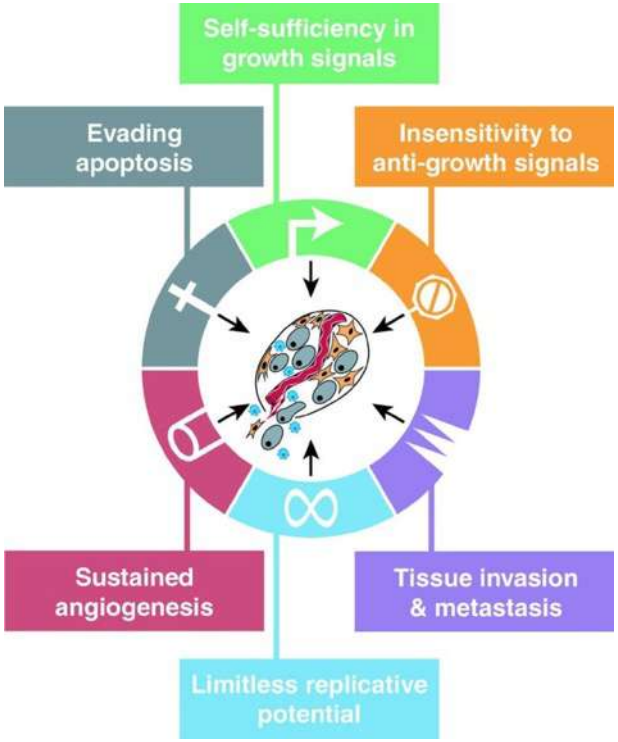
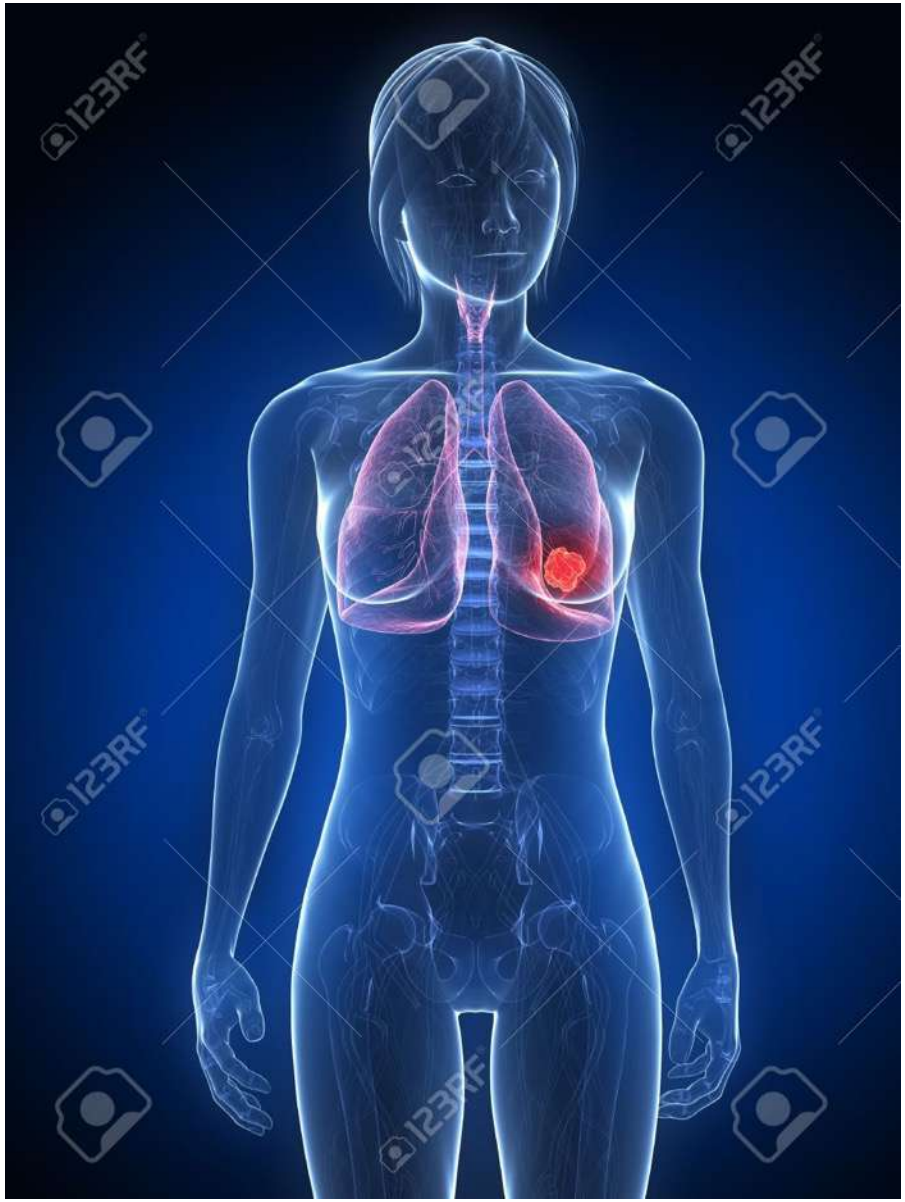
OBJECTIVES

1. List the major hallmarks of cancer
2. Relate specific genes/proteins to individual hallmarks
3. Explain how hallmarks of cancer lead to cancer development





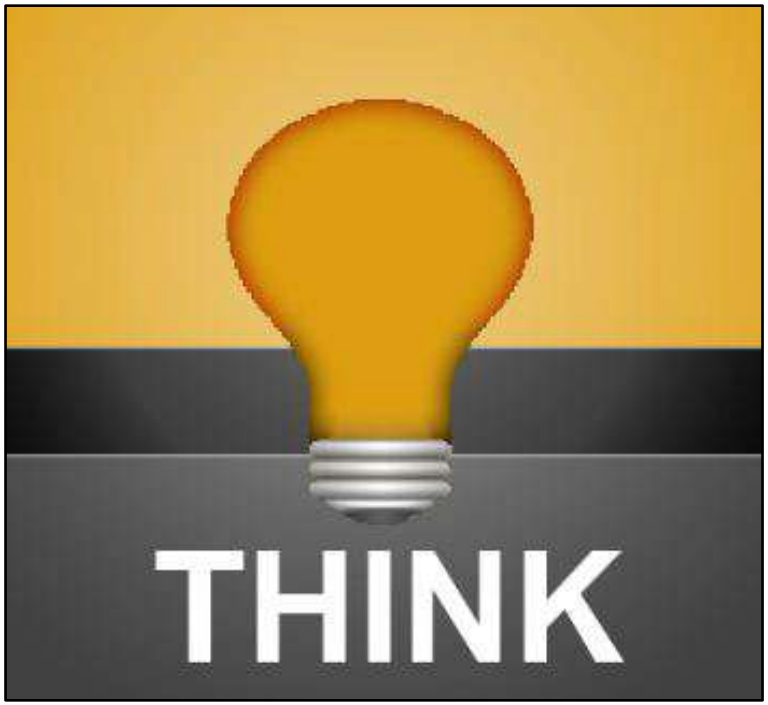
Source: www.123rf.com

Case Study

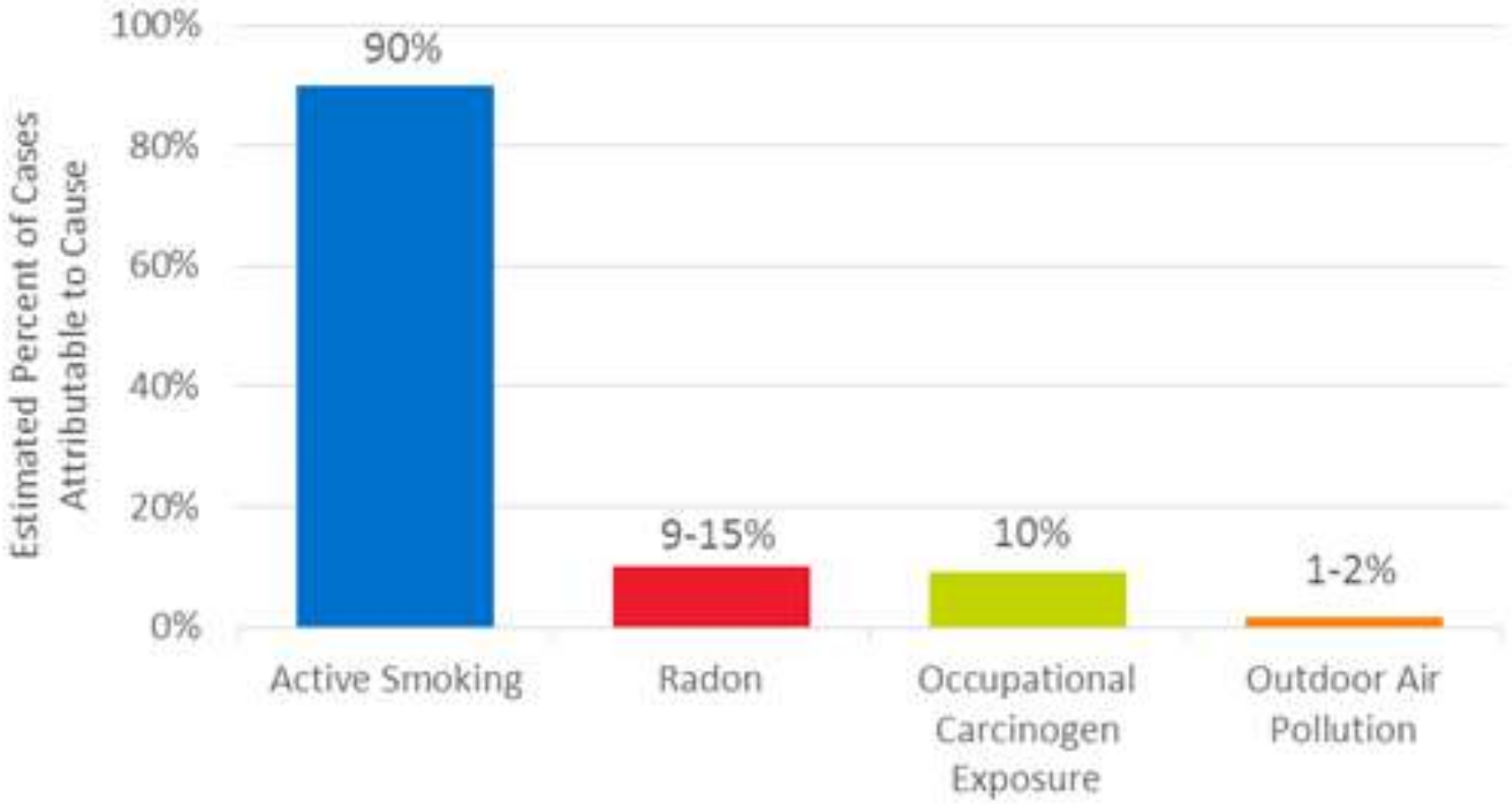
- 60 year old female
- Previously treated for breast cancer (5 years prior); no recurrence
- Presents with persistent cough, shortness of breath, fatigue
- X-ray reveals small, suspicious shadow in left lung
- A biopsy is performed on this region

A physician meets with this patient.

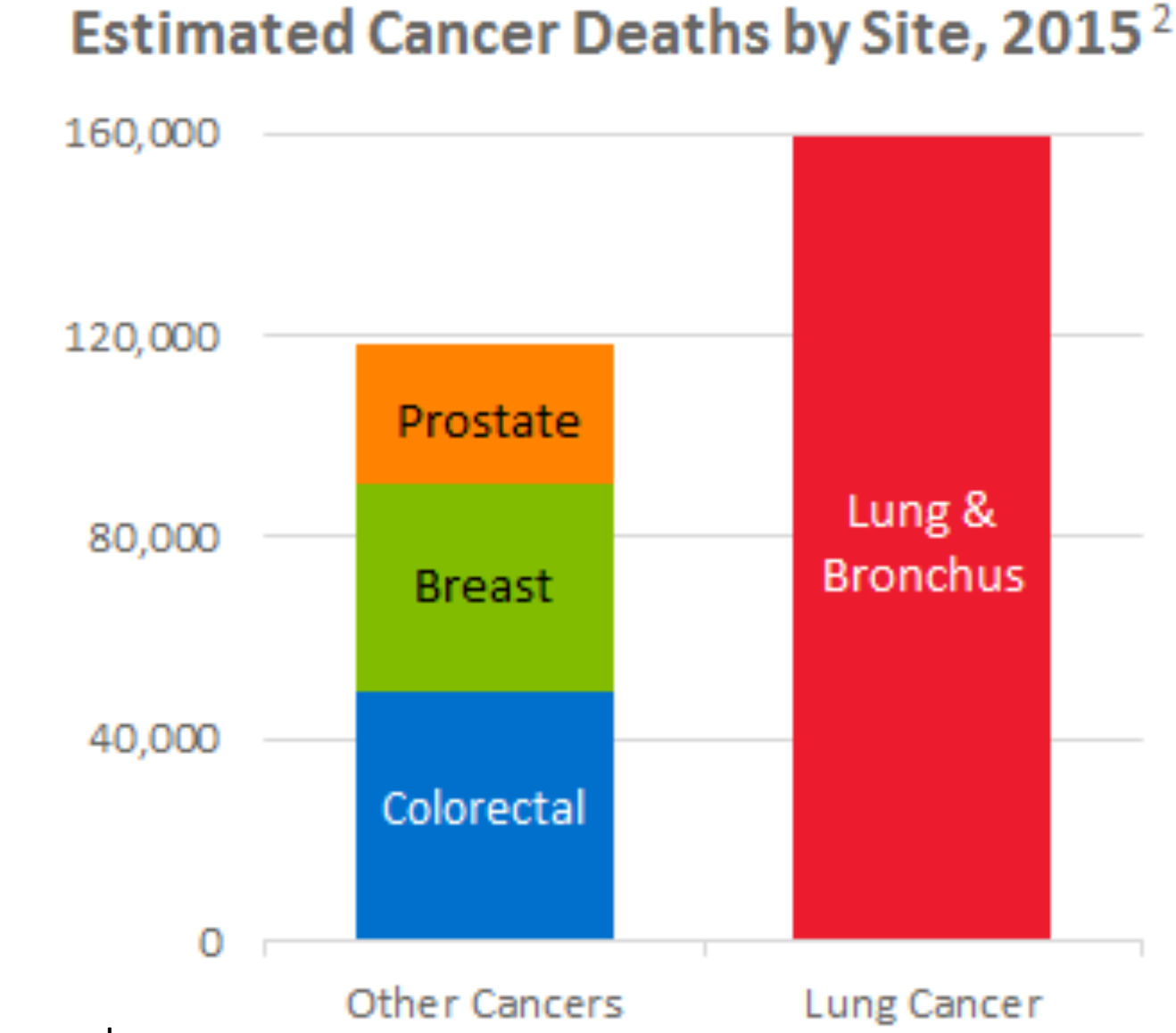
What is the *first* question she asks about the patient's lifestyle?



Estimated Attributable Portion of Lung Cancer Cases by Cause [11]



www.lung.org

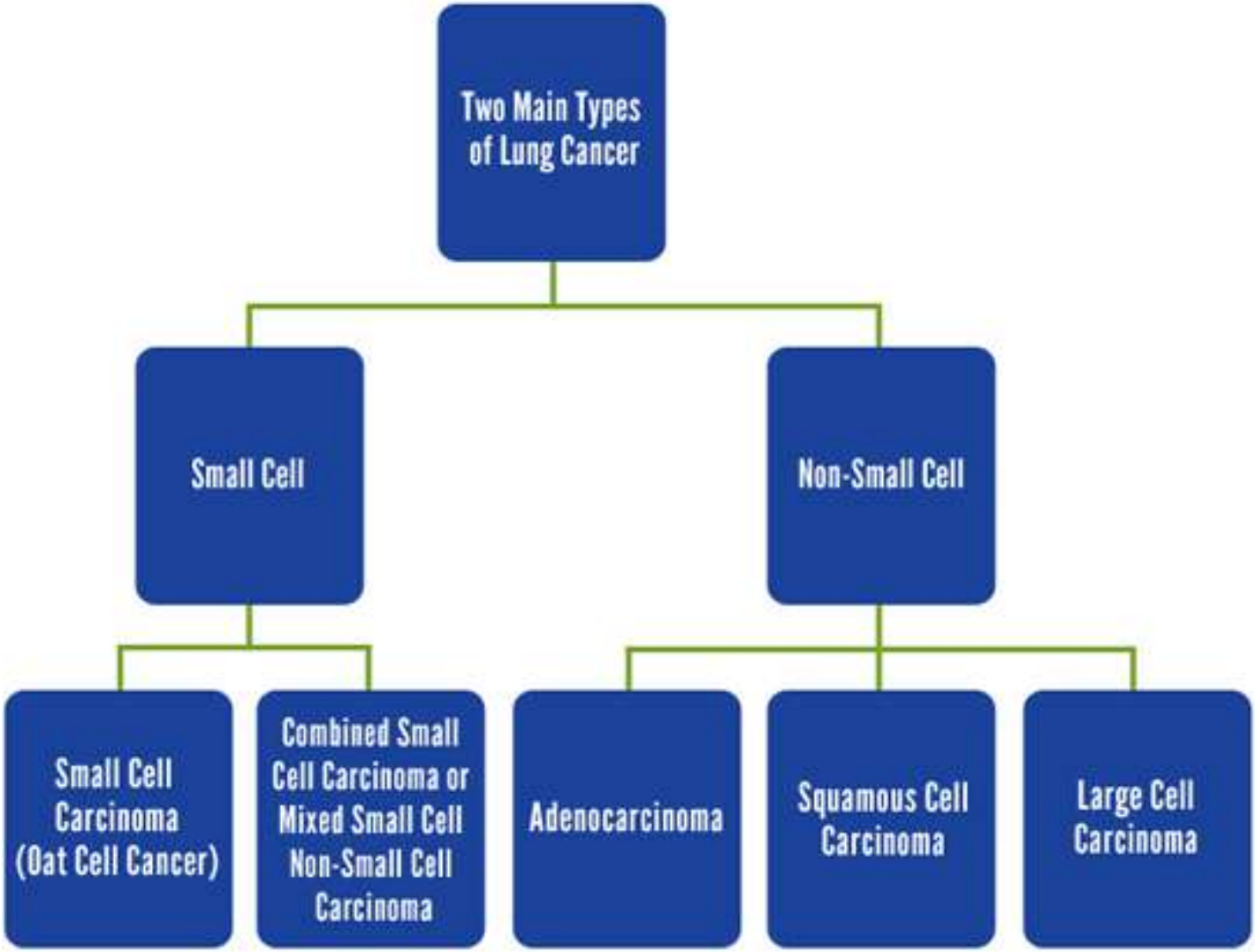

Estimated Cancer Deaths by Site, 2015 [2]
160,000
120,000
80,000
40,000
0
Prostate
Breast
Colorectal
Lung & Bronchus
Other Cancers
Lung Cancer

www.lung.org

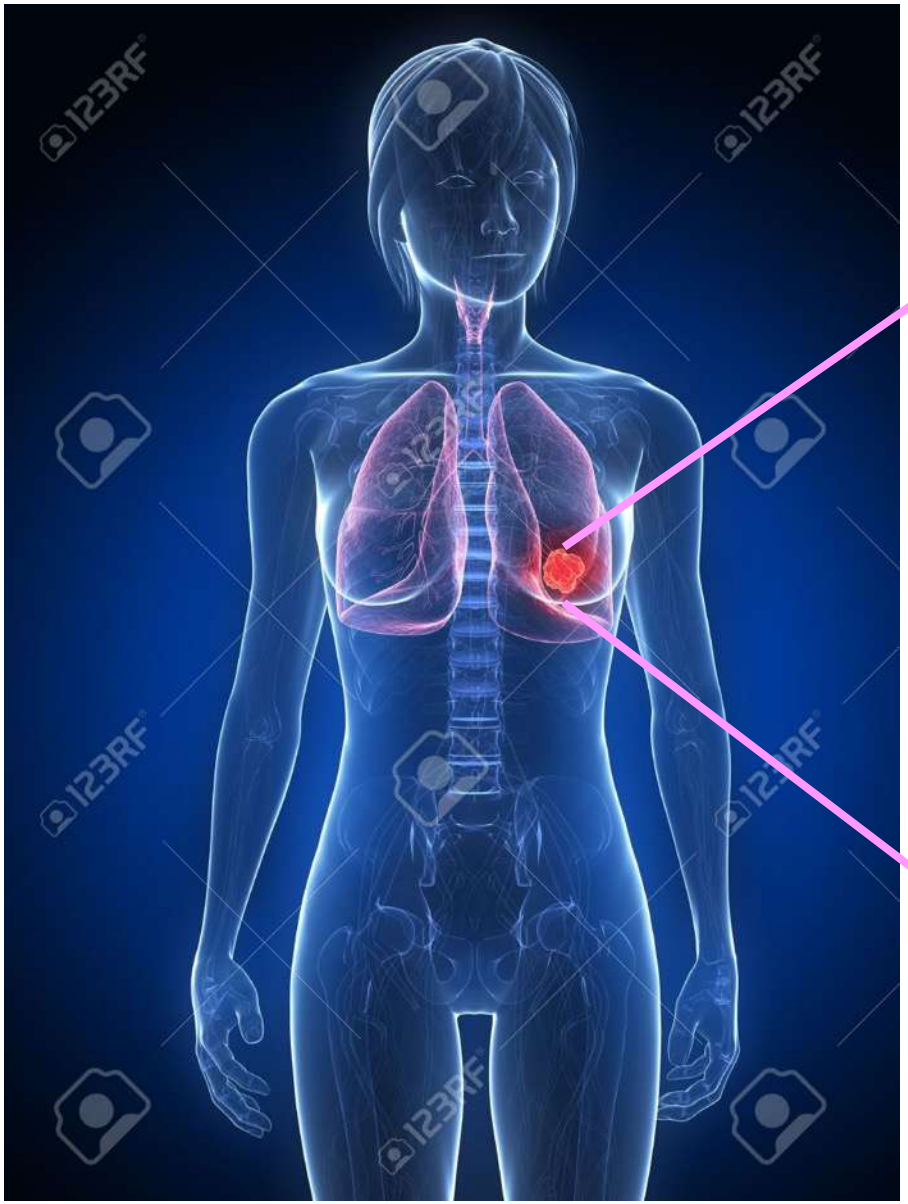
brainstorming

A pathologist analyzes the biopsy sample. What does she look for?, *i.e*.
What information is gained from the analysis of the biopsy?

TYPES OF LUNG CANCER



www.lung.org



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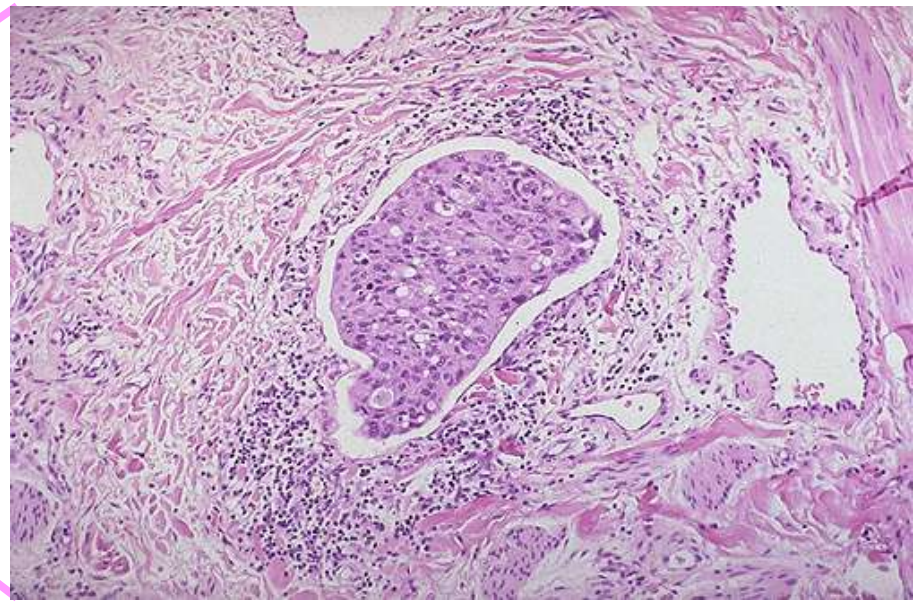
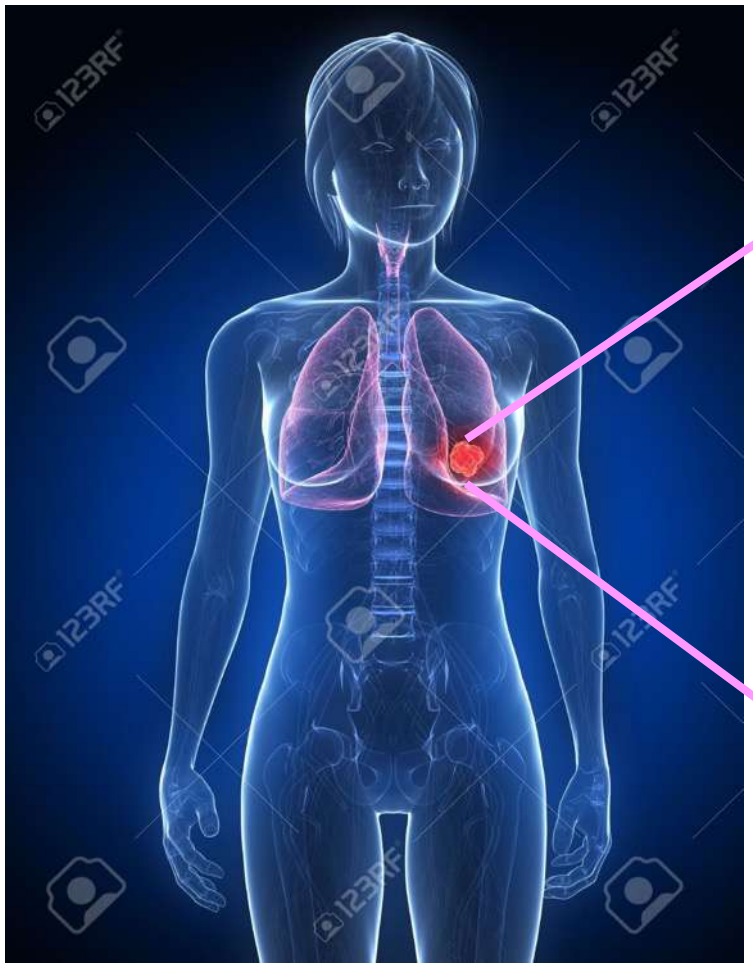


QUESTION – What changes occurred to a breast epithelial cell that led to the formation of a metastatic tumor in the lung?



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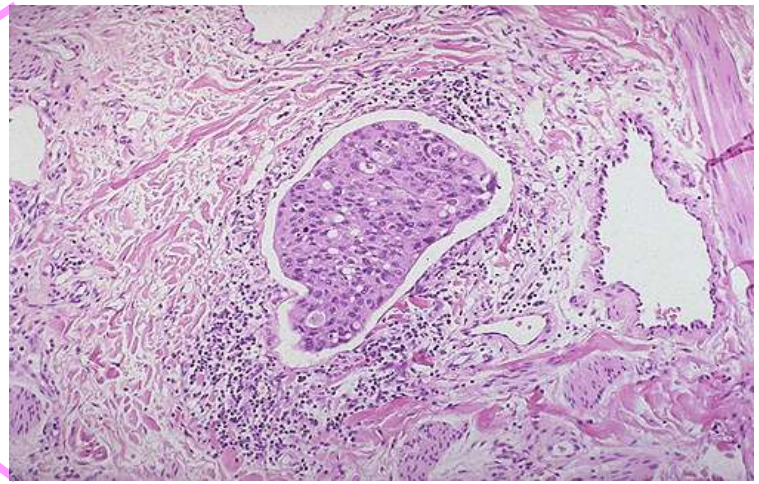
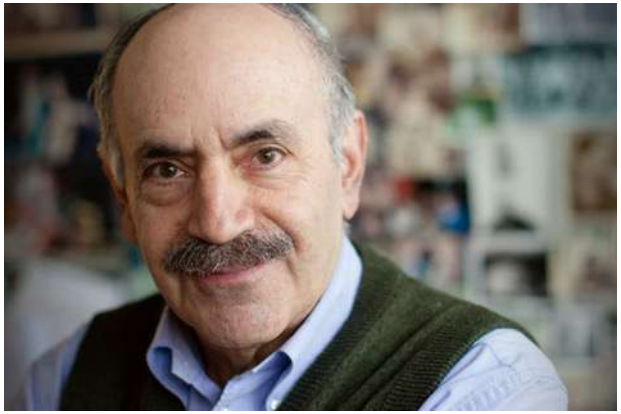


Douglas Hanahan

Robert Weinberg



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†
*Department of Biochemistry and Biophysics and Hormone Research Institute
University of California at San Francisco
San Francisco, California 94143
†Whitehead Institute for Biomedical Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02142

After a quarter century of rapid advances, cancer research has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome. The foundation has been set in the discovery of mutations that produce oncogenes with dominant gain of function and tumor suppressor genes with recessive loss of function; both classes of cancer genes have been identified through their alteration in human and animal cancer cells and by their elicitation of cancer phenotypes in experimental models (Bishop and Weinberg, 1996).

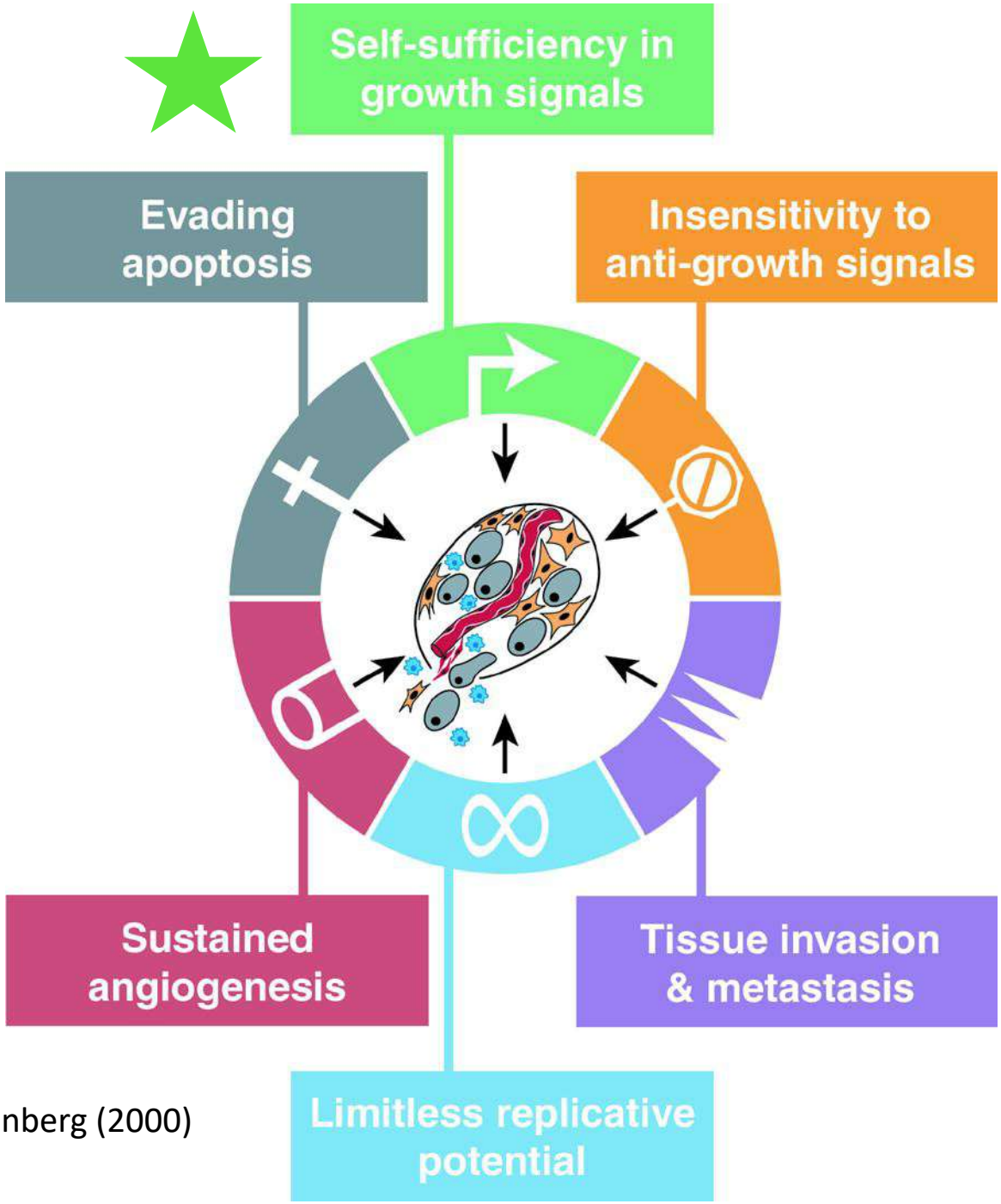
Some would argue that the search for the origin and treatment of this disease will continue over the next quarter century in much the same manner as it has in the recent past, by adding further layers of complexity to a scientific literature that is already complex almost beyond measure. But we anticipate otherwise: those researching the cancer problem will be practicing a dramatically different type of science than we have experienced over the past 25 years. Surely much of this change will be apparent at the technical level. But ultimately, the more fundamental change will be conceptual.

We foresee cancer research developing into a logical science, where the complexities of the disease, described in the laboratory and clinic, will become understandable in terms of a small number of underlying principles. Some of these principles are even now in the midst of being codified. We discuss one set of them in the present essay: rules that govern the transformation evolve progressively from normalcy via a series of premalignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a multistep process: rodent cells require at least two introduced genetic changes before they acquire tumorigenic competence, while their human counterparts are more difficult to transform (Hahn et al., 1999). Transgenic models of tumorigenesis have repeatedly supported the conclusion that tumorigenesis in mice involves multiple rate-limiting steps (Bergers et al., 1998; see *Oncogene*, 1999, R. DePinho and T. E. Jacks, volume 18[38], pp. 5248–5362). Taken together, observations of human cancers and animal models argue that tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells (Foulds, 1954; Nowell, 1976).

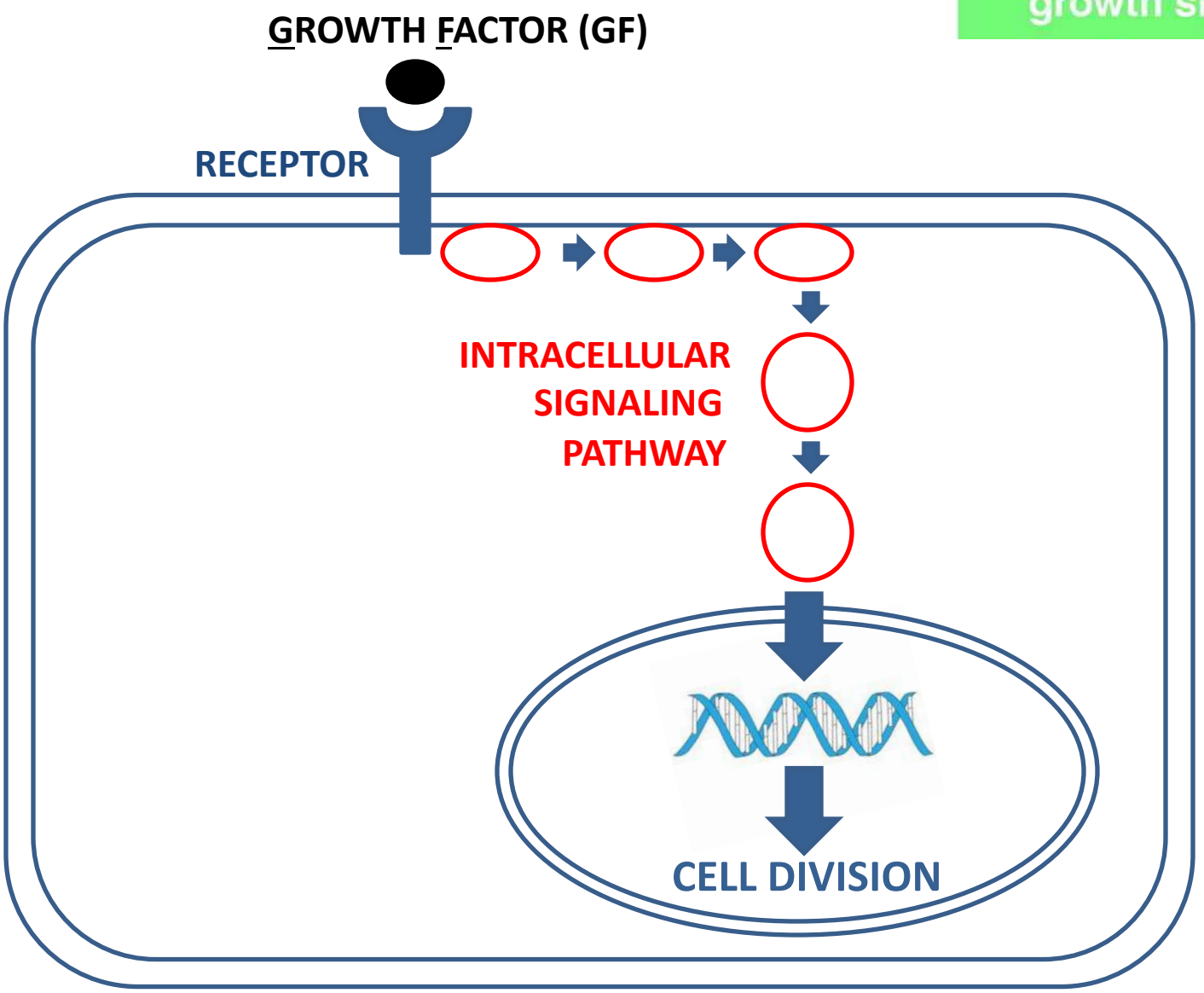
An Enumeration of the Traits

The barriers to development of cancer are embodied in a teleology: cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis. There are more than 100 distinct types of cancer, and subtypes of tumors can be found within specific organs. This complexity provokes a number of questions. How many distinct regulatory circuits within each type of target cell must be disrupted in order for such a cell to become cancerous? Does the same set of cellular regulatory circuits suffer disruption in the cells of the disparate neoplasms arising in the human body? Which of these circuits operate on a cell-autonomous basis, and which are coupled to the signals that cells

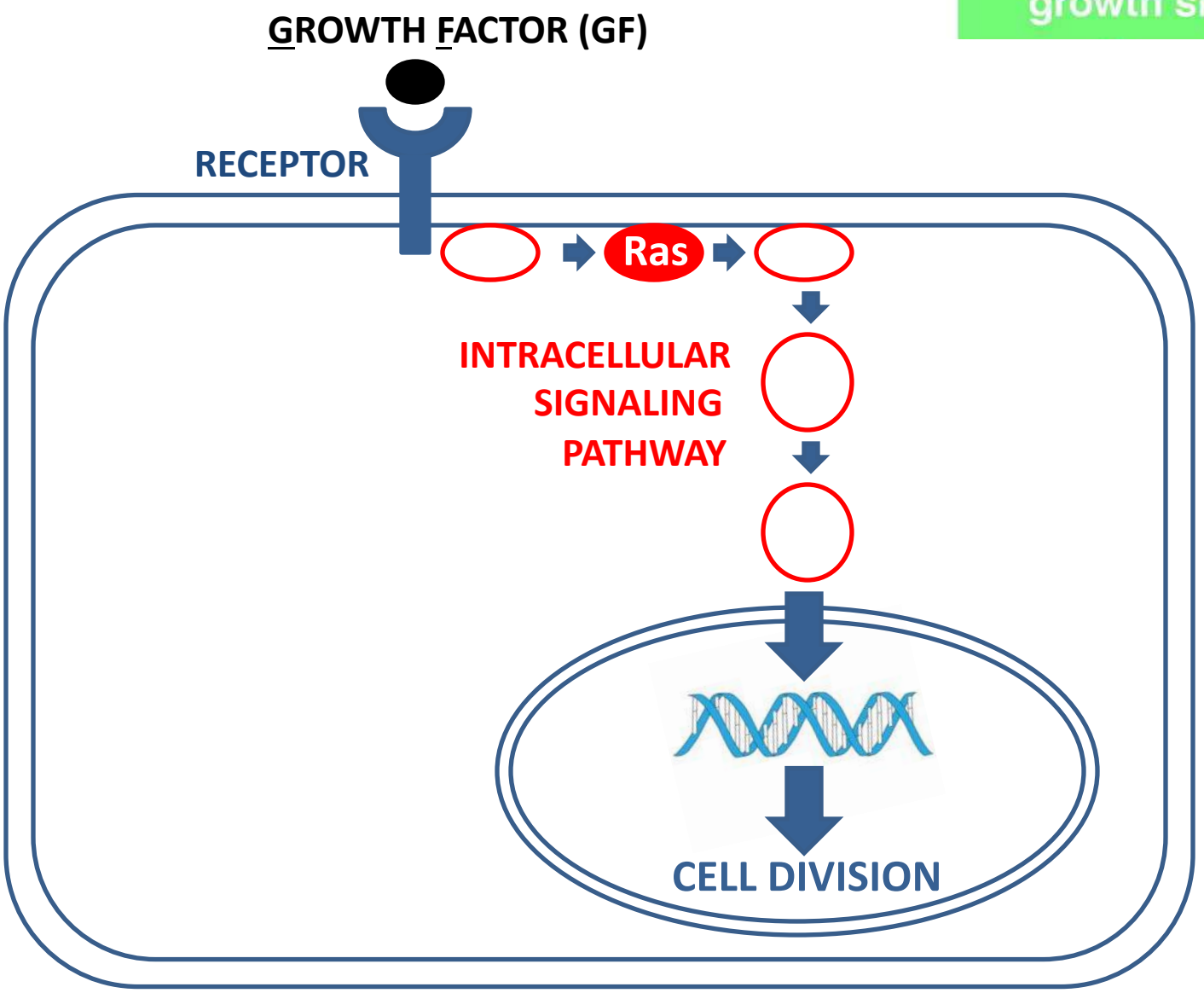


Hanahan and Weinberg (2000)
Cell, 100: 57 – 70.

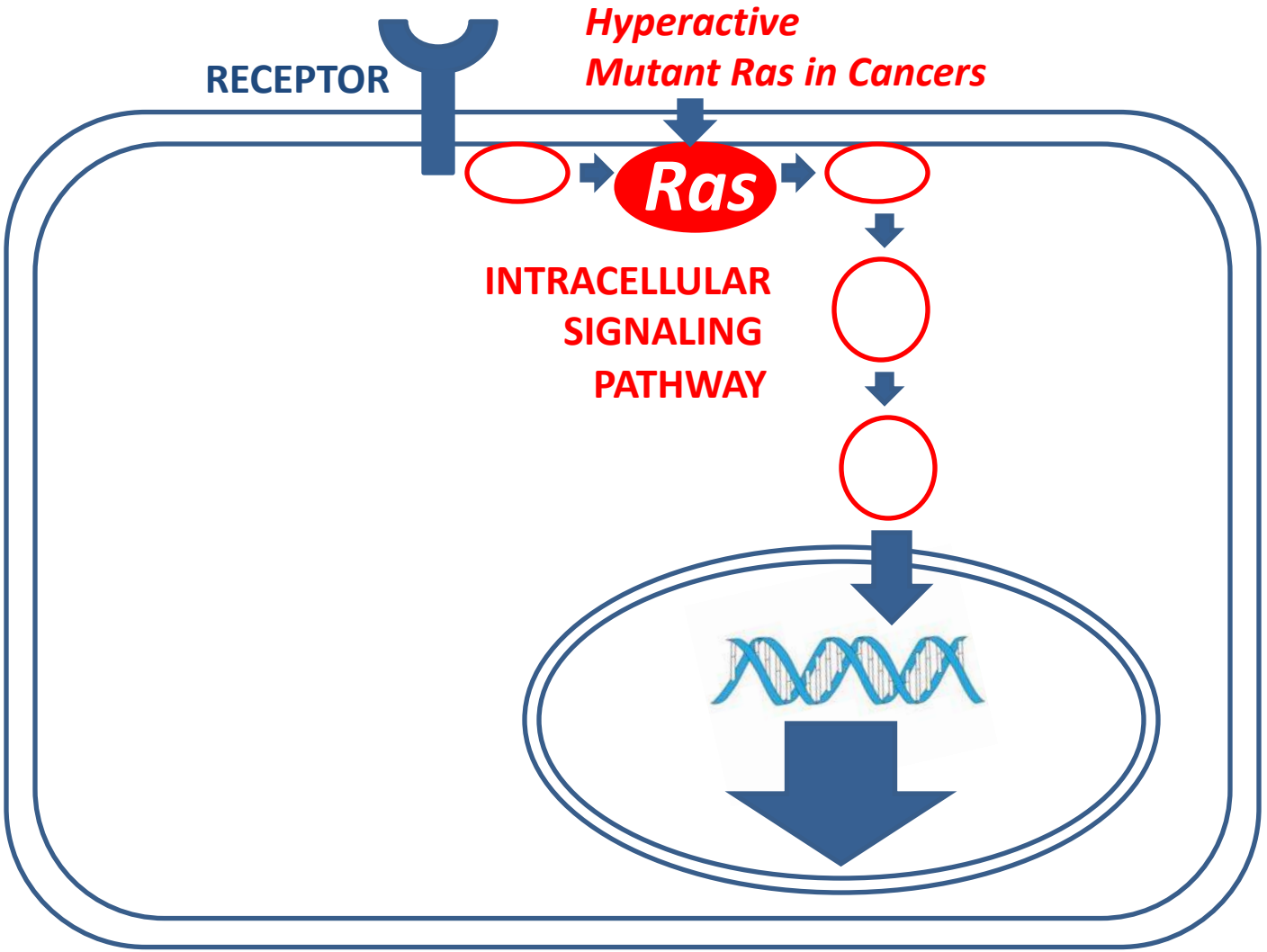
Self-sufficiency in growth signals



Self-sufficiency in growth signals



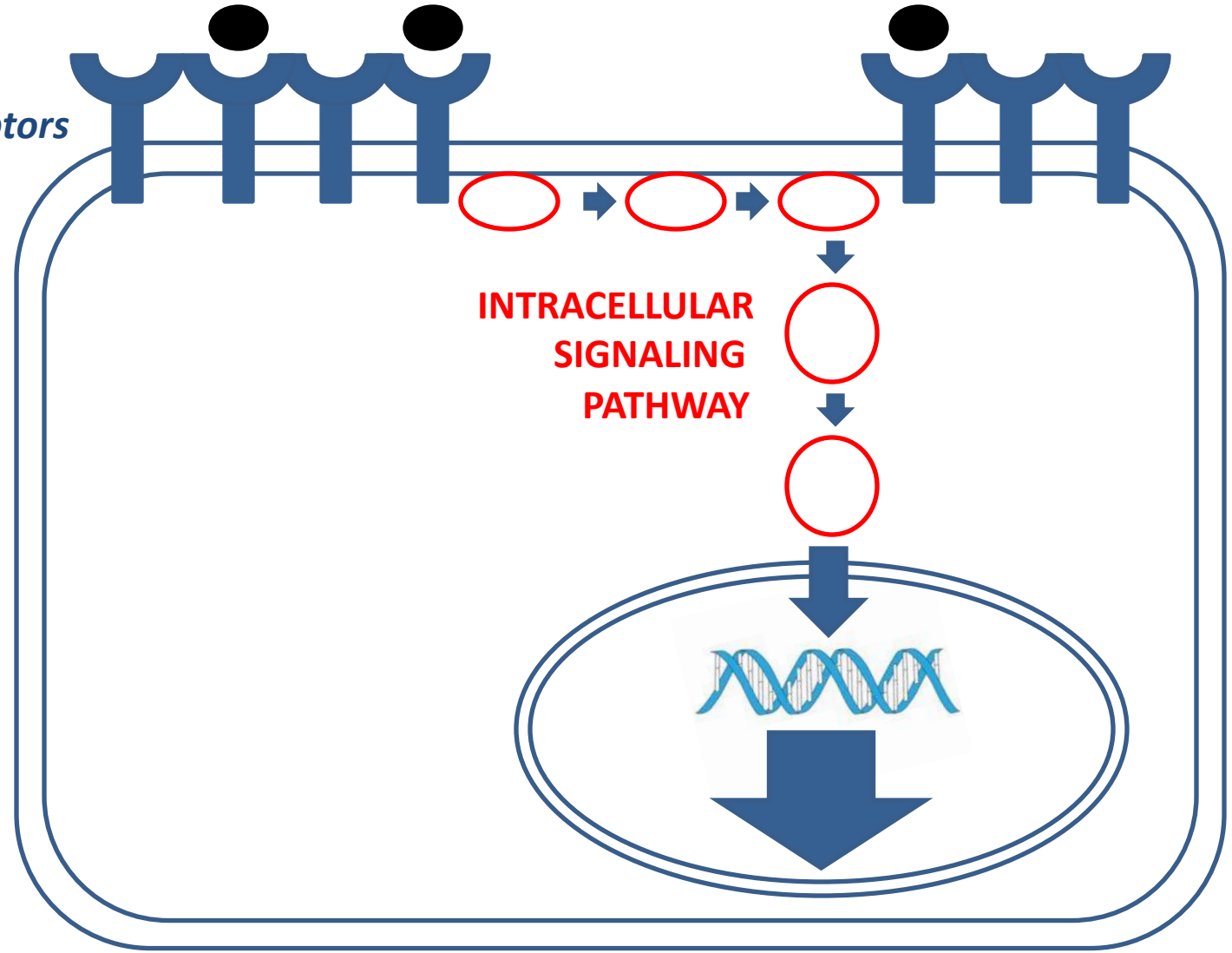
Self-sufficiency in growth signals



Self-sufficiency in growth signals

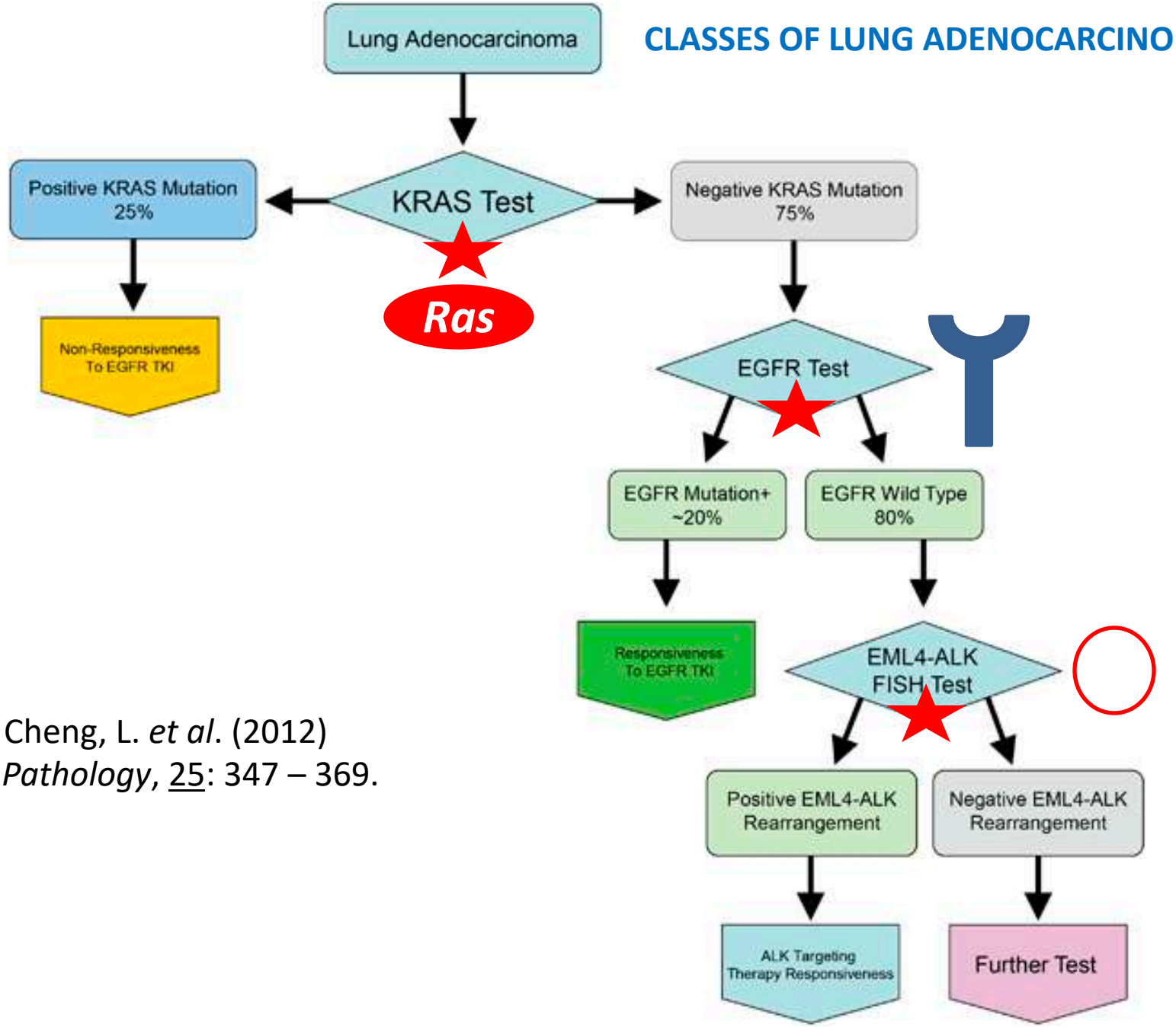
GROWTH FACTOR (GF)

Amplified EGF Receptors in Cancer



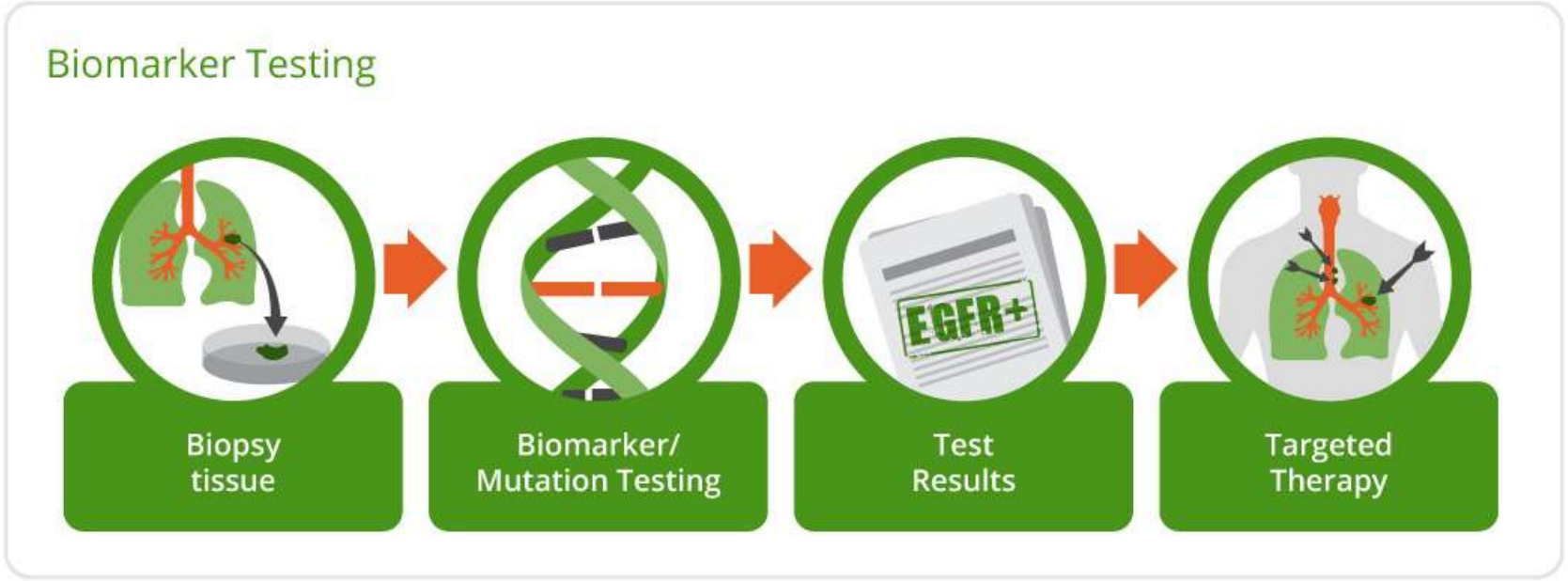
CELL DIVISION

CLASSES OF LUNG ADENOCARCINOMA



Source: Cheng, L. *et al*. (2012)
Modern Pathology, 25: 347 – 369.

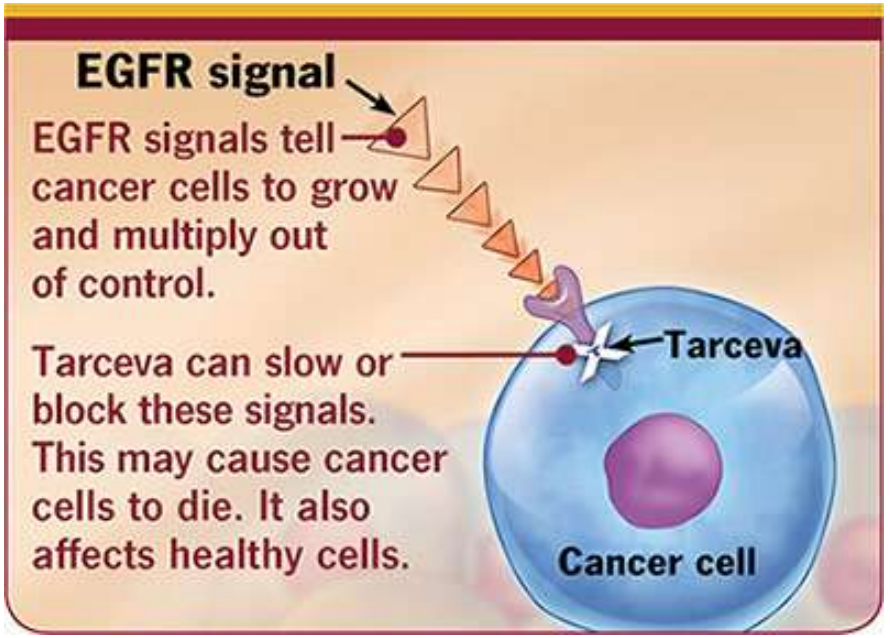
TARCEVA – A DRUG WHICH TARGETS EGF RECEPTOR IN LUNG CANCER

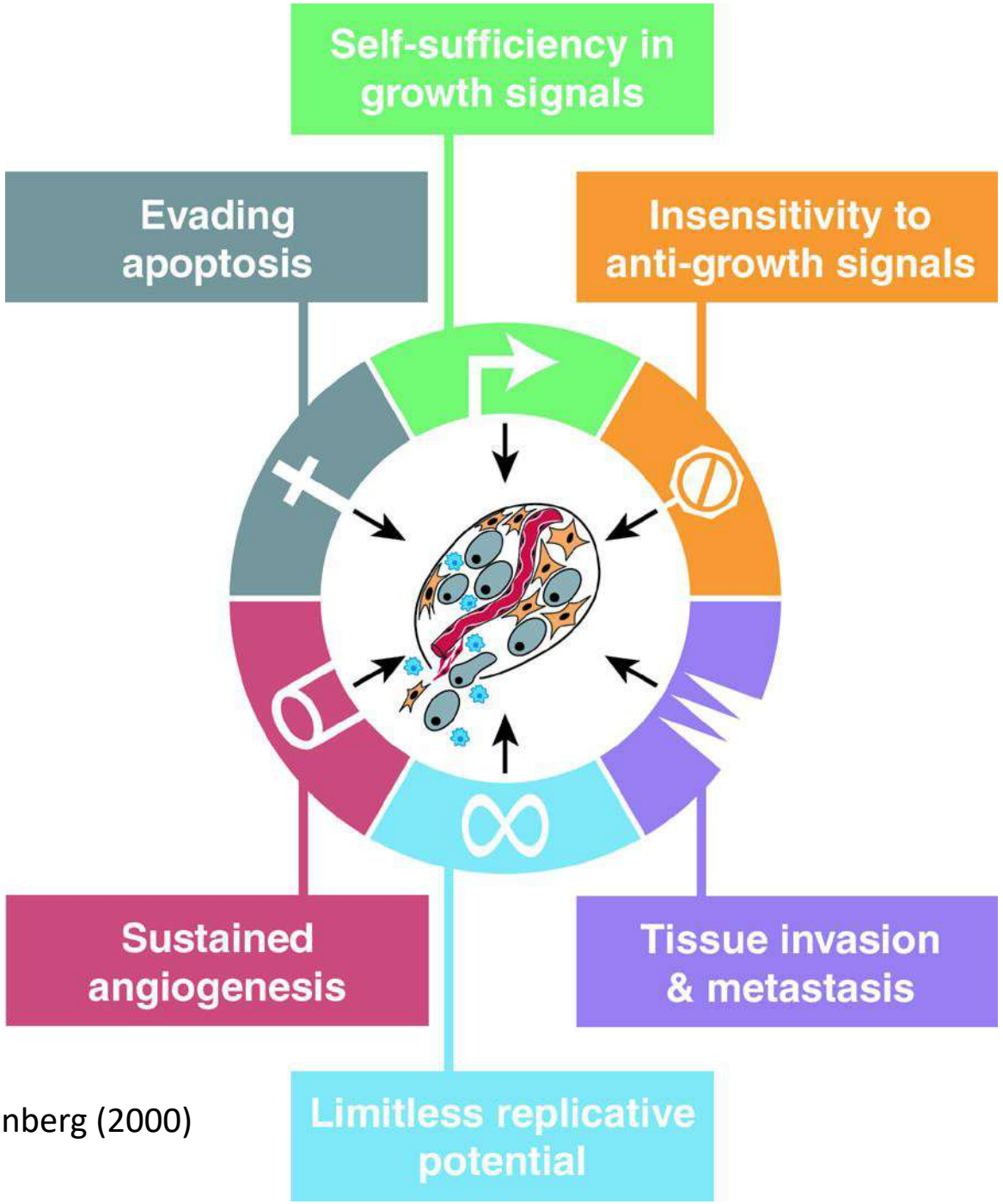


www.lifewithlungcancer.org

Tarceva®
erlotinib
tablets

www.tarceva.com

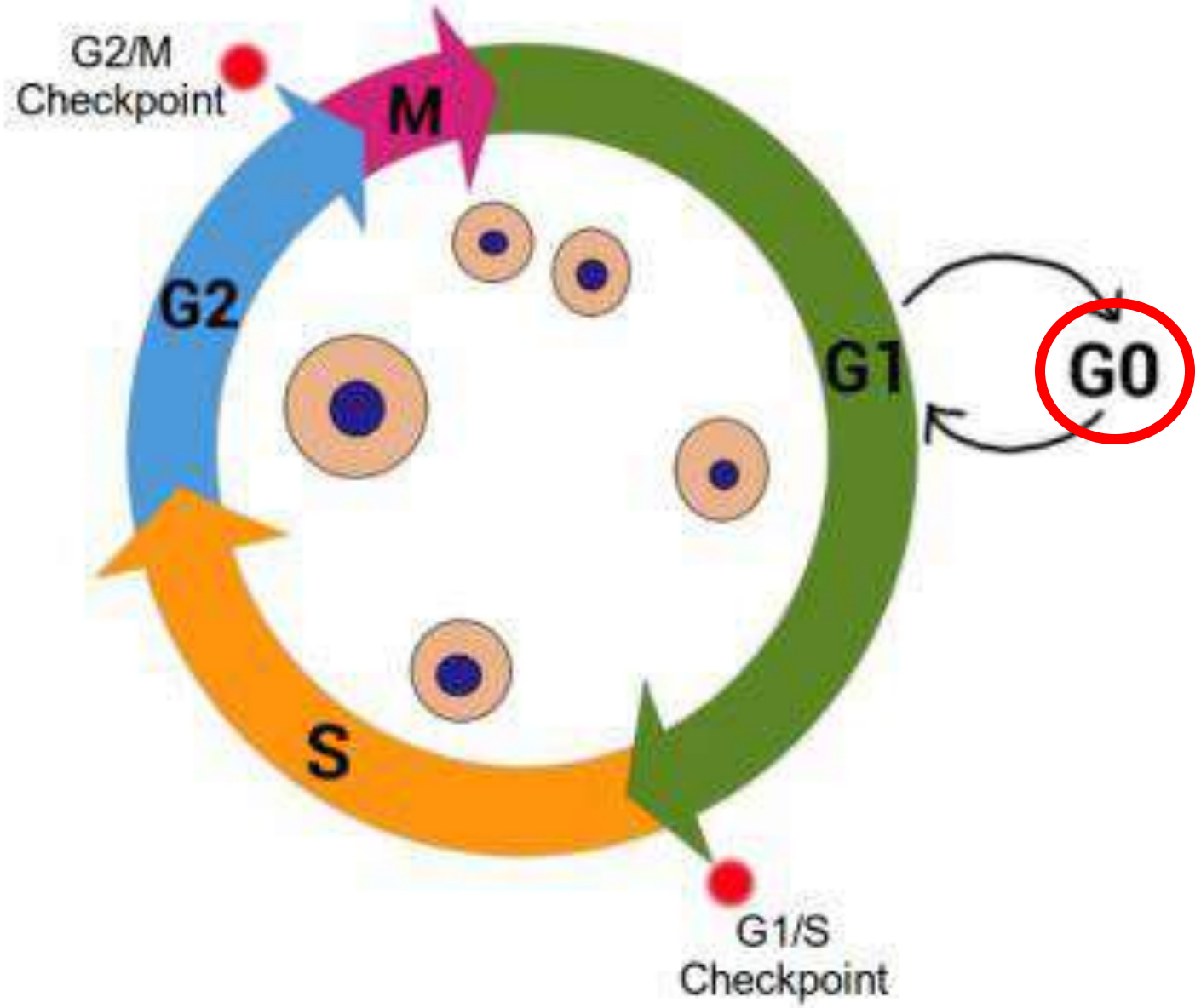




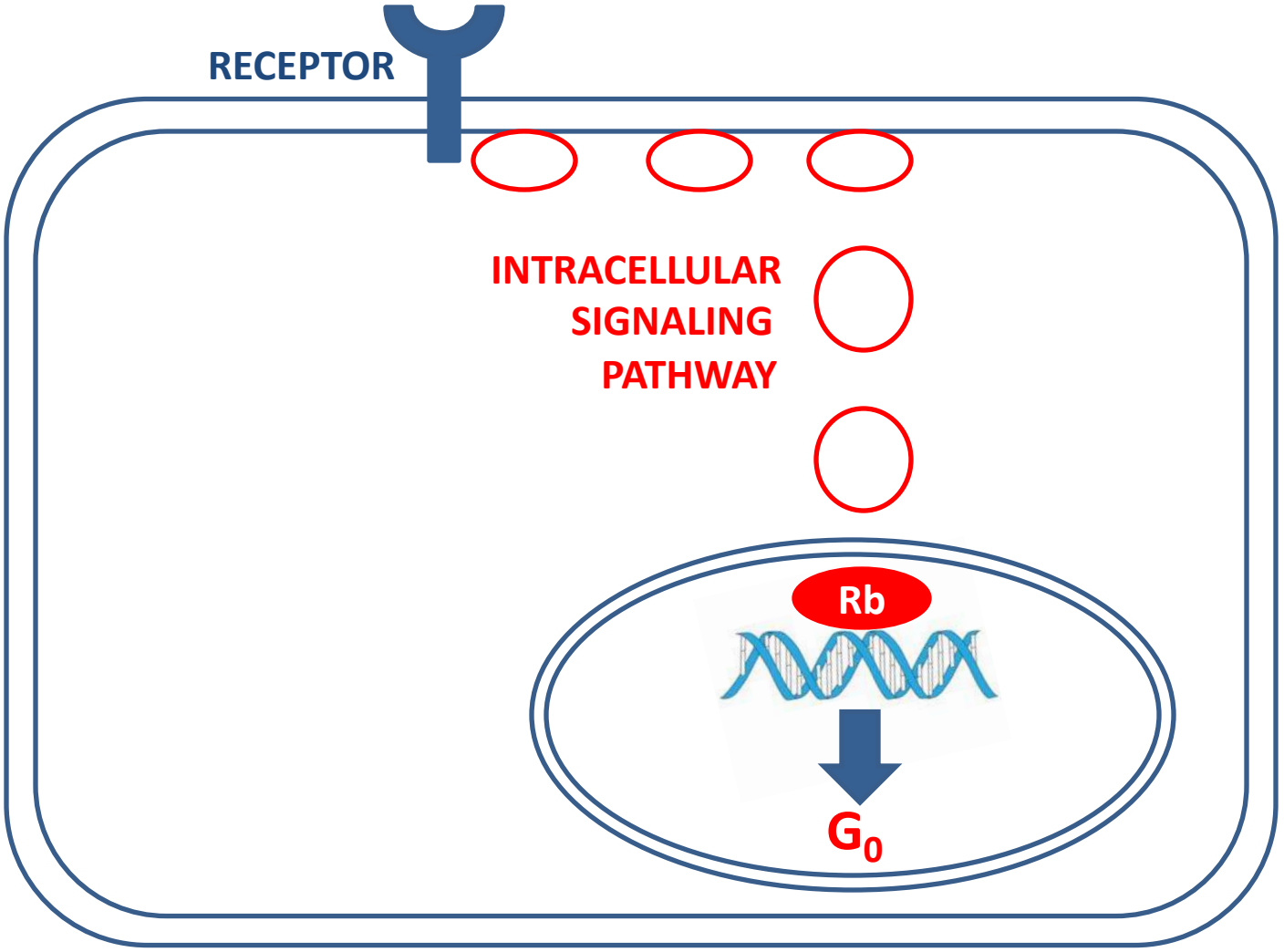
Hanahan and Weinberg (2000)
Cell, 100: 57 – 70.

EUKARYOTIC CELL CYCLE

Insensitivity to anti-growth signals



Insensitivity to anti-growth signals



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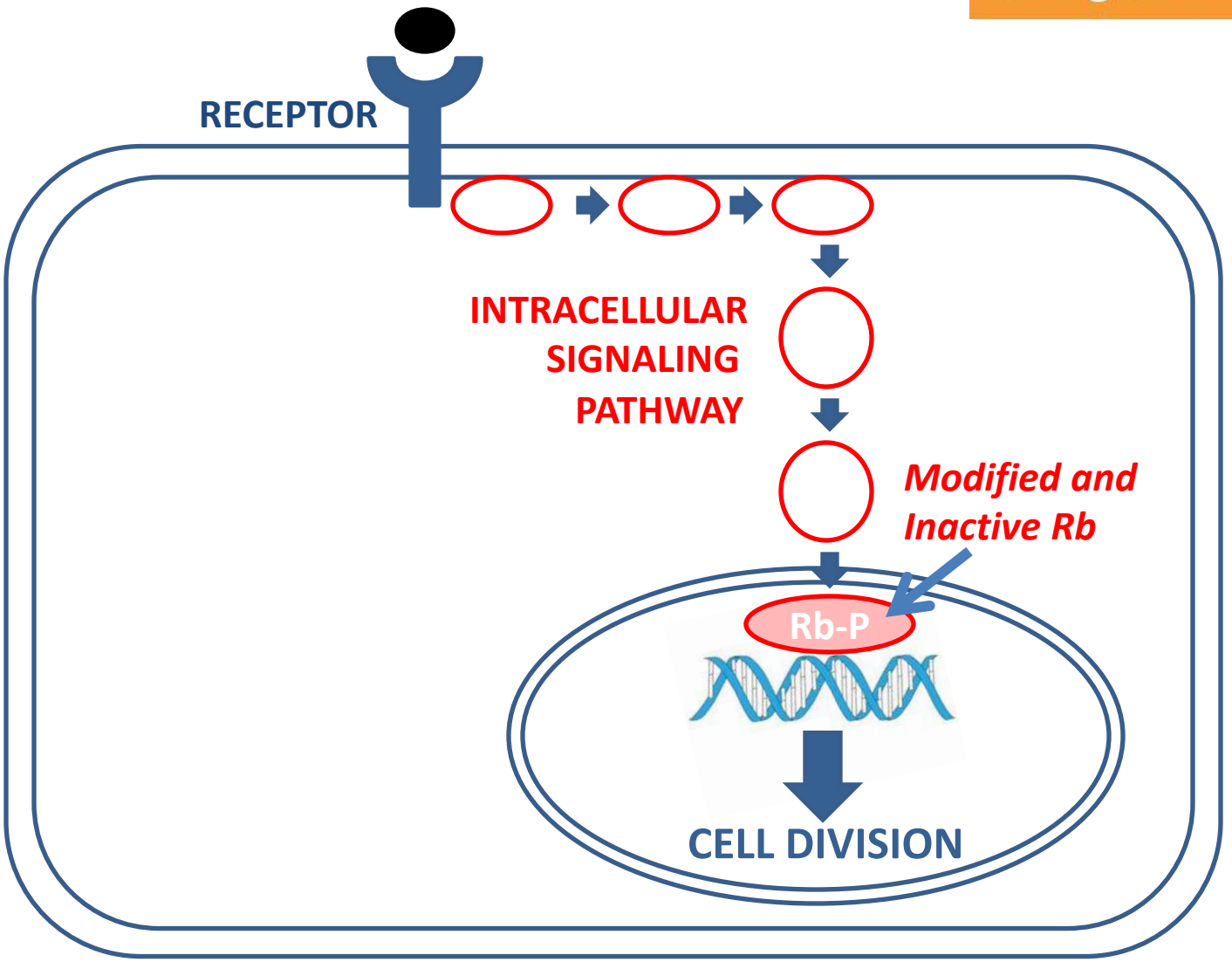

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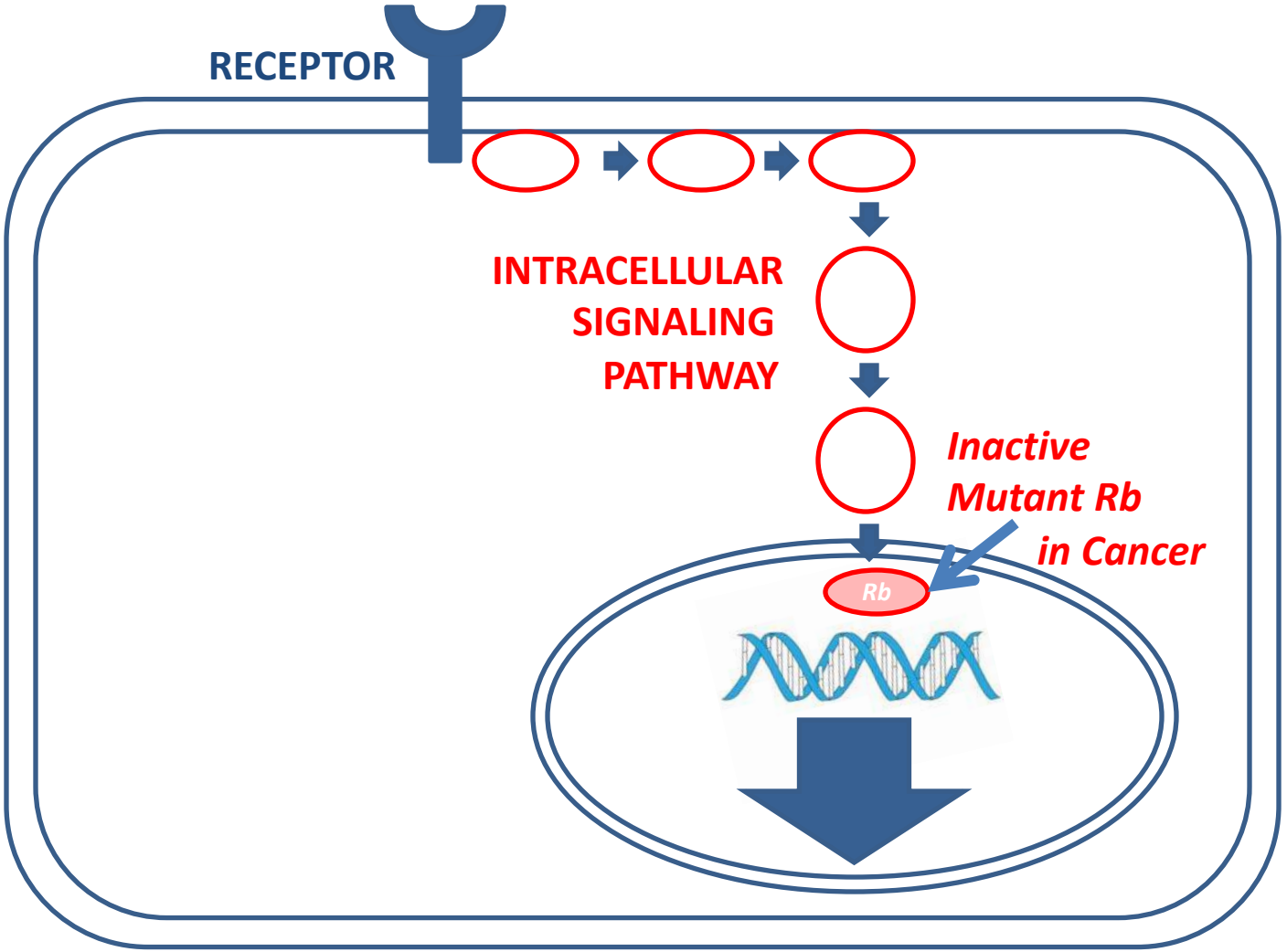
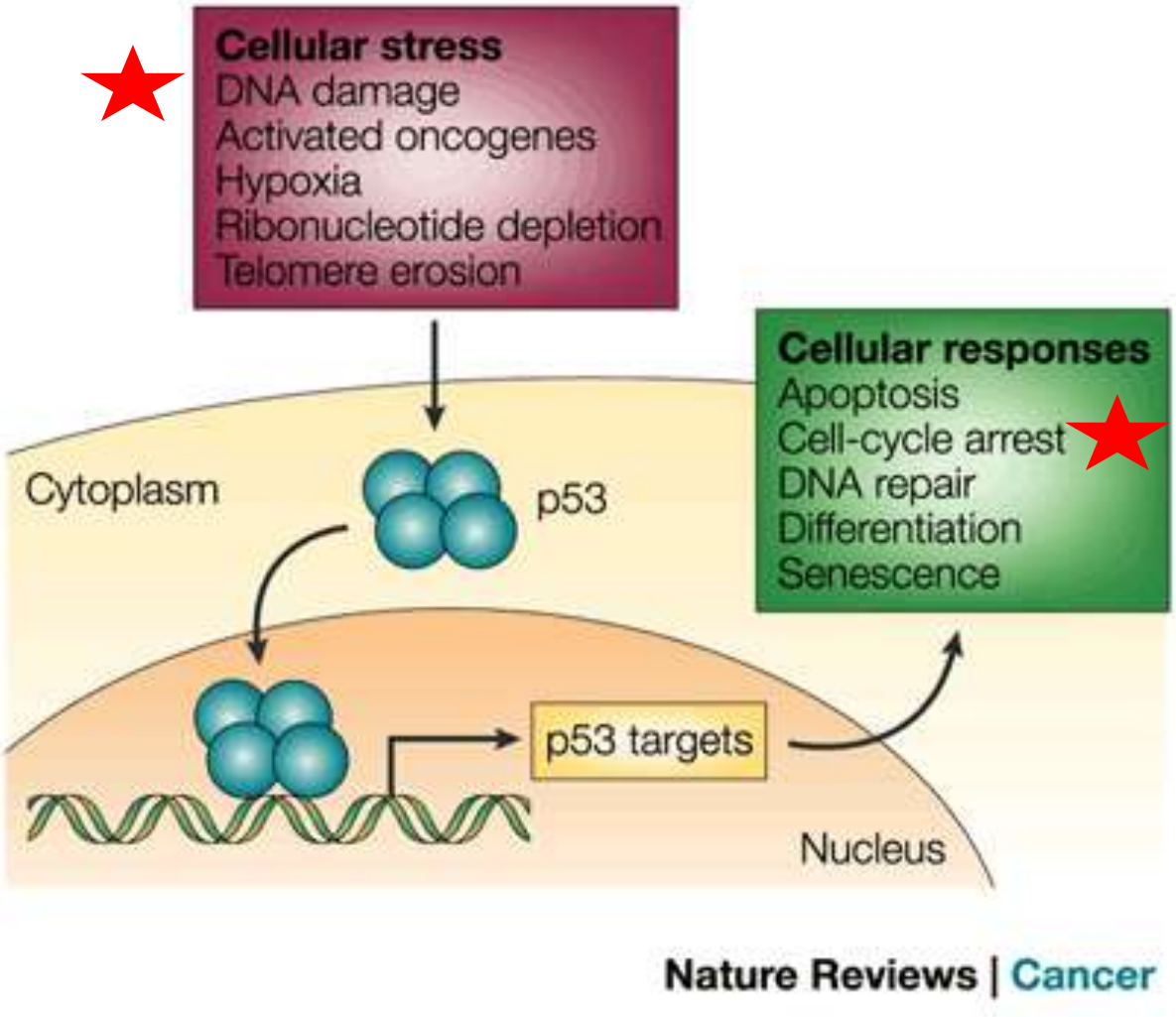


CELL DIVISION

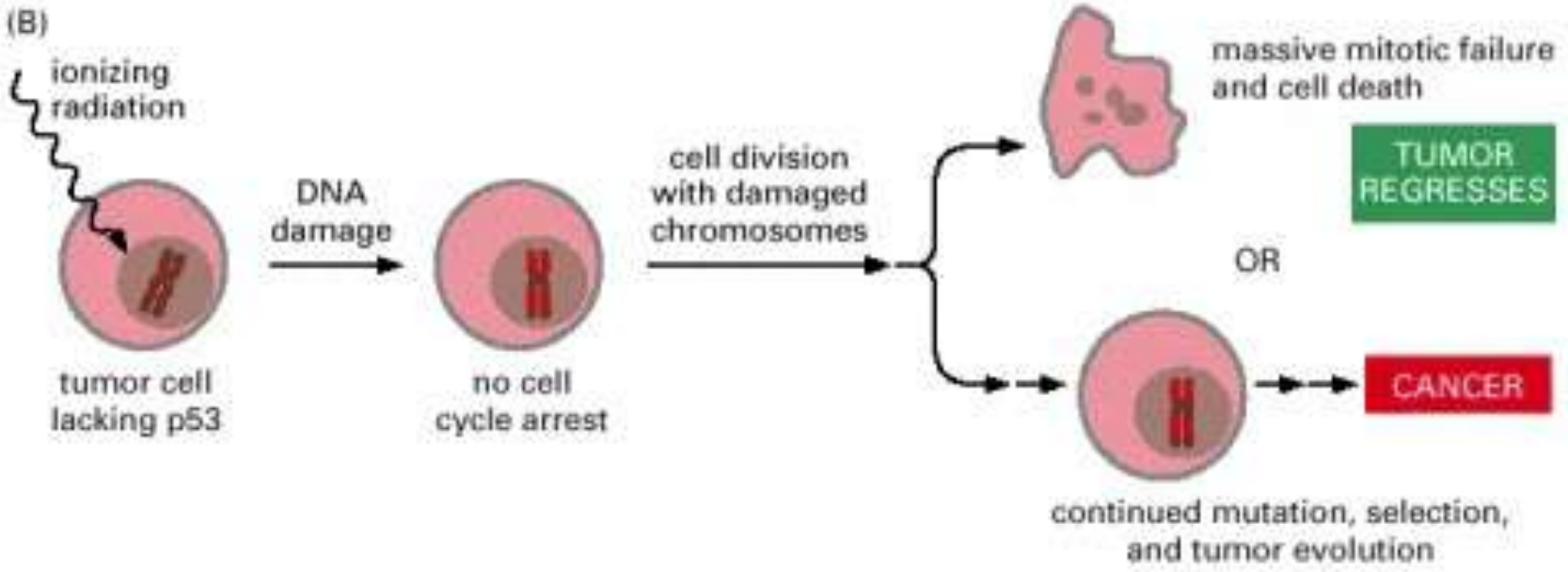
p53's NORMAL ROLE IS TO INHIBIT CELL DIVISION IN RESPONSE TO CELLULAR STRESSES LIKE DNA DAMAGE

Insensitivity to anti-growth signals

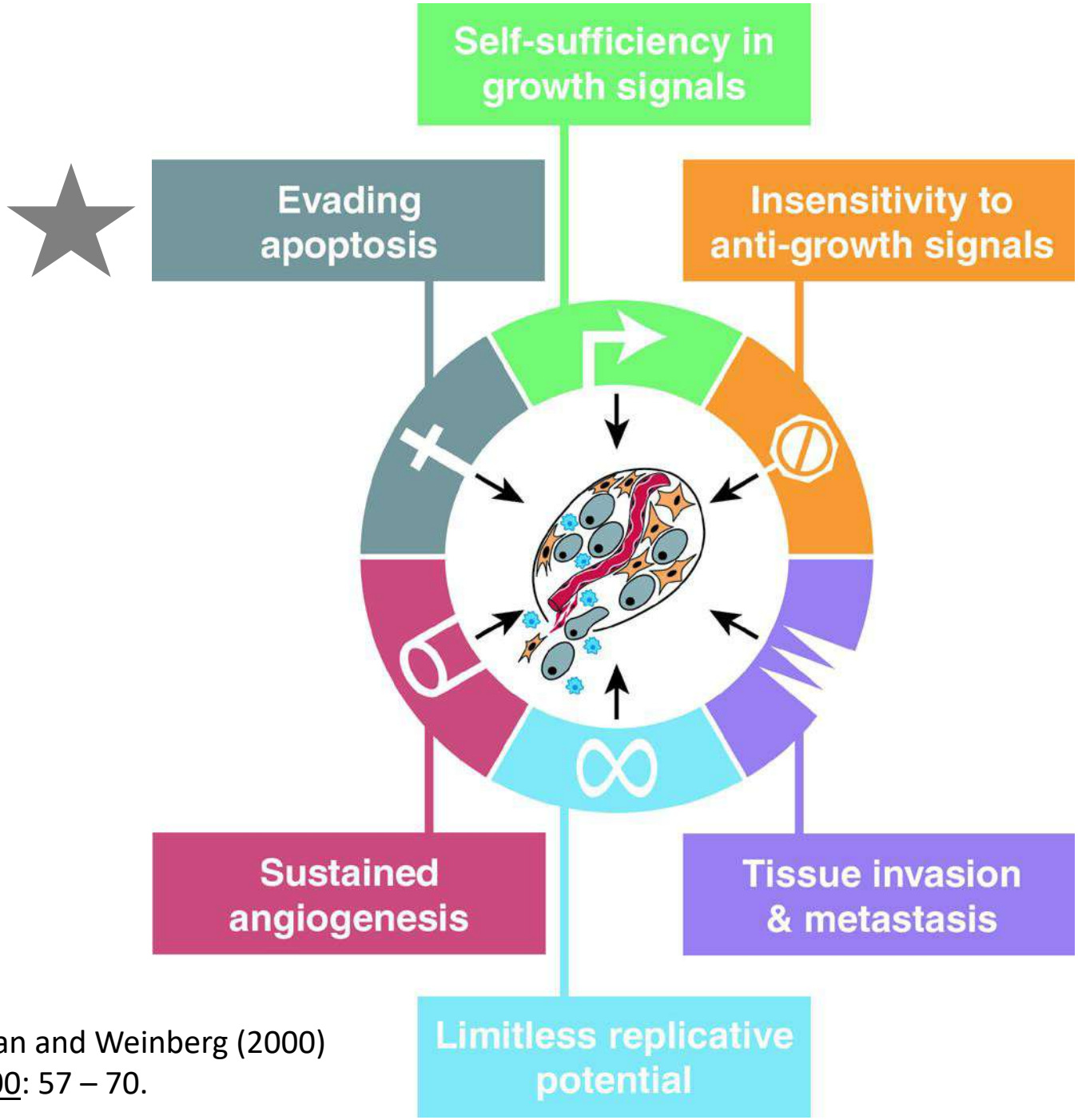


Insensitivity to anti-growth signals

TUMOR CELLS LACKING p53 DO NOT ARREST CELL CYCLE



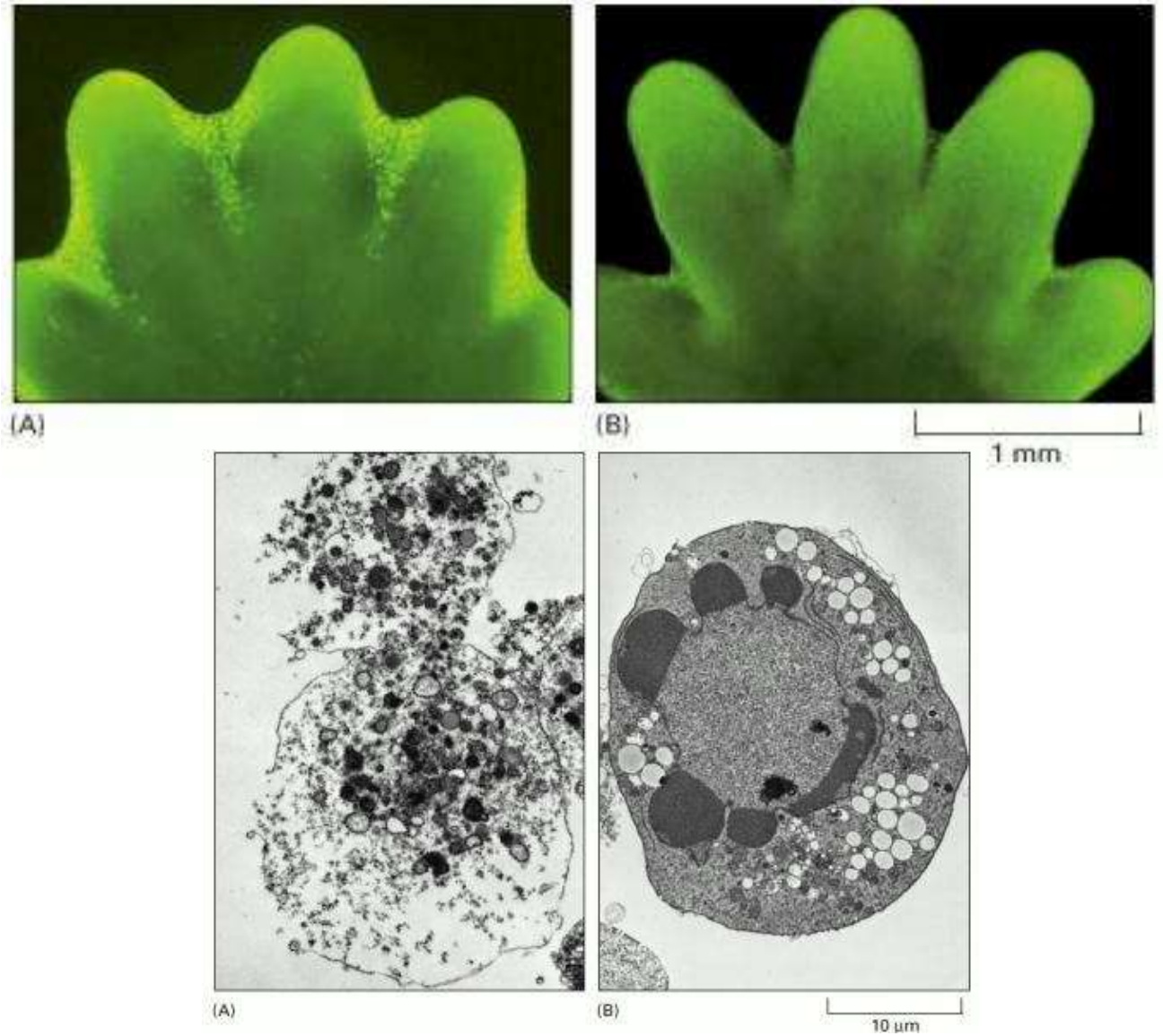
Source: *Molecular Biology of the Cell*, Alberts *et al*.



Hanahan and Weinberg (2000)
Cell, 100: 57 – 70.

APOPTOSIS – PROGRAMMED CELL DEATH

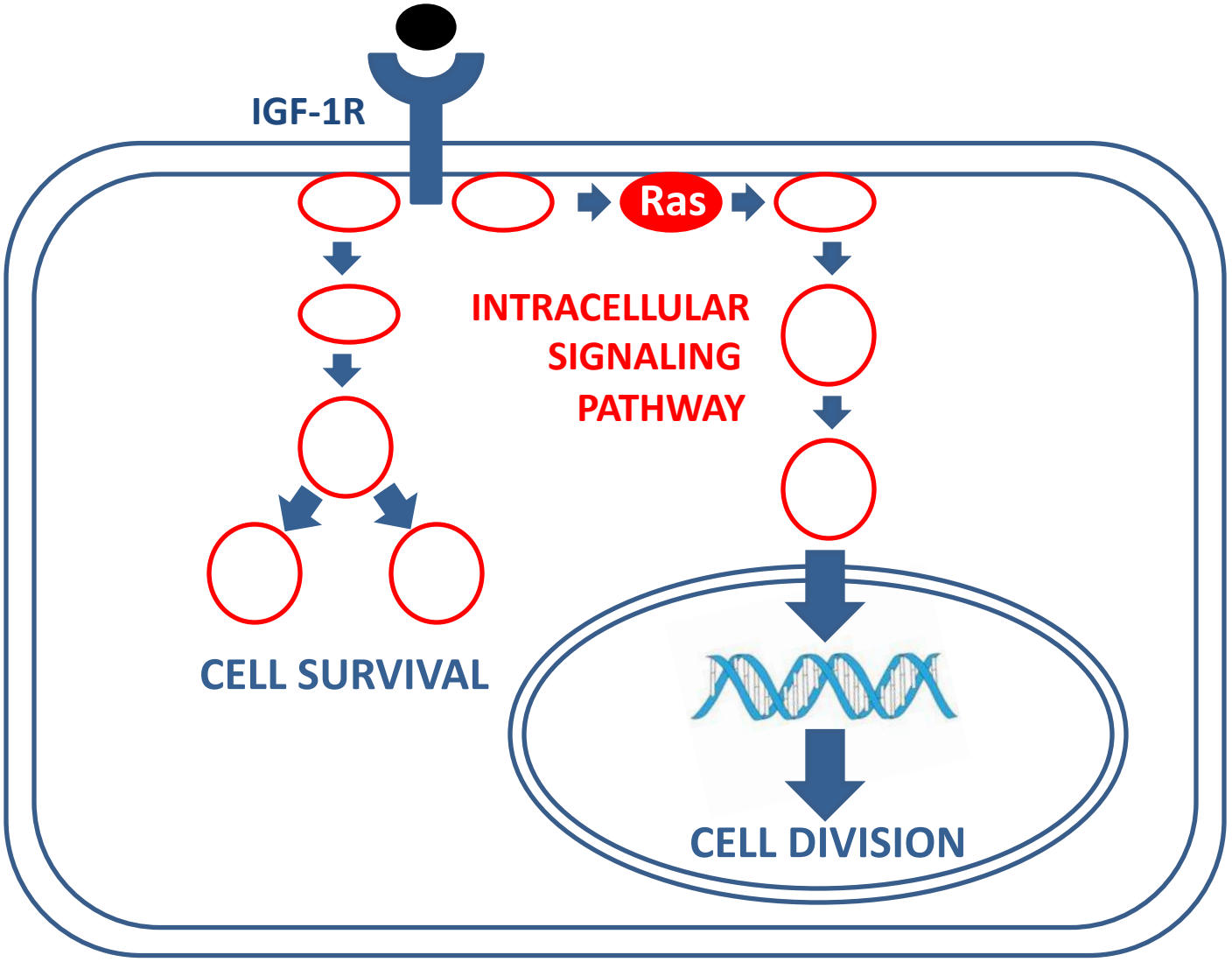
Evading apoptosis



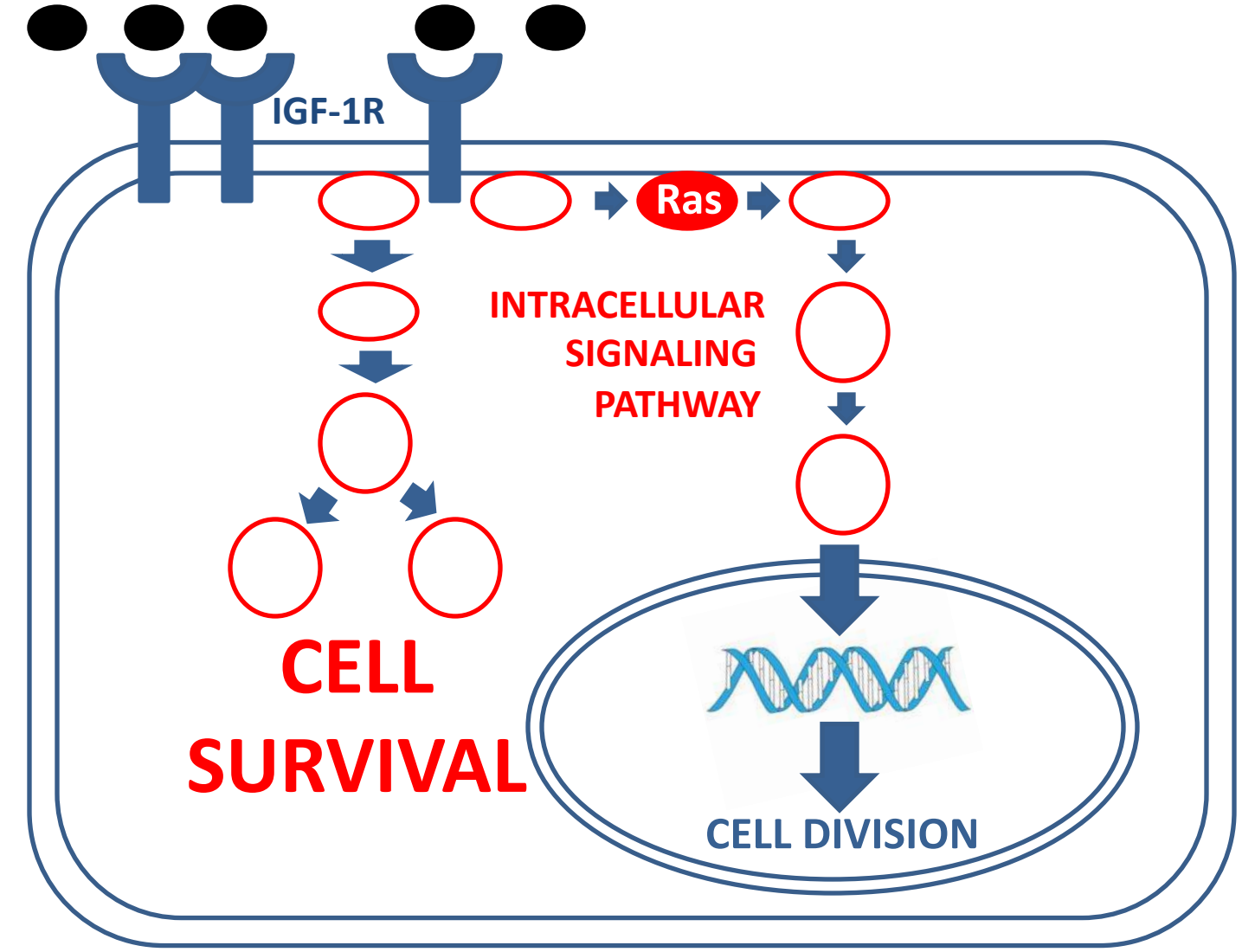
Source: *Molecular Biology of the Cell*, Alberts *et al*.

Evading apoptosis

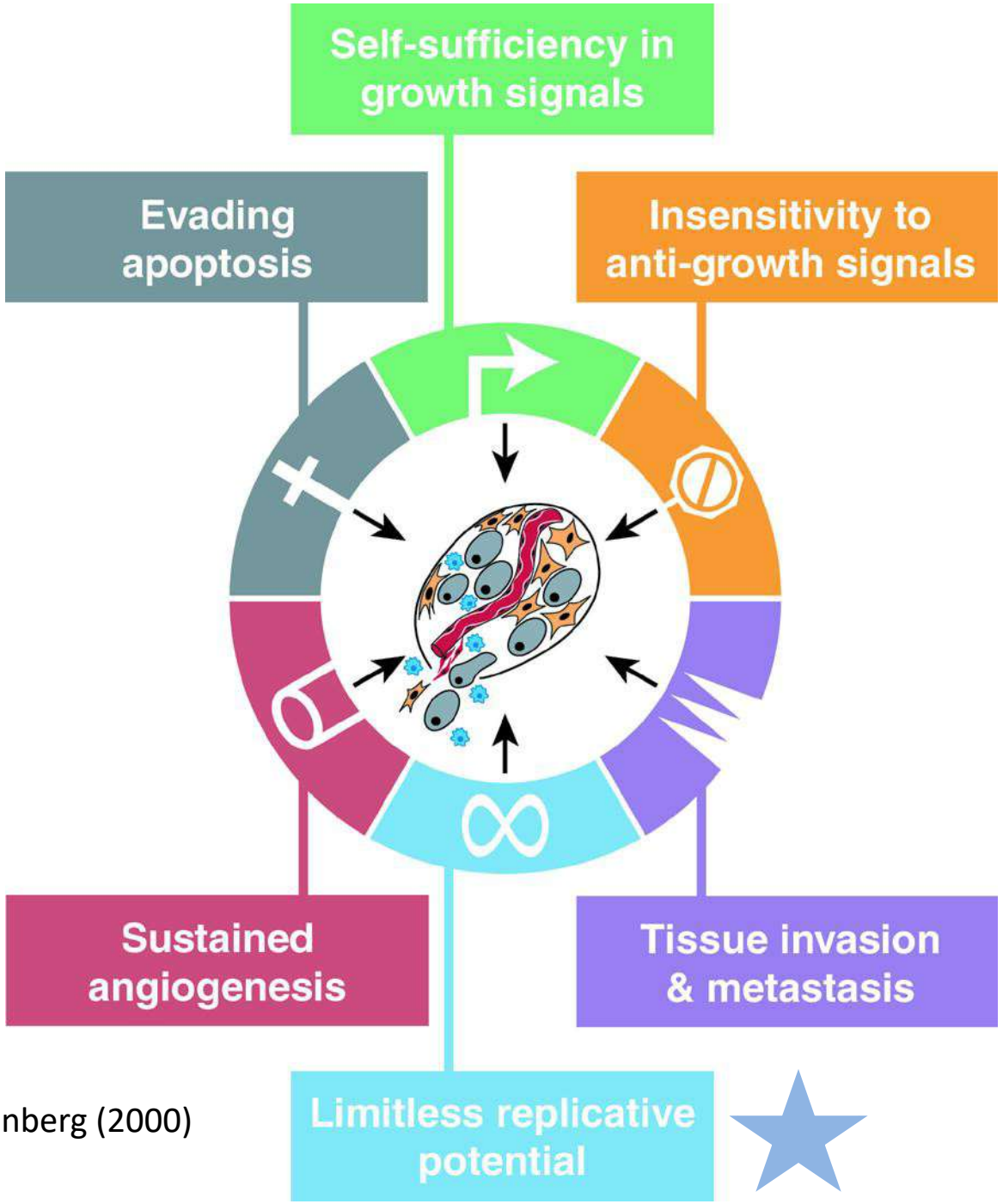
INSULIN-LIKE GROWTH FACTOR (IGF-1)



Evading apoptosis



SOME CANCER CELLS UPREGULATE CELL SURVIVAL PATHWAYS TO EVADE APOPTOSIS



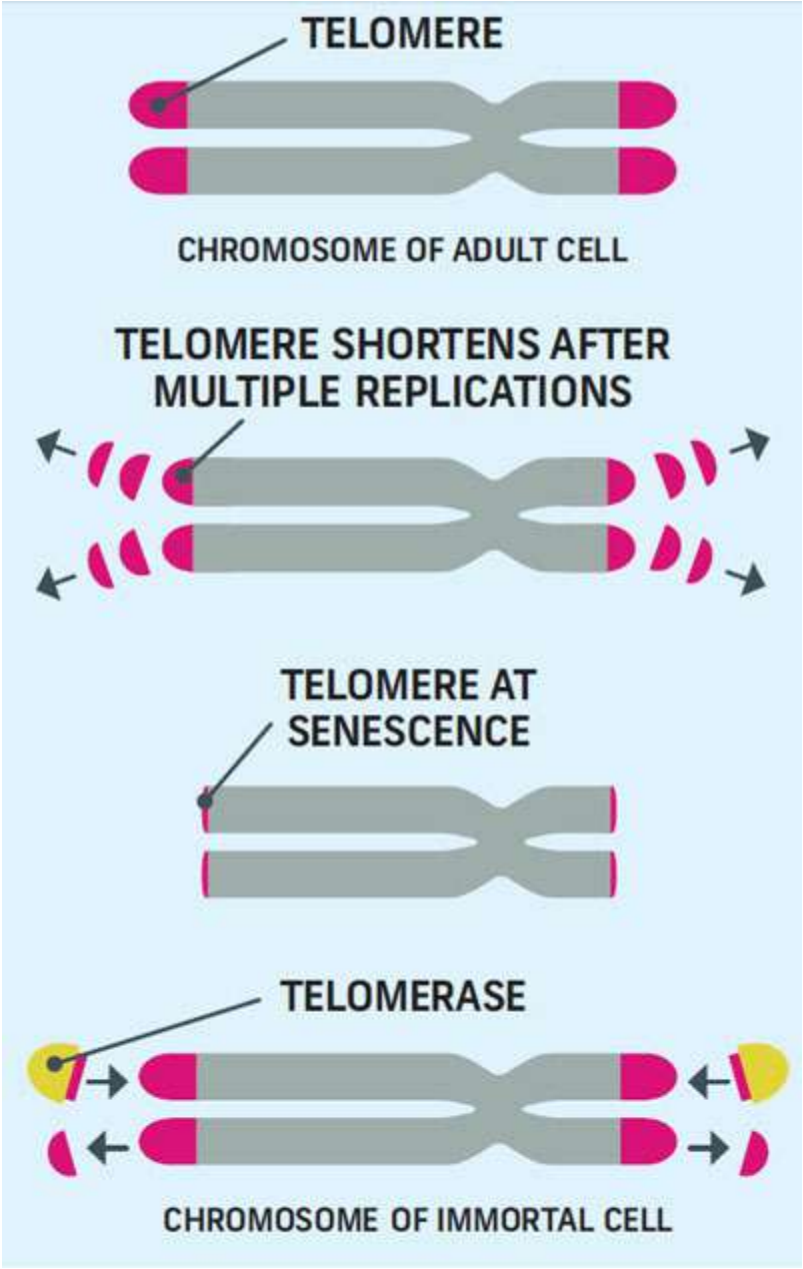
Hanahan and Weinberg (2000)
Cell, 100: 57 – 70.

Limitless replicative potential

TELOMERES ARE CHROMOSOME ENDS

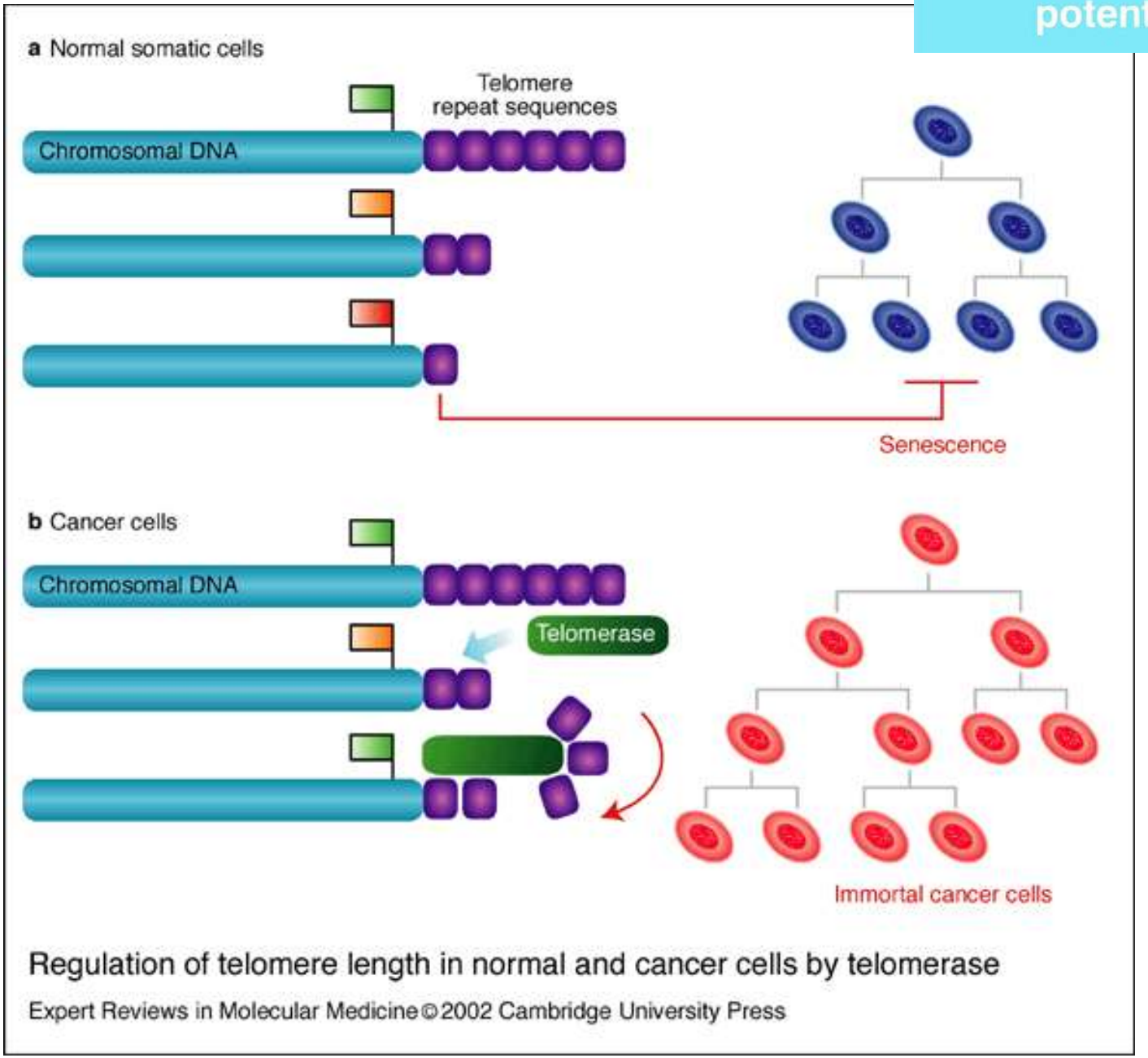
TELOMERES ARE MADE BY TELOMERASE EARLY IN DEVELOPMENT; THEN TELOMERASE ACTIVITY IS NORMALLY TURNED OFF

TELOMERES SHORTEN WITH EACH CELL DIVISION, ULTIMATELY LEADING TO SENESCENCE

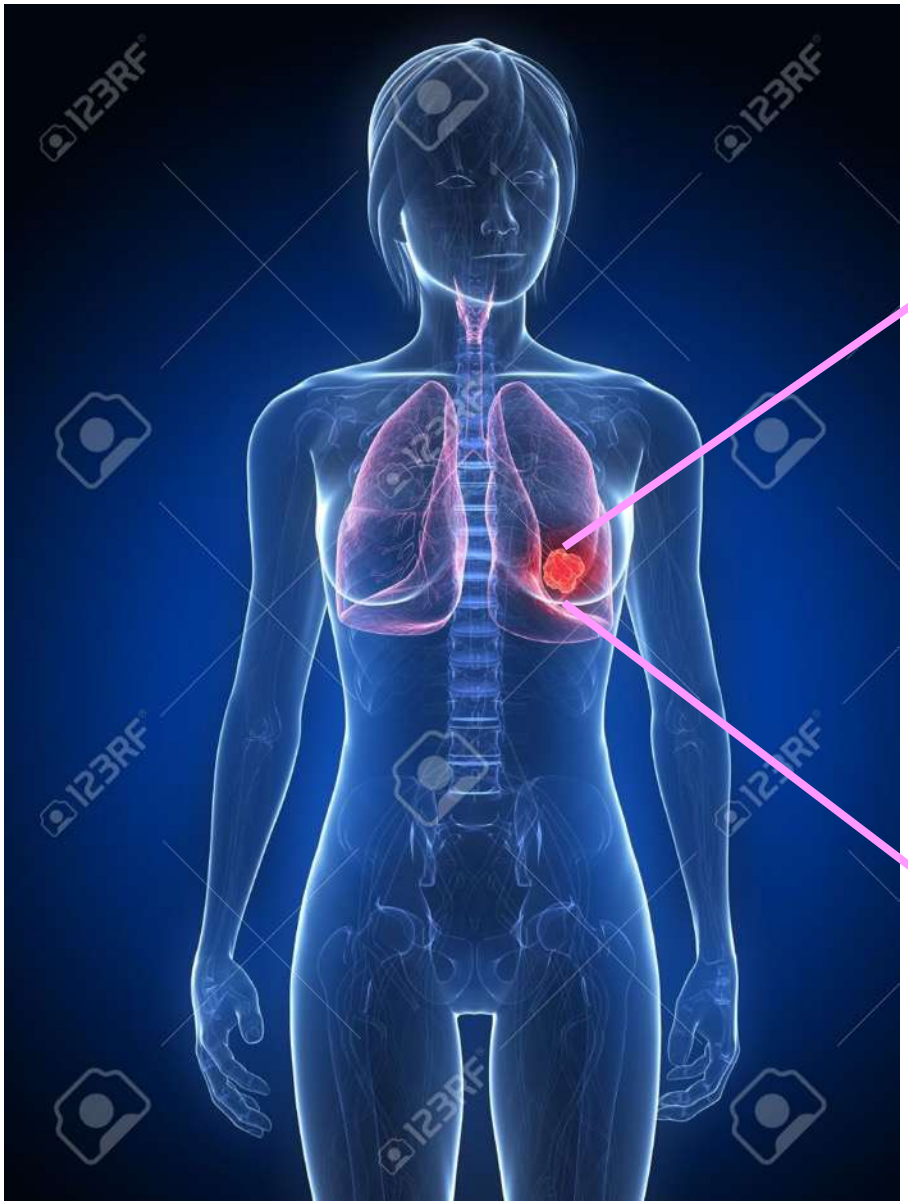


CANCER CELLS *REACTIVATE* TELOMERASE

Limitless replicative potential



Regulation of telomere length in normal and cancer cells by telomerase



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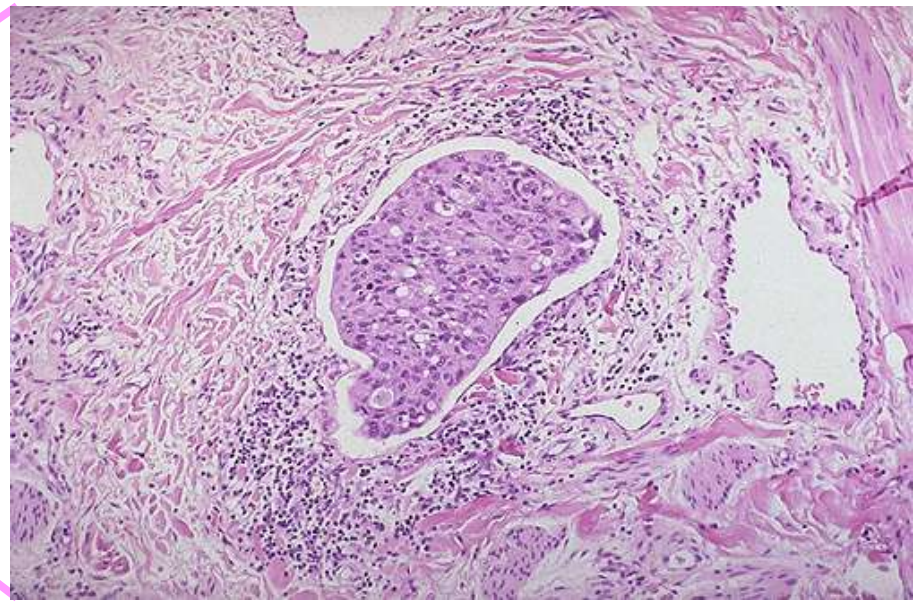
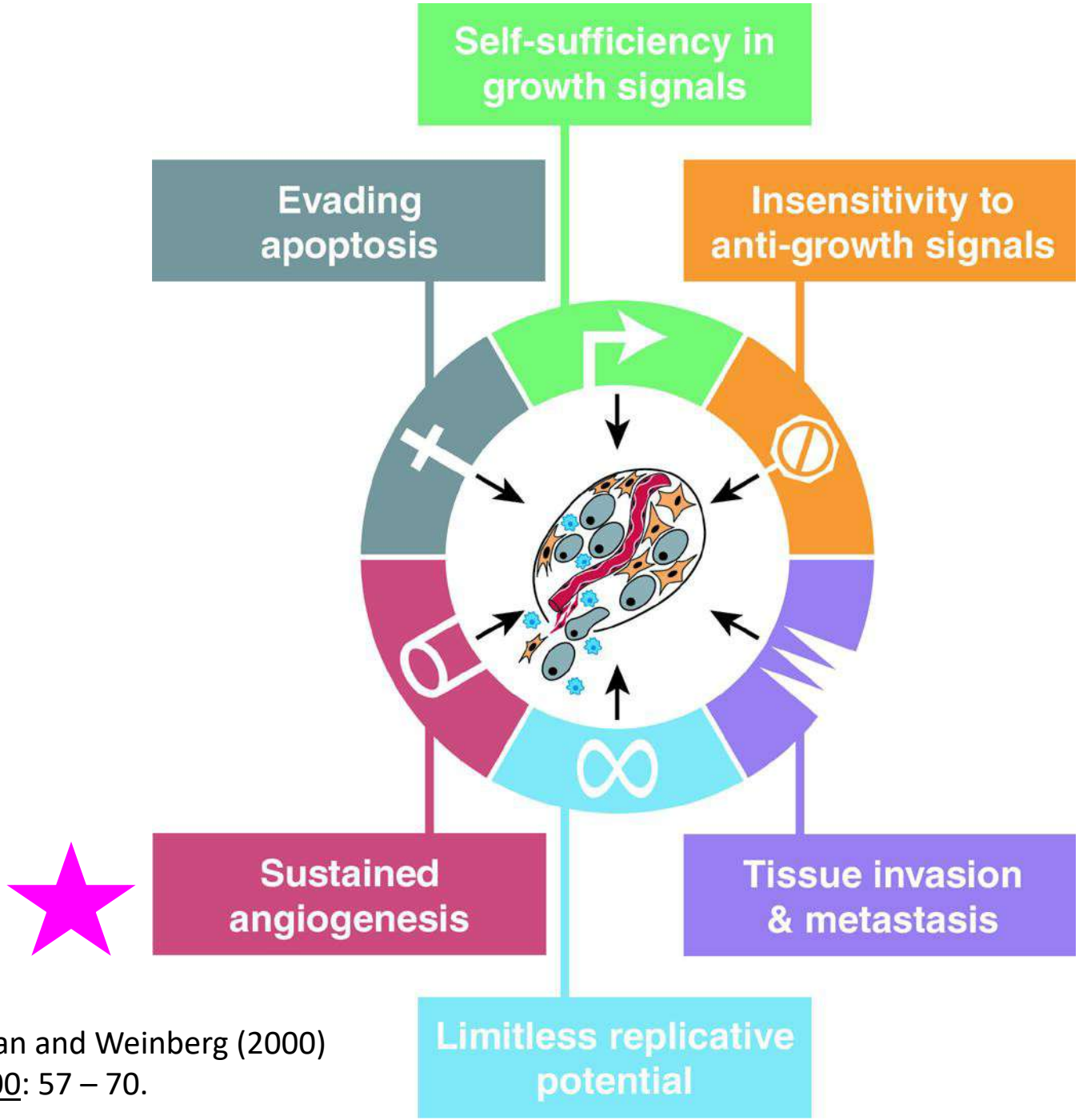
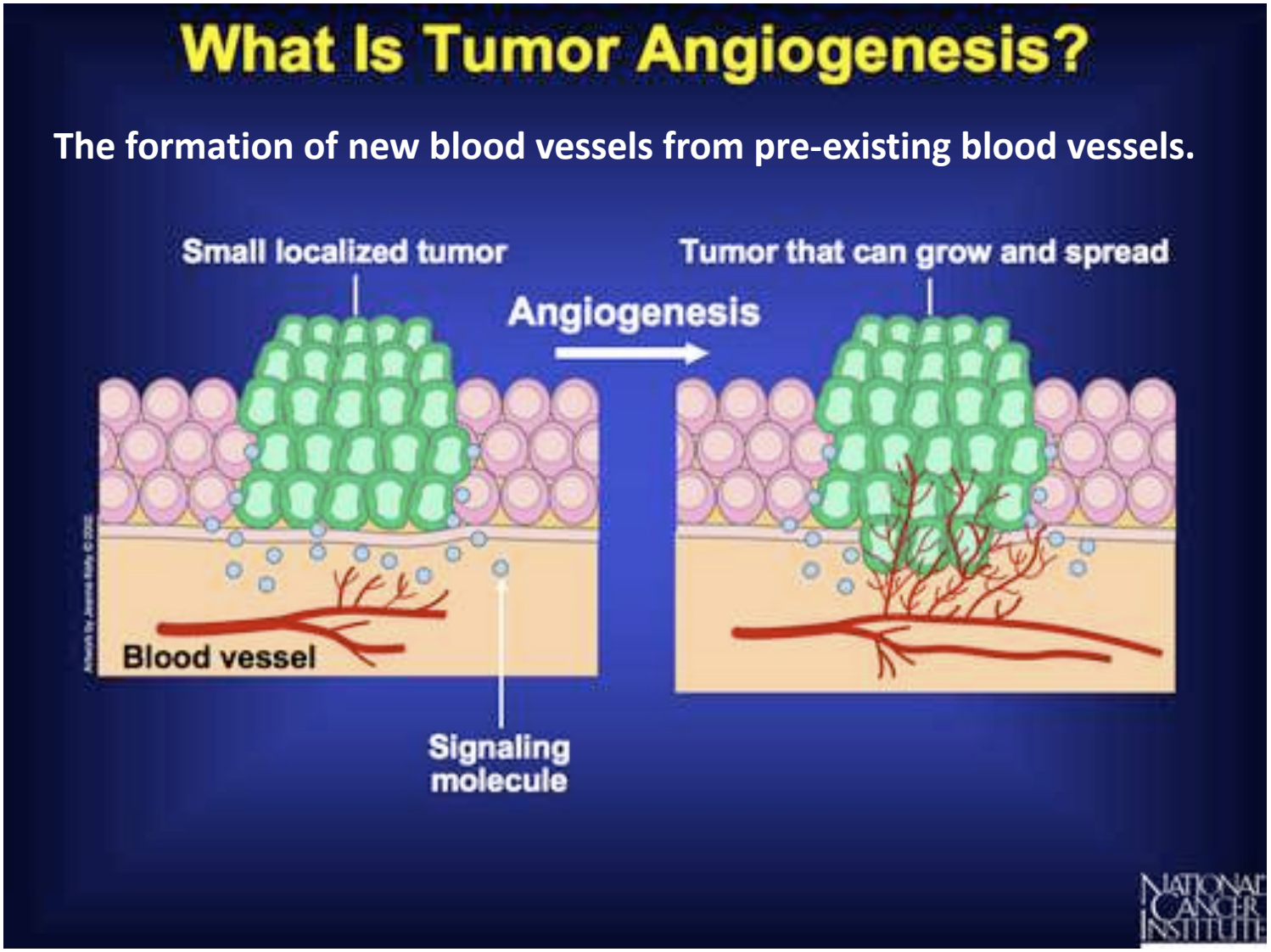


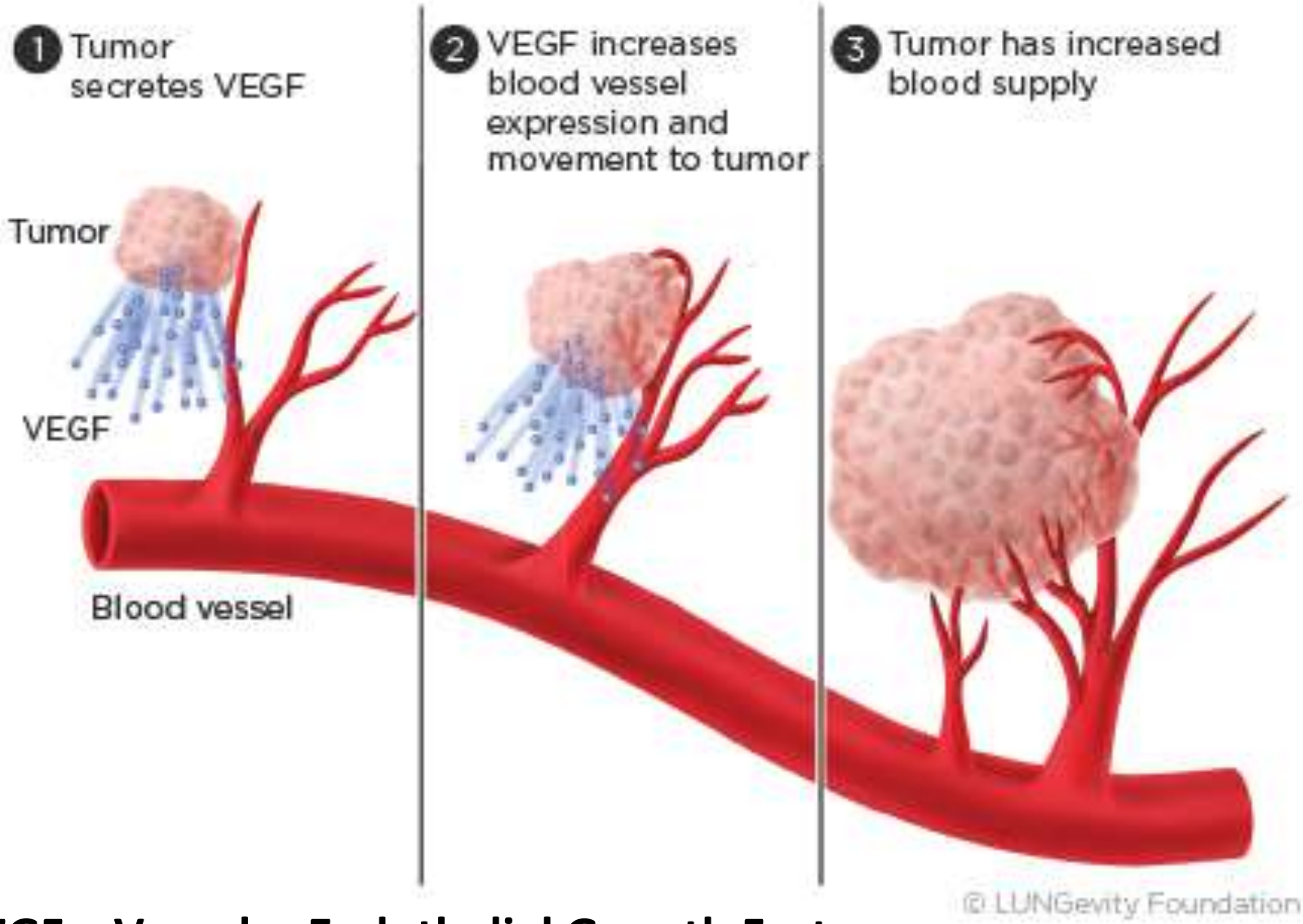


Hanahan and Weinberg (2000)
Cell, 100: 57 – 70.

Sustained angiogenesis



Sustained angiogenesis

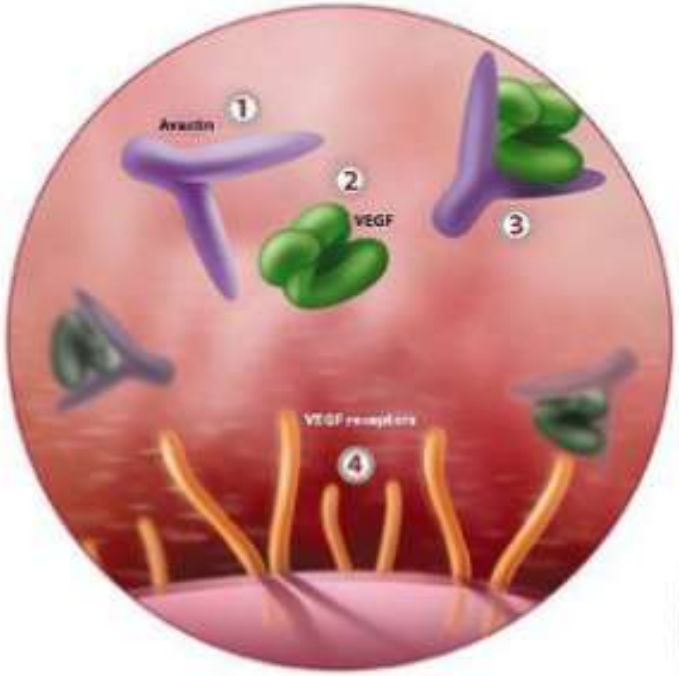


VEGF = Vascular Endothelial Growth Factor

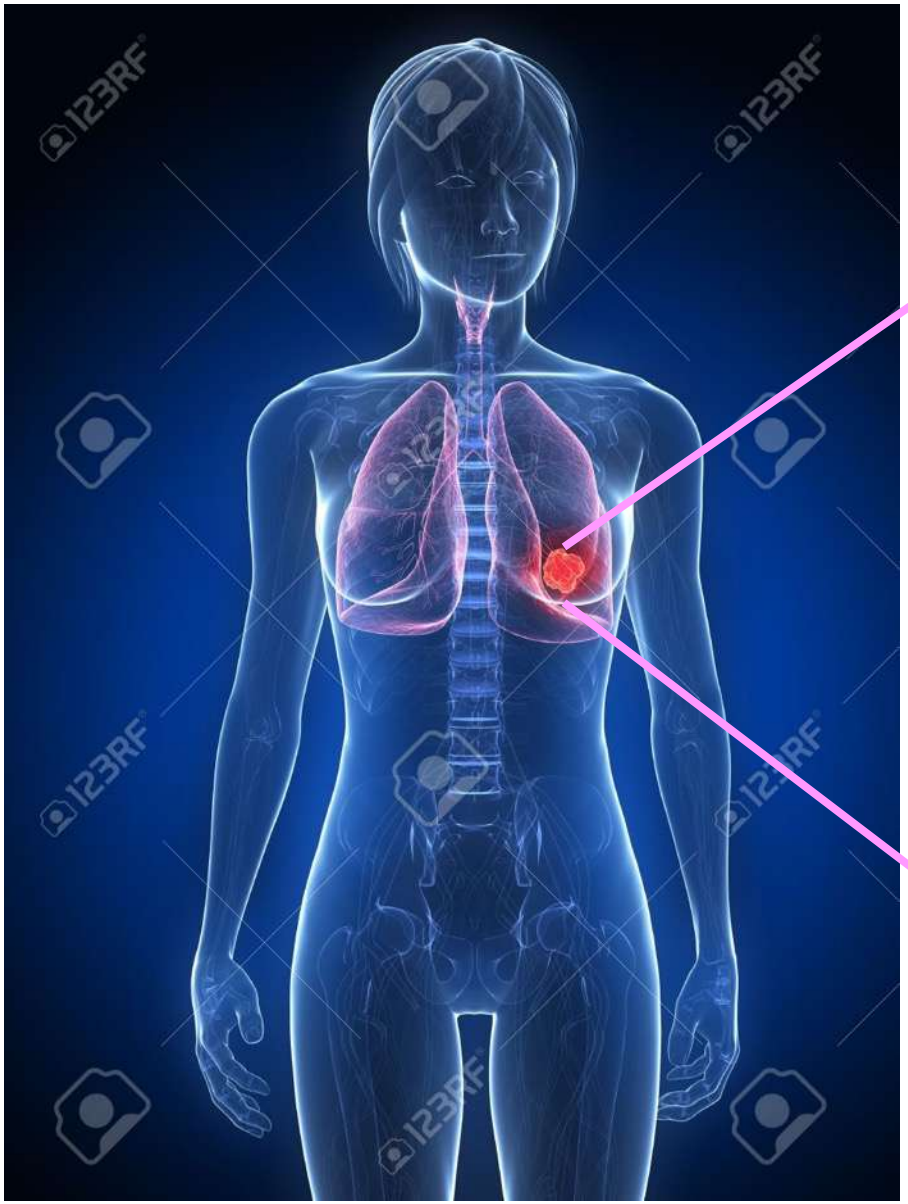
Sustained angiogenesis

Targeted Therapies

AVASTIN (bevacizumab)



Targets the VEGF and inhibits angiogenesis in NSCLC and colorectal cancer



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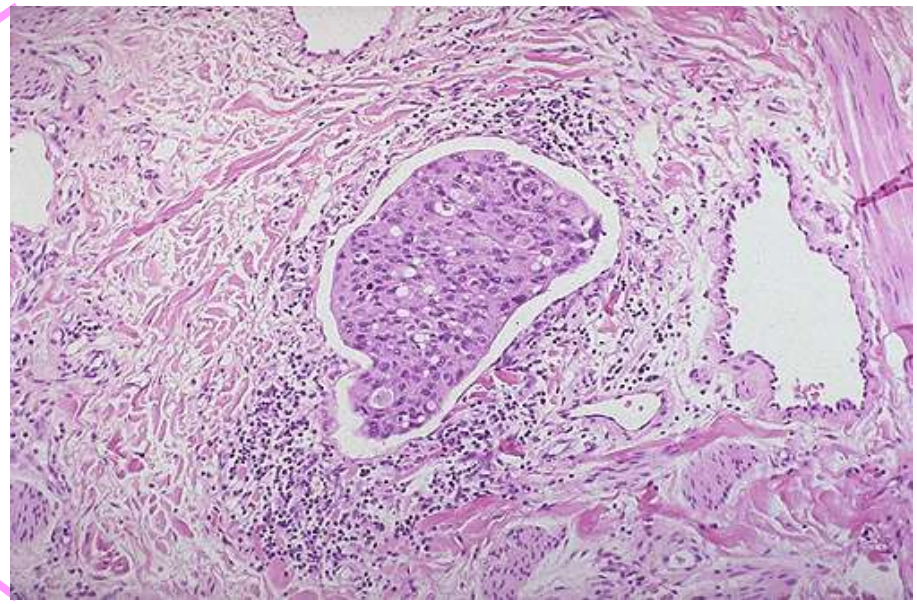
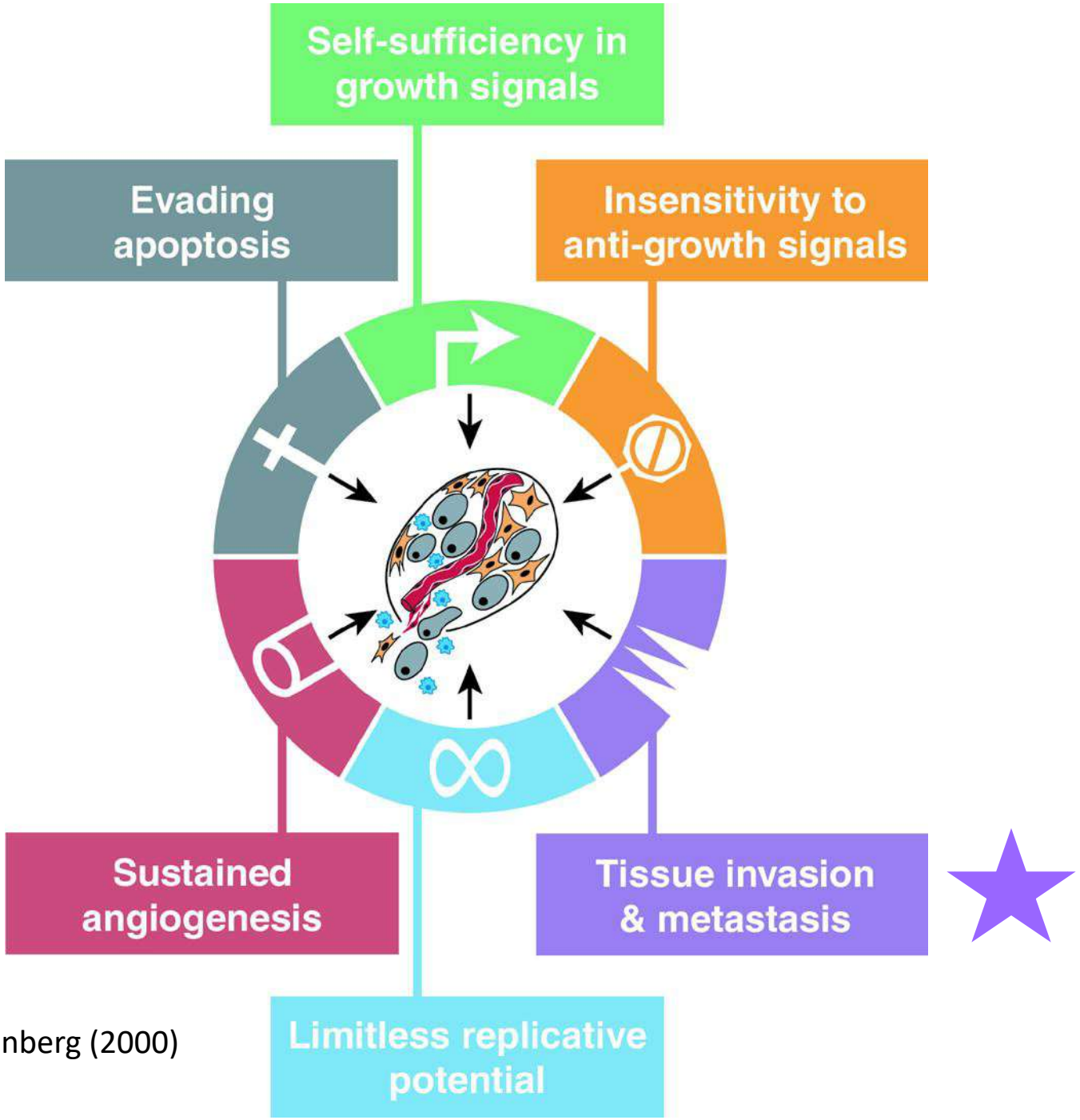
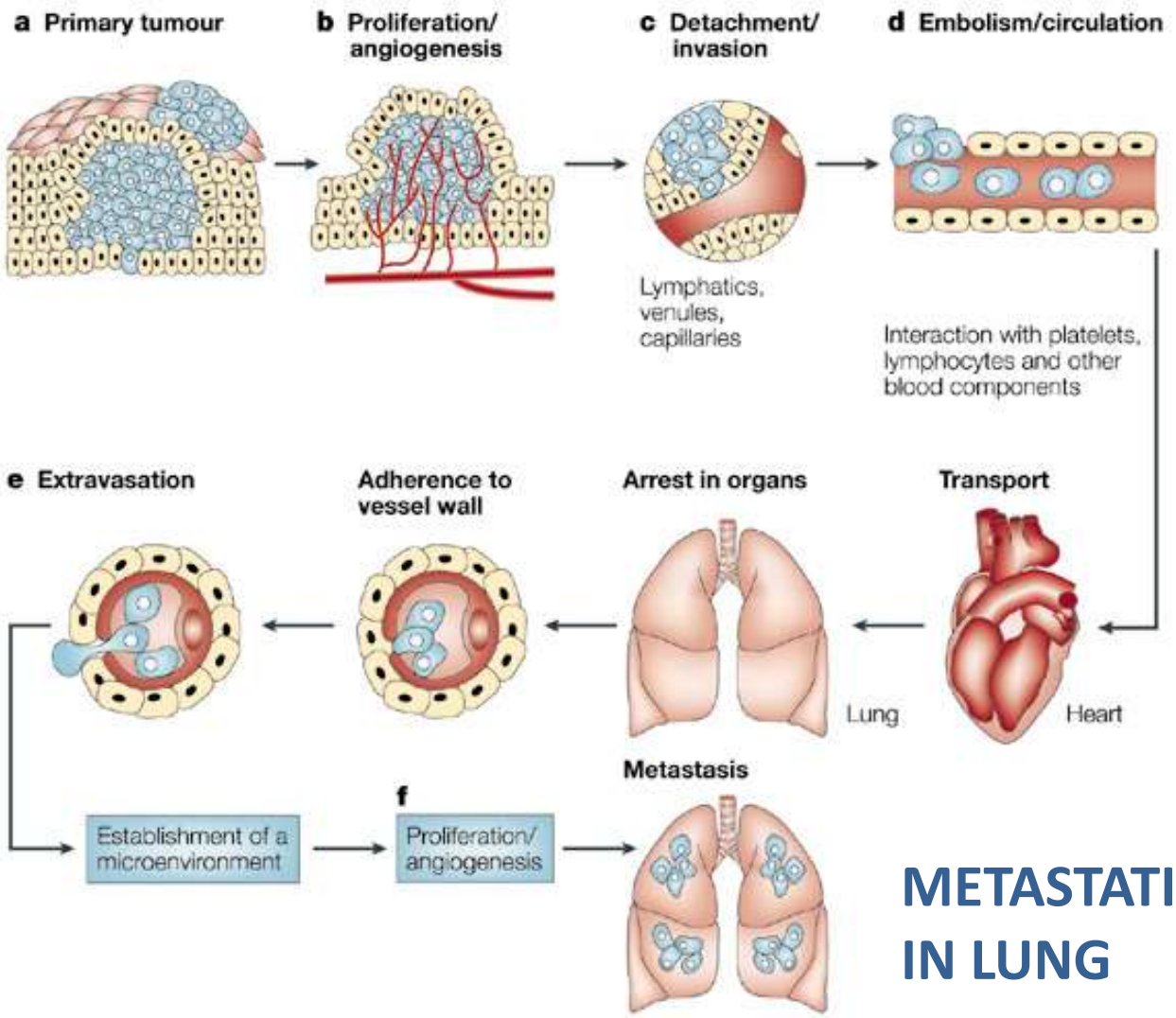




Hanahan and Weinberg (2000)
Cell, 100: 57 – 70.

PRIMARY BREAST CARCINOMA

Tissue invasion & metastasis

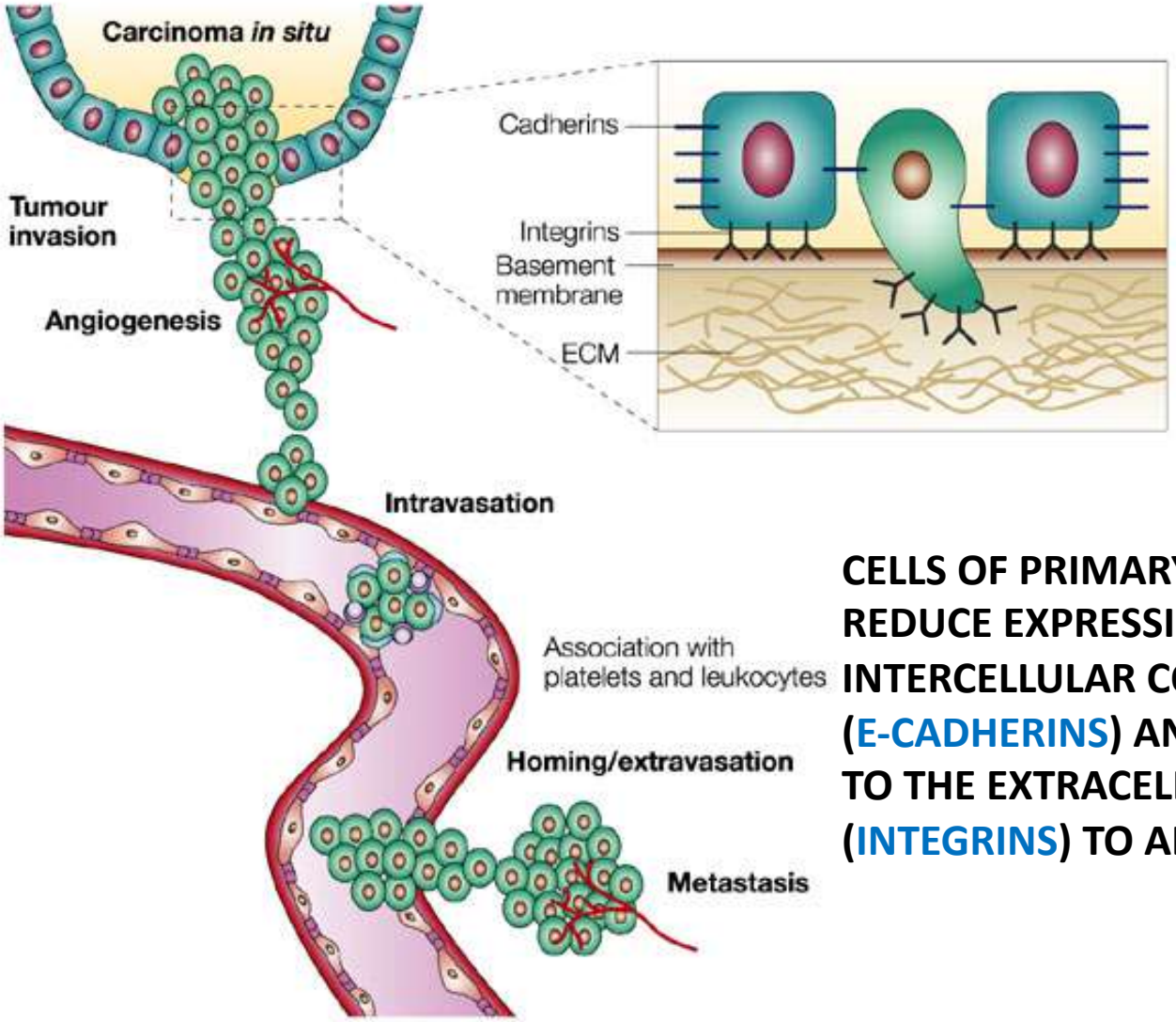


METASTATIC TUMOR IN LUNG

Nature Reviews | Cancer

METASTASIS

Tissue invasion & metastasis



CELLS OF PRIMARY TUMOR REDUCE EXPRESSION OF INTERCELLULAR CONNECTIONS (E-CADHERINS) AND CONNECTIONS TO THE EXTRACELLULAR MATRIX (INTEGRINS) TO ALLOW METASTASIS

Nature Reviews | Molecular Cell Biology

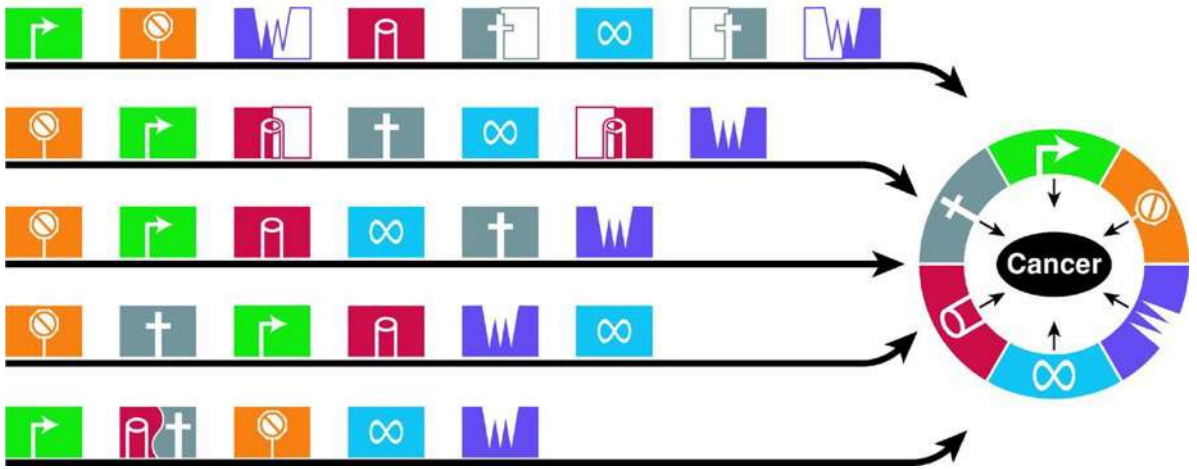
CANCER DEVELOPMENT IS A MULTI-STEP PROCESS.

INDIVIDUAL STEPS CAN OCCUR IS DIFFERENT ORDER.

A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B



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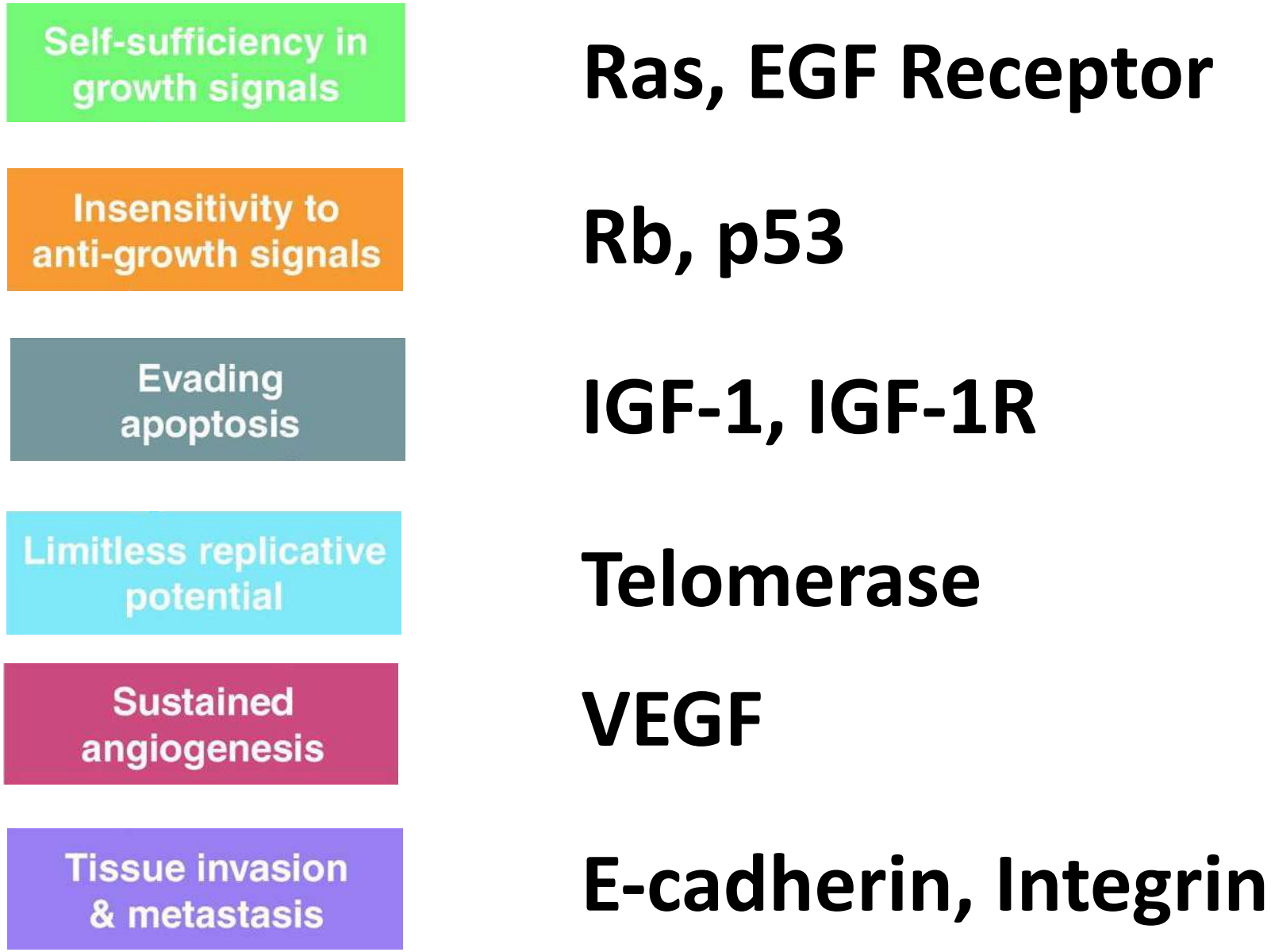
Cell, 100: 57 – 70.

THE HALLMARKS OF CANCER



You should be able to . . .

1. List the major hallmarks of cancer

2. Relate specific genes/proteins to individual hallmarks

3. Explain how hallmarks of cancer lead to cancer development