Mechanisms of cellular rejection in transplantation

By: Yadollah Shakiba
MD, PhD

Transplantation antigens

- Major histocompatibility antigens (MHC).
- Cause fast and strong rejection

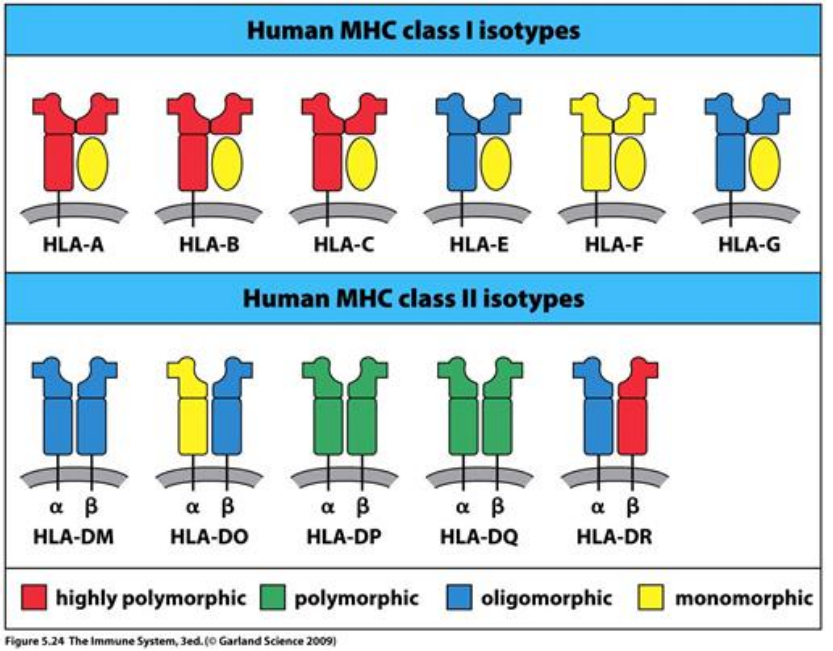
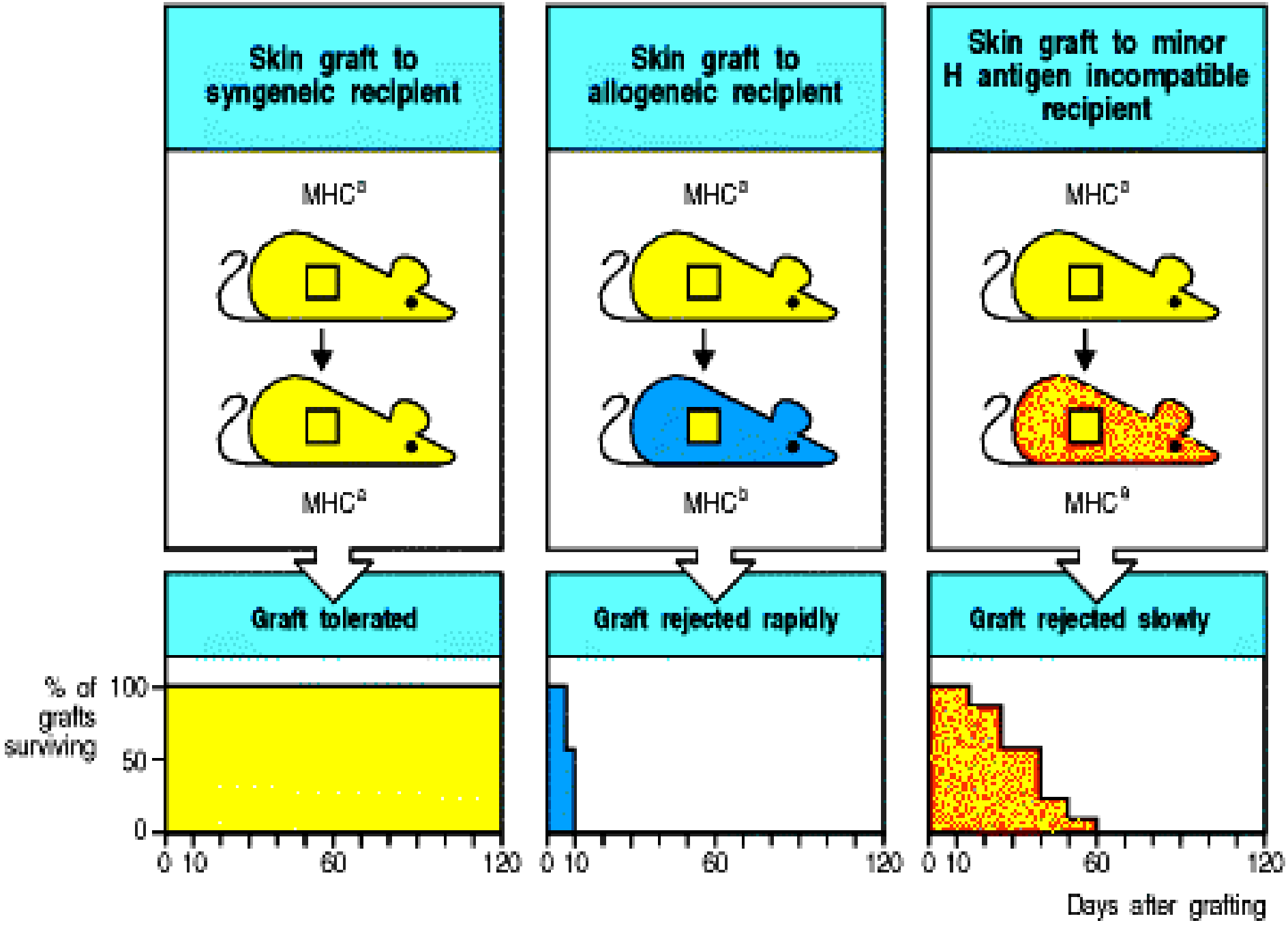


Figure 5.24 The Immune System, 3ed. (© Garland Science 2009)

- Minor histocompatibility
- slow and weak rejection

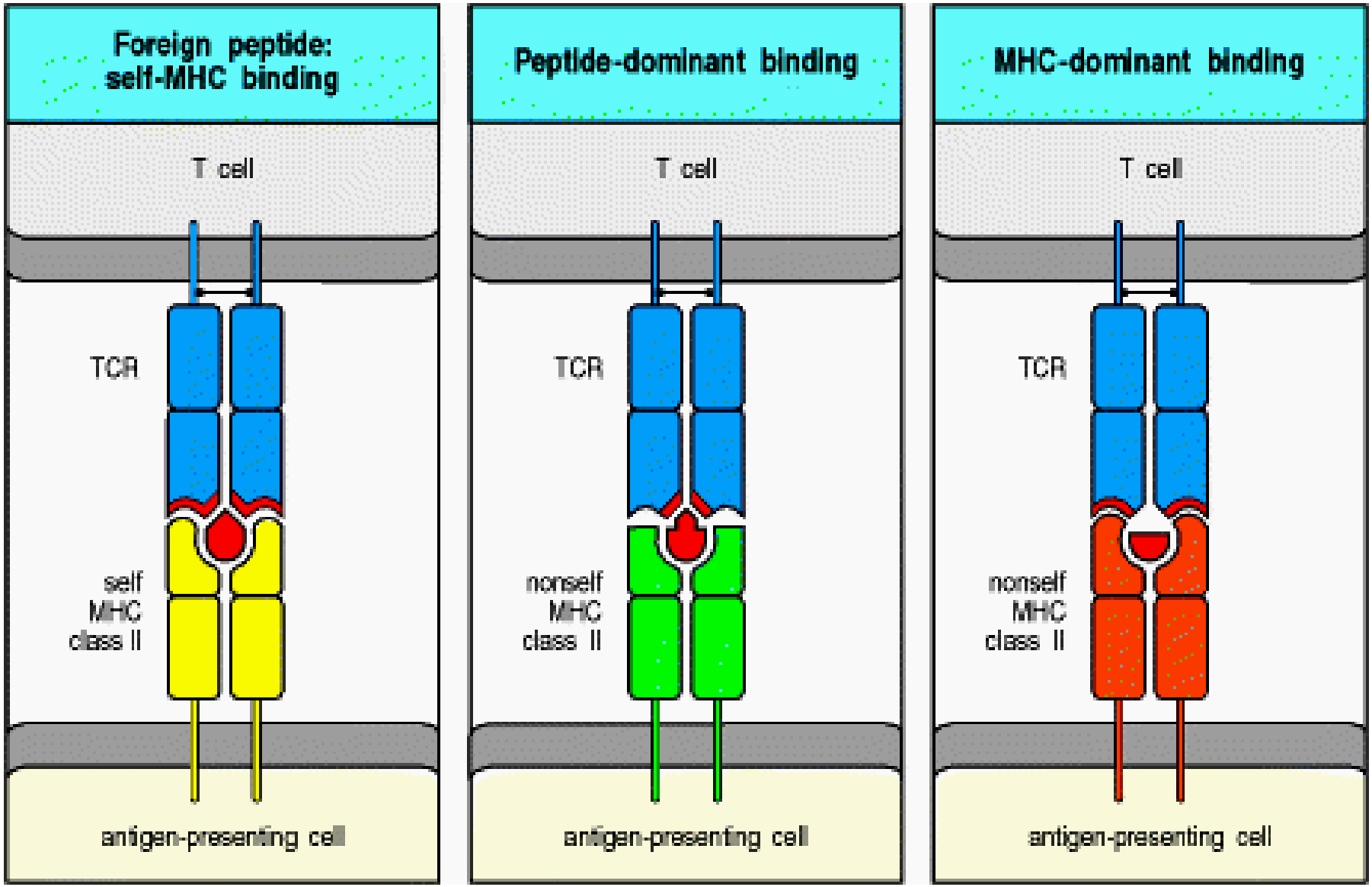

Skin graft to syngeneic recipient
Skin graft to allogeneic recipient
Skin graft to minor H antigen incompatible recipient
MHC^a
MHC^a
MHC^a
MHC^b
MHC^a
Graft tolerated
Graft rejected rapidly
Graft rejected slowly
% of grafts surviving
100
50
0
0 10 60 120
0 10 60 120
0 10 60 120
Days after grafting

Molecular Mechanisms of Allogeneic Recognition

T cells of the recipient recognize the allogeneic MHC molecules

Many T cells can recognize allogeneic MHC molecules

- **10^{-5}-10^{-4} of specific T cells recognize conventional antigens**
- **1%-10% of T cells recognize allogeneic MHC molecules**



- **Cross recognition**

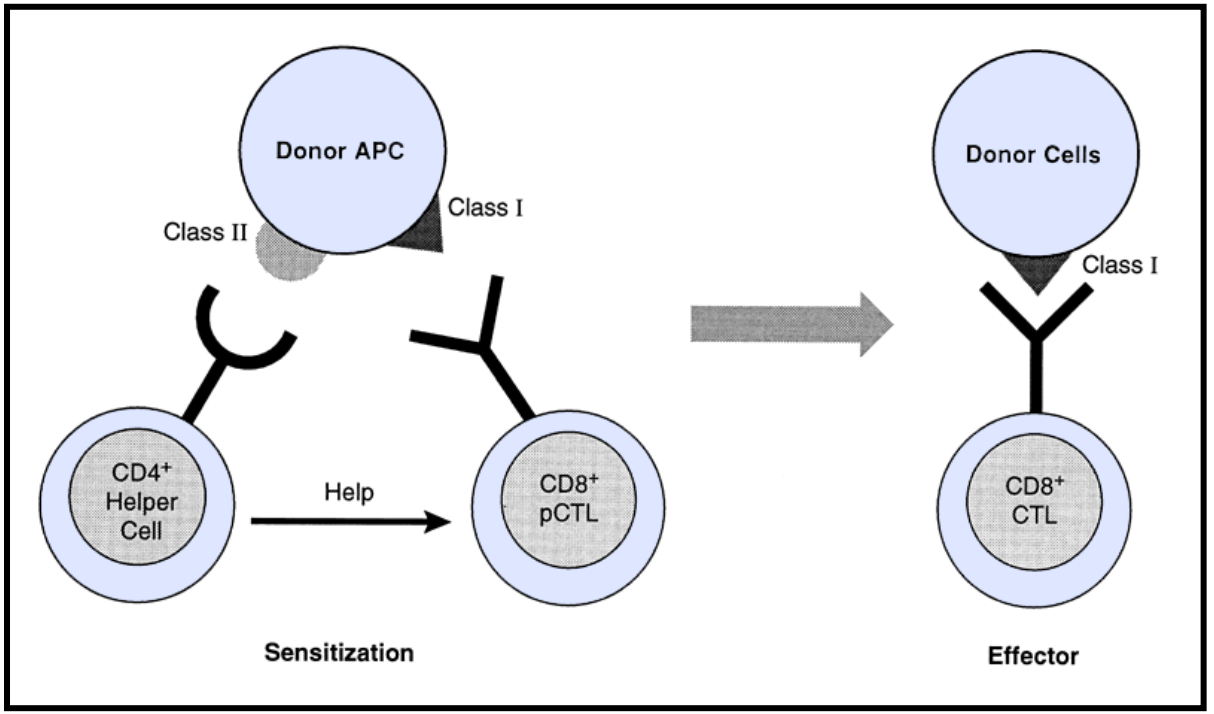
Allorecognition

Sensitization stage

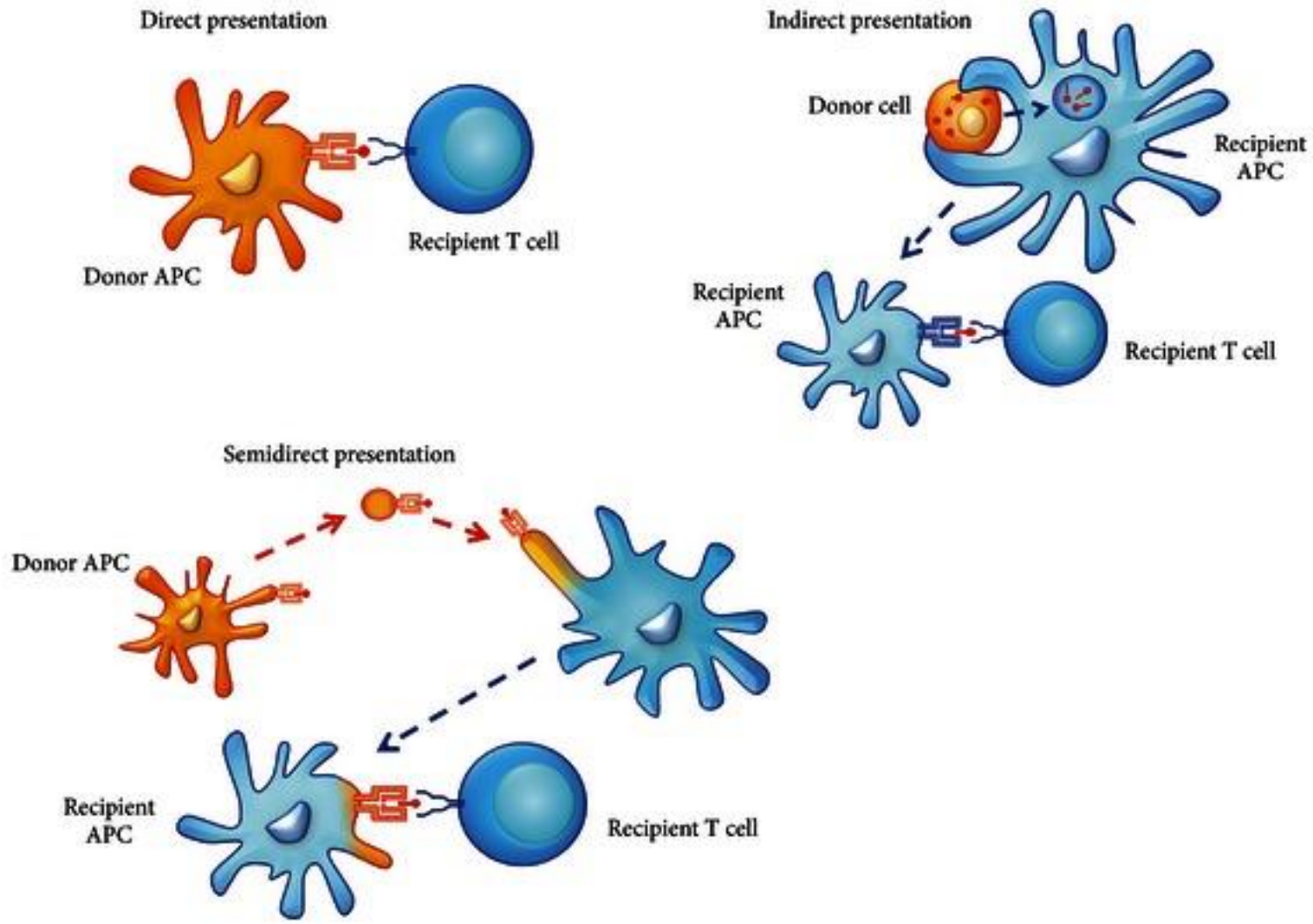
Direct pathway

indirect pathway

Effector stage



Direct and indirect pathway



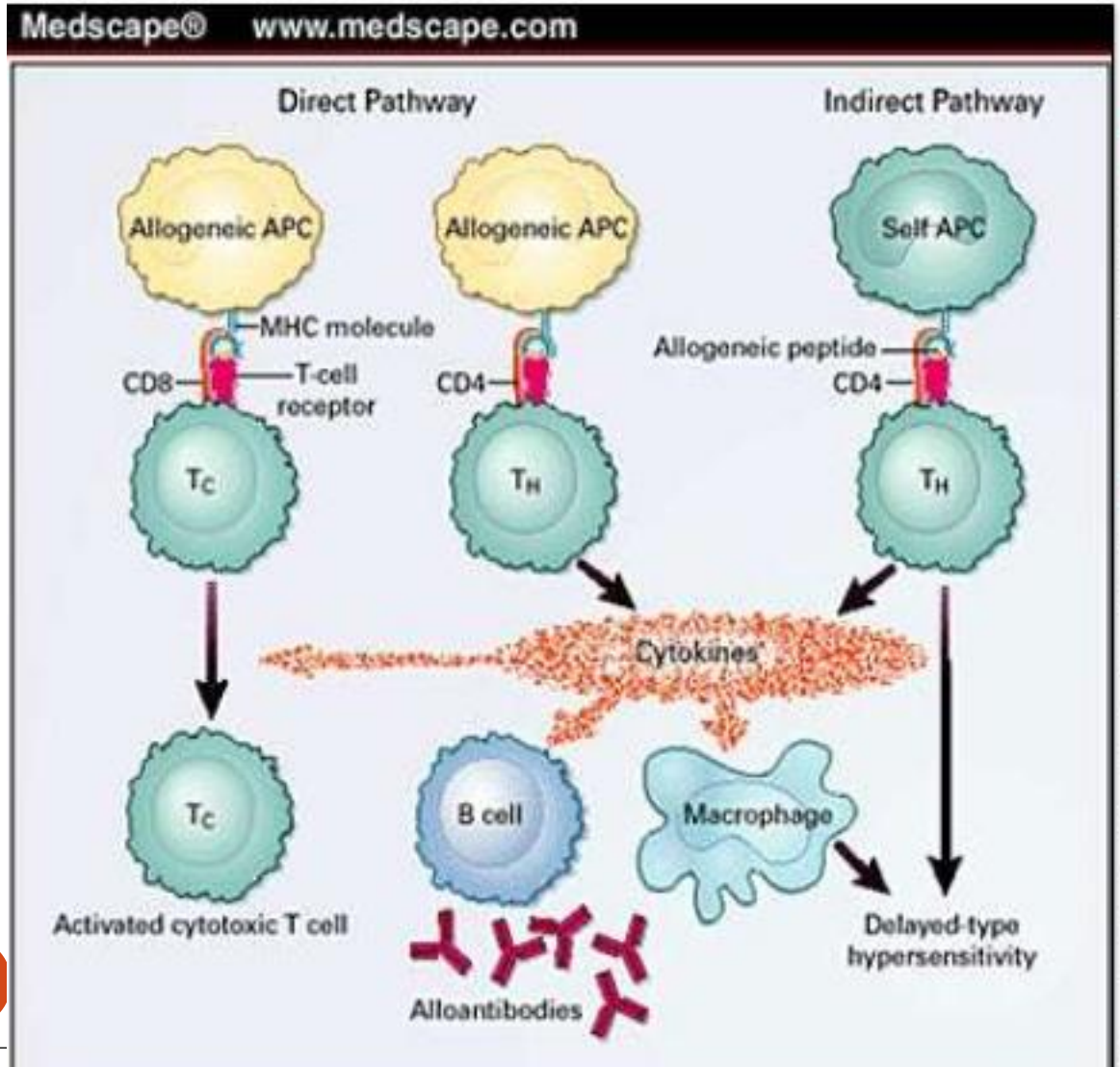
The recipient T cells recognize the allogeneic MHC molecules

- Direct Recognition
- Passenger leukocytes
  - Donor APCs that exist in grafts, such as DC, MΦ
  - Early phase of acute rejection
  - Fast and strong recognition

Indirect recognition

- Uptake and presentation of allogeneic donor MHC molecules by recipient APC in "normal way"
- Recognition by T cells like conventional foreign antigens

Effector Phase



•Direct recognition :-

•Recognitio of an intact MHC molecule displayed by donor APC in the graft

•Involves both $CD8^+$ and $CD4^+$ T cells. n

•Indirect recognition :-

• Donor MHC is processed and presented by recipient APC.

•Basically, donor MHC molecule is handled like any other foreign Ag.

• Involve only CD4+ T cells.

•Antigen presentation by class II MHC molecules.

Difference between Direct Recognition and Indirect Recognition

	Direct Recognition	Indirect Recognition
Allogeneic MHC molecule	Intact allogeneic MHC molecule	Peptide of allogeneic MHC molecule
APCs	Recipient APCs are not necessary	Recipient APCs
Activated T cells	$CD4^+$T cells and/or $CD8^+$T cells	$CD4^+$T cells and/or $CD8^+$T cells
Roles in rejection	Acute rejection	Chronic rejection
Degree of rejection	Vigorous	Weak

Role of $CD4^+$T cells and $CD8^+$T cells

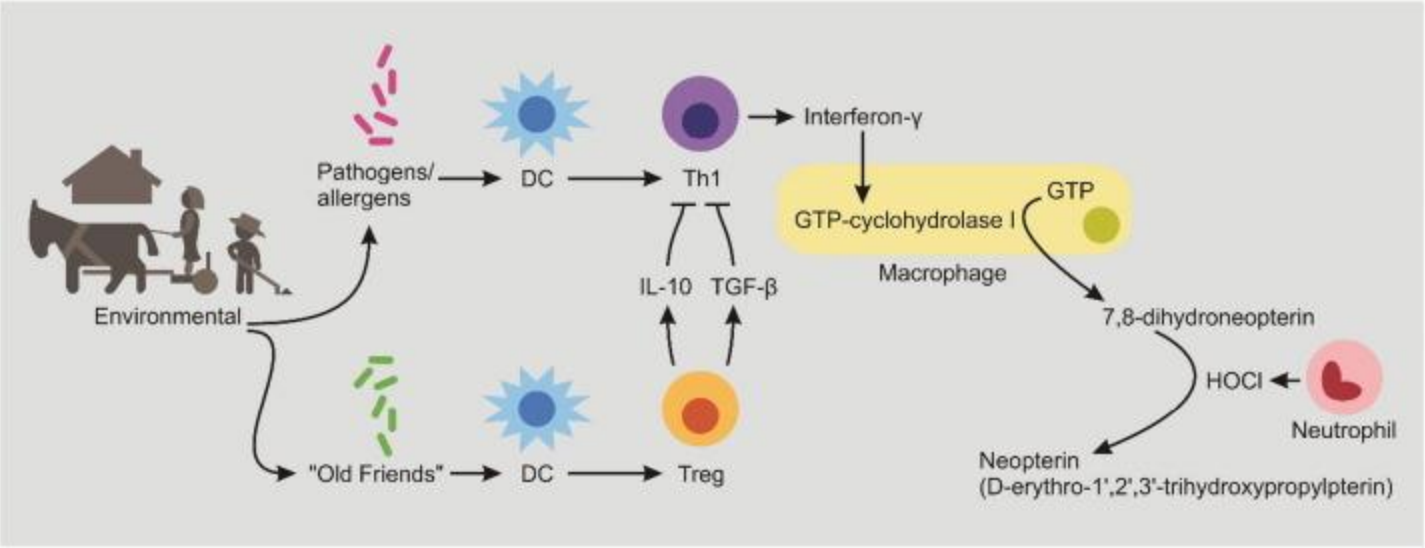
- Activated $CD4^+$T by direct and indirect recognition
  - CK secretion
  - MΦ activation and recruitment
- Activated $CD8^+$T by direct recognition
  - Kill the graft cells directly
- Activated $CD8^+$T by indirect recognition
  - Can not kill the graft cells directly

In vitro detection of cellular rejection

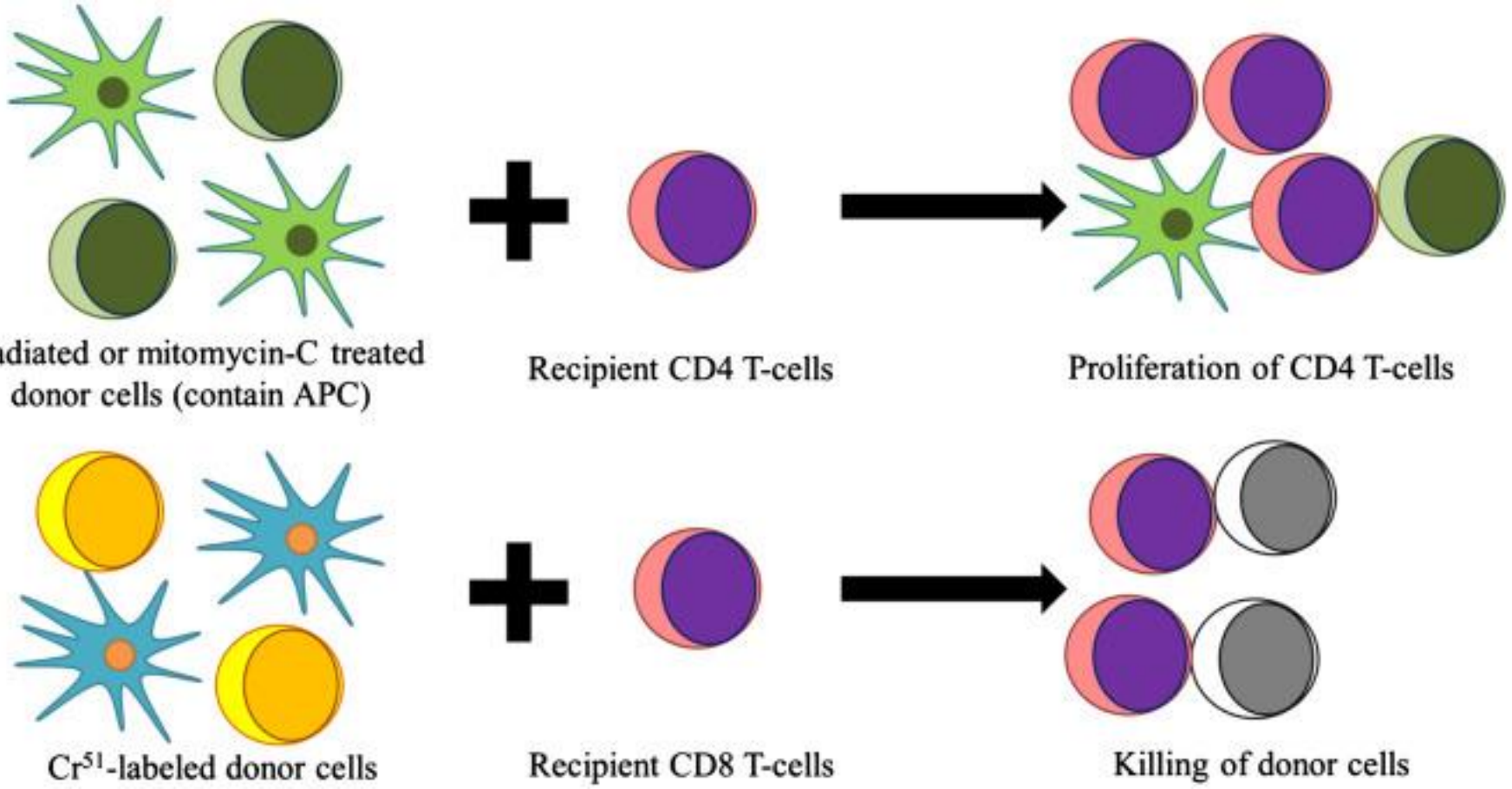
- Neopterin
- Mixed lymphocyte reaction (MLR)
- ImmunKnow®
- Enzyme-linked immunospot (ELISPOT)
- Gene expression assay
- Proteomic assay

Neopterin

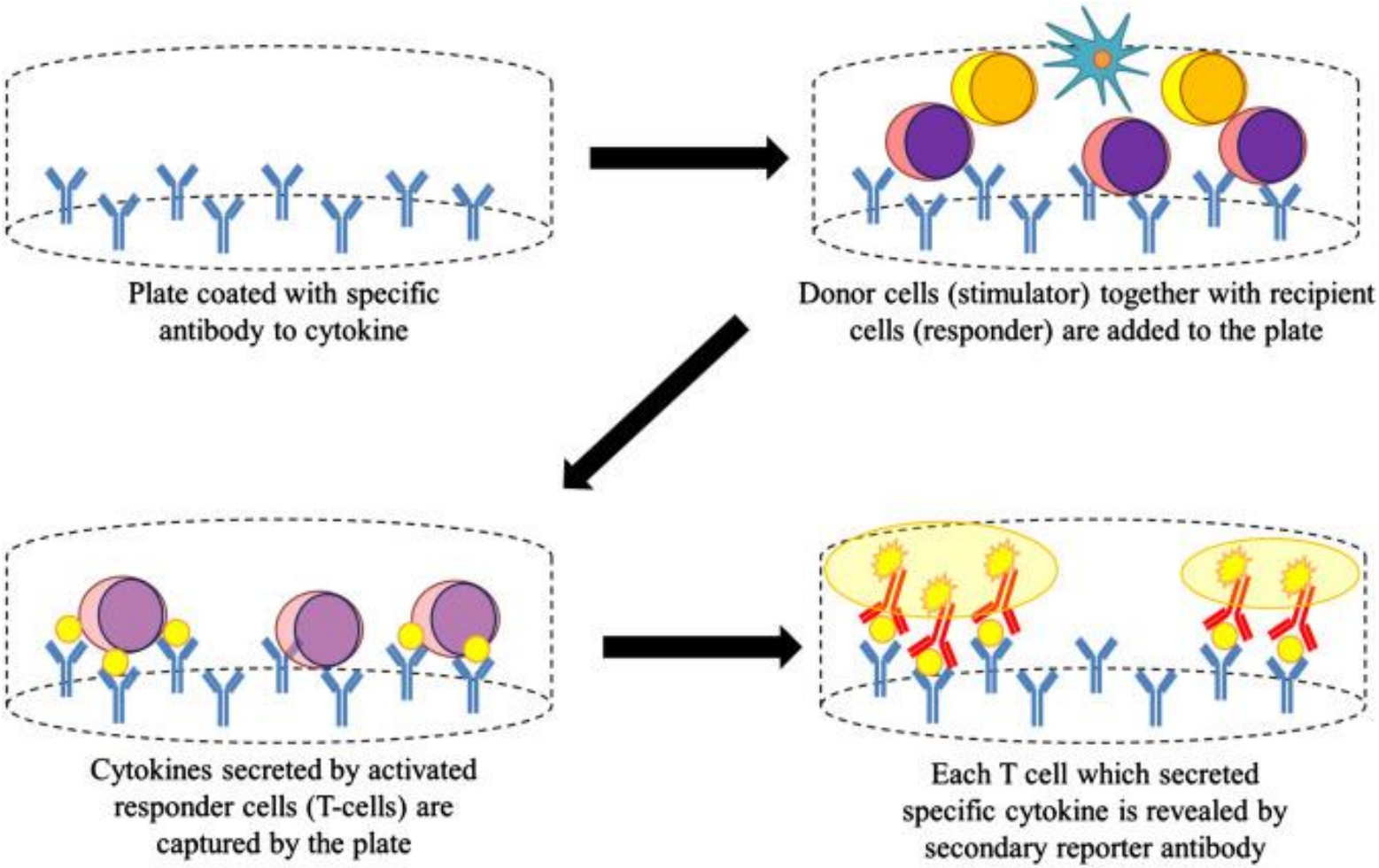
- **Neopterin** is a catabolic product of guanosine triphosphate (GTP)
- **Neopterin** is a marker for cellular immune system activation
- It is synthesised by human macrophages upon stimulation with the cytokine interferon-gamma



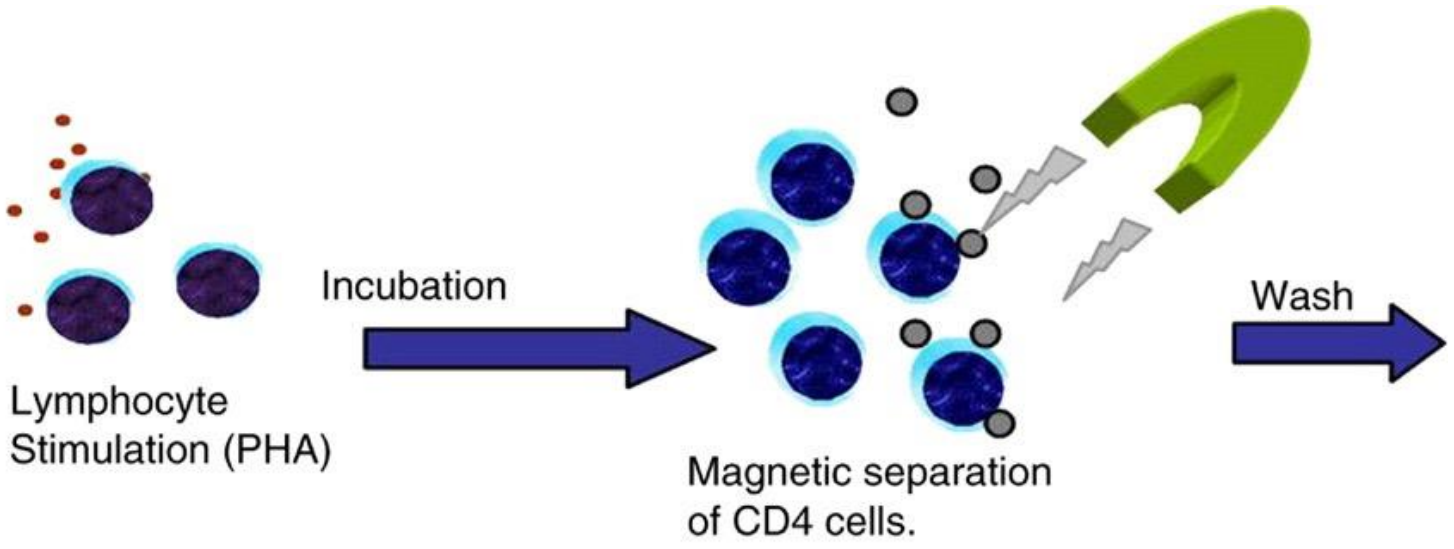
Monitoring T cell alloreactivity
Mixed lymphocyte reaction (MLR)

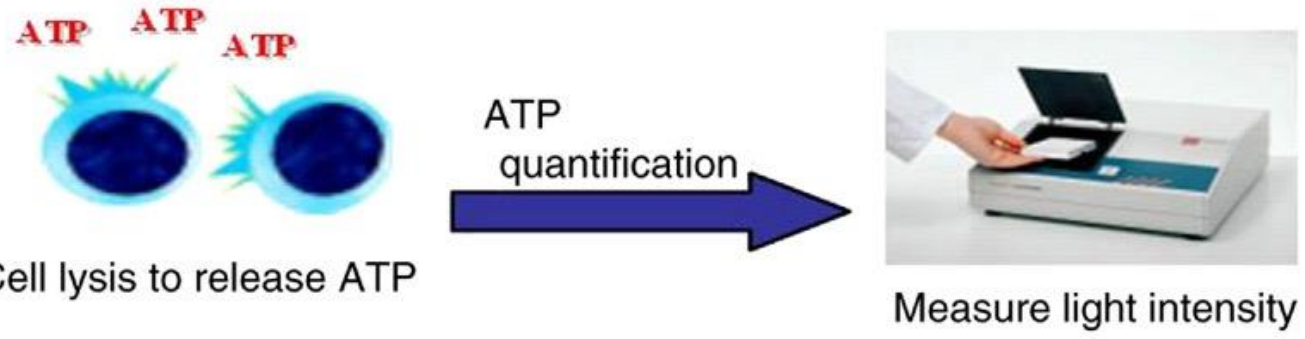


Enzyme-linked immunospot (ELISPOT)



ImmunKnow

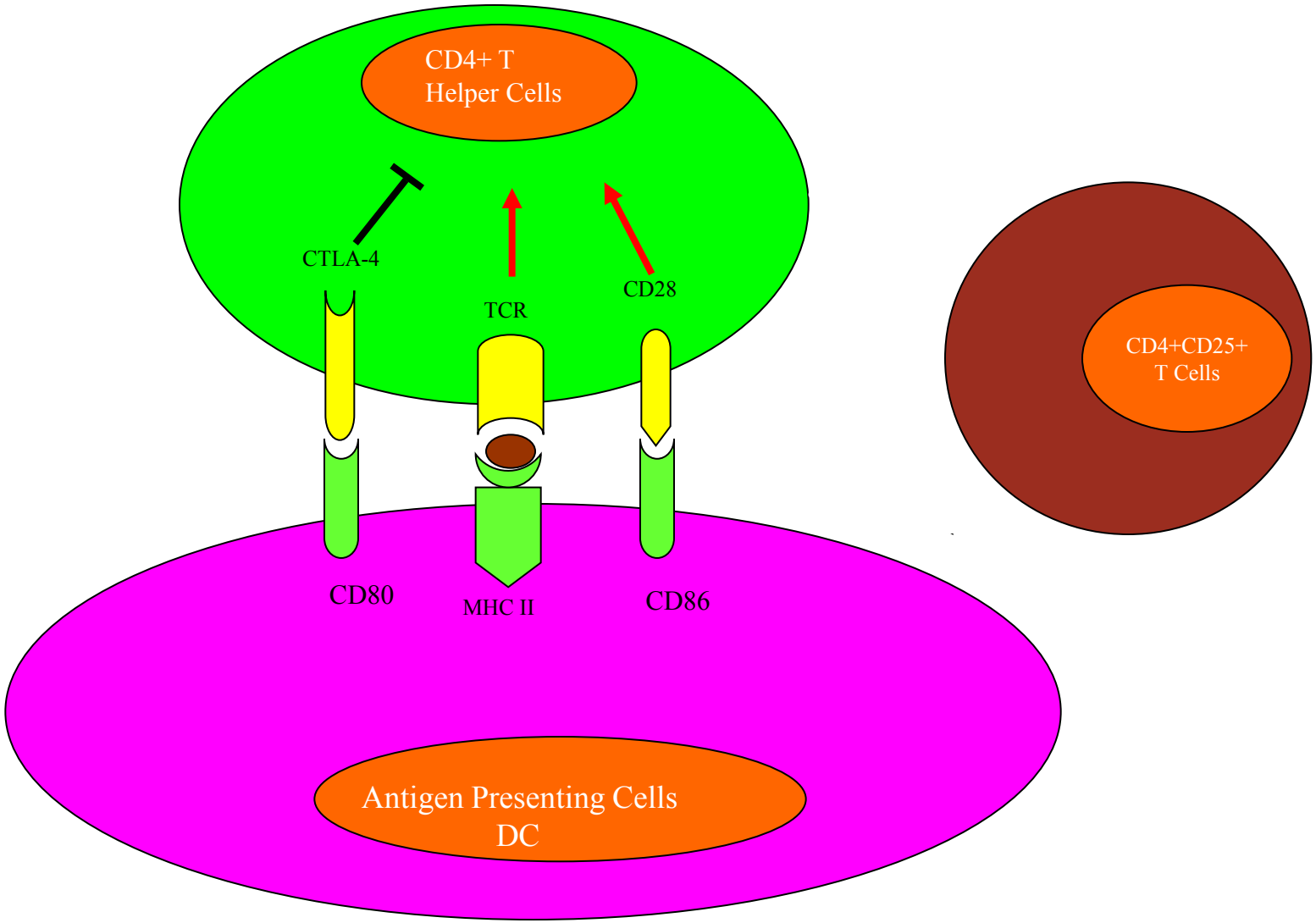

Incubation
Wash
Lymphocyte
Stimulation (PHA)
Magnetic separation
of CD4 cells.

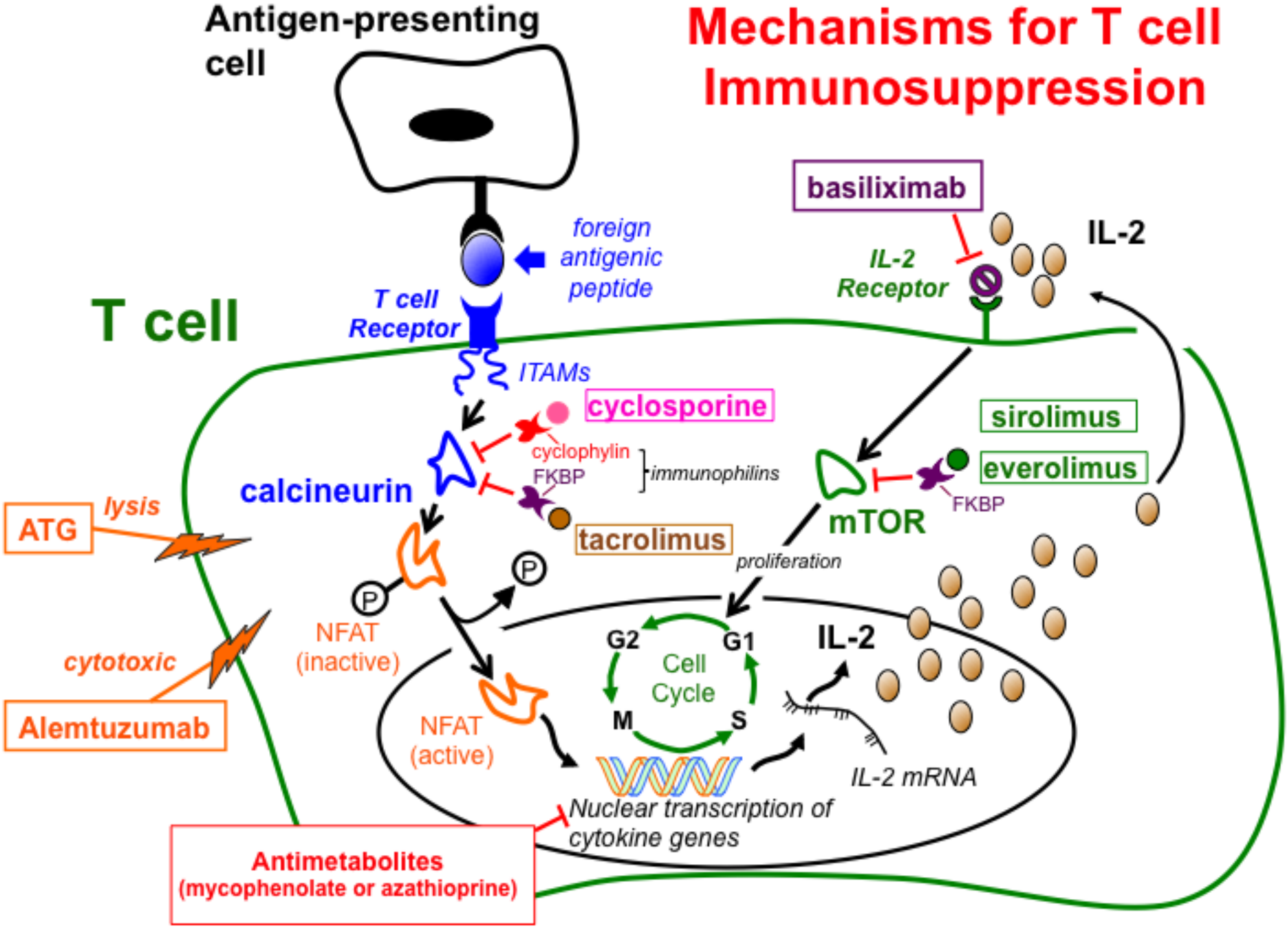

ATP
ATP
ATP
ATP
quantification
Cell lysis to release ATP
Measure light intensity

3

- Gene expression assay
- Proteomic assay

Activation (CD80/86:CD28) and Inhibition (B7:CTLA-4) of T-cell Function by APC (DC) and Immunoregulatory T cells ($CD4^+CD25^+$)




Mechanisms for T cell Immunosuppression
Antigen-presenting cell
foreign antigenic peptide
T cell
T cell Receptor
ITAMs
basiliximab
IL-2
IL-2 Receptor
cyclosporine
cyclophylin
FKBP
immunophilins
calcineurin
tacrolimus
sirolimus
everolimus
FKBP
mTOR
ATG
lysis
proliferation
P
NFAT (inactive)
NFAT (active)
G2
G1
Cell Cycle
M
S
IL-2
IL-2 mRNA
Nuclear transcription of cytokine genes
cytotoxic
Alemtuzumab
Antimetabolites
(mycophenolate or azathioprine)