

ADVANCE RESEARCH ON MONOCLONAL ANTIBODY FOR CANCER TREATMENT

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Received:4 June 2013, Revised and Accepted:5 June 2013

ABSTRACT

Research and development of antitumor monoclonal antibody agents have shown substantial progress. Monoclonal antibodies (McAb) or their immunoconjugates can be used as clinically therapeutic agents for cancer treatment. As reported, McAb agents display specific binding to tumor-related targets, exhibit selective cytotoxicity to target cancer cells, and show highly therapeutic effects in animal experiments. Recently, some of the McAb agents have been applied in clinical therapy. Major trends in the study of McAb agents are searching for new relevant molecular targets, humanizing of the antibody, and downsizing of the immunoconjugate molecule. Due to high specificity of McAb to related molecular target, there is a great potential to develop highly effective antitumor agents. That's why McAb agents may play an important role in cancer therapy.

Keywords: monoclonal antibody, immunoconjugates, cytotoxicity, antitumor, molecular antibody

INTRODUCTION

Antibodies with desired specificity could be used as "magic bullets" to target disease- associated with proteins. The development of technology to clone and sequence immunoglobulin genes provided the tools necessary to construct antibody-based molecules and fusion proteins for the treatment and diagnosis of cancer, auto immune diseases and other infectious diseases. In 2003, the US Food and Drug Administration approved 14 antibody-based pharmaceuticals, of which 70 were in late-stage clinical trials (Phase II+) and > 1000 were in preclinical development. Additional growth in the area of hybridoma and monoclonal antibody production technology is projected as genomic and proteomic high-throughput programs identify new proteins that will require immunoanalyses and/or purification for further characterization. Although standard procedures for generating antibodies of desired specificity have been used for approximately 30 yr, the development of more efficient techniques and resources would be a more efficient for biomedical research.

DISCOVERY

The idea of a "magic bullet" was first proposed by Paul Ehrlich, at the beginning of the 20th century. If a compound could be made that selectively targeted against a disease-causing organism, then a toxin for that organism could be delivered along with the agent of selectivity. He and Élie Metchnikoff received the 1908 Nobel Prize for Physiology or Medicine for this work, which led to an effective syphilis treatment by 1910.

Production of monoclonal antibodies involving human–mouse hybrid cells was described by Jerrold Schwaber in 1973^[1] and remains widely cited among those using human-derived hybridomas,^[2] but claims of priority have been controversial. A science history paper on the subject gave some credit to Schwaber for inventing a technique that was widely cited, but stopped short of suggesting that he had been cheated.^[3] The invention was conceived by George Piczenik, with John Sedat, Elizabeth Blackburn's husband, as a witness and reduced to practice by Cotton and Milstein, and then by Kohler and Milstein. Georges Köhler, César Milstein, and Niels Kaj Jerne in 1975;^[4] who shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery.

In 1988, Greg Winter and his team discovered the techniques to humanize monoclonal antibodies,^[5] removing the reactions that many monoclonal antibodies caused in some patients.

PRODUCTION

Monoclonal antibodies are typically made by fusing myeloma cells with the spleen cells from a mouse who has been immunized with the desired antigen. Now a days rabbit B-cells also used to form a Rabbit Hybridoma. Polyethylene glycol is generally used to fuse adjacent plasma membranes, 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 lack the ability to synthesize hypoxanthine-guanine-phosphoribosyl transferase (HGPRT), an enzyme necessary for the salvage synthesis of nucleic acids. The absence of HGPRT is not a problem for these cells unless the de novo purine synthesis pathway is also disrupted. By exposing cells to aminopterin (a folic acid analogue, which inhibits dihydrofolate reductase, DHFR), they cannot use the de novo pathway and become fully auxotrophic for nucleic acids and require supplementation to survive.

The selective culture medium is called HAT medium because it contains hypoxanthine, aminopterin and thymidine. This medium is selective for fused 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 media because the spleen cell partner supplies HGPRT and the myeloma partner has traits that make it immortal (similar to a cancer cell).

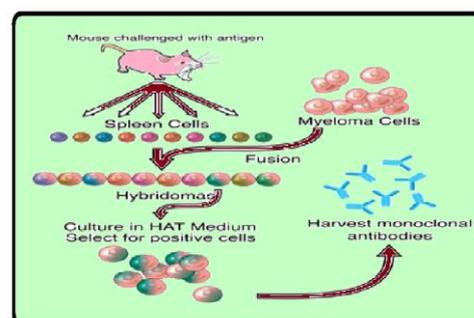


Figure 1: Production of Mab from spleen of mouse

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 ELISA or Antigen Microarray Assay) or immuno-dot blot. 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 ascites 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-medium conditioned by macrophages can also be used. Production in cell culture is usually preferred as the ascites technique is painful to the animal. Where alternate techniques exist, this method (ascites) is considered unethical.

TYPES OF MAb

Murine monoclonal antibodies (suffix -omab)

Initially, murine antibodies were obtained by hybridoma technology. Major problems associated with murine antibodies included reduced stimulation of cytotoxicity and the formation complexes after repeated administration, which resulted in mild allergic reactions and sometimes anaphylactic shock.[6]

Chimeric and humanized monoclonal antibodies (suffixes -ximab, -zumab respectively)

To reduce murine antibody immunogenicity, murine molecules were engineered to remove immunogenic content and to increase their immunologic efficiency.[6] This was initially achieved by the production of chimeric and humanized antibodies. Chimeric antibodies are composed of murine variable regions fused onto human constant regions.

Humanised antibodies are produced by grafting murine hypervariable[disambiguation needed] amino acid domains into human antibodies. This results in a molecule of approximately 95% human origin. However it has been shown in several studies that humanised antibodies bind antigen much more weakly than the parent murine monoclonal antibody, with reported decreases in affinity of up to several hundredfold.[7][8] Increases in antibody-antigen binding strength have been achieved by introducing mutations into the complementarity determining regions (CDR),[9] using techniques such as chain-shuffling, randomization of complementarity determining regions and generation of antibody libraries with mutations within the variable regions by error-prone PCR, E. coli mutator strains, and site-specific mutagenesis.[10]

Human monoclonal antibodies (suffix -umab)

Human monoclonal antibodies are produced by transferring human immunoglobulin genes into the murine genome, after which the transgenic mouse is vaccinated against the desired antigen, leading to the production of monoclonal antibodies,[11] allowing the transformation of murine antibodies in vitro into fully human antibodies.[12]

The heavy and light chains of human IgG proteins are expressed in structural polymorphic (allotypic) forms. Human IgG allotype has been considered as one of the many factors that can contribute to immunogenicity.[13] The general scheme of a monoclonal antibody development program is described in.[14]

HOW MAb WORKS

When a monoclonal antibody attaches to a cancer cell, it can:

- **Make the cancer cell more visible to the immune system.** The immune system attacks foreign invaders in body, but it cannot always recognize cancer cells as enemies. A monoclonal antibody can be directed to attach to certain parts of a cancer cell. In this way, the antibody marks the cancer cell and makes it easier for the immune system to find.

The monoclonal antibody drug rituximab (Rituxan) attaches to a specific protein (CD20) found only on B cells, one type of white blood cell. Certain types of lymphomas arise from these same B cells. When rituximab attaches to this protein on the B cells, it makes the cells more visible to the immune system, which can then attack.[15]

- **Block growth signals.** Chemicals known as growth factors attach to receptors on the surface of normal cells and cancer cells and signaling the cells to grow. Certain cancer cells make extra copies of the growth factor receptor. This makes them grow faster than the normal cells. Monoclonal antibodies can block these receptors and prevent the growth signal from getting through.

Cetuximab (Erbix), a monoclonal antibody approved to treat colon cancer and head and neck cancers, attaches to receptors on cancer cells that accept a certain growth signal. Blocking this signal from reaching its target on the cancer cells may slow or stop the cancer from growing. [15]

- **Stop new blood vessels from forming.** Cancer cells depend on blood vessels for the oxygen and nutrients they need to grow. To attract blood vessels, cancer cells send out growth signals. Monoclonal antibodies that block these growth signals may help prevent a tumor from developing a blood supply, so that it remains small. Or in the case of a tumor with an already-established network of blood vessels, blocking the growth signals could cause the blood vessels to die and the tumor to shrink.

The monoclonal antibody bevacizumab (Avastin) is approved to treat a number of cancers, not including breast cancer. Bevacizumab targets a growth signal called vascular endothelial growth factor (VEGF) that cancer cells send out to attract new blood vessels. Bevacizumab intercepts a tumor's VEGF signals and stops them from connecting with their targets. [15]

- **Deliver radiation to cancer cells.** In combination with monoclonal antibody, doctors can deliver radiation directly to the cancer cells. This way, most of the surrounding healthy cells are not damaged. Radiation-linked monoclonal antibodies deliver a low level of radiation over a longer period of time, which is as effective as the more conventional high-dose external beam radiation.

Ibritumomab (Zevalin), approved for non-Hodgkin's lymphoma, combines a monoclonal antibody with radioactive particles. The ibritumomab monoclonal antibody attaches to receptors on cancerous blood cells and delivers the radiation.[15]

OTHER APPLICATIONS

Diagnostic tests

Monoclonal antibodies for a particular substance have been produced, then they can be used to detect the presence of that substance. The Western blot test and immuno dot blot tests detect the protein on a membrane. They are also useful in immunohistochemistry, which detect antigen in fixed tissue sections and immunofluorescence test, which detect the substance in a frozen tissue section or in live cells.

Therapeutic treatment

Most effective treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immunological response against the target cancer cell. Such mAb could also be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate; bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell.

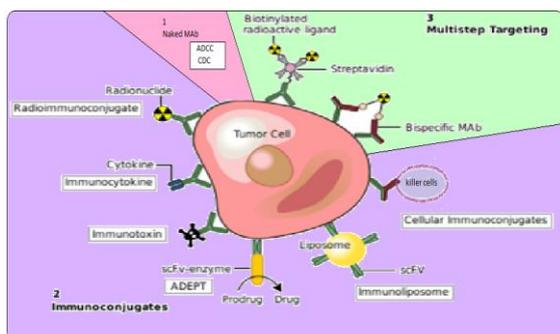


Figure 2: Mechanism by which MAb treat the cancer cells.

Monoclonal antibodies for cancer. ADEPT (antibody directed enzyme prodrug therapy), ADCC (antibody dependent cell-mediated cytotoxicity), CDC (complement dependent cytotoxicity), MAb (monoclonal antibody), scFv (single-chain Fv fragment).[16]

Autoimmune diseases

Monoclonal antibodies used for autoimmune diseases include infliximab and adalimumab, which are mainly effective in diseases like rheumatoid arthritis, Crohn's disease and ulcerative Colitis by their ability to bind to and inhibit TNF- α ,[29] while Basiliximab and daclizumab inhibit IL-2 on activated T cells and so help to prevent acute rejection of kidney transplants.[29] Omalizumab inhibits human immunoglobulin E (IgE) and is useful in moderate-to-severe allergic asthma

Table 1: List of Mab approved by FDA

Main category	Type	Application	Mechanism/Target	Mode
Anti-inflammatory	infliximab ^[18]	<ul style="list-style-type: none"> rheumatoid arthritis Crohn's disease Ulcerative Colitis 	inhibits TNF- α	Chimeric
	adalimumab	<ul style="list-style-type: none"> rheumatoid arthritis Crohn's disease Ulcerative Colitis 	inhibits TNF- α	Human
	basiliximab ^[18]	<ul style="list-style-type: none"> Acute rejection of kidney transplants 	inhibits IL-2 on activated T cells	Chimeric
	daclizumab ^[18]	<ul style="list-style-type: none"> Acute rejection of kidney transplants 	inhibits IL-2 on activated T cells	Humanized
	omalizumab	<ul style="list-style-type: none"> moderate-to-severe allergic asthma 	inhibits human immunoglobulin E (IgE)	Humanized
	gemtuzumab ^[18]	<ul style="list-style-type: none"> relapsed acute myeloid leukemia 	targets myeloid cell surface antigen CD33 on leukemia cells	Humanized
	alemtuzumab ^[18]	<ul style="list-style-type: none"> B cell leukemia 	targets an antigen CD52 on T- and B-lymphocytes	Humanized
Anti-cancer	rituximab ^[18]	<ul style="list-style-type: none"> non-Hodgkin's lymphoma 	targets phosphoprotein CD20 on B lymphocytes	Chimeric
	trastuzumab	<ul style="list-style-type: none"> breast cancer with HER2/neu overexpression 	targets the HER2/neu (erbB2) receptor	Humanized
	nimotuzumab	<ul style="list-style-type: none"> Approved in squamous cell carcinomas, Glioma Clinical trials for other indications underway 	EGFR inhibitor	Humanized
	cetuximab	<ul style="list-style-type: none"> Approved in squamous cell carcinomas, colorectal carcinoma 	EGFR inhibitor	Chimeric
	bevacizumab	<ul style="list-style-type: none"> Anti-angiogenic cancer therapy 	inhibits VEGF	Humanized
Other	palivizumab ^[18]	<ul style="list-style-type: none"> RSV infections in children 	inhibits an RSV fusion (F) protein	Humanized
	abciximab ^[18]	<ul style="list-style-type: none"> Prevent coagulation in coronary angioplasty 	inhibits the receptor GpIIb/IIIa on platelets	Chimeric

TRANSTUZUMAB (Herceptin ®)[26]

How Herceptin works

Cancers have too much of a protein called human epidermal growth factor receptor 2 (HER2) on the surface. These are called HER2 positive cancers. The extra HER2 receptors stimulate the cancer cells to divide and grow. Herceptin locks on to the HER2 protein. This blocks the receptor and stops the cells from dividing and growing.[19]

Herceptin only works in people who have cancer with high levels of the HER2 protein. Several tests are available to measure HER2 levels. Testing can be done at the same time as initial cancer surgery, or samples of cancer cells from previous biopsies or surgery may be used.

When Herceptin is used

Breast cancer

Herceptin is licensed to treat people with HER2 positive early stage breast cancer following surgery and chemotherapy, or sometimes at

the same time as chemotherapy. It's given to reduce the risk of the cancer coming back and increase the chance of a cure.

Herceptin is also given to people with advanced (or metastatic) breast cancer that has spread to other parts of the body or come back after initial treatment. In this situation, it's either given on its own or in combination with chemotherapy and/or hormone therapy. [20]

Stomach cancer

Herceptin is licensed to treat people with HER2 positive adenocarcinoma of the stomach that has spread (metastatic or advanced gastric cancer). It may also be used to treat advanced cancers in the area where the oesophagus joins the stomach - the gastro-oesophageal junction. It is used in combination with chemotherapy in both cases.[20,21]

The National Institute for Health and Clinical Excellence (NICE) gives advice on which new drugs or treatments should be available on the

NHS in England and Wales. The Scottish Medicines Consortium (SMC) makes recommendations on the use of new drugs within the NHS in Scotland. NICE recommends the use of Herceptin in the treatment of both breast and gastric (stomach) cancer. The SMC only recommends its use in breast cancer.

If you live in Northern Ireland, speak to your cancer specialist about whether Herceptin is recommended to treat your type of cancer.

If Herceptin isn't recommended for you, it may not be available on the NHS, although you may be given it as part of a cancer research trial (clinical trial). We have more information on what you can do if a treatment isn't available.

CETUXIMAB (Erbix®)[26]

How cetuximab works

Some types of cancer have large numbers of receptors on their surface called epidermal growth factor receptors (EGFRs)^[25]. When the receptors are activated they trigger the cancer cells to divide and grow.

Cetuximab locks on to the EGFRs. This stops them from stimulating the cancer cells to divide and grow. It may also make the cancer cells more sensitive to the effects of chemotherapy and radiotherapy^[27,28]. Cetuximab is most likely to work for cancers with large numbers of EGFRs on their surfaces.

Cetuximab only works for bowel cancers that have a normal KRAS gene. So before it's used to treat bowel cancer, the cancer cells are tested to see if there are changes (mutations) in the KRAS gene.^[29] This helps the doctors decide if treatment with cetuximab is appropriate. Cancer cells can be tested during the same procedure that diagnoses the cancer. Or tests can be done using cells from previous biopsies or surgery. This test is not needed for head and neck cancers.

When cetuximab is used

Cetuximab is licensed as a treatment for advanced (metastatic) large bowel cancer and for head and neck cancer. It's also being tested in research trials as a possible treatment for other types of cancer.

The National Institute for Health and Clinical Excellence (NICE) gives advice on which new drugs or treatments should be available on the NHS in England and Wales. The Scottish Medicines Consortium (SMC) makes recommendations on the use of new drugs within the NHS in Scotland. Both NICE and the SMC have issued guidelines on when cetuximab can be used by the NHS.

For bowel cancer

Cetuximab is licensed to treat advanced bowel cancer:

- in combination with chemotherapy
- as a treatment on its own for people who have already been treated with the chemotherapy drugs oxaliplatin and irinotecan.

NICE and the SMC have both approved cetuximab in combination with chemotherapy as a possible treatment for bowel cancer that has spread to the liver, but hasn't previously been treated with chemotherapy. The guidance doesn't recommend cetuximab for everyone in this situation. Your cancer specialist can tell you if it's appropriate for you.

For head and neck cancer

Cetuximab is licensed to treat

- head and neck cancers that have started to spread into surrounding tissues (locally advanced head and neck cancers). It's given in combination with radiotherapy.^[30]
- head and neck cancers that have come back after treatment (are recurrent) or have spread (advanced or metastatic). It's given in combination with a chemotherapy regimen containing a platinum drug (such as cisplatin).

NICE and the SMC have both recommended the use of cetuximab in combination with radiotherapy to treat locally advanced head and neck cancers. However, neither of them recommend cetuximab in combination with a platinum-based chemotherapy as a treatment for metastatic head and neck cancer.

If you live in Northern Ireland, speak to your cancer specialist about whether cetuximab is recommended to treat your type of cancer.

If cetuximab isn't recommended for you it may not be available on the NHS^[31], although you may be given it as part of a clinical trial. We have more information about what you can do if a treatment isn't available.

BEVASIZUMAB (Avastin®)[26]

How bevacizumab works

Bevacizumab targets a protein called vascular endothelial growth factor (VEGF). This is a protein that helps cancer cells develop a new blood supply. Bevacizumab blocks the protein and stops the cancer from developing new blood vessels. This reduces its supply of oxygen and nutrients so the tumour shrinks or stops growing.^[32,33] Drugs that interfere with blood vessel growth are called angiogenesis inhibitors or anti-angiogenics.

When bevacizumab is used

Bevacizumab is licensed to treat some types of cancer that have spread from where they first started (advanced or metastatic cancers). It may be used to treat advanced non-small cell lung cancer or advanced cancers of the bowel, breast or kidney.

The National Institute for Health and Clinical Excellence (NICE) gives advice on which new drugs or treatments should be available on the NHS in England and Wales. The Scottish Medicines Consortium (SMC)^[34,35] makes recommendations on the use of new drugs within the NHS in Scotland. Neither NICE nor the SMC have recommended the use of bevacizumab^[36]. As a result, bevacizumab may not be widely available on the NHS, although you may be given it as part of a clinical trial.

PANITUMUMAB (Vectibix®)[26]

How panitumumab works

Some types of cancer have large numbers of receptors on their surface, called epidermal growth factor receptors (EGFRs)^[37]. When the receptors are activated, they trigger the cancer cells to divide and grow.

Panitumumab locks on to the EGFRs. This stops them stimulating the cancer cells to divide and grow. It is most likely to work for cancers with large numbers of EGFRs on their surface.

Panitumumab only works for bowel cancers that have a normal KRAS^[38] gene. So before it's used to treat bowel cancer, the cancer cells are tested for changes (mutations) in the KRAS gene. This helps the doctors decide whether the treatment is appropriate. Testing can be done on samples of the cancer cells at the same time as diagnosis of the cancer, or by using cells from previous biopsies or surgery.

When panitumumab is used

Panitumumab is licensed to treat people with bowel cancer that has spread to other areas of the body (advanced or metastatic cancer). It can be used:

- as the first treatment, in combination with the chemotherapy regimen FOLFOX
- as the second-line treatment, in combination with the chemotherapy regimen FOLFIRI
- on its own (known as monotherapy) after other chemotherapy treatments, such as 5FU^[39] (fluorouracil), irinotecan or oxaliplatin, have already been tried.

The National Institute for Health and Clinical Excellence (NICE) currently gives advice on which new drugs or treatments should be available on the NHS in England and Wales. The Scottish Medicines

Consortium (SMC) makes recommendations on the use of new drugs within the NHS in Scotland. Neither NICE nor the SMC have recommended the use of panitumumab as a treatment for people with advanced colorectal cancer.

As a result, panitumumab may not be widely available on the NHS, although you may be given it as part of a clinical trial. We have more information about what you can do if a treatment isn't available.

CONCLUSION AND PERSPECTIVES FOR

FUTURE RESEARCH

Thorough understanding of the complex interactions between components of the immunological response has led to interest in antibody-based therapy for solid tumors. A number of theories have emerged attempting to describe possible mechanisms through which certain antibodies may exert therapeutic effects through interference with cancer cell biology. Some MAbs have increased the efficacy of treatment of certain tumors, with acceptable safety profiles. Stabilization of disease and inhibition of metastases have been observed in some studies, validating the significance of MAb application in clinical practice. Issues to be addressed include dosing strategies, timing, and schedule of antibody administration; duration of treatment; need for tailoring; and further testing under specific circumstances. The discovery of effective combinations with other biologic agents would be very useful. Multimodality approaches, based on synergistic effects observed with the combination of antibodies with chemotherapeutic drugs and/or radiotherapy also merit further investigation. Immunemediated effects may be further exploited with the use of bispecific molecules. Stratification of patient subpopulations with tumors overexpressing disease-related clinical biomarkers could result in improving both efficacy and specificity of antibody-based treatment for solid tumors.

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