Receptor Signaling Networks: Receptors

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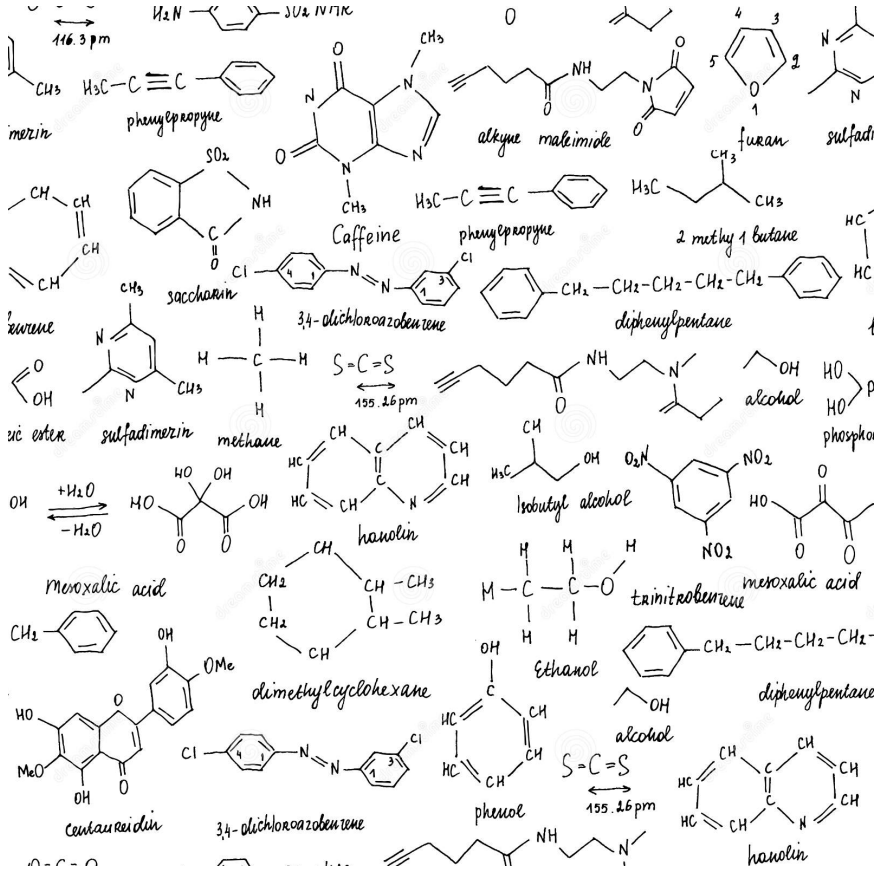
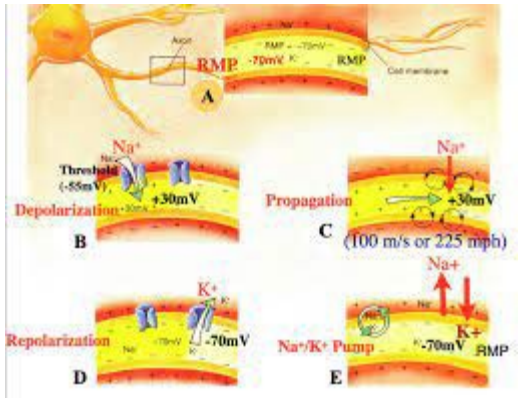
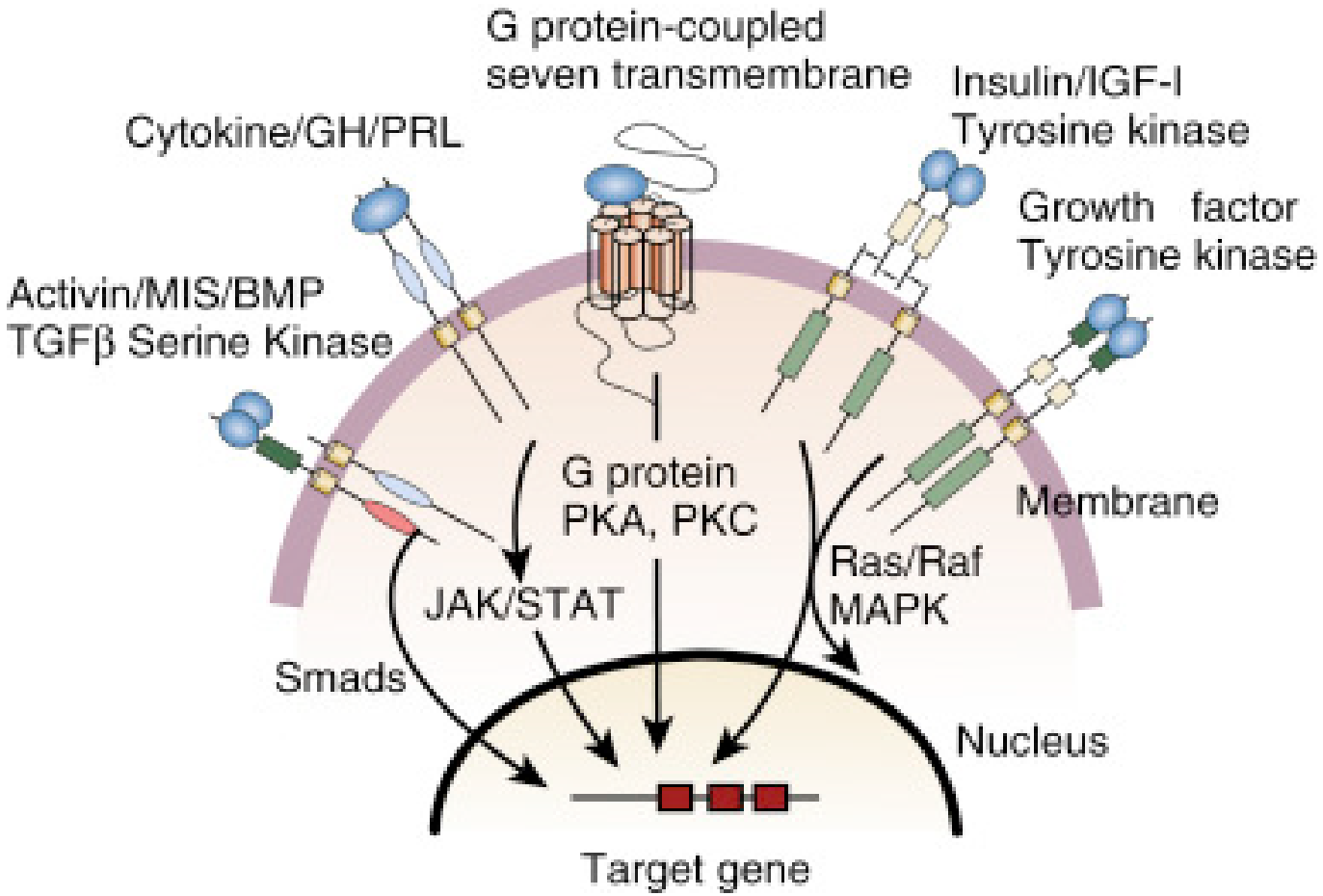
Information Processing by the Body





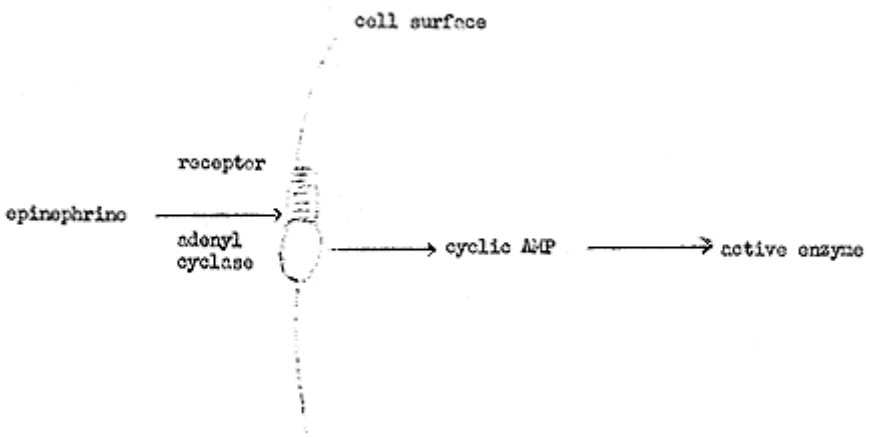
Receptors


G protein-coupled
seven transmembrane
Cytokine/GH/PRL
Insulin/IGF-I
Tyrosine kinase
Growth factor
Tyrosine kinase
Activin/MIS/BMP
TGFβ Serine Kinase
G protein
PKA, PKC
Membrane
JAK/STAT
Ras/Raf
MAPK
Smads
Nucleus
Target gene

G protein-coupled receptors

Largest superfamily of receptors -~ 800 in the human genome

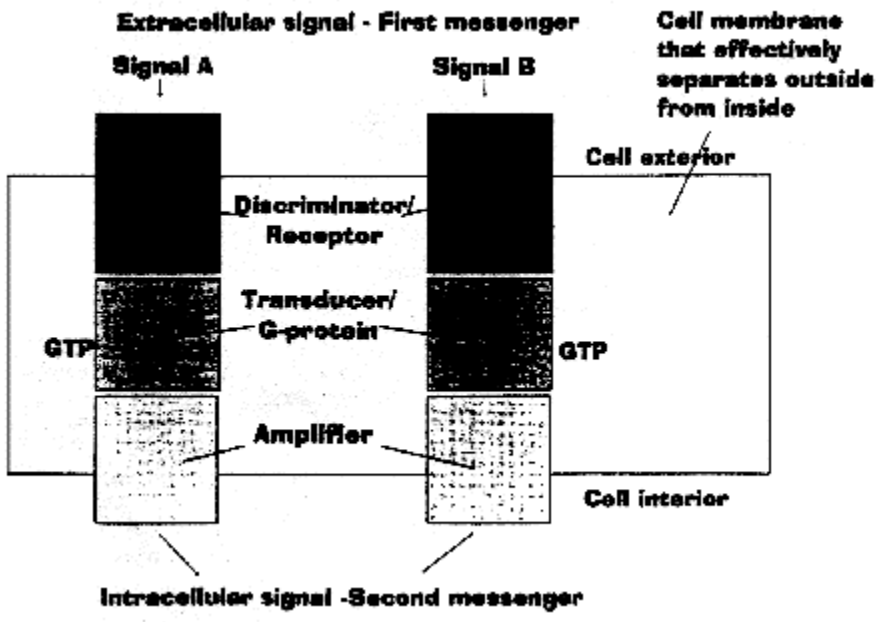
Earl Sutherland



- Work done in the 1950-1960s
- Primary messenger: Epinephrine
- Bound to cell surface that led to activation of adenylyl cyclase
- Second messenger: cyclic AMP
- Activation of glycogen phosphorylase

https://www.nobelprize.org/

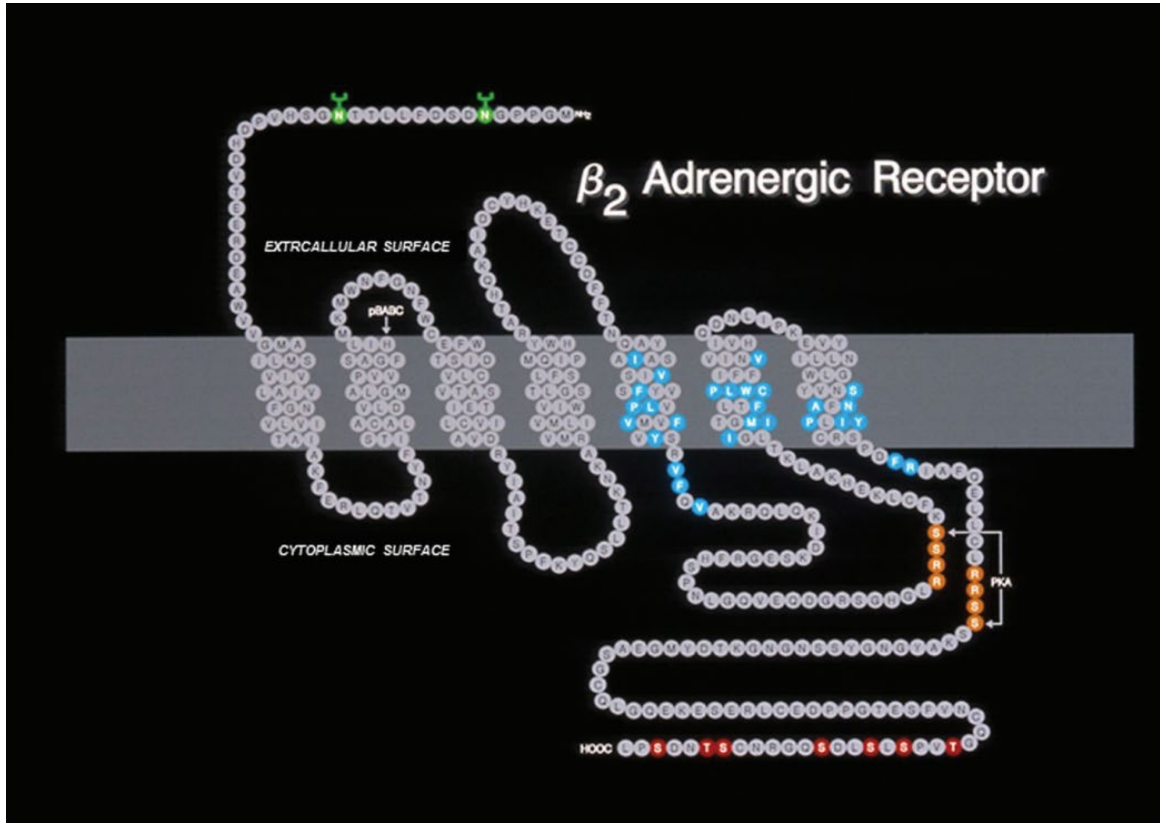
Martin Rodbell and Al Gilman



- Rodbell 1971 – Transduction required the first messenger, a transducer that required GTP, amplifier that generates second messenger
- Gilman 1980 – Isolated heterotrimeric G protein, which requires GTP for activity

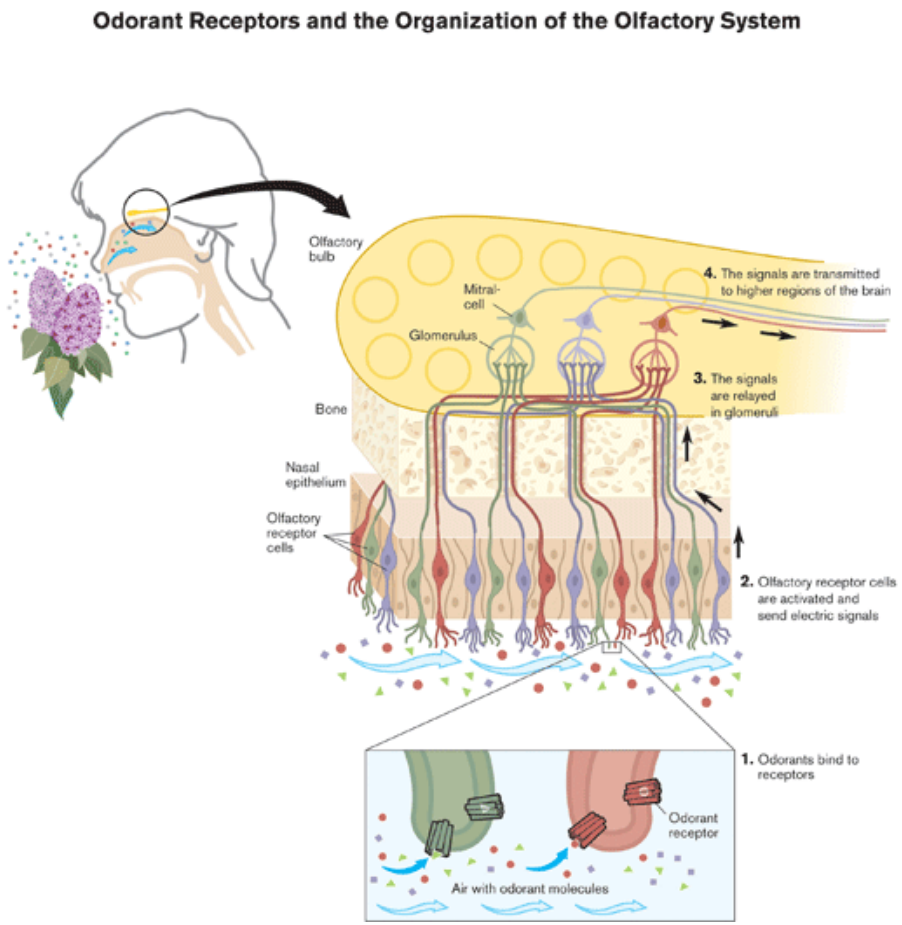
https://www.nobelprize.org/

Bob Lefkowitz



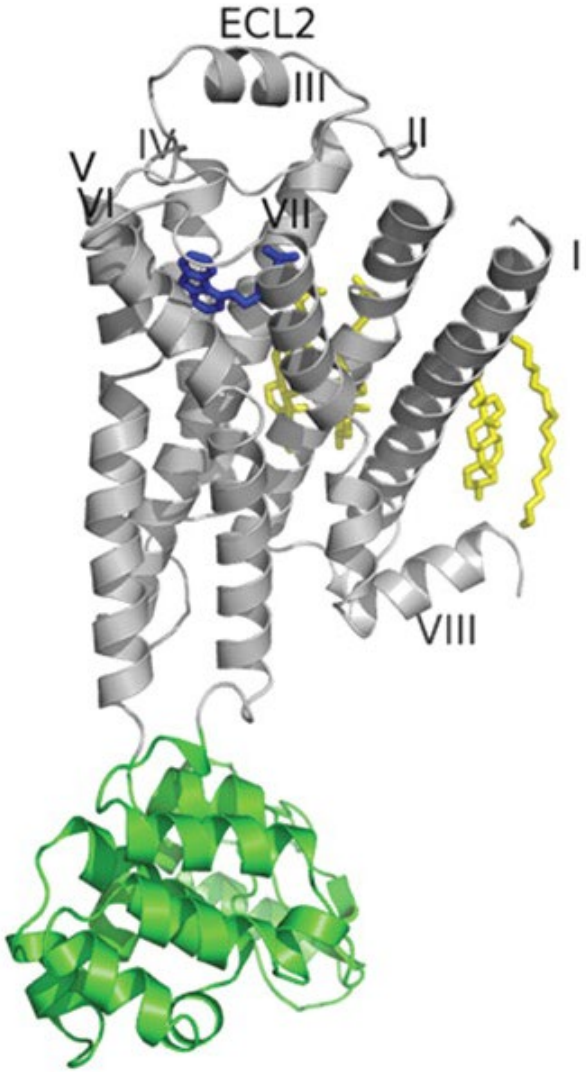
- Developed radioligand binding assays for GPCRs
- 1971: Labeled β-adrenergic receptors and demonstrated their GTP regulation
- 1970-80s: Isolated and determined their biochemistry
- 1980s: Cloned β2AR – receptor superfamily
- 1990s: Arrestins

Richard Axel and Linda Buck



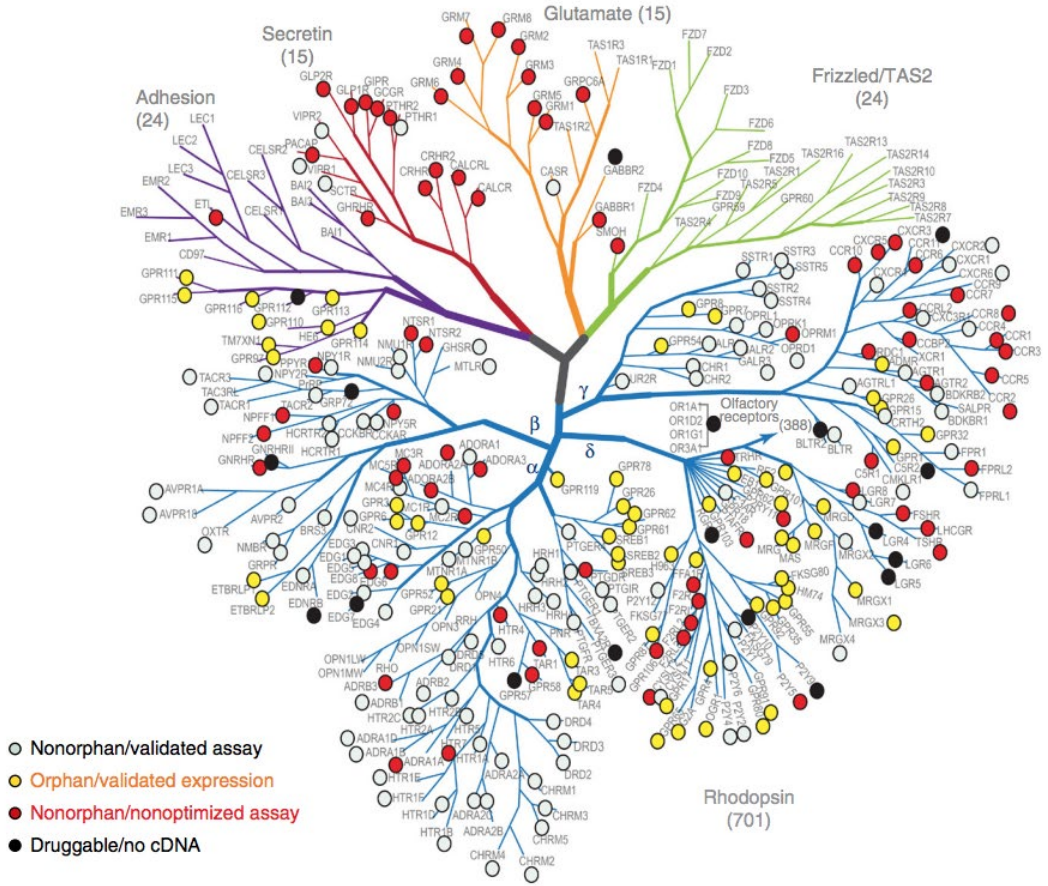
- 1991 – described the family of odorant receptors (type of GPCR)
- Found that every single olfactory receptor expresses one and only one odorant receptor

Brian Kobilka



- 1980s: Worked in Lefkowitz lab, cloning the β2AR
- 2006: First structure of a non-rhodopsin GPCR, the b2AR
- Followed this by structures of other receptors, including those complexed to heterotrimeric G proteins

GPCRs are the most common receptors in the genome

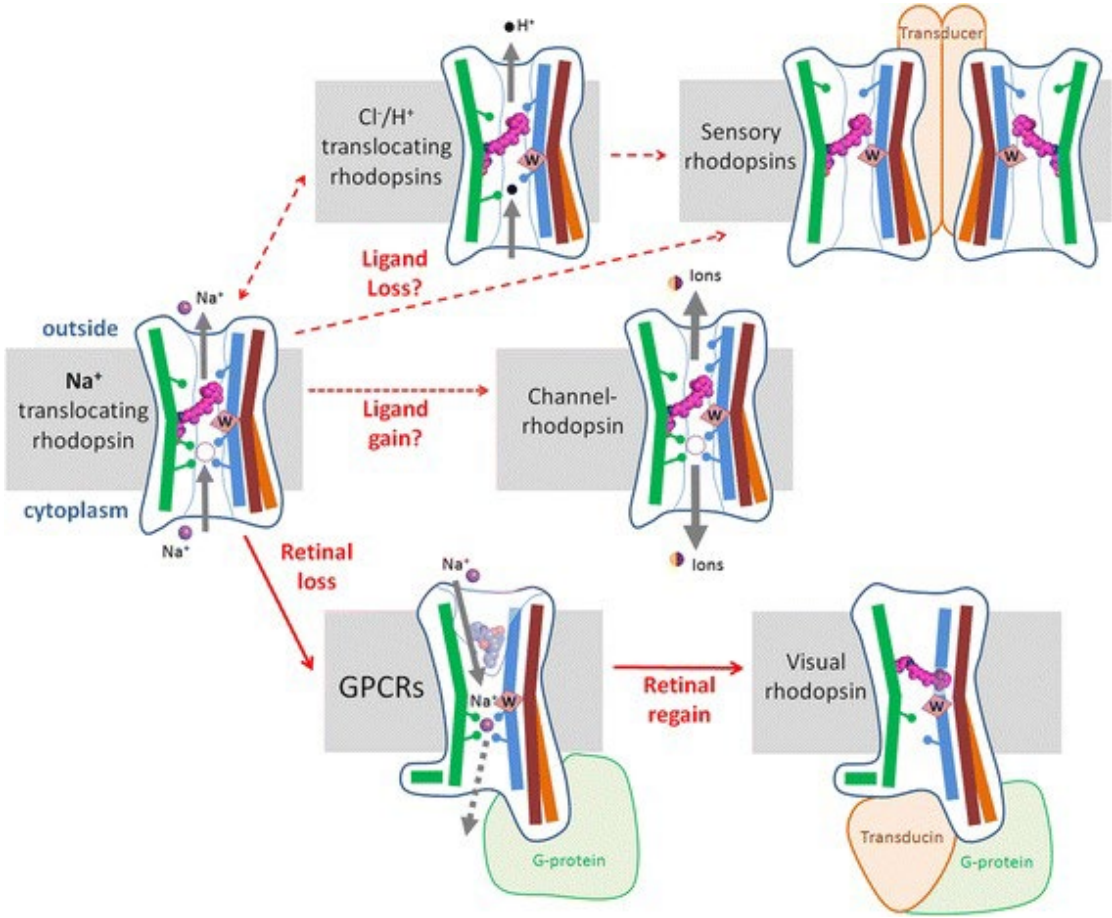


- ~ 800 human GPCRs in 5 families
  - **G**lutamate (Family C)
  - **R**hodopsin (Family A)
    - α, β, γ, δ groups
  - **A**dhesion
  - **F**rizzled/Taste2
  - **S**ecretin (Family B)

- 2004 Nobel Prize in Physiology/Medicine: Axel and Buck
- 2012 Nobel Prize in Chemistry: Lefkowitz and Kobilka

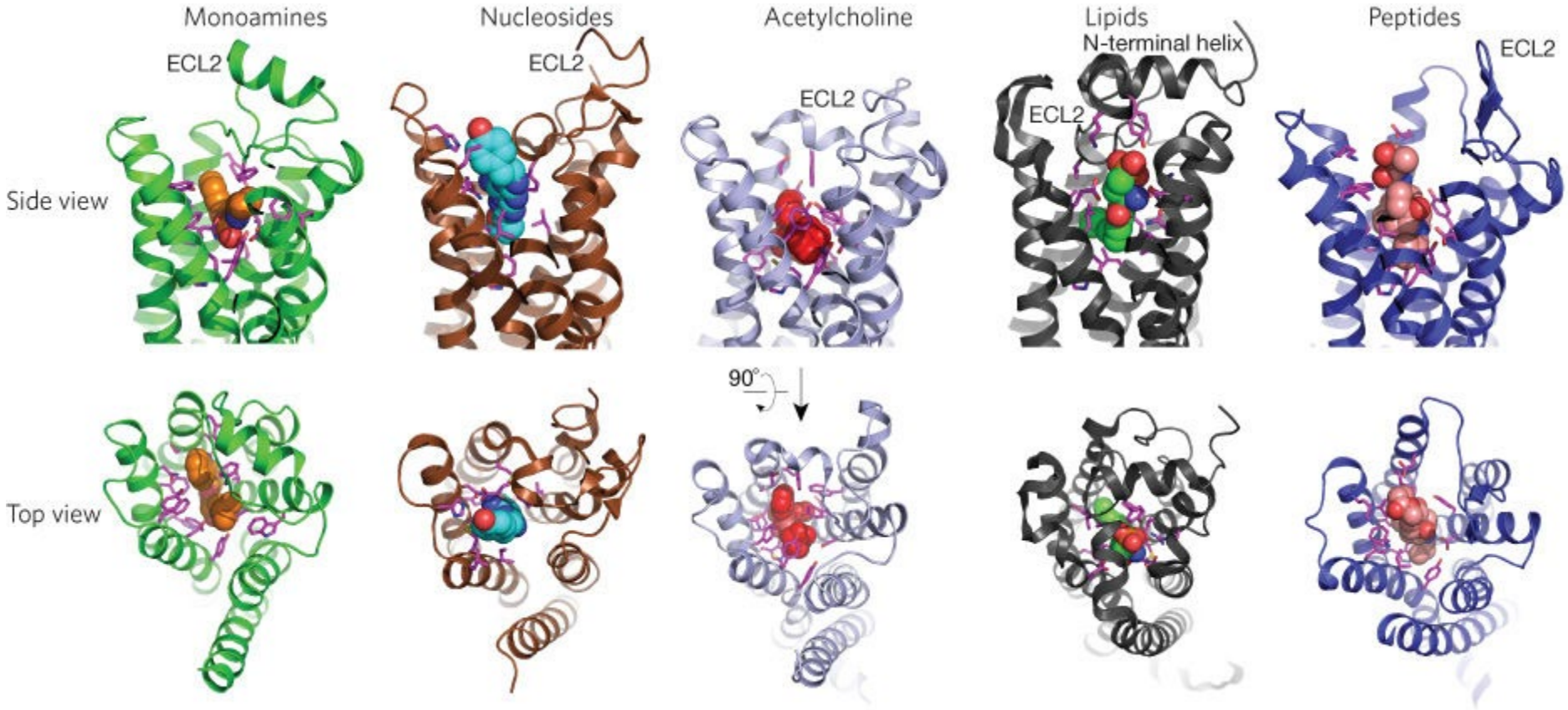
https://gpcr.usc.edu/

Architecture conserved from bacteria



Biol Direct. 2015 Oct 15;10:63

Diversity of Rhodopsin family ligand binding



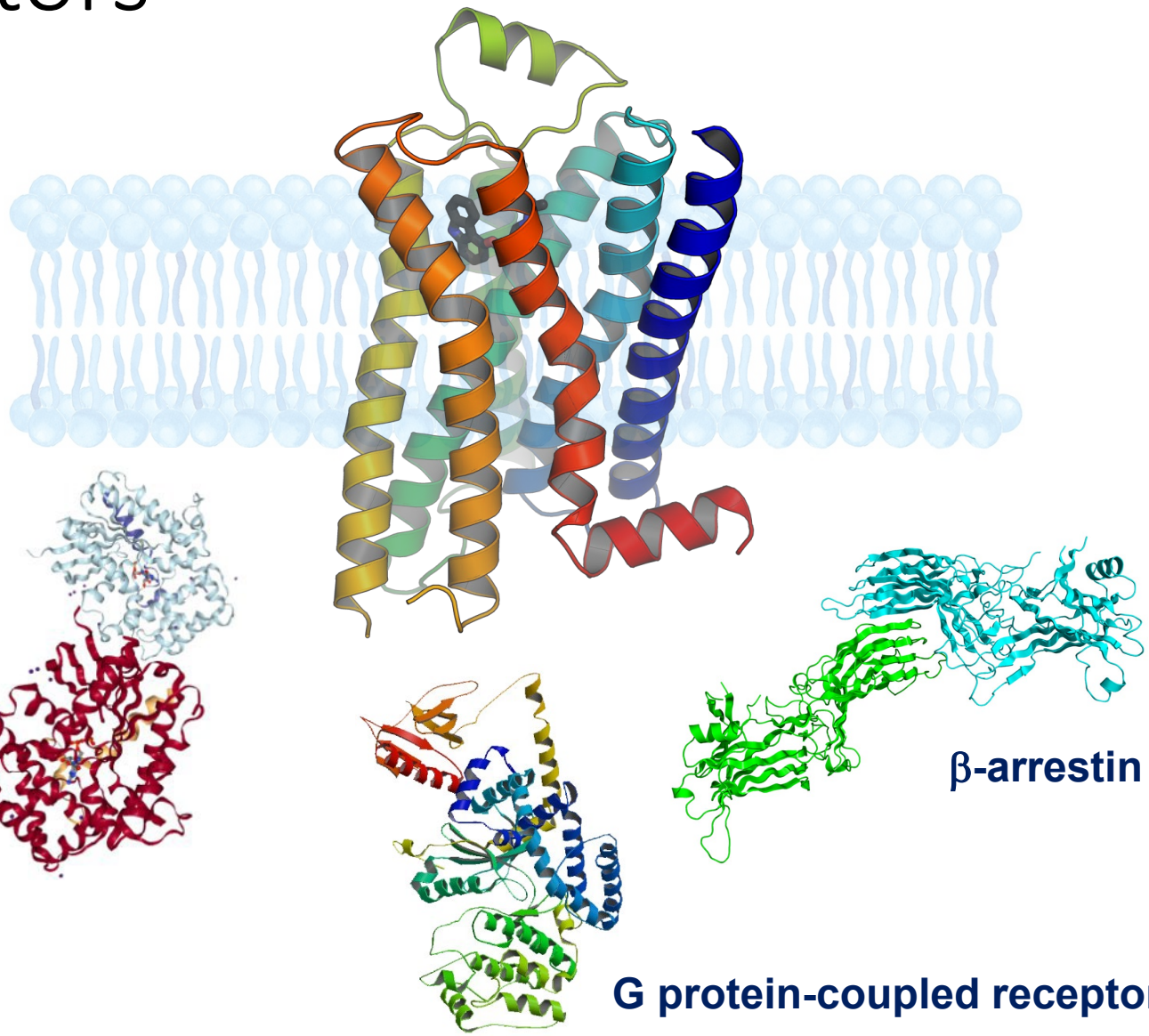
β2AR A2AR M2 S1P1 μOR

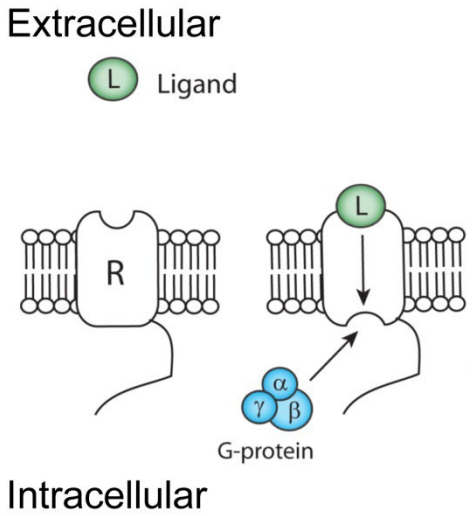
Nature Chemical Biology 8, 670–673 (2012)

Outline

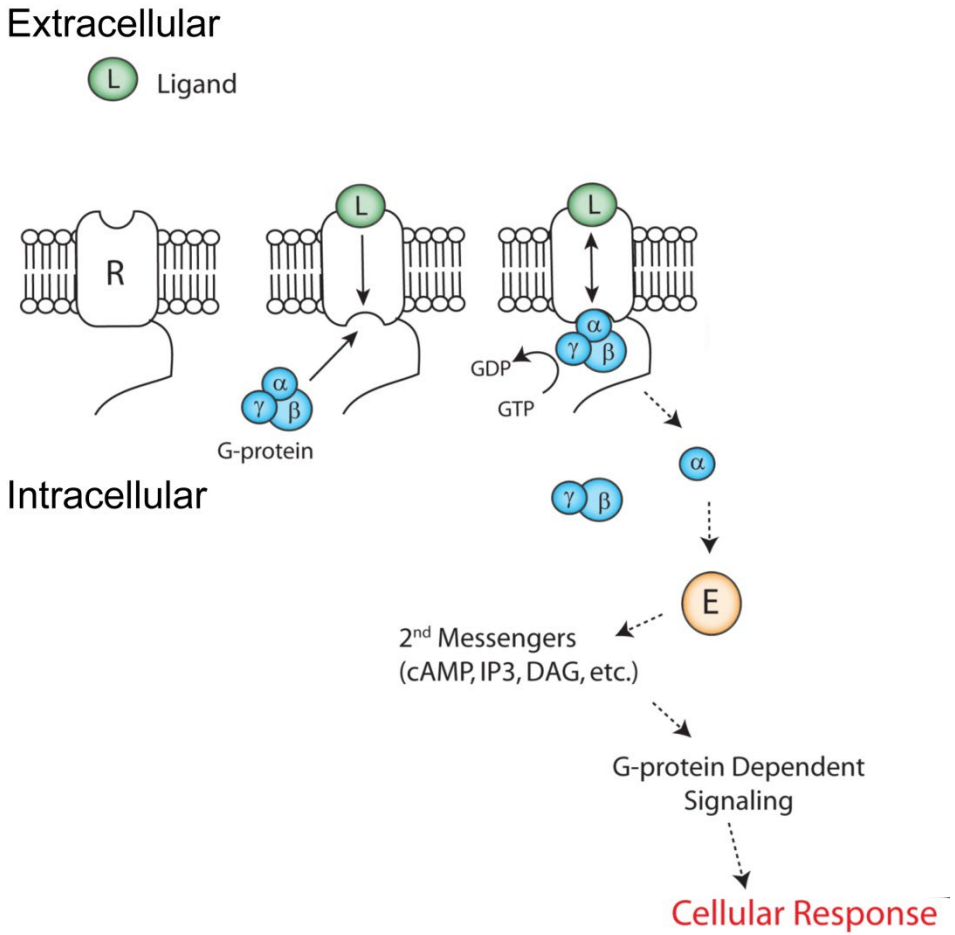
- Introduction to GPCRs
- **Basics of GPCR Signaling**
- GPCRs in disease
- Drugs targeting GPCRs

GPCR Effectors





Modified from Dean Staus



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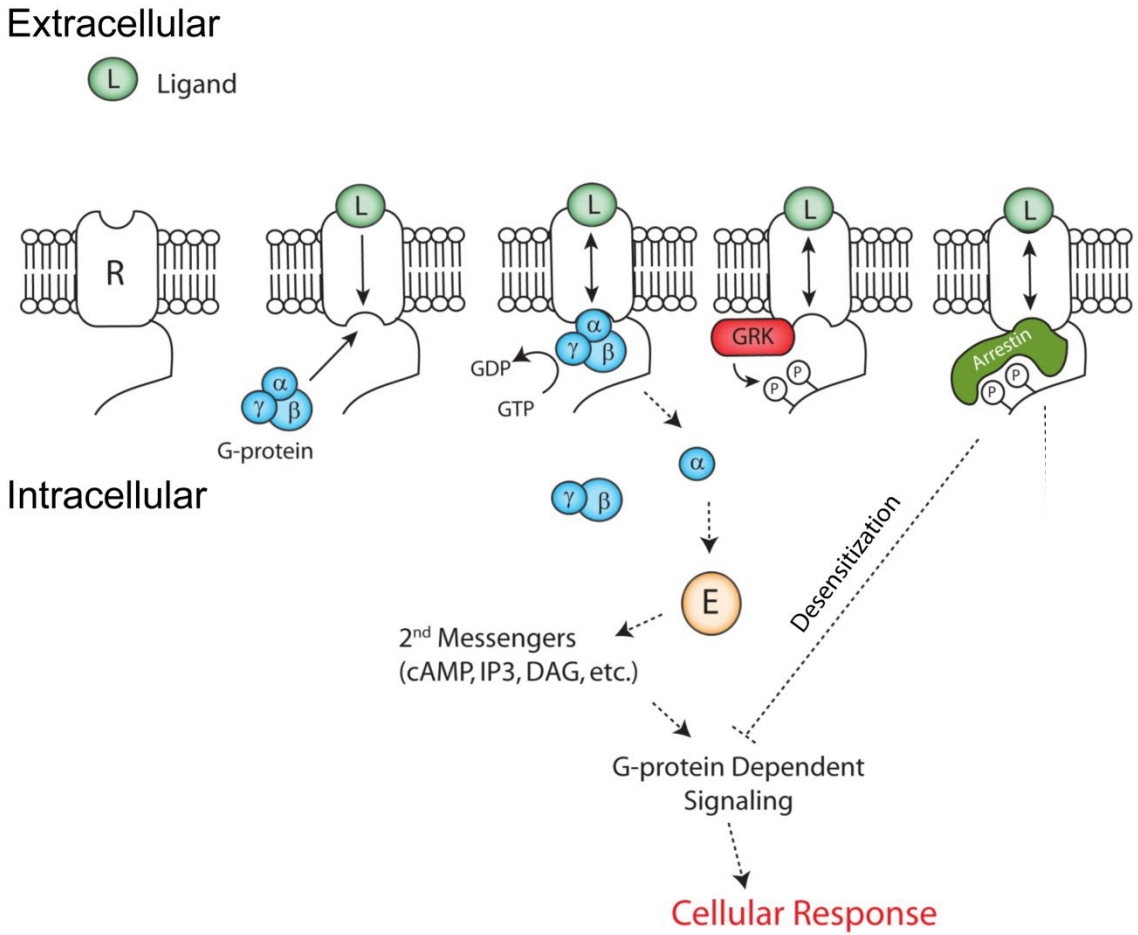

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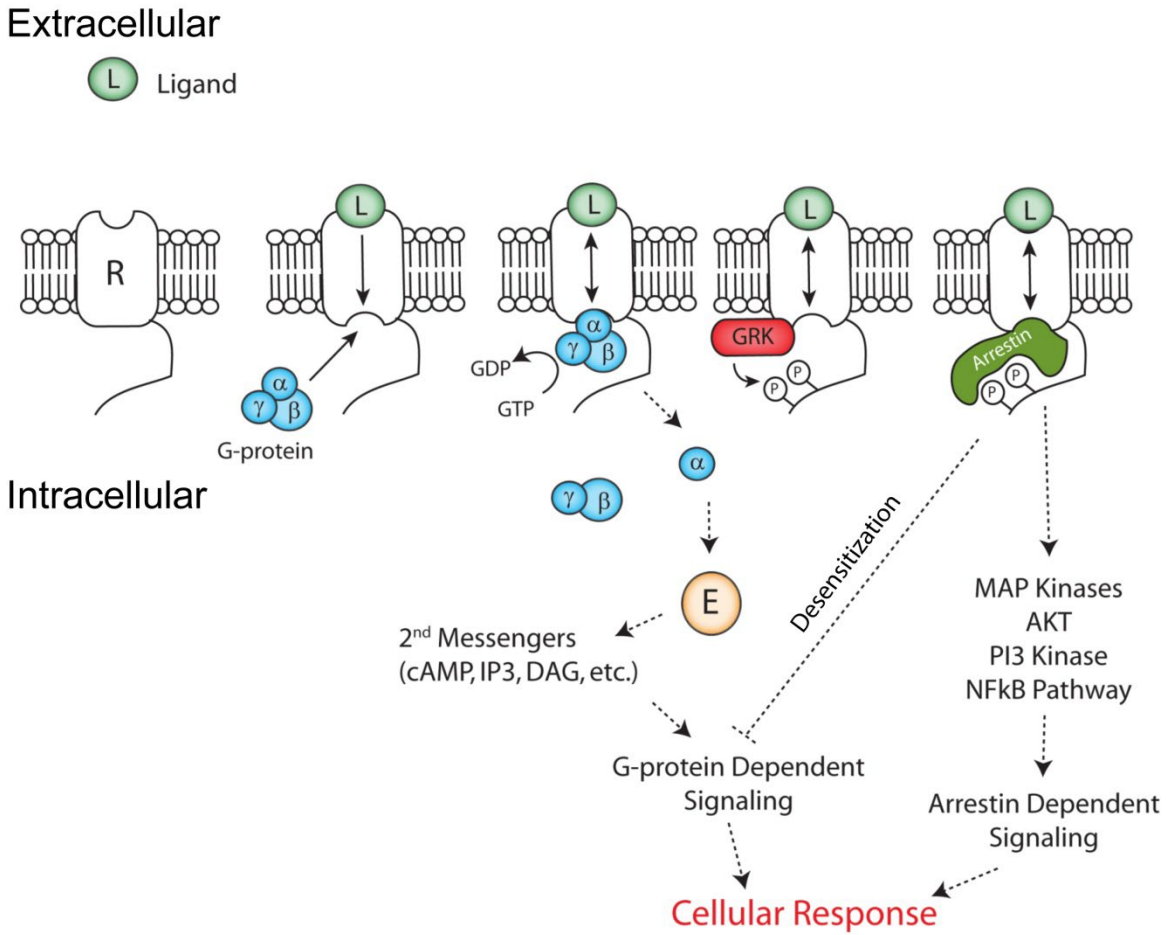
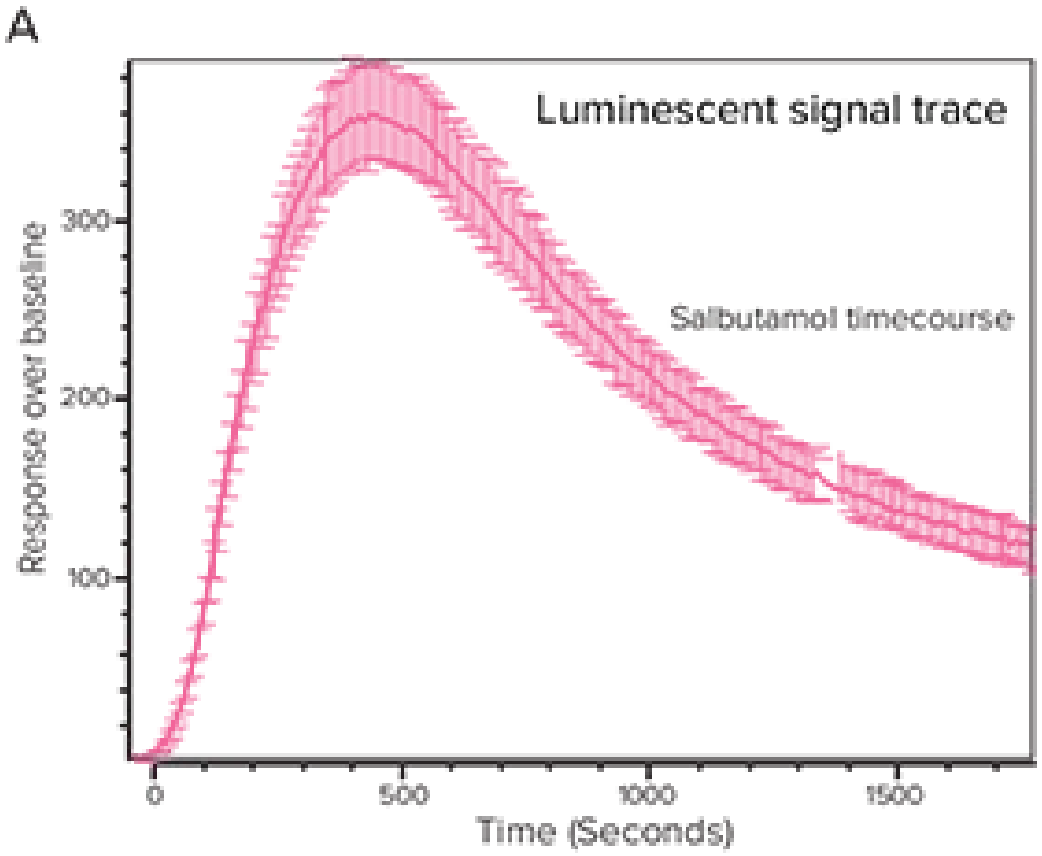
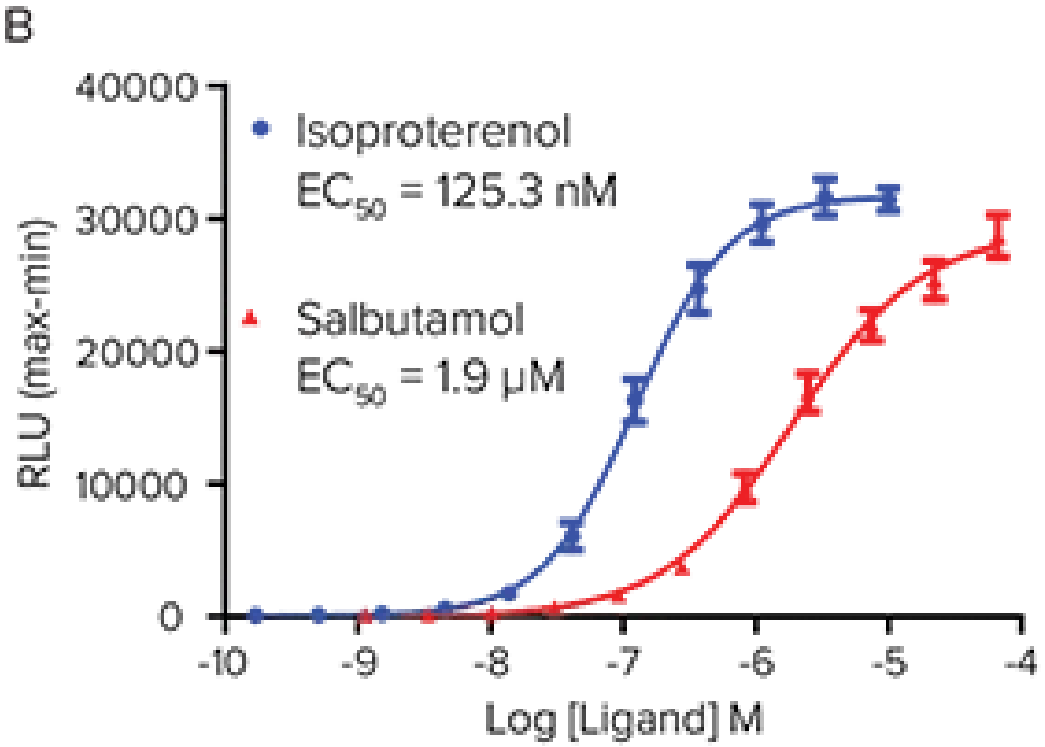


Modified from Dean Staus

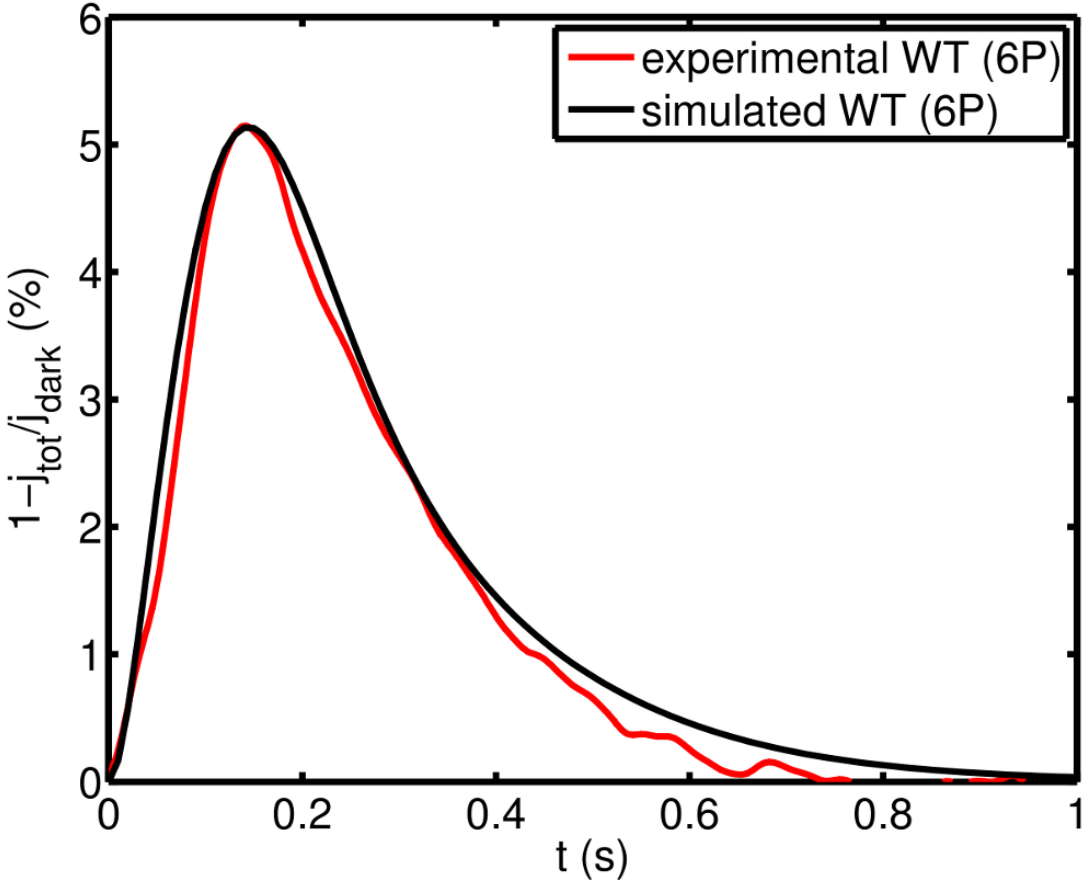
cAMP kinetics





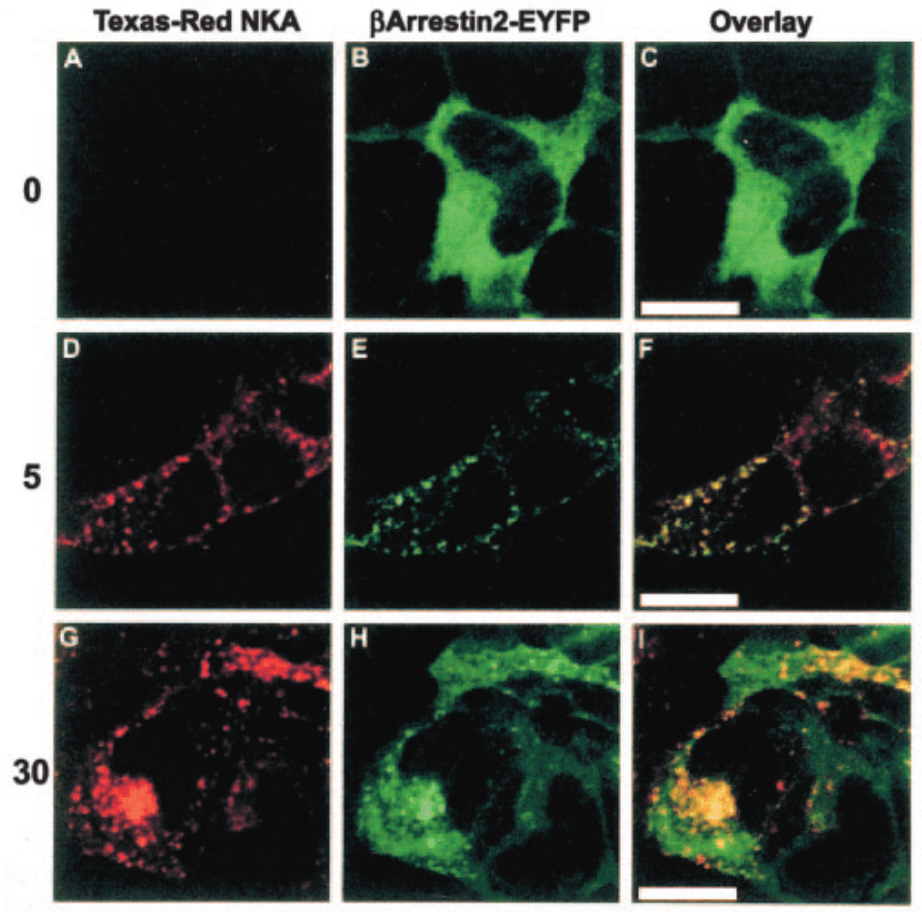
https://www.moleculardevices.com/en/assets/app-note/dd/flipr/live-cell-gi-and-gs-coupled-gpcr-second-messenger-signaling-on-flipr-tetra#gref

Rhodopsin



doi: https://doi.org/10.1371/journal.pcbi.1001031.g004

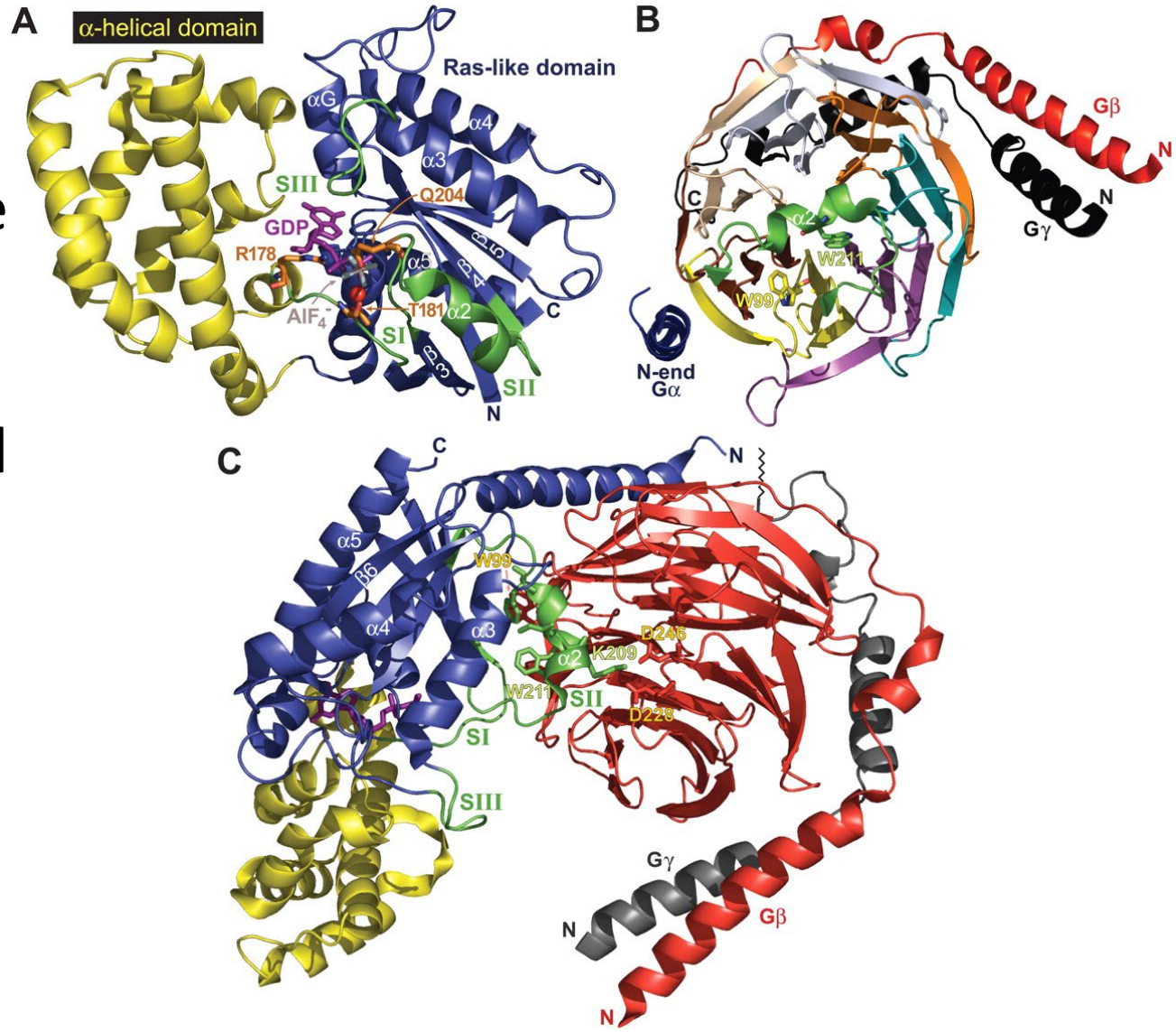
Arrestin recruitment



Stolen from Researchgate

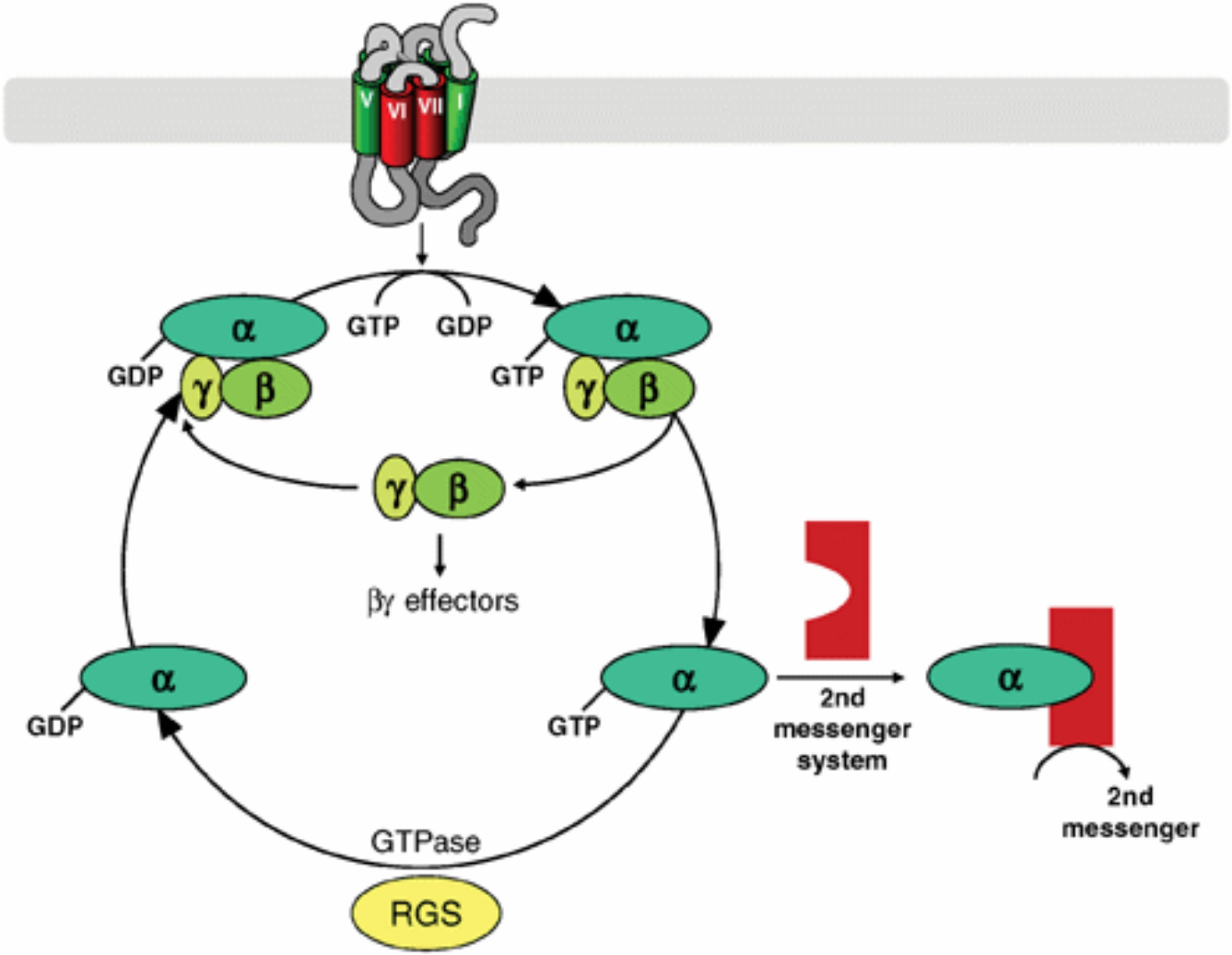
Heterotrimeric G proteins

- 1950-60s: Hormone-stimulated production of cAMP (Nobel Prize for Sutherland)
- 1980s: Isolation of heterotrimeric G proteins (Nobel Prize for Gilman and Rodbell)
- Composed of
  - Gα (16 different subunits)
  - Gβ (5 different subunits)
  - Gγ (12 different subunits)



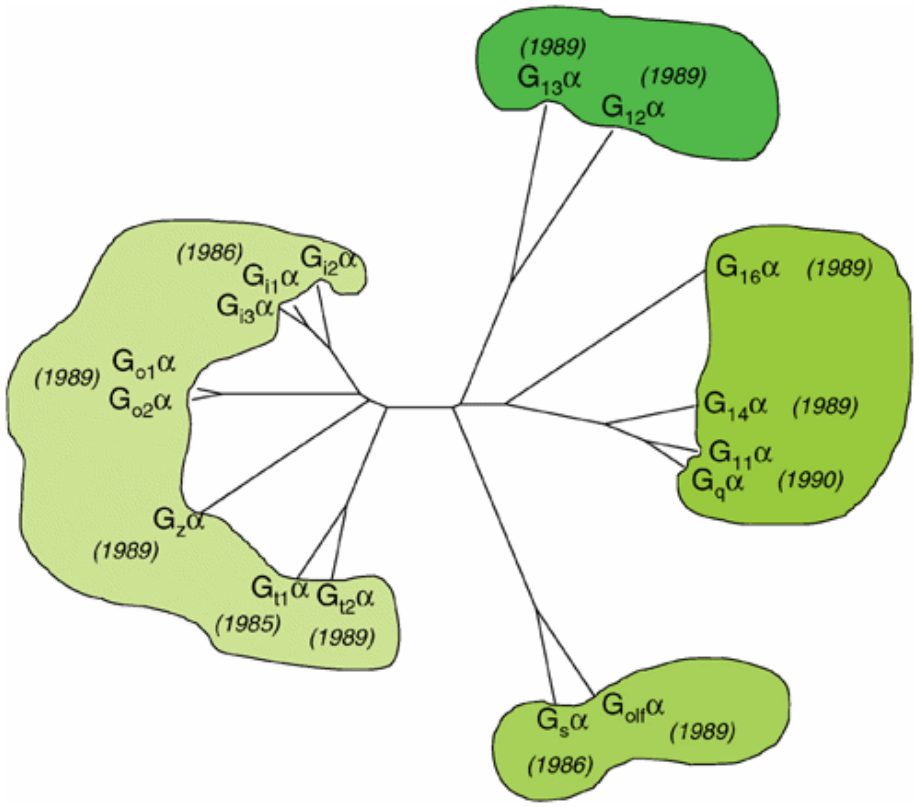
Christopher A. Johnston, and David P. Siderovski Mol Pharmacol 2007;72:219-230

Activation of heterotrimeric G proteins



Heterotrimeric G-proteins: a short history, Volume: 147, Issue: S1, Pages: S46-S55, First published: 02 February 2009, DOI: (10.1038/sj.bjp.0706405)

Gα subfamilies



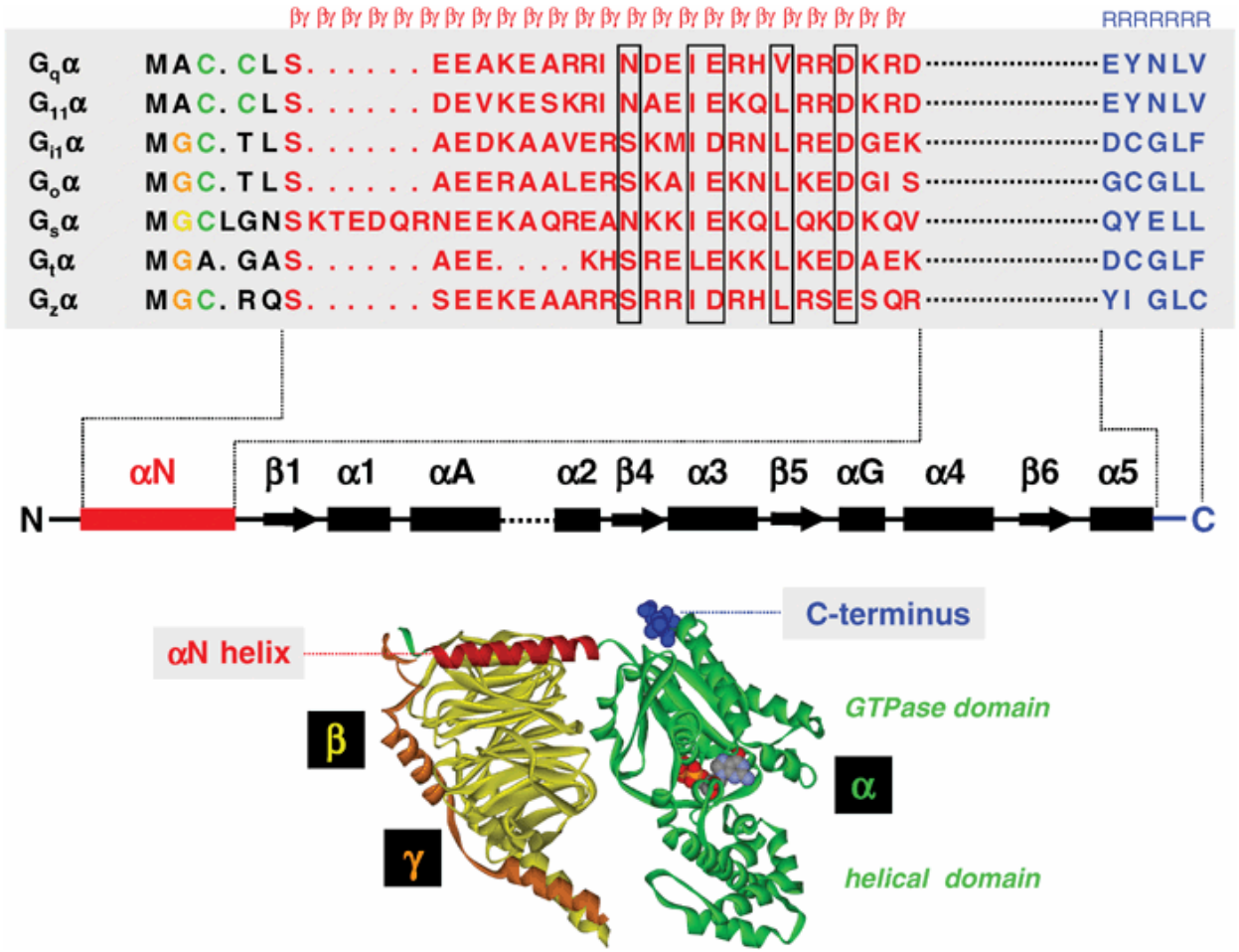
- Gs
  - Stimulates adenylyl cyclase (stimulates formation of cAMP)
- Gi/o
  - Inhibits adenylyl cyclase (decreases cAMP levels)
- Gq/11
  - Activates phospholipase C
- G12/13
  - Activates Rho GTPases

Heterotrimeric G-proteins: a short history, Volume: 147, Issue: S1, Pages: S46-S55, First published: 02 February 2009, DOI: (10.1038/sj.bjp.0706405)

Family	*Subtype*	*Effectors*	*Expression*	*Disease relevance*	*Pharmacological modulation*
$G_s\alpha$	$G_{s(S)}\alpha$ $G_{s(L)}\alpha$ $G_{s(XL)}\alpha$ $G_{olf}\alpha$	Adenylyl cyclases ↑ ($G_{s,s(XL),olf}\alpha$) Maxi K channel ↑ ($G_s\alpha$) Src tyrosine kinases (c-Src, Hck) ↑ ($G_s\alpha$) GTPase of tubulin ↑ ($G_s\alpha$)	$G_s\alpha$: ubiquitous $G_{olf}\alpha$: olfactory neurons, certain CNS ganglia; digestive and urogenital tract	$G_{s(XL)}\alpha$: brachydactyly, trauma-related bleeding tendency, neurological problems $G_s\alpha$: McCune–Albright syndrome, cholera, pseudohypoparathyroidism type Ia/b, testotoxicosis, adenomas of pituitary and thyroid	$G_s\alpha$: CTX $G_{olf}\alpha$: CTX
$G_{i/o}\alpha$	$G_{o1}\alpha$ $G_{o2}\alpha$ $G_{i1-i3}\alpha$ $G_z\alpha$ $G_{t1/2}\alpha$ $G_{gust}\alpha$	Adenylyl cyclase ↓ ($G_{i,o,z}\alpha$) Rap1GAPII-dependent ERK/MAPkinase activation ↑ ($G_i\alpha$) Ca^{2+} channels ↓ ($G_{i,o,z}\alpha$) K^+ channels ↑ ($G_{i,o,z}\alpha$) GTPase of tubulin ↑ ($G_i\alpha$) Src tyrosine kinases (c-Src, Hck) ↑ ($G_i\alpha$) Rap1GAP ↑ ($G_z\alpha$) GRIN1-mediated activation of Cdc42 ↑ ($G_{i,o,z}\alpha$) cGMP-PDE ↑ ($G_{t}\alpha$) $G_{gust}\alpha$: ?	$G_{o1-2}\alpha$: neurons, neuroendocrine cells, astroglia, heart $G_{i1-i3}\alpha$: neurons and many others $G_z\alpha$: platelets, neurons, adrenal chromaffin cells, neurosecretory cells $G_{t1}\alpha$: rod outer segments, taste buds $G_{t2}\alpha$: cone outer segments $G_{gust}\alpha$: sweet and/or bitter taste buds, chemoreceptor cells in the airways	$G_i\alpha$: whooping cough, adrenal and ovarian adenomas $G_t\alpha$: congenital cone dysfunction, night blindness	$G_{o(1/2)}\alpha$: PTX $G_{i1-i3}\alpha$: PTX $G_z\alpha$: ? $G_{t1/2}\alpha$: PTX, CTX $G_{gust}\alpha$: PTX
$G_{q/11}\alpha$	$G_q\alpha$ $G_{11}\alpha$ $G_{14}\alpha$ $G_{15}\alpha$ $G_{16}\alpha$	Phospholipase Cβ isoforms ↑ p63-RhoGEF ↑ ($G_{q/11}\alpha$) Bruton's tyrosine kinase ↑ ($G_q\alpha$) K^+ channels ↑ ($G_q\alpha$)	$G_{q/11}\alpha$: ubiquitous $G_{15/16}\alpha$: hematopoietic cells	$G_{q/11}\alpha$: dermal hyperpigmentation and melanocytosis?	$G_{q/11}\alpha$: YM-254890 $G_{14}\alpha$: ? $G_{15}\alpha$: ? $G_{16}\alpha$: ?
$G_{12/13}\alpha$	$G\alpha_{12}$ $G\alpha_{13}$	Phospholipase D ↑ Phospholipase Cε ↑ NHE-1 ↑ iNOS ↑ E-cadherin-mediated cell adhesion: ↑ p115RhoGEF ↑ PDZ-RhoGEF ↑ Leukaemia-associated RhoGEF (LARG) ↑ Radixin ↑ Protein phosphatase 5 (PP5) ↑ AKAP110-mediated activation of PKA ↑ HSP90 ↑	Ubiquitous	Recent SNPs identified but no disease correlation yet	$G_{12}\alpha$: ? $G_{13}\alpha$: ?
$G\beta/\gamma$	β_{1-5} γ_{1-12}	PLCβs ↑ Adenylyl cyclase I ↓ Adenylyl cyclases II, IV, VII ↑ PI-3 kinases ↑ K^+ channels (GIRK1,2,4) ↑ Ca^{2+} (N-, P/Q-, R-type) channels ↓ P-Rex1 (guanine nucleotide exchange factor for the small GTPase Rac) ↑ c-Jun N-terminal kinase (JNK) ↑ Src kinases ↑ Tubulin GTPase activity ↑ G-protein-coupled receptor kinase recruitment to membrane ↑ Protein kinase D ↑ Bruton's tyrosine kinase ↑ p114-RhoGEF ↑	$\beta_1\gamma_1$: retinal rod cells $\beta_3\gamma_8$: retinal cone cells β_5: neurons and neuroendocrine organs $\beta_{5(L)}$: retina Most cell types express multiple β and γ subtypes	Gβ_3: atherosclerosis, hypertension, metabolic syndrome	G$\beta\gamma$: ?

CTX = cholera toxin; PTX = pertussis toxin; ↑ = enhances function; ↓ = reduces function; YM-254890 = a cyclic depsipeptide isolated from *Chromobacterium* sp QS3666.

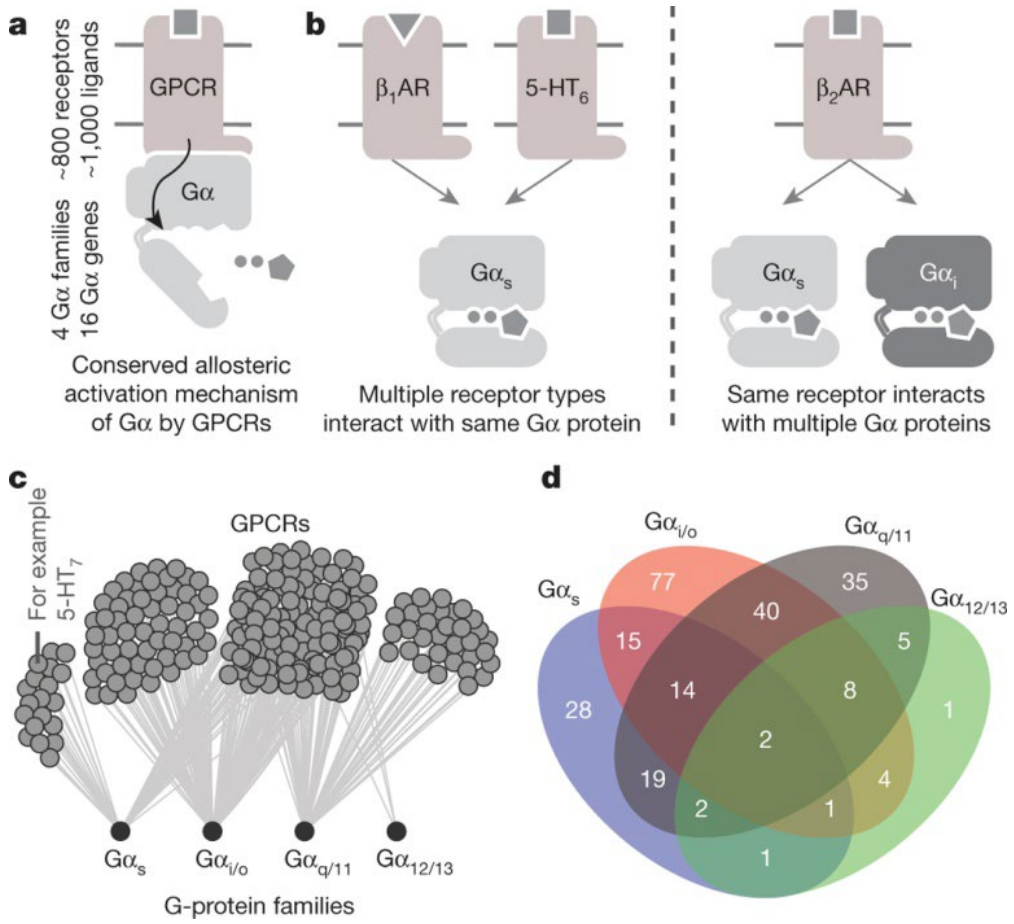
The Gα and Gβγ interaction motifs



- N-terminus of Gα interacts with the βγ subunits
- N-terminus is also palmitoylated or myristoylated
- C-terminal helix interacts with the receptor

Heterotrimeric G-proteins: a short history, Volume: 147, Issue: S1, Pages: S46-S55, First published: 02 February 2009, DOI: (10.1038/sj.bjp.0706405)

Selectivity in GPCR–G-protein signaling

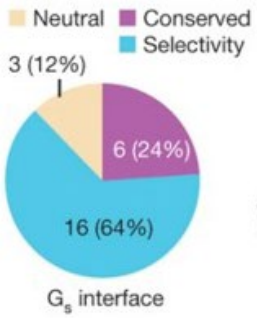


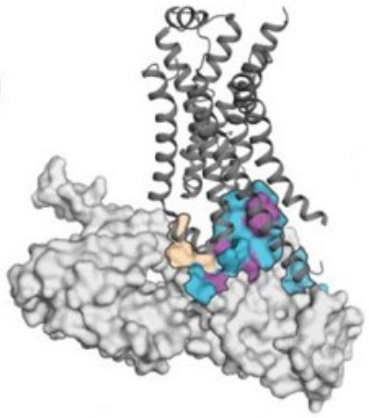
- Many GPCRs couple to multiple classes of G proteins
- Many G proteins couple to multiple GPCRs
- Bioinformatics approach to identify structural motifs responsible for the GPCR:G protein interaction

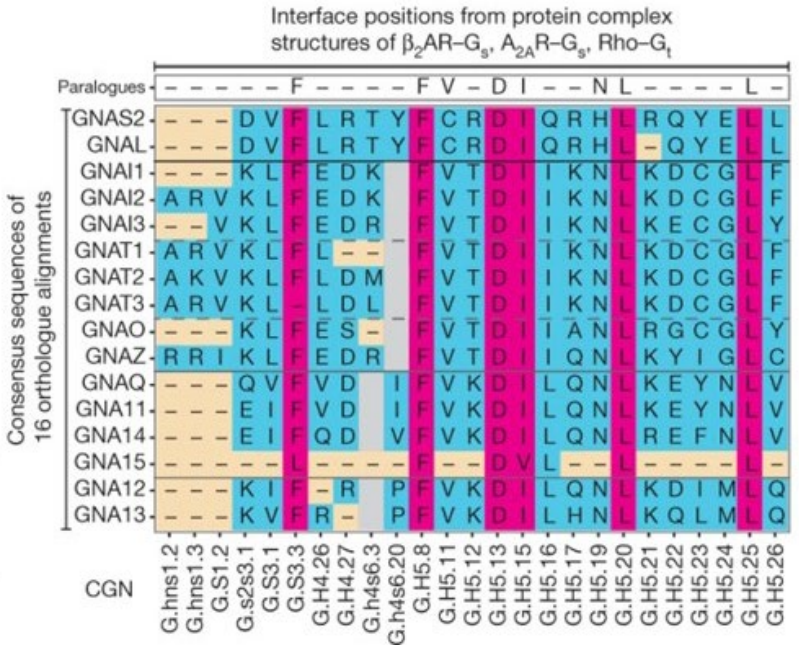
T Flock *et al. Nature* 1–6 (2017) doi:10.1038/nature22070

nature

Subtype-specific residues and Gα selectivity barcode



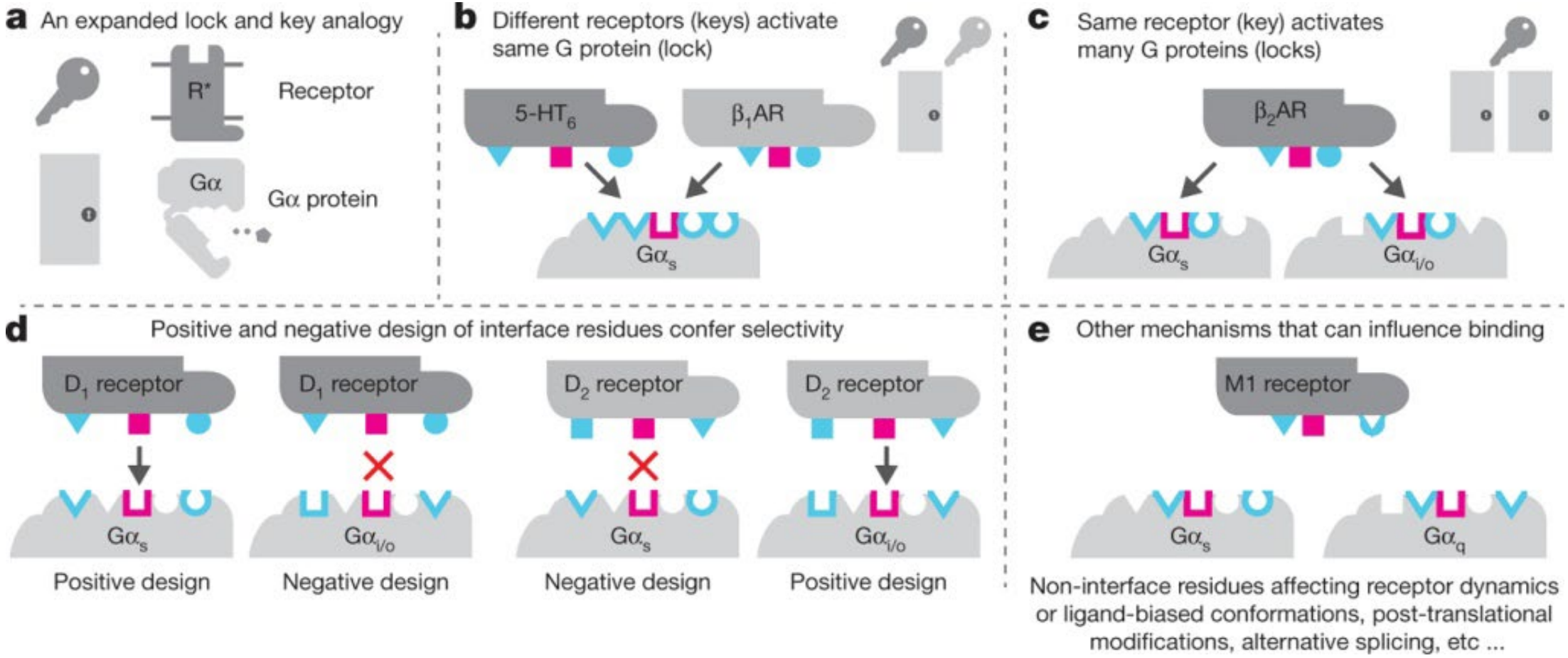




- Interface positions are primarily in helix 5 of Gα
- While some residues are highly conserved, others are responsible for the specificity for GPCR:Gα coupling

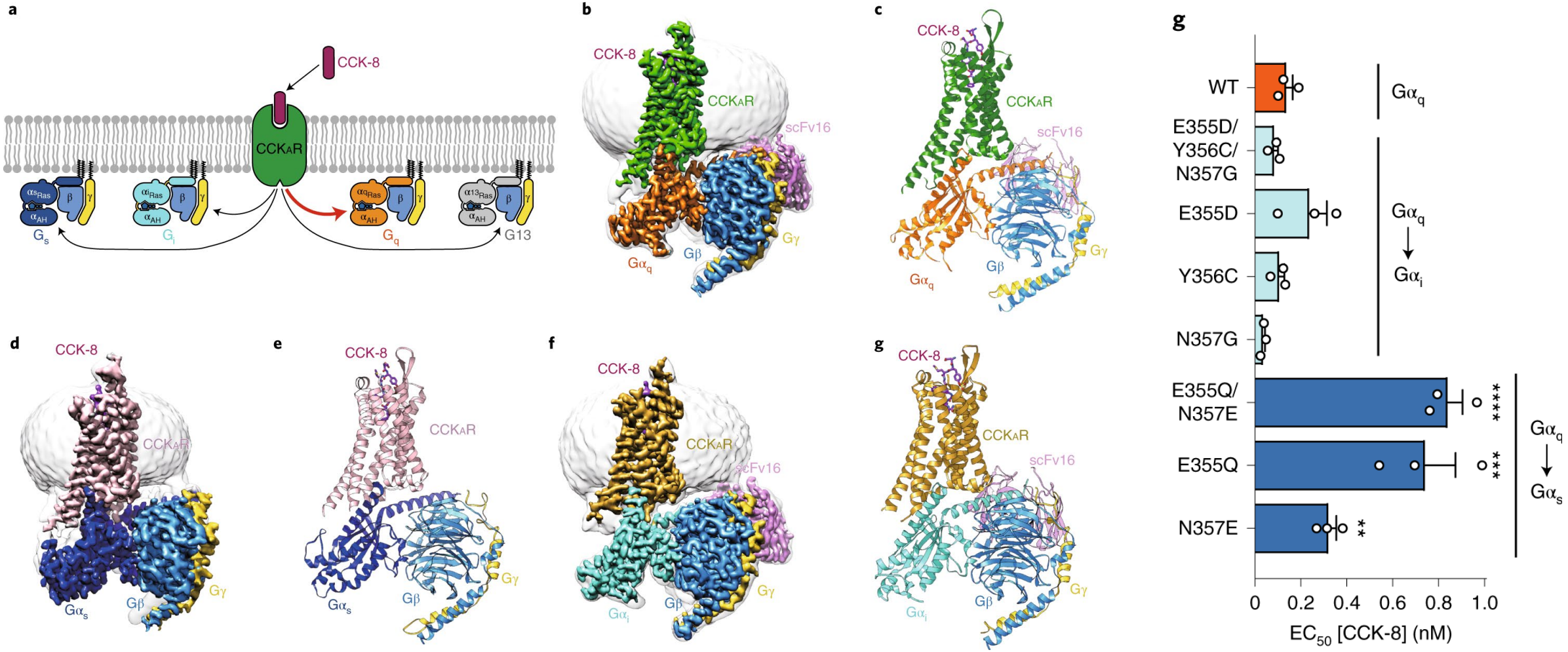
T Flock *et al. Nature* 1–6 (2017) doi:10.1038/nature22070

Model for interaction between GPCR and Gα



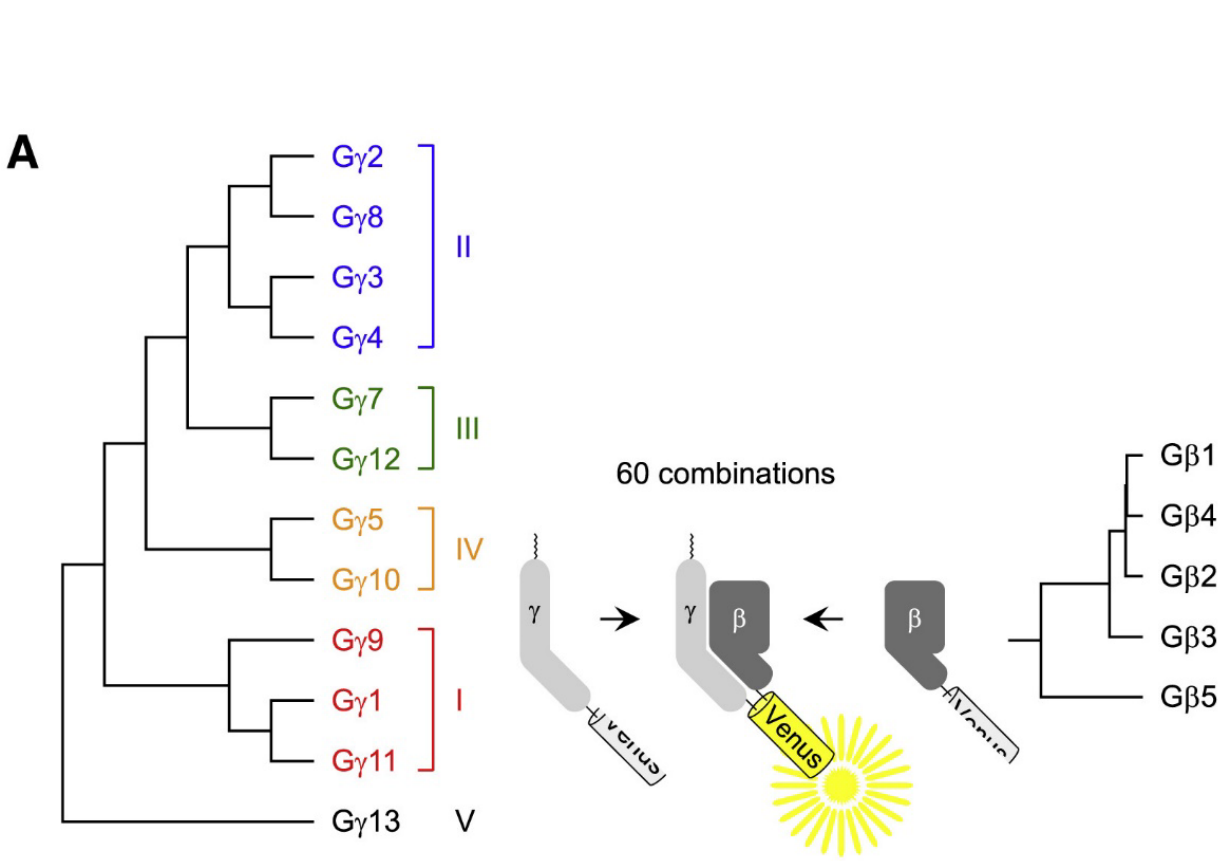
T Flock *et al. Nature* 1–6 (2017) doi:10.1038/nature22070

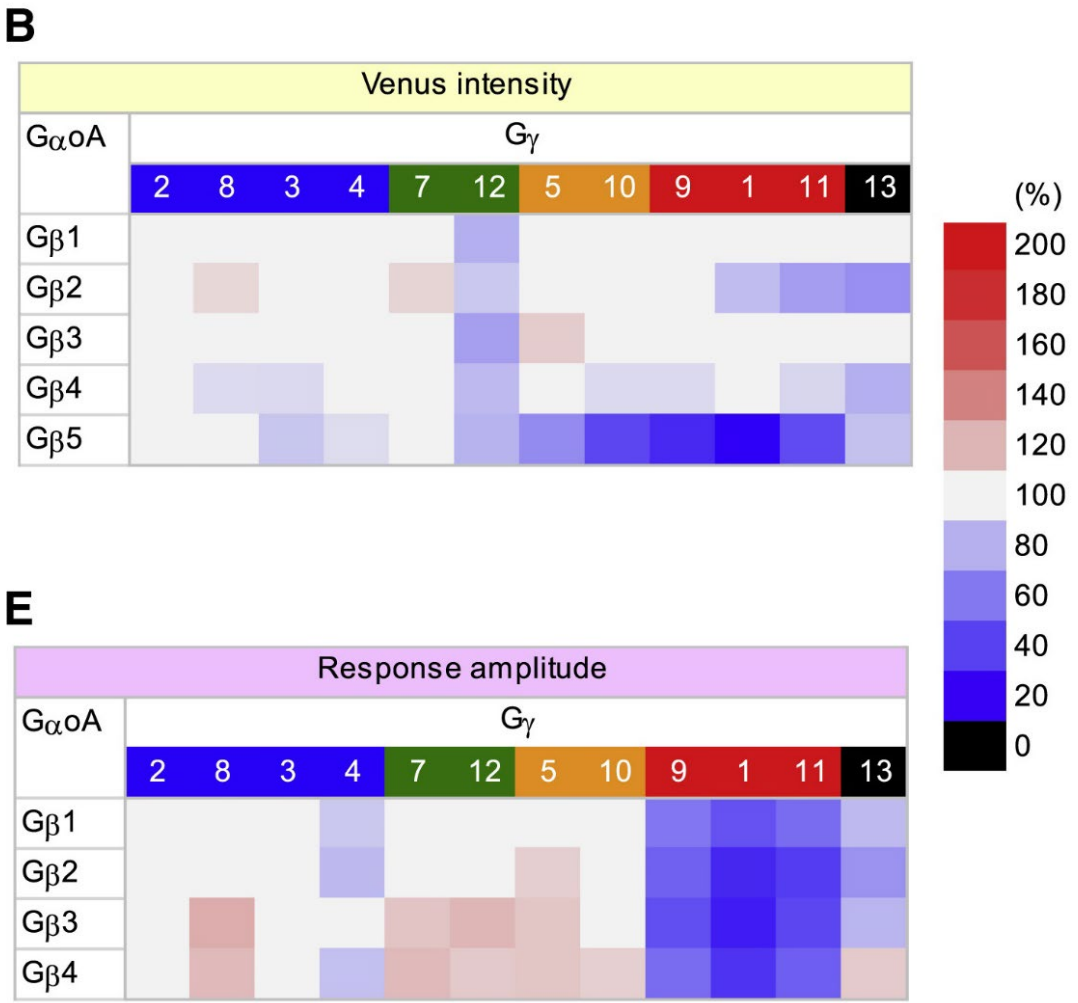
Structural evidence for importance of α5CT



Nat Chem Biol (2021). https://doi.org/10.1038/s41589-021-00841-3

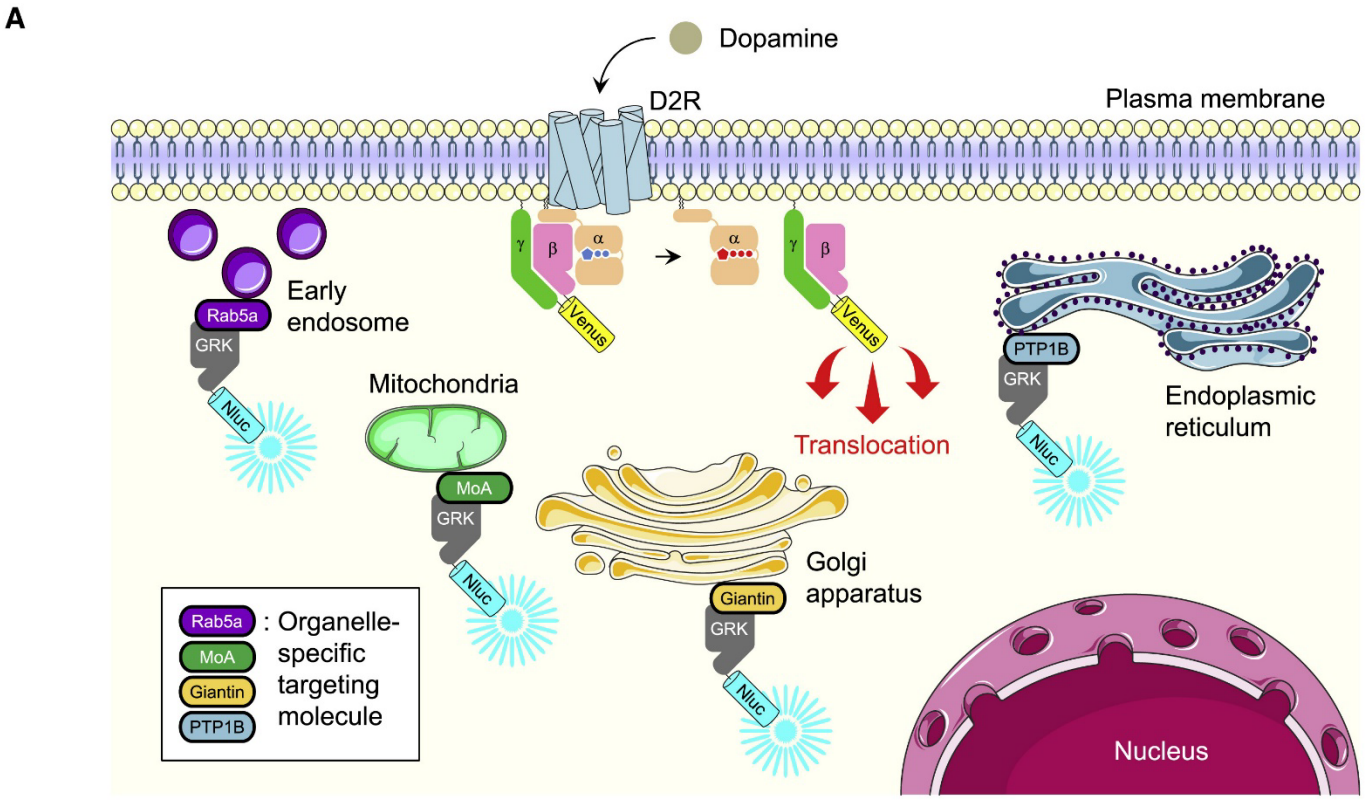
Assessing all 60 Gβγ combinations with GαoA

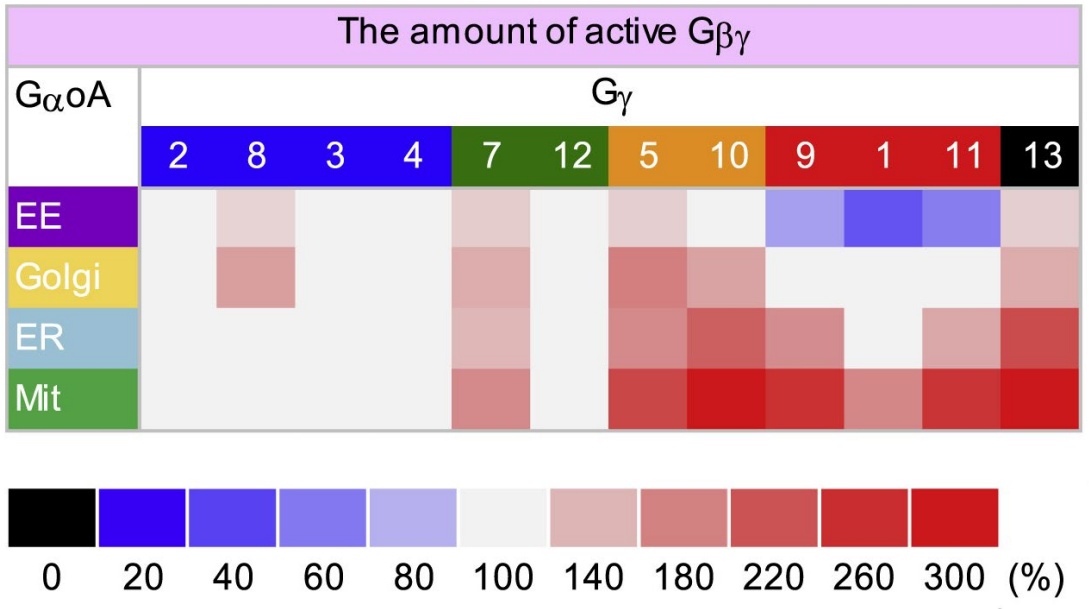




Cell Syst. 2021 Apr 21;12(4):324-337.e5.

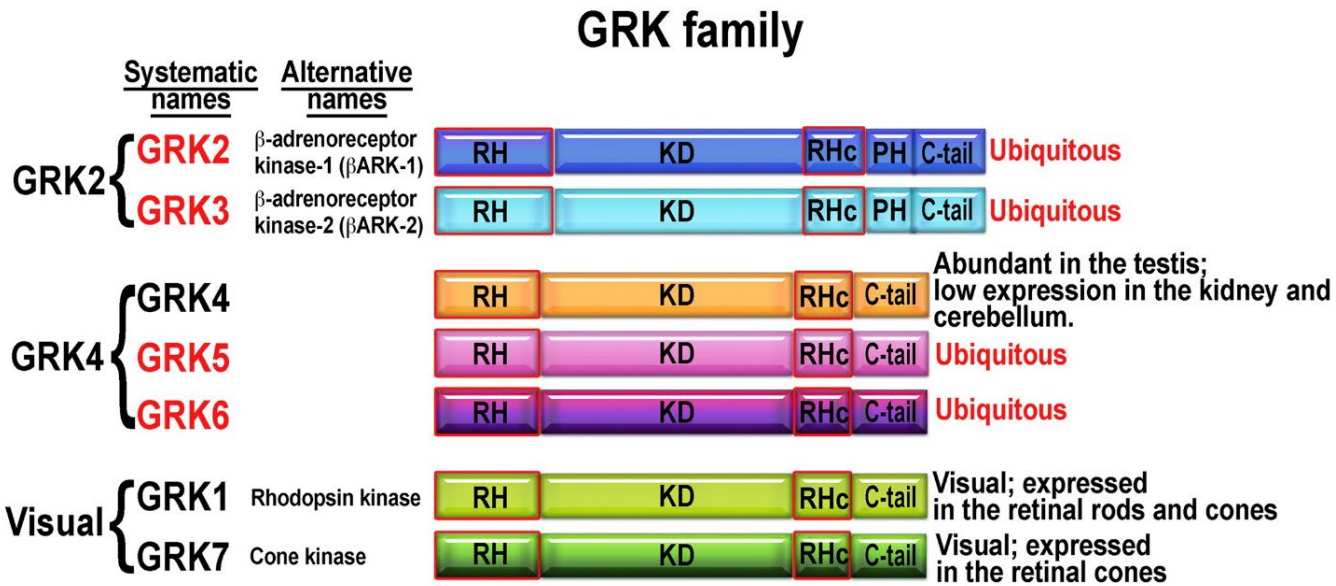
Gβγ: Translocation to different compartments





Cell Syst. 2021 Apr 21;12(4):324-337.e5.

G protein-coupled receptor kinases (GRKs)

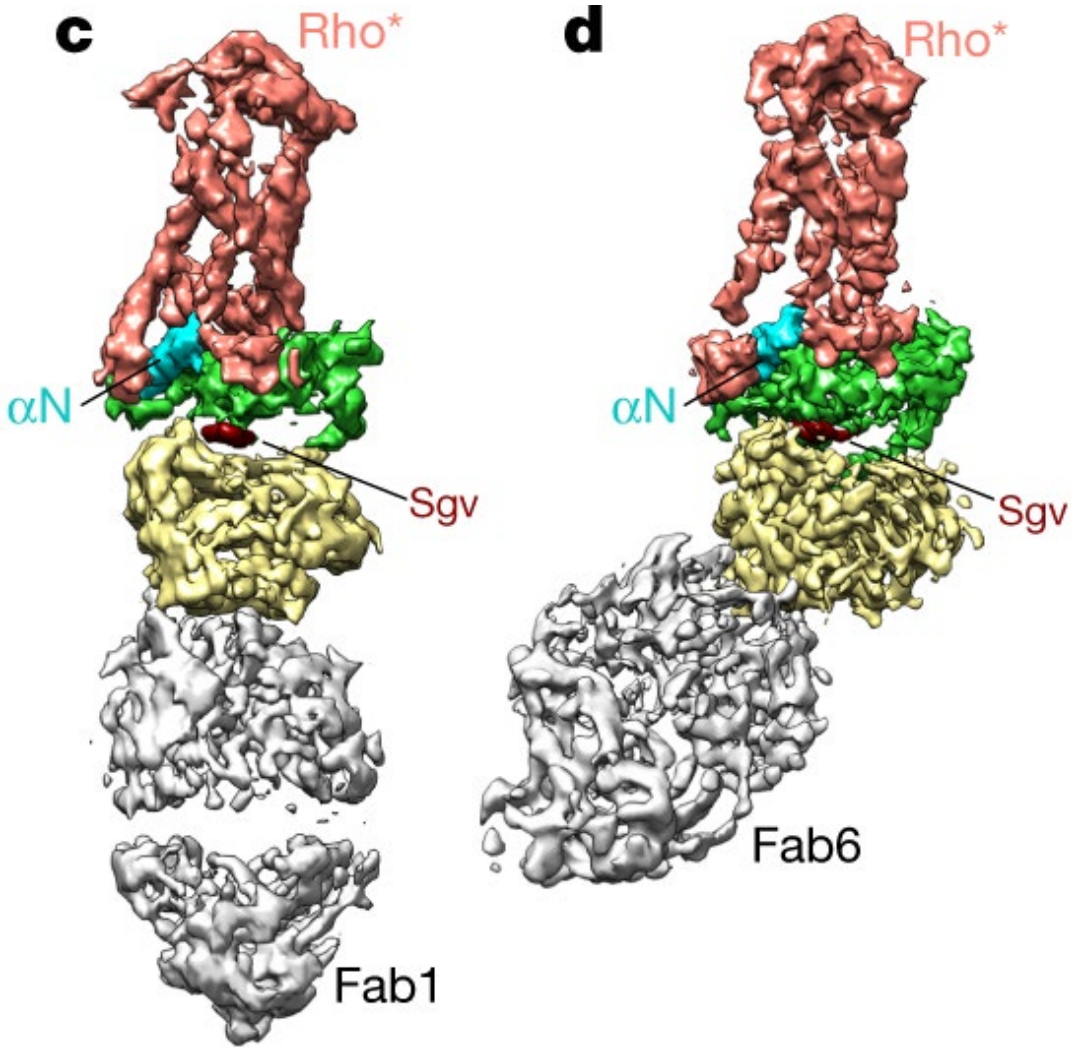


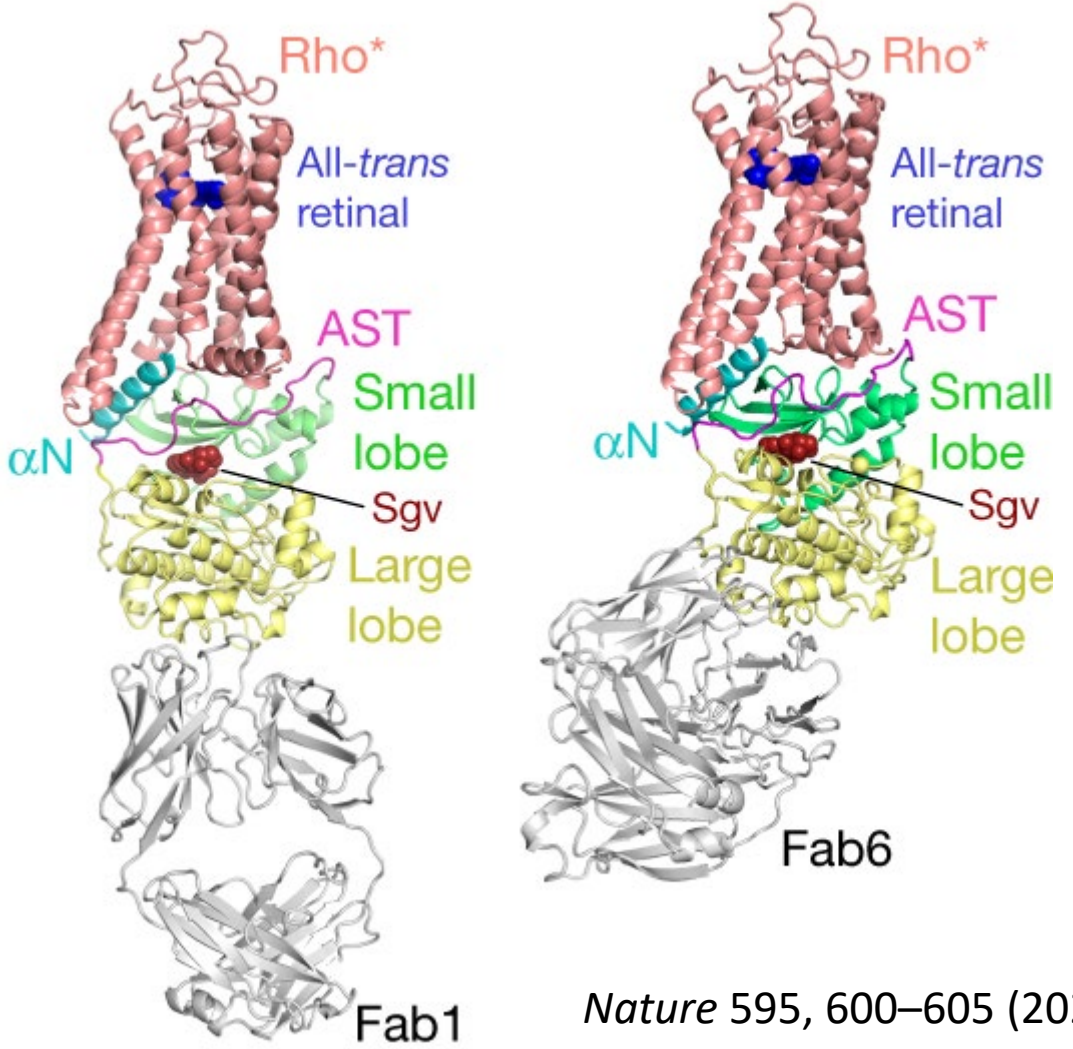
- 3 subfamilies
  - GRK2
    - Contain a PH domain for interaction with PIP2
    - Require recruitment by Gβγ to the receptor
  - GRK4
    - Palmitoylated
  - Visual
    - Only expressed in the visual system
    - Prenylated

Pharmacological Research Volume 111, September 2016, Pages 1-16

Activation Mechanism of GRKs

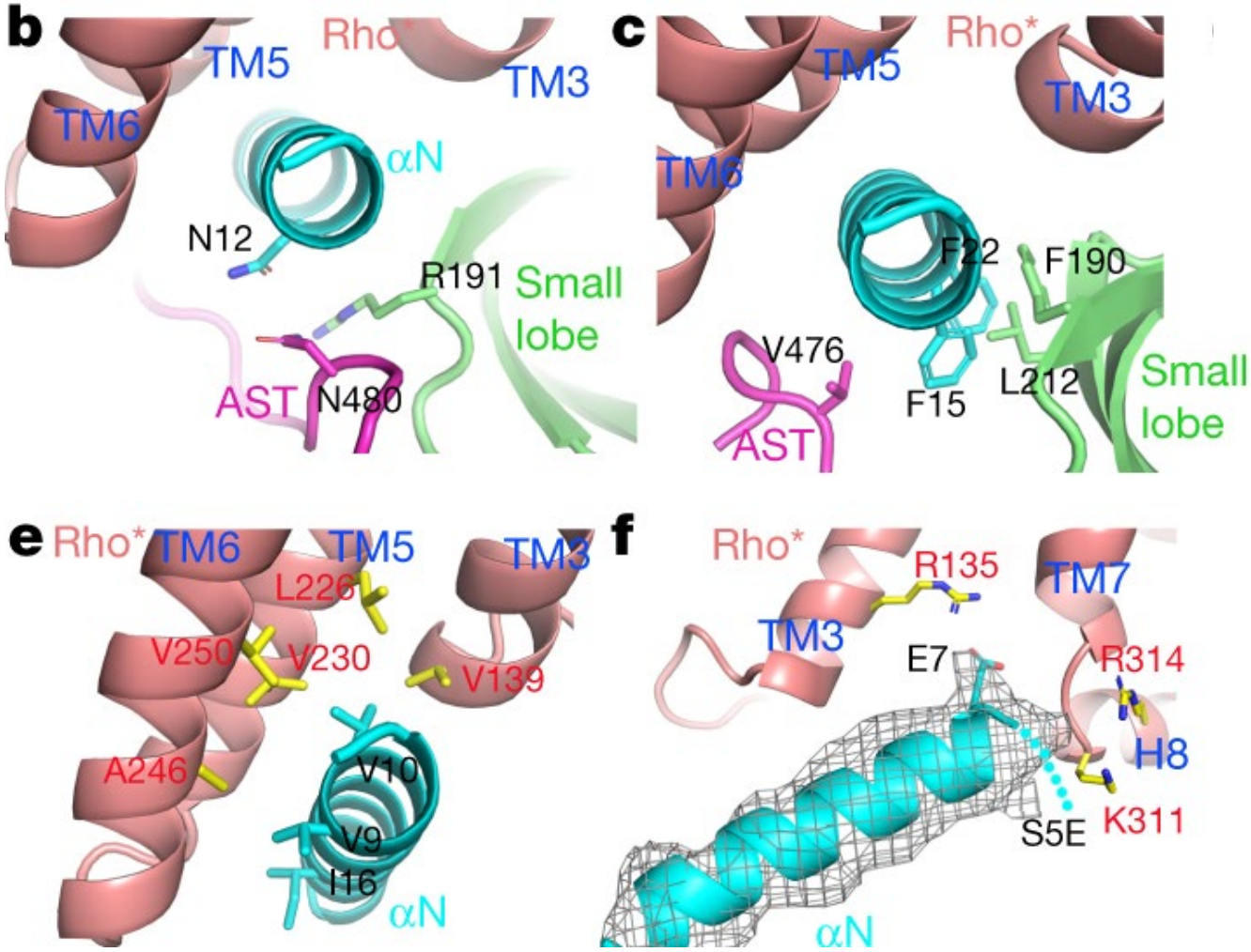
Sangivamycin (Sgv): adenosine analogue with a 180 nM inhibition constant (Ki) against GRK1





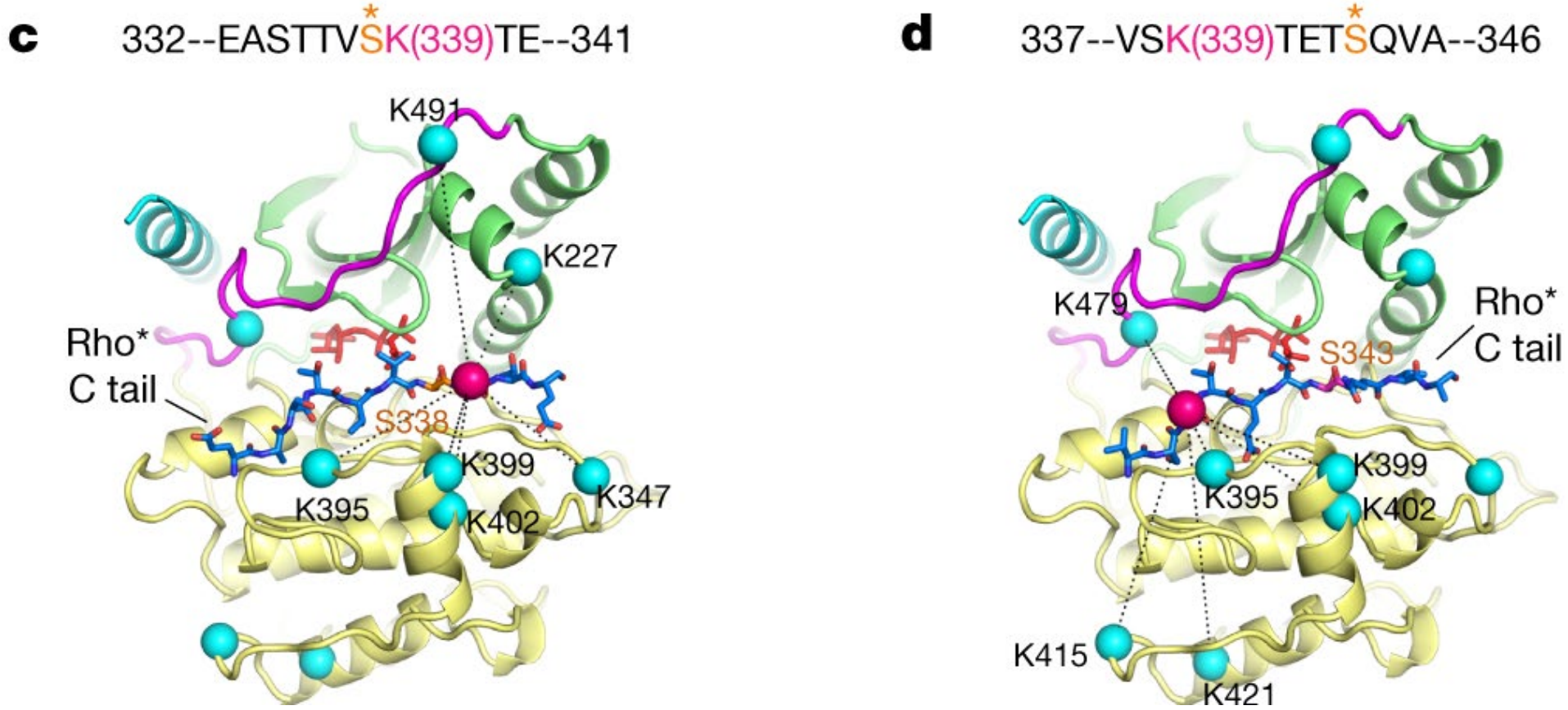
Nature 595, 600–605 (2021)

GRK1 αN interacts with same cleft as Gα in Rho



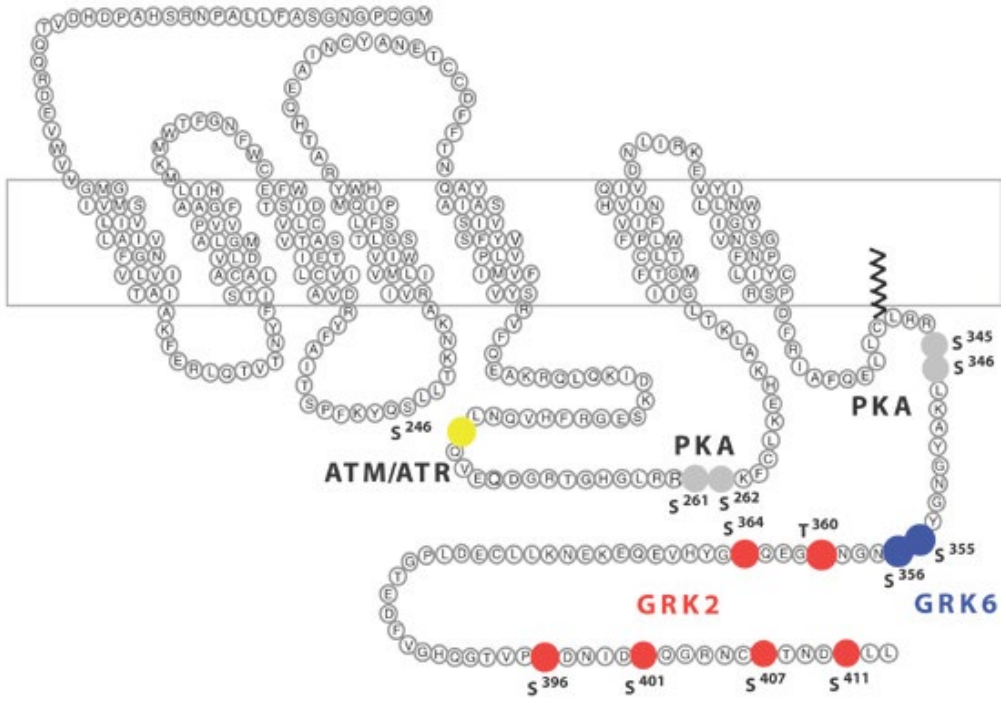
Nature 595, 600–605 (2021)

Modeling the Rhodopsin C-terminus in GRK1



Nature 595, 600–605 (2021)

Different phosphorylation sites at the β2AR



- At the β2AR, different serines are phosphorylated by GRK2 and GRK6
- In addition, there are phosphorylation sites for other kinases (PKA, ATM, etc.)
- These different sites are responsible for homologous and heterologous desensitization and specific interactions with β -arrestins

Science Signaling
AAAS

Kelly N. Nobles et al., Sci. Signal. 2011;4:ra51

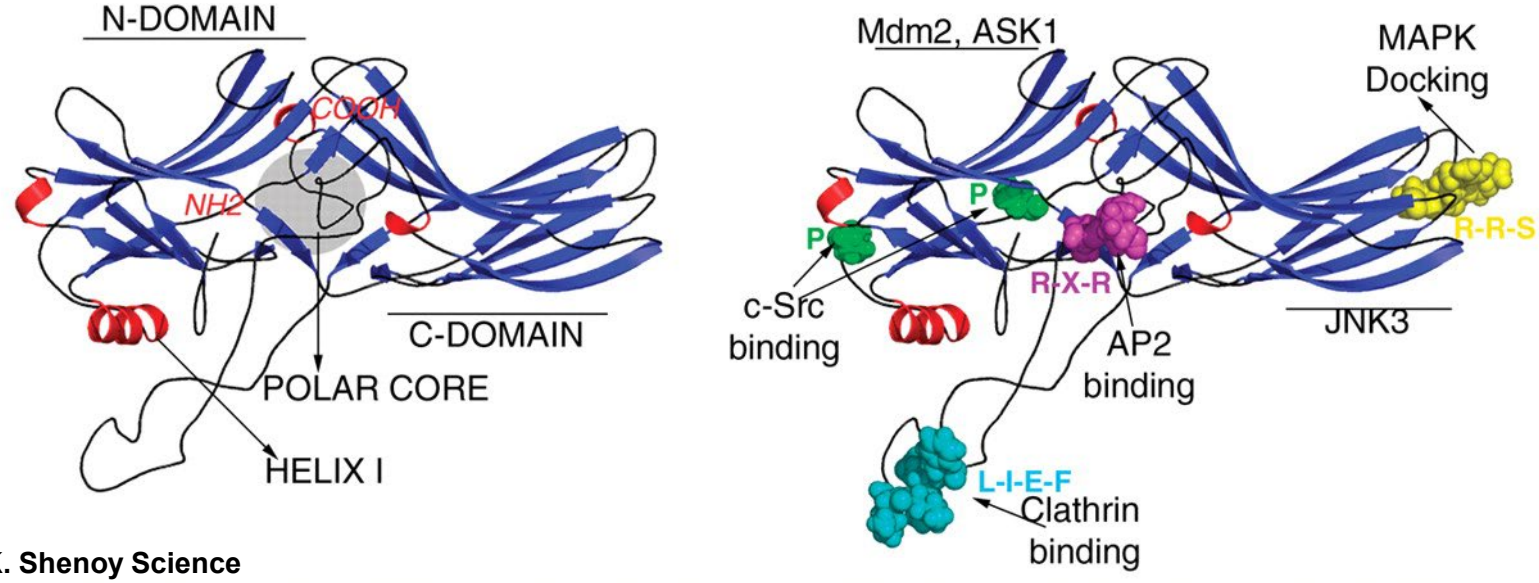
Non-kinase activities of GRKs

GRK isoform	Binding partner	Function	Reference
GRK2	$G\alpha_q$	Regulation of $G\alpha_q$ signaling	[27,28]
	mGluR1	Regulation of G protein signaling in a phosphorylation-independent manner	[29]
	Gβγ	Regulation of Gβγ-stimulated signaling	[31]
	PDGFRβ	Phosphorylation of PDGFRβ by GRK2 reduces PDGFRβ signaling	[78,79]
	HDAC6	GRK2 associates with and phosphorylates HDAC6 to enhance α-tubulin deacetylase activity and cell motility	[81]
	Akt	Interaction of GRK2 with Akt inhibits Akt activity	[82]
	p38	Phosphorylation of p38 by GRK2 impairs MKK6-induced p38 activation	[88]
	APC	Interaction of GRK2 with APC inhibits canonical Wnt signaling	[89]
	GIT1	Interaction between GRK2 and GIT1 is important for GRK2-mediated cell motility	[90]
	CDK2	Phosphorylation of GRK2 by CDK2 is important for cell cycle progression	[91]
	MEK	GRK2 negatively regulates CC chemokine ligand 2-induced ERK activation by the interaction with MEK	[93]
	IRS-1	Phosphorylation of IRS-1 by GRK2 mediates endothelin-1-induced insulin resistance	[94]
	clathrin	Interaction of GRK2 with clathrin promotes GPCR internalization	[95]
	PI3K	Translocation of PI3K to the plasma membrane is involved in GPCR internalization	[96]
	HSP90	Interaction of GRK2 with HSP90 at the mitochondria promotes pro-death signaling after ischemic injury	[100]
GRK5	β-arrestin1	Phosphorylation of β-arrestin1 by GRK5 down-regulates G protein-independent signaling	[80]
	HDAC5	Phosphorylation of HDAC5 promotes maladaptive cardiac hypertrophy	[83]
	p105	Interaction with p105 results in inhibition of lipopolysaccharide-induced ERK activation	[84]
	IκBα	Regulation of NF-κB signaling	[85,86]
	γ-tubulin centrin pericentrin	Co-localization of GRK5 with γ-tubulin, centrin, and pericentrin is important for regulation of microtubule nucleation and cell cycle progression	[92]
	p53	Phosphorylation of p53 by GRK5 inhibits DNA damage-induced apoptosis	[106]
	raptor	Grk5l, which is the closest homolog of GRK5 in zebrafish, interacts with raptor, and regulates mTOR signaling	[108]
GRK6	GIT1	GRK6 cooperates with GIT1 to enhance Rac1 activity, and promotes engulfment of apoptotic cells	[43]

Watari et al. Journal of Molecular Signaling 2014, 9:1

The β-arrestins

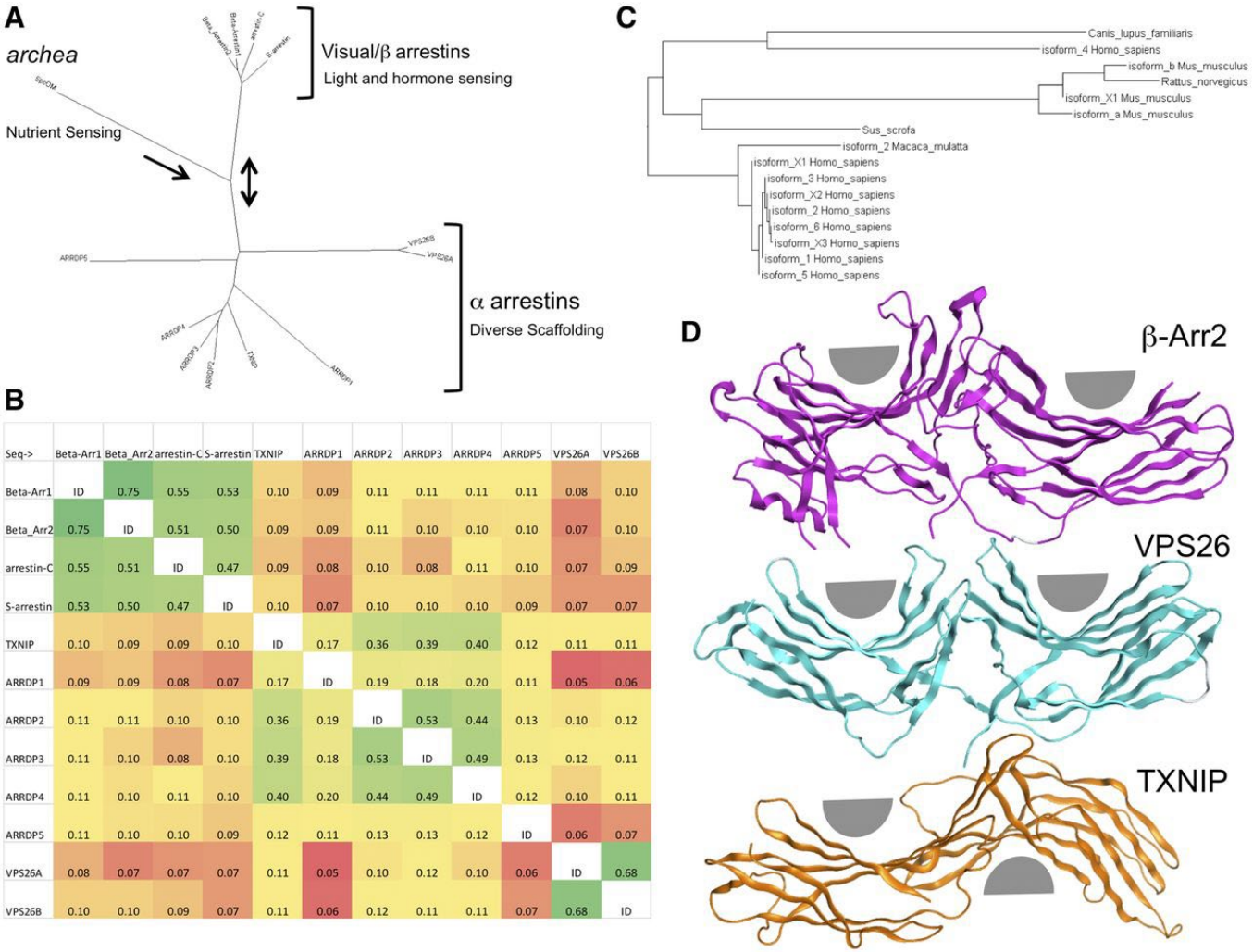
- Finger loop interacts with the GPCR transmembrane core
- Polar core between two globular domains binds to the phosphorylated GPCR C terminus
- Acts as a scaffold for a number of signaling proteins



Robert J. Lefkowitz, and Sudha K. Shenoy Science 2005;308:512-517

Science
AAAS

The Arrestin Fold

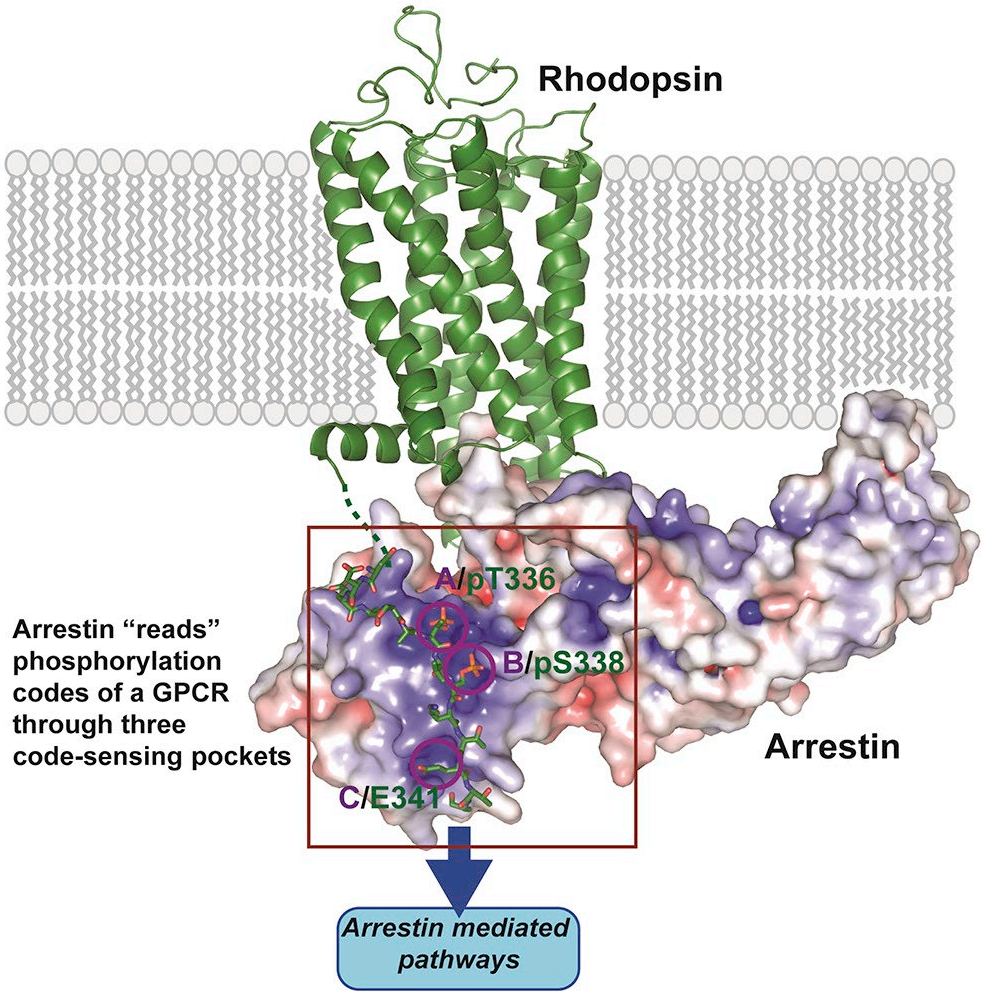


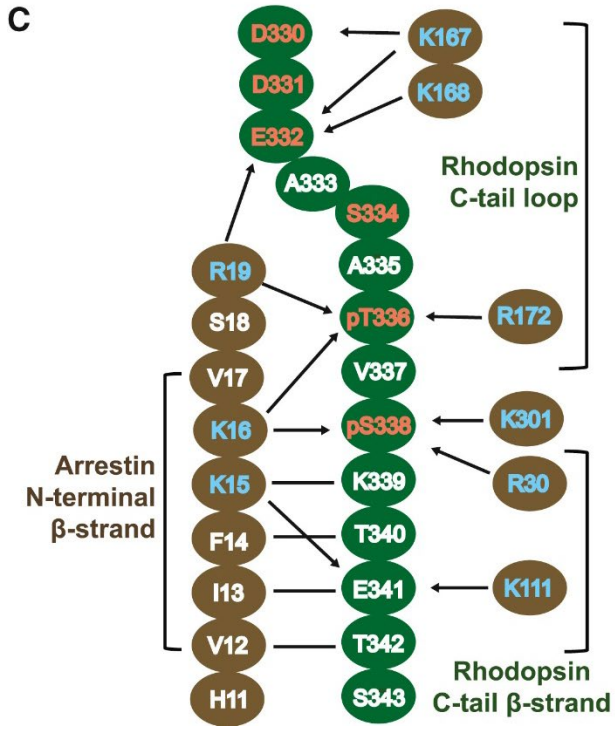
Seq->	Beta-Arr1	Beta_Arr2	arrestin-C	S-arrestin	TXNIP	ARRDP1	ARRDP2	ARRDP3	ARRDP4	ARRDP5	VPS26A	VPS26B
Beta-Arr1	ID	0.75	0.55	0.53	0.10	0.09	0.11	0.11	0.11	0.11	0.08	0.10
Beta_Arr2	0.75	ID	0.51	0.50	0.09	0.09	0.11	0.10	0.10	0.10	0.07	0.10
arrestin-C	0.55	0.51	ID	0.47	0.09	0.08	0.10	0.08	0.11	0.10	0.07	0.09
S-arrestin	0.53	0.50	0.47	ID	0.10	0.07	0.10	0.10	0.10	0.09	0.07	0.07
TXNIP	0.10	0.09	0.09	0.10	ID	0.17	0.36	0.39	0.40	0.12	0.11	0.11
ARRDP1	0.09	0.09	0.08	0.07	0.17	ID	0.19	0.18	0.20	0.11	0.05	0.06
ARRDP2	0.11	0.11	0.10	0.10	0.36	0.19	ID	0.53	0.44	0.13	0.10	0.12
ARRDP3	0.11	0.10	0.08	0.10	0.39	0.18	0.53	ID	0.49	0.13	0.12	0.11
ARRDP4	0.11	0.10	0.11	0.10	0.40	0.20	0.44	0.49	ID	0.12	0.10	0.11
ARRDP5	0.11	0.10	0.10	0.09	0.12	0.11	0.13	0.13	0.12	ID	0.06	0.07
VPS26A	0.08	0.07	0.07	0.07	0.11	0.05	0.10	0.12	0.10	0.06	ID	0.68
VPS26B	0.10	0.10	0.09	0.07	0.11	0.06	0.12	0.11	0.11	0.07	0.68	ID

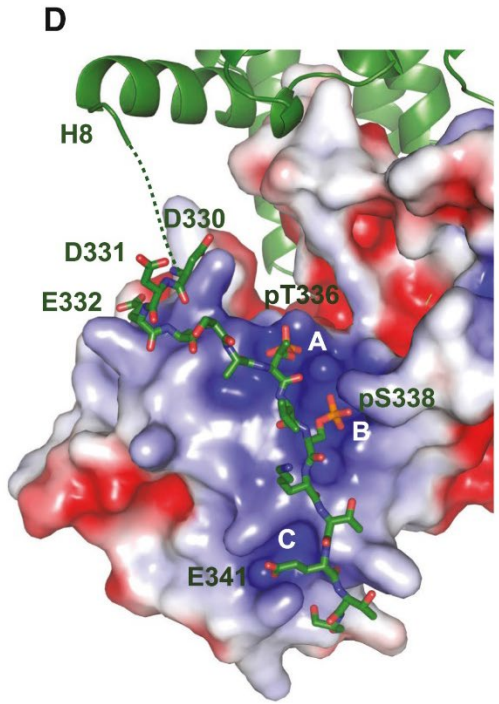
Yuri K. Peterson, and Louis M. Luttrell Pharmacol Rev 2017;69:256-297

ASPET PHARMACOLOGICAL REVIEWS

Phosphorylation barcode for arrestin interaction

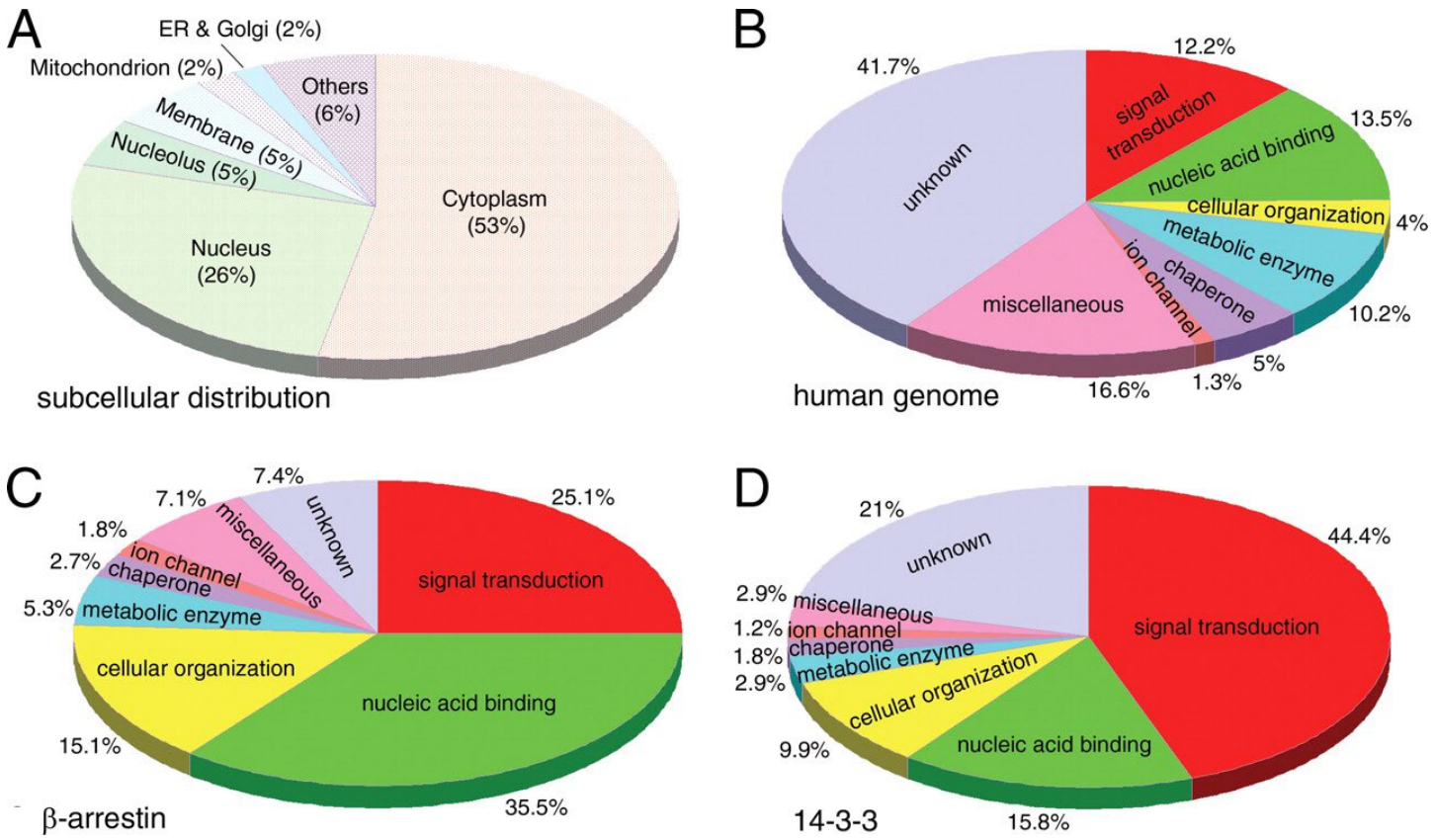






Cell Volume 170, Issue 3, 27 July 2017, Pages 457-469.e13

β-arrestins interact with a wide array of proteins

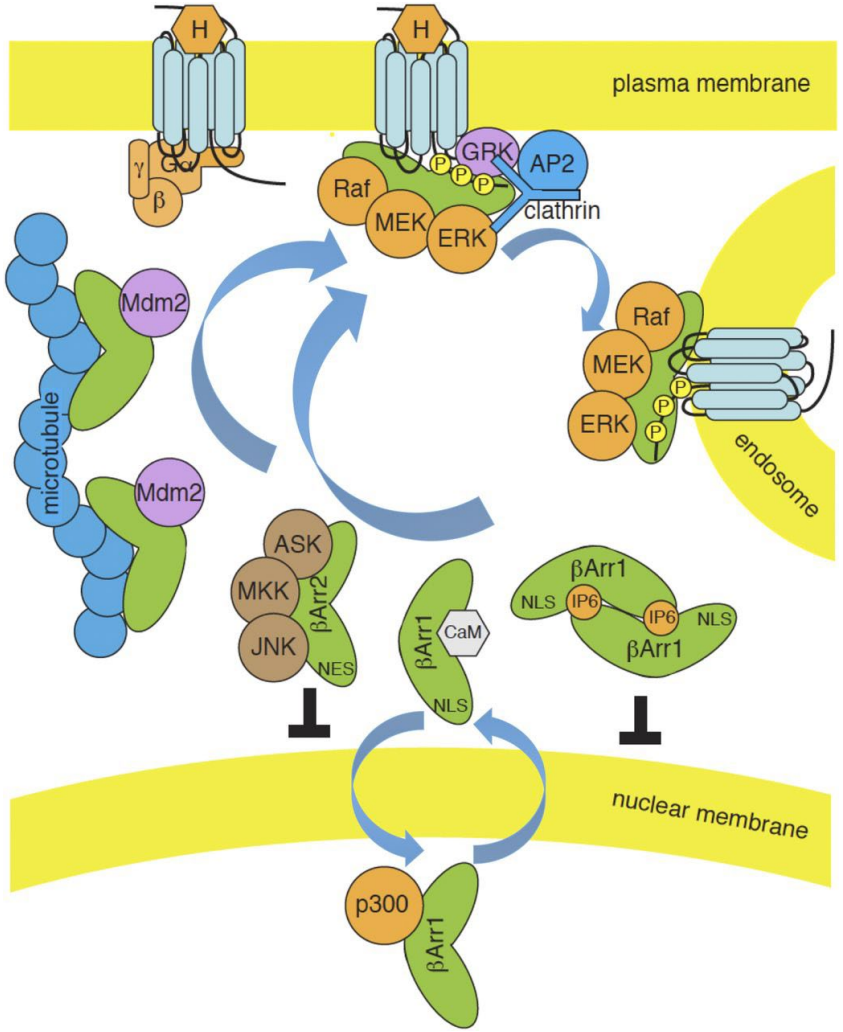


- Mass-spectrometry-based interactome demonstrates a wide array of proteins interact with the β-arrestins
  - Kinases, Phosphatases
  - Trafficking proteins
  - Small GTPases
  - Metabolic enzymes
  - Cytoskeletal proteins

Kunhong Xiao et al. PNAS 2007;104:29:12011-12016

PNAS

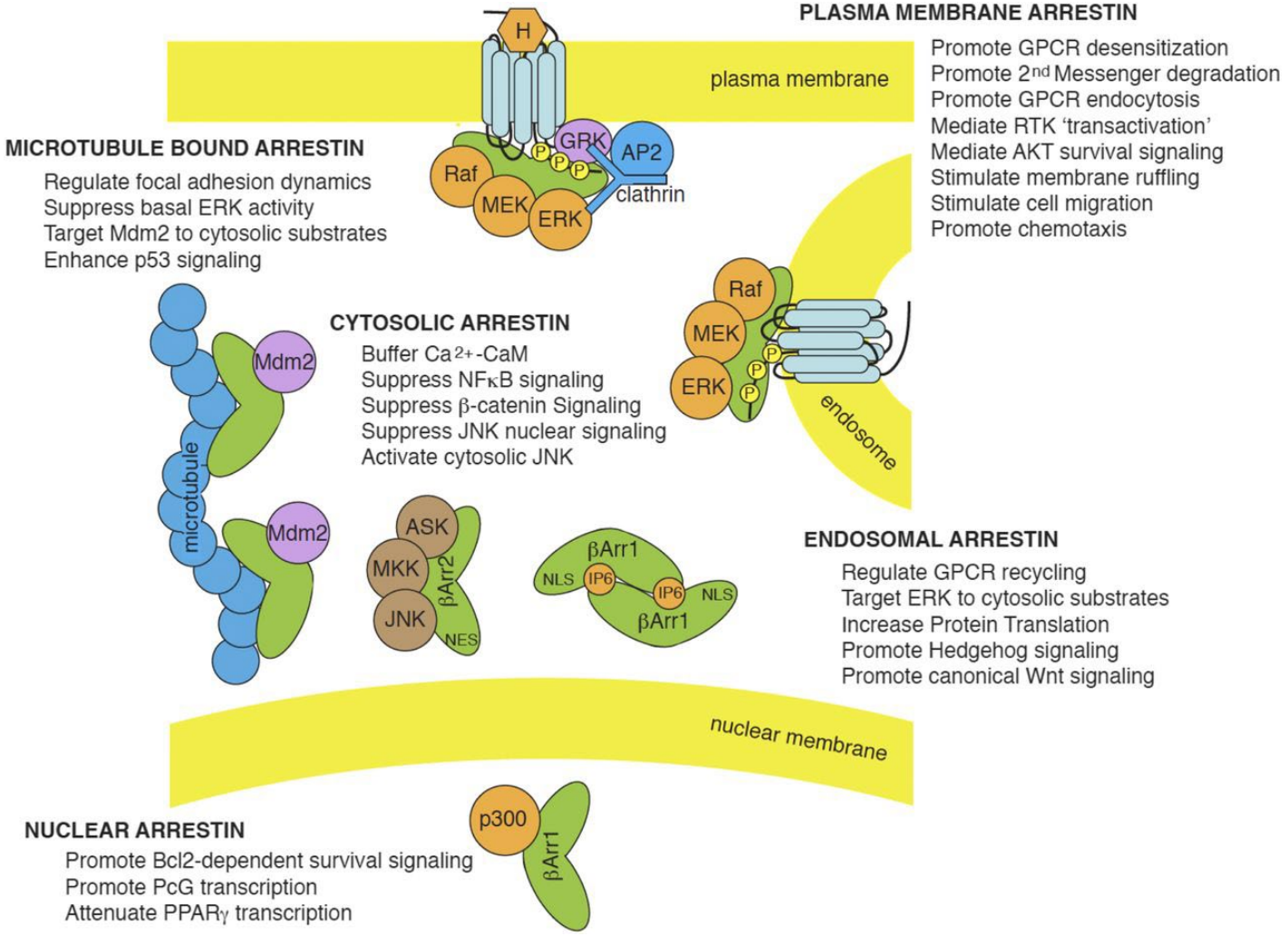
Functionally discrete arrestin pools



Yuri K. Peterson, and Louis M. Luttrell Pharmacol Rev 2017;69:256-297

ASPET | PHARMACOLOGICAL REVIEWS

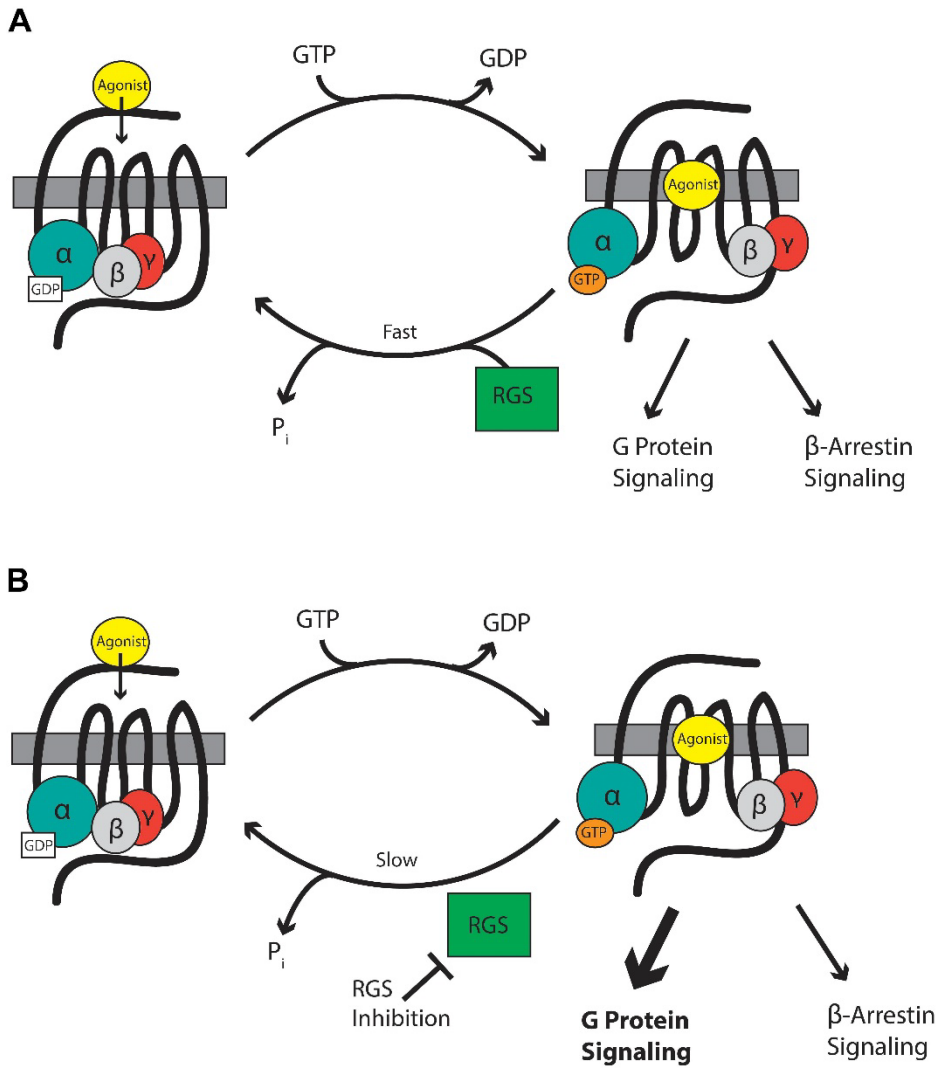
Diverse cellular functions of arrestin scaffolds



Yuri K. Peterson, and Louis M. Luttrell Pharmacol Rev 2017;69:256-297

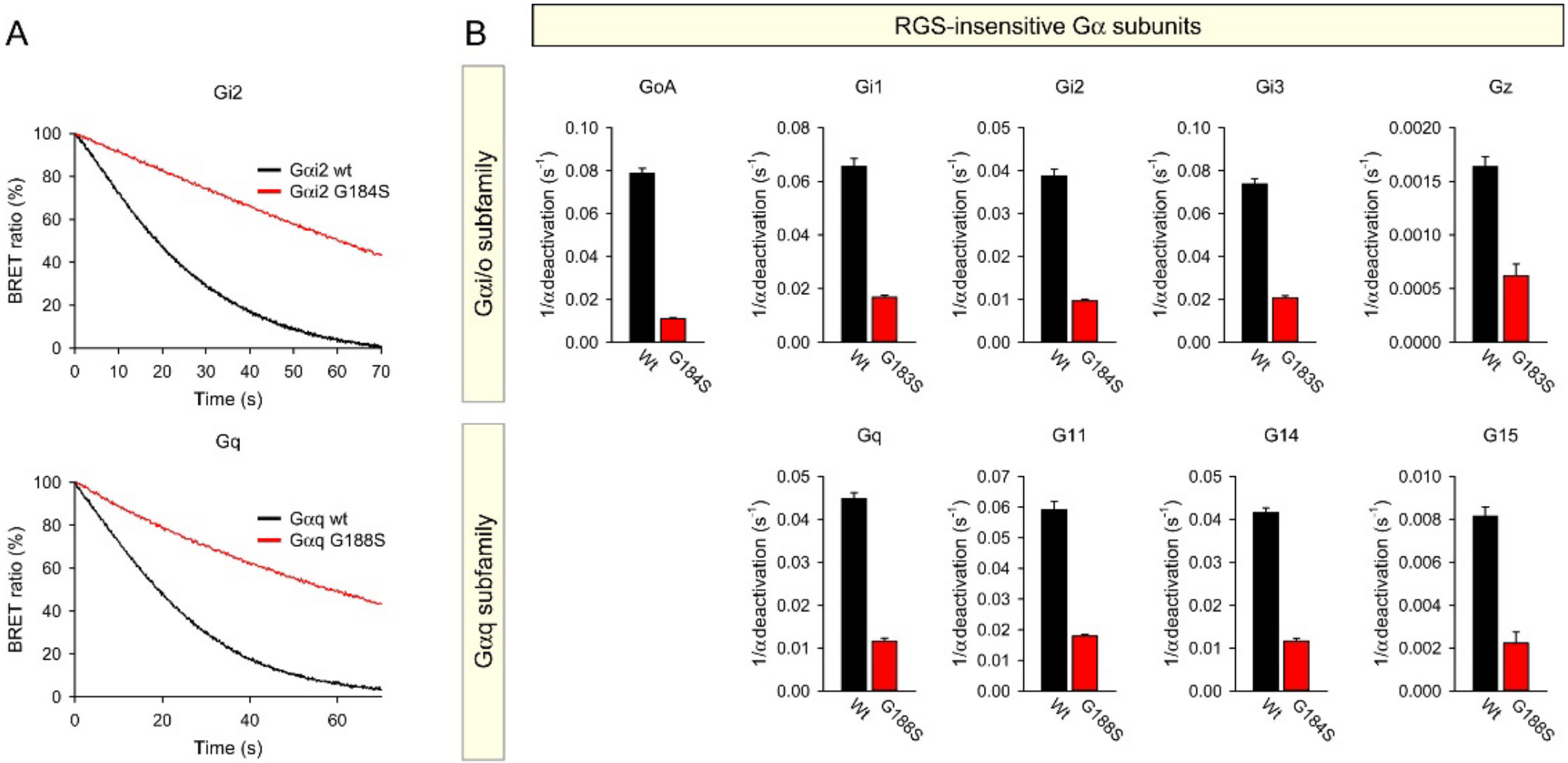
ASPET PHARMACOLOGICAL REVIEWS

RGS proteins – G protein deactivation



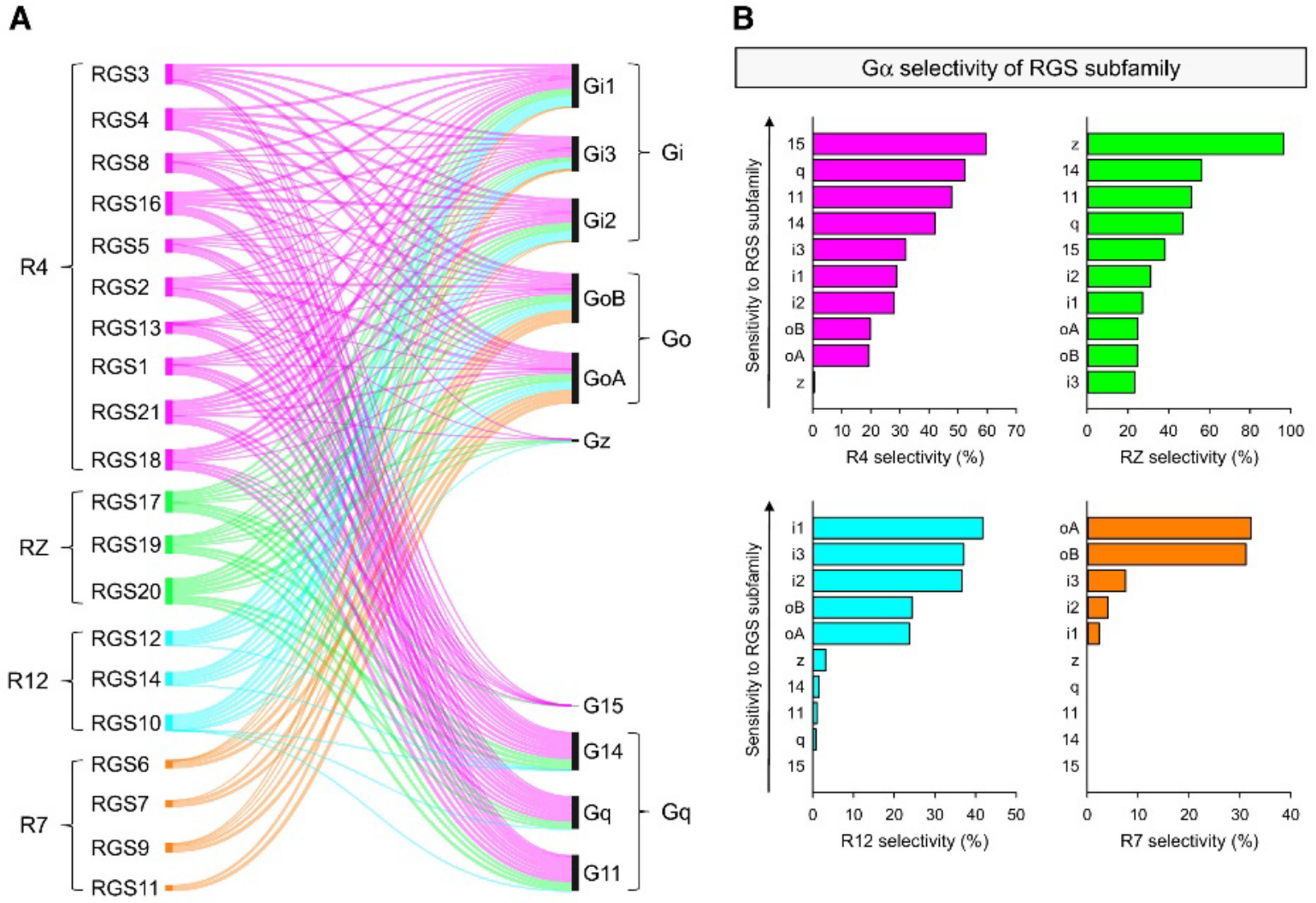
https://doi.org/10.3389/fnmol.2020.00005

RGS proteins bind to specific sites in Gα



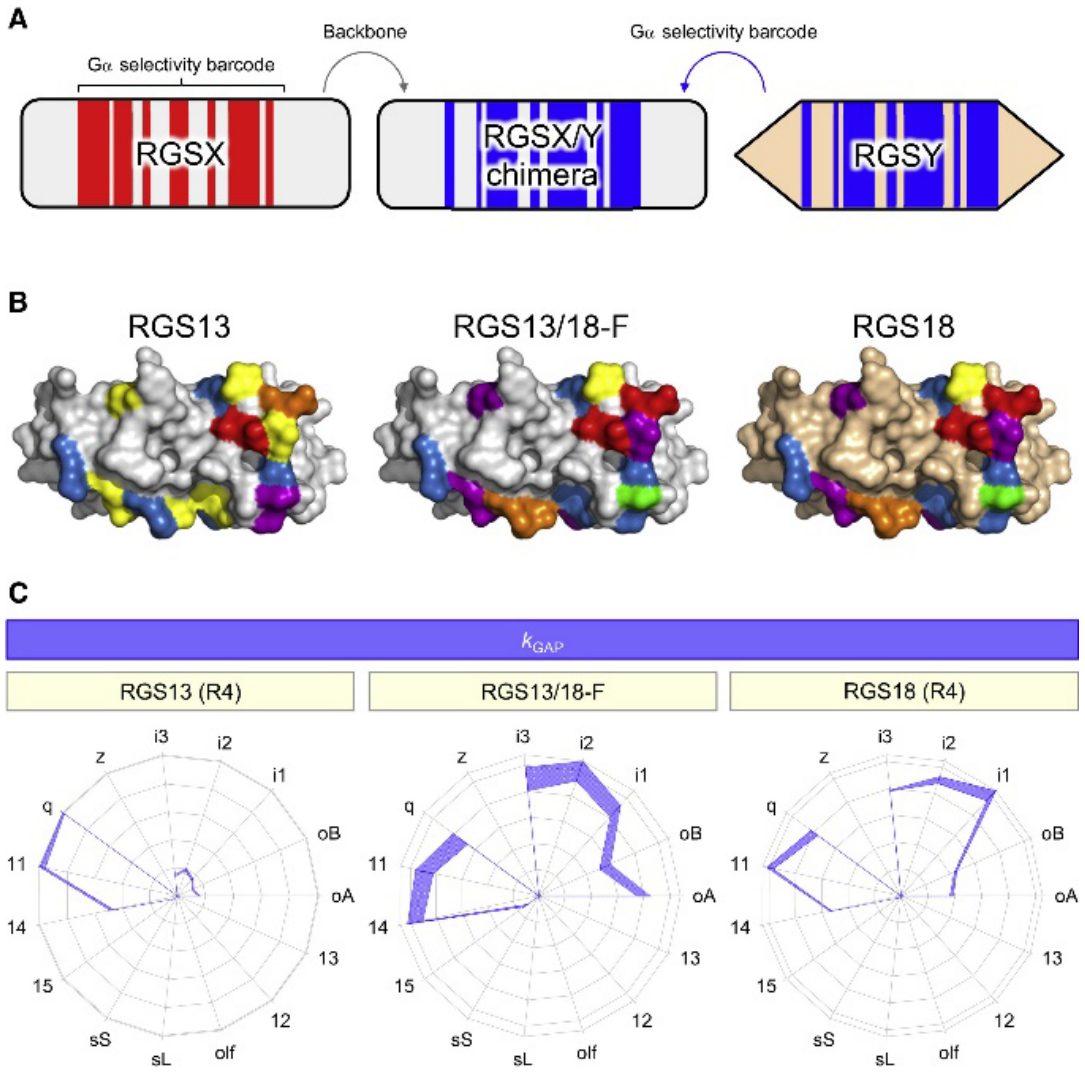
Cell DOI: (10.1016/j.cell.2020.08.052)

Specificity of RGS proteins



Cell DOI: (10.1016/j.cell.2020.08.052)

Specificity of RGS proteins can be modified

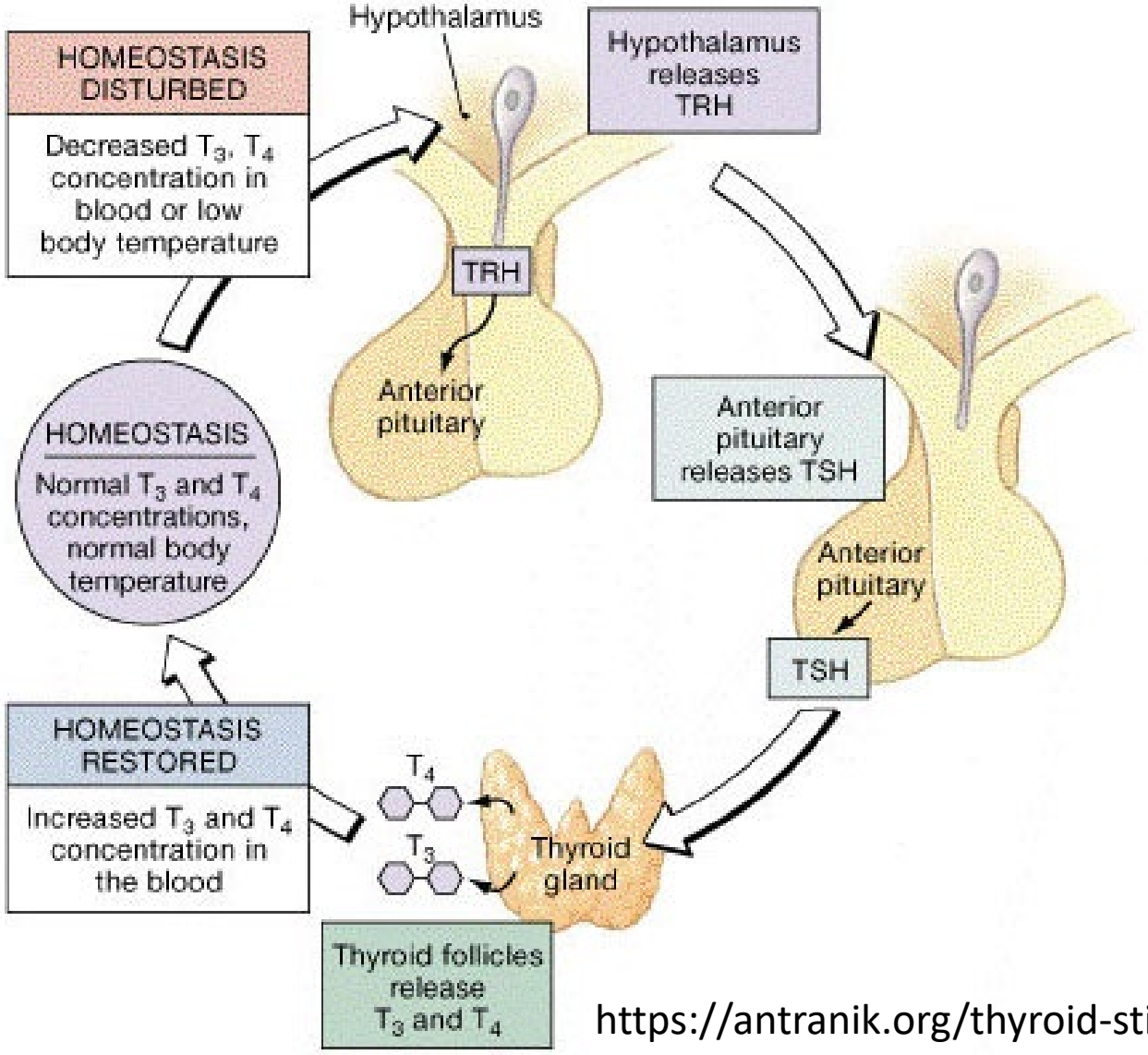


Cell DOI: (10.1016/j.cell.2020.08.052)

Outline

- Introduction to GPCRs
- Basics of GPCR Signaling
- **GPCRs in disease**
- Drugs targeting GPCRs

GPCRs in action: Regulation of thyroid hormones



https://antranik.org/thyroid-stimulating-hormone-thyrotropin/

GoF mutations in disease

Table 1
Diseases caused by activating mutations in G-protein-coupled receptors (GPCR)

GPCR gene (OMIM)	Receptor (IUPHAR)	Gain-of-function disease	Reference
Family A GPCR			
FSHR	follitropin (FSH)	ovarian hyperstimulation syndrome	Smits et al., 2003; Vasseur et al., 2003
KSHV-GPCR		Kaposi's sarcoma	Arvanitakis et al., 1997
MC2R	melanocortin (MC_2)	ACTH-independent Cushing's syndrome	Swords et al., 2002
LHR	lutropin (LHCG)	male-limited precocious puberty, seminoma, Leydig-cell tumor	Shenker et al., 1993; Martin et al., 1998; Liu et al., 1999a
RHO	rhodopsin	congenital stationary night blindness	Robinson et al., 1992; Rao et al., 1994
TSHR	thyrotropin (TSH)	hyperthyroidism, thyroid carcinoma	Parma et al., 1993; Russo et al., 1995
Family B GPCR			
PTHR1	PTH/PTHrP (PTH_1)	Jansens's metaphyseal chondrodysplasia	Schipani et al., 1995
Family C GPCR			
CASR	calcium-sensing (CaS)	dominant and sporadic hypoparathyroidism	Baron et al., 1996
Other GPCR			
SMOH	smoothened (SMO)	sporadic basal-cell carcinoma	Xie et al., 1998

Full-length receptor names are given under 'Abbreviations' at the beginning of the chapter.

Pharmacol Ther. 2004 Dec;104(3):173-206.

LoF mutations in disease

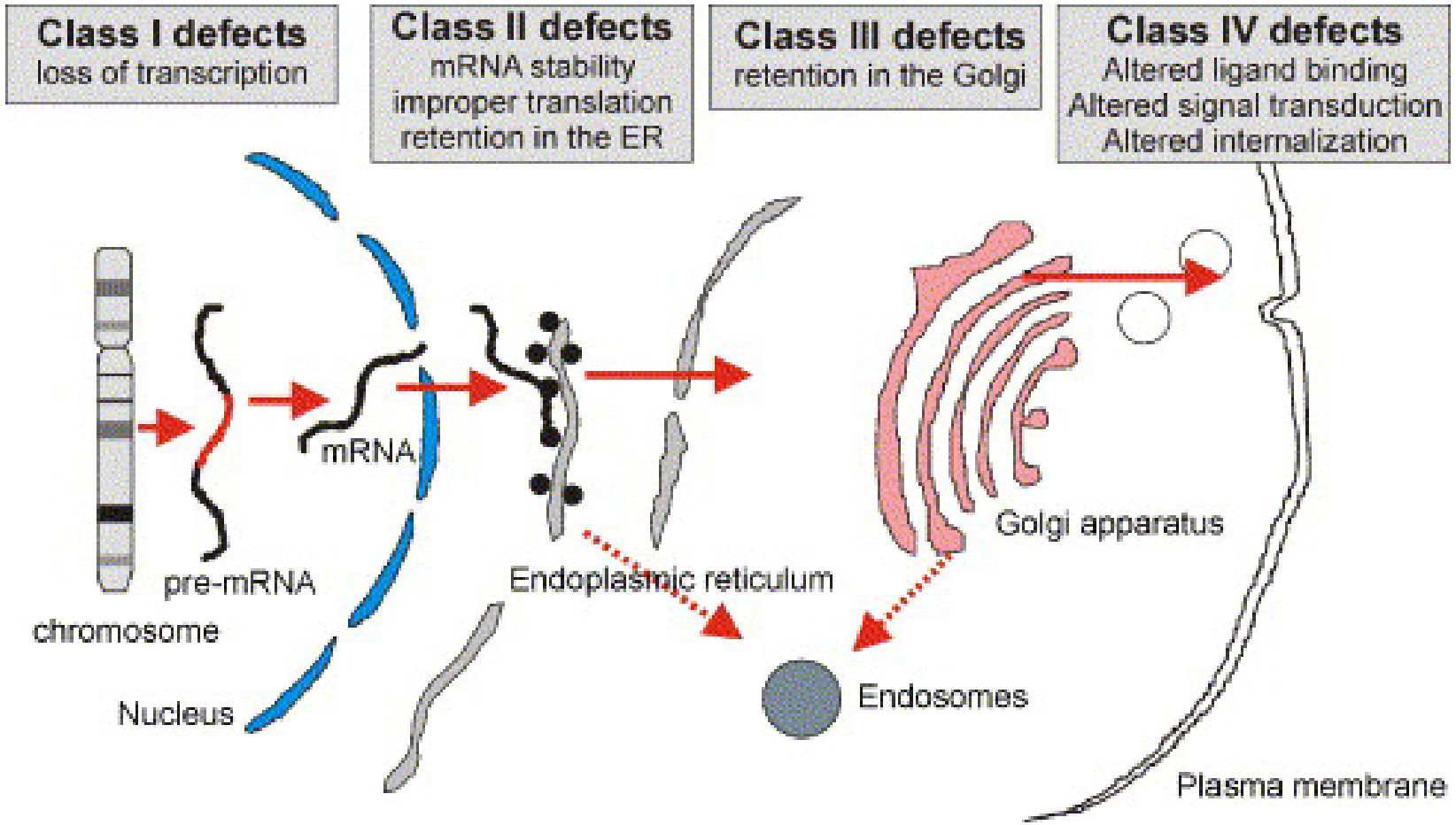
Table 2
Diseases caused by inactivating mutations in G-protein-coupled receptors (GPCR)

GPCR gene (OMIM)	GPCR (IUPHAR)	Loss-of-function disease	Reference
Family A GPCR			
AGTR2	angiotensin (AT_2)	X-linked mental retardation	Vervoort et al., 2002
AVPR2	vasopressin (V_2)	nephrogenic diabetes insipidus (NDI), partial NDI	Rosenthal et al., 1992; Sadeghi et al., 1997
EDNRB	endothelin (ET_B)	Hirschsprung's disease	Puffenberger et al., 1994
FPR1	*N*-formyl-peptide (FPR)	juvenile periodontitis	Gwinn et al., 1999
FSHR	follitropin (FSH)	ovarian dysplasia, amenorrhea, secondary amenorrhea	Aittomäki et al., 1995; Beau et al., 1998
GNRHR	GnRH (GnRH)	hypogonadotropic hypogonadism	de Roux et al., 1997; Layman et al., 1998
GPR54	GPR54	hypogonadotropic hypogonadism	de Roux et al., 2003; Seminara et al., 2003
LGR8	LGR8 (INSL3)	cryptorchidism	Gorlov et al., 2002
LHR	lutropin (LHCG)	pseudohermaphroditism, hypospadias	Kremer et al., 1995; Misrahi et al., 1997
MC1R	melanocortin (MC_1)	UV-induced skin damage	Valverde et al., 1995
MC2R	melanocortin (MC_2)	ACTH resistance syndrome	Clark et al., 1993; Tsigos et al., 1993
MC4R	melanocortin (MC_4)	dominant and recessive obesity	Vaisse et al., 1998; Yeo et al., 1998; Farooqi et al., 2000
P2RY12	purinoceptor ($P2Y_{12}$)	bleeding disorder	Hollopeter et al., 2001
OPN1SW	blue opsin	color blindness	Weitz et al., 1992
RGR	retinal GPCR	retinitis pigmentosa	Morimura et al., 1999
RHO	rhodopsin	retinitis pigmentosa	Dryja et al., 1990
TBXA2R	thromboxane (TP)	bleeding disorder	Hirata et al., 1994
TRHR	TRH	isolated central hypothyroidism	Collu et al., 1997
TSHR	thyrotropin (TSH)	hypothyroidism, thyroid hypoplasia	Biebermann et al., 1997
Family B GPCR			
GHRHR	GHRH	dwarfism	Wajnrajch et al., 1996
GPR56	GPR56	bilateral frontoparietal polymicrogyria	Piao et al., 2004
PTHR1	PTH/PTHrP (PTH_1)	Blomstrand chondrodysplasia	Jobert et al., 1998
MASS1 (VLGR1)	MASS1	febrile seizures, Usher syndrome	Nakayama et al., 2002; Weston et al., 2004
Family C GPCR			
CASR	calcium-sensing (CaS)	hyperparathyroidism	Pollak et al., 1993
Other GPCR			
FZD4	frizzled/wnt (FZD_4)	exudative vitreoretinopathy	Robitaille et al., 2002
OA1	ocular albinism type 1	ocular albinism	Bassi et al., 1995

Full-length receptor names are given under 'Abbreviations' at the beginning of the chapter.

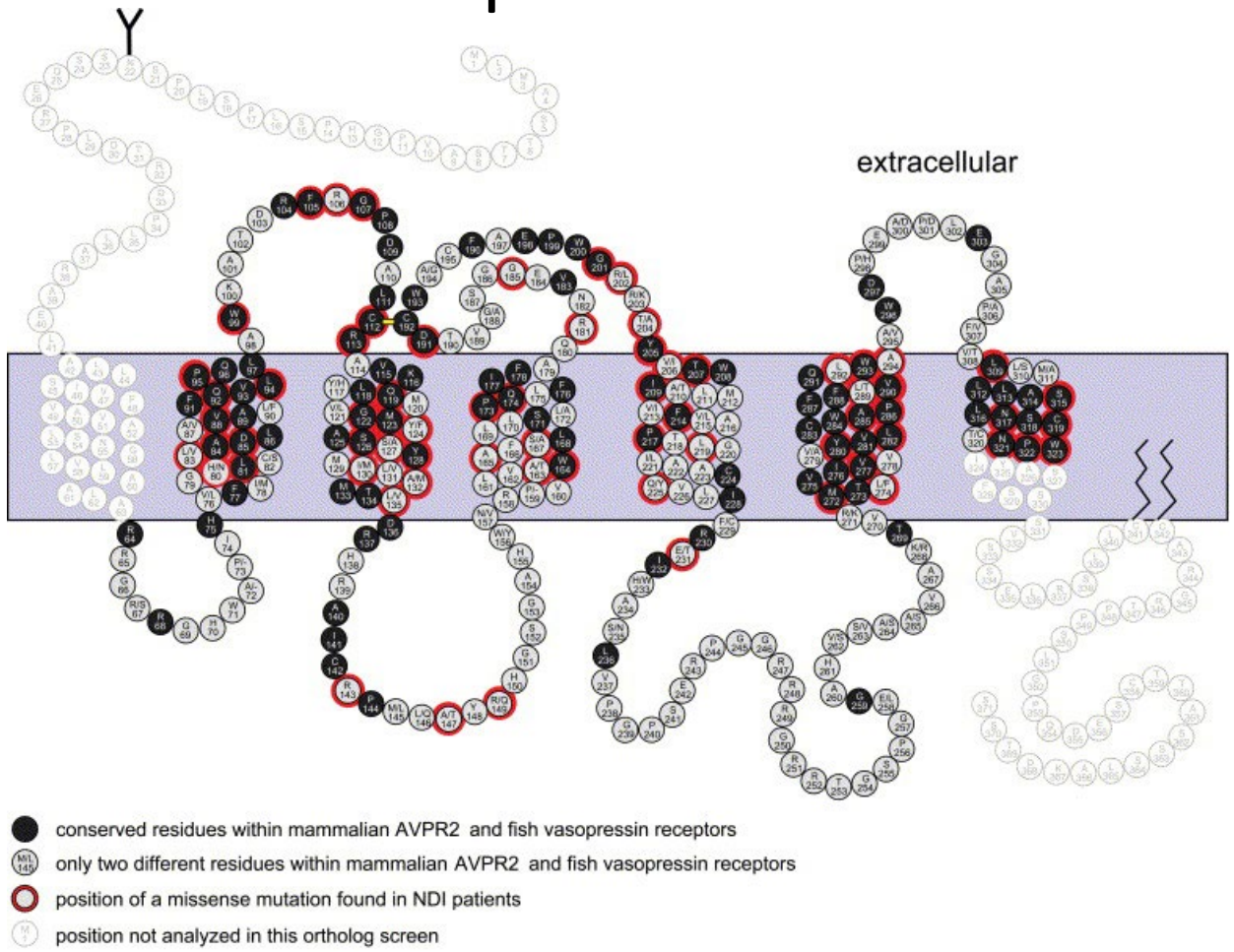
Pharmacol Ther. 2004 Dec;104(3):173-206.

Multiple mechanisms underlie LoF mutations



Pharmacol Ther. 2004 Dec;104(3):173-206.

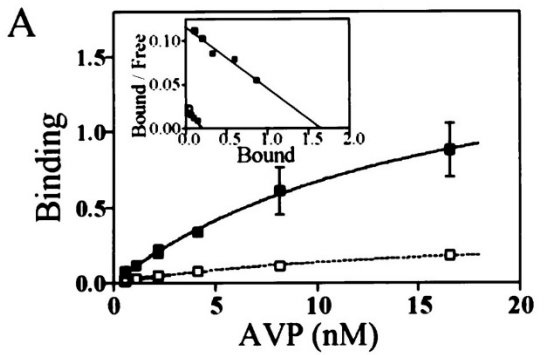
V2 Vasopressin receptor mutations



	total	hit by mutation
conserved residues	40%	62%
partially conserved residues	24%	26%
non-conserved residues	36%	12%

Pharmacol Ther. 2004 Dec;104(3):173-206.

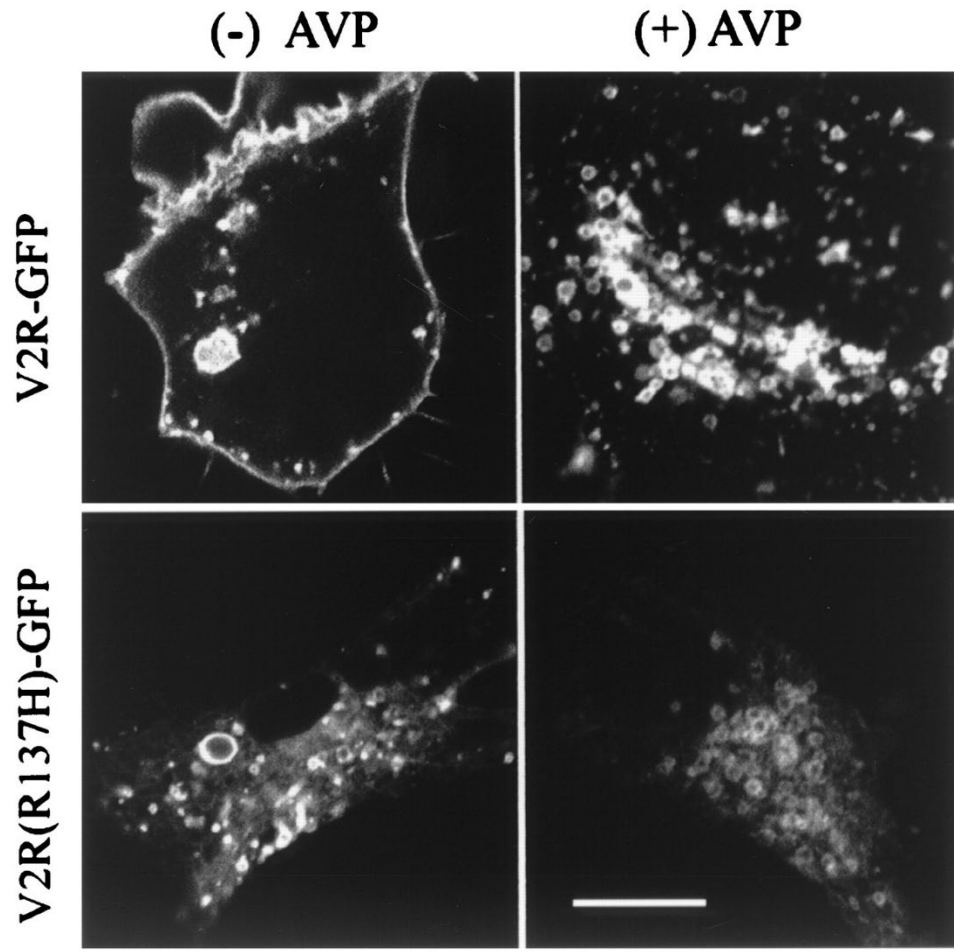
Expression and adenylyl cyclase stimulation of V2R and V2R(R137H) in HEK-293 cells



Larry S. Barak et al. PNAS 2001;98:1:93-98

PNAS

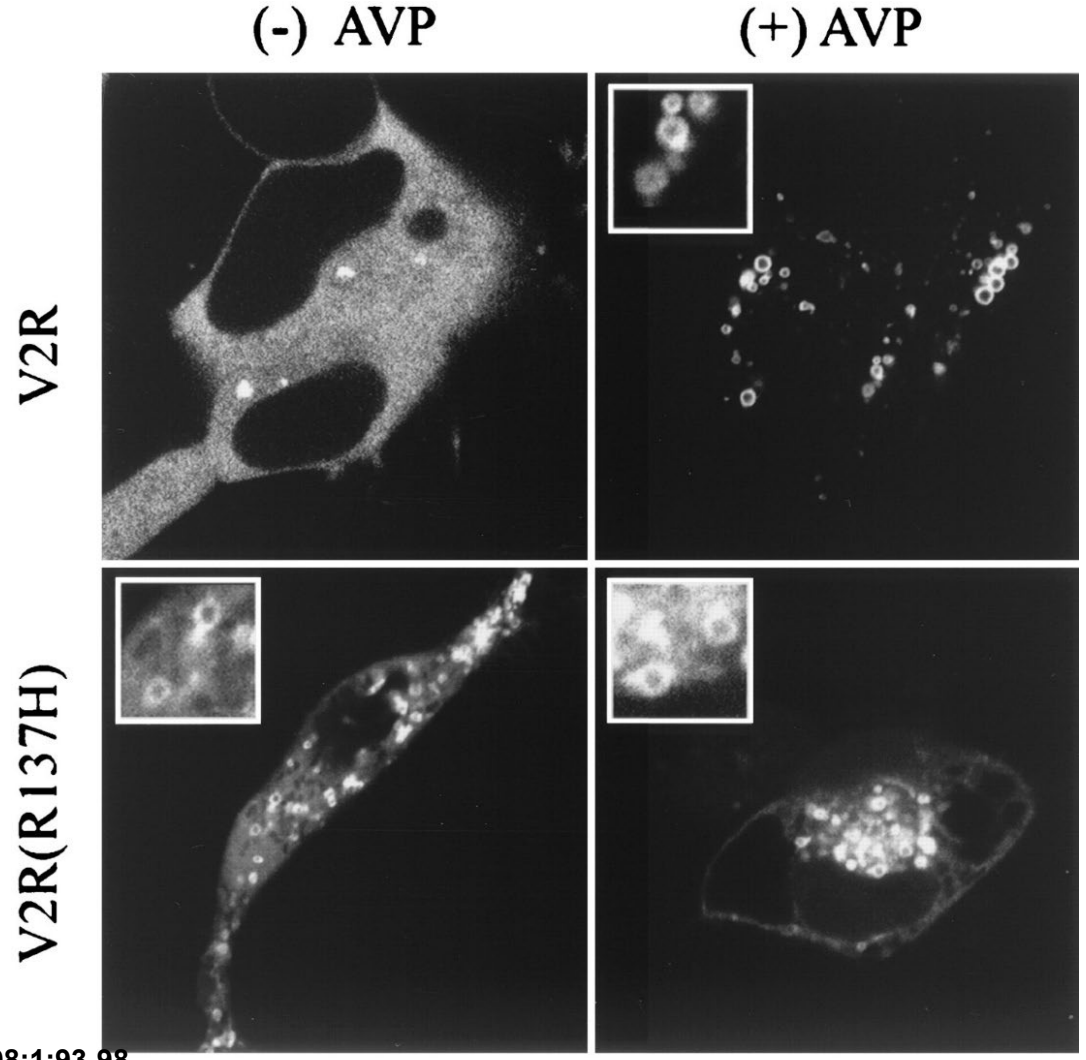
V2R(R137H) is not expressed at the PM



Larry S. Barak et al. PNAS 2001;98:1:93-98

PNAS

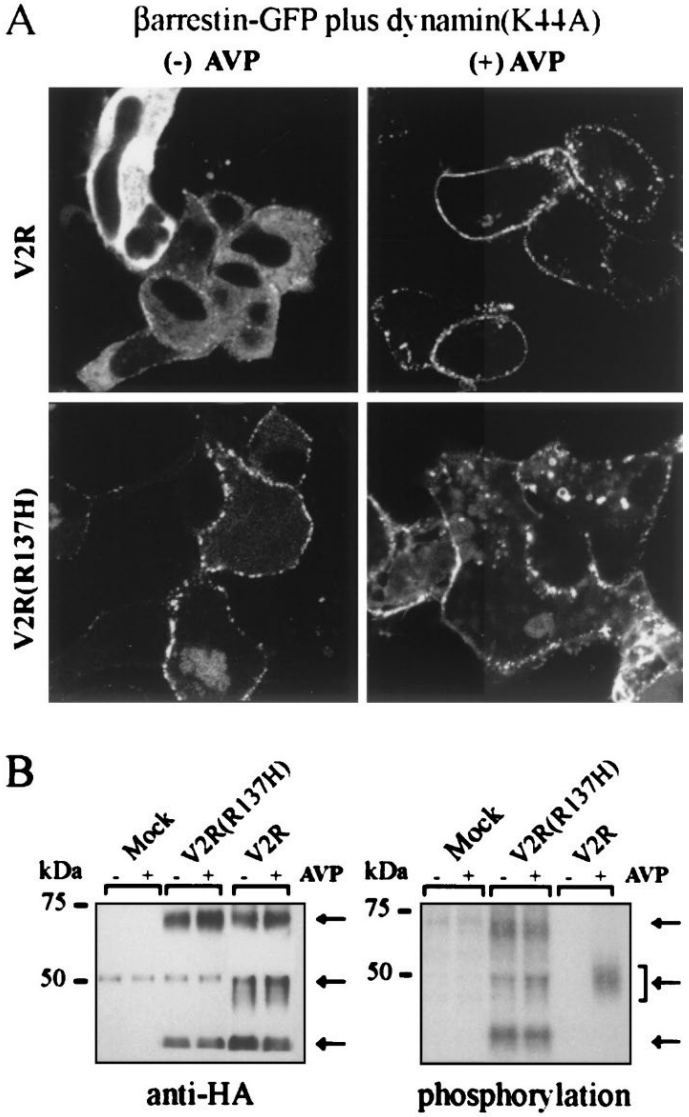
βarrestin2-GFP and V2R or V2R(R137H)



Larry S. Barak et al. PNAS 2001;98:1:93-98

PNAS

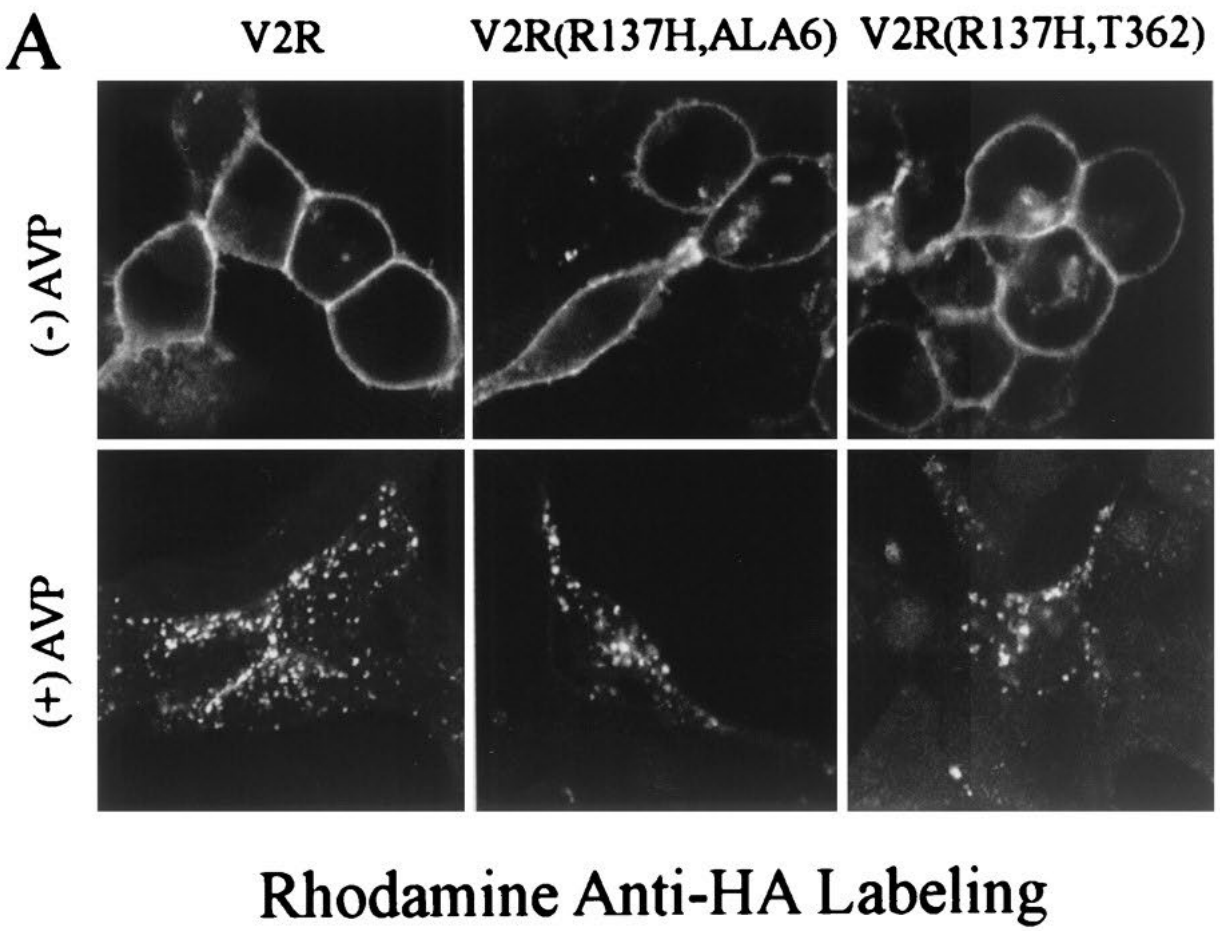
βarrestin2 association with and phosphorylation of V2R and V2R(R137H)

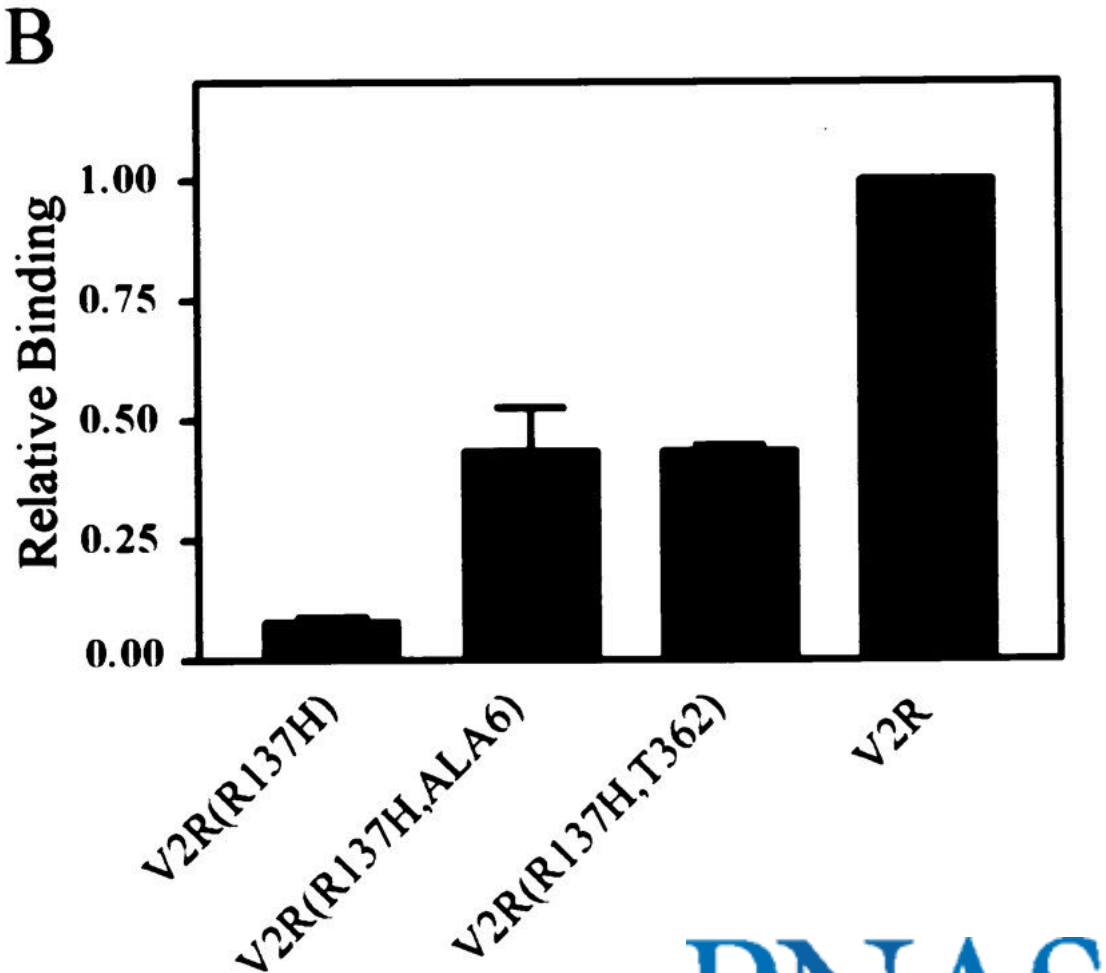


Larry S. Barak et al. PNAS 2001;98:1:93-98

PNAS

Expression of V2R, V2R(R137H,Ala6), and V2R(R137H,T362)

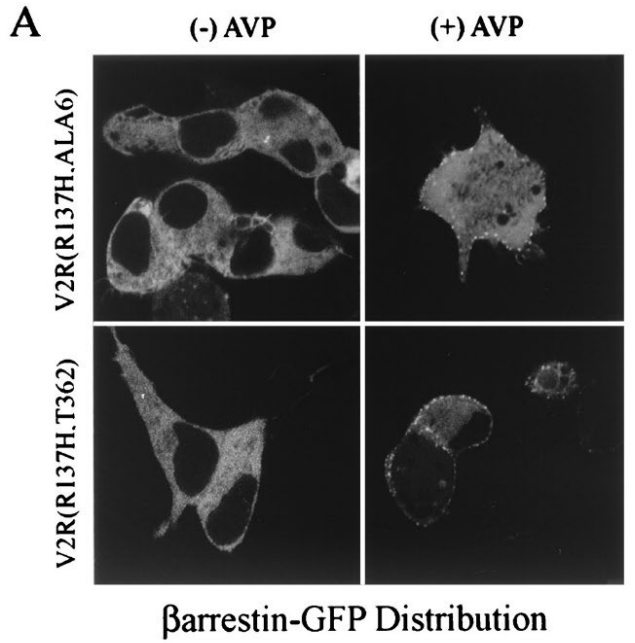




Larry S. Barak et al. PNAS 2001;98:1:93-98

PNAS

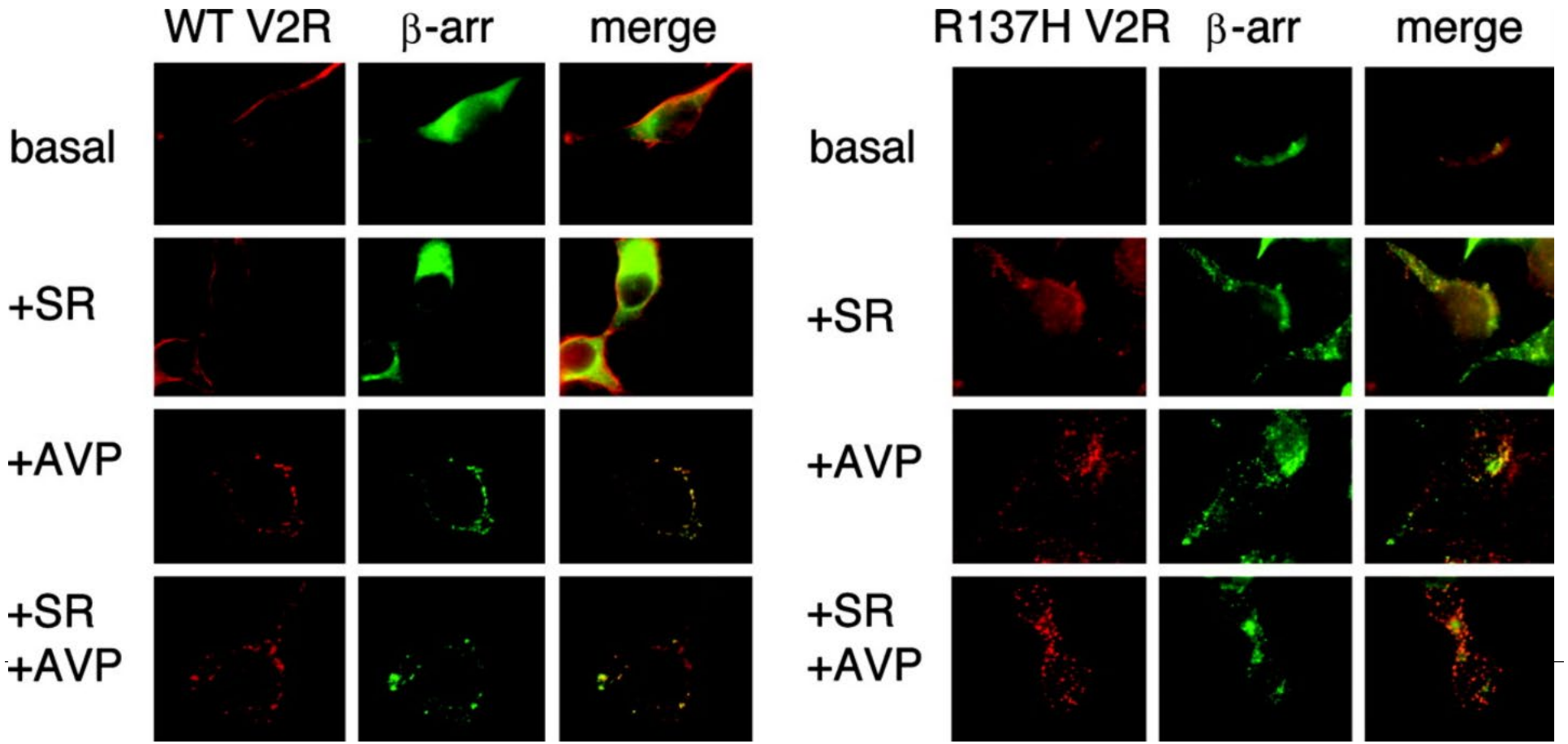
Rescue of the R137H mutation



Larry S. Barak et al. PNAS 2001;98:1:93-98

PNAS

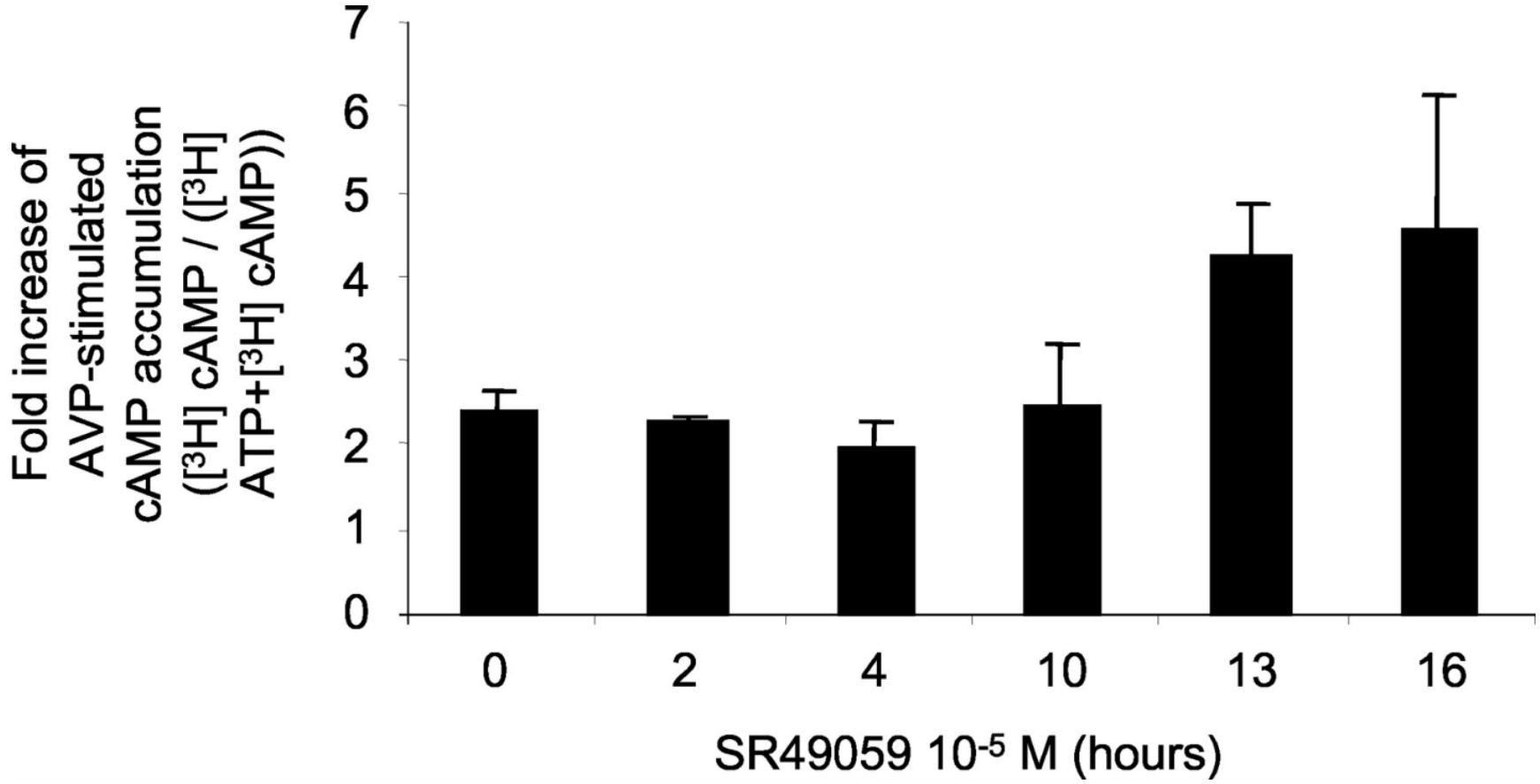
A pharmacological chaperone to rescue R137H V2R expression



From: Functional Rescue of the Constitutively Internalized V2 Vasopressin Receptor Mutant R137H by the Pharmacological Chaperone Action of SR49059

Mol Endocrinol. 2004;18(8):2074-2084. doi:10.1210/me.2004-0080

Rescue of receptor expression increases cAMP response



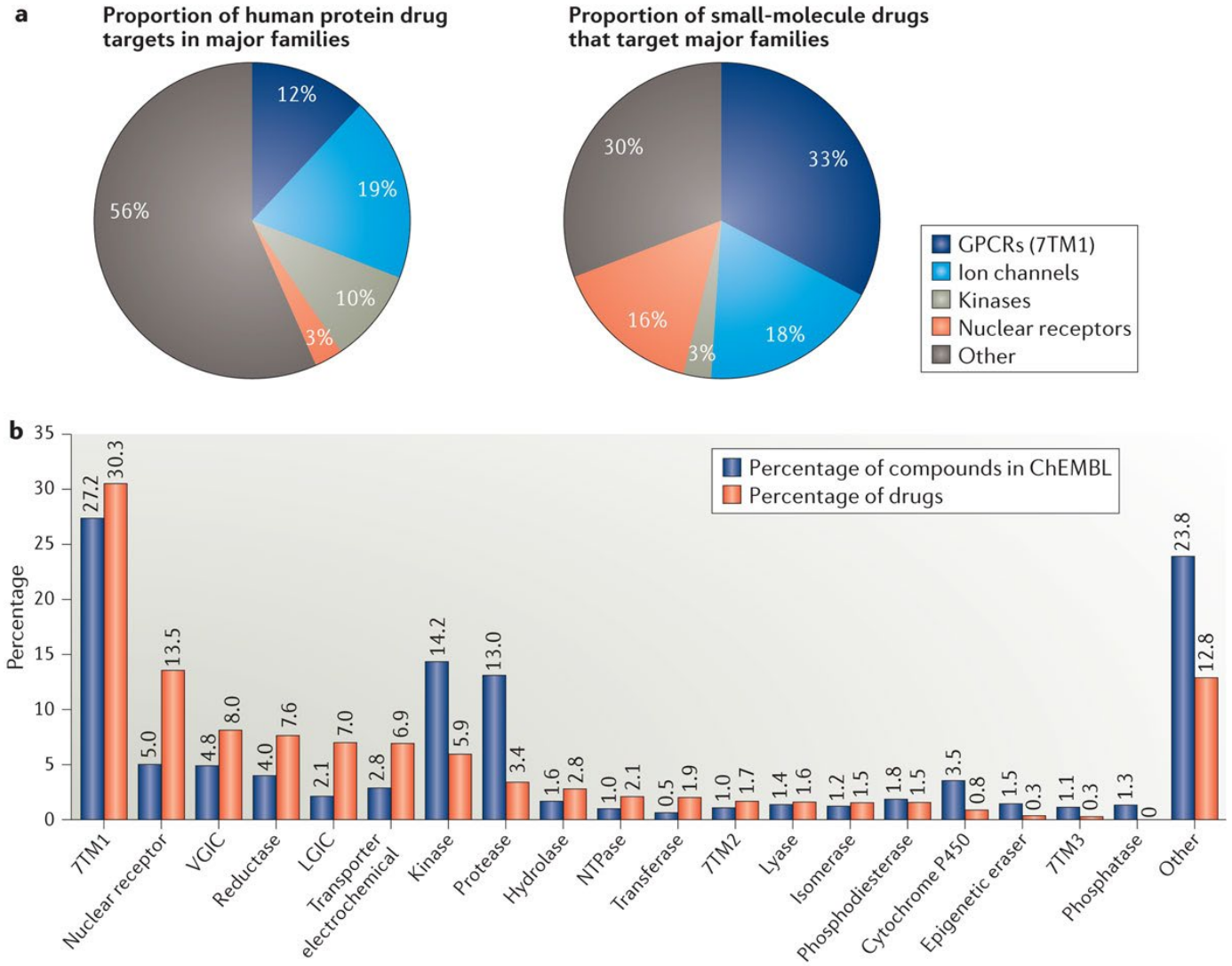
From: Functional Rescue of the Constitutively Internalized V2 Vasopressin Receptor Mutant R137H by the Pharmacological Chaperone Action of SR49059

Mol Endocrinol. 2004;18(8):2074-2084. doi:10.1210/me.2004-0080

Outline

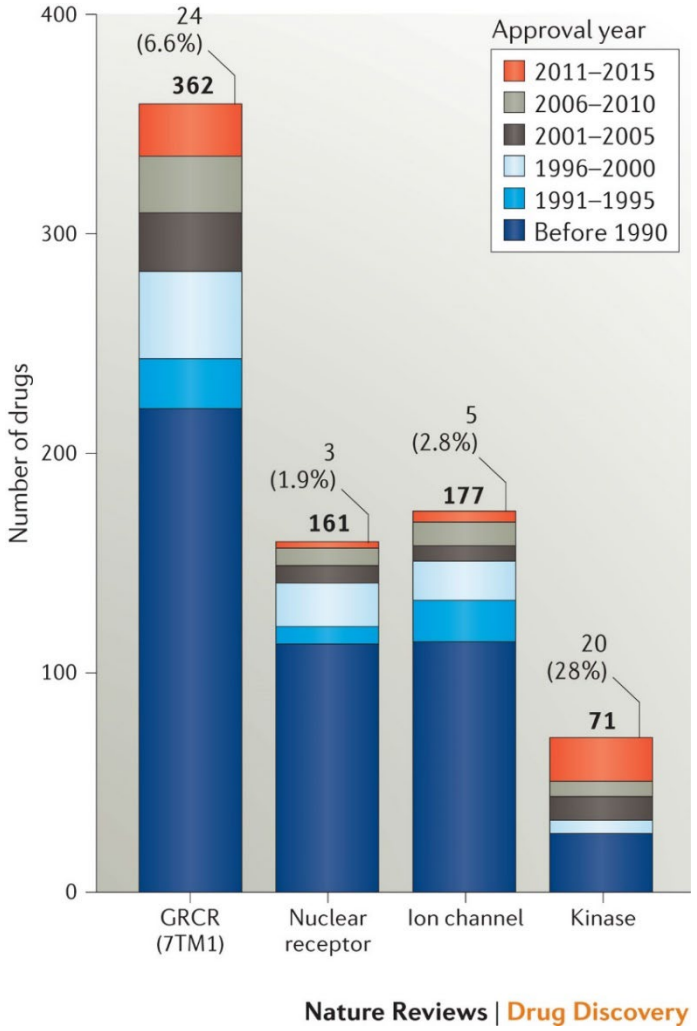
- Introduction to GPCRs
- Basics of GPCR Signaling
- GPCRs in disease
- **Drugs targeting GPCRs**

GPCRs are a common drug target in the genome



Nat Rev Drug Discov. 2017 Jan;16(1):19-34

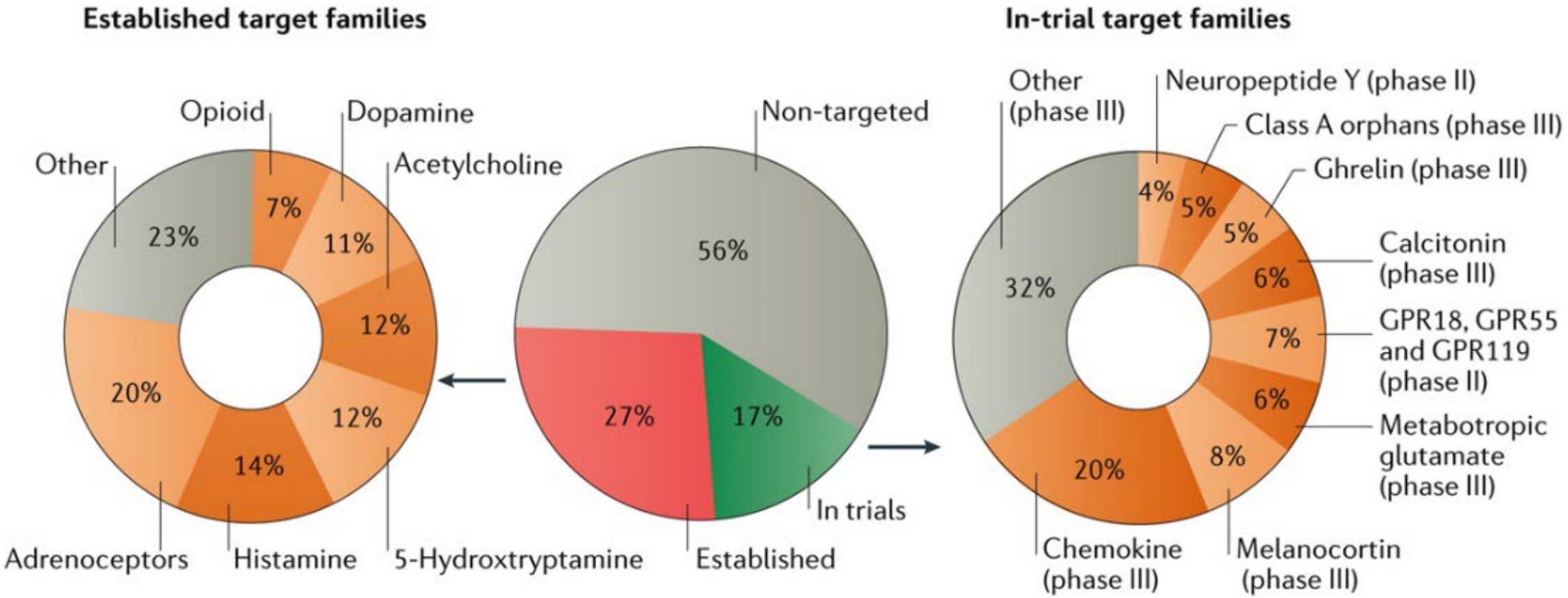
GPCRs are still an active area for drug discovery



- GPCRs are still an active area for drug discovery
- Still a number of orphan GPCRs for which no endogenous ligand have been identified

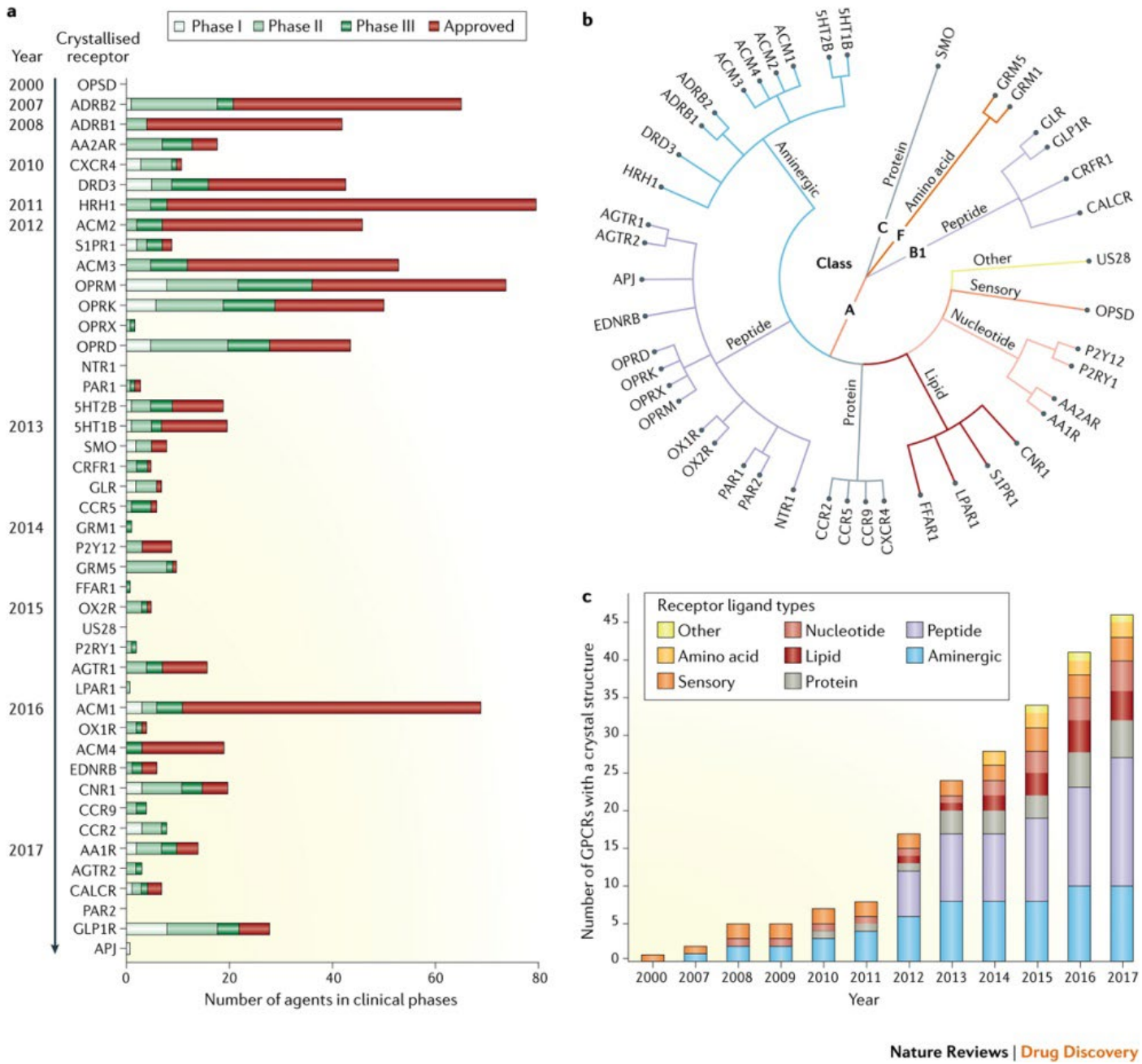
Nat Rev Drug Discov. 2017 Jan;16(1):19-34

GPCR drug targets



Nature Reviews | Drug Discovery

Nat Rev Drug Discov. 2017 Dec;16(12):829-842



Nat Rev Drug Discov. 2017 Dec;16(12):829-842

Table 1 | **New molecular entities acting via GPCRs approved by the FDA since 2014**

Substance	Brand name	Indications	Targets*	Approval year
Droxidopa	Northera	Orthostatic hypotension	ADRB1–3, ADA2A/B/C and ADA1A/B/D	2014
Dulaglutide	Trulicity	Type 2 diabetes	GLP1R	2014
Hydrocodone bitartrate	Hycodan	Narcotic cough	OPRD and OPRM	2014
Naloxegol	Movantik	Opioid-induced constipation	OPRM	2014
Netupitant	Akynzeo	Nausea and/or vomiting	NK1R	2014
Olodaterol	Striverdi respimat	COPD	ADRB2	2014
Suvorexant	Belsomra	Insomnia	OX2R and OX1R	2014
Tasimelteon	Hetlioz	Non-24-hour sleep-wake disorder	MTR1A and MTR1B	2014
Vorapaxar	Zontivity	Cardiovascular risk reduction	PAR1	2014
Aripiprazole lauroxil	Aristada	Schizophrenia	5HT1A, 5HT2A and DRD2	2015
Brexpiprazole	Rexulti	Depression	5HT2A, 5HT1A, DRD2 and 5HT7R	2015
Cangrelor	Kengreal	Percutaneous coronary intervention	P2Y12	2015
Cariprazine	Vraylar	Schizophrenia and bipolar disorder	DRD3 and DRD2	2015
Eluxadoline	Viberzi	Irritable bowel syndrome	OPRM and OPRD	2015
Flibanserin	Addyi	Hypoactive sexual desire disorder	5HT2A and 5HT1A	2015
Parathyroid hormone	Natpara	Hypoparathyroidism	PTH1R and PTH2R	2015
Rolapitant	Varubi	Nausea and/or vomiting	NK1R	2015
Selexipag	Uptravi	Pulmonary hypertension	PI2R	2015
Sonidegib	Odomzo	Basal cell carcinoma	SMO	2015
Lixisenatide	Adlyxin	Type 2 diabetes	GLP1R	2016
Pimavanserin	Nuplazid	Parkinson disease psychosis	5HT2A	2016
Abaloparatide	Tymlos	Osteoporosis	PTHR1	2017
Etelcalcetide	Parsabiv	Hyperparathyroidism	CASR	2017
Naldemedine	Symproic	Opioid-induced constipation	OPRM	2017

COPD, chronic obstructive pulmonary disease; GPCR, G protein-coupled receptor. *Listed using the protein name in UniProt; for details on receptor nomenclature, see the IUPHAR/BPS Guide to PHARMACOLOGY (see Further information)

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Table 2 | **New GPCR target families and late-stage targets for agents currently in clinical trials**

Receptor family	Targets*	Indications	Agents
Angiotensin	AGTR2	Catecholamine resistant hypotension	LJPC-501
Apelin	APJ	Cardiovascular disorders and insulin sensitivity	Apelin
Bile acid	GPBAR	Liver fibrosis	INT-767
Calcitonin	CALCRL	Migraine	Erenumab and ubrogepant
Chemerin	CML1	Dry eye	RX-10045
Chemokine	CCR2, CCR4 and CXCR1	HIV infection, cancer and type 1 diabetes	Cenicriviroc, mogamulizumab and reparixin
Class A orphans	GPR84, GPR35, MAS and LGR5	Ulcerative colitis, irritable bowel syndrome, autoimmune diseases, multiple myeloma and colorectal cancer	GLPG1205, PA101B, TXA127 (angiotensin 1–7) and BNC101
Complement peptide	C5AR1	Autoimmune diseases	CCX168
Free fatty acid	FFAR2	Neutrophil-driven inflammation and ulcerative colitis	GLPG0974
GPR18, GPR55 and GPR119	GPR55	Spasticity related to multiple sclerosis and epilepsy	VSN16R, cannabidiol (GWP42003) and cannabidivarin (GWP42006)
Ghrelin	GHSR	Appetite stimulant, antidiabetic, cancer cachexia, gastroparesis and digestive system disease	Unacylated ghrelin (AZP-531), anamorelin, macimorelin and ulimorelin
LPA	LPAR1	Pulmonary fibrosis	AM-152
Melanocortin	MC1R, MC3R and MC4R	Sexual dysfunction, anti-obesity and dermatological	Bremelanotide, RM-493 and afamelanotide
Motilin	MTLR	Gastroparesis	Camicinal
Prostanoid	PD2R2 (GPR44)	Asthma and allergic rhinitis	Fevipiprant and setipiprant
Relaxin	RXFP1 and RXFP2	Heart failure	Serelaxin
Tachykinin	NK3R	Polycystic ovarian syndrome	MLE-4901 and AZD4901
VIP and PACAP	VIPR1 and VIPR2	Sexual dysfunction and hypertension	Vasomera (PB1046) and vasoactive intestinal peptide

GPCR, G protein-coupled receptor; LPA, lysophosphatidic acid; PACAP, pituitary adenylate cyclase-activating peptide; VIP, vasoactive intestinal peptide. *Listed using the protein name in UniProt; for details on receptor nomenclature, see the IUPHAR/BPS Guide to PHARMACOLOGY (see Further information).

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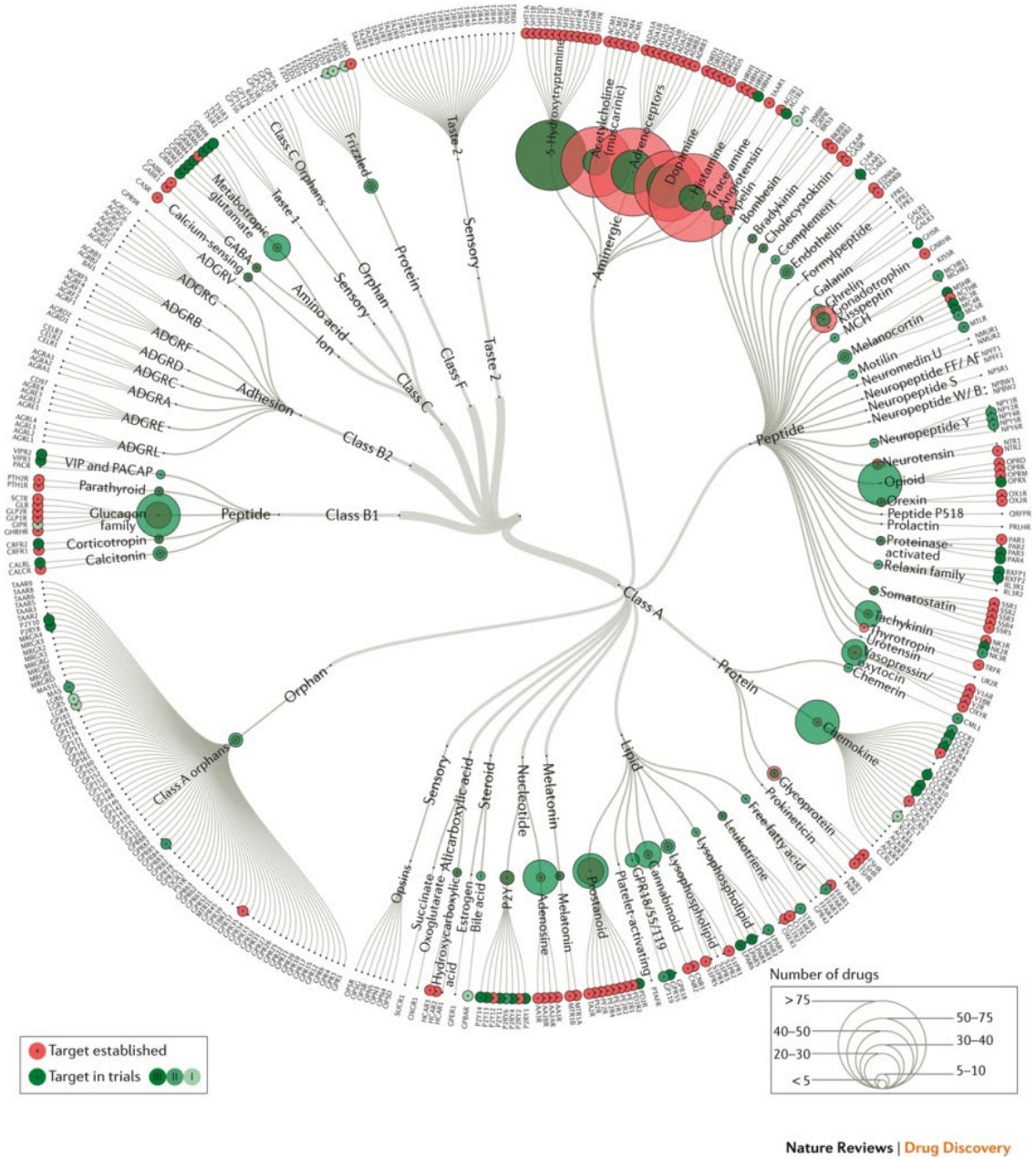

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