Global Focus on Knowledge Lecture Series

Wed, 10 June 2009

Kohei Miyazono, School of Medicine
（miyazono@m.u-tokyo.ac.jp）

Cell Signaling Systems:
The Biology of Cancer
— How Cancer Spreads and Metastasizes

Figure removed due to
copyright restrictions

Bruce Alberts,
"*Molecular Biology of the Cell*" *(4th edition)*
Translator:Keiko Nakamura, Kenichi Matsubara
Newton Press, 2004

Figure removed due to
copyright restrictions

Bruce Alberts,
Molecular Biology of the Cell, 5th edition,
Garland Science, 2008

Figure removed due to
copyright restrictions

Robert A. Weinberg, *The Biology of Cancer*,
Garland Science, 2006

http://commons.wikimedia.org/wiki/File:Yamagiwa.JPG

‡ Courtesy of the specimen room of faculty of medicine ,the university of Tokyo.

Katsusaburo Yamagiwa

The coal tar contained a carcinogen.

The carcinogen harmed genes.

Cancers are . . .

Gene disorders.

Cancer results when genes are harmed.

Causes of Cancer

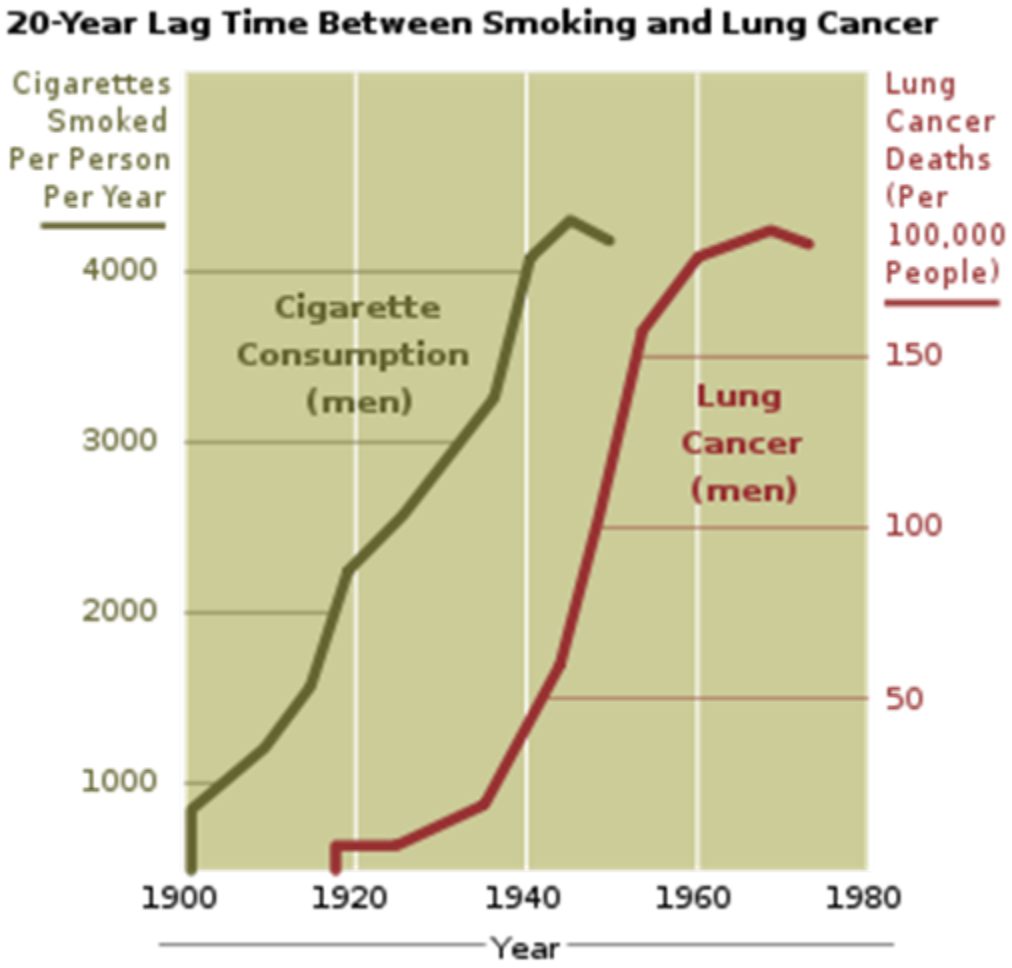
- Physical causes: Radiation and ultraviolet rays
  Also asbestos?

- Chemical causes: Carcinogens
  → Tobacco and lung cancer

- Viral & bacterial infection
  → Heliobacter pylori and gastric cancer

- Many causes remain uncertain

Sharp Rise in Incidence of Lung Cancer Lags Increase in Tobacco Consumption by Several Decades



http://en.wikipedia.org/wiki/File:Cancer_smoking_lung_cancer_correlation_from_NIH.svg

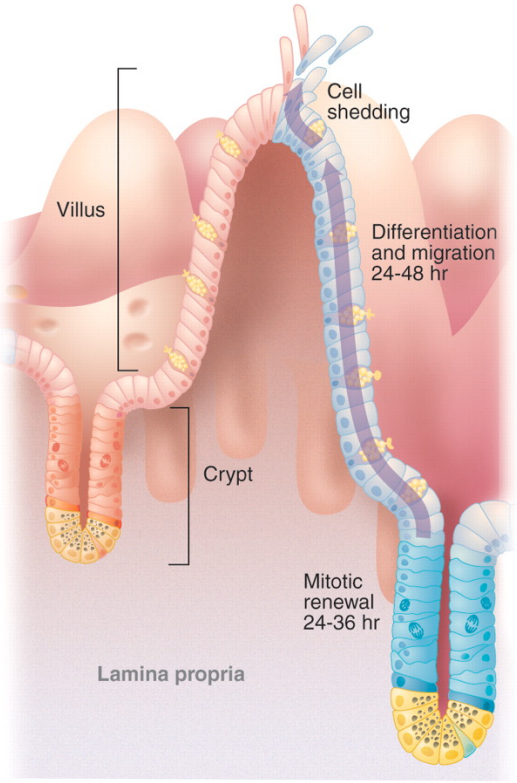
How a Cancer Grows

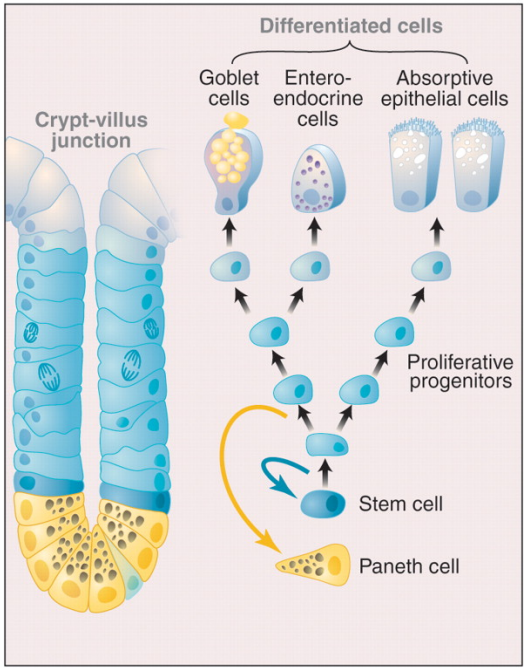
1. Cancer cells multiply proliferously and form a large localized lump (tumor).

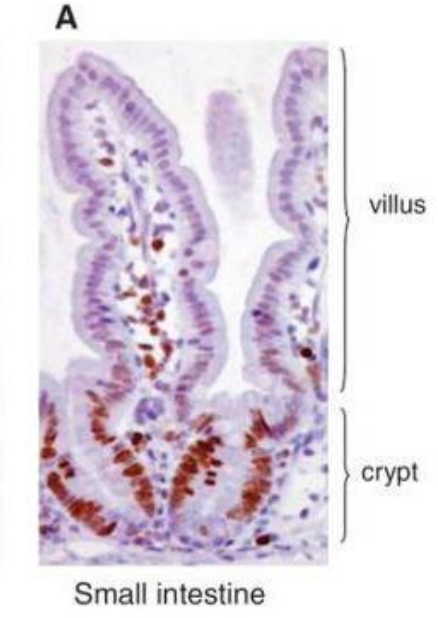
2. The cancer cells migrate to other parts of the body and begin multiplying anew (metastasis).

3. Due to the proliferation of cancer cells in the body, the patient is deprived of nutrients and declines (cachexia).

The Life of an Intestinal Epithelium Cell







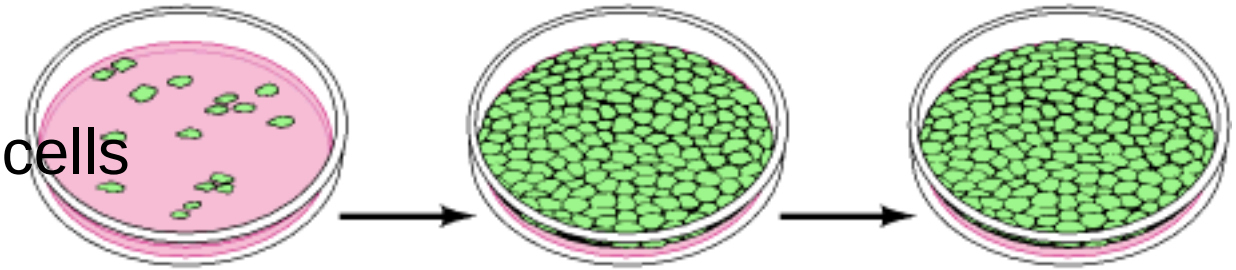
‡ ‡

From *Science*, vol.307, no.5717, pp.1904 - 1909. Reprinted with permission from AAAS.

Even after Running out of Space, Cancer Cells Continue to Multiply

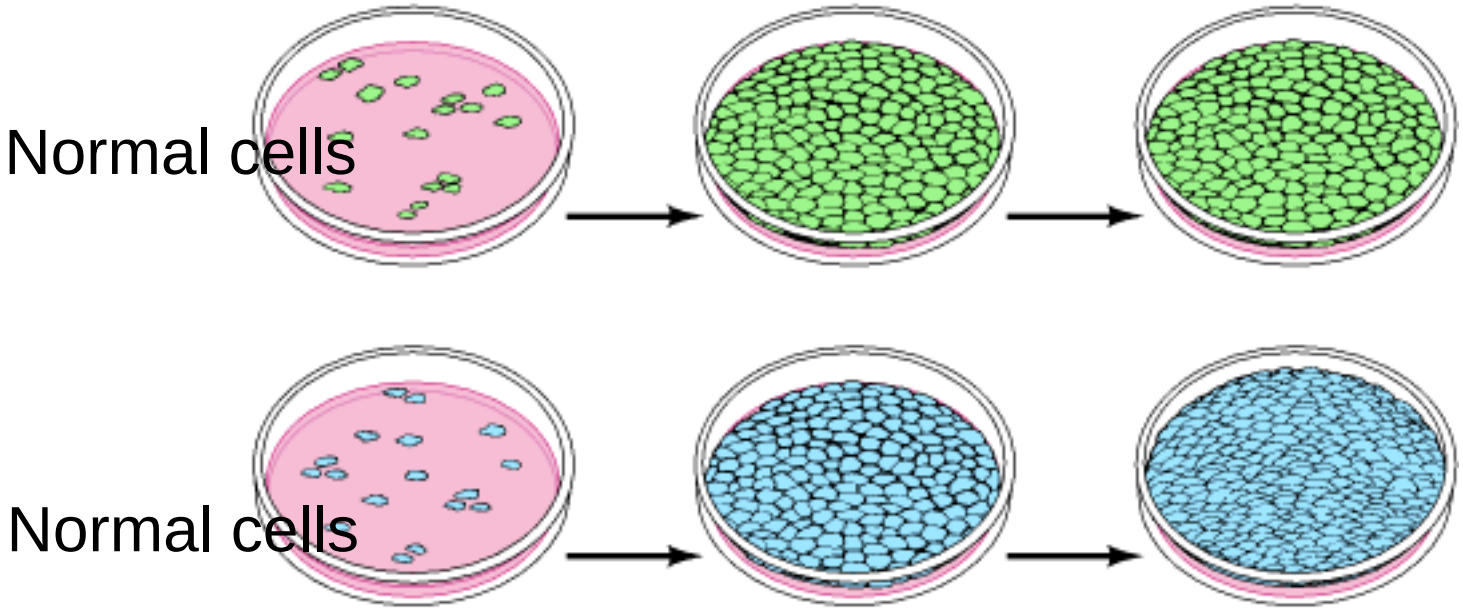
Contact inhibition

Normal cells



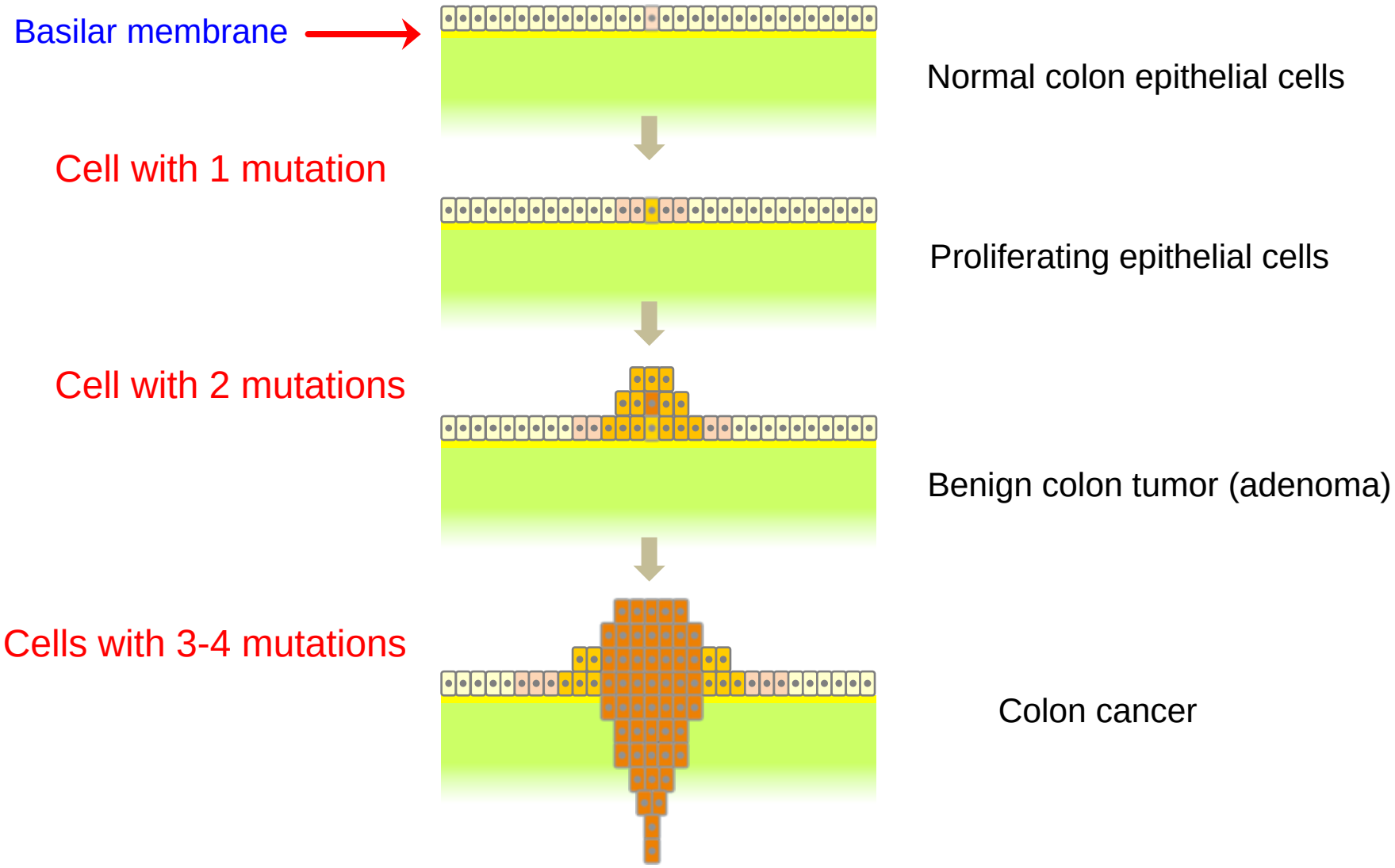
Even after Running out of Space, Cancer Cells Continue to Multiply

Contact inhibition



No contact inhibition

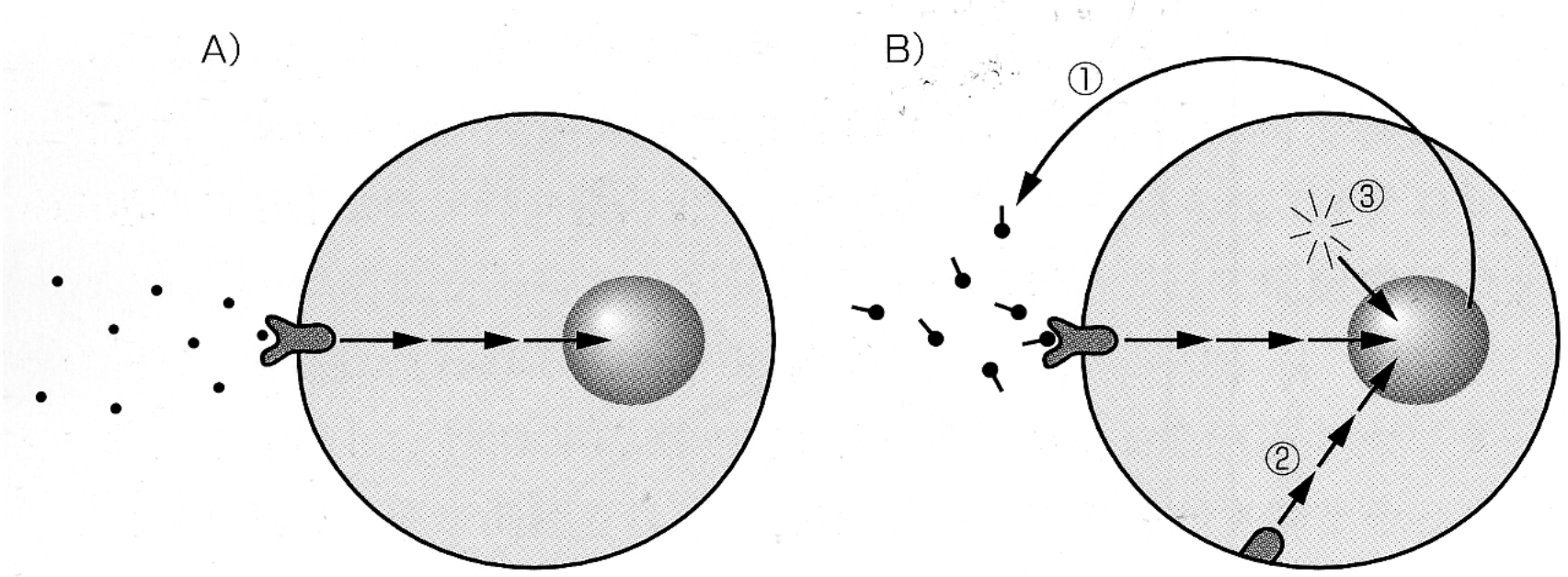
Cancer "Evolves": Clonal Evolution



Growth Factor Signaling and Cancer

Normal cell

Cancer cell



Cancer cells exhibit excessive growth factor signaling.

→ Runaway signaling

Colon Cancer Malignancy and Gene Abnormalities

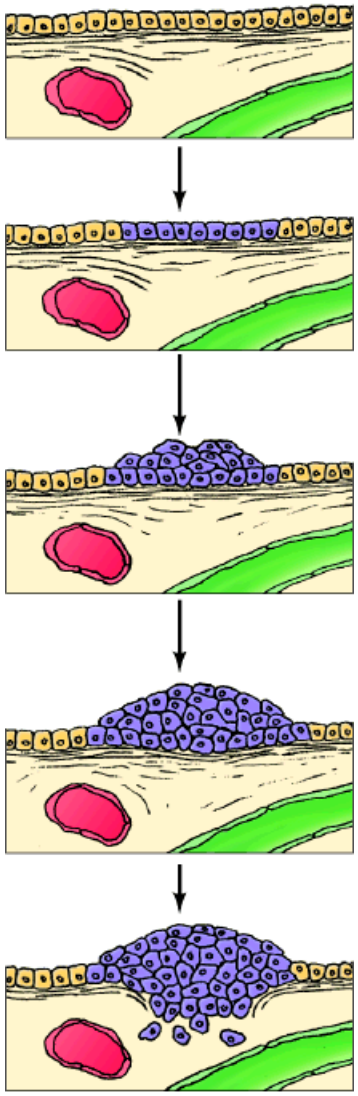
Normal colon epithelial cells

Proliferating epithelial cells

Early-stage benign colon tumor (adenoma)

Late-stage benign colon tumor (adenoma)

Colon cancer



APC = Suppressor oncogene

K-Ras = Oncogene

Smad4 = Suppressor oncogene

p53 = Suppressor oncogene

Other oncogenes and suppressor oncogenes

がん ＝ Cancer

Chronic Myelogenous Leukemia (CML)

- Marked proliferation of leukocytes (and sometimes platelets and red blood cells)

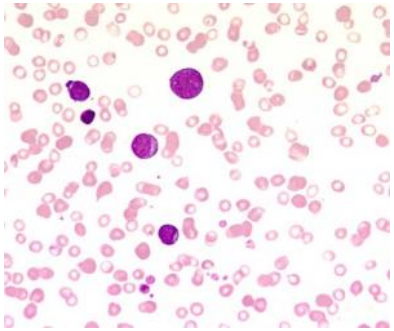
- Unlike acute leukemia, found in all leukocytes, from immature through differentiated.

− Characterized by Philadelphia$_1$chromosome (Ph^1) expression.

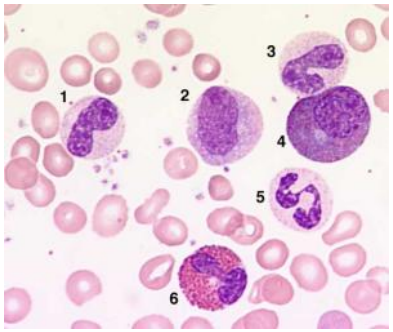
− Progresses to acute leukemia in 3 to 10 years. Once developed into blast crisis, treatment with anti-cancer agents is rarely effective.

Transition from Chronic Phase to Accelerated Phase to Blast Crisis

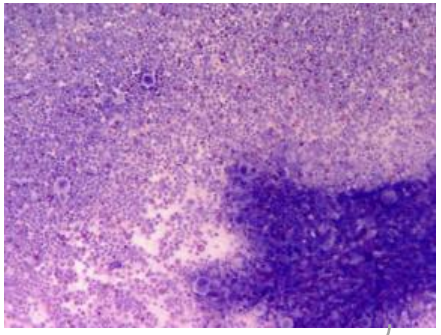
1



2



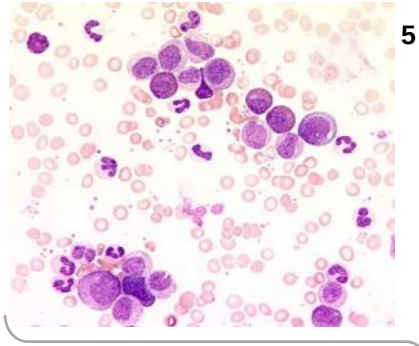
3



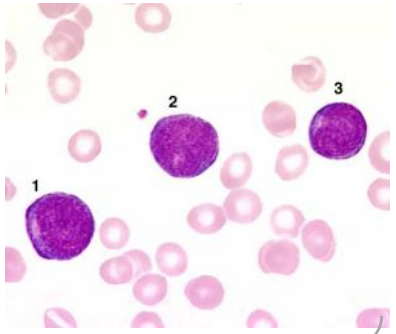
Chronic Phase

Accelerated Phase

4



5

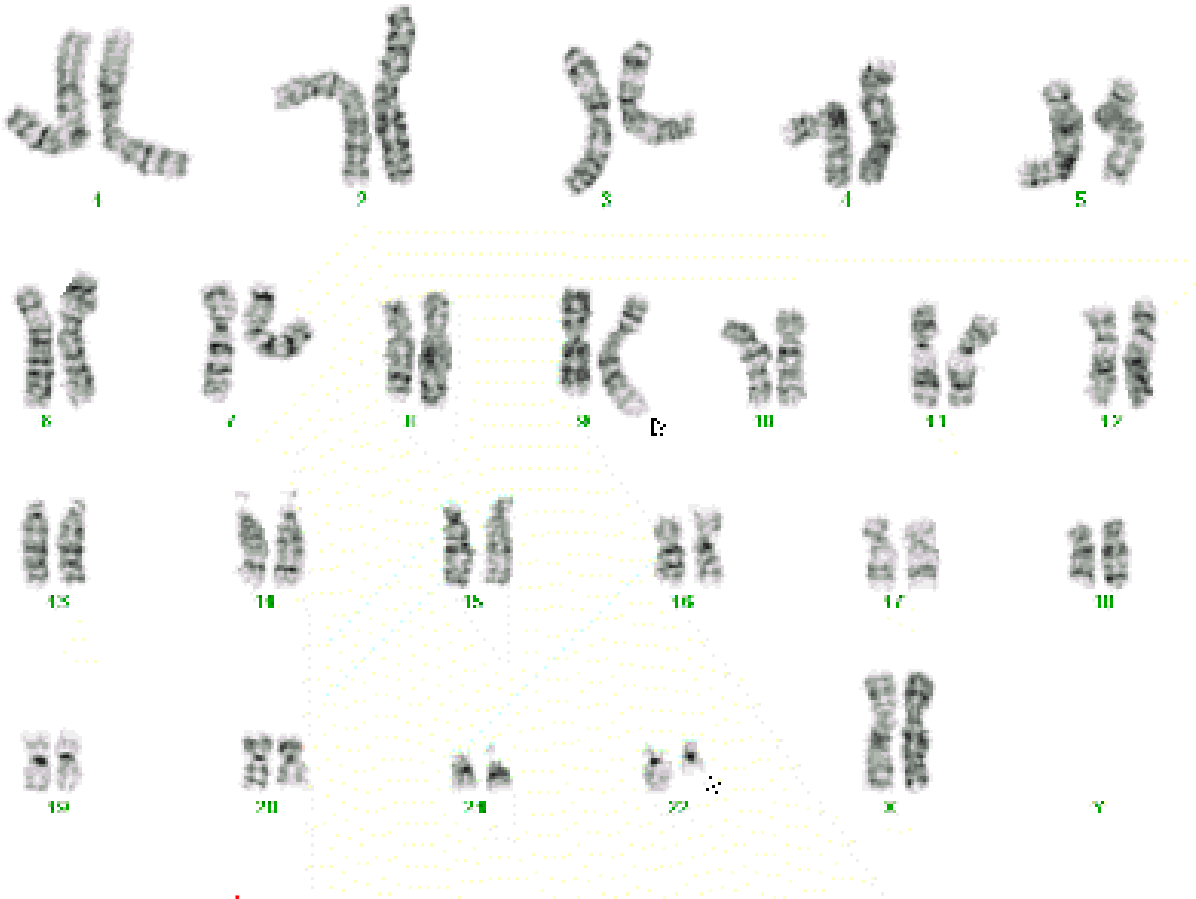


Blast Crisis

‡ All images on this page are taken from HemoSurf - An Interactive Atlas of Hematology http://e-learning.studmed.unibe.ch/hemosurf_demo/. Courtesy of U. Woermann, MD, Education andl Media Unit, Institute for Medical Education, University of Bern, Switzerland.

<Chronic phase of Chronic Myelogenous Leukemia (CML) >
1. Blood smear at 400x magnification showing increased number of leukocytes with many progenitor cells of the myeloid lineage as well as basophils and neutorphils with pseudo Pelger. Increased number of thrombocytes.
2. Blood smear at 1000x magnification showing a metamyelocyte (1), a myelocyte (2), a band neutrophil (3), a promyelocyte(4), a segmented neutrophil (5) and an eosinophil (6).
3. Bone marrow smear at 400x magnification showing of clear hypercellularity and increased number of megakaryocytes.
<Blast crisis Chronic Myelogenous Leukemia (CML) >
4. Blood smear at 400x magnification showing monomorphic progenitor cells of the myeloid lineage.
5. Blood smear at 1000x magnification showing three leukemic blasts.

Philadelphia Chromosome



‡ Karyotype showing the Philadelphia chromosome.
46,XX,t(9;22)(q34.1;q11.2
http://www.lhsc.on.ca/lab/cytogen/cml.htm
Courtesy of Dr. Janice Little.

Why Does Chronic Leukemia Become Acute Leukemia?

Leukemia cells keep proliferating.

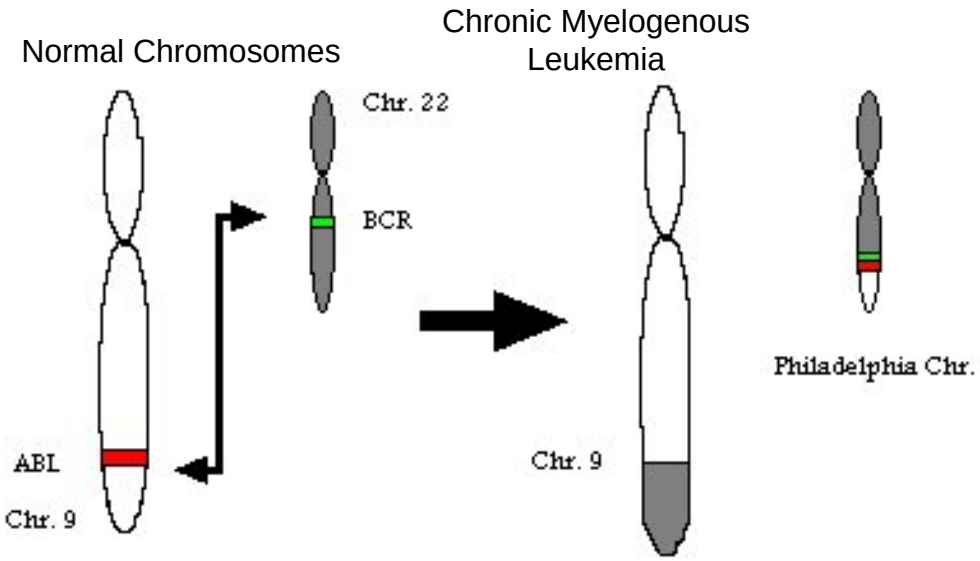
Does another gene abnormality join in while proliferation is ongoing?

Chromosomes in a Case that Developed into Acute Leukemia

Figure removed due to copyright restrictions

Vinay Kumar et al., 2010,
Robbins and Cotran pathologic basis of disease 8th Edition,
Saunders/Elsevier,
Image6, Case 4, Systemic Pathology, Hematophology
(in CD-ROM)

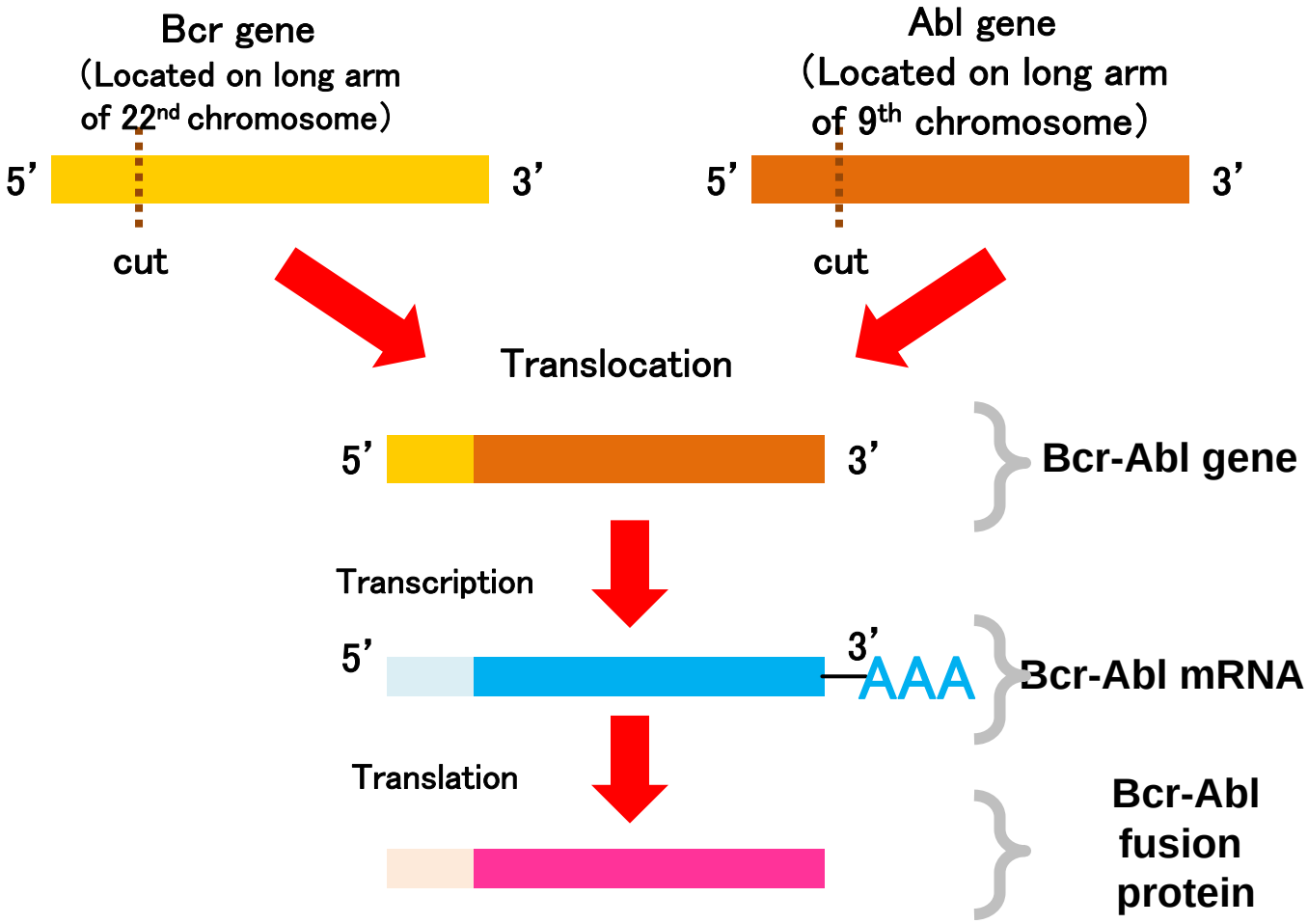
Idiopathy of the Philadelphia Chromosome



http://en.wikipedia.org/wiki/File:Philadelphia_chromosome.jpg

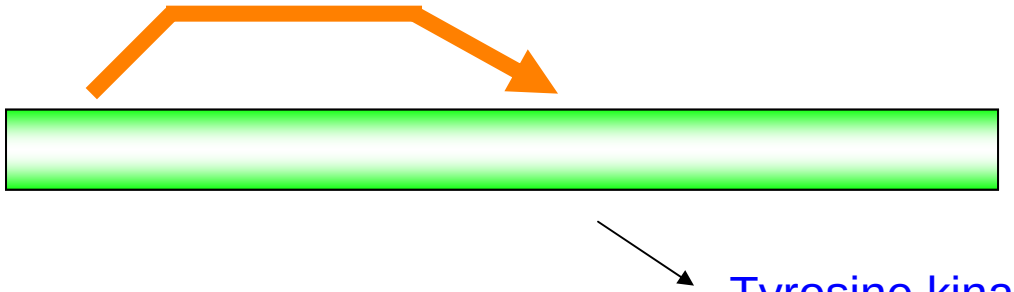
Translocation of chromosomes 9 and 22

Formation of the BCR-ABL Fusion Gene



What the BCR-ABL Fusion Gene Does

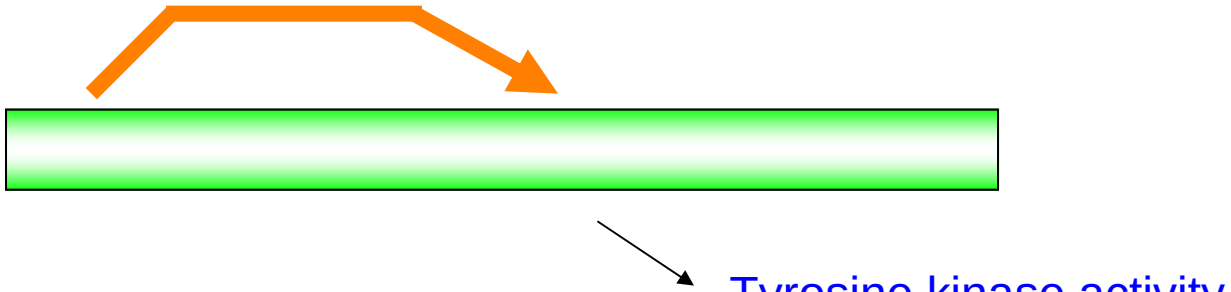
Protein generated by a normal ABL gene



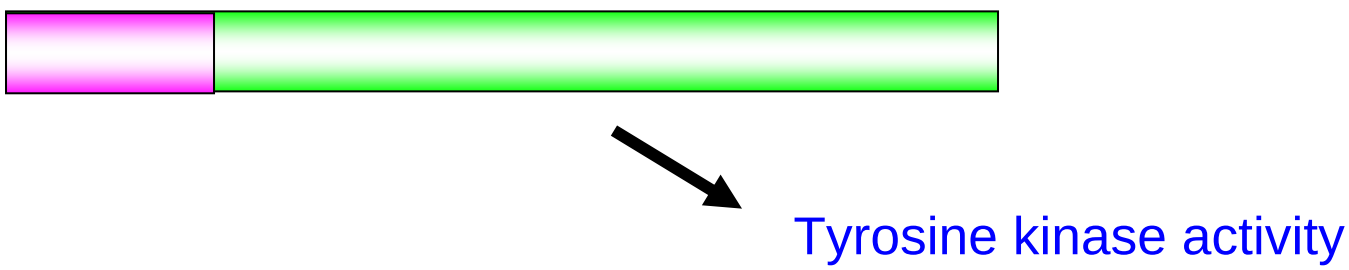
Tyrosine kinase activity

Function of the BCR-ABL Fusion Gene

Protein generated by a normal ABL gene

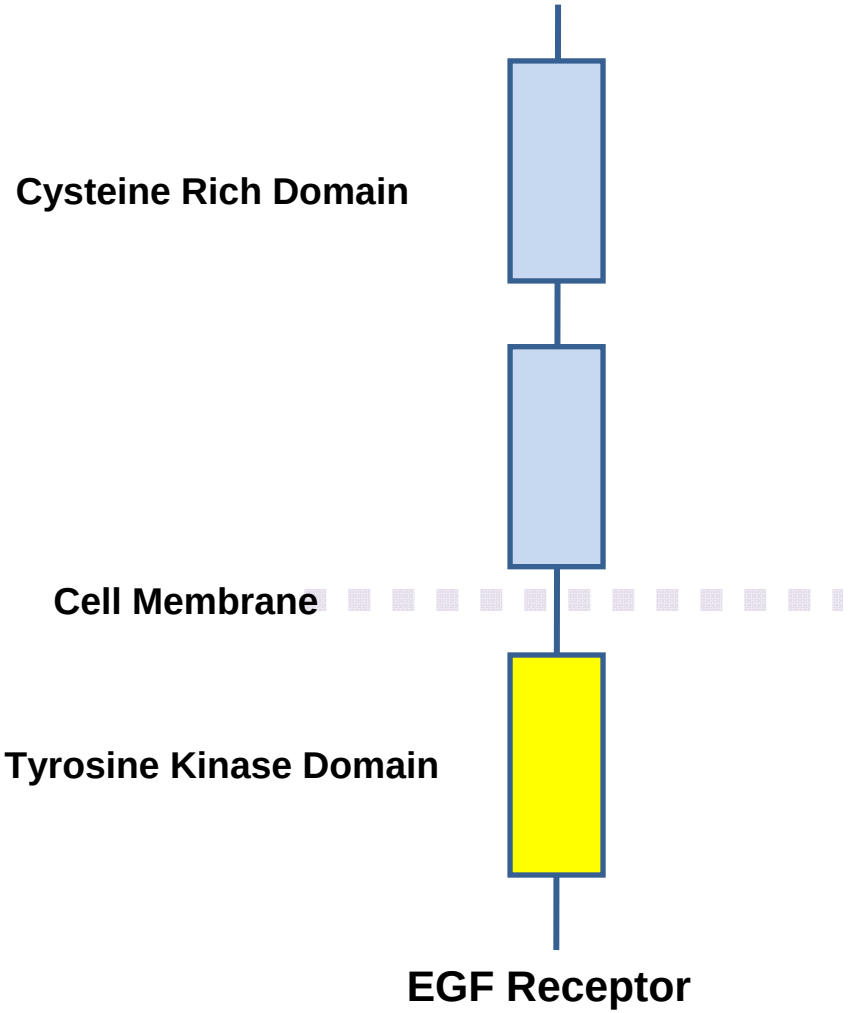


Protein generated by a Bcr-Abl fusion gene

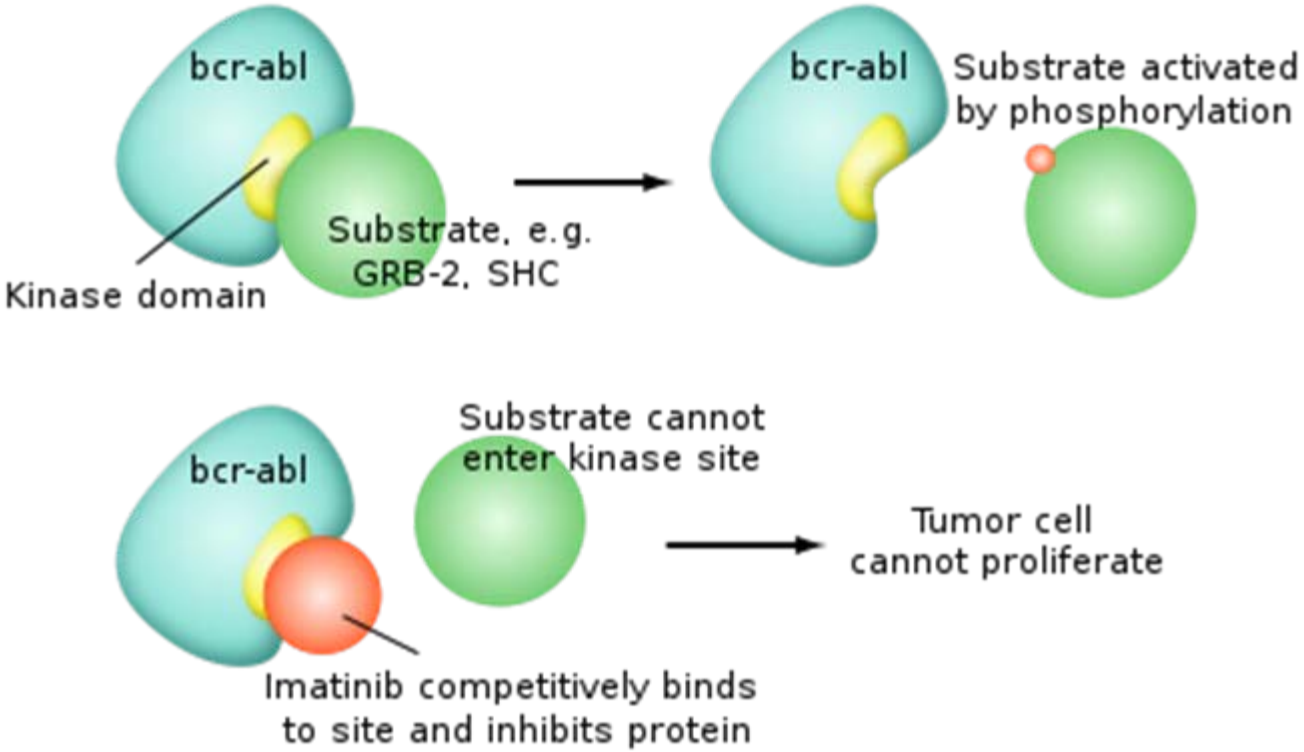


The Epidermal Growth Factor (EGF) Receptor

- Characterized by the presence of tyrosine kinase, which phosphorylates tyrosine residues in the cell.
- The oncogene Src is one that exhibits tyrosine kinase activity.

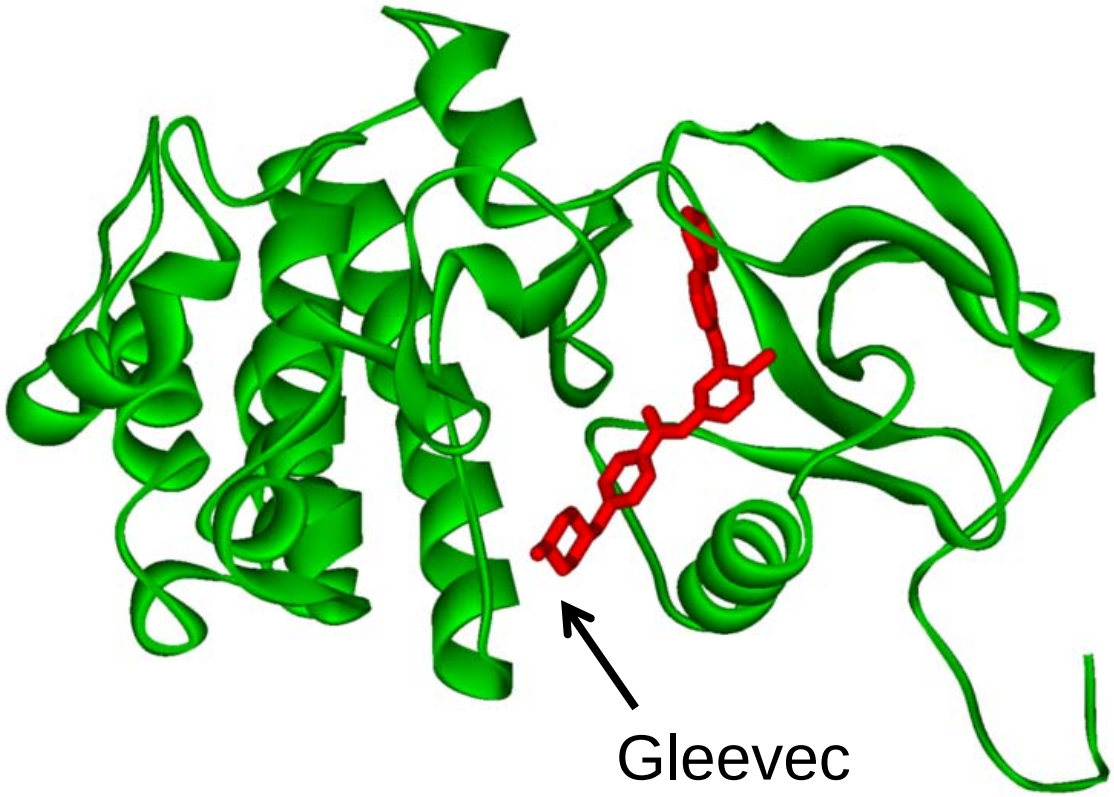


Regulating BCR-ABL Proteins with Gleevec



‡ http://en.wikipedia.org/wiki/File:Mechanism_imatinib.svg

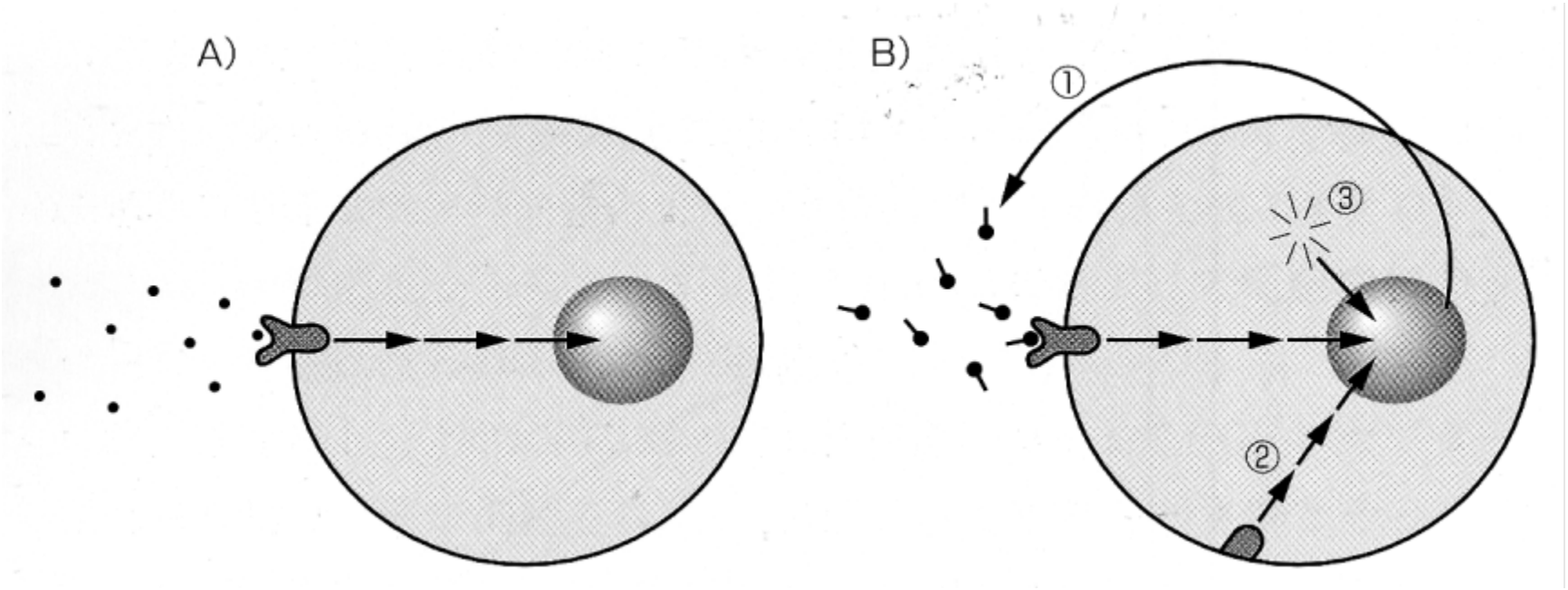
Regulating BCR-ABL Proteins with Gleevec



http://en.wikipedia.org/wiki/File:Bcr_abl_STI_1IEP.png

Growth Factor Signaling and Cancer

Normal cell　　Cancer cell



Cancer cells exhibit excessive growth factor signaling.

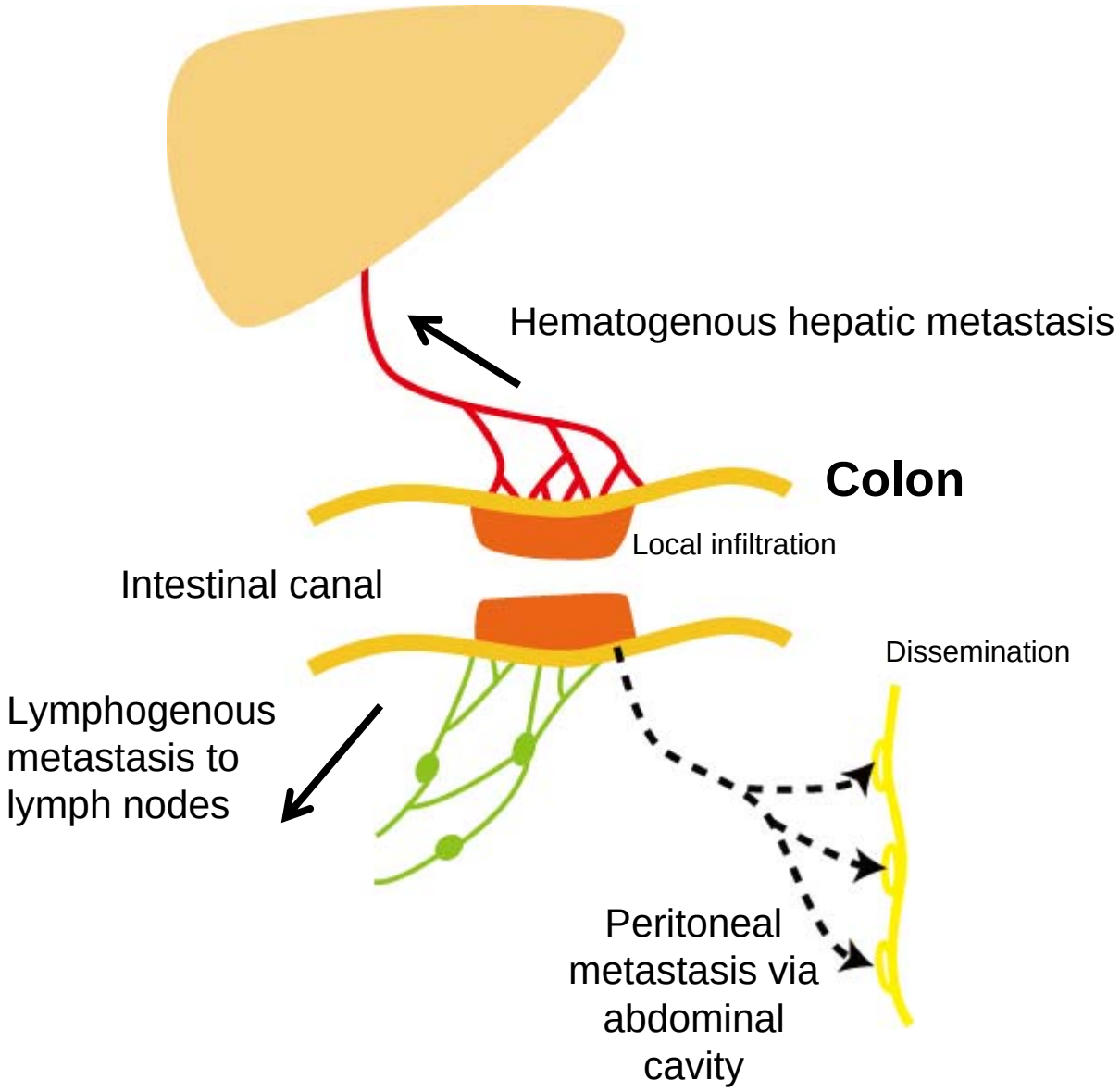
→　Runaway signaling

‡ K. Miyazawa, K. Yokote, M. Kouhei(2000)
"Biology of a Factor that Propagetes New Cell(Shin saibou zoushoku inshi no biology)"
P26, Fig. 1-6, Yodosha

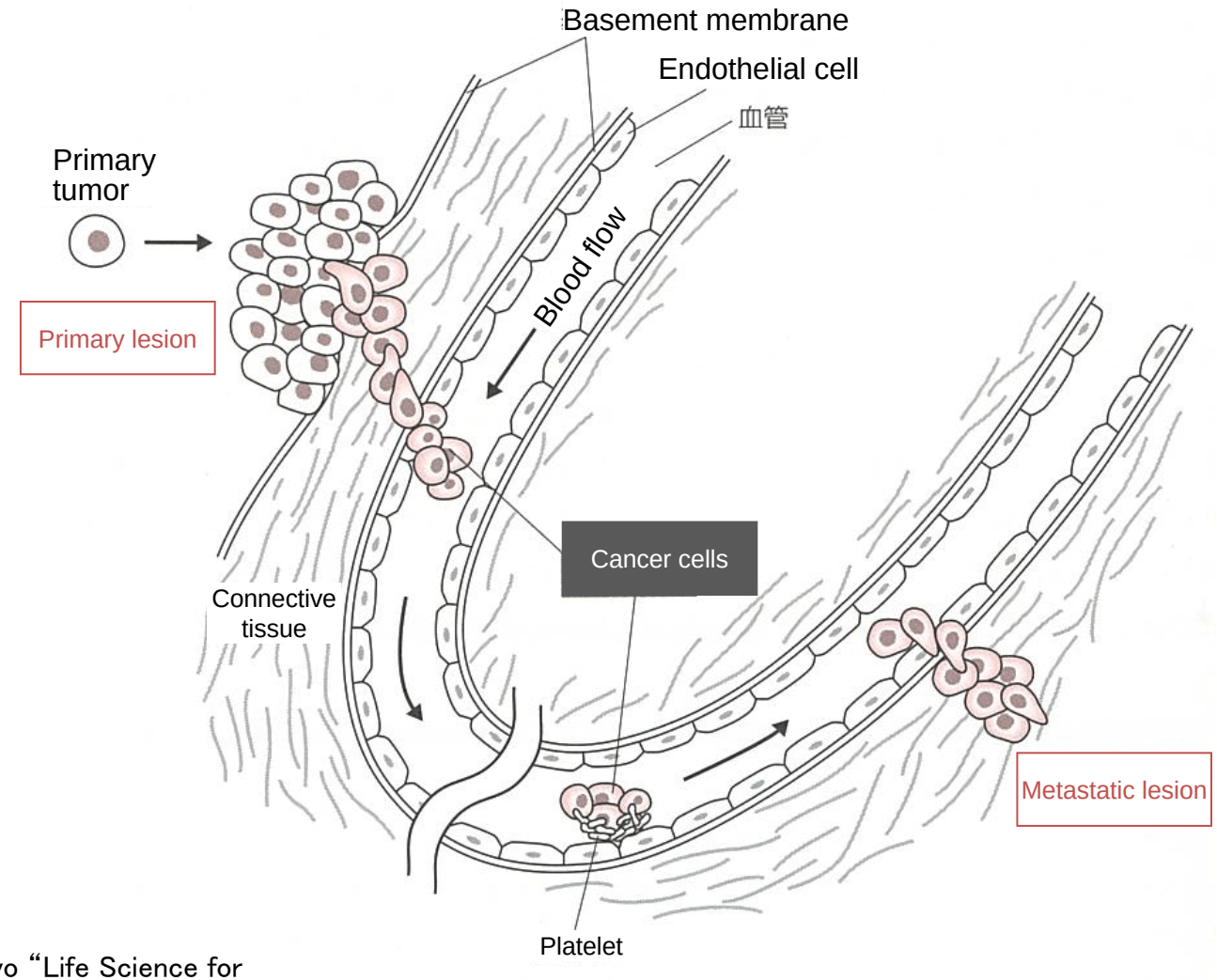
Growth Factors and Oncogenes

Oncogene	Growth factor	Human cancers
sis	PDGF-B chain	Human cancers Brain, bone
erb-B1	EGF receptor	Lung
ras	Signaling molecules	Lung, pancreas, colon, other
abl	Signaling molecules	CML

How Cancer Spreads



Cancer Cells Metastasize

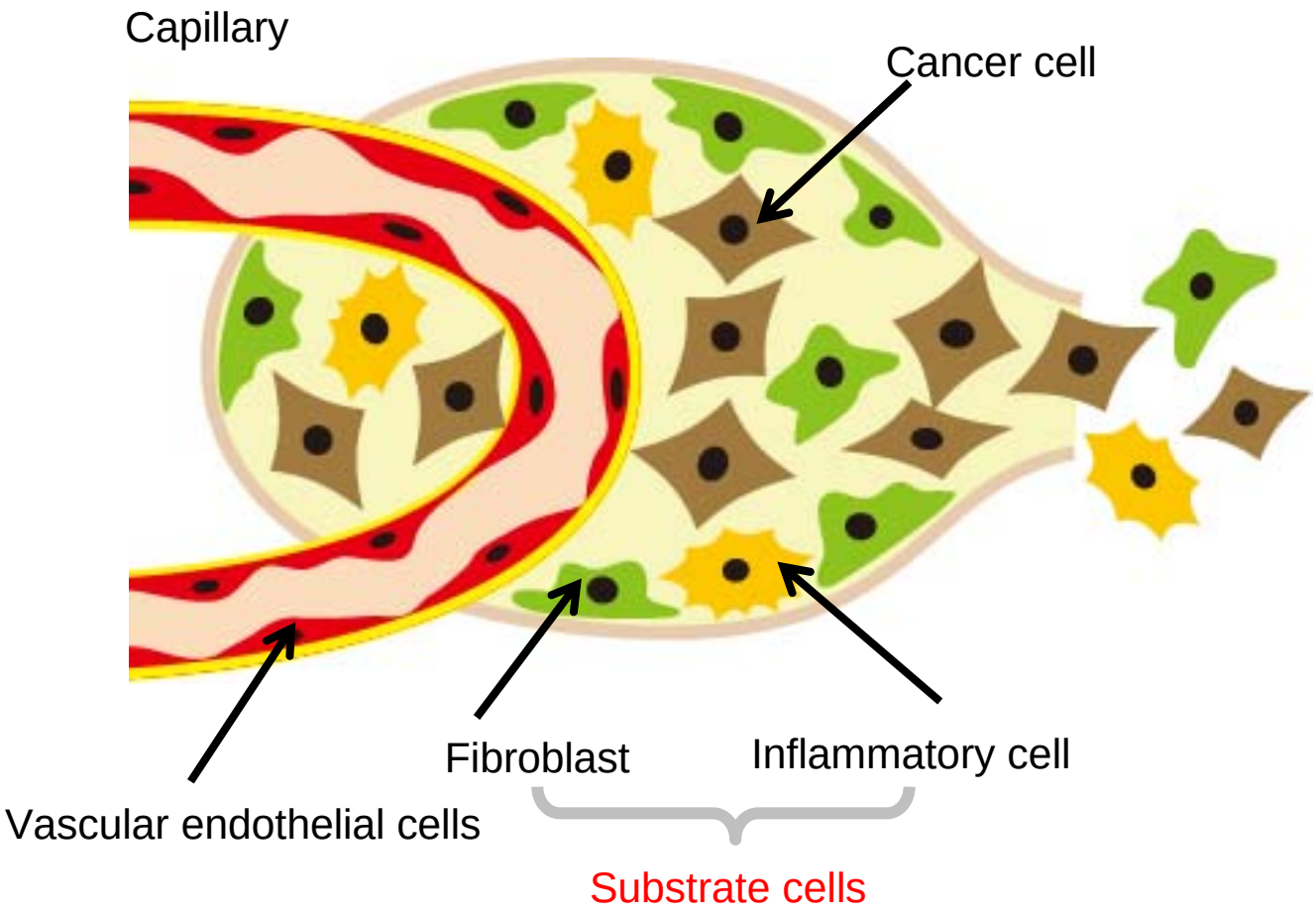


‡

The university of Tokyo “Life Science for Humanities(Bunkei no tame no seimeikagaku)” Yodosha, 2008

The Microenvironment of Cancer

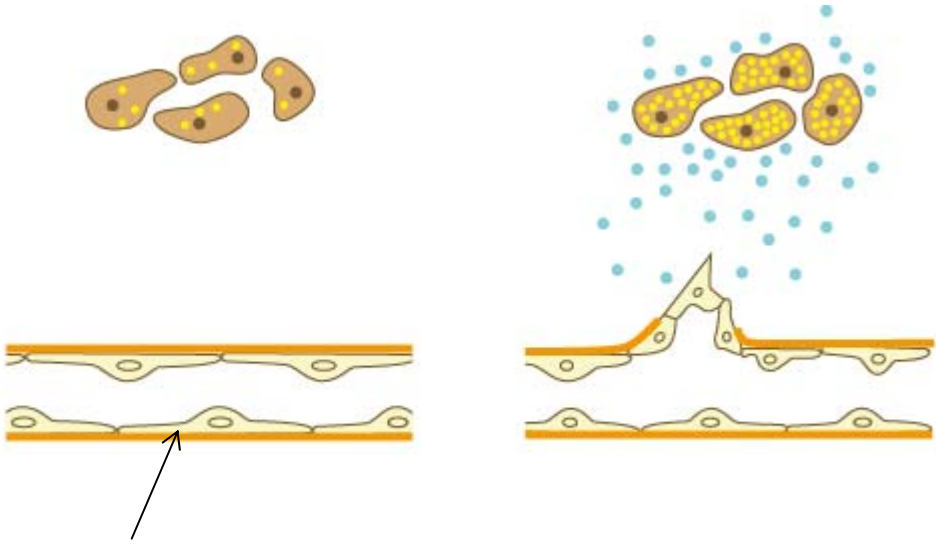
Cancer Is Present in Several Distinctive Environments



Cancer Cells Lack Sufficient Nutrients and Oxygen → Cancer Cells Summon Blood Vessels

Early-stage cancer cells

Cancer cells producing the growth factor that fashions blood vessels



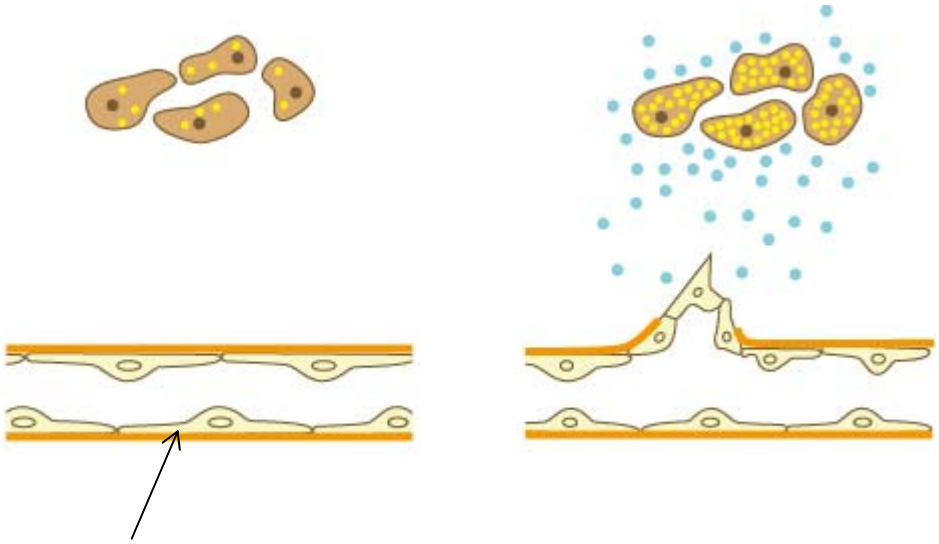
Vascular endothelial cells

VEGF, vascular endothelial growth factor

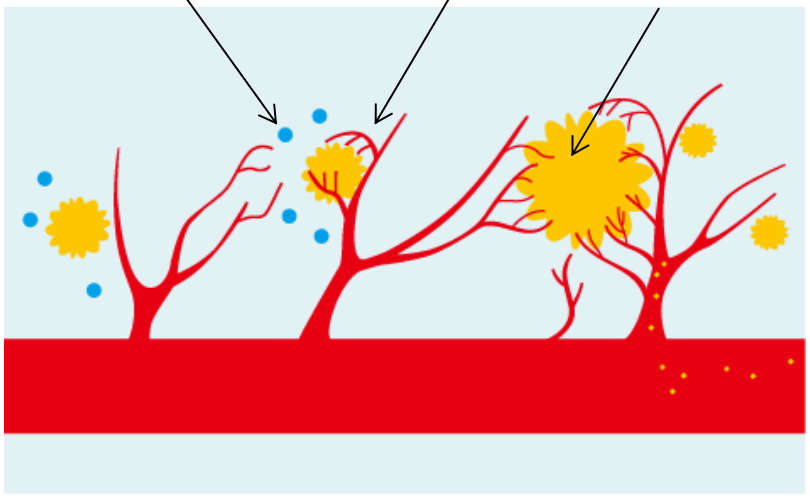
Cancer Cells Lack Sufficient Nutrients and Oxygen → Cancer Cells Summon Blood Vessels

Early-stage cancer cells

Cancer cells producing the growth factor that fashions blood vessels

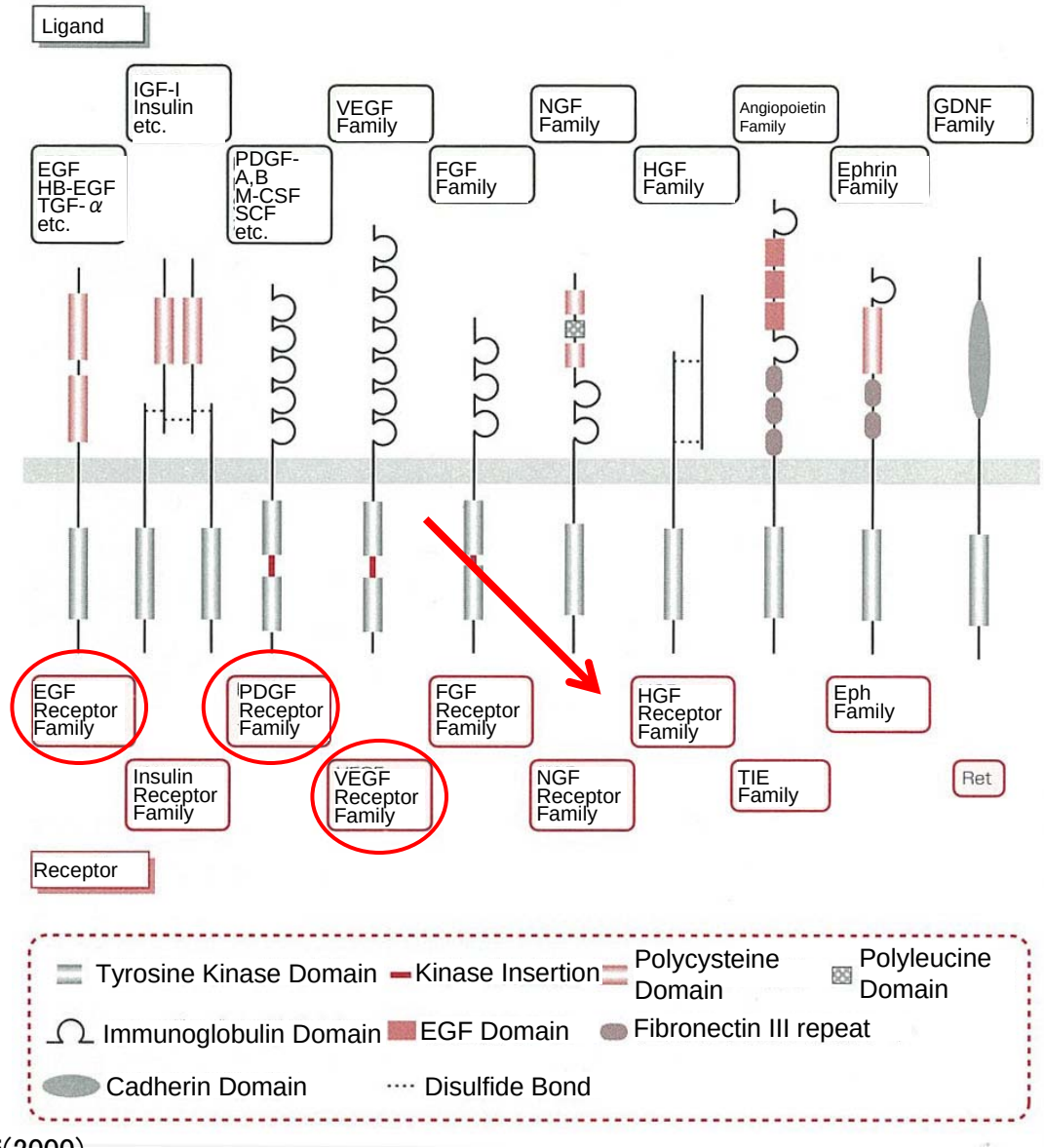


Vascular endothelial cells



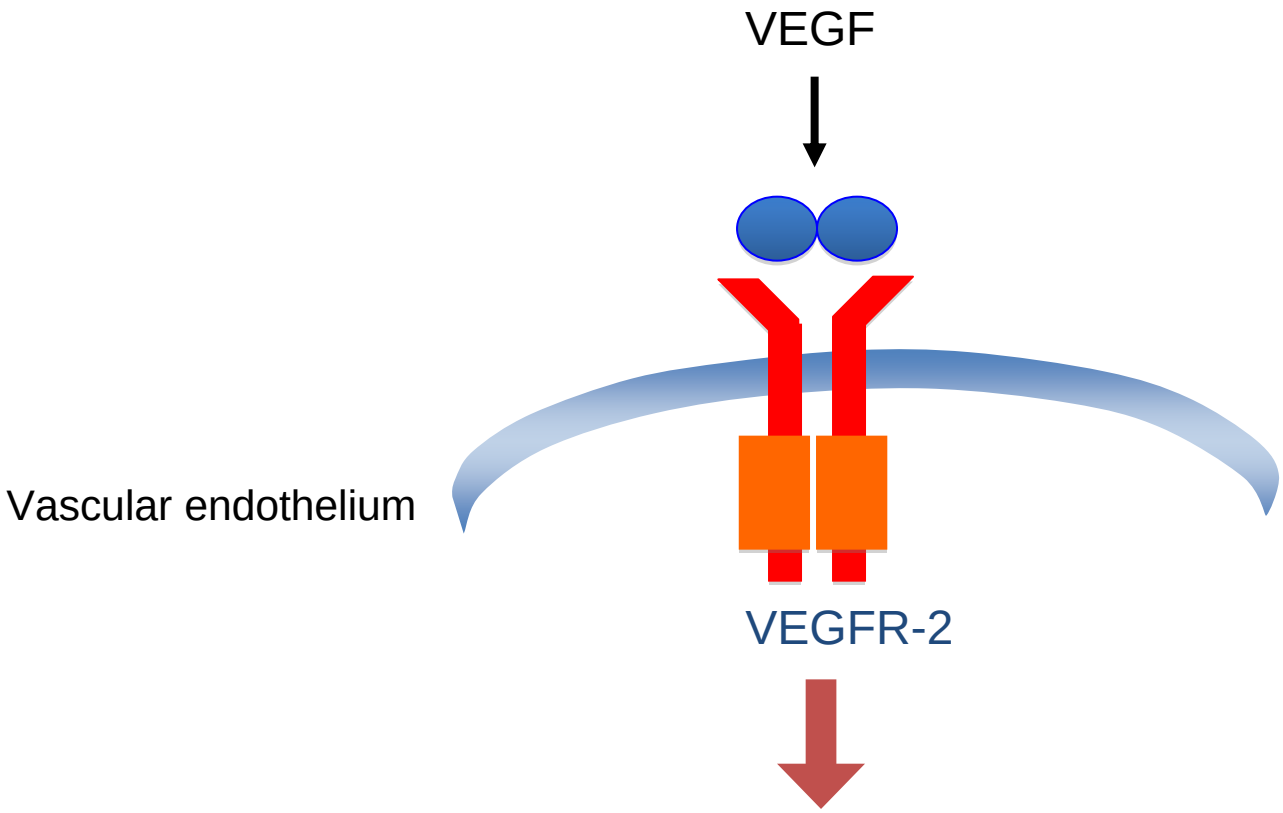
VEGF, vascular endothelial growth factor

Primary Tyrosine Kinase Receptors and Their Ligands



‡ K. Miyazawa, K. Yokote, M. Kouhei(2000)
"Biology of a Factor that Propagetes New Cell(Shin saibou zoushoku inshi no biology)"
Yodosha

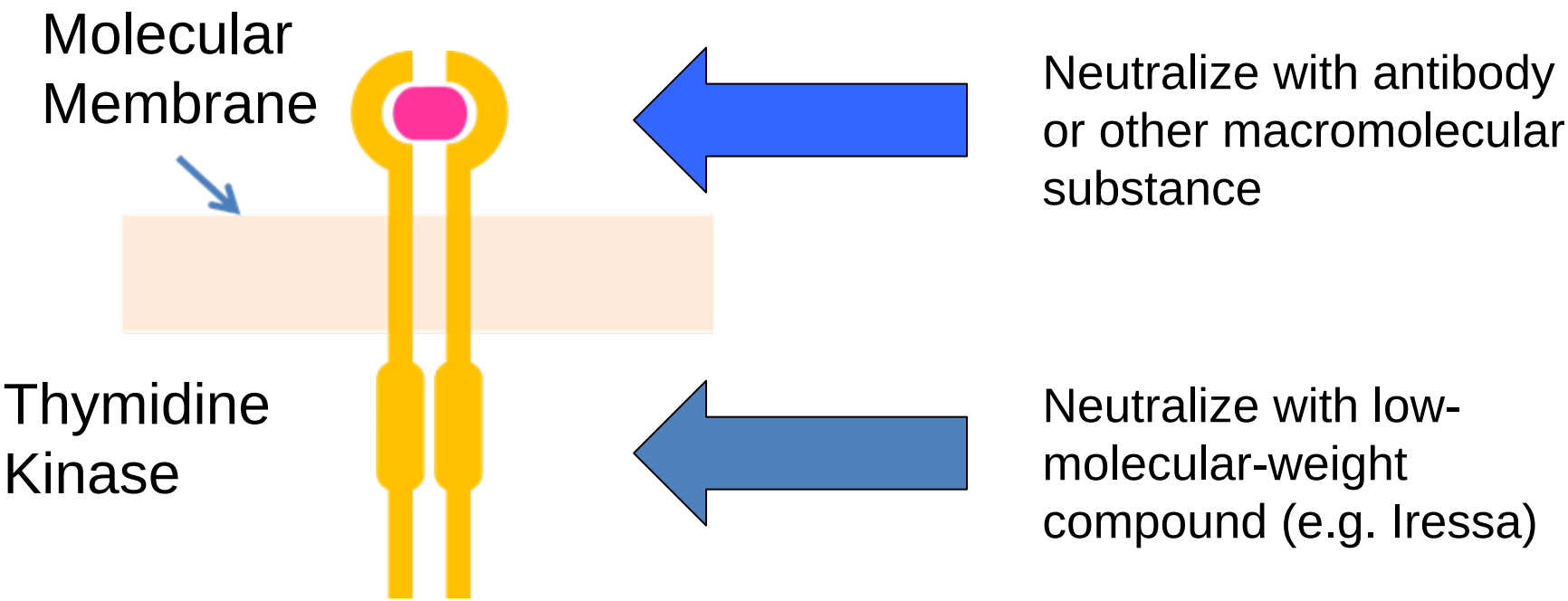
VEGF Receptor Signals



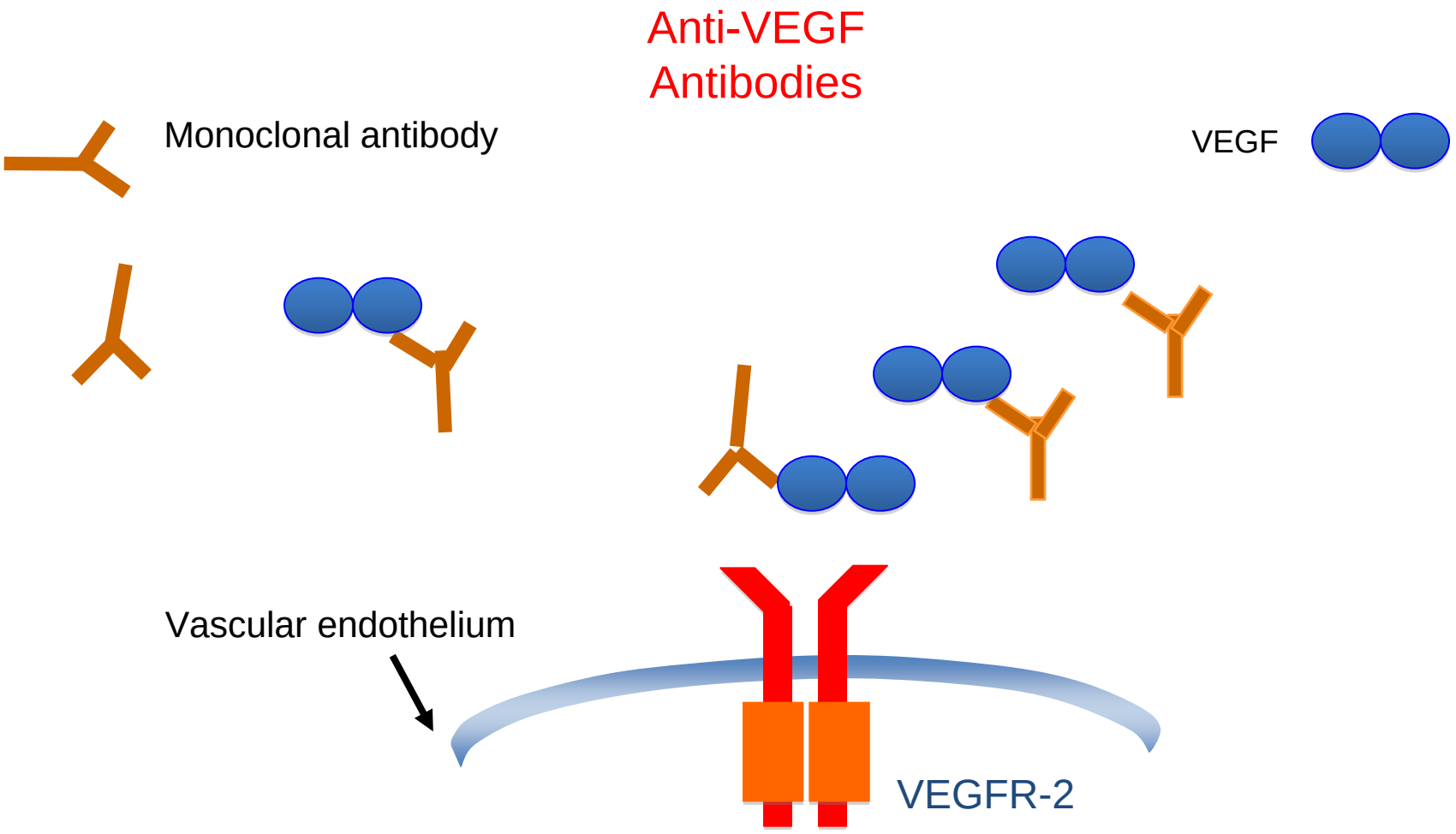
Proliferation, vascular permeability enhancement, movement, subsistence

VEGF, vascular endothelial growth factor
VEGFR, vascular endothelial growth factor receptor

How to Cut Off Growth Factor Signals?



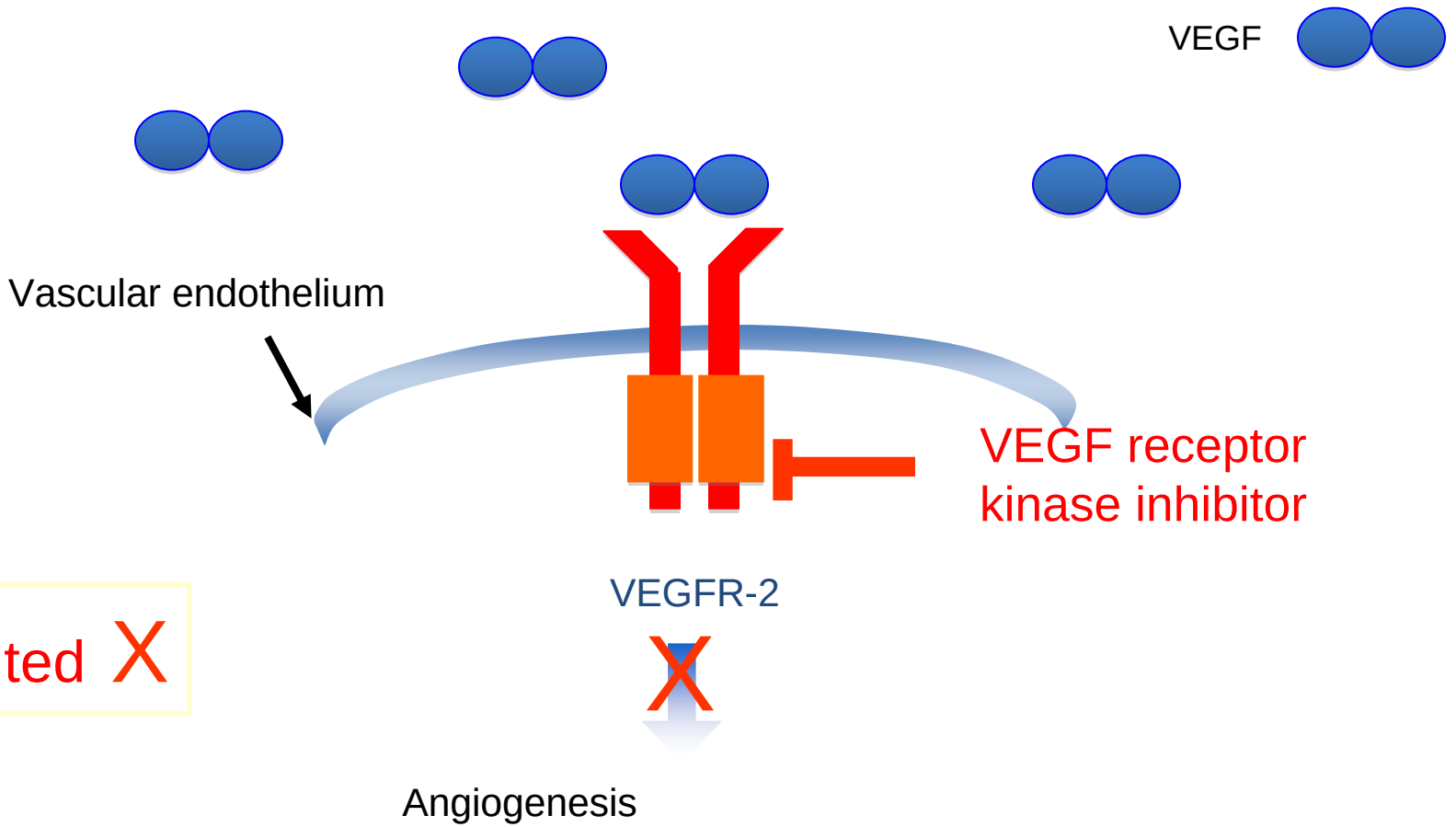
Inhibiting VEGF Receptor Signals



Avastin: A monoclonal anti-VEGF antibody

Inhibiting VEGF Receptor Signals

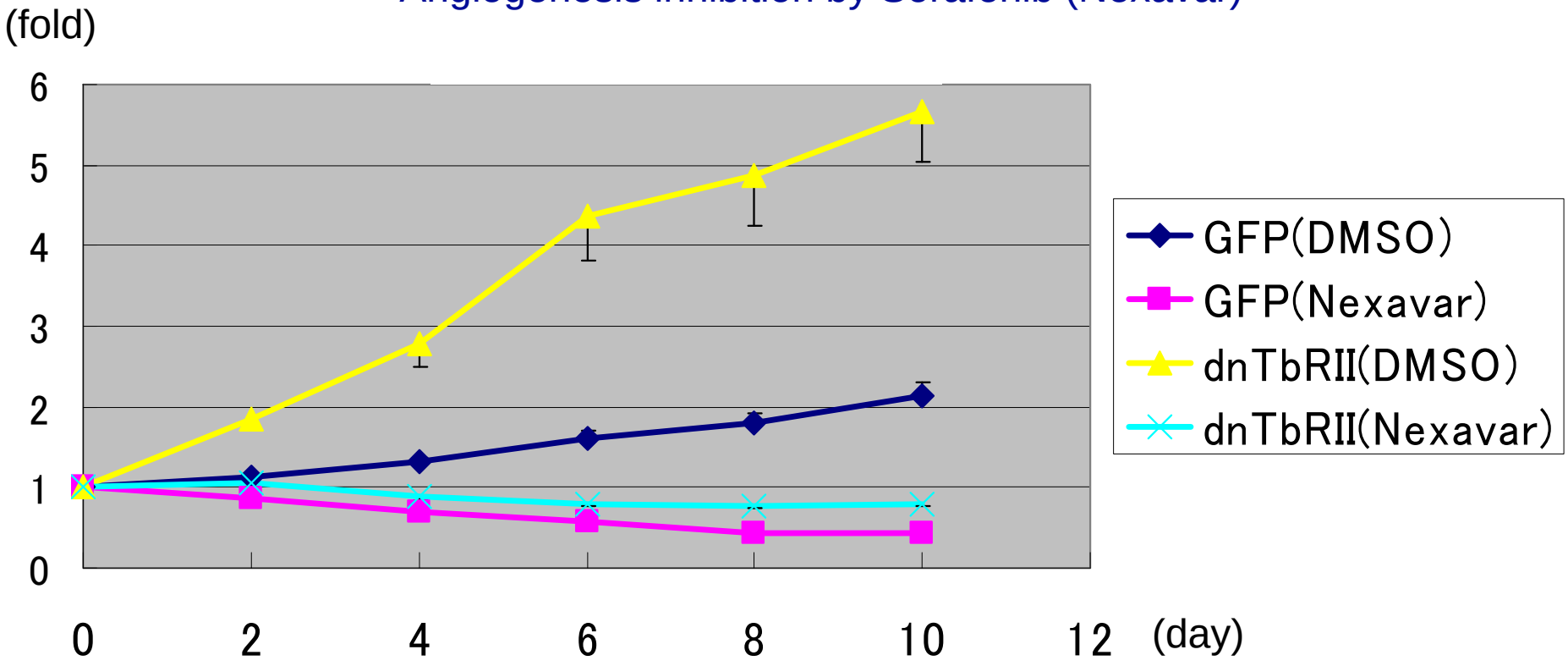
VEGF Receptor Kinase Inhibitors

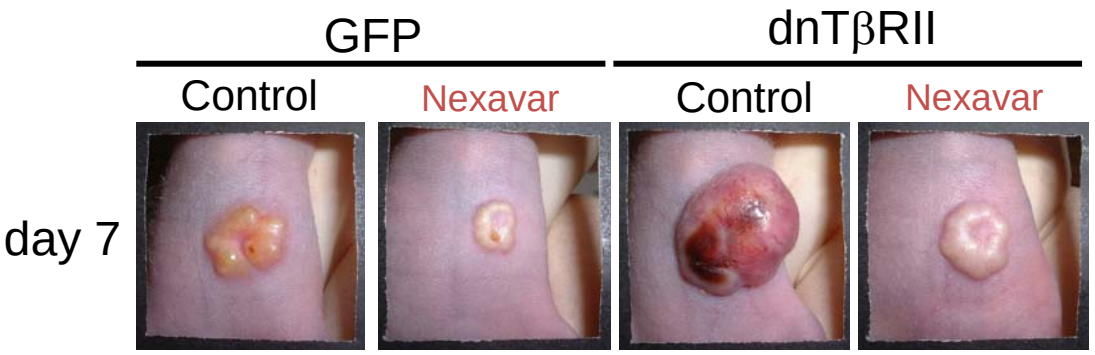


Sorafenib: A VEGF receptor kinase inhibitor

Therapeutic Effect of Angiogenesis Inhibitors on Gastric Cancer Cells

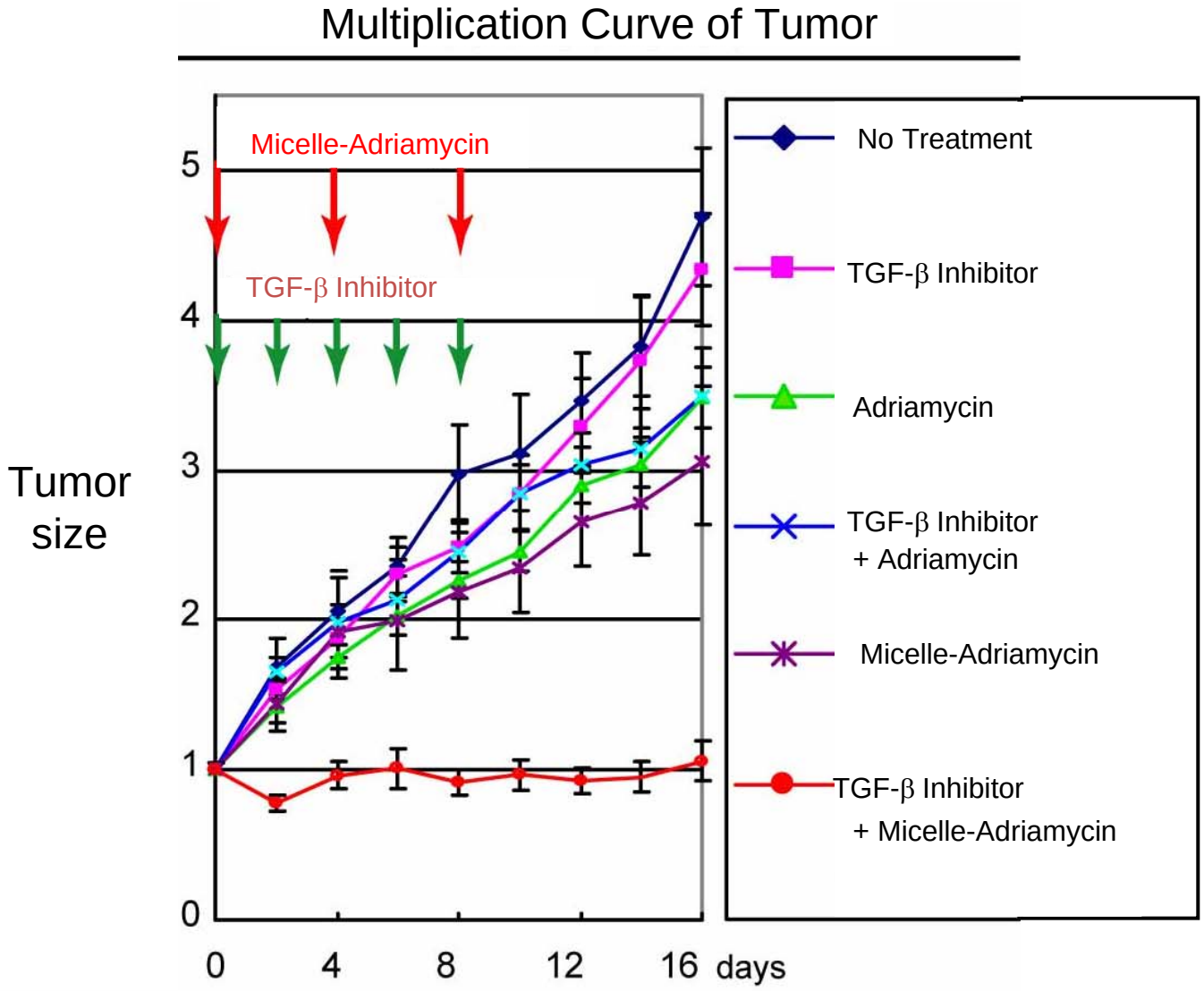
Angiogenesis inhibition by Sorafenib (Nexavar)





Treatment Using Micelle-Adriamycin and TGF-β Inhibitor

(case of transplanting pancreatic cancer BxPC3)

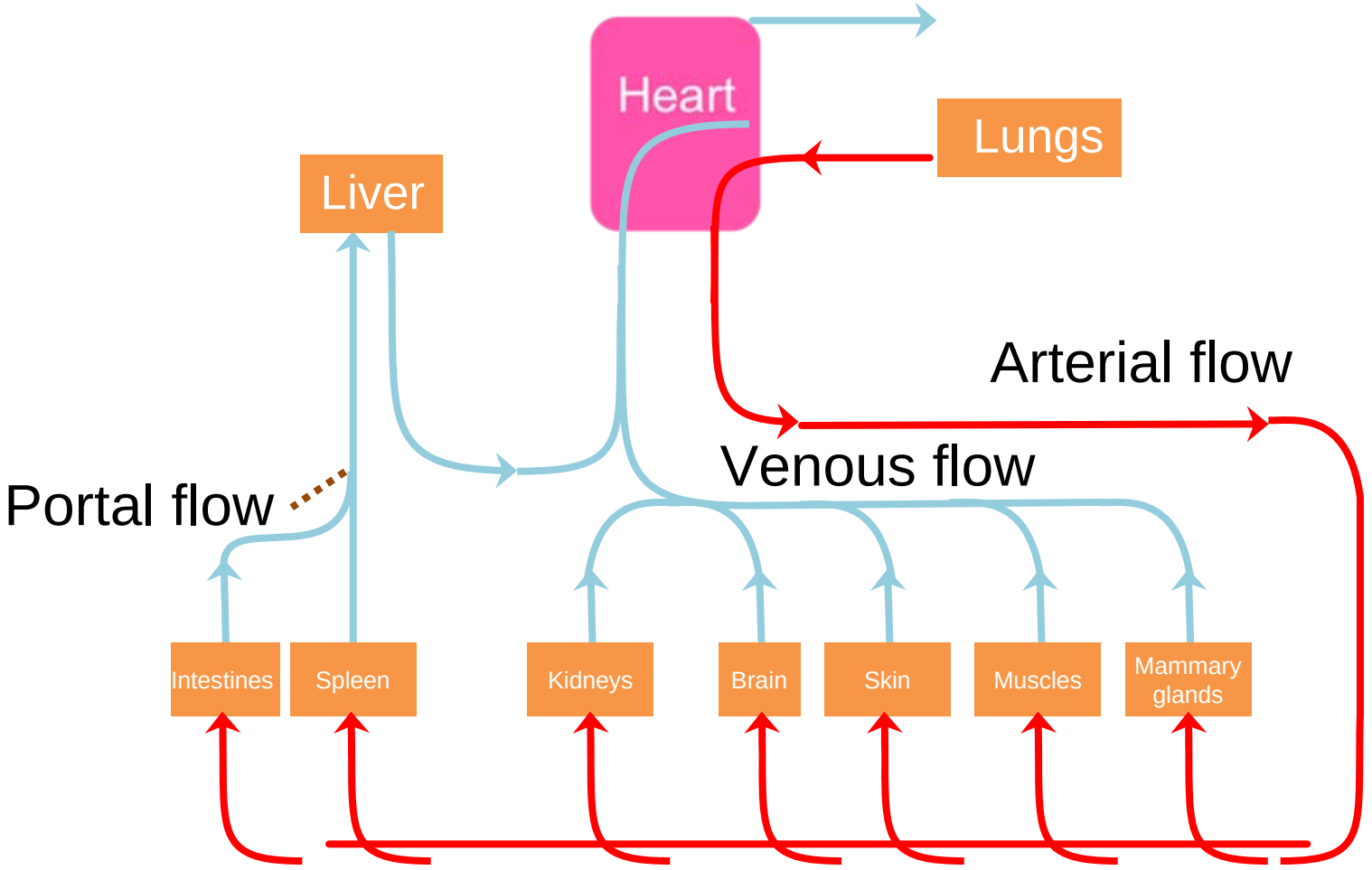


Where Do Cancers Metastasize to?
→The Two Classical Views of Metastasis

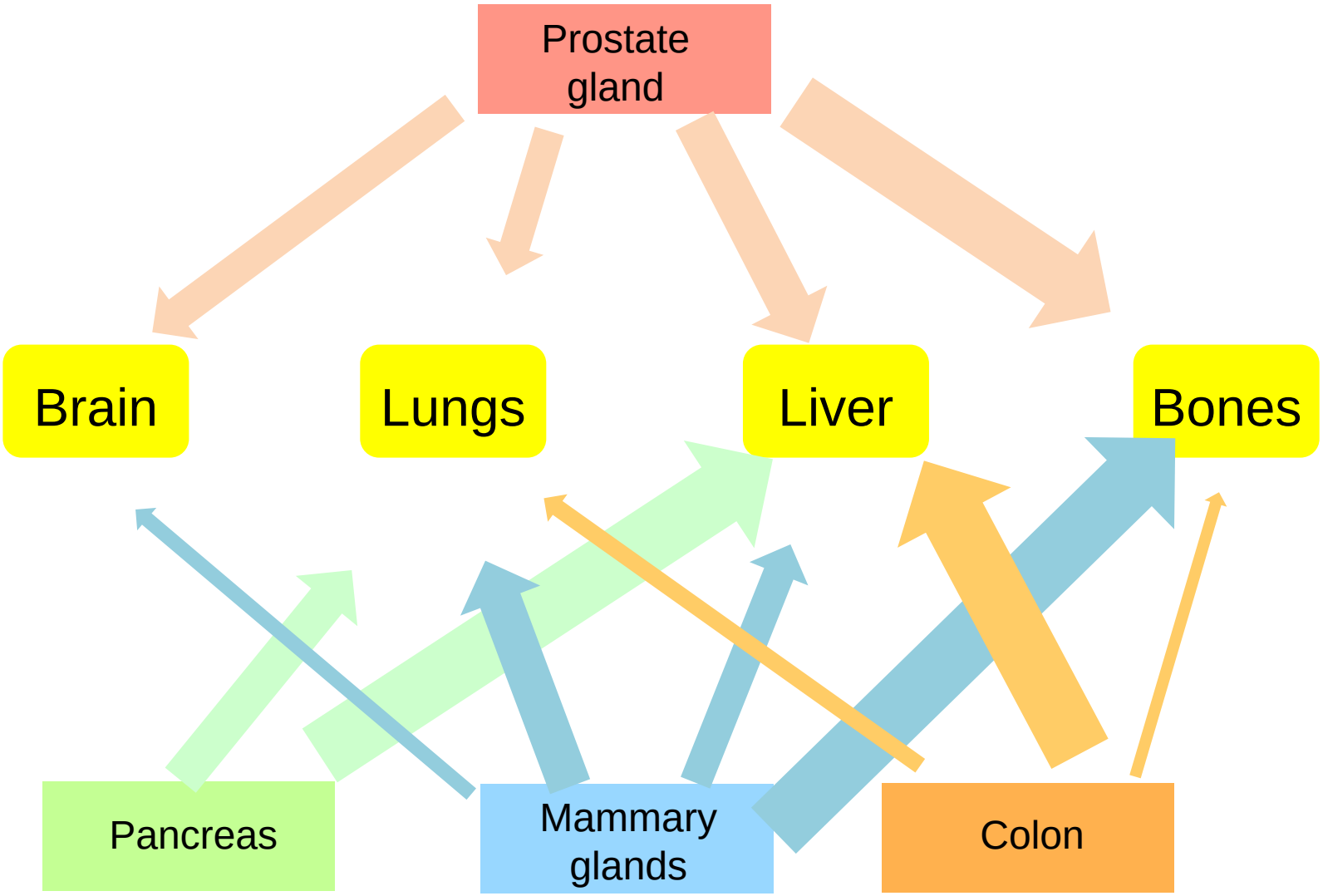
Hemodynamic theory

Seed and soil theory

The Relationship between Metastasis and the Bloodstream

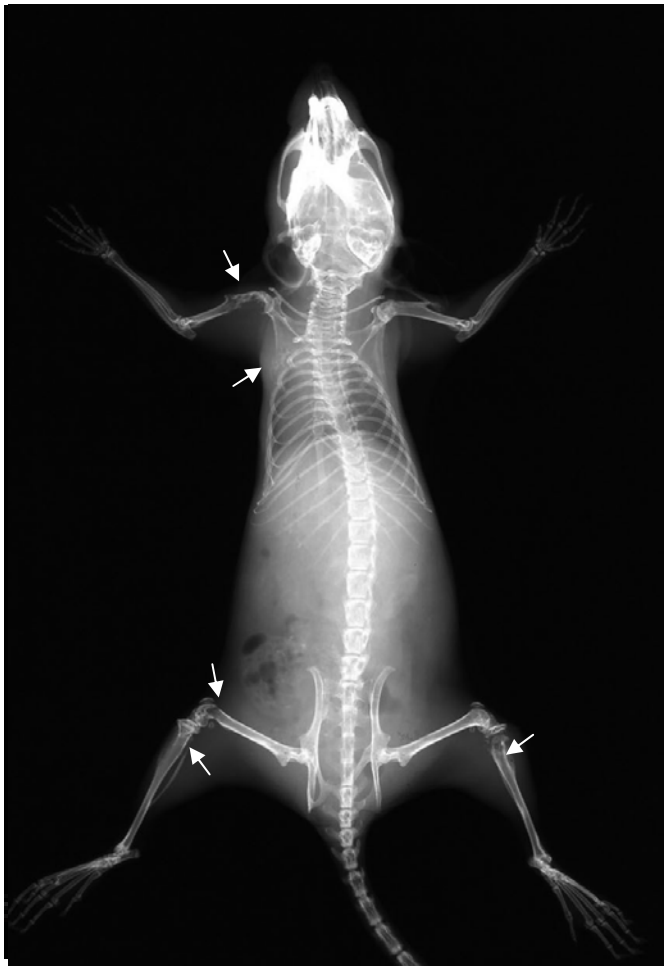


Where a Cancer Finds it Easy to Migrate Varies with the Type of Cancer



Human breast cancer cells injected into a mouse heart

→ In time the cancer metastasizes to bone



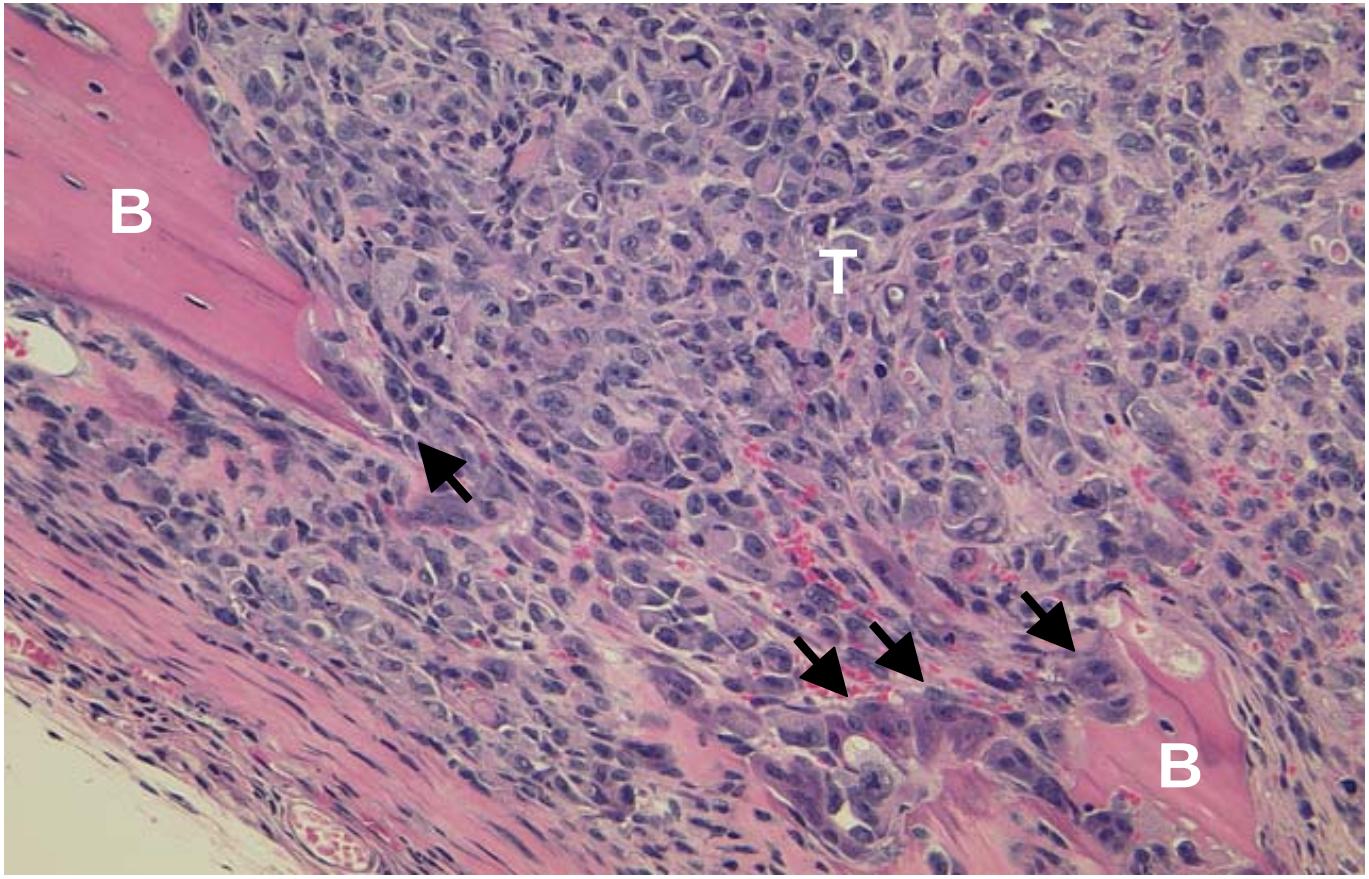
Week 4

Week 5

Week 6

‡ Ehata et al., Cancer Science, Volume 98, Issue 1, 127-133, copyright (2007)

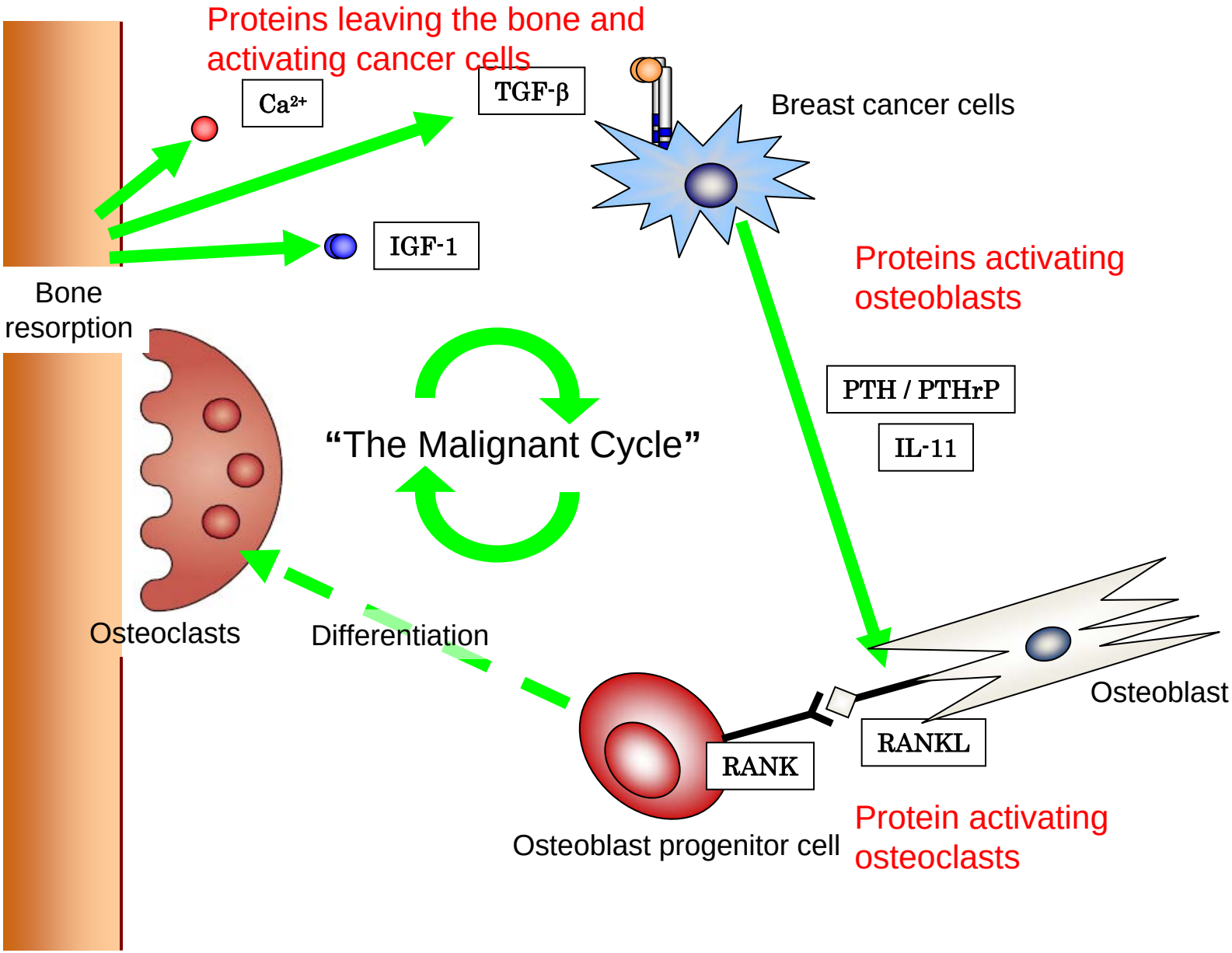
Tumor Cells and Osteoclasts in Bone Metastasis of Breast Cancer



T, Cancer cells ; **B,** Bone ; Arrows: Osteoclasts

‡ Ehata et al., Cancer Science, Volume 98, Issue 1, 127-133, copyright (2007)

The Malignant Cycle in Bone Metastasis of Breast Cancer



How to Treat Bone Metastasis with Drugs

Disrupt the Malignant Cycle!

These needn't be drugs that act on cancer cells.
We need drugs that interrupt the malignant cycle at some point, or drugs that are ingested by osteoclasts and cause cell death (e.g. bisphosphonates).

Summary

- Cancer spreads by local infiltration, lymphogenous metastasis, hematogenous metastasis and causing dissemination.

- Accumulation of many gene abnormalities leads to severely malignant cancers.

- The microenvironment of cancer plays an important role in cancer formation.

- Treatments targeting angiogenesis are among new therapeutic strategies that offer hope for treating cancer.