THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: Catalytic receptors

Stephen PH Alexander1, Doriano Fabbro2, Eamonn Kelly3, Neil Marrion3, John A Peters4, Helen E Benson5, Elena Faccenda5, Adam J Pawson5, Joanna L Sharman5, Christopher Southan5, Jamie A Davies5 and CGTP Collaborators

1School of Biomedical Sciences, University of Nottingham Medical School, Nottingham, NG7 2UH, UK
2PIQUR Therapeutics, Basel 4057, Switzerland
3School of Physiology and Pharmacology, University of Bristol, Bristol, BS8 1TD, UK
4Neuroscience Division, Medical Education Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY, UK
5Centre for Integrative Physiology, University of Edinburgh, Edinburgh, EH8 9XD, UK

Abstract

The Concise Guide to PHARMACOLOGY 2015/16 provides concise overviews of the key properties of over 1750 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full. G protein-coupled receptors are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The Concise Guide is published in landscape format in order to facilitate comparison of related targets. It is a condensed version of material contemporary to late 2015, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in the previous Guides to Receptors & Channels and the Concise Guide to PHARMACOLOGY 2013/14. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

Conflict of interest

The authors state that there are no conflicts of interest to declare.

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Overview: Catalytic receptors are cell-surface proteins, usually dimeric in nature, which encompass ligand binding and functional domains in one polypeptide chain. The ligand binding domain is placed on the extracellular surface of the plasma membrane and separated from the functional domain by a single transmembrane-spanning domain of 20-25 hydrophobic amino acids. The functional domain on the intracellular face of the plasma membrane has catalytic activity, or interacts with particular enzymes, giving the superfamily of receptors its name. Endogenous agonists of the catalytic receptor superfamily are peptides or proteins, the binding of which may induce dimerization of the receptor, which is the functional version of the receptor. Amongst the catalytic receptors, particular subfamilies may be readily identified dependent on the function of the enzymatic portion of the receptor. The smallest group is the particulate guanylyl cyclases of the natriuretic peptide receptor family. The most widely recognized group is probably the receptor tyrosine kinase (RTK) family, epitomized by the neurotrophin receptor family, where a crucial initial step is the activation of a signalling cascade by autophosphorylation of the receptor on intracellular tyrosine residue(s) catalyzed by enzyme activity intrinsic to the receptor. A third group is the extrinsic protein tyrosine kinase receptors, where the catalytic activity resides in a separate protein from the binding site. Examples of this group include the GDNF and ErbB receptor families, where one, catalytically silent, member of the heterodimer is activated upon binding the ligand, causing the second member of the heterodimer, lacking ligand...
binding capacity, to initiate signaling through tyrosine phosphorylation. A fourth group, the receptor threonine/serine kinase (RSTK) family, exemplified by TGF-β and BMP receptors, has intrinsic serine/threonine protein kinase activity in the heterodimeric functional unit. A fifth group is the receptor tyrosine phosphatases (RTP), which appear to lack cognate ligands, but may be triggered by events such as cell:cell contact and have identified roles in the skeletal, hematopoietic and immune systems.

A sixth group of catalytic receptors in the Guide is the integrins, which have roles in cell:cell communication, often associated with signaling in the blood.

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Cytokine receptor family

Overview: Cytokines are not a clearly defined group of agents, other than having an impact on immune signalling pathways, although many cytokines have effects on other systems, such as development. A feature of some cytokines, which allows them to be distinguished from hormones, is that they may be produced by “non-secretory” cells, for example, endothelial cells. Within the cytokine receptor family, some subfamilies may be identified, which are described elsewhere in the Guide to PHARMACOLOGY, receptors for the TNF family, the TGFB family and the chemokines. Within this group of records are described Type 1 cytokine receptors, typified by interleukin receptors, and Type II cytokine receptors, exemplified by interferon receptors. These receptors possess a conserved extracellular region, known as the cytokine receptor homology domain (CHD), along with a range of other structural modules, including extracellular immunoglobulin (Ig)-like and fibronectin type III (FNIII)-like domains, a transmembrane domain, and intracellular homology domains. An unusual feature of this group of agents is the existence of soluble and decoy receptors. These bind cytokines without allowing signalling to occur. A further attribute is the production of endogenous antagonist molecules, which bind to the receptors selectively and prevent signalling. A commonality of these families of receptors is the ligand-induced homo- or hetero-oligomerisation, which results in the recruitment of intracellular protein partners to evoke cellular responses, particularly in inflammatory or haematopoietic signalling. Although not an exclusive signalling pathway, a common feature of the majority of cytokine receptors is activation of the JAK/STAT pathway. This cascade is based around the protein tyrosine kinase activity of the Janus kinases (JAK), which phosphorylate the receptor and thereby facilitate the recruitment of signal transducers and activators of transcription (STATs). The activated homo- or heterodimeric STATs function principally as transcription factors in the nucleus.

Type I cytokine receptors are characterized by two pairs of conserved cysteines linked via disulfide bonds and a C-terminal WSXWS motif within their CHD. Type I receptors are commonly classified into five groups, based on sequence and structural homology of the receptor and its cytokine ligand, which is potentially more reflective of evolutionary relationships than an earlier scheme based on the use of common signal transducing chains within a receptor complex. These are the IL-2, IL-3, IL-6, IL-12 and prolactin families.

Type II cytokine receptors also have two pairs of conserved cysteines but with a different arrangement to Type I and also lack the WSXWS motif. The type II cytokine receptors include the interferon, IL-10, IL-1 and IL-17 receptors.

IL-2 receptor family

Overview: The IL-2 receptor family consists of one or more ligand-selective subunits, and a common γ chain (γc): IL2RG, P31785), though IL-4 and IL-7 receptors can form complexes with other receptor chains. Receptors of this family associate with Jak1 and Jak3, primarily activating Stat5, although certain family members can also activate Stat1, Stat3, or Stat6. Ro264550 has been described as a selective IL-2 receptor antagonist, which binds to IL-2 [177].

| Nomenclature | Interleukin-2 receptor | Interleukin-4 receptor type I | Interleukin-4 receptor type II | Interleukin-7 receptor | Interleukin-9 receptor |
|--------------|------------------------|-------------------------------|-------------------------------|-----------------------|-----------------------|
| Subunits     | Interleukin-2 receptor subunit β (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit), Interleukin-2 receptor subunit α (Ligand-binding subunit) | Interleukin-4 receptor subunit α (Ligand-binding subunit), Interleukin-4 receptor subunit γ (Other subunit) | Interleukin-13 receptor subunit α1 (Other subunit), Interleukin-4 receptor subunit α (Ligand-binding subunit) | Interleukin-7 receptor (Other subunit), Interleukin-7 receptor subunit α (Ligand-binding subunit) | Interleukin-9 receptor (Other subunit), Interleukin-9 receptor (Ligand-binding subunit) |
| Endogenous agonists | IL-2 (IL2, P60568) | IL-4 (IL4, P05112) | IL-13 (IL13, P35225), IL-4 (IL4, P05112) | IL-7 (IL7, P13232) | IL-9 (IL9, P15248) |
| Endogenous antagonists | IL-1 receptor antagonist (IL1RN, P18510) | – | – | – | – |
| Antagonists | Ro26-4550 [177] | – | – | – | – |
| Selective antagonists | AF1219B [3] | – | – | – | – |
| Nomenclature                                                                 | Interleukin 13 receptor, α2 | Interleukin-15 receptor | Interleukin-21 receptor | Thymic stromal lymphopoietin receptor |
|-------------------------------------------------------------------------------|-----------------------------|------------------------|------------------------|-------------------------------------|
| HGNC, UniProt                                                                | IL13RA2, Q14627             | –                      | –                      | –                                   |
| Subunits                                                                      | –                           | Interleukin-2 receptor subunit β (Ligand-binding subunit), Interleukin-15 receptor subunit α (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) | Interleukin-2 receptor subunit γ (Other subunit), Interleukin 21 receptor (Ligand-binding subunit) | Cytokine receptor-like factor 2 (Other subunit), Interleukin-7 receptor subunit α (Ligand-binding subunit) |
| Endogenous agonists                                                          | –                           | IL-15 (IL15, P40933)   | IL-21 (IL21, Q9HBE4)   | thymic stromal lymphopoietin (TSLP, Q969D9) |
| Comments                                                                     | Decoy receptor that binds IL-13 (IL13, P35225) as a monomer. | –                      | –                      | –                                   |

**Subunits**

| Nomenclature                                                                 | Interleukin-2 receptor subunit α | Interleukin-2 receptor subunit β | Interleukin-2 receptor subunit γ | Interleukin-4 receptor subunit α | Interleukin-7 receptor subunit α |
|-------------------------------------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| HGNC, UniProt                                                                | IL2RA, P01589                    | IL2RB, P14784                    | IL2RC, P31785                    | IL4R, P24394                      | IL7R, P16871                      |
| Antibodies                                                                    | daclizumab (Binding) (pKd >8)    | –                                | –                                | dupilumab (Binding) (pIC50 11.1)  | –                                |
|                                                                                | [154], basiliximab (Binding)     |                                  |                                  | [121]                            |                                  |

| Nomenclature                                                                 | Interleukin 9 receptor | Interleukin-13 receptor subunit α1 | Interleukin-15 receptor subunit α | Interleukin 21 receptor | Cytokine receptor-like factor 2 |
|-------------------------------------------------------------------------------|-----------------------|-----------------------------------|--------------------------|------------------------|-------------------------------|
| HGNC, UniProt                                                                | IL9R, Q01113          | IL13RA1, P78552                   | IL15RA, Q13261           | IL21R, Q9HBE5           | CRLF2, Q9HC73                  |

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IL-3 receptor family

Overview: The IL-3 receptor family signal through a receptor complex comprising of a ligand-specific α subunit and a common β chain (CSF2RB, P32927), which is associated with Jak2 and signals primarily through Stat5.

| Nomenclature | Interleukin-3 receptor | Interleukin-5 receptor | Granulocyte macrophage colony-stimulating factor receptor |
|--------------|------------------------|------------------------|----------------------------------------------------------|
| Subunits     | Interleukin 3 receptor, α subunit (Ligand-binding subunit), Cytokine receptor common β subunit (Other subunit) | Interleukin 5 receptor, α subunit (Ligand-binding subunit), Cytokine receptor common β subunit (Other subunit) | GM-CSF receptor, α subunit (Ligand-binding subunit), Cytokine receptor common β subunit (Other subunit) |
| Endogenous agonists | IL-3 (IL3, P08700) | IL-5 (IL5, P05113) | G-CSF (CSF3, P09919), GM-CSF (CSF2, P04141) |
| Selective antagonists | YM90709 [133] | – | – |

IL-6 receptor family

Overview: The IL-6 receptor family signal through a ternary receptor complex consisting of the cognate receptor and either the IL-6 signal transducer gp130 (IL6ST, P40189) or the oncostatin M-specific receptor, β subunit (OSMR, Q99650), which then activates the JAK/STAT, Ras/Raf/MAPK and PI 3-kinase/PKB signalling modules. Unusually amongst the cytokine receptors, the CNTF receptor is a glycerophosphatidylinositol-linked protein.
### Interleukin-6 receptor family

| Nomenclature            | Subunits                                      | Endogenous agonists | Agonists      | Antibodies                |
|-------------------------|-----------------------------------------------|---------------------|---------------|--------------------------|
| IL-6 receptor           | Interleukin-6 receptor, α subunit (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit) | IL-6 (IL6, P05231) | –             | tocilizumab (Binding) (pKᵩ 8.6) |
| IL-11 receptor          | Interleukin-11 receptor, α subunit (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit) | IL-11 (IL11, P20809) | –             | –                        |
| IL-31 receptor          | Interleukin-31 receptor, α subunit (Ligand-binding subunit), Oncostatin M-specific receptor, β subunit (Other subunit) | IL-31 (IL31, Q6EBC2) | –             | –                        |
| Ciliary neutrophic factor | Ciliary neutrophic factor receptor, β subunit (Ligand-binding subunit) | CRCF1/CLC1 heterodimer (CLCF1 CRLF1, O75462 Q9UBD9), ciliary neutrophic factor (CNTF, P26441) | –             | –                        |

| Nomenclature            | Leukemia inhibitory factor receptor           | Oncostatin-M receptor | Interleukin-27 receptor |
|-------------------------|-----------------------------------------------|-----------------------|------------------------|
| Leptin receptor         | Leukemia inhibitory factor receptor           | Oncostatin-M receptor | Interleukin-27 receptor |
| HGNC, UniProt           | LEPR, P48357                                  | –                     | –                      |
| Subunits                | –                                             | –                     | –                      |
| Endogenous agonists     | leptin (LEP, P41159)                          | LIF (LIF, P15018), cardiotrophin-1 (CTF1, Q16619), oncostatin M (OSM, P13725) | –                     |
| Antigons                | sarilumab (Binding) (pKᵩ 10.6–11.1) [171]    | –                     | –                      |
| Antibodies              | sarilumab (Binding) (pKᵩ 10.6–11.1) [171]    | –                     | –                      |

### IL-6 receptor family

| Nomenclature            | Interleukin-6 receptor, α subunit | Interleukin-6 receptor, β subunit | Interleukin-11 receptor, α subunit | Interleukin 27 receptor, alpha |
|-------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------------------|
| HGNC, UniProt           | IL6R, P08887                       | IL6ST, P40189                     | IL11RA, Q14626                   | IL27RA, Q6UWB1                |
| Antibodies              | sarilumab (Binding) (pKᵩ 10.6–11.1) [171] | –                                 | –                                 | –                             |

| Nomenclature            | Interleukin-31 receptor, α subunit | Ciliary neutrophic factor receptor α subunit | Leukemia inhibitory factor receptor | Oncostatin M-specific receptor, β subunit |
|-------------------------|-----------------------------------|--------------------------------------------|------------------------------------|------------------------------------------|
| HGNC, UniProt           | IL31RA, Q8NI17                    | CNTFR, P26992                             | LIFR, P42702                       | OSMR, Q99650                           |

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IL-12 receptor family

Catalytic receptors → Cytokine receptor family → IL-12 receptor family

Overview: IL-12 receptors are a subfamily of the IL-6 receptor family. IL12RB1 is shared between receptors for IL-12 and IL-23; the functional agonist at IL-12 receptors is a heterodimer of IL-12A/IL-12B, while that for IL-23 receptors is a heterodimer of IL-12B/IL-23A.

| Nomenclature | Interleukin-12 receptor | Interleukin-23 receptor | Interleukin-12 receptor, β1 subunit | Interleukin-12 receptor, β2 subunit | Interleukin 23 receptor |
|--------------|-------------------------|------------------------|-------------------------------------|-------------------------------------|------------------------|
| HGNC, UniProt | –                       | –                      | IL12RB1, P42701                     | IL12RB2, Q99665                  | IL23R, Q5VWKS          |
| Subunits     | Interleukin-12 receptor, β2 subunit (Other subunit), Interleukin-12 receptor, β1 subunit (Ligand-binding subunit) | Interleukin 23 receptor (Ligand-binding subunit), Interleukin-12 receptor, β1 subunit (Ligand-binding subunit) | –                                  | –                     | –                      |
| Endogenous agonists | IL-12 (IL12A IL12B, P29459 P29460) | IL-23 (IL12B IL23A, P29460) | –                                  | –                     | –                      |

Prolactin receptor family

Catalytic receptors → Cytokine receptor family → Prolactin receptor family

Overview: Prolactin family receptors form homodimers in the presence of their respective ligands, associate exclusively with Jak2 and signal via Stat5.

| Nomenclature | Erythropoietin receptor | Granulocyte colony-stimulating factor receptor | Growth hormone receptor | Prolactin receptor | Thrombopoietin receptor |
|--------------|-------------------------|-----------------------------------------------|-------------------------|------------------|------------------------|
| HGNC, UniProt | EPOR, P19235            | CSF3R, Q99062                                 | GHR, P10912             | PRLR, P16471     | MPL, P40238             |
| Endogenous agonists | erythropoietin (EPOR, P01588) (Selective) (plC50 11.1) [48] | G-CSF (CSF3, P09919) | growth hormone 1 (GH1, P01241), growth hormone 2 (GH2, P01242) | –                 | –                      |
| Agonists     | peginesatide (plC50 10.4) [48] | pegfilgrastim                                | –                      | –                 | romiplostim             |
| Selective agonists | –                          | –                                             | –                      | –                 | eltrombopag (pEC50 7.4) [119] |
| Antagonists  | –                       | –                                             | pegvisomant [180]      | –                 | –                      |

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Interferon receptor family

**Overview:** The interferon receptor family includes receptors for type I (α, β, κ, and ω) and type II (γ) interferons. There are at least 13 different genes encoding IFN-α subunits in a cluster on human chromosome 9p22: α1 (IFNA1, P01562), α2 (IFNA2, P01563), α4 (IFNA4, P05014), α5 (IFNA5, P01569), α6 (IFNA6, P05013), α7 (IFNA7, P01567), α8 (IFNA8, P32881), α10 (IFNA10, P01566), α13 (IFNA13, P01562), α14 (IFNA14, P01570), α16 (IFNA16, P05015), α17 (IFNA17, P01571) and α21 (IFNA21, P01568).

| Nomenclature                      | Interferon-α/β receptor | Interferon-γ-receptor |
|-----------------------------------|-------------------------|-----------------------|
| Subunits                          | Interferon α/β receptor 2 (Other subunit), interferon α/β receptor 1 (Ligand-binding subunit) | Interferon γ receptor 2 (Other subunit), Interferon γ receptor 1 (Ligand-binding subunit) |
| Endogenous agonists               | IFN-α1/13 (IFNA1 IFNA13, P01562), IFN-α10 (IFNA10, P01566), IFN-α14 (IFNA14, P01570), IFN-α16 (IFNA16, P05015), IFN-α17 (IFNA17, P01571), IFN-α2 (IFNA2, P01563), IFN-α21 (IFNA21, P01568), IFN-α4 (IFNA4, P05014), IFN-α5 (IFNA5, P01569), IFN-α6 (IFNA6, P05013), IFN-α7 (IFNA7, P01567), IFN-α8 (IFNA8, P32881), IFN-β (IFNB1, P01574), IFN-κ (IFNK, Q9P0W0), IFN-ω (IFNW1, P05000) | IFN-γ (IFNG, P01579) |
| Selective agonists                | peginterferon alfa-2b [191] | – |

**Subunits**

| Nomenclature                      | interferon α/β receptor 1 | interferon α/β receptor 2 | Interferon γ receptor 1 | Interferon γ receptor 2 |
|-----------------------------------|---------------------------|---------------------------|-------------------------|-------------------------|
| HGNC, UniProt                     | IFNAR1, P17181            | IFNAR2, P48551            | IFNGR1, P15260          | IFNGR2, P38484          |
| Selective agonists                | peginterferon alfa-2b [191]| –                         | –                       | –                       |
| Antibodies                        | anifrolumab (Binding) (pK₅D >10) [21] | –                         | –                       | –                       |

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Interferon receptor family 5986
## IL-10 receptor family

Catalytic receptors → Cytokine receptor family → IL-10 receptor family

**Overview:** The IL-10 family of receptors are heterodimeric combinations of family members: IL10RA/IL10RB responds to IL-10; IL20RA/IL20RB responds to IL-19, IL-20 and IL-24; IL22RA1/IL10RB responds to IL-22; IL28RA/IL10RB responds to IL-28A, IL-28B and IL-29.

| Nomenclature | IL-10 receptor | Interleukin-20 receptor | Interleukin-22α1/20β heteromer | Interleukin-22α1/10β heteromer | Interleukin-22 receptor α2 | Interferon-α receptor 1 |
|--------------|----------------|------------------------|-------------------------------|-------------------------------|---------------------------|--------------------------|
| HGNC, UniProt | Interleukin 10 receptor, α subunit | Interleukin 20 receptor, β subunit | Interleukin 22 receptor, α1 subunit | Interleukin 22 receptor, α1 subunit | Interferon-α receptor subunit |  |
| Subunits     | Interleukin 10 receptor, β subunit | (Other subunit) | Interleukin 20 receptor, α subunit | Interleukin 20 receptor, β subunit | (Ligand-binding subunit) |  |
| Endogenous agonists | IL-10 (IL10, P22301) | IL-19 (IL19, Q9UHD0), IL-20 (IL20, Q9NNY1), IL-24 (IL24, Q13007) | IL-20 (IL20, Q9NYY1), IL-24 (IL24, Q13007) | IL-22 (IL22, Q9GZX6) | – | Interferon-α receptor subunit 1 |
| Comments     | – | – | – | – | Soluble decoy receptor that binds IL-22 (IL22, Q9GZX6) as a monomer. | – |

**Subunits**

| Nomenclature | Interleukin 10 receptor, α subunit | Interleukin 10 receptor, β subunit | Interleukin 20 receptor, α subunit | Interleukin 20 receptor, β subunit | Interleukin 22 receptor, α1 subunit | Interferon-α receptor subunit 1 |
|--------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------------------|
| HGNC, UniProt | IL10RA, Q13651 | IL10RB, Q08334 | IL20RA, Q9UHF4 | IL20RB, Q6UXL0 | IL22RA1, Q8N6P7 | IFNL1, Q8IUS7 |

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**Immunoglobulin-like family of IL-1 receptors**

**Overview:** The immunoglobulin-like family of IL-1 receptors are heterodimeric receptors made up of a cognate receptor subunit and an IL-1 receptor accessory protein, *IL1RAP* (Q9NPH3, also known as C3orf13, IL-1RacP, IL1R3). They are characterised by extracellular immunoglobulin-like domains and an intracellular Toll/Interleukin-1R (TIR) domain.

| Nomenclature | Subunits | Inhibitors | Endogenous agonists | Endogenous antagonists | Selective antagonists | Comments |
|--------------|----------|------------|---------------------|-----------------------|----------------------|---------|
| Interleukin-1 receptor, type I | IL-1 receptor accessory protein (Other subunit), *IL1R1* (P14778), *IL1R2* (P27930) | anakinra (pKd 7.8) [44] | IL-1α (*IL1A*, P01583), IL-1β (*IL1B*, P01584) | Interleukin-1 receptor antagonist (*IL1RN*, P18510) | AF12198 [3] | Decoy receptor that binds IL-1α (*IL1A*, P01583), IL-1β (*IL1B*, P01584) and IL-1 receptor antagonist (*IL1RN*, P18510). |
| Interleukin-33 receptor | IL-1 receptor accessory protein (Other subunit), *IL1R1* (P14778), *IL1R2* (P27930) | – | IL-33 (*IL33*, Q95760) | – | – | |
| Interleukin-36 receptor | IL-1 receptor accessory protein (Other subunit), *IL1R1* (Q01638), *IL1R2* (Q9HB29) | – | – | – | – | |
| Interleukin-1 receptor, type II | IL-1 receptor accessory protein (Other subunit), *IL1R1* (P14778), *IL1R2* (P27930) | – | – | – | – | |
| Interleukin-18 receptor | IL-18 receptor accessory protein (Other subunit), *IL18R1* (Q13478) | – | – | – | – | |

**Subunits**

| Nomenclature | HGNPC, UniProt |
|--------------|---------------|
| Interleukin 1 receptor, type I | *IL1R1*, P14778 |
| Interleukin 1 receptor, type II | *IL1R2*, P27930 |
| Interleukin-1 receptor-like 1 | *IL1RL1*, Q01638 |
| Interleukin-1 receptor-like 2 | *IL1RL2*, Q9HB29 |
| Interleukin-18 | *IL18R1*, Q13478 |

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IL-17 receptor family

Catalytic receptors → Cytokine receptor family → IL-17 receptor family

Overview: The IL17 cytokine family consists of six ligands (IL-17A-F), which signal through five receptors (IL-17RA-E).

| Nomenclature | Interleukin-17 receptor | Interleukin-25 receptor | Interleukin-17C receptor |
|--------------|------------------------|------------------------|-------------------------|
| Subunits     | Interleukin 17 receptor A (Ligand-binding subunit), interleukin 17 receptor C (Other subunit) | Interleukin 17 receptor B (Ligand-binding subunit), interleukin 17 receptor A (Other subunit) | Interleukin 17 receptor A (Other subunit), Interleukin 17 receptor E (Ligand-binding subunit) |
| Endogenous agonists | IL-17A (IL17A, Q16552), IL-17A/IL-17F (IL17A IL17F, Q16552 Q96PD4), IL-17F (IL17F, Q96PD4) | IL-17B (IL17B, Q9UHFS), IL-25 (IL25, Q9H293) | IL-17C (IL17C, Q9P0M4) |

Subunits

| Nomenclature | Interleukin 17 receptor A | Interleukin 17 receptor B | interleukin 17 receptor C | Interleukin-17 receptor D | Interleukin-17 receptor E |
|--------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| HGNC, UniProt | I17RA, Q96F46 | I17RB, Q9NRM6 | I17RC, Q8NAC3 | I17RD, Q8NFM7 | I17RE, Q8NFR9 |
| Antibodies   | brodalumab (Binding) (pKd 9.2) [179] | – | – | – | – |
| Comments     | – | – | – | The endogenous agonist for this receptor is unknown. | – |

Further Reading

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Palmer G et al. (2011) Interleukin-33 biology with potential insights into human diseases. *Nat Rev Rheumatol* 7: 321-9 [PMID:21519352]

Pappu R et al. (2011) The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases. *Immunology* 134: 8-16 [PMID:21726218]

Rincon M. (2012) Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. *Trends Immunol.* 33: 571-7 [PMID:22883707]
GDNF receptor family

Catalytic receptors → GDNF receptor family

**Overview:** GDNF family receptors (provisional nomenclature) are extrinsic tyrosine kinase receptors. Ligand binding to the extracellular domain of the glycosylphosphatidylinositol-linked cell-surface receptors (tabulated below) activates a transmembrane tyrosine kinase enzyme, RET (see Receptor Tyrosine Kinases). The endogenous ligands are typically dimeric, linked through disulphide bridges: glial cell-derived neurotrophic factor GDNF (GDNF, P39905) (211 aa); neurturin (NRTN, Q99748) (197 aa); artemin (ARTN, Q5T4W7) (237 aa) and persephin (PSPN, O60542) (PSPN, 156 aa).

| Nomenclature | GDNF family receptor α1 | GDNF family receptor α2 | GDNF family receptor α3 | GDNF family receptor α4 |
|--------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Common abreviation | GFRα1 | GFRα2 | GFRα3 | GFRα4 |
| HGNC, UniProt | GFRα1, P56159 | GFRα2, O00451 | GFRα3, O60609 | GFRα4, Q9GZZ7 |
| Potency order | GDNF (GDNF, P39905) > neurturin (NRTN, Q99748) > artemin (ARTN, Q5T4W7) | neurturin (NRTN, Q99748) > GDNF (GDNF, P39905) | artemin (ARTN, Q5T4W7) > persephin (PSPN, O60542) |
| Labelled ligands | [125I]GDNF (rat) (pKₐ 10.2–11.5) [92, 182] | – | – | – |

**Comments:** Inhibitors of other receptor tyrosine kinases, such as semaxanib, which inhibits VEGF receptor function, may also inhibit Ret function [131]. 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.

**Further Reading**

Allen SJ et al. (2013) GDNF, NGF and BDNF as therapeutic options for neurodegeneration. Pharmacol. Ther. 138: 155-75 [PMID:23348013]

Carnicella S et al. (2009) GDNF—a potential target to treat addiction. Pharmacol. Ther. 122: 9-18 [PMID:19136027]

Liu H et al. (2012) Role of glial cell line-derived neurotrophic factor in perineural invasion of pancreatic cancer. Biochim. Biophys. Acta 1826: 112-20 [PMID:22503821]

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Pascual A et al. (2011) GDNF and protection of adult central catecholaminergic neurons. J. Mol. Endocrinol. 46: R83-92 [PMID:21357726]

Rangasamy SB et al. (2010) Neurotrophic factor therapy for Parkinson’s disease. Prog. Brain Res. 184: 237-64 [PMID:20887879]
**Overview:** Integrins are unusual signalling proteins that function to signal both from the extracellular environment into the cell, but also from the cytoplasm to the external of the cell. The intracellular signalling cascades associated with integrin activation focus on protein kinase activities, such as focal adhesion kinase and Src. Based on this association between extracellular signals and intracellular protein kinase activity, we have chosen to include integrins in the ‘Catalytic receptors’ section of the database until more stringent criteria from NC-IUPHAR allows precise definition of their classification.

Integrins are heterodimeric entities, composed of α and β subunits, each 1TM proteins, which bind components of the extracellular matrix or counter-receptors expressed on other cells. One class of integrin contains an inserted domain (I) in its α subunit, and if present (α1, α2, α10, α11, αE, αL, αM and αX), this I domain contains the ligand binding site. All β subunits possess a similar I-like domain, which has the capacity to bind ligand, often recognising the RGD motif. The presence of an α subunit I domain precludes ligand binding through the β subunit. Integrins provide a link between ligand and the actin cytoskeleton (through typically short intracellular domains). Integrins bind several divalent cations, including a Mg$^{2+}$ ion in the I or I-like domain that is essential for ligand binding. Other cation binding sites may regulate integrin activity or stabilise the 3D structure. Integrins regulate the activity of particular protein kinases, including focal adhesion kinase and integrin-linked kinase. Cellular activation regulates integrin ligand affinity via inside-out signalling and ligand binding to integrins can regulate cellular activity via outside-in signalling.

| Nomenclature | integrin α1β1 | integrin α2β1 | integrin αIIbβ3 | integrin α4β1 |
|--------------|---------------|---------------|----------------|---------------|
|              | integrin, beta 1 subunit | integrin, beta 1 subunit | integrin, alpha IIIb subunit | integrin, beta 1 subunit |
|              | (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 1 subunit | (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 2 subunit (CD49B, alpha 2 subunit of VLA-2 receptor) | (platelet glycoprotein IIIa, antigen CD61), integrin, alpha IIb subunit | (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor) |
| Subunits     | collagen, laminin | collagen, laminin, thrombospondin | fibrinogen ($FGA\ FGB\ FGG$, P02671 P02675 P02679), fibronectin ($FN1$, P02751), von Willebrand factor ($VWF$, P04275), vitronectin ($VTN$, P04004), thrombospondin | fibrinectin ($FN1$, P02751), vascular cell adhesion protein 1 ($VCAM1$, P19320), osteopontin ($SPP1$, P10451), thrombospondin |
| Ligands      | collagen, laminin | collagen, laminin, thrombospondin | fibrinogen ($FGA\ FGB\ FGG$, P02671 P02675 P02679), fibronectin ($FN1$, P02751), von Willebrand factor ($VWF$, P04275), vitronectin ($VTN$, P04004), thrombospondin | fibrinectin ($FN1$, P02751), vascular cell adhesion protein 1 ($VCAM1$, P19320), osteopontin ($SPP1$, P10451), thrombospondin |
| Inhibitors   | obtustatin (pIC_{50} 9.1) [118] | TC115 (pIC_{50} 7.9) [128] | G4120 [124], GR 144053, epifibatide, tirofiban | BIO1211 (pIC_{50} 8.3–9) [108], TCS2314 |
| Antibodies   | – | – | abciximab (Binding) [31] | natalizumab (Inhibition) [1] |
| Comments     | – | – | – | LDV-FITC is used as a probe at this receptor. |

**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)  
**Full Contents of ConciseGuide:** [http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full)
### Integrins α4β7

**Subunits**
- Integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor), integrin, beta 7 subunit

**Ligands**
- Fibronectin (FN1, P02751)

**Antibodies**
- Vedolizumab (Antagonist) (pIC_{50} 8.3) [151]

### Integrins α5β1

**Subunits**
- Integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide)

**Antibodies**
- Vedolizumab (Antagonist) (pIC_{50} 8.3) [151]

### Integrins α6β1

**Subunits**
- Integrin, alpha 6 subunit (fibronectin receptor, alpha polypeptide)

**Antibodies**
- Vedolizumab (Antagonist) (pIC_{50} 8.3) [151]

### Integrins α10β1

**Subunits**
- Integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 10 subunit

**Antibodies**
- Vedolizumab (Antagonist) (pIC_{50} 8.3) [151]

### Integrins α11β1

**Subunits**
- Integrin, alpha 11 subunit

**Ligands**
- Collagen

**Antibodies**
- Vedolizumab (Binding) (pK_{d} 6.3) [201]

### Comments: Integrin ligands

**Collagen** is the most abundant protein in metazoa, rich in glycine and proline residues, made up of cross-linked triple helical structures, generated primarily by fibroblasts. Extensive post-translational processing is conducted by prolyl and lysyl hydroxylases, as well as transglutaminases. Over 40 genes for collagen-α subunits have been identified in the human genome. The collagen-binding integrins α1β1, α2β1, α10β1 and α11β1 recognise a range of triple-helical peptide motifs including GFOGER (O = hydroxyproline), a synthetic peptide derived from the primary sequence of collagen I (COL1A1 (COL1A1, P02452)) and collagen II (COL2A1 (COL2A1, P02458)).

**Laminin** is an extracellular glycoprotein composed of α, β and γ chains, for which five, four and three genes, respectively, are identified in the human genome. It binds to α1β1, α2β1, α3β1,
αβ1 and α6β4 integrins.

**fibrinogen (FGA, FGB, FGG, P02671, P02675, P02679)** is a glycosylated hexamer composed of two α (FGA, P02671), two β (FGB, P02675) and two γ (FGG, P02679) subunits, linked by disulphide bridges. It is found in plasma and alpha granules of platelets. It forms cross-links between activated platelets mediating aggregation by binding αIIbβ3; proteolysis by thrombin cleaves short peptides termed fibrinopeptides to generate fibrin, which polymerises as part of the blood coagulation cascade.

**fibrinogen** is a glycosylated hexamer composed of two α (FGA, P02671), two β (FGB, P02675) and two γ (FGG, P02679) subunits, linked by disulphide bridges. It is found in plasma and alpha granules of platelets. It forms cross-links between activated platelets mediating aggregation by binding αIIbβ3; proteolysis by thrombin cleaves short peptides termed fibrinopeptides to generate fibrin, which polymerises as part of the blood coagulation cascade.

**fibronectin (FN1, P02751)** is a disulphide-linked homodimer found as two major forms; a soluble dimeric form found in the plasma and a tissue version that is polymeric, which is secreted into the extracellular matrix by fibroblasts. Splice variation of the gene product (FN1, P02751) generates multiple isoforms.

**vitronectin (VTN, P04004)** is a serum glycoprotein and extracellular matrix protein which is found either as a monomer or, following proteolysis, a disulphide-linked dimer.

**osteopontin (SPP1, P10451)** forms an integral part of the mineralized matrix in bone, where it undergoes extensive post-translation processing, including proteolysis and phosphorylation.

**von Willebrand factor (VWF, P04275)** is a glycoprotein synthesised in vascular endothelial cells as a disulphide-linked homodimer, but multimerises further in plasma and is deposited on vessel wall collagen as a high molecular weight multimer. It is responsible for capturing platelets under arterial shear flow (via GPIb) and in thrombus propagation (via integrin αIIbβ3).

### Subunits

| Nomenclature | HGNC, UniProt | Antibodies |
|--------------|--------------|------------|
| integrin, alpha 1 subunit | ITGA1, P56199 | – |
| integrin, alpha 2 subunit (CD49B, alpha 2 subunit of VLA-2 receptor) | ITGA2, P08514 | – |
| integrin, alpha Ibb subunit (platelet glycoprotein Ibb of Ibb/Illa complex, antigen CD41) | ITGA2B, P17301 | – |
| integrin, alpha 3 subunit (antigen CD49C, alpha 3 subunit of VLA-3 receptor) | ITGA3, P26006 | – |
| integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor) | ITGA4, P13612 | natalizumab (Inhibition) [1] |
| integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide) | ITGA5, P08648 | – |

| Nomenclature | HGNC, UniProt | Antibodies |
|--------------|--------------|------------|
| integrin, alpha 6 subunit | ITGA6, P23229 | – |
| integrin, alpha 7 subunit | ITGA7, Q13683 | – |
| integrin, alpha 8 subunit | ITGA8, P53708 | – |
| integrin, alpha 9 subunit | ITGA9, Q13797 | – |
| integrin, alpha 10 subunit | ITGA10, O75578 | – |
| integrin, alpha 11 subunit | ITGA11, Q9UKXS | – |
| integrin, alpha D subunit | ITGAD, Q13349 | – |

| Nomenclature | HGNC, UniProt | Antibodies |
|--------------|--------------|------------|
| integrin, alpha E subunit (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide) | ITGAE, P38570 | efalizumab (Binding) (pKd 11.4) [81] |
| integrin, alpha L subunit (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide) | ITGAL, P20701 | – |
| integrin, alpha M subunit (complement component 3 receptor 3 subunit) | ITGAM, P11215 | – |
| integrin, alpha V subunit (complement component 3 receptor 4 subunit) | ITGAV, P06756 | – |
| integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) | ITGB1, P05556 | – |

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Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full)
Natriuretic peptide receptor family

Catalytic receptors → Natriuretic peptide receptor family

Overview: Natriuretic peptide receptors (provisional nomenclature) are a family of 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 atrial natriuretic peptide (NPPA, P01160), brain natriuretic peptide (NPPB, P16860) and C-type natriuretic peptide (NPPC, P23582). Another family member is GC-C, the receptor for guanylin (GUCA2A, Q02747) and uroguanylin (GUCA2B, Q16661). Family members have conserved ligand-binding, catalytic (guanylyl cyclase) and regulatory domains with the exception of NPR-C which has an extracellular binding domain homologous to that of other NPRs, 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 [136].
Nomenclature

- guanylate cyclase 2C
- NPR-A
- NPR-B
- NPR-C

HGNC, UniProt

- GUCY2C, P25092
- NPR1, P16066
- NPR2, P20594
- NPR3, P17342

Potency order

- uroguanylin (GUCA2B, Q16661) -> guanylin (GUCA2A, Q02747)
- atrial natriuretic peptide (NPPA, P01160) -> brain natriuretic peptide (NPPB, P16860) -> C-type natriuretic peptide (NPPC, P23582) [173]
- C-type natriuretic peptide (NPPC, P23582) -> atrial natriuretic peptide (NPPA, P01160) -> brain natriuretic peptide (NPPB, P16860) [173]

Endogenous agonists

- atrial natriuretic peptide (NPPA, P01160) (Selective) [144]
- brain natriuretic peptide (NPPB, P16860) (Selective) [144]
- C-type natriuretic peptide (NPPC, P23582) (Selective) [173]
- osteocrin (OSTN, P61366) (Selective) [129]

Selective agonists

- linaclotide (pK_i 8.9) [20, 67], E. coli heat-stable enterotoxin (STa) (pK_i 8.8) [20]
- sANP [144]
- [Ser11](N-CNP, C-ANP)pBNP2-15
- [125I]JANP (human) (Agonist) [125I]JANP (human) [125I]JANP (human)

Selective antagonists

- A-71915 (pK_i 9.2–9.5) [41], [Asu7,23']B-ANP-(7-28) (pK_i 7.5) [83], anantin [202]
- [Ser11]J-N(CNP,C-ANP)pBNP2-15
- AP811 (pK_i 9.3) [185], M372049

Labelled ligands

- [125I]Sta (Agonist) (pK_d 7.8) [66]
- [125I]ANP (human) (Agonist) [125I]JANP (human) [125I]JANP (human)

Comments: The polysaccharide obtained from fermentation of Aureobasidium species, HS142-1, acts as an antagonist at both NPR-A and NPR-B receptors [132].

Further Reading

Kuhn M. (2012) Endothelial actions of atrial and B-type natriuretic peptides. Br. J. Pharmacol. 166: 522-31 [PMID:22220822]
Misono KS et al. (2011) Structure, signaling mechanism and regulation of the natriuretic peptide receptor guanylyl cyclase. FEBS J. 278: 1818-29 [PMID:21375693]
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Potter LR. (2011) Natriuretic peptide metabolism, clearance and degradation. FEBS J. 278: 1808-17 [PMID:21375692]
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Potter LR. (2011) Guanylyl cyclase structure, function and regulation. Cell. Signal. 23: 1921-6 [PMID:21914472]

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Guanylyl cyclase activating peptides GCAP1 (GUCA1A, 43080), GCAP2 (GUCA1B, Q9UMX6) and GCAP3 (GUCA1C, O95843) [78].

Natriuretic peptide receptor family 5995
# Pattern recognition receptors

Catalytic receptors → Pattern recognition receptors

**Overview:** Pattern Recognition Receptors (PRRs, \[174\]) (nomenclature as agreed by NC-IUPHAR sub-committee on Pattern Recognition Receptors, \[18\]) participate in the innate immune response to microbial agents, the stimulation of which leads to activation of intracellular enzymes and regulation of gene transcription. PRRs include both cell-surface and intracellular proteins, including toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs, also known as NOD-like receptors) and the mannos receptor family (ENSF000250000004089). PRRs may be divided into signalling-associated members, identified here, and endocytic members (such as the mannos receptor family), the function of which appears to be to recognise particular microbial motifs for subsequent cell attachment, internalisation and destruction.

PRRs express multiple leucine-rich regions to bind a range of microbially-derived ligands, termed PAMPs or pathogen-associated molecular patterns, which includes peptides, carbohydrates, peptidoglycans, lipoproteins, lipopolysaccharides, and nucleic acids.

**Further Reading**

Bryant CE *et al.* (2015) International Union of Basic and Clinical Pharmacology. XCVI. Pattern recognition receptors in health and disease. *Pharmacol. Rev.* 67: 462-504 [PMID:25829385]

Davis BR *et al.* (2011) The inflammasome NLRs in immunity, inflammation, and associated diseases. *Annu. Rev. Immunol.* 29: 707-35 [PMID:21219188]

Ting JP *et al.* (2008) The NLR gene family: a standard nomenclature. *Immunity* 28: 285-7 [PMID:18341998]

# Toll-like receptor family

Catalytic receptors → Pattern recognition receptors → Toll-like receptor family

**Overview:** Members of the toll-like family of receptors (nomenclature recommended by the NC-IUPHAR subgroup on pattern recognition receptors, \[18\]) share significant homology with the interleukin-1 receptor family and appear to require dimerization either as homo- or heterodimers for functional activity. Heterodimerization appears to influence the potency of ligand binding substantially (e.g. TLR1/2 and TLR2/6, \[175, 176\]). TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11 are cell-surface proteins, while other members are associated with intracellular organelles, signalling through the MyD88-dependent pathways (with the exception of TLR3). 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 (HSPD1, P10809) \[141\].

| Nomenclature | TLR1  |
|-------------|-------|
| HGNC, UniProt | TLR1, Q15399 |
| Agonists | Functions as a heterodimer with TLR2 in detection of triacylated lipoproteins. Activated by the synthetic analogue Pam3CSK4. |
| Comments | Functions as a heterodimer with TLR2, O60603 peptidoglycan [165, 205] |

| Nomenclature | TLR2  |
|-------------|-------|
| HGNC, UniProt | TLR2, O60603 |
| Agonists | Functions as a heterodimer with either TLR1 or TLR6 in the detection of triacylated and diacylated lipopeptides respectively. TLR1/2 and 2/6 heterodimers can be activated by the synthetic lipopeptides Pam3CSK4 and Pam2CSK4 respectively. There is some debate in the field as to whether or not peptidoglycan is a direct agonist of TLR2, or whether the early studies reporting this contained contaminating lipoproteins. |
| Comments | Involved in endosomal detection of dsRNA; pro-inflammatory. |

| Nomenclature | TLR3  |
|-------------|-------|
| HGNC, UniProt | TLR3, O15455 |
| Agonists | polyIC [6] |
| Comments | Involved in endosomal detection of dsRNA; pro-inflammatory. |

| Nomenclature | TLR4  |
|-------------|-------|
| HGNC, UniProt | TLR4, O00206 |
| Agonists | LPS [150], paclitaxel [85] eritoran (E5564) is a lipid A analogue, which has been described as a TLR4 antagonist [80]. TLR4 signals in conjunction with the co-factor MD2. |
| Comments | Involved in the detection of bacterial flagellin; pro-inflammatory. |

| Nomenclature | TLR5  |
|-------------|-------|
| HGNC, UniProt | TLR5, O60602 |
| Agonists | |
| Comments | |

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Overview: The nucleotide-binding oligomerization domain, leucine-rich repeat (NLR) family of receptors (nomenclature recommended by the IUPHAR Subcommittee on Pattern Recognition Receptors) consists of an N-terminal effector domain, a central nucleotide-binding and oligomerization domain (NOD), and a C-terminal leucine-rich repeats (LR). Upon activation, the NLR family members NOD1 (NLR1) and NOD2 (NLR2) recruit a serine/threonine kinase RIPK2 (receptor interacting serine/threonine kinase 2, O43353), also known as CARD3, CARDIAK, RICK, RIP2, leading to signaling through NFκB and MAP kinase. Activation of NLR family members NLRP1 and NLRP3 leads to formation of multiprotein complex known as the inflammasome. In addition to NLR proteins, other key members of the inflammasome include the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD, PYCARD, CARD5, TMS1, Q9ULZ3) and inflammatory caspases. The inflammasome activates the pro-inflammatory cytokines IL-1β (IL1B, P01584) and IL-18 (IL18, Q14116) and IL-1A (IL1A, P01585) and IL-18 (IL18, Q14116) [18, 37].

Further Reading
Bryant CE et al. (2015) International Union of Basic and Clinical Pharmacology. XLV. Pattern recognition receptors in health and disease. Pharmacol. Rev. 67, 462-504 [PMID:25829385]
| Nomenclature | nucleotide-binding oligomerization domain containing 1 | nucleotide-binding oligomerization domain containing 2 | NLRC3 | NLRC4 | NLRC5 |
|--------------|------------------------------------------------------|------------------------------------------------------|-------|-------|-------|
| Common abreviation | NOD1 | NOD2 | – | – | – |
| HGNC, UniProt | **NOD1, Q9Y239** | **NOD2, Q9HC29** | **NLRC3, Q7RTR2** | **NLRC4, Q9NP4** | **NLRC5, Q86W13** |
| Agonists | meso-DAP | – | – | – | – |
| Comments | NOD2 has also been reported to be activated by ssRNA [160] although this has not been widely reproduced. | – | – | – | – |

**Nomenclature**

| **NLRX1** | **CIITA** | **NLRP1** | **NLRP2** |
|-----------|------------|-----------|-----------|
| HGNC, UniProt | **NLRX1, Q86UT6** | **CIITA, P33076** | **NLRP1, Q9C000** |
| Agonists | – | – | – |
| Comments | – | – | – |

**Nomenclature**

| **NLRP3** | **NLRP4** | **NLRP5** | **NLRP6** |
|-----------|------------|-----------|-----------|
| HGNC, UniProt | **NLRP3, Q96P20** | – | – |
| Inhibitors | MCC950 (pIC<sub>50</sub> >8) [30] | – | – |
| Comments | Multiple virus particles have been shown to act as agonists, including Sendai and influenza. NLRP3 has been shown to be activated following disruption of cellular haemostasis by a wide-variety of exogenous and endogenous molecules. The identity of the precise agonist that interacts with NLRP3 remains enigmatic. | Expanded in the mouse resulting in 7 orthologues. | – |
Receptor serine/threonine kinase (RSTK) family

**Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family**

**Overview:** Receptor serine/threonine kinases (RSTK), EC 2.7.11.30, respond to particular cytokines, the transforming growth factor β (TGFβ) and bone morphogenetic protein (BMP) families, and may be divided into two subfamilies on the basis of structural similarities. Agonist binding initiates formation of a cell-surface complex of type I and type II RSTK, possibly heterotrameric, where where both subunits express serine/threonine kinase activity. The type I receptor serine/threonine kinases are also known as activin receptors or activin receptor-like kinases, ALKs, for which a systematic nomenclature has been proposed (ALK1-7). The type II protein phosphorylates the kinase domain of the type I partner (sometimes referred to as the signal propagating subunit), causing displacement of the protein partners, such as the FKBPI2 FK506-binding protein FKBPIA (P62942) and allowing the binding and phosphorylation of particular members of the Smad family. These migrate to the nucleus and act as complexes to regulate gene transcription. Type III receptors, sometimes called co-receptors or accessory proteins, regulate the signalling of the receptor complex, in either enhancing (for example, presenting the ligand to the receptor) or inhibitory manners. TGFβ family ligand signalling may be inhibited by endogenous proteins, such as follistatin (FST, P19883), which binds and neutralizes activins to prevent activation of the target receptors. Endogenous agonists, approximately 30 in man, are often described as paracrine messengers acting close to the source of production. They are characterized by six conserved cysteine residues and are divided into two subfamilies on the basis of sequence comparison and signalling pathways activated, the TGFβ/activin/nodal subfamily and the BMP/GDF (growth/differentiation factor)/MIS (Müllerian inhibiting substance) subfamily. Ligands active at RSTKs appear to be generated as large precursors which undergo complex maturation processes [105]. Some are known to form disulphide-linked homo- and/or heterodimeric complexes. Thus, inhibins are α subunits linked to a variety of β chains, while activins are combinations of β subunits.

**Further Reading**
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**Searchable database:** [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full)
Comments: A number of endogenous inhibitory ligands have been identified for RSTKs, including BMP-3 (BMP3, P12645), inhibin α (INHA, P05111), inhibin βC (INHBC, P55103) and inhibin βE (INHBE, P58166).

An appraisal of small molecule inhibitors of TGFβ and BMP signalling concluded that TGFβ pathway inhibitors were more selective than BMP signalling inhibitors [186]. The authors confirmed the selectivity of TGF-beta RI inhibitor III to inhibit TGFβ signalling through ALK4, ALK5, ALK7 [36]. Dorsomorphin inhibits BMP signalling through ALK2 and ALK3, it also inhibits AMP kinase [209].

Smads were identified as mammalian orthologues of Drosophila genes termed “mothers against decapentaplegic” and may be divided into Receptor-regulated Smads (R-Smads, including Smad1, Smad2, Smad3, Smad5 and Smad8), Co-mediated Smad (Co-Smad, Smad4) and Inhibitory Smads (I-Smad, Smad6 and Smad7). R-Smads form heteromeric complexes with Co-Smad. I-Smads compete for binding of R-Smad with both receptors and Co-Smad.

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Type I receptor serine/threonine kinases

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → Type I receptor serine/threonine kinases

Overview: The type I receptor serine/threonine kinases are also known as activin receptors or activin receptor-like kinases, ALKs, for which a systematic nomenclature has been proposed (ALK1-7).

| Nomenclature | activin A receptor type II-like 1 | activin A receptor, type I | bone morphogenetic protein receptor, type IA | activin A receptor, type IB |
|--------------|----------------------------------|---------------------------|---------------------------------------------|---------------------------|
| Common abreviation | ALK1                             | ALK2                      | BMPR1A                                       | ALK4                       |
| HGNC, UniProt | ACVRL1, P37023                   | ACVR1, Q04771             | BMRPR1A, P36894                              | ACVR1B, P36896             |
| EC number    | 2.7.11.30                        | 2.7.11.30                 | 2.7.11.30                                    | 2.7.11.30                 |
| Inhibitors   | compound 13d [PMID: 23639540] (pIC50 > 8.3) [45] | compound 13d [PMID: 23639540] (pIC50 > 8.3) [45] | compound 13d [PMID: 23639540] (pIC50 > 8.3) [45] | compound 13d [PMID: 23639540] (pIC50 > 8.3) [45] |
| Selective inhibitors | –                                | –                         | –                                           | EW-7197 (pIC50 7.9) [82] |

Searchable database: http://www.guidetopharmacology.org/index.jsp

Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full
### Nomenclature

| Nomenclature | transforming growth factor, beta receptor 1 | bone morphogenetic protein receptor, type IB | activin A receptor, type IC |
|--------------|---------------------------------------------|---------------------------------------------|-----------------------------|
| Common abreviation | TGFBR1 | BMPR1B | ALK7 |
| HGNC, UniProt | TGFBR1, P36897 | BMPR1B, Q00238 | ACVR1C, Q8NER5 |
| EC number | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 |
| Inhibitors | LY2109761 (pK_i 7.4) [125], compound 15b [PMID: 16539403] (pIC_50 7.1) [104] | compound 13d [PMID: 23639540] (pIC_50 >8.3) [45] | – |
| Selective inhibitors | EW-7197 (pIC_50 8) [82] | – | – |

### Type II receptor serine/threonine kinases

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → Type II receptor serine/threonine kinases

| Nomenclature | activin A receptor, type IIA | activin A receptor, type IIB | anti-Mullerian hormone receptor, type II | bone morphogenetic protein receptor, type II (serine/threonine kinase) | transforming growth factor, beta receptor II (70/80kDa) |
|--------------|-----------------------------|-----------------------------|------------------------------------------|-------------------------------------------------|--------------------------------------------------|
| Common abreviation | ActR2 | ActR2B | MISR2 | BMPR2 | TGFBR2 |
| HGNC, UniProt | ACVR2A, P27037 | ACVR2B, Q13705 | AMHR2, Q16671 | BMPR2, Q13873 | TGFBR2, P37173 |
| EC number | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 |
| Inhibitors | – | – | – | – | compound 13d [PMID: 23639540] (pIC_50 7.6) [45] |
| Antibodies | – | bimagrumab (Binding) (pK_d 11.8) [12] | – | – | – |

### Type III receptor serine/threonine kinases

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → Type III receptor serine/threonine kinases

| Nomenclature | transforming growth factor, beta receptor III |
|--------------|---------------------------------------------|
| Common abreviation | TGFBR3 |
| HGNC, UniProt | TGFBR3, Q03167 |

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full)
# RSTK functional heteromers

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → RSTK functional heteromers

Overview: For the receptors listed on this page, the exact combination of subunits forming the functional heteromeric receptors is unknown.

| Nomenclature | Transforming growth factor β receptor transforming growth factor, beta receptor I (Type I), transforming growth factor, beta receptor III (Type III), transforming growth factor, beta receptor II (70/80kDa) (Type II) | Bone morphogenetic protein receptors bone morphogenetic protein receptor, type IB (Type I), activin A receptor, type IIB (Type II), activin A receptor, type IIA (Type II), activin A receptor type II-like 1 (Type I), activin A receptor, type IA (Type I), bone morphogenetic protein receptor, type IA (Type I), bone morphogenetic protein receptor, type II (serine/threonine kinase) (Type II) | Growth/differentiation factor receptors transforming growth factor, beta receptor 1 (Type I), bone morphogenetic protein receptor, type IB (Type I), activin A receptor, type IIB (Type II), activin A receptor, type IIA (Type II), activin A receptor, type IIA (Type II), activin A receptor, type IC (Type I), activin A receptor, type IB (Type I) | Activin receptors activin A receptor, type IIB (Type II), activin A receptor, type IIA (Type II), activin A receptor, type IC (Type I), activin A receptor, type IB (Type I) | Anti-Müllerian hormone receptors anti-Müllerian hormone receptor, type II (Type II), bone morphogenetic protein receptor, type I (Type I), activin A receptor, type I (Type I), bone morphogenetic protein receptor, type IA (Type I) |
|--------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Subunits     |                                                                 |                                                                                                |                                                                                              |                                                                                              |                                                                                                 |
| Coupling     | Smad2, Smad3 [134, 167]                                        | Smad1, Smad5, Smad8 [134, 167]                                                                  | Smad1, Smad5, Smad8 [134, 167]                                                              | Smad2, Smad3 [167]                                                                            | Smad1, Smad5, Smad8 [134, 167]                                                                 |
| Endogenous agonists | TGFB1 (TGF81, P01137), TGFB2 (TGF82, P61812), TGFB3 (TGF83, P10600) | BMP-10 (BMP10, O95393), BMP-2 (BMP2, P12643), BMP-4 (BMP4, P12644), BMP-5 (BMP5, P22003), BMP-6 (BMP6, P22004), BMP-7 (BMP7, P18075), BMP-8A (BMP8A, Q7Z516), BMP-8B (BMP8B, P34820), BMP-9 (GDF2, Q9UK05) | growth/differentiation factor-1 (GDF1, P27539), growth/differentiation factor-10 (GDF10, P55107), growth/differentiation factor-3 (GDF3, Q9NR23), growth/differentiation factor-7 (GDF7, Q7Z4P5), growth/differentiation factor-9 (GDF9, O60383) | activin A (INHBA, P08476), activin AB (INHBA INHBB, P08476 P09529), activin B (INHBB, P09529), inhibin A (INHA INHBB, P05111 P08476) | Müllerian inhibiting substance (AMH, P03971) |
| Comments     | –                                                               |                                                                                                | –                                                                                            | –                                                                                            | –                                                                                                 |
Receptor tyrosine kinases

**Overview:** Receptor tyrosine kinases (RTKs), a family of cell-surface receptors, which transduce signals to polypeptide and protein hormones, cytokines and growth factors are key regulators of critical cellular processes, such as proliferation and differentiation, cell survival and metabolism, cell migration and cell cycle control [14, 62, 184]. In the human genome, 58 RTKs have been identified, which fall into 20 families [102]. All RTKs display an extracellular ligand binding domain, a single transmembrane helix, a cytoplasmic region containing the protein tyrosine kinase activity (occasionally split into two domains by an insertion, termed the kinase insertion), with juxta-membrane and C-terminal regulatory regions. Agonist binding to the extracellular domain evokes dimerization, and sometimes oligomerization, of RTKs (a small subset of RTKs forms multimers even in the absence of activating ligand). This leads to autophosphorylation in the tyrosine kinase domain in a trans orientation, serving as a site of assembly of protein complexes and stimulation of multiple signal transduction pathways, including phospholipase C-γ, mitogen-activated protein kinases and phosphatidylinositol 3-kinase [184]. RTKs are of widespread interest not only through physiological functions, but also as drug targets in many types of cancer and other disease states. Many diseases result from genetic changes or abnormalities that either alter the activity, abundance, cellular distribution and/or regulation of RTKs. Therefore, drugs that modify the dysregulated functions of these RTKs have been developed which fall into two categories. One group is often described as 'biologicals', which block the activation of RTKs directly or by chelating the cognate ligands, while the second are small molecules designed to inhibit the tyrosine kinase activity directly.

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Type I RTKs: ErbB (epidermal growth factor) receptor family

Overview: ErbB family receptors are Class I receptor tyrosine kinases [62]. ERBB2 (also known as HER-2 or NEU) appears to act as an essential partner for the other members of the family without itself being activated by a cognate ligand [63]. Ligands of the ErbB family of receptors are peptides, many of which are generated by proteolytic cleavage of cell-surface proteins. HER/ErbB is the viral counterpart to the receptor tyrosine kinase EGFR. All family members heterodimerize with each other to activate downstream signalling pathways and are aberrantly expressed in many cancers, particularly forms of breast cancer.

| Nomenclature | epidermal growth factor receptor | erb-b2 receptor tyrosine kinase | erb-b2 receptor tyrosine kinase 3 | erb-b2 receptor tyrosine kinase 4 |
|--------------|---------------------------------|---------------------------------|-----------------------------------|-----------------------------------|
| Common abreviation | EGFR | HER2 | HER3 | HER4 |
| HGNC, UniProt | EGF, P00533 | EBB82, P04626 | EBB83, P21860 | EBB4, Q15303 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | EGF (EGF, P01133) (Binding), HB-EGF (HBEGF, Q99075) (Binding), TGFα (TGFA, P01135) (Binding), amphiregulin (AREG, P15514) (Binding), betacellulin (BTC, P35070) (Binding), epigen (EPGN, Q6UW88) (Binding), epiregulin (EREG, O14944) (Binding) | – | neuregulin-1 (NRG1, Q02297), neuregulin-2 (NRG2, Q15411) | HB-EGF (HBEGF, Q99075), betacellulin (BTC, P35070), epiregulin (EREG, O14944), neuregulin-1 (NRG1, Q02297), neuregulin-2 (NRG2, Q15411), neuregulin-3 (NRG3, P56975), neuregulin-4 (NRG4, Q8WGG1) |
| Inhibitors | canertinib (pKd 9.7) [38], afatinib (pKd 9.6) [38], XL-647 (pIC50 9.5) [57], afatinib (pIC50 8–9.3) [33, 103], erlotinib (pKd 9.2) [38], erlotinib (pIC50 9) [207], gefitinib (pKd 9) [38], canertinib (pIC50 8.8) [170], BMS-690514 (pIC50 8.3) [117], gefitinib (pKi 8.3) [197], AG1478 (pIC50 8.2) [181], poziotinib (pIC50 8.1) [140], lapatinib (pIC50 8) [159], CP-724714 (pIC50 7.9) [65], XL-647 (pIC50 7.8) [57], BMS-690514 (pIC50 7.7) [117], neratinib (pIC50 7.2) [183], EGF/ErbB-2 inhibitor (pIC50 7.1) [28] | poziotinib (pIC50 8.3) [140], neratinib (pKd 8.2) [38], lapatinib (pKd 8.1) [38], lapatinib (pIC50 8) [159], CP-724714 (pIC50 7.9) [65], XL-647 (pIC50 7.8) [57], BMS-690514 (pIC50 7.7) [117], neratinib (pIC50 7.2) [183], EGF/ErbB-2 inhibitor (pIC50 7.1) [28] | – | poziotinib (pIC50 7.6) [140] |
| Antibodies | necitumumab (Binding) (pKd 9.5) [111], cetuximab (Binding) (pKd 9.4) [60], panitumumab (Inhibition) | pertuzumab (Inhibition) (pIC50 >8) [84], trastuzumab (Inhibition) | – | – |

Comments: [125I]EGF (human) has been used to label the ErbB1 EGF receptor. 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, [54]), gefitinib, erlotinib and tyrphostins AG879 and AG1478.
Type II RTKs: Insulin receptor family

Overview: The circulating peptide hormones insulin (INS, P01308) and the related insulin-like growth factors (IGF) activate Class II receptor tyrosine kinases [62], to evoke cellular responses, mediated through multiple intracellular adaptor proteins. Exceptionally amongst the catalytic receptors, the functional receptor in the insulin receptor family is derived from a single gene product, cleaved post-translationally into two peptides, which then cross-link via disulphide bridges to form a heterotetramer. Intriguingly, the endogenous peptide ligands are formed in a parallel fashion with post-translational processing producing a heterodimer linked by disulphide bridges. Signalling through the receptors is mediated through a rapid autophosphorylation event at intracellular tyrosine residues, followed by recruitment of multiple adaptor proteins, notably IRS1 (P35568), IRS2 (Q9Y4H2), SHC1 (P29353), GRB2 (P62993) and SOS1 (Q07889). Serum levels of free IGFS are kept low by the action of IGFBP binding proteins (IGFBP1-5, P08833, P18065, P17936, P22692, P24593), which sequester the IGFS; overexpression of IGFBPs may induce apoptosis, while IGFBP levels are also altered in some cancers.

| Nomenclature | Insulin receptor | Insulin-like growth factor I receptor | Insulin receptor-related receptor |
|--------------|----------------|-------------------------------------|---------------------------------|
| Common abreviation | InsR | IGF1R | IRR |
| HGNC, UniProt | IRS, P06213 | IGF1R, P08069 | INSRR, P14616 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | – | BMS-754807 (pIC50 8.7) [199], GSK-1838705A (pIC50 8.7) [161], GSK-1838705A (pKd 8.1) [38], PQ401 (pIC50 >6) [50], AG 1024 (pIC50 4.7) [153] | – |
| Selective inhibitors | – | NVP-AEW541 (pIC50 9.4) [53] | – |
| Endogenous agonists | insulin (INS, P01308) | insulin-like growth factor 1 (IGF1, P05019), insulin-like growth factor 2 (IGF2, P01344) | – |

Comments: There is evidence for low potency binding and activation of insulin receptors by IGF1. IGF2 also binds and activates the cation-independent mannose 6-phosphate receptor (also known as the insulin-like growth factor II receptor), which lacks classical signalling capacity and appears to subserve a trafficking role [115]. INSRR, which has a much more discrete localization, being predominant in the kidney [95], currently lacks a cognate ligand or evidence for functional impact. Antibodies targeting IGF1, IGF2 and the extracellular portion of the IGF1 receptor are in clinical trials. PQ401 inhibits the insulin-like growth factor receptor [5], while BMS-536924 inhibits both the insulin receptor and the insulin-like growth factor receptor [198].

Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family

Overview: Type III RTKs include PDGFR, CSF-1R (Ems), Kit and FLT3, which function as homo- or heterodimers. Endogenous ligands of PDGF receptors are homo- or heterodimeric: PDGFA, PDGFB, VEGF and PDGF (PDGF, Q9GZP0) combine as homo- or heterodimers to activate homo- or heterodimeric PDGF receptors. SCF is a dimeric ligand for KIT. Ligands for CSF1R are either monomeric or dimeric glycoproteins, while the endogenous agonist for FLT3 is a homodimer.

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full
### Nomenclature
- Platelet-derived growth factor receptor, alpha polypeptide (PDGFRα)
- Platelet-derived growth factor receptor, beta polypeptide (PDGFRβ)
- v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (Kit)
- Colony stimulating factor 1 receptor (CSF1R)
- Fms-related tyrosine kinase 3 (FLT3)

### Common abbreviations
- PDGFRα
- PDGFRβ
- KIT, P10721
- CSF1R, P09603
- FLT3, P36888

### EC numbers
- 2.7.10.1

### Endogenous ligands
- PDGF
- Stem cell factor (KITLG, P21583)
- Granulocyte colony-stimulating factor (G-CSF, CSF3, P09919)
- Granulocyte-macrophage colony-stimulating factor (GM-CSF, CSF2, P04141)
- Macrophage colony-stimulating factor (M-CSF, CSF1, P09603)
- Fms-related tyrosine kinase 3 ligand (FLT3LG, P49771)

### Inhibitors
| Inhibitors | PDGF (pIC₅₀ 8.7) [7] | crenolanib (pKᵦ 8.5) [71] | sunitinib (pKᵦ 9.4) [38] | famitinib (pIC₅₀ 8.7) [24] | masitinib (pKᵦ 8.1) [38] | SU-14813 (pIC₅₀ 7.8) [147] | AKN-028 (pIC₅₀ 7.5) [46] | sunitinib (pIC₅₀ 7.2) [196] | JNJ-28312141 (pIC₅₀ 9.2) [116] | Ki-20227 (pKᵦ 9.1) [38] | Ki-20227 (pIC₅₀ 8.7) [143] | GW-2580 (pKᵦ 8.7) [38] | JNJ-28312141 (pKᵦ 8.5) [38] | AC710 (pKᵦ 9.3) [109] | linifanib (pKᵦ 9.2) [38] | dovitinib (pKᵦ 9.2) [38] | crenolanib (pKᵦ 9.1) [71] | AST-487 (pKᵦ 9.1) [38] | compound 8h [PMID: 22765894] | dovitinib (pIC₅₀ 8.5–9) [157, 183] | ENMD-2076 (pIC₅₀ 8.5) [149] | tandutinib (pKᵦ 8.5) [38] | quazartinib (pIC₅₀ 8.4) [206] | AKN-028 (pIC₅₀ 8.2) [46] | KW-2449 (pIC₅₀ 8.2) [168] | lestaurtinib (pKᵦ 8.1) [38] | midostaurin (pKᵦ 8.3) [38] | KW-2449 (pKᵦ 7.8) [38] | sunitinib (pIC₅₀ 7.2) [196] | AST-487 (pKᵦ 6.9) [193] | tandutinib (pIC₅₀ 6.7) [86] | AST-487 (pIC₅₀ 6.3) [2] | midostaurin (pIC₅₀ 6.3) [192] | 5'-fluoroindirubinoxime has been described as a selective FLT3 inhibitor [25].

### Comments
- Various small molecular inhibitors of type III RTKs have been described, including imatinib and nilotinib (targetting PDGFR, KIT and CSF1R); midostaurin and AC220 (quazartinib; FLT3), as well as pan-type III RTK inhibitors such as sunitinib and sorafenib [148]; 5'-fluoroindirubinoxime has been described as a selective FLT3 inhibitor [2].
**Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family**

**Overview:** VEGF receptors are homo- and heterodimeric proteins, which are characterized by seven Ig-like loops in their extracellular domains and a split kinase domain in the cytoplasmic region. They are key regulators of angiogenesis and lymphangiogenesis; as such, they have been the focus of drug discovery for conditions such as metastatic cancer. Splice variants of VEGFR1 and VEGFR2 generate truncated proteins limited to the extracellular domains, capable of homodimerisation and binding VEGF ligands as a soluble, non-signalling entity. Ligands at VEGF receptors are typically homodimeric. VEGFA (VEGFA, P15692) is able to activate VEGFR1 homodimers, VEGFR1/2 heterodimers and VEGFR2/3 heterodimers. VEGFB (VEGFB, P49765) and placental growth factor (PGF, P49763) activate VEGFR1 homodimers, while VEGFC (VEGFC, P49767) and VEGFD (FIGF, O43915) activate VEGFR2/3 heterodimers and VEGFR3 homodimers, and, following proteolysis, VEGFR2 homodimers.

| Nomenclature | fms-related tyrosine kinase 1 | kinase insert domain receptor | fms-related tyrosine kinase 4 |
|--------------|------------------------------|------------------------------|------------------------------|
| Common abreviation | VEGFR-1 | VEGFR-2 | VEGFR-3 |
| HGNC, UniProt | FLT1, P17948 | KDR, P35968 | FLT4, P35916 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | VEGFA (VEGFA, P15692), VEGFB (VEGFB, P49765) | VEGFA (VEGFA, P15692), VEGFC (VEGFC, P49767), VEGFE (PDGFC, Q9NRA1) | VEGF (VEGFC, P49767), VEGFD (FIGF, O43915), VEGFE (PDGFC, Q9NRA1) |
| Inhibitors | SU-14813 (pIC<sub>50</sub> 8.7) [147], CEP-11981 (pIC<sub>50</sub> 8.5) [77], semaxanib (pIC<sub>50</sub> 8.1) [15] | axitinib (pIC<sub>50</sub> 9.6) [100], caboazitinib (pIC<sub>50</sub> 9.5) [203], foretinib (pIC<sub>50</sub> 8.2-9.1) [137], cediranib (pK<sub>d</sub> 9) [38], XL-647 (pIC<sub>50</sub> 8.8) [57], compound 13a (pIC<sub>50</sub> 8.8) [45], SU-14813 (pIC<sub>50</sub> 8.6) [38], motesanib (pK<sub>d</sub> 8.6) [38], famitinib (pIC<sub>50</sub> 8.3) [24], axitinib (pK<sub>d</sub> 8.2) [38], PLX-4720 (pK<sub>i</sub> 8.1) [126], CP-547632 (pIC<sub>50</sub> 8) [11], PP121 (pIC<sub>50</sub> 7.9) [7], golvatinib (pIC<sub>50</sub> 7.8) [139], brivanib (pIC<sub>50</sub> 7.6) [13], ENMD-2076 (pIC<sub>50</sub> 7.4) [149], BMS-690548 (pIC<sub>50</sub> 7.3) [117], SU-14813 (pIC<sub>50</sub> 7.3) [117], sorafenib (pK<sub>d</sub> 7.2) [38], vatalanib (pK<sub>d</sub> 7.2) [38], sorafenib (pIC<sub>50</sub> 7.1) [196] | XL-647 (pIC<sub>50</sub> 8.1) [57], sunitinib (pIC<sub>50</sub> 8.1) [87], nintedanib (pIC<sub>50</sub> 7.9) [74] |
| (Sub)family-selective inhibitors | pazopanib (pIC<sub>50</sub> 8) [68] | pazopanib (pK<sub>d</sub> 7.8) [38], pazopanib (pIC<sub>50</sub> 7.5) [68] | pazopanib (pIC<sub>50</sub> 7.3) [68] |
| Antibodies | – | ramucirumab (Antagonist) (pIC<sub>50</sub> 9) [113] | – |

**Comments:** The VEGFR, as well as VEGF ligands, have been targeted by antibodies and tyrosine kinase inhibitors. DMH4 [49], Ki8751 [94] and ZM323881, a novel inhibitor of vascular endothelial growth factor-receptor-2 tyrosine kinase activity [195] are described as VEGFR2-selective tyrosine kinase inhibitors. Bevacizumab is a monoclonal antibody directed against VEGF-A, used clinically for the treatment of certain metastatic cancers; an antibody fragment has been used for wet age-related macular degeneration.
Type V RTKs: FGF (fibroblast growth factor) receptor family

Overview: Fibroblast growth factor (FGF) family receptors act as homo- and heterodimers, and are characterized by Ig-like loops in the extracellular domain, in which disulphide bridges may form across protein partners to allow the formation of covalent dimers which may be constitutively active. FGF receptors have been implicated in achondroplasia, angiogenesis and numerous congenital disorders. At least 22 members of the FGF gene family have been identified in the human genome [11]. Within this group, subfamilies of FGF may be divided into canonical, intracellular and hormone-like FGFs. FGF1-FGF10 have been identified to act through FGF receptors, while FGF11-14 appear to signal through intracellular targets. Other family members are less well characterized [194].

| Nomenclature                                                                 | fibroblast growth factor receptor 1 | fibroblast growth factor receptor 2 | fibroblast growth factor receptor 3 | fibroblast growth factor receptor 4 |
|------------------------------------------------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Common abbreviation                                                         | FGFR1                               | FGFR2                               | FGFR3                               | FGFR4                               |
| HGNC, UniProt                                                                | FGFR1, P11362                       | FGFR2, P21802                       | FGFR3, P22607                       | FGFR4, P22455                       |
| EC number                                                                    | 2.7.10.1                            | 2.7.10.1                            | 2.7.10.1                            | 2.7.10.1                            |
| Endogenous ligands                                                           | FGF-1 (FGF1, P05230), FGF-2 (FGF2, P09038), FGF-4 (FGF4, P08620) – FGF-5 (FGF5, P12034), FGF-6 (FGF6, P10767) [145] | FGF-1 (FGF1, P05230) – FGF-4 (FGF4, P08620), FGF-7 (FGF7, P21781), FGF-9 (FGF9, P31371) – FGF-2 (FGF2, P09038), FGF-6 (FGF6, P10767) [145] | FGF-1 (FGF1, P05230), FGF-2 (FGF2, P09038), FGF-4 (FGF4, P08620), FGF-9 (FGF9, P31371) – FGF-6 (FGF6, P10767), FGF-8 (FGF8, P55075) [145] | FGF-1 (FGF1, P05230), FGF-2 (FGF2, P09038), FGF-4 (FGF4, P08620), FGF-9 (FGF9, P31371) – FGF-6 (FGF6, P10767), FGF-8 (FGF8, P55075) [145] |
| (Sub)family-selective inhibitors                                              | LY287455 (pIC_{50} 8.6) [208]       | LY287455 (pIC_{50} 8.6) [208]       | LY287455 (pIC_{50} 8.2) [208]       | LY287455 (pIC_{50} 8.2) [208]       |
| Agonists                                                                     | –                                   | palifermin                          | –                                   | –                                   |
| **Comments**: Splice variation of the receptors can influence agonist responses. FGFRL1 (Q8N444) is a truncated kinase-null analogue. Various antibodies and tyrosine kinase inhibitors have been developed against FGF receptors [107, 210]. PD161570 is an FGFR tyrosine kinase inhibitor [10], while PD173074 has been described to inhibit FGFR1 and FGFR3 [169].

Type VI RTKs: PTK7/CCK4

Overview: The PTK7 receptor is associated with polarization of epithelial cells and the development of neural structures. Sequence analysis suggests that the gene product is catalytically inactive as a protein kinase, although there is evidence for a role in Wnt signalling [152].

| Nomenclature                                                                 | protein tyrosine kinase 7 (inactive) |
|------------------------------------------------------------------------------|-------------------------------------|
| Common abbreviation                                                         | CCK4                                 |
| HGNC, UniProt                                                                | PTK7, Q13308                         |
| EC number                                                                    | 2.7.10.1                             |
Type VII RTKs: Neurotrophin receptor/Trk family

Overview: The neurotrophin receptor family of RTKs include trkA, trkB and trkC (tropomyosin-related kinase) receptors, which respond to NGF, BDNF and neurotrophin-3, respectively. They are associated primarily with proliferative and migration effects in neural systems. Various isoforms of neurotrophin receptors exist, including truncated forms of trkB and trkC, which lack catalytic domains. p75 (TNFRSF16, also known as nerve growth factor receptor), which has homologies with tumour necrosis factor receptors, 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 | neurotrophic tyrosine kinase, receptor, type 1 | neurotrophic tyrosine kinase, receptor, type 2 | neurotrophic tyrosine kinase, receptor, type 3 |
|--------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Common abreviation | trkA | trkB | trkC |
| HGNC, UniProt | NTRK1, P04629 | NTRK2, Q16620 | NTRK3, Q16288 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | NGF (NGF, P01138) > neurotrophin-3 (NTF3, P20783) | BDNF (BDNF, P23560), neurotrophin-4 (NTF4, P34130) > neurotrophin-3 (NTF3, P20783) | – |
| Inhibitors | compound 2c [PMID: 24900538] (pIC₅₀ 8.9) [189], milciclib (pIC₅₀ 7.3) [17] | – | neurotrophin-3 (NTF3, P20783) |
| (Sub)family-selective inhibitors | AZD1332 (pIC₅₀ > 8.3) [9], GNF-5837 (pIC₅₀ 8.5) [5] | AZD1332 (pIC₅₀ > 8.3) [9], GNF-5837 (pIC₅₀ 8.1) [5] | AZD1332 (pIC₅₀ > 8.3) [9], GNF-5837 (pIC₅₀ 8.1) [5] |

Comments: [125I]NGF (human) and [125I]BDNF (human) have been used to label the trkA and trkB receptor, respectively. p75 influences the binding of NGF (NGF, P01138) and neurotrophin-3 (NTF3, P20783) to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neurones, it binds neurotrophin-3 (NTF3, P20783) with comparable affinity to trkC [40]. Small molecular agonists of trkB have been described, including LM22A4 [123], while ANA12 has been described as a non-competitive antagonist of BDNF binding to trkB [23]. GNF5837 is a family-selective tyrosine kinase inhibitor [4], while the tyrosine kinase activity of the trkA receptor can be inhibited by GW441756 (pIC₅₀= 8.7, [200]) and tyrphostin AG879 [142].

Comments: Thus far, no selective PTK7 inhibitors have been described.

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full
Type VIII RTKs: ROR family

Overview: Members of the ROR family appear to be activated by ligands complexing with other cell-surface proteins. Thus, ROR1 and ROR2 appear to be activated by Wnt-5a (WNT5A, P41221) binding to a Frizzled receptor thereby forming a cell-surface multiprotein complex [64].

| Nomenclature | receptor tyrosine kinase-like orphan receptor 1 | receptor tyrosine kinase-like orphan receptor 2 |
|--------------|-----------------------------------------------|-----------------------------------------------|
| Common abreviation | ROR1 | ROR2 |
| HGNC, UniProt | ROR1, Q01973 | ROR2, Q01974 |
| EC number | 2.7.10.1 | 2.7.10.1 |

Type IX RTKs: MuSK

Overview: The muscle-specific kinase MuSK is associated with the formation and organisation of the neuromuscular junction from the skeletal muscle side. Agrin (AGRN, O00468) forms a complex with low-density lipoprotein receptor-related protein 4 (LRP4, O75096) to activate MuSK [89].

| Nomenclature | muscle, skeletal, receptor tyrosine kinase |
|--------------|-------------------------------------------|
| Common abreviation | MuSK |
| HGNC, UniProt | MUSK, O15146 |
| EC number | 2.7.10.1 |

Comments: Thus far, no selective MuSK inhibitors have been described.

Type X RTKs: HGF (hepatocyte growth factor) receptor family

Overview: HGF receptors regulate maturation of the liver in the embryo, as well as having roles in the adult, for example, in the innate immune system. HGF is synthesized as a single gene product, which is post-translationally processed to yield a heterodimer linked by a disulphide bridge. The maturation of HGF is enhanced by a serine protease, HGF activating complex, and inhibited by HGF-inhibitor 1 (SPINT1, O43278), a serine protease inhibitor. MST1, the ligand of RON, is a two disulphide-linked peptide chains generated by proteolysis of a single gene product.
### Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family

**Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family**

**Overview:** Members of this RTK family represented a novel structural motif, when sequenced. The ligands for this family, growth arrest specific protein 6 (GAS6, Q14393) and protein S (PROS1, P07225), are secreted plasma proteins which undergo vitamin K-dependent post-translational modifications generating carboxyglutamate-rich domains which are able to bind to negatively-charged surfaces of apoptotic cells.

| Nomenclature                        | AXL receptor tyrosine kinase | TYRO3 protein tyrosine kinase | MER proto-oncogene, tyrosine kinase |
|-------------------------------------|------------------------------|--------------------------------|-------------------------------------|
| Common abbreviation                | Axl                          | Tyro3                          | Mer                                 |
| HGNC, UniProt                      | AXL, P30530                  | TYRO3, Q06418                  | MERTK, Q12866                       |
| EC number                          | 2.7.10.1                     | 2.7.10.1                       | 2.7.10.1                            |
| Endogenous ligands                 | growth arrest specific protein 6 (GAS6, Q14393) [138], protein S (PROS1, P07225) [172] | growth arrest specific protein 6 (GAS6, Q14393) [138], protein S (PROS1, P07225) [172] | growth arrest specific protein 6 (GAS6, Q14393) [138] |

**Comments:** AXL tyrosine kinase inhibitors have been described [130].

### Nomenclature

| MET proto-oncogene, receptor tyrosine kinase | macrophage stimulating 1 receptor |
|--------------------------------------------|-----------------------------------|
| Common abbreviation                        | HGNC, UniProt                     |
| MET                                         | MET, P08581                        |
| HGNC, UniProt                               | MST1R, Q04912                     |
| EC number                                  | 2.7.10.1                           |
| Endogenous ligands                         | hepatocyte growth factor (HGF, P14210) |
| Inhibitors                                  | capmatinib (pIC$_{50}$ 9.9) [112], SGX-523 (pK$_{d}$ 9.7) [38], PHA-665752 (pK$_{d}$ 9.6) [38], foretinib (pIC$_{50}$ 9.3–9.4) [106, 137], cabozantinib (pIC$_{50}$ 8.9) [203], foretinib (pK$_{d}$ 8.9) [38], MK-2461 (pIC$_{50}$ 8.6) [146], BMS-777607 (pIC$_{50}$ 8.7) [164], \[ | capmatinib (pIC$_{50}$ 9.9) [112], SGX-523 (pK$_{d}$ 9.7) [38], PHA-665752 (pK$_{d}$ 9.6) [38], foretinib (pIC$_{50}$ 9.3–9.4) [106, 137], cabozantinib (pIC$_{50}$ 8.9) [203], foretinib (pK$_{d}$ 8.9) [38], MK-2461 (pIC$_{50}$ 8.6) [146], BMS-777607 (pIC$_{50}$ 8.7) [164], \[ |
| Selective inhibitors                       | SGX-523 (pIC$_{50}$ 8.4) [19]     | BMS-777607 (pK$_{i}$ 8.4) [26], SU11274 (pIC$_{50}$ 8) [190], golvatinib (pIC$_{50}$ 7.8) [139], tivantinib (pK$_{i}$ 6.4) [135], | BMS-777607 (pIC$_{50}$ 8.4) [19] |

**Comments:** PF04217903 is a selective Met tyrosine kinase inhibitor [34]. SU11274 is an inhibitor of the HGF receptor [162], with the possibility of further targets [8].

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
### Type XII RTKs: TIE family of angiopoietin receptors

**Overview:** The TIE family were initially associated with formation of blood vessels. Endogenous ligands are angiopoietin-1 (ANGPT1, Q15389), angiopoietin-2 (ANGPT2, O15123), and angiopoietin-4 (ANGPT4, Q9Y264). Angiopoietin-2 (ANGPT2, O15123) appears to act as an endogenous antagonist of angiopoietin-1 function.

| Nomenclature | tyrosine kinase with immunoglobulin-like and EGF-like domains 1 | TEK tyrosine kinase, endothelial |
|--------------|------------------------------------------------------------------|---------------------------------|
| Common abbr. | TIE1                                                             | TIE2                            |
| HGNC, UniProt| TIE1, P35590                                                      | TEK, Q02763                     |
| EC number    | 2.7.10.1                                                          | 2.7.10.1                        |
| Endogenous ligands | –                                                                 | angiopoietin-1 (ANGPT1, Q15389), angiopoietin-4 (ANGPT4, Q9Y264) |

### Type XIII RTKs: Ephrin receptor family

**Overview:** Ephrin receptors are a family of 15 RTKs (the largest family of RTKs) with two identified subfamilies (EphA and EphB), which have a role in the regulation of neuronal development, cell migration, patterning and angiogenesis. Their ligands are membrane-associated proteins, thought to be glycosylphosphatidylinositol-linked for EphA (ephrin-A1 (EFNA1, P20827), ephrin-A2 (EFNA2, O43921), ephrin-A3 (EFNA3, P52797), ephrin-A4 (EFNA4, P52798) and ephrin-A5 (EFNA5, P52803)) and 1TM proteins for Ephrin B (ENSFM00250000002014: ephrin-B1 (EFNB1, P98172), ephrin-B2 (EFNR2, P52799) and ephrin-B3 (EFNB3, Q15768)), although the relationship between ligands and receptors has been incompletely defined.

| Nomenclature | EPH receptor A1 | EPH receptor A2 | EPH receptor A3 | EPH receptor A4 | EPH receptor A5 | EPH receptor A6 | EPH receptor A7 |
|--------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------------|
| Common abbr. | EphA1           | EphA2           | EphA3           | EphA4           | EphA5           | EphA6           | EphA7           |
| HGNC, UniProt| EPHA1, P21709   | EPHA2, P29317   | EPHA3, P29320   | EPHA4, P54764   | EPHA5, P54756   | EPHA6, Q9UF33   | EPHA7, Q15375   |
| EC number    | 2.7.10.1        | 2.7.10.1        | 2.7.10.1        | 2.7.10.1        | 2.7.10.1        | 2.7.10.1        | 2.7.10.1        |
| Inhibitors   | –               | –               | –               | –               | –               | –               | –               |
|              | [PMID: 23489211](pIC<sub>50</sub> 5.6) [79] |                  |                  |                  |                  |                  |                  |

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full)
**Nomenclature**

| Common abbreviation | EPH receptor A8 | EPH receptor A10 | EPH receptor B1 | EPH receptor B2 | EPH receptor B3 | EPH receptor B4 | EPH receptor B6 |
|---------------------|----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| HGNC, UniProt       | EphA8          | EphA10          | EphB1          | EphB2          | EphB3          | EphB4          | EphB6          |
| EC number           | 2.7.10.1        | 2.7.10.1        | 2.7.10.1       | 2.7.10.1       | 2.7.10.1       | 2.7.10.1       | 2.7.10.1       |
| Inhibitors          | –              | –               | compound 66 [PMID: 19788238] (pIC50 9) [97] | –              | –              | XL-647 (pIC50 8.9) [57] | –              |

**Type XIV RTKs: RET**

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → Type XIV RTKs: RET

**Overview:** Ret proto-oncogene (Rearranged during transfection) is a transmembrane tyrosine kinase enzyme which is employed as a signalling partner for members of the GDNF family receptors. Ligand-activated GFR appears to recruit Ret as a dimer, leading to activation of further intracellular signalling pathways. Ret appears to be involved in neural crest development, while mutations may be involved in multiple endocrine neoplasia, Hirschsprung's disease, and medullary thyroid carcinoma.

| Common abbreviation | ret proto-oncogene |
|---------------------|---------------------|
| HGNC, UniProt       | RET, P07949         |
| EC number           | 2.7.10.1            |
| Inhibitors          | tamatinib (pIC50 8.3) [27], vandetanib (pKd 7.5) [38], vandetanib (pIC50 7) [22] |

**Comments:** A number of tyrosine kinase inhibitors targeting RET have been described [47].
Type XV RTKs: RYK

**Overview:** The ‘related to tyrosine kinase receptor’ (Ryk) is structurally atypical of the family of RTKs, particularly in the activation and ATP-binding domains. RYK has been suggested to lack kinase activity and appears to be involved, with FZD8, in the Wnt signalling system [152].

| Nomenclature | receptor-like tyrosine kinase |
|--------------|------------------------------|
| Common abbreviation | RYK |
| HGNC, UniProt | RYK, P34925 |
| EC number | 2.7.10.1 |

**Comments:** Thus far, no selective RYK inhibitors have been described.

Type XVI RTKs: DDR (collagen receptor) family

**Overview:** Discoidin domain receptors 1 and 2 (DDR1 and DDR2) are structurally-related membrane protein tyrosine kinases activated by collagen. Collagen is probably the most abundant protein in man, with at least 29 families of genes encoding proteins, which undergo splice variation and post-translational processing, and may exist in monomeric or polymeric forms, producing a triple-stranded, twine-like structure. In man, principal family members include COL1A1 (COL1A1, P02452), COL2A1 (COL2A1, P02458), COL3A1 (COL3A1, P02461) and COL4A1 (COL4A1, P02462).

| Nomenclature | discoidin domain receptor tyrosine kinase 1 | discoidin domain receptor tyrosine kinase 2 |
|--------------|---------------------------------|---------------------------------|
| Common abbreviation | DDR1 | DDR2 |
| HGNC, UniProt | DDR1, Q08345 | DDR2, Q16832 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | compound 7k [PMID: 23521020] (pIC50 8.6) [51] | – |

**Comments:** The tyrosine kinase inhibitors of DDR, imatinib and nilotinib, were identified from proteomic analysis [39]. Other collagen receptors include glycoprotein VI (Q9HCN6), leukocyte-associated immunoglobulin-like receptor 1 (Q6GTX8), leukocyte-associated immunoglobulin-like receptor 2 (Q6ISS4) and osteoclast-associated immunoglobulin-like receptor (Q8IYSS).

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Type XVII RTKs: ROS receptors

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → Type XVII RTKs: ROS receptors

| Nomenclature | c-ros oncogene 1, receptor tyrosine kinase |
|--------------|-------------------------------------------|
| Common abreviation | ROS |
| HGNC, UniProt | ROST1, P08922 |
| EC number | 2.7.10.1 |

Comments: crizotinib is a tyrosine kinase inhibitor, anti-cancer drug targeting ALK and ROS1.

Type XVIII RTKs: LMR family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → Type XVIII RTKs: LMR family

Overview: The LMR kinases are unusual amongst the RTKs in possessing a short extracellular domain and extended intracellular domain (hence the 'lemur' name reflecting the long tail). A precise function for these receptors has yet to be defined, although LMR1 was identified as a potential marker of apoptosis [52], giving rise to the name AATYK (Apoptosis-associated tyrosine kinase); while over-expression induces differentiation in neuroblastoma cells [156].

| Nomenclature | apoptosis-associated tyrosine kinase | lemur tyrosine kinase 2 | lemur tyrosine kinase 3 |
|--------------|-------------------------------------|-------------------------|-------------------------|
| Common abreviation | Lmr1 | Lmr2 | Lmr3 |
| HGNC, UniProt | AATK, Q6ZMQ8 | LMTK2, Q8IWU2 | LMTK3, Q96Q04 |
| EC number | 2.7.11.1 | 2.7.11.1 | 2.7.11.1 |

Comments: As yet no selective inhibitors of the LMR family have been described.

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full)
Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family

Overview: The LTK family appear to lack endogenous ligands. LTK is subject to tissue-specific splice variation, which appears to generate products in distinct subcellular locations. ALK fusions created by gene translocations and rearrangements are associated with many types of cancer, including large cell lymphomas, inflammatory myofibrolastic tumours and non-small cell lung cancer [120].

| Nomenclature | leukocyte receptor tyrosine kinase | anaplastic lymphoma receptor tyrosine kinase |
|--------------|-----------------------------------|--------------------------------------------|
| Common abreviation | LTK | ALK |
| HGNC, UniProt | LTK, P29376 | ALK, Q9UM73 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | – | GSK-1838705A (pIC\textsubscript{50} 9.3) [161], compound 8e [PMID: 24432909] (pIC\textsubscript{50} 9.1) [76], crizotinib (pIC\textsubscript{50} 9) [35], NVP-TAE684 (pK\textsubscript{d} 9) [38], compound 25b [PMID: 22564207] (pIC\textsubscript{50} 8.7) [59] |
| Selective inhibitors | – | ceritinib (pIC\textsubscript{50} 9.7) [120] |
| Comments | – | crizotinib appears to be a selective ALK inhibitor acting on the tyrosine kinase activity [58] |

Type XX RTKs: STYK1

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → Type XX RTKs: STYK1

Overview: Similar to the LMR RTK family, STYK1 has a truncated extracellular domain, but also displays a relatively short intracellular tail beyond the split kinase domain. STYK1 (also known as Novel Oncogene with Kinase-domain, NOK) has been suggested to co-localize with activated EGF receptor [43].

| Nomenclature | serine/threonine/tyrosine kinase 1 |
|--------------|-----------------------------------|
| Common abreviation | STYK1 |
| HGNC, UniProt | STYK1, Q6J9G0 |
| EC number | 2.7.10.2 |

Comments: As yet, no selective inhibitors of STYK1 have been described.
# Receptor tyrosine phosphatases (RTP)

Catalytic receptors → Receptor tyrosine phosphatases (RTP)

**Overview**: Receptor tyrosine phosphatases (RTP) are cell-surface proteins with a single TM region and intracellular phosphotyrosine phosphatase activity. Many family members exhibit constitutive activity in heterologous expression, dephosphorylating intracellular targets such as Src tyrosine kinase (SRC) to activate signalling cascades. Family members bind components of the extracellular matrix or cell-surface proteins indicating a role in intercellular communication. Listed here are those family members with putative endogenous ligands.

### Nomenclature

| Type   | HGNC, UniProt | Putative endogenous ligands |
|--------|---------------|----------------------------|
| Type C | PTPRC, P08575 | galectin-1 (LGALS1, P09382) [188] |
| Type D | PTPRD, P23468 | netrin-G3 ligand (LRRC48, Q9NT99) [96] |
| Type F | PTPRF, P10586 | netrin-G3 ligand (LRRC48, Q9NT99) [96] |
| Type G | PTPRG, P23470 | contactin-3 (CNTN3, Q9P232), contactin-4 (CNTN4, Q8WV2), contactin-5 (CNTN5, Q94779), contactin-6 (CNTN6, Q9UQS2) [16] |

### RTP Type K

| HGNC, UniProt | Putative endogenous ligands |
|---------------|----------------------------|
| PTPRK, Q15262 | galectin-3 (LGALS1, P17931), galectin-3 binding protein (LGALS3BP, Q08380) [90] |

### RTP Type S

| HGNC, UniProt | Putative endogenous ligands |
|---------------|----------------------------|
| PTPRS, Q13332 | chondroitin sulphate proteoglycan 3 (NCAN, O14594), netrin-G3 ligand (LRRC48, Q9NT99) [96, 166] |

### RTP Type Z1

| HGNC, UniProt | Putative endogenous ligands |
|---------------|----------------------------|
| PTPRZ1, P23471 | contactin-1 (CNTN1, Q12860), pleiotrophin (PTN, C9JR52) (acts as a negative regulator) [16, 127] |

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**Tumour necrosis factor (TNF) receptor family**

**Catalytic receptors → Tumour necrosis factor (TNF) receptor 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). Several of these receptors contain cytoplasmic motifs known as ‘death domains’, which upon activation serve to recruit death domain- and death effector domain-containing proteins crucial for the initiation of an apoptotic response. Additional signalling pathways include the regulation of the nuclear factor κB 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**). Some mutated forms of TNF ligands are capable of selecting for different receptor subtypes.

| Nomenclature | tumor necrosis factor receptor 1 | tumor necrosis factor receptor 2 | lymphotoxin β receptor | OX40 | CD40 |
|--------------|---------------------------------|---------------------------------|-----------------------|------|------|
| Systematic nomenclature | TNFRSF1A | TNFRSF1B | TNFRSF3 | TNFRSF4 | TNFRSF5 |
| Common abbreviation | TNFR1 | TNFR2 | – | – | – |
| HGNC, UniProt | TNFRSF1A, P19438 | TNFRSF1B, P20333 | LTBR, P36941 | TNFRSF4, P43489 | CD40, P25942 |
| Adaptor proteins | TRADD | TRAF1, TRAF2, TRAF5 | TRAF3, TRAF4, TRAF5 | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| Endogenous ligands | lymphotoxin-α (LTA, P01374), tumour necrosis factor membrane form (TNF, P01375), tumour necrosis factor shed form (TNF, P01375) | lymphotoxin-α (LTA, P01374), tumour necrosis factor membrane form (TNF, P01375) | LIGHT (TNFSF14, O43557), lymphotoxin β₂α₁ heterotrimer (LTA LTβ, P01374 Q06643) | OX-40 ligand (TNFSF4, P23510) | CD40 ligand (CD40LG, P29965) |

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| Nomenclature | Fas | decoy receptor 3 | CD27 | CD30 | 4-1BB |
|--------------|-----|-----------------|------|------|-------|
| Systematic nomenclature | TNFRSF6 | TNFRSF6B | TNFRSF7 | TNFRSF8 | TNFRSF9 |
| HGNC, UniProt | FAS, P25445 | TNFRSF6B, O95407 | CD27, P26842 | TNFRSF8, P28908 | TNFRSF9, Q07011 |
| Adaptor proteins | FADD | – | TRAF2, SIVA | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1, TRAF2, TRAF3 |
| Endogenous ligands | Fas ligand (FASLG, P48023) | – | CD70 (CD70, P32970) | CD30 ligand (TNFSF8, P32971) | 4-1BB ligand (TNFSF9, P41273) |
| Antibodies | – | – | – | brentuximab vedotin (Inhibition) | – |
| Comments | – | Decoy receptor for LIGHT (TNFSF4, O43557), TL1A (TNFSF15, O95130) and Fas ligand (FASLG, P48023). | – | – | – |

| Nomenclature | death receptor 4 | death receptor 5 | decoy receptor 1 | decoy receptor 2 | receptor activator of NF-kappa B |
|--------------|-----------------|-----------------|-----------------|-----------------|-------------------------------|
| Systematic nomenclature | TNFRSF10A | TNFRSF10B | TNFRSF10C | TNFRSF10D | TNFRSF11A |
| Common abbreviation | DR4 | DRS | – | – | RANK |
| HGNC, UniProt | TNFRSF10A, O00220 | TNFRSF10B, O14763 | TNFRSF10C, Q14798 | TNFRSF10D, Q9UBN6 | TNFRSF11A, Q9Y6Q6 |
| Adaptor proteins | FADD | FADD | – | – | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| Endogenous ligands | TRAIL (TNFSF10, P50591) | TRAIL (TNFSF10, P50591) | – | – | RANK ligand (TNFSF11, O14788) |
| Comments | – | – | Decoy receptor for TRAIL (TNFSF10, P50591). | Decoy receptor for TRAIL (TNFSF10, P50591). | – |
| Nomenclature | osteoprotegerin | death receptor 3 | TWEAK receptor | TACI |
|--------------|----------------|-----------------|----------------|------|
| Systematic nomenclature | TNFRSF11B | TNFRSF25 | TNFRSF12A | TNFRSF13B |
| Common abbreviation | OPG | DR3 | – | – |
| HGNC, UniProt | TNFRSF11B, Q00300 | TNFRSF25, Q9038 | TNFRSF12A, Q9NP84 | – |
| Adaptor proteins | – | TRADD | TRAF1, TRAF2, TRAF3 | TRAF2, TRAF5, TRAF6 |
| Endogenous ligands | – | TL1A (TNFSF15, Q95150) | TWEAK (TNFSF12, O43508) | APRIL (TNFSF13, O75888), BAFF (TNFRSF13B, Q9Y275) |
| Comments | Acts as a decoy receptor for RANK ligand (TNFSF11, O14788) and possibly for TRAIL (TNFSF10, P50591). | – | – | – |

| Nomenclature | BAFF receptor | herpes virus entry mediator | nerve growth factor receptor | B cell maturation antigen |
|--------------|----------------|-----------------------------|-----------------------------|---------------------------|
| Systematic nomenclature | TNFRSF13C | TNFRSF14 | TNFRSF16 | TNFRSF17 |
| Common abbreviation | BAFF-R | HVEM | – | BCMA |
| HGNC, UniProt | TNFRSF13C, Q96RJ3 | TNFRSF14, Q92956 | NGFR, P08138 | TNFRSF17, Q02223 |
| Adaptor proteins | TRAF3 | TRAF2, TRAF3, TRAF5 | TRAF2, TRAF4, TRAF6 | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| Endogenous ligands | BAFF (TNFSF13B, Q9Y275) | B and T lymphocyte attenuator (BTLA, Q726A9), LIGHT (TNFSF14, O43557), lymphotixin-α (LTA, P01374) | BDNF (BDNF, P23560), NGF (NGF, P01138), neurotrophin-3 (NTF3, P20783), neurotrophin-4 (NTF4, P34130) | APRIL (TNFSF13, O75888), BAFF (TNFRSF13B, Q9Y275) |

| Nomenclature | glucocorticoid-induced TNF receptor | toxicity and JNK inducer | RELT | death receptor 6 |
|--------------|-----------------------------------|--------------------------|------|------------------|
| Systematic nomenclature | TNFRSF18 | TNFRSF19 | TNFRSF19L | TNFRSF21 |
| Common abbreviation | GITR | TAJ | – | DR6 |
| HGNC, UniProt | TNFRSF18, Q9YSUS | TNFRSF19, Q9NS68 | RELT, Q969Z4 | TNFRSF21, O75509 |
| Adaptor proteins | TRAF1, TRAF2, TRAF3, SIVA | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1 | TRADD |
| Endogenous ligands | TL6 (TNFSF18, Q9UNG2) | lymphotixin-α (LTA, P01374) | – | – |
Nomenclature

| Systematic nomenclature | TNFRSF22 | TNFRSF23 | ectodysplasin A2 isoform receptor | ectodysplasin 1, anhidrotic receptor |
|-------------------------|----------|----------|----------------------------------|--------------------------------------|
| HGNC, UniProt           | –        | –        | TNFRS27                          | –                                    |
| Adaptor proteins        | –        | –        | TRAF1, TRAF3, TRAF6               | TRAF1, TRAF2, TRAF3                  |
| Endogenous ligands      | –        | –        | ectodysplasin A2 (EDA, Q92838) [204] | ectodysplasin A1 (EDA, Q92838) [204] |

**Comments:** TNFRSF1A is preferentially activated by the shed form of TNF ligand, whereas the membrane-bound form of TNF serves to activate TNFRSF1A and TNFRSF1B equally. The neurotrophins nerve growth factor (NGF (NGF, P01138)), brain-derived neurotrophic factor (BDNF (BDNF, P23560)), neurotrophin-3 (NTF3, P20783) (NTF3) and neurotrophin-4 (NTF4, P34130) (NTF4) are structurally unrelated to the TNF ligand superfamily but exert some of their actions through the "low affinity nerve growth factor receptor" (NGFR (TNFRSF16)) as well as through the TRK family of receptor tyrosine kinases. The endogenous ligands for EDAR and EDA2R are, respectively, the membrane (Q92838[1-391]) and secreted (Q92838[160-391]) isoforms of Ectodysplasin-A (EDA, Q92838).

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