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Future Prospective of Targeted Therapeutic Approaches over Conventional Therapies for Various Cancer Types

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ABSTRACT

Unlike other diseases, the treatment of cancer is difficult and challenging because they are alike in metabolism and DNA replication processes with the body cells. Thereof, cancer is very dangerous disease which feared by people due to difficulty to cure the problem. The treatment of cancer needs immense effort than other diseases found in this world and One fourth of death in world has been covered merely by cancer disease. Different conventional cancer treatment methods have been devised namely: surgery, radiotherapy and chemotherapy methods such as platinum derivatives, nucleoside analogues, topoisomerase inhibitors, and taxanes and vinca alkaloids were designed to hinder highly dividing cells by causing cytotoxicity. However, these methods of treatment are not effective due to lack of specificity to tumor cell. Hence, to overcome this problem, researchers and drug companies are looking on targeted cancer therapy, to increase the specificity and effectiveness of the drugs on cancer cell. Thus, producing targeted therapeutic approaches are the recent revolution for combat cancer. This review paper focuses on the different targeted therapeutic cancer approaches which are currently practiced and in clinical stage with the aim of proposing the future prospects of novel strategy for cancer treatment.

KEYWORDS

Cancer; Chemotherapy; Cytotoxic drug; Targeted therapy

INTRODUCTION

Cancer is cell growth out of control, causing the development of tumors which disrupt normal body function. This may occur in any part of the body as tumor in the form of solid masses of cells or liquid tumors that comprise blood cells. Cell cycle controls the growth and production of cell. Normal cell has low life span, after cell replaced by the new cell and it goes to apoptosis but cancer cells do not [1,2]. Change of DNA sequence of the genome (mutation) or epigenetic change that can arise as a result of changes in hormone exposure, or exposure to chemicals in the environment and in diet can lead to cancer rise. According to Jacquie et al. (2008) cancers have their own hall mark which make them differ from others cells; 1) uncontrolled growth; No response to signals start or stop cell division, 2) evading death; the ability to represssignal for

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apoptosis and becoming immortal, 3) Angiogenesis; the ability to attract new blood vessels to get nutrients and oxygen as well as to remove wastes (CO2, water and urine), 4) Tissue invasion or metastasis; capable of invading nearby and even remote tissues, 5) Promoting mutations; acquired mutations at a faster rate. Many methods have been developed through time to treat cancer. The most common traditional type of therapies of cancers comprise; surgery, radiotherapy and chemotherapy [3]. Surgery therapy is the process of taking out of cancer tumors from its site of the body [4]. Radiotherapy treatment of cancer is carried out using ionizing radiation for destruction of the tumor [5]. Chemotherapy of cancer is the other way of treatment in which drugs (chemo toxic drugs) that cause cytotoxicity are applied to repress the highly dividing cells. These drugs are targeting rapidly dividing tissues and causes problems on other normal tissues [6]. Many commonly used chemotherapeutic drugs lack tumor specificity, and the doses required to reach therapeutic levels in the tumor are often toxic to the surrounding normal tissues [7]. In order to circumvent the drawback of chemo toxic drugs, many researches and pharmaceutical companies are looking on targeted therapeutic drugs which are a much sharper instrument with fewer side effects [8]. This review shows the new approaches of targeted therapy in cancer treatment.

Cytotoxic Therapy

Currently and during the last several decades, chemotherapy has been used as a primary treatment of cancer. The drug exerts its oncotoxtic actions by inhibiting proliferation or by arresting cell cycle at a certain phase [9,10]. As oncotoxic drugs are endowed with poor selectivity, they affect not only neoplastic cells but also rapidly proliferating normal body cells such as: bone marrow, gut epithelia, hair follicles, lymphatic cells and gamete cells [10]. Antimetabolites, Alkylating agents and DNA-binding agents are the three main groups of molecules that can be used to interfere with DNA replication or cell cycle [9]. In compare to the above mechanisms of cancer interfering molecules, DNA-binding agents are better but most of the time DNA binding agents are used with the combination of several of group drugs to be more efficient [10]. Moreover, these drugs have side effects namely nausea, immunosuppression, ulceration and hair loss. Currently, different drugs are being produced which solely target the cancer cell to avoid the side effects of chemo toxic drugs [9].

Cytostatic Therapy

Cytostatic therapy is another approach by which applied for cancer treatment by increasing the specificity of the cancer drugs to cancer cells. Cytostatic drug targets mainly on the cell communication way that give signal to quickly divide the cancer cell [11]. This process is carried out by handicap signal transduction process of cancer proliferation in which a specific lipid or hormone bind to the cell membrane receptors. Thus, through signals that come from the receptors, phosphorylation activates kinase enzyme then DNA replication and cell division takes place. Cancer cells have unique cell receptor called the epidermal growth factor receptor (EGFR) than normal cells. These drugs are selectively block tyrosine kinase enzyme. This could be achieved by drugs which bind either at the ATP site (phosphorylation site), or at the ligand site (EGFR). However, inhibiting of ATP bind site is difficult because it's resembled with ATP bind site of non-target enzymes. Therefore, inhibiting the activity EGFR enzyme is the best way to block tyrosine kinase [9]. Imatinib, the first small molecule drug that effectively blocks the activity of the BCR-ABL kinase protein in chronic myeloid leukemia (CML) [12]. The success rate of imatinib treatment and conventional chemotherapy are 90% and 35% respectively. Gefitinib have a higher response rate (75%) for non-small cell lung cancer (NSCLC) when 3

compared with standard chemotherapy (30%) [13]. Vemurafenib is also another cytostatic drug that is exploited to melanomas treatment.

Enzyme-activated prodrugs

Prodrug cancer therapy is designed to increase the specificity of cancer cells and to reduce the side effects of cytotoxic cancer drugs. Ideally, prodrugs must meet the following criteria: a) they must be less toxic or non-toxic prior to activation (cleavage) by the suicide gene product; b) they must have a selective binding affinity for the transfected suicide gene product; and c) an active metabolite of the prodrug must have an extended half-life so that the treatment dose can be reduced [14]. Thus drugs such as 5-Fluorodeoxyuridylate (F-dUMP) is an irreversible inhibitor of thymidylate synthase in all cells. There are two main approaches to carry out enzyme activated prodrug therapy method; Gene-directed enzyme prodrug therapy (GDEPT) and Antibody directed enzyme prodrug therapy (ADEPT) [15]. Both methods activate inactive prodrug when the prodrug is reached at the cancer area which is more illustrated below (Figure1).

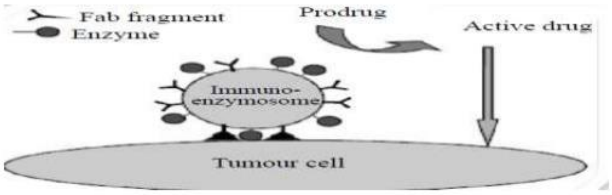

Figure 1:Prodrug activated in to active drug by enzyme.

Gene-directed enzyme prodrug therapy (GDEPT) is one of another method of minimizing cytotoxicity of drug for cancer therapy which is normally used by conventional method of chemotherapy. This is done through the introduction of catalytic enzymes that convert low or non-toxic prodrugs into toxic metabolites in tumor cells [16]. This system of therapeutics contains the inactive form prodrug and enzyme coding gene. Genetically modified tumor cell which comprise gene that codes a specific enzyme that converts 4 prodrug in to toxic metabolite by the action of this enzyme is leading to the selective killing of the tumor cells [7,17]. The toxic metabolite is producing around the area of local tumor site where the gene was delivered; this decreases the movement of toxic drug from tumor cells to other normal cells. To carry out gene directed enzyme prodrug therapy, the introduced gene must; a) not be expressed or expressed in low level of the host, b) have high catalytic ability to achieve high toxicity of tumor [14].

Herpes Simplex Virus-1 Thymidine Kinase (HSV-TK)

This is the most common type of gene that codes prodrug activating enzyme and it is a well characterized suicide gene that can be isolated from the *Herpes simplex* virus or *E.coli* [18]. HSV-TK converts the systemically administered prodrug gancyclovir (GCV) into a toxic metabolite that kills cancer cells [19]. The mechanism of HSV-TK is catalyzing of GCV into monophosphorylated GCV (GCV-MP), which is then converted into the toxic triphosphate form of GCV (deoxythymidine triphosphate). This triphosphate metabolite is an analog of purine; incorporation of this analog during DNA synthesis inhibits DNA polymerase, leading to the observed toxicity [14]. This combination method has been successfully applied to many clinical areas, such as gene therapy for cancer treatment and graft-versus-host disease (GVHD) [20]. However, this blending method is not efficient for malignant cancer because the gene expression level is low gene product in vivo and in vitro. So, this needs high concentration of GCV but the highly concentrated GCV has side effect associated to hematologic toxicities, such as leucopenia and thrombocytopenia, renal toxicity [21]. According to Hong et al., (2014), the low expression is due to not the combination of the two rather the transinfaction efficiency gene delivery process. The success of gene target cancer therapy mainly depends on the appropriate transfer of suicide gene in to the targeted tumor cell. The

introduction process is mostly carried out by virus vectors, which allow high efficiency gene transfer [22]. However, beside of its advance, it also has limitation. This virus may be toxic (our body consider it as antigen) as well as their may be also genetic recombination with our chromosome and the other drawback is viral vector preparation is expensive and labor intensive [23]. For that reason, alternative gene delivery method directly deliver the therapeutic agent on to around the tumor cells is needed. As Hong et al. [7] deals, to overcome the side effect of viral based gene therapy problem, transposon based is more 5 attractive. Transposons are segments of DNA that have the inherent ability to move from site to site and can replicate themselves within the genome using the host cell's organelles and other machinery. This method is favorable by eliminating the risk of vector infection.

Antibody Directed Enzyme Prodrug Therapy

ADEPT is another way of delivering for enzyme/prodrug to treat cancer. This approach uses active enzyme on tumor tissue which will be delivered to patient and also known as prodrug activation therapy or Antibody-Directed Catalysis (ADC) [24]. The mechanism of this therapy is first, antibodies which specifically bind to tumor antigen are conjugated with the enzyme and then the cytotoxicity of the prodrug will be activated at the tumor tissue. This prodrug must substrate to the enzymes in order to activate the cytotoxicity on tumor cell. The converted prodrugs do not merely kill the tumor tissue but also the neighboring tumor cell. There are two steps of ADEP. First, a drug-activating enzyme is targeted and expressed in tumors. In the second step nontoxic prodrug called a substrate of the exogenous enzyme is now expressed in tumors and it is administered by parenteral route [25]. Today there are many enzymes used for activation of prodrugs. Some of these are Carboxypeptidase G2, β-lactamase, β-glucuronidase, β-galactosidase, Alkaline phosphatase, Penicillin V-amidase, Cytosine Deaminase, Nitroreductase, CarboxypeptidaseA and catalytic antibodies [26]. The heterogeneity of antigen expression of tumor cells is challenging to treat cancer effectively. Besides ADEPT it has also drawbacks such as the administration of drugs or prodrugs to body via blood circulation may cause somewhat failure by some other pharmacological activity [15]. Enzyme conjugate with prodrug can increase the administration of prodrug. On the other hand in order to minimize degradation of enzyme and to increase its penetration in to biological membranes, encapsulating enzymes with certain biological materials is mandatory. This can be done through encapsulating an enzyme to the surface of the lipid vesicles or surface of liposomes are called enzymosomes [15].

Prodrug Activation by Hypoxic Cancer Cells

This drug design method is solely concerned on the chronic hypoxia (oxygen deprivation) area of the body. This means that around tumor cell area there is scarcity of oxygen than other normal cells; because cancer cells have no well sufficient amount of blood vessels to get oxygen for their 6 respiration [5]. Produrgs are drugs that will get activated at the specific site or by the specific molecules from its non-activate form. This type of cancer drugs are not active and do not cause cytotoxicity on the normal cells but they will be activated at hypoxia cancer cell by reducing themselves (i.e. pick up an electron from cellular enzymes) because less oxygen is available there [5]. Research Laboratory in Auckland designated SN (screen number) 25246, contains the $N(CH_2CH_2Cl)_2$ group known as a mustard group. This prodrug is rapidly reduced by enzymes present in all cells, resulting in an intermediate radical anion. In normal cells, there is sufficient amount of oxygen present and the reduced molecule or radical anion becomes re-oxidized and then inactive prodrug. However, in the absence of oxygen the radical anion eventually fragments, releasing the mechlorethamine

mustard and cause death to cancer cells [9]. Molecular therapies for cancer to directly regulate telomere integrity Telomere is heterochromatin region ofDNA which is found at the end of linear chromosome. It comprises TTAGGG repeats, nucleosome, t-loop and telomere binding proteins. Telomere has different functions such as to protect the end of chromosome and to facilitate replication; prevent recognition of DNA break as well as senor of genotoxic stress [27]. In the normal process of cell cycle the telomere length becomes short and short then leads programmed cell death called apoptosis. This process is carried out by cell check point cycle. But if p53 and Rh check point is deficient, telomere will not become shortened and chromosome end fusion occur which leading to genome instability that drives oncogenesis [27]. In order to for cancer cell to continue division, it must maintain the telomere length. This can be carried out by cancer cells either by expressing telomerase or initiating a recombination-dependent alternative-lengthening-of telomeres (ALT) pathway [28]. Targeted therapy of cancer can apply by interfering telomere stability with telomere synthesis or protection. Molecular targets that play a direct role in maintaining telomere integrity are telomere DNA, telomere synthesis, and telomere protection [27].

Telomere DNA

Targets At the end of human telomere DNA, long guanine tandem repeat sequence and short cytosine rich strand are found. With different DNA binding molecules such as G4 ligand, these strands 7 produce secondary structure called G-quadruplex [19]. G4 ligands are small molecules that disrupt telomere synthesis by interfering telomere elongation. These ligands show the promise of target cancer therapy on telomere integrity and it leads to search molecules which interact and stabilize G-quadruplex [29]. Telomere synthesis targets Telomerase is a ribonucleoprotein DNA polymerase that synthesizes telomeres de novo, and it is over expressed in the majority of cancer cells [30]. It comprise two components the reverse transcriptase and its associated template RNA. By targeting of the two components of telomerase, cancer can be treated. There are several molecules that are being tested for their ability to inhibit telomerase and limit tumor growth. For instance, in vitro characterization of Imetelstat showed that it inhibits telomerase, induces telomere shortening, senescence, or apoptosis, and can reduce tumor growth in a DU145 mouse xenografts model of prostate cancer [31]. Telomere protection targets, ends of telomeres are protected from genomic rearrangements by the proteins called shelterin proteins. The shelterin complex binds to telomeres, and protects telomeres by repressing DNA damage response at telomeres and preventing chromosome fusions [32]. Targeting of sheltering protein is also another approach for cancer treatment. Monoclonal Antibodies are one way to specifically targeting a protein that is deregulated during tumor genesis is by producing a monoclonal antibody against the target protein. Researchers have designed monoclonal antibodies that target a wide range of proteins that are involved in specific cancers. There are three main mechanisms of disrupting the functions of the cancerous cell; disruption of protein function and possible downstream signaling, antibody-dependent cytotoxicity and complement dependent cytotoxicity [33]. Monoclonal antibodies (mAbs) are produced in vitro rather inside the body that are used to stimulate immunity. The first mAbs ware produced through the fusion of B cell (lymphocyte) and mouse cancer cell (myeloma). This process is known as hybridoma technology. Over the past decade, multiple monoclonal antibodies have gained FDA approval to treat a wide range of cancers [33]. Radioimmunotherapy comprises both the targeted radiotherapy as well as immune therapy using monoclonal antibody of cancer cell or to suppress the immune component of host cells for allogeneic transplantation [34]. Monoclonal antibodies are produced

through the process of hybridoma technology that is specific and quantitative method of production [35]. The native mAbs exert their tumoricidal effects through antibody directed cellular cytotoxicity (ADCC) and complement dependent cytotoxicity. In addition, antitumor can be induce apoptosis, interfere interaction of ligand receptors and with synergy of chemotherapy [36]. But tumor cells escape this process through several reasons: tumor cellsare inaccessible to mAbs become poorly refuse and large tumors are difficult to immunotherapy, insufficient amounts of mAbs bound to their cell membrane to initiate cytotoxicity; and the other reason is tumor cells can develop resistance to antibody-induced signaling events by up-regulating counteracting proteins [34,37]. The limited efficiency of native mAbs leads the use of conjugative therapeutic approach. This approach deals with the application of radionuclides, toxins, cytokines and chemotherapies with monoclonal antibody [34]. Especially, radioisotopes are the good approach to monoclonal antibodies specifically kill and easily recognize tumor cells. But the choice of radioisotopes depends on the characteristics of tumor cells, labeling techniques, bio distribution, pharmacokinetics of the mAbs, and practical issues such as radiation safety and handling. The half-life must be longer enough to make immunoconjugation before decay. Today, two approaches of radioimmunotherapy have been used in clinic. The first approach is direct conjugation of radioisotopes with monoclonal antibody [34]. This method is good to target the tumor cells specifically than other normal cells but it has poor penetration of tumor cells if tumor cells are large size [38]. The second approach uses pretargeting of the tumor. Pretargeting involves the administration of a mAb-streptavidin conjugate followed by injection of a clearing agent to remove from the circulation any unbound mAb-streptavidin. This strategy takes advantage of the rapid pharmacokinetics of the small biotin molecule and the high affinity of biotin conjugation [39]. Bispecific antibody 9 mAb has various applications on treatment of different types of disease (Figure 2). The therapeutic use of mAb comprises in activation of antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) [40]. Besides, currently therapeutic antibodies are specific for particular molecular part of antigen, called epitome. mAb for cancer therapy is not successful because cancer cells are multifunctional activity or performance, where tumor passes for mutation and has redundancy multiplication and proliferation pathway [41]. Single target dose of therapeutic antibody has no sufficient specificity to destroy cancer cell. In order to overcome this problem; the therapeutic antibody can be used clinically that can recognize two antigen molecules. This type of antibody is called Bispecific antibodies [40]. Bispecific antibodies are proteins capable of simultaneously binding two different epitops, on the same or on different antigens. Through recognize different antibody, bsAbs can serve as mediators to redirections of immune effector cells, such as Natural Killers cells and T-cells, to tumor cells. In addition to this, bsAbs can also induce modification cell signals [40]. Bispecific antibodies can be obtained by different biochemical methods such as chemical conjugation of two antibodies, fusion of two antibody producing cell lines, or genetic approaches resulting in recombinant bispecific antibody molecules [41]. The advance of genetic engineering leads the high improvement of bsAbs production that was the problem of the previous bispecific antibody production approaches. Currently, Most of developed therapeutic bsAbs in clinical trial have very efficient anti-cancer effect [42].

Anaerobic bacteria spores have the ability to resist difficult environmental conditions; even they can live for long period of time at highly oxygenated area, although they cannot grow or multiply there. But once they meet favorable conditions, such as the dead areas inside

tumors, the spores can germinate and the bacteria thrive, making them ideal to target cancers [43]. Like viruses, bacteria also serve as vectors or vehicles for preferentially delivering anticancer agents, cytotoxic peptides, therapeutic proteins or prodrug converting enzymes to solid tumors [48,50]. There are two ways of bacterial vector used for cancer therapy.

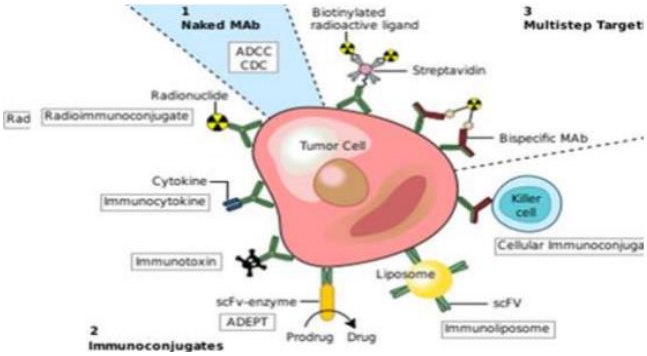

Figure 2: Three mechanisms of mAb that could be responsible for the cancer treatment; 1) mAbs act directly binding to cancer specific antigens and induce immunological response. 2) mAbsmay be modified for delivery of a toxin, radioisotope (radioimmunotherapy), cytokine or otheractive conjugates. 3) mAb act also bispecific antibodies that can bind with target antigen and to aconjugate or effector cell.

Targeted Therapies of Cancer through Bacteria

During the end of 19thcentury, bacteria were used unintentionally for cancer cell treatment. Starting from 1946, chemotherapy gradually became the principal therapeutic strategy in cancer and bacterial therapies were largely forgotten [43]. Like the formerly mentioned targeted cancer therapy approaches, bacterial cancer therapy is the one way to treat cancer [43]. Tumor cells are highly dividing cells and it needs nutrients and oxygen for continuing their life cycle. In order to get this, tumor cell will produce their blood vessels. Still they have no sufficient nutrients on around the cancer cell site because of the presence of enormous mass of cells in the area. This site will be oxygen deficient and commonly known as oxygen deprived area or oxygen hypoxia [44]. Oxygen concentration is one of the most important signals for anaerobic bacteria and is of particular interest in anticancer therapy since hypoxia is a common feature of tumors. These bacteria multiply and destroy cancerous cells present in anaerobic portion of solid tumors. Moreover, the natural ability of bacteria to receive signals via chemoreceptors can be used to effectively target this unique microenvironment and this was the efficient way of treating cancer until the problem of infection caused by bacteria aroused [45]. The natural ability of bacteria to receive signals via chemoreceptors can be used to effectively target the heterogenic and complex metabolites of tumor tissue. Auxotrophic bacterial strains that rely on the uptake of certain metabolites can recognize the tumor microenvironment as a source of nutrients. This phenomenon can facilitate specific accumulation of bacteria in the tumor and the bacteria will attack the tumor cell [45]. Bacterial therapies can benefit from microbial metabolism, motility and sensitivity to address a number of issues related to currently used treatment modalities. Bacteria are able to penetrate deep into the tumor tissue and perform specific actions, e.g. express proteins or transfer genes, to tumor cells localized remotely from the vasculature. This feature can also allow bacteria to cross physiological barriers and accumulate in cellular regions that are either distant or inaccessible 11 for passive therapeutics or quiescent and unresponsive to chemotherapy [46]. For instance Salmonella can penetrate tumor cells in vitro. On the other way the role of motility is not known in vivo [47]. The metabolic activity and the specificity of bacteria on tumor cell are higher than chemodrugs even also greater than viruses. These include the production of cytotoxic agents (e.g. bacterial toxin), expression of immunomodulatory molecules (e.g. cytokine) or enzymatic conversion of a prodrug into an active therapeutic [43]. Once if the treatment is accomplished and if there is also high level of bacteria which we suspect to infection, bacterial can be easily administered or control the propagation. In contrast to viral vectors, bacterial therapeutics is susceptible to antibiotic treatment [43]bacterial cancer therapy methods. Because of the occurrence bacterial

infection and distribution of the immune cells site, bacteria cannot be inoculated directly into the body. In order to address this problem, attenuated bacteria were used for cancer treatment. The use of live, attenuated or weakened or genetically modified bacteria began to emerge as potential anticancer agents [44]. The other drawback of bacteria is that they don't consume all parts of the malignant tissue thus underlying the need of combining the therapy with chemotherapeutic treatments. Actually there are different applications of bacteria for cancer treatment. This therapy can be carried out by whole live, attenuated or genetically-modified form bacteria, bacteria as vector, as immunotherapeutic agent, bacterial toxin and bacterial spores [48]. Bacteria belonging to the Clostridium class were the primary ones experimented for cancer therapy. Even though it showed acute toxicity which cause death on experimental animals. This led people to focus on non-pathogenic strains of Clostridium such as M55, which showed promising results.

Bacterial Cancer Therapy Methods

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CONCLUSION

In conclusion, unlike other diseases the treatment of cancer is difficult and challenging because they mimic metabolism and DNA replication processes of the body cells. Conventional drugs are applied for cancer treatments which were designed to hinder highly dividing cells by causing cytotoxicity. These methods of treatments are not effective due to lack of specificity to tumor. In order to increase the specificity and effectiveness of the drugs on cancer cell, producing targeted therapeutic approaches are the recent revolution

of designing tumor drugs. Currently, targeted therapy has been tried to solve the drawbacks of conventional drugs and hopefully, for the future this type of tumor therapy will be exploited to treat different cancer disease.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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