

# Glycosylation-Based Therapeutics: A Precision Approach

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## ABSTRACT

Glycosylation, a fundamental post-translational modification, plays a crucial role in various physiological and pathological processes. Due to its impact on protein interactions, signaling cascades, and mechanisms of disease, this intricate and highly regulated post-translational modification has attracted considerable interest in the therapeutics sector. Glycosylation-based therapeutics (GBT), an emerging discipline, uses a precise technique to target and regulate glycosylation processes to create novel therapies for various disorders. An outline of the GBT's principles and uses is given in this chapter. The significance of glycosylation in health and disease is emphasized, along with the role that abnormal glycosylation patterns play in a number of diseases including cancer, autoimmune disorders, and hereditary disorders. The inherent variability of glycosylation offers therapeutic approaches both difficulties and opportunity. GBT adopts a multifaceted approach that includes comprehending the complex mechanisms of glycosylation, creating medicines that have been glyco-engineered, and developing interventions to regulate patterns of glycosylation. To target glycosylation-related processes, researchers and pharmaceutical companies are actively investigating a variety of strategies, including small compounds, antibodies, gene therapies, and sophisticated biologics. Glycosylation can be precisely engineered to increase medicinal effectiveness, lessen side effects, and enable personalized medical techniques. The creations of glyco-targeted medicines, which specifically interfere with glycan structures linked to disease and obstruct pathogenic processes, is a significant development in GBT. Additionally, glycoconjugate vaccines have become a promising way to activate the immune system in the fight against infections and other diseases with glycan-rich surfaces. The complicated interactions between glycosylation patterns and disease states, as well as the technical difficulties of highly selective glycosylation modification, pose problems for GBT despite its potential. The development of pharmaceuticals based on glycosylation is also complicated by manufacturing issues and regulatory issues. The precision-focused approach offered by glycosylation-based therapeutics has the potential to completely transform the way that many diseases are treated. Researchers and clinicians are getting closer to creating focused therapies that take advantage of the significance of glycans in the pathways of health and illness by utilizing the complex world of glycosylation. The future of GBT is bright in terms of making a contribution to more efficient and individualized therapy techniques as our knowledge of glycosylation develops and technical capabilities increase.

**Keywords**— Glycosylation; therapeutics; cancer; biomarkers

## I. INTRODUCTION

Glycosylation refers to the cellular process in which a carbohydrate moiety (glycan) covalently attaches to a protein or lipid molecule in order to form a glycoconjugate. Protein glycosylation is the most complex form of protein post-translational modification [1]. A sequence of enzymatic reactions which occur as a consequence of linkage of monosaccharides to amino acid chains lead to the formation of glycoproteins.

Glycosylation in mammalian cells can be classified as *N*-linked and *O*-linked glycosylation. Incorporation of an oligosaccharide chain onto an asparagine residue (Asn) in an Asn-X-Ser/Thr tri-peptide sequence, results in the *N*-glycans biosynthesis within the Endoplasmic Reticulum (ER). The biosynthesis of *O*-glycans in the Golgi apparatus (GA), ER or cytosol is an outcome of the progressive enzyme transfer of monosaccharides. Transfer of the *N*-acetylgalactosamine (GalNAc) to a Ser/Thr residue results in the formation of the Thomsennouvelle antigen (Tn Ag) which consequently initiates the synthesis of *O*-GalNAc

glycans [1, 2]. Additionally, the cellular morphology and biochemical processes are altered due to glycosylation processes.

Alterations in tumor-linked glycans include highly branched  $\beta$ 1-6 N-linked chains, an increase in the density of O-glycans and the assembly of unusual terminal formations that occur due to fucosylation and sialylation [1]. The alterations and cellular modifications that take place during protein glycosylation play vital role as essential biomarkers whilst providing an understanding of diverse diseases and their principal mechanisms. [3]

Aging is an inevitable biological process that affects all living organisms, leading to a gradual decline in physiological functions and an increased susceptibility to various diseases. As life expectancy continues to rise globally, the burden of age-related diseases becomes a pressing concern for public health and healthcare systems. The search for effective and targeted therapeutic approaches to combat age-related ailments has become a paramount endeavor in medical research.

In recent years, glycosylation, a fundamental post-translational modification process, has emerged as a promising avenue for novel therapeutic interventions in age-related diseases. Glycosylation involves the addition of complex carbohydrate structures (glycans) to proteins and lipids, playing critical roles in cellular processes, such as protein folding, stability, and signaling. The dynamic and intricate nature of glycosylation enables it to participate in various physiological and pathological mechanisms, making it an attractive target for therapeutic manipulation.

This article aims to explore the potential of glycosylation as a novel therapeutic paradigm for age-related diseases. We will delve into the significance of glycosylation in various biological contexts and its involvement in the pathogenesis of age-related conditions. Moreover, we will discuss recent advancements in glycoscience that have unveiled new insights into the complexity and diversity of glycans and their functional roles in aging.

Understanding the dynamic interplay between glycosylation and age-related diseases holds the promise of developing age-targeted therapies that can intervene at the molecular level to alleviate disease progression and enhance overall health span. We will review current research findings and clinical applications that support the notion of glycosylation as a key player in aging processes and explore the potential for glycosylation-based interventions in age-related disorders.

With the increasing understanding of the glycome and the development of sophisticated glycoengineering techniques, the possibility of personalized glycosylation-based therapies tailored to individual patients becomes an exciting prospect. Challenges and opportunities in this emerging field will also be discussed, aiming to shed light on future directions and the potential impact of glycosylation-targeted approaches in age-related therapeutic strategies.

## GLYCOSYLATION IN ASSOCIATION WITH CANCER

The activity and capabilities possessed by cancer cells is solely accredited to its hallmarks which are attributes that these cells gain during disease development. Glycosylation has been observed to play an active role in processes associated with the regulation of the hallmarks of cancer – it mediates an interaction between the tumor cells and the tumor microenvironment (TME) [2]. The TME and glycosylation events enhance the progression of cancer hallmarks; and these factors add to the intricacy of disease progression by affecting cell membrane interactions and other cellular attributes such as adhesion and cellular recognition [4]. However, certain glycans and glycoconjugates have also demonstrated anti-oncogenic properties [2]. Further we shall discuss different studies that emphasize the role of glycosylation in association with the known hallmarks of cancer.

***Sustained Signaling for Cellular Proliferation:*** Cancer cells uphold their cellular propagation by autocrine signaling or by mitotic factors provided by the stimulation of stromal cells [2, 5]. Cancer associated fibroblasts (CAF) produce various ECM proteoglycans such as syndecan-1, syndecan-2 and versican that mediate proliferative signaling in cancer cells. Syndecan-1 and versican promote EGF receptor signaling which causes proliferation of cancer cells in human breast cancer [6, 7, 8] and myeloma [9]. The proteoglycans perlecan activates the fibroblast growth factor (FGF) pathway which also leads to continual proliferation of tumor cells [10]. Contrastingly, the proteoglycan decorin seems to exhibit an anti-cancerous role. It has been observed in murine xenograft models that decorin inhibits signaling of tumor growth factor  $\beta$  (TGF- $\beta$ ) and downregulates the Met receptors and EGFR resulting in metastasis and minimization of tumor growth [11,12]. Decorin also inhibits the growth of breast cancer cells by mediating the activation of ERBB4 [13].

Glycosylation drives the activation of growth factor receptors and modifications in the molecular structures. Critical transcription factors such as c-MYC, cyclin D1 and FoxM1 undergo O-GlcNAc modifications which attribute to the oncogenesis of cells [2]. Cancer-linked glycans, proteoglycans and glycosyltransferases mediate the activity of various tyrosine kinase receptors (RTKs) present on the cellular surface. The potential to induce or inhibit cancer cell proliferation is attributed to the branching degree of N-glycans of these RTKs [14, 15] which cements the ideology that N-glycans are critical in mediating cellular proliferation [2]. Multiple studies put into light the importance of glycosyltransferases in the signaling of cancer cell proliferation – core 1  $\beta$ 1-3-galactosyltransferase (C1GALT1) was found to accelerate the cellular proliferation of hepatocellular cancer [16];  $\beta$ 1,6-GlcNAc-branched N-glycans were found to be important for the regulation of proliferation signal pathways [17]. The appearance of O-GalNAc STn antigens in bladder cancers advocates an unrevealed method of mediation of cell proliferation by O-glycosylation [18, 19]. Decrease in the growth of tumor cells has been observed due to the expression of short O-glycan chains, which holds an advantage to chemotherapy involving cancer cells which are less responsive to chemotherapies [2].

**Cellular Apoptotic Resistance:** Glycosylation tends to regulate the extrinsic signaling pathways involving negative regulator TRAILR (induces cancer cell apoptosis), Fas death receptors, and cell signaling mediated by integrin and galectin. The amount of O-glycosylation of the TRAIL-R1 and -R2 receptors mediate the binding of necrosis-linked ligand which induces cellular apoptosis (APO2/TRAIL) [2]. Clinical studies showed that enzymes associated with O-Glycosylation such as GALNT14 and GALNT3 have proven to be beneficial in the study of cancer patient response to therapies based on TRAIL [20]. Apoptosis mediated by TRAIL-R1 is also critically regulated by N-glycosylation.

It has been seen in bladder cancers that glycosyltransferases such as GALNT1 are known activate focal adhesion kinase (FAK) in bladder cells which consequently express certain survival signals that repress cellular apoptosis. Studies have shown hyper-O-GlcNAcylation in cancer cells also inhibit the cellular apoptosis [21]. A study emphasizing protein glycosylation in association with cellular apoptosis due the interaction of lectins and the death receptors has shown Galectin-3 (Gal-3) to be able to inhibit cellular apoptosis (when Gal-3 is present in cytoplasm) as well as promote cellular apoptosis (when Gal-3 is present in nucleus) [22].

**Reprogramming Cellular Energetics:** Cellular energetics is synchronized by the TME to acclimatize to the metabolic changes and ensure the survival of cancer cells. Glycosylation mediates the activity of Glucose-6-phosphate (G6PD). Under low oxygen concentrations at tissue level (hypoxia), the activity of PPP Glucose-6-phosphate (G6PD) dehydrogenase is downregulated in many types of cancers [23]. During hypoxia, G6PD is specifically O-GlcNAcylated; further it has been observed in both in vivo and in vitro studies that blocking the glycosylation of G6PD decreases the proliferation of cancer cells [24]. Similarly, another study has shown that during hypoxia, blocking O-GlcNAcylation of phosphofructokinase 1 (PFK1) at serine 529 effectively inhibits the proliferation of cancer cells and inhibits the growth of tumor, in vitro and in vivo respectively [25]. Hypoxia also causes a decrease in the fucosylation of glycans present on the cell surface, a significant increase in the expression of galectins and sialylated O-glycan (short chain) expression. Various studies indicate that hyper-O-GlcNAcylation mediates cancer transcription factors and consequently affects the cell metabolism attributing to the tumor progression [2].

**Evading Growth Suppressors:** Over the course of tumor progression, cancer cells have been observed to evolve in methods that enable it to escape the tumor suppressor genes. by O-GlcNAcylation regulates the activity of p53 and Retinoblastoma (RB), both of which involve pathways that are known to suppress the proliferation of cancer cells [26, 27]. Cancer cells develop certain glycosidic alterations which allow them to bypass p53 and RB suppressors by negatively regulating their activity [2].

**Instability of Genome and Resulting Mutations:** Cancer cells are well known for mutations caused by uncontrolled cell proliferation, leading to genomic instability [28]. Currently, epigenetic changes in association with glycosylation do not have any specific link to the disease progression. Non-mutational O-GlcNAc modifications of the H2A, H2B and H4 histones are the only known basis of glycosylation being involved in the genomic transcription [2, 29].

**Unlimited Cellular Proliferation:** The regulation of telomerase activity attributes to the replicative immortality of cancer cells. A novel mechanism which mediates the telomerase activity in cancer cells was found in the telomerase reverse transcriptase (TERT) gene. It was observed that activation of c-MYC under hypoxia further mediated the transcription rate of TERT. This has led to a speculation if c-MYC stabilization due to the activity of O-GlcNAc could further activate telomerase activity leading the replicative immortality of cancer cells [2].

**Induction of Angiogenesis:** Proteoglycans acquired from stromal cells mediate the regulation of angiogenesis; a vital process indispensable for the proliferation of cancer progression [2, 30]. Initiation of angiogenesis in breast cancer is due to the expression of proteoglycan Syndecan-1 [31]. Modulations of glycans and glycan binding proteins seem to effectively modulate angiogenesis. O-GlcNAc and O-GalNAc regulate angiogenesis by influencing the Notch signaling pathway [2]. In contrast, a class II proteoglycan, lumican hampers with the activity of  $\alpha 2\beta 1$  receptor, resulting in the obstruction of melanoma angiogenesis and further suppresses the metastasis in the lung [32, 33].

**Invasion and Metastasis:** Invasion and metastasis of cancers such as breast cancer [34], ovarian cancer [35], and prostate cancer [36] are up-regulated by versican and serglycin (proteoglycans) [2]. On the same note, studies involving breast cancer cells [37], prostate cancer cells [38] and melanoma cells [39] have indicated a significant involvement of Hyaluronic acid (HA) and biglycans in the cancer metastasis [2]. Targeted therapies today tend to obstruct the HA mechanism of the tumor cells in order to improve the efficacy of the therapy. Another study involving breast cancer treatment found a significant role of the proteoglycan decorin in activation of Cadm1; a known tumor suppressing molecule [40]. Glycans play a significant role in processes involving sialylation, transformation of malignant tumor cells and metastasis. O-glycosylated proteins involved in adhesion seemed to contain a significant amount of STn antigens. Studies showed that glycosidic modulations of STn such as ST6GalNAc.I and ST6Gal.I seemed to have an effect on the cellular adhesion and tumor invasion properties. ST6GalNAc.I lowered cellular adhesion in prostate cancer but amplified the invasive capabilities of cancer cells in breast, bladder and gastric cancers. The study involving ST6Gal.I showed this inflection on mediating the  $\alpha 2,6$  sialylation of breast cancer reduced cellular adhesion but contrastingly improves the invasive capabilities of the tumor cells [2]. Cancer invasion and metastasis inducing glycosyltransferase GnT-V adds GlcNAc modifications in  $\beta 1,6$  linkage which makes it a suitable biomarker for cancer progression [1]. Another study; in which N-glycosylation of Asn-554 was denied using N-acetylglucosaminotransferase V (GnT-V) had a down regulating effect on E-cadherin, which led to suppression of tumor activity [2, 41]. Cancer metastasis is dynamically regulated, both positively and negatively by the activity of glycosyltransferases. ST6GalNAcV and N-acetylgalactosaminyltransferase GalNT9 seem to positively regulate metastasis in breast cancer whereas ST6GalNAcII was found to inhibit cancer metastasis [2].

**Tumor Enhancing Inflammations:** Alterations in the glycome, such as  $Sle^{a/x}$  interactions with selectins E-, P- and L- ;have shown induction of pro-inflammatory factors leading to initiation of cancer metastasis [2,42]. Recruitment of pro-inflammatory cytokines in pancreatic and gastric carcinomas, such as IL-1 $\beta$  and IL-6 mediate the activity of glycosyltransferases to enhance the expression of  $Sle^{a/x}$ . [2]. O-GlcNAcylation has also been acknowledged to regulate the activity of inflammatory mediators such as NF-KB [43]. These studies highlight the role of glycans and glycoconjugates in mediating tumor enhancing inflammations by recruiting pro-inflammatory cytokines and adding up of lymphocytes in the tumor cell [2].

**Immune Evasion:** Tumor cells gain the ability to evade immunological barriers by enlisting the aid of immunosuppressive cells. Proteoglycans such as decorin (CAF-derived proteoglycan) reduce the activity of immunomodulatory genes in breast carcinoma xenografts; implying that CAF or CAF-related secretome targeting could lessen the immunosuppressive cell employment and also diminish dysfunctions of immune effector cells. In myeloma tumors, versikine upregulates the tumor immune sensing and also alters the tolerogenic effects of amassing of versican. The chief role glycans play during mediation of immune response results in immune suppression due to interactions with lectin receptors in these cells. Exploitation due to sialylated structures as seen in melanoma cells greatly elevates the function of tumor linked regulatory T-cells (Treg). Elements such as sialic-acid binding immunoglobulin like lectins interplay with sialoglycans to elevate activity of Treg cells. An example can be observed in the case of myeloid tumor cells, STnAg binds Siglec-15 causing elevated TGF- $\beta$  secretion within TME and development of tumor. Immune response is interfered by the action of hypersialylation of certain tumor ligands, thereby allowing the tumor cells to evade the immune system vigilance. 2 O-glycosylated MUC1 (from bladder tumor cells expressing C2GnT) interacts with Gal-3, resulting

in the longevity of tumor cells, allowing them to metastasize. In this context, we may gather that events like fucosylation and sialylation of antigens encourage the formation of immunosuppressive TME that enables tumors to escape the immune system [2].

**Table 1: Summary of the Glycans, Glycoproteins, Proteoglycans and Glycan-binding proteins associated with each hallmark of cancer [2].**

Cancer Hallmark	Associated Glycans, Glycoproteins, Proteoglycans and glycan-binding proteins
Sustained signalling for cellular proliferation	Versican, Perlecan, Decorin, STn, HA, Syndecan-1 and 2
Cellular apoptotic resistance	O-GlcNAc, Lumican, Serglycin
Reprogramming cellular energetics	O-GlcNAc
Evading growth suppressors	O-GlcNAc
Instability of genome and resulting mutations	O-GlcNAc
Unlimited cellular proliferation	O-GlcNAc
Induction of angiogenesis	HA, O-GlcNAc, Neuropilin-1 and 2, Decorin, $\alpha$ 2-6-Sia, $\beta$ 1-6 GlcNAc N-glycans
Invasion and metastasis	HA, Sle, STn, Sia, Versican, Serglycin, Fuc, $\beta$ 1-6 GlcNAc
Tumor enhancing inflammations	Sle(a/x), GlcNAc, Neu5Gc, Versican
Immune evasion	ST, STn, Le, Sia

## TARGETING GLYCOSYLATION: ROLE AS BIOMARKERS AND TARGETED THERAPEUTICS

Previously in this article, we have highlighted studies and processes emphasizing the role of glycosylation in regulating the activity of cancer hallmarks. The modulations occurring due to glycosylation or glycosylation-linked processes result in the emergence of highly specific glycosignatures which make them a suitable target for cancer therapeutics. Today, clinical therapeutics recruits the use of multiple glyco-biomarkers due to their high sensitivity and high specificity in targeted cancer therapy [2, 44, 45]. Techniques such as High-throughput Screening (HTS) involving mass spectroscopy, radiolabelling and fluorescence techniques are being incorporated in targeted cancer therapies to improve efficacy in obtaining reports highlighting structural information, target specificity and sensitivity [2,46]. This would enable the advancement of therapies involving glycans, glycosyltransferases, and cancer glycoepitope-binding antibodies (used in novel nanotherapies [47, 48]) [2]. These glycoepitope-binding antibodies can also be incorporated in creation of improved glycopeptide specific chimeric antigen receptors (CAR-T) for improved glycospecificity in cancer therapies. This was previously observed in a study involving T cell leukemia and pancreatic cancer, where a CAR binding to the cancer specific Tn glycoform of MUC1 incited cytotoxicity in the cancer cell xenografts. [46,49]. Novel therapeutic strategies also involve targeting dendritic cells using glycopeptides as dendritic cells possess the ability to induce CD4<sup>+</sup> and CD8<sup>+</sup> cellular responses which can target specific tumors [2]. Another interesting therapeutic approach involves the use of glycan based anti-cancer vaccines which entails conjugation of T-cell epitopes with glycan antigens, allowing the vaccine to be proficient by bypassing the immuno-evasive mechanism of cancer cells [50,51].

Glycosyltransferases have cemented a foothold in cancer therapeutics as a strong candidate for glycan-specific therapies. They actively control various cellular processes such as adhesion, biosynthesis and cellular signaling making them a suitable biomarker to target cellular alterations.

### *Glycosyltransferases and their impact as biomarkers*

In this section we emphasize the role of glycosyltransferases as effective biomarkers and further discuss methodologies for targeting glycosyltransferases for therapeutics. Various studies have highlighted the importance of glycosyltransferases as biomarkers in cancer related therapeutics. These studies showed that upon initiation of N- and/or O- glycosylation, glycosyltransferases target certain protein-linked pathways which facilitate the prognosis of cancers such as neuroblastoma (NB), colorectal cancer (CRC), hepatocellular carcinoma (HCC) and oral squamous cell carcinoma (OSCC) [1].

A study of neuroblastoma cells showed that  $\beta$ 1,3-N-acetylglucosaminyltransferase (B3GNT3) censored the activity of focal adhesion kinase, protein kinase B and activated the extracellular signal kinase which stopped further invasion and migration of NB cells; making it a marker for good prognosis of the disease [52].

Upon N- and O-glycosylation,  $\beta$ 1,4-N-acetylgalactosaminyltransferase 3 (B4GALNT3) inhibits the Akt activation and initiation of ERK signal pathways by transfiguring the  $\beta$ 1 integrin along with LacdiNAc, effectively stopping the downstream signaling. This inhibited the invasion and migration of NB cells [53]. In a contrasting study involving CRC cells, it was found that B4GALNT3 uses MAPK pathways and increases the oncogenic activities of CRC cells by LacdiNAc enhanced N-glycans on EGFR glycosylation and consequent downstream signaling [54].

The activity of B1,4-galactosyltransferase 3 (B4GALT3) was observed in studies involving NB and CRC cells. The studies showed that B4GALT3 acts as a poor prognosis indicator in NB as it deferred the  $\beta$ 1 integrin degeneration by transforming the  $\beta$ 1 integrin lactosamine structures which led to an increase downstream signaling [55]. However, in the case of CRC cells, B4GALT3 decreased the poly-N-Acetylglucosamine activity on  $\beta$ 1 integrin N-glycans, causing a decrease in downstream signaling of  $\beta$ 1 integrin. CRC cell invasion and migration was stopped from progressing further [56].

Studies of NB, HCC and OSCC were conducted regarding the O-glycosylation activity of N-acetylgalactosaminyltransferase 2 (GALNT2). In NB cells; GALNT2 modified the IGFR-1R O-glycans, inhibiting the IGFR-1 dimerization and consequent downstream signaling. GALNT2 acts as a good prognosis indicator as it inhibits NB cell progression [57]. Similarly, GALNT2 acts as a good prognosis indicator in HCC cells, as it stops cellular invasion, proliferation and migration by stopping the EGFR endocytosis and downstream signaling due to the activity of modified EGFR O-glycans [58]. However, in the case of OSCC, up-regulation of O-glycosylation and EGFR activity due to GALNT2 promotes downstream signaling which further encourages the OSCC cell invasion and migration; acting as a poor prognosis marker for the disease[59].

N-Glycosylation activity of N-acetylglucosaminyltransferase V (GnT-V; MGAT5) evaluated in NB cells showed that the knockdown of GnT-V caused retinoic acid to decrease cellular apoptosis, indicating N-acetylglucosaminyltransferase V as a marker for good prognosis in NB [60].

The studies aforementioned [1] emphasize the significance of glycosyltransferases as biomarkers in targeted therapies of various types of cancers.

The result of miRNA interactions with glycogenes affiliated with cancer cell surface glycosylation emerges to be a possible target for studying various diseases. Research associated with miRNA based approach are mentioned as follows-

miR-30b/30d targets GALNT1 and GALNT7 which are actively involved in melanoma metastasis [61]. miR-378 targets GALNT7 which is important in mediating the differentiation of osteoblast [62]. miR-122 is a potential target for therapeutics as it targets GALNT10 which is associated with regulatory pathways linked with HBV infected hepatoma cells [63]. miR-27a upregulates the activity of B4GALT3 which leads to promotion of carcinogenic activities in cervical cancer, making it a candidate for possible biomarkers [64]. miR-148b seems to be a promising biomarker candidate in association with IgA nephropathy as it can influence regulation of C1GALT1 [65]. miR-199b-5p targets FUT4, which is a known marker for medulloblastoma cultivating cells [66]. miR-34a targets and alters levels of FUT8, which hampers the fucosylation process in hepatocellular carcinoma [67].

The studies mentioned above [1] highlight the role of miRNA interactions with enzymes associated with protein glycosylation making them effective biomarkers for a range of diseases.

### ***Targeting Glycosyltransferases:***

In the previous section we have highlighted the role of glycosyltransferases in various cancers and how their activity can lead to identification of biomarkers. In this section we shall discuss various techniques and methods which can be implemented in targeting these glycosyltransferases. Current methods in glyco-specific targeting are based on High-throughput Screening (HTS) assays involving radiolabelling, fluorescence techniques, microarrays, etc; discussed as follows:

Radiolabeled HTS Assays involve two methods- Solid-phase glycosyltransferase assay and Scintillation proximity assay. Solid-phase glycosyltransferase assay was established during the early foundations of HTS assays. In a study focusing on the Core2 GlcNAc-T glycosyltransferase, this assay was used to scan a library of microbial extracts. This solid phase assay gave a 5-6 times higher output as compared to

commonly used solution assay. The solid phase assay seemed effectively sensitive in screening the extract library and efficiently identified the extracts which seemed to inhibit the Core 2GlcNAc-T [68].

Scintillation proximity assay (SPA) is another type of HTS assay involving radiolabelling. In this biochemical assay, a scintillant (a compound with fluorescence properties) embedded in the SPA beads is used to detect radiolabeled target molecules. These radiolabeled molecules bind to the surface of the SPA beads and trigger the scintillant to emit light which can be detected as a successful hit. Anti-inflammatory and anti-metastatic inhibitors of FUT7 were able to be identified through an SPA study [69].

Another domain of HTS assay involves the use of fluorescence techniques to identify target molecules; these techniques involve: Fluorescence-resonance energy transfer (FRET), Fluorescence polarization, use of fluorescence labels and sensors.

Fluorescence-resonance energy transfer (FRET) is used to determine protein interactions in a cell. It calculates the emission spectra to estimate distance of interactions of fluorophore-tagged proteins. A FRET based HTS assay focusing on O-GlcNAc transferase (OGT) was conducted which helped target compounds that inhibit OGT and also act as Gtf inhibitors [70]. Fluorescence polarization measures the relation between the molecular rotation and the degree of polarization of a fluorophore. Various studies have utilized the strategy of fluorescence polarization based HTS assays to screen for inhibitors of enzymes such as OGT [71], ST3Gal III, ST6Gal I, ST3Gal I ST, FUT6, FUT7 [72] and bacterial  $\beta$ -Kdo glycosyltransferases [73]. Cell-based Fluorescence sensors in HTS assay put into operation the use of living cells (due to their high sensitivity towards biochemical changes) to detect target molecules. In a study focusing ppGalNAc-T3, the assay was able to detect an anti-metastatic inhibitor of ppGalNAc-T3. Further study of the inhibitor in mice cells found that the ppGalNAc-T3 inhibitor also benefited the regulation of FGF23 making it a candidate to also study the potential therapeutics involving treating chronic kidney diseases [74].

Some HTS assays have been utilized for the targeting of carbohydrate units present on the target cell. Enzyme-linked lectin assay (ELLA) is one such technique enabling the detection of specific carbohydrates on the cellular surface. In a study focusing on ppGalNAcT-1, a uridine library was screened to detect uridine-based inhibitors of ppGalNAcT-1 [75]. Use of non-covalent carbohydrate microarray is another HTS based technique used to screen a large library to detect particular molecules. In a microarray study, focusing on the inflammation-mediator synthesizing enzyme FUT6, a carbohydrate microarray was screened to efficiently detect inhibitors of FUT6 [76].

These studies summarize the different types of robust and efficient HTS assays incorporated in targeted therapeutics [46].

### ***Targeting glycosylation in other diseases***

Apart from cancer, therapeutic approaches targeting glycosylation have been used in the treatment of viral diseases such as HIV, Hepatitis B and Hepatitis C virus (HBV and HCV), bovine viral diarrhoea (BVD) and certain glycosphingolipid storage disorders (GSL). Clinical approaches involving imino-sugars as glycosylation inhibitors have been used in treatment of these diseases [77]. Imino sugars have an enzyme inhibiting effect which alters biochemical pathways and cellular biosynthesis, thus exhibiting a potential to treat various diseases.

### ***Study of imino sugar inhibitors in viral diseases:***

The protein folding of glycoproteins is synchronized by ER chaperons such as calnexin and calreticulin as they mediate this interaction by removal of ER  $\alpha$ -glucosidases from their N-glycan chain, leading to proper protein folding of glycoproteins. Some viral glycoproteins mediate protein folding with these chaperone-dependent interactions. Viruses depend on host cell machinery to mutate the proteins present on their viral envelope. A possible therapeutic approach can be seen in targeting the N-linked glycans and ER  $\alpha$ -glucosidases to inhibit its activity, consequently interfering with the proper folding of the viral proteins [77]. N-linked glycan targeting has been incorporated in anti-viral clinical studies of HIV, Hepatitis -B and -C and HBV.

In HIV, it is seen that gp120 and gp40 (envelope glycoproteins), mediate the viral entry into the cell. Both gp120 and gp40 are densely glycosylated due to the presence of multiple N-glycan sites. In a medical study, HIV-1 was treated with an inhibitor of ER  $\alpha$ -glycosidase- N-butyldeoxynojirimycin (NB-DNJ). The NB-DNJ results demonstrated reduced viral infectivity by preventing the fusion of viral glycoproteins on cell surface [78]. Despite being an efficient HIV-suppressing agent, NB-DNJ did not seem viable against viraemia and osmotic diarrhea was a major side-effect observed after the administration of NB-DNJ [79].

HBV has three key proteins encompassing its envelope, – large (L), medium (M) and small (S). Interestingly, in HBV studies N-glycosylation pathway inhibitors such as NB-DNJ, DMJ and tunicamycin [80, 81], showed no effect on S and L glycoproteins as their folding is not dependent on chaperones and ER  $\alpha$ -glucosidase [82]. Since the remaining M protein in question, is imperatively calnexin dependent to mediate protein folding, it was considered a potential target to prevent its interaction and inhibit consequent viral envelop formation. Woodchuck hepatitis virus (WHV) being a close relative to HBV, was identified as a potential animal test model to test and study antiviral therapeutics for human diseases. In a clinical study of WHV, woodchucks suffering from WHV were treated with N-nonyl-DNJ (NN-DNJ). Decrease of WHV levels was observed when NN-DNJ was administered in a dose-dependent manner [83]. Since serum glycoprotein glycosylation did not seem to be affected, it was speculated that its selectivity might be against HBV.

For HCV assays a close relative of HCV i.e. BVDV was used to determine drug screening assays of probable anti-HCV drugs. The E1 and E2 glycoproteins present on the envelope of both HCV and BVDV are calnexin dependent for proper folding [84, 85]. An in-vitro clinical study of BVDV showed strong anti-viral activity upon treatment with NB-DNJ and NN-DNJ [86, 87]. Inhibition of ER  $\alpha$ -glucosidases, inhibition of glycosphingolipid biosynthesis by inhibiting ceramide galactosyltransferase (CerGlcT) and activity of alkyl-side chains were attributed as mediators of this antiviral activity.

### **Study of imino-sugar inhibitors in Glycosphingolipid (GSL) lysosomal storage diseases:**

GSL diseases are inherited, mutation-linked disorders in which degeneration of GSL pathways cause GSLs to get stored in lysosomes. GSL storage diseases generally affect the nervous and immune systems which include diseases such as Tay–Sachs disease, Sandhoff disease, Fabry disease, Gaucher diseases and GM2 gangliosidosis. As these diseases were mostly neuro-linked, primitive clinical studies were difficult to conduct. In the early years of clinical study, research focused on treating GSL storage diseases had been focused mainly on approaches such as enzyme replacement, gene therapy and bone marrow transplantation; all of which had a good amount of potential but lots of drawbacks and queries associated with them prohibited the efficient application of these approaches in therapeutics [77].

Another technique, **Substrate-Reduction Therapy (SRT)** was considered a promising approach in the treatment of GSL storage diseases. In this approach, the balance of the deficient enzyme is maintained by reducing the substrate level, instead of replacing that deficient enzyme [88]. Early studies based on imino sugars demonstrated that N-alkylated imino sugars were successfully able to inhibit CerGlcT which led to the subsequent inhibition of GSL biosynthesis [89]. An orally ingested drug which can be introduced to the CNS easily and affect an early step in the GSL biosynthesis pathway is the key principle in the incorporation of SRT. Primitive clinical studies of GSL storage diseases were conducted in mouse models [90].

**SRT in Tay-Sachs disease:** insufficient levels of degradation enzyme,  $\beta$ -hexosaminidase causes an accumulation of GM2 ganglioside.  $\beta$ -hexosaminidase has two iso-enzymes, Hexosaminidase-A and hexosaminidase-B. Mutations in the genes encoding for Hex-A causes Tay-Sachs disease. SRT was tested in mice models to establish if the therapy would prevent the accumulation of GM2 ganglioside in the mice brain. The mice were subjected to NB-DNJ (mixed in their diet) and results showed reduced levels of GM2 ganglioside storage due to inhibition of GSL biosynthesis [91].

**SRT in Sandhoff disease:** Sandhoff disease follows a similar pathway to that of Tay-Sachs disease, where the lack of  $\beta$ -hexosaminidase causes Sandhoff disease. The distinction is that Sandhoff disease is caused by mutations in the genes encoding for Hex-B. SRT tests in mice models treated with NB-DNJ showed a significant decrease of GSL storage in brain and steady improvement in the conditions of mice led to a longer life expectancy [92].

**SRT in Gaucher Disease (Type 1):** Clinical trials of SRT in Gaucher disease conducted in human patients treated with NB-DNJ (compound named as OGT918 in the trials), showed very promising results. A significant reduction in the Gaucher disease marker-enzyme, Chitotriosidase was observed and reduction in GSL levels led to the decrease in Gaucher symptoms such as decrease in Gaucher symptoms such as decrease in the volume of enlarged organs like liver and spleen [93].

## Glycan Targeting Drugs

Throughout this document, a good amount of focus has been imparted upon glycans justifying their roles in cellular processes and their potential as biomarkers for diseases. Glycans have gradually made their mark as worthy candidates in therapeutics, along with research focused on the treatment of very complex diseases. In the table below mentioned, we shall discuss few glycan-based drugs that have been used in the treatment of various diseases.

**Table2: Examples of glycan-based drugs, their target diseases, and clinical trial data.**

S. No.	Drugs	Disease	Observations & Clinical trial data	Clinical approval
1	<b>Relenza</b> (Zanamivir) and <b>Tamiflu</b> (Oseltamivir)	Treatment of Influenza A and B	These drugs mimic sialic acid and hinder neuraminidase located on influenza cell surface, which disallows the virion to escape from its host cell and prevents spread of infection to other cells [94].	FDA approval of Relenza (Zanamivir) in 1999.  FDA approval of Tamiflu (Oseltamivir) in 2000.
2	<b>Adakveo</b> (Crizanlizumab)	Prevention of vaso-occlusive crisis (VOD) in Sickle-cell Disease (SCD)	Crizanlizumab binds to Selectin-P and, hence contact with P-selectin glycoprotein 1 (PSGL-1) is prohibited. Blood platelet aggregates subsequently fail to form; and this maintains a normal blood flow [95].	FDA approval of Adakveo (Crizanlizumab) in 2019
3	<b>Rivipansel</b>	Treatment of VOD and SCD	All 3 selectins (E, L, and P) are targeted by Rivipansel; that blocks leukocyte rolling and decreases chances of growth of vascular occlusions.  Phase 1 and 2 clinical trials of Rivipansel in mouse [96] and humans [97] respectively, were successful.  Phase 3 clinical trials were unsuccessful in reaching optimal results, but it was found that early stage administration of the drug provided relief from VOC pain [98].	Rivipansel is not an FDA approved drug yet, but the FDA has granted it a Rare Pediatric Disease designation, qualifying it for further drug development.
4	<b>Uproleselan</b>	Treatment of Acute Myeloid Leukemia (AML)	Uproleselan (an E-selectin inhibitor), prevents the E-selectin from fastening to tumor cells, thus eliminating pathways vital for the survival of malignant cells.  Uproleselan in amalgamation with chemotherapy has shown promising outcomes in Phase 1 and 2 clinical trials of AML treatment [99]. Phase 3 clinical trials are ongoing and results are expected in 2023.	Uproleselan is not an FDA approved drug yet, but it has been granted Breakthrough Therapy Designation by the FDA, qualifying it for further drug development.

5	<b>Mylotarg</b>	Treatment of CD33 positive AML	It is a siglec targeting drug comprised of a DNA damaging agent Calicheamicin combined with an anti-CD33 monoclonal antibody (MAb). Upon interaction with CD33 expressing AML cells, it obstructed the growth of malignant cells [100].	Mylotarg was FDA approved in 2017.
6	<b>Herceptin</b> (Trastuzumab)	Treatment of Breast cancer and stomach cancer	Trastuzumab is the combination of an anti-HER2 antibody coupled to a sialidase (bacterial). In vitro studies of Trastuzumab treatment showed erasure of siglec ligands on tumor cells by desialylation and amplified affinity to Natural Killer Cells of the host [101].	Herceptin (Trastuzumab) was approved by FDA in 1998 for treatment of breast cancer.  Herceptin (Trastuzumab) was approved by FDA in 2010 for treatment of HER2-positive stomach cancer.
7	<b>Lirentelimab</b>	Treatment of Eosinophilic gastritis and duodenitis	It is a siglec targeting drug comprising of an anti-siglec8 MAb which suppresses mast cells and reduces levels of eosinophils.  It has successfully proven its efficacy in Phase 2 clinical trials in treating eosinophilic gastritis and duodenitis [102]. Phase 3 clinical trials are on-going with results expected in mid 2022.	Lirentelimab is not an FDA approved drug yet.
8	<b>Unituxin</b> (Dinutuximab)	Treatment of high-risk pediatric neuroblastoma	Dinutuximab is a MAb which binds to GD2 gangliosides on neuroblastoma cell surface. This interaction induced cell-mediated toxicity which resulted in lysis of neuroblastoma cells [103].	Unituxin (Dinutuximab) was approved by FDA in 2015
9	<b>Prennar and Synflorix</b>	Treatment of infections caused by <i>Streptococcus pneumoniae</i>	Prennar and Synflorix vaccines in combination with <i>Streptococcus pneumoniae</i> oligosaccharide glycoconjugates demonstrated immunostimulant activity and elicited a strong immune response to protect the body against pneumococcal infections [104].	Synflorix was approved by the EMA in 2009.  Prennar-13 was approved by the FDA in 2010.  Prennar-20 was approved by the FDA in 2021.
10	<b>Zavesca</b> (Miglustat)	Treatment of Gaucher Type-1 disease	Miglustat (imino-sugar) trials demonstrated it to inhibit the glucosylceramide synthase enzyme, subsequently preventing the glycosylation of ceramide in the first step of GSL synthesis [105].	Zavesca was approved by the FDA in 2003.  FDA further approved the use of generic Miglustat in 2018.

## Conclusion

In conclusion, this article sets out to demonstrate how glycosylation represents a novel therapeutic paradigm with great potential for transforming the landscape of age-related disease treatments. By unraveling the intricate language of glycans and their roles in aging biology, we hope to inspire further research and collaboration, ultimately paving the way for a new era of age-specific therapies that enhance the quality of life for the aging population.

In recent years, researchers have recognized the significance of glycosylation in various diseases, including cancer, infectious diseases, and autoimmune disorders. Glycosylation patterns can be altered in diseased states, making them attractive targets for therapeutic interventions.

A new age-targeted therapeutic approach involving glycosylation might involve:

- a. Glycan-based vaccines: Designing vaccines that target specific glycan structures on pathogens to trigger an immune response and prevent infection.
- b. Glycosylation inhibitors: Developing drugs that can inhibit specific enzymes involved in glycosylation to interfere with disease-related glycan modifications.
- c. Glycan-based therapies: Using glycans or glycan-binding proteins as therapeutic agents to modulate immune responses or cell signaling pathways.
- d. Personalized medicine: Tailoring glycosylation-targeted therapies based on an individual's glycan profile to improve treatment efficacy and reduce side effects.
- e. Glycosylation biomarkers: Identifying disease-specific glycan patterns as diagnostic or prognostic markers for early detection and monitoring of disease progression.

In conclusion, glycosylation is a promising area of research with the potential to open new avenues for age-targeted therapeutic approaches in various diseases. However, the specific conclusion of the article you mentioned would depend on the findings and data presented within the paper. To obtain the accurate conclusion, it's best to refer to the original article directly.

## Future prospects

As researchers continue to delve deeper into the field of glycosylation and its implications in aging biology and age-related diseases, several potential avenues and prospects emerge:

1. Identification of Novel Glycosylation Targets: Advancements in glycomics and glycoproteomics technologies will likely lead to the discovery of new glycosylation targets associated with age-related diseases. By understanding the specific glycan structures involved in disease pathogenesis, researchers can develop targeted therapies to modulate these glycans and potentially halt or reverse disease progression.
2. Glycosylation Biomarkers for Early Diagnosis: Glycosylation patterns can vary with age and disease status. As researchers uncover disease-specific glycan signatures, these glycans could serve as potential biomarkers for early disease detection and risk assessment. Early diagnosis can lead to timely interventions and improved patient outcomes.
3. Personalized Glycosylation-Based Therapies: With advancements in personalized medicine, it is conceivable that glycosylation profiles of individual patients could be analyzed, and tailored therapeutic strategies could be designed accordingly. Personalized glycosylation-based therapies hold the potential to optimize treatment efficacy while minimizing adverse effects.
4. Glycan-Targeted Vaccines: Glycosylation plays a crucial role in the interaction between pathogens and the immune system. Developing glycan-targeted vaccines could provide a new approach to prevent infectious diseases in the aging population, boosting their immune response to pathogens.
5. Glycoengineering and Therapeutic Innovation: Glycoengineering techniques, such as glycan synthesis and modification, have the potential to be harnessed for therapeutic purposes. Novel glycan structures or glycan-based molecules might be designed to exert specific effects on disease-related pathways, opening up new possibilities for drug development.
6. Combination Therapies: Glycosylation-based therapies could be combined with other treatments, such as traditional pharmaceuticals or gene therapies, to enhance their effectiveness. Synergistic approaches might provide more comprehensive and targeted interventions for age-related diseases.
7. Translation into Clinical Practice: As the understanding of glycosylation's role in aging and diseases deepens, there is potential for clinical trials and applications of glycosylation-based therapies. Moving from basic research to clinical implementation will be crucial for realizing the full potential of glycosylation-targeted treatments.
8. Regulatory Considerations: The development of glycosylation-based therapies will require careful consideration of regulatory aspects, including safety, efficacy, and potential side effects. Regulatory bodies will play a vital role in evaluating and approving such novel therapies.

The future prospects of this topic hold significant promise for transforming the landscape of age-related disease treatments. Continued research and collaboration in this field are likely to yield groundbreaking discoveries and innovative therapies that could enhance the health and well-being of the aging population. The exploration of glycosylation as a therapeutic approach opens up a new frontier in medicine, where intricate sugar molecules become powerful tools in the fight against age-related ailments.

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