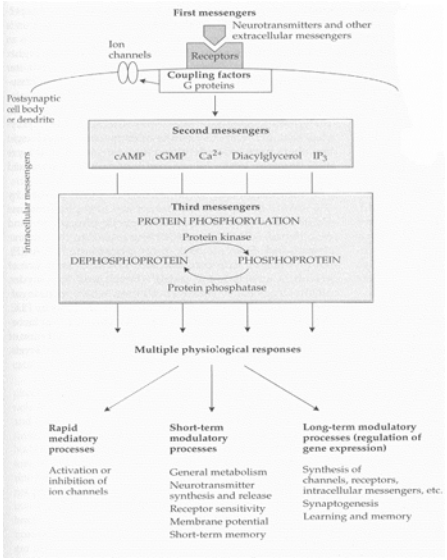
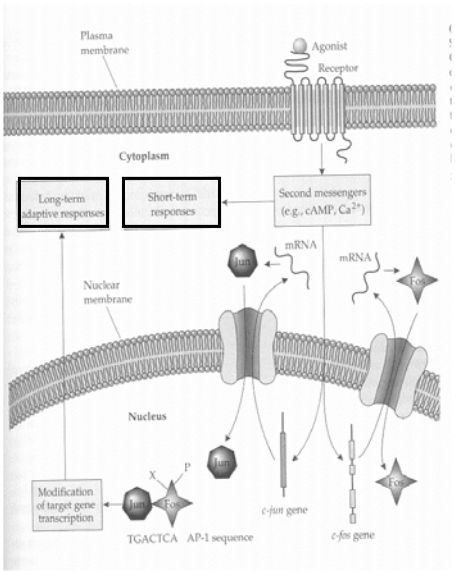
Pharmacologie spéciale FARM 2146 - MP Mingeot

- Cibles pharmacologiques
- Transmission de l'information

2004-2005

TRANSDUCTION DU SIGNAL - MESSAGERS INTRACELULAIRES

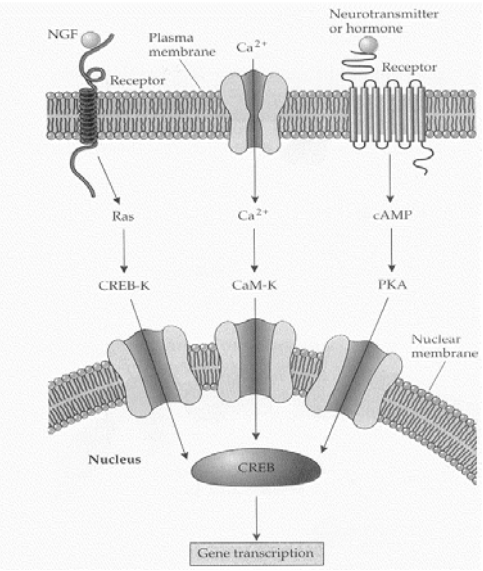


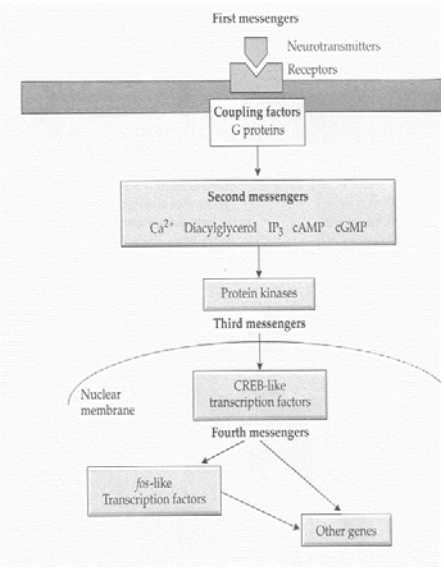


From Principles of neuropsychopharmacology, 1997; pp213, 225

2004-2005

TRANSDUCTION DU SIGNAL
LONG TERME ADAPTIVE RESPONSE

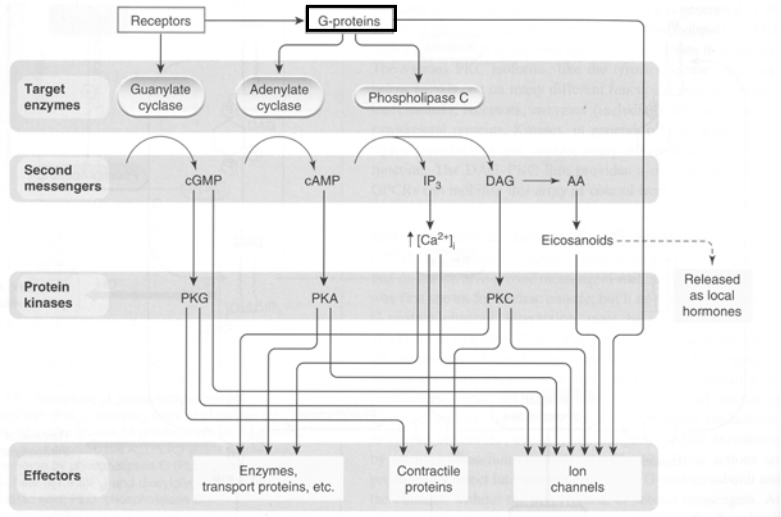




From Principles of neuropsychopharmacology; 1997; pp224, 226

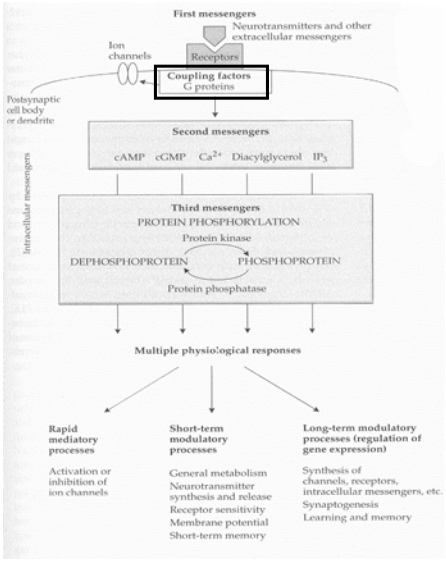
2004-2005

TRANSDUCTION DU SIGNAL
COUPLAGE AUX PROTEINES G



2004-2005

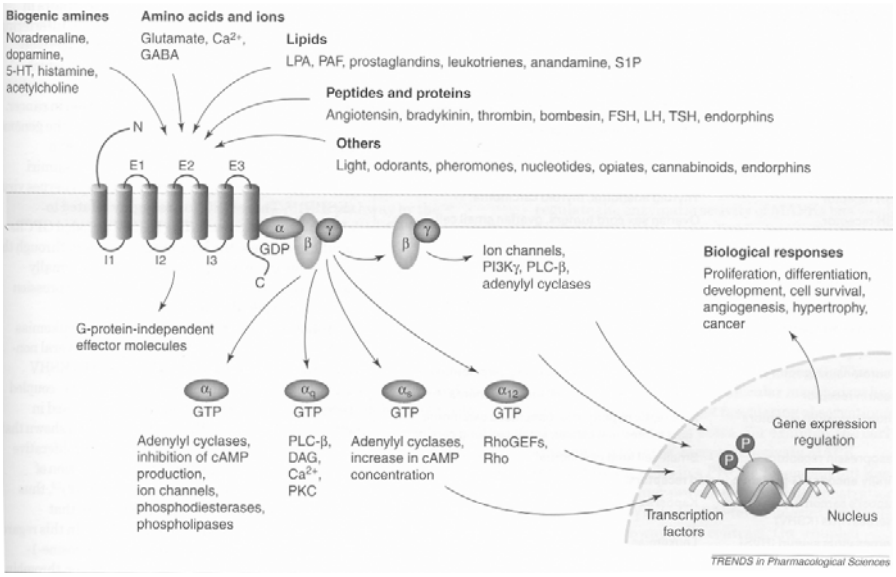
TRANSDUCTION DU SIGNAL COUPLAGE AUX PROTEINES G



From Principles of neuropsychopharmacology, 1997; pp213, 225

2004-2005

G-PROTEIN-COUPLED RECEPTORS DIVERSITY



Marinissen and Gutkind 2001, 22: 368-376

2004-2005

TRANSDUCTION DU SIGNAL COUPLAGE AUX PROTEINES G

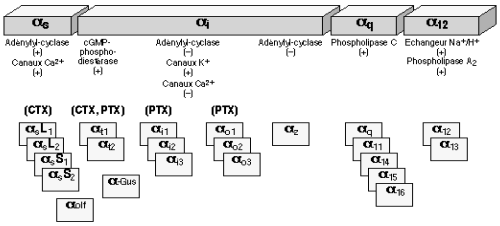
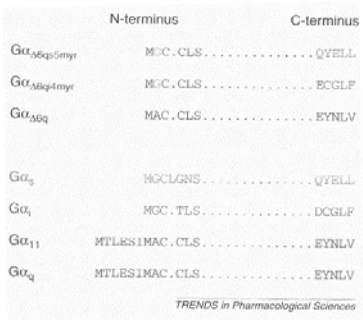


Table 6.2 G Proteins Involved in Neurotransmission

G protein	Second messenger action	Toxin sensitivity
G_s	↑Adenylyl cyclase	Cholera
G_i	↓Adenylyl cyclase	Pertussis
G_q	↑Phospholipase C	—
G_{olf}	↑Adenylyl cyclase (olfactory)	Cholera
G_t	↑cGMP phosphodiesterase (retina)	Cholera, pertussis
G_o	None	Pertussis



2004-2005

TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G

Adenylate cyclase - isoforms

Table 1. Mammalian isforms of adenylate cyclase

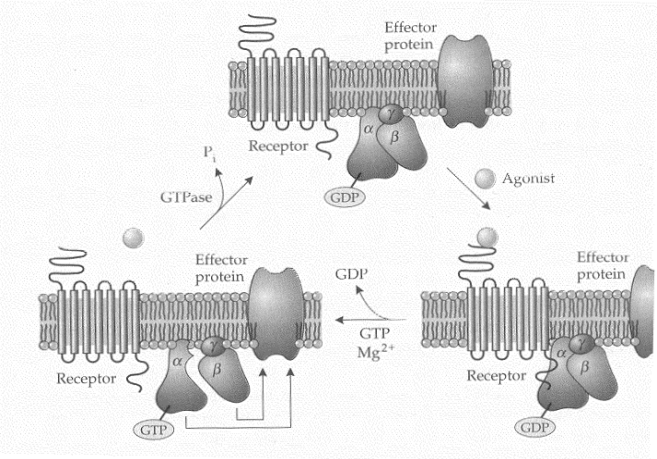
Adenylate cyclase (AC) type	Size (no. of amino acids)	mRNA expression
AC1	1134	Brain, retina, adrenal medulla
AC2	1090	Brain, olfactory bulb > lung
AC3	1144	Olfactory neurones, brain, retina, aorta, lung, testis
AC4	1064	Kidney, brain, heart, liver, lung
AC5	1184	Heart > brain > kidney
AC6	1165	Heart, brain > kidney, testis, spleen, liver
AC7	1099	Lung, heart, spleen, kidney, brain
AC8	1248	Brain[a]
AC9	1353	Skeletal muscle, brain > kidney lung, liver, heart

Simmonds 1999 TiPS 20: 66-73

2004-2005

TRANSDUCTION DU SIGNAL
COUPLAGE AUX PROTEINES G

Mechanisms



From Principles of neuropsychopharmacology
Ed. Feldman, Meyer and Quenzer
Sinauer Ass., Inc., Publish., 1997; pp210

2004-2005

PROTEINES G ET RECEPTEURS COUPLES AUX PROTEINES G

Potentialités thérapeutiques

Table 1. G proteins and G-protein-coupled receptors in tumorigenesis

	Type of tumor
Activating mutations:	
G proteins	
$G\alpha_s$	Thyroid toxic adenomas, thyroid carcinomas, growth-hormone-secreting pituitary adenomas, *McCune–Albright syndrome*
$G\alpha_{i2}$	*Ovarian sex cord tumors, adrenal cortical tumors*
G-protein-coupled receptors	
TSH receptor	Thyroid adenoma, thyroid carcinoma
FSH receptor	Ovarian sex cord tumors, ovarian small cell carcinoma
LH receptor	Leydig cell hyperplasia, male precocious puberty
CCK_2 receptor	Colorectal cancer
Ca^{2+}-sensing receptor	Autosomal-dominant hypocalcemia, neoplasms
Autocrine and paracrine activation:	
Neuromedin B receptor	*Small-cell lung carcinoma*
Neurotensin receptor	*Prostate cancer, small-cell lung carcinoma*
Gastrin receptor	*Gastric cancer, small-cell lung carcinoma*
Cholecystokinin receptors	*Pancreatic hyperplasia, pancreatic carcinoma, gastrointestinal cancer, small-cell lung carcinoma*
Vasopressin receptors	Small-cell lung carcinoma
Virally encoded G-protein-coupled receptors:	
Kaposi's sarcoma-associated herpesvirus (KSHV)	Kaposi's sarcoma
Herpes virus saimiri (HVS)	*Leukemias and lymphomas in non-human primates*
Jaagsiekte sheep retrovirus (JSRV)	*Ovine pulmonary carcinoma*

Marinissen and Gutkind 2001, 22: 368-376

2004-2005

PROTEINES G ET PETITES PROTEINES G

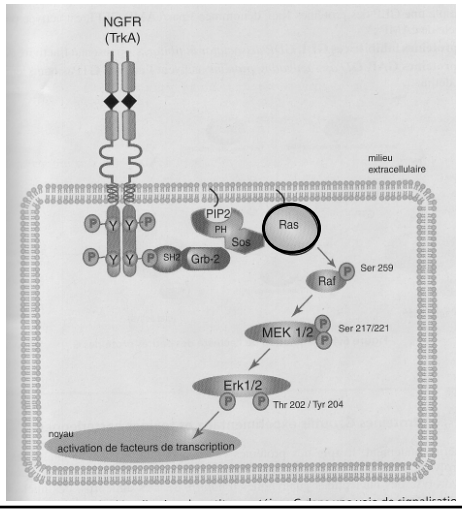
Les petites protéines G

- **Protéines monomériques**
- **Masse de 20 à 30 kDa**
- **Structure proche de celle des sous-unités α des protéines G trimériques**
- **Lient les nucléotides guanyliques GDP et GTP**
- **Possèdent une activité GTPasique intrinsèque**
- **Présentes sous 2 formes interconvertibles, la forme inactive liant le GDP et la forme active liant le GTP**
- **Ancrées à la face interne de la membrane plasmique et aux membranes intracellulaires par isoprénylation, résidus farnésyls (famille Ras) ou géranyl-géranyls (Rap, famille Rho, Rac…)**
- **La liaison au GTP implique un changement de conformation favorable à l'interaction de la petite protéine G à une protéine effectrice (ex: MAP kinase)**

2004-2005

PROTEINES G ET PETITES PROTEINES G

Implication des petites protéines G dans l'activation du récepteur NGF (nerve growth factor)



From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 123

2004-2005

PROTEINES G ET PETITES PROTEINES G

Intérêt potentiel, d'un point de vue thérapeutique des petites protéines G

Inhibiteurs de farnésyl transférases

- visent essenciellement les protéines Ras;
- molécules en essais cliniques pour certains types de cancers

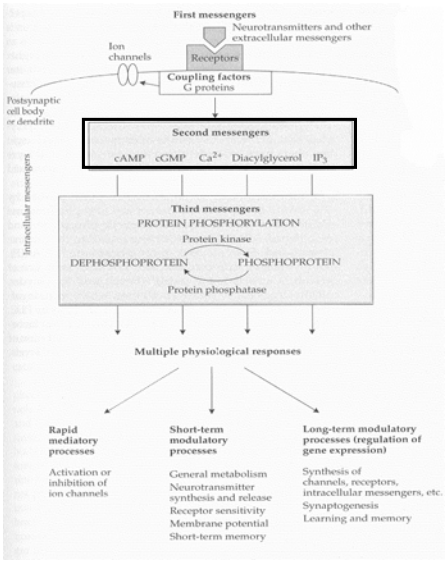
Inhibiteurs de géranylgéranyltransférases

- visent les protéines Rho/Rac/Cdc42
- molécules en essais cliniques pour certains types de cancers (induction d'apoptose)

- visent les protéines rab
- inhibent la résorption osseuse et pourraient être utiles dans le cas de l'ostéoporose

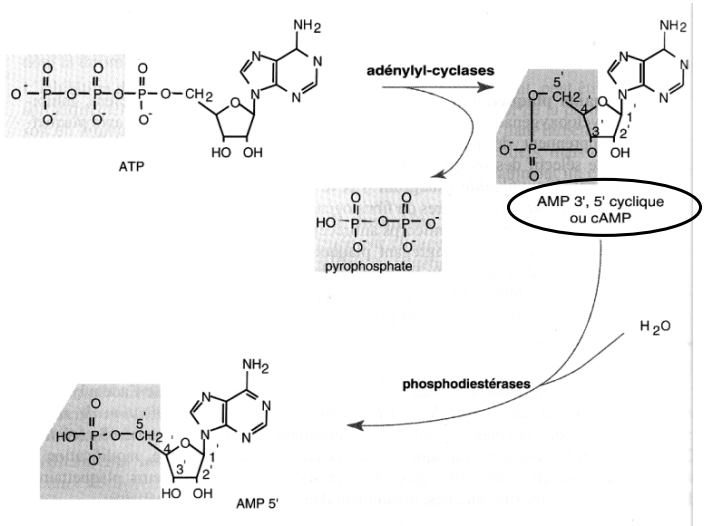
2004-2005

TRANSDUCTION DU SIGNAL SECONDS MESSAGERS



Messager	Source	Effets
AMPc	**Adenylate cyclase**	**Active les protéines kinases**
GMPc	Guanylate cyclase	Active les protéines kinases Régule des canaux ioniques Régule des phosphodiestérases
Ca^{2+}	Canaux ioniques du RE et de la membrane plasmique	Active des protéines kinases Active des protéines à fonctions modulées par le calcium
IP3	Action de PLC sur PI	Active les canaux calciques
DAG	Action de PLC sur PI	Active la protéine kinase C
Acide phosphatidique	Action de PLD	Active les canaux calciques Inhibe l'adénylate cyclase
Céramide	Action de PLC sur SM	Active les protéines kinases
NO	NO synthase	Active la guanylate cyclase Stimule la relaxation des muscles lisses
ADP-ribose c	ADP-ribose synthase	Active les canaux calciques

AMP cyclique
EXEMPLE DE SECOND MESSAGER



From Pharmacologie, Landry et Gies, Ed Dunod (2003)

2004-2005

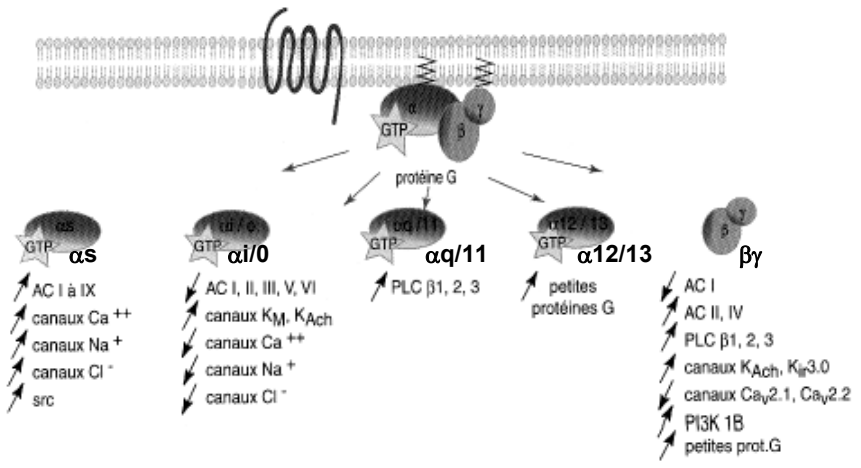
AMP cyclique – EFFET DE DIFFERENTS LIGANDS SUR SA CONCENTRATION

Médiateurs (n° du chapitre à consulter)	Récepteurs couplés à Gs: augmentation de cAMP	Récepteurs couplés à Gi: diminution de cAMP	Récepteurs couplés à Gq: augmentation de DAG et IP_3
Acétylcholine (11)		M_2, M_4	M_1, M_3, M_5
Adénosine	A_{2A}, A_{2B}	A_1 A_3	
Adrénaline, noradrénaline (12)	β1, β2, (β3), β4	α_{2A}, α_{2B}, α_{2C}, (β3)	α_{1A}, α_{1B}, α_{1D}
Cannabinoïdes		CB_1, CB_2	
Cholécystokinines et gastrine (14)	CCK1		CCK1,2
CRF (9)	CRF_1, CRF_2		
Dopamine (13)	D_1,D_5	D_2, D_3, D_4	
FSH (9)	FSHR		
GABA (15)		$GABA_B$	
Galanine		GAL, 1, 2, 3	GAL 2
Glutamate (15)		mglu-2, -3, -4, -6, -7, -8	mglu-1, -5
Histamine (14)	H_2	H_3 , H_4	H_1
Mélanocortine (MSH)	MC1 à 5		
Mélatonine (14)		MT1, MT2	
Neuropeptide Y (16)		Y_1, 2, 4, 5, 6	
Opioïdes (16)		δ, μ, κ, ORL-1	
Prostanoïdes (6)	DP, IP, EP_2, EP_4, (EP_3)	(EP_3)	TP, EP_1, (EP_3)
Sérotonine (14)	5HT-4, 5HT-6, 5HT-7	5HT-1 (A, B, D, E, F)	5HT-2 (A, B, C)
Somatostatine (7)		sst1 à 5	
Vasopressine (9)	V_2		V_{1A}, V_{1B}
VIP (Vasointestinal peptide)	$VPAC_1$, $VPAC_2$		

Activators	
Corticotropin (ACTH)	Lipotropin
Calcitonin	Melanocyte-stimulating hormones (MSH)
Catecholamines (acting on ß1 and ß2 receptors)	Parathormone (PTH)
Choriogonadotropin	Secretin
Follicle-stimulating hormone (FSH)	Thyrotropin regulatory hormone (TRH)
Glucagon	Thyrotropin (TSH)
Gonadotropin-releasing hormone (GnRH)	Vasoactive intestinal peptide (VIP)
Growth hormone-releasing hormone	Vasopressin
Luteinizing hormone (LH)	
Inhibitors	
Angiotensin	
Catecholamines (acting on α_2 receptors)	

2004-2005

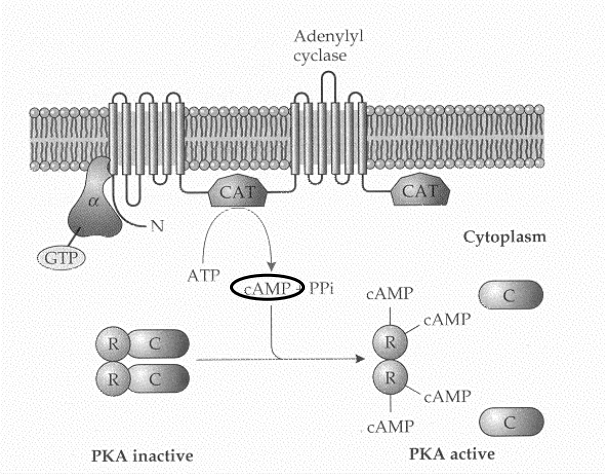
AMP cyclique: FAMILLES DE PROTEINES G TRIMERIQUES ET EFFETS SUR L'ADENYLATE CYCLASE



From Pharmacologie, Landry et Gies, Ed Dunod (2003)

2004-2005

AMP cyclique: CONSEQUENCES DE L'ACTIVATION DE L'ADENLATE CYCLASE



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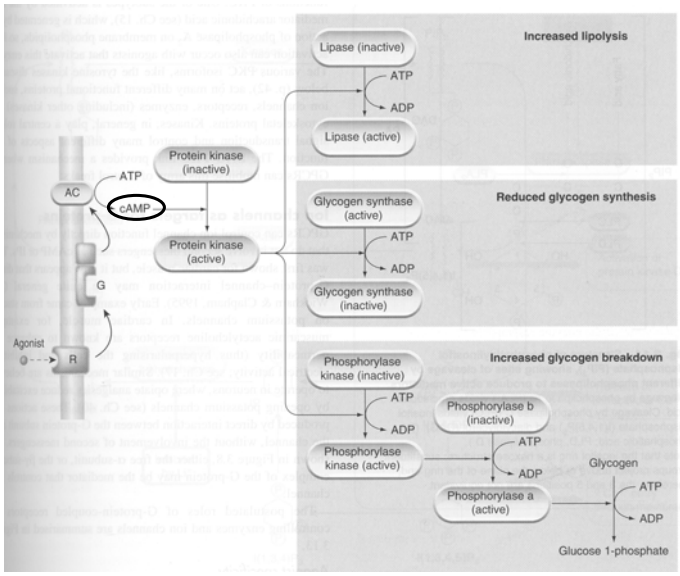
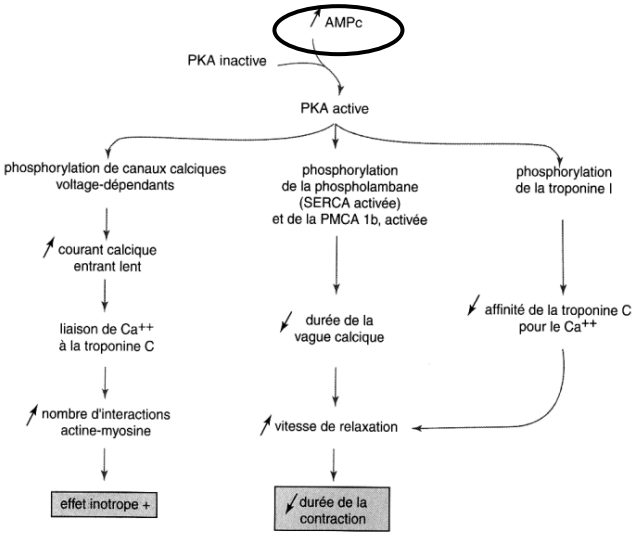
2004-2005

AMP cyclique: CONSEQUENCES DE L'ACTIVATION DE L'ADENLATE CYCLASE



2004-2005

AMP cyclique: CONSEQUENCES DE L'ACTIVATION DE L'ADENLATE CYCLASE



From Pharmacologie, Landry et Gies, Ed Dunod (2003) 2004-2005

AMP cyclique: CONSEQUENCES DE L'ACTIVATION DE L'ADENLATE CYCLASE

adénylyl-cyclases (AC)	I	II	III	IV	V	VI	VII	VIII	IX
nombre de résidus	1134	1090	1144	1064	1084	1165	1099	1248	1353
localisation des ARNm	cerveau, rétine	cerveau, bulbe olfactif > poumon	neurones olfactifs, cerveau, rétine, aorte, poumon, testicule	rein, cerveau, coeur, foie, poumon	coeur > cerveau > rein	coeur, cerveau > rein, testicule, foie	poumon, coeur, rein, cerveau	cerveau	muscles squelettiques, cerveau > rein, poumon, foie, coeur
modulateurs									
Gαs	↗	↗	↗	↗	↗	↗	↗	↗	↗
Gαi	–	–	↘	–	↘	↘	–	–	↘
Gβγ	↘	↗	–	↗	–	–	–	–	–
NO	↘	–	–	–	–	↘	–	–	–
Ca^{++}	↗	–	↗	–	–	–	–	↗	↘
PKC	–	↗	–	↘	↗	↘	↗	–	–
PKA	–	–	–	–	↘	↘	–	–	–
CamK	↘	–	↘	–	–	–	–	–	–

From Pharmacologie, Landry et Gies, Ed Dunod (2003) 2004-2005

Messager	Source	Effets
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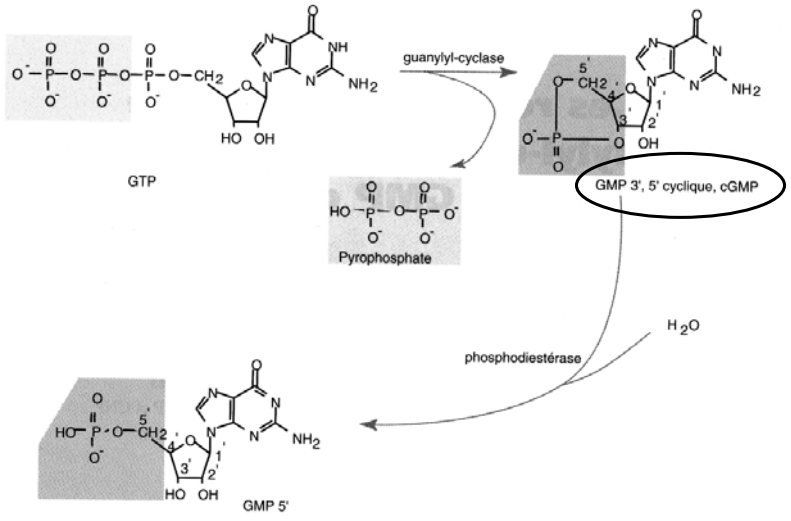
ADP-ribose c	ADP-ribose synthase	Active les canaux calciques

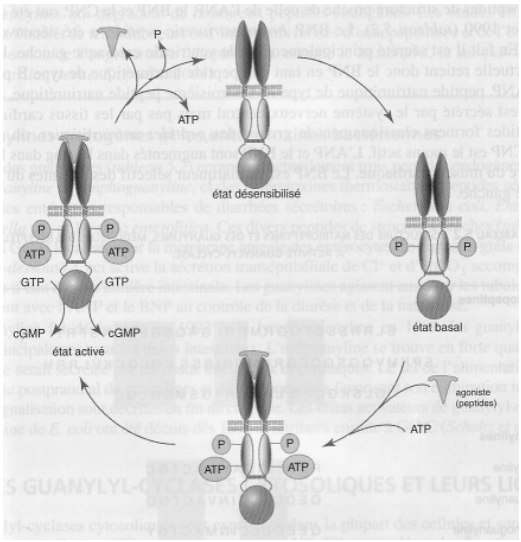
GMP cyclique
EXEMPLE DE SECOND MESSAGER



From Pharmacologie, Landry et Gies, Ed Dunod (2003)

2004-2005

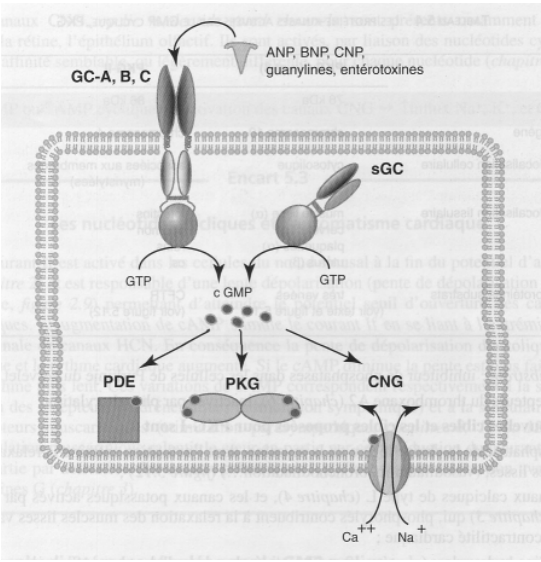
GMP cyclique: CYCLE D'ACTIVATION DES RECEPTEURS A ACTIVITE GUANYLYL-CYCLASE



From Pharmacologie,
Landry et Gies, Ed Dunod (2003); pp 95

2004-2005

GMP cyclique : CIBLES



- **PDE: phosphodiesterases**
- **PKG: protéines kinases dépendantes du GMPcyclique**
- **CNG: cyclic nucleotide-gated channels**

From Pharmacologie,
Landry et Gies, Ed Dunod (2003); pp 103

2004-2005

GMP cyclique ET EFFETS MEDIES PAR LES PHOSPHODIESTERASES

familles	substrats	régulateurs de l'activité	inhibiteurs séléctifs
PDE1	cAMP / cGMP	Ca^{++} - calmoduline ↗ PKA ↗	----
PDE2	cAMP / cGMP	cGMP ↗	----
PDE3	cAMP > cGMP	cGMP ↘ PKA ↗	milrinone énoximone
PDE4	cAMP	PKA ↗	rolipram cilomilast
PDE5	cGMP	cGMP ↗	sildénafil
PDE6	cGMP	cGMP ↗ photons ↗	----
PDE7	cAMP	----	----
PDE8	cAMP	----	----
PDE9	cGMP	----	----
PDE10	cAMP / cGMP	cGMP ↗	----
PDE11	cAMP / cGMP	cGMP ↗	----

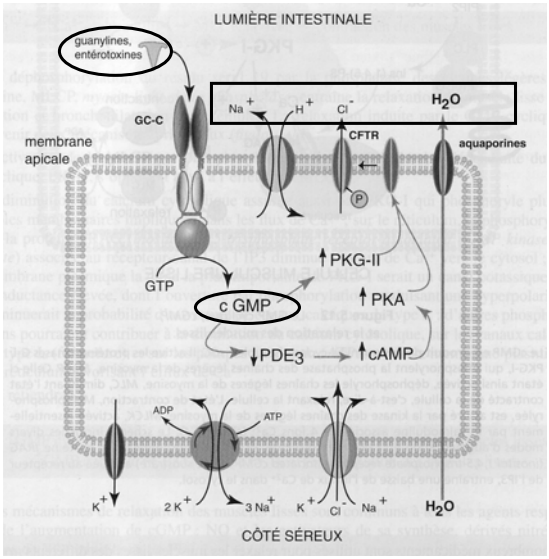
~~Inhibiteurs PDE3~~: utilisés pour leurs propriétés inotropes positives et vasodilatatrices

Inhibiteurs PDE4: en cours d'études dans des pathologies inflammatoires, dont l'asthme et la bronchite chronique

Inhibiteurs PDE5: utilisés pour favoriser l'érection pénienne

From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 106 2004-2005

GMP cyclique: CONSEQUENCES DE L'EFFET SUR LA PDE 3



From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 112

2004-2005

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ADP-ribose c	ADP-ribose synthase	Active les canaux calciques

CIBLES DU Ca^{2+}, EXEMPLE DE SECOND MESSAGER

Protéines de liaison au Ca2+

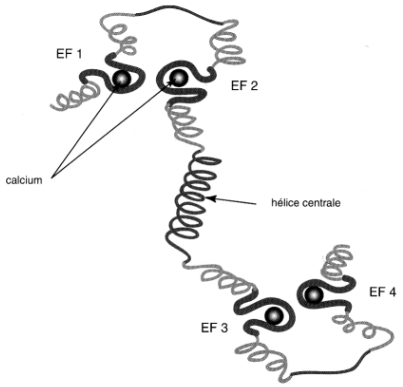
- **Protéines de la superfamille de la calmoduline**
- **Protéines faisant partie de différentes voies de signalisation dont les protéines kinases C et les synaptotagmines***
- **Annexines***

(* Possèdent aussi des sites de liaison aux membranes)

2004-2005

Ca $^{2+}$, EFFET SUR LES PROTEINES DE LA SUPERFAMILLE DE LA CALMODULINE

Lorsque le Ca^{2+} se lie à la calmoduline, un léger changement de conformation expose les sites hydrophobes des hélices adjacentes vers la surface de la protéine, permettant l'interaction avec de nombreuses protéines membranaires



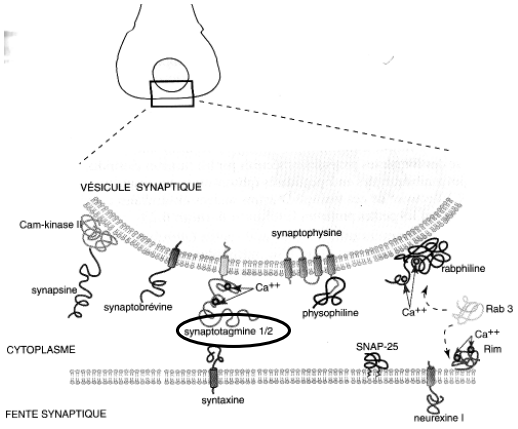
La calmoduline joue un rôle dans la contraction et la relaxation des muscles lisses ainsi que dans la phototransduction

From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 81 2004-2005

Ca $^{2+}$, EFFET SUR LES PROTEINES F FAISANT PARTIE DE DIFFERENTES VOIES DE SIGNALISATION, DONT LES PKC, ET LES SYNAPTOTAGMINES

Synaptotagmines

Les synaptotagmines participent principalement à l'exocytose des neuromédiateurs.



From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 271 2004-2005

Ca^{2+}, EFFET SUR LES PROTEINES F FAISANT PARTIE DE DIFFERENTES VOIES DE SIGNALISATION, DONT LES PKC, ET LES SYNAPTOTAGMINES

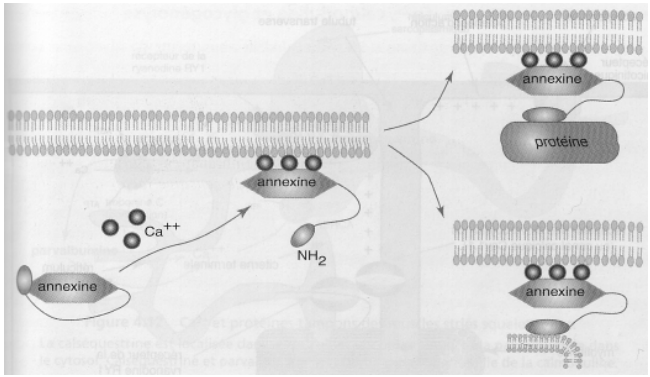
Intérêt des toxines comme bloqueur de l'exocytose.

La toxine botulique type A est utilisée en thérapeutique pour bloquer l'exocytose de l'acétylcholine par les fibres nerveuses motrices. Elle est indiquée dans

- **les troubles de l'oculomotricité**
- **le blépharospasme**
- **l'hémispasme facial**
- **le torticolis spasmodique**
- **la chirurgie esthétique (paralysie musculaire locale)**

2004-2005

Ca^{2+}, EFFET SUR LES PROTEINES DE TYPE ANNEXINES



Protéines impliquées dans les interactions membrane-membrane comme exocytose, l'endocytose et le trafic intracellulaire des protéines dans le réticulum et le Golgi.

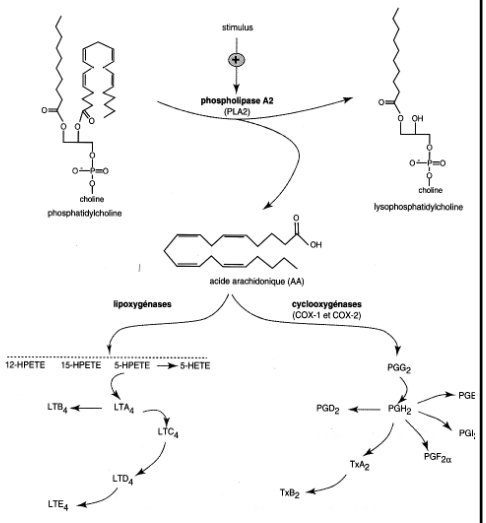
From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 83

2004-2005

Ca $^{2+}$, EFFET SUR LES PROTEINES DE TYPE ANNEXINES

Annexines

De part leur affinité particulière pour les lipides, les annexines pourraient entrer en compétition pour la liaison aux lipides avec la phospholipase A_2, entrainant ainsi une diminution de la production de l'acide arachidonique et un effet anti-inflammatoire



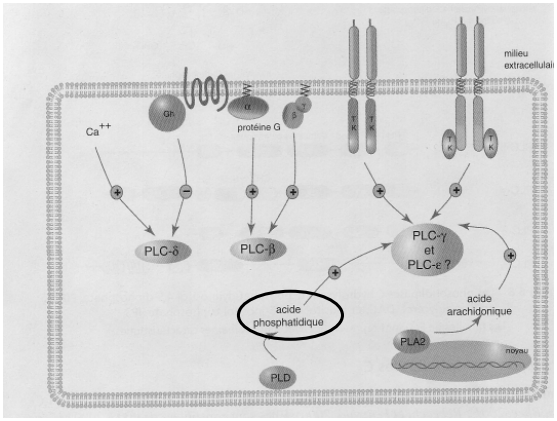
From Pharmacologie, Landry et Gies, Ed Dunod (2003)

2004-2005

Messager	Source	Effets
AMPc	Adenylate cyclase	Active les protéines kinases
GMPc	Guanylate cyclase	Active les protéines kinases Régule des canaux ioniques Régule des phosphodiestérases
Ca $^{2+}$	Canaux ioniques du RE et de la membrane plasmique	Active des protéines kinases Active des protéines à fonctions modulées par le calcium
IP3	**Action de PLC sur PI**	**Active les canaux calciques**
DAG	**Action de PLC sur PI**	**Active la protéine kinase C**
Acide phosphatidique	**Action de PLD**	**Active les canaux calciques** **Inhibe l'adénylate cyclase**
Céramide	Action de PLC sur SM	Active les protéines kinases
NO	NO synthase	Active la guanylate cyclase Stimule la relaxation des muscles lisses
ADP-ribose c	ADP-ribose synthase	Active les canaux calciques

2004-2005

ACIDE PHOSPHATIDIQUE ET ACTIVATION DES PHOSPHOLIPASES C

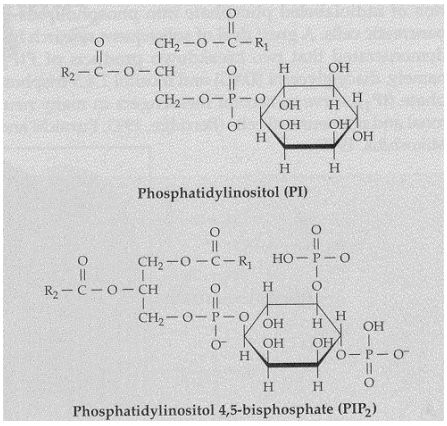


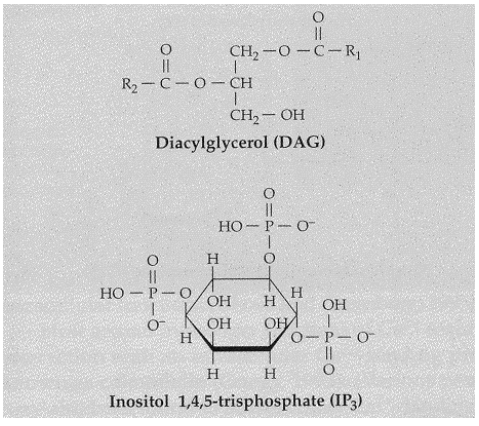
Les phospholipases C peuvent être activées non seulement par la stimulation des récepteurs couplés aux protéines G mais aussi par celle des récepteurs à activité tyrosyl-kinase, par les ions calciques, l'acide arachidonique, et par l'acide phosphatidique

From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 128

2004-2005

DAG AND IP_3, DES EXEMPLES DE SECOND MESSAGER





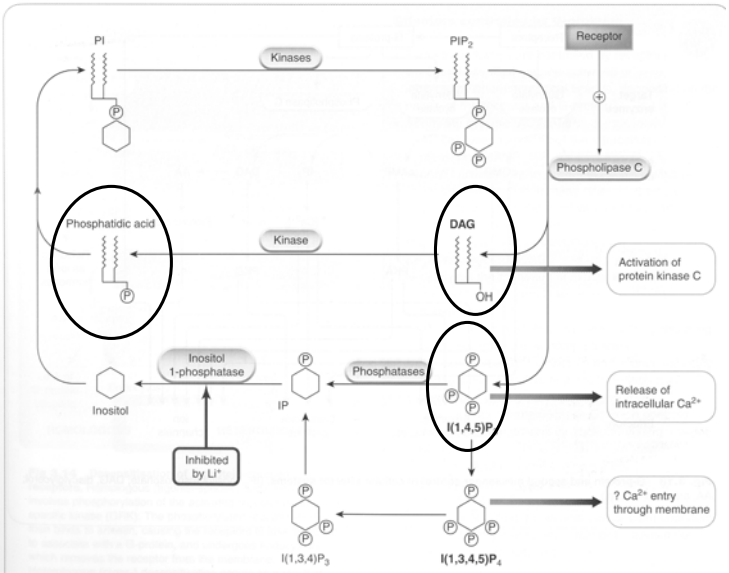
2004-2005

DAG ET IP3: MODULATION DE LEURS CONCENTRATIONS

Médiateurs (n° du chapitre à consulter)	Récepteurs couplés à Gs: augmentation de cAMP	Récepteurs couplés à Gi: diminution de cAMP	Récepteurs couplés à Gq: augmentation de DAG et IP_3
Acétylcholine (11)		M_2, M_4	M_1, M_3, M_5
Adénosine	A_{2A}, A_{2B}	A_1 A_3	
Adrénaline, noradrénaline (12)	β1, β2, (β3), β4	α_{2A}, α_{2B}, α_{2C}, (β3)	α_{1A}, α_{1B}, α_{1D}
Cannabinoïdes		CB_1, CB_2	
Cholécystokinines et gastrine (14)	CCK1		CCK1,2
CRF (9)	CRF_1, CRF_2		
Dopamine (13)	D_1,D_5	D_2, D_3, D_4	
FSH (9)	FSHR		
GABA (15)		$GABA_B$	
Galanine		GAL, 1, 2, 3	GAL 2
Glutamate (15)		mglu-2, -3, -4, -6, -7, -8	mglu-1, -5
Histamine (14)	H_2	H_3 , H_4	H_1
Mélanocortine (MSH)	MC1 à 5		
Mélatonine (14)		MT1, MT2	
Neuropeptide Y (16)		Y_1, 2, 4, 5, 6	
Opioïdes (16)		δ, μ, κ, ORL-1	
Prostanoïdes (6)	DP, IP, EP_2, EP_4, (EP_3)	(EP_3)	TP, EP_1, (EP_3)
Sérotonine (14)	5HT-4, 5HT-6, 5HT-7	5HT-1 (A, B, D, E, F)	5HT-2 (A, B, C)
Somatostatine (7)		sst1 à 5	
Vasopressine (9)	V_2		V_{1A}, V_{1B}
VIP (Vasointestinal peptide)	$VPAC_1$, $VPAC_2$		

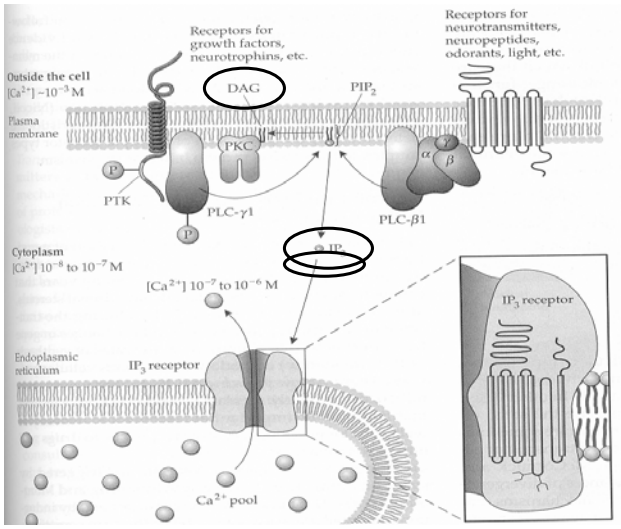
2004-2005

DAG, IP3 ET ACIDE PHOSPHATIDIQUE, DES EXEMPLES DE SECOND MESSAGER



2004-2005

DAG ET IP3, DES EXEMPLES DE SECOND MESSAGER



2004-2005

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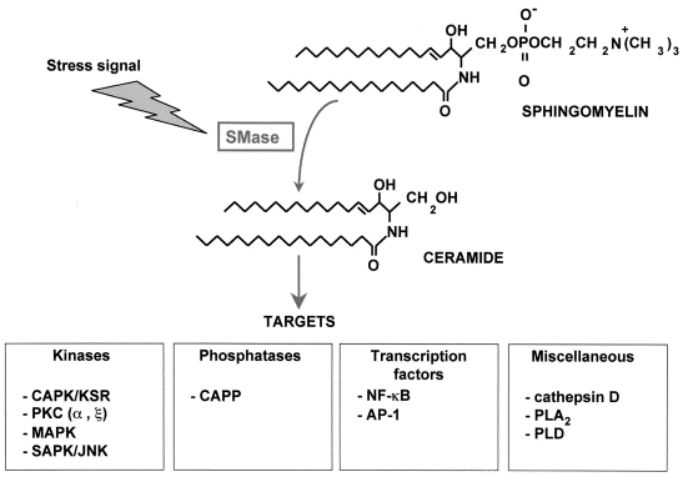
ADP-ribose c	ADP-ribose synthase	Active les canaux calciques

CERAMIDE
EXEMPLE DE SECOND MESSAGER



2004-2005

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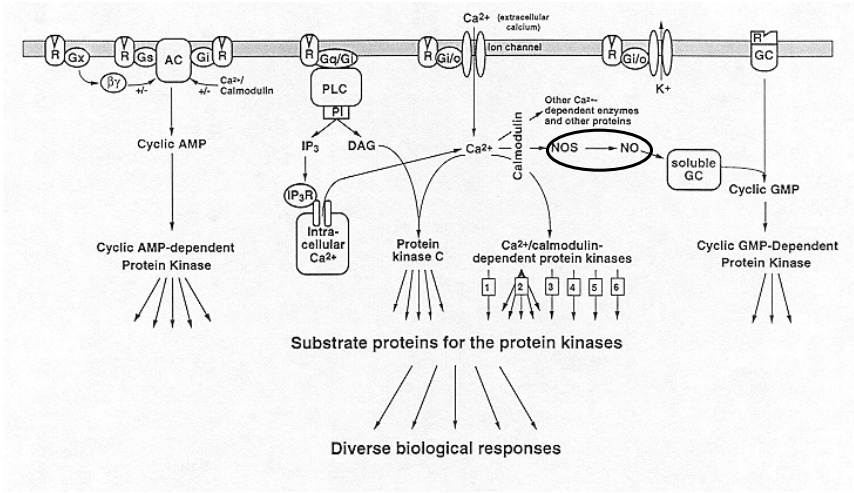
Céramide	Action de PLC sur SM	Active les protéines kinases
NO	**NO synthase**	**Active la guanylate cyclase** **Stimule la relaxation des muscles lisses**
ADP-ribose c	ADP-ribose synthase	Active les canaux calciques

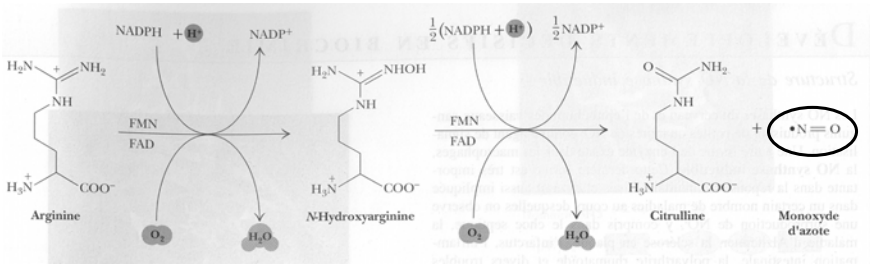
TRANSDUCTION DU SIGNAL – PROTEINE G ET VOIE DU NO



2004-2005

TRANSDUCTION DU SIGNAL ET NO

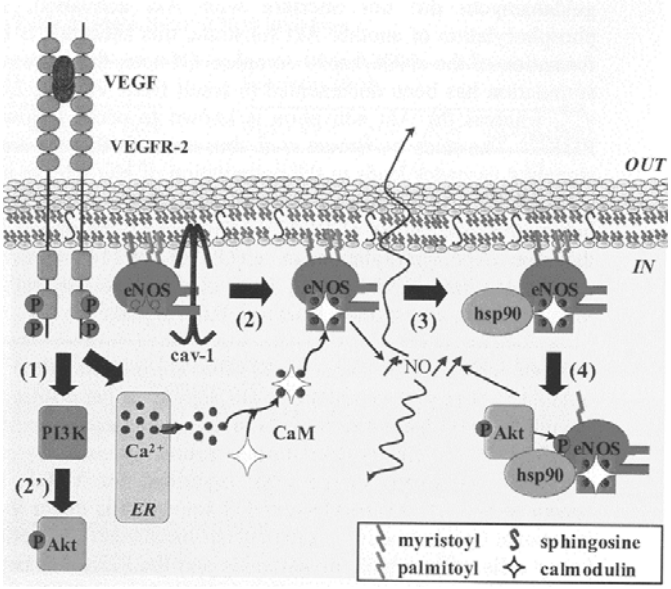
Production du NO



Garrett and Grisham, Biochimie, De Boeck, 2000, pg 1160

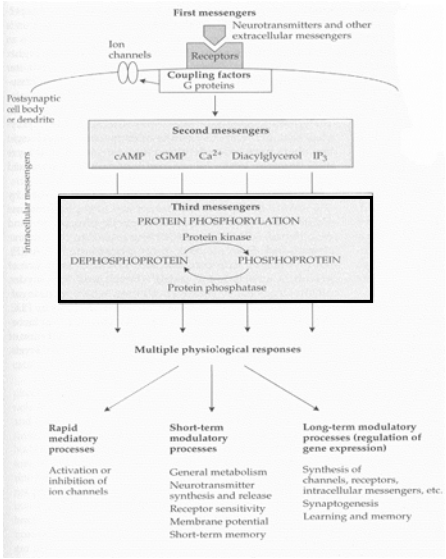
2004-2005

TRANSDUCTION DU SIGNAL ET NO



2004-2005

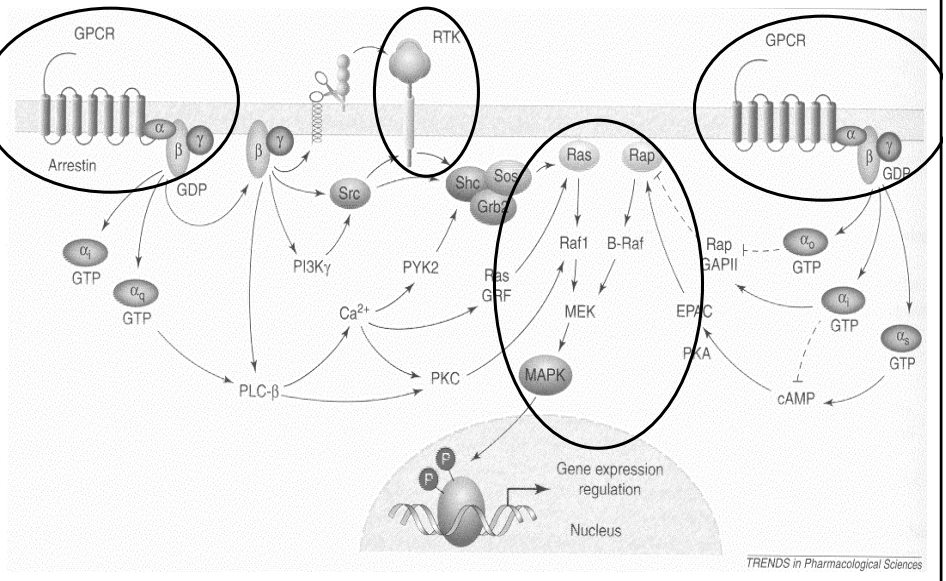
TROISIEMES MESSAGERS TRANSDUCTION DU SIGNAL



From Principles of neuropsychopharmacology, 1997; pp213, 225

2004-2005

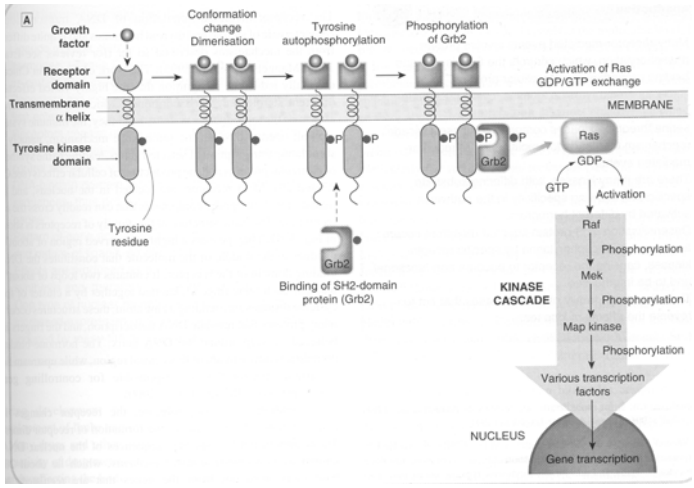
TRANSDUCTION DU SIGNAL - PROTEINES G ET VOIE DES MAPK



Marinissen and Gutkind 2001 TiPS, 22: 368-376

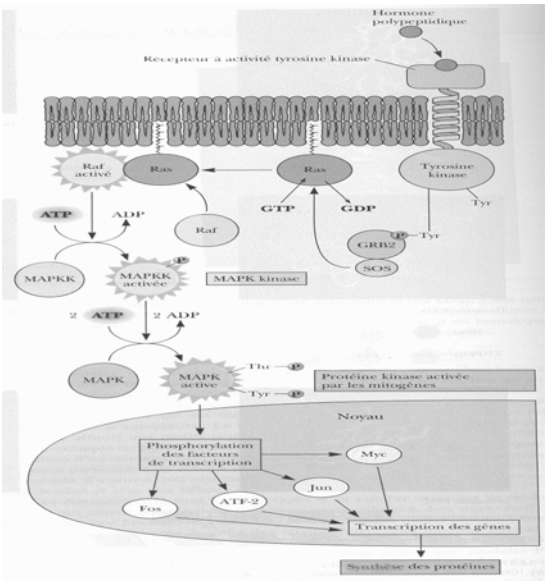
2004-2005

TRANSDUCTION DU SIGNAL ET RECEPTEUR TYROSINE KINASE - VOIE DES MAPK



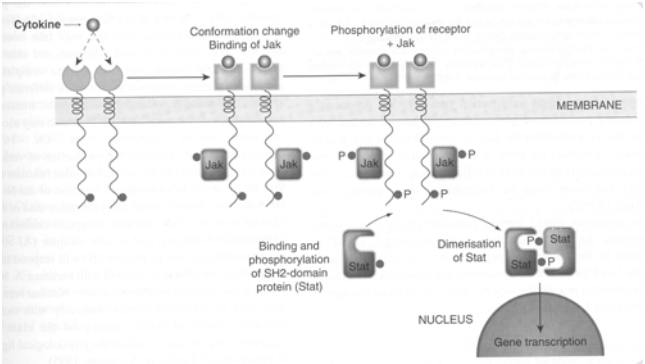
2004-2005

TRANSDUCTION DU SIGNAL - RECEPTEUR TYROSINE KINASE ET VOIE DES MAPK



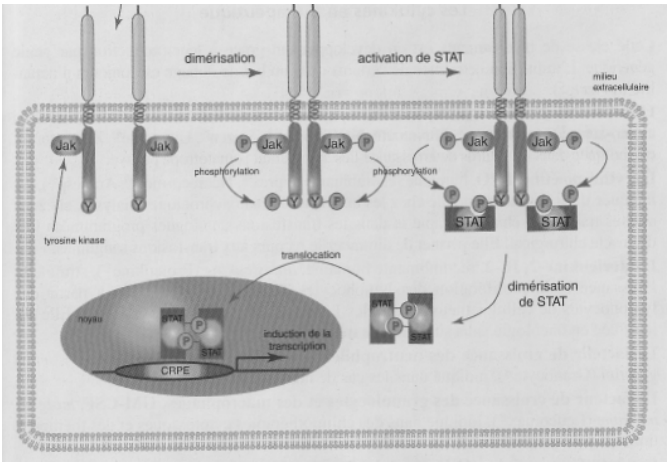
2004-2005

TRANSDUCTION DU SIGNAL ET RECEPTEUR TYROSINE KINASE - VOIE DES MAPK



2004-2005

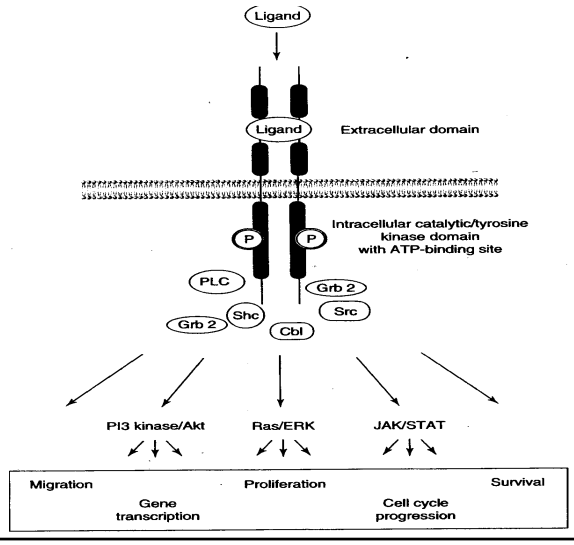
COUPLAGE DES RECEPTEURS AUX CYTOKINES AUX TYROSYLS-KINASES CYTOSOLIQUES JAK ET ACTIVATION DES FACTEURS DE TRANSCRIPTION STAT



From Pharmacologie, Landry et Gies, Ed Dunod (2003); pp 167

2004-2005

TRANSDUCTION DU SIGNAL ET CIBLE PHARMACOLOGIQUE - RECEPTEUR TYROSINE KINASE - VOIE DES MAPK



Zwick et al *TiPS* 2002 8: 17-23

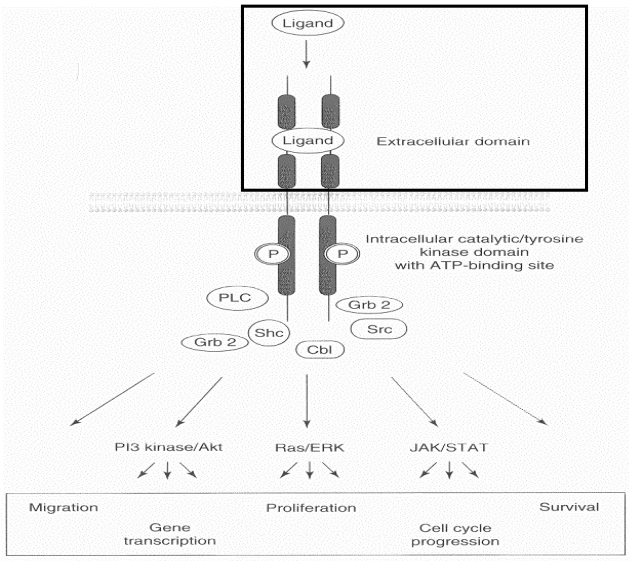
2004-2005

RECEPTOR TYROSINE KINASE- EXTRACELLULAR SITE

Binding of extracellular ligand

DIMERIZATION

Increase of receptor tyrosine kinase activity



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23

2004-2005

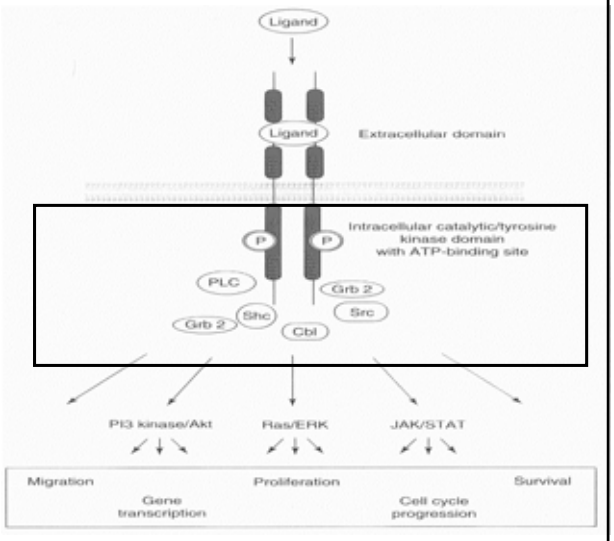
RECEPTOR TYROSINE KINASE- INTRACELLULAR BINDING SITE

Catalyse of recepteur autophosphorylation of cytoplasmic tyrosine residues

→Docking sites for Src homology (SH) and phosphotyrosine-binding (PTB) containing molecules (PLC, Src, …)

Recrutment of additional effectors molecules containing SH2, SH3, PTB,PH (pleckstrin) domain

⇨Activation of a cascade of intracellular biochemical signals

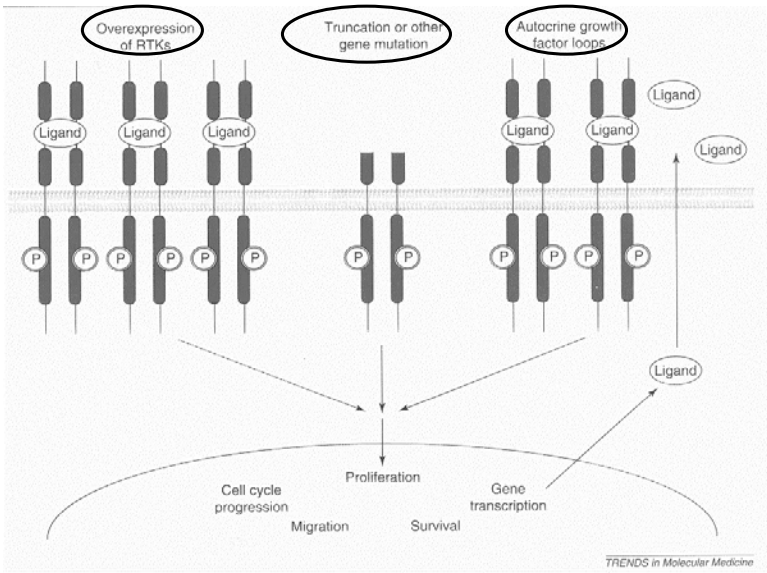


Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23

2004-2005

ROLE PLAYED BY RECEPTOR TYROSINE KINASE IN CANCER

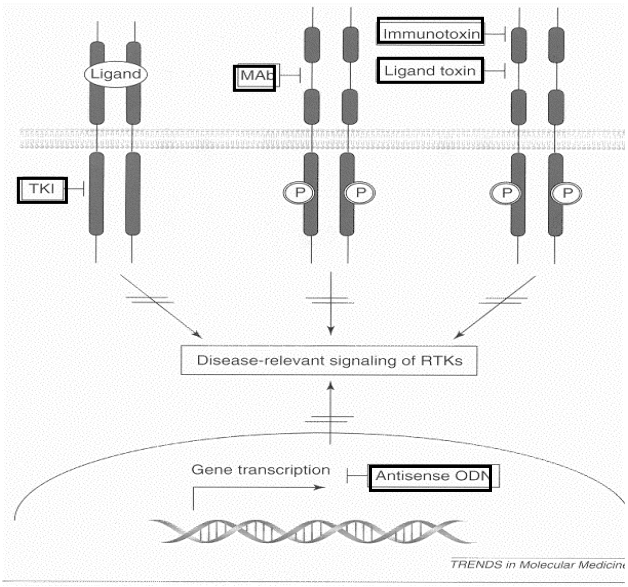
Constitutive activation of receptor tyrosine kinase ~ malignant transformation



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23

2004-2005

TYROSINE KINASE RECEPTOR AS A CIBLE FOR CHEMOTHERAPY



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23

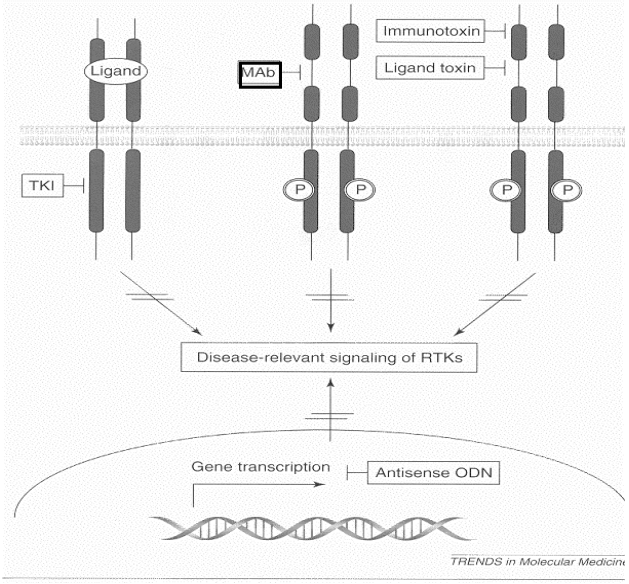
2004-2005

MONOCLONAL ANTIBODIES AS ANTI-TYROSINE KINASE RECEPTOR DRUGS

Anti-RTK mAbs block the ligand-receptor interaction

⇨ inhibition of ligand-induced RTK signaling

⇨ increase of RTK down regulation and internalization



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23 2004-2005

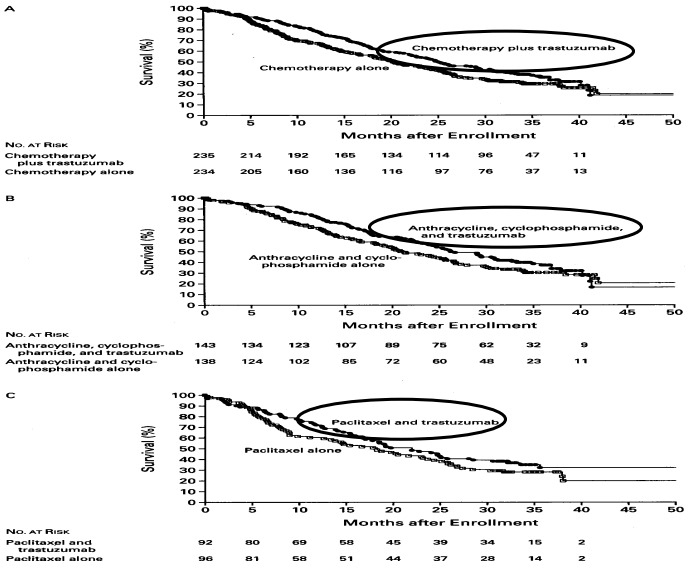
RECEPTOR TYROSINE KINASE -BASED DRUGS IN CLINICAL TRIALS - monoclonal antibodies

RTK	Drug	Company	Description	Status
HER2	Trastuzumab Herceptin	Genentech	MAb directed against HER2	Approved by the FDA 1998
HER2	BsAb 2B-1, NSC-673928	Chiron	Bispecific MAb inducing lysis of HER2-expressing tumor cells	Phase Ib/II (03/98)
HER2	APC8024	Dendreon	Vaccine against HER2-overexpressing tumors	Phase I
EGFR	C225 Cetuximab	ImClone Systems	MAb directed against EGFR	Phase III
EGFR	MDX-447	Medarex	Bispecific Mab against EGFR	Phase II
EGFR	ABX-EGF	Abgenix	MAb against EGFR	Phase II
EGFR	ZD18539 Iressa	AstraZeneca	TKI that inhibits EGFR signalling	Phase III
EGFR	DAB389EGF	Seragen	Recombinant diphtheria toxin-hEGF fusion protein	Phase II
EGFR	OSI-774 Tarceva	OSI Pharmaceuticals	Small-molecule that directly inhibits EGFR	Phase III
Abl/ PDGFR/ c-Kit	STI 571 Gleevec	Novartis	TKI that interferes with Abl, PDGFR and c-Kit	Phase III Approved by the FDA 2001
VEGFR2	SU5416	SUGEN	TKI that inhibits VEGFR2	Phase II
VEGFR2	IMC-1C11	ImClone Systems	MAb against VEGFR2	Phase I
VEGFR1	RPI.4610 Angiozyme	Ribozyme Pharmaceuticals	Nuclease-stabilized hairpin ribozyme targeting VEGFR1 mRNA	Phase I/II
VEGFR/ FGFR/ IGF1R	SU6668	SUGEN	RTK inhibition of VEGFR, FGFR and PDGFR	Phase I
	INX-4437	INEX USA	Antisense ODN targeting IGF1R mRNA	Phase I
TRK	CEP-701	Cephalon	TKI of TRK receptor kinase	Phase II

[a]Abbreviations: FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; MAb, monoclonal antibody; ODN, oligodeoxynucleotide; PDGFR, platelet derived growth factor receptor; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23 2004-2005

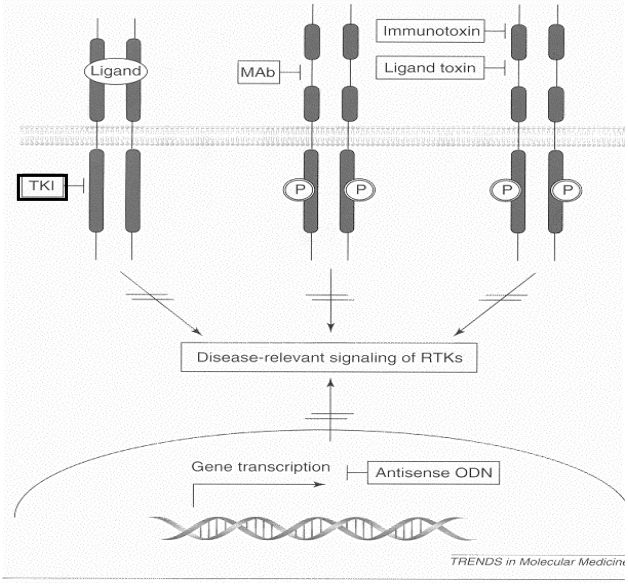
USE OF A MONOCLONAL ANTIBODY AGAINST HER2 (+ Chemotherapy) FOR METASTATIC BREAST CANCER



Slamon et al, New Engl. J. Med (2001) 344: 783-792

2004-2005

INHIBITORS OF TYROSINE KINASE AS A CIBLE FOR CHEMOTHERAPY



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23

2004-2005

RECEPTOR TYROSINE KINASE -BASED DRUGS IN CLINICAL TRIALS - Inhibitors of TRK

RTK	Drug	Company	Description	Status
HER2	Trastuzumab Herceptin	Genentech	MAb directed against HER2	Approved by the FDA 1998
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EGFR	DAB389EGF	Seragen	Recombinant diphtheria toxin-hEGF fusion protein	Phase II
EGFR	OSI-774 Tarceva	OSI Pharmaceuticals	Small-molecule that directly inhibits EGFR	Phase III
Abl/ PDGFR/ c-Kit	STI 571 Gleevec	Novartis	TKI that interferes with Abl, PDGFR and c-Kit	Phase III Approved by the FDA 2001
VEGFR2	SU5416	SUGEN	TKI that inhibits VEGFR2	Phase II
VEGFR2	IMC-1C11	ImClone Systems	MAb against VEGFR2	Phase I
VEGFR1	RPI.4610 Angiozyme	Ribozyme Pharmaceuticals	Nuclease-stabilized hairpin ribozyme targeting VEGFR1 mRNA	Phase I/II
VEGFR/ FGFR/ IGF1R	SU6668	SUGEN	RTK inhibition of VEGFR, FGFR and PDGFR	Phase I
	INX-4437	INEX USA	Antisense ODN targeting IGF1R mRNA	Phase I
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Zwick et al. Trends in Molecular Medicine (2002) 8: 17-23

2004-2005

RECEPTOR TYROSINE KINASE INHIBITORS - Gefitinib - ZD 1839 - STRUCTURE

ATP analogues of the quinazoline/pyridopyrimidine family
compete with ATP for the ATP binding site of the receptor
tyrosine kinase domain.

Registry Number: 184475-35-2

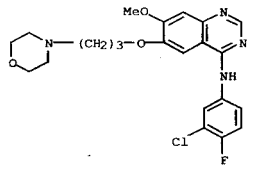
CA Index Name: 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (9CI)

Other Names: Gefitinib; Iressa; ZD 1839

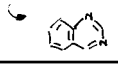
Formula: C22 H24 Cl F N4 O3

STN Files: CAPLUS, BIOSIS, CA, DRUGNL, DRUGPAT, DRUGUPDATES, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL

(Additional information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)



ATP analogue of quinazoline

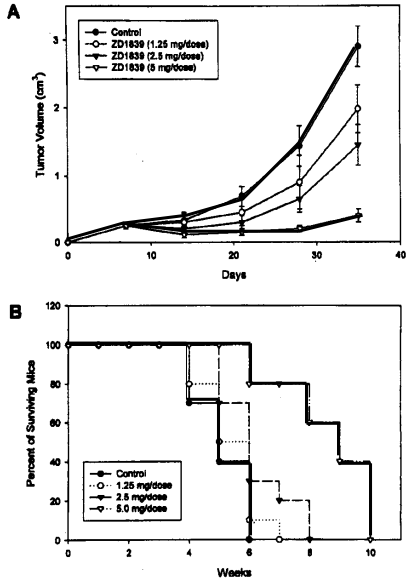


2004-2005

RECEPTOR TYROSINE KINASE INHIBITORS ACTIVITY - ZD 1839

Antitumor activity
- volume tumor
- % of surviving mice

of ZD-1839 on established GEO human colon carcinoma xenographs: effet dose



Ciardiello et al (2000) Clin. Res. Cancer 6: 2053-2063

2004-2005

RECEPTOR TYROSINE KINASE INHIBITORS - Imatinib - STI 571

ATP analogues of the quinazoline/pyridopyrimidine family
compete with ATP for the ATP binding site of the receptor
tyrosine kinase domain.

Registry Number: 152459-95-5

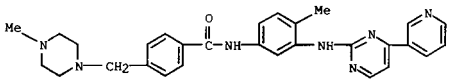
CA Index Name: Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI)

Other Names: CGP 57148; CGP 57148B; Gleevac; Gleevec; Glivec; Imatinib; STI 571

Formula: C29 H31 N7 O

STN Files: CAPLUS, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, PHAR, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)



ATP - analogue of the pyridopyrimidine

2004-2005

Quick success for cancer kinase treatment

Last month the US Food and Drug Administration (FDA) approved STI571 for the treatment of chronic myeloid leukemia (CML). Although Phase III clinical trials are not complete, meaning that the long-term efficacy and safety profile of the drug is not yet determined, the preliminary results from Phase I and II trials were so encouraging that the manufacturer, Novartis, applied for a fast-track review last February. The FDA should be applauded for its alacrity, enabling a highly promising cancer drug to become available much sooner to patients.

CML is a rare form of leukemia affecting 4,500 people in the US each year. It is a clonal hematopoietic stem-cell disorder characterized by the Philadelphia chromosome, the result of a balanced translocation between chromosomes 9 and 22. This translocation leads to a gene fusion the product of which, BCR-ABL, is constitutively 'on' and activates a number of signal transduction pathways involved in cell proliferation and apoptosis, leading to myeloid proliferation.

CML is a particularly good disease target since it is one of the few malignancies that can be ascribed to an underlying defect in a single molecule. STI571 specifically inhibits ABL1 protein tyrosine kinase, and these results elegantly illustrate the power of research founded on a good understanding of the underlying mechanisms of biological action. In addition, STI571 blocks autophosphorylation of the Kit and PDGF receptors, and the drug is now in clinical trials for cancers in which these kinases are activated, such as gastrointestinal stromal tumors, some gliomas and tissue sarcomas.

Of course, it's not all good news. Although STI571 therapy has yielded impressive results for patients in the chronic phase of CML, the drug is not effective in the acute phase and long-term treatment has led to the development of drug-resistant tumors. Combination therapies are now being developed that may circumvent these problems.

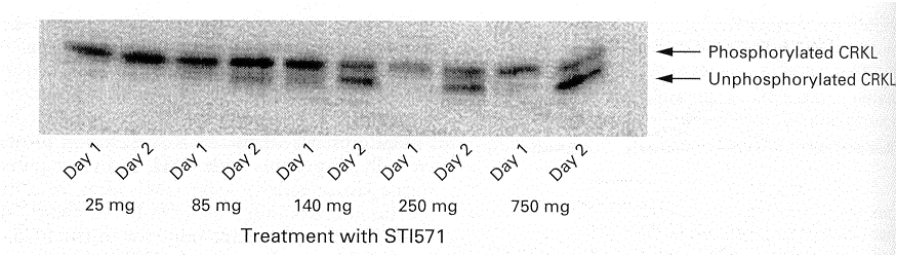
Nevertheless, STI571 is one of over 16 new kinase inhibitors that are now in development and its success offers real hope that molecular targeted therapy is finally becoming a reality.

Nature Medecine (2001) 7: 637

2004-2005

EFFICACY OF A SPECIFIC INHIBITOR (STI571) OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

Immunoblot assays demonstrating the degree of phosphorylation of the BCR-ABL substrate CRKL in individual patients in the group receiving increasing dose of STI 571

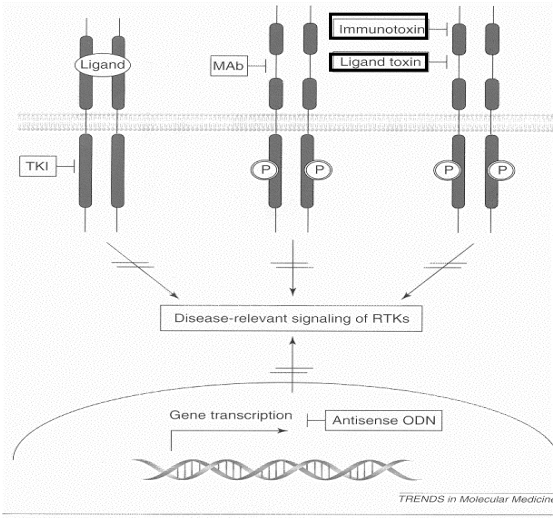


From: Drucker et al, 2001 N. Engl. J. Med. 344 1031-1037

2004-2005

IMMUNOTOXIN CONJUGATES AND LIGAND BINDING CYTOTOXIC AGENTS TO INHIBIT THE RECEPTOR TYROSINE KINASE SIGNALING

- Fusion/conjugaison between immunotoxins and specific ligand
- Binding to cell surface receptors
- Internalization into the endosome and translocation to the cytosol
- Inhibition of protein synthesis



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23 2004-2005

RECEPTOR TYROSINE KINASE -BASED DRUGS IN CLINICAL TRIALS-Immunotoxin conjugates

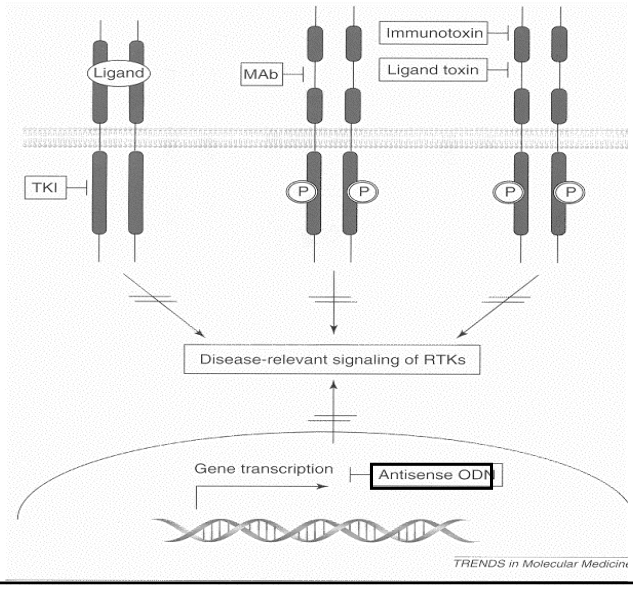
RTK	Drug	Company	Description	Status
HER2	Trastuzumab Herceptin	Genentech	MAb directed against HER2	Approved by the FDA 1998
HER2	BsAb 2B-1, NSC-673928	Chiron	Bispecific MAb inducing lysis of HER2-expressing tumor cells	Phase Ib/II (03/98)
HER2	APC8024	Dendreon	Vaccine against HER2-overexpressing tumors	Phase I
EGFR	C225 Cetuximab	ImClone Systems	MAb directed against EGFR	Phase III
EGFR	MDX-447	Medarex	Bispecific Mab against EGFR	Phase II
EGFR	ABX-EGF	Abgenix	MAb against EGFR	Phase II
EGFR	ZD18539 Iressa	AstraZeneca	TKI that inhibits EGFR signalling	Phase III
EGFR	DAB389EGF	Seragen	Recombinant diphtheria toxin-hEGF fusion protein	Phase II
EGFR	OSI-774 Tarceva	OSI Pharmaceuticals	Small-molecule that directly inhibits EGFR	Phase III
Abl/ PDGFR/ c-Kit	STI 571 Gleevec	Novartis	TKI that interferes with Abl, PDGFR and c-Kit	Phase III Approved by the FDA 2001
VEGFR2	SU5416	SUGEN	TKI that inhibits VEGFR2	Phase II
VEGFR2	IMC-1C11	ImClone Systems	MAb against VEGFR2	Phase I
VEGFR1	RPI.4610 Angiozyme	Ribozyme Pharmaceuticals	Nuclease-stabilized hairpin ribozyme targeting VEGFR1 mRNA	Phase I/II
VEGFR/ FGFR/ IGF1R	SU6668	SUGEN	RTK inhibition of VEGFR, FGFR and PDGFR	Phase I
	INX-4437	INEX USA	Antisense ODN targeting IGF1R mRNA	Phase I
TRK	CEP-701	Cephalon	TKI of TRK receptor kinase	Phase II

[a]Abbreviations: FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; MAb, monoclonal antibody; ODN, oligodeoxynucleotide; PDGFR, platelet derived growth factor receptor; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23 2004-2005

TYROSINE KINASE RECEPTOR AS A CIBLE FOR CHEMOTHERAPY- Antisens oligonucleotide

Antisens oligonucleotide interact with the RNAm to block the transcription and thus the expression of specific target proteins



Zwick et al, Trends in Molecular Medicine (2002) 8: 17-23

2004-2005

ANTISENS OLIGONUCLEOTIDE AS RECEPTOR TYROSINE KINASE -BASED DRUGS IN CLINICAL TRIALS

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VEGFR1	RPI.4610 Angiozyme	Ribozyme Pharmaceuticals	Nuclease-stabilized hairpin ribozyme targeting VEGFR1 mRNA	Phase I/II
VEGFR/ FGFR/	SU6668	SUGEN	RTK inhibition of VEGFR, FGFR and PDGFR	Phase I
IGF1R	INX-4437	INEX USA	Antisense ODN targeting IGF1R mRNA	Phase I
TRK	CEP-701	Cephalon	TKI of TRK receptor kinase	Phase II

[a]Abbreviations: FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; MAb, monoclonal antibody; ODN, oligodeoxynucleotide; PDGFR, platelet derived growth factor receptor; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

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2004-2005