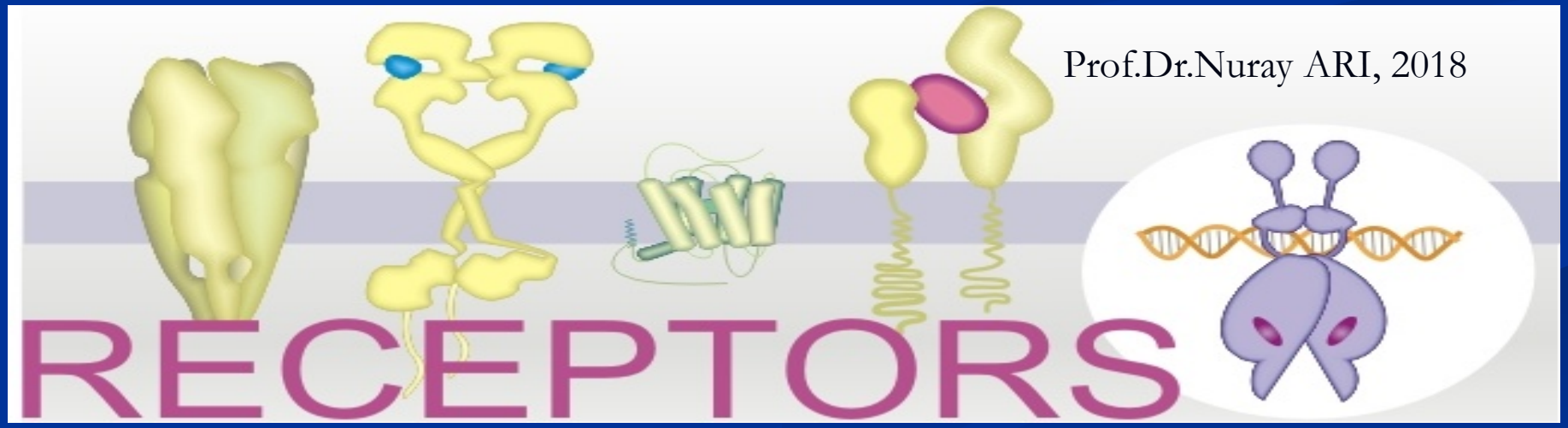
Receptors / G proteins / GPCR signaling



Subcellular Organization of GPCR Signaling.

Trends Pharmacol Sci. 2018 Feb;39(2):200-208. doi: 10.1016/j.tips.2017.11.009. Epub 2018 Jan 28. Eichel K, von Zastrow M.

Abstract

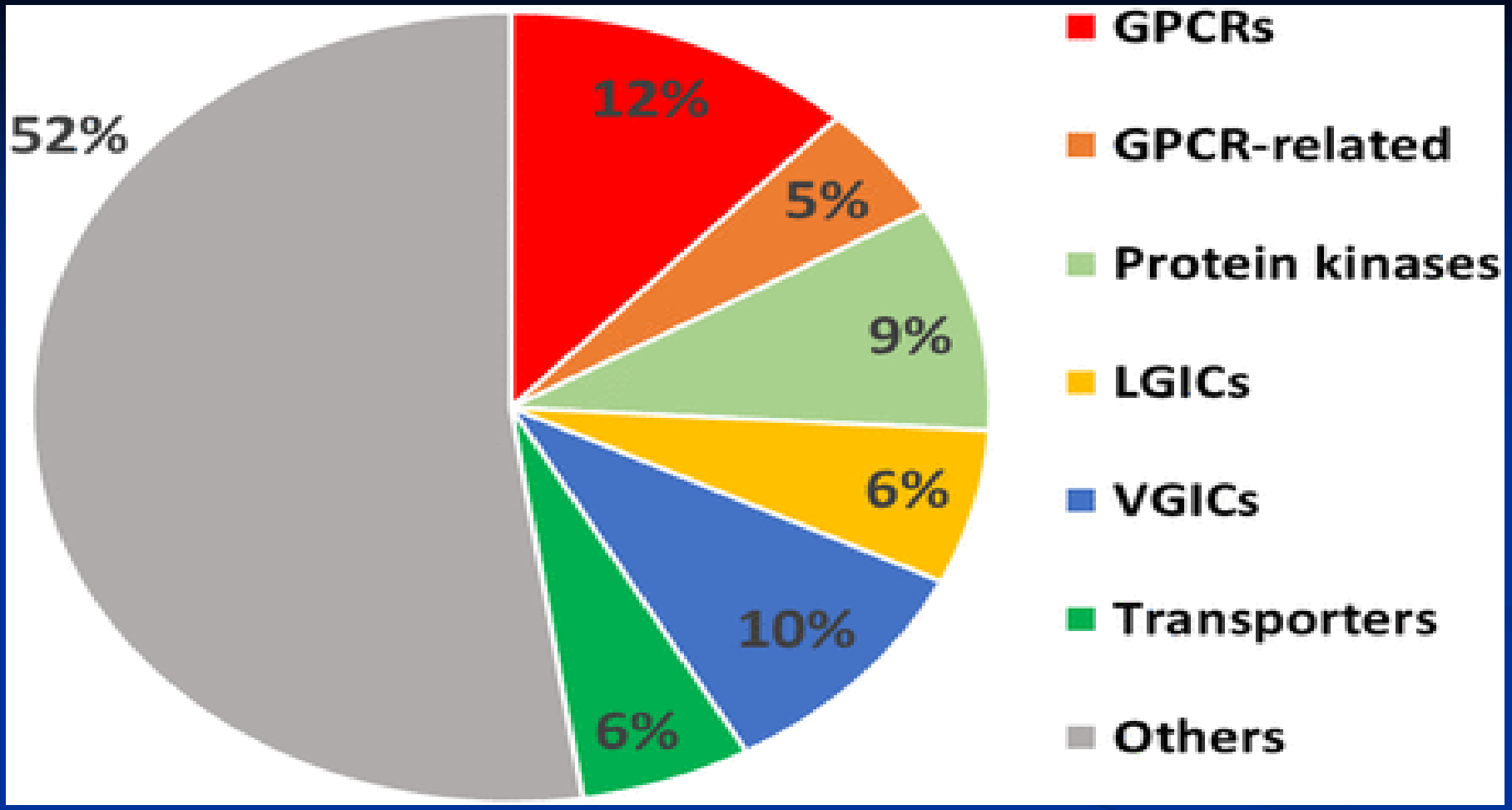
G protein-coupled receptors (GPCRs) comprise a large and diverse class of signal-transducing receptors that undergo dynamic and isoform-specific membrane trafficking. GPCRs thus have an inherent potential to initiate or regulate signaling reactions from multiple membrane locations. This review discusses emerging insights into the subcellular organization of GPCR function in mammalian cells, focusing on signaling transduced by heterotrimeric G proteins and β-arrestins. We summarize recent evidence indicating that GPCR-mediated activation of G proteins occurs not only from the plasma membrane (PM) but also from endosomes and Golgi membranes and that β-arrestin-dependent signaling can be transduced from the PM by β-arrestin trafficking to clathrin-coated pits (CCPs) after dissociation from a ligand-activated GPCR.

New Insights into Modes of GPCR Activation.

Trends Pharmacol Sci. 2018 Jan 30. pii: S0165-6147(18)30024-5. doi: 10.1016/j.tips.2018.01.001. [Epub ahead of print] Wang W, Qiao Y, Li Z.

Abstract

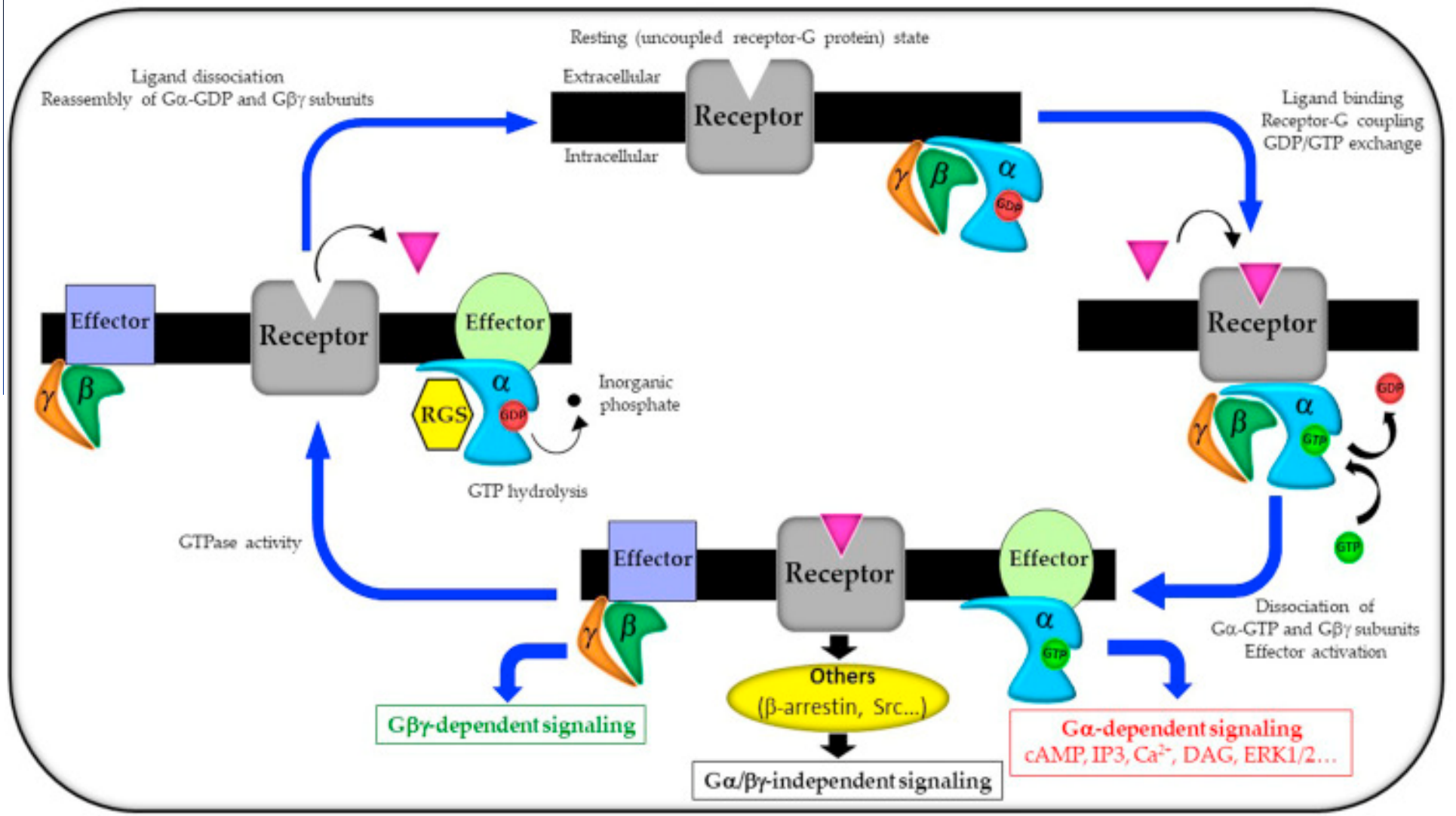
In classical G-protein-coupled receptor (GPCR) activation, GPCRs couple to a variety of heterotrimeric G proteins on the membrane and then activate downstream signaling pathways. More recently, GPCRs have been found to couple to different effector proteins, including different G protein subtypes and regulatory proteins, such as arrestins. Some novel modes of GPCR activation have been proposed to explain their complex behaviors. In this review, we summarize the main novel modes of GPCR activation, including biased activation, intracellular activation, dimerization activation, transactivation, and biphasic activation. In addition, we also discuss the relationship among the five modes to show the complex picture of GPCR activation. The complex activation modes regulate precisely GPCR downstream signaling, including physiological and pathological signaling. Thus, there is the potential to develop GPCR precision drugs that target precise GPCR activation modes to accurately strengthen their beneficial functions and block specific pathological processes.



The estimated proportion of genes from different gene families that are targets for approved drugs. GPCRs comprise the single largest such group. VGICs: voltage-gated ion channels; LGICs: ligand-gated ion channels.

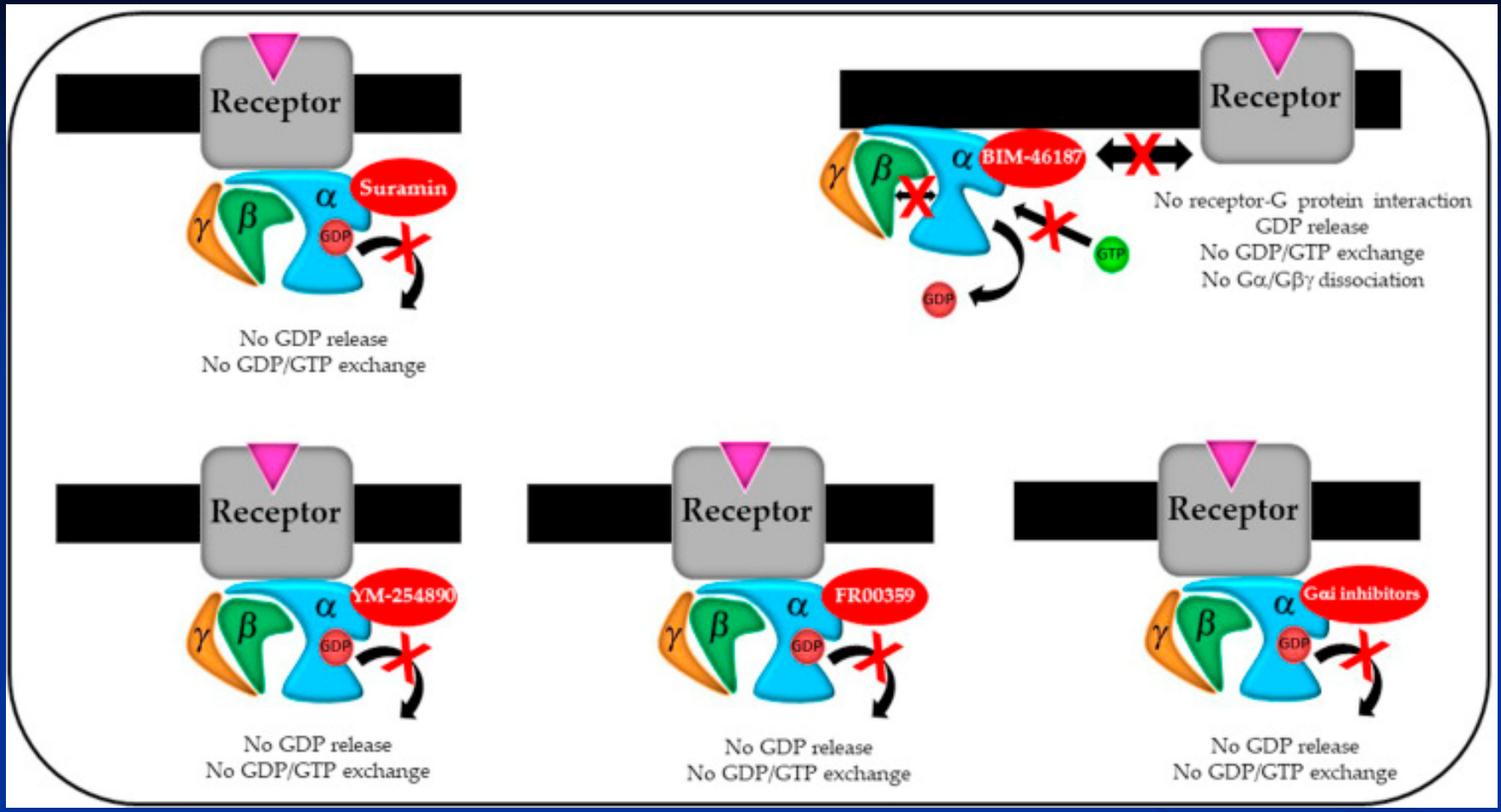
Mol Pharmacol. 2018 Apr;93(4):251-258. doi: 10.1124/mol.117.111062. Epub 2018 Jan 3.

G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs? *Sriram K, Insel PA.*



The classical GPCR-G protein activation/deactivation cycle.

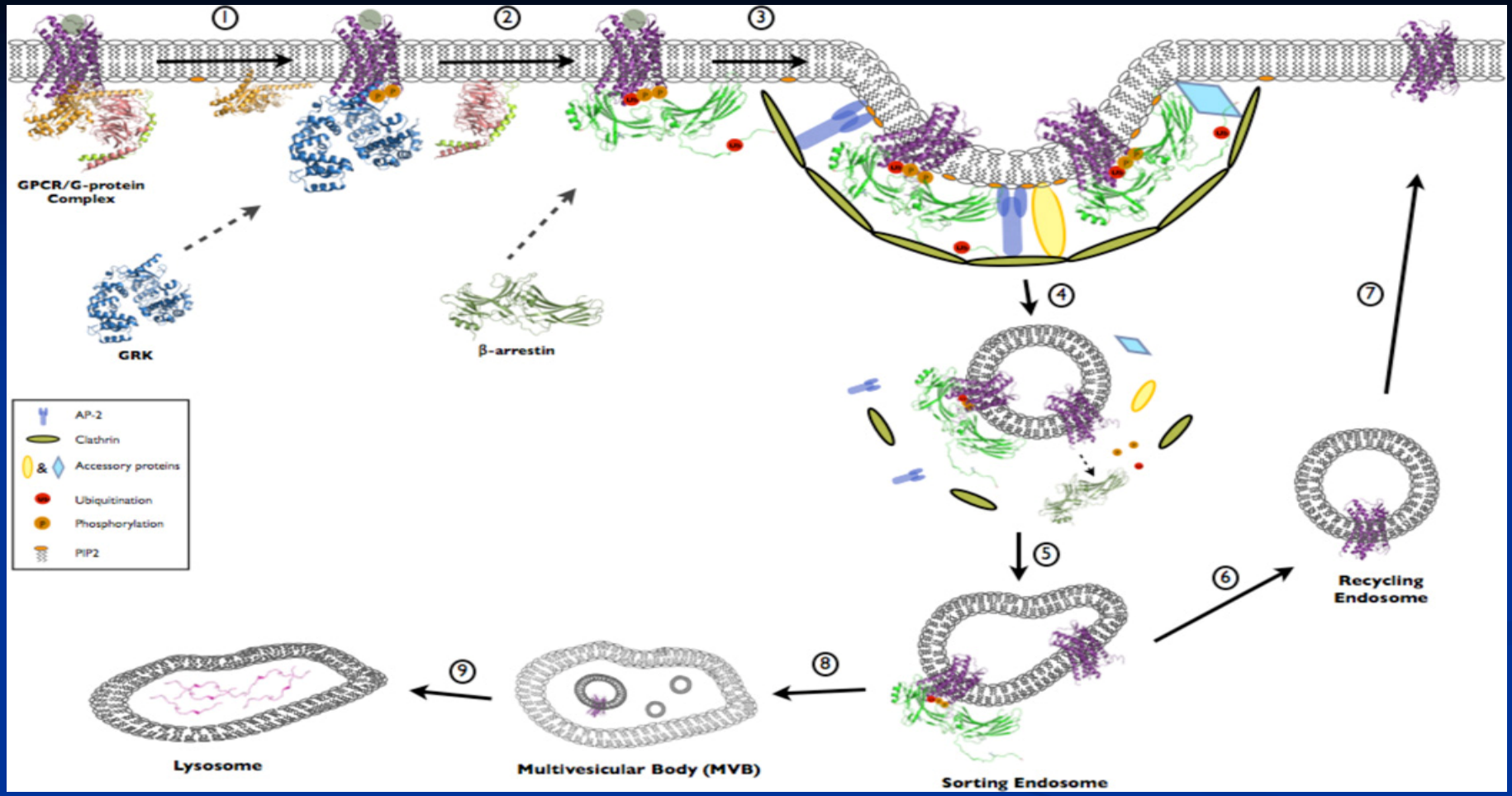
Eur J Pharmacol. 2018 Mar 6;826:169-178. doi: 10.1016/j.ejphar.2018.03.003. [Epub ahead of print] **Small molecules targeting heterotrimeric G proteins.** Ayoub MA.



The different modes of action of Gα subunit inhibitors. The small molecule binds to the Gα subunit and inhibits GDP/GTP exchange by disrupting either GDP release, GTP binding, receptor-Gα protein interaction or even the dissociation or the molecular rearrangements between Gα-Gβγ subunits.

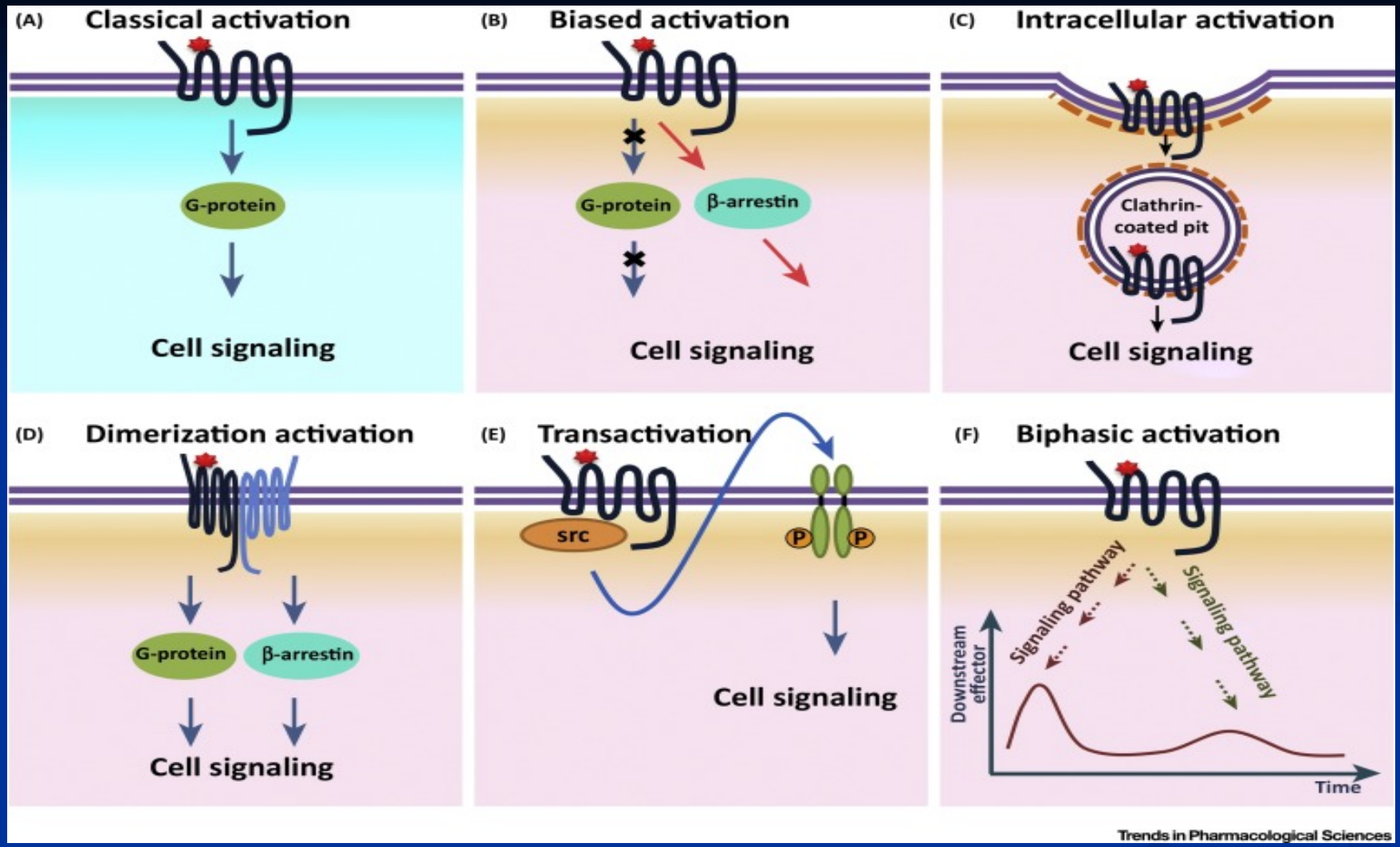
Eur J Pharmacol. 2018 Mar 6;826:169-178. doi: 10.1016/j.ejphar.2018.03.003. [Epub ahead of print]

.Small molecules targeting heterotrimeric G proteins. *Ayoub MA*[1]



Role of β-arrestins in GPCR trafficking

(1) Agonist binding to a GPCR results in heterotrimeric G protein activation leading to dissociation of Gα from Gβγ subunits. This promotes GRK association with the agonist-bound GPCR which mediates receptor phosphorylation and (2) promotes β-arrestin recruitment to the receptor. (3) β-arrestin association with the phosphorylated GPCR mediates conformational changes in arrestin that promote association of the GPCR-β-arrestin complex with the endocytic machinery and subsequent endocytosis (4). GPCRs then traffic to sorting endosomes (5) and ultimately either recycle back to the plasma membrane through recycling endosomes (6 and 7) or are sorted to lysosomes where they are degraded (8 and 9). Handb Exp Pharmacol. 2014;219:173-86. doi: 10.1007/978-3-642-41199-1_9.**β-arrestins and G protein-coupled receptor trafficking.** Tian X



Classical and Novel Modes of G-Protein-Coupled Receptor Activation. (A) Classical mode, (B) biased activation, (C) intracellular activation, (D) dimerization activation, (E) transactivation, and (F) biphasic activation.

Trends Pharmacol Sci. 2018 Jan 30. pii: S0165-6147(18)30024-5. doi: 10.1016/j.tips.2018.01.001. [Epub ahead of print]**New Insights into Modes of GPCR Activation.** Wang W et al.

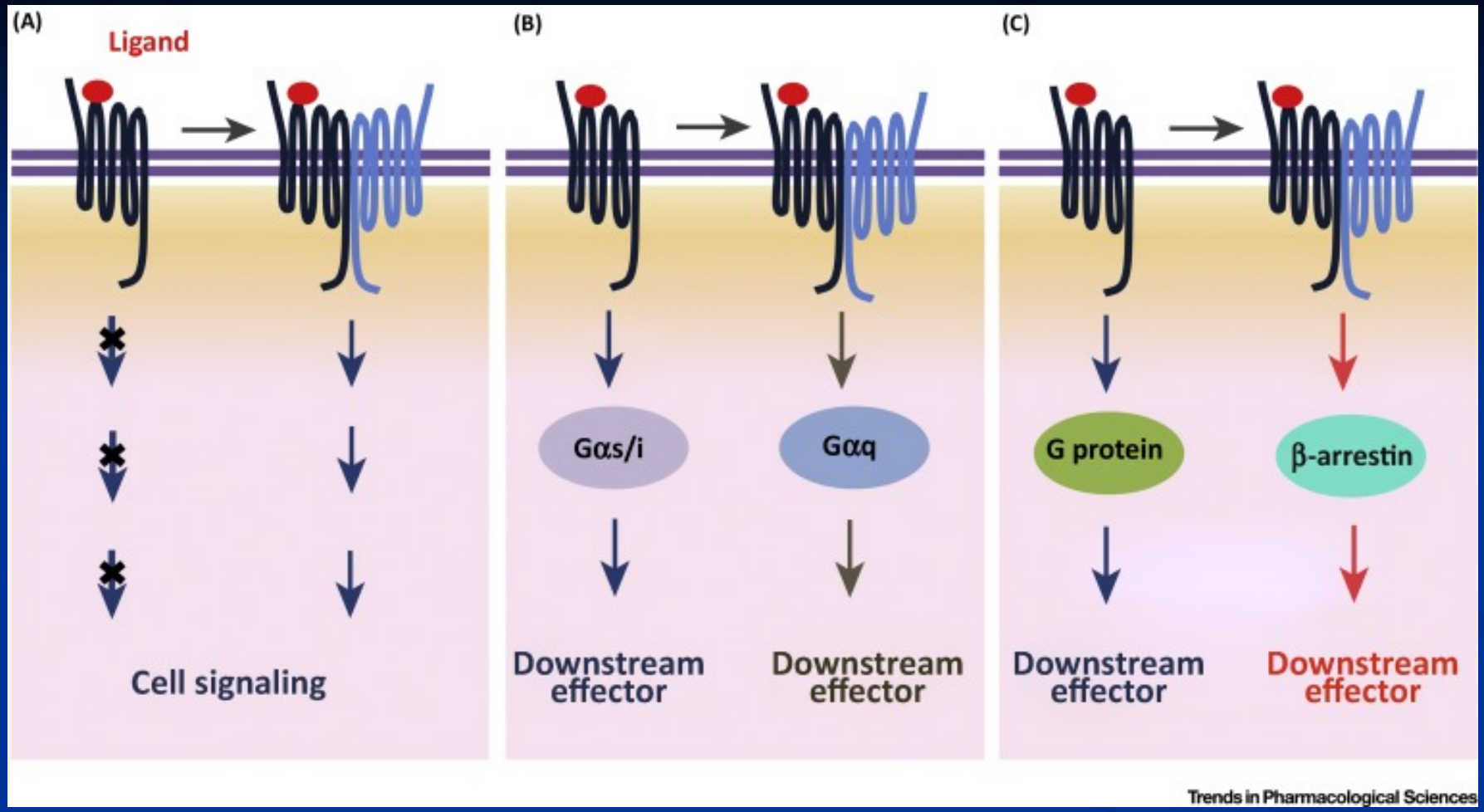
- GPCRs adopt multiple conformational states that can activate or block distinct intracellular signalling pathways, such as those regulated by heterotrimeric G proteins or β-arrestins.
- Different agonists for the same receptor can stabilize distinct GPCR conformational states. Agonists that preferentially activate certain intracellular pathways relative to others are referred to as biased agonists.
- Structural studies support a model in which GPCRs act as allosteric microprocessors that integrate diverse extracellular and intracellular stimuli to generate distinct conformations that result in varied intracellular responses.
- In addition to biased agonists, biased signalling may be encoded by the receptor ('receptor bias') or by the relative expression levels of transducers ('system bias').
- Biased signalling is also observed in other receptor families, such as nuclear hormone receptors and receptor tyrosine kinases.
- Recent preclinical and clinical work suggests that by more selectively targeting signalling pathways of interest, biased agonists have the potential to increase clinical efficacy while reducing undesirable side effects.

Nat Rev Drug Discov. 2018 Jan 5. doi: 10.1038/nrd.2017.229. [Epub ahead of print] ***Biased signalling: from simple switches to allosteric microprocessors.*** *Smith JS*

Highlights

- •β-arrestins affect all the facets of GPCRs signalling, not just desensitization.
- •β-arrestins are recruited to most hormone-responsive GPCR classes.
- •β-arrestins control GPCR-mediated signals in intensity, time and space.
- •There is a close connection between β-arrestin signalling and biased pharmacology.
- •The understanding of β-arrestin-dependent mechanisms is rapidly evolving.

Mol Cell Endocrinol. 2017 Jul 5;449:28-41. ***β-arrestin signalling and bias in hormone-responsive GPCRs.*** *Reiter E et al*



Dimerization Activation. Two major patterns of dimerization activation: (A) G-protein-coupled receptors (GPCRs) can mediate signaling only in the condition of dimerization; and (B,C) dimers couple with different effector proteins from monomers.

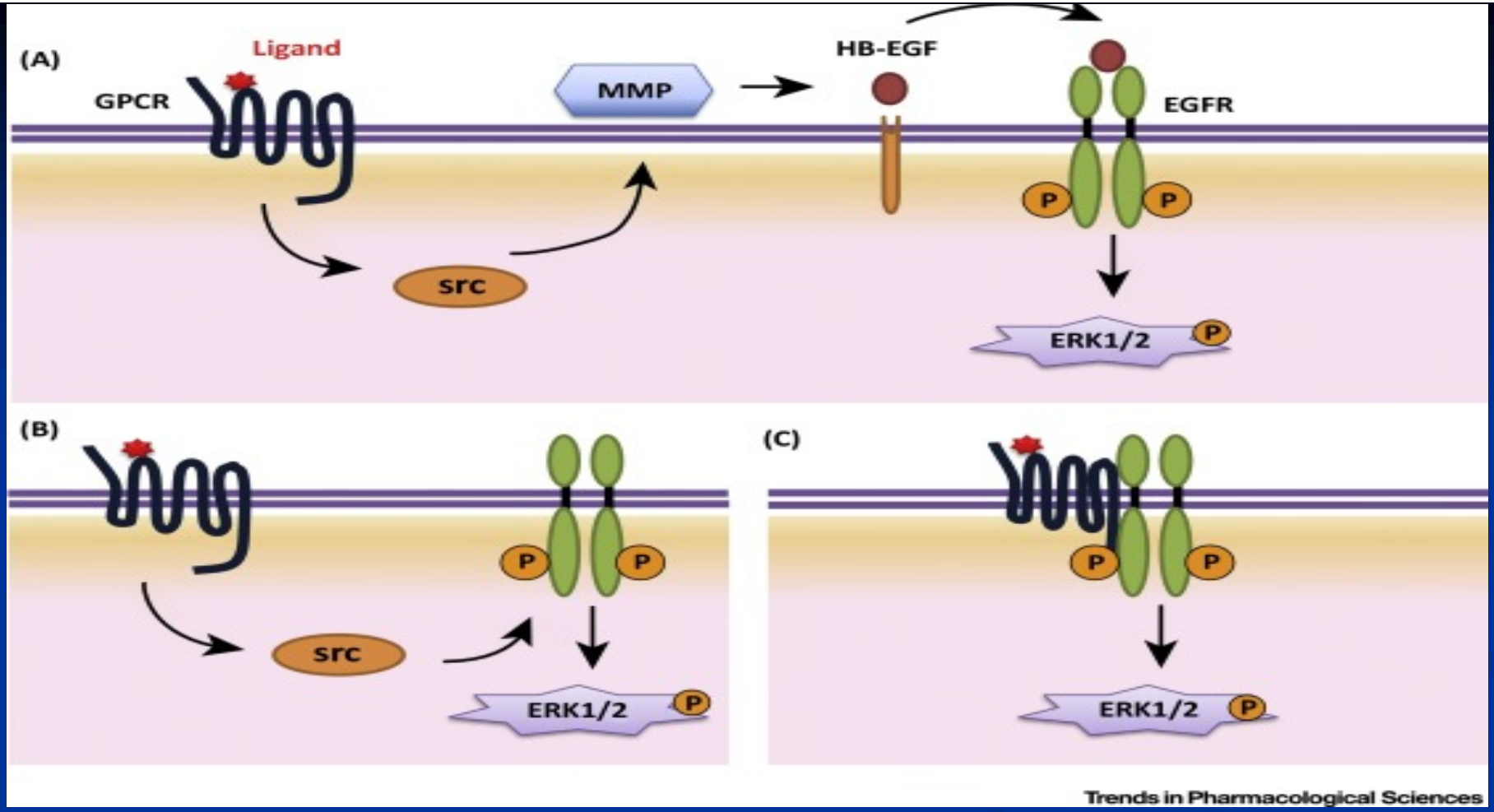
Trends Pharmacol Sci. 2018 Jan 30. pii: S0165-6147(18)30024-5. doi: 10.1016/j.tips.2018.01.001. [Epub ahead of print] ***New Insights into Modes of GPCR Activation.*** *Wang W et al.*

Biased signalling: from simple switches to allosteric microprocessors.

Smith JS[1], Lefkowitz RJ, Rajagopal S. Nat Rev Drug Discov. 2018 Jan 5. doi: 10.1038/nrd.2017.229. [Epub ahead of print]

Abstract

GPCRs are the largest class of receptors in the human genome and some of the most common drug targets. It is now well established that GPCRs can signal through multiple transducers, including heterotrimeric G proteins, GPCR kinases and β-arrestins. While these signalling pathways can be activated or blocked by 'balanced' agonists or antagonists, they can also be selectively activated in a 'biased' response. Biased responses can be induced by biased ligands, biased receptors or system bias, any of which can result in preferential signalling through G proteins or β-arrestins. At many GPCRs, signalling events mediated by G proteins and β-arrestins have been shown to have distinct biochemical and physiological actions from one another, and an accurate evaluation of biased signalling from pharmacology through physiology is crucial for preclinical drug development. Recent structural studies have provided snapshots of GPCR-transducer complexes, which should aid in the structure-based design of novel biased therapies. Our understanding of GPCRs has evolved from that of two-state, on-and-off switches to that of multistate allosteric microprocessors, in which biased ligands transmit distinct structural information that is processed into distinct biological outputs. The development of biased ligands as therapeutics heralds an era of increased drug efficacy with reduced drug side effects.



Transactivation. Three major patterns are proposed for GPCR-mediated epidermal growth factor receptor (EGFR) transactivation. (A) In the ligand-dependent pathway, the Src activated by GPCRs enhances matrix metalloproteinases (MMP) expression, which leads to cleavage and shedding of heparin-binding EGF-like growth factor (HB-EGF) from the membrane. The fallen HB-EGF binds to EGFR and induces its activation. The ligand-independent pathway includes (B) direct phosphorylation of EGFR in the cytoplasm by Src and (C) activation of EGFR through formation of GPCR–EGFR signaling complexes. Direct phosphorylation of EGFR by Src means that activated Src could directly phosphorylate the cytosolic tyrosine residues of EGFR. In addition, some GPCRs can form GPCR–EGFR signaling complexes and trigger EGFR transactivation. *Trends Pharmacol Sci. 2018 Jan 30. pii: S0165-6147(18)30024-5. doi: 10.1016/j.tips.2018.01.001. [Epub ahead of print]* ***New Insights into Modes of GPCR Activation.*** *Wang W*[1]