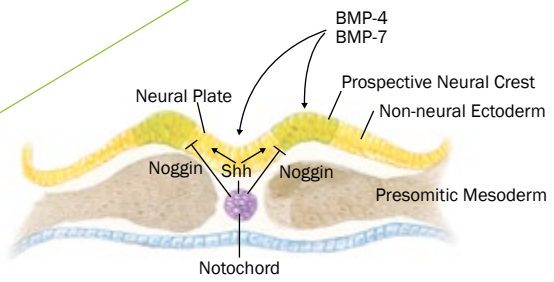
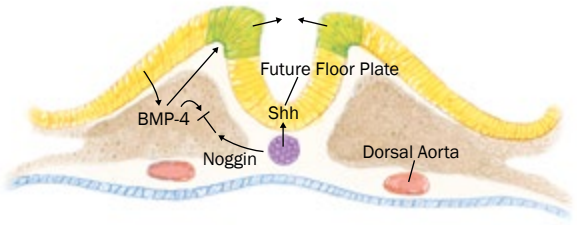
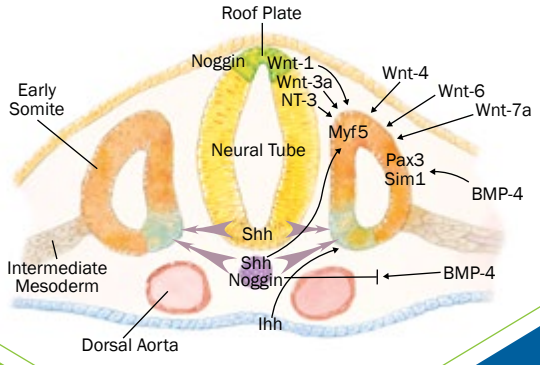
bio-techne®

Morphogen Research







R&D SYSTEMS®

TOCRIS®

Morphogens

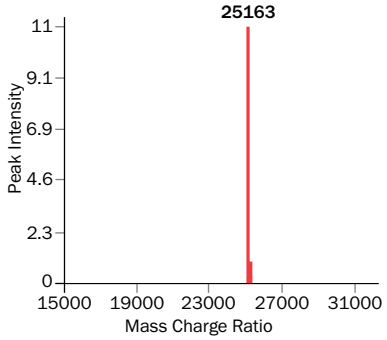
Morphogens are molecules that regulate cell fate during development. Formation of morphogen concentration gradients directs the biological responses of surrounding cells. Graded activation or inactivation of morphogen-specific signaling pathways provides positional information that ultimately determines tissue organization and morphology. Morphogens have been shown to regulate dorso-ventral and anterior-posterior axis formation, anterior-posterior polarity during limb development, mesoderm patterning, and numerous other processes that establish an organism's basic body structure. These processes are directed by proteins belonging to the Wingless/Wnt, Notch, Hedgehog, and TGF-β families of morphogen. R&D Systems offers a wide selection of proteins, antibodies, ELISAs, and small molecules from Tocris Bioscience for morphogen-related developmental research.

TGF-β Superfamily

The Transforming Growth Factor Beta (TGF-β) superfamily consists of TGF-β proteins, Bone Morphogenetic Proteins (BMPs), Growth Differentiation Factors (GDFs), Glial-derived Neurotrophic Factors (GDNFs), Activins, Inhibins, Nodal, Lefty, and Müllerian Inhibiting Substance (MIS). Many of these molecules act as morphogens during embryonic development. Ligands of the TGF-β superfamily form dimers that bind to heterodimeric receptor complexes consisting of type I and type II receptor subunits with serine/ threonine kinase domains. Following ligand binding, the type II receptor phosphorylates and activates the type I receptor, initiating a Smad-dependent signaling cascade that induces or represses transcriptional activity. During development, members of the TGF-β family are required for dorso-ventral patterning, mesoderm induction and patterning, limb bud formation, bone and cartilage formation, neuron differentiation, and the development of a variety of different tissues and organs.

World Class Purity for Worry-Free Experimentation

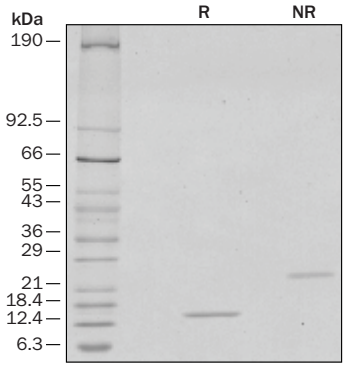
Our TGF-β superfamily proteins are highly pure and, at minimum, must meet our industry-leading endotoxin specification (< 0.1 EU/μg).



GDF-11/BMP-11 Purity Confirmed by Mass Spectrometry. ESI analysis of Recombinant Human/Mouse/Rat GDF-11/BMP-11 (Catalog # 1958-GD) shows a peak at 25163 Da, corresponding to the calculated molecular mass of the disulfide linked homodimer, 25163 Da.

Ligands are Dimerized for Maximum Bioactivity

All of our TGF-β superfamily ligands are produced and tested with rigorous quality standards to guarantee that they form bioactive homo- or heterodimers.



Activin A Dimerization Verified by SDS-PAGE. 1 μg/lane of Recombinant Human/Mouse/Rat Activin A (Catalog # 338-AC) was resolved with SDS-PAGE. Under reducing (**R**) conditions the Activin A monomer is shown as a 14 kDa band. Under non-reducing (**NR**) conditions the Activin A homodimer resolves as a 24 kDa band.

TGF-β Superfamily Heterodimers: Exclusive Availability

Molecule	BMP-2/7	BMP-4/7	BMP-2/6	Activin AC
Species	Human	Human	Human	Human
ED_{50}	10–40 ng/mL	15–75 ng/mL	4–20 ng/mL	0.8–4 nM
Catalog #	3229-BM	3727-BP	7145-BP	4879-AC

Products for TGF-β Research

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
Activin A	H M R	H M R	H M R	
Activin AB	H			
Activin B	H M	H		
Activin C	H M	H M		
Activin RIA/ALK-2	H M	H		Yes
Activin RIB/ALK-4	H M	H M		Yes
Activin RIIA	H M	H		Yes
Activin RIIA/B		H		
Activin RIIB	H M	H		
ALK-1	H M	H M	H M	Yes
ALK-7	R	H R		Yes
Amnionless	H	H M		
BAMBI/NMA	H M	H M		
BMP-1/PCP	H	H		Yes
BMP-2	H M R Z	H Z	H M R	
BMP-2/BMP-4		H Z		
BMP-2a	Z			
BMP-3	H	H		
BMP-3b/GDF-10	H	H		
BMP-4	H M Z	H M Z	H	
BMP-5	H M	H M	H	
BMP-6	H M	H M	H	
BMP-7	H M	H M	H	
BMP-8		H		
BMP-8a	H M			
BMP-8b		H M		
BMP-9	H M	H M	H M	
BMP-10	H M	H M		
BMP-15/GDF-9B	H	H M R		
BMPR-IA/ALK-3	H M	H		Yes
BMPR-IB/ALK-6	H M	H M		Yes
BMPR-II	H M	H		
Cerberus 1	M	H M		
Chordin	M	M	M	
Chordin-like 1/CHRDL1	H	H		
Chordin-like 2/CHRDL2	M	H M		
COCO	H M	H M	H	
CRIM1	H M	H		
Cripto	H M	H M	H	Yes
Crossveinless-2/CV-2	H M	H M		
Cryptic	H	H M		
DAN	H M	H M	H M	
Decorin	H M	H M	H M	
Dermatopontin	H M	H		
Endoglin/CD105	H M R P	H M R	H M	
Follistatin	H M	H M	H	
Follistatin-like 1/FSTL1	H M	H M R	H	
Follistatin-like 4/FSTL4	H	H M R		
Follistatin-related Gene Protein/FLRG	H M	H M	H	
GDF-1	H	H M		
GDF-3	H M	H M		
GDF-5/BMP-14	H M	M	M	

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
GDF-6/BMP-13	M	M		
GDF-7/BMP-12	H M	M		
GDF-8/Myostatin	H M R	H M R	H M	
GDF-9	H M	H M		
GDF-11/BMP-11	H M R	H M R		
GDF-11/GDF-8		H M R		
GDF-15	H	H M	H M R	
GDNF	H R	H R	H	
GFRα-1/GDNF Rα-1	H R	H R		
GFRα-2/GDNF Rα-2	H M	H M		
GFRα-3/GDNF Rα-3	H M	H M		
GFRα-4/GDNF Rα-4		H M		
Gremlin	H M	M	M	
Inhibin α	H M	H		
Lefty		H M		
Lefty-1	M	M		
Lefty-2		M		
Lefty-A	H	H		
MIS/AMH	H	H M R	H	
MIS RII	H R	H R	H	
Nodal	H M	H M		
Noggin	H M	M		
PDK-1	H	H M R		Yes
Persephin	H M	H M	H	
PRDC/GREM2	H M	M	M	
Ret	H M	H M	H	Yes
RGM-A	H M	H M Ch	H M R	
RGM-B	H M	H M	H	
RGM-C/Hemojuvelin	H M	H M	H M R	
Smad1		H	H M	
Smad2		H M D		
Smad2/3		H M		
Smad3		H M		Yes
SOST/Sclerostin	H M	H M	H M R	
Syndecan-3	H M	H M	H	
TGF-β		M		Yes
TGF-β1	H M P E	H M	H M R P Ca	
TGF-β1, 2, 3		M		
TGF-β1.2	H	M		
TGF-β1/1.2		M		
TGF-β2	H M P	M	H M R P Ca	
TGF-β2/1.2		M		
TGF-β3	H	M	H	
TGF-β5	A	M		
Latent TGF-β bp1		H		
Latent TGF-β bp2/LTBP-2		H		
Latent TGF-β bp4	H	M		
TGF-β RI/ALK-5	H M	H M		Yes
TGF-β RII	H M	H M	H	
TGF-β RIII	H M	H M	H	
TSG	H M	M		
Tsukushi/TSK	H	H M		
USAG1	H	H		

Species Key: H Human **M** Mouse **R** Rat **A** Amphibian **Ca** Canine **Ch** Chicken **D** *Drosophila* **E** E quine **P** Porcine **Z** Zebrafish

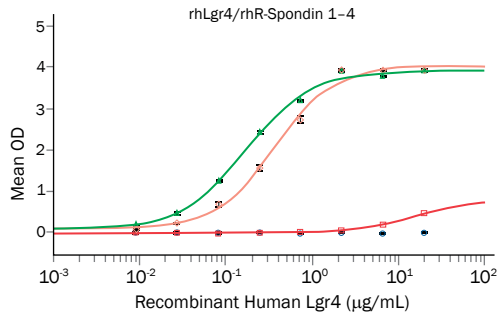
Wnt Family

Wnt signaling pathways have a central role in many processes involved in embryonic development and adult tissue homeostasis. The biological effects of Wnt ligands are mediated through an increasingly complex interplay of Wnt receptors, transmembrane regulators, and soluble inhibitors. The combination of these proteins are critical in determining whether a particular Wnt ligand will initiate beta-Catenin-dependent or -independent signaling cascades. R&D Systems is globally recognized as providing the highest quality and largest selection of Wnt reagents on the market, including difficult-to-isolate Wnt ligands, our selection of recently discovered transmembrane regulators of Wnt (RNF43, ZNRF3, LGR 4–6, and TROY), our range of Wnt-related antibodies, and Tocris small molecules that target the Wnt pathway.

Cutting Edge Research from R&D Systems

Lgr4–6 Show Different R-Spondin Binding Preferences and Affinities

A.



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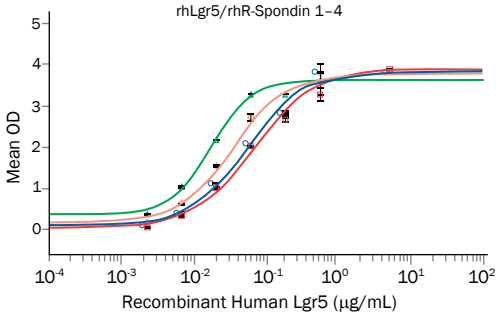

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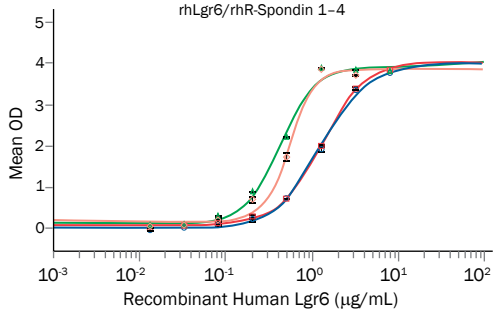


D.

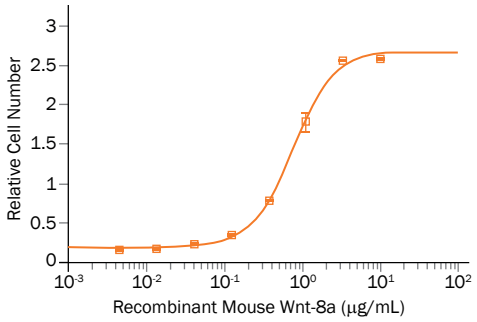
		rhLgr4	rhLgr5	rhLgr6
rhR-Spondin 1		No binding	2.1 nM	21.9 nM
rhR-Spondin 2		No binding	2.6 nM	22.0 nM
rhR-Spondin 3		6.6 nM	0.66 nM	5.8 nM
rhR-Spondin 4		14.5 nM	1.4 nM	7.7 nM

Analysis of Lgr Receptor Affinity for R-Spondin. Binding Activity of Recombinant Human (rh)Lgr4, rhLgr5, and rhLgr6 to rhR-Spondin 1 (blue), rhR-Spondin 2 (red), rhR-Spondin 3 (green), and rhR-Spondin 4 (peach) was analyzed using ELISA. **(A)** Binding curves of rhLgr4 with rhR-Spondins 1–4. **(B)** Binding curves of Lgr5 with rhR-Spondins 1–4. **(C)** Binding curves of Lgr6 with rhR-Spondins 1–4. **(D)** Table of dissociation constants (Kd) for all Lgr/R-Spondin combinations tested.

Most Extensive Offering of Wnt Reagents

Molecule	Proteins	Antibodies
Wnt-1		M
Wnt-2		H
Wnt-2b	M	H M
Wnt-3a	H M	H M
Wnt-4	H M	H M
Wnt-5a	H M	H M R
Wnt-5b	H M	M
Wnt-7a	H	H
Wnt-7b		H
Wnt-8a	M	M
Wnt-8b		H M
Wnt-9a	M	H
Wnt-9b	M	H M
Wnt-10b	H M	H M
Wnt-16b	H	

Species Key: H Human **M** Mouse **R** Rat



Recombinant Mouse Wnt-8a Activates Osteoblast Differentiation of Mouse Mesenchymal Stem Cells. Addition of Recombinant Mouse (rm)Wnt-8a (Catalog # 8419-WN) to C3H10T1/2 mouse mesenchymal stem cells induced osteoblast differentiation as quantified with a dose responsive increase in alkaline phosphatase production. In this assay the typical ED_{50} rmWnt-8a ranges from 0.5–2.5 µg/mL.

Products for Wnt Research

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
APC		H		
ASCL2/Mash2		H		
Axin-1		H M R		
Axin-2		H H		
β-Catenin		H M R	H M	Yes
Bcl-9		H		
Bcl9-2		H		
Calcineurin	H			Yes
CaM Kinase II		H M R B Ch X		Yes
CaM Kinase IIα, δ, γ		H M R B Ch X		Yes
Casein Kinase 1α, γ, δ, ε		H M R		Yes
Casein Kinase 2α, β		H		Yes
Ccd1/DIXDC1		M		
c-Fos		H		
Cripto	H M	H M	H	Yes
Dishevelled-1, -2, -3		H		
Dkk-1	H M R	H M R	H M	
Dkk-2	H M	M		
Dkk-3	H	H M	H	
Dkk-4	H M	H M	H	
Draxin	H M	H M R		
Frizzled-1	H M	H M		
Frizzled-2	H M	H M		
Frizzled-3		H M		
Frizzled-4	H M	H M		
Frizzled-5	H	H		
Frizzled-6		H M		
Frizzled-7	H M	H M		
Frizzled-8	H M	M		
Frizzled-9	M	M		
Frizzled-10	H			
Glypican 1	H M	H		
Glypican 2	H M	H M		
Glypican 3	H M	H	H	
Glypican 5	H M	H M		
Glypican 6	H	H M		
GSK-3α/β		H M R	H M R	Yes
GSK-3α		H M R	H M R	Yes
GSK-3β	H	H M R	H M R	Yes
ICAT		H		
IGFBP-4	H M	H	H	
JNK		H M R	H M R	Yes
JNK1/JNK2		H M R		Yes
JNK1	M	H M R	H M R	Yes
JNK2, 3		H M R	H M R	Yes
JunB		H		Yes
c-Jun		H M	H M R	
Kremen-1	M	H M	M	
Kremen-2	H M R	H M		
Lgr4/GPR48	H M	H		
Lgr5/GPR49	H	H M		

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
LRP-1		H		
LRP-1 Cluster II, III	H	H		
LRP-1 Cluster IV	H			
LRP-4	H	H R		
LRP-5	M	H		
LRP-6	H M	H M		
MESDC2	M	H M		
MFRP	H	H M		
MKK7		H		
MuSK		H R		
Myocilin		H		
NeuroD1		H M		
Norrin	H M	H M		Yes
PKCα		H M R		
PKCβ1		H R		Yes
PKCβ2		H M		Yes
PKCγ		H M R		
PKCε		H M R		Yes
PKCδ	H	H		Yes
PKCι/λ		H M R		Yes
PKCι/λ/ζ		H M R		Yes
PKCθ		H M		
Pygopus-1		H M		
Pygopus-2		H		
ROCK1	H	H M R		Yes
ROCK2		H M R		Yes
ROR1		H	H	
ROR2	H	H	H	
R-Spondin 1	H M	H M	H	
R-Spondin 2	H M	H		
R-Spondin 3	H M	H M	H M	
R-Spondin 4	H M	M	H	
Ryk	H M	H M		
sFRP-1	H	H		Yes
sFRP-2, -3	H M	H M		
sFRP-4	H	H		
sFRP-5	H M	H	H	
Shisa-4		H M		
Soggy-1/DkkL1	H M	H M	M	
SOST/Sclerostin	H M	H M	H M R	
Syndecan-1/CD138	H M	H M	H	
Syndecan-2, -3	H M	H M		
Syndecan-4	H M	H	H	
TAK1		H		Yes
Tiki1/TRABD2A		H		
USAG1	H	H		
Vang-like Protein 1/VANGL1		H		
Vang-like Protein 2/VANGL2		H M R		
WIF-1	H M	H M	H	
ZNRF3	H M			

Species Key: H Human **M** Mouse **R** Rat **B** Bovine **Ch** Chicken **X** *Xenopus*

Hedgehog Family

The Hedgehog family is represented by at least three members: Desert hedgehog (Dhh), Indian hedgehog (Ihh), and Sonic hedgehog (Shh). Hedgehog signaling occurs through two transmembrane proteins, Patched (Ptc) and Smoothened (Smo). In the absence of the Hedgehog ligand, Ptc inhibits Smo activity, and downstream target genes are inactivated by a processed form of the transcriptional repressor, Cubitus interruptus (Ci) in Drosophila, or Gli-1, -2, or -3 in vertebrates, which have context-dependent repressor/activator functions. Shh signaling in vertebrates is involved in diverse areas of development, including patterning of the central nervous system, somite, and limb.

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
β-TrCP1/BTRC		H		
BOC	H	H M		
C2CD3		H		
CDO	H	H M		
Desert Hedgehog/Dhh	H M	M		
DISP1		H		
DISP2		H		
Gas1	H M	H M	H M	
GLI-1		H M		Yes
GLI-2		H M		Yes
GLI-3		H M		Yes
Glypican 3	H M	H	H	

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
GSK-3α/β		H M R	H M R	Yes
GSK-3α		H M R	H M R	Yes
GSK-3β	H	H M R	H M R	Yes
Hip	M	M	M	
Indian Hedgehog/Ihh	H M	H M		
LIN-41		H		
Patched 1/PTCH		H M		Yes
Patched 2/PTCH2		H M		Yes
SCUBE3	H			
Sonic Hedgehog/Shh	H M	H M	H M	

Species Key: H Human **M** Mouse **R** Rat

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FGF Family

The Fibroblast Growth Factor (FGF) superfamily of proteins consists of at least 18 members that are grouped into six subfamilies based on sequence similarity and functional characteristics. A seventh group of numbered FGFs (FGF-11–14, known as FGF homologous factors) have high sequence and structural homology with the FGFs, but do not bind to FGF receptors. During development, FGF signaling regulates multiple processes, including patterning of the midbrain and hindbrain, branching morphogenesis, limb, lung, and heart formation, and kidney development.

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
α2-Macroglobulin	H	H M	H	
α2-Macroglobulin-like 1	H			
FGF acidic	H M B	H M B	H M	
FGF basic	H M R B Ca E	H B	H M R	Yes
FGF-3	H	H		
FGF-4	H M	H M	H	
FGF-5	H	H		
FGF-6	H M	H M		
KGF/FGF-7	H M Ca	H Ca	H	
FGF-8	H M	H M		
FGF-9	H M	H	H	
FGF-10	H M R	H M		
FGF-11		H		
FGF-12	H	H		
FGF-13		H		
FGF-15		M		
FGF-16	H	H		
FGF-17	H M	H		
FGF-19	H	H	H	
FGF-20	H	H		
FGF-21	H M	H M	H M R	
FGF-22	H	H		

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
FGF-23	H M	H M	H	
FGF-BP	H R	H R	H	
FGF R1-4		H		Yes
FGF R1	H	H	H	Yes
FGF R1α	H	H		Yes
FGF R1β	H	H		Yes
FGF R2	H M	H M	H	Yes
FGF R2α	H M	H	H	Yes
FGF R2β	H M	H		Yes
FGF R3	H M	H M	H	Yes
FGF R4	H M	H M	H	Yes
FGF R5/FGFRL1	M	H M		Yes
FRS2		H M R	H M R	
Golgi Glycoprotein 1/GLG1		H M R		
Klotho	H M	H M	H	
Klotho β	H M	H M	H	
Pentraxin 3/TSG-14	H M	H M	H M	
Shisa-4		H M		
SPRY1		H		
SPRY2		H M		
SPRY3		H		

Species Key: H Human **M** Mouse **R** Rat **B** Bovine **Ca** Canine **E** Equine

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Notch Family

Notch receptors (Notch 1-4) are single-pass transmembrane proteins composed of a large extracellular domain that is non-covalently linked to a smaller transmembrane and intracellular domain. Invertebrate Notch ligands include Delta, Serrate, and Lag2 (DSL), while their DSL counterparts in mammals include Delta-like (DLL)-1, -3, -4, Jagged 1, and Jagged 2. Notch receptor activation requires a direct cell-cell interaction of the receptor's extracellular domain with the extracellular domain of a Notch ligand. Additional integral membrane, GPI-linked, and secreted proteins have also been reported to be Notch ligands. Notch signaling is highly conserved in multicellular organisms and is important for specifying cell fates, regulating pattern formation, and defining boundaries between different cell types during early development. It is required for vasculogenesis, angiogenesis, hematopoiesis, somatogenesis, myogenesis, and neurogenesis.

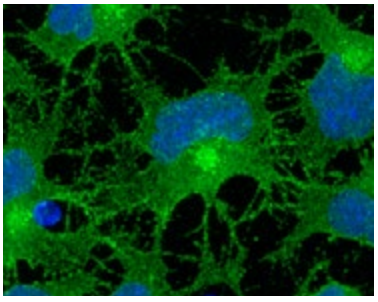
Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
ADAM10	H M	H M		Yes
APH1A		H		
ASCL2/Mash2		H		
CBP		H M R		Yes
Contactin-1	H	H M R		
Contactin-6	H M	M		
DLL1	H M R	H M R	H	
DLL3		H		
DLL4	H M	H M	M	
DNER	H M	H M		
DTX1		H		
FBXW7/Cdc4		H		
FIH-1/HIF-1AN		H M		
Furin	H M	H	H	Yes
HES-1		H		
HES-4		H		
Jagged 1	H R	H M R	H R	
Jagged 1/Jagged 2		H M		
Jagged 2	H M	H M		
MAGP-1/MFAP2		M		
MAGP-2/MFAP5	H M	H		
MFNG		H		
Mind Bomb 1/MIB1		H M R		

Molecule	Proteins	Antibodies	ELISAs	Tocris Small Molecules
Netrin-1	H M Ch	H M R Ch		
Nicastrin		H		
Notch-1	H M R	H M R	H	
Notch-2	H M R	H M R		
Notch-3	H M	H M		
Notch-4		H		
NOV/CCN3	H M	H M	H M	
NRARP		H M		
Numb		H H	H M R	
Periostin/OSF-2	H M	H M	H M	
Pref-1/DLK1/FA1	H M	H M	H	
Presenilin-1		H	H	
Presenilin-2		H		
PSENEN		H		
RFNG		H		
Secretase Inhibitors				Yes
γ-Secretase				Yes
TACE/ADAM17	H M	H	H	
Thrombospondin-2	H	H	H	
Thrombospondin-3	H			
Thrombospondin-4	H M	H M		
Tsukushi/TSK	H	H M		

Species Key: H Human **M** Mouse **R** Rat **Ch** Chicken

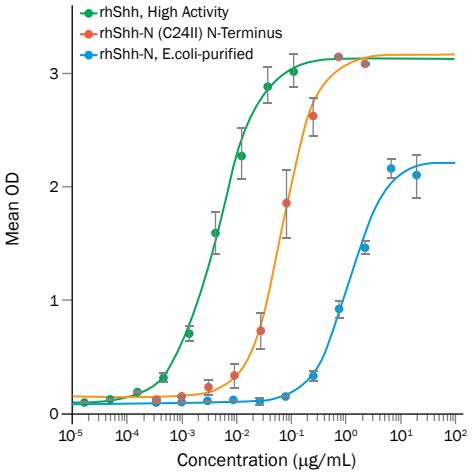
Mouse/Rat Notch-1 Antibody: Characterized for Multiple Applications

Applications	Recommended Concentration	Comments
Western Blot	0.1 µg/mL	Binding assay against Recombinant Rat Notch 1 Fc Chimera (Catalog # 1057-TK)
Flow Cytometry	2.5 µg/10^6 cells	Rat cortical stem cells
Blockade of Receptor-ligand Interaction	1–3 µg/mL	At 20 µg/mL this antibody will block > 80% of the binding.
Immunocytochemistry	5–15 µg/mL	See data
Immunohistochemistry	5–15 µg/mL	Immersion fixed paraffin-embedded sections of rat embryo (13 d.p.c.)

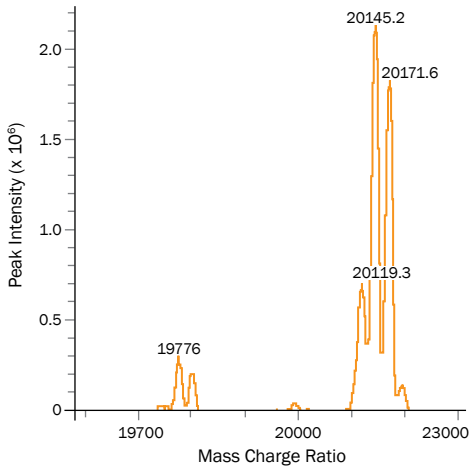


Notch-1 in Rat Cortical Stem Cells. Notch-1 was detected in immersion fixed undifferentiated rat cortical stem cells using Goat Anti-Mouse/Rat Notch-1 Antigen Affinity-purified Polyclonal Antibody (Catalog # AF1057) at 10 µg/mL for 3 hours at room temperature. Cells were stained using the NorthernLights™ 493-conjugated Anti-Goat IgG Secondary Antibody (green; Catalog # NL003) and counterstained with DAPI (blue). Specific staining was localized to cell surfaces.

Naturally-modified Human Sonic Hedgehog/Shh: Highest Bioactivity on the Market



Naturally-modified Recombinant Human Shh is Over 200-fold More Active than other Available Shh Proteins. Recombinant Human Shh proteins induce alkaline phosphatase production when added to mouse mesenchymal stem cells. Recombinant Human Shh, High Activity (Catalog # 8908-SH; green), purified from HEK293 cells and containing the correct post-translational modifications, is over 14-fold more active than E. coli-purified Recombinant Human Shh-N (C24II) N-Terminus (Catalog # 1845-SH; red line), and over 200-fold more active than E. coli-purified Recombinant Human Shh-N (Catalog # 1314-SH; blue line).



Post-translational Modification Analysis of Naturally-modified Recombinant Human Shh. LC/ESI-MS analysis of Recombinant Human (rh)Shh, High Activity (Catalog # 8908-SH) shows mass peaks at 20119 and 20145 Da, indicating that rhShh is modified with a single cholesterol molecule at the C-terminus. The peak at 20172 Da indicates that rhShh is also modified with a single fatty acid at the N-terminus. The small mass peak at 19776 Da corresponds to rhShh modified with only cholesterol.