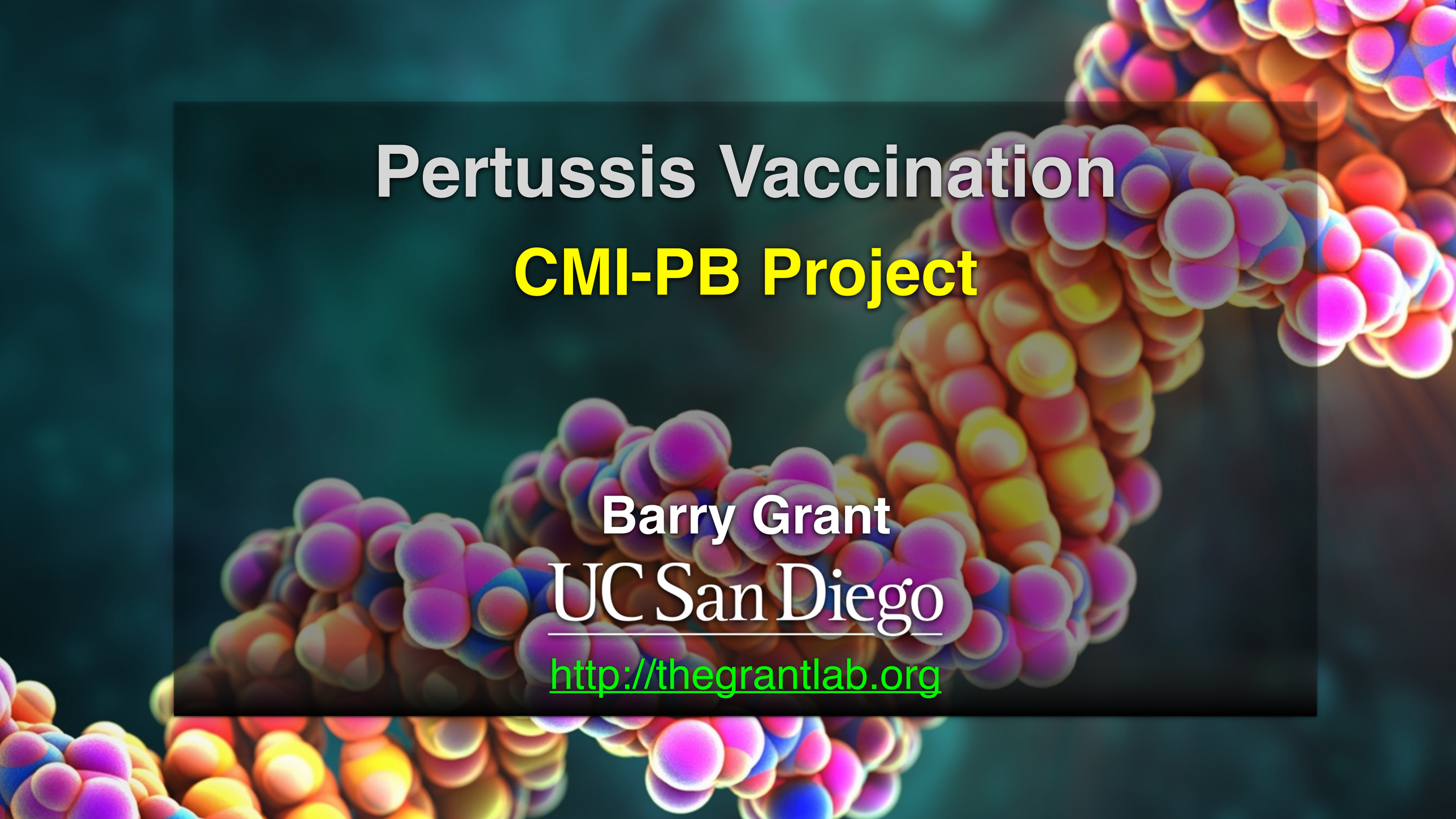


Pertussis Vaccination

CMI-PB Project

Barry Grant

UC San Diego

http://thegrantlab.org

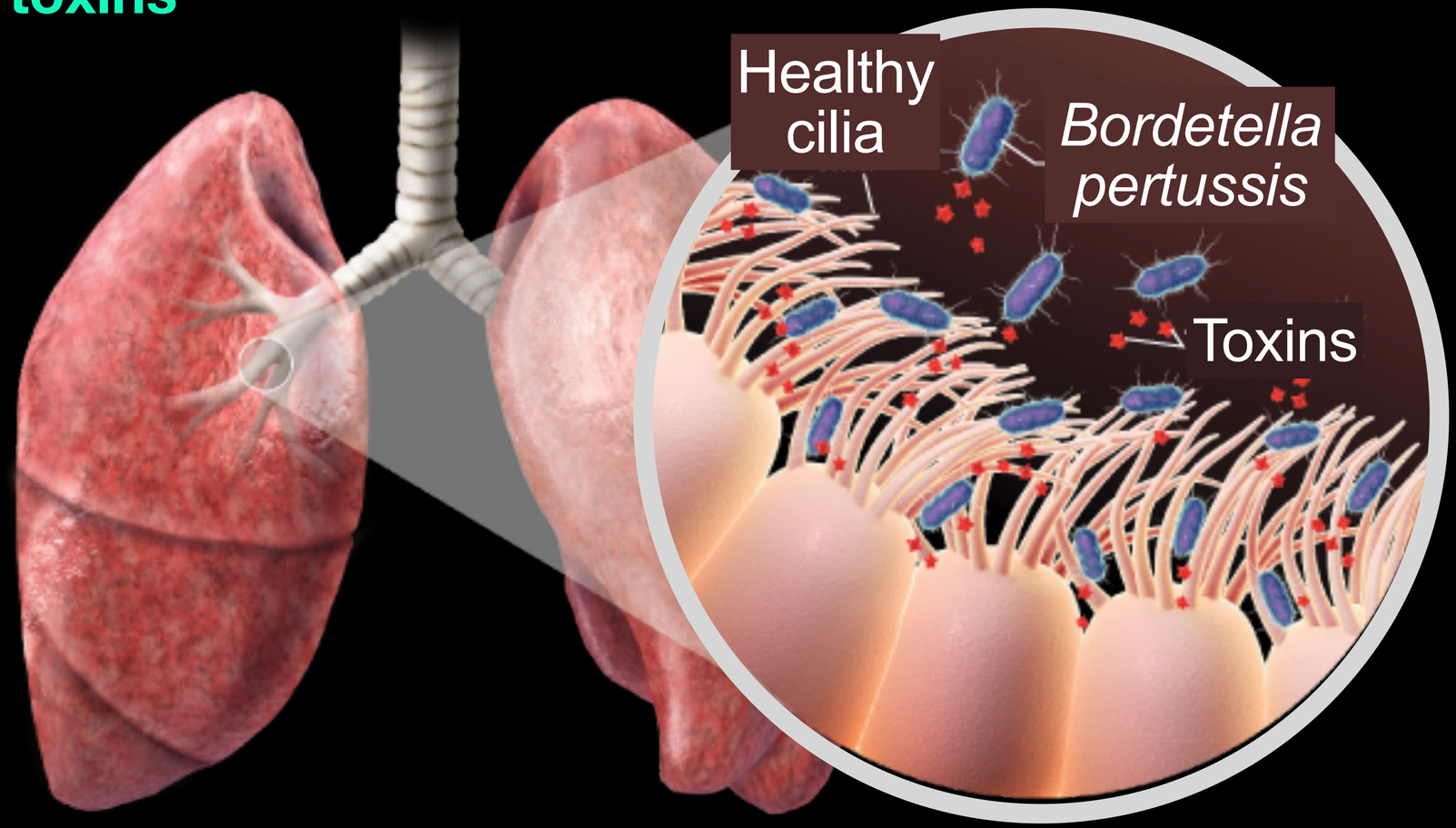
Pertussis is a leading causes of vaccine-preventable deaths

Pertussis, or **whooping cough**, is a highly contagious lung infection caused by the bacteria *Bordetella pertussis*.

- Estimated 16 million cases and 200,000 associated infant deaths annually.
- Can infect people of all ages but is most severe and life threatening for infants under a year old
- Transmission occurs primarily through bacteria laden respiratory droplets produced when an infected individual coughs and sneezes

Bordetella pertussis attacks cells lining the airways

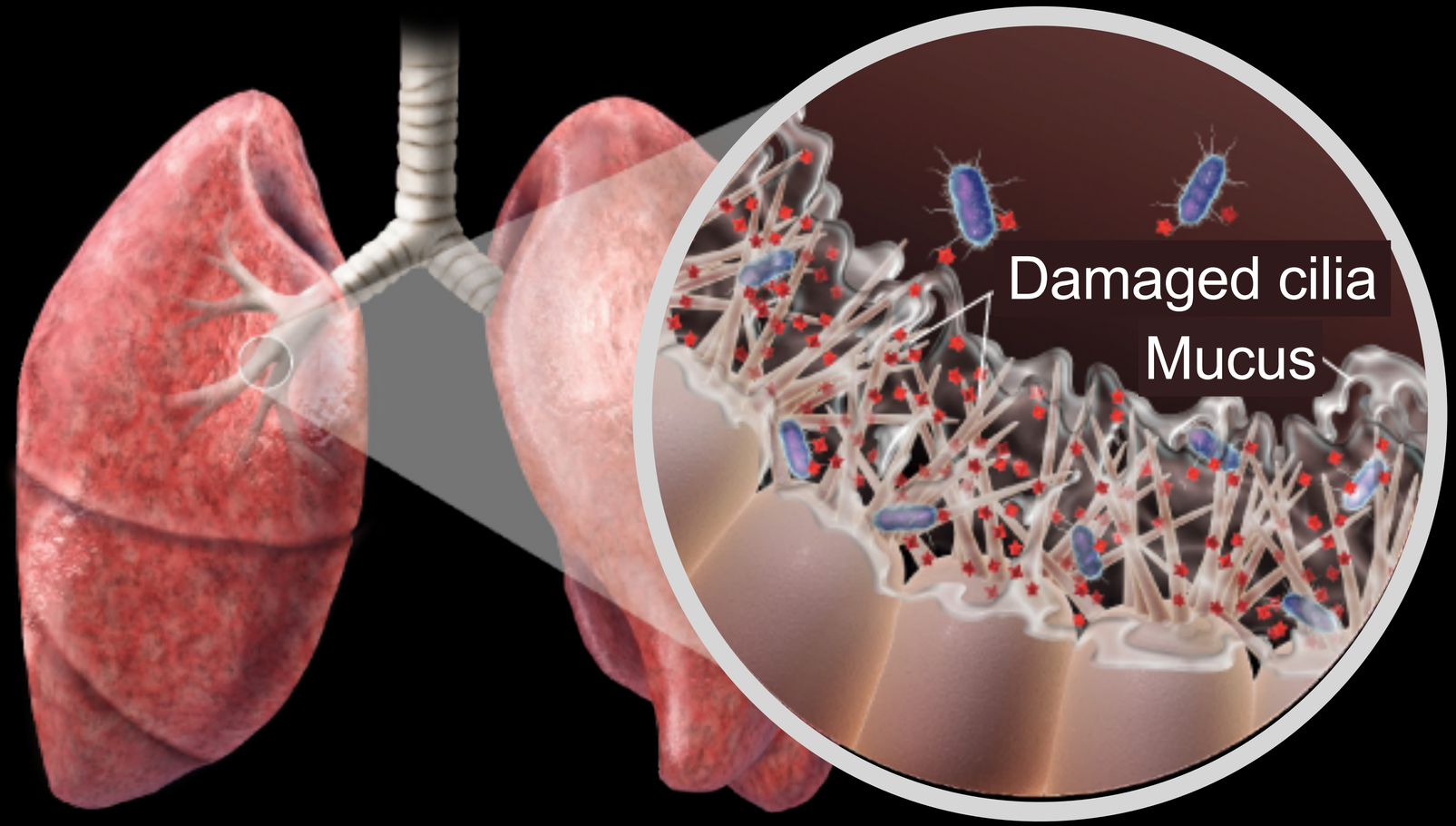
The bacteria use adhesive proteins to stick to ciliated cells whilst releasing **toxins**



More detals >

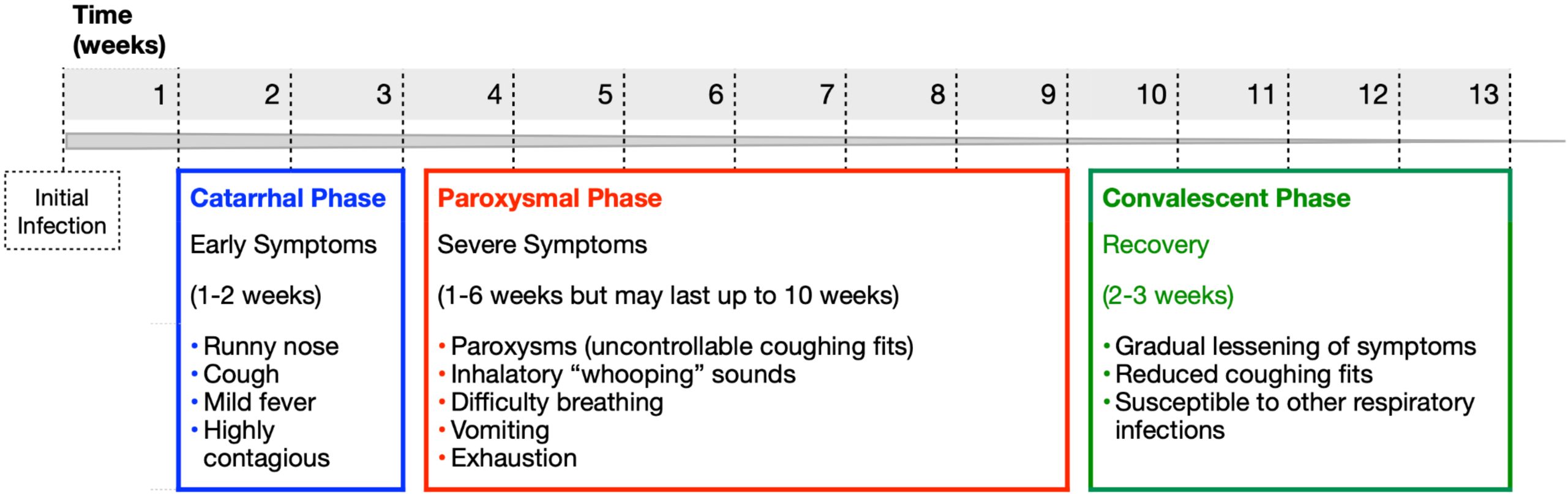
Pertussis is primarily a toxin-mediated disease

These toxins damage cilia, suppress the immune response and disrupt signaling leading to inflammation, mucus buildup and impaired function



More detals >

Pertussis develops in three main phases



More detals >

Fascinating history

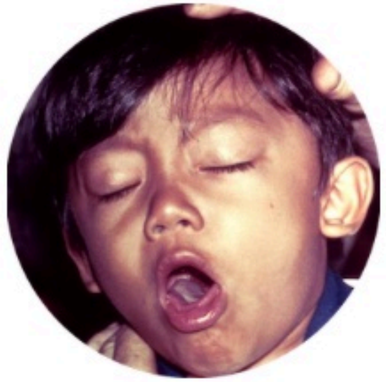
1578

First Epidemic Reported

The oldest known pertussis epidemic is thought to be the Paris outbreak of 1578. This was documented in detail by the French physician Guillaume de Baillou who described the classic symptoms of the disease.

Read more

1679

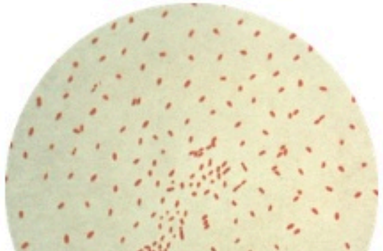


The Name "Pertussis" First Appears

The name pertussis (from Latin for "intensive cough") was first introduced by the English physician Thomas Sydenham in 1670. This name took over by the end of the decade. Earlier names included hooping cough, tusis perennis, tussis epidemica infantum, and tusis quinta.

Read more

1900

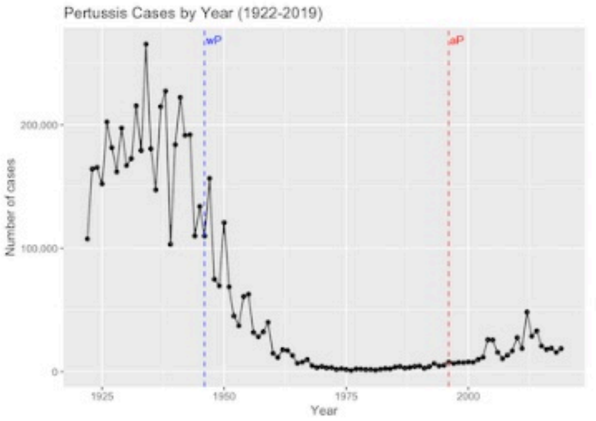


Timeline >

1942

First DPT Vaccine

Pearl Kendrick at the Michigan Department of Health combined a refined whole-cell pertussis vaccine with Diphtheria and Tetanus toxoids to create the first combination DPT vaccine.



1970

Decline of Whooping Cough

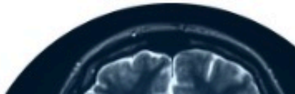
First Whole-cell Pertussis Vaccine Tested on a Wide Scale

Danish physician Thorvald Madsen tested a whole-cell pertussis vaccine on a wide scale for the first time reporting promising results.

1947

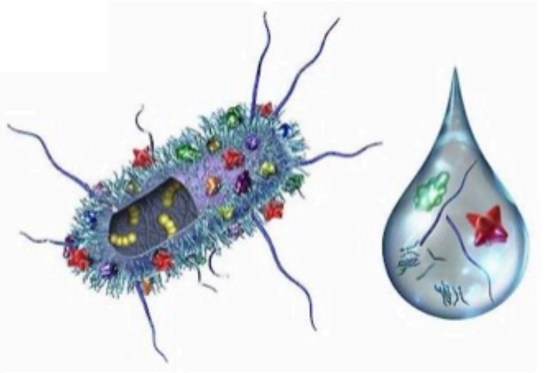
Routine Vaccination

In 1944, the Committee on Infectious Diseases of the American Academy of Pediatrics suggests routine use of pertussis vaccine and, in 1947, recommends its use in the form of the DPT combination. Routine childhood vaccination begins and is made made compulsory in some states by the end of the decade.



Timeline >

1981



Creation of DTaP Vaccine

Japanese scientist Yugi Sato created an acellular pertussis vaccine that contained purified haemagglutinins from *B. Pertussis*. This **aP vaccine** was first used in Japan soon after and was demonstrated to have fewer side effects than the whole-cell (**wP**) vaccine. It was later used in other countries (with additional components of *B. Pertussis*) as the combined DTaP vaccine.

Read more

1982

"DPT: Vaccine Roulette"

In 1982 negative publicity was encouraged from a documentary called "DPT: Vaccine Roulette", which led to a massive amount of lawsuits against the vaccine manufacturers. This documentary depicted the lives of children whose severe disabilities were **incorrectly** blamed on the DPT vaccine.

Read more

1984

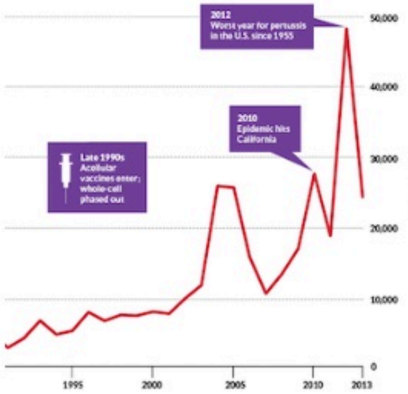
Liability

By 1984 DPT vaccine manufacturers had a hard time obtaining liability insurance. By the end of the year, only one DPT manufacturer remained. Scientists respond by ramping up development and testing of safer new acellular pertussis vaccines. These would replace the older whole cell vaccine in many countries with a decade.

1985

Timeline >

Later studies showed that their was no connection between the DPT vaccine and the permanent brain damage. It was in fact called a "Myth" and "Nonsense" by the Journal of American Medical Association in 1990.

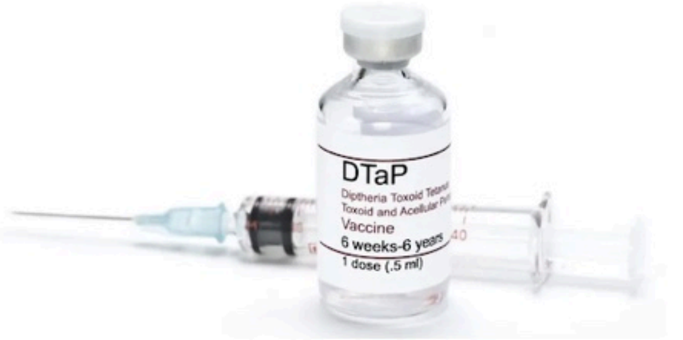


Pertussis Outbreaks

Major pertussis epidemics and outbreaks are once again a major public health concern. With epidemics typically occurring every 3 to 5 years in the U.S. as was evident in the pre-vaccine years. TO FINISH mention CA outbreak.

2010

1992



aP Vaccine Approved in the U.S.

The acellular pertussis (aP) vaccine was approved in the U.S in 1992, the the older wP formalization was phased out and completely replaced with the DTaP vaccine combination in 1996.

2020

CMI-PB
COMPUTATIONAL MODELS OF IMMUNITY
PERTUSSIS BOOST

CMI-PB Project

A new systems vaccinology project is launced that combines systems biology and genomics to provide a more holistic picture of protective pertussis-specific immune mechanisms. The project provides the scientific community with comprehensive, high-quality, and freely accessible resources related to Pertussis booster vaccination.

These resources, and associated prediction challenges, are geared towards engaging both experts and enthusiasts in developing and improving **computational models** of the immune response to vaccination and in turn informing new intervention strategies to curb the increasing frequency of *B. pertussis* infection.

Timeline >

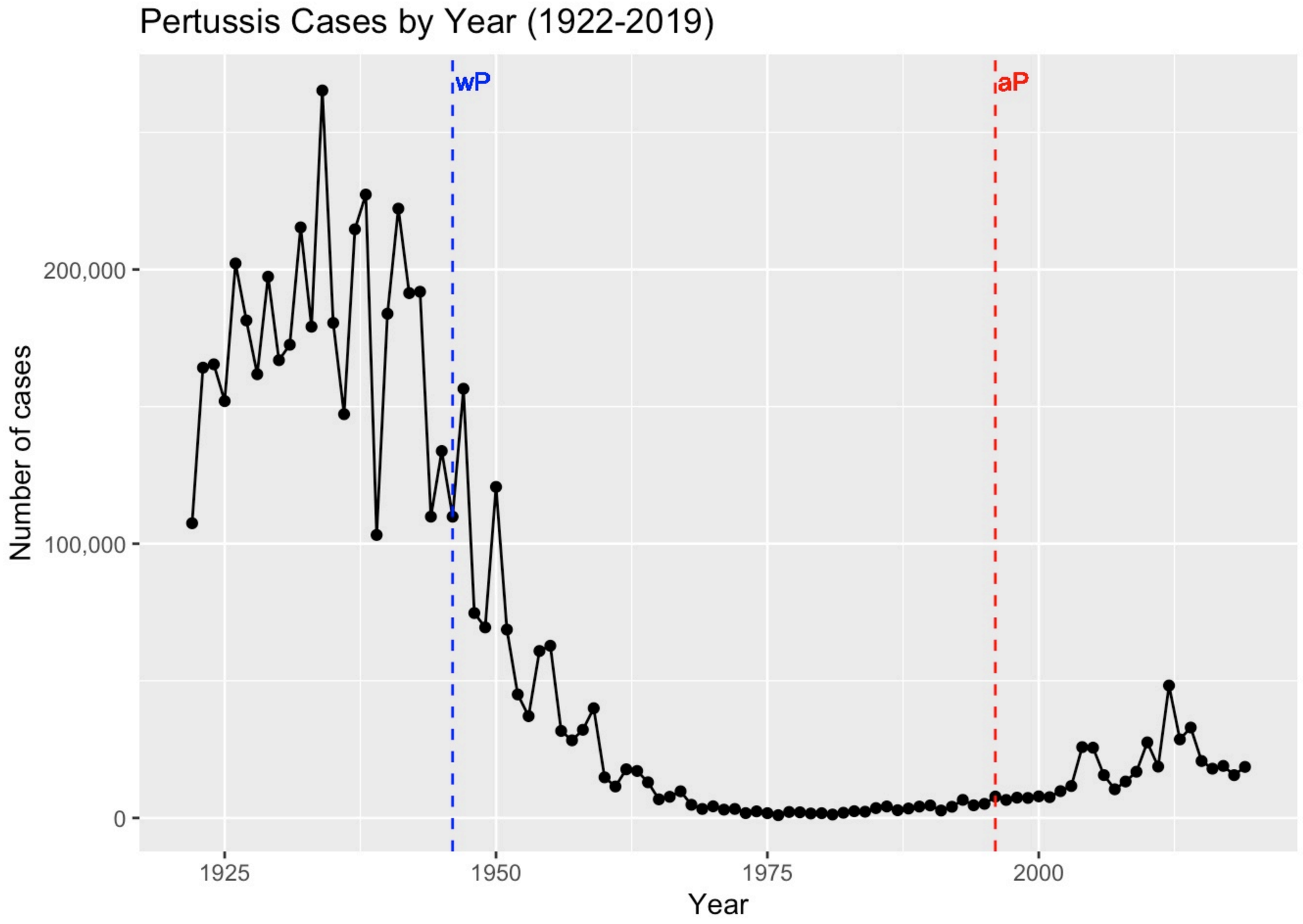
Pertussis Home
About Pertussis +
Vaccination
Pregnancy & Whooping Cough
Outbreaks
Clinicians +
Public Health Professionals +
Surveillance & Reporting –

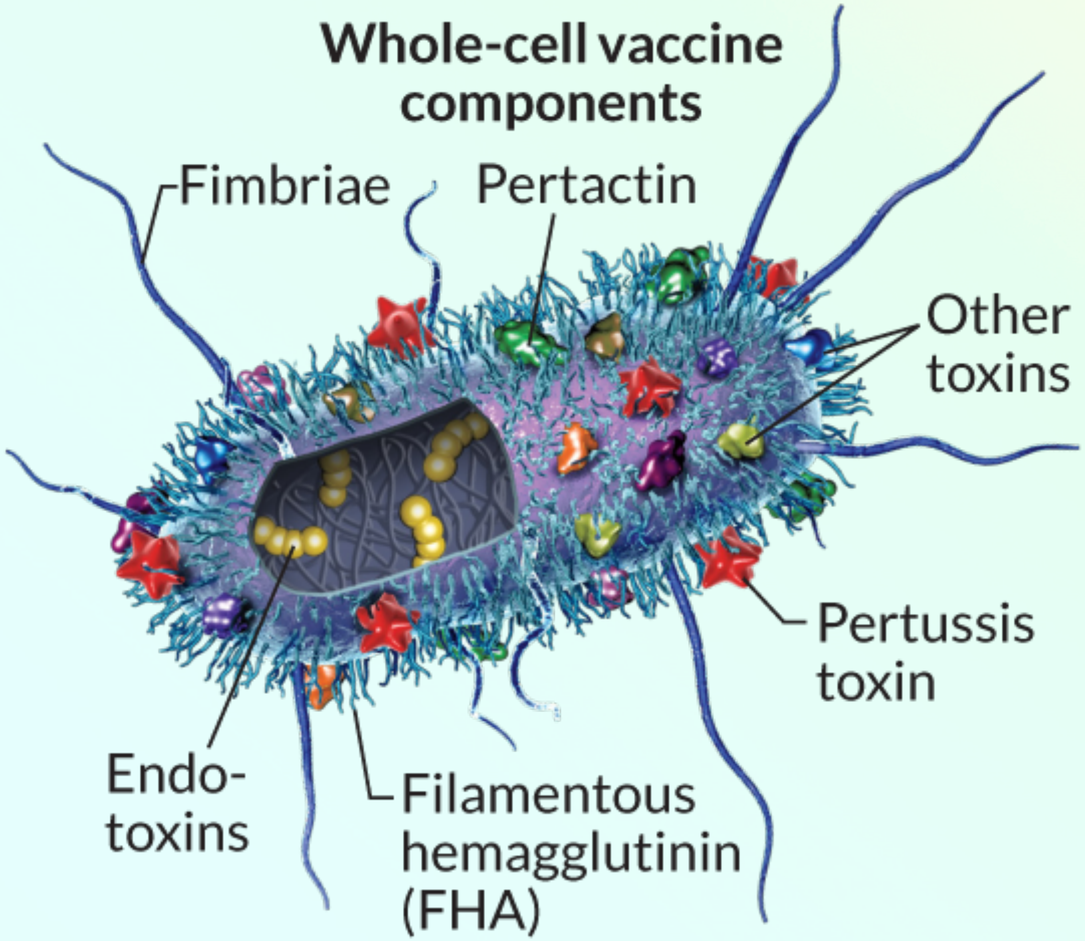
Pertussis Cases by Year (1922-2019)

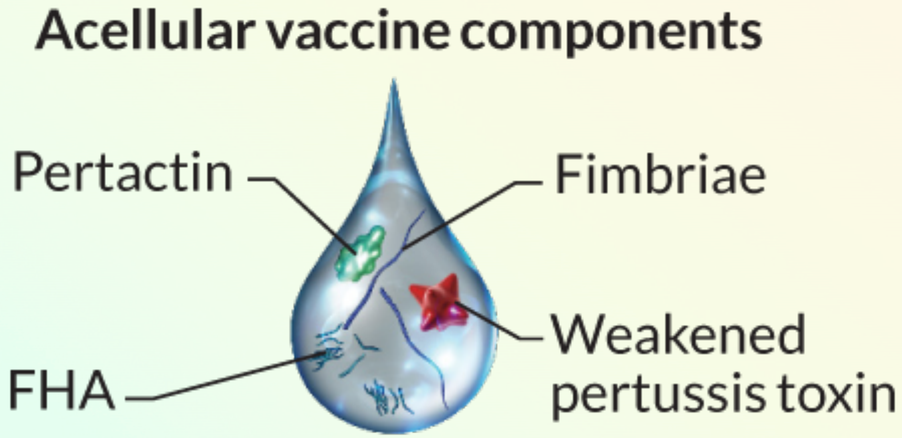
Print

This table shows reported pertussis cases in the United States since 1922. The related trend charts can be found on the Surveillance and Reporting page.

Year	No. Reported Pertussis Cases
1922	107,473
1923	164,191
1924	165,418
1925	152,003
1926	202,210


Pertussis Cases by Year (1922-2019)
wP
aP
200,000
100,000
0
Number of cases
1925
1950
1975
2000
Year


Whole-cell vaccine components
Fimbriae
Pertactin
Other toxins
Pertussis toxin
Endo-toxins
Filamentous hemagglutinin (FHA)


Acellular vaccine components
Pertactin
Fimbriae
Weakened pertussis toxin
FHA

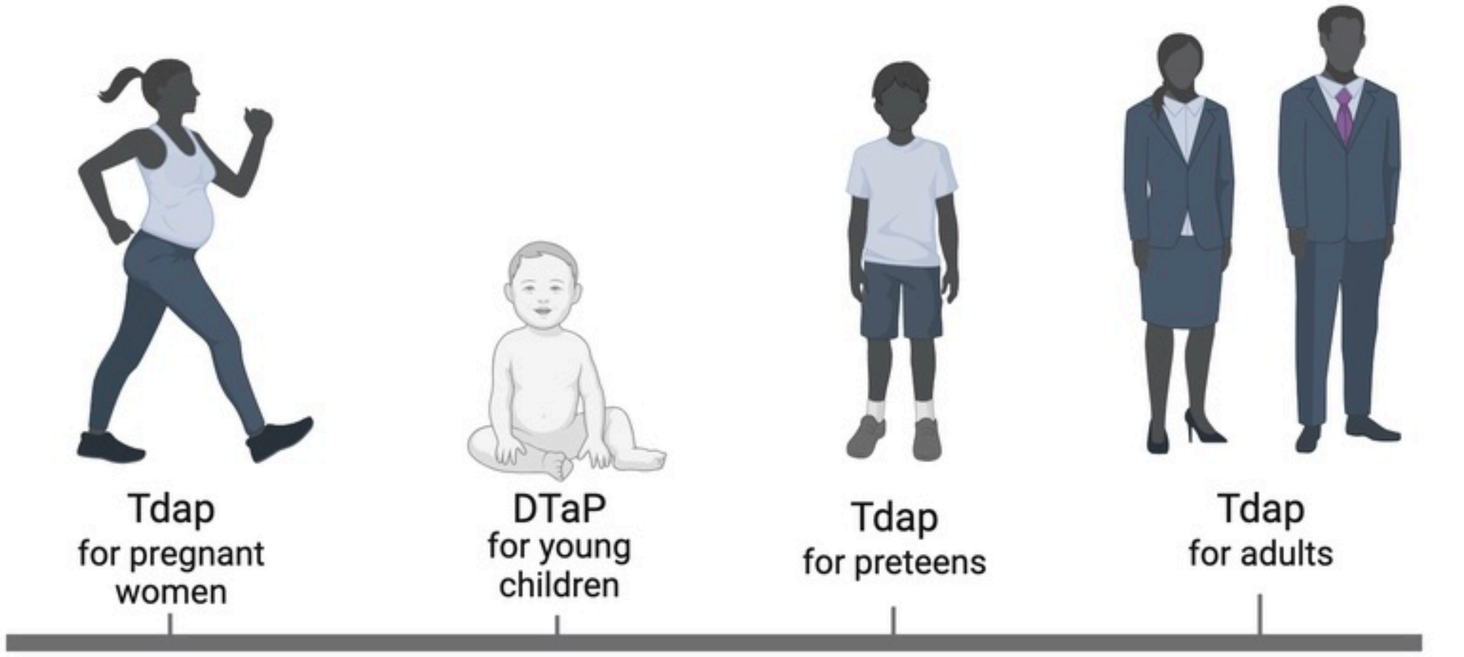
More detals >

Major aP vaccines (US)

Vaccine	Trade Name	Manufacturers	Components (Concentrations)
DTaP	Daptacel, Infanrix	Sanofi Pasteur, GlaxoSmithKline	Inactivated PT: 10-20 µg, FHA: 5-20 µg, PRN: 3-5 µg, FIM 2+3: 5-10 µg
Tdap	Adacel, Boostrix	Sanofi Pasteur, GlaxoSmithKline	Inactivated PT: 2.5-8 µg, FHA: 5-8 µg, PRN: 3-5 µg, FIM 2+3: 5-8 µg

More detals >

Major aP vaccines (US)



Tdap
for pregnant women

- During the 27-36th week of each pregnancy

DTaP
for young children

- 2, 4 and 6 months
- 15 through 18 months
- 4 through 6 years

Tdap
for preteens

- 11 through 12 years

Tdap
for adults

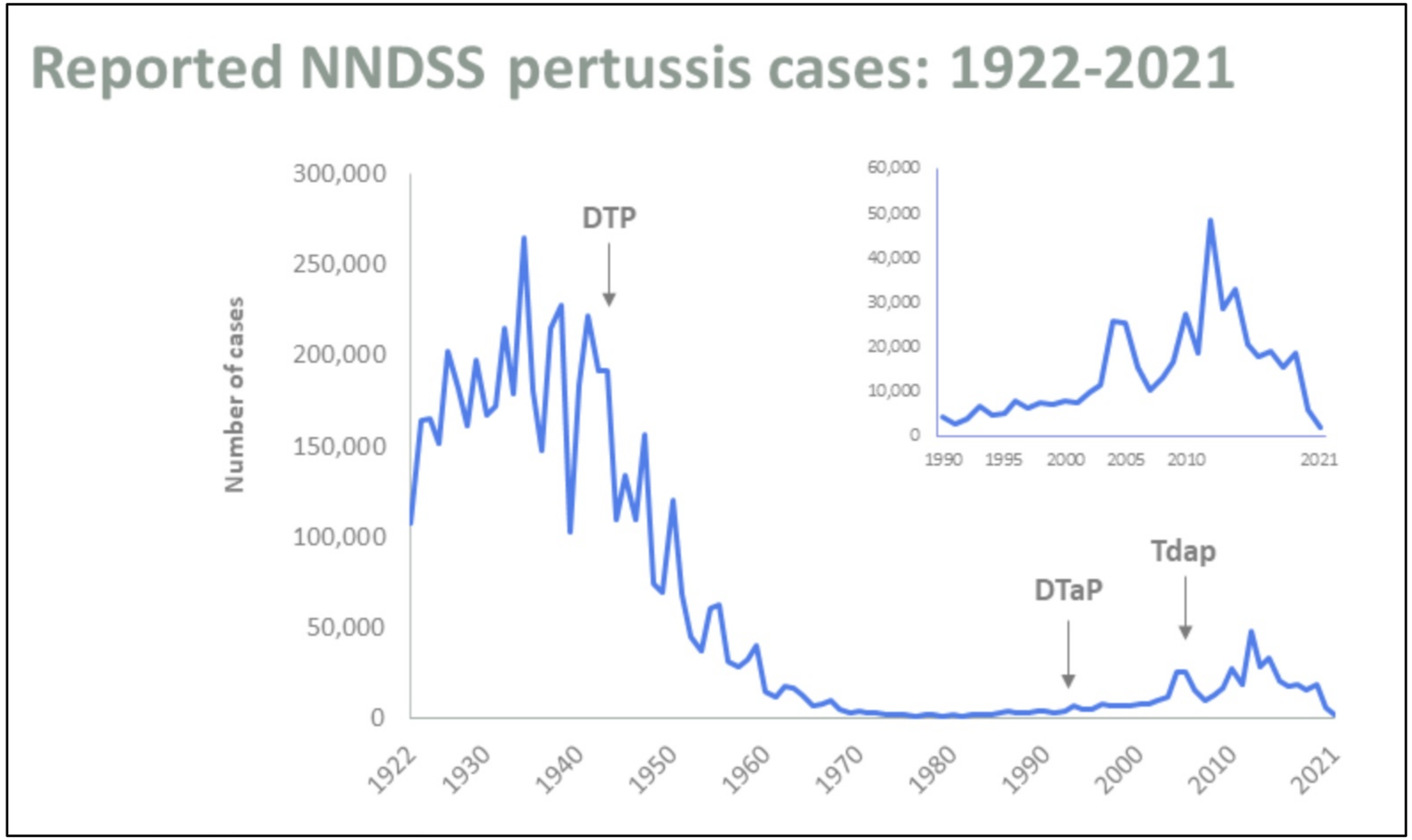
- Anytime for those who have never received it
- Subsequent boosters at 10 year intervals following initial vaccine

Source: Centers for Disease Control

[More detals >]

Waning Immunity from aP pertussis vaccination

- 1940s: Introduction of an inactivated whole bacteria PT vaccine (**wP**) dramatically decreased cases
- 1995: Vaccine-related side effects led to a replacement with the acellular PT vaccine (**aP**) in the USA
- aP induced protection wanes faster than wP → **Why?**



Source: National Notifiable Diseases Surveillance System, CDC

Slide credit: **Parmod Shinde**

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Sign in to CMI-PB

Ab titer | Search

The mission of CMI-PB is to provide the scientific community with a comprehensive, high-quality and freely accessible resource of Pertussis booster vaccination.

LEARN ABOUT THE PROJECT

The NIH funded CMI network

What is pertussis vaccination?

What are the open scientific questions?

The CMI-PB approach: A community

UNDERSTAND THE DATA

How do we measure immune responses?

What data is available?

Our approach to data standardization

Browse our terminology

ACCESS THE DATA

Data statistics

Use the API in your programs

Download all data (SFTP)

More ...

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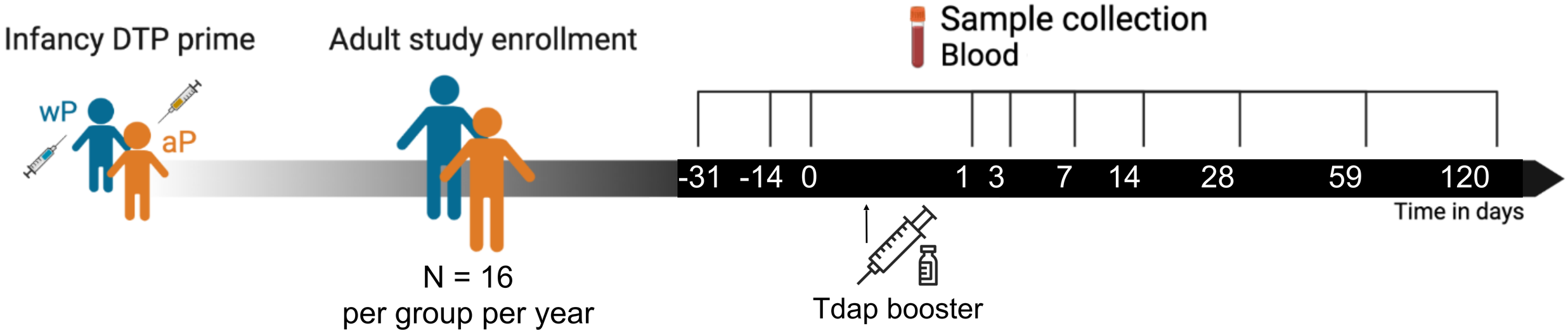
Data statistics

Use the API in your programs

Download all data (SFTP)

More ...

Recruitment Strategy



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Characterizing immune responses - Multiomics approach

PBMC cell frequencies by flow cytometry

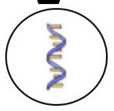
- Total of 37 distinct cell populations

Plasma antigen-specific antibody titers by Luminex

- Antibody Isotypes: IgG, IgG1, IgG2, IgG3, IgG4
- Vaccine Antigens
  - Pertussis Toxin (PT), PRN, FHA, FIM2/3
  - Tetanus Toxoids (TT)
  - Diphtheria Toxoids (DT)
  - OVA (irrelevant control)

Plasma proteomics by Olink

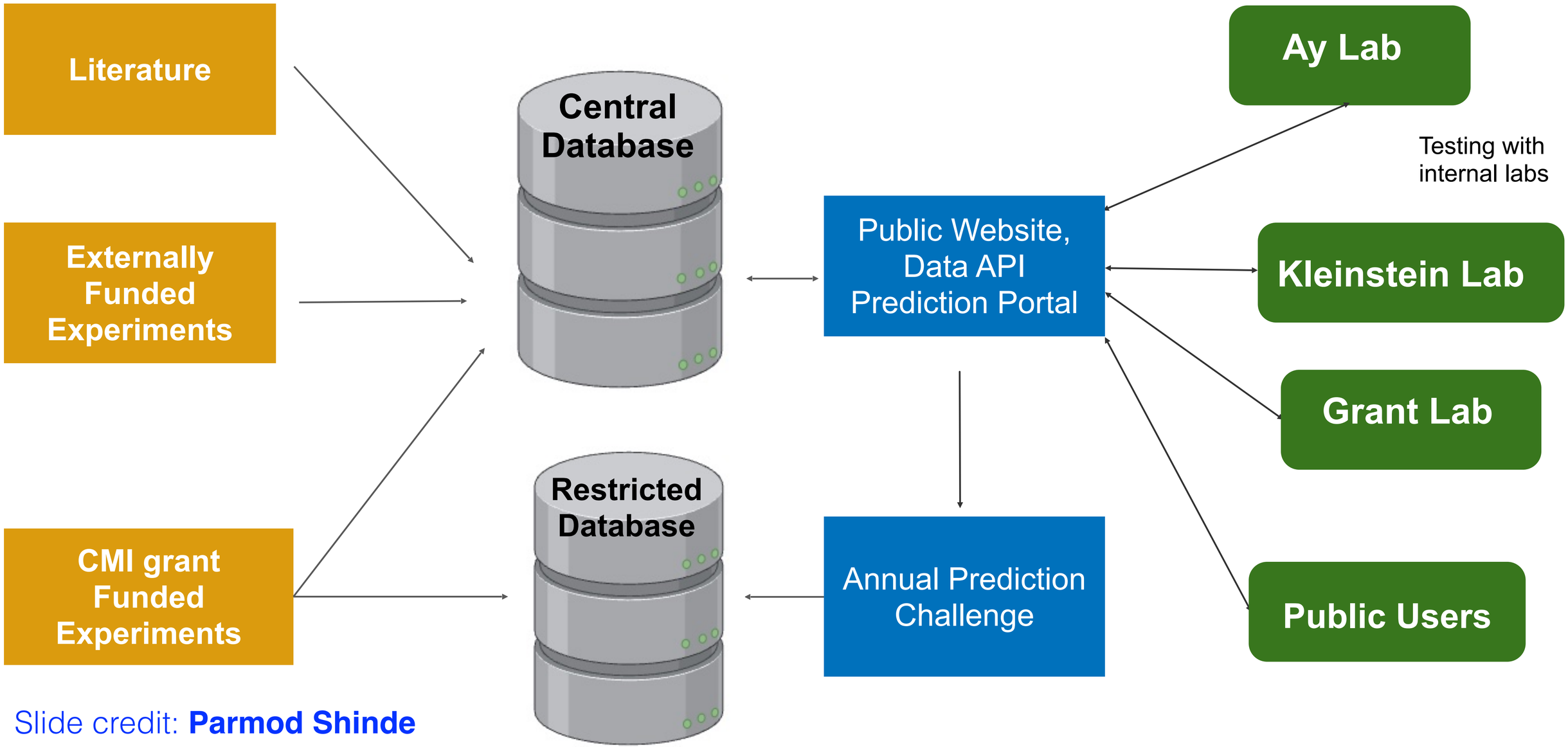
- Concentration of 45 cytokines



Transcriptomics by bulk RNA-Seq

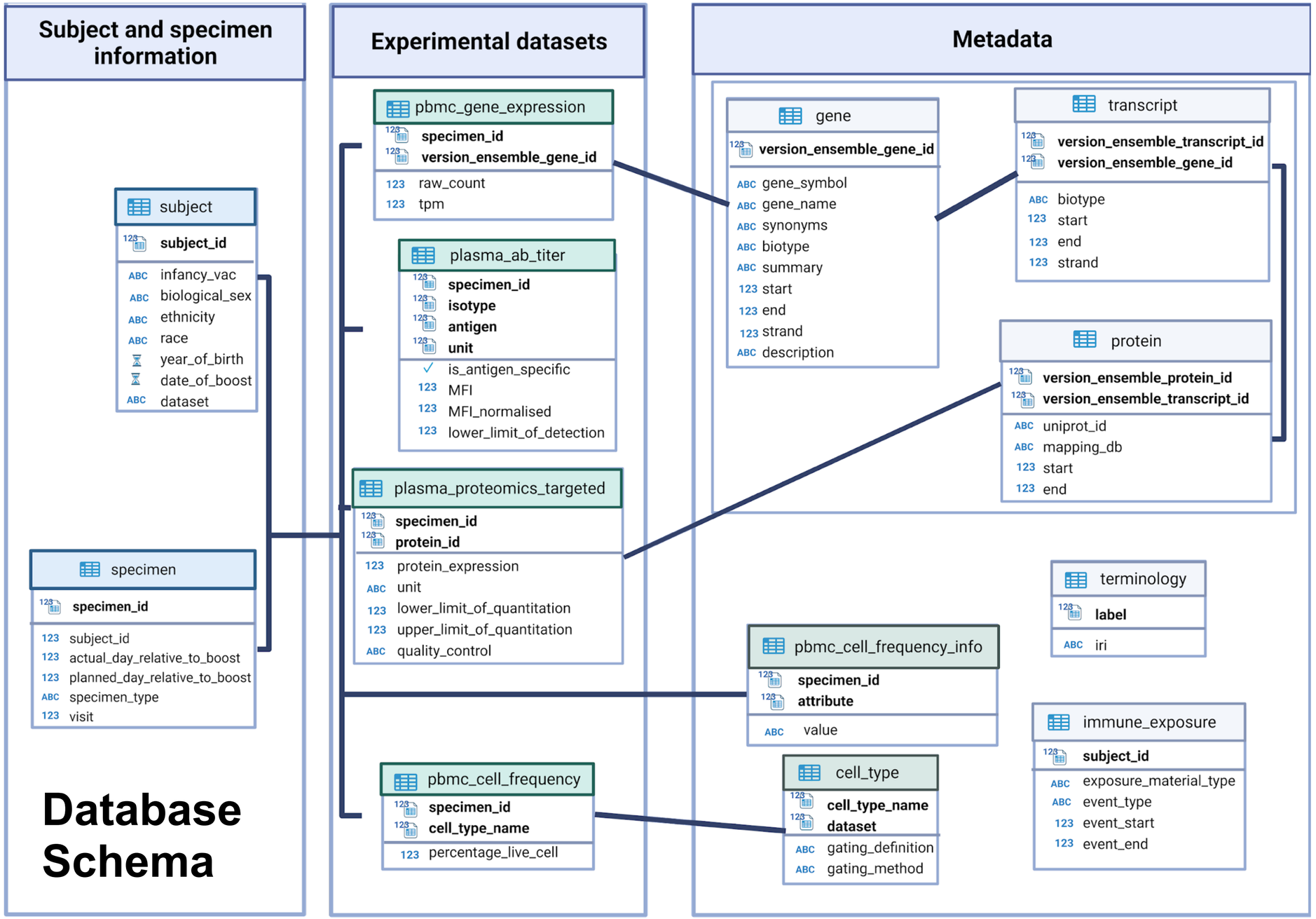
Slide credit: **Parmod Shinde**

d. Databases, Model building, and Prediction Challenge



Slide credit: **Parmod Shinde**

e. Providing access to experimental data in a standardized format



INFORMATION TABLES

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biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset

SPECIMEN
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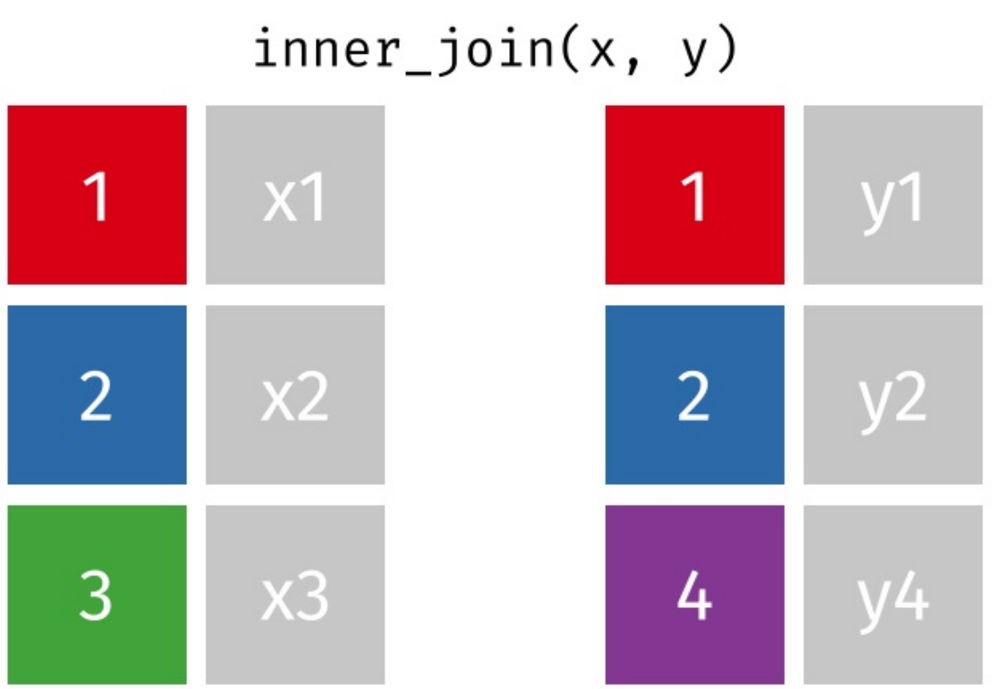
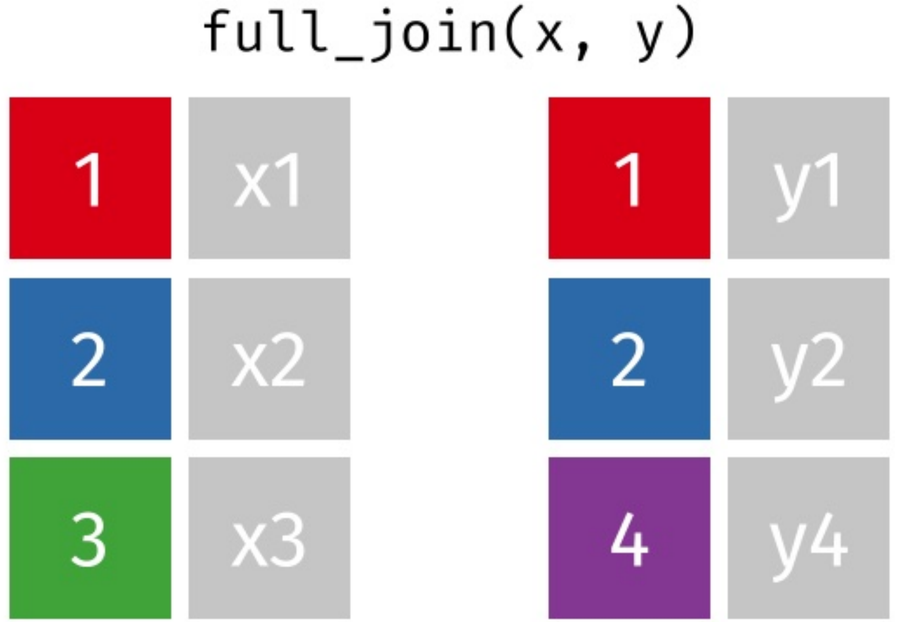
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit

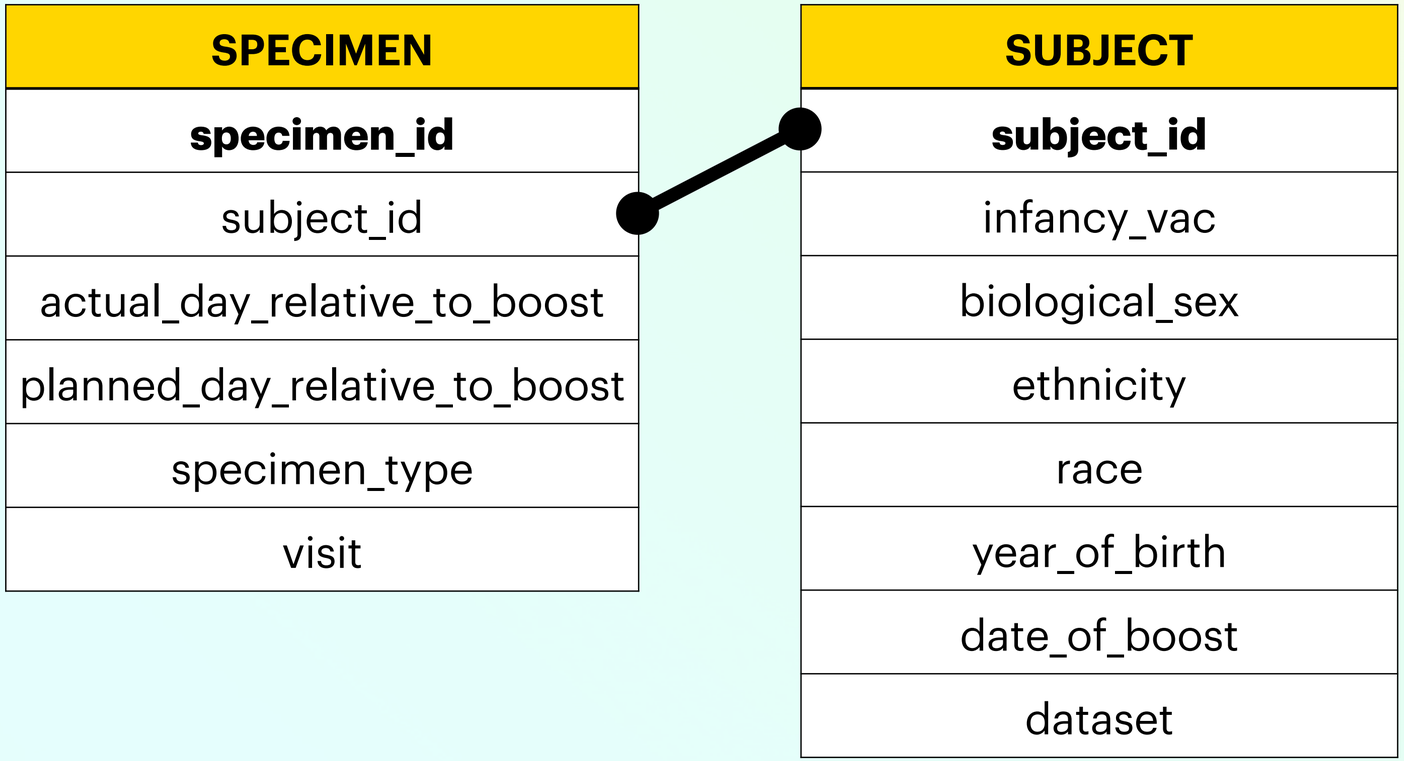
DPLYR *_JOIN() FUNCTIONS...





INFORMATION TABLES

CAN BE LINKED BY "SUBJECT_ID"



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planned_day_relative_to_boost
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visit

SUBJECT
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biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset

WE WANT ONE META TABLE

USE DPLYR *_JOIN() FUNCTIONS...

SPECIMEN
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit

SUBJECT
subject_id
infancy_vac
biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset

=

META
specimen_id
subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit
infancy_vac
biological_sex
ethnicity
race
year_of_birth
date_of_boost
dataset

JOIN WITH EXPEREMENT TABLES

USE DPLYR *_JOIN() FUNCTIONS...

META
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subject_id
actual_day_relative_to_boost
planned_day_relative_to_boost
specimen_type
visit
infancy_vac
biological_sex
ethnicity
...

AB_TITER
specimen_id
isotype
is_antigen_specific
antigen
MFI
MFI_normalised
unit
lower_limit_of_detection

META + EXPERIMENT

HAS EVERYTHING WE NEED FOR FURTHER ANALYSIS...

META
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planned_day_relative_to_boost
specimen_type
visit
infancy_vac
biological_sex
ethnicity
...

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is_antigen_specific
antigen
MFI
MFI_normalised
unit
lower_limit_of_detection

=

ABDATA
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planned_day_relative_to_boost
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ethnicity
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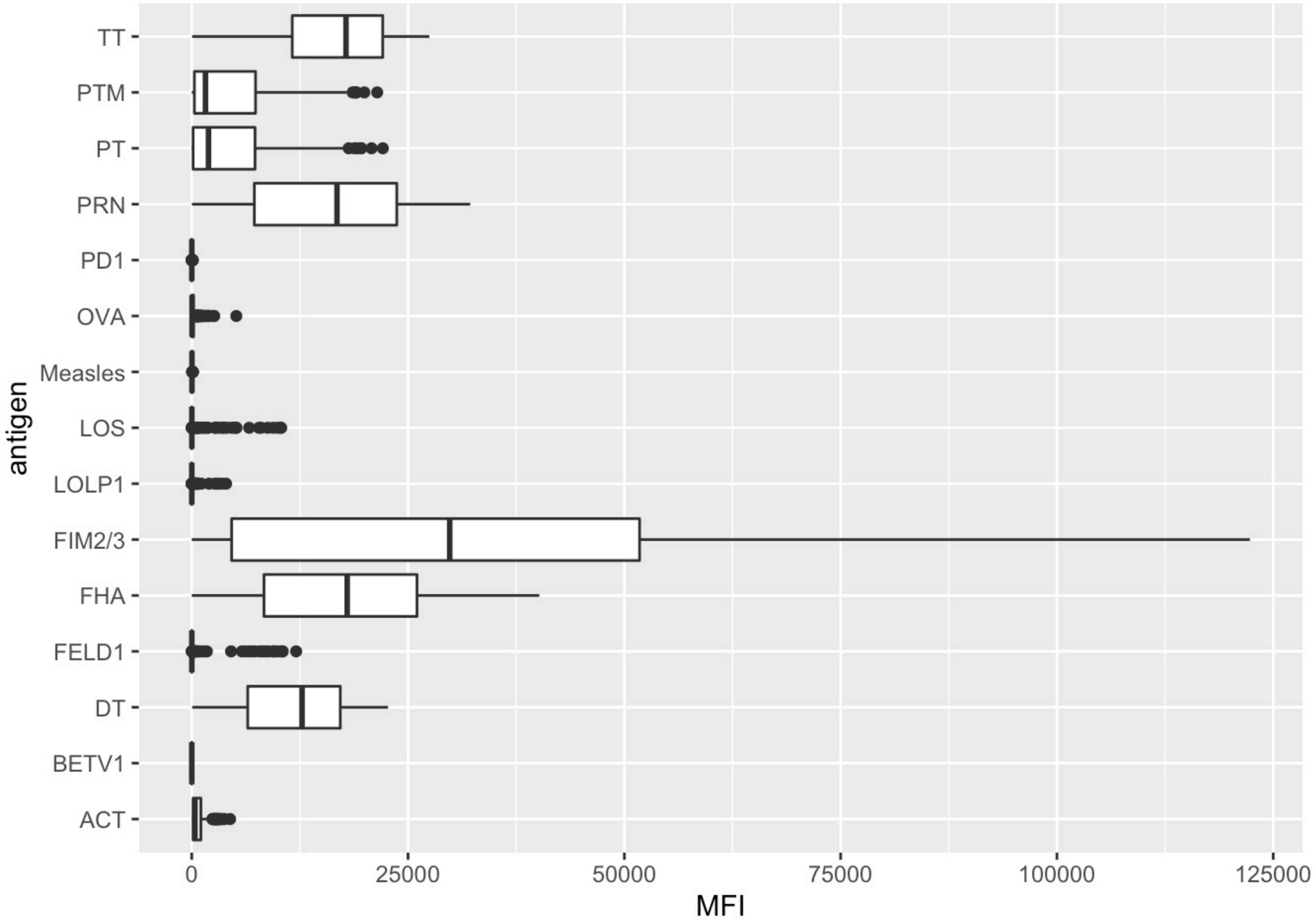
unit
lower_limit_of_detection


TT
PTM
PT
PRN
PD1
OVA
Measles
LOS
LOLP1
FIM2/3
FHA
FELD1
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BETV1
ACT
antigen
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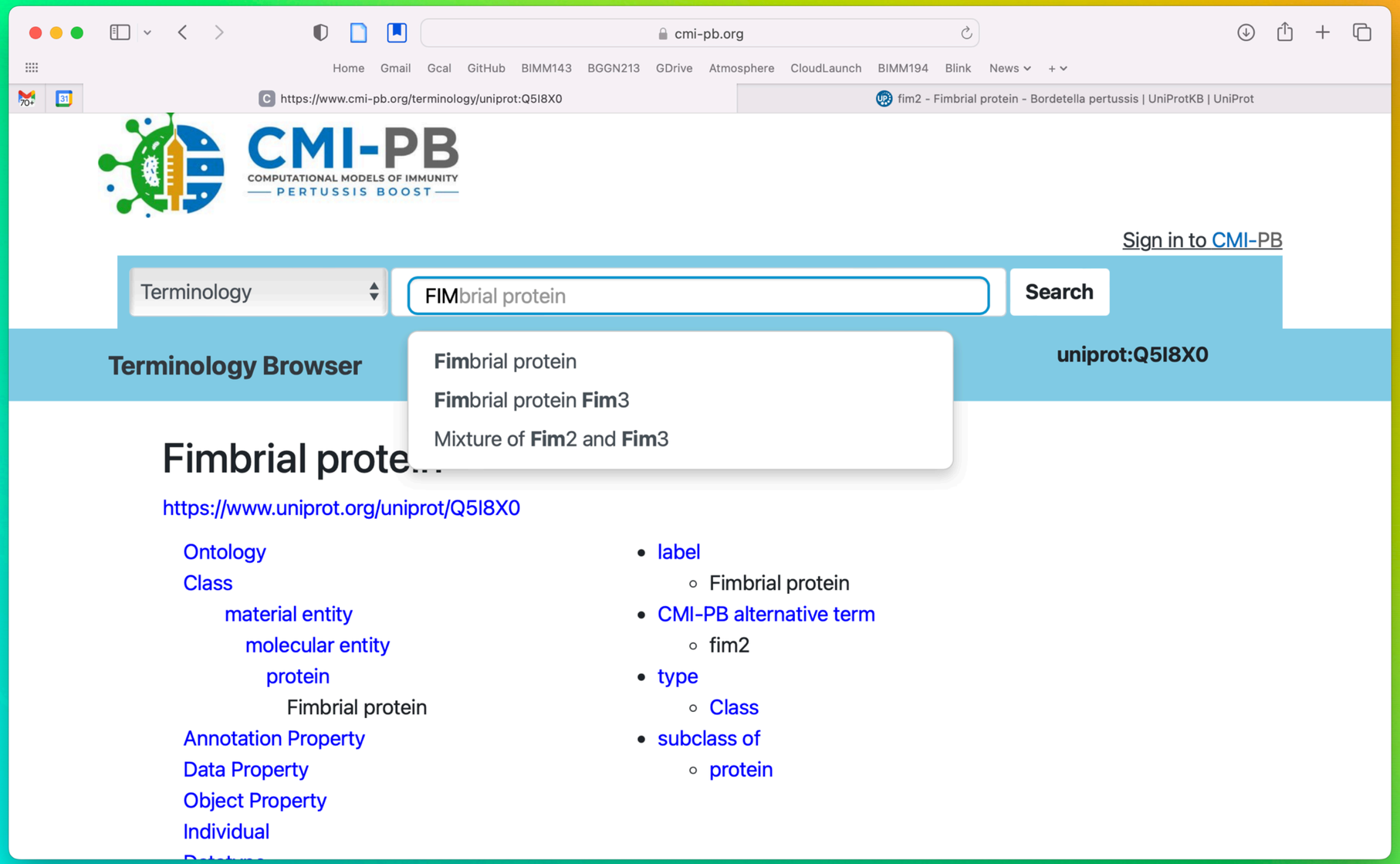
50000
75000
100000
125000
MFI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fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt
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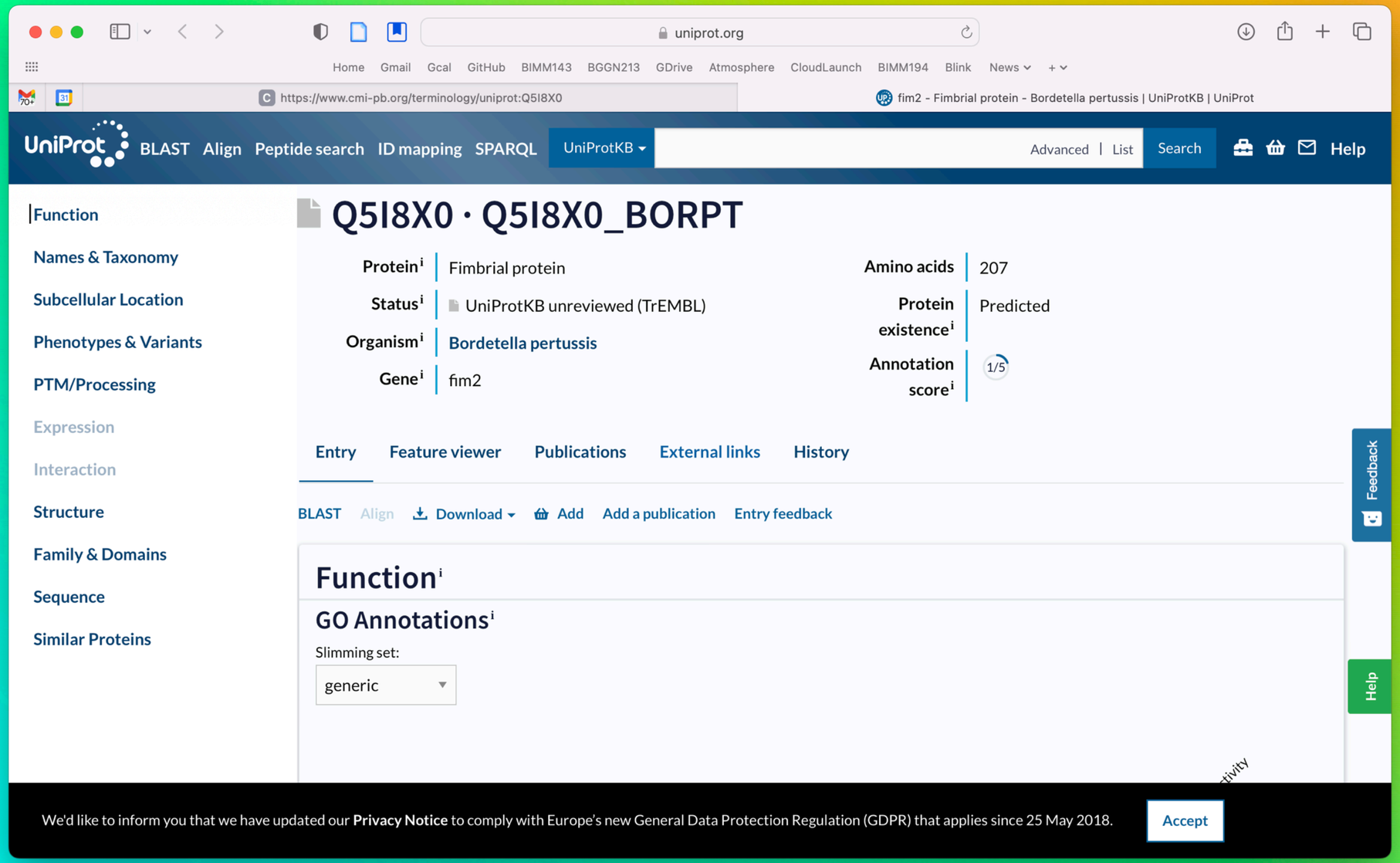
Terminology
FIMbrial protein
Search
Fimbrial protein
Fimbrial protein Fim3
Mixture of Fim2 and Fim3
Terminology Browser
uniprot:Q5I8X0
Fimbrial prote...
https://www.uniprot.org/uniprot/Q5I8X0
Ontology
Class
material entity
molecular entity
protein
Fimbrial protein
Annotation Property
Data Property
Object Property
Individual
label
Fimbrial protein
CMI-PB alternative term
fim2
type
Class
subclass of
protein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https://www.cmi-pb.org/terminology/uniprot:Q5I8X0
fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt
UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB Advanced | List Search Help
Function
Names & Taxonomy
Subcellular Location
Phenotypes & Variants
PTM/Processing
Expression
Interaction
Structure
Family & Domains
Sequence
Similar Proteins
Q5I8X0 · Q5I8X0_BORPT
Protein Fimbrial protein
Status UniProtKB unreviewed (TrEMBL)
Organism Bordetella pertussis
Gene fim2
Amino acids 207
Protein existence Predicted
Annotation score 1/5
Entry Feature viewer Publications External links History
BLAST Align Download Add Add a publication Entry feedback
Function
GO Annotations
Slimming set:
generic
Feedback
Help
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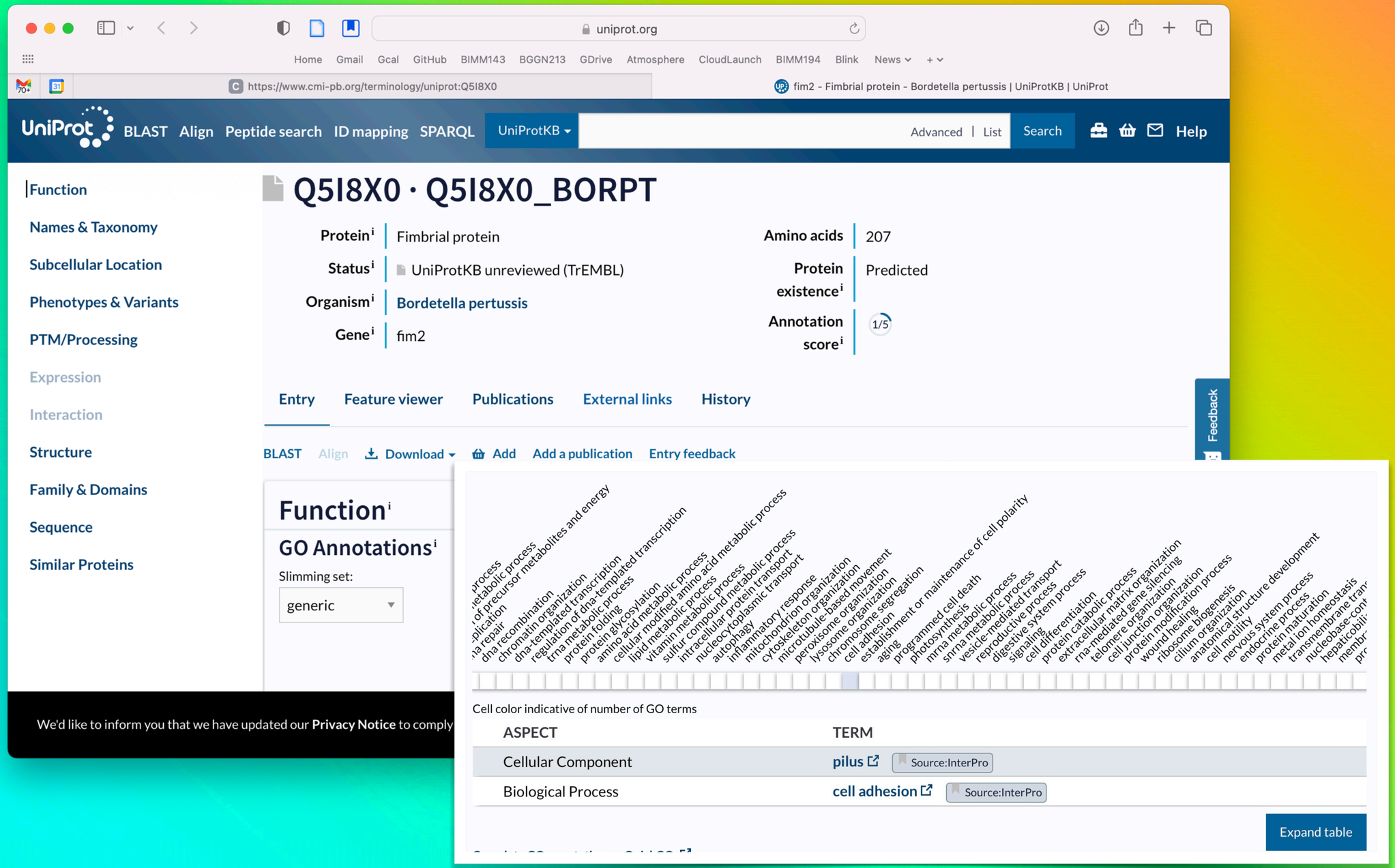
Accept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https://www.cmi-pb.org/terminology/uniprot:Q5I8X0
fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt
UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB Advanced | List Search Help
Function
Names & Taxonomy
Subcellular Location
Phenotypes & Variants
PTM/Processing
Expression
Interaction
Structure
Family & Domains
Sequence
Similar Proteins
Q5I8X0 · Q5I8X0_BORPT
Protein Fimbrial protein
Status UniProtKB unreviewed (TrEMBL)
Organism Bordetella pertussis
Gene fim2
Amino acids 207
Protein existence Predicted
Annotation score 1/5
Entry Feature viewer Publications External links History
BLAST Align Download Add Add a publication Entry feedback
Feedback
Function
GO Annotations
Slimming set:
generic
Cell color indicative of number of GO terms
ASPECT TERM
Cellular Component pilus Source:InterPro
Biological Process cell adhesion Source:InterPro
Expand table
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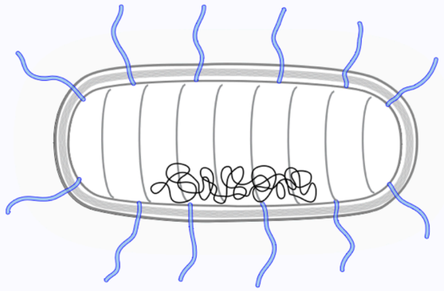
https://www.cmi-pb.org/terminology/uniprot:Q5I8X0

fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt

UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB Advanced | List Search Help

Subcellular Location

UniProt Annotation | GO Annotation



pilus

Complete GO annotation on QuickGO

Feedback

Help

uniprot.org

Home Gmail Gcal GitHub BIMM143 BGGN213 GDrive Atmosphere CloudLaunch BIMM194 Blink News +

https://www.cmi-pb.org/terminology/uniprot:Q5I8X0

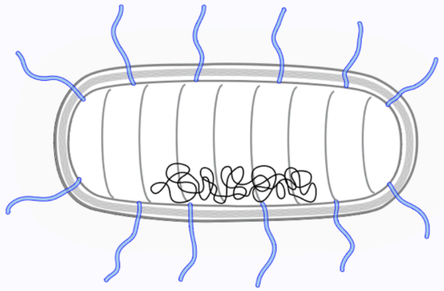
fim2 - Fimbrial protein - Bordetella pertussis | UniProtKB | UniProt

UniProt BLAST Align Peptide search ID mapping SPARQL UniProtKB Advanced | List Search Help

- Function
- Names & Taxonomy
- Subcellular Location
- Phenotypes & Variants
- PTM/Processing
- Expression
- Interaction
- Structure
- Family & Domains
- Sequence
- Similar Proteins

Subcellular Location

UniProt Annotation | GO Annotation



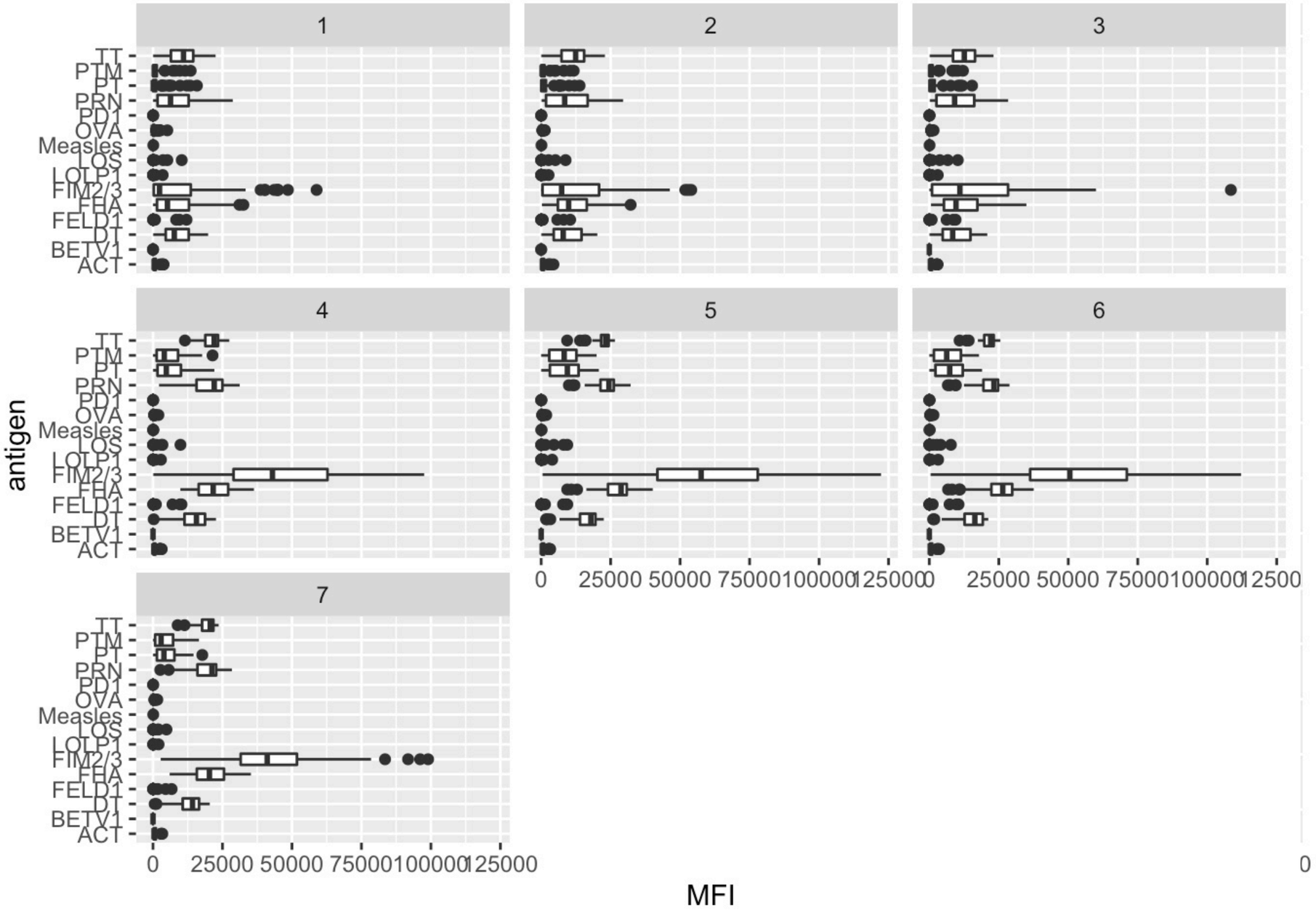
pilus

Complete GO annotation on QuickGO

Fimbrium
A fimbrium or pilus is a hair-like, non-flagellar, polymeric filamentous appendage that extend from the bacterial or archaeal cell surface, such as type 1 pili, P-pili, type IV pili or curli. Pili perform a variety of functions, including surface adhesion, motility, cell-cell interactions, biofilm formation, conjugation, DNA uptake, and twitching motility.

Feedback

Help


1
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PT
PRN
PD1
OVA
Measles
LQS
LOLP1
FIM2/3
FHA
FELD1
DT
BETV1
ACT
antigen
0
25000
50000
75000
100000
125000
MFI

a. Past and future CMI-PB annual prediction challenges

	Annual prediction challenge title	Contestants	Number of subjects		Current status
			Training dataset	Test dataset	
1	**First Challenge:** Internal dry run	CMI-PB consortium	60 (28 aP + 32 wP)	36 (19 aP + 17 wP)	May 2022
2	**Second Challenge:** Invited challenge	Invited contestants	96 (47 aP + 49 wP)	22 (13 aP + 9 wP)	Announced on September 12, 2023
3	**Third Challenge:** Open Challenge 1	Public	118 (60 aP + 58 wP)	32 (16 aP + 16 wP)	Will be announced in April 2024
4	**Fourth Challenge:** Open Challenge 2	Public	150 (76 aP + 74 wP)	32 (16 aP + 16 wP)*	Will be announced in December 2024

Slide credit: **Parmod Shinde**

b. Prediction challenge outline

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2nd CMI-PB Prediction Challenge Outline

Revolutionizing computational modelling approaches for immune response prediction

Challenge announcement

1 Read about CMI-PB challenge

2 Access multi-omics immune response data

3 Build your predictive models

4 Submit predictions

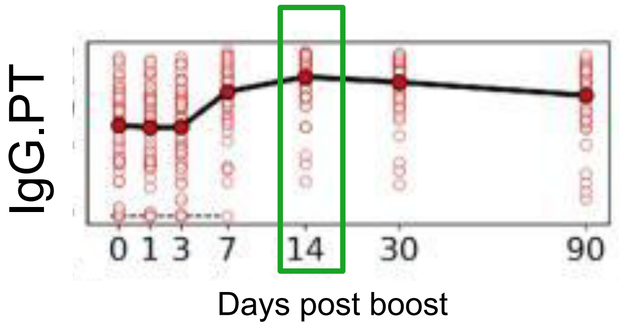
5 View challenge results

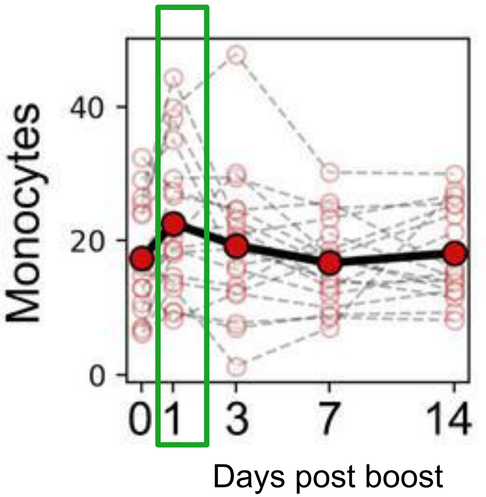
c. Formulating prediction tasks for CMI-PB Challenge

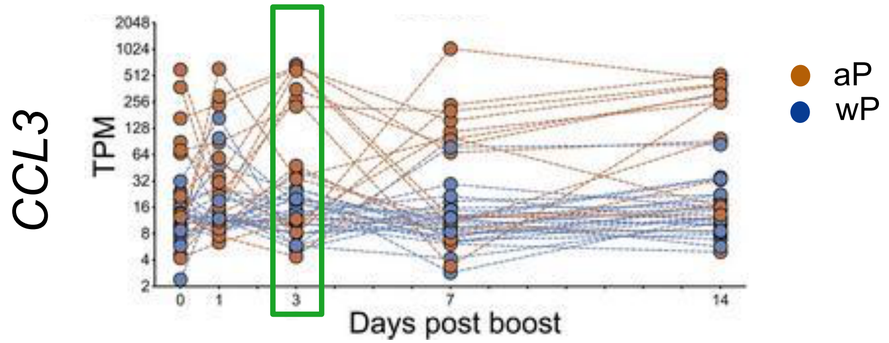
- Previously identified **vaccine responses** are formulated as prediction tasks*

- **General vaccine responses**:
  - Plasma IgG levels increased at day 14 post-booster vaccination compared to baseline
  - Increase in the percentage of monocytes on day 1 post-booster than baseline

- **aP/wP specific vaccine responses:**
  - A subset of aP-primed individuals showed an increased expression of proinflammatory genes, including *CCL3* at day 3 post-booster vaccination







* **A system-view of *Bordetella pertussis* booster vaccine responses in adults primed with whole-cell versus acellular vaccine in infancy**

Ricardo da Silva Antunes, … , Alessandro Sette, Bjoern Peters

JCI Insight. 2021;6(7):e141023. https://doi.org/10.1172/jci.insight.141023.

c. Formulating prediction tasks for CMI-PB Challenge

List of tasks

1) Antibody titer tasks

1.1) Rank the individuals by IgG antibody titers against pertussis toxin (PT) that we detect in plasma 14 days post booster vaccinations.

1.2) Rank the individuals by fold change of IgG antibody titers against pertussis toxin (PT) that we detect in plasma 14 days post booster vaccinations compared to titer values at day 0.

2) Cell frequencies tasks

2.1) Rank the individuals by predicted frequency of Monocytes on day 1 post boost after vaccination.

2.2) Rank the individuals by fold change of predicted frequency of Monocytes on day 1 post booster vaccination compared to cell frequency values at day 0.

3) Gene expression tasks

3.1) Rank the individuals by predicted gene expression of CCL3 on day 3 post-booster vaccination.

3.2) Rank the individuals by fold change of predicted gene expression of CCL3 on day 3 post booster vaccination compared to gene expression values at day 0.

predicted values

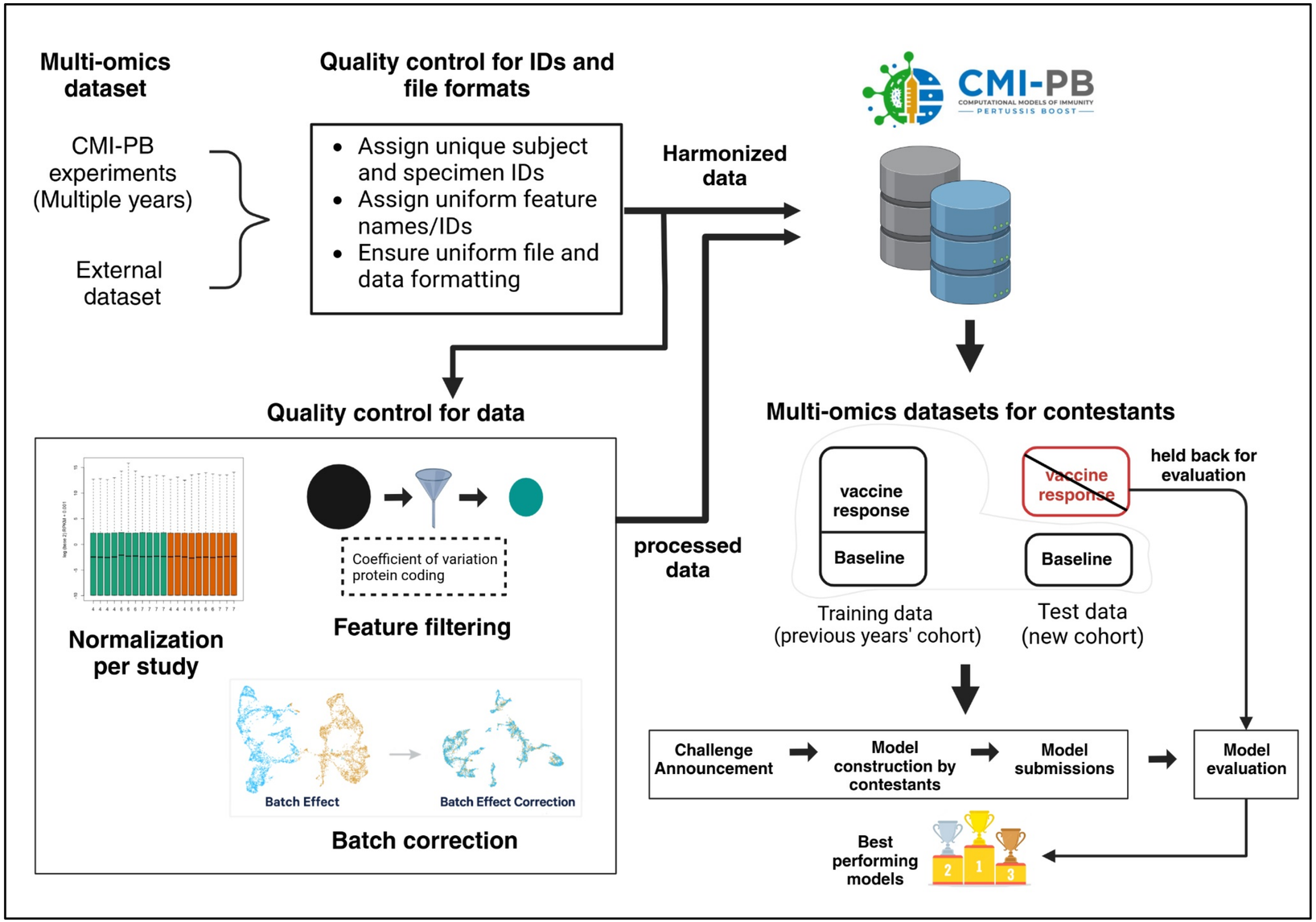
predicted fold-change values

Example of Rankings

Subject ID	Predicted value	Rank
101	2.9	4
102	**9.1**	**1**
103	**1.2**	**5**
104	4.5	3
105	4.7	2

The ultimate goal is to model as many of the tasks as possible. However, contestants are not required to submit answers for all tasks.

d. Overview of the CMI-PB Challenge data



Challenge related information and Data access is provided via the CMI-PB website

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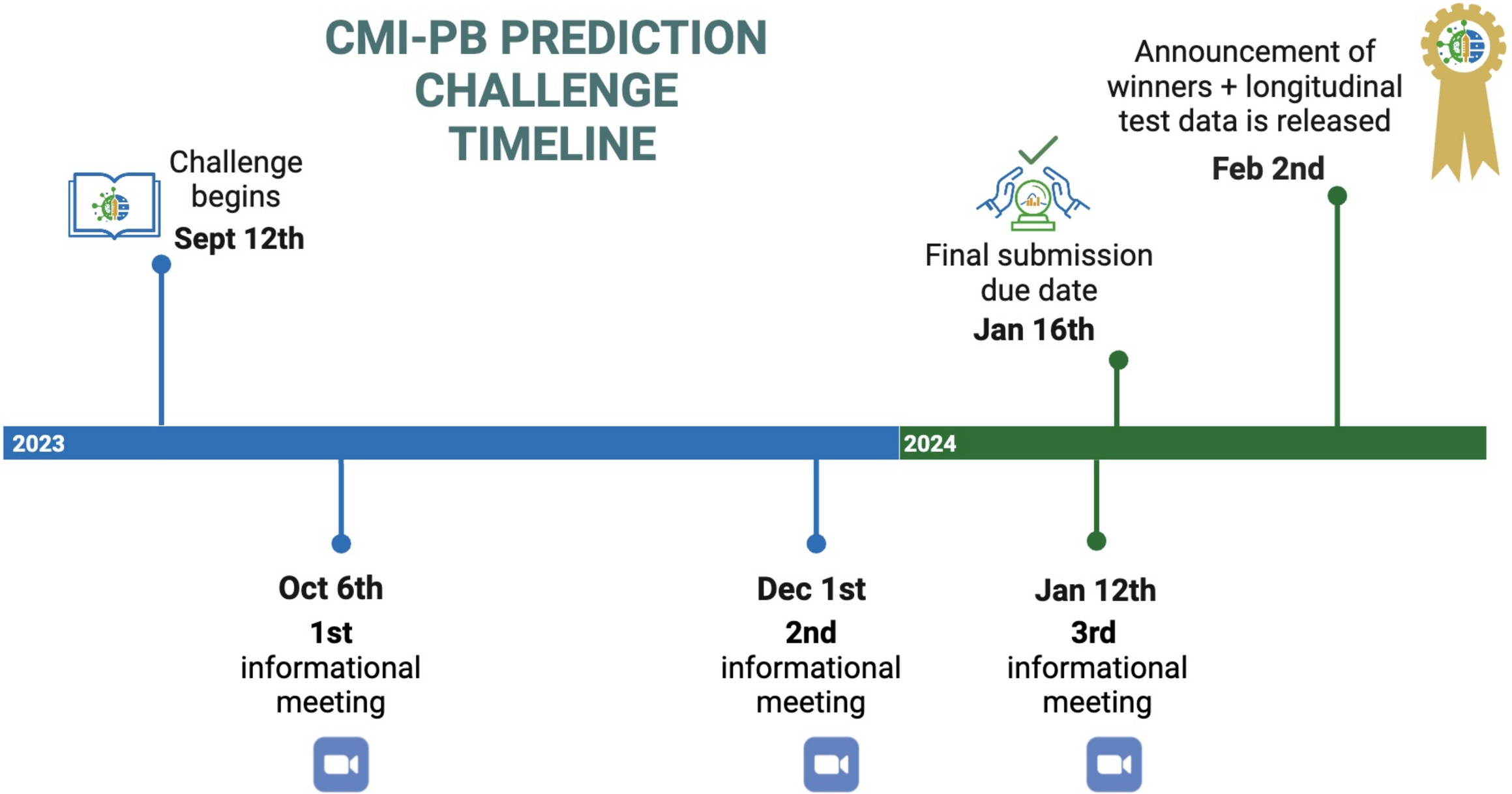
CMI-PB PREDICTION CHALLENGE TIMELINE



The CMI-PB team

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Kleinstein Lab (Yale)

- Expertise: A combination of "big data" analysis and immunology domain.
- Collaborating on data and models being released to the community to support reproducibility and the prediction contest, and also participate in the prediction challenge.

Steven Kleinstein
Jeremy Gygi
Leying Guan
Anna Konstorum

Grant Lab (UCSD)

- Expertise: the use of computational approaches, based on both biophysics and bioinformatics, to study the structure, function and evolution of key biological macromolecules.
- Dr. Grant will engage and advise over 40 biology graduate students in the CMI-PB Prediction Challenge.

Barry Grant

Ay Lab (LJI)

- Expertise: Development of bioinformatics tools that utilize high-dimensional and high-throughput datasets to deduce insights into chromatin conformation, genetic variation, and the regulation of gene expression.
- The Ay lab is focused on developing predictive machine learning models, which will serve as examples and baselines for participants in the CMI-PB challenge.

Ferhat Ay
Joaquin Reyna

Peters Lab (LJI)

- Expertise: Both experimental and computational studies to better understand human immune responses in the context of infectious diseases, allergy, cancer and vaccines.
- The team is responsible for the generation of experimental data, making it accessible in a central and standardized fashion, and coordinating the creation and coordination of the prediction contest.

Bjoern Peters
Jason Greenbaum
James Overton
Brendan Ha
Pramod Shinde
Mari Kojima
Rasteh Haji Kazem Nili
Jiyeun Lee
Lisa Willemsen
Shelby Orfield

And thank you to the Sette Lab, Crotty lab, LJI Clinical Core, LJI Bioinformatics Core

The CMI-PB team members


Bjoern Peters


Steven Kleinstein


Ferhat Ay


Barry Grant


Shane Crotty


Alessandro Sette


Pramod Shinde


Shelby Orfield


Lisa Willemsen


Leying Guan


Joaquin Reyna


Mari Kojima


Ferran Soldevila


Rasteh Nili


Jason Greenbaum


Brendan Ha


Jiyeun Lee


Ricardo De Silva Antunes


Jeremy Gygi


Anna Konstorum