

Immunosuppressants & immunomodulants

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BCPS

Overview

The immune system is one of the most complex organ systems in the body, which can make it difficult to manipulate. Immunosuppressants are drugs that reduce the activation or efficacy of the immune system to treat certain conditions, such as autoimmune diseases, or to lower the body's ability to reject a transplanted organ.

Autoimmune diseases can arise when the immune system mistakenly identifies an individual's own tissues as foreign and directs a destructive response against them. The goal of treatment for these diseases is to use drug therapy to stop this inappropriate and harmful process. In the case of organ transplantation, foreign tissue is purposely implanted into the recipient, but the goal remains the same—to use drug therapy to limit the damage inflicted by the immune system and potential rejection of the transplanted organ. Transplantation of organs and tissues (for example, kidney, heart, or bone marrow) has become routine due to improved

These diseases include

- a broad spectrum of autoimmune diseases such as rheumatoid arthritis,
- type I diabetes mellitus,
- systemic lupus erythematosus,
- multiple sclerosis; solid tumors
- hematologic malignancies;
- infectious diseases;
- asthma;
- and various allergic conditions.

Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Because of their severe toxicities when used as monotherapy, a combination of immunosuppressive agents, usually at lower doses, is generally employed. Immunosuppressive drug regimens typically consist of two to four agents with different mechanisms of action that disrupt various levels of T-cell activation.

IMMUNOMODULATORS

Drugs used to modulate the immune response in three ways: immunosuppression, tolerance, and immunostimulation.

IMMUNOSUPPRESSION

Four major classes of immunosuppressive drugs

- glucocorticoids

- calcineurin inhibitors,

- antiproliferative

- antimetabolic agents

- antibodies.

General Approach to Organ Transplantation Therapy

Organ transplant therapy is organized around five general principles. The first principle is careful patient preparation and selection of the best available ABO blood type-compatible HLA match for organ donation. Second, a multitiered approach to immunosuppressive drug therapy, similar to that in cancer chemotherapy, is employed. Several agents are used simultaneously, each of which is directed at a different molecular target within the allograft response. Synergistic effects permit use of the various agents at relatively low doses, thereby limiting specific toxicities while maximizing the immunosuppressive effect. The third principle is that greater immunosuppression is required to gain early engraftment and/or to treat established rejection than to maintain long-term immunosuppression. Therefore, intensive induction and lower-dose maintenance drug protocols are employed. Fourth, careful investigation of each episode of transplant dysfunction is required, including evaluation for rejection, drug toxicity, and infection, keeping in mind that these various problems can and often do coexist. Organ-specific problems (e.g., obstruction in the case of kidney transplants) must also be considered. The fifth principle, which is common to all drugs, is that a drug should be reduced or withdrawn if its toxicity exceeds its benefit.

SITES OF ACTION OF SELECTED IMMUNOSUPPRESSIVE AGENTS ON T-CELL ACTIVATION



Therapy for Established Rejection. Although low doses of prednisone, calcineurin inhibitors, purine metabolism inhibitors, or sirolimus are effective in preventing acute cellular rejection, they are less effective in blocking activated T lymphocytes, and thus are not very effective against established, acute rejection or for the total prevention of chronic rejection. Therefore, treatment of established rejection requires the use of agents directed against activated T cells. These include glucocorticoids in high doses (pulse therapy), polyclonal antilymphocyte antibodies(ATG), or muromonab-CD3 mAb.

Adrenocortical Steroids

Mechanism of Action.

The immunosuppressive effects of glucocorticoids have long been known, but the specific mechanism(s) of their immunosuppressive action remains somewhat elusive. Glucocorticoids lyse (in some species) and induce the redistribution of lymphocytes, causing a rapid, transient decrease in peripheral blood lymphocyte counts. To effect longer-term responses, steroids bind to receptors inside cells; either these receptors, glucocorticoid induced proteins, or interacting proteins regulate the transcription of numerous other genes.

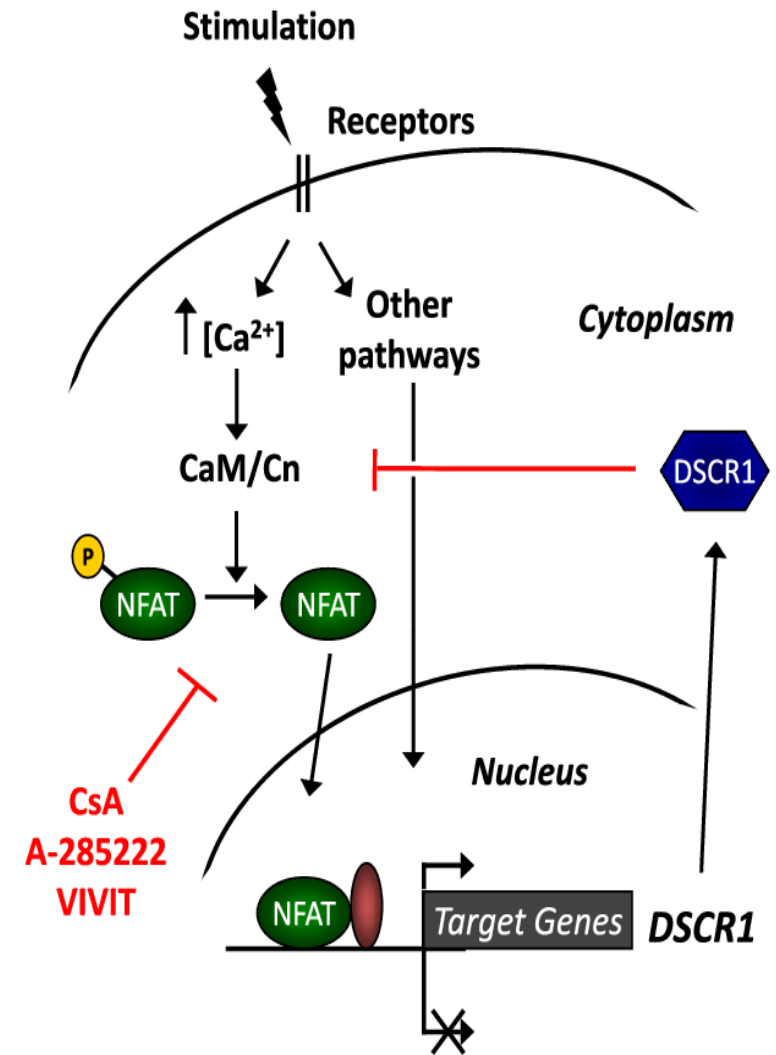
Additionally, glucocorticoid- receptor complexes increase I κ B expression, thereby curtailing activation of NF- κ B, which increases apoptosis of activated cells. Of central importance, key proinflammatory cytokines such as IL-1 and IL-6 are downregulated. T cells are inhibited from making IL-2 and proliferating. The activation of cytotoxic T lymphocytes is inhibited. Neutrophils and monocytes display poor chemotaxis and decreased lysosomal enzyme release. Therefore, glucocorticoids have broad antiinflammatory effects on multiple components of cellular immunity. In contrast, they have relatively little effect on humoral immunity.

Therapeutic Uses. There are numerous indications for glucocorticoids. They commonly are combined with other immunosuppressive agents to prevent and treat transplant rejection. High dose pulses of intravenous methylprednisolone sodium succinate (SOLU-MEDROL) are used to reverse acute transplant rejection and acute exacerbations of selected autoimmune disorders. Glucocorticoids also are efficacious for treatment of graft-versus-host disease in bone-marrow transplantation. Glucocorticoids are used routinely to treat autoimmune disorders such as rheumatoid and other arthritis, systemic lupus erythematosus, systemic dermatomyositis, psoriasis and other skin conditions, asthma and other allergic disorders, inflammatory bowel disease, inflammatory ophthalmic diseases, autoimmune hematologic disorders, and acute exacerbations of multiple sclerosis. In addition, glucocorticoids limit allergic reactions that occur with other immunosuppressive agents and are used in transplant recipients to block first-dose cytokine storm caused by treatment with muromonab-CD3 and to a lesser extent

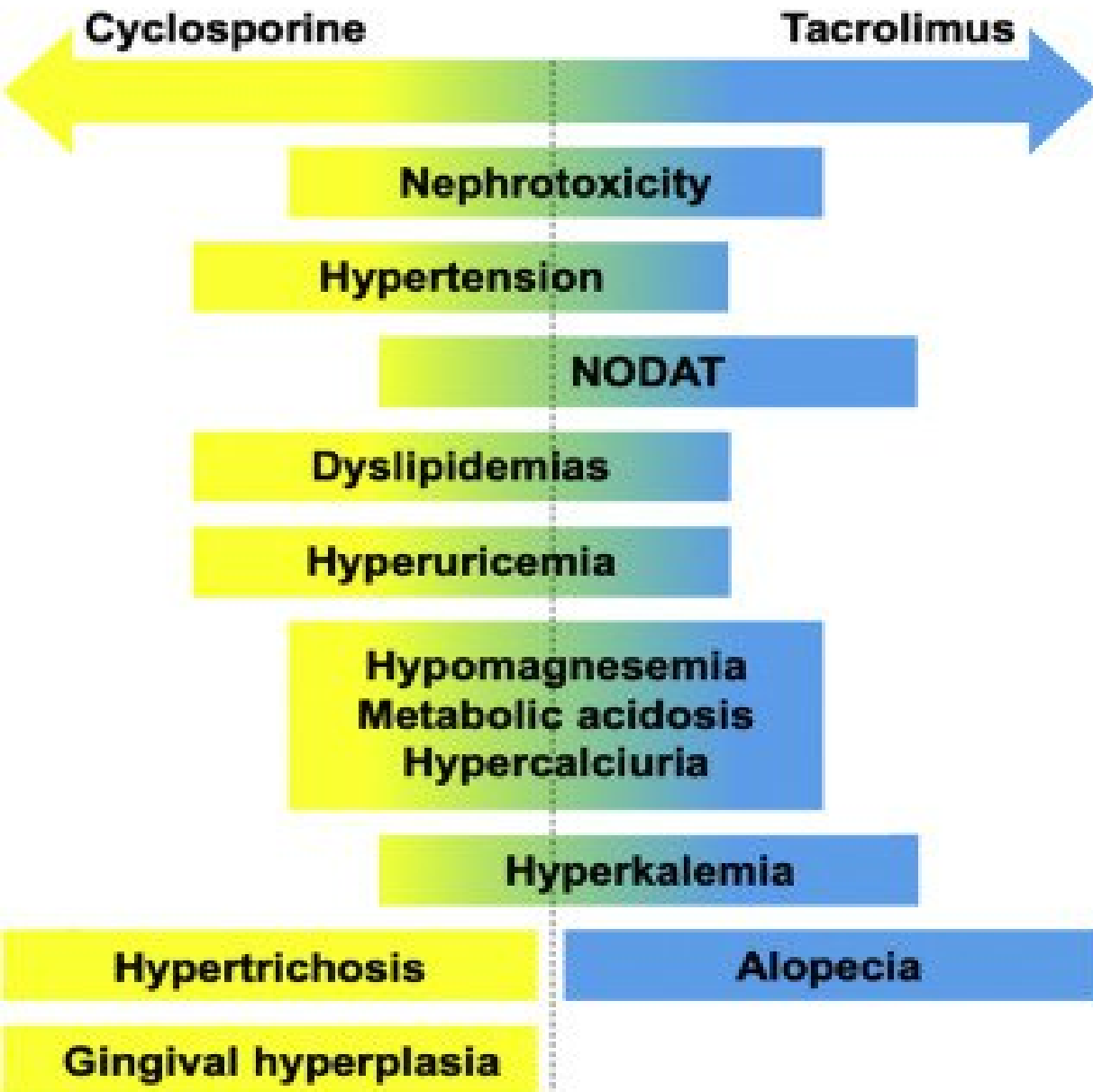
Toxicity. Unfortunately, the extensive use of steroids often results in disabling and life-threatening adverse effects. These effects include growth retardation in children, avascular necrosis of bone, osteopenia, increased risk of infection, poor wound healing, cataracts, hyperglycemia, and hypertension. The advent of combined glucocorticoid/cyclosporine regimens has allowed reduced doses of steroids, but steroid-induced morbidity remains a major problem in many transplant patients.

Calcineurin Inhibitors

the most effective immunosuppressive drugs in routine use are the calcineurin inhibitors, cyclosporine and tacrolimus, which target intracellular signaling pathways induced as a consequence of T-cell–receptor activation. Although they are structurally unrelated and bind to distinct, albeit related molecular targets, they inhibit normal T-cell signal transduction essentially by the same mechanism. Cyclosporine and tacrolimus do not act per se as immunosuppressive agents. Instead, these drugs bind to an immunophilin (cyclophilin for cyclosporine or FKBP-12 for tacrolimus), resulting in subsequent interaction with calcineurin to block its phosphatase activity. Calcineurin-catalyzed dephosphorylation is required for movement of a component of the nuclear factor of activated T lymphocytes (NFAT) into the nucleus. NFAT, in turn, is required to induce a number of cytokine genes, including that for interleukin-2 (IL-2), a prototypic T-cell growth and differentiation factor.



Calcineurin Inhibitor Toxicities



CYCLOSPORINE Since SANDIMMUNE and NEORAL differ in terms of their pharmacokinetics and are definitely not bioequivalent, their generic versions cannot be used interchangeably

After oral administration of cyclosporine (as NEORAL), the time to peak blood concentrations is 1.5 to 2 hours. Administration with food delays and decreases absorption. High and low-fat meals consumed within 30 minutes of administration decrease the AUC by approximately 13% and the maximum concentration by 33%.

Therapeutic Uses. Clinical indications for cyclosporine are kidney, liver, heart, and other organ transplantation; rheumatoid arthritis; and psoriasis. Cyclosporine usually is combined with other agents, especially glucocorticoids and either azathioprine or mycophenolate mofetil, and most recently, sirolimus. The dose of cyclosporine varies, depending on the organ transplanted and the other drugs used in the specific treatment protocol(s). The initial dose generally is not given before the transplant because of the concern about nephrotoxicity. Especially for renal transplant patients.

Cyclosporine reportedly is effective in Behcet's acute ocular syndrome, endogenous uveitis, atopic dermatitis,

Tacrolimus. Tacrolimus (PROGRAF, FK506) is a macrolide antibiotic produced by *Streptomyces tsukubaensis*.

Therapeutic Uses. Tacrolimus is indicated for the prophylaxis of solid-organ allograft rejection in a manner similar to cyclosporine and as rescue therapy in patients with rejection episodes despite “therapeutic” levels of cyclosporine. Toxicity. Nephrotoxicity, neurotoxicity (tremor, headache, motor disturbances, Seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes are all associated with tacrolimus use. As with cyclosporine, nephrotoxicity is limiting

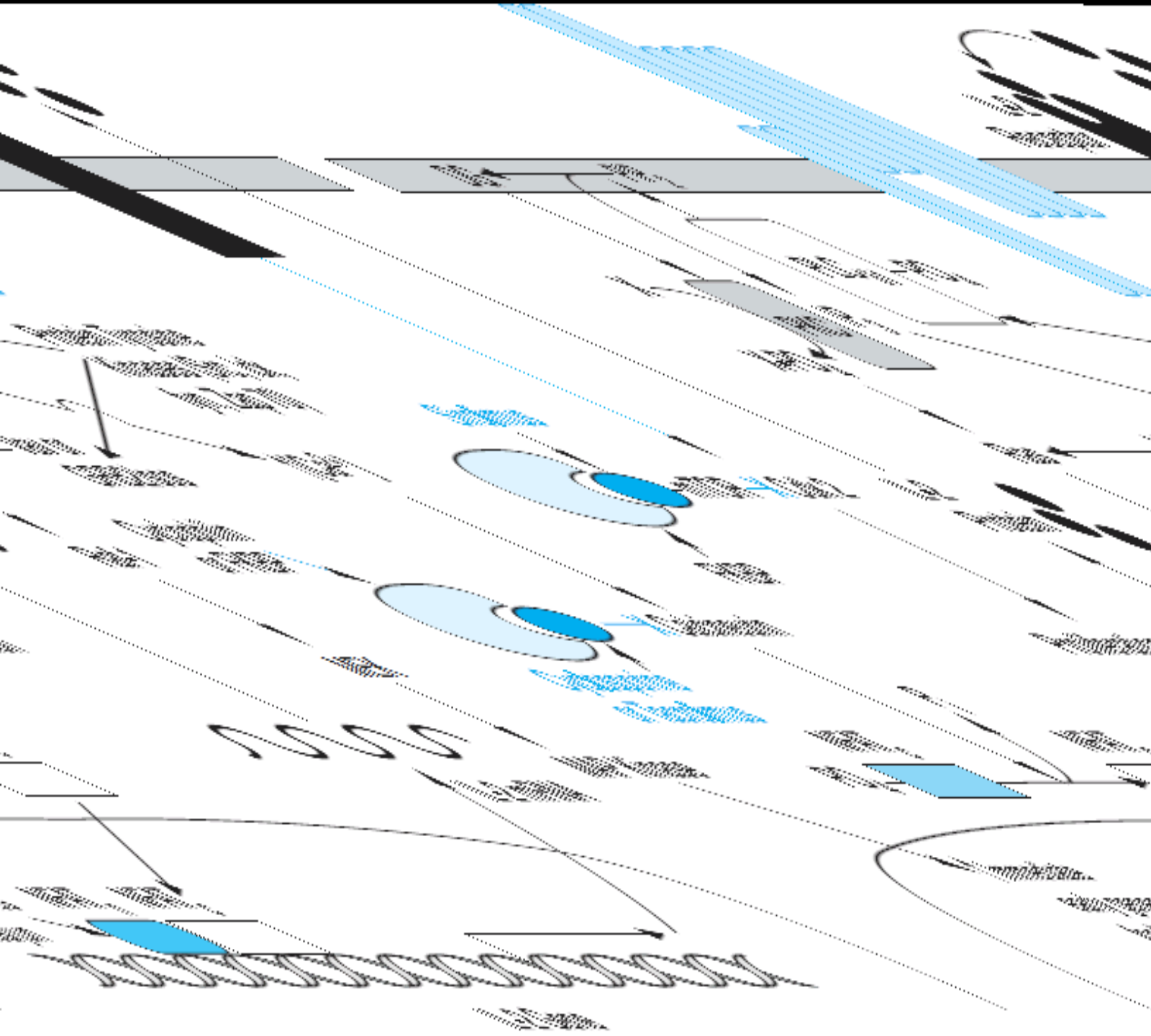
Antiproliferative and Antimetabolic Drugs

Sirolimus (rapamycin; RAPAMUNE)

Mechanism of Action. Sirolimus inhibits T-lymphocyte activation and Proliferation downstream of the IL-2 and other T-cell growth factor receptors. Like cyclosporine and tacrolimus, therapeutic action of sirolimus requires formation of a complex with an immunophilin, in this case FKBP-12. However, the sirolimus–FKBP-12 complex does not affect calcineurin activity. It binds to and inhibits a protein kinase, designated mammalian target of rapamycin (mTOR), which is a key enzyme in cell-cycle progression.

Therapeutic Uses. Sirolimus is indicated for prophylaxis of organ transplant rejection in combination with a calcineurin inhibitor and glucocorticoids. In patients experiencing or at high risk for calcineurin inhibitor–associated Nephrotoxicity, sirolimus has been used with glucocorticoids and mycophenolate mofetil to avoid permanent renal damage.

cyclosporine and sirolimus interact, and their administration should be separated by time. Dose adjustment may be required when sirolimus is coadministered with diltiazem or rifampin. The combination of sirolimus plus tacrolimus probably is more nephrotoxic than cyclosporine plus sirolimus.



Mechanisms of action of cyclosporine, tacrolimus, and sirolimus on T cells. Both cyclosporine and Tacrolimus bind to immunophilins (cyclophilin and FK506-binding protein [FKBP], respectively), forming a complex that binds the phosphatase calcineurin and inhibits the calcineurin-catalyzed dephosphorylation essential to permit movement of the nuclear factor of activated T cells (NFAT) into the nucleus. NFAT is required for transcription of interleukin-2 (IL-2) and other growth and differentiation-associated cytokines (lymphokines). Sirolimus (rapamycin) works at a later stage in T-cell activation, downstream of the IL-2 receptor. Sirolimus also binds FKBP, but the FKBP-sirolimus complex binds to and inhibits the mammalian target of rapamycin (mTOR), a kinase involved in cell-cycle progression (proliferation). TCR, T-cell receptor.

Everolimus. (ethyl-rapamycin)

is closely related chemically and clinically to sirolimus but has distinct Pharmacokinetics. The main difference is a shorter half-life.

Azathioprine

Azathioprine (IMURAN) is a purine antimetabolite. It is an imidazolyl derivative of 6-mercaptopurine.

Mechanism of Action. Following exposure to nucleophiles such as glutathione, azathioprine is cleaved to 6-mercaptopurine, which in turn is converted to additional metabolites which incorporated into DNA that inhibit de novo purine synthesis. Cell proliferation is thereby inhibited, impairing a variety of lymphocyte functions. Azathioprine appears to be a more potent immunosuppressive agent than 6-mercaptopurine, which may reflect differences in drug uptake or pharmacokinetic differences in the resulting metabolites.

Toxicity. The major side effect of azathioprine is bone marrow suppression, including leukopenia (common), thrombocytopenia (less common), and/or anemia (uncommon).

Other important adverse effects include increased susceptibility to infections (especially varicella and herpes simplex viruses), hepatotoxicity, alopecia, GI toxicity, pancreatitis, and increased risk of neoplasia

Drug Interactions. Xanthine oxidase, an enzyme of major importance in the catabolism of azathioprine metabolites, is blocked by allopurinol. If azathioprine and allopurinol are used concurrently, the azathioprine dose must be decreased to 25% to 33% of the usual dose.

Mycophenolate Mofetil, cellcept 500mg)(Mycophenolate Na, myfortic 360mg)

Mechanism of Action. Mycophenolate mofetil is a prodrug that is rapidly hydrolyzed to the active drug, mycophenolic acid (MPA), a selective, noncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). An important enzyme in the de novo pathway of guanine nucleotide synthesis. B and T lymphocytes are highly dependent on this pathway for cell proliferation, while other cell types can use salvage pathways; MPA therefore selectively inhibits lymphocyte proliferation and functions, including antibody formation, cellular adhesion, and migration.

- **Therapeutic Uses.** Mycophenolate mofetil is indicated for prophylaxis of transplant rejection, and it typically is used in combination with glucocorticoids and a calcineurin inhibitor, but not with azathioprine. Combined treatment with sirolimus is possible, although potential drug interactions necessitate careful monitoring of drug levels. For renal transplants, 1 g is administered orally or intravenously (over 2 hours) twice daily (2 g per day). A higher dose, 1.5 g twice daily (3 g per day), is recommended for African- American renal transplant patients and all cardiac transplant patients. Use of mycophenolate mofetil in other clinical settings is under investigation.
- **Toxicity.** The principal toxicities of mycophenolate mofetil are gastrointestinal and hematologic. These include leukopenia, diarrhea, and vomiting. There also is an increased incidence of some infections, especially sepsis associated with cytomegalovirus. Tacrolimus in combination with mycophenolate mofetil has been associated with devastating viral infections including polyoma nephritis.

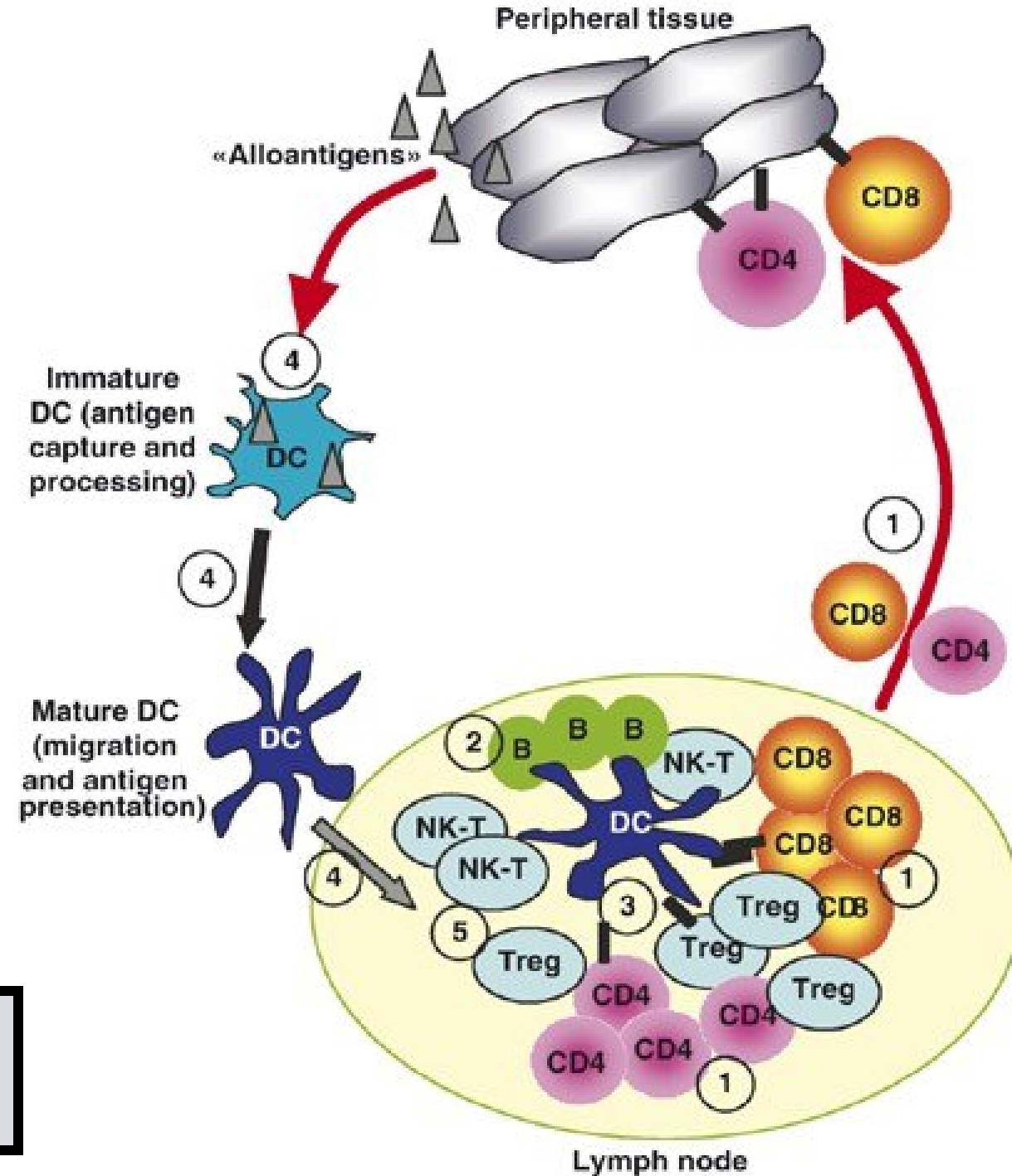
Antibodies

Both polyclonal and monoclonal antibodies against lymphocyte cell-surface antigens are widely used for prevention and treatment of organ transplant rejection. Polyclonal antisera are generated by repeated injections of human thymocytes (antithymocyte globulin, ATG) or lymphocytes (antilymphocyte globulin, ALG) into animals such as horses, rabbits, sheep, or goats, and then purifying the serum immunoglobulin fraction. Although highly effective immunosuppressive agents, these preparations vary in efficacy and toxicity from batch to batch. The advent of hybridoma technology to produce monoclonal antibodies was a major advance in immunology

Antithymocyte
globulin (ATG)

- Proposed mechanisms through which ATG can interfere with the immune response. (1) T-cell depletion in blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis; (2) induction of B-cell apoptosis; (3) modulation of key cell-surface molecules (adhesion and chemokine receptors) that mediate leukocyte/endothelium interactions; (4) Interference with DC functional properties (maturation and migration); and (5) Induction of Treg and NK-T cells

The distribution of cell types in the thymus includes T lymphocytes (72%), B lymphocytes (6%), and antigen-presenting cells (APC) and stromal cells (22%)



Antithymocyte Globulin.

Antithymocyte globulin is a purified gamma globulin from the serum of rabbits immunized with human thymocytes. It is provided as a sterile, freeze-dried product for intravenous administration after reconstitution with sterile water.

Mechanism of Action. Antithymocyte globulin contains cytotoxic antibodies that bind to CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, and HLA class I and II molecules on the surface of human T lymphocytes. The antibodies deplete circulating lymphocytes by direct cytotoxicity (both complement and cell-mediated) and block lymphocyte function by binding to cell surface molecules involved in the regulation of cell function.

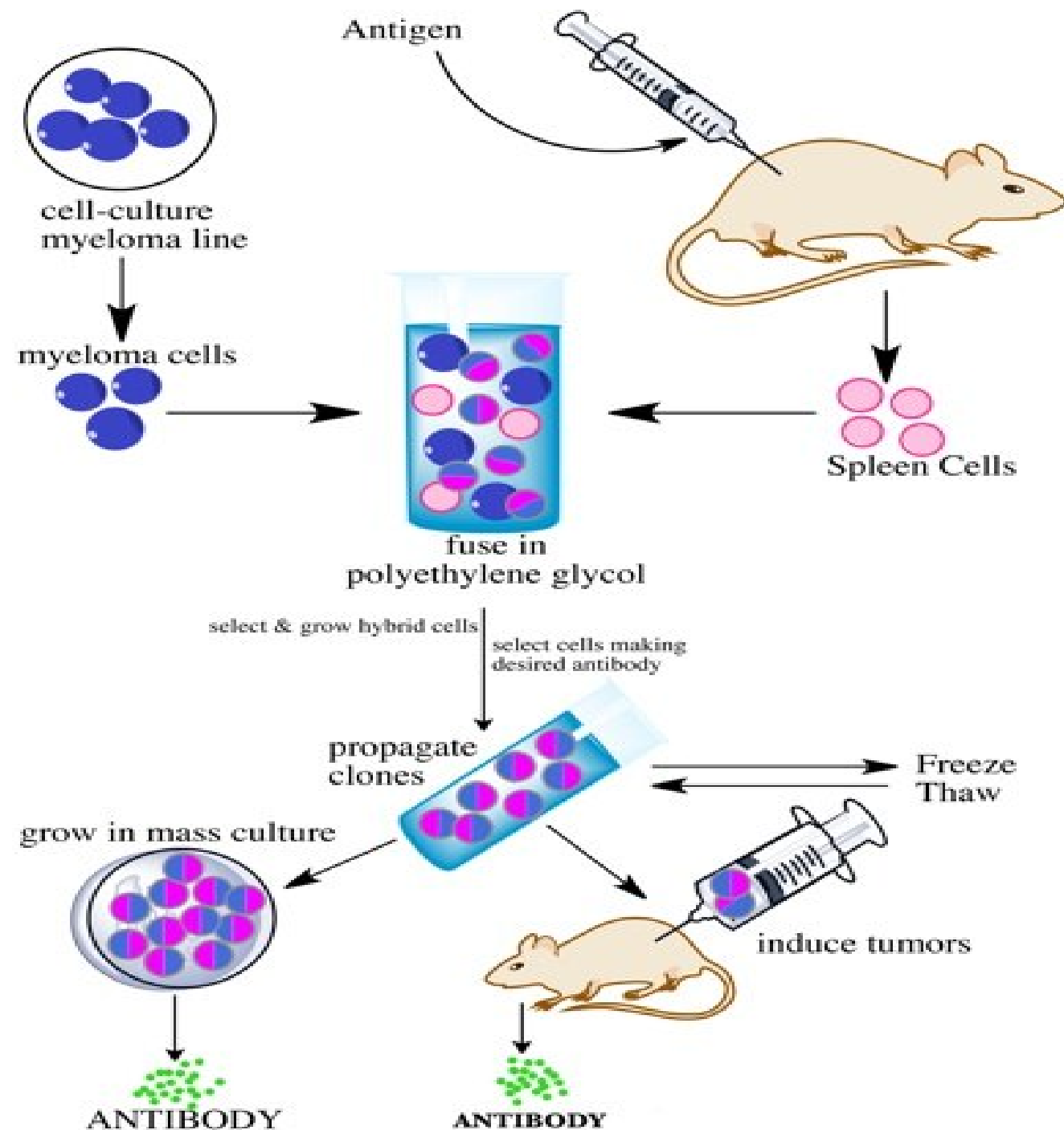
Therapeutic Uses. Antithymocyte globulin is used for induction Immunosuppression, although the only approved indication is in the treatment of acute renal transplant rejection in combination with other

Monoclonal antibodies

Production of monoclonal antibodies (mAb) is central to all efforts in the Diagnostics Discovery Laboratory (DDL). MAbs are monospecific antibodies that are exactly the same because they are made by identical immune cells that are clones of a unique parent cell.

MAb production begins with immunization of a mouse with an antigen. Several weeks after immunization, spleen cells are harvested. B cells in the spleen produce antibody but cannot grow in culture. The spleen cells are fused with cells of a myeloma line. The myeloma cells cannot produce antibody, but they will grow in culture. The two cells (spleen cells and myeloma cells) are fused together to produce a hybrid cell (hybridoma) that has the best properties of both cells—the hybridoma grows in culture and makes antibody.

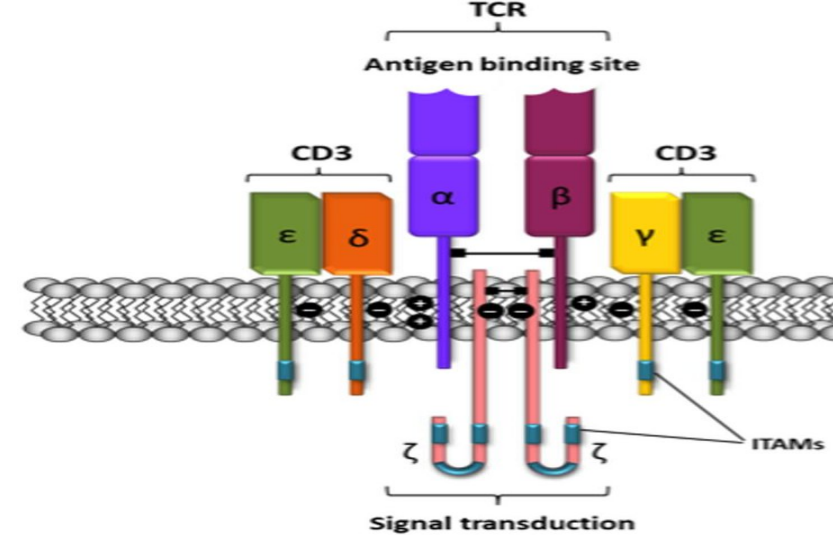
Hybridoma cells are cloned to ensure that all cells in the culture are making exactly the same mAbs. Once cloned, the cells can be mass produced in tissue culture to make large amounts of the mAbs. Cell lines made in this manner are immortal; they can be frozen for years.



Monoclonal Antibodies . Anti-CD3 Monoclonal Antibodies.

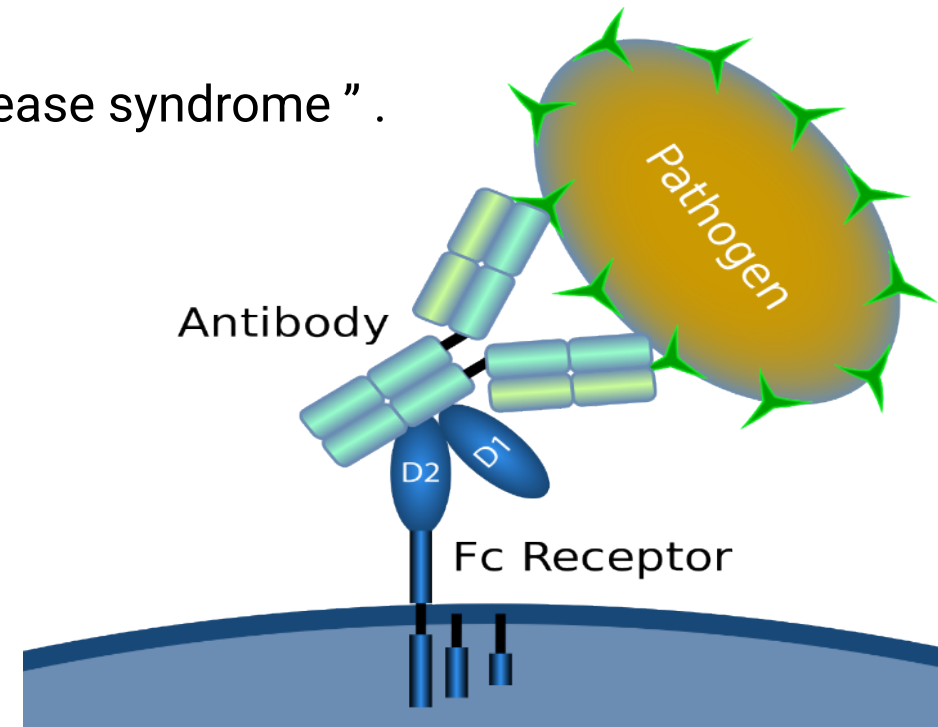
Antibodies directed at the ϵ chain of CD3, a trimeric molecule adjacent to the T-cell receptor on the surface of human T lymphocytes, have been used with considerable efficacy since the early 1980s in human transplantation. The original mouse IgG2a antihuman CD3 monoclonal antibody, muromonab-CD3, still is used to reverse glucocorticoid-resistant rejection episodes

Mechanism of Action. Muromonab-CD3 binds to the ϵ chain of CD3, a monomorphic component of the T-cell receptor complex involved in antigen recognition, cell signaling, and proliferation. Antibody treatment induces rapid internalization of the T-cell receptor, thereby preventing subsequent antigen recognition. Administration of the antibody is followed rapidly by depletion and extravasation of a majority of T cells from the bloodstream and peripheral lymphoid organs such as lymph nodes and spleen. This absence of detectable T cells from the usual lymphoid regions is secondary both to cell death following complement activation and activation-induced cell death and to margination of T cells onto vascular endothelial walls and redistribution of T cells to nonlymphoid organs such as the lungs. Muromonab-CD3 also reduces function of the remaining T cells, as defined by lack of IL-2 production and great reduction in the production of multiple cytokines, perhaps with the exception of IL-4 and IL-10.

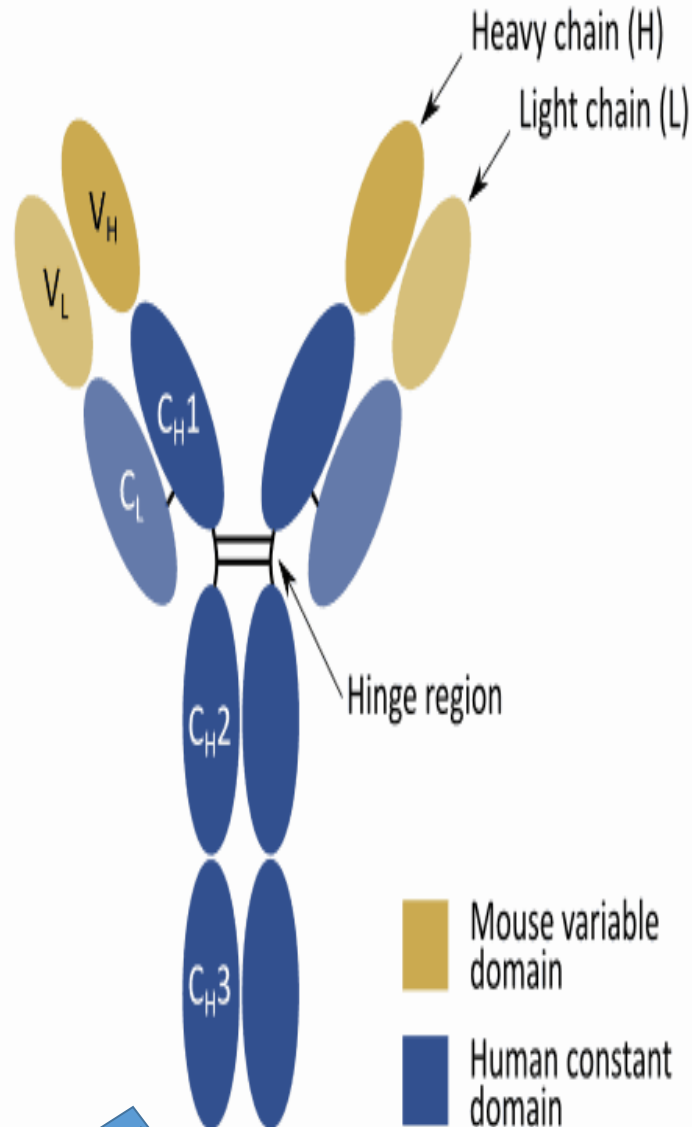
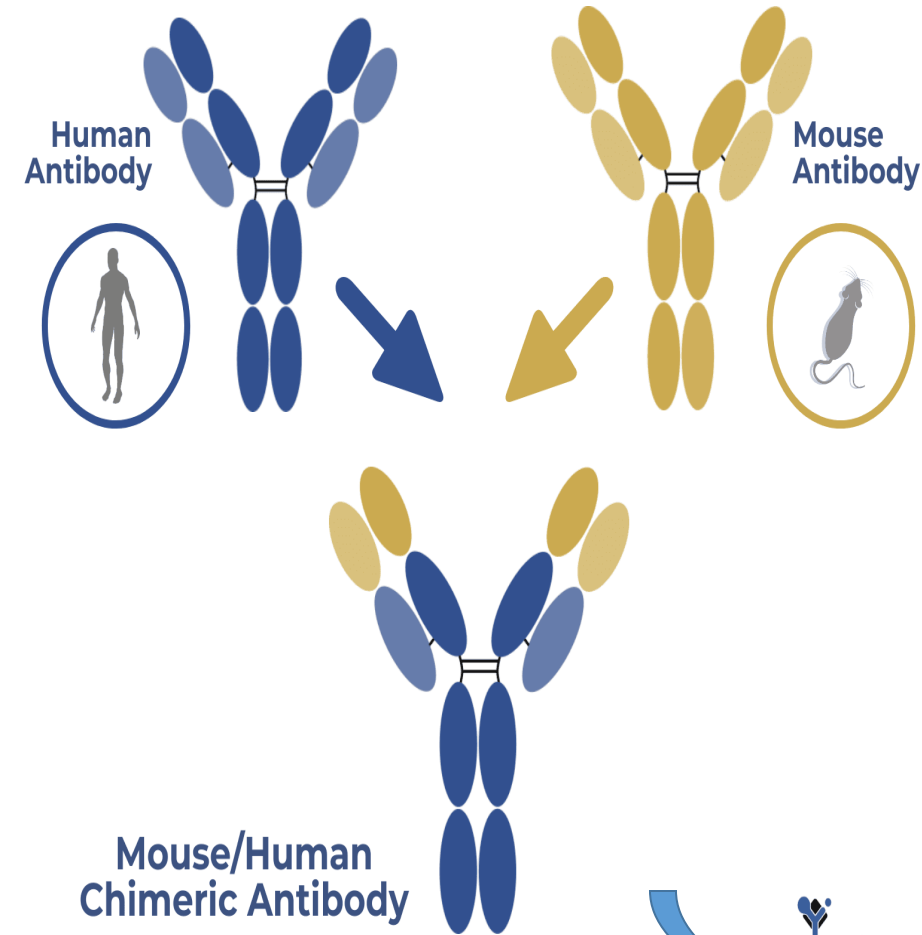


Therapeutic Uses . Muromonab-CD3 is indicated for treatment of acute organ transplant rejection. Muromonab-CD3 is provided as a sterile solution containing 5 mg per ampule. a single intravenous bolus (less than 1 minute) for 10 to 14 days. Antibody levels increase over the first 3 days and then plateau. Circulating T cells disappear from the blood within minutes of administration and return within approximately 1 week after termination of therapy. Repeated use of muromonab-CD3 results in the immunization of the patient against the mouse determinants of the antibody, which can neutralize and prevent its immunosuppressive efficacy. Thus, repeated treatment with the muromonab-CD3 or other mouse monoclonal antibodies generally is contraindicated. The use of muromonab-CD3 for induction and rejection therapy has diminished substantially in the past 5 years because of its toxicity and the availability of antithymocyte globulin.

Toxicity. The major side effect of anti-CD3 therapy is the “cytokine release syndrome” . The Syndrome typically begins 30 minutes after infusion of the antibody (but can occur later) and may persist for hours. Antibody binding to the T-cell receptor complex combined with Fc receptor (FcR)–mediated crosslinking is the basis for the initial activating properties of this agent. The syndrome is associated with and attributed to increased serum levels of cytokines (including tumor necrosis factor [TNF]- α , IL-2, IL-6, and interferon- γ),



What are chimeric antibodies



Most limitations of murine-based mAbs generally were overcome by the introduction of chimeric or humanized mAbs that lack antigenicity and have a prolonged serum $t_{1/2}$. Antibodies derived from transgenic mice carrying human antibody genes are labeled “humanized” (90%–95% human) or “fully human” (100% human); antibodies derived from human cells are labeled “human.” However, all three types of antibodies are of equal efficacy and safety. Chimeric antibodies generally contain about 33% mouse protein and 67% human protein and can still produce an antibody response that results in reduced efficacy and shorter $t_{1/2}$.

Anti-IL-2 Receptor (Anti-CD25) Antibodies. Daclizumab, a humanized murine complementarity determining region (CDR)/human IgG1 chimeric monoclonal antibody, and basiliximab (SIMULECT), a murine-human chimeric monoclonal antibody, have been produced by recombinant DNA technology. The composite daclizumab antibody consists of human (90%) constant domains of IgG1 and variable framework regions murine (10%).

Anti-TNF Reagents.

Infliximab.

is a chimeric anti-TNF- α monoclonal antibody containing a human constant region and a murine variable region. It binds with high affinity to TNF- α and prevents the cytokine from binding to its receptors.

Adalimumab (HUMIRA) is another anti-TNF product for intravenous use. This recombinant human IgG1 monoclonal antibody was created by phage display technology and is approved for use in rheumatoid arthritis.

Although not a monoclonal antibody, Etanercept (ENBREL) is mechanistically related to infliximab because it also targets TNF- α . Etanercept contains the ligand binding portion of a human TNF- α receptor fused to the Fc portion of human IgG1, and binds to TNF- α and prevents it from interacting with its receptors.

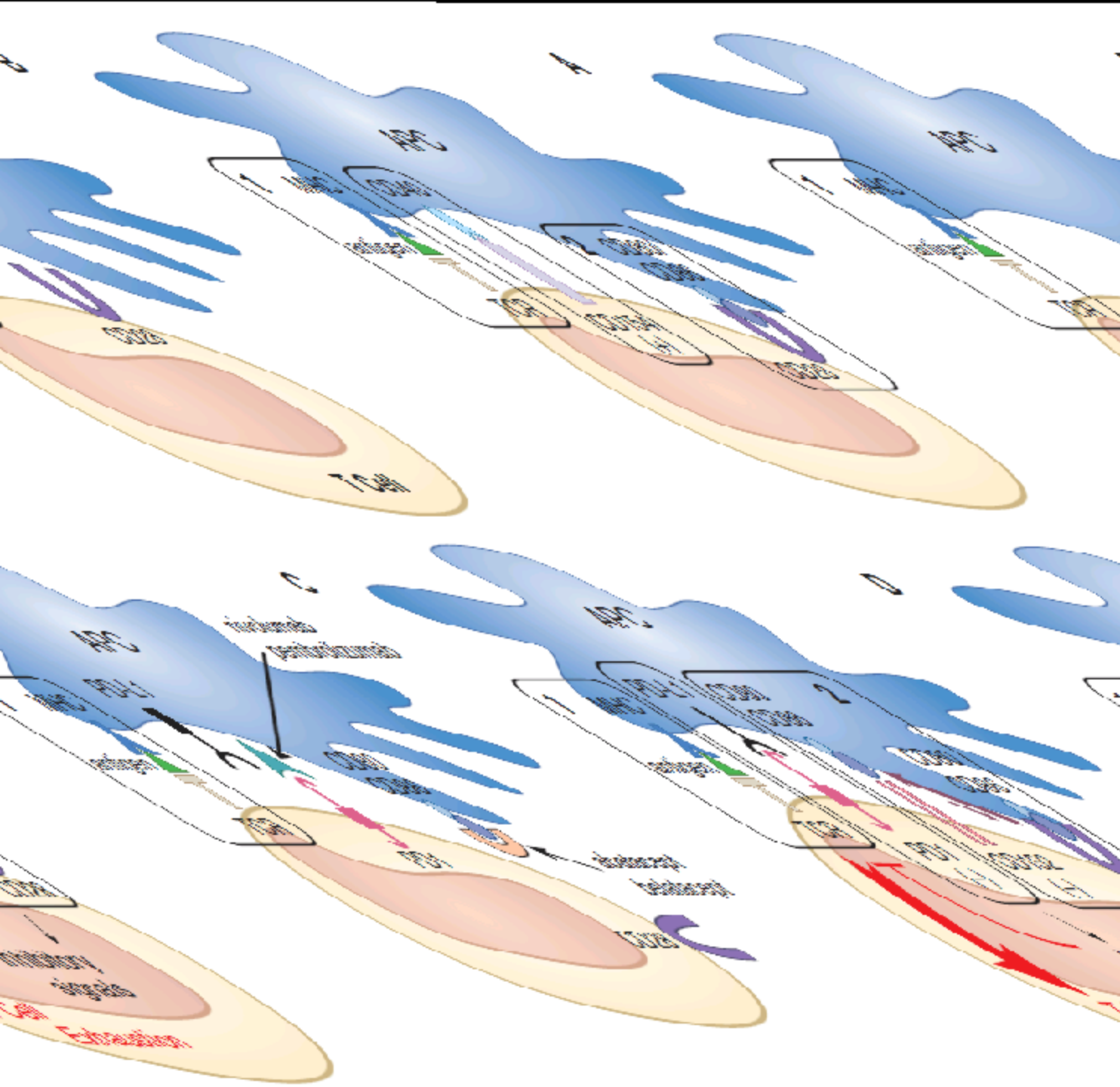
Tolerance

Immunosuppression has concomitant risks of opportunistic infections and secondary tumors. Therefore, the ultimate goal of research on organ transplantation and autoimmune diseases is to induce and maintain immunological tolerance, the active state of antigen-specific nonresponsiveness. Tolerance, if attainable, would represent a true cure for conditions discussed previously without the side effects of the various immunosuppressive therapies. The calcineurin inhibitors prevent tolerance induction in some, but not all, preclinical models. In these same model systems, sirolimus does not prevent tolerance and may even promote tolerance. In experimental animals, sirolimus promotes regulatory T cells, a subtype of T cells shown to suppress all immunity, and promotes tolerance. Studies in kidney transplant recipients showed that sirolimus spared regulatory T cells in the periphery, unlike calcineurin inhibitors, which reduced their percentage.

Costimulatory Blockade

Inhibition of the costimulatory signal has been shown to induce tolerance.

Abatacept is a fusion protein that contains the binding region of CTLA4 (CD152), which is a CD28 homolog, and the Fc region of the human IgG1. CTLA4-Ig competitively



presentation of an antigen ligand to the TCR and signaling by an additional “costimulatory” pair. A. The primary signal, signal 1, is the interaction of the TCR with the MHC-antigen complex on the APC. Activation requires a second, costimulatory interaction. B. Signal 2, the costimulatory interaction between CD28 on the T cell (the costimulatory receptor) and the costimulatory ligand on the APC, CD80/CD86, leads to T-cell activation. Additional costimulatory signals, such as the interaction of CD154 with CD40 on the APC, can further enhance T-cell activation (+). In the absence of costimulation, a T cell can become anergic or unresponsive. C. Additional APC–T-cell interactions can occur after T-cell activation, and some can be inhibitory, providing immune checkpoints that are important for reducing autoimmunity and for regulating the size and extent of immune responses. For example, the interaction of CD152 (CTLA4) with CD80/86 produces inhibitory signals that attenuate T-cell activation and proliferation (-). CD28 and CD152 compete for binding to CD80/CD86. As the figure suggests, the affinity of CD152 for CD80/CD86 exceeds that of CD28, and the equilibrium lies toward the formation of the inhibitory signaling complex, CD152-CD80/CD86. T cells may express varying amounts of another important modifier, PD1 (CD279). When

IMMUNOSTIMULATION

In contrast to immunosuppressive agents that inhibit the immune response in transplant rejection and autoimmunity, a few immunostimulatory drugs have been developed with applicability to infection, immunodeficiency, and cancer. Problems with such drugs include systemic (generalized) effects at one extreme or limited efficacy at the other. Nonspecific immunoglobulins or highly specific immunoglobulins may be provided based upon the indication.



Introduction

Passive immunization

Transfer person's immunity to another:

From mother to infant (placenta/ breast milk)

Immunoglobulin (IG)

Active immunization :

Immun system stimulation to produce an Ab

Permanent

Methods

Post infection :memory B cells

Post vaccination



Immunization

- Immune Globulin . Passive immunization is indicated when an individual is deficient in antibodies because of a congenital or acquired immunodeficiency, when an individual with a high degree of risk is exposed to an agent and there is inadequate time for active immunization (e.g., measles, rabies, hepatitis B), or when a disease is already present but can be ameliorated by passive antibodies (e.g., botulism, diphtheria, tetanus). Passive immunization may be provided by several different products, Nonspecific immunoglobulins or highly specific immunoglobulins may be provided based upon the indication.



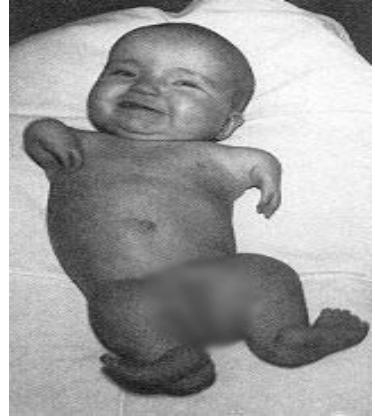
Immunostimulants

Levamisole. Levamisole was synthesized originally as an anthelmintic but appears to “restore” depressed immune function of B lymphocytes, T lymphocytes, monocytes, and macrophages. Its only clinical indication is as adjuvant therapy with 5-fluorouracil after surgical resection in patients with Dukes’ stage C colon cancer

Thalidomide.

Is best known for the severe, life-threatening birth defects it caused when administered to pregnant women. For this reason, it is available only under a restricted distribution program and can be prescribed only by specially licensed physicians who understand the risk of teratogenicity if thalidomide is used during pregnancy. Thalidomide should never be taken by women who are pregnant or who could become pregnant while taking the drug. Nevertheless, it is indicated for the treatment of patients with erythema nodosum leprosum and also is used in conditions such as multiple myeloma. Its mechanism of action is unclear. Reported immunologic effects vary substantially under different conditions. For example, thalidomide has been reported to decrease circulating TNF- α in patients with erythema nodosum leprosum, but to increase it in patients who are HIV-seropositive. Alternatively, it has been suggested that the drug affects angiogenesis. The anti- TNF- α effect has led to its evaluation as a treatment for severe, refractory rheumatoid arthritis

Linalidomid- myelodysplastic syndrome, multiple Myeloma, mantle cell lymphoma



Recombinant Cytokines .

Interferons. Although interferons (alpha, beta, and gamma) initially were identified by their antiviral activity, these agents also have important immunomodulatory activities. The interferons bind to specific cell-surface receptors that initiate a series of intracellular events: induction of certain enzymes, inhibition of cell proliferation, and enhancement of immune activities, including increased phagocytosis by macrophages and augmentation of specific cytotoxicity by T lymphocytes. Recombinant interferon alfa-2b (IFN- α 2, INTRON A) is obtained from *Escherichia coli* by recombinant expression.

Interferon alfa-2b is indicated in the treatment of a variety of tumors, including hairy cell leukemia, malignant melanoma, follicular lymphoma, and AIDS-related Kaposi's sarcoma. In addition, it is supplied in combination with ribavirin (REBETRON) for treatment of chronic hepatitis C in patients with compensated liver function not treated previously with interferon alfa-2b or who have relapsed after interferon alfa-2b therapy. Interferon gamma-1b (ACTIMMUNE) is a recombinant polypeptide that activates phagocytes and induces their generation of oxygen metabolites that are toxic to a number of microorganisms. It is indicated to reduce the frequency and severity of serious infections associated with chronic granulomatous disease.

Interferon beta-1a (AVONEX, REBIF), a 166–amino acid recombinant glycoprotein, and interferon beta-1b (BETASERON), a 165–amino acid recombinant protein, have antiviral and immunomodulatory properties. They are FDA approved for the treatment of relapsing and relapsing remitting multiple sclerosis to reduce the frequency of clinical exacerbations. The mechanism of their action in multiple sclerosis is unclear.

Interleukin-2. (Aldesleukin) Human recombinant interleukin-2 is produced by recombinant DNA technology in *E. coli*. This recombinant form differs from native IL-2 in that it is not glycosylated. Aldesleukin has the following in vitro biologic activities of native IL-2: enhancement of lymphocyte proliferation and growth of IL-2–dependent cell lines; enhancement of lymphocyte-mediated cytotoxicity and killer cell activity; and induction of interferon- γ activity. Aldesleukin is indicated for the treatment of adults with metastatic renal cell carcinoma and melanoma.