

# TRANSDUCTION DU SIGNAL

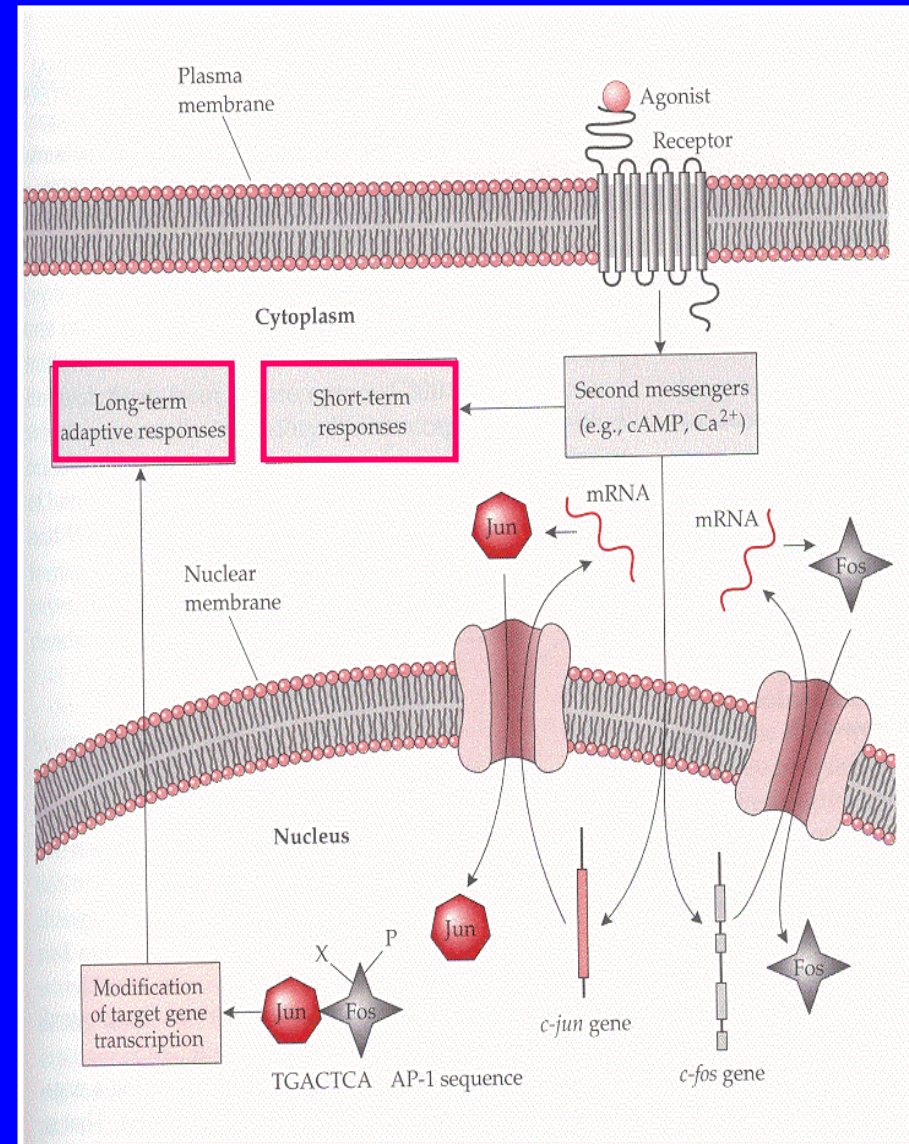
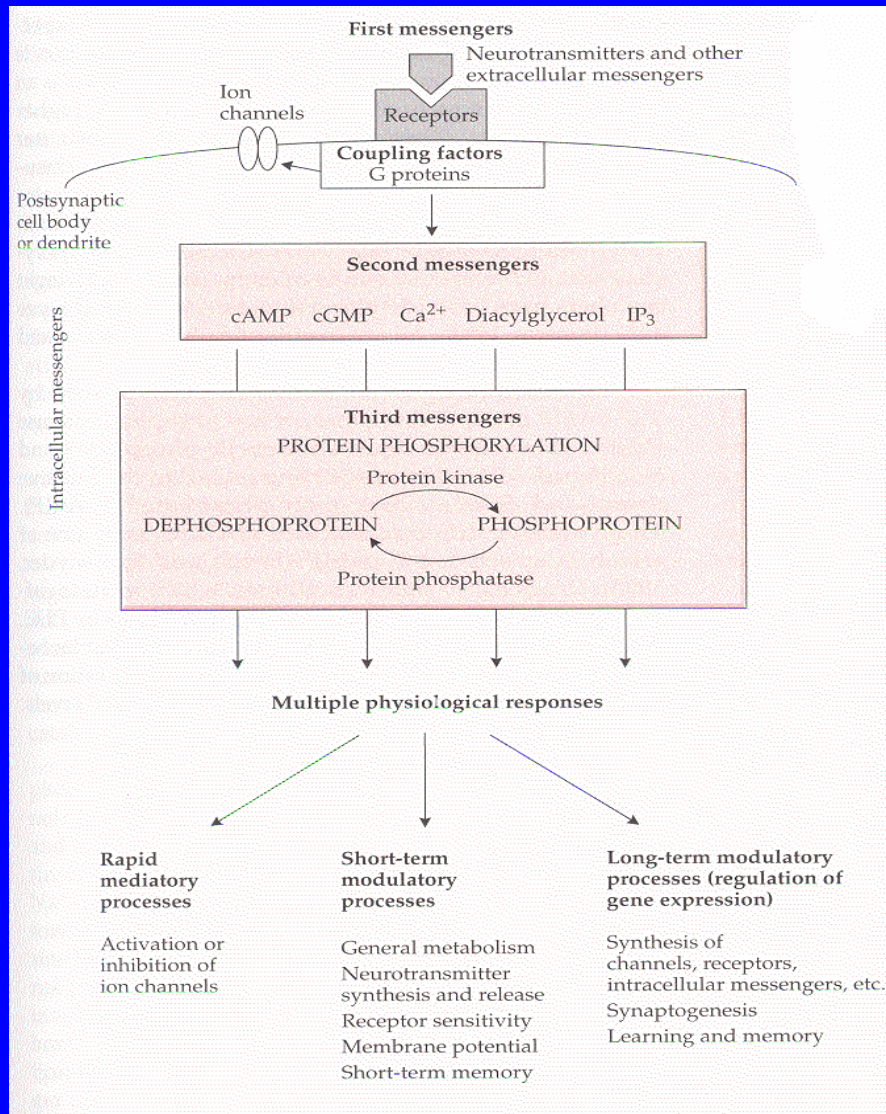
**Messageurs intracellulaires**

**Couplage aux protéines G**

**Transmission via la voie des MAP kinases**

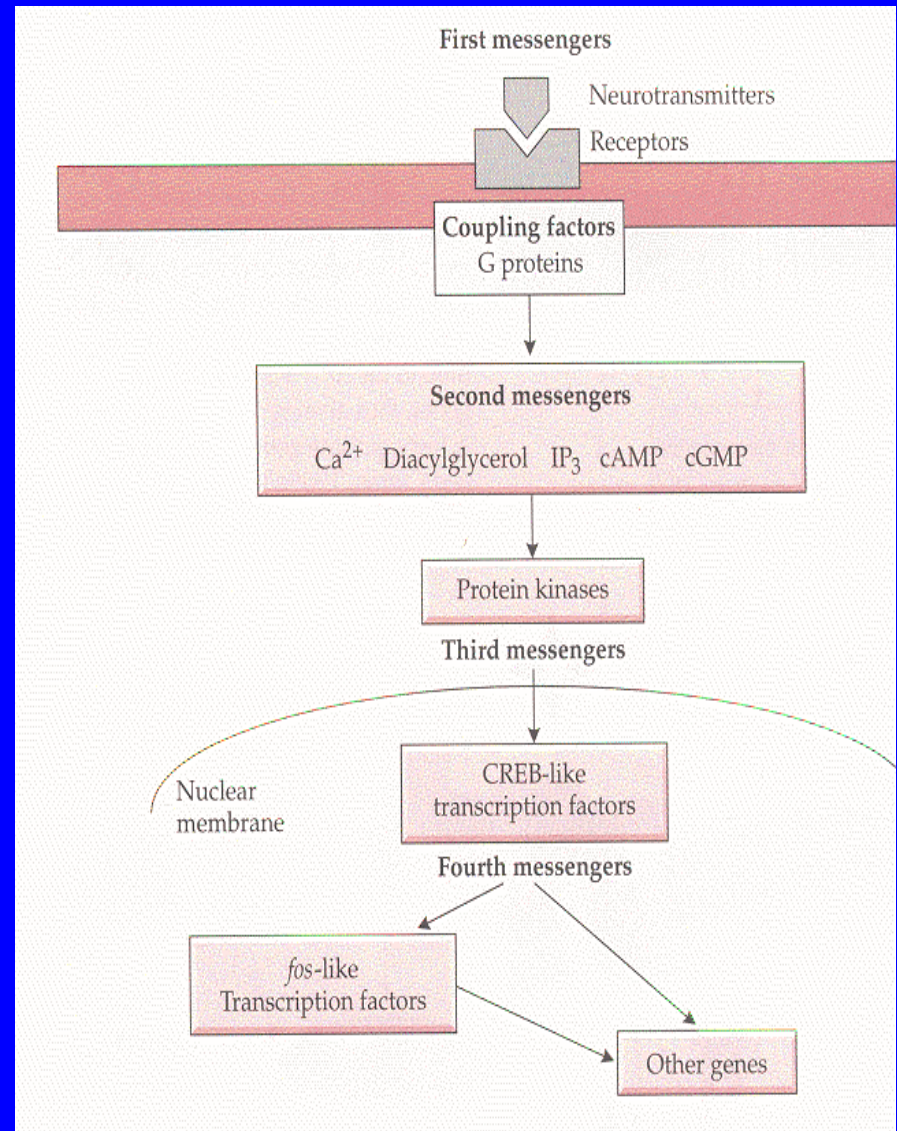
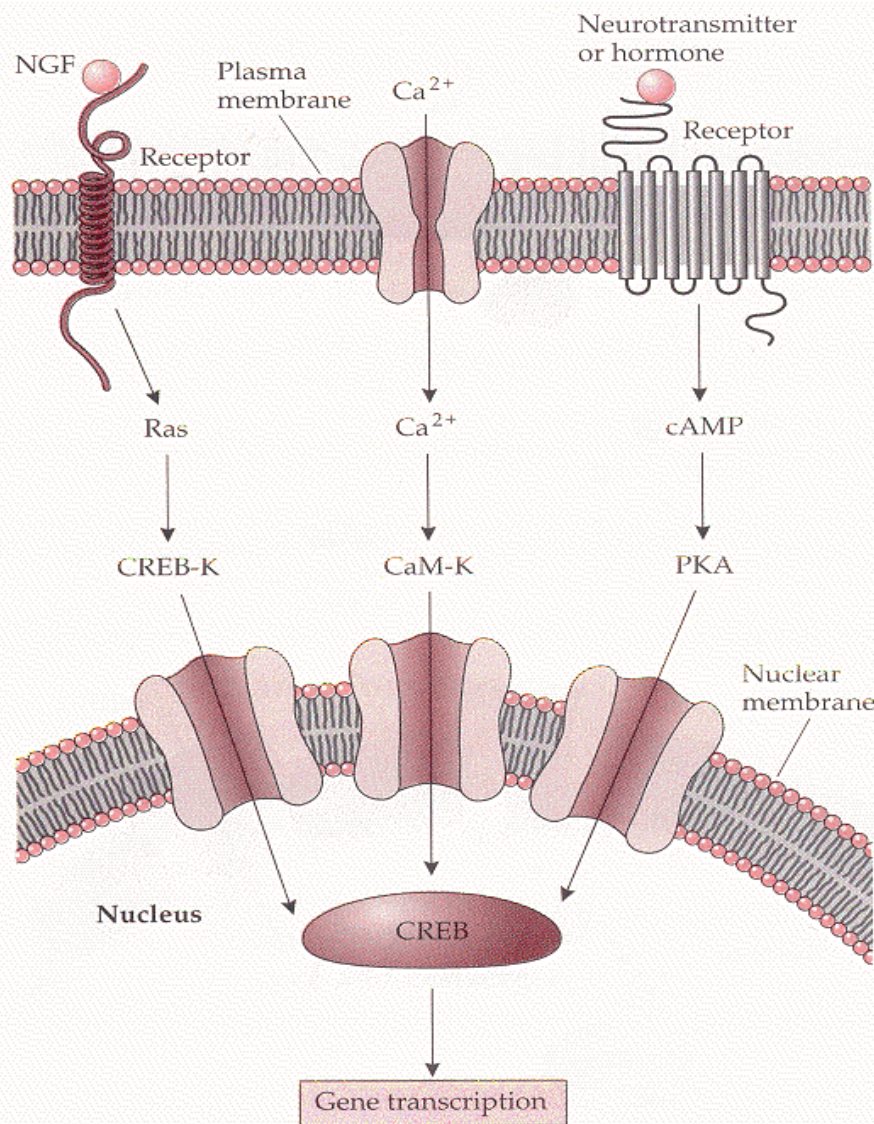
**Transmission via la voie du NO**

# TRANSDUCTION DU SIGNAL - MESSAGERS INTRACELULAIRES





# TRANSDUCTION DU SIGNAL LONG TERME ADAPTIVE RESPONSE



<b>Messageur</b>	<b>Source</b>	<b>Effets</b>
AMPc	Adenylate cyclase	Active les protéines kinases
GMPc	Guanylate cyclase	Active les protéines kinases Régule des canaux ioniques Régule des phosphodiesterases
Ca <sup>2+</sup>	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

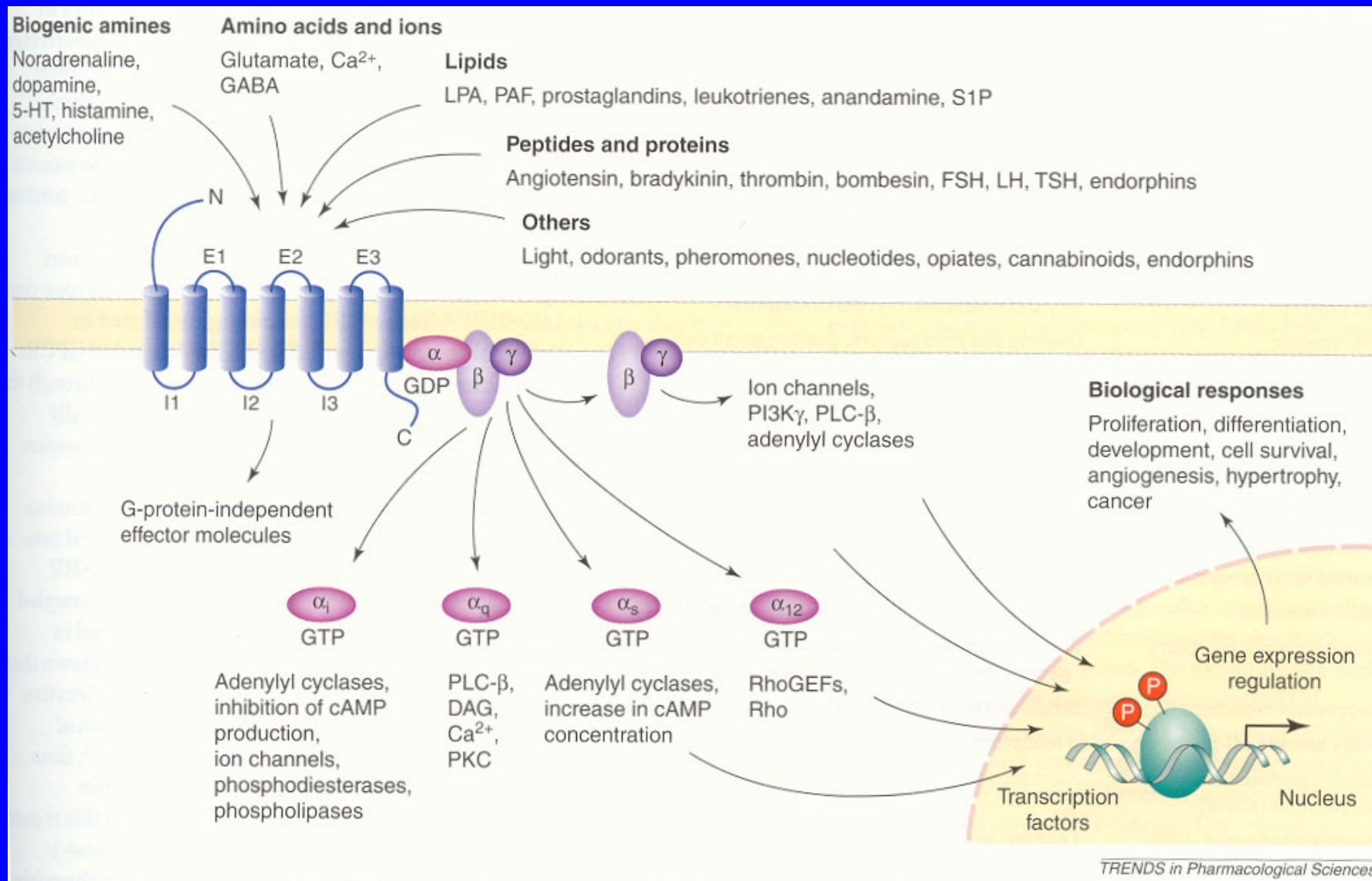
# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G

## Système d'amplification

Un unique complexe agoniste-récepteur peut activer plusieurs protéines G dont chacune s'associera à une enzyme effectrice pendant un temps suffisamment long pour produire de nombreuses molécules



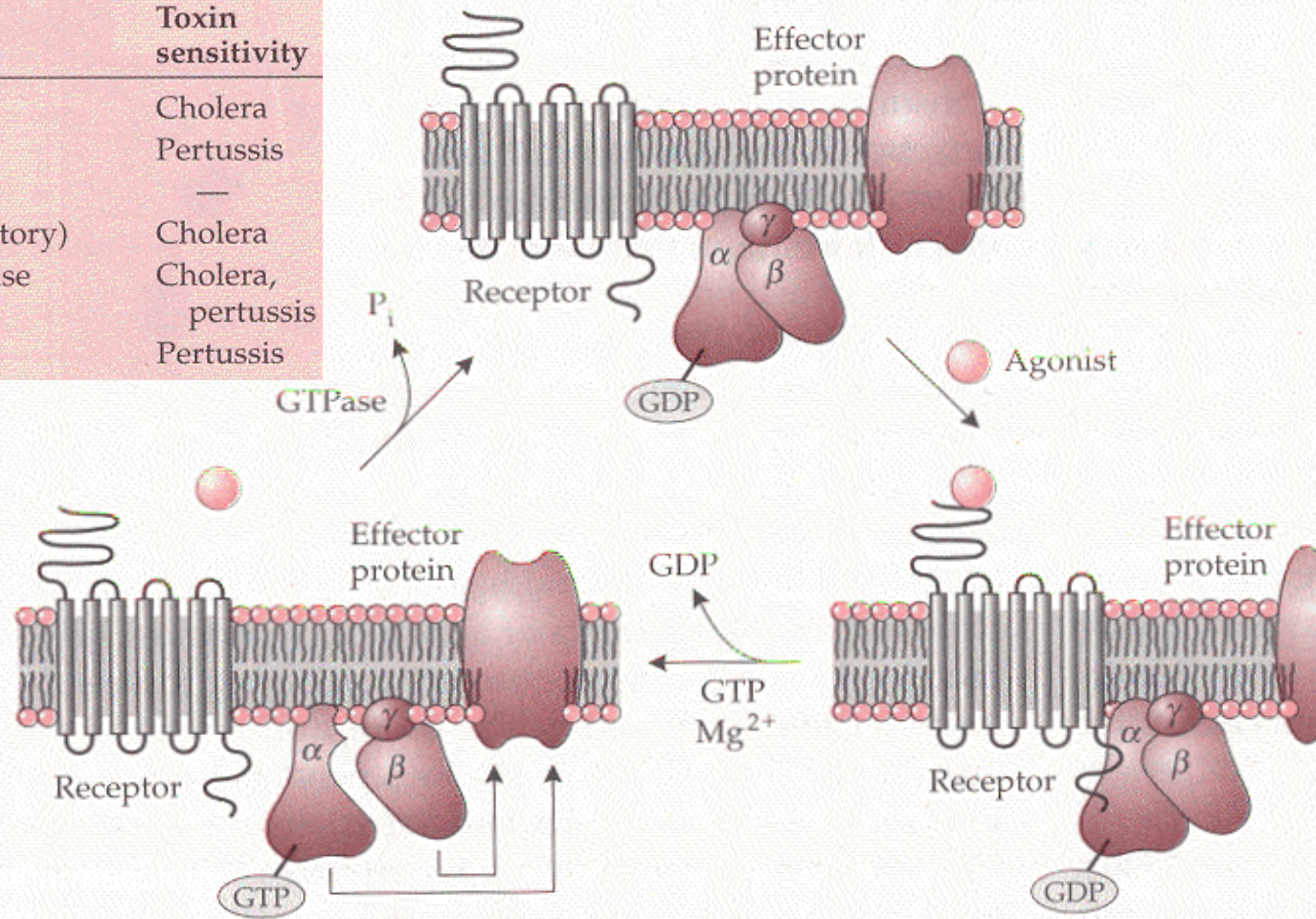
# G-PROTEIN-COUPLED RECEPTORS DIVERSITY



# 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





# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G

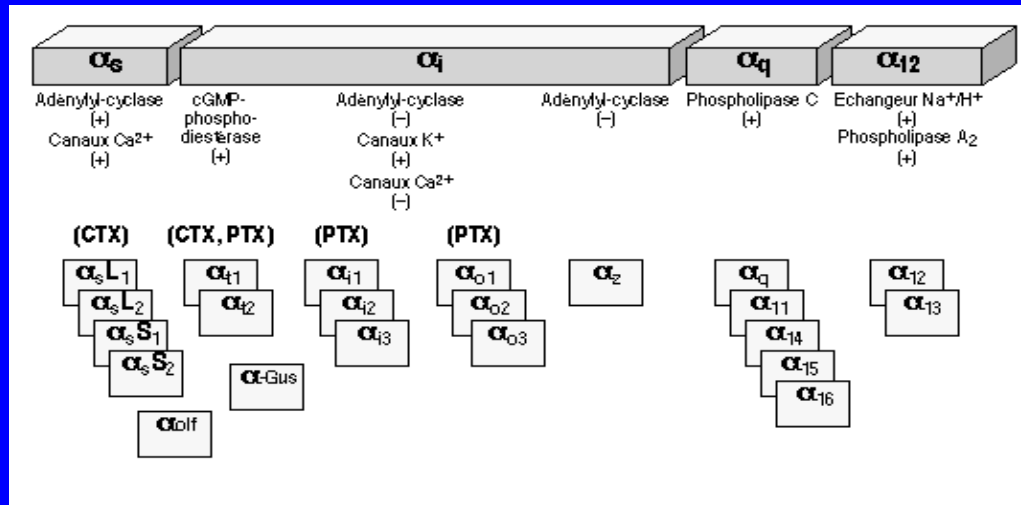
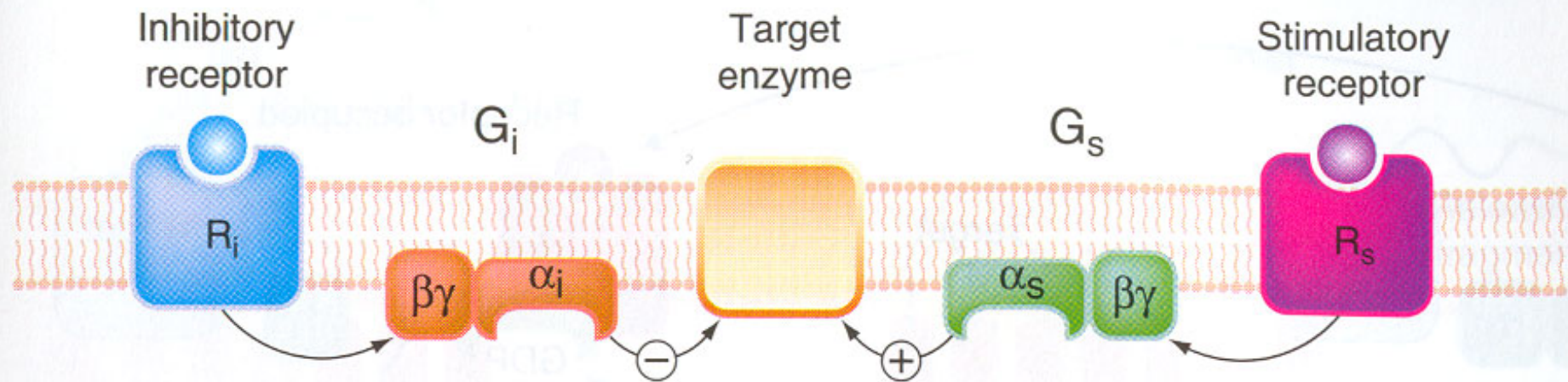


Table 6.2 G Proteins Involved in Neurotransmission

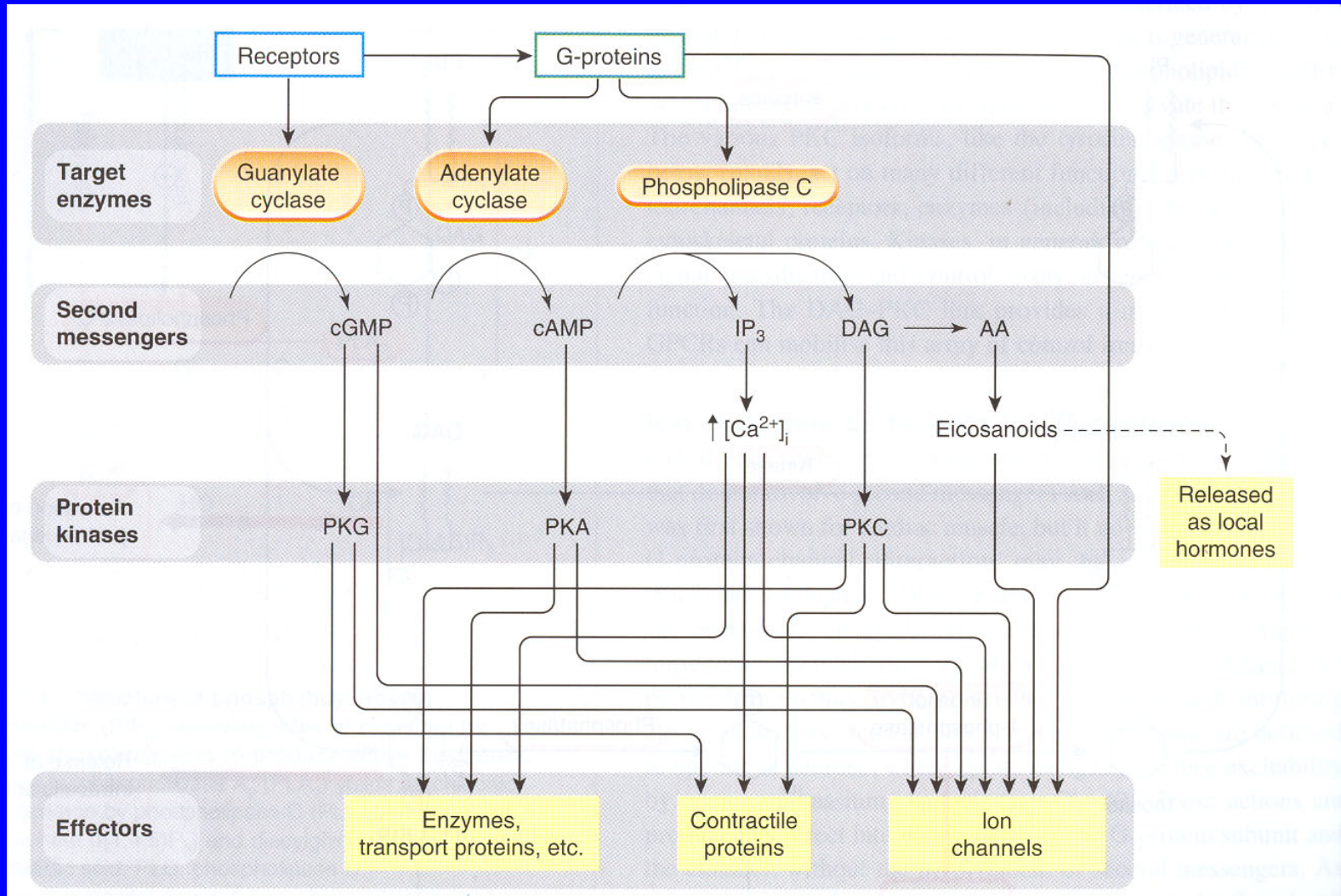
G protein	Second messenger action	Toxin sensitivity
G <sub>s</sub>	↑ Adénylyl cyclase	Cholera
G <sub>i</sub>	↓ Adénylyl cyclase	Pertussis
G <sub>q</sub>	↑ Phospholipase C	—
G <sub>olf</sub>	↑ Adénylyl cyclase (olfactory)	Cholera
G <sub>t</sub>	↑ cGMP phosphodiesterase (retina)	Cholera, pertussis
G <sub>o</sub>	None	Pertussis

	N-terminus	C-terminus
G $\alpha_{\Delta 6q5myr}$	MGC . CLS . . . . .	QYELL
G $\alpha_{\Delta 6q4myr}$	MGC . CLS . . . . .	ECGLF
G $\alpha_{\Delta 6q}$	MAC . CLS . . . . .	EYNLV
G $\alpha_s$	MGCLGNS . . . . .	QYELL
G $\alpha_i$	MGC . TLS . . . . .	DCGLF
G $\alpha_{11}$	MTLESIMAC . CLS . . . . .	EYNLV
G $\alpha_q$	MTLESIMAC . CLS . . . . .	EYNLV



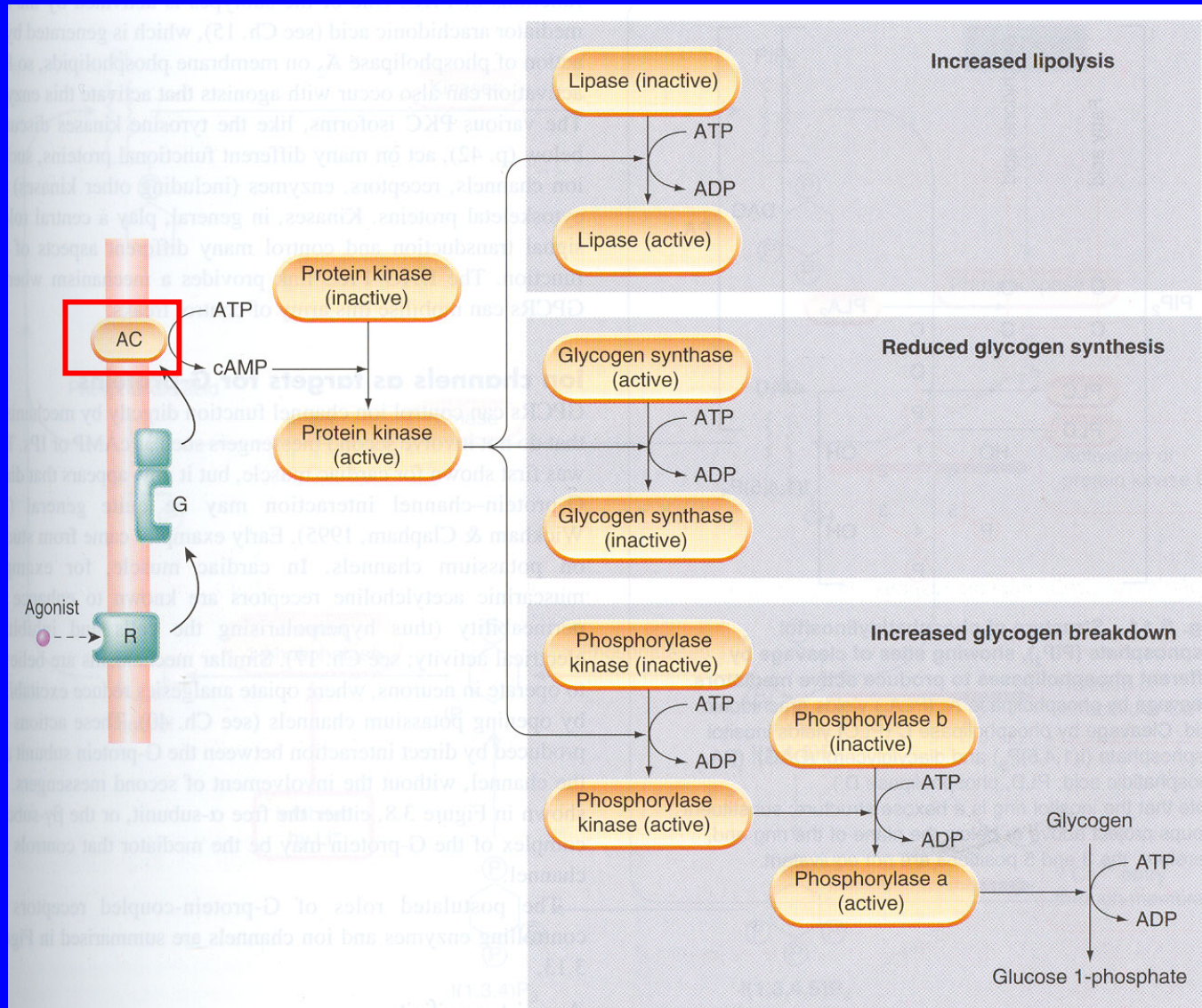


# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G





# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G - Adenylate cyclase





# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G – Hormones that activate or inhibit adenylate cyclase

<b><u>Activators</u></b> Corticotropin (ACTH) Calcitonin Catecholamines (acting on $\beta_1$ and $\beta_2$ receptors ) Choriogonadotropin Follicle-stimulating hormone (FSH) Glucagon Gonadotropin-releasing hormone (GnRH) Growth hormone-releasing hormone Luteinizing hormone (LH)	Lipotropin Melanocyte-stimulating hormones (MSH) Parathormone (PTH) Secretin Thyrotropin regulatory hormone (TRH) Thyrotropin (TSH) Vasoactive intestinal peptide (VIP) Vasopressin
<b><u>Inhibitors</u></b> Angiotensin Catecholamines (acting on $\alpha_2$ receptors)	

# Adenylate cyclase



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

# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G - Adenylate cyclase

**Table 2. Adenylate cyclase: type-specific patterns of regulation**

Adenylate cyclase type	Regulatory signal											
	G <sub>i</sub> α		Gβγ		PKA		PKC <sup>d</sup>		Ca <sup>2+</sup> /CaM		Other Ca <sup>2+</sup> - mediated effects	
	Effect	Refs	Effect	Refs	Effect	Refs	Effect	Refs	Effect	Refs	Effect	Refs
AC1	↓	a	↓	25, 26			↑	e, 30, 31	↑	35	↓	g
AC2	—	b	↑	25–27			↑	27, 32–34	—	7		
AC3	↓	22	—	25			↑	30, 31	↑	36	↓	h
AC4			↑	11			↓	f	—	11		
AC5	↓	23			↓	28			—	12	↓	i
AC6	↓	22, 24	—	13	↓	29	—	30	—	16	↓	j
AC7			(↑)	c			↑	17, 18	—	17		
AC8									↑	19	—	g
AC9			—	20					—	20	↓	i

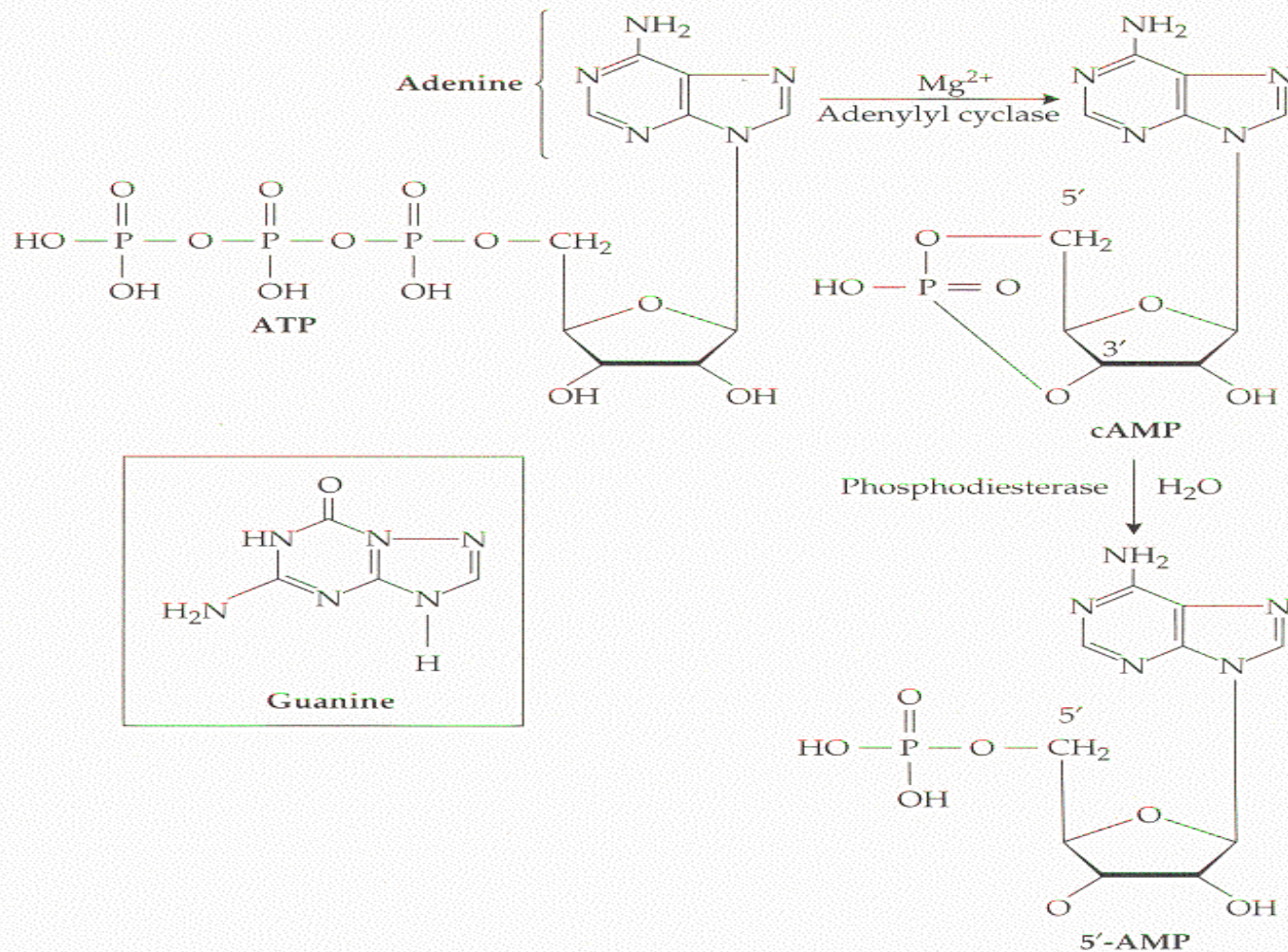


# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G - Adenylate cyclase - isoforms

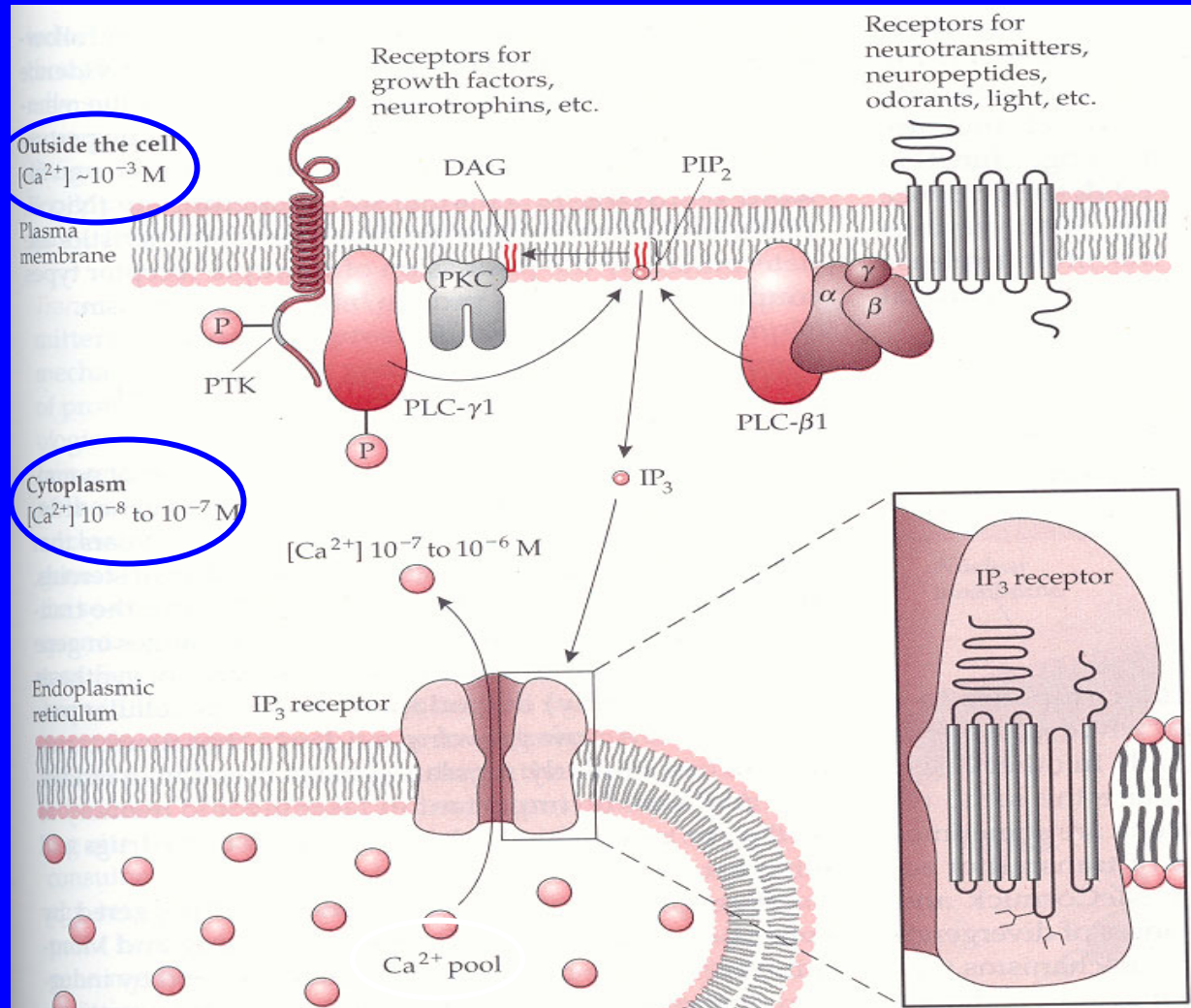
**Table 1. Mammalian isoforms of adenylate cyclase**

<b>Adenylate cyclase (AC) type</b>	<b>Size (no. of amino acids)</b>	<b>mRNA expression</b>
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 <sup>a</sup>
AC9	1353	Skeletal muscle, brain > kidney lung, liver, heart

# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G - AMP cyclique

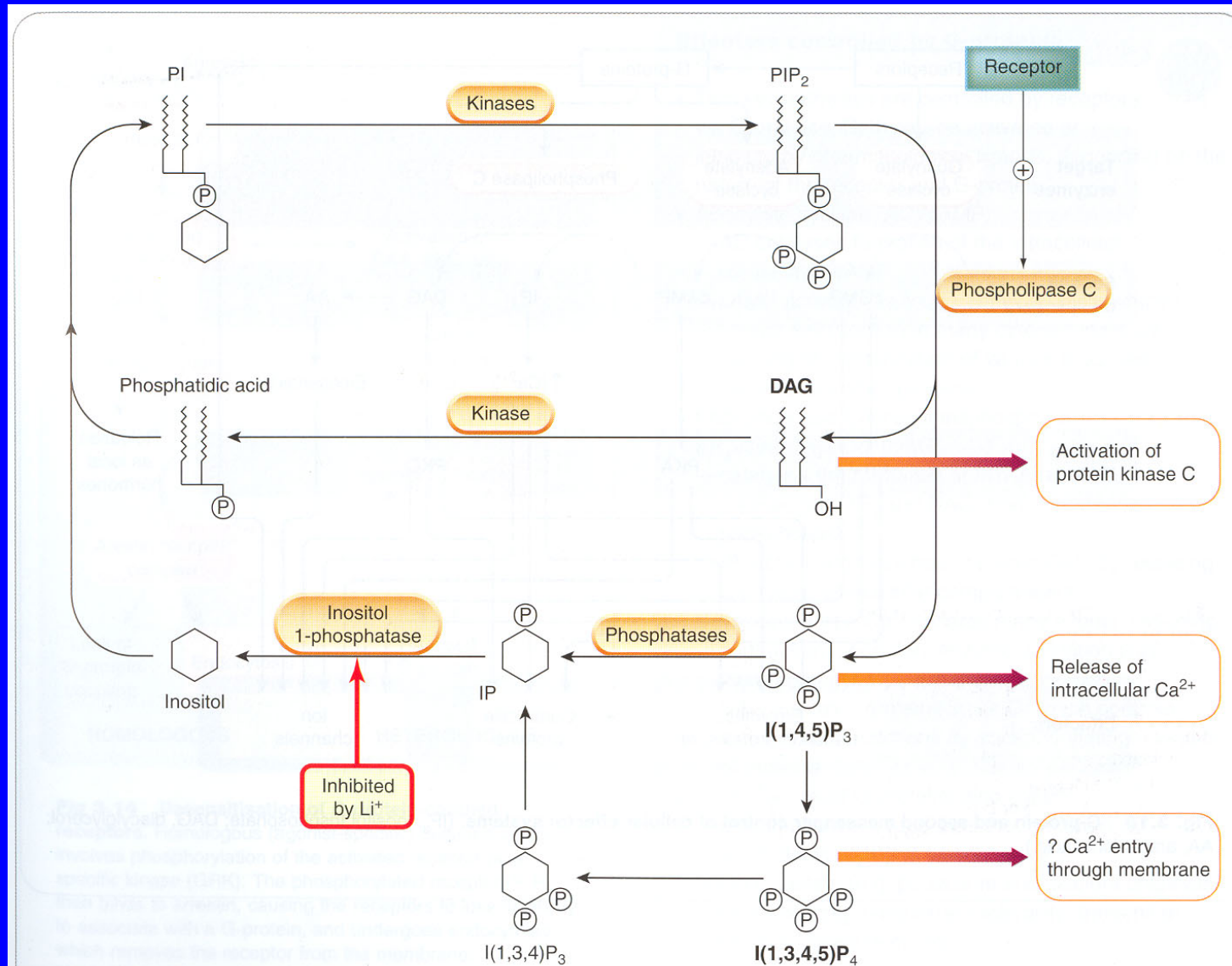


# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G - Phospholipase C

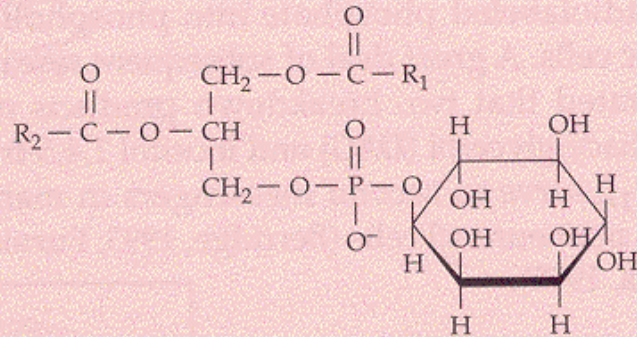




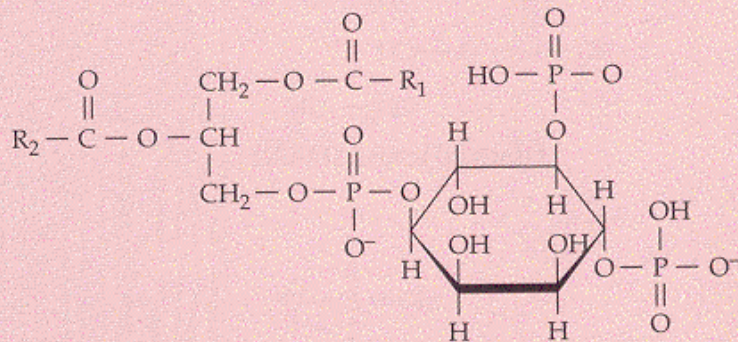
# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G - Phospholipase C



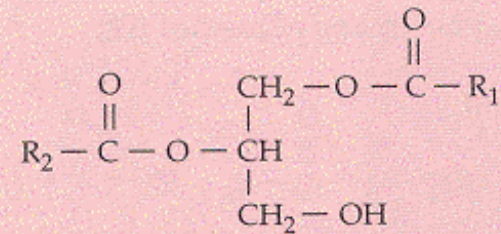
# TRANSDUCTION DU SIGNAL - COUPLAGE AUX PROTEINES G PI, PIP<sub>2</sub>, DAG AND IP<sub>3</sub>



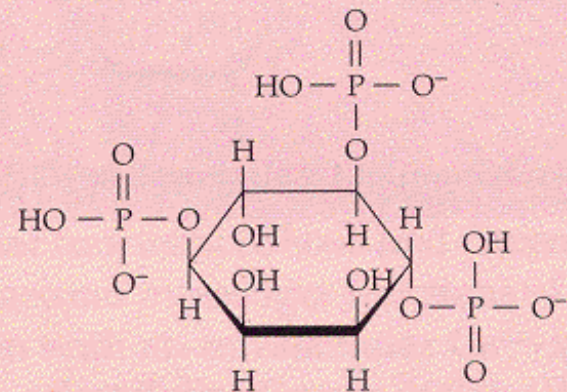
Phosphatidylinositol (PI)



Phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>)



Diacylglycerol (DAG)



Inositol 1,4,5-trisphosphate (IP<sub>3</sub>)

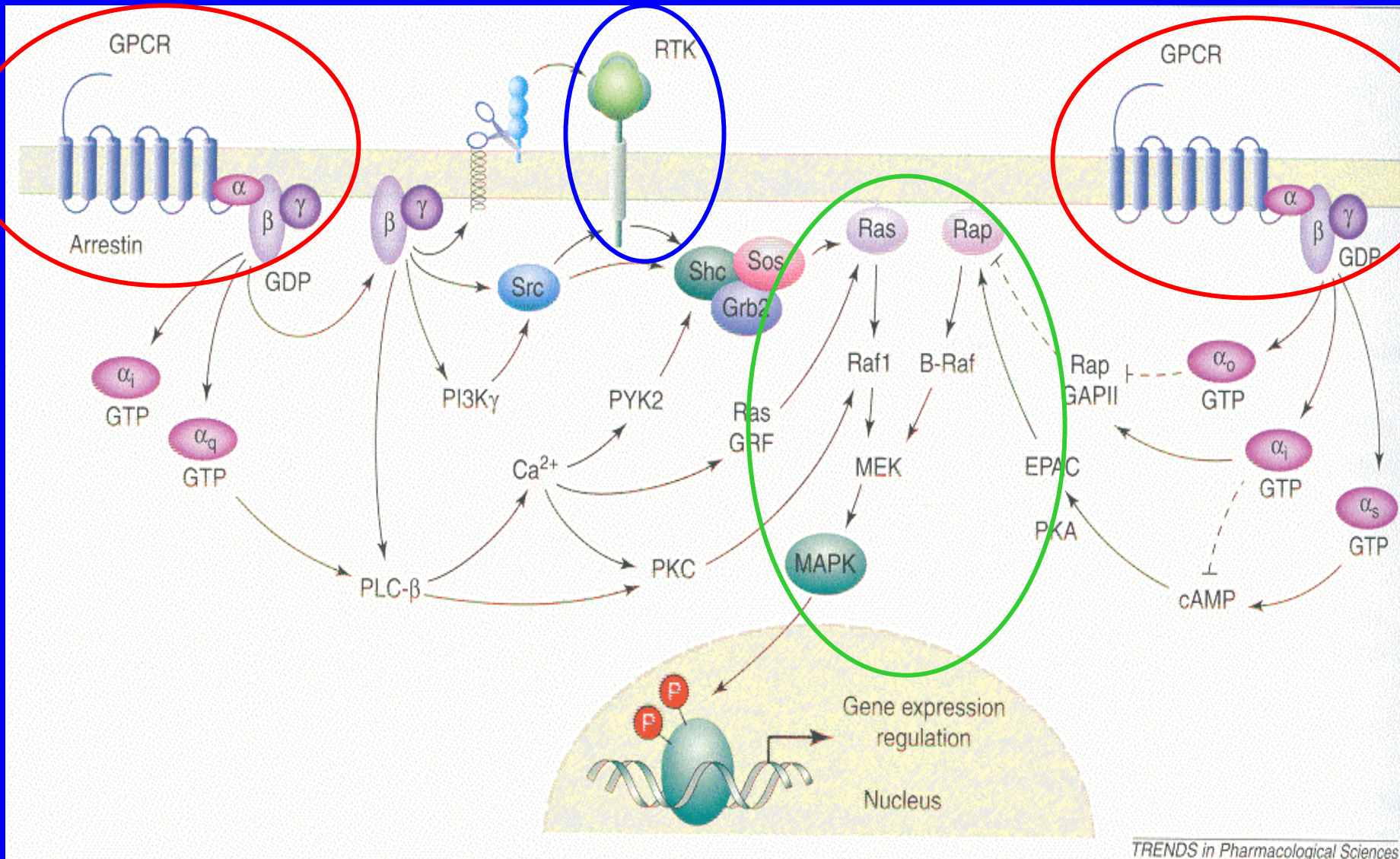
# PROTEINES G ET RECEPTEURS COUPLES AUX PROTEINES G - POTENTIALITES THERAPEUTIOQUES

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

Type of tumor	
<b>Activating mutations:</b>	
<b>G proteins</b>	
G $\alpha_s$	Thyroid toxic adenomas, thyroid carcinomas, growth-hormone-secreting pituitary adenomas, McCune-Albright syndrome
G $\alpha_{12}$	Ovarian sex cord tumors, adrenal cortical tumors
<b>G-protein-coupled receptors</b>	
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 <sub>2</sub> receptor	Colorectal cancer
Ca <sup>2+</sup> -sensing receptor	Autosomal-dominant hypocalcemia, neoplasms
<b>Autocrine and paracrine activation:</b>	
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
<b>Virally encoded G-protein-coupled receptors:</b>	
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



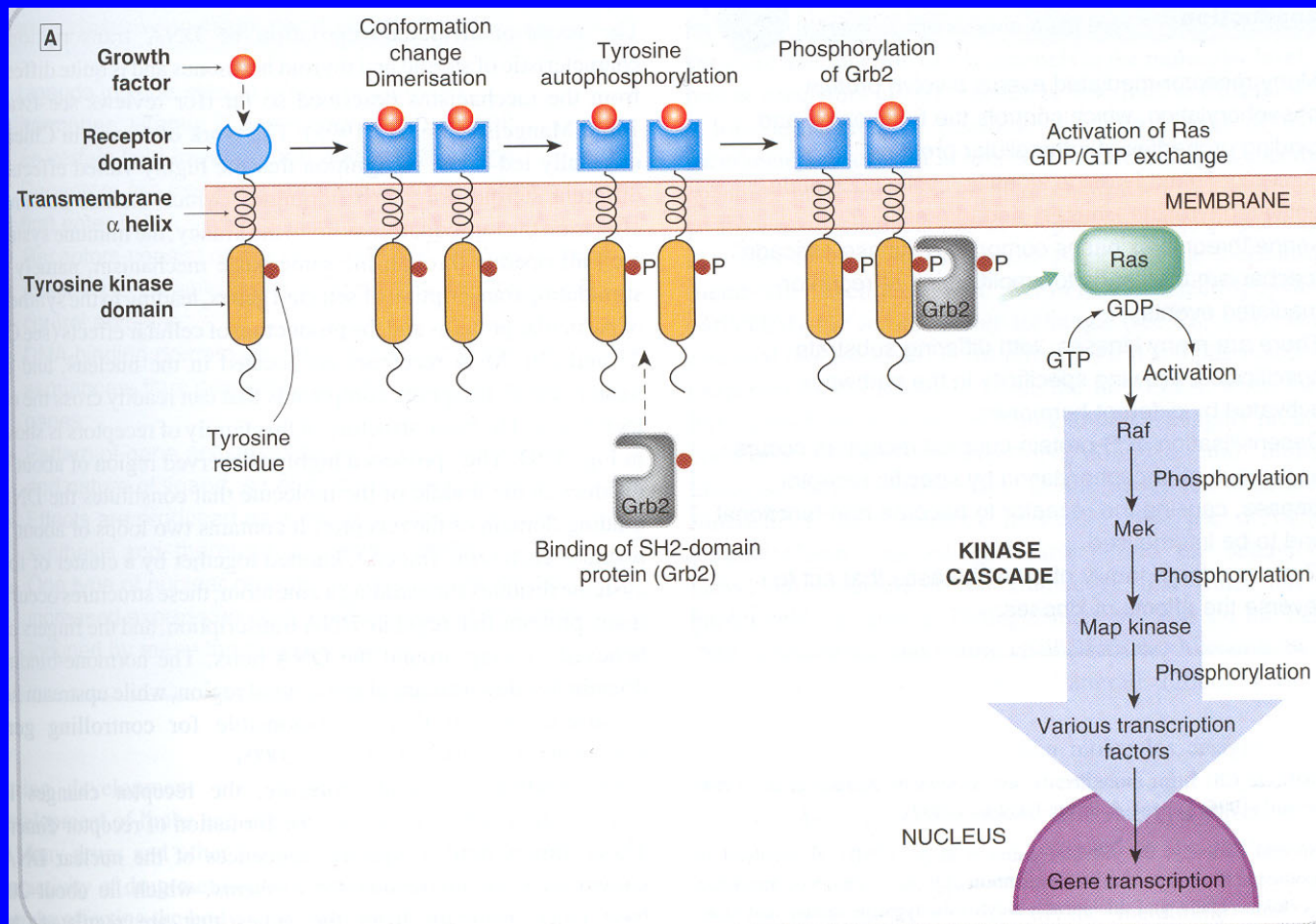
# TRANSDUCTION DU SIGNAL - PROTEINES G ET VOIE DES MAPK



TRENDS in Pharmacological Sciences

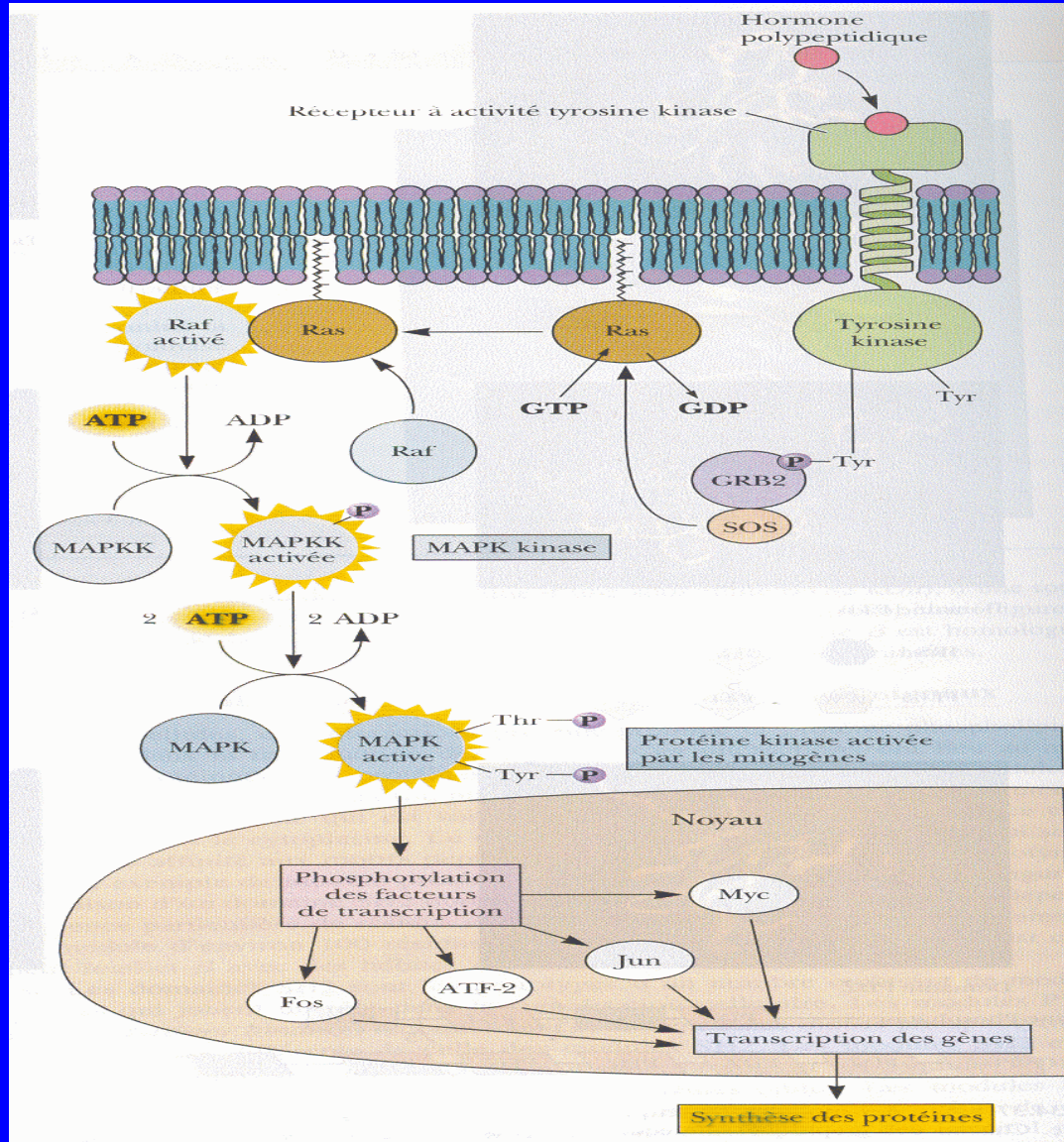
# TRANSDUCTION DU SIGNAL ET RECEPTEUR

## TYROSINE KINASE - VOIE DES MAPK



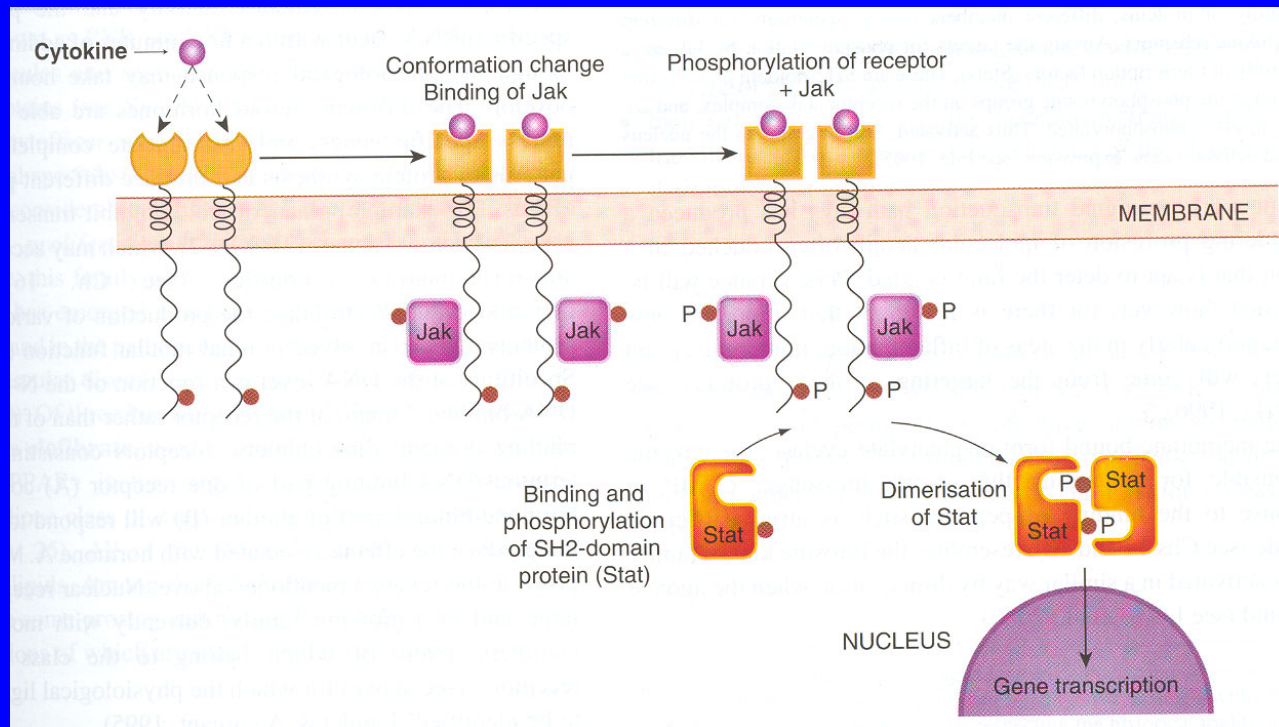


# TRANSDUCTION DU SIGNAL - RECEPTEUR TYROSINE KINASE ET VOIE DES MAPK

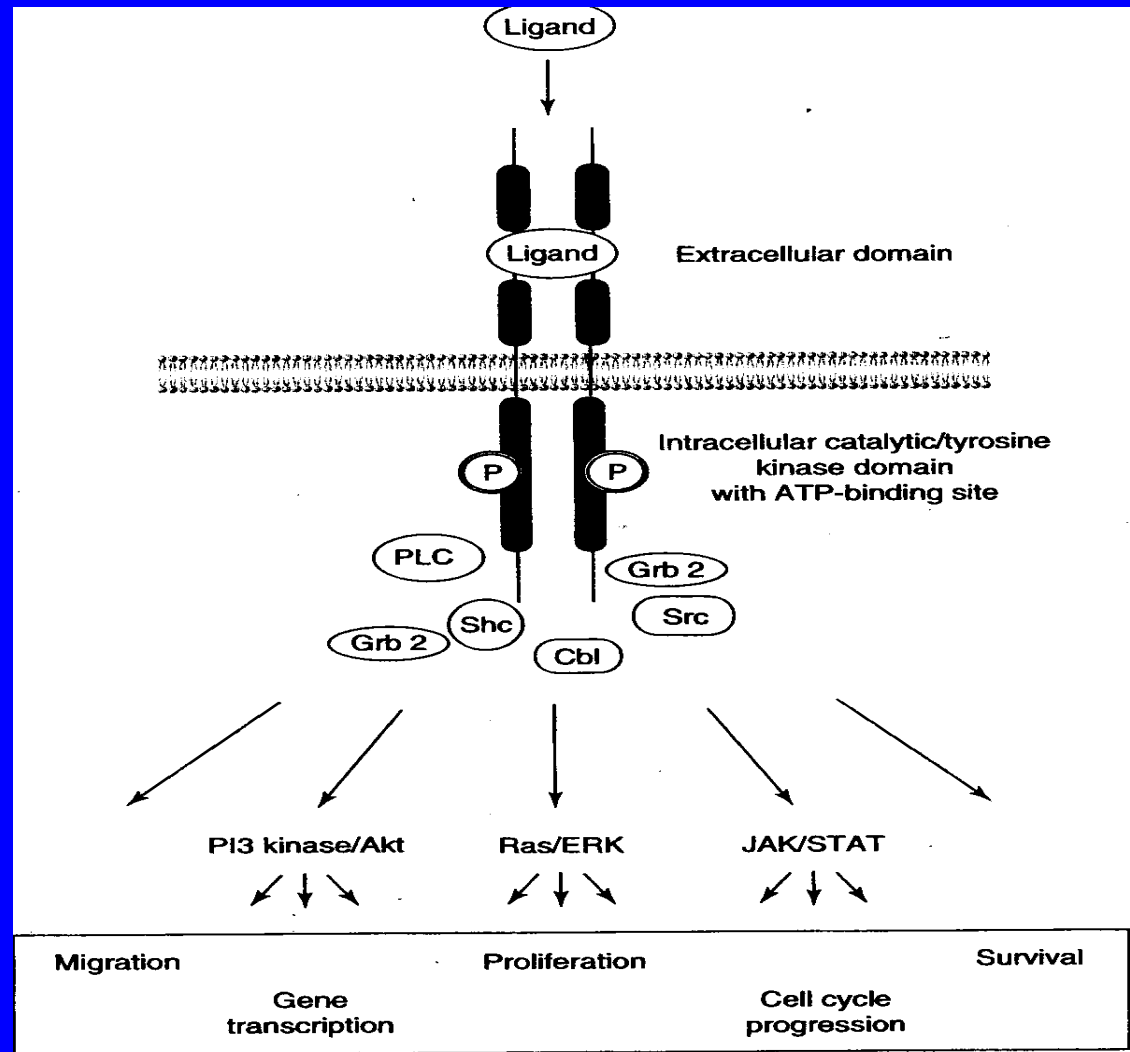




# TRANSDUCTION DU SIGNAL ET RECEPTEUR TYROSINE KINASE - VOIE DES MAPK



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

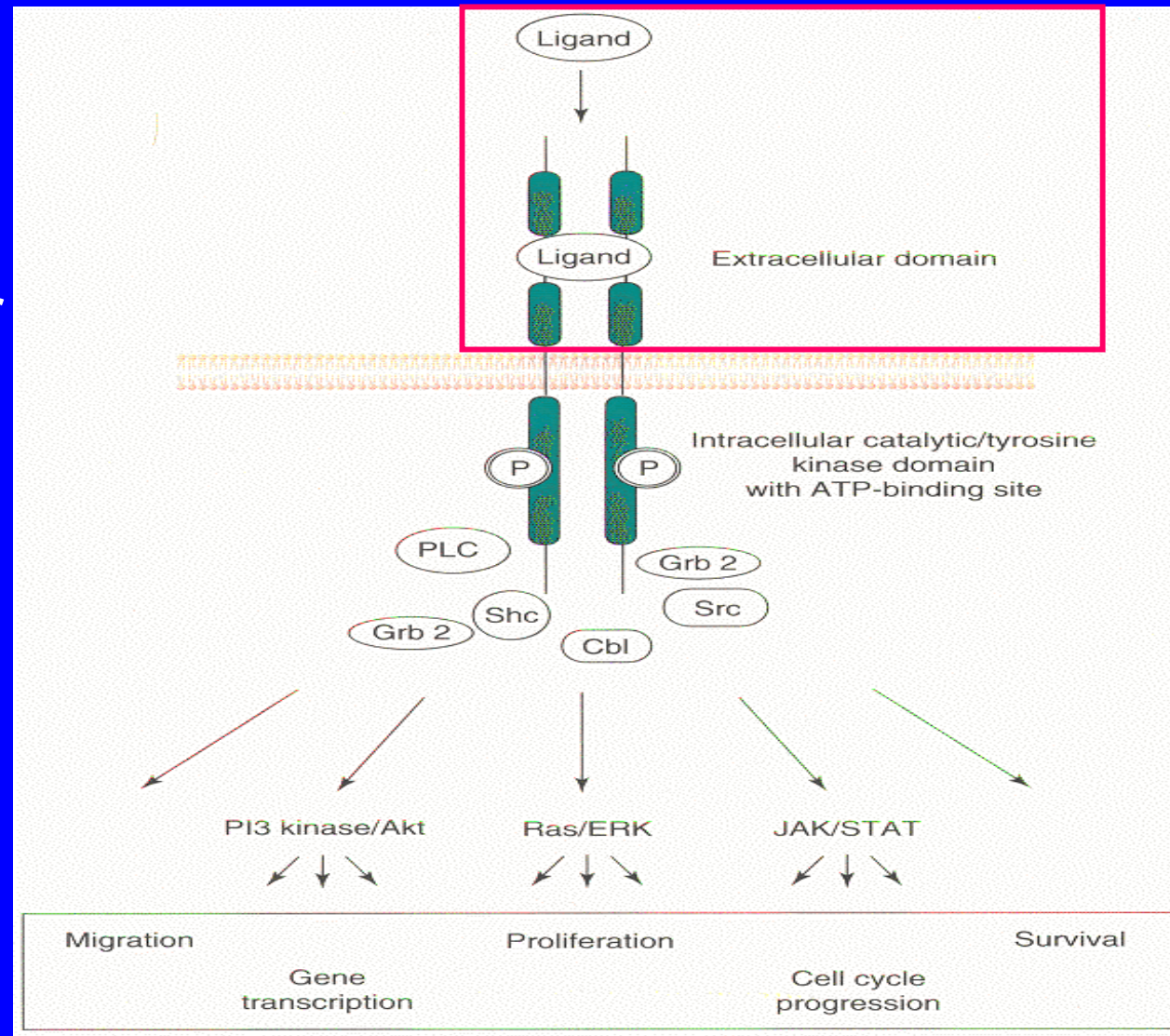


# RECEPTOR TYROSINE KINASE- EXTRACELLULAR SITE

Binding of extracellular  
ligand

DIMERIZATION

Increase of receptor  
tyrosine kinase activity





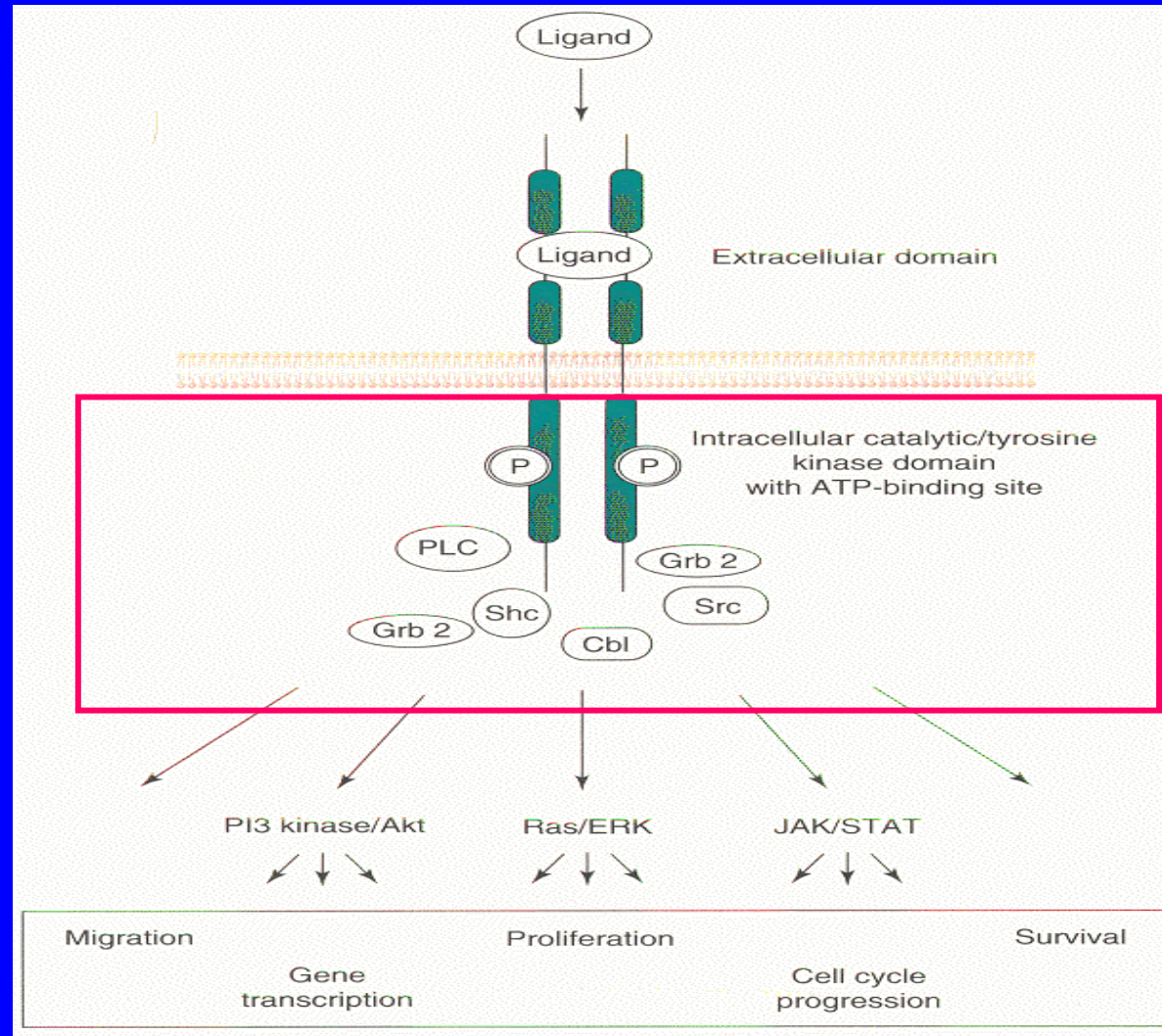
# RECEPTOR TYROSINE KINASE- INTRACELLULAR BINDING SITE

Catalyse of recepteur  
autophosphorylation of  
cytoplasmic  
tyrosine residues

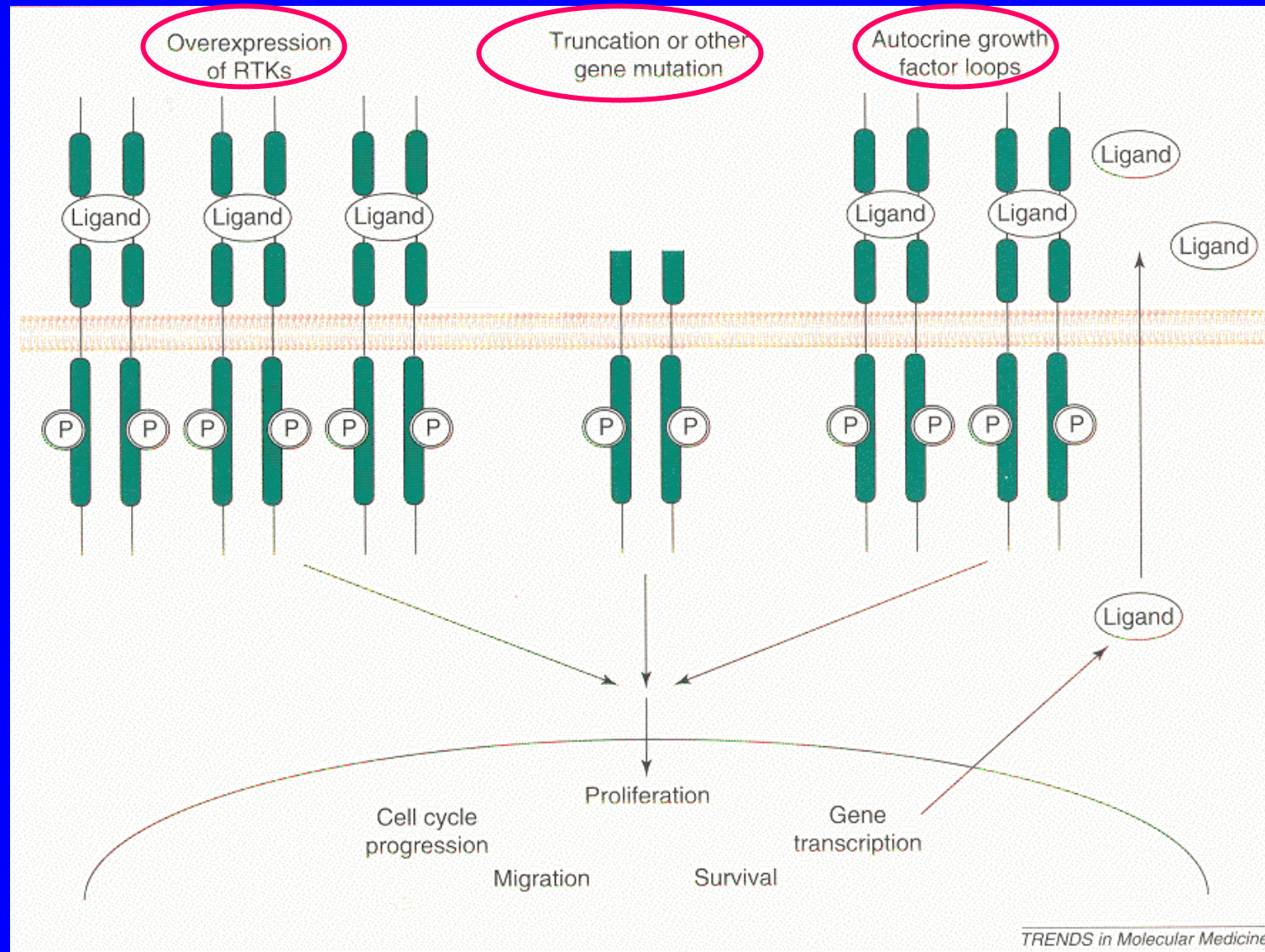
→ Docking sites for Src  
homology (SH) and  
phosphotyrosine-binding  
(PTB) containing molecules  
(PLC, Src, ...)

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

⇒ Activation of a cascade of  
intracellular biochemical  
signals



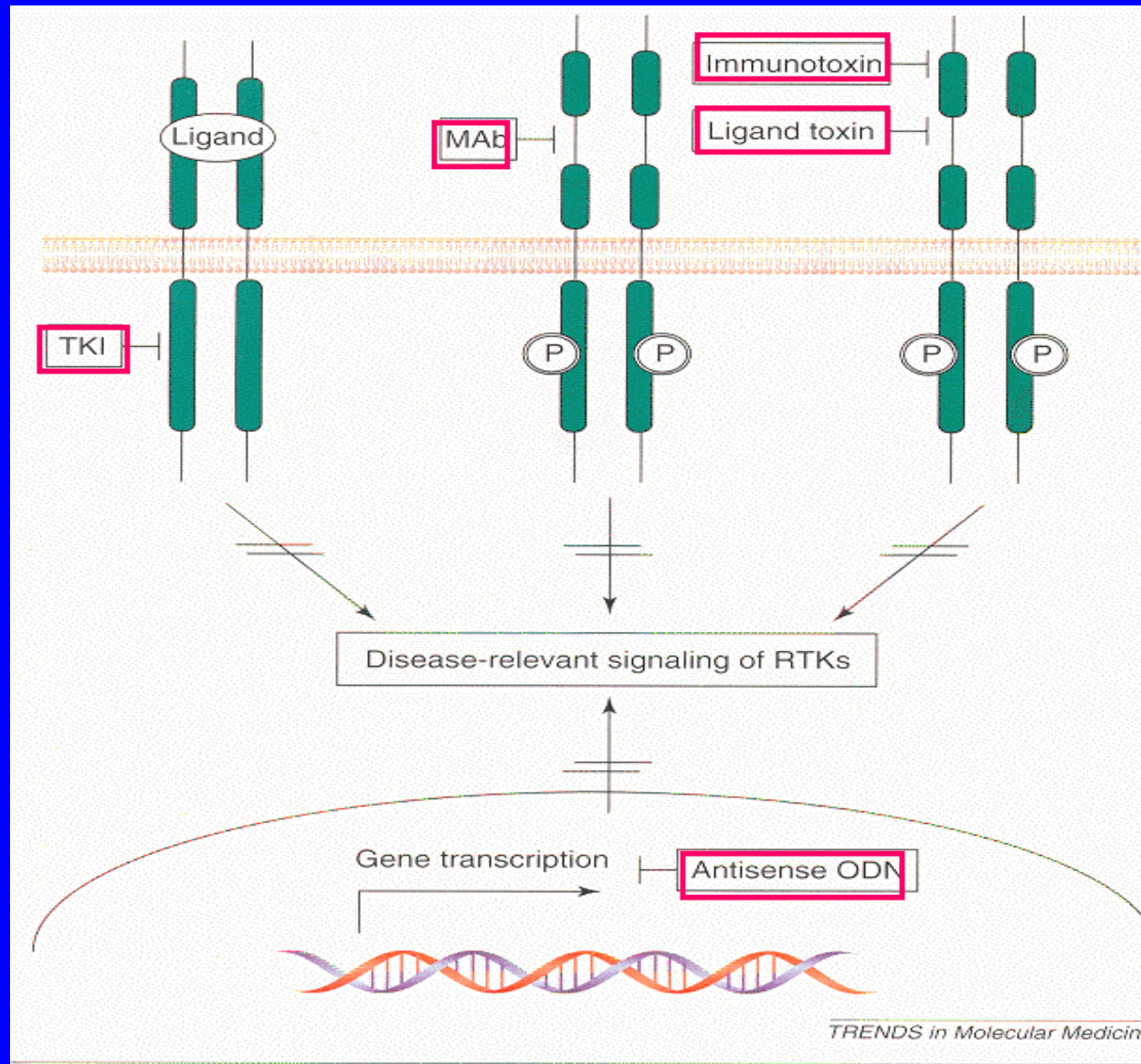
# ROLE PLAYED BY RECEPTOR TYROSINE KINASE IN CANCER



Constitutive  
activation  
of receptor  
tyrosine  
kinase  
~ malignant  
transformati  
on

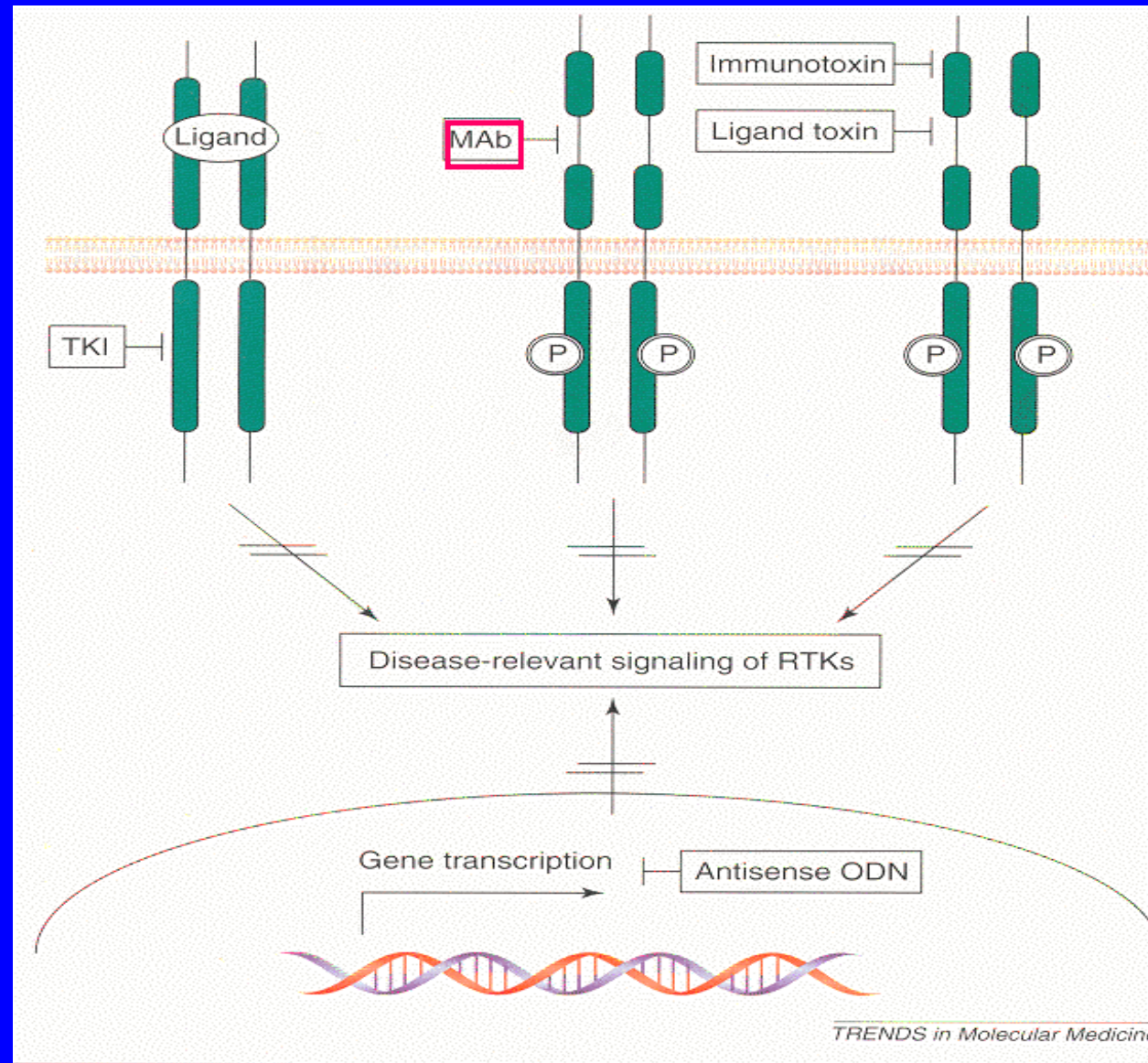


# TYROSINE KINASE RECEPTOR AS A CIBLE FOR CHEMOTHERAPY





# MONOCLONAL ANTIBODIES AS ANTI-TYROSINE KINASE RECEPTOR DRUGS



Anti-RTK mAbs block the ligand-receptor interaction

⇒ inhibition of ligand-induced RTK signaling

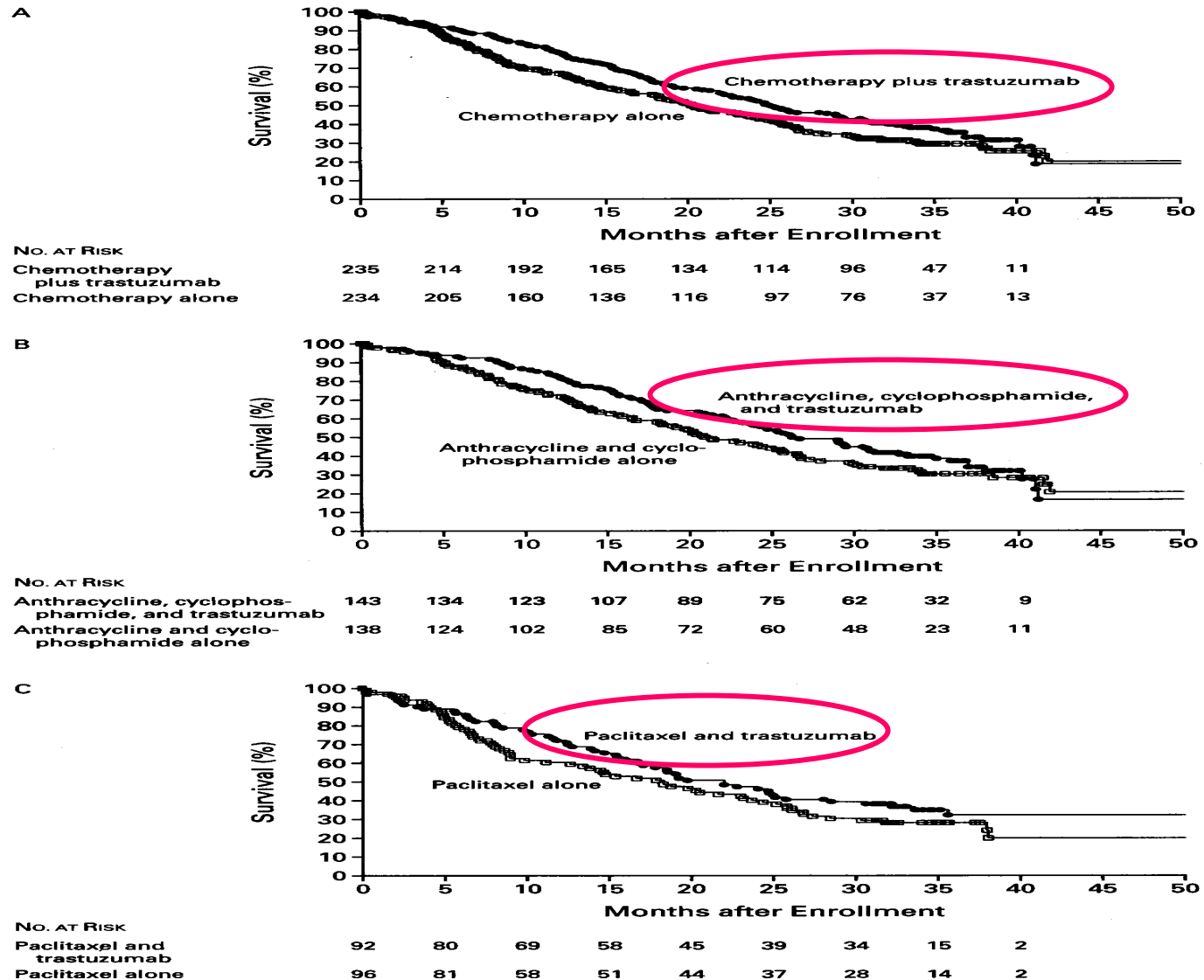
⇒ increase of RTK down regulation and internalization

# 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
IGF1R	INX-4437	INEX USA	Antisense ODN targeting IGF1R mRNA	Phase I
TRK	CEP-701	Cephalon	TKI of TRK receptor kinase	Phase II

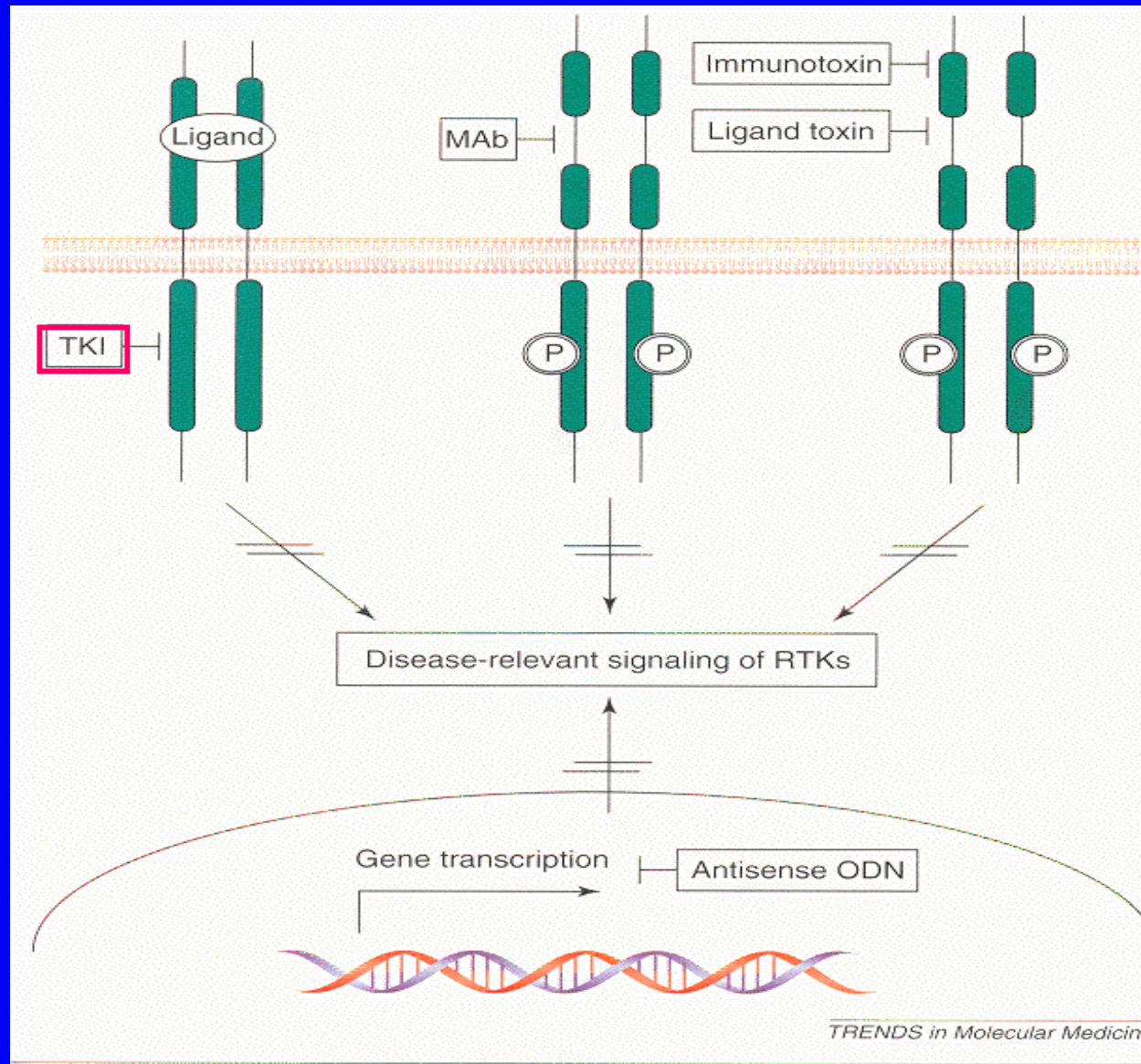
\*Abbreviations: FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; MAb, monoclonal antibody; ODN, oligodeoxynucleotide; PDGFR, platelet derived growth factor receptor; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

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





# INHIBITORS OF TYROSINE KINASE AS A CIBLE FOR CHEMOTHERAPY



# 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
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
IGF1R	INX-4437	INEX USA	Antisense ODN targeting IGF1R mRNA	Phase I
TRK	CEP-701	Cephalon	TKI of TRK receptor kinase	Phase II

\*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.

# 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

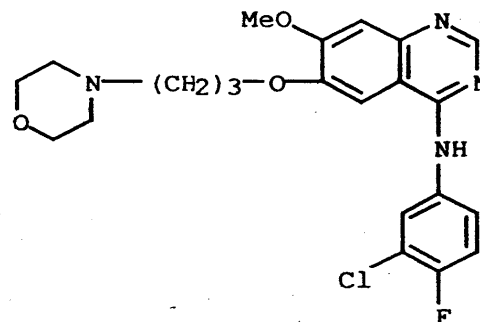
**CA Index Name:** 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (9CI)

**Other Names:** Gefitinib; Iressa; ZD 1839

**Formula:** C<sub>22</sub> H<sub>24</sub> Cl F N<sub>4</sub> O<sub>3</sub>

**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

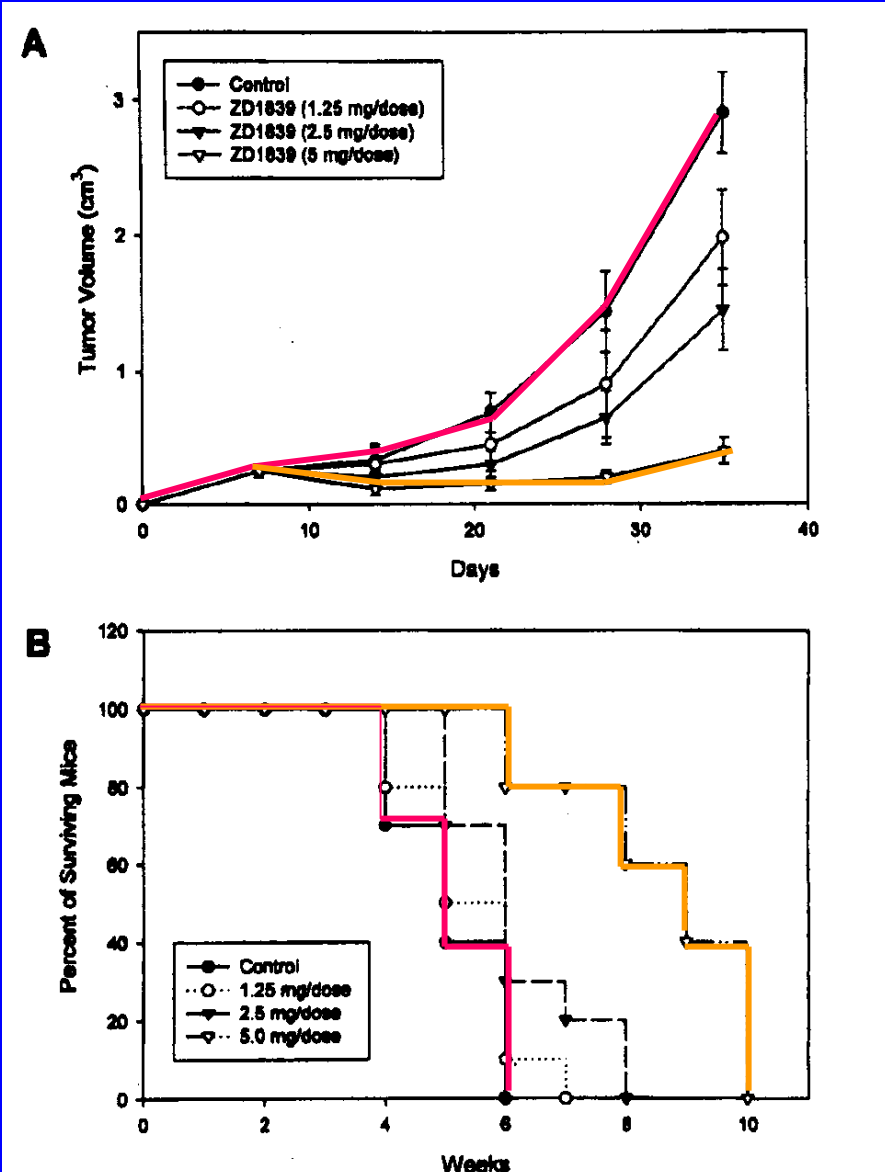




# RECEPTOR TYROSINE KINASE INHIBITORS ACTIVITY - ZD 1839

## Antitumor activity

- volume tumor
  - % of surviving mice
- of ZD-1839 on  
established GEO human  
colon carcinoma  
xenographs: effet dose



# 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

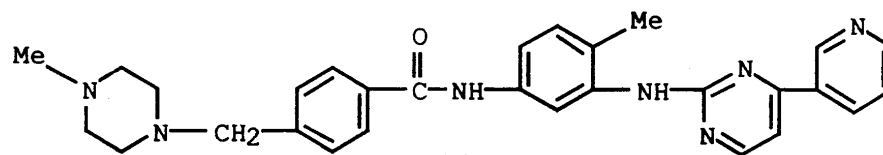
**CA Index Name:** Benzamide,  
4-[[4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridin  
yl)-2-pyrimidinyl]amino]phenyl]- (9CI)

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

**Formula:** C<sub>29</sub> H<sub>31</sub> N<sub>7</sub> 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

# 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 chromo-

some, 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.

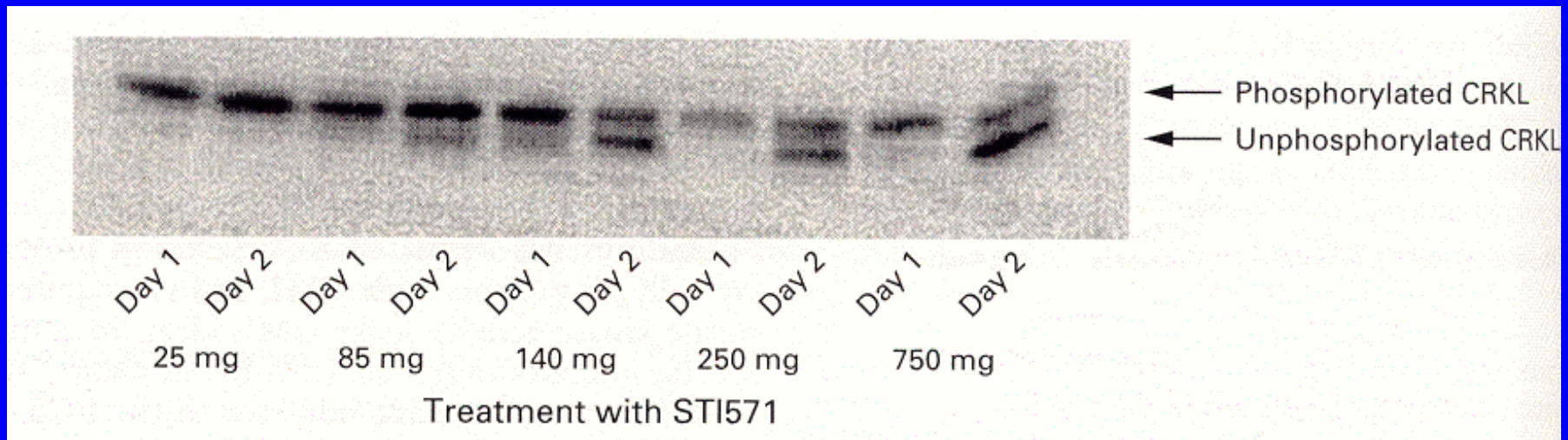
Of course, it's not all good news. Although STI571 therapy has yielded impressive results for patients in the chronic phase of CML, the drug is not effective in the acute phase and long-term treatment has led to the development of drug-resistant tumors. Combination therapies are now being developed that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



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

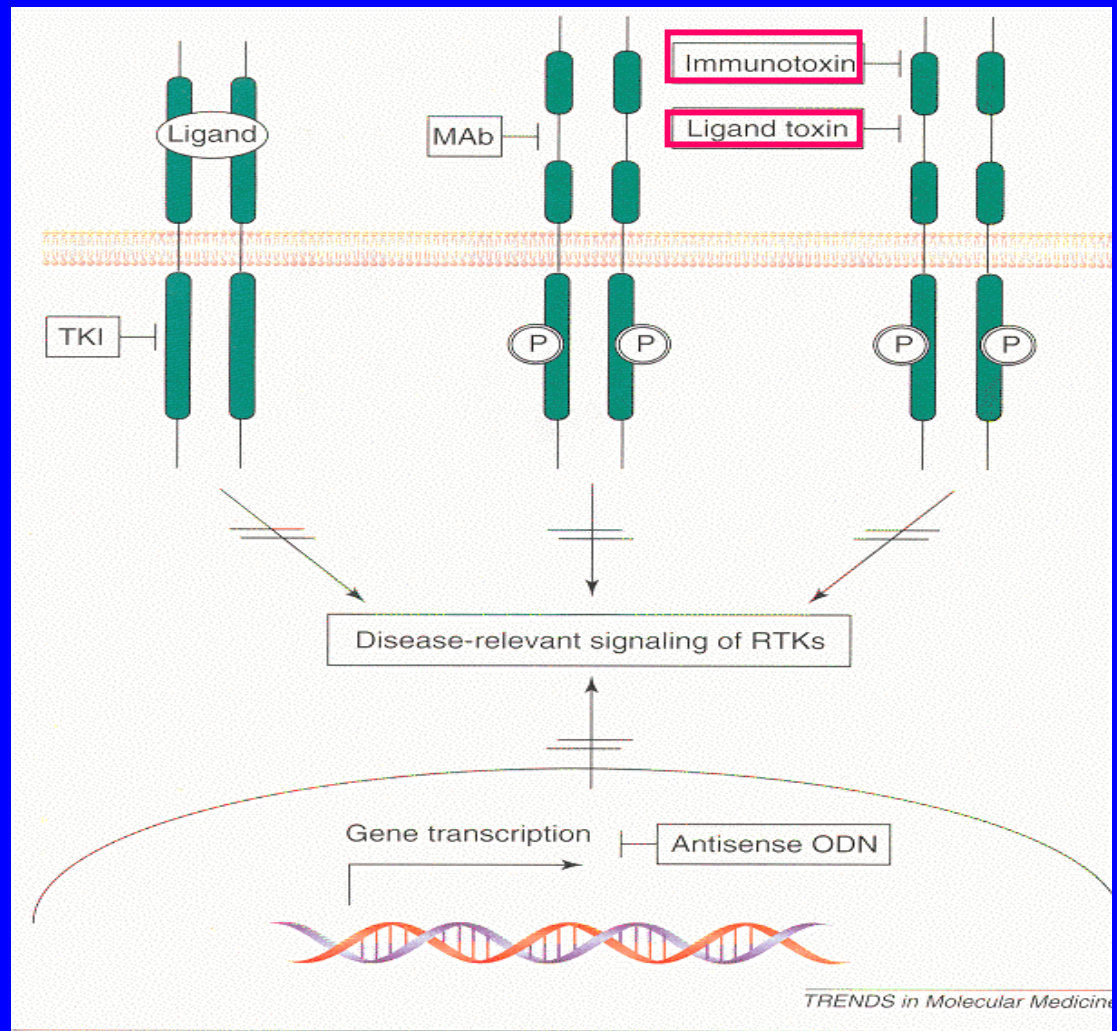
Immunoblot assays demonstrating the degree of phosphorylation of the BCR-ABL substrate CRKL in individual patients in the group receiving increasing dose of STI 571



From: Drucker et al, 2001 N. Engl. J. Med. [344](#) 1031-1037

# 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



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

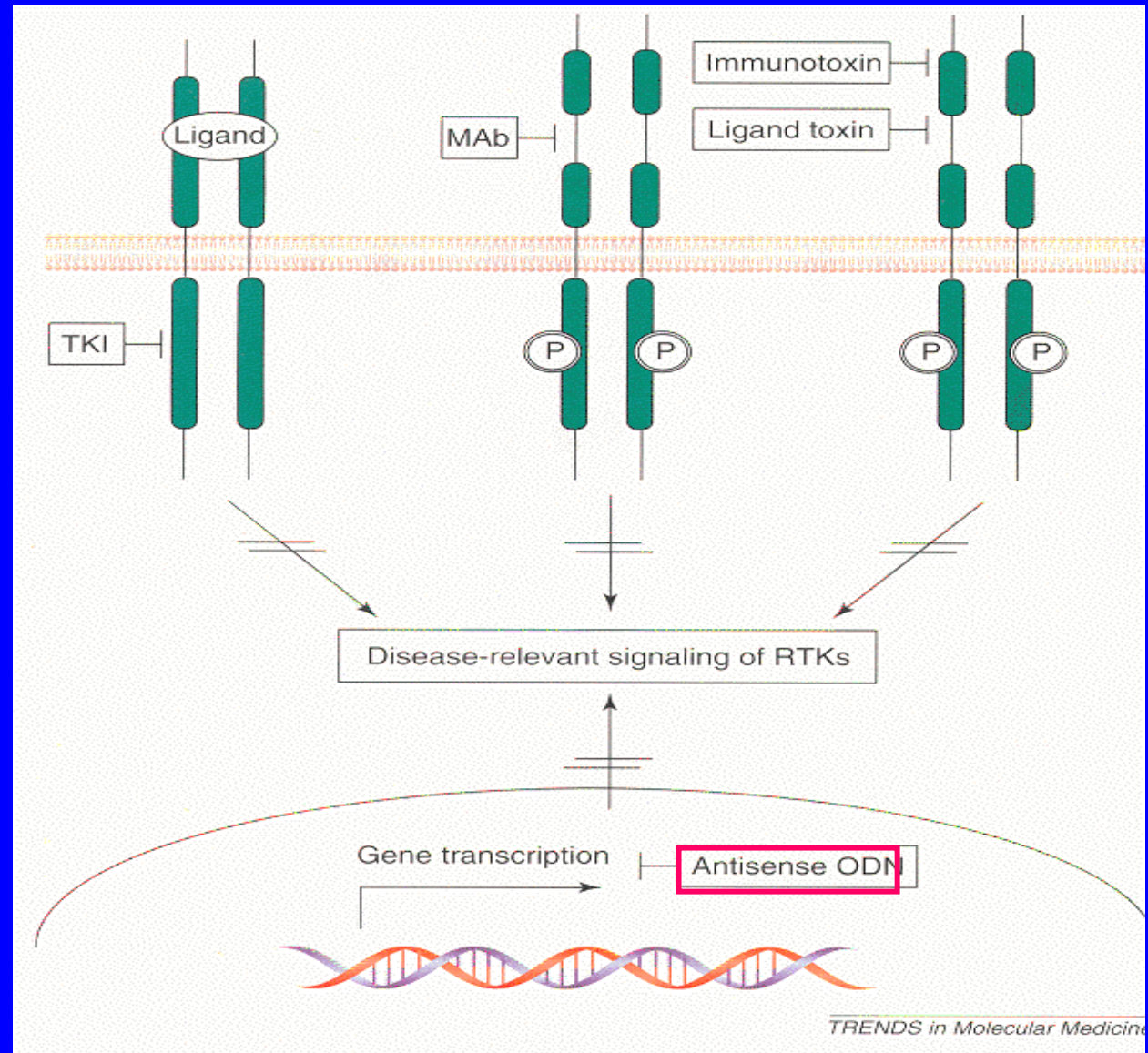
RTK	Drug	Company	Description	Status
HER2	Trastuzumab Herceptin	Genentech	MAB directed against HER2	Approved by the FDA 1998
HER2	BsAb 2B-1, NSC-673928	Chiron	Bispecific MAb inducing lysis of HER2-expressing tumor cells	Phase Ib/II (03/98)
HER2	APC8024	Dendreon	Vaccine against HER2- overexpressing tumors	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

\*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.



# 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

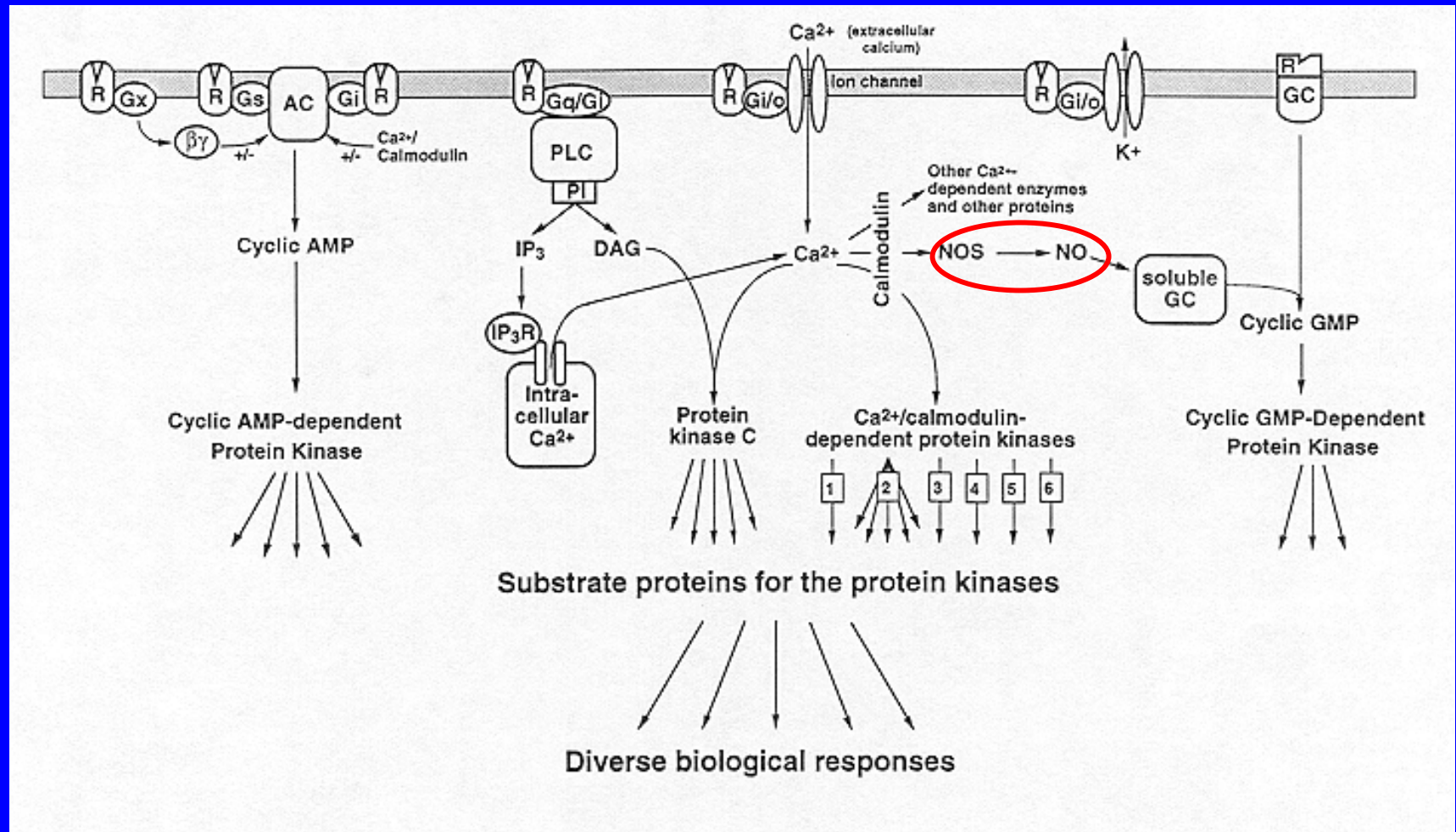
2003-2004

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

RTK	Drug	Company	Description	Status
HER2	Trastuzumab Herceptin	Genentech	MAB directed against HER2	Approved by the FDA 1998
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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

\*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.

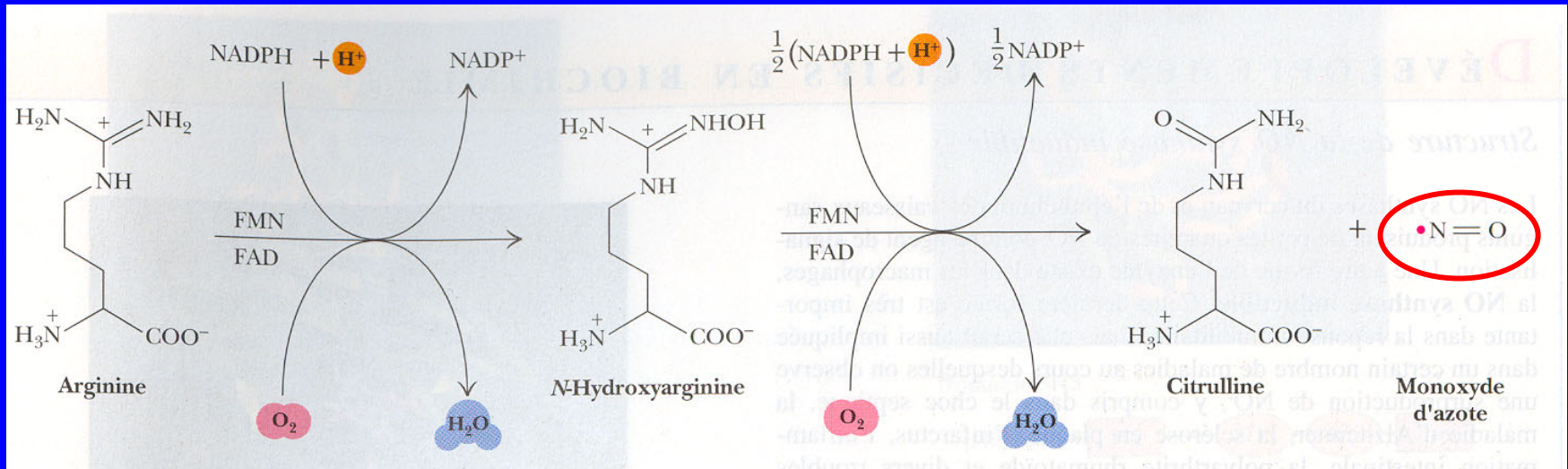
# TRANSDUCTION DU SIGNAL – PROTEINE G ET VOIE DU NO



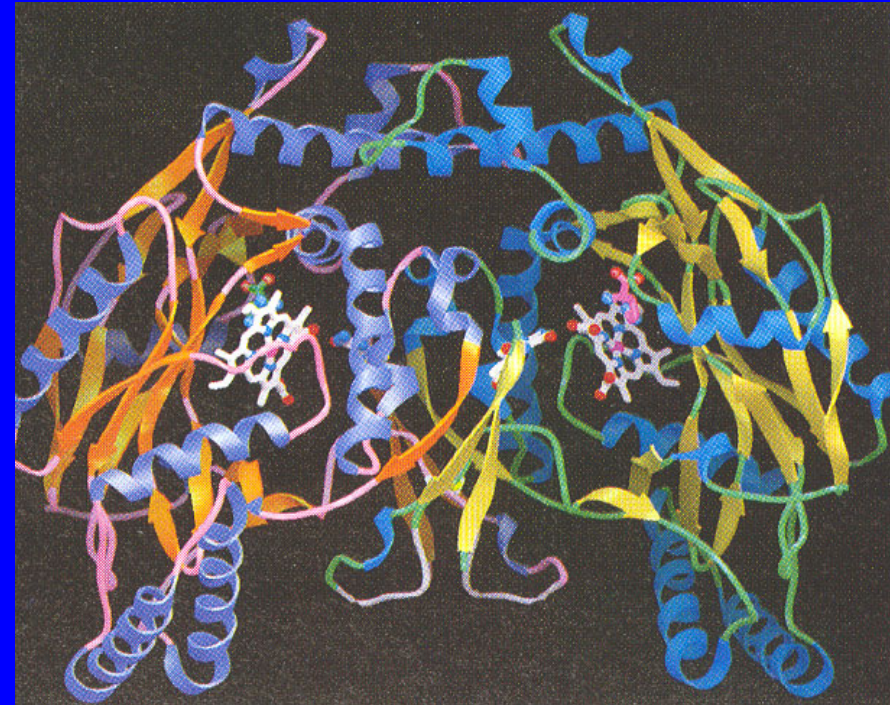
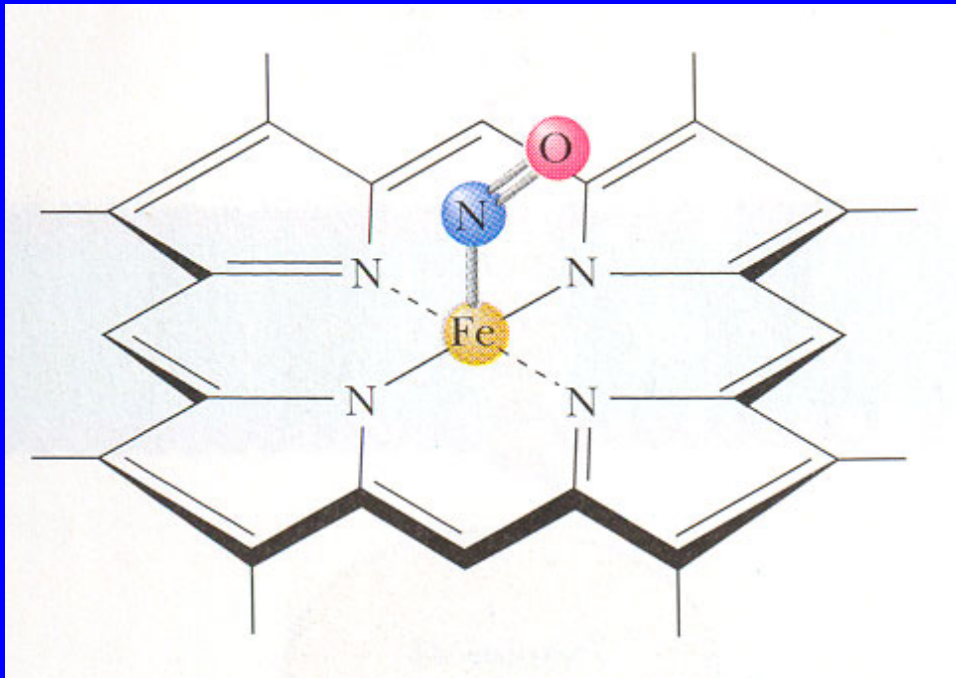


# TRANSDUCTION DU SIGNAL ET NO

## PRODUCTION DU NO



# TRANSDUCTION DU SIGNAL ET NO PRODUCTION DU NO- NO SYNTHASE



L'hème essentiel à l'activité de l'enzyme est au centre de la partie concave du feuillet beta



# TRANSDUCTION DU SIGNAL ET NO

