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Monoclonal antibody

A **monoclonal antibody** (**mAb** or **moAb**) is an antibody made by <u>cloning</u> a unique <u>white blood</u> <u>cell</u>. All subsequent antibodies derived this way trace back to a unique parent cell.

<u>Monoclonal</u> antibodies can have <u>monovalent</u> affinity, binding only to the same <u>epitope</u> (the part of an <u>antigen</u> that is recognized by the antibody). In contrast, <u>polyclonal</u> antibodies bind to multiple epitopes and are usually made by several different antibody secreting <u>plasma cell</u> lineages. <u>Bispecific</u> <u>monoclonal</u> antibodies can also be engineered, by increasing the therapeutic targets of one monoclonal antibody to two epitopes.

It is possible to produce monoclonal antibodies that specifically bind to virtually any suitable substance; they can then serve to detect or purify it. This capability has become an important tool in biochemistry, molecular biology, and medicine.



A general representation of the method used to produce monoclonal antibodies.[1][2]

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History

In the early 1900s, immunologist Paul Ehrlich proposed the idea of a *Zauberkugel* – "magic bullet", conceived of as a compound which selectively targeted a disease-causing organism, and could deliver a toxin for that organism. This underpinned the concept of monoclonal antibodies and monoclonal drug conjugates. Ehrlich and Élie Metchnikoff received the 1908 Nobel Prize for Physiology or Medicine for providing the theoretical basis for immunology.

By the 1970s, lymphocytes producing a single antibody were known, in the form of <u>multiple</u> <u>myeloma</u> – a cancer affecting <u>B-cells</u>. These abnormal antibodies or <u>paraproteins</u> were used to study the structure of antibodies, but it was not yet possible to produce identical antibodies specific to a given <u>antigen.^{[3]:324}</u> In 1973, Jerrold Schwaber described the production of monoclonal antibodies using human–mouse hybrid cells.^[4] This work remains widely cited among those using human-derived <u>hybridomas.^[5]</u> In 1975, <u>Georges Köhler</u> and <u>César Milstein</u> succeeded in making fusions of myeloma cell lines with B cells to create hybridomas that could produce antibodies, specific to known antigens and that were immortalized.^[6] They and <u>Niels Kaj Jerne</u> shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery.^[6]

In 1988, Greg Winter and his team pioneered the techniques to <u>humanize</u> monoclonal antibodies, $\overline{[7]}$ eliminating the reactions that many monoclonal antibodies caused in some patients. By the 1990s research was making progress in using monoclonal antibodies therapeutically, and in 2018, James P. Allison and Tasuku Honjo received the Nobel Prize in Physiology or Medicine for their discovery of cancer therapy by inhibition of negative immune regulation, using monoclonal antibodies that prevent inhibitory linkages. [8]

Production

Hybridoma development

Much of the work behind production of monoclonal antibodies is rooted in the production of hybridomas, which involves identifying antigen-specific plasma/plasmablast cells (ASPC) that produce antibodies specific to an antigen of interest and <u>fusing</u> these cells with <u>myeloma</u> cells.^[6] Rabbit B-cells can be used to form a <u>rabbit hybridoma</u>. Polyethylene glycol is used to fuse adjacent plasma membranes,^[9] but the success rate is low, so a selective medium in which only fused cells can grow is used. This is possible because myeloma cells have lost the ability to synthesize <u>hypoxanthine-guanine-phosphoribosyl</u> transferase (HGPRT), an enzyme necessary for the <u>salvage synthesis</u> of nucleic acids. The absence of HGPRT is not a problem for these cells unless the <u>de novo purine synthesis</u> pathway is also



Researchers looking at slides of cultures of cells that make monoclonal antibodies. These are grown in a lab and the researchers are analyzing the products to select the most promising of them.

disrupted. Exposing cells to <u>aminopterin</u> (a <u>folic acid</u> analogue, which inhibits <u>dihydrofolate</u> reductase, DHFR), makes them unable to use the de novo pathway and become fully <u>auxotrophic</u> for <u>nucleic acids</u>, thus requiring supplementation to survive.

The selective culture medium is called <u>HAT medium</u> because it contains <u>hypoxanthine</u>, aminopterin and <u>thymidine</u>. This medium is selective for fused (<u>hybridoma</u>) cells. Unfused myeloma cells cannot grow because they lack HGPRT and thus cannot replicate their DNA. Unfused spleen cells cannot grow indefinitely because of their limited life span. Only fused hybrid

cells referred to as hybridomas, are able to grow indefinitely in the medium because the spleen cell partner supplies HGPRT and the myeloma partner has traits that make it immortal (similar to a cancer cell).

This mixture of cells is then diluted and clones are grown from single parent cells on microtitre wells. The antibodies secreted by the different clones are then assayed for their ability to bind to the antigen (with a test such as <u>ELISA</u> or antigen microarray assay) or immuno-<u>dot blot</u>. The most productive and stable clone is then selected for future use.

The hybridomas can be grown indefinitely in a suitable cell culture medium. They can also be injected into mice (in the peritoneal cavity, surrounding the gut). There, they produce tumors secreting an antibody-rich fluid called <u>ascites</u> fluid.

The medium must be enriched during *in vitro* selection to further favour hybridoma growth. This can be achieved by the use of a layer of feeder fibrocyte cells or supplement medium such as briclone. Culture-media conditioned by macrophages can be used. Production in cell culture is usually preferred as the ascites technique is painful to the animal. Where alternate techniques exist, ascites is considered unethical.^[10]

Novel mAb development technology

Several monoclonal antibody technologies have been developed recently,^[11] such as phage display,^[12] single B cell culture,^[13] amplification various single cell from В cell populations [14][15][16][17][18] and single plasma cell interrogation technologies. Different from traditional hybridoma technology, the newer technologies use molecular biology techniques to amplify the heavy and light chains of the antibody genes by PCR and produce in either bacterial or mammalian systems with recombinant technology. One of the advantages of the new technologies is applicable to multiple animals, such as rabbit, llama, chicken and other common experimental animals in the laboratory.

Purification

After obtaining either a media sample of cultured hybridomas or a sample of ascites fluid, the desired antibodies must be extracted. Cell culture sample contaminants consist primarily of



Monoclonal antibodies can be grown in unlimited quantities in the bottles shown in this picture.



Technician hand-filling wells with a liquid for a research test. This test involves preparation of cultures in which hybrids are grown in large quantities to produce desired antibody. This is effected by fusing a <u>myeloma</u> cell and a <u>mouse lymphocyte</u> to form a hybrid cell (hybridoma).



Lab technician bathing prepared slides in a solution. This technician prepares slides of monoclonal antibodies for researchers. The cells shown are labeling human <u>breast</u> cancer.

media components such as growth factors, <u>hormones</u> and <u>transferrins</u>. In contrast, the *in vivo* sample is likely to have host antibodies, <u>proteases</u>, <u>nucleases</u>, <u>nucleic</u> acids and <u>viruses</u>. In both cases, other secretions by the hybridomas such as <u>cytokines</u> may be present. There may also be bacterial contamination and, as a result, <u>endotoxins</u> that are secreted by the bacteria. Depending on the complexity of the media required in cell culture and thus the contaminants, one or the other method (*in vivo* or *in vitro*) may be preferable.

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The sample is first conditioned, or prepared for purification. Cells, cell debris, lipids, and clotted material are first removed, typically by centrifugation followed by filtration with a 0.45 μ m filter. These large particles can cause a phenomenon called membrane fouling in later purification steps. In addition, the concentration of product in the sample may not be sufficient, especially in cases where the desired antibody is produced by a low-secreting cell line. The sample is therefore concentrated by ultrafiltration or dialysis.

Most of the charged impurities are usually anions such as nucleic acids and endotoxins. These can be separated by <u>ion exchange chromatography</u>.^[19] Either <u>cation</u> exchange <u>chromatography</u> is used at a low enough <u>pH</u> that the desired antibody binds to the column while anions flow through, or <u>anion exchange chromatography</u> is used at a high enough pH that the desired antibody flows through the column while anions bind to it. Various proteins can also be separated along with the anions based on their <u>isoelectric point</u> (pI). In proteins, the isoelectric point (pI) is defined as the pH at which a protein has no net charge. When the pH > pI, a protein has a net negative charge, and when the pH < pI, a protein has a net positive charge. For example, <u>albumin has a pI of 4.8</u>, which is significantly lower than that of most monoclonal antibodies, which have a pI of 6.1. Thus, at a pH between 4.8 and 6.1, the average charge of albumin molecules is likely to be more negative, while mAbs molecules are positively charged and hence it is possible to separate them. Transferrin, on the other hand, has a pI of 5.9, so it cannot be easily separated by this method. A difference in pI of at least 1 is necessary for a good separation.

Transferrin can instead be removed by <u>size exclusion chromatography</u>. This method is one of the more reliable chromatography techniques. Since we are dealing with proteins, properties such as charge and affinity are not consistent and vary with pH as molecules are protonated and deprotonated, while size stays relatively constant. Nonetheless, it has drawbacks such as low resolution, low capacity and low elution times.

A much quicker, single-step method of separation is protein A/G affinity chromatography. The antibody selectively binds to protein A/G, so a high level of purity (generally >80%) is obtained. However, this method may be problematic for antibodies that are easily damaged, as harsh conditions are generally used. A low pH can break the bonds to remove the antibody from the column. In addition to possibly affecting the product, low pH can cause protein A/G itself to leak off the column and appear in the eluted sample. Gentle elution buffer systems that employ high salt concentrations are available to avoid exposing sensitive antibodies to low pH. Cost is also an important consideration with this method because immobilized protein A/G is a more expensive resin.

To achieve maximum purity in a single step, affinity purification can be performed, using the antigen to provide specificity for the antibody. In this method, the antigen used to generate the antibody is covalently attached to an <u>agarose</u> support. If the antigen is a <u>peptide</u>, it is commonly synthesized with a terminal <u>cysteine</u>, which allows selective attachment to a carrier protein, such as <u>KLH</u> during development and to support purification. The antibody-containing medium is then incubated with the immobilized antigen, either in batch or as the antibody is passed through a column, where it selectively binds and can be retained while impurities are washed away. An elution with a low pH buffer or a more gentle, high salt elution buffer is then used to recover purified antibody from the support.

Antibody heterogeneity

Product heterogeneity is common in monoclonal antibodies and other recombinant biological products and is typically introduced either upstream during expression or downstream during manufacturing.

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These variants are typically aggregates, <u>deamidation</u> products, <u>glycosylation</u> variants, oxidized amino acid side chains, as well as amino and carboxyl terminal amino acid additions.^[20] These seemingly minute structural changes can affect preclinical stability and process optimization as well as therapeutic product potency, <u>bioavailability</u> and <u>immunogenicity</u>. The generally accepted purification method of process streams for monoclonal antibodies includes capture of the product target with <u>protein A</u>, elution, acidification to inactivate potential mammalian viruses, followed by ion chromatography, first with anion beads and then with cation beads.

Displacement chromatography has been used to identify and characterize these often unseen variants in quantities that are suitable for subsequent preclinical evaluation regimens such as animal <u>pharmacokinetic</u> studies.^{[21][22]} Knowledge gained during the preclinical development phase is critical for enhanced product quality understanding and provides a basis for risk management and increased regulatory flexibility. The recent Food and Drug Administration's <u>Quality by Design</u> initiative attempts to provide guidance on development and to facilitate design of products and processes that maximizes efficacy and safety profile while enhancing product manufacturability.^[23]

Recombinant

The production of recombinant monoclonal antibodies involves repertoire cloning, CRISPR/Cas9, or phage display/yeast display technologies.^[24] Recombinant antibody engineering involves antibody production by the use of viruses or yeast, rather than mice. These techniques rely on rapid cloning of immunoglobulin gene segments to create libraries of antibodies with slightly different amino acid sequences from which antibodies with desired specificities can be selected.^[25] The phage antibody libraries are a variant of phage antigen libraries.^[26] These techniques can be used to enhance the specificity with which antibodies recognize antigens, their stability in various environmental conditions, their therapeutic efficacy and their detectability in diagnostic applications.^[27] Fermentation chambers have been used for large scale antibody production.

Chimeric antibodies

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

Recombinant DNA has been explored since the late 1980s to increase residence times. In one approach, mouse DNA encoding the binding portion of a monoclonal antibody was merged with human antibody-producing DNA in living cells. The expression of this "chimeric" or "humanised" DNA through <u>cell culture</u> yielded part-mouse, part-human antibodies.^{[28][29]}

Human antibodies

Ever since the discovery that monoclonal antibodies could be generated, scientists have targeted the creation of *fully* human products to reduce the side effects of humanised or chimeric antibodies. Several successful approaches have been identified: <u>transgenic mice</u>, ^[30] <u>phage</u> <u>display^[12]</u> and single B cell cloning: ^[11]

As of November 2016, thirteen of the nineteen *fully* human monoclonal antibody therapeutics on the market were derived from transgenic mice technology.

Adopting organizations who market transgenic technology include:

- Abgenix which marketed the Xenomouse technology.
 Abgenix was acquired in April 2006 by <u>Amgen</u>.^{[31][32]}
- <u>Regeneron Pharmaceuticals</u> VelocImmune technology.^[33]
- Kymab who market their Kymouse technology.^[34]
- Open Monoclonal Technology's OmniRat[™] and OmniMouse[™] platform.^[35]
- TRIANNI, Inc. who market their <u>TRIANNI</u> Mouse platform.^[36]
- Ablexis, LLC who market their AlivaMab Mouse platform.^[37]

<u>Phage display</u> can be used to express variable antibody domains on filamentous phage coat proteins (<u>Phage major</u> <u>coat protein</u>).^{[38][39][40]} These phage display antibodies can be used for various research applications.^{[41][42]} ProAb was announced in December $1997^{[43]}$ and involved high



Approaches have been developed to isolate human monoclonal antibodies^[11]

throughput screening of antibody libraries against diseased and non-diseased tissue, whilst Proximol used a free radical enzymatic reaction to label molecules in proximity to a given protein.^{[44][45]}

Monoclonal antibodies have been approved to treat cancer, cardiovascular disease, inflammatory diseases, macular degeneration, transplant rejection, multiple sclerosis and viral infection.

In August 2006, the Pharmaceutical Research and Manufacturers of America reported that U.S. companies had 160 different monoclonal antibodies in clinical trials or awaiting approval by the Food and Drug Administration.^[46]

Cost

Monoclonal antibodies are more expensive to manufacture than small molecules due to the complex processes involved and the general size of the molecules, all in addition to the enormous research and development costs involved in bringing a new chemical entity to patients. They are priced to enable manufacturers to recoup the typically large investment costs, and where there are no price controls, such as the United States, prices can be higher if they provide great value. Seven University of Pittsburgh researchers concluded, "The annual price of mAb therapies is about \$100,000 higher in oncology and hematology than in other disease states," comparing them on a per patient basis, to those for cardiovascular or metabolic disorders, immunology, infectious diseases, allergy, and ophthalmology.^[47]

Applications

Diagnostic tests

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

Analytic and chemical uses

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

Therapeutic uses

Therapeutic monoclonal antibodies act through multiple mechanisms, such as blocking of targeted molecule functions, inducing <u>apoptosis</u> in cells which express the target, or by modulating signalling pathways. [48][49]

Cancer treatment

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

MAbs approved by the FDA for cancer include: [51]

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

Autoimmune diseases

Monoclonal antibodies used for autoimmune diseases include infliximab and adalimumab,

Biotinylated Naked MAb Multistep Targeting radioactive ligand ADCC CDC Streptavidin Radionuclid Radioimmunoconjugate Bispecific MAb Tumor Cell Cytokine Immunocytokine Cellular Immunoconjugates Immunotoxin Liposome scFv-enzyme scFV ADEPT Immunoliposome 2 Prodrug Drug Immunoconiugates

Monoclonal antibodies for cancer. <u>ADEPT</u>, antibody directed enzyme prodrug therapy; <u>ADCC</u>: antibody dependent cell-mediated cytotoxicity; CDC: <u>complement-dependent cytotoxicity</u>; MAb: monoclonal antibody; scFv, single-chain Fv fragment.^[50]

which are effective in rheumatoid arthritis, Crohn's disease, ulcerative colitis and ankylosing spondylitis by their ability to bind to and inhibit $TNF-\alpha$.^[52] Basiliximab and daclizumab inhibit IL-2 on activated T cells and thereby help prevent acute rejection of kidney transplants.^[52] Omalizumab inhibits human immunoglobulin E (IgE) and is useful in treating moderate-to-severe allergic asthma.

Examples of therapeutic monoclonal antibodies

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

Main category	Туре	Application	Mechanism/Target	Mode
Anti- inflammatory	<u>infliximab^[52]</u>	 rheumatoid arthritis Crohn's disease ulcerative colitis ankylosing spondylitis 	inhibits <u>TNF-α</u>	chimeric
	adalimumab	 rheumatoid arthritis Crohn's disease ulcerative colitis ankylosing spondylitis 	inhibits <u>TNF-α</u>	human
	basiliximab ^[52]	 acute rejection of kidney transplants 	inhibits <u>IL-2</u> on activated <u>T cells</u>	chimeric
	daclizumab ^[52]	 acute rejection of kidney transplants 	inhibits <u>IL-2</u> on activated <u>T cells</u>	humanized
	omalizumab	 moderate-to- severe allergic asthma 	inhibits human immunoglobulin E (IgE)	humanized
Anti-cancer	gemtuzumab ^[52]	 relapsed <u>acute</u> myeloid leukemia 	targets myeloid cell surface antigen CD33 on leukemia cells	humanized
	alemtuzumab ^[52]	 B cell leukemia 	targets an antigen CD52 on T- and B- lymphocytes	humanized
	<u>rituximab^[52]</u>	 non-Hodgkin's lymphoma rheumatoid arthritis 	targets phosphoprotein <u>CD20</u> on <u>B lymphocytes</u>	chimeric
	trastuzumab	 breast cancer with <u>HER2/neu</u> overexpression 	targets the <u>HER2/neu</u> (erbB2) receptor	humanized
	<u>nimotuzumab</u>	 approved in squamous cell carcinomas, Glioma clinical trials for other indications underway 	EGFR inhibitor	humanized
	<u>cetuximab</u>	 approved in squamous cell carcinomas, colorectal carcinoma 	EGFR inhibitor	chimeric
	bevacizumab & ranibizumab	 Anti-angiogenic 	inhibits VEGF	humanized

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		cancer therapy		
Anti-cancer and anti-viral	bavituximab ^[53]	 cancer, <u>hepatitis</u> <u>C</u> infection 	immunotherapy, targets phosphatidylserine ^[53]	chimeric
Anti-viral	<u>casirivimab/imdevimab^[54]</u>	 SARS-CoV-2 coronavirus causing the COVID-19 pandemic 	immunotherapy, targets spike protein of SARS-CoV-2	chimeric
	bamlanivimab/etesevimab ^[55]	 SARS-CoV-2 coronavirus causing the COVID-19 pandemic 	immunotherapy, targets spike protein of SARS-CoV-2	chimeric
Other	palivizumab ^[52]	 <u>RSV</u> infections in children 	inhibits an RSV fusion (F) protein	humanized
	abciximab ^[52]	 prevent coagulation coronary angioplasty 	inhibits the receptor GpIIb/IIIa on platelets	chimeric

Side effects

Several monoclonal antibodies, such as <u>bevacizumab</u> and <u>cetuximab</u>, can cause different kinds of side effects.^[56] These side effects can be categorized into common and serious side effects.^[57]

Some common side effects include:

- Dizziness
- Headaches
- Allergies
- Diarrhea
- Cough
- Fever
- Itching
- Back pain
- General weakness
- Loss of appetite
- Insomnia
- Constipation^[58]

Among the possible serious side effects are:

- Anaphylaxis
- Bleeding
- Arterial and venous blood clots
- Autoimmune thyroiditis
- Hypothyroidism
- Hepatitis

- Heart failure
- Cancer
- Anemia
- Decrease in white blood cells
- Stomatitis
- Enterocolitis
- Gastrointestinal perforation
- Mucositis^[58]

See also

- Affimer
- Antibody mimetic
- Aptamer
- Immunotoxins, which sometimes use monoclonal antibodies as the targeting mechanism
- List of monoclonal antibodies
- Monoclonal antibody therapy
- Nomenclature of monoclonal antibodies
- Polyclonal antibodies
- Monoclonal Antibody Journal

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Further reading

- 2019 Historical overview of monoclonal antibodies in the journal Nature (https://www.nature.co m/articles/d41586-019-02840-w)
- Monoclonal Antibodies (https://web.archive.org/web/20130112205725/http://users.rcn.com/jkim ball.ma.ultranet/BiologyPages/M/Monoclonals.html), from John W. Kimball's online biology textbook

External links

- Monoclonal+antibodies (https://meshb.nlm.nih.gov/record/ui?name=Monoclonal%20antibodie s) at the US National Library of Medicine Medical Subject Headings (MeSH)
- Antibodypedia (http://www.antibodypedia.com), open-access virtual repository publishing data and commentary on any antibodies available to the scientific community.
- Antibody Purification Handbook (http://www.gelifesciences.com/handbooks)

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