Université de Lille

FACULTE DE MEDECINE HENRI WAREMBOURG

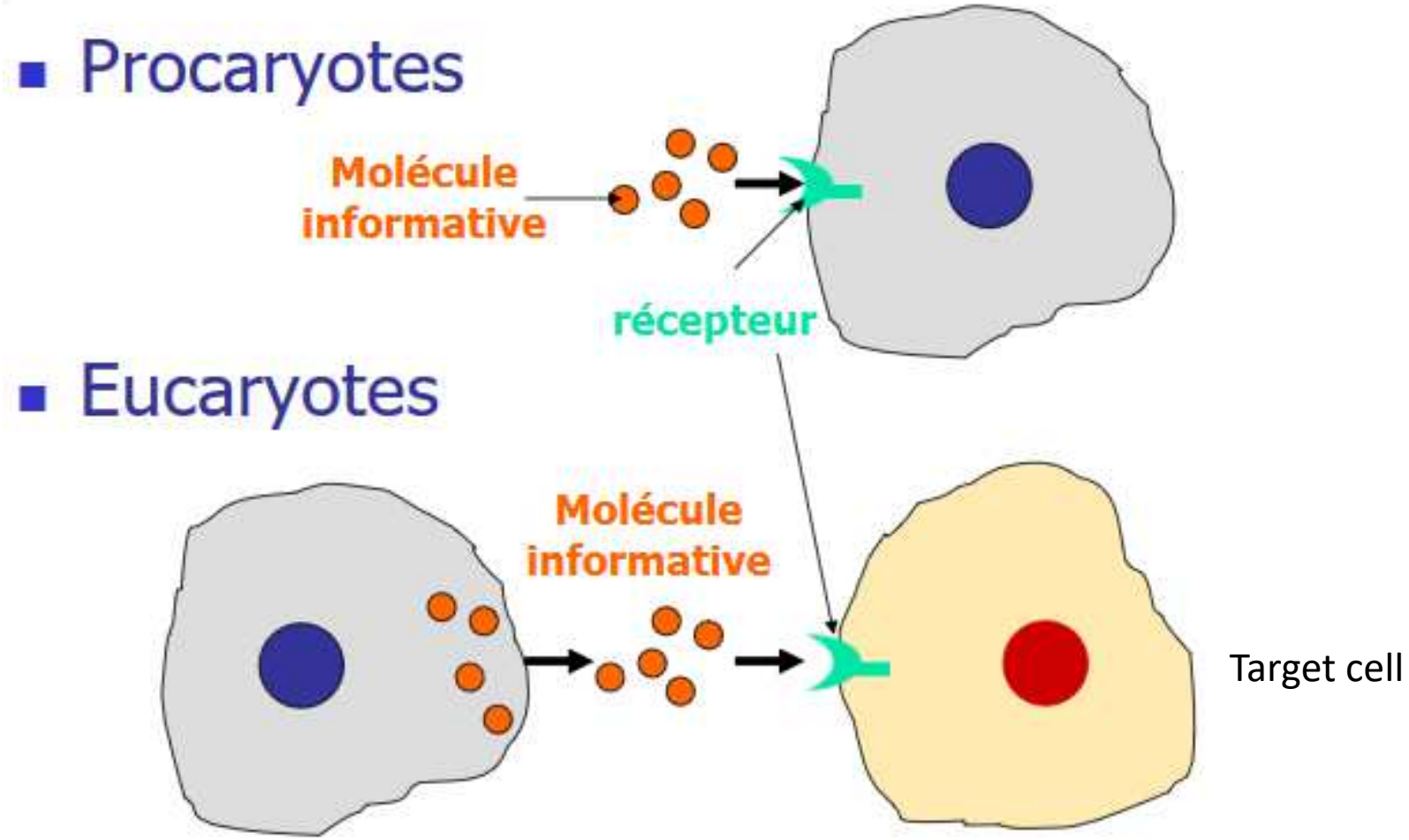
Receptor, ligand, signal transduction

Olivier PLUQUET

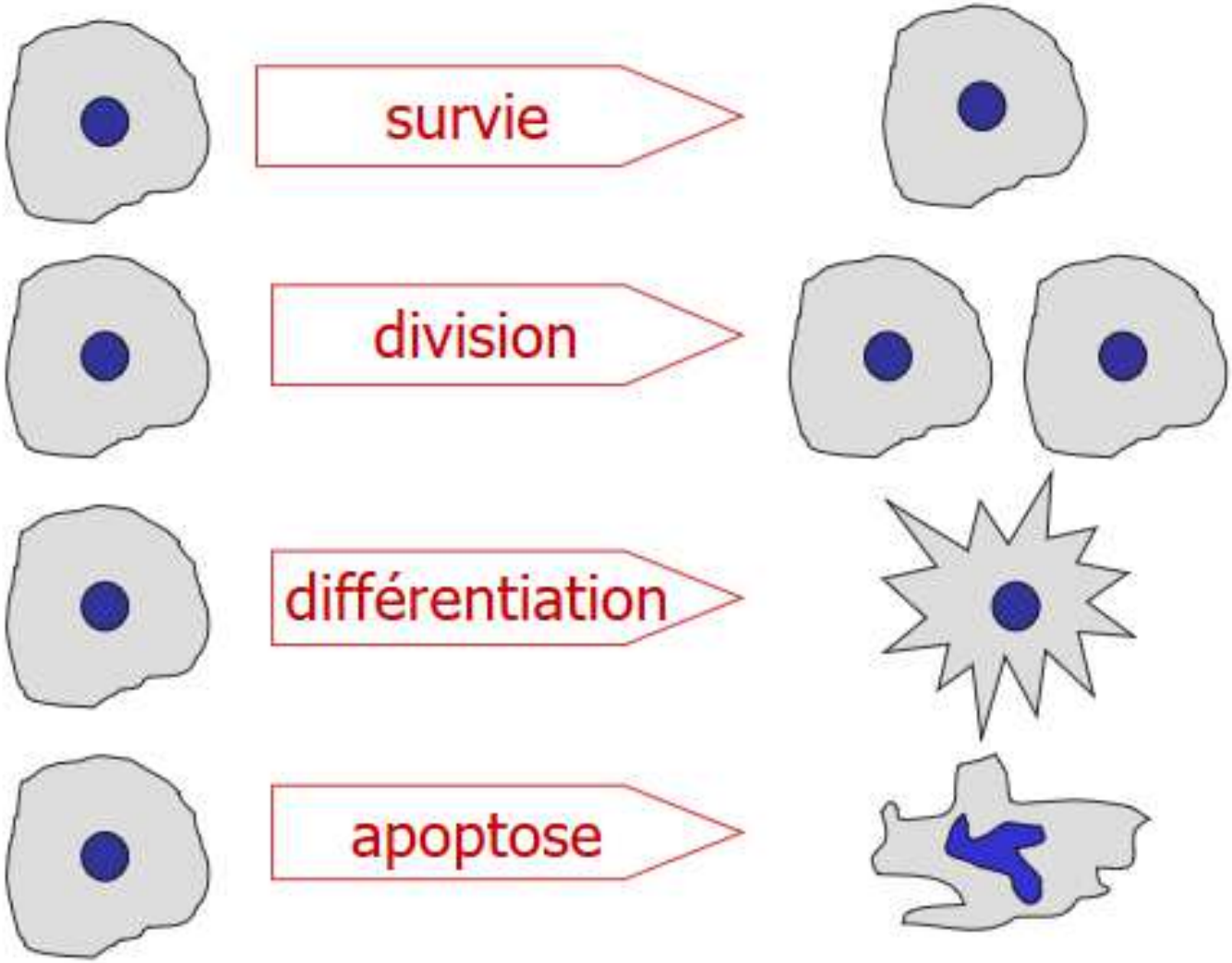
Master 1 MISO

19 janvier 2022

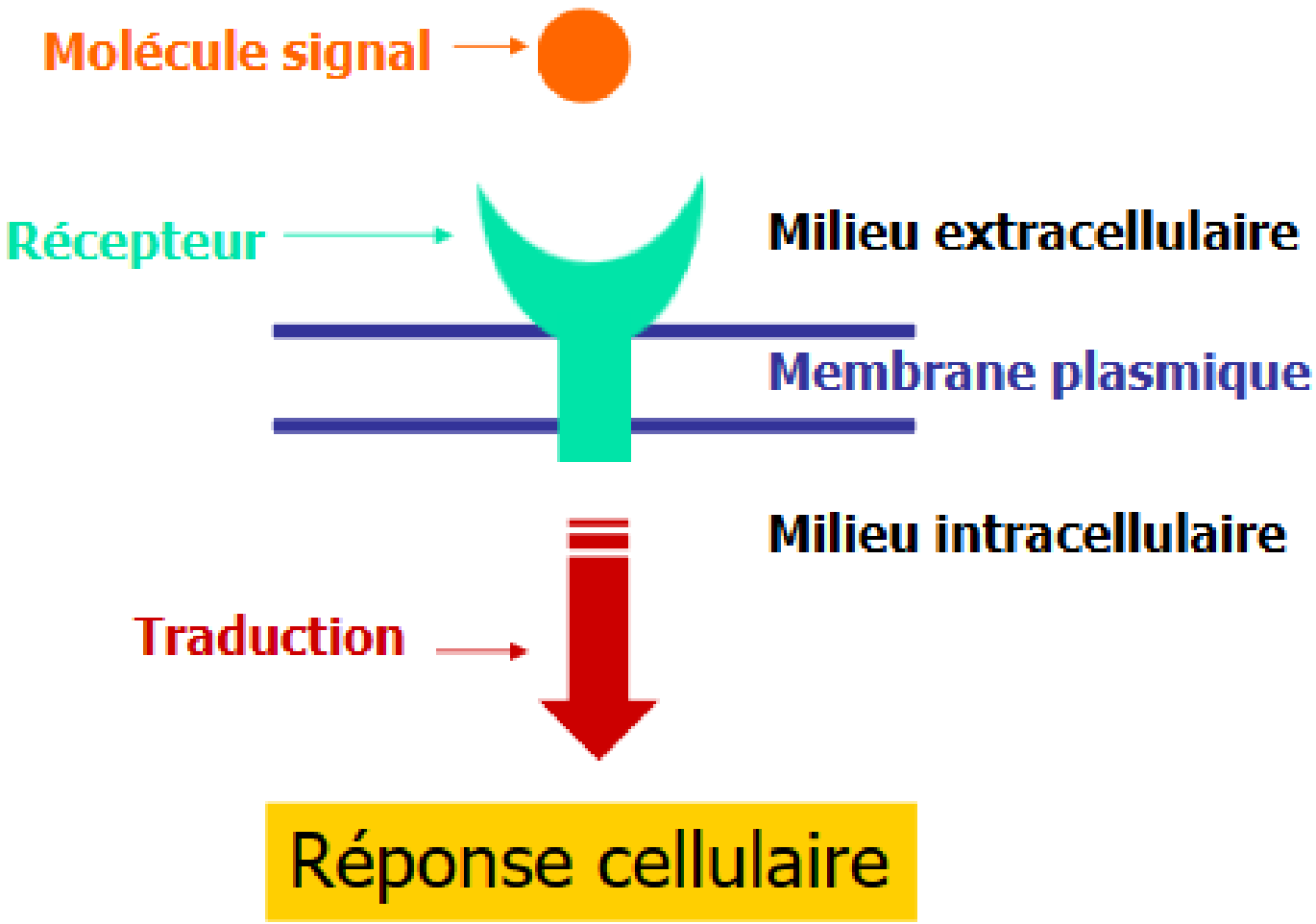
Communication between cells



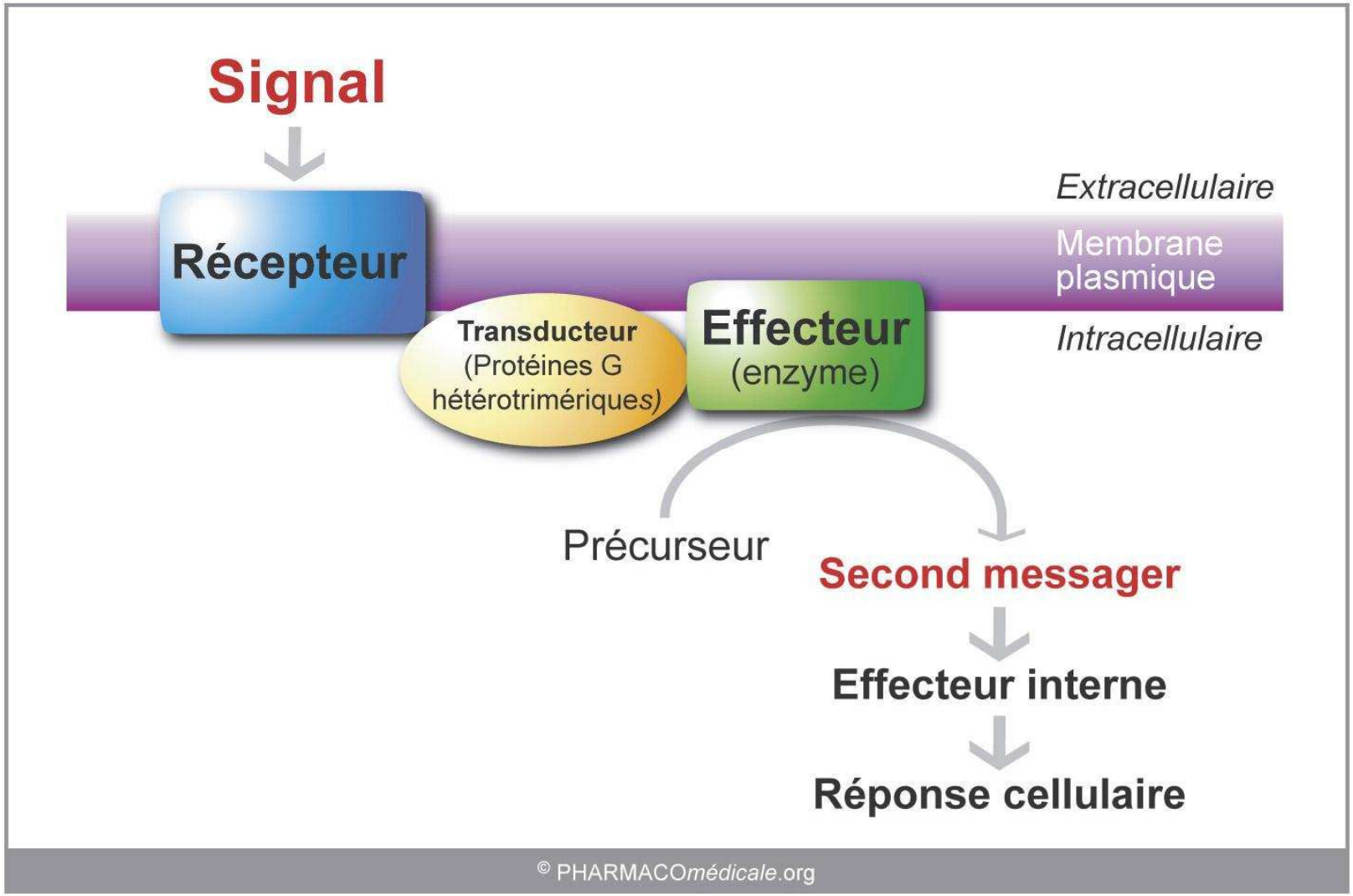
Communication, to do what ?



Basic signal transduction

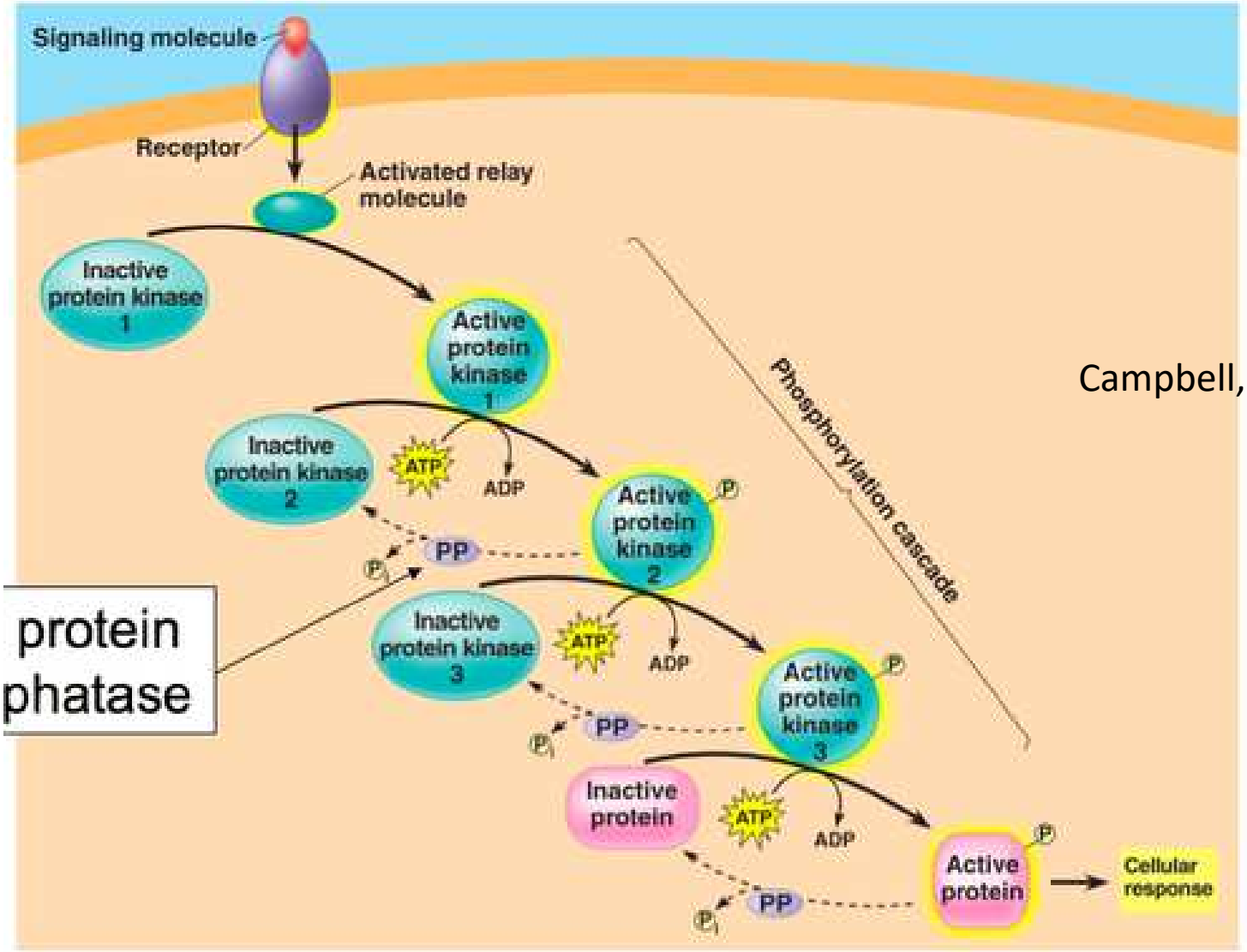


To go further…



https://www.youtube.com/watch?v=FtVb7r8aHco

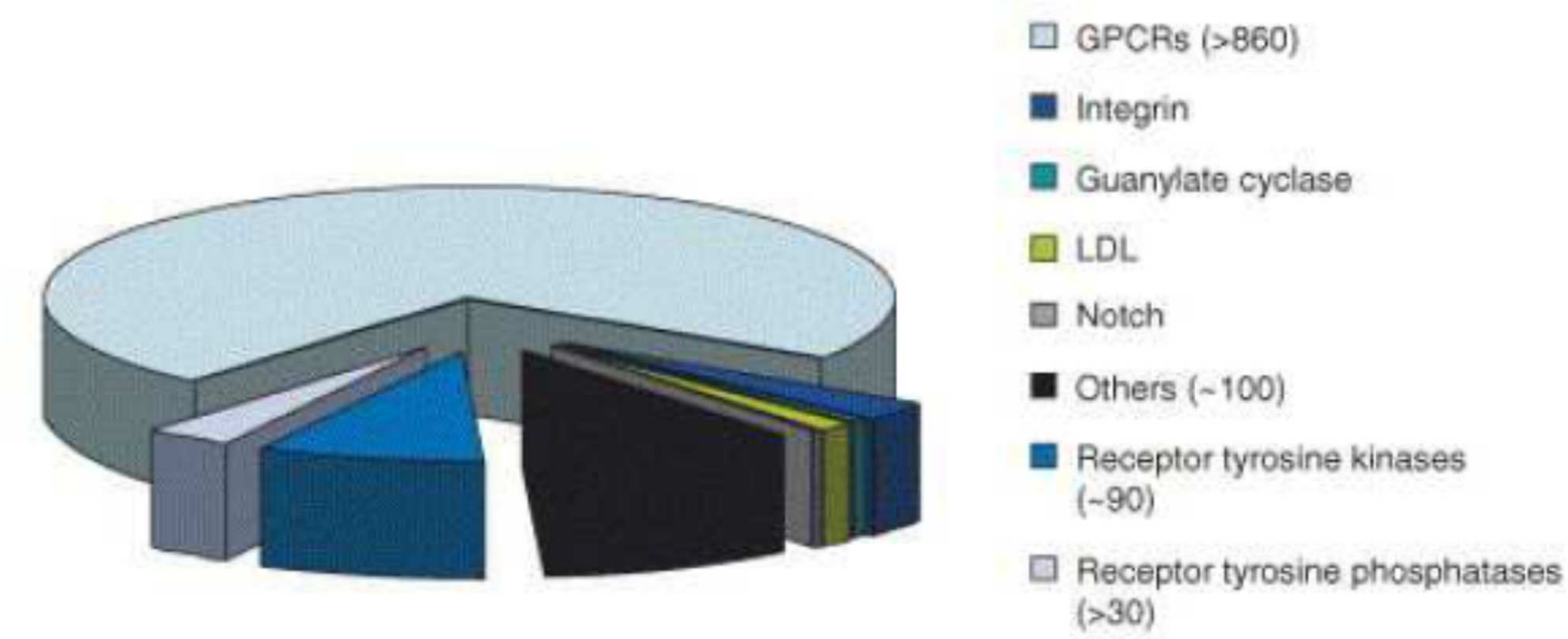
Concept of phosphorylation/dephosphorylation



Campbell, Biology

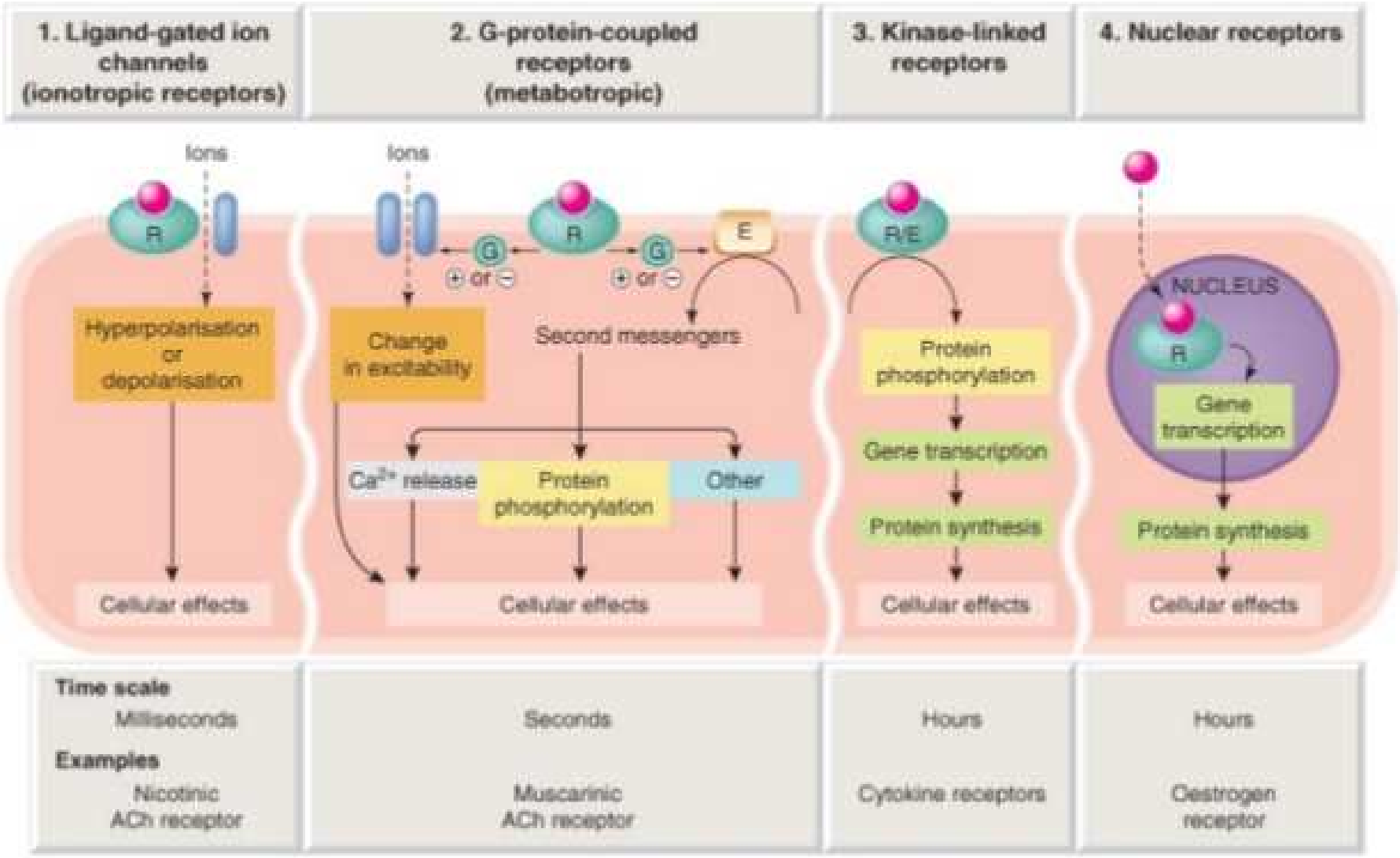
https://www.youtube.com/watch?v=xG2WOd_fWqo

The human receptorome

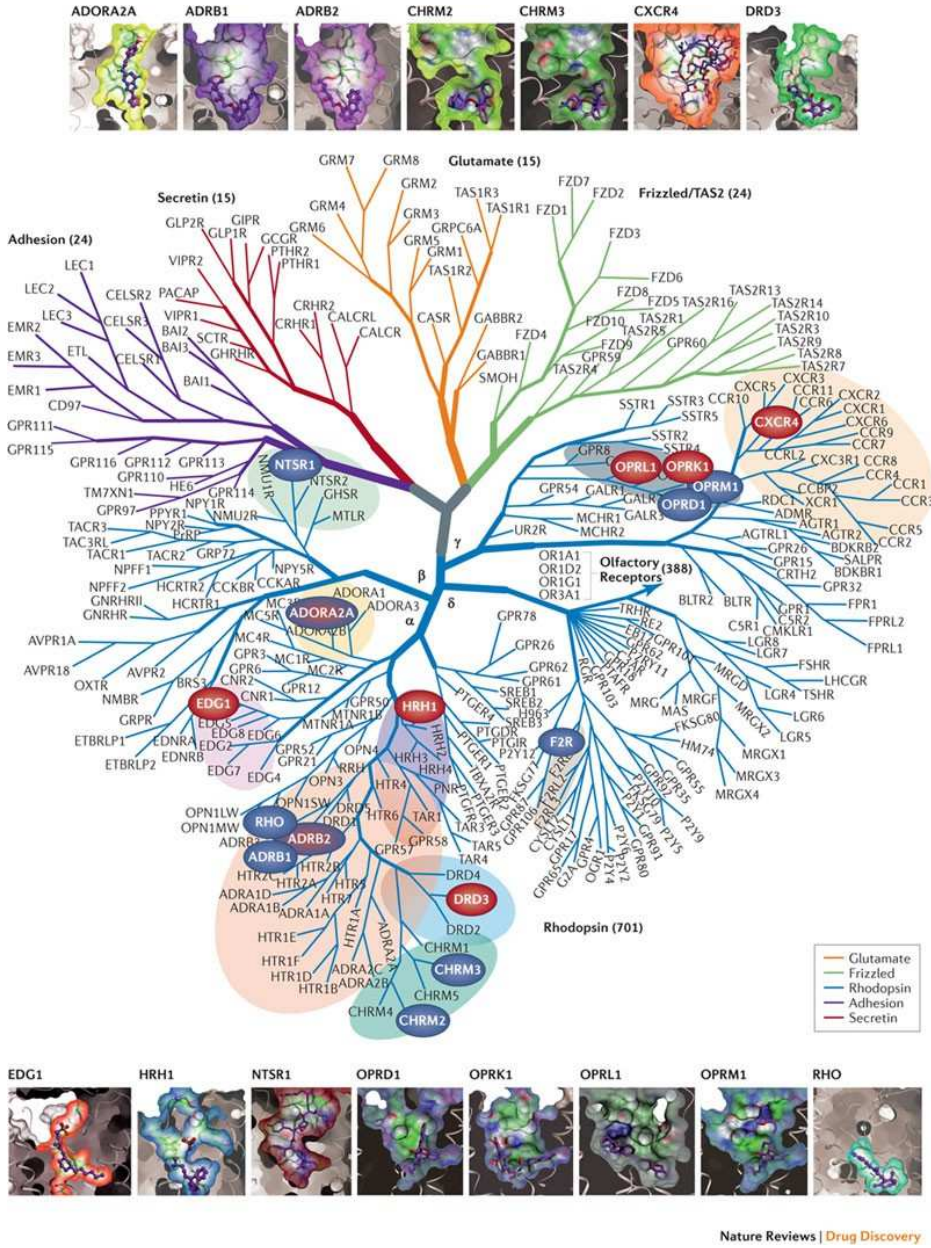


More than 1000 membrane receptors
More than 20 families
5% of the human genome

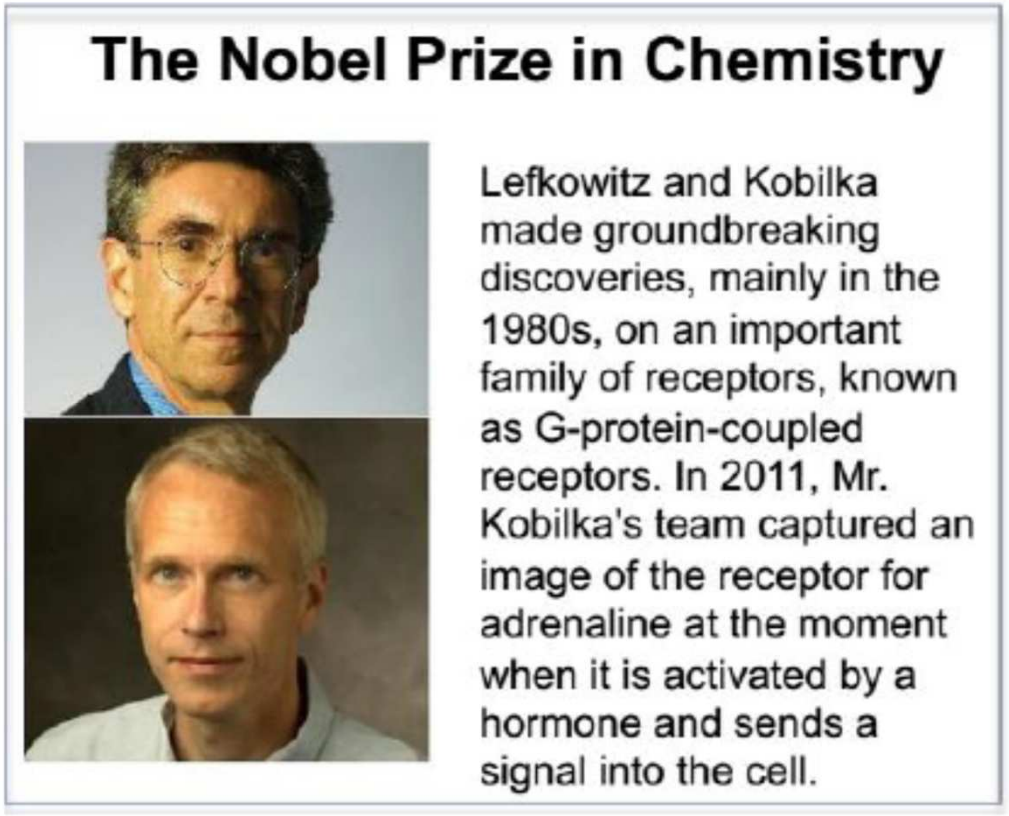
Classification



1-G protein coupled receptors

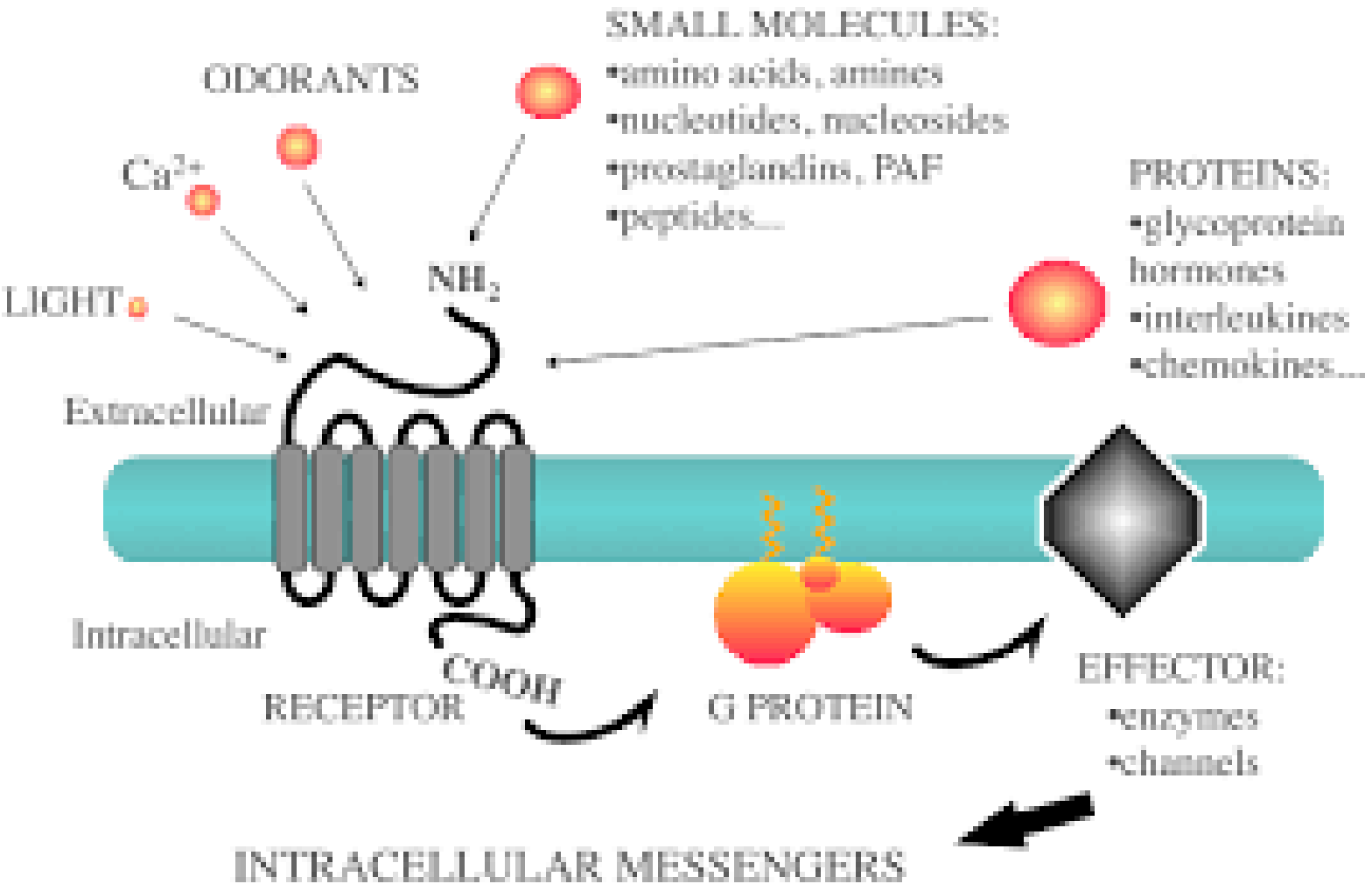


GPCR overview

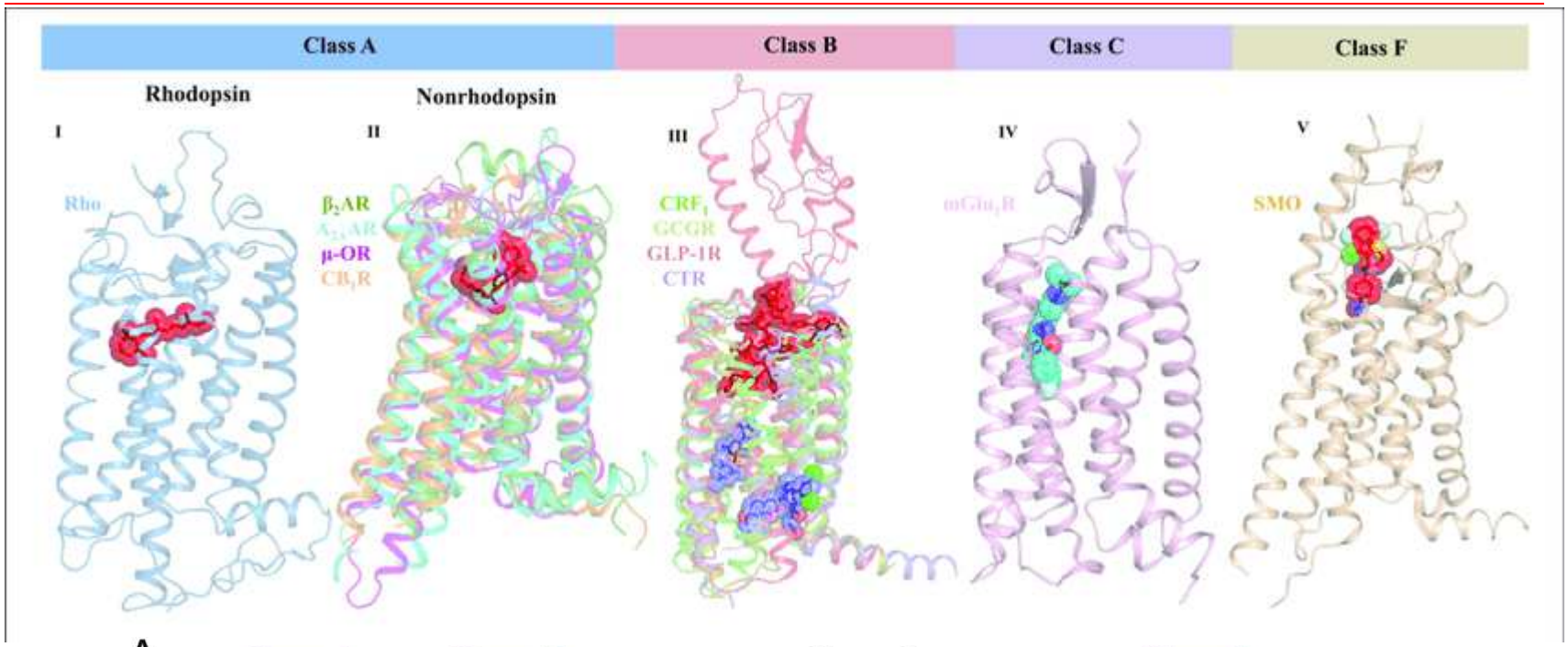


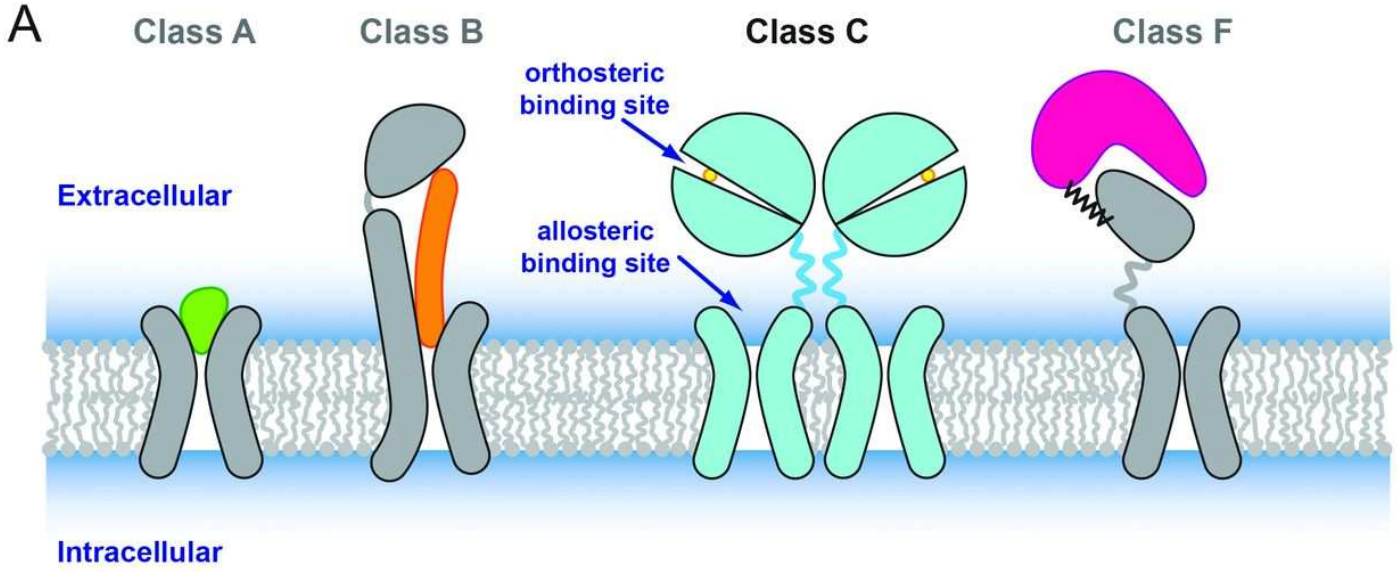
- Plus de 40% des agents pharmacologiques ciblent les RCPG
- Environ 1000 gènes codent les RCPG
- Les RCPG sont responsables de la plupart des réponse physiologiques
- Leur fonction est déréglée au cours du développement de pathologies

GPCR signal transduction



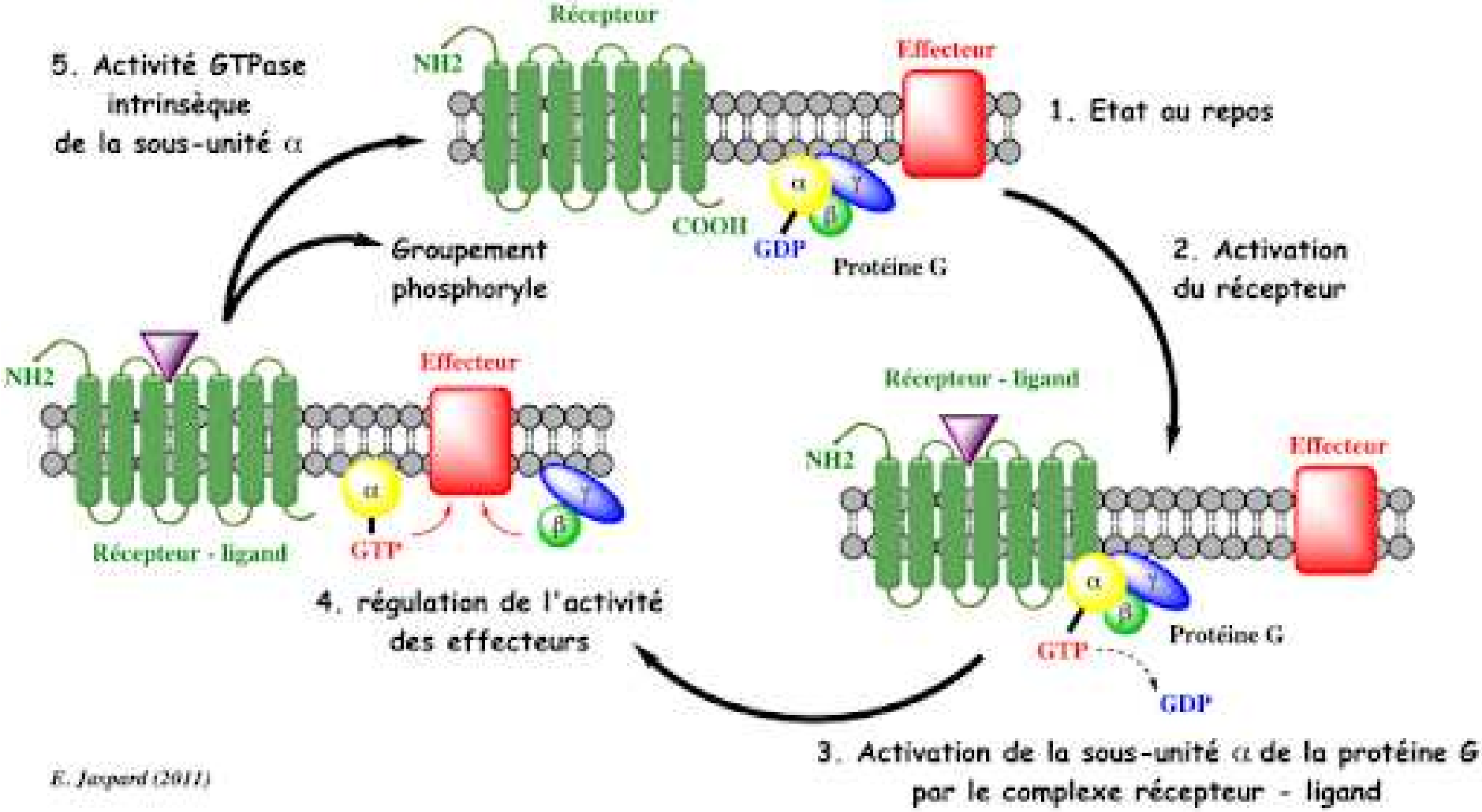
The G protein coupled receptor main families





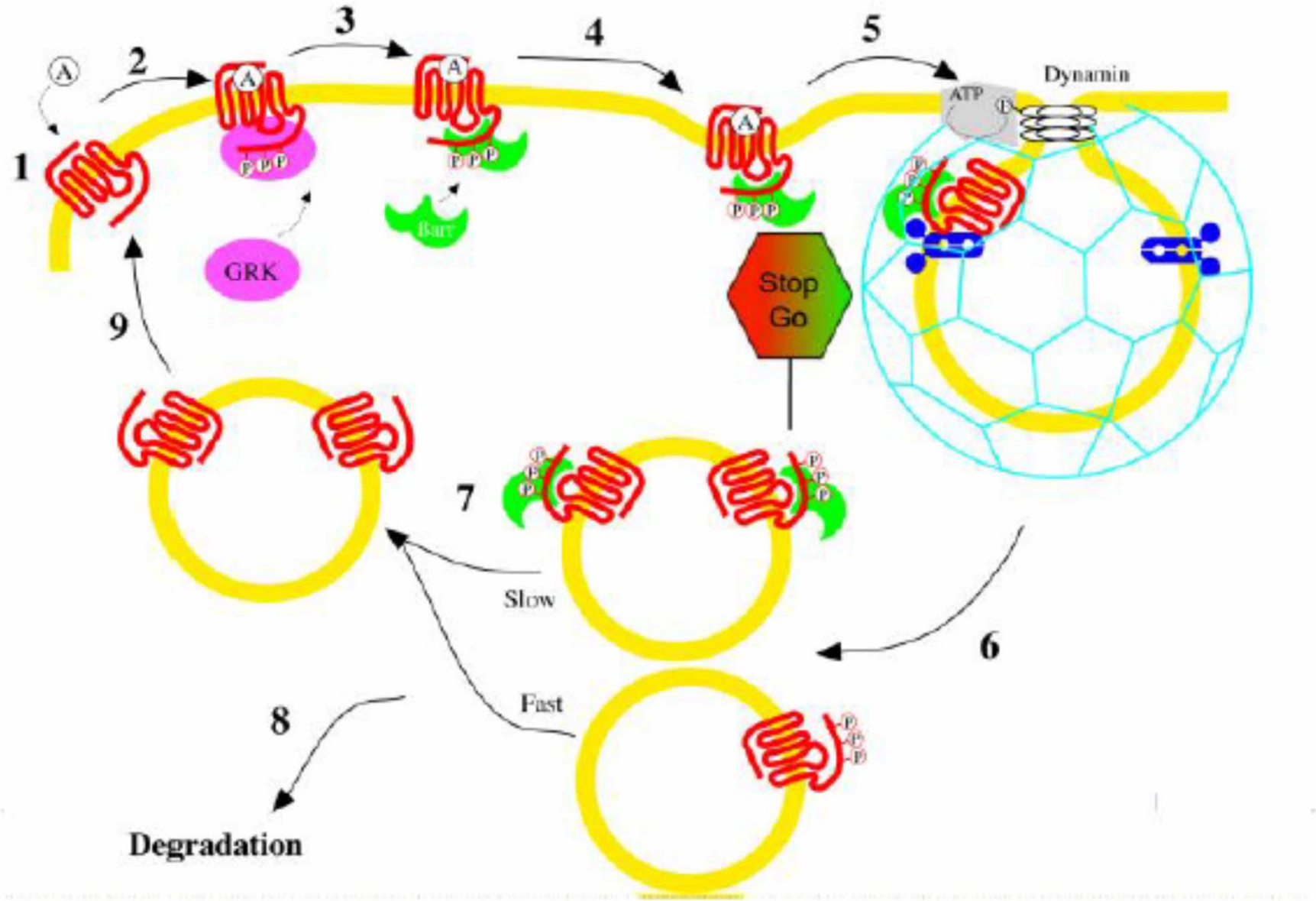
https://www.youtube.com/watch?v=lkEvLrlPj-U

Summary

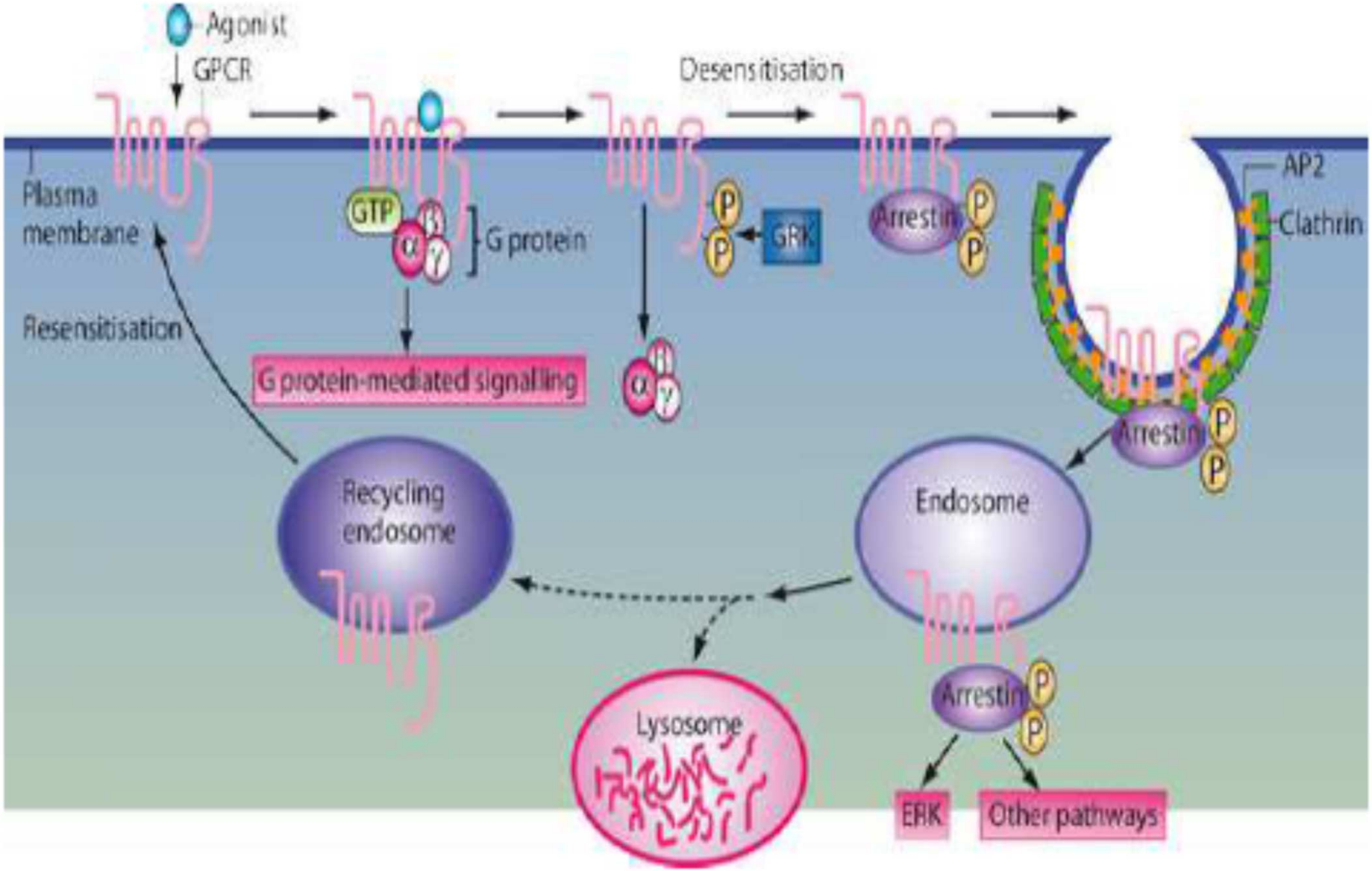


E. Jacquard (2011)

GPCR degradation



GPCR degradation (2)



Nature Reviews/Molecular Cell biology

Biological processes associated with RCPG activation

- ß-adrénergique R: contrôle du rythme cardiaque
- Angiotensine II R: contrôle de la pression artérielle
- Rhodopsin R: vision
- Dopamine R: comportement et contrôle de l'humeur
- Histamine R: contrôle de la réponse inflammatoire
- Acétylcholine R: contrôle de la transmission nerveuse
- Opioïd R: contrôle de la douleur
- Oxytocine R: contrôle de la contraction de l'utérus
- Etc…..

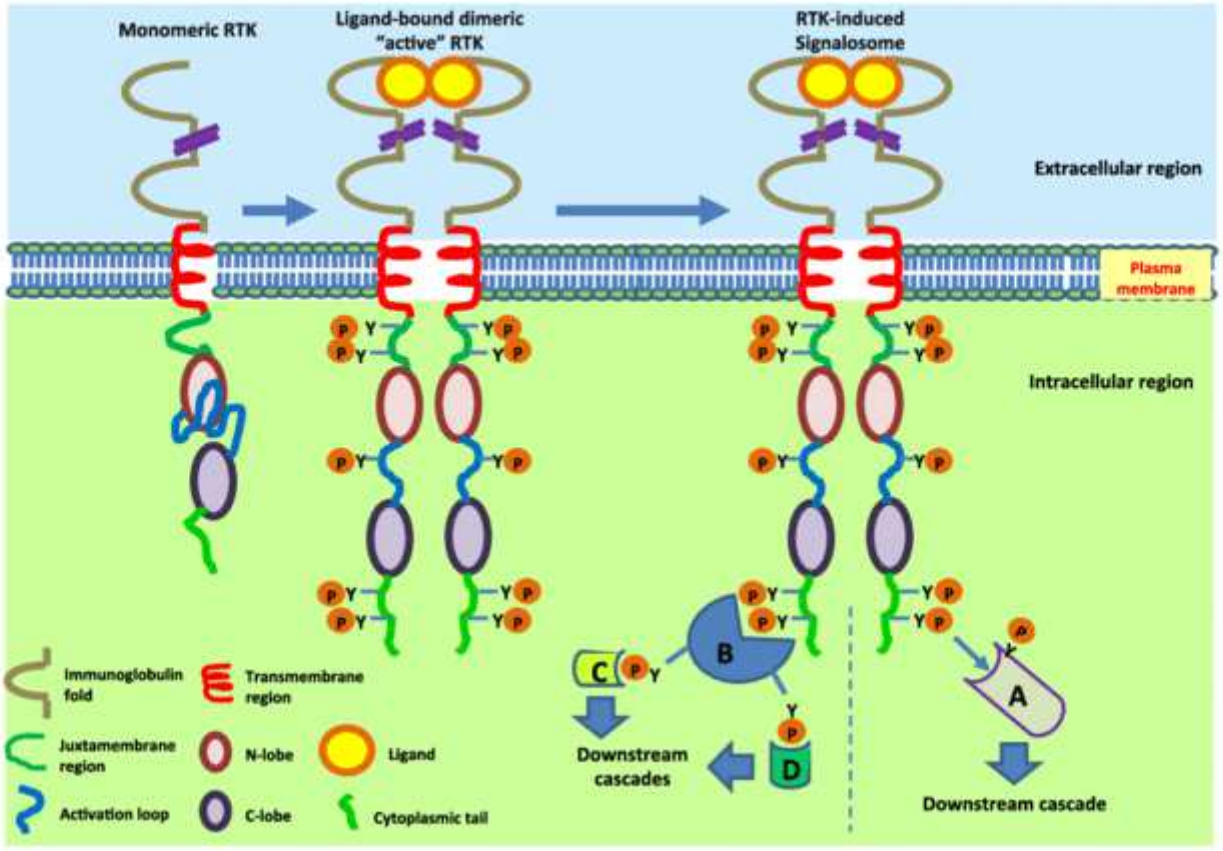
GPCR and human pathologies

Receptor/Gene name	Mutation	Disease
Calcium-Sensing (CaS)/CaSR	Multiple (e.g., Arg185Gln)	Autosomal Dominant Hypocalcemia (ADH)
		Sporadic Hypoparathyroidism
		Familial Hypoparathyroidism
CXCR4	Multiple (e.g., Ser338X)	WHIM syndrome
Endothelin receptor B (ET_B)/EDNRB	Multiple (e.g., Trp276Cys)	Hirschsprung's disease
Follicle-stimulating hormone (FSH)/FSHR	Multiple (e.g., Ala189Val)	Female infertility
N-formyl-peptide (FPR)/FPR1	Phe110Ser, Cys126Trp	Juvenile periodontitis
Frizzled (FZD_4)/FZD4	Multiple (e.g., Arg417Gln)	Familial exudative vitreoretinopathy (FEVR)
Goandotropin-releasing hormone (GnRH)/GNRHR	Multiple (e.g., Arg262Gln)	Hypogonadotropic hypogonadism (HH)
GPR54/GPR54	Multiple (e.g., Cys223Arg)	Hypogonadotropic hypogonadism (HH)
GPR56/GPR56	Multiple (e.g., Cys223Arg)	Bilateral frontoparietal polymicrogyria (BFPP)
vGPCR/KSHV-GPCR	(constitutively active)	Kaposi's sarcoma (KS)
Relaxin family peptide receptor 2 (RXFP2)/LGR8	Multiple (e.g., Thr222Pro)	Cryptorchidism
MASS1 (also called VLGR1, USH2C)/MASS1	Multiple (e.g., Ser2652X))	Usher syndrome Febrile seizures (FS)
Melanocortin (MC_4)/MC4R	Multiple (e.g., Pro78Leu)	Dominant and recessive obesity
Rhodopsin/RHO	Multiple (e.g., Pro23His)	Retinitis pigmentosa (RP)
Vasopressin receptor (V_2)/AVPR2	Multiple (e.g., Arg113Trp)	Nephrogenic diabetes insipidus (NDI)

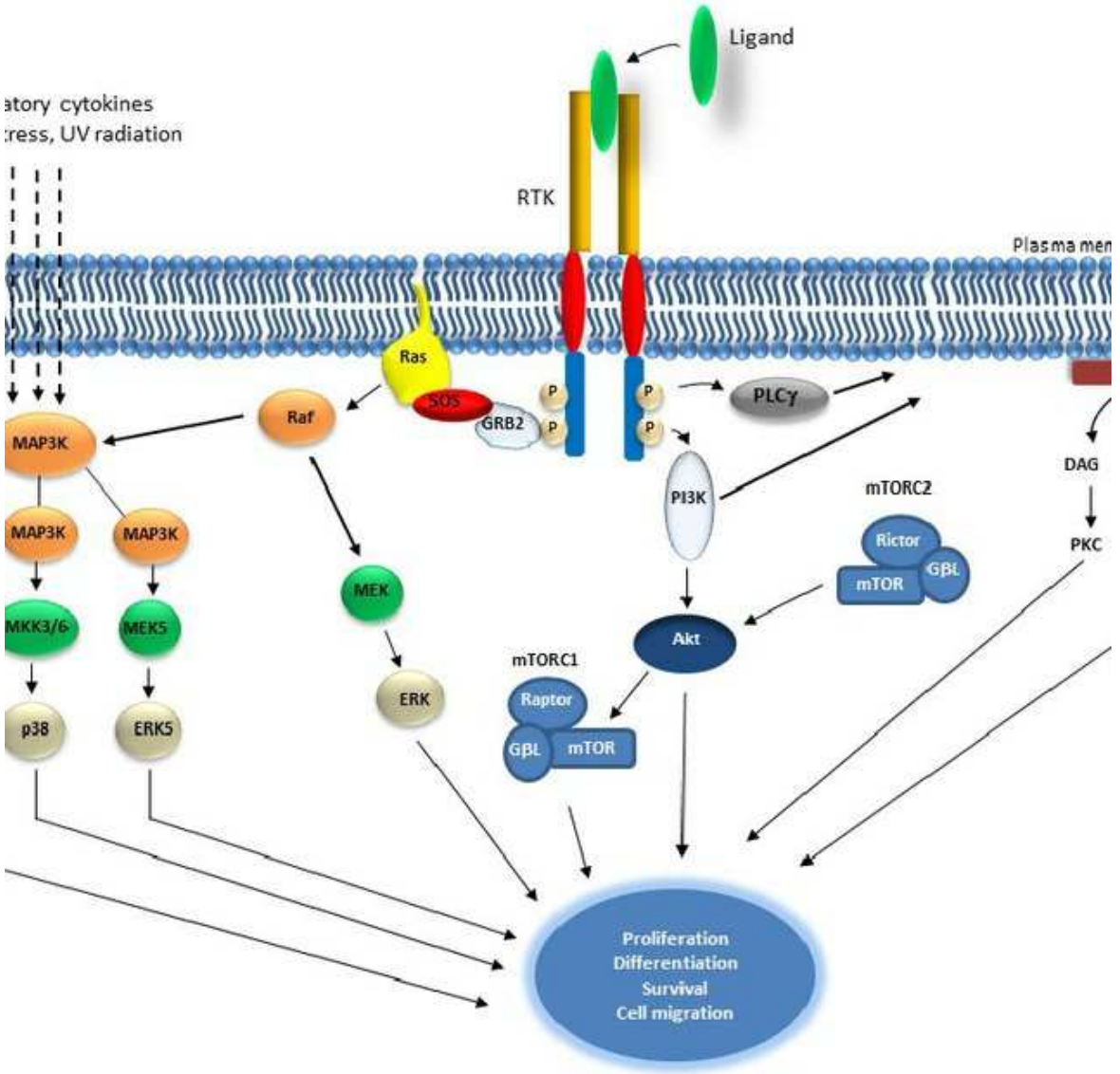
GPCR and human pathologies

Receptor	Polymorphisms	Examples of disease associations
β_1 Adrenergic receptor	Arg389Gly	Heart failure
β_2 Adrenergic receptor	Multiple	Hypertension, Asthma
β_3 Adrenergic receptor	Trp64Arg	Obesity
CC chemokine receptor 2 (CCR2)	Val64Ile	Delayed progression of AIDS
CC chemokine receptor 5 (CCR5)	Multiple	Associated with progression of AIDS
Dopamine receptor 2 (D_2)	3'UTR52A/G	Associated with depression and anxiety
Dopamine receptor 3 (D_3)	Ser9Gly, Promoter SNPs	Haplotype associated with schizophrenia
Muscarinic receptor subtype 3 (M_3)	Promoter haplotype	Possible association with asthma and atopy
Neuropeptide S receptor	Haplotypes H1, H5	
(NPSR; also called GPR154, GPRA)	Asn107Ile, rs324981	Asthma susceptibility
$P2Y_{12}$	CA deletion at Codon 240	Associated with bleeding diathesis

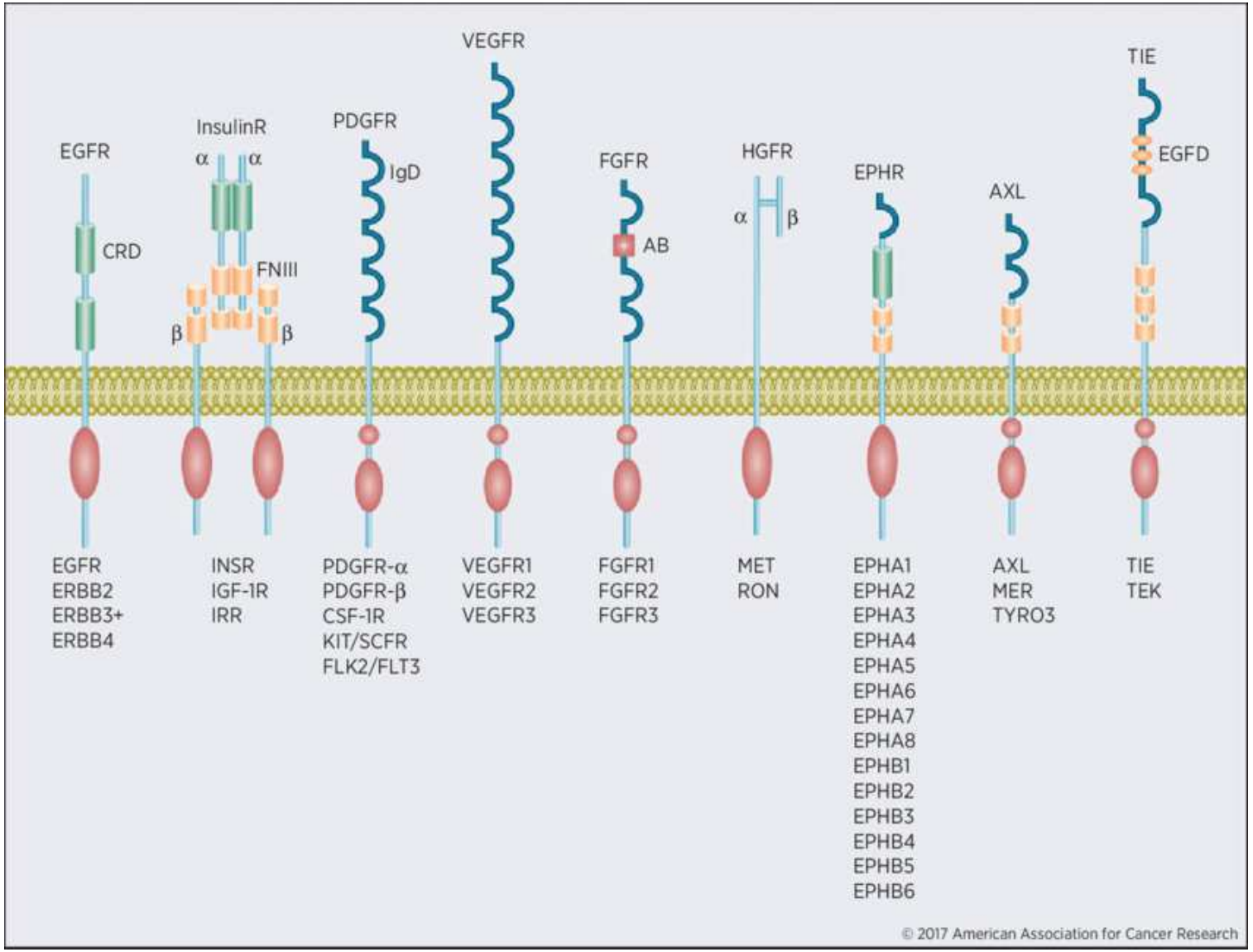
2-Receptor tyrosine kinases



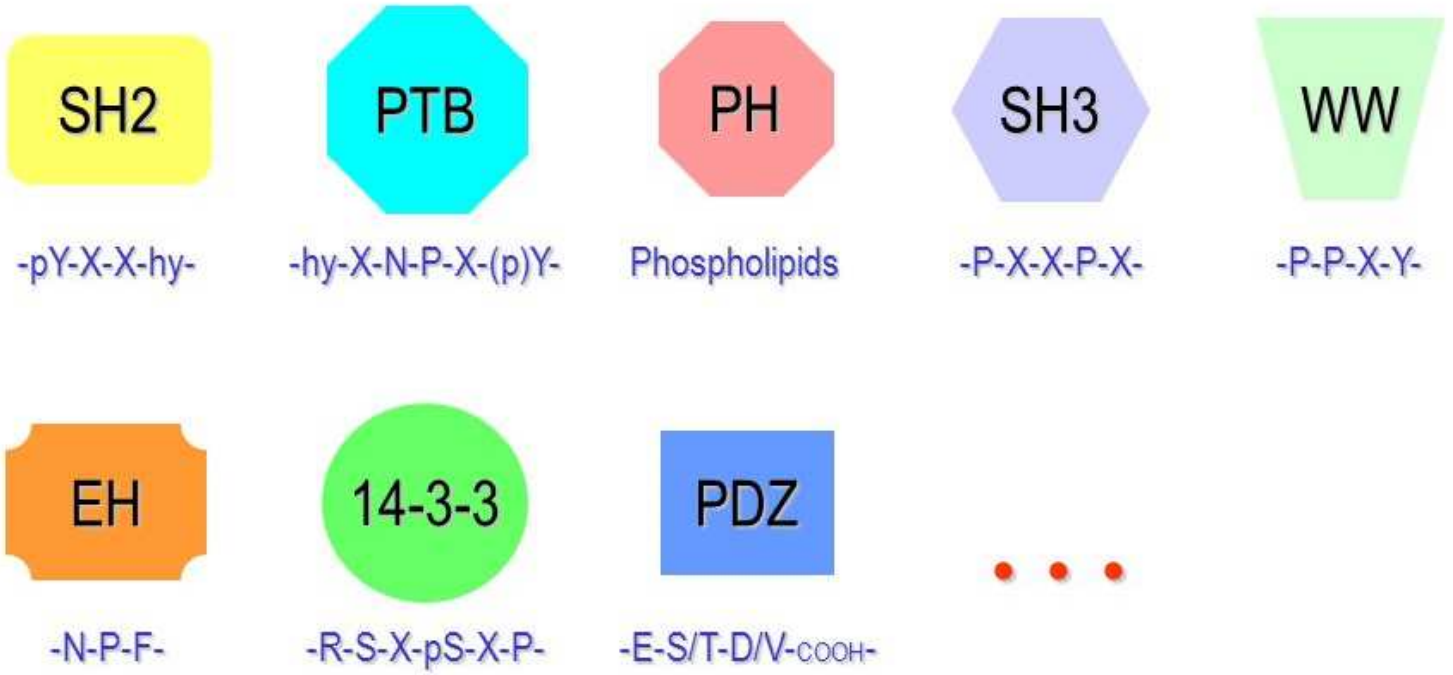
RTK signaling



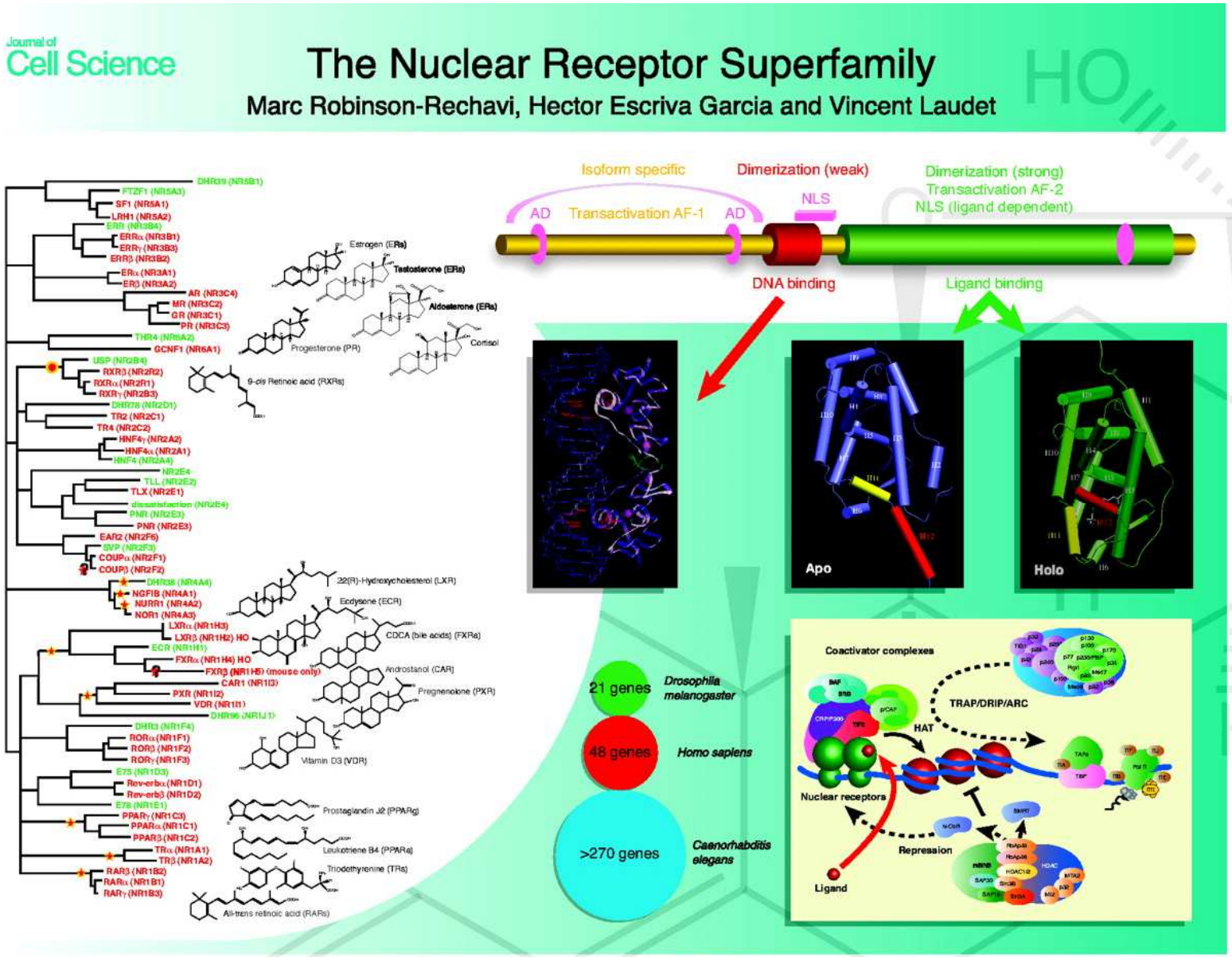
RTK families



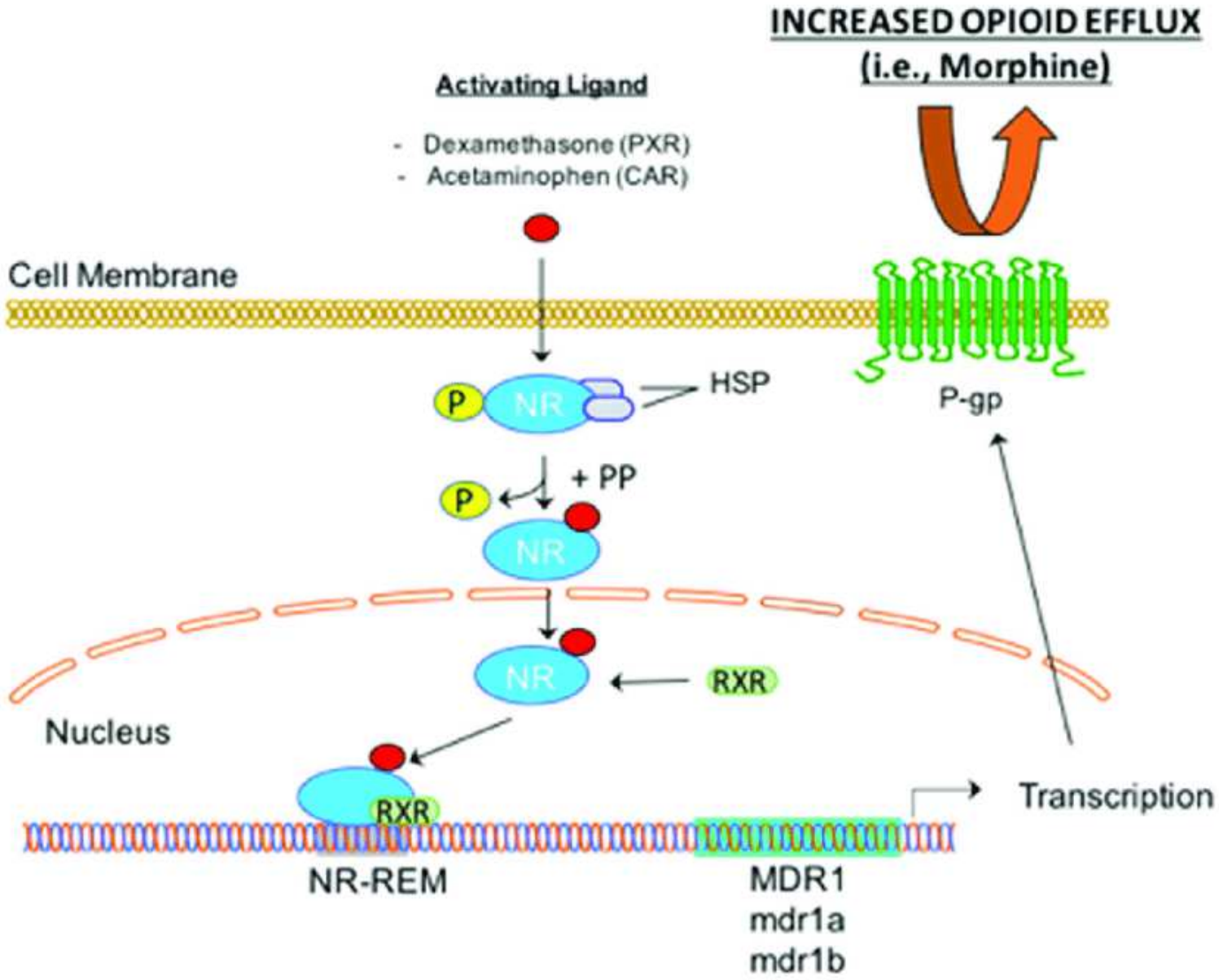
Proteins domains in cell signal transduction



3-Nuclear receptors



Nuclear receptor signaling



Nuclear receptor and human pathologies

Orphan Nuclear Receptor (ONR)	NRNC[a] symbol	Disease association	Possible interventions	
			Agonist	Antagonist
Pregnane X Receptor (PXR)	NR1I2	(1) Colon, breast and ovarian cancer (91, 93, 94) (2) Drug- drug interactions (91, 92) (3) Alcoholic and non-alcoholic hepatosis (101) (4) Acetaminophen-induced hepatotoxicity (103, 104) (5) Osteomalacia (102)		Ketoconazole, Suphoraphane, ET-743, Coumesterol
		(6) Intestinal inflammation (109) (7) Osteoporosis (106) (8) Bile-acid-induced cholestasis (99)	Rifampicin PCN, PB, SR12813	
Constitutive Androstane Receptor (CAR)	NR1I3 (α), NR1I4 (β)	(1) Liver cancer (125)		Clotrimazole, Androstenol
		(2) Hyperthyroidism (126) (3) Obesity (127) (4) Metabolic disorders (128-130)	PB, TCPOBOP	
Farnesoid X Receptor (FXR)	NR1H4	(1) Hypertriglyceridemia (153) (2) Cholesterol gall stone disease (151) (3) Colon and breast cancer (158, 159)	Chenodeoxycholic acid, 1,1-bisphosphonate esters, GW4064	
		(4) Hypo-HDL cholesterolemia (152)		Guggulsterone
Liver X Receptor (LXR)	NR1H3 (α), NR1H2 (β)	(1) Atherosclerosis (138-140) (2) Inflammation (145, 146) (3) Prostate, breast and colon cancer (142-144) (4) Cholesterol- related neurodegenerative disorders (148)	Oxysterol, 22(R)-hydroxycholesterol, GW3965	
		(5) Hepatic lipogenesis (136, 137)		Fenofibrate esters

Récepteurs nucléaires et pathologie humaine

erte et caractérisation des **récepteurs stéroïdiens** :
rès décisifs dans les domaines clinique et thérapeutique

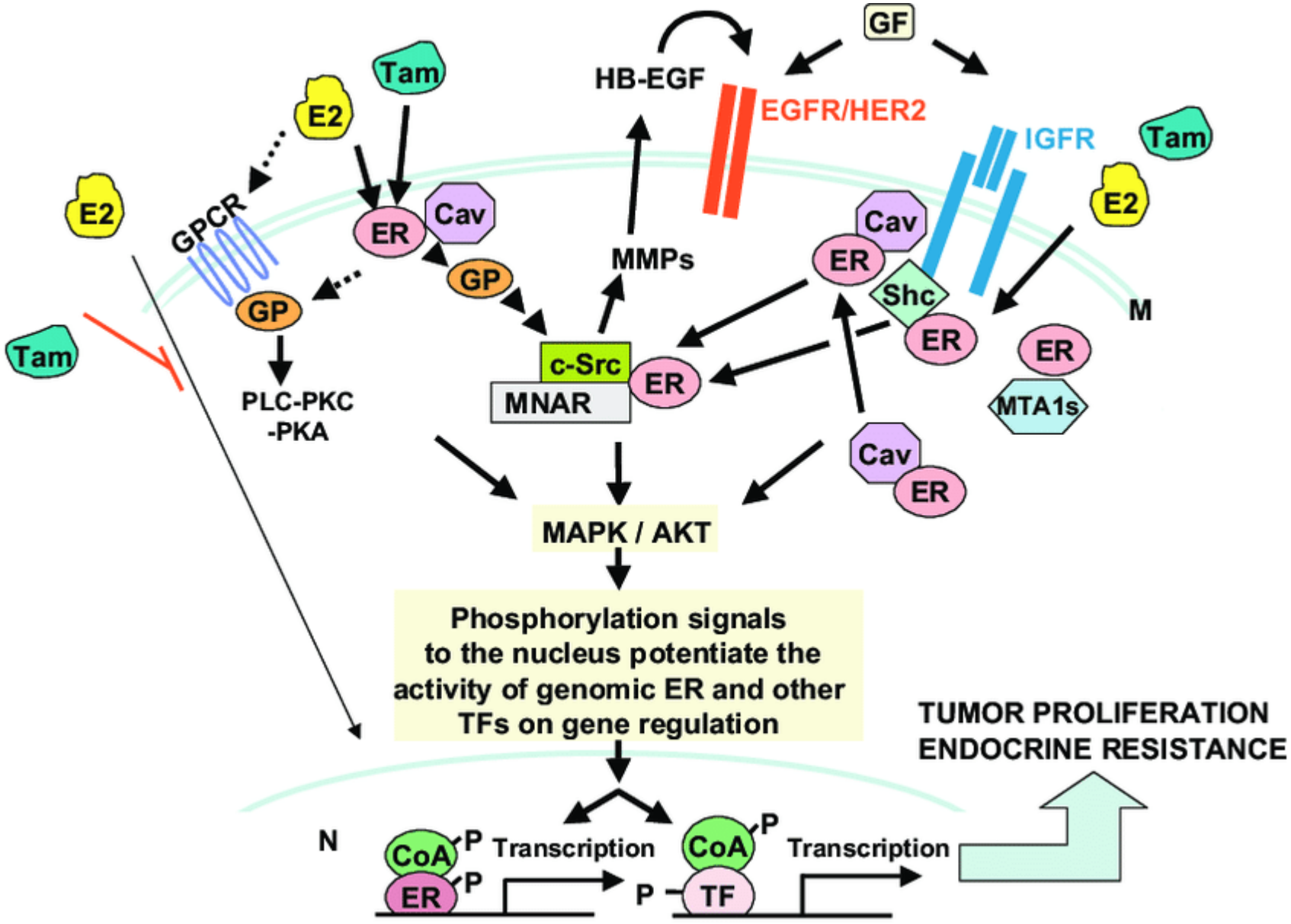
ugmentation de la diversité des récepteurs et des ligands

rogrès diagnostiques avec mise en évidence de mutations es récepteurs

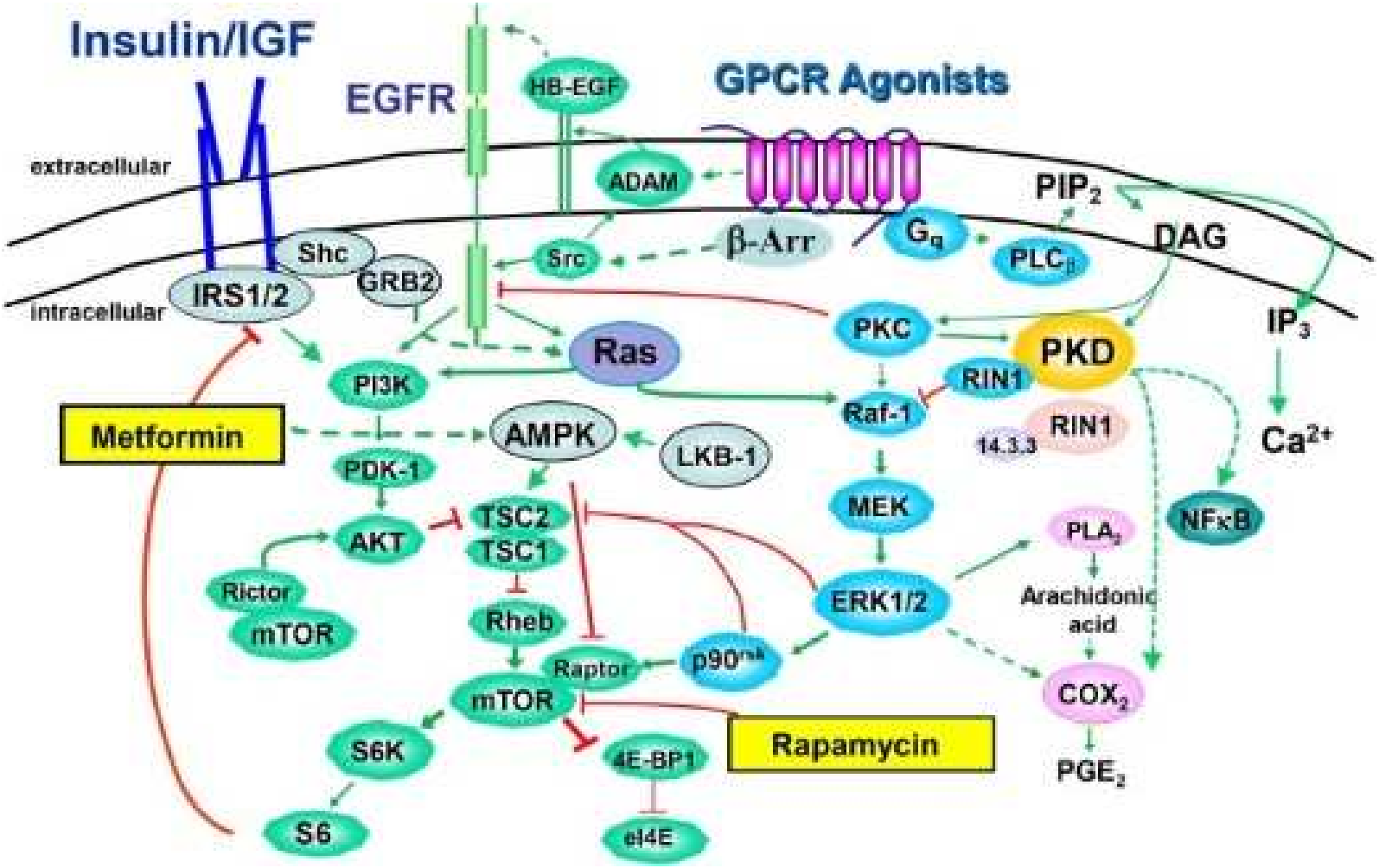
mergence d'une nouvelle classe de médicaments : les **antihormones »**

rogrès **pronostiques** dans le domaine du **cancer**

4-Crosstalk between receptors signaling



Crosstalk between receptors signaling



Contact: olivier.pluquet2@univ-lille.fr