## Proposed EC/sub-subclass

2.4.1.102

## Accepted name

Core 2 beta-1,6-N-acetylglucosaminyltransferase

## Phylogeny

GCNT1 is a conserved enzyme with orthologs in mammals such as mice, rats, and cattle, highlighting its essential role in mucin-type O-glycosylation pathways. It shares significant sequence identity with isoenzymes like Core2GlcNAcT-III, indicating preserved catalytic mechanisms among core-branching glycosyltransferases. Phylogenetic studies place GCNT1 within glycosyltransferases involved in O-glycan elongation and branching, conserved across metazoans (PubMed: 1329093, 23027862).

## Glycosyltransferase family

GT14

## Reaction Catalyzed

GCNT1 catalyzes the transfer of an N-acetylglucosamine (GlcNAc) unit from UDP-GlcNAc to the 6-hydroxyl group of the galactose residue in a mucin-type core 1 O-glycan, forming the core 2 structure:  
UDP-GlcNAc + Galβ1-3GalNAcα-Ser/Thr → UDP + Galβ1-3(GlcNAcβ1-6)GalNAcα-Ser/Thr (PubMed: 1329093, 23027862).

## Cofactor Requirements

GCNT1 operates independently of metal ions, unlike many glycosyltransferases that require divalent metal ions for activity (PubMed: 1329093, 23027862).

## Substrate Specificity

GCNT1 specifically acts on mucin-type core 1 O-glycan motifs, Galβ1-3GalNAc linked to serine or threonine residues. It can also transfer GlcNAc to glycolipid substrates like GalGb4Cer globosides, contributing to SSEA-1 determinant synthesis (PubMed: 1329093, 23027862).

## Structure

GCNT1 is a type II transmembrane protein with a short N-terminal cytosolic tail, a transmembrane domain, a stem region, and a large lumenal catalytic domain. The catalytic domain adopts a GT-A fold, characterized by a central mixed β-sheet flanked by α-helices. Key residues include Cys217 and Glu320, essential for catalysis and substrate activation (PubMed: 1329093, 23027862).

## Regulation

GCNT1 expression is regulated by transcription factors like Sp1 and cytokines such as IL-2, IL-4, and IL-15. Its localization to the Golgi is mediated by signals in its transmembrane and stem domains. N-linked glycosylation sites contribute to its stability and retention within Golgi membranes (PubMed: 1329093, 23027862).

## Function

GCNT1 synthesizes mucin-type core 2 O-glycans, crucial for generating selectin ligands like sialyl Lewis X, essential for leukocyte adhesion and extravasation. It is expressed in various tissues, notably in leukocytes, and influences immune cell function and inflammatory responses (PubMed: 1329093, 23027862).

## Disease relevance

Increased GCNT1 expression is associated with aggressive tumor behavior in cancers such as colorectal, prostate, and lung carcinomas. It affects cell adhesion, migration, and immune interactions. Dysregulation of GCNT1-mediated glycosylation is linked to immune-related syndromes and congenital disorders of glycosylation (PubMed: 1329093, 23027862).

## Other Comments

GCNT1’s substrate flexibility extends to glycolipid substrates, contributing to glycoconjugate diversification. Its metal ion-independent catalytic mechanism distinguishes it from other glycosyltransferases, highlighting a specialized catalytic strategy within the GT-A fold (PubMed: 1329093, 23027862).

## References

1. PubMed: 1329093
2. PubMed: 23027862