Bioinformatics 1 -- Lecture 22

IMMUNOINFORMATICS:
Bioinformatics Challenges in Immunology

Most slides courtesy of

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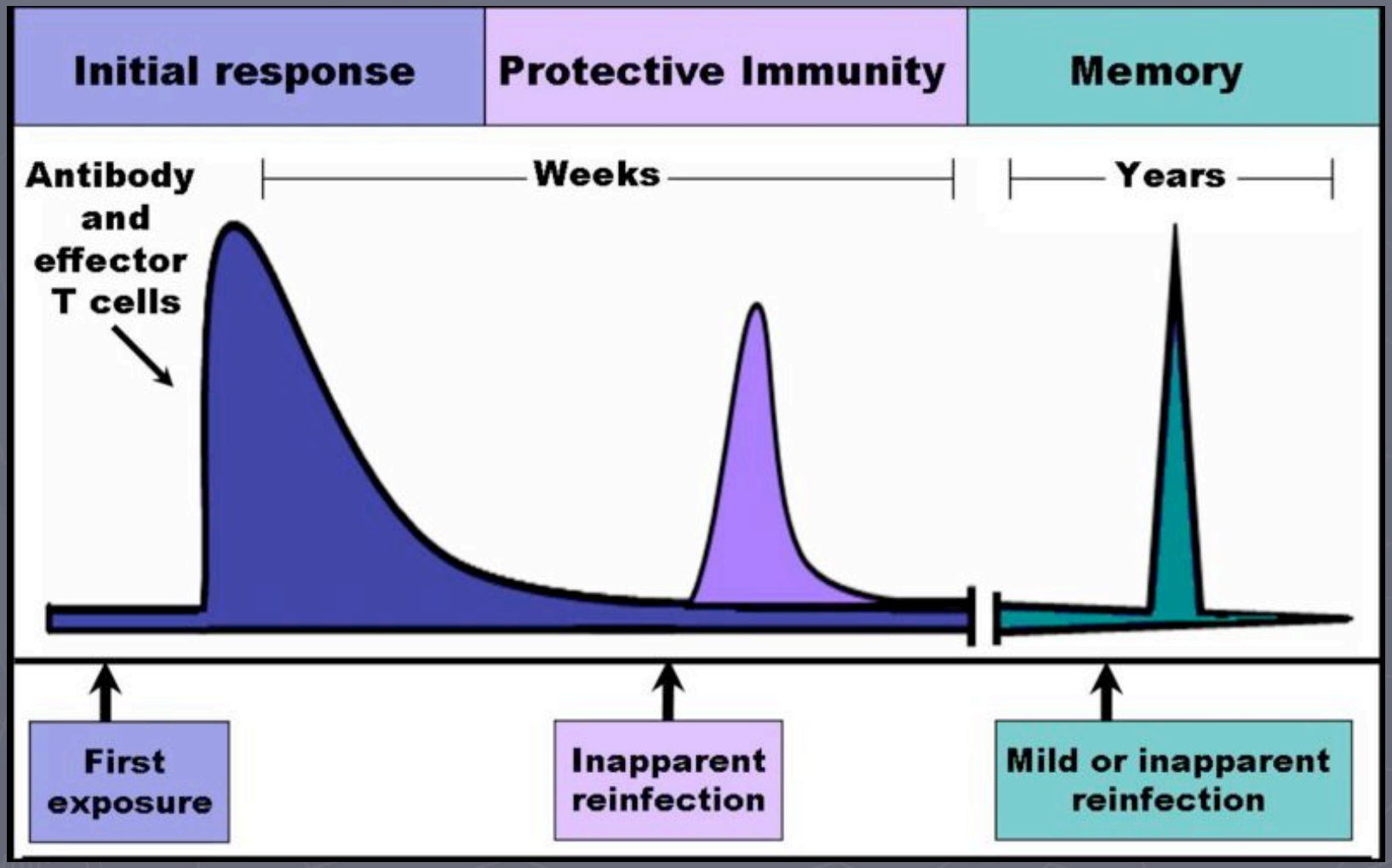
or

Oliver Kohlbacher, WSI/ZBIT, Eberhard-Karls-Universität Tübingen

The Immune Reaction



Vaccines have been made for 36 of >400 human pathogens

Organism	Type	Vaccine Type	Year
Variola virus	Virus	Live	1798
Rabies virus	Virus	Inactivated	1885
Salmonella typhi	Bacteria	Live	1896
Vibrio cholerae	Bacteria	Inactivated	1896
Yersinia pestis	Bacteria	Inactivated	1897
Corynebacterium diphtheriae	Bacteria	Toxoid	1923
Bordetella pertussis	Bacteria	Acellular	1926
Clostridium tetani	Bacteria	Toxoid	1927
Mycobacterium tuberculosis	Bacteria	Live	1927
Yellow fever virus	Virus	Live	1935
Influenza virus type A	Virus	Inactivated	1936
Influenza virus type B	Virus	Inactivated	1936
Coxiella burnetii	Bacteria	Inactivated	1938
Rickettsia prowazekii	Bacteria	Inactivated	1938
Rickettsia rickettsii	Bacteria	Inactivated	1938
Central European encephalitis virus	Virus	Inactivated	1939
Poliovirus types 1, 2, and 3	Virus	Inactivated/Live	1962
Measles virus	Virus	Live	1963
Mumps virus	Virus	Live	1967
Rubivirus	Virus	Live	1969
Staphylococcus aureus	Bacteria	Staphage lysate	1976
Streptococcus pneumoniae	Bacteria	Polysaccharide	1977
Human adenovirus types 4 and 7	Virus	Live	1980
Neisseria meningitidis	Bacteria	Polysaccharide	1981
Hepatitis B	Virus	Recombinant	1986
Haemophilus influenzae	Bacteria	Conjugate	1987
Hantaan virus	Virus	Inactivated	1989
Japanese encephalitis virus	Virus	Inactivated	1992
Varicella-zoster virus	Virus	Live	1994
Hepatitis A	Virus	Inactivated	1995
Escherichia coli	Bacteria	Inactivated	1995
Junin virus	Virus	Live	1996
Bacillus anthracis	Bacteria	Adsorbed	1998
Borrelia burgdorferi	Bacteria	Recombinant	1998

+HPV & Rotavirus

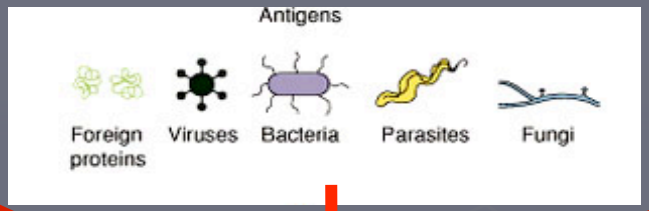
Immunological Bioinformatics, 2005 The MIT press.

Epitope

- Quantum unit of immunity
- Surface on which an antibody binds
- Comprises antigenic matter
- *Linear epitope* consists of a short AA sequence
- *Conformational epitope* depends on tertiary structure.

Two branches of immunity

Innate immunity



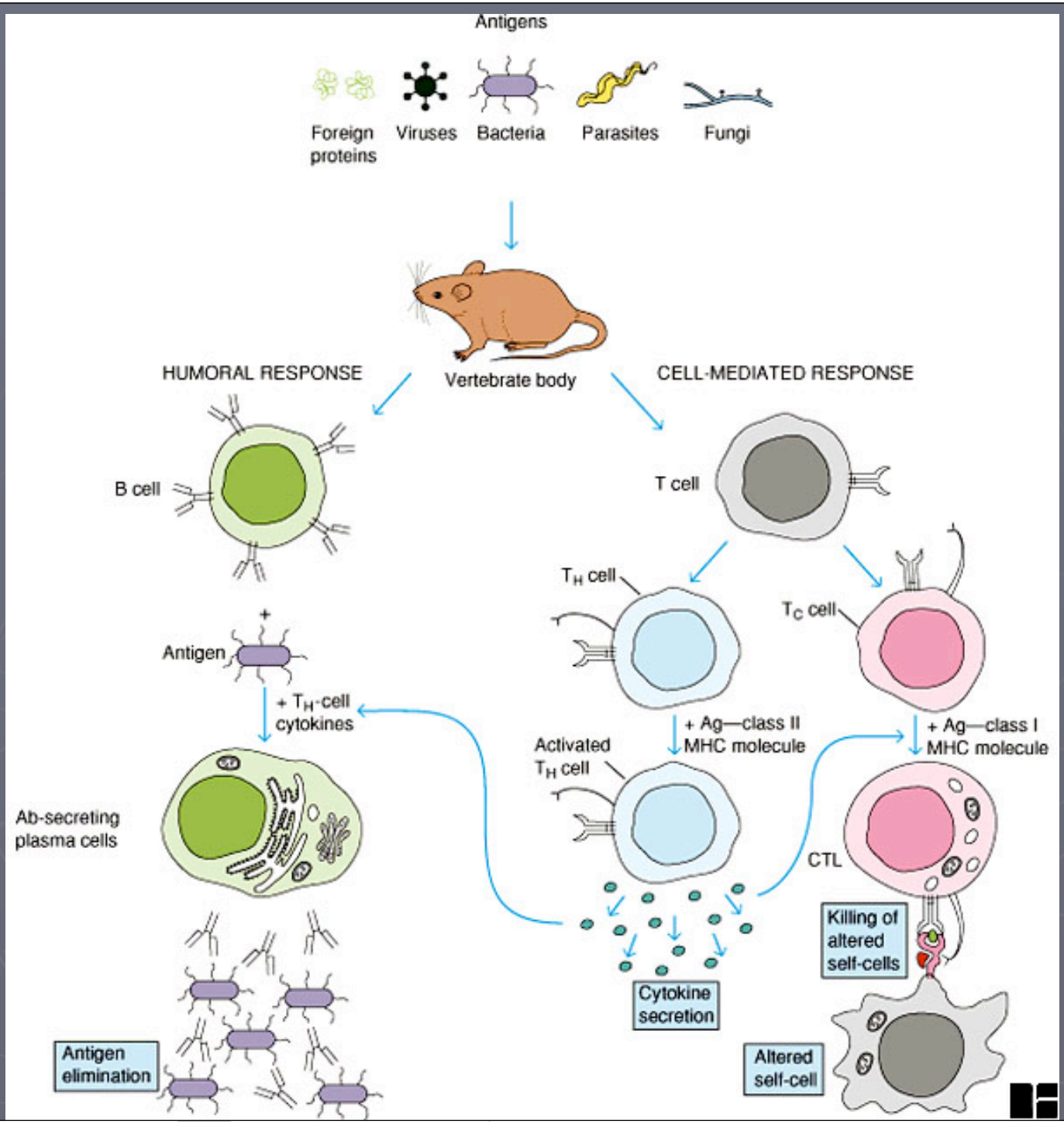
Adaptive immunity

- Recognizes molecules, called pathogen-associated molecular patterns (~10^3), or PAMPs shared by groups of related microbes; e.g. LPS from the gram-negative cell wall, RNA from viruses, flagellin, and glucans from fungal cell walls.
- Is antigen-nonspecific.
- Immediate or within several hours response.
- Involves body defense cells that have pattern-recognition receptors:
  - Leukocytes: neutrophils, eosinophils, basophils and monocytes;
  - cells that release inflammatory mediators: macrophages and mast cells;
  - natural killer cells (NK cells); and
  - complement proteins and cytokines.
- Does not improve with repeated exposure to a given infection.

- Recognizes epitopes; that are specific B- and T-cell recognition sites on antigens.
- Is antigen-specific.
- 3 to 10 days response.
- Involves the following:
  - antigen-presenting cells (APCs) such as macrophages and dendritic cells;
  - antigen-specific B-lymphocytes (~10^9);
  - antigen-specific T-lymphocytes (~ 10^{12}); and
  - cytokines.
- Improves with repeated exposure and becomes protective.

Components of the immune system

Innate immune system	Adaptive immune system
Response is non-specific	Pathogen and antigen specific response
Exposure leads to immediate maximal response	Lag time between exposure and maximal response
Cell-mediated and humoral components	Cell-mediated and humoral components
No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in jawed vertebrates


Antigens
Foreign proteins
Viruses
Bacteria
Parasites
Fungi
Vertebrate body
HUMORAL RESPONSE
CELL-MEDIATED RESPONSE
B cell
T cell
T_H cell
T_C cell
Antigen
+ T_H-cell cytokines
+ Ag—class II MHC molecule
+ Ag—class I MHC molecule
Activated T_H cell
Ab-secreting plasma cells
CTL
Killing of altered self-cells
Cytokine secretion
Antigen elimination
Altered self-cell

B and T cells recognize different epitopes of the same protein

T-cell epitope

Denatured antigen

Linear (often) peptide 8-37 aa

Internal (often)

Binding to T cell receptor:

K_d 10^{-5} – 10^{-7} M (low affinity)

Slow on-rate, slow off-rate
(once bound, peptide may stay associated for hours to many days)

B-cell epitope

Native or denatured (rare) antigen

Sequential (continuous) or conformational (discontinuous)

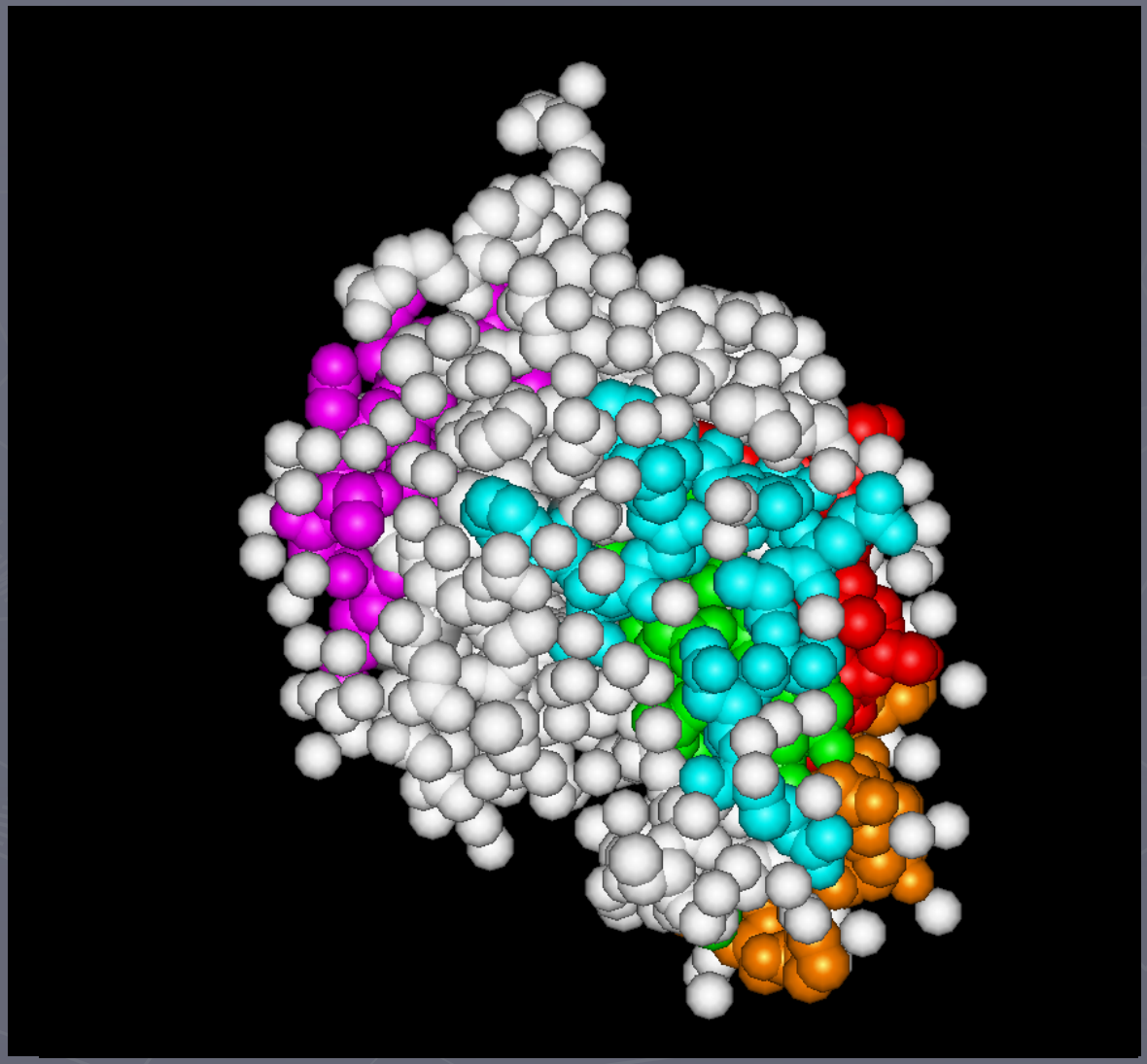
Accessible, hydrophilic, mobile, usually on the surface or could be exposed as a result of physicochemical change

Binding to antibody:

K_d 10^{-7} – 10^{-11} M (high affinity)

Rapid on-rate, variable off-rate

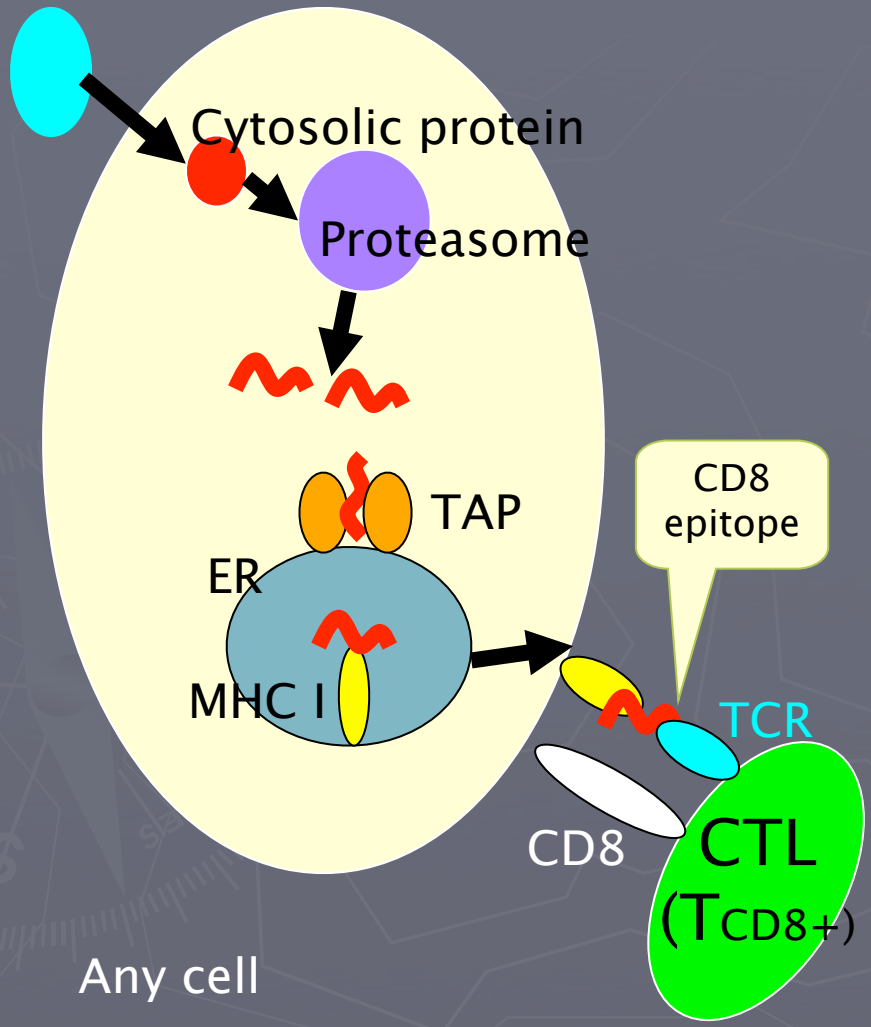
B cell (magenta, orange) and T cell epitopes (blue, green, red)
of hen egg-white lysozyme



PDB:

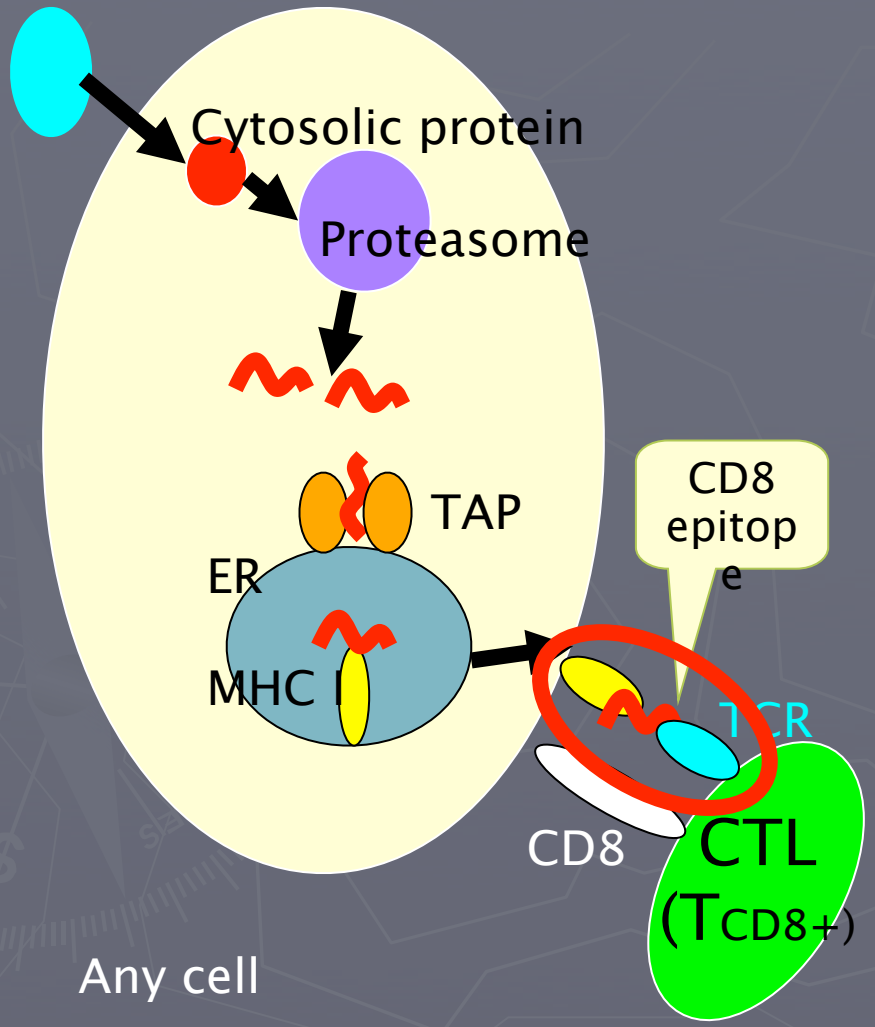
MHC class I pathway

Intracellular pathogen
(virus, mycobacteria)

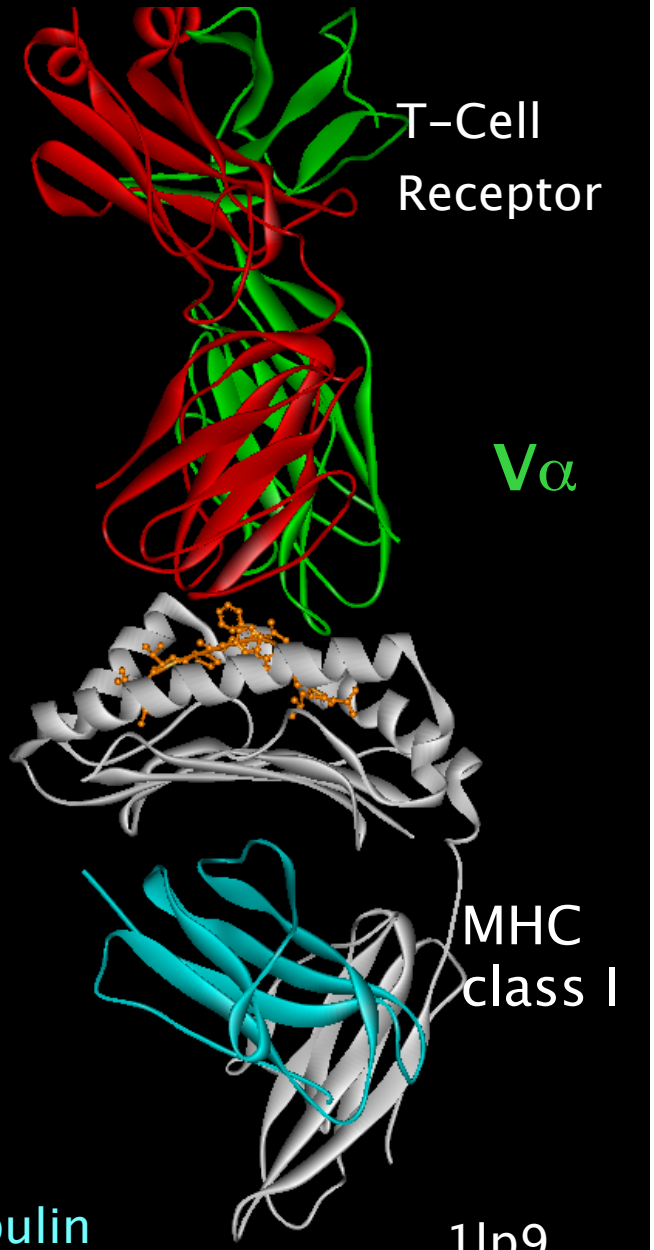


MHC class I pathway

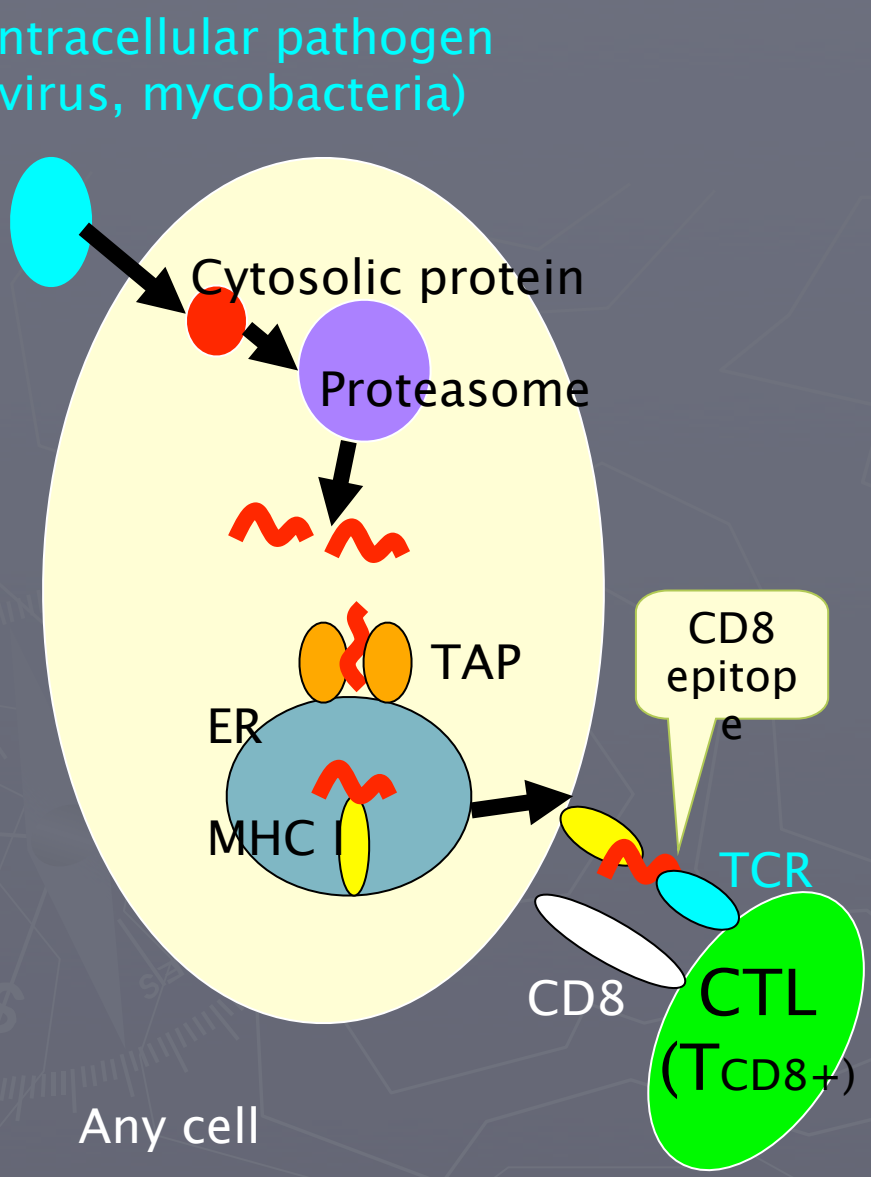
Intracellular pathogen
(virus, mycobacteria)



Xenoreactive Complex AHIII 12.2 TCR bound to P1049 (ALWGFFPVLS) /HLA-A2.1



MHC class I pathway



Bioinformatics approaches at epitope prediction:

(1) Prediction of proteosomal cleavage sites (several methods exist based on small amount of in vitro data).

(2) Prediction of peptide-TAP binding (ibid.).

(3) **Prediction of peptide-MHC binding.**

(4) Prediction of pMHC-TCR binding.

MHC class I epitope prediction: Challenges

- High rate of pathogen mutations. Pathogens evolve to escape:
  - Proteosomal cleavage (HIV);
  - TAP binding (HIV, HSV type I);
  - MHC binding.
- MHC genes are highly polymorphic (2,292 human alleles/1,670 – 2 yeas ago).
- MHC polymorphism is essential to protect the population from invasion by pathogens. But it generates problem for epitope-based vaccine design: a vaccine needs to contain a unique epitope binding to each MHC allele.
- Every normal (heterozygous) human expresses six different MHC class I molecules on every cell, containing α-chains derived from the two alleles of HLA-A, HLA-B, HLA-C genes that inherited from the parents.
- Every human has ~10^{12} lymphoid cells with a T-cell receptors repertoire of ~10^{7} , depending on her immunological status (vaccinations, disease history, environment, etc.).

Prediction of MHC class I binding peptide – potential epitopes

ALAKAAAAM

ALAKAAAAN

ALAKAAAAV

ALAKAAAAT

GMNERPILT

GILGFVFTM

TLNAWVKVV

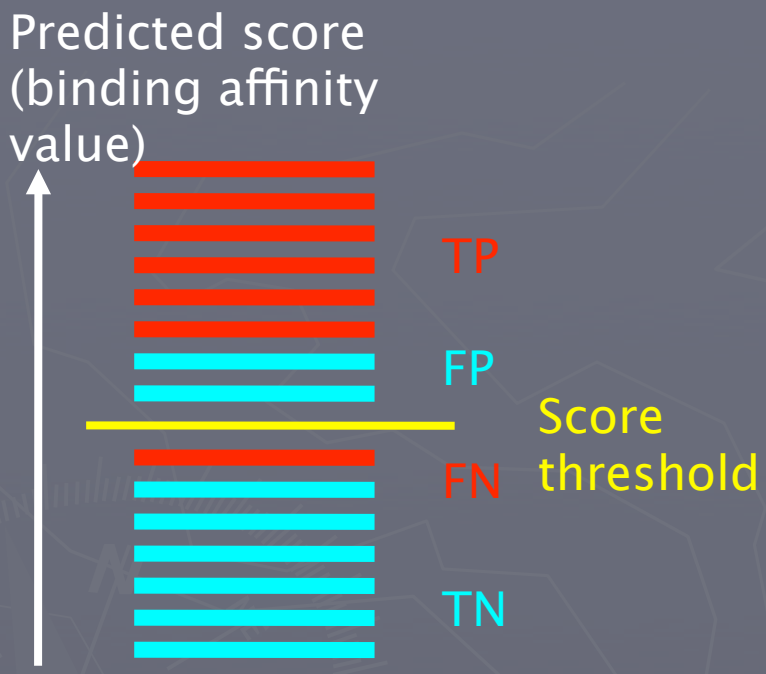
KLNEPVLLL

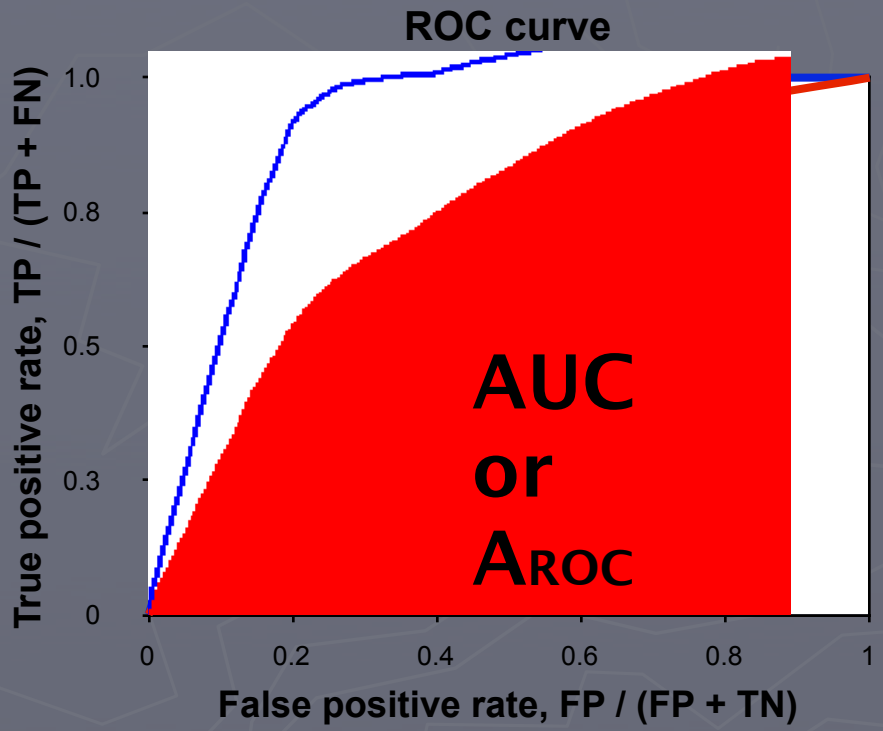
AVVPFIVSV

Peptides known to bind to the HLA-A*0201 molecule.

- MHC allele or allele supertype (similar in sequences alleles bind similar peptides) specific.
- Peptide length (8-, 9-, 10-, 11-mers) specific.
- Sequence-based approaches:
  - Gibbs sampling (when the training peptides are of different lengths)
  - Hidden Markov Models (ibid.)
  - Sequence motifs, position weight matrices
  - Artificial Neural Networks (require a large number of training examples)
  - SVM*

Performance measures for prediction methods





TP+FN – actual binders (based on a defined threshold on binding affinity values)

TN+ FP – actual non-binders (ibid.)

Sensitivity = TP / (TP + FN) = 6/7= 0.86

Specificity = TN / (TN + FP) = 6/8 = 0.75

Performance measures for prediction methods (cont)

Pearson's correlation coefficient

$$r = \frac{\sum_i (a_i - \bar{a})(p_i - \bar{p})}{\sqrt{\sum_i (p_i - \bar{p})^2} \sqrt{\sum_i (a_i - \bar{a})^2}}$$

TP+FN – actual binders (based on a defined threshold on actual binding affinity values a_i)

TN+ FP – actual non-binders (ibid.)

Sensitivity = TP / (TP + FN) = 6/7= 0.86

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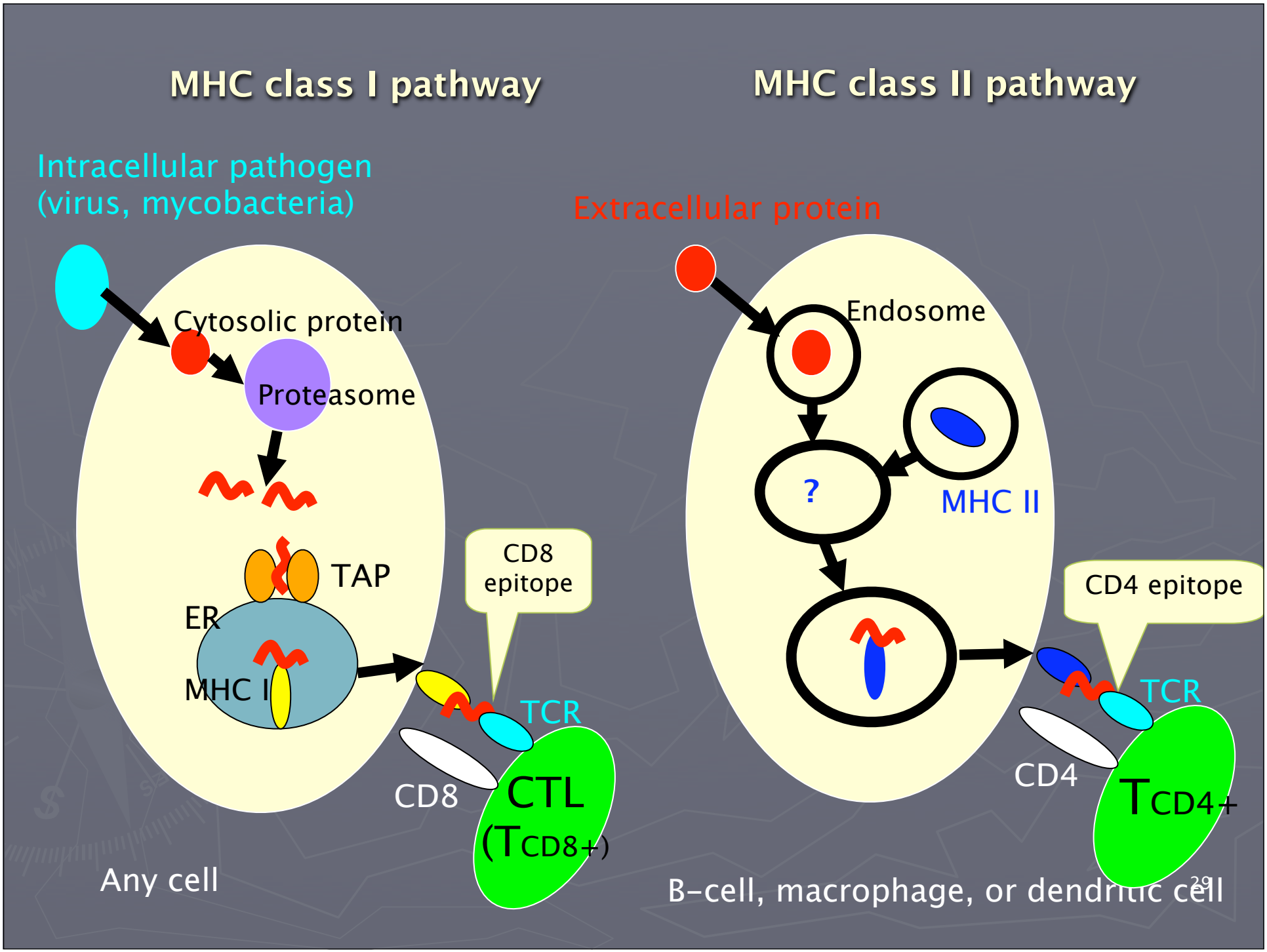
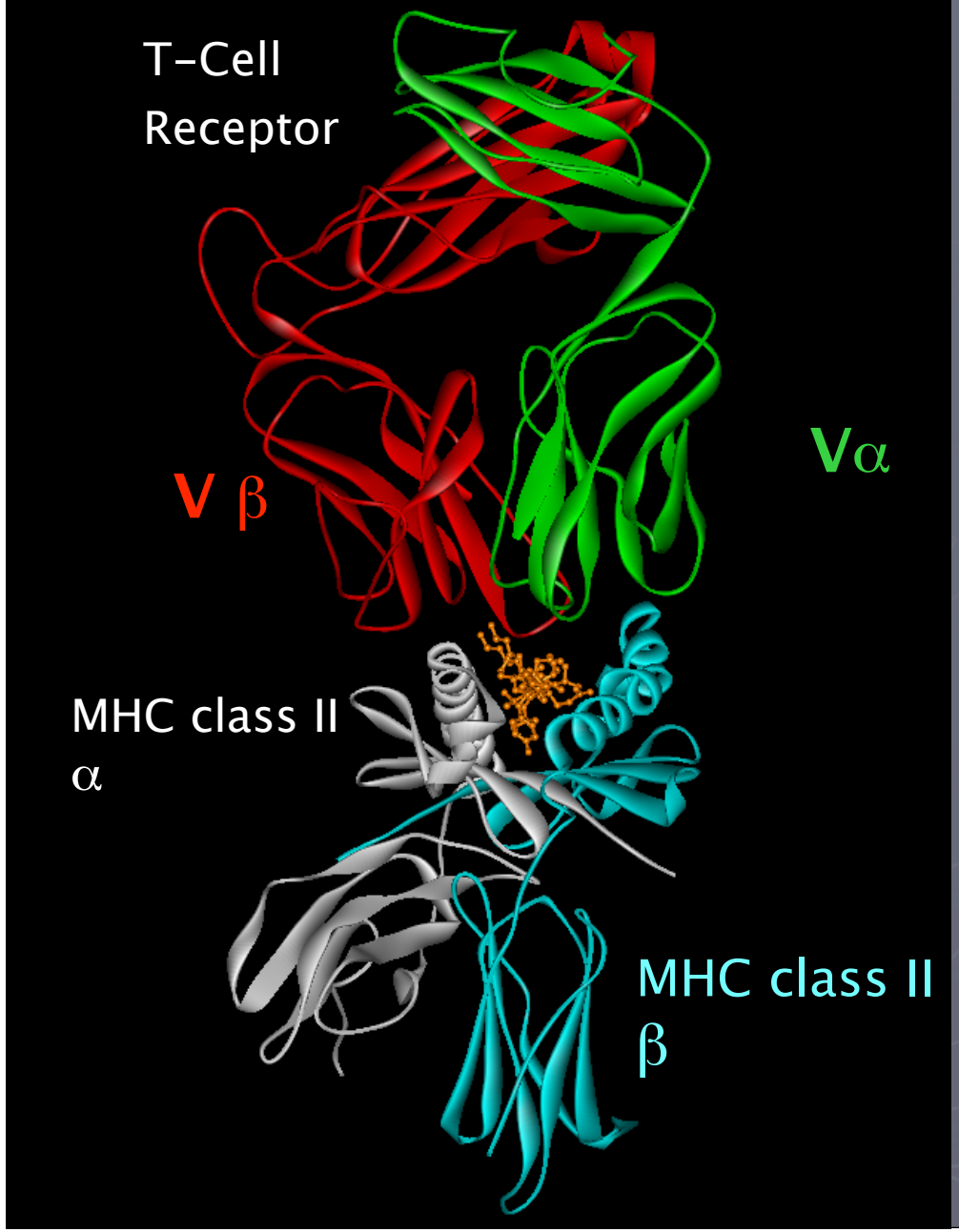
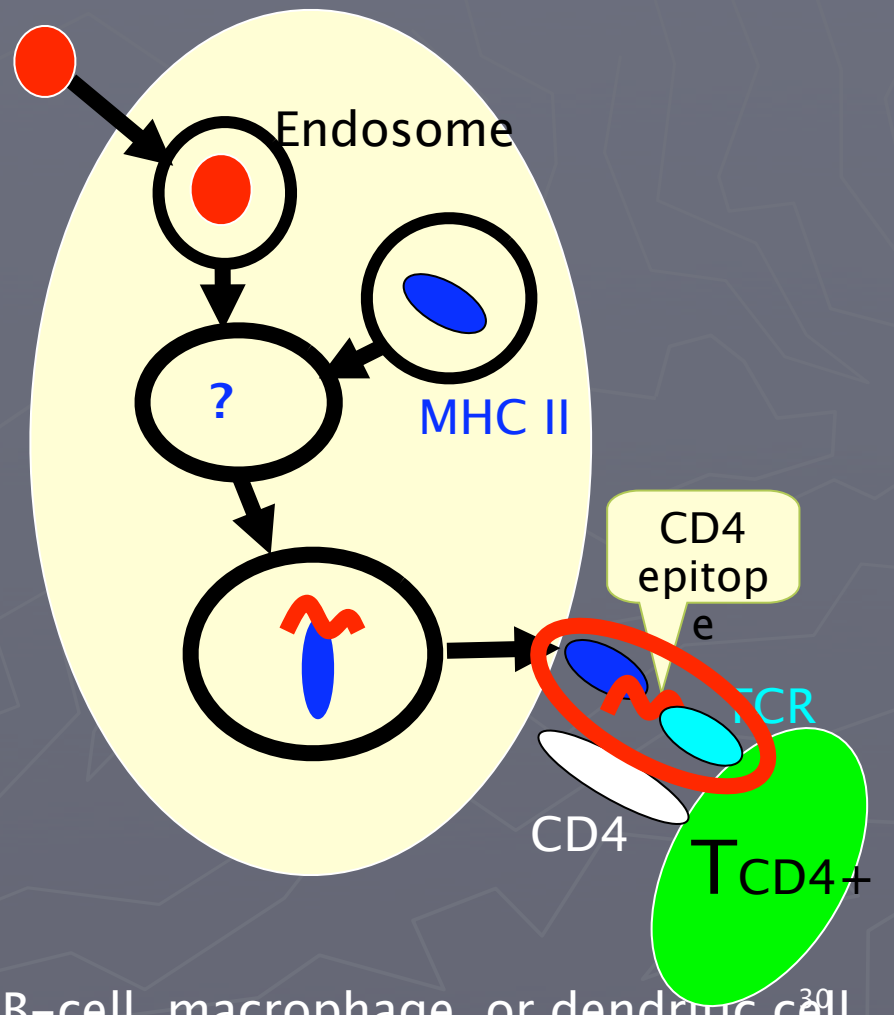
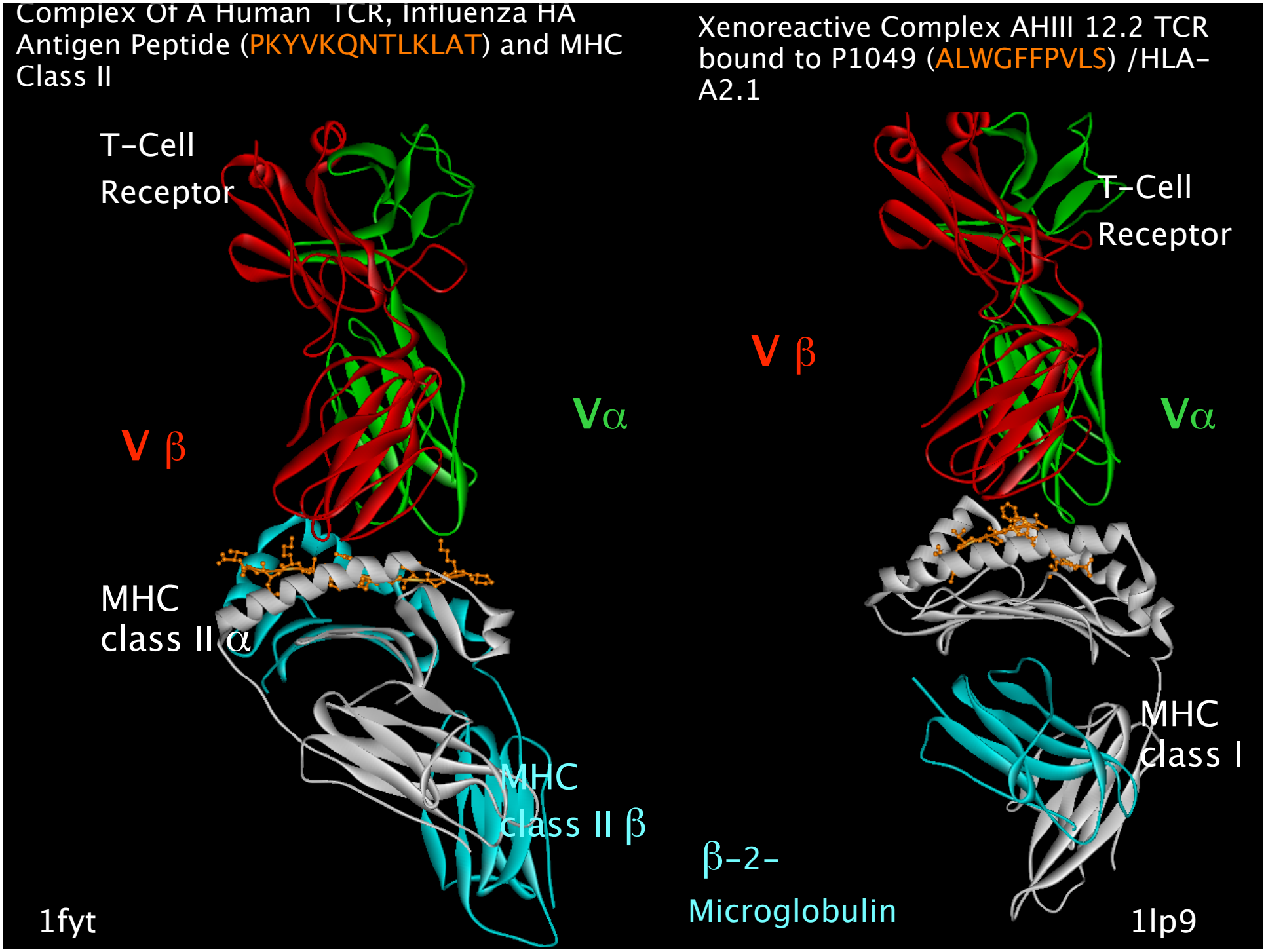

MHC class I pathway
MHC class II pathway
Intracellular pathogen
(virus, mycobacteria)
Extracellular protein
Cytosolic protein
Proteasome
TAP
ER
MHC I
CD8
epitope
TCR
CD8
CTL
(TCD8+)
Any cell
Endosome
?
MHC II
CD4 epitope
TCR
CD4
TCD4+
B-cell, macrophage, or dendritic cell

Complex Of A Human TCR, Influenza HA Antigen Peptide (PKYVKQNTLKLAT) and MHC Class II



MHC class II pathway

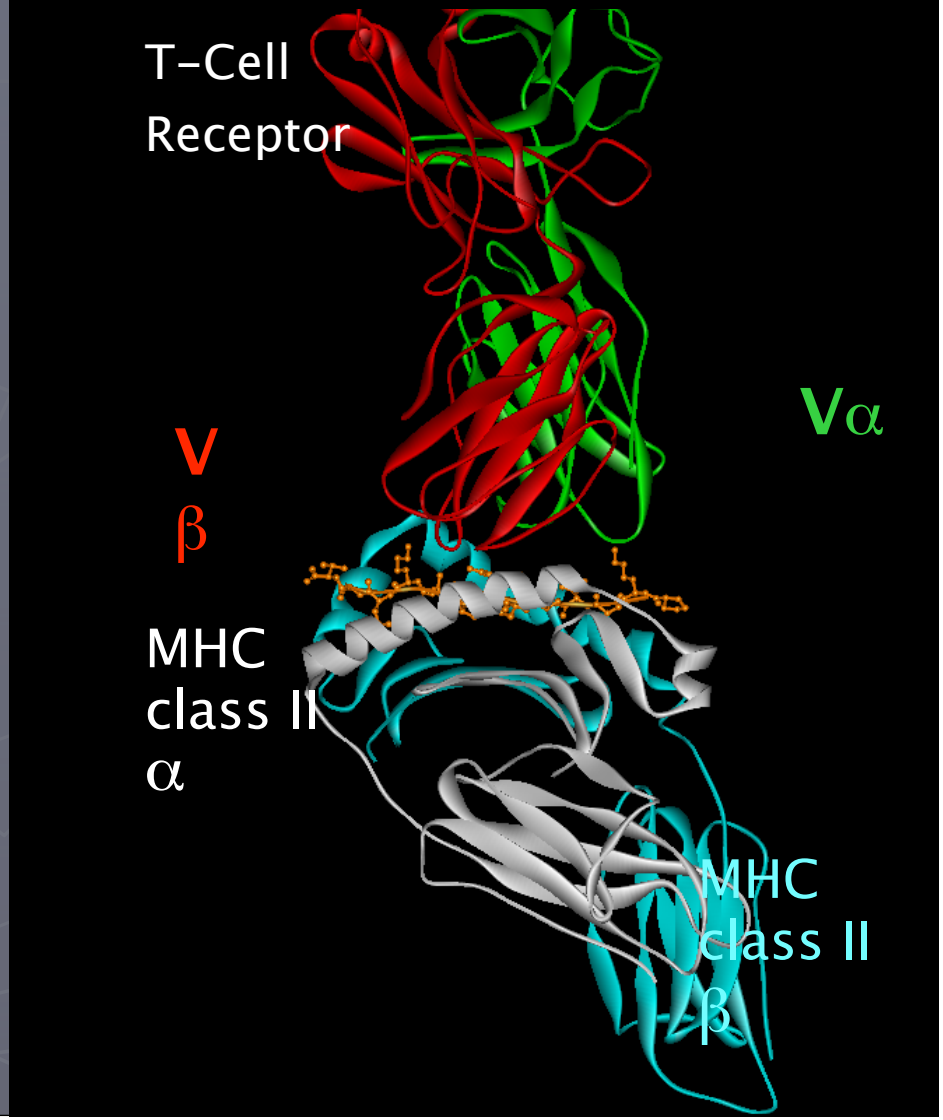



Complex Of A Human TCR, Influenza HA Antigen Peptide (PKYVKQNTLKLAT) and MHC Class II
T-Cell Receptor
V β
Vα
MHC class II α
MHC class II β
1fyt
Xenoreactive Complex AHIII 12.2 TCR bound to P1049 (ALWGFFPVLS) /HLA-A2.1
T-Cell Receptor
V β
Vα
MHC class I
β-2-Microglobulin
1lp9

MHC class II epitope prediction: Challenges

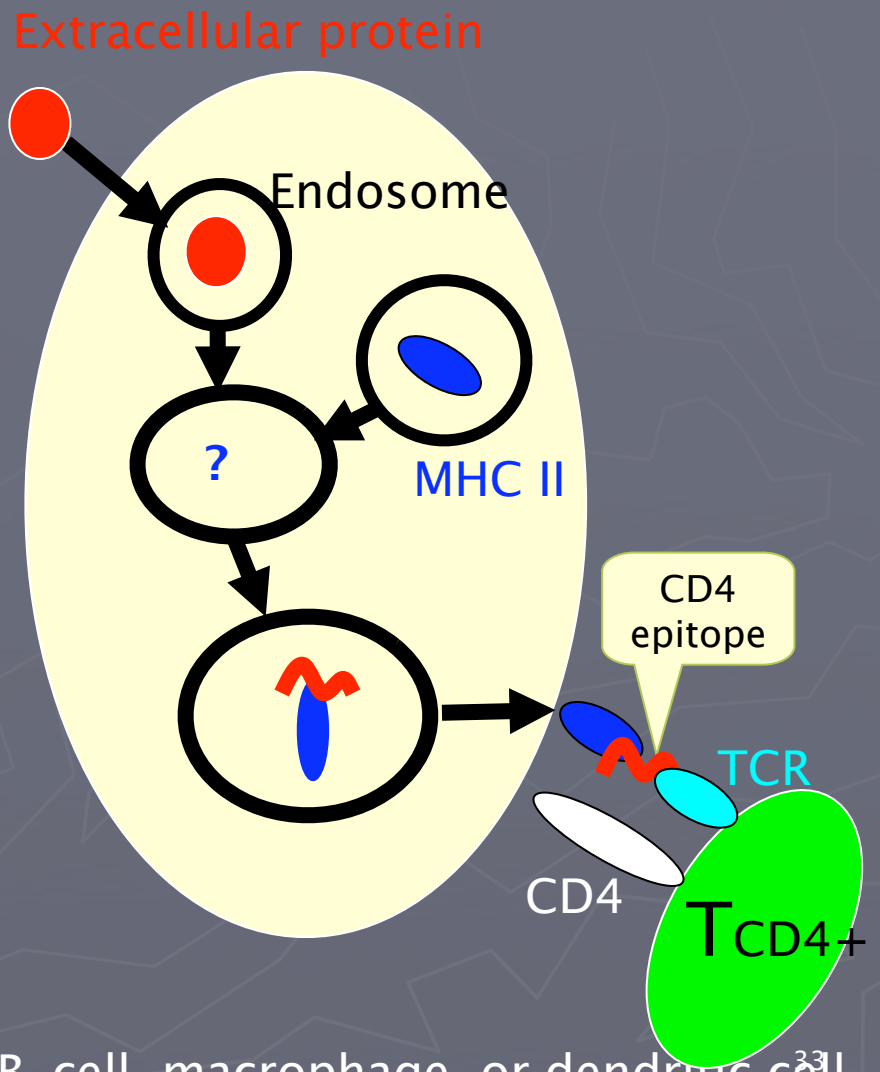
- MHC class II genes are as highly polymorphic as MHC class I (1,012 human alleles for today).
- The repertoire of T-cell receptors is ~10^7 and depends on an individual's immunological status (vaccinations, disease history, environment, etc.).
- The epitope length 9-37 aa.
- The peptide may have non-linear conformation.
- The MHC binding groove is open from both sides and it is known that residues outside the groove effect peptide binding.

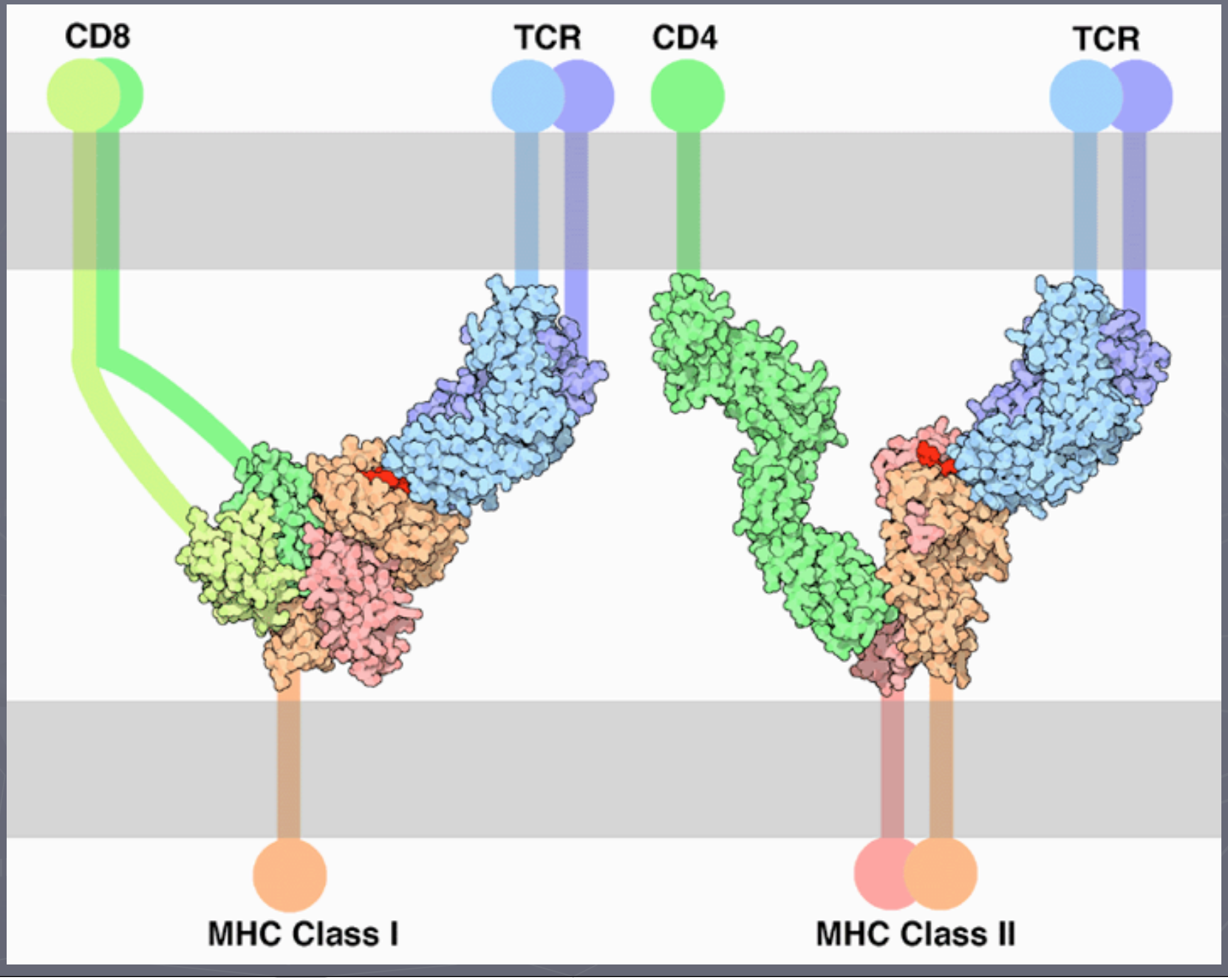
Complex Of A Human TCR, Influenza HA Antigen Peptide (PKYVKQNTLKLAT) and MHC Class II



MHC class II epitope prediction: Challenges

- The processing of MHC class II epitopes is still a mystery and likely depends on the antigen structure, the cell type and other factors.




CD8
TCR
CD4
TCR
MHC Class I
MHC Class II

Prediction of MHC class II binding peptide – potential epitopes

- MHC allele or allele supertype (similar in sequences alleles bind similar peptides) specific.
- Predictions for peptides of length 9 aa (the peptide–MHC binding core)
- Sequence-based approaches:
  - Gibbs sampling
  - Sequence motifs, position weight matrices
  - Machine learning: SVM, HMM, evolutionary algorithms

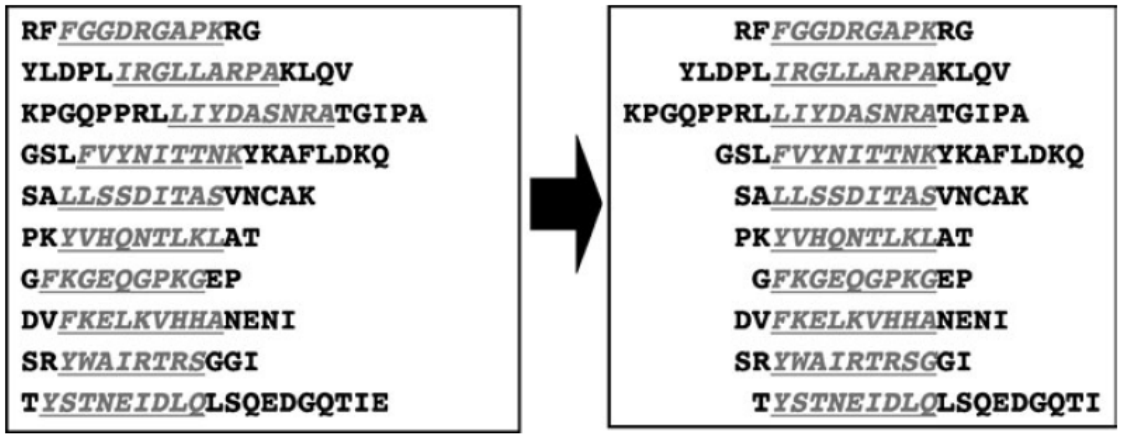


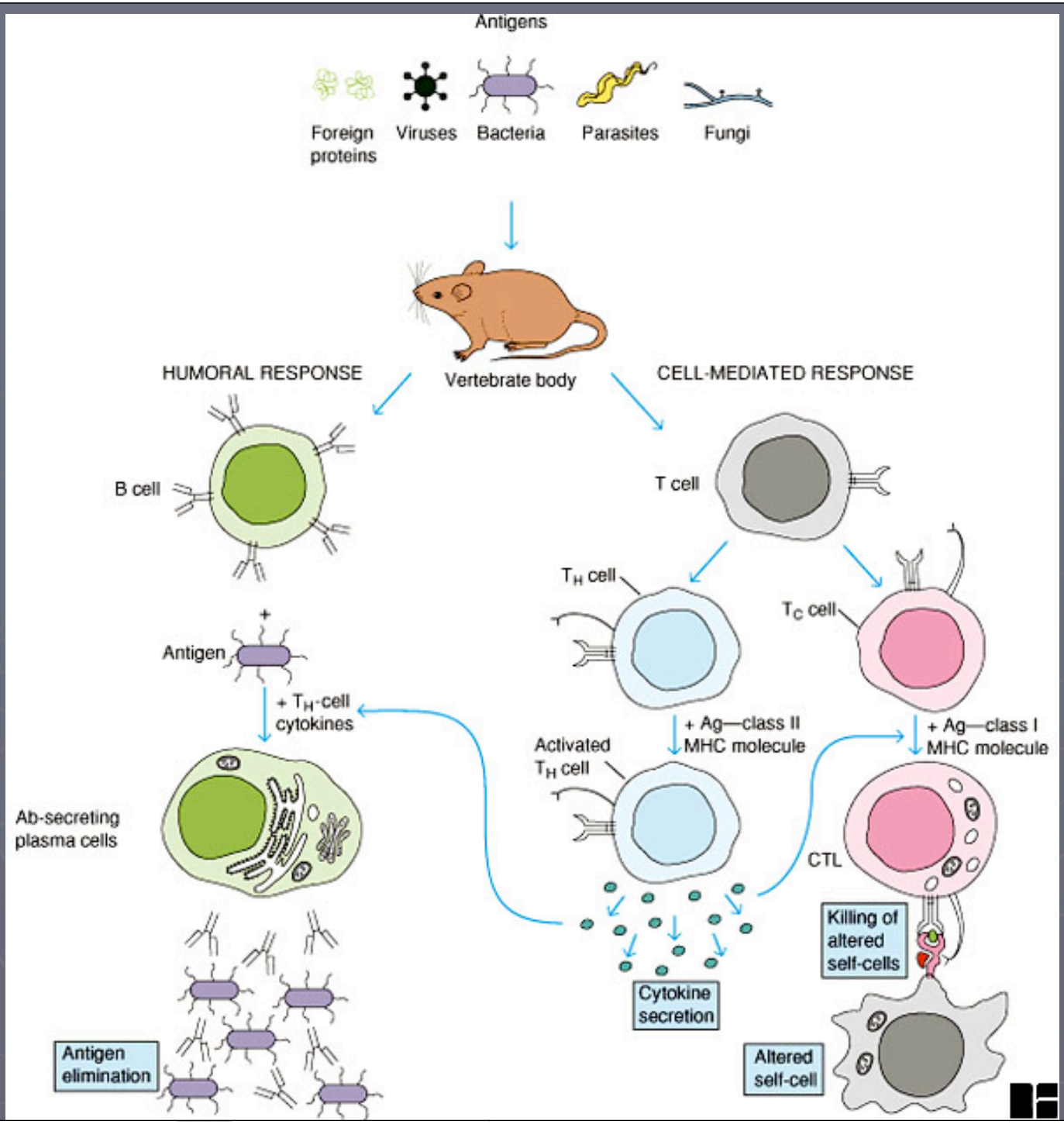
Fig. 5. An alignment generated by the Gibbs sampler for the DR4(B1*0401) binding motif. In the left panel are shown the unaligned sequences, and in the right panel the aligned sequences. The core motif is shown underlined and in italic.

Nielsen et al., Bioinformatics 2004

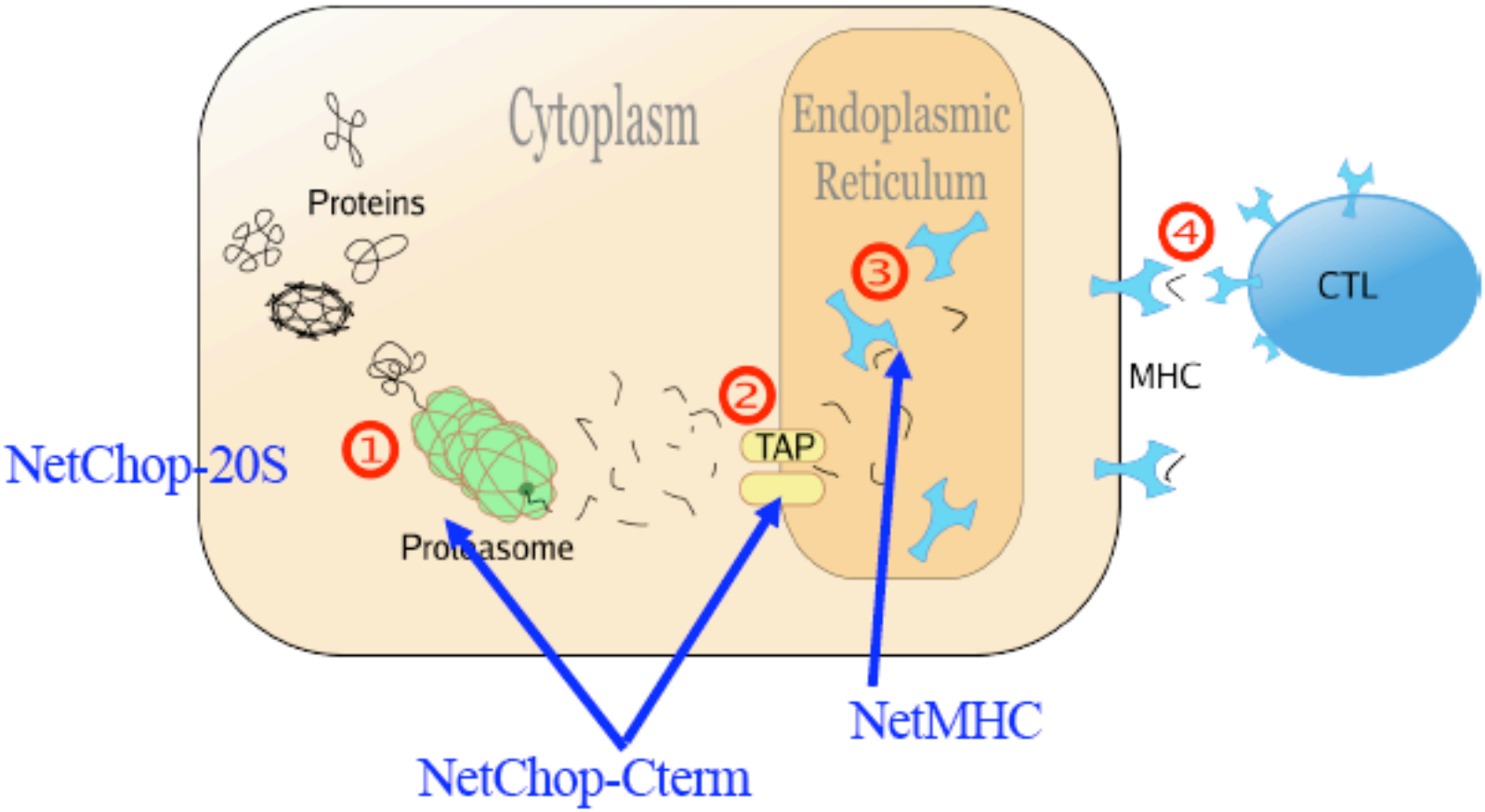
Benchmarking predictions of peptide binding to MHC II

(Wang et al. PLoS Comput Biol. 2007)

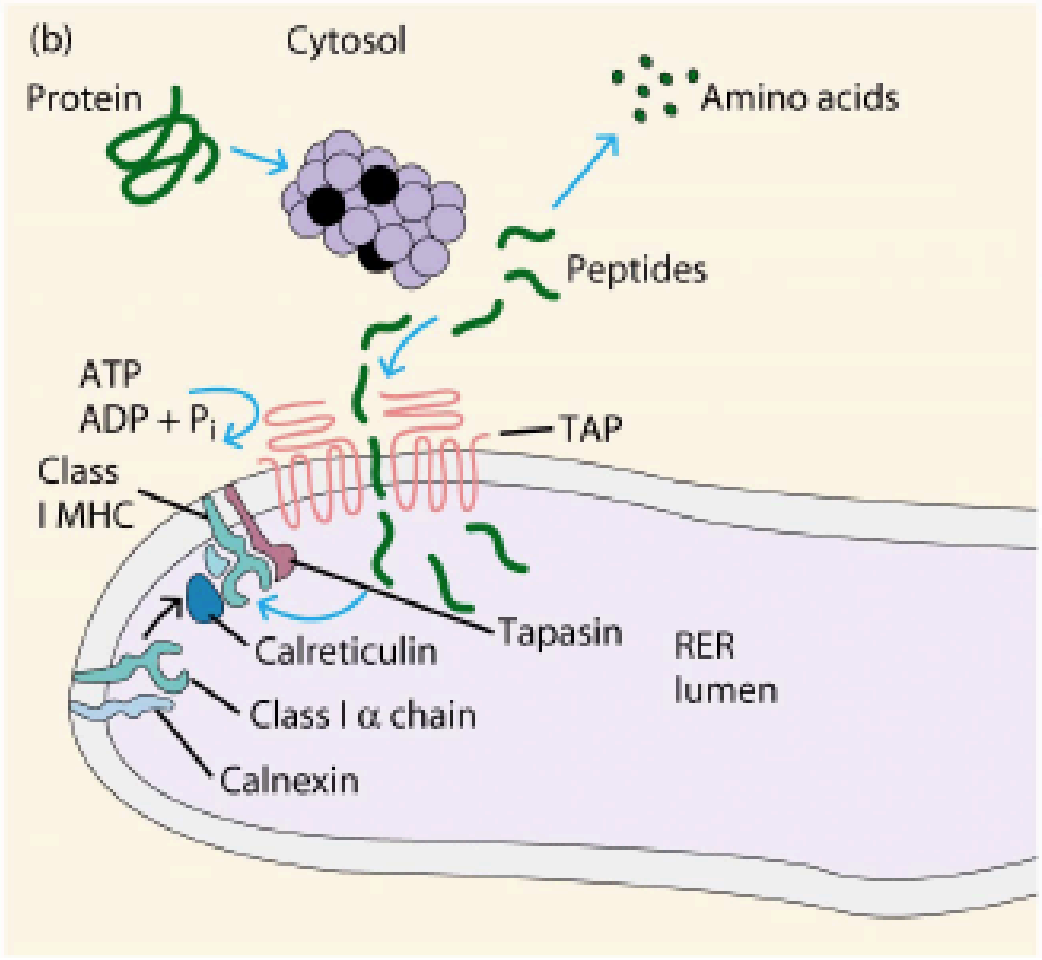
- Data: pairs {peptide – affinity value in terms of IC_{50} nM} for a given MHC allele
- 16 different mouse and human MHC class II alleles.
- 10,017 data points.
- 9 different methods were evaluated: 6 matrix-based, 2 SVM, 1 QSAR-based.
- AUC values varied from 0.5 (random prediction) to 0.83, depending on the allele.
- Comparison with 29 X-ray structures of peptide-MHC II complexes (14 different alleles):
  - The success level of the binding core recognition was 21%-62%,
  - with exception of TEPETOPE method (100%) that is based on structural information and measured affinity values for mutant variants of MHC class II and peptides (Sturniolo et al., Nature Biotechnology, 1999).
- => Structural information together with peptide-MHC binding data should improve the prediction.


Antigens
Foreign proteins
Viruses
Bacteria
Parasites
Fungi
Vertebrate body
HUMORAL RESPONSE
CELL-MEDIATED RESPONSE
B cell
T cell
T_H cell
T_C cell
Antigen
+ T_H-cell cytokines
+ Ag—class II MHC molecule
+ Ag—class I MHC molecule
Activated T_H cell
Ab-secreting plasma cells
CTL
Killing of altered self-cells
Cytokine secretion
Antigen elimination
Altered self-cell

Antigen Processing and Presentation: CBS tools



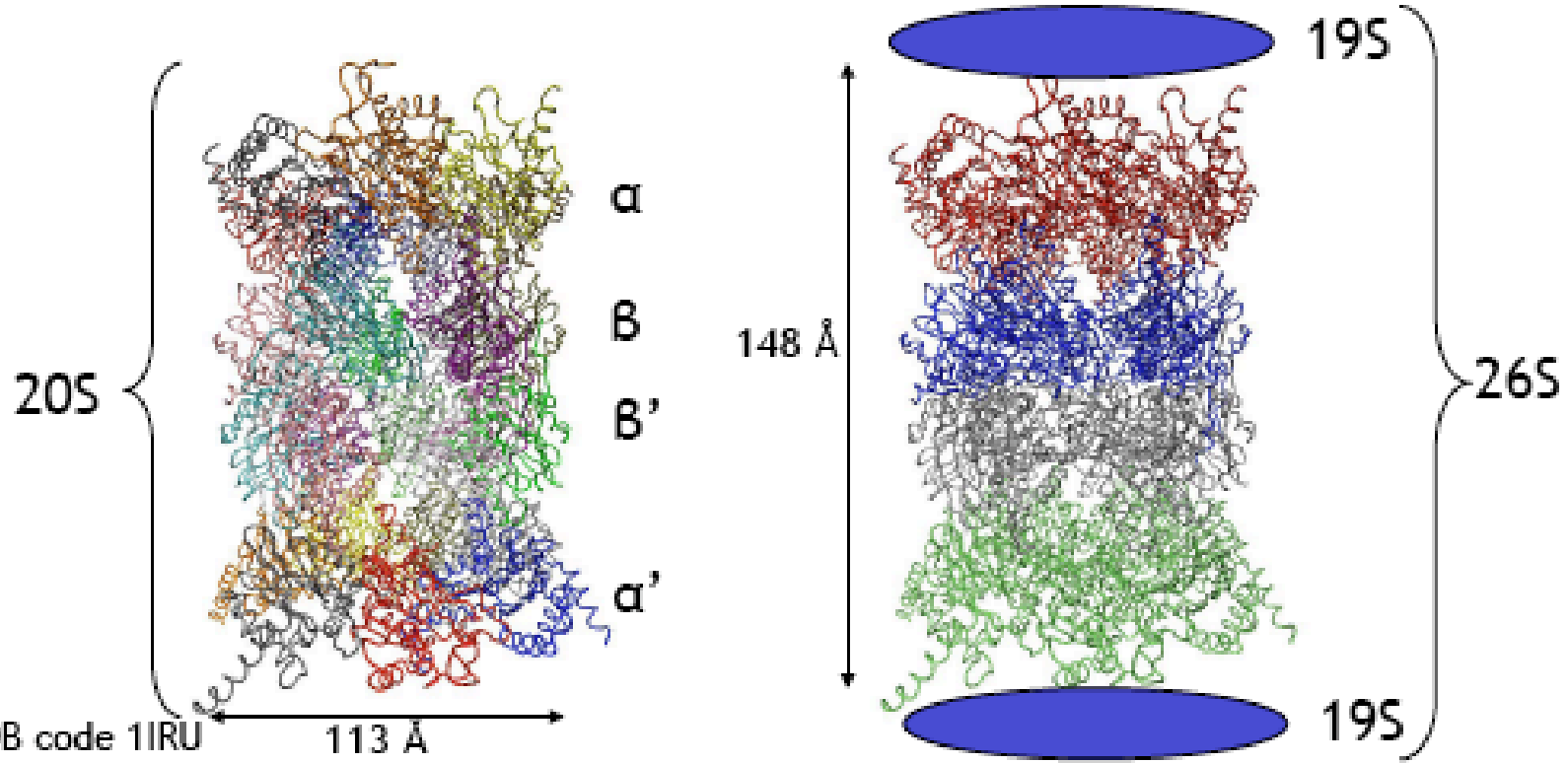
Class I Ag Processing



The Proteasome

Eberhard Karls
Universität
Tübingen

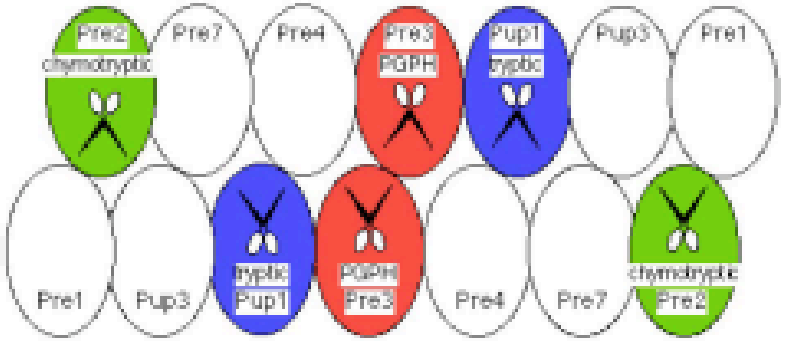
- 20S proteasome consists of four rings of protein subunits with a central channel



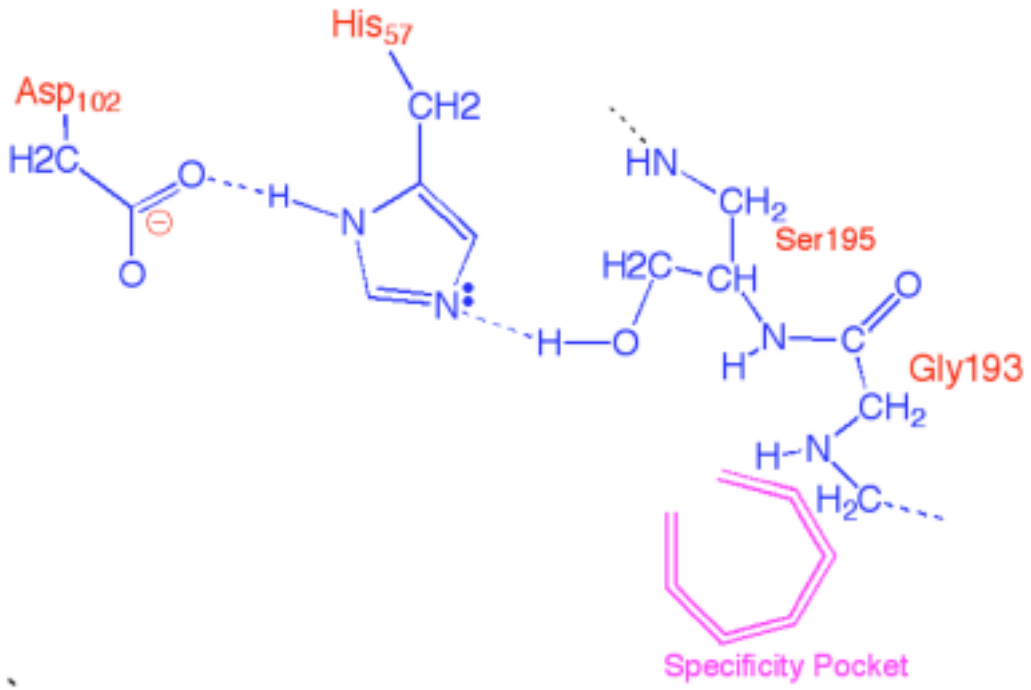
The 20S Proteasome - Cleavage Sites

- There is a total of six major catalytic sites in the proteasome, described as:
  - Trypsin-like (Arg, Lys)
  - Chymotrypsin-like (Phe, Tyr, Trp)
  - Peptidylglutamyl-peptide hydrolyzing (PGPH) (Asp, Glu)

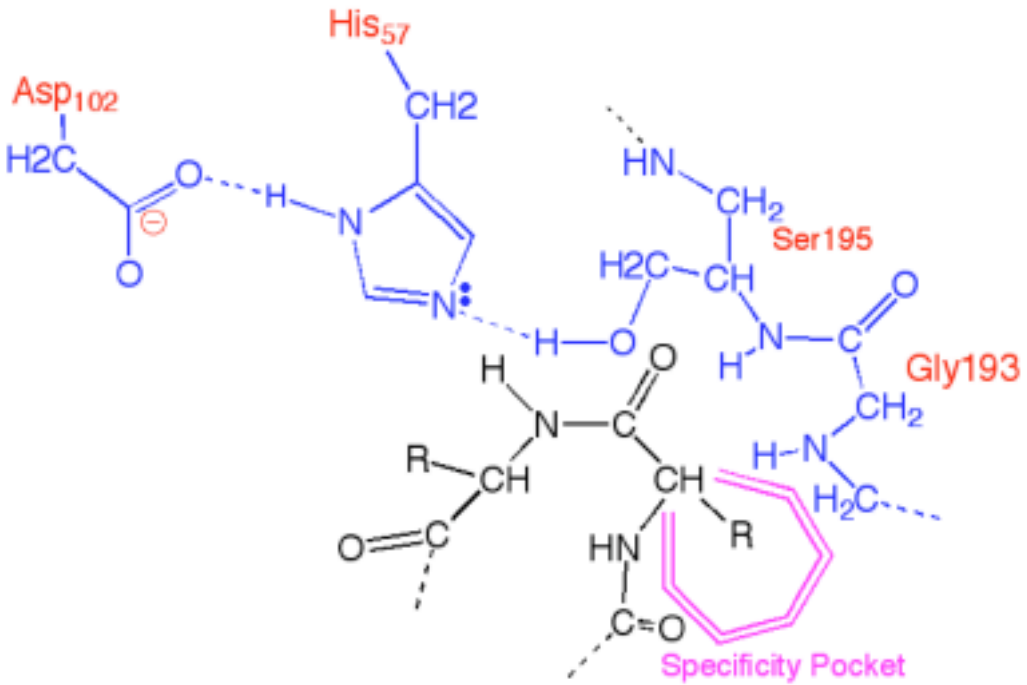
The active sites of the yeast 20S proteasome



Serine Protease Mechanism

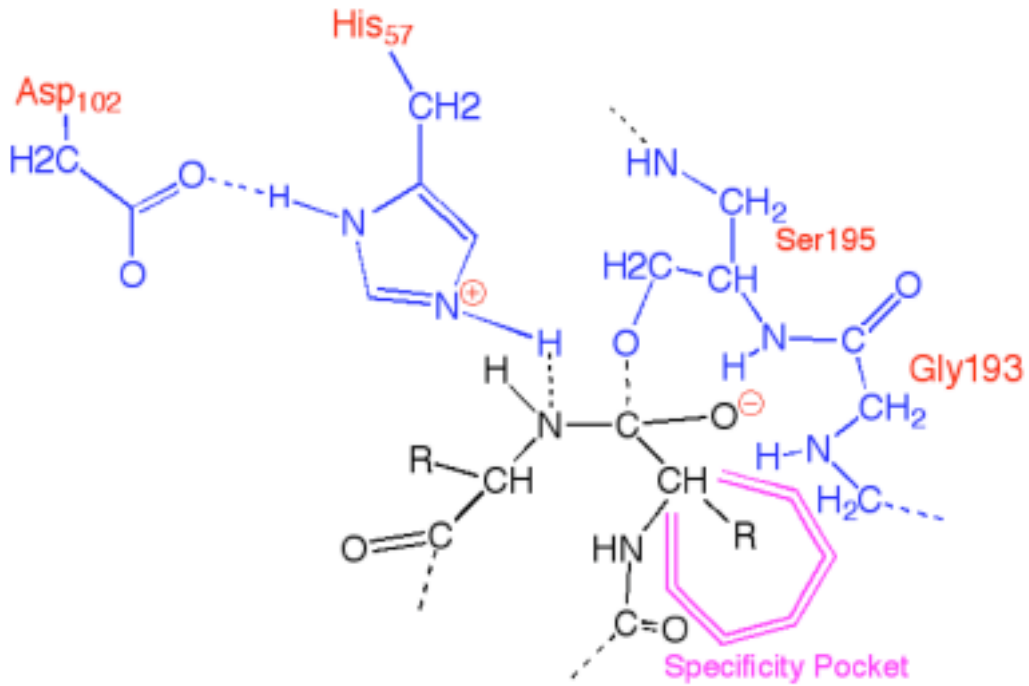


Serine Protease Mechanism



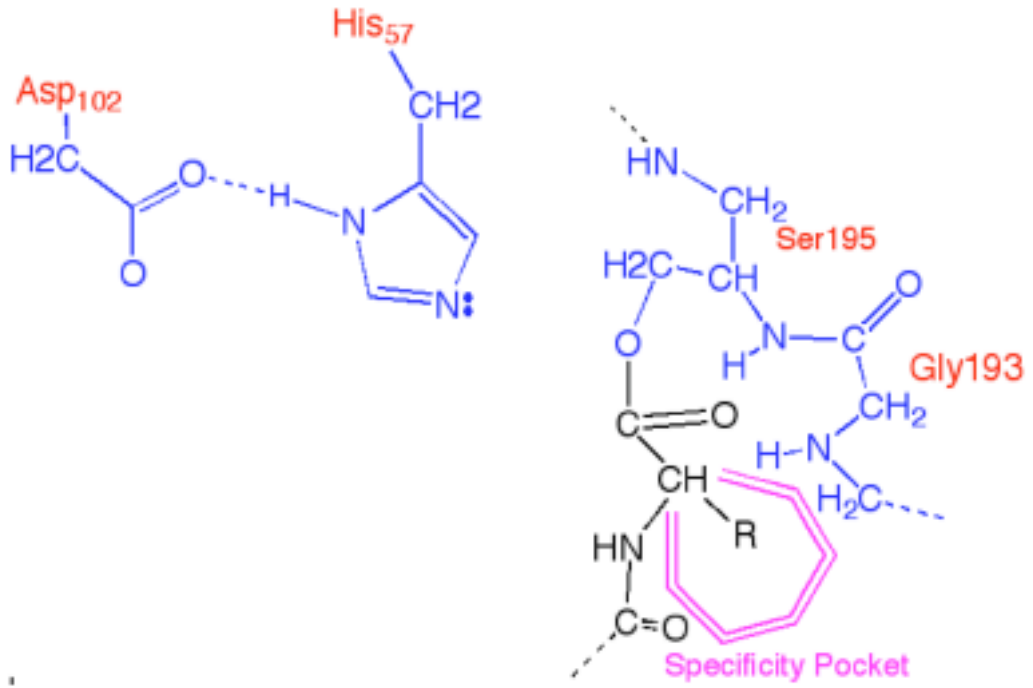
There is a nucleophilic attack of the O from a Ser on the carbonyl C of the peptide bond to be broken.

Serine Protease Mechanism



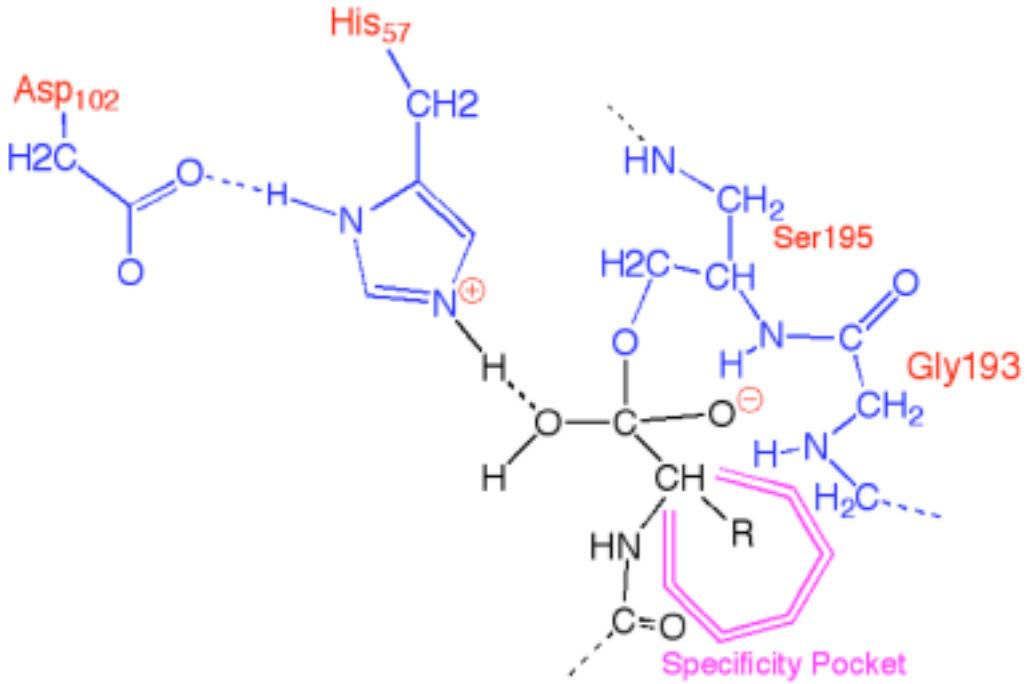
The oxyanion intermediate state.

Serine Protease Mechanism



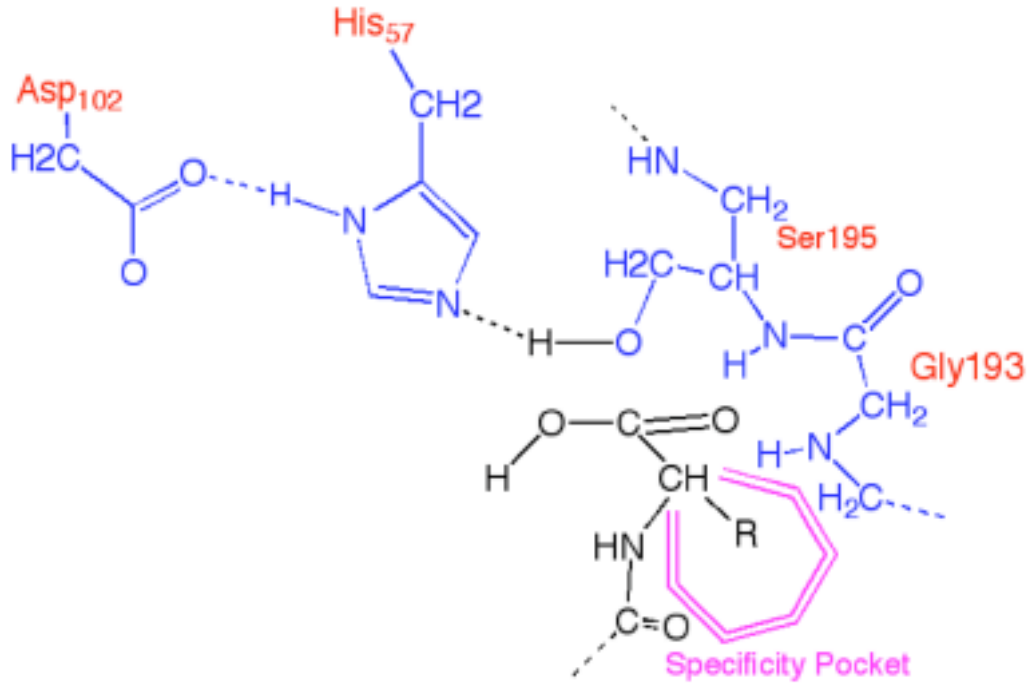
The amine product leaves the complex and we have an acyl-enzyme (ester) intermediate.

Serine Protease Mechanism



Water joins the game and another oxyanion intermediate state is formed.

Serine Protease Mechanism



The peptide bond is cleaved and the enzyme is restored to its initial state.

Determination of Cleavage Sites

- Experimental identification of proteasomal cleavage sites entails the following steps:
  - Purification of proteasomes
  - Isolation of a protein to be cleaved
  - Degradation experiment - incubation of the protein to be cleaved with proteasomes
  - Separation and analysis of cleavage products
- All published reports on whole protein digestion experiments involve people from Tübingen

Analysis of Cleavage Products

- HPLC is used to separate the cleavage products
- MS can be used to identify peptide fragments and **Edman degradation** to quantify the amounts of a certain cleavage product/peptide
- Identified cleavage products can then be mapped back onto the protein sequence to determine the actual cleavage patters

Determination of Cleavage Sites

- Tenzer *et al*. determined the cleavage pattern for both the constitutive(c20S) and the immuno-proteasome(i20S) on a prion protein (210 aa)
- For the c20S (i20S) they identified 104 (113) different cleavage fragments with an average length of 20.2 (17.5) aa
- They observed different cleavage patterns for the two proteasome types

ZBIT

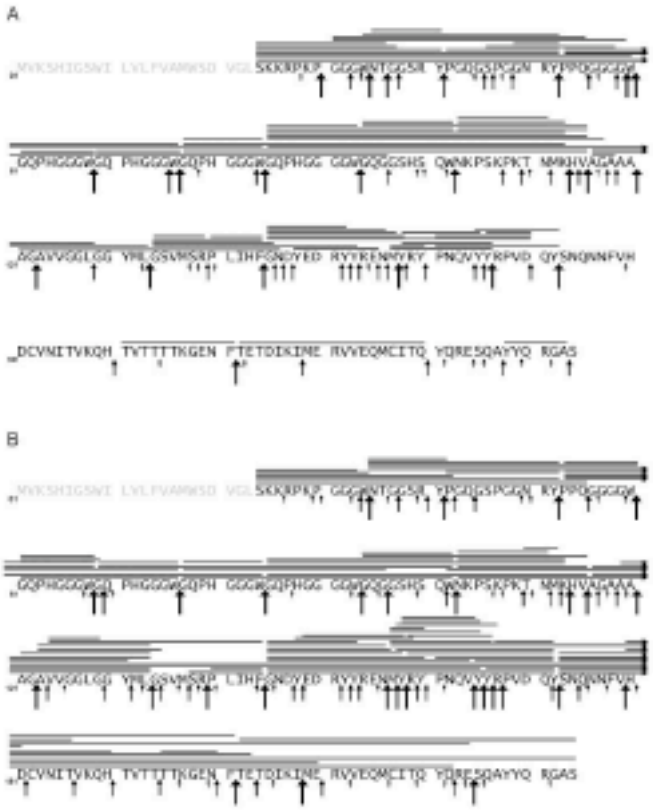
Tenzer *et al*, Quantitative analysis of prion-protein degradation by constitutive and immuno-20S proteasomes indicates differences correlated with disease susceptibility, 2004, Journal of Immunology ,172: 1083-1091

Prion Protein Cleavages

Eberhard Karls Universität Tübingen

c20S

i20S



ZBT

Tenzer *et al*, Quantitative analysis of prion-protein degradation by constitutive and immuno-20S proteasomes indicates differences correlated with disease susceptibility, 2004, Journal of Immunology, 172: 1083-1091

Prion Protein Cleavages by i20S

Tenzer *et al*, Quantitative analysis of prion-protein degradation by constitutive and immuno-20S proteasomes indicates differences correlated with disease susceptibility, 2004, Journal of Immunology, 172: 1083-1091

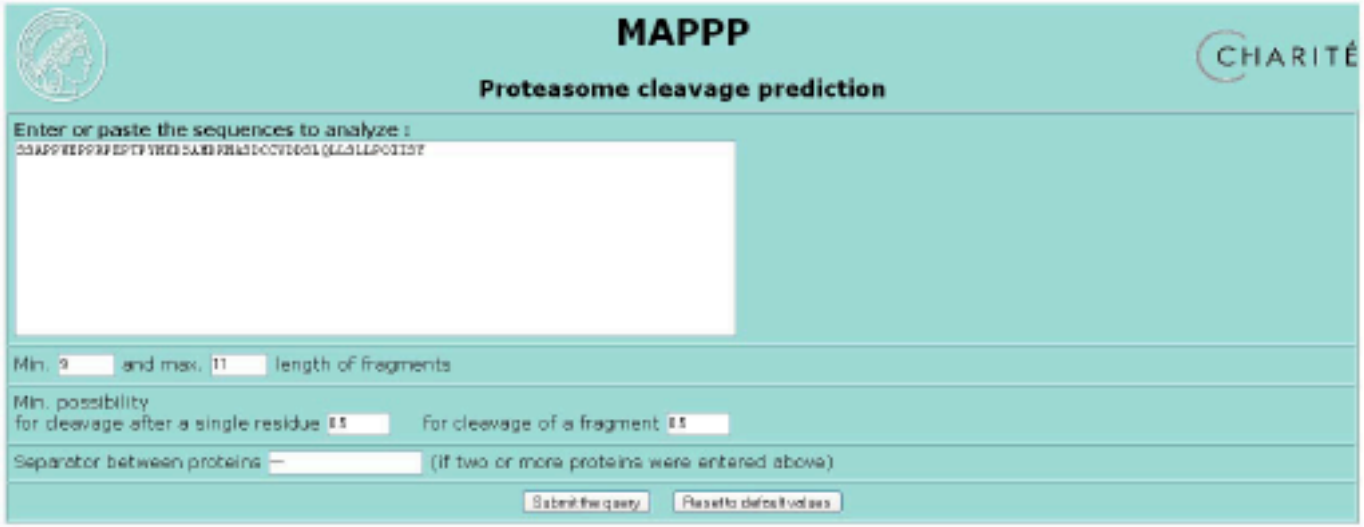
Prediction of Proteasomal Cleavage

- There is a number of methods for cleavage prediction available at the moment (standard methods, all of them)
- Key problem:

  scarcity of data available
- Some of the benchmarking procedures used are not state of the art
- Method performances are not as good as one would hope

MAPPP Cleavage Prediction

Eberhard Karls Universität Tübingen



MAPPP

Proteasome cleavage prediction

CHARITÉ

Enter or paste the sequences to analyze :

Min. 9 and max. 11 length of fragments

Min. possibility
for cleavage after a single residue 0.5 For cleavage of a fragment 0.5

Separator between proteins — (if two or more proteins were entered above)

Submit the query | Reset to default values

Comments on the output :

Sequence and fragments
The sequence and its predicted peptide fragments can be found at the bottom of the page.
- For every single residue with a cleavage probability higher than the specified minimum, the value of the probability is shown by moving the mouse pointer over the residue. It is represented as a (non-functional) WWW-link.
- Directly beneath the residues one can find the number of peptide fragments a single residue takes places in.
- The stair beneath the sequence represents the fragments with a cleavage probability higher than the specified minimum and its places within the sequence.

Example
Example output for the default values with p60

Based on FRAGPREDICT developed by H.-G. Holzhütter et. al.

ZBIT

http://www.mpiib-berlin.mpg.de/MAPPP/cleavage.html

MAPPP Cleavage Prediction

Eberhard Karls Universität Tübingen

Query results

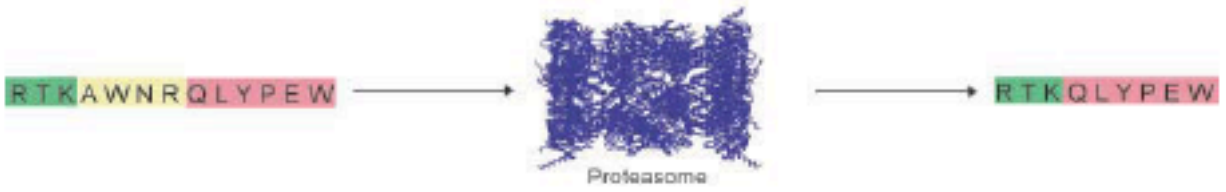
Parameters	
Length of sequence	47
Range for length of peptide fragments	9..11
Min. probability for cleavage after a single residue	0.5
Min. probability for cleavage of a fragment	0.5

Prediction results	
No. of possible fragments	17
Total no. of fragments	111
Percentage (fragments / total fragments)	15.31%
Highest fragment cleavage probability (at pos. 0@1)	1
Highest residue cleavage probability (at pos. 2@1)	0.9562

```
SSAPPWEPPRPEPTPYMKDSAMDKMASDCCVDDSLQLLSLLPIISY
111111 1111111124666557111877777643223333222222
                     000
SSAPPWEPP(1)
          RPEPTPYMKD(0.9463)
               PYMKDSAMDKM(1)
                 YMKDSAMDKM(0.9224)
                 YMKDSAMDKMA(0.5519)
                  MKDSAMDKM(0.6257)
                  MKDSAMDKMA(0.5489)
                        MDKMASDCCV(0.5714)
                        MDKMASDCCVD(0.9991)
                          DKMASDCCV(0.5364)
                          DKMASDCCVD(0.9999)
                          DKMASDCCVDD(0.9999)
                              ASDCCVDDS(0.5015)
                                SDCCVDDSLQL(1)
                                      DDSLQLLSL(0.6041)
                                            LLSLLPIISY(1)
```

Proteasomal Splicing

- Two papers published in 2004 put an extra twist in the tale
- Hanada *et al.* found a peptide that was generated from two non-contiguous parts of its source proteins
- Vigneron *et al.* even proved that a specific peptide could be produced from longer fragments by means of proteasomal splicing



Hanada *et al.*, Immune recognition of a human renal antigen through post-translational protein splicing, 2004, Nature, 427:252-256
Vigneron *et al.*, An antigenic peptide produced by peptide splicing in the proteasome, 2004, Science, 304:587-590

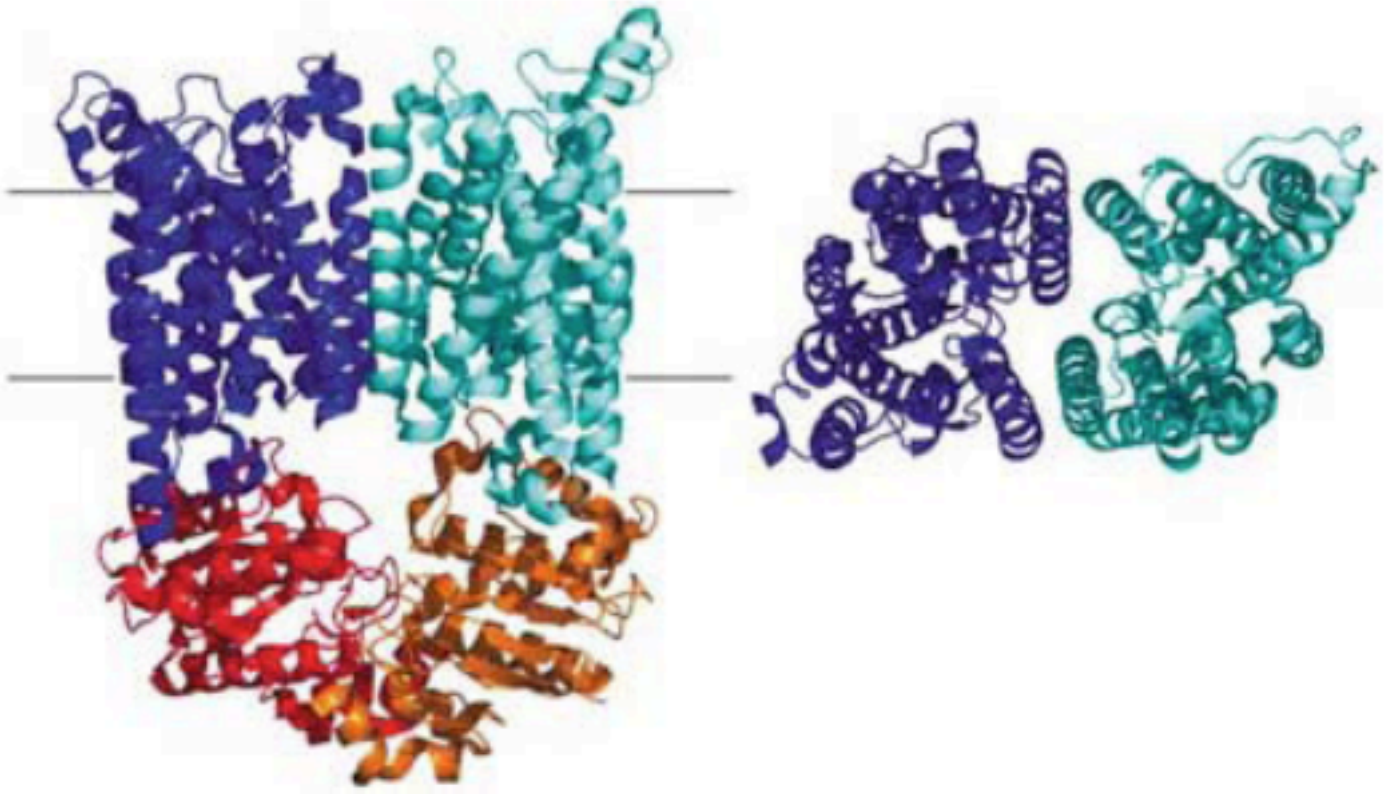
TAP

- TAP - the transporter associated with antigen processing
- TAP transports the peptides created by the proteasome into the ER
- TAP is an active transporter and requires energy to transport the peptides
- This energy is provided by ATP
  - ATP is the main energy "currency" in a cell
  - ATP is cleaved into ADP and P_i
  - Breaking the bond provides significant energy, which can be used for transport

ABC Transporters

- TAP is member of the ABC transporter family (ABC = ATP binding cassette)
- ABC transporters have a wide range of roles: from transport of vitamins, over drug-resistance transporters, to their role in Ag processing
- ABC transporters contain
  - Transmembrane domains (TMDs)
  - Nucleotide-binding domains (NBDs)
- ABC transporters are usually dimeric, either
  - Homodimers: $(TMD\text{-}NBD)_2$
  - Heterodimers: $TMD^A\text{-}NBD^A{:}TMD^B\text{-}NBD^B$
- TAP is a heterodimer formed by TAP1 and TAP2 chains

Structure of Vitamin B_{12} Transporter

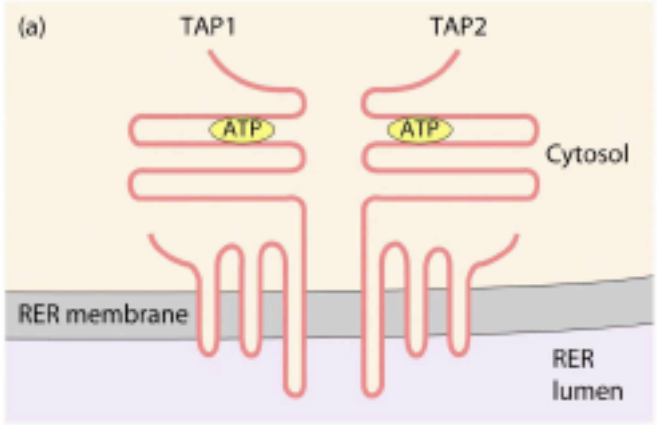


ZBIT

PDB: 1L7V
Beismann-Driemeyer, Angew. Chem. Int Ed. (2004), 43, 4014

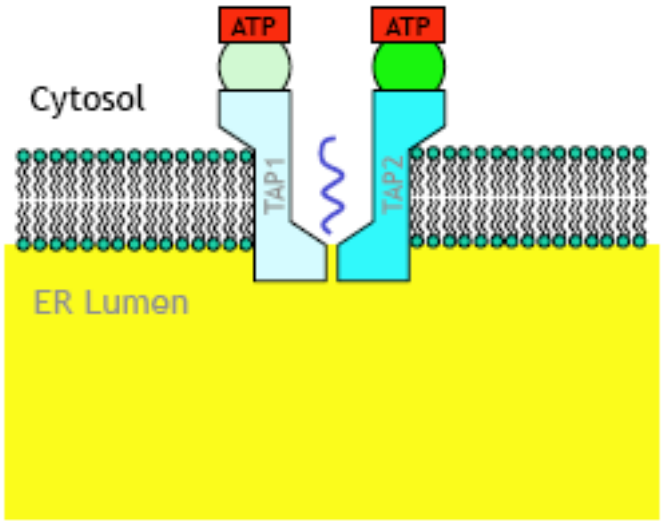
TAP Structure

- Known details of the architecture
  - NBD pointing into cytosol
  - TMDs possess probably eight (TAP1) resp. seven (TAP2) transmembrane segments
  - NBD structure known
  - Dimerzation of TAP1,2 NBDs probably required for ATP cleavage
  - Interface between TMDs is responsible for peptide binding



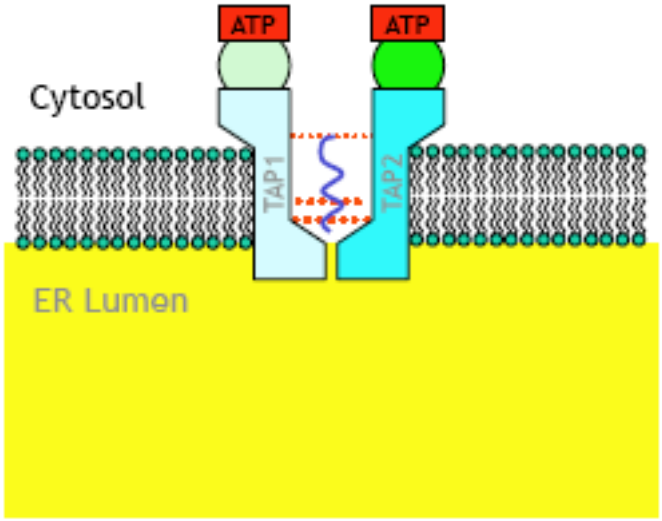
Vos et al., J. Immunol. (1999), 159, 554

TAP in Action



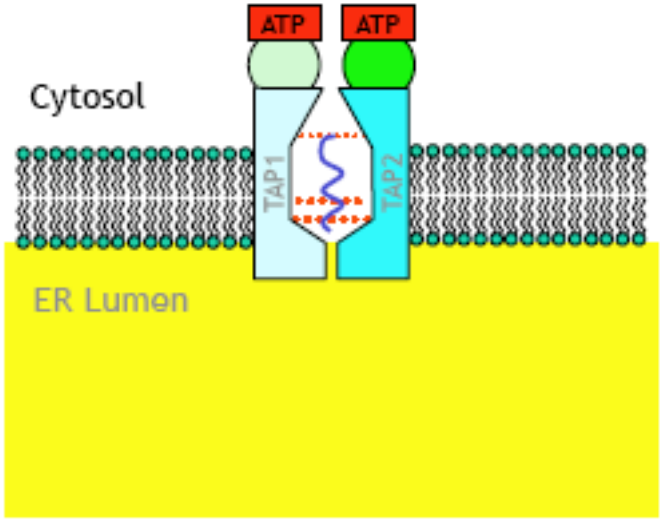
TAP in Action

- ATP is required for transport, not for binding
- Both subunits are involved in binding

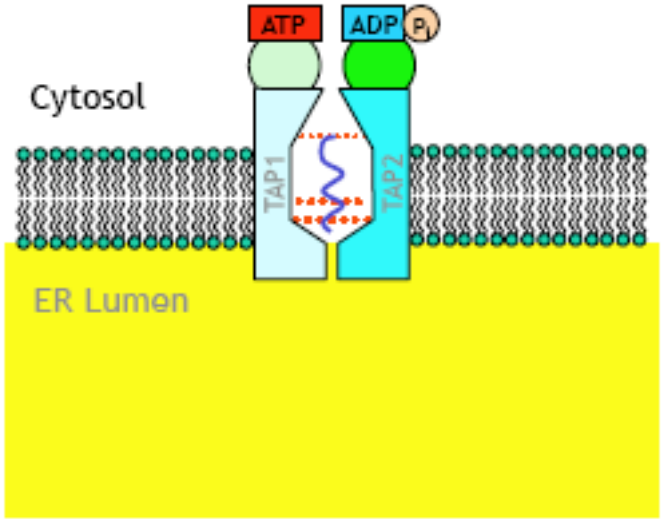


TAP in Action

- C & N terminus crucial for binding specificity
- Peptide binding induces ATP cleavage

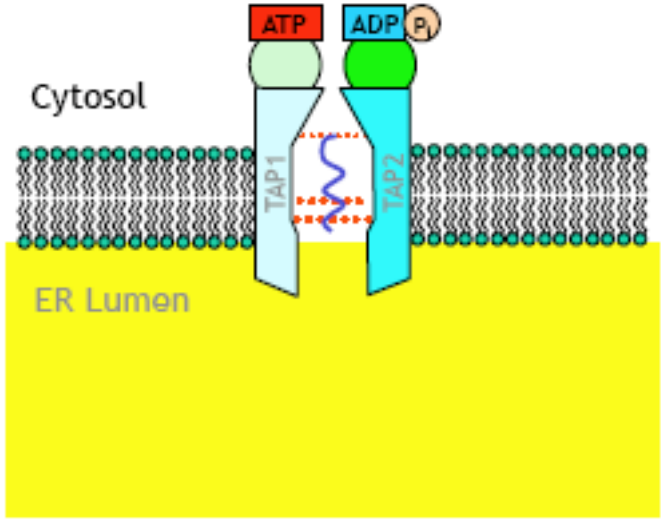


TAP in Action

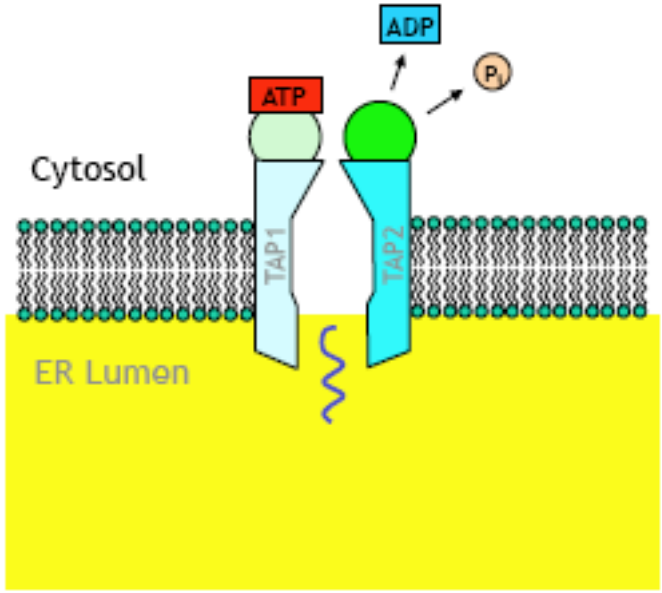


TAP in Action

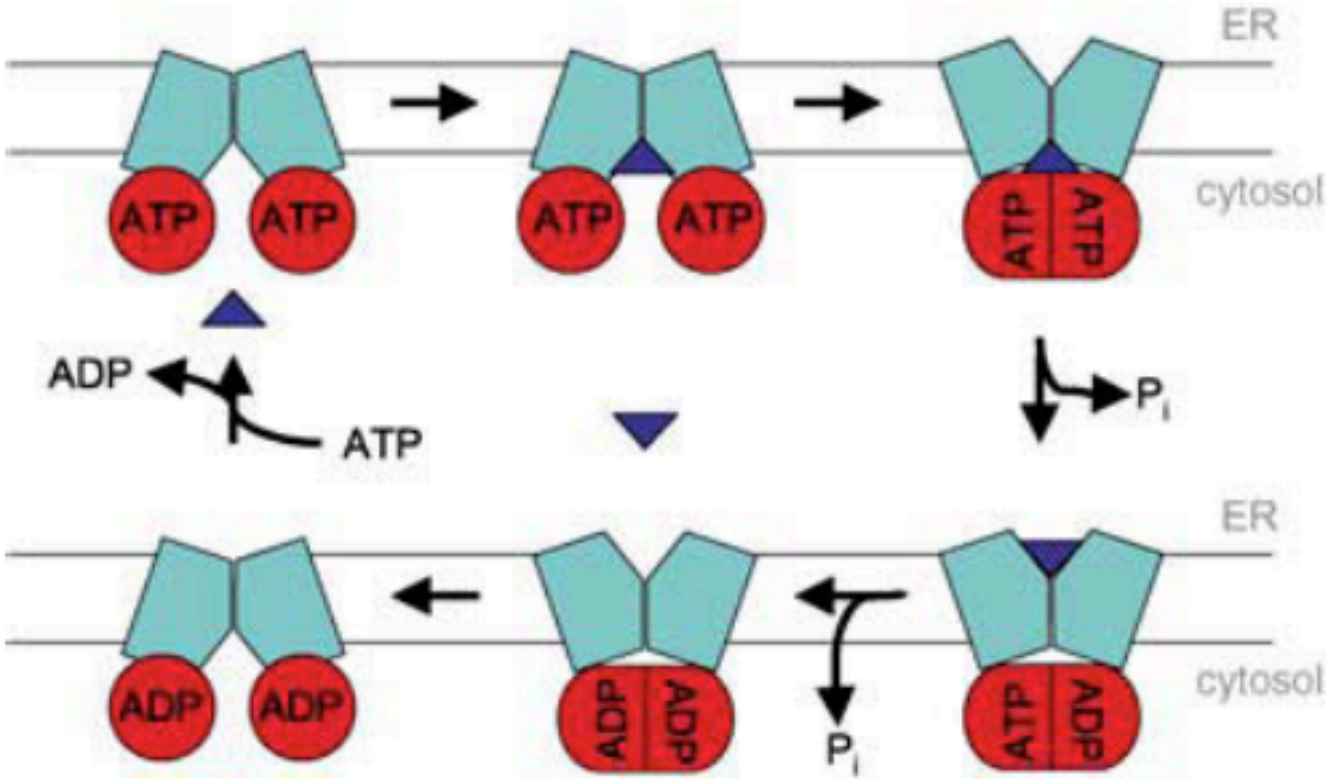
- ATP cleavage liberates peptide
- Exact order of events uncertain



TAP in Action



Mechanistic Details



TAP and Immune Evasion

- TAP is also a target for immune evasion for some viruses
- Inhibiting TAP or reducing its expression seriously affects Ag presentation and thus avoids detection of the virus infected cell
- Example:
  - Adenoviruses possess a protein (E3/19K) binding to - and thus inactivating - TAP
  - Eppstein-Barr Virus (EBV) expresses LMP-1, which in turn induces expression of TAP2 while down-regulating TAP1

    ⇒ disequilibrium leads to few active TAP1/2 complexes

Affinity vs. Transport

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- TAP **transport is difficult to measure**
- Simpler is a measurement of TAP **affinity**:
  - If no ATP is present, no transport is observed
  - Binding to the TAP heterodimer occurs nevertheless
  - Binding affinity was found to be correlated to transport efficiency
  - Binding studies can be done on a larger scale

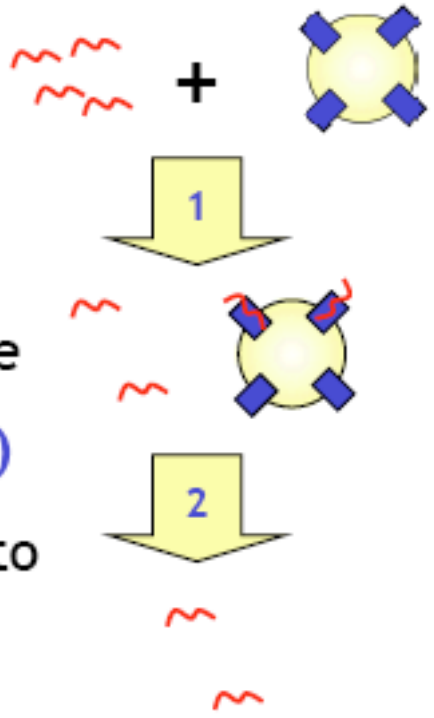
ZBIT

Van Endert et al., Immunity (1994), 1, 491

TAP Specificity: Binding

- Binding assays
  - Radio-labeled peptides
  - TAP-overexpressed microsomes
  - ATP depletion, low temperature

    ⇒ no transport, but **binding (1)**
  - **Centrifugation (2)**, γ counting to determine concentration of unbound peptide



Proteasome, TAP & MHC

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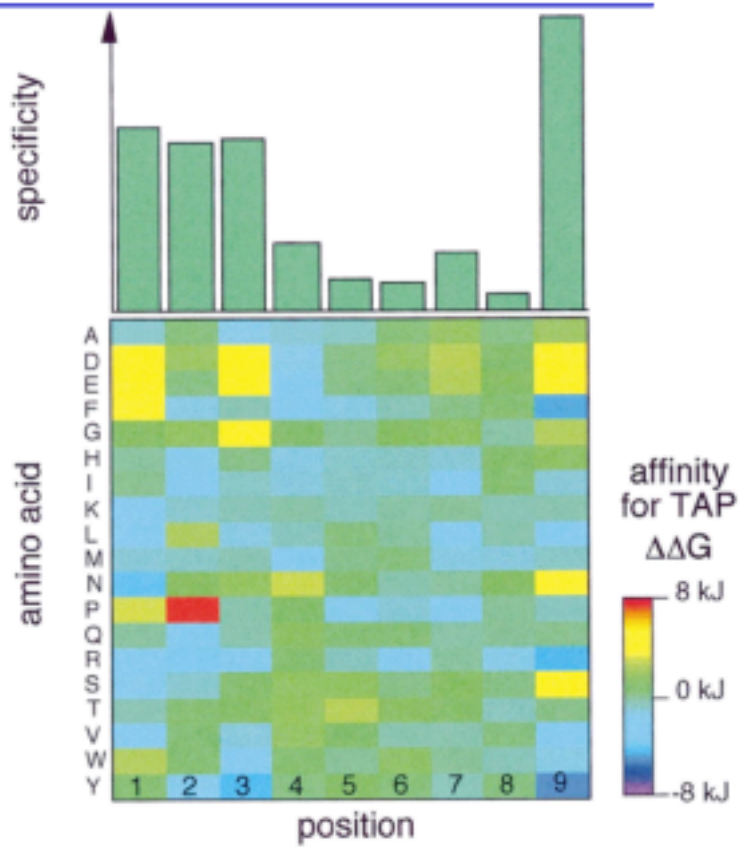
- Length distributions of peptides created by proteasome, transported by TAP, and bound by MHC overlap significantly
- Length preferences of proteasome and TAP create and transport the full range of MHC peptides
- Proteasome
  - 3-22 aa long
- TAP
  - 6-16 aa long
- MHC
  - 8-11 aa long - after cleavage by ER peptidases

ZBIT

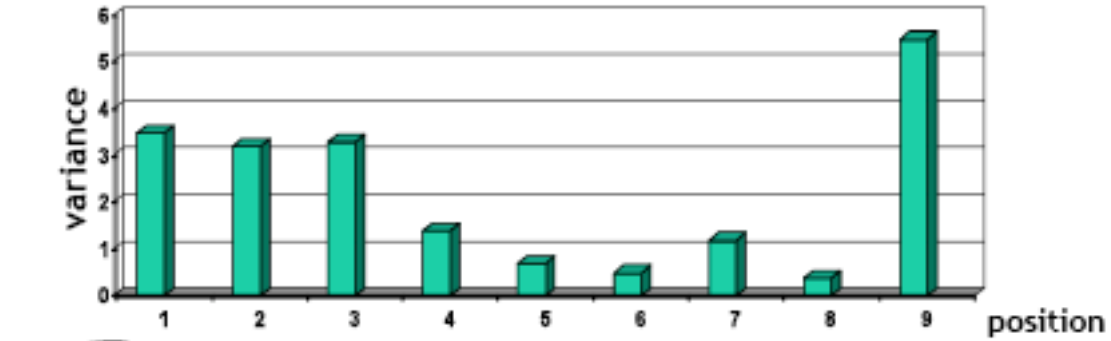
TAP Specificity

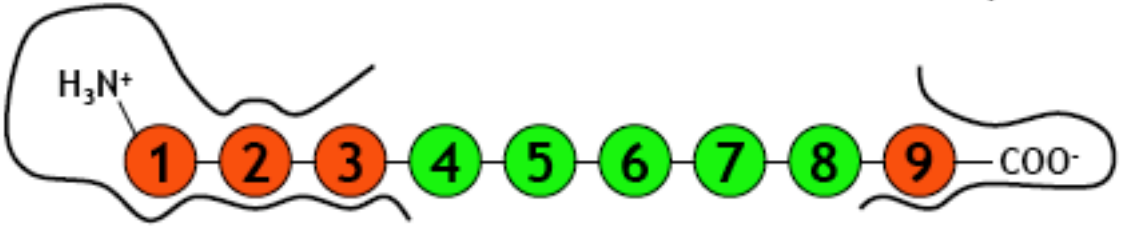
- Specificity is mostly determined by C-terminus (9) and three N-terminal positions (1-3)
- TAP favors peptides with basic, aromatic or hydrophobic C-termini
  - Phe, Tyr, Trp
  - Ile, Leu, Val
  - Arg
- Pro at position 2 is very unfavorable



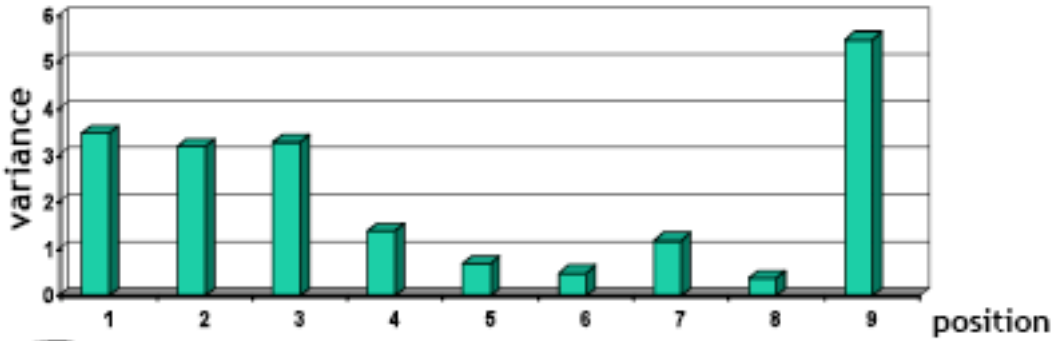
Lankat-Buttgereit, Tampé, Physiol Rev. (2002), 82, 187

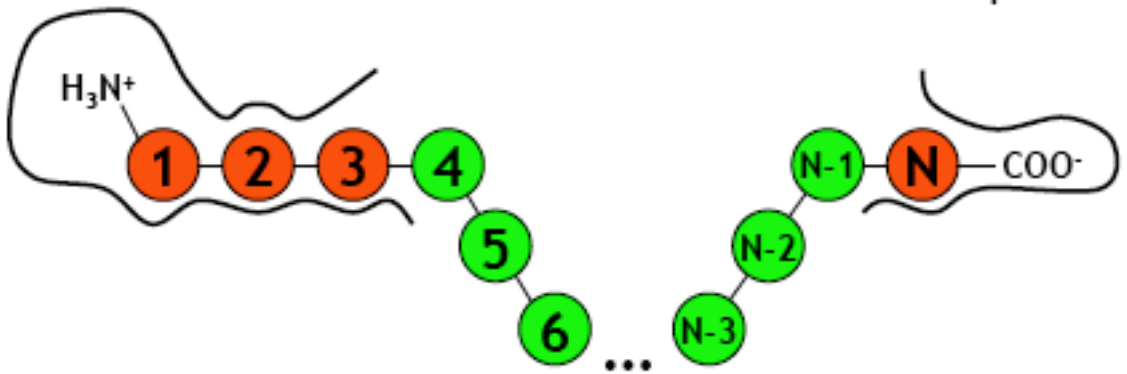
Binding Mode





Binding Mode

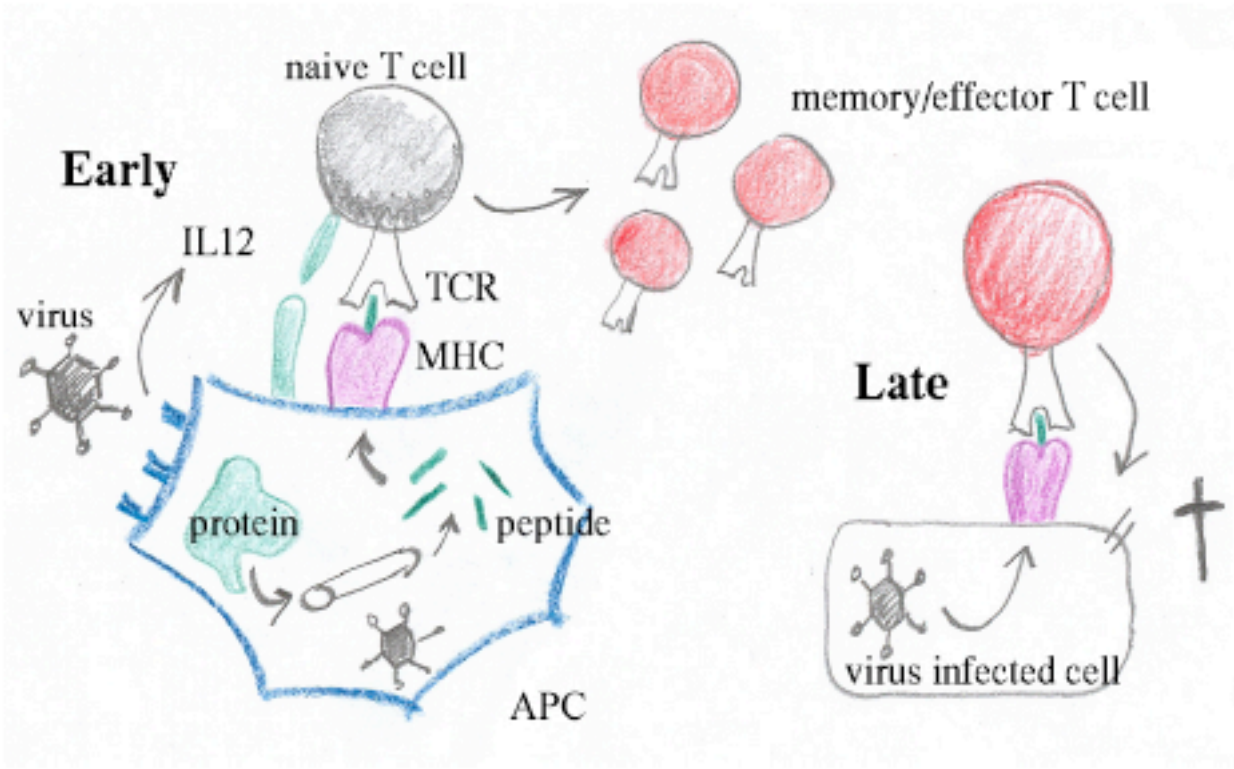




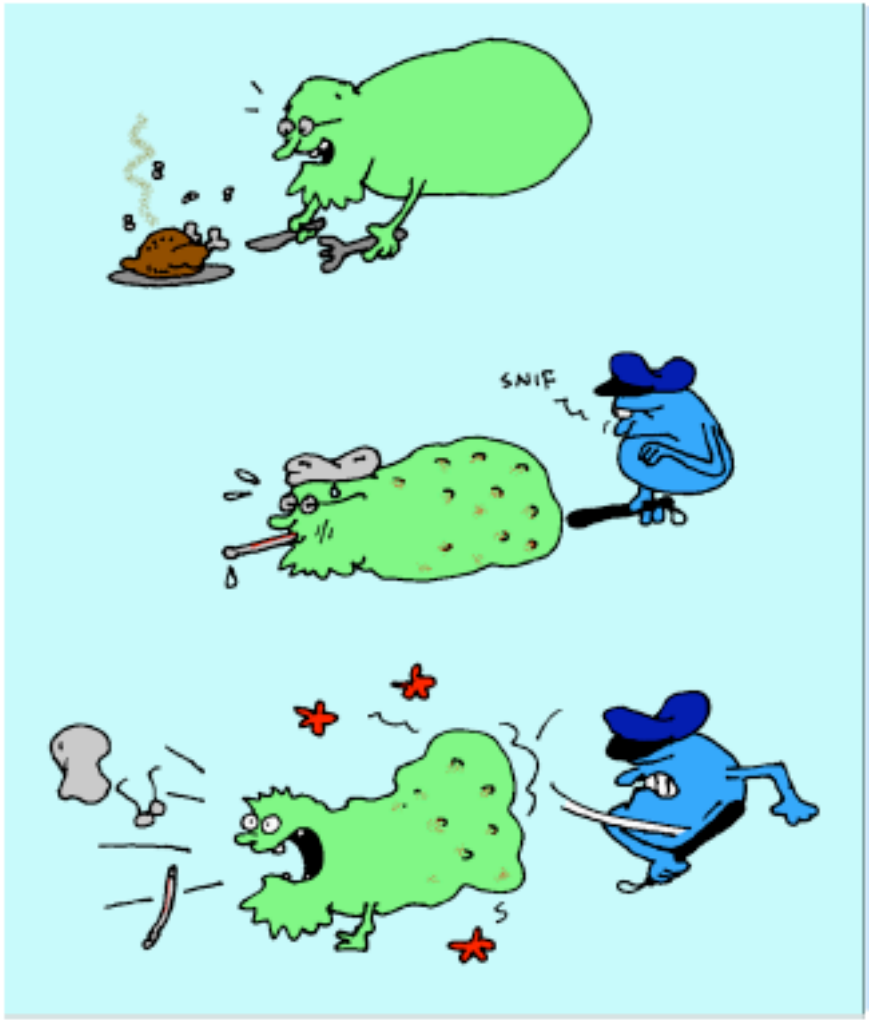
Outstanding problems in TAP/ Proteosome/MHC peptide prediction

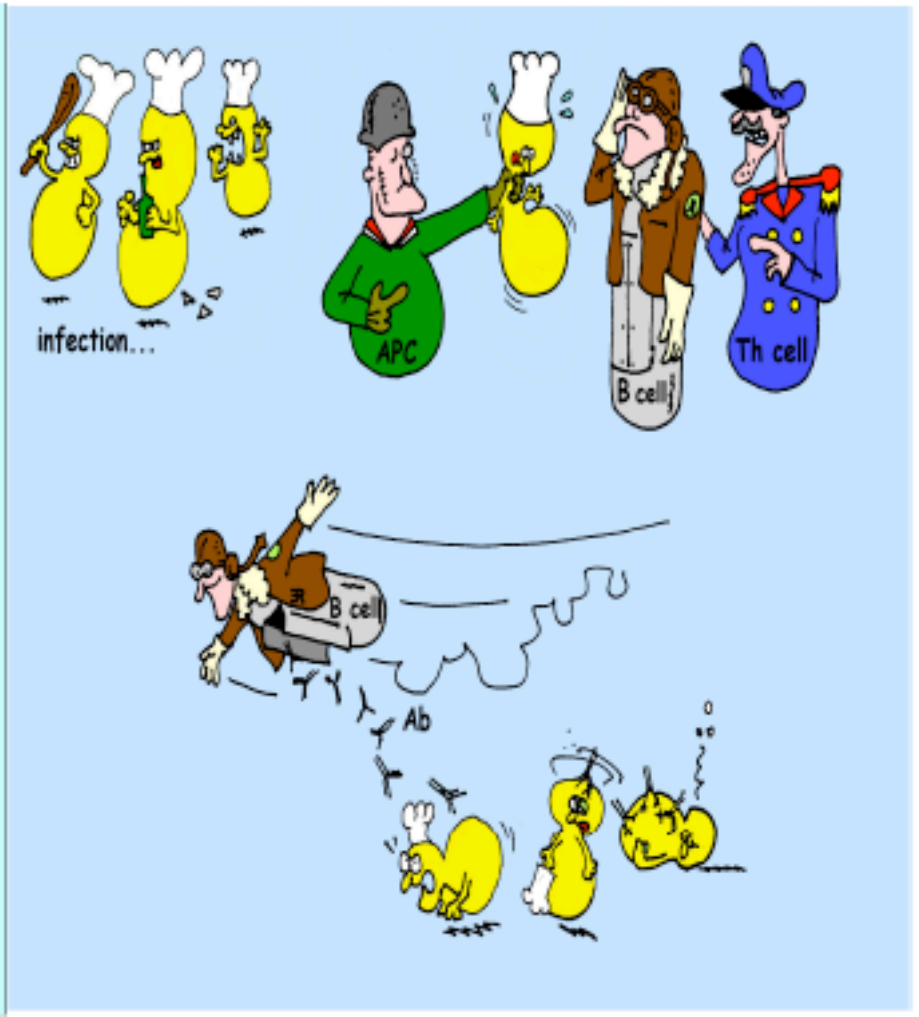
- High throughput data generation
  - Currently few verified peptide sequences.
  - Overfitting likely
- Something better than the usual machine learning approach?
  - Structure-based motifs, length preferences?
  - Combine multiple motifs, reflecting multiple enzymes?
- Vaccine design to incorporate cleavage motifs
  - Optimize recombinant vaccine for cleavage?

Cellular immunity



How does our immune system detect infections?





Epitope-based vaccines

- A major reason for analyzing and predicting epitopes is because they may lead to the development of peptide-based synthetic vaccines.
- Thousands of peptides have been pre-clinically examined; over 100 of them have progressed to phase I clinical trials and about 30 to phase II, including vaccines for foot-and-mouth virus infection, influenza, HIV.
- However, not a single peptide vaccine has passed phase III and became available to the public.
- The only successful synthetic peptide vaccine has been made against canine parvovirus (causing enteritis and myocarditis in dogs and minks). It consists of several peptides from the N-terminal region of the viral VP2 protein (residues 1–15, 7– 1, and 3–19) coupled to a carrier induced an immune response in dogs and minks. However, it is expensive and has lower than the conventional vaccine (attenuated virus) coverage.

Immunoinformatics

- The goals:
  - Modeling of the immune system at the population and individual levels (in silico immune system).
  - Design of medical diagnostics and therapeutic/prophylactic vaccines for cancers, allergies, autoimmune and infectious diseases.
- **Epitope discovery**: how the antigens are recognized by the cells of the immune system.
- Data collection and analysis: IEDB, HIV database, AntiJen (UK), IMGT (France)
- Evolution of the adaptive and innate immune system: Gary Litman (FL), Louis Du Pasquier (Switzerland)
- Evolution of pathogens and co-evolution of host and pathogen.
- Modeling of host-pathogen interactions: Leor Weinberger (UCSD)
- Deciphering regulatory networks in APCs, lymphocytes and other cells.