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REVIEW

Recent advances in carbohydrate-based cancer vaccines

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Abstract Cancer is a complex multifactorial disease for which many promising therapeutic strategies such as immunotherapy are emerging. Malignant cells frequently express aberrant cell surface carbohydrates, which differentiate them from normal "healthy" cells. This characteristic presents a window for the development of synthetic carbohydrate antigen-based cancer vaccines which can be recognized by the immune system and can bring about T cell-dependent immune responses. Antibodies generated against the carbohydrate antigens partake in the inactivation of carbohydrate-decorated cancer cells, by slowing down tumor cell growth and inducing cancer cell apoptosis. Novel synthetic strategies for carbohydrate antigens have led to several synthetic cancer vaccine candidates. In the present review, we describe the latest progress in carbohydrate-based cancer vaccines and their clinical evaluation in various cancers.

Keywords Cancer vaccines · Carbohydrate · Immunotherapy · Tumor-associated carbohydrate antigens

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Introduction

Carbohydrates are a major class of biological molecules that regulate all aspects of cell physiology (Ferraro et al. 2013; Sartorius et al. 2016). They are involved in cellular energy production, cell signalling, and the cell-to-cell contacts required for the development of multicellular organs (Handa and Hakomori 2012). Protein glycosylation is the most varied and frequent protein modification and all cell types harbor an array of intracellular and cell surface-expressed covalently-attached oligosaccharides (Babiuch et al. 2015). When expressed on the cell surface, glycoproteins and glycolipids mediate cell interactions with pathogens, parasites, antibodies and other cell types (Tessitore et al. 2017; Tsoukalas et al. 2017). In addition to their extracellular roles, glycosylated proteins are abundant in both the cytoplasm and nucleus, acting as functional switches that regulate gene expression and subsequent cellular phenotypes (Ndombera et al. 2016). Alterations in both protein glycosylation and expression, which can occur through variations in the glycosylation sites or glycan structures, correlate with the development and progression of an array of human diseases, most commonly cancer. Glycans regulate numerous aspects of tumor development, such as invasion, proliferation and metastasis. Accordingly, changes in glycosylation patterns were detected in an array of human cancers.

In spite of the progress made in cancer therapy, cancer remains a devastating disease responsible for about 9.6 million deaths in 2018 alone (Fidler et al. 2018). Hence, it is crucial to develop novel approaches to battle cancer. Vaccines are historically considered as preventative measures for diseases. In contrast to prophylactic vaccines, therapeutic cancer vaccines are used to eradicate the initial tumors and hinder the malignant tissues from relapsing following the elimination of initial tumors. Therapeutic cancer vaccines have garnered interest in the medical arena due to their capacity to drive the immune system against a tumor (Chuang et al. 2013; Heimburg-Molinaro et al. 2011; Hevey and Ling 2012). For cancer immunotherapy, the glycans uniquely overexpressed by tumors i.e., tumor-associated carbohydrate antigens (TACAs), are promising therapeutic targets (Aldakkak et al. 2015; Bauer et al. 2013; Bergquist et al. 2016). Since carbohydrates are now established as clinically-relevant antigens, several cancer vaccines have been developed based on carbohydrates. Some notable examples include: The BCG vaccine (TheraCys®) for non-muscle invasive bladder cancer (Granados Loarca and Ambrosio 2004), Sipuleucel-T (Provenge®) for prostate cancer (Cheng and Fong 2014; Dawson and Roesch 2014; Dorff et al. 2014); and the oncolytic talimogene laherparepvec vaccine (T-VEC or Imlygic®) for melanoma (Andtbacka et al. 2016; Ott and Hodi 2016; Puzanov et al. 2016).

Most carbohydrate antigens are T-cell-independent and produce a weak immune response (Payandeh et al. 2018). Thus, while carbohydrate antigens are potentially suited for immune recognition and killing, their use in cancer vaccines has remained challenging due to the difficulties associated with overcoming immunotolerance and immunosuppression. Carbohydrate antigens are devoid of the inherent immunogenicity of bacterial antigens and techniques to improve their immunological recognition, including defining the appropriate TACA, chemically modifying the antigens, and increasing immunological reactivity, are being investigated (Hutchins et al. 2017; Qin et al. 2014). To date, the gains have been modest, primarily due to immune escape produced by the selection of tumor cells lacking carbohydrate-based immunogenic antigens. Resistance emerges through the tumor-mediated silencing of cellular components involved in antigen processing and the upregulation of T-cell inhibitory receptors within the tumor microenvironment (Chen et al. 2015; Dorff et al. 2014). In the current review, we summarize the most recent efforts to surmount these problems and present an overview of the promising results shown by several carbohydrate-based cancer vaccine candidates.

Tumor-associated carbohydrate antigens (TACAs)

Cancer cells are typically distinguished from healthy cells by the number and type carbohydrate structures on their cell surfaces, termed TACAs. TACAs are divided into two major classes: glycoprotein antigens, such as Thomsen-nouveau (Tn), Thomsen-Friedenreich (TF), and sialyl-Tn (sTn), in which the TACAs are linked to the hydroxyl group of a serine or threonine residue in proteins, overexpressed in epithelial cancers; and glycolipid antigens (carbohydrates linked to ceramides) overexpressed in melanoma, lung, ovarian, breast, colon, and prostate tumors (Hutchins et al. 2017). The glycolipids are additionally classified

as follows: gangliosides including GD2, GD3, GM2, GM3, and fucosyl-GM1; globo class including Globo-H, Gb3, Gb4, and Gb5 (SSEA-3); blood group-related TACAs including Lewis x (SSEA-1), Lewis y, and their sialylated analogs.

The aberrant expression of these TACAs on malignant cells distinguishes them from their normal counterparts. TACAs are shared by a range of cancer cell types (Fig. 1), including Lewis y and the ganglioside GD2 in breast cancer, Tn and sialyl-Tn in colorectal and lung cancers; and GM2, GD2, and GD3 gangliosides in brain tumors (Hutchins et al. 2017). As such, vaccines against TACAs have the potential to target an array of cancer types. More recently, TACAs have been shown to be significantly expressed in cancer stem cells and also vital in tumor cell metastasis and signal transduction (Ferraro et al. 2013; Heublein et al. 2016; Liu et al. 2016; Lo Re et al. 2018; Starbuck et al. 2018). Dendritic cell vaccines, peptide and protein vaccines and lentivector based TACA vaccines have all been developed.

TACA-based cancer vaccines

Earlier, researchers obtained TACAs mostly by the process of time-consuming and difficult separation from tumors. In the last two decades, several novel oligosaccharide synthetic strategies have been developed, including solid-phase, chemoselective, and chemo-enzymatic methods, which aid the large-scale acquisition of pure and homogeneous TACAs (Yin et al. 2017; Zhou et al. 2017). Such technological advances have enabled the synthesis of TACA-based cancer vaccines. Carbohydrate antigens are mostly T-cell-independent and generate a weak immune response by activating differentiation of B cells to plasma B cells (Heimburg-Molinaro et al. 2011). Plasma B cells give rise to short-lived IgM antibodies, which induce an inadequate immune response to combat cancer. In this context, covalently linking carbohydrates to immunologically active proteins or peptides can augment their immunogenicity, converting them from T cell-independent to T cell-dependent antigens (Hevey and Ling 2012). The most widely adopted technique is to couple TACAs to carrier proteins to produce semi-synthetic glycoproteins. Examples of carrier proteins include Keyhole limpet haemocyanin (KLH), serum albumin, ovalbumin, CRM197, diphtheria toxoid and tetanus toxoid.

The immunological activity of oligosaccharides can be also enhanced by conjugation with potent immunostimulant adjuvants like monophosphoryl lipid A (MPLA) or α-galactosylceramide (α-GalCer), which yields peptide-free vaccine candidates (Wang et al. 2012). Synthetic vaccines may be considered as small molecule drugs that can be fully characterized structurally, facilitate structure–activity relationship (SAR) investigations, and can shorten the regulatory application procedure. Furthermore, multi-component vaccine candidates need complex synthetic strategies. Thus, simple platforms that allow easy access to fully-synthetic vaccines are greatly attractive. Recently, a range of fully-synthetic antigenic peptide-free vaccine candidates based on TACAs have been reported. For instance, Yin et al. (2017) synthesized a two-component self-adjuvanting synthetic cancer vaccine candidate composed of sTn and α-GalCer (sTn-α-GalCer; Fig. 2A), through covalent conjugation. α-GalCer

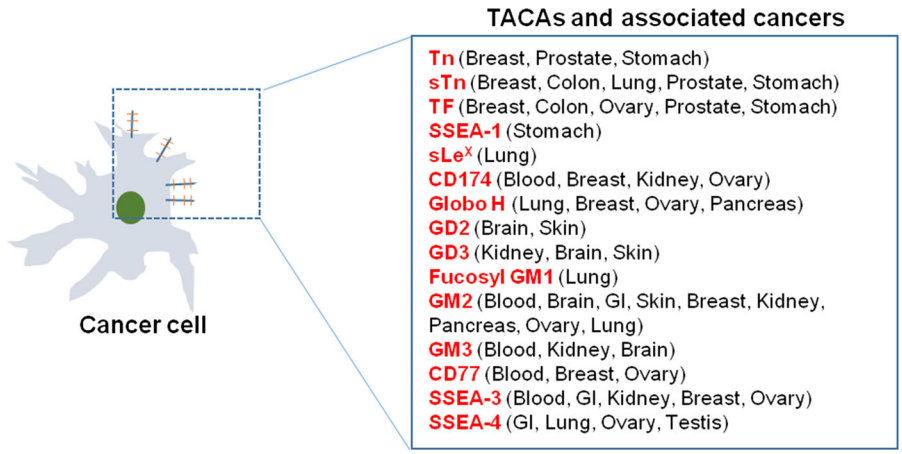

Fig. 1 Examples of aberrantly expressed TACAs on tumor surface and their associated cancers

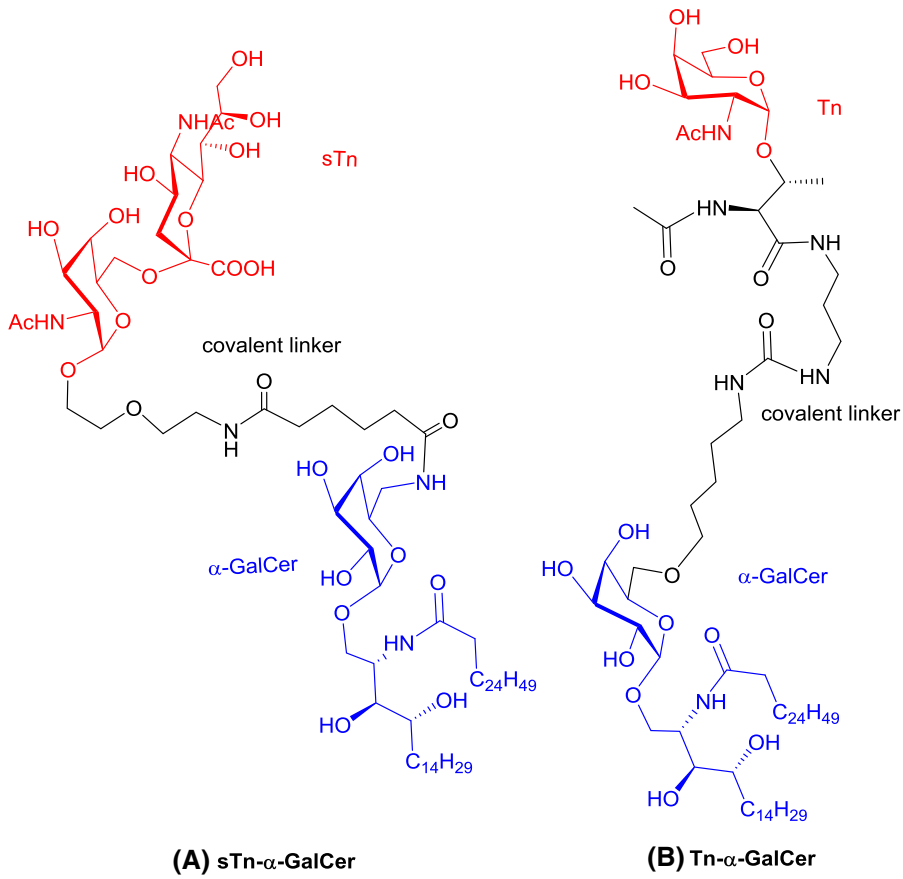

Fig. 2 Chemical structures of fully-synthetic vaccine candidates: (**A**) sTn-α-GalCer and (**B**) Tn-α-GalCer

acted as a built-in adjuvant and sTn-α-GalCer induced a strong anti-sTn IgG antibody response. Seeberger and colleagues reported a fully-synthetic two-component Tn-α-GalCer conjugate vaccine candidate (Fig. 2B) free from external adjuvants (Broecker et al. 2018). Liposome-formulated Tn-α-GalCer generated strong T cell-dependent immunity with high-affinity IgG in mice.

The carrier proteins are usually tethered to the carbohydrate antigens through covalent conjugation with a linker. Hence, the choice of the carbohydrate-protein linker is also critical since it can impact the immunogenicity of the resultant conjugate (Hutchins et al. 2017; Kozbor 2010; Liu and Ye 2012). Immunologically inactive and non-covalent linkers are considered a promising strategy for fabricating TACA-based cancer vaccines since linkers may elicit antilinker antibodies, which suppress the IgG antibody responses against TACAs. Liu and colleagues synthesized a membrane-bound glycoprotein mucin 1 (MUC1)-based antitumor vaccine candidate (Fig. 3A) through supramolecular self-assembly, in which the Nap-G^{D}F^{D}F^{D}Y^{D}K (^{D}F denotes D-phenylalanine, ^{D}Y denotes D-tyrosine, ^{D}K denotes D-lysine) nanovector was employed as a multivalent carrier and an adjuvant (Liu et al. 2017). The MUC1(Tn)-Nap vaccine self-assembles into nanoparticles and elicits a potent immune response. Sun et al. (2016) developed self-assembled three- and four-component nano-vaccines containing Pam3CSK4 and CpG (Toll-like receptor agonists) which could stimulate macrophages and induce strong antitumor immune responses. Though non-covalent self-assembly of vaccines clearly reduces the difficulties associated with their preparation, the applications of these vaccines may be restricted by their fragility.

TACA vaccines are classified based on the number and nature of TACAs that are linked to the carrier. Three major classes exist namely: (1) mono-epitopic vaccines that possess a single TACA; (2) mono-epitopic cluster vaccines that possess several copies of the same TACA; and (3) multi-epitopic vaccines

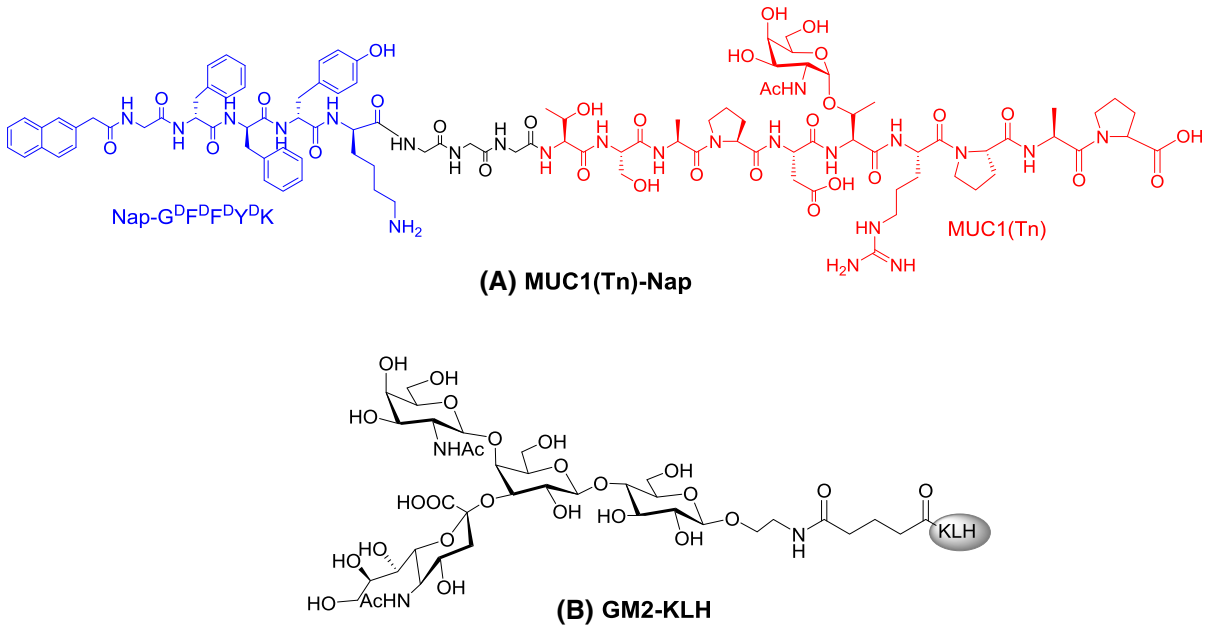

Fig. 3 Chemical structures of (**A**) MUC1(Tn)-Nap and (**B**) GM2-KLH vaccine candidates

composed of different types of TACAs (Hutchins et al. 2017). In the last 20 years, an array of vaccines has made it to clinical trials but the reduction in disease progression times and overall survival as yet remains limited. Among these, only five TACA-targeted vaccines have reached randomized phase III: Theratope, OPT-822, GM2-KLH, Racotumomab and GD2-directed monoclonal antibody. Herein, we present an overview of the present status of different cancer vaccine candidates that have been developed, in the context of clinical studies.

Melanoma

Gangliosides are diverse acidic glycosphingolipids constituted by sialic acid, carbohydrates, and ceramides that are expressed on the outer leaflet of the plasma membrane and in specific lipid raft microdomains (Eggermont et al. 2013). Accordingly, they contribute to a range of receptor-mediated signaling pathways. Melanomas are skin cancers that develop from melanocytes. As early as 1987, the ganglioside composition of human malignant melanomas was investigated in biopsied specimens and cell culture lines (Tsuchida et al. 1987), which revealed that GM3, GD3, GM2, GD2 and alkali-labile ganglioside were frequently expressed by the melanomas. GM2, GD2 and alkali-labile gangliosides displayed the most frequent, but the variable expression on cultured cell lines compared with biopsied melanomas (Tsuchida et al. 1987). Elevated production of these gangliosides has since been detected in many tumors. It is now considered that malignant melanomas and neuroblastoma cells overexpress GD3, GD2, and GM2, which are cleaved and released into the tumor microenvironments (Bennaceur et al. 2006).

Amongst the TACAs identified to-date, GM2 has emerged as the most attractive for vaccine development in melanomas (Eggermont et al. 2013). The benefits of GM2 for tumor targeting include the fact that it is cancer-specific, anti-GM2 antibodies are cytotoxic to GM2-positive cancer cell lines and small titers of natural anti-GM2 IgM antibodies are observed in patients (Eggermont et al. 2013). Accordingly, the immunization of melanoma patients using a GM2 conjugate elicits anti-GM2 antibodies, which correlates with better survival and prolonged disease-free duration (Zhou et al. 2017). Importantly, no severe side effects are observed with immune responses to GM2, highlighting its potential as a cancer therapeutic (Wang et al. 2012; Yin et al. 2017). A recent clinical trial in 970 stage II melanoma patients receiving GM2-KLH/QS-21 vaccinations (Fig. 3B) displayed prognostic serum antibody responses and correlated with

favorable outcomes (Michels et al. 2018). The results of this trial contrast with earlier trials that observed little to modest improvement in four-year recurrence-free survival (Chapman et al. 2000). Since the vaccine targets only a single carbohydrate antigen expressed on melanomas, a combination of therapies that target the heterogeneous expression of TACAs to activate diverse B-cell populations may induce a multi-faceted response that improves the anticancer efficacy.

Breast cancer

It is estimated that the average risk to a woman in the Western world developing breast cancer (Bca) at some point in their life is approximately 12% (Sun et al. 2018). TACAs that support Bca cell survival, viz. Lewis y and the ganglioside GD2, can be targeted with anti-TACA antibodies to inhibit breast tumors. Hutchings and colleagues hypothesized that immunity to Lewis y and GD2 could be induced through the production of a carbohydrate mimicking peptide (CMP) that mimics both receptors (Hutchins et al. 2017). The CMP (P10s) in Phase I dose-escalation trials with the adjuvant MONTANIDE ISA 51 VG was performed in Bca patients over a 19 week period in which antibody responses to P10s, GD2, and Le^Y occurred in all six of the patients assessed. Immunization using the p10 vaccine was well-tolerated and induced functional antibodies, suggesting its clinical benefits (Hutchins et al. 2017).

More recently, Abbas et al. (2018) performed multiplex bead-based measurements of the humoral immune responses against tumor-associated antigens to assess their mechanisms of action. In the study, they highlighted the benefits of the P10s carbohydrate-based vaccine to activate Natural Killer (NK) cells, aid their tumor infiltration, and shape the adaptive responses towards a T helper type 1 (Th1) profile in mouse models. Stage IV metastatic Bca patients had a Th1 cytokine environment marked by considerable IFN-γ elevation (Abbas et al. 2018). P10s-PADRE immunization was shown to induce the expression of pro-apoptotic antibodies that were caspase-3 dependent leading to ADCC targeting of human Bca cells in vitro, further emphasizing the role of activated NK cells. Thus, immunization with the CMP vaccine mediated the activation of anti-tumor NK responses. This vaccine strategy is now in human clinical trials for further assessment (Trial number: NCT01390064).

Recently, a large randomized phase II/III trial was performed with Globo H-KLH conjugate vaccine (OPT-822) in 349 metastatic breast cancer patients who had < 2 episodes of progressive disease, and who attained stable disease after more than a course of therapy (Huang et al. 2016). Patients were randomized 2:1 to receive either the vaccine or PBS control, along with a low dose of cyclophosphamide. Progression-free survival and overall survival were significantly augmented in 50% of patients who developed early specific antibody responses to OPT-822 irrespective of the breast cancer subtype.

Pancreatic cancer

Pancreatic cancer remains one of the most lethal cancers globally (Aldakkak et al. 2015). Upon its diagnosis, if cancer does not spread outside the pancreas and surgery can be performed, between 7 and 25% of patients will survive ≥ 5 years (Bauer et al. 2013). Single-agent immunotherapy has been shown to be largely futile for poorly immunogenic cancers like pancreatic ductal adenocarcinoma (PDAC). In attempts to improve these responses, Furukawa et al. processed surgically resected human tumors to prepare α-gal epitopes onto the carbohydrate chains of cell surface-expressed glycoproteins. The α-gal(+) PDAC tumor lysate vaccine showed significant production of antibodies against multiple tumor-associated antigens, leading to the activation of multiple tumor-specific T cells (Furukawa et al. 2017). In animal models, the vaccine achieved a strong immune response, tumor suppression, and a considerable improvement in survival (Furukawa et al. 2017). This highlights α-gal(+) PDAC tumor lysate vaccination as an effective and practical immunotherapeutic method for PDAC.

GVAX Pancreas, a granulocyte–macrophage colony-stimulating factor-modified whole-cell vaccine earlier showed positive results in a phase II clinical trial, inducing cancer regression in patients who failed chemotherapy (Le et al. 2015). Using glyco-antigen microarrays, Xia et al. (2016) demonstrated that the GVAX Pancreas induces IgG and IgM responses to TACAs. Antibody responses to alpha-Gal, a glycan present in fetal bovine serum (FBS) utilized to fabricate vaccines, were observed and inversely correlated with overall survival (Xia et al. 2016), most likely due to competition with productive

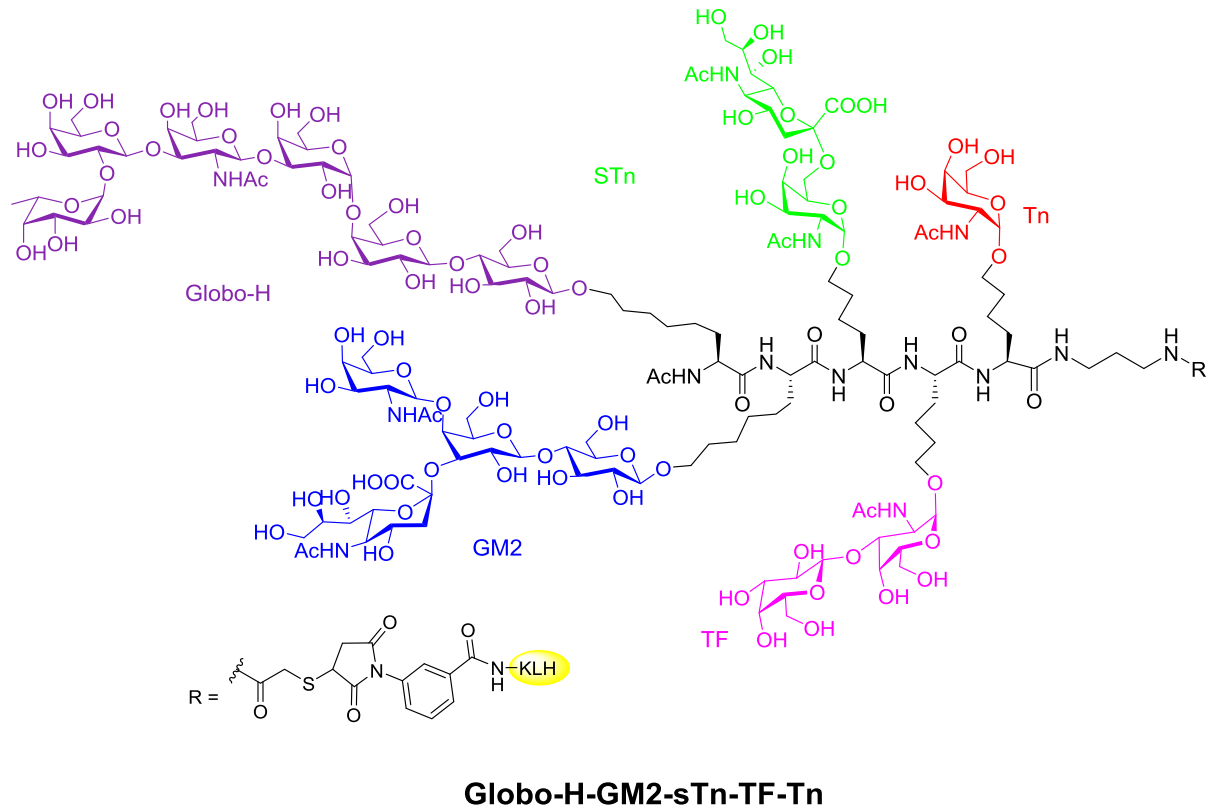

Fig. 4 Chemical structure of Globo-H-GM2-sTn-TF-Tn vaccine candidate

responses to the vaccine. These findings were significant as they suggested that reducing the levels of FBS during production can improve the efficacy of carbohydrate vaccines.

Ovarian cancer

While most of the advanced epithelial ovarian cancer (Oca) patients enter remission after surgery and chemotherapy, a few will relapse and eventually develop chemoresistance (Ferraro et al. 2013). Thus, effectual immune-directed maintenance methods are essential to avert recurrence or to prolong remission. Oca expresses an extensive range of TACAs, including GM2, Globo-H, Lewis y, sTn, and TF. Though monovalent vaccination induces immunologic responses, a multivalent approach may generate a broader immunologic response due to the heterogeneity of TACA expression. A phase I study was conducted in 24 advanced-stage, first-remission Oca patients to assess the safety and efficacy of a synthetic pentavalent Globo-H-GM2-sTn-TF-Tn vaccine supported on a peptide scaffold, conjugated to KLH, and mixed with the adjuvant QS-21 (Fig. 4). This unimolecular vaccine simplifies manufacture, allows the addition or substitution of antigens, and aids scalability (O'Cearbhaill et al. 2016). The vaccine was safe to use and the immunological characteristics of the five antigens were preserved. Thus, including several diverse TACAs onto a peptide scaffold might be a feasible tactic to mimic tumor microheterogeneity.

Outlook and future perspectives

Recent work in this area highlights that carbohydrates are promising targets for cancer vaccine development as the cell surface glycans play a leading role in cancer progression and development. The oncogenic transformation is now known to be associated with aberrant cell surface glycosylation of both proteins and lipids leading to the generation of TACAs. Our enhanced knowledge of glycobiology has led to advances in the development of immunotherapy and cancer

carbohydrates are now established as key targets in the development of safe and effective cancer vaccines. The effectiveness of carbohydrate vaccines to melanoma, breast, pancreatic and ovarian cancers has been highlighted and their success will be judged on their ability to induce T-cell mediated immunity with immunological memory. As discussed, carbohydrates used in isolation are only poorly immunogenic, and to augment immunogenicity, they have been conjugated to carrier proteins or chemically modified. Whilst this has benefits, drawbacks are unavoidable, for example, peptide-based immune responses may inhibit antibodies directly targeted at the TACAs. The future on this field will depend upon the development of promising new carriers of carbohydrate antigens and large scale clinical trials to ensure they achieve the maximal and desired levels of immunological responses. In addition, targeting multiple heterogeneous populations of tumor expressed-TACAs as opposed to individual TACA targets likely represents the most effective anticancer strategy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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