

ErbB family

Overview: ErbB family receptors (ENSF00000000164, provisional nomenclature) are cell-surface receptors, which, when activated by members of the epidermal growth factor (EGF) family, activate a transmembrane tyrosine kinase activity (E.C. 2.7.1.112) leading to the stimulation of multiple signal transduction pathways (see Yarden and Sliwkowski, 2001). ErbB2 (also known as HER-2 or NEU, ENSG00000141736) appears to act as an essential partner for the other members of the family without itself being activated by a cognate ligand (Graus-Porta *et al.*, 1997). Ligands of the ErbB family of receptors are peptides including EGF (ENSG00000138798), amphiregulin (also known as colorectal cell-derived growth factor, ENSG00000109321), betacellulin (ENSG00000174808), epigen (ENSG00000182585), epiregulin (ENSG00000124882), heparin-binding EGF-like growth factor (HB-EGF or diphtheria toxin receptor, ENSG00000113070), neuregulins (NRG-1, also known as Neu differentiation factor, acetylcholine receptor-inducing activity, heregulin or glial growth factor, ENSG00000157168; NRG-2, ENSG00000158458; NRG-3, ENSG00000185737 and NRG-4, ENSG00000169752) and transforming growth factor- α (TGF α , ENSG00000163235). These ligands appear to be generated by proteolytic cleavage of cell-surface peptides.

Nomenclature	ErbB1	ErbB3	ErbB4
Other names	EGF, HER1	HER3	HER4
Ensembl ID	ENSG00000146648	ENSG00000065361	ENSG00000178568
Agonists	EGF, amphiregulin, betacellulin, epigen, epiregulin, HB-EGF, TGF α	NRG-1, NRG-2	Betacellulin, epiregulin, HB-EGF, NRG-1, NRG-2, NRG-3, NRG-4
Probes	[¹²⁵ I]-EGF	—	—

The extracellular domain of ErbB2 can be targeted by the antibodies trastuzumab and pertuzumab to inhibit ErbB family action. The intracellular ATP-binding site of the tyrosine kinase domain can be inhibited by GW583340 (7.9–8.0, Gaul *et al.*, 2003), gefitinib, erlotinib and typhostins AG879 and AG1478.

Abbreviations: **Erlotinib**, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, also known as OSI774; **gefitinib**, N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine, also known as ZD1839; **GW583340**, N-(3-chloro-4-[[3-fluorophenyl]methoxy]phenyl)-6-(2-[(2-[methylsulfonyl]ethyl)amino]methyl)-4-thiazolyl)-4-quinazolinamine dihydrochloride; **tyrphostin AG1478**, N-(3-chlorophenyl)-6,7-dimethoxyquinazolin-4-amine hydrochloride; **tyrphostin AG879**, α -cyano-(3,5-di-*t*-butyl-4-hydroxy)thiocinnamide

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GDNF family

Overview: GDNF family receptors (provisional nomenclature, ENSF00000001137) are glycosylphosphatidylinositol-linked cell-surface receptors, which, when activated by members of the glial cell-derived neurotrophic factor (GDNF) family, activate a transmembrane tyrosine kinase enzyme, Ret (ENSG00000165731). The endogenous ligands are typically dimeric, linked through disulphide bridges: glial cell line-derived neurotrophic factor (GDNF; 211 aa, ENSG00000168621); neurturin (197 aa, ENSG00000171119); artemin (237 aa, ENSG00000117407) and persephin (156 aa, ENSG00000125650).

Nomenclature	GFR α 1	GFR α 2	GFR α 3	GFR α 4
Other names	GDNF, GDNF family receptor α 1	Neurturin, GDNF family receptor α 2	Artemin, GDNF family receptor α 3	Persephin, GDNF family receptor α 4
Ensembl ID	ENSG00000151892	ENSG00000168546	ENSG00000146013	ENSG00000125861
Potency order	GDNF > neurturin > artemin	Neurturin > GDNF	Artemin	Persephin
Probes	[¹²⁵ I]-GDNF (3–63 pM, Treanor <i>et al.</i> , 1996; Klein <i>et al.</i> , 1997)	—	—	—

Mutations of Ret and GDNF genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

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Natriuretic peptide

Overview: Natriuretic peptide receptors (provisional nomenclature) are homodimeric, catalytic receptors with a single TM domain and guanylyl cyclase (EC 4.6.1.2) activity on the intracellular domain of the protein sequence. Isoforms are activated by the peptide hormones α -atrial natriuretic peptide (ANP, ENSG00000175206), brain natriuretic peptide (BNP, ENSG00000120937) and type C-natriuretic peptide (CNP, ENSG00000163273). Another family member is the receptor for guanylin (ENSG00000113389) and uroguanylin (ENSG00000044012). Family members have conserved catalytic and regulatory domains, but divergent ligand-binding domains. The NPR3 receptor has an extracellular binding domain homologous to that of the NPR1 and 2 receptors, but with a truncated intracellular domain which appears to couple, *via* the $G_{i/o}$ family of G-proteins, to activation of phospholipase C, inwardly-rectifying potassium channels, and inhibition of adenylyl cyclase activity (Murthy & Makhlof, 1999; Ahluwalia & Hobbs, 2005); NPR3 also binds and removes natriuretic peptides from the circulation, and consequently is often termed the 'clearance receptor'.

Nomenclature	NPR1	NPR2	NPR3	ST _a R
Other names	GC-A, ANP _A receptor, NPR-A	GC-B, ANP _B receptor, NPR-B	ANP _C receptor, NPR-C, clearance receptor	GC-C, guanylin receptor
Ensembl ID	ENSG00000169418	ENSG00000159899	ENSG00000113389	ENSG00000070019
Potency order	ANP > BNP > > CNP	CNP > > ANP > BNP	ANP > CNP > BNP	Uroguanylin > guanylin
Selective agonists	ANP, BNP, sANP (Olson <i>et al.</i> , 1996)	CNP	cANF ⁴⁻²³ (Maack <i>et al.</i> , 1987)	<i>E. coli</i> heat-stable enterotoxin (ST _a), linacotide (Harris and Crowell, 2007)
Selective antagonists	A71915 (9.2–9.5, Delporte <i>et al.</i> , 1991), [Asu7,23']- β -ANP ⁷⁻²⁸ (7.5, Kambayashi <i>et al.</i> , 1989), anantin (Wyss <i>et al.</i> , 1991)	Monoclonal antibody 3G12 (Drewett <i>et al.</i> , 1995)	AP811 (9.3, Veale <i>et al.</i> , 2000), M372049 (Hobbs <i>et al.</i> , 2004)	—
Probes	[¹²⁵ I]-ANP	[¹²⁵ I]-CNP	[¹²⁵ I]-ANP	—

The polysaccharide obtained from fermentation of *Aureobasidium* species, HS142-1, acts as an antagonist for NPR1 and NPR2 receptors (Morishita *et al.*, 1991).

Orphan receptors GC-D, GC-E (RetGC-1, ENSG00000132518), GC-F (RetGC-2, ENSG00000101890) and GC-G (ENSG00000080218) have been cloned from various mammals. GC-G exhibits structural similarity to the natriuretic peptide receptors (Schulz *et al.*, 1998).

Abbreviations: A71915, ([Arg⁶, Cha⁸]ANP⁶⁻¹⁵-d-Tic-Arg-Cys-NH₂; **anantin**, cyclo(Gly-Phe-Ile-Gly-Trp-Gly-Asn- β -Asp)-Ile-Phe-Gly-His-Tyr-Ser-Gly-Asp-Phe; **AP811**, (s)-N²-[(4-[(2-naphthalenylcarbonyl)amino]phenyl)acetyl]-l-arginyl-l-isoleucyl-l- α -aspartyl-N-(2-methylbutyl)-l-argininamide; [Asu7,23']- β -ANP(7-28), an antiparallel dimer linked by 7-23' and 7'-23 disulphide bonds (Asu, l- α -aminosuberic acid); cANF⁴⁻²³, des[Gln¹⁸,Ser¹⁹,Gly²⁰,Leu²¹,Gly²²]ANP⁴⁻²³-NH₂; **HS142-1**, *Aureobasidium*-derived polysaccharide; **M372049**, (structure not known); **sANP**, [G9T, R11S, G16R]ANP

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Neurotrophin

Overview: The trk neurotrophin receptors (provisional nomenclature) exhibit a single TM domain, with an intracellular tyrosine kinase catalytic domain (E.C. 2.7.1.112), although various isoforms exist, including truncated forms of trkB and trkC, which lack catalytic domains. The endogenous ligands are small proteins (ca. 120 aa) and include nerve growth factor (NGF, ENSG00000134259), neurotrophin (NT) 3 (ENSG00000185652), NT4/5 (ENSG00000167744) and brain-derived neurotrophic factor (BDNF, ENSG00000176697). p75, which has homologies with the tumour necrosis factor receptor, lacks a tyrosine kinase domain, but can signal *via* ceramide release and nuclear factor κ B (NF- κ B) activation. Both trkA and trkB contain two leucine-rich regions and can exist in monomeric or dimeric forms.

Nomenclature	trkA	trkB	trkC	p75
Other names	gp140 ^{trk} , high-affinity, slow-dissociating NGF receptor	gp145 ^{trkB}	gp145 ^{trkC}	p75 ^{NTR} , low-affinity neurotrophin receptor, NGFR
Ensembl ID	ENSG00000117029	ENSG00000148053	ENSG00000140538	ENSG00000064300
Potency order	NGF > NT3	BDNF, NT4/5 > NT3	NT3	NGF, BDNF, NT3, NT4/5
Probes	[¹²⁵ I]-NGF	[¹²⁵ I]-BDNF	—	—

An additional related receptor, termed trk3 (ENSG00000162733), has been identified. The selectivity of small molecule peptide mimetics of NGF has not been ascertained (Massa *et al.*, 2003). There are, as yet, no selective antagonists, but activation can be blocked using anti-neurotrophin antisera or selective immunoadhesins that sequester neurotrophins (Shelton *et al.*, 1995). p75 influences the binding of NGF and NT3 to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neurones, it binds NT3 with comparable affinity to trkC (Dechant *et al.*, 1997).

The intracellular tyrosine kinase activity of the trkA receptor can be inhibited by GW441756 (8.7, Wood *et al.*, 2004) and tyrphostin AG879 (Ohmichi *et al.*, 1993).

Abbreviations: BDNF, brain-derived neurotrophic factor; **GW441756**, 1,3-dihydro-3-[(1-methyl-1H-indol-3-yl)methylene]-2H-pyrrolo[3, 2-b]pyridin-2-one hydrochloride; NGF, nerve growth factor; **tyrphostin AG879**, α -cyano-(3, 5-di-t-butyl-4-hydroxy)thiocinnamide

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Toll-like family

Overview: Toll-like receptors are single TM cell-surface proteins with multiple leucine-rich regions in the extracellular portion, which participate in the innate immune response to microbial agents, the stimulation of which leads to activation of intracellular protein kinases and regulation of gene transcription. As well as responding to exogenous infectious agents, it has been suggested that selected members of the family may be activated by endogenous ligands, such as hsp60 (Ohashi *et al.*, 2000).

Nomenclature	TLR2	TLR3	TLR4	TLR5
Other names	CD282	CD283	CD284	—
Ensembl ID	ENSG00000137462	ENSG00000164342	ENSG00000136869	ENSG00000187554
Selective agonists	Peptidoglycan (Schwandner <i>et al.</i> , 1999; Yoshimura <i>et al.</i> , 1999)	PolyIC (Alexopoulou <i>et al.</i> , 2001)	LPS (Poltorak <i>et al.</i> , 1998), taxol (Kawasaki <i>et al.</i> , 2000)	Flagellin (Hayashi <i>et al.</i> , 2001)

Nomenclature	TLR7	TLR8	TLR9
Other names	—	—	CD289
Ensembl ID	ENSG00000196664	ENSG00000101916	ENSG00000173366
Selective agonists	R848 (Hemmi <i>et al.</i> , 2002), imiquimod (Hemmi <i>et al.</i> , 2002)	R848 (Hemmi <i>et al.</i> , 2002), imiquimod	CpG (Hemmi <i>et al.</i> , 2000)

Members of the family appear to interact in the recognition of many ligands such that the potency of ligands is altered with different combination patterns (e.g. TLR1/2 and TLR2/6, Takeuchi *et al.*, 2001, 2002).

Further members of the family, which includes TLR1 (Toll/interleukin-1 receptor-like protein, CD281, ENSG00000174125), TLR6 (ENSG00000174130), TLR10 (ENSG00000174123) and TLR11 (ENSMUSG00000051969), have been less well characterised.

Abbreviations: CpG, DNA enriched in cytosine:guanosine pairs; **imiquimod**, 1-(4-amino-imidazo[4,5-c]quinolin-1-yl)-2-methylpropane, also known as R837; **LPS**, lipopolysaccharide derived from Gram-negative bacteria; **polyIC**, polyinosine-polycytosine; **R848**, 1-(4-amino-2-ethoxymethyl-imidazo[4,5-c]quinolin-1-yl)-2-methyl-propan-2-ol, also known as resiquimod and S28463

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Tumor necrosis factor (TNF) family

Overview: The TNF receptor superfamily (TNFRSF, provisional nomenclature) displays limited homology beyond an extracellular domain rich in cysteine residues and is activated by at least 18 different human homologues of TNF referred to as the TNF superfamily (TNFSF). Some homologues lacking transmembrane and cytoplasmic domains function as decoy receptors binding ligand without inducing cell signalling. Many of these receptors and ligands function as multimeric entities. Signalling through these receptors is complex and involves interaction with cytoplasmic adaptor proteins (such as TRADD and TRAF1) to evoke apoptosis or regulation of the nuclear factor κ B or mitogen-activated protein kinase pathways. Pharmacological manipulation of these receptors is mainly enacted through chelating the endogenous agonists with humanised monoclonal antibodies (e.g. infliximab or adalimumab) or recombinant fusion proteins of IgG and soluble receptors (e.g. etanercept).

Nomenclature	TNFRSF1A	TNFRSF1B	TNFRSF3	TNFRSF4	TNFRSF5
Other names	TNFR1, CD120a, p55TNFR, TNFAR, TNFR60	TNFR2, CD120b, p75TNFR, p80, TNFR	TNFR III, LTBR, TNFCR, TNFR-RP, TNFR2-RP, CD18	OX-40, ACT35, TXGP1L, CD134	CD40, Bp50, p50
Ensembl ID	ENSG00000067182	ENSG00000028137	ENSG00000111321	ENSG00000186827	ENSG00000101017
Adaptor proteins	TRADD	TRAF1, 2, 5	TRAF3, 4, 5	TRAF1, 2, 3, 5	TRAF1, 2, 3, 5, 6
Endogenous ligands	TNFSF1, TNFSF2	TNFSF1, TNFSF2	TNFSF3, TNFSF14	TNFSF4	TNFSF5

Nomenclature	TNFRSF6	TNFRSF7	TNFRSF8	TNFRSF9
Other names	Fas, CD95, APO-1, APT1, TNFRSF6A	CD27, S152, Tp55, T14	CD30, Ki-1	4-1BB, CDw137, ILA
Ensembl ID	ENSG00000026103	ENSG00000139193	ENSG00000120949	ENSG00000049249
Adaptor proteins	FADD	TRAF2, SIVA	TRAF1, 2, 3, 5	TRAF1, 2, 3
Endogenous ligands	TNFSF6	TNFSF7	TNFSF8	TNFSF9

TNFRSF6B (ENSG00000026036, also known as the decoy receptor for Fas ligand, DcR3, TR6, M68) acts as a non-functional target for TNFSF14, TNFSF15 and TNFSF6.

Nomenclature	TNFRSF10A	TNFRSF10B	TNFRSF11A	TNFRSF11B
Other names	DR4, TNF-related apoptosis-inducing ligand receptor 1, TRAIL-R1, APO-2, CD261	DR5, TNF-related apoptosis-inducing ligand receptor 2, TRAIL-R2, KILLER, CD262, TRICK2A, TRICKB	Receptor activator of NF- κ B, RANK, osteoclast differentiation factor receptor, ODFR, TRANCE-R, CD265	Osteoprotegerin, OPG, osteoclastogenesis inhibitory factor, OCIF, TR1
Ensembl ID	ENSG00000104689	ENSG00000120889	ENSG00000141655	ENSG00000164761
Adaptor proteins	FADD	FADD	TRAF1, 2, 3, 5, 6	
Endogenous ligands	TNFSF10	TNFSF10	TNFSF11	TNFSF11

TNFRSF10C (ENSG00000173535, also known as decoy receptor 1, DcR1, decoy TRAIL receptor without death domain, TNF-related apoptosis-inducing ligand receptor 3, TRAIL-R3, LIT, TRID, CD263) and TNFRSF10D (ENSG00000173530, also known as decoy receptor 2, DcR2, TNF-related apoptosis-inducing ligand receptor 4, TRAIL-R4, TRUND, CD264) act as non-functional targets for TNFSF10.

Nomenclature	TNFRSF12	TNFRSF12A	TNFRSF13B	TNFRSF13C
Other names	TRS, WSL-1, LARD, WSL-LR, apoptosis-mediating receptor DR3, apoptosis-mediating receptor TRAMP, death domain receptor 3	TWEAK-R, Fn14, FGF-inducible 14, CD266 antigen	Transmembrane activator and CAML interactor, TACI, CD267	B cell-activating factor receptor, BAFF-R, CD268, BR3
Ensembl ID	ENSG00000171680	ENSG00000006327	ENSG00000108516	ENSG00000159958
Adaptor proteins	TRADD	TRAF1, 2, 3, 5	TRAF2, 5, 6	TRAF3
Endogenous ligands	TNFSF15, TNFSF12	TNFSF12	TNFSF13B	TNFSF13B

Nomenclature	TNFRSF14	TNFRSF16	TNFRSF17	TNFRSF18	TNFRSF19
Other names	Herpesvirus entry mediator A, HVEM, tumor necrosis factor receptor-like 2, TR2, LIGHT-R, ATAR, HVEA	Low affinity nerve growth factor receptor, NGF receptor, Gp80-LNGFR, p75, p75 ^{NTR} , NGF-R, NTR, CD271	BCMA, BCM, TNFRSF13, CD269	Glucocorticoid-induced TNFR-related protein, GITR, activation-inducible TNFR family receptor, AITR	Toxicity and JNK inducer, TAJ, TROY, TAJ- α , TRADE
Ensembl ID	ENSG00000157873	ENSG00000064300	ENSG00000048462	ENSG00000186891	ENSG00000127863
Adaptor proteins	TRAF1,2,3,5	TRAF2, 4, 6	TRAF1,2,3,5,6	TRAF1, 2, 3	TRAF1,2,3,5
Endogenous ligands	TNFSF14, TNFSF1, BTLA	NGF, BDNF, NT-3, NT-4	TNFSF13B, TNFSF13	TNFSF18	—

Nomenclature	TNFRSF19L	TNFRSF21	TNFRSF22	TNFRSF23	TNFRSF27
Other names	Receptor expressed in lymphoid tissues, RELT	Death receptor 6, DR6	SOBa; Tnfrh2, Tnfrsf1a12, mDcTrailr2	mSOB, Tnfrh1, mDcTrailr1	X-linked ectodysplasin-A2 receptor, EDA-A2 receptor
Ensembl ID	ENSG00000054967	ENSG00000146072	ENSMUSG00000010751	ENSMUSG00000037613	ENSG00000131080
Adaptor proteins	TRAF1	TRADD	—	—	—

The tumor necrosis factor ligand superfamily includes TNFSF1 (ENSG00000204496, TNF β , lymphotoxin- α , LT α), TNFSF2 (ENSG00000204490, TNF, TNF α , cachectin, necrosin, cytotoxin, DIF), TNFSF3 (ENSG00000206327 TNFC, LT β , lymphotoxin- β , LT β), TNFSF4 (ENSG00000117586, OX-40 ligand, CD252, glycoprotein Gp34, TAX transcriptionally-activated glycoprotein 1, TXGP-1), TNFSF5 (ENSG00000102245, CD40 ligand, CD154, gp39, TNF-related activation protein, TRAP), TNFSF6 (ENSG00000117560, Fas ligand, CD95L, CD178, Apo1 L, Apoptosis antigen ligand), TNFSF7 (ENSG00000125726, CD70, CD27 ligand, Ki-24), TNFSF8 (ENSG00000106952, CD30 ligand, CD153), TNFSF9 (ENSG00000125657, 4-1BB ligand, CDw137L), TNFSF10 (ENSG00000121858, TRAIL, Apo-2 ligand (Apo-2L), TL2, CD253), TNFSF11 (ENSG00000120659, Receptor activator of nuclear factor κ B ligand, RANKL, TNF-related activation-induced cytokine, TRANCE, osteoprotegerin ligand, OPGL, osteoclast differentiation factor, ODF, CD254 antigen), TNFSF12 (TNF-related weak inducer of apoptosis, TWEAK, Apo-3 ligand, Apo3L, CD255), TNFSF13 (ENSG00000161955, APRIL, TALL2, TRDL-1, ZTNF2, TNFSF13A, CD256), TNFSF13B (ENSG00000102524, zTNF4, THANK, TNF- and APOL-related leukocyte expressed ligand 1, TALL-1, B lymphocyte stimulator, BLyS, B cell-activating factor, BAFF, dendritic cell-derived TNF-like molecule, DTL, CD257 antigen), TNFSF14 (ENSG00000125735, LIGHT, LTg, TR2, Herpesvirus entry mediator-ligand, CD258), TNFSF15 (ENSG00000181634, TL1, TL1A, VEG1, vascular endothelial cell growth inhibitor, TNF ligand-related molecule 1), and TNFSF18 (ENSG00000120337, TL6, glucocorticoid- induced TNF-related ligand, activation-inducible TNF-related ligand).

Abbreviations: BDNF, brain-derived neurotrophic factor (ENSG00000176697); BTLA, B- and T-lymphocyte attenuator (ENSG00000186265); FADD, Fas-associated death domain (ENSG00000168040); NT-3, neurotrophin-3 (ENSG00000185652); NT-4, neurotrophin-4 (ENSG00000167744); SIVA, ENSG00000184990; TNFRSF, TNF receptor superfamily; TNFSF, TNF superfamily; TRADD, TNF receptor-associated death domain (ENSG00000102871); TRAF, TNF receptor-associated factor (ENSG00000000597)

Further Reading

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