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Antibody-Based Targeted Therapy: A Novel Cancer Treatment

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Abstract

Antibody based targeted therapy has considered more than other immunotherapeutic methods for cancer treatment due to extensive capacity of antibodies for targeting specific antigens. Antibodies and antibody fragments can target particular antigens that are expressed by cancer cells and lead them to apoptosis. However, conjugation of antibodies to cytotoxic agents such as drugs, radionuclides, and toxins improves the efficacy of antibody-based targeted therapy. The use of antibodies as carriers to deliver cytotoxic agents to the target cells has led to the emergence of immunoconjugates. The immunoconjugates not only are more effective than naked antibodies but also prevent the side effects of cytotoxic agents by delivering them only to the target cells. Targeted therapy has received more attention due to its fewer side effects on normal cells. This review provides a brief definition of various antibody therapies which are in development and in clinical use for different cancers treatment, as well as describes the mechanism of action of each method.

Keywords: Antibody based targeted therapy • Immunoconjugates • Antibody fragments • Antibody-drug conjugates • Immunotherapy

Introduction

Cancer is one of the leading causes of death worldwide and according to studies by the American Cancer Society, has been known as second leading cause of death in the United States. Moreover, this organization has predicted that by 2020, more than 1.8 million new cases of cancer will occur in the USA [1]. Various types of cancer can affect different tissues. In this regard, the World Health Organization (WHO) has listed lung, breast, colorectal, prostate, skin cancer (non-melanoma), and stomach as the most common types of cancer in the world in 2018, respectively [2]. Considering this global burden for cancer, there are many conventional therapeutic methods such as tumor surgery, chemotherapy, radiotherapy and hormone therapy, that usually two or more of these are recommended depending on the patient's conditions. Despite these methods' effectiveness, these treatments have some limitations. For instance, in hematological malignancies, tumor surgery is not possible, and chemotherapy damages non-cancerous cells by introducing too much toxin into the body and its side effects are unacceptable. The main limitation of all these conventional methods is their inability to prevent metastasis and recurrence of cancer [3]. Therefore, limitation of traditional methods, cause cancer immunotherapy as a new treatment method that has been widely considered in the past decade [4]. Antibody based targeted therapy is one of the cancer immunotherapy methods, which has been extensively discussed by researchers.

Antibody based targeted therapy as one of the immunotherapy methods for treating cancer has devised since 40 years ago. It was the time when researchers found the expression of antigens by tumor cells by the use of serological techniques in 1960 [5]. Subsequently, Cesar Milstein and George J.F. Köhler produced monoclonal antibodies for the first time in 1975 using the hybridoma technology [6]. However, the use of antibodies and then antibody based targeted therapy as a successful method for the treatment of hematological malignancies and solid tumors became popular with the identification and introduction of Rituximab as the first full length chimeric antibody for the treatment of Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma in 1997 [7]. Antibodies usually act by targeting specific antigens expressed on the surface of tumor cells. For instance Rituximab kills cancer cells by targeting CD20 in non-Hodgkin B cell lymphoma, Trastuzumab targets HER2 and Cetuximab targets EGFR in breast cancer and colorectal cancer, respectively [8].

Antibody based targeted therapy is highly regarded due to one of the important features of this method, which is selectivity. It means the ability to detect tumor cells by the use of antibody based targeted therapy not only makes treatment faster, but also reduces the side effects. However, the use of naked antibodies is limited due to some factors such as antigen heterogeneity, interference by inhibitory receptors and etc. various modifying methods have been proposed to improve the effectiveness of this treatment method, among them the use of immonoconjugated antibodies has been extremely considered [9]. Antibodies can conjugate with radionuclides, toxins and drugs. Thus, combining conventional therapies such as chemotherapy with immunotherapy can lead to a significant efficiency. The present article will discuss antibody based targeted therapy on the basis of evaluation of current data from clinical trials.

Antibodies

Antibodies are Y-shaped proteins that are produced by the immune system to protect the host against foreign invasion. When an antigen enters the host, the innate immune system and adoptive immune system will become activated. In the first step, macrophages begin to phagocytosis foreign material (virus, bacteria, toxins and etc.). Then, antigenic subunits escorted to the macrophage surface and this antigen presented to T cell. In the next stage, macrophage and T cell stimulate B cells that lead B cells to produce antibody [10]. Antibodies, commonly used in form of immunoglobulins (Igs)

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are classified into five groups: IgA, IgD, IgE, IgG, and IgM. These classes have differences in overall structure, and the IgG class is known as the most common type, which is used in immunotherapy. Generally, an antibody has made of two main parts: Antigen-binding fragments (Fab) and Fc-region, which binds to serum proteins (complement) or cells [11]. As shown in Figure 1, each Y-shaped antibody has been made of heavy chains and light chains that are linked together by disulfide linkages. The unique ability of antibodies to target a specific antigen has made them known as an effective cancer therapeutic method.

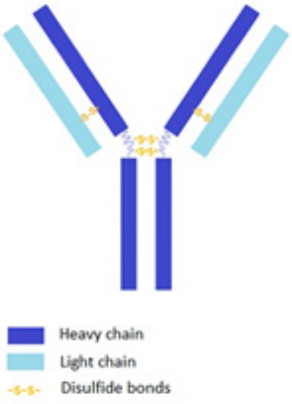

Figure 1. Schematic view of antibody; two heavy chains and two light chains are linked by disulfide bonds.

In addition to antibodies, other essential components in antibody based targeted therapy are tumor antigens. Tumor cells express different groups of glycoproteins, lipids, and carbohydrates, called antigens, which can be found at the surface of tumor cells. These tumor antigens are classified into two group: (1) tumor-specific antigens (TSAs), which are expressed only by tumor cells; (2) tumor-associated antigens (TAAs), which can be represented by both normal and tumor cells [12]. For instance CD105 is known as TAA, which is not only overexpressed on tumor cells as marker of neovascularization, but also expressed in healthy cells as a specific endothelial marker [13]. Several factors should be considered in targeting TAAs, such as the potential of these antigens to be detected with antibodies and the immune system. Moreover, finding specific epitopes that may be different between the same antigens which are expressed at the surface of normal and tumor cells, and targeting these epitopes with modification of antibodies, is one of the foresees antibody based targeted therapy [14].

The mechanism of antibody based targeted therapy as a therapeutic method for cancer generally works in two separate pathways, which include: direct and indirect effect; in the direct pathway, antibodies mainly alter intracellular signals which lead tumor cells to apoptosis. These changes usually occur with inhabitation of growth factor receptors and dysfunction of adhesive molecules [15]. In the indirect pathway, antibodies are not directly responsible for the apoptosis of target cancerous target cells. But antibodies introduce cancer cells to host immune system effectors by marking cancer cells. The immune system attacks the labeled cells in two ways as follows:

Antibody dependent cellular cytotoxicity (ADCC); in this immune mechanism, the Fcγ receptors of the effector cells can detect and kill antibody marked target cells. This pathway begins with the identification of antibody labeled cells by the effector cells, which results in the activation of cellular src family protein tyrosine kinases. Then, the phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) leads to downstream signaling pathways initiate in the effector cells. Finally, the target cells are killed via predominant perforin/granzyme cell death pathway [16] (Figure 2).

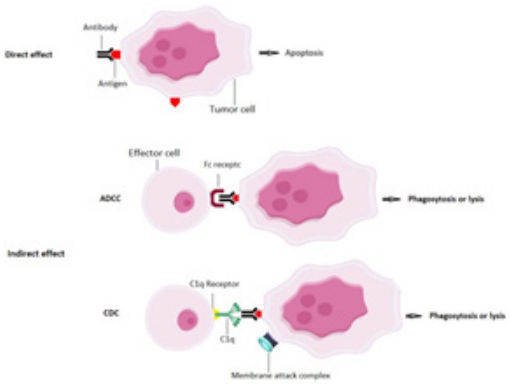

Figure 2. Direct and indirect pathways of antibody function in exposure to tumor cells. ADCC: Antibody Dependent Cellular Cytotoxicity; CDC: Complement Dependent Cytotoxicity.

Complement-Dependent Cytotoxicity (CMC); in this process, complement proteins act as a cascade. This cascade initiates when complement component C1q binds to the Fc region of the antibody, which is attached to the tumor cell, and in the end, lead the target cell to be lysis or phagocytosis. Furthermore, activation of complement due to this cascade can lead to the formation of membrane attack complex which results in disruption of tumor cell membrane [17,18].

Antibody Fragments

Antibody based targeted therapy has proved as an effective cancer treatment, with various examples of clinical trials which have evaluated the use of antibodies for the treatment of hematological malignancies and solid tumors [19,20]. However, there are limitations in the efficacy of this method, especially in treatment of solid tumors. Inability of the antibodies to penetrate the tumor due to the high molecular weight of the whole antibodies can be known as the most important limitation factor for the effectiveness of antibody based therapies [21]. In this regard, antibody fragments have been suggested as a solution. Antibody fragments as simple structures are smaller than whole antibodies. Due to the structure and molecular weight, three kinds of antibody fragments have been assessed for targeting tumor cells, include: Antigen-binding fragments (Fab) (composed of both constant and variable domains of each of the heavy and light chains); Single chain variable fragments (scFV) (variable regions of light and heavy chains which are linked together by a peptide linker); and single-domain antibodies (sdAbs) or nanobodies (Nbs) (consist of only one variable domain of heavy chain) [22,23], which are shown in Figure 3.

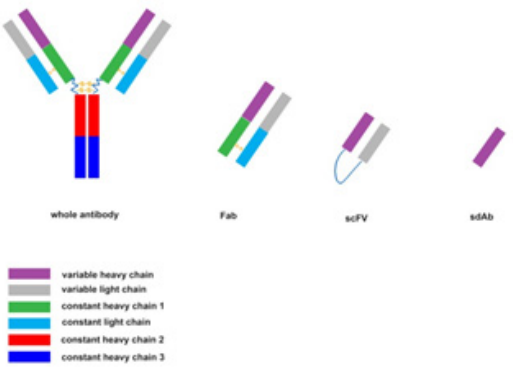

Figure 3. Schematic view of whole antibody and different antibody fragments. Fab: Antigen Binding Fragment; scFV: Single Chain Variable Fragment; sdAb: Single Domain Antibody.

As mentioned above, the main limitation of antibody based targeted therapy for solid tumors is heterogeneous targeting which occurs due to the high molecular size, low binding affinity, and shape of the antibodies. The antibody entering the host must pass through various barriers such as vessel wall and extracellular matrix (ECM) of targeted tissue, to reach the tumor cells. Therefore, this is clear that the use of antibody fragments with low molecular weight and high binding affinity in comparison with the whole antibody is much more useful to penetrate these barriers and target tumor cells [24]. Table 1 shows the correlation between the molecular weight of the intact antibody and the molecular weight of different antibody fragments.

Table 1. Molecular weight of whole antibody and antibody fragments. Fab: Antigen Binding Fragment; scFV: Single Chain Variable Fragment; sdAb: Single Domain Antibody; KDa: Kilodalton.

Antibody and Antibody Fragments	Molecular Weight	Ref
Whole antibody	~150KDa4	Grieger et al.[27]
Fab	~50KDa	Harmsen et al.[28]
ScFV	~27KDa	Sun et al.[29]
SdAb	~15KDa	Schrankel et al.[30]

Despite all the advantages of antibody fragments, in comparison with full-length antibody, the stability of Fab and scFV is less. Moreover, these antibody fragments are more sensitive to thermal stress which leads them to be cleared more quickly before they can be useful in destroying cancer cells. However, the third generation of antibody fragments, which have considered more than Fab and scFV in recent years, despite their small size, have relatively high stability, as well as Nbs can bind to an antigen more precisely [25]. Furthermore, this kind of antibody fragments are less immunogenic than the other types of antibody fragments and full length antibody [26].

Numerous clinical and pre-clinical experiments have been performed, especially in the last decade, to investigate the efficiency of antibody fragments to detect and kill cancer cells. In this regard, et al. have evaluated EpCAM-F800, a novel fluorescent anti-EpCAM antibody fragment, for detecting epithelial cell adhesion molecule (EpCAM), which overexpress on epithelial-derived cancers. They produced this Fab and illustrated its feasibility for intra-operative fluorescence-guided tumor detection by the use of entering breast and colorectal cancer cells into mice animal model [31]. In another research which has conducted in 2019, Moradi Kalbolandi and colleges invented a novel method for detecting leukemic cancer stem cells (LSCs) by anti-CD45 scFv conjugated quantum dot. After the production of CD45RA scFv and conjugation with carbon dots, they assessed its ability for detecting CD45RA+ cells in vitro, besides they used CD45RA-cells as a control cell line. The results of this study have demonstrated that CD45RA scFv conjugated C dots can detect CD45RA+ cells with high accuracy [32]. Moreover, Chinese researchers have investigated anti-HER2 immunotoxins based on sdAb. They have performed this in vivo test via entering human gastric carcinoma and breast cancer cells, which overexpress human epidermal growth factor receptor 2 (HER2), into mice. Then, they used three different anti-HER2 sdAb molecules with improved PE24X7 toxin for targeting HER2+ cells [33].

Immunoconjugates

The most important goal of cancer treatment methods is to destroy tumor cells without affecting healthy cells. Although antibody based targeted therapy with the pathways mentioned in Figure 1 has been successful to a large extent in achieving this goal, the combination of antibodies with agents that are used in conventional methods such as radiotherapy and chemotherapy can maximize the efficacy of treatment. This new therapeutic approach, which is called immunoconjugates, consists of Antibody as carrier, cytotoxic agent, and chemical linker, which makes a connection between cytotoxic agent and antibody. Immunoconjugates not only reduce the side effects by lowering the dose of active cytotoxic agents, but also prevent the target cells from escaping and recurrence of the cancer by delivering these agents specifically to target cells [34]. The linker section is a significant part of immunoconjugates. The linkers must be stable in the systemic circulation and be able to accurately control the release of cytotoxic agents into target cells [35]. These linkers generally classified into two groups: non-cleavable linkers and cleavable linkers that the release mechanisms of cytotoxic agents by them as well as their degree of stability in circulation, are different [36].

Cleavable linkers

These kinds of linkers utilize specific conditions to release cytotoxic agents into the target cell environment. This is to say that these linkers cleave when they move from bloodstream and extracellular matrix into intracellular milieu by feeling the alternation in conditions such as hydrolysis, pH and some enzymes levels. Chiefly, there are three kinds of cleavable linkers, including Reducible disulfides, Acid cleavable linkers, and Cleavage by exogenous stimuli [37].

Non-cleavable linkers

In spite of cleavable linkers, in non-cleavable linkers do not exist any fragile region that can be cleaved by hydrolases or pH and enzyme level alteration. These stable and degradation-resistant bonds lead whole immunoconjugates degradation in the lysosome. Depending on the type of antigen and the cytotoxic agent, non-cleavable linkers are preferred to the cleavable types when the stability of the immunoconjugates are more important than the rapid release of the cytotoxic agents [38].

Generally, there are three classes of cytotoxic agents including chemotherapeutic drug, radionuclides and toxins (protein enzymes with both bacterial and plant origins). these cytotoxic agents can be conjugated to antibodies to produce various immunoconjugates [39].

Antibody Drug Conjugates (ADCs)

In this section the word “drug” is related to a chemotherapeutic drug. Chemotherapy, as a primary conventional cancer treatment, is used for elimination of both solid and hematological malignancies. There are more than 100 chemotherapy drugs that have been licensed by FDA (Food and Drug Administration). For instance, Paclitaxel, Docetaxel, Cyclophosphamide, and Bendamustine are common chemotherapeutic drugs that have been used for breast cancer, non-small-cell lung cancer (OAK), Primary Central Nervous System Lymphoma (PCNSL), and advanced chronic lymphocytic leukaemia (CLL10) treatment respectively [40-43]. Among the numerous chemotherapy regimens, the choice of an appropriate regimens depends on several factors such as type and progression level of cancer, history of other disease, age, previous treatment, hematological examination, liver and kidney function [44]. Chemotherapy agents lead cells with high division rates to apoptosis by destroying DNA or preventing mitotic division. But in addition to tumor cells, some healthy cells in the bone marrow or the cells of hair follicles which have high cell division rates, are affected by chemotherapy [45]. Furthermore, cancer stem cells which are resistant to chemotherapy agents despite cancer cells, survive after chemotherapy, and can lead to a new tumor formation [46]. Therefore, side effects such as myelosuppression and recurrence of the disease are counted as limitations of chemotherapy.

Chemotherapy usually has a low therapeutic window that results from poor specialization in targeting tumor cells. In this regard, drugs conjugated to antibodies are considered to be useful by improving selectivity and specificity. The chemotherapeutic drugs have been specially introduced into cancer cells through the antibodies. Targeted delivery of medicine not only prevents side effects of chemotherapy, but also approximately total amount of injected drugs reach tumor cells, which lead to a decrease in required dose of drugs that should be injected to the host [47]. According to the benefits of ADCs, several ADCs were established and approved by FDA. For instance Gemtuzumab ozogamicin which is known with Mylotarg trade

name is the first ADC that was approved by FDA. This ADC was used to target CD33-positive cells in acute myeloid leukemia (AML) patients in 2001 [48]. Moreover, ADCETRIS® (brentuximab vedotin), a CD30-specific ADC, received approval by FDA in 2011, which is used against relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma (ALCL) [49]. Polatuzumab vedotin is another ADC that consist of monoclonal antibody against CD79b, monomethyl auristatin (MMAE), and a cleavable linker. The US FDA gave approval to this ADC in combination with bendamustine plus rituximab in 2019 for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) treatment [50].

Antibody Radionuclide Conjugates (ARCs)

Radiotherapy, as an old cancer treatment method, is more effective in eliminating local tumors. Radiotherapy can affects the DNA of cells and lead them to damage through two direct and indirect pathways. It means that radiation can directly destroy DNA or an exact indirect route by ionization of intracellular components, which lead to formation of free radicals, destroys DNA [51]. This DNA damage due to radiation can induce different types of cell death, such as apoptosis, mitotic cell death, and mitotic catastrophe. However, radiotherapy has been considered according to the fact that radiotherapy not only affects localized irradiated tumors, but also can cause changes in the immune response against cancer antigens. This refers to the abscopal effect, which was introduced in 1953 [52]. According to abscopal phenomena, the radiation produces tumor associated antigens (TAAs) in the primary tumor. Then, These TAAs are identified by antigen presenting cells (APCs) and are introducing to T cells. As a result, an immune-mediated anti-tumor response will be created, which prevents the recurrence of the disease by eliminating the secondary tumor [53].

During the last decade, attention to radiotherapy has increased due to its capacity to prevent metastasis and recurrence of the disease. Researchers are looking to increase the stimulation of the immune system against malignant cells by combining this method with immunotherapy. Conjugation of radionuclides to antibodies is one of these mixed methods that have received more attention due to its selectivity. ARCs are used to target radioactivity specifically to the tumor cells without affecting healthy cells [54]. In this regard, Ryan D, Cassaday et al. in a phase I study, which was conducted in 2019, evaluated an anti-CD45 ARC for the treatment of lymphoma. They used BC8 antibody conjugated to iodine-131 (131I) in patients with B-cell non-Hodgkin lymphoma (B-NHL), T-cell NHL (T-NHL), or Hodgkin lymphoma [55]. In another clinical examination which was conducted by Dawicki and colleagues, daratumumab conjugated to alpha-emitter 225Actinium was used for therapy of multiple myeloma (MM) [56].

Antibody-Toxin Conjugates

In this type of immunoconjugates, the antibody conjugates to a biological toxin with bacterial or planet origins. Among various plant and bacterial protein toxins, diphtheria toxin and Pseudomonas exotoxin, which are bacterial toxins as well as ricin and gelonin with plant origin most commonly used in conjugation with antibodies [57]. DAB389IL2 or denileukin diftitox (DD; Ontak®) was the first antibody-toxin conjugate that was approved by FDA. This immunotoxin used for the treatment of chronic lymphocytic leukaemia [58]. Previously, whole antibody linked full-length toxin was used, but due to the large size, there were some crucial problems such as not penetrating into solid tumors. Therefore, the use of antibody fragments conjugated to toxin fragments has been considered dramatically. For instance, Lee et al. in an in vitro examination evaluated the efficiency of scFv of trastuzumab conjugated to PE24 fragment of Pseudomonas exotoxin A exposed to HER2-expressing breast cancer cell lines. The results of this study demonstrate the effectiveness of this antibody-toxin conjugates [59]. However, according to some other limitation such as instability, too toxicity and immunogenicity, use of antibody-toxin conjugates is not common in clinical trials [60].

Conclusion

The development of antibody based targeted therapy as a novel cancer treatment has been an attractive area of research in recent years. The specificity and selectivity of antibodies for targeting tumor cells in combination with cytotoxic agents which are used in conventional treatments such as chemotherapy and radiotherapy, have made this treatment method effective. Although the use of this method leads to a considerable decline in the side effects of cytotoxic agents, cross-reactivity of immunoconjugates with healthy cells still exist since targeted antigens are not restricted to cancer cells. However, considering the epitops, which can be different in the same antigen in cancer cell and normal cell, and targeting them by antibody fragments could be a solution.

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Author Contributions

Conceptualization: Javad Mohammadi; Investigation: Bahareh Sadri, Shirin Nouraein, Taravat Khodaei and Negin Vahedi; Writing – original draft: Bahareh Sadri; Writing – review and editing: Javad Mohammadi and Shirin Nouraein.

Conflict of Interest

Bahareh Sadri, Shirin Nouraein, Taravat Khodaei, Negin Vahedi and Javad Mohammadi declare that there are no conflicts of interest.

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References

1. Siegel, Rebecca L and Miller Kimberly D. “Cancer statistics.” *CA CANCER J CLIN* 70 (2020): 7-30.
2. World Health Organization. *Cancer* (2018)
3. Sengupta, Somoshree and Balla Vamsi K. “A review on the use of magnetic fields and ultrasound for non-invasive cancer treatment.” *J Adv Res* 14 (2018): 97-111.
4. Gotwals, Philip, Cameron Scott, Cipolletta Daniela and Cremasco Viviana et al. “Prospects for combining targeted and conventional cancer therapy with immunotherapy.” *Nat Rev Cancer* 17 (2017): 286-301.
5. Rettig, W J and Old LJ. “Immunogenetics of human cell surface differentiation.” *Annu Rev Immunol* 7 (1989): 481-511.
6. Köhler, G and Milstein C. “Continuous cultures of fused cells secreting antibody of predefined specificity.” *Nature* 256 (1975): 495-497.
7. Maloney, D, G Grillo-López A J, White C A and Bodkin D et al. “IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed

low-grade non-Hodgkin's lymphoma." *Blood* 90 (1997): 2188-2195.

8. Weiner, Louis M, Murray Joseph C and Shuptrine Casey W. "Antibody-based immunotherapy of cancer." *Cell* 148 (2012): 1081-1084.
9. Dobrenkov, Konstantin and Cheung Nai-Kong V. "30-Therapeutic antibodies and immunologic conjugates." *Abeloff's Clinical Oncology Elsevier* (2020): 486-499.e8.
10. van Regenmortel, Marc H V. "Specificity, polyspecificity, and heterospecificity of antibody-antigen recognition." *J Mol Recognit* 27 (2014): 627-639.
11. Wang, Xinhua, Mathieu Mary and Brezski Randall J. "IgG Fc engineering to modulate antibody effector functions." *Protein Cell* 9 (2018): 63-73.
12. Newkirk, Kimberly M., Brannick Erin M. and Kusewitt Donna F. "Neoplasia and tumor biology." *Pathologic Basis of Veterinary Disease* (2017): 286-321. e1.
13. Cîmpean, Anca Maria, Raica M and Suciu C. "CD105/smooth muscle actin double immunostaining discriminate between immature and mature tumor blood vessels." *Rom J Morphol Embryol* 48 (2007): 41-45.
14. Hollingsworth, Robert E and Jansen Kathrin. "Turning the corner on therapeutic cancer vaccines." *NPJ Vaccines* 4 (2019): 7.
15. van de Donk, Niels W C J, Moreau Philippe, Plesner Torben and Palumbo Antonio et al. "Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma." *Blood* 127 (2016): 681-695.
16. Román, Victor RaúlGómez, Murray Joseph C. and Weiner Louis M. "Antibody-dependent cellular cytotoxicity (ADCC)." *Antibody Fc* (2014): 1-27.
17. Niehues, Tim. "Therapeutic monoclonal antibodies as immunomodulators and anti-cancer agents: development, evidence of efficacy, mechanisms of actions, adverse effects." *Antibody Therapy* (2017): 291-341.
18. Carter, Paul. "Improving the efficacy of antibody-based cancer therapies." *Nat Rev Cancer* 1 (2001): 118-129.
19. Patel, Jitendrakumar, Amrutiya Jitendra, Bhatt Priyanka and Javia Ankit et al. "Targeted delivery of monoclonal antibody conjugated docetaxel loaded PLGA nanoparticles into EGFR overexpressed lung tumour cells." *J Microencapsul* 35 (2018): 204-217.
20. Chari, Ajai, Suvannasankha Attaya, Fay Joseph W and Arnulf Bertrand et al. "Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma." *Blood* 130 (2017): 974-981.
21. Debie, Pieterjan, Lafont Chrystel, Defrise Michel and Hansen Inge et al. "Size and affinity kinetics of nanobodies influence targeting and penetration of solid tumours." *J Control Release* 317 (2020): 34-42.
22. T.Xenaki, Katerina, Oliveira Sabrina and van Bergen Henegouwen Paul M. P. van Bergen. "Antibody or antibody fragments: implications for molecular imaging and targeted therapy of solid tumors." *Front Immunol* 8 (2017): 1287.
23. Schrankel, Catherine S, Gökirmak Tufan, Lee Chang-Wook and Chang Geoffrey et al. "Generation, expression and utilization of single-domain antibodies for in vivo protein localization and manipulation in sea urchin embryos." *Methods Cell Biol* 151 (2019): 353-376.
24. Kholodenko, Roman V, Kalinovsky Daniel V, Doronin Igor I and Ponomarev Eugene D et al. "Antibody fragments as potential biopharmaceuticals for cancer therapy: success and limitations." *Curr Med Chem* 26 (2019): 396-426.
25. Lee, Jiwon, Der Bryan S, Karamitros Christos S and Li Wenzong et al. "Computer-based engineering of thermostabilized antibody fragments." *AIChE J* 66 (2020): e16864.
26. Khodabakhsh, Farnaz, Behdani Mahdi, Rami Abbas and Kazemi-Lomedasht Fatemeh. "Single-domain antibodies or nanobodies: a class of next-generation antibodies." *Int Rev Immunol* 37 (2018): 316-322.
27. Grieger, Elena, Gresch Gerrit, Niesen Judith and Woitok Mira et al. "Efficient targeting of CD13 on cancer cells by the immunotoxin scFv13-ETA' and the bispecific scFv [13xds16]." *J Cancer Res Clin Oncol* 143 (2017): 2159-2170.
28. Harmsen, M. M. and De Haard H. J. De. "Properties, production, and applications of camelid single-domain antibody fragments." *Appl Microbiol Biotechnol* 77 (2007): 13-22.
29. Sun, H., Wu G.M., Chen Y.Y. and Tian Y et al. "Expression, production, and renaturation of a functional single-chain variable antibody fragment (scFv) against human ICAM-1." *Braz J Med Biol Res* 47 (2014): 540-547.
30. Schrankel, Catherine S., Gökirmak Tufan, Lee Chang-Wook and Chang Geoffrey et al. "Chapter 14-Generation, expression and utilization of single-domain antibodies for in vivo protein localization and manipulation in sea urchin embryos." *Methods in Cell Biology* 151 (2019): 353-376.
31. Boogerd, Leonora S F, Boonstra Martin C, Prevoo Hendrica A J M and Handgraaf Henricus J M et al. "Fluorescence-guided tumor detection with a novel anti-EpCAM targeted antibody fragment: Preclinical validation." *Surg Oncol* 28 (2019): 1-8.
32. Moradi-Kalbolandi, Shima, Dashtestani Fariba, Salehi Malihe and Jalili Neda et al. "Development of an anti-CD45RA-quantum dots conjugated scFv to detect leukemic cancer stem cells." *Mol Biol Rep* 47 (2020): 225-234.
33. Cao, Li, Li Qiyu, Tong Zhen and Xing Yutong et al. "HER2-specific immunotoxins constructed based on single-domain antibodies and the improved toxin PE24X7." *Int J Pharm* 574 (2020): 118939.
34. Mercatelli, Daniele, Bortolotti Massimo, Bazzocchi Alberto and Bolognesi Andrea et al. "Immunoconjugates for osteosarcoma therapy: preclinical experiences and future perspectives." *Biomedicines* 6 (2018): 19.
35. Alley, Stephen C, Benjamin Dennis R, Jeffrey Scott C and Okeley Nicole M et al. "Contribution of linker stability to the activities of anticancer immunoconjugates." *Bioconjug Chem* 19 (2008): 759-765.
36. Lu, Jun, Jiang Feng, Lu Aiping and Zhang Ge. "Linkers having a crucial role in antibody-drug conjugates." *Int J Mol* Sci 17 (2016): 561.
37. Bargh, Jonathan D, Isidro-Llobet Albert, Parker Jeremy S and Spring David R. "Cleavable linkers in antibody-drug conjugates." *Chem Soc Rev* 48 (2019): 4361-4374.
38. Walles, M, Connor A and Hainzl D. "ADME and safety aspects of non-cleavable linkers in drug discovery and development." *Curr Top Med Chem* 17 (2017): 3463-3475.
39. Smaglo, Brandon G, Aldeghaither Dalal and Weiner Louis M. "The development of immunoconjugates for targeted cancer therapy." *Nat Rev Clin Oncol* 11 (2014): 637-648.
40. Bernstein, V, Ellard S L, Dent S F and Tu D et al. "A randomized phase II study of weekly paclitaxel with or without pelareorep in patients with metastatic breast cancer: Final analysis of Canadian Cancer Trials Group IND.213." *Breast Cancer Res Treat* 167 (2018): 485-493.
41. Rittmeyer, Achim, Barlesi Fabrice, Waterkamp Daniel and Park Keunchil et al. "Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial." *The Lancet* 389 (2017): 255-265.
42. DeFilipp, Zachariah, Li Shuli, El-Jawahri Areej and Armand Philippe et al. "High-dose chemotherapy with thiotepa, busulfan, and cyclophosphamide and autologous stem cell transplantation for patients with primary central nervous system lymphoma in first complete remission." *Cancer* 123 (2017): 3073-3079.
43. Eichhorst, Barbara, Fink Anna-Maria, Bahlo Jasmin and Busch Raymonde et al. "First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): An international, open-label, randomised, phase 3, non-inferiority trial." *Lancet Oncology* 17 (2016): 928-942.
44. Edward, Chu, and DeVita Jr. Vincent T. "Physicians' cancer chemotherapy drug manual 2020." *Jones & Bartlett Learning* (2020).
45. Demaria, Marco, O'Leary Monique N, Chang Jianhui and Shao Lijian et al. "Cellular senescence promotes adverse effects of chemotherapy and cancer relapse." *Cancer Discov* 7 (2017): 165-176.
46. Prieto-Vila, Marta, Takahashi Ryou-U, Usuba Wataru and Kohama Isaku et al. "Drug resistance driven by cancer stem cells and their niche." Int *J Mol Sci* 18 (2017): 2574.
47. Dan, Nirnoy, Setua Saini, Kashyap Vivek K and Khan Sheema et al. "Antibody-drug conjugates for cancer therapy: chemistry to clinical implications." *Pharmaceuticals* (Basel) 11 (2018): 32.

48. Sievers, E L, Larson R A, Stadtmauer E A and Estey E et al. "Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse." *J Clin Oncol* 19 (2001): 3244-3254.

49. Senter, Peter D, and Sievers Eric L. "The discovery and development of brentuximab vedotin for use in relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma." *Nat Biotechnol* 30 (2012): 631-637.

50. Deeks, Emma D. "Polatuzumab Vedotin: First Global Approval." *Drugs* 79 (2019): 1467-1475.

51. Baskar, Rajamanickam, Lee Kuo Ann, Yeo Richard and Yeoh Kheng-Wei. "Cancer and radiation therapy: Current advances and future directions." Int *J Med Sci* 9 (2012): 193-199.

52. Mole, R H. "Whole body irradiation; radiobiology or medicine?." *Br J Radiol* 26 (1953): 234-241.

53. Yilmaz, Melek Tugce, Elmali Aysenur and Yazici Gozde. "Abscopal effect, from myth to reality: from radiation oncologists' perspective." *Cureus* 11 (2019): e3860.

54. Steiner, Martina, and Neri Dario. "Antibody-radionuclide conjugates for cancer therapy: Historical considerations and new trends." *Clin Cancer Res* 17 (2011): 6406-6416.

55. Cassaday, Ryan D, Press Oliver W, Pagel John M and Rajendran Joseph G et al. "Phase I study of a CD45-targeted antibody-radionuclide conjugate for high-risk lymphoma." *Clin Cancer Res* 25 (2019): 6932-6938.

56. Dawicki, Wojciech, Allen Kevin J.H., Jiao Rubin and Malo Mackenzie E. et al. "Daratumumab-225 Actinium conjugate demonstrates greatly enhanced antitumor activity against experimental multiple myeloma tumors." *Oncoimmunology* 8 (2019): 1607673.

57. Allahyari, Hossein, Heidari Sahar, Ghamgosha Mehdi and Saffarian Parvaneh et al. "Immunotoxin: A new tool for cancer therapy." *Tumour Biol* 39 (2017): 1010428317692226.

58. Frankel, Arthur E, Fleming Donald R, Powell Bayard L and Gartenhaus Ronald. "DAB389IL2 (ONTAK) fusion protein therapy of chronic lymphocytic leukaemia." *Expert Opin Biol Ther* 3 (2003): 179-186.

59. Lee, Sunju, Park Sangsu, Nguyen Minh Tan and Lee Eunyoung et al. "A chemical conjugate between HER2-targeting antibody fragment and Pseudomonas exotoxin A fragment demonstrates cytotoxic effects on HER2-expressing breast cancer cells." *BMB Rep* 52 (2019): 496-501.

60. Teicher, Beverly A, and Chari Ravi V J. "Antibody conjugate therapeutics: Challenges and potential." *Clin Cancer Res* 17 (2011): 6389-6397.

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