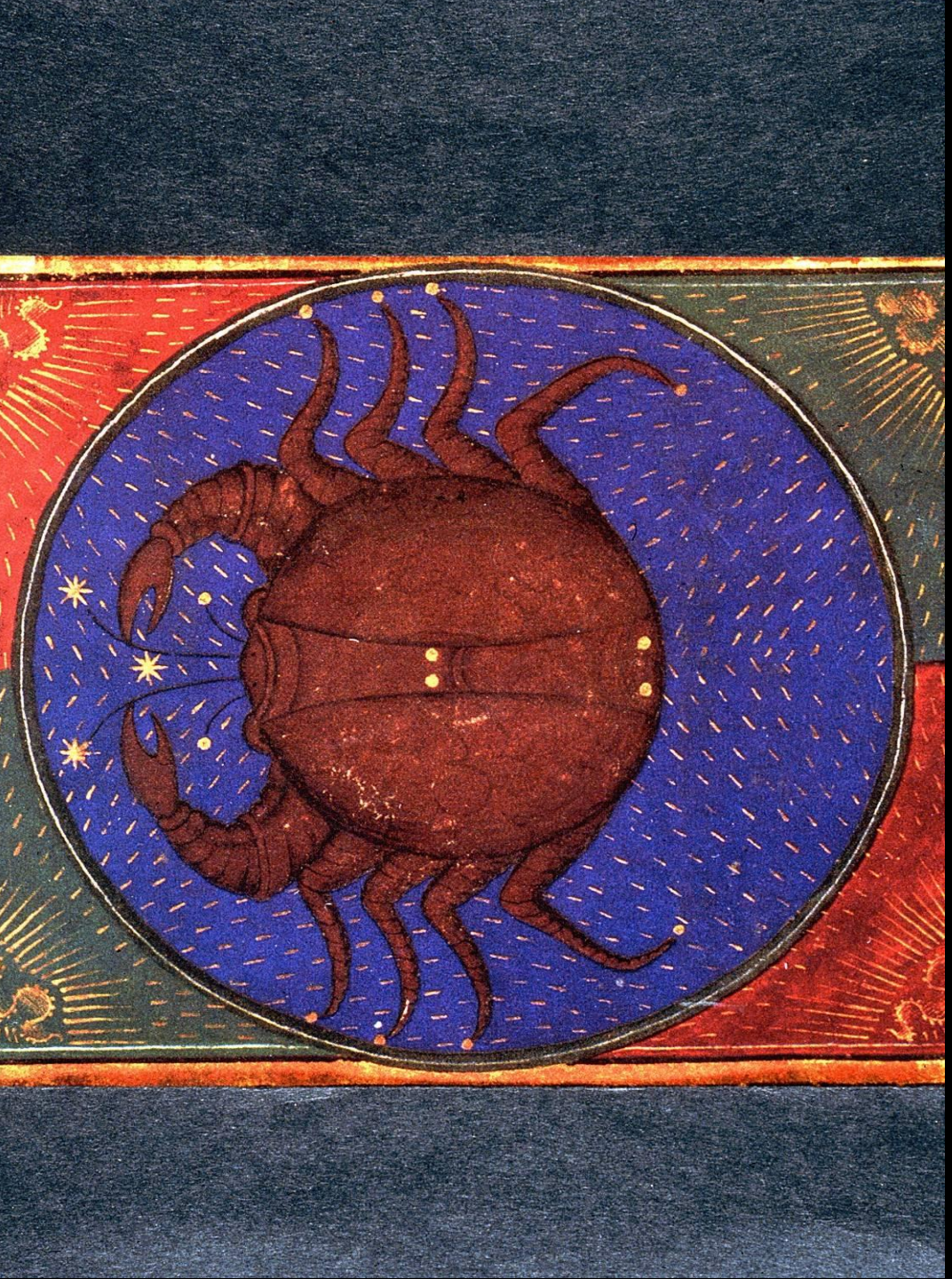
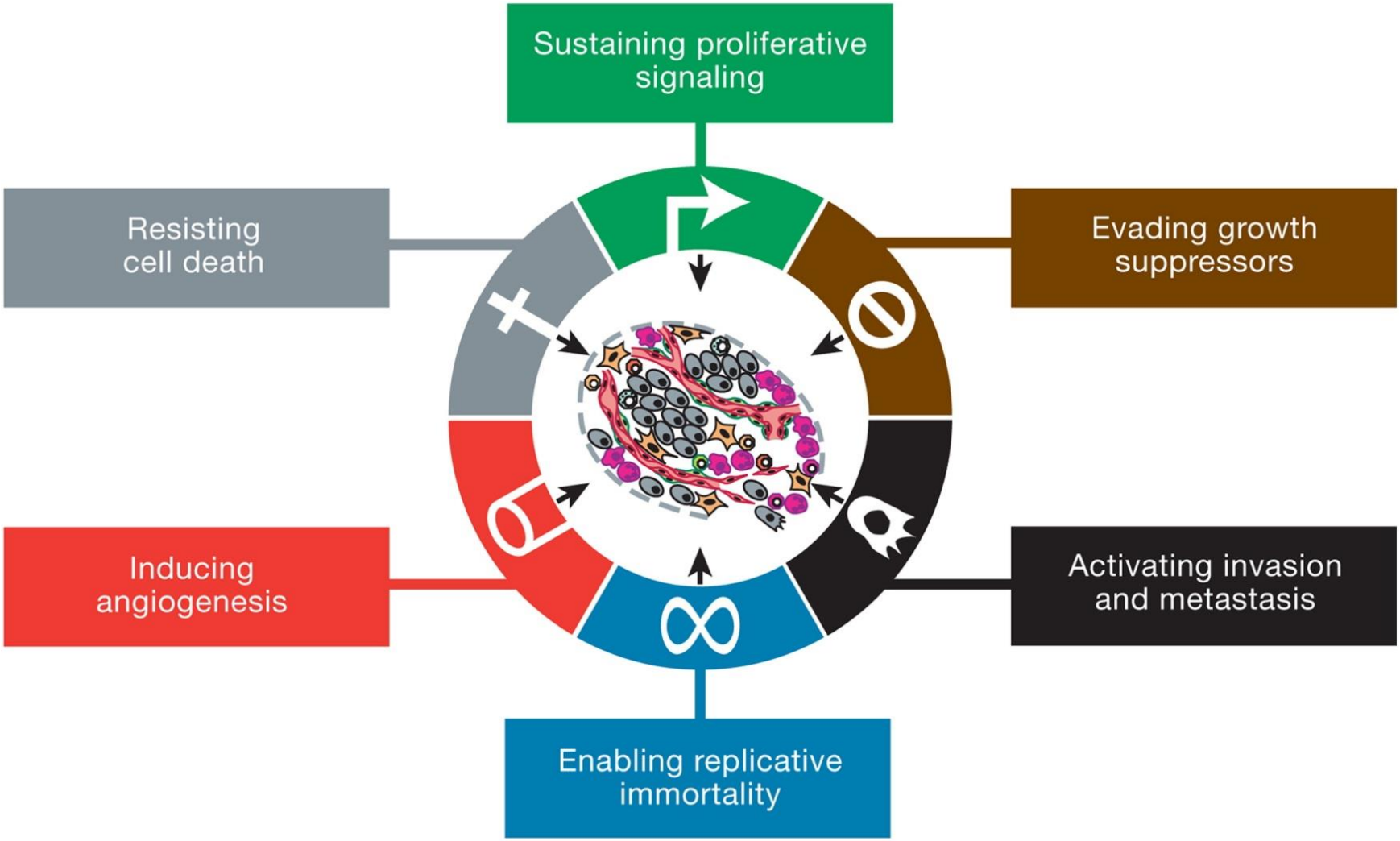
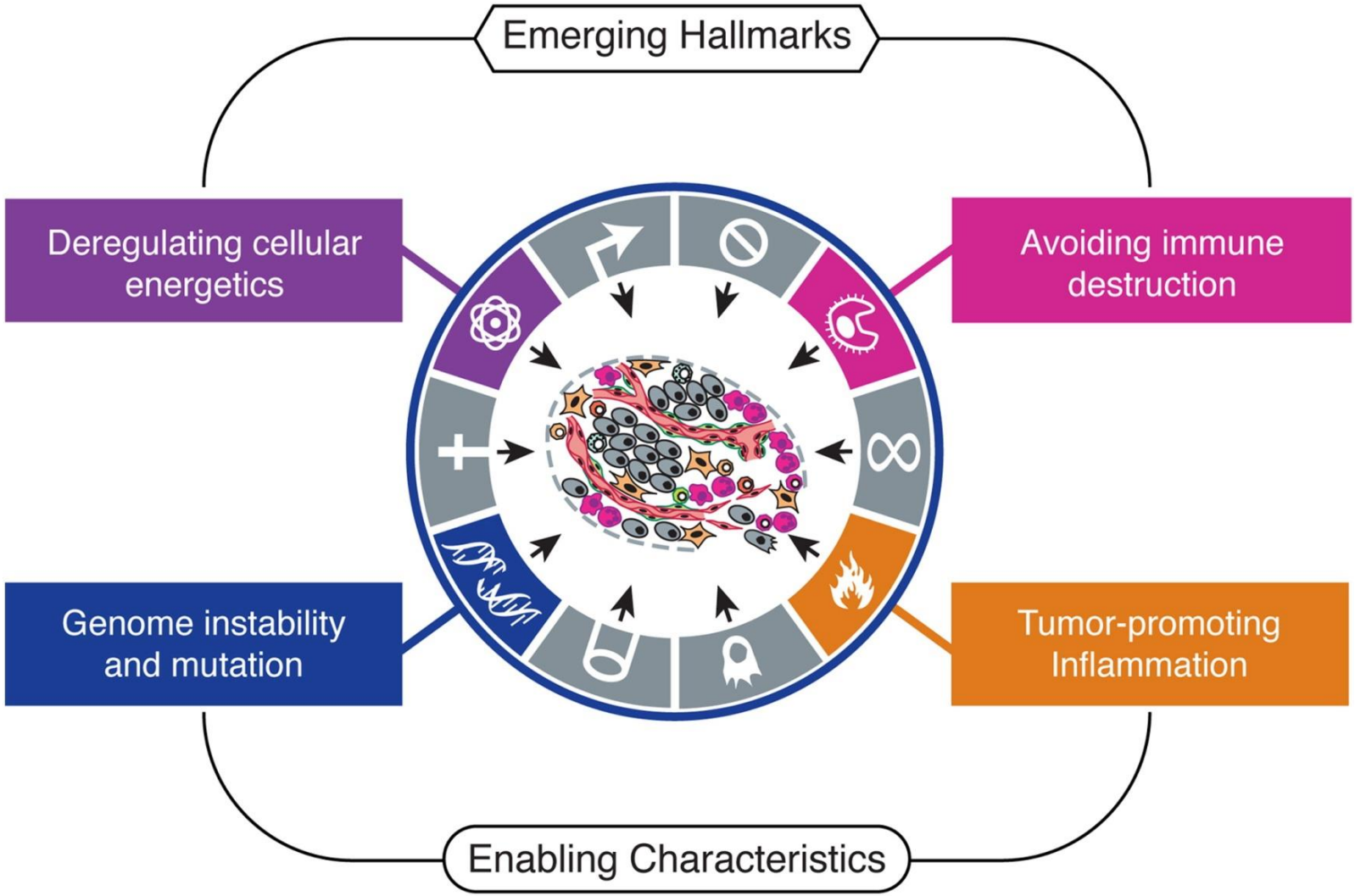


ANGIONESESIS
EMT
METASTASIS



Hallmarks of Cancer: original six hallmarks, proposed by Hanahan and Weinberg in 2000, that enable tumor growth and metastasis. Provided an overview for understanding the biology of cancer.



Updated Hallmarks of Cancer: Hanahan and Weinberg in 2011 added two emerging hallmarks and two enabling characteristics that facilitate cancer devlopment.

Cancer is a disease of tissues, not just cells!

- For a long time, cancer research has focused mainly on cancer cells and their defective genes.
- In many cancers, non-neoplastic cells account for up to 90% of the cells in the tumor mass.
- The “tumor stroma”, both inside the tumor mass and also surrounding it, contains these non-neoplastic cells.
- Interactions between the tumor cells and stroma cells (“heterotypic signaling”) influence tumor growth and progression.

EMT, microenvironment, and metastasis

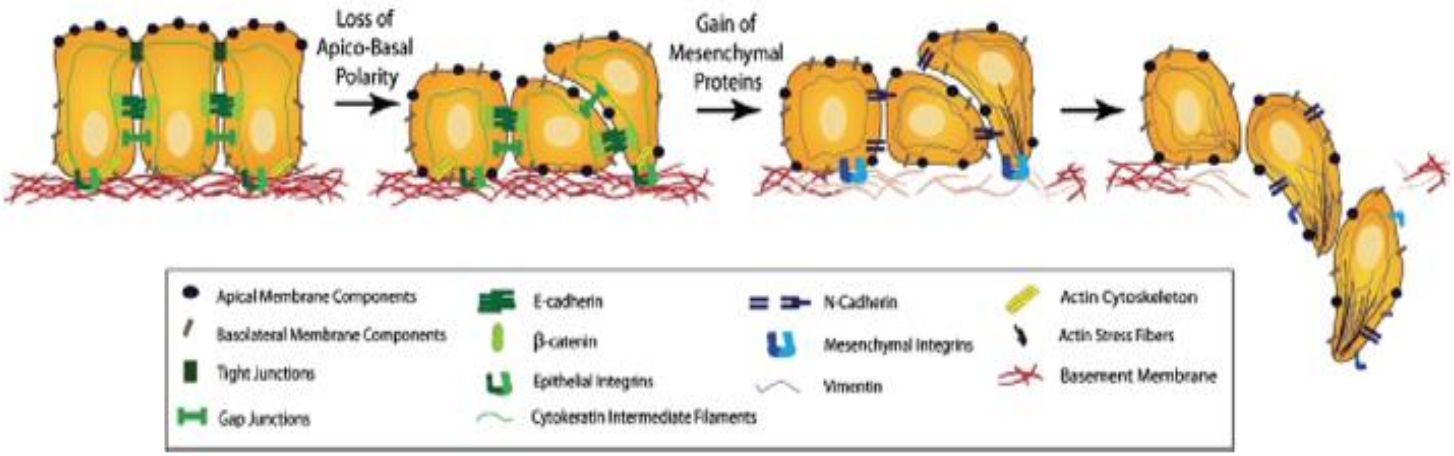
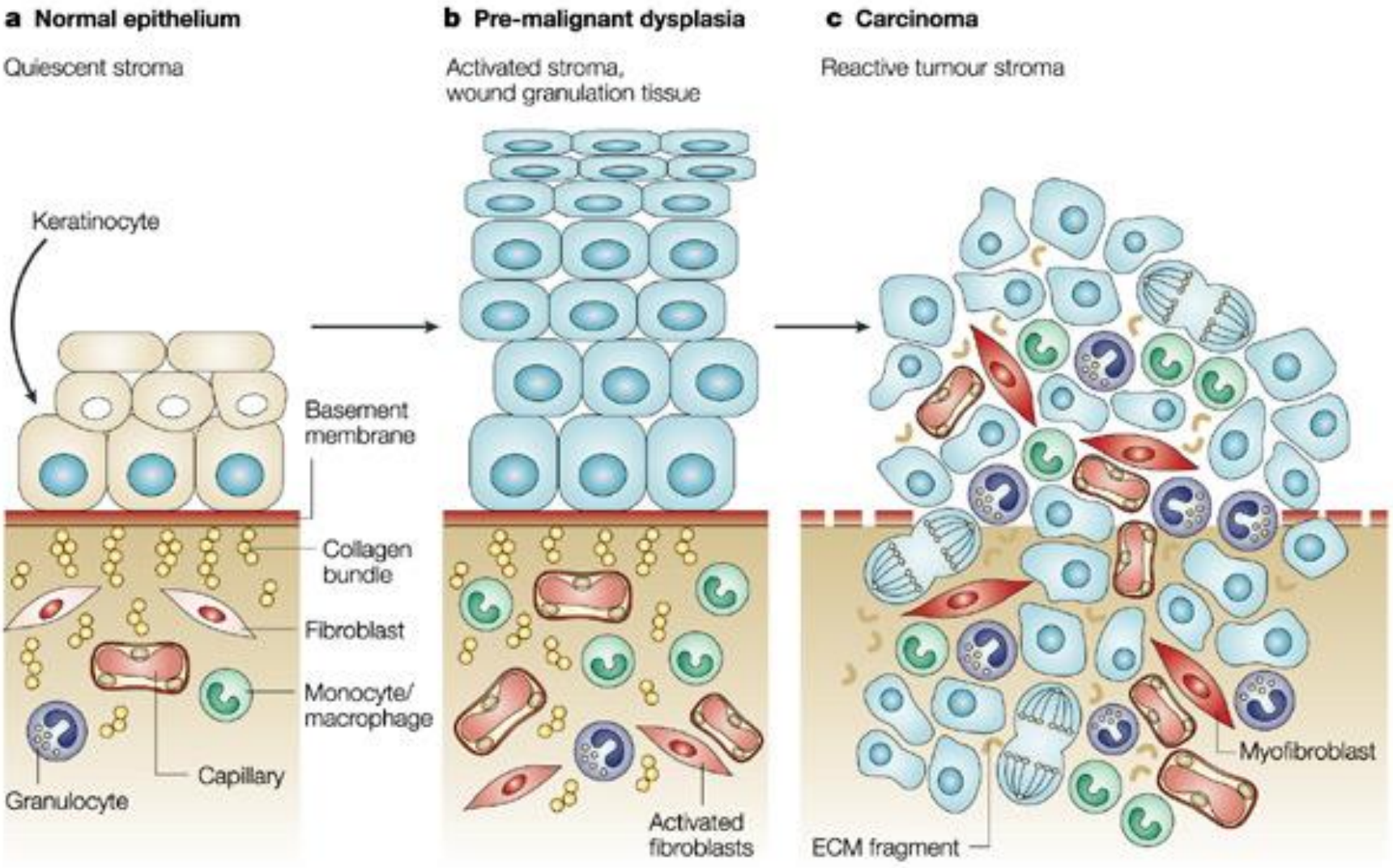
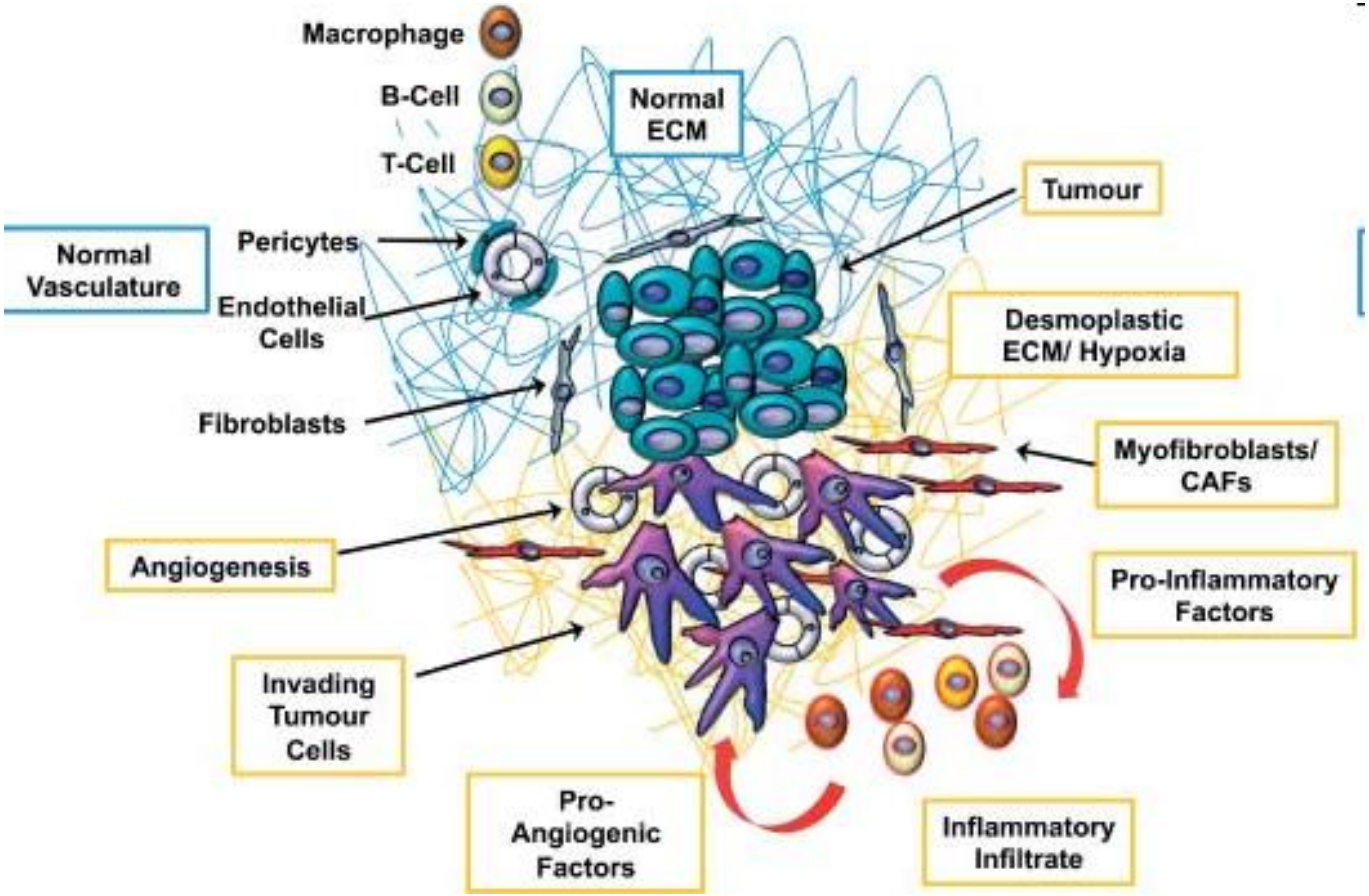
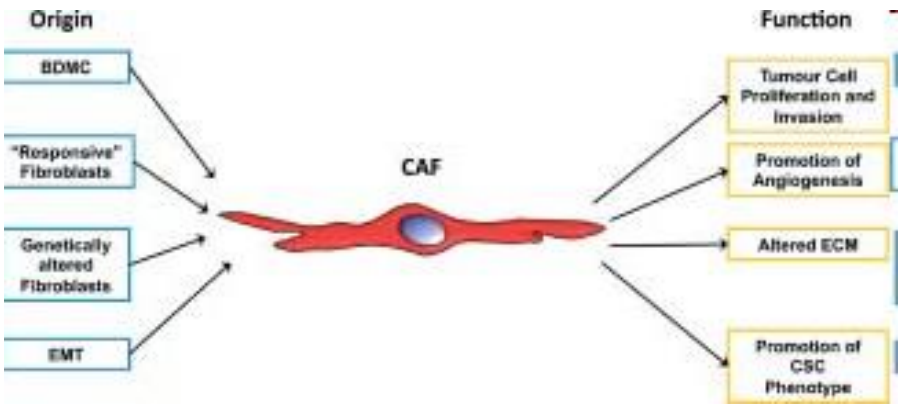


Figure 1. Conceptual diagram of molecular, phenotypic, and behavioral transitions of cells undergoing EMT. Reproduced with permission from Micalizzi DS, Farabaugh SM, and Ford HL, Epithelial-mesenchymal transition in cancer: parallels between normal development and tumor progression. J Mammary Gland Biol Neoplasia 2010; 15: 117-134.

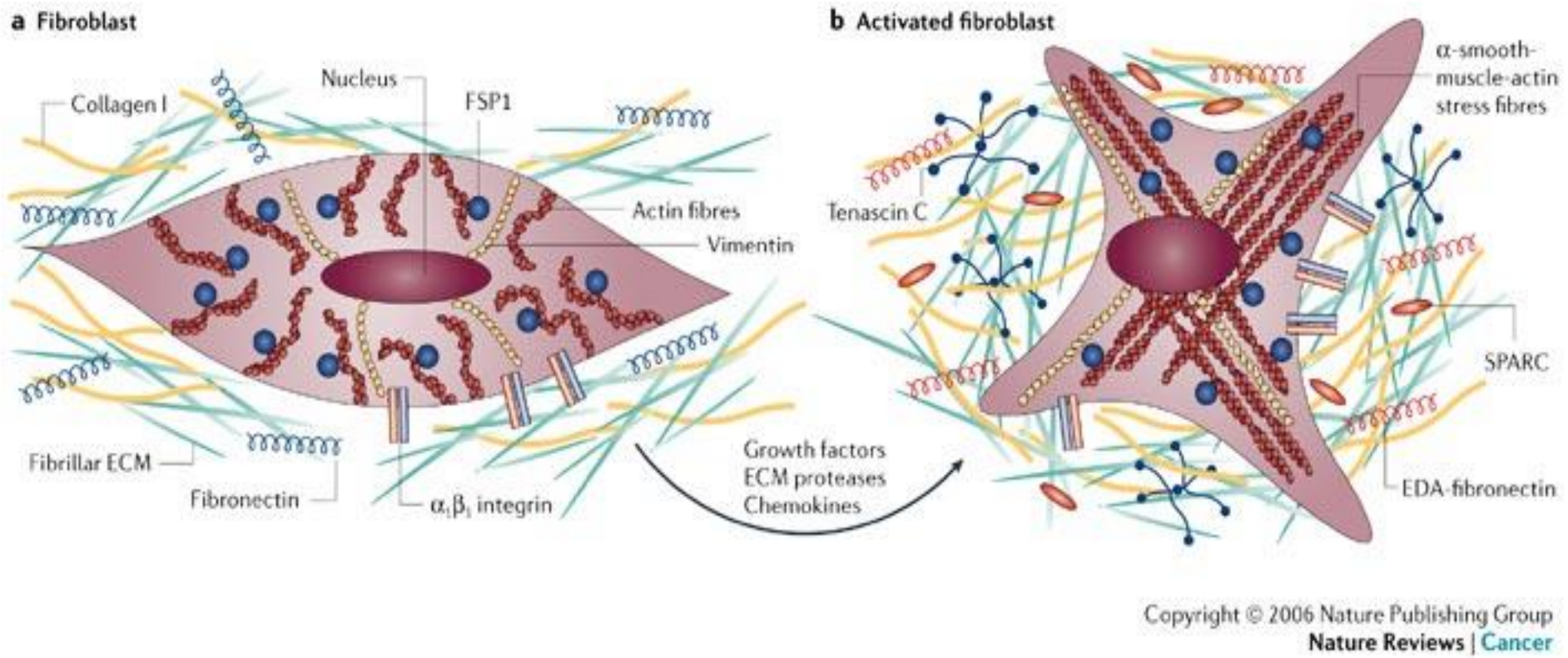
Extracellular matrix in CANCER

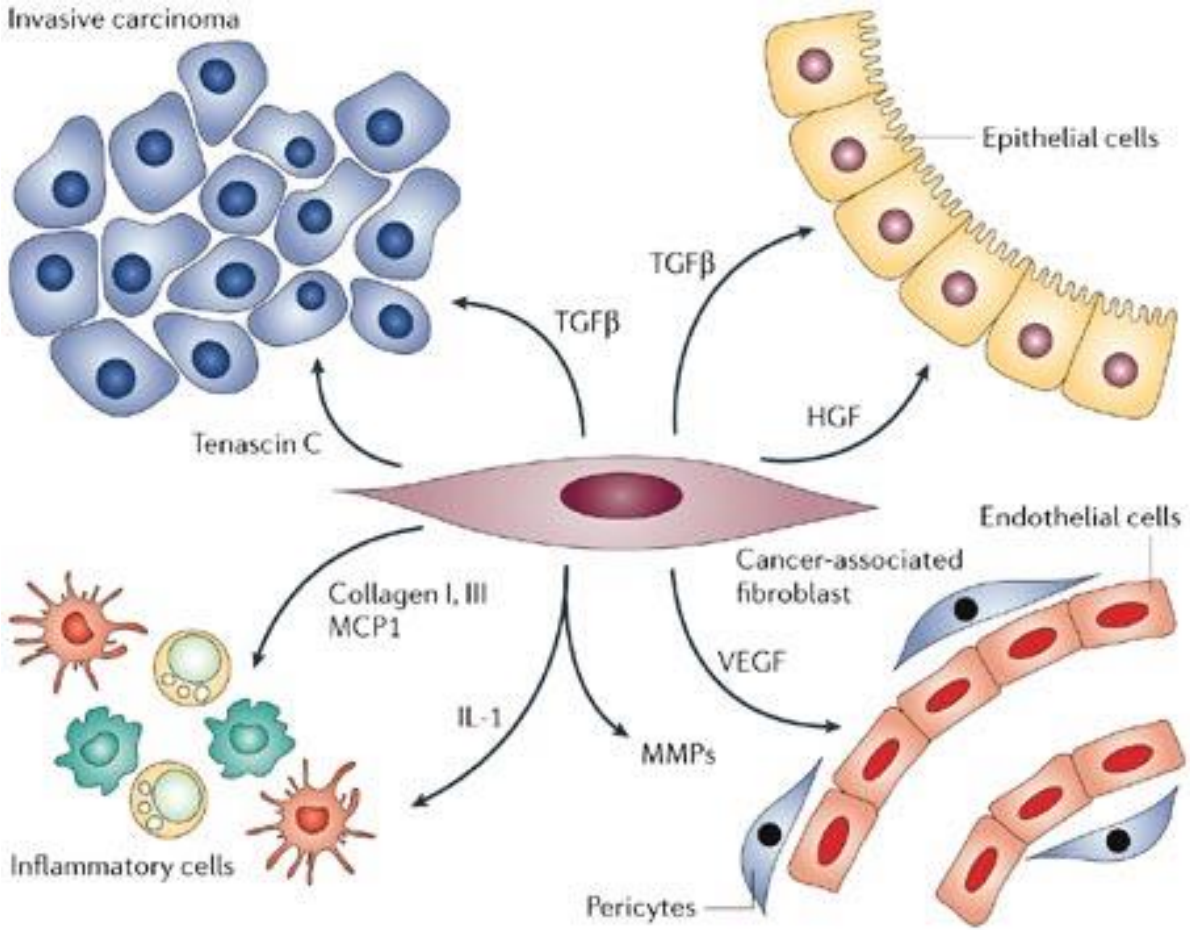



Macrophage
B-Cell
T-Cell
Normal ECM
Tumour
Normal Vasculature
Pericytes
Endothelial Cells
Desmoplastic ECM/ Hypoxia
Fibroblasts
Myofibroblasts/ CAFs
Angiogenesis
Pro-Inflammatory Factors
Invading Tumour Cells
Pro-Angiogenic Factors
Inflammatory Infiltrate


Origin
BDMC
"Responsive" Fibroblasts
Genetically altered Fibroblasts
EMT
CAF
Function
Tumour Cell Proliferation and Invasion
Promotion of Angiogenesis
Altered ECM
Promotion of CSC Phenotype

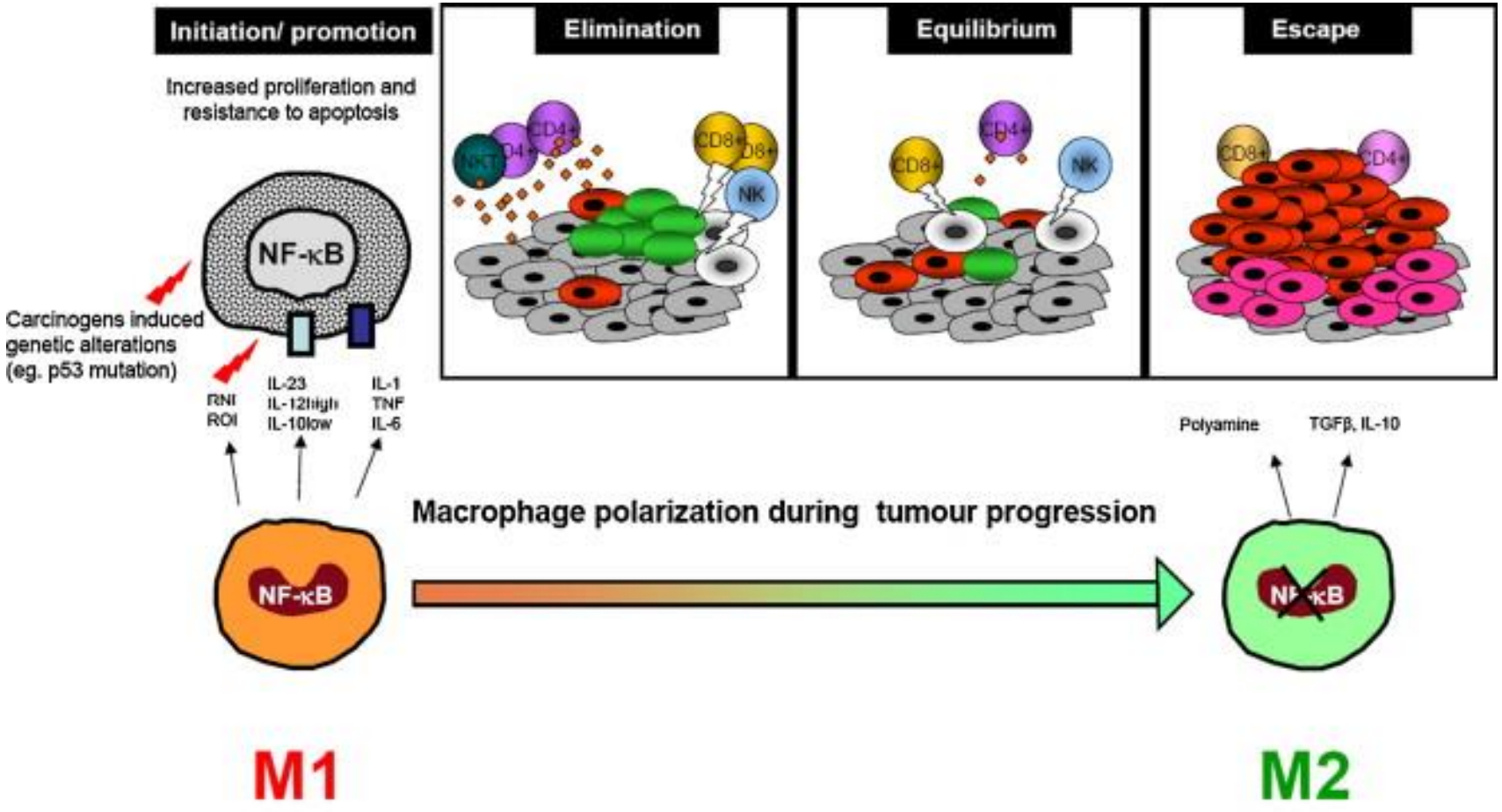
CANCER ASSOCIATED FIBROBLASTS





Nature Reviews | Cancer

M1/M2 MACROPHAGE POLARIZATION



Adapted from Dunn GP et al *Nat. Immunol* 2002

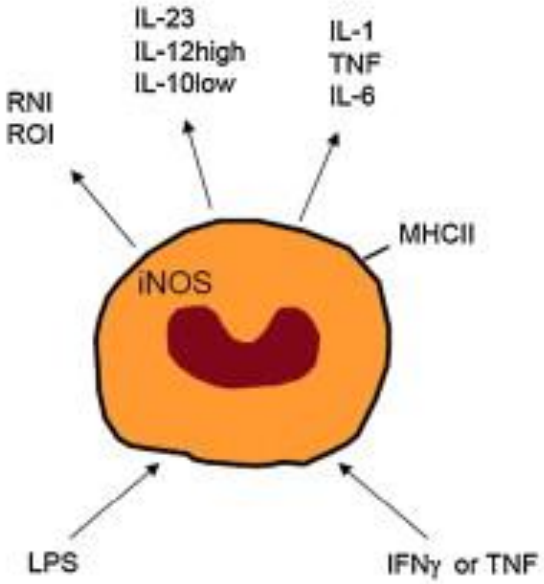
EFFECTS of M1/M2 macrophage polarization

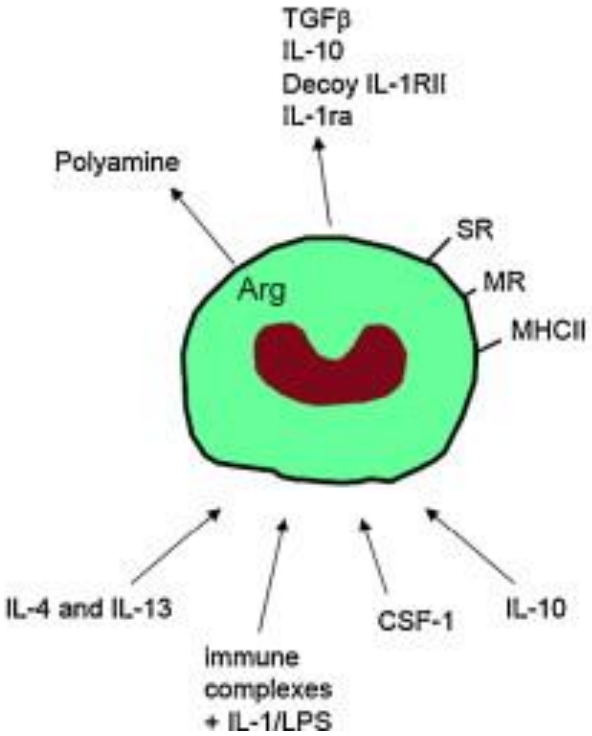
M1

FUNCTIONS
- Th1 RESPONSES
- TYPE I INFLAMMATION; DTH
- KILLING OF INTRACELLULAR PARASYTES
- TUMOR RESISTANCE

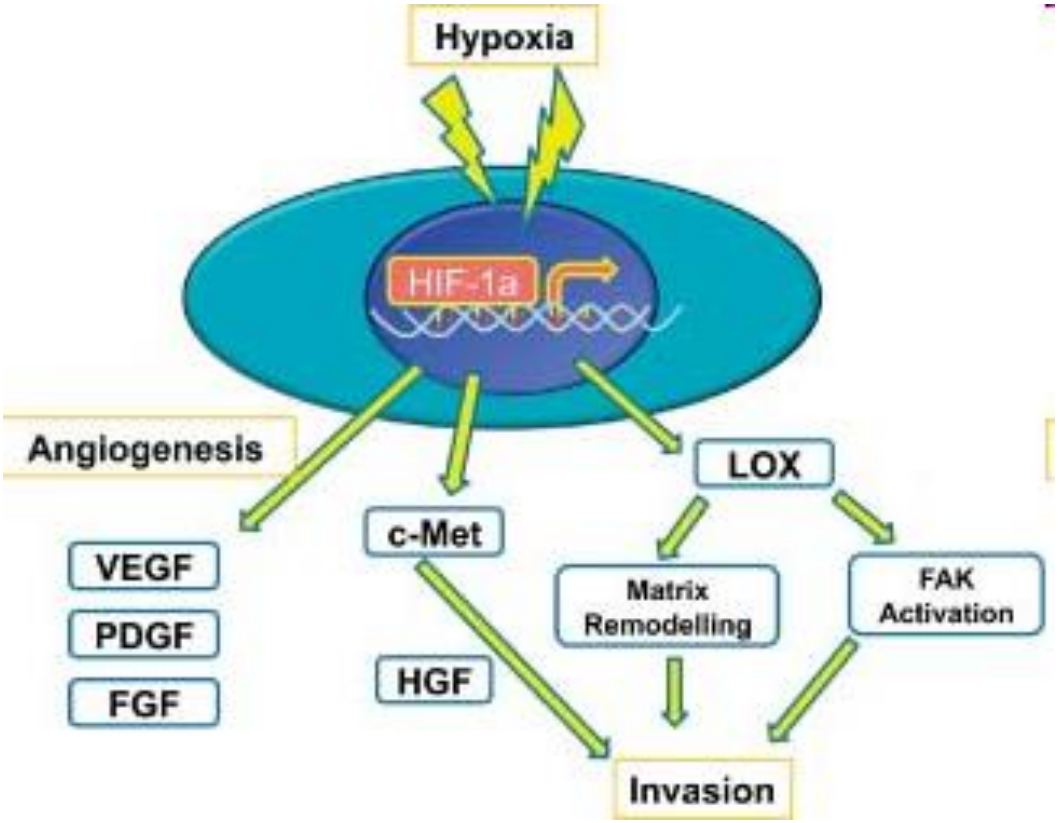
M2

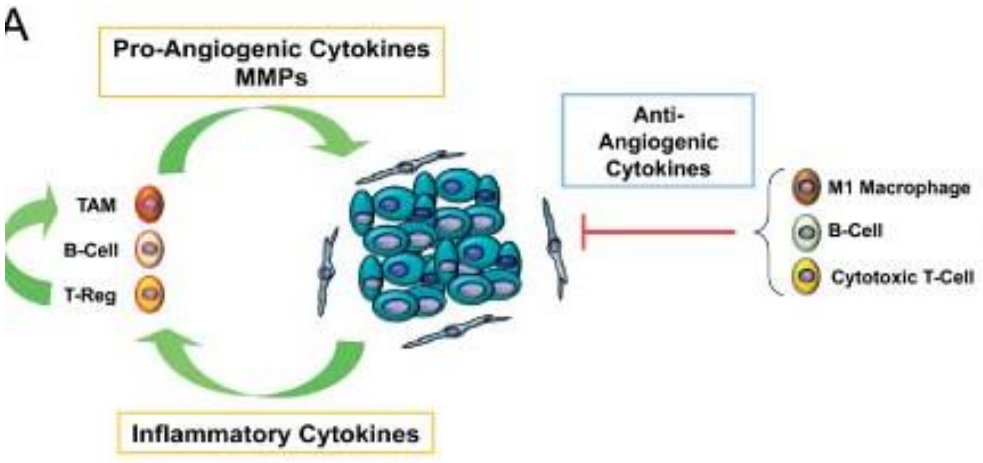
- Th2 RESPONSES;
- TYPE II INFLAMMATION; ALLERGY;
- KILLING AND ENCAPSULATION OF PARASYTES;
- MATRIX DEPOSITION AND REMODELLING;
- TUMOR PROMOTION

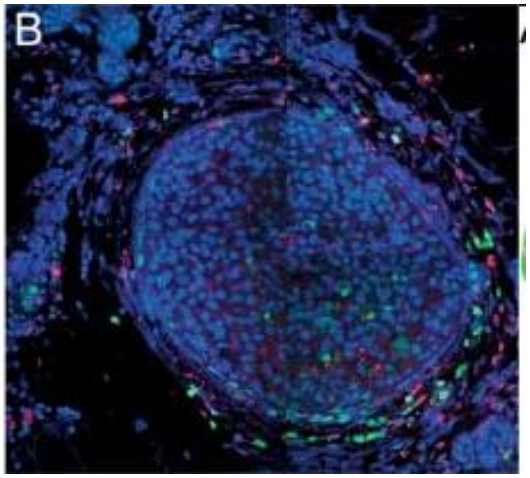




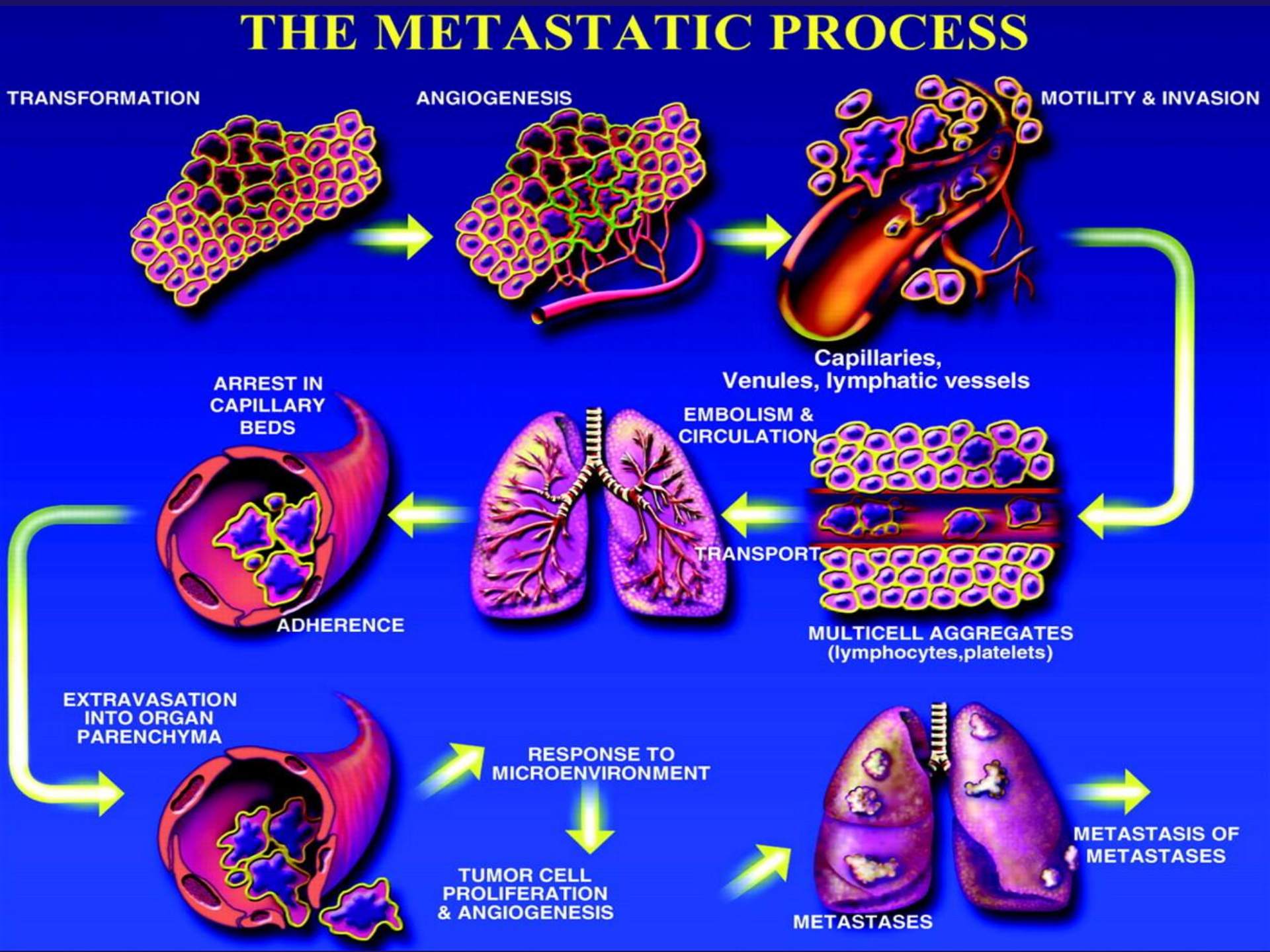
HYPOXIA PROMOTES ANGIOGENESIS AND METASTASIS

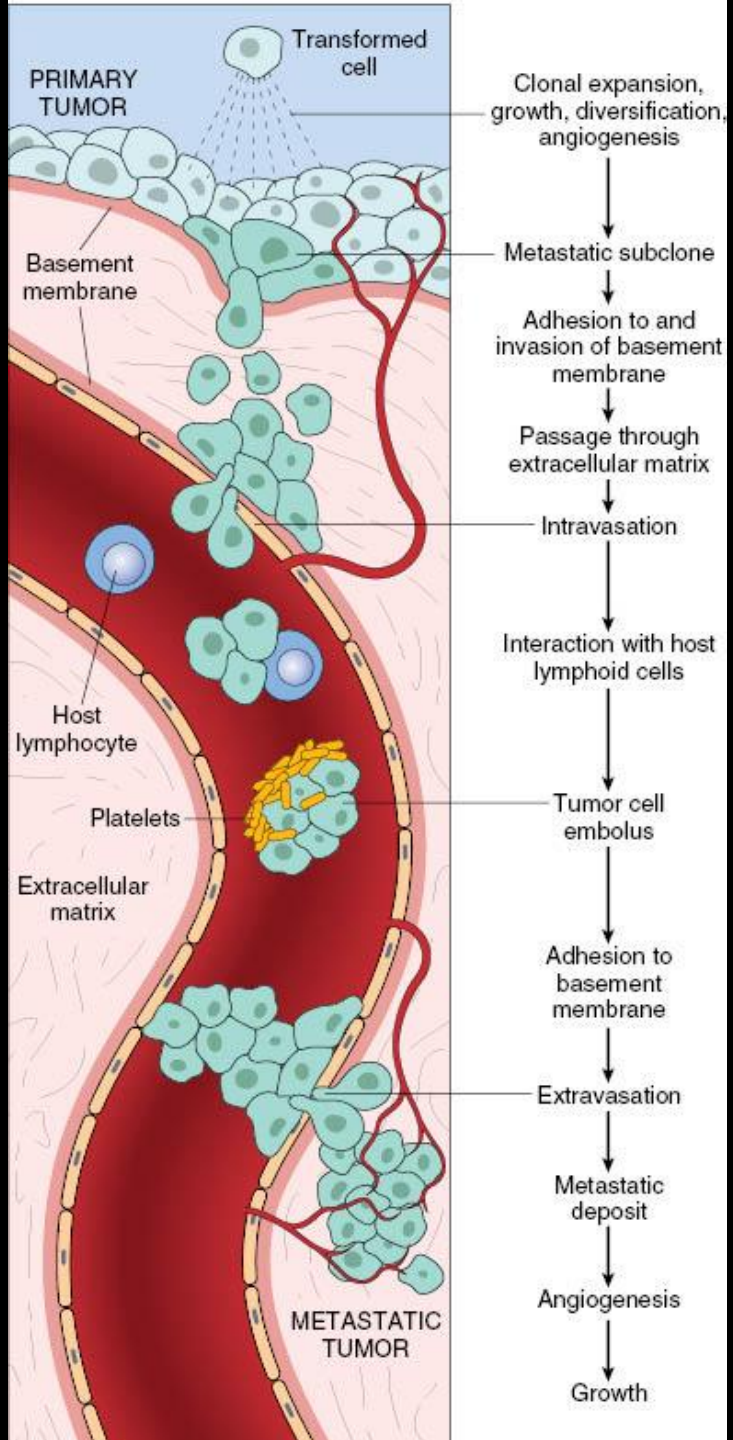




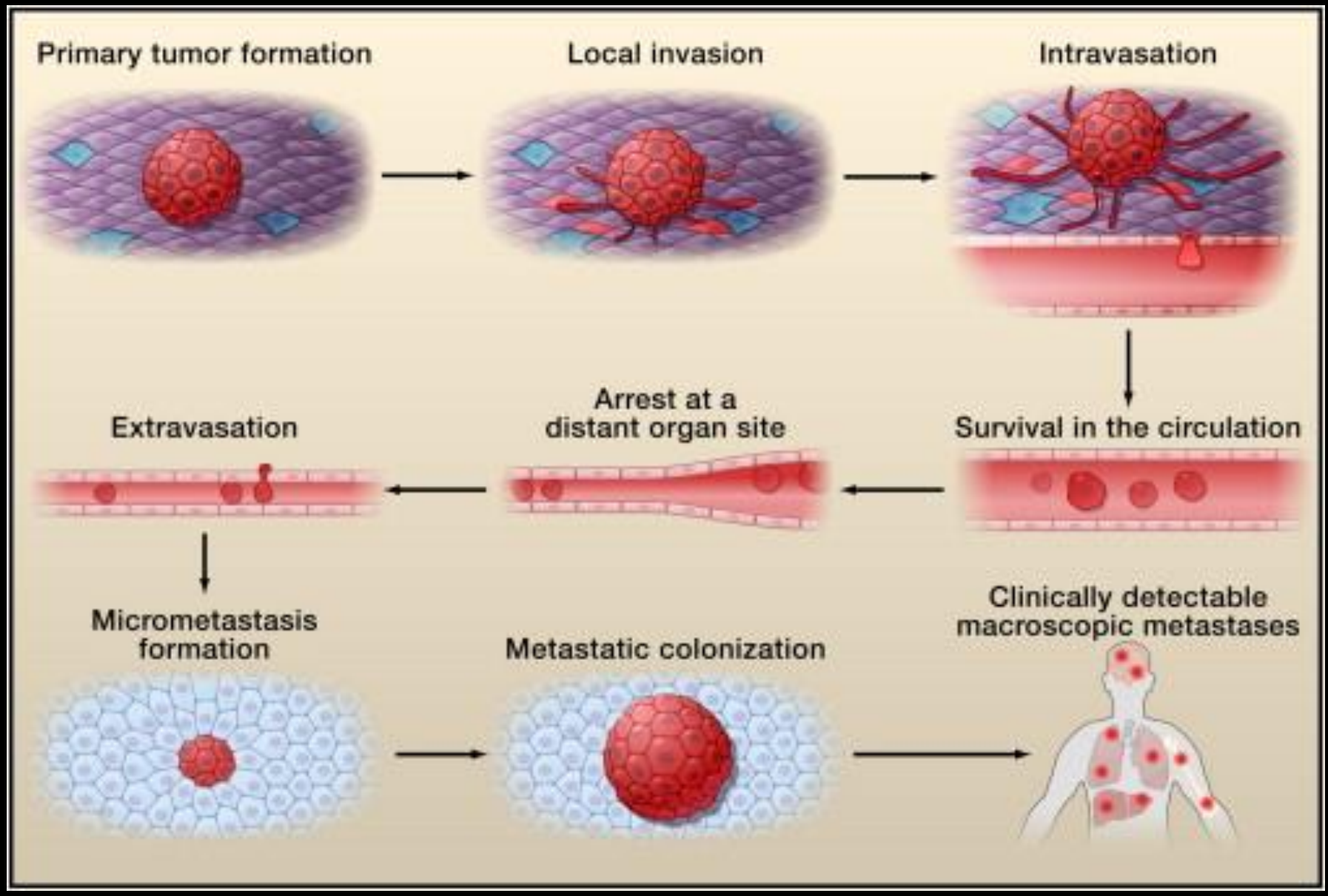


THE METASTATIC PROCESS

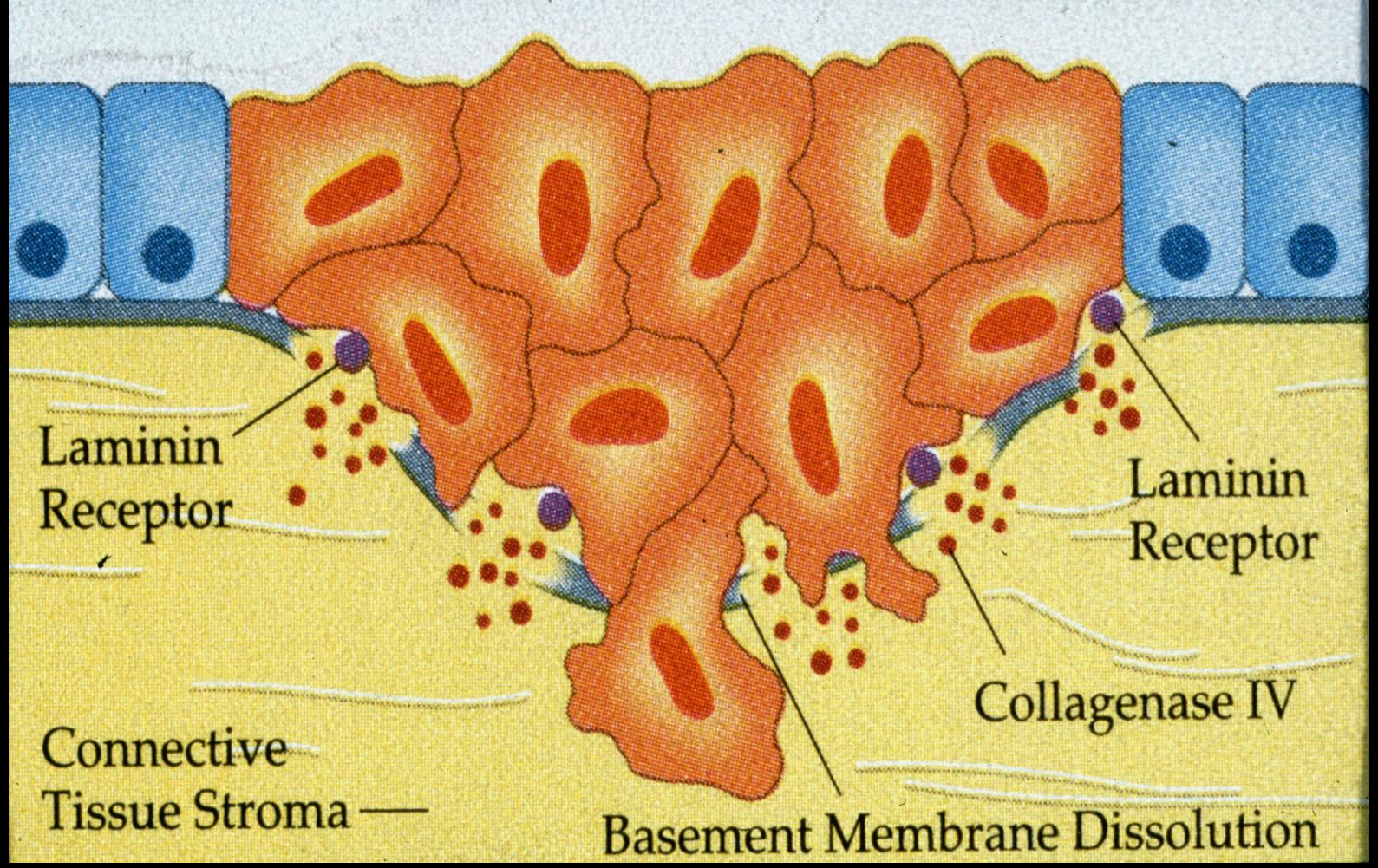




Metastatic cascade: hematogenous spread of a tumor



Invasion –Metastasis Cascade



Invasion: Tumors cells, secrete enzymes, such as metalloproteinases, (Type IV collagenase) that degrade the basement membrane and express high levels of laminin and fibronectin receptors, that mediate ECM attachment.

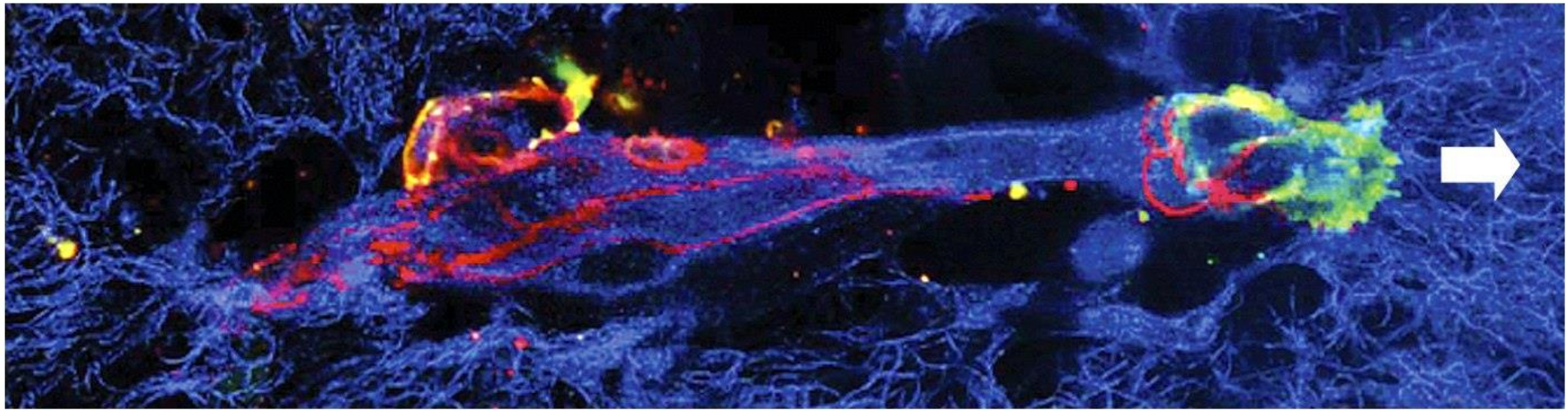


Figure 14-5b The Biology of Cancer (© Garland Science 2007)

Cancer cell migrating through the stroma. Note the large space in the stroma matrix, that has been degraded by the advancing cell.

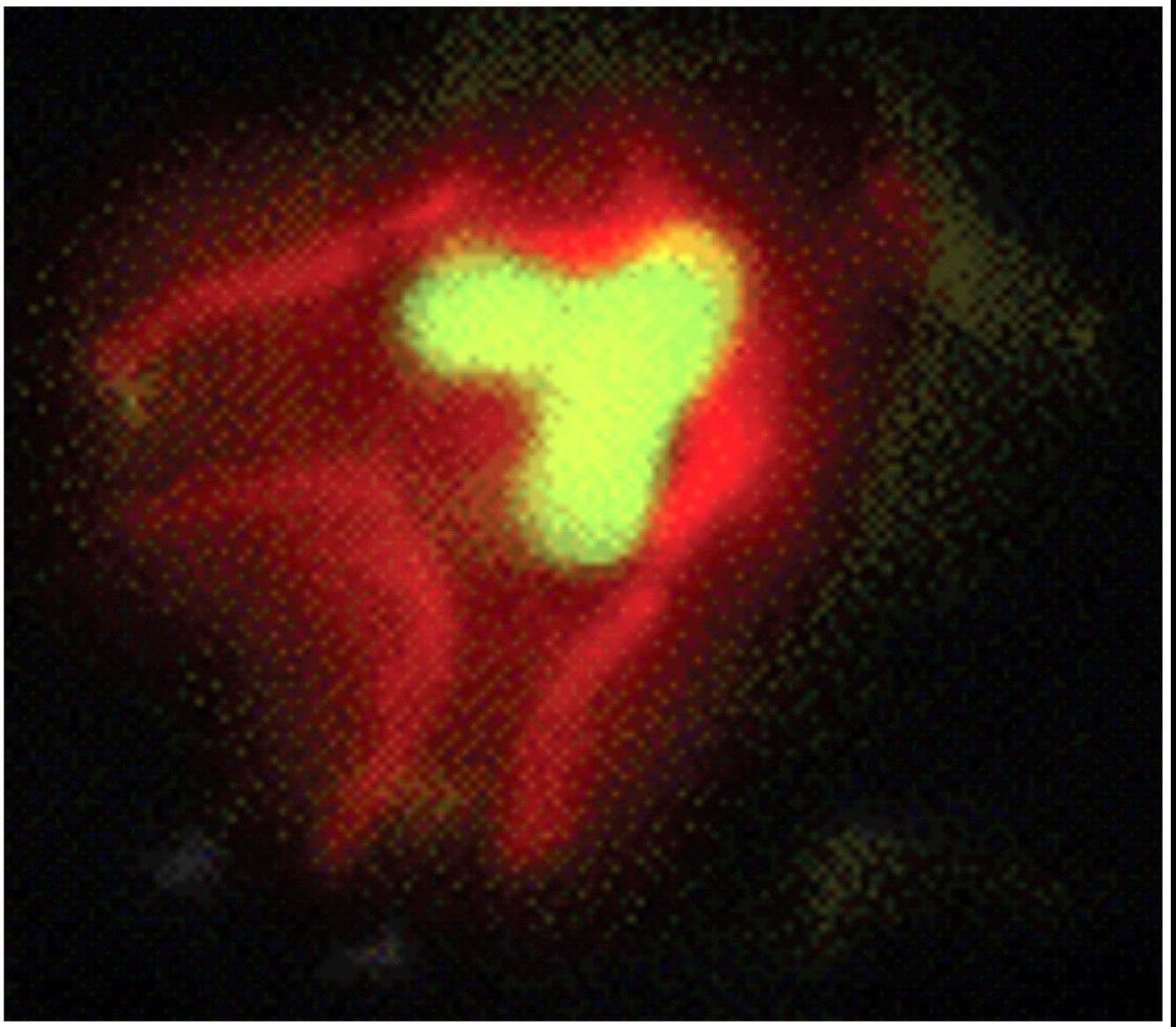


Figure 14-8 The Biology of Cancer (© Garland Science 2007)

Cancer cells (expressing GFP) growing within the lumen of a blood vessel.

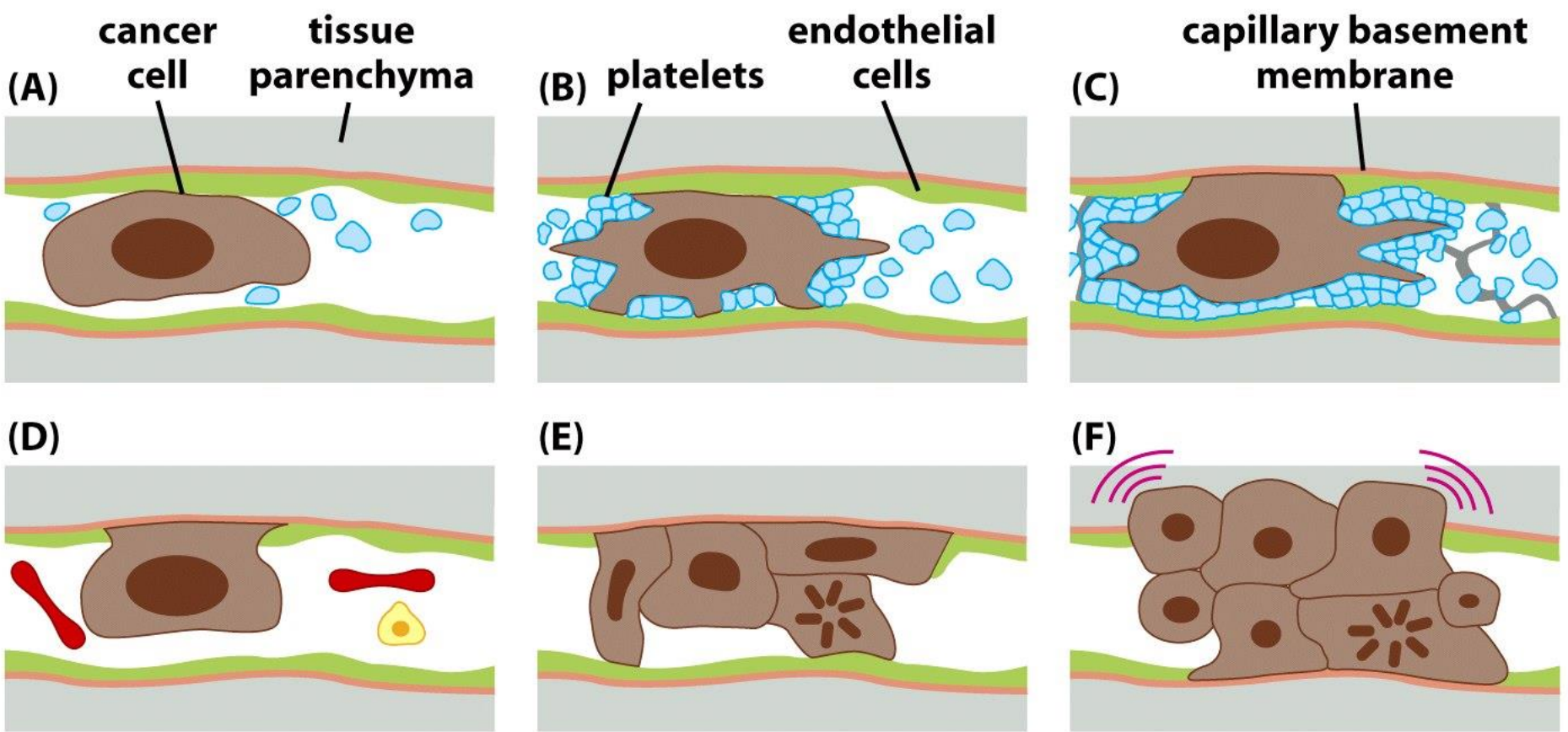
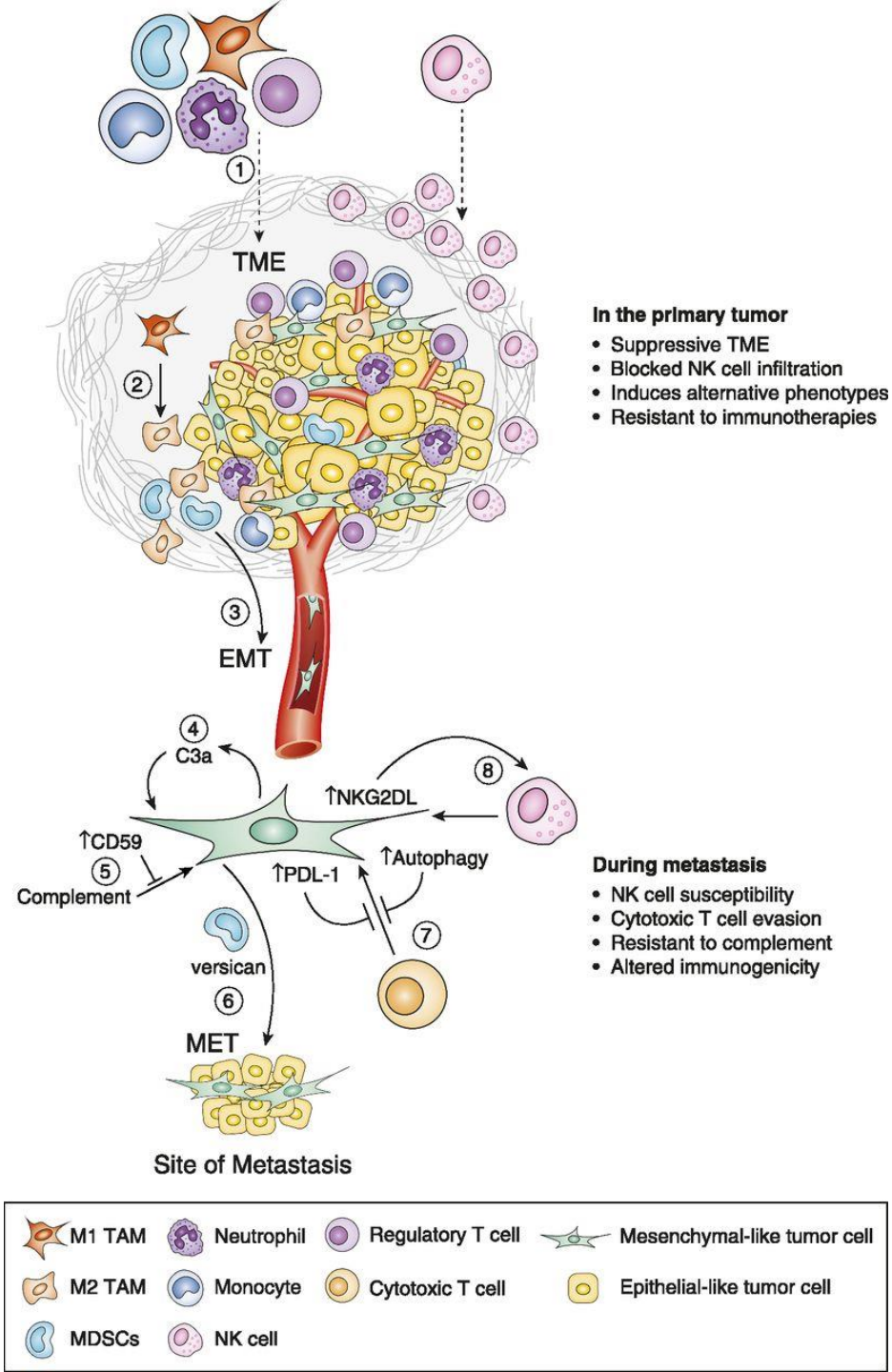


Figure 14-9 The Biology of Cancer (© Garland Science 2007)

Extravasation of Cancer Cells

Cancer cells become trapped in capillaries, microthrombi are formed, endothelial cells are pushed aside and cancer cells contact basement membrane, cancer cell proliferates, and eventually tumor cells break through the basement membrane.


1
TME
2
3
EMT
4
C3a
↑CD59
5
Complement
versican
6
MET
Site of Metastasis
↑NKG2DL
8
↑Autophagy
↑PDL-1
7
In the primary tumor
• Suppressive TME
• Blocked NK cell infiltration
• Induces alternative phenotypes
• Resistant to immunotherapies
During metastasis
• NK cell susceptibility
• Cytotoxic T cell evasion
• Resistant to complement
• Altered immunogenicity
M1 TAM
M2 TAM
MDSCs
Neutrophil
Monocyte
NK cell
Regulatory T cell
Cytotoxic T cell
Mesenchymal-like tumor cell
Epithelial-like tumor cell

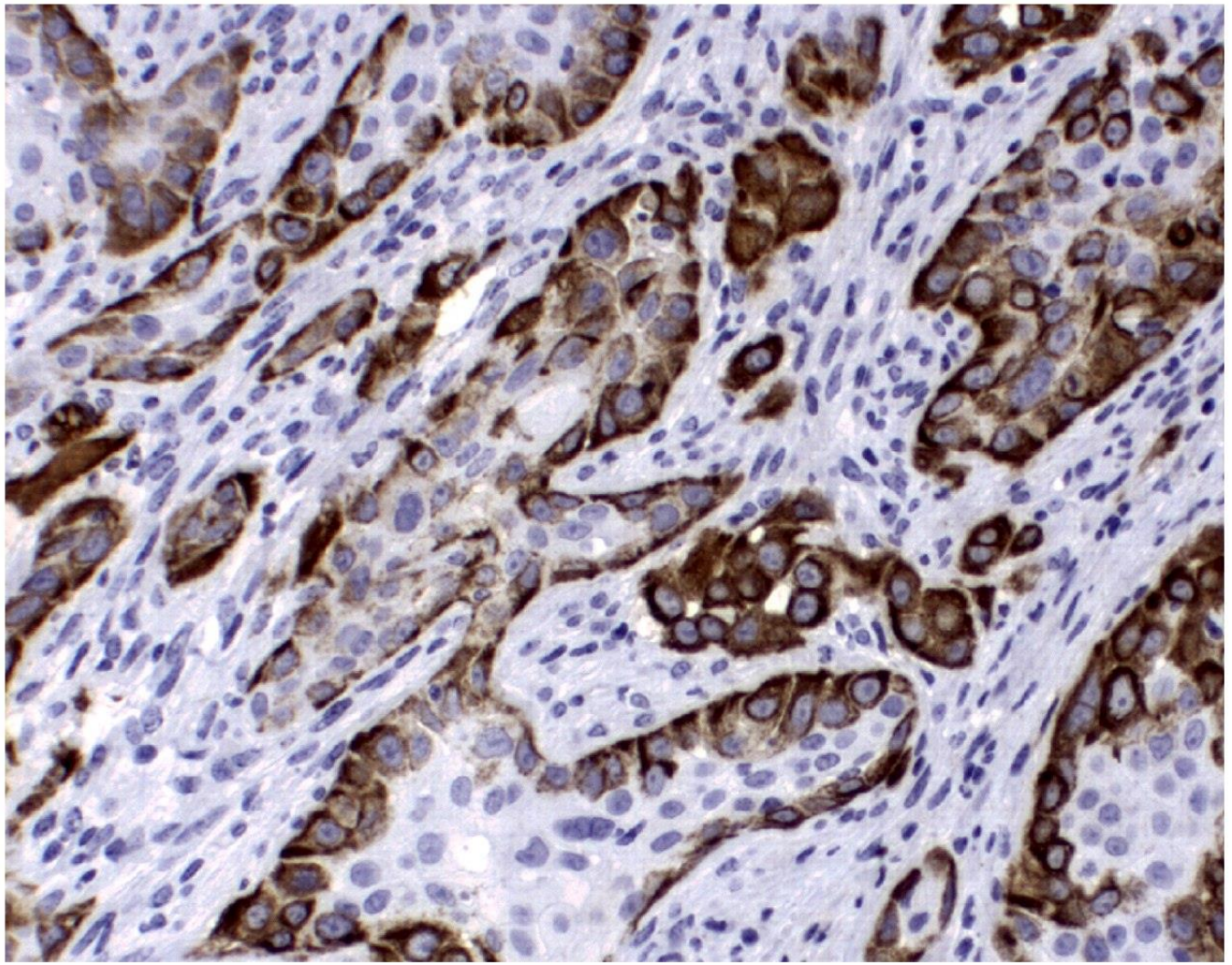


Figure 14-19d The Biology of Cancer (© Garland Science 2007)

Epithelial-mesenchymal transition (EMT): Carcinoma cells at edge of invading islets in direct contact with the stroma have undergone EMT, and are expressing vimentin.

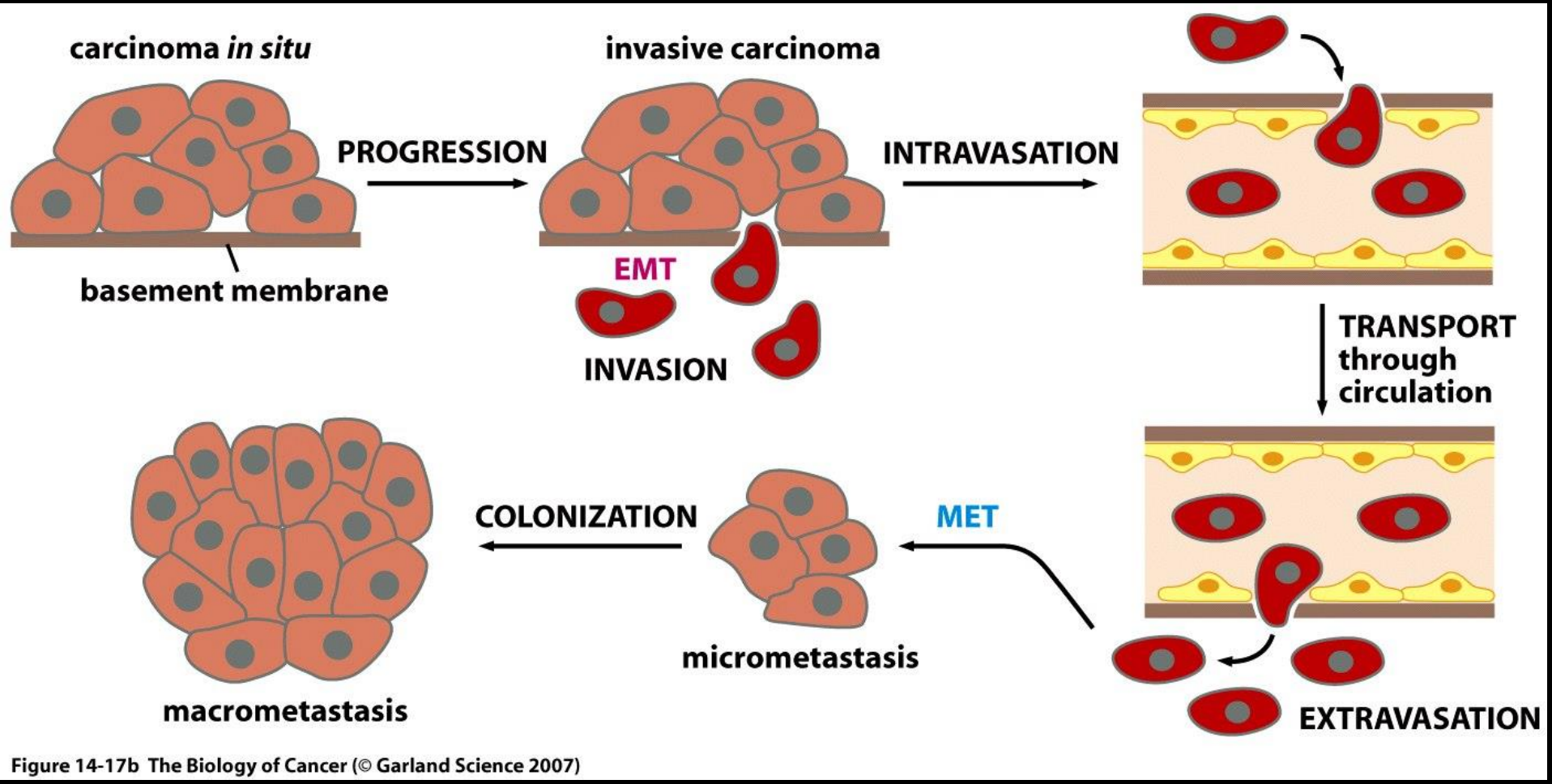


Figure 14-17b The Biology of Cancer (© Garland Science 2007)

Concept of reversibility of epithelial-mesenchymal transition (EMT).

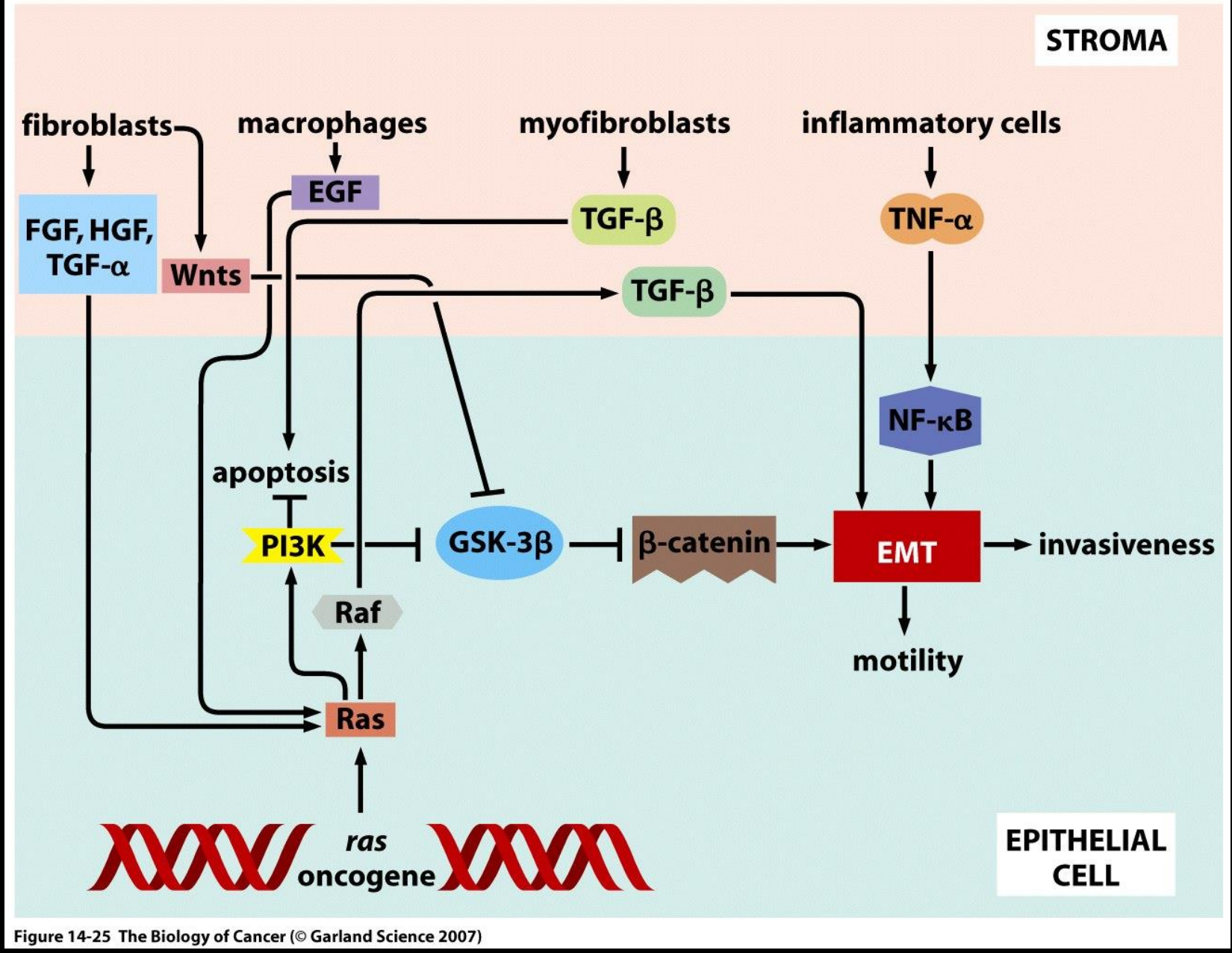


Figure 14-25 The Biology of Cancer (© Garland Science 2007)

Signals that mediate EMT

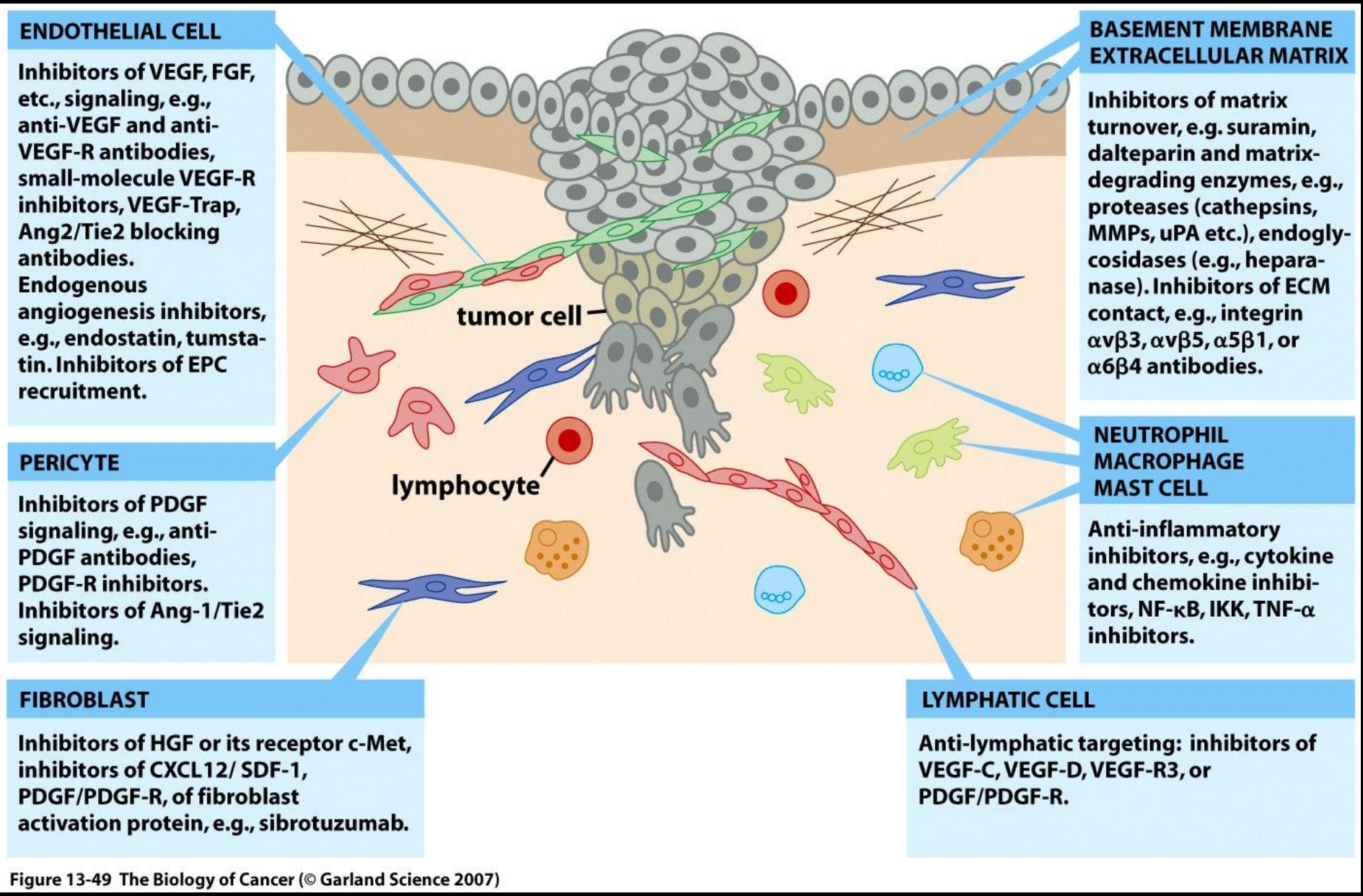
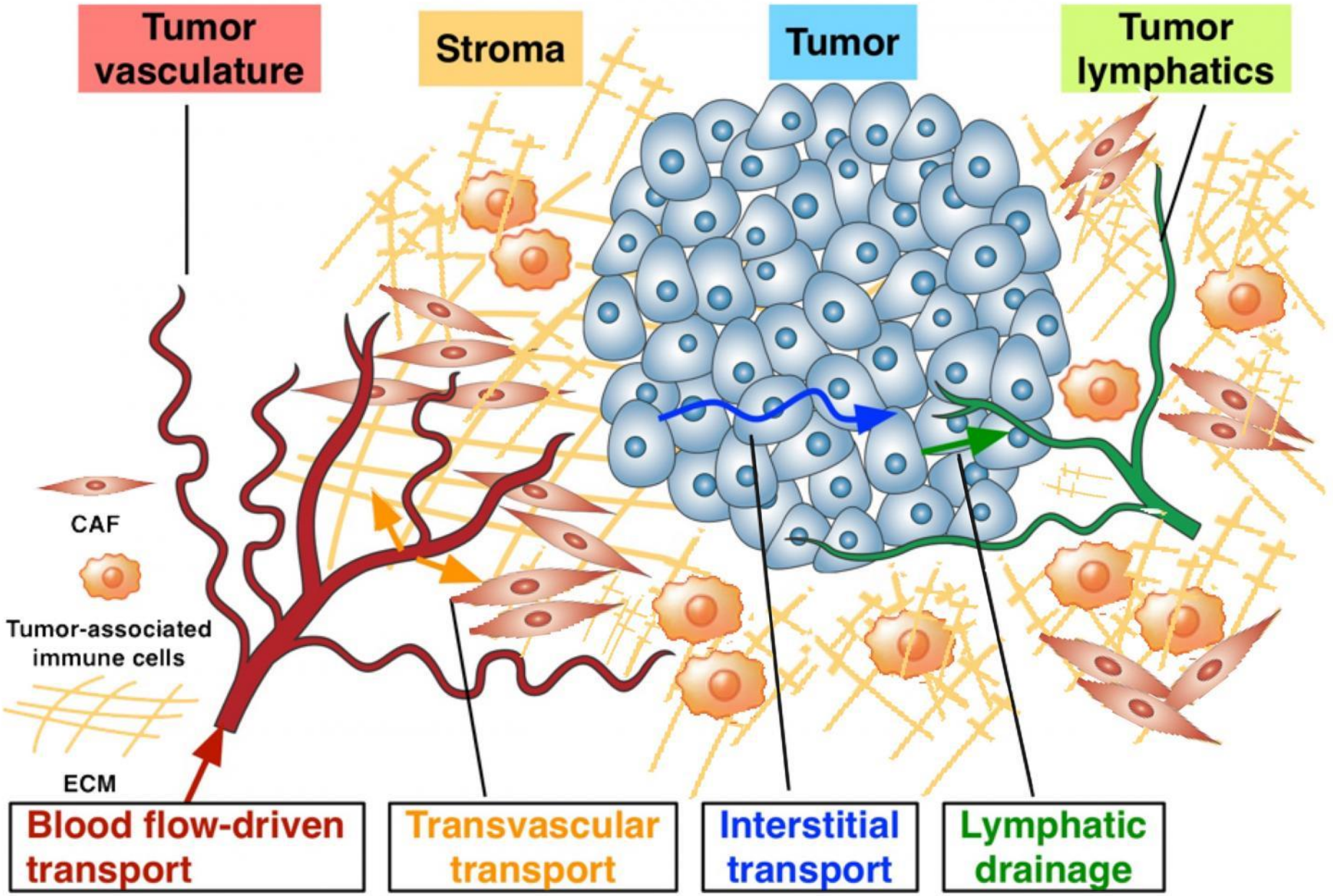
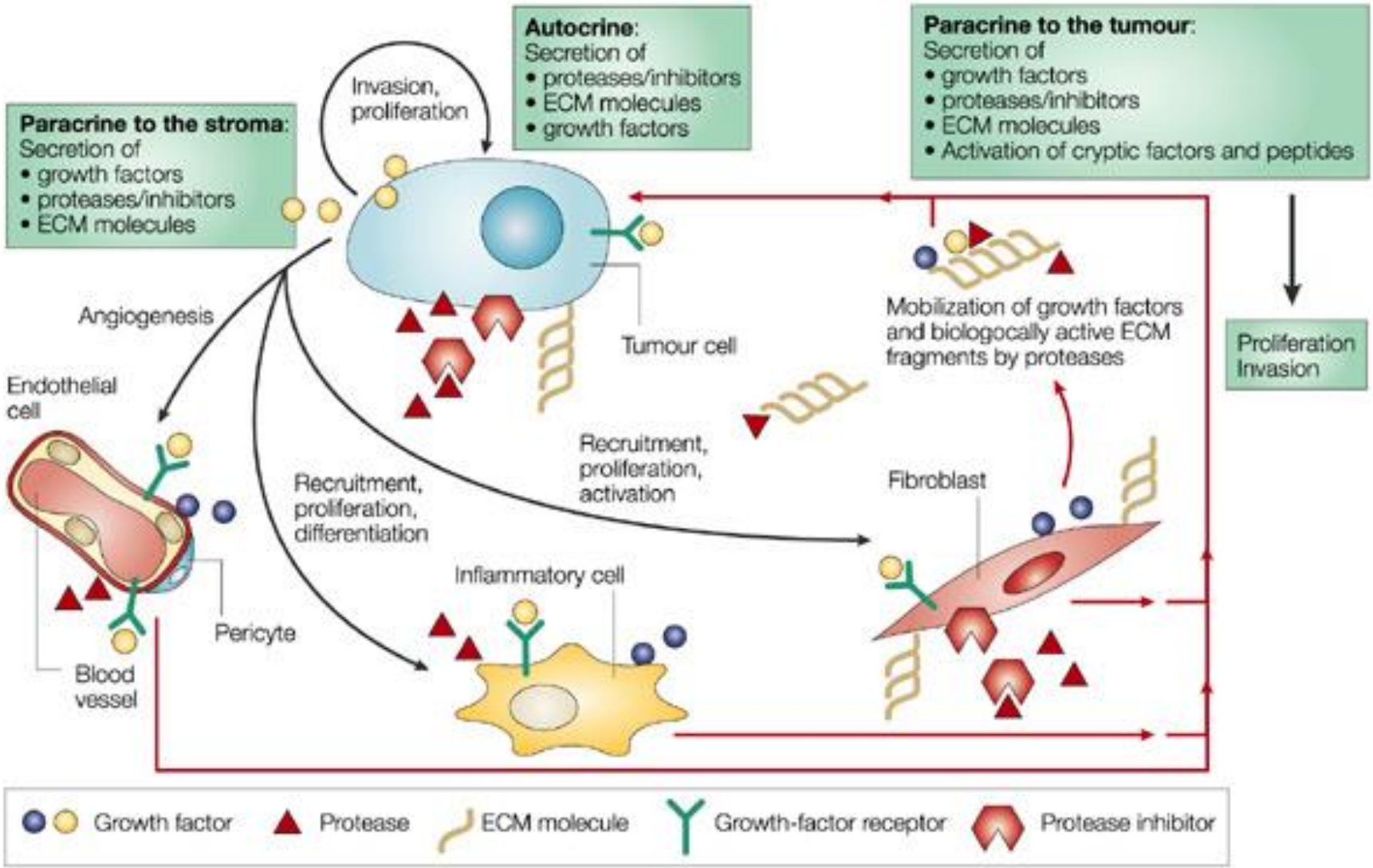


Figure 13-49 The Biology of Cancer (© Garland Science 2007)

Heterotypic Interactions: Targets for Cancer Therapy


Tumor vasculature
Stroma
Tumor
Tumor lymphatics
CAF
Tumor-associated immune cells
ECM
Blood flow-driven transport
Transvascular transport
Interstitial transport
Lymphatic drainage


Autocrine:
Secretion of
• proteases/inhibitors
• ECM molecules
• growth factors
Paracrine to the tumour:
Secretion of
• growth factors
• proteases/inhibitors
• ECM molecules
• Activation of cryptic factors and peptides
Paracrine to the stroma:
Secretion of
• growth factors
• proteases/inhibitors
• ECM molecules
Invasion, proliferation
Angiogenesis
Tumour cell
Mobilization of growth factors and biologocally active ECM fragments by proteases
Proliferation Invasion
Endothelial cell
Recruitment, proliferation, activation
Recruitment, proliferation, differentiation
Fibroblast
Inflammatory cell
Pericyte
Blood vessel
Growth factor
Protease
ECM molecule
Growth-factor receptor
Protease inhibitor

Tumor Angiogenesis

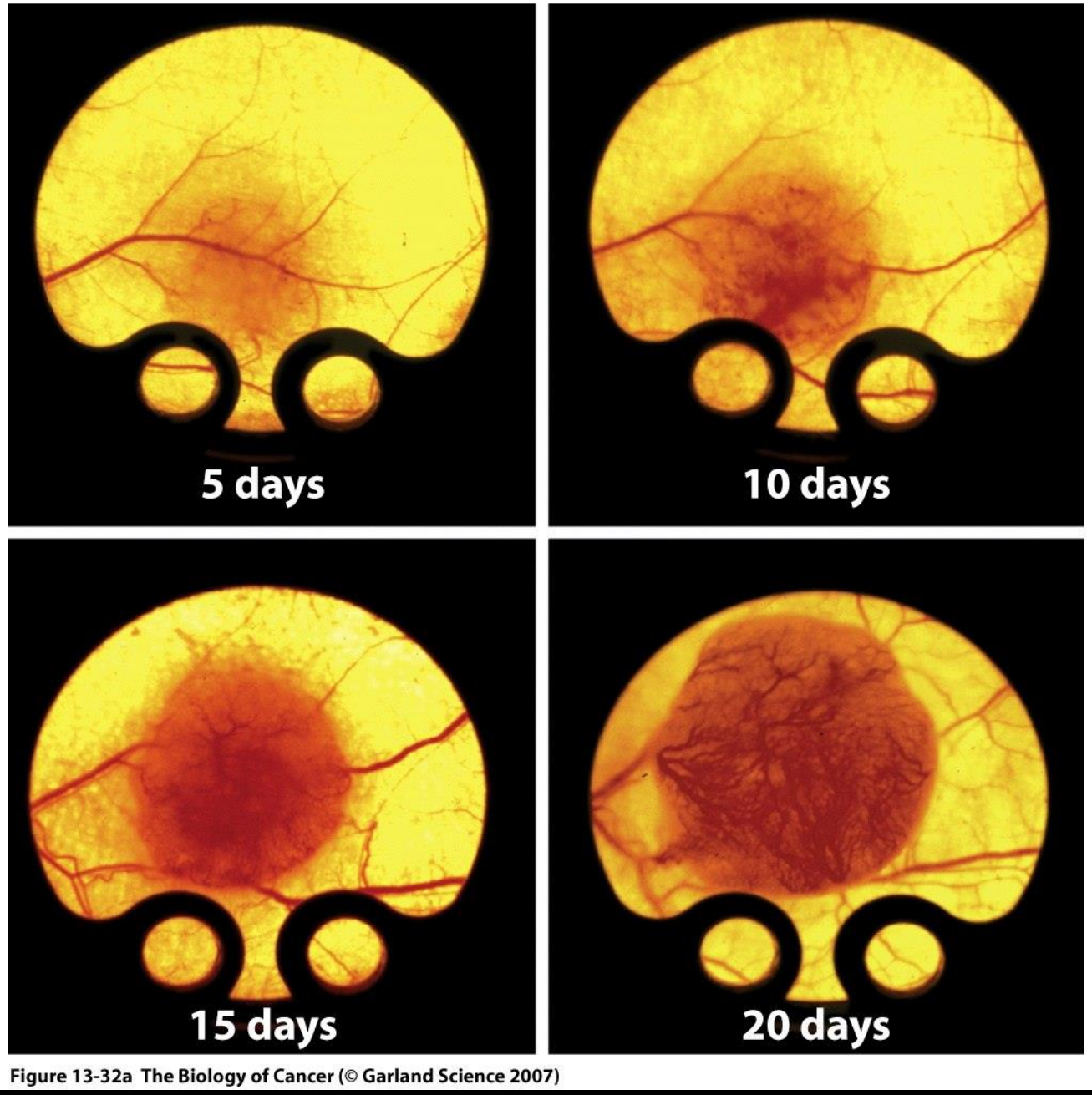
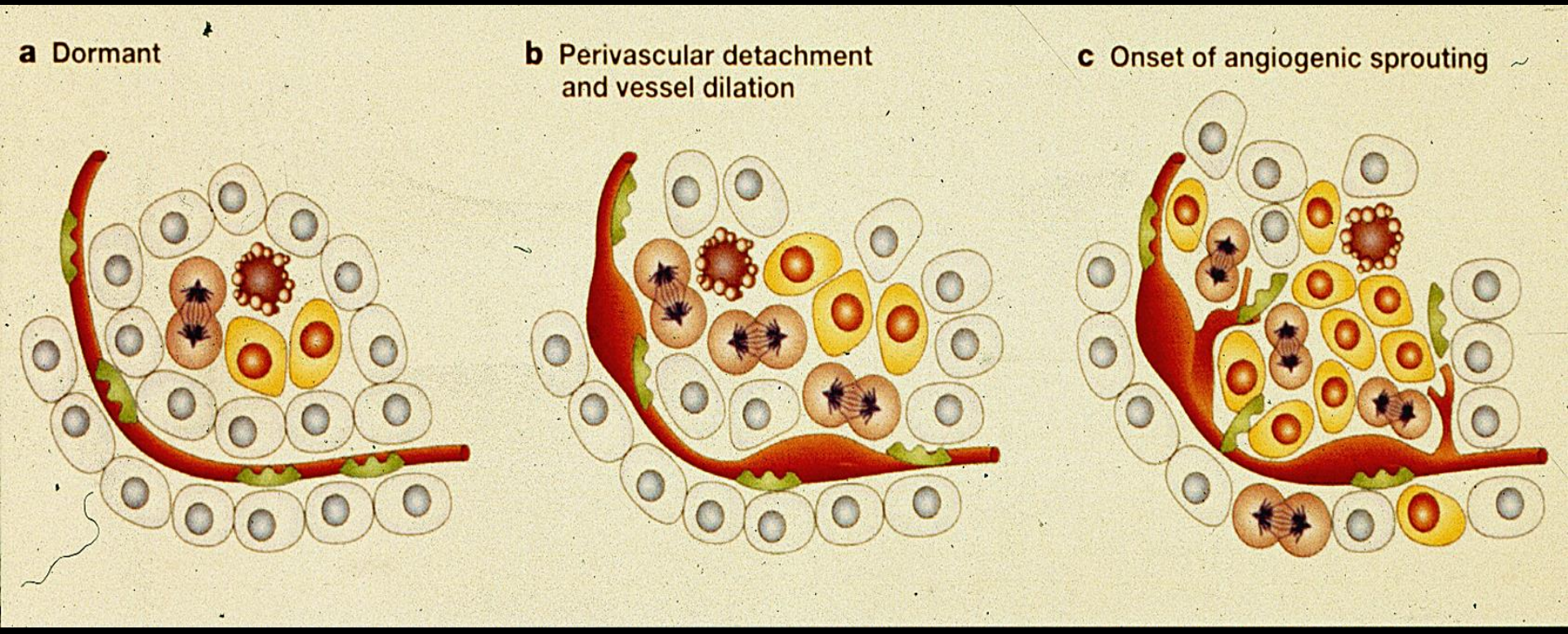
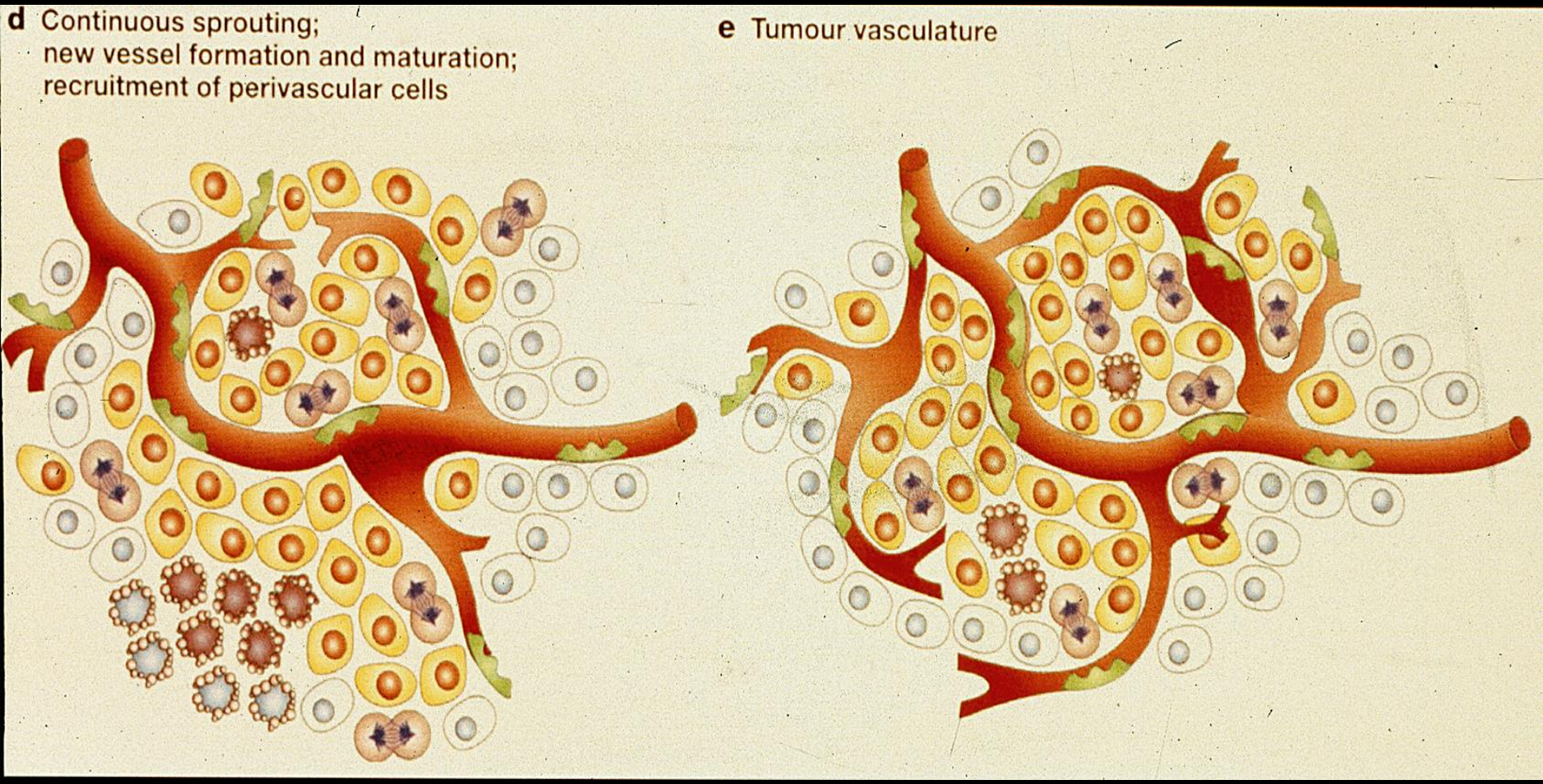


Figure 13-32a The Biology of Cancer (© Garland Science 2007)

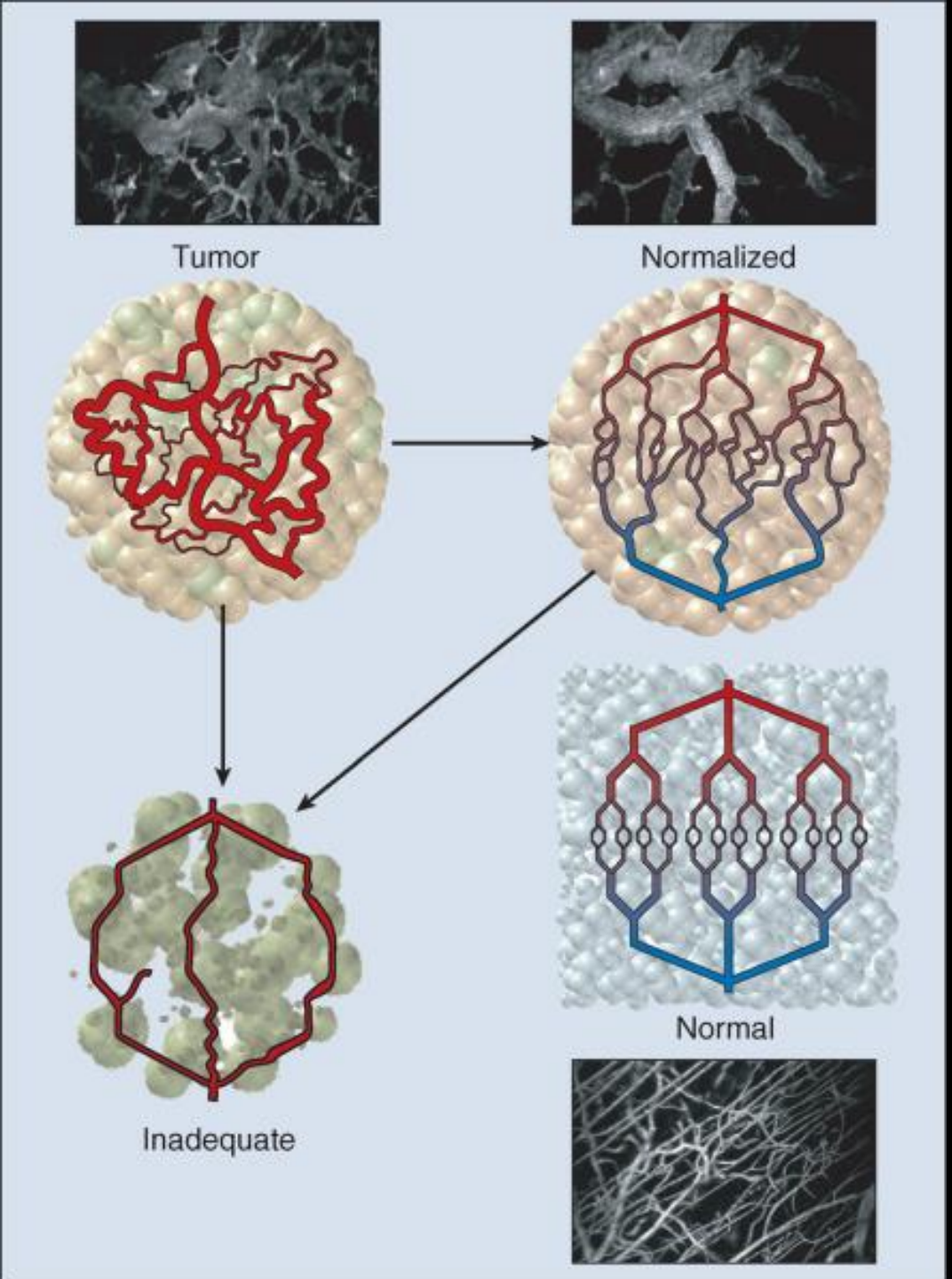
Recruitment of blood vessels by implanted tumor – first evidence of angiogenic factors in tumorigenesis



A. Most tumors start as avascular nodules (dormant). B. The "angiogenic switch" begins with pericyte detachment and vessel dilatation. C. Angiogenic sprouting occurs by endothelial migration (guided by pericytes).

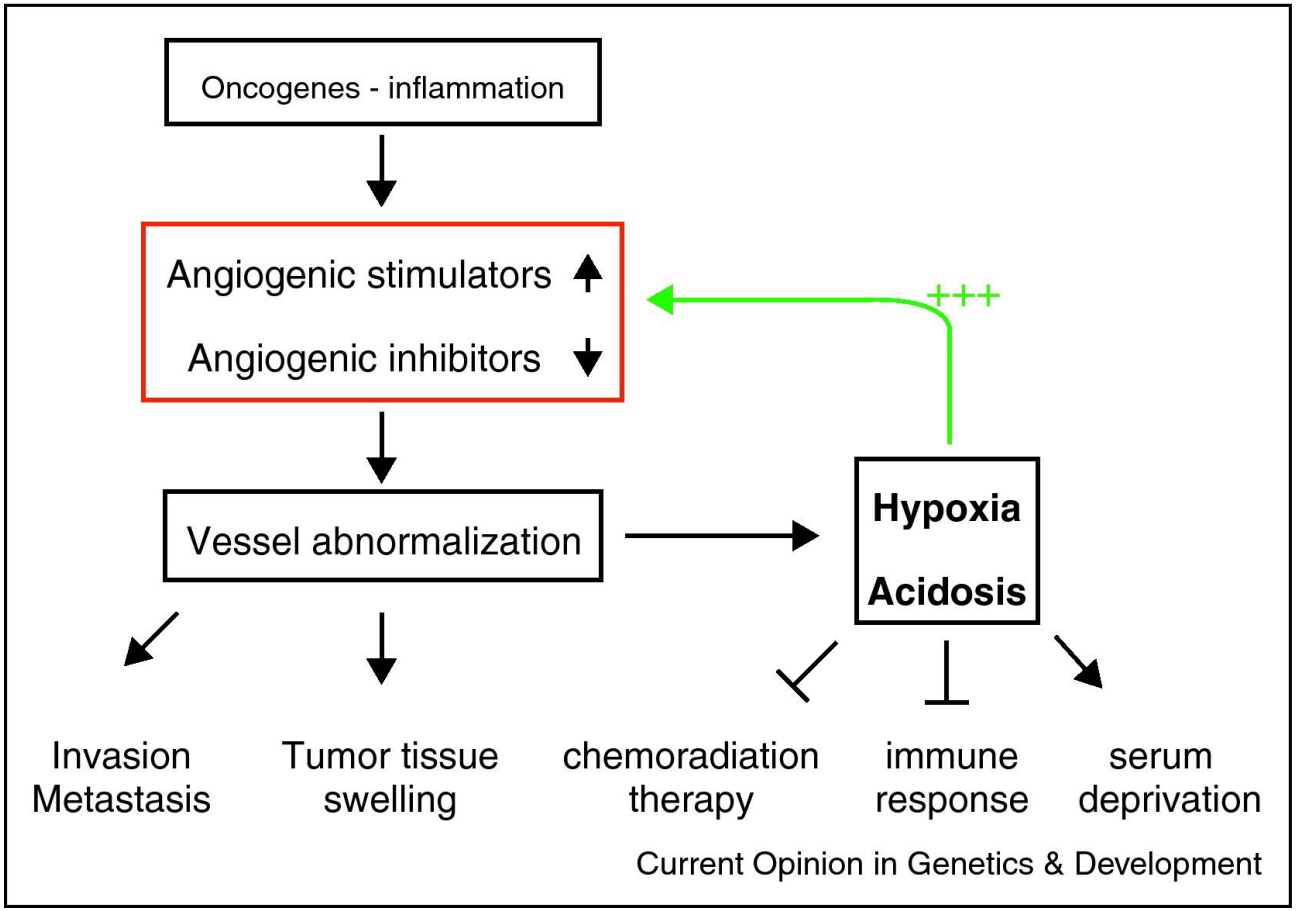


D. Angiogenic sprouting continues as endothelial cells proliferate, adhere to each other, and create lumens.
E. Sprouts fuse with other sprouts forming a complex tumor vasculature.

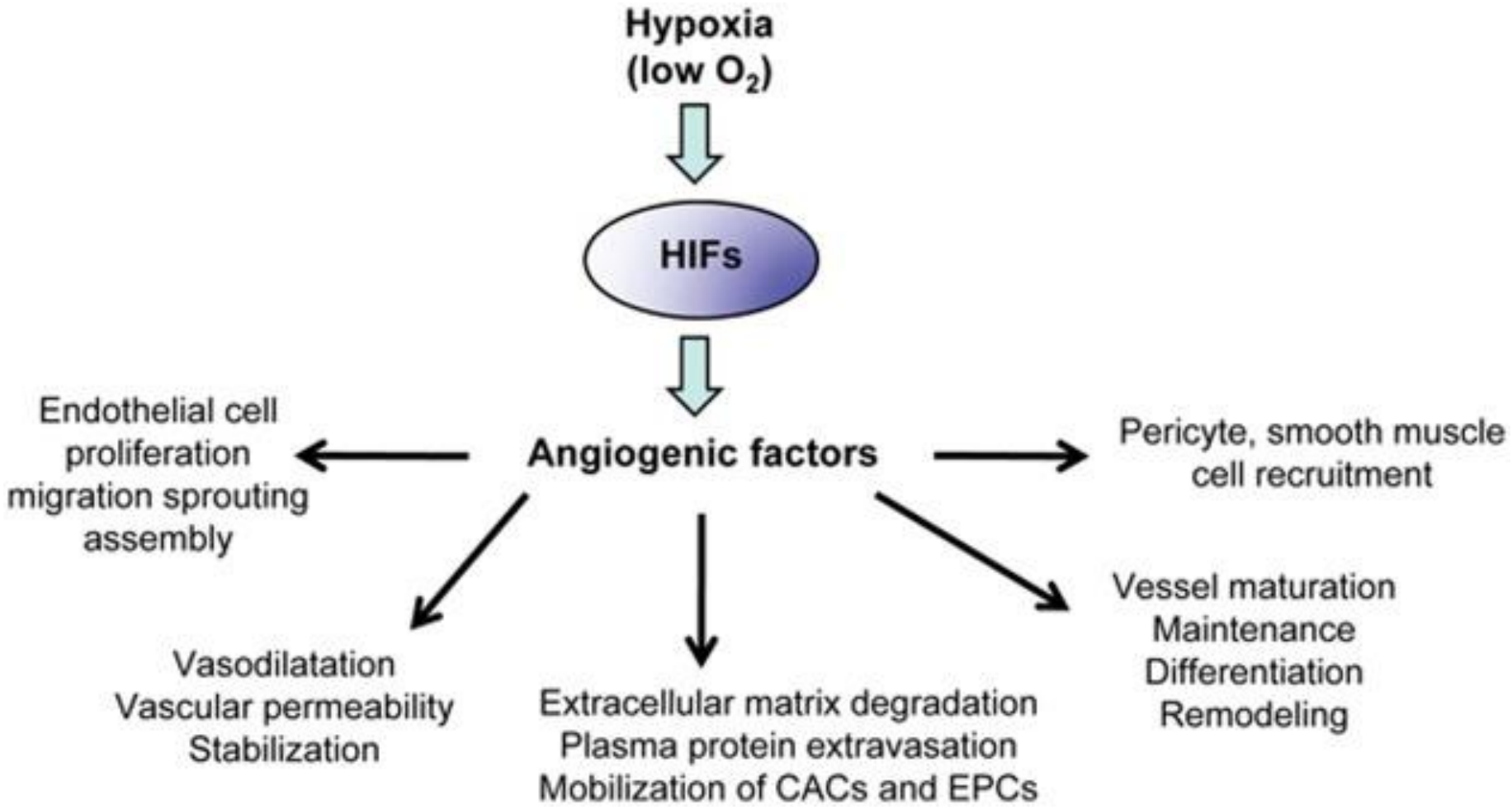


The capillaries inside of tumors are chaotic.

Angiogenesis inhibitors (anti-VEGF therapy) associated with “normalization” of tumor vasculature. The goal of therapy is total vessel collapse and inadequate support for tumor growth. Normalization of the tumor vasculature enhances chemotherapeutic drug delivery.



Mechanism of abnormal tumor vasculature. Angiogenic growth factors are in excess of angiogenic inhibitors leading to vessel abnormalization. This results in continual tumor hypoxia and acidosis creating a self-perpetuating cycle of abnormal angiogenesis which promotes tumor invasion and metastasis and hinders chemoradiation therapy.



Hypoxia-inducible factors (HIFs): transcription factors that mediate the cellular response to physiologic hypoxia also regulate angiogenic factors, such as VEGF, which execute some of the steps in tumor angiogenesis.

Angiogenesis increases with tumor invasion

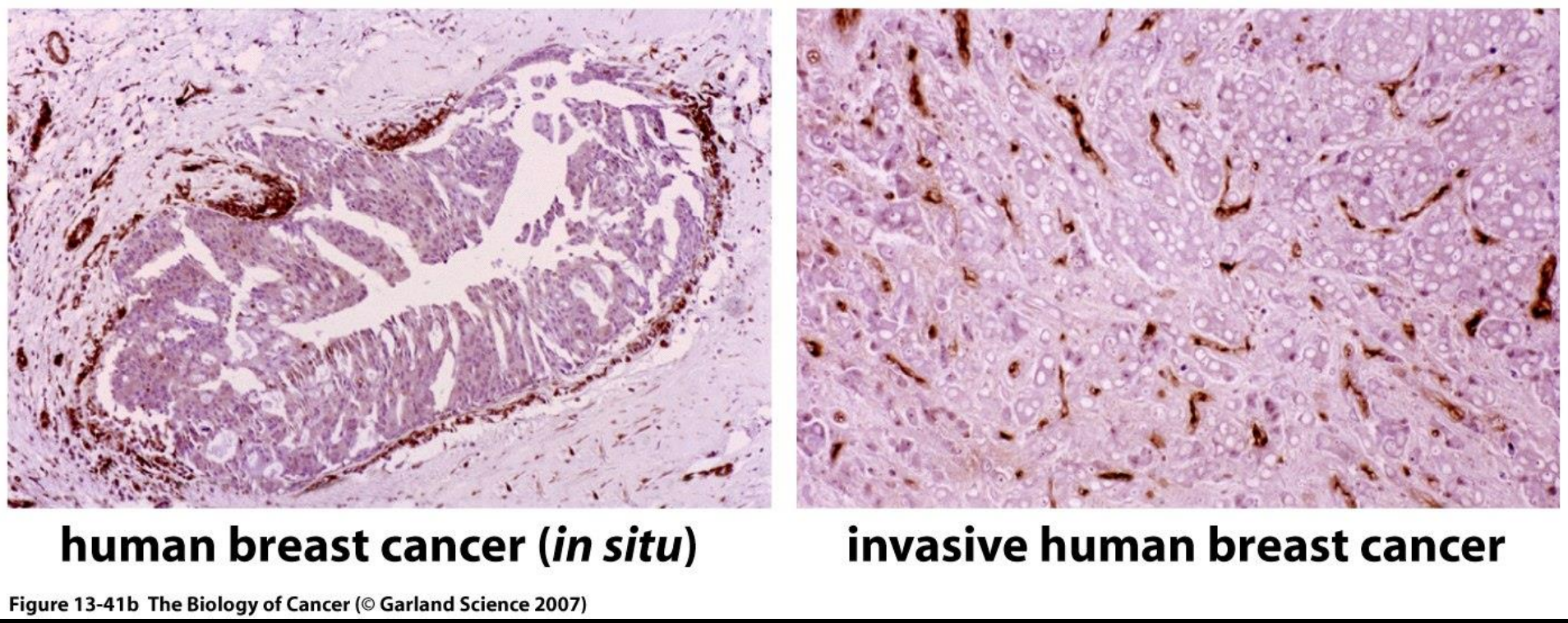


Figure 13-41b The Biology of Cancer (© Garland Science 2007)

A higher density of capillaries, (expressing factor VIII by IHC) is present with invasion.

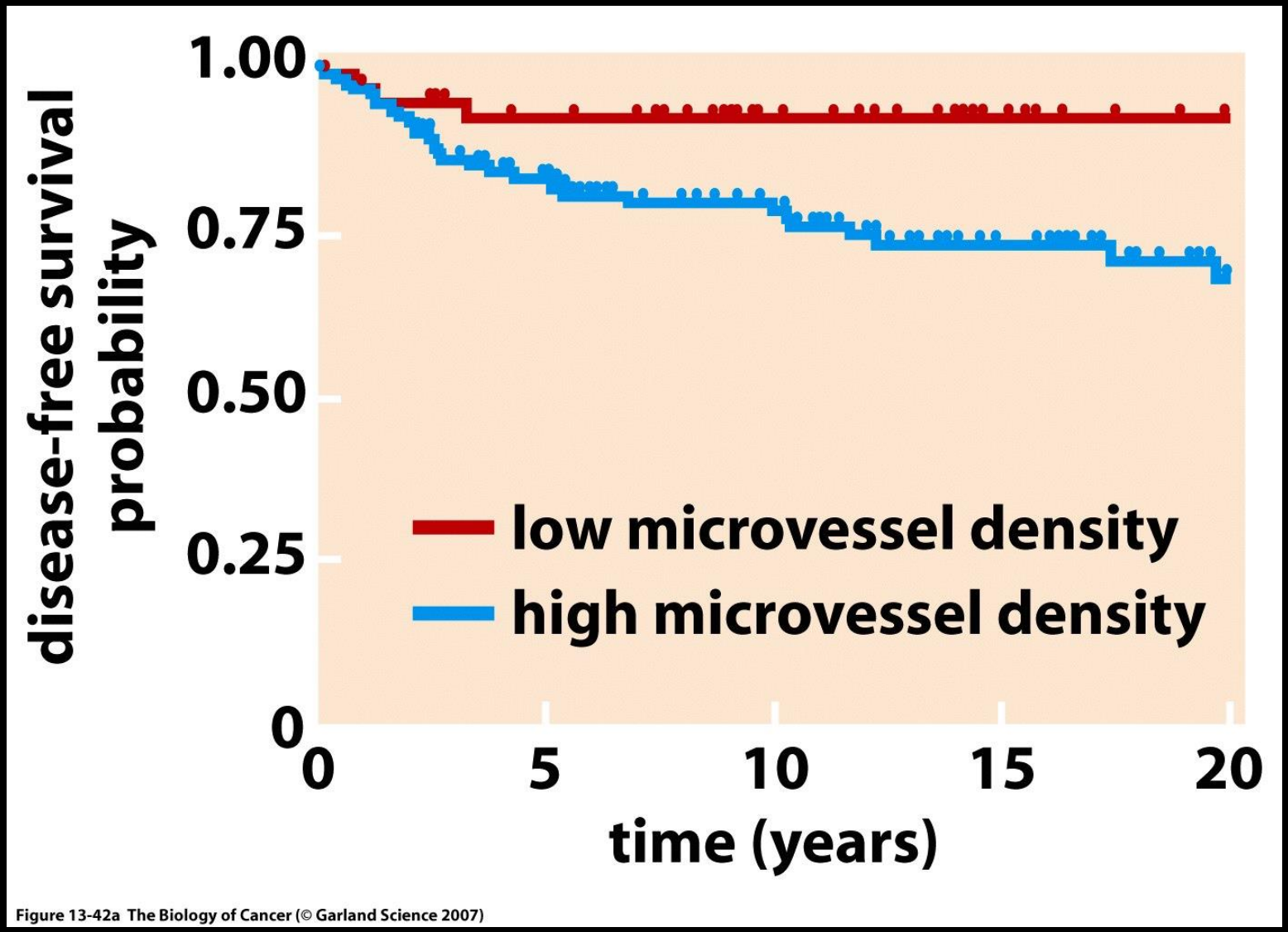
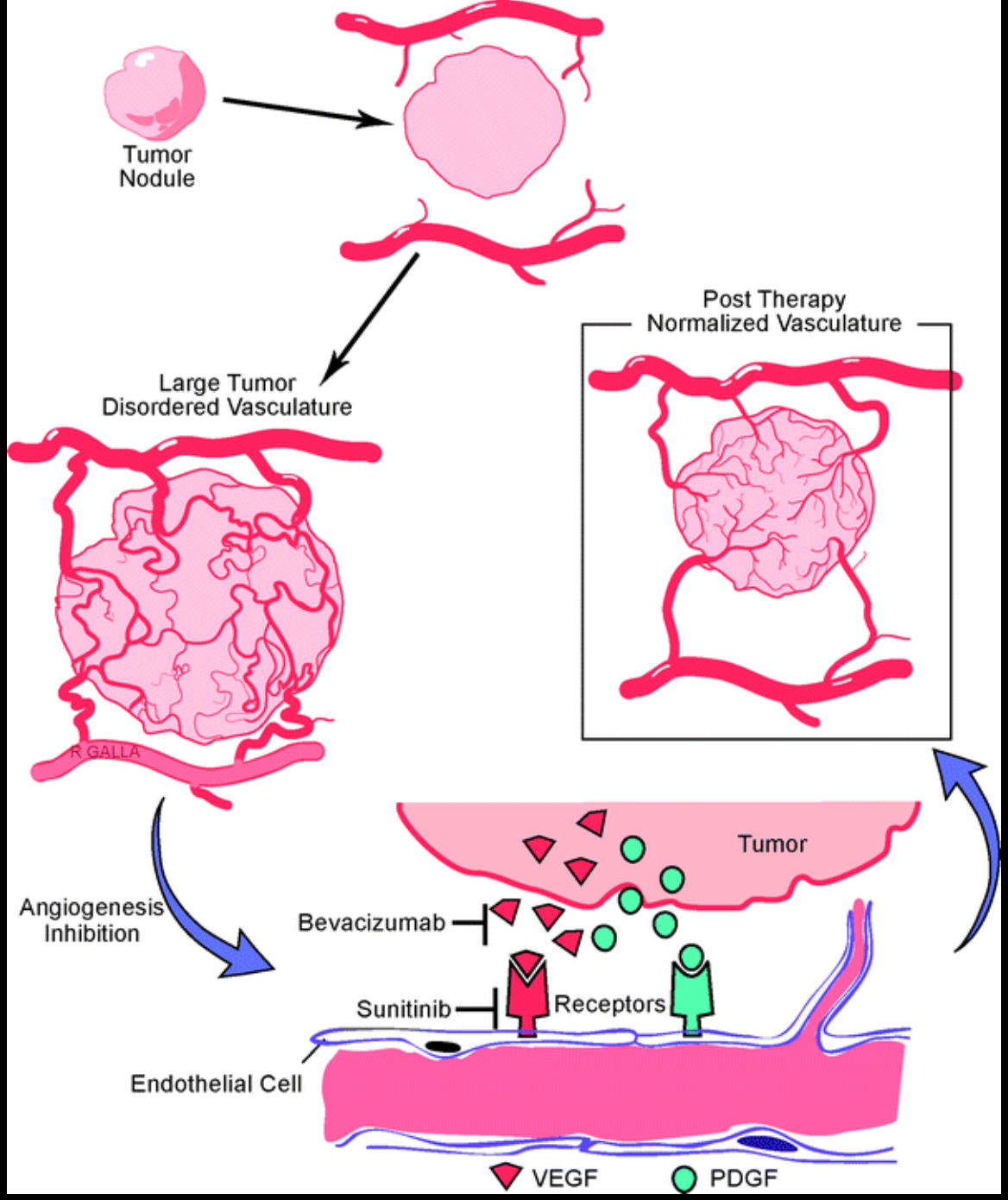


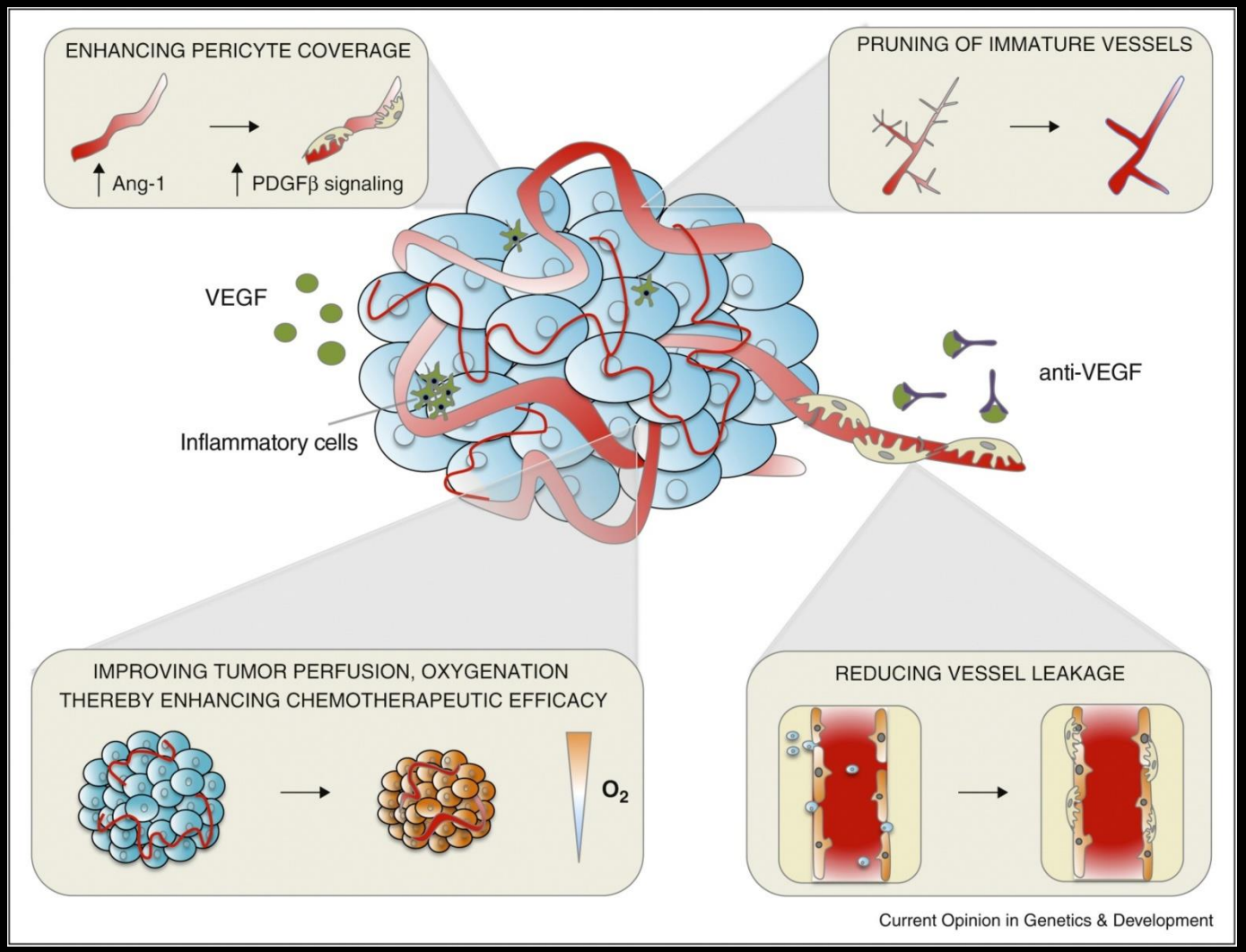
Figure 13-42a The Biology of Cancer (© Garland Science 2007)

Breast Cancer: increased angiogenesis (higher microvessel density) associated with worse prognosis.



Tumor angiogenesis and therapeutic angiogenesis inhibitors:

Tumors secrete VEGF and PDGF. Current clinical approaches include bevacizumab (Avastatin), an antibody against VEGF, and sunitinib (Sutent) a small molecule inhibitor of the VEGF receptor,



Anti-VEGF therapy induces normalization of the tumor vasculature. It increases pericyte coverage (thru Ang-1 and PDGFβ signaling), destroys existing vessels and prevents new vessel growth ("vessel pruning"), improves tumor perfusion and oxygenation, and enhances drug delivery.

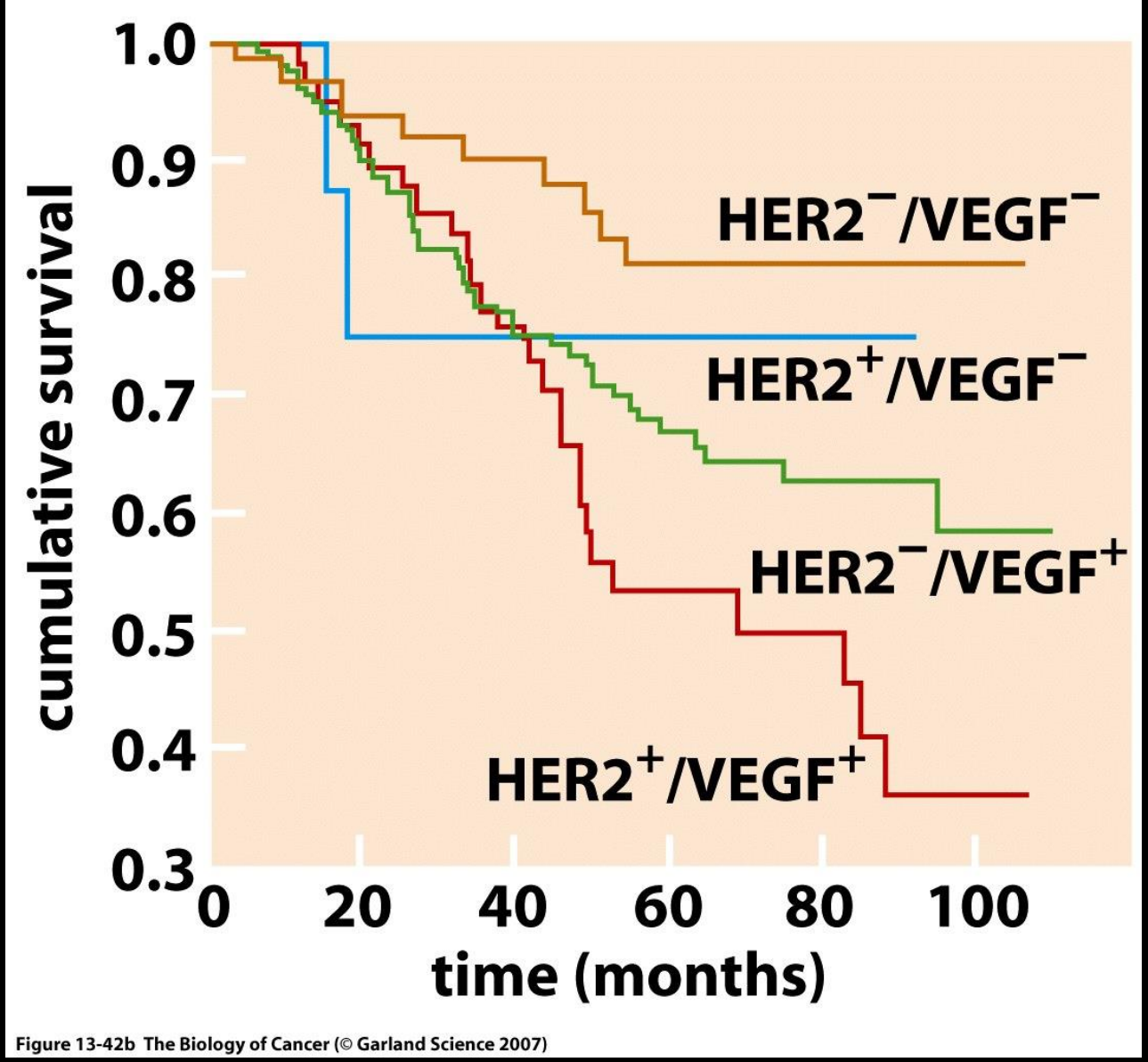


Figure 13-42b The Biology of Cancer (© Garland Science 2007)

Breast Cancer: tumors with high VEGF expression (in addition to HER2) have worse prognosis.

Figure 14-43 The Biology of Cancer (© Garland Science 2007)

Stephen Paget: British physician proposed the "seed and soil" hypothesis in 1889. He believed that the non-random nature of metastasis depends on an interaction between the cancer cell (*seed*) and a specific organ micro-environment (*soil*).

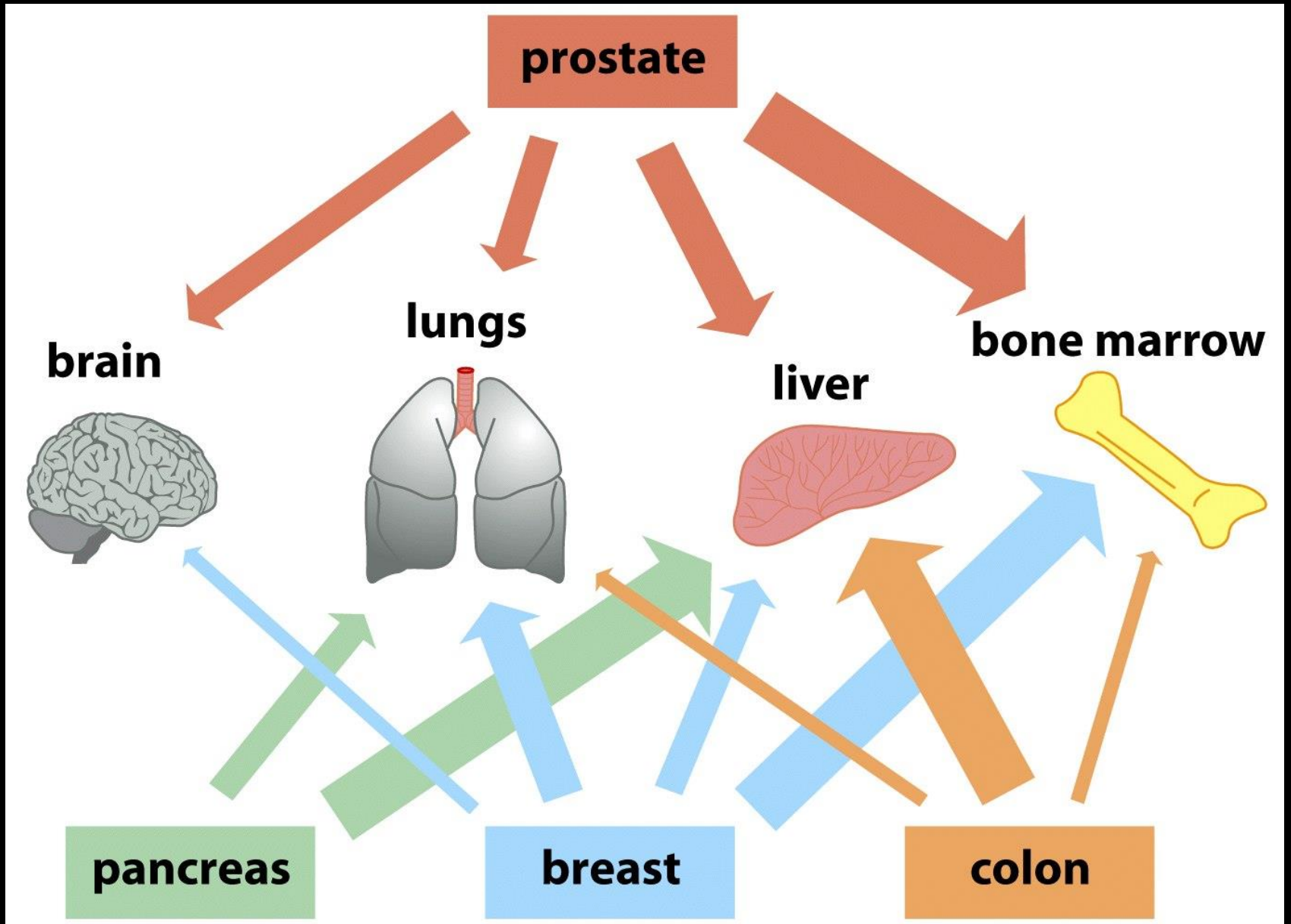
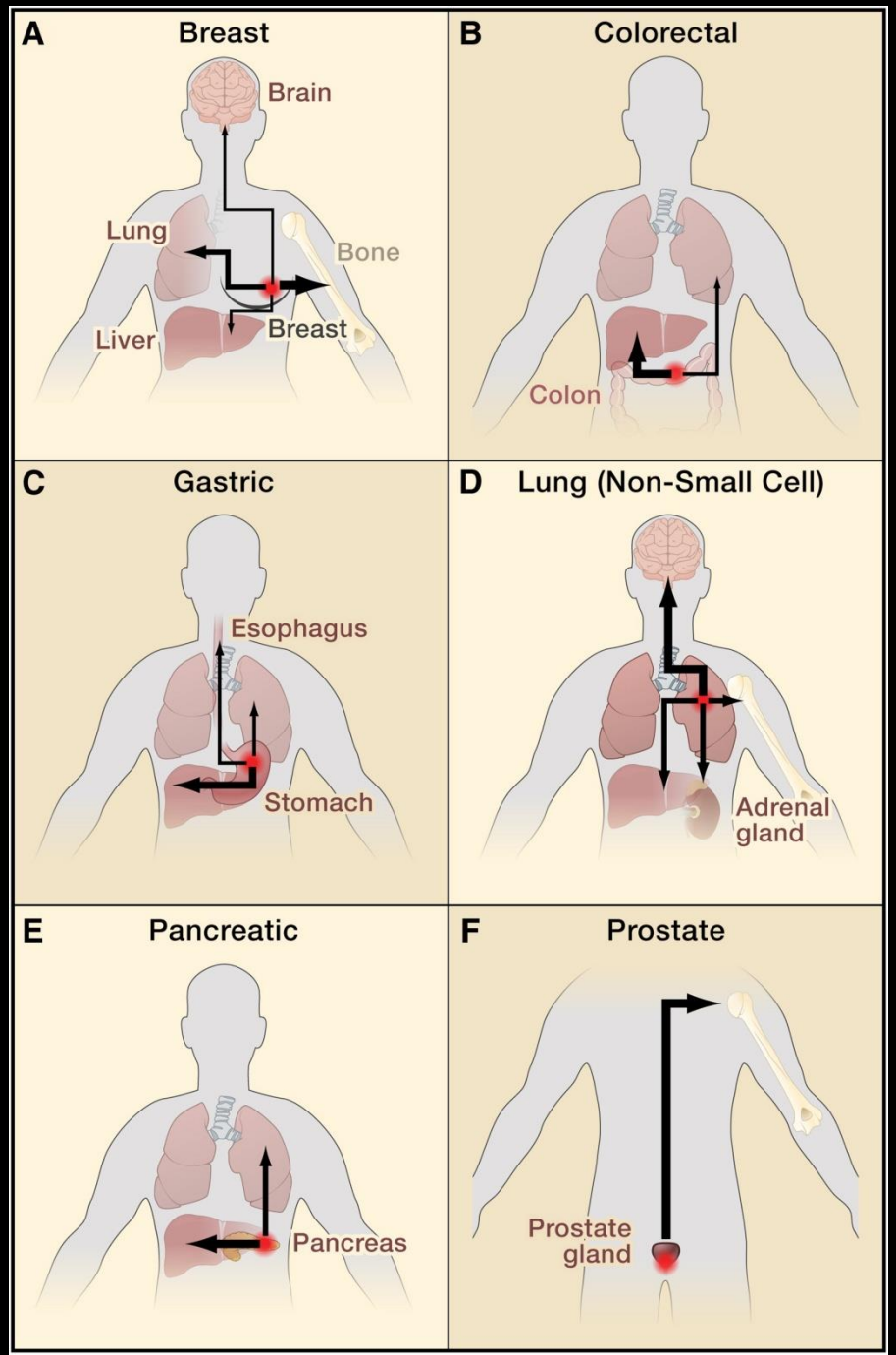


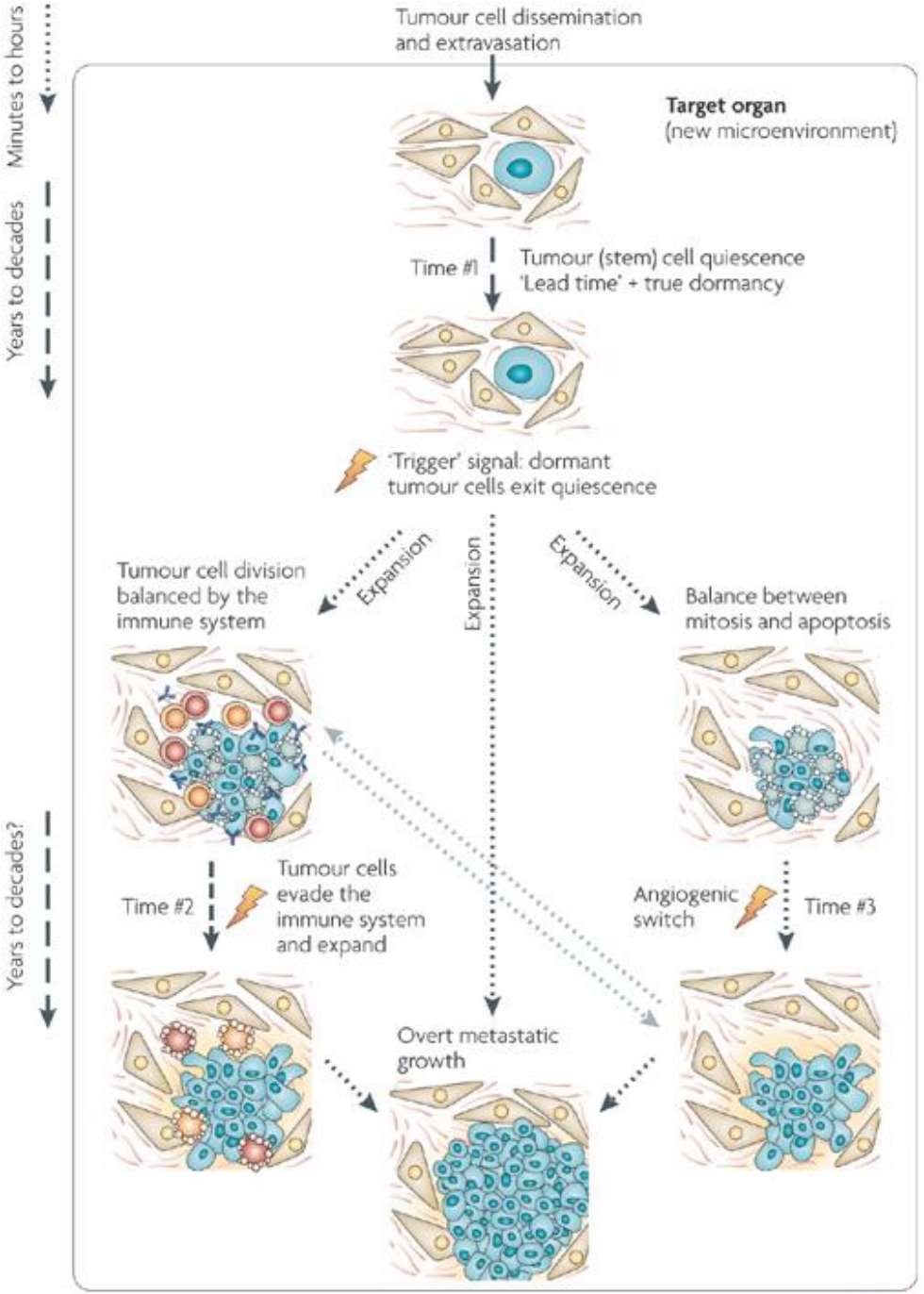
Figure 14-42 The Biology of Cancer (© Garland Science 2007)

Primary cancers and their metastatic tropisms



Metastatic Tropism:

thickness of black lines reflects the relative frequencies in which a primary tumor type metastasizes to the indicated distant organ site)


Minutes to hours
Years to decades
Years to decades?
Tumour cell dissemination and extravasation
Target organ (new microenvironment)
Time #1
Tumour (stem) cell quiescence 'Lead time' + true dormancy
'Trigger' signal: dormant tumour cells exit quiescence
Expansion
Expansion
Expansion
Tumour cell division balanced by the immune system
Balance between mitosis and apoptosis
Time #2
Tumour cells evade the immune system and expand
Angiogenic switch
Time #3
Overt metastatic growth