Translational Research In Oncology

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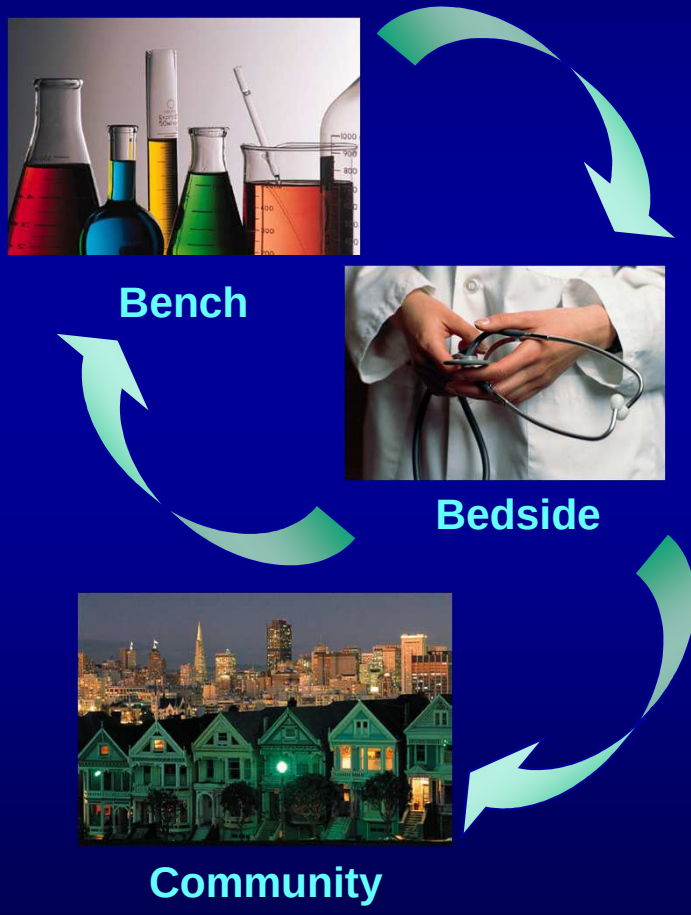
Translational Research

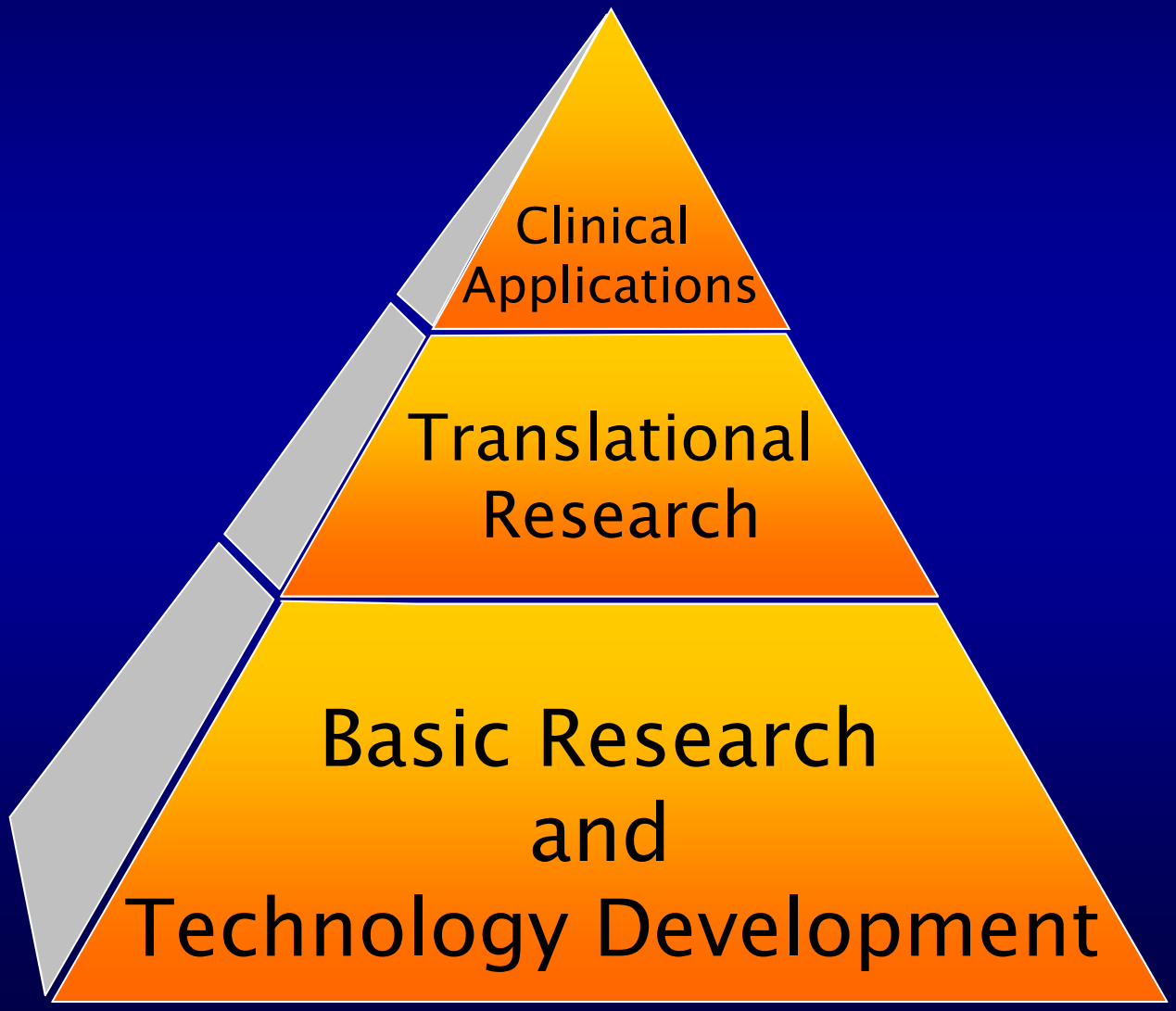
- To improve human health, scientific discoveries must be translated into practical applications.
- Such discoveries typically begin at ***"the bench"*** with basic research — in which scientists study disease at a molecular or cellular level — then progress to the clinical level, or the patient's ***"bedside."***



Definition of Translational Research

- "Translational research transforms scientific discoveries arising from laboratory, clinical or population studies into clinical or population-based applications to improve health by reducing disease incidence, morbidity and mortality"
    - Modified from the NCI translational research working group (2006)

Basic Discovery Today Provides the Foundation for Tomorrow's Medicine

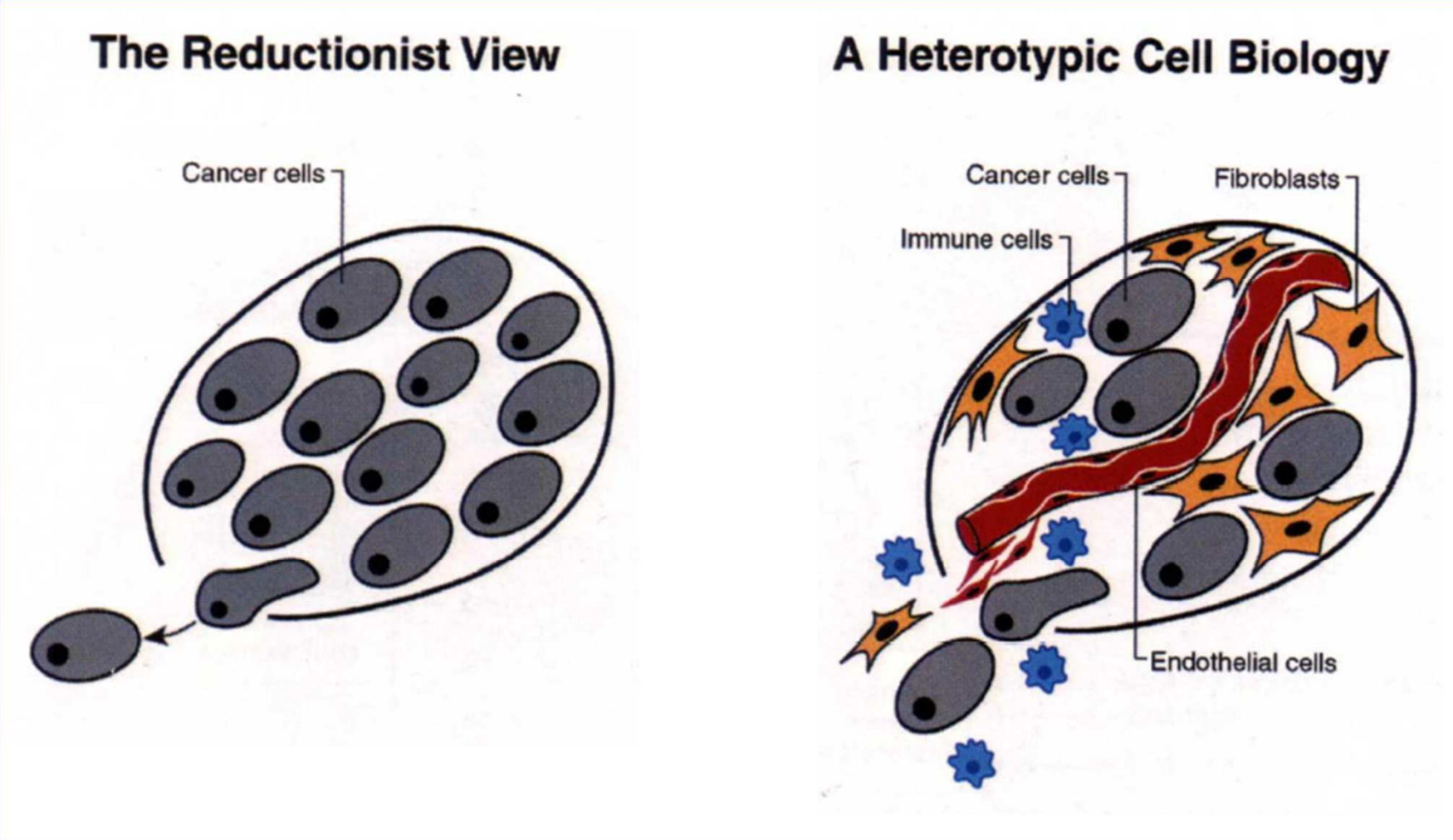


Elias Zerhouni, M.D., Director, NIH

Targeted Therapy in Oncology

- **Goals**
  - Identify **agents** that target tumor-specific molecules, thus sparing normal cells
    - Increased specificity leads to decreased toxicity
  - Identify ideal drug **target**
    - Drives tumor growth
    - Turns on key mechanisms of cancer progression
    - Reversible by inhibition with agent
    - Dispensable in normal cells
    - Target measurable in tumor tissue

Targets in Radiation Oncology



Hanahan D, Weinberg RA. Cell 2000;100:57-70

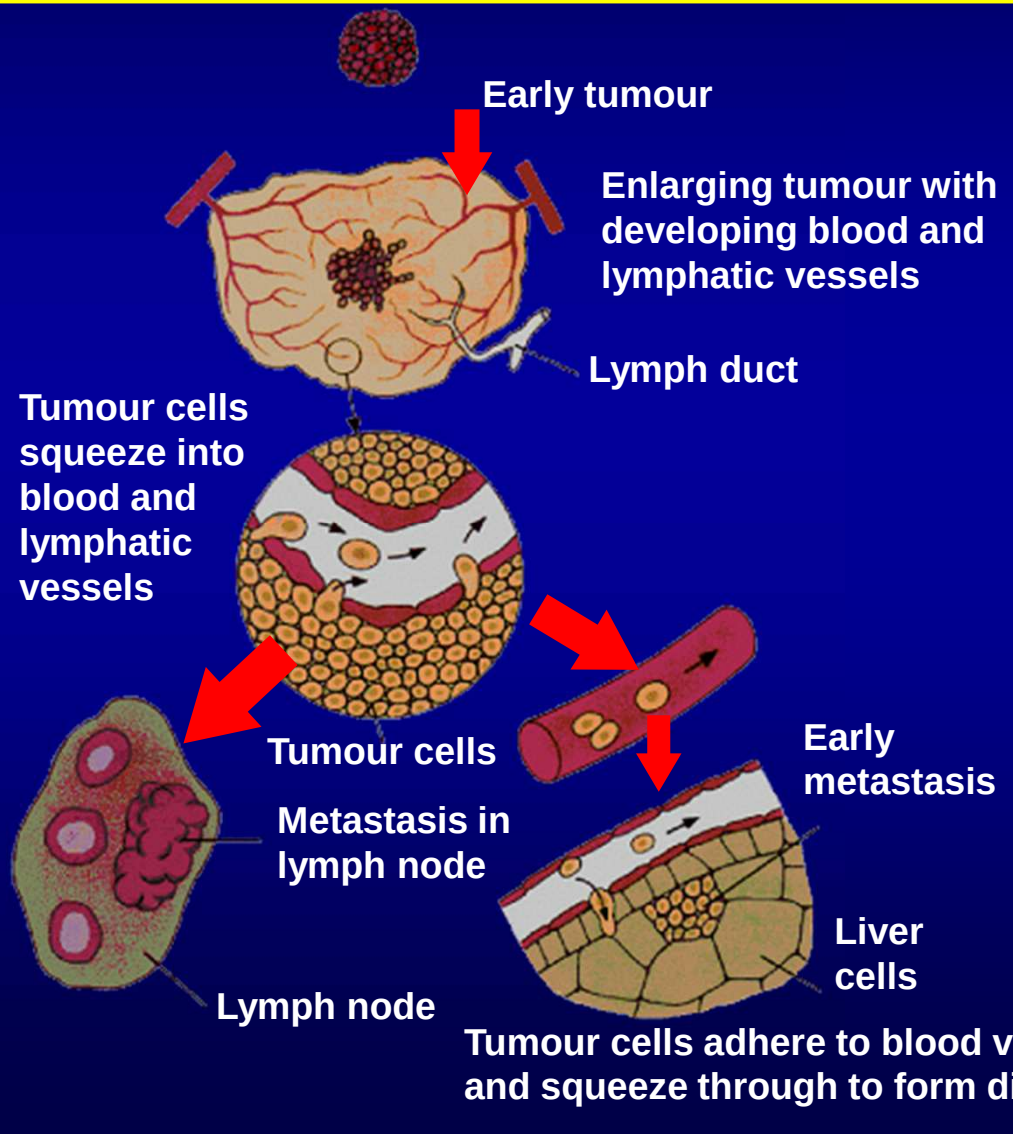
Molecular Targeting with Radiotherapy (RT)

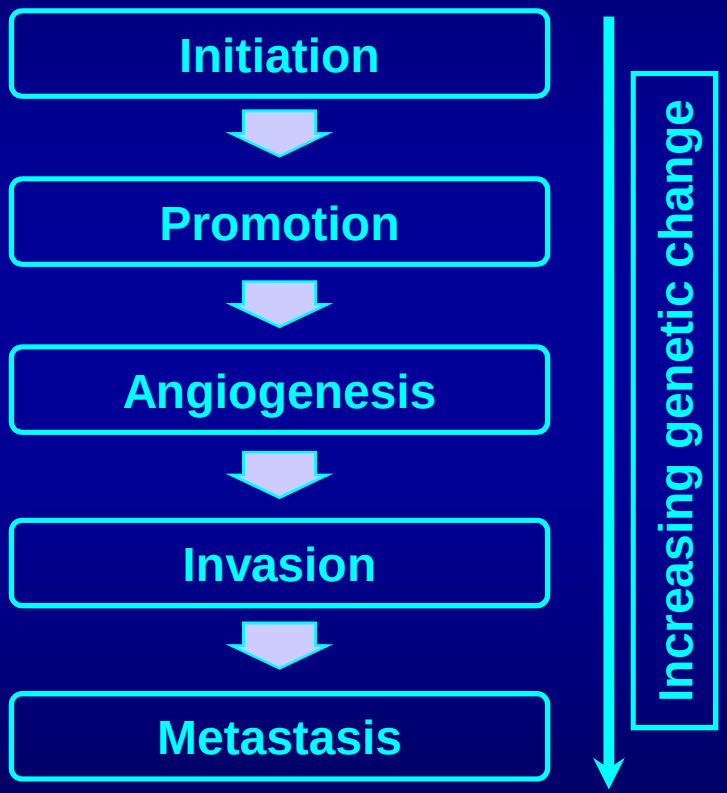
- Novel therapeutic agents are not curative.
- RT is extremely efficient in the eradication of clonogenic cells.
- RT, in contrast to chemotherapy, can be modified in terms of dose, time AND space.
- Recurrence can occur from single surviving cell.

“The Hallmarks of Cancer”

1. Evading apoptosis
2. Self-sufficiency in growth signals
3. Insensitivity to anti-growth signals
4. Tissue invasion & metastasis
5. Limitless replication potential
6. Sustained angiogenesis

Understanding the Molecular Basis of Cancer





Many Potential Therapeutic Targets in the Tumour and the Host

Tumour targets – biological processes in the tumour cell itself

Growth factor stimuli
Exogenous growth factors

Cell-cycle control
Mediators of cell division

Intracellular signalling
Downstream transduction enzymes

Host targets – biological processes in the body that facilitate the growth and spread of the tumour

Angiogenesis
The growth of new blood vessels

Vascular permeability
Restriction of tumour blood flow

Invasion/metastasis
The movement and dissemination of tumour cells in host tissues

Example: Cell proliferation and self-sustained growth

How do cells grow and divide?
How do cells learn self-sustained growth?

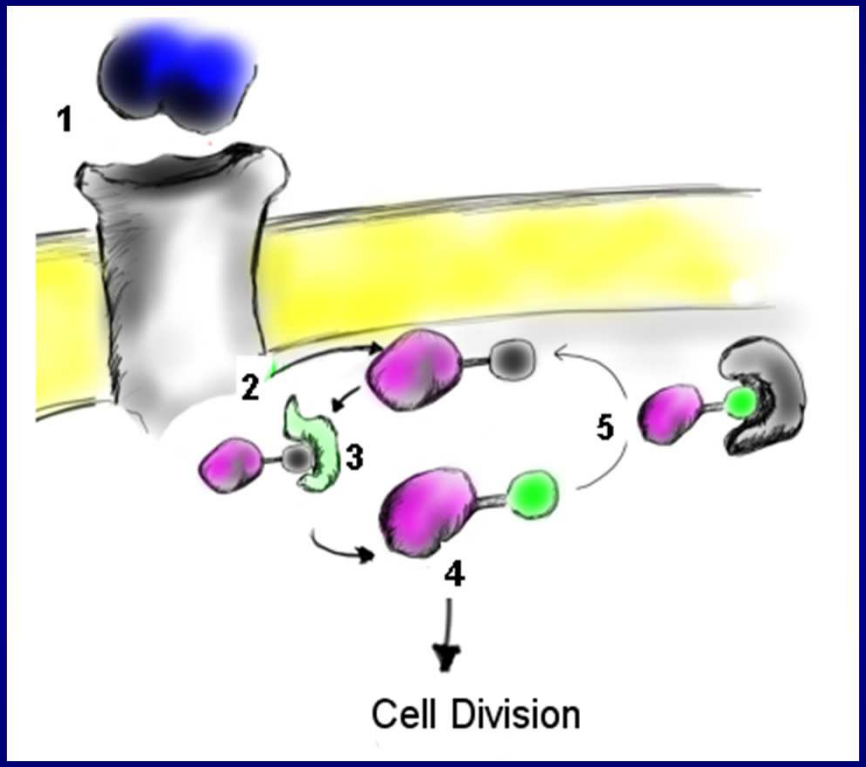
What causes a cell to divide?

- Start with synthesis of the EGF Receptor protein
  - Central Dogma
- Localization to the cell membrane
  - Trans-membrane protein
- EGF and EGF receptor binding → signal into the cell
  - **EGF-EGFR crystal structure**
- Cascade leads to a protein called RAS
  - Molecular Switch
    - "ON" → cell proliferation

What is different about cancer cells?

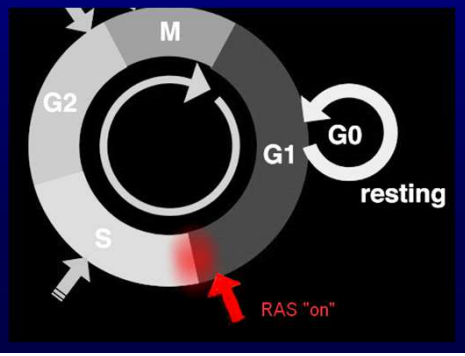
- e.g. cancer cells require little growth factors

A simple view of the pathway



1. EGF binds to EGFR
2. 2 EGFRs activate a series of proteins that lead to activation of RAS
3. RAS is activated to the “on” position
4. Cell Division
5. RAS is turned “off”

Cell enters irreversibly into “S” phase



Receptor locations

- Cytosolic or Nuclear
  - Lipophilic ligand enters cell
  - Often activates gene
  - Slower response
- Cell membrane
  - Lipophobic ligand can't enter cell
  - Outer surface receptor
  - Fast response

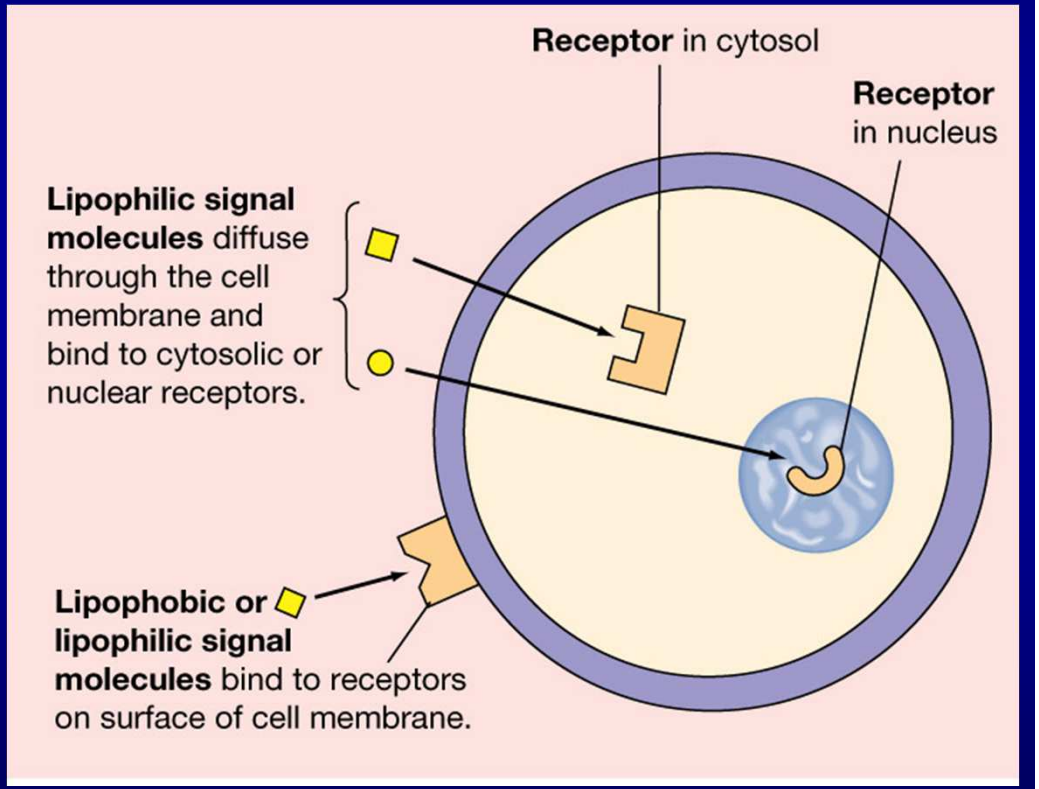


Figure 6-4: Target cell receptors

Membrane Receptor Classes

- Ligand- gated channel
- Receptor enzymes
- G-protein-coupled
- Integrin

Membrane Receptor Classes

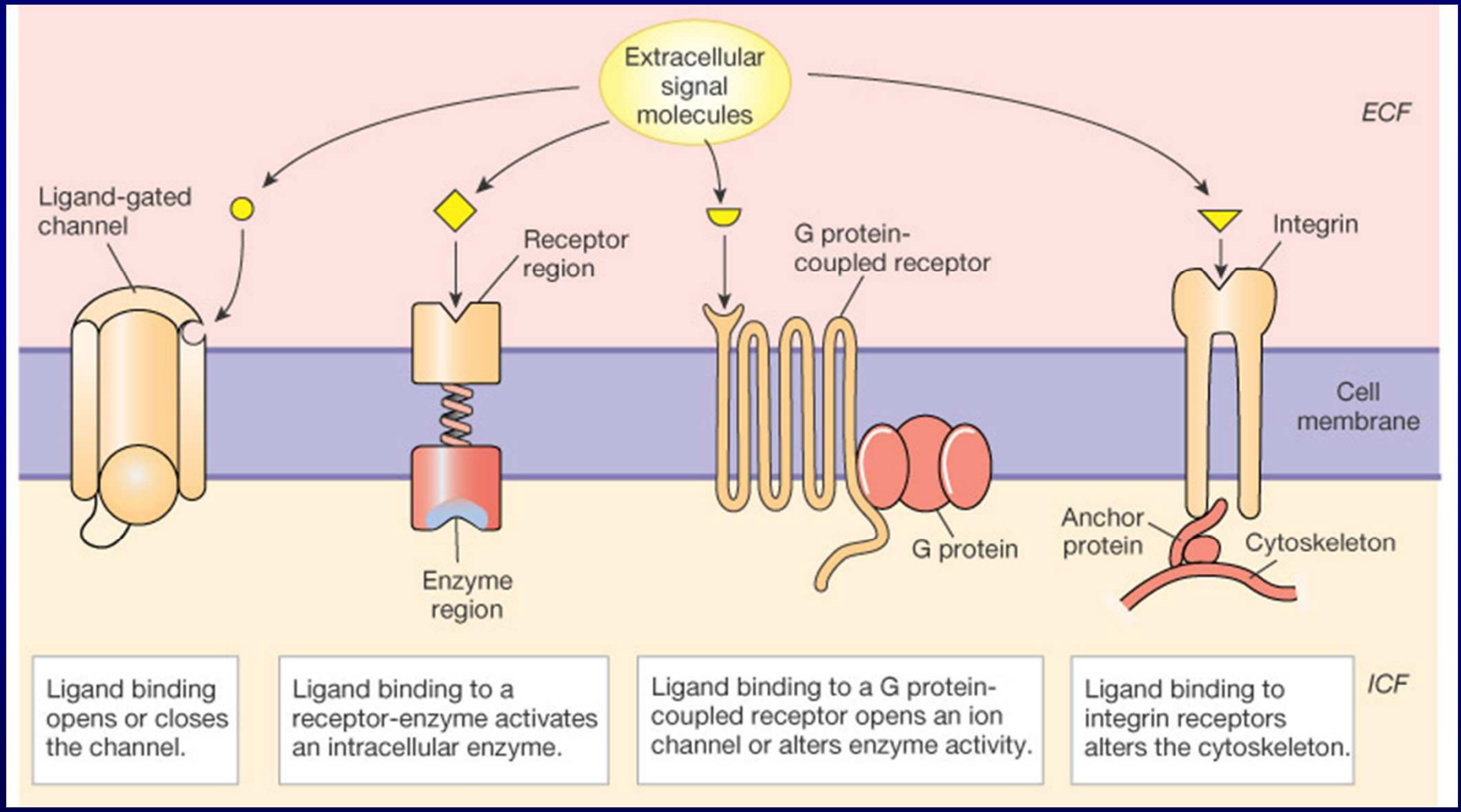


Figure 6-5: Four classes of membrane receptors

Signal Transduction

- Transforms signal energy
- Protein kinase
- Second messenger
- Activate proteins
  - Phosporylation
  - Bind calcium
- Cell response

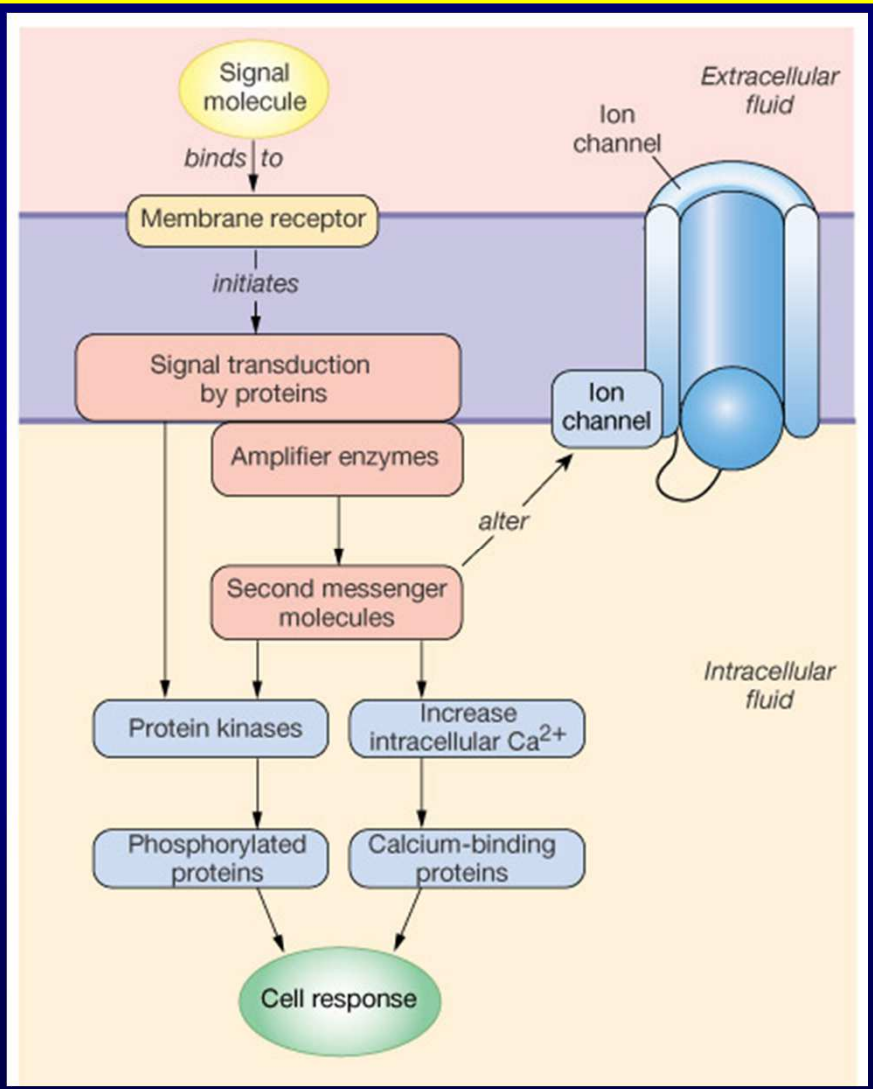


Figure 6-8: Biological signal transduction

Signal Amplification

- Small signal produces large cell response
- Amplification enzyme
- Cascade

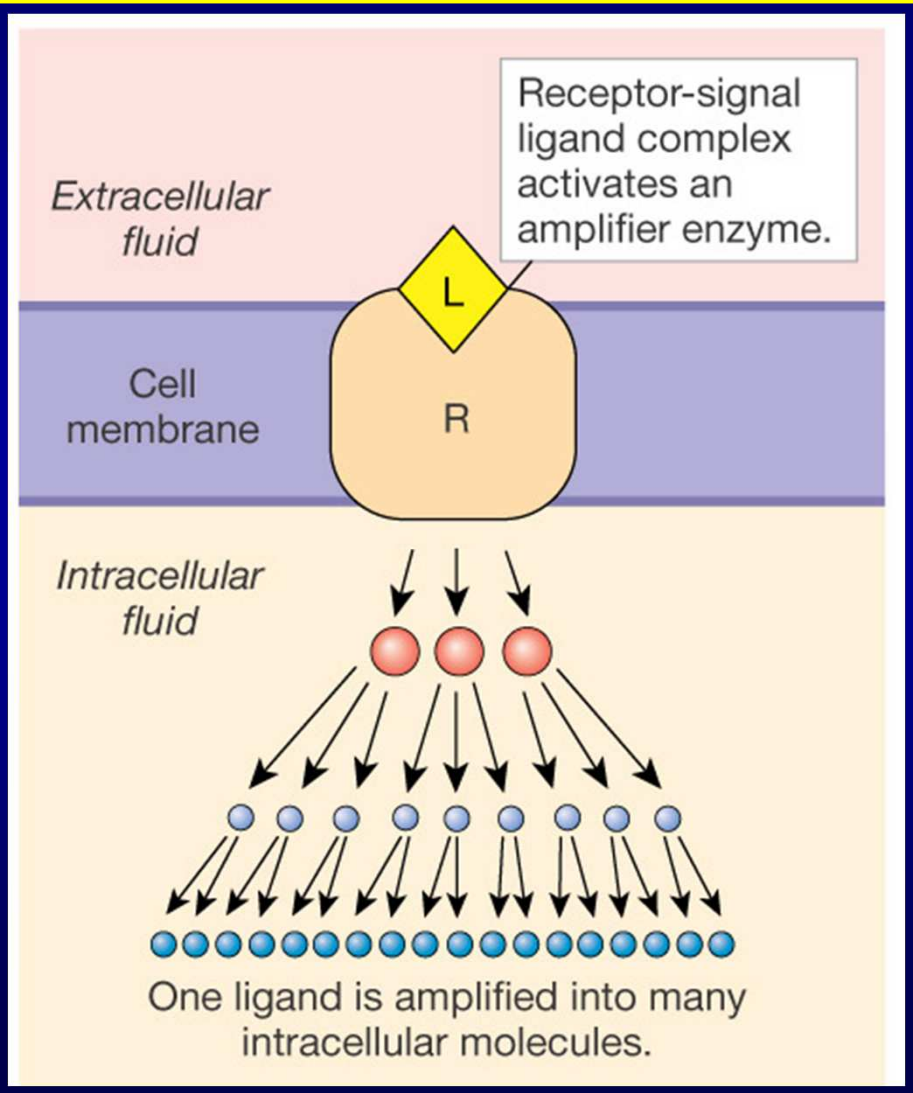


Figure 6-7: Signal amplification

Receptor Enzymes

- Transduction
- Activation cytoplasmic
  - Side enzyme
- Example: Tyrosine kinase

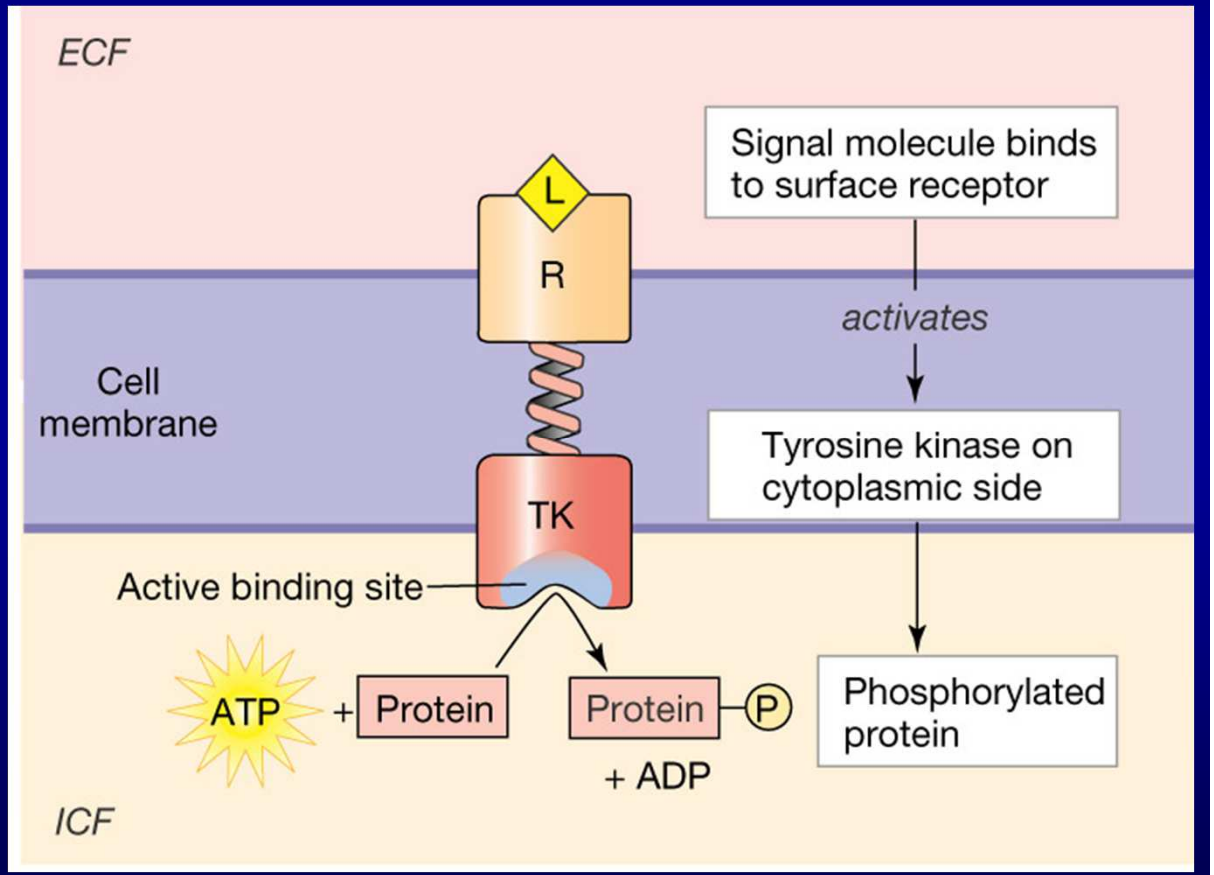


Figure 6-10: Tyrosine kinase, an example of a receptor-enzyme

G-Protein-coupled Receptors

- Hundreds of types
- Main signal transducers
  - Activate enzymes
  - Open ion channels
  - Amplify:
    - adenyl cyclase-cAMP
  - Activates synthesis

G-Protein-coupled Receptors

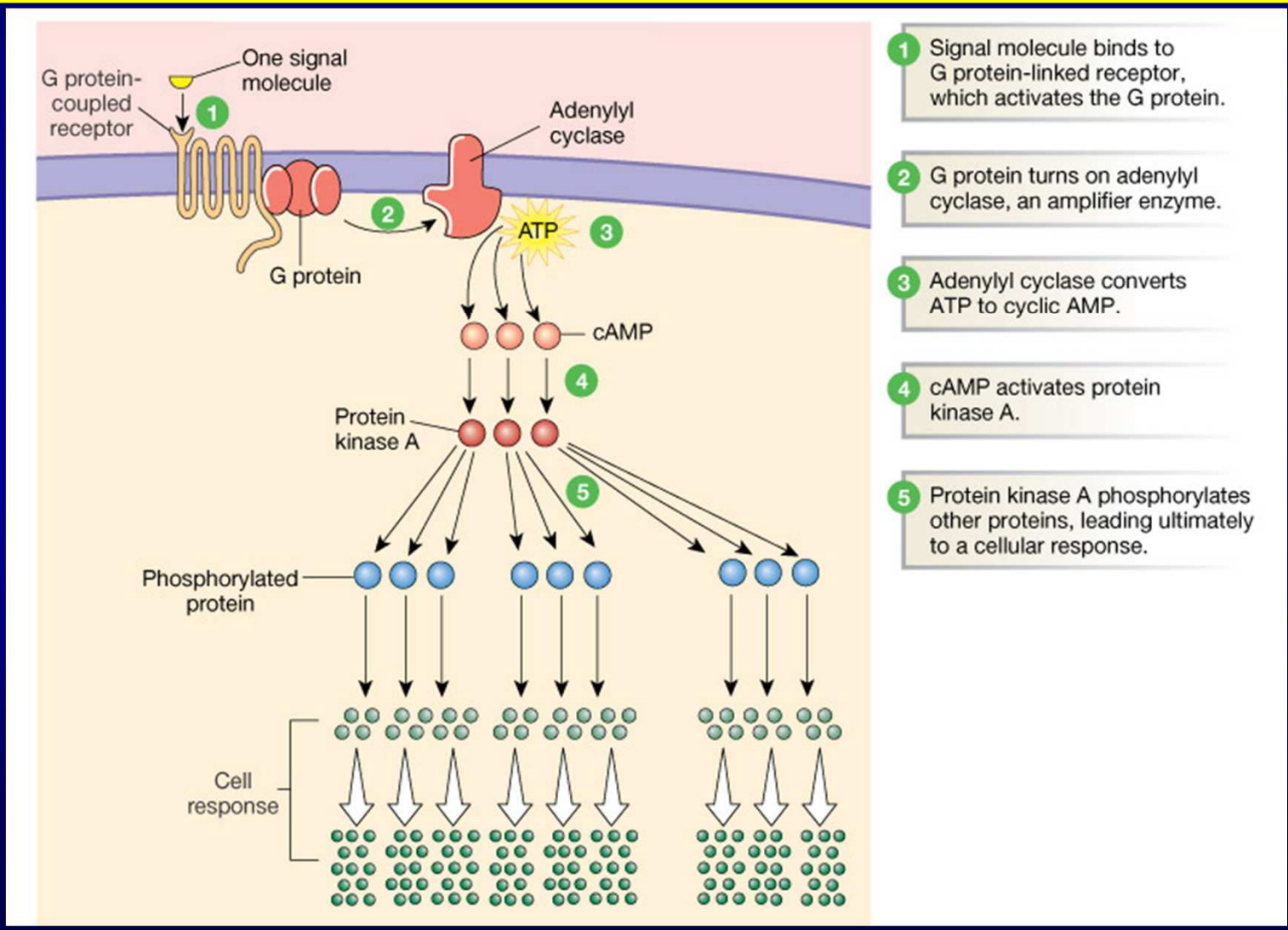
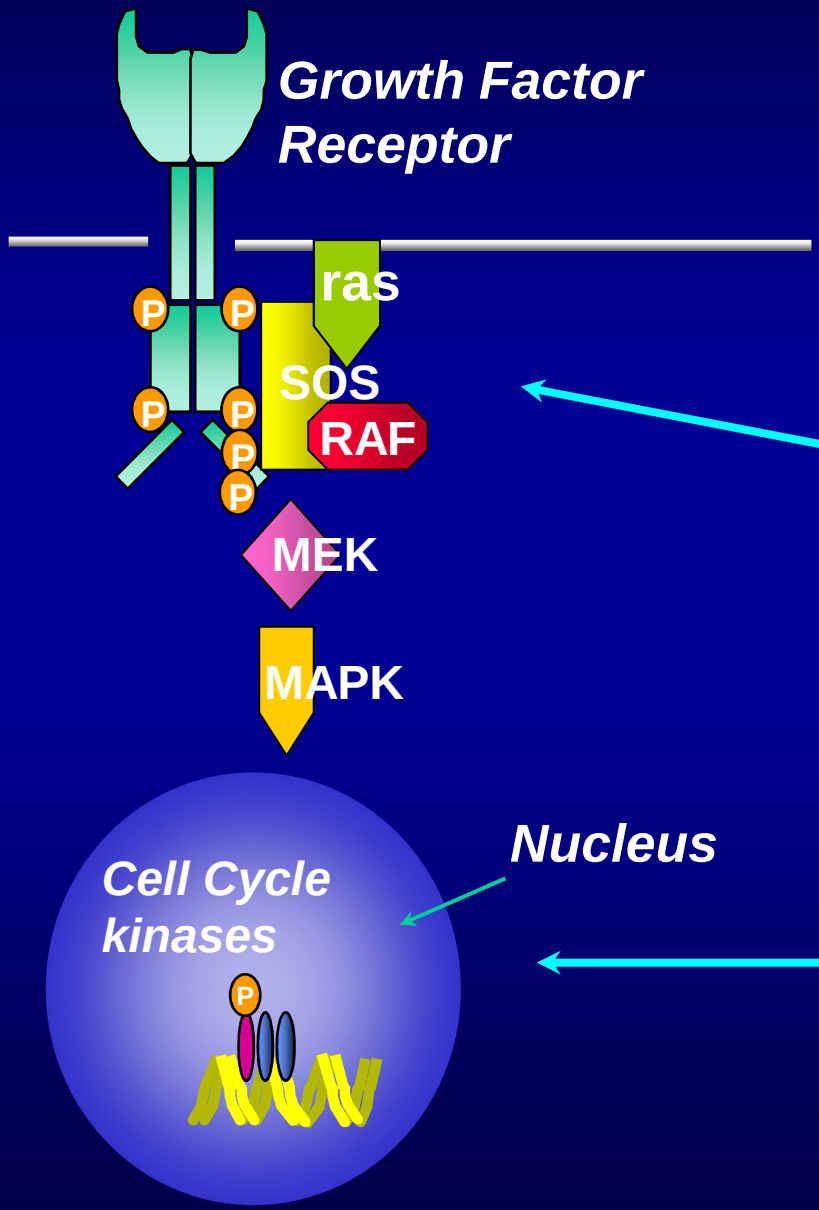


Figure 6-11: The G protein-coupled adenylyl cyclase-cAMP system

Signal Transduction Pathways & Molecular Targets in Oncology

Proliferation



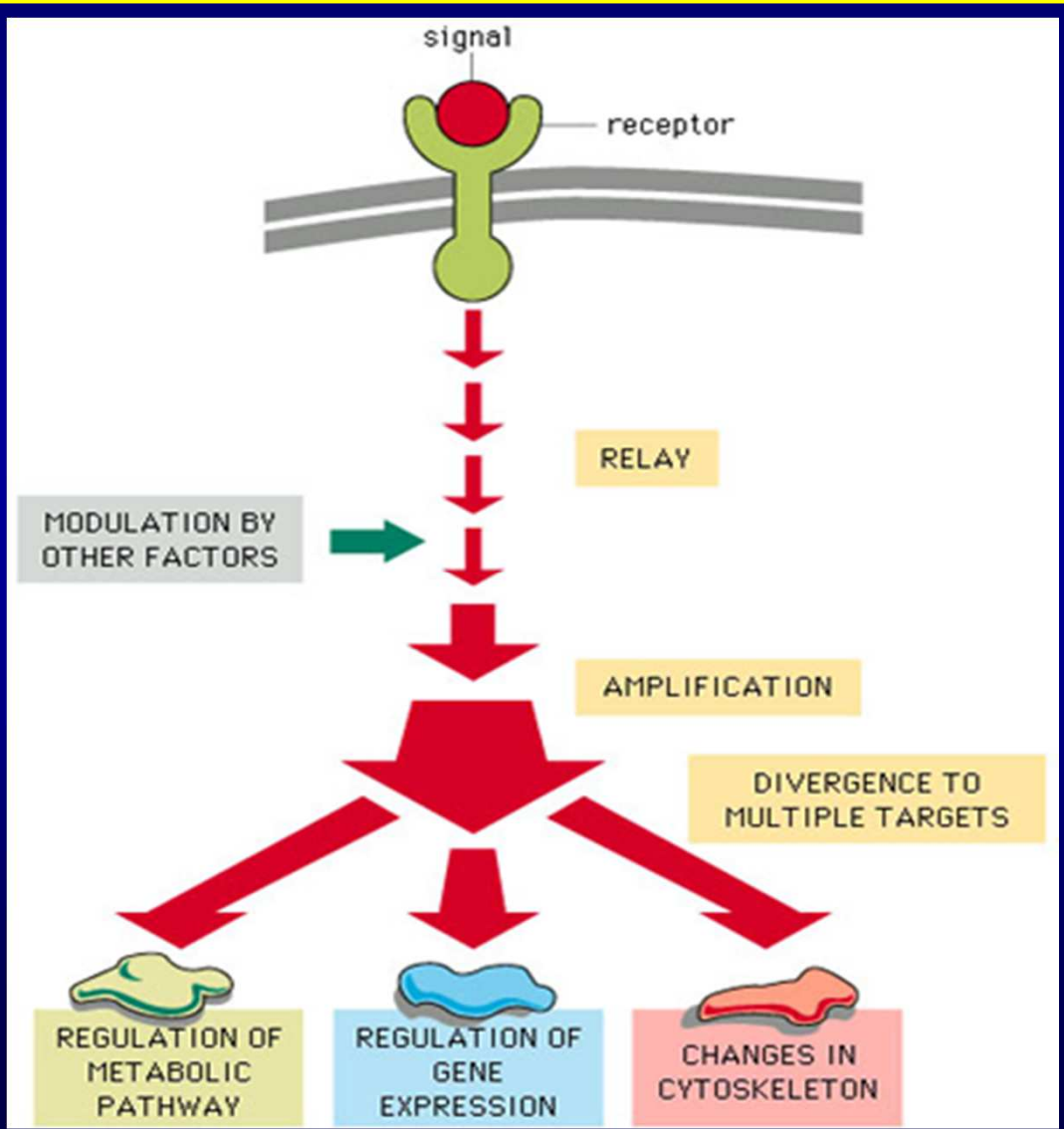
Receptor TKIs
IRESSA, ZD6474

Downstream Signal Inhibitors
AZD3409

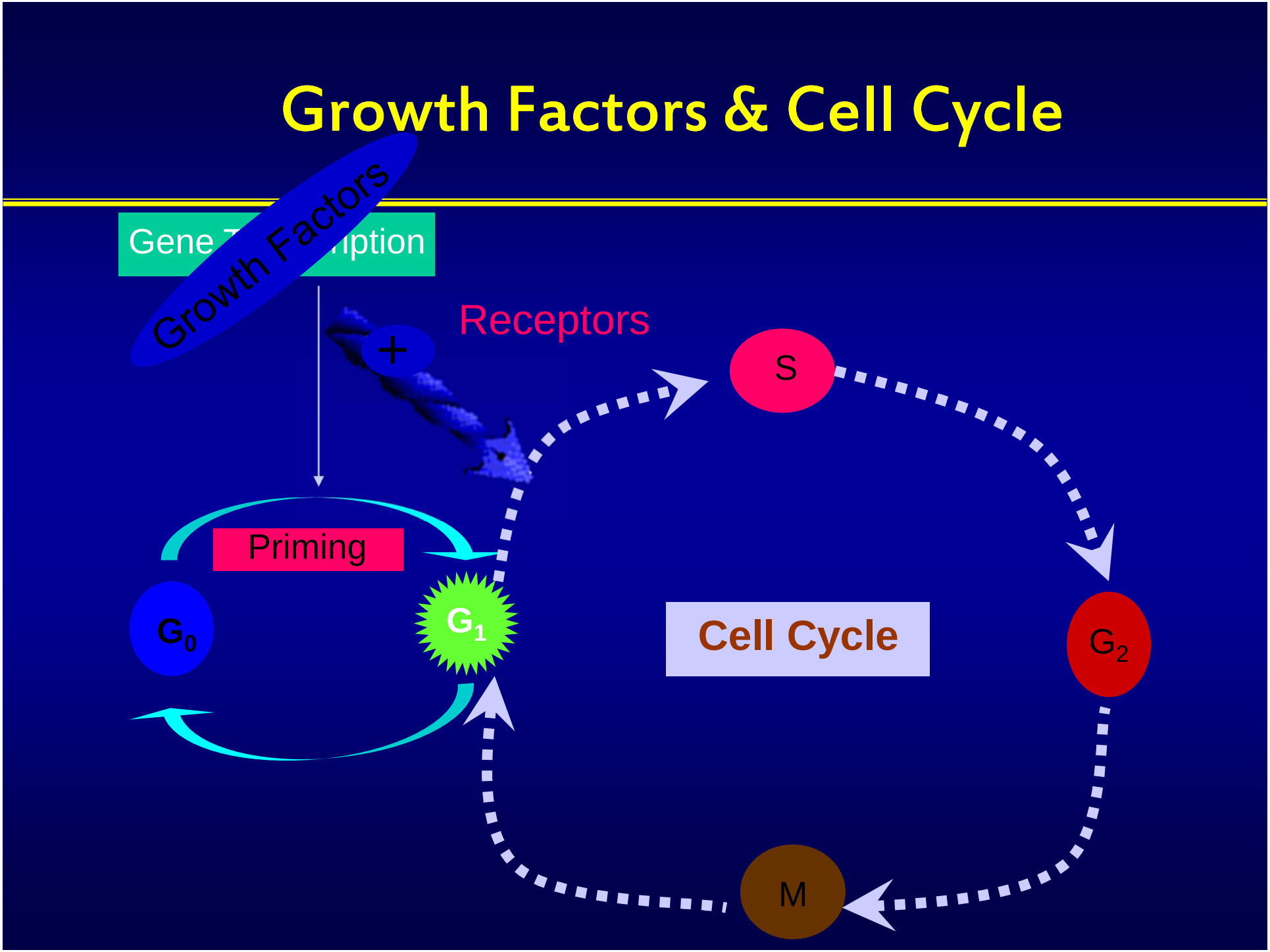
Cell Cycle Inhibition
AZD1152, AZD5438

Signal Transduction and Kinase Pathways

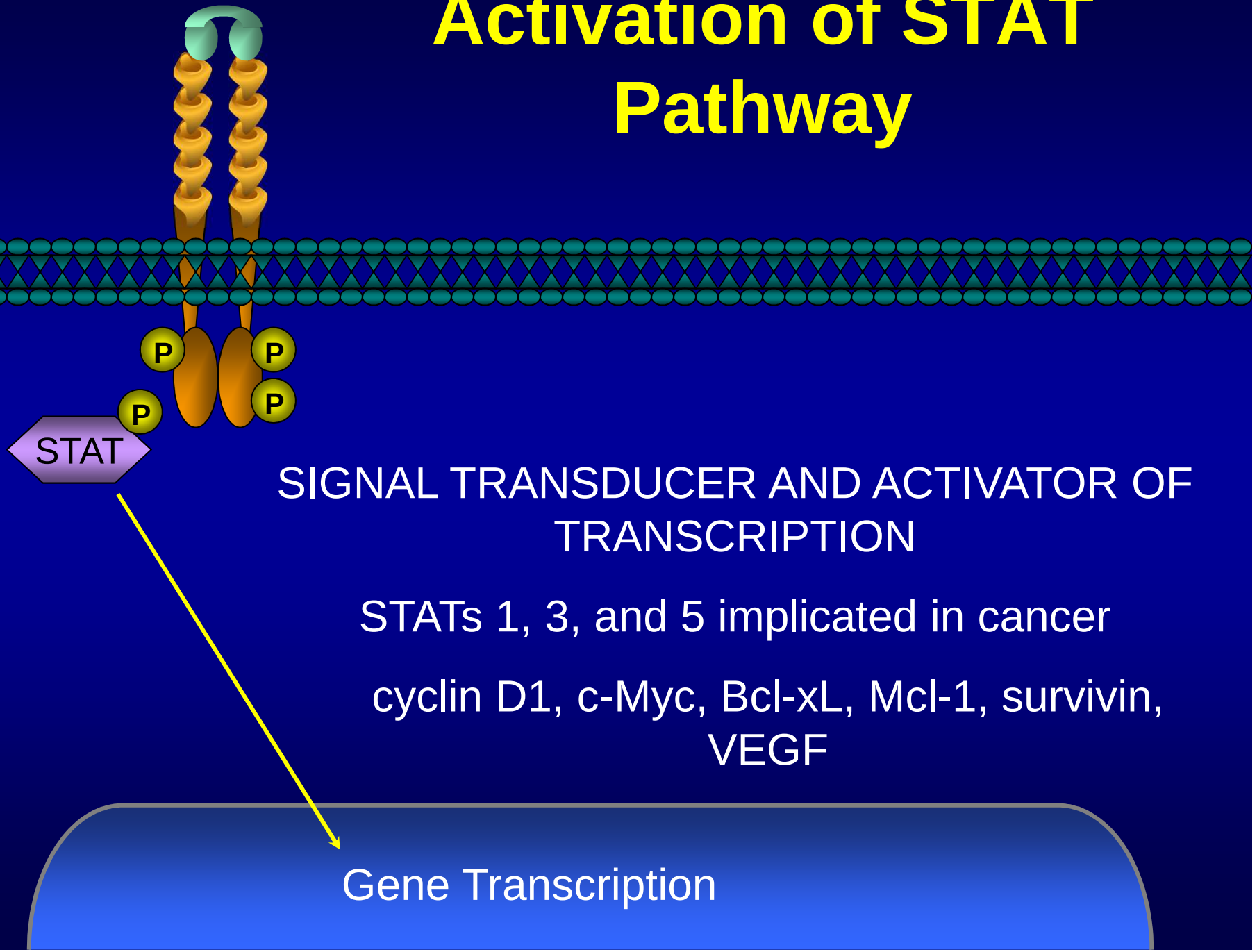
Phosphorylation: primary mechanism for information transfer.



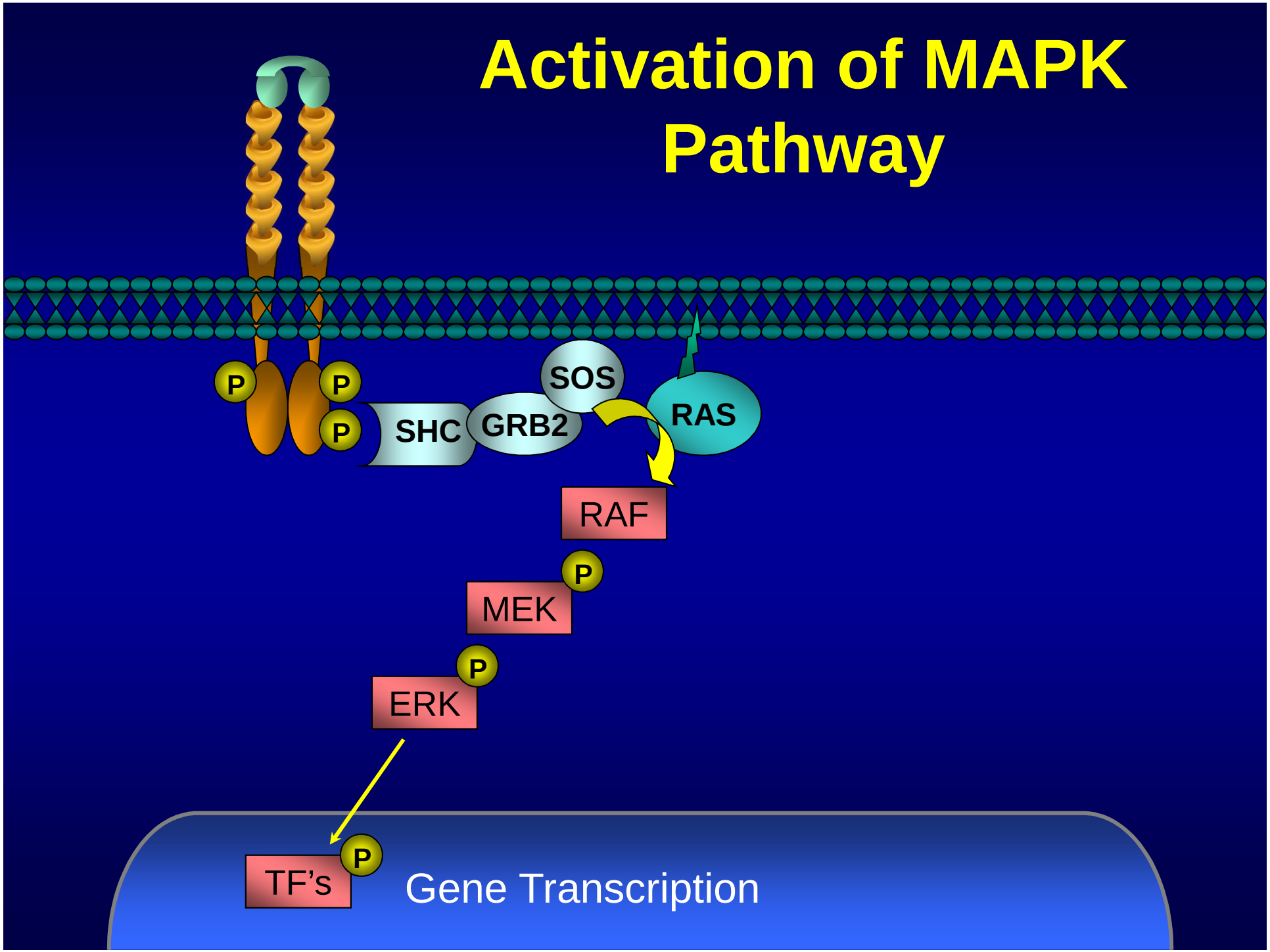
Growth Factors & Cell Cycle



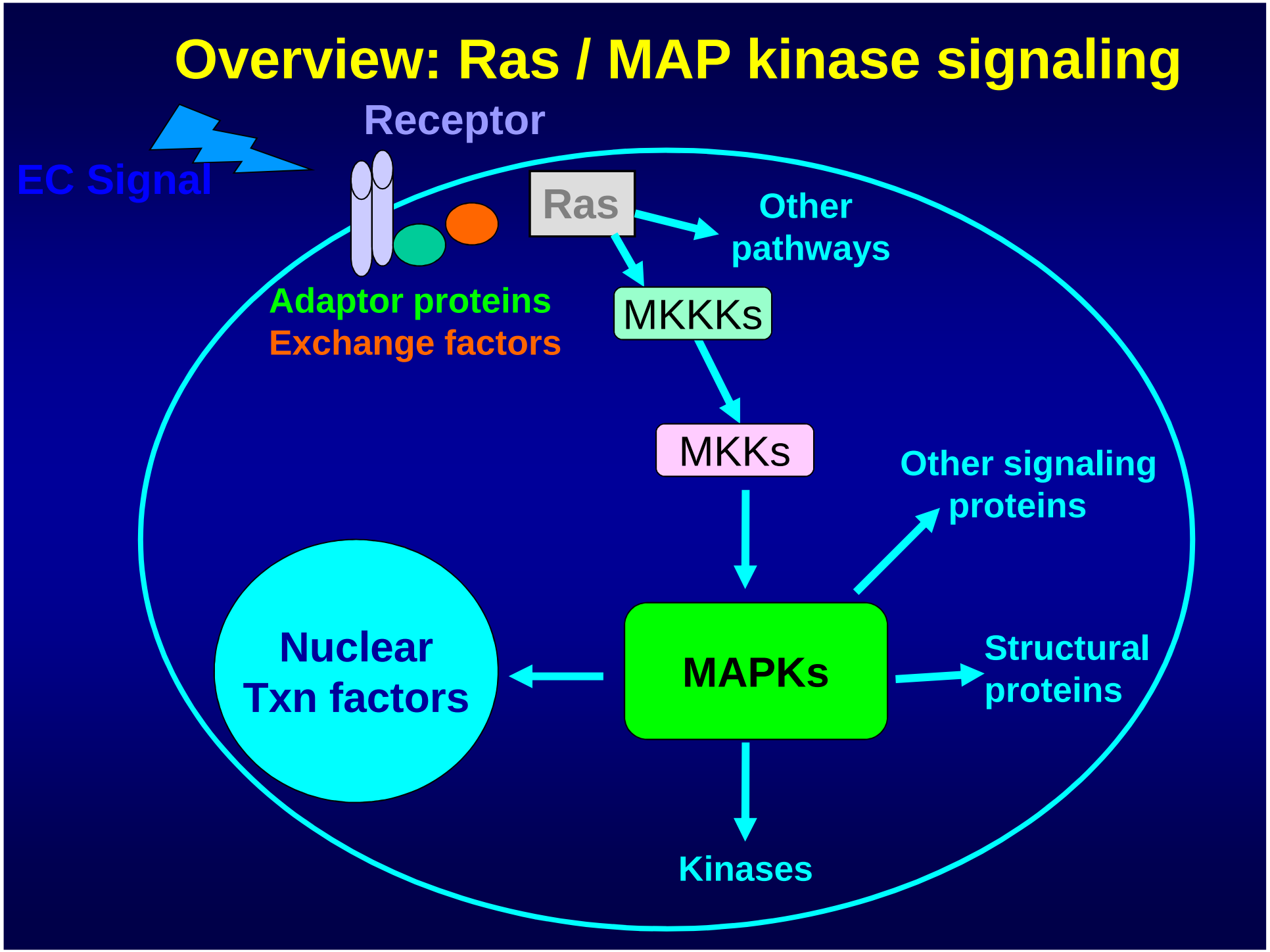
Activation of STAT Pathway

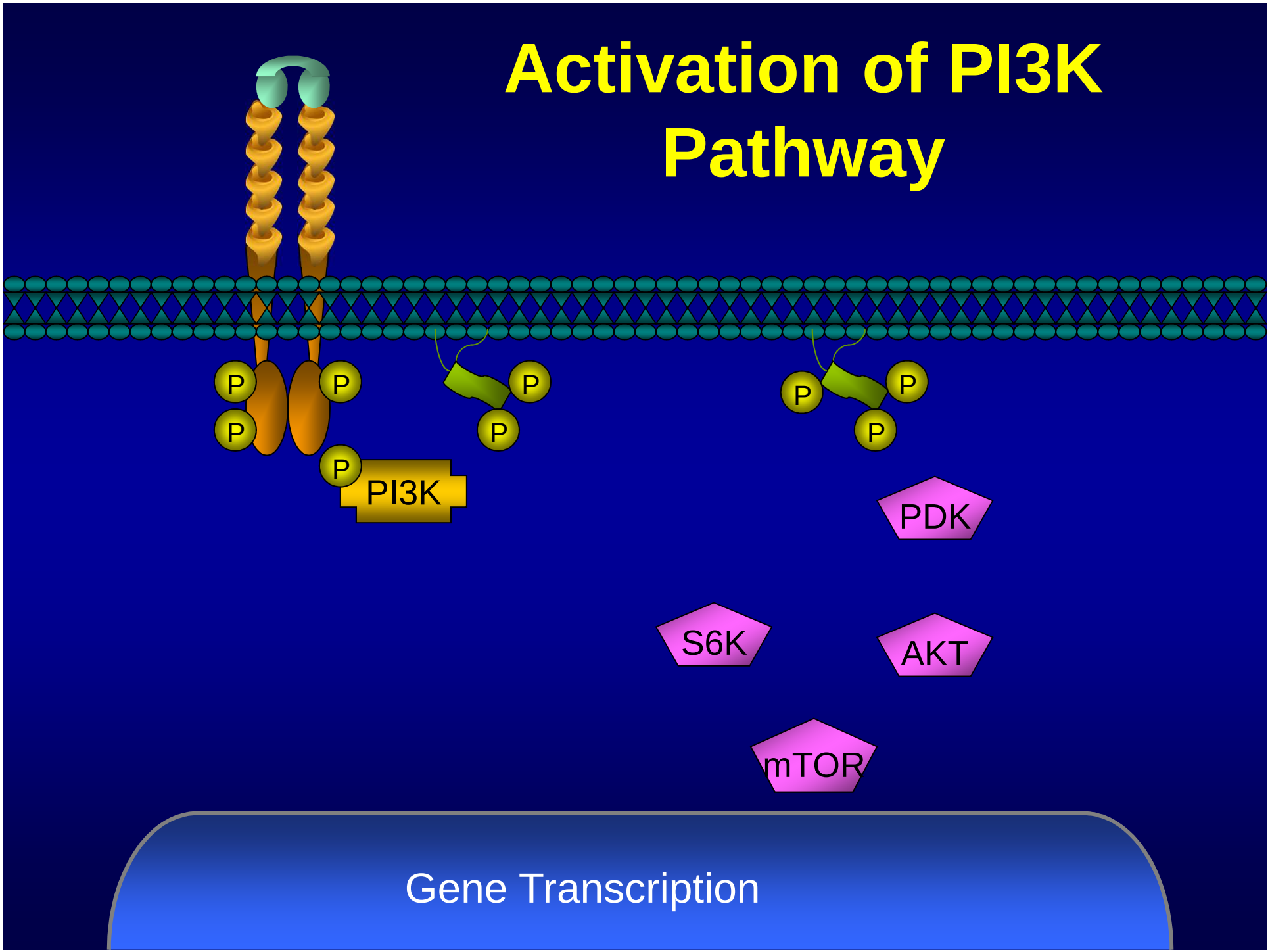


Activation of MAPK Pathway

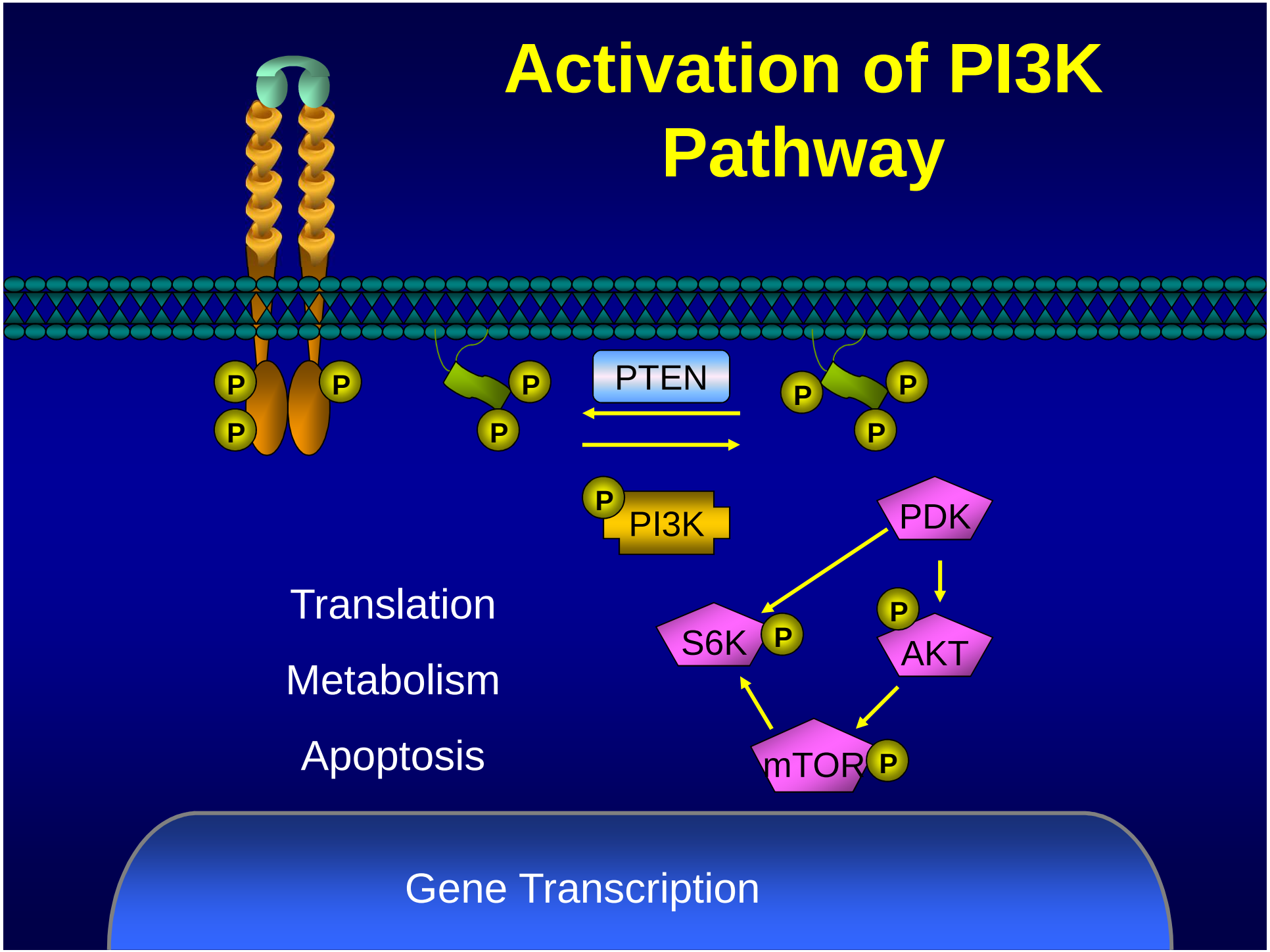


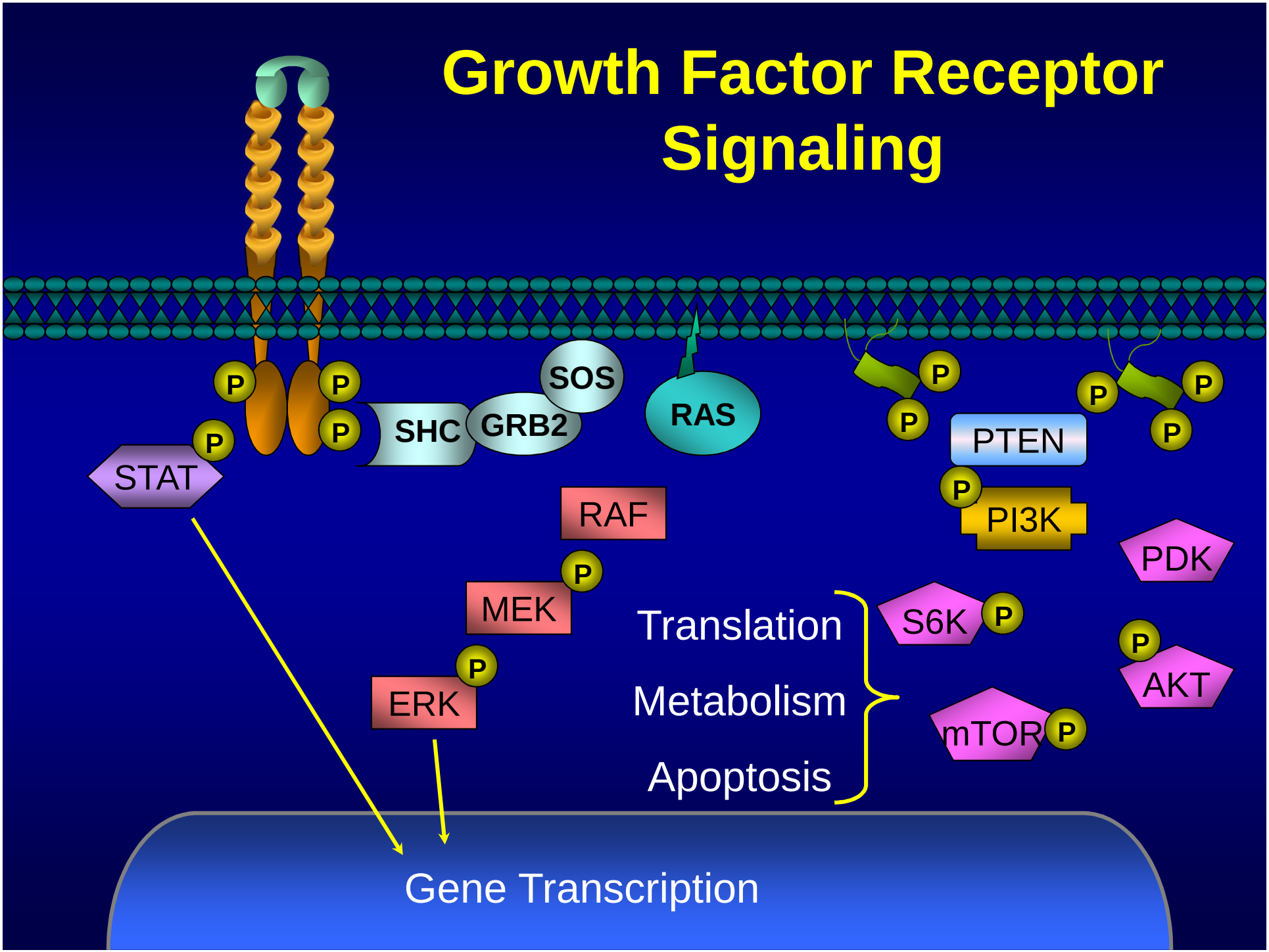
Overview: Ras / MAP kinase signaling



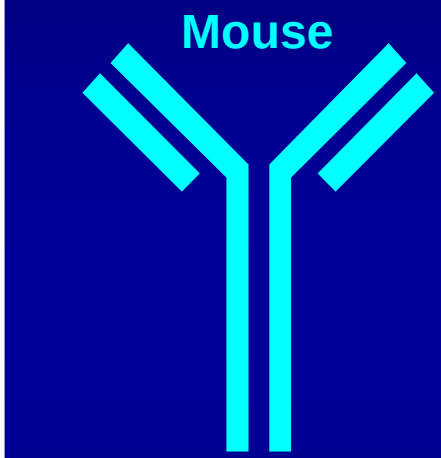

Activation of PI3K Pathway
P
P
P
P
P
P
P
P
P
PI3K
PDK
S6K
AKT
mTOR
Gene Transcription

Activation of PI3K Pathway

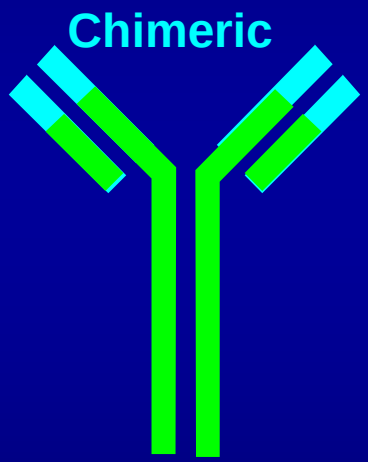



Growth Factor Receptor Signaling
P
P
P
P
STAT
SHC
GRB2
SOS
RAS
P
P
PTEN
P
P
P
P
RAF
P
MEK
P
ERK
Translation
Metabolism
Apoptosis
S6K
P
PDK
P
AKT
mTOR
P
Gene Transcription

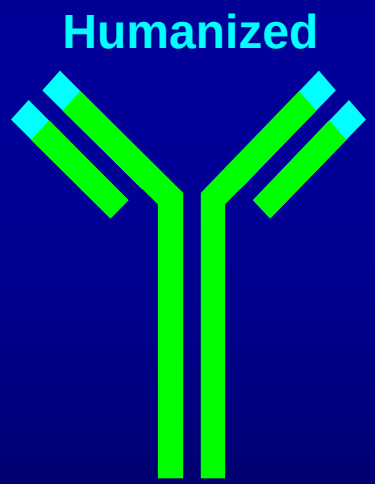
Monoclonal Antibodies- Hybridoma Technology: Evolution



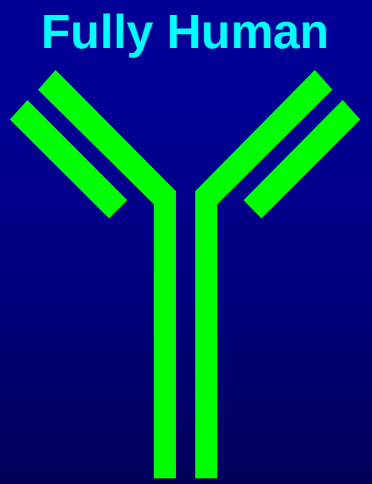
100% mouse protein



34% mouse protein



10% mouse protein

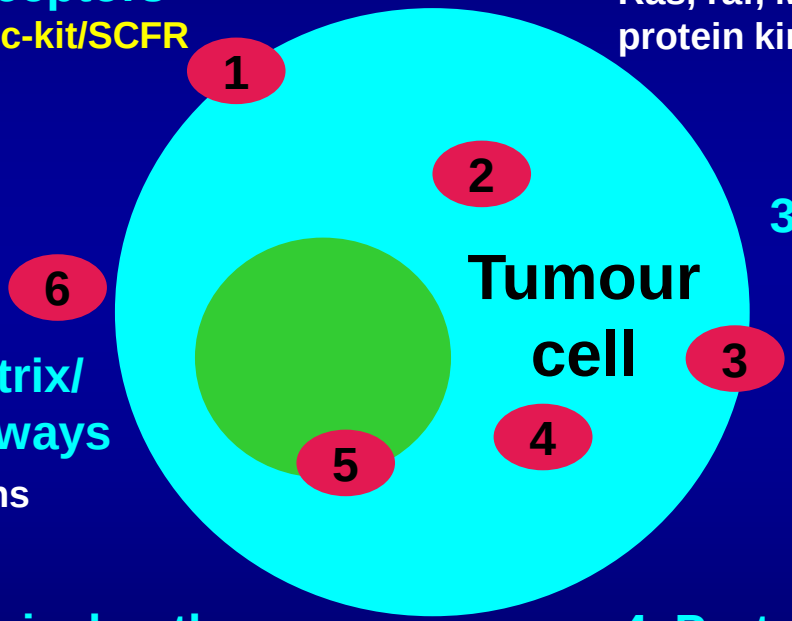


100% human protein

Introduction of molecular-targeted agents: an important paradigm-shift in our approach to the treatment of cancer

1. Growth factors and growth-factor receptors
HER family, VEGF/R, c-kit/SCFR

2. Signal-transduction pathways
Ras, raf, MAPK, MEK, ERK, protein kinase C, PI3K



3. Tumor-associated antigens/markers
Gangliosides, CEA, MAGE, CD20, CD22

6. Extracellular matrix/ angiogenic pathways
MMPs, VEGF, integrins

5. Cell-survival pathways
Cyclin-dependent kinases, mTOR, cGMP, COX-2, p53, Bcl-2

4. Proteasome

Ullrich A. Oncology 2002;63(Suppl. 1):1–5

Biological Agents for Solid Tumors

- **Signal Transduction/Cell-Cycle Inhibitors**
  - Farnesyl transferase
  - Flavopiridol
  - Retinoids
  - UCN-101
- **Gene Therapy**
  - GM-CSF
  - Wild-type p53
  - Antisense
    - c-*myc*
    - PKC
- **Vaccines**
  - Tumor cells
  - Peptides
  - Dendritic cells
  - Viral vaccines
- **Angiogenesis Inhibitors**
  - SU5416/SU6668
  - Anti-VEGF antibodies
  - Interferon-a/b
  - Marimastat
  - ZD6474
  - LY317615
  - TNP-470
  - Endostatin/angiostatin
- **Receptor-Targeted Therapy**
  - Trastuzumab
  - Anti-EGFR
    - Gefitinib
    - Erlotinib
    - Cetuximab
    - Panitumumab

HER (erbB) & VEGF Family)

- **HER & erbB Family**
  - EGFR Inhibitors
    - Monoclonal Antibodies- Cetuximab, Panitumumab
    - Tyrosine Kinase Inhibitors- Gefitinib, Erlotinib
  - HER 2 Inhibitors
    - Monoclonal Antibodies- Trastuzumab, Pertuzumab
    - Tyrosine Kinase Inhibitors
- **VEGF Family**
  - VEGF Inhibitors
    - Monoclonal Antibodies- Bevacizumab
    - Tyrosine Kinase Inhibitors

Multi Targeted Therapies

- **Dual kinase Inhibitor**
  - EGFR/VEGF Inhibitors
    - Tyrosine Kinase Inhibitors- Vandatanib (ZD6474)
  - EGFR/HER 2 Inhibitors
    - Tyrosine Kinase Inhibitors- Lapatinib
- **Multi kinase Inhibitor**
  - VEGFR, PDGFR, KIT and FLT3R
    - Tyrosine Kinase inhibitor- Sunitinib
  - VEGFR2 and VEGFR3, FLT-3, PDGFR, c-KIT
    - Tyrosine Kinase Inhibitor- Sorafenib
      - **Sorafenib is an oral inhibitor of RAF**

Targeted Therapies

- **Kinase Inhibitors**
  - PDGFR Inhibitors-
    - Tyrosine Kinase Inhibitors- Imatinib
  - Proteosome Inhibitors – Apoptosis
    - Tyrosine Kinase Inhibitors- Bortezomib

Epidermal Growth Factor Receptor (EGFR)

Some Landmarks in EGFR Signalling

Stanley Cohen

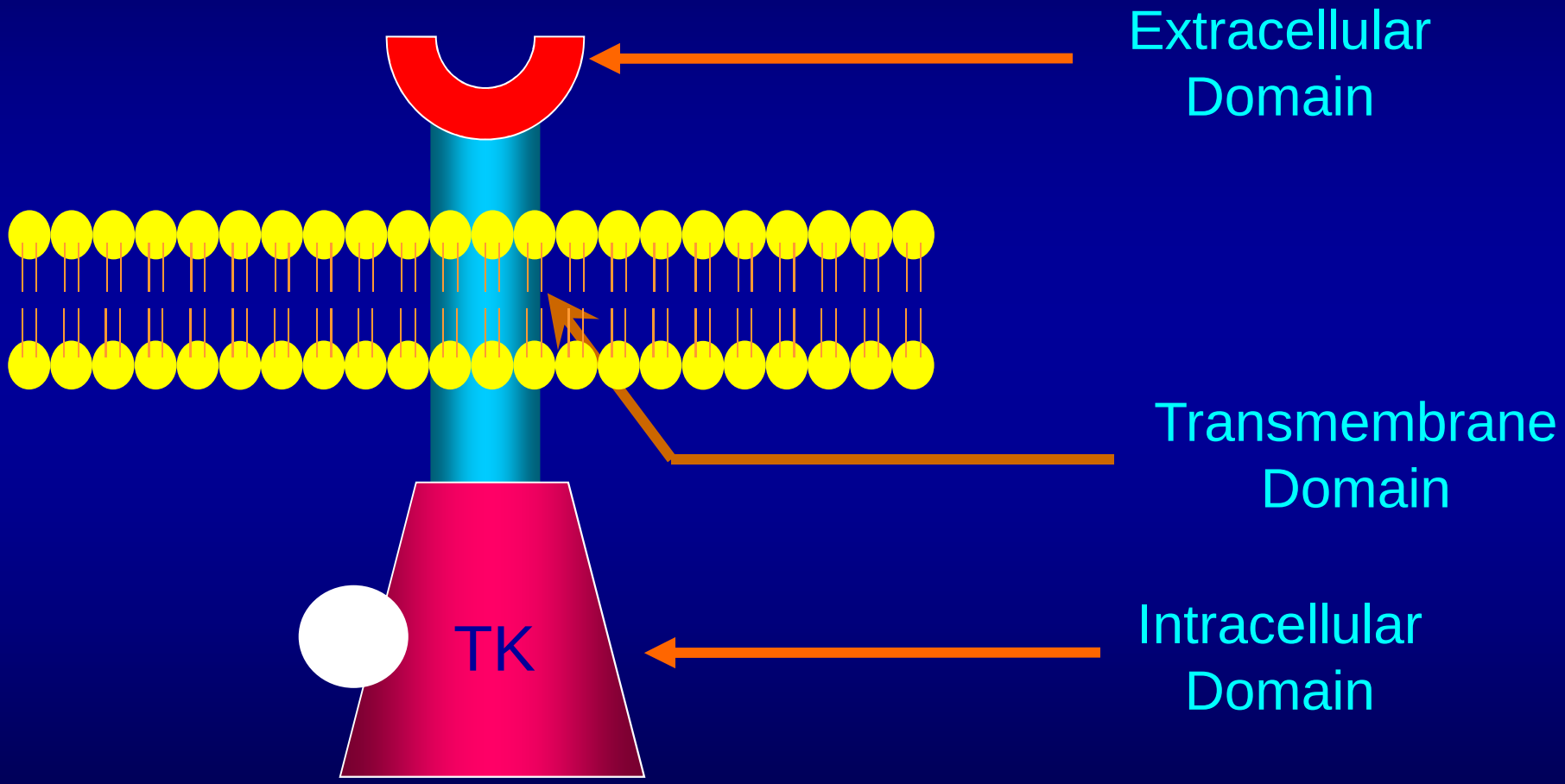
- EGF in mice (1960's)
- Human EGF (1970's)
- Isolation and cloning of EGFR (1980's). Link between EGFR and malignant transformation of cells demonstrated

Mendelsohn et al.,

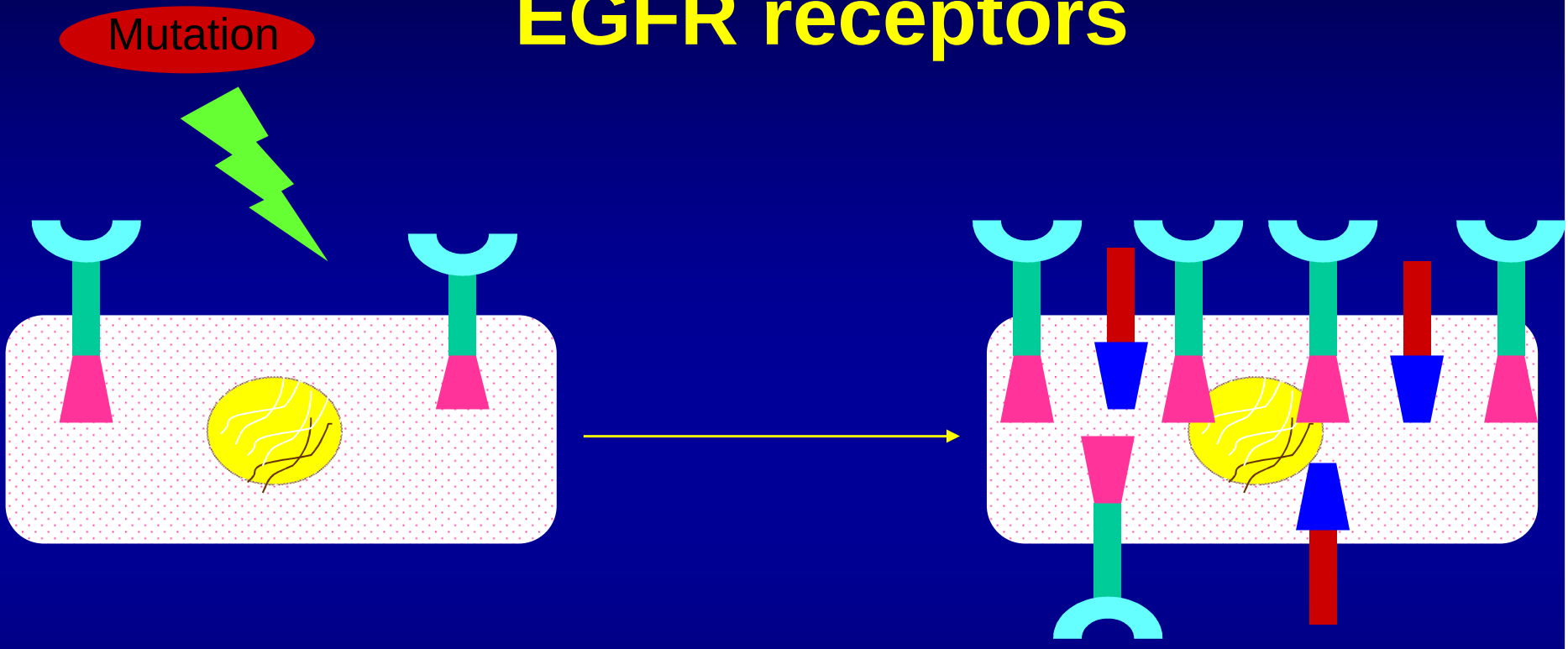
- Blocking EGFR signalling to treat cancer
- Murine monoclonal antibodies targeting EGFR-TK→ Human:murine chimeric version

More than 20 anti-EGFR agents in development

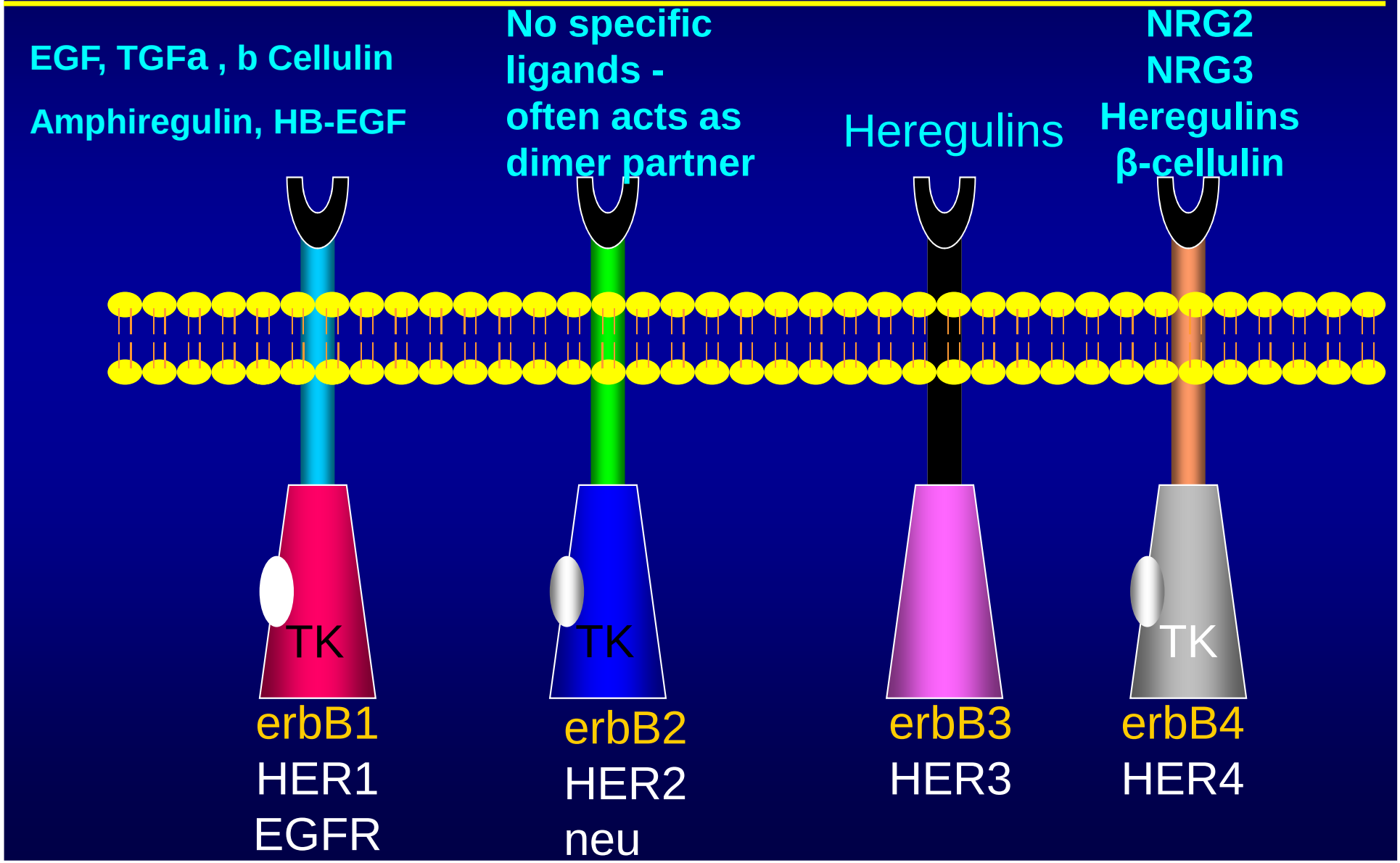
EGFR Structure



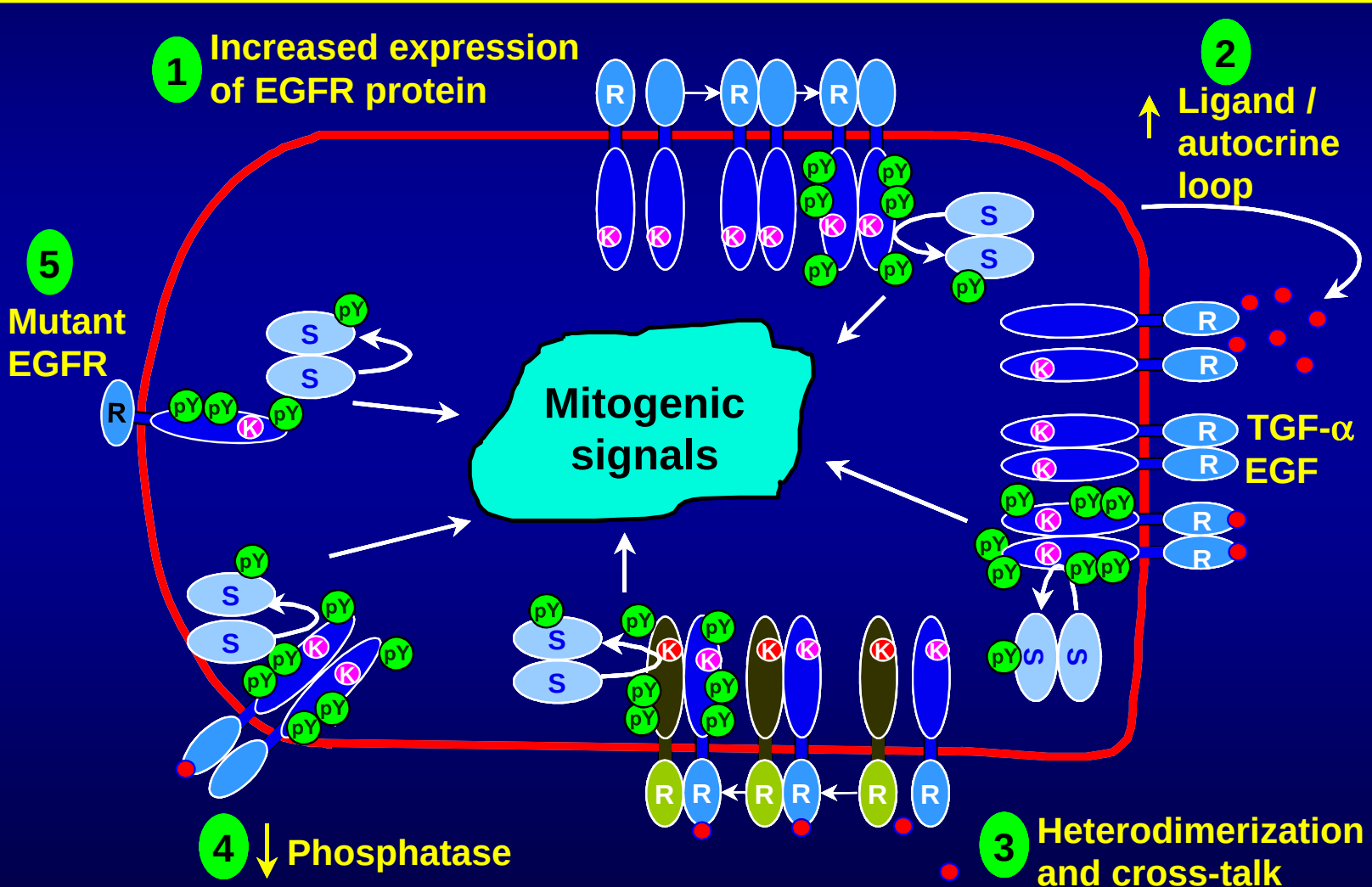
Consequence of proliferation of EGFR receptors



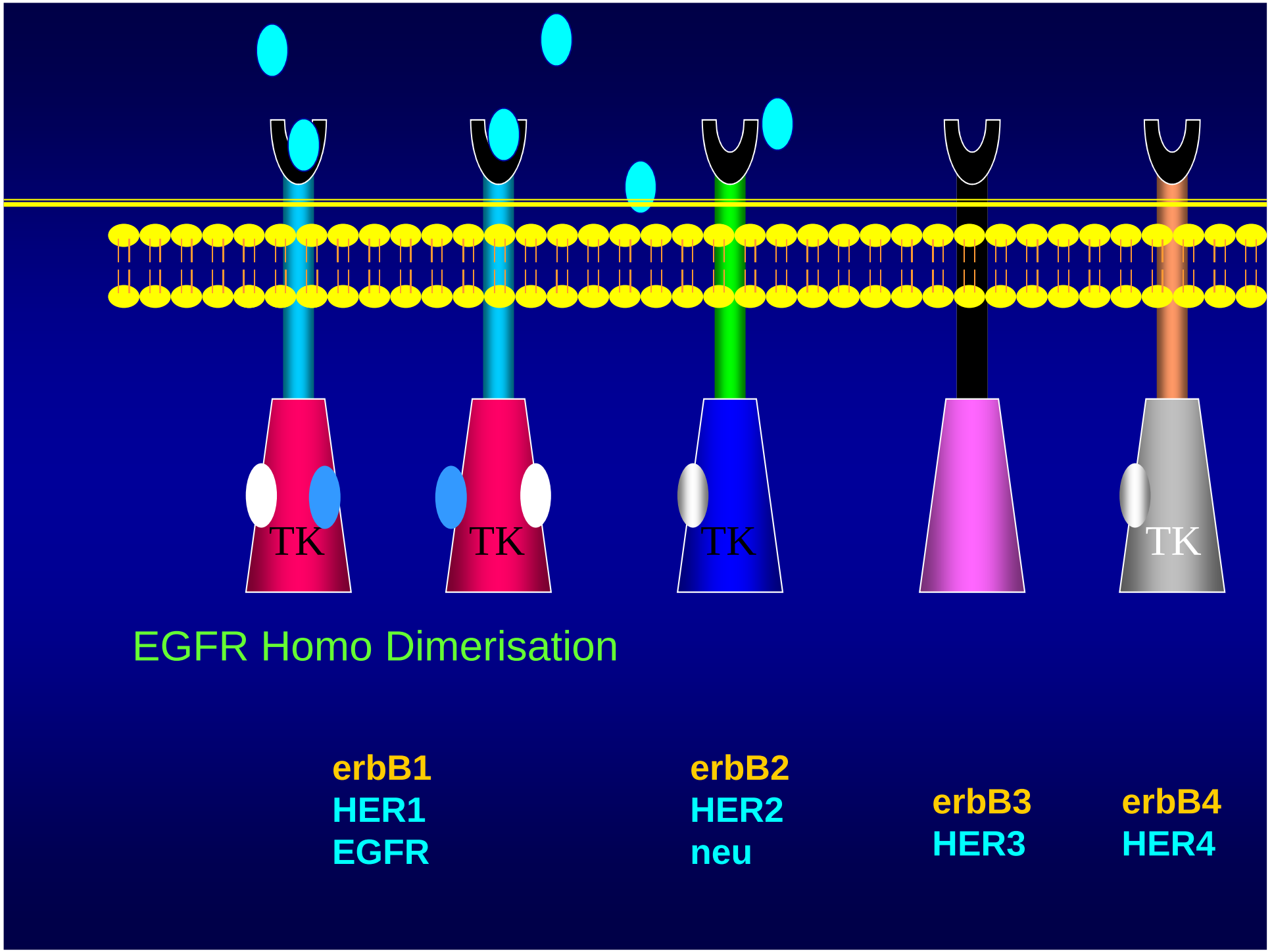
Human Epidermal Growth Factor Receptor Family

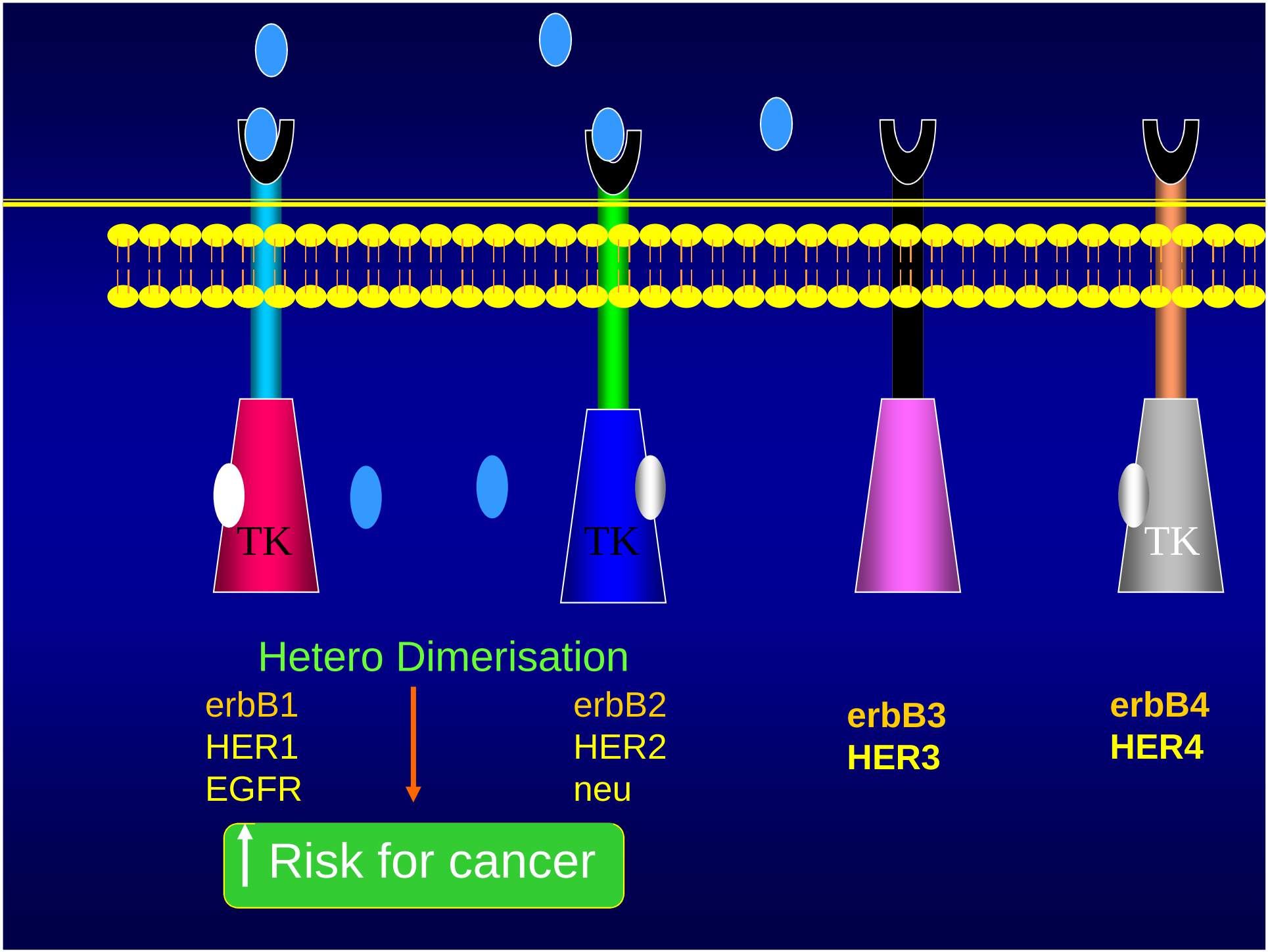


Mechanisms of increased EGFR activation

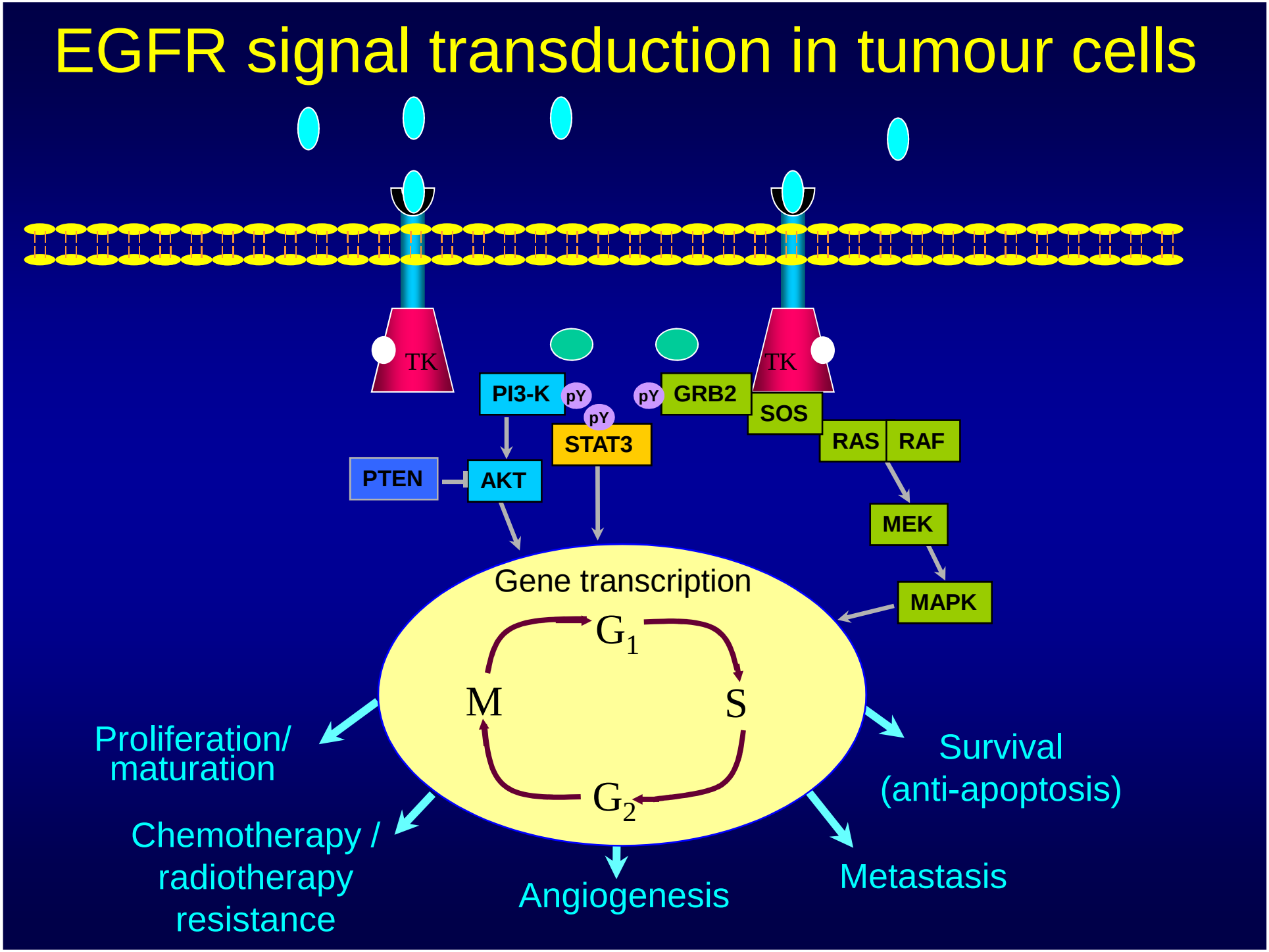


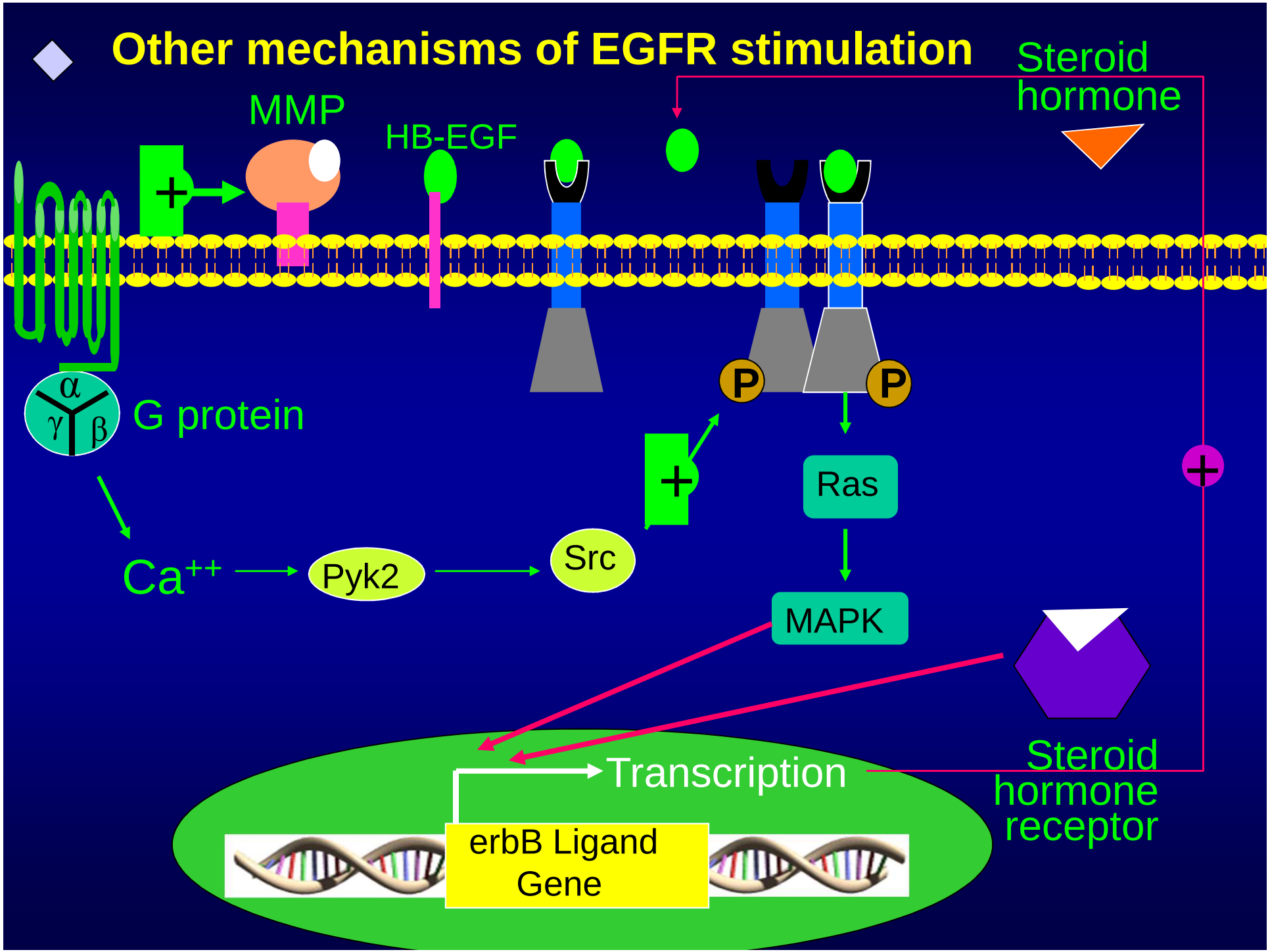
Arteaga 2002

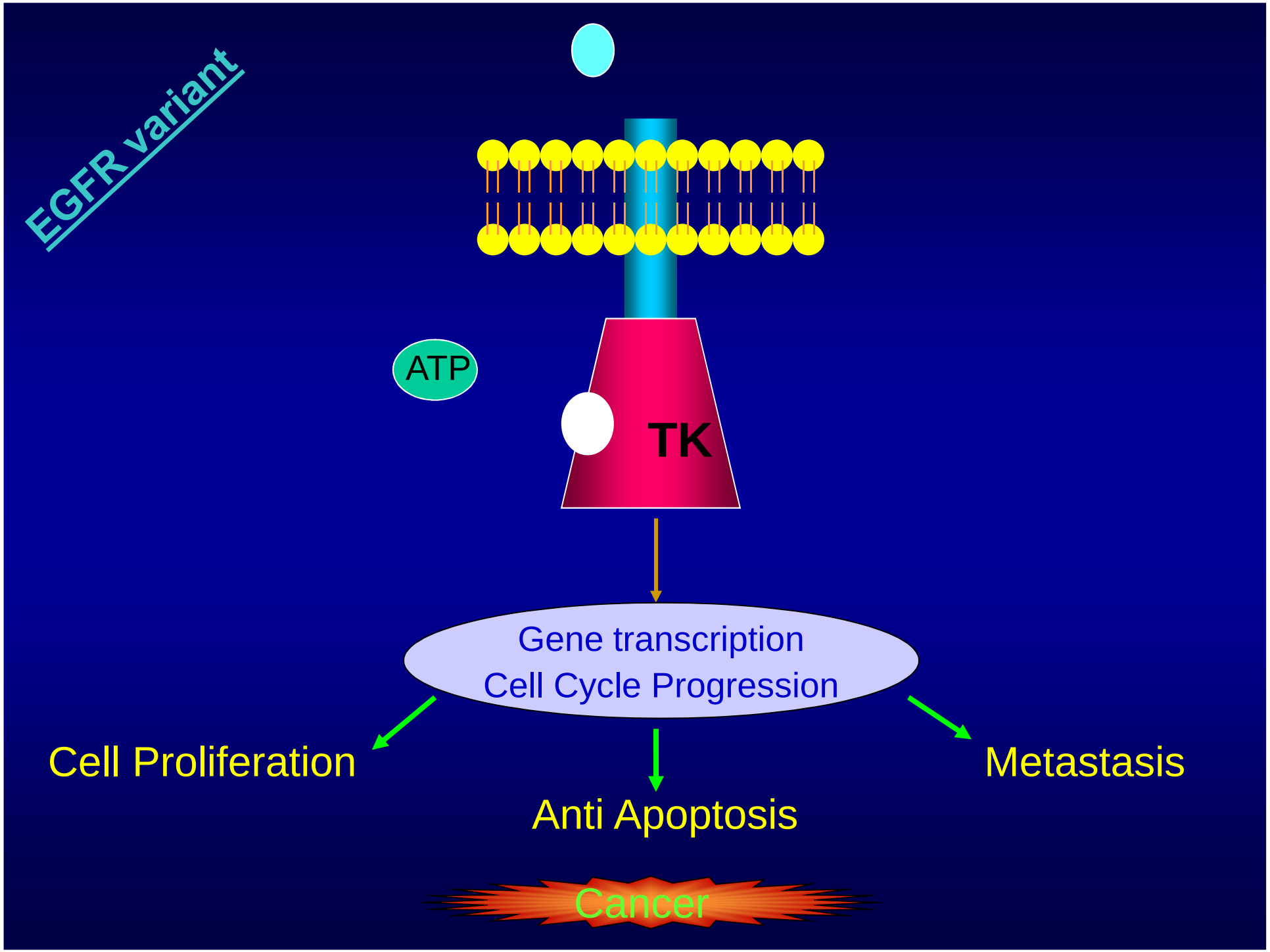

TK
TK
TK
TK
EGFR Homo Dimerisation
erbB1
HER1
EGFR
erbB2
HER2
neu
erbB3
HER3
erbB4
HER4


TK
TK
TK
Hetero Dimerisation
erbB1
HER1
EGFR
erbB2
HER2
neu
erbB3
HER3
erbB4
HER4
Risk for cancer

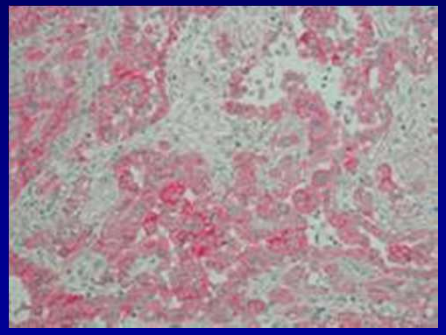
EGFR signal transduction in tumour cells



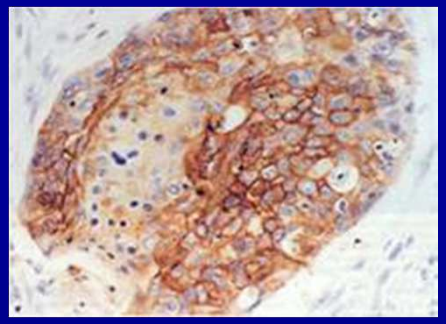

Other mechanisms of EGFR stimulation
Steroid hormone
MMP
HB-EGF
G protein
α
γ
β
P
P
Ras
Ca++
Pyk2
Src
MAPK
Transcription
erbB Ligand Gene
Steroid hormone receptor


EGFR variant
ATP
TK
Gene transcription
Cell Cycle Progression
Cell Proliferation
Anti Apoptosis
Metastasis
Cancer

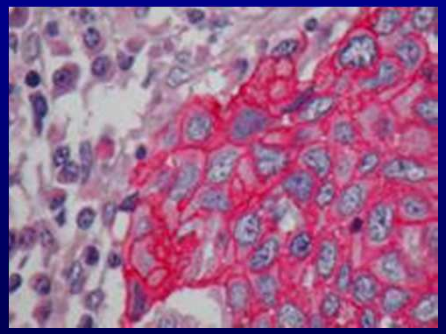
EGFR Expression in Solid Tumors



Colorectal



Lung (NSCLC)



Head and neck (SCCHN)

EGFR is expressed in a variety of solid tumors

Tumor Target	%
Head and neck cancer	95–100
Colorectal cancer	72–89
Pancreas	upto 95 %
Lung cancer (NSCLC)	40–80
Breast cancer	14–91
Ovarian cancer	35–70
Renal cell cancer	50–90

Cunningham et al. *N Engl J Med* 2004;351:337–345; Grandis et al. *Cancer* 1996;78:1284–1292; Salomon et al. *Crit Rev Oncol Hematol* 1995;19:183–232; Walker & Dearing. *Breast Cancer Res Treat* 1999;53:167–176; Folprecht et al. ASCO 2004 (Abstract #283).

Tumor EGFR Expression as a Prognostic Factor

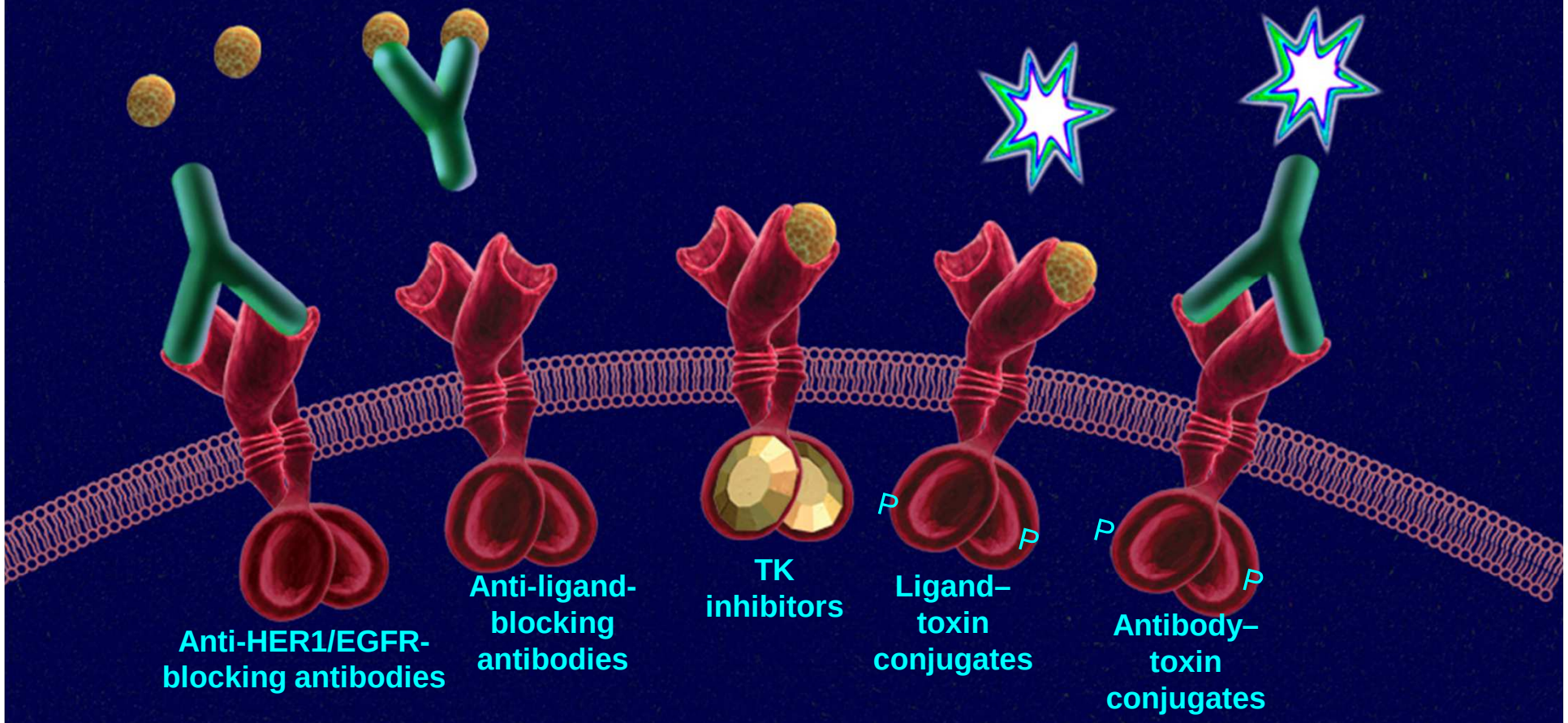
- EGFR expression correlates with poor prognosis.

Tumor type	Prognosis	Survival	Risk of metastasis	References
Colorectal	Poor	-	Increased	Hemming (1992)
Lung	Poor	Decreased OS	-	Ohsaki (2000)
(NSCLC)	Poor	-	Increased	Pavelic (1993)
Head & neck (SCCHN	Poor	Decreased DFS	-	Grandis (1998)
		Decreased OS		Maurizi (1996)

- EGFR expression also linked to reduced response, and/or increased resistance to chemotherapy

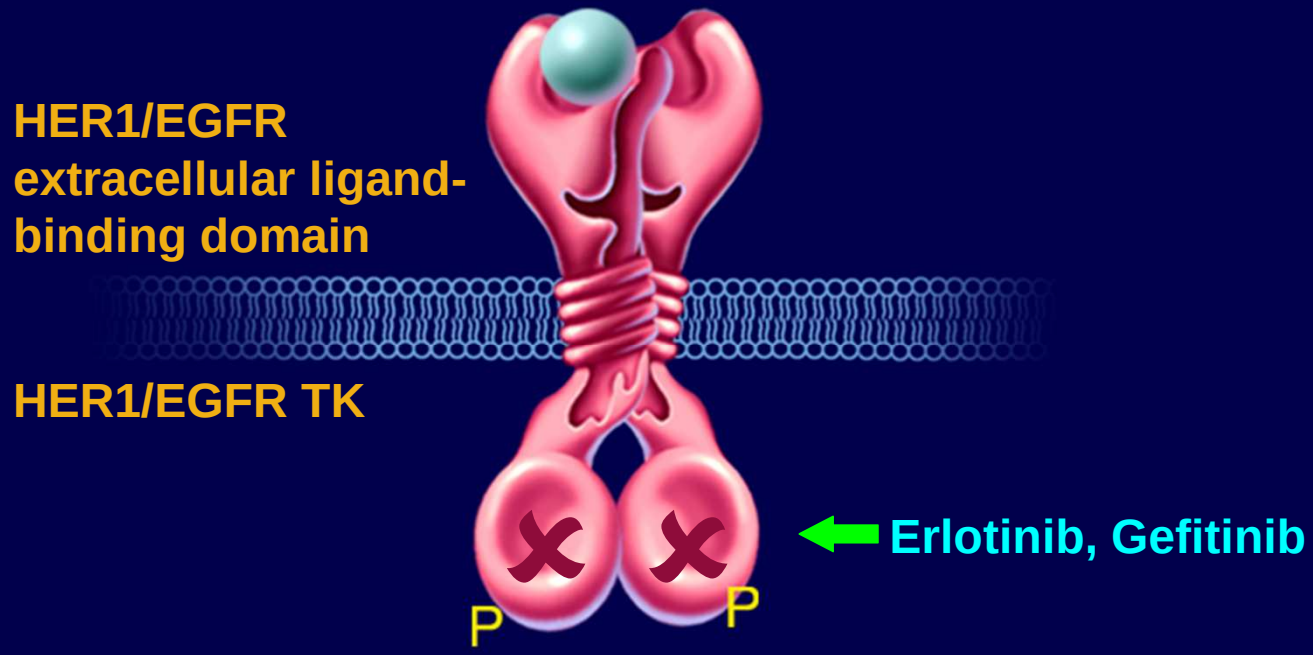
DFS = Disease-free survival;
OS = overall survival

Common Approaches to Targeting HER1/EGFR



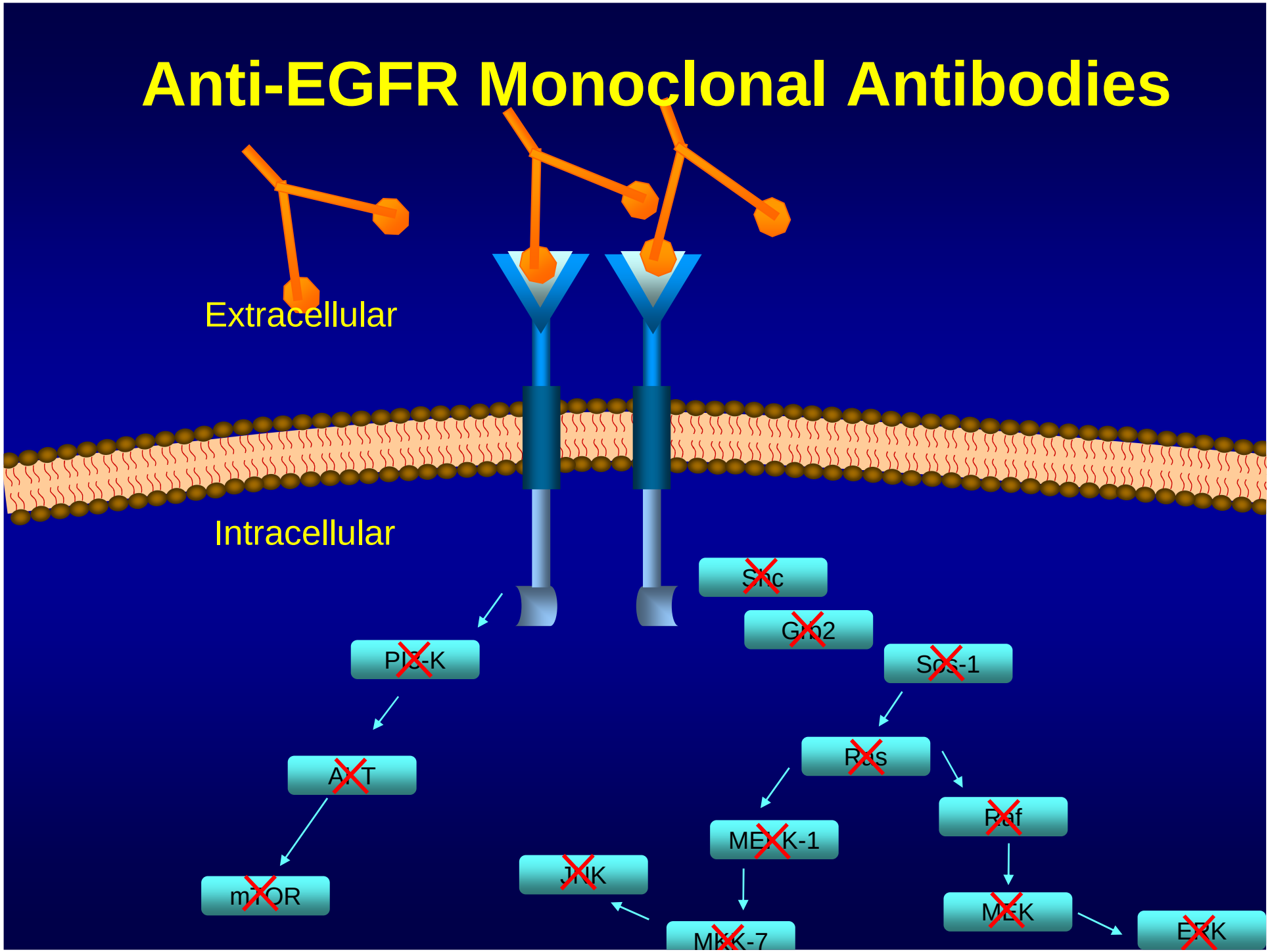
Slamon DJ, Leyland-Jones B, Shak S, et al. *N Engl J Med.* 2001;344:783-792; Mendelsohn J, Baselga J. *Oncogene.* 2000;19:6550-6565; Noonberg SB, Benz CC. *Drugs.* 2000;59:753-767; Raymond E, Faivre S, Armann JP. *Drugs.* 2000;60(Suppl 1):15-23; Arteaga C. *J Clin Oncol.* 2001;19:32s-40s; Pedersen MW, Meltom M, Damstrup L, et al. *Ann Oncol.* 2001;12:745-760.

Tyrosine Kinase EGFR Inhibitor-Gefitinib, Erlotinib

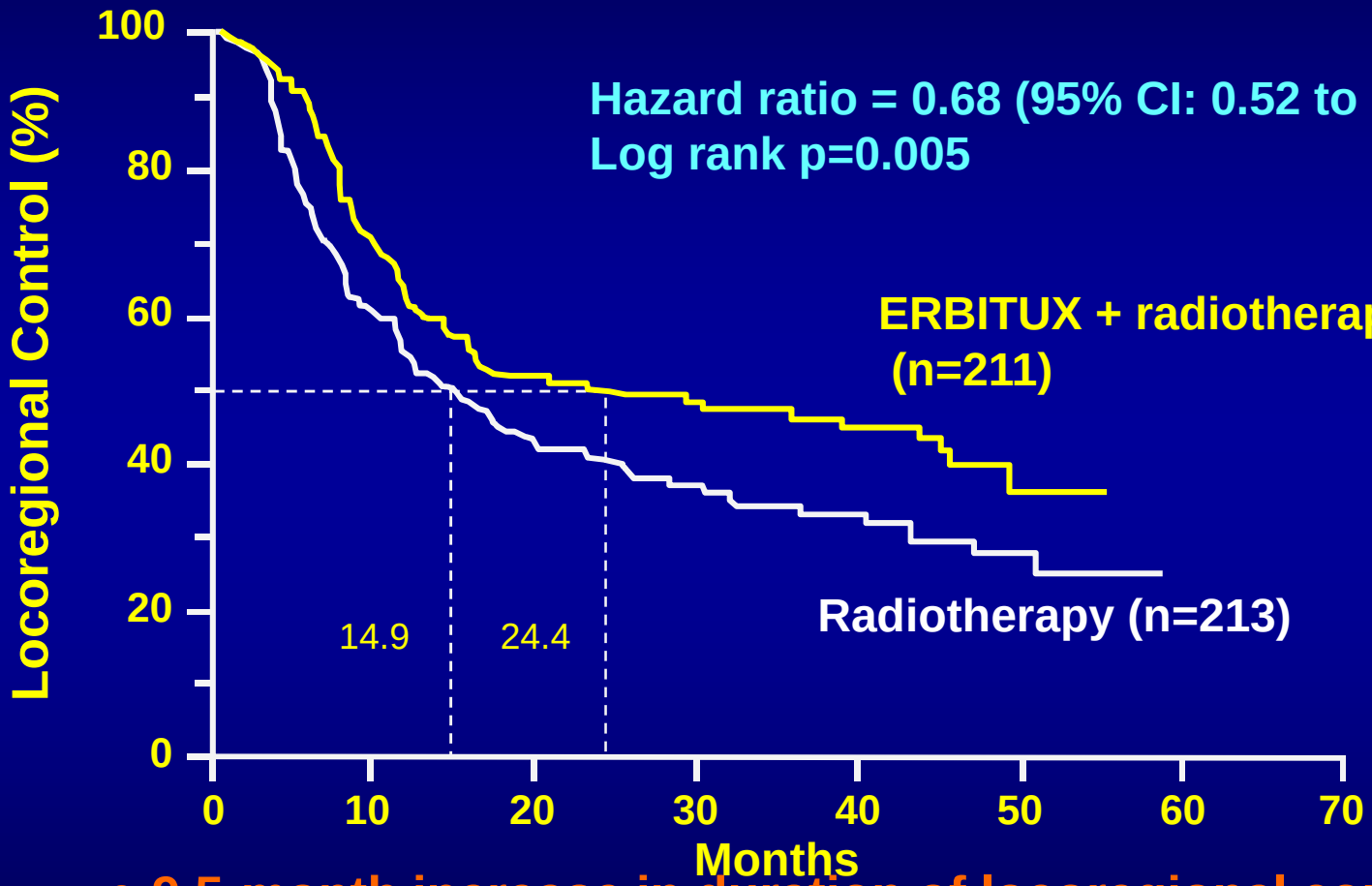


- Small-molecule inhibitor of HER1/EGFR TK
- Chemical class: quinazoline
- Previously known as CP-385,774 and OSI-774
- A joint global development program with Roche, OSI Pharmaceuticals Inc. and Genentech Inc.

Anti-EGFR Monoclonal Antibodies



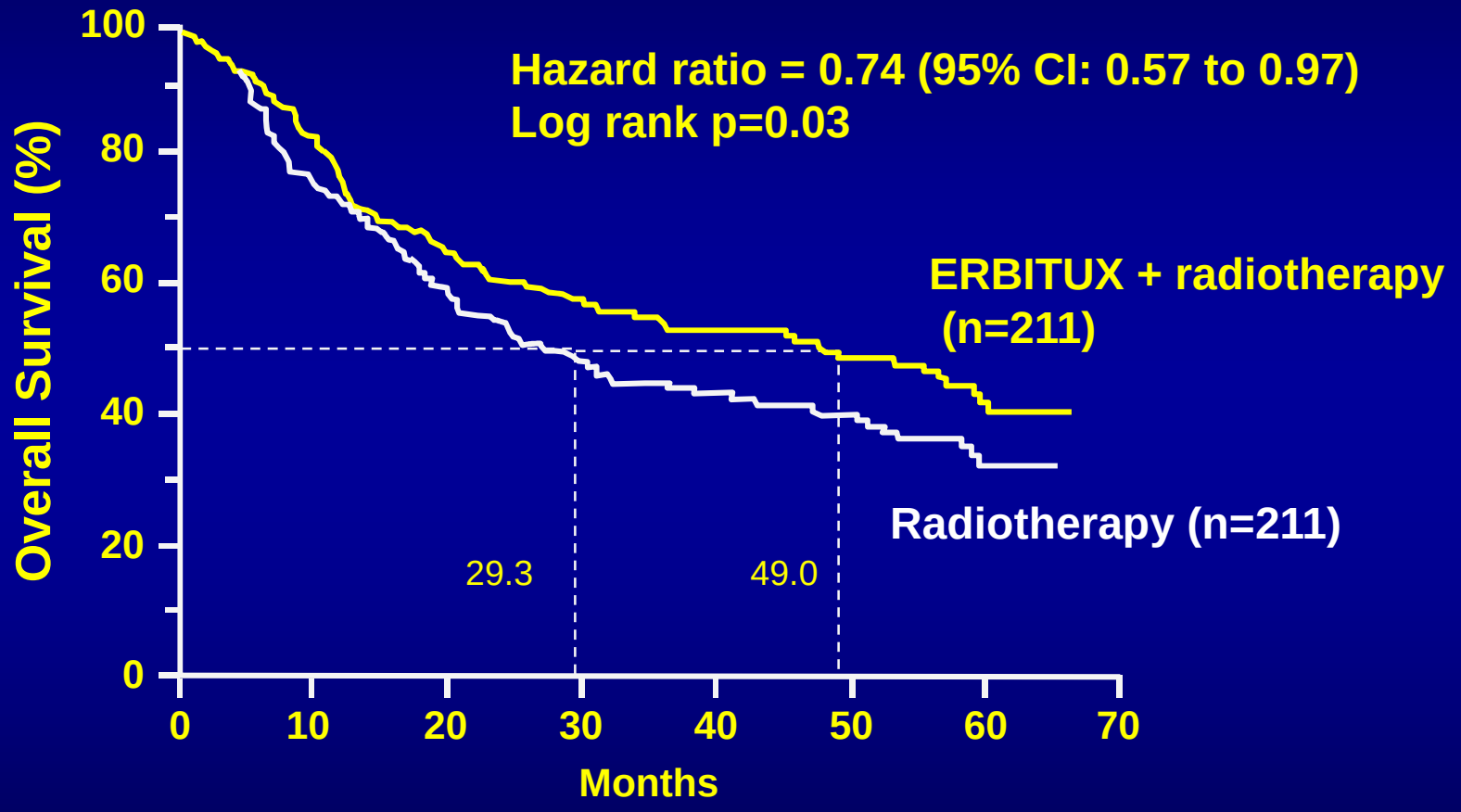
ERBITUX + RT improves locoregional control over RT alone in locally advanced SCCHN



- 9.5-month increase in duration of locoregional control (24.4 vs 14.9 months)
- 32% reduction in the risk of locoregional progression

Bonner J…Ang, K. N Engl J Med 2006:354:567–578

ERBITUX + RT prolongs survival over RT alone in locally advanced SCCHN



- Almost 20 months increase in overall survival (49 vs 29.3 months).
- 26% reduction in Risk of death

Bonner J…Ang, K. N Engl J Med 2006;354:567–578

CETUXIMAB + RT prolongs survival over RT alone in locally advanced SCCHN (1)

	RT (n=213)	**Cetuximab + RT** (n=211)	p-value
Median overall survival	**29.3 months**	**49.0 months**	0.03
Survival rate 3 year	45%	55%	0.05

- Addition of Cetuximab to RT:
  - Increased median survival by nearly 20 months (49.0 vs 29.3 months)

Bonner J…Ang, K. N Engl J Med 2006;354:567–578

CETUXIMAB does not increase acute RT-induced toxicity in locally advanced SCCHN

Relevant Grade 3–5 Side Effects

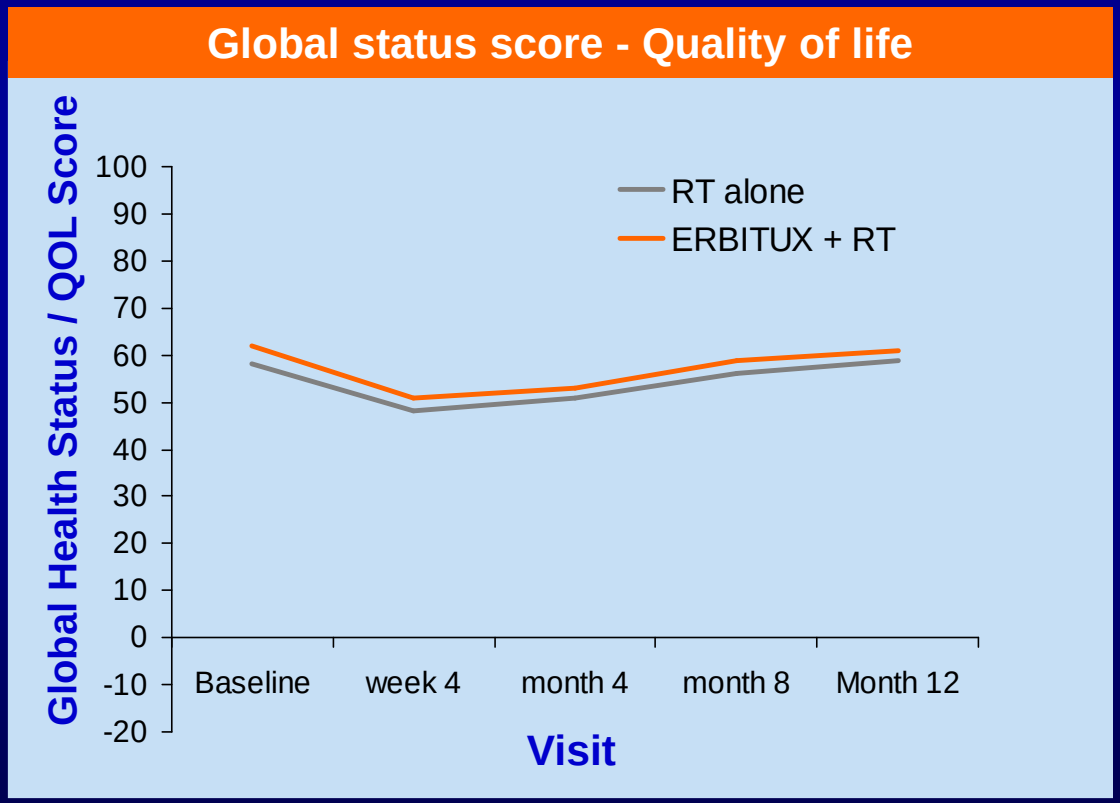
Side effect	RT (n=212)	**ERBITUX + RT**	p-value[a]
Mucositis/stomatitis	52%	56%	0.44
Dysphagia	30%	26%	0.45
Xerostomia	3%	5%	0.32
Fatigue/malaise	5%	4%	0.64
Acne-like rash	1%	17%**	<0.001
Infusion-related reactions[b]	0%	3%*	0.01

[a]Fisher's exact test
[b]Listed for its relationship to ERBITUX

Bonner J…Ang, K. N Engl J Med 2006;354:567–578

ERBITUX Quality of life

ERBITUX plus RT increased overall survival without adversely affecting quality of life

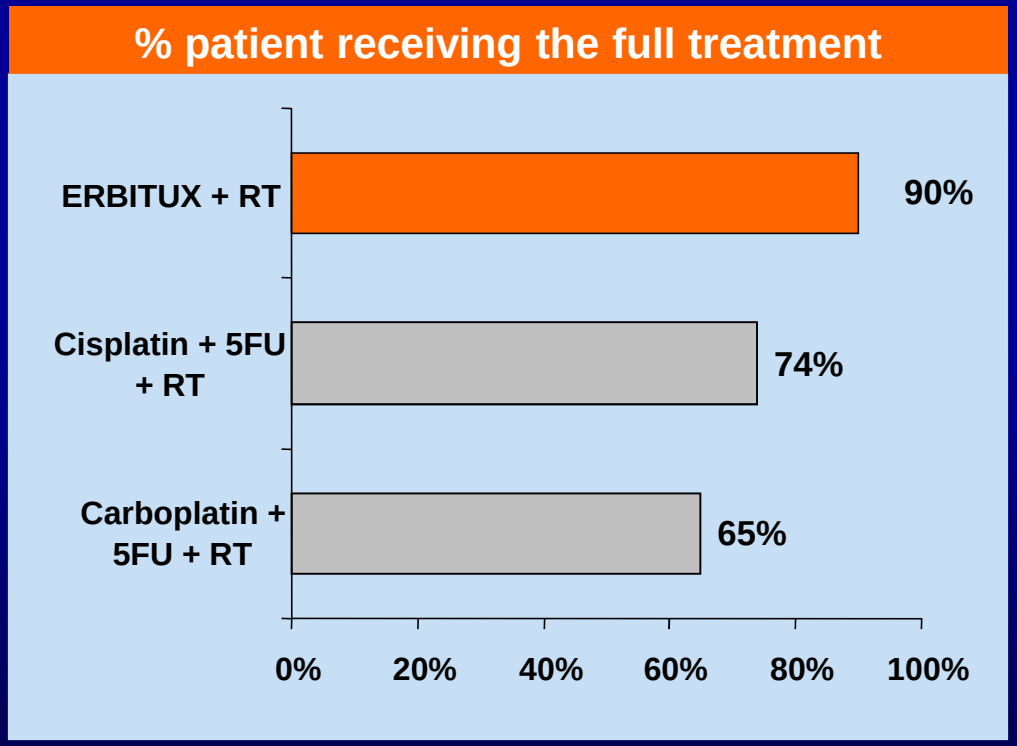


- No significantly difference in Quality of life scores between patients treated with ERBITUX plus radiotherapy and radiotherapy alone

Curran D, et al. J Clin Oncol, 2007

Comparison ERBITUX compliance

Compliance to the treatment is higher when using ERBITUX plus RT instead of CRT

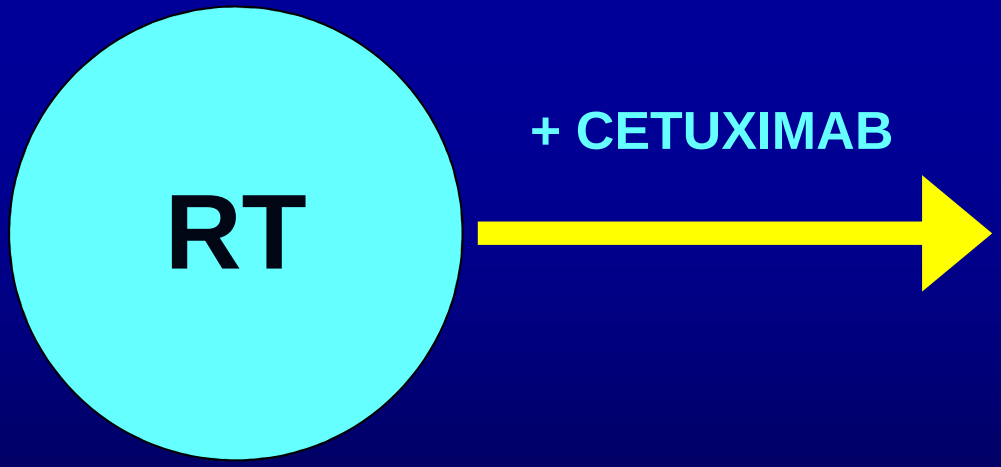


- **90% of the patients treated by ERBITUX + RT receive the full treatment**
- **26 % to 35% patient will not receive the full treatment of chemo-radiotherapy**

1 Bonner J, et al. N Engl J Med 2006;354:567–578
2 Calais G, et al. J natl Cancer Inst 1999;9 1 (24):2 081-6
3 Huguenin P, et al. J Clin Oncol 2004; 6Bonner JA, et al. N Engl J Med 2006

CETUXIMAB in locally advanced SCCHN: Summary

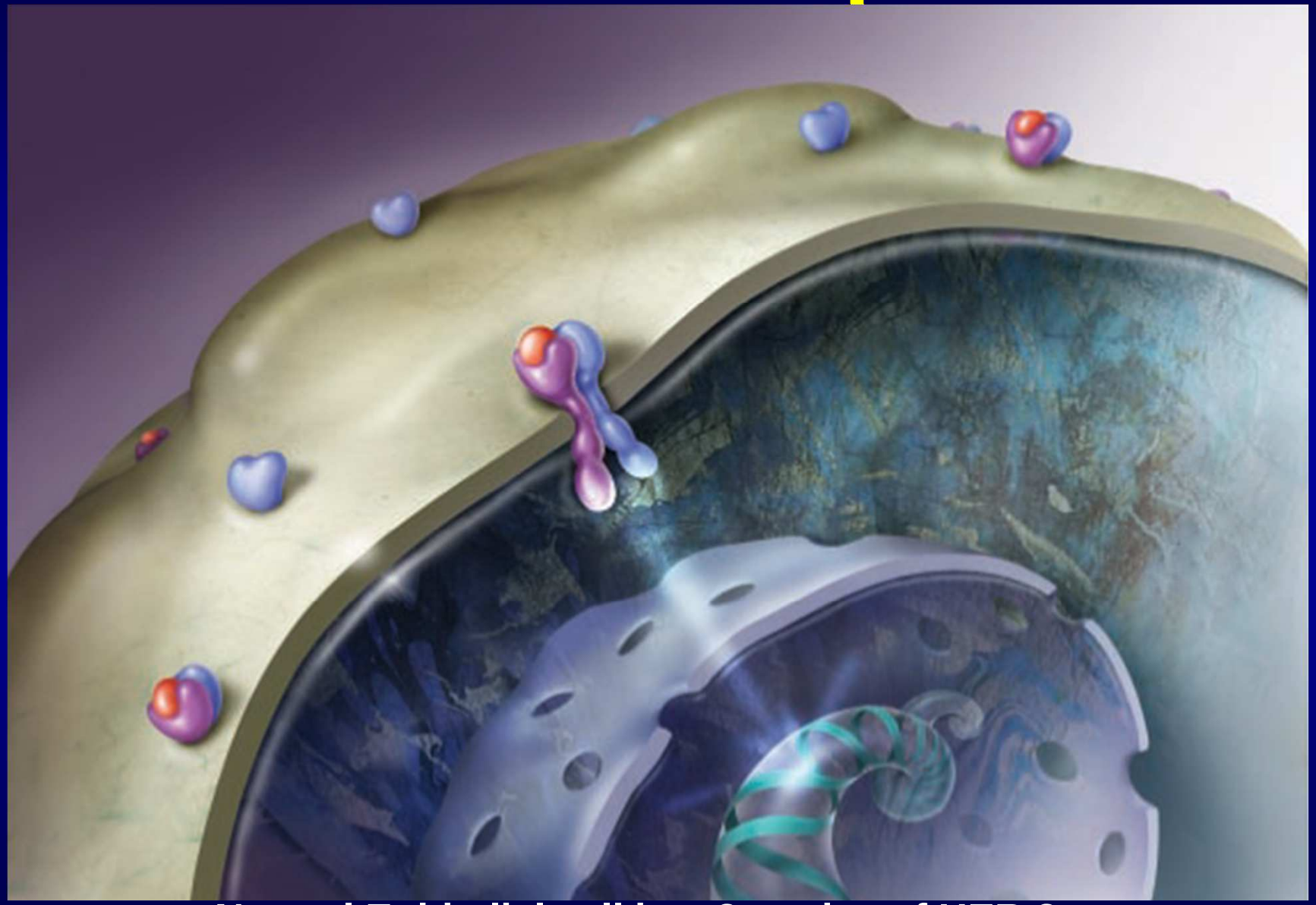
- **CETUXIMAB + high-dose RT demonstrated significant efficacy benefits over high-dose RT alone**



- 26% reduction in Risk of death
- 32% reduction in locoregional relapse
- Extends survival by nearly 20 months
- No increase in acute RT-related side effects

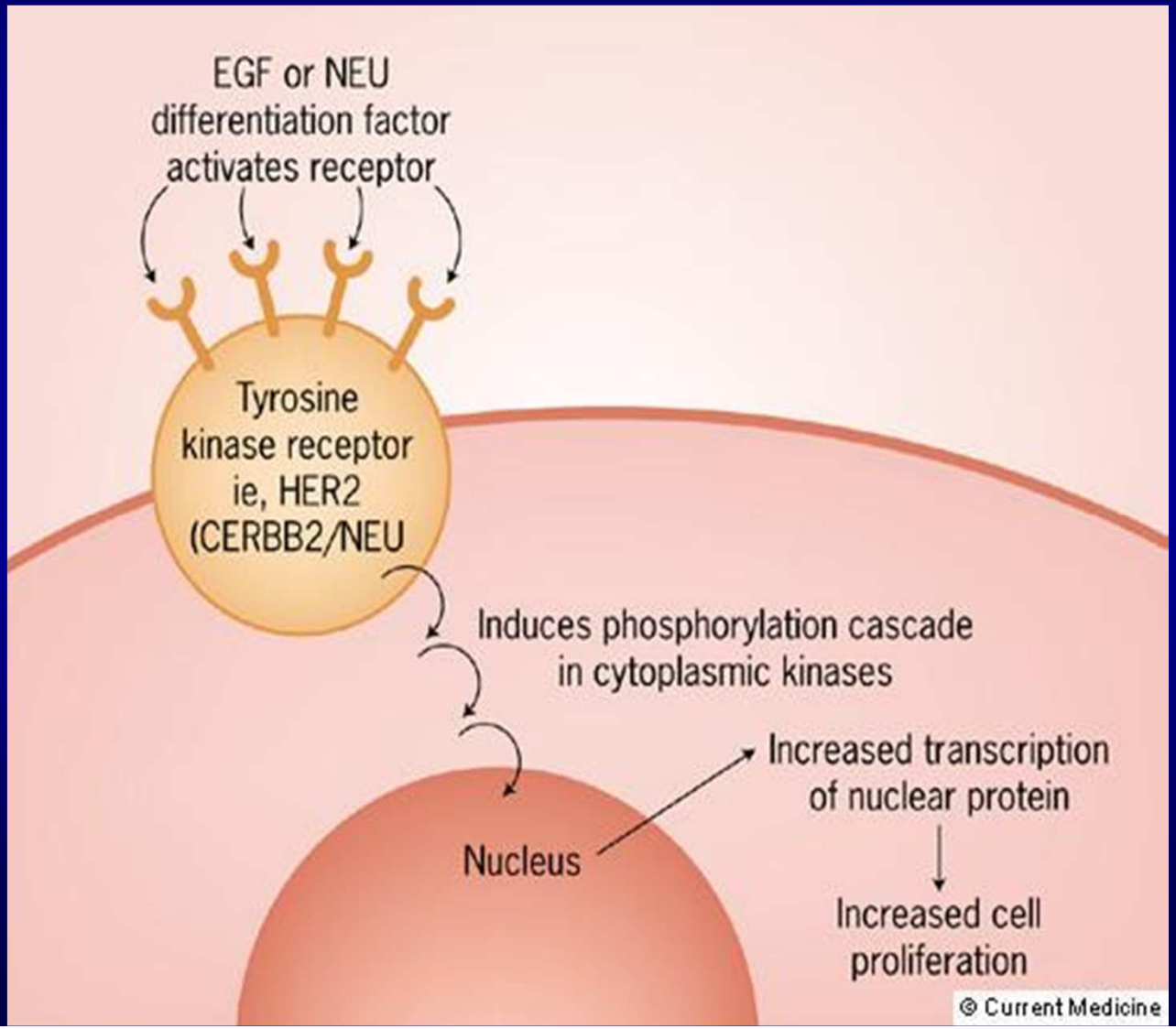
Bonner et al. N Eng J Med 2006;354:567-578

Normal HER2 expression

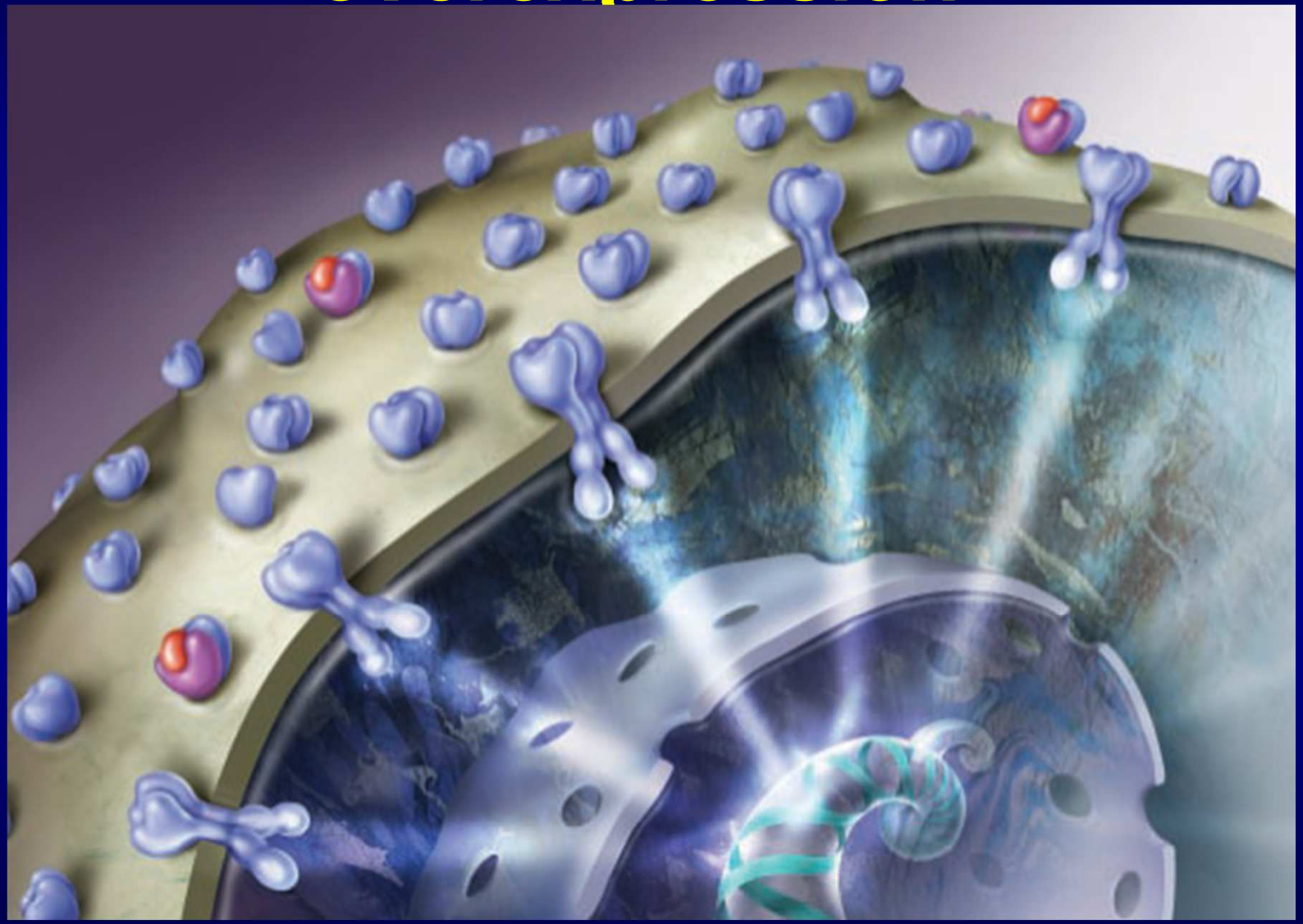


Normal Epithelial cell has 2 copies of HER 2 gene & 20000 to 50000 HER 2 receptors on cell surface

Molecular pathway for activation of HER2/NEU

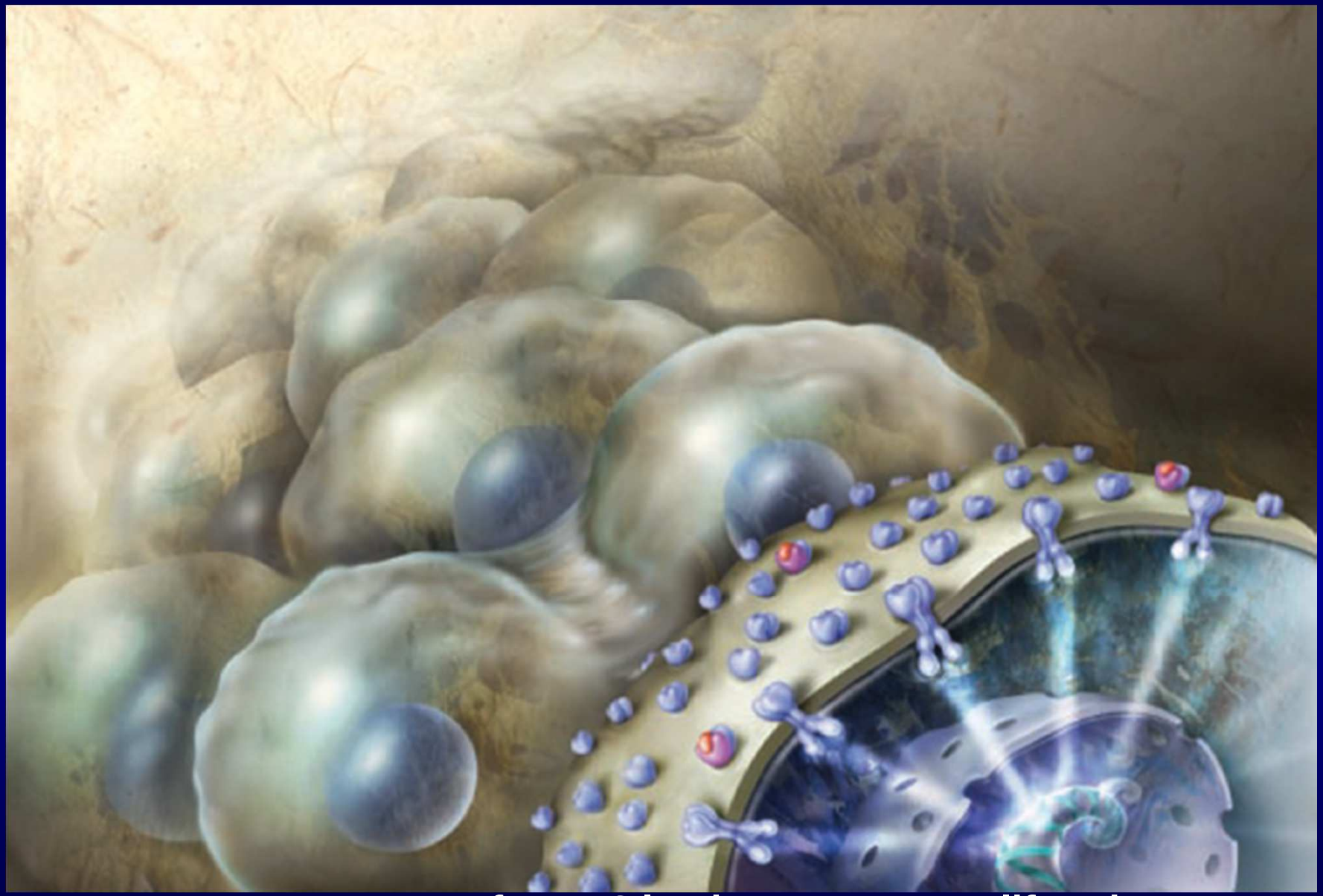


HER2 amplification → HER2 overexpression



Mutations affecting HER 2 gene results in gene amplification thereby Causing 100 fold increase in no. of HER 2 receptors on cell surface

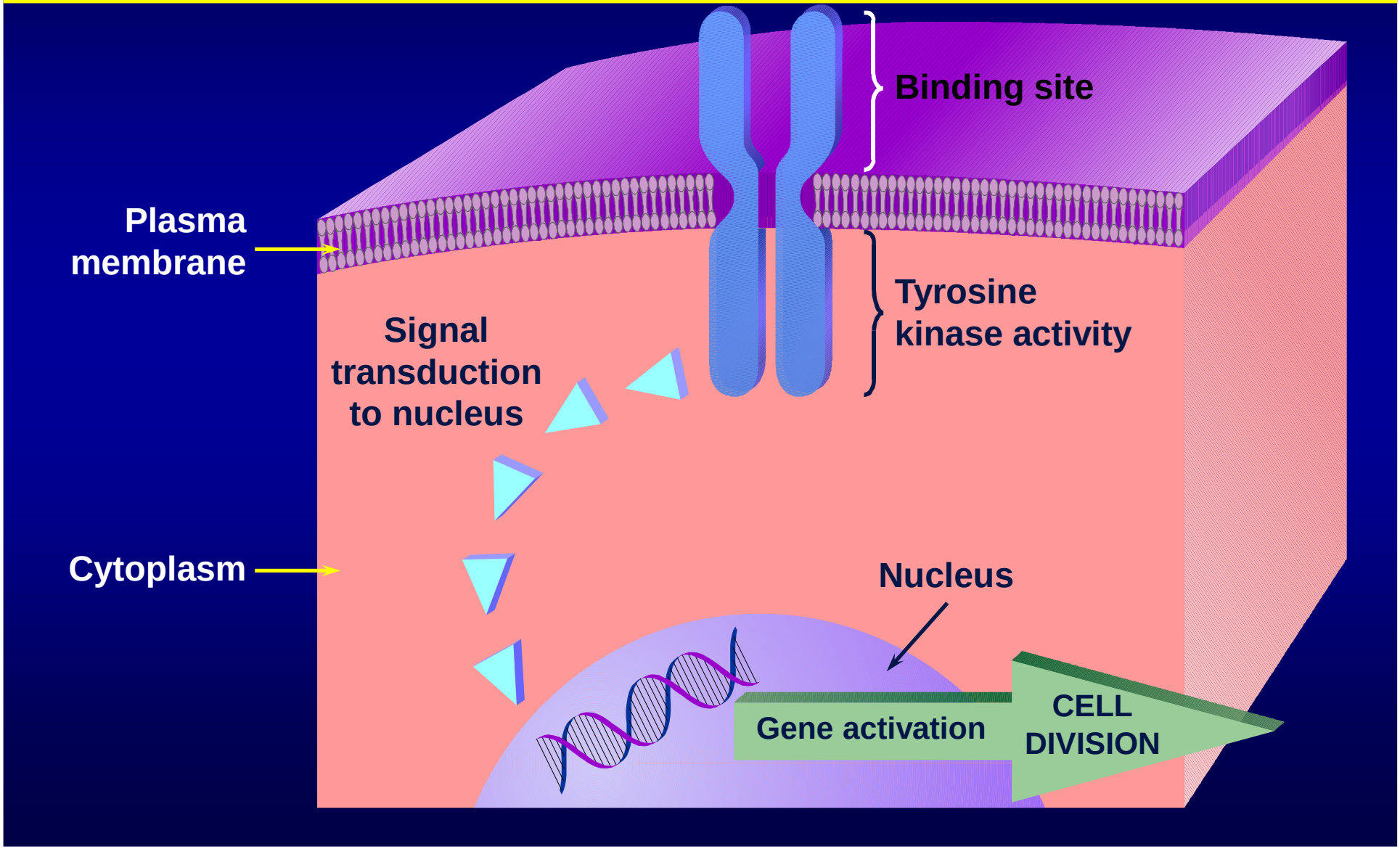
HER2 overexpression → tumour proliferation



Excess amounts of HER 2 leads to Tumor Proliferation

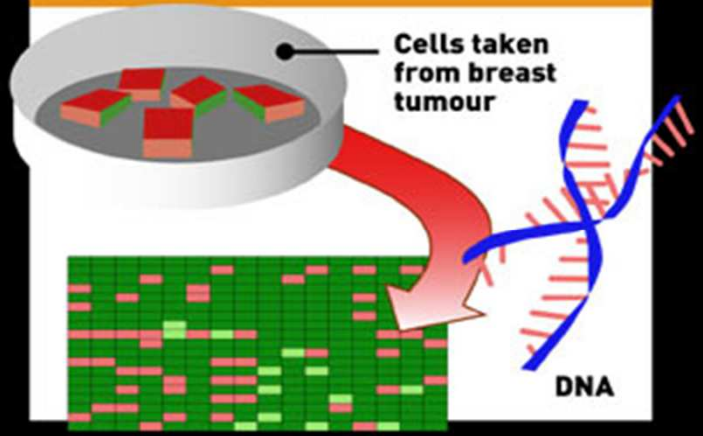
Prof. Tim Cooke at Special EONS symposia, ECCO 10, Austria

HER2 Receptor Provides an Extra- Cellular Therapeutic Target



Molecular Targeting of Breast Cancer

MOLECULAR FORECASTING



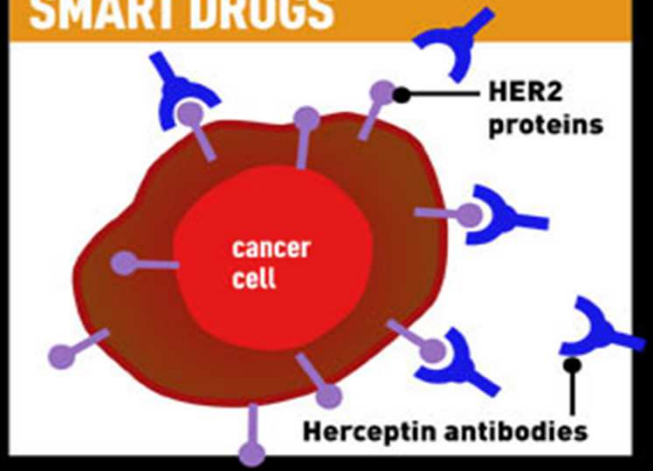
How it's done

With microarrays, scientists can study patterns of gene activity using strands of cancer DNA and predict which tumours are likely to spread. The technique may someday be used to design customised treatments.

Availability

Clinical trials for breast cancer are starting this year; treatment may be widely available within the decade.

SMART DRUGS



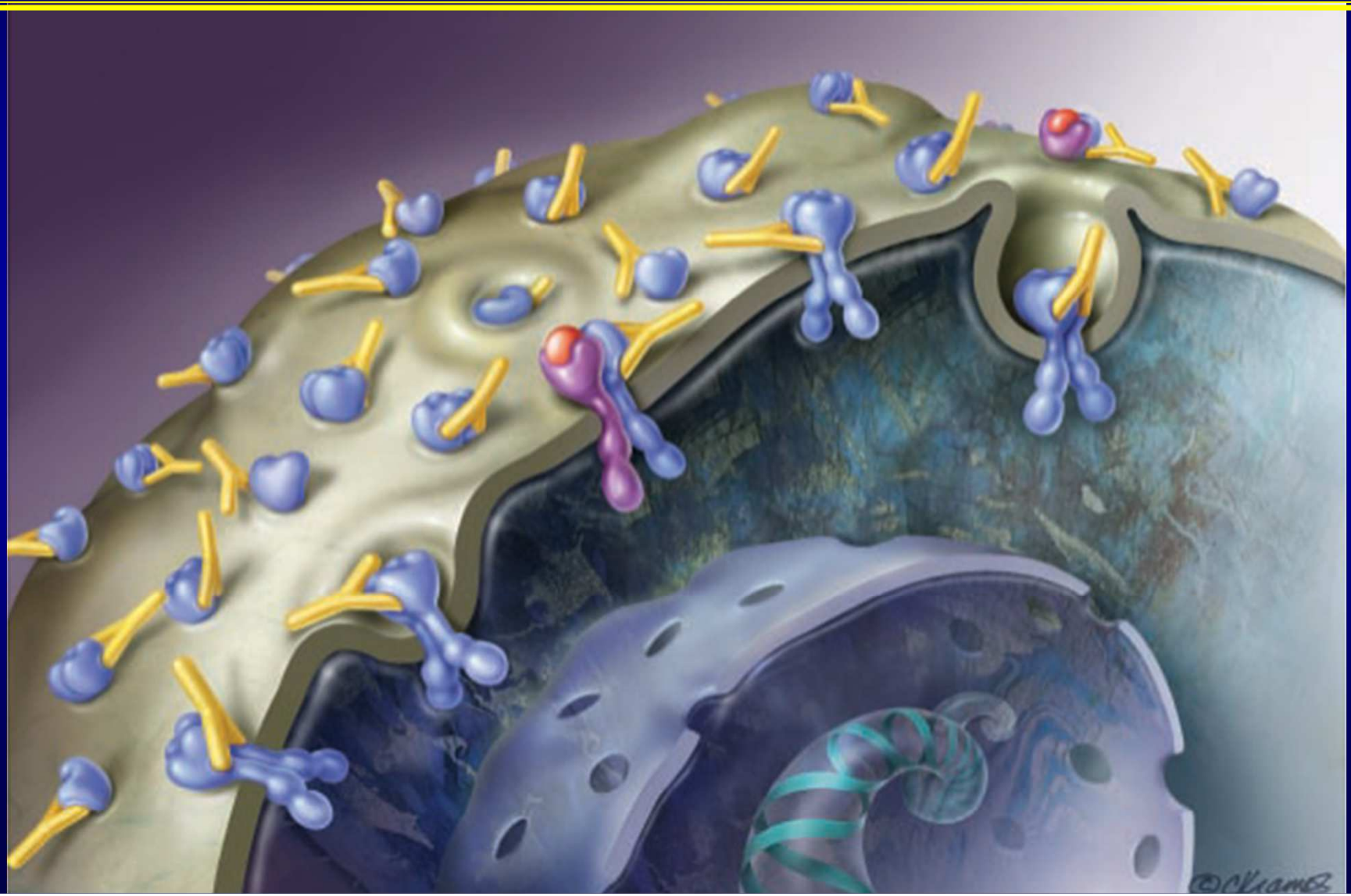
How it's done

As scientists come to understand at the molecular level precisely how tumours form, they are designing a new generation of smart drugs that bind to specific receptors or block particular proteins.

Availability

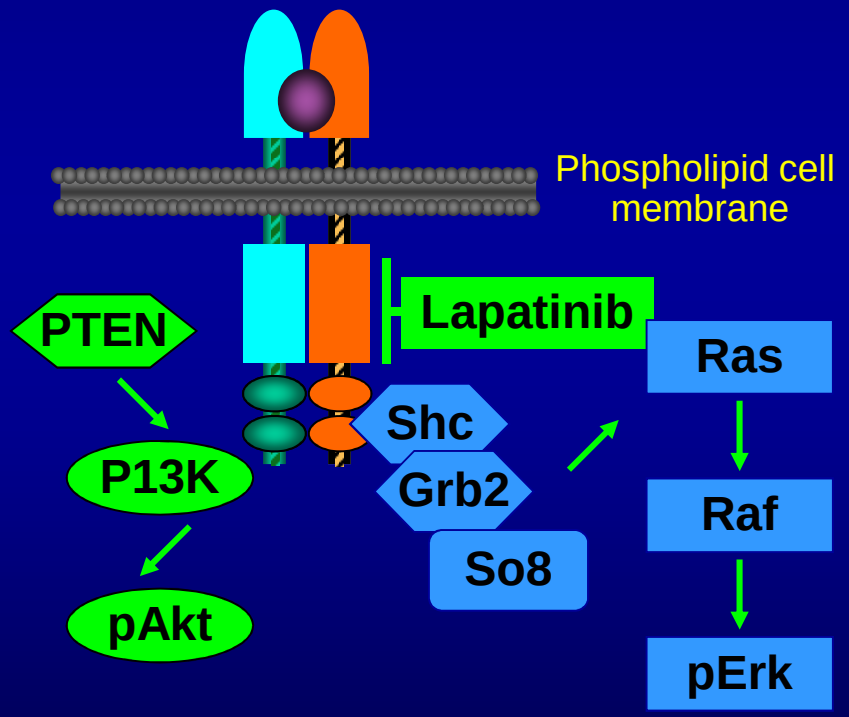
Herceptin, the first of these smart drugs for breast cancer is available for certain advanced cancers.

Binding of Trastuzumab to HER2



Lapatinib: Targeting EGFR and HER2

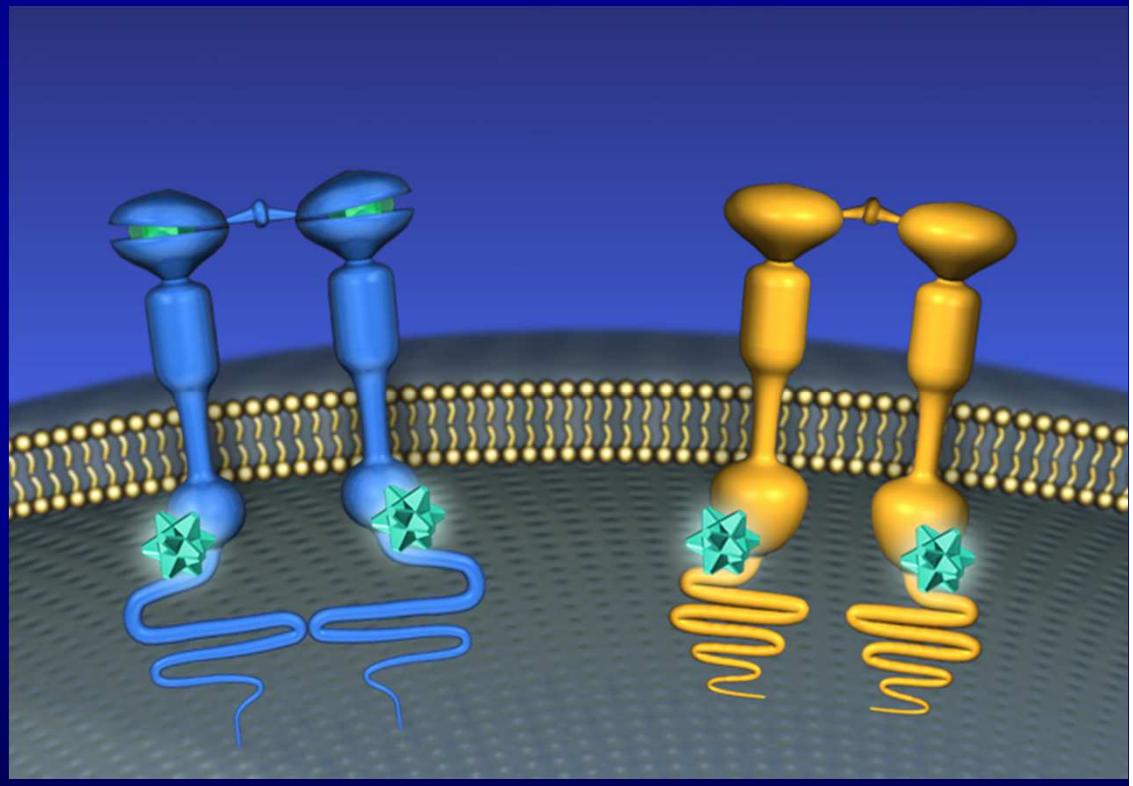
- Lapatinib oral tyrosine kinase inhibitor of ErbB1 and ErbB2
  - Blocks signaling through EGFR and HER2 homodimers and heterodimers
  - May also prevent signaling between ErbB1/ErbB2 and other ErbB family members



Rusnak DW, et al. Mol Cancer Ther. 2001;1:85-94.
Xia W, et al. Oncogene. 2002;21:6255-6263.

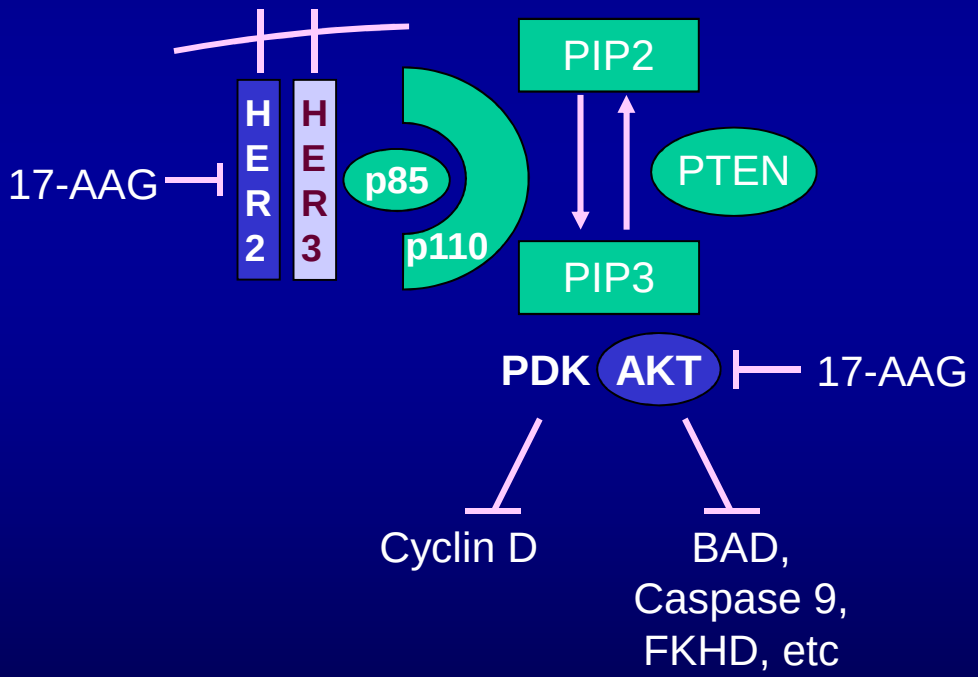
Lapatinib—A Dual Receptor Tyrosine Kinase Inhibitor

- Potent, oral, reversible dual tyrosine kinase inhibitor
- Binds to ATP site of erbB-1 and erbB-2 receptor kinases, blocking kinase activity and downstream signaling



Targeting HER2 via HSP-90

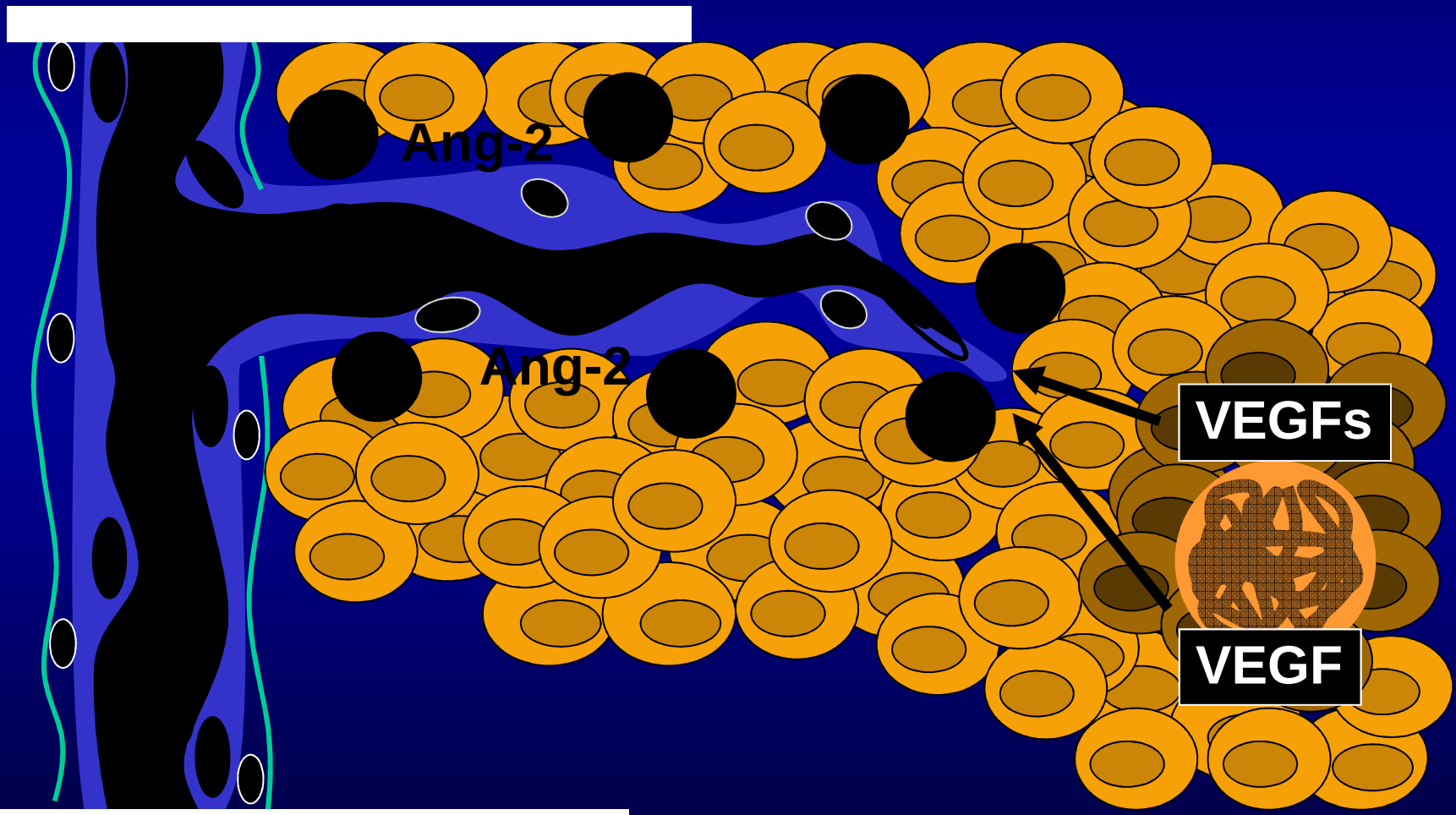
- Heat shock protein-90 (HSP-90) is a chaperone protein for a variety of oncogenic proteins, including HER2, ER/PR, AKT, MET, and Raf kinase
- 17-AAG (KOS-953), an inhibitor of HSP-90, suppresses tumor growth in mouse xenograft models of HER2+ human breast cancers



Modi S, et al. ASCO 2006. Abstract 501.

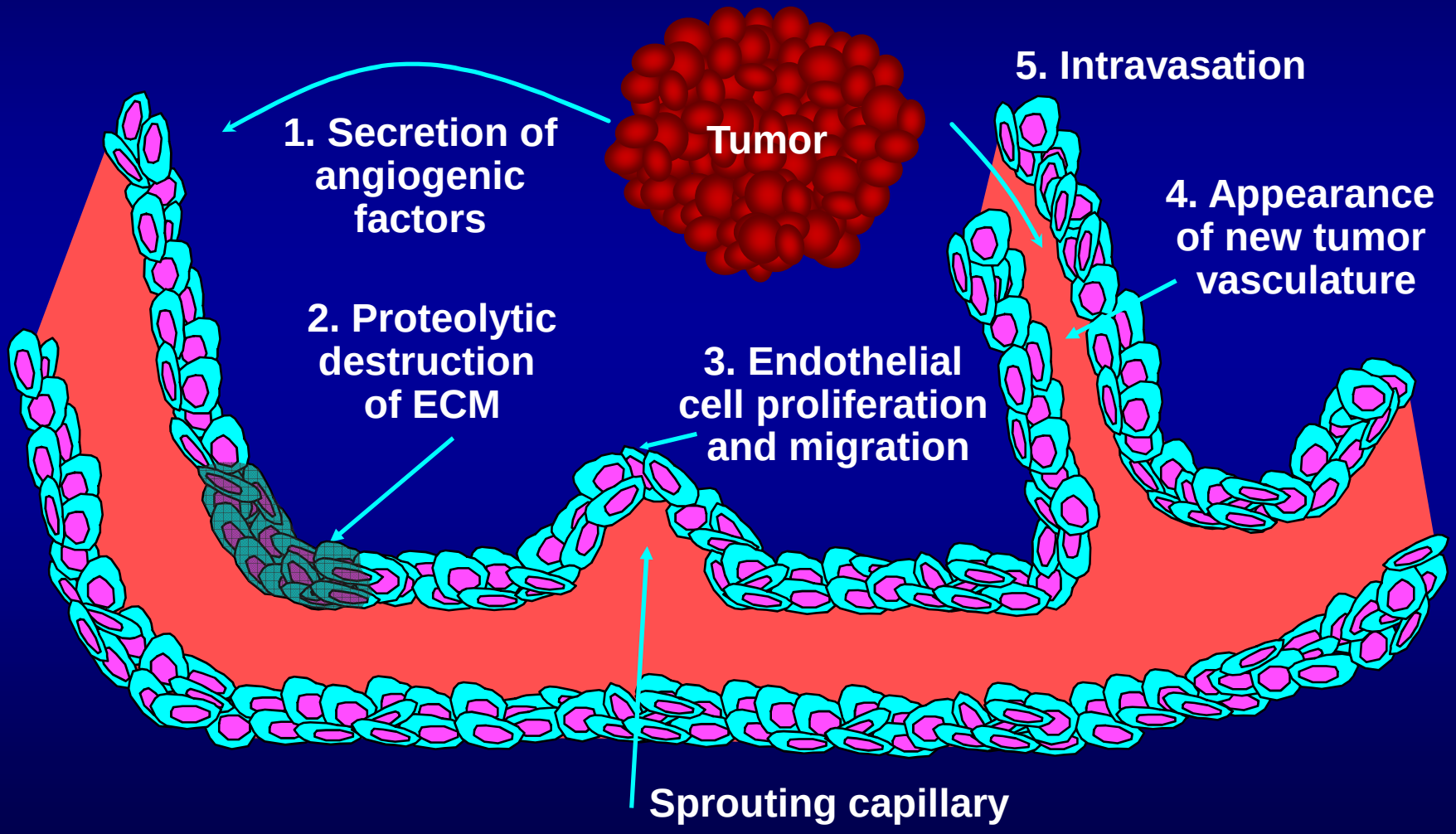

Angiogenesis
VEGF

Tumor Angiogenesis by Vascular Sprouting



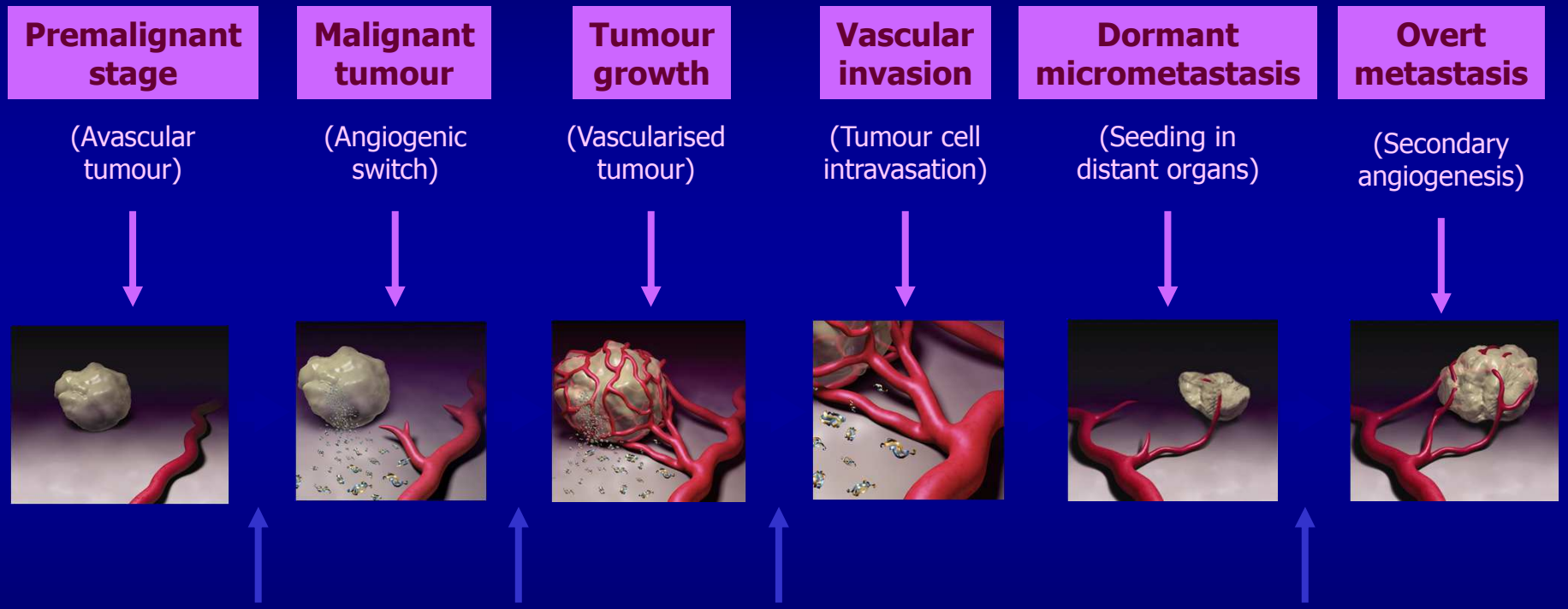
Veikkola T, et al. Semin Cancer Biol. 2001;20:1223-1231.

Tumor angiogenesis



ECM, extracellular matrix

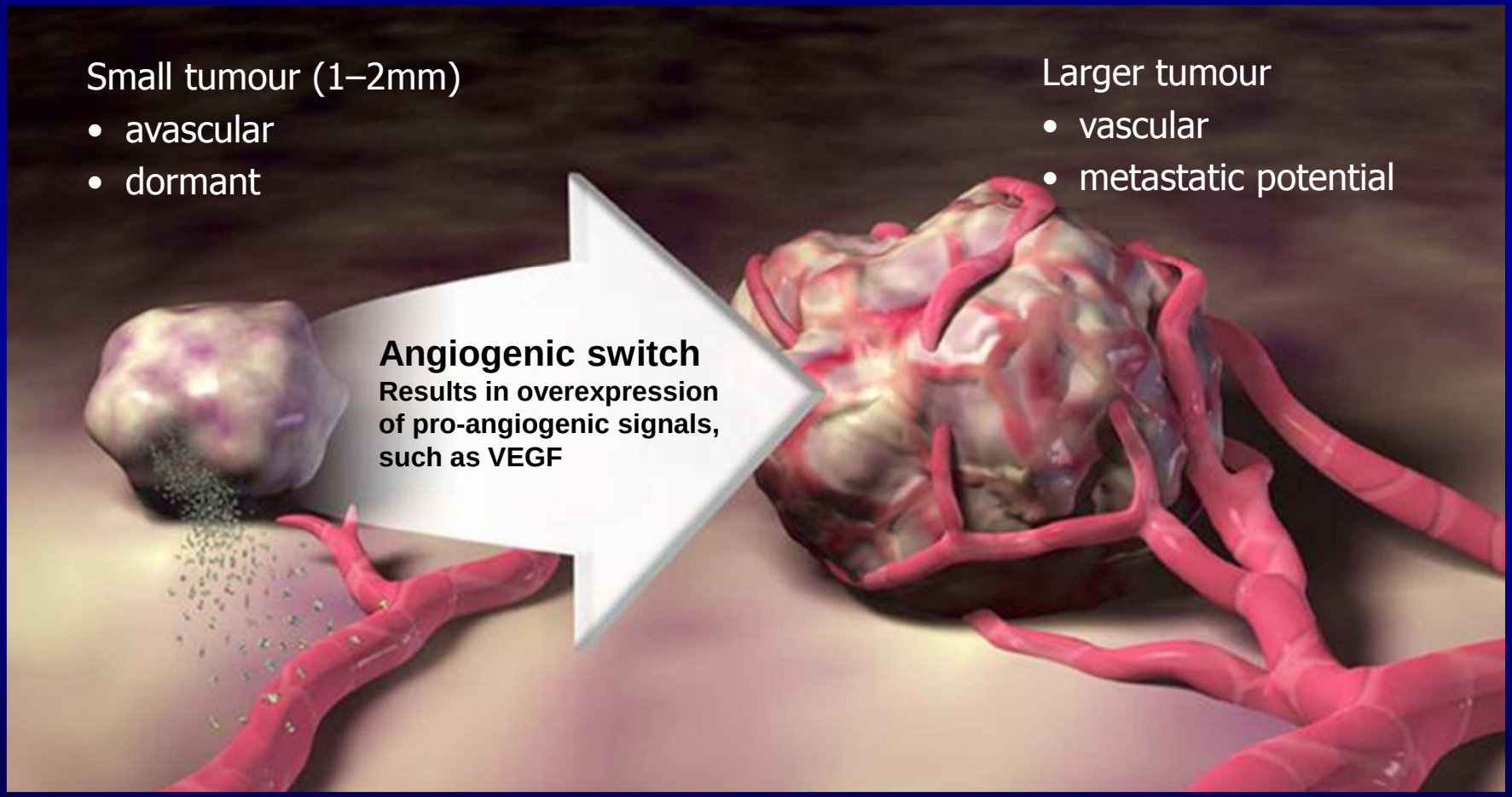
Angiogenesis is involved throughout tumour formation, growth & metastasis



Stages at which angiogenesis plays a role in tumour progression

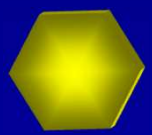
Adapted from Poon RT-P, et al. J Clin Oncol 2001;19:1207–25

The angiogenic switch in tumour development



Adapted from Bergers G, et al. Nat Rev Cancer 2002;3:401–10

VEGF: A Key Mediator of Angiogenesis



Environmental factors
(hypoxia, pH)

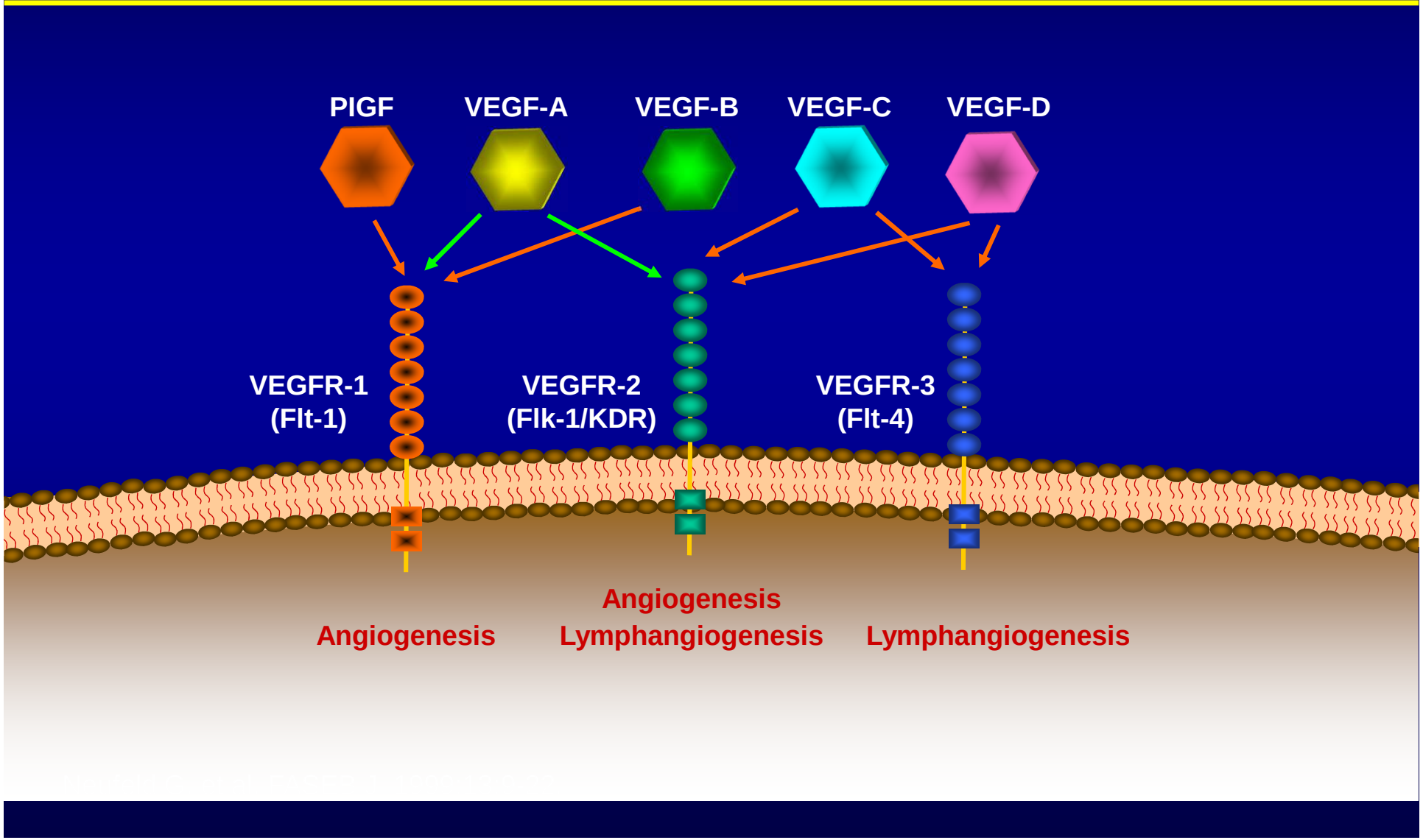
Growth factors, hormones
(EGF, bFGF, PDGF,
IGF-1, IL-1α, IL-6,
estrogen)

Genes implicated in
tumorigenesis
(*p53, p73, src, ras,*
vHL, bcr-abl)

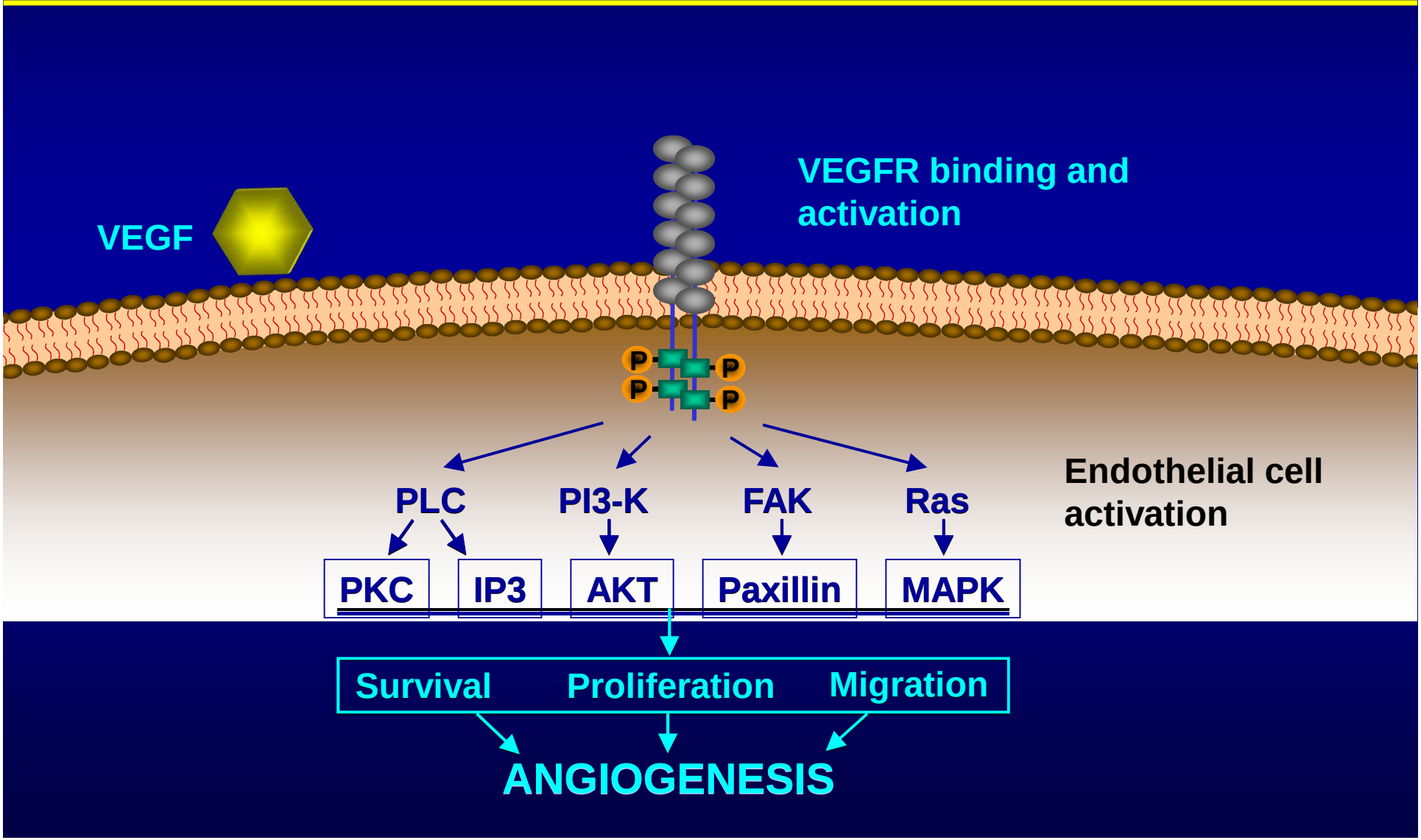
bFGF, basic fibroblast growth factors; EGF, epidermal growth factor; IGF, insulin-like growth factor; IL, interleukin; PDGF, platelet-derived growth factor; VEGFR, VEGF receptor.

1. Dvorak HF. *J Clin Oncol*. 2002;20:4368-4380; 2. Ebos JM, et al. *Mol Cancer Res*. 2002;1:89-95; 3. Ferrara N, et al. *Nat Med.* 2003;9:669-676.

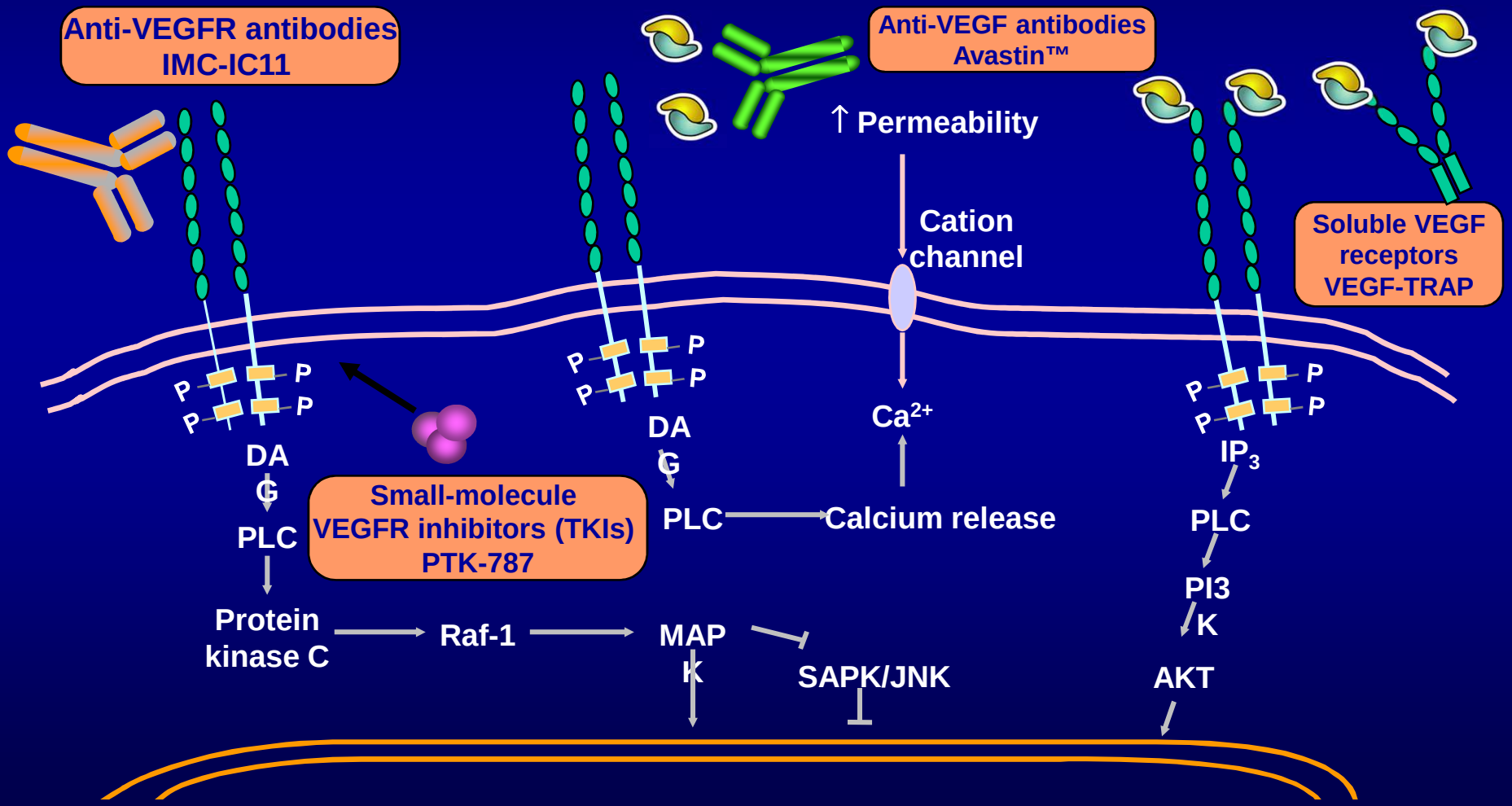
The VEGF Family and Its Receptors

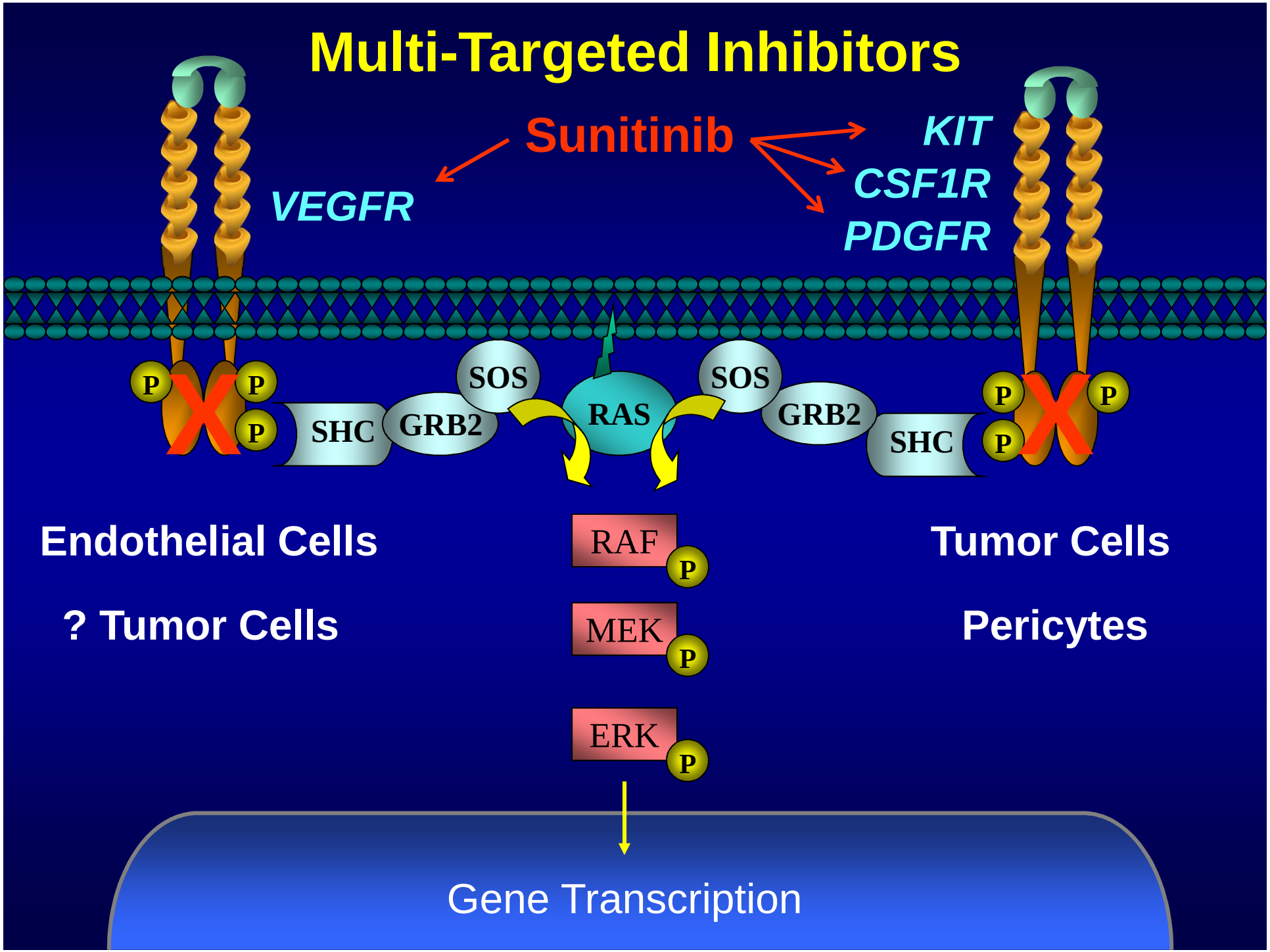


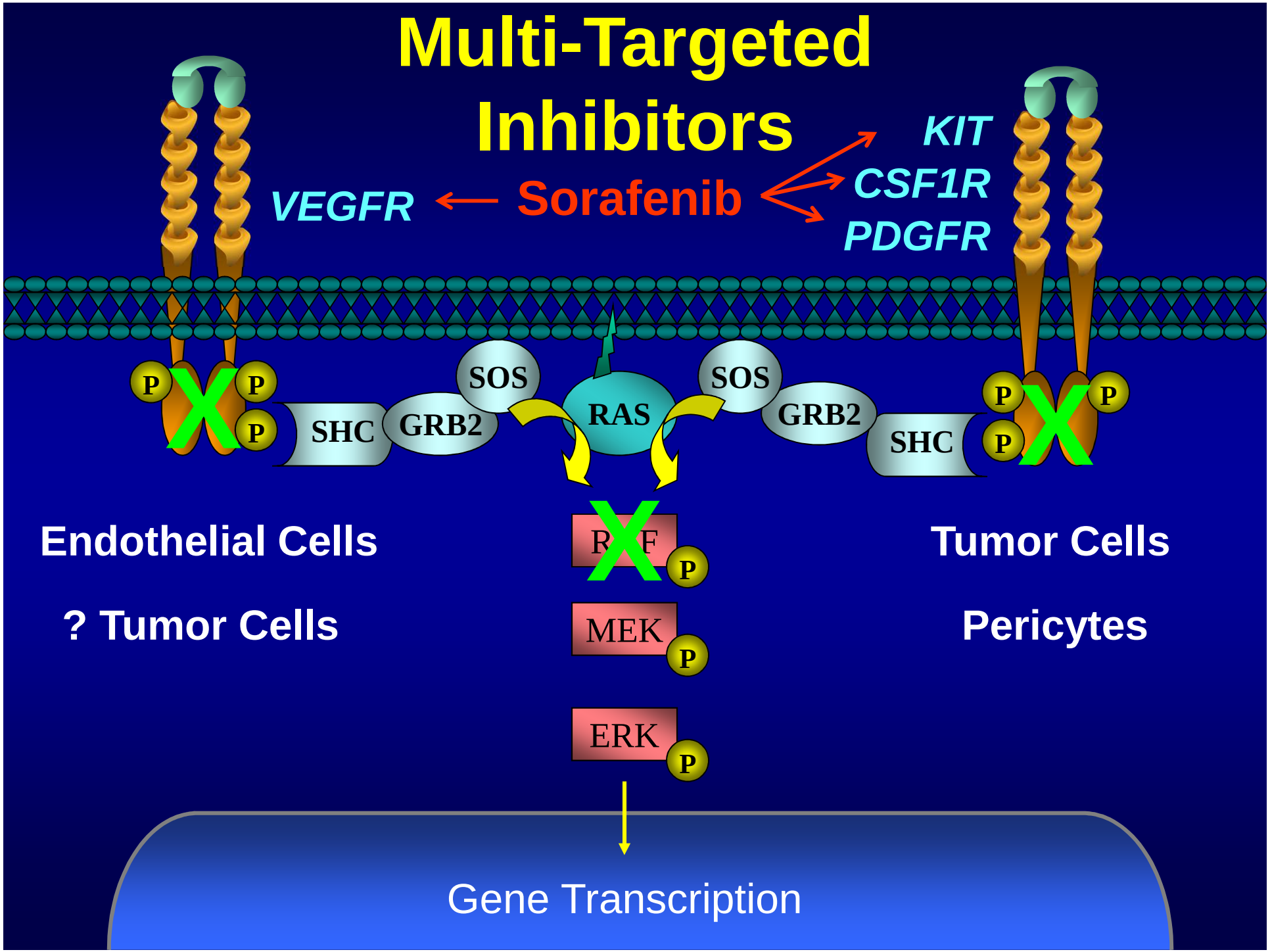
VEGF: A Key Mediator of Angiogenesis



Agents targeting the VEGF pathway




Multi-Targeted Inhibitors
Sunitinib
VEGFR
KIT
CSF1R
PDGFR
P
P
P
P
SHC
GRB2
SOS
RAS
SOS
GRB2
SHC
P
P
P
P
Endothelial Cells
? Tumor Cells
Tumor Cells
Pericytes
RAF
P
MEK
P
ERK
P
Gene Transcription


Multi-Targeted Inhibitors
VEGFR
Sorafenib
KIT
CSF1R
PDGFR
P
P
P
P
SHC
GRB2
SOS
RAS
SOS
GRB2
SHC
P
P
P
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RAF
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MEK
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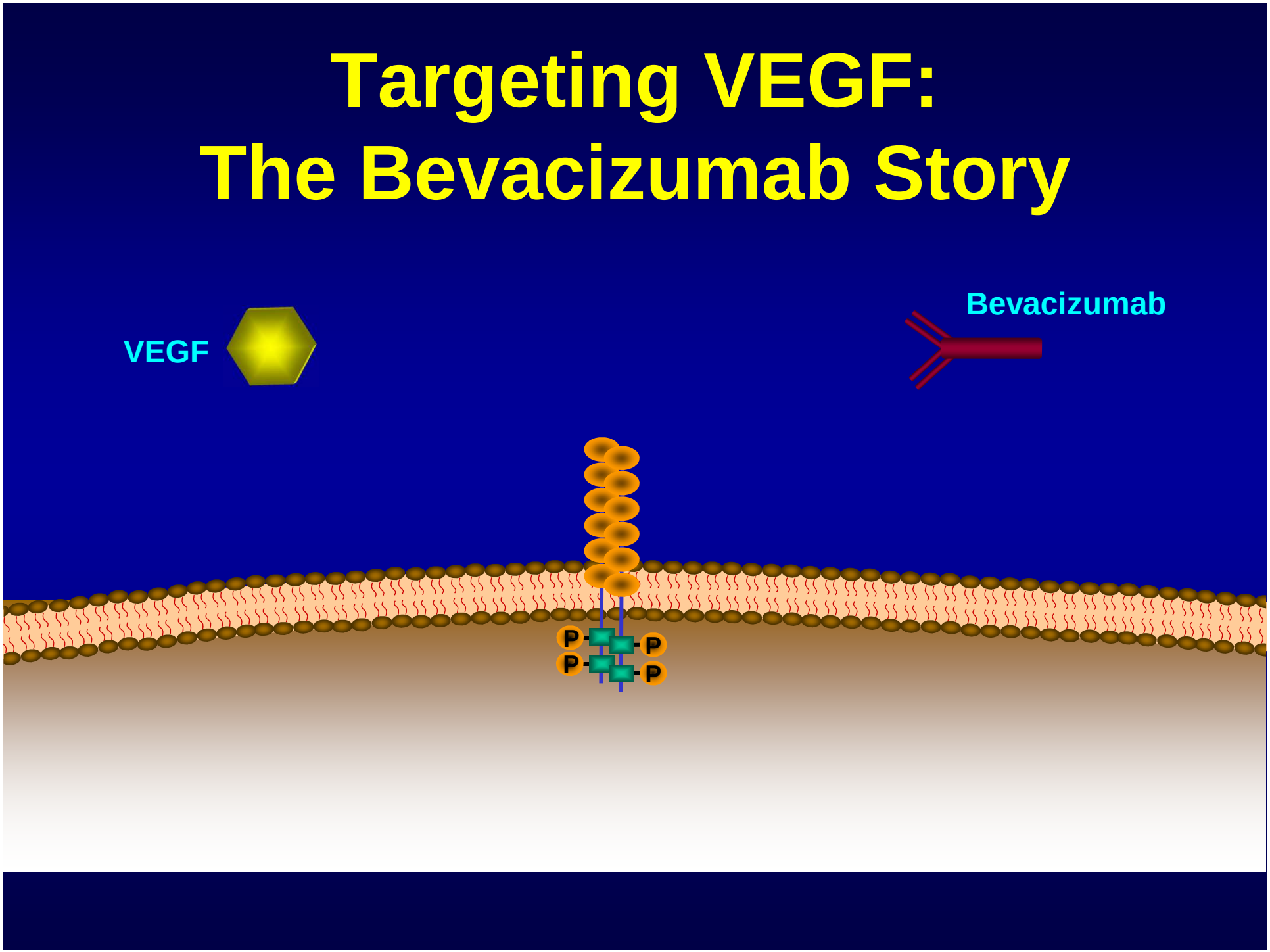
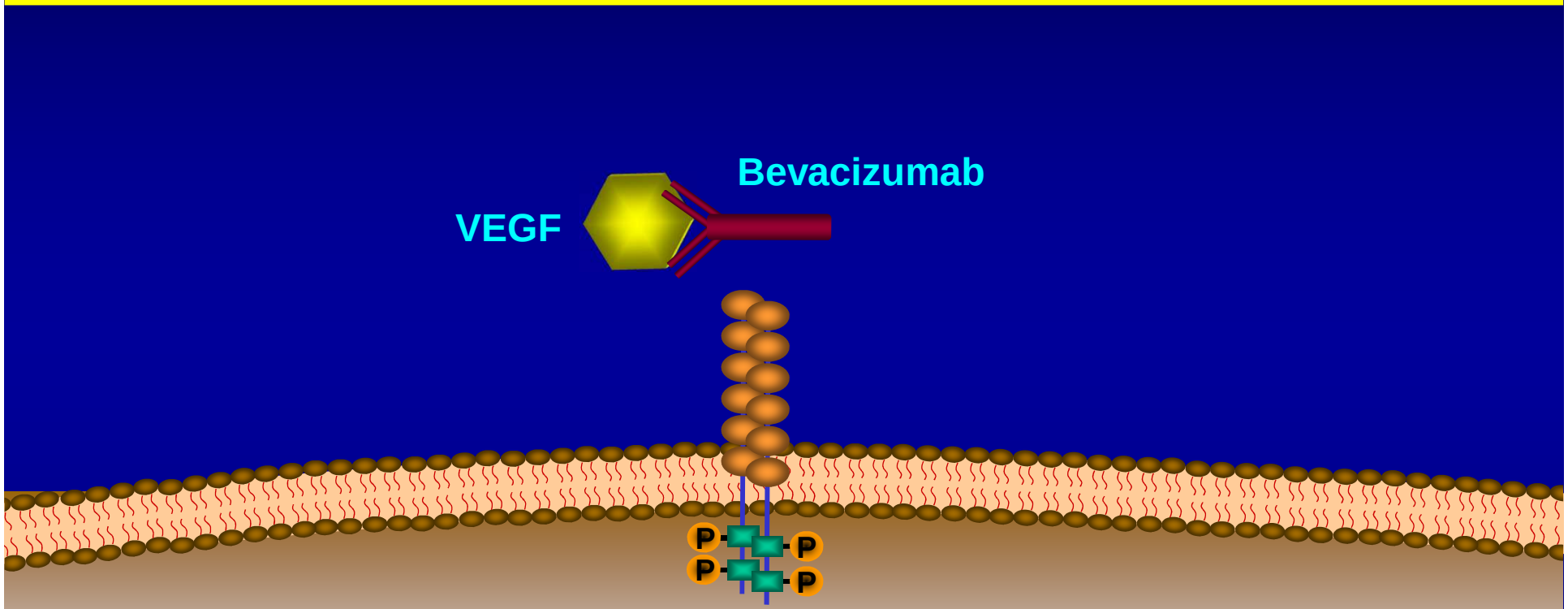
ERK
P
Endothelial Cells
? Tumor Cells
Tumor Cells
Pericytes
Gene Transcription

Targeting VEGF: The Bevacizumab Story



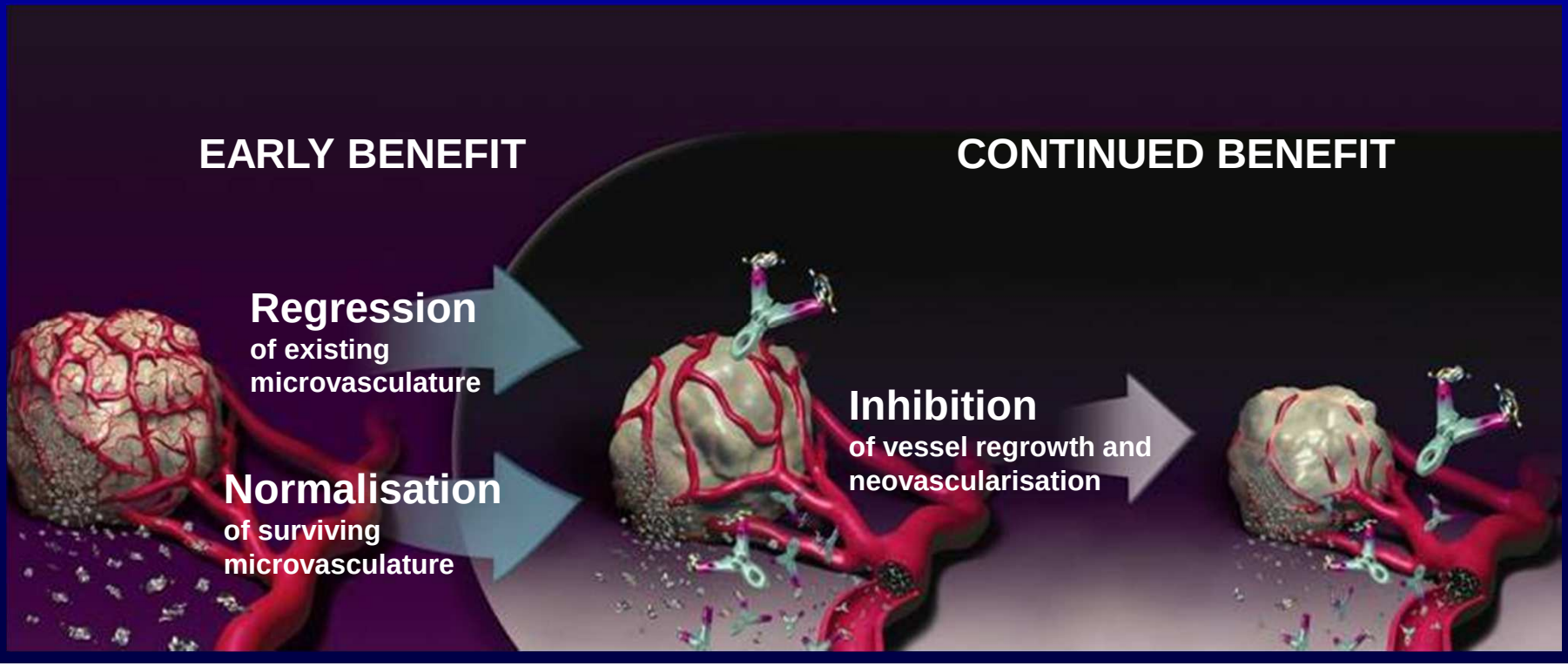
Targeting VEGF: The Bevacizumab Story



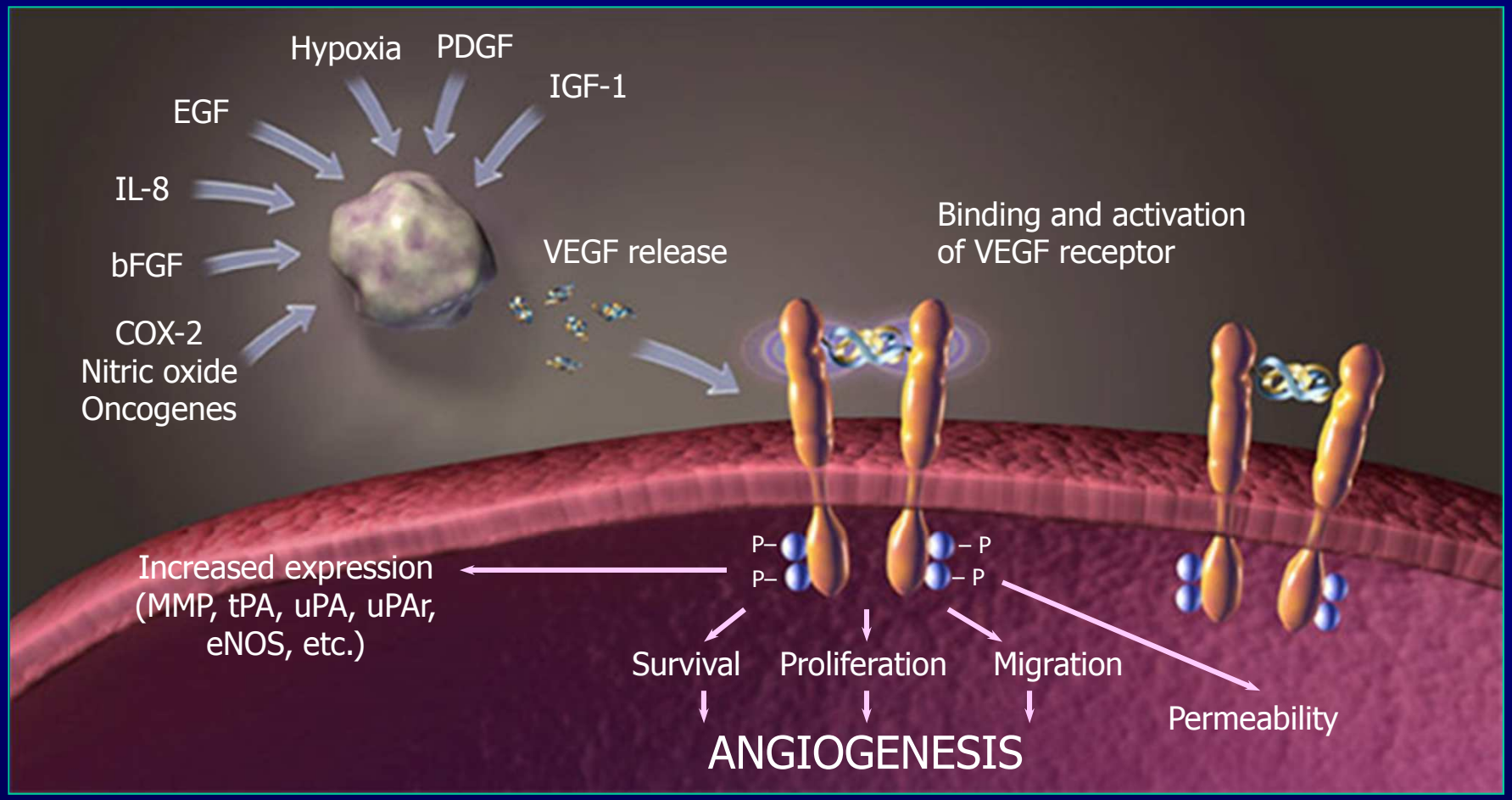
VEGF Activation BLOCKED

Bevacizumab - MOA

- Regression of existing microvasculature
- Normalisation of existing vasculature
- Inhibition of tumour vessel growth

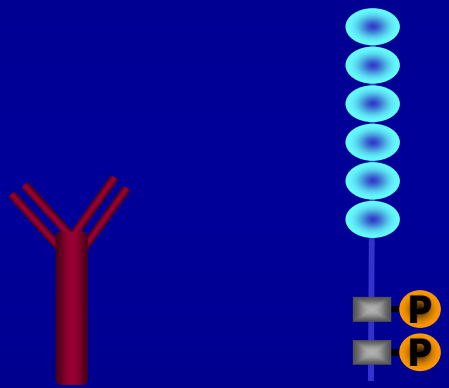


Tumour characteristics and environment promote VEGF expression

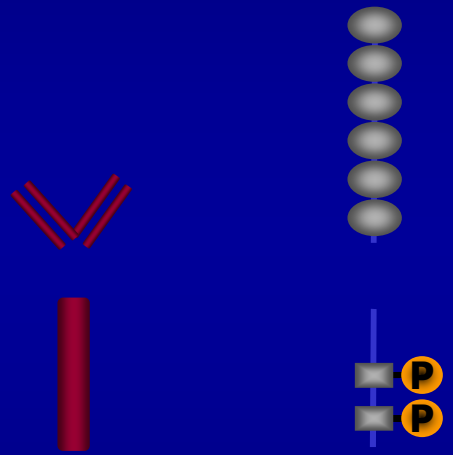


IGF = insulin-like growth factor; PDGF = platelet-derived growth factor

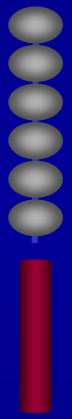
VEGF Trap



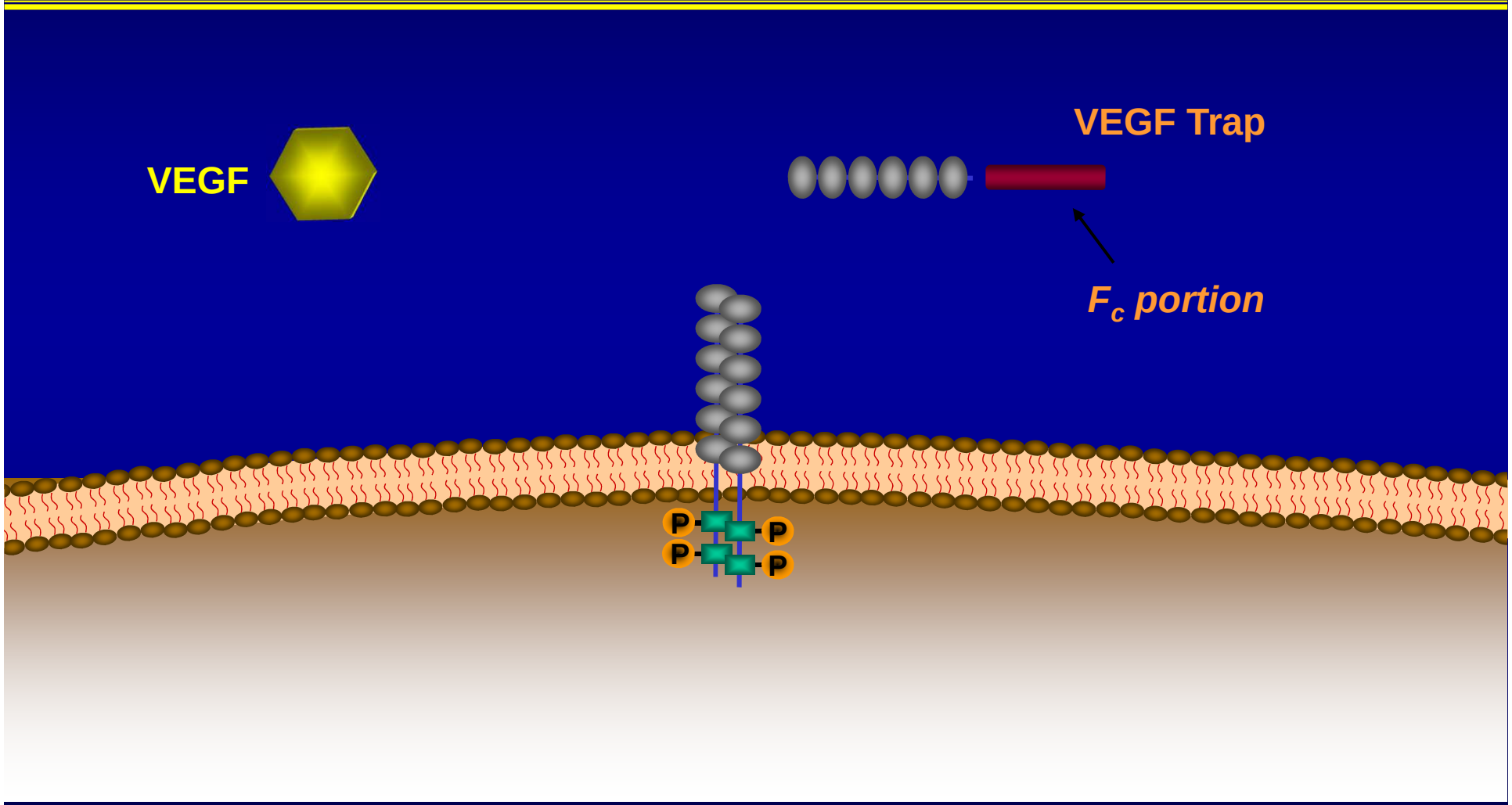
VEGF Trap



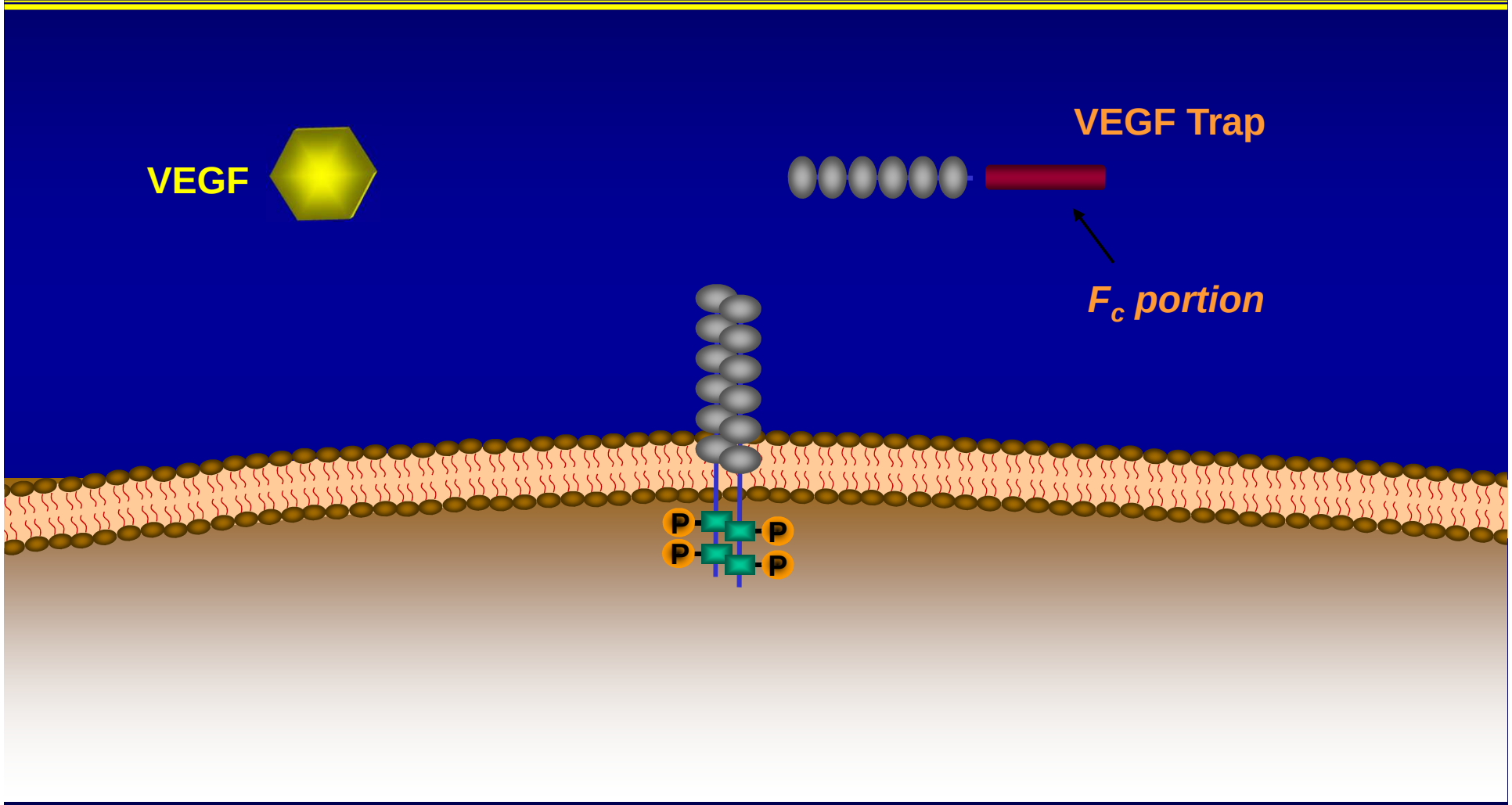
VEGF Trap



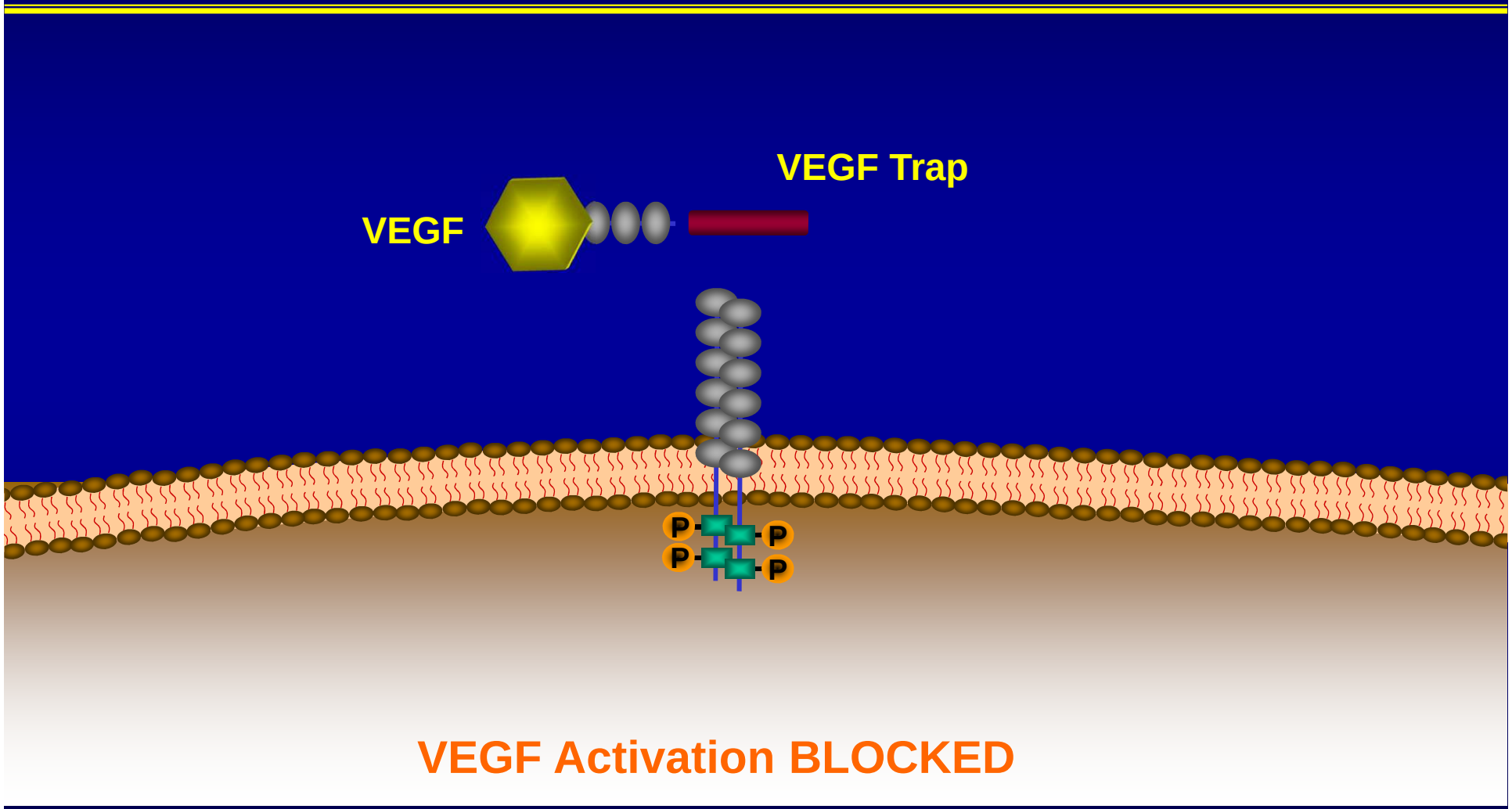
VEGF Trap



VEGF Trap

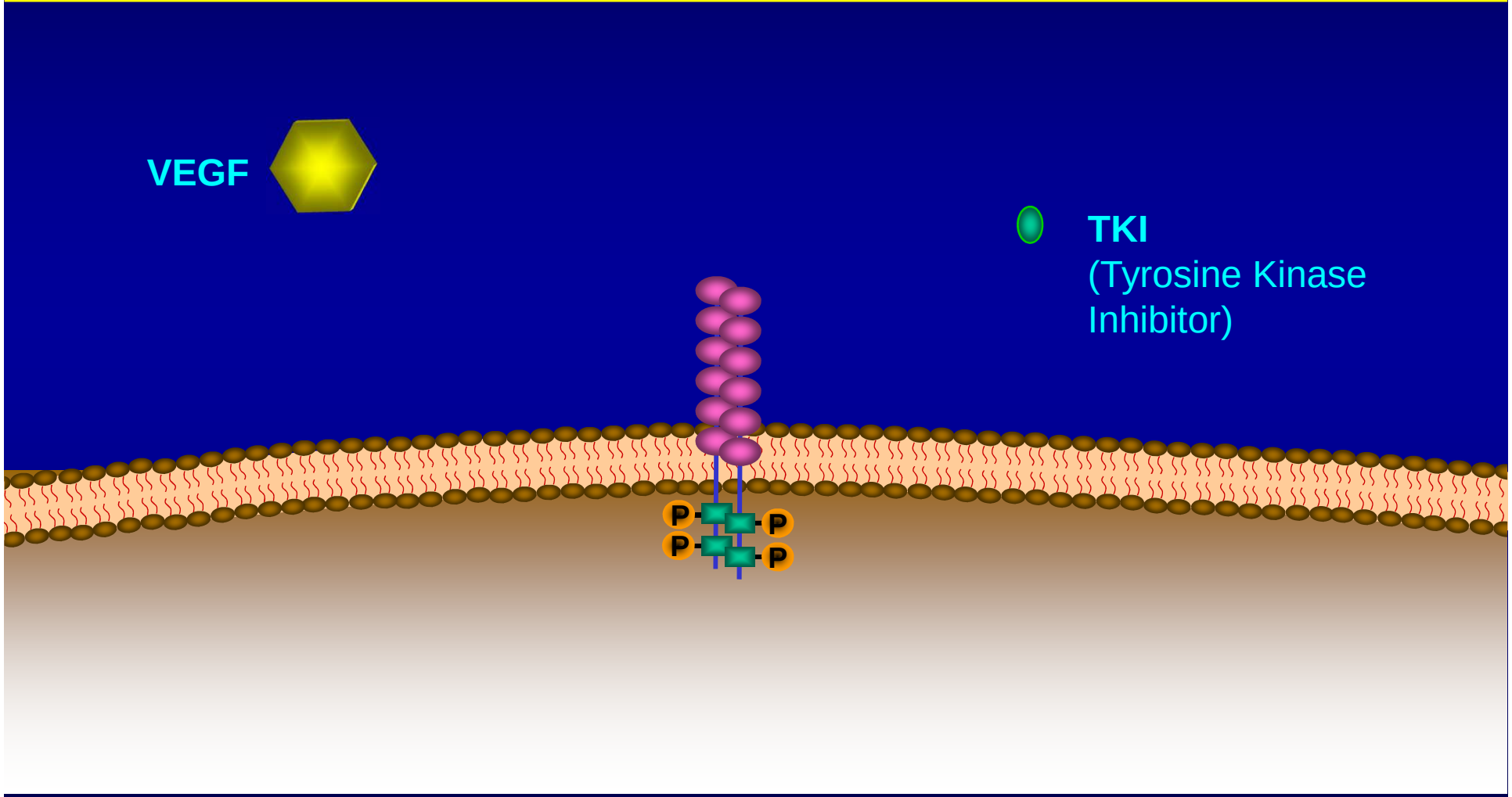


VEGF Trap

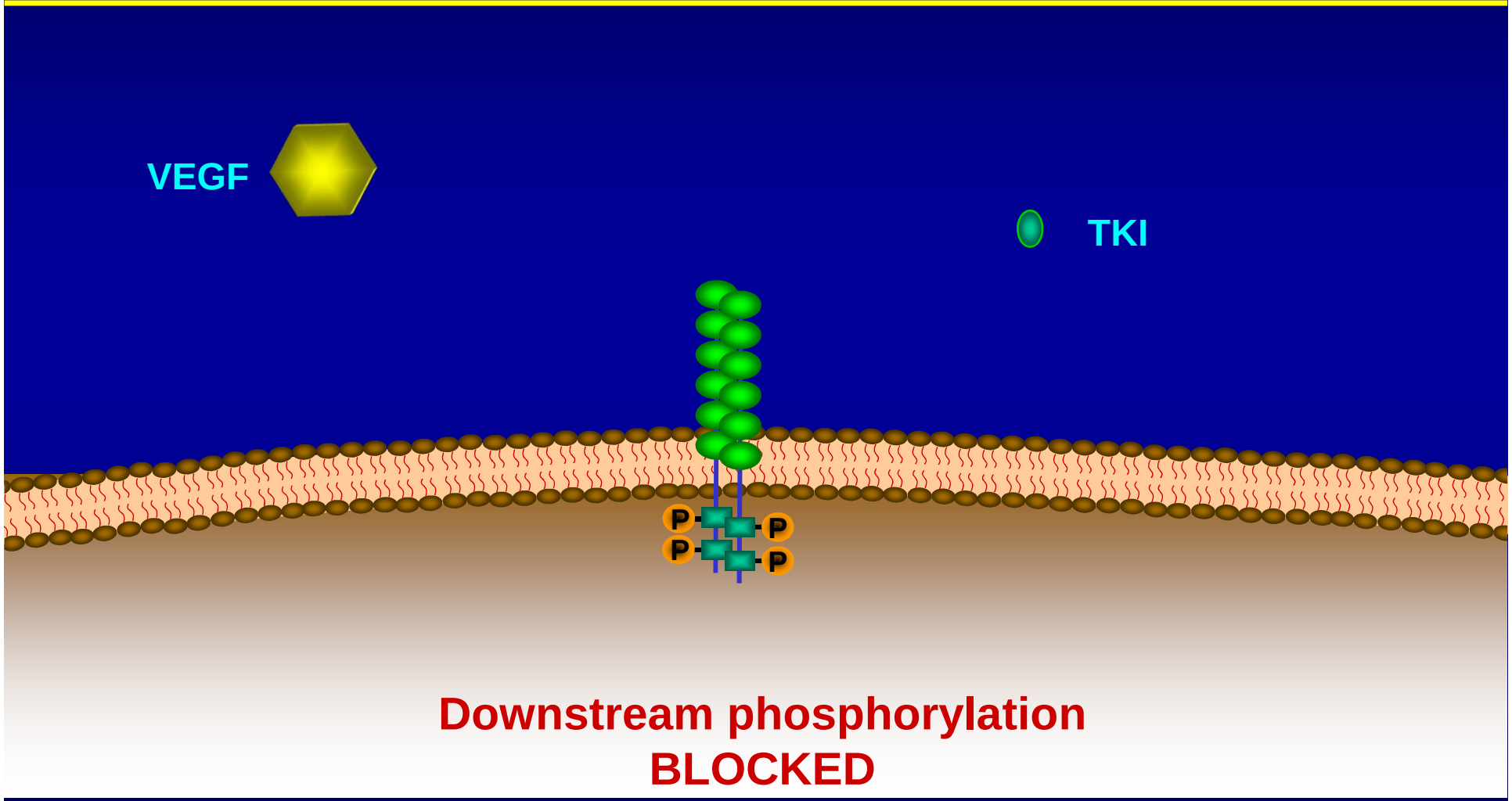


VEGF Activation BLOCKED

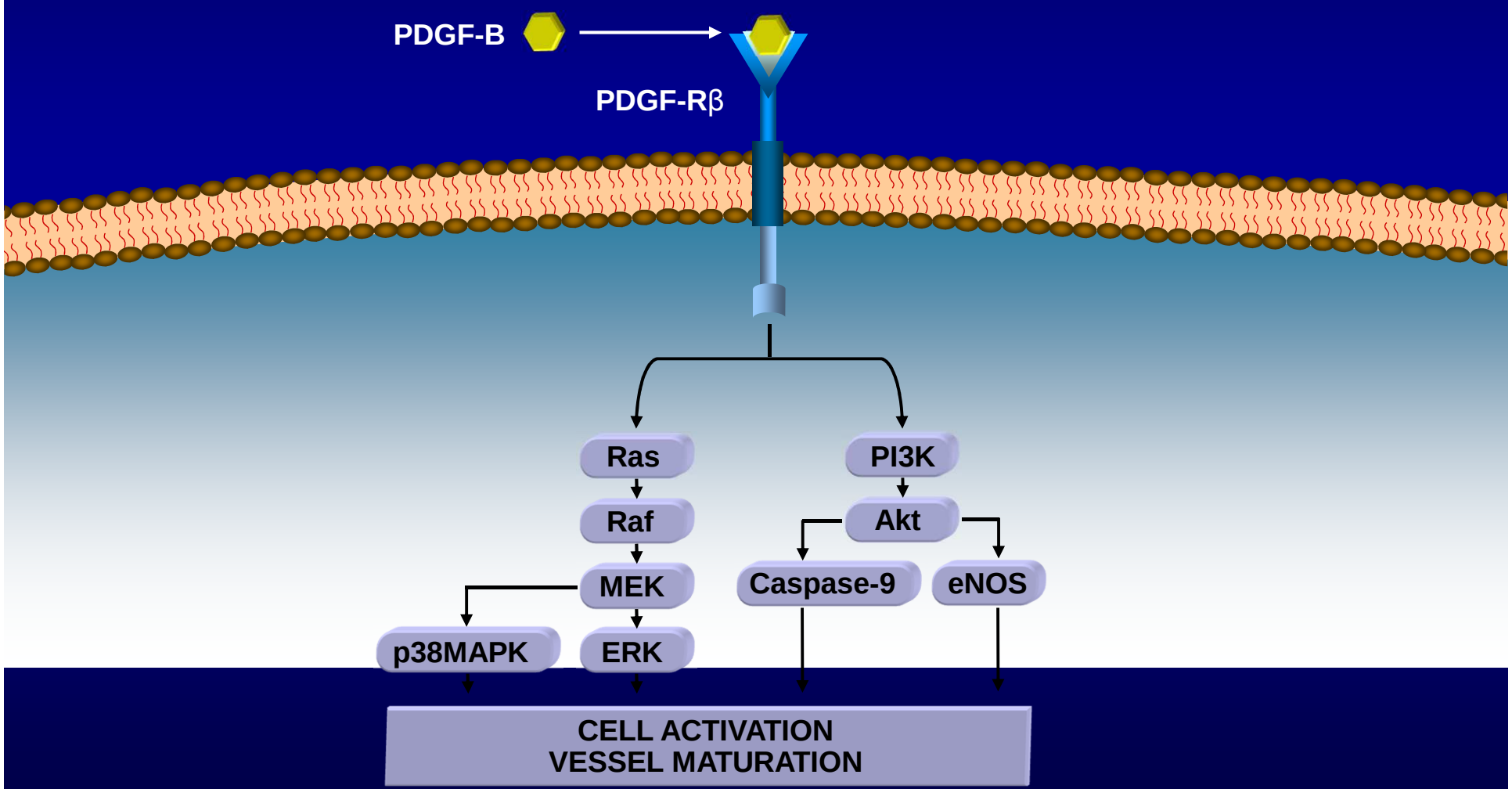
Tyrosine Kinase Inhibition and VEGF

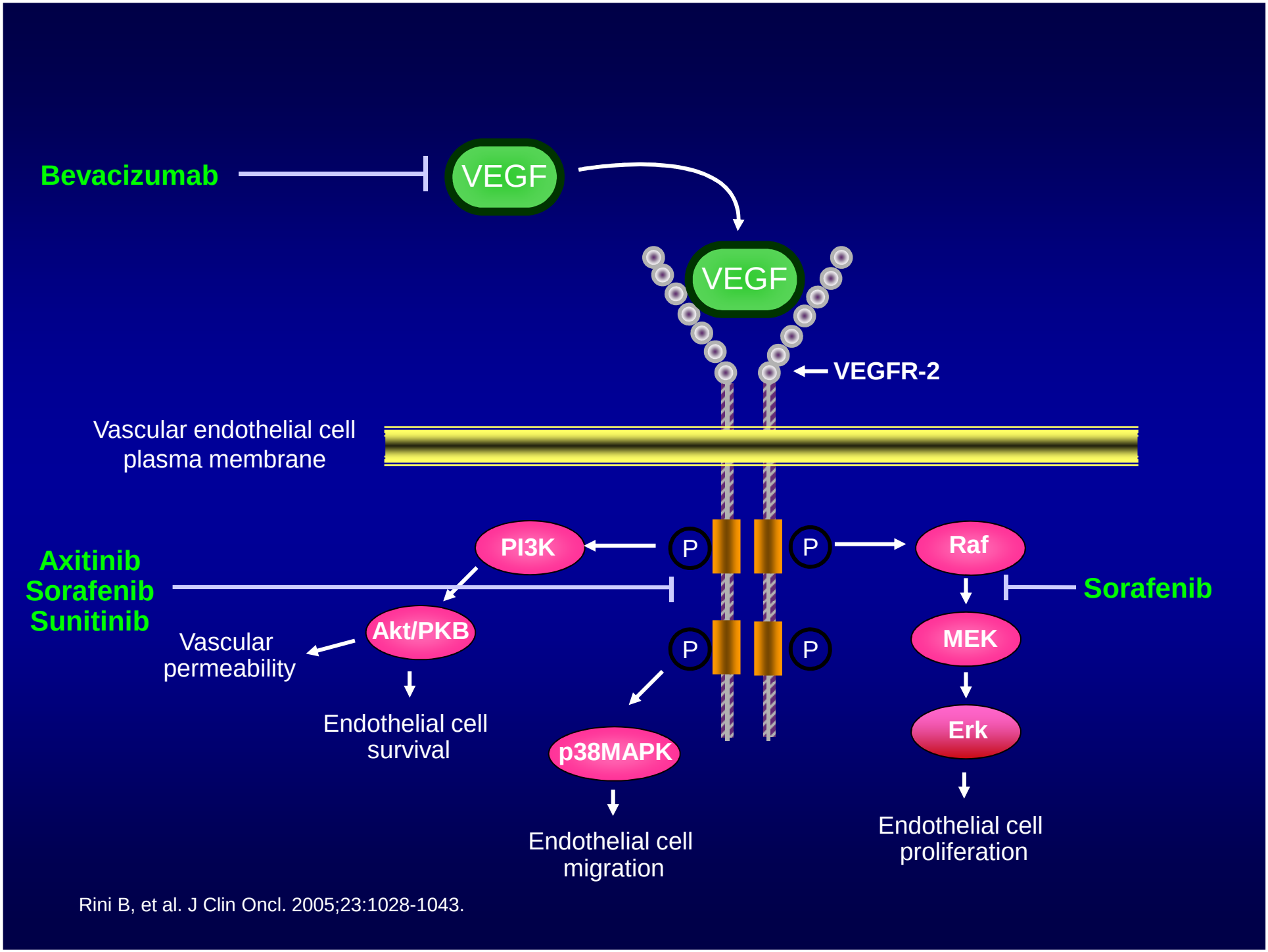


Tyrosine Kinase Inhibition and VEGF



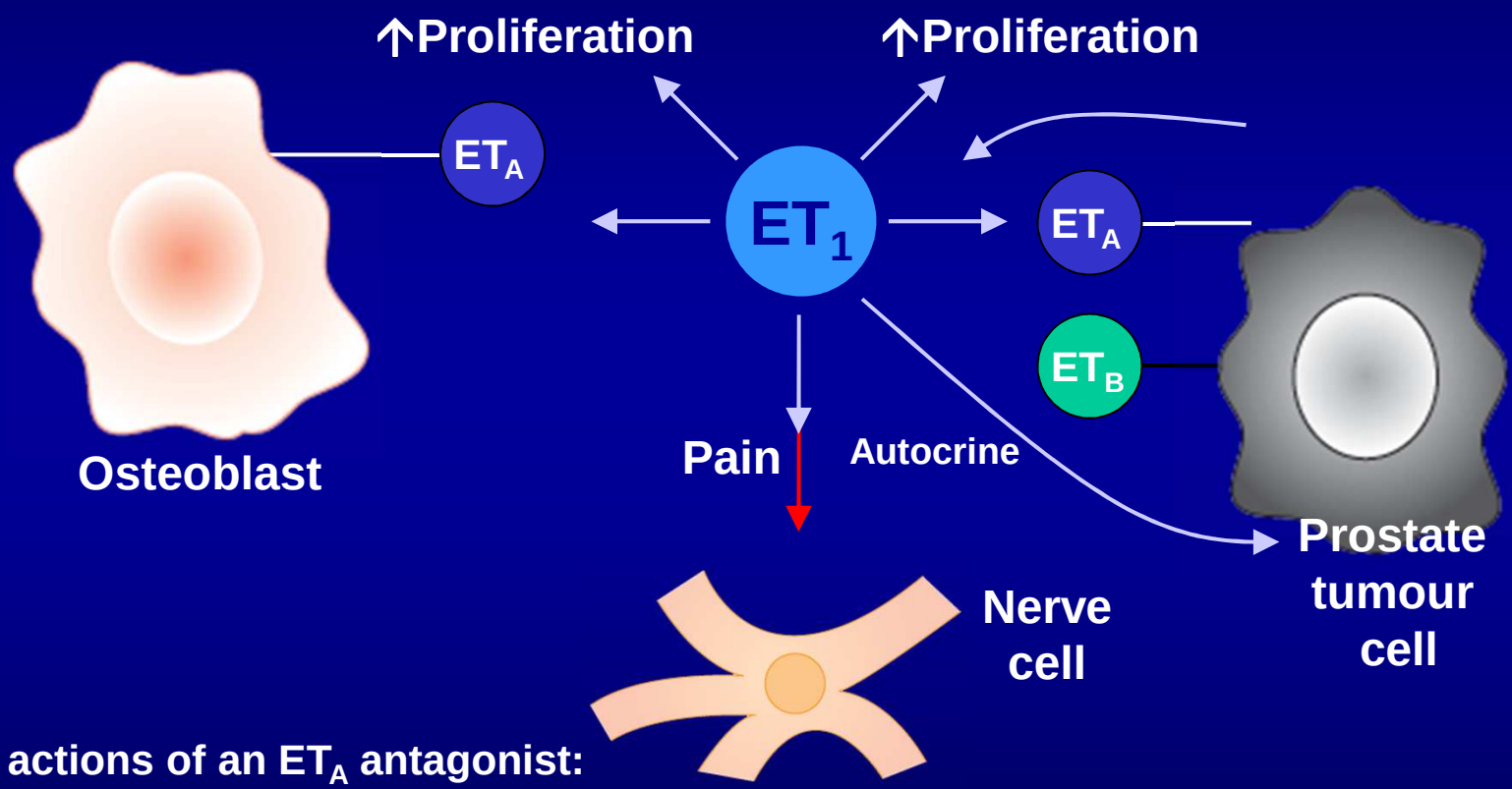
Pericyte


PDGF-B
PDGF-Rβ
Ras
Raf
MEK
ERK
p38MAPK
PI3K
Akt
Caspase-9
eNOS
CELL ACTIVATION
VESSEL MATURATION



Rini B, et al. J Clin Oncl. 2005;23:1028-1043.

A Specific Endothelin-A Receptor Antagonist

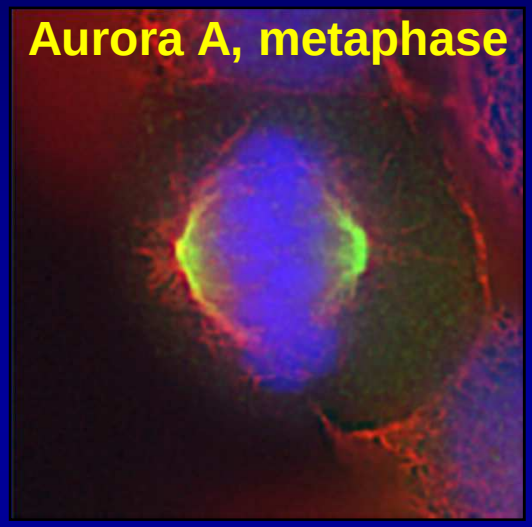


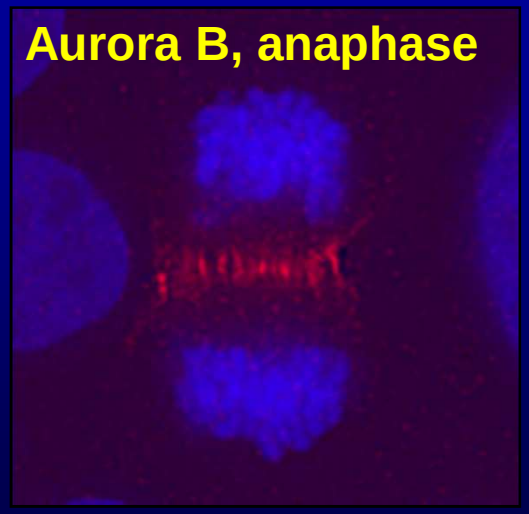
Potential actions of an ET_A antagonist:

- Inhibition of prostate tumour cell proliferation
- Promotion of tumour cell apoptosis
- Inhibition of osteoblast proliferation
- Reduction in pain

ZD4054 is in clinical development

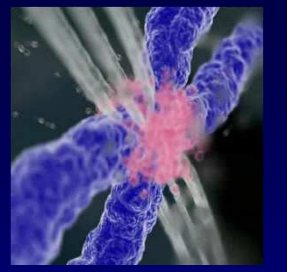
Role of Aurora kinases in mitosis and cell division





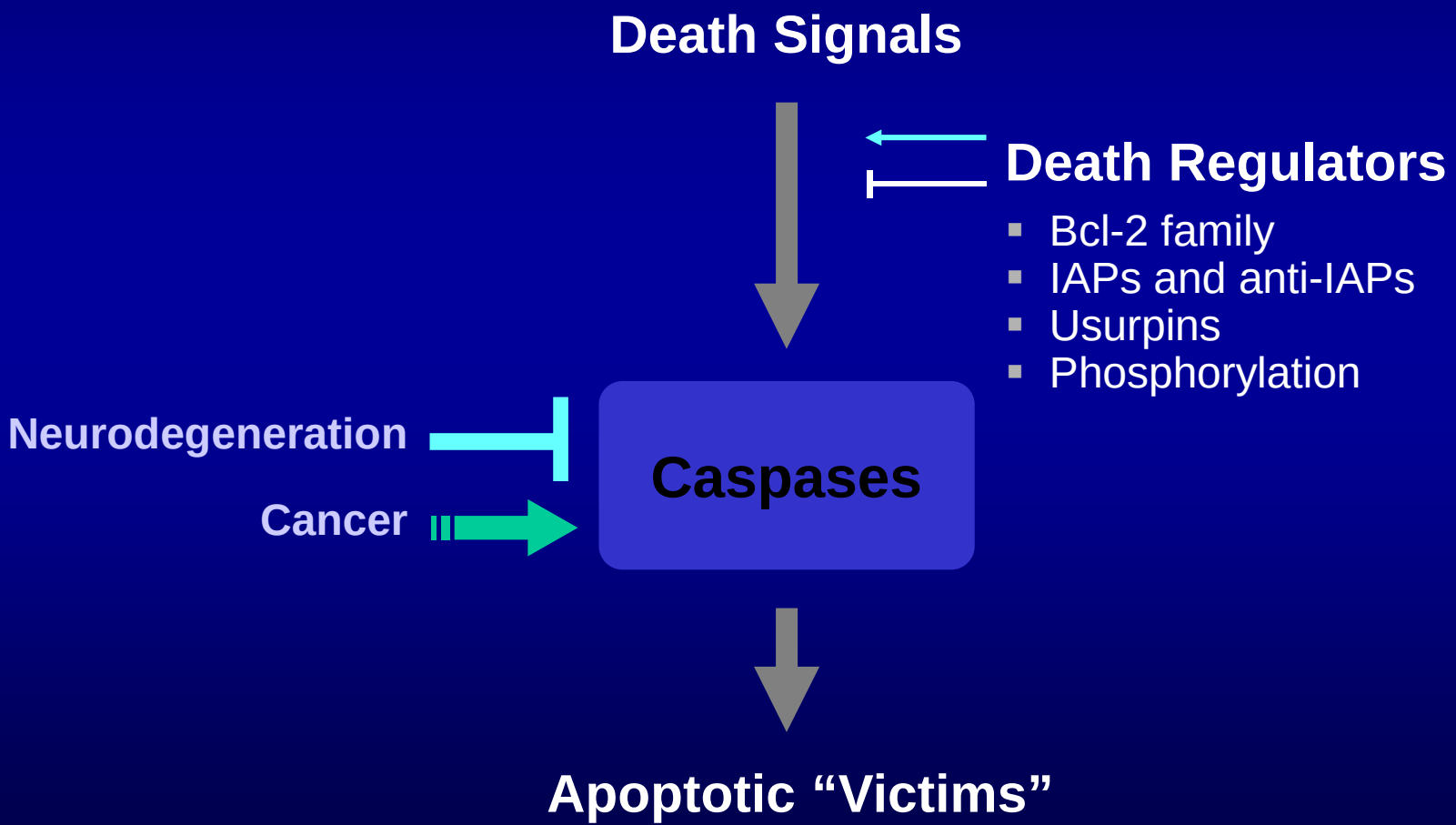
- Aurora A
  - localized at the spindle poles
  - role in spindle assembly
- Aurora B
  - initially localized at the centromeres
  - role in chromatid alignment and segregation, and in cytokinesis
  - moves to the midzone during cytokinesis

Aurora kinase inhibition: A new anticancer approach

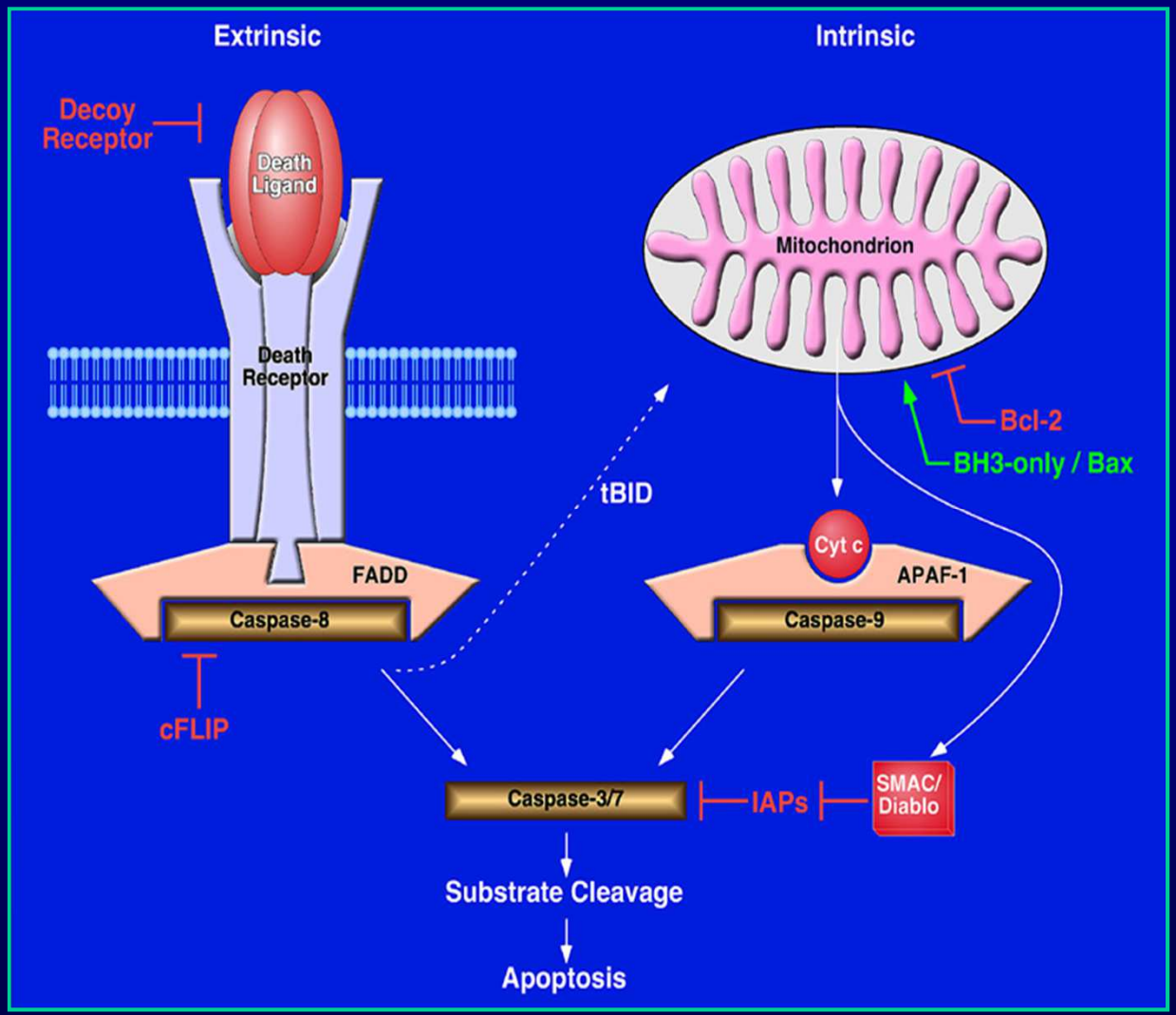


- Aurora A and B are overexpressed in cancer
- Aurora A is oncogenic when overexpressed
- Selectively inhibiting Aurora kinase activity leads to chromosome segregation errors and deregulation of the spindle checkpoint
  - mitosis occurs in a highly disordered manner
  - cytokinesis fails
  - proliferating tumor cells apoptose

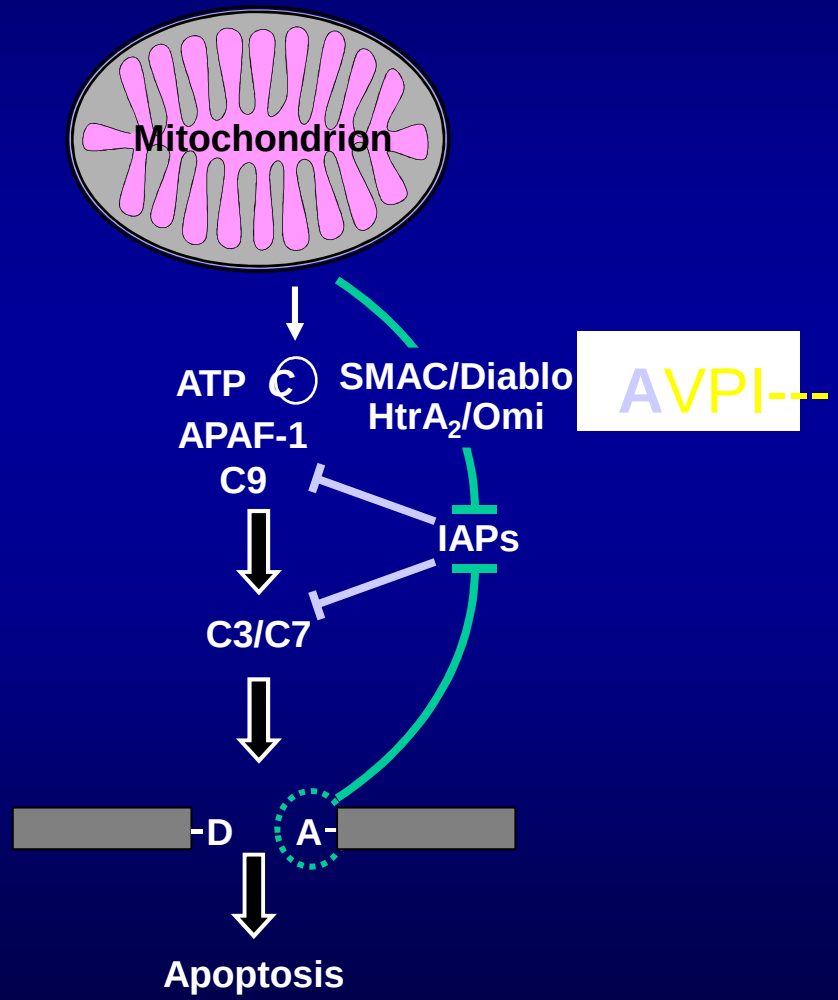
Core Components of the Apoptotic Pathway

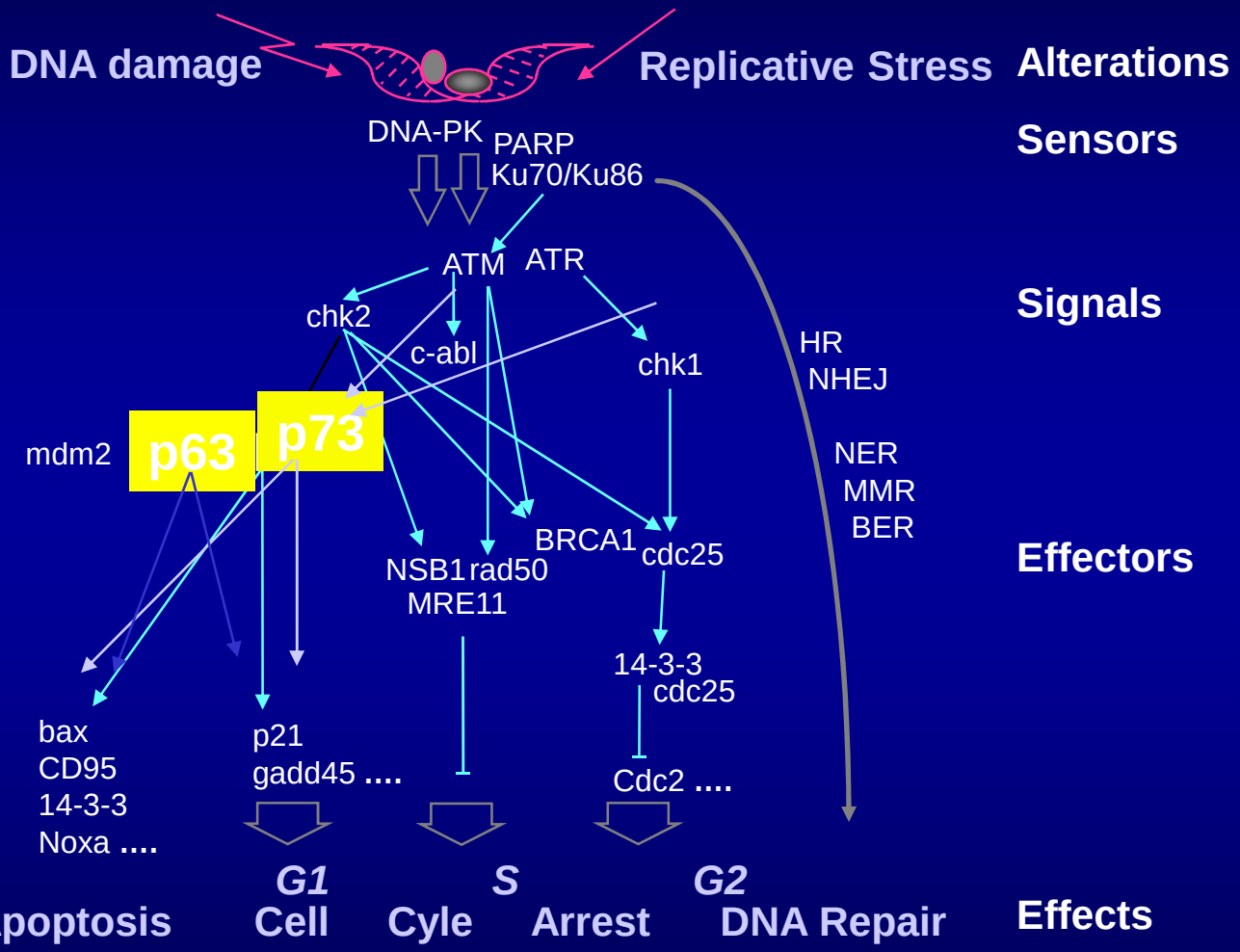


Extrinsic and Intrinsic Cell Death Pathways



IAP Antagonism During Apoptosis





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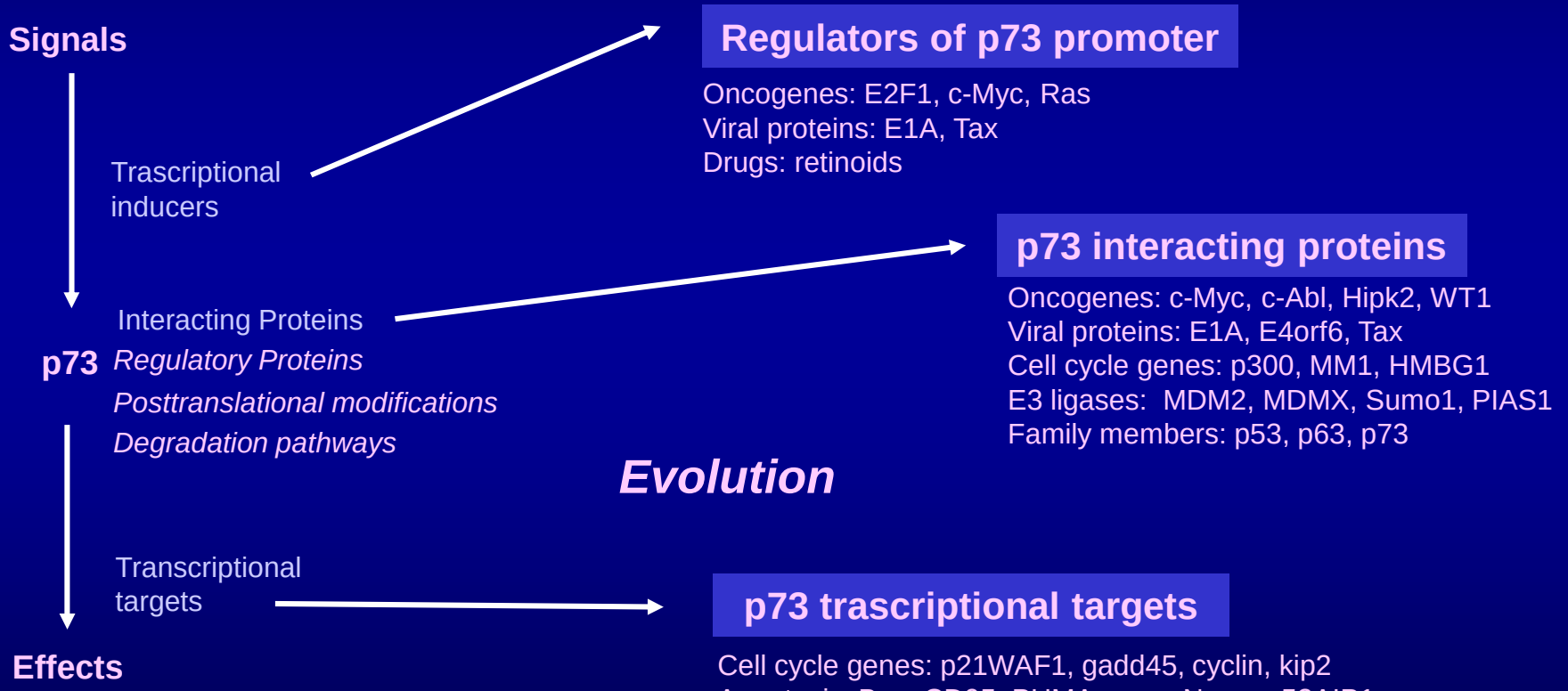
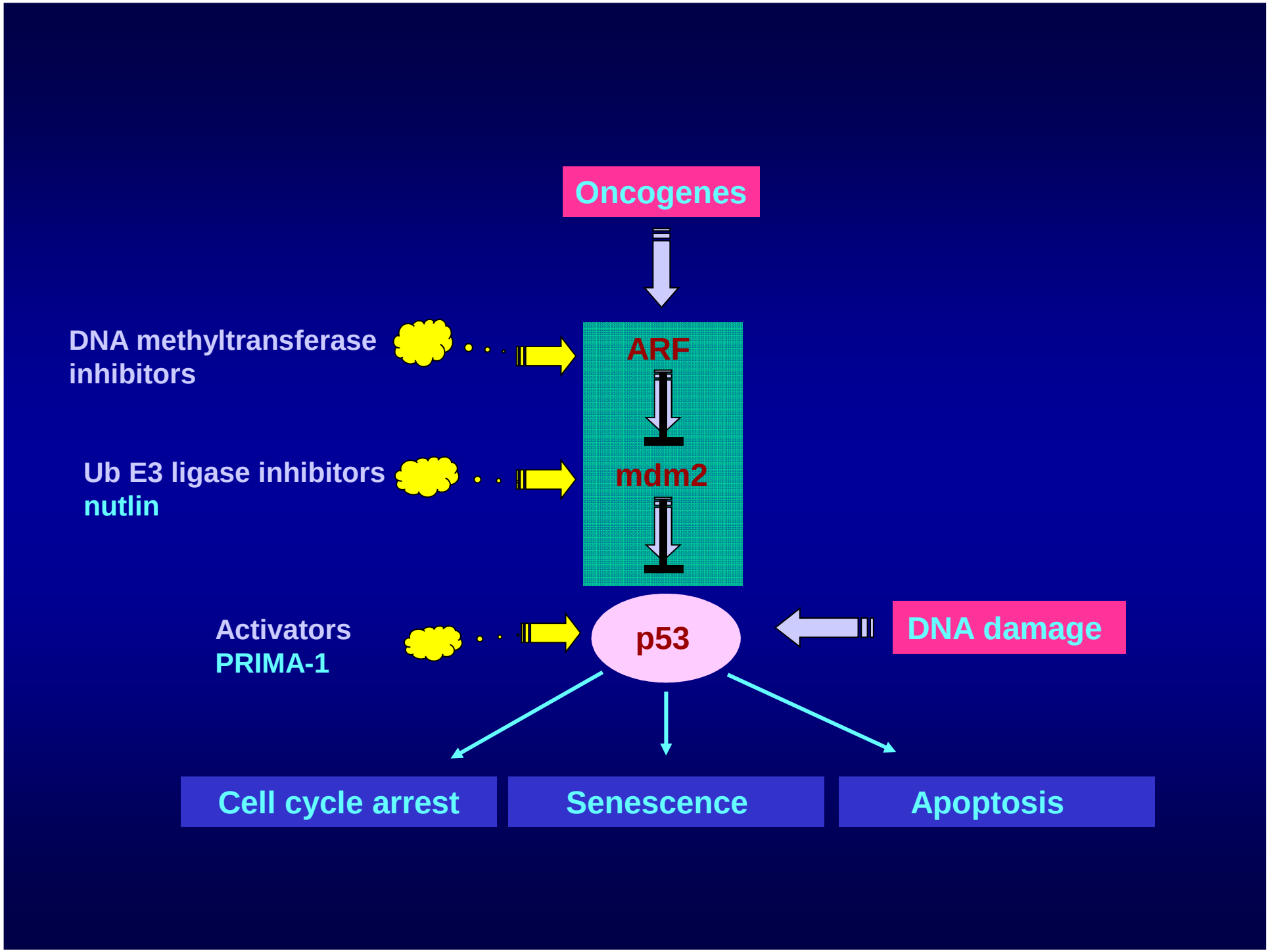
Gressner et al. EMBO J. 2005;24:2458.

Mueller et al. Cell Death Differ. 2005;12:1564.
Flinterman et al. J Biol Chem. 2005;280:5945.
Vigano et al. EMBO J. 2006;25:5105.
Rossi et al. PNAS. 2006;103:12753

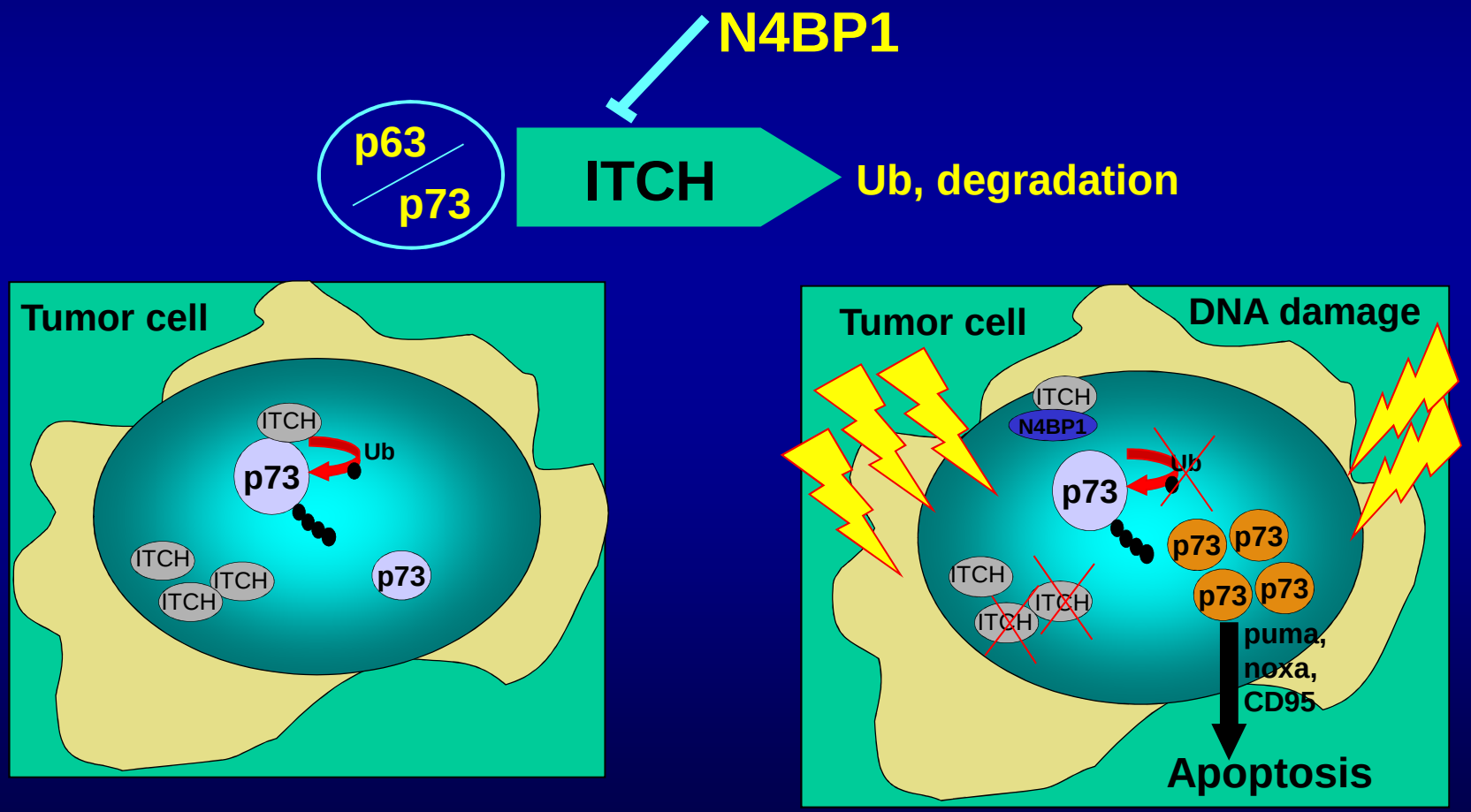
Sayan et al. J Biol Chem. 2006;281:13566.

p73 Promoter, Proteins, and Translational Targets




Oncogenes
DNA methyltransferase inhibitors
ARF
Ub E3 ligase inhibitors
nutlin
mdm2
Activators
PRIMA-1
p53
DNA damage
Cell cycle arrest
Senescence
Apoptosis

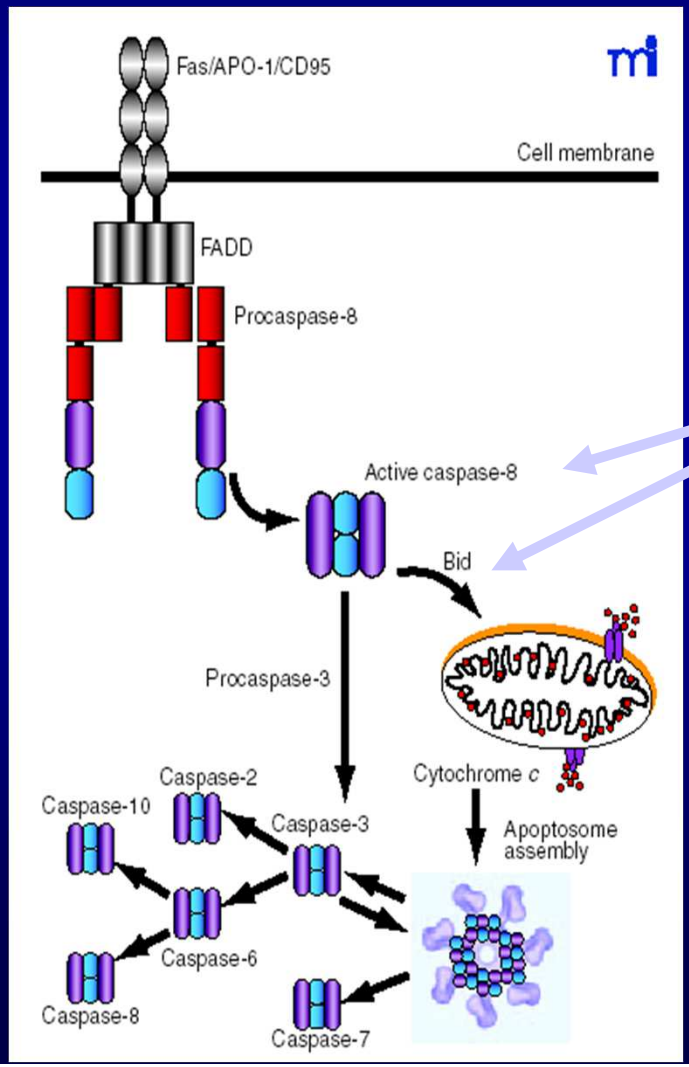
A Model for ITCH-Mediated Regulation of p73 Function



Caspase Activation Cascades

(1) Extrinsic

Death receptors



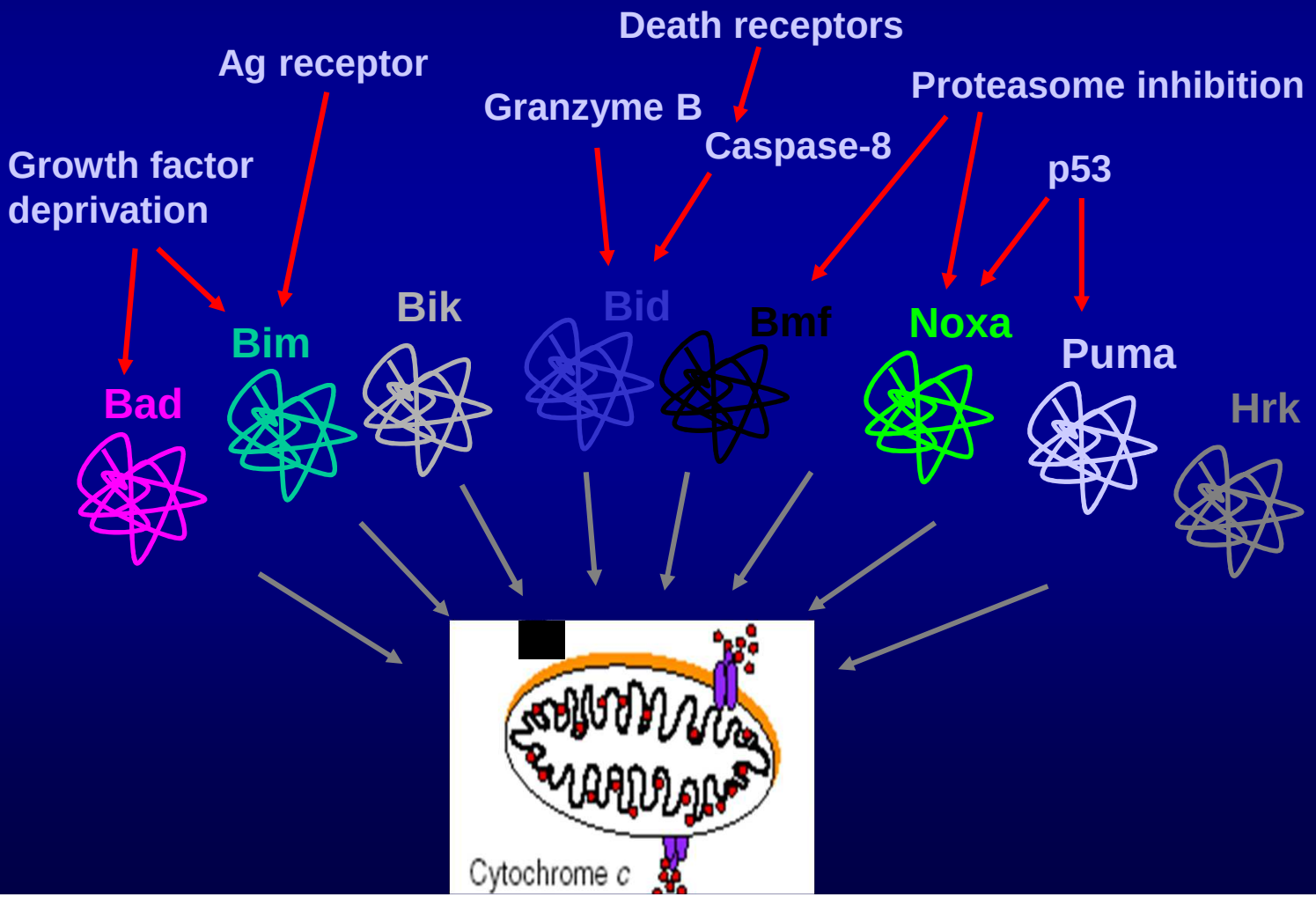
(3) Granzyme B

CTL/NK cells

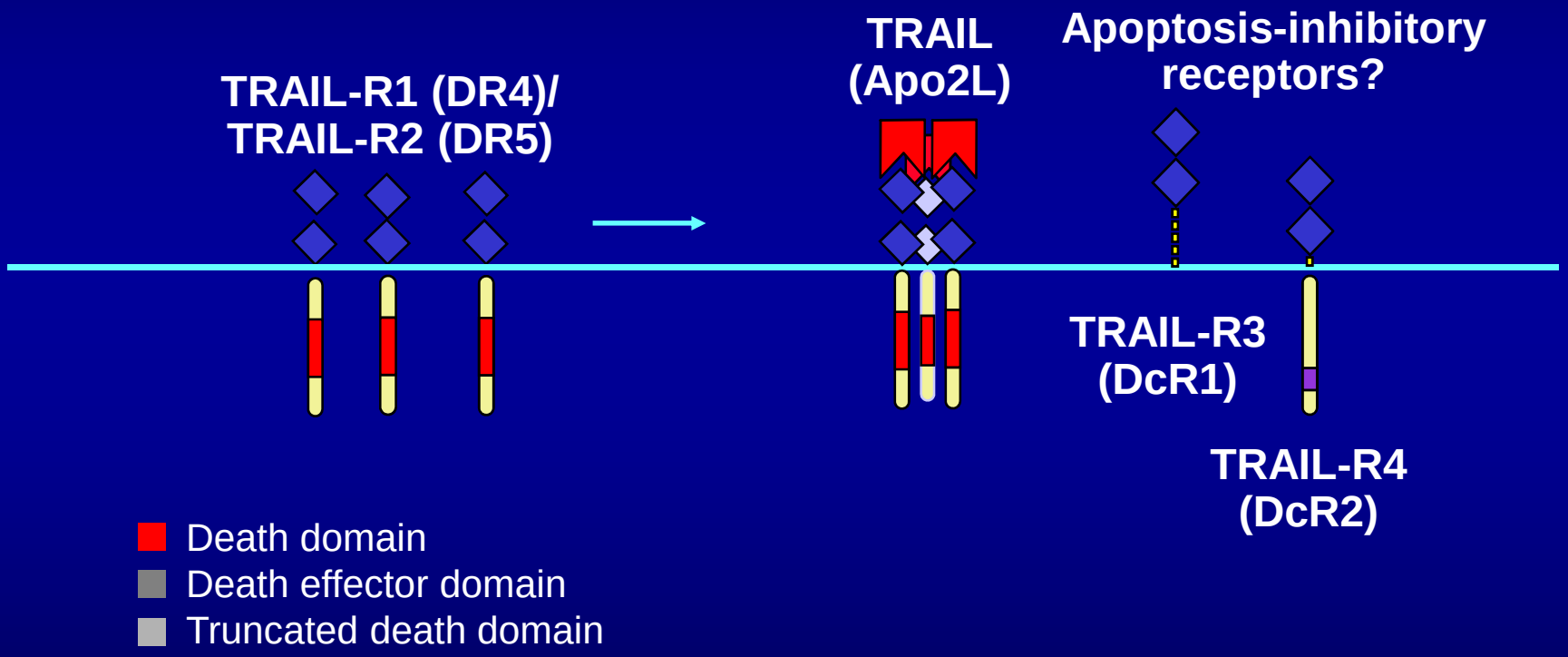
(2) Intrinsic

BH3-only proteins

BH3-Only Proteins: Pathway-Specific Sensors of Stress and Damage

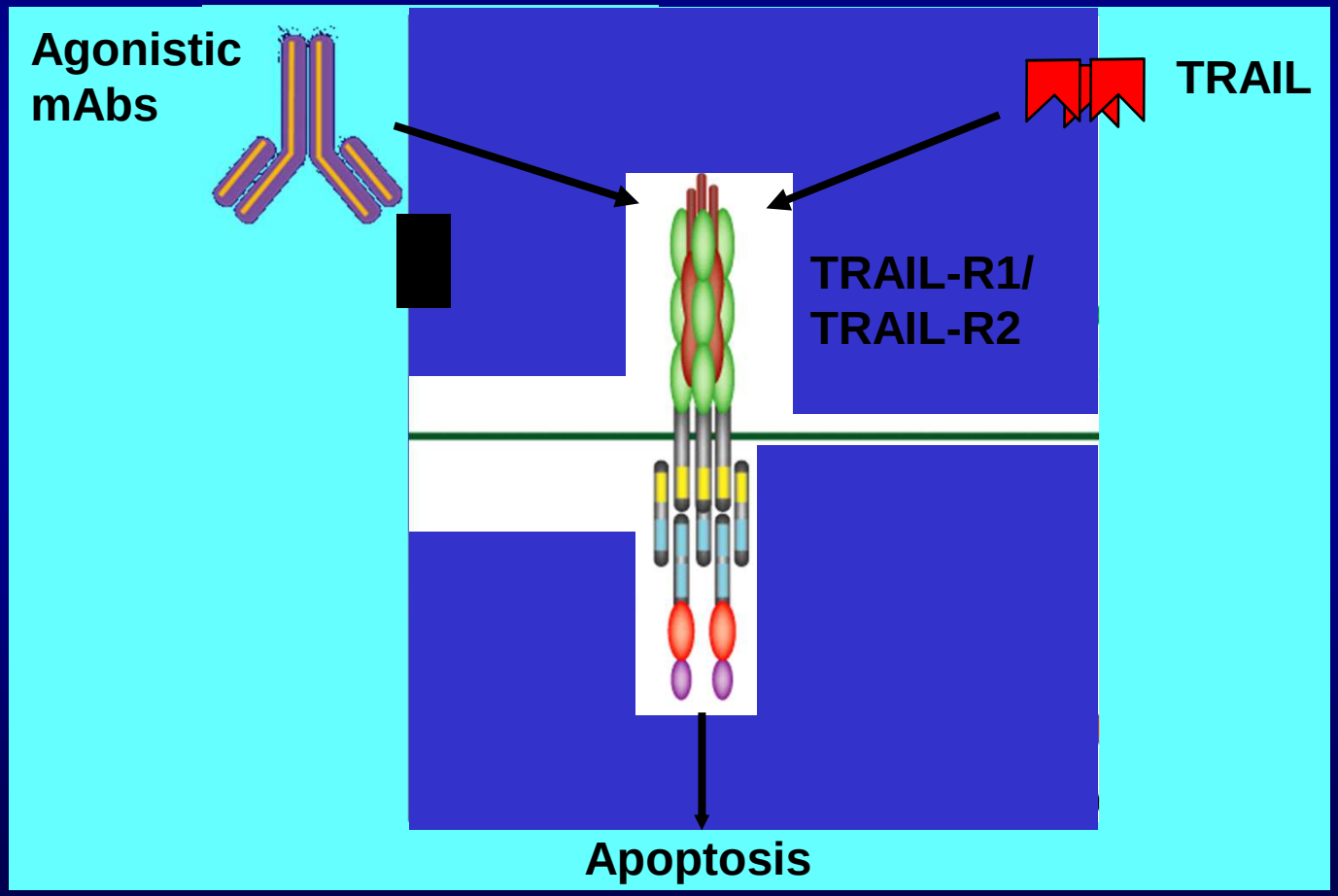


The TRAIL–TRAIL-R System



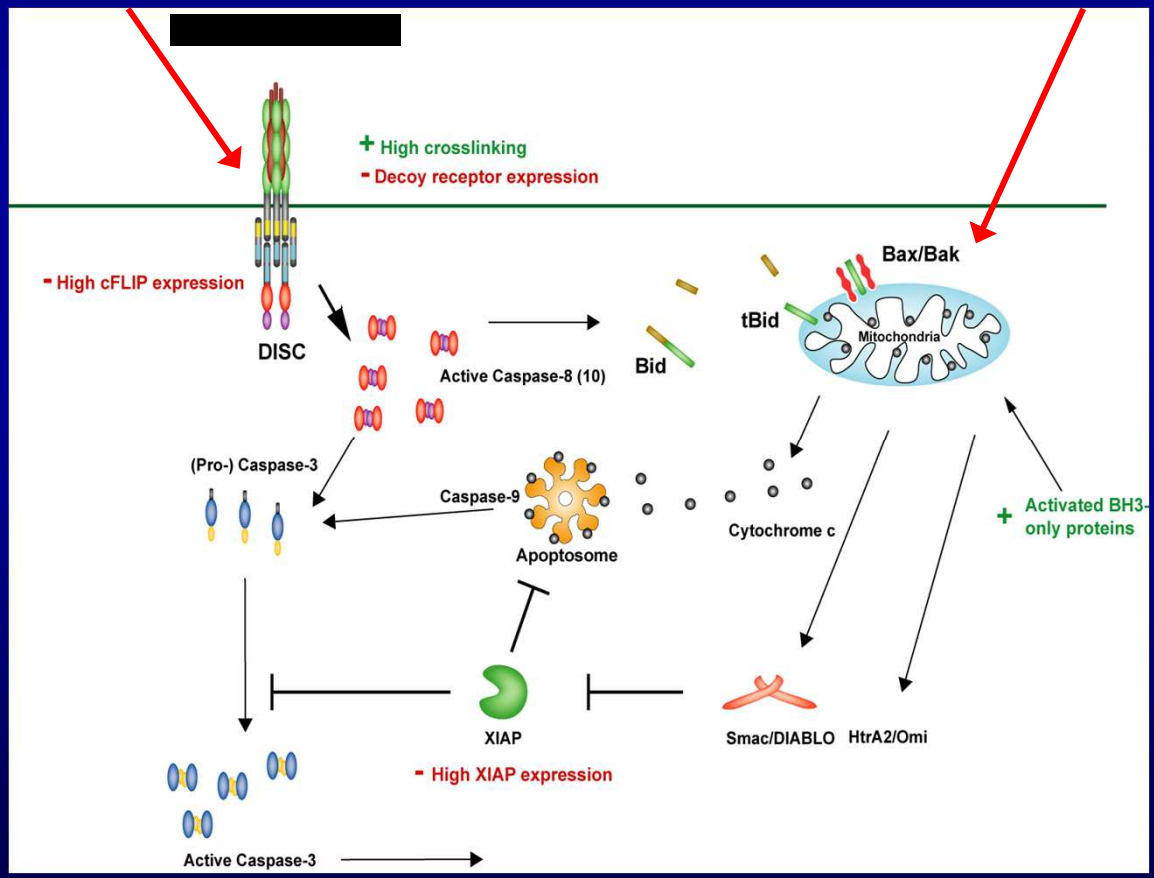
Walczak H, et al. EMBO J. 1997;16:5386-5397.
Degli-Esposti MA, et al. J Exp Med. 1997;186:1165-1170.
Degli-Esposti MA, et al. Immunity. 1997;7:813-820.

TRAIL Receptor Agonists Currently in Clinical Trials



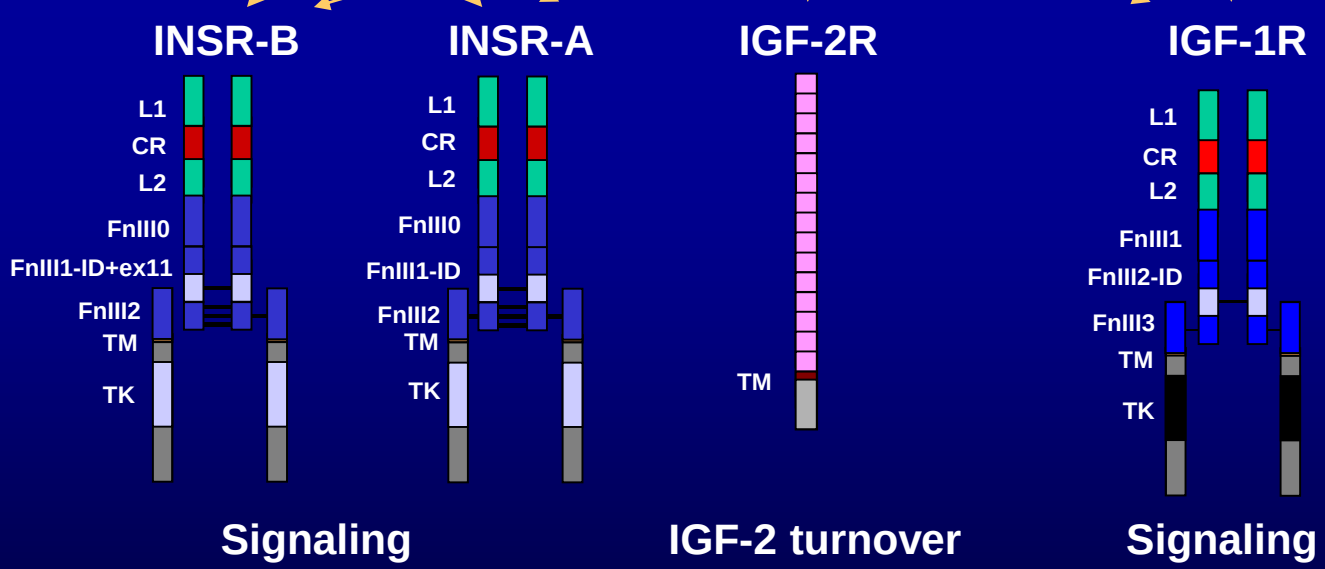
Double Hit on Tumor Cells

TRAIL receptor agonists Chemotherapy radiotherapy



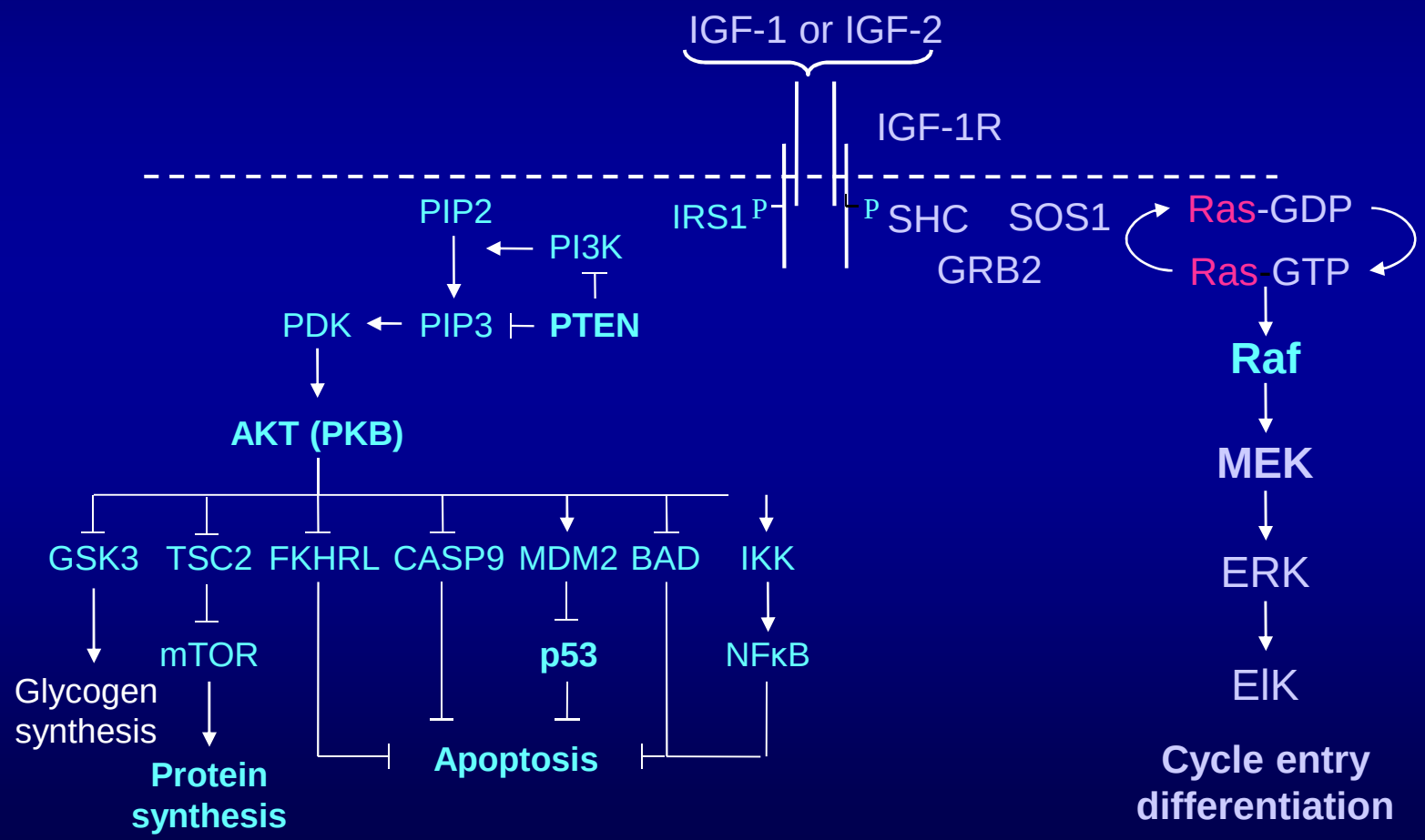
The Insulin and IGF-1R Signaling Axis

Adult Serum Concentration, nM	Insulin	IGF-2 ⊢ IGFBP ⊣	IGF-1
Mouse	0.1-1.5		60-85
Human	0.1-1.5	80-130	9-35

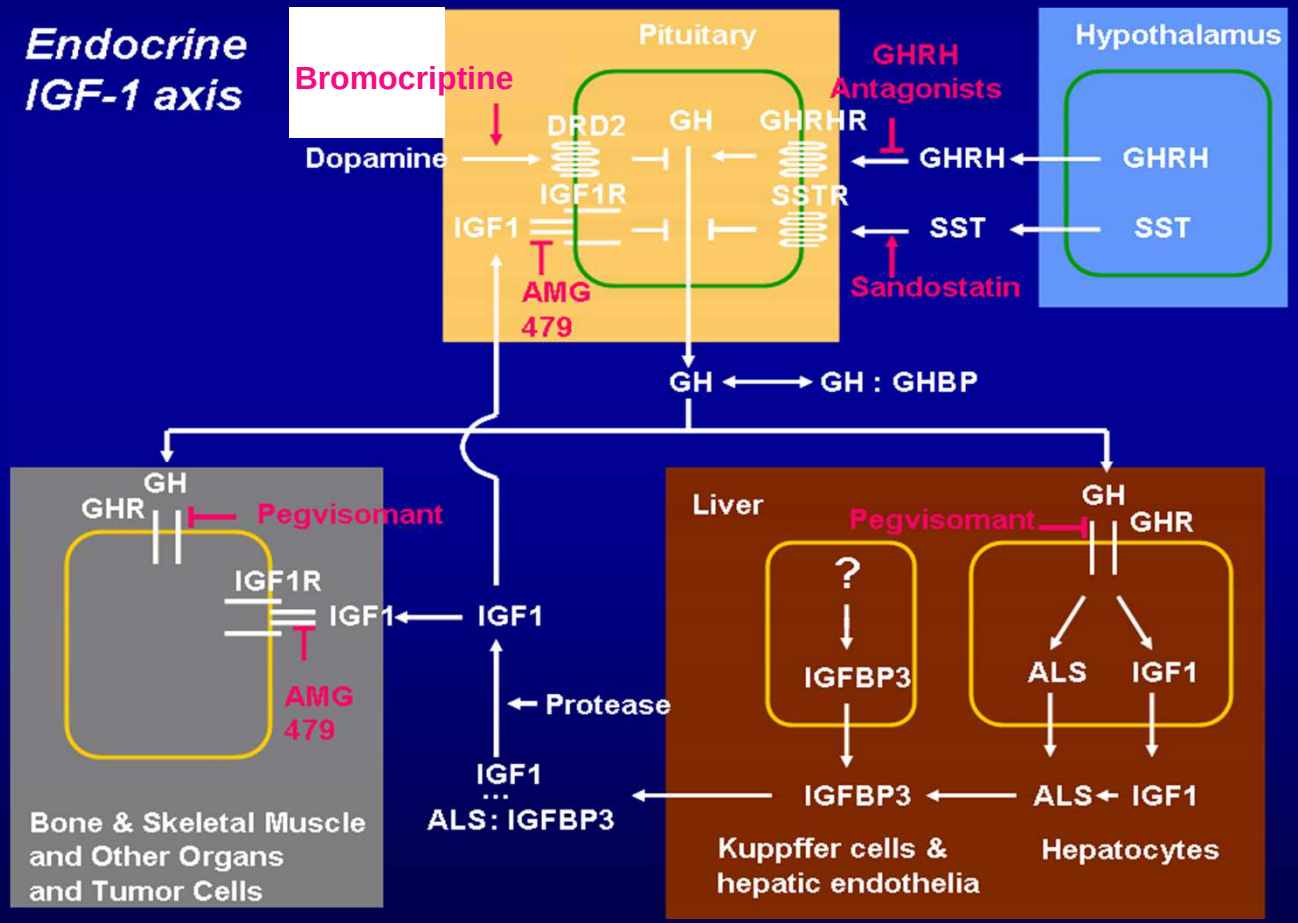


Unpublished data.

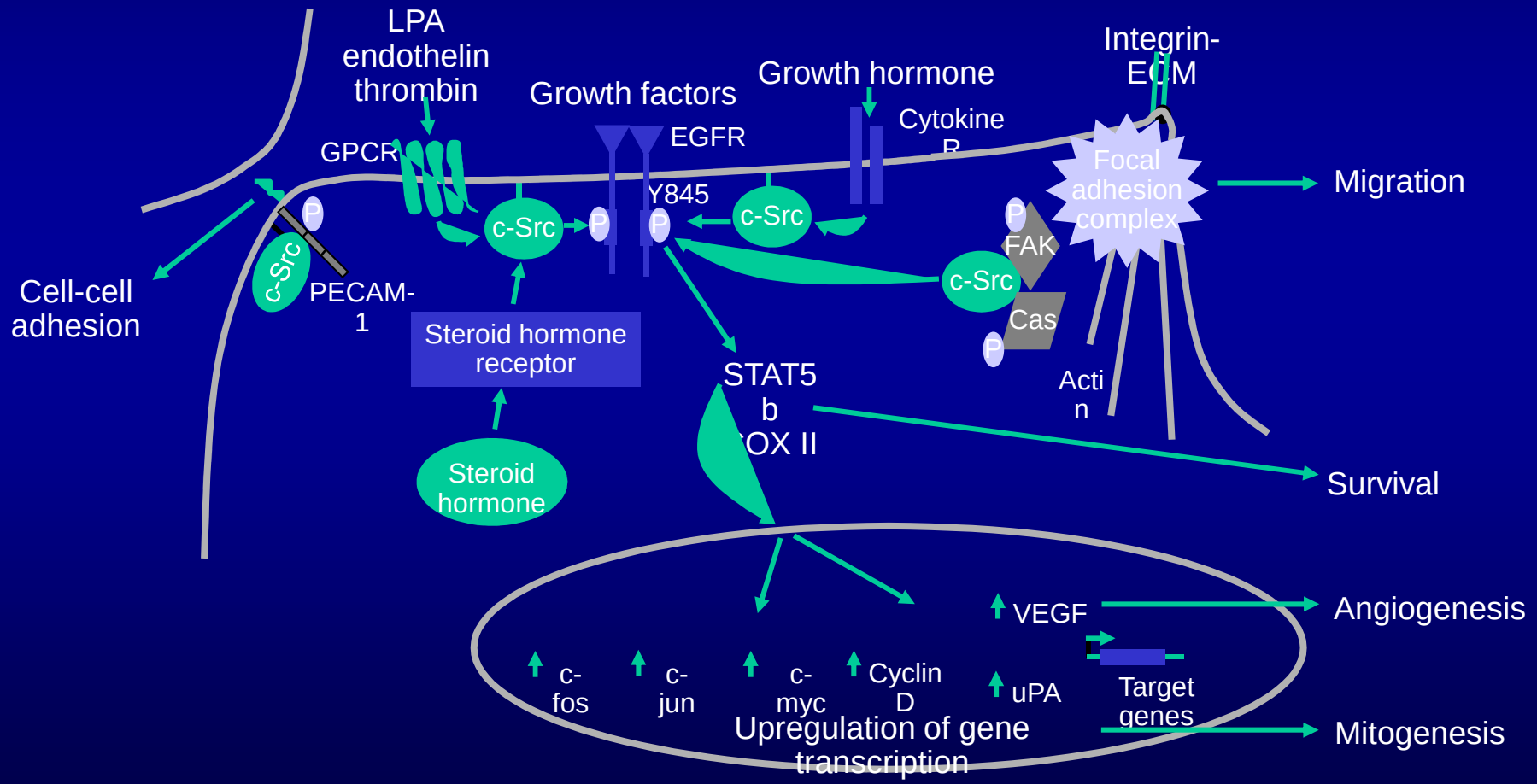
IGF-1R Signaling Pathways



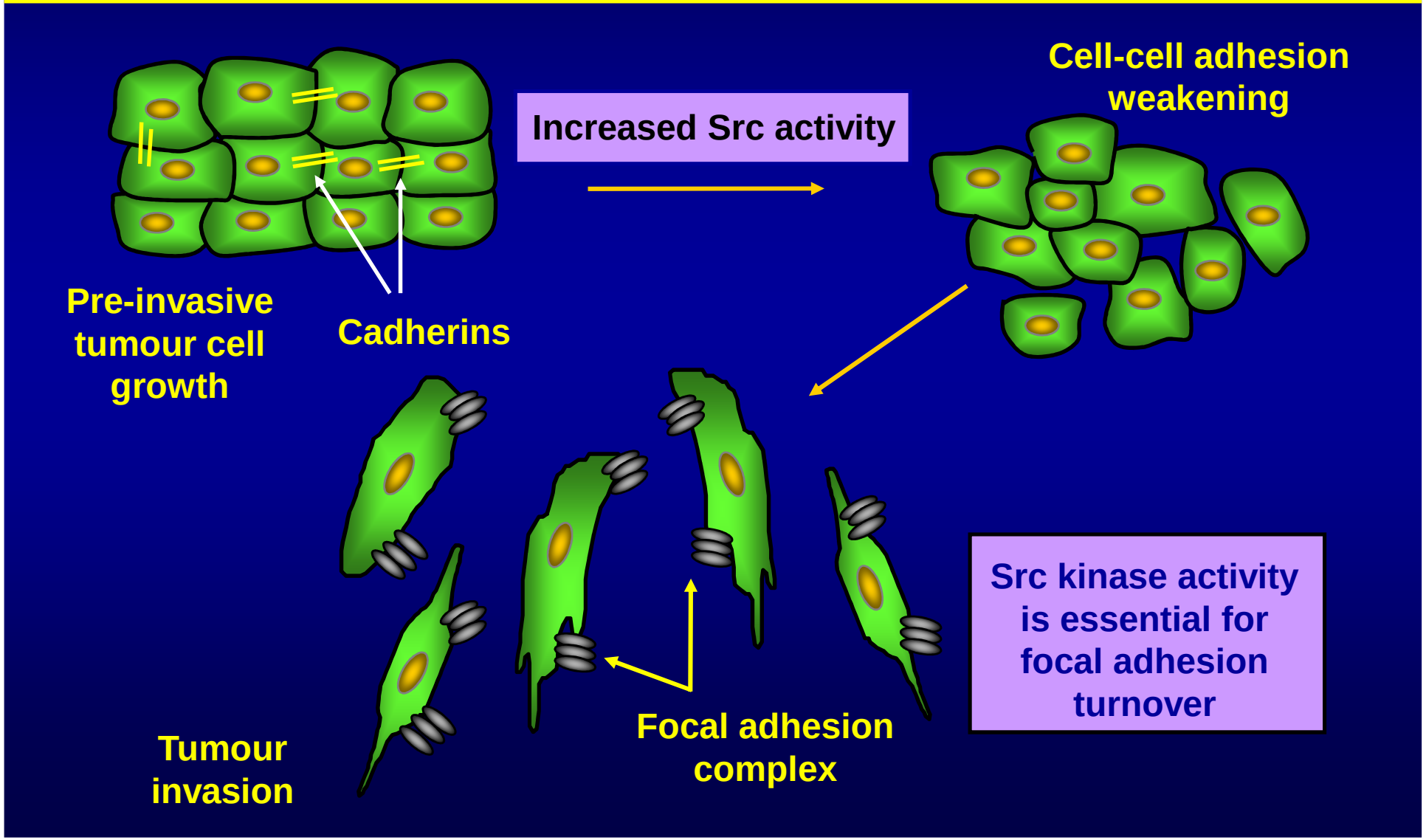
Plasma IGF-1 Suppresses GH Release Through IGF-1R Signaling in Pituitary



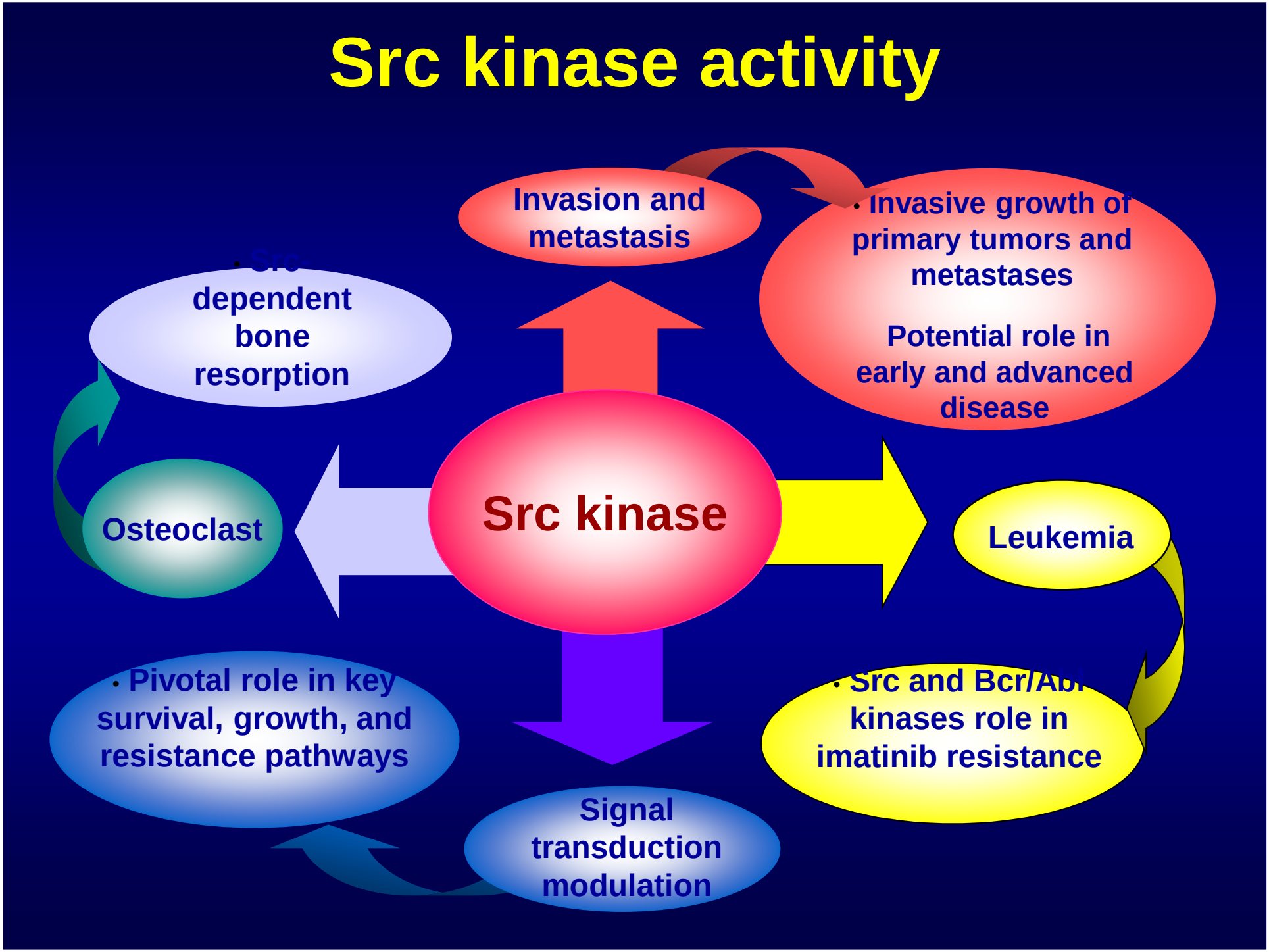
Src


LPA
endothelin
thrombin
Growth factors
Growth hormone
Integrin-
ECM
GPCR
EGFR
Cytokine
R
Focal
adhesion
complex
Migration
Y845
c-Src
c-Src
c-Src
c-Src
P
FAK
Cas
Cell-cell
adhesion
PECAM-
1
Steroid hormone
receptor
Steroid
hormone
STAT5
b
OX II
Acti
n
Survival
VEGF
Angiogenesis
c-
fos
c-
jun
c-
myc
Cyclin
D
uPA
Target
genes
Upregulation of gene
transcription
Mitogenesis

Deregulated Src activity and tumour invasion



Src kinase activity



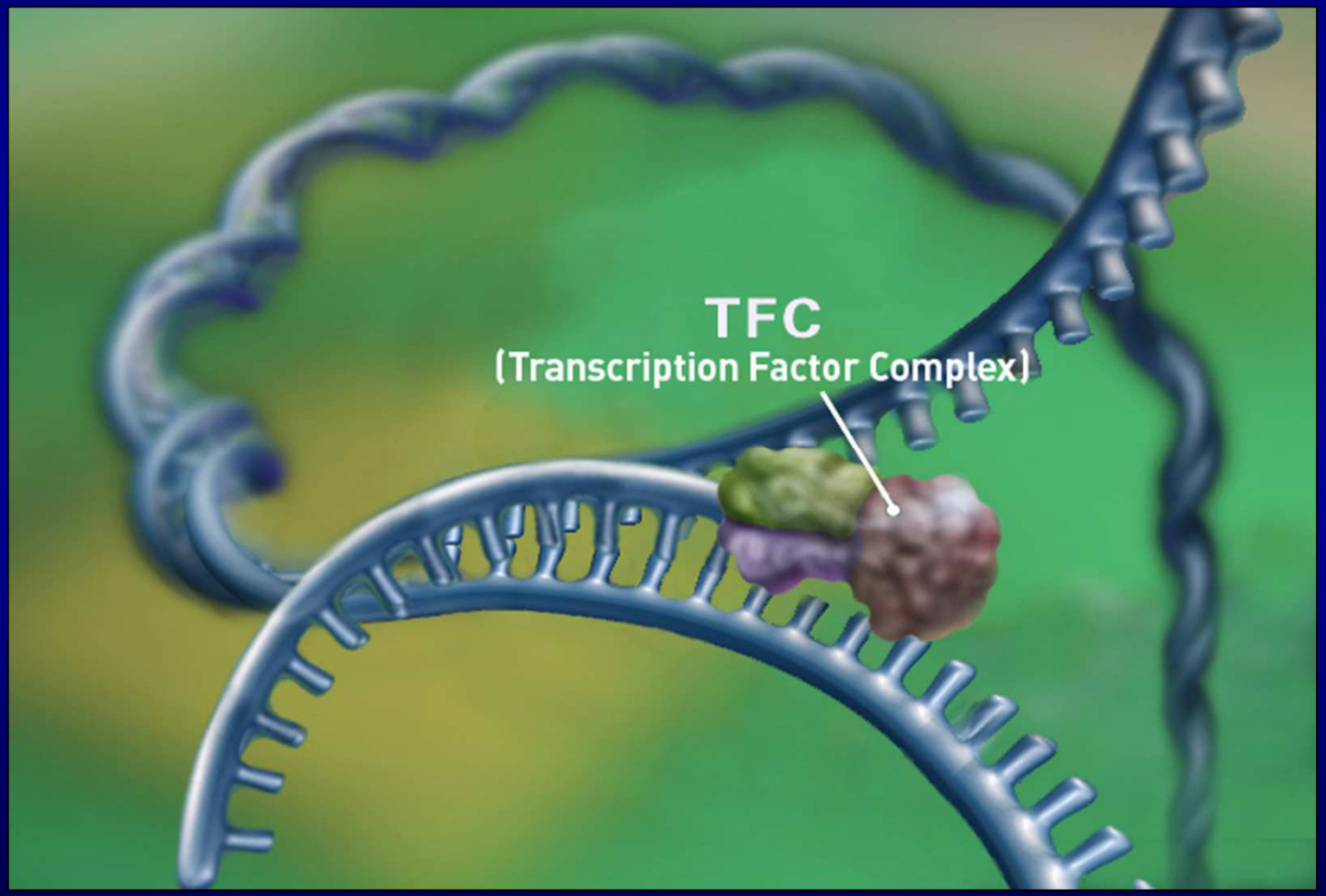
Potential Clinical Application of Src Inhibition

- Antiangiogenesis
- Osteoclast activation
- Invasion
- Proliferation

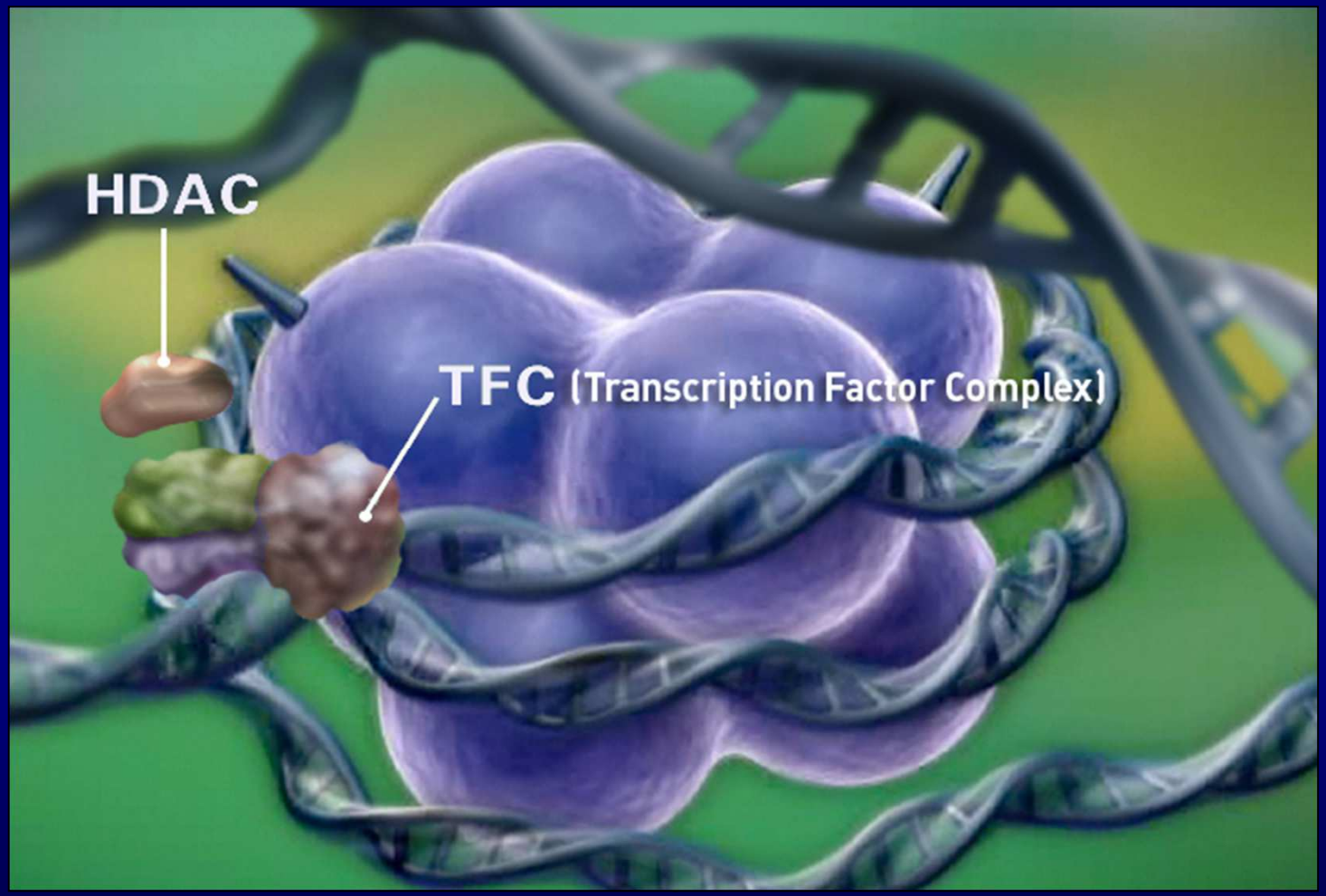
→

- **Tumor growth**
- **Bone metastasis**
- **Metastasis/adjuvant**
- **Tumor growth**

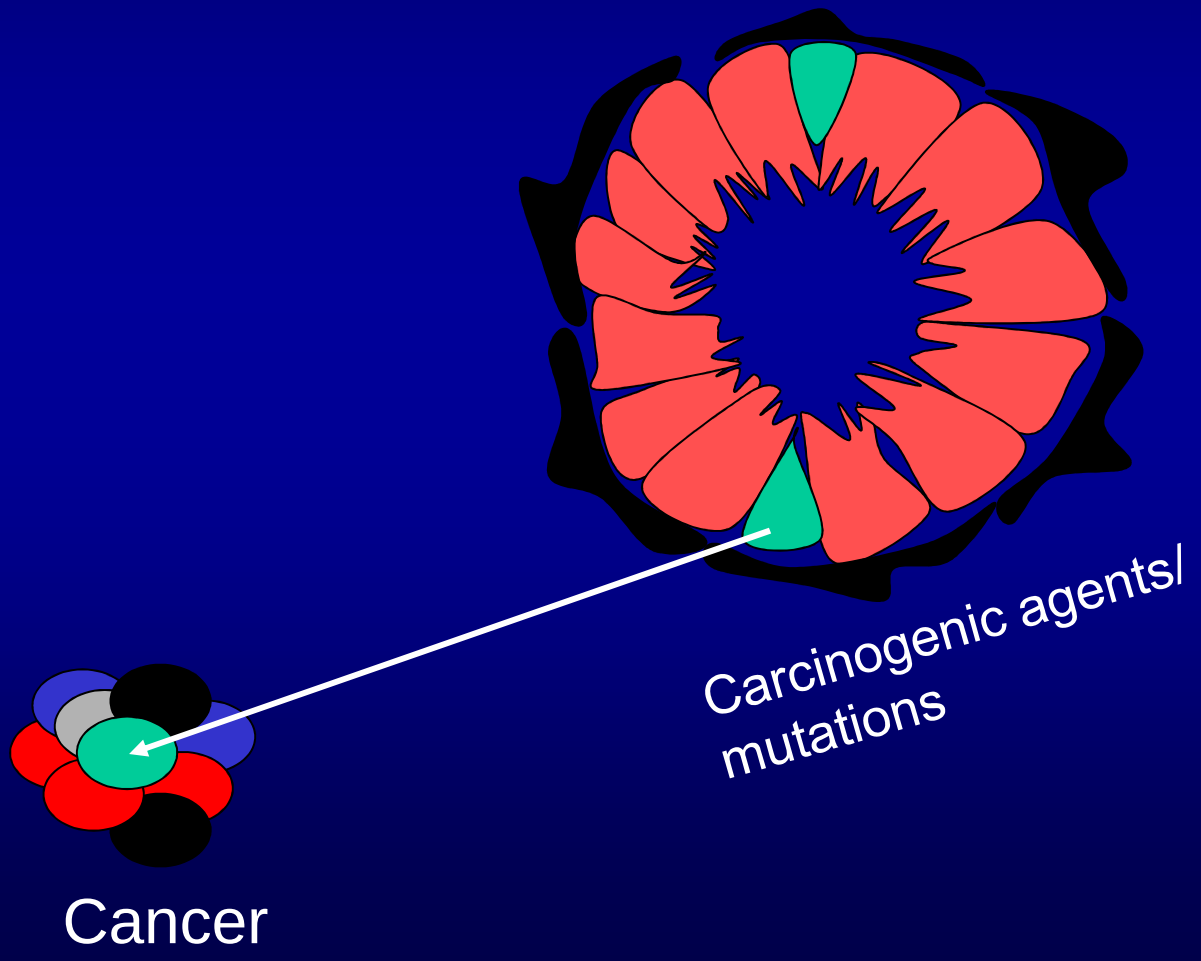
Gene Transcription



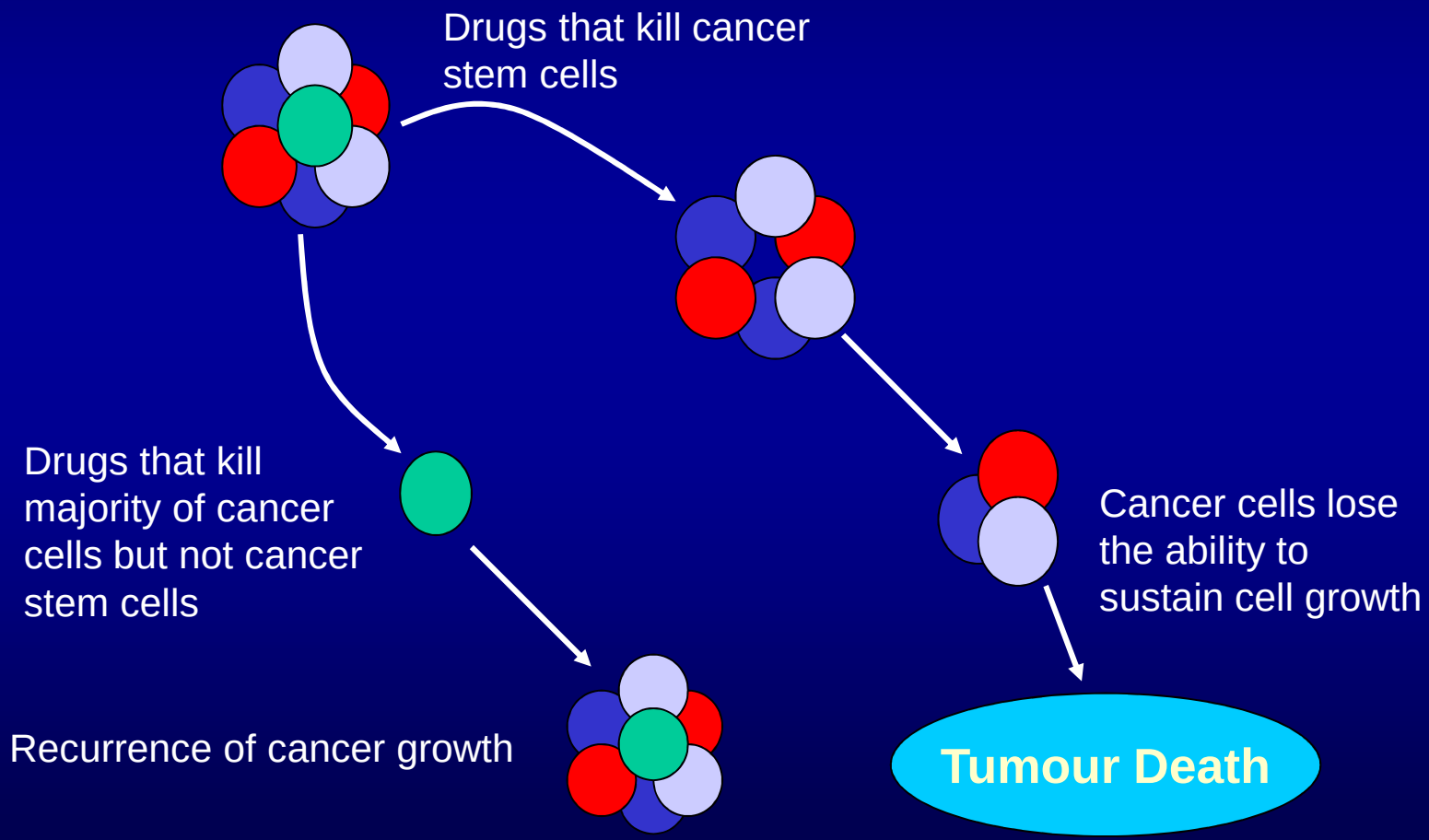
HDAC and Gene Expression



Breast Epithelial Stem Cells & Cancer Stem Cells

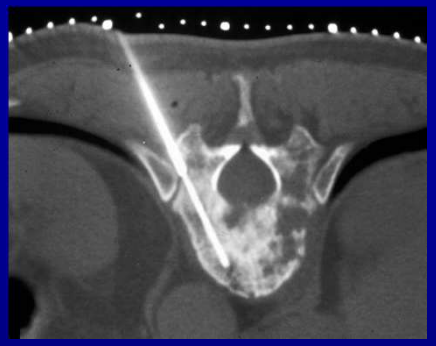


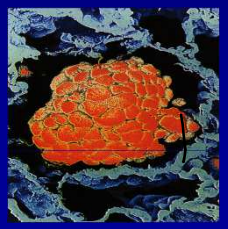
Drug Development : Cancer Stem Cells



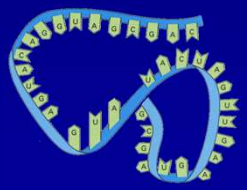
Research Process

Cancer patient with suspected relapsed lesion

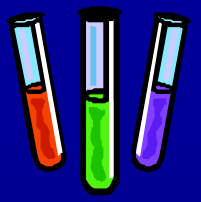




Collect tumor sample



Extract mRNA



Analysis

Initiate treatment

Collect data

CONCLUSIONS

- Targeted therapies are molecular radiosensitisers
- Can be combined with RT or CT for a better survival benefit
- Preclinical studies have been authenticated by clinical data (Bonner’s trial)
- Hitting the right target with the right drug can produce great results

Gastric & Breast Cancer e-journal
DOI: 10.2122/gbc.2008.0082

Special Article

Prognostic Value of Epidermal Growth Factor Receptor in Breast Cancer: An Indian Experience.

Renita Bhamrah, PhD, Pramod Kumar Julka, MD, Omana Nair, PhD, Rajinder Parshad, MS, Siddhartha Dattagupta, MD, Ranju Ralhan, PhD, Sadanand Dwivedi, PhD, Darpreet Singh Bhamrah, MS, Guresh Kumar, PhD, Sanjay Gupta, M Pharm, Gaurav Dhawan, MBBS, Goura Kishor Rath, MD.

Abstract:

We studied the prognostic impact of EGFR positivity in Indian scenario and its correlation with known prognostic markers such as Estrogen receptor (ER) and HER-2/ neu oncogene. 210 women aged less than 70 years with histopathologically proven carcinoma breast and having ambulatory general condition were included in the study. EGFR, Her-2/neu and ER expressions were evaluated immunohistochemically. Of the 210 patients, the EGFR, ER and HER-2/neu expressions were positive in 87 (41%), 139 (66%) and 60 (29%) patients respectively. EGFR had a positive correlation with systemic recurrence and inverse correlation with overall survival of the patient. In multivariate analysis it was observed that EGFR and node positivity were significant factors for overall survival and disease free survival. Our study reveals that expression of EGFR may serve as a prognostic indicator for poor survival in breast cancer patients.

Clinical Oncology (2004) **16**: 115–118
doi:10.1016/j.clon.2003.11.013

Original Article

Trastuzumab and Docetaxel for Metastatic Breast Cancer: An Experience from a Cancer Centre in India

P. K. Julka, D. N. Sharma, P. Mukhopadhyay, G. K. Rath

Department of Radiotherapy and Oncology, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT:

Aims: To study the toxicity profile and effectiveness of combination of trastuzumab and docetaxel in women with metastatic breast cancer showing HER-2 overexpression (IHC 3+).

Materials and methods: Sixteen women with metastatic breast cancer were treated with trastuzumab (2 mg/kg every week) and docetaxel (100 mg/m^2) as first-line therapy. A loading dose of 4 mg/kg trastuzumab was given on week 1. We planned to give a minimum of six cycles of docetaxel chemotherapy.

Results: A total of 89 cycles of docetaxel chemotherapy was given (median five cycles per patient). Median number of cycles of trastuzumab was 44 with a range of 20–71. Of the 16 patients, seven (44%) had complete response (CR), whereas five patients (31%) had partial response (PR). The overall response rate (CR+PR) was 75%. Two patients died of progressive disease, and the other two died at home, for which the cause of death could not be known. No anaphylaxis, cardio-toxicity or febrile neutropenia was observed in any patient. Overall, the toxicity was within tolerable limits.

Conclusion: The combination of trastuzumab and docetaxel in women with metastatic breast cancer showing HER-2 overexpression (IHC 3+) is a safe and effective regimen. However, further randomised trials are needed to establish its role in metastatic breast cancer. Julka P. *et al.* (2004). *Clinical Oncology* **16,** 115–118

British Journal of Cancer (2008) 00, 000 – 000

www.bjcancer.com

Full Paper

A phase II study of sequential neoadjuvant gemcitabine plus doxorubicin followed by gemcitabine plus cisplatin in patients with operable breast cancer: prediction of response using molecular profiling

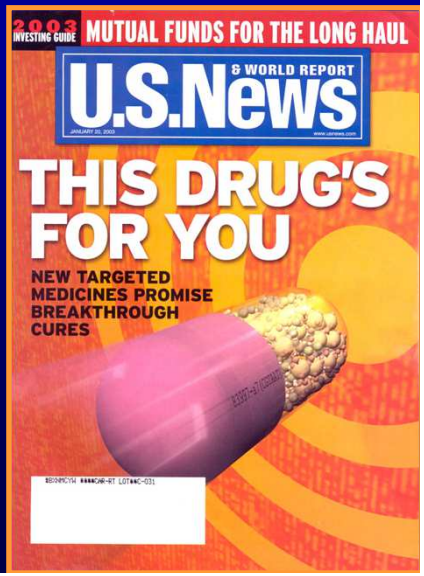
PK Julka*[,1], RT Chacko[2], S Nag[3], R Parshad[1], A Nair[2], DS Oh[4], Z Hu[4], CB Koppiker[3], S Nair[2], R Dawar[1], N Dhindsa[5], ID Miller[6], D Ma[7], B Lin[7], B Awasthy[8] and CM Perou*[,4]

[1]Department of Radiotherapy and Oncology, AIIMS, New Delhi 110029, India; [2]Department of Medical Oncology, Christian Medical College, Vellore, Tamil Nadu 632004, India; [3]Department of Medical Oncology, HCJMRI, Pune, Maharashtra 411001, India; [4]Departments of Genetics and Pathology and Laboratory Medicine, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [5]Eli Lilly and Company (India) Pvt. Ltd., Gurgaon, Haryana 122001, India; [6]Department of Pathology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZD, UK; [7]Eli Lilly and Company, Indianapolis, IN 46285, USA; [8]Health Care Global Enterprises, Curie Centre of Oncology, St John's Hospital Campus, Koramangala, Bangalore 560034, India

CONCLUSION (Cont.)

- Kinase inhibitors are most effective against tumors that are heavily, perhaps solely, dependent on the targeted kinase.
- Monotherapy with TKIs is limited by the development of resistance.

Translational research studies are critical to understanding the results from clinical trials of targeted therapeutics.



Thank You