The Immunology of Bone Marrow Transplantation

Dr Christian Harkensee

Post-Doctoral JSPS Fellow

Tokai University, Isehara, Kanagawa

Who I am – Chris Harkensee

Who I am – Chris Harkensee

- Born 1968 in Hamburg, grown up in Bremen, Germany

Germany


WOLFINGER

Mercedes

Audi

Mercedes

Audi

Mercedes

BMW

Volkswagen

Mercedes

Audi

BMW

Volkswagen

Mercedes

Audi

BMW

Opel

Porsche

Volkswagen

Audi

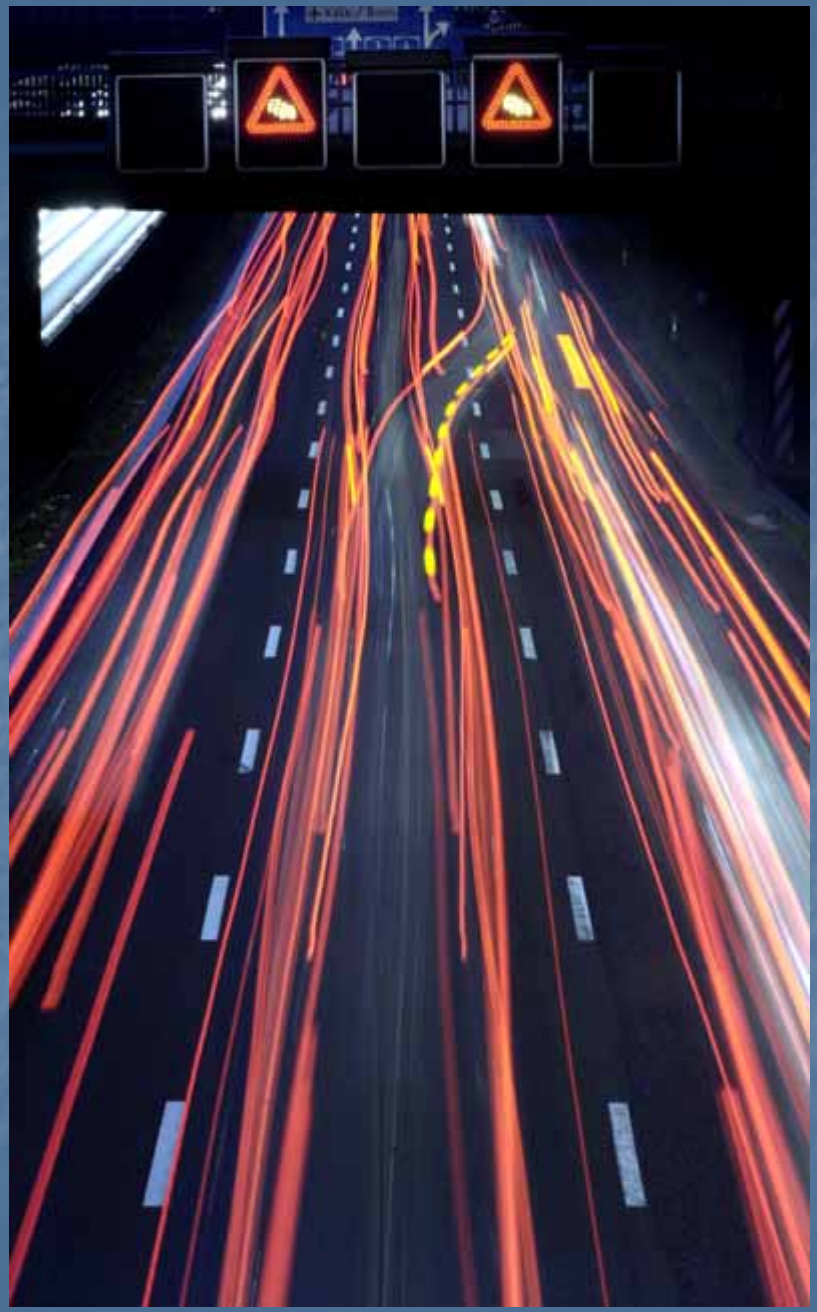
Mercedes

BMW

Opel

Porsche

Volkswagen



Autobahn

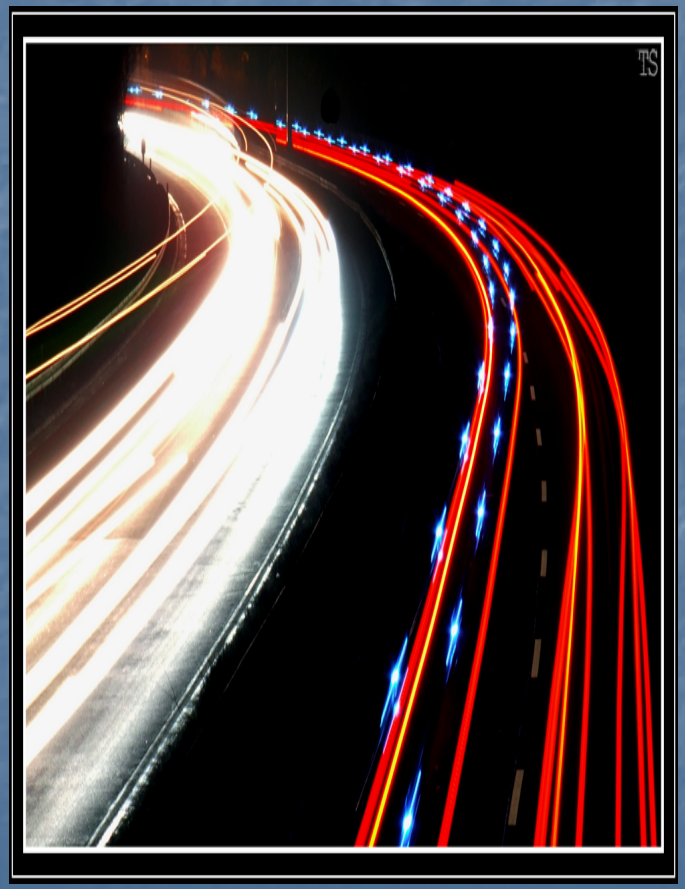
Audi

Mercedes

BMW

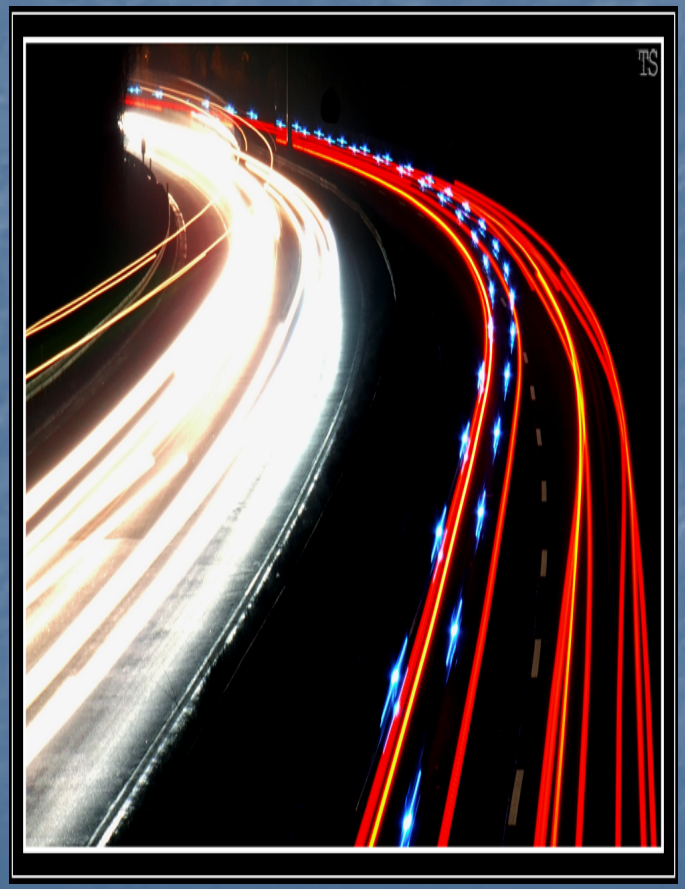
Opel

Autobahn Quiz



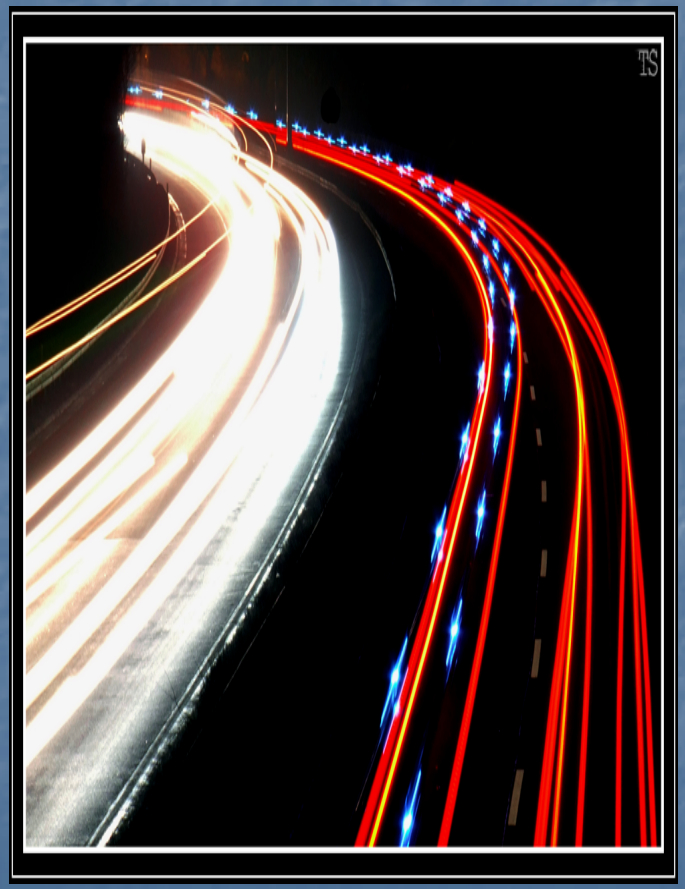
- What is the **Speed Limit** on the Autobahn ?

Autobahn Quiz



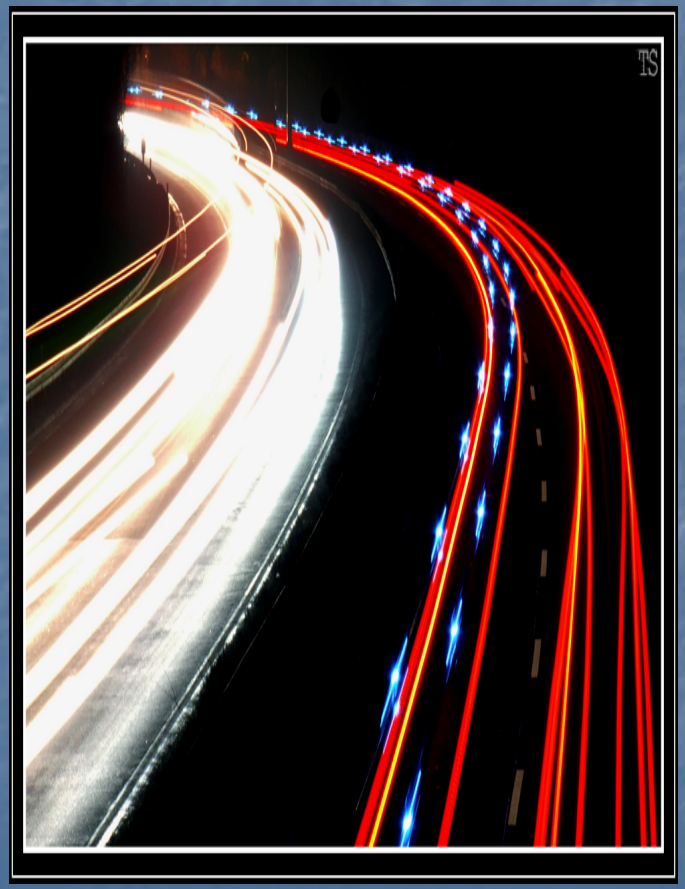
- What is the **Speed Limit** on the Autobahn ?
- ◊ 110 km/h

Autobahn Quiz



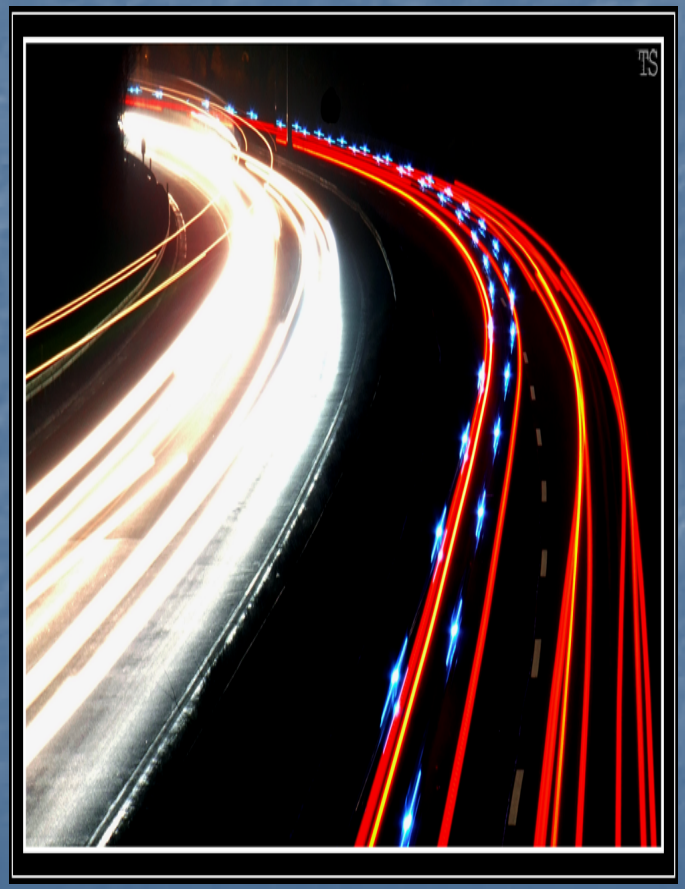
- What is the **Speed Limit** on the Autobahn ?
- ◊ 110 km/h
- ◊ 220 km/h

Autobahn Quiz



- What is the **Speed Limit** on the Autobahn ?
- ◊ 110 km/h
- ◊ 220 km/h
- ◊ 330 km/h

Autobahn Quiz



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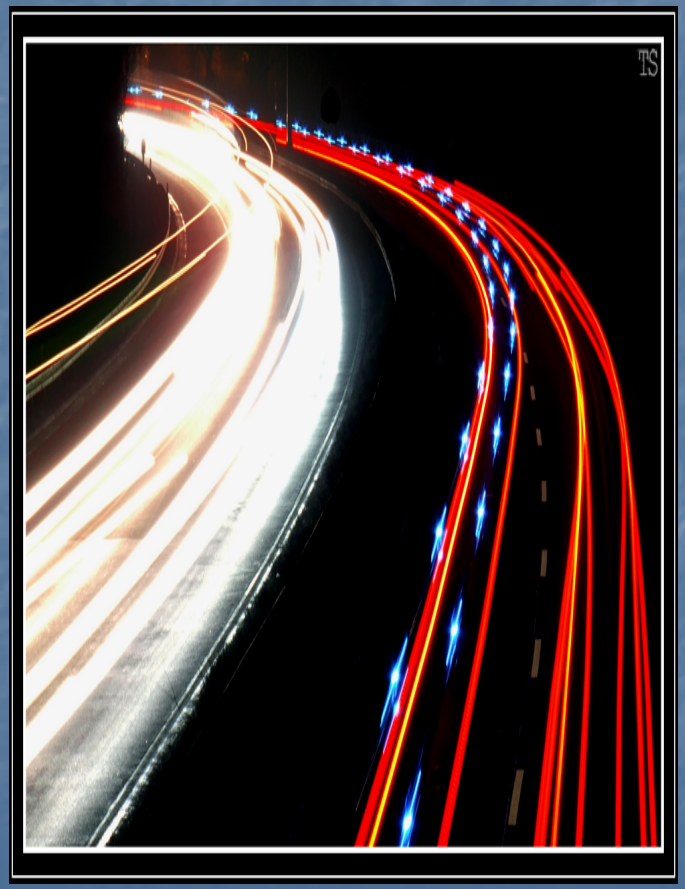
- ◊ 330 km/h
- ◊ no speed limit

Autobahn Quiz



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- ◊ 110 km/h
- ◊ 220 km/h
- ◊ 330 km/h
- ◊ **no speed limit**


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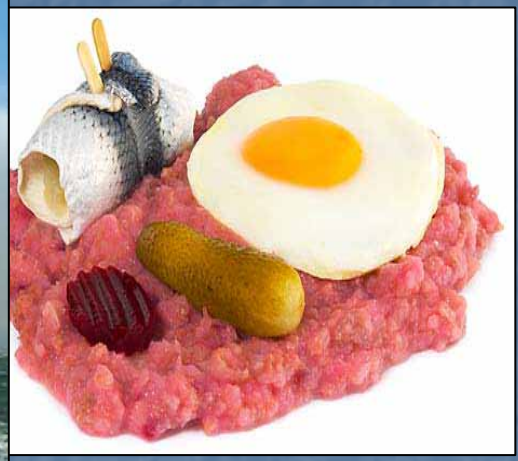
Bremen and North West Germany



Bremen

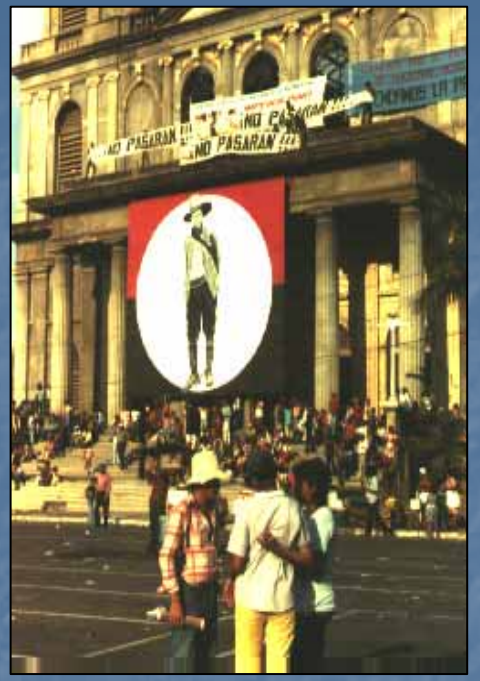
Fairy Tale by the Brothers Grimm:

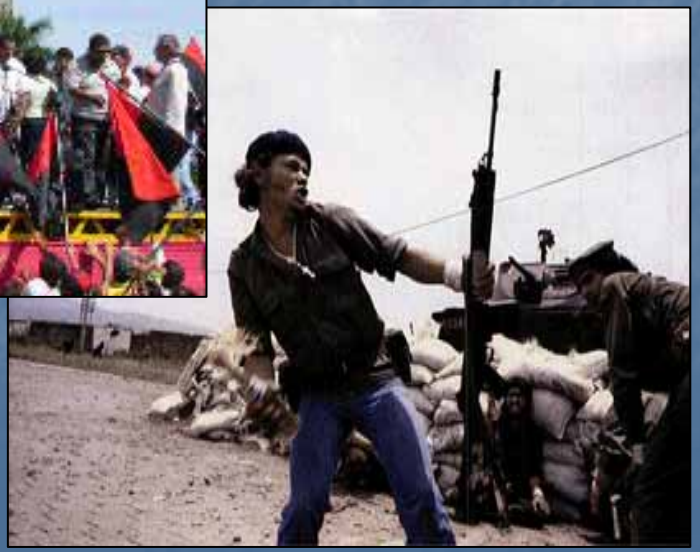
The Musicians of Bremen

(Die Bremer Stadtmusikanten)

Who I am – Chris Harkensee

- Born 1968 in Hamburg, grown up in Bremen, Germany
- 1987 Grammar School Graduation, Bremen Travel to Nicaragua, Costa Rica. National Service in Bremen





As Freelance Photographer and Journalist in Nicaragua, 1987

Who I am – Chris Harkensee

- Born 1968 in Hamburg, grown up in Bremen, Germany
- 1987 Grammar School Graduation, Bremen Travel to Nicaragua, Costa Rica. National Service in Bremen
- 1989 – 1997 Medical School at Humboldt University, Berlin. Internships in Bolivia, Peru, USA. Graduation as a Doctor of Medicine

Berlin 1989-1997

9 November 1989 – Fall of Berlin Wall

Christo wraps Reichstag Building

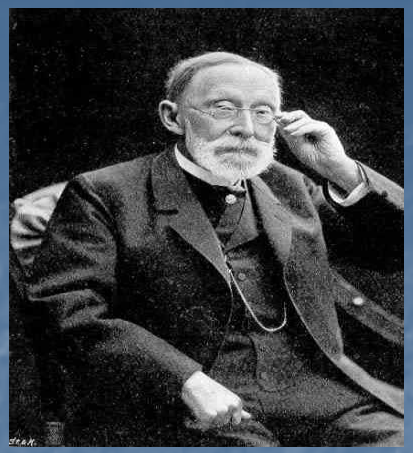
3 October 1990 – German Reunification

Tacheles Club

Potsdamer Platz rebuild

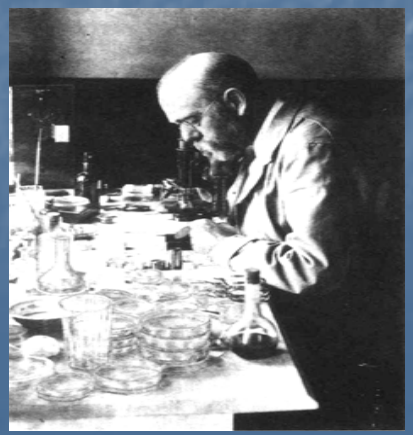
Love Parade

Love Parade



Rudolf Virchow
Founder of cellular pathology

Emil von Behring
Discoverer of Diphteria
Pioneer in vaccine development



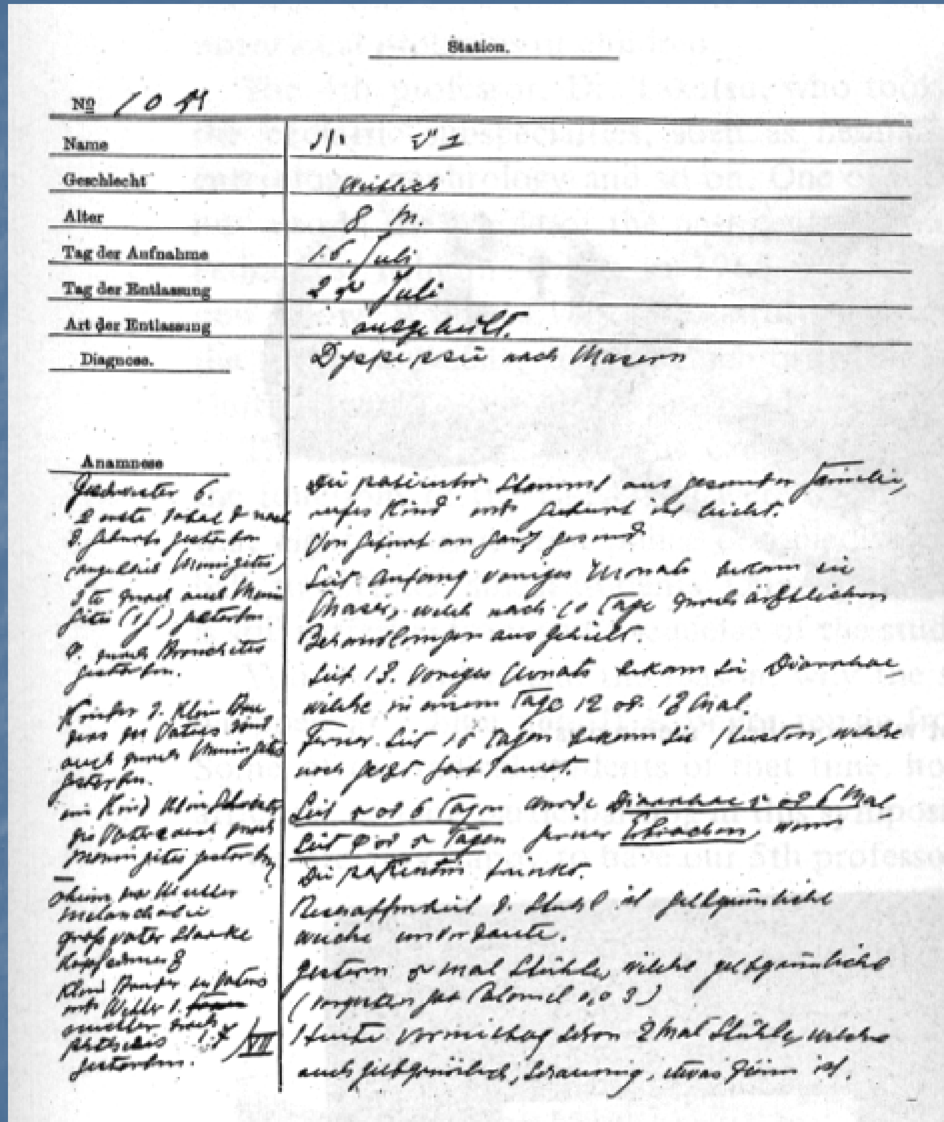
Robert Koch
Discoverer of TB, cholera
Founder of Microbiology
And Infectiology

Charité University Hospital
Humboldt University Berlin

Charité Doctors introducing Western Medicine to Japan – 1854-1912

Monument to Professor Barth
at Tokyo Medical School

Japan's first Paediatric Hospital,
Tokyo University (1874)



Station.

No	1041
Name	
Geschlecht	weiblich
Alter	8 M.
Tag der Aufnahme	15. Juli
Tag der Entlassung	24 Juli
Art der Entlassung	ausgeheilt.
Diagnose.	Dyspepsie nach Masern

Anamnese

Patient file

Mexico

New York, US

Cuba

Bolivia

Peru

California, US

Brasil

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- 1987 Grammar School Graduation, Bremen Travel to Nicaragua, Costa Rica. National Service in Bremen
- 1989 – 1997 Medical School at Humboldt University, Berlin. Internships in Bolivia, Peru, USA. Graduation as a Doctor of Medicine
- 1998-2000 Doctor in a children's rehabilitation hospital in Murnau, Bavaria – met my future wife

Murnau

Who I am – Chris Harkensee

- Since 2000 – working as a children's doctor in the United Kingdom (Scarborough, Chester, Liverpool, Newcastle). Training as a specialist in immunology and infection

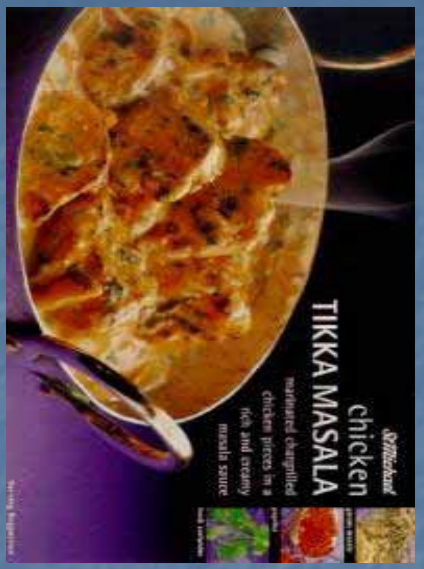
The United Kingdom

Breakfast

Lunch

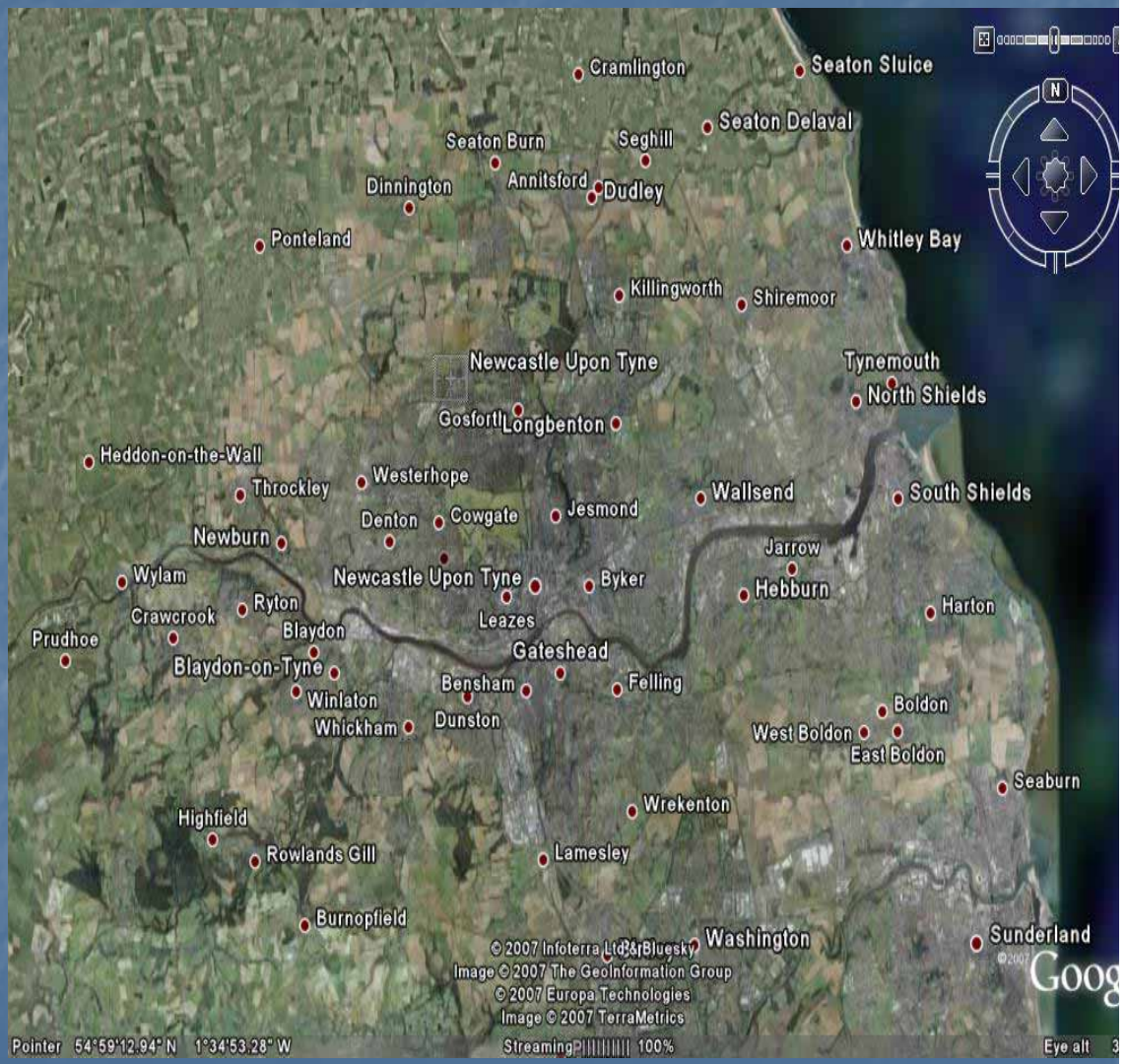
Tea

Dinner



Evening

Newcastle upon Tyne

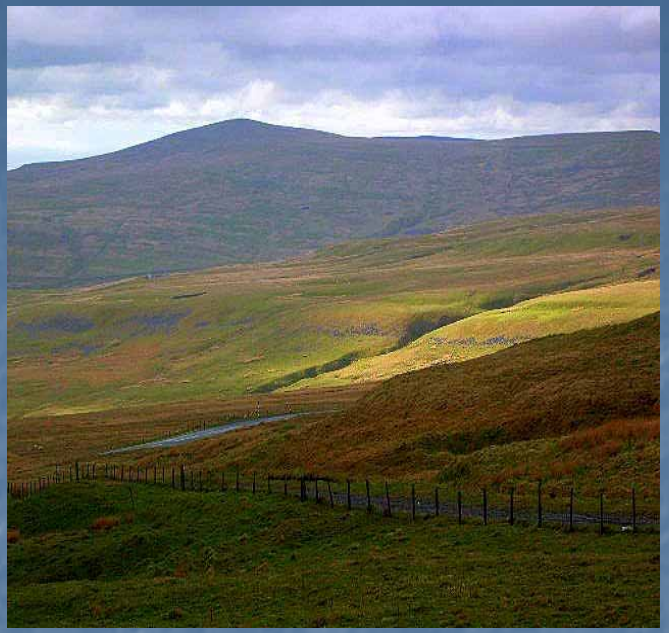


Newcastle

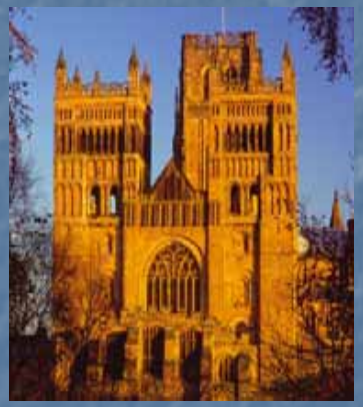
NEWCASTLE UNITED

Around Newcastle

Farne Islands

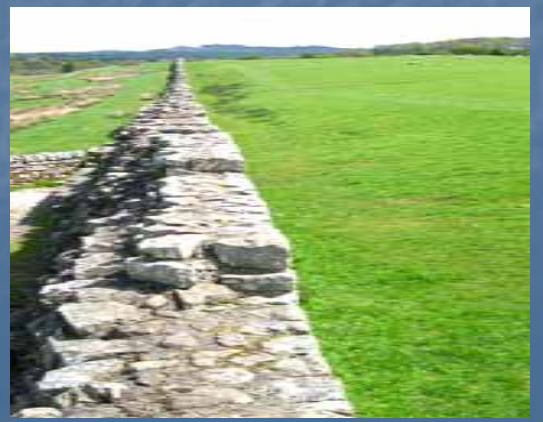


Hadrian's Wall



Durham

Bamborough Castle



University of Newcastle

Royal Victoria Infirmary

University Medical School

On the Children's Bone Marrow Transplant Unit

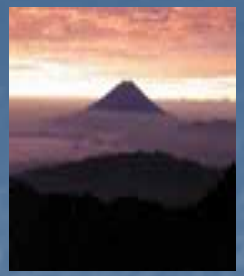
Who I am – Chris Harkensee

- Since 2000 – working as a children's doctor in the United Kingdom (Scarborough, Chester, Liverpool, Newcastle). Training as a specialist in immunology and infection
- Two children – born 2004 and 2007

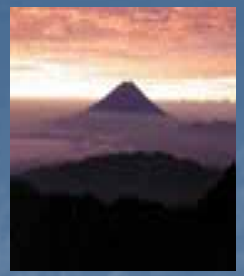
Tynemouth

Who I am – Chris Harkensee

- Since 2000 – working as a children's doctor in the United Kingdom (Scarborough, Chester, Liverpool, Newcastle). Training as a specialist in immunology and infection
- Two children – born 2004 and 2007
- Researcher with a JSPS fellowship at Tokai University, Kanagawa



JAPAN



Professor Hidetoshi Inoko

Tokai University
Isehara, Kanagawa

The Immunology of Bone Marrow Transplantation

Dr Christian Harkensee

Aims

Aims

- Share the fascination of how the immune system works

Aims

- Share the fascination of how the immune system works
- Learn something ‘cutting edge’ about a scientific hot topic – bone marrow transplantation

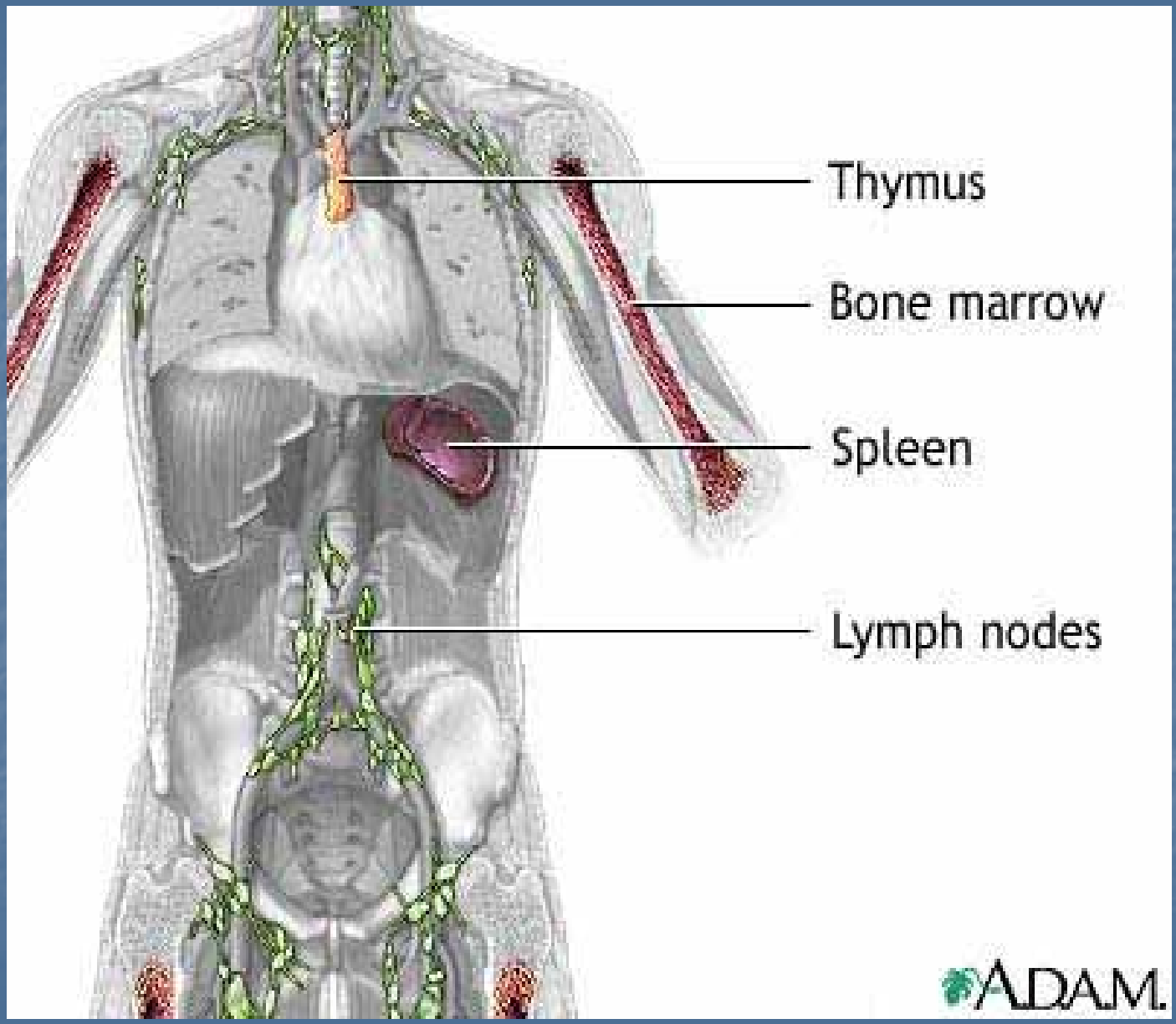
Overview

- Introduction to the immune system
- Bone Marrow Transplantation, its successes and difficulties

Immune System

- A body system of organs, tissues and cells, that differentiates self from nonself, recognises danger (tissue signals, tumour cells) and eliminates antigens (kills pathogenic organisms, like bacteria and viruses)

Where is our Immune System?


Thymus
Bone marrow
Spleen
Lymph nodes
A.D.A.M.

Where is our Immune System?

- Immune cells are found in *all* tissues and organs

Where is our Immune System?

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- Some immune cells circulate in the blood and lymph system

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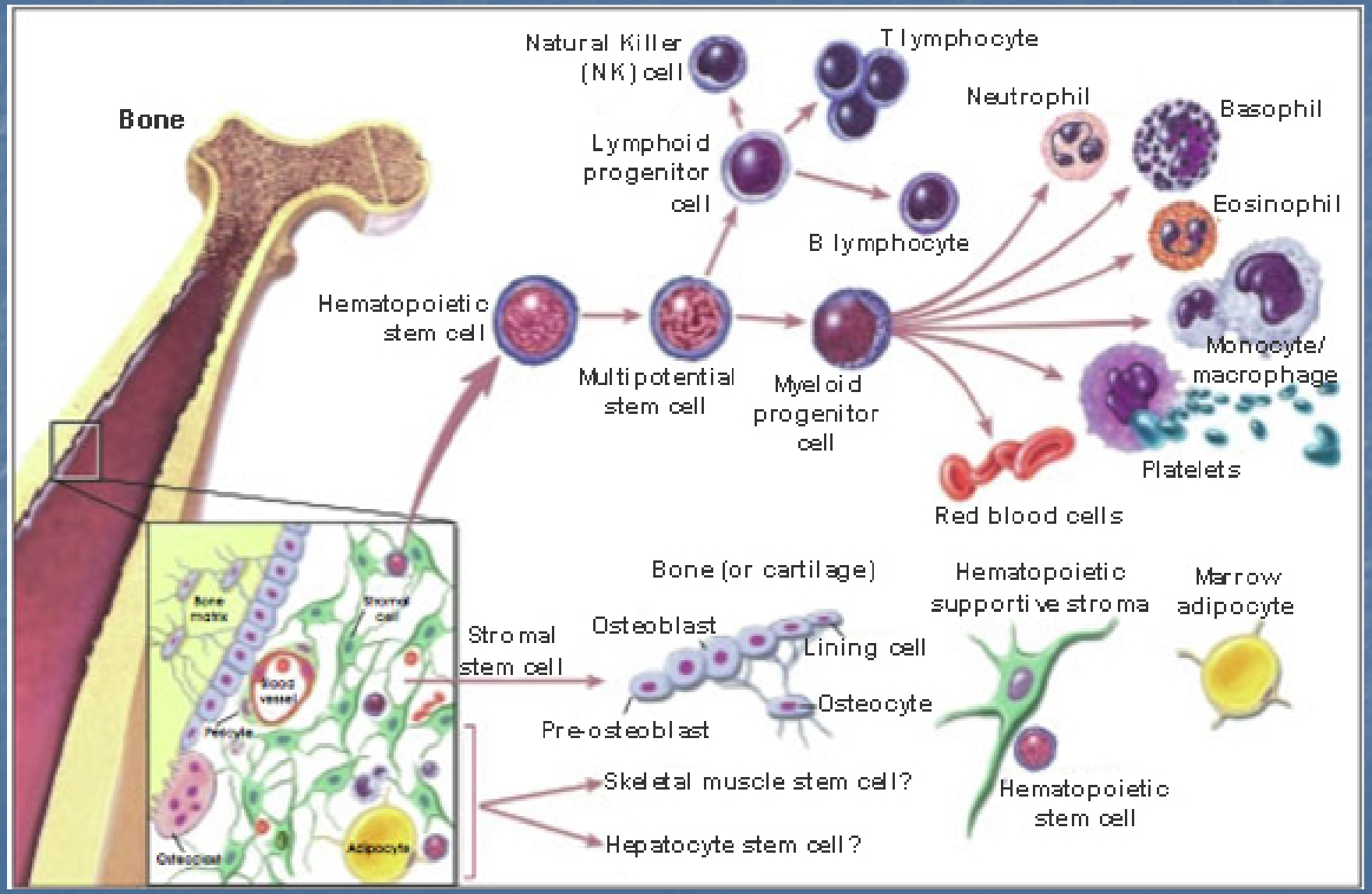
Where is our Immune System?

- Immune cells are found in *all* tissues and organs
- Some immune cells circulate in the blood and lymph system
- Immune cells are produced, and develop, in the bone marrow and thymus
- The spleen is a special filter organ for cells in the blood

Bone Marrow


Bone
Natural Killer (NK) cell
T lymphocyte
Neutrophil
Basophil
Lymphoid progenitor cell
Eosinophil
B lymphocyte
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Monocyte/ macrophage
Platelets
Red blood cells
Bone (or cartilage)
Hematopoietic supportive stroma
Marrow adipocyte
Stromal stem cell
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic stem cell

Components of the Immune System

Components of the Immune System

- Innate Immune System

Components of the Immune System

- Innate Immune System
- Adaptive Immune System

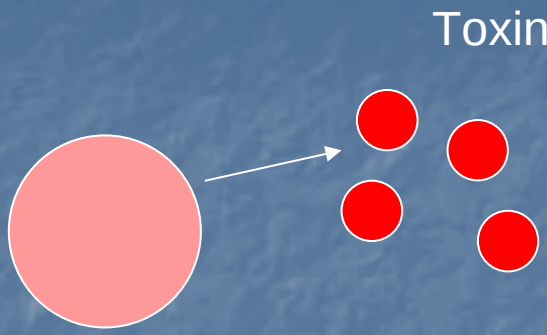
Innate Immune System

- Inherited / born with
- Recognises self/non-self, danger
- Non-specific, broad activity
- Does not change / learn
- Mainly protects against pathogens living outside cells (extracellular)

Macrophage (‘big eater’)

Macrophage (‘big eater’)

Macrophage (‘big eater’)

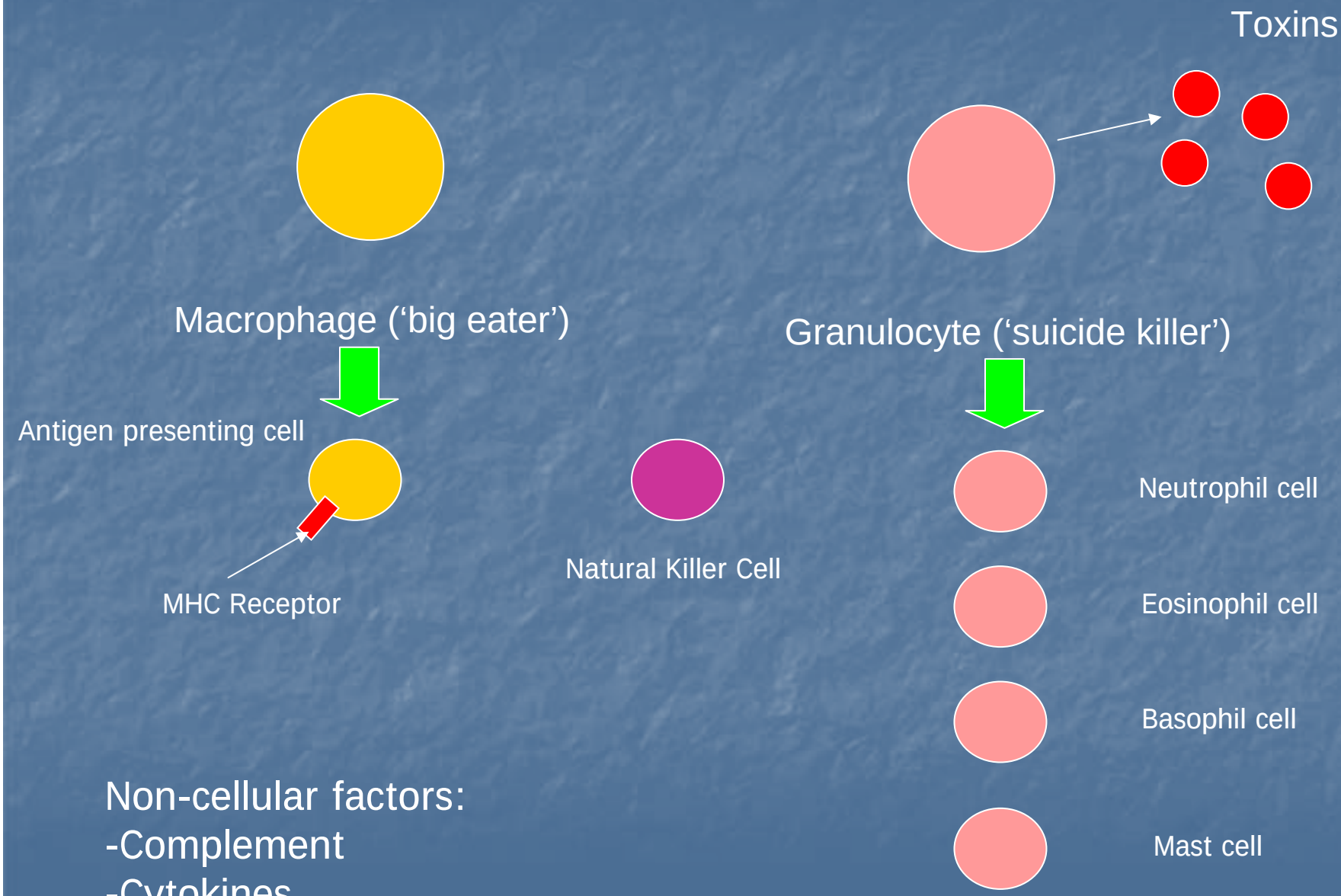


Granulocyte (‘suicide killer’)

Innate Immunity

- Components
- Cells: Macrophages, granulocytes
- Toxins: Acids, complement
- Signal molecules: Cytokines

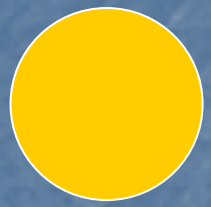
The Innate Immune System



Non-cellular factors:
-Complement
-Cytokines

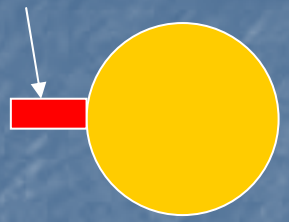
Adaptive Immunity

- Develops throughout life
- Recognises self/non-self, infected cells
- Highly specific against pathogens, learns from contact to pathogens
- Effective against both intracellular and extracellular pathogens

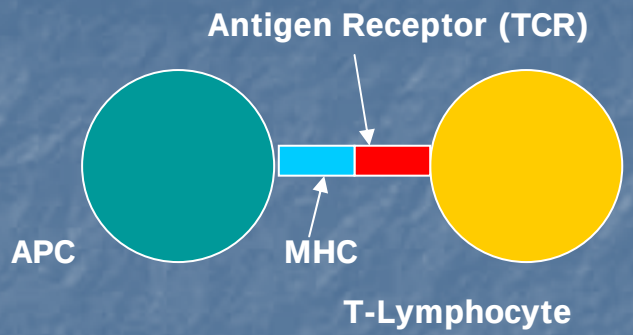


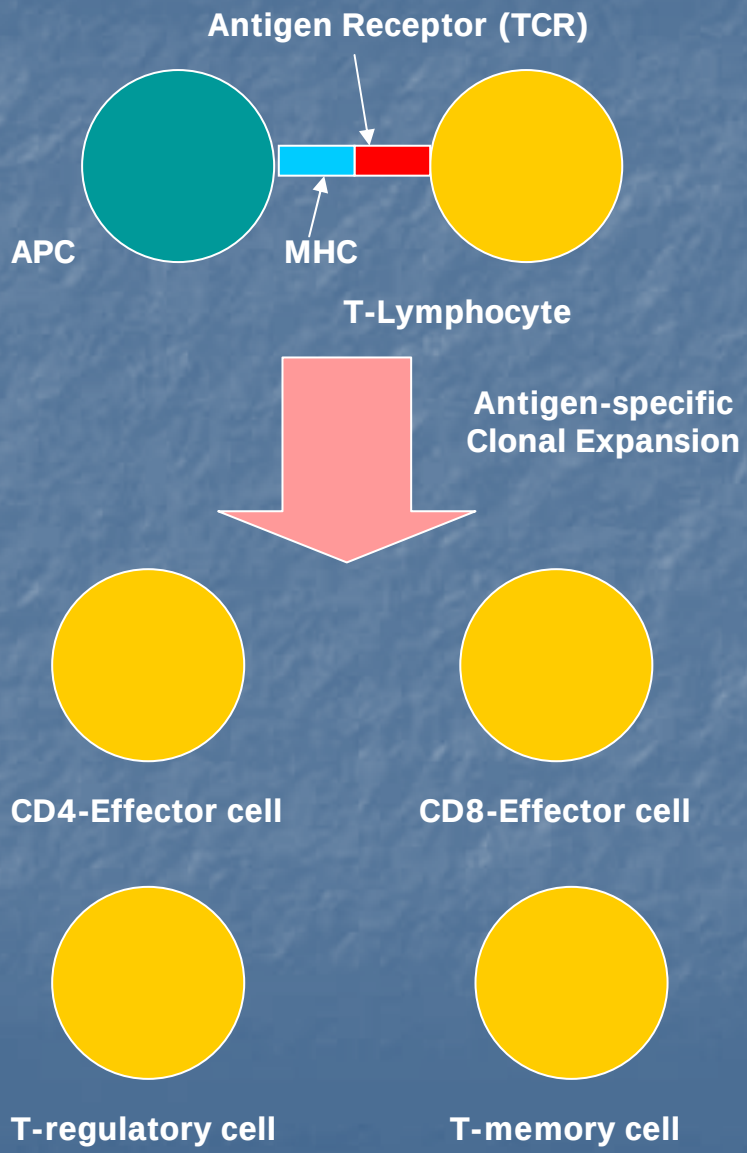
T-Lymphocyte

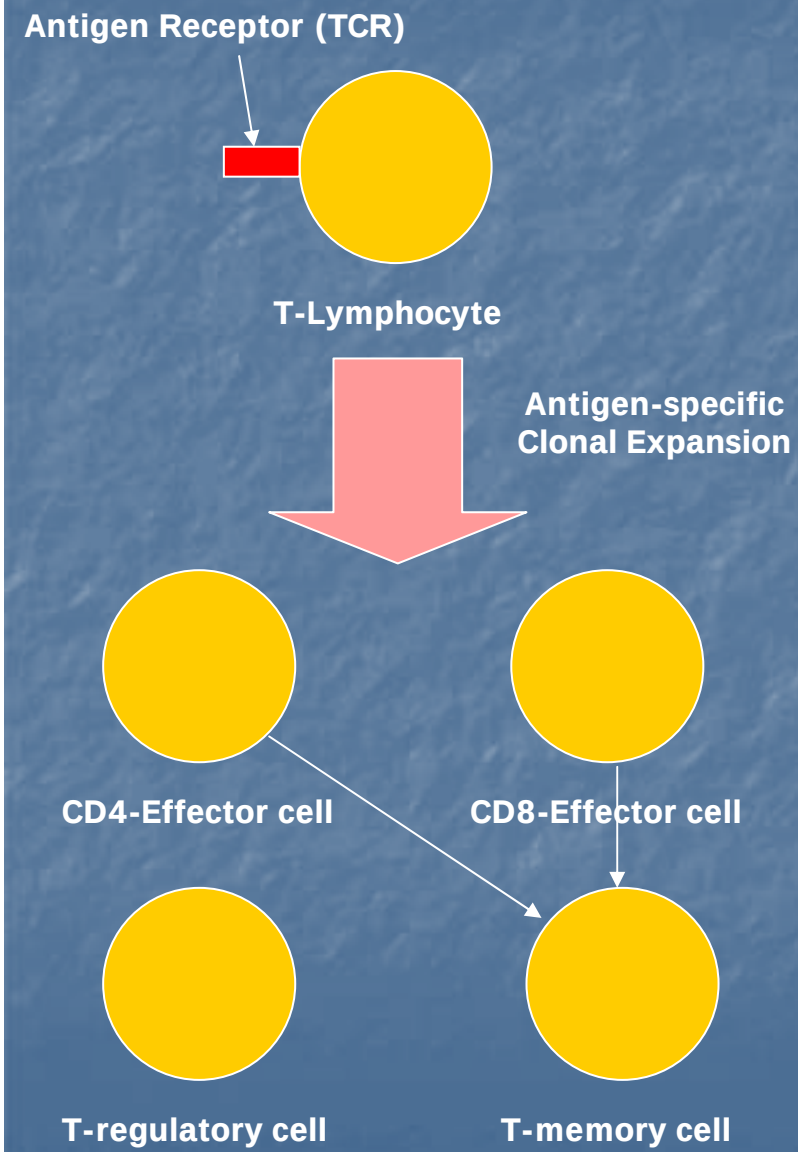
Antigen Receptor (TCR)



T-Lymphocyte


Antigen Receptor (TCR)
APC
MHC
T-Lymphocyte


Antigen Receptor (TCR)
APC
MHC
T-Lymphocyte
Antigen-specific
Clonal Expansion
CD4-Effector cell
CD8-Effector cell
T-regulatory cell
T-memory cell


Antigen Receptor (TCR)
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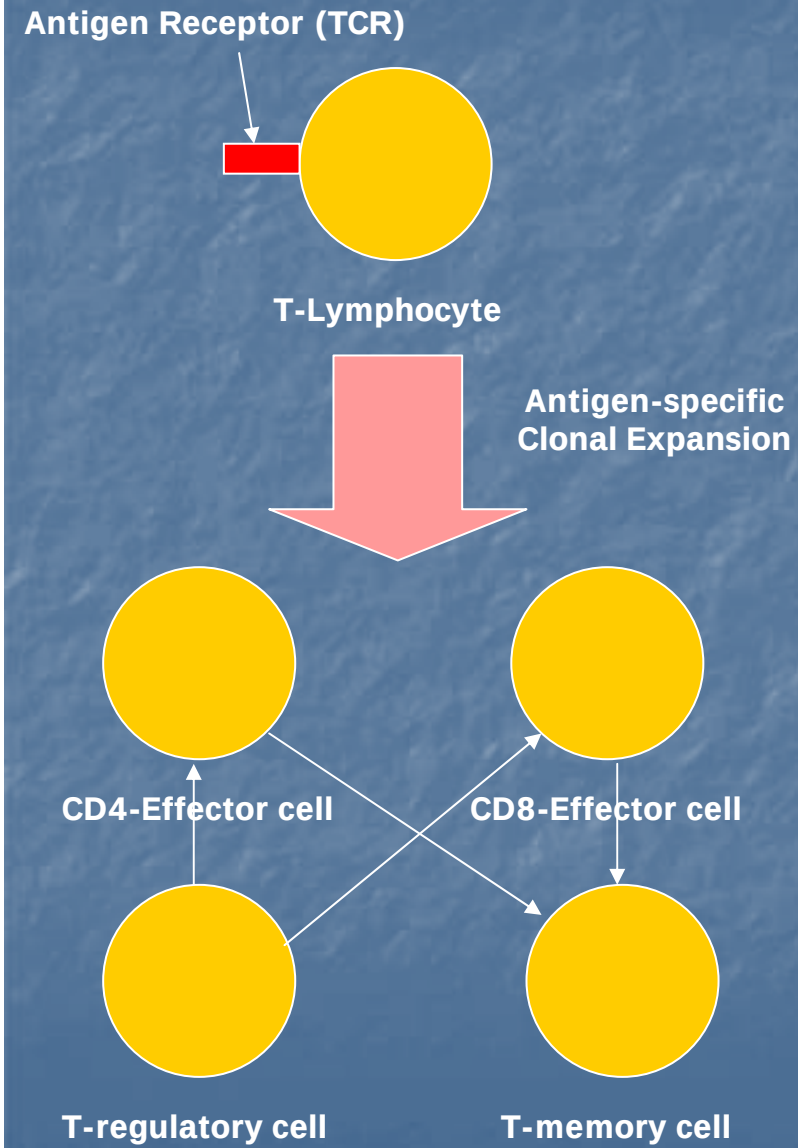
Antigen Receptor (TCR)
T-Lymphocyte
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Clonal Expansion
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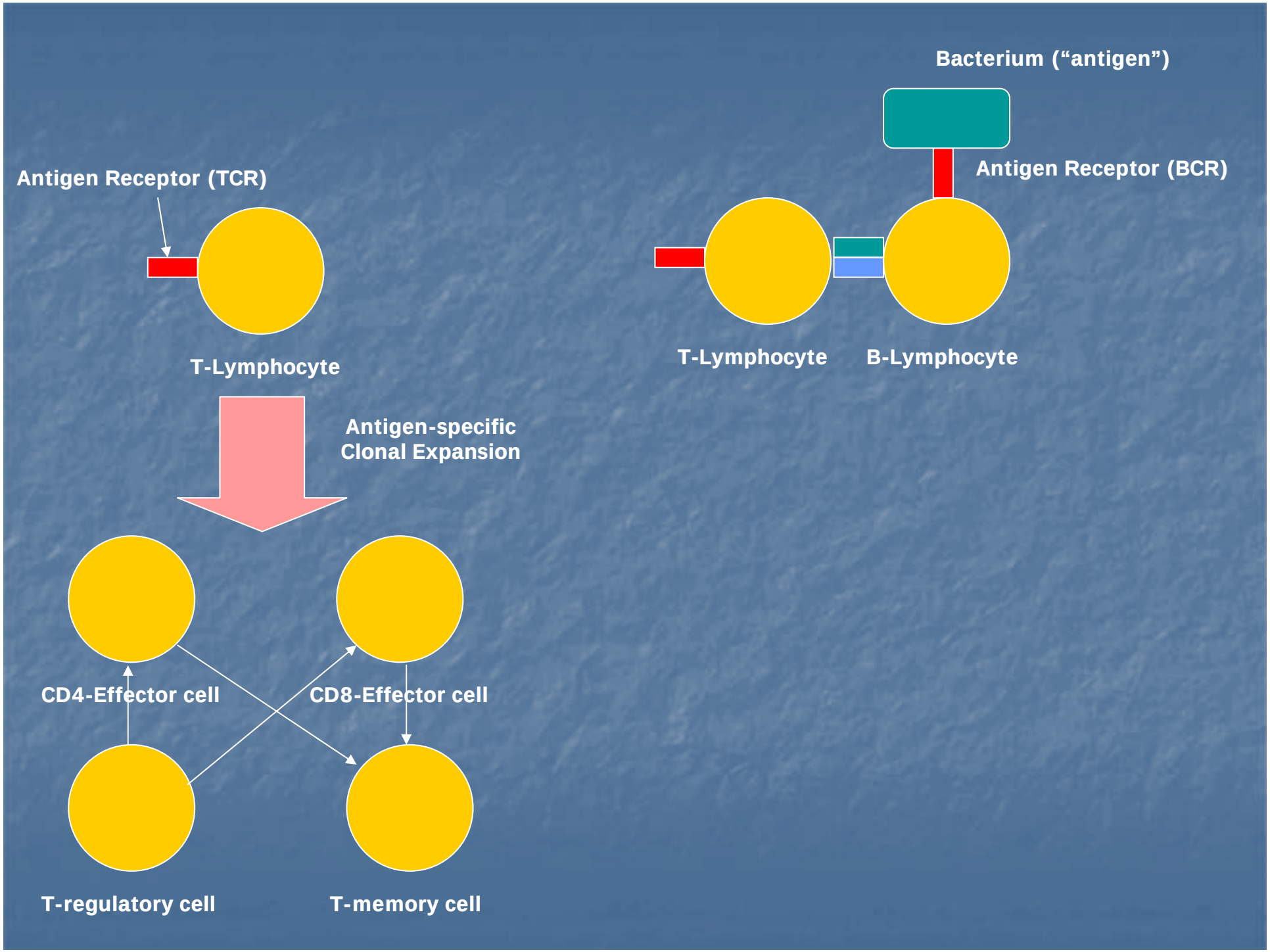
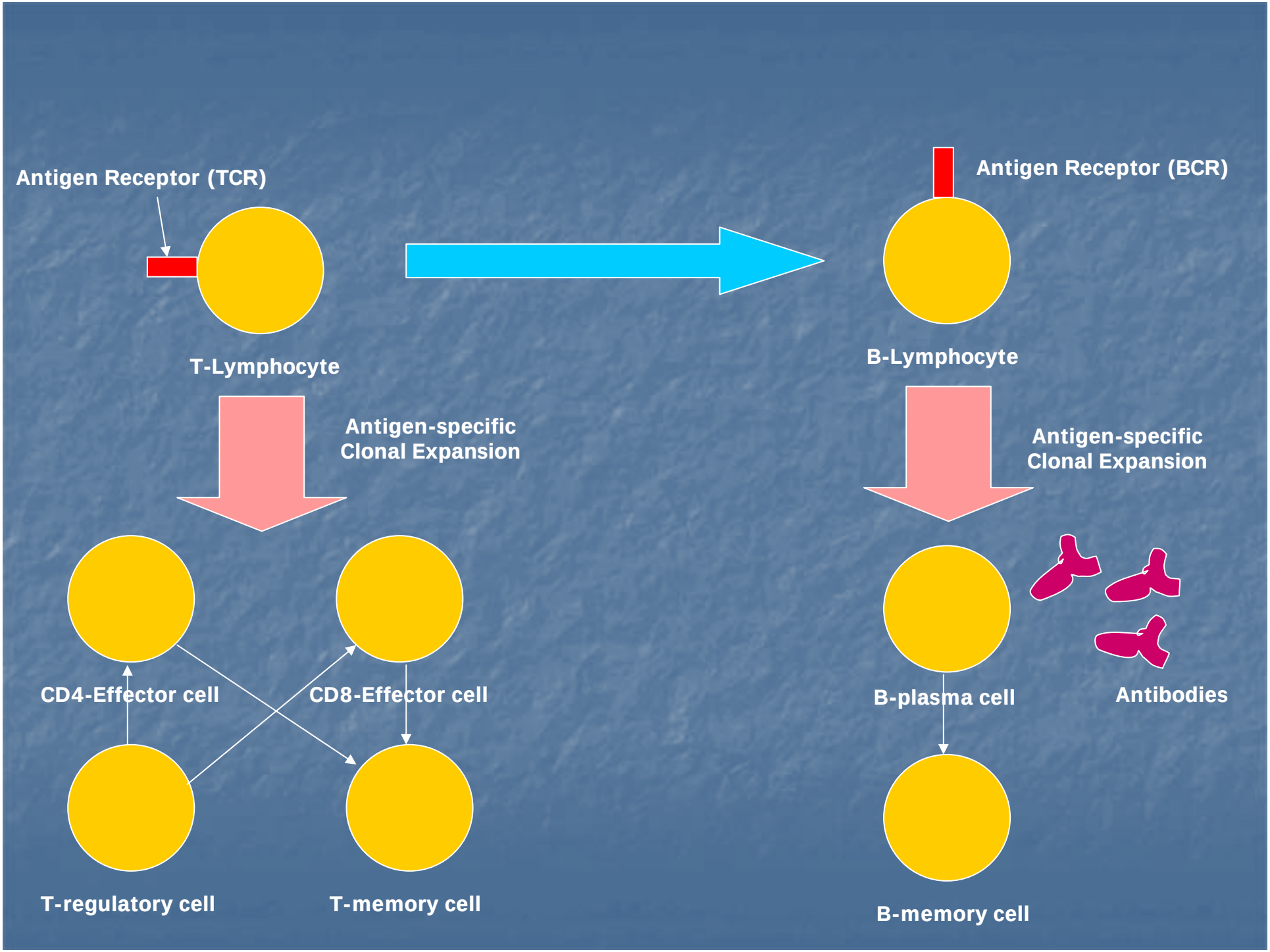
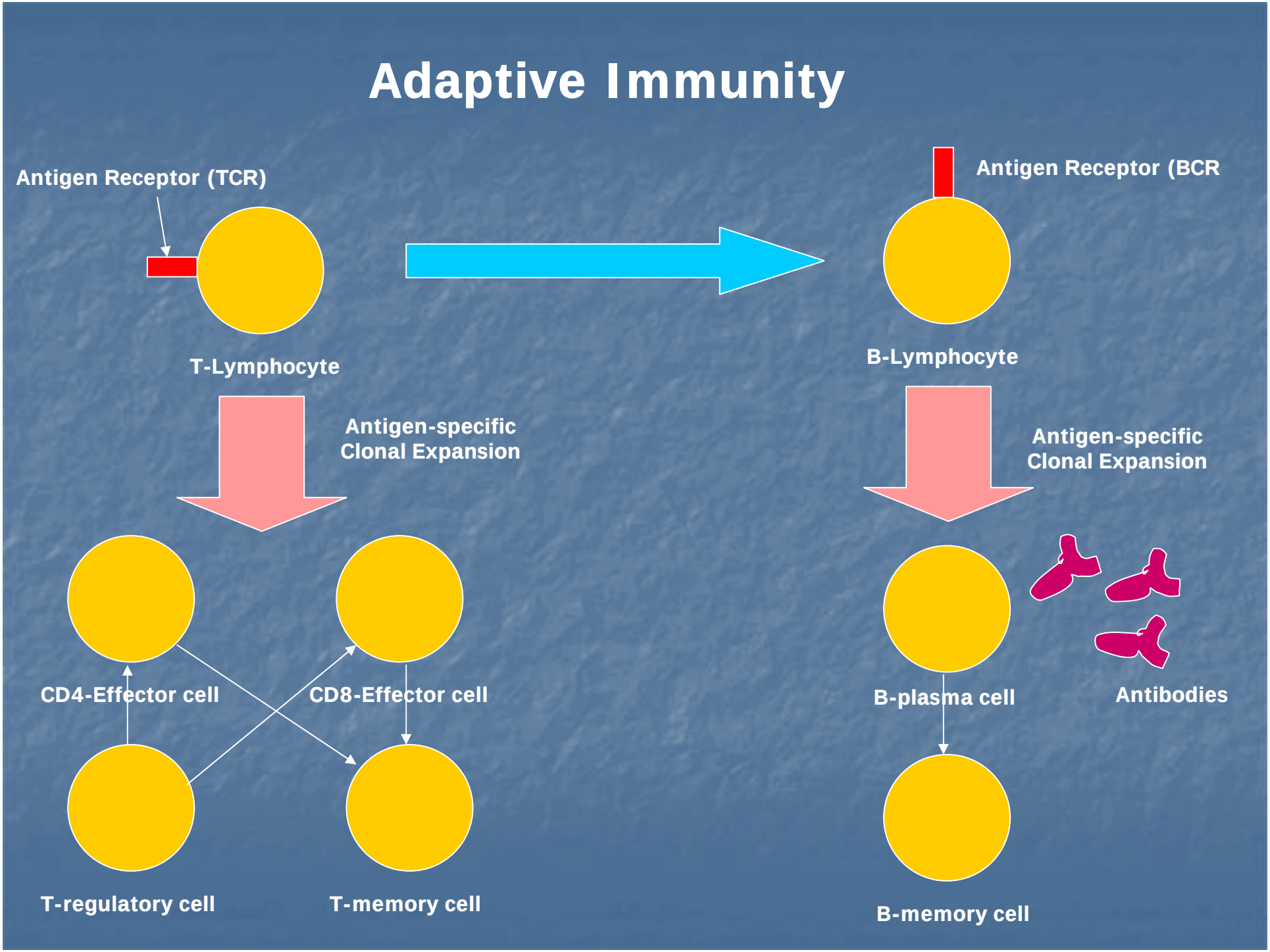
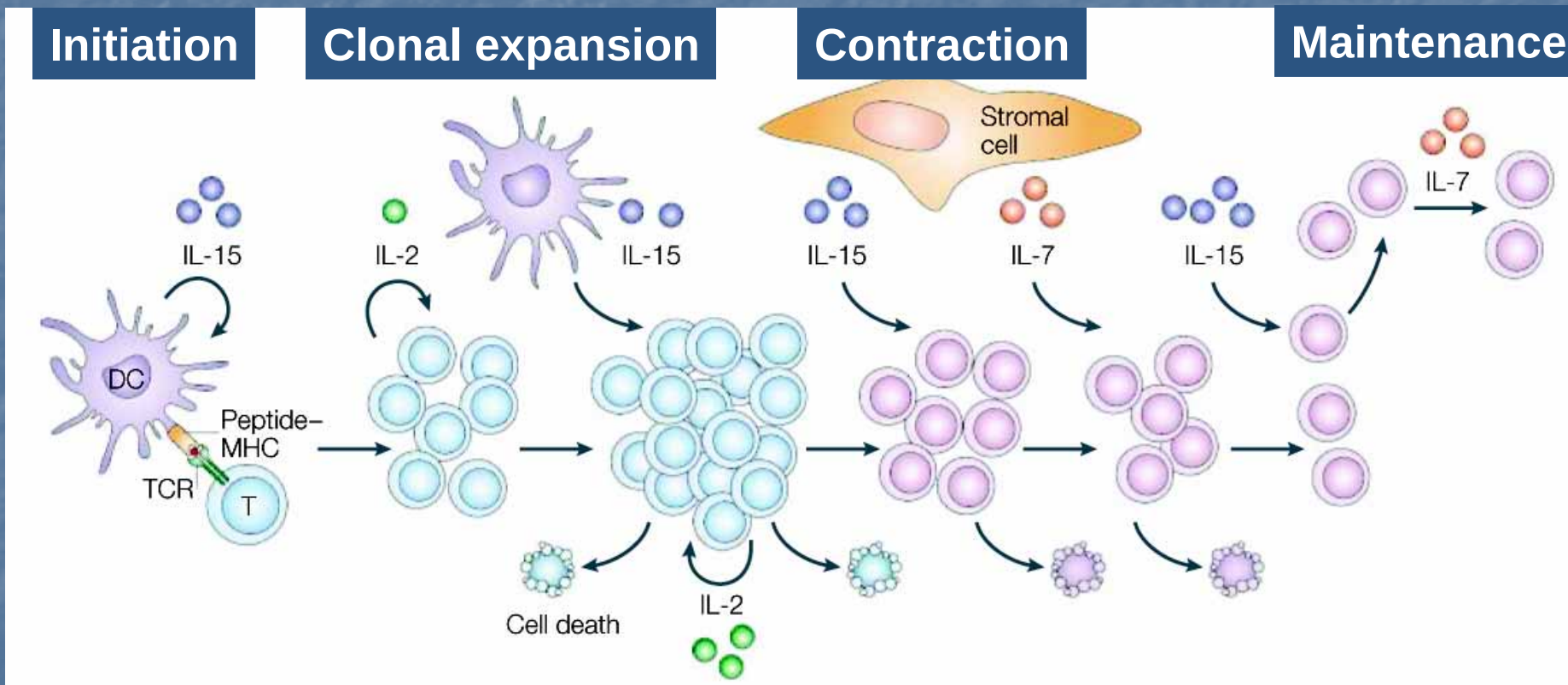

Bacterium (“antigen”)
Antigen Receptor (BCR)
Antigen Receptor (TCR)
T-Lymphocyte
B-Lymphocyte
T-Lymphocyte
Antigen-specific
Clonal Expansion
CD4-Effector cell
CD8-Effector cell
T-regulatory cell
T-memory cell


Antigen Receptor (TCR)
T-Lymphocyte
Antigen Receptor (BCR)
B-Lymphocyte
Antigen-specific
Clonal Expansion
Antigen-specific
Clonal Expansion
CD4-Effector cell
CD8-Effector cell
B-plasma cell
Antibodies
T-regulatory cell
T-memory cell
B-memory cell

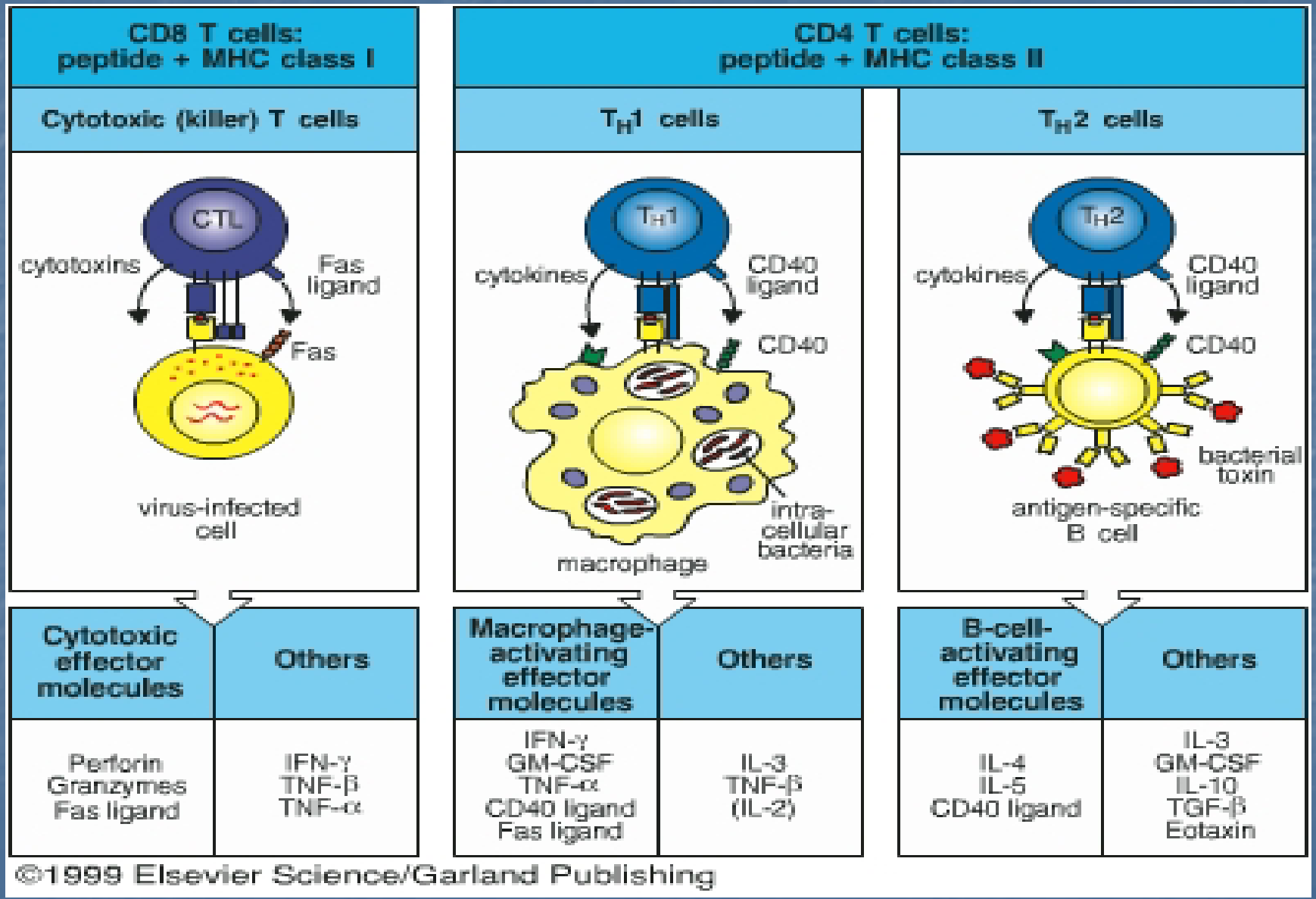
Adaptive Immunity



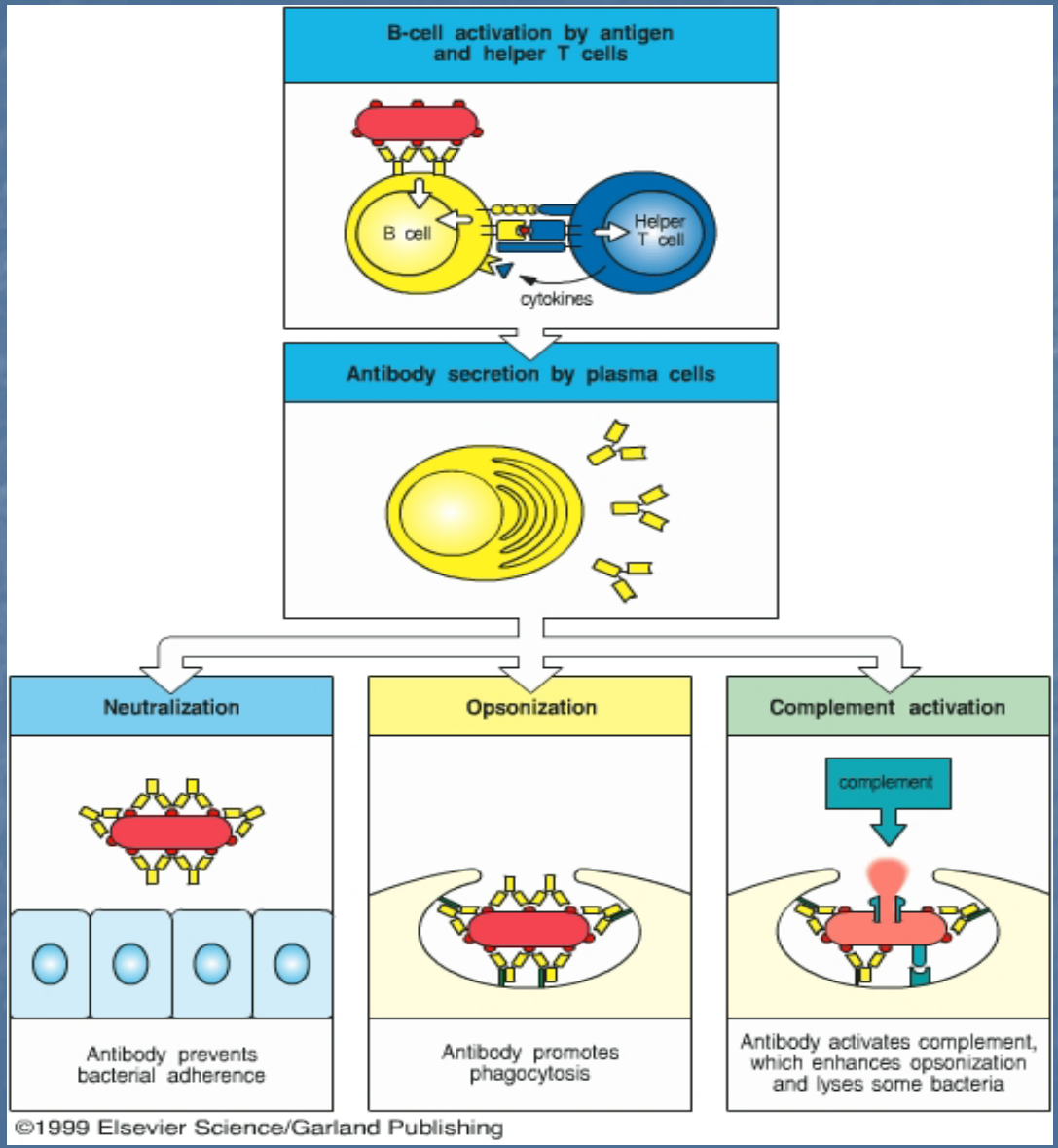
The kinetics of the T cell response



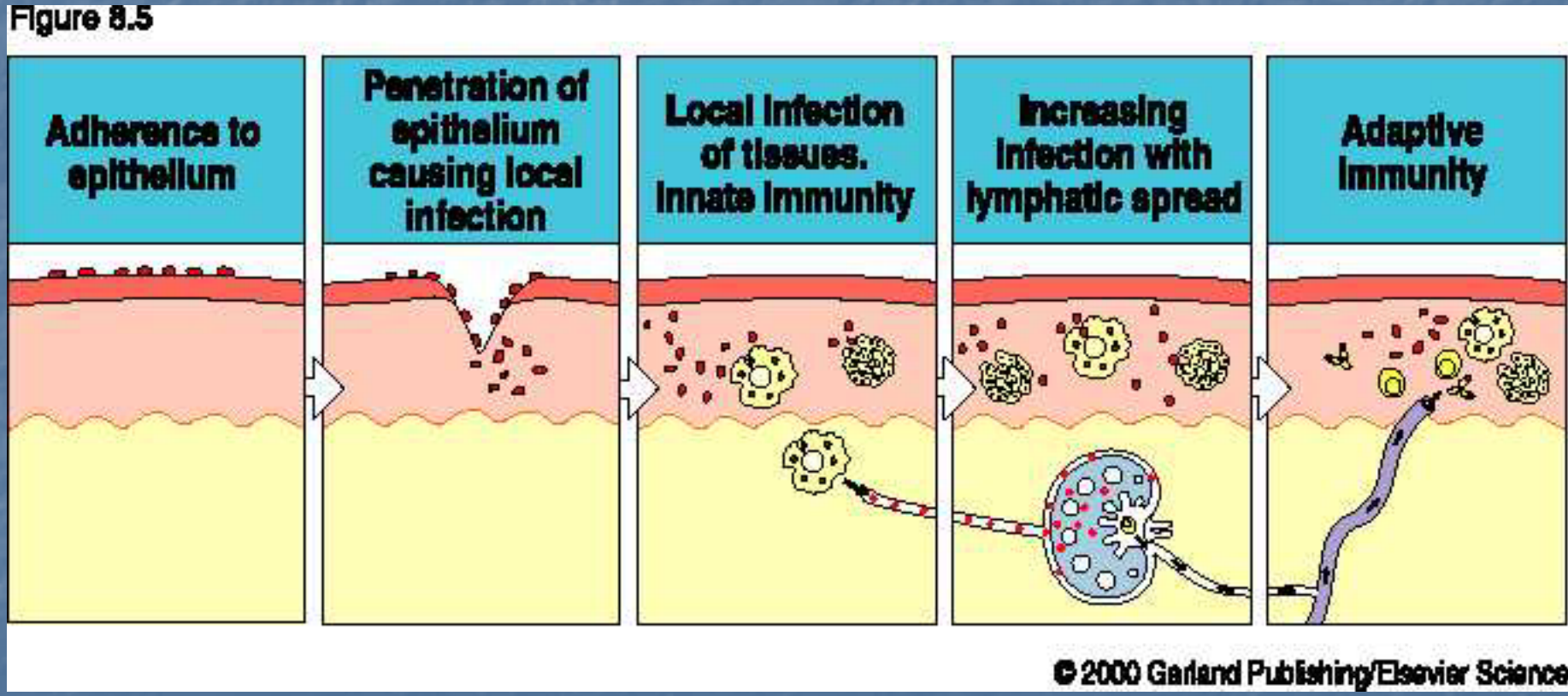
Effects of B-cells and T-cells



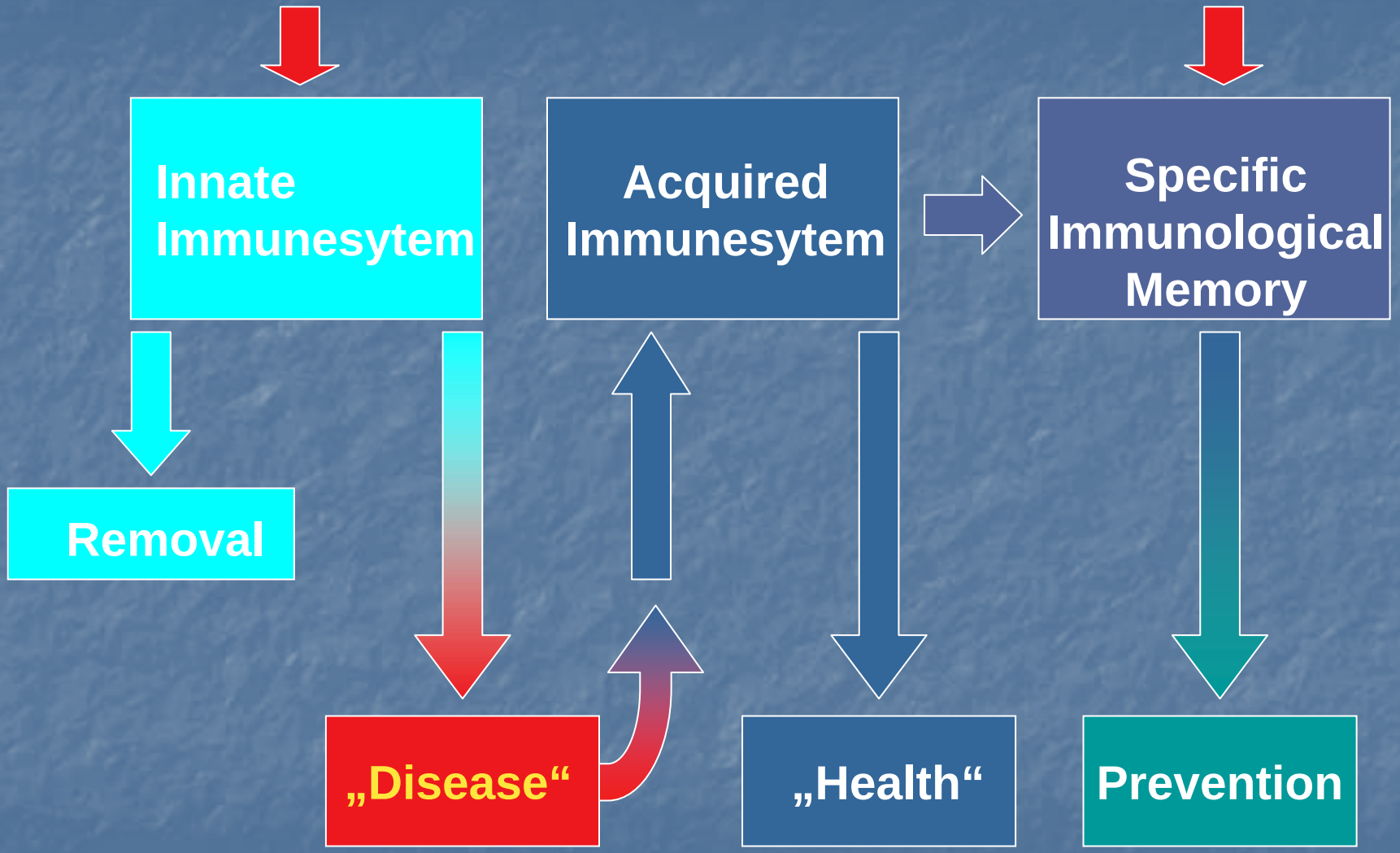
Effects of B-cells and T-cells



What happens if you have an injury ?



Summary of Innate and Adaptive Immunity



MHC and HLA polymorphism

MHC and HLA polymorphism

- What is MHC ? – Major Histocompatibility Complex (MHC) is a cell receptor on antigen presenting cells recognising the body's self/non-self

MHC and HLA polymorphism

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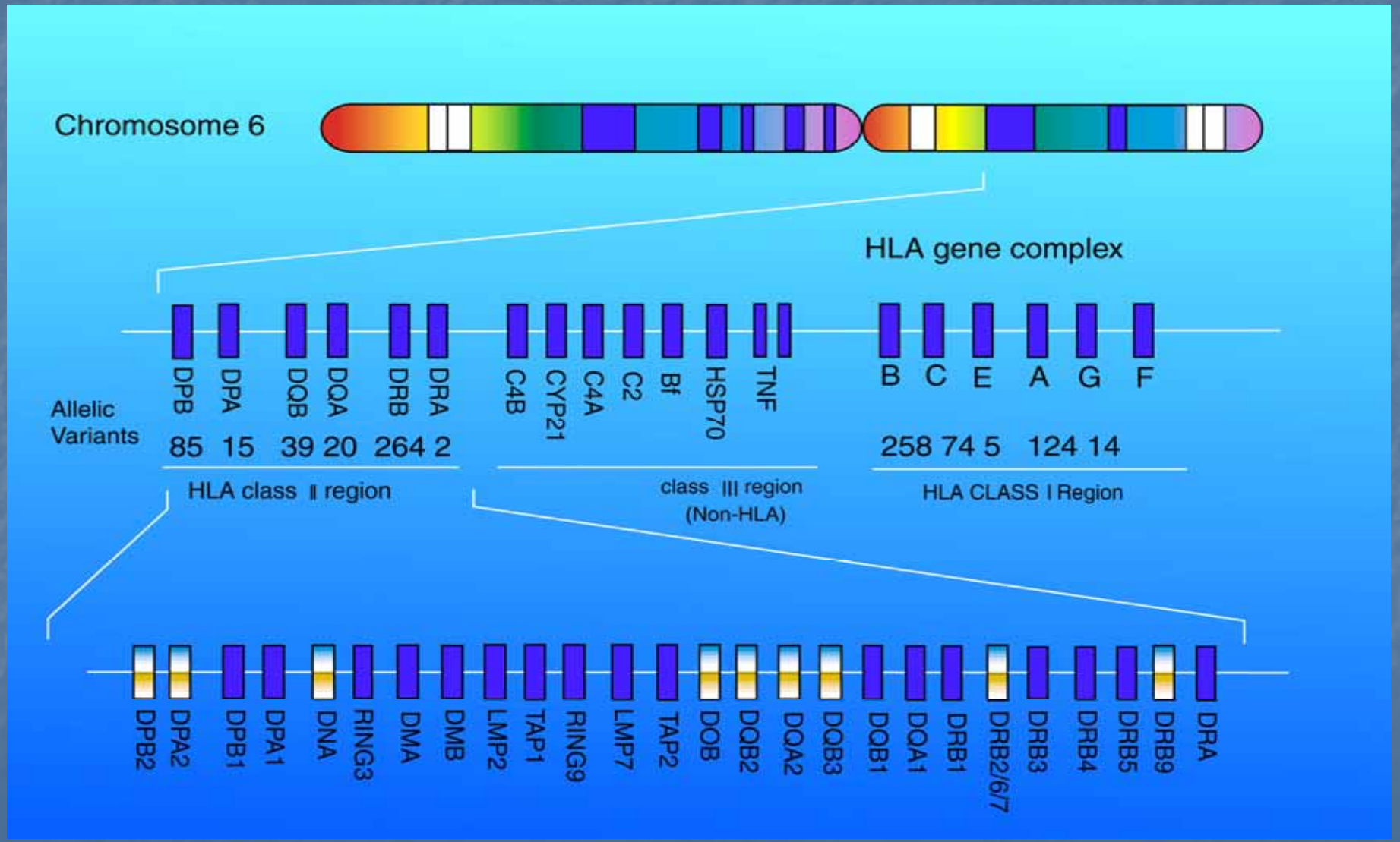
- What is HLA ? – Human Leukocyte Antigen (HLA) are the genes encoding for MHC

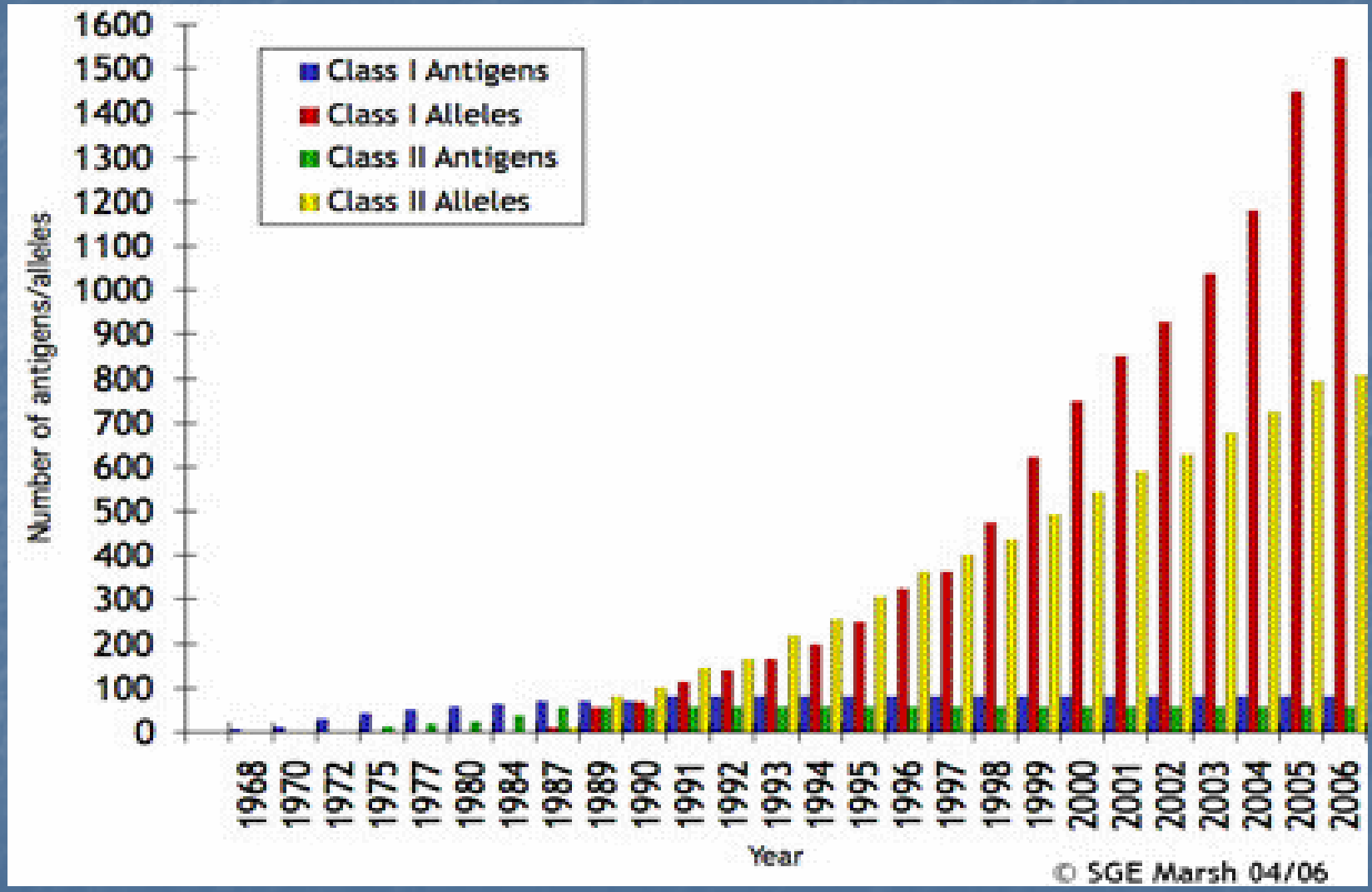
MHC and HLA polymorphism

- What is MHC ? – Major Histocompatibility Complex (MHC) is a cell receptor on antigen presenting cells recognising the body's self/non-self
- What is HLA ? – Human Leukocyte Antigen (HLA) are the genes encoding for MHC
- What is polymorphism ? – variations between people in the sequence of their genes

HLA Gene Cluster



HLA Polymorphism



Bone Marrow Transplantation

Bone Marrow Transplantation

What is Bone Marrow Transplantation?

What is Bone Marrow Transplantation?

- Transfer of Bone Marrow from a healthy donor into a patient with Bone Marrow or Blood Disease

What is Bone Marrow Transplantation?

- Transfer of Bone Marrow from a healthy donor into a patient with Bone Marrow or Blood Disease
- Donor Bone Marrow replaces sick patient's marrow with a healthy marrow, curing patient's underlying disease

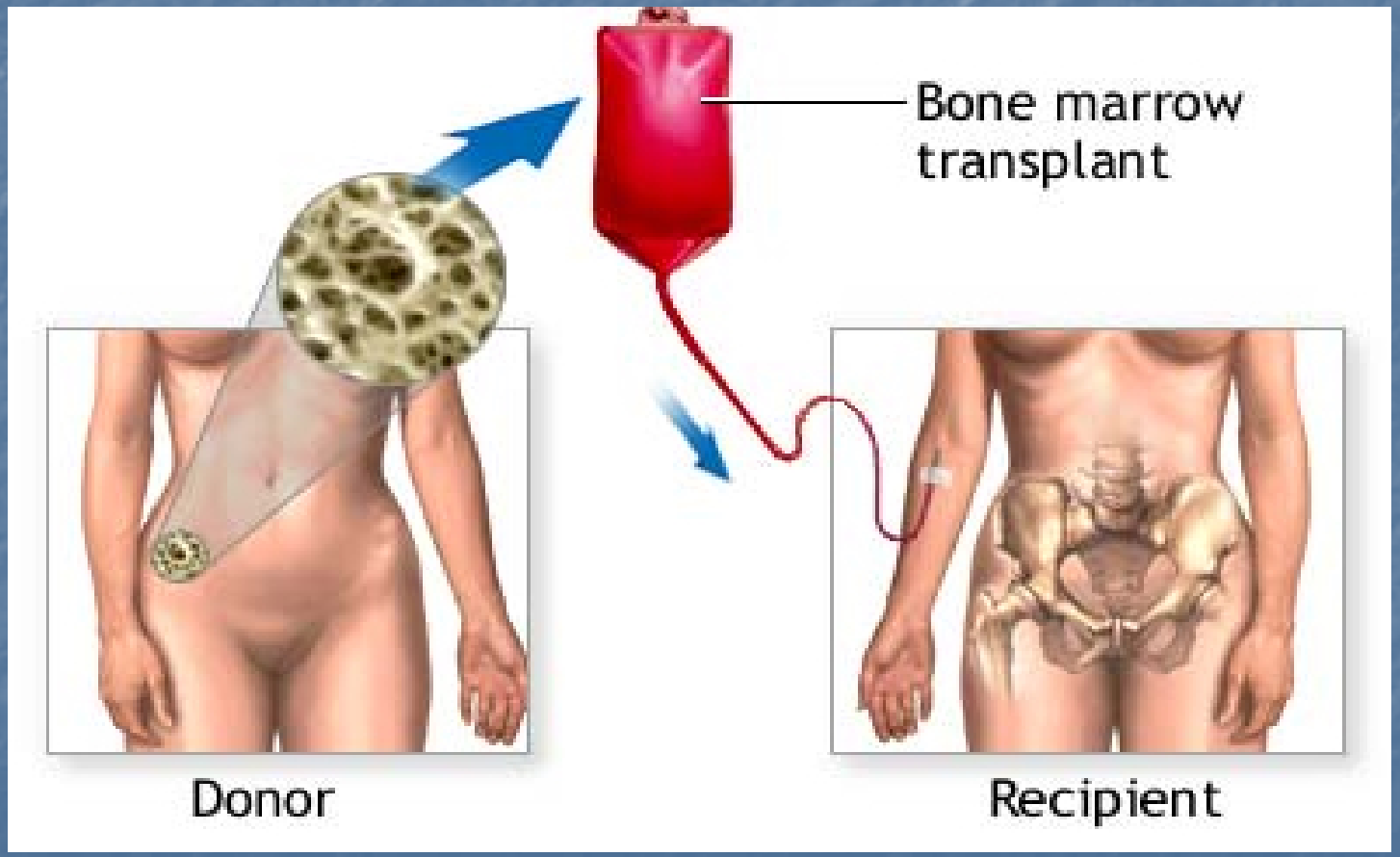
Terminology

- The person who is ill and receives the bone marrow transplant is called *host* or *recipient.*
- The person who gives the bone marrow is called the *donor.*
- The bone marrow that is given to the host is called *graft, bone marrow transplant (BMT) or haematopoietic stem cell transplant (HSCT).*

Bone Marrow Transplantation – why ?

Disease	1970 – Cure %	2005 – Cure %
Lethal Radiation Dose	0	80
Inborn severe Anaemia	0	90
Acute Leukaemia	10-30	80-100
Inborn Immune Deficiency	0	90
Inborn Metabolic Disease	0	90
Severe Autoimmune Disease	10	80

Bone Marrow Transplantation



Bone Marrow Harvest

Bone Marrow Transplantation – Early History

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- 1975: First donor registry (UK)

Observations after Transplantation

Bone Marrow Transplant

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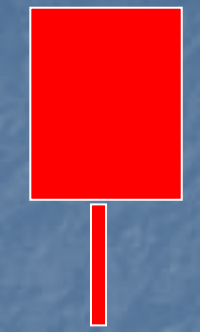
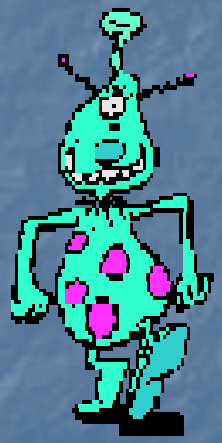
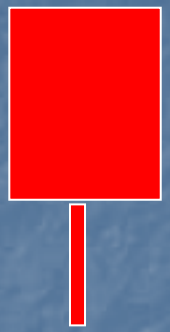


Bone Marrow Transplant

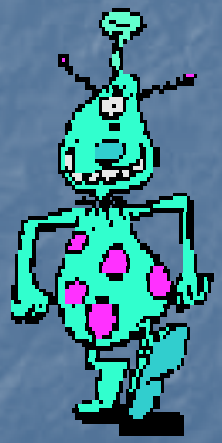


Host immune system stronger than graft:
Host attacks transplant-
Transplant is destroyed
=Graft rejection

Observations after Transplantation



Bone Marrow Transplant



Graft immune system
Stronger than host:
Transplant attacks host-
Host severely ill / killed
=Graft-versus-Host Disease, GVHD

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- Graft-versus-tumor effect (also mediated by donor T-cells) is the most powerful mechanism known to erradicate tumor cells

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- Problem: Graft-versus-tumor effect was lost – more patients dying. GVHD largest Problem after transplantation.

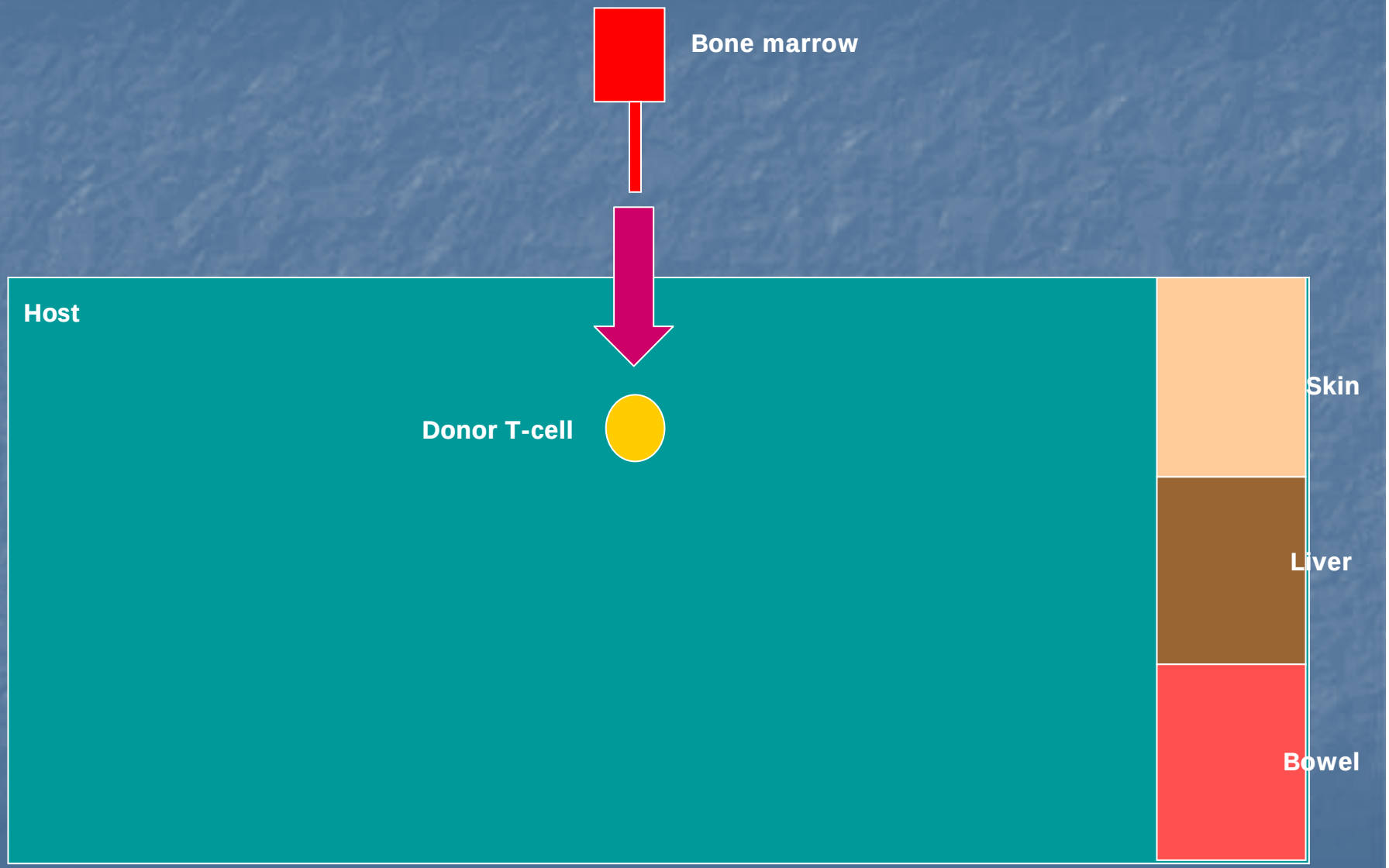
Graft versus Host Disease

- An immune reaction of the bone marrow graft against tissue and organs of the host
- Usually starts between 20-100 days after transplant

Graft versus Host Disease

- GVHD mostly affects skin, liver and bowel
- GVHD also makes prone to severe infection
- It ranges from mild (grade 1) to severe (grade 4)
- 20-50% of hosts get GVHD
- 20-30% of GVHD patients die of GVHD or infection

Graft-versus-Host Disease



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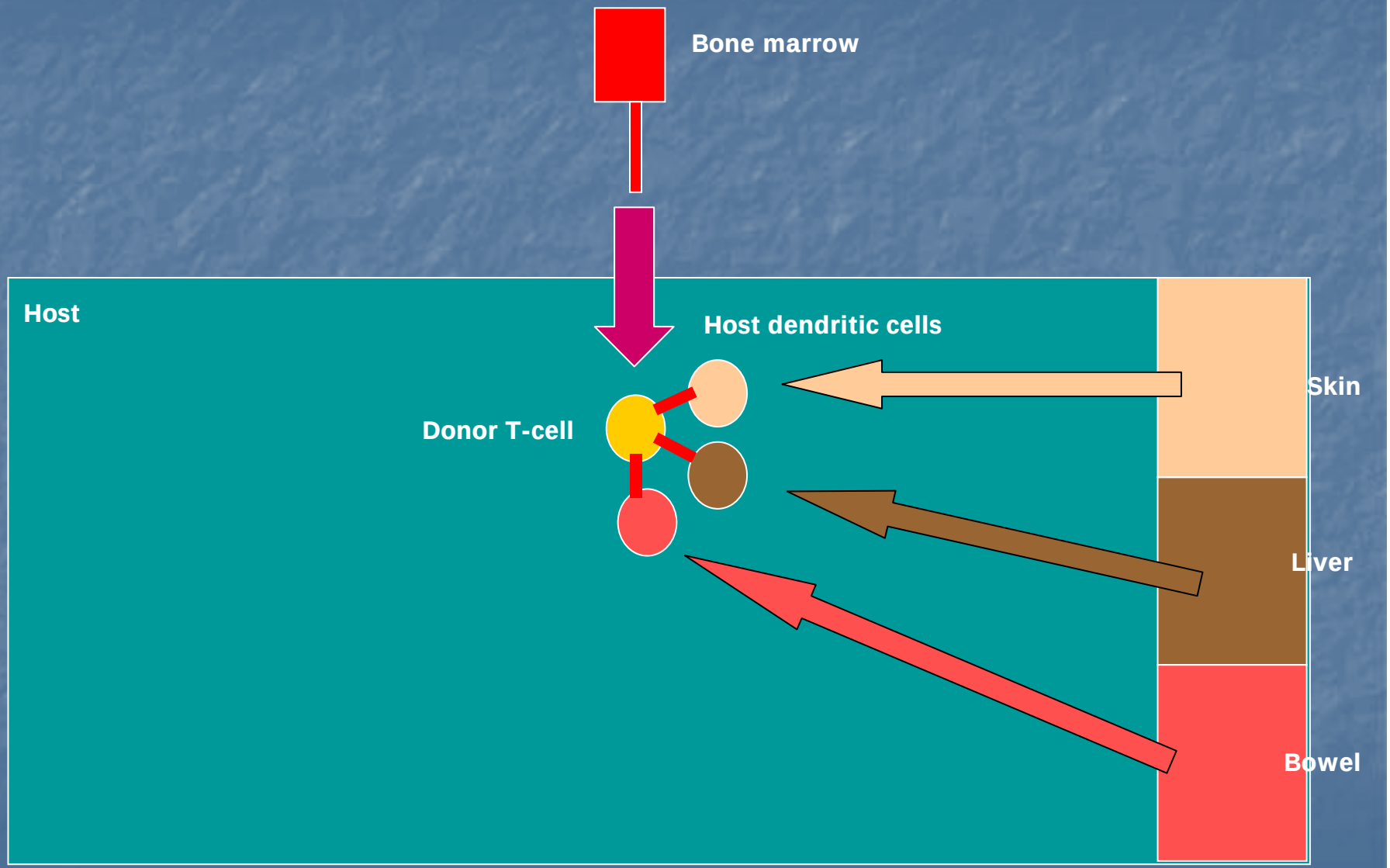

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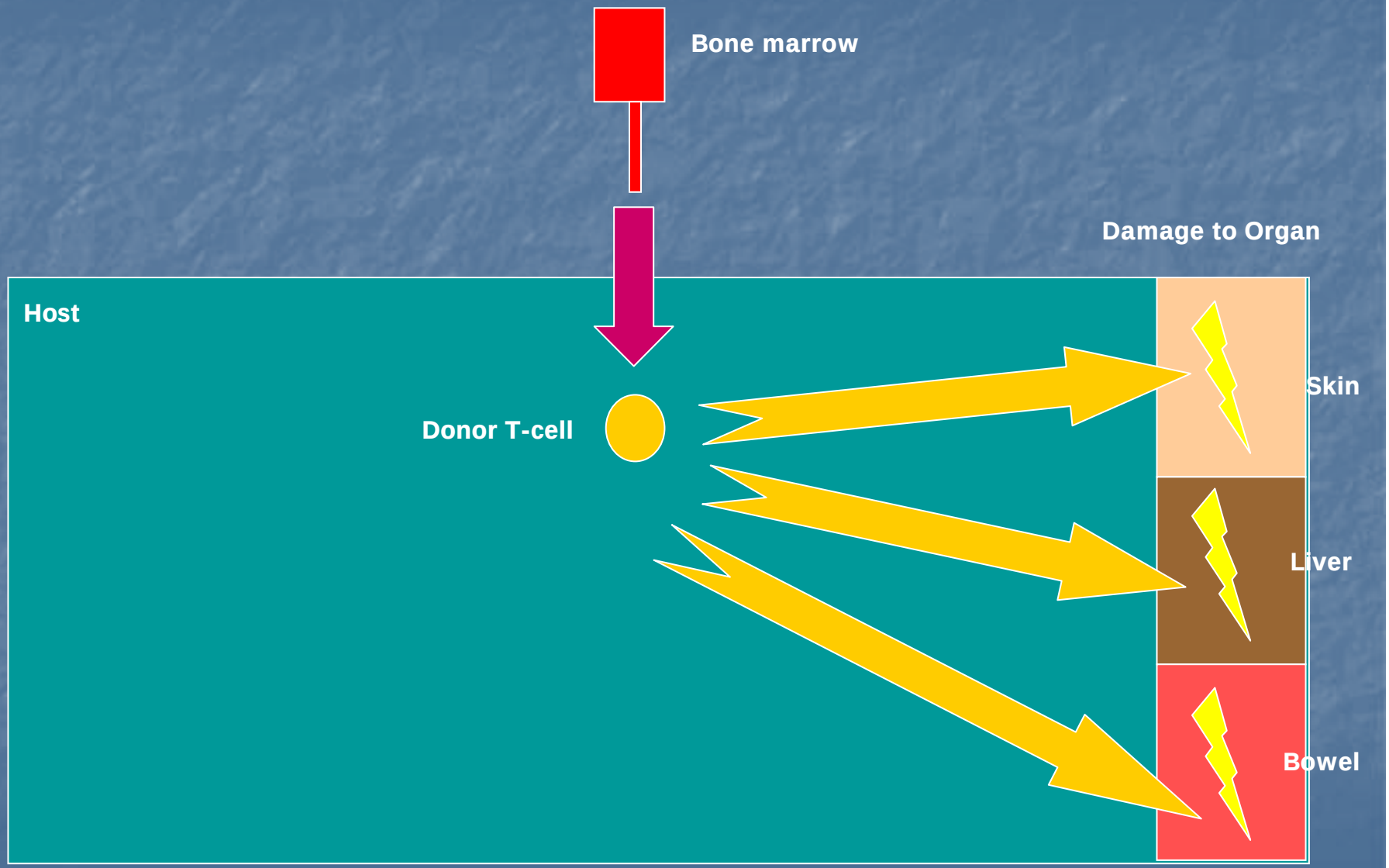
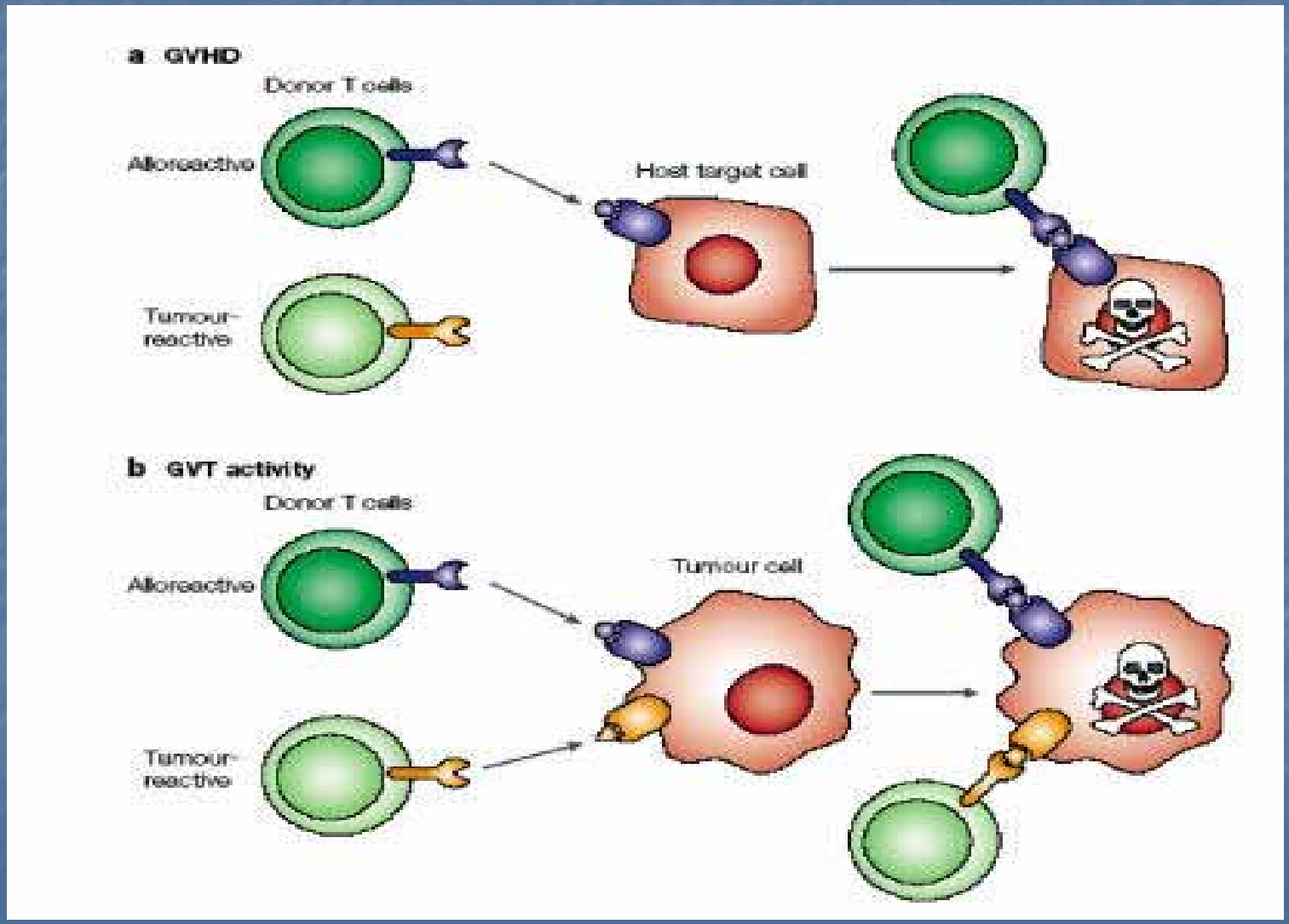
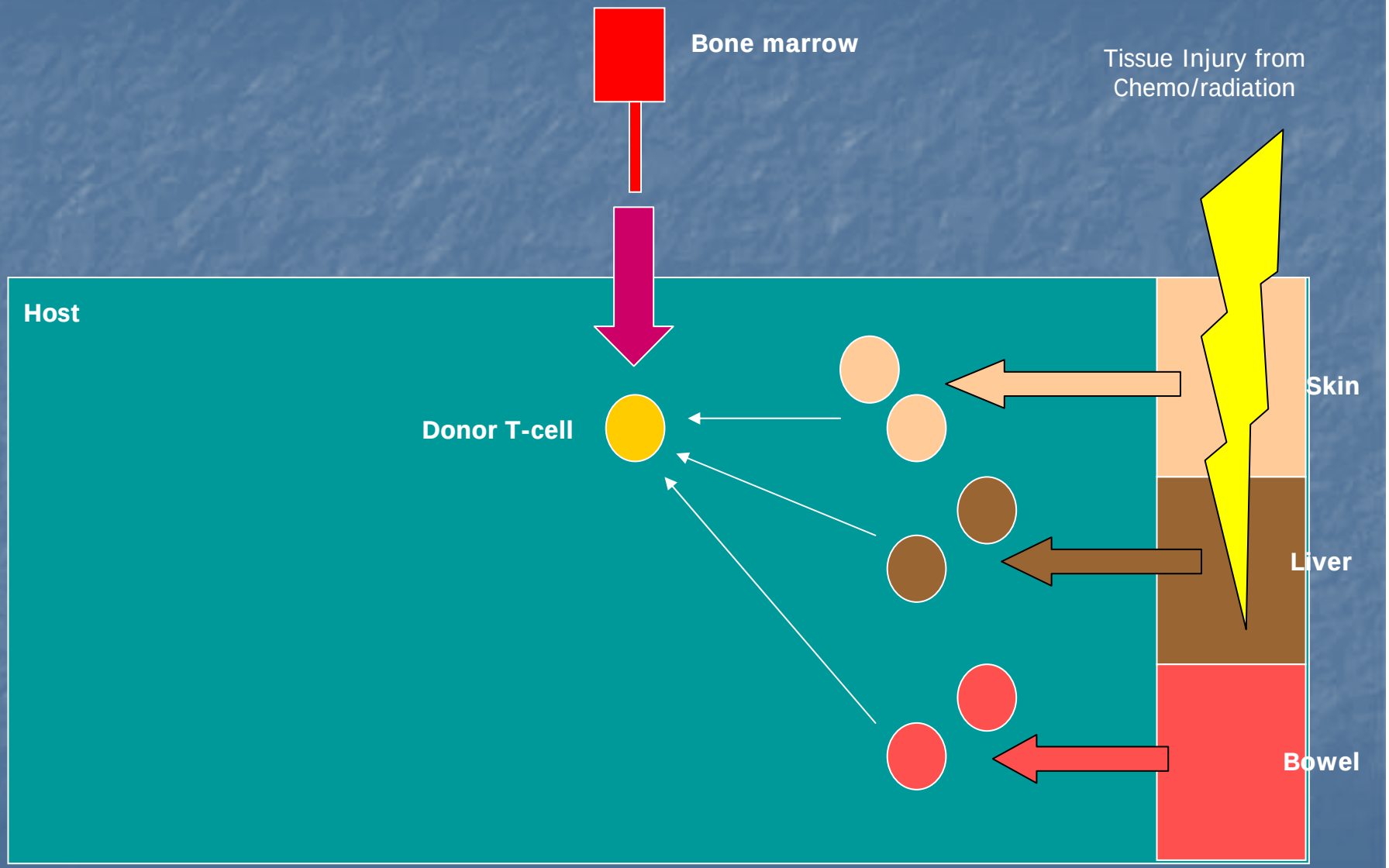


GVHD and GVT


a GVHD
Donor T cells
Alloreactive
Tumour-reactive
Host target cell
b GVT activity
Donor T cells
Alloreactive
Tumour-reactive
Tumour cell

GVHD – a complex disease

Graft-versus-Host Disease



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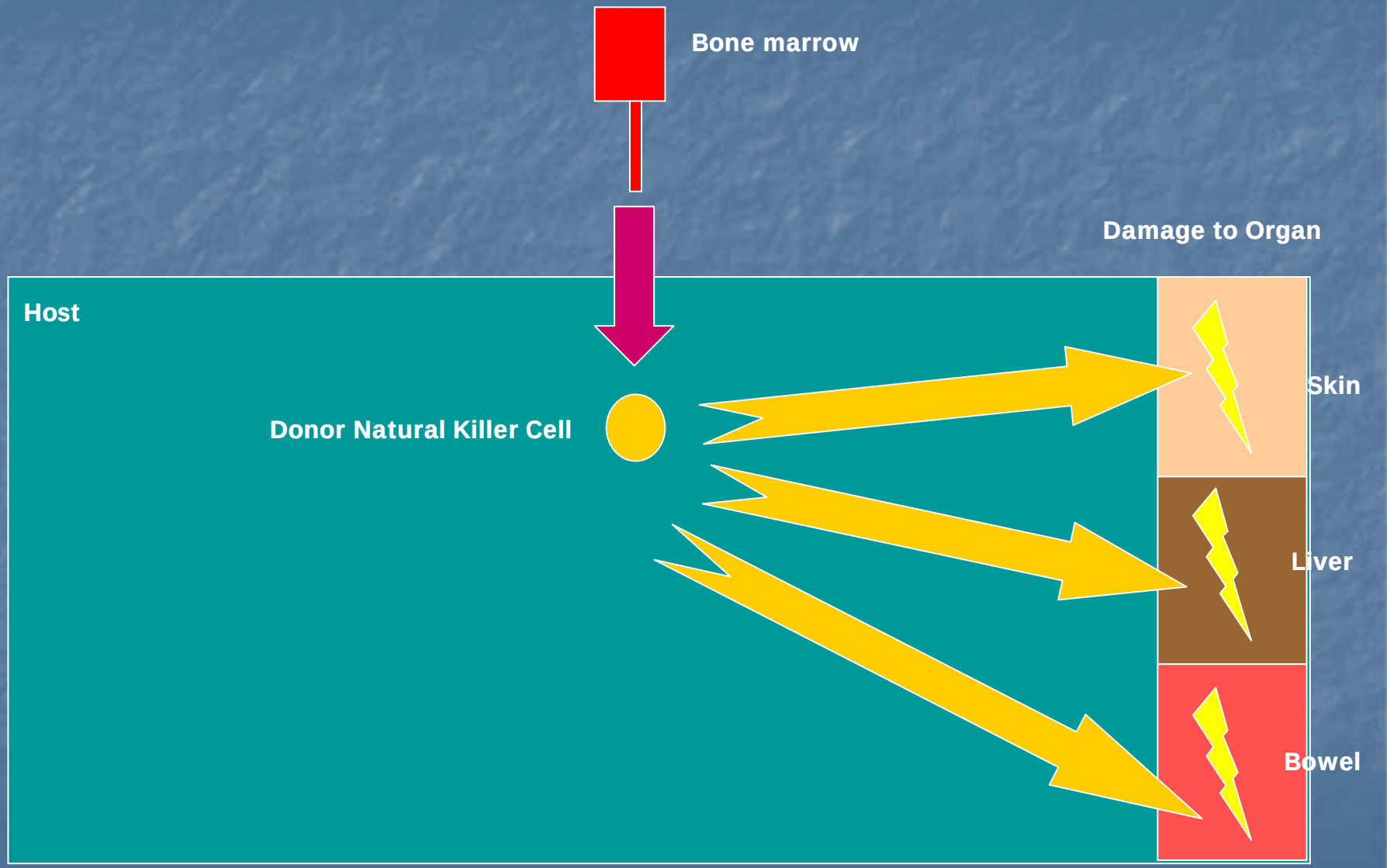

GVHD – a complex disease

- Cellular mechanisms: Antigen presenting cells, T-cells (CD4, CD8, T-regulatory cells), Natural Killer Cells, stem cells
- Minor histocompatibility antigens
- Organ mechanisms: Thymus, GVHD target organs
- Self/foreign recognition versus Danger signal recognition
- Signal molecules: Cytokines, apoptosis

GVHD – Genetics beyond HLA

- Polymorphisms in genes other than HLA have been linked to GVHD:
- Natural Killer Cell immune receptors
- Cytokines
- Apoptosis molecules
- Etc. etc...

Research at Tokai University into the Genetics of GVHD

- Research Project on 800 bone marrow transplant donor/recipient pairs from the Japanese Marrow Donor Programme (JMDP) registry
- Testing of polymorphisms (SNP, MS) in 3000 candidate genes of the immune system
- Goal is to develop a tool that can reliably predict GVHD before transplantation, enabling doctors to take steps to stop GVHD from happening

Future directions in GVHD

- Less tissue damage: Less chemotherapy and radiotherapy
- Preventing GVHD and enhancing GVT by T-cell depletion plus enrichment with tumor-specific T-cell clones
- Study of genetic risks – improved matching, improved clinical management
- Use of specific T-regulatory cells, stem cells, dendritic cells

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Summary

- Our immune system is amazing in keeping us healthy every day in the face of the constant threat from infections and tumors
- Bone Marrow Transplantation is a new therapy with enormous life saving potential for many diseases
- Graft-versus-Host Disease is the biggest problem in preventing a successful transplant
- Researchers all over the world are working on making transplants safer

Consider becoming a donor ?

- Find out more: http://www.jmdp.or.jp/

Thank You !!!