

# Immune system overview in 10 minutes

The non-immunologist guide to the  
immune system

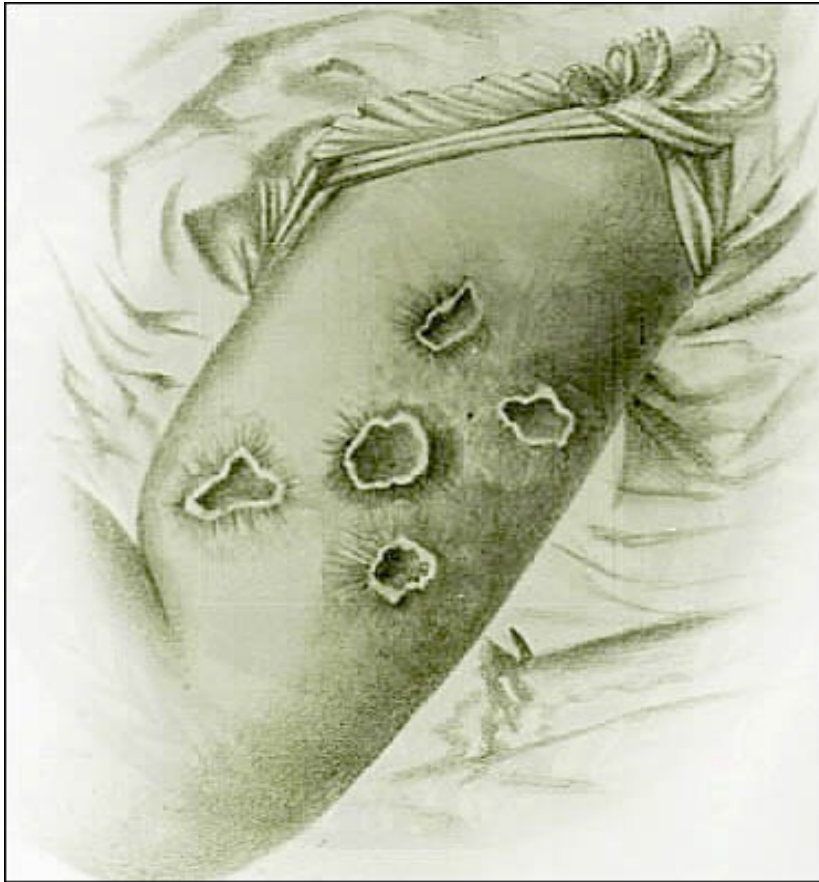
Morten Nielsen

Department of Health Technology, DTU

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# Vaccine development!

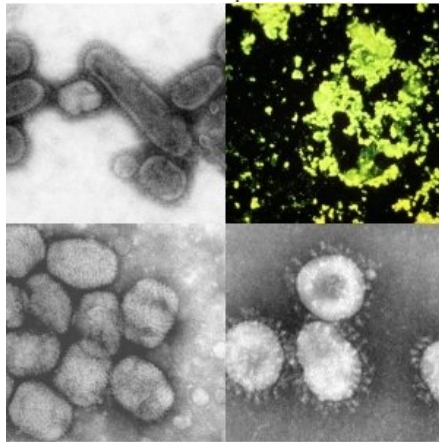
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The arm of Sarah Nelmes, a dairy maid, who had contracted cowpox. Jenner used material from her arm to vaccinate an eight year old boy, James Phipps. (1798).

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# Vaccine review



From left to right: the reconstructed 1918 flu, Plaque. Smallpox. SARS

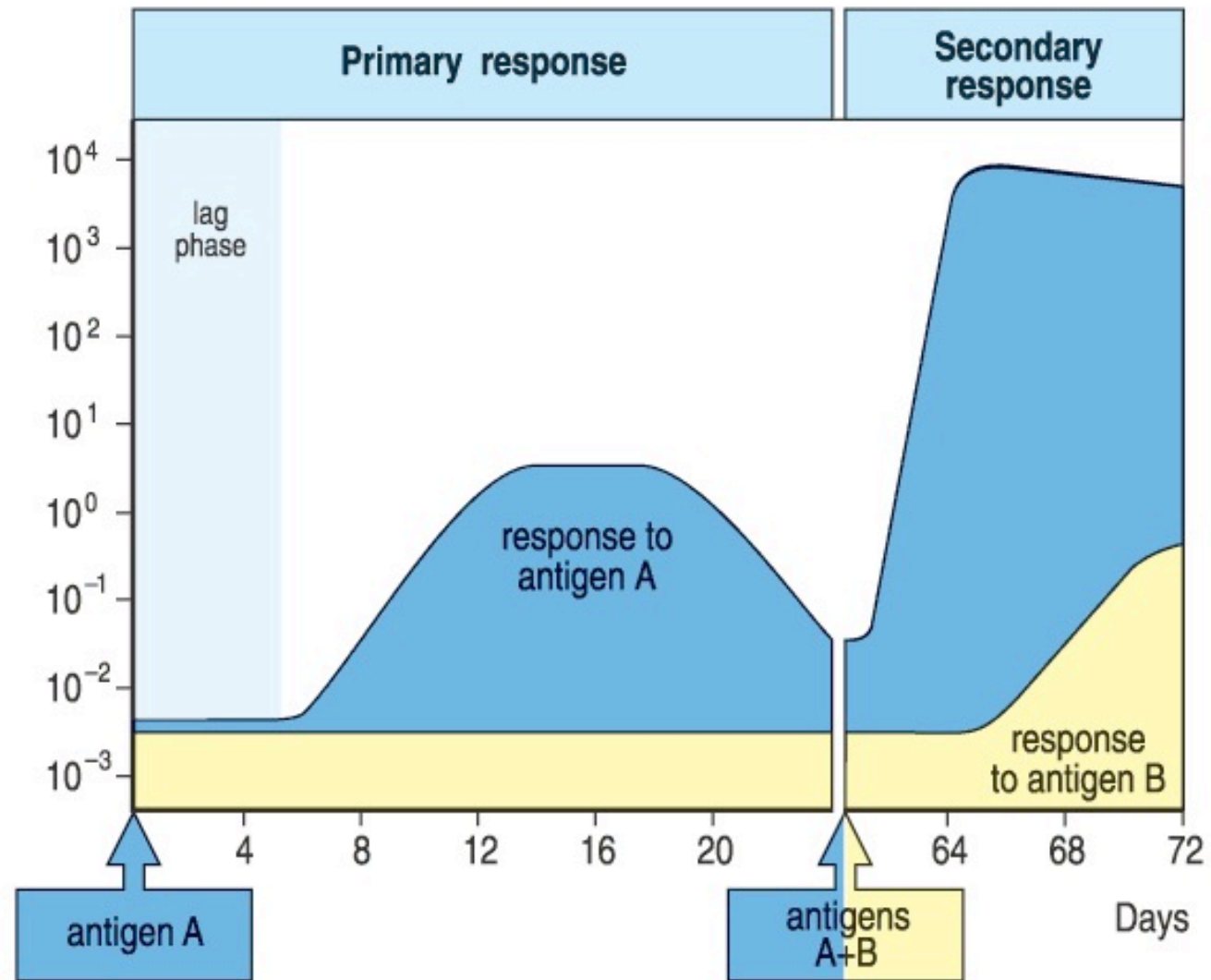
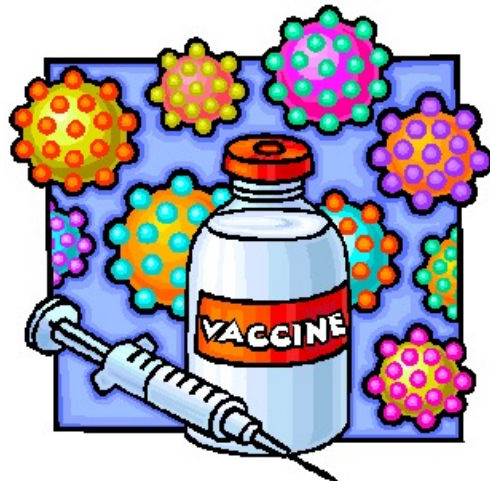


Fig 1.20 © 2001 Garland Science

# Vaccines can eradicate pathogens and save lives

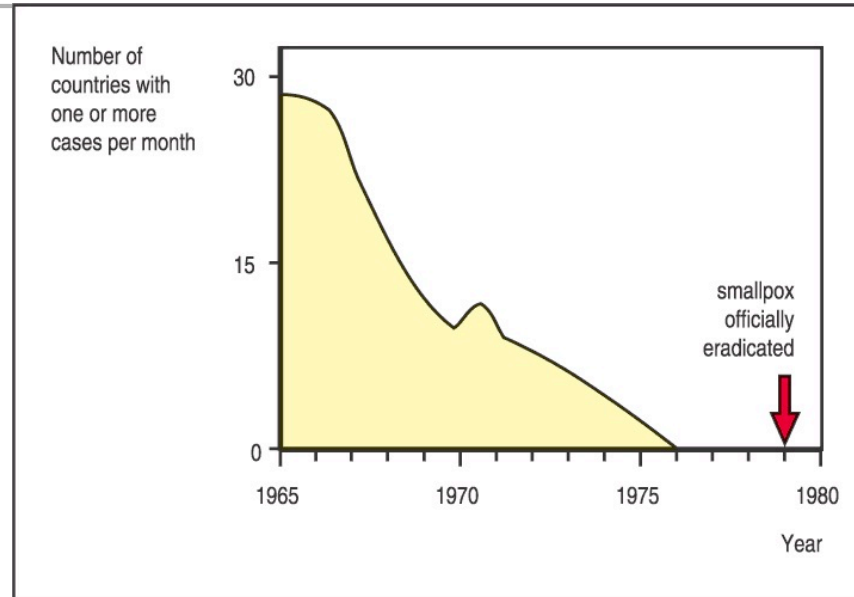


Fig 1.2 © 2001 Garland Science

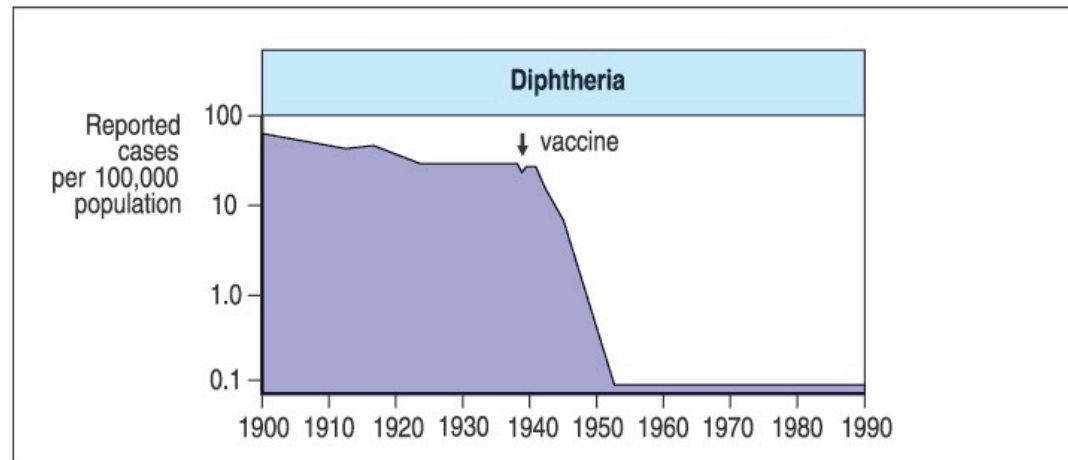


Fig 1.33 part 1 of 3 © 2001 Garland Science

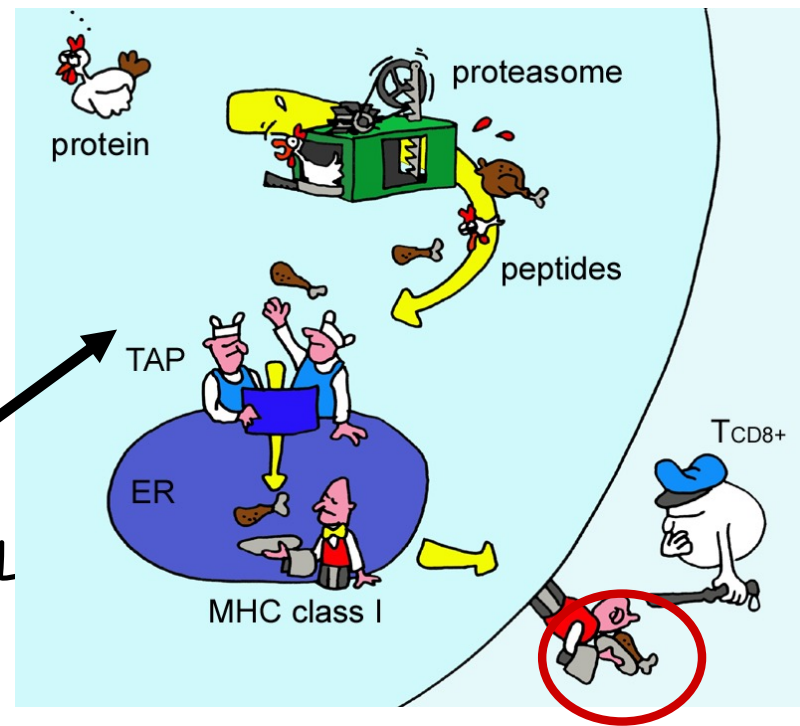
Vaccines have been made for 36 of >400 human pathogens

Organism	Type	Vaccine Type	Year
Variola virus	Virus	Live	1798
Rabies virus	Virus	Inactivated	1885
<i>Salmonella typhi</i>	Bacteria	Live	1896
<i>Vibrio cholerae</i>	Bacteria	Inactivated	1896
<i>Yersinia pestis</i>	Bacteria	Inactivated	1897
<i>Corynebacterium diphtheriae</i>	Bacteria	Toxoid	1923
<i>Bordetella pertussis</i>	Bacteria	Acellular	1926
<i>Clostridium tetani</i>	Bacteria	Toxoid	1927
<i>Mycobacterium tuberculosis</i>	Bacteria	Live	1927
Yellow fever virus	Virus	Live	1935
Influenza virus type A	Virus	Inactivated	1936
Influenza virus type B	Virus	Inactivated	1936
<i>Coxiella burnetii</i>	Bacteria	Inactivated	1938
<i>Rickettsia prowazekii</i>	Bacteria	Inactivated	1938
<i>Rickettsia rickettsii</i>	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
<i>Staphylococcus aureus</i>	Bacteria	Staphage lysate	1976
<i>Streptococcus pneumoniae</i>	Bacteria	Polysaccharide	1977
Human adenovirus types 4 and 7	Virus	Live	1980
<i>Neisseria meningitidis</i>	Bacteria	Polysaccharide	1981
Hepatitis B	Virus	Recombinant	1986
<i>Haemophilus influenzae</i>	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
<i>Escherichia coli</i>	Bacteria	Inactivated	1995
Junin virus	Virus	Live	1996
<i>Bacillus anthracis</i>	Bacteria	Adsorbed	1998
<i>Borrelia burgdorferi</i>	Bacteria	Recombinant	1998

+HPV & Rotavirus

# Immune system

- Innate - fast...
- Addaptive - remembers...
  - Cellular
    - Cytotoxic T lymphocytes (CTL)
    - Helper T lymphocytes (HTL)
  - Humoral
    - B lymphocytes



## Epitopes

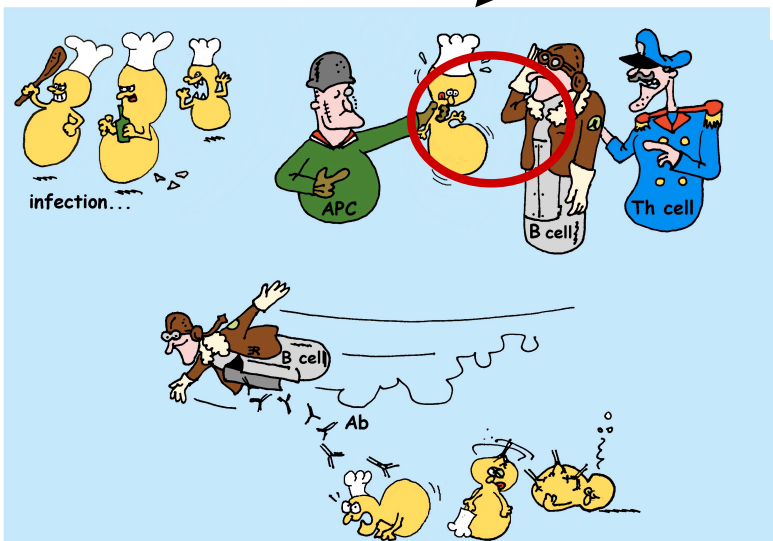
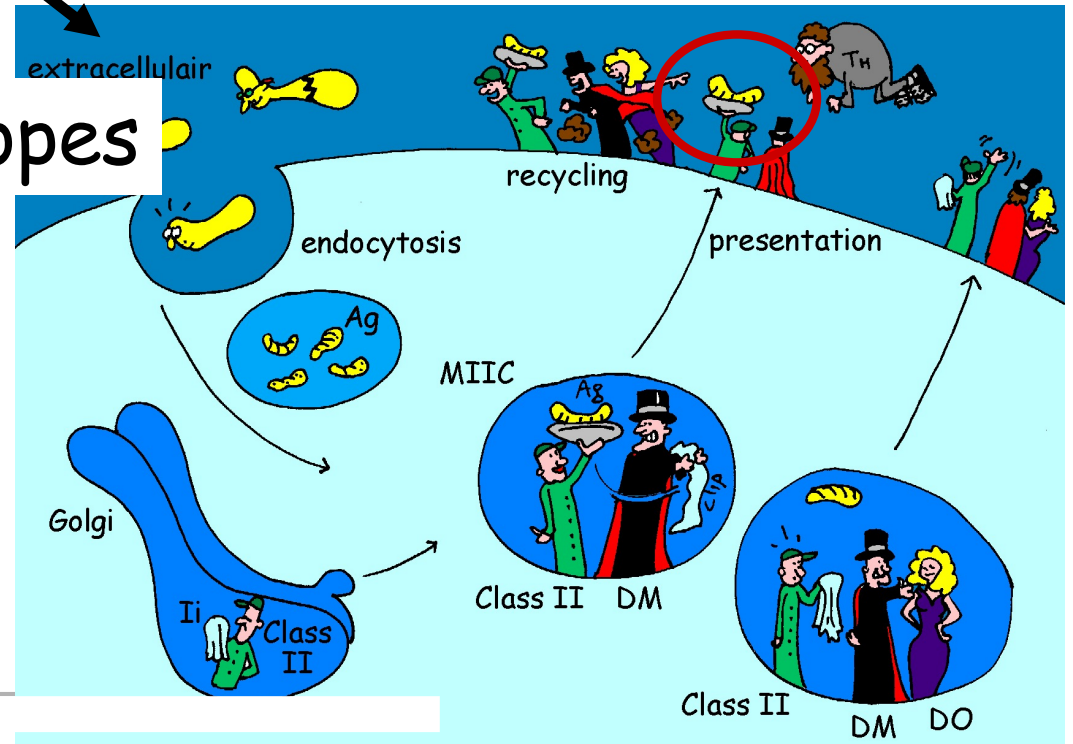
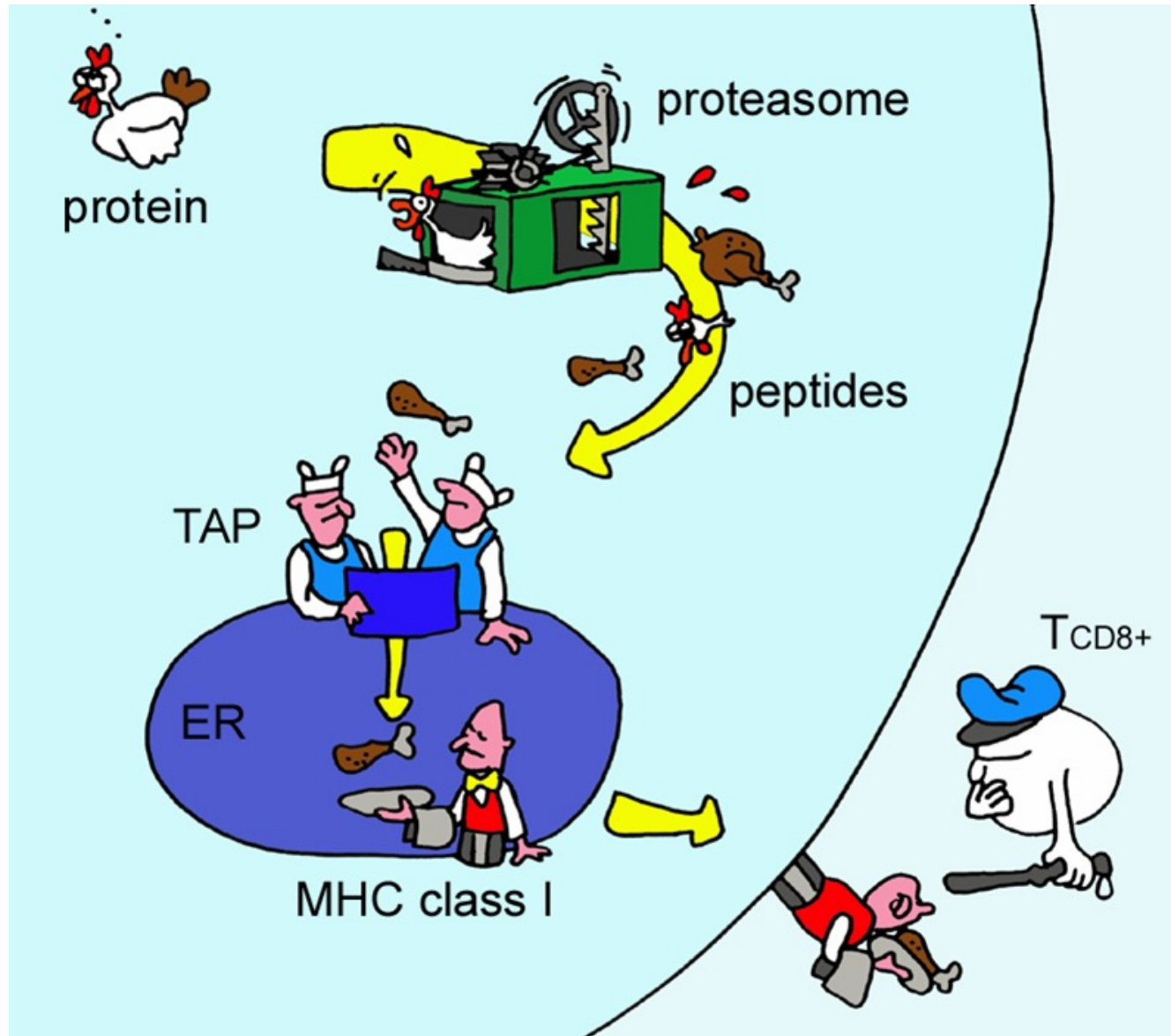


Figure by Eric A.J. Reits

# MHC Class I pathway



# MHC-I molecules present peptides on the surface of most cells

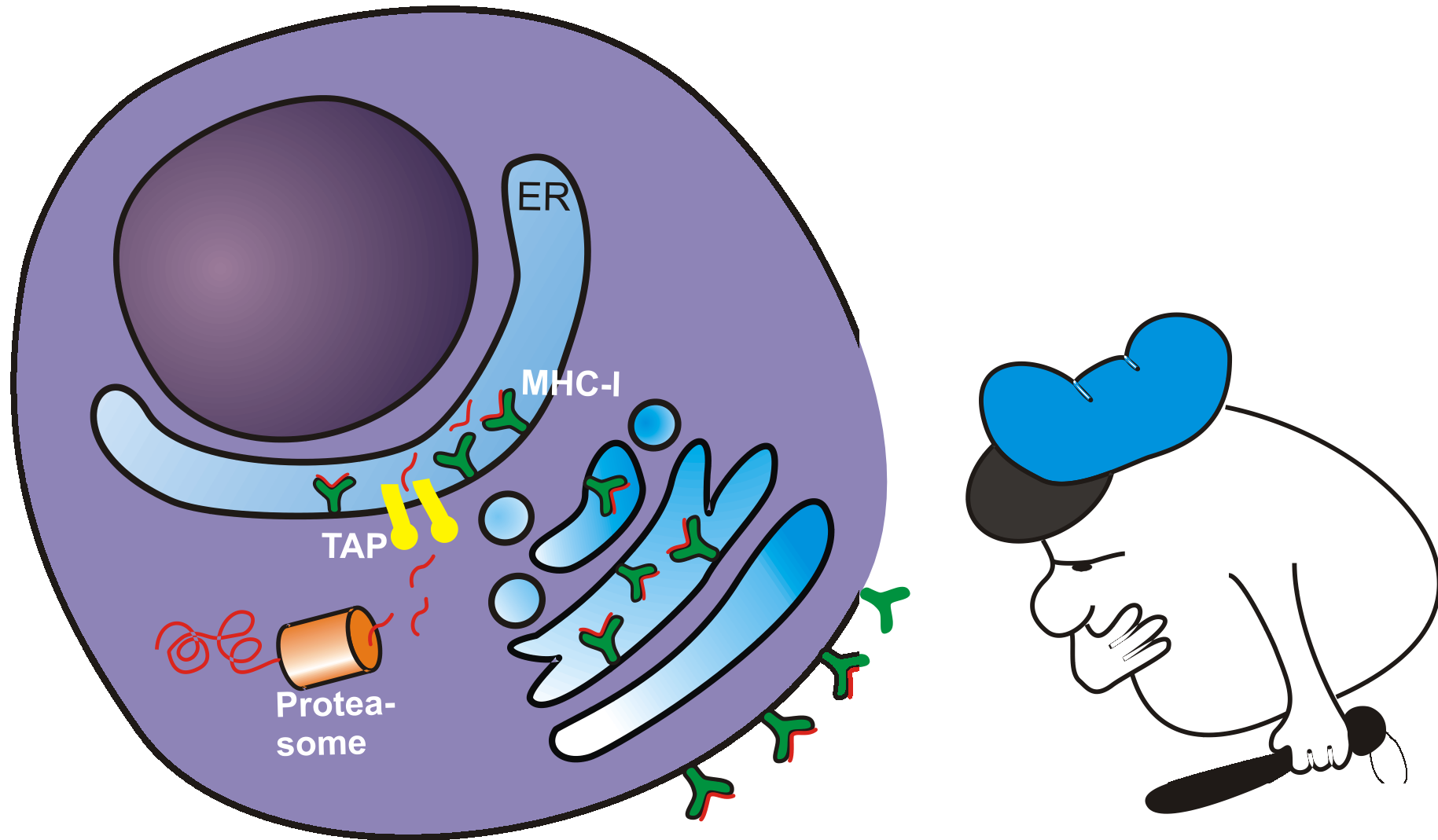


Figure courtesy Mette Voldby Larsen



# CTL response

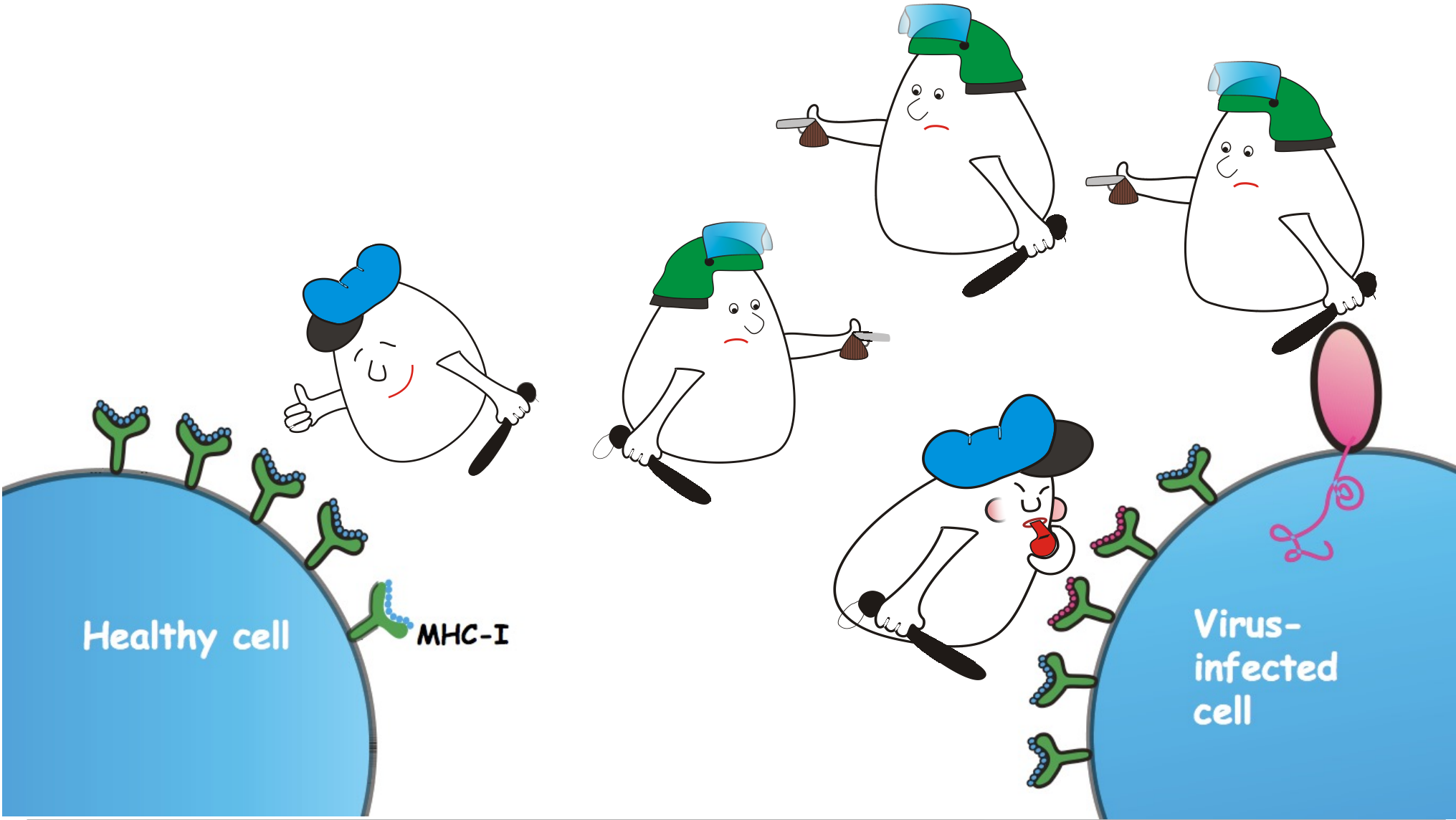
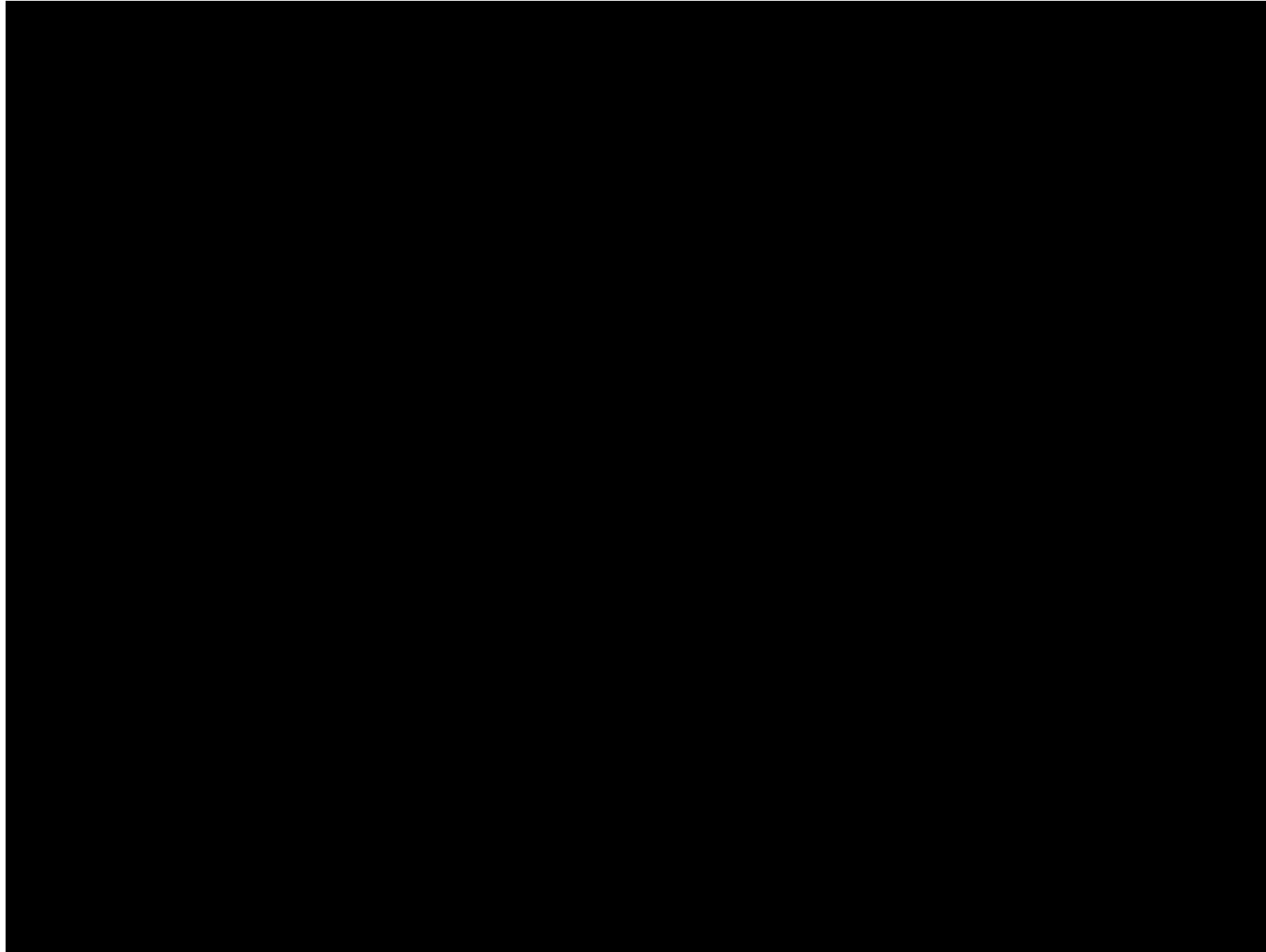


Figure courtesy Mette Voldby Larsen

# Encounter with death

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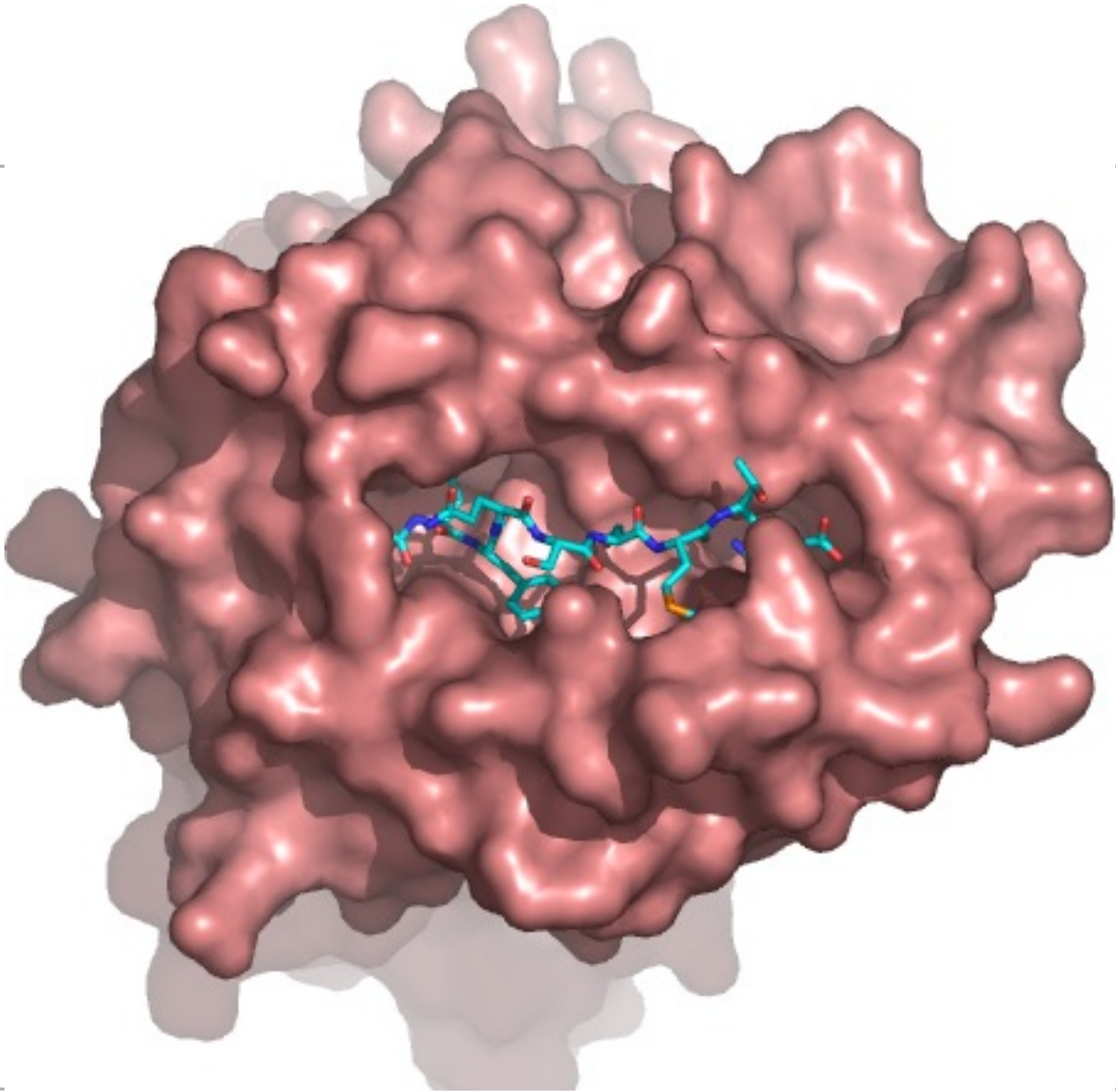


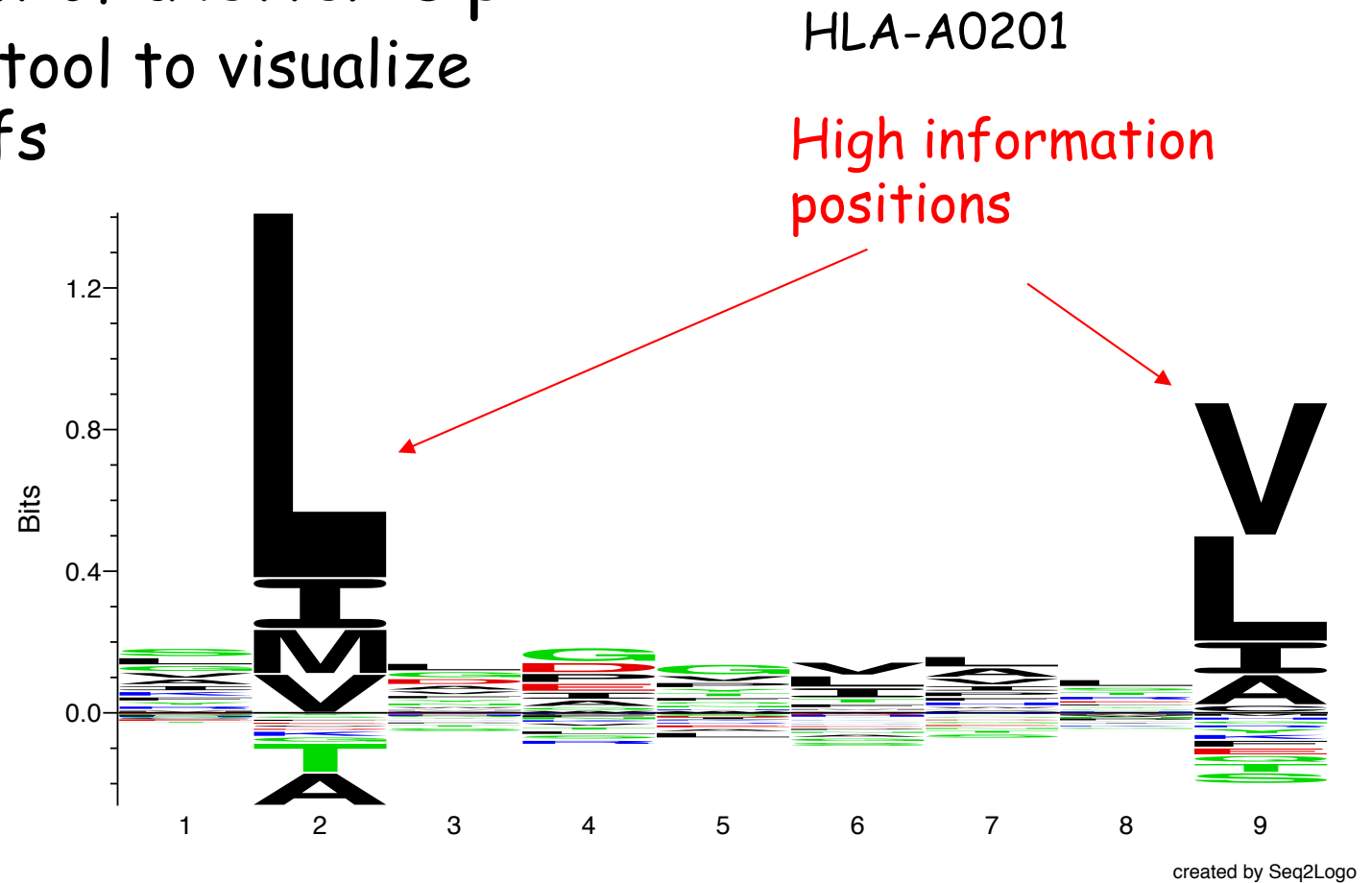
Figure by Anne Mølgaard

# HLA binding motif

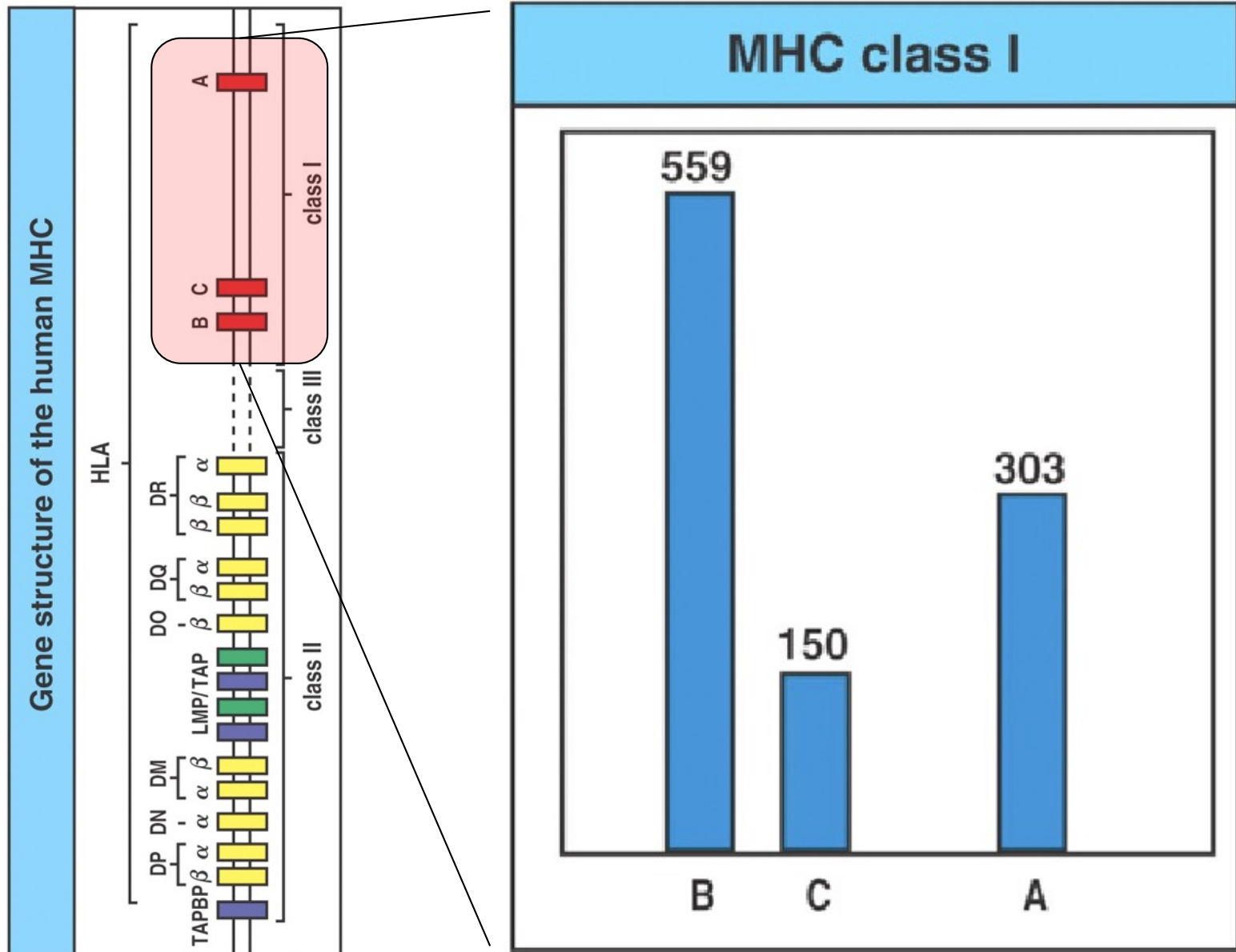
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LLDVPTAAV VLFRRGPRG MVDGTLFFF YMNGTMSQV MLLSVPLLL SLLGLLVEV ALLPPINIL TLIKIQHTL  
HLIDYLVTS ILAPPVVKL ALFPQLVIL GILGFVFTL STNRQSGRQ GLDVLTAKV RILGAVAKV QVCERIPTI  
ILFGHENRV ILMEHIHKL ILDQKINEV SLAGGIIGV LLIENVASL FLLWATAEA SLPDFGISY KKREEAPSL  
LERPGGNEI ALSNLEVKL ALNELLQHV DLERKVESL FLGENISNF ALSDHHIYL GLSEFTEYL STAPPAHGV  
PLDGEYFTL GVLVGVALI RTLDKVLEV HLSTAFARV RLDSYVRSL YMNGTMSQV GILGFVFTL ILKEPVHGV  
ILGFVFTLT LLFGYPVYV GLSPTVWLS WLSLLVPFV FLPSDFFPS CLGGLLTMV FIAGNSAYE KLGEFYNQM  
KLVALGINA DLMGYIPLV RLVTLKDIV MLLAVLYCL AAGIGILTV YLEPGPVTA LLDGTATLR ITDQVPFSV  
KTWGQYWQV TITDQVPFS AFHHVAREL YLNKIQNSL MMRKLAILS AIMDKNIIL IMDKNIILK SMVGNWAKV  
SLLAPGAKQ KIFGSLAFL ELVSEFSRM KLTPLCVTL VLYRYGSFS YIGEVLVSV CINGVCWTV VMNILLQYV  
ILTVILGVL KVLEYVIKV FLWGPRALV GLSRYVARL FLLTRILTI HLGNVKYL V GIAGGLALL GLQDCTMLV  
TGAPVTYST VIYQYRDDL VLPDVFIRC VLPDVFIRC AVGIGIAVV LVVLGLLAV ALGLGLLPV GIGIGVLAA  
GAGIGVAVL IAGIGILAI LIVIGILIL LAGIGLIAA VDGIGILTI GAGIGVLT AAGIGIIQI QAGIGILLA  
KARDPHSGH KACDPHSGH ACDPHSGHF SLYNTVATL RGPGRAFTV NLVPMVATV GLHCYEQLV PLKQHFQIV  
AVFDRKSDA LLDFVRFMG VLVKSPNHV GLAPPQHLL LLGRNSFEV PLTFGWICYK VLEWRFDSR TLNAWVKV  
GLCTLVAML FIDSYICQV IISAVVGIL VMAGVGSPY LLWTLVLL SVRDRLARL LLMDCSGSI CLTSTVQLV  
VLHDDLLEA LMWITQCFL SLLMWITQC QLSLLMWIT LLGATCMFV RLTRFLSRV YMDGTMSQV FLTPKKLQC  
ISNDVCAQV VKTDGNPPE SVYDFFVWL FLYGALLA VLFSSDFRI LMWAKIGPV SLLLELEEVEV SLSRFSWGA  
YTAFTIPSI RLMKQDFSV RLPRIFCSC FLWGPRAYA RLLQETELV SLFEGIDFY SLDQSVVEL RLNMFTPYI  
NMFTPYIGV LMI IPLINV TLFIGSHVV SLVIVTTFV VLQWASLAV ILAKFLHWL STAPPHVNV LLLLTVLTV  
VVLGVVFGI ILHNGAYSL MIMVKCMMI MLGHTTMEV MLGHTTMEV SLADTNSLA LLWAARPR L GVALQTMKQ  
GLYDGM EHL KMVELVHFL YLQLVFGIE MLMAQEALA LMAQEALAF VYDGREHTV YLSGANLNL RMFPNAPYL  
EAAGIGILT TLDSQVMSL STPPPGRV KVAELVHFL IMIGVLVGV ALCRWGLLL LLFAGVQCQ VLLCESTAV  
YLSTAFARV YLLEMLWRL SLDDYNHLV RTLDKVLEV GLPVEYLQV KLIANNTRV FIYAGLSA KLVANNTRL  
FLDEFMEGV ALQPGTALL VLDGLDVLL SLYSFPEPE ALYVDSLFF SLLQHLIGL ELTLGEFLK MINAYLDKL  
AAGIGILTV FLPSDFFPS SVRDRLARL SLREWLLRI LLSAWILTA AAGIGILTV AVPDEIPPL FAYDGKDYI  
AAGIGILTV FLPSDFFPS AAGIGILTV FLPSDFFPS AAGIGILTV FLWGPRALV ETVSEQSNV ITLWQRPLV

# Sequence logos

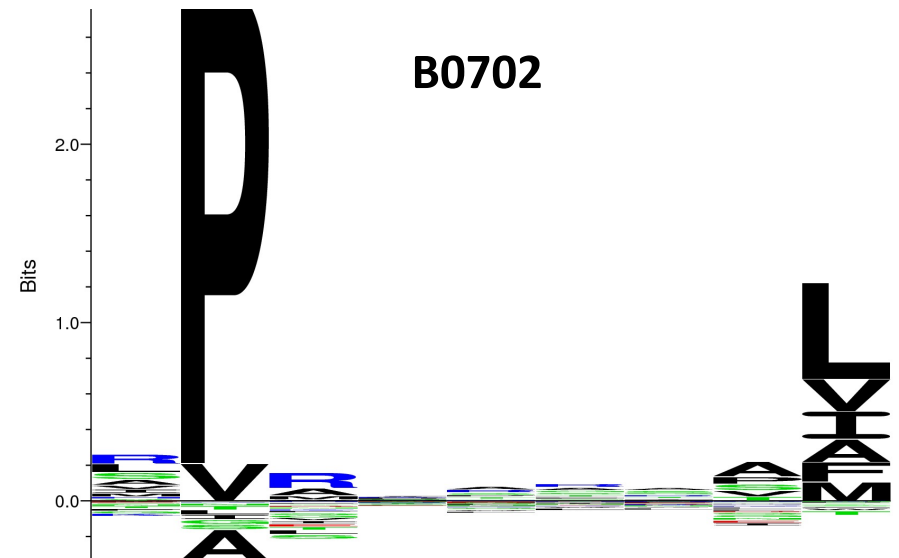
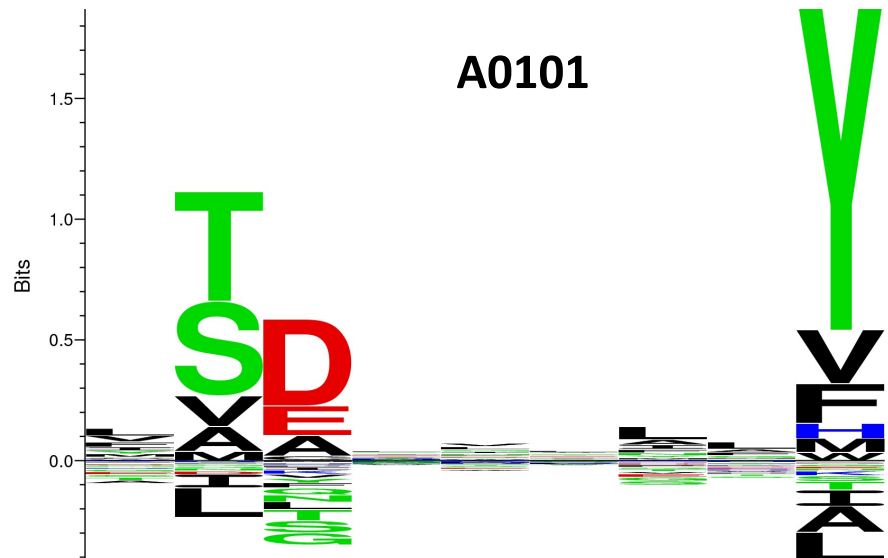
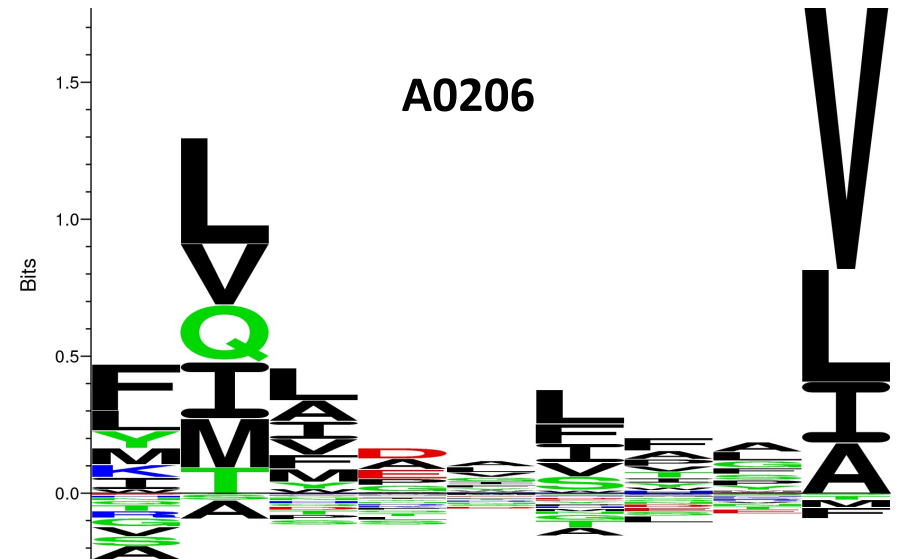
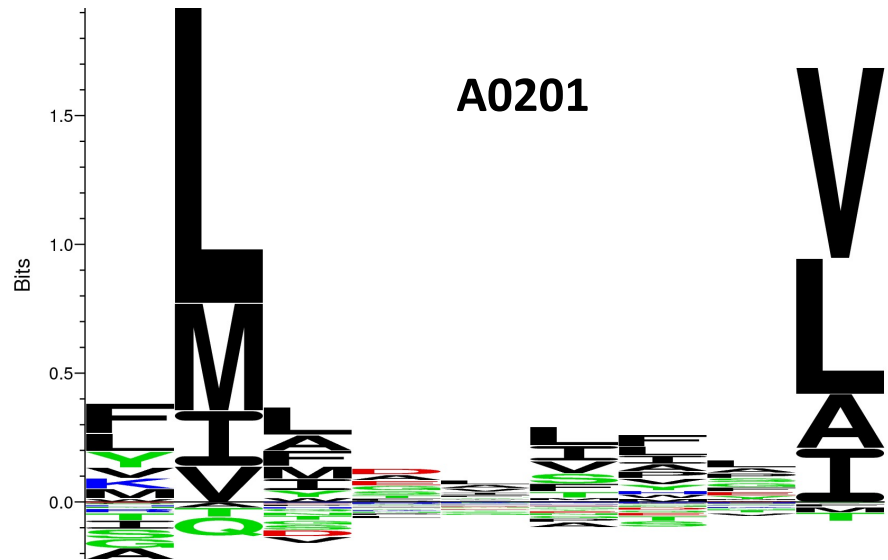
- Height of a column equal to  $I$
- Relative height of a letter is  $p$
- Highly useful tool to visualize sequence motifs



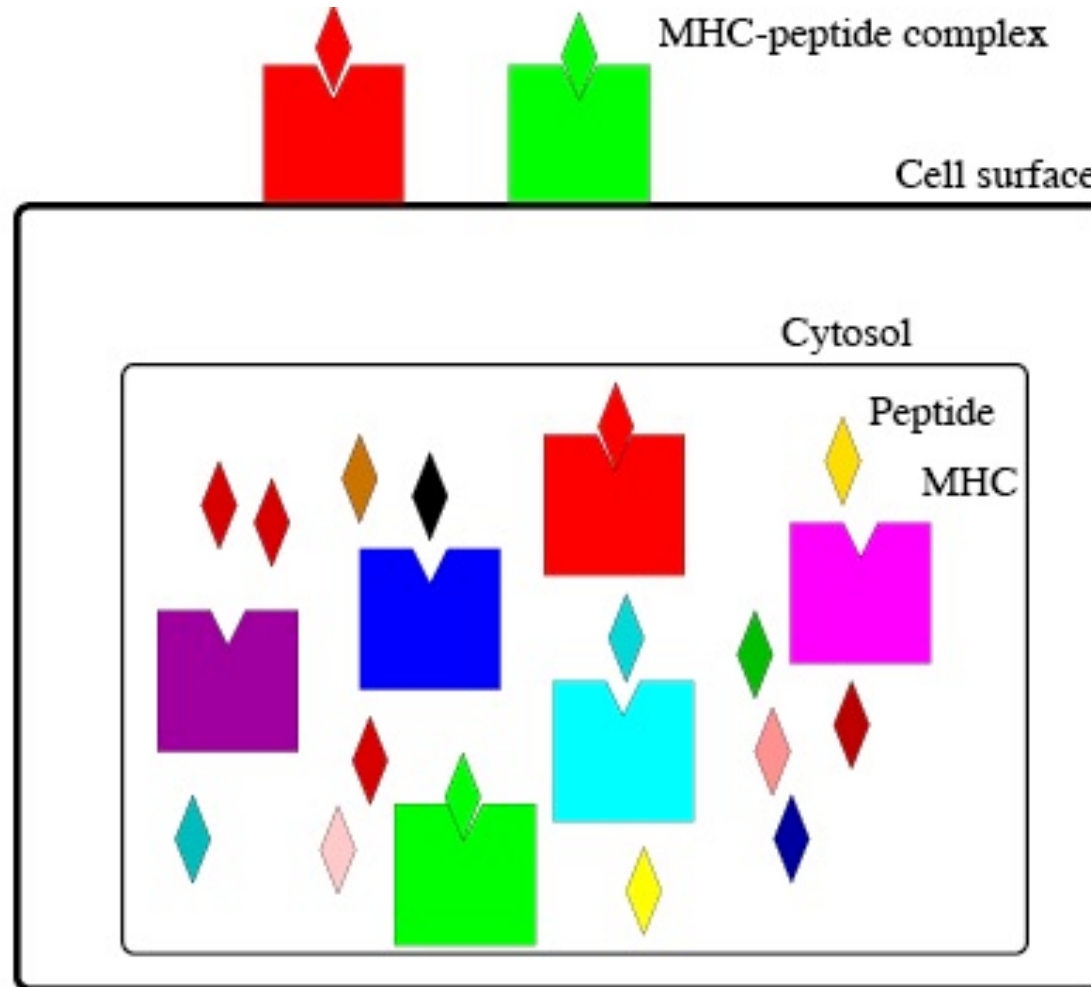
# HLA polymorphism



# HLA specificity clustering



# More MHC molecules: more diversity in the presented peptides



- 1% probability that MHC molecule presents a peptide
- Different hosts sample different peptides from same pathogen.



# Viral escape/variation

The virus of today is different from the virus of tomorrow (Viral escape)

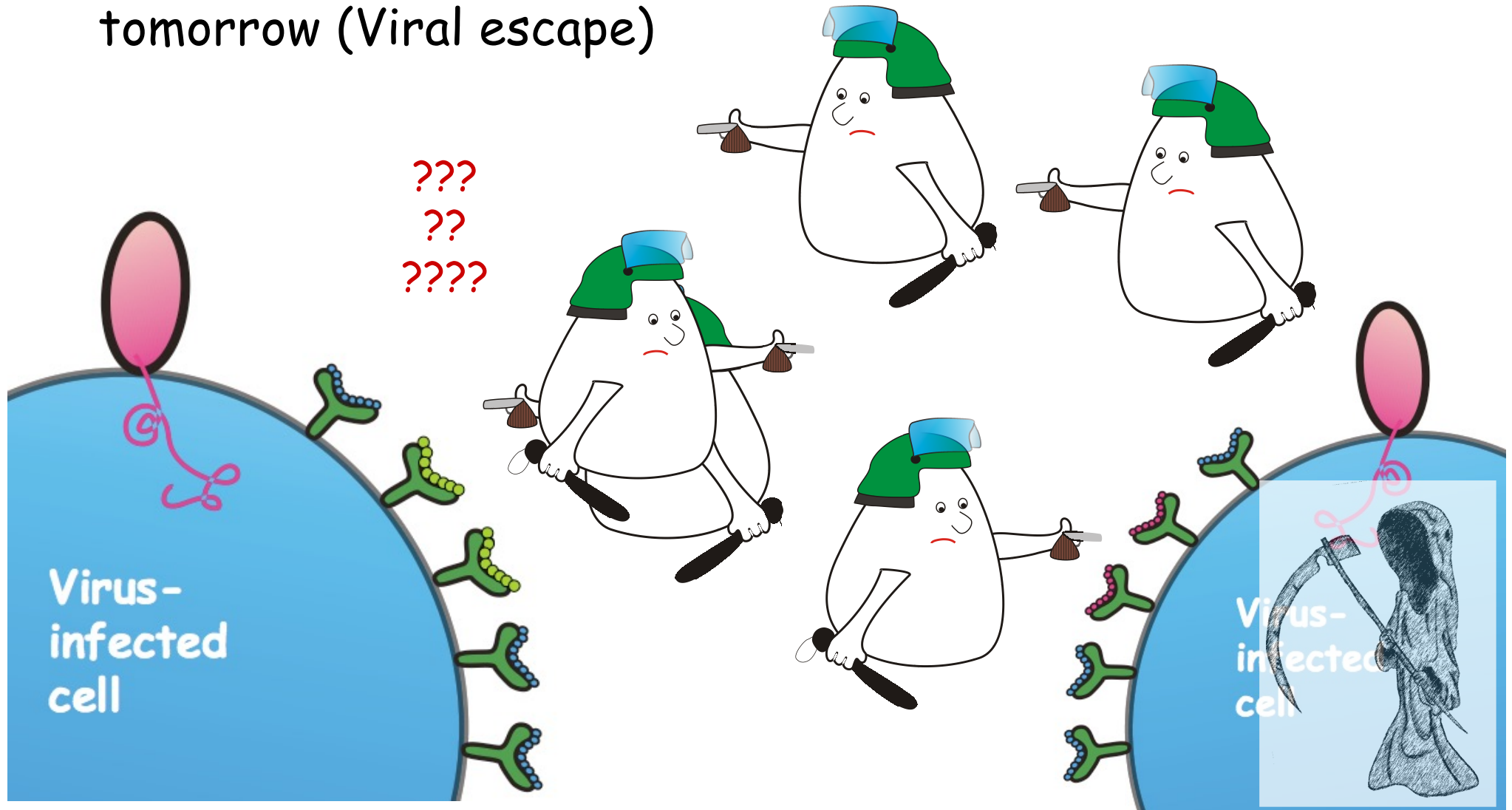
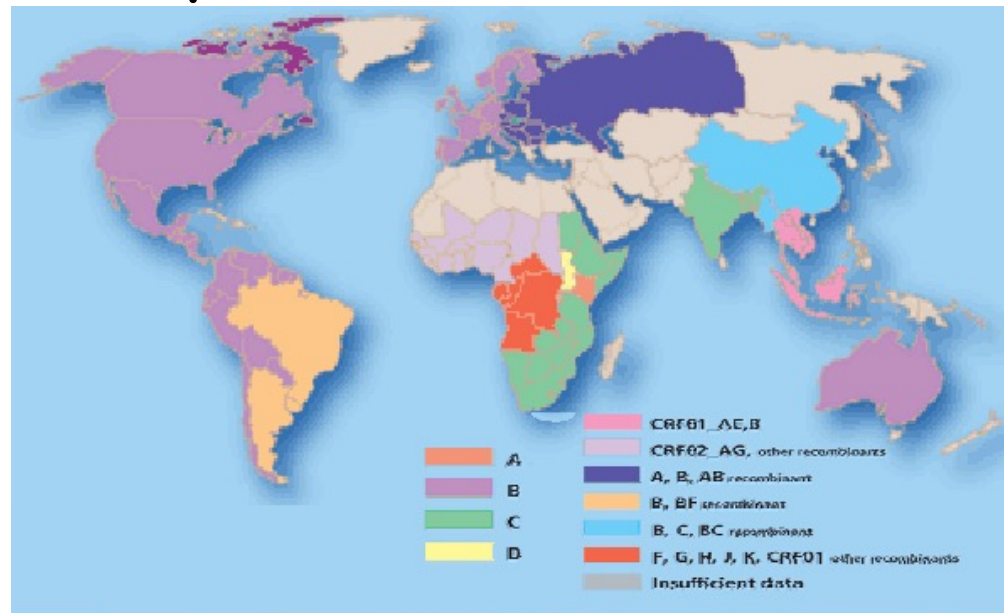


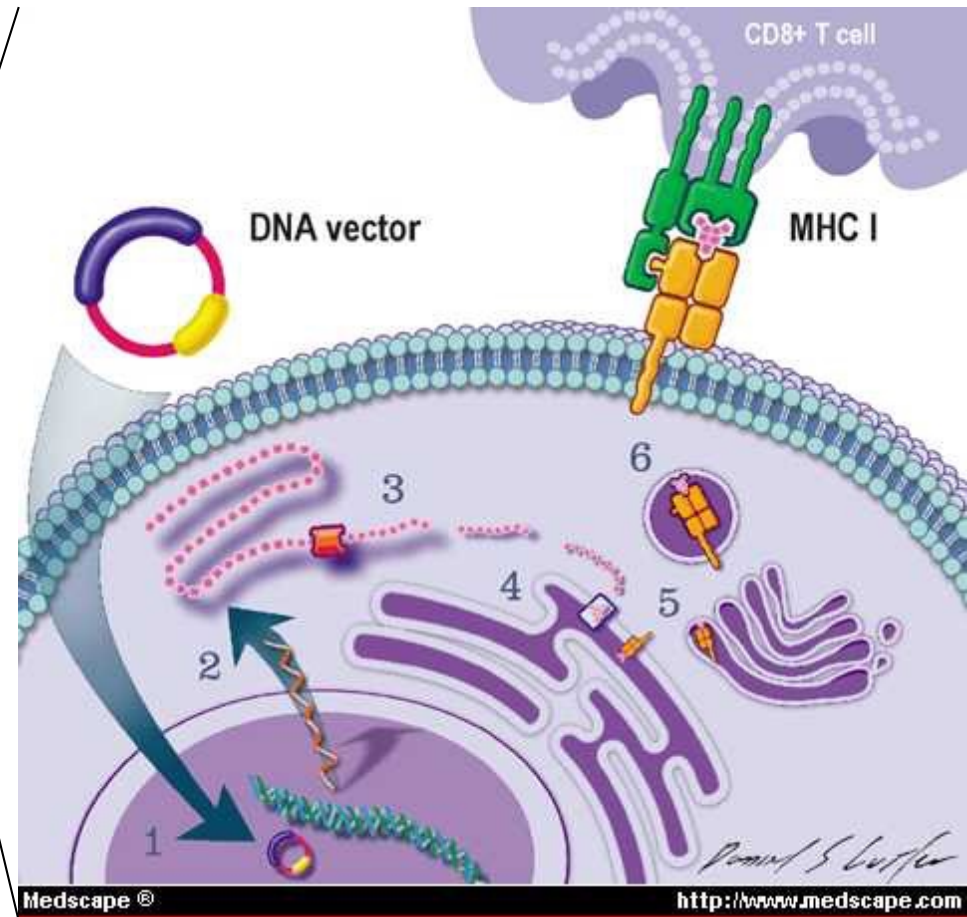
Figure courtesy Mette Voldby Larsen

# Pathogen variability

- Pathogen variability
  - Millions of viral particles within a given host
- Pathogen diversity
  - Different viral subtypes circulating in different parts of the world



# DNA vaccine



# Key bioinformatics challenges understanding immune system data

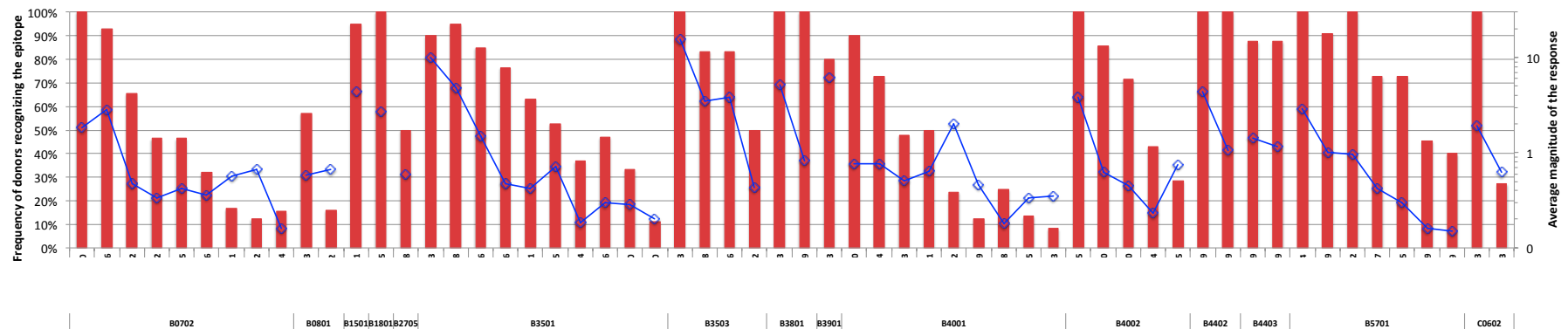
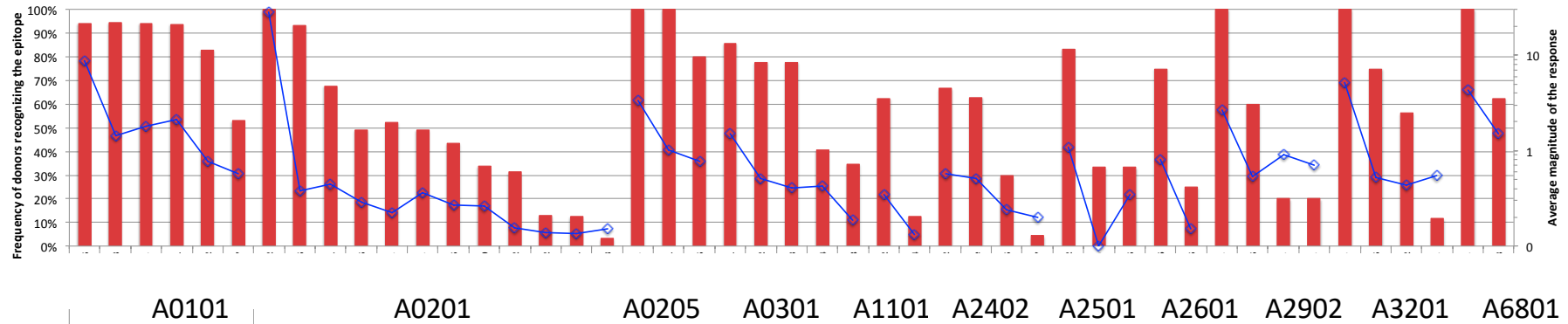
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# Identifying the targets of T cells

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- Yellow Fever genome encodes for close to 3500 unique 9mer peptides
  - In a cohort with > 50 patients, we find > 26 different prevalent HLA-A and HLA-B molecules
  - This gives all-together > 90,000 different HLA:peptide combinations
  - ⇒ Only 55 (<0.1%) of these are immunogens
  - Can we understand why this is, and more importantly can we predict these immunogenic peptides?
-

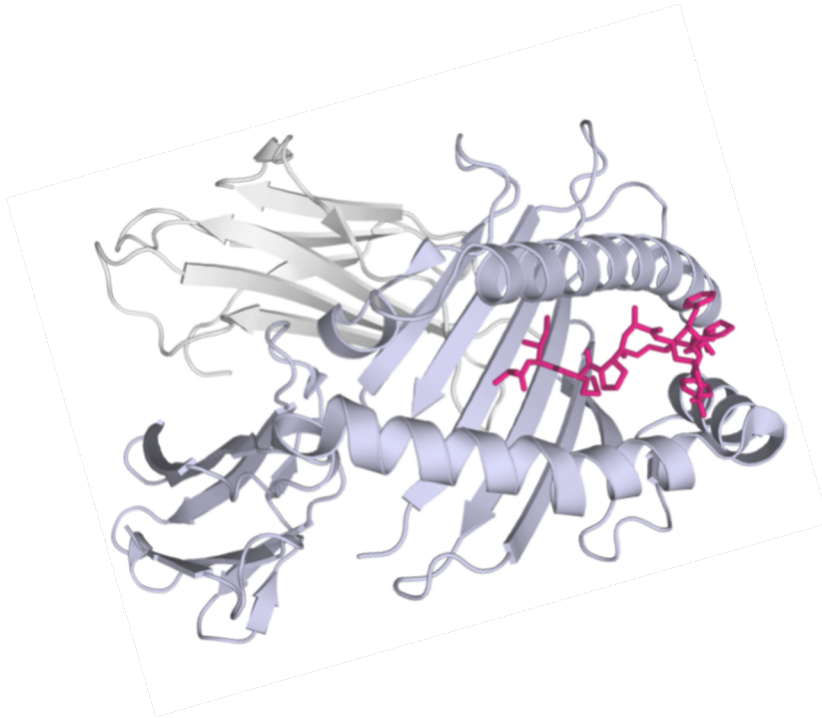
# Immuno dominance



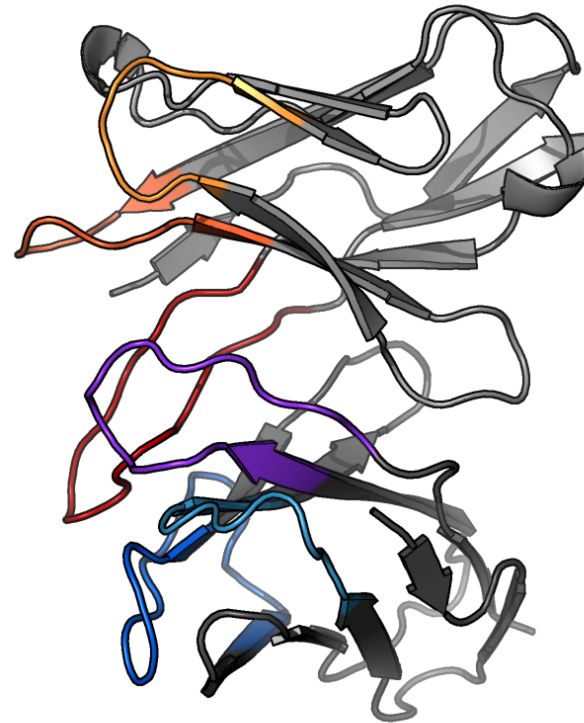
**Figure 12. Epitope dominance.** Every epitope was evaluated for dominance both in the population and within the individual donor. Shown for each epitope is, the frequency of analyzed donors that recognize the epitope (red columns); and the average frequency of activated CD8<sup>+</sup> T cells recognizing the epitope within the responding donors (blue circle). The epitopes are organized according to restriction elements. Top figure shows the HLA-A restriction elements; Bottom figure shows the HLA-B and -C restriction elements. Only blood samples drawn 13-21 days post vaccination are included, and only HLA molecules analyzed in 5 or more donors are included.

# T cell interaction models

MHC+peptide

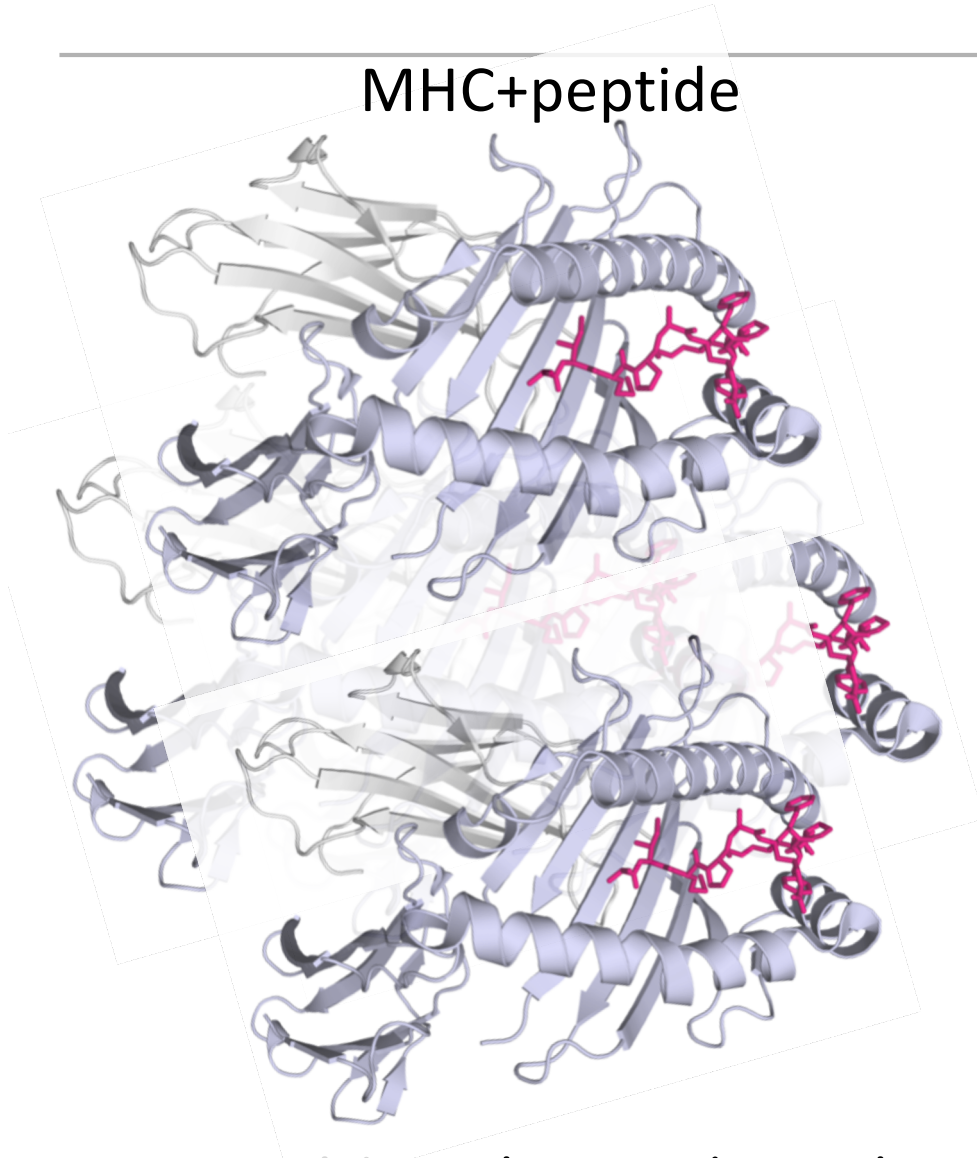


TCR

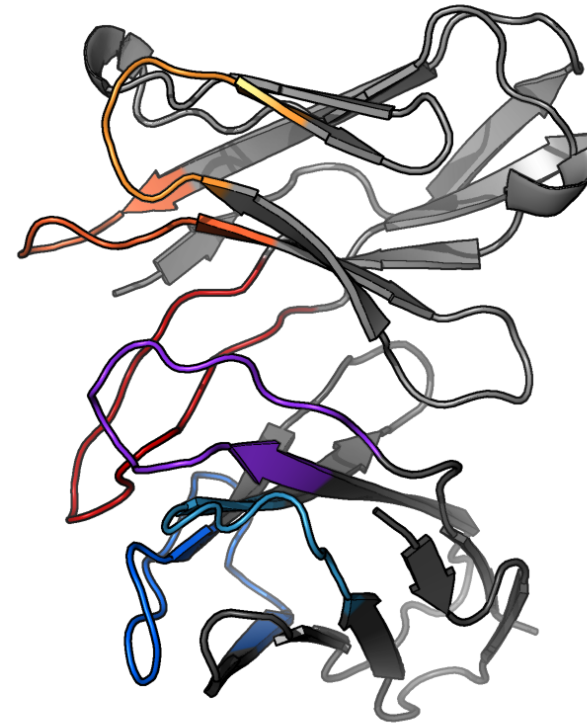


# T cell interaction models

MHC+peptide



TCR



Could we learn the rules and predict TCR targets?

LYRA, a webservice for lymphocyte receptor structural modeling.

NAR webservice issue, 2015



## Personalized cancer immunotherapy

- From blood and biopsy to Immunotherapy
- High throughput biology for understanding
  - Antigens (locks)
  - Receptors (keys)

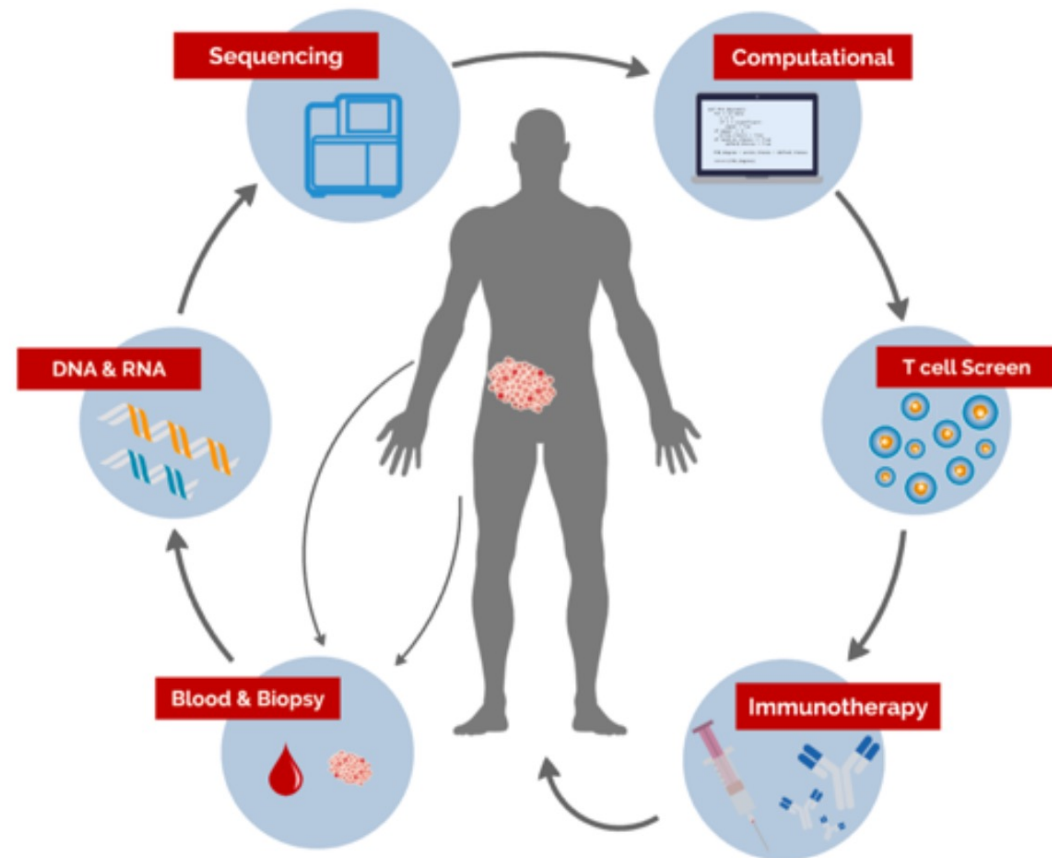


Figure courtesy of AM Bjerregaard

# Cancer Immunotherapy

