Module 04 COURSE: B.PHARMACY SUBJECT: PHARMACOLOGY-III, CODE: BP602
Module 04 CHEMOTHERAPY

COURSE: B.PHARMACY
SEMESTER: 6TH
SUBJECT: PHARMACOLOGY-III

CODE: BP602T
SUBJECT TEACHER: MS. KIRAN SAINI

- **Chemotherapy**
- Urinary tract infections and sexually transmitted diseases. Chemotherapy of malignancy
- **immunopharmacology**
- Immunostimulants, Immunosuppressant, Protein drugs, monoclonal antibodies, target drugs to antigen, biosimilars

DRUGS USED IN URINARY TRACT INFECTION

 URINARY ANTISEPTICS Urinary antiseptics are oral agents that exert antibacterial activity in the urine o but have little or no systemic antibacterial effects. Their usefulness is limited to lower urinary tract infections.

 DRUGS USED AS URINARY ANTISEPTICS Nitrofurantoin Methenamine Nalidixic acid

 NITROFURANTOIN: Primarily bacteriostatic Activity limited to E. coli

Mechanism of Action: Sensitive bacteria reduce the drug to an active agent that inhibits various enzymes damage bacterial DNA. Antibacterial concentration is not attained in blood or tissues. Not to be used with Probenecid, azotemic patients: interferes with tubular secretion of drug.

 NITROFURANTOIN Adverse Effects: ↑Gastrointestinal Intolerance: Nausea, epigastric pain, diarrhoea ↑Hypersensitivity : fever, chills ↑Peripheral neuritis and other neurological effects with long term use ↑Hematologic disorders: leukopenia, granulocytopenia, Hemolytic anemia in G6PD deficient patients

NITROFURANTOIN: USES Treatment for uncomplicated lower urinary tract infection.Not associated with prostatitis. Supportive long term therapy. Long term porphylaxis. Following catheterization, instrumentation, in women with recurrent cystitis

METHENAMINE (HEXAMINE) Prodrug Mechanism of Action: Decomposes slowly in acidic urine(Ph 5.5 or less) to release formaldehyde which inhibits all bacteria. No antimicrobial activty in blood and tissues. Needs to be administered with mandelic acid or hippuric acid

Use As Methenamine mandelate in Chronic and resistant UTI not involving kidneys. Not Effective for Acute UTI Catheter prophylaxis

Side Effects: Gastritis Chemical cystitis, hematuria Occasional CNS Symptoms

NALIDIXIC ACID: Nonfluorinated quinolone

Bactericidal. Mechanism of Action:Inhibit the replication of bacterial by interfering with the action of DNA gyrase during bacterial growth and development. Resistance Develops rather rapidly

Uses: Second Line Drugs for UTI Recurrent cases- On the basis of Sensitivity Reports ¬ ADR: Infrequent: GI upset, rashes ¬ Headache drowsiness, vertigo, visual disturbances ¬ Seizures in children, Nausea ,Vomiting and abdominal pain, Photosensitivity, urticaria and Fever Contraindicated in infants

URINARY TRACT INFECTION: TREATMENT Mostly gram negative organisms ↑Acute episode: single organism, ↑Chronic/recurrent: mixed infection Acute Infection: largely self limiting ↑High urine flow rate ↑Frequent bladder voiding ↑Lower UTI: Single Dose Antibiotic or 3 Days Course Suffice ↑Upper UTI: Longer Treatment

URINARY TRACT INFECTION: TREATMENT Bacterial Investigation very important Smaller than usual doses required for treatment of Lower UTI. Upper UTI requires normal doses as for any other infection. Least Toxic and cheaper drugs should be chosen, for proper duration. Drug should not disrupt normal gut and perineal flora ϖFrequent recurrences: chronic suppressive treatment with co-trimoxazole, nitrofurantoin, methenamine, cephalexin,

STATUS OF ANTIMICROBIAL AGENTS OTHER THAN URINARY ANTISEPTICS IN UTI ESulfonamides: E Decreased dependability for acute UTI; E Not used as single drug; employed for suppressive or prophylactic therapy E Cotrimoxazole: E Declined responsiveness E Employed for acute UTI (broad spectrum) E Prophylaxis for recurrent cystitis in women, catheterized patients EQuinolones: E FQs (norfloxacin and ciprofloxacin) EAmpicillin/Amoxicillin E Frequently used in the past E Higher failure and relapse rates E

Amoxicillin + Clavulanic Acid used these days E Coamoxiclav+ Gentamycin: initial treatment for acute pyelonephritis

STATUS OF ANTIMICROBIAL AGENTS OTHER THAN URINARY ANTISEPTICS IN UTI ECephalosporin: E Increasing use especially in nosocomial Klebsiella and Proteus infection E Employed on the basis of sensitivity report, employed for community acquired infections as well E Cephalexin: alternative for prophylaxis of recurrent UTI, especially women likely to get pregnant E Gentamycin: E Sensitive against Pseudomonas E Narrow margin of safety, parenteral administration: bacterial sensitivity awaited

URINARY PH AND ANTI MICROBIAL AGENTS Acidic urine required for Methenamine Inadequate response, in complicated cases: measurement and correction of urinary pH may be attempted Urease positive Proteus infections: drugs acting at higher pH should be administered Favourable urinary pH for antimicrobial action Acidic Alkaline pH immaterial Nitrofurantion Cotrimoxazole Chloramphenicol Methenamine Aminoglycosides Ampicillin Cloxacillin Cephalosporin Fluoroquinolone

URINARY TRACT INFECTIONS (UTI)
URINARY INFECTION IN PATIENTS WITH RENAL IMPAIRMENT ¬ Difficult to treat Drugs Contraindicated:Methamine mandelate, Tetracyclines, Cephalosporin (some) Drugs avoided: Nitrofurantion, Nalidixic acid, Aminoglycosides Potassium salts and acidifying agents contraindicated

PROPHYLAXIS FOR UTI This may be given when: (a) Women of child bearing age have recurrent cystitis. (b) Catheterization or instrumentation inflicting trauma to the lining of the urinary tract is performed; bacteremia frequently occurs and injured lining is especially susceptible. (c) Indwelling catheters are placed. (d) Uncorrectable abnormalities of the urinary tract are present. (e) Inoperable prostate enlargement or other chronic obstruction causes urinary stasis.

Methenamine (Hexamine)

It is hexamethylene-tetramine; inactive as such; decomposes slowly in acidic urine to release formaldehyde which inhibits all bacteria. This drug exerts no antimicrobial activity in blood and tissues, including kidney parenchyma. Acidic urine is essential for its action; urinary pH

must be kept below 5.5 by administering some organic acid which is excreted as such, e.g. mandelic acid or ascorbic acid. Methenamine is administered in enteric coated tablets to protect it from decomposing in gastric juice.

Adverse effects Gastritis can occur due to release of formaldehyde in stomach-patient compliance is often poor due to this . Chemical cystitis and haematuria may develop with high doses given for long periods. CNS symptoms are produced occasionally. Methenamine mandelate is contraindicated in renal failure

Treatment for (STD) HIV Infection

Prior to approval of zidovudine in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients rather than on inhibiting HIV itself.

This multi drug regimen is commonly referred to as ehighly active antiretroviral therapy,â€ or HAART. There are five classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors and the integrase inhibitors. The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor or an NNRTI. Selection of the appropriate combination is based on

1) avoiding the use of two agents of the same nucleoside analog,

2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the Svirus,

3) patient factors such as disease symptoms and concurrent illnesses,

4) impact of drug interactions,

5) ease of adherence to a frequently complex administration regimen. The goals of therapy are to maximally and durably suppress viral load replication, to restore and preserve immunologic function, to reduce HIV-relatedmorbidity and mortality, and to improve quality of life.

Drugs used to prevent HIV from replicating. [NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

Nrtis Used to Treat HIV Infection

A. Overview of NRTIs

Mechanism of action: Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3'-hydroxyl group. **Once they enter cells, they are phosphorylated by a variety of cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by virus reverse transcriptase**. Because the 3'-hydroxyl group is not present, a 3'-5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated. Drugs used to prevent HIV from replicating. [NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

VI. Nrtis Used to Treat HIV Infection

Pharmacokinetics: The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir,* which is metabolized by alcohol dehydrogenase and glucuronyl transferase. Dosage adjustment is required when the creatinine clearance drops below 50 mL/min.

Adverse effects: Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as *zalcitabine, didanosine,* and *stavudine,* have a greater affinity for the mitochondrial DNA polymerase, leading to such toxicities as peripheral neuropathy, pancreatitis, and lipoatrophy. When more than one NRTI is given, care is taken not to have overlapping toxicities. All the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis.

Drug interactions: Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for *zidovudine* and *tenofovir.*

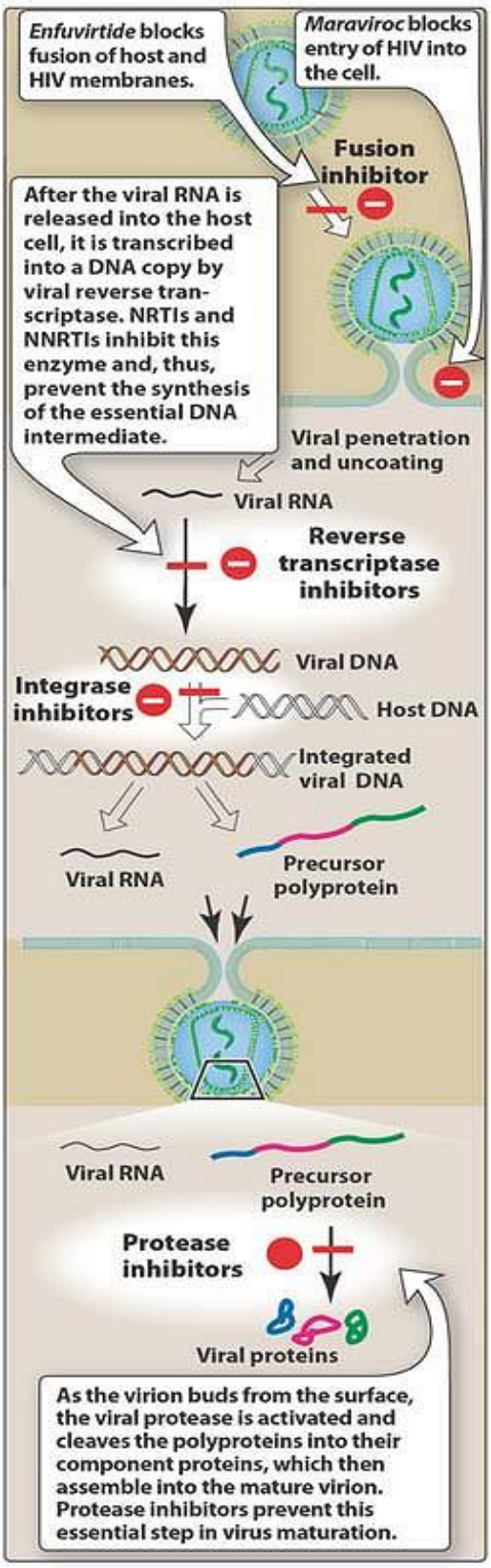
Resistance: NRTI resistance is well characterized, and the most common mutation is the mutation at viral codon which confers a high degree of resistance to *lamivudine* but, more importantly, restores sensitivity to zidovudine and tenofovir. Cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine and adenosine)

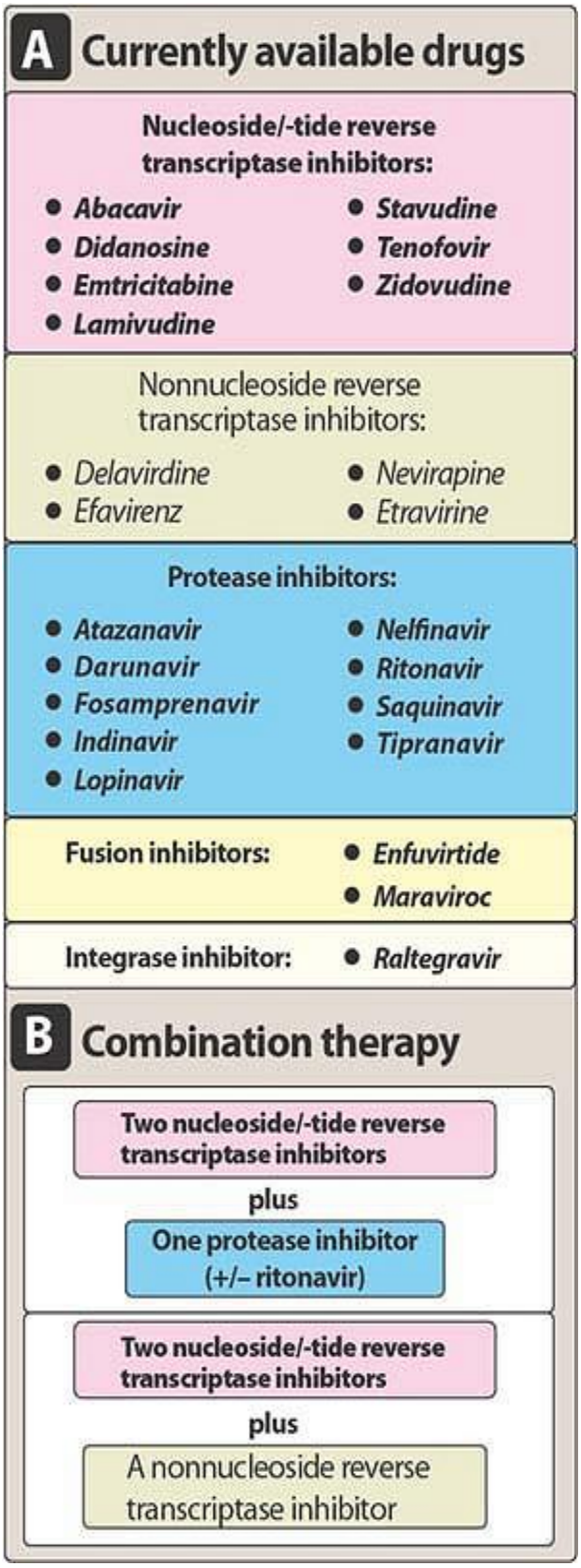
Highly active antiretroviral therapy (HAART).

B. Zidovudine (AZT)

Approved in 1987, the first agent available for treatment of HIV infection is the pyrimidine analog, 3'-azido- 3'-deoxythymidine (AZT). AZT has the generic name of zidovudine [zye-DOE-vyoo-deen]. AZT is approved for use in children and adults and to prevent prenatal

infection in pregnancy. It is also recommended for prophylaxis in individuals exposed to HIV infection. The drug is well absorbed after oral administration. If taken with food, peak levels may be lower, but the total amount of drug absorbed is not affected. Penetration across the blood-brain barrier is excellent, and the drug has a half-life of 1 hour. The intracellular half-life, however, is approximately 3 hours. Most of the AZT is glucuronylated by the liver and then excreted in the urine.





38.16 Highly active antiretroviral therapy (HAART).

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Anticancer Drugs

I. Overview

It is estimated that 25 percent of the population of the United States will face a diagnosis of cancer during their lifetime, with 1.3 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness

II. Principles of Cancer Chemotherapy

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication ”for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA Synthesis. Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects.

A. Treatment strategies

Goal of treatment:

- ✓ The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell.
- ✓ If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life.
- ✓ This allows the individual to maintain a normal existence, with the cancer thus being treated as a chronic disease. In either case, the neoplastic cell burden is

initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, or a combination of these treatment modalities.

CLASSI FICATION

A. Drugs acting directly on cells (Cytotoxic drugs)

1. Alkylating agents

Nitrogen mustards: Mechlorethamine (Mustine HCl), Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan

Ethylenimine Thio-TEPA

Alkyl sulfonate Busulfan

Nitrosoureas Carmustine (BCNU), Lomustine (CCNU)

Triazine Dacarbazine (OTIC)

2. Antimetabolites**: Folate antagonist** Methotrexate (Mtx)

Purine antagonist6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), Azathioprine, Fludarabine

Pyrimidine antagonist: 5-Fluorouracil (5-FU), Cytarabine, (cytosine arabinoside)

3. Vinca alkaloids Vincristine (Oncovin), Vinblastine

4. Taxanes Paclitaxel, Docetaxel

5. Epipodophyllotoxin: Etoposide

6. Camptothecin analogues: Topotecan, Irinotecan

7. Antibiotics: Actinomycin D, (Dactinomycin), Doxorubicin, Daunorubicin (Rubidomycin)

Mitoxantrone Bleomycins, Mitomycin C

8. Miscellaneous Hydroxyurea, Procarbazine, L-Asparaginase, Cisplatin Carboplatin Imatinib

B. Drugs altering hormonal m ilieu

1 . Glucocorticoids Prednisolone and others

2. Estrogens Fosfestrol, Ethinylestradiol

3. Selective estrogen Tamoxifen,

receptor modulators Toremifene

4. Selective estrogen receptor down regulators: Fulvestrant
5. Aromatase inhibitors Letrozole, Anastrozole, Exemestane
6. Antiandrogen Flutamide, Bicalutamide
7. 5-a reductase inhibitor Finasteride, Dutasteride
8. GnRH analogues Nafarelin, Triptorelin
9. Progestins Hydroxyprogesterone acetate, etc.

ALKYLATI NG AGE NTS

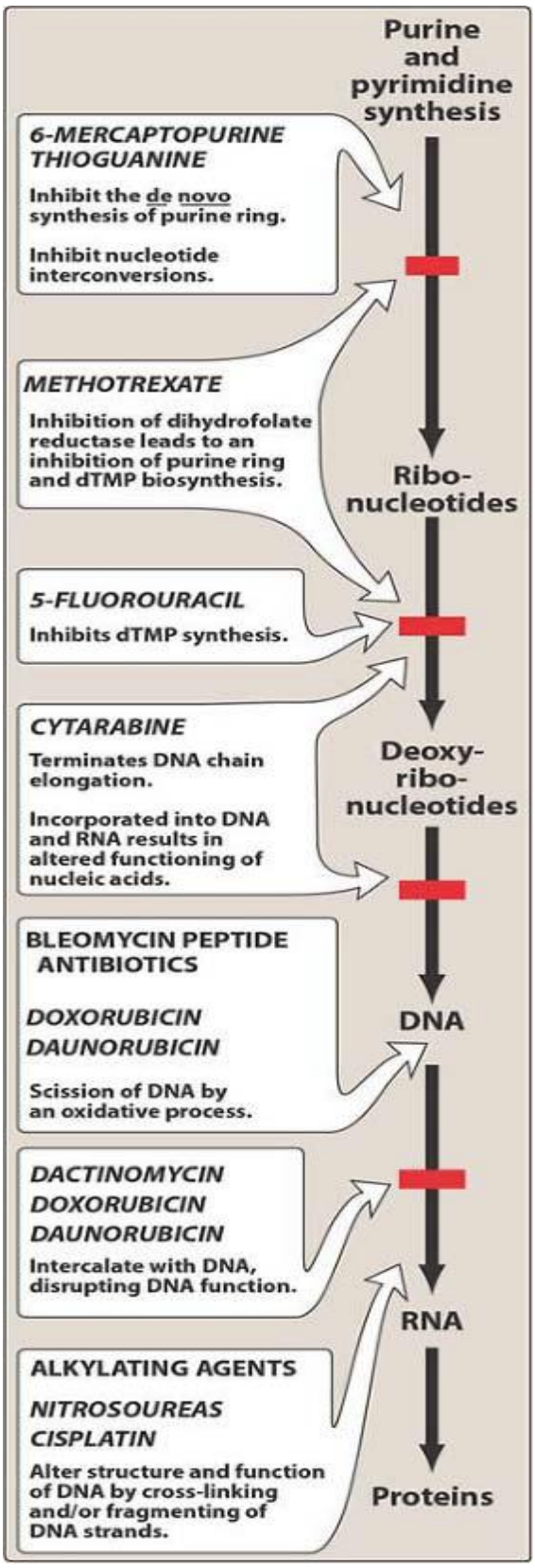
These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. The position 7 of guanine residues in DNA is especially susceptible, but other molecular sites are also involved. Alkylation results in cross linking/ abnormal base pairing/ scission of DNA strand. Cross linking of nucleic (like ionizing radiation) actions.

Mechlorethamine (Mustine HCI) It is the first nitrogen mustard; highly reactive and local vesicant-c an be given only by i.v. route. It produces many acute effects like nausea, vomiting and haemodynamic changes. Extravasation during i.v. injection may cause sloughing.

ANTI MET ABO LITES

These are analogues related to normal components of DNA or of coenzymes involved in nucleic acid synthesis. They competitively inhibit utilization of the normal substrate or get themselves incorporated forming dysfunctionalmacromolecules.

1. Folate antagonist Methotrexate (Mtx) It is one of the oldest and highly efficacious antineoplastic drugs**; inhibits dihydrofolate reductase (DHFRase)-blocking the conversion of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA)** which is an essential coenzyme required for one carbon transfer reactions in de novo purine synthesis and amino acid interconversions. Methotrexate has cell cycle specific actionkills cells in S phase; primarily inhibits DNA synthesis, but also affects RNA and protein synthesis. It exerts major toxicity on bone marrow-low doses given repeatedly cause megaloblastic anaemia, but high doses produce pancytopenia. Desquamation and bleeding may occur in g.i.t.



2. Purine antagonists

Mercaptopurine (6-MP) and thioguanine (6-TG) These are highly effective antineoplastic drugs. They are converted in the body to the corresponding monoribonucleotides ***which inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides.***

There is also feedbackinhibition of de novo purine synthesis. They are especially useful in childhood acute leukaemia, choriocarcinoma and have been employed in some solid tumours as well. In acute leukaemia, both have been used in combination regimens to induce remission and 6-MP to maintain it as well.

Pyrimidine antagonists: Pyrimidine analogues have varied applications as antineoplastic, antifungal and antipsoriatic agents.

Fluorouracil U, -FU) is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate, ***which inhibits thymidylate synthase and blocks the conversion of deoxyuridilic acid to deoxythymidylic acid***. Selective failure of DNA synthesis occurs due to non-availability of thymidylate: thymidine can partially reverse its toxicity. Fluorouracil itself gets incorporated into nucleic acids and this may contribute to its toxicity. Even resting cells are affected, though rapidly multiplying ones are more susceptible.

VINCA ALKALOIDS

These *are mitotic inhibitors, bind to microtubular protein-'tubulin', prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle and interfere with cytoskeletal function.* The chromosomes fail to move apart during mitosis: metaphase arrest occurs. They are cell cycle specific and act in the mitotic phase. Vincristine and vinblastine, though closely related chemically, have somewhat different spectrum of anti tumour activity and toxicity.

Vincristine (oncovin) It is a rapidly acting drug, very useful for inducing remission in childhood acute leukaemia, but is not good for maintenance therapy. Other indications are lymphosarcoma, Hodgkin's disease, Wilms' tumour, Ewing's sarcoma and carcinoma lung. Prominent adverse effects are peripheral neuropathy and alopecia. Bone marrow depression is minimal.

TAXANES

Paclitaxel It is a complex diterpin taxane obtained from bark of the Western yew tree, which exerts cytotoxic action by a novel mechanism. It enhances polymerization of tubulin: a mechanism opposite to that of vinca alkaloids. The microtubules are stabilized and their depolymerization is prevented. This stability results in inhibition of normal dynamicreorganization of the microtubule network that is essential for vital interphase and

mitotic functions. Abnormal arrays or 'bundles' of microtubules are produced throughout the cell cycle.

IMMUNOSUPPRESSANT DRUGS

These are drugs which inhibit cellular /humoral or both immune response and have their major use in organ transplantation and autoimmune diseases. The drugs are:

1 . Calcineurin inhibitors (Specific T-cell inhibitors) Cyclosporine (Ciclosporin), Tacrolimus

2. Antiproliferative drugs (Cytotoxic drugs) Azathioprine, Cyclophosphamide, Methotrexate, Chlorambucil, Mycophenolate mofetil (MMF)

3. Glucocorticoids: Prednisolone and others

4. Antibodies: Muromonab CD3, Antithymocyte globulin (ATG), Rho (D) immuneglobulin

Calcineurin inhibitors (Specific T-cell inhibitors)

A. Cyclosporine

Cyclosporine [sye-kloe-SPOR-een] (*CsA*) is a lipophillic cyclic polypeptide composed of 11 amino acids (several are methylated on the peptidyl nitrogen). The drug is extracted from a soil fungus. *CsA* is used to prevent rejection of kidney, liver, and cardiac allogeneic transplants.

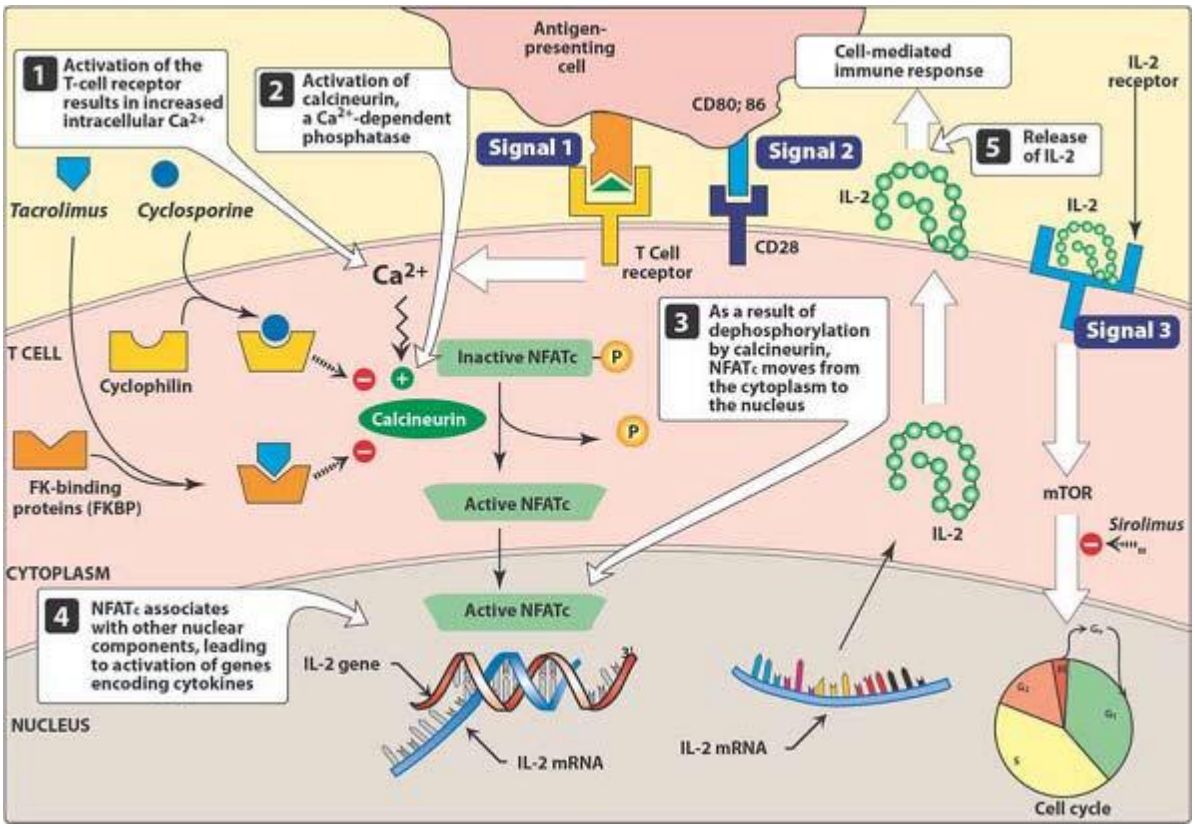
Mechanism of action: *Cyclosporine* preferentially suppresses cell-mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, *CsA* binds to a cyclophilin (more generally called an immunophilin) to form a complex that binds to calcineurin. The latter is responsible for dephosphorylating NFATc (**c**ytosolic **N**uclear **F**actor of **A**ctivated **T** cells). The *CsA*-calcineurin complex cannot perform this reaction; thus, NFATc cannot enter the nucleus to promote the reactions that are required for the synthesis of a number of cytokines, including IL-2.

Pharmacokinetics: *Cyclosporine* may be given either orally or by intravenous infusion. Oral absorption is variable. Interpatient variability may be due to metabolism by a cytochrome P450 (CYP3A4) in the gastrointestinal tract, where the drug is metabolized. About 50 percent of the drug is associated with the blood fraction

Adverse effects: Many of the adverse effects caused by *CsA* are dose dependent; therefore, it is important to monitor blood levels of the drug. Nephrotoxicity is the most common and important adverse effect of *CsA*. It is therefore critical to monitor kidney function.

B. Tacrolimus

Tacrolimus (*TAC*, originally called *FK506*) is a macrolide that is isolated from a soil fungus. *TAC* is approved for the prevention of rejection of liver and kidney transplants and is given with a corticosteroids and/or an antimetabolite. This drug has found favor over *CsA*, not only because of its potency and decreased episodes of rejection but also because lower doses of corticosteroids can be used, thus reducing the likelihood of steroid-associated adverse effects. An ointment preparation has been approved for moderate to severe atopic dermatitis that does not respond to conventional therapies.



Immunosuppressive Antimetabolites

Immunosuppressive antimetabolite agents are generally used in combination with corticosteroids, and the calcineurin inhibitors, *CsA* and *TAC*.

A. Azathioprine

Azathioprine [ay-za-THYE-oh-preen] was the first agent to achieve widespread use in organ transplantation. It is a prodrug that is converted first to *6-mercaptopurine* (*6-MP*) and then to the corresponding nucleotide, thioinosinic acid. The immunosuppressive effects of *azathioprine* are due to this nucleotide analog. Because of their rapid proliferation in the

immune response and their dependence on the de novo synthesis of purines required for cell division, lymphocytes are predominantly affected by the cytotoxic effects of *azathioprine*.

[Its major nonimmune toxicity is bone marrow suppression. Concomitant use with angiotensin-converting enzyme inhibitors or *cotrimoxazole* in renal transplant patients can lead to an exaggerated leukopenic response.

Immunosuppressant antibodies:

Muromonab CD3 It is a murine monoclonal antibody against the CD3 glycoprotein located near to the T cell receptor on helper T cells. Binding of muromonab CD3 to the CD3 antigen obstructs the binding of MHC II-antigen complex to the T cell receptor: antigen recognition is interfered, so that participation of T cells in the immune response is prevented and T cells rapidly disappear from circulation leading to an immune blocked state.

Mechanism of action: *Binding to the CD3 protein results in a disruption of T-lymphocyte function, because access of antigen to the recognition site is blocked. Circulating T cells are depleted; thus, their participation in the immune response is decreased. Because muromonab-CD3 recognizes only one antigenic site, the immunosuppression is less broad than that seen with the polyclonal antibodies. T cells usually return to normal within 48 hours of discontinuation of therapy.*

Muromonab CD3 has been used as induction therapy together with corticosteroids and azathioprine with delayed use of cyclosporine in 'sequential regimen' for organ transplantation. Thls serves to postpone potential nephro- and hepatotoxicity of cyclosporine.

IMMUNOSTIMULANT DRUGS

Immunostimulants**, also known as** immunostimulators**, are substances (drugs and nutrients) that stimulate the immune system by inducing activation or increasing activity of any of its components. One notable example is the granulocyte macrophage colony-stimulating factor. Classification**

There are two main categories of immunostimulants:

1. **Specific immunostimulants** provide antigenic specificity in immune response, such as vaccines or any antigen.

2. **Non-specific immunostimulants** act irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific immunostimulators.

Innate immune response – first line of defense against an antigenic insult. Includes

• defenses like physical (skin),

• Biochemical (complement, lysozyme, interferons)

• cellular components (neutrophils, monocytes, macrophages).

• Adaptive immune response a) Humoral immunity - Antibody production – killing extracellular organisms. b) Cell mediated immunity – cytotoxic / killer T cells – killing virus and tumour cells.

IMMUNOSUPPRESSIVE DRUGS • Those drugs that suppress the immune system. • Particularly important for transplantation, autoimmune disorders, allergies, and all the cases where immune system is too active.

IMMUNOSTIMULANT DRUGS • Those drugs that stimulate the immune system. • Particularly important for the treatment of infectious diseases, tumors, immuno deficiencies and all the cases where the immune system needs a boost.

Immunotherapy deals with the idea of boosting an individuals' immune system, to allow it to destroy microbes and tumors.The boost can be biological (microbial-derived products), pharmacological, or cell-based.

IMMUNOSTIMULANT DRUGS – MICROBIAL PRODUCTS • Many bacterial products are PAMPs, and they strongly stimulate inflammation by triggering cytokine production in APCs. These, in turn, stimulate the adaptive immunity and, overall, increase leukocytes number by boosting hematopoiesis.

The Bacillus Calmette–Guérin (BCG) is an attenuated (less virulent, but still alive) mycobacterium bovis strain. • This is able to infect human cells, but not to induce any pathology. Rather, it can stimulate the production of Igs by B-cell and thus behave as a vaccine against mycobacterium tuberculosis. • It has a strong inflammatory effect on some tissues, and has thus been also approved as a treatment for bladder cancer.

The bad side is that PAMPs can induce massive cytokine production, which can result in fever and shock. This is especially true with cytokines, which can also have direct toxic effects.

Immunotherapy – cytokine therapies • Since cytokines control the whole immune system, and mostly stimulate it, it is logical to use them whenever there is the need to boost immune system activity. • They are used in clinical practice, but they are burdened by severe side effects.

ACTIVE VACCINATION • Active vaccination is the process of injecting individuals with microbial antigens, heat- killed microbes or attenuated living microbes to induce antibody production and memory B-cells formation. • The individual acquires the ability to respond to the microbe he/she has been vaccinated against.

To ensure memory B-cells formation, whole microbes (either killed or attenuated) are preferred, as they also trigger fever and inflammation that boost B-cells activation and memory cells formation. • Attenuated microbes are those living strains which are still able to infect an individual, but that generate a less-dangerous pathological manifestation, which is generally inflammation/flu. • Side-effects are generally low, but sometimes they can be extremely severe.

PASSIVE VACCINATION • In passive vaccination, individuals are injected with preformed immunoglobulins (from donors). Thus, individuals acquire pools of immunoglobulins (good for immunodeficiencies) and the ability to respond to certain microbes. Transfusion of immunoglobulins is called intravenous immunoglobulins (igv). generally, igvs contain igG and igA. • Anti-microbial igvs are used against hepatitis b, botulism, diphtheria, tetanus, rabies. • It's generally well-tolerated, but sporadic side- effects can be extremely severe.

ADJUVANTS USED FOR VACCINATION • Injecting a living microbe can be dangerous, and reducing the amount of microbe to the minimum is mandatory. Here's the need for adjuvants. • Adjuvants are chemical or biological products that can either boost T-cells, activate inflammation or help to stabilize the antigen so that it can stimulate B-cells for a longer time. • Adjuvants have been also implicated in clinical side- effects of vaccinations, like the onset of juvenile diabetes in the case of Freund's adjuvant.

ADOPTIVE CELL TRANSFER • Adoptive cell transfer deals with the idea of isolating immune cells from individuals, expand them in culture and then re-infuse them. This is a wonderful strategy to kill tumors. • Tumor-infiltrated lymphocytes (TIL) are a heterogeneous

population which includes Th and CTLs able to recognize and kill the tumor. The problem is that the cytokines released from the tumor suppress them. Taking these "good cells" out of the tumor mass and re-injecting them upon expansion strongly increases the ability of the immune system to react against tumors.

CELL-BASED VACCINATION • Dendritic cells can be "prepared" in vitro to show tumor antigens, and then re-injected into the patient to stimulate tumor antigens' recognition and tumor killing. This is currently defined as cell-based vaccination.

IMMUNOSTIMULANTS USES • Immunodeficiency disorders • Chronic infections • Cancer Thalidomide Isoprinosine . Immunocynin Recombinant Cytokines- Interferons, Interleukins, Colonystimulating factors Bacillus Calmette- Guerin (BCG) Levamisole Other drugs– inosiplex, azimexon, imexon, thymosin, methylinosine monophosphate Immunization - Vaccines , Immune Globulin

Bacillus Calmette-Guerin (BCG) • Live, attenuated culture of BCG strain of Mycobacterium Bovis MOA • Induction of a granulomatous reaction at the site of administration. It causes activation of macrophages to make them more effective killer cells

Therapeutic uses • Treatment and prophylaxis of carcinoma of the urinary bladder, Prophylaxis of primary and recurrent stage of papillary tumors after transurethral resection. Adverse effects • Hypersensitivity, shock, chills, fever, malaise, and immune complex disease.

Levamisole /Ergamisol • synthesized originally as an anthelmintic but appears to restore depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages Therapeutic uses: • Adjuvant therapy with 5-fluorouracil colon cancer, agranulocytosis. Used to treat immunodeficiency associated with Hodgkins disease Adverse effects : • Flu-like symptoms, allergic manifestation, nausea and muscle pain .

Thalidomide MOA • Enhanced T-cell production of cytokines – IL-2, IFN- γ • NK cell-mediated cytotoxicity against tumor cells. Decrease circulating TNF-α in patients with erythema nodosum leprosum, but increase in HIV-seropositive patients, It affects angiogenesis also. Therapeutic uses • Severe, refractory rheumatoid arthritis . Multiple myeloma Adverse effects • Teratogenicity

• Hormone like, small low molecular weight polypeptides. • Maintain communication among cells to co-ordinate immune response. • Act synergistically or antagonistically thereby enhancing or supressing their own production • Autocrine, paracrine or endocrine in action. •

Causes tissue repair and provide resistance to infection

Cytokines : Properties Cytokine: Action Autocrine Paracine Endocrine

Cytokines-based therapies in clinical use

Isoprinosine(Inosiplex) • Complex of the pacetamidobenzoate salt of N,N- dimethylamino-2- propanol: inosine in a 3:1 molar ratio MOA • Augment production of cytokines such as IL-1, IL-2 and IFN-γ ,increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes

Nonspecific immunoglobulins Antibody-deficiency disorders Specific immune globulins.

High titers of desired antibody Hepatitis B, Rabies, Tetanus.

PROTEIN DRUGS, MONOCLONAL ANTIBODIES, TARGET DRUGS TO ANTIGEN, BIOSIMILARS

PROTEIN DRUGS

Linear POLYPEPTIDES that are synthesized on RIBOSOMES and may be further modified, crosslinked, cleaved, or assembled into complex proteins with several subunits. The specific sequence of AMINO ACIDS determines the shape the polypeptide will take, during PROTEIN FOLDING, and the function of the protein.

Therapeutic protein drugs are an important class of medicines serving patients most in need of novel therapies. Recently approved recombinant protein therapeutics have been developed to treat a wide variety of clinical indications, including cancers, autoimmunity/inflammation, exposure to infectious agents, and genetic disorders. The latest advances in protein-engineering technologies have allowed drug developers and manufacturers to fine-tune and exploit desirable functional characteristics of proteins of interest while maintaining (and in some cases enhancing) product safety or efficacy or both. In this review, we highlight the emerging trends and approaches in protein drug development by using examples of therapeutic proteins approved by the U.S. Food and Drug Administration over the previous five years (2011–2016, namely January 1, 2011, through August 31, 2016).

Drug Name **Drug Description**

Lepirudin A protein-based direct thrombin inhibitor used to reverse and prevent thrombus formation in heparin-induced thrombocytopenia.

Cetuximab An endothelial growth factor receptor binding fragment used to treat colorectal cancer as well as squamous cell carcinoma of the head and neck.

Dornase alfa A synthetic form of human deoxyribonuclease I used to break down extracellular DNA in the lungs, a major source of mucous viscosity in cystic fibrosis.

Denileukin diftitox A recombinant cytotoxic protein based on a combination of diphtheria toxin fragments and interleukin-2 used to treat cutaneous T-cell lymphoma by targeting the interleukin-2 receptor.

Etanercept A protein therapy based on the binding fragment of the tumour necrosis factor alpha receptor used to treat severe rheumatoid arthritis and moderate to severe plaque psoriasis.

Bivalirudin A direct thrombin inhibitor used to treat heparin-induced thrombocytopenia and to prevent thrombosis during percutaneous coronary intervention.

Leuprolide A protein-based luteinizing hormone antagonist used to treat prostate cancer, endometriosis, and precocious puberty.

Peginterferon alfa-2a A modified form of recombinant human interferon used to stimulate the innate antiviral response in the treatment of hepatitis B and C viruses.

Alteplase A recombinant form of human tissue plasminogen activator used in the emergency treatment of myocardial infarction, ischemic stroke, and pulmonary emboli.

Sermorelin For the treatment of dwarfism, prevention of HIV-induced weight loss

MONOCLONAL ANTIBODIES

Monoclonal antibodies (**mAb** or **moAb**) are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have monovalent affinity, in that they bind to the same epitope (the part of an antigen that is recognized by the antibody). In contrast, polyclonal antibodies bind to multiple epitopes and are usually made

by several different plasma cell (antibody secreting immune cell) lineages. Bispecific monoclonal antibodies can also be engineered, by increasing the therapeutic targets of one single monoclonal antibody to two epitopes.

Outline of production of MAbs

The main objective is to produce a homogenous population of MAbs against a pre-fixed immunogen. The basic strategy includes (i) purification and characterization of the desired antigen in adequate quantity, (ii) immunization of mice with the purified antigen, (iii) culture of myeloma cells which are unable to synthesize hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) enzyme necessary for the salvage pathway of nucleic acids, (iv) removal of spleen cells from mice and its fusion with the myeloma cells, (v) following fusion, the hybridomas were grown in hypoxanthine aminopterin thymidine (HAT) medium. The fused cells are not affected in the absence of HGPRT unless their de novo synthesis pathway is also disrupted. In the presence of aminopterin, the cells are unable to use the de novo pathway and thus these cells become auxotrophic for nucleic acids as a supplement to HAT medium. In this medium, only fused cells will grow. Unfused myeloma cell does not have ability to grow in this HAT medium because they lack HGPRT, and thus cannot produce DNA. Unfused spleen cells can¬not grow because of their short life spans. Only fused hybrid cells or hybridomas can grow in HAT medium. Hybrid cells have the capacity to grow in the HAT medium since spleen cell partners produce HGPRT. (vi) The hybrid cell clones are generated from single host cells (vii) the antibodies secreted by the different clones are then tested for their ability to bind to the antigen using an enzyme-linked immunosorbent assay (ELISA). (viii) The clone is then selected for future use.

Examples of therapeutic monoclonal antibodies

Monoclonal antibodies for research applications can be found directly from antibody suppliers, or through use of a specialist search engine like CiteAb. Below are examples of clinically important monoclonal antibodies.

Main category	Type	Application	Mechanism/Target	Mode
Anti-inflammatory	**infliximab**	• rheumatoid arthritis • Crohn's disease	inhibits TNF-α	chimeric

		• ulcerative colitis • ankylosing spondylitis		
	adalimumab	• rheumatoid arthritis • Crohn's disease • ulcerative colitis • ankylosing spondylitis	inhibits TNF-α	human
	basiliximab	• acute rejection of kidney transplants	inhibits IL-2 on activated T cells	chimeric
	daclizumab	• acute rejection of kidney transplants	inhibits IL-2 on activated T cells	humanized
	omalizumab	• moderate-to-severe allergic asthma	inhibits human immunoglobulin E (IgE)	humanized
	gemtuzumab	• relapsed acute myeloid leukemia	targets myeloid cell surface antigen CD33 on leukemia cells	humanized
Anti-cancer	**alemtuzumab**	• B cell leukemia	targets an antigen CD52 on T- and B-lymphocytes	humanized
	rituximab	• non-Hodgkin's lymphoma • rheumatoid arthritis	targets phosphoprotein CD20 on B lymphocytes	chimeric

	trastuzumab	• breast cancer with HER2/neu overexpression	targets the HER2/neu (erbB2) receptor	humanized
	nimotuzumab	• approved in squamous cell carcinomas, Glioma • clinical trials for other indications underway	EGFR inhibitor	humanized
	cetuximab	• approved in squamous cell carcinomas, colorectal carcinoma	EGFR inhibitor	chimeric
	bevacizumab & ranibizumab	• Anti-angiogenic cancer therapy	inhibits VEGF	humanized
Anti-cancer and anti-viral	**bavituximab**	• cancer, hepatitis C infection	immunotherapy, targets phosphatidylserine	chimeric
	palivizumab	• RSV infections in children	inhibits an RSV fusion (F) protein	humanized
Other	**abciximab**	• prevent coagulation in coronary angioplasty	inhibits the receptor GpIIb/IIIa on platelets	chimeric

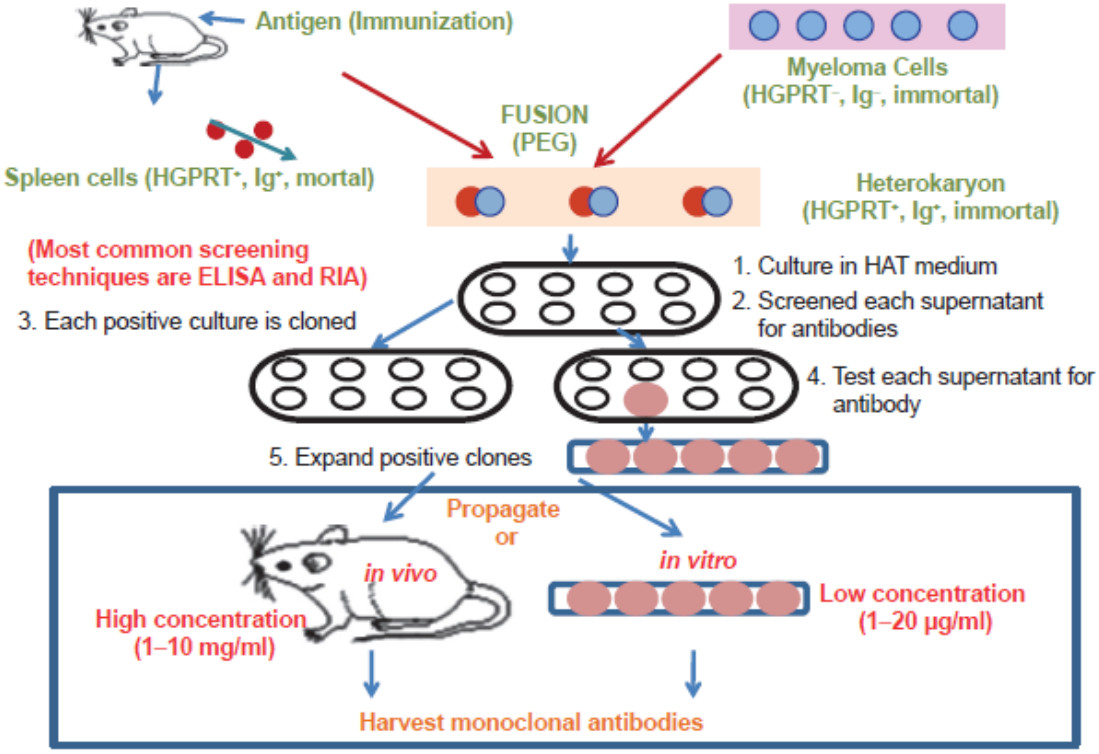


Figure 1. Production of monoclonal antibody by hybridoma technology. The hybridoma technology outline involves the isolation of spleen cells from immunized mice, their fusion with immortal myeloma cells and the production and further propagation of monoclonal antibodies from the hybrid cells.[2]

Immunization schedule Depending on the purity and nature of the purified antigen, an immunization protocol is determined. For immunization, the desired protein should be available in adequate quantity (a few milligrams). However, in case of a complex multi-molecular antigen, it is quite stringent to purify it in adequate quantity. Thus, depending on its screening and selection abilities, MAbs can purify a target antigen from an antigen mixture. Mice must be immunized with antigen 6–10 weeks before fusion to allow them to develop a robust immune response before generating hybridomas. The injection schedule and the actual timing may vary depending on the antigen used for the immunization as well as other factors. It is desirable to immunize mice with a pure antigen, as this simplifies the screening of hybridomas. However, complex antigenic mixtures can be used. Collection of pre-immune serum is required prior to immunization to use as a baseline control for antibody screening. The mouse is bled by cutting approximately 1–2 mm off the tip of the tail thereby collecting 100–200 μL of blood in a capillary tube from where the serum is collected and can be cryo-preserved. A typical immunization schedule includes intra-peritonial injections of 2–4 adult mice (eg, BALB/c mice) with 20–100 μg of purified antigen in a total volume of 200 μL (ie, 200 μL of a 1:1 emulsion of antigen in saline: adjuvant). A stable emulsion is critical for generating a strong immune response. The injection is repeated 14–30 days later and booster doses are administered for 2–3 times until a good titer of antibody is obtained. Next, 10–14 days after the last injection, 100–200 μL of blood is collected from the tip of the tail or from the eye and serum is separated. The antibody levels in serum can be detected by applying different immune-techniques such as ELISA, immunofluorescence, flow cytometry, and immuno blotting, and the antibody titer of the post-immune serum is compared with the pre-immune serum from the same animal. The mouse with the highest antibody titer swas selected for fusion. Between one and four days prior to fusion, the selected mouse is boosted intravenously via the tail vein. Following this step, spleen cells are prepared for fusion.

Myeloma cell line culture

In myeloma culture, hybridomas should grow continuously and selectively by suppressing the growth of the parent myeloma. It is desirable to obtain a parental myeloma cell that has been proven to yield stable hybridomas. The selected myeloma cell lines should have lost their capability to produce nucleotides using the salvage pathway. Myeloma cells are cultured in presence of 8-azaguanine so that they are unable to synthesize the HGPRT enzyme necessary for the salvage pathway of nucleic acids. Parental myeloma cells are cultured for at least one week prior to fusion to ensure that the cells are well-adapted to HGPRT-negative

conditions. Cells are seeded at a density of approximately 5 × 104 cells/mL and passaged every 2 days; those growing in the early-mid log phase prior to fusion are selected for fusion.

After fusion, by using the drug aminopterin, de novo synthesis pathways can be blocked and thus the myeloma cells (where salvage pathway was previously blocked) cannot produce RNA or DNA and die. On the other hand, hybridomas have a functional salvage pathway (derived from the spleen cells of mouse) and can grow when they are cultured in medium containing the substrates for the pathway, ie, thymidine and hypoxanthine. This selective culture medium is HAT medium containing hypoxanthine, aminopterin, and thymidine respectively.

Fusion

The parental myeloma cells used to make the hybridoma must match the strain of mouse being immunized (eg, for BALB/c mice the myeloma cells must be of BALB/c origin) and must not secrete any of their own immunoglobulin chains. The parental myeloma cells should be mycoplasma-free, fuse well, and allow the formation of stable hybridomas that continually secrete specific MAbs. SP2/0 and X63Ag8. 653 are widely used parental myeloma cells that meet all of these criteria. There are various agents that induce the somatic cell to fuse. There are some physical agents, such as electro-fusion and chemical agents, including polyethylene glycol (PEG) and calcium ions, among others. Large numbers of cells can be fused in the presence of PEG within a short time. During electro-fusion, a continuous electric potential is maintained in the fusion medium. Current is applied in short pulses at high voltage with short duration or in low voltage with long duration. The factors that are controlled during electro-fusion were specific resistance, osmotic strength, field strength, and ionic composition of the fusion medium. The cells should be given proteolytic pretreatment.

An immunized mouse, 48–72 hours after tail vein injection, is euthanized and the spleen can be removed and disaggregated into a single cell suspension under sterile conditions. At the same time, the myeloma cells are harvested and added to fusion medium and mixed with spleen cells together with PEG solution to yield single hybridoma colonies. The fused cell mixture is plated in culture plates containing a feeder layer prepared from control un-immunized mice

Growth and selection of MAbs

Within 7–14 days after fusion, the growth of hybridomas occurs gradually together with the addition of interleukin 6 (IL-6), the hybridoma growth factor.

Applications of m**onoclonal** a**ntibodies**

MAbs have proved to be extremely valuable for basic immunological and molecular research because of their high specificity. They are used in human therapy, commercial protein purification, suppressing immune response, diagnosis of diseases, cancer therapy, diagnosis of allergy, hormone test, purification of complex mixtures, structure of cell membrane, identification of specialized cells, preparation of vaccines, and increasing the effectiveness of medical substances

Diagnostic tools in research and laboratory

To detect the presence of this substance/antigen, MAbs can be used. Different technologies in which MAbs are used include Western blot, immunodot blot, ELISA, radioimmuno assay (RIA), flow cytometry, immunohistochemistry, fluorescence microscopy, electron microscopy, confocal microscopy, as well as other biotechnological applications.

Gene cloning

One of the difficulties of gene cloning is identifying the cells that contain the desired gene. If an MAb that recognizes that the gene product is available, it can be used as a probe for detecting those cells that make the product and therapy to detect the gene.

To identify cell types

MAbs contribute to the identification of many different types of cells that participate in the immune response and to unravel interactions occurring during this process. For example, in the lymphocytes with B, T helper (TH) cells and suppressor T, the use of MAbs has established that the various types of T-cells carry cell surface antigens on their surfaces that allow one type to be distinguished from another. The MAbs were also helpful in defining changes in T and B-cells during development.

Protein purification

MAb affinity columns are readily prepared by coupling MAbs to a cyanogen bromide-activated chromatography matrix, eg, Sepharose. Since the MAbs have unique specificity for the desired protein, the level of contamination by unwanted protein species usually is very low. Since the MAb-antigen complex has a single binding affinity it is possible to elute the required protein in a single, sharp peak. The concentration of the relative protein relative to total protein in a mixture can ever be very low. This method also has limitations. Achieving 100% pure protein is difficult because there is always a tendency for small amounts of

immunoglobulin to leak off the immune-affinity column. Additionally, MAb do not distinguish between intact protein molecules and fragments containing the antigenic site.

Recombinant

The production of recombinant monoclonal antibodies involves repertoire cloning, CRISPR/Cas9, or phage display/yeast display technologies.[22] Recombinant antibody engineering involves antibody production by the use of viruses or yeast, rather than mice. These techniques rely on rapid cloning of immunoglobulin gene segments to create libraries of antibodies with slightly different amino acid sequences from which antibodies with desired specificities can be selected. The phage antibody libraries are a variant of phage antigen libraries.[24] These techniques can be used to enhance the specificity with which antibodies recognize antigens, their stability in various environmental conditions, their therapeutic efficacy and their delectability in diagnostic applications. Fermentation chambers have been used for large scale antibody production.

Chimeric antibodies

While mouse and human antibodies are structurally similar, the differences between them were sufficient to invoke an immune response when murine monoclonal antibodies were injected into humans, resulting in their rapid removal from the blood, as well as systemic inflammatory effects and the production of human anti-mouse antibodies (HAMA).

Recombinant DNA has been explored since the late 1980s to increase residence times. In one approach, mouse DNA encoding the binding portion of a monoclonal antibody was merged with human antibody-producing DNA in living cells. The expression of this "chimeric" or "humanised" DNA through cell culture yielded part-mouse, part-human antibodies.

Human antibodies

Ever since the discovery that monoclonal antibodies could be generated, scientists have targeted the creation of *fully* human products to reduce the side effects of humanised or chimeric antibodies. Two successful approaches have been identified: transgenic mice and phage display.

Applications

Diagnostic tests

Once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence of this substance. Proteins can be detected using the Western blot and immuno dot blot tests. In immunohistochemistry, monoclonal antibodies can be used to detect antigens in fixed tissue sections, and similarly, immunofluorescence can be used to detect a substance in either frozen tissue section or live cells.

Analytic and chemical uses

Antibodies can also be used to purify their target compounds from mixtures, using the method of immunoprecipitation.

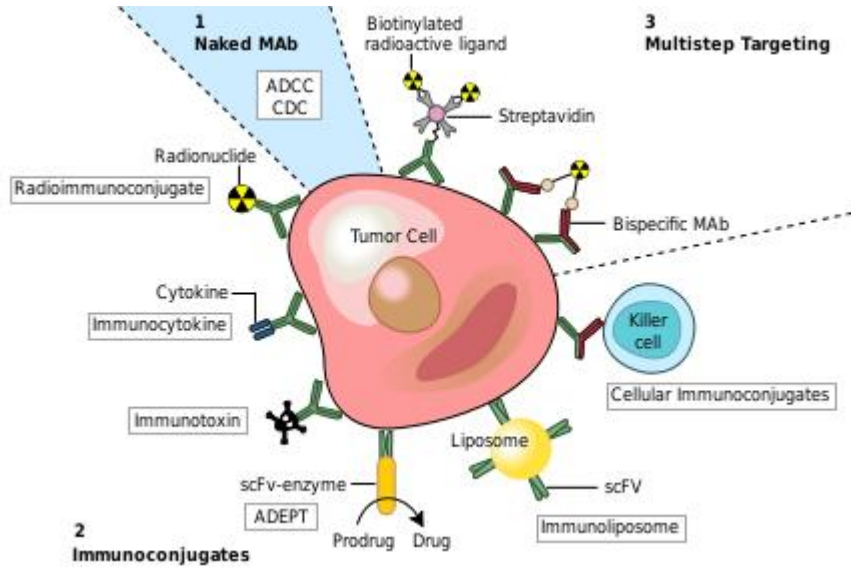
Therapeutic uses

Main article: Monoclonal antibody therapy

Therapeutic monoclonal antibodies act through multiple mechanisms, such as blocking of targeted molecule functions, inducing apoptosis in cells which express the target, or by modulating signalling pathways.[44][45]

Cancer treatment

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immune response against the target cancer cell. Such mAbs can be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate or to design bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell. Every intact antibody can bind to cell receptors or other proteins with its Fc region.



Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme prodrug therapy; ADCC: antibody dependent cell-mediated cytotoxicity; CDC: complement-dependent cytotoxicity; MAb: monoclonal antibody; scFv, single-chain Fv fragment.[46]

MAbs approved by the FDA for cancer include

- Alemtuzumab
- Bevacizumab
- Cetuximab
- Gemtuzumab ozogamicin
- Ipilimumab
- Ofatumumab
- Panitumumab
- Pembrolizumab
- Ranibizumab
- Rituximab
- Trastuzumab

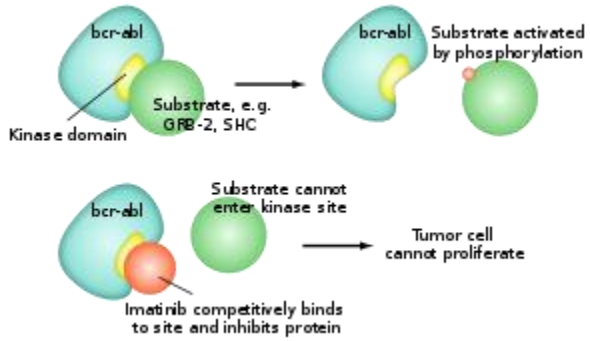
Autoimmune diseases

Monoclonal antibodies used for autoimmune diseases include infliximab and adalimumab, which are effective in rheumatoid arthritis, Crohn's disease, ulcerative colitis and ankylosing spondylitis by their ability to bind to and inhibit TNF-α. Basiliximab and daclizumab inhibit IL-2 on activated T cells and thereby help prevent acute rejection of kidney transplants.[48]

Omalizumab inhibits human immunoglobulin E (IgE) and is useful in treating moderate-to-severe allergic asthma.

The main categories of targeted therapy are currently *small molecules* and *monoclonal antibodies.*

Small molecules



Mechanism of imatinib

Many are tyrosine-kinase inhibitors.

- Imatinib (Gleevec, also known as STI–571) is approved for chronic myelogenous leukemia, gastrointestinal stromal tumor and some other types of cancer. Early clinical trials indicate that imatinib may be effective in treatment of dermatofibrosarcoma protuberans.
- Gefitinib (Iressa, also known as ZD1839), targets the epidermal growth factor receptor (EGFR) tyrosine kinase and is approved in the U.S. for non small cell lung cancer.
- Erlotinib (marketed as Tarceva). Erlotinib inhibits epidermal growth factor receptor, and works through a similar mechanism as gefitinib. Erlotinib has been shown to increase survival in metastatic non small cell lung cancer when used as second line therapy. Because of this finding, erlotinib has replaced gefitinib in this setting.
- Sorafenib (Nexavar)[13]
- Sunitinib (Sutent)
- Dasatinib (Sprycel)
- Lapatinib (Tykerb)
- Nilotinib (Tasigna)

- Bortezomib (Velcade) is an apoptosis-inducing proteasome inhibitor drug that causes cancer cells to undergo cell death by interfering with proteins. It is approved in the U.S. to treat multiple myeloma that has not responded to other treatments.
- The selective estrogen receptor modulator tamoxifen has been described as the foundation of targeted therapy.[14]
- Janus kinase inhibitors, e.g. FDA approved tofacitinib
- ALK inhibitors, e.g. crizotinib
- Bcl-2 inhibitors (e.g. obatoclax in clinical trials, navitoclax, and gossypol.
- PARP inhibitors (e.g. Iniparib, Olaparib in clinical trials)
- PI3K inhibitors (e.g. perifosine in a phase III trial)
- Apatinib is a selective VEGF Receptor 2 inhibitor which has shown encouraging anti-tumor activity in a broad range of malignancies in clinical trials. Apatinib is currently in clinical development for metastatic gastric carcinoma, metastatic breast cancer and advanced hepatocellular carcinoma.
- Zoptarelin doxorubicin (AN-152), doxorubicin linked to [D-Lys(6)]- LHRH, Phase II results for ovarian cancer.
- Braf inhibitors (vemurafenib, dabrafenib, LGX818) used to treat metastatic melanoma that harbors BRAF V600E mutation
- MEK inhibitors (trametinib, MEK162) are used in experiments, often in combination with BRAF inhibitors to treat melanoma
- CDK inhibitors, e.g. PD-0332991, LEE011 in clinical trials
- Hsp90 inhibitors, some in clinical trials
- salinomycin has demonstrated potency in killing cancer stem cells in both laboratory-created and naturally occurring breast tumors in mice.
- VAL-083 (dianhydrogalactitol), a “first-in-class” DNA-targeting agent with a unique bi-functional DNA cross-linking mechanism. NCI-sponsored clinical trials have demonstrated clinical activity against a number of different cancers including glioblastoma, ovarian cancer, and lung cancer. VAL-083 is currently undergoing Phase 2

and Phase 3 clinical trials as a potential treatment for glioblastoma (GBM) and ovarian cancer. As of July 2017, four different trials of VAL-083 are registered.

Small molecule drug conjugates

- Vintafolide is a small molecule drug conjugate consisting of a small molecule targeting the folate receptor. It is currently in clinical trials for platinum-resistant ovarian cancer (PROCEED trial) and a Phase 2b study(TARGET trial) in non-small-cell lung carcinoma (NSCLC).

Serine/threonine kinase inhibitors (small molecules)

- Temsirolimus (Torisel)
- Everolimus (Afinitor)
- Vemurafenib (Zelboraf)
- Trametinib (Mekinist)
- Dabrafenib (Tafinlar)

Monoclonal antibodies

Several are in development and a few have been licensed by the FDA and the European Commission. Examples of licensed monoclonal antibodies include:

- Pembrolizumab (Keytruda) binds to PD-1 proteins found on T cells. Pembrolizumab blocks PD-1 and help the immune system kill cancer cells.[23] It is used to treat melanoma, hodgkin's lymphoma, non-small cell lung carcinoma and several other types of cancer.
- Rituximab targets CD20 found on B cells. It is used in non Hodgkin lymphoma
- Trastuzumab targets the Her2/neu (also known as ErbB2) receptor expressed in some types of breast cancer
- Alemtuzumab

- Cetuximab target the epidermal growth factor receptor (EGFR). It is approved for use in the treatment of metastatic colorectal cancer, and squamous cell carcinoma of the head and neck.
- Panitumumab also targets the EGFR. It is approved for the use in the treatment of metastatic colorectal cancer.
- Bevacizumab targets circulating VEGF ligand. It is approved for use in the treatment of colon cancer, breast cancer, non-small cell lung cancer, and is investigational in the treatment of sarcoma. Its use for the treatment of brain tumors has been recommended.
- Ipilimumab (Yervoy)

Many antibody-drug conjugates (ADCs) are being developed. See also ADEPT (antibody-directed enzyme prodrug therapy).

CD antigens as drug target

Special drugs have been designed that identify and attack cells that have a particular type of CD antigens. These drugs are called monoclonal antibodies and they can attack only the type of cell that contains the specific target CD antigens. Monoclonal antibodies can also be tagged to drugs or radiation-emitting substances that add to the ability to kill cells that have the specific CD marker on their surface.

Examples of CD antigens targeted in lymphoma treatment:

Rituxan (Rituximab) - a monoclonal antibody against CD20.
Zevalin (Ibritumomab Tiuxetan) - another antibody against CD20, tagged with a radiation emitting substance (Y90).
Bexxar (Tositumomab) - similar to Zevalin, only the radiation emitting substance is different (I131)
Gazyva (Obinutuzumab): targets CD20 antigen, used in initial treatment for small lymphocytic lymphoma/chronic lymphocytic leukemia.

Arzerra (Ofatumumab): targets CD 20 antigen, used in SLL/CLL. Campath (Alemtuzumab): targets CD52 antigen in SLL/CLL and peripheral T-cell lymphomas. Adcetris (Brentuximab vedotin): targets CD30 and is attached to a chemotherapy drug. Used in anaplastic large cell lymphoma.

Biosimilar

A biosimilar is a biologic medical product (also known as biologic) highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. Biosimilars are officially approved versions of original "innovator" products and can be manufactured when the original product's patent expires.[2] Reference to the innovator product is an integral component of the approval.

Unlike with generic drugs of the more common small-molecule type, biologics generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes. Despite that heterogeneity, all biopharmaceuticals, including biosimilars, must maintain consistent quality and clinical performance throughout their lifecycle. A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular micro-heterogeneity. Drug-related authorities such as the EU's European Medicines Agency (EMA), the US's Food and Drug Administration (FDA), and the Health Products and Food Branch of Health Canada hold their own guidance on requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy. According to them, analytical studies demonstrate that the biological product is highly similar to the reference product, despite minor differences in clinically inactive components, animal studies (including the assessment of toxicity), and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics). They are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which

the reference product is licensed and is intended to be used and for which licensure is sought for the biological product.

The World Health Organization (WHO) published its "Guidelines for the evaluation of similar biotherapeutic products (SBPs)" in 2009. The purpose of this guideline is to provide an international norm for evaluating biosimilars with a high degree of similarity with an already licensed, reference biotherapeutic medicine.

Europe was the first region in the world to develop a legal, regulatory, and scientific framework for approving biosimilar medicines. The EMA has granted a marketing authorisation for more than 50 biosimilars since 2006 (first approved biosimilar Somatropin(Growth hormone)). The first monoclonal antibody that was approved in 2013, was infliximab, putting the EU at the forefront of biologics regulatory science.. Meanwhile, on March 6, 2015, the FDA approved the United States's first biosimilar product, the biosimilar of filgrastim called filgrastim-sndz (trade name Zarxio) by Sandoz.