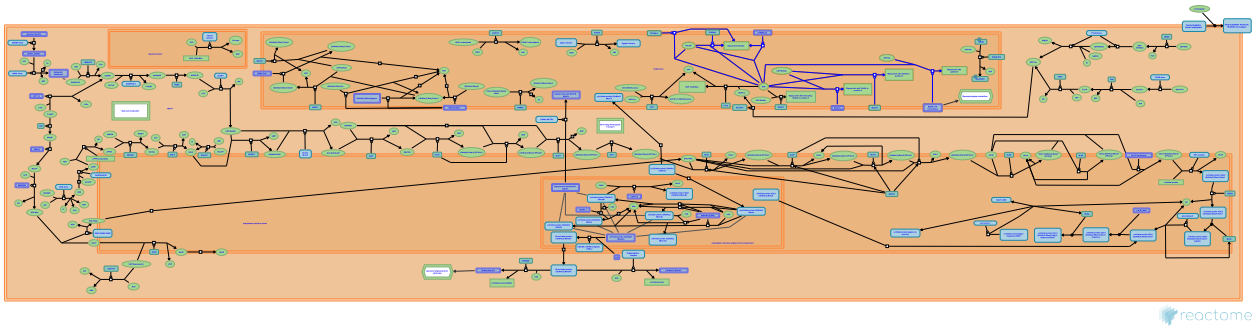
# N-Glycan antennae elongation



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# Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

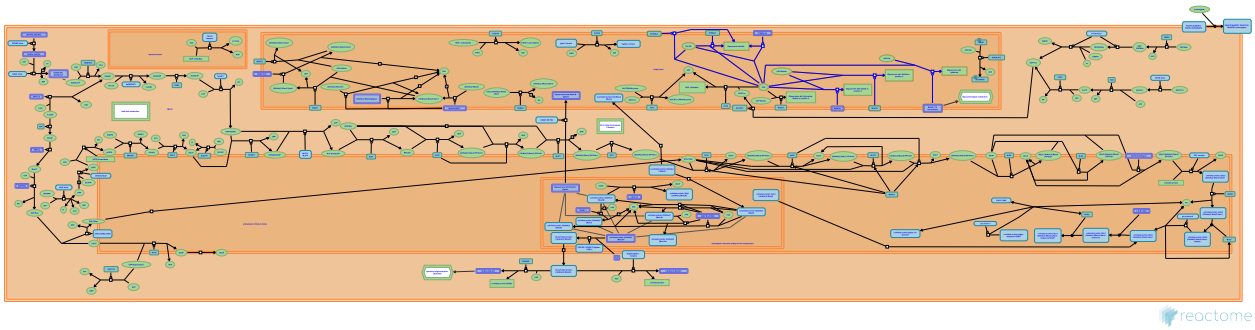
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

## N-Glycan antennae elongation ↗

**Stable identifier:** R-HSA-975577



N-glycans are further modified after the commitment to Complex or Hybrid N-glycans. The exact structure of the network of metabolic reactions involved is complex and not yet validated experimentally. Here we will show a generic reaction for each of the genes known to be involved in N-Glycosylation.
For a better annotation of the reactions and genes involved in the synthesis of Complex and Hybrid N-glycans we recommend the GlycoGene Database (Ito H. et al, 2010) (http://riodb.ibase.aist.go.jp/rcmg/ggdb/textsearch.jsp) for annotations of genes, and the Consortium for Functional Genomics (http://riodb.ibase.aist.go.jp/rcmg/ggdb/textsearch.jsp) for annotation of Glycan structures and reactions. Moreover, a computationally inferred prediction for the structure of this network is available through the software GlycoVis (Hossler P. et. al. 2006).

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Hu, WS., Lee, MM., Hossler, P., Goh, LT. (2006). GlycoVis: visualizing glycan distribution in the protein N-glycosylation pathway in mammalian cells. *Biotechnol Bioeng, 95*, 946-60. ↗

Ito, H., Narimatsu, H., Sato, T., Kameyama, A., Chiba, Y. (2010). In vitro and in vivo enzymatic syntheses and mass spectrometric database for N-glycans and o-glycans. *Methods Enzymol, 478*, 127-49. ↗


## Editions

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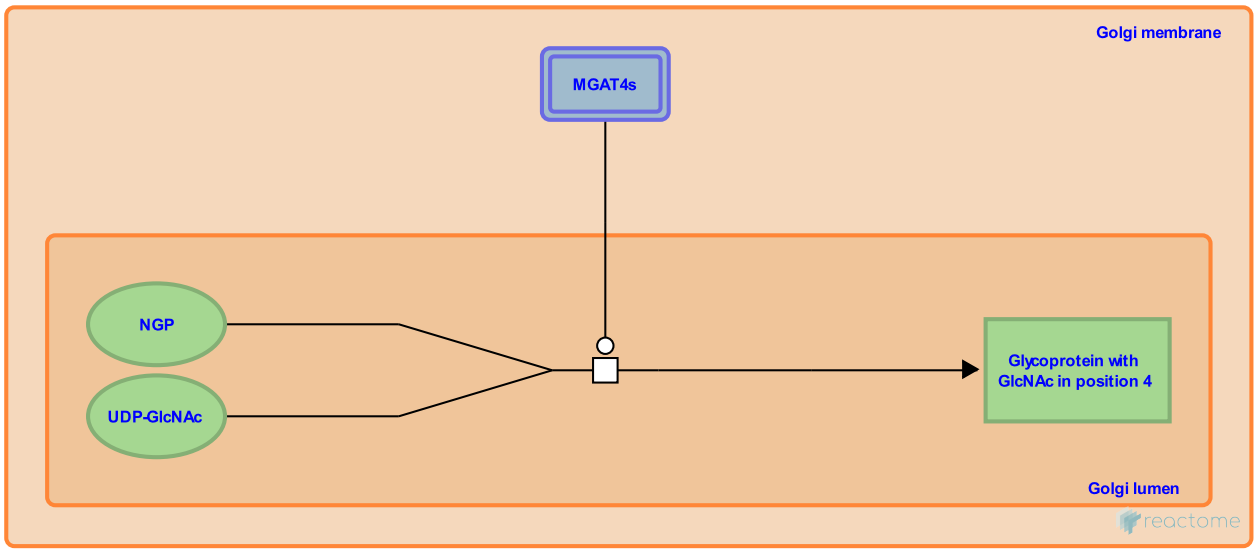
## Addition of GlcNAc to position 4 by N-acetylglucosaminyltransferase (GnT)-IV ↗

**Location:** N-Glycan antennae elongation

**Stable identifier:** R-HSA-975903

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane




N-acetylglucosaminyltransferase (GnT)-IV catalyzes the addition of GlcNAc beta,1,4 on the GlcNAc beta1,2 Man,alpha1,3 arm of both complex and hybrid N-glycans (Oguri S et al, 2006). Two human GnT-IV isozymes have been characterized (MGAT4A, MGAT4B) , plus a putative MGAT4C on chromosome 2 (Furukawa T et al, 1999). Aberrant expression of MGAT4A or MGAT4B is associated with pancreatic cancer (Ide Y et al, 2006; Kudo T et al , 2007)

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Hayashi, Y., Hoshi, M., Fukushige, S., Horii, A., Yokoyama, T., Inoue, H. et al. (1999). Cloning and characterization of the human UDP-N-acetylglucosamine: alpha-1,3-D-mannoside beta-1,4-N-acetylglucosaminyltransferase IV-homologue (hGnT-IV-H) gene. *J Hum Genet, 44*, 397-401. ↗

Deguchi, K., Nakagawa, T., Nakagawa, H., Kudo, T., Hamaguchi, J., Nishimura, S. et al. (2007). N-glycan alterations are associated with drug resistance in human hepatocellular carcinoma. *Mol Cancer, 6*, 32. ↗

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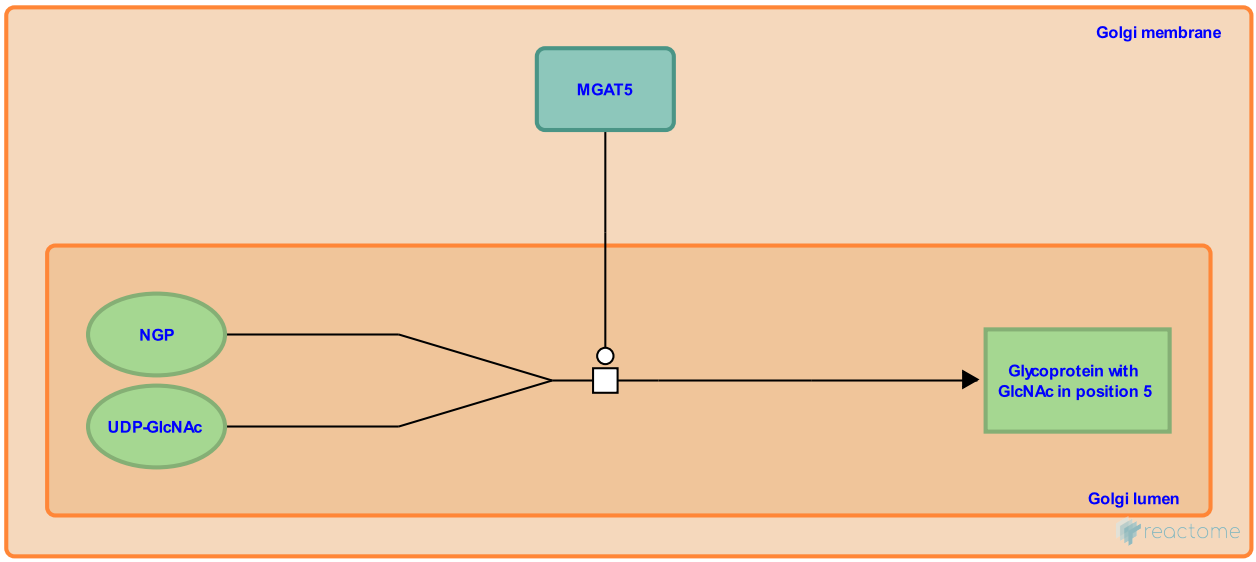
## Addition of GlcNAc to position 5 by MGAT5 ↗

**Location:** N-Glycan antennae elongation

**Stable identifier:** R-HSA-975916

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane




N-acetylglucosaminyltransferase (GnT)-V catalyzes the addition of GlcNAc beta 1,4 on the GlcNAc beta1,2 Man,alpha1,6 arm of complex type N-Glycans (Park C et al, 1999; Granowski M et al, 2000; Wang L et al, 2007). The activity of MGAT5 competes with MGAT3 (Pinho SS et al, 2009) and is associated with gastric cancer (Tian H et al, 2008) and multiple sclerosis (Brynedal B et al, 2010).

## Literature references


Tsujimoto, M., Miyoshi, E., Matsuura, N., Taniguchi, N., Ito, Y., Shaker, M. et al. (2008). The implication of N-acetylglucosaminyltransferase V expression in gastric cancer. *Pathobiology, 75*, 288-94. ↗

Magalhães, AM., Figueiredo, J., Carneiro, F., Xiaogang, W., Ferreira, AC., Gärtner, F. et al. (2009). The role of N-acetylglucosaminyltransferase III and V in the post-transcriptional modifications of E-cadherin. *Hum Mol Genet, 18*, 2599-608. ↗

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Martinelli-Boneschi, F., Brynedal, B., Edan, G., Comi, G., Wojcik, J., Hillert, J. et al. (2010). MGAT5 alters the severity of multiple sclerosis. *J Neuroimmunol, 220*, 120-4. ↗

Zha, X., Wu, G., Cai, X., Liang, Y., Zhang, W., Jin, J. et al. (2007). Increase in beta1-6 GlcNAc branching caused by N-acetylglucosaminyltransferase V directs integrin beta1 stability in human hepatocellular carcinoma cell line SMMC-7721. *J Cell Biochem, 100*, 230-41. ↗


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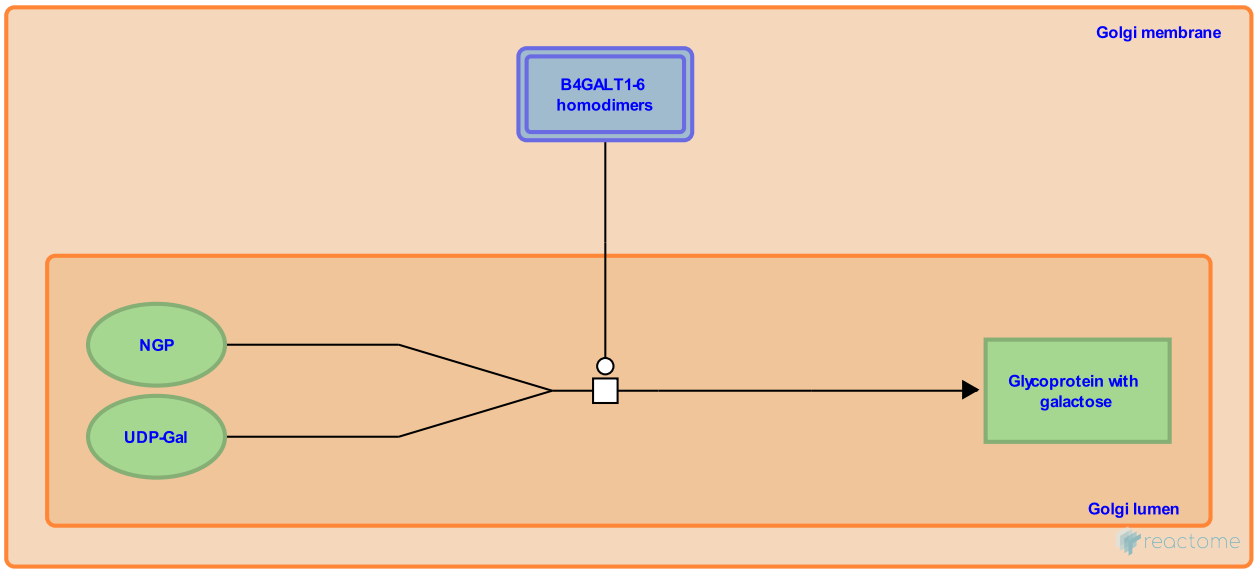
## Addition of galactose by beta 4-galactosyltransferases ↗

**Location:** N-Glycan antennae elongation

**Stable identifier:** R-HSA-975919

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane




Addition of a galactose residue on N-acetylglucosamine. The family of beta 4-galactosyltransferases is composed by at least six known members with different K(m) and acceptor specifities (Guo S et al, 2001) and probably originated by duplication (Lo NW et al, 1998). B4GALT1 is associated with Congenital Disorder of Glycosylation of type IId (Hansske B et al, 2002), and is expressed as two splicing isoforms of which only one is localizated in the Golgi system (Lopez LC et al, 1991; Schaub BE et al, 2006). B4GALT2 is key in the regulation of proteins involved in neuronal development (Sasaki N et
al, 2005).

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Rohrer, J., Berger, B., Berger, EG., Schaub, BE. (2006). Transition of galactosyltransferase 1 from trans-Golgi cisterna to the trans-Golgi network is signal mediated. *Mol Biol Cell, 17*, 5153-62. ↗

Hoffmann, GF., Lübke, T., Peters, V., Hansske, B., Körner, C., Heidemann, PH. et al. (2002). Deficiency of UDP-galactose:N-acetylglucosamine beta-1,4-galactosyltransferase I causes the congenital disorder of glycosylation type IId. *J Clin Invest, 109*, 725-33. ↗

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Shur, BD., Lopez, LC., Youakim, A., Evans, SC. (1991). Evidence for a molecular distinction between Golgi and cell surface forms of beta 1,4-galactosyltransferase. *J Biol Chem, 266*, 15984-91. ↗

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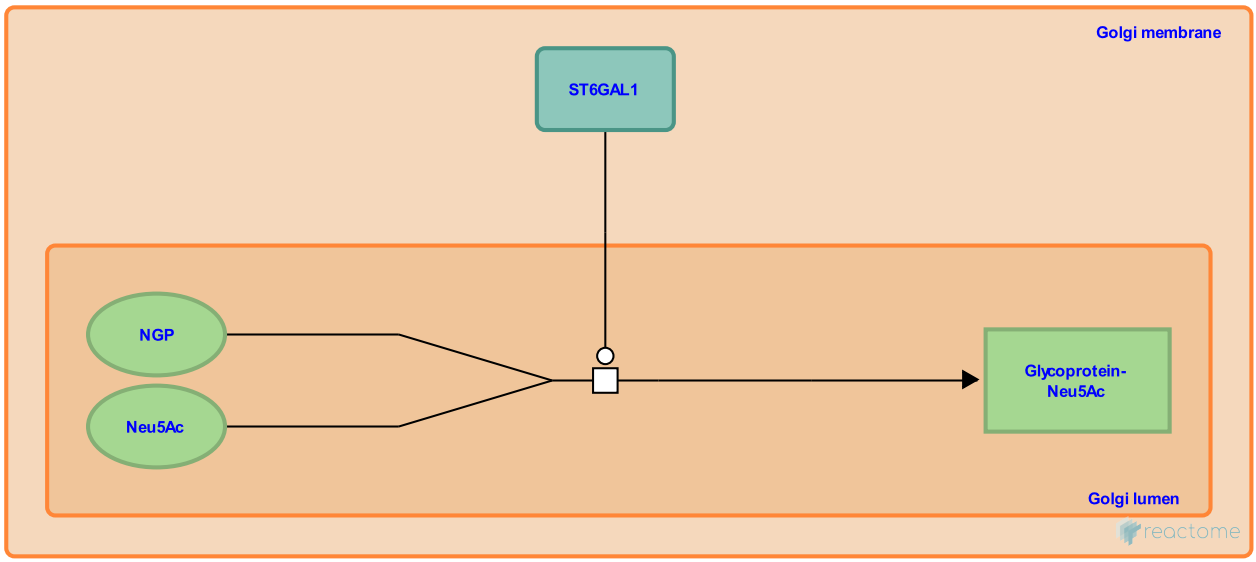
## ST6GAL1 transfers Neu5Ac to terminal Gal of N-glycans

**Location:** N-Glycan antennae elongation

**Stable identifier:** R-HSA-975902

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane




Addition of sialic acid to galactose-containing N-glycan. Sialic acid is usually found at terminal positions of the N-glycan. This imparts a negative charge at neutral pH which affects the chemico-physical and biological properties of the N-glycans (for review, see Schauer 2000); moreover, this modification can lead to the addition of extraordinarily long antennae such as polysialic acid (hundreds of sials) or polylactosamine repeats (dozens of disaccharide repeats) (Harduin-Lepers 2001), while the number of modifications on the antennae of N-glycans is usually lower.
There are over 20 sialyltransferases known in humans, 5 of which are known to act on N-glycans. Beta-galactoside alpha-2,6-sialyltransferase 1 (ST6GAL1) is the only sialyltransferase known to transfer sialic acid to galactose on N-Glycans (Dall'Olio 2000). A second beta-galactoside alpha-2,6-sialyltransferase has been characterized, but this enzyme acts mainly on oligosaccharides (Krzewinski-Recchi et al. 2003). Neu5Ac can also be added via an alpha-2,3-linkage to galactose on N-glycans by CMP-N-acetylneuraminate-beta-galactosamide-alpha-2,3-sialyltransferase 4 (ST3GAL4) (Ellies et al. 2002). ST8Sia II (ST8SIA2), ST8Sia III (ST8SIA3), and ST8Sia IV (ST8SIA6) have alpha-2,8-activity (Angata et al. 1997, Angata et al. 2000, Angata & Fuduka 2003).

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Vallejo-Ruiz, V., Harduin-Lepers, A., Delannoy, P., Samyn-Petit, B., Krzewinski-Recchi, MA., Julien, S. (2001). The human sialyltransferase family. *Biochimie, 83*, 727-37.

Fukuda, M., Suzuki, M., Hindsgaul, O., Angata, K., Ding, Y., McAuliffe, J. (2000). Differential biosynthesis of polysialic acid on neural cell adhesion molecule (NCAM) and oligosaccharide acceptors by three distinct alpha 2,8-sialyltransferases, ST8Sia IV (PST), ST8Sia II (STX), and ST8Sia III. *J Biol Chem, 275*, 18594-601.

Schauer, R. (2000). Achievements and challenges of sialic acid research. *Glycoconj J, 17*, 485-99.

Teintenier-Lelièvre, M., Harduin-Lepers, A., Mir, AM., Delannoy, P., Samyn-Petit, B., Cerutti, M. et al. (2003). Identification and functional expression of a second human beta-galactoside alpha2,6-sialyltransferase, ST6Gal II. *Eur J Biochem, 270*, 950-61.


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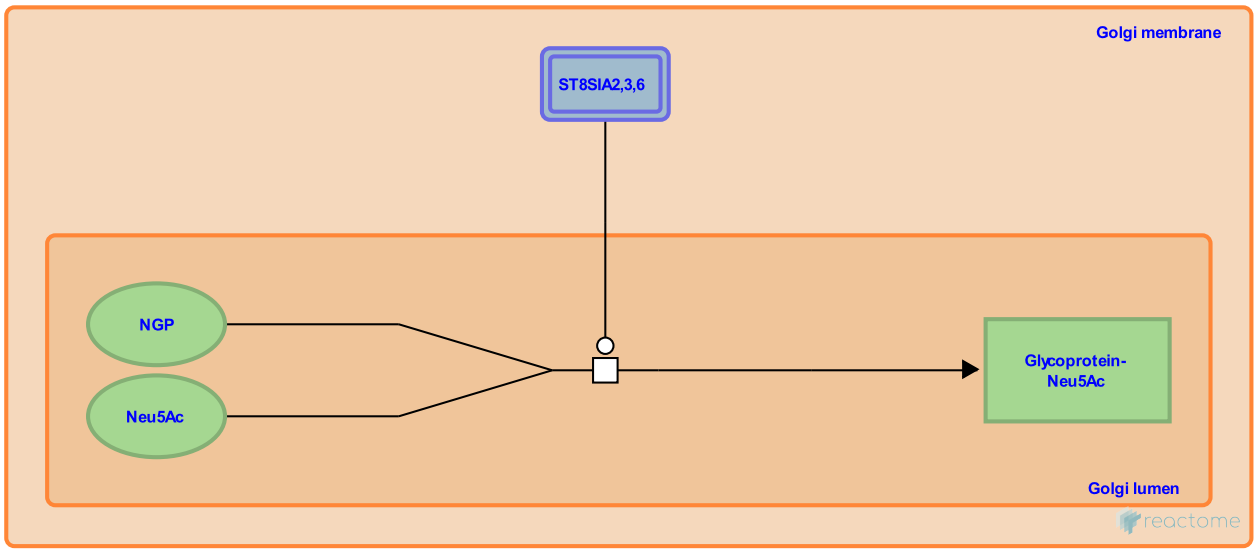
## ST8SIA2,3,6 transfer Neu5Ac to terminal Gal of N-glycans ↗

**Location:** N-Glycan antennae elongation

**Stable identifier:** R-HSA-1022133

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane




Addition of sialic acid (Neu5Ac) to galactose-containing N-glycan. Sialic acid is usually found at terminal positions of the N-glycan. This imparts a negative charge at neutral pH which affects the chemico-physical and biological properties of the N-glycans (for a review, see Schauer 2000); moreover, this modification can lead to the addition of extraordinarily long antennae such as polysialic acid (hundreds of sials) or polylactosamine repeats (dozens of disaccharide repeats) (Harduin-Lepers 2001), while the number of modifications on the antennae of N-glycans is usually lower.
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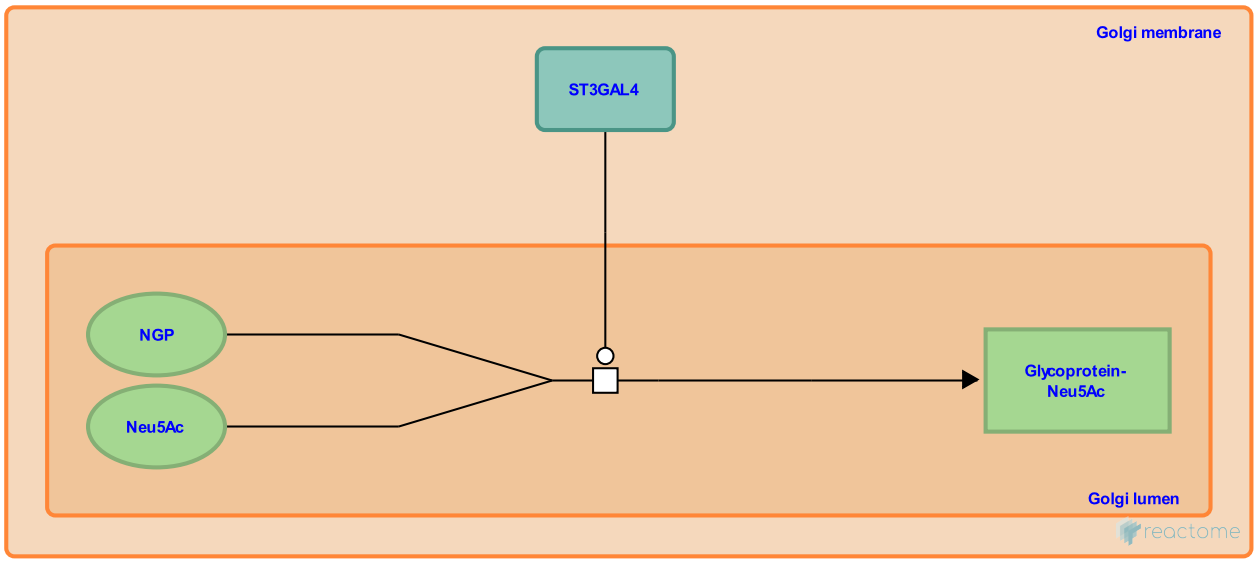
## ST3GAL4 transfers Neu5Ac to terminal Gal of N-glycans ↗

**Location:** N-Glycan antennae elongation

**Stable identifier:** R-HSA-1022129

**Type:** transition

**Compartments:** Golgi lumen, Golgi membrane




Addition of sialic acid (Neu5Ac) to galactose-containing N-glycan. Neu5Ac is usually found at terminal positions of the N-glycan. This imparts a negative charge at neutral pH which affects the chemico-physical and biological properties of the N-glycans (for a review, see Schauer 2000); moreover, this modification can lead to the addition of extraordinarily long antennae such as polysialic acid (hundreds of sials) or polylactosamine repeats (dozens of disaccharide repeats) (Harduin-Lepers 2001), while the number of modifications on the antennae of N-glycans is usually lower.
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Fukuda, M., Suzuki, M., Hindsgaul, O., Angata, K., Ding, Y., McAuliffe, J. (2000). Differential biosynthesis of polysialic acid on neural cell adhesion molecule (NCAM) and oligosaccharide acceptors by three distinct alpha 2,8-sialyltransferases, ST8Sia IV (PST), ST8Sia II (STX), and ST8Sia III. *J Biol Chem, 275*, 18594-601. ↗

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Teintenier-Lelièvre, M., Harduin-Lepers, A., Mir, AM., Delannoy, P., Samyn-Petit, B., Cerutti, M. et al. (2003). Identification and functional expression of a second human beta-galactoside alpha2,6-sialyltransferase, ST6Gal II. *Eur J Biochem, 270*, 950-61. ↗

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