Mustansiriyah University
College of Pharmacy
Department of Pharmacology and Toxicology

Immunosuppressants

Pharmacology 4th Stage

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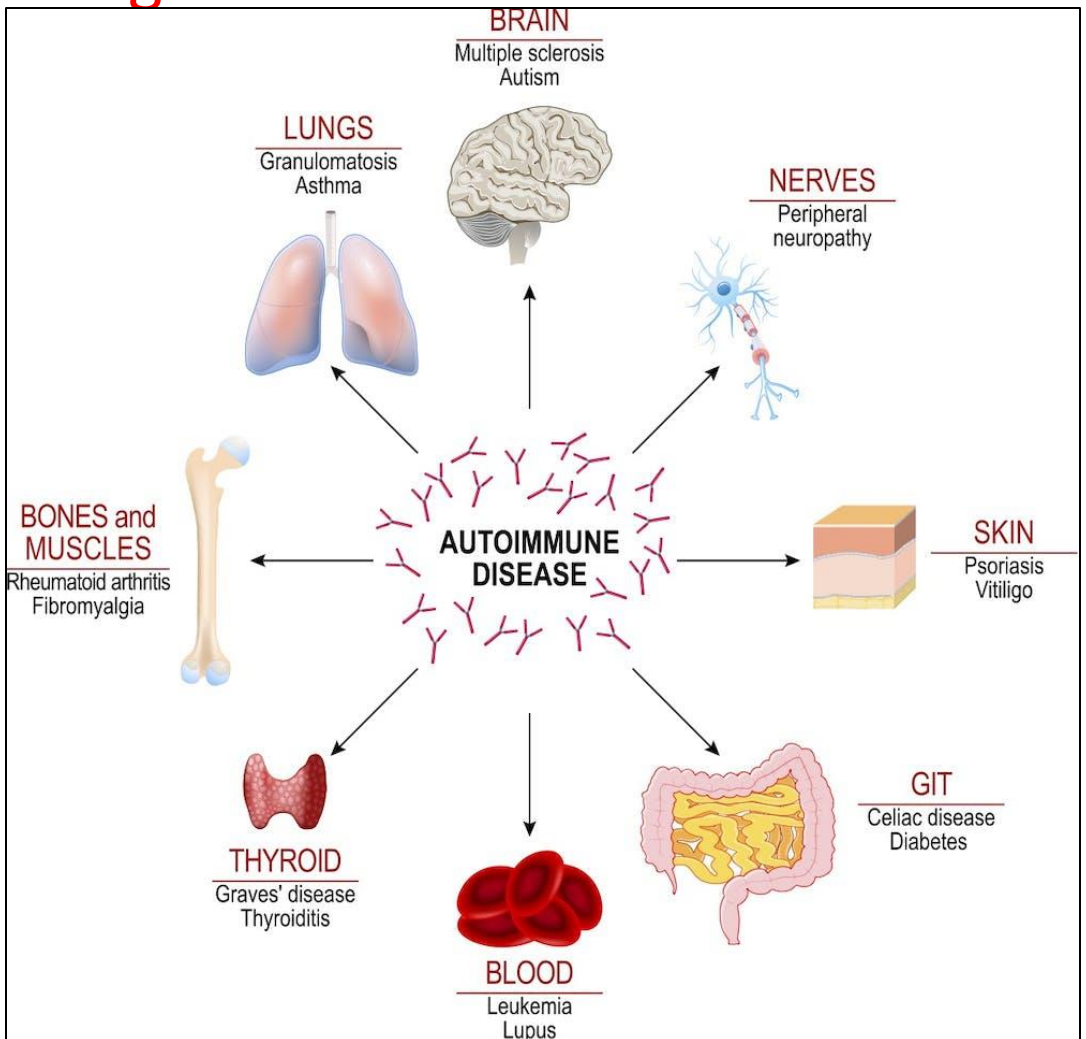
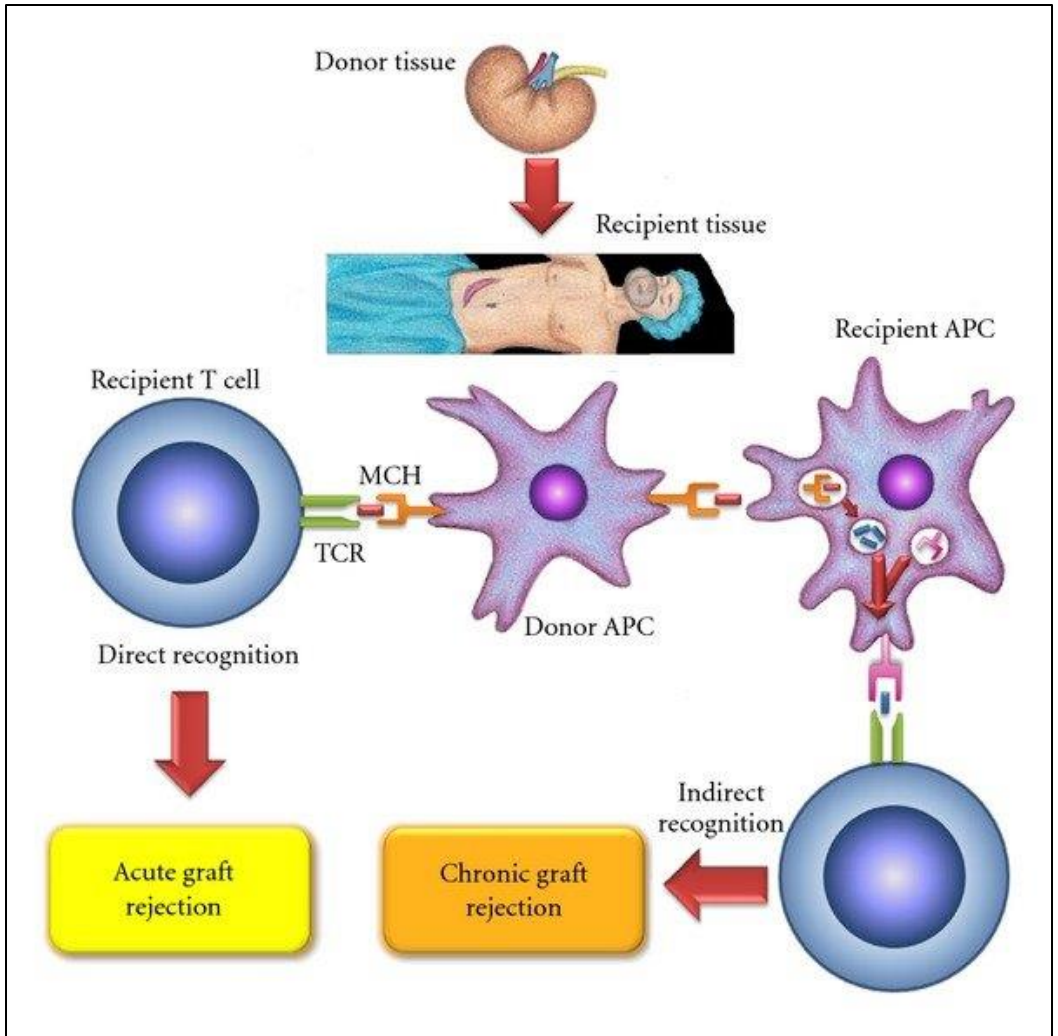
Overview

- The immune system is essential for protection against pathogens. However, when dysregulated, its powerful destructive mechanisms may do more harm than good.



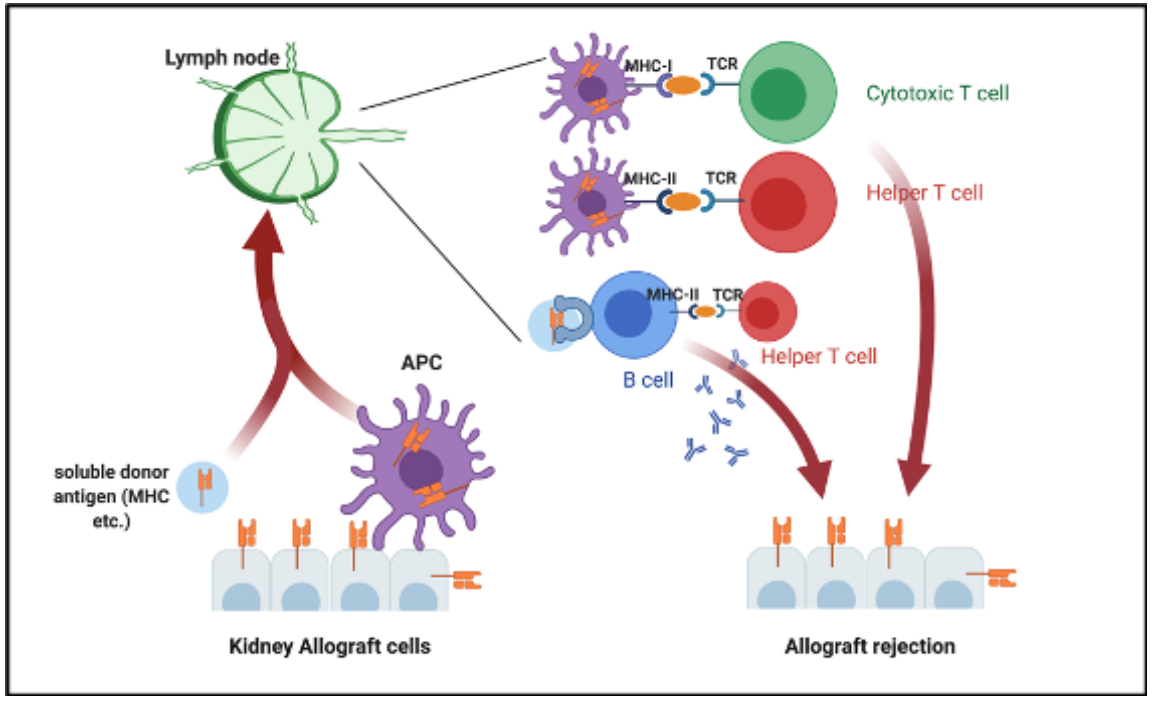


Immunosuppressants

Immunosuppressants are drugs that reduce the activation or efficacy of the immune system to treat certain conditions, such as:

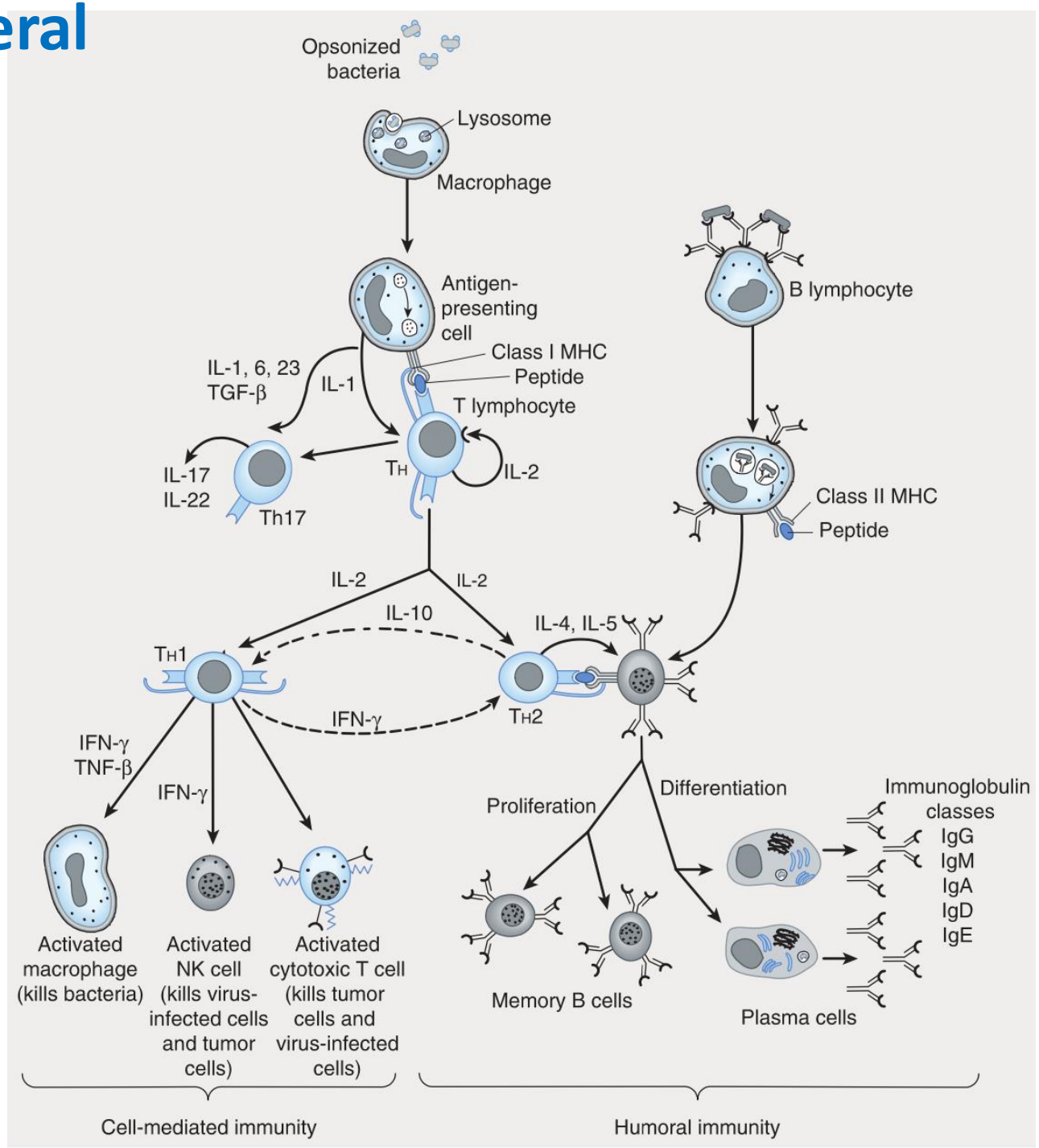
1. **Autoimmune diseases** can arise when the immune system mistakenly identifies an individual's own tissues as foreign and directs a destructive response against them. (e.g, inflammatory bowel disease, multiple sclerosis, lupus, psoriasis, and rheumatoid arthritis).

2. **Organ transplantation**, when a foreign tissue is purposely implanted into the recipient (i.e. An **allograft**



Scheme of cell-mediated and humeral immune responses.

- An Immune response Is initiated by internalization and processing of antigen by an APC such as a macrophage.
- The class I MHC-peptide complex is recognized by the TCR on TH cells, resulting in T-cell activation.
- Activated TH cells secrete cytokines such as IL-2, which cause proliferation and activation of TH1 and TH2 cells.
- TH1 cells produce IFN-y and TNF-β, which activate macrophages and NK cells (cell mediated immunity).
- A humeral response is triggered when B lymphocytes bind antigen via their surface immunoglobulins. They are then induced by TH2-derived cytokines (eg, IL-4, IL-5) to proliferate and differentiate into memory cells and antibody-secreting plasma cells.



The immune activation cascade can be described as a three-signal model

- **Signal 1** constitutes T-cell triggering at the CD3 receptor (TCR) complex by an antigen on the surface of APC. Signal 1 alone is insufficient for T-cell activation and requires signal 2.
- **Signal 2**, also referred to as co-stimulation, occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells. Both signals 1 and 2 activate calcium--calcineurin pathway to trigger the production IL-2. IL-2 then binds to the IL-2 receptor (also known as CD25) on the surface of other T cells, thereby providing signal 3.
- **Signal 3,** activating the cell cycle via mammalian target of *rapamycin* (mTOR), and leading to T-cell proliferation.

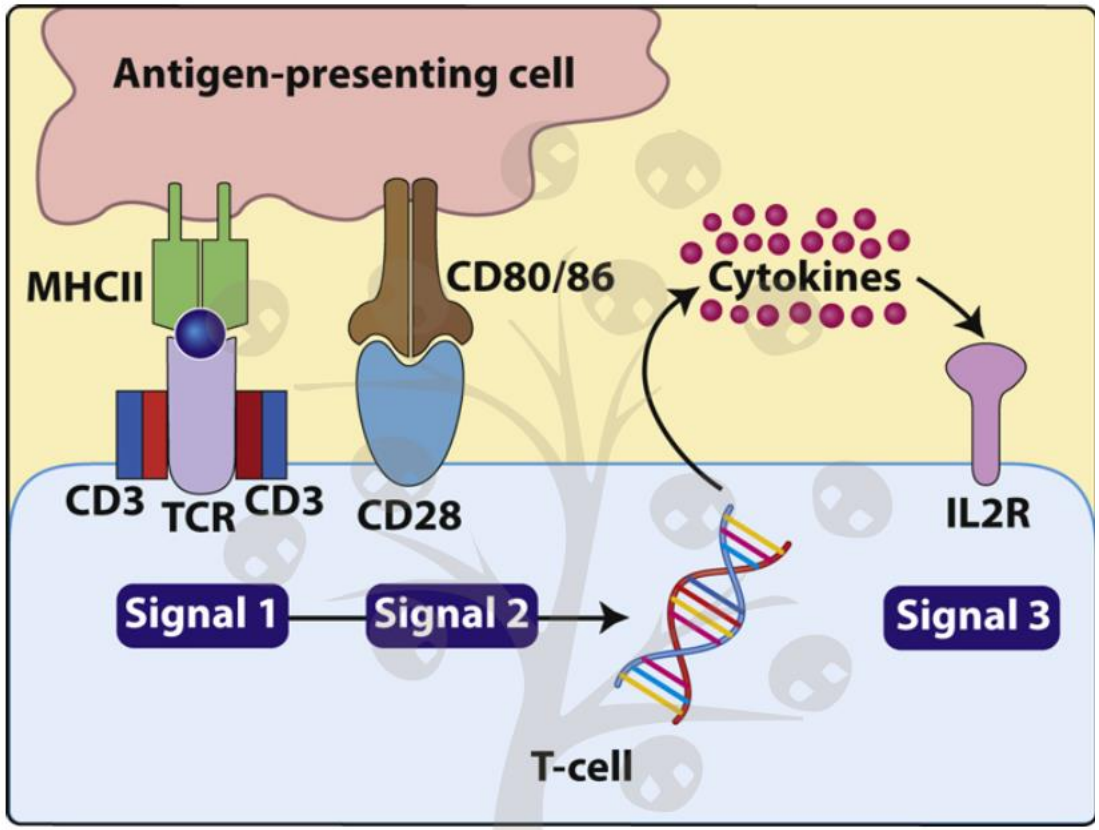
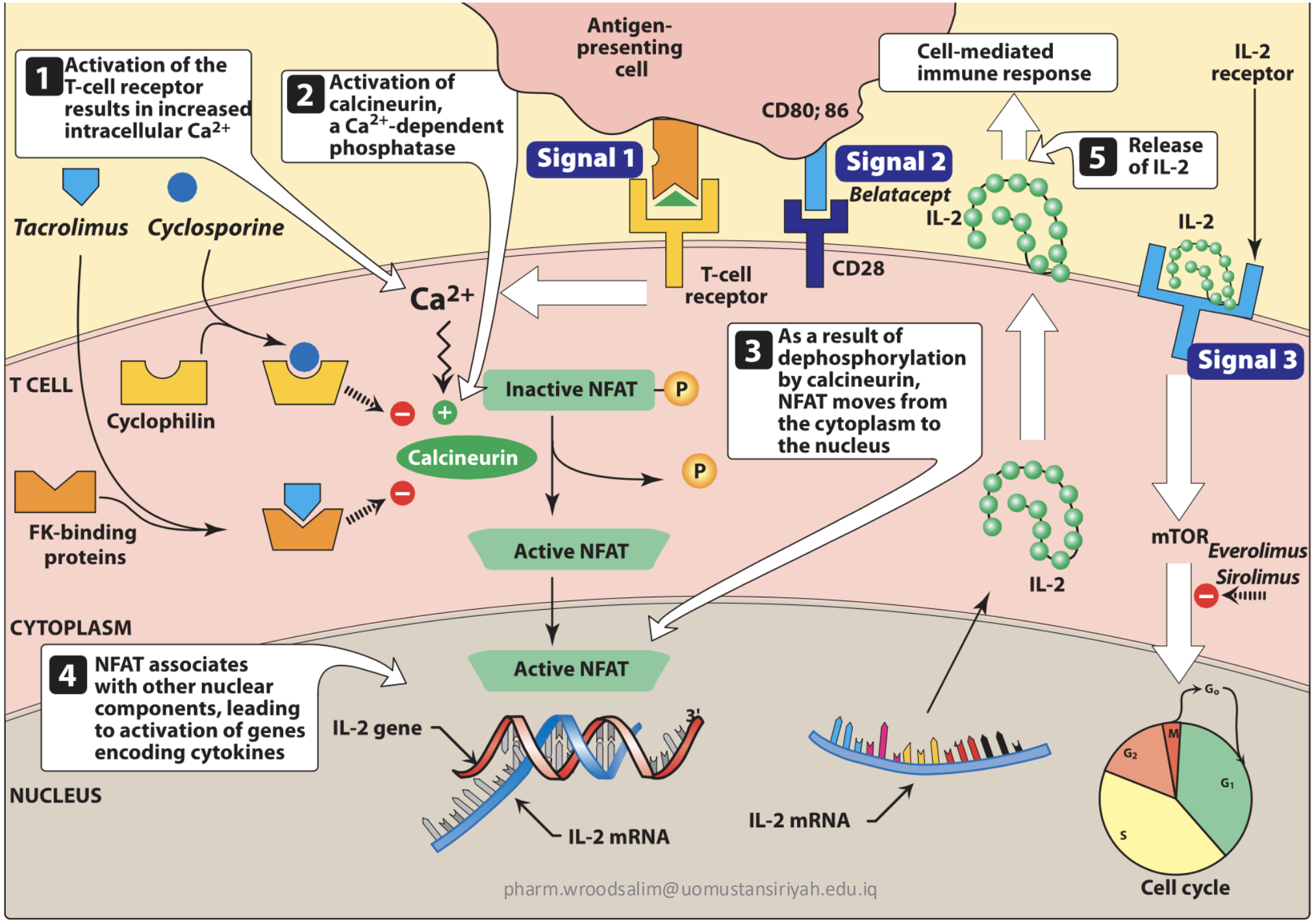


Figure 38.2 Simplified immune activation cascade.IL2 = interleukin 2; MHC = major histocompatibility complex; TCR = T-cell receptor.



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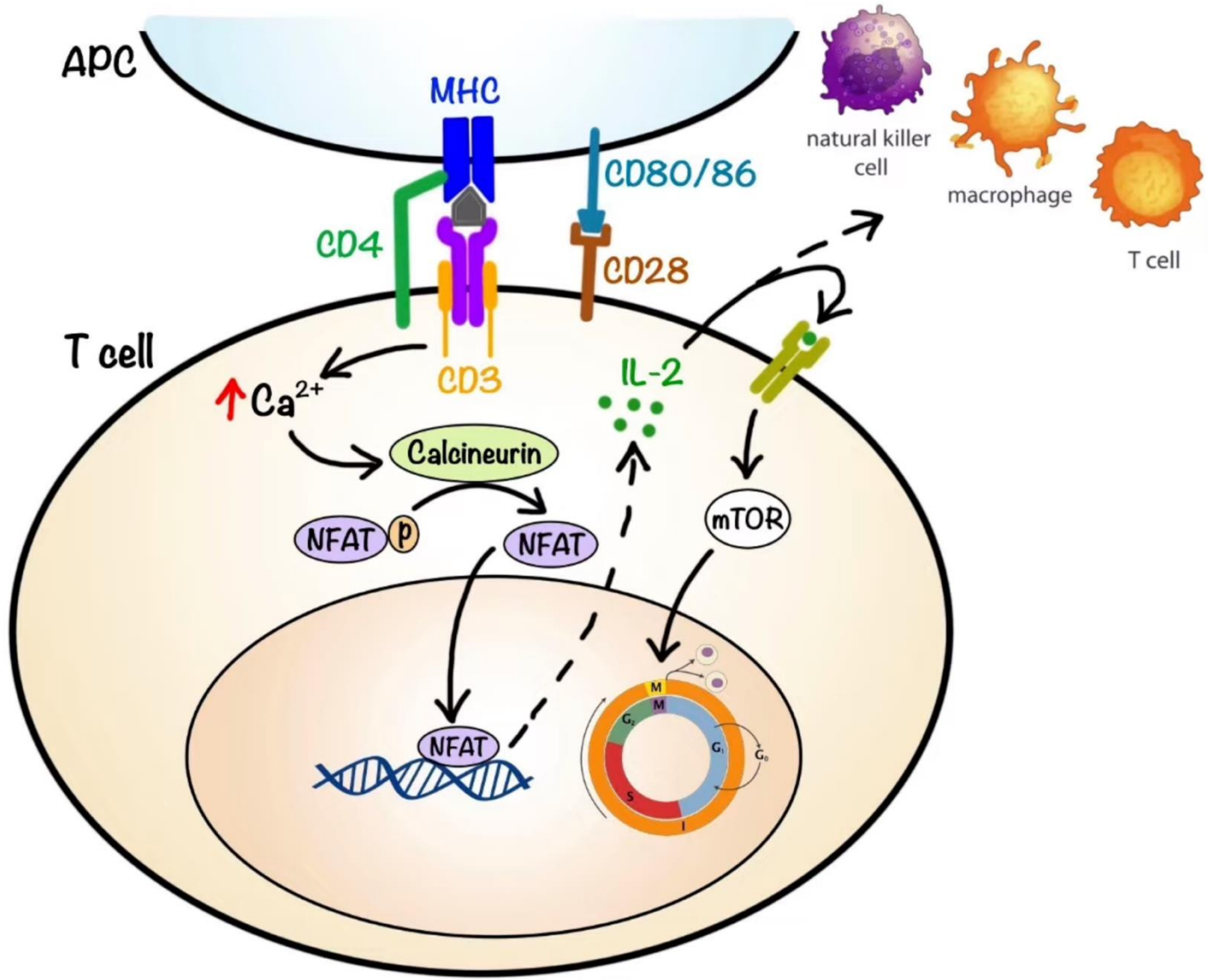

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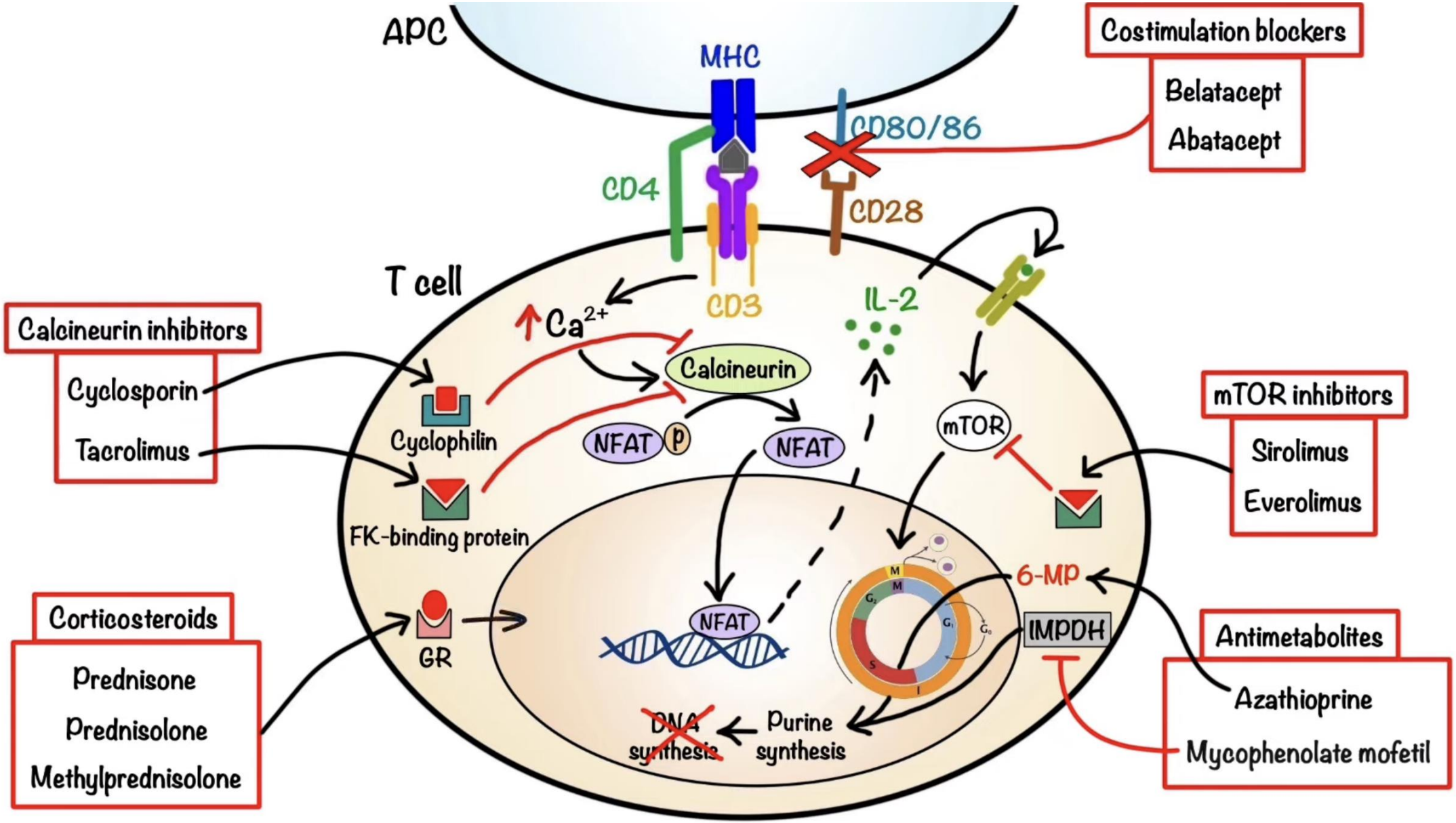

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Immunosuppressants are classified according their mechanism of action.

ANTIBODIES

Alemtuzumab CAMPATH
Antithymocyte globulins ATGAM, THYMOGLOBULIN
Basiliximab SIMULECT
Rituximab RITUXAN

CALCINEURIN INHIBITORS

Cyclosporine NEORAL, SANDIMMUNE
Tacrolimus ASTAGRAF XL, ENVARSUS XR, PROGRAF

COSTIMULATION BLOCKER

Belatacept NULOJIX

mTOR INHIBITORS

Everolimus ZORTRESS
Sirolimus RAPAMUNE

ANTI-PROLIFERATIVES

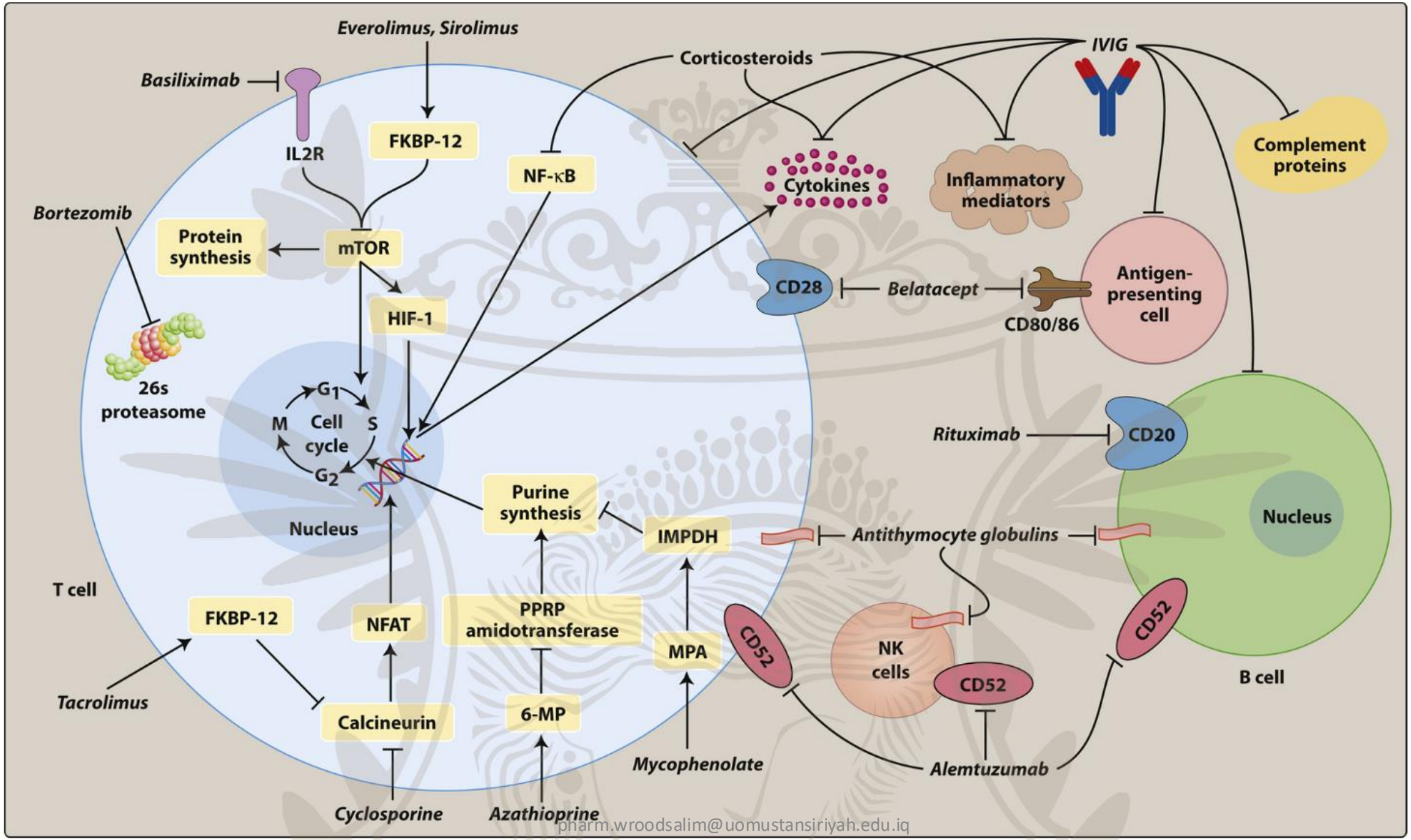
Azathioprine IMURAN
Mycophenolate mofetil CELLCEPT
Mycophenolate sodium MYFORTIC

ADRENOCORTICOIDS

Methylprednisolone MEDROL SOLU-MEDROL
Prednisolone ORAPRED, PRELONE
Prednison GENERIC ONLY

OTHER

Belimumab BENLYSTA
Bortezomib VELCADE
Eculizumab SOLIRIS
Intravenous immunoglobulin VARIOUS
Tofacitinib XELJANZ



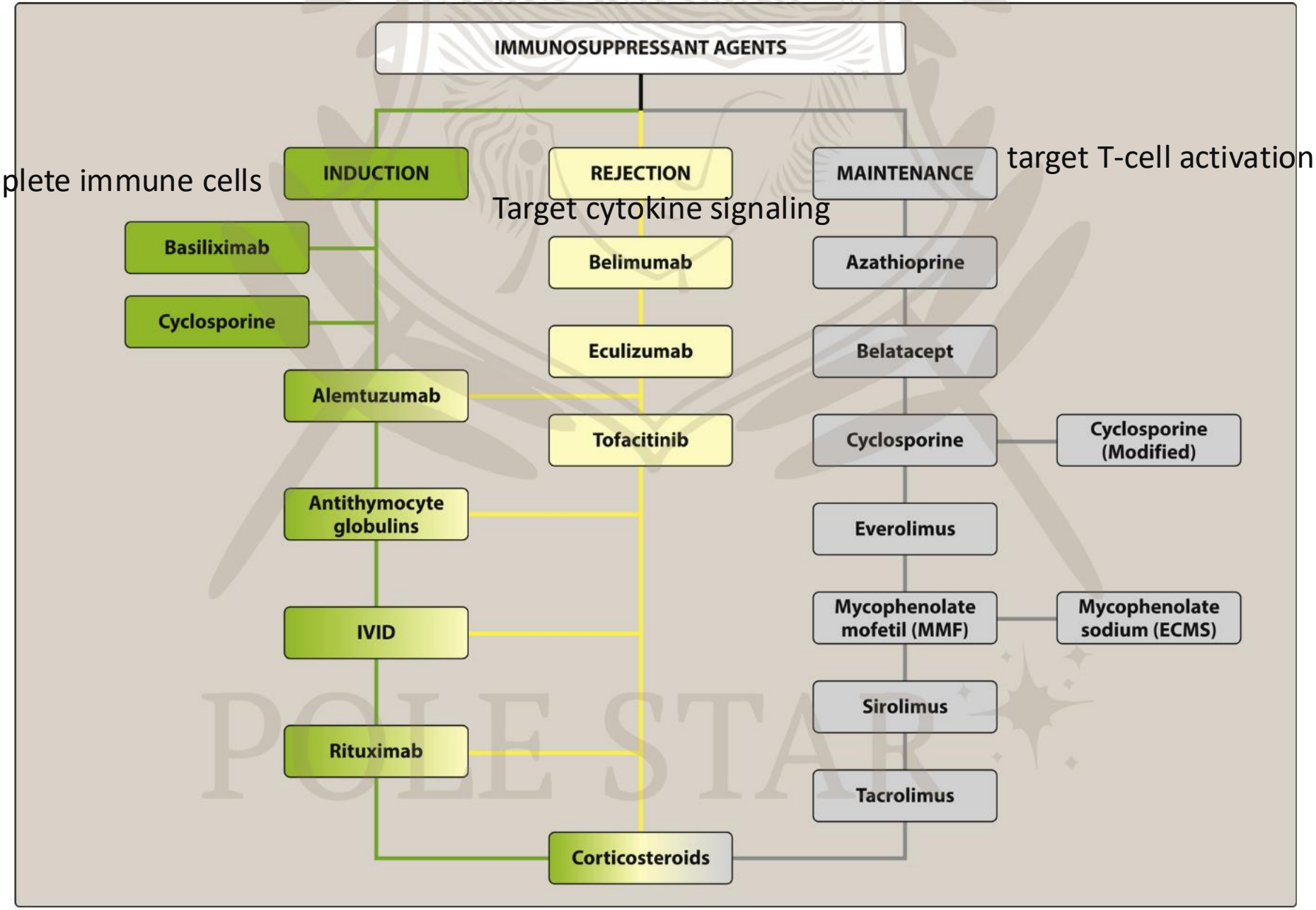
Immunosuppressants can be broadly categorized by their place in transplant therapy

1. **Induction therapy**: provide short-term, **broad immunosuppression** in the early posttransplant period, when the risk of acute allograft rejection is highest. It includes antibodies and/or intravenous immunoglobulins
2. **Maintenance drugs**, are **less potent immunosuppressants** are used to provide long-term immunological protection for the transplanted organs, (to inhibit chronic rejection), they often target T-cell activation and proliferation pathways and have with lower risk of infection than with the induction drugs. It includes calcineurin inhibitors, costimulation blockers, mTOR inhibitors, and/or antiproliferatives.
3. **Treatment of rejection**: it can be initiated, if induction therapy fails. It is aims to attenuate the host's immune response and prevent irreversible injury to the grafted organ. The pathophysiology associated with the type of rejection (cellular or humoral immunity) influences choice of treatment. Antirejection therapies, including antibodies, IVIG, and corticosteroids.

deplete immune cells

target T-cell activation and proliferation

Target cytokine signaling



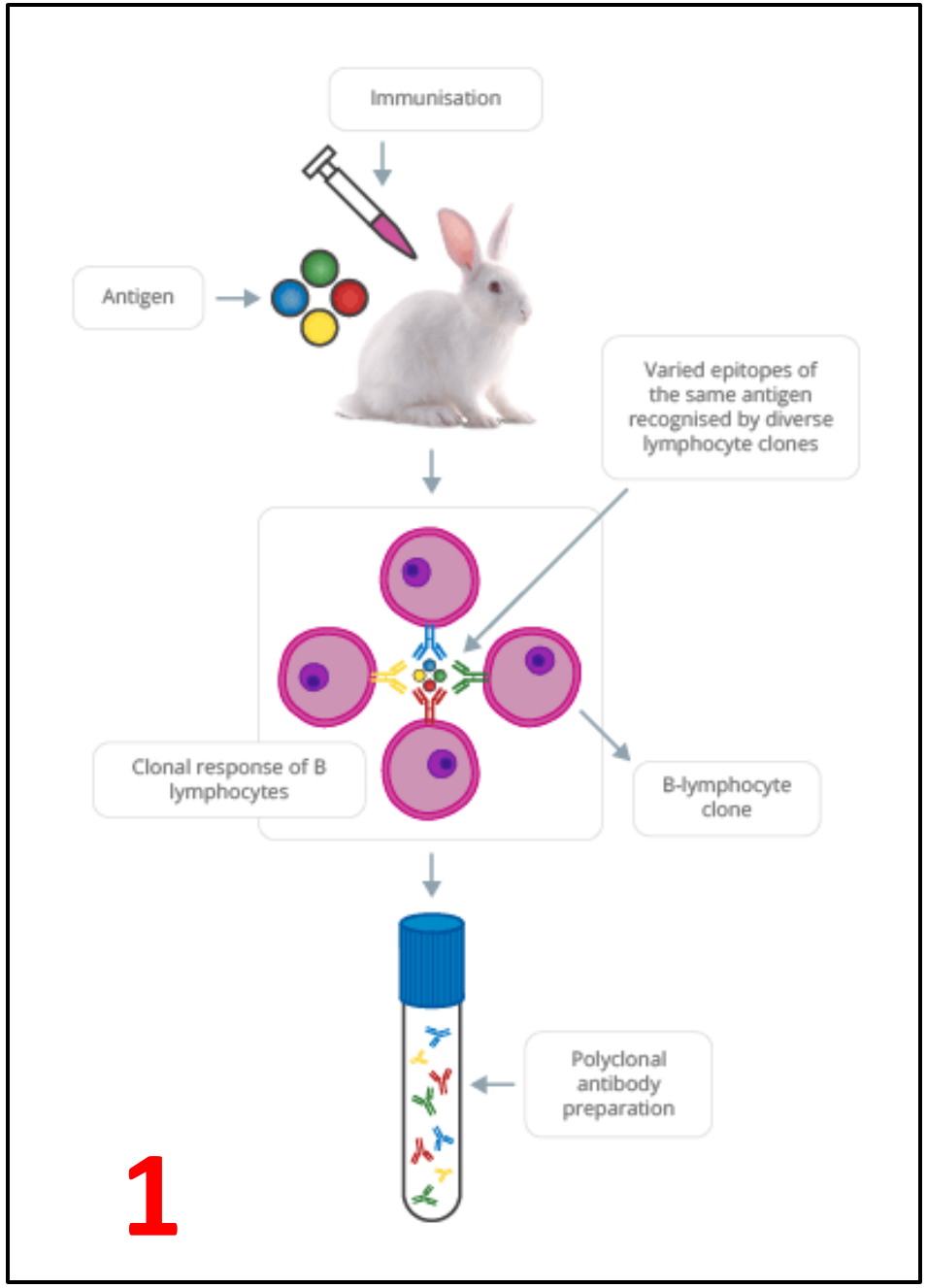
IMMUNOSUPPRESSANT DRUGS FOR INDUCTION AND REJECTION

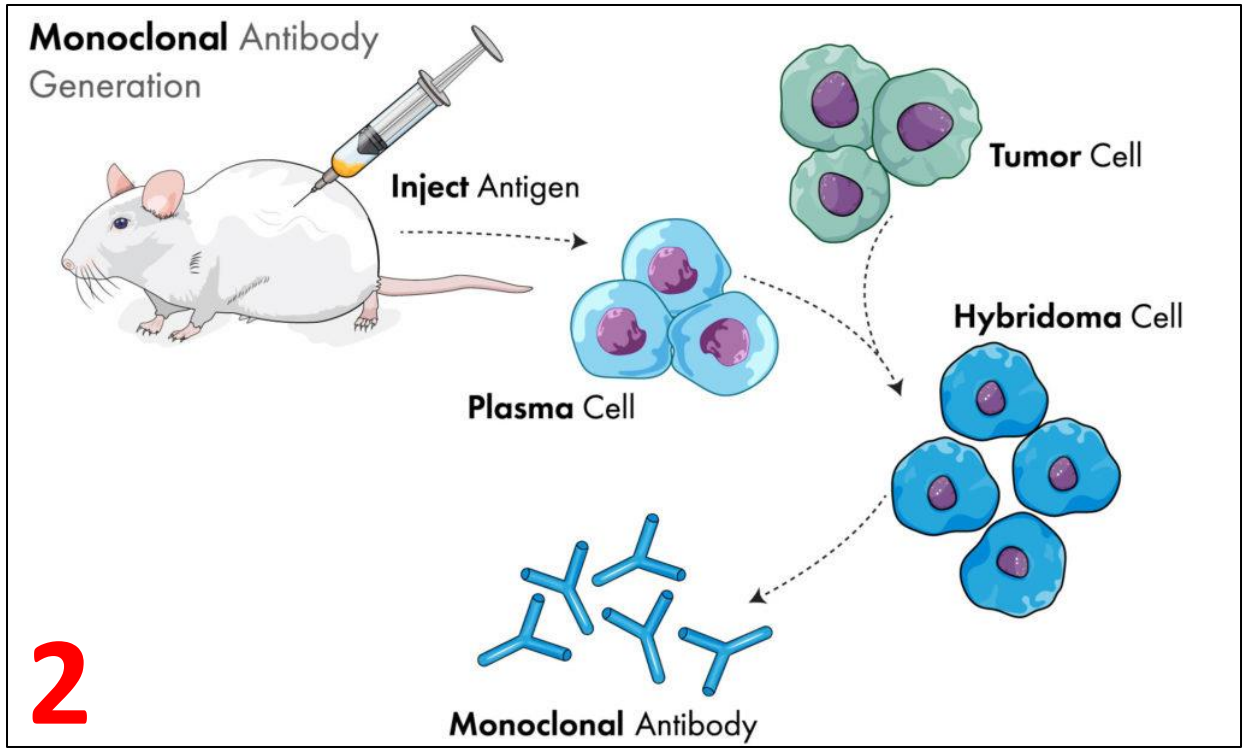
DRUG	CLASS	MECHANISM OF ACTION	INDICATIONS	ADVERSE EFFECTS
Alemtuzumab	Humanized monoclonal antibody	Binds to CD52 on B and T lymphocytes, causing T- and B-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), severe and prolonged leukopenia, neutropenia, thrombocytopenia, infections (CMV, HSV, and other viruses/fungi)
Antithymocyte globulins	Polyclonal antibody	T-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), leukopenia, thrombocytopenia, pulmonary edema, infections due to CMV or other viruses, skin rash
Basiliximab	Chimeric monoclonal antibody	IL-2 receptor antagonist on activated T-lymphocytes (nondepleting)	Induction	Generally well tolerated vs. placebo
Bortezomib	Proteasome inhibitor	Proteasome inhibition leads to plasma cell depletion	Treatment of antibody-mediated rejection	Leukopenia, anemia, thrombo-cytopenia, nausea/vomiting, diarrhea, peripheral neuropathy, hypotension, hepatotoxicity (less common)
Intravenous Immunoglobulin (IVIG)	Immune globulin	Exact mechanism of action unknown and likely multifactorial	Induction for highly sensitized patients, treatment of rejection	Infusion-related reactions, headache, hypotension, hemolytic anemia, pulmonary edema, thromboembolic events, aseptic meningitis, acute renal failure
Methylprednisolone	Corticosteroid	Nonspecific interleukin and TNF inhibition	Induction, treatment of rejection, maintenance	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
Rituximab	Chimeric monoclonal antibody	Binds to the CD20 antigen on B lymphocytes, mediating B cell lysis (depletion)	Induction, treatment of rejection	Infusion-related effects (chills, fever), infections (reactivation of hepatitis B virus, CMV, and other viruses/fungi), PML, leukopenia, thrombocytopenia, mucocutaneous reactions

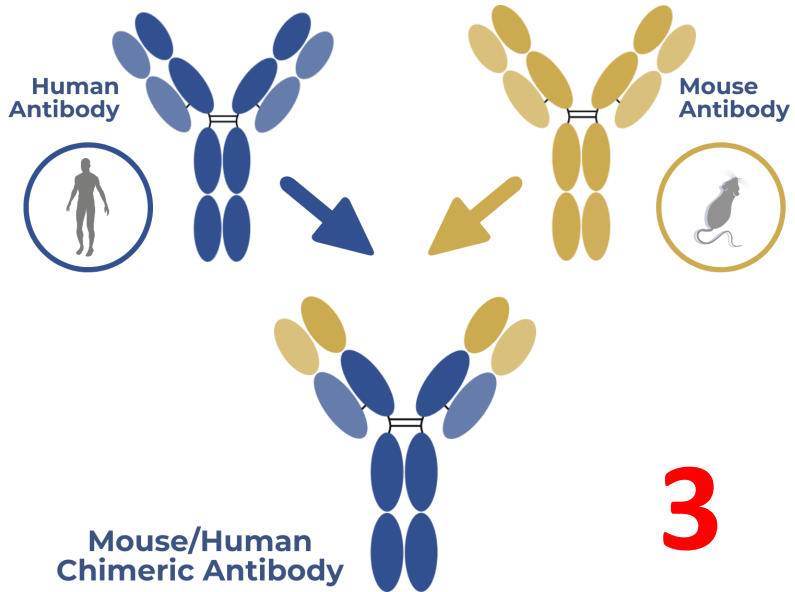
Monoclonal Antibodies

- Monoclonal antibodies (MAbs) have the **advantage of high specificity** because they can be developed for **interaction with a single molecule.**
- **Antibodies are prepared by**

1. **immunization** of either rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies or monoclonal antibodies).
2. **hybridoma technology** (producing antigen-specific monoclonal antibodies). Hybridomas are produced by fusing mouse antibody-producing cells with tumor cells.
3. **Recombinant DNA technology** can also be used to replace part of the mouse gene sequence with human genetic material, thus "humanizing" the antibodies and making them less antigenic.







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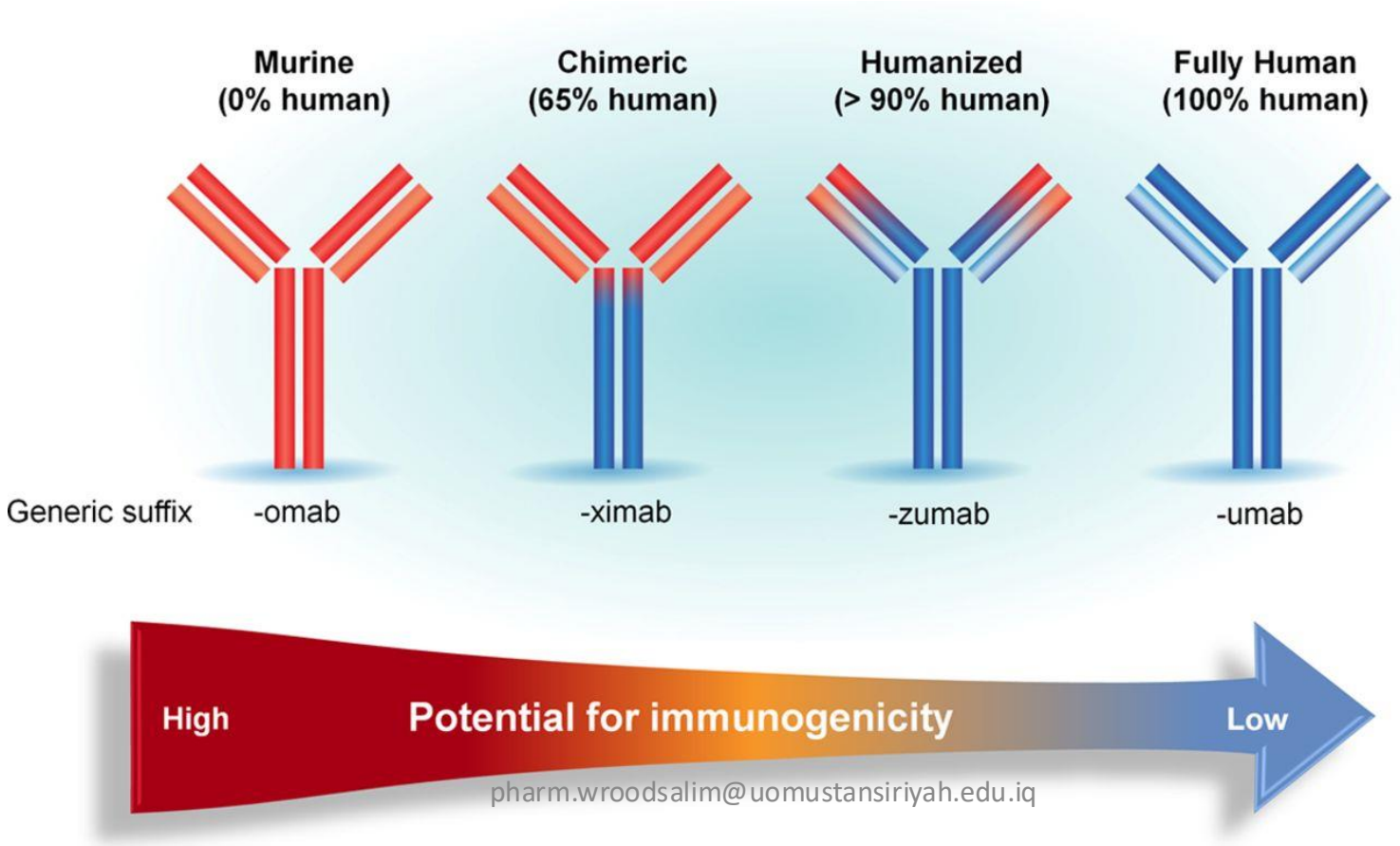
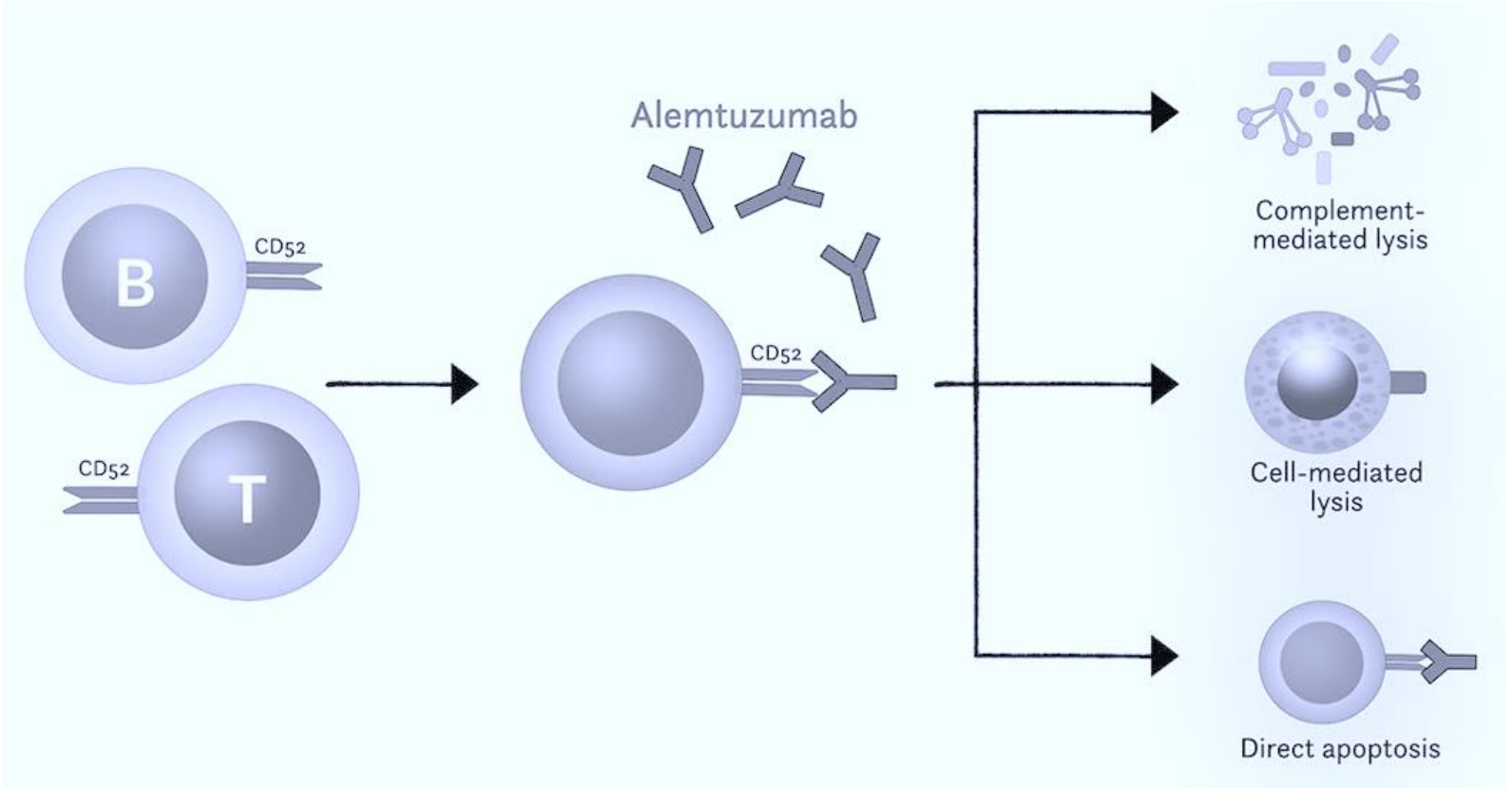
Names of monoclonal antibodies

- The names of monoclonal antibodies conventionally contain ”o” are murine, "xi” are chimerized , "zu" if they are or humanized , "u" if they are fully human.
- The suffix "-mab~ (monoclonal antibody) identifies the category of drug.



IMMUNOSUPPRESSANT DRUGS FOR INDUCTION AND REJECTION

1. Alemtuzumab is a humanized monoclonal antibody that binds to CD52 on both T and B cells, resulting in depletion of both lymphoid cell lines. T cells recover over 6–12 months, and B cells recover in 6 months or less.



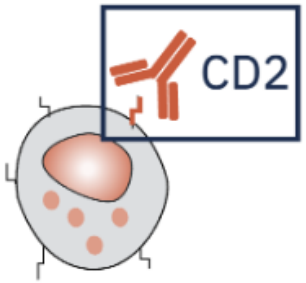
It used in transplantation as **an induction** and **antirejection agent** for both acute cellular rejection and antibody-mediated rejection (AMR) due to its activity against both T and B cells.

2. Antithymocyte Globulin (ATG)

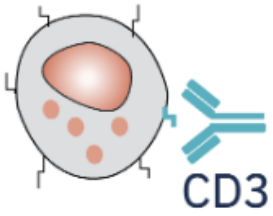
- **are polyclonal antibodies produced by isolating gamma- globulin fractions of serum obtained from rabbits or horses after immunization with human thymocytes.**
- **They cause depletion of circulating T cells and apoptosis of activated T cells.**
- The rabbit-derived antithymocyte globulin is primarily used at the time of transplantation to prevent early allograft rejection, along with other immunosuppressive agents.
- It may also be used to treat severe rejection episodes or corticosteroid-resistant acute rejection.
- It is usually used for 3–10 days to produce profound lymphopenia that may last beyond 1 year.

Antithymocyte Globulin

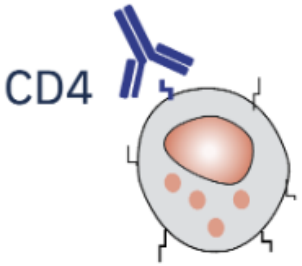
Multi-Target Binding of Thymoglobulin (rATG) IgG Polyclonal Antibodies



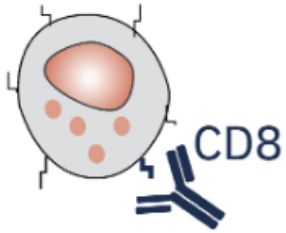
Lymphocytes



T-Lymphocytes



Helper T-Cells



Cytotoxic T-Cells

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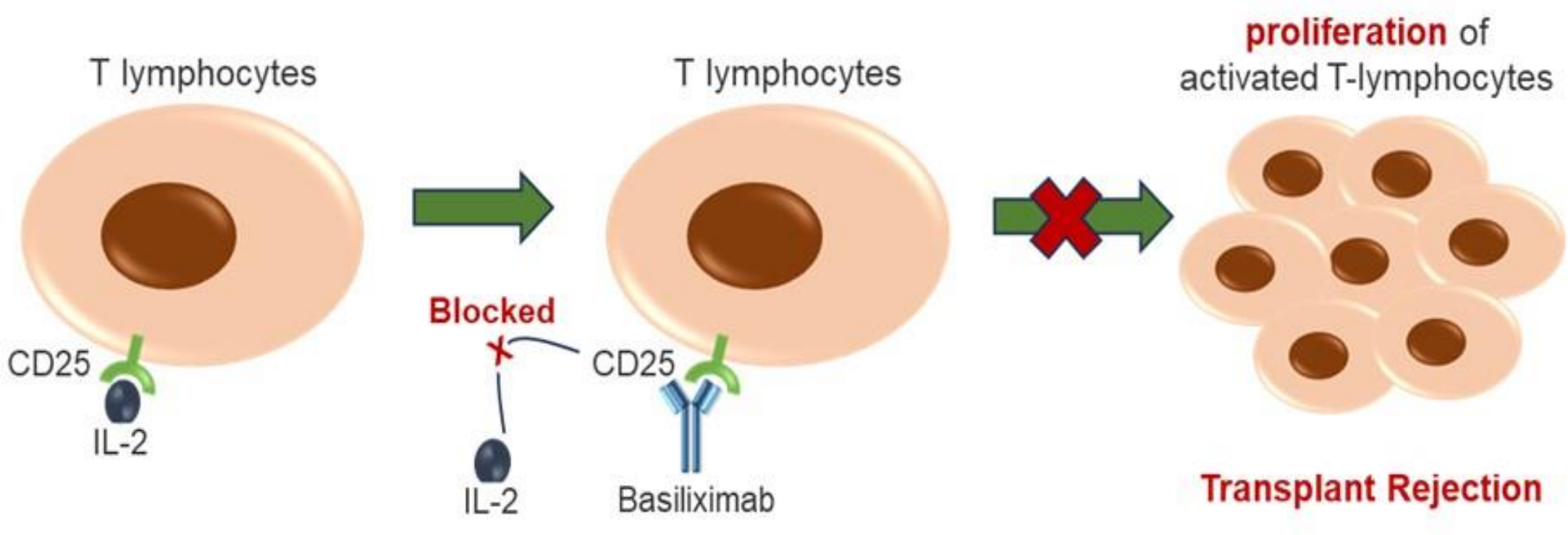
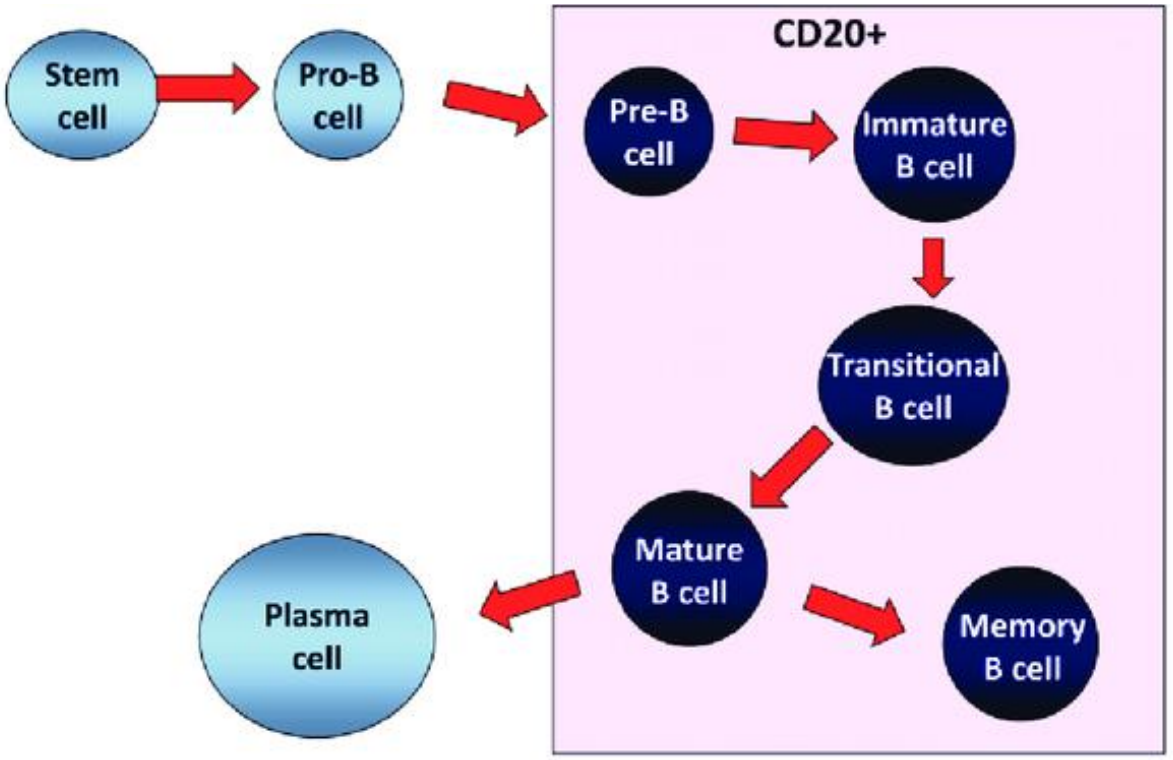
3. Basiliximab

- Basiliximab is a chimeric murine/human monoclonal antibody that binds to the α chain of the IL-2 receptor (CD25) on activated T cells and, thus, interferes with the proliferation of these cells.



4. Rituximab

- *Rituximab* is a chimeric monoclonal antibody against the antigen CD20 on pre-B cells, mature B cells, and memory B cells.
- *Rituximab* causes B-cell depletion by inducing B-cell lysis and blocking B-cell activation and eventual maturation to antibody-forming plasma cells.

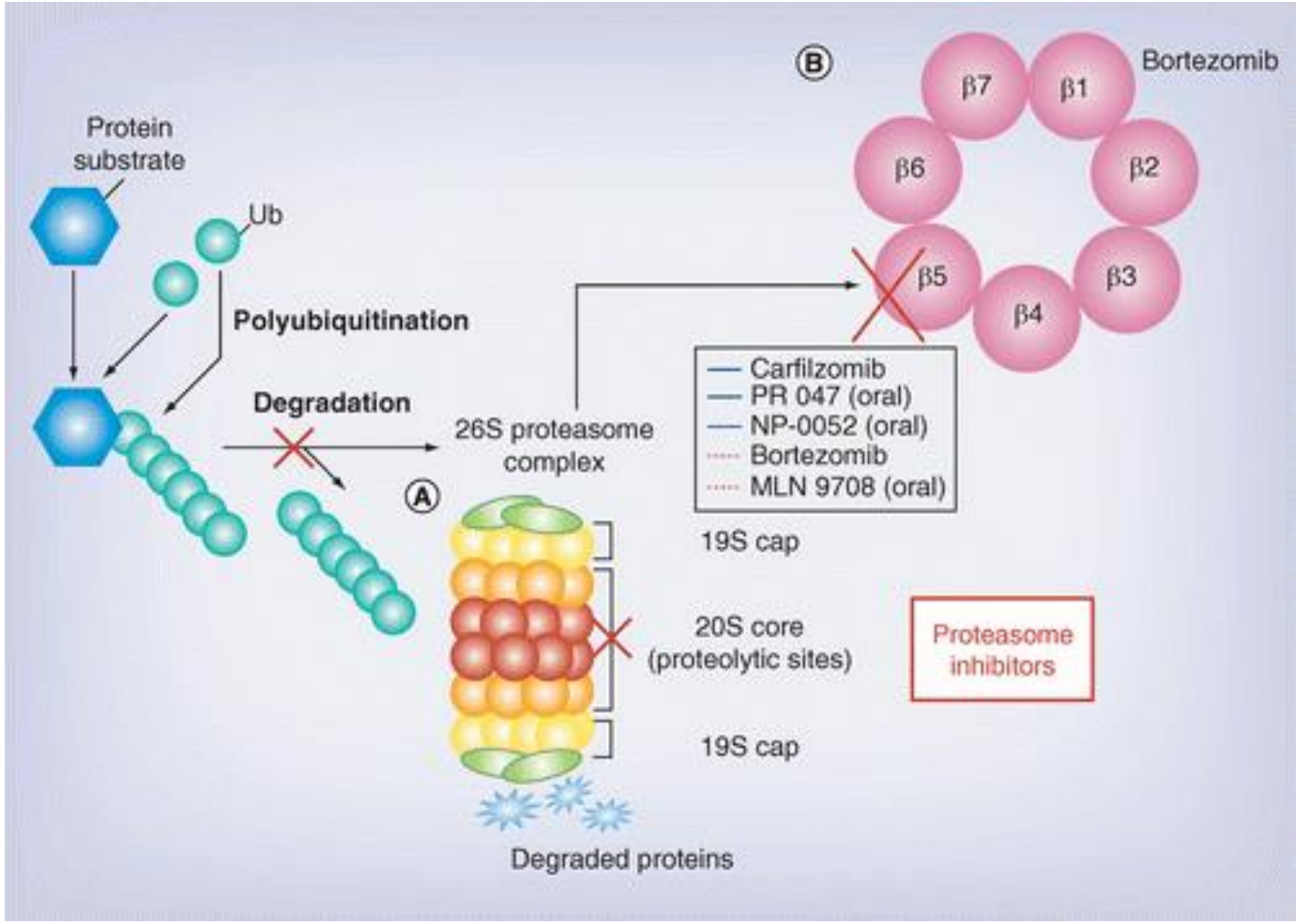


5. Bortezomib

- AMR (antibody mediated rejection) involves the production of high levels of antibodies by plasma cells, either newly made from B cells or from those that existed prior to transplant.
- One mechanism to control AMR is to target antibody production by plasma cells.
- *Bortezomib* is a proteasome inhibitor that leads to cell cycle arrest and apoptosis of normal plasma cells, thereby decreasing antibody production in sensitized patients.

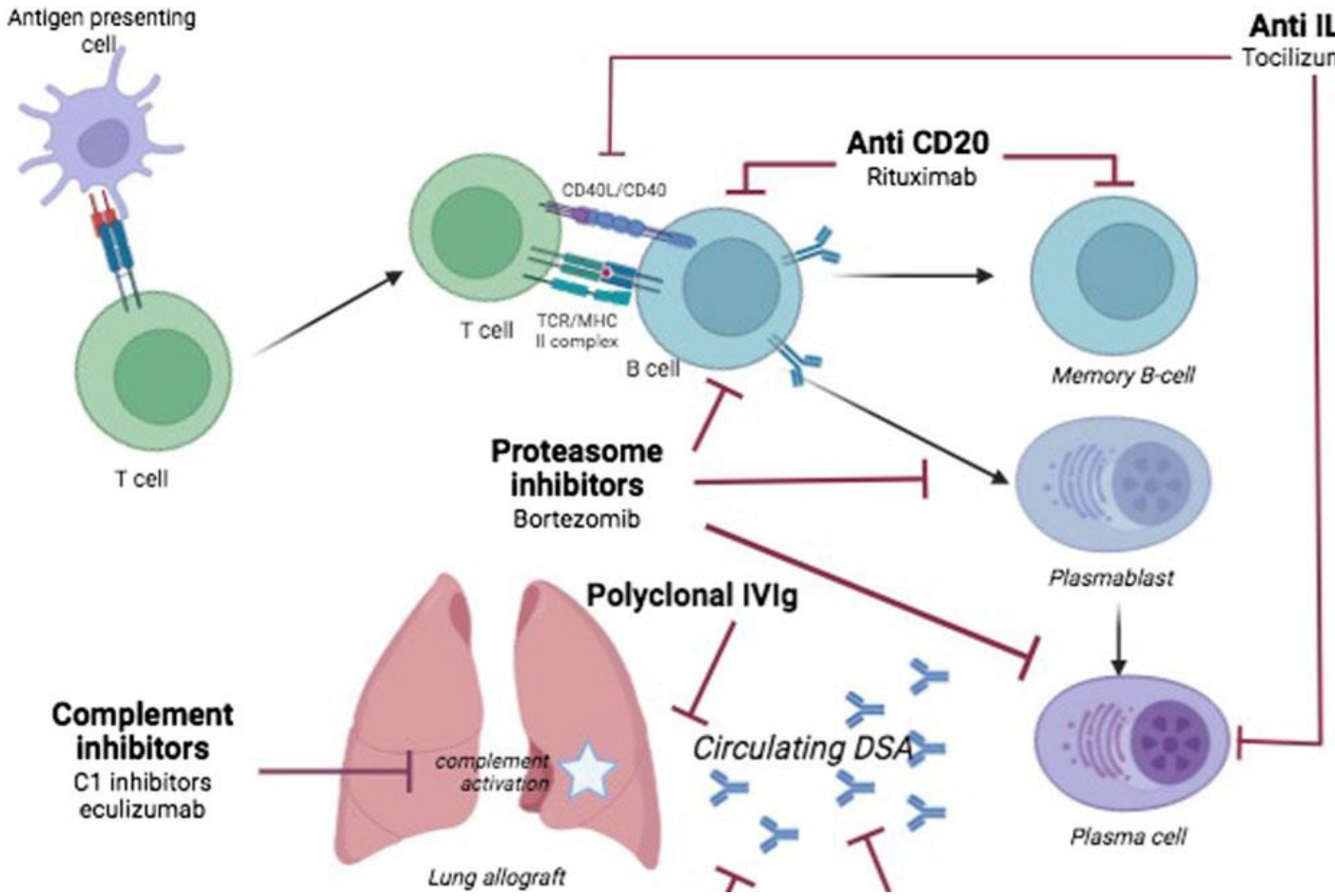
Bortezomib

Bortezomib reversibly binds to the 26S proteasome, resulting in its inhibition and preventing the degradation of various pro-apoptotic factors that leads apoptosis of normal plasma cells, thereby decreasing antibody production in sensitized patients.



6. Immune Globulin Intravenous

- Intravenous immunoglobulin (IVIG) contains immunoglobulins prepared by human plasma pooled from many donors.
- It has an immunomodulatory effect and is often used for autoimmune diseases, pretransplant desensitization protocols, and treatment of AMR.



high doses of IVIG appear to induce B-cell apoptosis and modulate B-cell signaling. It also inhibits binding of antibodies to the transplanted graft and activation of the complement system.

MAINTENANCE IMMUNOSUPPRESSANT MEDICATIONS

- Maintenance immunosuppressants are intended to provide adequate immunosuppression to prevent allograft rejection while minimizing infection, malignancy, and drug-induced adverse effects.
- Maintenance therapy is initiated at the time of surgery and is continued indefinitely to prevent loss of the allograft. Often, maintenance immunosuppressants are combined in regimens of two to four drugs, using medications with different mechanisms of action to minimize drug toxicity. **These drugs can be further divided into four main classes:**
- (1) calcineurin inhibitors (cyclosporine and tacrolimus),
- (2) costimulation blocker (belatacept),
- (3) mTOR inhibitors (sirolimus and everolimus),
- (4) antiproliferatives (azathioprine and mycophenolate)

MAINTENANCE IMMUNOSUPPRESSANT MEDICATIONS

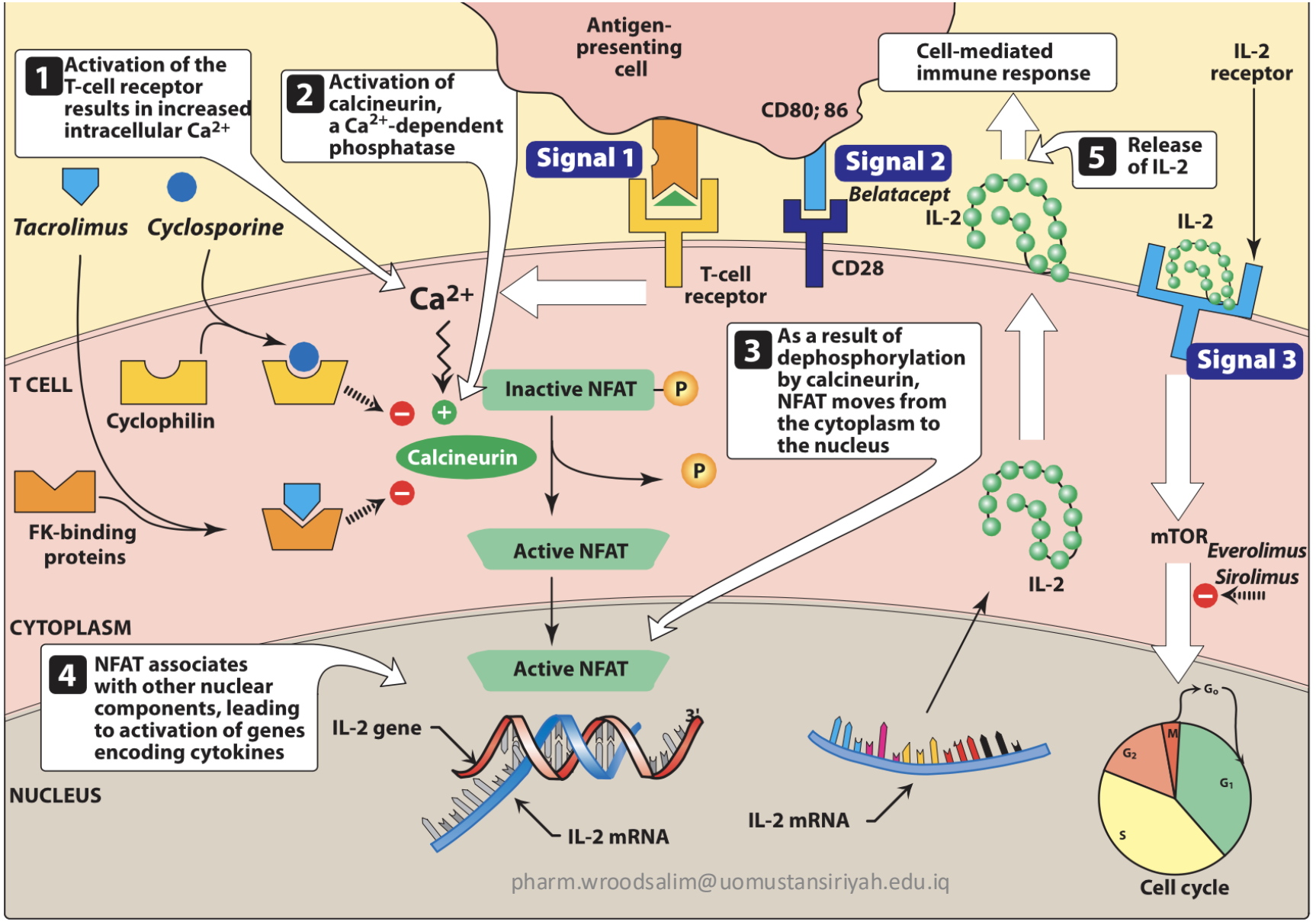
DRUG	CLASS	INDICATIONS	PHARMACOKINETICS	ADVERSE EFFECTS
Azathioprine	Antiproliferative	SOT (renal), RA, lupus	Activated by glutathione S-transferase DDIs (*allopurinol,* ACE inhibitors, *warfarin*)	Myelosuppression, nausea, vomiting, diarrhea, pancreatitis, hepatotoxicity
Belatacept	Costimulation blocker	SOT (renal)	Elimination half-life ~10 days	Anemia, leukopenia, diarrhea, increased risk of PTLD
Cyclosporine	Calcineurin inhibitor	SOT (renal, liver, heart), psoriasis, RA, GVHD	Metabolism by CYP3A4 Numerous DDIs Inhibitor of CYP3A4 and P-glycoprotein	HTN, HLD, hyperglycemia, hyperkalemia, hirsutism, gingival hyperplasia, neurotoxicity, nephrotoxicity
Everolimus	mTOR inhibitor	SOT (renal, liver), oncology	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression
Methylprednisolone, prednisolone, prednisone	Corticosteroid	Numerous indications	Activated to *prednisolone*	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
Mycophenolate	Antiproliferative	SOT (renal, liver, heart)	Metabolism by glucuronidation DDI (bile acid sequestrants; antacids for MMF)	Leukopenia, thrombocytopenia, nausea, vomiting, diarrhea
Sirolimus	mTOR inhibitor	SOT (renal, heart), lymphangio-leiomyomatosis, GVHD	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression, pneumonitis
Tacrolimus	Calcineurin inhibitor	SOT (renal, liver, heart), GVHD	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD, hyperglycemia, hyperkalemia, alopecia, neurotoxicity (hand tremor, headache, seizure), nephrotoxicity

1. Calcineurin Inhibitors

- Calcineurin inhibitors cyclosporine and tacrolimus block signal transduction through the calcium–calcineurin pathway, activated downstream of signal 1, to impair T-cell activation.

- Bind to cyclophilin (cyclosporine) or FK binding protein (tacrolimus) →↓ calcineurin (cytoplasmic phosphatase) →↓ activation of T cell transcription factors (NFAT) →↓ IL 2, IL 3, and interferon γ

Calcineurin and mTOR Inhibitors



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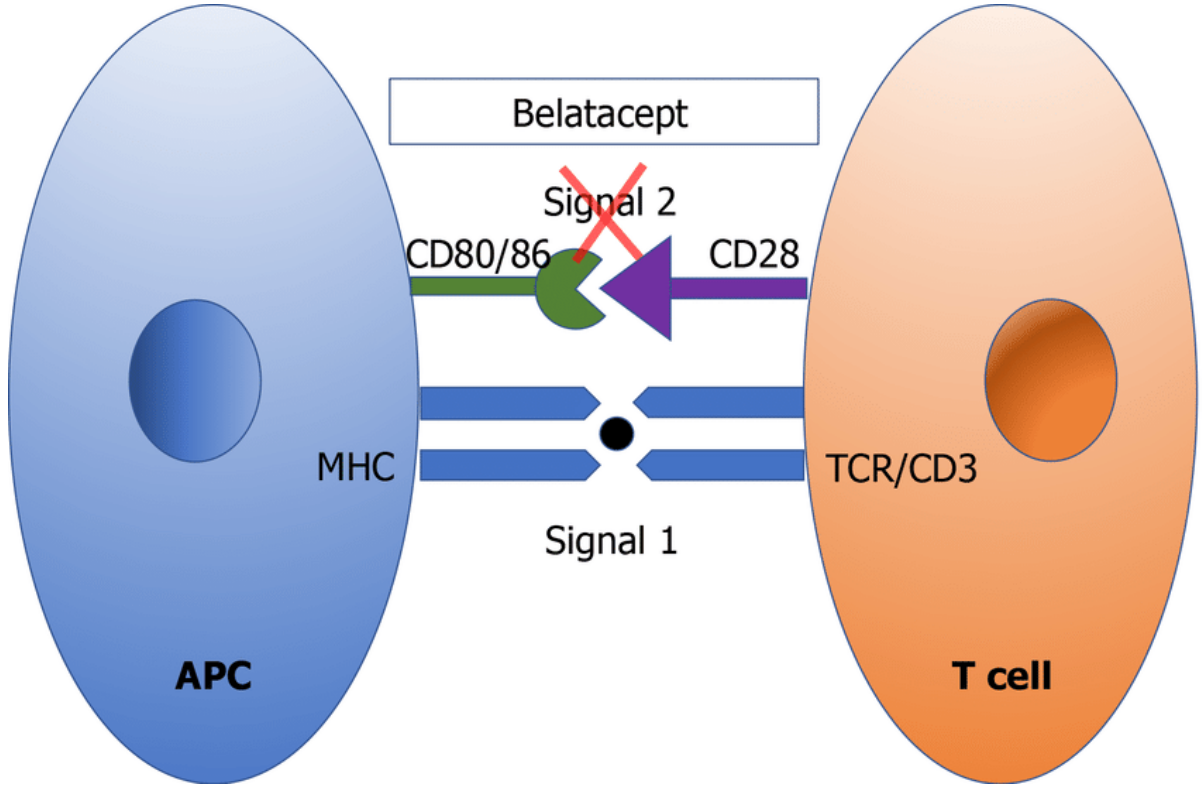
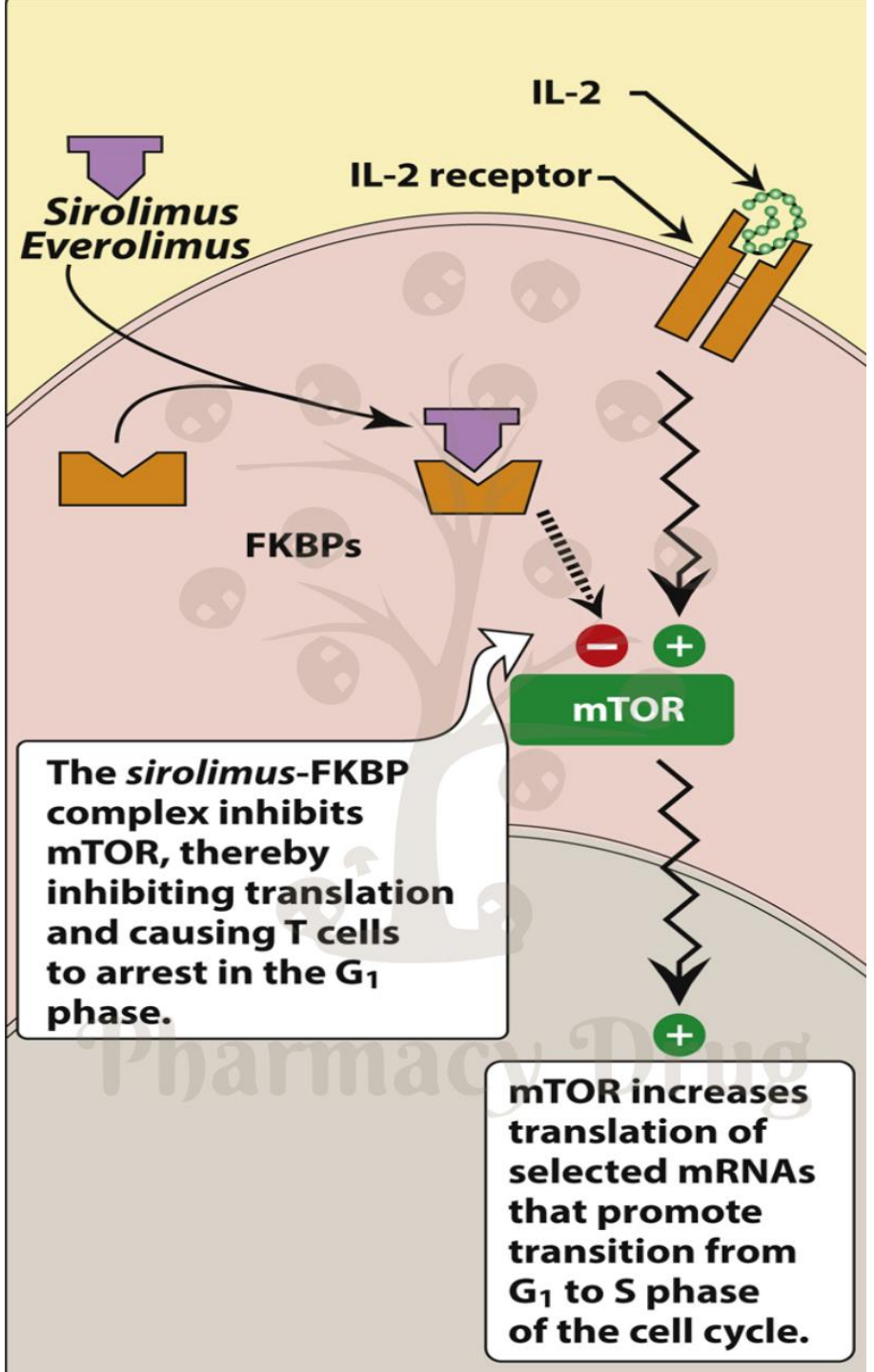
2. Co stimulation inhibition (Belatacept)

- a second-generation co stimulation blocker, is a recombinant fusion protein of CTLA-4, which like CD28, binds to CD80 and CD86 on APCs. Thus it prevents CD28 from binding to those molecules and, thus, inhibits signal 2 of the T-cell activation pathway.



3. mTOR Inhibitors

- Sirolimus (also known as rapamycin) and everolimus inhibit the protein mTOR, blocking the signal transduction pathway activated by signal 3. Progression into the cell cycle and T-cell proliferation is subsequently prevented



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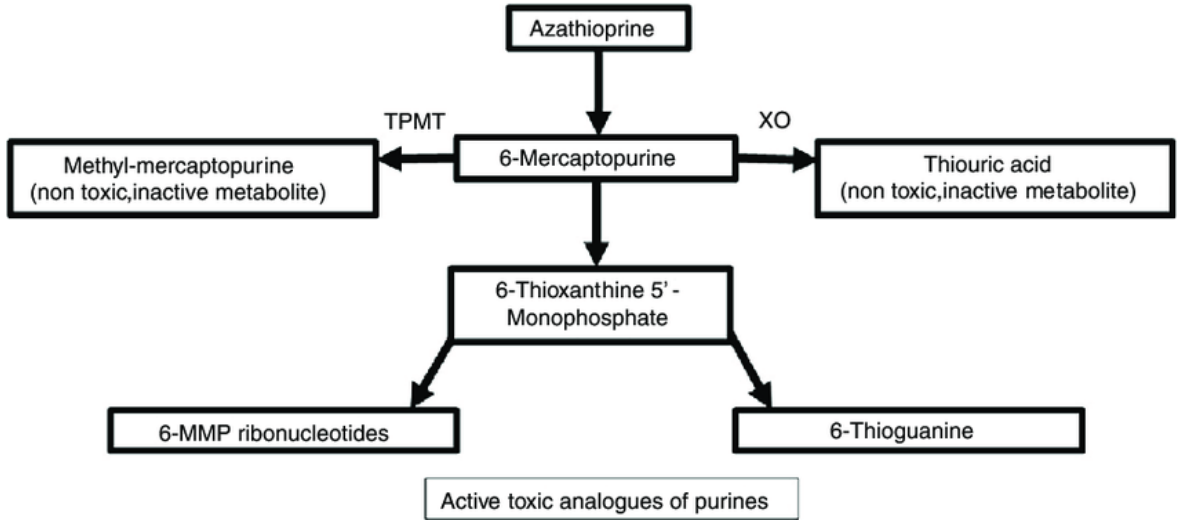
4. Antiproliferatives

- Antiproliferative agents (antimetabolites) act by inhibiting various targets in the signaling cascade, thus reducing cell proliferation and moderating cytotoxic immune response.
- The antiproliferatives azathioprine and mycophenolate block lymphocyte proliferation by inhibiting nucleic acid synthesis.

A) Azathioprine, is a prodrug that is converted first to 6-mercaptopurine (6-MP) and then to the corresponding nucleotide analogue, thioinosinic acid. The analog is incorporated into nucleic acid chains and blocks further elongation of the DNA.



B) Mycophenolate Mofetil

- ***Mechanism of action****-this* drug is rapidly converted into mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, an enzyme in the de novo pathway of guanosine triphosphate (GTP) synthesis. This action suppresses both B- and T-lymphocyte activation. Lymphocytes are particularly susceptible to inhibitors of the de novo pathway because they lack the enzymes necessary for the alternative salvage pathway for GTP synthesis.

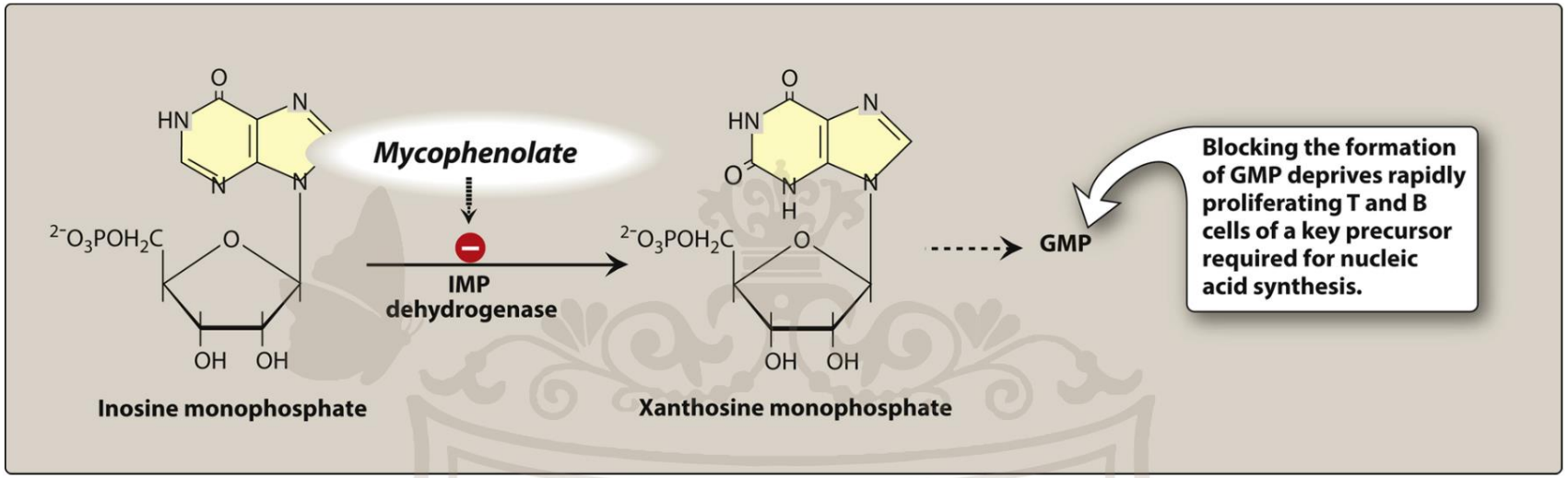


Figure 38.7 Mechanism of action of *mycophenolate*.IMP = inosine-5′-monophosphate; GMP = guanosine monophosphate.

5. Corticosteroids

- ***Mechanism of* action:** Glucocorticoids act at multiple cellular sites to produce broad effects on inflammatory and immune processes.
- At the biochemical level, their actions on gene expression decrease the synthesis of prostaglandins, leukotrienes, cytokines, and other signaling molecules that participate in immune responses.
- At the cellular level, the glucocorticoids inhibit the proliferation of T lymphocytes and are cytotoxic to certain subsets of T cells.
- humeral immunity is also reduced and continuous therapy lowers IgG levels by increasing the catabolic rate of this class of immunoglobulins.

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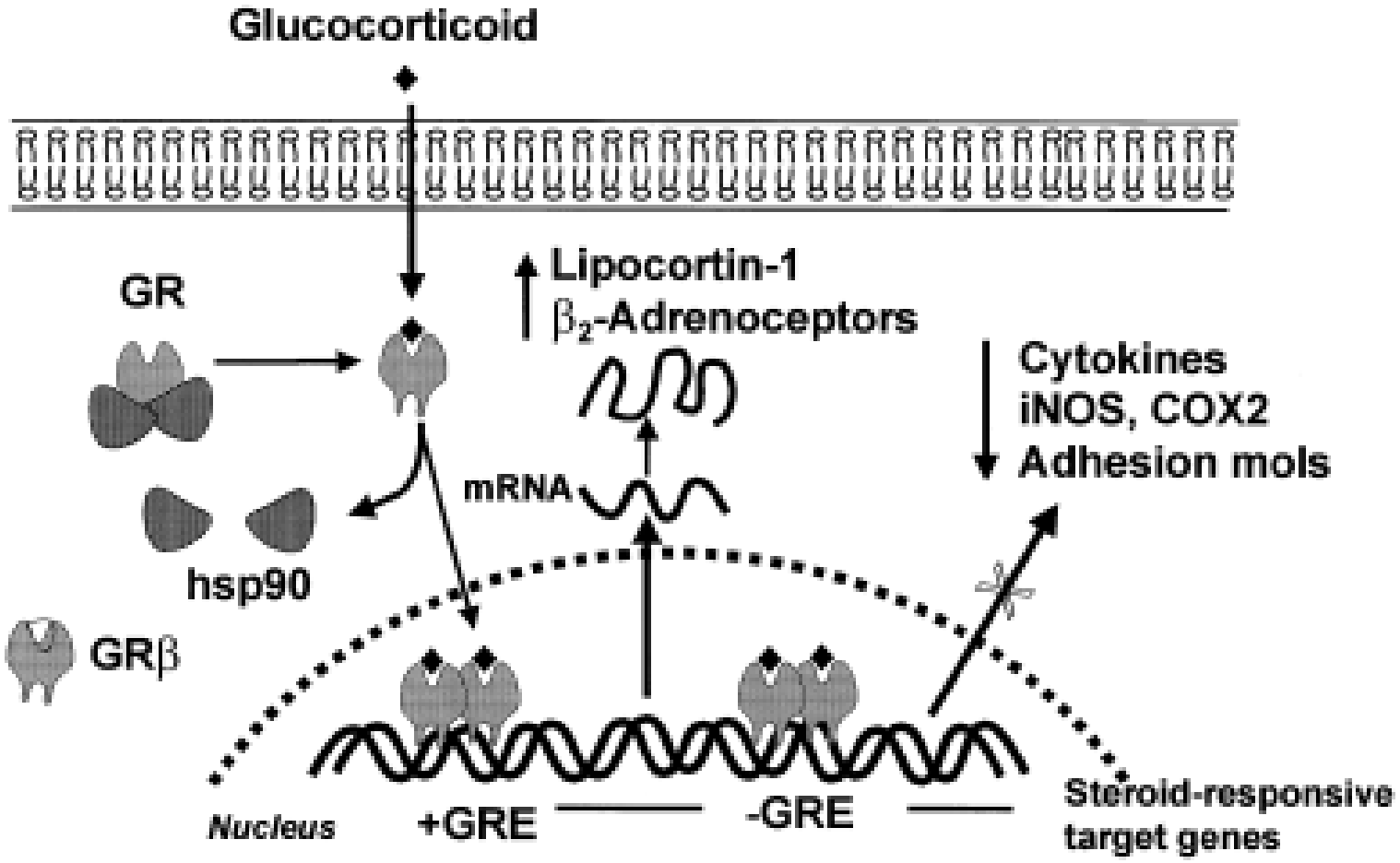
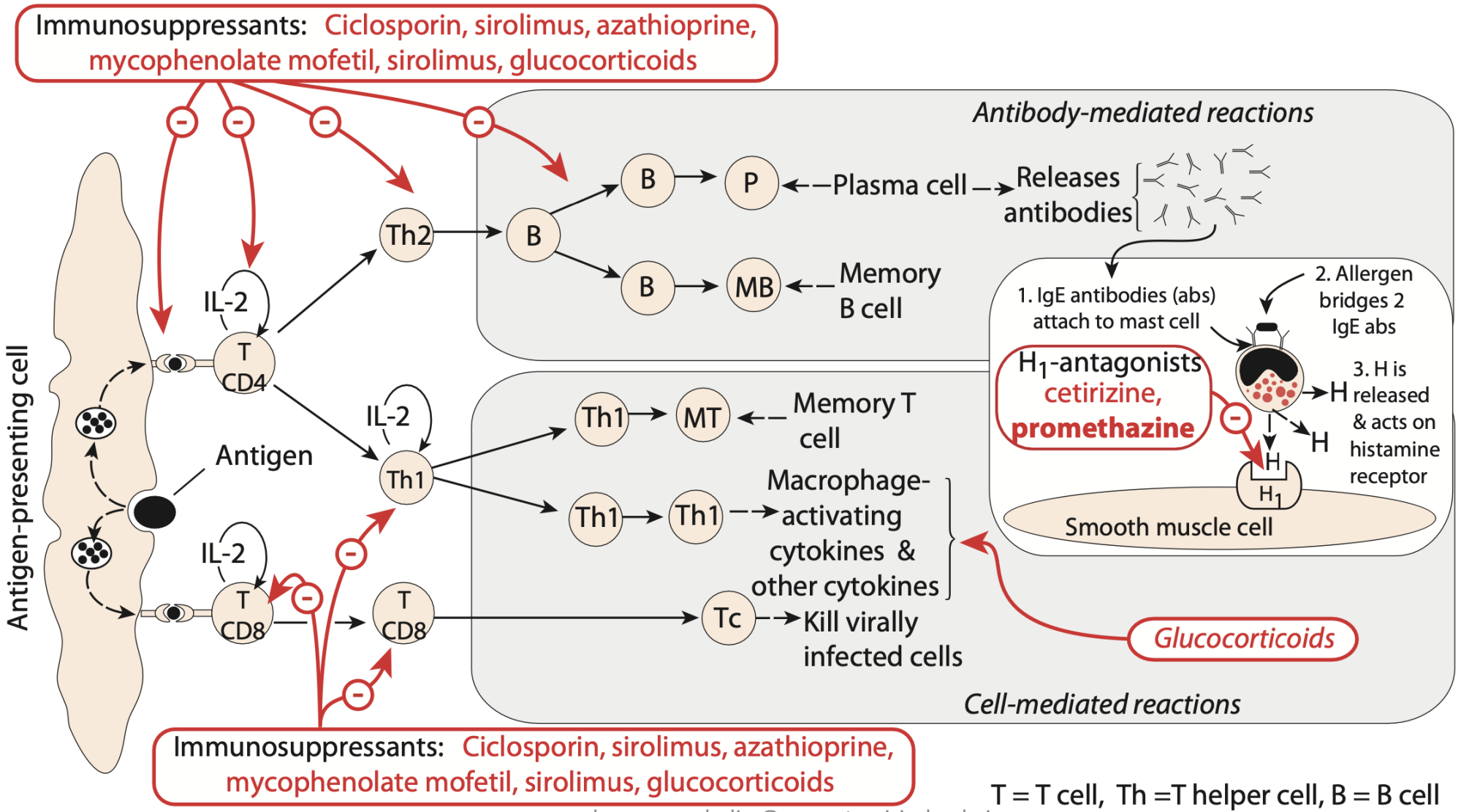

Glucocorticoid
GR
Lipocortin-1
β2-Adrenoceptors
Cytokines
iNOS, COX2
Adhesion mols
mRNA
hsp90
GRβ
Nucleus
+GRE
-GRE
Steroid-responsive
target genes

Drugs affecting the immune response



T = T cell, Th =T helper cell, B = B cell

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