THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: Catalytic receptors

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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 activating activity, to become activated and catalytically active.
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.

**Family structure**

| 5980 | Catalytic receptors |
|---|---|
| 5981 | Cytokine receptor family |
| 5981 | IL-2 receptor family |
| 5983 | IL-3 receptor family |
| 5983 | IL-6 receptor family |
| 5985 | IL-12 receptor family |
| 5985 | Prolactin receptor family |
| 5986 | Interferon receptor family |
| 5987 | IL-10 receptor family |
| 5988 | Immunoglobulin-like family of IL-1 receptors |
| 5989 | IL-17 receptor family |
| 5990 | GDNF receptor family |
| 5991 | Integrins |
| 5994 | Natriuretic peptide receptor family |
| 5996 | Pattern recognition receptors |
| 5996 | Toll-like receptor family |
| 5997 | NOD-like receptor family |
| 5997 | Other protein kinases |
| 5997 | TK: Tyrosine kinase |
| 5999 | Receptor serine/threonine kinase (RSTK) family |
| 6000 | Type I receptor serine/threonine kinases |
| 6001 | Type II receptor serine/threonine kinases |
| 6001 | Type III receptor serine/threonine kinases |
| 6002 | RSTK functional heteromers |
| 6003 | Receptor tyrosine kinases |
| 6004 | Type I RTKs: ErbB (epidermal growth factor) receptor family |
| 6005 | Type II RTKs: Insulin receptor family |
| 6005 | Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family |
| 6007 | Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family |
| 6008 | Type V RTKs: FGF (fibroblast growth factor) receptor family |
| 6008 | Type VI RTKs: PTK7/CCK4 |
| 6009 | Type VII RTKs: Neurotrophin receptor/Trk family |
| 6010 | Type VIII RTKs: ROR family |
| 6010 | Type IX RTKs: MuSK |
| 6010 | Type X RTKs: HGF (hepatocyte growth factor) receptor family |
| 6011 | Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family |
| 6012 | Type XII RTKs: TIE family of angiopoietin receptors |
| 6012 | Type XIII RTKs: Ephrin receptor family |
| 6013 | Type XIV RTKs: RET |
| 6014 | Type XV RTKs: RYK |
| 6014 | Type XVI RTKs: DDR (collagen receptor) family |
| 6015 | Type XVII RTKs: ROS receptors |
| 6015 | Type XVIII RTKs: LMR family |
| 6016 | Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family |
| 6016 | Type XX RTKs: STYK1 |
| 6016 | TKL: Tyrosine kinase-like |
| 6017 | Receptor tyrosine phosphatases (RTP) |
| 6018 | Tumour necrosis factor (TNF) receptor family |

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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 in 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 TGFβ family and the chemokines. Within this group of records are described Type I 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 antagonistic 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

| Subunits | Interleukin-2 receptor | Interleukin-4 receptor type I | Interleukin-4 receptor type II | Interleukin-7 receptor | Interleukin-9 receptor |
|----------|------------------------|-------------------------------|------------------------------|-----------------------|-----------------------|
| (Ligand-binding subunit) | Interleukin-2 receptor subunit β | Interleukin-4 receptor subunit α | Interleukin-4 receptor subunit α1 | Interleukin-7 receptor subunit γ | Interleukin-9 receptor subunit γ |
| (Other subunit) | Interleukin-2 receptor subunit γ | Interleukin-4 receptor subunit γ | Interleukin-4 receptor subunit γ | Interleukin-7 receptor subunit γ | Interleukin-9 receptor |
| (Ligand-binding subunit) | Interleukin-2 receptor subunit α | (Other subunit) | (Ligand-binding subunit) | (Ligand-binding subunit) | (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 | Interleukin-2 receptor subunit γ (Other subunit) | Cytokine receptor-like factor 2 (Other subunit) |
|              | Interleukin-15 receptor subunit α (Ligand-binding subunit) | Interleukin 21 receptor (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                   | IL2RG, P31785                   | IL4R, P24394                    | IL7R, P16871                    |
| Antibodies   | dacлизумаб (Binding) (pKd >8)  | –                               | –                               | dupилиумаб (Binding) (piC50 11.1) | –                               |
|              | [154]                            | [121]                           | [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-2 receptor family 5982
IL-3 receptor family

Catalytic receptors → Cytokine receptor family → 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] | – |

Subunits

| Nomenclature | Interleukin 3 receptor, α subunit | Interleukin 5 receptor, α subunit | GM-CSF receptor, α subunit | Cytokine receptor common β subunit |
|--------------|---------------------------------|---------------------------------|---------------------------|----------------------------------|
| HGNC, UniProt | IL3RA, P26951 | ILSRA, Q01344 | CSF2RA, P15509 | CSF2RB, P32927 |
| Endogenous agonists | IL-3 (IL3, P08700) | IL-5 (IL5, P05113) | GM-CSF (CSF2, P04141) | – |
| Antibodies | – | benralizumab (Binding) (pK_d 8.7) [93] | mavrilimumab (Binding) (pIC_{50} 9.9) [29] | – |

IL-6 receptor family

Catalytic receptors → Cytokine receptor family → 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.
### IL-6 Receptor Family

**Nomenclature**
- **Interleukin-6 receptor**
- **Interleukin-11 receptor**
- **Interleukin-31 receptor**
- **Ciliary neurotrophic factor receptor**

**Subunits**
- **Interleukin-6 receptor, α subunit** (Ligand-binding subunit)
- **Interleukin-6 receptor, β subunit** (Other subunit)
- **Interleukin-11 receptor, α subunit** (Ligand-binding subunit)
- **Interleukin-11 receptor, β subunit** (Other subunit)
- **Interleukin-31 receptor, α subunit** (Ligand-binding subunit)
- **Interleukin-31 receptor, β subunit** (Other subunit)
- **Oncostatin M-specific receptor, β subunit** (Ligand-binding subunit)

**Endogenous agonists**
- **IL-6** (*IL6*, P05231)
- **IL-11** (*IL11*, P20809)
- **IL-31** (*IL31*, Q6EBC2)

**Agonists**
- **CRCF1/CLCF1 heterodimer** (*CLCF1 CRLF1*, O75462 Q9UBD9)
- **ciliary neurotrophic factor** (*CNTF*, P26441)

**Antibodies**
- **tocilizumab** (Binding) (pK<sub>d</sub> 8.6)
- **oprelvekin**
- **sarilumab** (Binding) (pK<sub>d</sub> 10.6–11.1) [171]

**Endogenous agonists**
- **leptin** (*LEP*, P41159)
- **LIF** (*LIF*, P15018), cardiotrophin-1 (*CTF1*, Q16619), oncostatin M (*OSM*, P13725)
- **oncostatin M** (*OSM*, P13725)
- **IL-27** (*EBI3 IL27*, Q14213 Q8NEV9)

**Subunits**

**Nomenclature**
- **Leptin receptor**
- **Leukemia inhibitory factor receptor**
- **Oncostatin-M receptor**
- **Interleukin-27 receptor**

**HGNC, UniProt**
- **LEPR, P48357**
- **LIFR, P42702**
- **LIFR, P42702**
- **LIFR, P42702**

**Subunits**
- **Interleukin-6 receptor, α subunit** (Ligand-binding subunit)
- **Interleukin-6 receptor, β subunit** (Other subunit)
- **Interleukin-11 receptor, α subunit** (Ligand-binding subunit)
- **Interleukin-11 receptor, β subunit** (Other subunit)
- **Interleukin-27 receptor, α subunit**
- **Interleukin-27 receptor, β subunit** (Ligand-binding subunit)

**Antibodies**
- **sarilumab** (Binding) (pK<sub>d</sub> 10.6–11.1) [171]
## 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, Q5VWK5          |
| Subunits     | Interleukin-12 receptor, β2 subunit | Interleukin 23 receptor (Ligand-binding subunit) | –                                 | –                                 | –                      |
| Interleukin-12 receptor, ρ1 subunit | – | IL12 (IL12A IL12B, P29459 P29460) | – | – | – |
| 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) (pIC₅₀ 11.1) [48] | G-CSF (CSF3, P09919) | growth hormone 1 (GH1, P01241), growth hormone 2 (GH2, P01242) | – | thrombopoietin (THPO, P40225) |
| Agonists     | peginesatide (pIC₅₀ 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-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) (pKᵦ >10) [21] | –                           | –                       | –                       |

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## 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

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

### Endogenous Agonists

| Nomenclature | Interleukin-10 receptor | Interleukin-20 receptor | Interleukin-22 receptor α1/10β heteromer | Interleukin-22 receptor α2 |
|--------------|-------------------------|-------------------------|------------------------------------------|----------------------------|
| IL-10 (IL10, P22301) | – | Interleukin 20 receptor, α1 subunit | – | – |
| IL-19 (IL19, Q9UHD0), IL-20 (IL20, Q9NYY1), IL-24 (IL24, Q13007) | Interleukin 20 receptor, β subunit | Interleukin 22 receptor, α1 subunit | Interleukin 22 receptor, α2 | – |
| IL-22 (IL22, Q9GZX6) | Interleukin 22 receptor, β subunit | Interleukin 22 receptor, β subunit | – | – |

### Comments

- Soluble decoy receptor that binds IL-22 (IL22, Q9GZX6) as a monomer.

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Immunoglobulin-like family of IL-1 receptors

Catalytic receptors → Cytokine receptor family → 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, IL1RacP, IL1R3). They are characterised by extracellular immunoglobulin-like domains and an intracellular Toll/Interleukin-1R (TIR) domain.

| Nomenclature | Interleukin-1 receptor, type I | Interleukin-33 receptor | Interleukin-36 receptor | Interleukin-1 receptor, type II | Interleukin-18 receptor |
|--------------|-------------------------------|-------------------------|------------------------|-------------------------------|------------------------|
| Subunits     | IL-1 receptor accessory protein (Other subunit), Interleukin 1 receptor, type I (Ligand-binding subunit) | IL-1 receptor accessory protein (Other subunit), Interleukin-1 receptor-like 1 (Ligand-binding subunit) | IL-1 receptor accessory protein (Other subunit), Interleukin-1 receptor-like 2 (Ligand-binding subunit) | IL-1 receptor accessory protein (Other subunit), Interleukin 1 receptor, type II (Ligand-binding subunit) | IL-18 receptor accessory protein (Other subunit), Interleukin-18 1 (Ligand-binding subunit) |
| Inhibitors   | anakinra (pKd 7.8) [44] | – | IL-36α (IL36A, Q9UHA7), IL-36β (IL36B, Q9NZH7), IL-36γ (IL36G, Q9NZH8) | – | – |
| Endogenous agonists | IL-1α (IL1A, P01583), IL-1β (IL1B, P01584) | IL-33 (IL33, Q95760) | – | – | IL-18 (IL18, Q14116), IL-37 (IL37, Q9NZH6) |
| Endogenous antagonists | IL-1 receptor antagonist (IL1RN, P18510) | – | – | – | – |
| Selective antagonists | AF12198 [3] | – | – | – | – |
| Comments | – | – | IL-36 receptor antagonist (IL36RN, Q9UBH0) is a highly specific antagonist of the response to IL-36γ (IL36G, Q9NZH8). | – | – |

Decoy receptor that binds IL-1α (IL1A, P01583), IL-1β (IL1B, P01584) and IL-1 receptor antagonist (IL1RN, P18510).

Subunits

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

| Subunits                  | Interleukin-17 receptor | Interleukin-25 receptor | Interleukin-17C receptor |
|---------------------------|-------------------------|-------------------------|--------------------------|
| Ligand-binding subunit    | Interleukin 17 receptor A | Interleukin 17 receptor B | Interleukin 17 receptor A |
| Other subunit             | Interleukin 17 receptor C | Interleukin 17 receptor A | Interleukin 17 receptor E |

### Endogenous agonists

- IL-17A (IL17A, Q16552, IL-17A/IL-17F (IL17A IL17F, Q16552 Q96PD4), IL-17F (IL17F, Q96PD4)
- IL-17B (IL17B, Q9UHF5), 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 | IL17RA, Q96F46           | IL17RB, Q9NRM6           | IL17RC, Q8NAC3           | IL17RD, Q8NFM7           | IL17RE, Q8NFR9           |
| Antibodies   | brodalumab (Binding)     | –                        | –                        | –                        | –                        |
|              | (pKd 9.2) [179]          | –                        | –                        | –                        | –                        |
| Comments     | –                        | –                        | –                        | The endogenous agonist for this receptor is unknown. | –                        |

### 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)
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 (GFRα1) | GDNF family receptor α2 (GFRα2) | GDNF family receptor α3 (GFRα3) | GDNF family receptor α4 (GFRα4) |
|--------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 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) (pKd 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**

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

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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]
Integrins

Catalytic receptors → Integrins

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 (in 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 Mg²⁺ 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 αIβ3 | integrin α4β1 |
| Subunits | integran, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integran, alpha 1 subunit | integran, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integran, alpha 2 subunit (CD49B, alpha 2 subunit of VLA-2 receptor) | integran, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61), integran, alpha Ibb subunit (platelet glycoprotein IIbb of Ibb/Illa complex, antigen CD41) | integran, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integran, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor) |
| 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 | fibrinogen (FN1, P02751), vascular cell adhesion protein 1 (VCAM1, P19320), osteopontin (SPP1, P10451), thrombospondin |
| Inhibitors | obtustatin (pIC50 9.1) [118] | TCI15 (pIC50 7.9) [128] | G4120 [124], GR 144053, eptifibatide, tirofiban | BIO1211 (pIC50 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)
### Nomenclature

| Integrin | Subunits | Ligands | Antibodies |
|----------|----------|---------|------------|
| α4β1 | integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor), integrin, beta 7 subunit | fibronectin (FN1, P02751) | vedolizumab (Antagonist) (pIC50 8.3) [151] |
| α5β1 | integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide) | laminin | |
| α6β1 | integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 6 subunit | collagen | |
| α10β1 | integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12), integrin, alpha 10 subunit | | |

### Subunits

- integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
- integrin, beta 7 subunit
- integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide)
- integrin, alpha 6 subunit (fibronectin receptor, alpha polypeptide)
- integrin, alpha 10 subunit (fibronectin receptor, alpha polypeptide)

### Ligands

- fibronectin (FN1, P02751)
- laminin
- collagen

### Antibodies

- vedolizumab (Antagonist) (pIC50 8.3) [151]

### Inhibitors

- A286982 (pIC50 7.4–7.5) [110]
- echistatin (pIC50 11.7) [101], P11 (pIC50 11.6) [101], cilengitide (pIC50 8.5) [61]

### Antibodies

- etaracizumab (Binding) (pKd 6.3) [201]

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**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, P02452)).

**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, α3,β1,
α7β1 and α6β4 integrins10. 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.

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 | integrin, alpha 1 subunit | integrin, alpha 2 subunit | integrin, alpha IIB subunit | integrin, alpha 3 subunit | integrin, alpha 4 subunit | integrin, alpha 5 subunit |
|--------------|--------------------------|--------------------------|----------------------------|--------------------------|--------------------------|--------------------------|
| HGNC, UniProt | ITGA1, P56199            | ITGA2, P08514            | ITGA2B, P17301              | ITGA3, P26006            | ITGA4, P13612             | ITGA5, P08648             |
| Antibodies   | –                        | –                        | –                          | –                        | –                        | –                        |

| Nomenclature | integrin, alpha 6 subunit | integrin, alpha 7 subunit | integrin, alpha 8 subunit | integrin, alpha 9 subunit | integrin, alpha 10 subunit | integrin, alpha 11 subunit | integrin, alpha D subunit |
|--------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| HGNC, UniProt | ITGA6, P23229            | ITGA7, Q13683            | ITGA8, P53708             | ITGA9, Q13797             | ITGA10, O75578            | ITGA11, Q9UKX3            | ITGAD, Q13349             |

| Nomenclature | integrin, alpha E subunit | integrin, alpha L subunit | integrin, alpha M subunit | integrin, alpha V subunit | integrin, alpha X subunit | integrin, beta 1 subunit |
|--------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| HGNC, UniProt | ITGAE, P38570            | ITGAL, P20701            | ITGAM, P11215             | ITGAV, P06756             | ITGAX, P20702             | ITGB1, P05556             |
| Antibodies   | –                        | efalizumab (Binding) (pKd 11.4) [81] | –                        | –                        | –                        | –                        |
Natriuretic peptide receptor family

Natriuretic peptide receptor family → 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].

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| Nomenclature | intigrin, beta 2 subunit (complement component 3 receptor 3 and 4 subunit) | intigrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61) | intigrin, beta 4 subunit | intigrin, beta 5 subunit | intigrin, beta 6 subunit | intigrin, beta 7 subunit | intigrin, beta 8 subunit |
|--------------|--------------------------------------------------------------------------------|------------------------------------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| HGNC, UniProt| ITGB2, P05107                                                                 | ITGB3, P05106                                                    | ITGB4, P16144          | ITGB5, P18084          | ITGB6, P18564          | ITGB7, P26010           | ITGB8, P26012           |

Further Reading

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Hogg N et al. (2011) The insider’s guide to leukocyte integrin signalling and function. *Nat. Rev. Immunol.* **11**: 416-26 [PMID:21597477]

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Wickström SA et al. (2011) Regulation of membrane traffic by integrin signaling. *Trends Cell Biol.* **21**: 266-73 [PMID:21440440]
### Nomenclature

| Nomenclature | guanylate cyclase 2C | NPR-A | NPR-B | NPR-C |
|--------------|----------------------|-------|-------|-------|
| HGNC, UniProt | GUCY2C, P25092       | NPR1, P16066 | NPR2, P20594 | NPR3, P17342 |

### Potency order

| Endogenous agonists | – | atrial natriuretic peptide (NPPA, P01160) (Selective) [144] | atrial natriuretic peptide (NPPA, P01160) (Selective) [144] | osteocrin (OSTN, P61366) (Selective) [129] |

### Selective agonists

| Selective agonists | linclotide (pKᵢ 8.9) [20, 67], E. coli heat-stable enterotoxin (STa) (pKᵢ 8.8) [20] | sANP [144] | – | cANF⁴⁻²³ [114] |

### Selective antagonists

| Selective antagonists | – | A-71915 (pKᵢ 9.2–9.5) [41], [Asu7,23']B-ANP-(7-28) (pKᵢ 7.5) [83], anantin [202] | [Ser¹¹] (N-CNP-C-ANP)pBNP²-15 [42] | AP811 (pKᵢ 9.3) [185], M372049 [75] |

### Labelled ligands

| Labelled ligands | [¹²⁵]Sta (Agonist) (pKᵢ 7.8) [66] | [¹²⁵]JANP (human) (Agonist) [125] | [¹²⁵]JCPN (human) [125] | [¹²⁵]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

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Misono KS et al. (2011) Structure, signaling mechanism and regulation of the natriuretic peptide receptor guanylyl cyclase. FEBs J. 278: 1818-29 [PMID:21375693]
Pandey KN. (2011) The functional genomics of guanylyl cyclase/natriuretic peptide receptor-A: perspectives and paradigms. FEBs J. 278: 1792-807 [PMID:21375691]

GUCY2D (RetGC1, GC-E, P02846) and GUCY2F (RetGC2, GC-E, P51841) are predominantly retinal guanylyl cyclase activities, which are inhibited by calcium ions acting through the guanylyl cyclase activating peptides GCAP1 (GUCA1A, 43080), GCAP2 (GUCA1B, Q9UMX6) and GCAP3 (GUCA1C, O95843) [78].

Potter LR. (2011) Natriuretic peptide metabolism, clearance and degradation. FEBs J. 278: 1808-17 [PMID:21375692]
Potter LR. (2011) Regulation and therapeutic targeting of peptide-activated receptor guanylyl cyclases. Pharmacol. Ther. 130: 71-82 [PMID:2118563]
Potter LR. (2011) Guanylyl cyclase structure, function and regulation. Cell. Signal. 23: 1921-6 [PMID:21914472]
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 mannose receptor family (ENSM00000004089). PRRs may be divided into signalling-associated members, identified here, and endocytic members (such as the mannose 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 BK 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 sub-committee 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

|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 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.

TLR3

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

TLR4

|HGNC, UniProt| TLR4, O00206
|Agonists| LPS [150], paclitaxel [85]
|Comments| eritoran (E5564) is a lipid A analogue, which has been described as a TLR4 agonist [80]. TLR4 signals in conjunction with the co-factor MD2.

TLR5

|HGNC, UniProt| TLR5, O60602
|Agonists| flagellin [69]
|Comments| Involved in the detection of bacterial flagellin; pro-inflammatory.

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

| Nomenclature | TLR6 | TLR7 | TLR8 | TLR9 | TLR10 | TLR11 |
|--------------|------|------|------|------|-------|-------|
| HGNC, UniProt | TLR6, Q9Y2C9 | TLR7, Q9NYK1 | TLR8, Q9NR97 | TLR9, Q9NR96 | TLR10, Q9BX85 | — |

### Agonists

- imiquimod [72]
- loxoribine [70]
- resiquimod [72]

### Antagonists

- hydroxychloroquine (pIC₅₀ 5.6) [98]
- hydroxychloroquine (pIC₅₀ 7.1) [98]

### Comments

- Functions as a heterodimer with TLR2. Involved in the pro-inflammatory response to diacylated bacterial lipoproteins.
- Activated by imidazoquinoline derivatives and RNA oligoribonucleotides. Involved in endosomal detection of ssRNA; pro-inflammatory.
- Activated by imidazoquinoline derivatives and RNA oligoribonucleotides. Endosomal detection of ssRNA; pro-inflammatory.
- Toll-like receptor 9 interacts with unmethylated CpG dinucleotides from bacterial DNA [73]. Activated by CpG rich DNA sequences; pro-inflammatory.
- Murine TLR10 has a retroviral insertion that makes it non-functional.
- Found in mouse

### 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]

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**NOD-like receptor family**

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

**Overview:** The nucleotide-binding oligomerization domain, leucine-rich repeat (NLR) family of receptors (nomenclature recommended by the NC-IUPHAR subcommittee on pattern recognition receptors [18]) share a common domain organisation. This consists of an N-terminal effector domain, a central nucleotide-binding and oligomerization domain (NOD; also referred to as a NACHT domain), and C-terminal leucine-rich repeats (LRR) which have regulatory and ligand recognition functions. The type of effector domain has resulted in the division of NLR family members into two major sub-families, NLRC and NLRP, along with three smaller sub-families NLRA, NLRB and NRLX [178]. NLRC members express an N-terminal caspase recruitment domain (CARD) and NLRP members an N-terminal Pyrin domain (PyrD). Upon activation the NLRC family members NOD1 (NLRC1) and NOD2 (NLRC2) recruit a serine/threonine kinase RIPK2 (receptor interacting serine/threonine kinase) and NOD2 (NLRC2) recruit a serine/threonine kinase RIPK2 leading to signalling through NFκB and MAP kinase. Activation of NLRC4 (previously known as IPAF) and members of the NLRP3 family, including NLRP1 and NLRP3, leads to the formation of a large 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, also known as PYCARD, CARD5, TMS1, Q9ULZ3) and inflammatory caspases. The inflammasome activates the pro-inflammatory cytokines IL-1β (*IL1B*, P01584) and IL-18 (*IL18*, Q14116) [18, 37].
| 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, Q9NPP4 | NLRC5, Q86W13 |
| Agonists | meso-DAP | NOD2 has also been reported to be activated by ssRNA [160] although this has not been widely reproduced. | – | – | NLRC4 forms an inflammasome in conjunction with the NAIP proteins and responds to bacterial flagellin and type III secretion system rod proteins. |
| Comments | – | – | – | – | – |

| Nomenclature | NLRX1 | CIITA | NLRP1 | NLRP2 |
|--------------|-------|-------|-------|-------|
| HGNC, UniProt | NLRX1, Q86UT6 | CIITA, P33076 | NLRP1, Q9C000 | NLRP2, Q9NX02 |
| Agonists | – | – | muramyl dipeptide | – |
| Comments | – | – | NLRP1 has 3 murine orthologues which lack the N-terminal Pyrin domain. Murine NLRP1b (ENSMUSG00000070390) is the best characterised, responding to Anthrax Lethal Toxin. | Along with NLRP7, NLRP2 is the product of a primate-specific gene duplication. |

| Nomenclature | NLRP3 | NLRP4 | NLRP5 | NLRP6 |
|--------------|-------|-------|-------|-------|
| HGNC, UniProt | NLRP3, Q96P20 | NLRP4, Q96MN2 | NLRP5, P59047 | NLRP6, P59044 |
| Inhibitors | MCC950 (pIC\textsubscript{50} >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. | – | – |
| Nomenclature | HGNC, UniProt | Comments |
|--------------|--------------|----------|
| NLRP7 | NLRP7, Q8WX94 | Absent in mouse. Along with NLRP2 the product of a primate-specific gene duplication. |
| NLRP8 | NLRP8, Q86W28 | Absent in mouse |
| NLRP9 | NLRP9, Q7RT0 | This receptor has three murine orthologues. |
| NLRP10 | NLRP10, Q86W26 | – |

| Nomenclature | HGNC, UniProt | Comments |
|--------------|--------------|----------|
| NLRP11 | NLRP11, P59045 | Absent in mouse |
| NLRP12 | NLRP12, P59046 | – |
| NLRP13 | NLRP13, Q86W25 | Absent in mouse |
| NLRP14 | NLRP14, Q86W24 | – |

Comments: NLRP3 has also been reported to respond to host-derived products, known as danger-associated molecular patterns, or DAMPs, including uric acid [122], ATP, L-glucose, hyaluronan and amyloid β (APP, P05067) [163].

Loss-of-function mutations of NLRP3 are associated with cold auto-inflammatory and Muckle-Wells syndromes. This family also includes NLR family, apoptosis inhibitory protein (NAIP, Q13075) which can be found in the 'Inhibitors of apoptosis (IAP) protein family' in the Other protein targets section of the Guide.

Further Reading
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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 R-Smad trimers (Smad1, Smad2, Smad3, Smad5 and Smad8), Co-mediated Smad (Smad6 and Smad7) and Inhibitory Smads (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.

Further Reading

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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 I | activin A receptor, type IB |
|--------------|----------------------------------|---------------------------|--------------------------------------------|---------------------------|
| Common abreviation | ALK1 | ALK2 | BMPR1A | ALK4 |
| HGNC, UniProt | ACVRL1, P37023 | ACVR1, Q04771 | BMPR1A, 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 13r [PMID: 23639540] (pIC50 >8.3) [45] | compound 13d [PMID: 23639540] (pIC50 >8.3) | compound 13d [PMID: 23639540] (pIC50 >8.3) | compound 13d [PMID: 23639540] (pIC50 >8.3) |
| Selective inhibitors | – | – | – | EW-7197 (pIC50 7.9) [82] |
Nomenclature
- transforming growth factor, beta receptor 1
- bone morphogenetic protein receptor, type IB
- activin A receptor, type IC

Common abbreviation
- TGFBR1
- BMPR1B
- ALK7

HGNC, UniProt
- TGFBR1, P36897
- BMPR1B, O00238
- ACVR1C, Q8NER5

EC number
- 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 abbreviation
- ActR2
- ActR2B
- MISR2
- BMPR2
- TGFBR2

HGNC, UniProt
- ACVR2A, P27037
- ACVR2B, Q13705
- AMHR2, Q16671
- BMPR2, Q13873
- TGFBR2, Q37173

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 abbreviation
- 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 | Subunits | Comments |
|--------------|----------|----------|
| **Transforming growth factor β receptor transforming growth factor, beta receptor I**<br>(Type I), **transforming growth factor, beta receptor III**<br>(Type III), **transforming growth factor, beta receptor II (70/80kDa)**<br>(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) | Coupling Smad2, Smad3 [134, 167] |
| **Bone morphogenetic protein receptors** | **Growth/differentiation factor receptors** | **Activin 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) | Beta receptor 1, **transforming growth factor, beta receptor III**<br>(Type III), **transforming growth factor, beta receptor II (70/80kDa)**<br>(Type II) | Smad1, Smad5, Smad8 [134, 167] |
| **Activin receptors** | Activin receptors | Anti-Müllerian hormone receptors anti-Müllerian hormone receptor, type I (Type I), bone morphogenetic protein receptor, type I (Type I), activin A receptor, type I (Type I), activin A receptor, type II (Type II), activin A receptor, type III (Type III), activin A receptor, type IV (Type IV) | Smad2, Smad3 [167] |
| **Activin receptors** | endogenous agonists | Müllerian inhibiting substance (AMH, P03971) |
| | | | Smad1, Smad5, Smad8 [134, 167] |
| **Activin receptors** | | | |
Receptor tyrosine kinases

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → 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, 154]. 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 ‘biologica’ls’, 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**

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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 2 | erb-b2 receptor tyrosine kinase 3 | erb-b2 receptor tyrosine kinase 4 |
|--------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Common abreviation | EGFR | HER2 | HER3 | HER4 |
| HGNC, UniProt | EGF, P00533 | ERBB2, P04626 | ERBB3, P21860 | ERBB4, 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 (TGFα, P01135) (Binding), amphiregulin (AREG, P15514) (Binding), betacellulin (BTC, P35070) (Binding), epigen (EPGN, Q6UW88) (Binding), epiregulin (EREG, O14944) (Binding) | – | – | – |
| Inhibitors | canertinib (pIC₅₀ 9.7) [38], afatinib (pIC₅₀ 9.6) [38], XL-647 (pIC₅₀ 9.5) [57], afatinib (pIC₅₀ 8.9–9.3) [33, 103], erlotinib (pIC₅₀ 9.2) [38], erlotinib (pIC₅₀ 9) [207], gefitinib (pIC₅₀ 9) [38], canertinib (pIC₅₀ 8.8) [170], BMS-690514 (pIC₅₀ 8.3) [117], gefitinib (pIC₅₀ 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) [155], EGF/ErbB-2 inhibitor (pIC₅₀ 7.1) [28], AG112 (pIC₅₀ 6.9) [56], rociletinib (pIC₅₀ 6.5) [187], AG 490 (pIC₅₀ 6.4) [55] | poziotinib (pIC₅₀ 8.3) [140], neratinib (pIC₅₀ 8.2) [38], lapatinib (pIC₅₀ 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) [155], EGF/ErbB-2 inhibitor (pIC₅₀ 7.1) [28], AG112 (pIC₅₀ 6.9) [56], rociletinib (pIC₅₀ 6.5) [187], AG 490 (pIC₅₀ 6.4) [55] | – | – |
| Antibodies | necitumumab (Binding) (pKₐ 9.5) [111], cetuximab (Binding) (pKₐ 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

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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  | INSR, P06213    | IGF1R, P08069                         | INSR, P14616                      |
| EC number    | 2.7.10.1        | 2.7.10.1                             | 2.7.10.1                          |
| Inhibitors   | –               | BMS-754807 (pIC<sub>50</sub> 8.7) [199], GSK-1838705A (pIC<sub>50</sub> 8.7) [161], GSK-1838705A (pK<sub>d</sub> 8.1) [38], PQ401 (pIC<sub>50</sub> >6) [50], AG 1024 (pIC<sub>50</sub> 4.7) [153] | –                                 |
| Selective inhibitors | – | NVP-AEW541 (pIC<sub>50</sub> 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

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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 PDGFD (PDGFD, 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.
### Nomenclature

| Common abbreviation | HGNC, UniProt ID | EC Number | Endogenous ligands | Inhibitors |
|---------------------|-----------------|-----------|--------------------|------------|
| PDGFRα, PDGFRβ | PDGFR, P16234 | 2.7.10.1 | PDGF | PP121 (pIC₅₀ 8.7) [7], crenolanib (pKᵦ 8.7) [71], ENMD-2076 (pIC₅₀ 7.2) [149] |

### Plates

| Common abbreviation | HGNC, UniProt ID | EC Number | Endogenous ligands | Inhibitors |
|---------------------|-----------------|-----------|--------------------|------------|
| PDGFRβ | PDGFR, P09619 | 2.7.10.1 | PDGF | crenolanib (pKᵦ 8.5) [71], SU-14813 (pIC₅₀ 8.4) [147], famitinib (pIC₅₀ 8.4) [24], sunitinib (pIC₅₀ 8.2) [91], sunitinib (pKᵦ 8.1) [126] |

| Common abbreviation | HGNC, UniProt ID | EC Number | Endogenous ligands | Inhibitors |
|---------------------|-----------------|-----------|--------------------|------------|
| v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog | KIT, P10721 | 2.7.10.1 | stem cell factor (KITLG, P21583) | 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] |

### Platelet-derived growth factor receptor, beta polypeptide

| Common abbreviation | HGNC, UniProt ID | EC Number | Endogenous ligands | Inhibitors |
|---------------------|-----------------|-----------|--------------------|------------|
| PDGFRβ | PDGFR, P09619 | 2.7.10.1 | PDGF | 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], sorafenib (pIC₅₀ 7.2) [196] |

### Colony stimulating factor 1 receptor

| Common abbreviation | HGNC, UniProt ID | EC Number | Endogenous ligands | Inhibitors |
|---------------------|-----------------|-----------|--------------------|------------|
| CSF1R, P07333 | CSF1R, P07333 | 2.7.10.1 | – | G-CSF (CSF3, P09919), GM-CSF (CSF2, P04141), M-CSF (CSF1, P09603) |

### Fms-related tyrosine kinase 3

| Common abbreviation | HGNC, UniProt ID | EC Number | Endogenous ligands | Inhibitors |
|---------------------|-----------------|-----------|--------------------|------------|
| FLT3, P36888 | FLT3, P36888 | 2.7.10.1 | – | 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] (pIC₅₀ 9.1) [88], dovitinib (pIC₅₀ 8.5–9) [115, 183], ENMD-2076 (pIC₅₀ 8.5) [149], tandutinib (pKᵦ 8.5) [38], quartinib (pIC₅₀ 8.4) [206], AKN-028 (pIC₅₀ 8.2) [46], KW-2449 (pIC₅₀ 8.2) [168], lestaurtinib (pKᵦ 8.1) [38], midostaurin (pKᵦ 8) [38], KW-2449 (pKᵦ 7.8) [38], sorafenib (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] |

### Comments

- Various small molecular inhibitors of type III RTKs have been described, including imatinib and nilotinib (targetting PDGFR, KIT and CSF1R); midostaurin and AC220 (quartinib; 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 [25].
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) | VEGFC (VEGFC, P49767), VEGFD (FIGF, O43915), VEGFE (PDGFC, Q9NRA1) |
| Inhibitors | SU-14813 (pIC50 8.7) [147], CEP-11981 (pIC50 8.5) [77], semaxanib (pIC50 8.1) [15] | axitinib (pIC50 8.6) [100], caboazanib (pIC50 9.5) [203], foretinib (pIC50 8.2–9.1) [137], cediranib (pKi 9) [38], XL-647 (pIC50 8.8) [57], compound 13a [PMID: 23639540] (pIC50 8.8) [45], SU-14813 (pKi 8.6) [38], motesanib (pKi 8.6) [38], famitinib (pIC50 8.3) [24], axitinib (pKi 8.2) [38], PLX-4720 (pKi 8.1) [126], CP-547632 (pIC50 8) [11], PP121 (pIC50 7.9) [7], golvatinib (pIC50 7.8) [139], brivanib (pIC50 7.6) [13], ENMD-2076 (pIC50 7.4) [149], BMS-690514 (pIC50 7.3) [117], SU-14813 (pIC50 7.3) [147], sorafenib (pKd 7.2) [38], vatalanib (pKd 7.2) [38], sorafenib (pIC50 7.1) [196] | XL-647 (pIC50 8.1) [57], sunitinib (pIC50 8.1) [87], nintedanib (pIC50 7.9) [74] |
| (Sub)family-selective inhibitors | pazopanib (pIC50 8) [68] | pazopanib (pKd 7.8) [38], pazopanib (pIC50 7.5) [68] | pazopanib (pIC50 7.3) [68] |
| Antibodies | – | ramucirumab (Antagonist) (pIC50 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.

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13353/full
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 abreviation | FGFR1 | FGFR2 | FGFR3 | FGFR4 |
| HGNC, UniProt | P11362 | P21802 | P22607 | 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-9 (FGF9, P31371) = FGF-4 (FGF4, P08620), 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 | LY2874455 (pIC₅₀ 8.6) [208] | LY2874455 (pIC₅₀ 8.6) [208] | LY2874455 (pIC₅₀ 8.2) [208] | LY2874455 (pIC₅₀ 8.2) [208] |
| Agonists | – | palifermin | – | – |

**Comments:** Splice variation of the receptors can influence agonist responses. FGFR1 (Q8N441) 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 abreviation | 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 (TNF-RSF16, 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) | – |
| Endogenous ligands | –                                           | –                                           | neurotrophin-3 (NTF3, P20783)               |
| Inhibitors   | compound 2c [PMID: 24900538] (pIC50 8.9) [189], milciclib (pIC50 7.3) [17] | –                                           | –                                           |
| (Sub)family-selective inhibitors | AZD1332 (pIC50 > 8.3) [9], GNF-5837 (pIC50 8.1) [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 molecule 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].

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Type VIII RTKs: ROR family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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 two disulphide-linked peptide chains generated by proteolysis of a single gene product.

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**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**

| MET proto-oncogene, receptor tyrosine kinase | macrophage stimulating 1 receptor |
|---------------------------------------------|---------------------------------|
| MET, P08581 | Ron |
| **EC number** | **EC number** |
| 2.7.10.1 | 2.7.10.1 |

**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], caboza...)
- macphage stimulating protein 1 (MST1, P09603)
- BMS-777607 (pIC_{50} 8.7) ([164]

**Selective inhibitors**

- SGX-523 (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].

**Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family**

**Nomenclature**

| AXL receptor tyrosine kinase | TYRO3 protein tyrosine kinase | MER proto-oncogene, tyrosine kinase |
|------------------------------|-------------------------------|-----------------------------------|
| Axl | Tyro3 | Mer |
| **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** |
| AXL, P30530 | TYRO3, Q06418 | MERTK, Q12866 |
| **EC number** | **EC number** | **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].

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## 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 abreviation | 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 abreviation | 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 | compound 20 [PMID: 23489211] (pIC50 5.6) [79] | – | – | – | – | – | – |
**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.

| Nomenclature | Ret proto-oncogene |
|--------------|--------------------|
| Common abreviation | Ret |
| HGNC, UniProt | RET, P07949 |
| EC number | 2.7.10.1 |
| Inhibitors | tamatinib (pIC$_{50}$ 8.3) [27], vandetanib (pK$_{i}$ 7.5) [38], vandetanib (pIC$_{50}$ 7) [22] |

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

**Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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 abreviation | 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**

**Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases → 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 abreviation | DDR1 | DDR2 |
| HGNC, UniProt | DDR1, Q08345 | DDR2, Q16832 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | compound 7k [PMID: 23521020] (pIC\textsubscript{50} 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 (Q8IYS5).

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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)
**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 abbreviation                       | ROS                                        |
| HGNC, UniProt                             | ROS1, 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 LMRI 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       |
|-------------------------------------------|--------------------------------------------|
| Common abbreviation                       | Lmr1                                       |
| HGNC, UniProt                             | AATK, Q6ZMQ8                              |
| EC number                                 | 2.7.11.1                                   |

| Nomenclature                              | lemur tyrosine kinase 2                    |
|-------------------------------------------|--------------------------------------------|
| Common abbreviation                       | Lmr2                                       |
| HGNC, UniProt                             | LMTK2, Q8IWU2                              |
| EC number                                 | 2.7.11.1                                   |

| Nomenclature                              | lemur tyrosine kinase 3                    |
|-------------------------------------------|--------------------------------------------|
| Common abbreviation                       | Lmr3                                       |
| HGNC, UniProt                             | LMTK3, Q96Q04                              |
| EC number                                 | 2.7.11.1                                   |

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

**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, O69G0 |
| EC number | 2.7.10.2 |

**Comments**: As yet, no selective inhibitors of STYK1 have been described.
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 | RTP Type C | RTP Type D | RTP Type F | RTP Type G |
|--------------|------------|------------|------------|------------|
| HGNC, UniProt | PTPRC, P08575 | PTPRD, P23468 | PTPRF, P10586 | PTPRG, P23470 |
| Putative endogenous ligands | galectin-1 (LGALS1, P09382) | netrin-G3 ligand (LRRC48, Q9NT99) | netrin-G3 ligand (LRRC48, Q9NT99) | contactin-3 (CNTN3, Q9P232), contactin-4 (CNTN4, Q8WV2), contactin-5 (CNTN5, Q9779), contactin-6 (CNTN6, Q9UQ52) |

| Nomenclature | RTP Type K | RTP Type S | RTP Type Z1 |
|--------------|------------|------------|-------------|
| HGNC, UniProt | PTPRK, Q15262 | PTPRS, Q13332 | PTPRZ1, P23471 |
| Putative endogenous ligands | galectin-3 (LGALS3, P17931), galectin-3 binding protein (LGALS3BP, Q08380) | chondroitin sulphate proteoglycan 3 (NCAN, O14594), netrin-G3 ligand (LRRC48, Q9NT99) | contactin-1 (CNTN1, Q12860), pleiotrophin (PTN, C9JR52) (acts as a negative regulator) |

Further Reading

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Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
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 abreviation | 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, 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 β3-α1 heterotrimer (LTA LTB, P01374 Q06643) | OX-40 ligand (TNFSF4, P23510) | CD40 ligand (CD40LG, P29965) |

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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)
### Nomenclature

| Death receptor 4 | death receptor 5 | decoy receptor 1 | decoy receptor 2 | receptor activator of NF-kappa B |
|------------------|------------------|------------------|------------------|---------------------------------|
| TNFRSF10A       | TNFRSF10B       | TNFRSF10C       | TNFRSF10D       | TNFRSF11A                       |
| **Common abreviation** | **Decay receptor 4** | **Decay receptor 5** | **Decay receptor 1** | **Decay receptor 2** |
| DR4              | DR5              | –                | –                | –                               |
| **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** |
| TNFRSF10A, O00220 | TNFRSF10B, O14763 | TNFRSF10C, O14798 | TNFRSF10D, O91806 | TNFRSF11A, Q96Q6 |
| Adaptor proteins | FADD             | FADD             | –                | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| TRAIL (TNFSF10, P50591) | TRAIL (TNFSF10, P50591) | Decoy receptor for TRAIL (TNFSF10, P50591) | Decoy receptor for TRAIL (TNFSF10, P50591) | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6, RANK ligand (TNFSF11, O14788) |

| Death receptor 4 | death receptor 5 | decoy receptor 1 | decoy receptor 2 | receptor activator of NF-kappa B |
|------------------|------------------|------------------|------------------|---------------------------------|
| TNFRSF10A       | TNFRSF10B       | TNFRSF10C       | TNFRSF10D       | TNFRSF11A                       |
| **Common abreviation** | **Decay receptor 4** | **Decay receptor 5** | **Decay receptor 1** | **Decay receptor 2** |
| DR4              | DR5              | –                | –                | –                               |
| **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** |
| TNFRSF10A, O00220 | TNFRSF10B, O14763 | TNFRSF10C, O14798 | TNFRSF10D, O91806 | TNFRSF11A, Q96Q6 |
| Adaptor proteins | FADD             | FADD             | –                | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| TRAIL (TNFSF10, P50591) | TRAIL (TNFSF10, P50591) | Decoy receptor for TRAIL (TNFSF10, P50591) | Decoy receptor for TRAIL (TNFSF10, P50591) | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6, RANK ligand (TNFSF11, O14788) |

**Antibodies** – – – brentuximab vedotin (Inhibition)

**Comments** – Decoy receptor for TRAIL (TNFSF10, P50591).

**Adaptor proteins**

| Death receptor 4 | death receptor 5 | decoy receptor 1 | decoy receptor 2 | receptor activator of NF-kappa B |
|------------------|------------------|------------------|------------------|---------------------------------|
| TNFRSF10A       | TNFRSF10B       | TNFRSF10C       | TNFRSF10D       | TNFRSF11A                       |
| **Common abreviation** | **Decay receptor 4** | **Decay receptor 5** | **Decay receptor 1** | **Decay receptor 2** |
| DR4              | DR5              | –                | –                | –                               |
| **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** | **HGNC, UniProt** |
| TNFRSF10A, O00220 | TNFRSF10B, O14763 | TNFRSF10C, O14798 | TNFRSF10D, O91806 | TNFRSF11A, Q96Q6 |
| Adaptor proteins | FADD             | FADD             | –                | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| TRAIL (TNFSF10, P50591) | TRAIL (TNFSF10, P50591) | Decoy receptor for TRAIL (TNFSF10, P50591) | Decoy receptor for TRAIL (TNFSF10, P50591) | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6, RANK ligand (TNFSF11, O14788) |

**Antibodies** – – – brentuximab vedotin (Inhibition)

**Comments** – Decoy receptor for TRAIL (TNFSF10, P50591).
### Nomenclature

| 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 | TNFRSF13B, Q14836 |
| Adaptor proteins | – | TRADD | TRAF1, TRAF2, TRAF3 | TRAF2, TRAF5, TRAF6 |
| Endogenous ligands | – | TL1A (TNFSF15, O95150) | TWEAK (TNFSF12, O43508) | APRIL (TNFSF13, O75888), BAFF (TNFRSF13, Q9Y275) |
| Comments | Acts as a decoy receptor for RANK ligand (TNFSF11, O14788) and possibly for TRAIL (TNFSF10, P50591). | – | – | – |

### Nomenclature

| 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 | – | TNFRSF17, Q02223 |
| Adaptor proteins | TRAF3 | TRAF2, TRAF3, TRAF5 | TRAF2, TRAF4, TRAF6 | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 |
| Endogenous ligands | BAFF (TNFRSF13, Q9Y275) | B and T lymphocyte attenuator (BTLA, Q7Z6A9), LIGHT (TNFSF14, O43557), lymphotoxin-α (LTA, P01374) | BDNF (BDNF, P23560), NGF (NGF, P01138), neurotrophin-3 (NTF3, P20783), neurotrophin-4 (NTF4, P34130) | APRIL (TNFSF13, O75888), BAFF (TNFRSF13, Q9Y275) |

### Nomenclature

| 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, Q9Y5US | TNFRSF19, Q9NS68 | RELT, Q969Z4 | TNFRSF21, O75509 |
| Adaptor proteins | TRAF1, TRAF2, TRAF3, SIVA | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1 | TRADD |
| Endogenous ligands | TL6 (TNFSF18, Q9UNG2) | lymphotoxin-α (LTA, P01374) | – | – |
Nomenclature

- TNFRSF22
- TNFRSF23
- ectodysplasin A2 isoform receptor
- ectodysplasin 1, anhidrotic receptor

Systematic nomenclature
- TNFRS27
- EDA2R, Q9HAV5
- EDAR, Q9UNE0

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 superfamaily and 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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