The 2nd PSU International Teaching Platform on Tumour Immunology and Immunotherapy

Jointly organized by
Prince of Songkla University, Université Pierre et Marie Curie (Paris 6) and Institut Pasteur

December 15 – 20, 2003
At The Department of Biomedical Sciences
Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla, Thailand

Lecture 1:
Introduction to the immune system
Prof. Catherine Fridman

December 15, 2003

Introduction

THE IMMUNE SYSTEM

- THE FUNCTION OF THE IMMUNE SYSTEM IS TO **FIGHT AGAINST INFECTIONS**

- IT IS A **COMPLEX** SYSTEM WHICH INCLUDES MULTIPLE CELL TYPES AND SOLUBLE FACTORS (COMPLEMENT, ANTIBODIES CYTOKINES, CHEMOKINES)

- THESE DISTINCT ELEMENTS **COOPERATE** TO ELIMINATE MICROBES

- IMMUNE SYSTEM HAS **MEMORY** AND IS **TOLERANT** TO SELF COMPONENTS

BODY'S OWN COMPONENTS = "SELF "

FOREIGN COMPONENTS :

MICROORGANISMS, GRAFTS

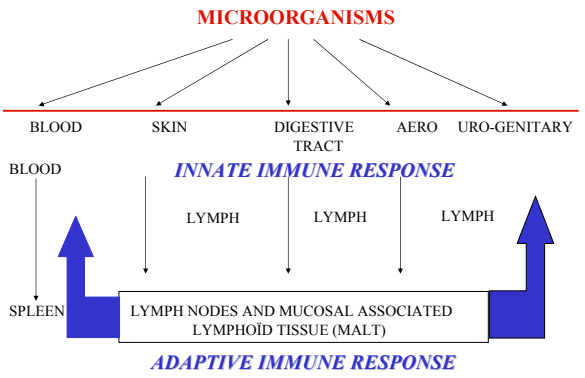
ARE THE "NON SELF"

THE IMMUNE SYSTEM IS TOLERANT TO SELF COMPONENTS (EXCEPT IN AUTO IMMUNE DISEASES)

THUS NON SELF COMPONENTS GENERATE AN IMMUNE RESPONSE

TWO TYPES OF IMMUNITY

NATURAL IMMUNITY INNATE IMMUNITY	ADAPTIVE IMMUNITY "SPECIFIC" IMMUNITY
-RAPID	-ANTIGEN SPECIFIC -MEMORY
-NO MEMORY	-LIMITED
-USES PREFORMED EFFECTOR (CELLS : PHAGOCYTES, NK CELLS) AND COMPLEMENT	-USES T AND B LYMPHOCYTES -REQUIRES LYMPHOCYTE DIFFERENTIATION

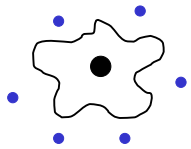


THE IMMUNE DEFENSES ARE SPECIALIZED

	BACTERIA	VIRUSES	PARASITES
INNATE IMMUNITY	++	+	±
ADAPTIVE IMMUNITY	+	++	++

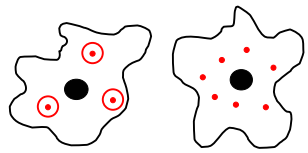
TWO CLASSES OF PATHOGENS

EXTRACELLULAR



BACTERIA:
Streptococcus, Staphylococcus, Neisseria, Salmonella
PARASITES
Plasmodium, Trypanosoma, Toxoplasma

INTRACELLULAR



VESICULAR
BACTERIA:
Mycobacteria, Chlamydia, Shigella, Legionella
PARASITES:
Leishmania, Schistosome

CYTOSOLIC
VIRUSES

HUMORAL IMMUNITYAND CELLULAR IMMUNITY

HUMORAL IMMUNITY (ANTIBODIES, COMPLEMENT) IS USED TO FIGHT AGAINST **EXTRACELLULAR BACTERIA**

CELLULAR IMMUNITY IS USED TO FIGHT AGAINST **INTRACELLULAR MICROBES** (CTL/VIRUSES; TH/INTRACELLULAR BACTERIA)

BOTH TYPES OF IMMUNITY HELP TO FIGHT AGAINST CANCER

INNATE IMMUNITY:
THE PRIMARY LINE OF DEFENSE AGAINST INFECTIONS

CELLS

PHAGOCYTES: NEUTROPHILS, MACROPHAGES

DENDRITIC CELLS (pDC and MDC)

EOSINOPHILS
BASOPHILS

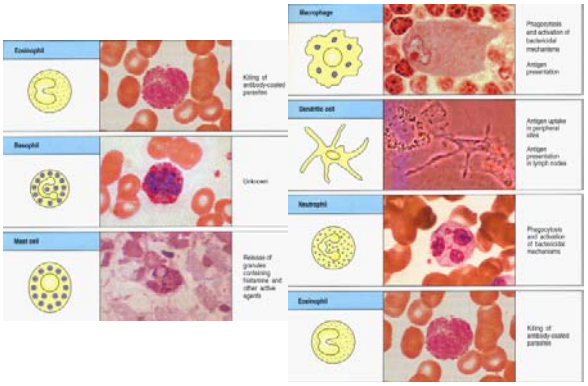
NATURAL KILLER CELLS

SOLUBLE FACTORS

COMPLEMENT
CYTOKINES
CHEMOKINES

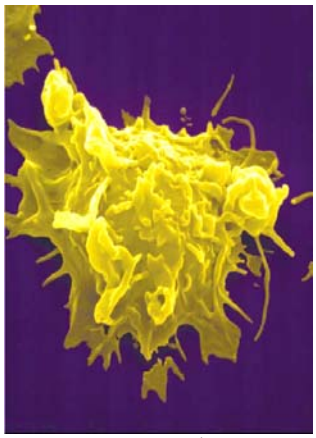
CELLS FROM INNATE IMMUNITY ARE PRESENT IN AREAS IN CONTACT THE OUTSIDE WORLD: SKIN, MUCOSA, IN LYMPHOID ORGANS AND IN BLOOD

CELLS FROM THE INNATE IMMUNE SYSTEM



PMM	MACROPHAGES
DO NOT DIVIDE	NO NOT DIVIDE
80% OF BLOOD LEUKOCYTES	DO NOT CIRCULATE
ABSENT IN NORMAL TISSUES	EXIST NORMALLY IN TISSUES (CONNECTIVE TISSUES, LIVER, LUNGS, SPLEEN …)
SHORT LIFE	LONG LIFE
CONTAIN PRIMARY AND SECONDARY GRANULES	
DEFENSE AGAINST EXTRACELLULAR BACTERIA	**DEFENSE AGAINST INTRACELLULAR BACTERIA**

DENDRITIC CELL



ADAPTIVE IMMUNITY

-ANTIGEN SPECIFIC
-MEMORY
-LIMITED
-USES T AND B LYMPHOCYTES
-REQUIRES LYMPHOCYTE DIFFERENTIATION

ADAPTIVE IMMUNITY

CELLS:

B AND T LYMPHOCYTES:

B LYMPHOCYTES DIFFERENTIATE INTO PLASMOCYTES WHICH MAKE ANTIBODIES

T LYMPHOCYTES ARE COMPOSED OF CD4 AND CD8 SUBSETS

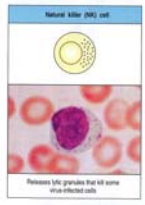
-

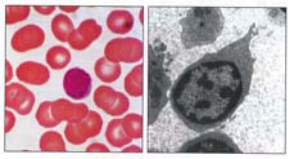
SOLUBLE FACTORS:

ANTIBODIES

CYTOKINES
CHEMOKINES

LYMPHOCYTES





THE FIVE LAWS OF LYMPHOCYTE RECOGNITION

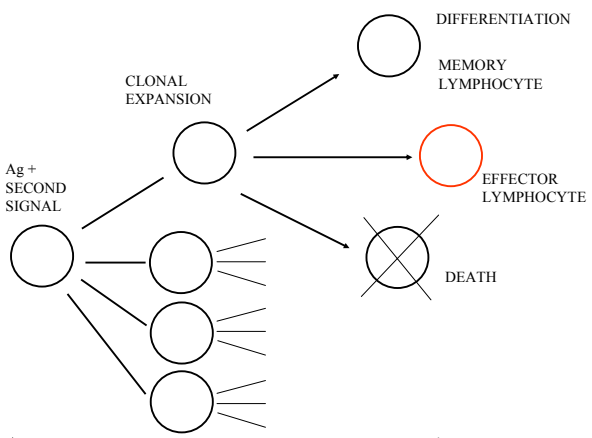
1-B AND T LYMPHOCYTES RECOGNIZE SPECIFICALLY ANTIGEN THROUGH MEMBRANE RECEPTOR MOLECULES

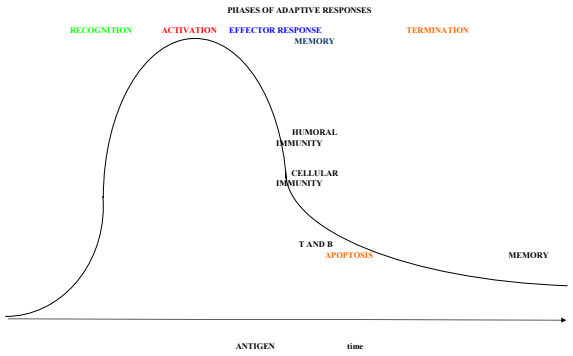
2-EXPRESSION OF LYMPHOCYTE RECEPTORS IS CLONAL

3-T LYMPHOCYTES RECOGNIZE A PEPTIDE DERIVED FROM ANTIGEN, ASSOCIATED TO SELF COMPONENTS

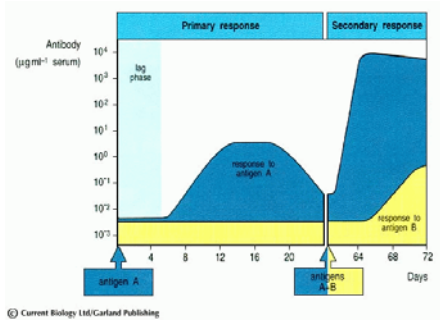
4-B LYMPHOCYTES RECOGNIZE THE ANTIGEN ALONE

5-B LYMPHOCYTES PRODUCE ANTIBODIES OF THE SAME SPECIFICITY THAN THEIR SURFACE RECEPTORS





Immunological memory



used for vaccination

MEMORY LYMPHOCYTES

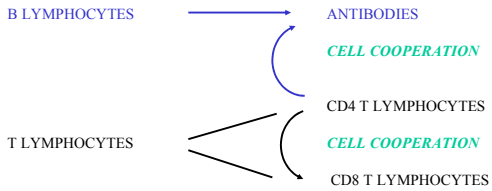
RESTING CELLS

CAN LIVE FOR YEARS IN THE BODY

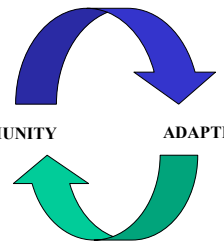
DO NOT NEED A SECOND SIGNAL FOR ACTIVATION

THEIR RESPONSE REQUIRES LESS ANTIGEN THAN THAT OF NAIVE LYMPHOCYTES

THE TWO SUBSETS OF LYMPHOCYTES COOPERATE TO MOUNTADAPTATIVE RESPONSES



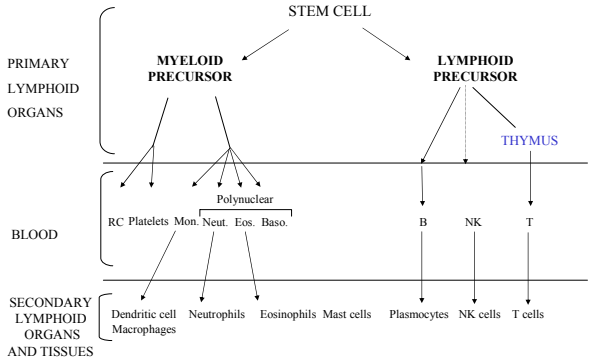
INFLAMMATORY REACTION



INNATE IMMUNITY **ADAPTIVE IMMUNITY**

COMPLEMENT, MACROPHAGES

EVERY CELL OF THE IMMUNE SYSTEM DERIVES FROM A UNIQUE PRECURSOR CELL



EVERY DAY THE PRIMARY LYMPHOID ORGANS PRODUCE LYMPHOCYTES WHICH ARE TOLERANT TO SELF COMPONENTS BUT RECOGNIZE NON SELF COMPONENTS

BONE MARROW:
40-60X10^6 CELLS/DAY
15-20X10^6/DAY GO TO THE PERIPHERY

THYMUS:
40-60X10^6/DAY
10^6/DAY GO TO THE PERIPHERY

PRIMARY LYMPHOID ORGANS

BONE MARROW
FETAL LIVER
THYMUS

→ ALLOW SELECTION OF LYMPHOCYTES WHICH ARE TOLERANT TO SELF COMPONENTS

B CELLS COME FROM BONE MARROW AND FETAL LIVER

T CELLS COME FROM THE THYMUS

SECONDARY LYMPHOID ORGANS

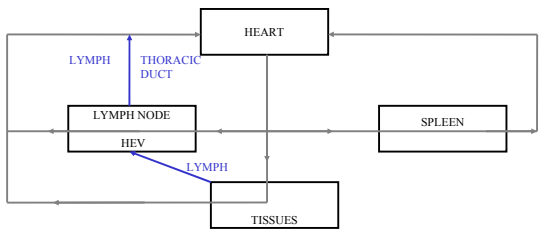
-LYMPH NODES
-SPLEEN
-MUCOSAL-ASSOCIATED-LYMPHOID-TISSUE (MALT)

→ ALLOW ACTIVATION AND DIFFERENTIATION OF LYMPHOCYTES INTO EFFECTOR AND MEMORY CELLS WHICH THEN MIGRATE TO PERIPHERAL TISSUES VIA CHEMOKINES

IN THE PERIPHERY, WHEN NAIVE LYMPHOCYTES ENCOUNTER NON SELF COMPONENTS ADAPTIVE IMMUNITY IS ACTIVATED

LYMPHOCYTES DIVIDE, AND DIFFERENTIATE INTO EFFECTOR AND MEMORY CELLS OR DIE

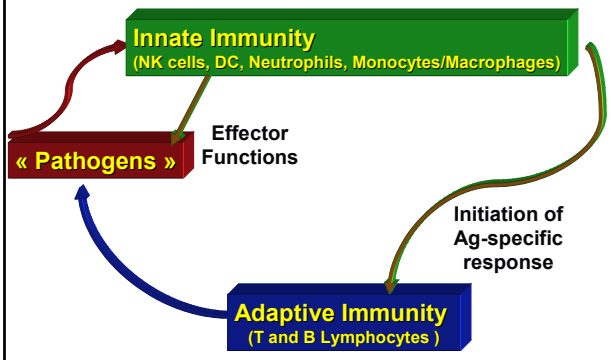
LYMPHOCYTE CIRCULATE VIA BLOOD AND LYMPH



Innate Immunity

IMMUNE DEFENSES USED TO FIGHT AGAINST

	BACTERIA	VIRUSES	PARASITES
INNATE IMMUNITY	++	+	±
ADAPTATIVE IMMUNITY	+	++	++



BACTERIA ACTIVATE INNATE IMMUNITY VIA

1 - PRODUCTION OF MICROBIAL PEPTIDES (FMLP)
7TM RECEPTORS

2 - EXPRESSION OF MANNANES
MANNOSE R

3 - EXPRESSION OF "PAMP" (PATHOGEN ASSOCIATED MOLECULAR PATTERN)
TOLL-R
- LACK IN MAMMALIAN CELLS
- COSTIMULATORY ACTION

4 - "DANGER" SIGNALS
- PRODUCED BY HOST (NECROSIS = Hsp, DNA, Poly IC)
- CD40L (T LYMPHOCYTES)

5 - COMPLEMENT ACTIVATION
7 TM RECEPTORS
- LEADS TO C5a AND C3a FORMATION (ANAPHYLATOXINS)

THE INFLAMMATORY REACTION

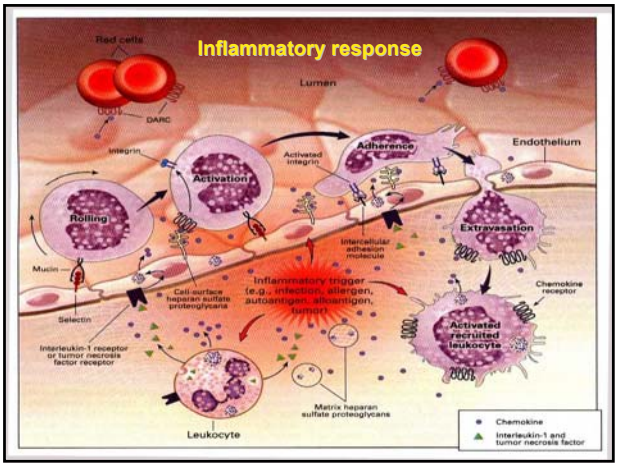
INFLAMMATION

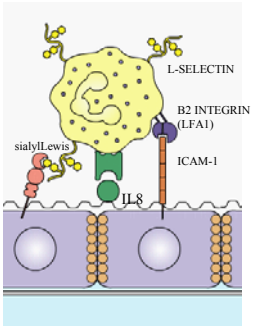
CALOR

DOLOR

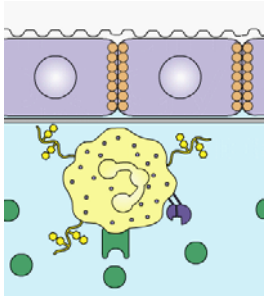
RUBOR

TUMOR

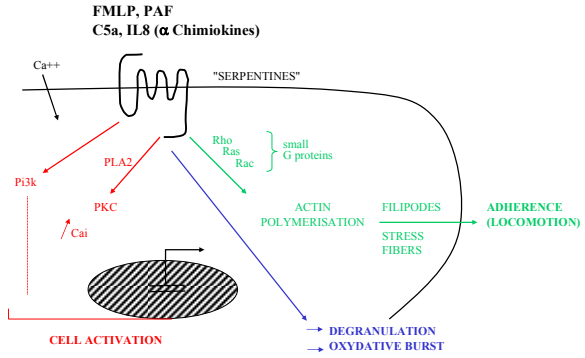




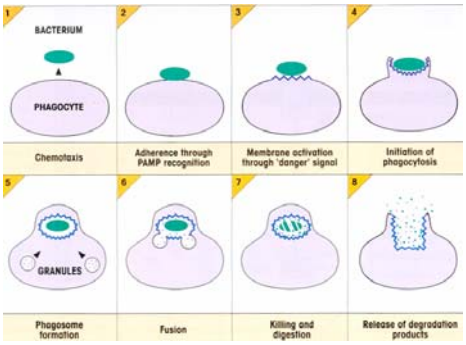
EXTRAVASATION OF NEUTROPHILS
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



THE NEUTROPHIL RESPONSE



Engulfed bacteria fuse with PMN granules
to form phagosome where bacteria are destroyed



PMM RESPONSE TO BACTERIA

1 - DEGRANULATION, OXYDATIVE BURST

2 - LIPID MEDIATORS RELEASE (LTB4, PAF)

3 - INFLAMMATORY CYTOKINE RELEASE (IL6, TNFα, IL12)

4 - CHEMOKINE RELEASE (IL8, Groα, IP10, RANTES, MIPIαβ)

5 - APOPTOSIS

6 - INFLAMMATION BUT TISSUE DAMAGE !

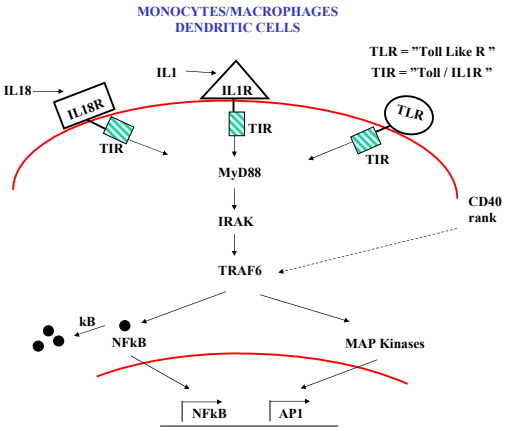
NEUTROPHILS
THEN MONOCYTES
THEN ACTIVATED T LYMPHOCYTES

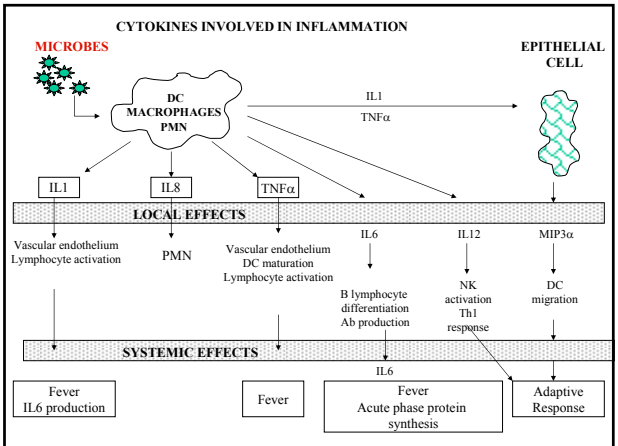
MIGRATE SUCCESSIVELY
TO THE INFLAMMED SITE

MONOCYTES WHICH LEAVE THE BLOOD
TRANSFORM INTO IMMATURE DC
OR MACROPHAGES

HUMAN TOLL RECEPTORS

TLR1	LEUKOCYTES
TLR2 TLR4	MONOCYTES, MYELOID CELLS, DENDRITIC CELLS B LYMPHOCYTES
TLR3	DENDRITIC CELLS
TLR5	MONOCYTES
TLR5	MACROPHAGES EPITHELIAL CELLS
TLR7	MYELOID AND PLASMACYTOID DENDRITIC CELLS
TLR9	PLASMACYTOID DENDRITIC CELLS





TNFα
TUMOR NECROSIS α

- INDUCES ADHESION OF PHAGOCYTES TO ENDOTHELIAL CELLS

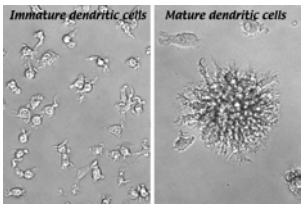
-INCREASES VASCULAR PERMEABILITY

THUS TNFα INDUCES LEUKOCYTE MIGRATION TO INFECTIOUS SITES

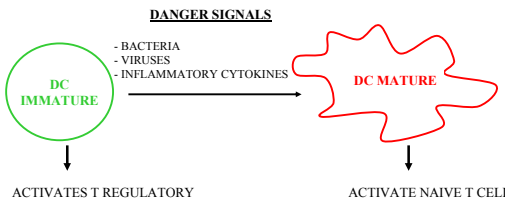
- INDUCES DC MATURATION

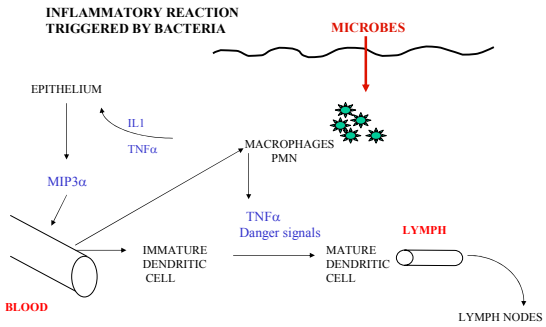
THUS TNFα FAVORS INDUCTION OF ADAPTIVE IMMUNE RESPONSE

THE INFLAMMATORY REACTION
STIMULATES THE ADAPTIVE RESPONSE

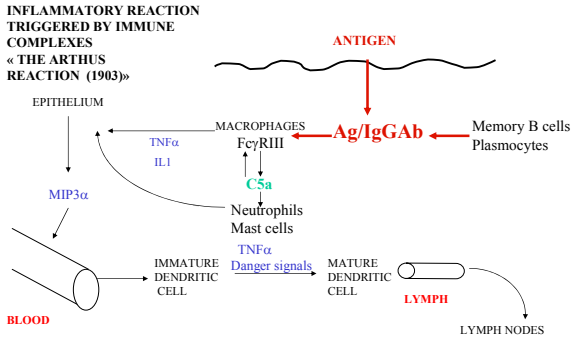


DENDRITIC CELL MATURATION

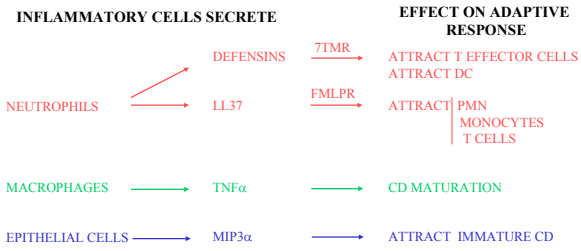




THE INFLAMMATORY REACTION INDUCES MIGRATION AND MATURATION OF DENDRITIC CELLS



C5a AMPLIFIES THE INFLAMMATORY REACTION

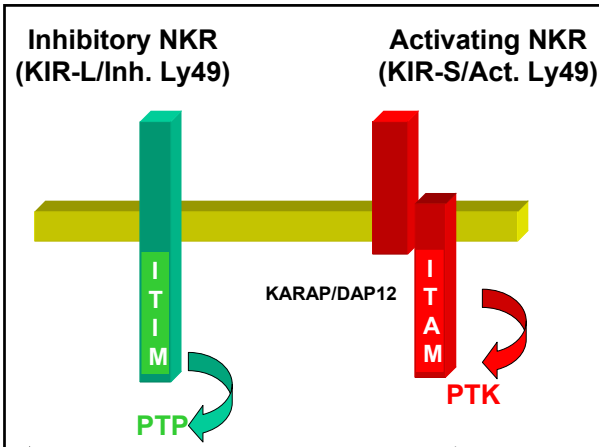


THE INFLAMMATORY REACTION STIMULATES THE ADAPTIVE RESPONSE

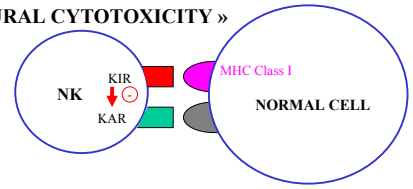
NATURAL KILLER CELLS

NATURAL KILLER CELLS

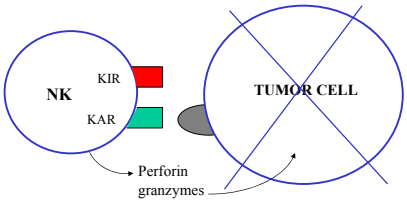
- LARGE GRANULAR "NK CELLS LYMPHOCYTES"
- PRESENT IN BLOOD, SPLEEN (10% PERIPHERAL BLOOD LYMPHOCYTES)
- REQUIRE IL15 FOR PRODUCTION
- EXPRESS Fcγ RECEPTORS AND KILLING ACTIVATING RECEPTOR (KAR)
- CYTOTOXIC CELLS (PERFORIN/GRANZYME PATHWAY)
- SECRETE CYTOKINES (IFNγ)



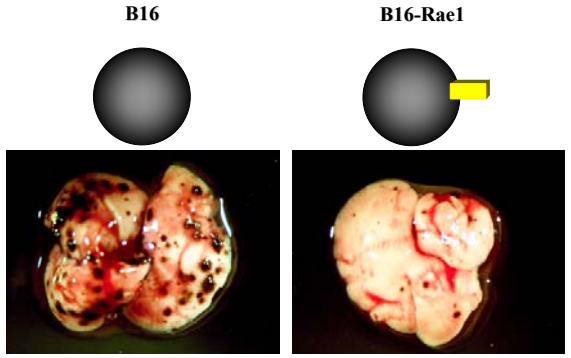
« NATURAL CYTOTOXICITY »

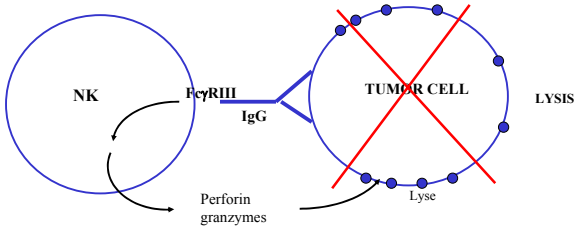


KAR "Killer Activating Receptors "
KIR "Killer Inhibitory Receptors "



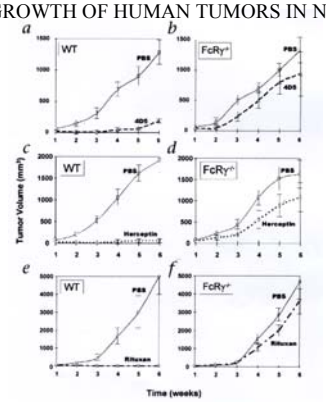
Role of NK cells in the control of tumour development





ADCC: ANTIBODY-DEPENDENT-CELL MEDIATED-CYTOTOXICITY

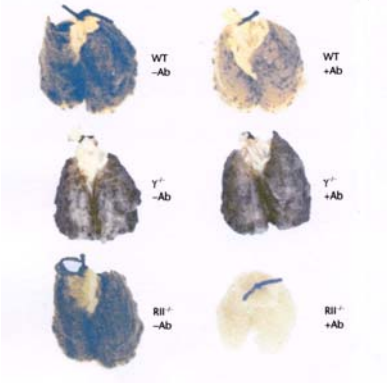
GROWTH OF HUMAN TUMORS IN NUDE MICE



Breast cancer + herceptin

Lymphoma + anti-CD20

B16 MELANOMA LUNG METASTASIS IN B6 AND γRFcKO MICE



INTERFERONS

- **ANTI-VIRAL ACTIVITY**

-**ACTIVATE NATURAL AND ADAPTIVE IMMUNE DEFENSES**

-**THREE TYPES OF INTERFERONS: α, β and γ**

The System of Complement

THE COMPLEMENT SYSTEM IS A GROUP OF 20 PROTEINS

THAT EXIST IN PLASMA AND AS CELL RECEPTORS

WHICH TRIGGER AND REGULATE INNATE AND ADAPTIVE RESPONSES

VIA FORMATION OF ENZYMATIC COMPLEXES THAT CLEAVE C3

2nd PSU Workshop on Tumour Immunology and Immunotherapy, December 15-20, 2003. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur

A SET OF PROTEINS WITH COMMON PROPERTIES

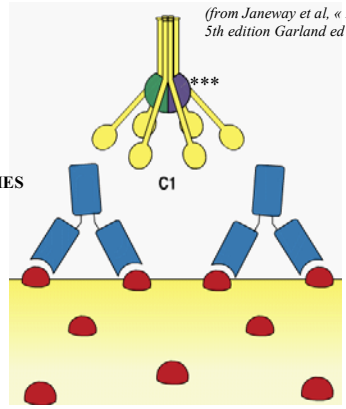
FUNCTIONS	**PATH**			**RELATIONSHIPS**
	ALTERNATE	**LECTIN**	**CLASSICAL**	
INITIATION	D	MASP	C1s	HOMOLOGY
BINDING COVALENT ONTO SURFACES	C3b	C4b	C4b	"
FORMATION CONVERTASES	Bb	C2b	C2b	"
REGULATION	CR1 H	CR1 C4bp	CR1 C4bp	"
OPSONIZATION	C3b	C3b	C3b	IDENTICAL
INITIATION OF LYSIS	C5b	C5b	C5b	"
LOCAL INFLAMMATION	C5a C3a	C5a C3a	C5a C3a	"

2nd PSU Workshop on Tumour Immunology and Immunotherapy, December 15-20, 2003. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur

ACTIVATION VIA THE CLASSICAL PATHWAY
(VIA ANTIBODIES)

2nd PSU Workshop on Tumour Immunology and Immunotherapy, December 15-20, 2003. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur

(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



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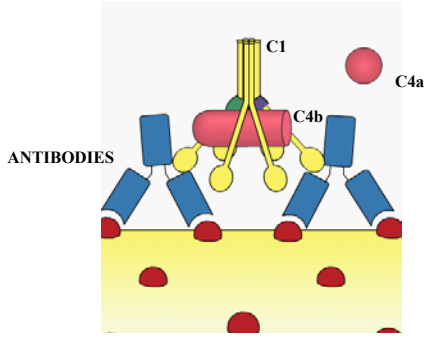

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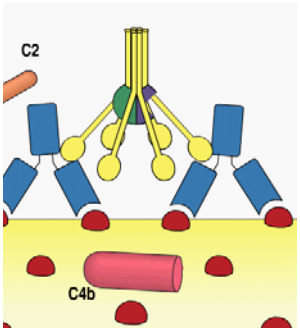

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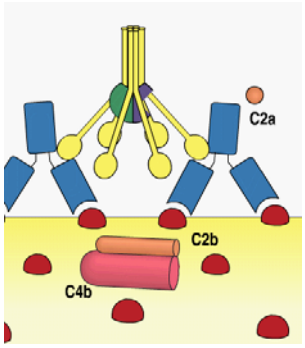

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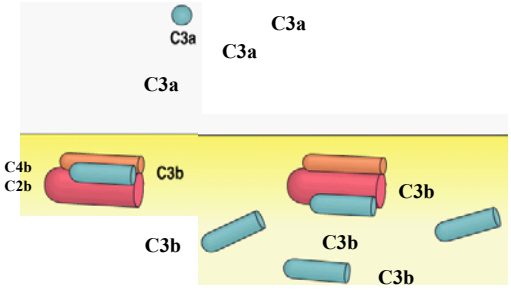
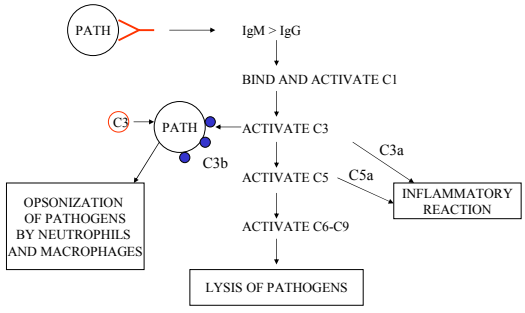
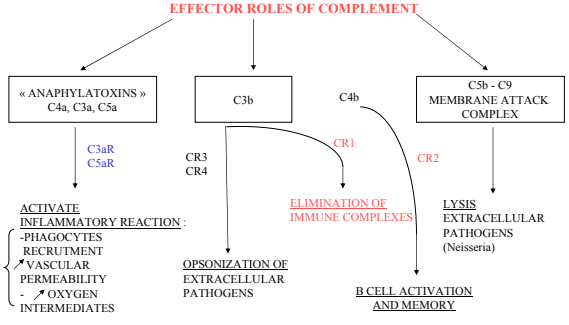


ANTIBODIES AND PATHOGENS ACTIVATE COMPLEMENT





FUNCTIONS OF THE MAJOR COMPLEMENT COMPONENTS

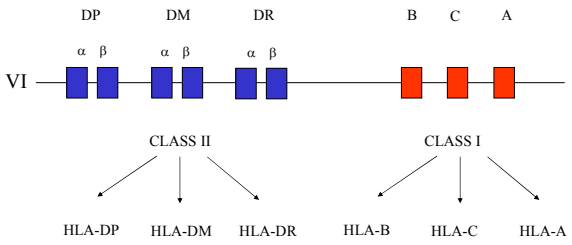
C1q	BINDS ANTIBODIES
MBL	BINDS MICROORGANISMS
ENZYMES	C1r, C1s, C2b, Bb, D, MASP-1, MASP-2
COVALENT BINDING PROTEINS	C4b, C3b
PEPTIDES INFLAMMATORY	C5a, C3a, C4a
MAC	C5b, C6, C7, C8, C9
COMPLEMENT RECEPTORS	CR1, CR2, CR3, CR4, C1qR, C5aR, C3aR
REGULATORS	C1 INH, C4bp, CR1, MCP, DAF, H, I, P, CD59

The Major Histocompatibility Complex

MAJOR HISTOCOMPATIBILITY COMPLEX

HLA : "Human Leukocyte Antigens
H-2 in mouse
J.Dausset, G.Snell, B.Benacerraf
1980

HUMAN MAJOR HISTOCOMPATIBILITY COMPLEX

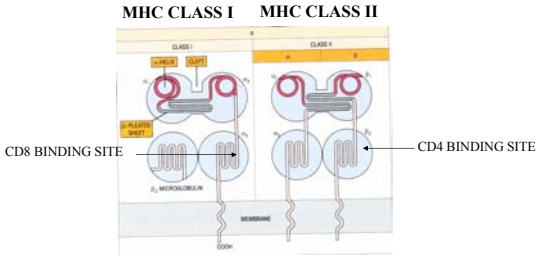


HLA = "HUMAN LEUKOCYTE ANTIGENS"

EXPRESSION OF MHC MOLECULES

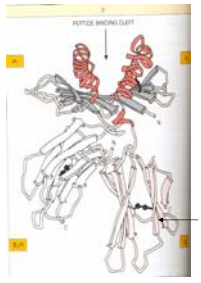
TISSUE	CLASS I	CLASS II
- ANTIGEN PRESENTING CELLS (APC) :		
B LYMPHOCYTES	+++	+++
MACROPHAGES	+++	++
DENDRITIC CELLS	+++	+++
THYMIC EPITHELIAL CELLS	+	+++
- NEUTROPHILS	+++	-
- T LYMPHOCYTES	+++	-
- OTHER TISSUES	+	-
	+	-
- RED CELLS	-	-

MHC CLASS I **MHC CLASS II**



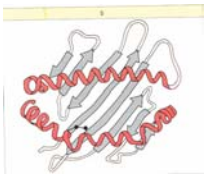
From Essential Immunology, Y.M. Roitt et al, 10th edition Blackwell science

MHC CLASS I



From Essential Immunology, Y.M. Roitt et al, 10th edition Blackwell science

THE PEPTIDE BINDING GROOVE



CLASSI PEPTIDES : 9 TO 11 AA
CLASS II PEPTIDES MORE THAN 13 AA

From Essential Immunology, Y.M. Roitt et al, 10th edition Blackwell science

POLYMORPHISM

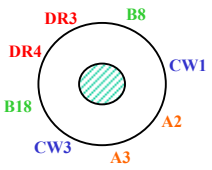
	CLASS II				CLASS I		
NUMBER OF	DPβ	DPα	DRβ	DRα	B	C	A
ALLELES	89	19	323	2	395	93	195

CO-DOMINANCE

CMH ALLELES

FATHER	DR3	B8	CW1	A2
MOTHER	DR4	B18	CW3	A3

PROTEINS



ANTIGEN PRESENTATION

MHC PROPERTIES

POLYGENIC

POLYMORPHISM

CO-DOMINANCE

THIS ALLOWS BINDING OF A LARGE NUMBER OF PEPTIDES

ONTO CELLS

- MHC MOLECULES BIND SELF AND NON SELF PEPTIDES
(ANTI-SELF T CELLS HAVE BEEN ELIMINATED)

-ONE MHC MOLECULE BIND A RESTRITED NUMBER OF PEPTIDES

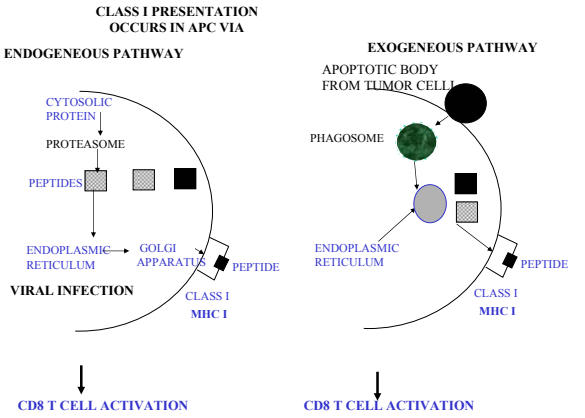
TWO CELL COMPARTMENTS

1. CYTOSOL

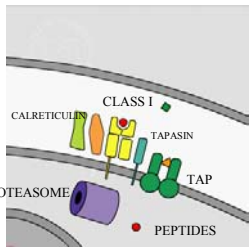
1. VESICULES

- ENDOPLASMIC RETICULUM
- GOLGI APPARATUS
- ENDOSOMES
- LYSOSOMES

SECRETORY VESICULES

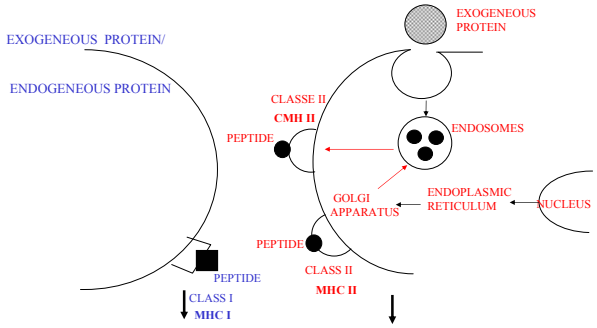


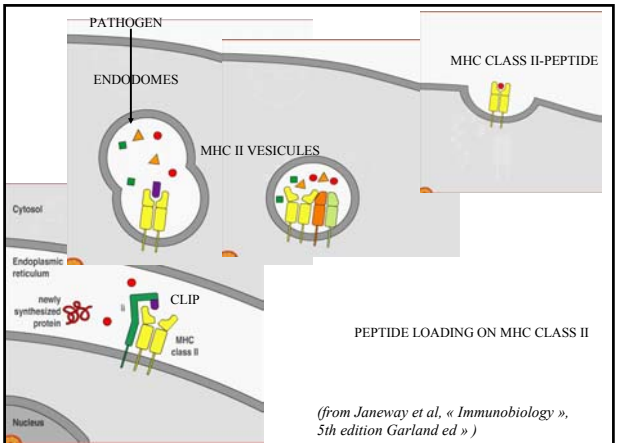
PEPTIDE LOADING ON MHC CLASS I



(from Janeway et al, « Immunobiology », 5th edition Garland ed »)

ANTIGEN PRESENTATION ON MHC CLASS II OCCURS VIA THE EXOGENEOUS PATHWAY





PEPTIDE LOADING ON MHC CLASS II

(from Janeway et al, « Immunobiology », 5th edition Garland ed »)

CMH/PEPTIDE INTERACTIONS

-CLASS I MOLECULES BIND ENDOGENEOUS AND EXOGENEOUS PEPTIDES "CROSS PRESENTATION »

- CLASS II MOLECULES BIND EXOGENEOUS PEPTIDES

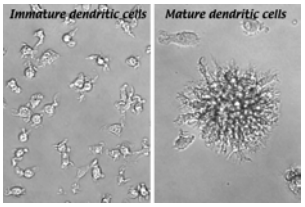
MHC CLASS I ALLOWS RECOGNITION BY CD8 T CELLS

MHC CLASS II ALLOWS RECOGNITION BY CD4 T CELLS

THE MHC-PEPTIDE COMPLEX IS PRESENTED TO NAIVE T LYMPHOCYTES BY « ANTIGEN-PRESENTING CELLS »

CHARACTERISTICS of APC

	DENDRITIC CELL	MACROPHAGE	B LYMPHOCYTE
Entry of antigen	Macropinocytosis Phagocytosis Viral Infection	Phagocytosis	Via Ag receptor
MHC Expression	high in lymphoïd tissues (mature DC)	Inducible - / +++	Constitutive Increased by activation
Expression of Cosignal	Constitutive (mature DC)	Inducible - / +++	Inducible - /+++
Ag presented	Peptides Viral Antigens Allergens	Extracellular and Intracellular pathogens	Solubles Toxins Viruses
Localization	Lymphoïd Tissue Connective Tissues Epithelia	Lymphoïd Tissue Connective Tissue Cavities (peritoneal, pleural…)	Lymphoïd Tissue Blood



PATHOGENS
ACUTE VIRAL INFECTIONS

IMMATURE DC	MATURE DC
Endocytosis +++	Endocytosis +
MHC +	MHC +++
COSTIMULATORY MOLECULES +	COSTIMULATORY MOLECULES +++
↓	↓
TOLERANCE	**IMMUNITY**

Adaptive Immunity

1-ACTIVATION OF NAÏVE T CELLS INTO EFFECTOR CELLS

NAÏVE MATURE T CELLS, CD4 OR CD8, LEAVE THE THYMUS
VIA BLOOD AND REACH THE SECONDARY LYMPHOID ORGANS
WHERE THEY MEET APC IN THE T CELL ZONE

WHAT HAPPENS?

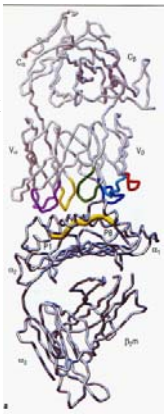
NAÏVE T CELLS REQUIRE
TWO SIGNALS FOR ACTIVATION:

SIGNAL 1 (MHC-PEPTIDE)
SIGNAL 2 (B7)
GIVES RESPONSE

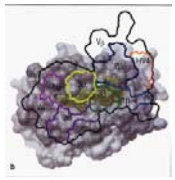
SIGNAL 1(MHC-PEPTIDE) `
GIVES ANERGY

SIGNAL 1(MHC-PEPTIDE)
SIGNAL 2 NEGATIVE: CTLA4
GIVES ANERGY

SIGNAL 1
TCR RECOGNIZES THE
MHC-PEPTIDE COMPLEX

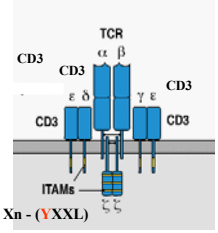


THE HV3 REGIONS OF THE TCR CONTACT
THE PEPTIDE AND THE MHC



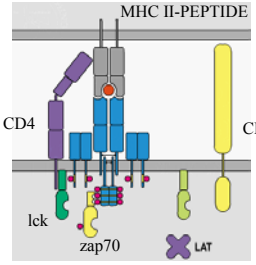
THUS T CELLS RESPOND TO SELF MHC-PEPTIDE COMPLEX

THE TCR IS ASSOCIATED TO SIGNAL
TRANSDUCING CHAINS



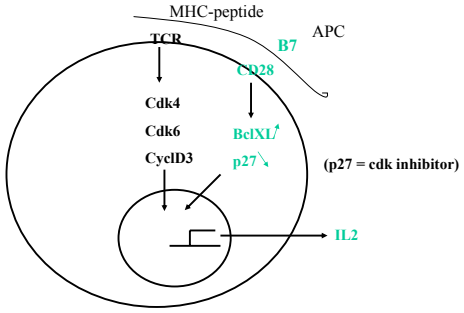
SIGNAL 1

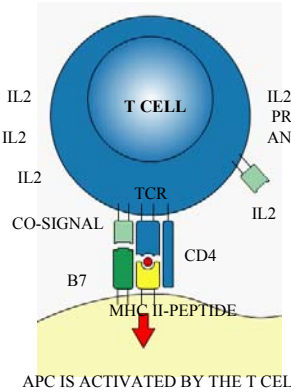
TYROSINE KINASES ARE ACTIVATED
WHICH PHOSPHORYLATE LAT



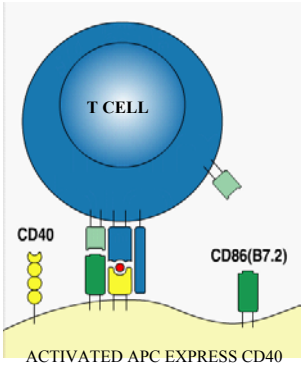
SIGNAL 2

A SECOND SIGNAL IS REQUIRED FOR ACTIVATION OF NAIVE T CELLS: IT LEADS TO IL2 SECRETION

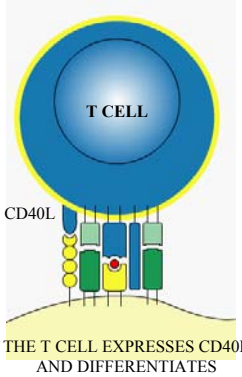




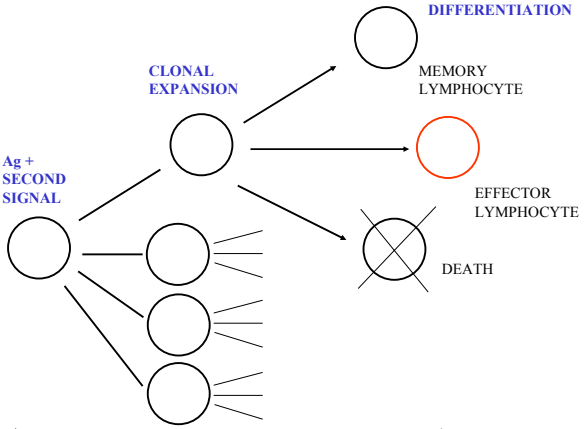
APC IS ACTIVATED BY THE T CELL



ACTIVATED APC EXPRESS CD40



THE T CELL EXPRESSES CD40L
AND DIFFERENTIATES
INTO AN EFFECTOR CD4 T CELL



CD4 EFFECTOR T CELLS ARE T HELPER CELLS

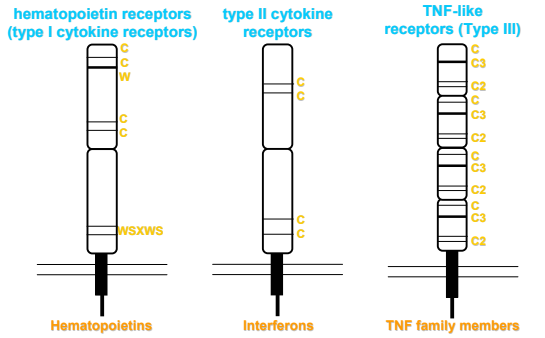
THEY SECRETE CYTOKINES
AND DO NOT REQUIRE CO-SIGNAL TO ACT

VIA CYTOKINES, CD4 T LYMPHOCYTES HELP:

1-CD8 T CELLS TO BECOME CYTOTOXIC T CELLS AND

2- B CELLS TO BECOME PLASMOCYTES

CYTOKINES AND CYTOKINE RECEPTORS



HUMAN SCID

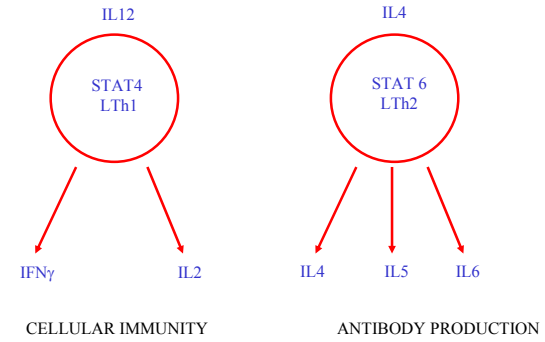
↘ DEVELOPMENT T AND NK CELLS

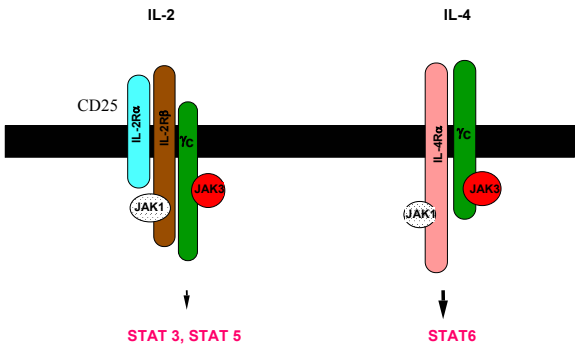
REDUCED B CELL FUNCTION (HYPOGAMMAGLOBULINEMIA)

X-SCID → MUTATION γ_c

AUTOSOMAL SCID → MUTATION JAK 3

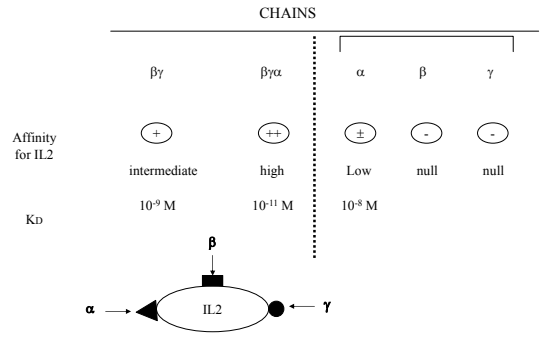
TWO SUBSETS OF HELPER CD4 T CELLS





TWO HEMATOPOIETINS RECEPTORS, IL2R AND IL4R

THE IL2 RECEPTOR



TWO OPPOSITES ROLES FOR IL2

NEGATIVE

SUPPRESS ANERGY
OF T REG CELLS

APOPTOSIS OF
ACTIVATED
T CELLS
(FasL/Fas)

IL2

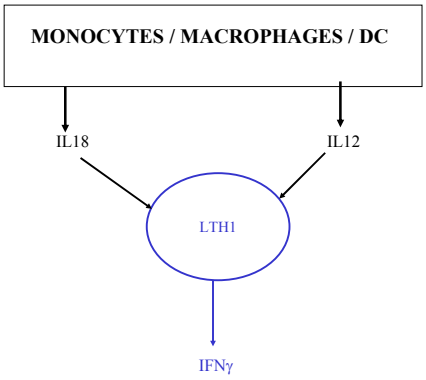
POSITIVE

PROLIFERATION
OF TH CELLS

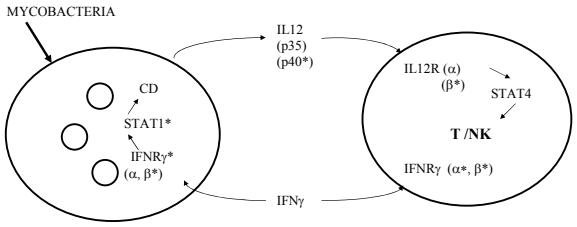
SURVIVAL OF
T CELLS
(SECOND SIGNAL)

CYTOTOXICITY OF
CD8 T CELLS

IL2 GENE DEFICIENT MICE	IL15 GENE DEFICIENT MICE
AUTOIMMUNITY LYMPHOPROLIFERATIONS	NK, NKT, CD8 and Tγδ DEFICIENCIES
IL2 RESPONSIBLE FOR ELIMINATION OF T CELLS	IL15 REQUIRED FOR PROLIFERATION AND SURVIVAL OF CYTOTOXIC CELLS

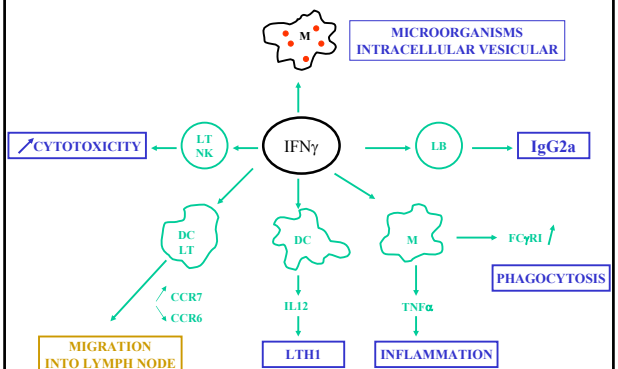


GENETIC CONTROL OF SUSCEPTIBILITY TO MYCOBACTERIAL INFECTIONS IN HUMAN (BCG)

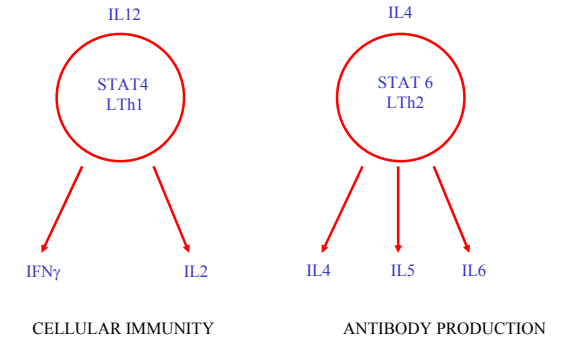


* IDENTIFIED
MUTATIONS

INTERFERON GAMMA A MAJOR CYTOKINE FOR IMMUNE DEFENSES



TWO SUBSETS OF HELPER CD4 T CELLS



CELLULAR IMMUNITY

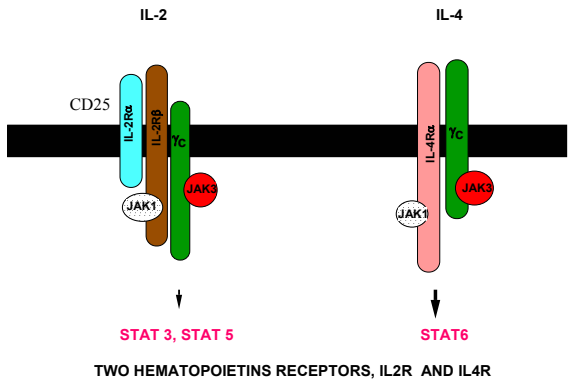
ANTIBODY PRODUCTION

IL4

- SECRETED BY - TH2
  - NKT, BASOPHILS, MASTOCYTES

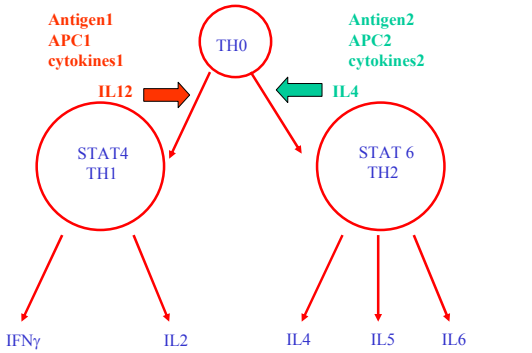
- TH2 PROLIFERATION FACTOR

- B CELL PROLIFERATION AND DIFFERENTIATION FACTOR (TOWARDS IgE)

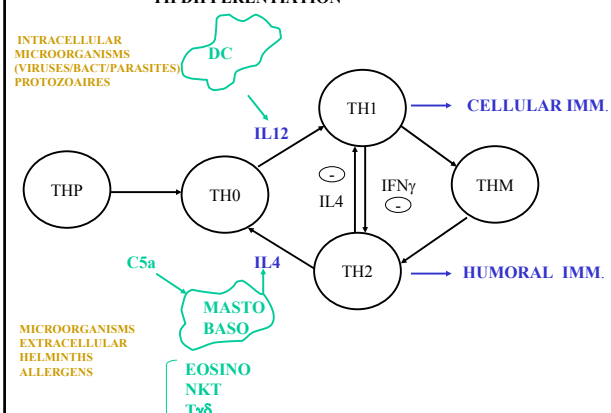


TWO HEMATOPOIETINS RECEPTORS, IL2R AND IL4R

TH1-TH2 NEGATIVE CROSS TALK



TH DIFFERENTIATION



CD4 T LYMPHOCYTES HELP :
1-CD8 T CELLS TO BECOME CYTOTOXIC T CELLS AND
2- B CELLS TO BECOME PLASMOCYTES

B CELLS DIFFERENTIATE INTO PLASMOCYTES TO MAKE ANTIBODIES

CELL COOPERATION VIA CYTOKINES

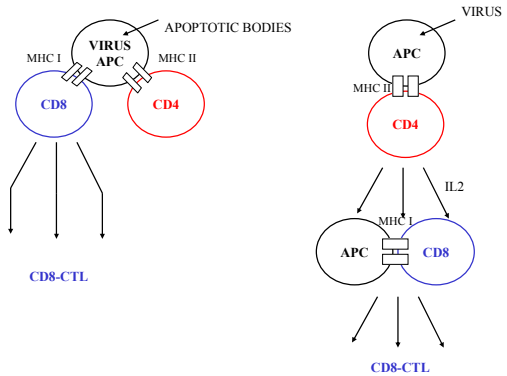
CD4 TH LYMPHOCYTES

CELL COOPERATION VIA CYTOKINES

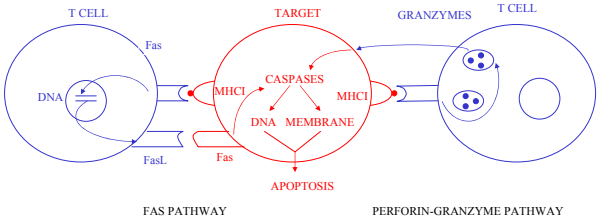
CD8 T LYMPHOCYTES DIFFERENTIATE INTO CYTOTOXIC CELLS

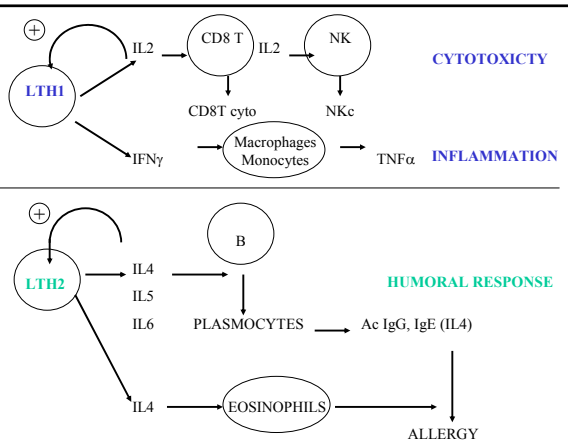
CD4 TH1-CD8 T CELL COOPERATION

CD8 T CELL DIFFERENTIATION INTO EFFECTOR CELLS REQUIRES CD4 TH CELLS



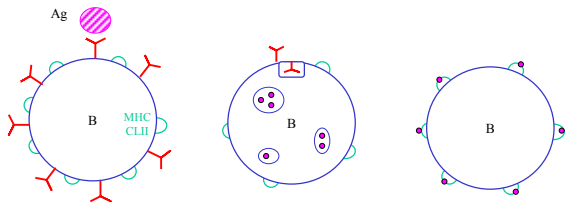
TWO PATHWAYS OF T CELL CYTOTOXICITY



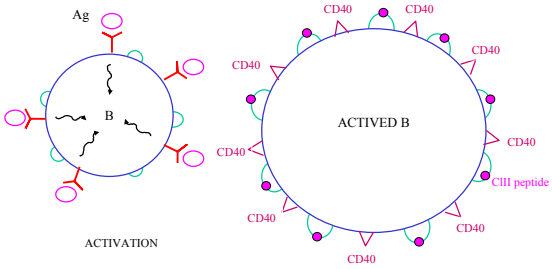


CD4 TH2-B CELL COOPERATION

ANTIGEN ENTRY AND PROCESSING

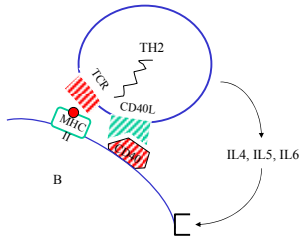


CD40 EXPRESSION INCREASES



B CELLS ACTIVATE TH2 CELLS

- TH2 (IL4, IL5, IL6)
- ACTIVATED BY MHC/pep + CD40

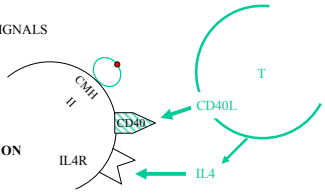


- T CELLS PRODUCE IL4, IL5, IL6

B CELL RESPONSE TO TH2 CELLS

- PROLIFERATION

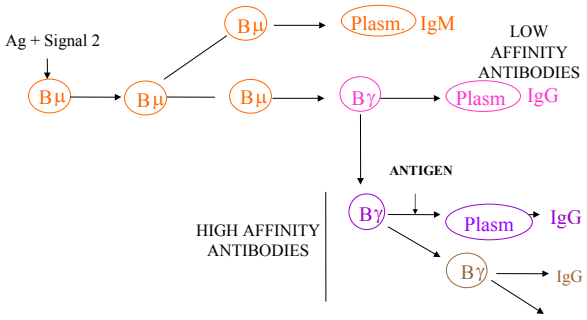
TO IL4 AND CD40L SIGNALS



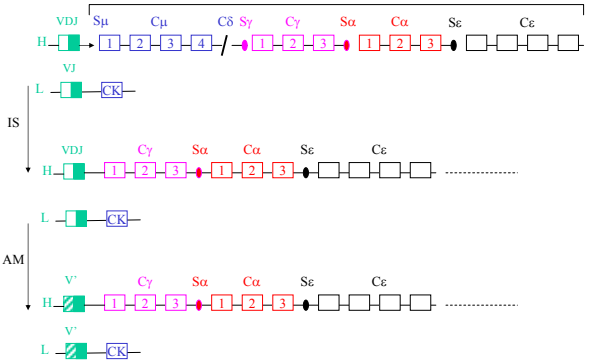
→ **B CELL PROLIFERATION**

- IL5/IL6 INDUCE B CELL DIFFERENTIATION

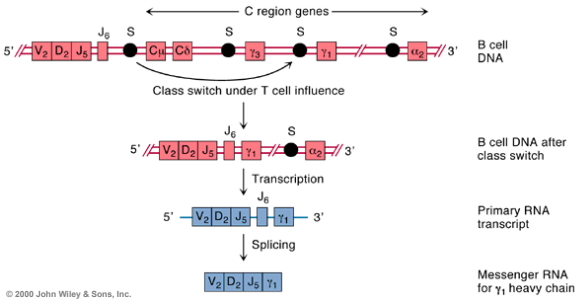
→ **PLASMOCYTES**



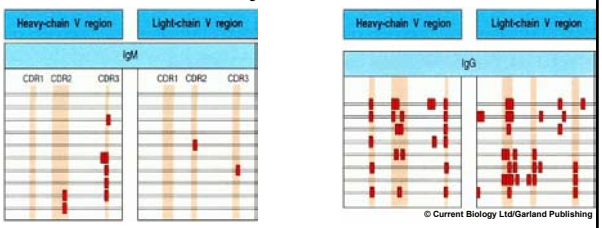
IN MATURE B CELLS: ISOTYPIC SWITCH AND AFFINITY MATURATION



Isotypic switch



Affinity maturation

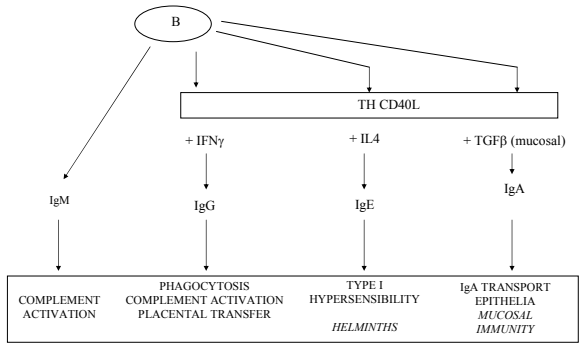


« Primary response »
7 days after 1st immunization

→

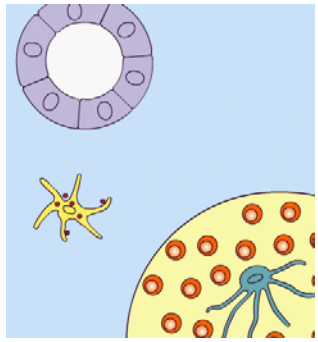
«Secondary Response»
7 days after the 2nd immunization at day 14

→ *Somatic Hypermutation occurs in germinal centres.*
→ *It is followed by selection of high affinity clones*



HOW B CELL RESPONSE OCCURS IN VIVO?

THE APC REACHES THE T CELL ZONE

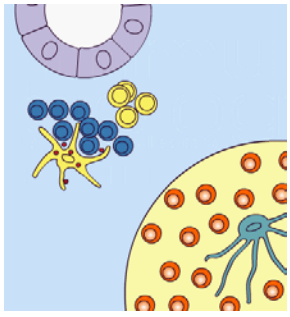


T cell zone

Follicular zone

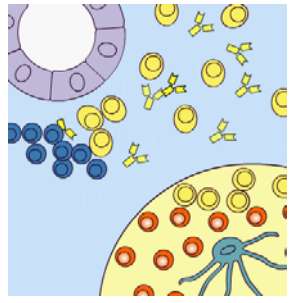
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)

APC ACTIVATE TH2



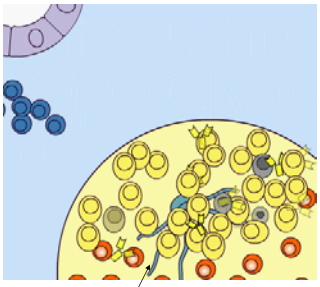
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)

B CELLS RESPOND AND SECRETE LOW AFFINITY Ab SOME REACH THE FOLLICULE



(from Janeway et al, « Immunobiology », 5th edition Garland ed »)

THEY PROLIFERATE, FORM A GERMINAL CENTRE WHERE SOMATIC MUTATION AND ISOTYPE SWITCH CAN OCCUR

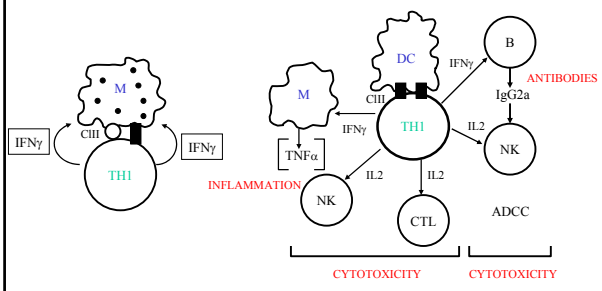


Follicular dendritic cells

(from Janeway et al, « Immunobiology », 5th edition Garland ed »)

ROLE OF TH1 AND TH2 DEFENSES
IN IMMUNE DEFENSES AGAINST PATHOGENS

TH1 DEFENSES

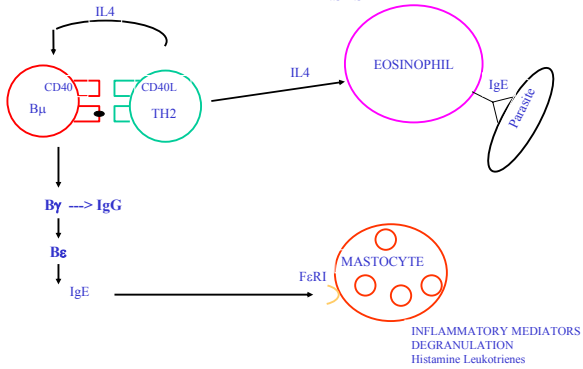


MICROORGANISM
INTRACELLULAR VESICULAR
BACTERIA, PARASITES

MICROORGANISM
INTRACELLULAR CYTOSOLIC
VIRUSES, BACTERIA

PROTECT AGAINST INTRACELLULAR MICROORGANISMS AND CANCERS

TH2 DEFENSES



PROTECT AGAINST EXTRACELLULAR MICROORGANISMS BUT ALLERGY !

ROLE OF REGULATORY T CELLS

REGULATORY CD4 T CELLS
« T REG »

10% CD4 T CELLS

EXPRESS IL2R (CD25) AND CTLA4 (CD152) CONSTITUTIVELY and GITR18

ANERGIC; THIS CAN BE BROKEN BY IL2

PRODUCE IL10, TGFβ

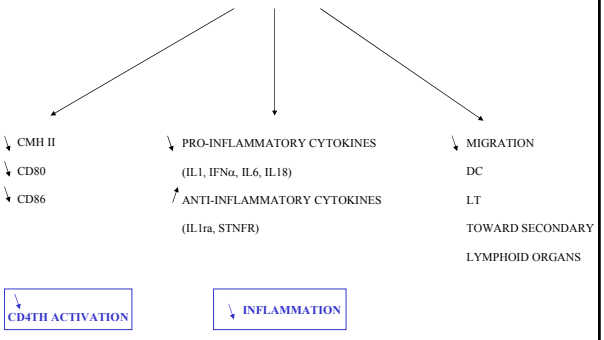
SUPPRESS CELLS OF PROLIFERATION OF CD4 TH1 AND CD8 CTL

ROLE: PERIPHERAL CONTROL OF AUTOIMMUNITY

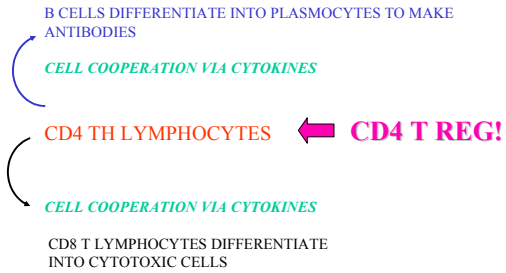
MAY BE GENERATED BY IMMATURE DC

ARE IN EXCESS IN CANCER PATIENTS (LUNG)

IL10, AN ANTI-INFLAMMATORY CYTOKINE



CD4 REGULATORY T LYMPHOCYTES CONTROL THE RESPONSE !



AUTOIMMUNITY INFLAMMATION GvHD

TH1 TREG

CANCER CHRONIC INFECTION

TH1 TREG