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A Study of Cancer Treatment Using Targeted Biologics

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Abstract: *Globally, cancer is a leading cause of death due to its intricate and aggressive genetic nature. Millions of cancer patients' lives have been greatly prolonged by protein-based biopharmaceuticals. The biological role and use of targeted anticancer biopharmaceuticals are reviewed in this article. First, we talk about the key pathways and particular antigens that are employed in the creation of targeted cancer therapies. Next, a review is given to the novel monoclonal antibodies, non-antibody proteins, and small compounds that target these antigens or pathways. Lastly, the difficulties now facing the development of anticancer biopharmaceuticals are examined, along with possible answers*

Keywords: Anticancer, biopharmaceuticals, Innovative biologics.

I. INTRODUCTION

Cancer kills many people globally due to the combination of oncogenes, tumor suppressor gene alterations, and environmental pollutants. Improved proliferation, decreased apoptosis, and aberrant metabolism are characteristics of cancer cells. Understanding the principles of autonomous tumor cell proliferation is crucial to controlling cancer cell transformation. Thus, the gene, protein, metabolite, and signaling pathway involved in cancer cell development have been extensively studied. These research identified antigens or mechanisms that aid anticancer drug development.

Targeted anticancer bio-pharmaceutical monoclonal antibodies have been shown to control numerous malignancies and increase cancer patients' quality of life and survival. Biopharmaceuticals generally target cancer-promoting antigens or signaling pathways. The mAb-based therapeutic protein category is increasing fastest. Over a dozen novel mAbs have been authorized by the FDA and EMA. Many novel non-antibody proteins and small molecule-based biopharmaceuticals treat cancer. Several generic biologics have been licensed and used to treat cancer in Europe and Asia.

Traditional medications can induce side effects without recognizing patient heterogeneity, despite advances in anticancer biopharmaceuticals. Personalized medications can solve this problem thanks to Omics technology. Increasing clinical efficiency is another biopharmaceutical development hurdle. To sustain therapeutic concentration in human serum, cancer patients need over several hundred mg of mAb every week. Glycoprotein's inadequate post-translational modifications may lower anticancer medication quality and increase dose. Effective biopharmaceutical bioprocessing produces high-efficiency biopharmaceuticals. This article first discusses cancer cell antigens and core pathways that could be targeted to kill cells, then reviews innovative and generic targeted therapeutic proteins, including monoclonal antibodies, non-antibody proteins, and small molecule drugs marketed in US, EU, and Asia, and finally discusses anticancer biopharmaceuticals development issues and possible solutions to improve efficacy.

Specific targets in cancer treatment

Targeting epigenetically and genetically abnormal molecules or pathways, using biopharmaceuticals is an effi- cient strategy in cancer treatment. The currently identified anti- gens and pathways are reviewed below.

Antigens

The ideal cancer antigens or regulators would be unique, survival-dependent, representative, and targetable. Cancer cells express the cluster of differentiation, a well-studied antigen that represents distinct glycoprotein and carbohydrate

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groups. Non-Hodgkin lymphoma, Hodgkin lymphoma, acute myelogenous leukemia, and chronic lymphocytic leukemia express hematopoietic CD20, CD30, CD33, and CD52, which bind well to anti-CD recombinant antibodies.
Growth factor is another microvasculature-forming antigen. Previous study has identified many growth factor antigens, including VEGF receptor integrin and receptor tyrosine-protein kinase. human epidermal growth factor receptor 2 and ErbB3. Breast cancer expressing HER2, non-small-cell lung carcinoma with EML4-ALK and EGFR mutations, and colorectal cancer overexpressing EGFR can be treated with ErbB-targeted tyrosine kinase inhibitors.

Core pathways

Carbon and energy from glycolysis promote normal and altered cell development and function. High-rate glycolysis and anaerobic respiration in the cytosol dominate energy generation in malignant tumor cells, according to the Warburg theory. Pyruvate kinase, the glycolysis pathway's last enzyme, controls intracellular energy and redox equilibrium. Various organs and proliferating cells contain the isoenzyme pyruvate kinase type M2. Cancer metabolism is linked to PKM2 transcription. In particular, raising the ratio of the tetramer and dimer of PKM2 accelerates glucose to pyruvate energy generation, while reducing it initiates nucleic acid, phospholipid, and amino acid synthesis. EGFR signals tumor cells expressing dimeric PKM2 early in carcinogenesis, hence inhibiting EGFR can effectively reduce cancer cell proliferation.
Metastatic malignancies deactivate essential tumor suppressive mechanisms. Omics technologies have helped discover fundamental signaling pathways from Pathway Commons, KEGG, Pathway Recognition Algorithm, and Ingenuity. In breast, colorectal, glioblastoma, and lung cancer, the receptor tyrosine kinase implicated in the signaling cascade of cell proliferation changed by phosphatidylinositide 3-kinases has been discovered. Activated B cells' nuclear factor kappa-light-chain-enhancer controls DNA transcription, immunological response to infection, and cellular response to stimuli. These findings suggest that an anticancer therapeutic protein that targets the core pathway independent of metastatic cancer aetiology is possible.

Innovative anticancer biopharmaceuticals

For cancer treatment, several biopharmaceuticals have been produced, including monoclonal antibodies, non-antibody proteins, and small compounds. Anticancer biopharmaceuticals target the central route, antigen, or regulator seen in different malignancies, as indicated in Fig. 1. Eight mAbs targeting CD antigens treat non-hodgkin's lymphoma, chronic lymphocytic leukemia, and leukemia; three target HER2; and two target EGFR to treat colorectal, lung, breast, and renal cancers. All therapeutic proteins are cancer-targeted.

Monoclonal antibody

mAb is one of the most successful cancer therapeutic proteins, which remains the fastest growing segment of the biopharmaceu- tical market. mAb targets specific antigens on the surface of tumor cells via the antigen binding site, the complementary determining region housed by the variable domain The constant domain plays a critical role in killing tumor cells and, there- fore, is responsible for the clinical efficiency of mAb.
The first-generation mAb-based biopharmaceuticals are the unmodified murine antibodies. However, its clinical efficiency is low due to the human body's response post-injection such as the generation of anti-mouse antibody. This issue has been overcome with the development of protein engineering technologies, i.e. chi- meric antibody and mAb humanization. The chimeric antibody is generated by splicing the gene sequence coding mouse-based Fv to the human-based Fc. In the humanized anti- body, the CDRs of human antibodies are replaced by the CDRs of murine antibody. The new-generation antibodies significantly 50% (8) CD antigen-targeted mAbs for non-hodgkin's lymphoma, chronic lymphocytic leukemia, lymphoma, and leukemia 19% (3) mAbs targeting HER2 for HER2-positive metastatic breast and gastric cancer; 13% (2) targeting EGFR for colorectal, lung, breast, and renal malignancies; Colorectal, non-small-cell lung, breast, glioblastoma, and renal malignancies treated with 6% (1) VEGF-targeted mAbs (1) mAb targeting CTLA-4 for unresectable or metastatic melanoma; (1) mAb targeting RANKL for giant cell bone tumor. reduce human immunogenicity and lengthen biopharmaceutical serum half-life. Smaller anti-body variants, fusion proteins, and bispecific antibodies have been engineered using these methods.

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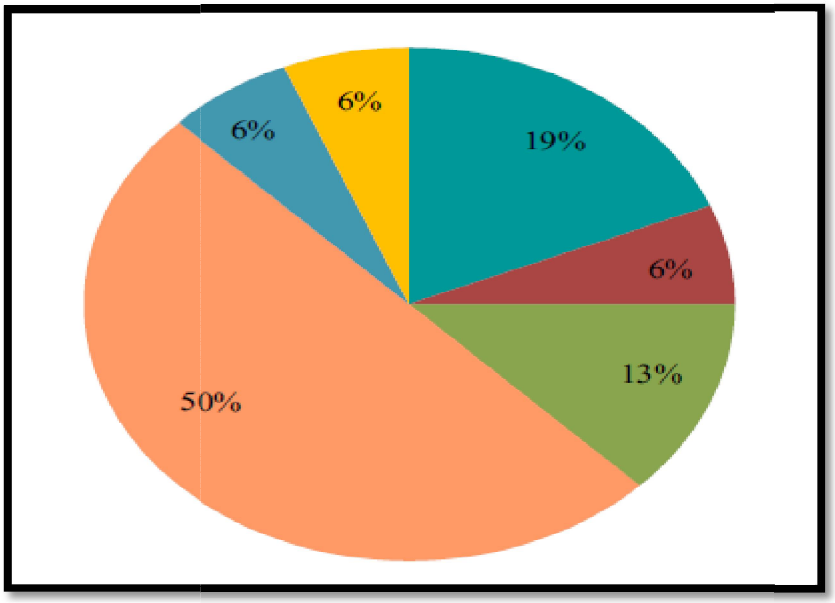

Fig. 1. Summary of innovative targeted anticancer monoclonal antibodies

The mechanics of antibody-based cancer therapy are well-studied. Antibodies can kill cancer cells directly and indirectly by inhibiting signaling, reducing proliferation, inducing apoptosis, or delivering medicine, radiation, or cytotoxin; inducing immune-mediated phagocytosis, complement-dependent cytotoxicity, or antibody-dependent cellular cytotoxicity targeting gene-modified T cells or activating T cells; or ablating vascular and stromal cells

mAb biopharmaceuticals in USA

mAbs have been created and are used to treat a variety of malignancies, including leukemia, non-Hodgkin lymphoma, kidney, lung, breast, and colorectal cancer. Table 1 lists and categorizes sixteen US FDA-approved anticancer mAbs according to their functions.

anti-breast cancer mAbs: As the second-leading cause of mortality for US women, breast cancer claimed the lives of around 40,996 in 2013, and an estimated 300,000 new cases are anticipated annually. Humanized IgG1 kappa, or trastuzumab, binds specifically to the extracellular domain of the protein known as human epidermal growth factor receptor 2. This receptor tyrosine kinase is bound to the surface of cells and is involved in signal transduction pathways that promote cell growth and differentiation. When used alone or in conjunction with chemotherapy, trastuzumab may increase the survival rate of patients with breast cancer by blocking HER2 signaling and causing ADCC.

Novel therapeutic proteins have been created in addition to the first-generation anti-HER2 mAb. Ado-trastuzumab Emtansine is a humanized IgG1-drug conjugate used to treat patients with HER2-positive metastatic breast cancer who have previously been treated with Trastuzumab and/or Taxane. It internalizes and degrades to produce intracellular small molecule cytotoxin and cause apoptotic cell death after binding to the HER2 receptor subdomain IV. Another example is pertuzumab, which works in conjunction with trastuzumab to target distinct HER2 epitopes. Combining trastuzumab and permetuzumab with docetaxel might greatly increase the effectiveness of cancer therapy by inhibiting two key signaling pathways: phosphoinositide 3-kinase and mitogen-activated protein kinase. This approach has significantly increased clinical effectiveness and tumor response.

Anti-colorectal cancer mAbs: Three mAbs that target antigens like EGFR or VEGF have been developed to treat colorectal cancer, which is the third most frequent cancer globally and the fourth major cause of death. The creation of new blood vessels and cell proliferation are brought about by the interaction of VEGF with its receptors on the surface of endothelial cells. An effective palliative therapy for first-line metastatic colorectal cancer, bevacizumab is a humanized IgG1 that targets and inhibits VEGF. It also enhances immune response, disease control, and survival. Additionally, it helps in the treatment of glioblastoma, metastatic renal cell carcinoma, breast cancer, non-small-cell lung cancer, and rectum cancer. Cetuximab, a human/mouse chimeric IgG1 consisting of human heavy and kappa light chain constant regions as well as murine Fv regions, is another commonly utilized monoclonal antibody.

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Cetuximab targets EGFR, which is overexpressed in more than 35% of solid tumors. It may be used alone or in conjunction with other therapies. Patients with metastatic colorectal cancer that is EGFR-positive and resistant to irinotecan-based chemotherapy can benefit from treatment with cetuximab and irinotecan together. Panitumumab human IgG2 kappa is an anti-colorectal cancer monoclonal antibody that works by competitively blocking EGFR to stop cell proliferation, trigger apoptosis, and lower the vascular growth factor.

Anti-hematopoietic cancers The glycosylated phosphorprotein known as mAbs CD20 is present on the surface of B-cells in hairy cell leukemia, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma. The FDA has authorized three unconjugated mAbs for the treatment of hematological malignancies. The first chimeric IgG1 therapy for CD20-positive B-cell NHL and CLL is rituzumab (Rituxan®), which works by locating the immune system and reducing the tumor size by CDC, ADCC, and apoptosis. With its Fab domain, human IgG1 ofatumumab selectively binds to both short and large extracellular loops of CD20. It may effectively treat CLL patients who are resistant to alemtuzumab and fludarabine by lysing CLL cells via ADCC and CDC, two Fc-mediated immune effector actions. The first-line therapy for CLL is obin-utuzumab, a humanized anti-CD20 IgG1 that induces B-cell lysis by ACC, CDC, and apoptosis. Radioimmunotherapy uses two types of monoclonal antibodies (mAb) coupled to radioactive isotopes: 131I-Tositumomab and 90Y-Ibritumomab tiuxetan. The cytotoxic radiation (Y-90 emission) is directed towards malignant cells to cause apoptosis after first targeting CD20. As part of the Rituxan therapy, 90Y-Ibritumomab tiuxetan may be used to treat low grade, follicular, or transformed B-cell NHL that has relapsed or is resistant. Tositumomab (131I) is a murine IgG2 mAb that is immunotherapeutic and anti-CD20. It consists of two murine c 2a heavy chains and two k light chains. Patients with follicular non-Hodgkin's lymphoma who have relapsed after receiving chemotherapy and are not responding to Rituximab treatment are treated with this medication.

Two antibody-drug conjugates with great efficacy in treating hematological malignancies are gemtuzumab and benuximab. Gemtuzumab enters myeloid cells' lysosomes and delivers a hazardous payload, targeting CD33, which is expressed in the majority of individuals with acute myeloid leukemia [9]. The synthetic drug payload is attached to the anti-CD30 antibody using a cleavable enzyme linker to form the component known as benuximab. It specifically destroys CD30-positive tumor cells, including those from systemic anaplastic large cell lymphoma and relapsed or resistant Hodgkin lymphoma.

Small molecule drugs and non-antibody proteins

Fusion proteins and tiny molecules are effective cancer biopharmaceuticals. Since tyrosine kinase is crucial to carcinogenesis, several small-molecule anticancer medicines inhibit it.

Table 2 Anticancer monoclonal antibody on Europe and Asia markets.

Name/brand name	Description	Company	Cancer treated
Trastuzumab/Herceptin®	Humanized mAb against HER 2	Roche	HER2-expressing metastatic breast cancer
Rituximab/Mabthera®, Rituxan®	Chimeric Mab directed against CD20 surface antigen of B-lymphocytes	Hoffmann-La Roche, IDEC	Non-Hodgkin's lymphoma
Alemtuzumab/ Mabcampath® (EU) or Campath® (US)	Humanized mAb directed against CD52 surface antigen of B-lymphocytes	Millennium, Berlex & ILEX	Chronic lymphocytic leukaemia
Catumaxomab/Removab®	Mouse biospecific mAb against CD3 and EpCAM	Fresenius Biotech and Trion Pharma	Malignant ascites generated by an EpCAM-positive tumor
Vivatuxin (^{131}I-chTNT®)	Radiolabeled chimeric IgG1κ against intracellular DNA-associated antigens	Shanghai MediPharm Biotech	Malignant lung cancer
Nimotuzumab/NIOMab, TheraCIM, Theraloc, CIMAger	Humanized IgG antibody against EGFR	Biocon (India), CIMYM Biosciences (Canada), Oncoscience (Europe), Center of Molecular Immunology (Cuba)	Head and neck cancer, glioma, nasopharyngeal cancer

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For example, (1) Afatinib, an EGFR and HER4 tyrosine kinase inhibitor, permanently inhibits autophosphorylation and downregulates ErbB signaling. It is the first-line therapy for metastatic NSCLC with mutant EGFR exon 19 deletion or exon 21 replacement. Regorafenib, an oral small drug, inhibits membrane-bound and intracellular kinases. These kinases regulate pathologic processes such oncogenesis, tumor angiogenesis, and tumor microenvironment maintenance or maintain normal cellular functioning. This medication treats metastatic or unresectable cancer.
gastrointestinal stromal tumor for imatinib mesylate and sunitinib malate patients. (3) Ibrutinib covalently bonds with BTK's cystein residue to decrease its enzymatic activity and impede trafficking, chemotaxis, and adhesion signaling. Ibrutinib treats CLL patients who have had at least one treatment. (4) Upregulation of mitogen-activated protein kinases activates RAS/RAF/MEK/ERK and promotes cell growth. Trametinib blocks these kinases' activity. It treats unresectable or metastatic melanoma with BRAF V600E or V600K mutations.
Recombinant hormones, cytokines, and vaccines against cancer have been produced alongside tiny molecular medicines. Recombinant haematopietic factors, interferon, and tumor necrosis factor have been marketed. Thyrotropin alfa treats thyroid cancer. Personalized antibody-generating vaccine Sipuleucel-T treats prostate cancer.

Generic biologics

The FDA draft guideline defines generic biologics as biopharmaceuticals that are "highly similar to the reference innovative product, notwithstanding minor differ- ences in clinically inactive components." Generic medications are made and sold when revolutionary biopharmaceuticals lose their patents. Use of generic biologics can reduce clinical costs. Omnitrope, the first EU biosimilar, was authorized by the EMEA in 2006, followed by 20 others, including Epoetin alfa. Filgrastim Asia also produced biosimilars swiftly. In India, Trastuzumab, a generic anti-breast cancer mAb, is sold as and. Rituximab, Epoetin alfa, darbepoetin alfa, Interferon alpha-2b, and filgrastim are other authorized generic mAbs

Challenges and strategies

Several targeted biopharmaceuticals have proven successful in treating cancer, but severe side effects, limited bioactivity, excessive dose, and immunogenic response remain hurdles in anticancer drug development. Here are some main challenges and possible remedies.

Personalized biomedicines

The "one treatment fits all" concept of classical anticancer biopharmaceuticals has effectively treated biomarker-positive cancer patients. It often has side effects since it ignores patient response variability. Alternative: individual treatment may solve this problem. Follow these steps to create personalized medicine: (1) Omics profiling patient cancer samples in vitro, (2) imaging cancer cells in vivo, (3) integrating disease risk assessment, driver factor diagnosis, patient response to targeted anticancer drugs, individual habits, and clinical history, and (4) rationally designing personalized medicine for specific patients. Drug dosage can be optimized by studying biopharmaceutical-metabolizing enzyme interactions. With an understanding of the oncogene and oncoprotein, an integrated cancer therapeutic strategy is possible. Personalized anticancer medicines can also treat genetic instability and uncommon genetic mutation-caused complicated cancer.

Clinical efficiency

Biopharmaceuticals' protein bioactivity and clinical efficacy depend on quality. Chinese hamster ovary (CHO) cells express most mammalian cell-based therapeutic proteins. Functional genomics of CHO cells shows that modifying post-translational modifications (PTMs) such galactosylation, sialylation, and fucosylation improves protein quality. In CHOnomics investigation, PTM metabolic pathway genes or regulators were found and used to construct cell engineering methodologies. The N-linked oligosaccharide structures generated by CHO cells overexpressing heterologous b1,4-glycosyltransferase are more homogeneous. Overexpression of a2,3-sialyltransferase has created many more sialylation branches. Anticancer therapeutic protein dose needs are rising due to a growing cancer patient population, hence protein productivity must be improved along with quality. The American Cancer Society reported 1,660,290 new cancer cases in 2013. Building high-producing cell lines and rationally designing biopharmaceutical

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bioprocessing can boost protein productivity. Anticancer medications also require host cell, media, and cell culture processes. Some proteins need insect-cell glycosylation, while biopharmaceuticals harmful to mammalian cells must be perfused.

II. CONCLUSION AND PERSPECTIVE

Targeted anticancer biopharmaceuticals have considerably improved cancer therapy. Due to decades of fundamental study and clinical diagnosis on the oncogene, signaling route, and core pathway related to cancer prognosis, anticancer therapeutic medication development has been successful. Understanding the complicated relationship between cancer cells and the immune system has refined antibodies and other proteins. Advanced CHOnomics has also enabled whole cell profiling and genome-scale comprehension of mammalian cell-based therapeutic protein expression. Together, clinically effective anticancer biopharmaceuticals might save millions of cancer patients.

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