université PARIS-SACLAY

Monoclonal Antibodies

History, Technology, Products, Applications, Markets, Actors, Perspectives

AMPBM 2024 course: Jan. 30th 2024

Pr. C. SOLA
UMR1137, INSERM-University of Paris

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Schedule

- 1. History, Definition, Structure, Genes
- 2. reminder on physiology and biochemistry and history of MAbs discoveries
- 3. Generalities on Biotherapies, Technologies of Mab obtention and their evolution
- 3. Principles of nomenclature
- 4. Perspectives
- 5. **Monographies**

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resssources 2018-2021

http://penite-depot.univ-lille2.fr/nuxeo/site/esupversions/20ea8b69-bad9-4ebe-9419-a7bdc0e66e47

Video course : Pr. Alain Fischer, cours du collège de France

https://www.college-de-france.fr/site/alain-fischer/course-2015-05-26-17h00.htm

http://www.college-de-france.fr/site/alain-fischer/course-2015-05-19-17h00.htm

http://mabimprove.univ-tours.fr/wp-content/uploads/biomedicaments2.pdf (***excellent review, in french***) Les biomédicaments2e partie : les anticorps thérapeutiquesManon Broutin et Hervé Watier

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A little bit of history

Emil von Behring
1854-1917

Shibasabaro Kitasato
1853-1931

E von Behring in Germany
1890 : existence of tetanos toxin immunity factor
1892 : transfert of immunity with serum
1894 : adaptation to diphteria
and **S. Kitasato** in Japan
invent« *serotherapy* »

Paul Ehrlich
1854-1915

Ilya Ilitch Metchnikov

Ilitch Metchnikov
1845-1916

P. Ehrlich is considered as the father of chemotherapy and inventor of the word « *antibody* » which appears for the first time in 1901.

He is with **Ilya Ilitch Metchnikov** Medicine Nobel price laureate in 1908. Metchnikov also discovers phagocytosis.

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History, Definition and Structure

E. Cohn 1940 :
(fraction II of Cohn) alcoholic plasma fractionation

O. Bruton 1952: discovery of Agammaglobulinemia Absence of Btk gene (Bruton tyrosine kinase, linked to Xq21.3) *BTK* is required for the proliferation and differentiation of B lymphocytes. (19 exons, 659 Aa)
Bruton OC (1952). "Agammaglobulinemia". Pediatrics. 9 (6): 722–8. PMID 14929630
Serotherapie : Administration IgG

The immune response involves a group of serum proteins with similar general properties
The Immunoglobulins

When they bind a molecule or a viral or bacterial particle, the **immunoglublins** are all designated by the name of antibodies, and the recognized entity is called antigen

The antibody plays an essential role in the immune response

- It is the receptor, at the surface of B lymphocytes or in solution in serum
- Is is the transmettor or activator of physiological signals

These two roles are held by distinct domains within an immunoglobulin molecule

Every antibody is characterized by two properties :

Ability to specifically fix one or many ligands and

Fab domain

participation to one or many effector functions (**complement activation**, phagocytosis activation, secreion of vasocactives amines...)

Fc domain

adapted from Pr. Jamal Taoufik, 3èmes Journées Pharmaceutiques du Gharb

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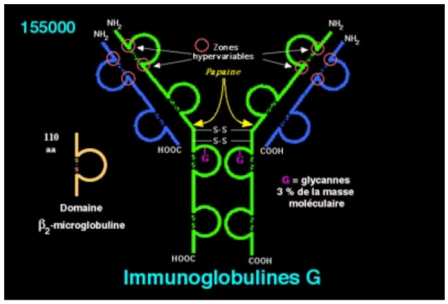
Definition and Structure



http://www.chups.jussieu.fr/polys/biochimie/Mbioch/POLY.Chp.7.2.html

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the ß2m domain

ß2M is associated with both antibodies
and the **Major Histocompatibility Complex class I** (MHC-I)

1.Beta-2 Microglobulin in Antibodies:

Antibodies are proteins produced by the immune system in response to the presence of foreign substances (antigens) in the body. ß2M is not a typical component of antibodies. Antibodies, also known as immunoglobulins, consist of two heavy chains and two light chains. The structure and function of antibodies are primarily determined by the **variable** regions of these chains, which form the antigen-binding site. ß2M is not part of the antibody structure.

1.Beta-2 Microglobulin in Major Histocompatibility Complex Class I (MHC-I):

ß2M is a component of the MHC class I molecule. MHC class I molecules are found on the surface of most nucleated cells and play a crucial role in presenting intracellular antigens to cytotoxic T cells. The MHC-I molecule consists of a heavy chain and beta-2 microglobulin. The heavy chain is encoded by the MHC gene, while beta-2 microglobulin is a smaller protein that is non-covalently associated with the heavy chain. Together, they form the MHC class I complex, which presents peptides derived from intracellular proteins to cytotoxic T cells, allowing the immune system to monitor the internal state of the cell.

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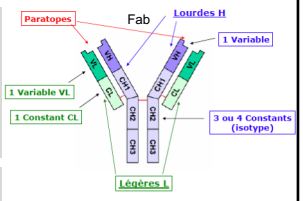
Definition and Structure

Antibodies are glycoproteins formed by two categories of polypeptidic chains, **Light chains L** and **Heavy chains H**
The type of heavy chain will define the class and the sub-class of Immunoglobulin :
Gamma1 for Ig **G1**, *Alpha* for IG**A**, *Mu* for Ig**M**
Delta for Ig**D** and *Epsilon* for Ig**E**.
These molecules are symetrical

Light chains (L) Kappa and Lamda are formed by two domains :
- a **variable domaine VL** (Vkappa or Vlambda)
- a **constant domain CL** (CKappa or CLambda)

Heavy chains (H) encompass :
-an N **terminal variable domain (VH)**
3 (delta, gamma, alpha) or **4** (mu, epsilon) **constant domains (CH)**



notions of
allotype (C)
isotype (C)
idiotype (V)
were developped during the studies of blood groups of immunoglobulin

Pr. Jamal Taoufik, 3èmes Journées Pharmaceutiques du Gharb
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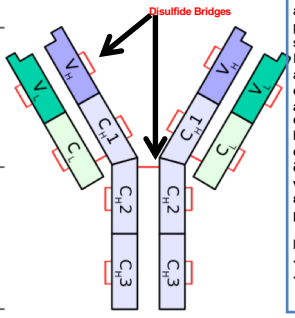
Allotype, Isotype, Idiotype

The **idiotype** is based upon the **variable regions** (labeled **VL** and **VH** in the diagram.)

The **allotype** depends on the **constant regions** (labeled **CL** and **CH1-3** in the diagram.)



The **isotype** refers to the class of antibody **ADGEM** according to predefined structural classes
In humans, there are **five heavy chain isotypes and two light chain isotypes**:
heavy chain
α - IgA **1, 2**
δ – IgD
γ - IgG **1, 2, 3, 4**
ε – IgE
μ – IgM

light chain
-κ
-λ

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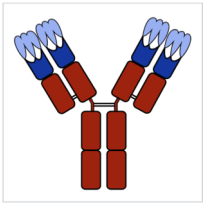
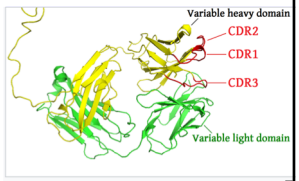
Complementarity-determining region

(also designated as Hypervariable regions)



Sketch of an antibody with the variable domains shown in blue, and the CDRs (which are part of the variable domains) in light blue



The "upper" part (Fab region) of an antibody. The complementarity-determining regions of the heavy chain are shown in red (PDB: 1IGT).

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Paratopes, epitopes, idiotypes and isotypes

Immunoglobulin-antigen interactions typically take place between: the **paratope**, the site on the Ig at which the antigen binds, and the **epitope**, which is the site on the antigen that is bound.

In vivo, Igs tend to be produced against intact antigens in soluble form, and thus preferentially identify surface epitopes that can represent conformational structures that are noncontiguous in the antigen's primary sequence.

This ability to identify component parts of the antigen independently of the rest makes it possible for the B cell to discriminate between two closely related antigens, each of which can be viewed as a collection of epitopes. It also permits the same antibody to bind divergent antigens that share equivalent or similar epitopes, a phenomenon referred to as **cross-reactivity**.

Immunization of heterologous species with monoclonal antibodies (or a restricted set of Igs) allowed the identification of both common and individual Igs antigenic determinants.

Individual determinant(s), termed **idiotype(s),** are contained within **VARIABLE** domains.

Common determinants, termed **isotypes**, are specific for the **CONSTANT** portion of the antibody and allow grouping of Igs into recognized classes, with each class defining an individual type of C domain.

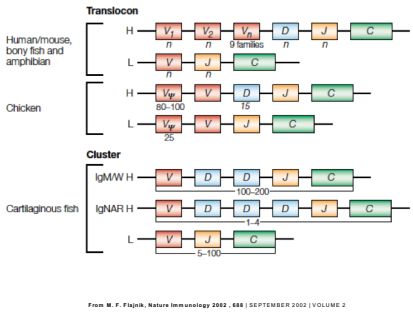
Determinants common to subsets of individuals within a species, yet differing between other members of that species, are termed **allotypes** and define inherited polymorphisms that result from gene alleles.

J. Allergy Clin Immunol . 2010, Schroeder and Cavacini

,11

Organisation of immunoglobulin genes

separate multigene families between H and L chains



From M. F. Flajnik, Nature Immunology 2002 , 688 | SEPTEMBER 2002 | VOLUME 2

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Rearrangement of IG light chain genes

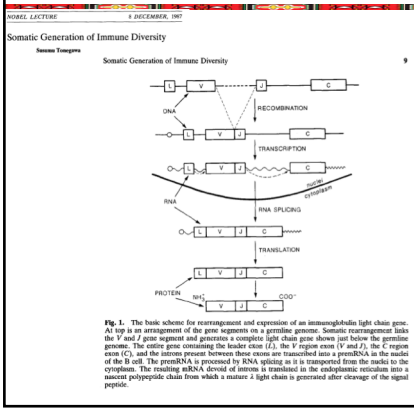

Fig. 1. The basic scheme for rearrangement and expression of an immunoglobulin light chain gene. At top is an arrangement of the gene segments on a germline genome. Somatic rearrangement links the *V* and *J* gene segment and generates a complete light chain gene shown just below the germline genome. The entire gene consisting the leader exon (*L*), the *V* region exon (*V* and *J*), the *C* region exon (*C*), and the introns present between these exons are transcribed into a premRNA in the nuclei of the B cell. The premRNA is processed by RNA splicing as it is transported from the nuclei to the cytoplasm. The resulting mRNA devoid of introns is translated in the endoplasmic reticulum into a nascent polypeptide chain from which a mature λ light chain is generated after cleavage of the signal peptide.

1939 –

Susumu Tonegawa

NOBEL PRIZE 1987

The somatic VDJ recombination concept

S. Tonegawa et al. 1987

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Heavy Chain Gene Rearrangement

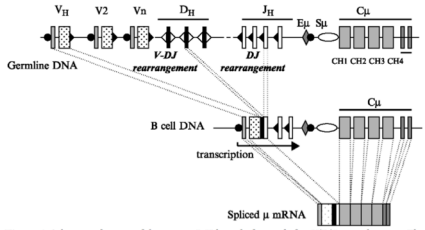

Figure 1 Schematic diagram of the murine IgH locus before and after V(D)J recombination. The V_H, D_H, and J_H gene segments are depicted as rectangles. The 12-bp RS sequences are shown as open triangles, and the 23-bp RS sequences as solid triangles. The μ constant region exons are shown as shaded rectangles, and the switch μ region as an oval. The position of the iEμ enhancer is indicated by a shaded diamond. The positions of the V_H and I exon promoters are shown as solid circles. Distances between the various elements are not drawn to scale.

Dudley et al. 2005

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Somatic hypermutation and Class switch recombination

In response to antigen, somatic hypermutation (**SHM**) and class switch recombination (**CSR**) induce further modifications of immunoglobulin genes in B cells

somatic hypermutation

Somatic hypermutation is a mechanism that introduces random mutations in the variable regions of immunoglobulin genes (genes that encode antibodies) within activated B cells. This process takes place in the ***germinal centers of lymphoid tissues, such as lymph nodes and the spleen****. The purpose of somatic hypermutation is to generate a diverse pool of antibody variants with slightly different antigen-binding properties.*

activation-induced cytidine deaminase (AID): transform C into U

class switch recombination (isotype switching)

The primary role of class switch recombination is to diversify the effector functions of antibodies without altering their antigen specificity. ***This process takes place in the germinal centers of secondary lymphoid organs, such as lymph nodes and the spleen.***

Cours MAGB-2018-1

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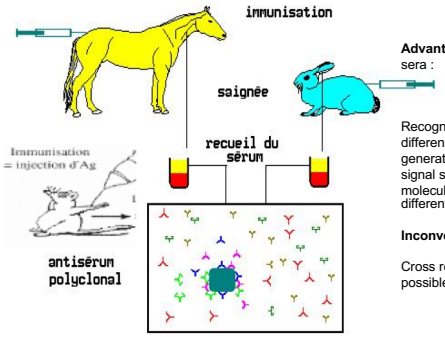
Before MAbs -> Polyclonal antibodies



Advantages of these sera :

Recognition of Ag by differents épitopes generating a stronger signal since a single Ag molecular may bind different antibodies.

Inconvenients :

Cross reactions are possible

http://www.ac-nancy-metz.fr

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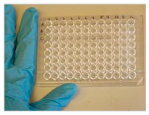
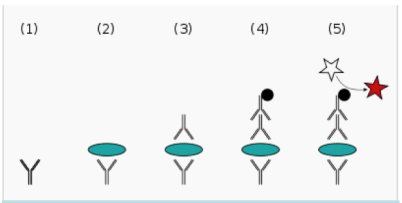
Physico-chemical properties of antibodies, importance for their assay

- Antibody molecules adsorb onto polystyrene surfaces and bind antigen.
- Antibody molecules do not adsorb onto glass surfaces





Sandwich ELISA : (1) the plate is covered with a capture antibody; (2) the sample is added, and all the antigen present will bind the capture antibody; (3) the detection antibody is added and it binds to the antigen; (4) the secondary antibody, linked to the enzyme, is added, and it binds to the detection antibody; (5) the substrat is added and is converted by the enzyme in a detectable molecule (either colored or fluorescent)

http://fr.wikipedia.org/wiki/M%C3%A9thode_immuno-enzymatique_ELISA

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Immunotherapy, history

Table 1 Passive immunotherapy with convalescent human serum

Year of study	Disease	Prophylaxis or treatment	Number of study subjects	Trend in benefit	Reference
1907	Measles (Rubeola)	Prophylaxis	Unknown	Prevention.	2
1918	Measles[a]	Prophylaxis	1	One child in a family of four children was given serum from the first infected child and was protected; the other two contracted measles.	96
1918	Measles	Prophylaxis	4	Prophylaxis was effective.	96
1918	1918 Pandemic flu	Treatment	56	Early administration generally resulted in distinct improvement in clinical symptoms.	97,98
1923	Varicella-Zoster virus	Prophylaxis	42	Seven contracted a mild form of the disease, 35 escaped without symptoms.	99
1963[b]	Bolivian hemorrhagic fever	Treatment	4	Individuals recovered after 6–8 weeks.	100
1959–1983	Argentine hemorrhagic fever	Treatment	4,433	Mortality rate of 3.29% (versus 42.85% in individuals treated before convalescent plasma was used).	101
1974–1978	Argentine hemorrhagic fever	Treatment	217	1.1% mortality rate of those treated with immune plasma.	102
1969	Lassa fever	Treatment	1	The individual recovered.	103
1984	Lassa fever	Prophylaxis and treatment	27	All study subjects given plasma on or before the 10th day survived with a rapid response to therapy.	104
1995	Ebola hemorrhagic fever	Treatment	8	12.5% fatality rate (versus overall case fatality rate of 80%); inconclusive regarding neutralizing antibodies in convalescent blood.	105
1993	HIV-1	Treatment of stage IV AIDS individuals	63	Randomized double-blind controlled trial. Study subjects were given 250 ml of HIV-immune plasma every 4 weeks. No significant toxicity and effect were found.	106
1995	HIV-1	Treatment of symptomatic HIV infection	86	Randomized double-blind controlled trial. Study subjects were given 300 ml of plasma rich in anti-HIV-1 antibody every 14 days for 1 year. Clinical benefit was observed.	107
2002[c]	HIV-1	Prevention of vertical transmission in Uganda	60	Phase 1/2 trial showed it is safe, well tolerated and similar pharmacokinetic property as other immunoglobulin products.	108
2003	SARS	Treatment	1	Fever decreased after administration of convalescent plasma.	109
2007	Influenza A (H5N1)	Treatment	1	Viral load was reduced after infusion of plasma; the individual recovered.	110

[a]Other studies refer to ref. 1. [b]Immune BHF gamma globulin was used. [c]HIV hyperimmune globulin was used.

Wayne A Marasco & Jianhua Sui, Nature Biotechnology, 2007

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MAb discovery history

1947-1995

1927-2002

1911-1994

Georges Köhler and Cesar Milstein 1975

« *Continuous cultures of fused cells secreting antibody of predefined specificity* » . *Nature*. 1975 Aug 7;256(5517):495-7.

Monoclonal antibody production technique

Nobel Price in Medecine in 1984 for the three !

(***idiotypic network theory***)

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Rappel on purins metabolism

HGPRT

Hypoxanthine ----------→ IMP (inosine monophosphate)
Guanine ----------→GMP (guanosine monophosphate)

This reaction transfers the 5-phosphoribosyl group from 5-phosphoribosyl 1-pyrophosphate towards purine. HGPRT plays a central role in generation of purin nucleotides via the purine **salvage pathway**.

Pyrimidines

Uridine phosphorylase adds ribose-1-phosphate to the free base uracil, forming uridine monophosphate. Uridine kinase then phosphorylates this nucleoside into its diphosphate and triphosphate forms. Deoxythymidine phosphorylase adds deoxyribose-1-phosphate to thymine, forming deoxythymidine monophosphate. **Thymidine kinase** can then phosphorylate this compound to deoxythymidine diphosphate and triphosphate.

Purines

Phosphoribosyltransferases add activated ribose-5-phosphate (called phosphoribosyl pyrophosphate or PRPP) to bases, creating nucleotide monophosphates. There are two types of phosphoribosyltransferases: adenine phosphoribosyltransferase (APRT) and **hypoxanthine-guanine phosphoribosyltransferase** (HGPRT). Lesch-Nyhan syndrome is associated with a deficiency of HGPRT.

http://en.wikipedia.org/wiki/Nucleotide_salvage

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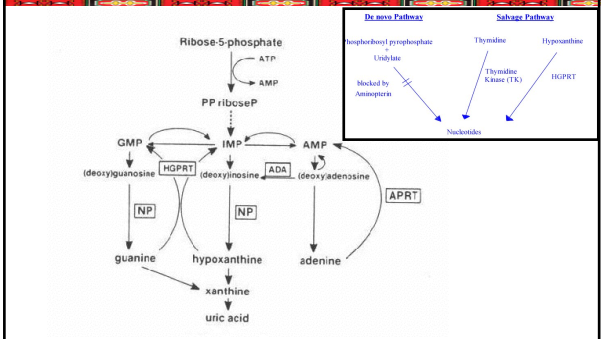
Biochemical Pathway of Purine Metabolism



http://img.medscape.com/pi/emed/ckb/pediatrics_general/884940-887823-2952.jpg

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Reminder on purins metabolism : Principle MAb

Hypoxanthine-guanine phosphoribosyltransferase (**HGPRT**) has been a valuable gene to work with.

One use of this gene is for **selection of hybrid cells**.

For example, a cancer cell that is deficient in HGPRT is fused to a normal cell that is HGPRT+ but TK- . The fusion of these two cells will create a hybrid that has both functional HGPRT and TK.

TK stands for thymidine kinase and is required for the cells to grow.

The hybrids are grown **on HAT medium** which contains Hypoxanthine, Aminopterin, and Thymine. ***Aminopterin blocks the de novo pathway forcing the cells to use the salvage pathway.*** Thus, cells that are HGPRT- or TK- cannot grow on HAT medium and **only** the hybrids cells will grow on the medium.

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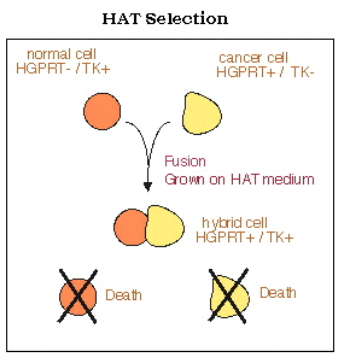
Reminder on purins metabolism : Principle MAb



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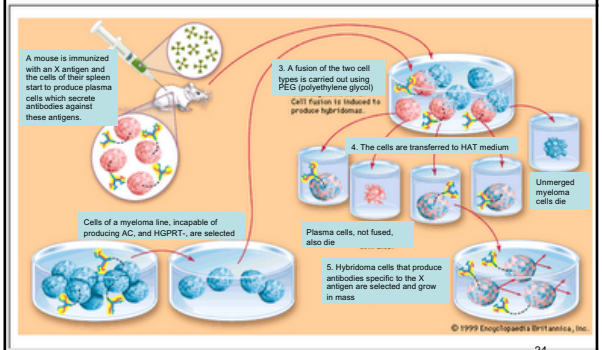
Technologie of production of Mab using Hybridomas



1999 Encyclopedia Britannica

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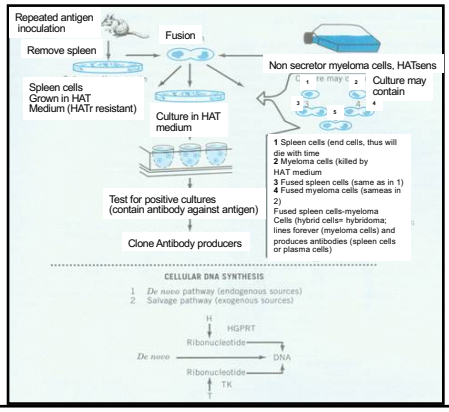
Technology of production monoclonal AB



Bispecific monoclonal antibody (BsMAb, BsAb)

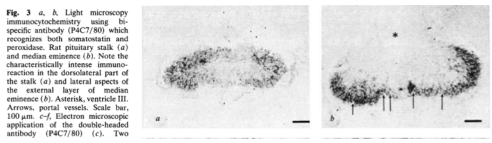
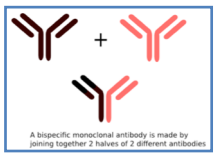


Fig. 3 *a, b*, Light microscopy immunocytochemistry using bi-specific antibody (P4C7/80) which recognizes both somatostatin and peroxidase. Rat pituitary stalk (*a*) and median eminence (*b*). Note the characteristically intense immuno-reaction in the dorsolateral part of the stalk (*a*) and lateral aspects of the external layer of median eminence (*b*). Asterisk, ventricle III. Arrows, portal vessels. Scale bar, 100 μm. *c–f*, Electron microscopic application of the double-headed antibody (P4C7/80) (*c*). Two



http://www.whatisbiotechnology.org/exhibitions/milstein/clinical

C.M. Milstein and A.C. Cuello, 'Hybrid hybridomas and their use in immunohistochemistry', Nature, 305 (1983), 537-40.

Advantages

1. possiblity of direct immunochemistry test without second antibody

2. Since 2012 : use in therapeutics : in cancer immunotherapy, where BsMAbs are engineered that simultaneously bind to a **cytotoxic cell (using a receptor like CD3) and a target like a tumour cell to be destroyed**

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Market Evolution

- 1% of Biomolecules market in 1995, 14% en 2002, **23% in 2014 to 27% in 2020**
- Global sales : **75 Billions US$ in 2014, 94 Billions forecasted for 2017, 125 Billions US$ by 2020** (source : BioPharm Int. 2016, 29,11,24)
- *Adalimumab* generated a turn-over of **4,5 Billion US$** in 2008
- **On the period 2006-12, the MAB market went through a yearly increase of 14.2% compared to 0.6% for small molecules**
- «new Blockbusters » are emerging every year
- Important historically for diagnostics markets (ELISA, IF, etc…) but these markets are nothing compared to therapeutical markets
- 20 molecules commercialized in 2008, 400 in development in 2012, 700 in 2016…

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2024-Wikipedia MAbs Listing

- **(N=408 in 2017), N>565 in 2024. (dynamic list)**
- **N=389 without trade name, N=176 with trade name in 2023, (N=82 in 2020)**
  - 3 **Fab** (Lucentis, ReoPro, Verluma)
  - 4 **3funct** (Ektomab Lymphomun Removab Rexomun)
  - 4 **BiTE** (Blincyto, Epkinly, Lunsumio, -)
  - 5 **BsAb** (Rybrevant, Hemlibra, Talvey, Columvi, Tecvayli)
  - 5 **F(ab')**2 (Indimacis-125,–,–,–,–)
  - 12 **Fab** (ReoPro, Verluma, Lucentis)
  - 5 **Fab'** (CEA-Scan, Cimzia, FibriScint, LeukoScan, LymphoScan)
  - 1 **di-scFv** (-)
  - 8 **scFv** (Mycograb, Beovu, Vicinium)
  - 1 **sdAb**
  - 483 **Mab** (Abegrin Actemra, RoActemra Actemra, RoActemra AFP-Cide Antova Arzerra Aurexis Avastin Benlysta, LymphoStat-B Blontress Bosatria CEA-Cide Cyramza Erbitux Gazyva Herceptin hPAM4-Cide HumaSPECT HuMax-CD4 HuMax-EGFr Humira HuZAF Hybri-ceaker Ilaris Kadcyla Lemtrada, Campath LeukArrest MabThera, Rituxan Mylotarg Myoscint NeutroSpec Numax Nuvion Omnitarg Opdivo Orthoclone OKT3 OvaRex Panorex Prolia Prostascint Raptiva Remicade Rencarex Scintimun Simponi Simulect Soliris Stelara Synagis, Abbosynagis Tactress Theracim, Theraloc Tysabri Vectibix Xolair Yervoy Zenapax Zevalin…)

update: 2024

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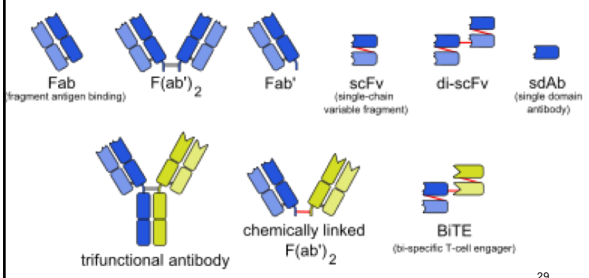
2024-Wikipedia MAbs Listing



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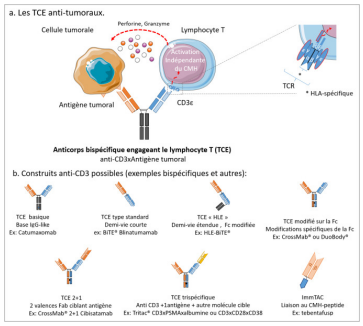
Anti-tumoral Antibodies



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Elranatamab : Anticorps bispecifique

*L'elranatamab est un anticorps **bispécifique IgG2 kappa** dérivé de deux anticorps monoclonaux (AcM). L'elranatamab est produit à partir de deux lignées cellulaires recombinantes issues d'ovaires de hamster chinois (CHO).*

Le 02/02/2023, la Haute Autorité de santé (HAS) a délivré une autorisation d'accès précoce, après avis de l'Agence Nationale de Sécurité du médicament et des produits de santé (ANSM) concernant le rapport bénéfice/risque présumé, pour le médicament ELRANATAMAB PFIZER dans l'indication : en monothérapie, pour le traitement des patients adultes atteints d'un myélome multiple en rechute et réfractaire, ayant reçu au moins trois traitements antérieurs, incluant un agent immunomodulateur, un inhibiteur du protéasome et un anticorps anti-CD38 et dont la maladie a progressé pendant le dernier traitement, lorsque toutes les options thérapeutiques sont épuisées (hors thérapies cellulaires), sur l'avis d'une réunion de concertation pluridisciplinaire (RCP). Ce médicament ne dispose pas encore d'une Autorisation de Mise sur le Marché (AMM).

Cette décision est susceptible d'évoluer (maintien, modification ou retrait) en fonction des nouvelles données. En cas de retrait ou de suspension, un dispositif de continuité de prise en charge des patients en cours de traitement est prévu.

https://www.youtube.com/watch?v=eKJu4_5Qy9Y

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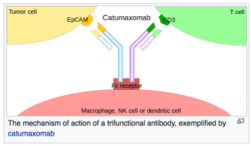
2024-Wikipedia MAbs Listing

- **By source**
- **Mouse n=53**, approved n=7
- **Chimeric n=49** (Erbitux MabThera, Rituxan Remicade Rencarex ReoPro Simulect)
- **Humanized n=242** (Abegrin Actemra, RoActemra Actemra, RoActemra AFP-Cide Antova Aurexis Avastin Bosatria CEA-Cide Cimzia Gazyva Herceptin hPAM4-Cide HuZAF Kadcyla Lemtrada, Campath LeukArrest Lucentis Mylotarg Numax Nuvion Omnitarg Raptiva Soliris Synagis, Abbosynagis Theracim, Theraloc Tysabri Xolair Zenapax)
- **Human n=195** (Arzerra Benlysta, LymphoStat-B Cyramza HumaSPECT HuMax-CD4 HuMax-EGFr Humira Ilaris Mycograb Opdivo Prolia Simponi Stelara Vectibix Yervoy)
- **Rat/Mouse Hybrid n=3** (Lymphomun Removab Rexomun)
- **Veterinary n=7** (Blontress, Tactress)
- **Rat/Mouse Hybrid, n=3**

update: 2024



The mechanism of action of a trifunctional antibody, exemplified by catumaxomab

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2024-Wikipedia MAbs Listing

- **By target**
- Alphafoetoprotein (1)
- Amyloid beta (2)
- Angiopoiztin2 (2)
- AOC3 (VAP-1) (2)
- **BAFF** (3)
- **C5** (6)
- **CA-125 (2/3)**
- CanAg (glycoform of MUC1)
- Carbonic hydrase 9 (CA-IX) (1)
- Cardiac myosin (1)
- CD11 CD18 (1)
- CD134 (2)
- CD137 (2) 4-1BB
- CD19 (**8**)
- CD154 (CD40L) (3)
- **CD20 (7/11)**
- CD22 (**5**)
- **CD25** (alpha chain of IL2 receptor/T cell)(**4**) **Basiliximab, Daclizumab**
- **CD3 (2/4) Muromonab**
- CD30 (2)
- CD33 (3), CD4 (7), CD40 (8)
- CD41 (integrin alpha-IIb) (1)

- **By target**
- **CD52 (2)**
- **CD70 (2)**
- **CEA (3)**
- CEA-related antigen (1)
- clostridium difficile (2)
- Clumping factor A (1)
- E. Coli shiga toxin 1 or 2
- **EGFR (2)**
- EpCAM (1)
- EpCAM, CD3 (1)
- F protein or RSV (1)
- Fibrin II, beta chain (1)
- GD2 ganglioside (1)
- **HER2/neu (4/5)**
- HER2/neu, CD3 (1)
- HGFR (3)
- Hsp90 (1)
- Interferon gamma (1)
- IgE FC region (1)
- IL1 ? (1)
- IL12, IL23 (2)
- IL13 (7)

- **By target**
- IL17A (5)
- IL23 (4)
- **IL6 (6)**
- **IL6 receptor (4)**
- Integrin alpha4 (1)
- Integrin alphavbeta3 (1)
- LFA-1 (CD11a) (1)
- **MUC1 (3)**
- NCA90 (granulose antigen) (1)
- **PD1 (10)**
- **PDGFRA (2)**
- Prostatic carcinoma cells (1)
- RANKL (1)
- Respiratory syncitial virus (2)
- Rh Factor (2)
- selectin P (2)
- spike prot rec bin dom SARSCov2 (9)
- **TNF-alpha (4/7)**
- Tumor antigen CTAA16.88 (1)
- **VEGF-A (3)**
- VEGFR2 (1)

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MAB against spike protein receptor binding domain of SARSCov2 (9)

Name	Brand name	Type	Source	Target	Approved
Bamlanivimab[295]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Emergency Use Authorization (EUA
Bebtelovimab[301]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Emergency Use Authorization (EUA
Casirivimab[296]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Yes when used with Imdevimab[297]
Cilgavimab[298]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Emergency Use Authorization (EUA
Etesevimab[296]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Emergency Use Authorization (EUA
Imdevimab[296]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Yes when used with casirivimab[297]
Regdanvimab[299]	Regkirona[300]	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Y[300]
Sotrovimab[302]	Xevudy	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Y[303][304]
Tixagevimab[298]	null	mab	human	spike protein receptor binding domain (RBD) of SARS-CoV-2	Emergency Use Authorization (EUA

Cours MAGB-2024

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Out of 49 NCE approved by FDA in 2019, 8 are Mabs

47.	Enhertu	fam-trastuzumab deruxtecan-nxki	12/20/2019	To treat metastatic breast cancer Press Release Drug Trials Snapshot
43.	Padcev	enfortumab vedotin-ejfv	12/18/2019	To treat refractory bladder cancer Press Release Drug Trials Snapshot
38.	Adakveo	crizanlizumab-tmca	11/15/2019	To treat patients with painful complication of sickle cell disease Press Release Drug Trials Snapshot
29.	Beovu	brolucizumab-dbll	10/7/2019	Treatment of wet age-related macular degeneration Drug Trials Snapshot
12.	Polivy	polatuzumab vedotin-piiq	6/10/2019	To treat adult patients with relapsed or refractory diffuse large B-cell lymphoma Press Release Drug Trials Snapshot
9.	Skyrizi	risankizumab-rzaa	4/23/2019	To treat moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy Drug Trials Snapshot
7.	Evenity	romosozumab-aqqg	4/9/2019	To treat osteoporosis in postmenopausal women at high risk of fracture Press Release Drug Trials Snapshot
2.	Cablivi	caplacizumab-yhdp	2/6/2019	To treat adult patients with acquired thrombotic thrombocytopenic purpura (aTTP) Press Release Drug Trials Snapshot

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https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019

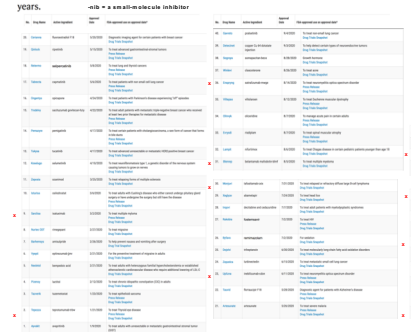
Out of 53 NCE approved by FDA in 2020, 8 are Mabs

NEWS · 05 JANUARY 2021 · UPDATE 18 JANUARY 2021

2020 FDA drug approvals

The FDA approved 53 novel drugs in 2020, the second highest count in over 20 years.

-nib = a small-molecule inhibitor



only 8 new MAB

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https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020

NEWS | 04 January 2022 | Update 19 January 2022

2021 FDA approvals

The FDA approved 50 novel drugs in 2021, including the first KRAS inhibitor for cancer and the first anti-amyloid antibody for Alzheimer's disease.

NEWS | 03 January 2023 | Update 16 January 2023

2022 FDA approvals

The FDA approved 37 novel drugs in 2022, the fewest to pass regulatory scrutiny since 2016.

NEWS | 02 January 2024

2023 FDA approvals

The FDA approved 55 novel therapeutics in 2023, the second highest count in the past 30 years.

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Neutralizing monoclonal antibodies. for treatment of COVID-19

Table 1 | **Neutralizing monoclonal antibodies for SARS-CoV-2 currently in development up to 11 December 2020**

Sponsors	Drug code/International proprietary name	Status	Trial ID	Actual start[a]	Estimated primary completion[a]
Junshi Biosciences and Eli Lilly and Company	JS016, etesevimab	EUA when used in combination with bamlanivimab[b]	NCT04441918	5 Jun. 2020	11 Dec. 2020
			NCT04411031	19 Jun. 2020	21 Oct. 2020[c]
			NCT04427501	17 Jun. 2020	20 Sep. 2020[c]
Tychan Pte Ltd	TY027	Phase I; phase II pending	NCT04429529	9 Jun. 2020	19 Nov. 2020[c]
			NCT04495515	4 Dec. 2020[c]	31 Aug. 2021
Bril Biosciences	BRII-196	Phase I	NCT04479631	12 Jul. 2020	Mar. 2021
Bril Biosciences	BRII-198	Phase I	NCT04479644	13 Jul. 2020	Mar. 2021
AbbVie	ABBV-47D11	Phase I pending	NCT04644120	10 Dec. 2020	5 Sep. 2021
Sorrento Therapeutics Inc.	COVI-GUARD (STI-1499)	Phase I	NCT04454398	Sep. 2020[c]	Jan. 2021
Mabwell (Shanghai) Bioscience Co. Ltd	MW33	Phase I	NCT04533048	7 Aug. 2020	16 Nov. 2020[c]
HFIBO Therapeutics	HFB30132A	Phase I	NCT04590430	20 Oct. 2020	Apr. 2021
Ology Bioservices	ADM03820	Phase I pending	NCT04592549	4 Dec. 2020	30 Sep. 2021
Hengenix Biotech Inc	HLX70	Phase I pending	NCT04561076	9 Dec. 2020[c]	6 Sep. 2021
University of Cologne and Boehringer Ingelheim	DZIF-10c	Phase I/II pending	NCT04631705	14 Dec. 2020	31 Jul. 2021
			NCT04631666	8 Dec. 2020	31 Jul. 2021
Sorrento Therapeutics Inc.	COVI-AMG (STI-2020)	Phase I/II pending	NCT04584697	Dec. 2020[c]	Apr. 2021
Celgene	BCB DXP593	Phase I; phase II pending	NCT04532294 (phase I)	8 Sep. 2020	19 Feb. 2021
			NCT04551898 (phase II pending)	2 Dec. 2020	25 Jan. 2021[c]
Sinocelltech Ltd	SCTA01	Phase I; phase I/II pending	NCT04483375	24 Jul. 2020	17 Nov. 2020[c]
			NCT04644185	10 Feb. 2021[c]	10 May 2021
AstraZeneca	AZD7442 (AZD8895 and AZD1061)	Phase I; phase II pending	NCT04507256	18 Aug. 2020	25 Oct. 2021
			NCT04625725	21 Nov. 2020	21 Apr. 2021
			NCT04625972	2 Dec. 2020	21 Jan. 2022
Celltrion	CT-P59	Phase I; phase I/II	NCT04525079	18 Jul. 2020	31 Aug. 2020
			NCT04593641	4 Sep. 2020	22 Oct. 2020
			NCT04602000	21 Sep. 2020	Dec. 2020
Vir Biotechnology Inc and GlaxoSmithKline	VIR-7831/GSK4182136	Phase II/II	NCT04545060	27 Aug. 2020	Mar. 2021
AbCellera and Eli Lilly and Company	Bamlanivimab; combination of bamlanivimab and etesevimab	EUA[b]	NCT04411628 (phase I)	28 May 2020	26 Aug. 2020[c]
			NCT04427501 (phase II)	17 Jun. 2020	20 Sep. 2020[c]
			NCT04497987 (phase III)	2 Aug. 2020	8 Mar. 2021
			NCT04501978 (phase III)	4 Aug. 2020	Jul. 2022
			NCT04518410 (phase I/II)	19 Aug. 2020	May 2023
Regeneron	REGN-COV2 (casirivimab and imdevimab)	EUA[b]	NCT04425629 (phase I/II)	16 Jun. 2020	10 Apr. 2021
			NCT04426695 (phase I/II)	11 Jun. 2020	16 Apr. 2021
			NCT04452318 (phase III)	13 Jul. 2020	15 Jun. 2021

Taylor PC et al. Nat Rev Immunol. 2021. PMID: 33875867

382 | June 2021 | volume 21

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Historical development MABs chronology

- We may distinguish arbitrarily four phases:
  - **A**. murine MAB development (1975-1985 and more) diagnostics applications
  - **B**. (partial) failure of therapeutic applications
  - **C**. Development of new applications with engineeded MABs (humanized, chimeric, fusion proteins, 1986-1994)
  - **D.** Development of new applications with human engineered MABs (1994-today)

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First therapeutical application aproved

- First therapeutic applications in 1986 with **muromonab** used in the treatment of episodes of acute rejection of hepatic or cardiac renal allograft. The immunosuppressive power of this treatment is responsible for an increase in the incidence of viral complications including cytomegalovirus infection and especially that of the lympho-proliferative disorders Epstein-Barr virus induced

Muromonab-CD3 was approved by the U.S. Food and Drug Administration (FDA) in **1986**

Basiliximab (**Simulect®**) is a chimeric mouse-human monoclonal antibody to the α chain (CD25) of the IL-2 receptor[1] of T cells.[2] It is used to prevent rejection in organ transplantation, especially in kidney transplants. It is a Novartis Pharmaceuticals product[3] and was approved by the Food and Drug Administration (FDA) in 1998.[4]

Daclizumab (**Zenapax®**) is a therapeutic humanized monoclonal antibody to the CD25 too . It is used to prevent rejection in organ transplantation, especially in kidney transplants.

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Fundamental Issues with murines MAbs

- Major problems associated with murine antibodies were :
  - **short half-life**
  - **reduced stimulation of cytotoxicity** (do not ligate very well to human FC receptors)
  - **Immunogenic**

  formation of complexes after repeated administration : mild allergic reactions and sometimes anaphylactic shock.

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Biotherapies & Immunotherapies, why such a development ?

- Increase of knowledge of immunopathology of inflammatory mechanisms, alowing to act on specific targets.
- Development of technological breakthrough in biotechnologies, i.e. allowing new drugs to be created.
- First application : cancerology, then auto-immune diseases

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Biotherapies : mode of action

MECHANISM OF ACTION

Monoclonal Antibodies may function according to three main modes of action

by **blocking** the action of molecules or of specific receptors
by **targeting** specific cells
or by functioning as **signalization** molecules

Pr. Jamal Taoufik, 3èmes Journées Pharmaceutiques du Gharb

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Biotherapies : mode of action

- **Block** a pro-inflammatory cytokine (i.e. TNFα, IL1) by using a MAB or a soluble receptor (**infliximab**).
- **Use an inhibitor that neutralizes a cell** (i.e. **rituximab** against CD20, specific of B lymphocytes).
- **Neutralizing a cell by limiting its proliferating capacities** (i.e. **abatacept**, CTLA-4-Ig that blocks auto-reactive T cell)
- **Use a recombinant with anti-inflammatory/immunomodulatory properties** like **rIL10**.
- **Block an important inflammatory mechanism** like pro-inflammatory cells recruitment, by chimiokines/integrines inhibitors : MABs like **natalizumab** (anti-integrin MAB)
- **Promote a regulatory mechanism** such as apoptosis to eliminate anormally activated self-reactives cells
- **Induce a regulatory immune response or inhibitory response** by antigen injection (vaccination like).

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Biotherapies : some important class of drugs

Anti-TNF

Three molecules commercialized in France in 2006
Inclusing two MABs
-**infliximab** (Remicade®)
-**adalimumab** (Humira®)
and a soluble récepteur **étanercept** (Enbrel®)
A fourth one in 2009 : **golimumab** (Simponi®).

Anti CD-20

RITUXIMAB: **MABTHERA***
Used for Hodgkin lymphomas treatment

IL-1 or IL-1Ra (anakinra/Kineret®) inhibitor
Use in polyarthritis, antagonist of IL1 receptor

Canakinumab (Ilaris) : MAB against IL1beta : antiinflammatory action

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Classification according to pathologies

1. Prevention/Treatment of Graft Reject (acute)

Eculizumab	**SOLIRIS®**	used in Kidney graft reject prevention

2. Treatment of Solid Tumours

Trastuzumab:	**HERCEPTIN®** :	breast cancer/ cancer du sein
Cetuximab:	**ERBITUX®**	Tumeurs épithéliales ORL, des voies aérodigestives supérieures et les adénocarcinomes colorectaux.
Bevacizumab:	**AVASTIN®**	colorectal Cancers
Edrecolomab:	**PANOREX®**	*colon solid tumours

3. Treatment of Hematopoietic Malignancies

Rituximab:	**MABTHERA®**	lymphomes Hodgkiniens.
Alemtuzumab:	**MABCAMPATH®**	Leucémies lymphoïdes chroniques.
Gemtuzumab-Ozogamycine:	**MYLOTARG®**	Leucémies myéloblastiques aiguës à CD 33+

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Classification according to pathologies

4. Treatment of Auto-immunes Diseases (Crohn's disease and rheumatoid arthritis)
Anti-TNF alpha : INFLIXIMAB (**REMICADE®**), Adalimumab (**HUMIRA®**)

5. Treatment of Asthma
Anti-CD11a : prevent activation of T lymphocytes; Efazilumab (**RAPTIVA®**)

6. Treatment of Multiple Sclerosis
Anti cellular adhesion molecule α4-integrin : Natazilumab (**TYSABRI®**)
Adverse event/effets indésirables
= Progressive multifocal leukoencephalopathy (PML) due to JC Virus.

7. Treatment of Cardiovascular Pathologies
Antagonists of platelets glycoproteins IIb-IIIa : Abciximab (**REOPRO®**)

8. Treatment of Infections
Against Respiratory infection due to SRV : Palivizumab (**SYNAGIS®**) premature children with fatal risks due to cardiopathy.
Against H glycoprotein of CMV Sevirumab (**PROTOVIR®**)

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Classification according to pathologies or use

9. Treatment of Allergy
IgG1- Anti IgE1 : Omalizumab (**XOLAIR®**)

10. Anti-Toxin antibodies
AMB against bacillus anthracis toxines or botulism toxins (biodefence)

11. Medical Imaging
Technetium (^{99m}Tc) arcitumomab is a drug used for the diagnostic imaging of colorectal cancers, marketed by Immunomedics

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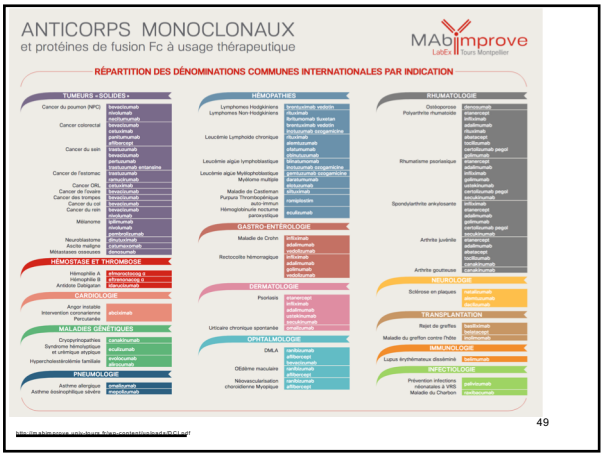

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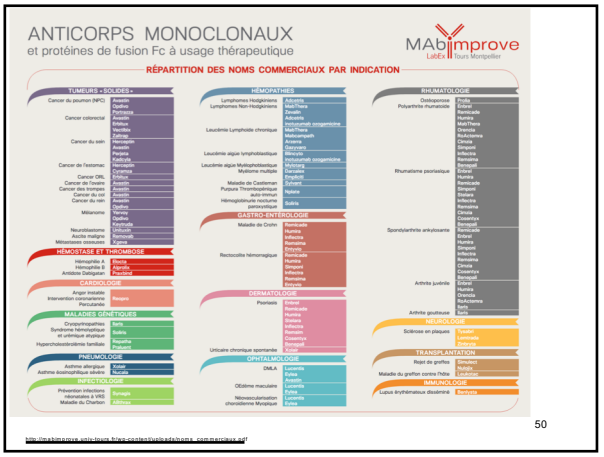

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Antibody Drug Conjugates

- **Antibody-targeted chemotherapy** *is a therapeutic strategy that involves the use of a* ***cytotoxic agent*** *chemically linked to a monoclonal antibody (mAb) that specifically recognizes a* **tumor-associated antigen.**

Association of an humanized antibody and a cellular toxin : calicheamicin
Gemtuzumab ozogamicin (marketed by Wyeth as Mylotarg)
Inotuzumab ozogamicin (trade name Besponsa)

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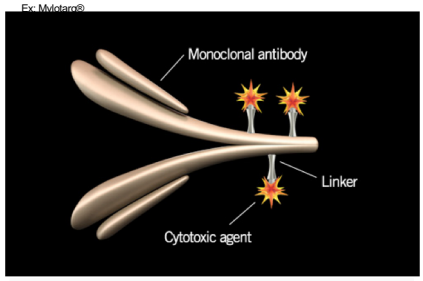
ADC= Antibody Drug Conjugates

Ex: Mylotarg®



Chari RVJ. Targeted cancer therapy: conferring specificity to cytotoxic drugs. *Acc Chem Res.* 2008;41:98-107.

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Evolution of Technologies

Murines Antibodies	-Classical Hybridomas
Chimeric or Humanized Antibodies	-engineering (gènes et protéines de fusion) -insertion de la région CDR
Human Antibodies	- phage display (Jespers *et al.* 1994) yeast display -transgenic mice with integrated human Ig

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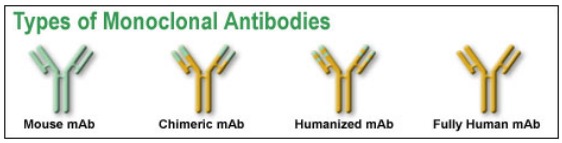
Monoclonal antibodies types



1	2	3	4
0%	65%	90%	100%

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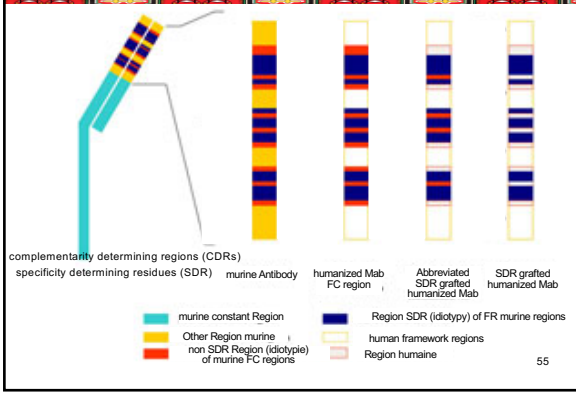
Monoclonal antibodies types



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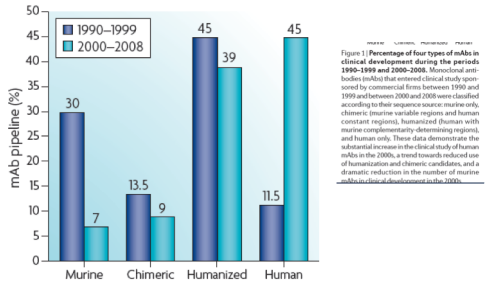
Pourcentages of 4 types of MAbs in clinic development from 1990-1999 and to 2000-2008



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Phage display

- Jespers LS, Roberts A, Mahler SM, Winter G, Hoogenboom HR: **Guiding the selection of human antibodies from phage display repertoires to a single epitope of an antigen**. *Biotechnology (N Y)* 1994, **12**(9):899-903.

The phage display method is a method which allows the selection of a peptide thanks to its presentation on the phage surface.

The growth and potential of human antiviral monoclonal antibody therapeutics
Wayne A Marasco & Jianhua Sui
Nature Biotechnology **25**, 1421 - 1434 (2007) Published online: 7 December 2007
doi:10.1038/nbt1363

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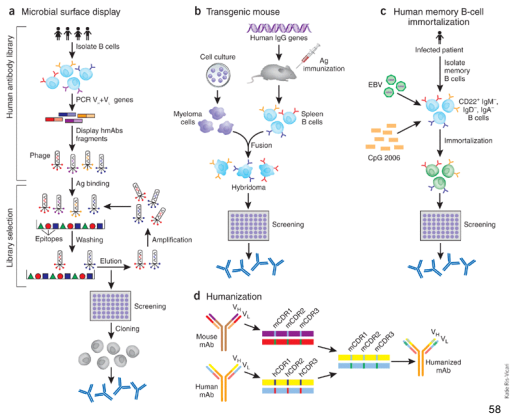

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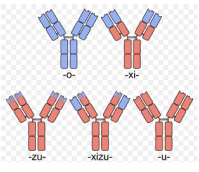
Marasco and Sui, 2007

Nomenclature building

- **Murine** monoclonal antibodies (suffix ~omab)
- **Chimeric** monoclonal antibodies (suffix ~**xi**mab)
- **Humanized** monoclonal antibodies (suffix ~**zu**mab)
- **Human** monoclonal antibodies (~**mu**mab)



a	rat
axo (pre-sub-stem)	rat/mouse
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
-xizu- (under discussion)	chimeric/humanized
zu	humanized

WHO

http://en.wikipedia.org/wiki/Monoclonal_antibody_therapy

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Nomenclature building

- Substem A indicates the target (molecule, cell, organ) class:

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion	neural
-s(o)-	bone
-tox(a)	toxin
t(u)	tumour
-v(i)-	viral

World Health Organization

INN Working Document 09.251 Revised
Distr.: PUBLIC
ENGLISH ONLY
18/12/2009

General policies for monoclonal antibodies

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Nomenclature building

Protéines de fusion (cept)
– cept Ex : étanercept (récepteur soluble du TNF de type 1 couplé au fragment Fc d'une IgG1 humaine) Ex : abatacept (molécule de costimulation (CTLA4) couplée au fragment Fc d'une IgG1 humaine Ex : alefacept (LFA3 couplé à un fragment Fc d'IgG)

Extracted from Sibilia et al. 2006

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Nomenclature building And reference list

http://en.wikipedia.org/wiki/List_of_monoclonal_antibodies

The abbreviations in the column *Type* are as follows:

- mab: whole monoclonal antibody
- Fab: fragment, antigen-binding (one arm)
  - $F(ab')_2$: fragment, antigen-binding, including hinge region (both arms)
  - Fab': fragment, antigen-binding, including hinge region (one arm)
- Variable fragments:
  - scFv: single-chain variable fragment
  - di-scFv: dimeric single-chain variable fragment
  - sdAb: single-domain antibody
- Bispecific monoclonal antibodies:
  - 3funct: trifunctional antibody
  - BiTE: bi-specific T-cell engager

http://en.wikipedia.org/wiki/List_of_monoclonal_antibodies

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Specific Problems of MAbs antiviral Therapies

- **Antigenic variability of circulating viral strains**
- **Ability of viruses to undergo neutralization escape**
- Among these approaches are the display technologies in which different microorganisms—including phage, yeast, bacteria and viruses—are used to display repertoires of :
  -single-chain variable antibody fragments (scFvs),
  -antigen-binding fragments (Fabs)
  -domain antibodies (Dabs) on their surfaces, from where they can be enriched and isolated through iterative cycles of panning.

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Cell types used to produce Mabs, some industrial parameters

- Initially : **Immortalized B cells**
- Now : **Engineered CHO cell lines** (**Chinese Hamster Ovary**)
  - Choice of cell culture media and supplement (from FCS to peptones and CD media)
  - Cell growth (viable cell density)
  - Type of reactor : flasks, microcarriers, etc…
  - Post translational modifications (PTMs): Proper glycosylation
  - Limited protein aggregation
  - Engineered CHO to improve Lipid metabolism

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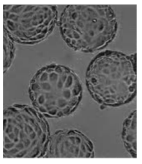
Microcarrier techniques to increase Yields and modify glycosylation profiles or folding



multigram per litre range

difficult-to-express (DTE) Mabs

morphology of the endoplasmic reticulum (ER)

ubiquitin proteasome system via ER-associated degradation (ERAD)

Springerplus. 2013 Dec;2(1):25. doi: 10.1186/2193-1801-2-25. Epub 2013 Jan 28.

The impact of microcarrier culture optimization on the glycosylation profile of a monoclonal antibody.

Costa AR[1], Withers J, Rodrigues ME, McLoughlin N, Henriques M, Oliveira R, Rudd PM, Azeredo J.

Biotechnol Bioeng. 2020 Jan;117(1):5-16. doi: 10.1002/bit.27196. Epub 2019 Nov 15.

Unraveling what makes a monoclonal antibody difficult-to-express: From intracellular accumulation to incomplete folding and degradation via ERAD.

Mathias S[1], Wippermann A[2], Raab N[1], Zeh N[1], Handrick R[1], Gorr I[3], Schulz P[2], Fischer S[4], Gamer M[2], Otte K[1].

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Specific methods to characterize industrially produced MAbs

- **Size-exclusion chromatography (SEC)**
  - Aggregate analysis
- **pH gradient based ion-exchange chromatography (pH-IEC)**
  - Charge variant analysis
- **Hydrophobic interactions chromatography (HIC)**
  - Oxydation variants analysis
- **Reverse Phase chromatography (RPC)**
  - Intact and mAb fragment analysis
- **Analytical ultracentrifugation (AUC)**
- **Isolectric focusing (IEF)**
- **Mass Spectrometry (MS)**

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Specific problems linked to administration of industrially produced MAbs

- **High Doses required for sc administration**
  - Range: hundreds of mg to g in small volume (cc: 100mg/ml)

  Challenges ! Stability, aggregation issues, viscosity issues
- **Concentration is achieved by tangential flow filtration**
  - Higher viscocity, higher industrial loss
- **Loss of structure : aggregation unfolding, adsorption**
  - Clogging during ultrafiltration and concentration procedures, chemical degradation
- **Thermal, Chemical, Mechanical stress**
  - Using excipients (sugars)

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Chimeric monoclonal antibodies (suffix ~**xi**mab)

1. Cétu**xi**mab- Erbitux® (Merck KGaA)
2. Ritu**xi**mab- MabThera®-antiCD20 (Roche)-Arthrite rhumatoide
3. Infli**xi**mab- Remicade®-antiTNFalpha (Schering-Plough)-Arthrite rhumatoide

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Humanized monoclonal antibodies (suffix ~**zu**mab)

1. Trastu**zu**mab- Herceptin®- antiRécepteurHEP2 (Roche)
2. Gemtu**zu**mab- Ozogamicin Mylotarg® (Wyeth)
3. Alamtu**zu**mab- Mabcampath® (Bayer ->Genzyme Europe BV)
4. Béváci**zu**mab- Avastin® (Genentech/Roche)
5. Deno**zu**mab- Prolia® (Amgen)

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Human monoclonal antibodies (~**mu**mab)

1. Adali**mu**mab- Humira® (Abbott) -Arthrite rhumatoide (anti TNF alpha)
2. **Figitumumab** (previously CP-751871) is a monoclonal antibody[1] targeting the insulin-like growth factor-1 receptor being investigated for the treatment of various types of cancer, for example adrenocortical carcinoma[2] and non-small cell lung cancer (NSCLC)[3] (developed by Pfizer)
3. **Fresolimumab** (**GC1008**) is a human monoclonal antibody[1] and an immunomodulator, developed by Genzyme. It is intended for the treatment of idiopathic pulmonary fibrosis (IPF), focal segmental glomerulosclerosis, and cancer.[2][3] It binds to and inhibits all isoforms of TGF-β.[2] As of June 2011[update] it is being tested in humans (clinical trials) against IPF, renal disease, and cancer.[4][5]

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Main actors

- **Schering Plough**
- **Pfizer**
- **Abbott**
- **Centocor**
- **Eli Lilly**
- **Amgen**
  - Lancement de l' Epo et du GM-CSF
- **Genzyme** Campath®
  - Le spécialiste des maladies « orphelines »
- **Merck,** 40000 personnes, 64 pays
  - 2003 Erbitux®: Entrée dans le domaine des anticancéreux créé en 1995
- **Roche/Genentech**
  - Acquisition en 2009 de Genentech
- **Novartis**
- **Johnson et Johnson**
- **Genmab**

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Merck Darmstadt (Merck KgaA)

Timeline | The name Merck | Possibilities

1668	Friedrich Jacob Merck acquires the Angel Pharmacy ("Engel-Apotheke")
1741	Johann Heinrich Merck, Goethe's friend, is born
1827	Heinrich Emanuel Merck: from a pharmacy trade to a research-based industrial company
1888	Comparative chemical analysis with "Merck's guaranteed pure reagents"
1900	Merck is represented on all continents
1904	First list of finished medicinal products; liquid crystal research begins
1917	U.S. subsidiary Merck & Co. expropriated - independent ever since
1920	For the first time, non-family members join the executive management
1945	Loss of subsidiaries abroad, new start from the ruins
1971	Firm re-establishement in the United States – after Asia and Latin America
1995	Establishment of Merck KGaA, public listing
2003	Erbitux®: Entry into targeted cancer therapy
2007	Serono acquisition, divestment of Generics, capital increase, admission to the DAX®
2010	Millipore acquisition

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Genzyme and rare diseases (enzymes, not MAB !)

Thérapies de remplacements enzymatiques= ERT (enzyme replacement therapies) (300-700 k€/an du coût de traitement, à vie !)

Key Dates:

1981: Henry Blair founds Genzyme.
1983: Henri Termeer becomes Genzyme chairman.
1988: Genzyme opens pharmaceutical chemical facility in the United Kingdom.
1991: Ceredase gains FDA approval.
1994: Genzyme receives FDA approval to market Cerezyme; Genzyme Tissue Repair Division is formed.
1997: Genzyme acquires PharmaGenics, Inc. to create Genzyme Molecular Oncology.
1999: Genzyme Surgical Products is formed.

Cerezyme
Gaucher' s Disease

Fabrazyme agalsidase beta
Fabry' s Disease

ALDURAZYME (LARONIDASE)
Mucopolysaccharidosis I (MPS I)

Lumizyme (alglucosidase alfa)
lysosomal glycogen-specific enzyme acid α-glucosidase (GAA) deficiency

Myozyme (alglucosidase alfa)
Pompe disease (GAA deficiency)

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Roche

Leukemia
Breast cancer
Lymphoma
Intestinal cancer
Lung cancer
Renal cancer
Skin cancer

Rheumatoid arthritis
Prevention of transplant rejection
Renal anemia
Hepatitis
Cystic fibrosis (mucoviscidosis)

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The race to become a giant company...

- Merck & Co. Became Number Two In The World By Acquiring Schering-Plow: **$ 41 Billion**
- Roche acquires Genentech, the second US biotechnology company: **$ 47 billion**
- Sanofi-Aventis acquired US biotech Genzyme for **$ 18.5 billion**.

- The world leader in the sector, Pfizer is also very active in the field of acquisitions. Less than a year after having taken over his compatriot Wyeth for **$ 68 billion**, he is again ready to invest several billion dollars to strengthen himself in emerging countries and in several fields of activity: generic drugs, treatments against pain, cancer, Alzheimer's disease, anti-inflammatory drugs and neuroscience..

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« Biosimilar »

Drug Product	Company	Reference Product and Sponsor	Marketing Status	FDA Approval Date
Mvasi™ (bevacizumab-awwb)	Amgen Allergan	Genentech/Roche Avastin® (bevacizumab)	Not available	Approved 9/14/2017
Cyltezo™ (adalimumab-adbm)	Boehringer Ingelheim International GmbH	AbbVie Humira® (adalimumab)	Not available	Approved 8/25/2017
Renflexis® (infliximab-abda)	Samsung Bioepis	Janssen Remicade® (infliximab)	Launched July 2017	Approved 4/21/2017
Amjevita® (adalimumab-atto)	Amgen	AbbVie Humira® (adalimumab)	Not Available	Approved 9/23/2016
Erelzi® (etanercept-szzs)	Sandoz	Amgen Enbrel® (etanercept)	Not Available	Approved 8/30/2016
Inflectra® (infliximab-dyyb)	Celltrion	Janssen Remicade® (infliximab)	Launched Nov. 2016	Approved 4/05/2016
Zarxio® (filgrastim-sndz)	Sandoz	Amgen Neupogen® (filgrastim)	Launched Sept. 2015	Approved 03/06/2015

Update: How the U.S. Compares to Europe on Biosimilar Approvals and Products in the Pipeline
https://www.lexology.com/library/detail.aspx?g=16cf8abe-bf58-4ef3-af3f-2893cd54e8d8

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Development costs are on the rise...

- **EPO** (Epogen®) : **4000-6000 US$/an**
- Hormone de croissance (®) : **12000-18000 US$/an**
- β-glucocerebrosidase (Ceredase®) : **150.000 US$/an**

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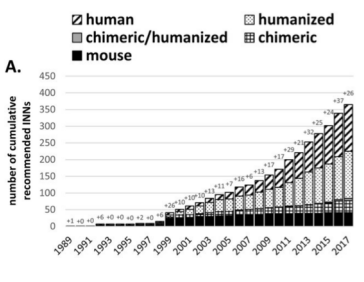
Nomenclature of humanized mAbs: Early concepts, current challenges and future perspectives



Figure

Caption

Fig. 1. Chronological summary of cumulative WHO-INN assignments (A) and EMA/FDA approvals (B). Antibody names were extracted from recommended WHO-INN lists or IMGT database (accessible on November 20th, 2017) and sorted according to their source infix. For each year, the number of new antibody names or approvals is explicitly stated. For 2017 only recommended INNs from list number 77 were included and does not represent all new INNs assigned in 2017. Note: the IMGT database states 1992 as the first approval year for the first approved (murine) therapeutic mAb Muromonab-CD3 although it was already approved by the FDA in 1986.

https://www.researchgate.net/publication/326726334_Nomenclature_of_humanized_mAbs_Early_concepts_current_challenges_and_future_perspectives/figures?lo=1

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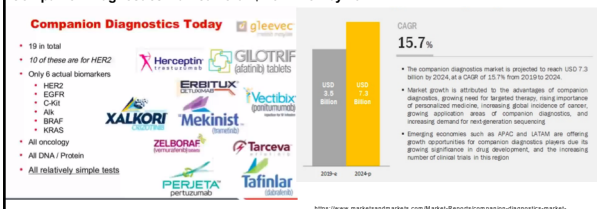
The emerging markets of companion diagnostics test

Companion Diagnostics Market worth $7.3 Billion by 2024



https://www.marketsandmarkets.com/Market-Reports/companion-diagnostics-market-155571681.html

Key Market Players

The prominent players operating in the global companion diagnostics market are F. **Hoffmann-La Roche AG** (Switzerland), **Agilent Technologies**, Inc. (US), **QIAGEN** N.V. (Germany), **Abbott Laboratories**, Inc. (US), **Almac Group** (UK), **Danaher Corporation** (US), **Illumina**, Inc. (US), **bioMérieux SA** (France), **Myriad Genetics**, Inc., (US), **Sysmex Corporation** (Japan), **Thermo Fisher Scientific Inc.** (US), **Abnova Corporation** (Taiwan), and **Guardant Health**, Inc. (US).

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PERSPECTIVES

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Antibodies to watch in 2024

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ABSTRACT

The 'Antibodies to Watch' article series provides an annual summary of commercially sponsored monoclonal antibody therapeutics currently in late-stage clinical development, regulatory review, and those recently granted a first approval in any country. In this installment, we discuss key details for 16 antibody therapeutics granted a first approval in 2023, as of November 17 (lecanemab (Leqembi), rozanolixizumab (RYSTIGGO), pozelimab (VEOPOZ), mirikizumab (Omvoh), talquetamab (Talvey), elranatamab (Elrexfio), epcoritamab (EPKINLY), gloftamab (COLUMVI), retifanlimab (Zynyz), concizumab (Alhemo), lebrikizumab (EBGLYSS), tafolecimab (SINTBILO), narlumosbart (Jinlitai), zuberitamab (Enrexib), adebrelimab (Arelii), and divozilimab (Ivlizi)). We briefly review 26 product candidates for which marketing applications are under consideration in at least one country or region, and 23 investigational antibody therapeutics that are forecast to enter regulatory review by the end of 2024 based on company disclosures. These nearly 50 product candidates include numerous innovative bispecific antibodies, such as odronextamab, ivonescimab, linvoseltamab, zenocutuzumab, and erfonrilimab, and antibody–drug conjugates, such as trastuzumab botidotin, patritumab deruxtecan, datopotamab deruxtecan, and MRG002, as well as a mixture of two immunocytokines (bifikafusp alfa and onfekafusp alfa). We also discuss clinical phase transition and overall approval success rates for antibody therapeutics, which are crucial to the biopharmaceutical industry because these rates inform decisions about resource allocation. Our analyses indicate that these molecules have approval success rates in the range of 14–32%, with higher rates associated with antibodies developed for non-cancer indications. Overall, our data suggest that antibody therapeutic development efforts by the biopharmaceutical industry are robust and increasingly successful.

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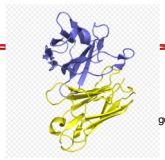
Antibody therapeutics; cancer; COVID-19; European Medicines Agency; Food and Drug Administration; immune-mediated disorders; SARS-CoV-2

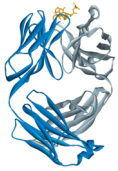
monoclonal antibodies

Monographies

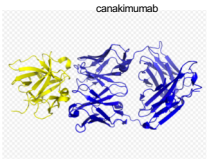


golimumab

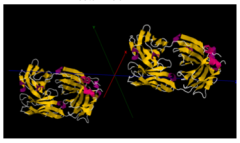
alemtuzumab



canakimumab



cetuximab



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