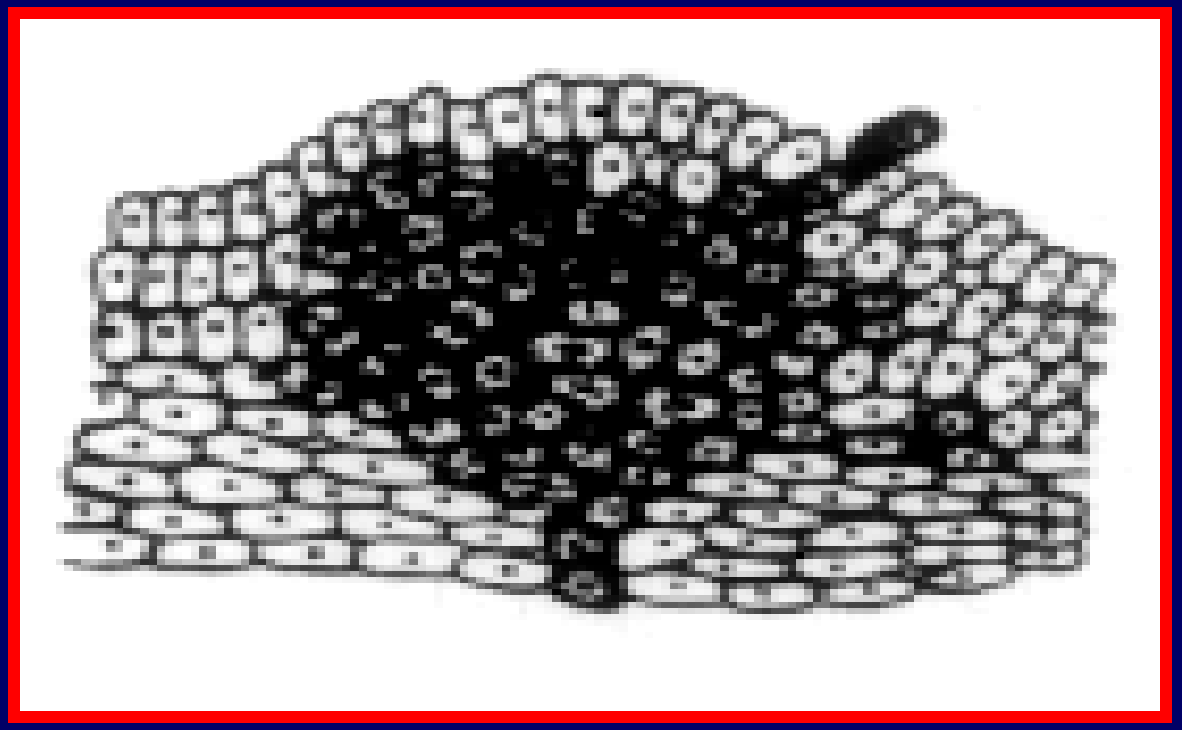
The Pathogenesis of a Metastasis

Primary malignant neoplasm



Inflammation as a critical component of tumor progression

Infections agents as antigens to prevent or treat cancer

Bacteria	*Helicobacter pylori*	Gastric cancer and lymphoma
Virus	*H. papiliomavirus* *Hepatitis B and C* *HIV* *Epstein-Barr virus*	Cervical and anal cancer Liver cancer Kaposi's sarcoma Lymphomas
Parasite	*Schistosomes*	Bladder cancer

Macrophages, neutophils, mast cells, eosinophils and activated T cells contribute to malignancies by releasing;

- Reactive oxygen and nitrogen species
- Pro-angiogenic factors
- Proteases
- Cytokines and Chemokines

P53 mutations are seen at frequencies similar to those in tumors in chronic inflammatory diseases such as RA and inflammatory bowel disease

P53 and MIF (macrophage migration inhibitory factor)

- Mutations in p53 are the most common genetic alteration in human tumors
- In a variety of tumors, p53 is functionally inactivated, but the gene remains intact
- Cells lacking p53 are capable of proliferation with damaged DNA, and thus are capable of accumulating multiple, potentially oncogenic mutations

Activation of cell proliferation by the SV40 DNA tumor virus

Viral protein sequesters p53

DNA

p53 activates safety brake on proliferation

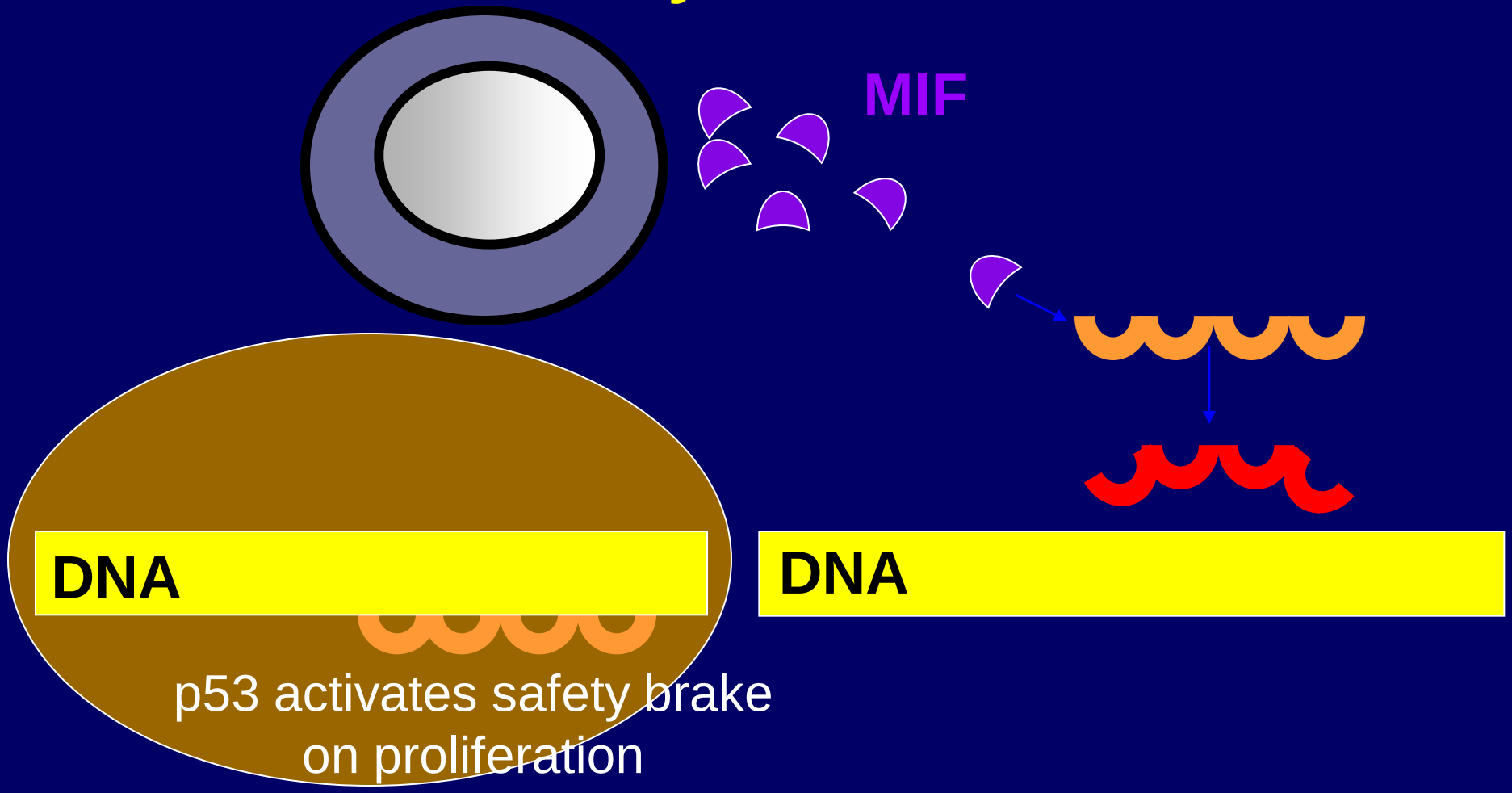
PROLIFERATION BLOCKED

PROLIFERATION ACTIVATED

MIF

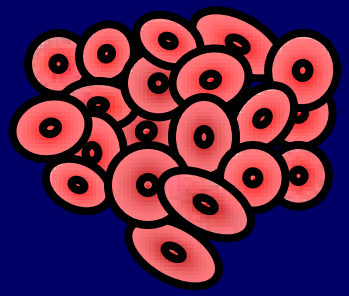
- MIF is released from T cells and macrophages at sites of inflammation, contributing to enhanced T cell activation and increased antimicrobial function of macrophages
- Can protect MIF producers from apoptosis
- Is capable of overcoming p53 function by supressing its transcriptional activity

Activation of cell proliferation by MIF



Cancer immunoediting

Normal cells

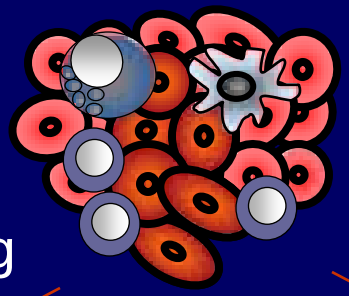


Intrinsic tumor suppressors Rb, p53

N. Transformation
- Carcinogens
- Radiation
- Ch. Inflammation
- Viruses

Transformed cells

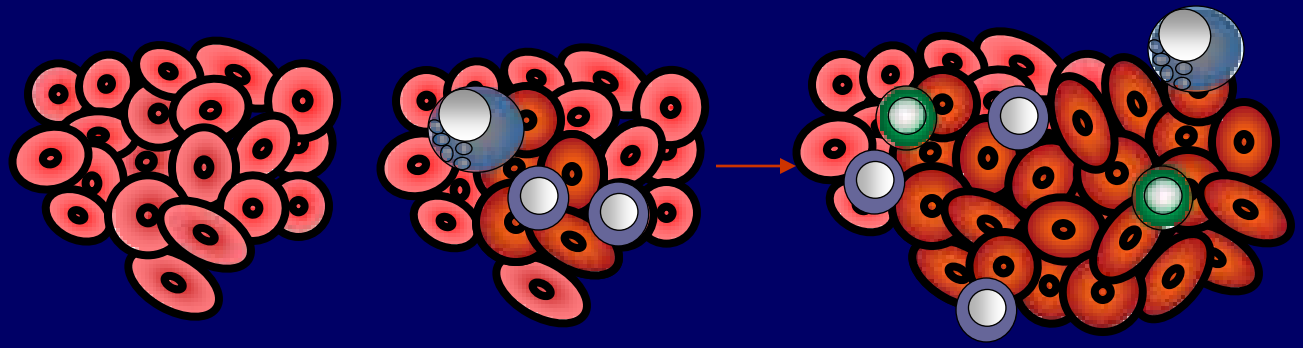
Cancer immunoediting



Stress-induced genes
Tumor antigens
Peptide-MHCI
Danger signals

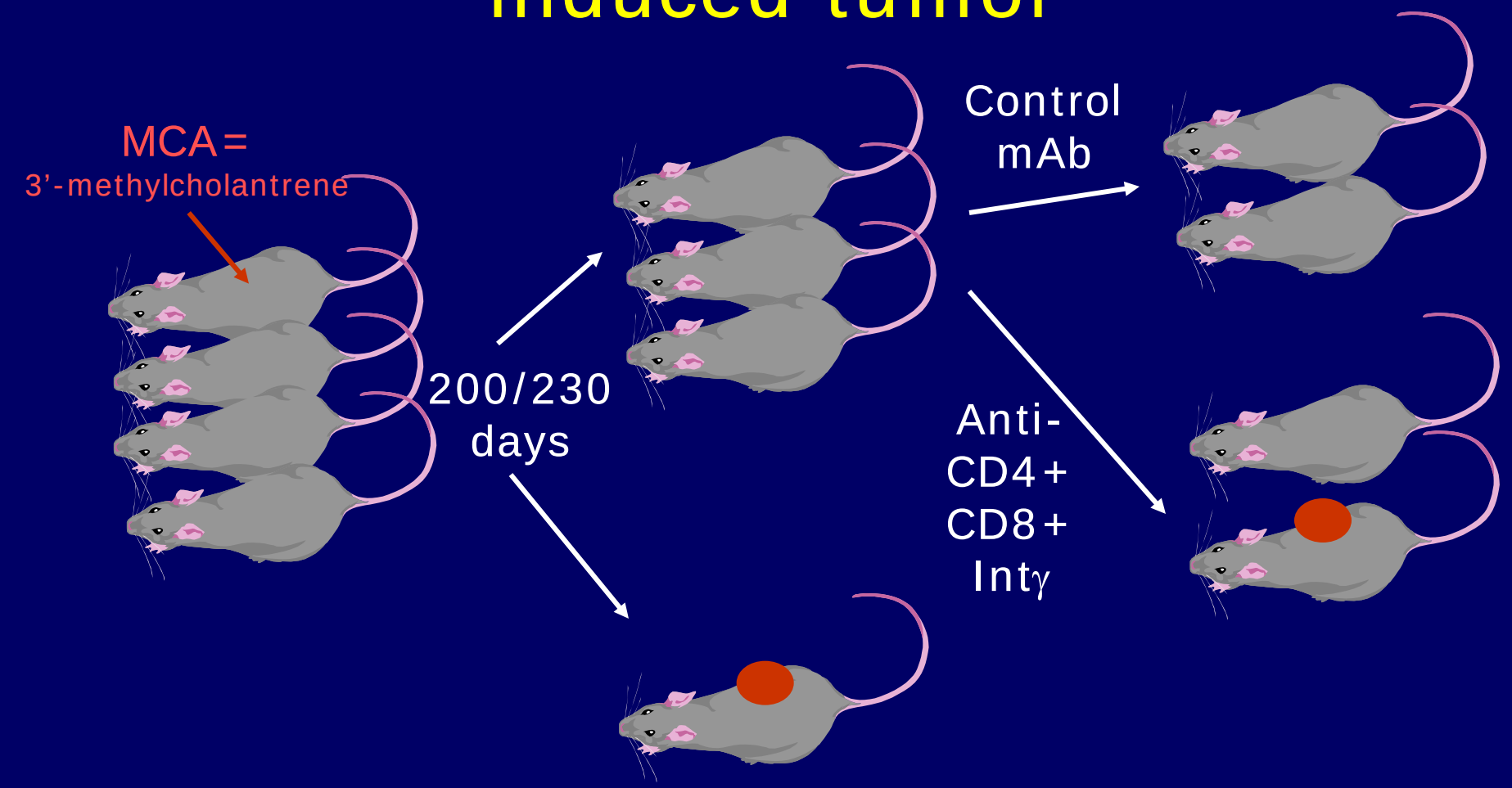
Innate & adaptive Immunity
- CD4+, CD8+ T cells
- NK, NKT cells
- DC
- Macrophages

ELIMINATION EQUILIBRIUM ESCAPE



- Non-immunogenic tumors
- Immune exhaustion
- Immune inhibition
- Tumor cell variants

The adaptive immune system promotes an equilibrium state in induced tumor



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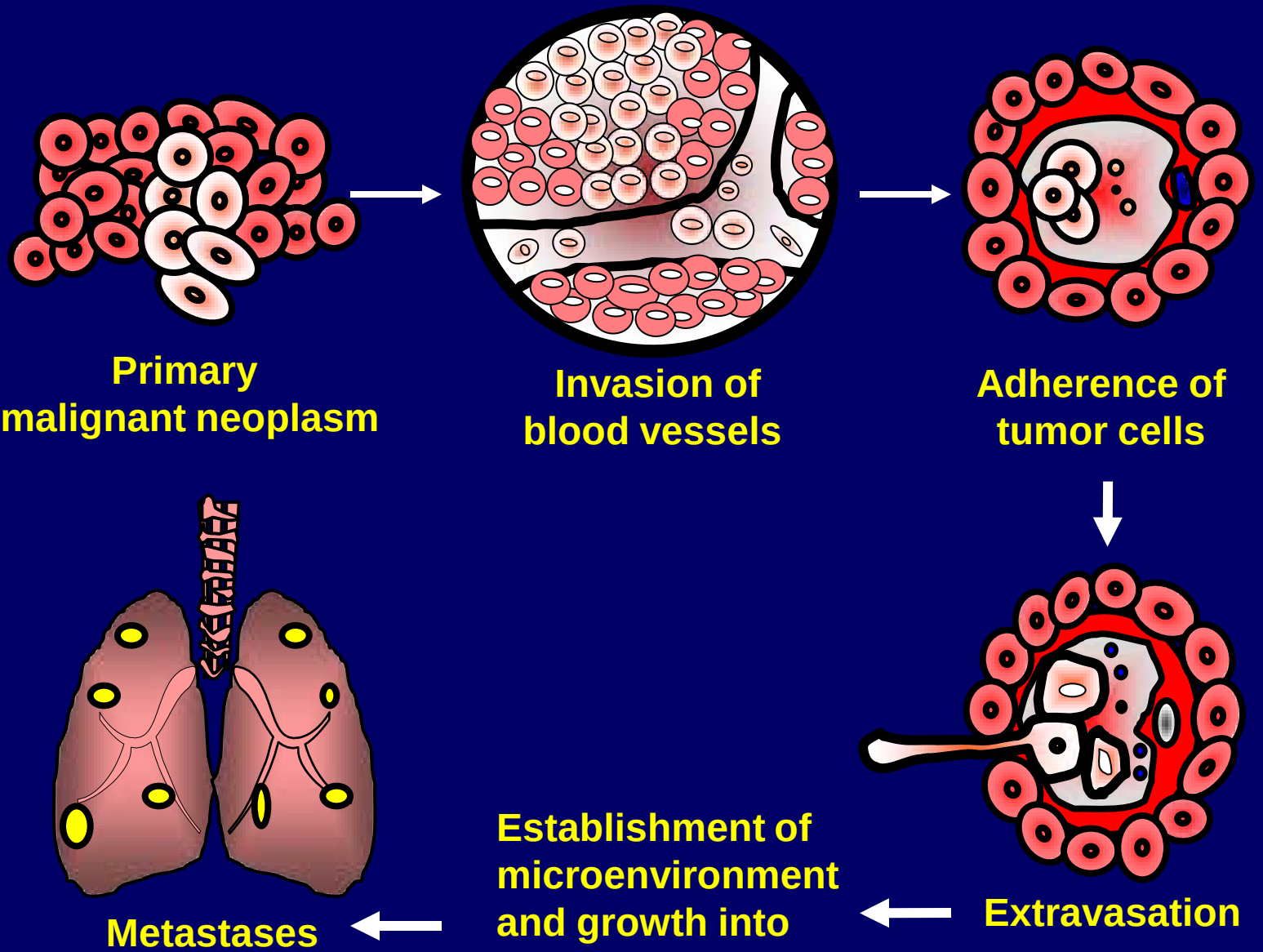
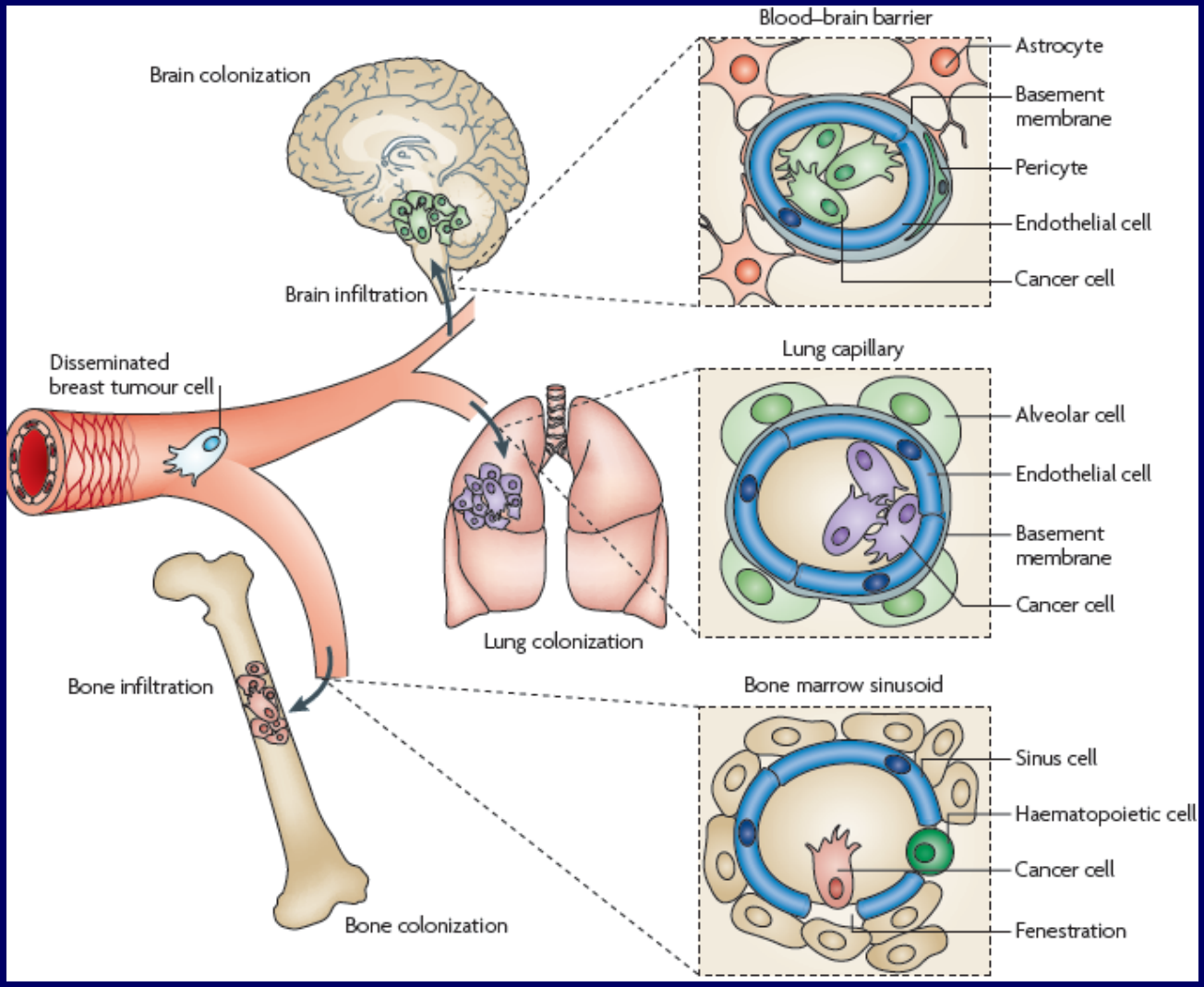


Organ-specific barriers to metastatic infiltration



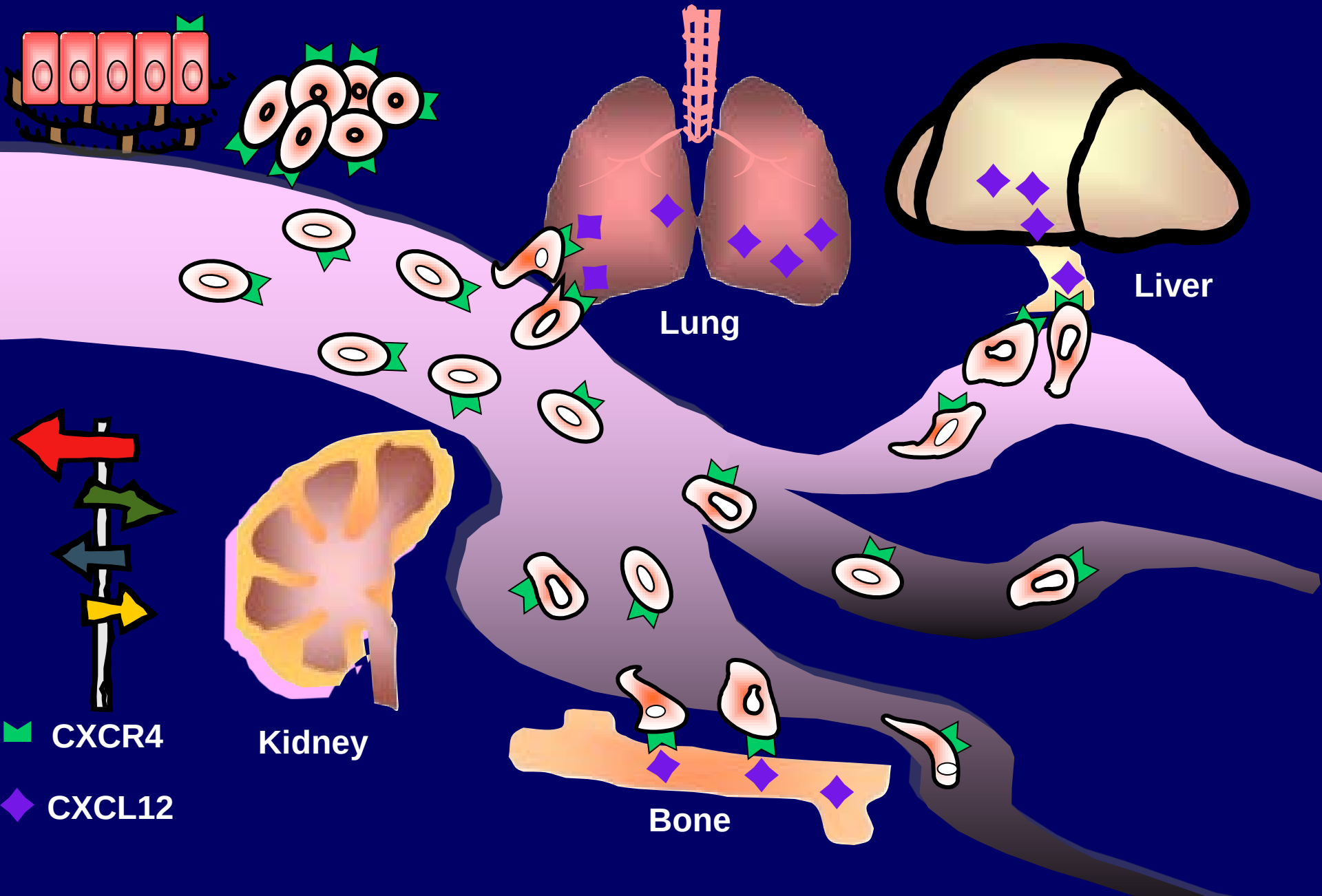
Tumor cells regulate their chemokine expression to;

- Help recruit inflammatory cells
- Stimulate tumor growth and progression
- Melanoma (GROα/CXCL1, GROβ/CXCL2, GROγ/CXCL3, IL8/CXCL8)
- Pancreatic carcinoma (MIP3α/CCL20)
- Activate an angiogenic programme

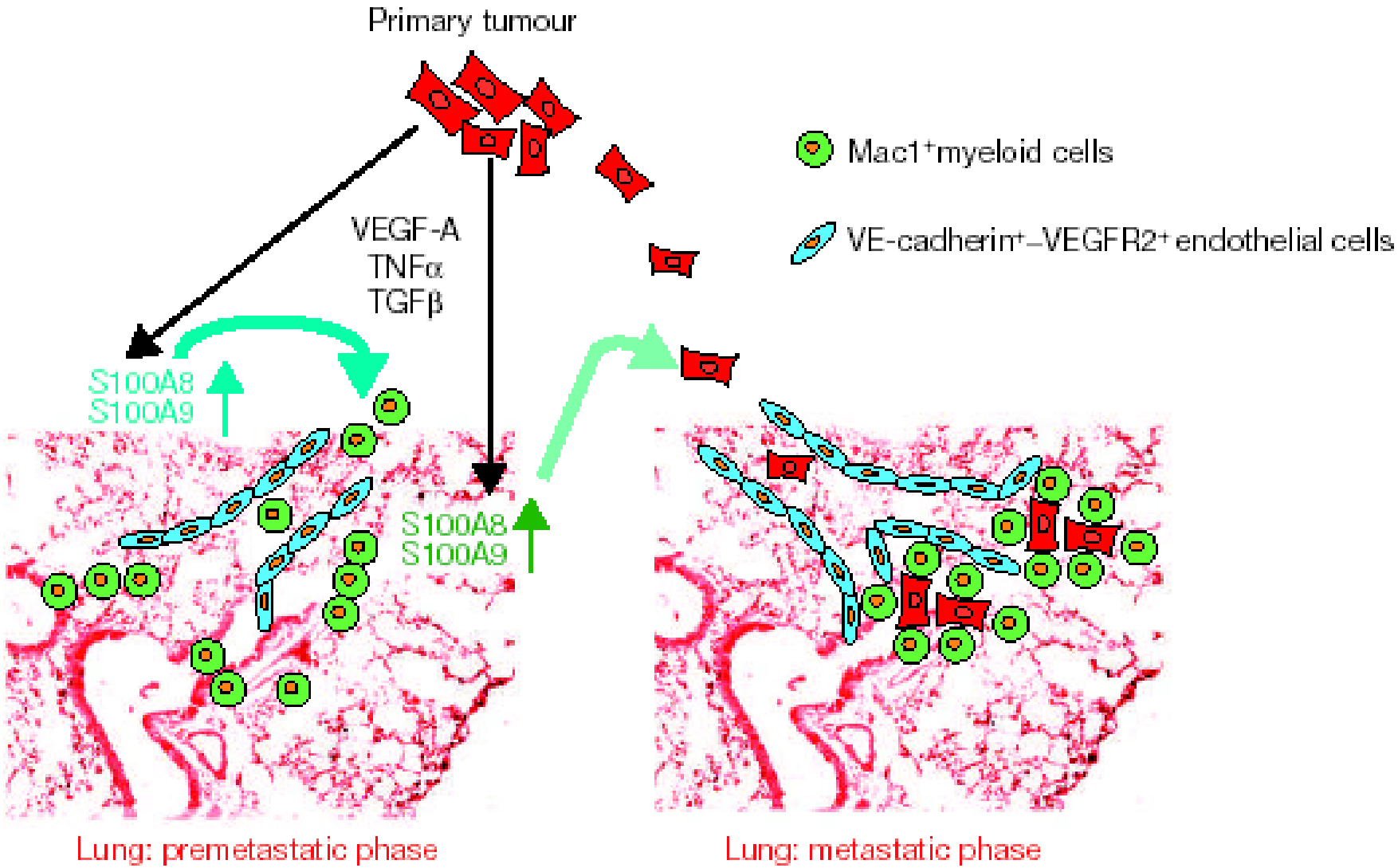
Chemokine-chemokine receptor system can be altered dramatically in neoplastic tissue, particularly at the invasive edges

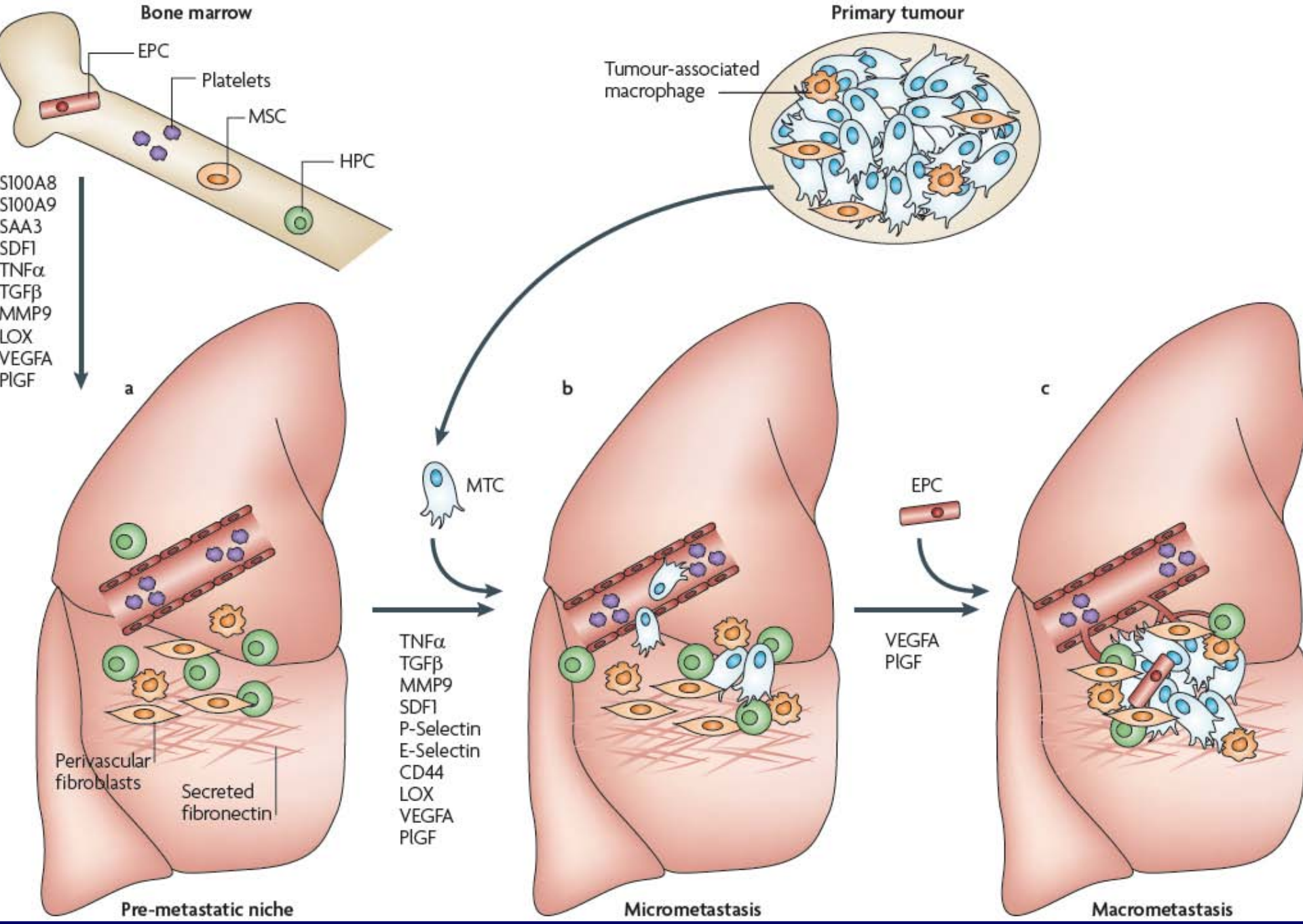
The pattern of tumor metastases is governed by specific interactions between chemokine receptors and their ligands

Targeted metastasis of breast cancer cells



Establishment of a premetastatic niche by tumor cells.

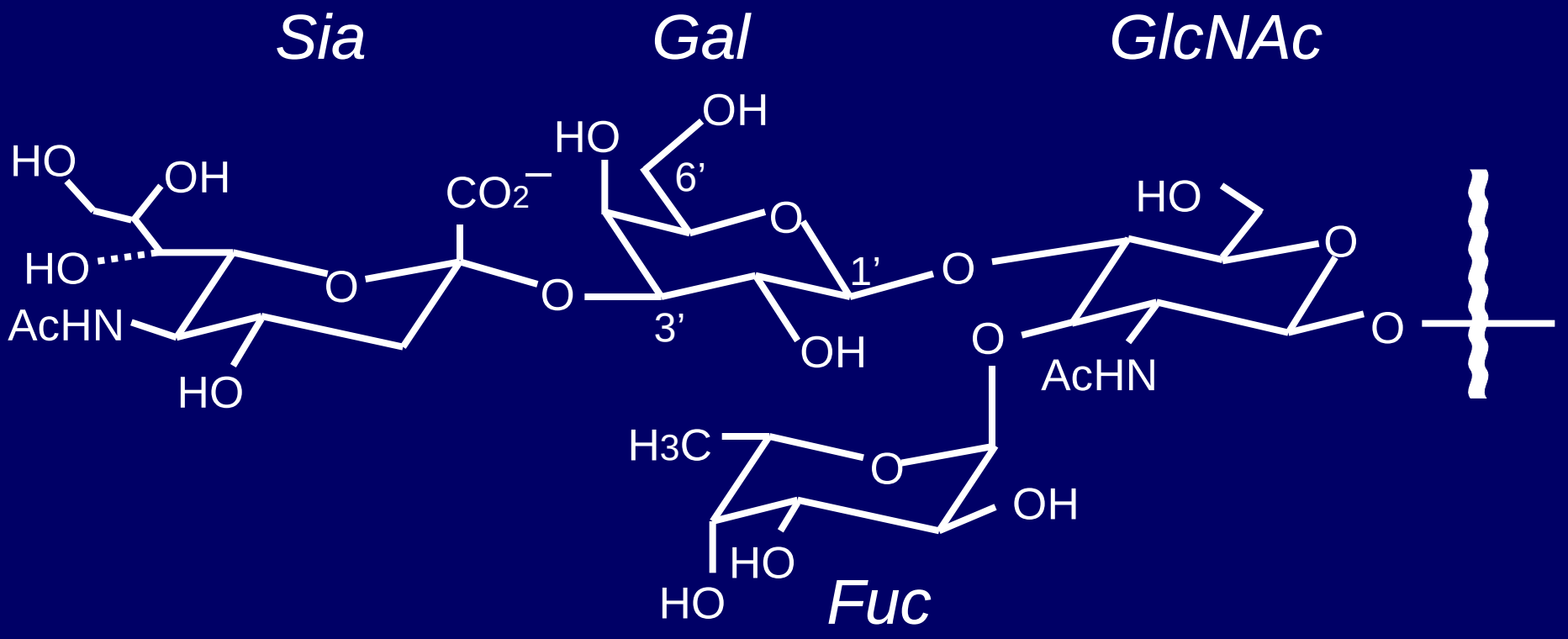



Bone marrow
EPC
Platelets
MSC
HPC
S100A8
S100A9
SAA3
SDF1
TNFα
TGFβ
MMP9
LOX
VEGFA
PlGF
Primary tumour
Tumour-associated macrophage
a
b
c
MTC
EPC
TNFα
TGFβ
MMP9
SDF1
P-Selectin
E-Selectin
CD44
LOX
VEGFA
PlGF
VEGFA
PlGF
Perivascular fibroblasts
Secreted fibronectin
Pre-metastatic niche
Micrometastasis
Macrometastasis

Tumor cells utilize leukocyte adhesion mechnisms to disseminate

- Metastatic progression of many epithelial carcinomas correlates with expression of sialyl-Lewis X epitope on tumor cells
- Lung colonization of sialyl-Lewis X-positive melanoma cells is significantly reduced in E/P-selectin-deficient mice

Sialyl Lewis x

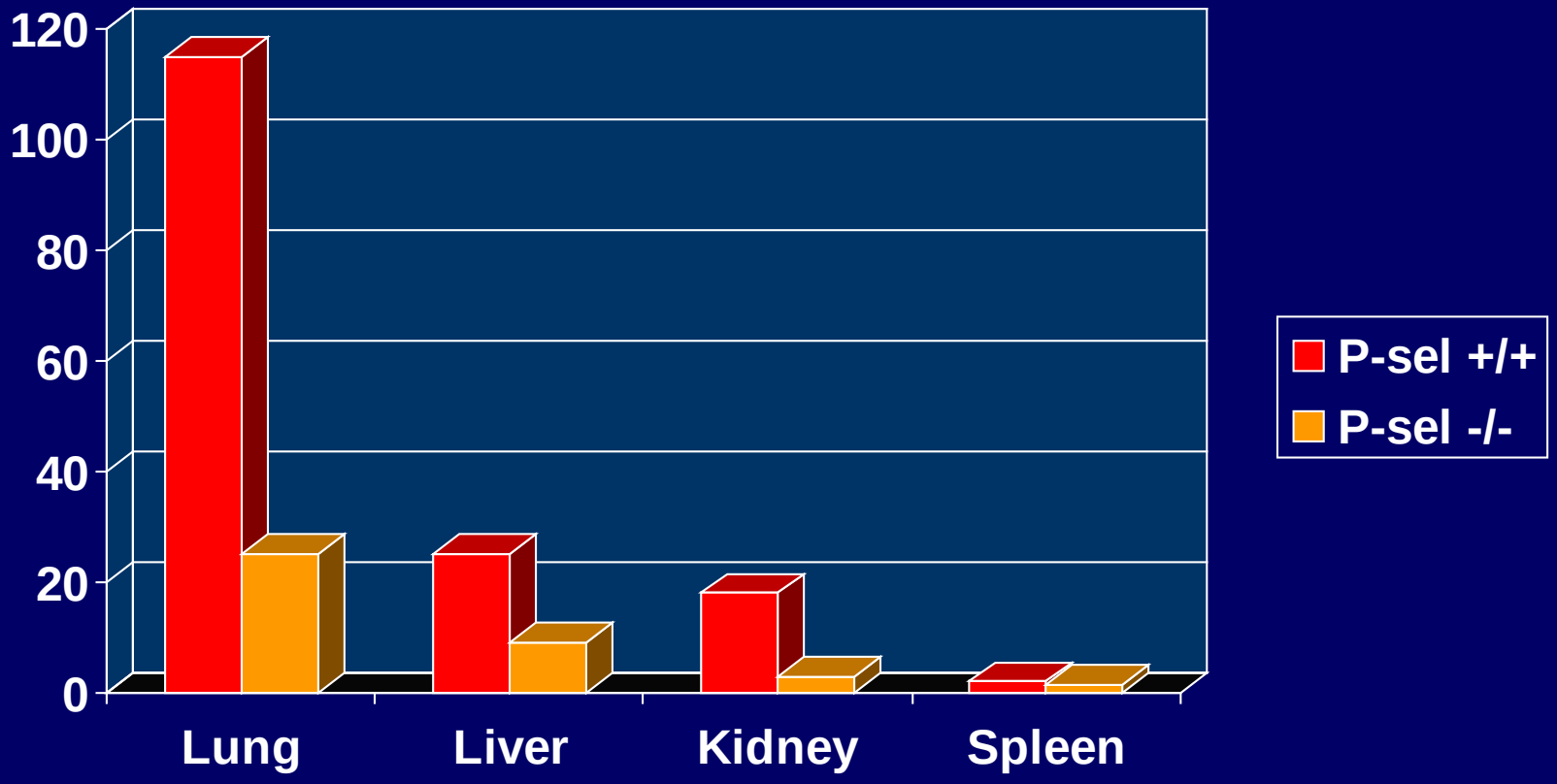


Siaα2 $\rightarrow$ 3Galβ1 $\rightarrow$ 4(Fucα1 $\rightarrow$ 3)GlcNAc

Tumor carbohydrate antigens

- Serve as useful cancer markers
- Sialyl Lewis A colorectal and pancreas adenocarcinomas
- Sialyl Lewis X brest carcinoma, colon and lung adenocarcinomas
- There is a positive correlation between sialyl Lewis A or X expression in cancer cells and poor prognosis

P-selectin affects the seeding of tumor cells



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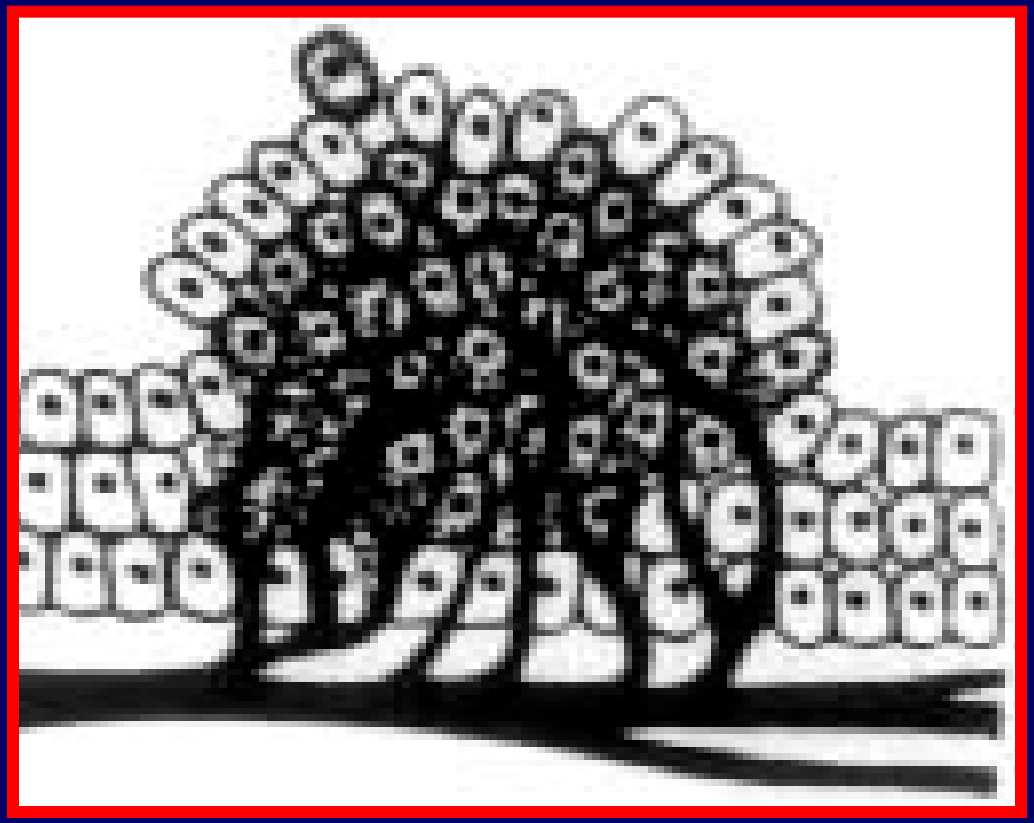
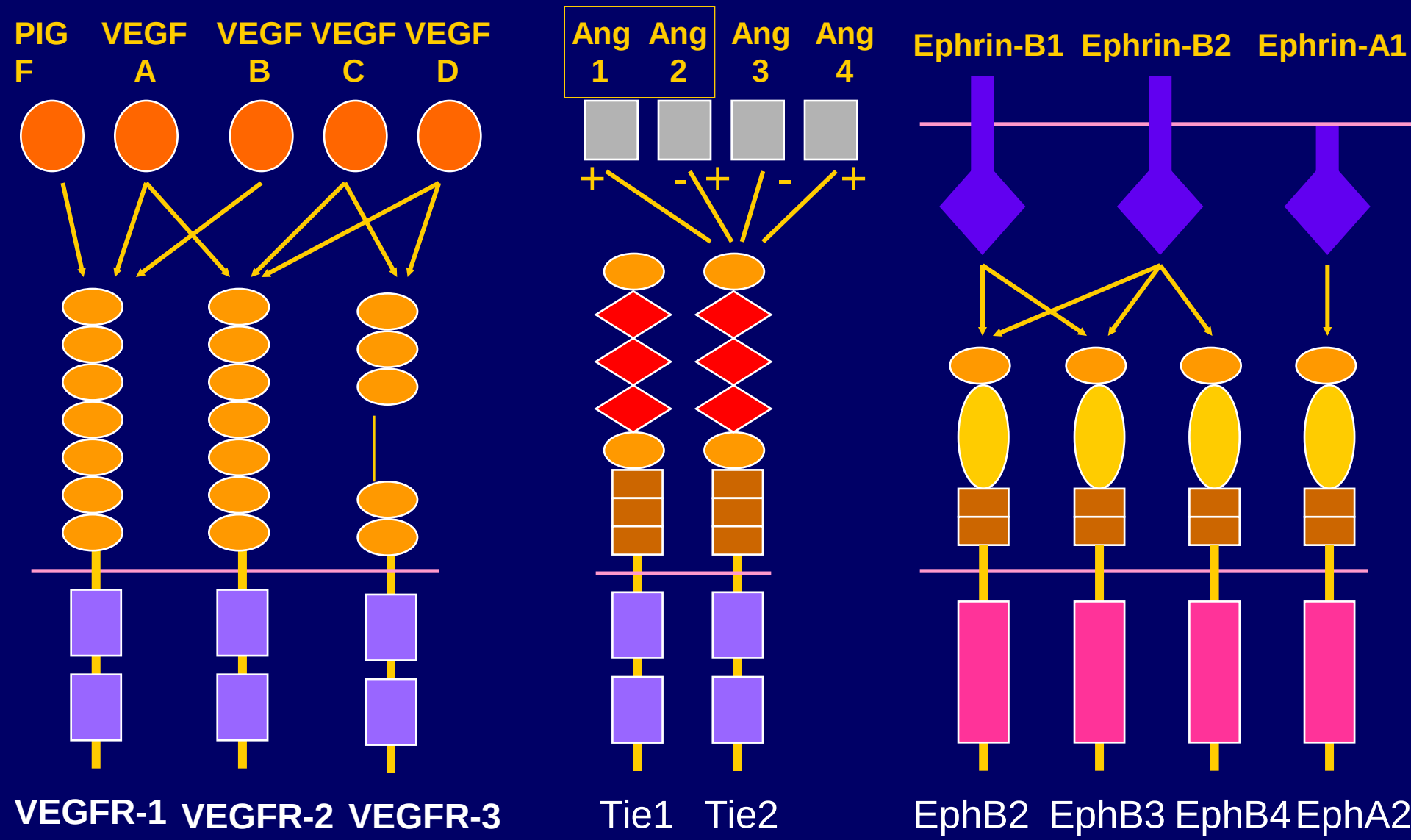
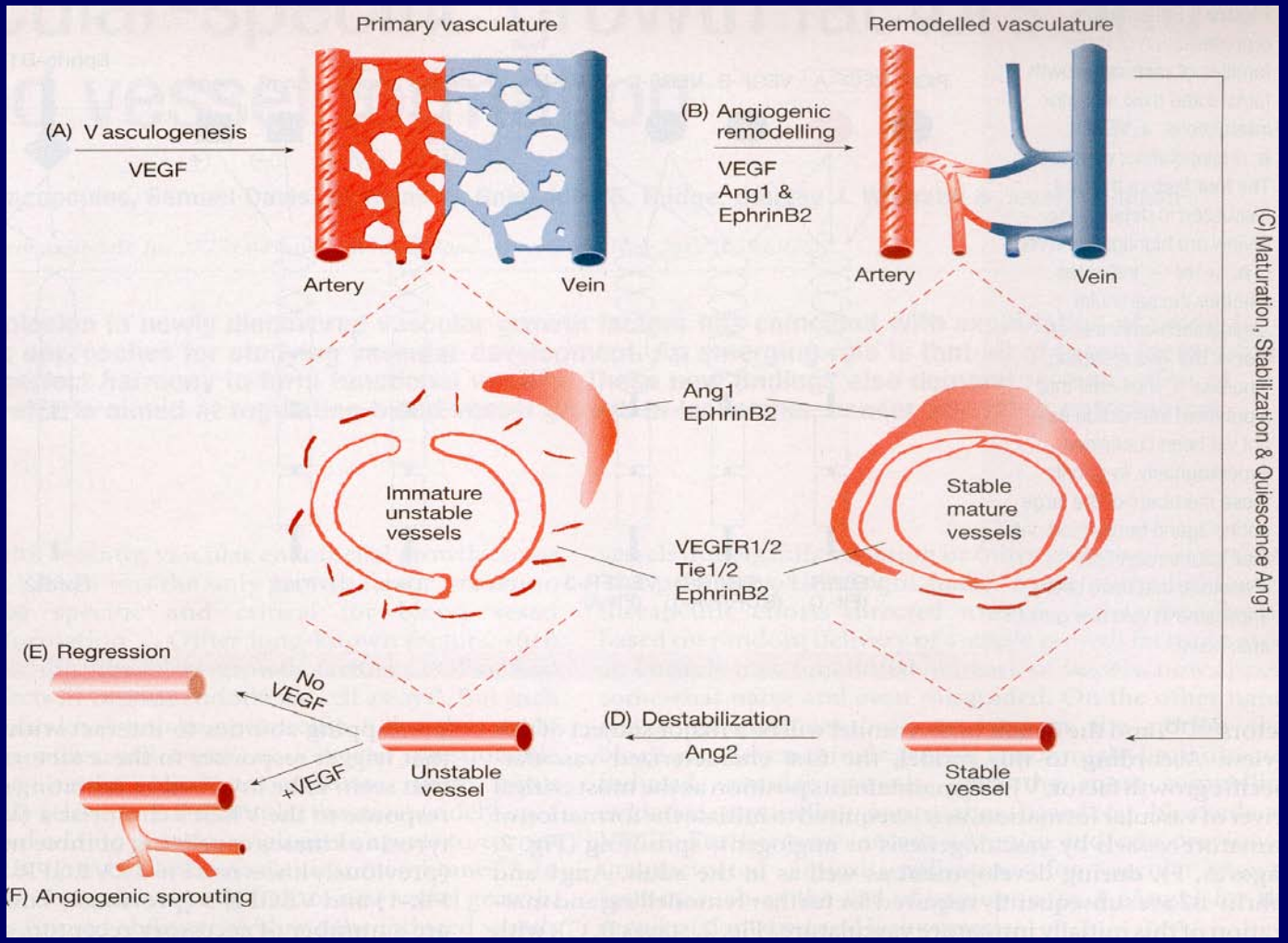
Vascularisation



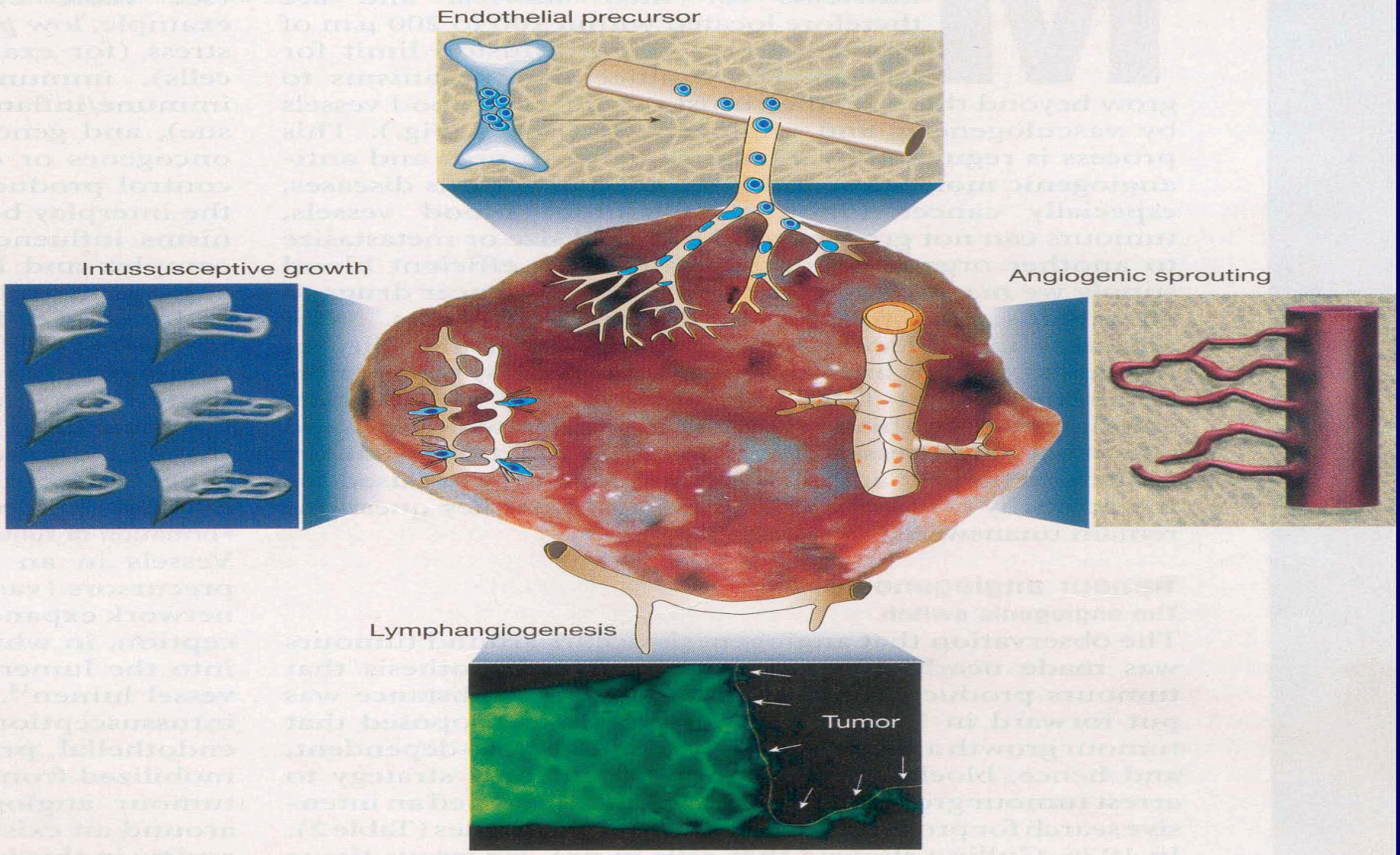
Angiogenic factors



The roles of vascular growth factors during vessels formation

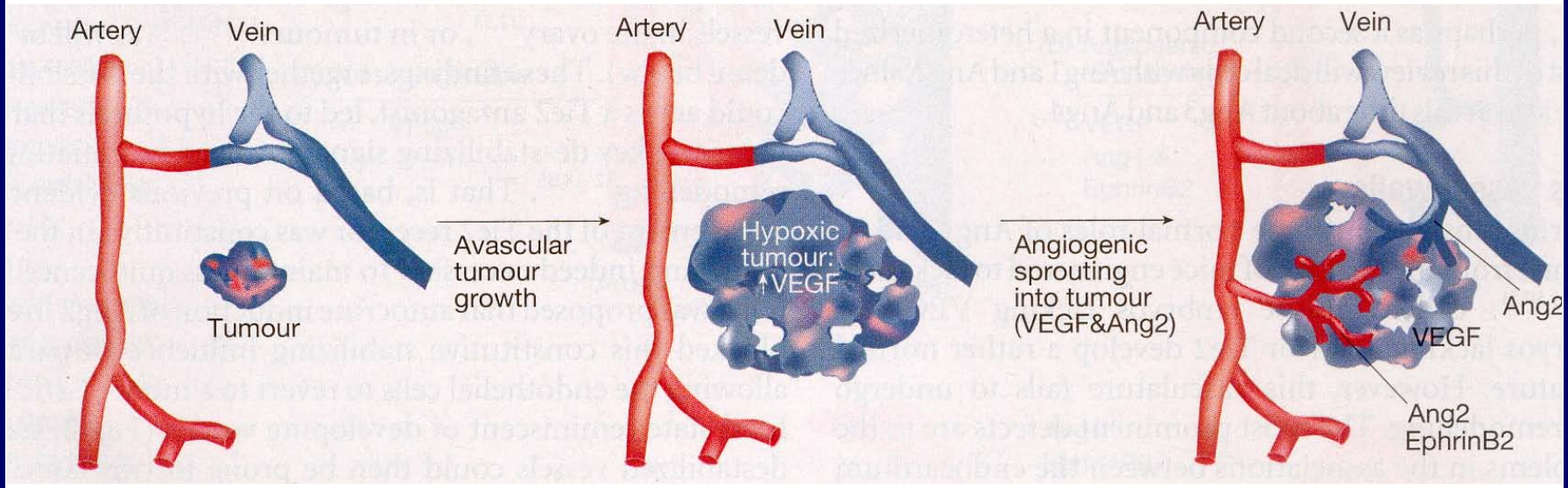


Formation of tumour vessels

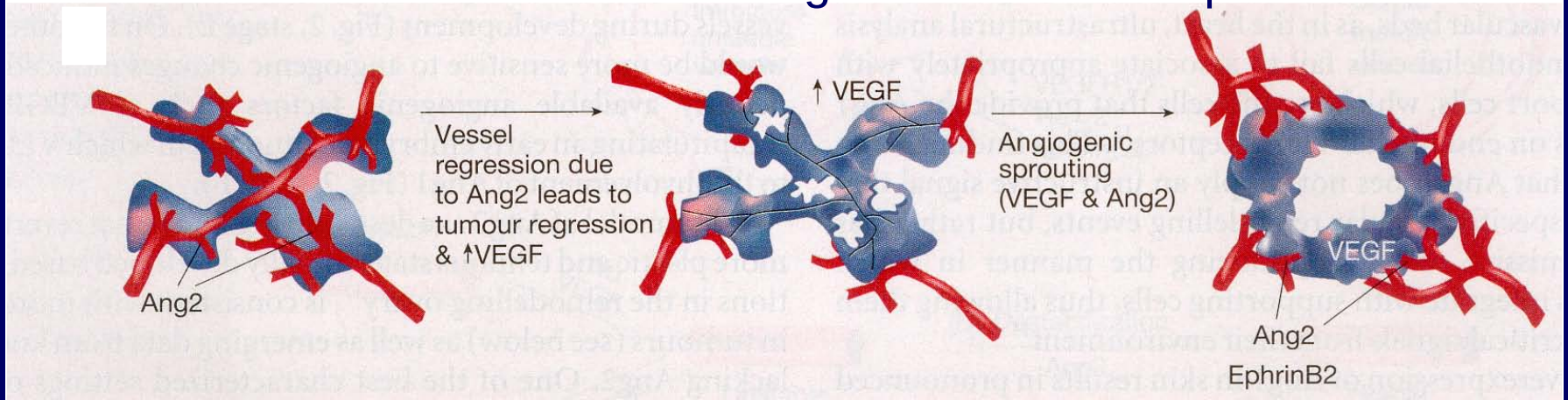


Models of tumour angiogenesis

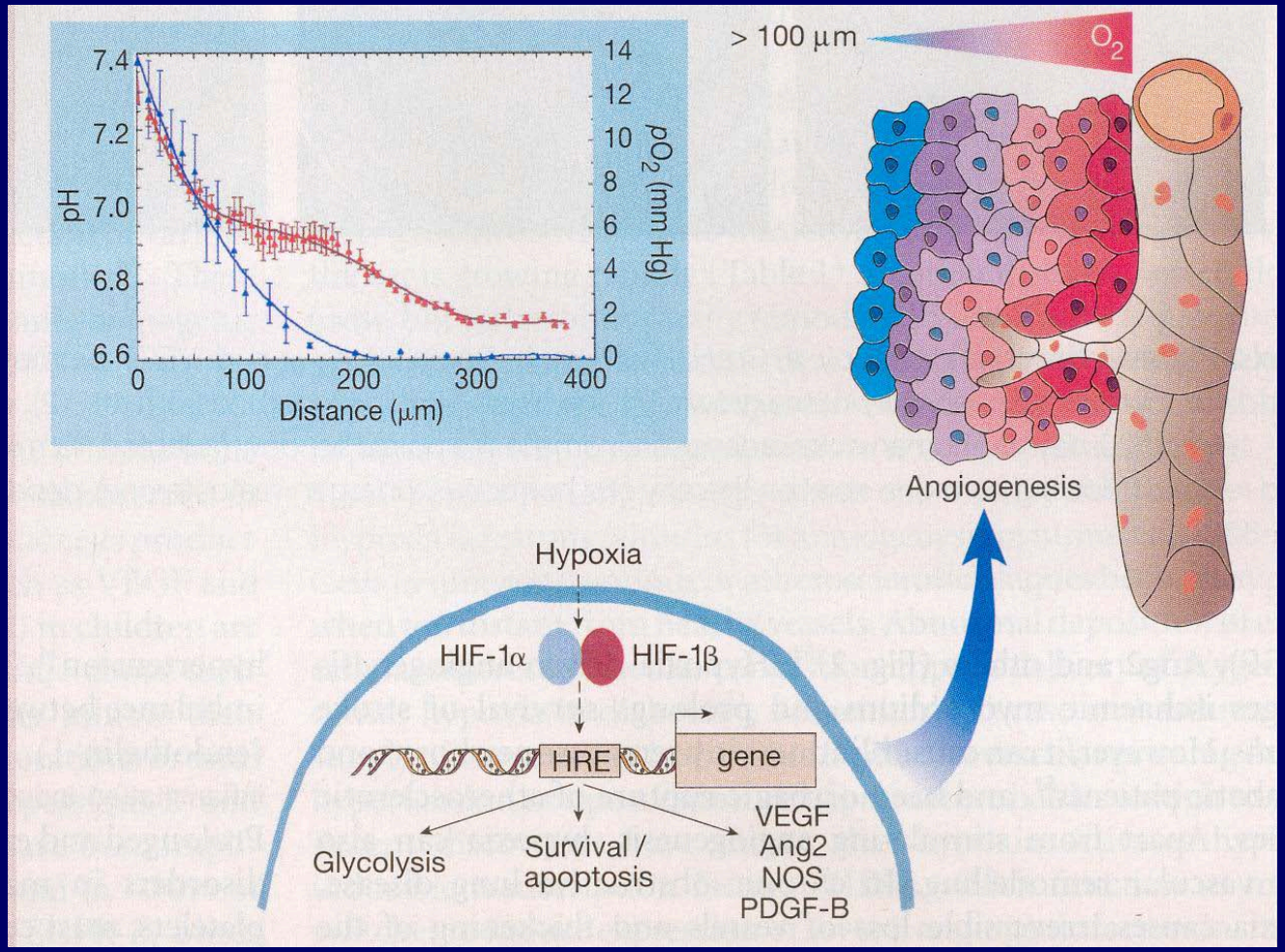
Model of avascular tumour initiation



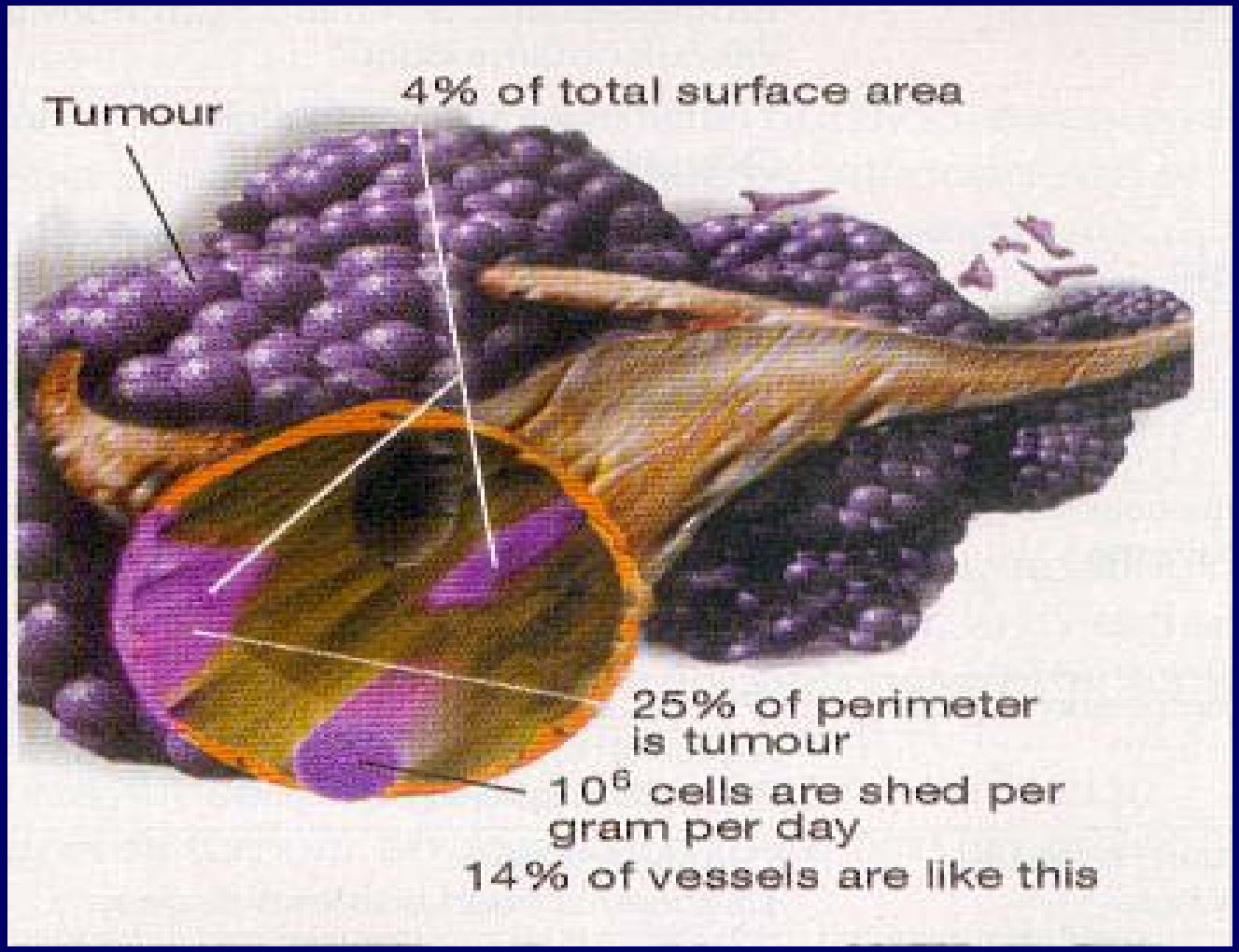
Tumour initiation involving host vessel co-option

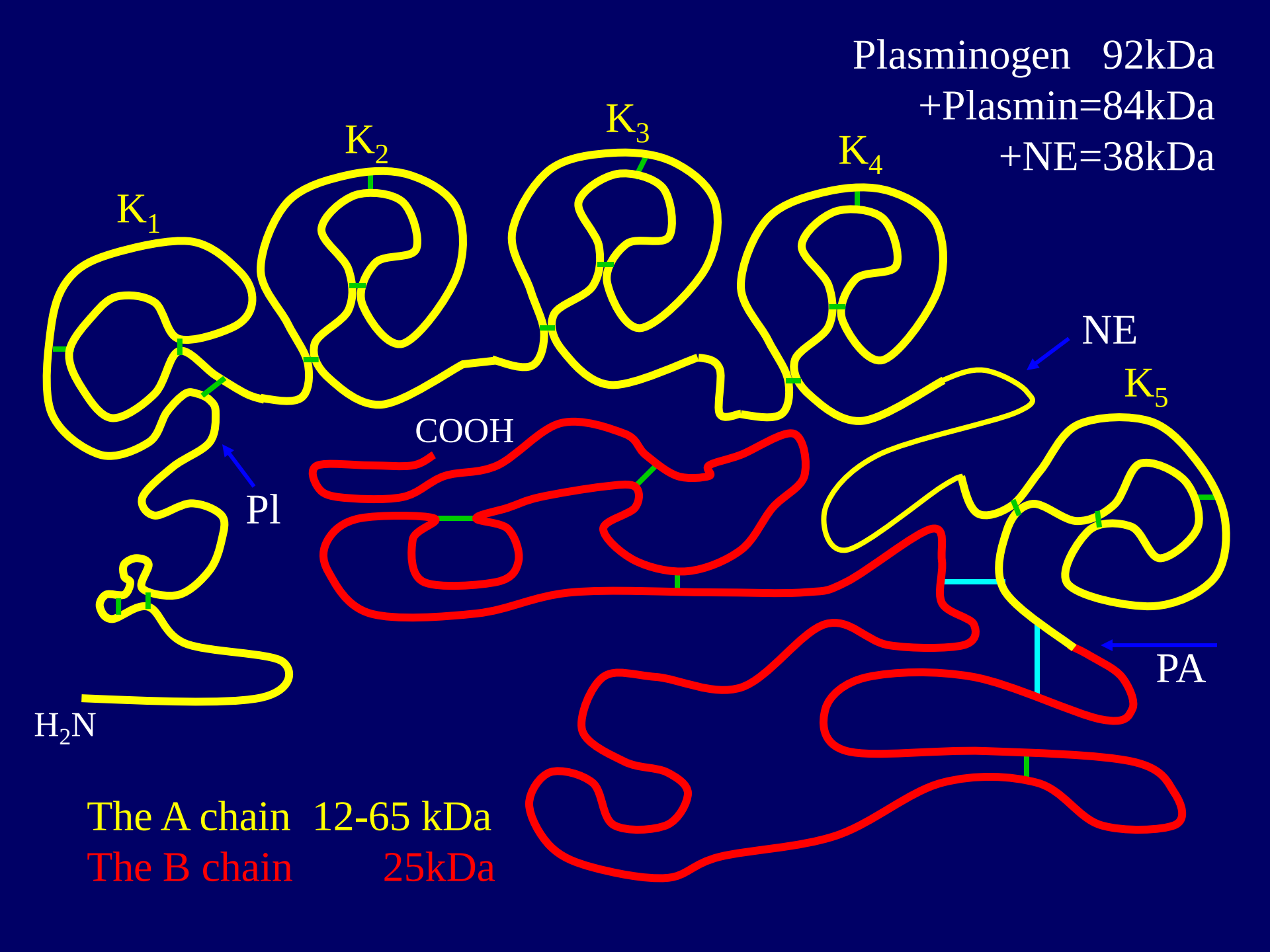


Role of hypoxia in tumour angiogenesis

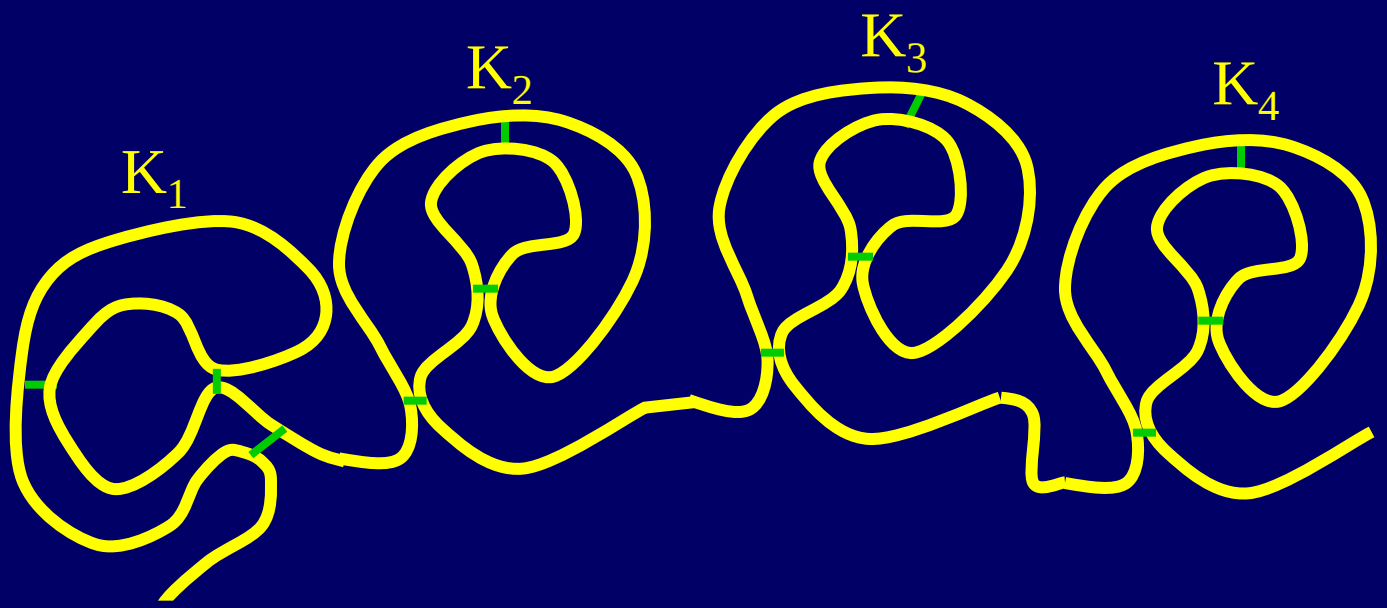


Mosaic vessels in tumours

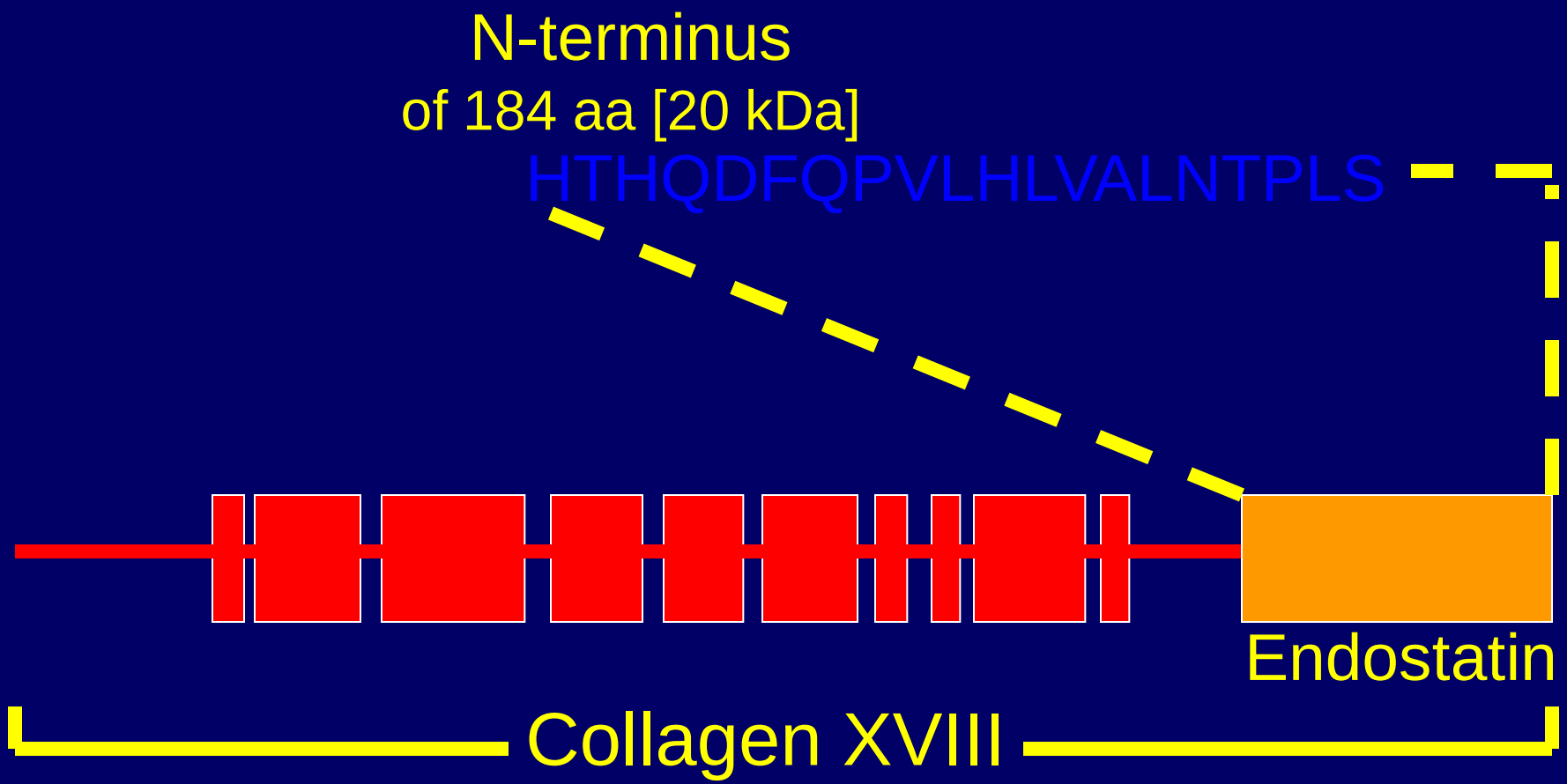



Plasminogen 92kDa
+Plasmin=84kDa
+NE=38kDa
K1
K2
K3
K4
K5
NE
COOH
Pl
PA
H2N
The A chain 12-65 kDa
The B chain 25kDa

Angiostatin



Endostatin


N-terminus
of 184 aa [20 kDa]
HTHQDFQPVLHLVALNTPLS
Endostatin
Collagen XVIII

Antiangiogenic molecules

- Angiostatin
- Endostatin
- Antiangiogenic fragment of antithrombin
- Antiangiogenic fragment of thrombospondin