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www.graslab.com

Health Research Using Synchrotron Techniques

*The Asia-Oceania Forum for Synchrotron Radiation Research
School 2024*

Tuesday 13th August 2024 – Australian Synchrotron

OUR LAB



Melbourne
Australia

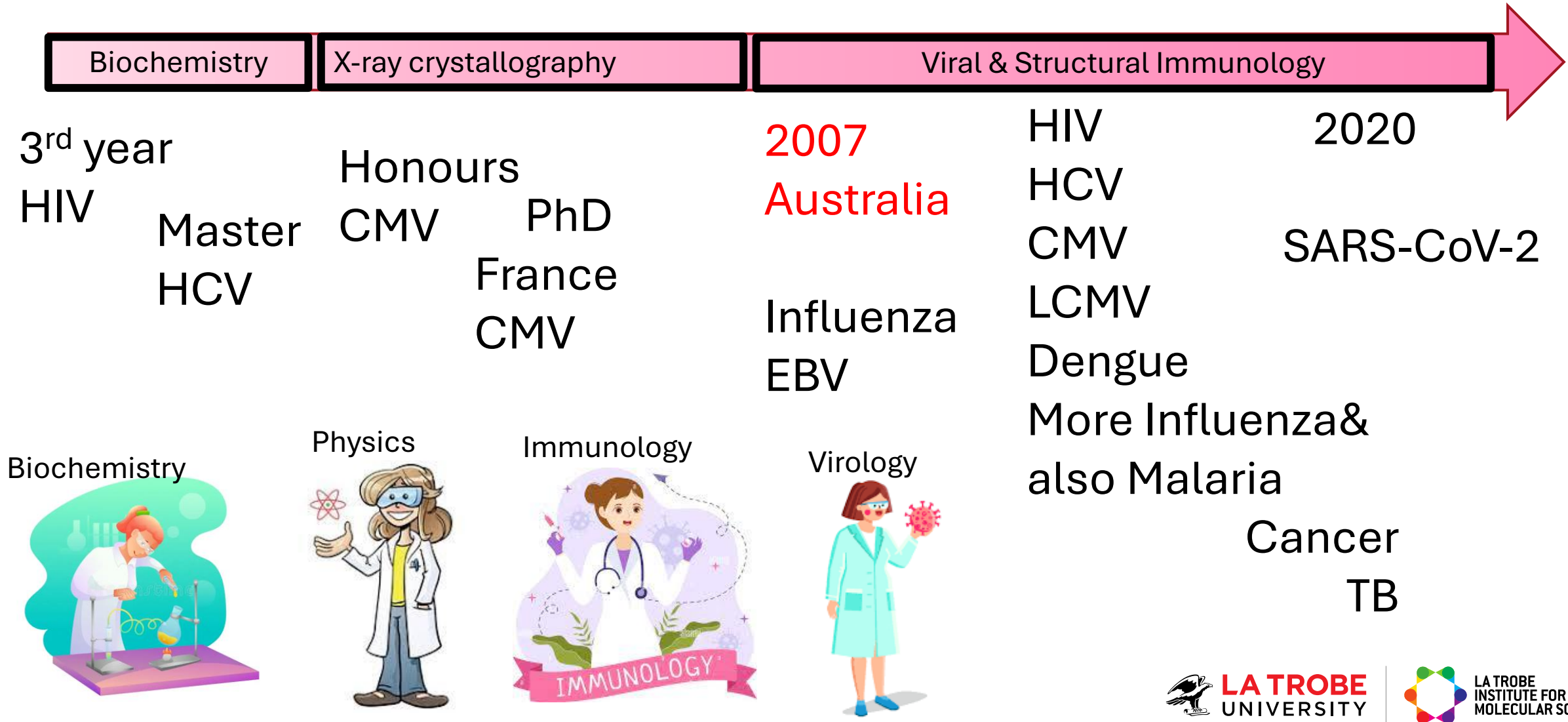


La Trobe University



La Trobe Institute for Molecular Science
(LIMS)

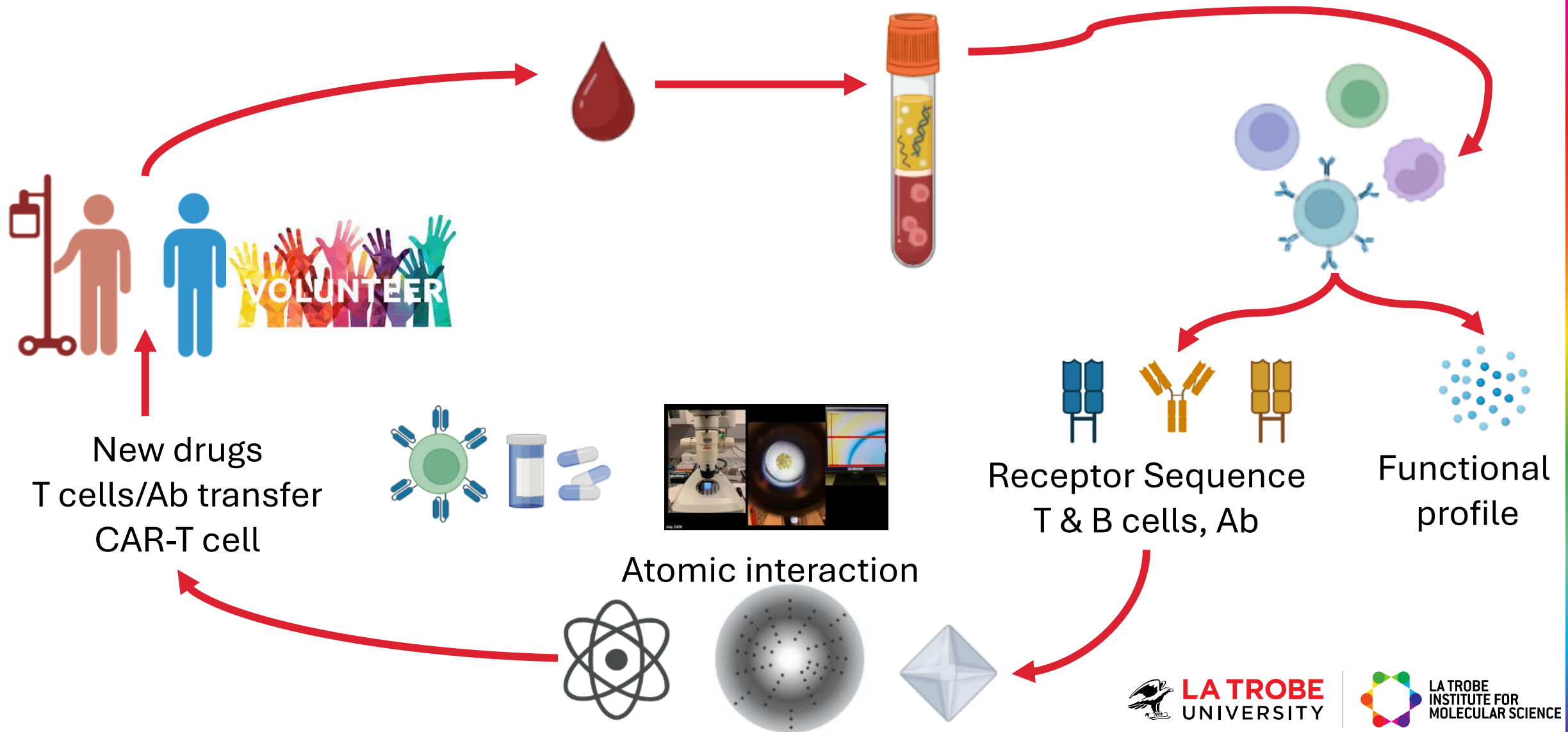
A Career in Structural Biology with a passion for viruses





OUR RESEARCH

Our research: *from patients to atoms* *... to translational research*



Our Lab

Focus on T cells & viruses

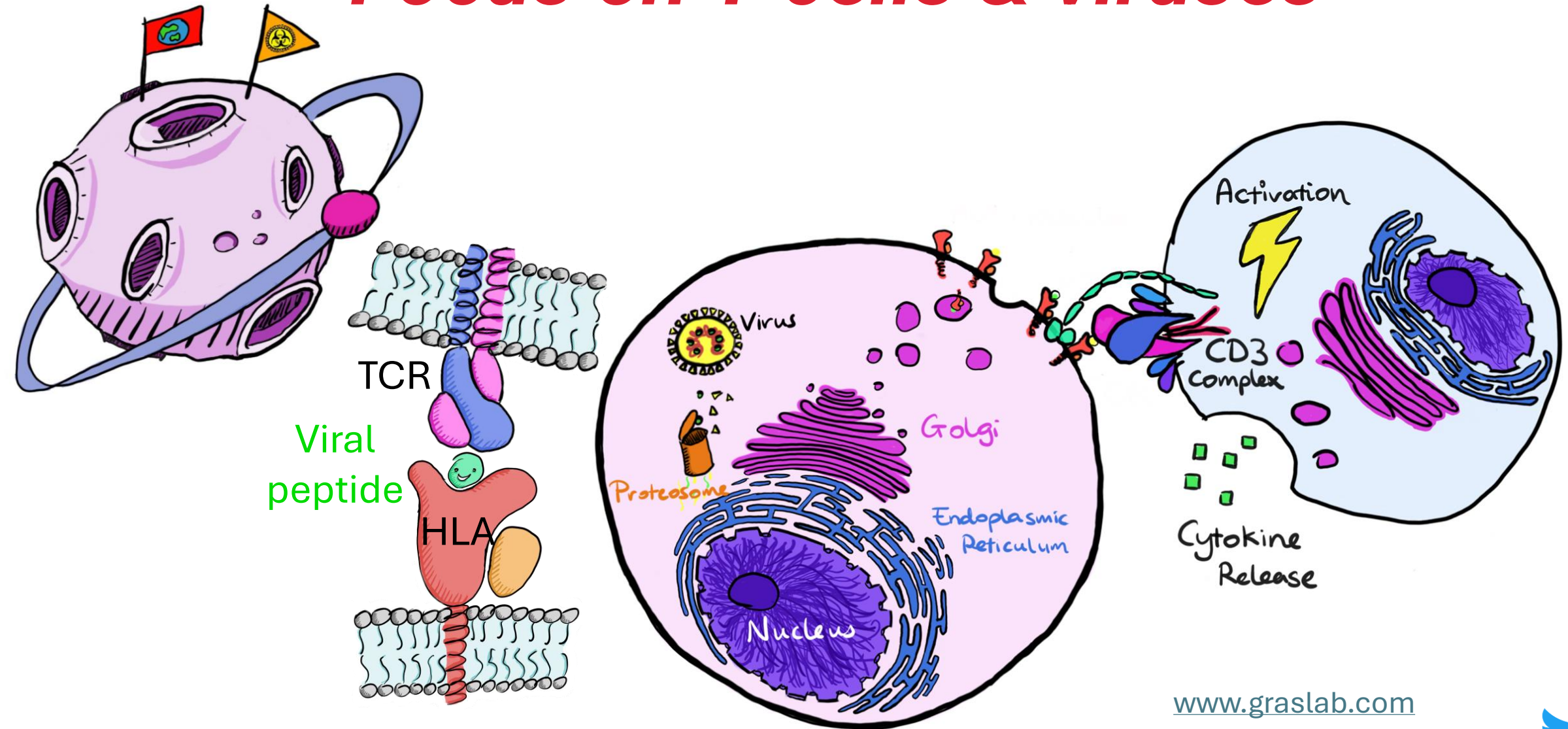


Illustration by Dr Christopher Szeto

www.graslab.com

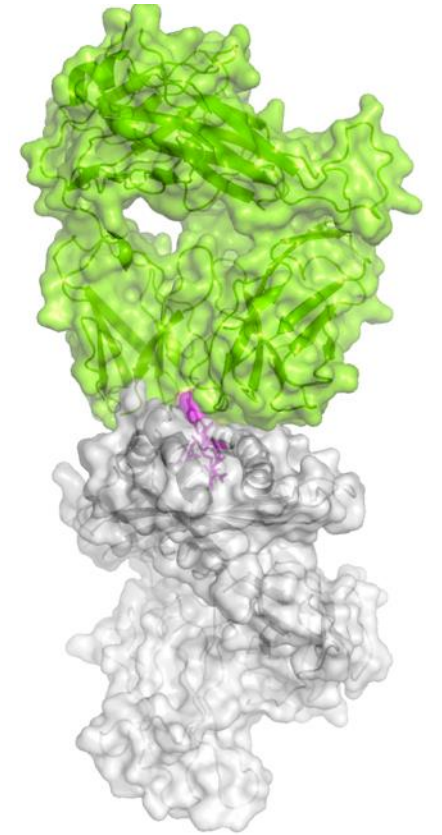
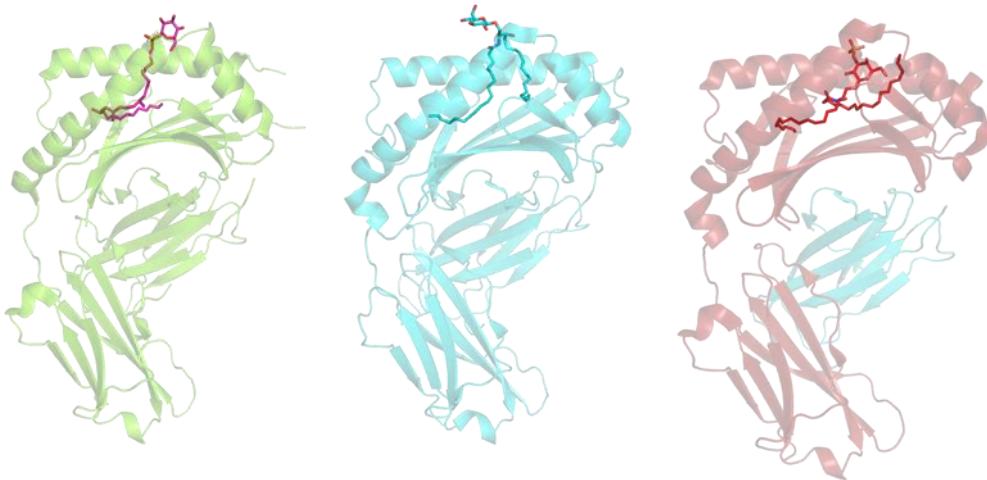
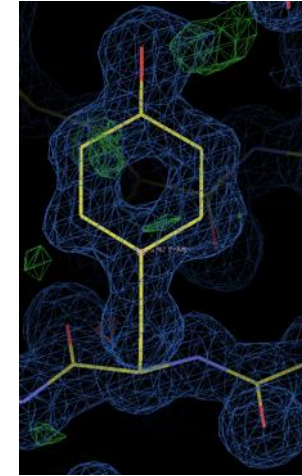
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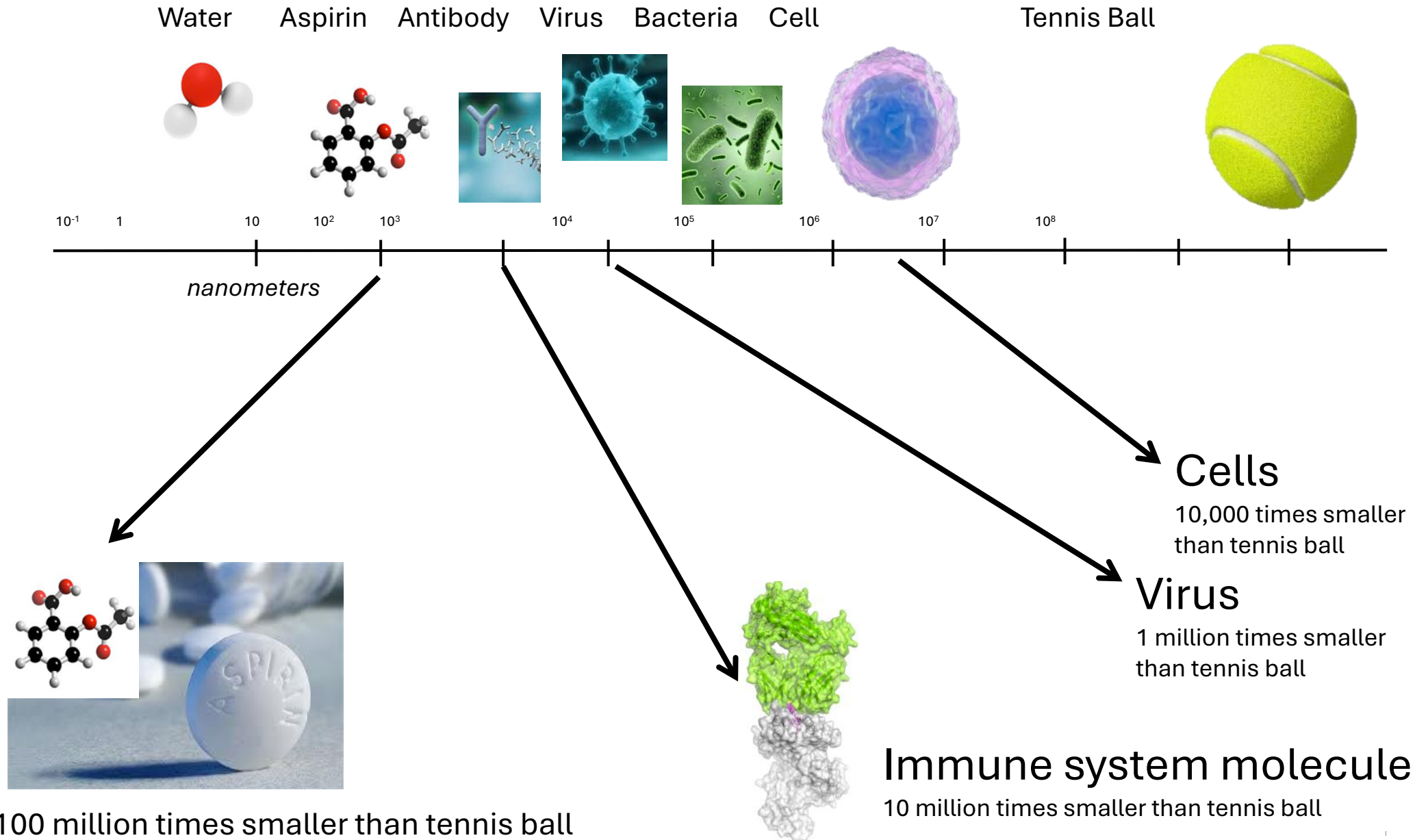
INTRODUCTION

How to "see" atoms: X-ray crystallography

- Atomic resolution microscopy
- Proteins interaction
- Protein with different ligands

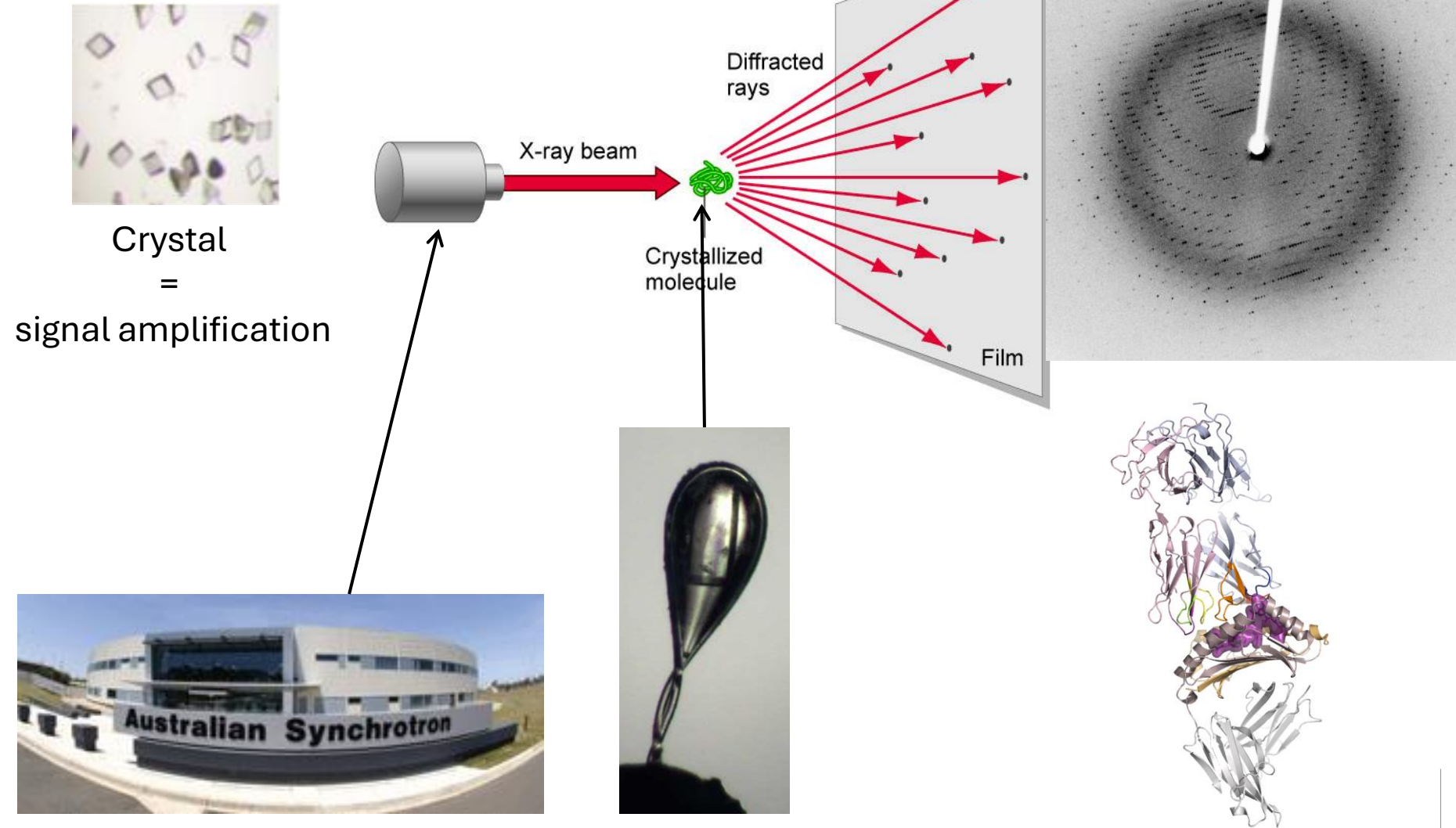


Things we are looking at?



X-ray crystallography: step by step

Protein Crystallisation



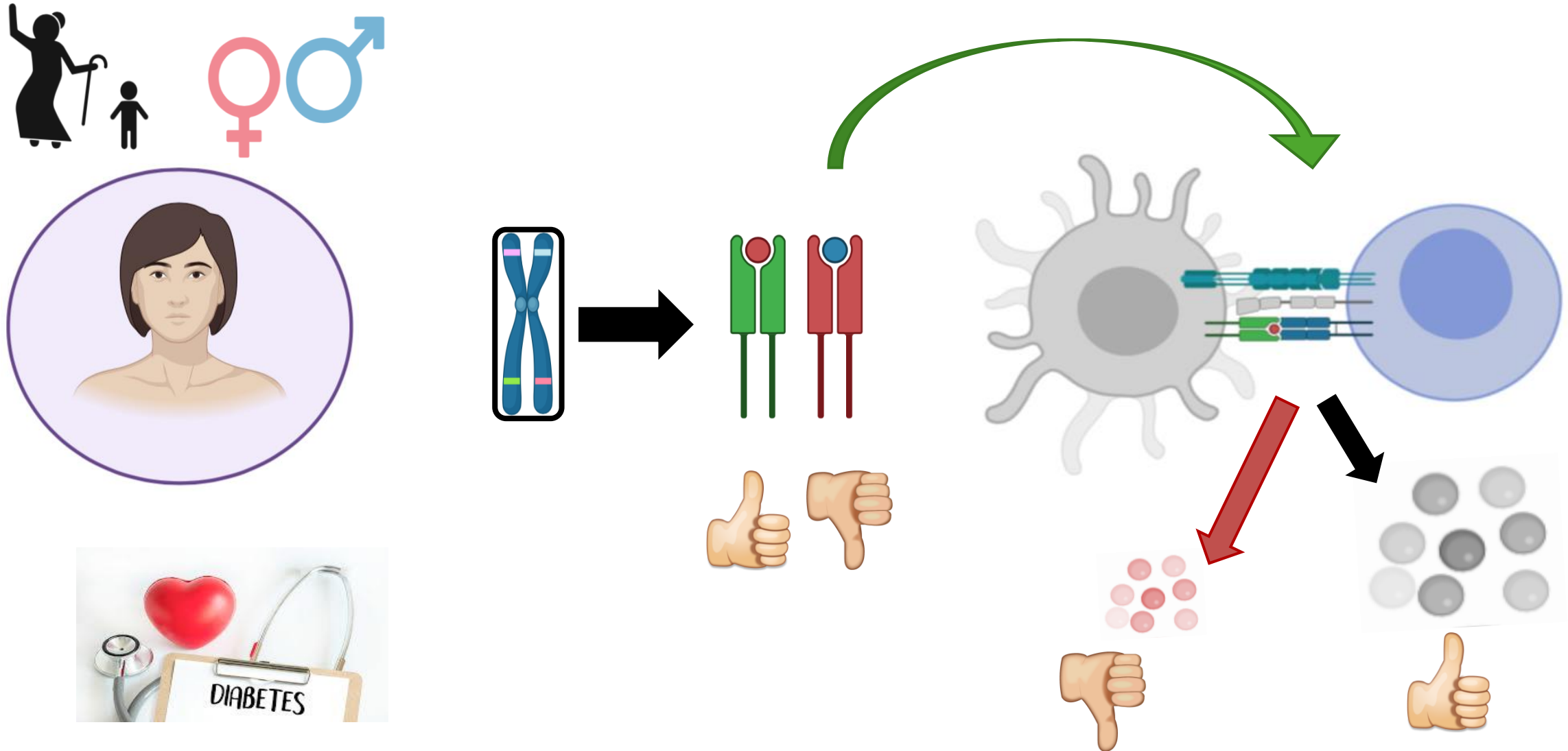


X-RAY CRYSTALLOGRAPHY APPLIED TO HEALTH RESEARCH



CENTRE FOR ADVANCED
MOLECULAR IMAGING

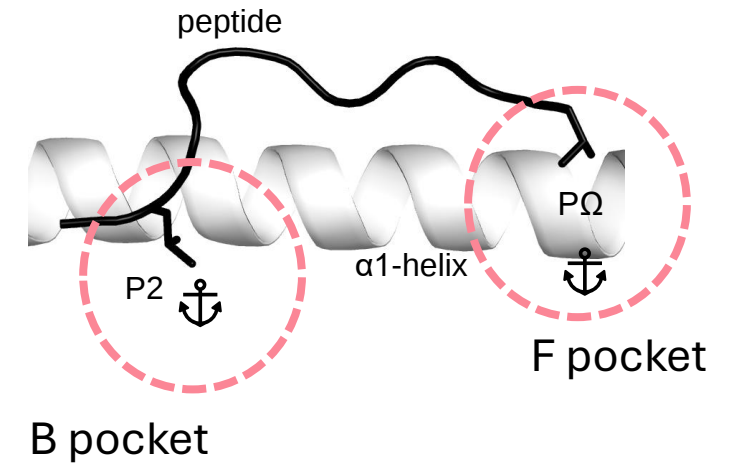
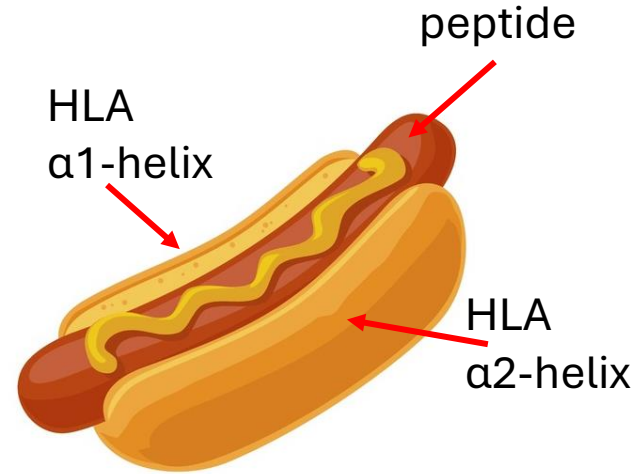
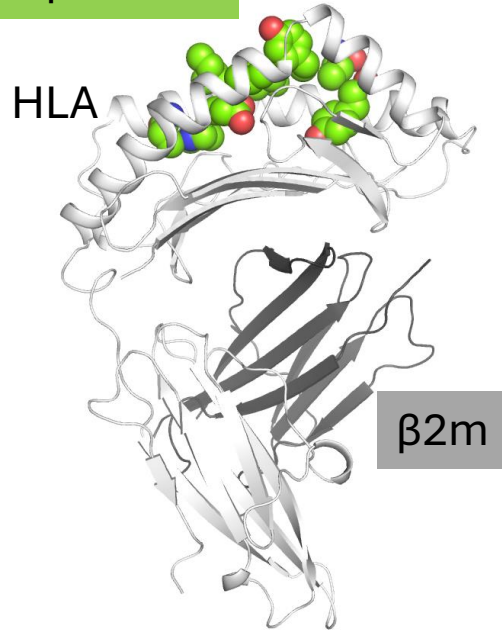
Host genetic & disease outcome



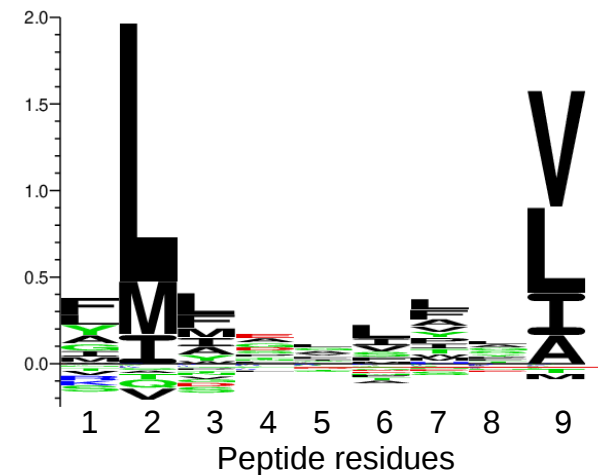
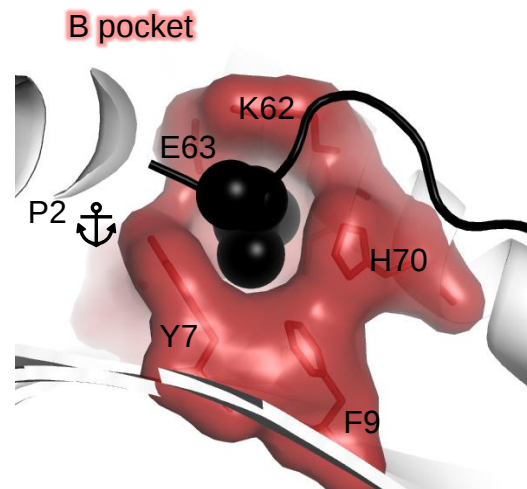
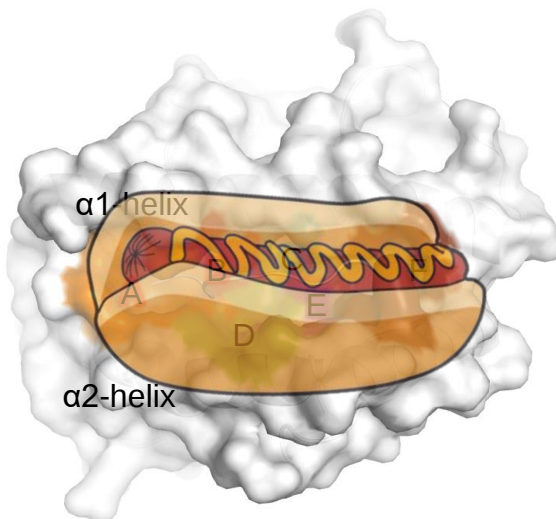
Role of HLA molecules & T cells?

HLA hold peptide in their pockets

Peptide

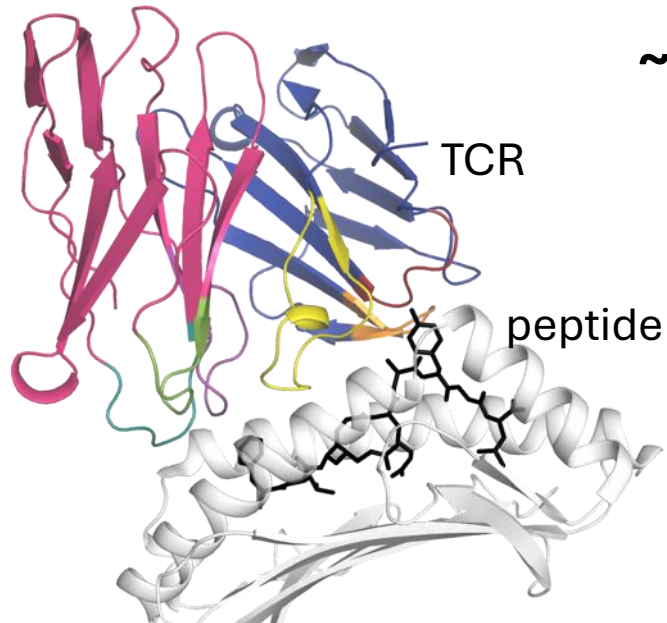
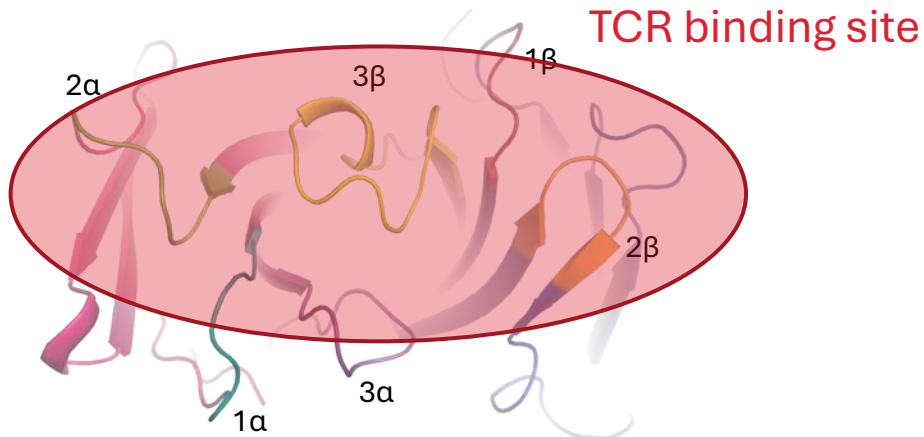


Keeping it anchored!



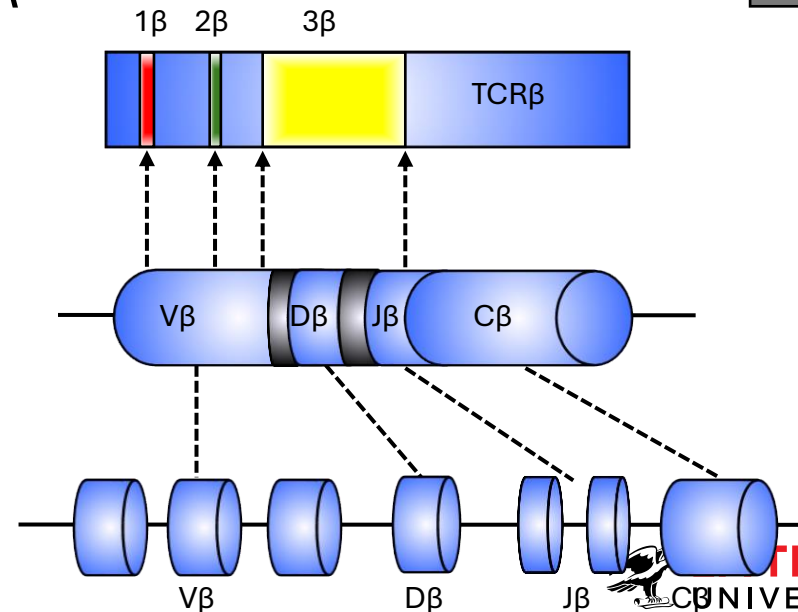
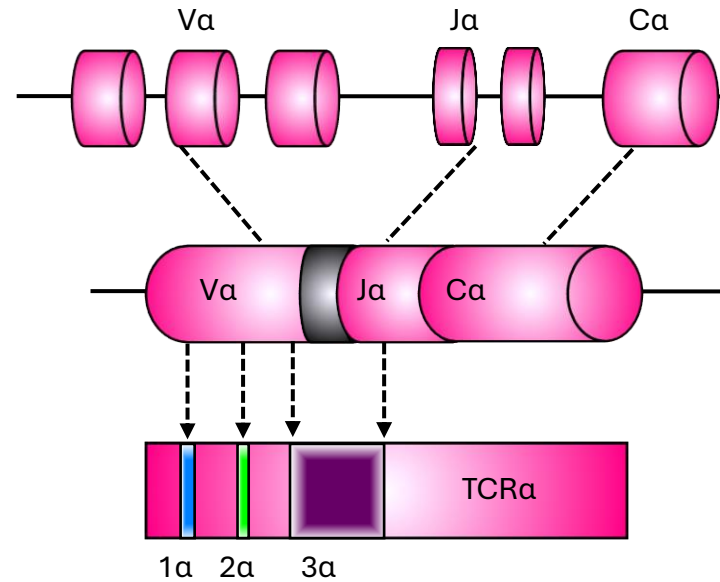
Peptide motif
=
preferred residue at
P2 and P9

TCR recognition and diversity



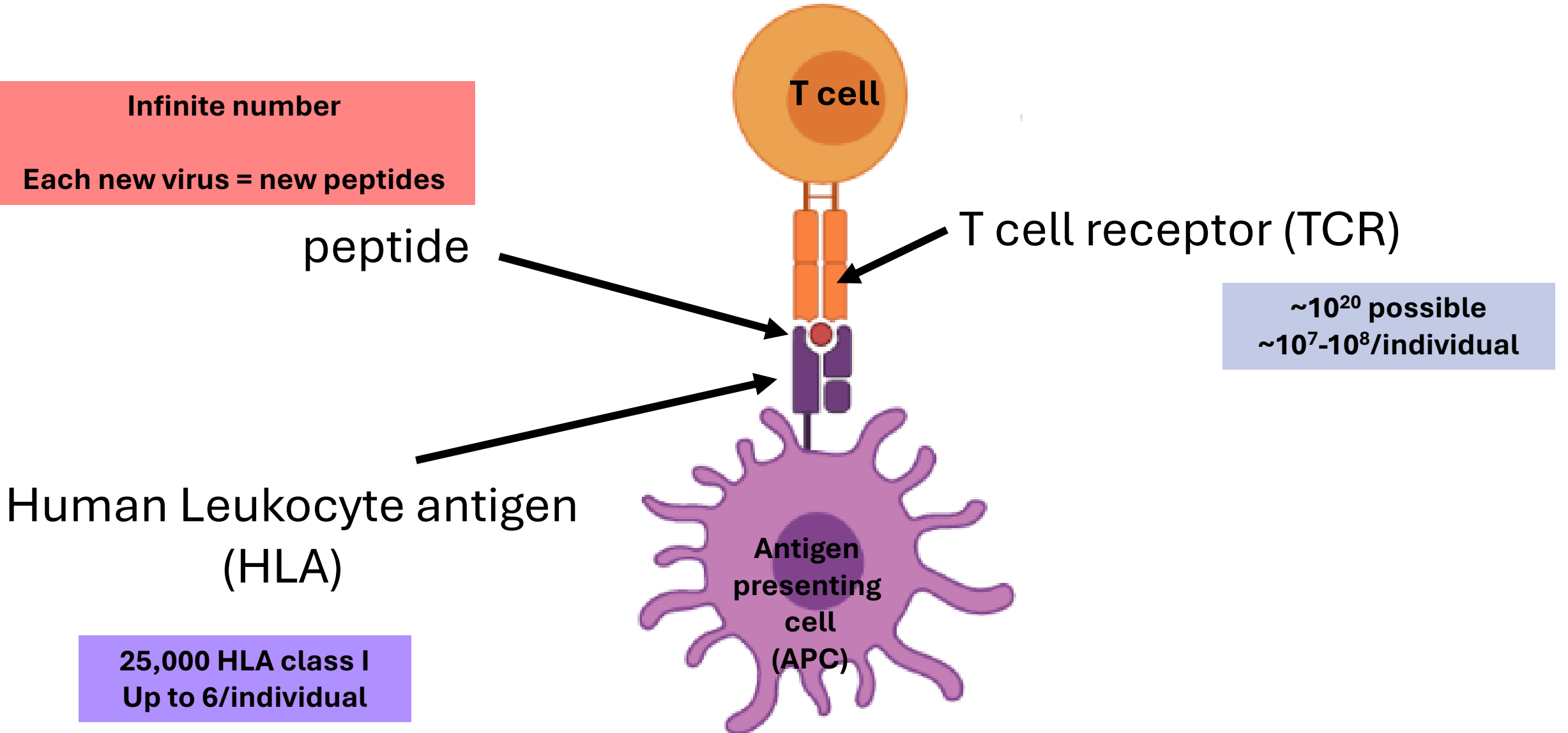
MHC (major histocompatibility complex)

~10²⁰ unique TCR structures
(one hundred quintillion)

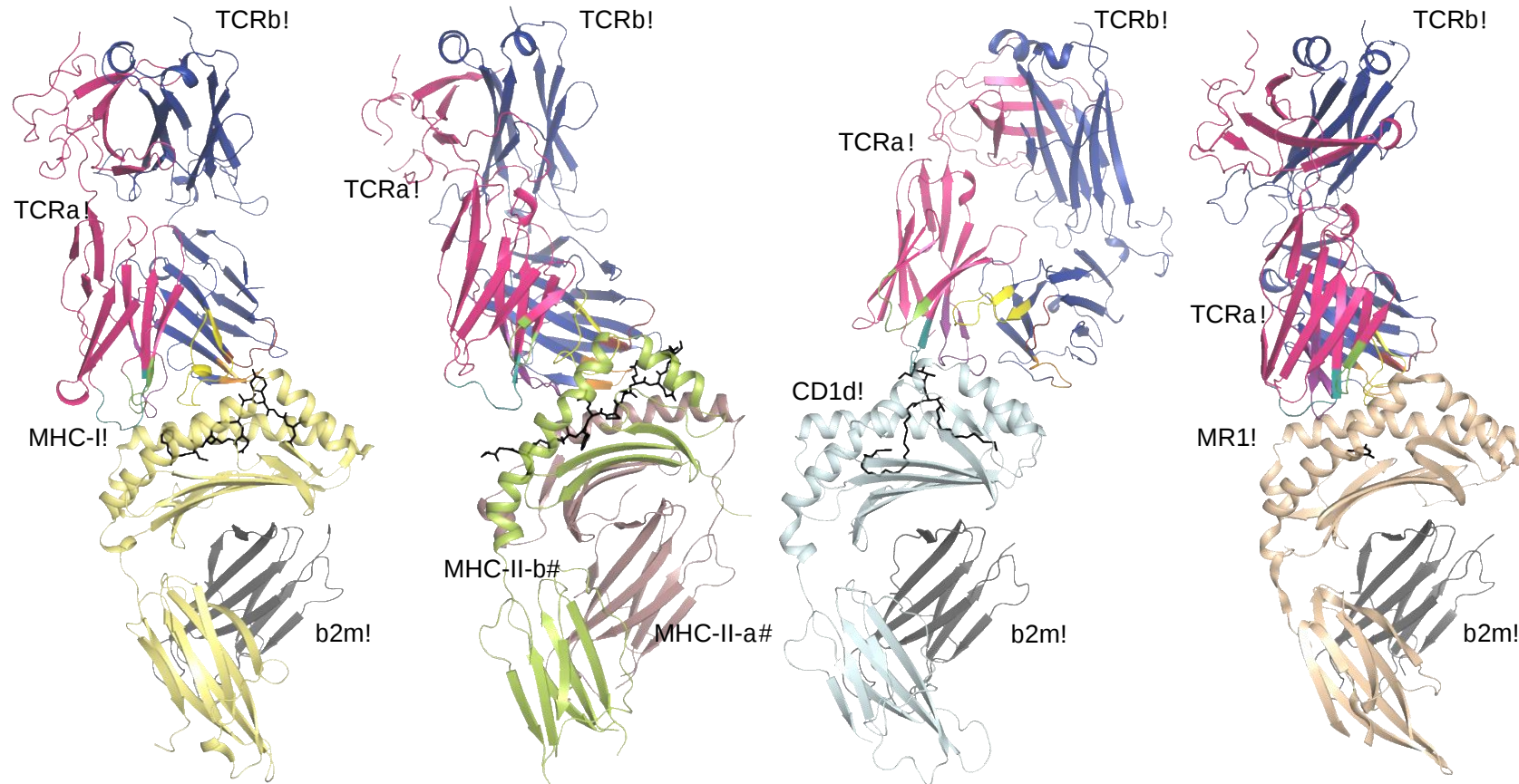


**TCRs are
extremely
diverse**

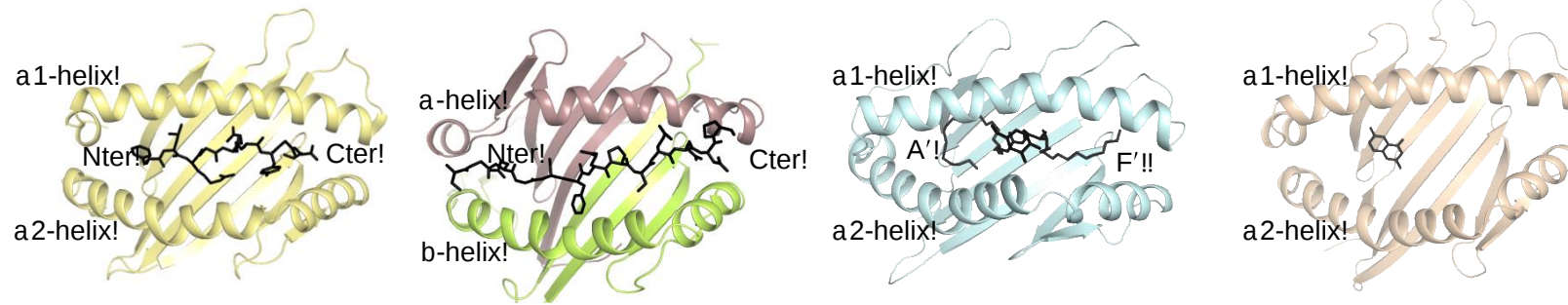
Complexity in diversity



X-ray crystallography: revealing T cell binding



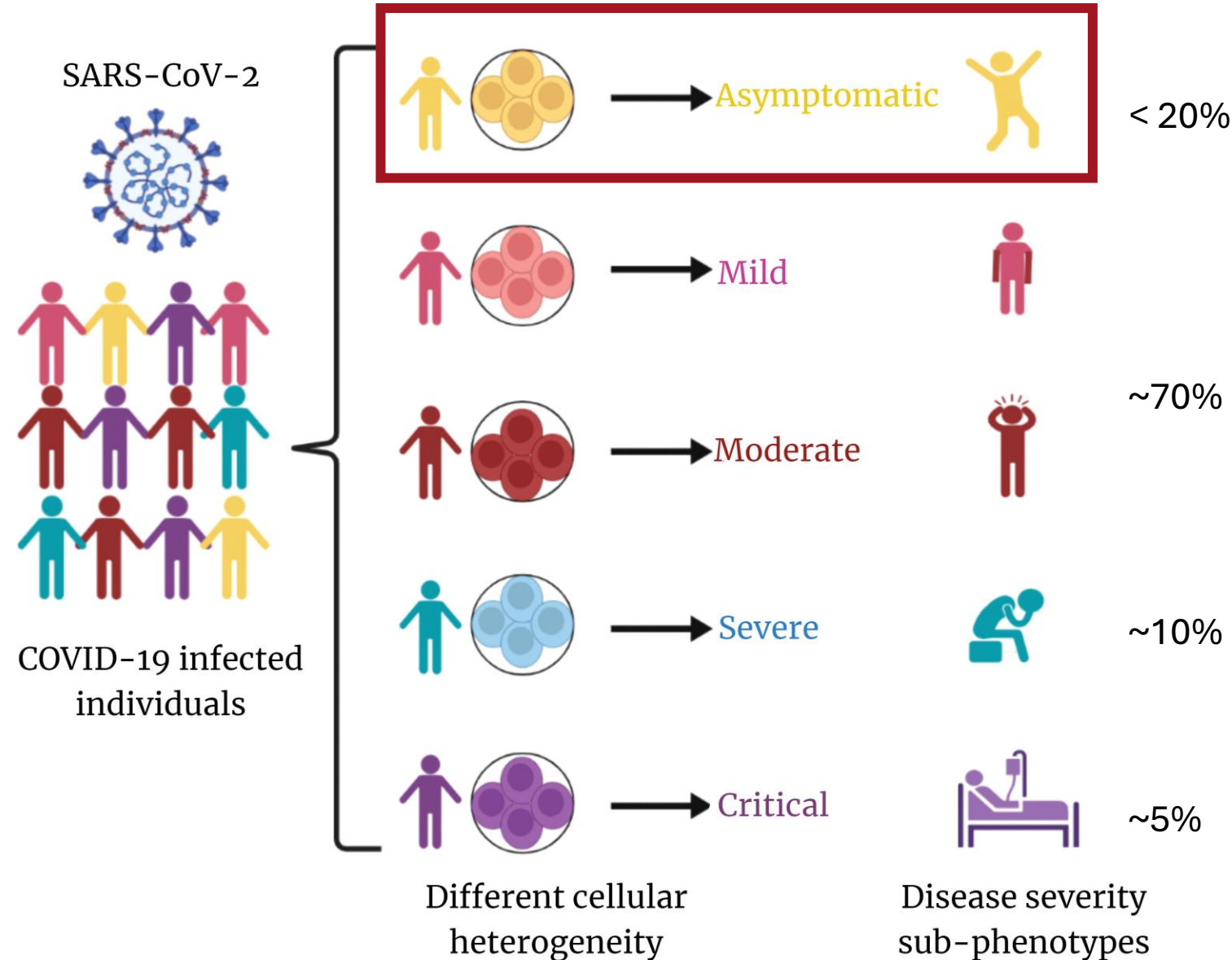
Antigen: Short peptide Long peptide Lipid Metabolite





WHY COVID-19 BENCHED YOU BUT NOT YOUR CO-WORKER

Why are we not all sick with COVID?



How some people dodge COVID?



Luck & genetics ?



DE
SITY

MOLECULAR SCIENCE

HLAs and COVID

Table 1

Summary of *HLA* associations with COVID-19 outcomes.

	Allele	OR (CI 95%)	<i>p</i> -value	corrected <i>p</i> -value	Country	Association with
Class I	HLA-A ^a 11:01	3.41 (1.50–7.73)		3.34E-03	Japan	Severe disease
	HLA-A ^a 11:01	2.33	8.51E-03		Japan	Severe disease
	HLA-A ^a 30:02	2.2 (1.4–3.6)	1.70E-03	1.00E-02	USA ^a	Infection
	HLA-B ^a 15		1.00E-02		Egypt	Survival
	HLA-B ^a 15:01	2.4 (1.54–3.64)	5.67E-05	1.70E-03	USA	Asymptomatic infection
	HLA-B ^a 51:01	3.38	0.007017		Japan	Severe disease
	HLA-C ^a 04:01	5.4 (1.9–15.1)	1.10E-04	7.40E-03	Germany	Severe disease
	HLA-C ^a 14:02	4.75	3.03E-03		Japan	Severe disease
Class II	HLA-DQB1 ^a 06:02		1.00E-04	1.60E-03	Italy	Infection
	HLA-DRB1 ^a 04	0.289	5.00E-03		Iran	Mild disease
	HLA-DRB1 ^a 04:01		3.00E-03		UK	Asymptomatic infection
	HLA-DRB1 ^a 08:02	9.0 (2.2–37.9)	1.00E-02	3.00E-02	USA ^b	Infection
	HLA-DRB1 ^a 09:01	3.62(1.57–8.35)	2.51E-03		Japan	Severe disease
	HLA-DRB1 ^a 15:01		1.50E-03	4.80E-02	Italy	Infection

OR = odds ratio; CI = confidence interval.

^a African American.

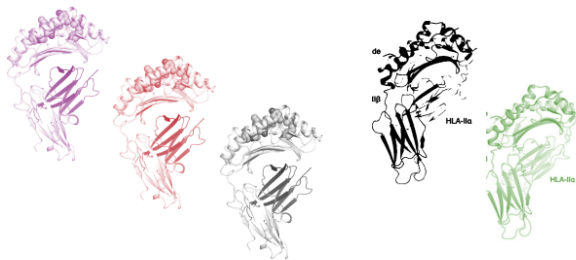
^b Hispanic.

Cohort of ~30,000 donors HLA typed



National Marrow Donor Program
(NMDP)

HLA typed individual
HLA-A, -B, -C, -DRB1 and -DQB1



UCSF Citizen Science study:
smartphone-based app
questionnaire
track COVID-19 symptoms
July 2020 – April 2021

29,947 individuals enrolled



1,428 SARS-CoV-2⁺

Symptomatic
~ 90%
(1,292)

Asymptomatic
~ 10%
(136)



**UCSF Citizen Science
study (n=1428)**

**asymptomatic
odds ratio (OR)**

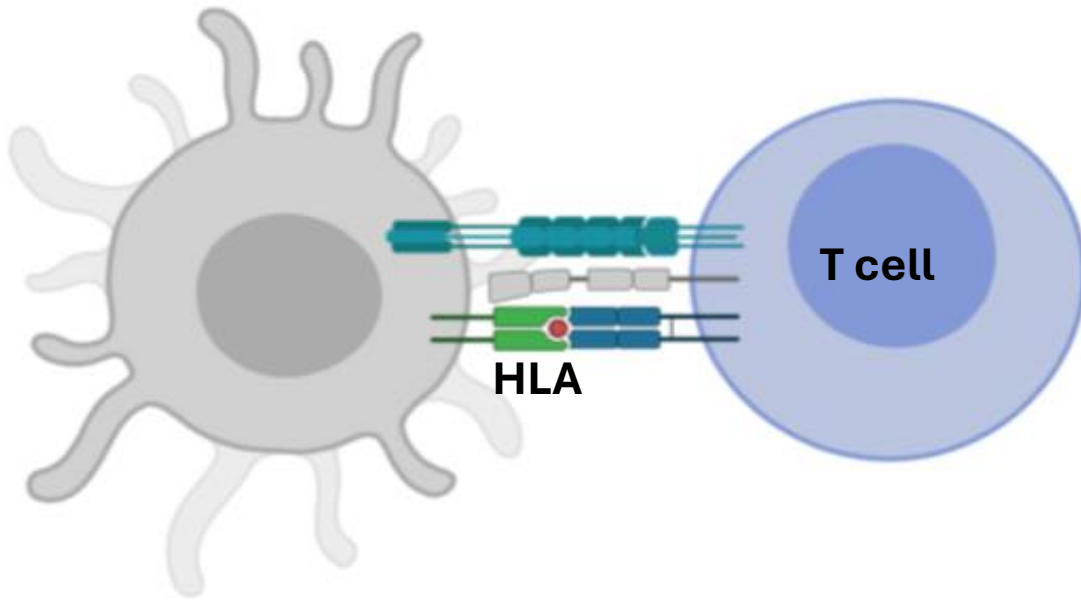
HLA-B*15:01

2.40

HLA-B*15:01/15:01

8.58

How HLA-B15⁺ individuals dodge COVID?



What did we know?

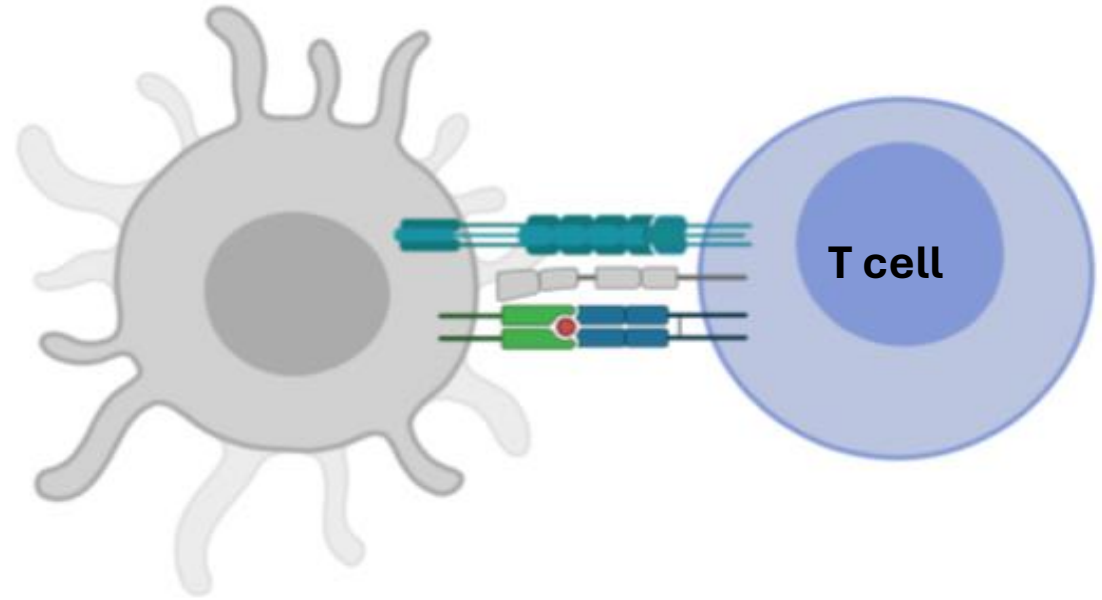
Four T cell epitopes from SARS-CoV-2

CVADYSVLY (Spike)

NQKLIANQF (Spike)

RVAGDSGFAAY (M)

HVGFIPVAY (ORF1)



Activating T cells
In COVID recovered donors

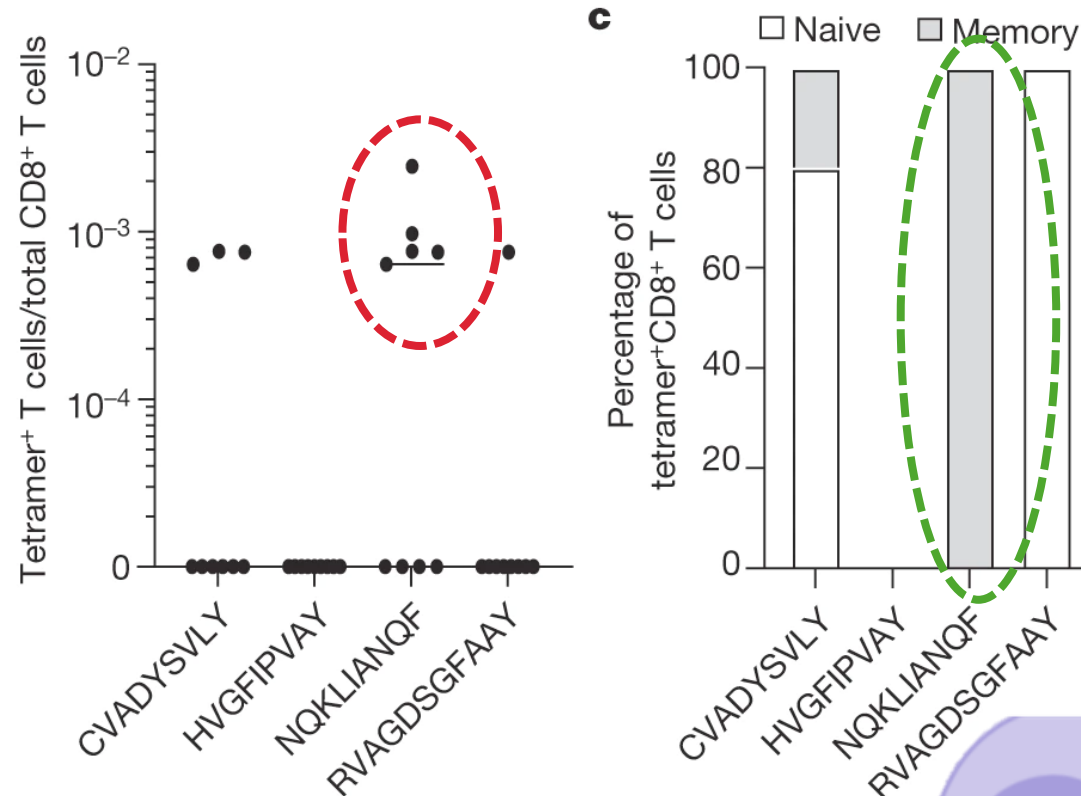
The Immune system remembers!

Pre-existing immunity to SARS-CoV-2

9 HLA-B15⁺ donors from USA
Blood collected in 1990's (before
COVID)

NQK peptide is recognised by
memory T cells!

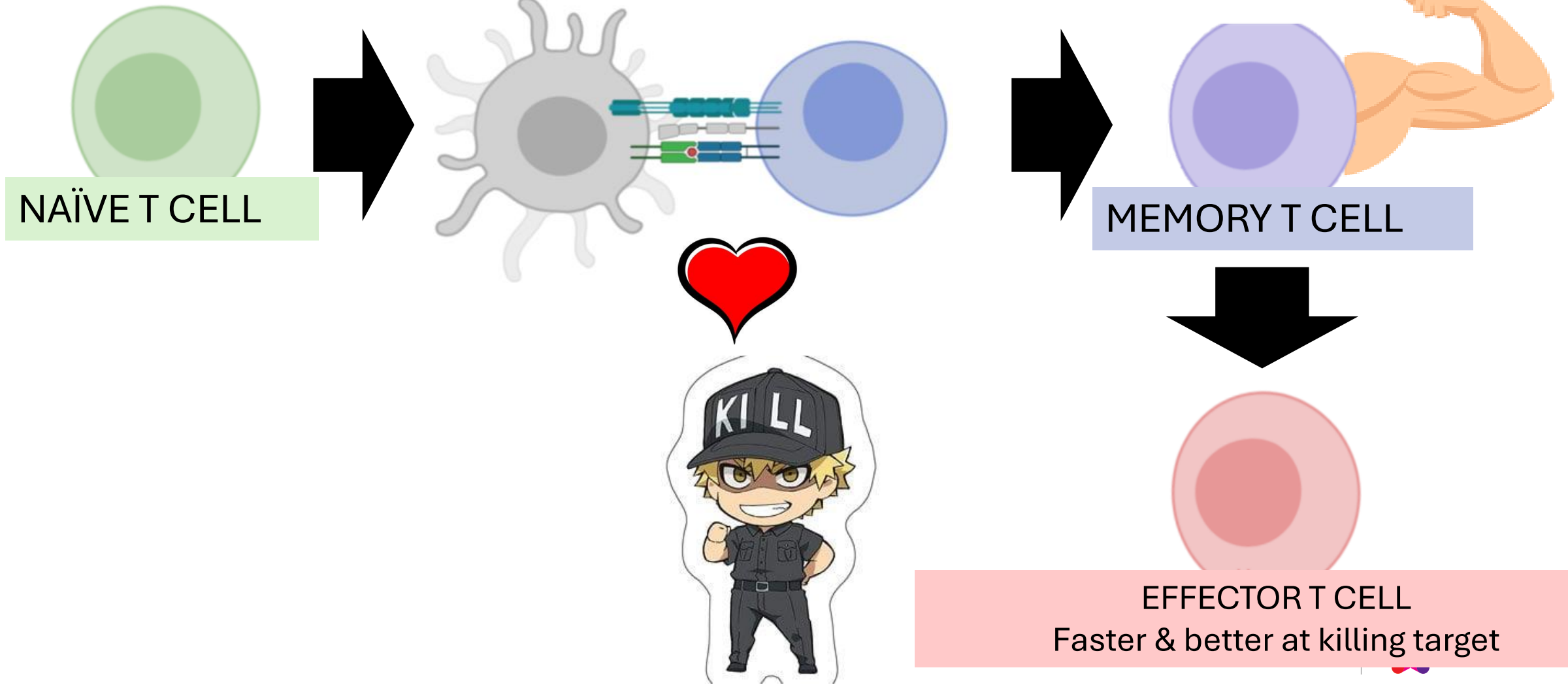
Memory T cells able to “see” SARS-
CoV-2 spike peptide
before COVID-19 pandemic !!!



MEMORY T CELL

Why memory T cells are important?

MEET THE ANTIGEN !

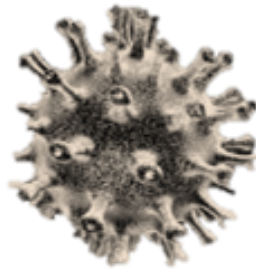
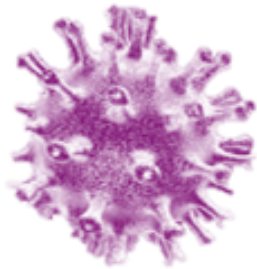
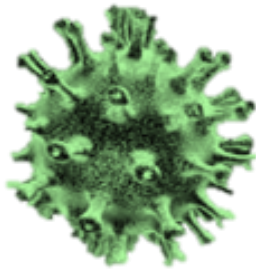




What did T cells see prior to COVID?

Origin of pre-existing immunity

seasonal human coronaviruses



OC43

HKU-1

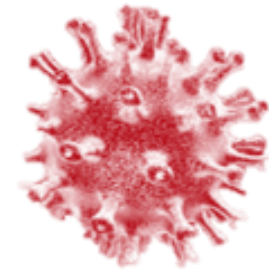
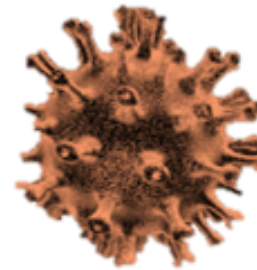
229E

NL63

Seasonal coronaviruses
(common cold)



NQKLIANAF (NQK-A8)



SARS

SARS-CoV-2

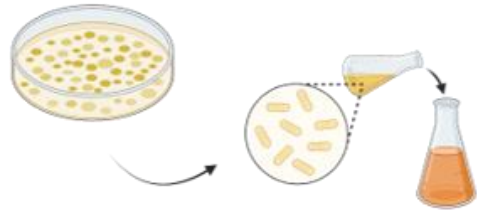
Epidemic/Pandemic
coronaviruses
(severe disease)



NQKLIANQF (NQK-Q8)

NQK PEPTIDES

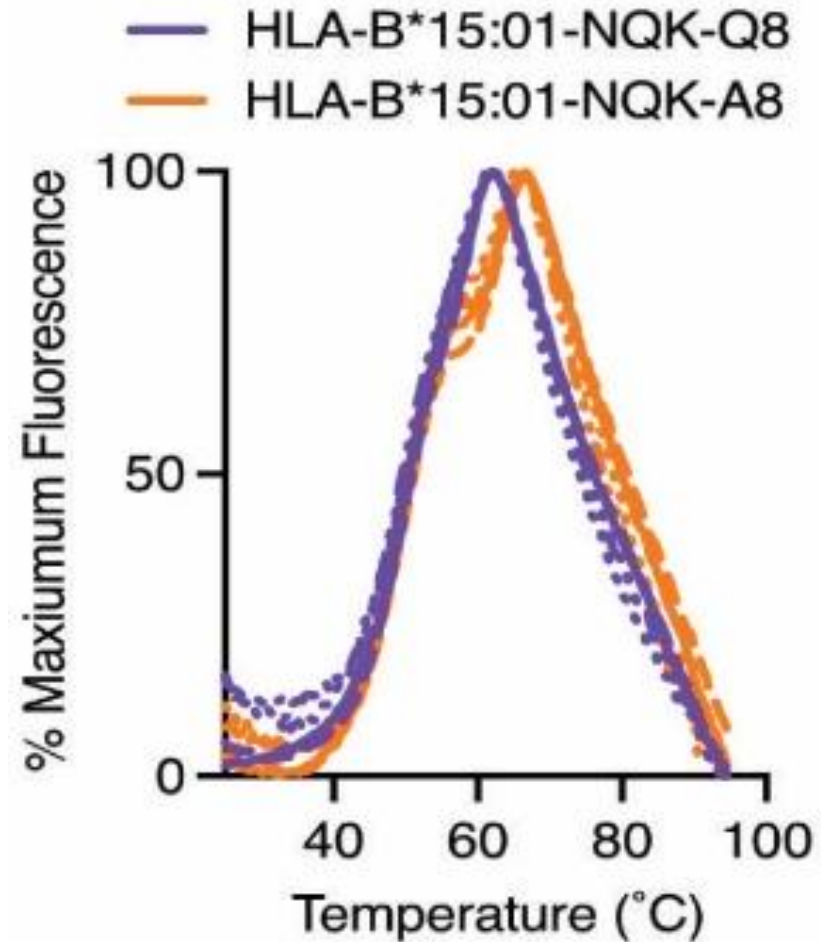
How do NQK-A8 and NQK-Q8 peptides look like?



NQKLIAN^{AF} (NQK-A8)
OC43/HKU-1

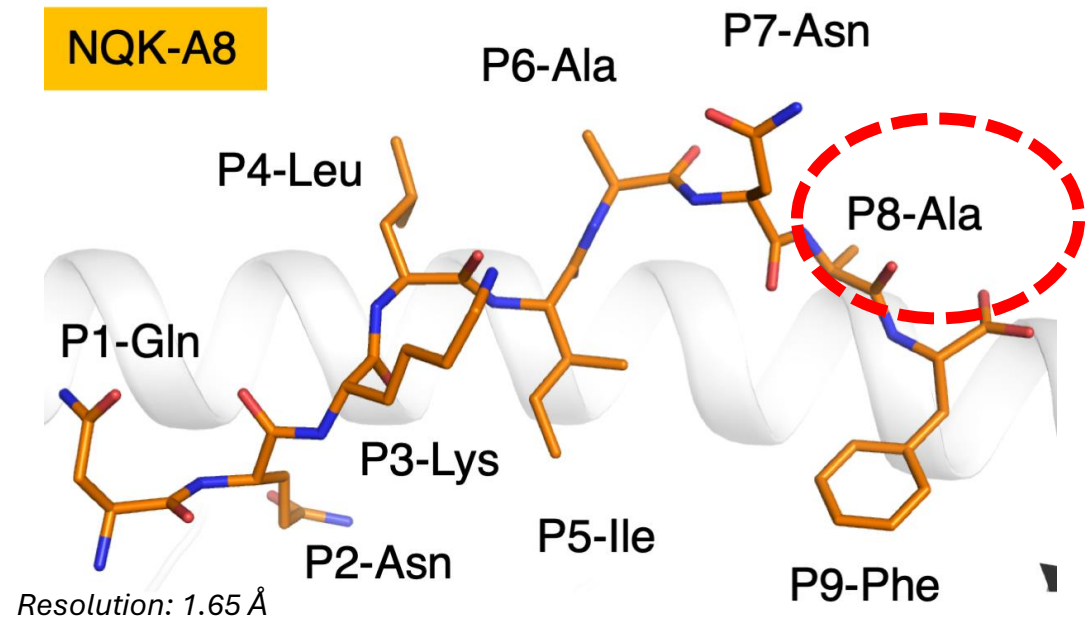
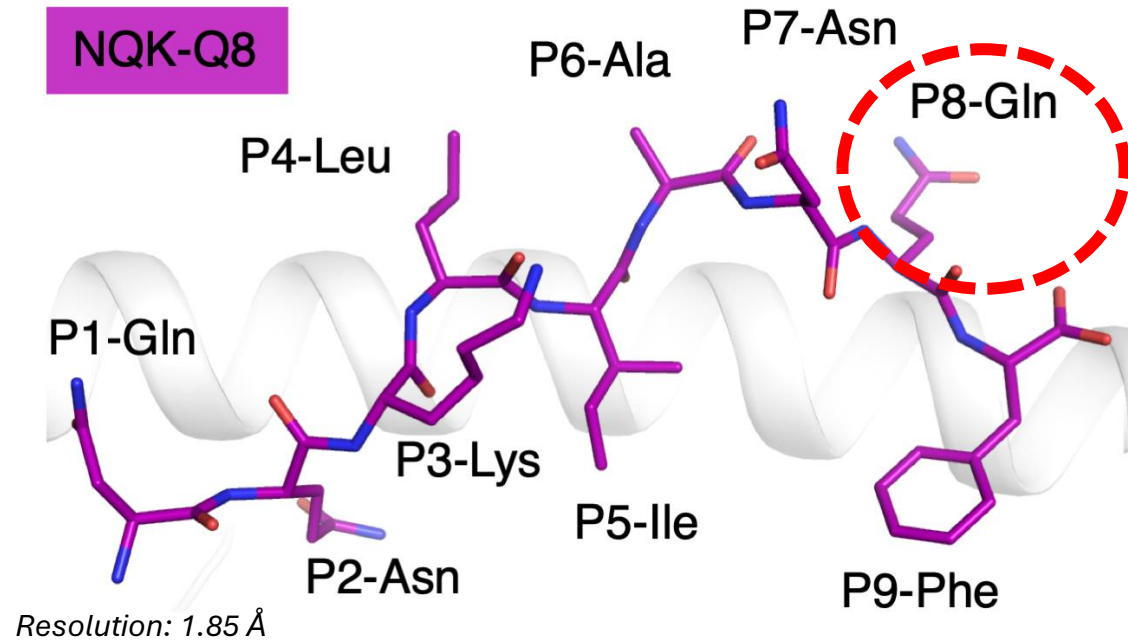


NQKLIAN^{QF} (NQK-Q8)
SARS-CoV-2



Same stability

How do NQK-A8 and NQK-Q8 peptides look like?

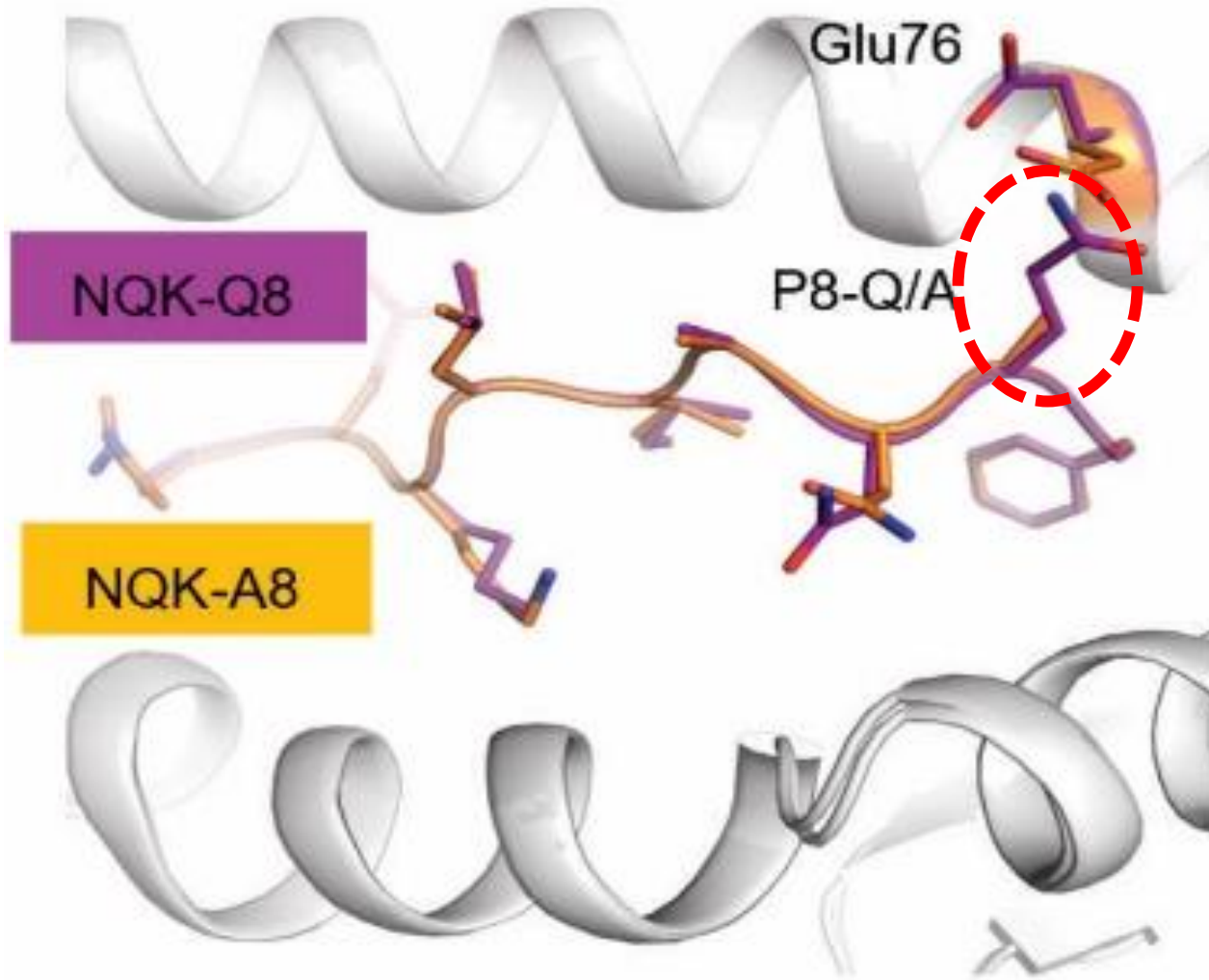


NQKLIAN**AF** (NQK-A8)
NQKLIAN**QF** (NQK-Q8)



How do NQK-A8 and nNQK-Q8 peptides look like?

HLA-B15 (white cartoon) in complex with **NQK-A8** and **NQK-Q8**

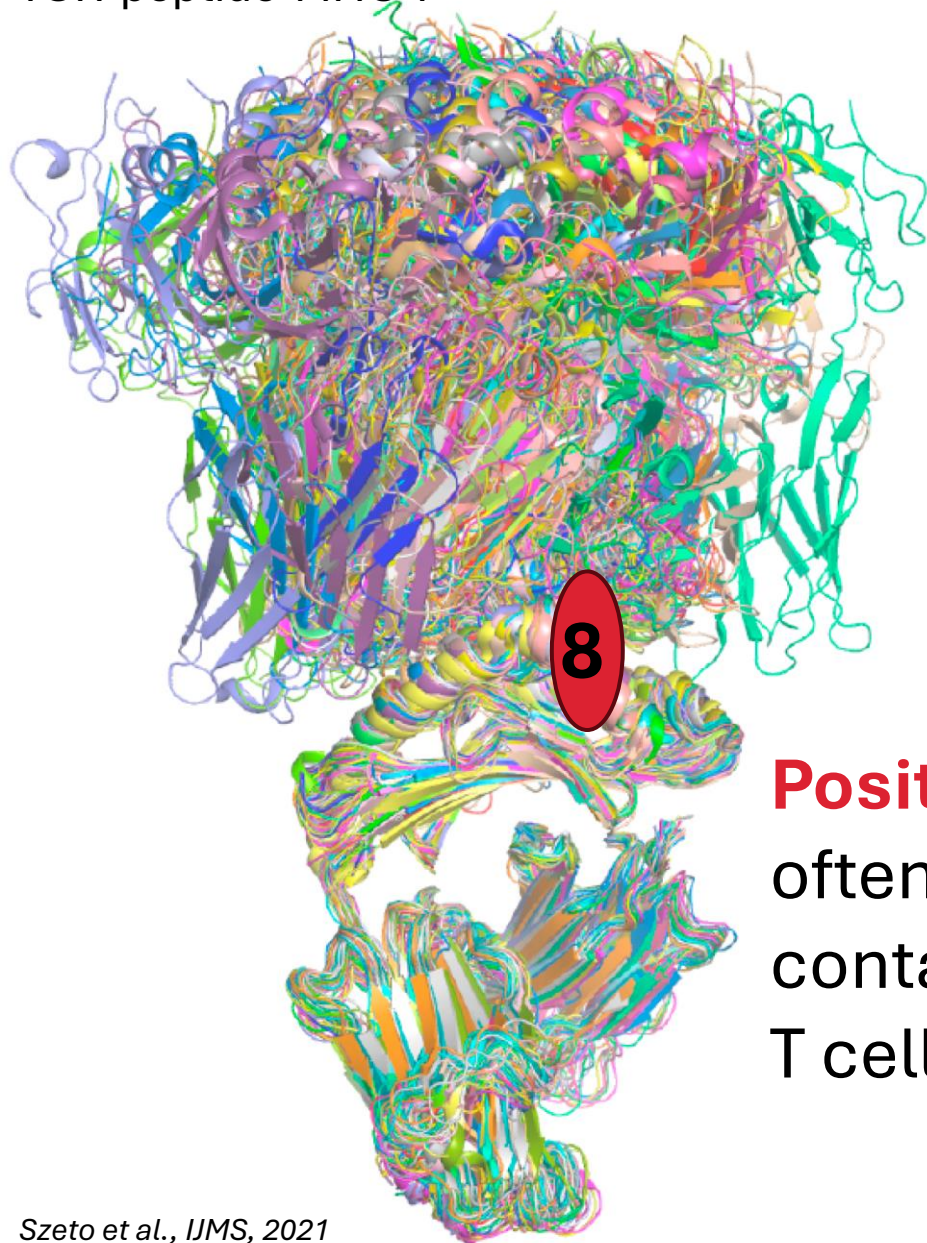


Same structure

NQK-SPECIFIC T CELLS

Can T cells can “see” both NQK-Q8 and NQK-A8 ?

TCR-peptide-MHC-I



Position 8 is
often
contacted by
T cells

NQKLIAN**AF** (NQK-A8)
NQKLIAN**QF** (NQK-Q8)

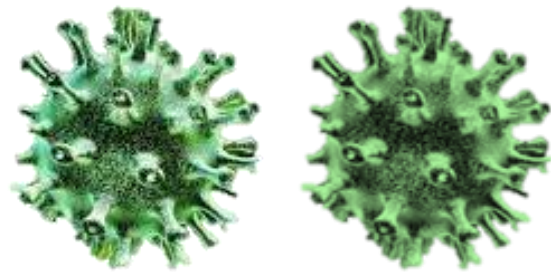
CD8⁺ T cells

→ Same T cell receptor (TCR)

OR

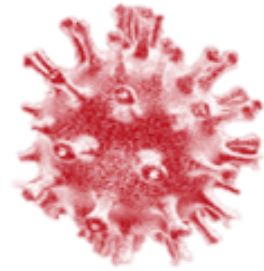
→ TCR specific for each peptides

Can T cells can “see” both NQK-Q8 and NQK-A8 ?



OC43

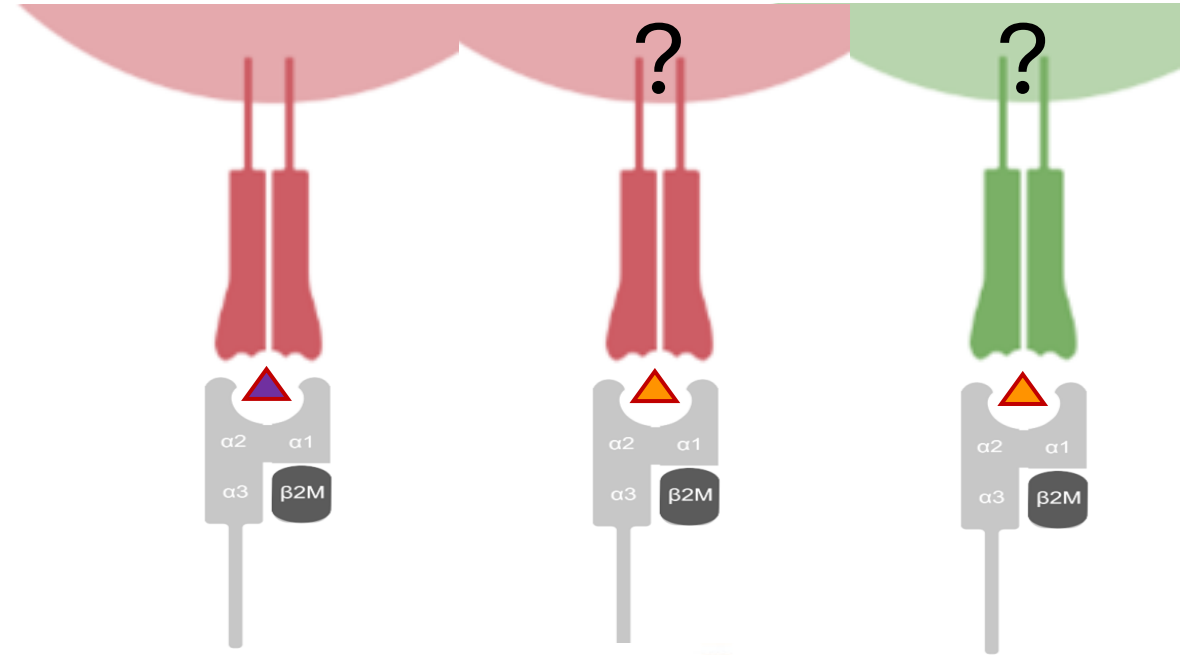
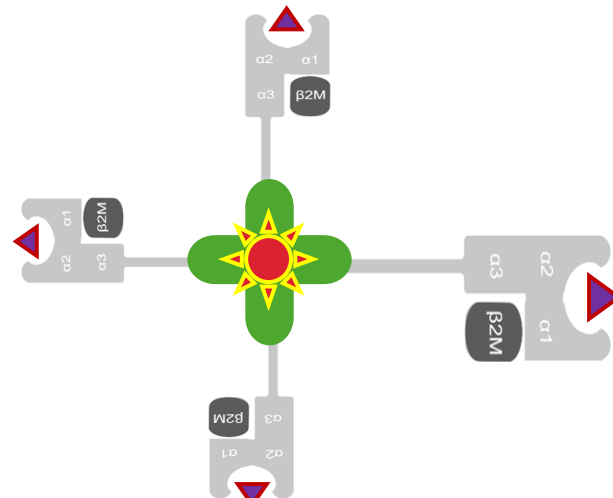
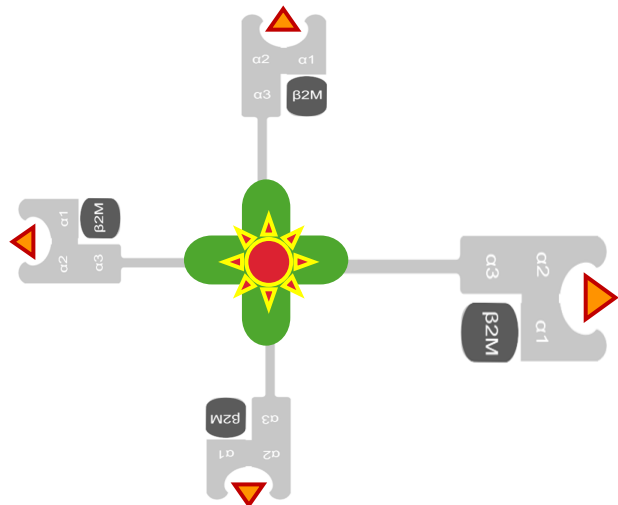
HKU-1



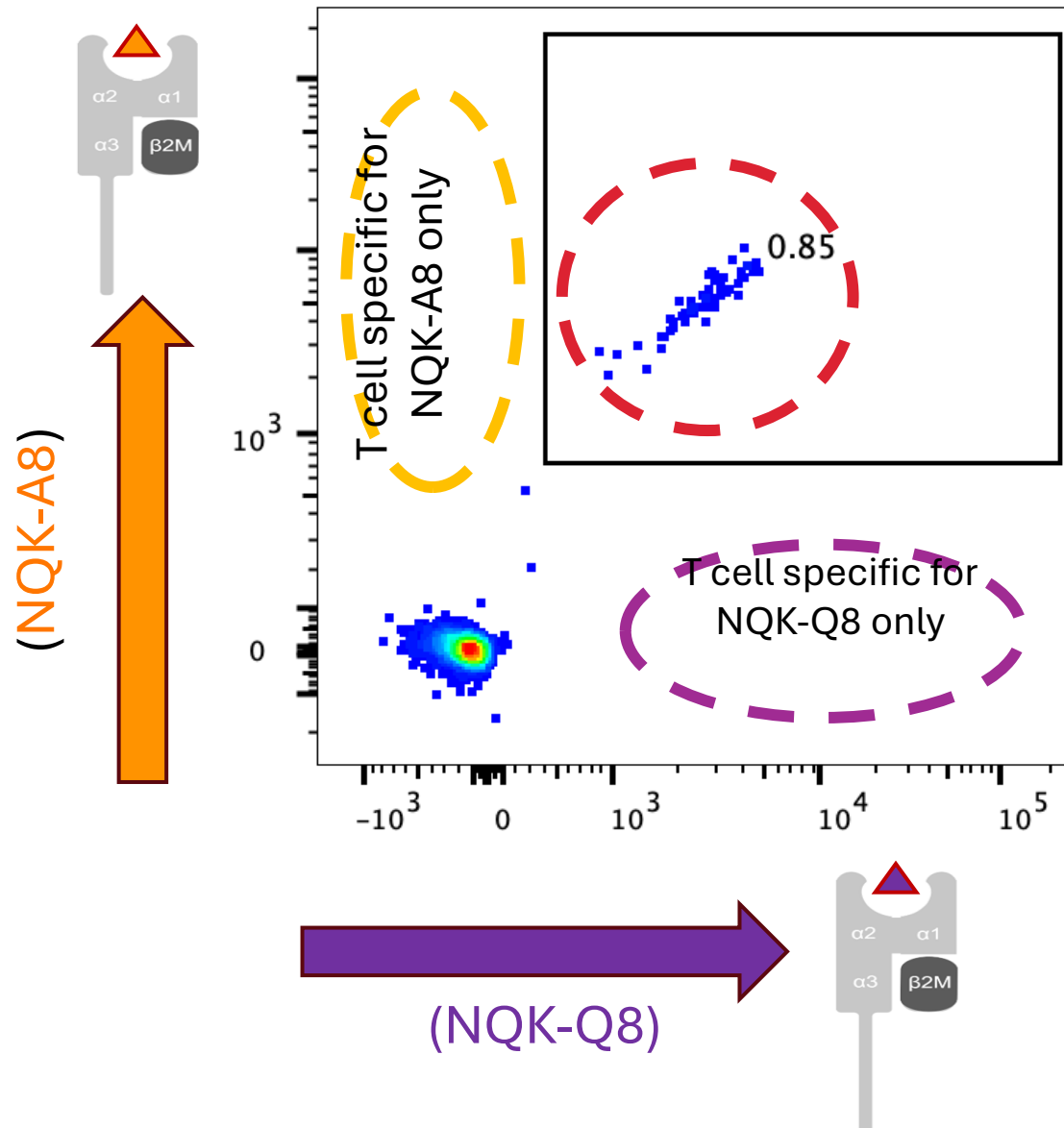
SARS-CoV-2

NQKLIANAF
(NQK-A8)

NQKLIANQF
(NQK-Q8)



Can T cells can “see” both NQK-Q8 and NQK-A8 ?



T cells able to bind to both peptides

=

Cross-reactive T cells

NQK-specific T cells share the same TCRs

D5A TCR



D9A TCR



Donors	Sample
R24#	Infected + vax 1 dose
R9#	Infected + vax 2 doses
R10#	Infected only
N9#	Vax 2 doses (only)
GR81*	unexposed
R1#	Infected only
SG133*	unexposed
VAC62*	Vax 3 doses

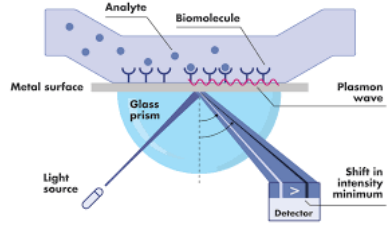
Found in **8 donors** across USA and AUS

Donors	Sample
R8#	Infected + vax 2 doses
GR29*	unexposed
VAC62*	Vax 3 doses
SG133*	unexposed

Found in **4 donors** across USA and AUS

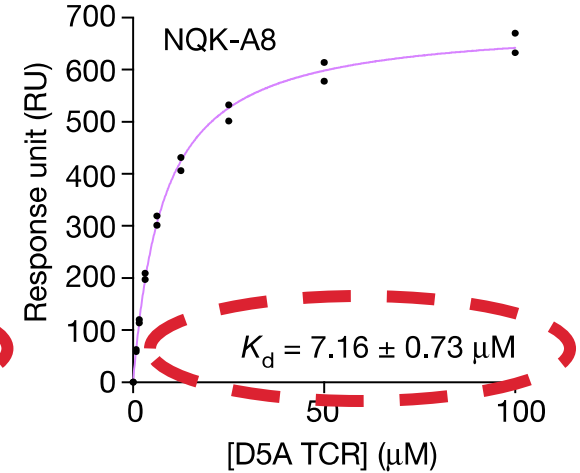
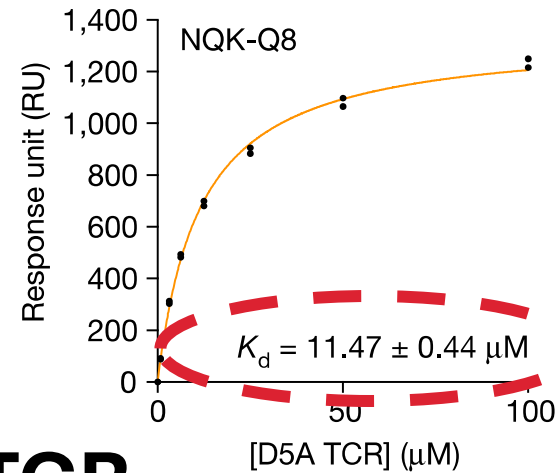
Same TCRs can “see” both NQK-A8 and NQK-Q8

Surface plasmon resonance

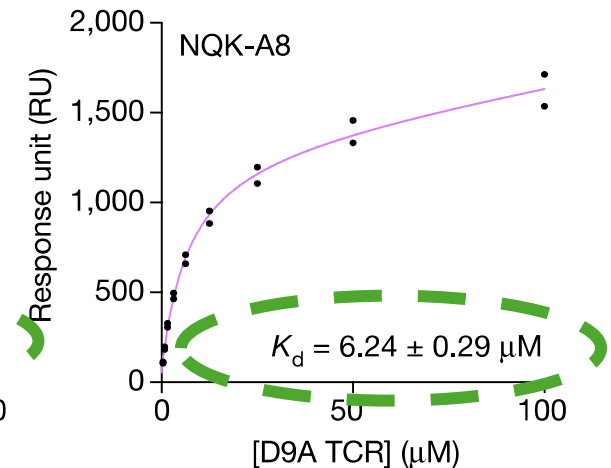
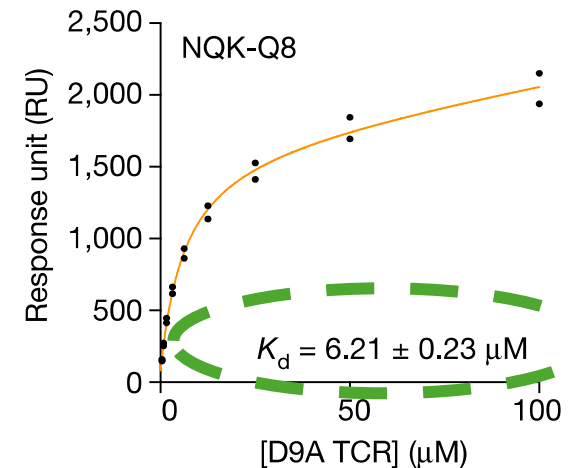


500 litres of LB later

D5A TCR



D9A TCR



Shared TCRs has **similar affinity for both peptides**

HLA-B15⁺ individuals can dodge COVID

Article | [Open access](#) | Published: 19 July 2023

A common allele of *HLA* is associated with asymptomatic SARS-CoV-2 infection

[Danillo G. Augusto](#), [Lawton D. Murdolo](#), [Demetra S. M. Chatzileontiadou](#), [Joseph J. Sabatino Jr](#), [Tasneem Yusufali](#), [Noah D. Peyser](#), [Xochitl Butcher](#), [Kerry Kizer](#), [Karoline Guthrie](#), [Victoria W. Murray](#), [Vivian Pae](#), [Sannidhi Sarvadhavabhatla](#), [Fiona Beltran](#), [Gurjot S. Gill](#), [Kara L. Lynch](#), [Cassandra Yun](#), [Colin T. Maguire](#), [Michael J. Peluso](#), [Rebecca Hoh](#), [Timothy J. Henrich](#), [Steven G. Deeks](#), [Michelle Davidson](#), [Scott Lu](#), [Sarah A. Goldberg](#), [J. Daniel Kelly](#), [Jeffrey N. Martin](#), [Cynthia A. Vierra-Green](#), [Stephen R. Spellman](#), [David J. Langton](#), [Michael J. Dewar-Oldis](#), [Corey Smith](#), [Peter J. Barnard](#), [Sulggi Lee](#), [Gregory M. Marcus](#), [Jeffrey E. Olgin](#), [Mark J. Pletcher](#), [Martin Maiers](#), [Stephanie Gras](#) & [Jill A. Hollenbach](#) ✉

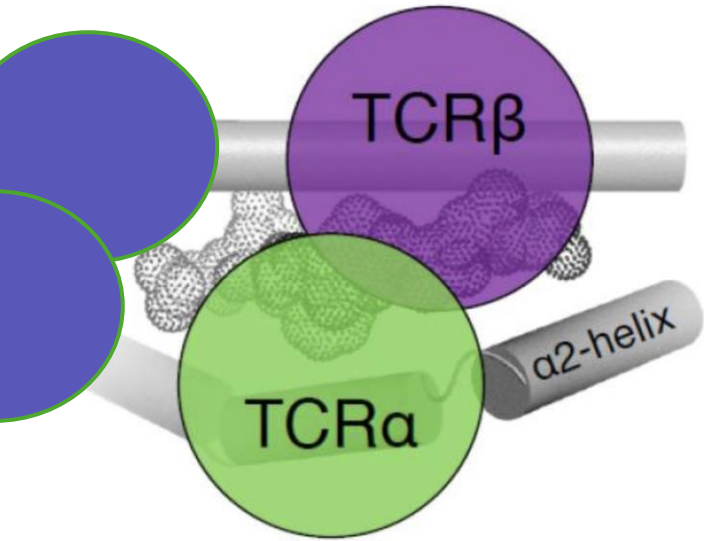
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[Nature](#) **620**, 128–136 (2023) | [Cite this article](#)

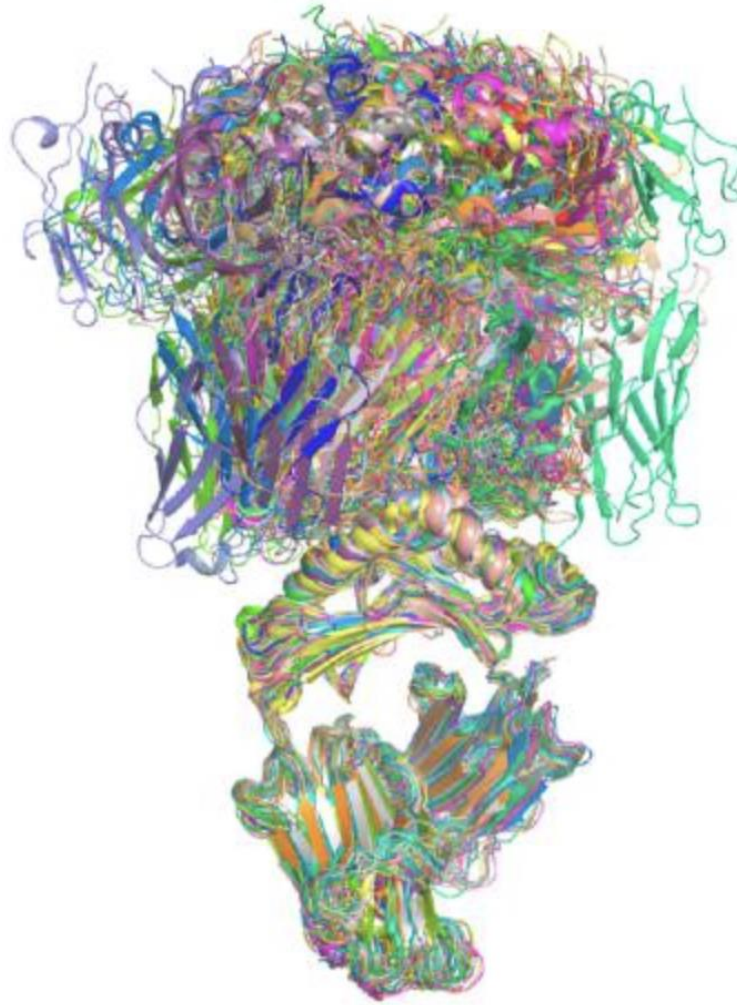
116k Accesses | **45** Citations | **2944** Altmetric | [Metrics](#)



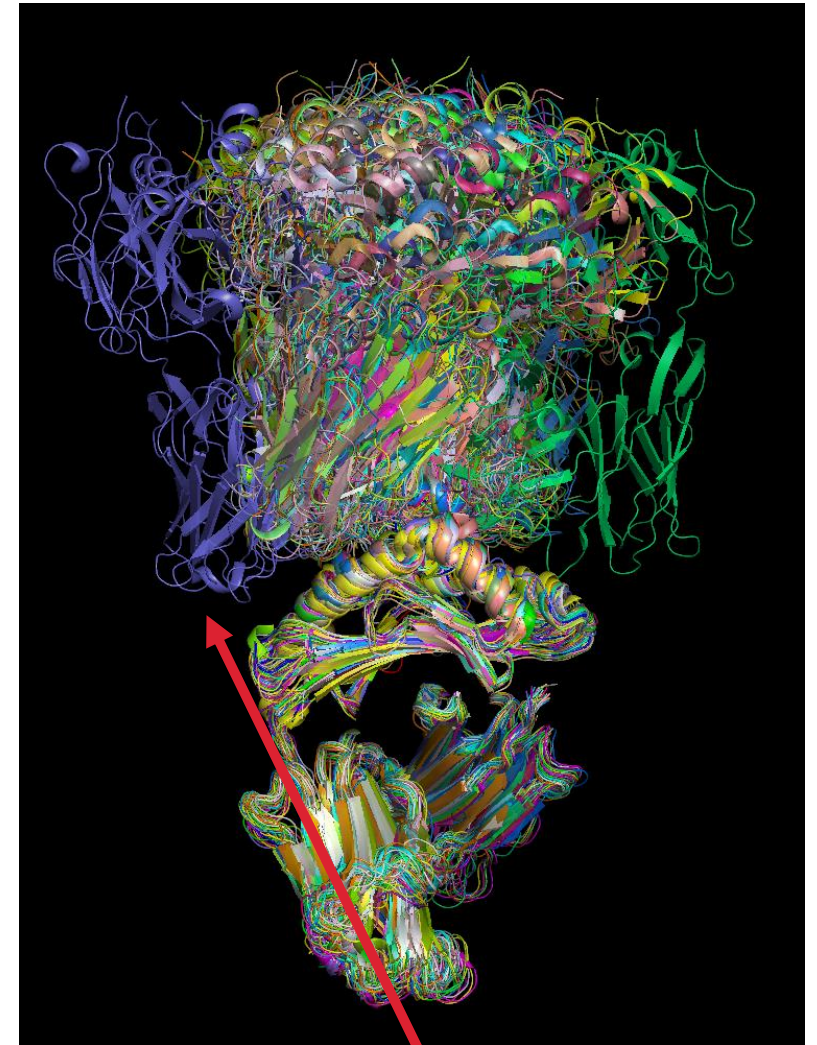
NQK-specific shared TCR binding is unusual



TCR Canonical binding

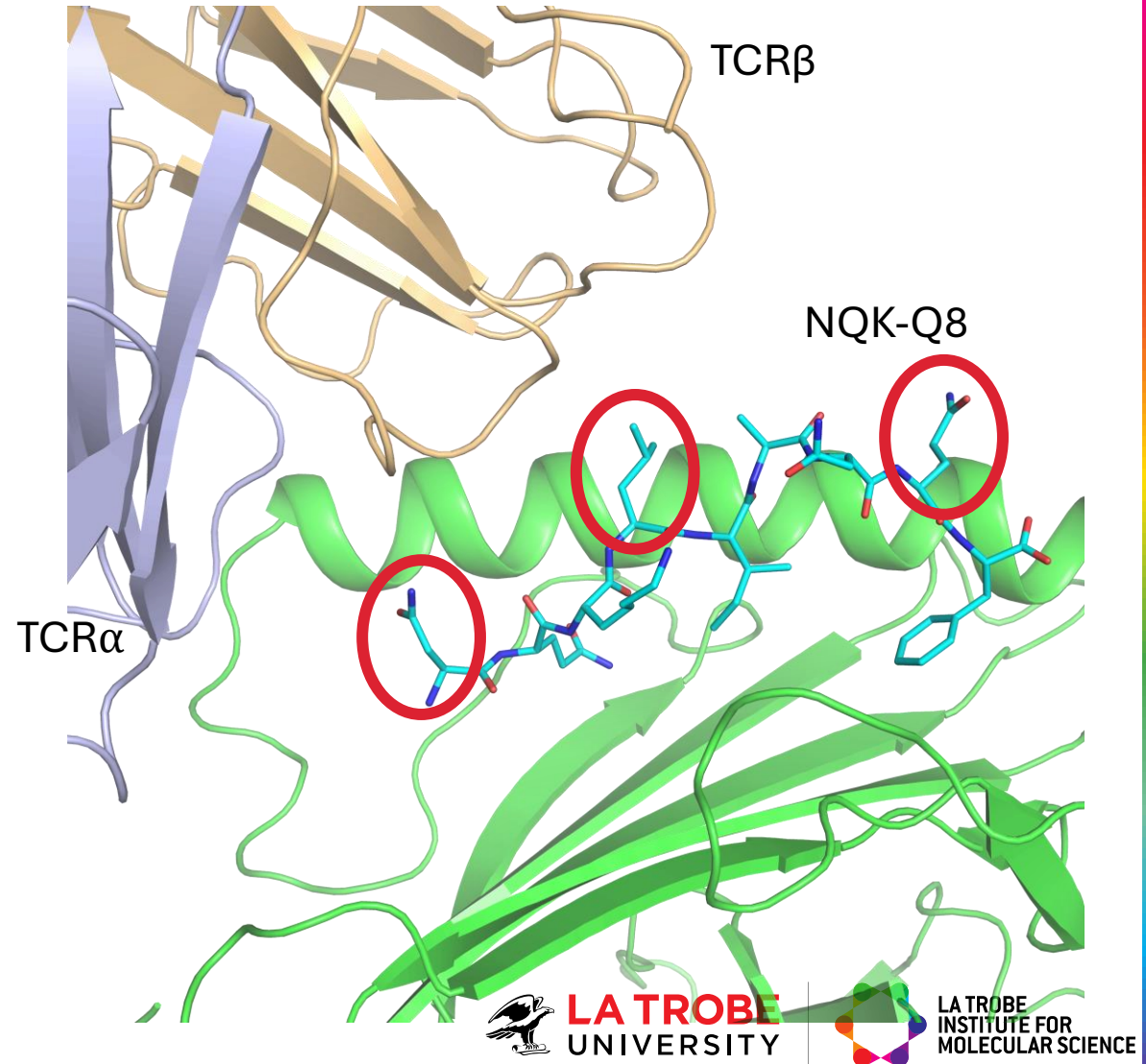
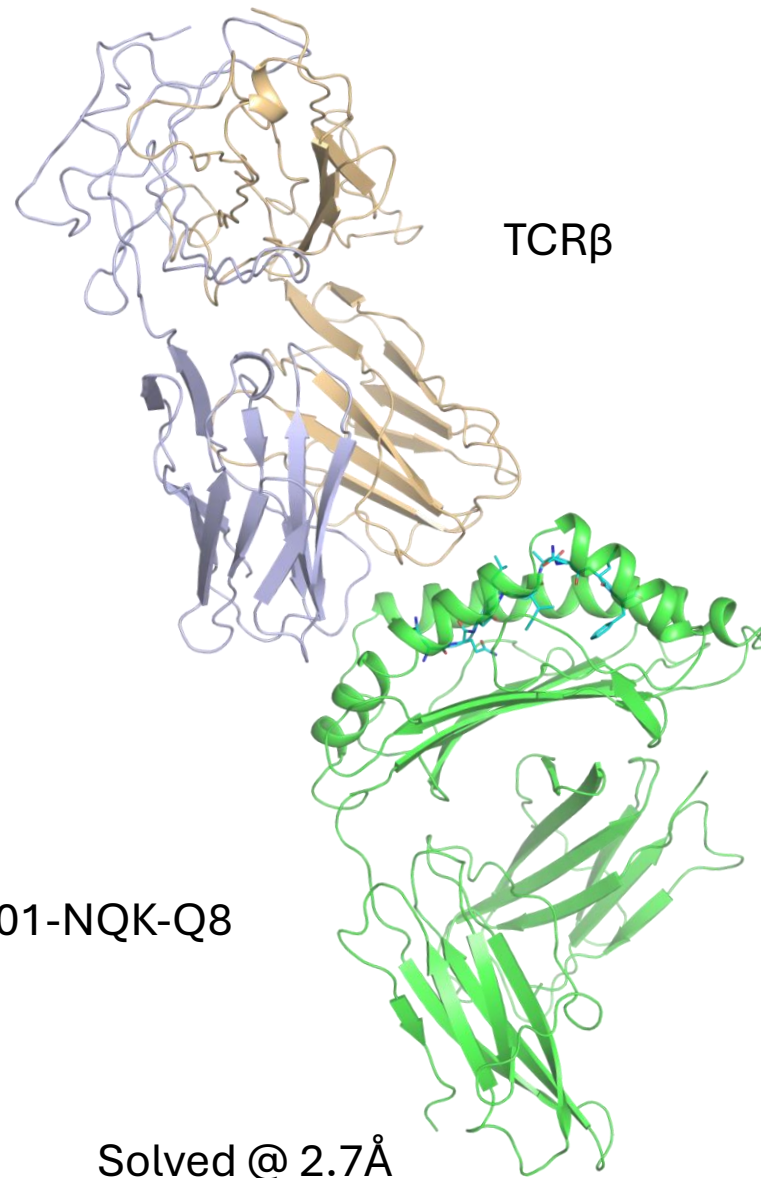


Crystal structure of TCR-pMHC-I



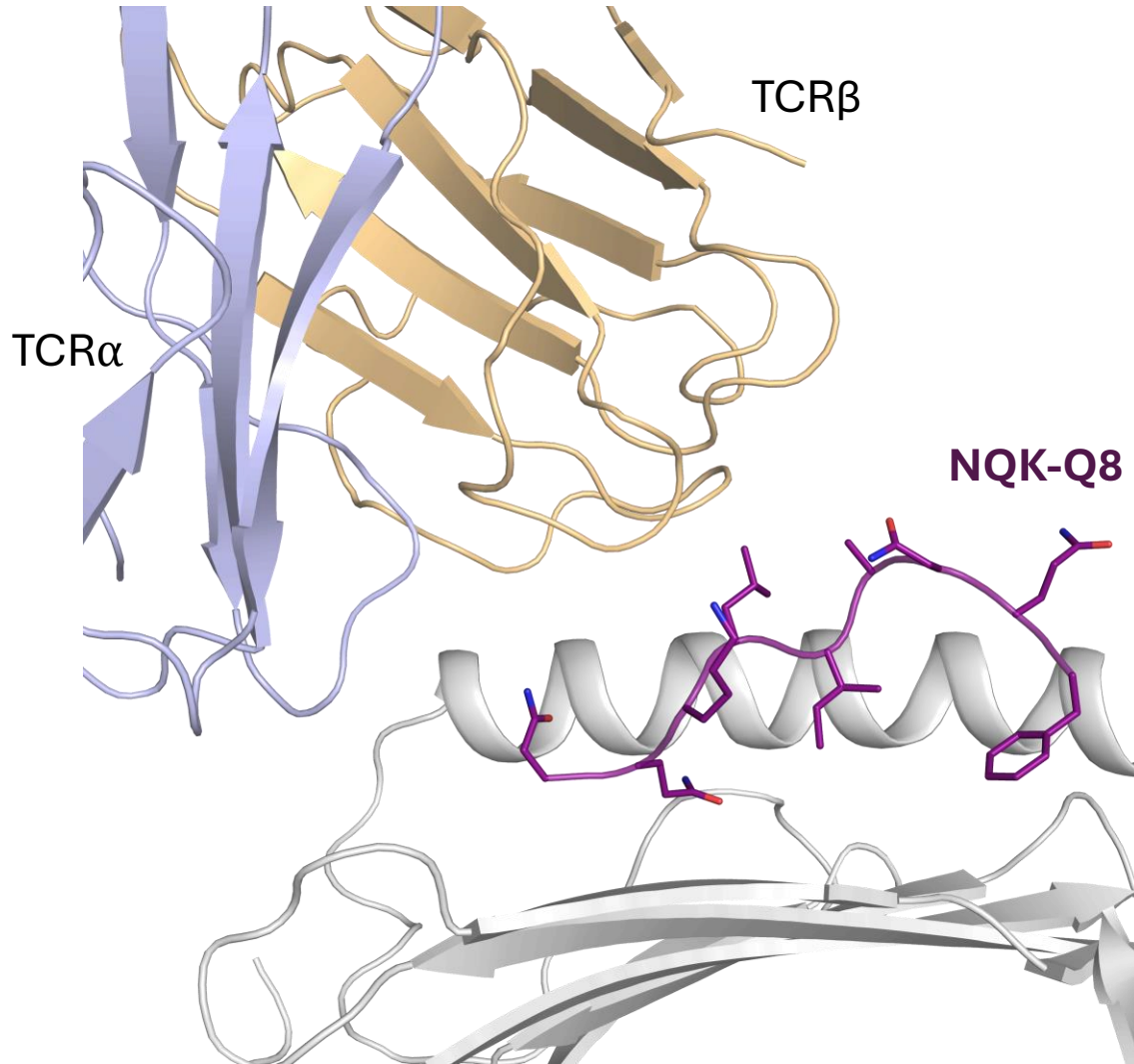
Shared TCR-HLA-B*15:01-NQK-Q8

NQK-specific shared TCR avoid the P8 residue

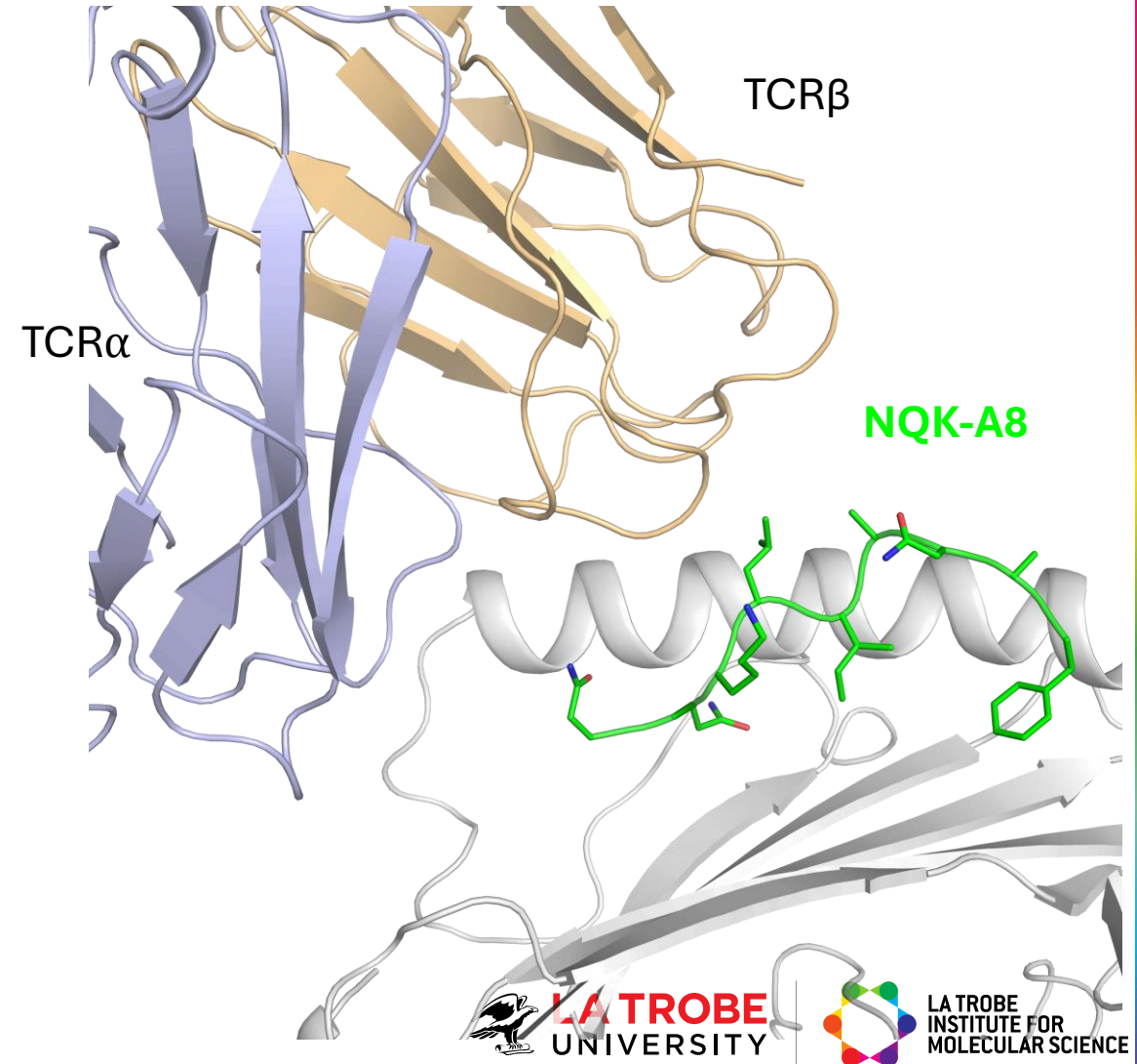


Unique pHLA-TCR interaction

Resolution: 2.7Å



Resolution: 3Å



Conclusion & Future directions

- First genetic link between HLA and asymptomatic COVID
- Strong memory T cells may provide protection
- Other protective HLAs?
- Towards a pan-coronavirus vaccine: the role of T cells

Using Synchrotron technique for Medical research

Understanding T cell response at the atomic level:

- impact of viral mutation and basis for viral escape (help with surveillance)
- role and mechanism of pre-existing immunity (help design better vaccine)
- fundamental concept of T cell biology (help design new drug to block or activate immune system)

T cells can protect from infection BEFORE the infection occurs

T cell response can increase upon vaccination (potential vaccine target)



Lawton Murdolo

Dimitra Chatzileontiadou

Dhilshan Jayasinghe

Emma Grant

Past lab member: Christopher Szeto, Andrea Nguyen, Hanim Halim, Christian Lobos, Hannah Sloane

Michael Dewar-Oldis

Peter Barnard

Monique Smith

Karla Helbig



UCSF Weill Institute for
Neurosciences

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To all our volunteers***

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Keng Yih Chew



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(now at UNC Charlotte)

Joseph Sabatino

Jill Hollenbach



James McMahon

Bradley Gardiner



QIMR Berghofer
Medical Research Institute

Corey Smith

Katie E. Lineburg

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Looking for Long COVID patients



Have you had a COVID-19 infection and are suffering from unexplained fatigue, respiratory issues, brain fog or muscle pain 3+ months post infection? Are your symptoms worse after exertion?

**You may be suffering Long COVID.
We would love to hear from you!**

If you live in Victoria and would be willing to donate a blood sample, please contact Dr. Sarah Annesley at S.Annesley@latrobe.edu.au or Prof. Stephanie Gras at S.Gras@latrobe.edu.au



To join the study and
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Seeking Participants COVID-19 study

- Are you a healthy individual over 18 years old?
- Have you recently received or are planning on receiving the the COVID-19 vaccine?
- Have you been infected with coronavirus (COVID-19)?
- Are you willing to donate a small mount of time (~90mins) and blood to medical research?



Ethics Reference
Number: HEC21097

The Gras Laboratory at La Trobe University investigates immune responses towards a large range of diseases and other ailments. We are currently recruiting participants for our research investigating the immune response towards coronavirus (COVID-19).

Want to know more?

If you would like more information about our research or volunteering, please contact

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