



## 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.

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## Literature references

- 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. [↗](#)

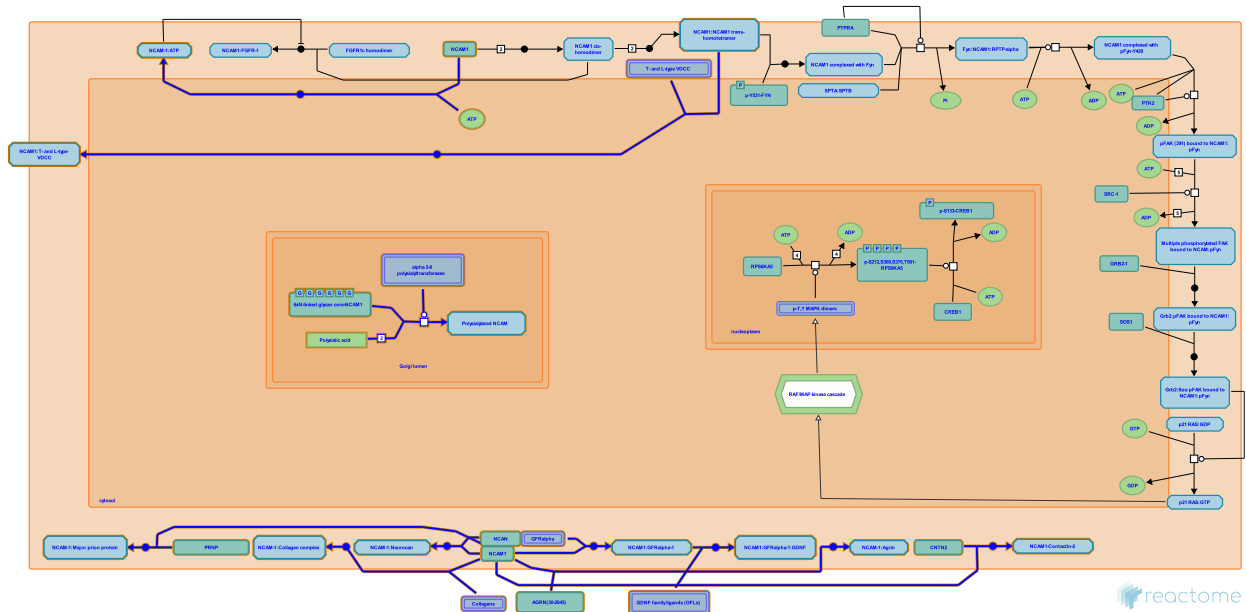
Reactome database release: 88

This document contains 1 pathway and 10 reactions ([see Table of Contents](#))

## NCAM1 interactions ↗

**Stable identifier:** R-HSA-419037

**Compartments:** plasma membrane



The neural cell adhesion molecule, NCAM1 is generally considered as a cell adhesion mediator, but it is also considered to be a signal transducing receptor molecule. NCAM1 is involved in multiple cis- and trans-homophilic interactions. It is also involved in several heterophilic interactions with a broad range of other molecules, thereby modulating diverse biological phenomena including cellular adhesion, migration, proliferation, differentiation, survival and synaptic plasticity.

### Literature references

Nielsen, J., Kulahin, N., Walmod, PS. (2008). Extracellular Protein Interactions Mediated by the Neural Cell Adhesion Molecule, NCAM: Heterophilic Interactions Between NCAM and Cell Adhesion Molecules, Extracellular Matrix Proteins, and Viruses. *Neurochem Res.* ↗

Walmod, PS., Kolkova, K., Berezin, V., Bock, E. (2004). Zippers make signals: NCAM-mediated molecular interactions and signal transduction. *Neurochem Res*, 29, 2015-35. ↗

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

## Interaction of NCAM1 with GFRalpha-1 ↗

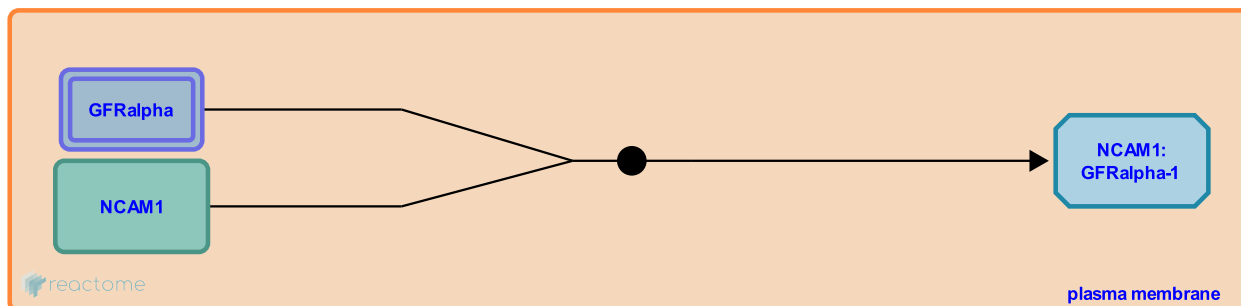
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375149

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [Interaction of NCAM1 with GFRalpha-1 \(Rattus norvegicus\)](#)



GFRalpha receptors GFRalpha1 and possibly also GFRalpha2 and GFRalpha4 subunit of the GDNF (glial cell line-derived neurotrophic factor) receptor interact in cis with NCAM and functions as a coreceptor for GDNF in the absence of RET. The NCAM1-GFRalpha1 interaction down regulates NCAM1-mediated cell adhesion and promotes GDNF-NCAM1 binding.

**Followed by:** [Interaction of NCAM1:GFRalpha-1 with GDNF](#)

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

## Interaction of NCAM1:GFRalpha-1 with GDNF ↗

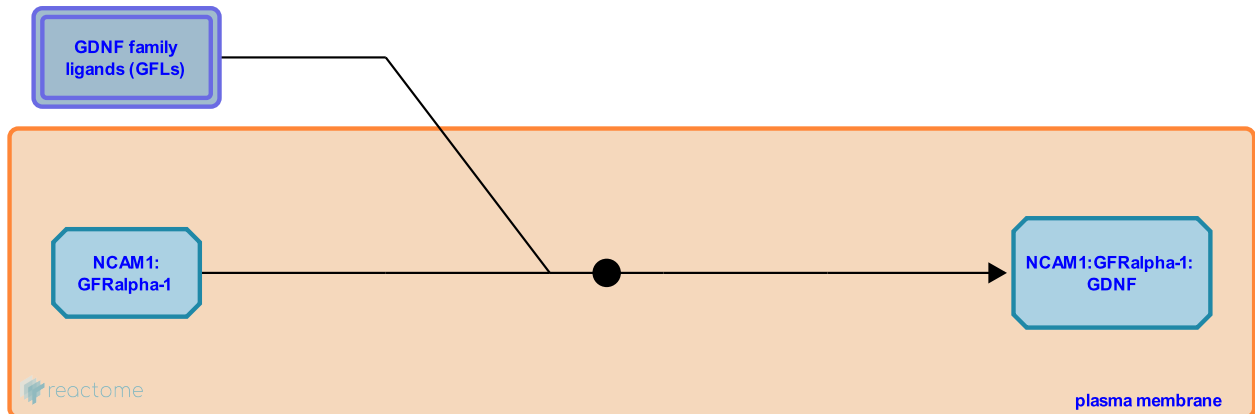
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375144

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [Interaction of NCAM1:GFRalpha-1 with GDNF \(Rattus norvegicus\)](#)



NCAM was identified as an alternative signaling receptor for GDNF family ligands (GFLs). The GFLs is a small group of soluble neurotrophic growth factors involved in neuronal survival, neurite growth and differentiation. Four members are known in the family including GDNF, Neurturin (NTN), Persephin (PSP), and Artemin (ART). NCAM, in collaboration with GFR $\alpha$  receptors, function as a signaling receptor for these GFLs. Signaling downstream of GDNF binding to the NCAM-GFR $\alpha$ 1 complex activates Fyn-FAK-MAPK signaling pathway and mediates long-range intercellular communication.

**Preceded by:** [Interaction of NCAM1 with GFRalpha-1](#)

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

## Interaction of NCAM1 with Neurocan ↗

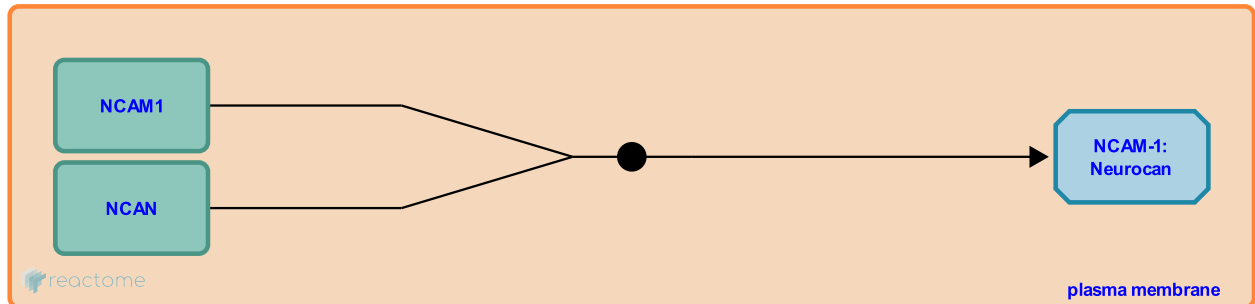
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375148

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [Interaction of NCAM-1 with Neurocan \(Rattus norvegicus\)](#)



NCAM1 bind all major components of neurocan (N-terminal, central and C-terminal regions as well as CS chains), a brain-specific chondroitin sulfate proteoglycan. This molecule interferes with homophilic NCAM1 interactions and inhibits neuronal adhesion and neurite outgrowth.

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
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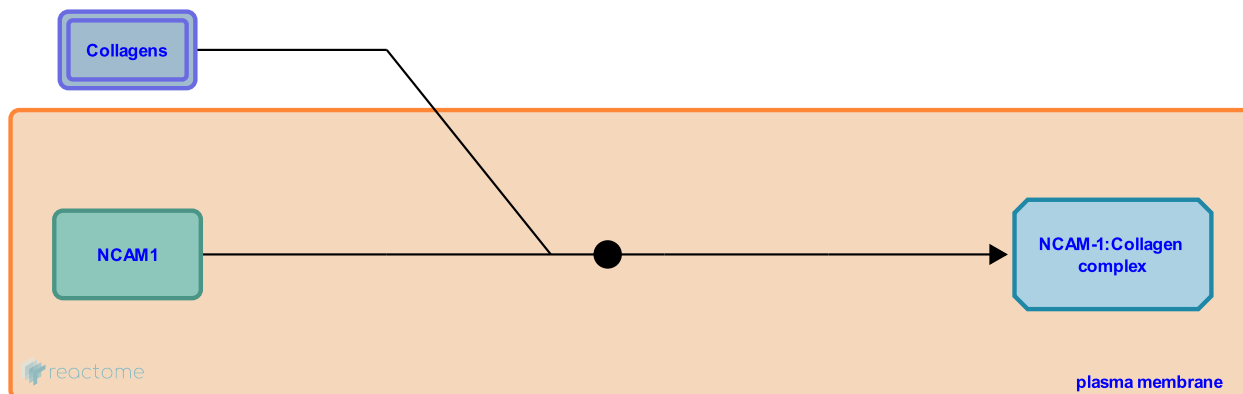
## Interaction of NCAM1 with collagens [↗](#)

**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375151

**Type:** binding

**Compartments:** plasma membrane, extracellular region



NCAM1 interacts with several extracellular matrix proteins. NCAM1 has been reported to bind collagens I-IV and IX.

### Literature references

Nielsen, J., Kulahin, N., Walmod, PS. (2008). Extracellular Protein Interactions Mediated by the Neural Cell Adhesion Molecule, NCAM: Heterophilic Interactions Between NCAM and Cell Adhesion Molecules, Extracellular Matrix Proteins, and Viruses. *Neurochem Res.* [↗](#)

Kuhn, K., Probstmeier, R., Schachner, M. (1989). Binding properties of the neural cell adhesion molecule to different components of the extracellular matrix. *J Neurochem*, 53, 1794-801. [↗](#)

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
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## Interaction of NCAM1 with Major prion protein (PrP) ↗

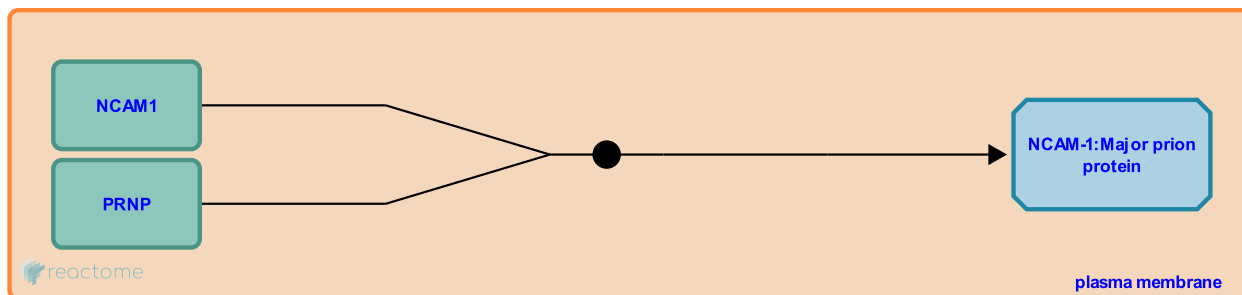
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375154

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [NCAM1 binds Major prion protein \(PrP\) \(Mus musculus\)](#)



Prion protein (PrP) is a GPI-anchored protein predominately localized in lipid rafts. NCAM1 is one of the membrane localized proteins that binds PrP. PrP is thought to bind NCAM1 at the IgV, F3I and/or F3II domains in an interaction not involving the various carbohydrate moieties of NCAM1. The functional relevance of this interaction is unknown, but may be related to the effects of PrP on activation and proliferation of haemopoietic cells expressing NCAM1.

### Editions

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## Interaction of NCAM1 with agrin ↗

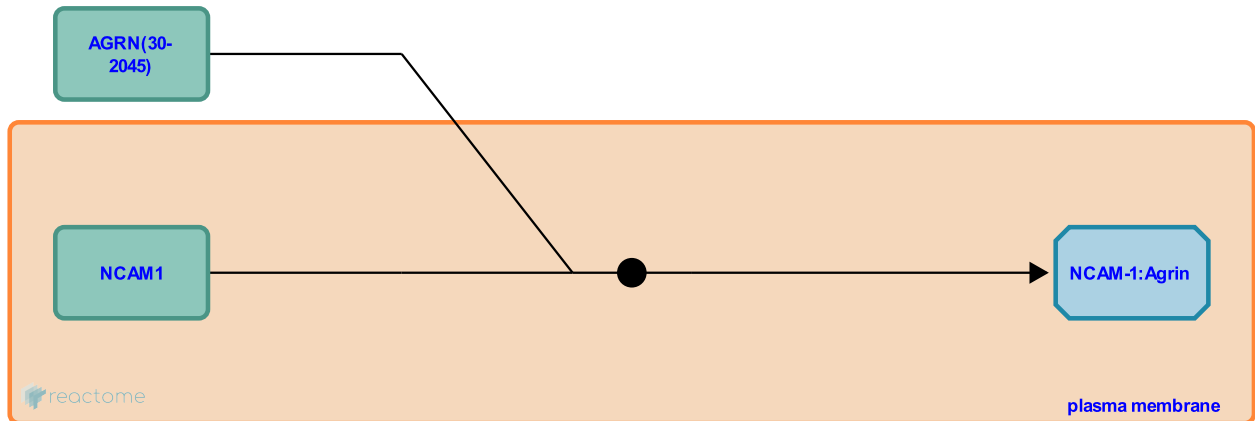
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375155

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [Interaction of NCAM1 with agrin \(Gallus gallus\)](#)



Agrin, a Heparin Sulfate Proteoglycan (HSPG), plays a role in synaptogenesis and axonal growth. It interacts with NCAM1 both via NCAM's heparin binding domain in the IgII domain and through polysialic acid on the IgV domain.

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
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## Interaction of NCAM1 with contactin-2 [↗](#)

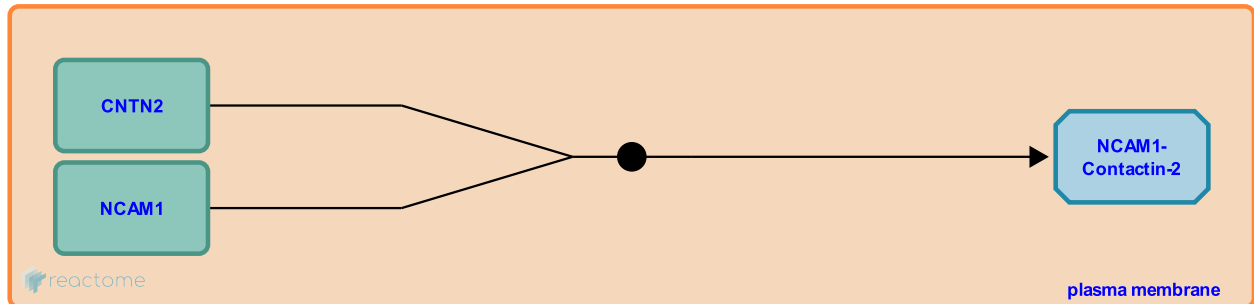
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375157

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [Interaction of NCAM1 with contactin-2 \(Gallus gallus\)](#)



NCAM1 binds with high affinity to the neuronal IgSF receptor, contactin-2/TAG-1/axonin-1.

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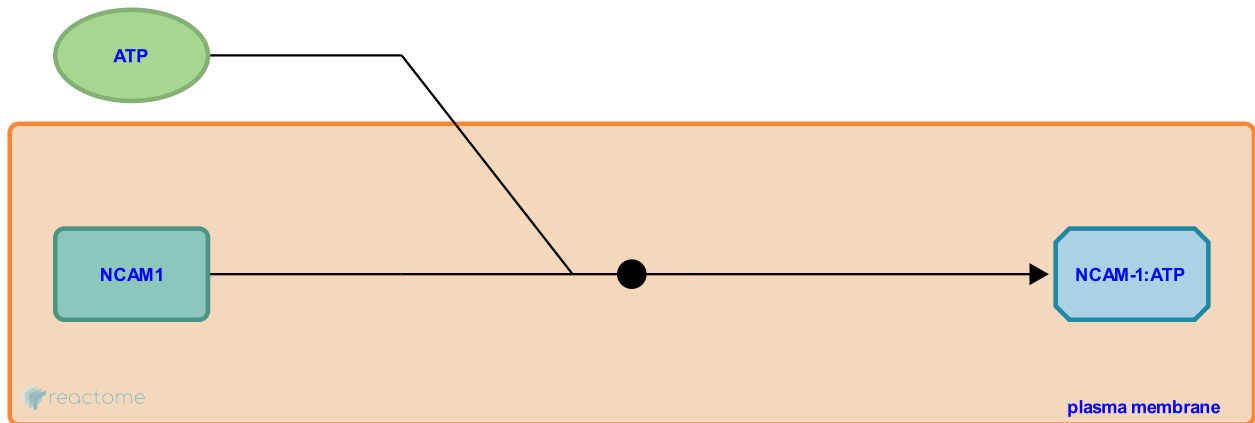
## NCAM1 binds to ATP ↗

**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-375160

**Type:** binding

**Compartments:** plasma membrane, extracellular region



NCAM1 has been demonstrated to possess ( $\text{Ca}^{++}$  or  $\text{Mg}^{++}$ ) dependant ATP hydrolyzing activity. ATP can bind to NCAM directly and that NCAM can act as an ecto-ATPase hydrolyzing around 1000 molecules of ATP/minute. Binding of ATP to NCAM1 inhibits cellular aggregation and neurite outgrowth induced by NCAM1-FGFR binding. The NCAM binding site to ATP overlaps with the site of NCAM-FGFR interaction, and ATP is capable of disrupting NCAM-FGFR binding.

### Literature references

Dzhandzhugazyan, K., Bock, E. (1997). Demonstration of an extracellular ATP-binding site in NCAM: functional implications of nucleotide binding. *Biochemistry*, 36, 15381-95. ↗

Dzhandzhugazyan, K., Bock, E. (1993). Demonstration of ( $\text{Ca}^{2+}$ - $\text{Mg}^{2+}$ )-ATPase activity of the neural cell adhesion molecule. *FEBS Lett*, 336, 279-83. ↗

### Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

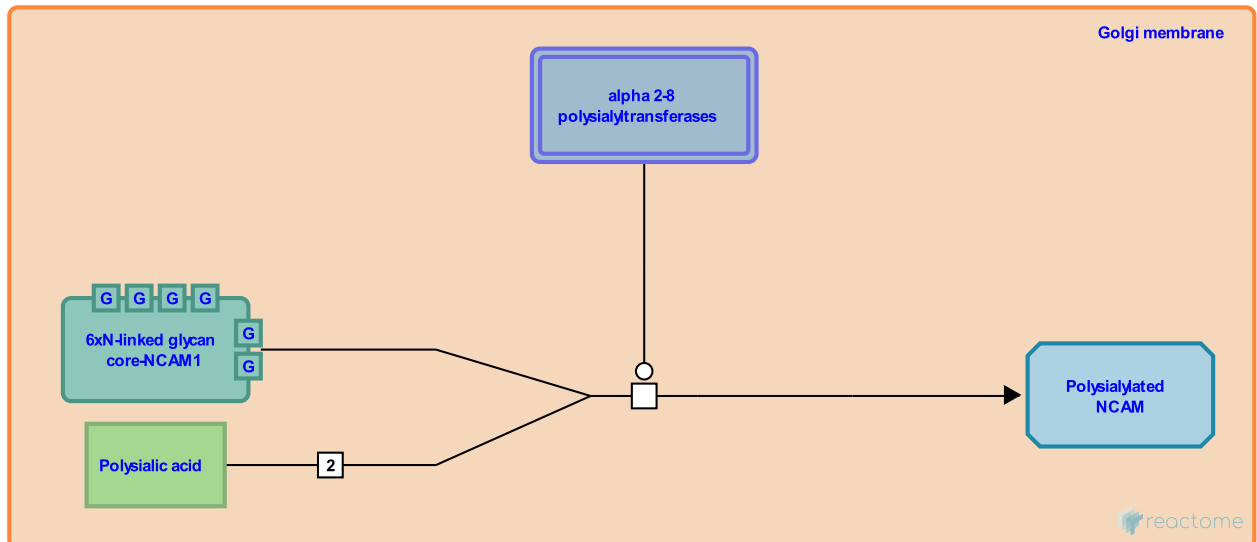
## Polysialylation of NCAM1 [↗](#)

**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-422454

**Type:** transition

**Compartments:** Golgi membrane



NCAM in the developing brain is highly polysialylated and is referred as the embryonic form of NCAM. Polysialic acid is a developmentally regulated, anti-adhesive glycan with a linear homopolymer of alpha2,8-linked sialic acid units. They are mainly attached to the fifth and sixth N-glycosylation sites of the fifth Ig-like domain of NCAM. Polysialylation of NCAM is catalyzed by two polysialyltransferases, ST8Sia II (STX) and ST8Sia IV (PST), which belong to the family of six genes encoding alpha2,8-sialyltransferases. These enzymes add polysialic acid to NCAM N-glycans until it reaches a certain size (up to 200 sialic acid residues), where neither enzyme can interact with polysialylated N-glycans, and the polymerization of sialic acid is terminated.

Due to the structure with its chemical nature, polysialic acid can attenuate the interaction of NCAM with NCAM and other molecules in the same membrane (cis-interaction) or in another cell membrane (trans-interaction). During axonal growth the presence of polysialic acid along axons seems to prevent inappropriate synapse formation.

### Literature references

Marth, JD., Röckle, I., Hildebrandt, H., Mühlhoff, M., Schertzinger, F., Seidenfaden, R. et al. (2005). Genetic ablation of polysialic acid causes severe neurodevelopmental defects rescued by deletion of the neural cell adhesion molecule. *J Biol Chem*, 280, 42971-7. [↗](#)

Rutishauser, U. (2008). Polysialic acid in the plasticity of the developing and adult vertebrate nervous system. *Nat Rev Neurosci*, 9, 26-35. [↗](#)

Fukuda, M., Angata, K. (2003). Polysialyltransferases: major players in polysialic acid synthesis on the neural cell adhesion molecule. *Biochimie*, 85, 195-206. [↗](#)

### Editions

2009-05-26	Reviewed	Maness, PF., Walmod, PS.
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## NCAM1 interacts with T- and L-type VDCC ↗

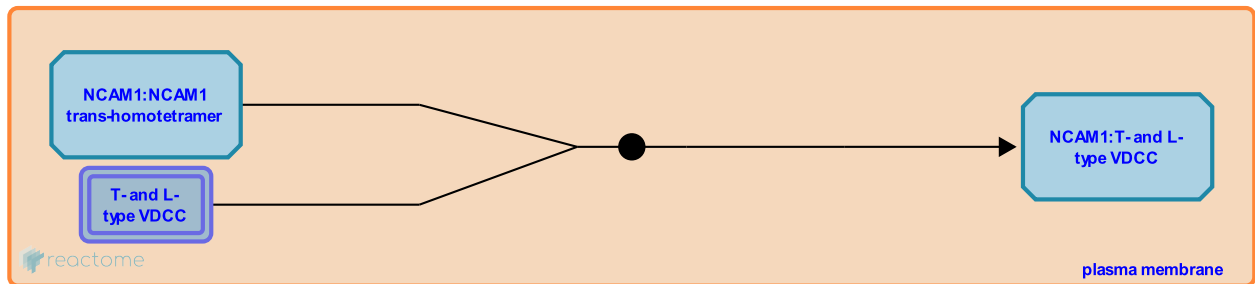
**Location:** [NCAM1 interactions](#)

**Stable identifier:** R-HSA-525833

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** [NCAM1 interacts with T- and L-type VDCC \(Mus musculus\)](#)



NCAM1 associates with T- and L-type voltage-dependent  $\text{Ca}^{+2}$  channels (VDCC) in growth cones at the sites of NCAM1 clustering. This interaction leads to the NCAM-dependent  $\text{Ca}^{+2}$  influx to the cell.

### Editions

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