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AN IMPORTANT APPROACH IN "MONOCLONAL ANTIBODIES USE FOR CANCER TREATMENT"

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ABSTRACT

Now it's proved- Monoclonal antibodies are very important therapeutic tools for cancer. Today, more than 314 Mabs products are in clinical study worldwide. The recent clinical success of anticancer Monoclonal antibodies like Catumaxomab, Brentuximab, Denosumab, Ipilimumab, Tocilizumab are widely used and these are proving of success rate about Monoclonal antibodies for different cancer treatment. Monoclonal antibody therapy has emerged as an important therapeutic modality for cancer. In 1975, Kohler and Milstein discovered how to prepare hybridomas: a new cell type, resulting from the fusion of B-lymphocytes (immune cells of mouse) with a myeloma (cancer) cell. Hybridomas are cells that have been engineered to produce a desired monoclonal antibody in large amounts. Monoclonal antibodies are targeted at specific receptors on cancer cells. Currently, there are more than 20 new monoclonal antibodies- including murine, chimeric, humanized and human that have won FDA approval, including those aimed at transplant rejection, auto-immune disorders, leukemia, colorectal cancer, breast cancer, non-Hodgkin lymphoma, certain viral infections, and macular degeneration. Past, present & future planning about Mabs are discussed.

Keywords: Monoclonal antibodies (Mabs), Hybridoma, Cancer

INTRODUCTION

Monoclonal antibodies (or MAb in medical shorthand) are antibodies that are identical, each derived from one type of immune cell and each a clone of a single parent cell. For science, that means that the extraordinarily specific nature of antibodies becomes a tool with wide and potentially revolutionary applications. In essence, they can be deployed to find a single targeted substance, such as an antigen found only on a cancer cell, and make it possible to pinpoint the cell and destroy it. In addition to cancer therapies, MAbs are also used in diagnostic tests for everything from pregnancy, to AIDS, to drug screening. Further, the antibodies can be used to lessen the problem of organ rejection in transplant patients and to treat viral diseases that are traditionally considered "untreatable." Scientists are looking at MAbs for a variety of illnesses including chronic inflammatory and infectious diseases. The antibodies bind to the surface of an intruding agent for the purpose of creation of conditions suitable for elimination of the intruder. The blood proteins called antibodies, or immunoglobins, have the ability to distinguish extraneous molecules from ones native to the body. Organisms produce immunoglobins in response to an invasion by an infectious agent such as a bacterium or a virus.

The antibody molecule has a recognition site that binds tightly to specific sites -- proteins or carbohydrates -- located on the surface of the infectious agent. Organisms produce antibodies in response to the intrusion of a foreign polymer that is larger than a certain size; such antibodies will bind tightly to the invading substance but will not bind to unrelated molecules. The binding of an antibody to a bacterium or virus allows certain white blood cells to recognize the invading body as hostile, and they respond by degrading it. In short, the antibody acts as a signal for the elimination of infectious agents. Most drugs are small molecules – on the order of 10

to 100 atoms. Monoclonal antibodies are enormous in comparison, on the order of 2000 to 20,000 atoms. Monoclonal antibodies (mAb or moAb) are mono specific antibodies that are the same because they are made by identical immune cells that are all clones of a unique parent cell. Given almost any substance, it is possible to produce monoclonal antibodies that specifically bind to that substance; they can then serve to detect or purify that substance.

DISCOVERY

The idea of a "magic bullet" was first proposed by Paul Ehrlich, who, at the beginning of the 20th century, postulated that, if a compound could be made that selectively targeted a disease-causing organism, and 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. In the 1970s, the B-cell cancer multiple myeloma was known, and it was understood that these cancerous B-cells all produce a single type of antibody (a paraprotein). This was used to study the structure of antibodies, but it was not yet possible to produce identical antibodies specific to a given antigen. Production of monoclonal antibodies involving human–mouse hybrid cells was described by Jerrold Schwaber in 1973 and remains widely cited among those using human-derived hybridomas, but claims to 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. The invention was conceived by George Pieczenik, 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; who shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery. The key idea was to use a line of myeloma cells that had lost their ability to secrete antibodies, come up with a technique to fuse these cells with healthy antibody-producing B-cells, and be able to select for the successfully fused cells.

PRODUCTION

Monoclonal antibodies are artificially produced antibodies. The technique of cell fusion followed by selection is widely used in the production of monoclonal antibodies. Body cells can be cultured from a single cell in a controlled medium. The chromosomes involved are large and easily visible as a result of staining (coloring), so individual chromosomes and their arrangements are identifiable Modern techniques allow to fuse the cells in a way that two nuclei function in one cell, which leads to the transfer of DNA into growing culture cells. Several somatic-cell genetic techniques involve the fusion of two cells in such way that the nuclei from both parents are brought within one joint cytoplasm. Spontaneous fusion of animal and human cells in culture occurs infrequently, but the rate increases substantially when certain viruses that have lipoprotein envelopes similar to the plasma membranes of animal cells are present. Cell fusion can also be accelerated by the addition of polyethylene glycol, which causes cell plasma membranes to adhere to those of any surrounding cells. In most fused animal cells the nuclei eventually also fuse, producing the desired cells that contain chromosomes from both "parents". Hybrids between cultured cells from different mammals also have been widely used. Early production of monoclonal antibodies was fraught with obstacles.

The biggest problem was that the antibodies the process yielded were mouse antibodies (murine), and the human immune system frequently reacted against them, as with any other foreign substance entering the body. That reaction produced problems ranging from rashes to swelling of the joints to kidney failure and death; it also destroyed the antibodies and defeated the mission. Even so, scientists went back to the labs and found a number of ways to address the problem successfully, largely by finding a variety of ways to make the antibodies more human and less murine. One technique is to create "chimeric" antibodies by replacing some of the problematic regions of mouse content with human protein in a fusion process that results in antibodies that are about 65 percent human.

At least four monoclonals now on the market in the U.S. are chimerics, including a drug called ReoPro, which binds to platelets to prevent blood clots. Another approach has been a grafting process that produces what are known as "**humanized MAbs**," wherein some 95 percent of the resulting molecule is human in origin. This technique is employed in such drugs as Herceptin, a monoclonal antibody used to target breast cancer. Meanwhile, other researchers have developed techniques to create hybridomas that produce fully human MAbs, including at least one successful effort in England to fuse fully human B cells and immortalized cells, although scientists say it remains unclear what the long term implications and efficacy of the technology might be. Other researchers have found ways to genetically alter the

mice themselves to produce fully human antibodies, by causing the animals to contain human antibody genes. Still others are experimenting with an altogether different process that dispenses with the mice. “Phage display” (the word is an abbreviated form of bacteriophage, a virus that infests bacteria) involves inserting DNA from B cells into bacteria and then allowing phages to infect the bacteria. As the phages replicate, they also recreate the proteins from the antibody genes, which can be cultured. Marketwarch reports that total sales of monoclonal antibodies hit $48 billion in 2010 and is expected to exceed $70 billion by 2015.

CURRENT POSITION

Number of Monoclonal Antibody Products in Development Continues to Increase, According to Tufts Centre for the Study of Drug Development

BOSTON, MA, Nov 08, 2011 Developers are steadily increasing the number of monoclonal antibody products -- known as mAbs -- for which they are initiating clinical studies, extending a trend that began in the 1990s, according to the Tufts Center for the Study of Drug Development. The number of novel mAbs entering clinical study worldwide annually rose from 19 in 1997 to 53 in 2010, peaking at 54 in 2008, continuing a trend dating back to the mid-1990s when about a dozen mAb candidates entered clinical study each year, a recently completed Tufts CSDD analysis found.

According to Tufts CSDD, from 1997 through 2010, clinical and FDA approval phases for mAb therapeutics averaged 7.2 and 1.0 years, respectively. Total development and approval times for mAbs compare favorably with small molecule drugs, which require an average of 7.5 years in total to follow the same path, as well as with all biotech products, which require an average of 8 years. "Advances in antibody engineering and design, improvement in cell lines and manufacturing, and better understanding of targets and mechanisms of action are some of the key reasons why more mAbs are entering clinical study," said Janice M. Reichert, author of the study, research assistant professor and senior research fellow at Tufts CSDD. Today, about 314 mAb products are in clinical study worldwide.

First developed in the 1980s, mAbs began enjoying commercial success in 1997 when the U.S. Food and Drug Administration (FDA) approved Rituximab(R). Since then, the market for mAb products has grown rapidly. Global sales of these products reached $48 billion in 2010 and are projected to approach $80 billion by 2015.

The Tufts CSDD study, reported in the November/December Tufts CSDD Impact Report, released today, also found that:

* The cumulative success rate -- mAbs that completed clinical trials and received FDA approval -- was 17% for all humanized mAb candidates, with a lower rate (13%) for anticancer candidates and a higher rate (26%) for immunological candidates.
* FDA approvals dropped slightly, from 16 in the 1997-04 period to 13 in 2005-11.
* Of mAbs in clinical study, 51% are focused on anticancer therapies, 27% on immunological treatments, and the remaining 22% on various indications.

MONOCLONAL ANTIBODIES USE FOR CANCER TREATMENT

Monoclonal antibody therapy is the use of monoclonal antibodies (or mAb) to specifically bind to target cells or proteins. This may then stimulate the patient's immune system to attack those cells. It is possible to create a mAb specific to almost any extracellular/ cell surface target, and thus there is a large amount of research and development currently being undergone to create monoclonal for numerous serious diseases (such as rheumatoid arthritis, multiple sclerosis and different types of cancers). There are a number of ways that mAbs can be used for therapy. For example: mAb therapy can be used to destroy malignant tumour cells and prevent tumour growth by blocking specific cell receptors. Variations also exist within this treatment, e.g. radio immunotherapy, where a radioactive dose localizes on target cell line, delivering lethal chemical doses t the target. One possible 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; it is also possible to design bi specific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effecter cell. In fact, every intact antibody can bind to cell receptors or other proteins with its Fc region.

Targeted Conditions (Cancer):

Anti-cancer monoclonal antibodies can be targeted against malignant cells by several mechanisms:

- Radio immunotherapy (RIT) involves the use of radioactively conjugated murine antibodies against cellular antigens. Most

research currently involved their application to lymphomas, as these are highly radio-sensitive malignancies. To limit radiation exposure, murine antibodies were especially chosen, as their high immunogenicity promotes rapid clearance from the body. Tositumomab is an exemplar used for non-Hodgkins lymphoma.

- Antibody-directed enzyme prodrug therapy (ADEPT) involves the application of cancer associated monoclonal antibodies which are linked to a drug-activating enzyme. Subsequent systemic administration of a non-toxic agent results in its conversion to a toxic drug, and resulting in a cytotoxic effect which can be targeted at malignant cells. The clinical success of ADEPT treatments has been limited to date. However it holds great promise, and recent reports suggest that it will have a role in future oncological treatment.
- Immunoliposomes are antibody-conjugated liposomes. Liposomes can carry drugs or therapeutic nucleotides and when conjugated with monoclonal antibodies, may be directed against malignant cells. Although this technique is still in its infancy, significant advances have been made. Immunoliposomes have been successfully used in vivo to achieve targeted delivery of tumour-suppressing genes into tumours, using an antibody fragment against the human transferrin receptor. Tissue-specific gene delivery using immunoliposomes has also been achieved in brain, and breast cancer tissue.

Fighting Cancer With Monoclonal Antibodies:

Trial treatment of cancer with MAbs started in the 1990s, but in recent years the interest in monoclonal antibodies for oncology has increased considerably. Rituximab (aka Rituxan or MabThera) was approcved by the FDA for non-Hodgkins lymphoma in 1997. Rituximab binds to the CD20 antigen on B-cell lymph cells. Alemtuzumab (aka Campath) recognizes the CD52 antigen on B-cell and T-cell lymph system components and has been used in treatment of chronic lymphocytic leulemia, the most common form of leukemia.

Panitumumab binds to the epidermal growth factor receptor (EGFR). It was approved by the FDA in 2006 for advanced colorectal cancer. Bevacizumab and Cetuximab were both approved by the FDA for colorectal cancer in 2004. Link Panitumumab, Cetuximab binds to EGFR and disrupts cancer cell proliferation. MAbs have been used both as single treatments and in combination with traditional chemotherpy drugs. EGFR inhibitos in particular help reverse the cancer's resistance to chemoptherapy agents.

Bevacizumab (trade name Avastin) was the first anti-angiogenesis drug approved by the FDA. It prevents (or at least slows) the growth of blood vessels. The idea is that the cancerous tumors can't get big if they can't grow capillaries to supply their cells with food and oxygen. One side effect is hypertension. At a molecular level, bevacizumab binds to vascular endothelial growth factor (it's called a VEGF inhibitor) and stops endothelial cell growth.

Cancer Treatment with Monoclonal Antibodies:

Monoclonal antibody drugs are used to combat various types of cancer. Unfortunately, some monoclonal antibody drugs have severe side effects. But it is also clear that these medications have a bright future because they enhance already existing body defenses, and can be improved dramatically as the new drug-production technologies evolve. There have been many failures (scientists have not had tremendous success in general with regard to cancer treatment), but the prospects are still bright and many scientists are working with mAbs for cancer.

Route of Antibody Administration: *MAbs for cancer treatment are usually injected to the bloodstream with a carrier although some clinical studies have involved the use of intraperitoneal administration of mAb where the treatment solution is injected to body cavities. Studies in experimental animals and in humans show that direct cavity injection targets smaller peritoneal tumors more efficiently than intravenous antibody treatment. Larger tumor masses are targeted more efficiently by the intravenous method, leading some researchers to hypothesize that the optimal situation will involve both delivery systems concurrently.*

Using antibodies to deliver drugs: Treatment with mAbs often uses them like missiles delivering a warhead. The warhead is the drug intended for the cancerous cell or defective areas of the body; the specitivity of the antibodies makes this a truly targeted treatment. Several toxins have been coupled to mAbs and have been analyzed. Treatment regimens either involve the induction of antibody by the body or the use of antibodies acting in conjunction with the complement system and/or effector cells (i.e., antibody-directed cell-mediated immunity).

One problem – and it is a big problem – with mABs for cancer treatment is that the antibodies that match

the malignant cells tend to not be poisonous to the cell. An antibody molecule might attach to a cell and the cell might go about its cancerous business dividing. Scientists try to build an effective therapy by literally attaching a toxin to the antibody. Such toxins as ricin and diptheria have been tried, as have been radioactive atoms for very precise and up-close radiotherapy. The FDA has approved toxin-laden antibodies for treatment of leukemia.

Types of monoclonal antibodies are used in cancer treatments:

Two types of monoclonal antibodies are used in cancer treatments:

- ***Naked monoclonal*** *antibodies* are those without any drug or radioactive material attached to them.
- ***Conjugated monoclonal*** *antibodies* are those joined to a chemotherapy drug, radioactive particle, or a toxin (a substance that poisons cells).

Naked monoclonal antibodies: Naked MAbs are the most commonly used MAbs at this time. Although they all work by attaching themselves to specific antigens, they can be helpful in different ways.

Markers for destruction: Some naked MAbs attach to cancer cells to act as a marker for the body's immune system to destroy them. Antibodies now in use in this group include:

Rituximab (Rituxan): Rituximab is used to treat B-cell non-Hodgkin lymphoma and some other diseases. It is a monoclonal antibody against the CD20 antigen, found on B cells. It works, in part, by labeling cells so that the immune system can attack them. Ofatumumab (Arzerra): Ofatumumab is another antibody against the CD20 antigen. It is used mainly to treat chronic lymphocytic leukemia when other treatments are no longer effective.

Alemtuzumab (Campath): Alemtuzumab is an antibody against the CD52 antigen, which is found on both B cells and T cells. It is used to treat some patients with B-cell chronic lymphocytic leukemia.

Activation blockers: Some naked MAbs don't really interact with a person's own immune system.

Their effects come from their ability to attach to the specific antigens that are working parts of cancer cells or other cells that help cancer cells grow, and stop them from working. These MAbs are also referred to as targeted therapies. Examples of FDA-approved MAbs of this type include:

Trastuzumab (Herceptin): Trastuzumab is an antibody against the HER2/neu protein. A large amount of this protein is present on tumor cells in some cancers. When HER2/neu is activated, it helps these cells grow. Trastuzumab stops these proteins from becoming active. It is used to treat breast cancers that have large amounts of this protein.

Cetuximab (Erbitux): Cetuximab is an antibody against the EGFR protein, which is present in large amounts on some tumor cells and helps them grow and divide. Cetuximab blocks the activation of EGFR. It is used to treat some advanced colorectal cancers as well as some head and neck cancers.

Panitumumab (Vectibix): This MAb also targets the EGFR antigen. It is used to treat some cases of advanced colorectal cancer.

Bevacizumab (Avastin): Bevacizumab targets the VEGF protein, which is normally made by tumor cells to attract new blood vessels to feed their growth. Bevacizumab attaches to VEGF, which blocks it from signaling for new blood vessels to form. This MAb is used along with chemotherapy to treat some colorectal, lung, breast, and kidney cancers, as well as glioblastomas (a type of brain tumor). It is being studied for use against other cancers.

Some of these antibodies have been used for many years. At first they were used mostly after other treatments had stopped working. But more studies have been done and continue to be done. Now, these antibodies are being used earlier in the course of cancer treatment.

Side effects- Monoclonal antibodies are given intravenously (injected into a vein). Compared with side effects of chemotherapy, the side effects of naked MAbs are usually fairly mild and are often more like an allergic reaction. If they do occur, it is most often while the drug is first being given.

Possible side effects can include:

- Fever
- Chills
- Weakness
- Headache
- Nausea
- Vomiting
- Diarrhea
- Low blood pressure
- Rashes

Some MAbs also have effects that are specific to the antigens they target. For instance, like most

chemotherapy drugs, some can affect the bone marrow. This can cause lower levels of blood cells, which can increase the risk of bleeding and infection in some people.

Conjugated monoclonal antibodies: Conjugated MAbs are monoclonal antibodies that are attached to drugs, toxins, or radioactive substances. The MAbs are used as homing devices to take these substances directly to the cancer cells. The MAb circulates in the body until it can find and hook onto the target antigen. It then delivers the toxic substance where it is needed most. This lessens the damage to normal cells in other parts of the body. Conjugated antibodies may pack more of a punch than naked MAbs, but for this reason they often cause more side effects, too. The side effects depend on which type of substance they're attached to. Conjugated MAbs are also sometimes referred to as *tagged*, *labeled*, or *loaded* antibodies. They can be divided into groups depending on what they are linked to.

- MAbs with radioactive particles attached are referred to as *radiolabeled*, and therapy with this type of antibody is known as *radioimmunotherapy* (RIT).
- MAbs with chemotherapy drugs attached are often referred to as *chemolabeled*.
- MAbs attached to toxins are called *immunotoxins*.

GLOBAL OPPORTUNITIES AND CHALLENGES

Monoclonal antibodies: the discovery in 1975, Köhler and Millstein discovered how to prepare hybridoma's: a new cell type, resulting from the fusion of B-lymphocytes (immune cells of a mouse) with a myeloma (cancer) cell. The hybridoma combines two characteristics of the parent cells: immortality of the cancer cell and specific antibody production of the B-lymphocyte. Since all hybridoma cells derived of this fusion product make the same cell antibody type, these antibodies are called monoclonal (coming from one clone) antibodies.

Optimism and hupe about usefulness: The monoclonal antibody technology was quickly adopted by scientists in both industry and academia and led to a hype in industry and academia about the almost unlimited usefulness of monoclonal antibodies. Their usefulness in research and diagnostics has by now been proven: it is difficult to find a research laboratory where monoclonal antibodies are not generated for research purposes, in particular for selection of compounds. Industrially, they are used to recognize proteins from a culture broth and thereby assist in purification processes. In diagnostics, numerous test kits are on the market featuring monoclonal antibodies that specifically recognize certain molecules. Among the over the counter products featuring monoclonal antibodies, easy-to-use pregnancy or fertility tests are best known among the public. This widespread use of monoclonal antibodies was based on such inherent characteristics as
- safety,
- a broad range of potential targets,
- high selectivity,
- high affinity and,
- ease of preparation (easy to generate).

Therapeutic disappointments in the 1980s: In the early 1980s, the hype about monoclonal antibodies extended to the field of therapeutics. The concept of the 'magic bullet' was born: a combination of a specific drug or toxin, bound to a monoclonal antibody that specifically zeroes in on its target and delivers the drug or toxin there where it is needed. However, in the mid and late 1980s the development of therapeutic monoclonal antibodies suffered a number of serious disappointments, which reduced faith in the therapeutic applicability of monoclonal antibodies considerably. These disappointments were caused by
- the need for high therapeutic doses,
- poor penetration in solid tumors,
- potential cross reactivity with other tumors,
- high production costs,
- potential viral safety problems,
- technical difficulties in large scale production and,
- relatively poor patent protection.

In addition, all monoclonal antibodies were derived from rodent cells, and these rodent-derived monoclonal antibodies suffered from
- a very short half life,
- poor recognition of the rodent IgG constant region by human effector function,
- HAMA response (generation of human anti-mouse antibodies).

Strategies to overcome drawbacks: All these drawbacks led to sophisticated technological developments and improvements, primary consisting of strategies to generate human(ized) monoclonal antibodies (mAbs). There are 5 such strategies:
- generation of true human mAbs (but these are instable and have only a limited number of targets),
- chimerization (the resulting monoclonal antibodies are 60-70% human),
- humanization (the resulting monoclonal antibodies are 90-95% human),

- use of phage display (resulting in fully human monoclonal antibodies),
- use of transgenics (resulting in fully human monoclonal antibodies).

Shortly, technological progress led to the development and approval of an increasing number of initially chimeric, then humanized therapeutic mononclonal antibodies.

Further challenges — no highly effective drugs without severe adverse events?

In 2005, as major challenges seemed to be overcome, Tysabri® was withdrawn from the US market only 3 month after its first approval to treat relapsing multiple sclerosis. 3 patients treated with Tysabri® developed PML (Progressive Multifocal Leukoencephalopathy) that occurs almost exclusively in people with severe immune deficiency. As no further cases of PML were observed, Tysabri® was re-launched in US and first approved for Europe in 2006. To this day, approx. 60.000 humans were medicated with Tysabri® in US and Europe and 4 further cases of PML were registered. In March 2006, the confidence in antibody drugs was shaken again by the horrible outcome of the TGN1412 phase I clinical trial. Tegenero tested a superagonistic monoclonal antibody that stimulates T-cell generation in healthy volunteers. However, the trial was immediately suspended by the MHRA after all six subjects that took TGN-1412 developed a life-threatening inflammatory reaction. In July 2006, the company filed for insolvency and all development by the company was discontinued. More recently, in March 2009, Actemra, a monoclonal antibody developed and launched by Chugai Pharmaceuticals, caused tongues to wag: 15 subjects suffering from rheumatoid arthritis died after being treated with Actemra. A causal connection between the administration of the drug and the cases of deaths was neither proven nor could it be excluded until yet. Raptiva, developed and launched by Genentech and Xoma and approved in the EU in 2004 to treat chronic moderate-to-severe plaque psoriasis, was voluntarily withdrawn due to increased risk of progressive multifocal leukoencephalopathy (PML) in April 2009. Regulatory authorities such as FDA and EMEA react: the prescription and the administration of monoclonal antibody drugs is strictly regulated as soon as particular risks are suspected.

Distributers are obliged to apply formal warnings; healthcare professionals are to inform patients properly. For some drugs, use is restricted to patients that meet well defined demands. But in many cases the medical benefit for the individual is to rate much higher than the related risk. Thousands of patients suffering from a wide variety of diseases already benefit from the possibility of the treatment with mAbs, were formerly no medication was available.

CONCLUSION

mAbs represent an important advance in the treatment of certain hematologic malignancies and solid tumors. Unlike many small molecules, mAbs offer unique target specificity. The field has evolved rapidly in recent years, and now it is much easier to create mAbs against a variety of targets of potential relevance to tumor growth and survival. Targets, including CD20, HER-2, VEGF, and EGFR, have now been validated by the clinical efficacy of mAbs. In the future, the list of viable targets is likely to expand. Two areas that may merit more attention are membrane transporters and stromal function. Positron emission tomography scans detecting selective uptake of fluoroglucose by tumor cells are already being used diagnostically. By targeting specific transporters, mAbs may eliminate the ability of tumor cells to survive in a nutrient-challenged environment. The stroma is the interface between tumor and host, and accordingly, mAbs against stromal antigens may make it more resistant to the onslaught of tumor cells. At first glance, the clinical efficacy of mAbs may be attributed to target-specific effects. By binding to their target, mAbs neutralize an important factor or receptor that drives cell proliferation and tumor growth. However, the therapeutic activity of mAbs may go beyond these target-related effects. Currently available mAbs are IgG antibodies, and consequently, they have the potential to activate immune-mediated effector functions, including ADCC and CDC. ADCC occurs when target-bound antibodies mobilize effector cells via interaction of their Fc domain with FcRs on the surface of immune cells. The interaction between the Ig Fc domain and FcRs on immune cells depends on the Fc domain (its sequence and glycosylation) and on the FcR structure (types and polymorphisms). Thus, the binding affinity of IgG for the FcgR mediating ADCC and other effector mechanisms varies by antibody isotype, and antibody-related effects may not be equal for all IgG isotypes or for all mAbs within a given isotype. The highest binding affinity for the various FcgR subclasses is found with IgG_1 and IgG_3, and therefore mAbs of these isotypes should be most likely to stimulate immune-mediated effector functions. Also, the intensity of ADCC is expected to fluctuate depending on the allelic *FcR*variants present in the host, and preliminary evidence points to an effect of those polymorphisms in clinical response to mAbs.

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Table 1: FDA-approved monoclonal antibodies for cancer treatment

Name	Target Cancer
Alemtuzumab (Campath)	Chronic lymphocytic leukemia
Bevacizumab (Avastin)	Breast cancer, colon cancer, lung cancer
Cetuximab (Erbitux)	Colon cancer, head and neck cancers
Gemtuzumab (Mylotarg)	Acute myelogenous leukemia
Ibritumomab (Zevalin)	Non-Hodgkin's lymphoma
Panitumumab (Vectibix)	Colon cancer
Rituximab (Rituxan)	Non-Hodgkin's lymphoma
Tositumomab (Bexxar)	Non-Hodgkin's lymphoma