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LECTURE 10: IMMUNODEFICIENCY DISEASES

Primary Immunodeficiencies

A primary immunodeficiency may affect either adaptive or innate immune functions. Deficiencies involving components of adaptive immunity, such as T or B cells, are thus differentiated from immunodeficiencies in which the nonspecific mediators of innate immunity, such as phagocytes or complement, are impaired.

Lymphoid Immunodeficiencies May Involve B Cells, T Cells, or Both

X-Linked Agammaglobulinemia

A B-cell defect called X-linked agammaglobulinemia (XLA) or Bruton's hypogammaglobulinemia is characterized by extremely low IgG levels and by the absence of other immunoglobulin classes. Individuals with XLA have no peripheral B cells and suffer from recurrent bacterial infections, beginning at about nine months of age. A palliative treatment for this condition is periodic administration of immunoglobulin, but patients seldom survive past their teens. There is a defect in B-cell signal transduction in this disorder, due to a defect in a transduction molecule called Bruton's tyrosine kinase (Btk), after the investigator who described the syndrome. B cells in the XLA patient remain in the pre-B stage with H chains rearranged but L chains in their germ-line configuration.

Immunodeficiencies of the Myeloid Lineage Affect Innate Immunity

Immunodeficiencies of the lymphoid lineage affect adaptive immunity. By contrast, defects in the myeloid cell lineage affect the innate immune functions. Most of these defects result in impaired phagocytic processes that are manifested by recurrent microbial infection of greater or lesser severity. There are several stages at which the phagocytic processes may be faulty; these include cell motility, adherence to and phagocytosis of organisms, and killing by macrophages.

Chronic Granulomatous Disease (Cgd)

CGD is a genetic disease that has at least two distinct forms: an X-linked form that occurs in about 70% of patients and an autosomal recessive form found in the rest. This disease is rooted in a defect in the oxidative pathway by which phagocytes generate hydrogen peroxide and the resulting reactive products, such as hypochlorous acid, that kill phagocytosed bacteria. CGD sufferers undergo excessive inflammatory reactions that result in gingivitis, swollen lymph nodes, and nonmalignant granulomas (lumpy subcutaneous cell masses); they are also susceptible to bacterial and fungal infection.

CGD patients are not subject to infection by those bacteria, such as pneumococcus, that generate their own hydrogen peroxide. In this case, the myeloperoxidase in the host cell can use the bacterial hydrogen peroxide to generate enough hypochlorous acid to thwart infection. Several related defects may lead to CGD; these include a missing or defective cytochrome (cyt *b*558) that functions in an oxidative pathway and defects in proteins (phagocyte oxidases, or phox) that stabilize the cytochrome. In addition to the general defect in the killer function of phagocytes, there is also a decrease in the ability of mononuclear cells to serve as APCs.

Both processing and presentation of antigen are impaired. Increased amounts of antigen are required to trigger T-cell help when mononuclear cells from CGD patients are used as APCs. The addition of IFN-γ has been shown to restore function to CGD granulocytes and monocytes in vitro. This observation prompted clinical trials of IFN-γ for CGD patients. Encouraging increases in oxidative function and restoration of cytoplasmic cytochrome have been reported in these patients. In addition, knowledge of the precise gene defects underlying CGD makes it a candidate for gene therapy, and replacement of the defective cytochrome has had promising results.

Complement Defects Result in Immunodeficiency or Immune-Complex Disease

Many complement deficiencies are associated with increased susceptibility to bacterial infections and/or immune-complex diseases. One of these complement disorders, a deficiency in properdin, which stabilizes the C3 convertase in the alternative complement pathway, is caused by a defect in a gene located on the X chromosome.

Immunodeficiency Disorders Are Treated by Replacement of the Defective Element

Although there are no cures for immunodeficiency disorders, there are several treatment possibilities. In addition to the drastic option of total isolation from exposure to any microbial agent, treatment options for the immunodeficiencies include:

→ replacement of a missing protein
→ replacement of a missing cell type or lineage
→ replacement of a missing or defective gene

AIDS and Other Acquired or Secondary Immunodeficiencies

As described above, a variety of defects in the immune system give rise to immunodeficiency. In addition to the primary immunodeficiencies, there are also acquired, or secondary, immunodeficiencies.

A Retrovirus, HIV-1, Is the Causative Agent of AIDS

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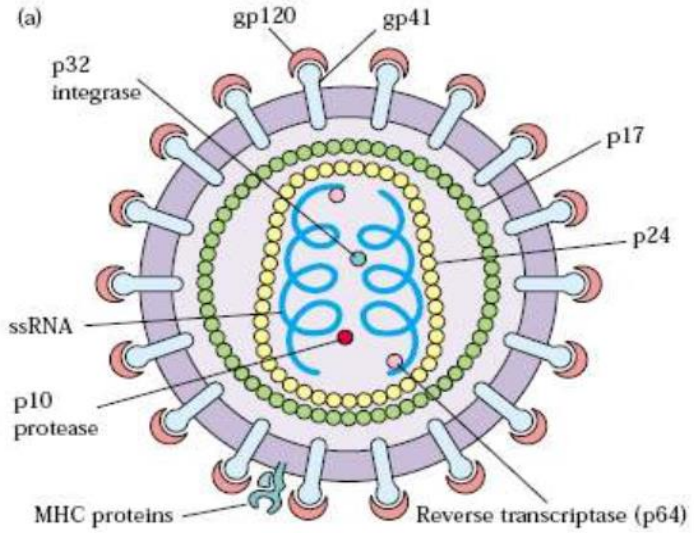
Retroviruses carry their genetic information in the form of RNA. When the virus enters a cell, the RNA is reverse transcribed to DNA by a virally encoded enzyme, reverse transcriptase (RT). As the name implies, RT reverses the normal transcription process and makes a DNA copy of the viral RNA genome. This copy, which is called a **provirus,** is integrated into the cell genome and is replicated along with the cell DNA. When the provirus is expressed to form new virion, the cell lyses. Alternatively, the provirus may remain latent in the cell until some regulatory signal starts the expression process.

HIV-1 Spreads by Sexual Contact, Infected Blood, and from Mother to Infant



Structure of HIV. Cross-sectional schematic diagram of HIV virion.

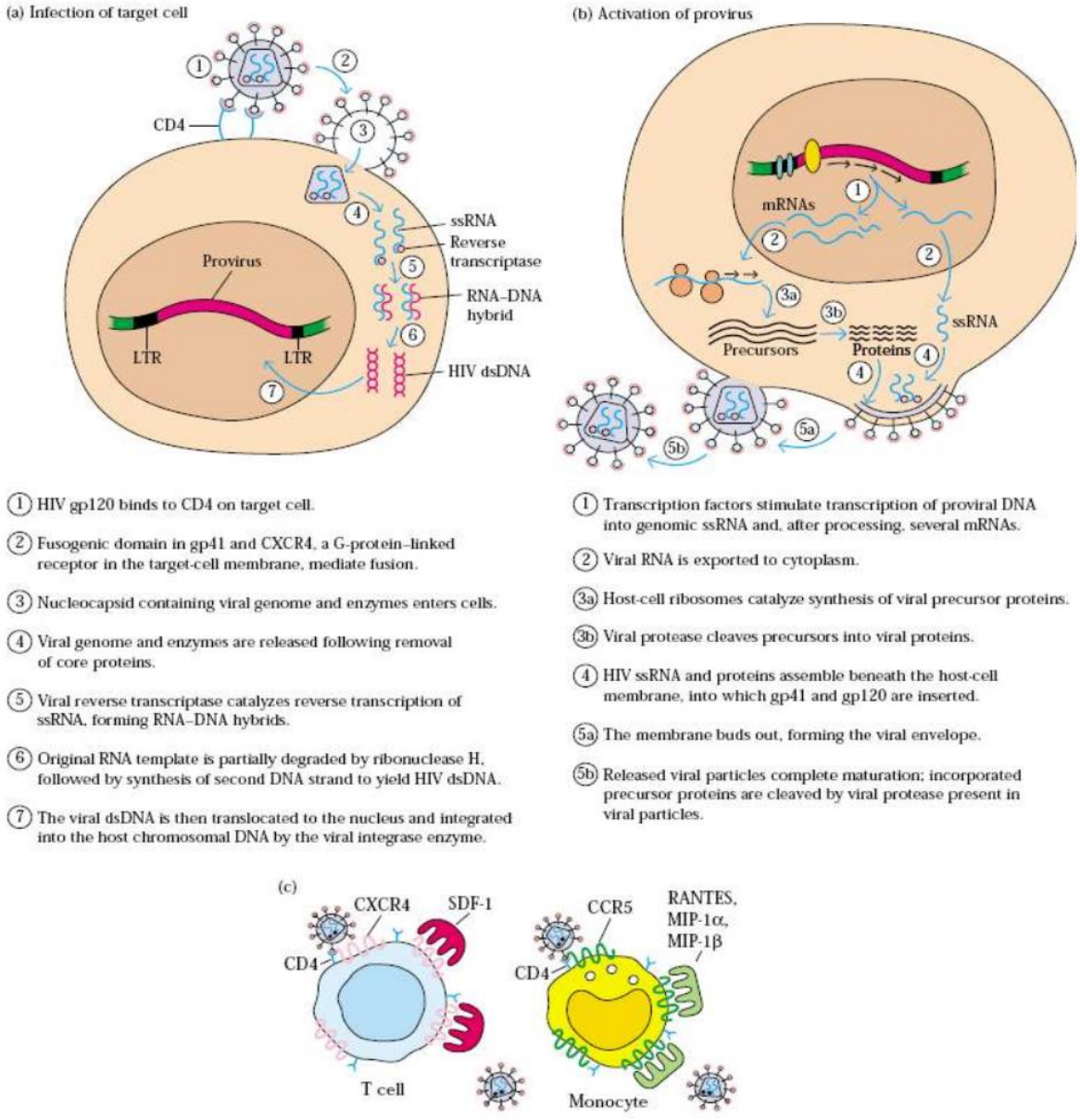
Each virion expresses 72 glycoprotein projections composed of gp120 and gp41. The gp41 molecule is a transmembrane molecule that crosses the lipid bilayer of the viral envelope. Gp120 is associated with gp41 and serves as the viral receptor for CD4 on host cells. The viral envelope derives from the host cell and contains some host-cell membrane proteins, including class I and class II MHC molecules. Within the envelope is the viral core, or nucleocapsid, which includes a layer of a protein called p17 and an inner layer of a protein, called p24. The HIV genome consists of two copies of single-stranded RNA, which are associated with two molecules of reverse transcriptase (p64) and nucleoid proteins p10, a protease, and p32, an integrase.

Overview of HIV infection of target cells and activation of provirus

(a) Following entry of HIV into cells and formation of dsDNA, integration of the viral DNA into the host-cell genome creates the provirus.

(b) The provirus remains latent until events in the infected cell trigger its activation, leading to formation and release of viral particles.

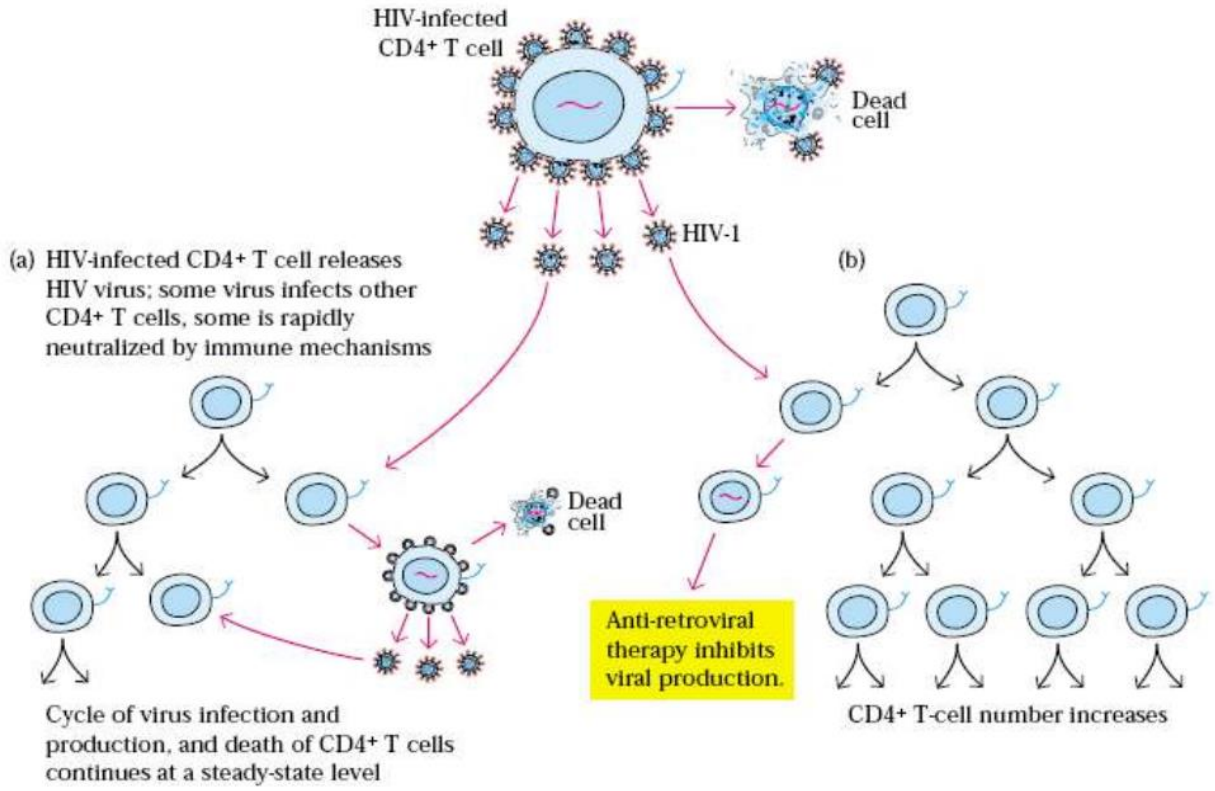
(c) Although CD4 binds to the envelope glycoprotein of HIV-1, a second receptor is necessary for entry and infection. The T-cell–tropic strains of HIV-1 use the coreceptor CXCR4, while the macrophage-tropic strains use CCR5. Both are receptors for chemokines, and their normal ligands can block HIV infection of the cell.



Production of virus by CD4_ T cells and maintenance of a steady state of viral load and T-cell number

(a) A dynamic relationship exists between the number of CD4_ cells and the amount of virus produced. As virus is produced, new CD4_ cells are infected, and these infected cells have a half-

life of 1.5 days. In progression to full AIDS, the viral load increases and the CD4_ T-cell count decreases before onset of opportunistic infections. (b) If the viral load is decreased by anti-retroviral treatment, the CD4_ T-cell number increases almost immediately.

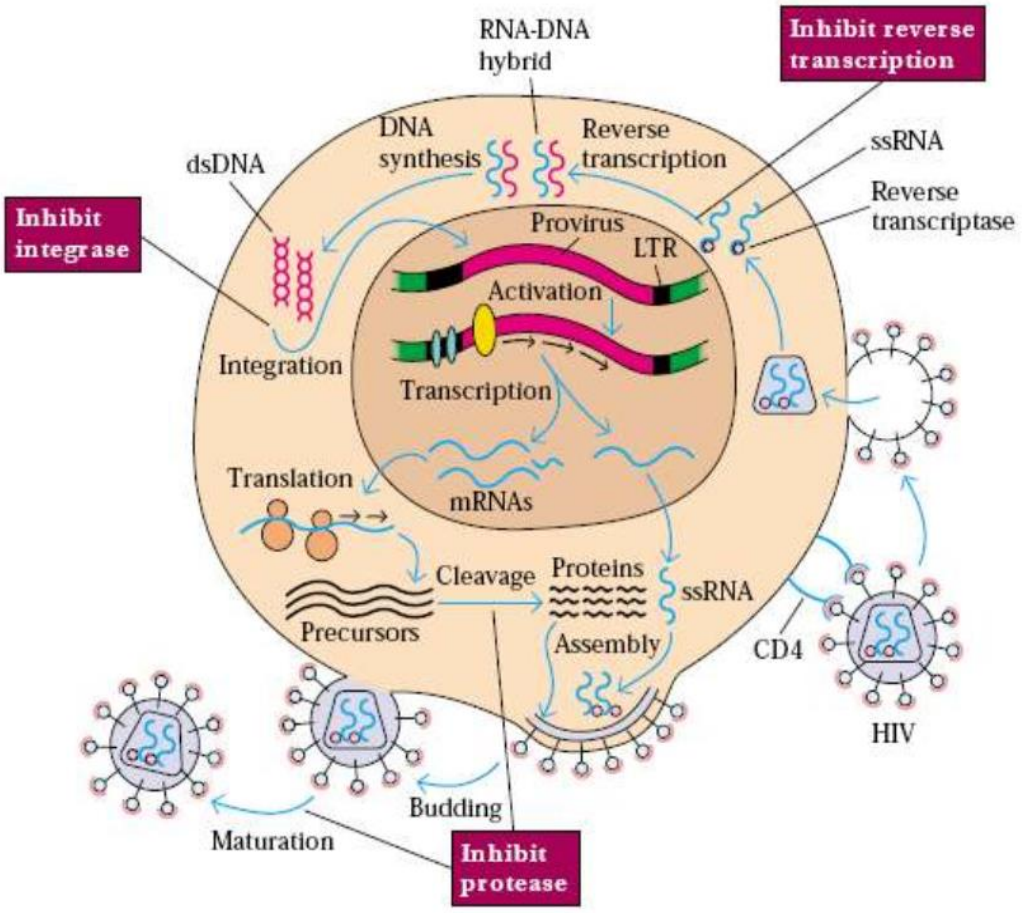


Immunologic abnormalities associated with HIV infection

Stage of infection	Typical abnormalities observed
	LYMPH NODE STRUCTURE
Early	Infection and destruction of dendritic cells; some structural disruption
Late	Extensive damage and tissue necrosis; loss of folicular dendritic cells and germinal centers; inability to trap antigens or support activation of T and B cells
	T HELPER (T_H) CELLS
Early	No in vitro proliferative response to specific antigen
Late	Decrease in T_H-cell numbers and corresponding helper activities; no response to T-cell mitogens or alloantigens
	ANTIBODY PRODUCTION
Early	Enhanced nonspecific IgG and IgA production but reduced IgM synthesis
Late	No proliferation of B cells specific for HIV-1: no detectable anti-HIV antibodies in some patients; increased numbers of B cells with low CD21 and enhanced Ig secretion.
	CYTOKINE PRODUCTION
Early	Increased levels of some cytokines
Late	Shift in cytokine production from T_H1 subset to T_H2 subset

	DELAYED-TYPE HYPERSENSITIVITY
Early	Highly significant reduction in proliferative capacity of T_{DTH} cells and reduction in skin-test reactivity
Late	Elimination of DTH response; complete absence of skin-test reactivity
	T CYTOTOXIC (T_C) CELLS
Early	Normal reactivity
Late	Reduction but not elimination of CTL activity due to impaired ability to generate CTLs from T_C cells

Therapeutic Agents Inhibit Retrovirus Replication



Stages in the viral replication cycle that provide targets for therapeutic antiretroviral drugs. At present, the licensed drugs with anti-HIV activity block the step of reverse transcription of viral RNA to cDNA or inhibit the viral protease necessary to cleave viral precursor proteins into the proteins needed to assemble a new virion and complete its maturation to infectious virus.

Some anti-HIV drugs in clinical use

Generic name (other names)	Typical dosage	Some potential side effects
	REVERSE TRANSCRIPTASE INHIBITORS: NUCLEOSIDE ANALOG	
Didanosine (Videx, ddI)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (Epivir, 3TC)	1 pill, 2 times a day	Usually none
Stavudine (Zerit, d4T)	1 pill, 2 times a day	Peripheral neuropathy
Zalcitabine (HIVID, ddC)	1 pill, 3 times a day	Peripheral neuropathy, mouth inflammation, pancreatic inflammation
Zidovudine (Retrovir, AZT)	1 pill, 2 times a day	Nausea, headache, anemia, neutropenia (reduced levels of neutrophil white blood cells), weakness, insomnia
Pill containing lamivudine and zidovudine (Combivir)	1 pill, 2 times a day	Same as for zidovudine
	REVERSE TRANSCRIPTASE INHIBITORS: NONNUCLEOSIDE ANALOGUES	
Delavirdine (Rescriptor)	4 pills, 3 times a day (mixed into water); not within an hour of antacids or didanosine	Rash, headache, hepatitis
Nevirapine (Viramune)	1 pill, 2 times a day	Rash, hepatitis
	PROTEASE INHIBITORS	
Indinavir (Crixivan)	2 pills, 3 times a day on empty stomach or with a low-fat snack and not within 2 hours of didanosine	Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Nelfinavir (Viracept)	3 pills, 3 times a day with some food	Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Ritonavir (Norvir)	6 pills, 2 times a day (or 4 pills, 2 times a day if taken with saquinavir) with food and not within 2 hours of didanosine	Nausea, vomiting, diarrhea, abdominal pain, headache, prickling sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Saquinavir (Invirase, a hard-gel capsule; Fortovase, a soft-gel capsule)	6 pills, 3 times a day (or 2 pills, 2 times a day if taken with ritonavir) with a large meal	Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

SOURCE: J. G. Bartlett and R. D. Moore, 1998, Improving HIV therapy, *Sci. Am.* 279(1):87.

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Active and Passive Immunization

Immunity to infectious microorganisms can be achieved by active or passive **immunization**. In each case, immunity can be acquired either by natural processes (usually by transfer from mother to fetus or by previous infection by the organism) or by artificial means such as injection of antibodies or vaccines (Table 18-1, on page 416). The agents used for inducing passive immunity include antibodies from humans or animals, whereas active immunization is achieved by inoculation with microbial pathogens that induce immunity but do not cause disease or with antigenic components from the pathogens. This section describes current usage of passive and active immunization techniques.

Acquisition of passive and active immunity

Type	Acquired through
Passive immunity	Natural maternal antibody
	Immune globulin*
	Humanized monoclonal antibody
	Antitoxin†
Active immunity	Natural infection
	Vaccines‡
	Attenuated organisms
	Inactivated organisms
	Purified microbial macromolecules
	Cloned microbial antigens
	Expressed as recombinant protein
	As cloned DNA alone or in virus vectors
	Multivalent complexes
	Toxoid§

Common agents used for passive immunization

Disease	Agent
Black widow spider bite	Horse antivenin
Botulism	Horse antitoxin
Diphtheria	Horse antitoxin
Hepatitis A and B	Pooled human immune gamma globulin

Measles	Pooled human immune gamma globulin
Rabies	Pooled human immune gamma globulin
Respiratory disease	Monoclonal anti-RSV*
Snake bite	Horse antivenin
Tetanus	Pooled human immune gamma globulin or horse antitoxin

*Respiratory syncytial virus

Classification of common vaccines for humans

Disease or pathogen	Type of vaccine
WHOLE ORGANISMS	
Bacterial cells	
Anthrax	Inactivated
Cholera	Inactivated
Pertussis*	Inactivated
Plague	Inactivated
Tuberculosis	Live attenuated BCG†
Typhoid	Live attenuated
Viral particles	
Hepatitis A	Inactivated
Influenza	Inactivated
Measles	Live attenuated
Mumps	Live attenuated
Polio (Sabin)	Live attenuated
Polio (Salk)	Inactivated
Rabies	Inactivated
Rotavirus	Live attenuated
Rubella	Inactivated
Varicella zoster (chickenpox)	Live attenuated
Yellow fever	Live attenuated

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PURIFIED MACROMOLECULES	
Toxoids	
Diphtheria	Inactivated exotoxin
Tetanus	Inactivated exotoxin
Capsular polysaccharides	
Haemophilus influenzae type b	Polysaccharide + protein carrier
Neissera meningitidis	Polysaccharide
Streptococcus pneumoniae	23 distinct capsular polysaccharides
Surface antigen	
Hepatitis B	Recombinant surface antigen (HBsAg)

Comparison of attenuated, killed and DNA vaccines

Characteristic	Attenuated vaccine	Inactivated vaccine	DNA vaccine
Production	Selection for avirulent organisms: virulent pathogen is grown under adverse culture conditions or prolonged passage of a virulent human pathogen through different hosts	Virulent pathogen is inactivated by chemicals or irradiation with γ-rays	Easily manufactured and purified
Booster requirement	Generally requires only a single booster	Requires multiple boosters	Single injection may suffice
Relative stability	Less stable	More stable	Highly stable
Type of immunity induced	Humoral and cell-mediated	Mainly humoral	Humoral and cell-mediated
Reversion tendency	May revert to virulent form	Cannot revert to virulent form	Cannot revert