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 (TGFα, 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
Agonist actvity	EGF, amphiregulin, betacellulin, epigen, epiregulin, HB-EGF, TGFα	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 tyrphostins 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	**GFRα1**	**GFRα2**	**GFRα3**	**GFRα4**
Other names	GDNF, GNDF family receptor α1	Neurturin, GNDF family receptor α2	Artemin, GNDF family receptor α3	Persephin, GNDF family receptor α4
Ensembl ID	ENSG00000151892	ENSG00000168546	ENSG00000146013	ENSG00000125861
Potency order	GDNF > neurturin > artemin	Neurturin > GDNF	Artemin	Persephin
Probes	[^{125}I]-GDNF (3-63 pM, Treanor *et al*., 1996; Klein *et al*., 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 & Makhlouf, 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_aR**
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 *et al*., 1996)	CNP	$cANF^{4-23}$ (Maack *et al*., 1987)	*E. coli* heat-stable enterotoxin (ST_a)
Selective antagonists	A71915 (9.2–9.5, Delporte *et al*., 1991), [Asu7,23′]-β-ANP^{7-28} (7.5, Kambayashi *et al*., 1989), anantin (Wyss *et al*., 1991)	Monoclonal antibody 3G12 (Drewett *et al*., 1995)	AP811 (9.3, Veale *et al*., 2000), M372049 (Hobbs *et al*., 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**, ([Arg^6,Cha^8]ANP^{6-15}-d-Tic-Arg-Cys-NH_2; **anantin**, cyclo(Gly-Phe-Ile-Gly-Trp-Gly-Asn-β-Asp)-Ile-Phe-Gly-His-Tyr-Ser-Gly-Asp-Phe; **AP811**, (s)-N^2-([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); **$cANF^{4-23}$**, des[Gln^{18},Ser^{19},Gly^{20},Leu^{21},Gly^{22}]ANP^{4-23}-NH_2; **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 κB (NF-κB) 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-1*H*-indol-3-yl)methylene]-2*H*-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 *et al*., 1999; Yoshimura *et al*., 1999)	PolyIC (Alexopoulou *et al*., 2001)	LPS (Poltorak *et al*., 1998), taxol (Kawasaki *et al*., 2000)	Flagellin (Hayashi *et al*., 2001)

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