PROTEIN DRUGS, MONOCLONAL ANTIBODIES, TARGET DRUGS TOANTIGEN, BIOSIMILARS

PROTEIN DRUGS

Linear POLYPEPTIDES that are synthesized on RIBOSOMES and may be further modified, crosslinked, cleaved, or assembled into complex proteins with several subunits. The specific sequence of AMINO ACIDS determines the shape the polypeptide will take, during PROTEIN FOLDING, and the function of the protein.

Therapeutic protein drugs are an important class of medicines serving patients most in need of novel therapies. Recently approved recombinant protein therapeutics have been developed to treat a wide variety of clinical indications, including cancers, autoimmunity/inflammation, exposure to infectious agents, and genetic disorders. The latest advances in protein-engineering technologies have allowed drug developers and manufacturers to fine-tune and exploit desirable functional characteristics of proteins of interest while maintaining (and in some cases enhancing) product safety or efficacy or both. In this review, we highlight the emerging trends and approaches in protein drug development by using examples of therapeutic proteins approved by the U.S. Food and Drug Administration over the previous five years (2011–2016, namely January 1, 2011, through August 31, 2016).

Drug Name	Drug Description
Lepirudin	A protein-based direct thrombin inhibitor used to reverse and prevent thrombus formation in heparin-induced thrombocytopenia.
Cetuximab	An endothelial growth factor receptor binding fragment used to treat colorectal cancer as well as squamous cell carcinoma of the head and neck.
Dornase alfa	A synthetic form of human deoxyribonuclease I used to break down extracellular DNA in the lungs, a major source of mucous viscosity in cystic fibrosis.
Denileukin diftitox	A recombinant cytotoxic protein based on a combination of diphtheria toxin fragments and interleukin-2 used to treat cutaneous T-cell lymphoma by targeting the interleukin-2 receptor.

Etanercept	A protein therapy based on the binding fragment of the tumour necrosis factor alpha receptor used to treat severe rheumatoid arthritis and moderate to severe plaque psoriasis.
Bivalirudin	A direct thrombin inhibitor used to treat heparin-induced thrombocytopenia and to prevent thrombosis during percutaneous coronary intervention.
Leuprolide	A protein-based luteinizing hormone antagonist used to treat prostate cancer, endometriosis, and precocious puberty.
Peginterferon alfa-2a	A modified form of recombinant human interferon used to stimulate the innate antiviral response in the treatment of hepatitis B and C viruses.
Alteplase	A recombinant form of human tissue plasminogen activator used in the emergency treatment of myocardial infarction, ischemic stroke, and pulmonary emboli.
Sermorelin	For the treatment of dwarfism, prevention of HIV-induced weight loss

MONOCLONAL ANTIBODIES

Monoclonal antibodies (**mAb** or **moAb**) are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have monovalent affinity, in that they bind to the same epitope (the part of an antigen that is recognized by the antibody). In contrast, polyclonal antibodies bind to multiple epitopes and are usually made by several different plasma cell (antibody secreting immune cell) lineages. Bispecific monoclonal antibodies can also be engineered, by increasing the therapeutic targets of one single monoclonal antibody to two epitopes.

Outline of production of MAbs

The main objective is to produce a homogenous population of MAbs against a pre-fixed immunogen. The basic strategy includes (i) purification and characterization of the desired antigen in adequate quantity, (ii) immunization of mice with the purified antigen, (iii) culture of myeloma cells which are unable to synthesize hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) enzyme necessary for the salvage pathway of nucleic acids, (iv) removal of spleen cells from mice and its fusion with the myeloma cells, (v) followingfusion, the hybridomas were grown in hypoxanthine aminopterin thymidine (HAT) medium. The fused cells are not affected in the absence of HGPRT unless their de novo synthesis pathway is also disrupted. In the presence of aminopterin, the cells are unable to use the de novo pathway and thus these cells become auxotrophic for nucleic acids as a supplement to HAT medium. In this medium, only fused cells will grow. Unfused myeloma cell does not have ability to grow in this HAT medium because they lack HGPRT, and thus cannot produce DNA. Unfused spleen cells can¬not grow because of their short life spans. Only fused hybrid cells or hybridomas can grow in HAT medium. Hybrid cells have the capacity togrow in the HAT medium since spleen cell partners produce HGPRT. (vi) The hybrid cell clones are generated from single host cells (vii) the antibodies secreted by the different clonesare then tested for their ability to bind to the antigen using an enzyme-linked immunosorbent assay (ELISA). (viii) The clone is then selected for future use.

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 CiteAb. Below are examples of clinically important monoclonal antibodies.

Main category	Type	Application	Mechanism/Target	Mode
Anti-inflammatory	**infliximab**	• rheumatoid arthritis • Crohn's disease	inhibits TNF-α	chimeric
	adalimumab	• rheumatoid arthritis • Crohn's disease • ulcerative colitis • ankylosing spondylitis	inhibits TNF-α	human
	basiliximab	• acute rejection of kidney transplants	inhibits IL-2 on activated T cells	chimeric
	daclizumab	• acute rejection of kidney transplants	inhibits IL-2 on activated T cells	humanized
	omalizumab	• moderate-to-severe allergic asthma	inhibits human immunoglobulin E (IgE)	humanized
	gemtuzumab	• relapsed acute myeloid leukemia	targets myeloid cell surface antigen CD33 on leukemia cells	humanized
Anti-cancer	**alemtuzumab**	• B cell leukemia	targets an antigen CD52 on T- and B-lymphocytes	humanized
	rituximab	• non-Hodgkin's lymphoma • rheumatoid arthritis	targets phosphoprotein CD20 on B lymphocytes	chimeric

	trastuzumab	• breast cancer with HER2/neu overexpression	targets the HER2/neu (erbB2) receptor	humanized
	nimotuzumab	• approved in squamous cell carcinomas, Glioma • clinical trials for other indications underway	EGFR inhibitor	humanized
	cetuximab	• approved in squamous cell carcinomas, colorectal carcinoma	EGFR inhibitor	chimeric
	bevacizumab & ranibizumab	• Anti-angiogenic cancer therapy	inhibits VEGF	humanized
Anti-cancer and anti-viral	**bavituximab**	• cancer, hepatitis C infection	immunotherapy, targets phosphatidylserine	chimeric
	palivizumab	• RSV infections in children	inhibits an RSV fusion (F) protein	humanized
Other	**abciximab**	• prevent coagulation in coronary angioplasty	inhibits the receptor GpIIb/IIIa on platelets	chimeric

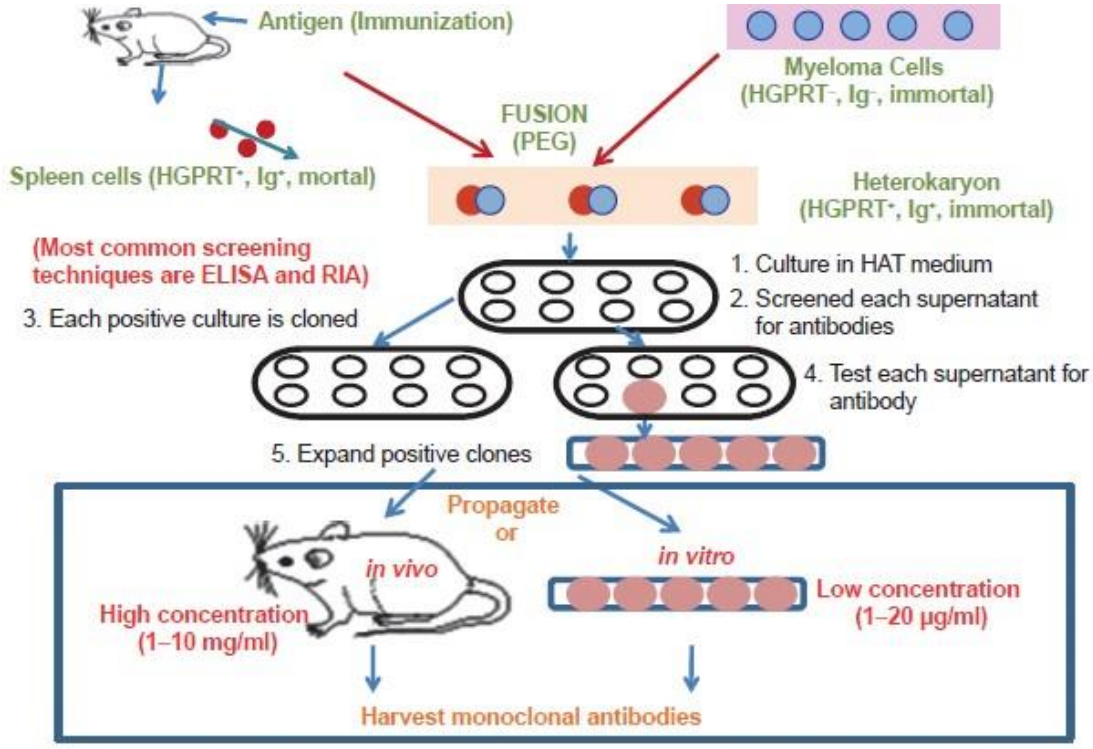


Figure 1. Production of monoclonal antibody by hybridoma technology. The hybridoma technology outline involves the isolation of spleen cells from immunized mice, their fusion with immortal myeloma cells and the production and further propagation of monoclonal antibodies from the hybrid cells.[2]

Immunization schedule Depending on the purity and nature of the purified antigen, an immunization protocol is determined. For immunization, the desired protein should be available in adequate quantity (a few milligrams). However, in case of a complex multi-molecular antigen, it is quite stringent to purify it in adequate quantity. Thus, depending on its screening and selection abilities, MAbs can purify a target antigen from an antigen mixture. Mice must be immunized with antigen 6–10 weeks before fusion to allow them to develop a robust immune response before generating hybridomas. The injection schedule and the actual timing may vary depending on the antigen used for the immunization as well as other factors. It is desirable to immunize mice with a pure antigen, as this simplifies the screening of hybridomas. However, complex antigenic mixtures can be used. Collection of pre-immune serum is required prior to immunization to use as a baseline control for antibody screening. The mouse is bled by cutting approximately 1–2 mm off the tip of the tail thereby collecting 100–200 µL of blood in a capillary tube from where the serum is collected and can be cryo-preserved. A typical immunization schedule includes intra-peritonial injections of 2– 4 adult mice (eg, BALB/c mice) with 20–100 µg of purified antigen in a total volume of 200 µL (ie, 200 µL of a 1:1 emulsion of antigen in saline: adjuvant). A stable emulsion is critical for generating a strong immune response. The injection is repeated 14–30 days later and booster doses are administered for 2–3 times until a good titer of antibody is obtained. Next, 10–14 days after the last injection, 100–200 µL of blood is collected from the tip of the tail orfrom the

eye and serum is separated. The antibody levels in serum can be detected by applying different immune-techniques such as ELISA, immunofluorescence, flow cytometry, and immuno blotting, and the antibody titer of the post-immune serum is compared with the pre-immune serum from the same animal. The mouse with the highest antibody titer swas selected for fusion. Between one and four days prior to fusion, the selected mouse is boosted intravenously via the tail vein. Following this step, spleen cells are prepared for fusion.

Myeloma cell line culture

In myeloma culture, hybridomas should grow continuously and selectively by suppressing the growth of the parent myeloma. It is desirable to obtain a parental myeloma cell that has been proven to yield stable hybridomas. The selected myeloma cell lines should have lost their capability to produce nucleotides using the salvage pathway. Myeloma cells are cultured in presence of 8-azaguanine so that they are unable to synthesize the HGPRT enzymenecessary for the salvage pathway of nucleic acids. Parental myeloma cells are cultured for atleast one week prior to fusion to ensure that the cells are well-adapted to HGPRT-negative

conditions. Cells are seeded at a density of approximately 5 × 104 cells/mL and passaged every 2 days; those growing in the early-mid log phase prior to fusion are selected for fusion.

After fusion, by using the drug aminopterin, de novo synthesis pathways can be blocked and thus the myeloma cells (where salvage pathway was previously blocked) cannot produce RNA or DNA and die. On the other hand, hybridomas have a functional salvage pathway (derived from the spleen cells of mouse) and can grow when they are cultured in medium containing the substrates for the pathway, ie, thymidine and hypoxanthine. This selective culture medium is HAT medium containing hypoxanthine, aminopterin, and thymidine respectively.

Fusion

The parental myeloma cells used to make the hybridoma must match the strain of mouse being immunized (eg, for BALB/c mice the myeloma cells must be of BALB/c origin) and must not secrete any of their own immunoglobulin chains. The parental myeloma cells should be mycoplasma-free, fuse well, and allow the formation of stable hybridomas that continually secrete specific MAbs. SP2/0 and X63Ag8. 653 are widely used parental myeloma cells that meet all of these criteria. There are various agents that induce the somatic cell to fuse. There are some physical agents, such as electro-fusion and chemical agents, including polyethylene glycol (PEG) and calcium ions, among others. Large numbers of cells can be fused in the

presence of PEG within a short time. During electro-fusion, a continuous electric potential is maintained in the fusion medium. Current is applied in short pulses at high voltage with short duration or in low voltage with long duration. The factors that are controlled during electro-fusion were specific resistance, osmotic strength, field strength, and ionic composition of the fusion medium. The cells should be given proteolytic pretreatment.

An immunized mouse, 48–72 hours after tail vein injection, is euthanized and the spleen can be removed and disaggregated into a single cell suspension under sterile conditions. At the same time, the myeloma cells are harvested and added to fusion medium and mixed with spleen cells together with PEG solution to yield single hybridoma colonies. The fused cell mixture is plated in culture plates containing a feeder layer prepared from control un- immunized mice

Growth and selection of MAbs

Within 7–14 days after fusion, the growth of hybridomas occurs gradually together with the addition of interleukin 6 (IL-6), the hybridoma growth factor.

Applications of m**onoclonal** a**ntibodies**

MAbs have proved to be extremely valuable for basic immunological and molecular research because of their high specificity. They are used in human therapy, commercial protein purification, suppressing immune response, diagnosis of diseases, cancer therapy, diagnosis of allergy, hormone test, purification of complex mixtures, structure of cell membrane, identification of specialized cells, preparation of vaccines, and increasing the effectiveness of medical substances

Diagnostic tools in research and laboratory

To detect the presence of this substance/antigen, MAbs can be used. Different technologies in which MAbs are used include Western blot, immunodot blot, ELISA, radioimmuno assay (RIA), flow cytometry, immunohistochemistry, fluorescence microscopy, electronmicroscopy, confocal microscopy, as well as other biotechnological applications.

Gene cloning

One of the difficulties of gene cloning is identifying the cells that contain the desired gene. If an MAb that recognizes that the gene product is available, it can be used as a probe for detecting those cells that make the product and therapy to detect the gene.

To identify cell types

MAbs contribute to the identification of many different types of cells that participate in the immune response and to unravel interactions occurring during this process. For example, in the

lymphocytes with B, T helper (TH) cells and suppressor T, the use of MAbs has established that the various types of T-cells carry cell surface antigens on their surfaces that allow one type to be distinguished from another. The MAbs were also helpful in defining changes in T and B-cells during development.

Protein purification

MAb affinity columns are readily prepared by coupling MAbs to a cyanogen bromide-activated chromatography matrix, eg, Sepharose. Since the MAbs have unique specificity for the desired protein, the level of contamination by unwanted protein species usually is very low. Since the MAb-antigen complex has a single binding affinity it is possible to elute the required protein in a single, sharp peak. The concentration of the relative protein relative to total protein in a mixture can ever be very low. This method also has limitations. Achieving 100% pure protein is difficult because there is always a tendency for small amounts of immunoglobulin to leak off the immune-affinity column. Additionally, MAb do not distinguish between intact protein molecules and fragments containing the antigenic site.

Recombinant

The production of recombinant monoclonal antibodies involves repertoire cloning, CRISPR/Cas9, or phage display/yeast display technologies.[22] 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. The phage antibody libraries are a variant of phage antigen libraries.[24] 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 delectability in diagnostic applications. 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 murine monoclonal antibodies were injected into humans, resulting in their rapid removal from the blood, as well as systemic inflammatory effects and the production of human anti-mouse antibodies (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 cell culture yielded part-mouse, part-human antibodies.

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. Two successful approaches have been identified: transgenic mice and phage display.

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 Western blot and immuno dot blot tests. In immunohistochemistry, monoclonal antibodies can be used to detect antigens in fixed tissue sections, and similarly, immunofluorescence 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

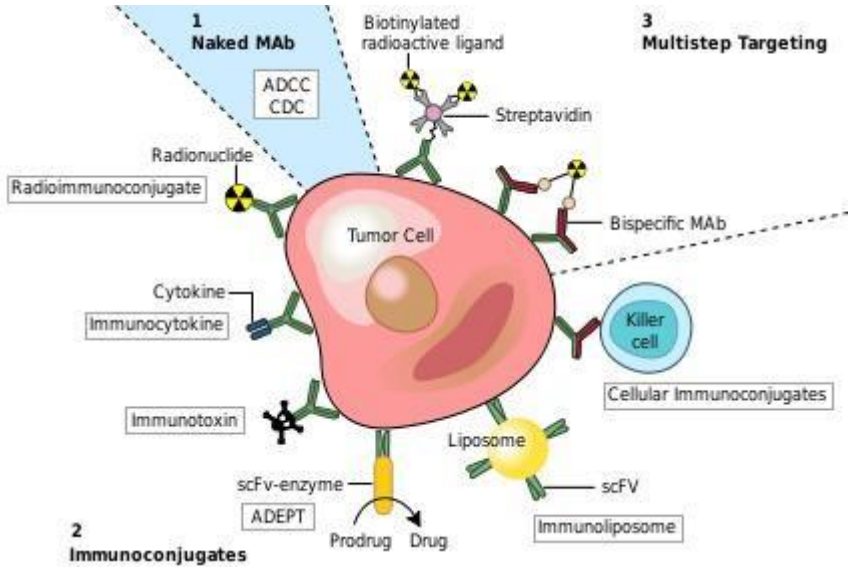
Main article: Monoclonal antibody therapy

Therapeutic monoclonal antibodies act through multiple mechanisms, such as blocking of targeted molecule functions, inducing apoptosis in cells which express the target, or by modulating signalling pathways.[44][45]

Cancer treatment

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immune response against the target cancer cell. Such mAbs can be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate or to design bispecific antibodies that can bind with their Fab regions both to targetantigen and to a

conjugate or effector cell. Every intact antibody can bind to cell receptors or other proteins with its Fc region.



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.[46]

MAbs approved by the FDA for cancer include

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

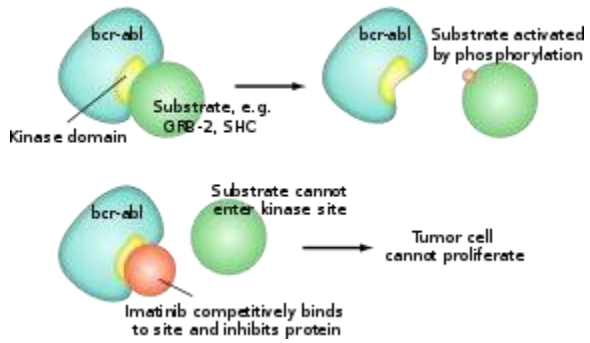
Autoimmune diseases

Monoclonal antibodies used for autoimmune diseases include infliximab and adalimumab, which are effective in rheumatoid arthritis, Crohn's disease, ulcerative colitis and ankylosing spondylitis by their ability to bind to and inhibit TNF-α. Basiliximab and daclizumab inhibit IL-2 on activated T cells and thereby help prevent acute rejection of kidney transplants.[48]

Omalizumab inhibits human immunoglobulin E (IgE) and is useful in treating moderate-to-severe allergic asthma.

The main categories of targeted therapy are currently *small molecules* and *monoclonal antibodies.*

Small molecules



Mechanism of imatinib

Many are tyrosine-kinase inhibitors.

- Imatinib (Gleevec, also known as STI–571) is approved for chronic myelogenous leukemia, gastrointestinal stromal tumor and some other types of cancer. Early clinical trials indicate that imatinib may be effective in treatment of dermatofibrosarcoma protuberans.
- Gefitinib (Iressa, also known as ZD1839), targets the epidermal growth factor receptor (EGFR) tyrosine kinase and is approved in the U.S. for non small cell lung cancer.
- Erlotinib (marketed as Tarceva). Erlotinib inhibits epidermal growth factor receptor, and works through a similar mechanism as gefitinib. Erlotinib has been shown to increase survival in metastatic non small cell lung cancer when used as second line therapy. Because of this finding, erlotinib has replaced gefitinib in this setting.
- Sorafenib (Nexavar)[13]
- Sunitinib (Sutent)
- Dasatinib (Sprycel)
- Lapatinib (Tykerb)
- Nilotinib (Tasigna

- Bortezomib (Velcade) is an apoptosis-inducing proteasome inhibitor drug that causes cancer cells to undergo cell death by interfering with proteins. It is approved in the U.S. to treat multiple myeloma that has not responded to other treatments.
- The selective estrogen receptor modulator tamoxifen has been described as the foundation of targeted therapy.[14]
- Janus kinase inhibitors, e.g. FDA approved tofacitinib
- ALK inhibitors, e.g. crizotinib
- Bcl-2 inhibitors (e.g. obatoclax in clinical trials, navitoclax, and gossypol.
- PARP inhibitors (e.g. Iniparib, Olaparib in clinical trials)
- PI3K inhibitors (e.g. perifosine in a phase III trial)
- Apatinib is a selective VEGF Receptor 2 inhibitor which has shown encouraging anti-tumor activity in a broad range of malignancies in clinical trials. Apatinib is currently in clinical development for metastatic gastric carcinoma, metastatic breast cancer and advanced hepatocellular carcinoma.
- Zoptarelin doxorubicin (AN-152), doxorubicin linked to [D-Lys(6)]- LHRH, Phase II results for ovarian cancer.
- Braf inhibitors (vemurafenib, dabrafenib, LGX818) used to treat metastatic melanoma that harbors BRAF V600E mutation
- MEK inhibitors (trametinib, MEK162) are used in experiments, often in combination with BRAF inhibitors to treat melanoma
- CDK inhibitors, e.g. PD-0332991, LEE011 in clinical trials
- Hsp90 inhibitors, some in clinical trials
- salinomycin has demonstrated potency in killing cancer stem cells in both laboratory-created and naturally occurring breast tumors in mice.
- VAL-083 (dianhydrogalactitol), a “first-in-class” DNA-targeting agent with a unique bi-functional DNA cross-linking mechanism. NCI-sponsored clinical trials have demonstrated clinical activity against a number of different cancers including glioblastoma, ovarian cancer, and lung cancer. VAL-083 is currently undergoing Phase 2

  and Phase 3 clinical trials as a potential treatment for glioblastoma (GBM) and ovarian

cancer. As of July 2017, four different trials of VAL-083 are registered.

Small molecule drug conjugates

- Vintafolide is a small molecule drug conjugate consisting of a small molecule targeting the folate receptor. It is currently in clinical trials for platinum-resistant ovarian cancer (PROCEED trial) and a Phase 2b study(TARGET trial) in non-small-cell lung carcinoma (NSCLC).

Serine/threonine kinase inhibitors (small molecules)

- Temsirolimus (Torisel)
- Everolimus (Afinitor)
- Vemurafenib (Zelboraf)
- Trametinib (Mekinist)
- Dabrafenib (Tafinlar)

Monoclonal antibodies

Several are in development and a few have been licensed by the FDA and the European Commission. Examples of licensed monoclonal antibodies include:

- Pembrolizumab (Keytruda) binds to PD-1 proteins found on T cells. Pembrolizumab blocks PD-1 and help the immune system kill cancer cells.[23] It is used to treat melanoma, hodgkin's lymphoma, non-small cell lung carcinoma and several other typesof cancer.
- Rituximab targets CD20 found on B cells. It is used in non Hodgkin lymphoma
- Trastuzumab targets the Her2/neu (also known as ErbB2) receptor expressed in some types of breast cancer
- Alemtuzumab

- Cetuximab target the epidermal growth factor receptor (EGFR). It is approved for use in the treatment of metastatic colorectal cancer, and squamous cell carcinoma of the head and neck.
- Panitumumab also targets the EGFR. It is approved for the use in the treatment of

metastatic colorectal cancer.

- Bevacizumab targets circulating VEGF ligand. It is approved for use in the treatment of colon cancer, breast cancer, non-small cell lung cancer, and is investigational in the treatment of sarcoma. Its use for the treatment of brain tumors has been recommended.
- Ipilimumab (Yervoy)

Many antibody-drug conjugates (ADCs) are being developed. See also ADEPT (antibody-directed enzyme prodrug therapy).

CD antigens as drug target

Special drugs have been designed that identify and attack cells that have a particular type of CD antigens. These drugs are called monoclonal antibodies and they can attack only the type of cell that contains the specific target CD antigens. Monoclonal antibodies can also be tagged to drugs or radiation-emitting substances that add to the ability to kill cells that have the specific CD marker on their surface.

Examples of CD antigens targeted in lymphoma treatment:

Rituxan (Rituximab) – a monoclonal antibody against CD20. Zevalin (Ibritumomab Tiuxetan) - another antibody against CD20, tagged with a radiation emitting substance (Y90). Bexxar (Tositumomab) - similar to Zevalin, only the radiation emitting substance is different (I131) Gazyva (Obinutuzumab): targets CD20 antigen, used in initial treatment for small lymphocytic lymphoma/chronic lymphocytic leukemia.

Arzerra (Ofatumumab): targets CD 20 antigen, used in SLL/CLL. Campath (Alemtuzumab): targets CD52 antigen in SLL/CLL and peripheral T-cell lymphomas. Adcetris (Brentuximab vedotin): targets CD30 and is attached to a chemotherapy drug. Used in anaplastic large cell lymphoma.

BIOSIMILAR

A biosimilar is a biologic medical product (also known as biologic) highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. Biosimilars are officially approved versions of original "innovator" products and can be manufactured when the original product's patent expires.[2] Reference to the innovator product is an integral component of the approval.

Unlike with generic drugs of the more common small-molecule type, biologics generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes. Despite that heterogeneity, all biopharmaceuticals, including biosimilars, must maintain consistent quality and clinical performance throughout their lifecycle. A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular micro-heterogeneity. Drug-related authorities such as the EU's European Medicines Agency (EMA), the US's Food and Drug Administration (FDA), and the Health Products and Food Branch of Health Canada hold their own guidance on requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy. According to them, analytical studies demonstrate that the biological product is highly similar to the referenceproduct, despite minor differences in clinically inactive components, animal studies (including the assessment of toxicity), and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics). They are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which

the reference product is licensed and is intended to be used and for which licensure is sought for the biological product.

The World Health Organization (WHO) published its "Guidelines for the evaluation of similar biotherapeutic products (SBPs)" in 2009. The purpose of this guideline is to provide an international norm for evaluating biosimilars with a high degree of similarity with an already licensed, reference biotherapeutic medicine.

Europe was the first region in the world to develop a legal, regulatory, and scientific framework for approving biosimilar medicines. The EMA has granted a marketing authorisation for more than 50 biosimilars since 2006 (first approved biosimilar Somatropin (Growth hormone)). The first monoclonal antibody that was approved in 2013, was infliximab, putting the EU at the forefront of biologics regulatory science.. Meanwhile, on March 6, 2015, the FDA approved the United States's first biosimilar product, the biosimilar of filgrastim called filgrastim-sndz (trade name Zarxio) by Sandoz.