Biologicals

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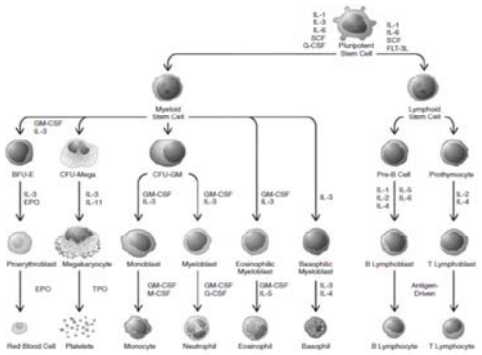
Overview

- ***Biologicals***
  - Haematopoietic growth factors and coagulation factors
  - Interferons
  - Hormones
  - Enzymes
  - Monoclonal antibodies
  - Vaccines

Biologicals

- Biologically based therapeutic products
- Genetically engineered proteins derived from human genes
- Not a homogenous group of drugs
- Differ significantly from traditional drugs in that they target specific components of the immune system instead of broadly affecting many areas of the immune system

Haematopoiesis



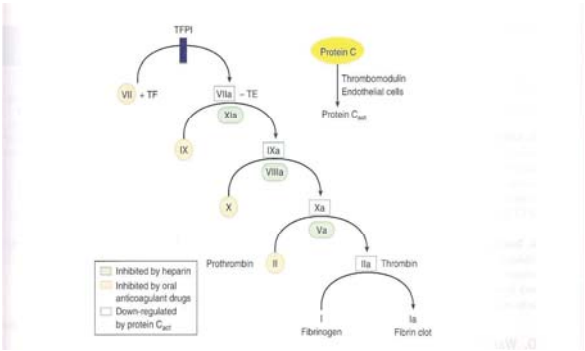
Erythrocyte-stimulating agents

- ***Subclass***
  - Recombinant human erythropoietins
    - Epoetin alfa
    - Methoxy polyethylene glycol-epoetin beta
    - Darbepoetin alfa
- ***Mechanism of Action***
  - Agonist of erythropoietin receptors expressed by red cell progenitors
  - Action dependent on iron stores in the body
- ***Clinical Applications***
  - Anaemia, especially associated with chronic renal failure, HIV infection, cancer, and prematurity; prevention of need for transfusion in patients undergoing certain types of elective surgery
- ***Pharmacokinetics***
  - Intravenous or subcutaneous administration 1–3 x per week (Epoetin alfa)
  - Long-acting glycosylated form administered weekly (Darbepoetin alfa)
  - Long-acting form administered 1–2 x per month (Methoxy polyethylene glycol-epoetin beta)
- ***Toxicities, Drug Interactions***
  - Hypertension, thrombotic complications, and, very rarely, pure red cell aplasia; to reduce the risk of serious cardiovascular events, haemoglobin levels should be maintained <12 g/dL

Myeloid growth factors

- ***Subclass***
  - Recombinant human granulocyte colony-stimulating factor(G-CSF)
    - Filgrastim
    - Pegfilgrastim
- ***Mechanism of Action***
  - Stimulates G-CSF receptors expressed on mature neutrophils and their progenitors
- ***Clinical Applications***
  - Neutropenia associated with congenital neutropenia, cyclic neutropenia, myelodysplasia, and aplastic anemia; ***secondary prevention of neutropenia in patients undergoing cytotoxic chemotherapy to prevent systemic infection***; mobilization of peripheral blood cells in preparation for autologous and allogenic stem cell transplantation
- ***Pharmacokinetics***
  - Daily subcutaneous administration
  - Filgrastim – half-life :3.5 hrs
  - Pegfilgrastim- half-life : 15-80 hrs
- ***Toxicities, Drug Interactions***
  - Bone pain; rarely, splenic rupture

Clotting cascade



Clotting factors

- ***Subclass***
  - Recombinant human factor VIII concentrate
    - *Kogenate FS®*
- ***Mechanism of Action***
  - Key factor in the clotting cascade
- ***Clinical Applications***
  - Hemophilia A
- ***Pharmacokinetics***
  - Parenteral administration
  - Half-life : 13 hrs
- ***Toxicities, Drug Interactions***
  - Infusion reaction, hypersensitivity reaction

Interferons

- In 1957 Isaacs and Lindemann noted that virally infected cells produced a protein that conferred viral resistance to naïve cells
- They called the substance “interferon.”
- Cytokines that demonstrate diverse immunomodulatory and antiproliferative properties in addition to their antiviral effects
- Recombinant IFNs are used as therapeutic agents in cancer, chronic viral infections and multiple sclerosis.
- Three classes of human interferons viz.
  - Interferon alfa
  - Interferon beta
  - Interferon gamma

Interferons

- ***Contraindications***
  - Seizure disorders, pre-existing cardiac disease, severe renal disease or hepatic impairmant
- ***Adverse effects***
  - “flu-like” symptoms therefore predose with paracetamol, fatigue, nausea, cardiovascular effects (hypotension and hypertension, arrhythmias), Myelosuppression (granulocytopenia and thrombocytopenia), elevation of liver enzymes.

Commercially available human interferons

Interferon Type	Commercial Name	Indications
Interferon-α2b	*Intron-A*	Melanoma, hepatitis B, Condylomata accuminata, Leukaemia, Kaposi Sarcoma
Peginterferon α2b	*Pegintron*	Chronic hepatitis C
Interferon-α2a	*Roferon-A*	Chronic Hepatitis C
Peginterferon-α2a	*Pegasys*	Chronic Hepatitis C
Interferon- β1a	*Avonex*	Multiple sclerosis
Interferon-β1b	*Betaferon*	Multiple sclerosis
Interferon-γ1b (not in SA)	*Actimmune*	Chronic granulomatous disease

Peptide and Protein hormones

TABLE 8.1. Clinically useful peptide and protein hormones in the pre-recombinant DNA era

Compound	Source(s)	Clinical Use
Insulin	Bovine and porcine pancreata	Treatment of insulin-dependent diabetes mellitus
Glucagon	Bovine and porcine pancreata	Treatment of acute hypoglycemia
Parathyroid hormone (PTH)	Bovine parathyroid glands	Differential diagnosis of hypocalcemia
Thyrotropin stimulating hormone (TSH)	Bovine pituitary	Identification of thyroid cancer metastases in patients previously treated for thyroid cancer
Adrenocortitropic hormone (ACTH)	Bovine pituitary	Diagnosis of adrenal disorders Treatment of gelastic seizures
Cosyntropin	Chemically synthesized active peptide fragment	Diagnosis of adrenal disorders
Antidiuretic hormone (ADH)	Bovine posterior pituitaries	Treatment of diabetes insipidus
Desmopressin Acetate (DDAVP)	Chemically synthesized analogue of arginine vasopressin	Treatment of diabetes insipidus
Somatotropin or growth hormone (GH)	Human cadaver pituitaries	Treatment of severe GH deficiency in children
Human menopausal gonadotropin (hMG)	Urine of postmenopausal women	Induction of ovulation
Human chorionic somatotropin (hCG)	Human placenta	Analogue of pituitary luteinizing hormone (LH) used for evaluation of testicular function and treatment of cryptorchidism

Peptide and Protein hormones

- ***Recombinant DNA era***
  - Insulin
  - Glucacon
  - Growth Hormone
  - Human chorionic ganadotrophin (hCG)
  - Follicular Stimulating hormone
  - Gonadotropin-releasing hormone (GnRH)
  - Oxytocin
  - Octreotide

Recombinant human insulin in diabetes mellitus

- Occasionally produces allergic reactions
- The effective dose may be less than animal insulin
- Patients are aware of hypoglycaemia as with other insulin preparations
- Can be given intravenously
- May be used in type 2 diabetes mellitus

Enzyme therapies

Enzyme	Clinical Use
Dornase Alfa	Cystic Fibrosis
Alteplase Tenecteplase	STEMI (ST segment elevation MI)
Drotrecogin alfa	Severe Sepsis

Alteplase

- The best course of treatment for STEMI

Monoclonal Antibodies (MoAbs)

- Proteins and/or derivatives that modulate the immune system , down regulate the inflammatory response or support tumour specific defense.
- Target specific part of the cell with the disease or cancer.
- ***Types of MoAbs***
  - Naked MoAbs- work independently
    - Antitumour
    - Immunosuppressants and anti-inflammatory
    - Antiplatelets
  - Conjugated MoAbs- joined to ChemoRx drug , radioactive particle, or a toxin (not available in South Africa)

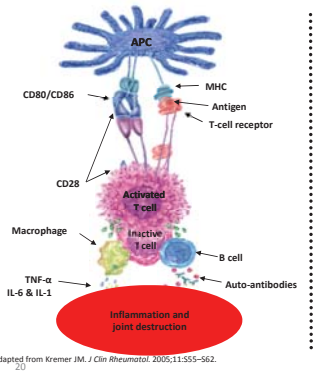
Immune System

- Complex network designed to protect the host from both external (such as bacteria and viruses) and internal threats (such as malignant transformation)
- Complement components, phagocytic cells, and natural killer (NK) cells, the ***innate*** **immune system** initiates the defense against pathogens and antigenic insult.
- If the innate response is inadequate, the ***adaptive*** **immune** response is mobilized → activation of T lymphocytes, the effectors of **cell-mediated immunity,** and the production of antibodies, by activated B lymphocytes, the effectors of **humoral immunity.**
- The subsets of lymphocytes that mediate different parts of the immune response can be identified by specific cell surface components or **clusters of differentiation (CDs).** Helper T (TH) cells bear the CD4 protein complex, whereas cytotoxic T lymphocytes express the CD8 protein complex.

Antigen Recognition and Processing

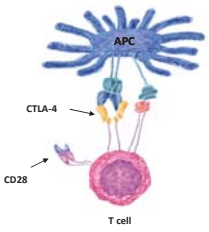
- First step in the adaptive immune response
- **Antigen-presenting cells (APCs)**, process antigens into small peptides that can be recognized by T-cell receptors (TCRs) on the surface of CD4 TH cells.
- The most important antigen-presenting cell surface molecules are the **major histocompatibility complex (MHC) class I** and **II** proteins.
- The activation of TH cells by the class II MHC-peptide complex requires the participation of costimulatory and adhesion molecules in addition to activation of T-cell receptors

T-cell Activation in the Normal Immune Response



Adapted from Kremer JM. *J Clin Rheumatol.* 2005;11:S55–S62.

Down-regulation of T cell



CTLA-4 binding: down-regulation of T cell

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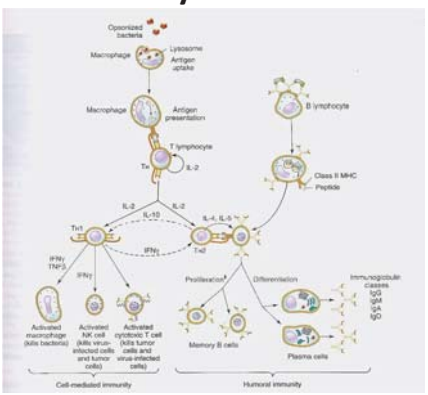
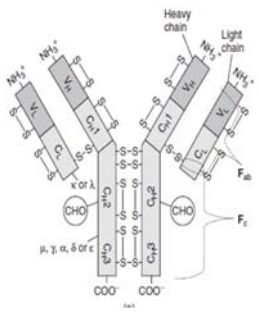
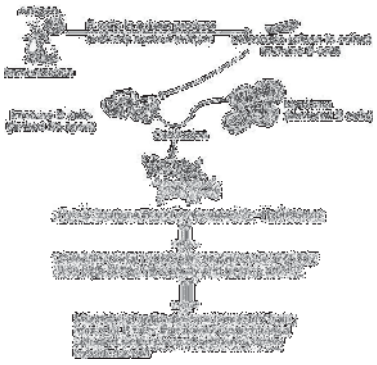
Immune System Overview

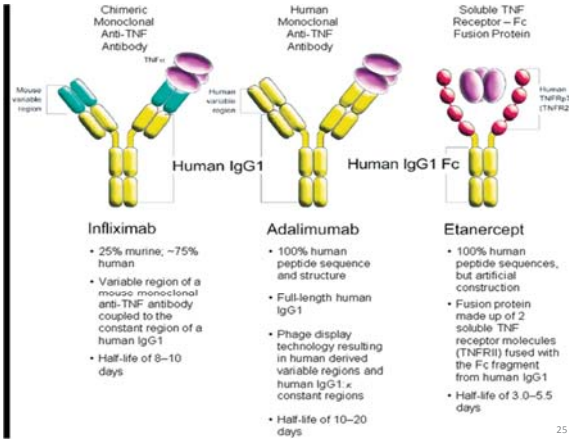


Immunoglobulin



Monoclonal Antibody production





Current naming convention

-ximab	Chimeric monoclonal antibody (infliximab, rituximab, etc)
-zumab	Humanised monoclonal antibody (efalizumab, etc)
-umab	Human monoclonal antibody (adalimumab, etc)
-cept	Receptor-antibody fusionprotein (alefacept, etanercept, onercept, etc)

Antitumour MoAbs

- ***Vascular endothelial growth factor (VEGF) inhibitors***
  - Bevacizumab
- ***Mechanism of Action***
  - Inhibits binding of VEGF to its receptor, resulting in inhibition of tumor vascularization
- ***Clinical Applications***
  - Colorectal, breast, non-small cell lung, and renal cancer
- ***Toxicities, Drug Interactions***
  - Hypertension, infusion reaction
  - Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, proteinuria

Antitumour MoAbs

- ***Growth factor receptor inhibitors***
  - Trastuzumab
- ***Mechanism of Action***
  - Inhibits the binding of EGF to the HER-2/*neu* growth receptor
- ***Clinical Applications***
  - HER-2/*neu* receptor positive breast cancer
- ***Toxicities, Drug Interactions***
  - Nausea, vomiting, chills, fever, headache
  - Cardiac dysfunction

Antitumour MoAbs

- ***Anti B lymphocyte***
  - Rituximab
- ***Mechanism of Action***
  - Against the CD20 antigen found on the surface of normal and malignant B lymphocytes.
- ***Clinical Applications***
  - Relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma (NHL)
  - Moderate to severe, active RA following inadequate response to TNF –α a blockers or in patients in whom the TNF –α blockers are contraindicated
- **Pharmacokinetics**
  - Two 1000-mg IV infusions separated by 2 weeks. To reduce the severity of infusion reactions, methylprednisolone at 100 mg IV or its equivalent is administered 30 minutes prior to each infusion. Time to reponse is usually 8 – 16 weeks
- ***Toxicities, Drug Interactions***
  - Infusion related reactions
  - Haematological side effects
  - Infections
  - Malignancies
  - Neurologic syndromes
  - Skin reactions

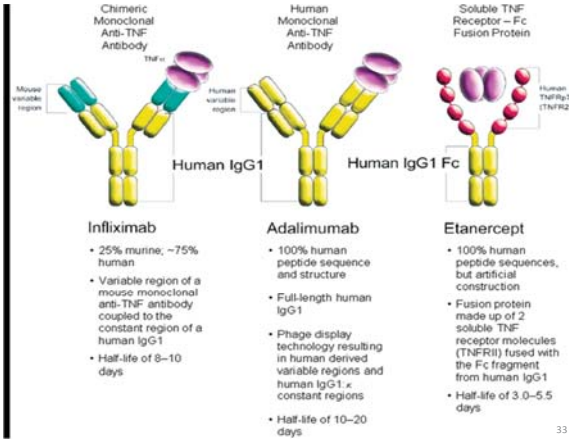
Immunosuppressant and Anti-inflammatory MoAbs

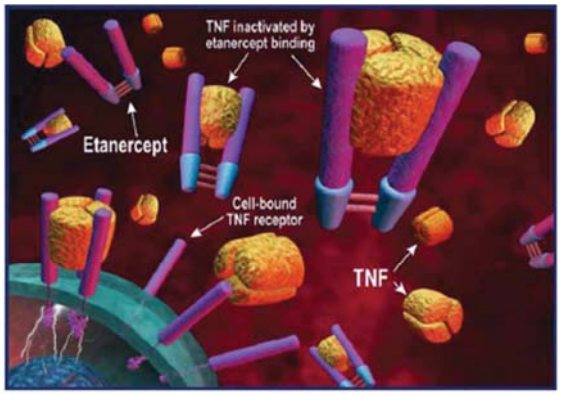
Anti-Cytokines

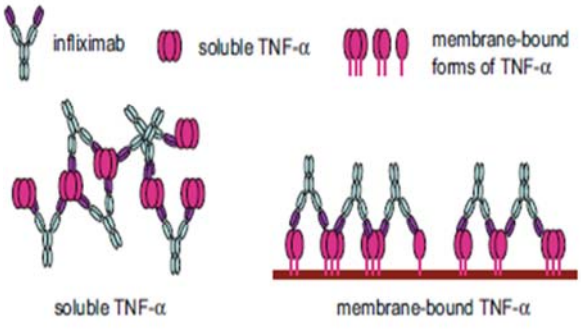
- ***Anti-TNF(tumour necrosis factor)***
  - Adalimumab
  - Infliximab
  - Etanercept
- ***Interleukin-6 antibody***
  - Tocilizumab

The TNF-alfa blockers

- ***Examples***
  - Adalimumab
  - Infliximab
  - Etanercept
- ***Mechanism of Action***
  - TNF-α and prevents it from activating TNF- α receptor
- ***Clinical Applications***
  - Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis
- ***Pharmacokinetics***
  - Parenteral-intravenous or subcutaneous
- ***Toxicities, Drug Interactions***
  - Hypersensitivity reactions, infection, malignancy







Biologicals- general considerations

- ATTRACT study proved that biologicals have the ability to halt damage in rheumatoid arthritis.
- Half-life of the biologicals
  - Infliximab 8-9 days
  - Etanercept 4 days
  - Adalimumab 15- 19 days
  - Rituximab 19-22 days
  - Abatacept 13 days
  - Tocilizumab 13 days

Infliximab

- Pharmacokinetics:
  - Infused IV over at least 2 hours every 8 weeks

Etanercept

- Given subcutaneously 25mg twice a week or 50mg weekly.
- The time to maximum serum concentration after a single injection is about 72 hours.

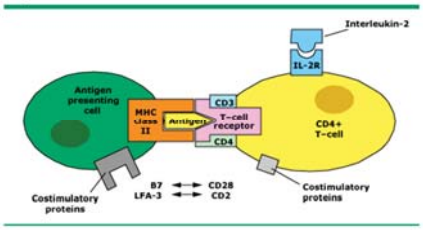
Interleukin-6 antibody

- ***Examples***
  - Tocilizumab
- ***Mechanism of Action***
  - IL-6 receptor monoclonal antibody
- ***Clinical Applications***
  - Rheumatoid arthritis, juvenile idiopathic arthritis
- ***Pharmacokinetics***
  - Intravenous infusion over 1 hour, every 4 weeks, dose of 8mg/kg.
- ***Toxicities, Drug Interactions***
  - Gastrointestinal, haematological, infections, hyperlipidaemia, malignancies , infusion reactions

T-cell targeted biologicals

- ***Fusion protein to CTLA-4***
  - Abatacept
- ***Anti-IL-2 receptor antibody***
  - Basiliximab- binds to IL-2 receptor on the surface of activated T cells → block IL-2 mediated T cell activation

Representation of T-cell activation



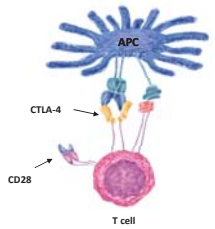
Schematic representation of initiation of the immunologic response to an antigen. The antigen binds to a groove in MHC class II molecules on antigen-presenting cells (APCs, such as macrophages). This binding allows the antigen to be presented to antigen receptors on autoreactive CD4 inducer or helper T cells which, in type 1 diabetes mellitus, initiate autoimmune injury to the pancreatic beta-cells. In addition, the respective binding of B7 proteins and LFA-3 (lymphocyte functional antigen-3) on APCs to CD28 and CD2 on T cells are important **costimulatory pathways** that further increase T-cell activation. Other molecules also can participate in the immune response, such as the binding of interleukin-2 to its receptor (IL-2R).

UpToDate

Abatacept

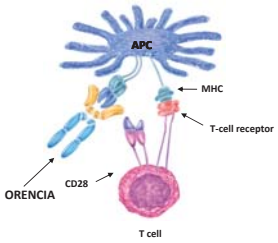
- ***Mode of Action***
  - Fusion protein to CTLA -4 that acts as a T-cell co-stimulation modulator inhibiting T-cell stimulation.
- ***Clinical applications***
  - Active, moderate to severe rheumatoid arthritis either after failure to respond to adequate treatment of chemical DMARDs or TNF- α blockers.
- ***Pharmacokinetics***
  - 750mg or 1000mg every 4 weeks with a loading dose of 3 doses given at weeks 0, 2 and 4. Response can be within 2 –4 weeks, but most patients respond within 12 –16 weeks.
- ***Adverse events***
  - Infections, malignancies and pulmonary disease

Down-regulation of T cell



CTLA-4 binding: down-regulation of T cell

Upstream T-cell Modulation with ORENCIA® (abatacept)



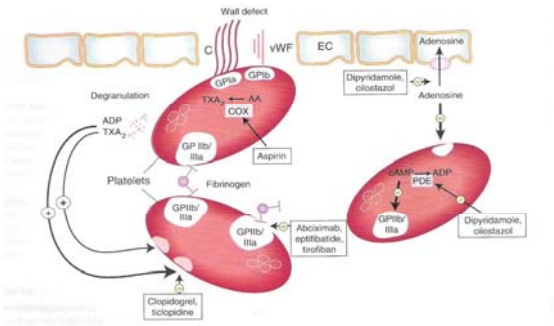
ORENCIA inhibits T-cell activation by binding to CD80 and CD86. The relationship of these biologic response markers to the mechanisms by which ORENCIA exerts its effects in rheumatoid arthritis (RA) is unknown.

Adapted from Kremer JM. *J Clin Rheumatol*. 2005;11:S55–S62.

Other Biologicals

- ***Glycoprotein IIb/IIIa inhibitor (GP IIb/IIIa)***
  - Abciximab
- ***Mechanism of Action***
  - Inhibits platelet aggregation by interfering with GPIIb/IIIa binding to fibrinogen and other ligands
- ***Clinical Applications***
  - Used during PCI to prevent restenosis; acute coronary syndrome
- ***Pharmacokinetics***
  - Parenteral administration
- ***Toxicities, Drug Interactions***
  - Bleeding, thrombocytopenia with prolonged use

Antiplatelet Agents



Pathogen	Types of Vaccines Available for Each Pathogen Attenuated	Whole Killed	Subcellular/Subunit
Viral			
	Smallpox		
	Polio	Polio	
	Measles/mumps/rubella		
	Varicella zoster		
	Influenza (cold-adapted)	Influenza	
	Adenovirus		
	Yellow fever		
		Rabies	
		Japanese encephalitis	
		Hepatitis A	
			Hepatitis B
Bacterial			
	Tuberculosis (BCG)		
	Salmonella typhi Ty21a	*Salmonella typhi*	Vi capsular polysaccharide
		Cholera	
		Plague	
		Lyme disease	
		Perstussis	Diptheria/tetanus/pertussis (acellular)
			Hemophilus influenza b
			Streptococcus pneumoniae
			Meningococcal

Box 1 History of immunotherapy

1796	Jenner introduces vaccinia (cowpox) immunization to prevent subsequent smallpox infection.
1879–1886	Louis Pasteur introduces first laboratory-weakened infectious agent (chicken cholera bacterium) and shortly thereafter develops weakened rabies for active immunization.
1888	Emile Roux and Alexandre Yersin isolate toxin from diphtheria.
1890	Emil von Behring and Shibasabo Kitasato in Koch's laboratory find that injecting diphtheria toxin into animals produces a serum containing an antitoxin that provides passive anti-diphtheria immunity to people.
1900	Paul Ehrlich suggests that molecules that react with tumors could play a key role in cancer therapy, presaging antibody-mediated passive immunotherapy.
1954–1955	Jonas Salk and Albert Sabin introduce killed and live attenuated polio vaccines that soon lead to the elimination of poliomyelitis.
1965	IgG anti-D (anti-RH) is administered to prevent of RH immunization and thus prevent erythroblastosis fetalis; this is a translation of the basic insight that passive administration of a specific IgG antibody inhibits the active production of that antibody.
1975	George Köhler and Cesar Milstein develop hybridoma technology for monoclonal antibody generation.
1977	Smallpox is declared eradicated through vaccination.
1982	The first report of successful use of a monoclonal antibody to treat a human neoplasm (patient-specific anti-idiotype antibody to treat B-cell lymphoma) is reported.
1986	The first monoclonal antibody, muromonab-CD3 (Orthoclone OKT3), is approved by the FDA.
1986	The first humanized antibody is produced by replacing the complementarity regions in a human antibody with those of a mouse.
1986–2000	IL-2, IFN-α, IFN-β and IFN-γ are approved for use in the treatment of neoplasia, hepatitis and multiple sclerosis.
1988–1991	The methodology for isolating tumor antigens recognized by CTLs is introduced; the first human antigen from melanoma patients identified by CTLs is isolated.
1997	The first humanized monoclonal antibody (daclizumab, Zenapax) is approved by the FDA.
1997	The first monoclonal antibody (rituximab, Rituxan) for the treatment of malignancy is approved.
1998	An antibody to TNF-α (infliximab, Remicade), and p75 TNF receptor linked to the Fc of IgG1 (etanercept, Enbrel) are approved for use in the treatment of rheumatoid arthritis and Crohn disease.
2000	The first toxin-linked monoclonal antibody (gemtuzumab ozogamicin Mylotarg) is approved by the FDA.
2002	The first radionuclide-linked monoclonal antibody (ibritumomab tiuxetan, Zevalin) is approved by the FDA.