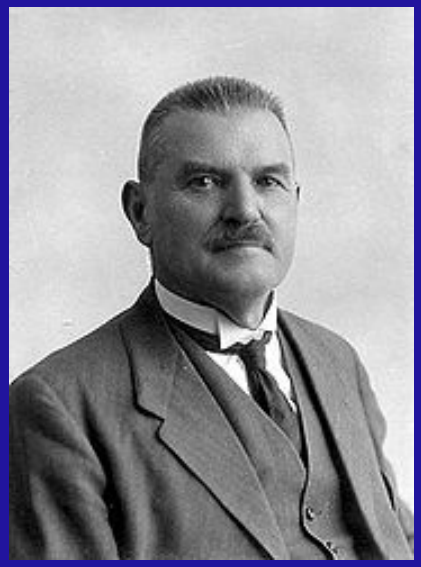
Adventures in Infection and Immunity

Peter C. Doherty,
University of Melbourne, and St Jude Children's Research Hospital, Memphis TN.

Sir Arnold Theiler Lecture 2009



Arnold Theiler
DVM, KCMG
1867-1936

Rinderpest vaccine
17D yellow fever vaccine

Max Theiler MD
1899-1972

Sir Arnold first came to public attention when he made a smallpox vaccine to combat an outbreak in mine workers

The careers of Arnold Theiler and Max Theiler exemplify the obvious truth that, when it comes to understanding infectious diseases and how to ameliorate their consequences there is little separation between the “human”and the “veterinary” world

One difference is that, so far as the funding agencies are concerned the veterinary area is more dominated by immediate, practical goals.

At least in the USA and Australia, it is much easier to access the very substantial resources that are required to do basic studies on infection and immunity if the research is badged as medical

The training that veterinarians receive provides an excellent grounding for this type of research, and a number of vets have made, or are making, very substantial contributions…to name a few….

Chris Goodnow…immunology

Yoshi Kawaoka

Ab Osterhaus….influenza

Graham Mitchell….parasitology

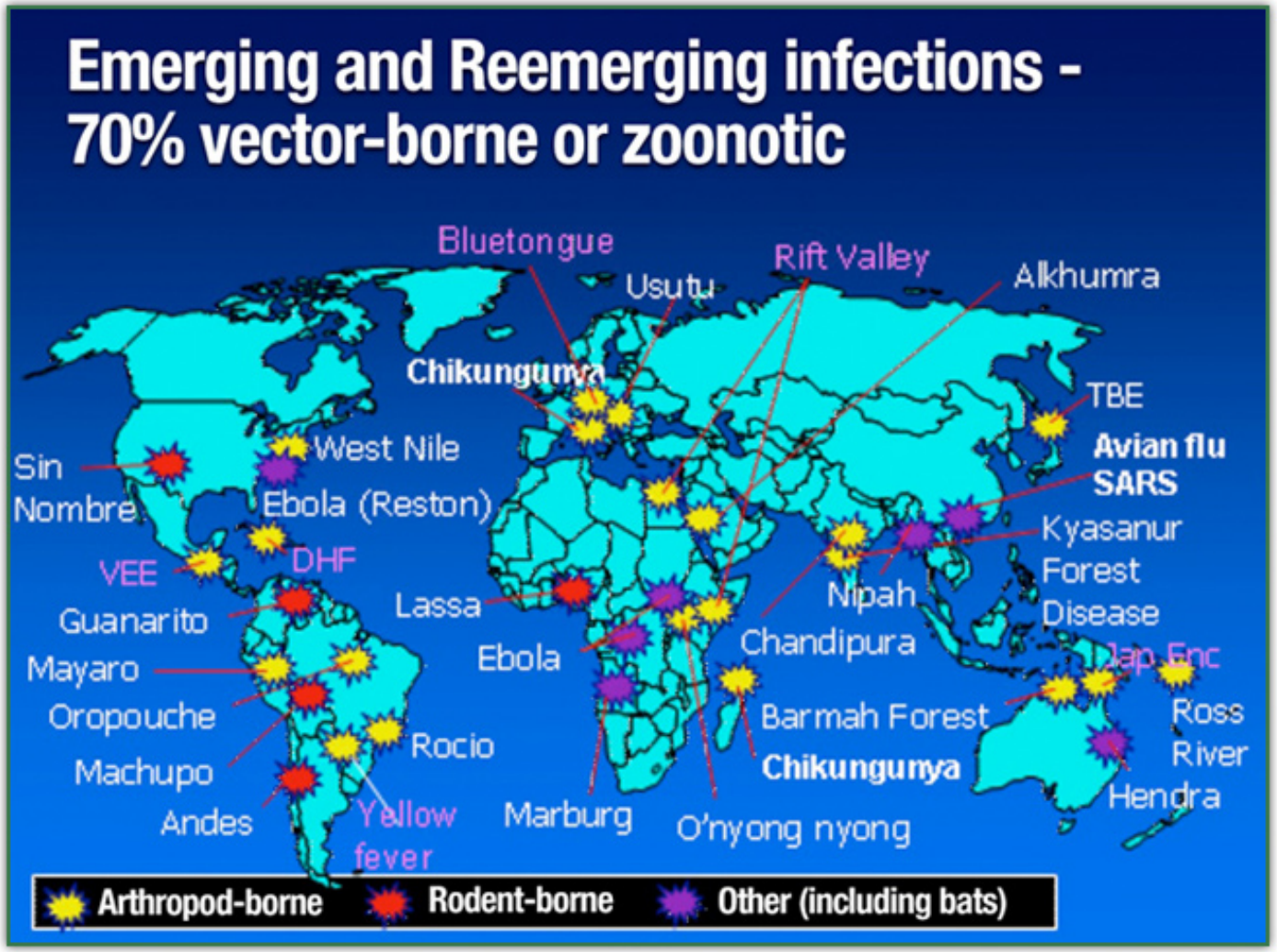
Max Essex….HIV/AIDS

The One Health Initiative, a movement to forge co-equal, all inclusive collaborations between physicians, veterinarians, and other scientific-health related disciplines, has been endorsed by various major medical organizations and health agencies, including the American Veterinary Medical Association, the American Medical Association, the American Society of Tropical Medicine and Hygiene, the American Society for Microbiology and the Centers for Disease Control and Prevention (CDC). Additionally, more than 400 prominent scientists, physicians and veterinarians worldwide have endorsed the initiative. http://www.onehealthinitiative.com/

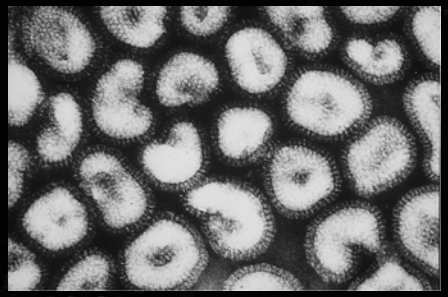
The global "One Health Initiative" would have been close to the hearts of Arnold and Max Theiler

One Health
initiative

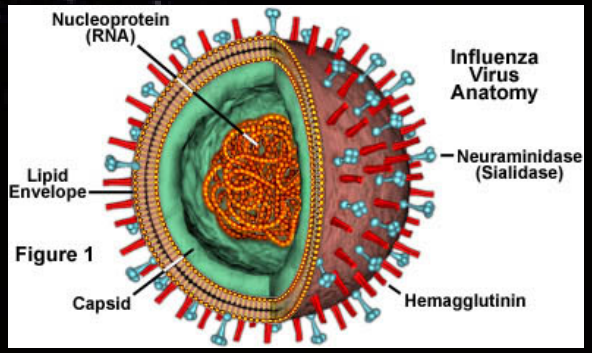
Emerging and Reemerging infections - 70% vector-borne or zoonotic



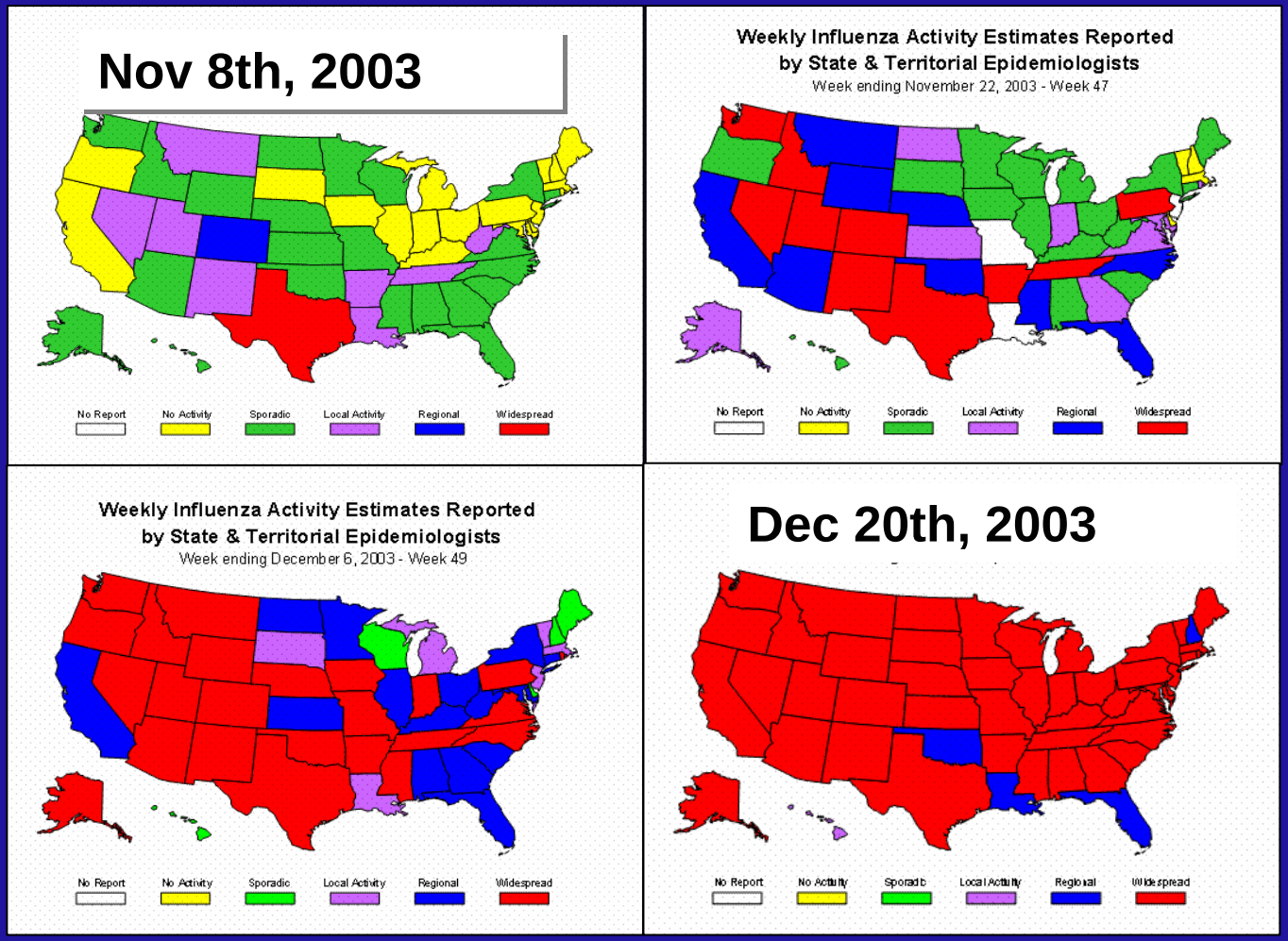
Influenza



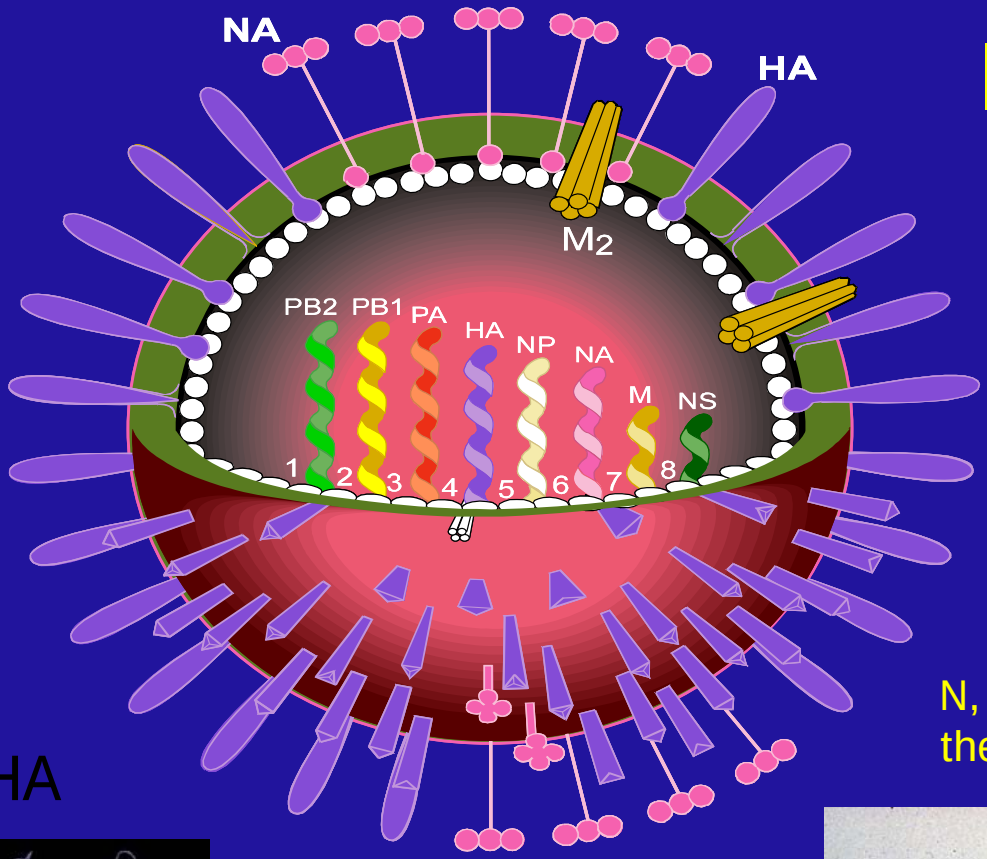
http://www.rit.edu/~andpph/photofile-c/sneeze-k-17.jpg



Rapid spread of a “seasonal” Influenza A virus



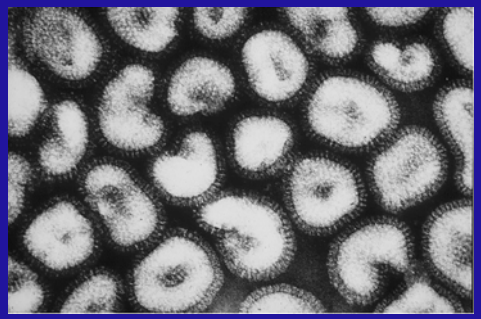
Influenza Virus



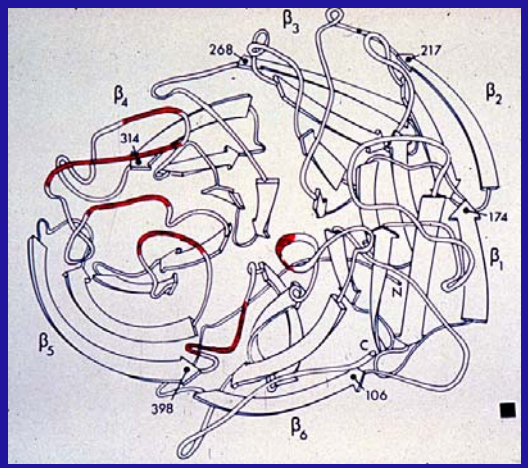
- Negative sense RNA virus
- No proof-reading during replication
- Segmented genomes
- Highly variable
- 16 HA and 9 NA subtypes

N, NA the neuraminidase that gets the virus away from the cell

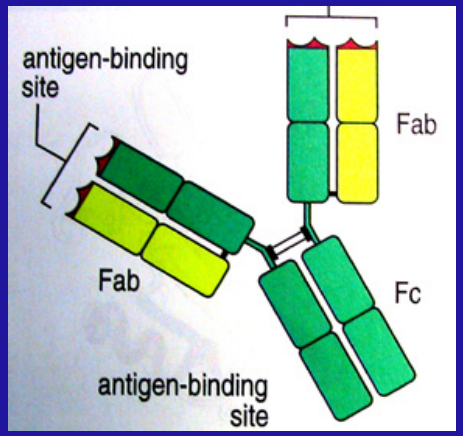
HA



H, HA the hemagglutinin molecule that gets the virus into the cell

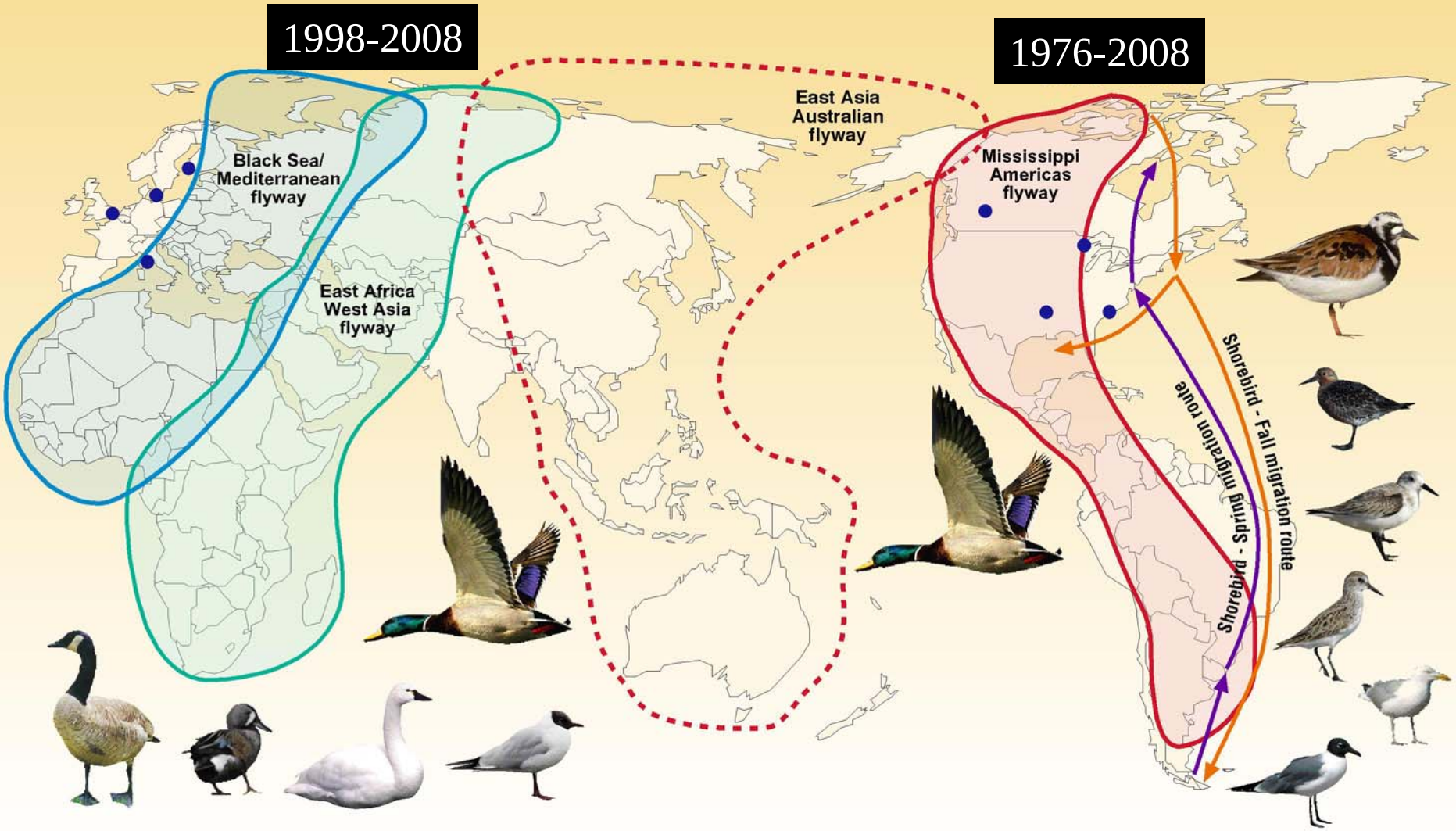


NA

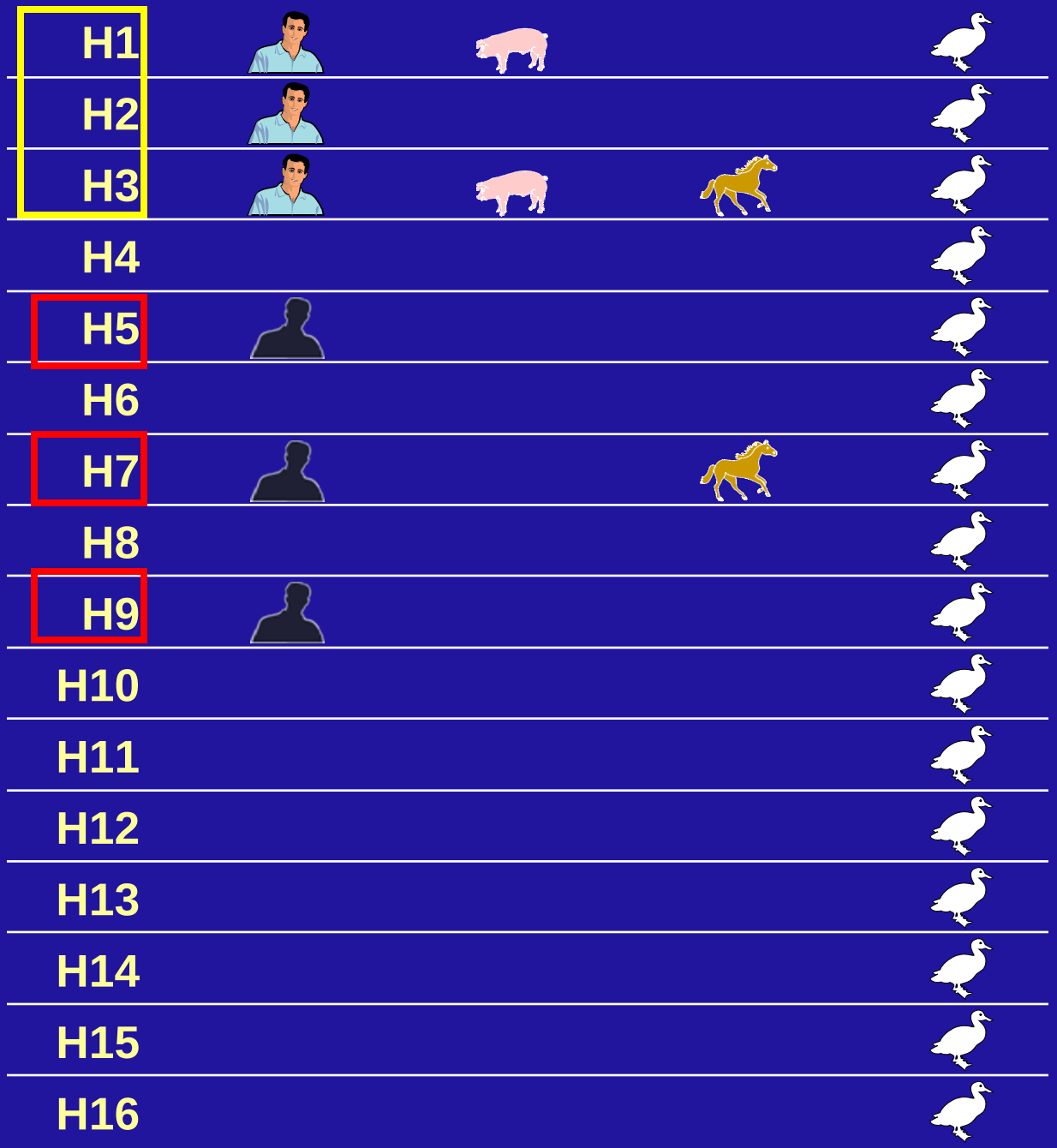


IgG

Influenza Surveillance in Migratory Waterfowl
Europe – Americas

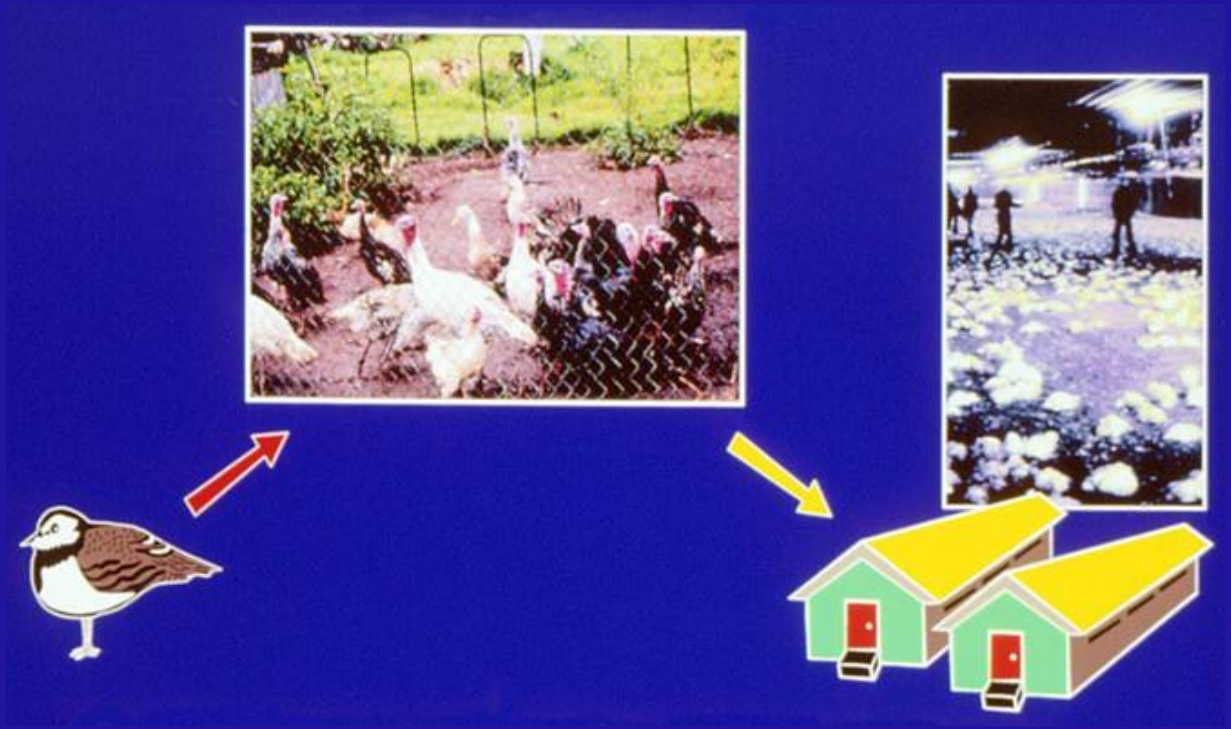


Influenza A Virus Host Range



The Ecology Of Influenza Viruses

- Influenza viruses in their natural reservoirs are in evolutionary stasis



- Rapid evolution occurs after transfer to new hosts

Don’t Forget H7N7…

Chickens:

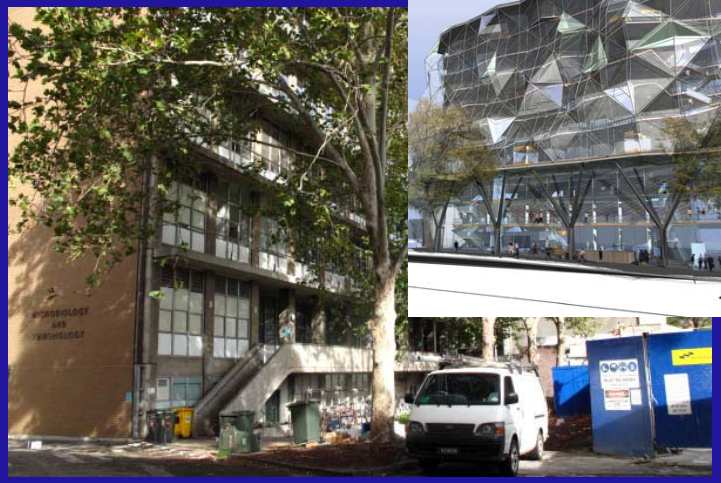
- March 2003 - Holland
- H7N7 - highly pathogenic
- 225 farms infected
- 30 million chickens killed

Humans:

- 347 persons with conjunctivitis
- 82 persons with confirmed H7N7
- Spread to 3 contact persons
- One human died of H7N7 infection
- (lys at residue 627 of PB2 gene)

Pigs:

- Serological evidence in pigs



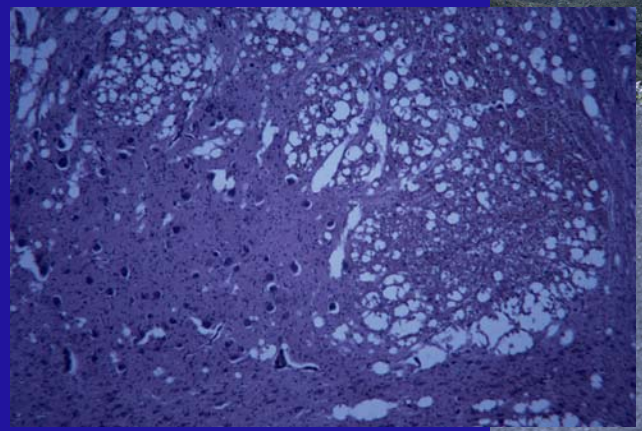
St Jude Children's Research Hospital

Melbourne University Medical School

Starting at age 17, I trained in veterinary science and graduated from the University of Queensland in 1962

After a short time in the field as a State Veterinary Officer, I spent 4 years at the ARI, Yeerongpilly, working as a diagnostic pathologist and doing research on leptospirosis in cattle (for an MVSc) and pigs, then avian infectious bronchitis. This introduced me to experimental science and to immunity and pathogenesis

PhD in neuropathology, University of Edinburgh, Scotland and Moredun Research Institute. This was by research thesis and publication, and I completed it in 3 years while working in the British Civil Service, 1967-71



Canberra, Philadelphia, and visits to Nairobi

JCSMR, ANU

Wistar Inst & U. Penn

ILRAD (now ILRI) Nairobi

When the cattle die the people die also

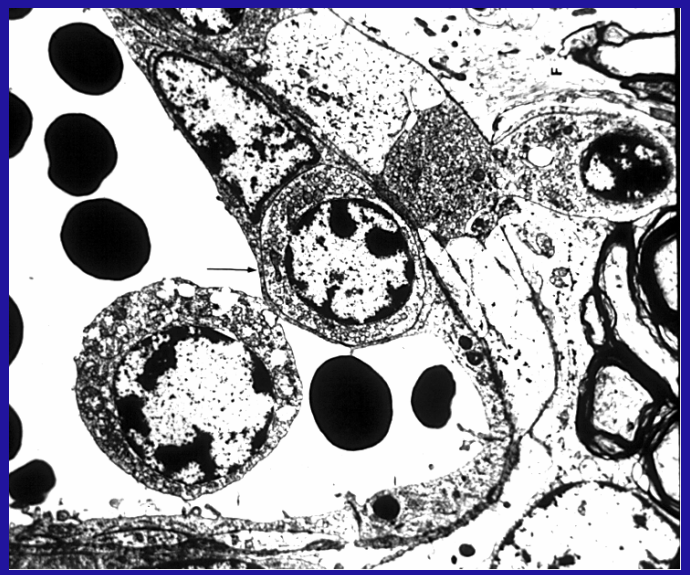
In research MD = mouse doctor, at least some of the time

One of the problems with science is that, once a seemingly satisfactory conceptual base is established, it proceeds "comfortably" by advances in technology

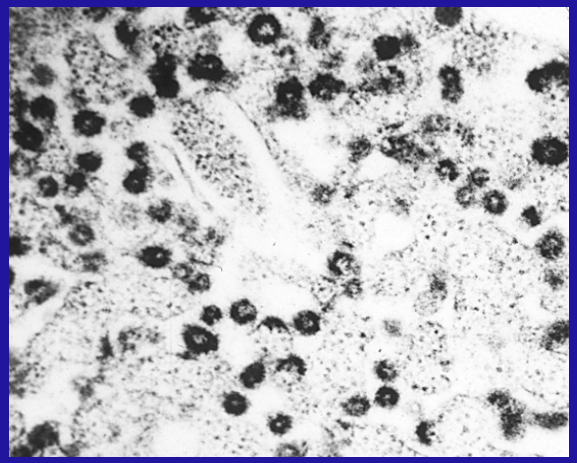
That's why young, fresh minds, or minds that have been trained in some other context (eg physics in the early days of molecular biology) are so important.

Quite a lot of the immunology of the time was of little value. Not being trained in the discipline was an advantage, I was not "captured" by it.

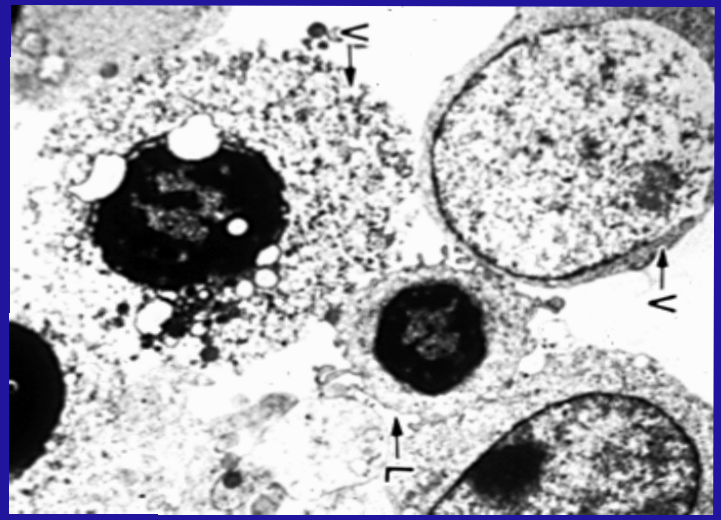
Virus-specific CD8$^+$ “killer T cells: the “hit men” of immunity



CD8$^+$ “killer”T cells cannot prevent infection, but clear lytic viruses following primary challenge and reduce both the duration and magnitude of virus growth following recall from memory



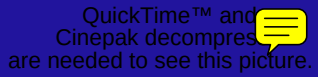
Induced apoptotic “suicide”of cell virus“factories”



The CD8+ “killer” T lymphocytes recirculate constantly from blood, to tissue to lymph.

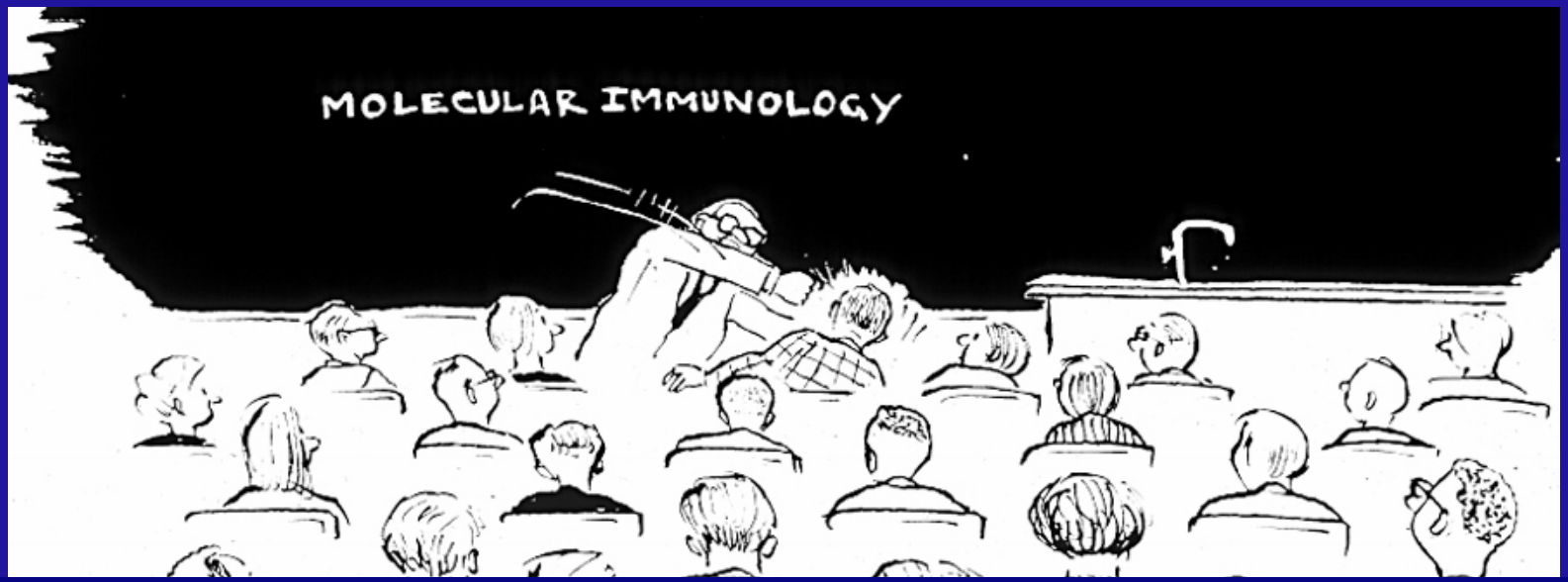
QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

The ultimate assassins, they kill silently by inducing apoptotic cell death. This involves disabling mitochondrial function to Minimize pro-inflammatory “danger signals” eg ATP release



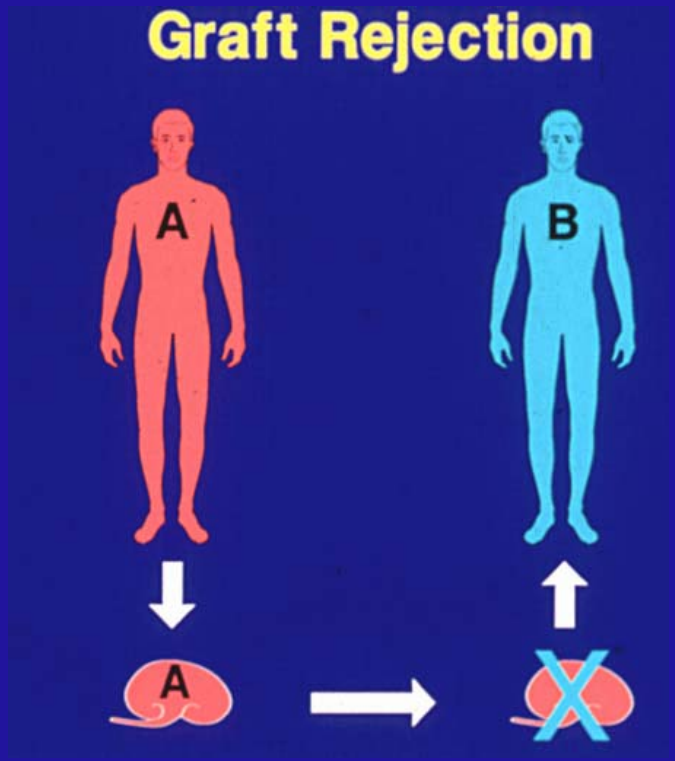
Movies by Misty Jenkins and Nigel Waterhouse
Jenkins et al Cell Death &Different 2009 E-pub, ahead of print

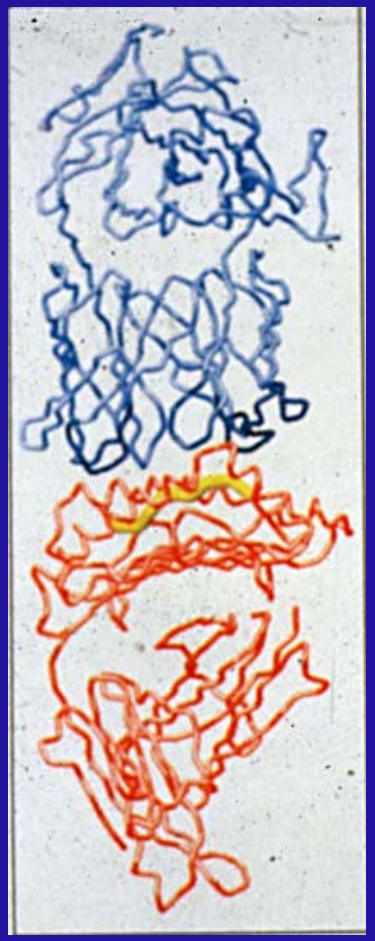
Cells that “hit” other cells must be precisely targeted.



The same basic mechanisms can operate to control some forms of cancer. A great deal of current research is aimed at making preventive or therapeutic cancer vaccines. The papilloma virus vaccine is showing great promise in cervical carcinoma.

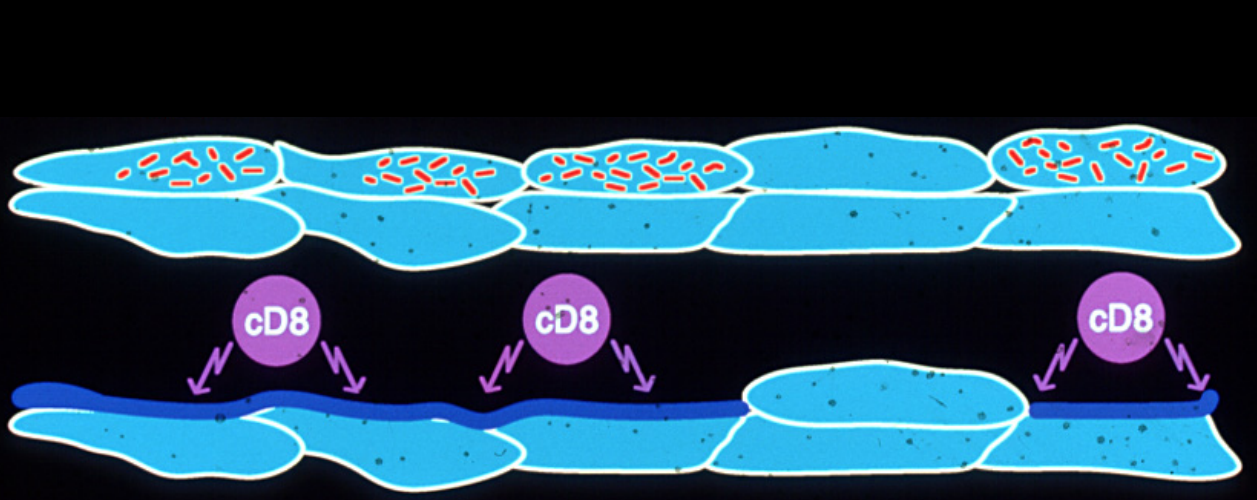
This cell-surface targeting/surveillance function works via the MHC class I glycoproteins





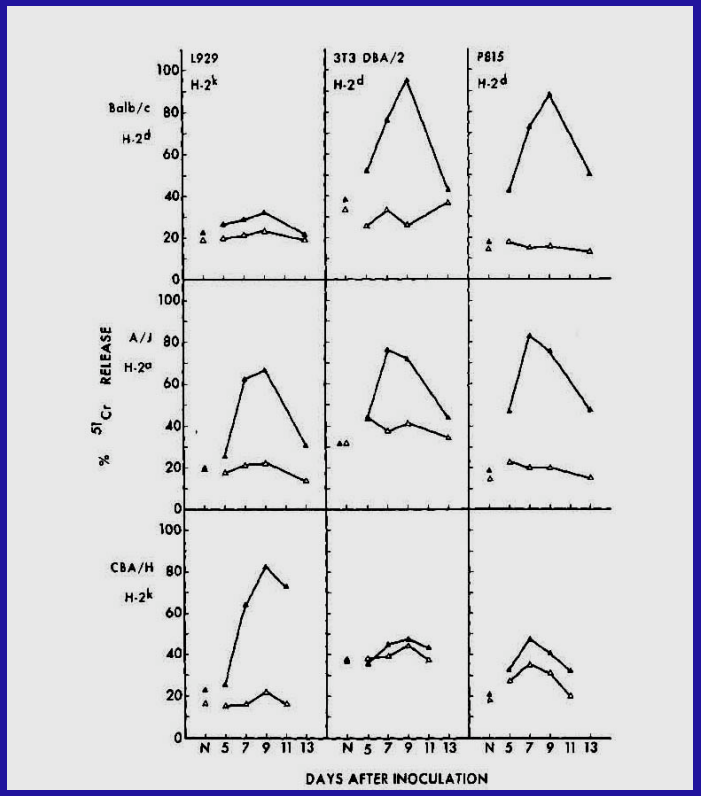
Graft rejection is an epiphenomenon of surveillance of self. The MHC-I genes are encoded at 3 loci and are very polymorphic. The CD8 T cell response is highly INDIVIDUALIZED

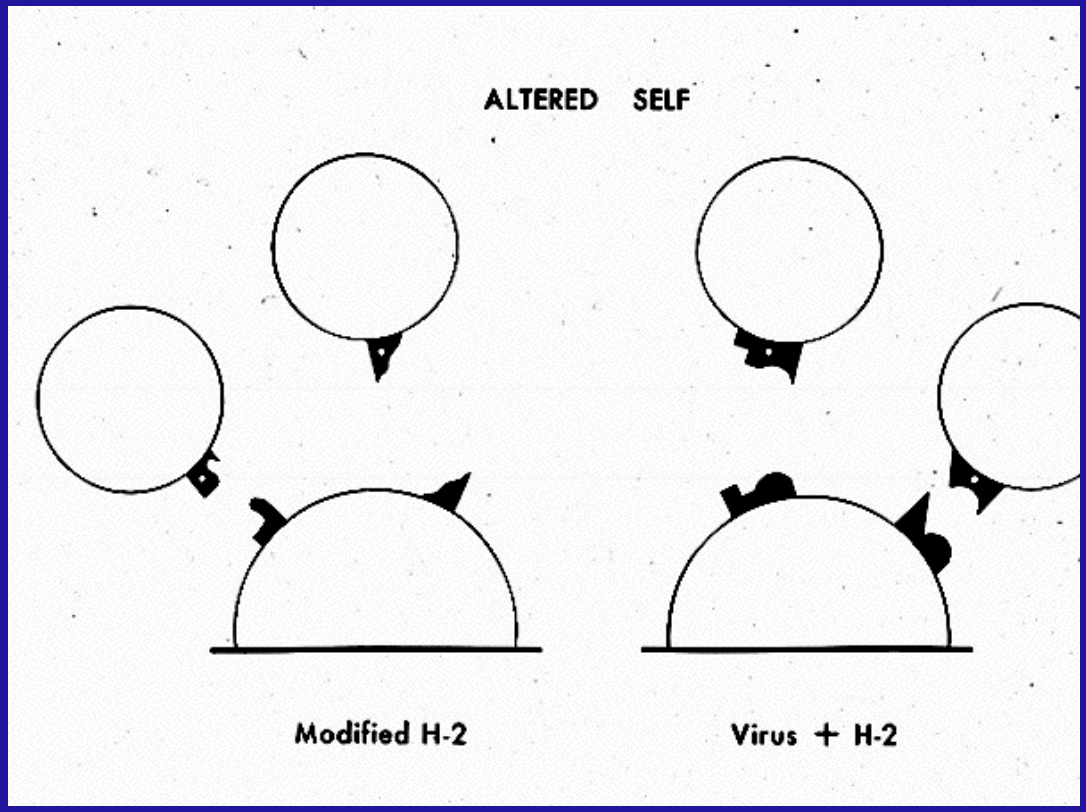
The basic principles of MHC-restricted T cell recognition were discovered 30 years ago from experiments aimed at understanding the basis of lymphocytic choriomeneningitis virus-induced immunopathology



LCM is a zoonosis that can cause severe human disease

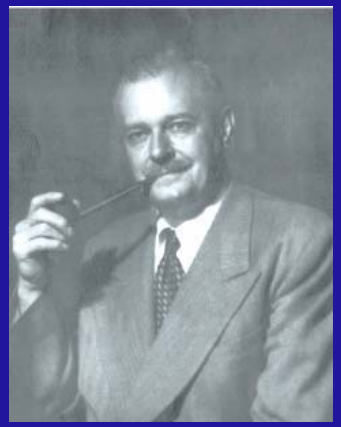
CD8$^+$ T Cell Recognition: 1974 "biology" version.



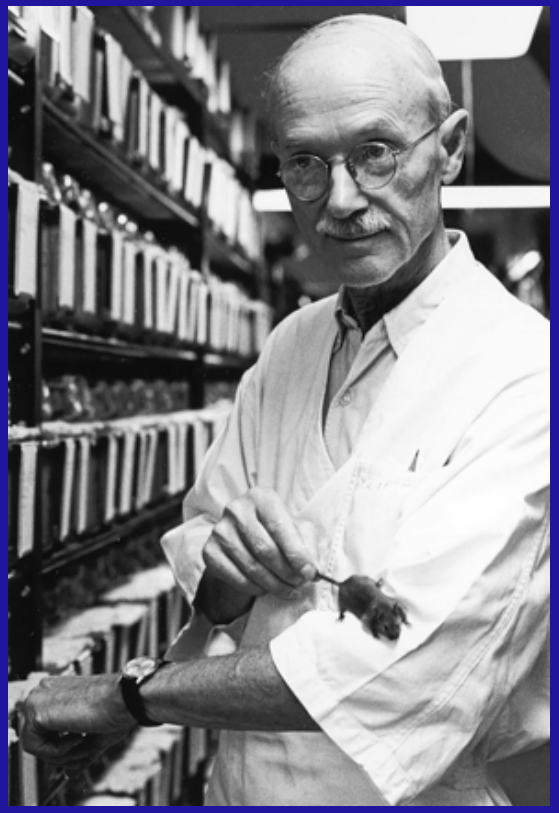


The discovery of MHC restriction told us that cytotoxic T lymphocytes (CTLs) are targeted to eliminate pathogen-modified cells rather than the pathogens themselves

Though science may advance by the type of "paradigm shift" that sometimes wins Nobel prizes, every discovery depends to some extent on what goes before.



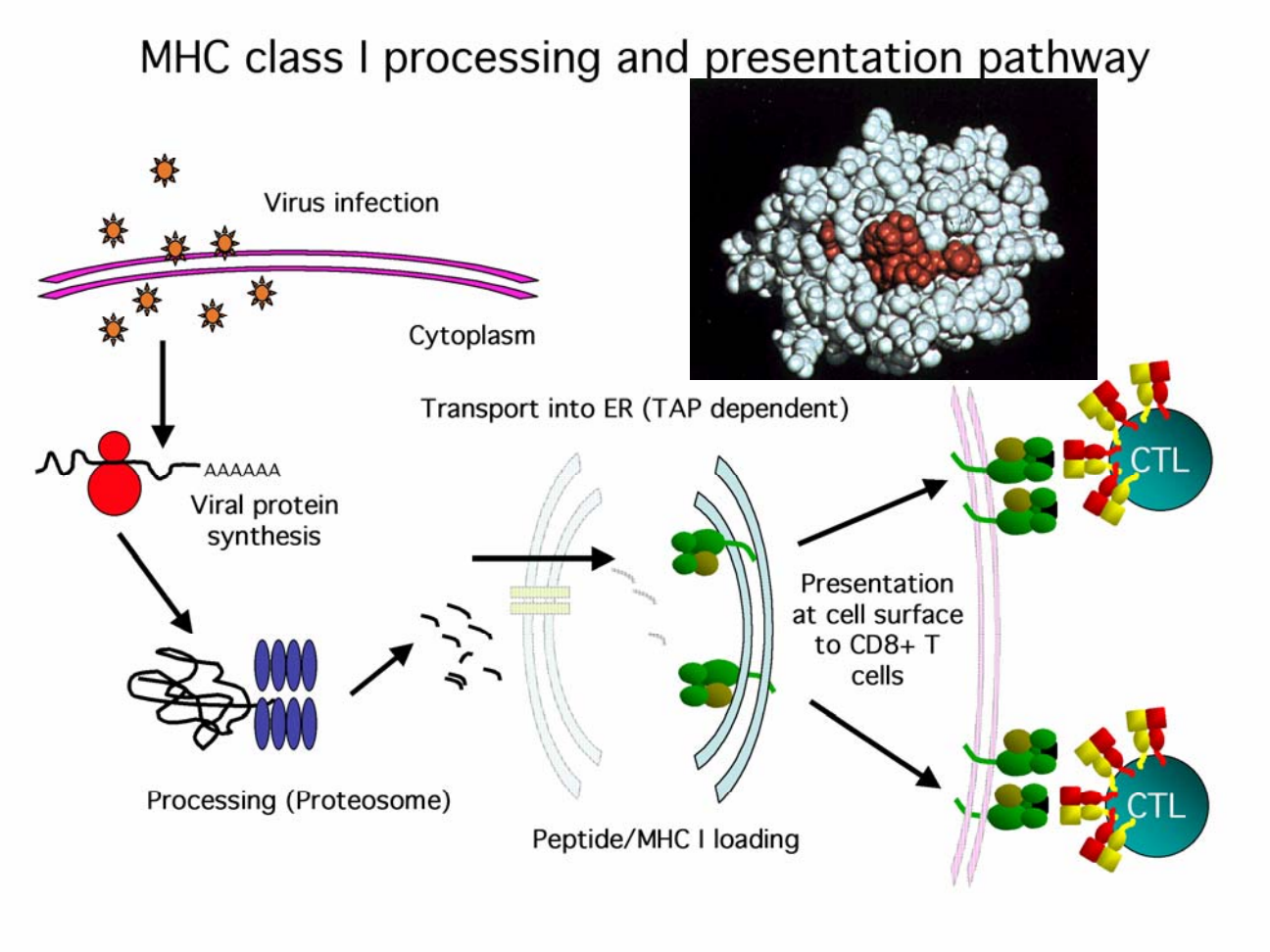
C.C. Little, started the Jackson Lab



George Snell shared the 1980 Nobel Prize

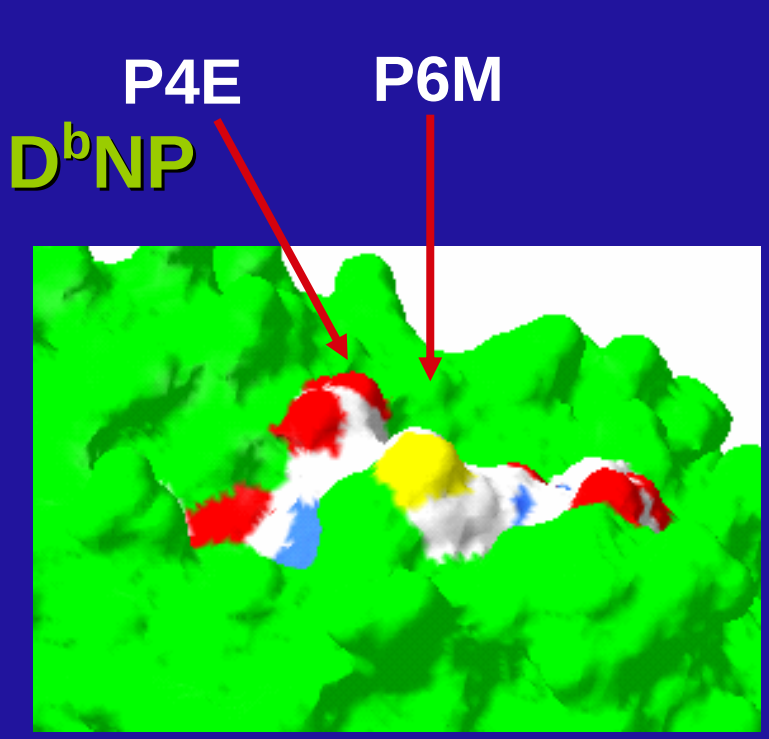
Miss Abbie Lathrop, former school teacher and ornamental mouse breeder who provided seed stock for the Roscoe B. Jackson Laboratories at Bar Harbor ME, Miss Abbie is the "mother of mouse genetics"

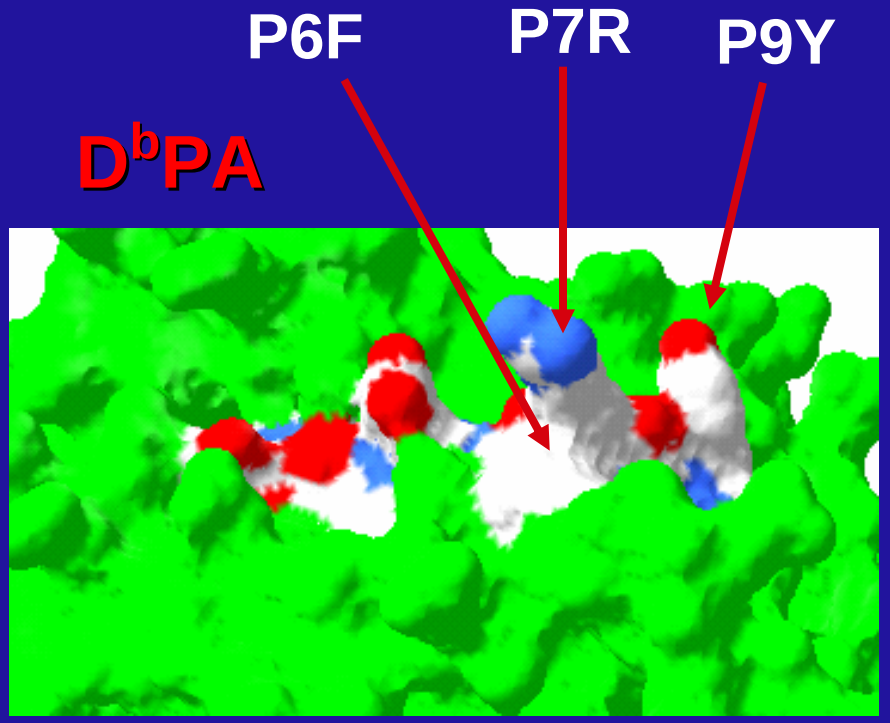
The antigen presenting cell (APC)



With the discovery by Alain Townsend that the "strong" transplantation molecules present viral peptides, a whole, new sub-discipline of antigen processing/presentation was born

Immunology comes back to complex chemistry: D^bNP presents less features to influenza specific CD8 T cells than D^bPA



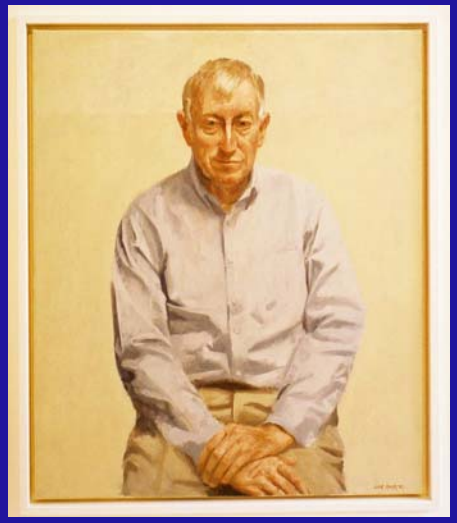


"Pistachio" vs "Chilli" peptide

Stage of Stockholm Concert Hall, December 10, 1996

King Karl XVI Gustaf

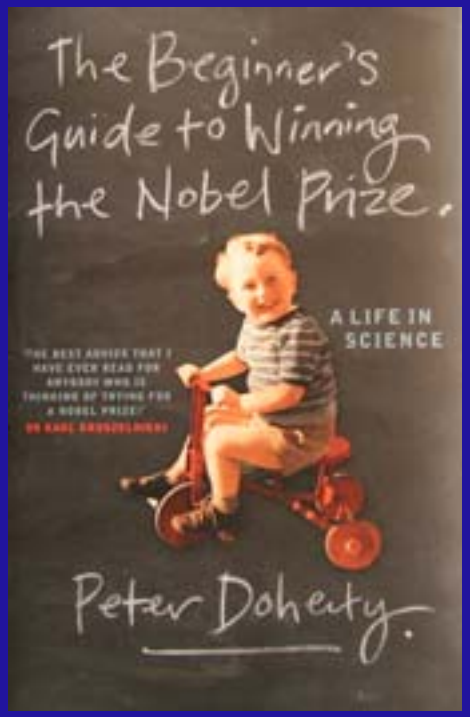
Marlo Thomas

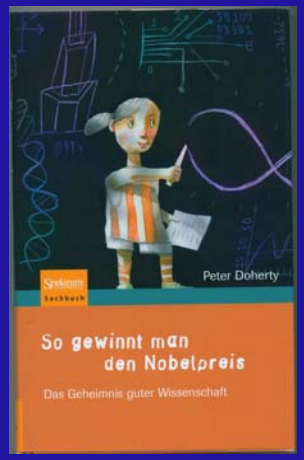


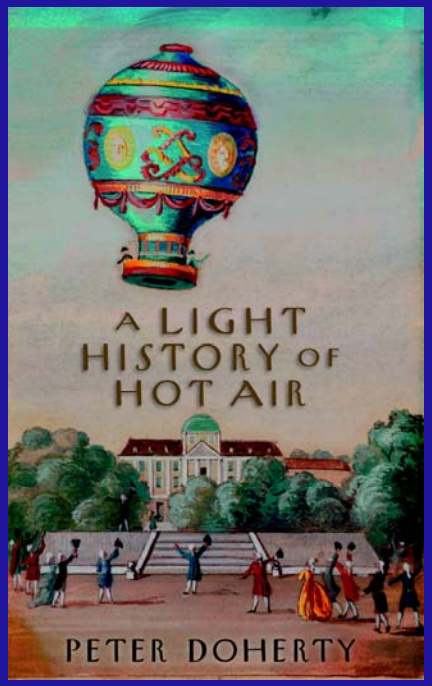
Science celebrity has about the same resonance in the broader community as being a minor character in a coffee commercial

Australian of the Year: January 26, 1997

SCIENCE COMMUNICATION IS FOR ALL OF US







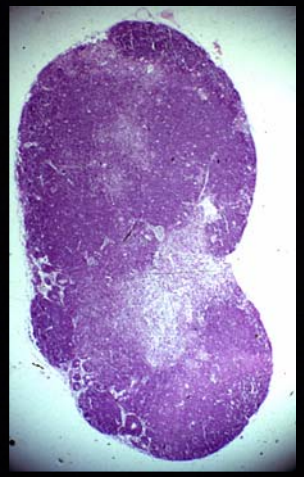
It's particularly Important to interest school children in the idea that science can solve problems

Too few people are speaking up for science in the contemporary, western world. As trained scientists in the community, every Veterinarian has the opportunity to communicate a value system that emphasizes evidence-based reality

CELLULAR IMMUNE RESPONSES TEND TO BE DEFINED BY NUMBERS

Primary

Clonal Expansion



6 Days

Secondary

3-5 DAYS

Naive

Differentiation

Te

Activated /Effector

Memory

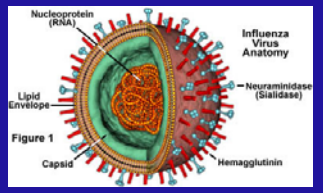
Te

Activated /Effector

Expanded memory

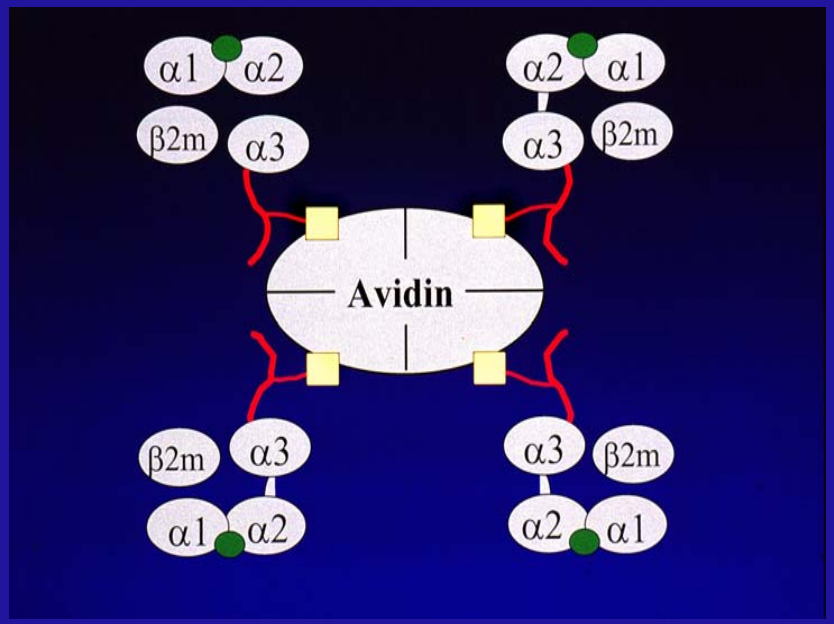
All the influenza A virus peptides in C57Bl/6 mice come from internal proteins..

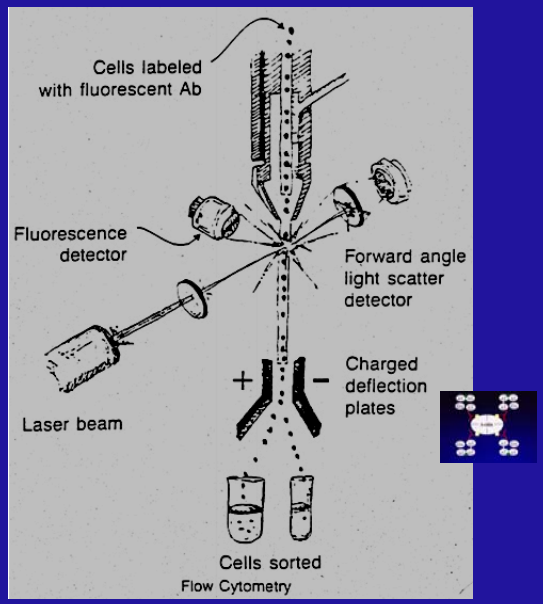
Thomas PG et al 2007 J Immunol 178:3091



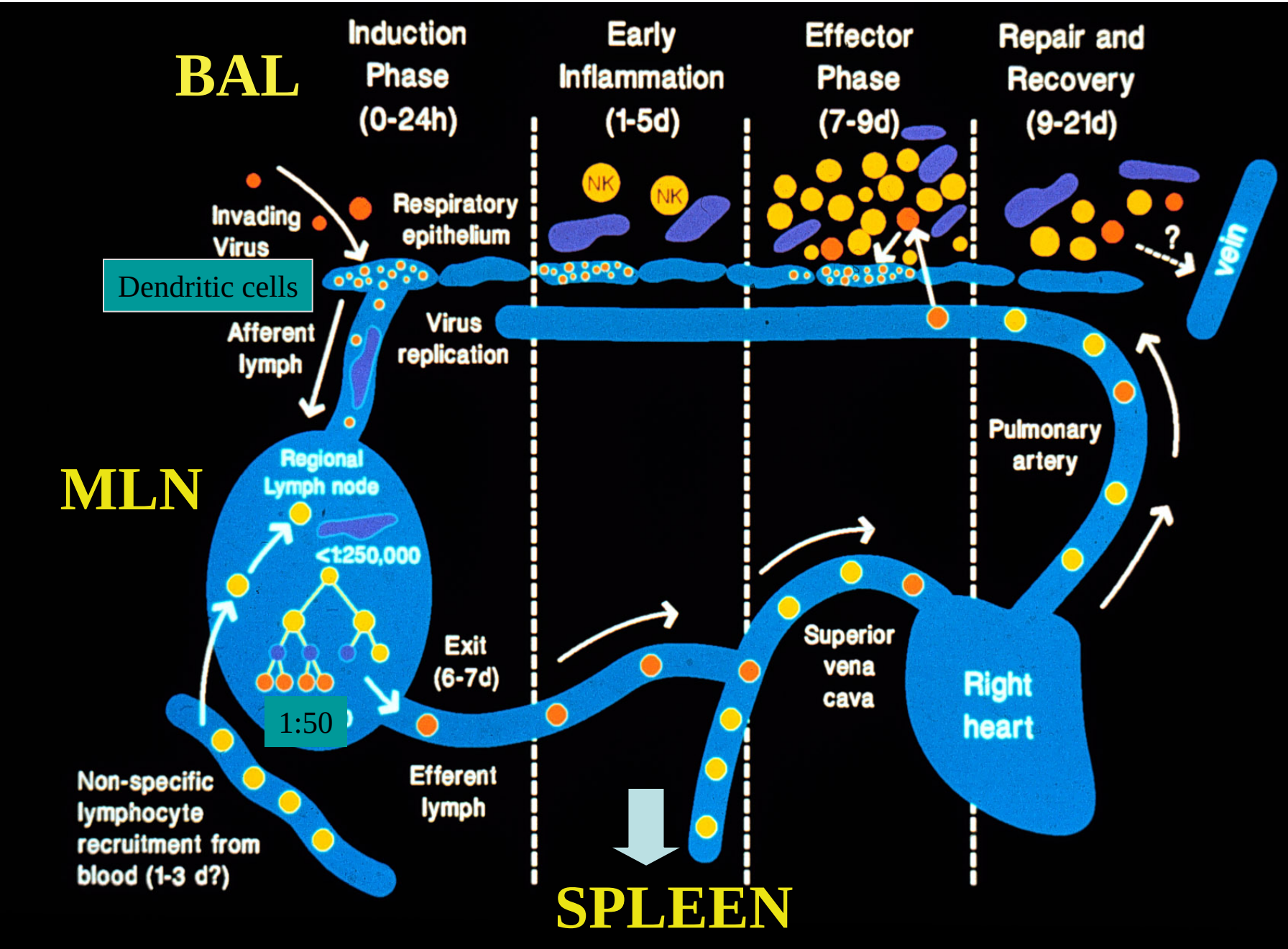
Nucleoprotein	$NP_{366-374}$	ASNENMETM	Binds D^b
Acid Polymerase	$PA_{224-233}$	SSLENFRAYV	Binds D^b
Polymerase 1	$PB1_{703-711}$	SSYRRPVGI	Binds K^b
Matrix Protein	$M1_{128-135}$	LSYSAGAL	Binds K^b
Nonstructural Protein 2	$NS2_{114-121}$	RTFSQLI	Binds K^b

Polymerase 1 $PB1\text{-}F2_{62-70}$ LSLRNPILV binds D^b



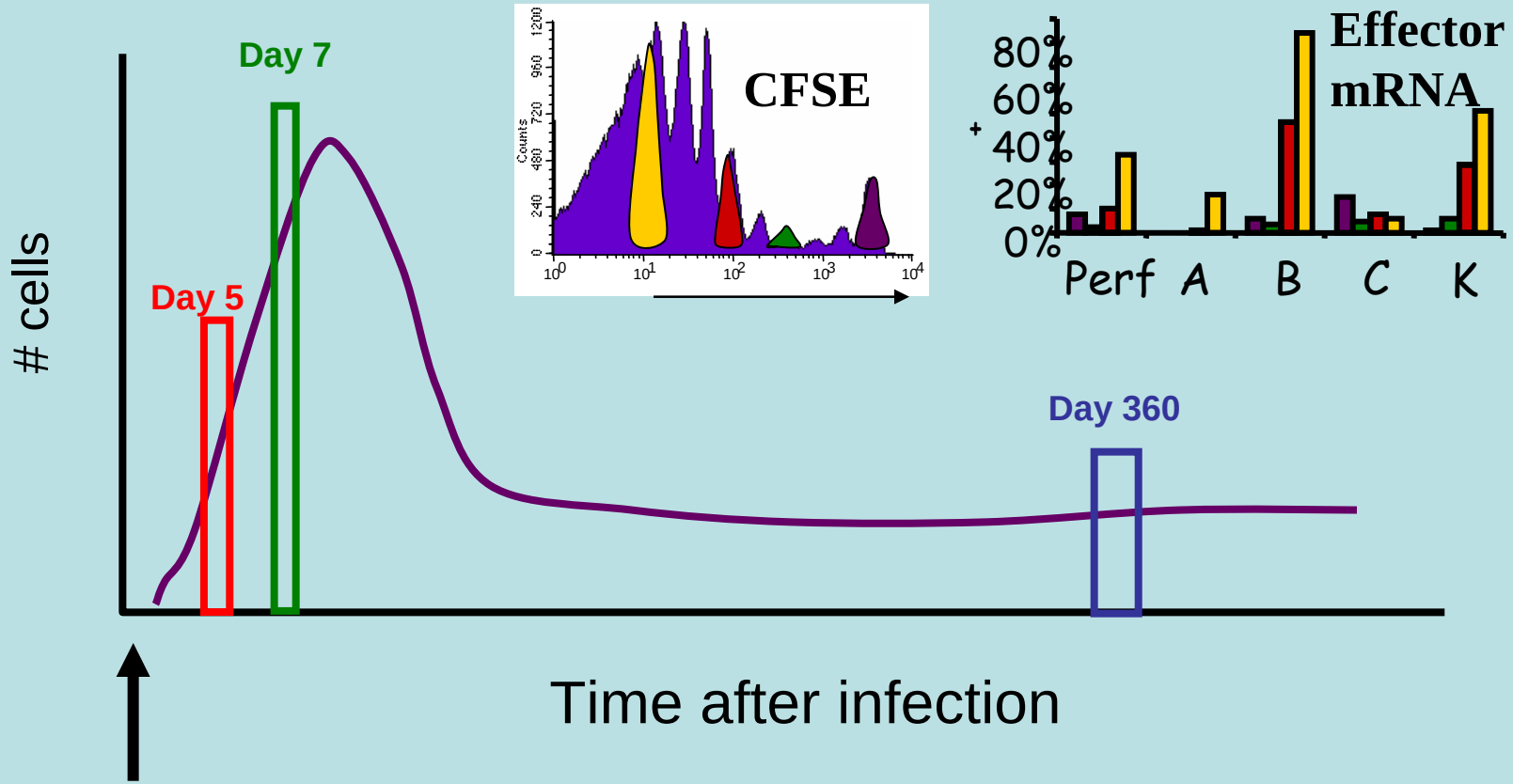


Challenge naïve or H1N1-primed B6 mice i.n. with H3N2 viruses



Increasing granzyme mRNA expression with cell division, and maintenance into long-term memory

Adoptively transferred OT1 cells HK/OVA infection

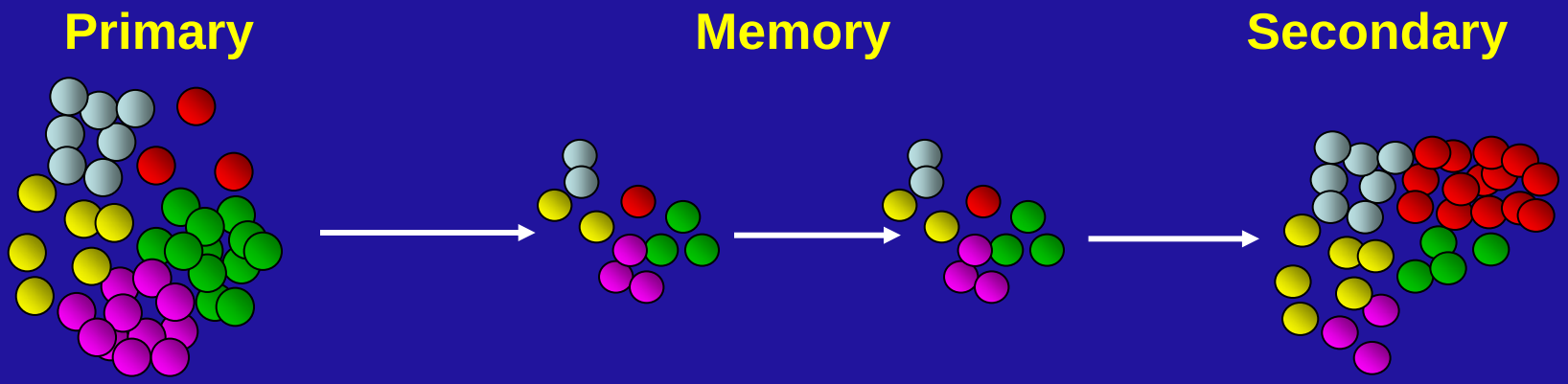


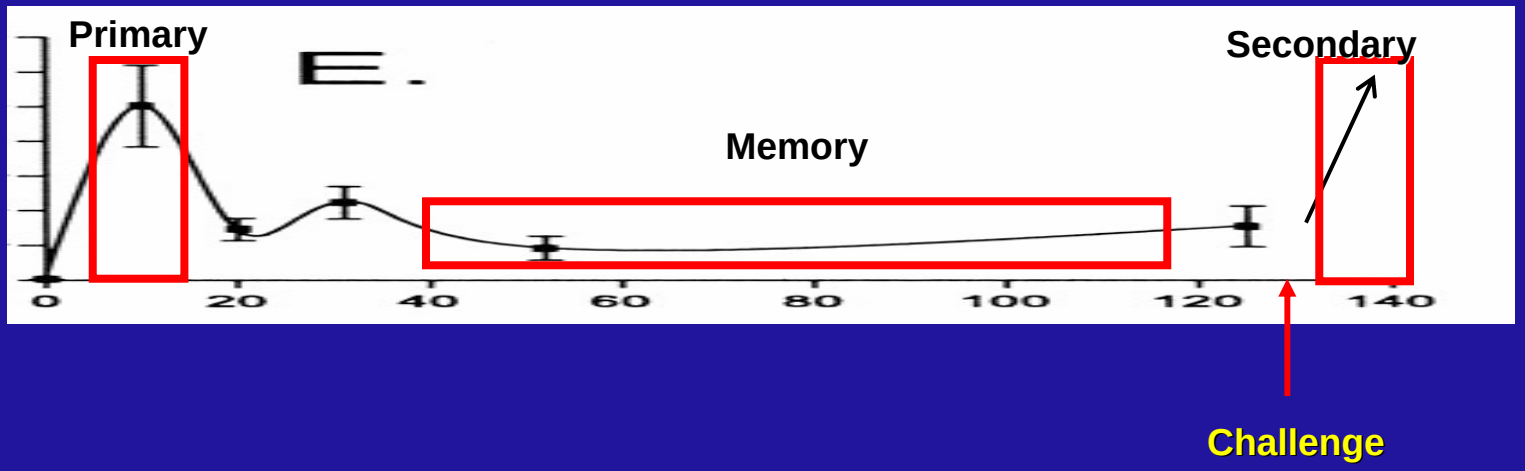
Primary infection with A/HKx31 OVA virus

Jenkins MR et al J Immunol 181, 3818,

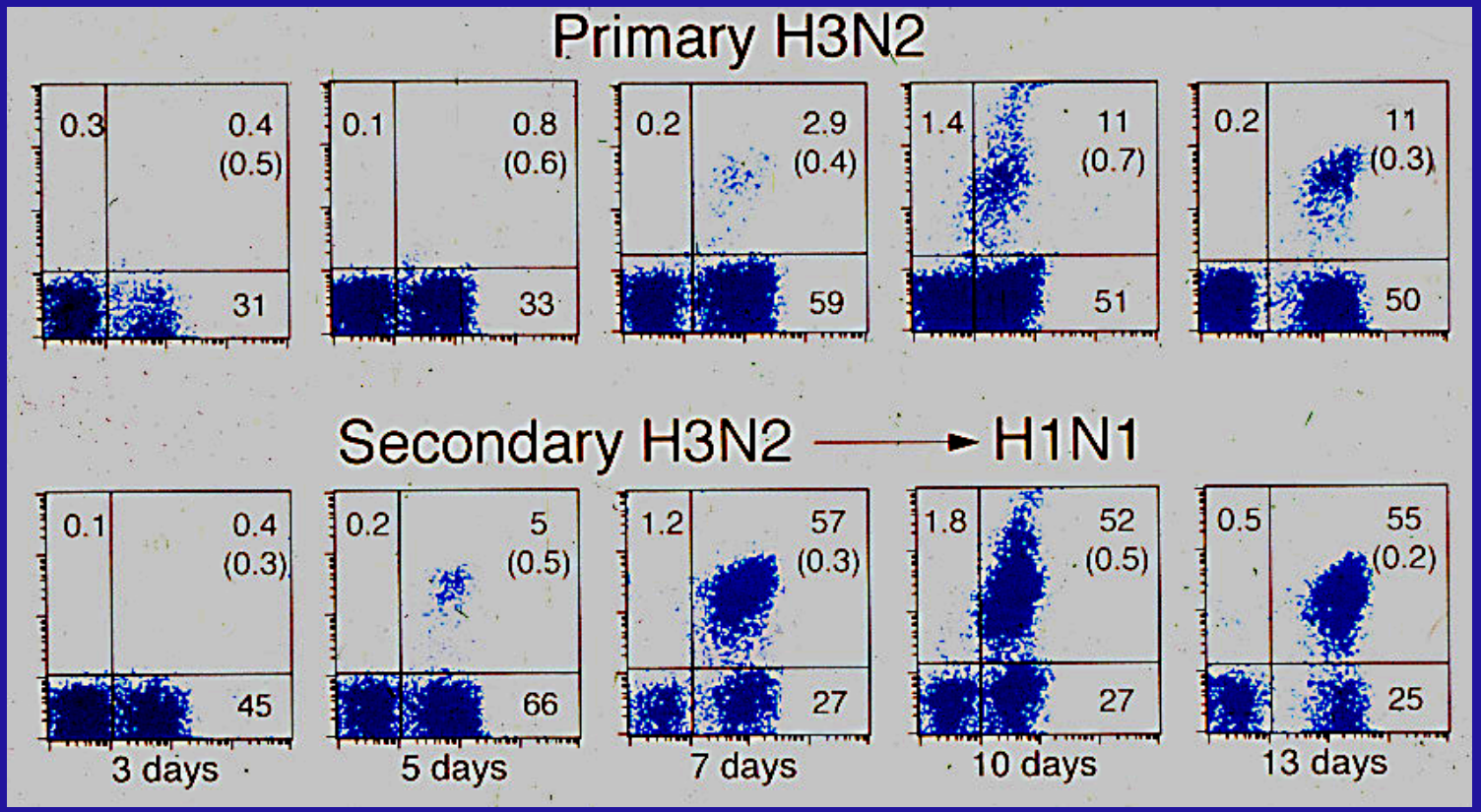
Generation of immune T cell repertoires

Establishment, persistence and recall of memory





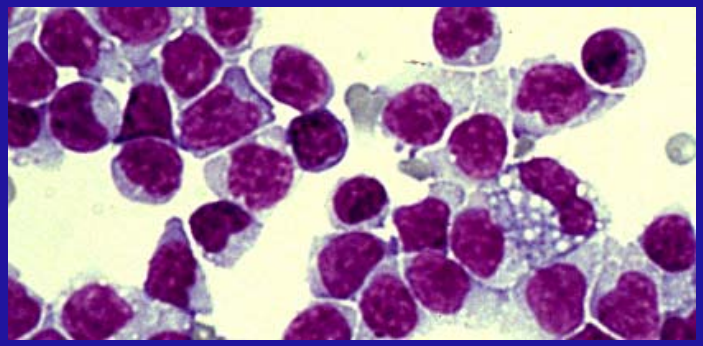
FACS analysis of the BAL



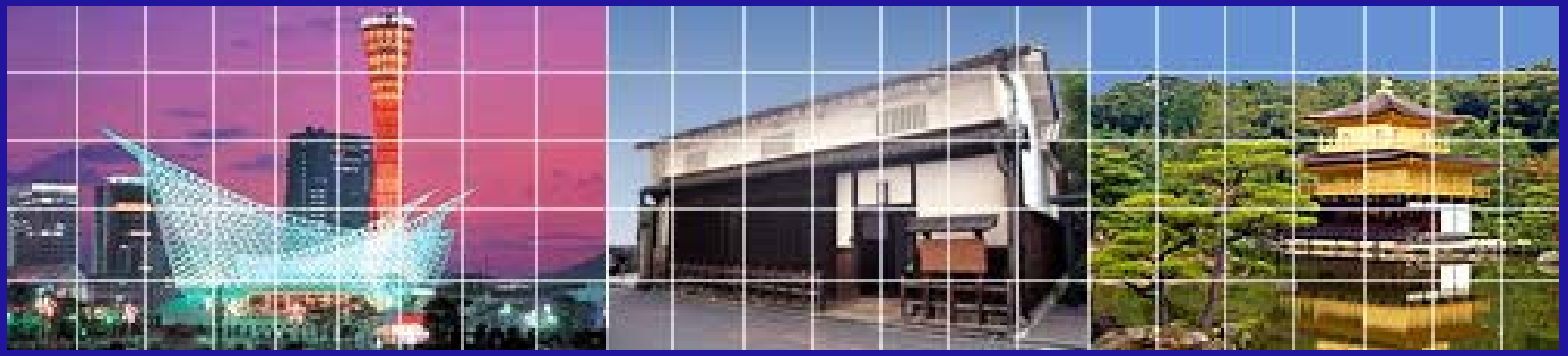
$D^bNP_{366}^+$

$CD8^+$

Primary HKx31 in naïve mice, secondary HKx31→PR8 in mice primed 7 months previously



Finally, apart from providing new insights into human disease, we also work to protect other species. Can we stop bird 'flu reaching Paris?



IUIS
international union
of immunological societies

14 th International Immunology Congress
August 22-27, Kobe Japan