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CRI

Introduction
The immune system

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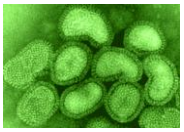
http://www.youtube.com/watch?v=yz4lFeqJPdU&feature=related
http://www.aimediaserver.com/studiodaily/harvard/harvard.swf

Outline

1. **What the immune system is for**
2. **Surface defences**
3. **How the immune system gets going**
4. **The B and T cell (acquired) responses**
5. ***The most useful application of immunology***

What is the immune system for?

To defend against:




- ❑ Viruses
- ❑ Bacteria
- ❑ Fungi
- ❑ Parasites

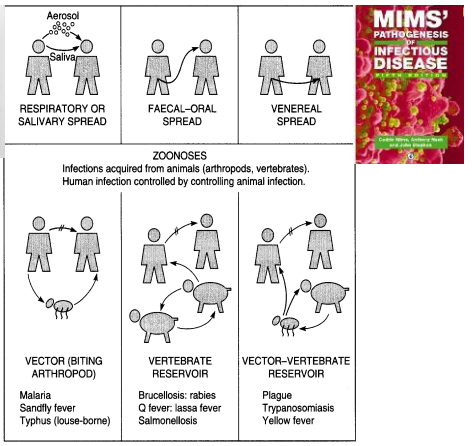
We are awash with microbes…

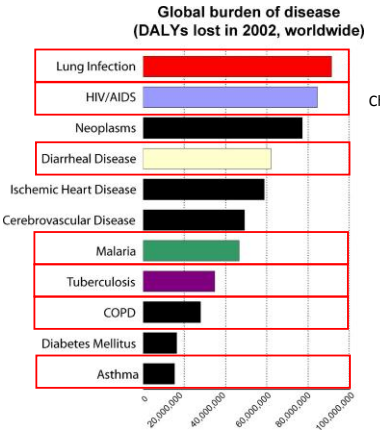
- Seawater has 10^6 bacteria and 10^7 viruses/ml
- Atmosphere contains ~1,000,000,000 Tonnes of particles
- Indoor air has 400-900 bacteria/m^3
- We inhale a potentially lethal pathogen every 7 seconds (10,000/d)
- Our bacteria outnumber our cells 10:1

Has to detect and react to dangerous things not the foreign but safe

http://www.youtube.com/watch?v=DZTkflzRJ_0


Cedric Mims





Childhood lung infections:
'A permanent global emergency'
Kim Mulholland
Lancet 2007

Lung Infection—
A Public Health Priority
Mizgerd JP (2006)
PLoS Med 3(2): e76

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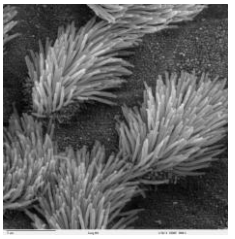
Surface defences against infections

- Coughing
- Sneezing
- Mucus
- Cilia
- Rapid cell turnover
- The wall of death…



Death: the first and last barrier

Dead already

Soon to die

General Surface defences

- **Mechanical:**
  Epithelial tight junctions
  Skin waterproofed by fatty secretions
  Social conditioning (e.g. washing)
- **Chemical:**
  Fatty acids (skin)
  Enzymes: lysozyme (saliva, sweat and tears), pepsin (gut)
  Low pH (stomach, sweat)
  Antibacterial peptides (Paneth cells in intestine)
- **Microbiological:**
  Normal flora compete for nutrients/attachment sites
  Production of antibacterial substances

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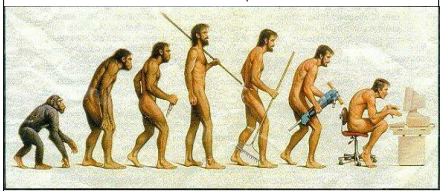
The sequential actions of the immune system

Pre-infection	Early infection	Late infection
'first line'	'second line'	'specific / acquired'
avoidance	phagocytes	
smell	opsonins	
taste	some lymphocytes	T cells
mucus	interferons	antibody
physical barriers	acute phase proteins	
surface environment	Toll-like receptors	



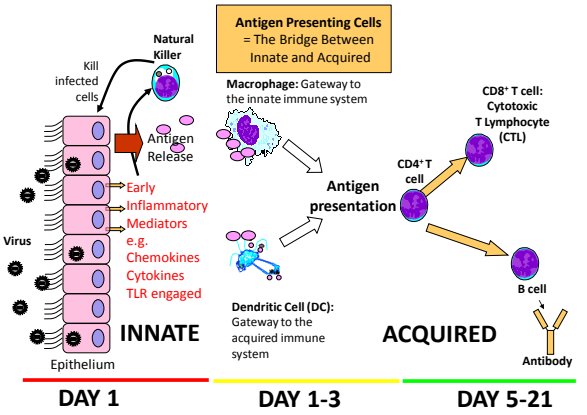
The sequential actions of the immune system

Pre-infection	Early infection	Late infection
'first line' avoidance smell taste mucus physical barriers surface environment	'second line' phagocytes opsonins some lymphocytes interferons acute phase proteins Toll-like receptors	'specific / acquired' T cells antibody

specificity

breadth

learning



Innate sensing

"Stranger" PAMPs
1992

Charlie Janeway

Hajime Kono and Kenneth L. Rock

NATURE REVIEWS | IMMUNOLOGY VOLUME 8 | APRIL 2008 | 279

"Danger" DAMPs
1994

Polly Matzinger
And Annie

Interferons

TYPE I/III: $\alpha/\beta/\lambda$

– activates NK cells

– upregulates MHC, Mx proteins

– activates RNase L, PKR

– induces anti-viral state

TYPE II: IFNγ

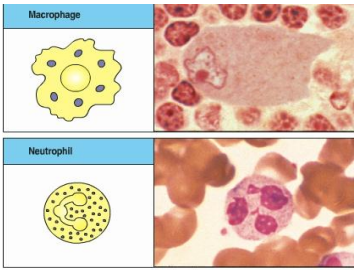
- proinflammatory
- Th1 cytokine
- "immune interferon"

Phagocytes

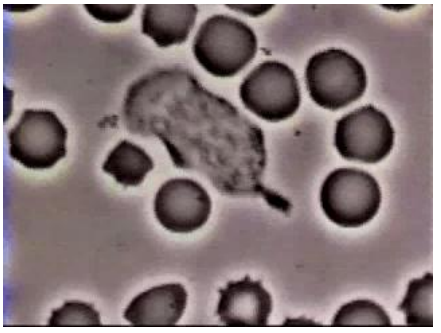
•Cells that engulf invaders

•Antigen is destroyed in intracellular vesicles

Leukocytes (white cells)

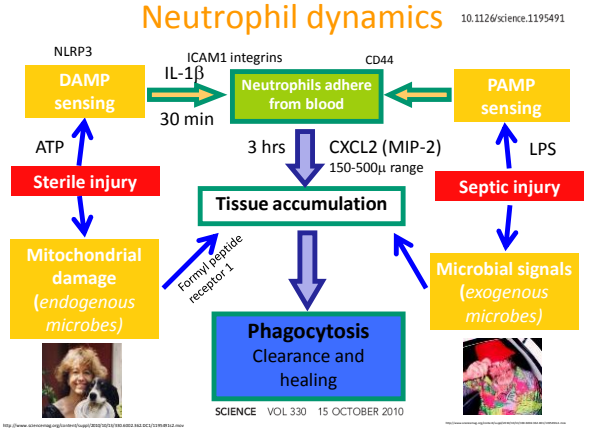


Neutrophil chasing bacteria

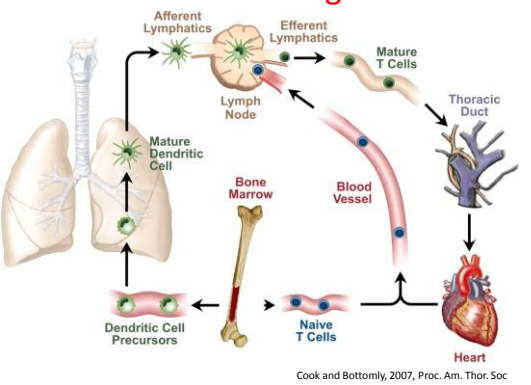


From 16mm movie, 1950s by David Rogers, Vanderbilt University
http://www.youtube.com/watch?v=I_xh-bkiv_c

Neutrophil dynamics



DC and T cell migration

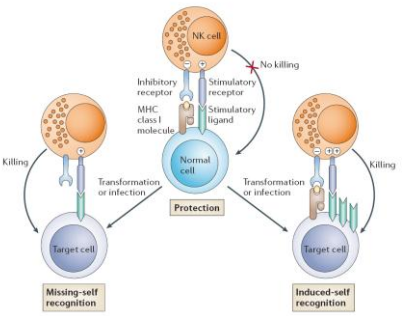


Cook and Bottomly, 2007, Proc. Am. Thor. Soc

Natural Killer Cells

- NK cells kill host cells that are:
  - Infected
  - Transformed
  - 'Stressed'
- Important in viral infections.
  - Viruses evade NK cell killing
  - NK deficiency leads to increased infections
- Important early source of cytokines
- Shape adaptive immune responses

Natural Killer Cell Activation



Raulet *et al. Nature Reviews Immunology* **6**, 520–531 (July 2006) |

nature REVIEWS IMMUNOLOGY

NK cell killing

15x

Fiona Culley, Imperial

http://www.youtube.com/watch?v=84MlWh1XN0Q

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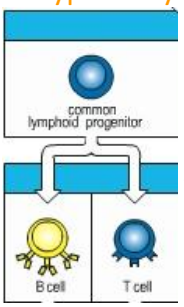
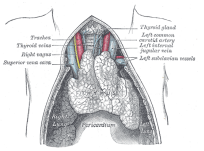
The acquired immune system

Two main types of lymphocyte

Hieronymus Fabricius
(Girolamo Fabrici)
1537-1619
'The Father of Embryology'



Bone marrow in mammals, Bursa of Fabricius (chickens)

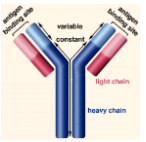


Arise in the bone marrow but mature in the Thymus

B cells express/secrete antibody

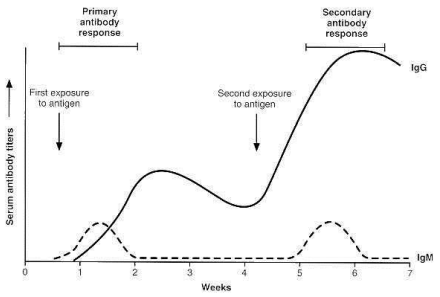
- Each antibody recognises one specific shape/charge combination
- Each B cell expresses one unique antibody

ANTIBODY



Georges Kohler & Cesar Milstein. Nature (1975) **256**: 495-7

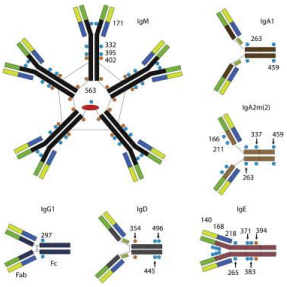
Typical antibody response to vaccines:

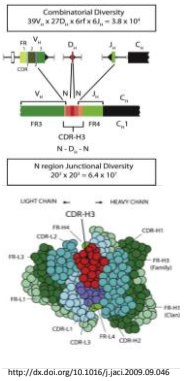


http://www.microbiologybytes.com/iandi/3b.html

Antibody is very diverse

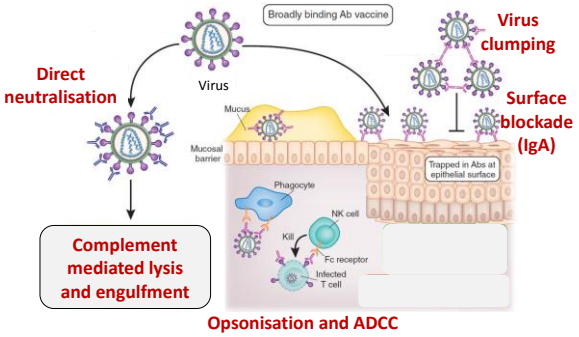
- Specialised classes of antibody
- 10^{14} potential VDJ combinations





http://dx.doi.org/10.1016/j.jaci.2009.09.046

The actions of antibody

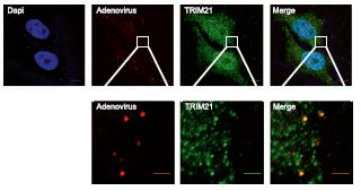


Adapted from Nature Medicine Volume: 17: 1195–1197 (2011) DOI: doi:10.1038/nm.2528

Antibodies mediate intracellular immunity through tripartite motif-containing 21 (TRIM21)

Donna L. Mallery[a,1], William A. McEwan[a,1], Susanna R. Bidgood[a,1], Greg J. Towers[b], Chris M. Johnson[a], and Leo C. James[a,2]

PNAS | November 16, 2010 | vol. 107 | no. 46 | 19985–19990

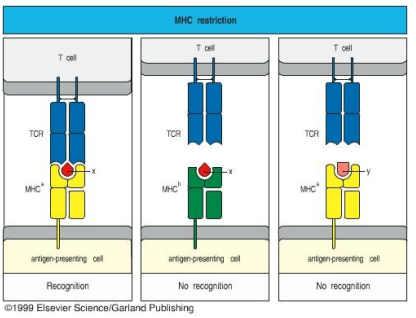


Hidden life of the cell: BBC2 October 2012
http://www.youtube.com/watch?v=v1MnNO4I9aU

Summary: antibodies

1. Made by B cells
2. Bind antigen
3. Cell membrane bound/secreted
4. Enhances phagocytes (opsonisation)
5. Recruits other toxic molecules/cells

T cells and their receptors (TcR)



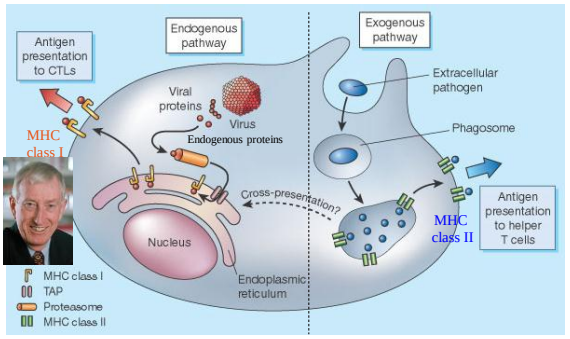
Each T cell expresses one TcR

There are potentially 10^{18} different TcRs

Each TcR sees a specific combination of MHC and peptide at high affinity

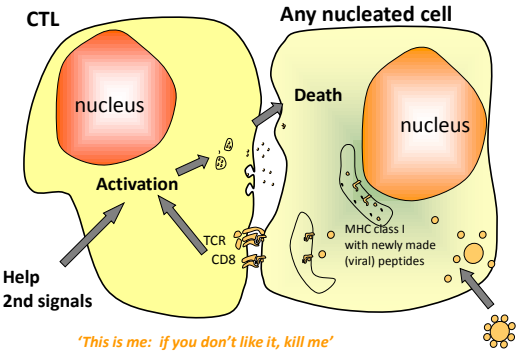
MHC: **major histocompatibility complex**

Antigen processing and presentation



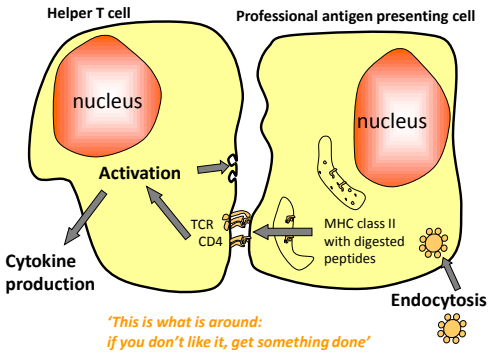
Adapted from Dept of VMP, Washington State University

The Class I - Cytotoxic T cell system



'This is me: if you don't like it, kill me'

The class II - Helper T cell system



'This is what is around: if you don't like it, get something done'

Defences against bacteria

- **Surface defences** (mechanical and chemical)
- **Antibody** opsonisation
- **Complement** (alternative pathway) causing lysis/opsonisation
- **Phagocytosis**
- Release of inflammatory mediators and **acute phase proteins** (also opsonins) *etc.*
- **Fever**

Defences against viruses

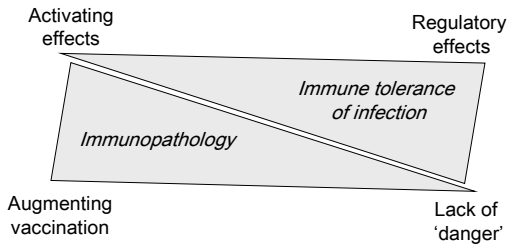
- Surface defences
- Interferons
- Inflammatory mediators and acute phase proteins/opsonins *etc.*
- NK cells
- Antibody, complement, ADCC
- T cells

Mucosal defences

1. Mannan binding proteins
2. Antimicrobial peptides
3. Enzymes (e.g. lysozyme)
4. Mucosal lymphocytes
5. Secretory IgA
6. Special antigen sampling
   - Waldeyer's ring
   - Peyer's patches
   - Dendritic cell networks

Balance Tolerance vs. Attack

The spectrum of activation and regulation



Inflammation is tightly regulated

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Vaccines

the most cost-effective drugs

NHS choices

Do you recognise this disease?

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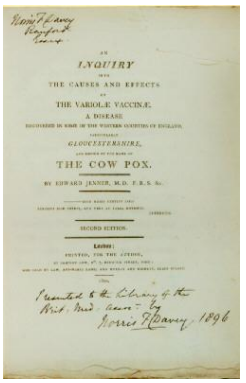
Edward Jenner



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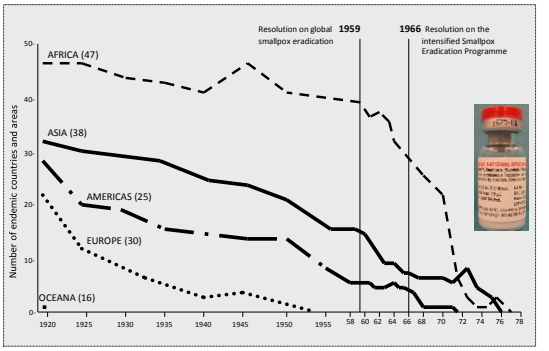
Global eradication of smallpox



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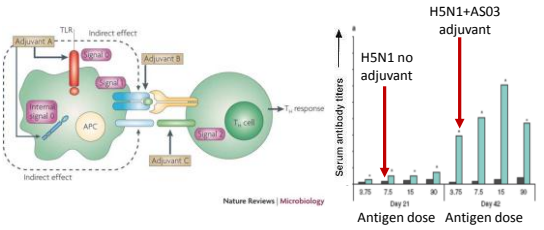
The 'dirty little secret' of the one-shot vaccine: **Adjuvants**



Immunity = antigen x adjuvant

Bruno Guy, Nat Rev Microbiol 5:505-517 (July 2007) doi:10.1038/nrmicro1681
Carter et al. BioDrugs 2008, 22:279

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Characteristics of an eradicable infectious disease

- Simple (and cheap) to diagnose
- Genetically stable pathogen
- Accessible host species
- Eliminates persistent infection, or persistently infected host can't transmit
- **Safe and effective vaccine**

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"Three million children die each year in poor countries from diseases that can be prevented by vaccination"

(World Bank, 1999)

Immunity

~ Defence against infection

Wealth, social stability