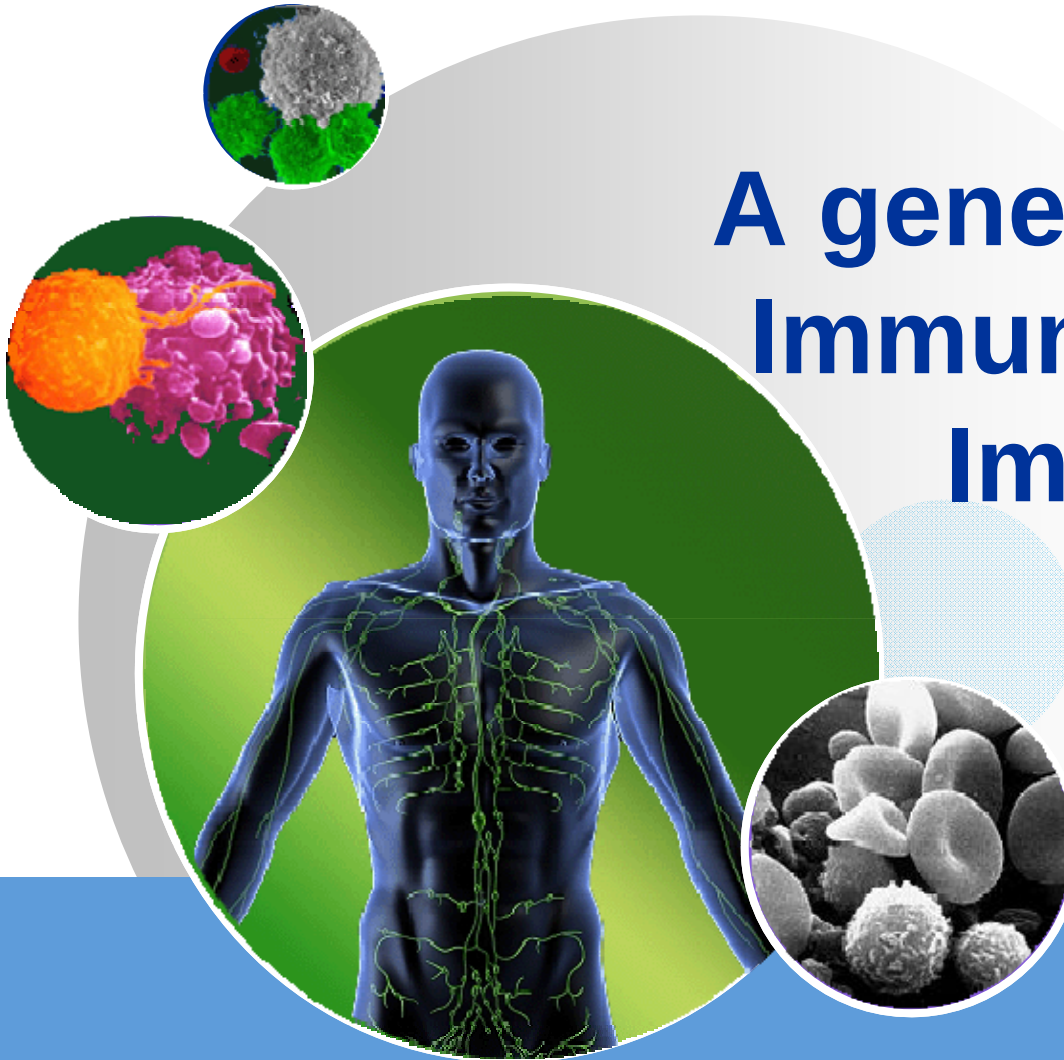


A general overview of Immune system and Immunology



Shuyan Li

2/4/2009



Definition

❖ Immune system

- a collection of biological processes within an organism that protects against disease by identifying and killing pathogens and tumor cells

❖ Immunology

- a science that examines the structure and function of the immune system



History of immunology

- ❖ The plague of Athens in 430 BC. Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time.
- ❖ 1796, Edward Jenner, discovered vaccination. Later, Louis Pasteur, germ theory of disease.
- ❖ 1891, Robert Koch got his proofs, that microorganisms were confirmed as the cause of infectious disease.(Nobel Prize in 1905).
- ❖ 1901, Walter Reed discovered viruses were confirmed as human pathogens, with the discovery of the yellow fever
- ❖ Late 19th century, great advance in the study of humoral immunity and cellular immunity. Paul Ehrlich proposed the side-chain theory to explain the specificity of the antigen-antibody reaction. Elie Metchnikoff, founded cellular immunology. (jointly awarded Nobel Prize 1908)



Vaccine developed with Immunology

❖ Big events of Vaccines

1796	Smallpox vaccine
1885	Rabies vaccine
1955	Injectable polio vaccine
1962	Oral polio vaccine
1967	Smallpox eradication program started
1979	Smallpox eradicated from the world
1986	First recombinant human vaccine
1994	Last case of polio in the Americas
1998	Infant immunisation rate ~80%
1999	Eradication of polio and measles in sight

- ❖ Forward to late 20th century, hepatitis A, hepatitis B, polio, mumps, measles, rubella, diphtheria, pertussis, tetanus, HiB, chickenpox, rotavirus, influenza, meningococcal disease and pneumonia, etc.



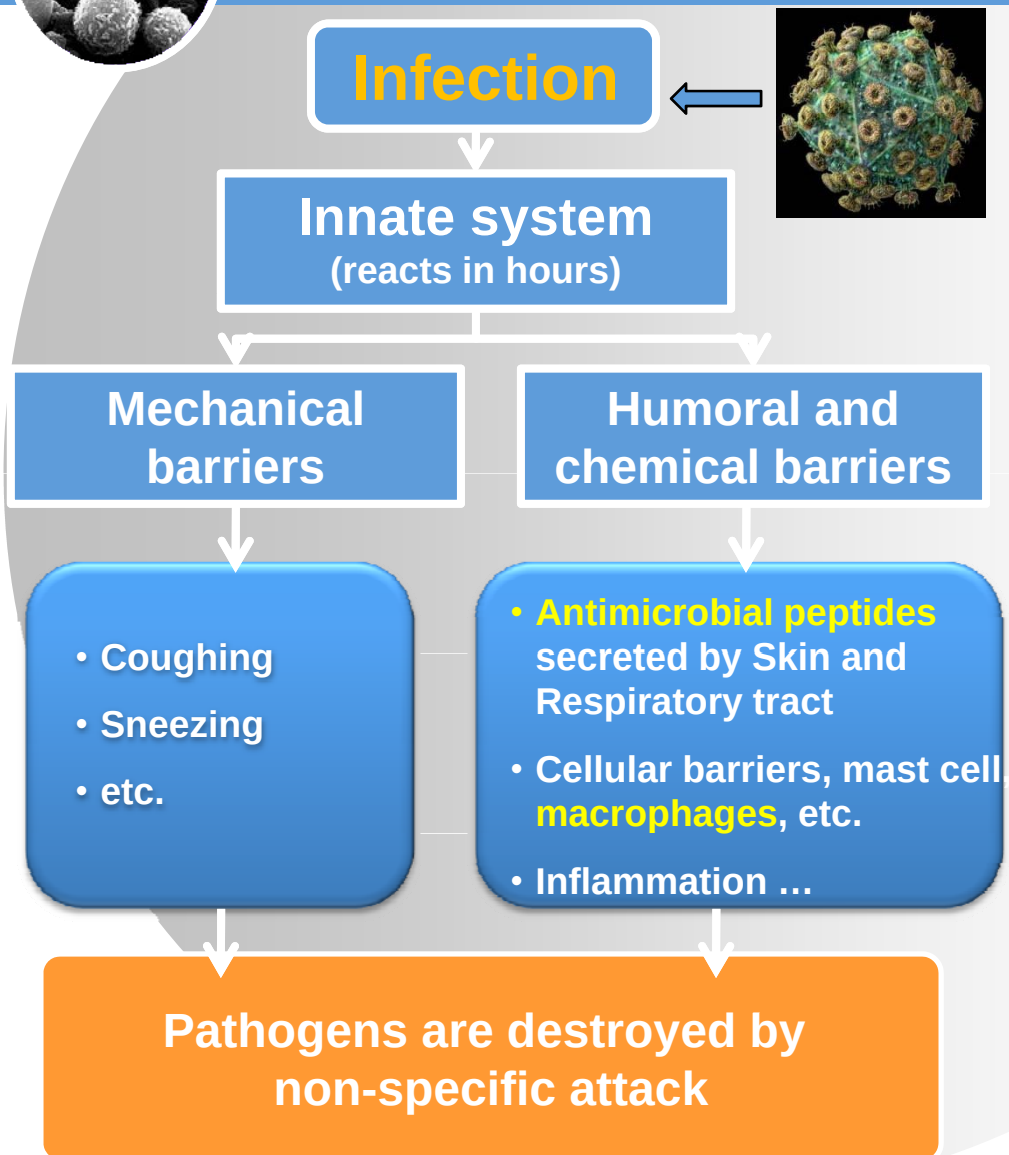
Immune system components

General characters of immune system components

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
No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in vertebrates



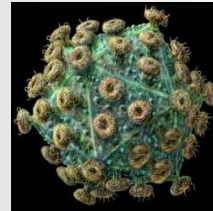
Components and Mechanisms



Layered defense Mechanisms



Infection



Innate system
(reacts in hours)

Mechanical barriers

- Coughing
- Sneezing
- etc.

Humoral and chemical barriers

- Antimicrobial peptides secreted by Skin and Respiratory tract
- Cellular barriers, mast cell, macrophages, etc.
- Inflammation ...

Pathogens are destroyed by non-specific attack

Adaptive system
(reacts in days)

Antigen presentation

Lymphocytes

T cell

B cell

Specific cytotoxic-T killer cell production

Specific antibody production



Adaptive immune system



- ❖ Lymphocytes, special types of leukocytes, are major derived from hematopoietic stem cells in the bone marrow



T cell

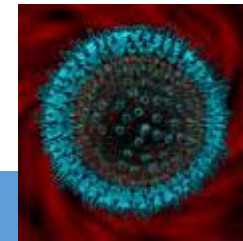
Recognize a “non-self” target, such as pathogen

Activated only after antigens (epitops, small fragments of the pathogen) have been processed and presented in combination with a “self” receptor called a **major histocompatibility complex (MHC)** molecule

Killer(Cytotoxic) T cells recognize antigens coupled to Class I MHC molecules (co-receptor called **CD8** or CD8+)

Helper T cells only recognize antigens coupled to Class II MHC molecules(co-receptor called **CD4** or CD4+)

γδ T cells ,Memory T cells, Regulatory T cells, Natural killer T cells

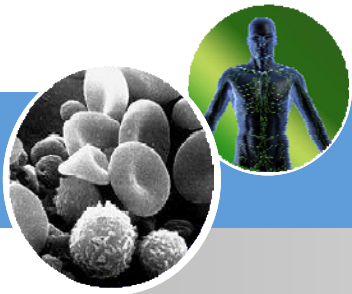


B cell

B cell antigen-specific receptor is an **antibody** molecule on the B cell surface

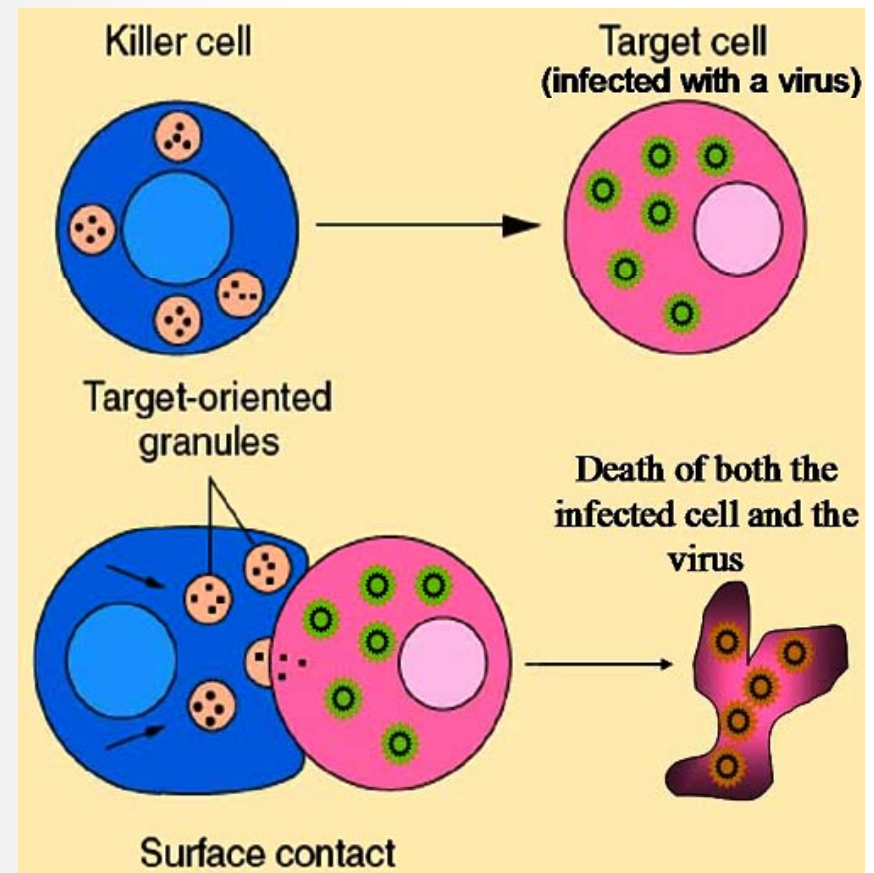
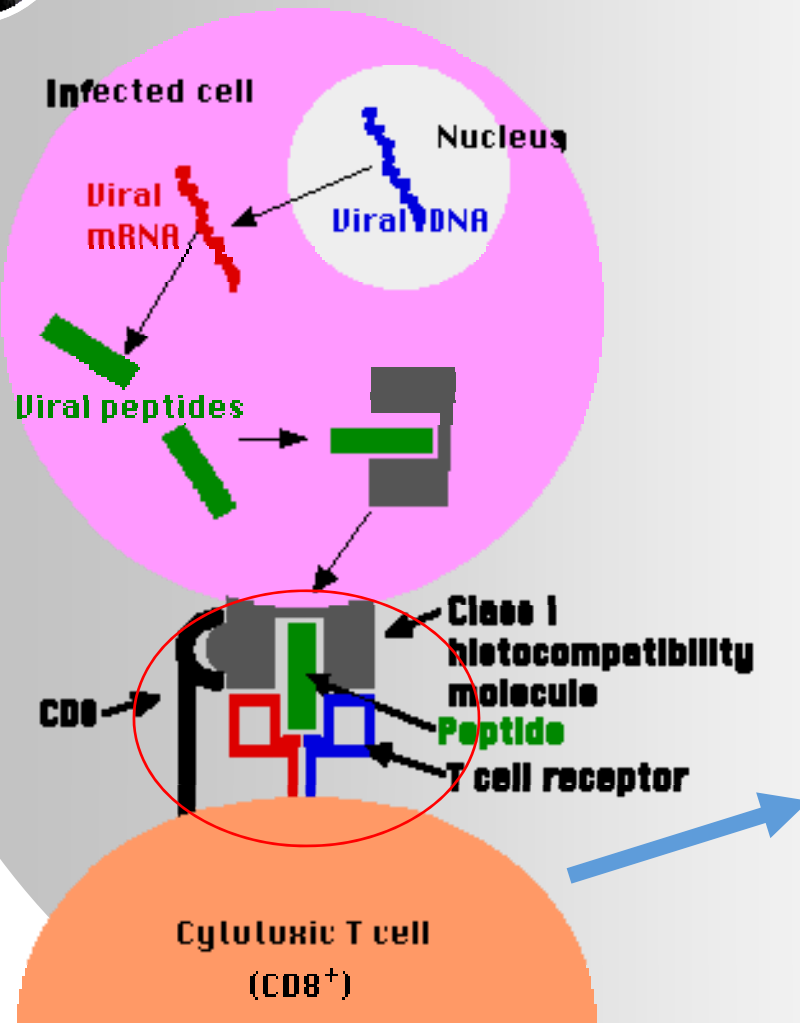
Recognizes whole pathogens without any need for antigen processing

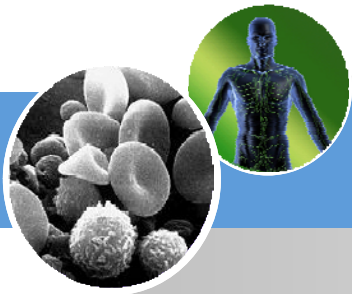
Each lineage of B cell expresses a different antibody, the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture



Adaptive immune system

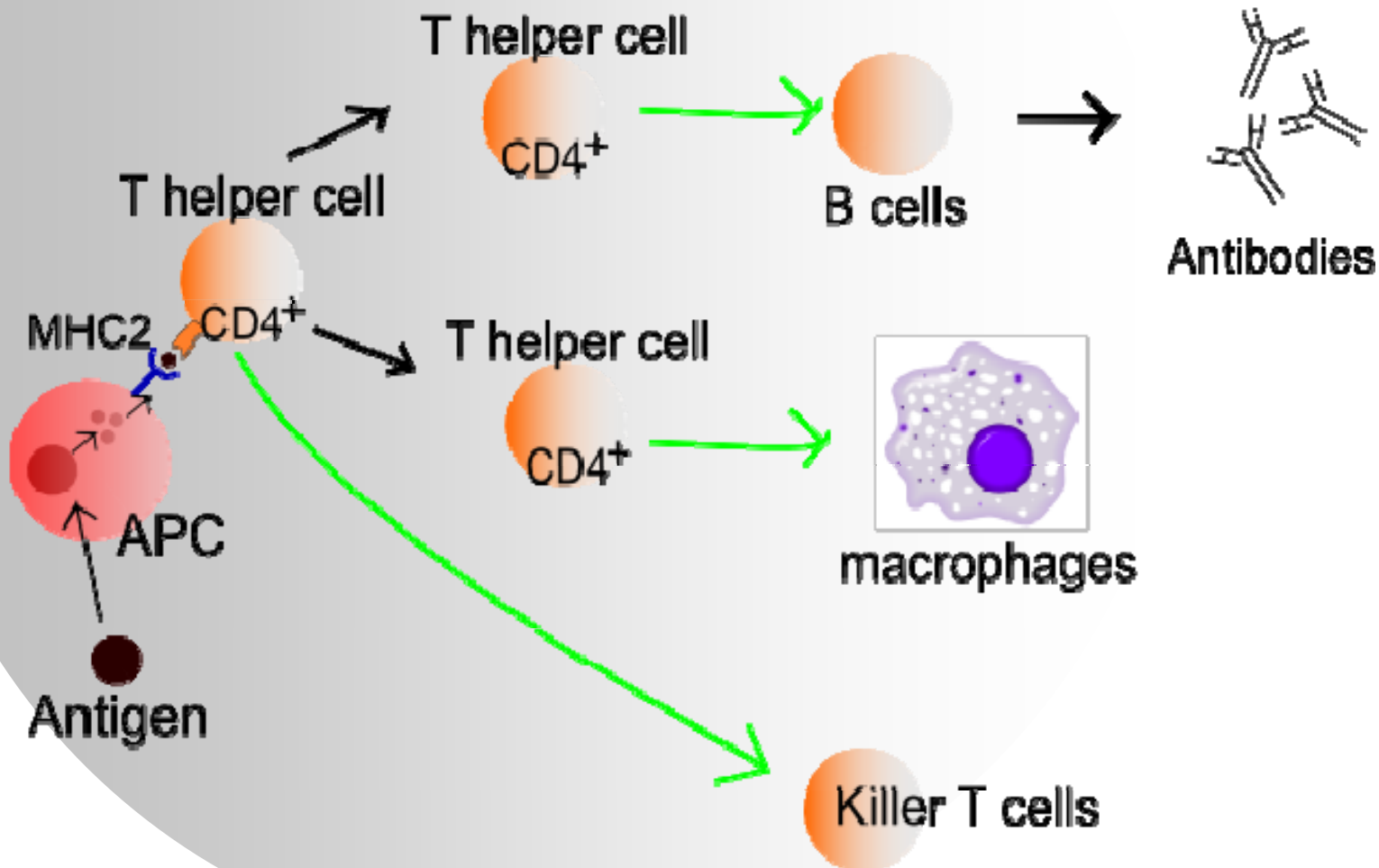
❖ Killer T cell(Cytotoxic T cell)





Adaptive immune system

❖ Helper T cell

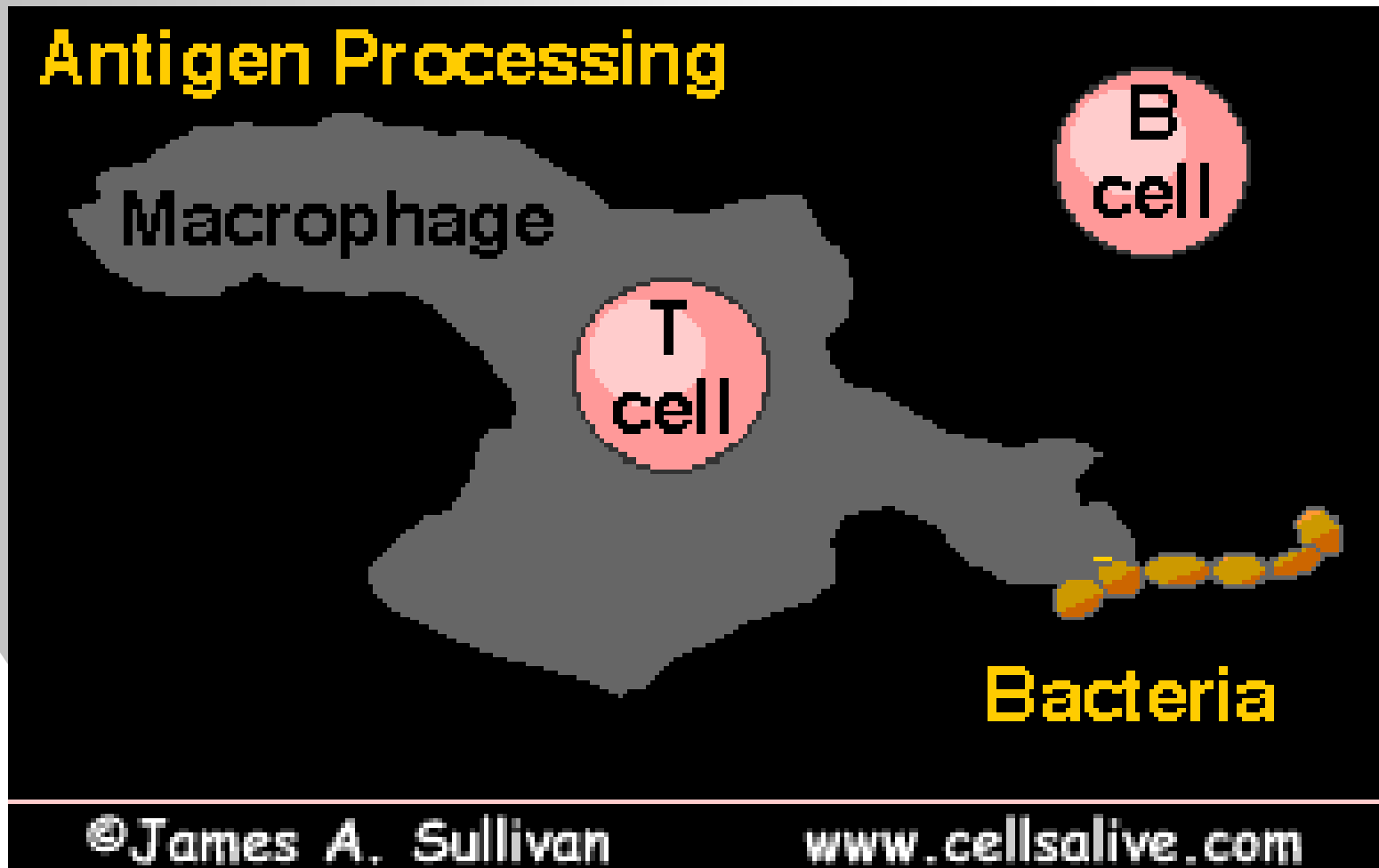




Adaptive immune system

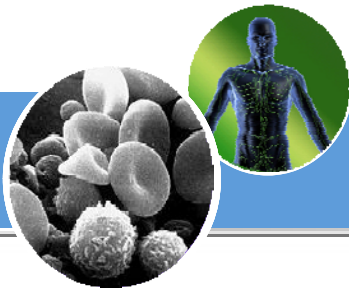
❖ Helper T cell

Antigen Processing

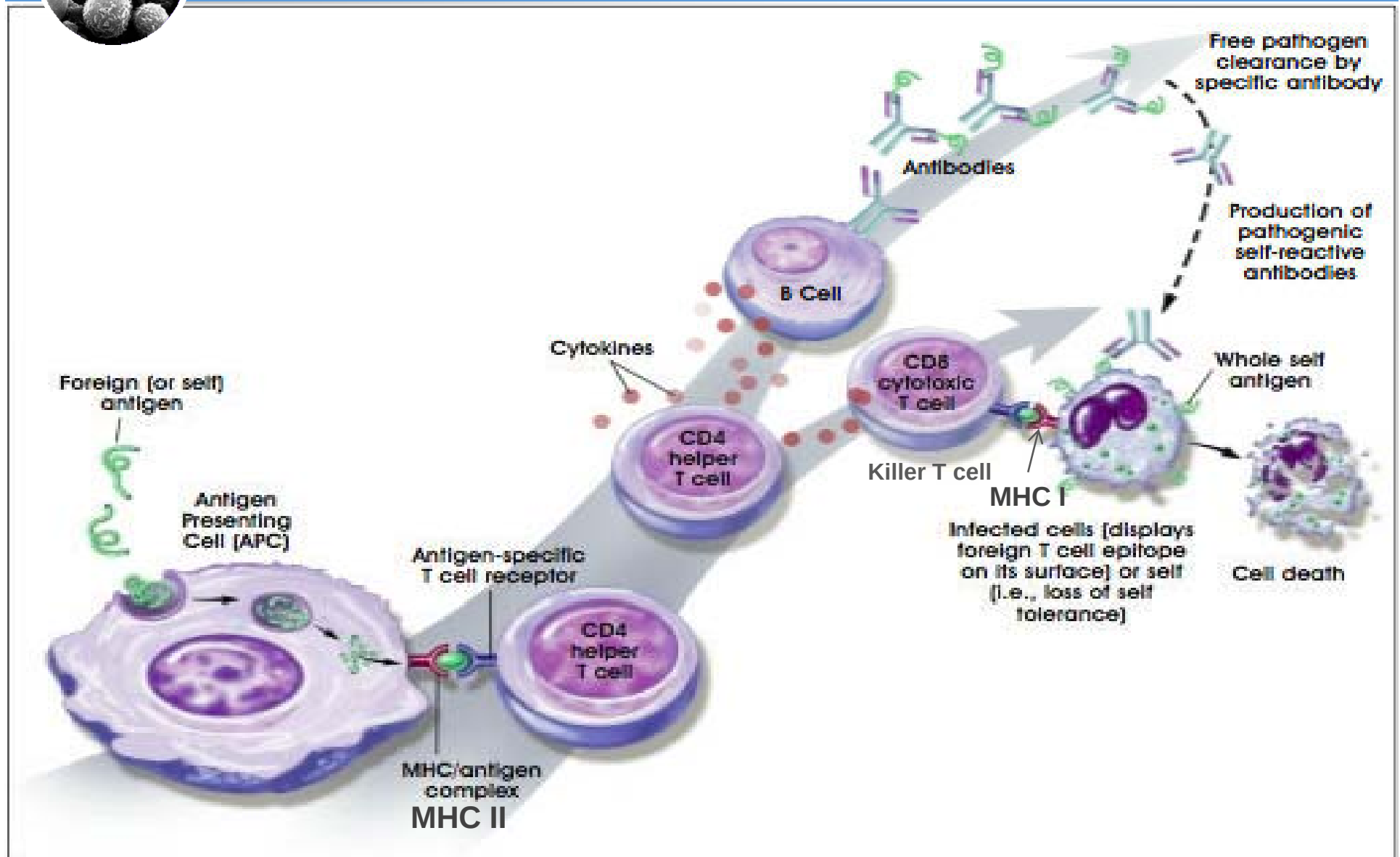


©James A. Sullivan

www.cellsalive.com



Adaptive immune system





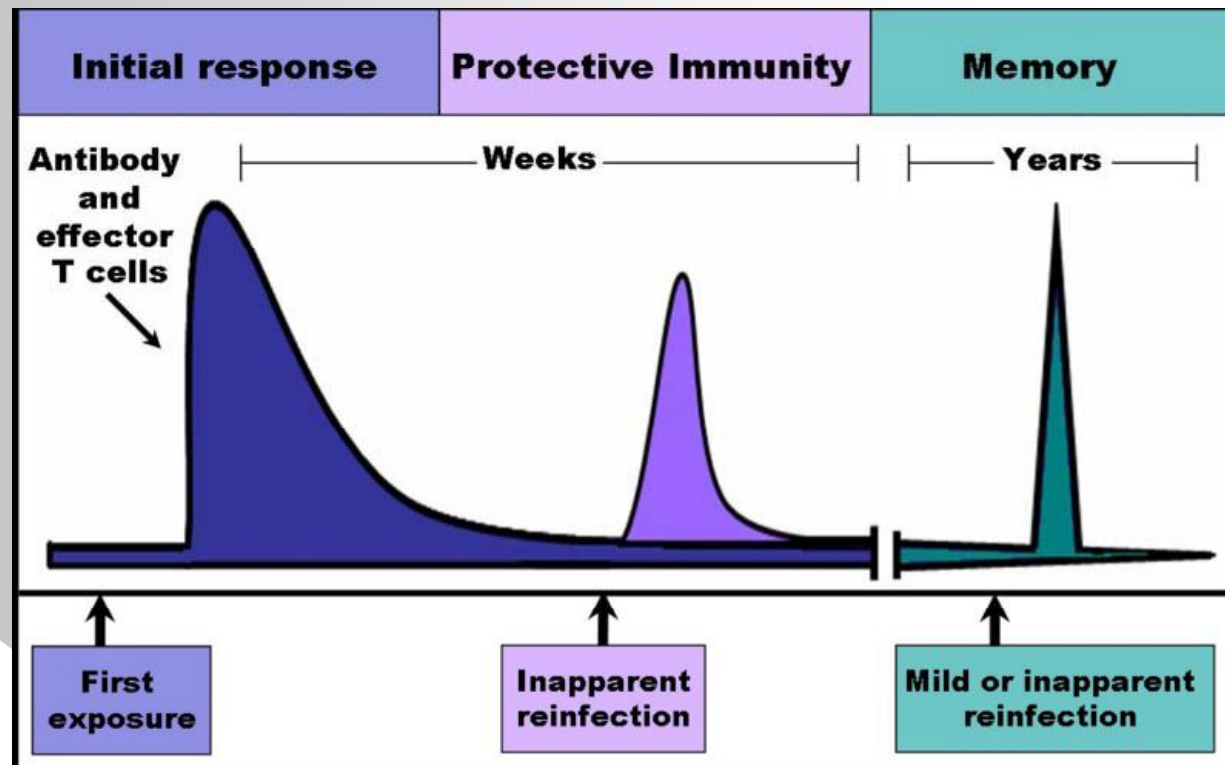
Immunological memory

❖ Passive memory

- Newborn infants are protected by mothers antibody by 6 months

❖ Active memory and immunization

- infection by activation of B and T cells
- through vaccination





Disorders of human immunity

❖ Immunodeficiencies

- components of the immune system are inactive
- alcoholism, and drug use are common causes of poor immune function
- can be inherited or 'acquired'
 - Inherited: Chronic granulomatous disease, congenital immunodeficiency
 - Acquired: AIDS, some types of cancer

❖ Autoimmunity

- fails to properly distinguish between self and non-self, and attacks part of the body

❖ Hypersensitivity: immune response damages the body's own tissues

Type	Alternative names	Often mentioned disorders
1	Allergy (immediate)	•Asthma
2	Cytotoxic, antibody-dependent	•Autoimmune hemolytic anemia
3	Immune complex disease	•System lupus
4	Delayed-type hypersensitivity (DTH), cell-mediated immune memory response, antibody-independent	•Multiple sclerosis

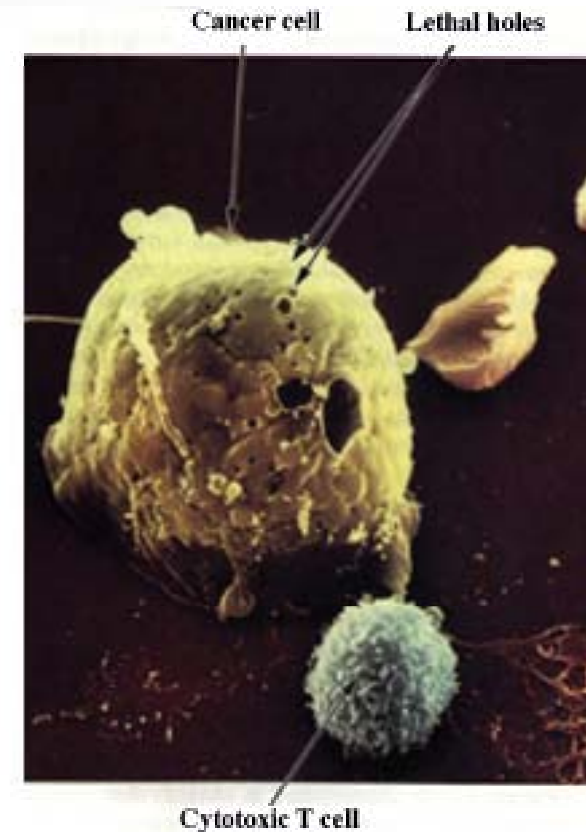


Tumor immunology



❖ **Cancer immunology:** another important role of the immune system is to identify and eliminate tumors

- tumors express antigens that are not found on normal cells
- Main is to destroy the abnormal cells using killer T cells
- Tumor cells often have a reduced number of MHC class I molecules on their surface, thus avoiding detection by killer T cells
- Some tumor cells also release products that inhibit the immune response





Other mechanisms

- ❖ **Antimicrobial peptides** called defensins, innate immune response found in all animals and plants
- ❖ The **complement system** and phagocytic cells, most forms of invertebrate life
- ❖ **Invertebrates** do not generate lymphocytes or an antibody-based humoral response
 - Bacteria unique using the restriction modification system to protect themselves from viral pathogens, called **bacteriophages**
 - Prokaryotes also possess acquired immunity, through a system that uses CRISPR sequences to retain fragments of the genomes of phage that they have come into contact with in the past, which allows them to block virus replication through a form of **RNA interference**
- ❖ **Plant**
 - Plant produces a localized **hypersensitive response**, whereby cells at the site of infection undergo rapid **apoptosis** to prevent the spread of the disease to other parts of the plant
 - **Systemic acquired resistance (SAR)** is a type of defensive response used by plants that renders the entire plant resistant to a particular infectious agent
 - **RNA silencing** mechanisms are particularly important in this systemic response as they can block virus replication



Manipulation in medicine

❖ Immunosuppressive drugs

- control autoimmune disorders or inflammation when excessive tissue damage occurs
- prevent transplant rejection after an organ transplant

❖ Inflammatory drugs

- control the effects of inflammation

❖ Vaccines

- Induce a antigen, that infect a host, while evading detection or destruction by the immune system



New area: Immunoinformatics

❖ Immunoinformatics : application of informatics techniques to molecules of the immune system

- From 1989, till now > 1000 paper
- to effective prediction of immunogenicity
 - T cell epitopes(antigens)
 - MHC I, MHC II binding complex
 - T cell receptors(TCRs), etc.

❖ Databases

IGMT	the International ImmunoGeneTics Information System for Immunoinformatics
IPD	The Immuno Polymorphism Database
SYFPEITHI	Database for Searching and T-Cell Epitope Prediction
MHCPEP	T-cell epitope and MHC-binding data
FIMM	MHC–peptide interactions
JenPep	kinetic, thermodynamic,functional, and cellular data within immunobiology

Immunoinformatics -Predicting Immunogenicity In Silico. Edited by **Darren R. Flower,**
2007, Humana Press Inc.



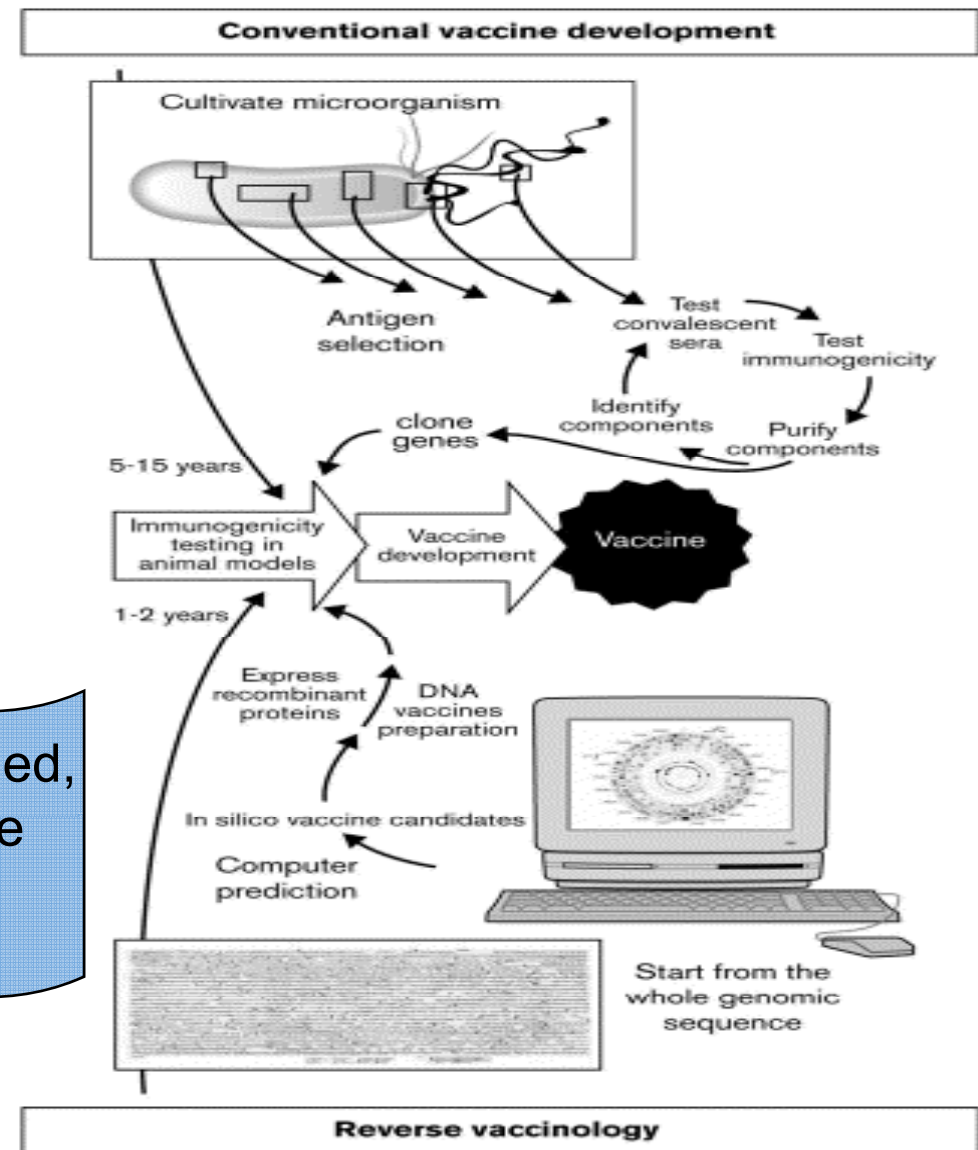
Immunoinformatics on vaccine development

❖ Vaccine development

- Pathogen:
 - With antigens and toxicity
- Vaccine
 - With antigens and no toxicity



❖ Once an T-cell epitope be identified, the corresponding vaccine can be easily developed





My work on Immunoinformatics



Shuyan Li et al., Anal. Chim. Acta, 2007, 584, 37-42

❖ T cell epitopes(antigen) prediction

■ dataset

- 203 10-mer cytotoxic cell (CTL) clone was derived from tumor-infiltrated lymph node cells of a melanoma patient
- Antigen recognition was assessed using a chromium release assay(Valmori et al, *J. Immunol.* 161 (1998) 6956)

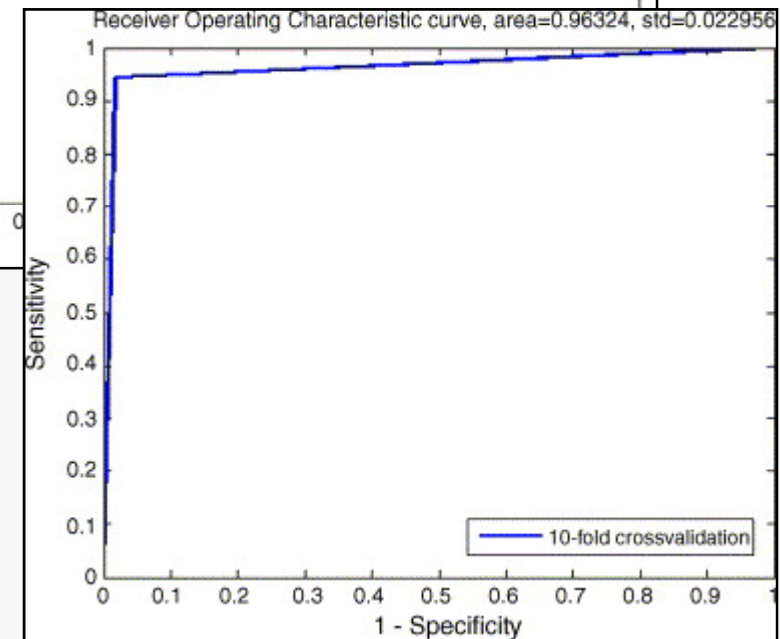
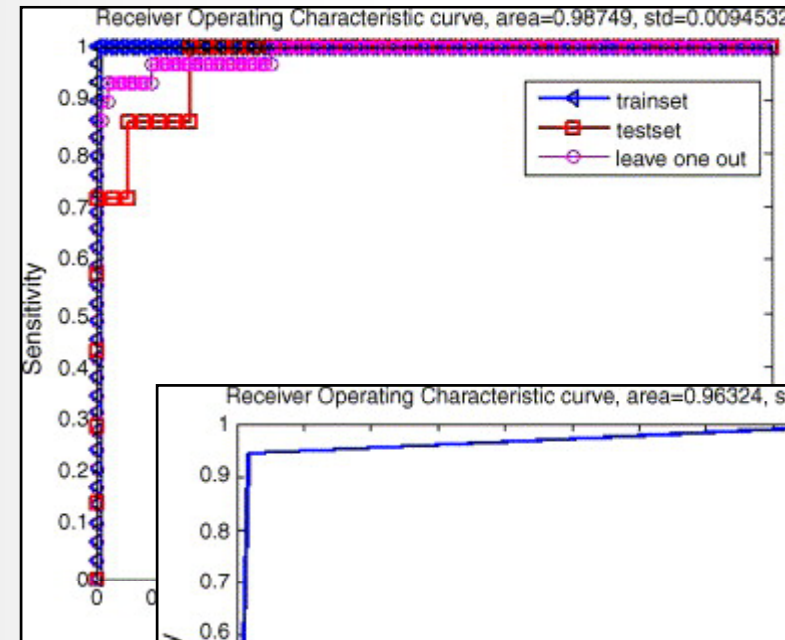
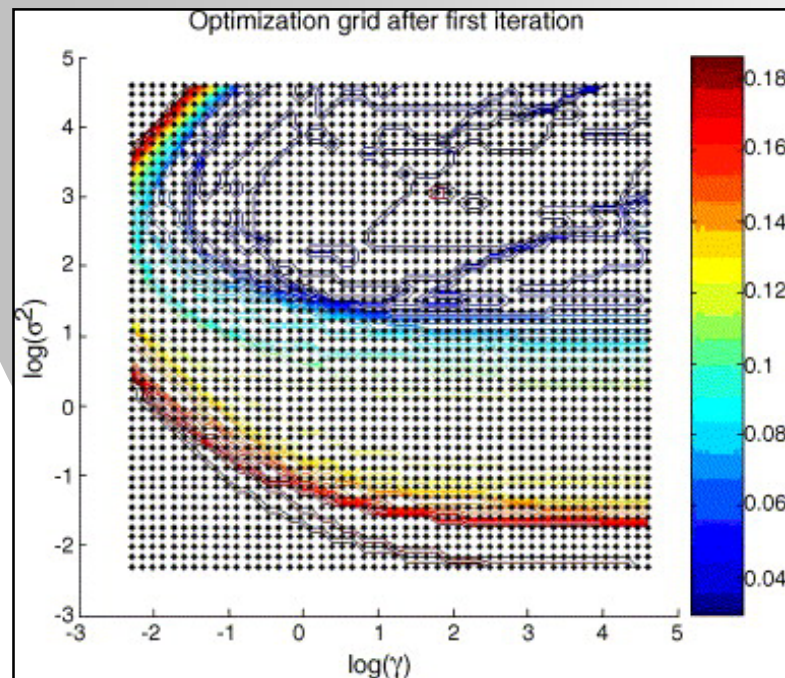
■ Informatics method

- Least-squared Support Vector machines(LS-SVMs)
 - A refined version of SVM
 - Result in a set of linear equations instead of a quadratic programming problem of SVMs
- *J.A.K. Suykens, et. al., Least Squares Support Vector Machines. Scientific Pub. Co., Singapore, 2002, 308 pp*
- <http://www.esat.kuleuven.ac.be/sista/lssvmlab/>



LS-SVM modeling

- ❖ Grid search for parameters
 - Sig^2 and gamma
- ❖ TP, TN, Roc curve

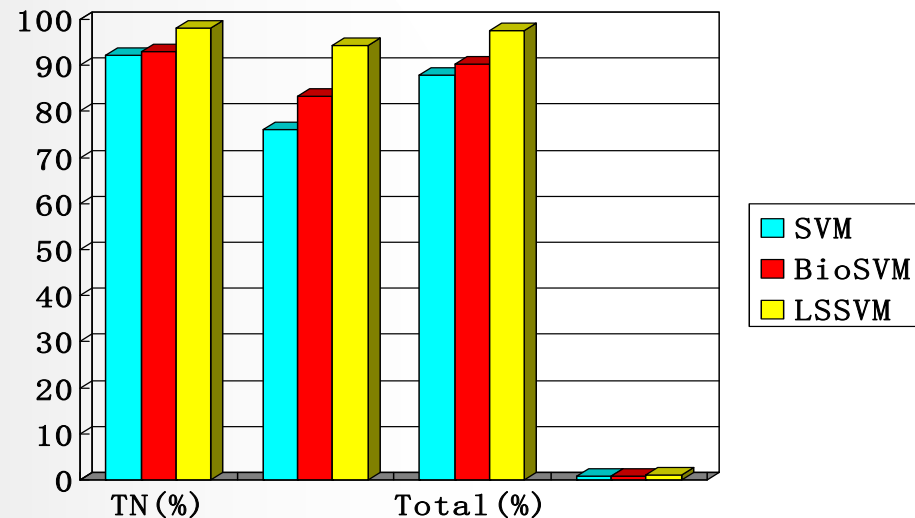


Li et al., Anal. Chim. Acta, 2007, 584, 37-42



Results Analysis

- ❖ Area under the ROC curve
 - training set (LOO): 0.9875
 - test set: 0.9734



Comparisons of different methods use 10-fold crossvalidation

Methods	TN(%)	TP(%)	Total(%)	ROC area
SVM ¹	92.24	76.21	87.86	0.919
BioSVM ²	93.06	83.29	90.31	0.931
LS-SVM	98.2	94.44	97.54	0.963

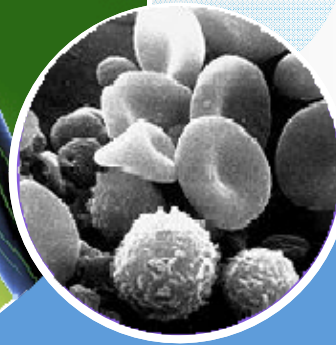
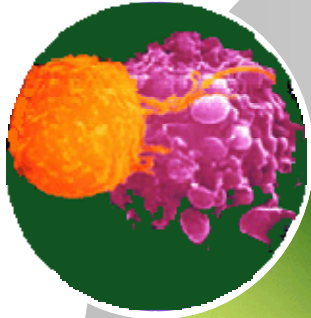
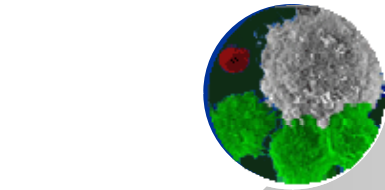
Note:¹Zhao et al, *Bioinformatics* 19(2003) 1978. ²Yang et al, *J. Chem. Inf. Model.* 45 (2005) 1424-1428



Summary

- ❖ Immune system is one of the most important components of life form
- ❖ Immunoinformatics has much potential as a newly discovered research area
- ❖ Challenge: Post-translational modification on Immune system molecules

How to dig out the relationships between immune system and post-translational modification(PTM)?



Thank You !