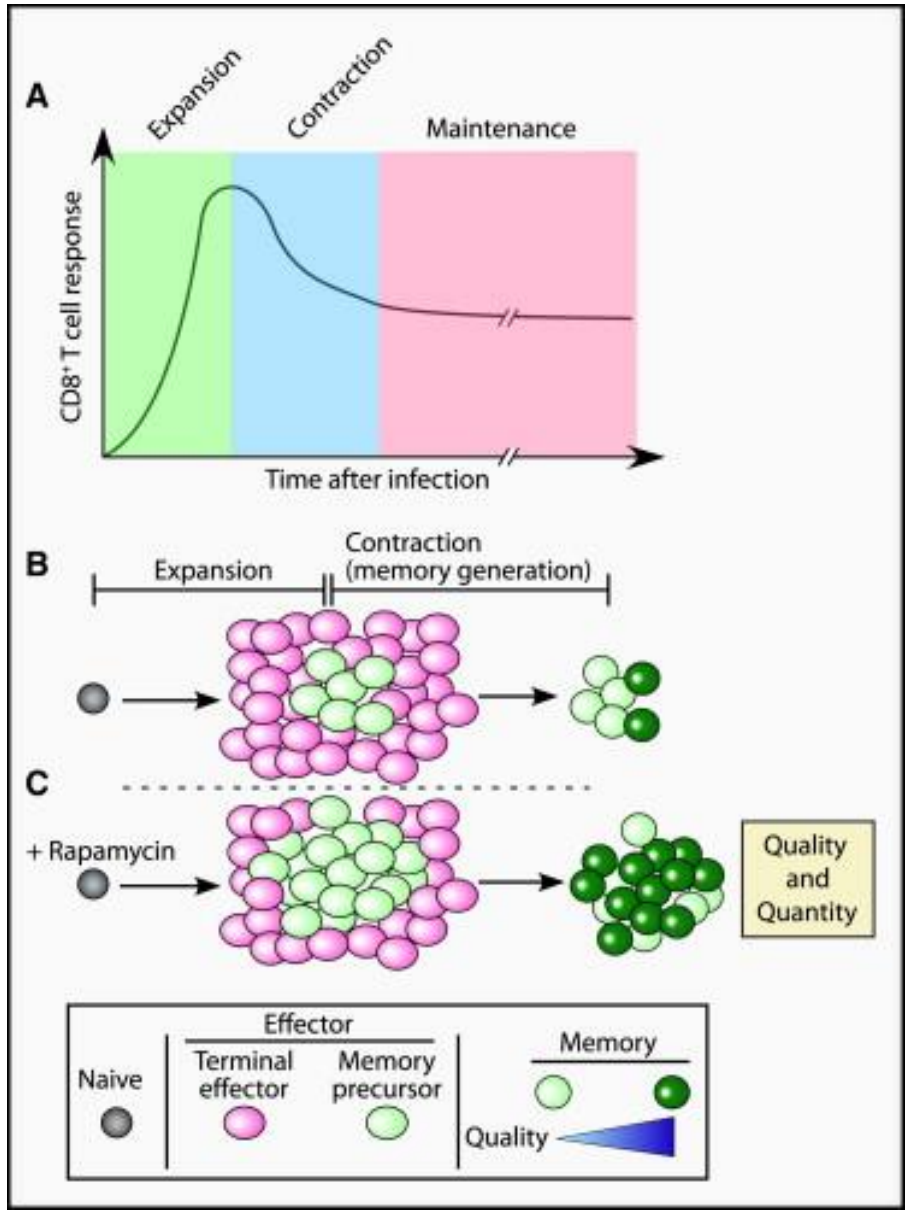
Antibody Response to Vaccination



Property	Primary response	Secondary response
Type of B cell involved	Naive B cell	Memory B cell
Lag time	4–7 days	1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak response	Depends on antigen	100-1000x higher than primary response
Isotype produced	IgM predominates	IgG predominates
Antibody affinity	Lower	Higher

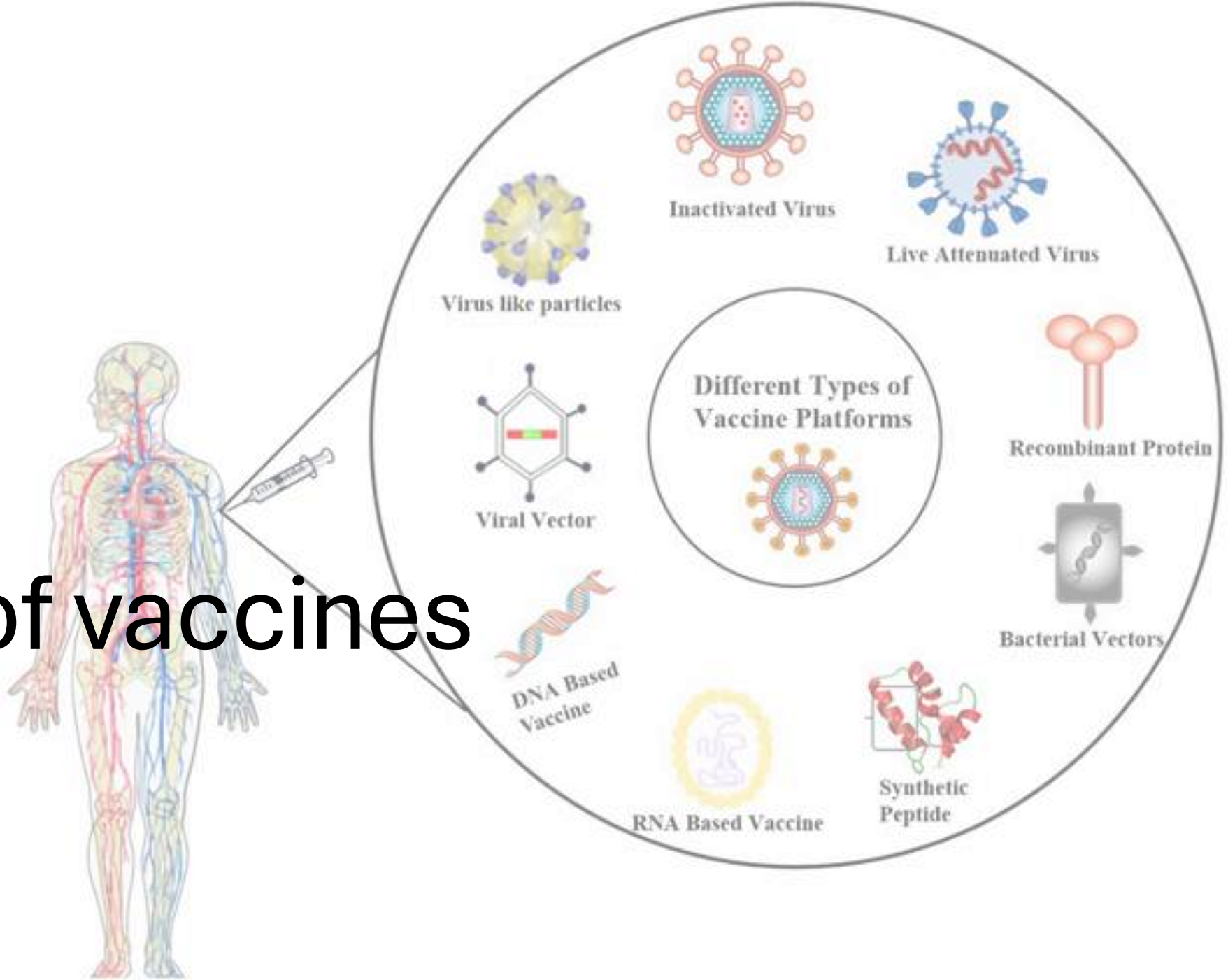
T Cell Response to Vaccination

- T cell response can be a mixture of CD4 or CD8 or one may predominate.
- Initial T cell response generates circulating effector memory T cells (T_{EM}).
- The T_{EM} cells apoptose and die.
- Central memory T cells (T_{CM}) also develop and persist in lymph nodes.
- T_{CM} can be boosted rapidly by vaccination or infection at a later date.
- Type of T cell response depends on the stimulus and type of vaccine e.g.
  - BCG induces a Th1 (IFN-γ) response
  - Whole cell pertussis Th1
  - Inactivated pertussis Th2



Sallusto et al. Immunity 2010; 33: 451

Types of vaccines



Vaccine Types

Live Vaccines

e.g. Measles, Mumps, Rubella, BCG

- Attenuated (weakened) organisms (viruses / bacteria)
- Organism must replicate for vaccine to be effective
- Immune response similar to natural infection & can cause the disease
- Immunity often from 1 dose

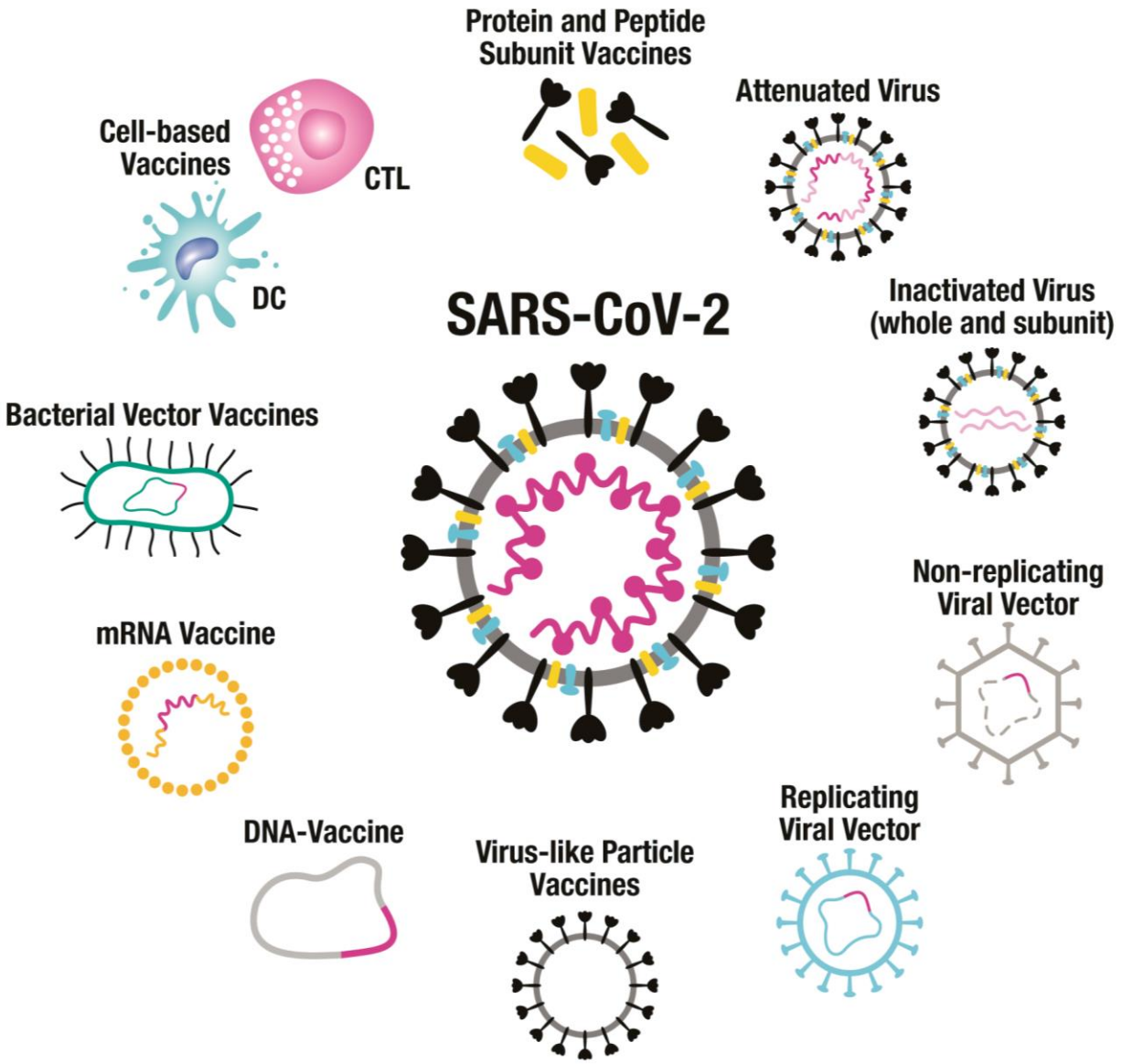
Non-live / Inactivated / Killed Vaccines

e.g. DTP, Influenza, Hepatitis B

- Parts of organisms / toxoids / polysaccharides that cannot replicate
- Usually contain adjuvant (alum) to increase immune response
- Less effective than live vaccines
- Multiple doses required

Wide Array of Vaccine Platforms

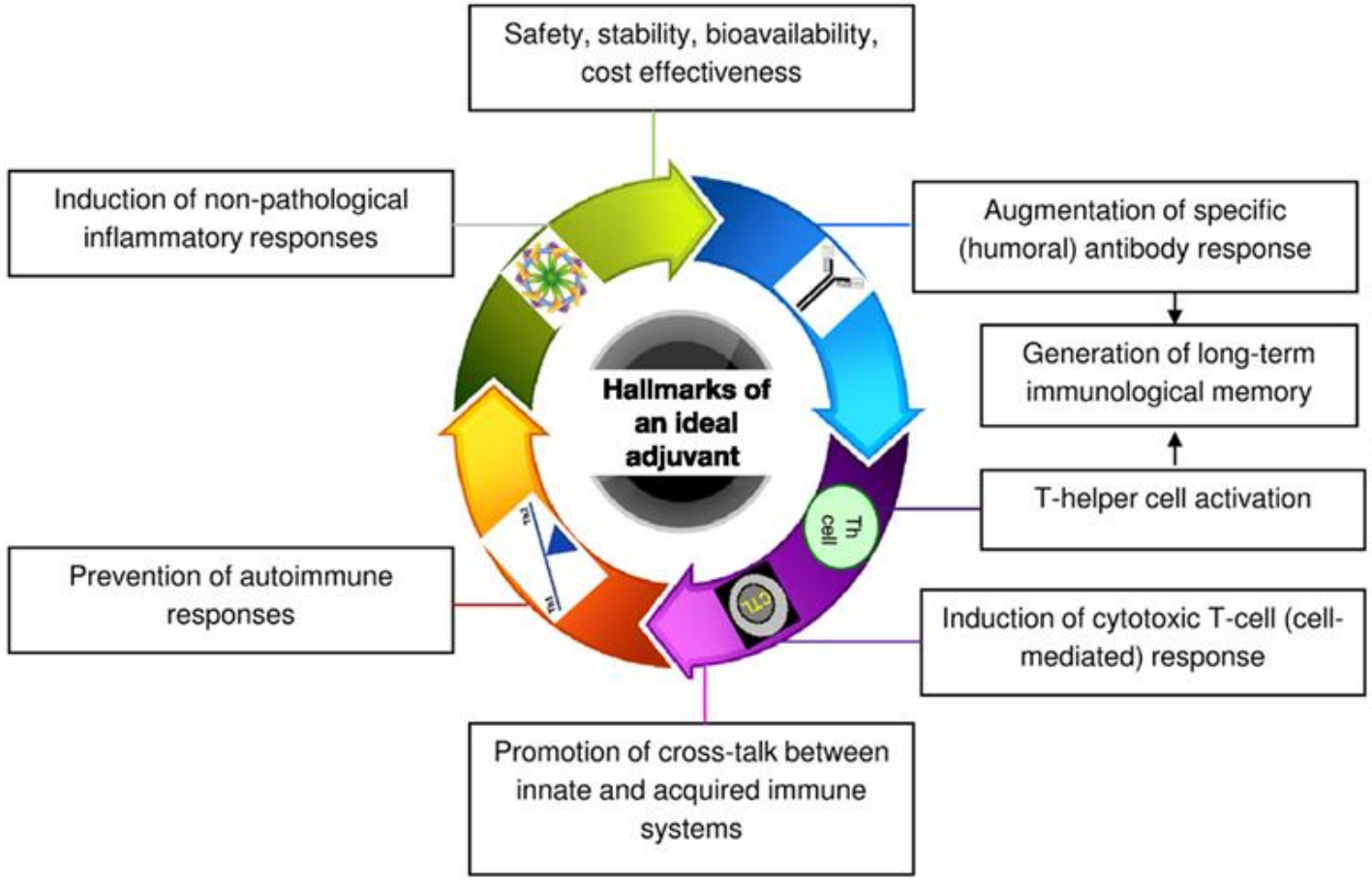
- The SARS-CoV-2 vaccine pipeline provides a good example of the variety of vaccine platforms
- There are also toxoid vaccines e.g. tetanus, diphtheria



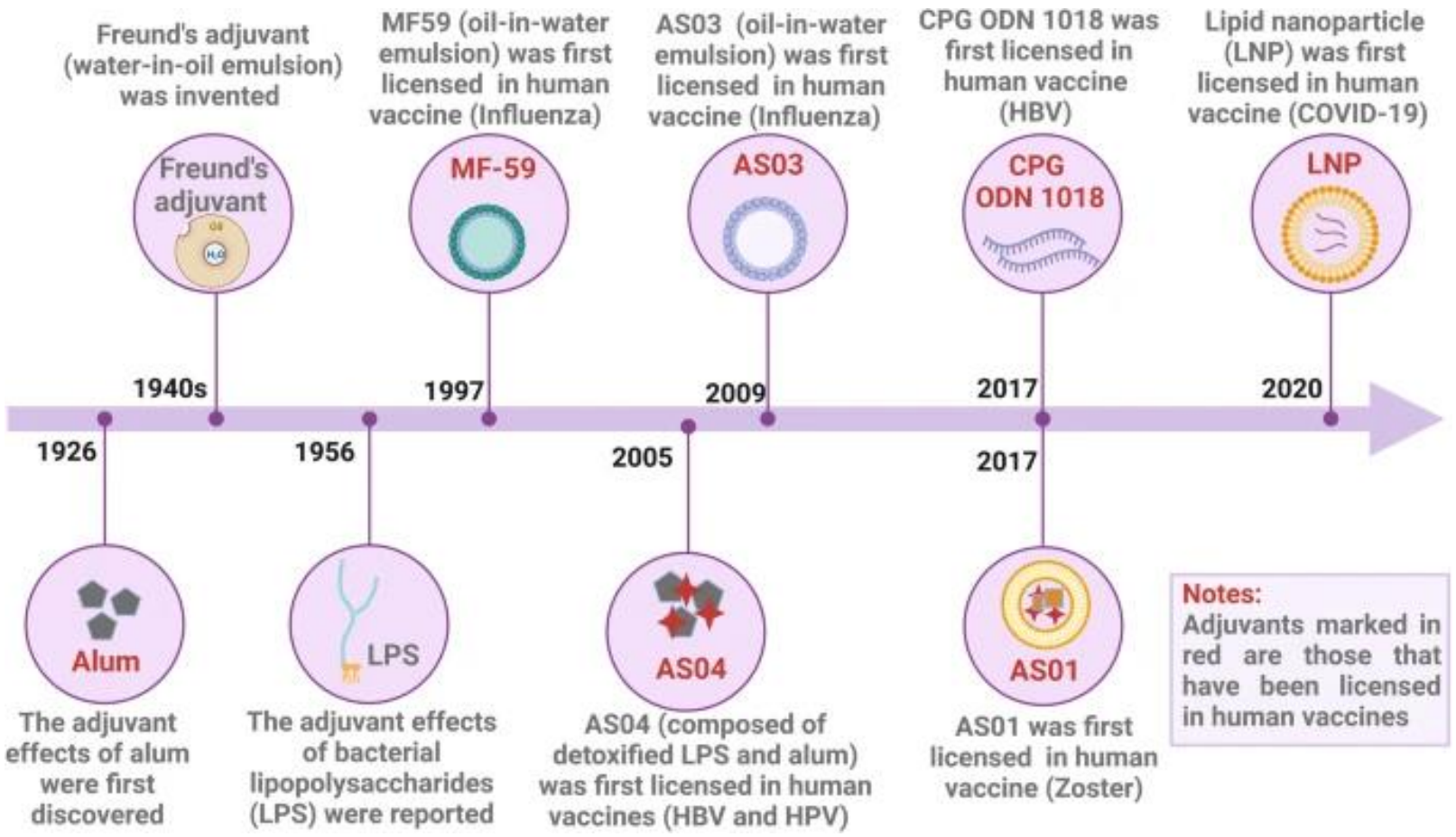
Flanagan et al, J Allergy Clin Immunol Pract 2021

Vaccine Adjuvants

- Many inactivated / killed vaccines require an adjuvant to create a strong enough immune response
- Act to stimulate the immune system to produce more robust and durable immunity

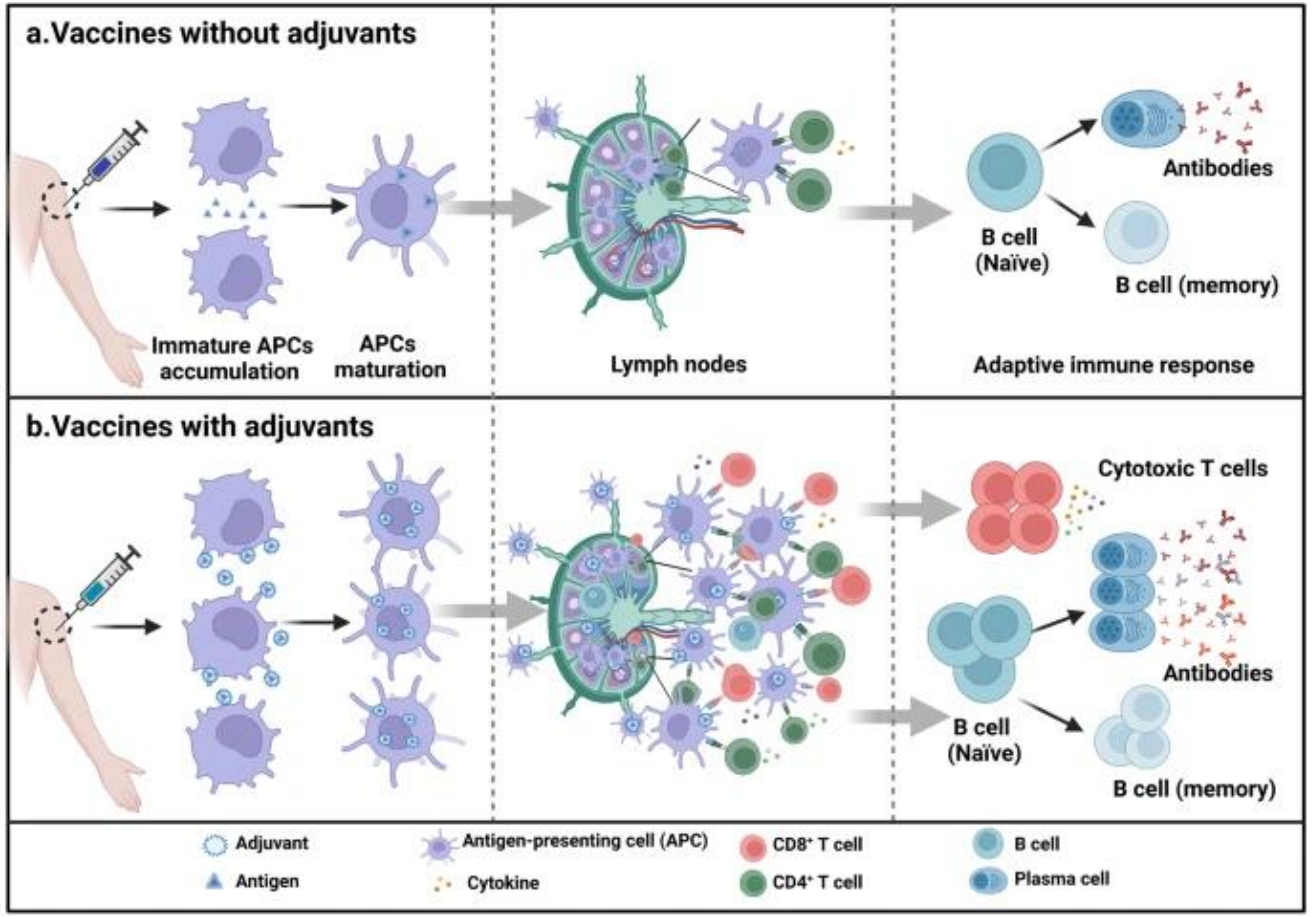


Development Timeline



Zhao et al. Signal Transduction Targeted Therapy 2023; 8: 283

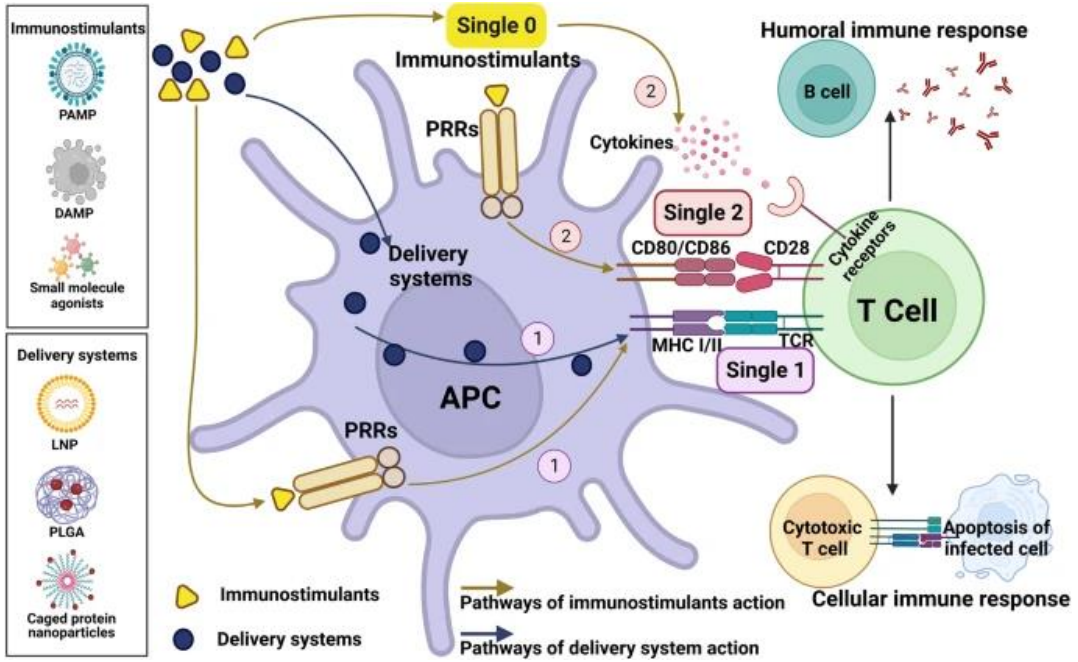
How They Work



Zhao et al. Signal Transduction Targeted Therapy 2023; 8: 283

- Promote maturation of more APCs
- Increase interaction between APCs and T cells
- Promote greater T helper polarising cytokines, multifunctional T cells and antibodies
- Net effect is broader and more durable immunity
- Also cost saving since lower antigen dose needed

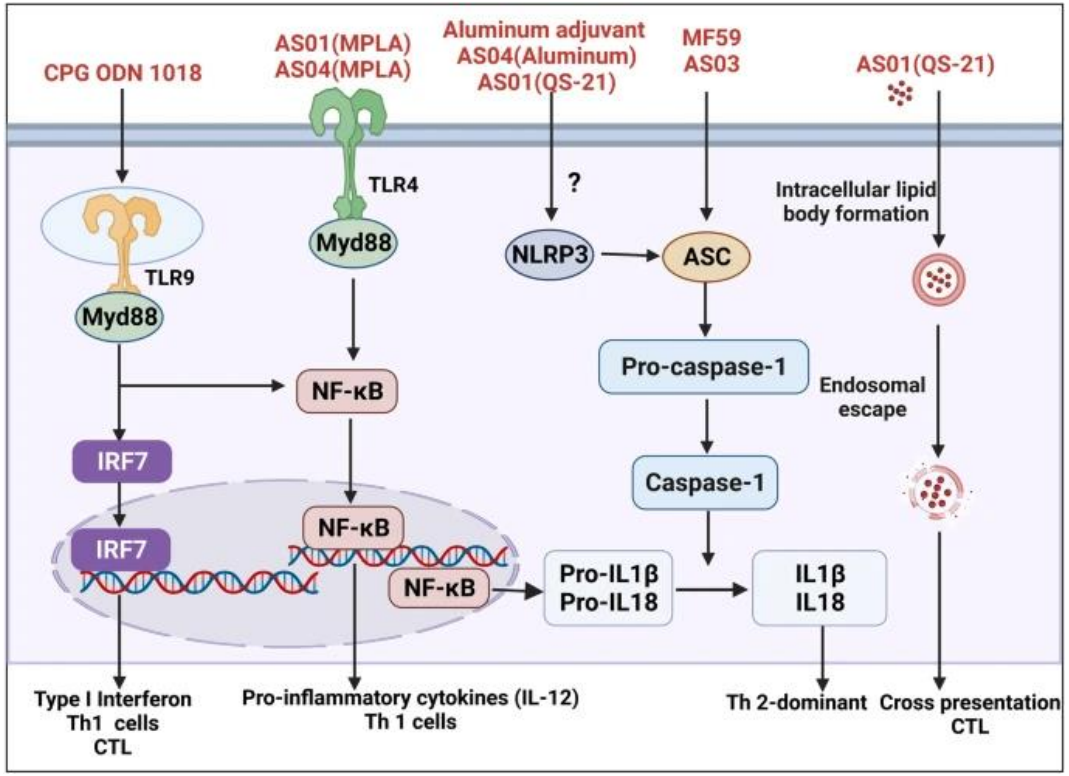
How They Work



Zhao et al. Signal Transduction Targeted Therapy 2023; 8: 283

- Immunostimulants act as danger signals to activate PRRs of APCs
- Delivery systems facilitate antigen presentation onto MHC e.g. by mimicking pathogens, prolonging Ag availability
- Net effect is enhanced B cell and T cell immunity

Major Adjuvant Signalling Pathways



- Different signalling pathways activated by different adjuvants
- Generally, cause a Th1 or Th2 bias

Zhao et al. Signal Transduction Targeted Therapy 2023; 8: 283

TLR Ligands

Intrinsic Adjuvants in many Vaccines

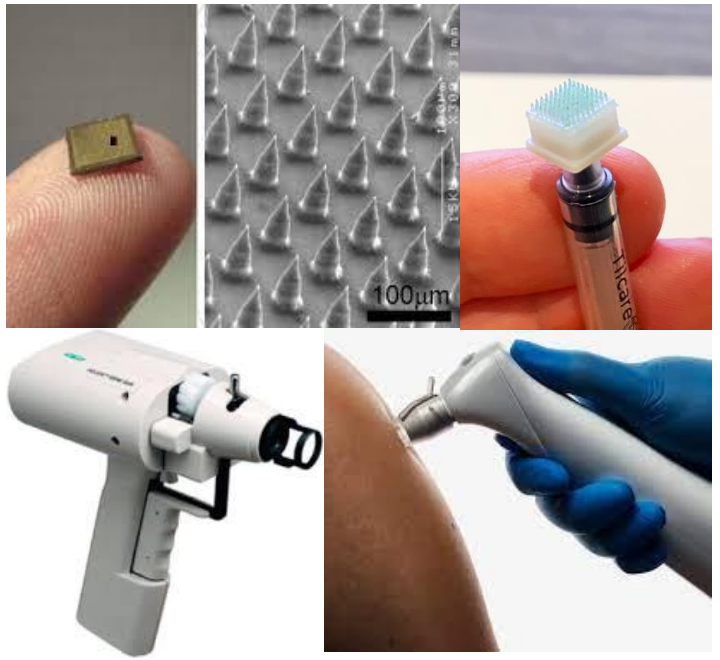
Vaccine	Intrinsic Adjuvant
Rabies	ssRNA, dsRNA, CpG
Polio	ssRNA, dsRNA, CpG
MMR	ssRNA, dsRNA, CpG
Varicella	ssRNA, dsRNA, CpG
Vaccinia	ssRNA, dsRNA, CpG
Yellow Fever	ssRNA, dsRNA, CpG
Typhoid	Peptidoglycan, LPS, CpG, Flagellin
Cholera	Peptidoglycan, LPS, CpG, Flagellin
BCG	Peptidoglycan, LPS, CpG, Flagellin
Anthrax	Peptidoglycan, LPS, CpG, Flagellin

Vaccine Pipeline

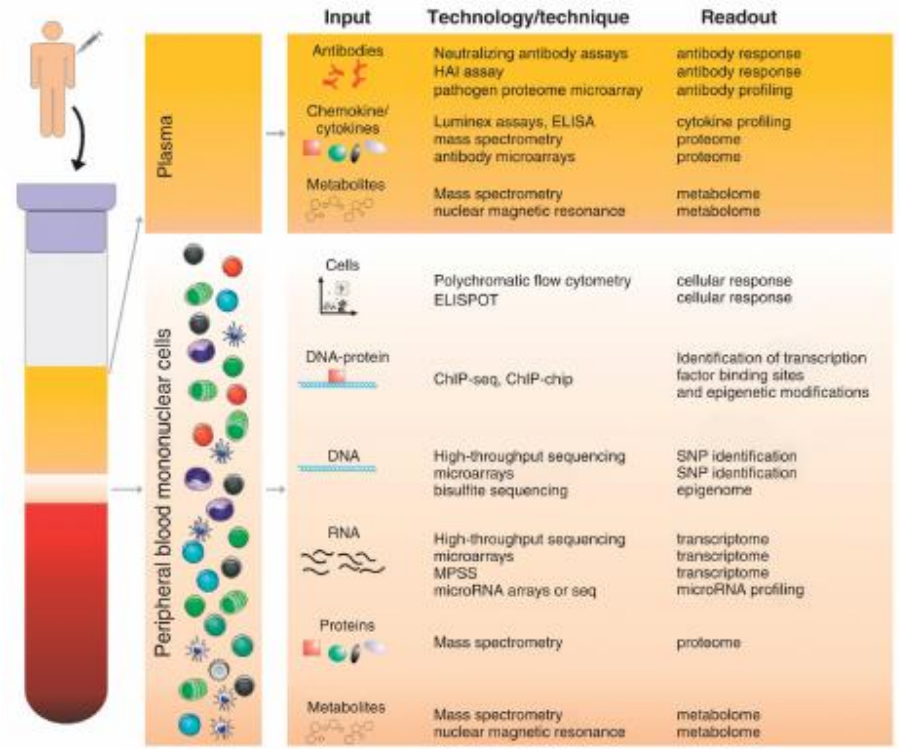
- Vaccines for new pathogens:
  - *C. difficile*, *E. coli*, *Staph aureus*, *Pseudomonas aeruginosa*, CMV, Group B streptococcus

- Combined respiratory virus vaccines:
  - Flu + COVID + RSV
  - RSV + hMPV + paraflu

- Novel Delivery Systems
  - Aerosol, transdermal patches, gene guns (DNA and RNA vaccines)

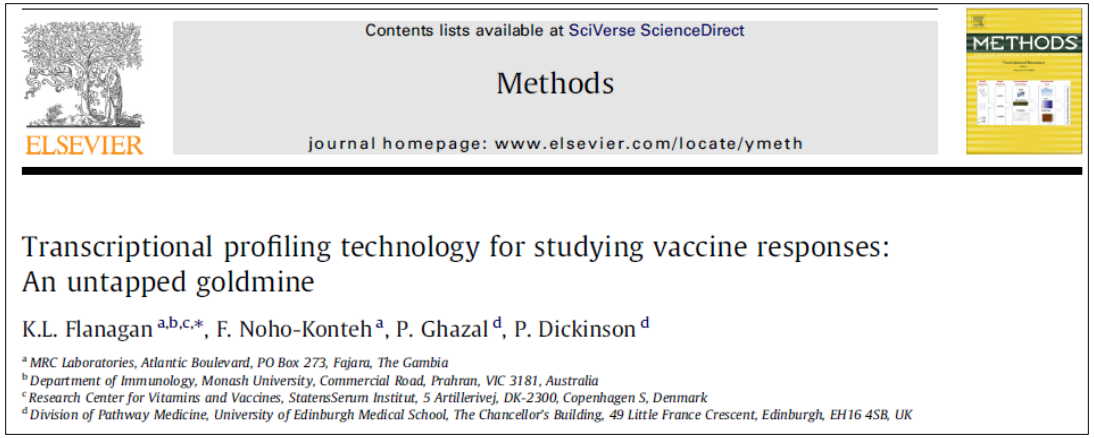


Systems Vaccinology



From Nakaya et al. Wiley Interdiscip Rev Syst Biol Med 2012;4(2):193

- Systems biology techniques of **genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics** combined with *in vitro* assays e.g. cytokine multiplex, tetramer, flow cytometry providing a very powerful tool to study vaccine responses
- Provides unprecedented insights into what vaccines do to the immune system and how they work


Contents lists available at SciVerse ScienceDirect
Methods
journal homepage: www.elsevier.com/locate/ymeth
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METHODS

Transcriptional profiling technology for studying vaccine responses: An untapped goldmine

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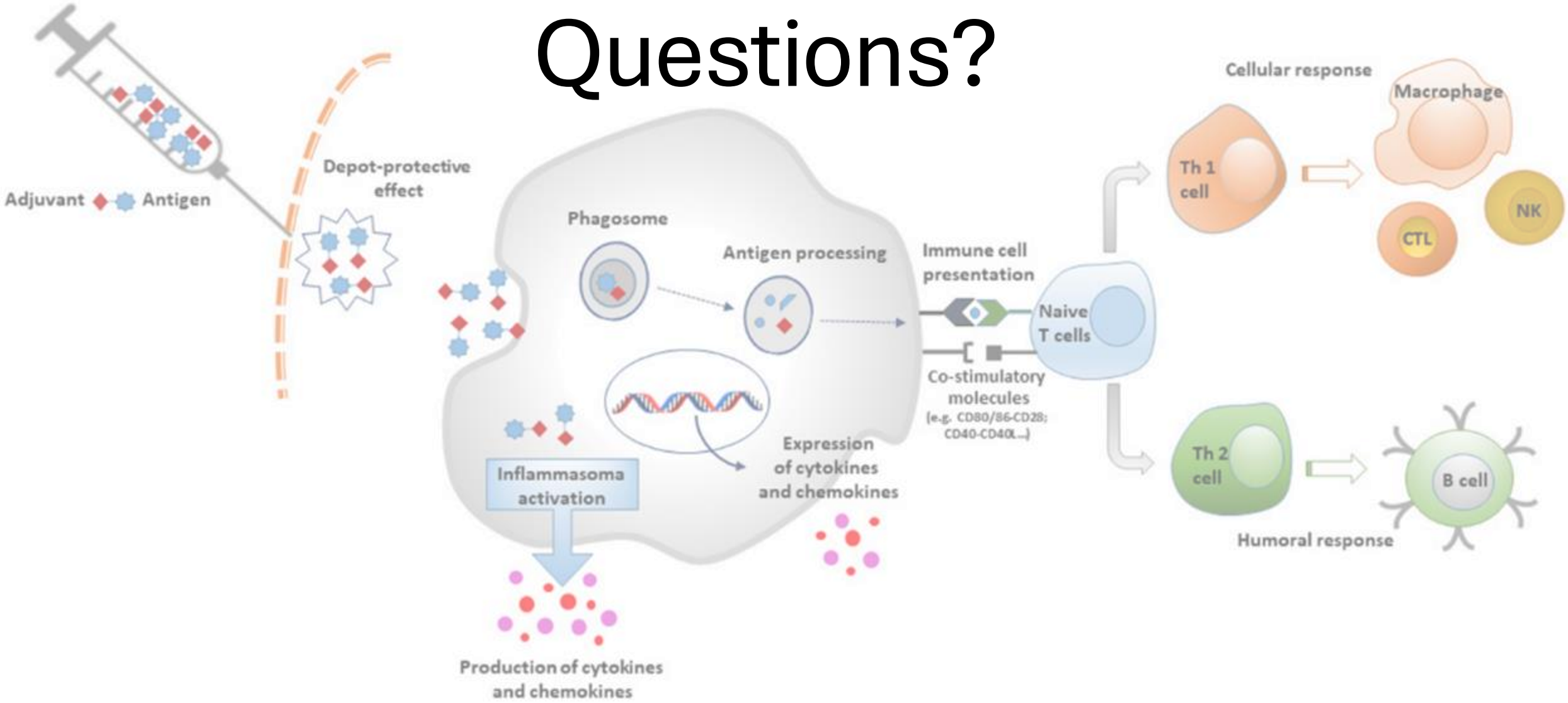
Described as the next **'golden age in vaccinology'**

Questions?


Adjuvant
Antigen
Depot-protective effect
Phagosome
Antigen processing
Immune cell presentation
Naive T cells
Co-stimulatory molecules
(e.g. CD80/86-CD28; CD40-CD40L...)
Inflammasoma activation
Expression of cytokines and chemokines
Production of cytokines and chemokines
Cellular response
Th 1 cell
Macrophage
NK
CTL
Th 2 cell
B cell
Humoral response