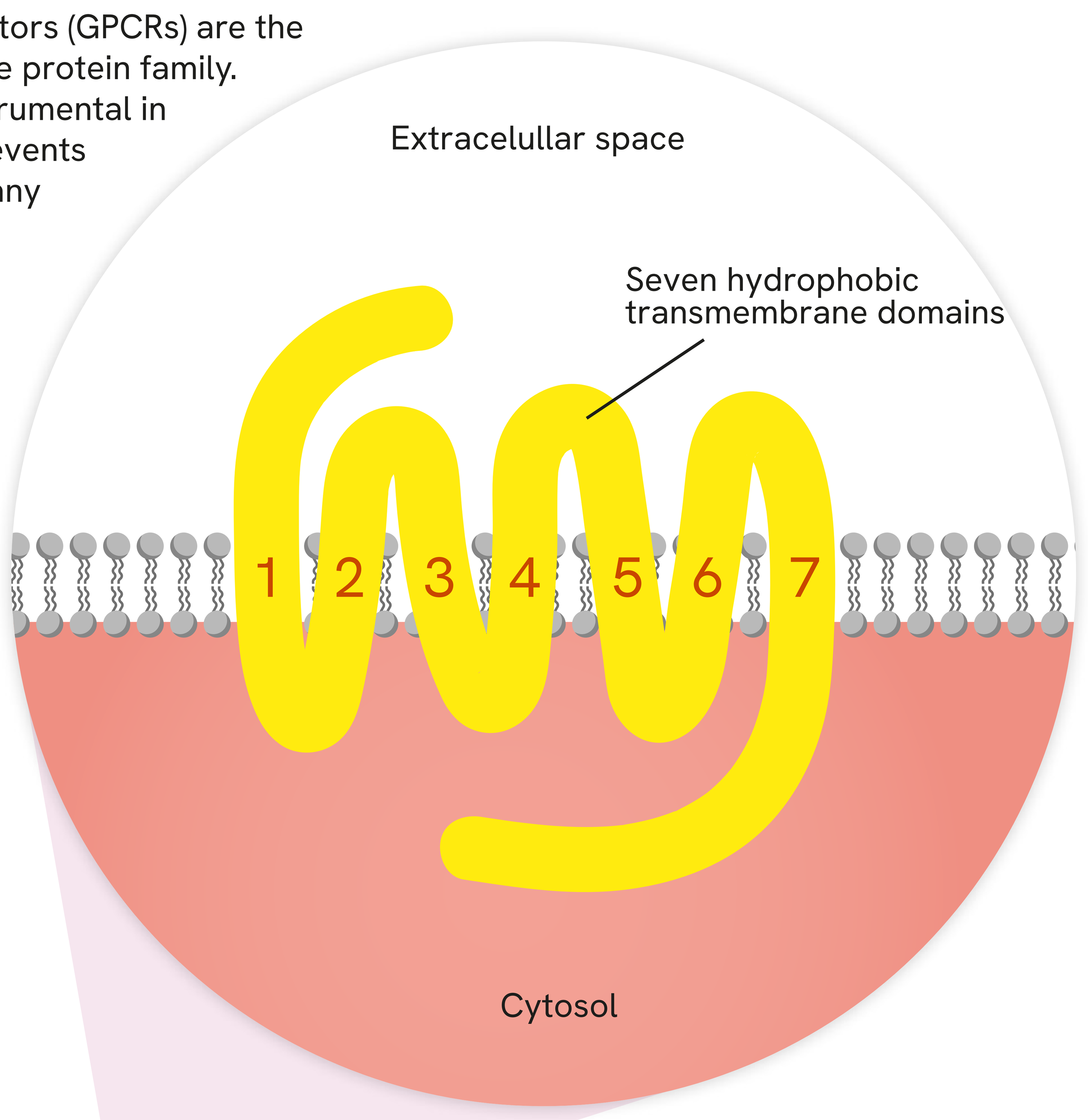
GPCRs and their prevalence in drug therapies.

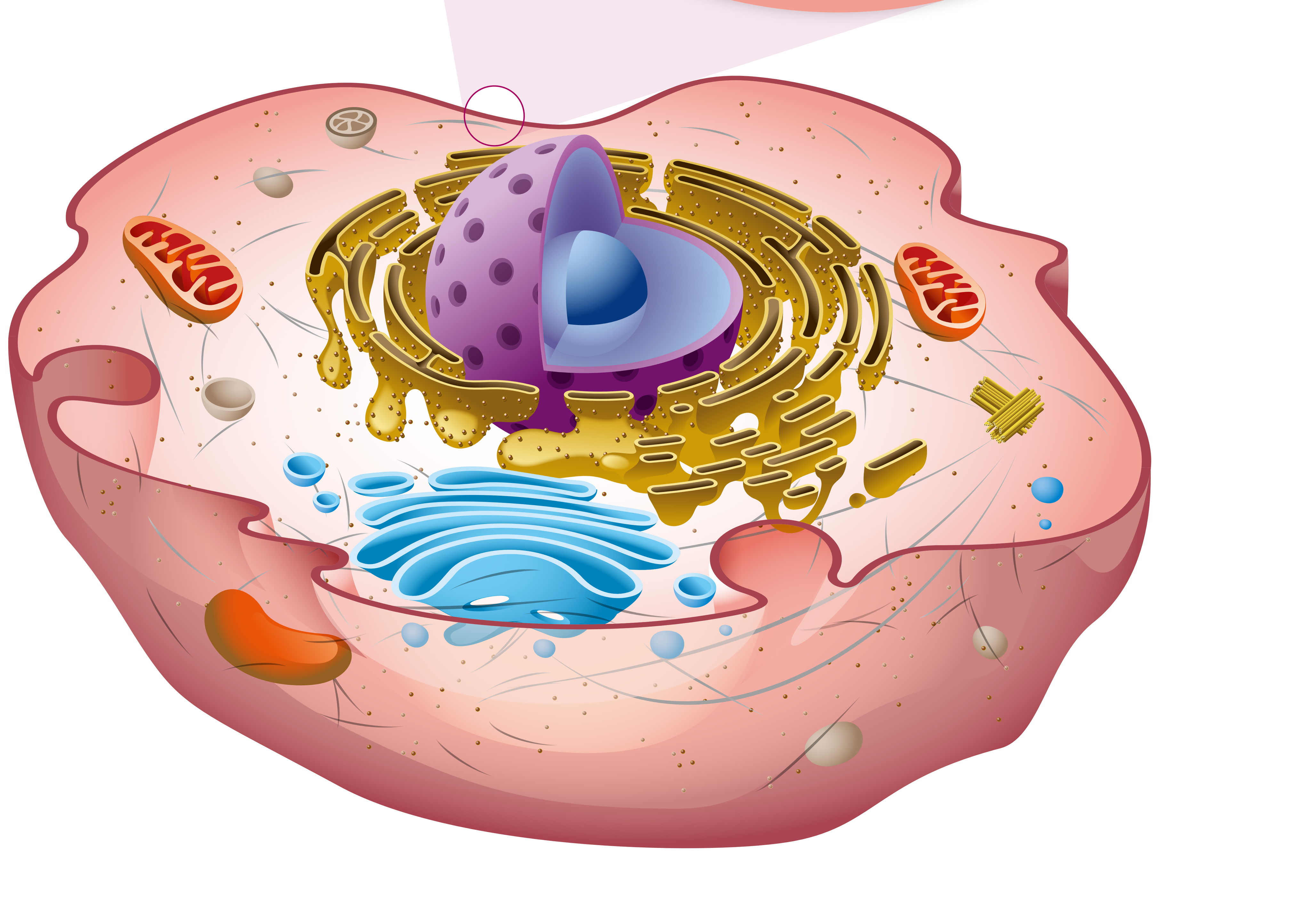
G protein-coupled receptors (GPCRs) are the largest human membrane protein family. These receptors are instrumental in numerous cell signaling events and play a key role in many physiological processes and pathological conditions.[1,2]

GPCRs can associate with a wide variety of ligands including...

- Hormones
- Neurotransmitters
- Lipids
- Nucleotides
- Ions

GPCR signaling pathways can be activated by canonical ligands or biased ligands



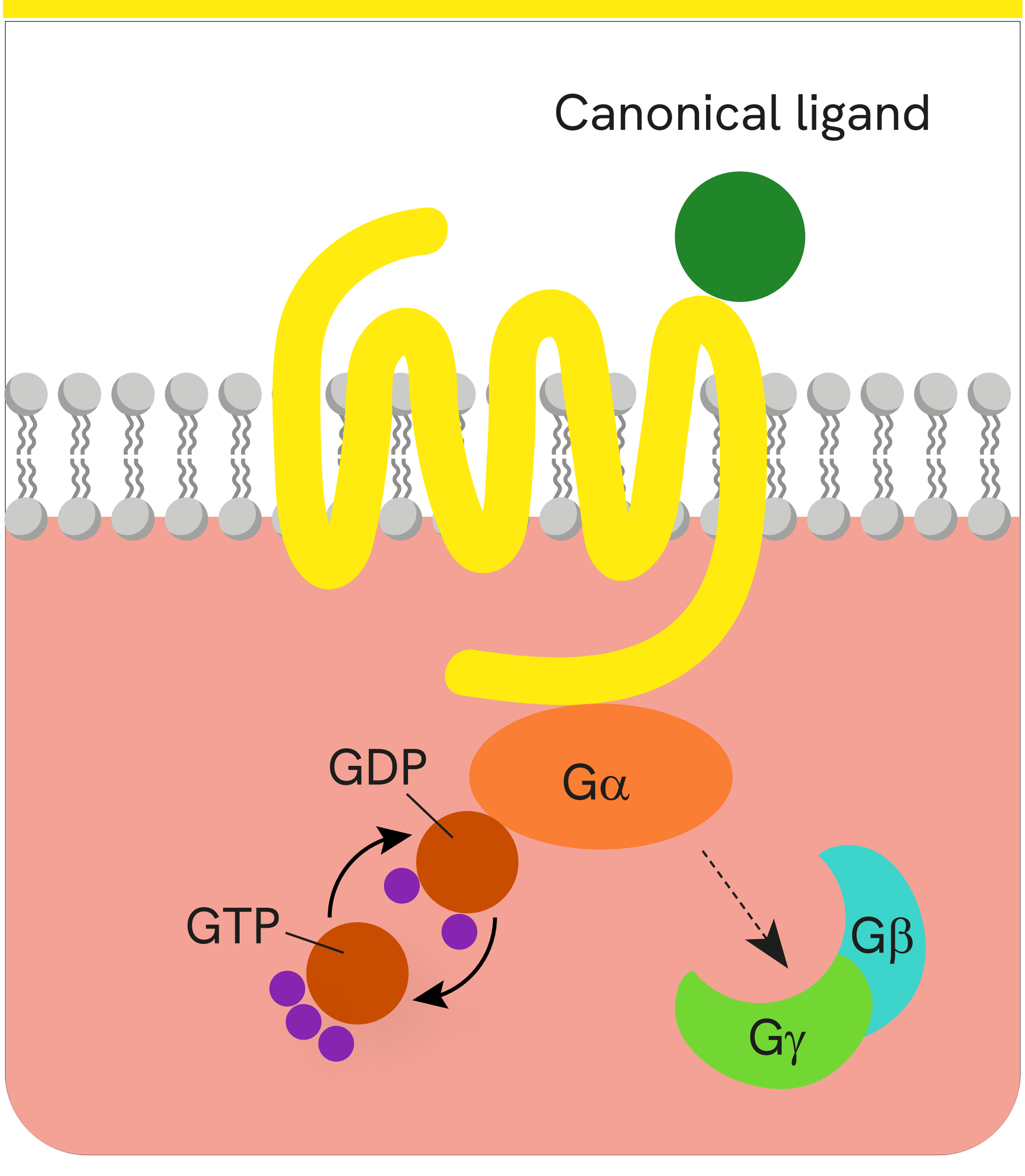


GPCR signaling via G-proteins

1. In the presence of a canonical ligand the inactive GPCR is "stimulated" altering its conformation and its association with the alpha subunit (Gα) of the G-protein.

2. GDP is exchanged for GTP and Gα dissociates from the beta (Gβ) and gamma (Gγ) subunits.

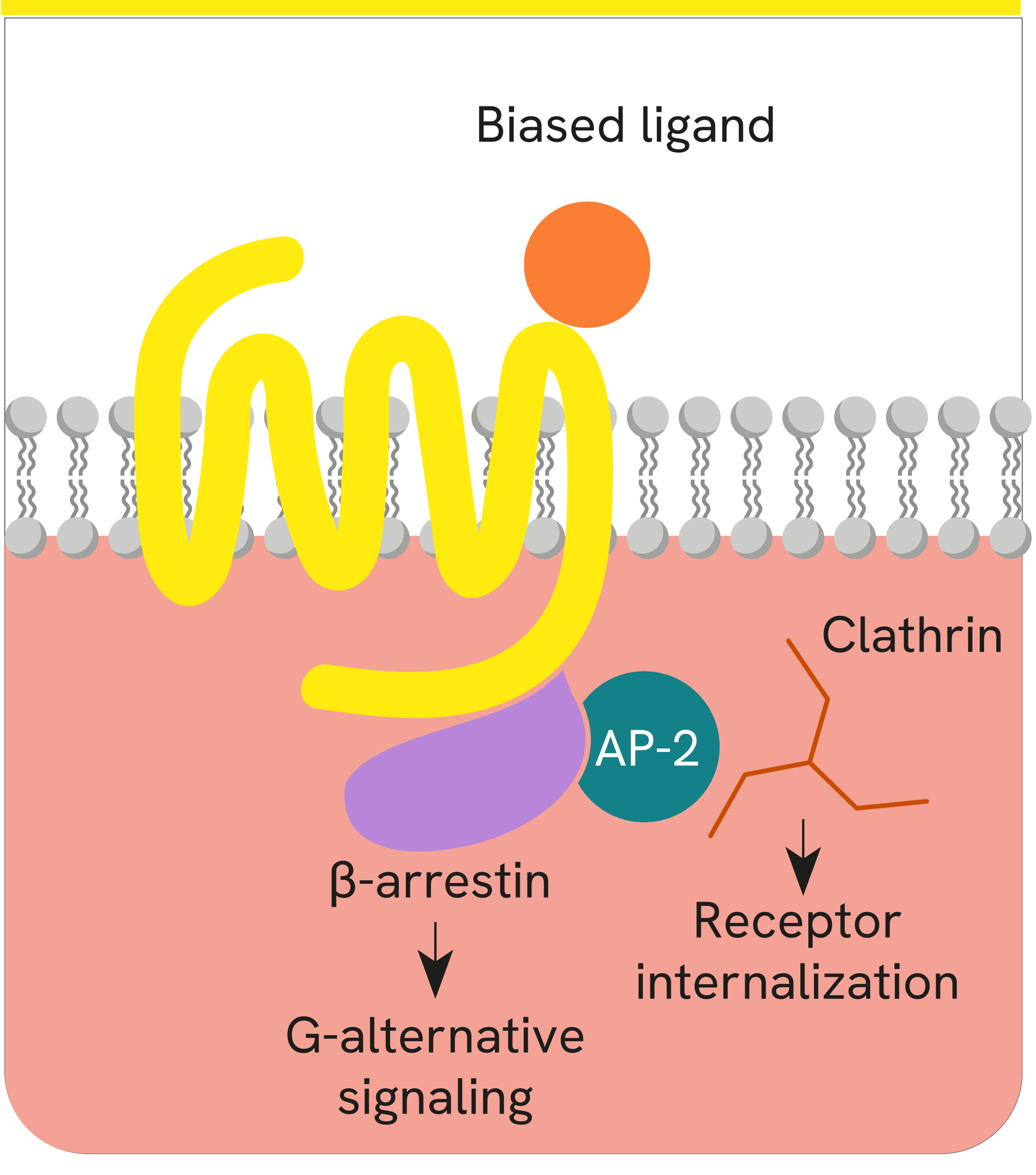
3. The dissociated Gα and Gβ-Gγ dimer can now interact with other proteins, stimulating cell signaling pathways.



Arrestin-mediated signaling

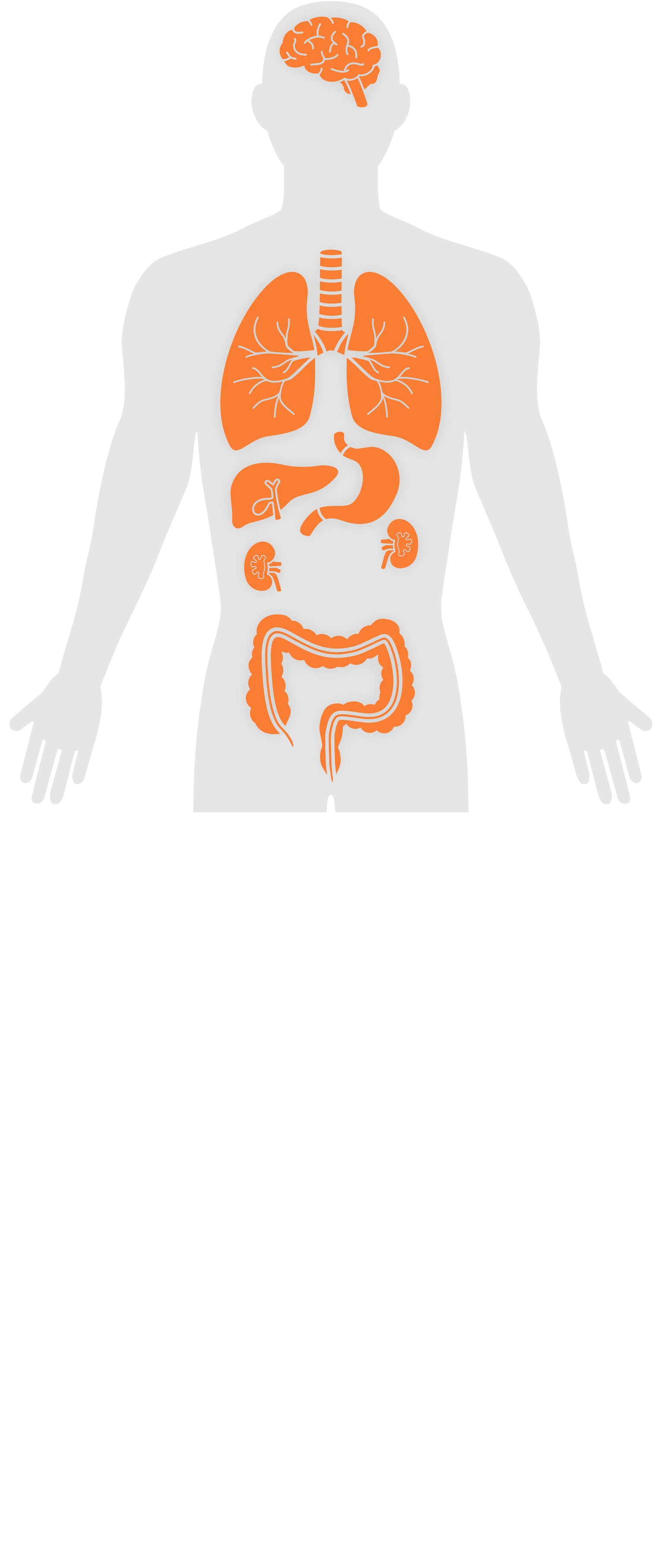
Arrestins can influence GPCR signaling in several ways.

In addition to competitively blocking the binding of G-proteins, arrestins also regulate GPCRs by facilitating their endocytosis via internalization into clathrin-coated pits.[3]



Most of the body's GPCRs are controlled by just two arrestin proteins, β-arrestin 1 and β-arrestin 2.

The flexible structure and versatile functions of arrestins make them highly pliable drug targets which, in time, will help to fine tune the disease-specificity of GPCR drugs, making them safer and more effective.



GPCR-targeted drugs already exist for numerous indications.[4,5,6,7]

Cardiovascular diseases	Atropine (Bradycardia treatment) *Competitive antagonist of acetylcholine muscarinic receptors* Carvedilol (Congestive heart failure/hypertension treatment) *Inverse agonist of the β-adrenergic receptor*
Neuroscience	Bupropion (Nicotine withdrawal treatment) *Partial agonist of acetylcholine nicotinic receptors* Morphine (Pain treatment) *Full agonist of μ-opioid receptors*
Metabolic diseases	Exenatide (Type 2 diabetes treatment) *Agonist of the glucagon-like peptide-1 receptor*
Oncology	Degarelix (Prostate cancer treatment) *Antagonist of gonadotropin-releasing hormone* Vismodegib (Basal cell carcinoma treatment) *Competitive antagonist of Smoothened (Smo)*
Immunology	CF 101 (Rheumatoid arthritis treatment) *Antagonist of the adenoside A3 receptor*

1. Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, & Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. Nature Reviews Drug Discovery. 2017;16(12):829–842. doi: 10.1038/nrd.2017.178 2.
2. Essentials of cell biology: g-protein-coupled receptors play many different roles in eukaryotic cell signaling. Nature Education. https://www.nature.com/scitable/e-books/essentials-of-cell-biology-14749010/122997540. Published 2014. Accessed May 21, 2021.
3. Mj L, C H. Arrestin interactions with G protein-coupled receptors. Handb Exp Pharmacol. 2014;219:15-56. doi: 10.1007/978-3-642-41199-1_
4. Pharmacology: Insight Into Ligand Classes. Revvity. Accessed May 21, 2021.
5. Exenatide. BNF: British National Formulary - NICE. https://bnf.nice.org.uk/drug/exenatide.html#drugAction. Accessed May 23, 2021.
6. Aditya S, Rattan A. Vismodegib: A smoothened inhibitor for the treatment of advanced basal cell carcinoma. Indian Dermatol Online J. 2013;4(4):365–368. doi: 10.4103/2229-5178.120685
7. Piclidenoson. DrugBank Online. https://go.drugbank.com/drugs/DB055111. Published 2007. Updated February 21, 2021. Accessed May 23, 2021.

revvity

Discover more on GPCRs on revvity.com

Revvity
940 Winter Street
Waltham, MA 02451 USA
(800) 762-4000
www.revvity.com

1073500 (957950)