Terapia alvo em oncologia

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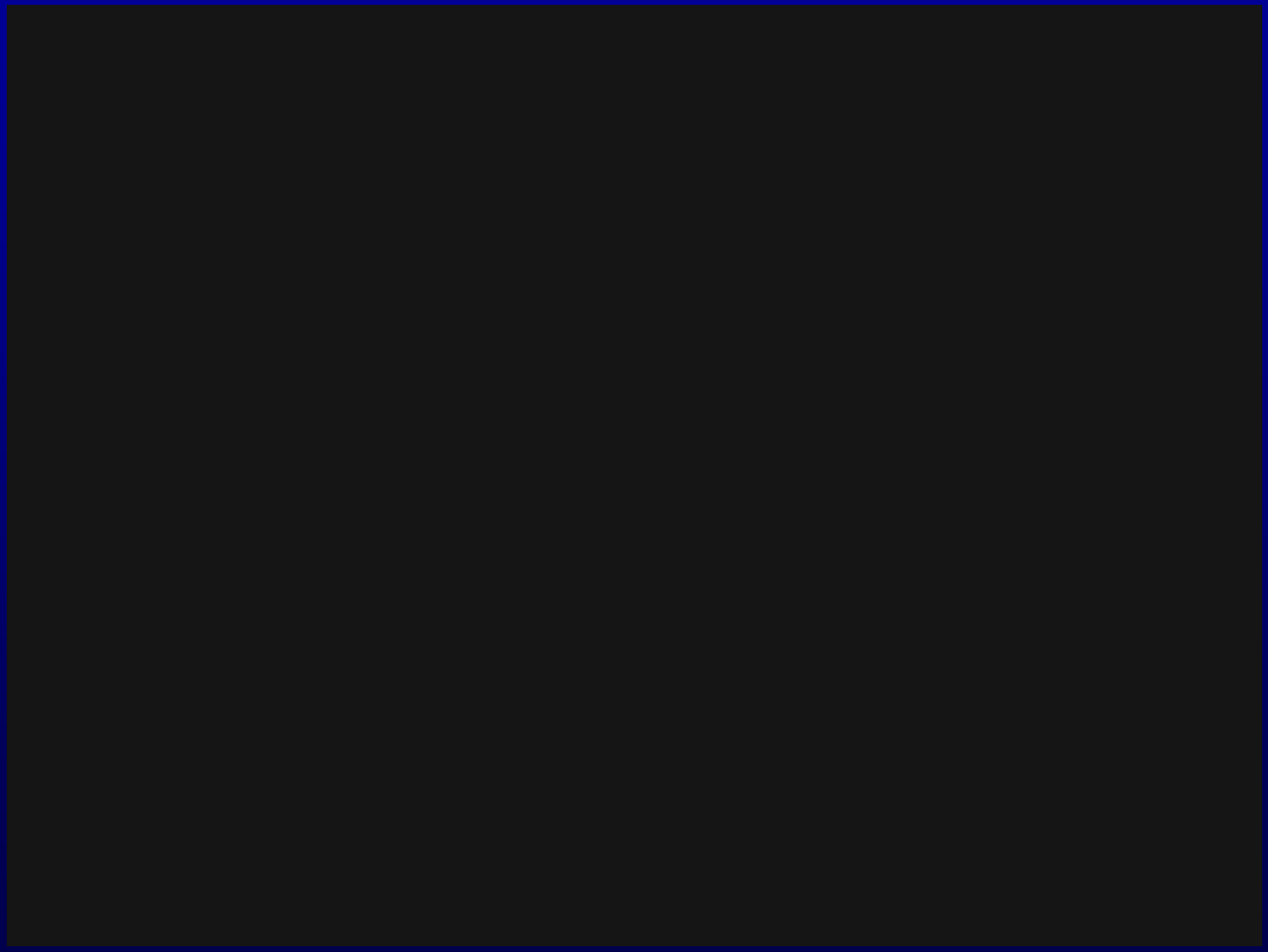
Biologia tumoral



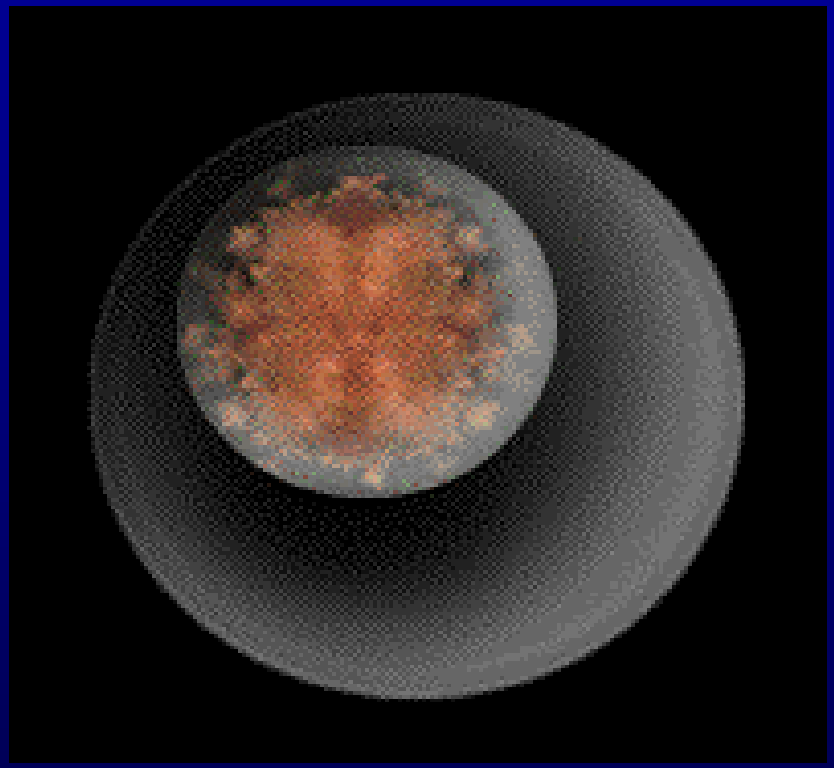
Características de Malignidade

Hanahan D, et al. Cell. 2000;100:57-70.

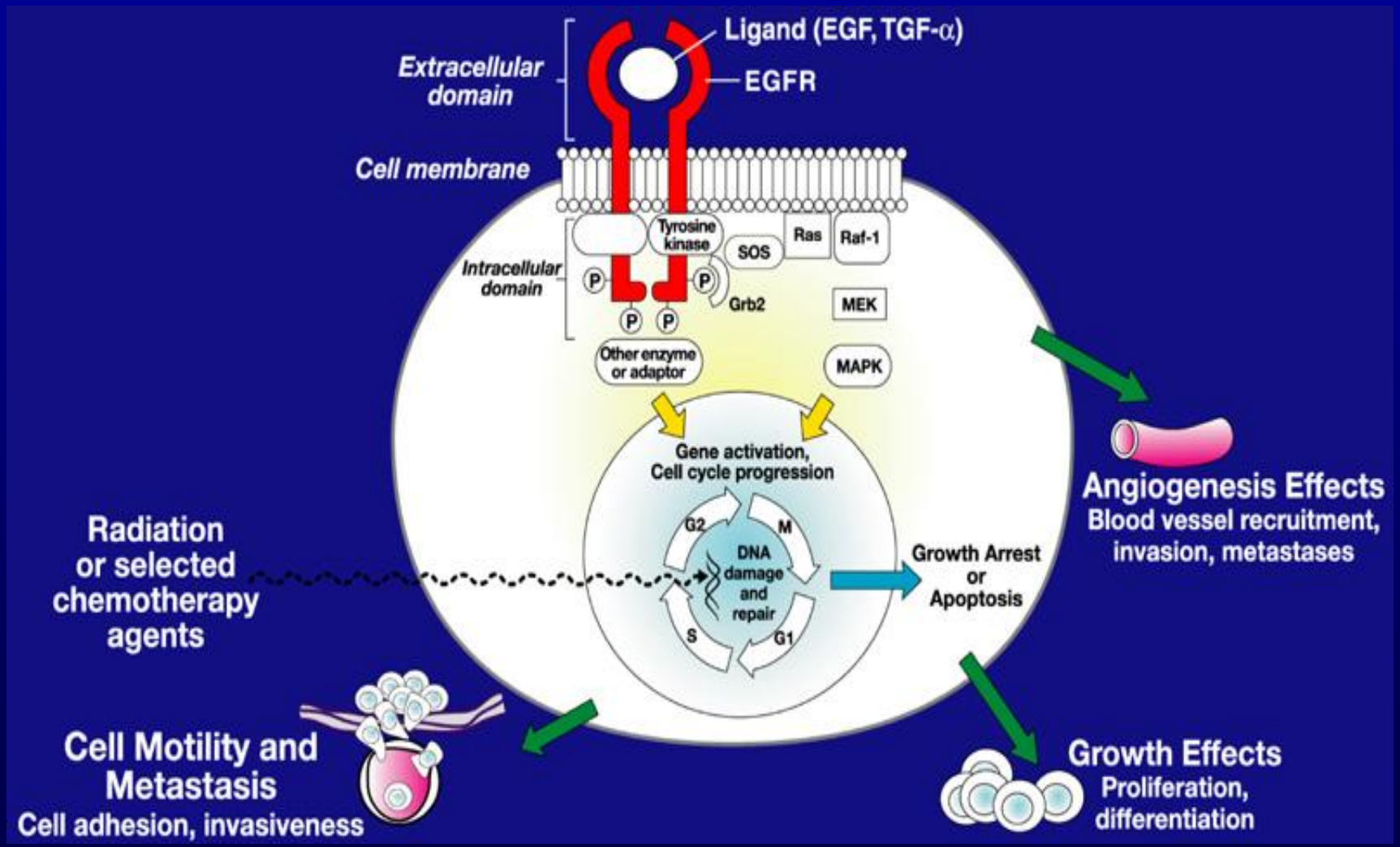
Terapia Alvo Ideal

- Crucial no fenótipo maligno
- Sem expressão significante nas tecidos normais
- Molécula com característica biológica relevante
- Resposta clínica significante nos tumores que expressam o alvo, quando este é inibido
- Resposta mínima nos pacientes cujos tumores não expressam o alvo

Proliferação Celular



Estimulação Celular

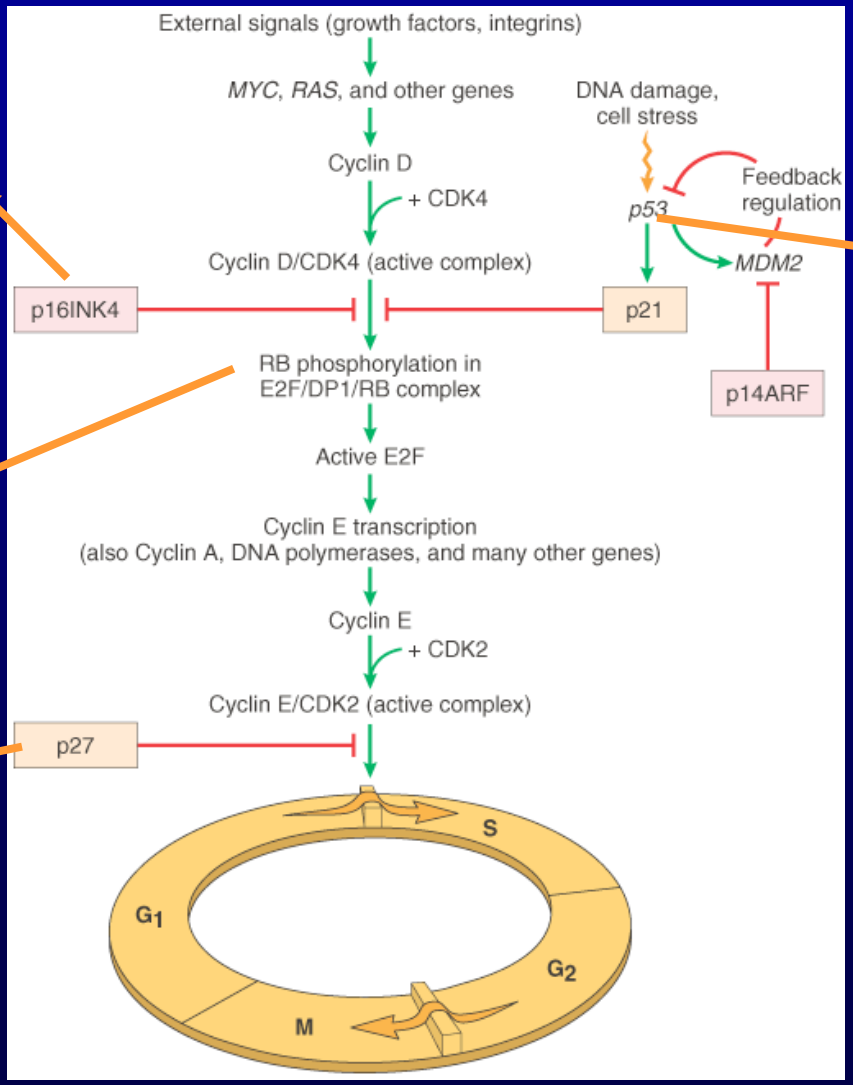


Proliferação Celular

**1- EXPRESSÃO REDUZIDA EM 55 A 89% DOS TUMORES,
2- ALT ASSOCIADA A < SOBREVIDA, > RECORRÊNCIA, PROGRESSÃO TUMORAL E METÁSTASES**

RB MUTADO CORRELACIONA-SE COM SOBREVIDA PEQUENA

NÍVEIS REDUZIDOS PODE ASSOCIAR A > PROLIFERAÇÃO CELULAR



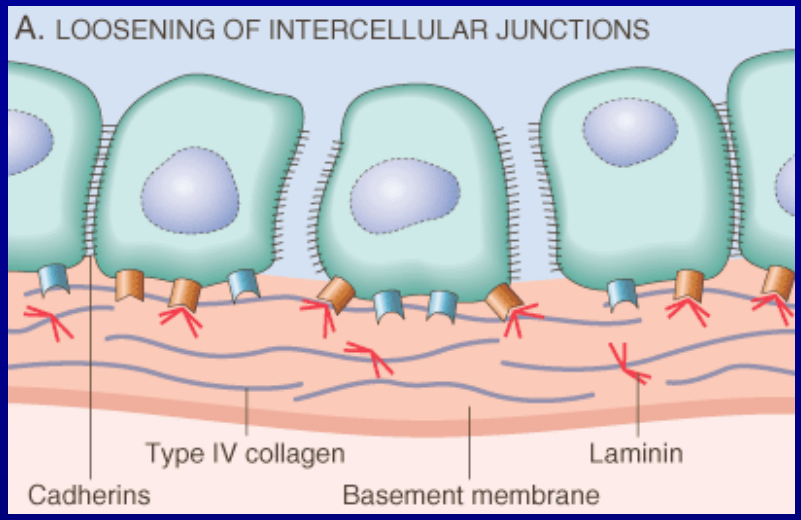
EVENTO PROCOCE NA CARCINOGÊNESE ASSOCIADO A EXPOSIÇÃO A ÁLCCOL E TABACO

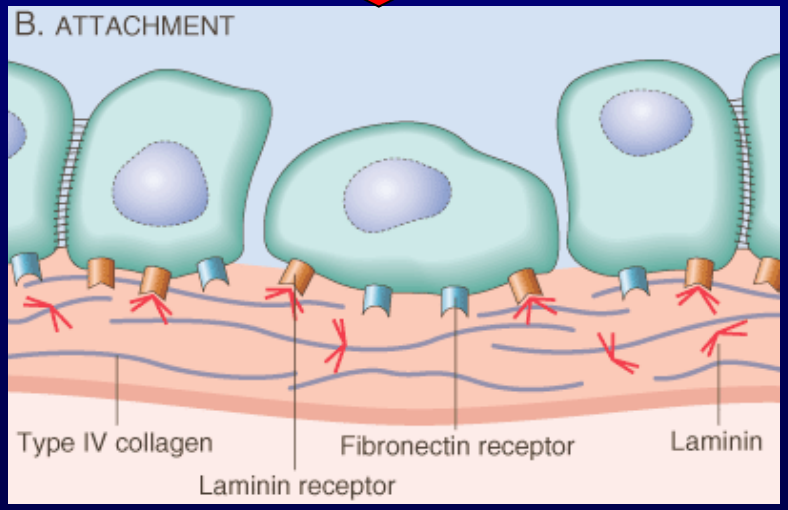
**1- ESTABILIDADE GENÔMICA,
2- PROGRESSÃO NO CICLO CEL,
3- DIFERENCIAÇÃO CELULAR,
4- REPARO NOS DANOS DO DNA,
5- APOPTOSE.
6- MAIS DE 50% DOS CA DE CCP TEM MUTAÇÃO NO TP53**

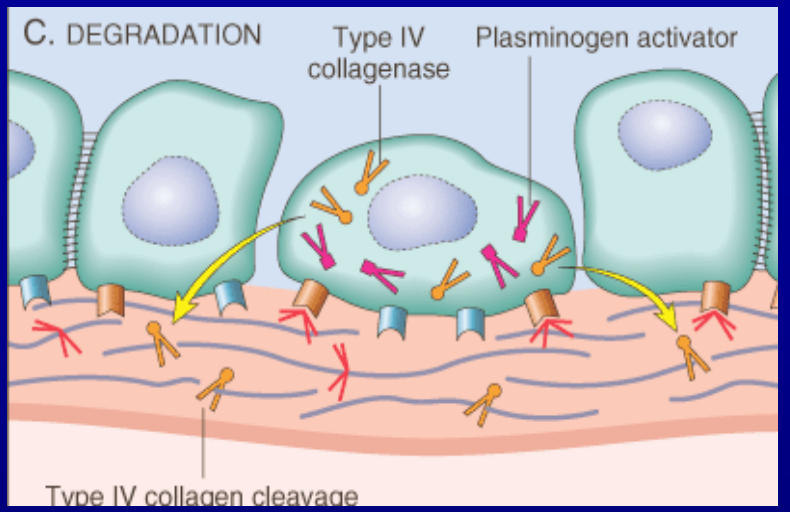
MUTAÇÕES NESTE GENE ASSOCIADAS A RECORRÊNCIA EM CURTO PERÍODO

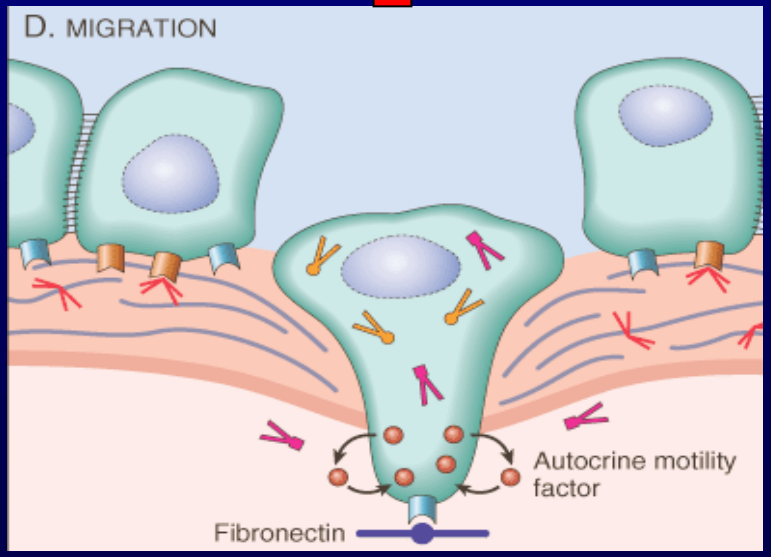
Cancer Control, 9 (5): 369-378, 2002.
Head & Neck, 683-691, 2001.
J Laryngol Otal, 112: 607-612, 1998.
Oral Oncol 39(2): 115-129, 2003.

INVASÃO LOCAL

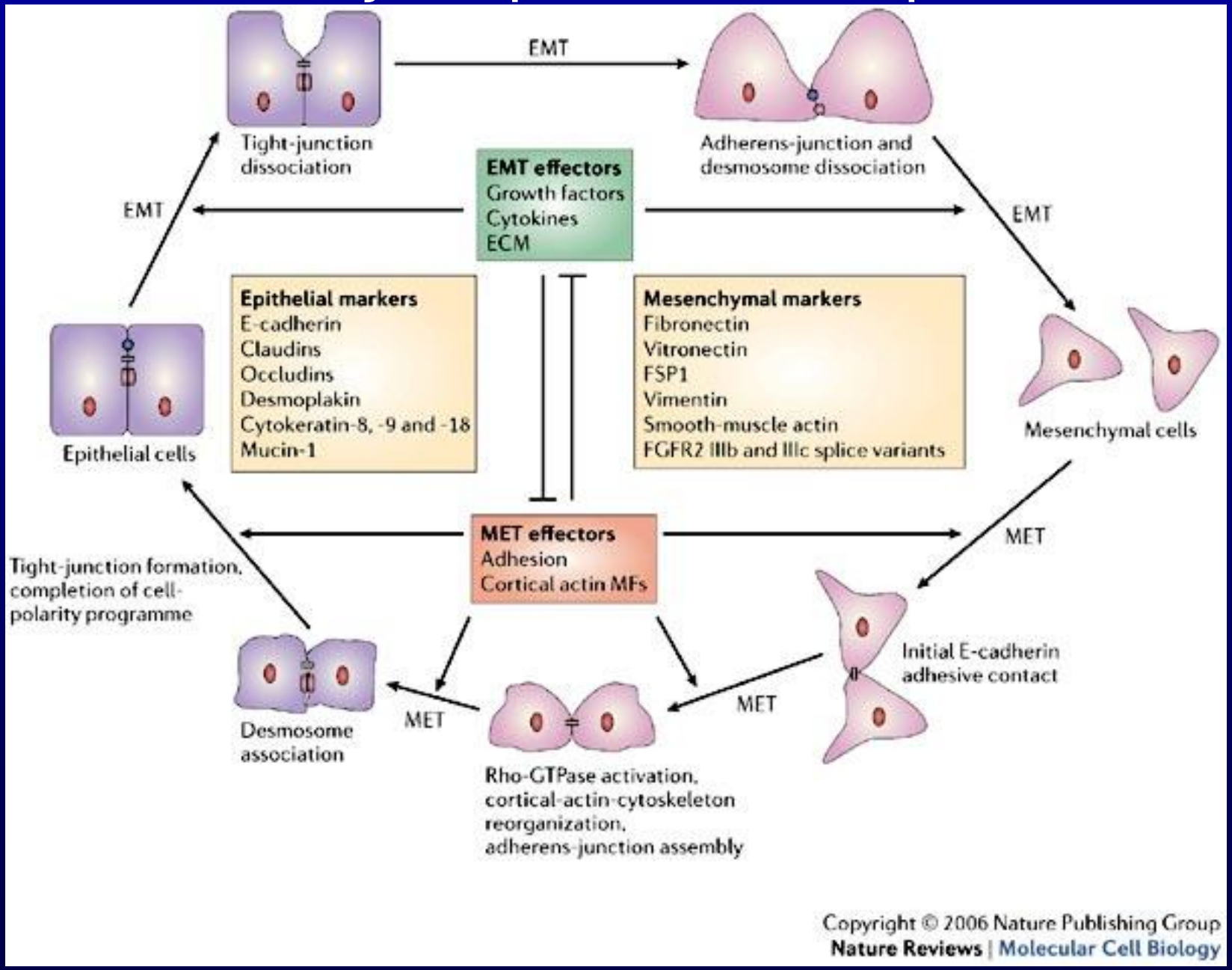


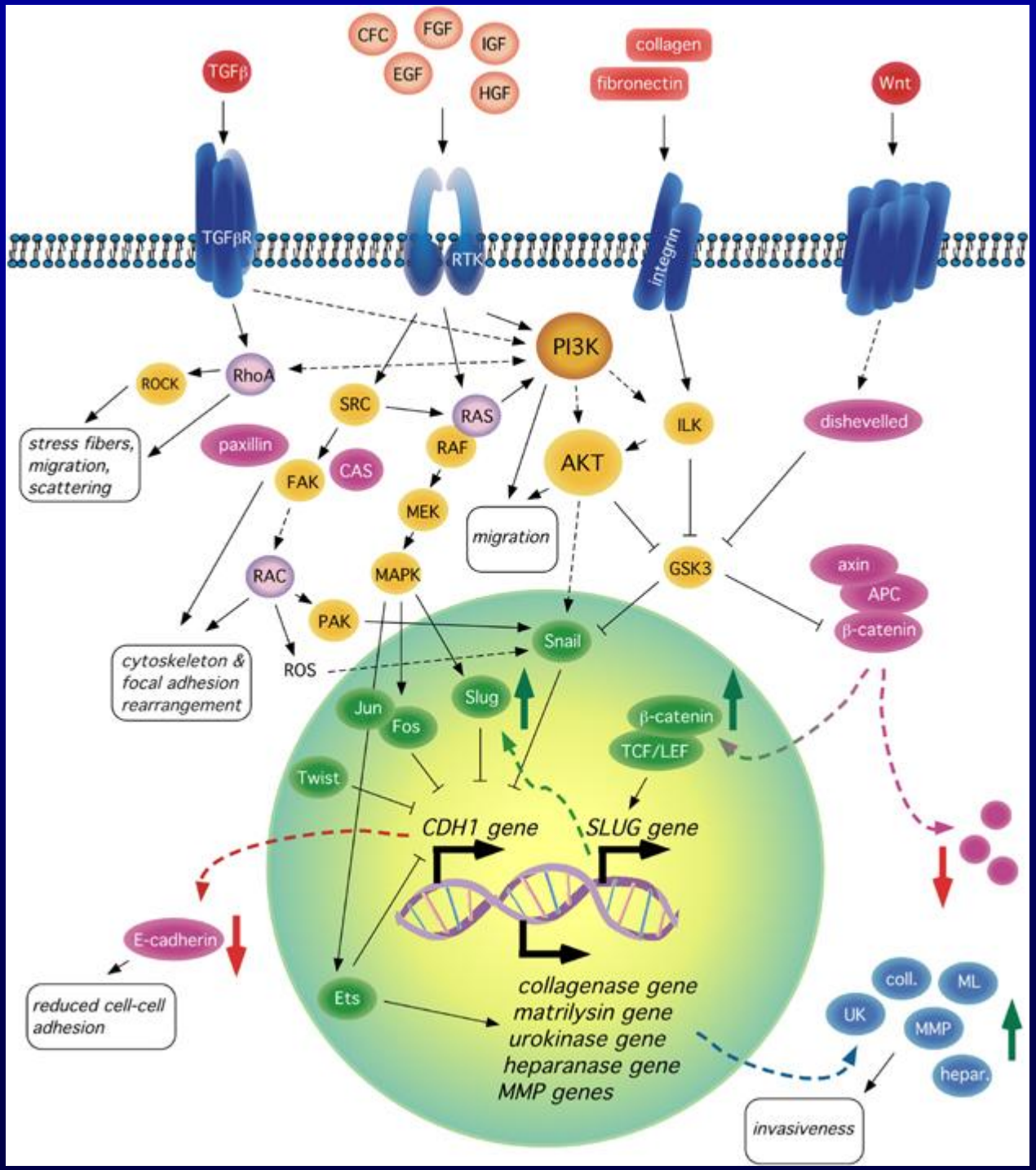




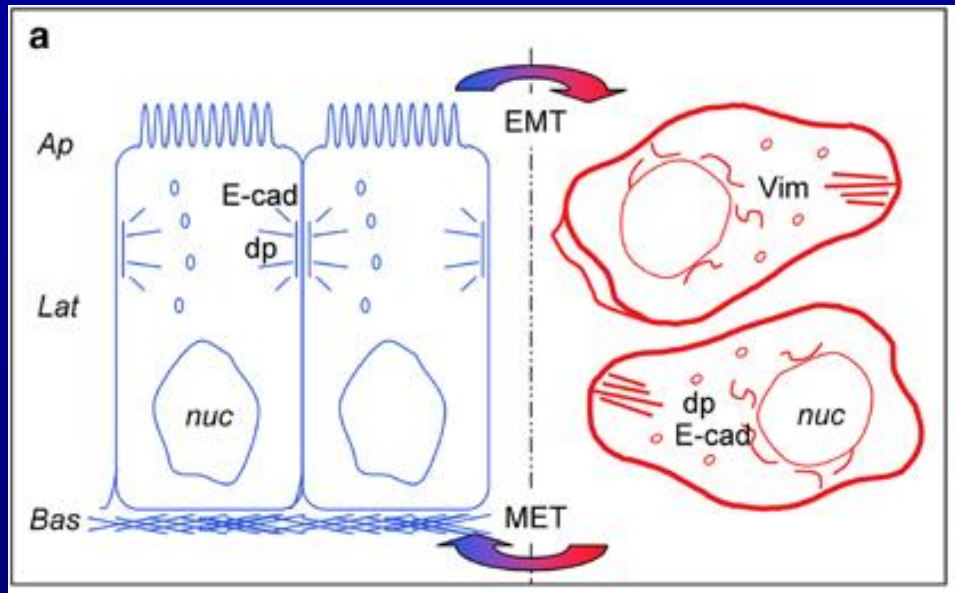


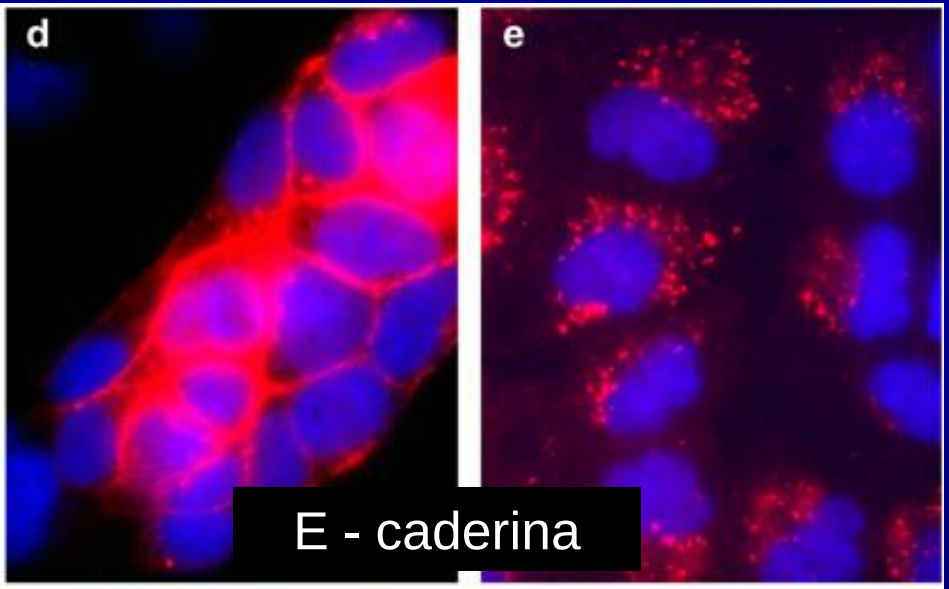
Transição epitélio mesênquima

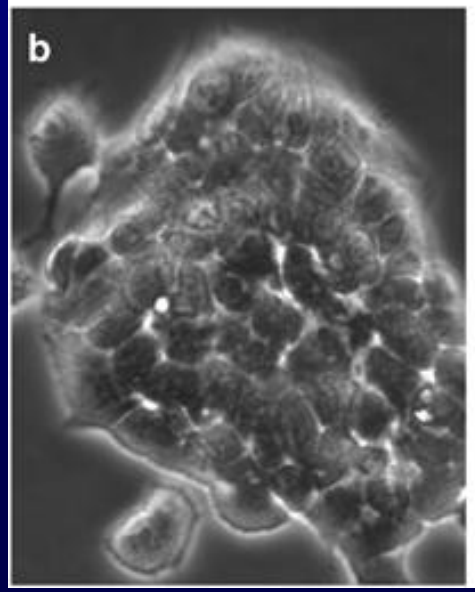


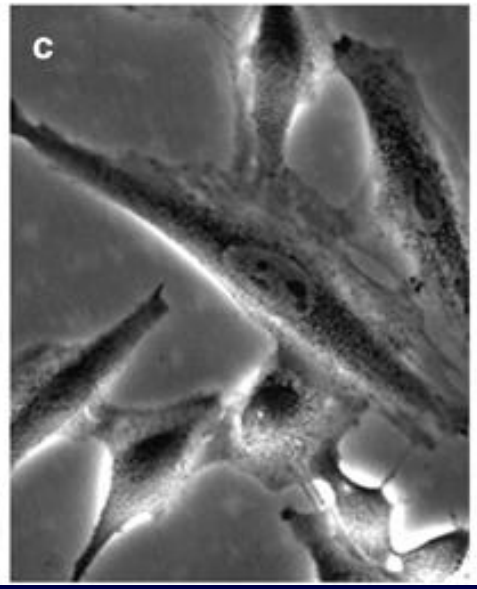

CFC
FGF
IGF
EGF
HGF
TGFβ
collagen
fibronectin
Wnt
TGFβR
RTK
integrin
PI3K
RhoA
ROCK
SRC
RAS
ILK
dishevelled
stress fibers,
migration,
scattering
paxillin
RAF
AKT
FAK
CAS
MEK
migration
RAC
MAPK
GSK3
axin
APC
β-catenin
PAK
Snail
cytoskeleton &
focal adhesion
rearrangement
ROS
Slug
Jun
Fos
β-catenin
TCF/LEF
Twist
CDH1 gene
SLUG gene
E-cadherin
reduced cell-cell
adhesion
Ets
collagenase gene
matrilysin gene
urokinase gene
heparanase gene
MMP genes
coll.
ML
UK
MMP
hepar.
invasiveness

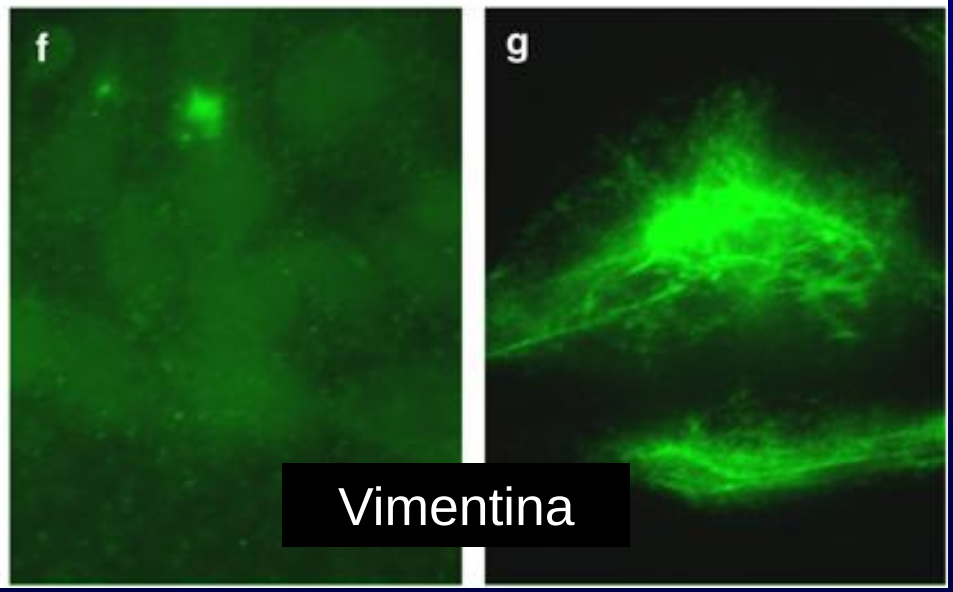
Transiçao epitélio mesenquima



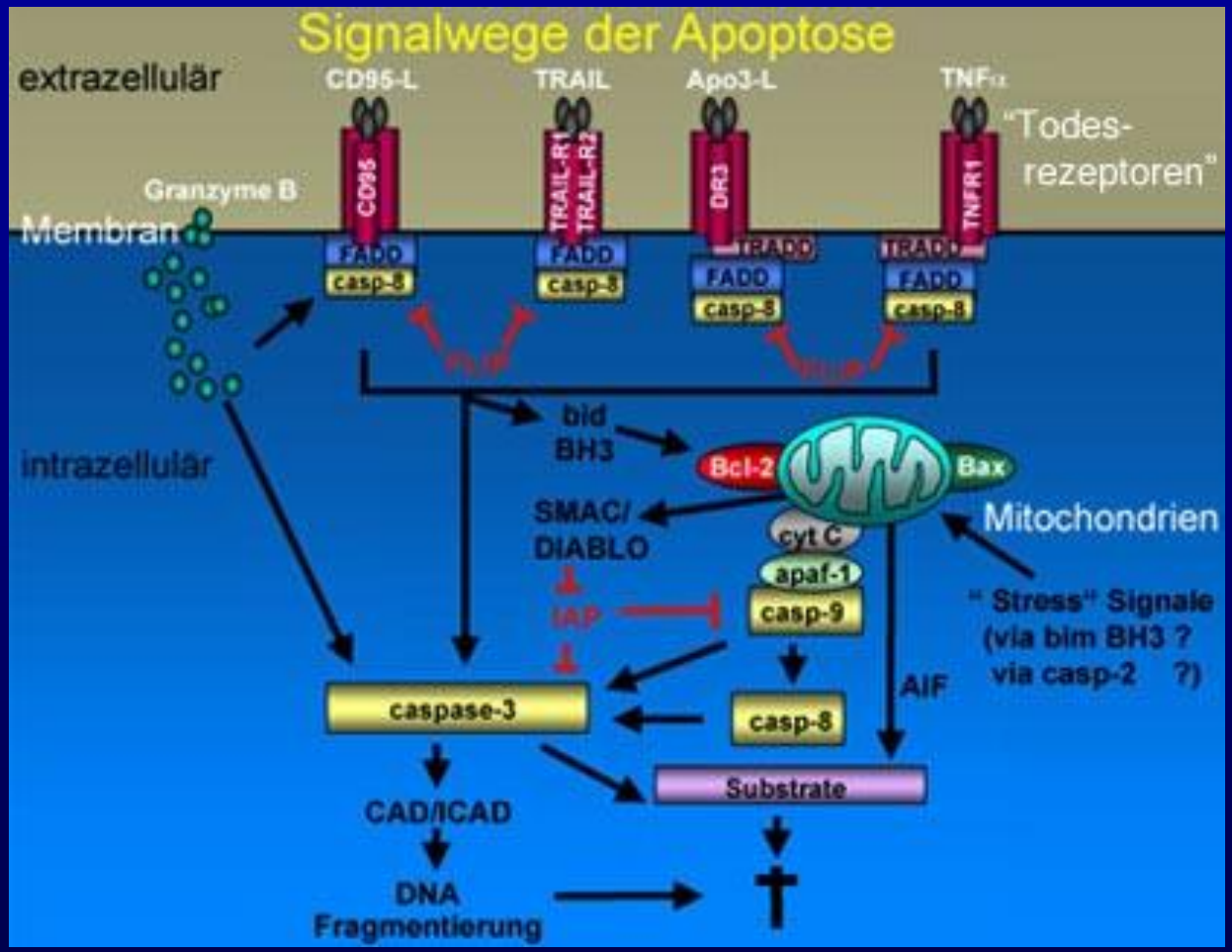




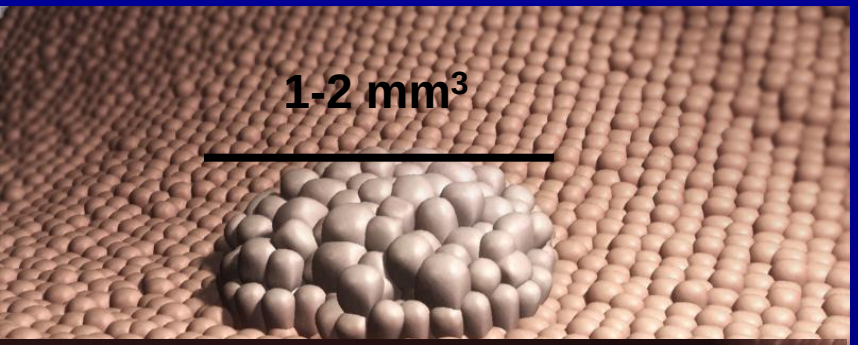


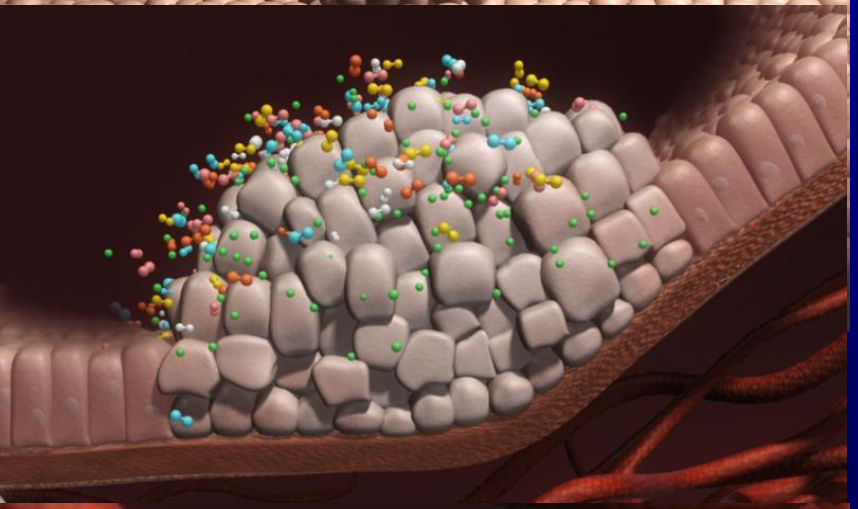


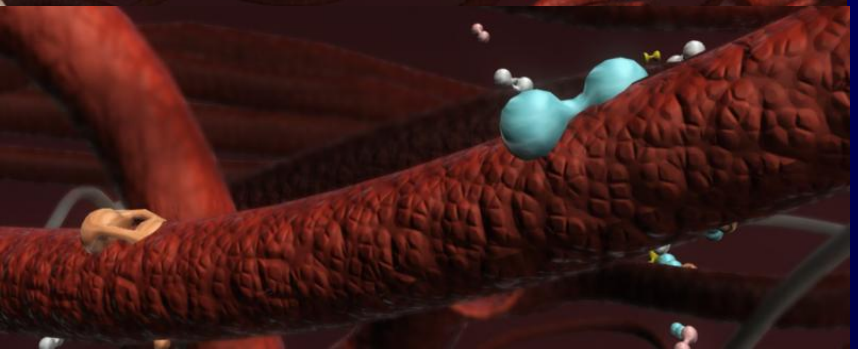
Apoptose


Signalwege der Apoptose
extrazellulär
CD95-L
TRAIL
Apo3-L
TNFα
"Todes-rezeptoren"
Granzyme B
Membran
CD95
TRAIL-R1
TRAIL-R2
DR3
TNFR1
FADD
casp-8
TRADD
intrazellulär
bid
BH3
Bcl-2
Bax
Mitochondrien
SMAC/
DIABLO
cyt C
apaf-1
casp-9
IAP
" Stress" Signale
(via bim BH3 ?
via casp-2 ?)
AIF
caspase-3
casp-8
Substrate
CAD/ICAD
DNA
Fragmentierung

ANGIOGÊNESE: FUNDAMENTAL NO DESENVOLVIMENTO TUMORAL





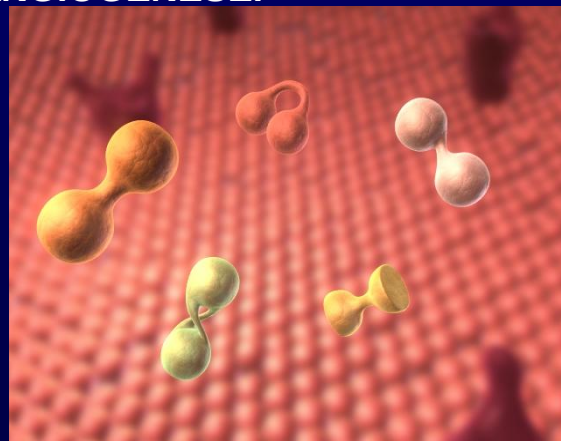


1- TUMOR MAIOR QUE 1 A 2 MM^3 NECESSITA DA FORMAÇÃO DE NOVOS VASOS,

2- A ANGIOGÊNESE INCIA-SE QUANDO O TUMOR, DEVIDO HIPÓXIA OU OUTROS ESTÍMULOS, SECRETA FATORES ANGIOGÊNICOS,

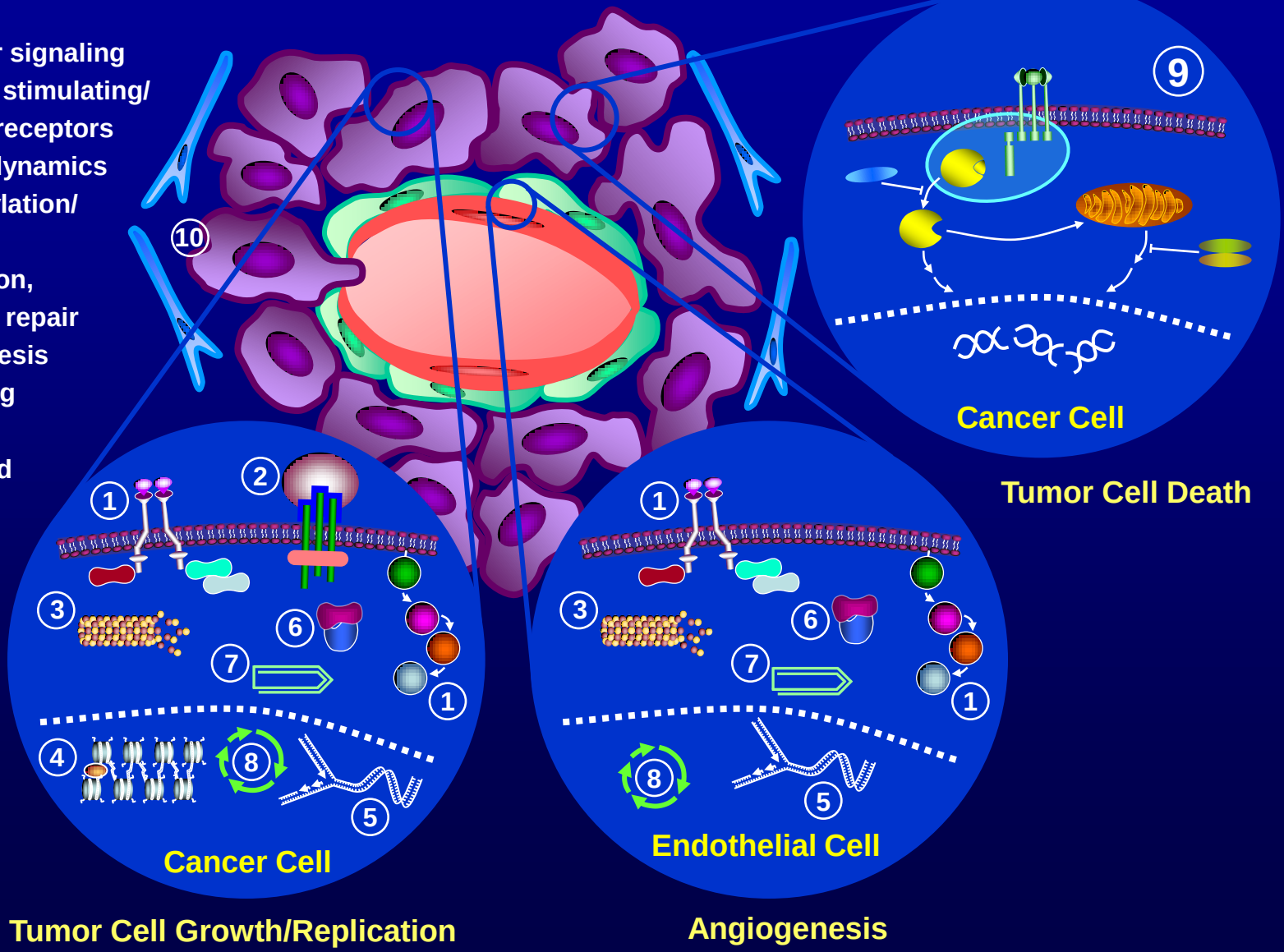
3- OS FATORES ANGIOGÊNICOS AGEM SOBRE AS CÉLULAS ENDOTELIAIS ESTIMULANDO SEU CRESCIMENTO, DIVISÃO E RESULTANDO NA FORMAÇÃO DE NOVOS VASOS,

4- A FAMÍLIA DOS FATORES DE CRESCIMENTO VEGF SECRETADA PELO TUMOR É UMA DAS MAIS IMPORTANTES MOLÉCULAS ESTIMULADORAS DE ANGIOGÊNESE E LINFANGIOGÊNESE.

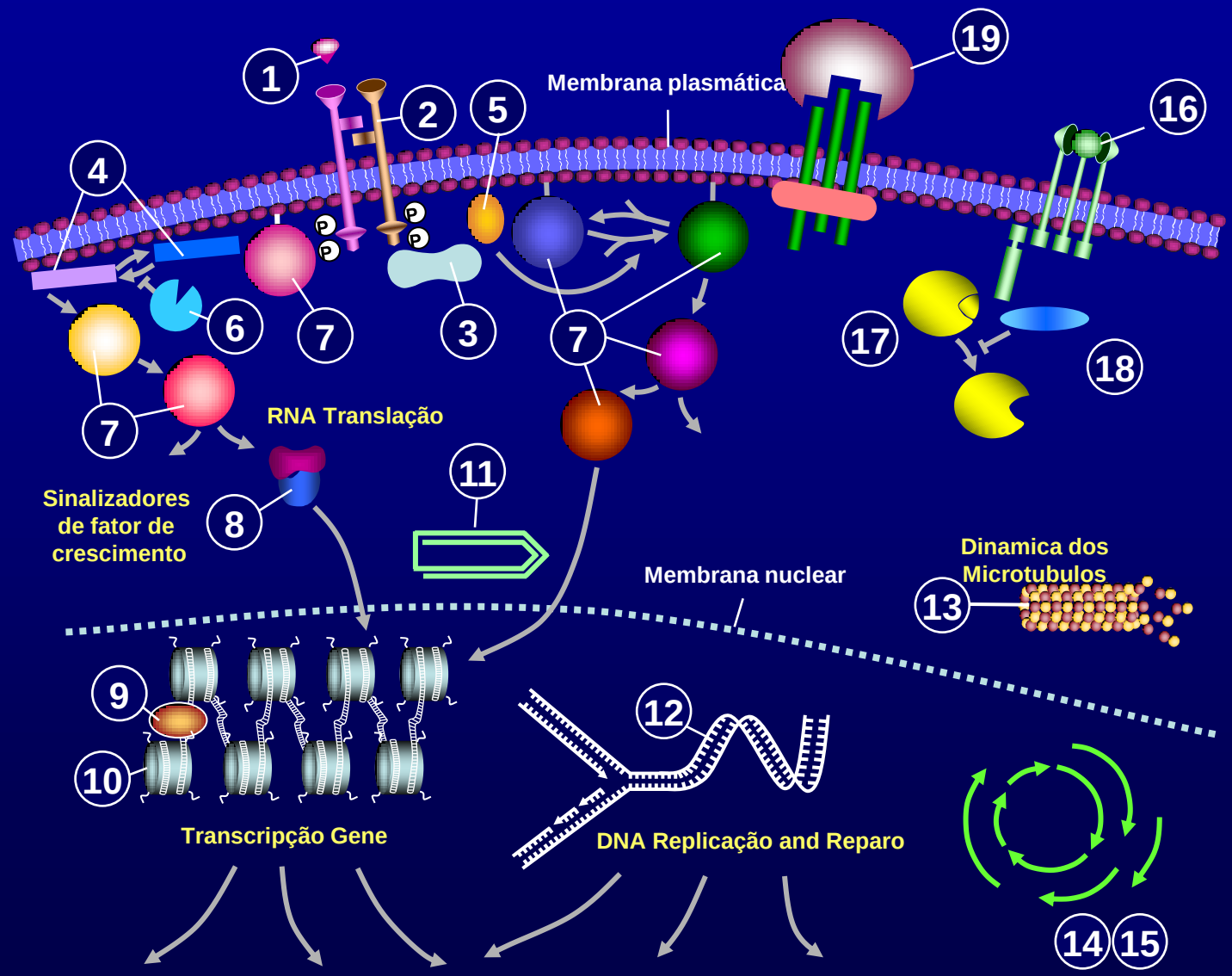


Alvos para terapia

1. Growth factor signaling
2. Other growth stimulating/ suppressing receptors
3. Microtubule dynamics
4. Histone acetylation/ deacetylation
5. DNA replication, transcription, repair
6. Protein synthesis
7. Protein folding
8. Cell cycle
9. Activators and inhibitors of apoptosis
10. Metastasis

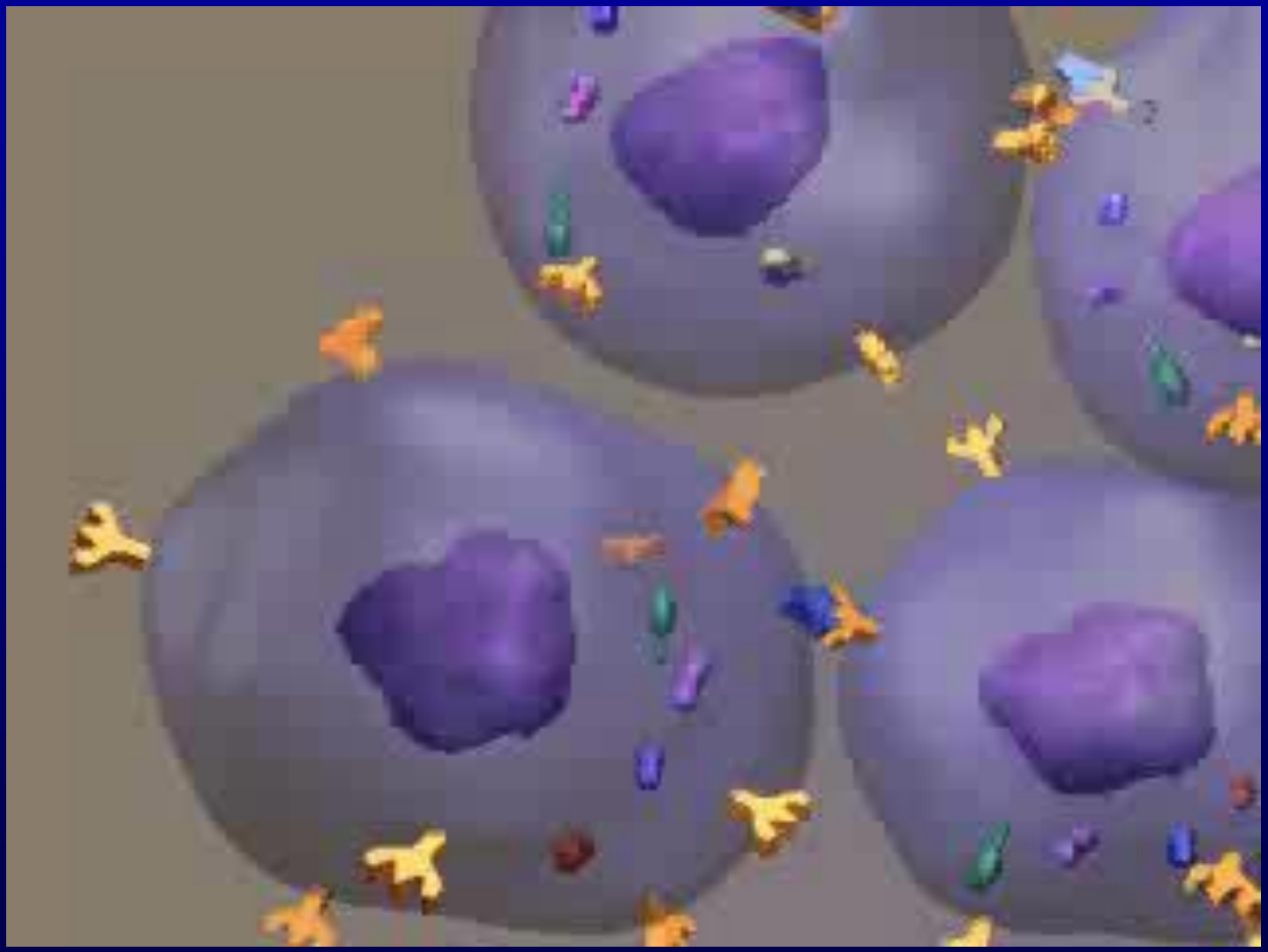


Célula Tumoral

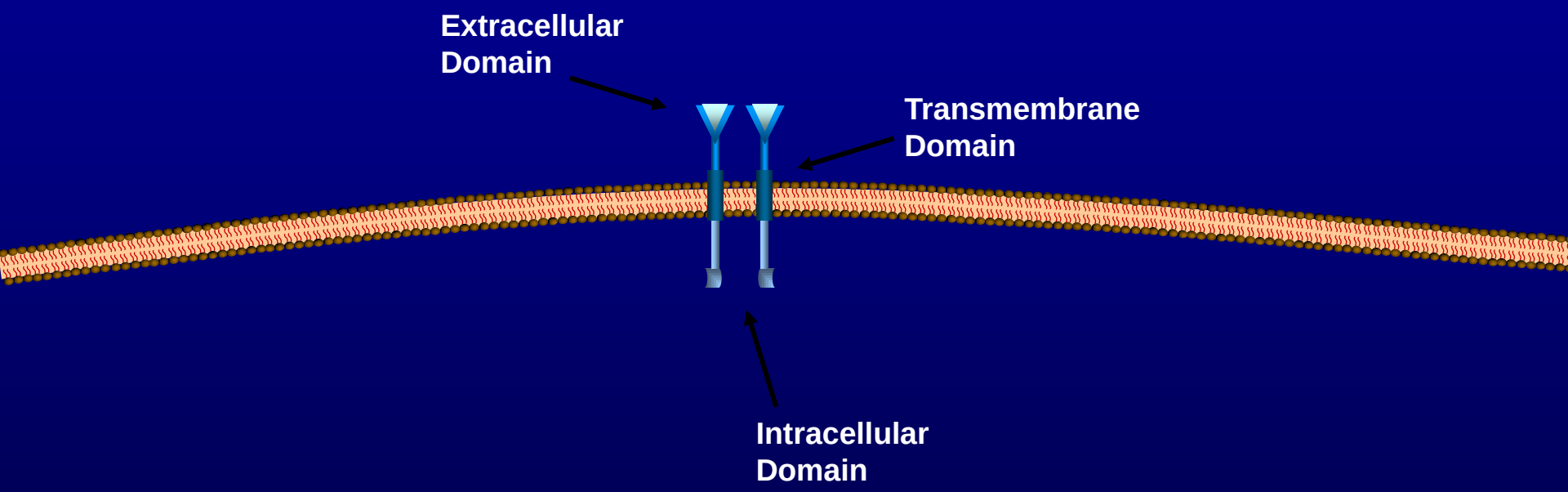


1. Growth factors
2. Growth factor receptors
3. Adaptor proteins
4. Docking proteins/ binding proteins
5. Guanine nucleotide exchange factors
6. Phosphatases and phospholipases
7. Signaling kinases
8. Ribosomes
9. Transcription factors
10. Histones
11. Molecular chaperones
12. DNA
13. Microtubules
14. Cyclins
15. Cyclin-dependent kinases
16. Cell death receptors
17. Apoptosis-effector caspases
18. Caspase inhibitors
19. CD40-CD40L

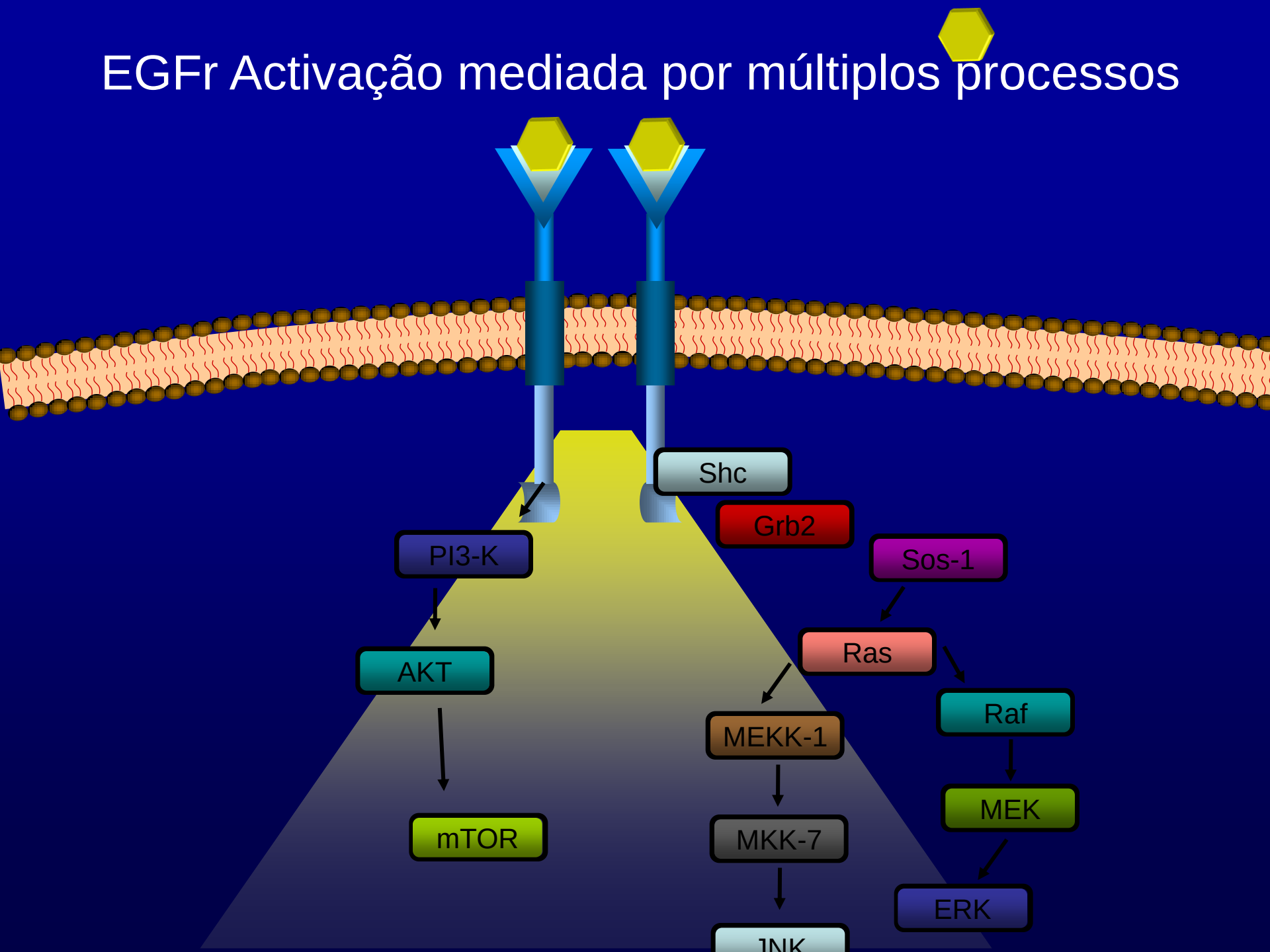
Transdução do Sinal



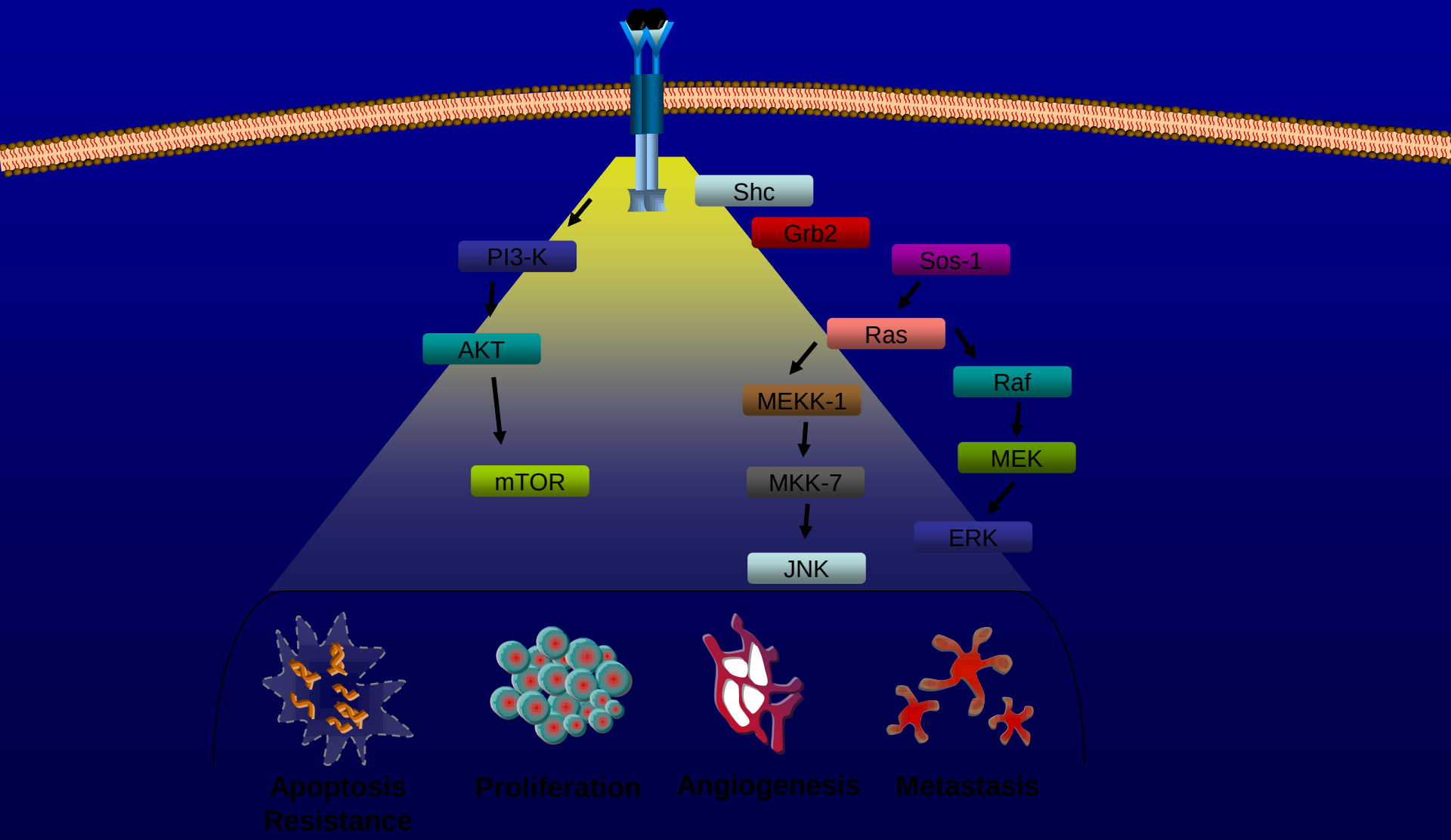
Processo de sinalizaçao EGFR



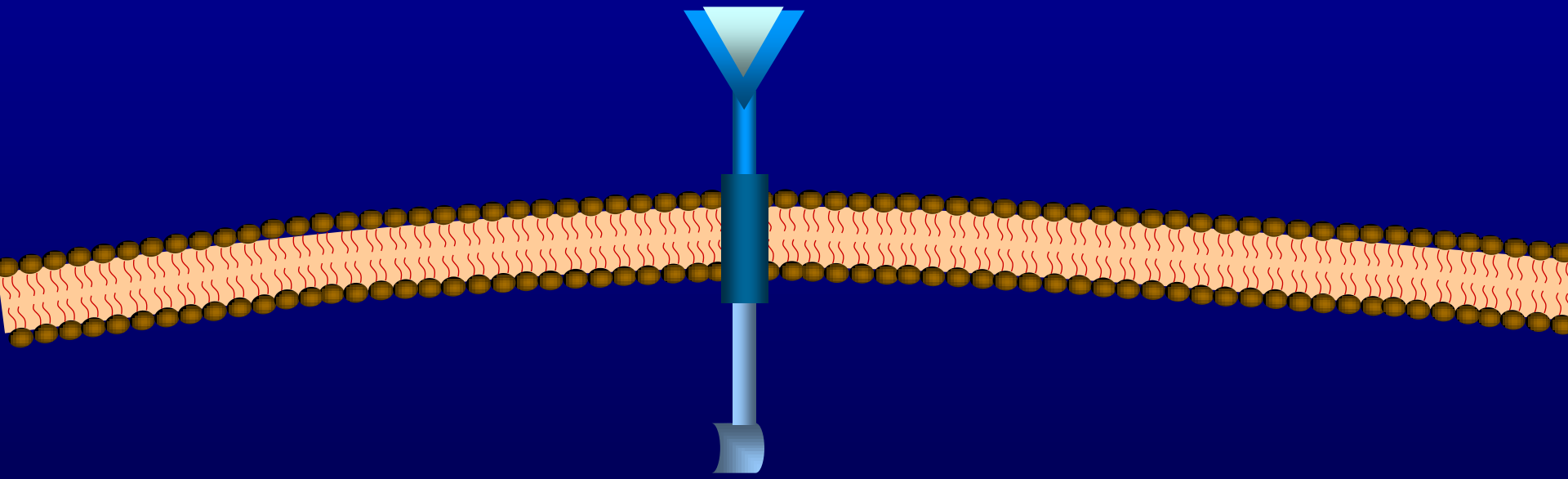
EGFr Activação mediada por múltiplos processos



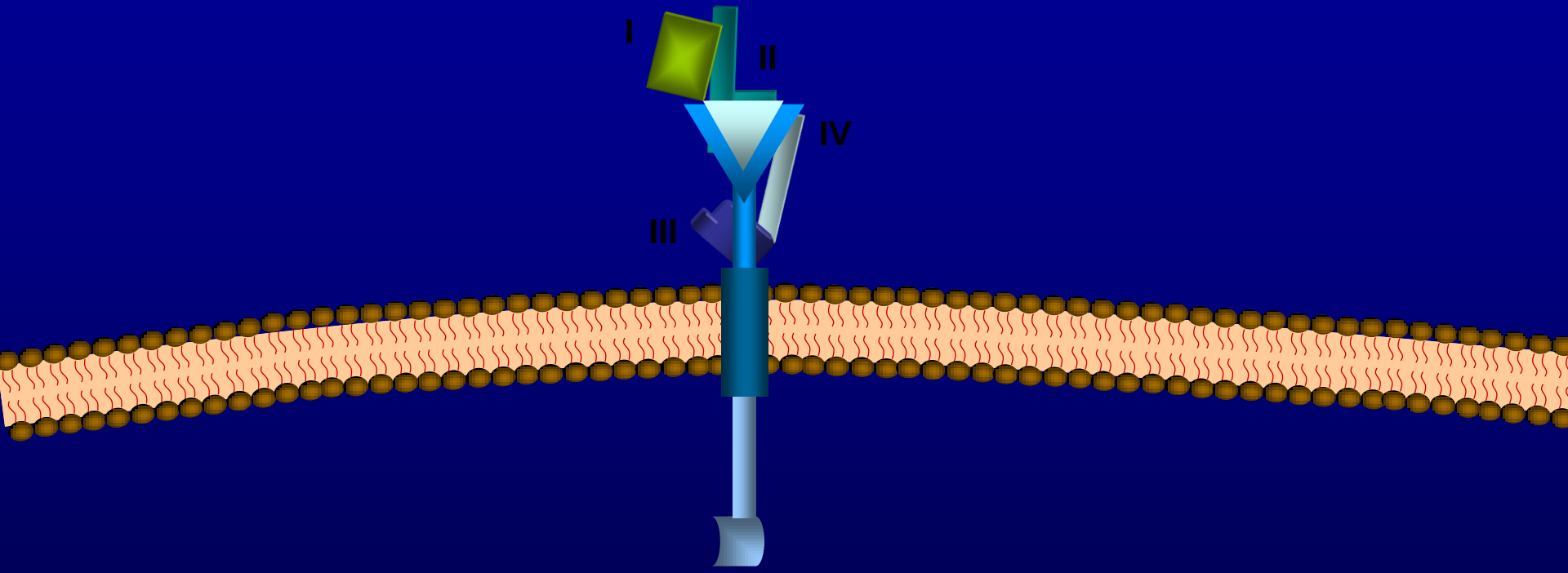
EGFr Activação mediada por múltiplos processos



EGFR

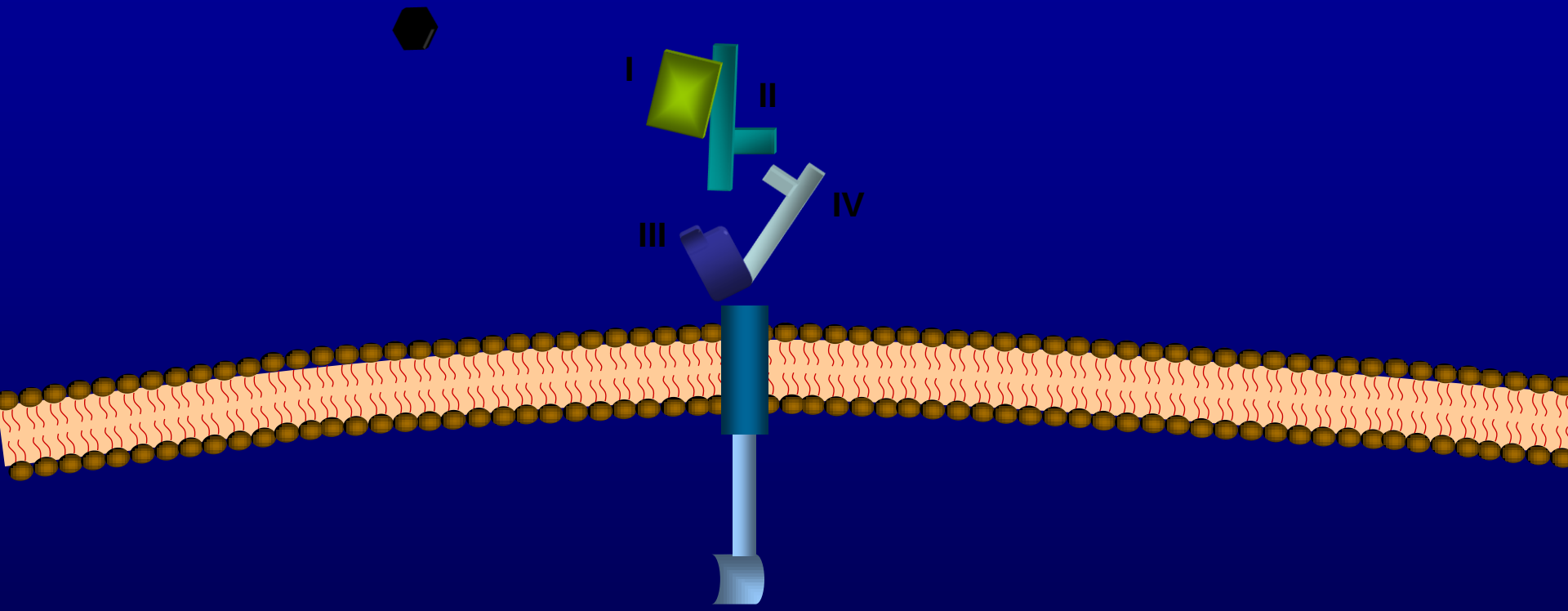


EGFR



Ferguson KM. Biochem Soc Trans. 2004;32:742-745.
Dawson JP, et al. Mol Cell Biol. 2005;25:7734-7742.

EGFR



Ferguson KM. Biochem Soc Trans. 2004;32:742-745.
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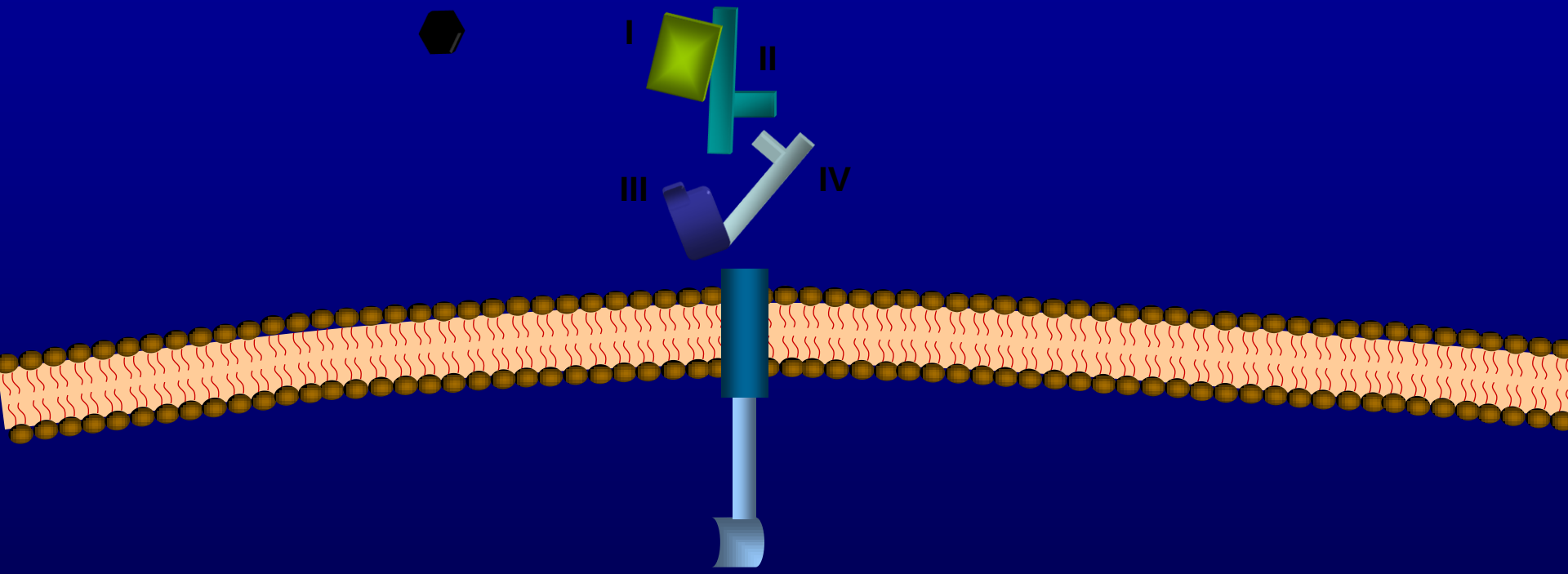
EGFR



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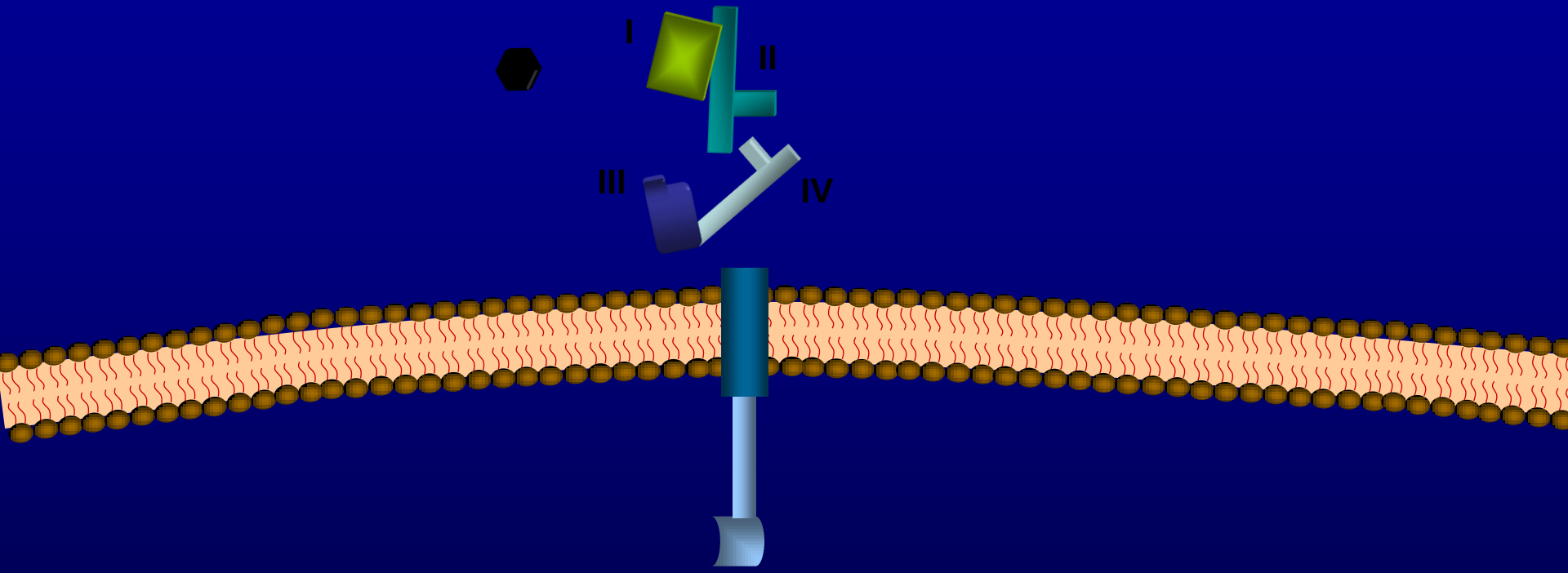
EGFR



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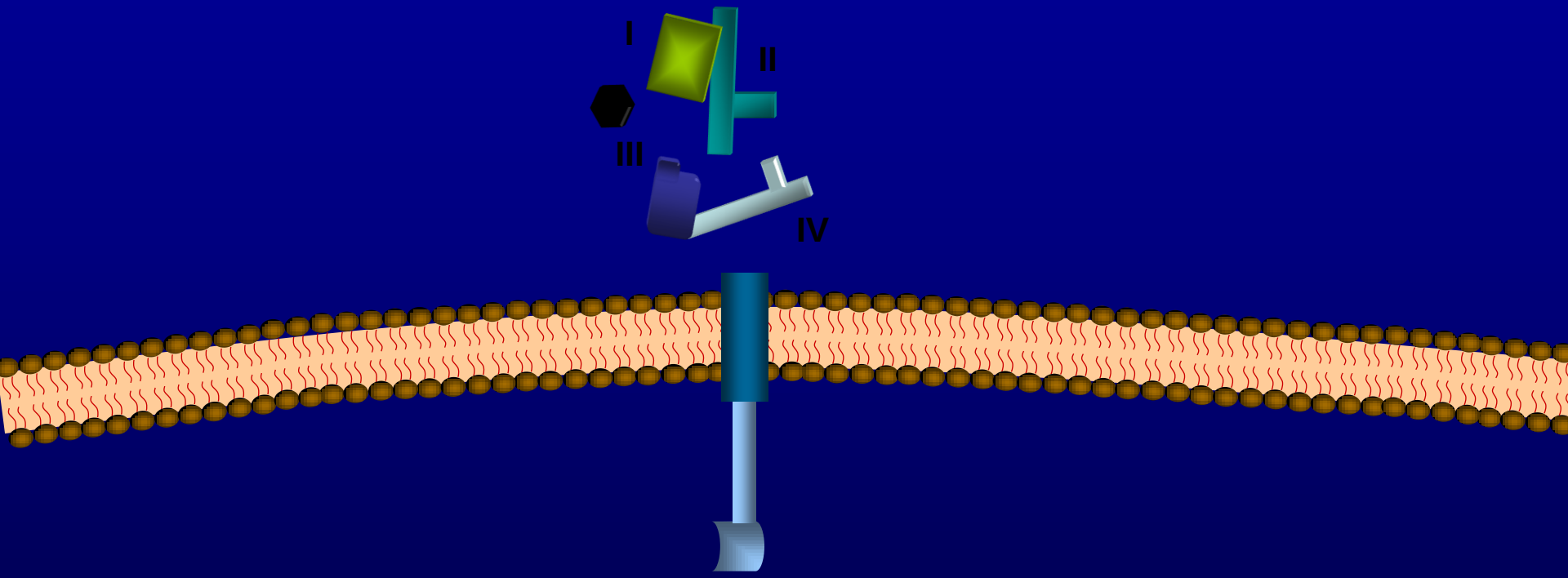
EGFR



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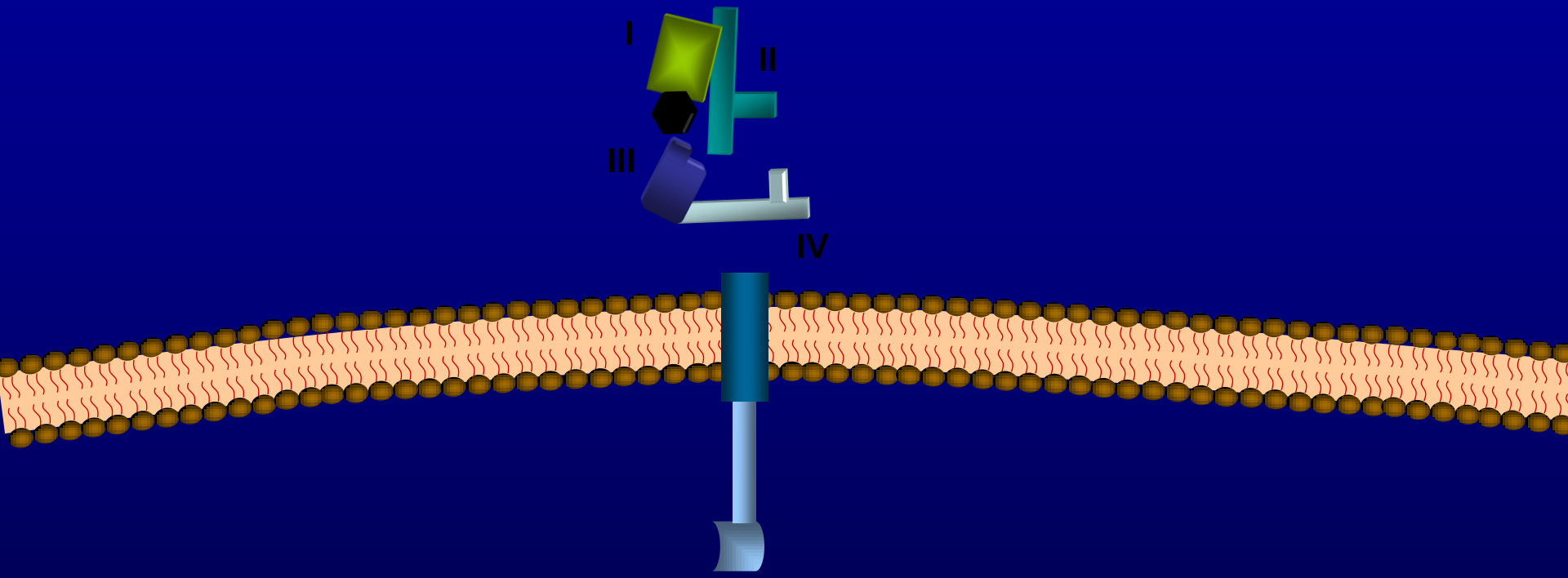
EGFR



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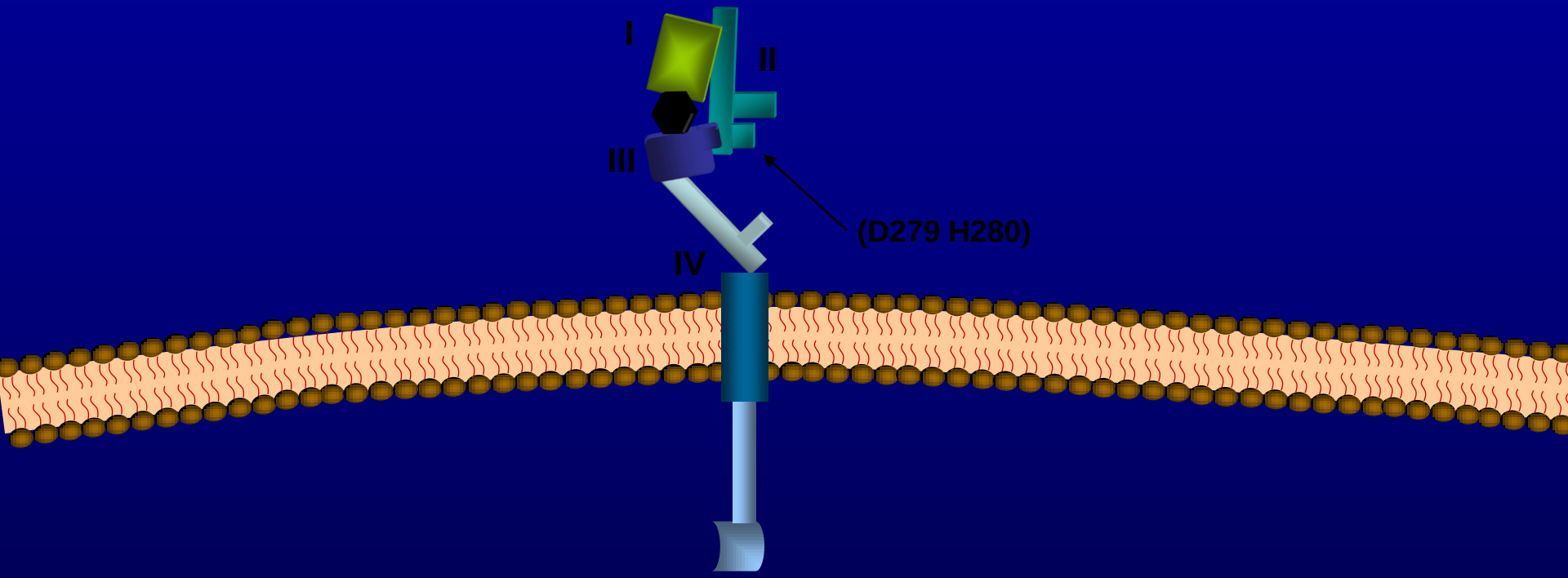
Dawson JP, et al. Mol Cell Biol. 2005;25:7734-7742.

EGFR



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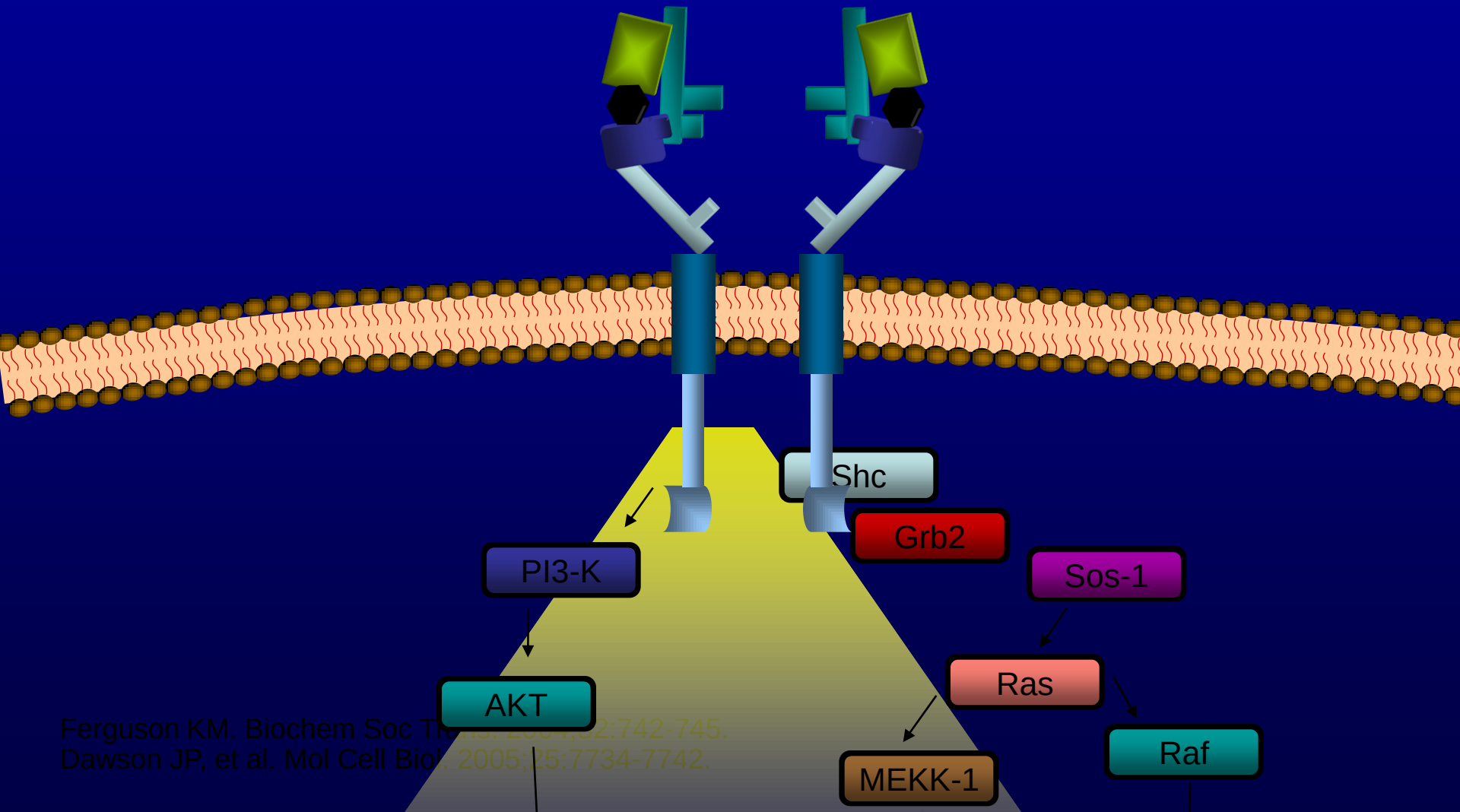
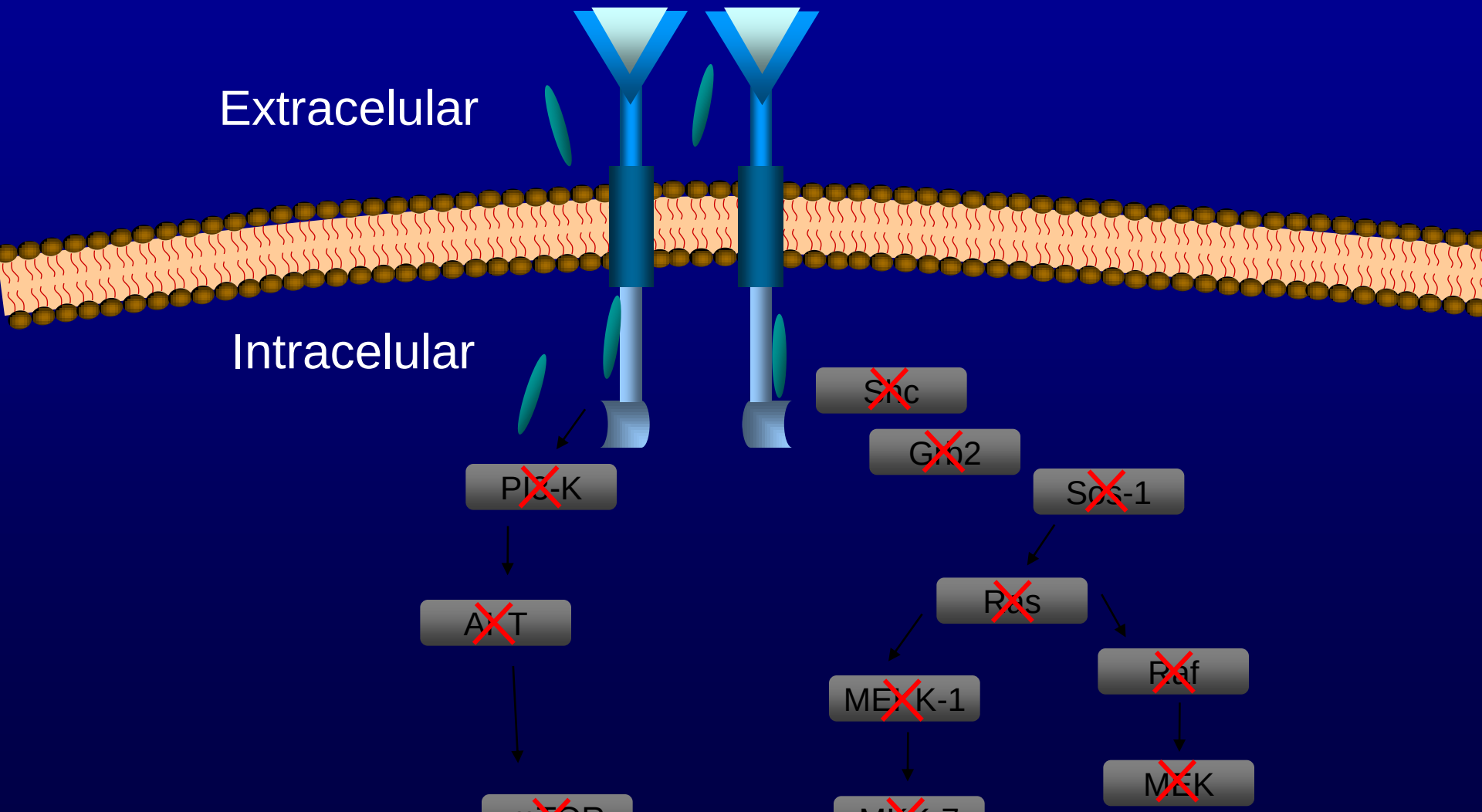
EGFR

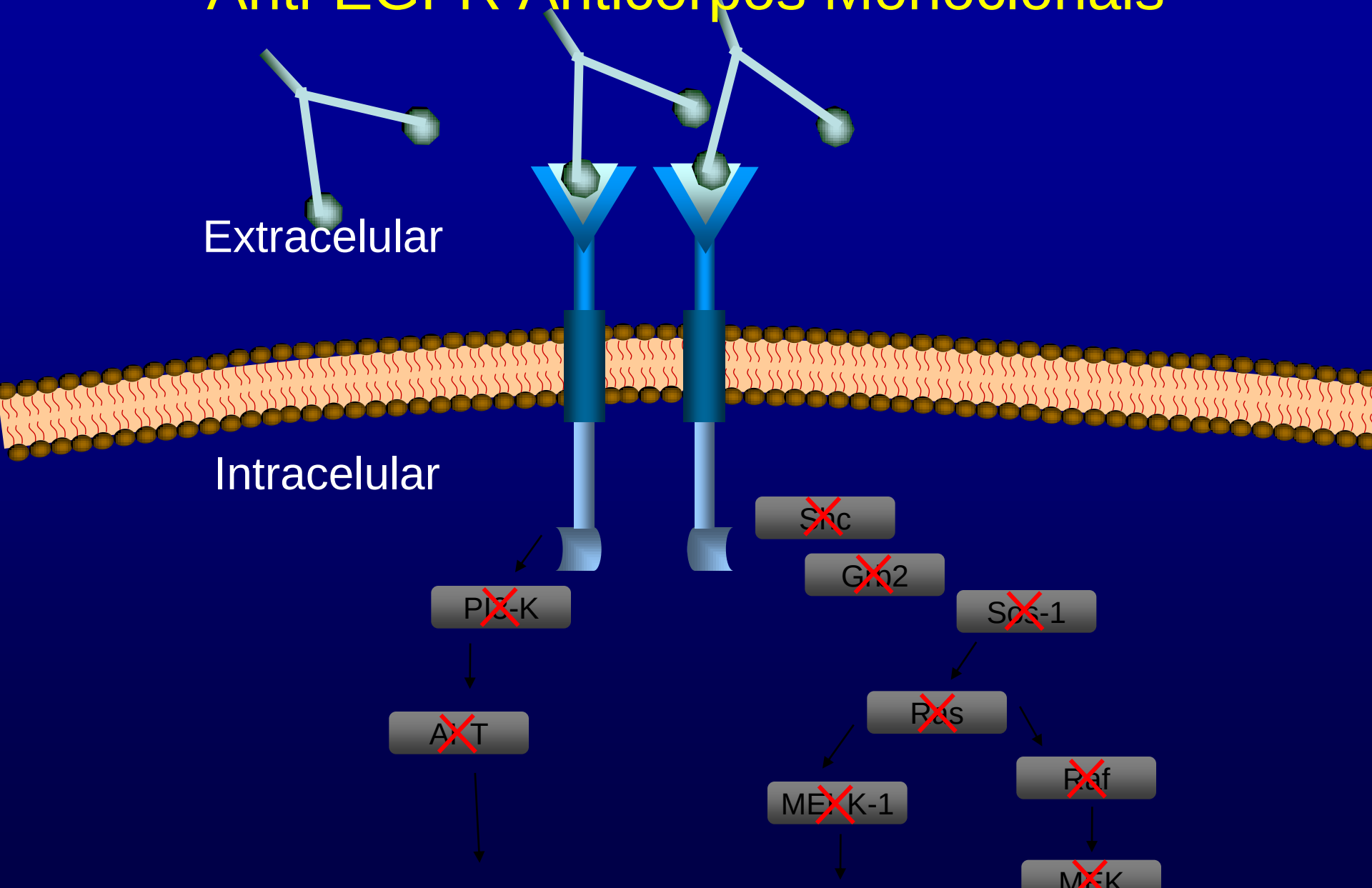


Ferguson KM. Biochem Soc Trans 2008;36:742-745.
Dawson JP, et al. Mol Cell Biol 2005;25:7734-7742.

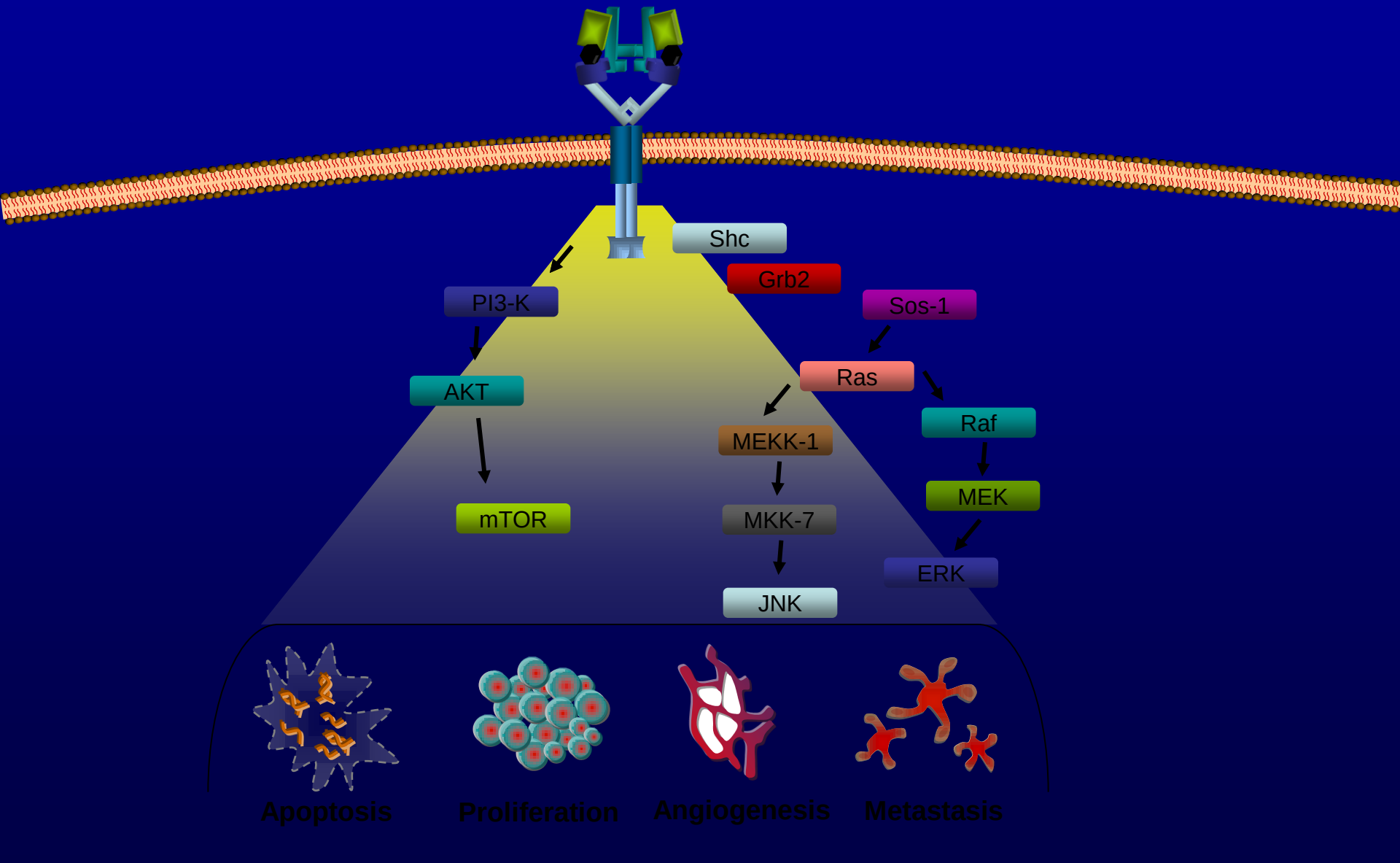
EGFR TK Inibidores



Anti-EGFR Anticorpos Monoclonais



Qual melhor alvo?



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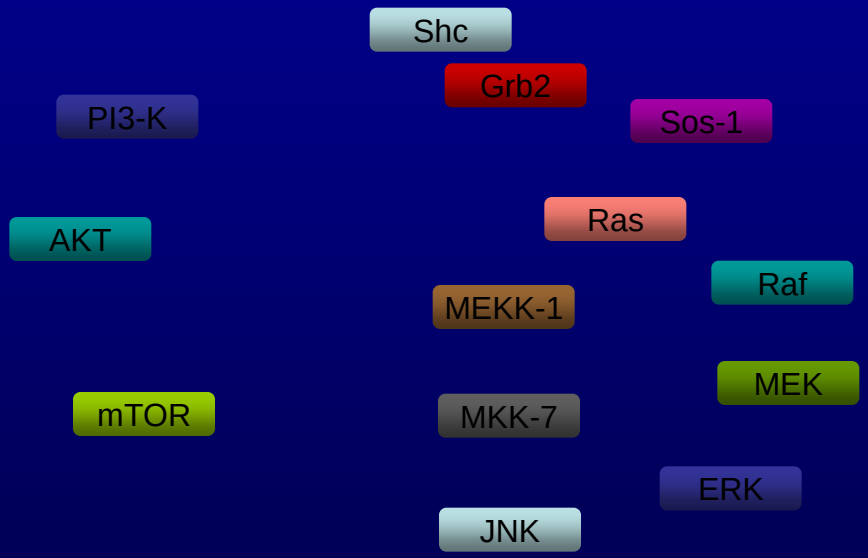
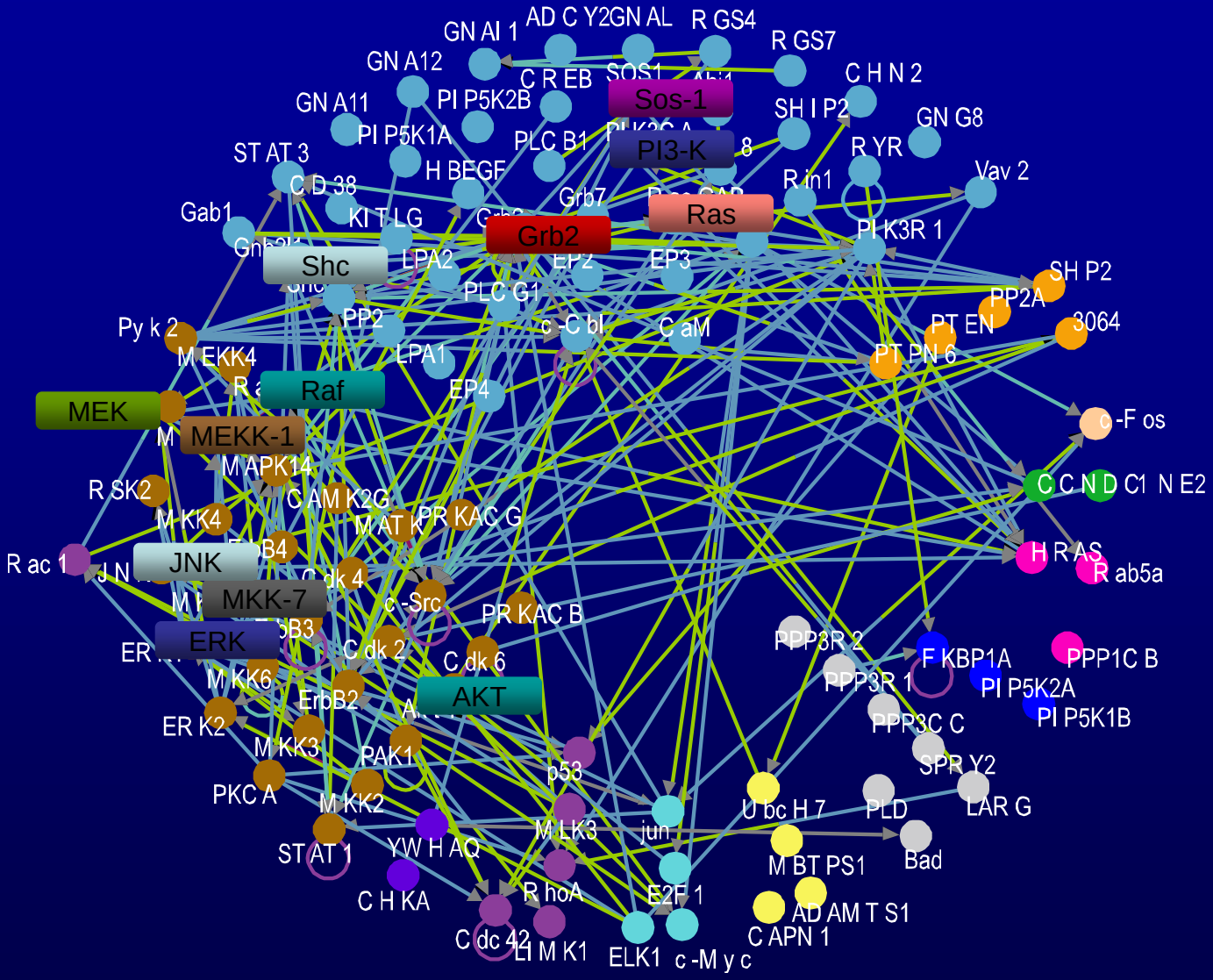


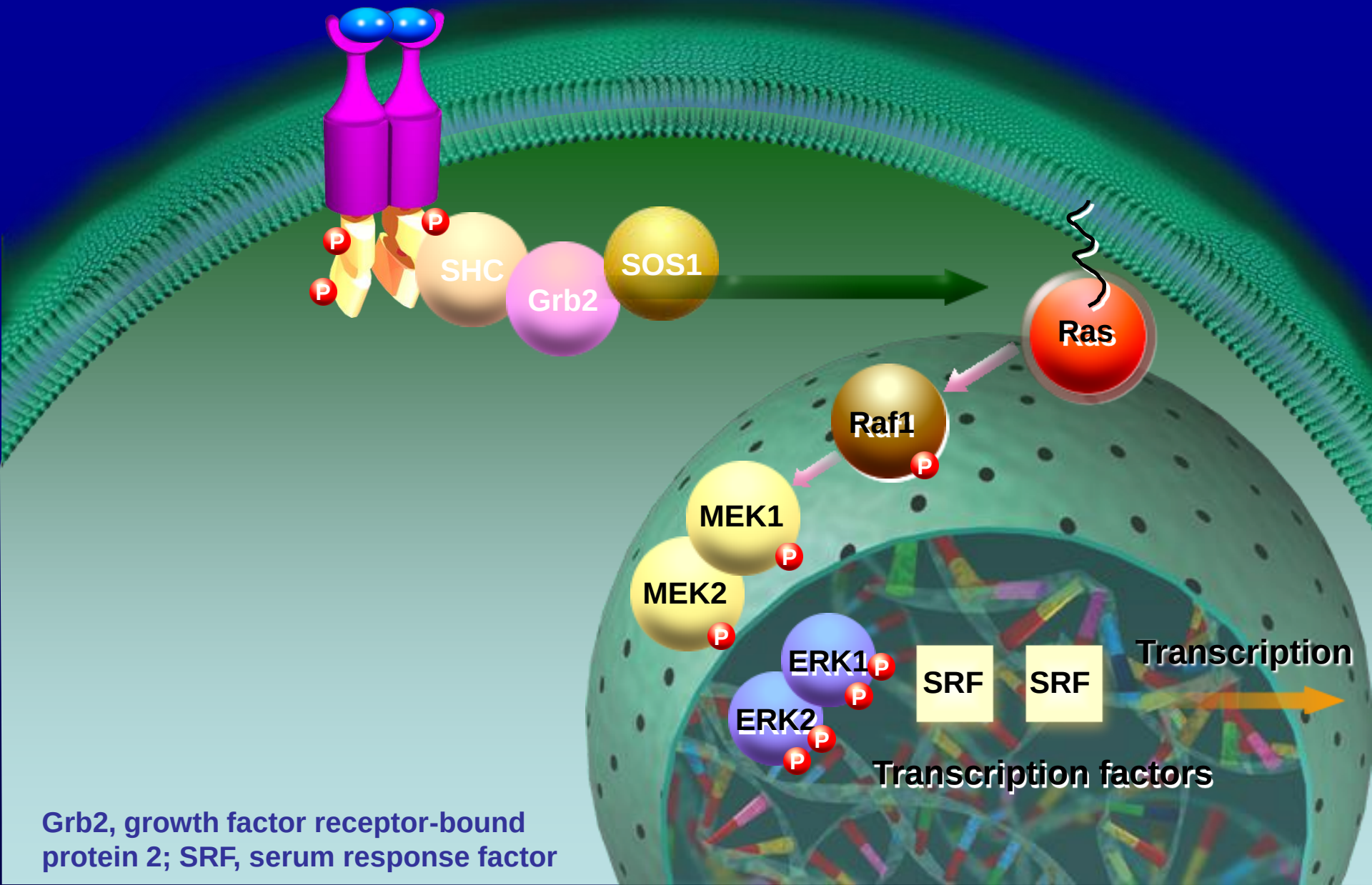


Courtesy of I. Serebriiskii and E. Golemis, Fox Chase Cancer Center.

Possilidades terapêuticas do EGFR

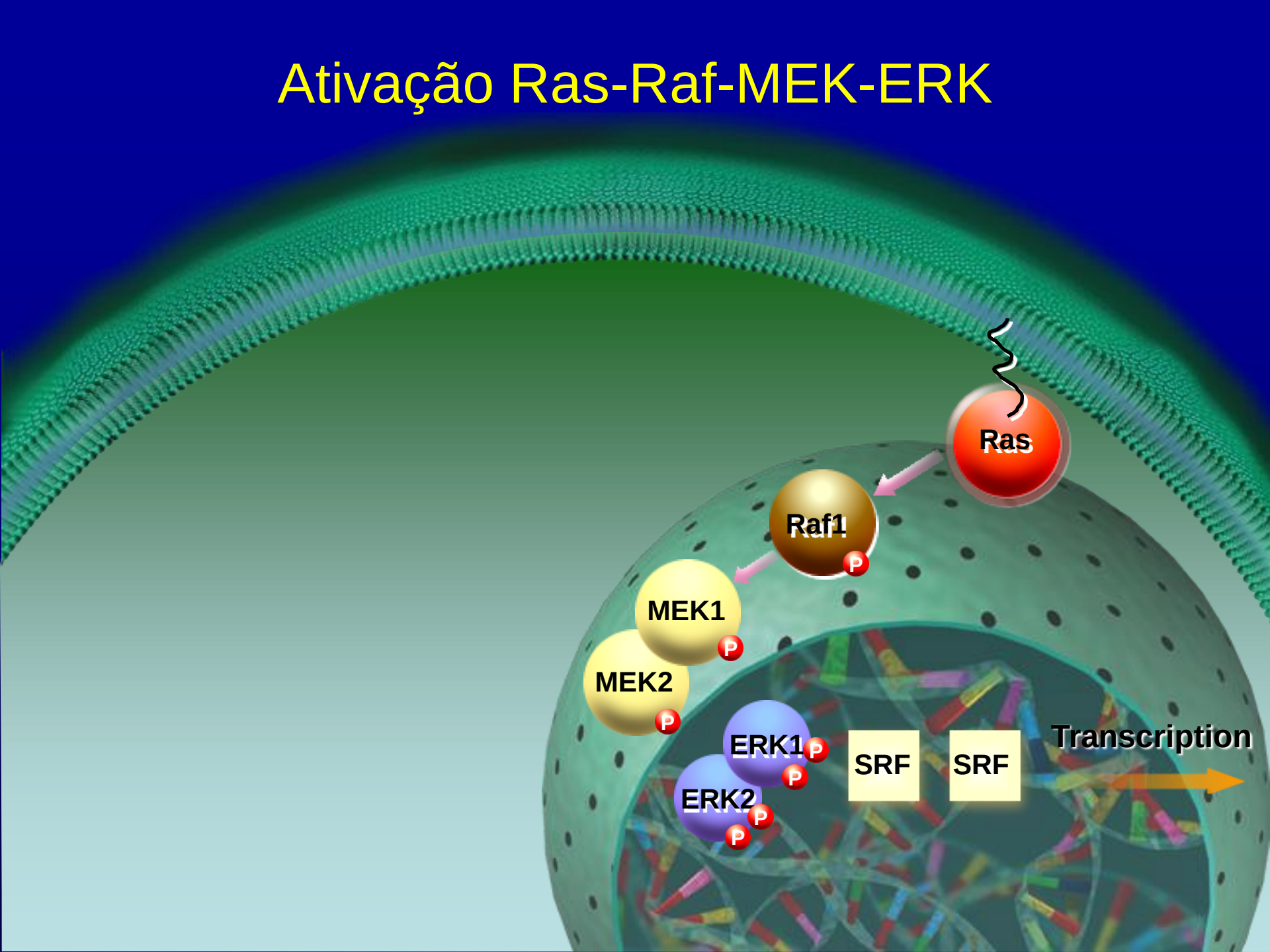
- Moléculas pequenas
  - Erlotinib, gefitinib
  - EGFR tyrosine kinase mutations identify responsive subsets in NSCLC
- Anticorpos monoclonais
  - Cetuximab
  - Panitumumab
  - Others
    - Allosteric conformational change inhibitors
    - Sheddase inhibitors

Função MEK1/2

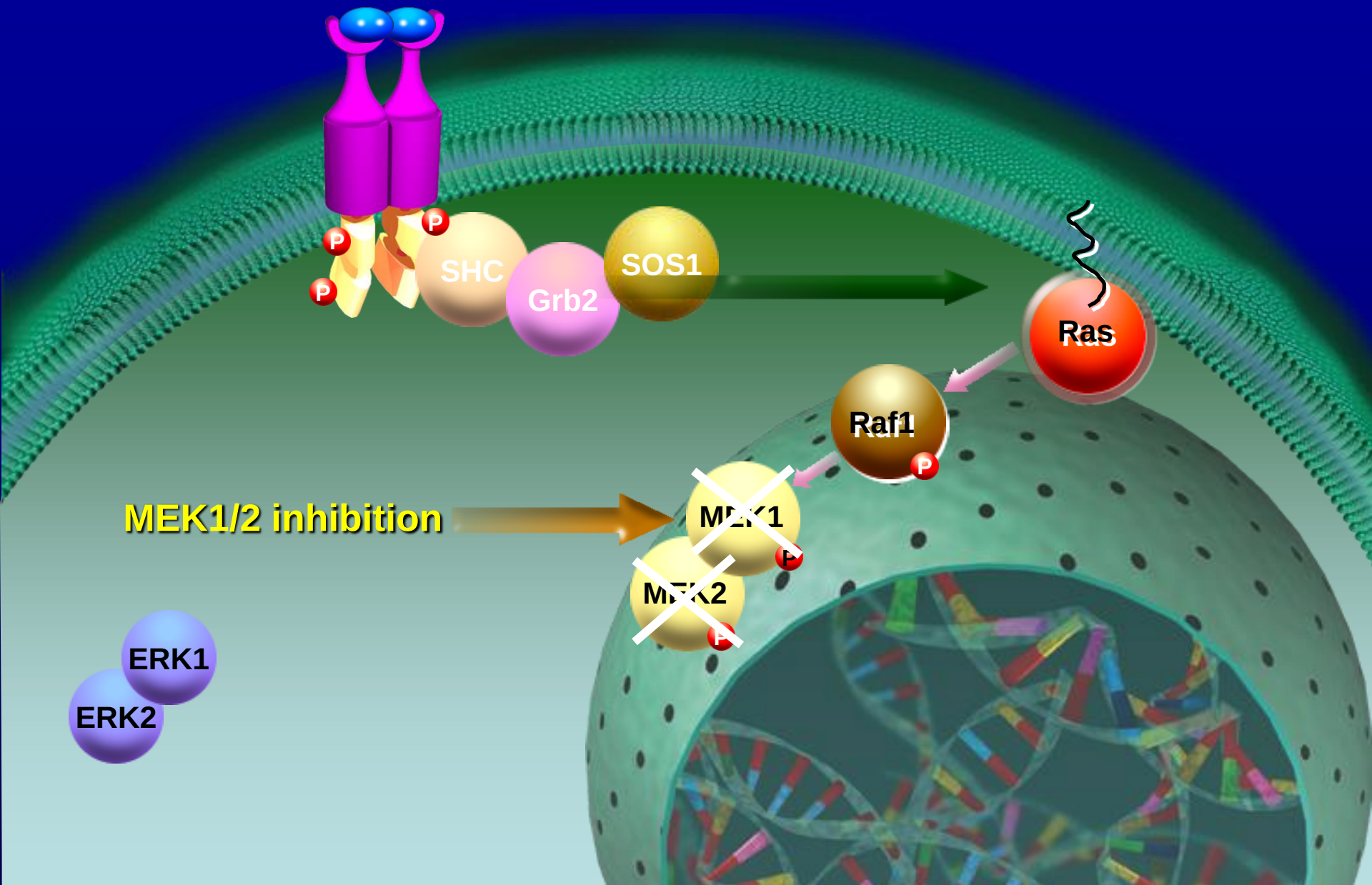


Grb2, growth factor receptor-bound protein 2; SRF, serum response factor

Ativação Ras-Raf-MEK-ERK



Inibição MEK1/2

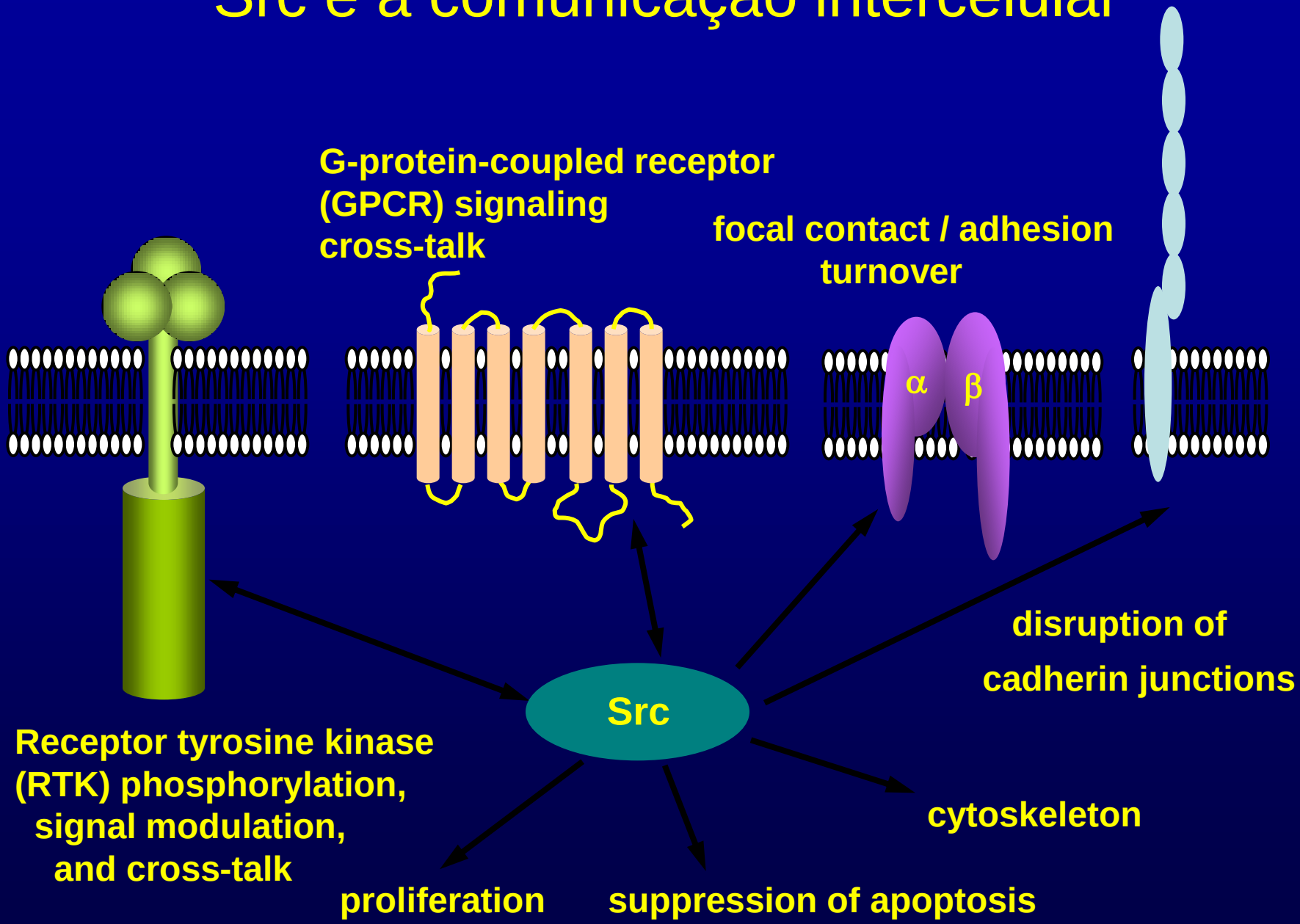


mTor

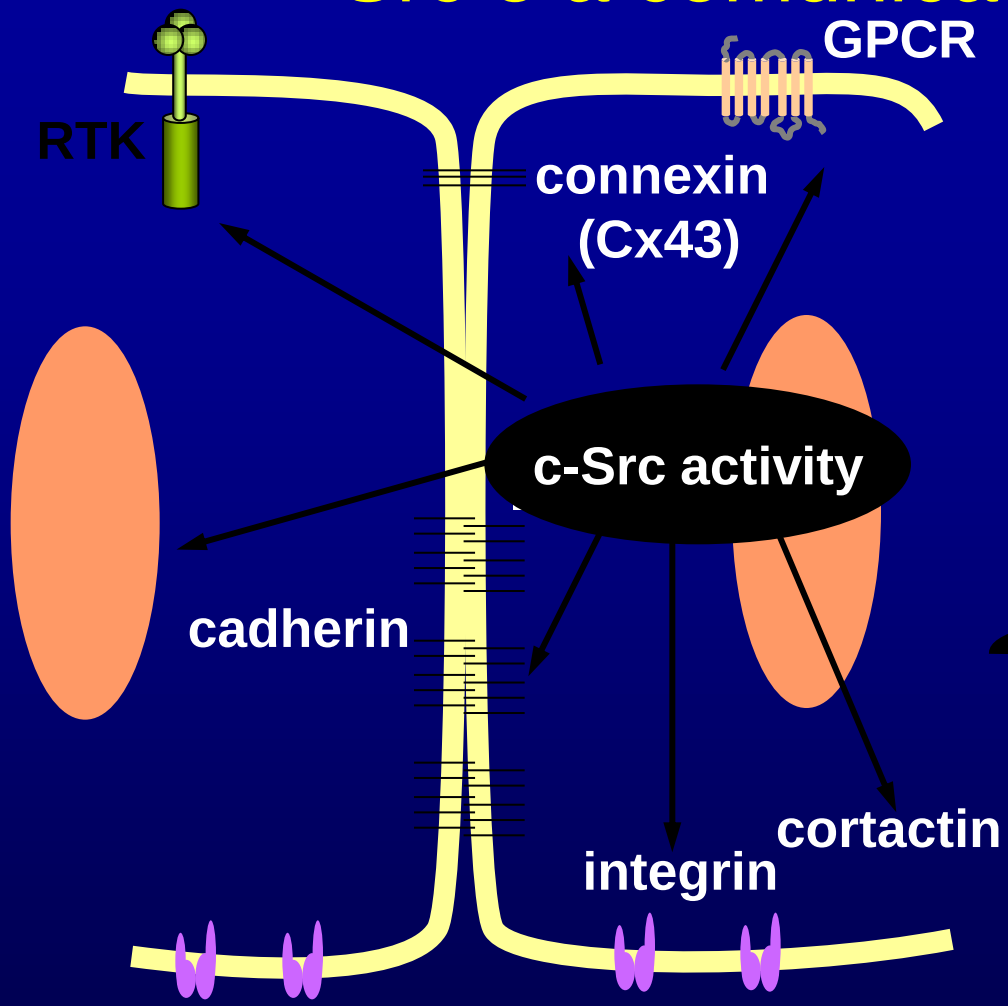
Microambiente tumoral

- Células normais e moléculas ao redor da célula tumoral
  - Fibroblastos
  - Cells precursoras dos vasos sanguineos
  - Céls imunológicas da circulação
  - Matrix extracelular
- Fatores de crescimento
- Oxigenação e ph

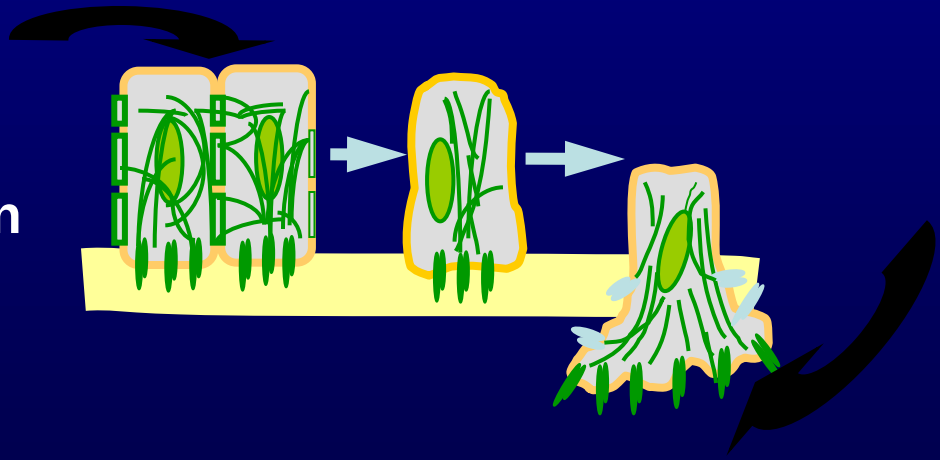
Src e a comunicação intercelular



Src e a comunicação intercelular



- Alteração na adesão entre células é um ponto chave na progressao tumoral e permite
  - proliferação
  - apoptose
  - invasão



Src: atividade elevada vários tumores

- Colon
- Mama
- Pâncreas
- Ovario
- Esophago
- Bexiga
- Melanoma
- Prostata
- Cabeça e pescoço

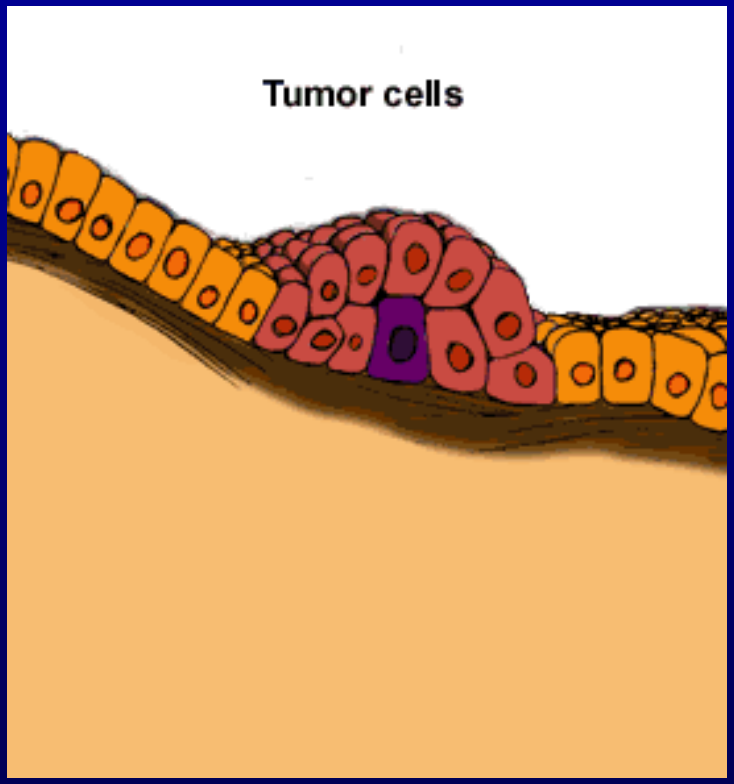
Trabalhos experimentais em andamento

Terapia Alvo

Epitélio

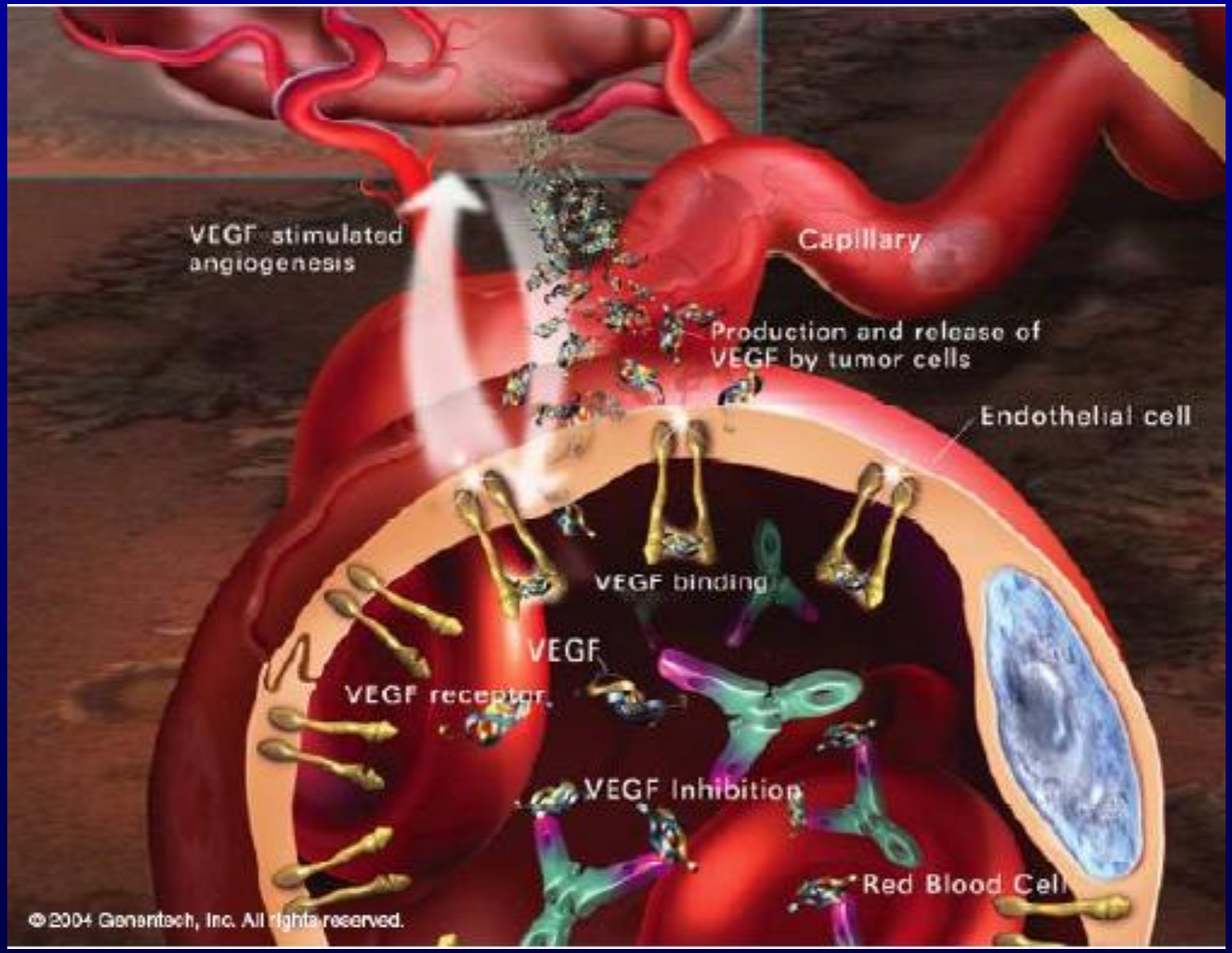
Membrana basal

Estroma



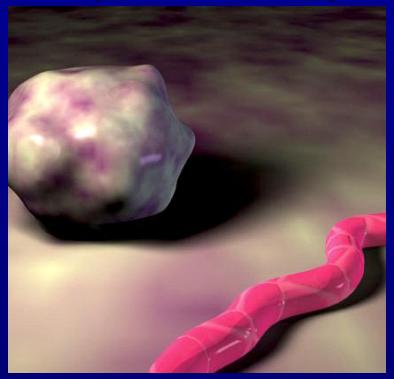
Evolução dos tumores

Angiogênesis



Angiogênese tumor

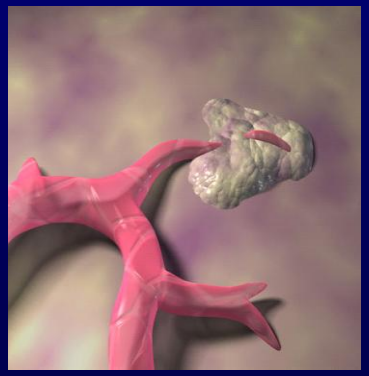
Fase avascular
Tumor 1 -2 mm
(dormência)



Estimulação
Pró-angiogênica

Fase vascular
Crescimento

Invasão vascular
Metástase



Angiogênese da
mestástases

Crescimento da
Metástase

Kerbel Nature Rev Cancer 2:727;2002

VEGF

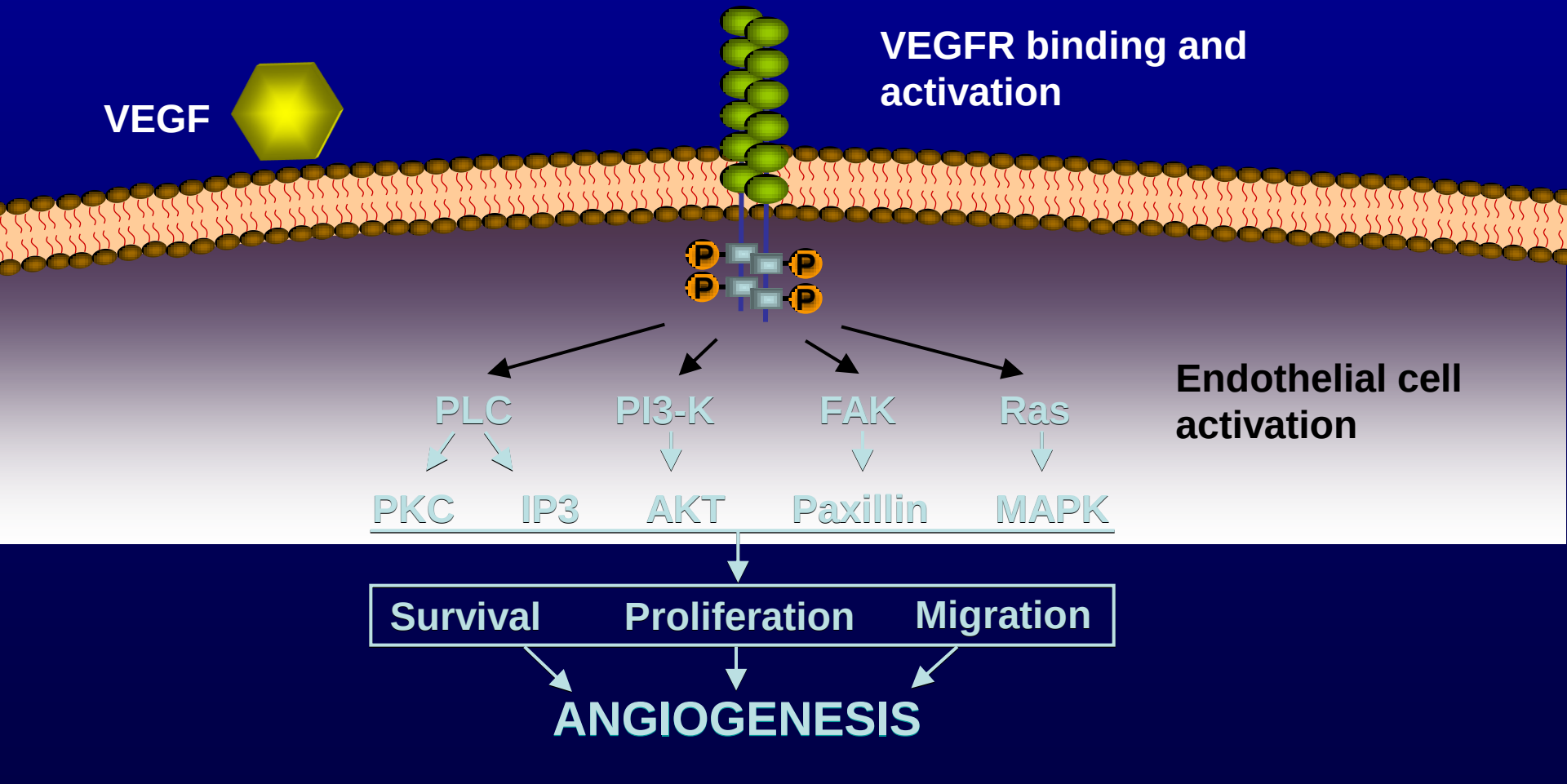
- Glicoproteina homodimérica
- Conhecida como VEGF-A
- Molecules relacionadas VEGF-B
  VEGF-C
  VEGF-D
- Peso molecular: 45,000Da
- Quatro isoformas
  - $VEGF_{121}$
  - $VEGF_{165}$*
  - $VEGF_{189}$
  - $VEGF_{206}$

Indução por isquemia

Hipoxia → HIFs → VEGF

(Fatores transcricionais induzidos por hipóxia)

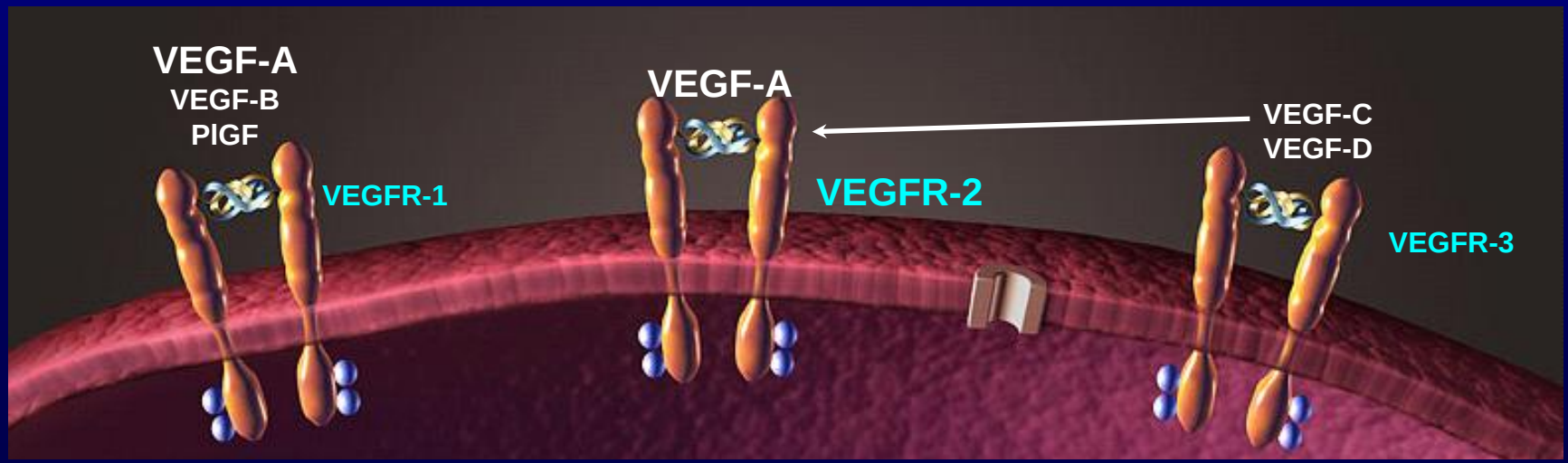
VEGF


VEGF
VEGFR binding and activation
P
P
P
P
PLC
PI3-K
FAK
Ras
PKC
IP3
AKT
Paxillin
MAPK
Endothelial cell activation
Survival
Proliferation
Migration
ANGIOGENESIS

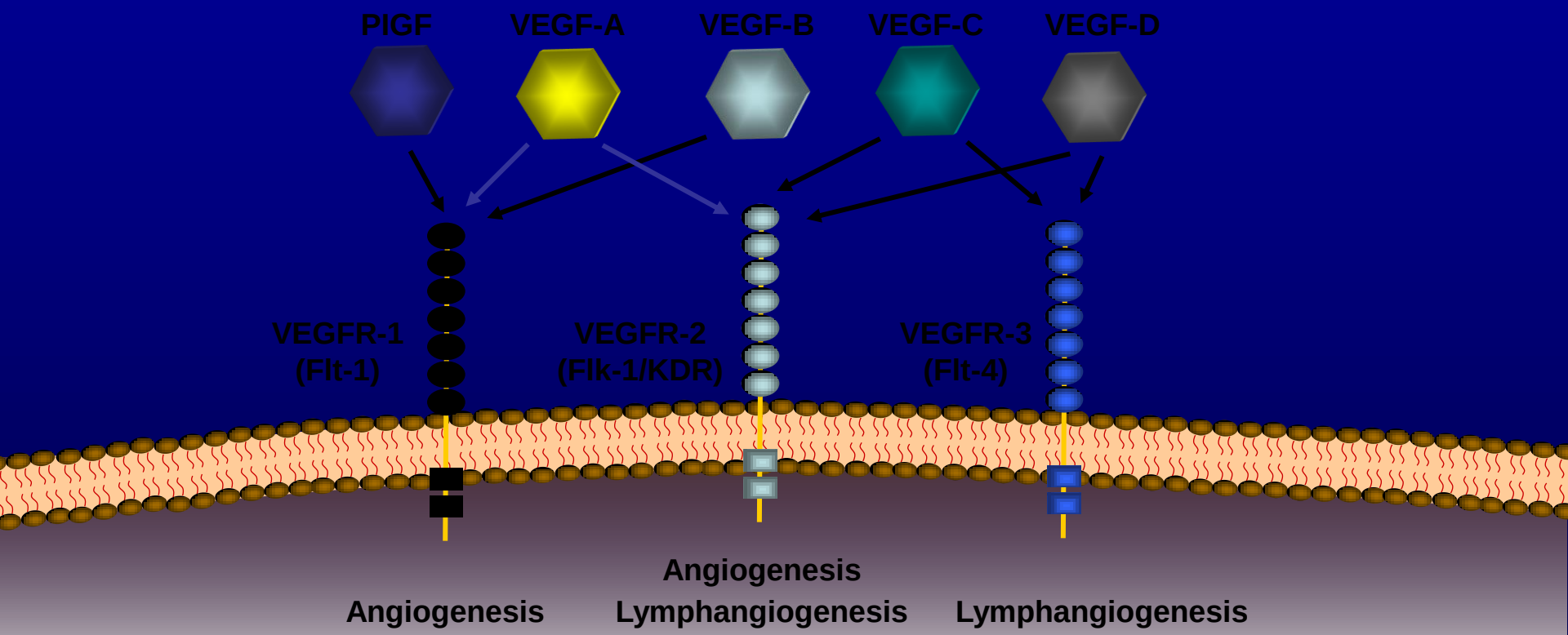
Família VEGF e Receptores

VEGFA	VEGFR2/1
VEGFC VEGFD	VEGFR2/3
VEGFB P1GF	VEGFR1

(Fator de crescimento placentário)

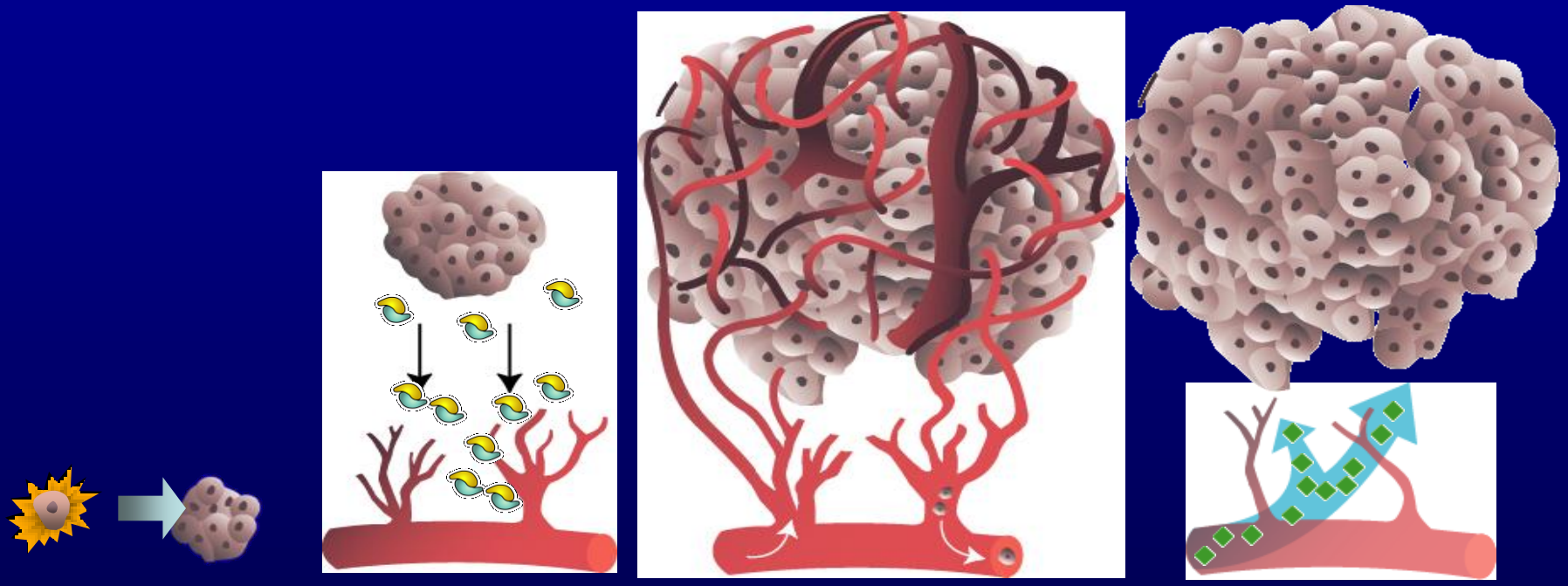


VEGF



Neufeld G, et al. FASEB J. 1999;13:9-22.

O efeito angiogênico e a terapia antiangiogênica



Somatic mutation

Small avascular tumor

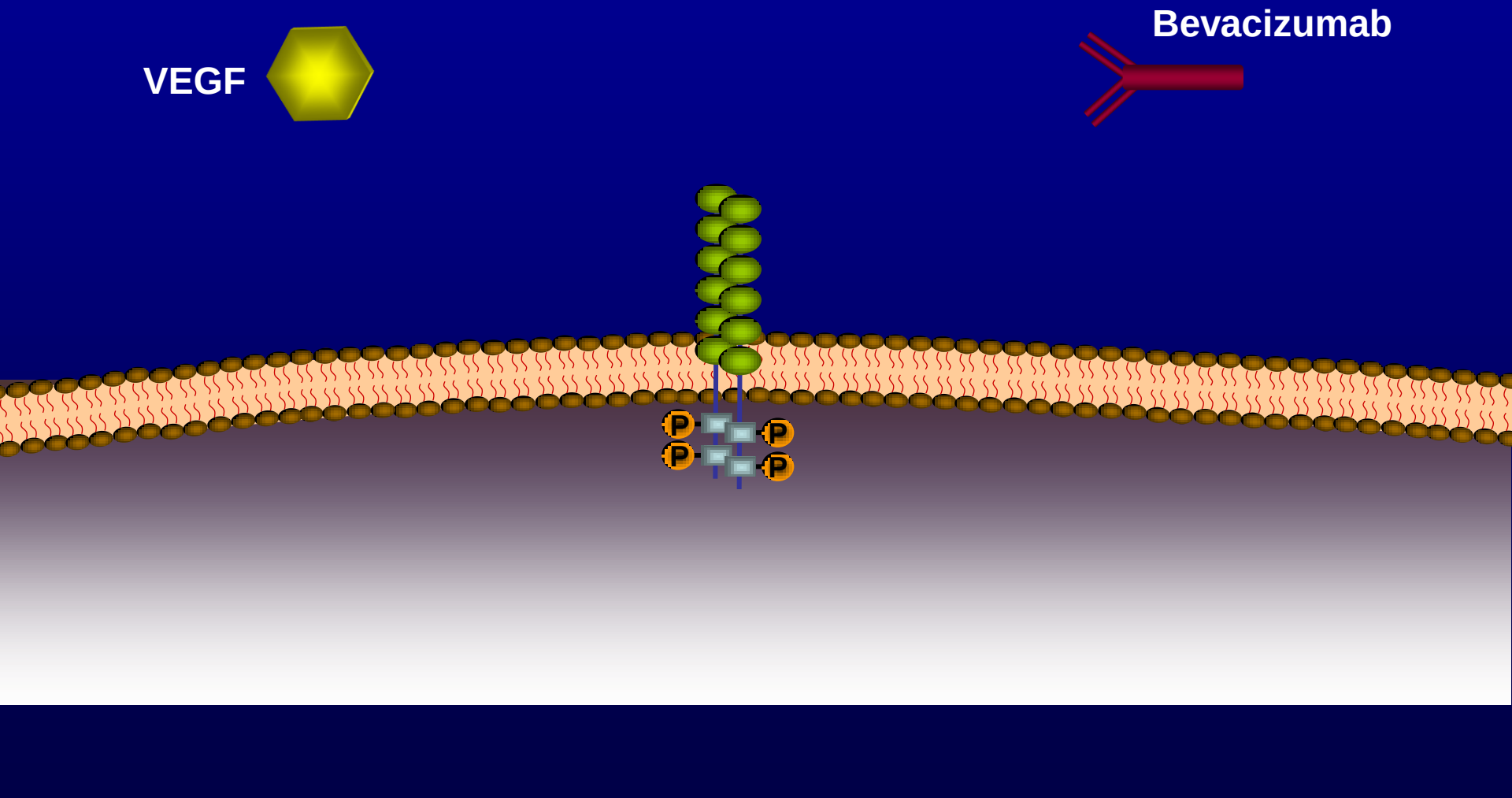
Tumor secretion of angiogenic factors stimulates angiogenesis

Rapid tumor growth and metastasis

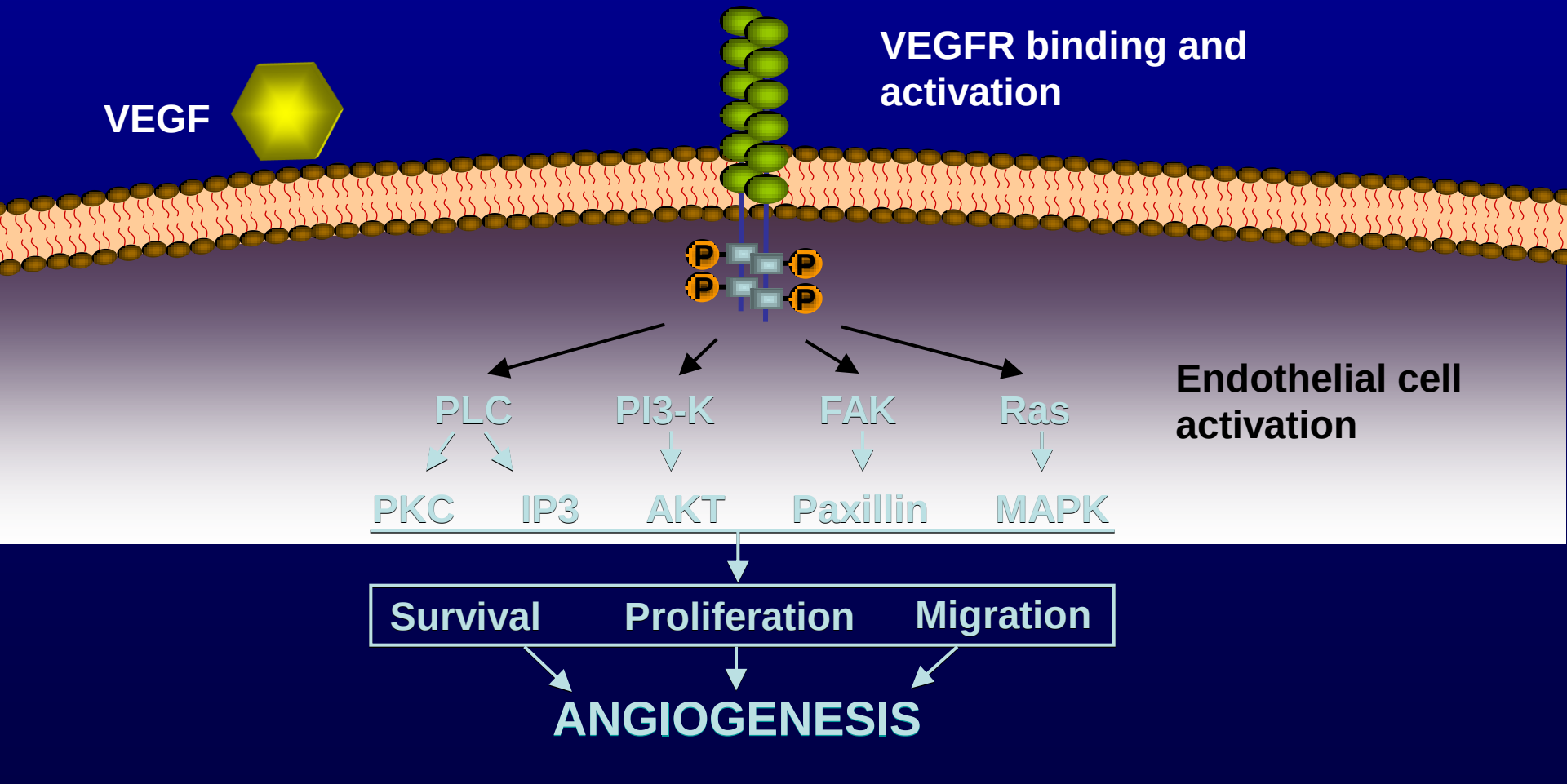
Angiogenic inhibitors may reverse this vascularization

Carmeliet and Jain. *Nature*. 2000;407:249.

Inibição do VEGF



VEGF


VEGF
VEGFR binding and activation
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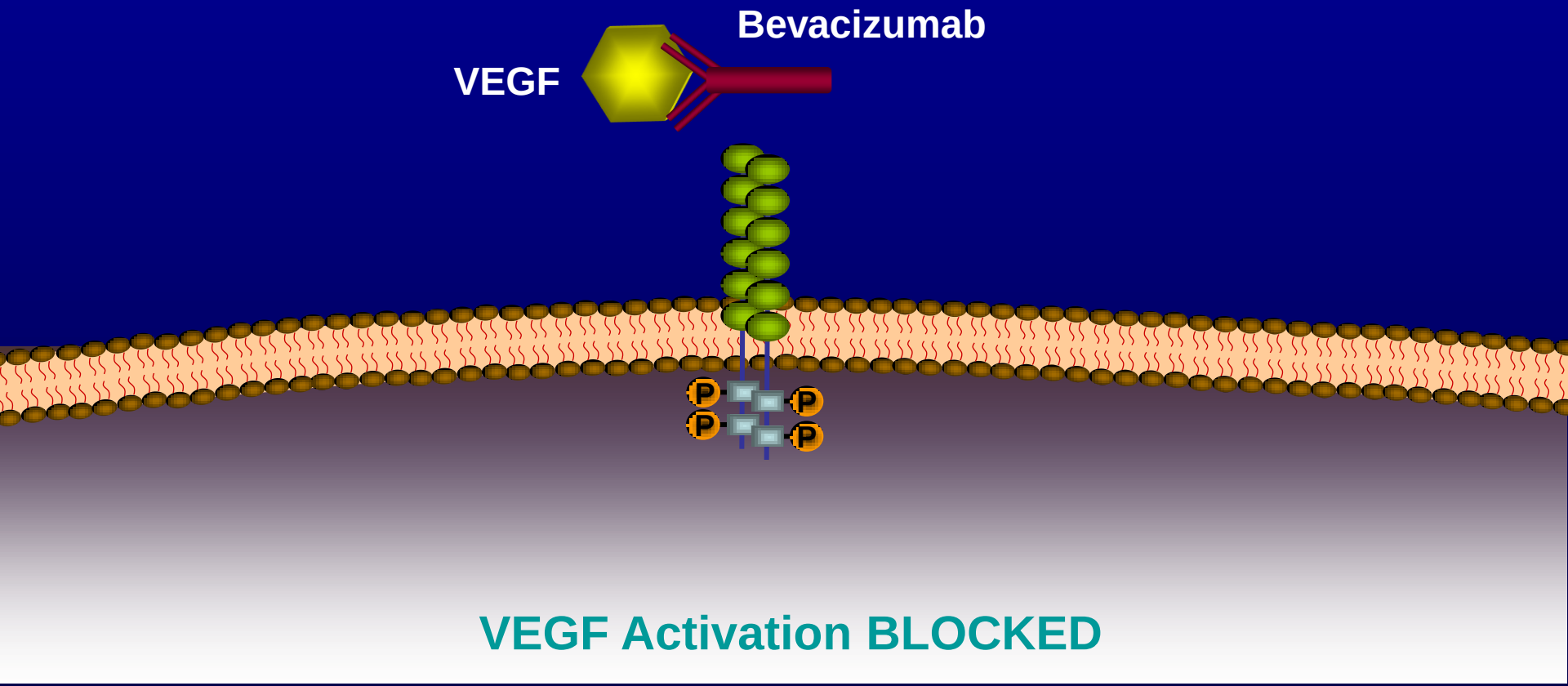
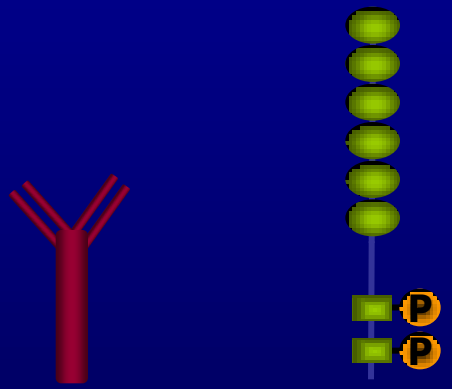
PI3-K
FAK
Ras
PKC
IP3
AKT
Paxillin
MAPK
Endothelial cell activation
Survival
Proliferation
Migration
ANGIOGENESIS

Inibição do VEGF

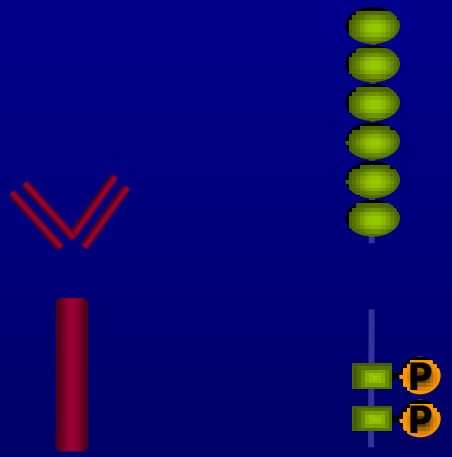


VEGF Activation BLOCKED

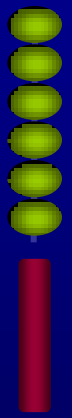
Inibição do VEGF



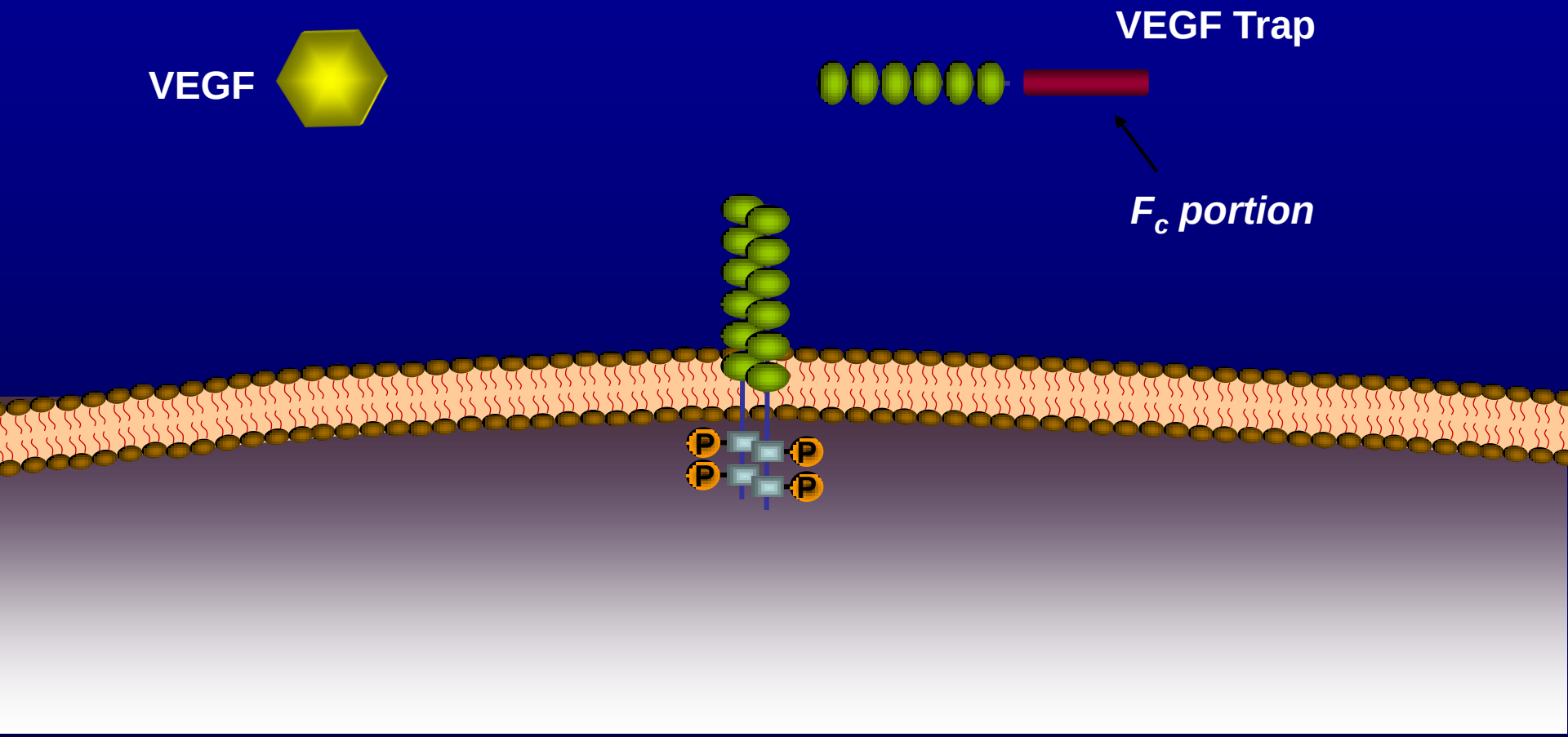
Inibição do VEGF



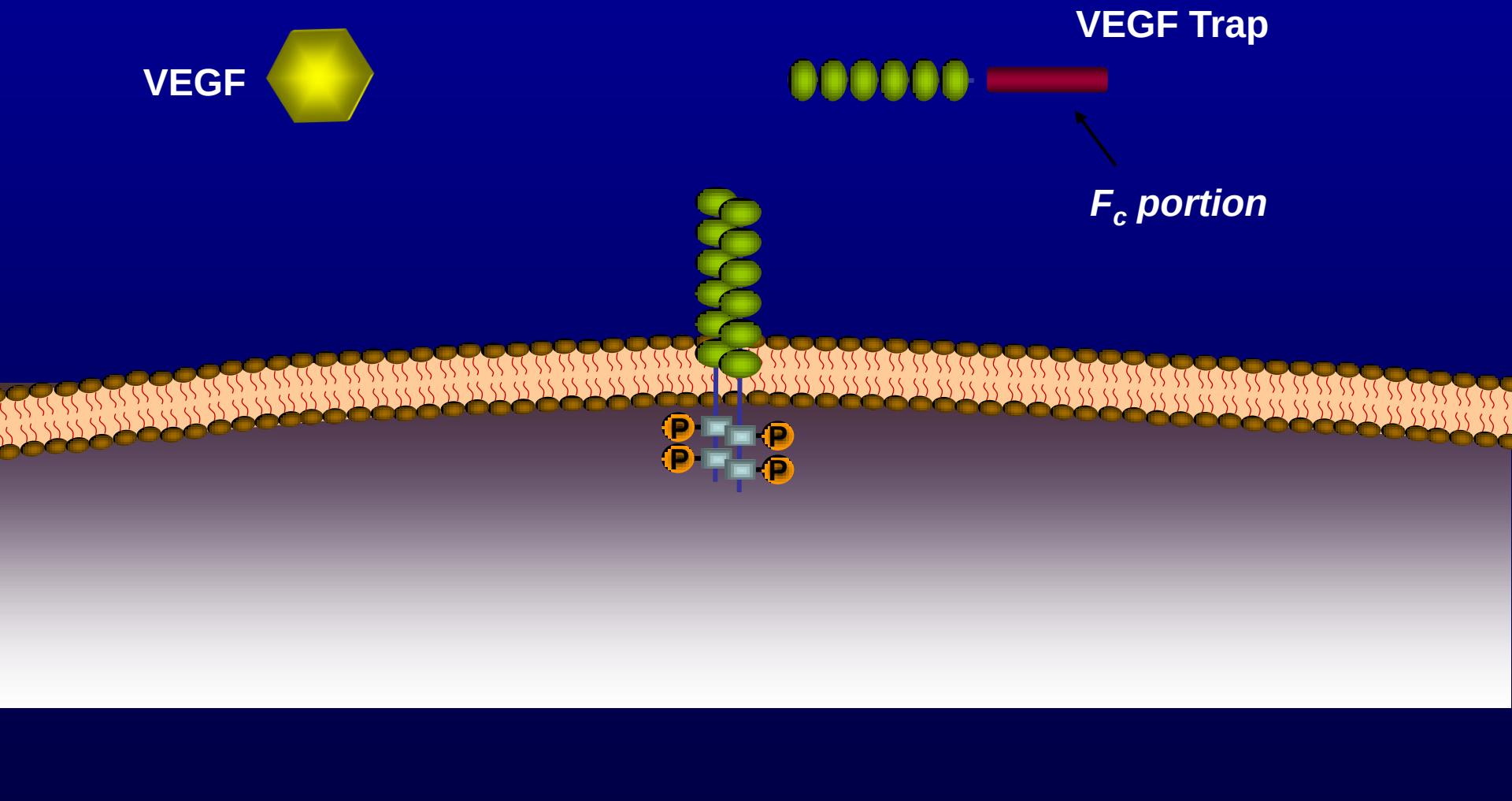
Inibição do VEGF



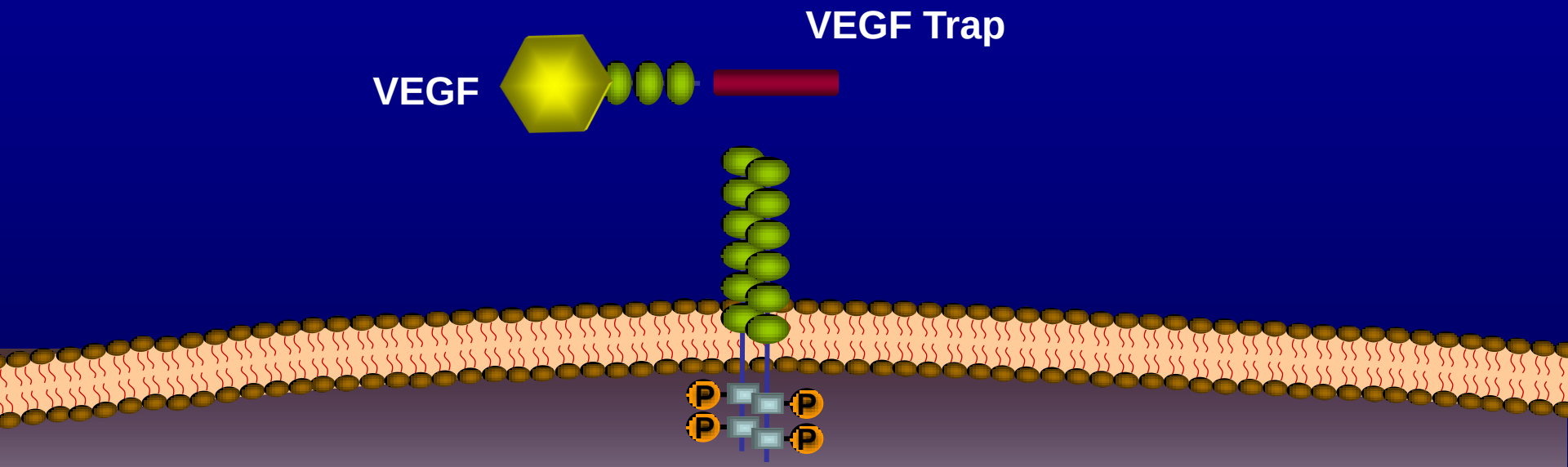
Inibição do VEGF



Inibição do VEGF

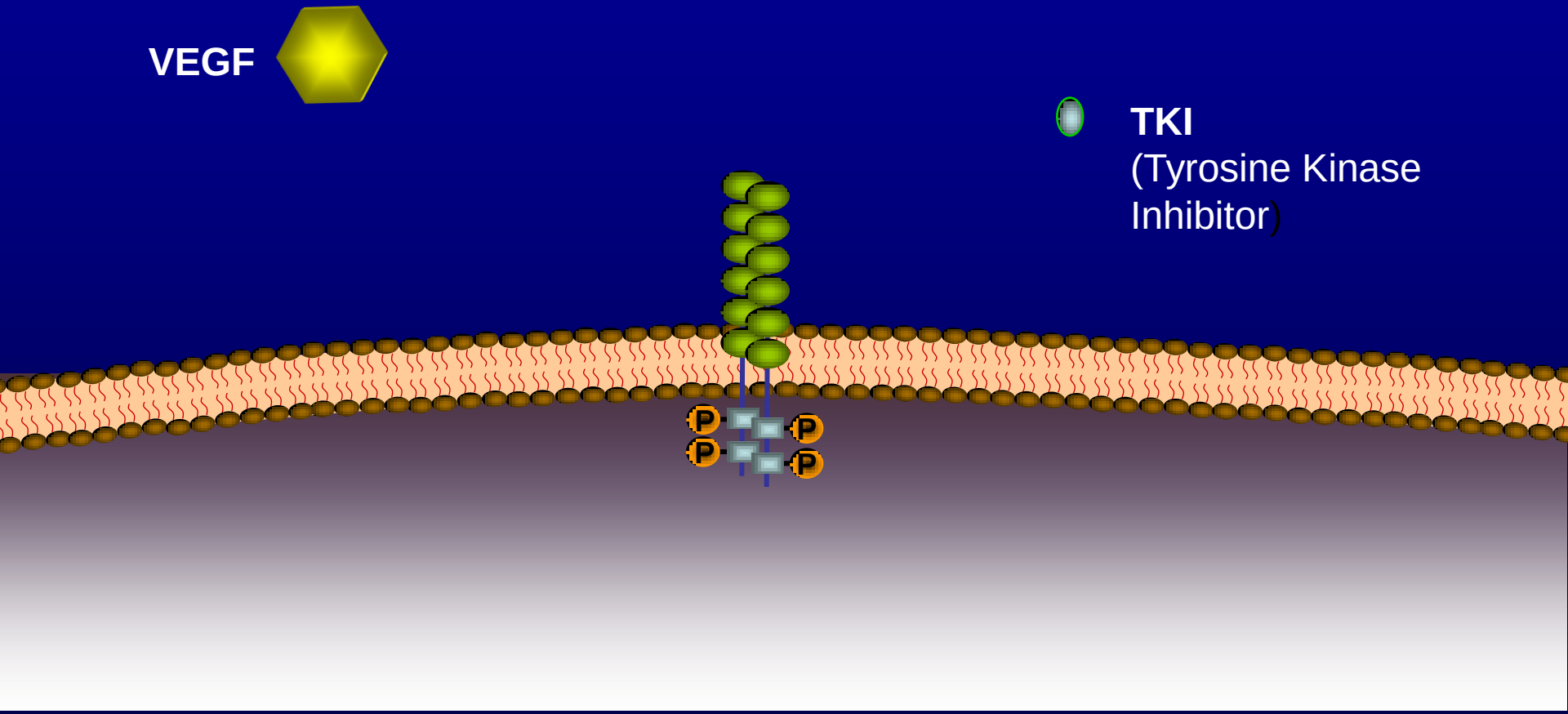


Inibição do VEGF

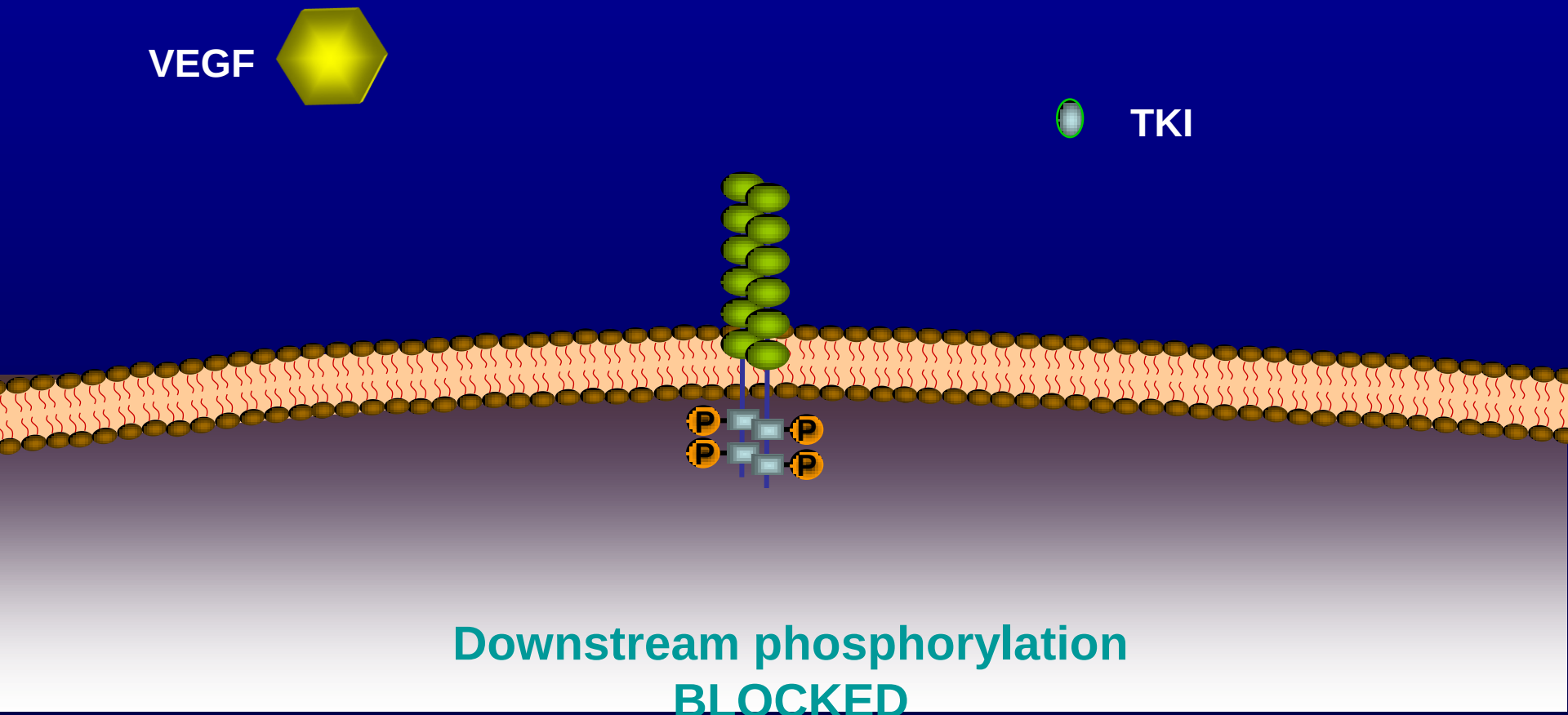


VEGF Activation BLOCKED

Inibição tirosina quinase do VEGF



Inibição tirosina quinase do VEGF



Downstream phosphorylation BLOCKED

Toxicidade do Anti-VEGF

- Hipertensão
- Fadiga
- Tromboses
- Sangramento (epistaxe, phemorragia pulmonar, associado ao tumor)
- Cefaléia
- Eventos neurológicos

- Cardiotoxicidade
- Dor no sítio tumoral
- Proteinuria
- Hipotireoidismo(?)

Correção do DNA -Parp

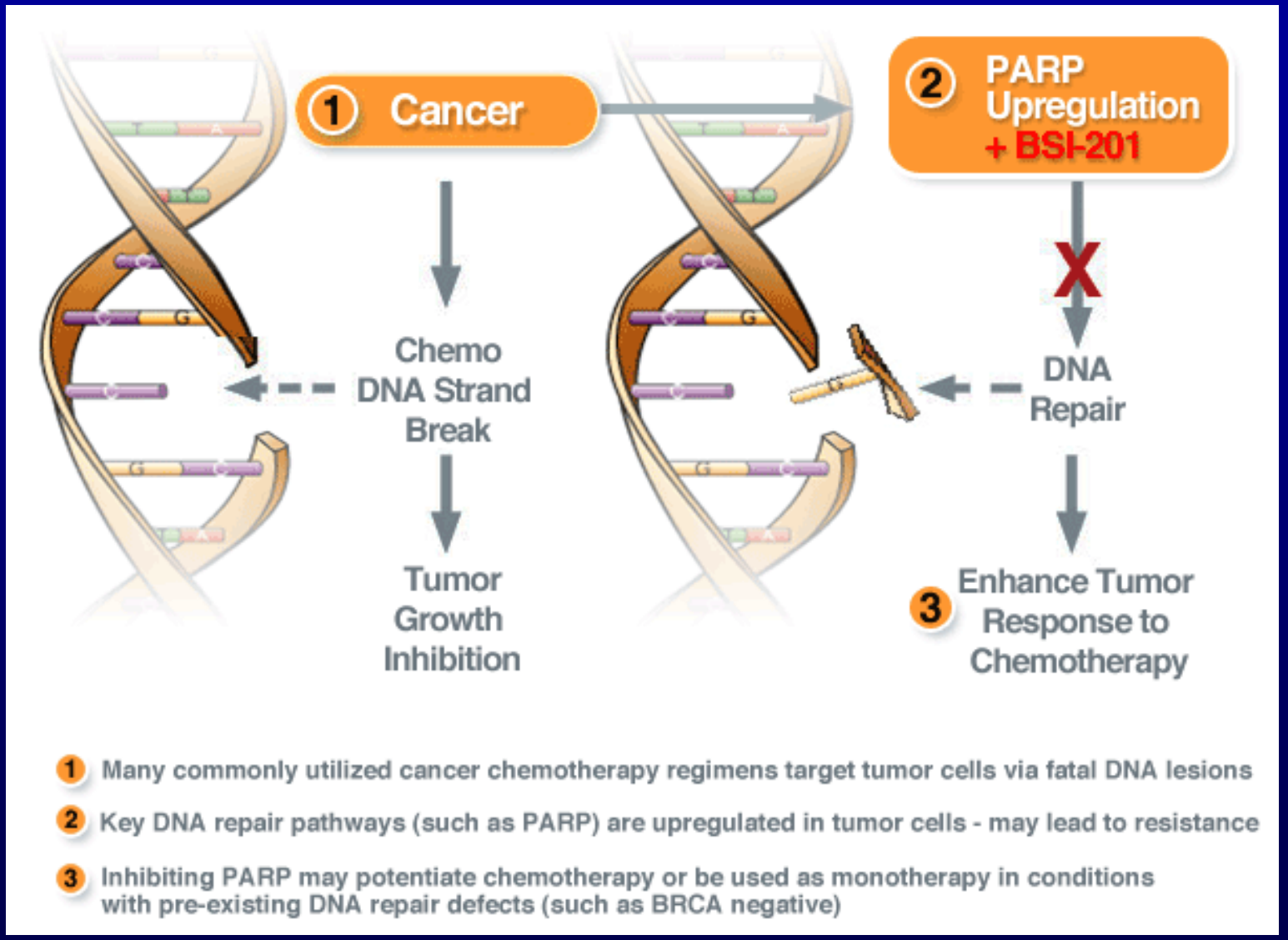
Parp – poli adenosine-disposfato-ribose

Enzima envolvida no reparo do DNA por base excisão

Mutaçoes Brca1/2 tem deficiência da outra forma de reparo de fita única tornando sensível ao iParp

Estudos de fase 2 com ganho de sobrevida livre de progresão (ASCO -2009)

Correção do DNA -Parp



Alvo	Agente
Epidermal growth factor receptor pathway	
Epidermal growth factor receptor	Cetuximab, ABX-EGF
Selective erbB-1 (HER1) tyrosine kinase inhibitors	Erlotinib, gefitinib
erbB-2 (HER2) inhibitors	Trastuzumab (Herceptin)
Pan-erbB inhibitors	CI-1033, GW-572016, EKB-569
Ras/Raf/mitogen-activated protein kinase pathway	
Farnesyl transferase inhibitors	Tipifarnib (Zarnestra, R115777), SCH6636, BMS 214662
Raf inhibitors	BAY 43-9006, ISIS 5132
MEK inhibitors	CI-1040
PI3K/Akt and mTOR	
Rapamycin analogs	CC-779, RAD001, AP23573
Apoptotic pathways	
Bcl-2 pathways	Oblimersen (G-3139, Genasense)
Tumor necrosis factor–related apoptosis ligand (TRAIL)	TRM-1
Histone deacetylase inhibitors	LAQ824, suberoylanilide, depsipeptide, MS-275, CI-994, hydroxamic acid
Angiogenesis inhibitors	
Anti–vascular endothelial growth factor (VEGF) antibody	Bevacizumab (Avastin), CP-547,632, PTK787/ZK222584
VEGF tyrosine kinase inhibitors	ZD6474, SU11248

Anticorpos Moniclonais

Table 1

Product Source Identifiers

IDENTIFIER	SOURCE
-u-	human
-o-	mouse
-a-	rat
-zu-	humanized
-e-	hamster
-i-	primate
-xi-	chimera

Source: Reference 2

Table 2

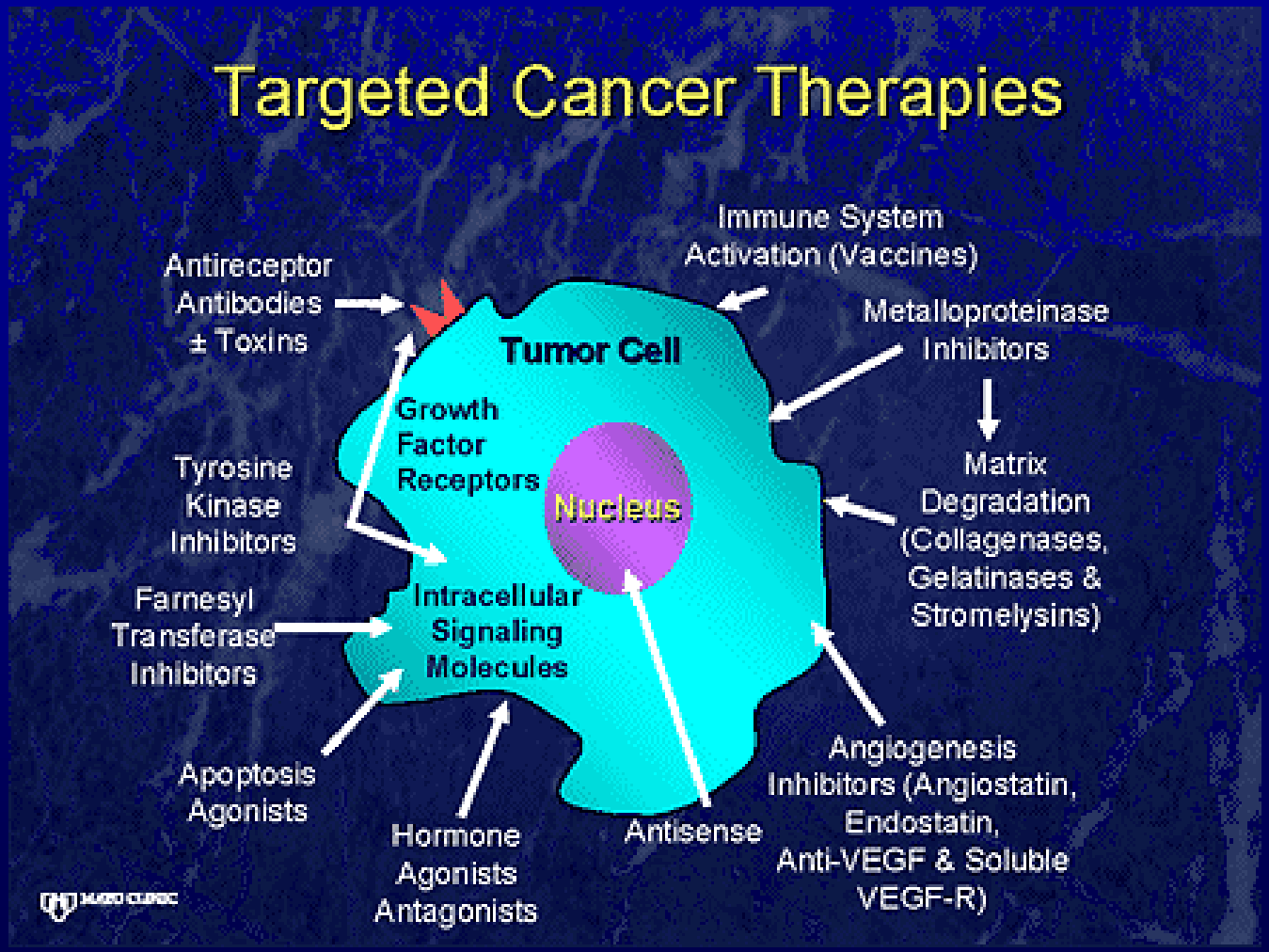
Disease or Target Class Identifiers

DISEASE	IDENTIFIER
viral	-vir-
bacterial	-bac-
immune	-lim-
infectious lesions	-les-
cardiovascular	-cir-
TUMORS	
colon	-col-
melanoma	-mel-
mammary	-mar-
testis	-got-
ovary	-gov-
prostate	-pr(o)-
miscellaneous	-tum-

Source: Reference 2


joe-ks.com

Câncer de Mama Metastático



Directly Targeting the Cancer Cell: Disadvantages

- Major heterogeneity across and between histologies[1]
- Biologically/genetically unstable target
- Acquired genetic instability
  - Increases with progression/stage/pretreatment
  - Limits efficacy of treatment
- Homeostatic response/selection of resistant clones (acquired and de novo resistance)

1. Sjoblom T, et al. Science. 2006;314:268-274.

Attraction of Targeting the Microenvironment

- Genetically stable substrate
  - Less amenable to mutation/acquired resistance
- Common final pathways possible
  - Less heterogeneity of target
  - Relatively predictable response of tissues to cancer
  - Addresses poorly understood and most lethal hallmark of malignancy: metastasis
- Plethora of potential novel targets

Metastatic Process

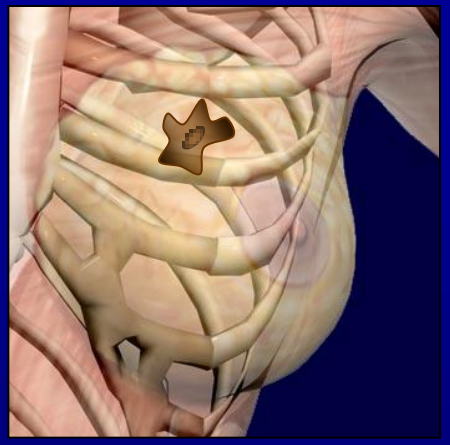
- Breast cancer “seed” cells circulate and take root in organ “soil”

Metastatic Process

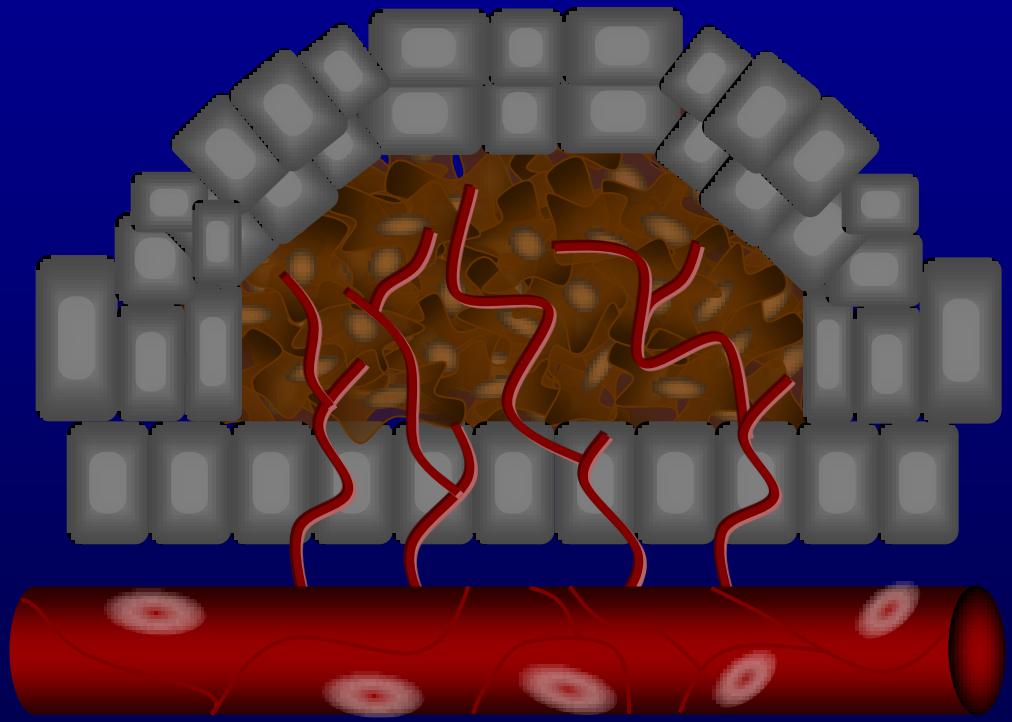
- Primary tumor

Metastatic Process

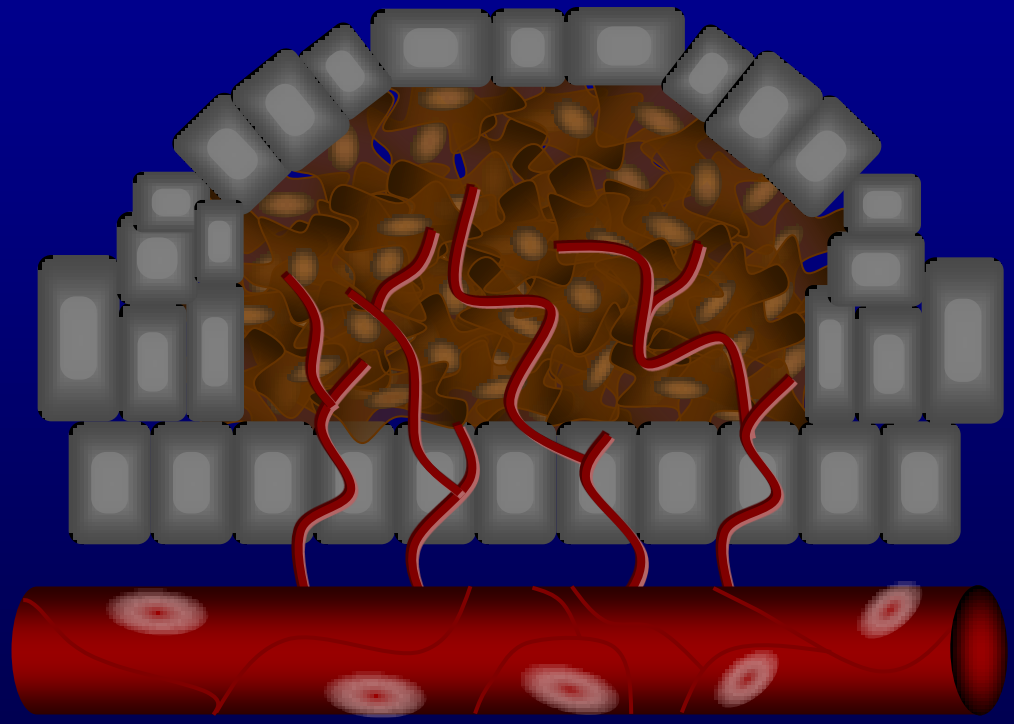
- Primary tumor



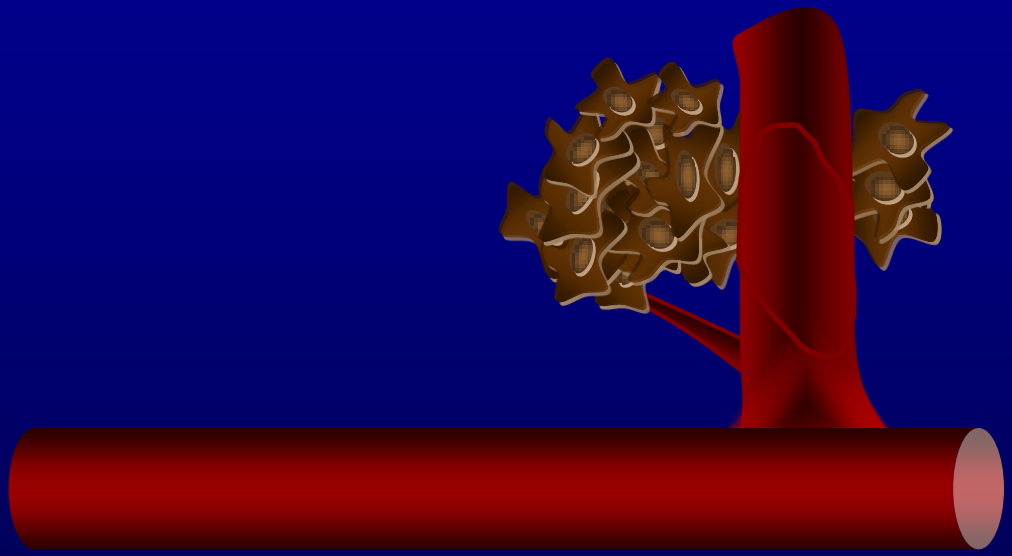
Metastatic Process: Angiogenesis and Proliferation



Metastatic Process: Angiogenesis and Proliferation



Metastatic Process: Invasion Into Circulation



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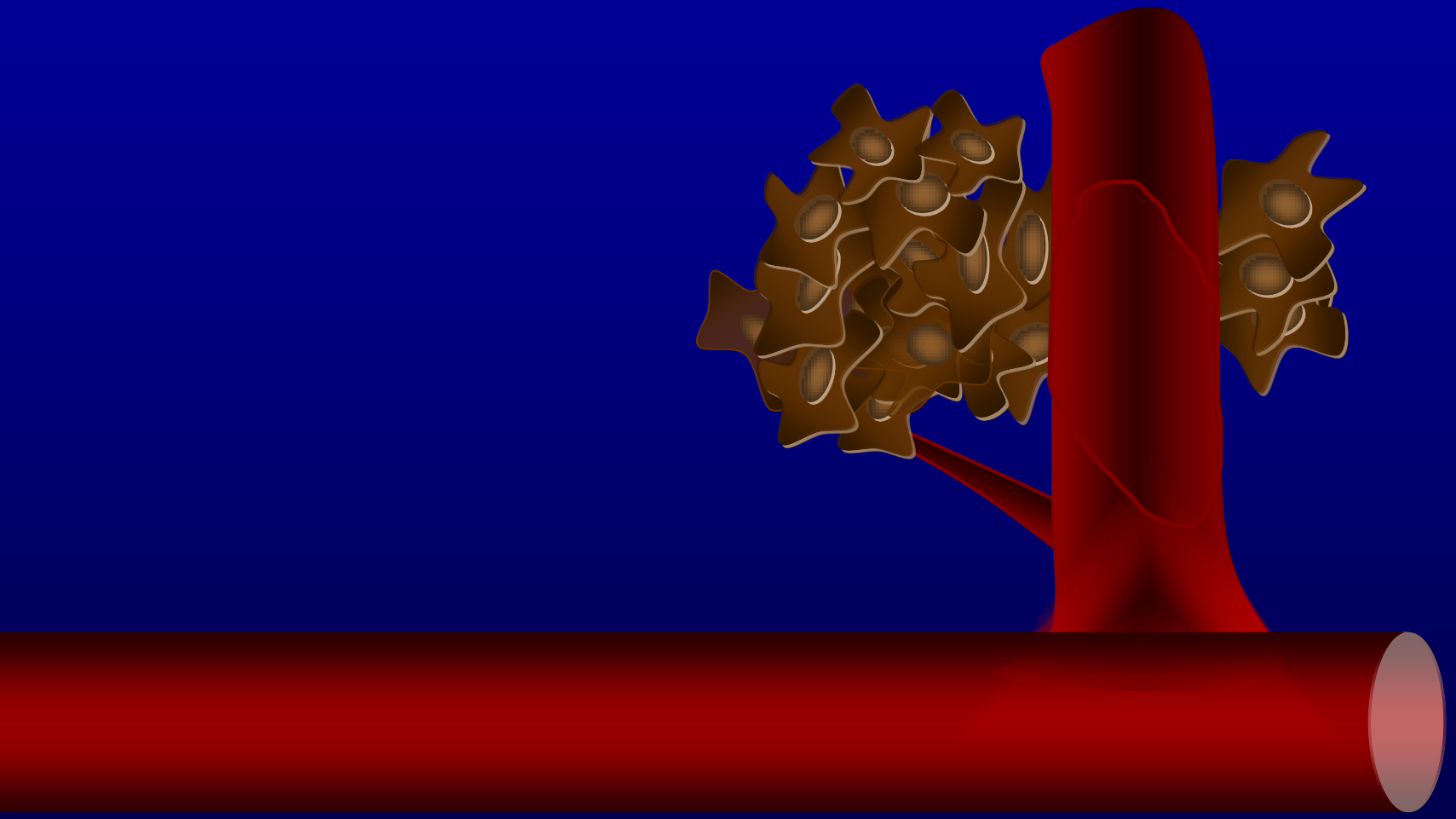

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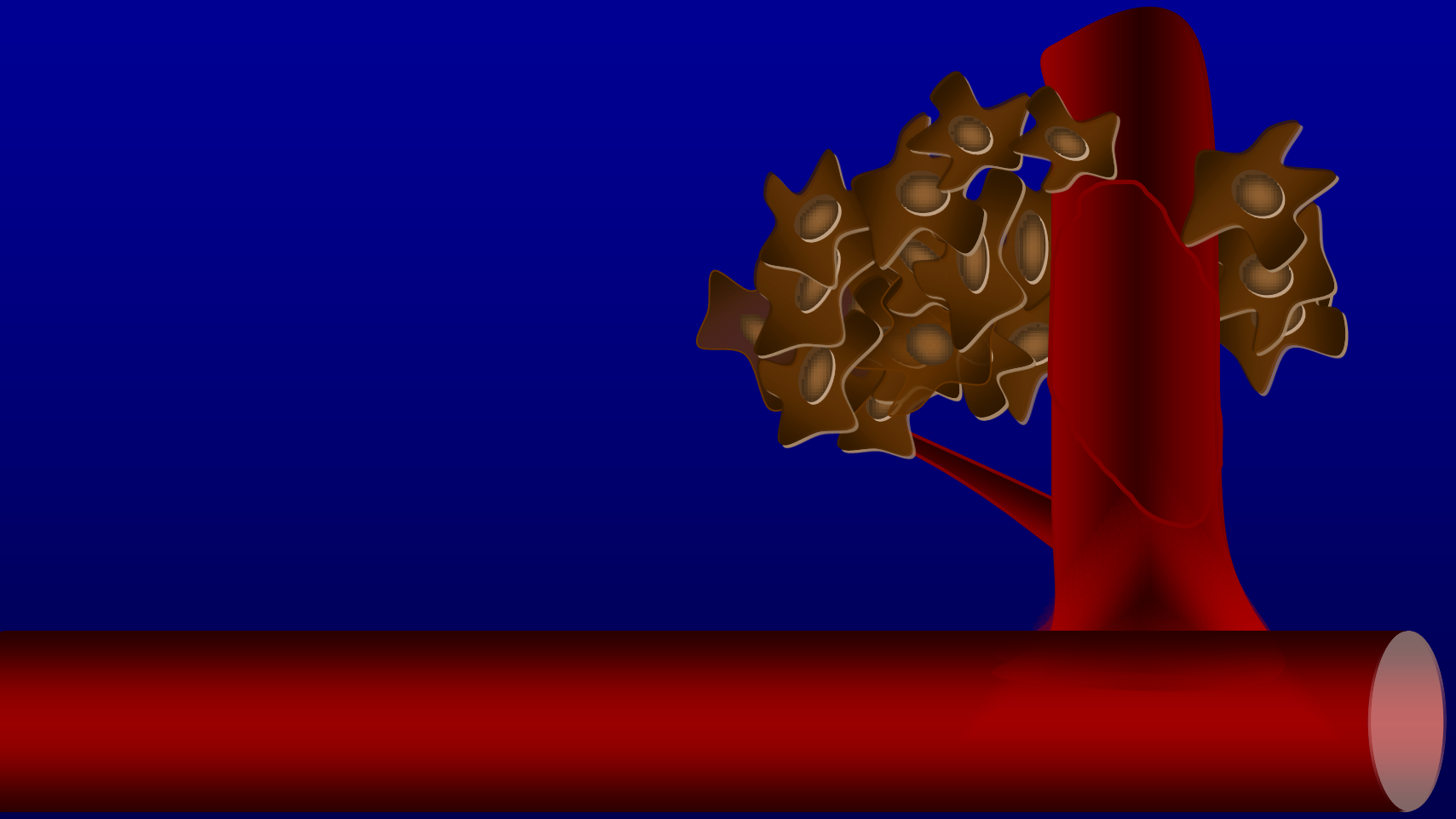
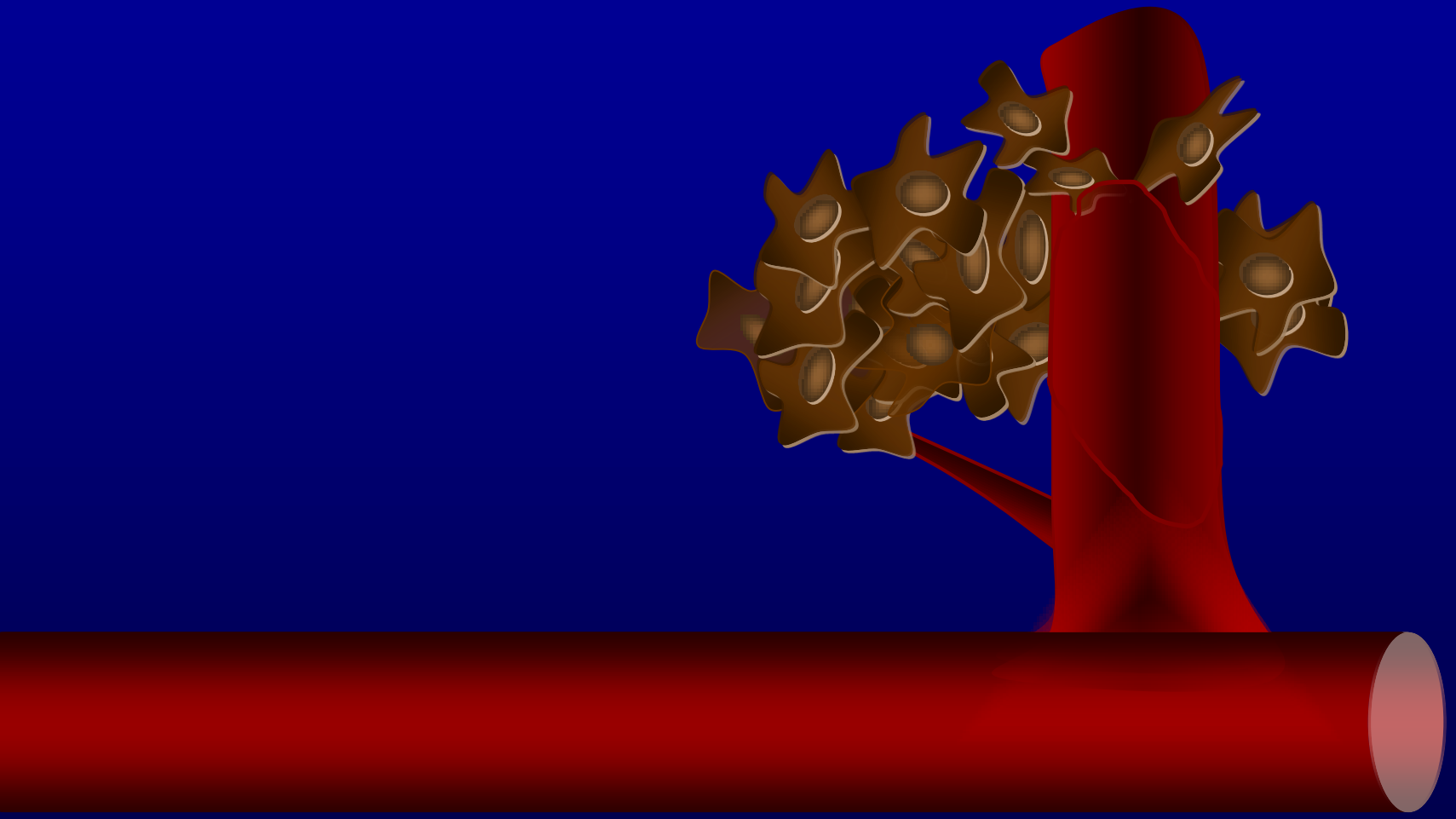
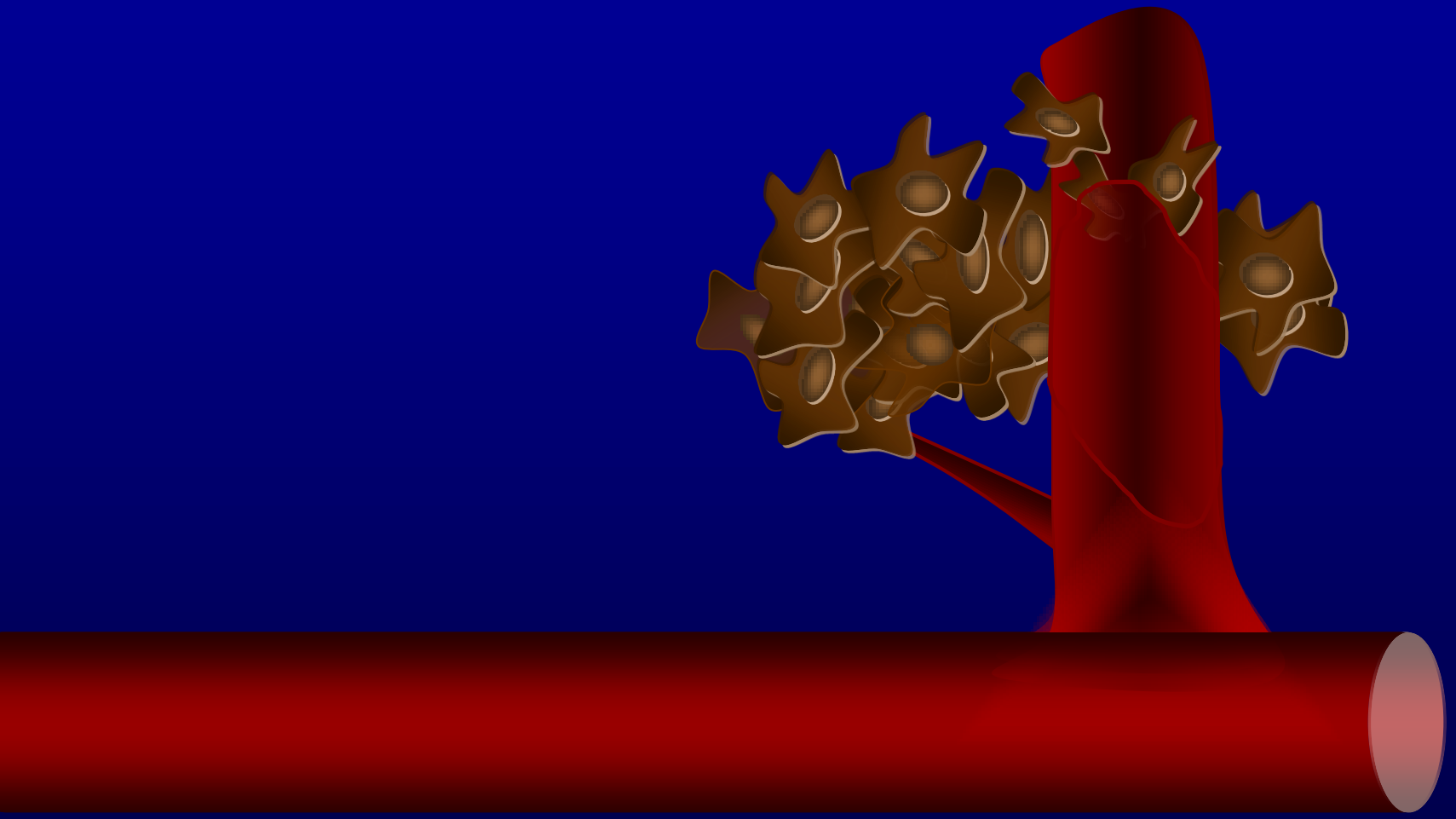


Metastatic Process: Invasion Into Circulation



Metastatic Process: Invasion Into Circulation



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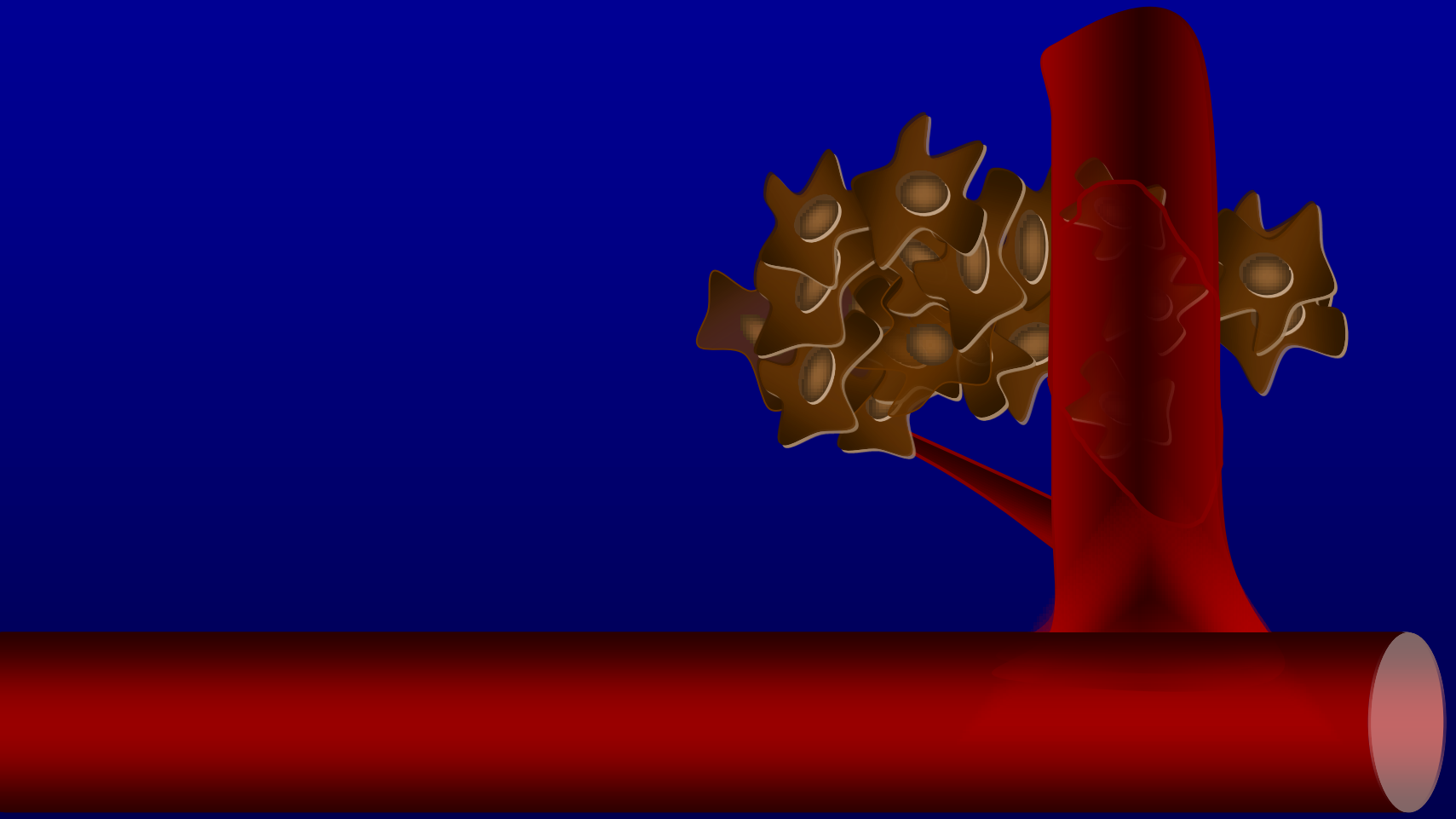
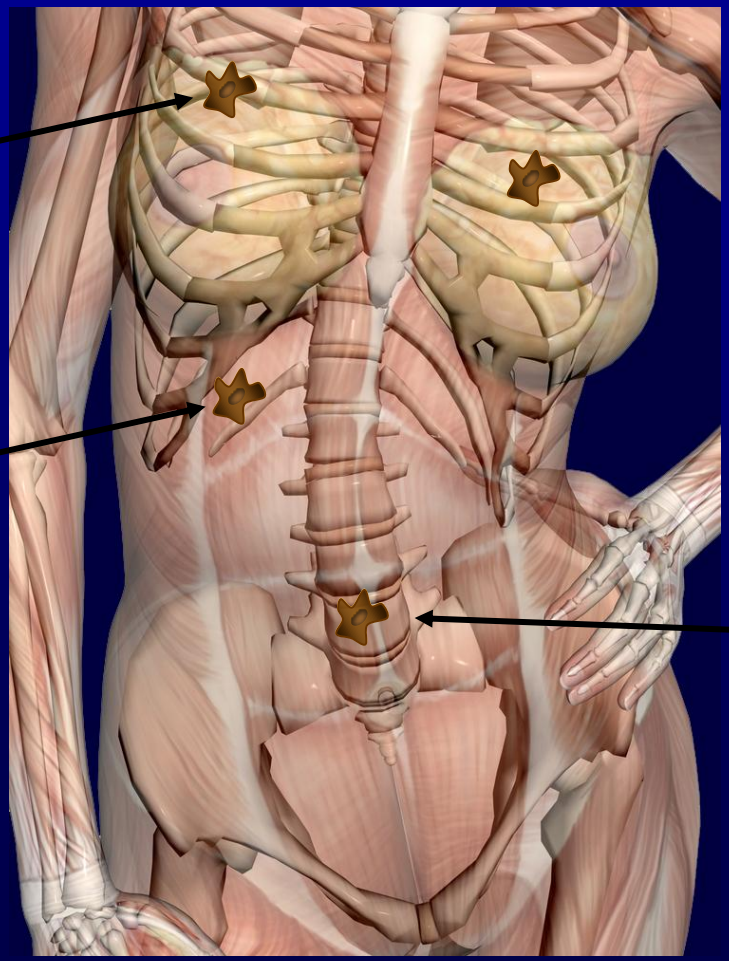
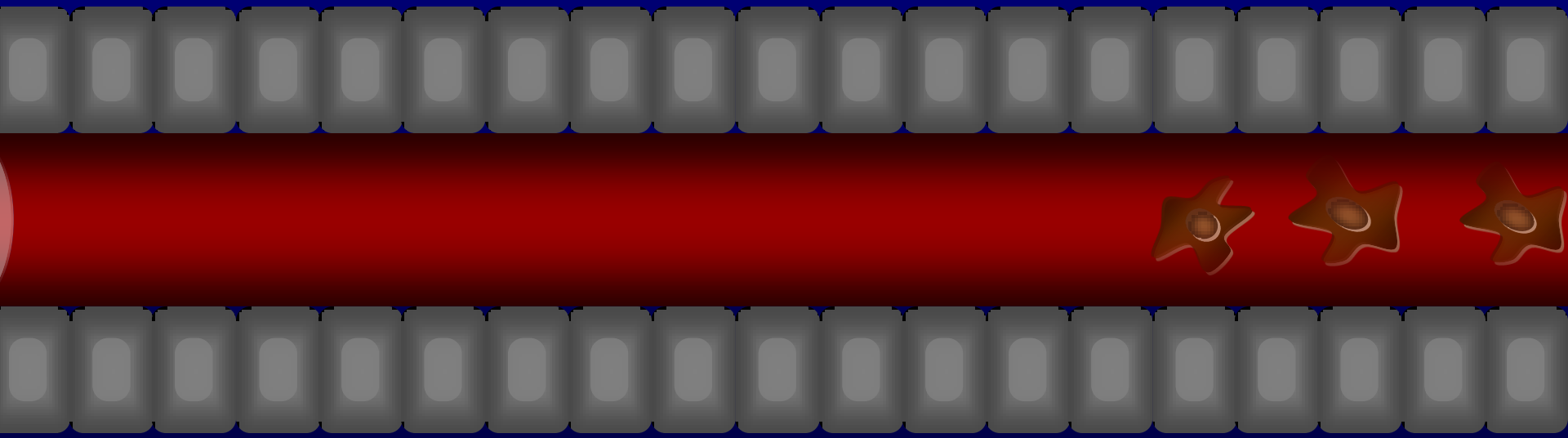


Metastatic Process: Arrest in Host Organs



Metastatic Process: Vessel Wall Adherence



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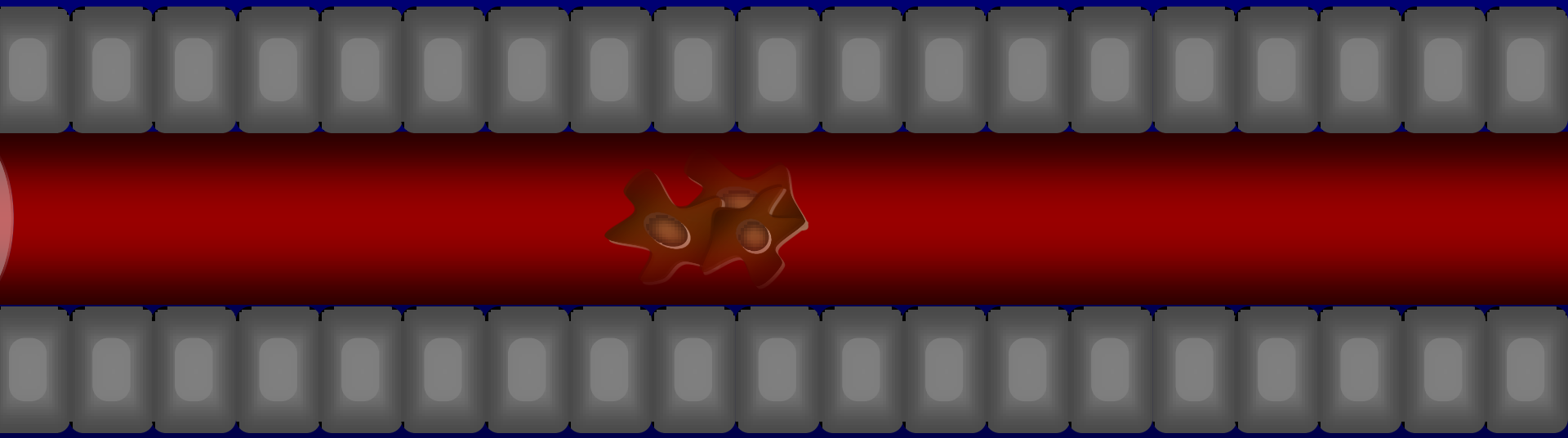
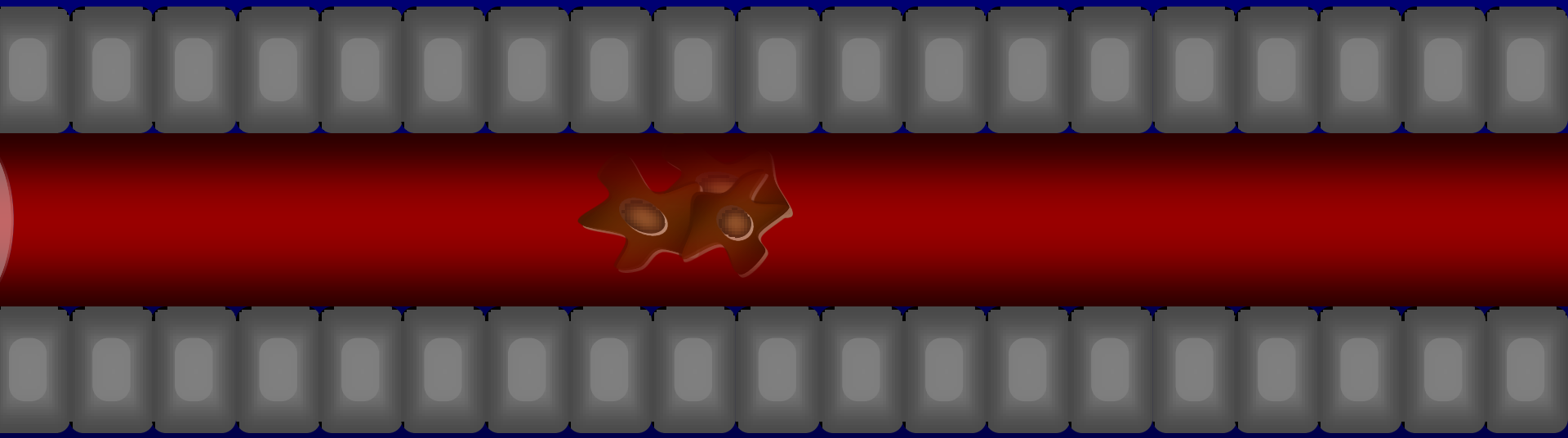
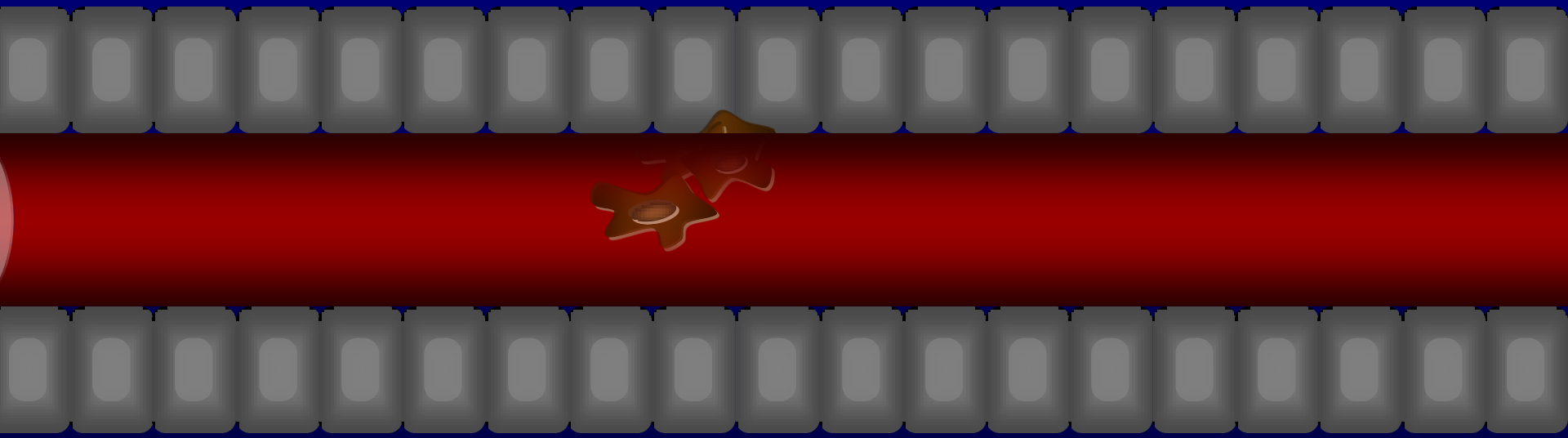


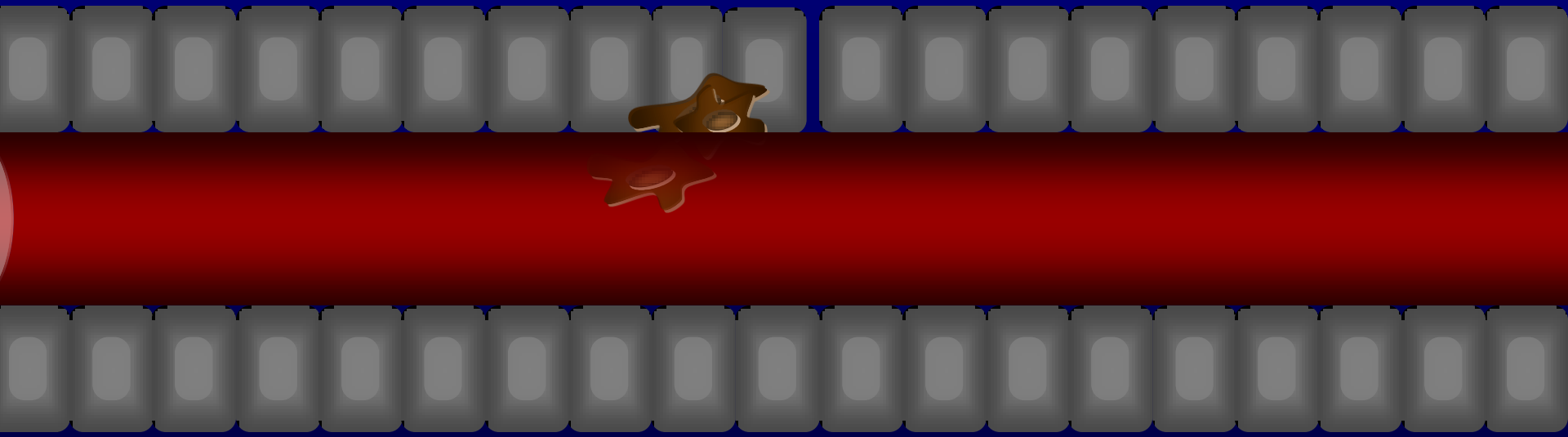
Metastatic Process: Vessel Wall Adherence



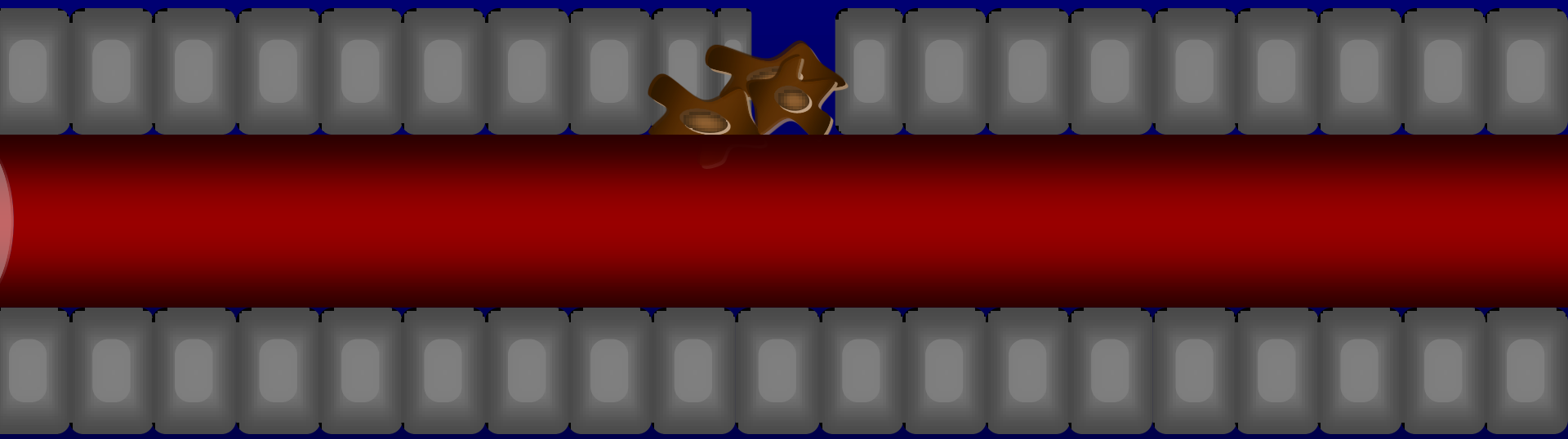
Metastatic Process: Extravasation



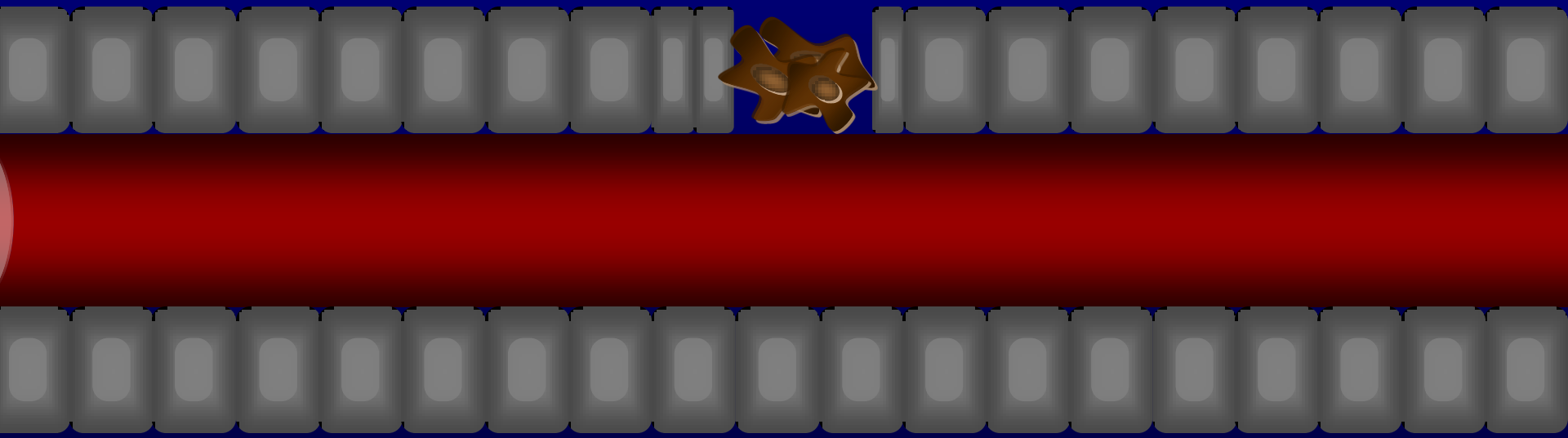
Metastatic Process: Extravasation



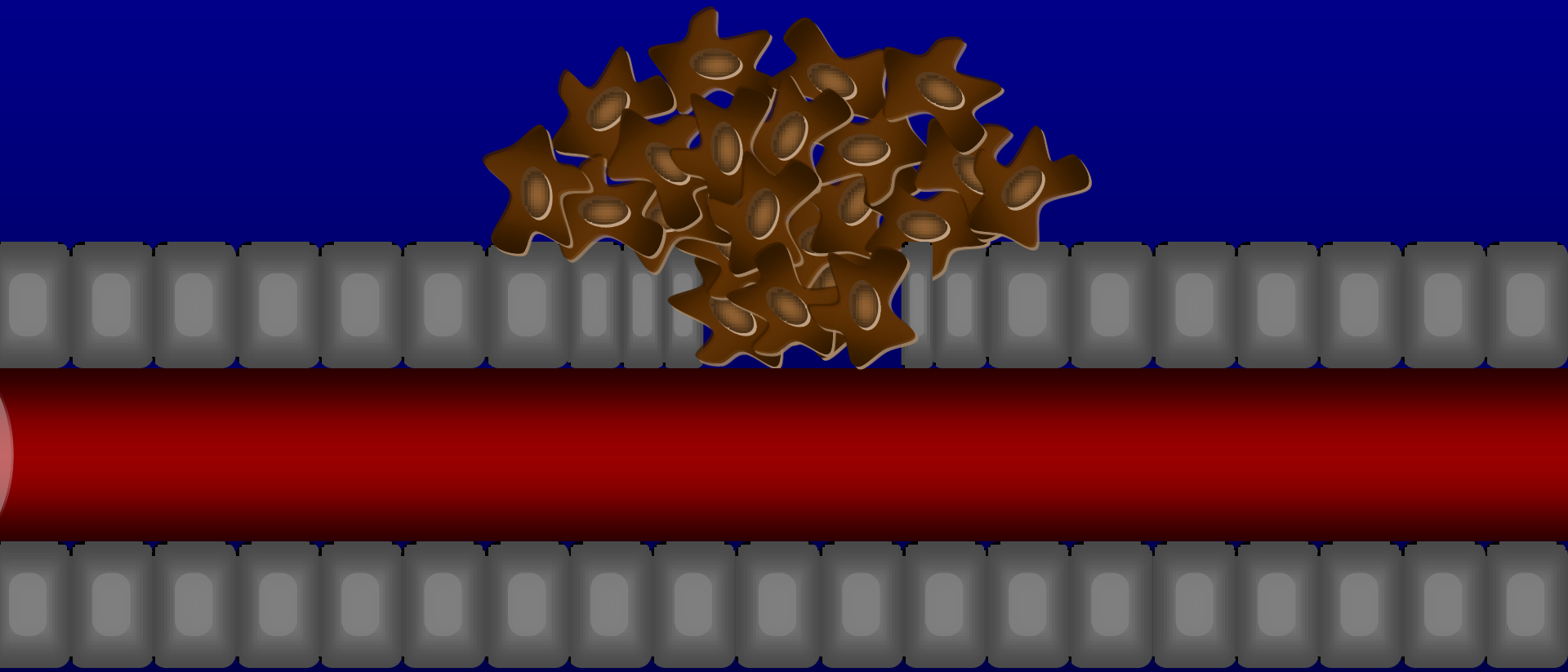
Metastatic Process: Extravasation



Metastatic Process: Extravasation



Metastatic Process: Formation of Metastasis



Regulation of Metastasis

Cell	Facilitation of Metastasis	Inhibition of Metastasis
Tumor	• Production of angiogenic factors • Production of growth factors/receptors • Motility, invasiveness • Aggregation, deformability • Cell-surface receptors and adhesion molecules	Inhibitors of angiogenesis Antigenicity Cohesion (E-cadherin) Tissue inhibitors of proteolytic enzymes
Host	• Paracrine and endocrine growth factors • Neovascularization • Platelets and their products • Immune cells and their products	Tissue barriers Blood turbulence, endothelial cells Tissue inhibitors of proteolytic enzymes Antiproliferative factors Inhibitors of angiogenesis

Marcel M, Leroy A. Physiol Rev. 2003;83:337-376.