Introduction to Radiobiology
Lesson 4

Master of Advanced Studies in Medical Physics
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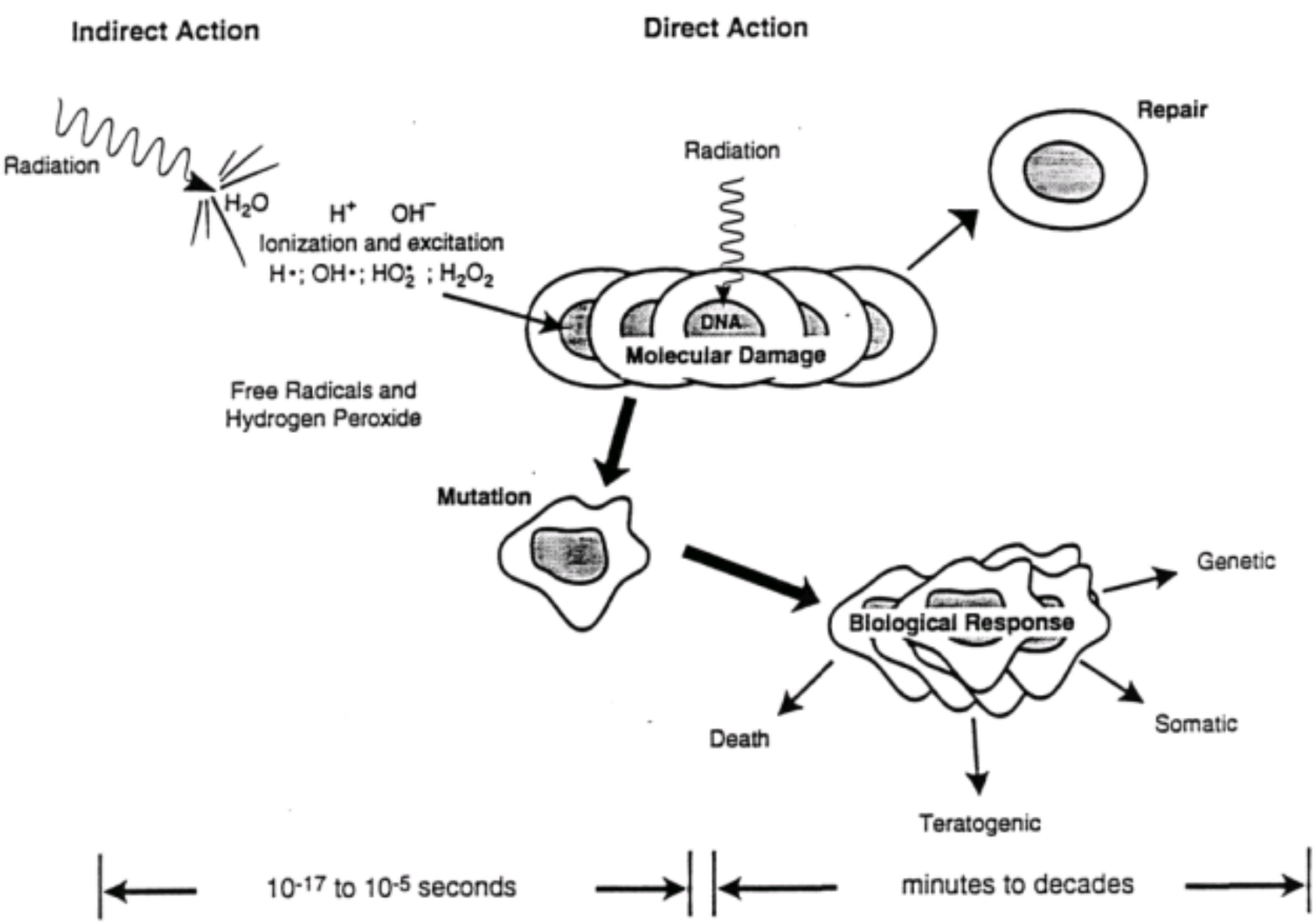


Physical and biological responses to ionizing radiation. Ionizing radiation causes damage either directly by damaging the molecular target or indirectly by ionizing water, which in turn generates free radicals that attack molecular targets. The physical steps that lead to energy deposition and free radical formation occur within 10^{-5} to 10^{-6} seconds, while the biological expression of the physical damage may occur seconds or decades later.

Timescales of cellular and organic effect

Timescale involved between the breakage of chemical bonds and the biological effect may be hours to years, depending on the type of damage.

Early effects. If cell kill is the result, it may happen in hours to days, when the damaged cell attempts to divide (early effect of radiation). This can result in early tissue reactions (deterministic effects) if many cells are killed.

Late effects. If the damage is oncogenic (cancer induction), then its expression may be delayed for years (late effect of radiation).

Cellular damage and cell death

Radiations damage cells in many ways, and in particular it can induce cell death.

Other consequences include:

- destruction of proteome (proteome: set of active proteins)
- deleterious mutations
  - cancer
  - senescence
- destruction of cellular membranes

Effects of irradiation:

- **Division delay**: The cell is delayed in going through division.
- **Apoptosis**: The cell dies before it can divide.
- **Reproductive failure**: The cell dies when attempting the mitosis.
- **Genomic instability**: High frequency of mutations.
- **Mutation**: The cell survives but contains a mutation.
- **Transformation**: The mutation leads to a transformed phenotype and possibly carcinogenesis.
- **Senescence**: The cell fails in performing some functions.
- **Bystander effects**: An irradiated cell may send signals to neighboring unirradiated cells and induce genetic damage in them.
- **Adaptive responses**: The irradiated cell becomes more radio-resistant.

Lethal damage

- Lethal damage, which is irreversible, irreparable and leads to cell death.
- Sublethal damage, which can be repaired in hours unless additional sublethal damage is added that eventually leads to lethal damage.
- Potentially lethal damage, which can be manipulated by repair when cells are allowed to remain in a non-dividing state.

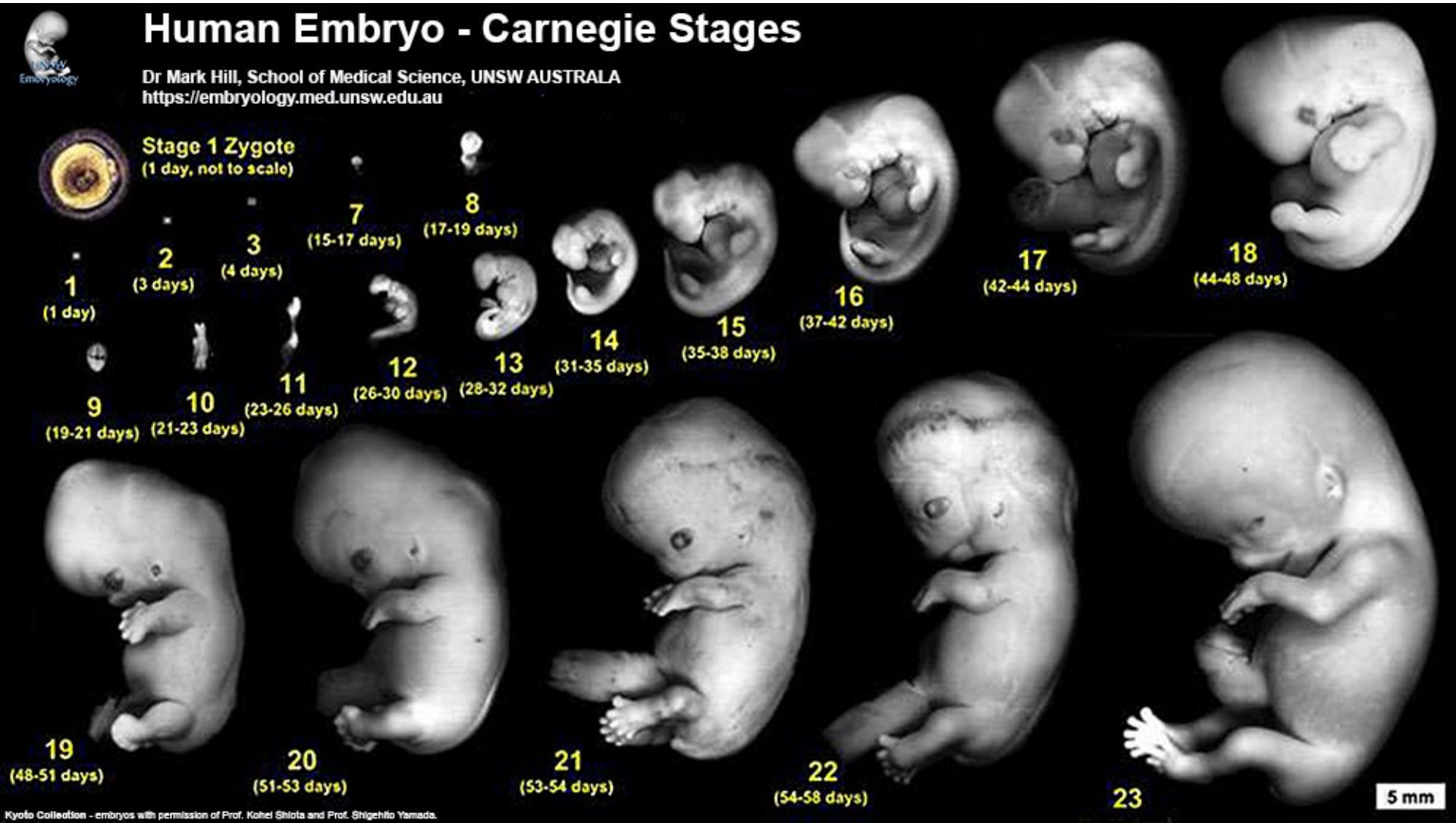
Cell death: apoptosis and necrosis, clonogenic death

Apoptosis, is synonymous with programmed cell death, which implies the existence of a genetic program of cell death. Apoptosis is believed to account for most cell death during development and in normal adult tissue turnover, and it can also be induced experimentally by various biological, chemical, or physical agents.

Necrosis, in contrast, is a passive degenerative phenomenon and is observed in a tissue subjected to direct toxic or physical injury-such as hyperthermia, hypoxia, and ischemia or to complement-mediated lysis.

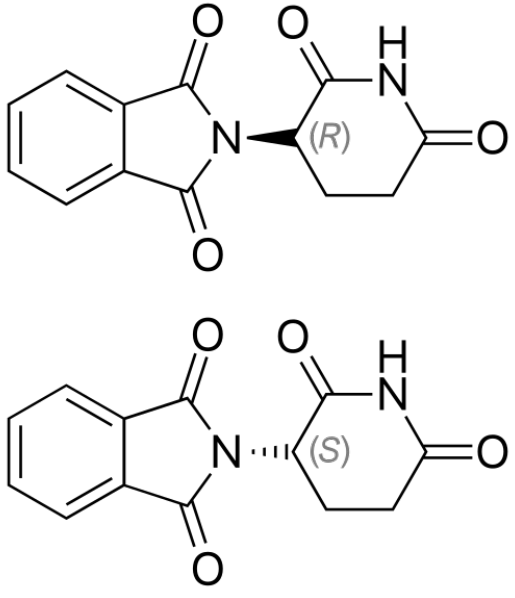
Clonogenic death occurs when cells lose the ability to proliferate (usually it takes two or three further generations until cells stop all proliferation).

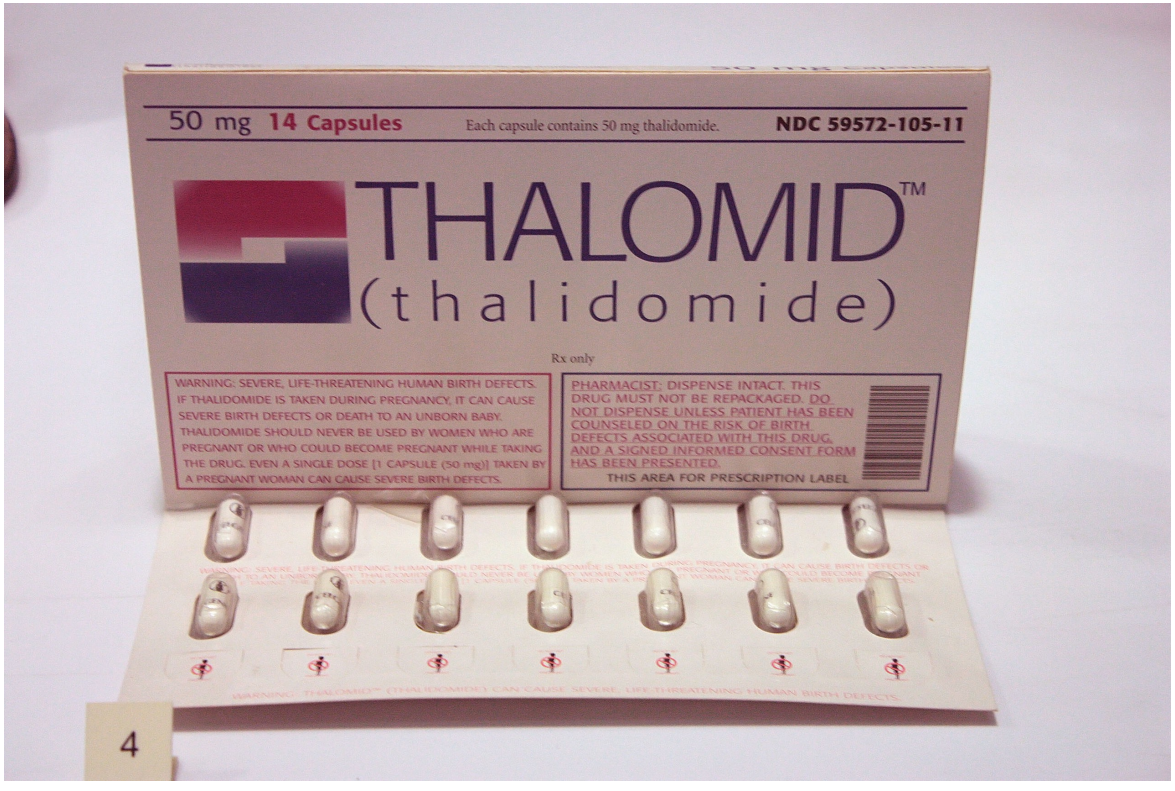
Short interlude on morphogenesis (tumors have no defined morphogenesis)



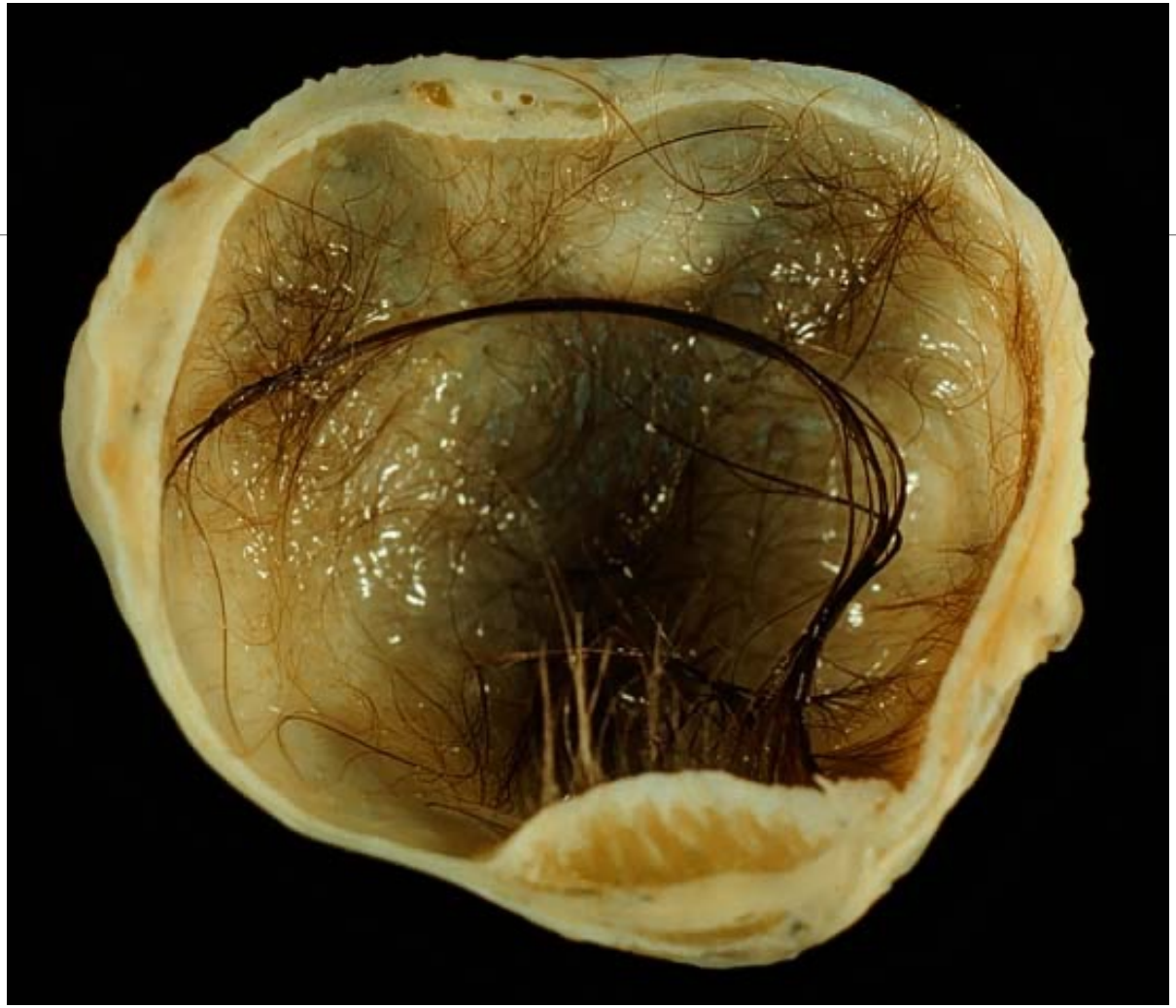
Thalidomide

Thalidomide is an immunomodulatory drug and the prototype of the thalidomide class of drugs. Initially it was used as a sedative. Today, thalidomide is used mainly as a treatment of certain cancers (multiple myeloma) and of a complication of leprosy.





The Thalidomide children



This 4-cm mature cystic teratoma of the ovary was found incidentally at the time of Caesarean section and removed. Like most ovarian teratomas (and unlike those of the testis) this one was benign, showing only mature tissues microscopically. In addition to the obvious cutaneous structures (giving rise to the hair seen here), histologically there was abundant neuroglia and even one neuron. Central nervous system tissue is very common in mature teratomas. (from Wikipedia)

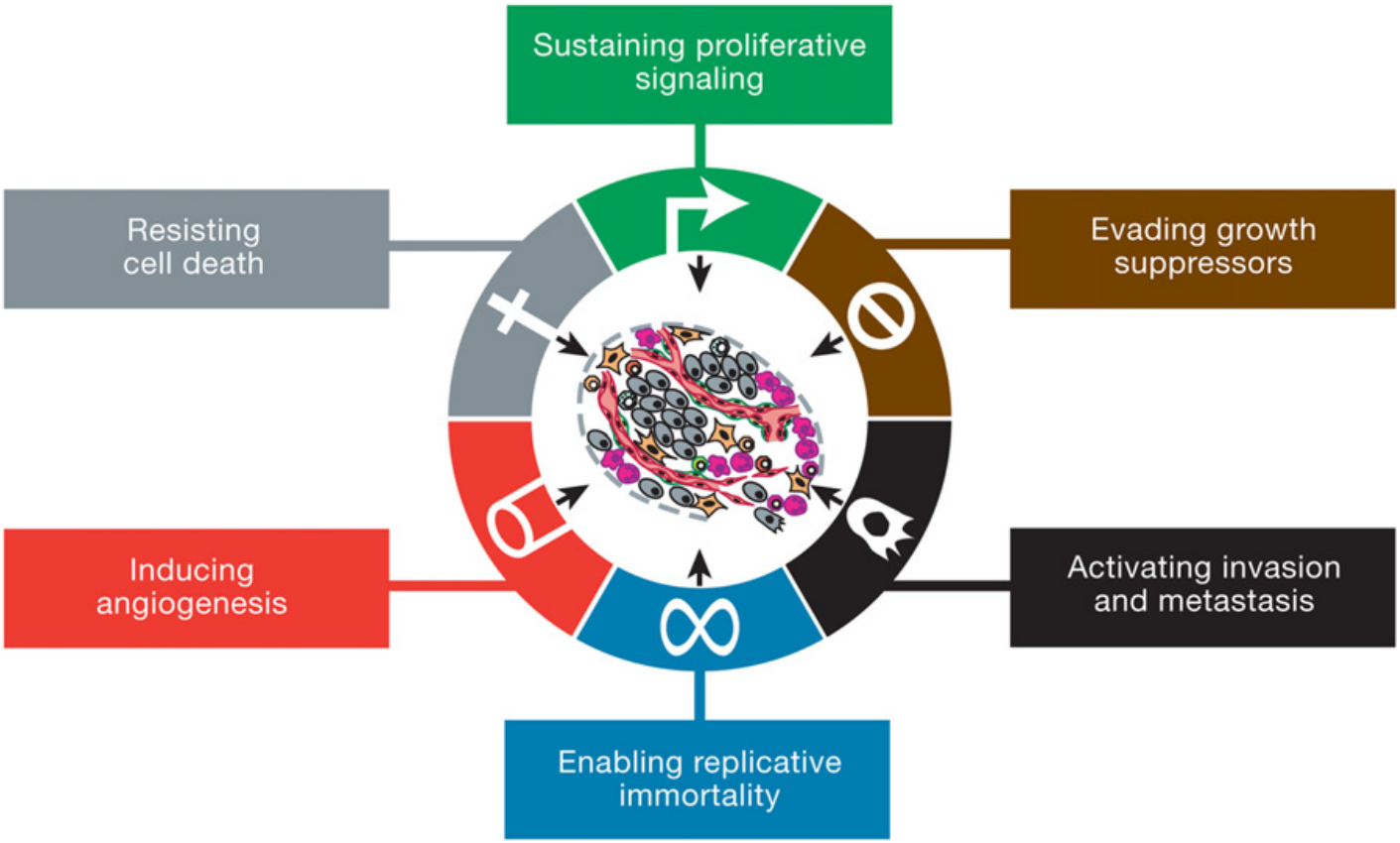
The dream of every cell is to become two cells.

(François Jacob)

François Jacob (17 June 1920 – 19 April 2013) was a French biologist who, together with Jacques Monod, originated the idea that control of enzyme levels in all cells occurs through regulation of transcription.

The hallmarks of cancer

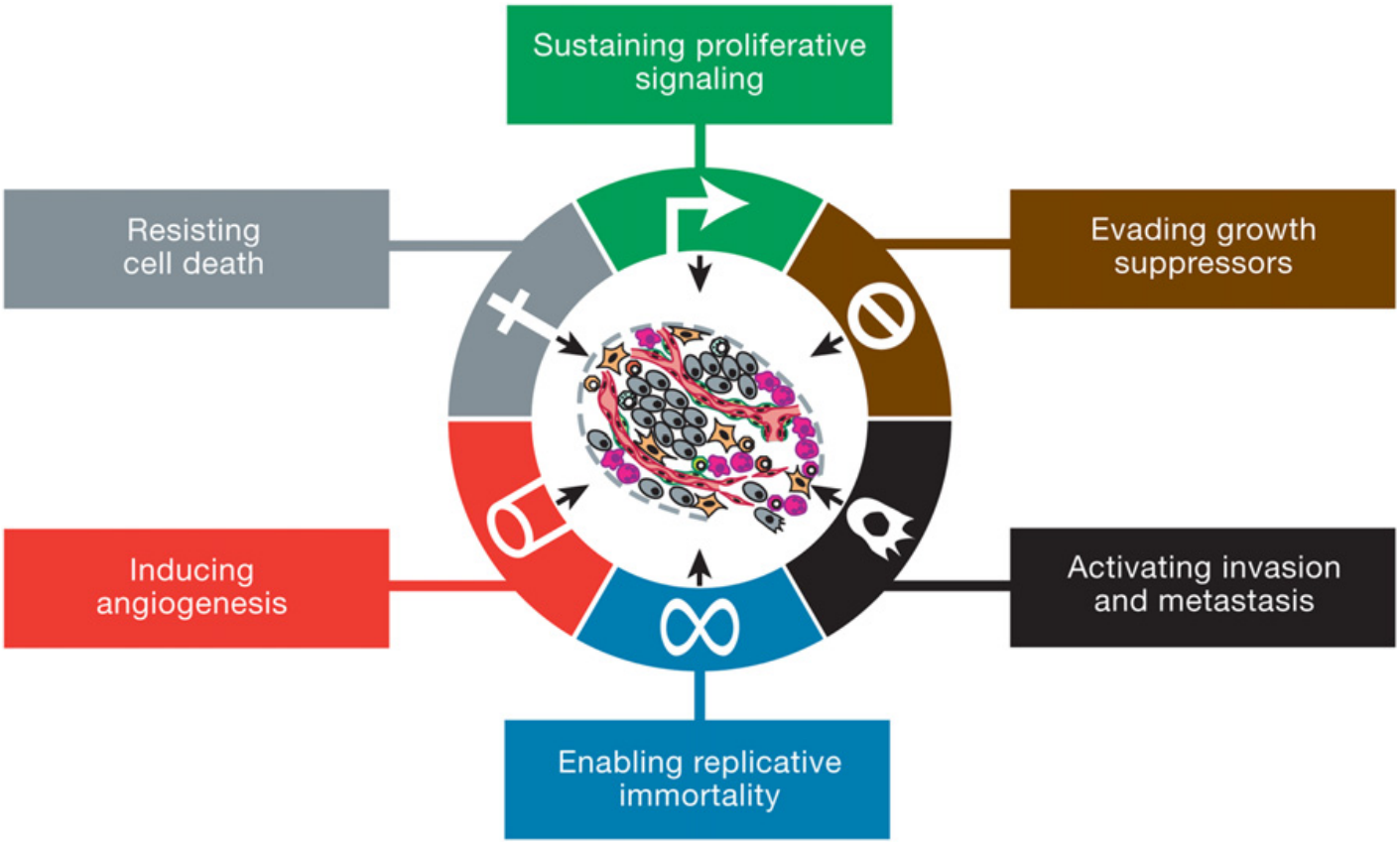
(from Hanahan & Weinberg, Cell **144** (2011) 646)



Cancer can be viewed as a problem of uncontrolled cell growth

The hallmarks of cancer

(from Hanahan & Weinberg, Cell **144** (2011) 646)



Gene modifications linked to cancer

(from Vogelstein et al., Nature **408** (2000) 307)

Oncogenes. These are analogous to the accelerators in a car.

Oncogenes stimulate appropriate cell growth under normal conditions, as required for the continued turnover and replenishment of the skin, gastrointestinal tract and blood, for example.

A mutation in an oncogene is tantamount to having a stuck accelerator: even when the driver releases his foot from the accelerator pedal, the car continues to move. Likewise, cells with mutant oncogenes continue to grow (or refuse to die) even when they are receiving no growth signals.

Examples are Ras, activated in pancreatic and colon cancers, and Bcl-2, activated in lymphoid tumours.

Gene modifications linked to cancer/ctd.

(from Vogelstein et al., Nature **408** (2000) 307)

Tumour-suppressor genes. When the accelerator is stuck to the floor, the driver can still stop the car by using the brakes.

Cells have brakes, too, called tumour-suppressor genes. These keep cell numbers down, either by inhibiting progress through the cell cycle and thereby preventing cell birth, or by promoting programmed cell death (also called apoptosis).

Just as a car has many brakes (the foot pedal, handbrake and ignition key), so too does each cell. When several of these brakes are rendered non-functional through mutation, the cell becomes malignant.

Examples are the gene encoding the retinoblastoma protein, inactivated in retinoblastomas, p53, and $p16^{INK4a}$, which inhibits cyclin-dependent kinases and is inactivated in many different tumours.

Gene modifications linked to cancer/ctd.

(from Vogelstein et al., Nature **408** (2000) 307)

Repair genes. Unlike oncogenes and tumour-suppressor genes, repair genes do not control cell birth or death directly. They simply control the rate of mutation of all genes.

When repair genes are mutated, cells acquire mutations in oncogenes and tumour-suppressor genes at an accelerated rate, driving the initiation and progression of tumours.

In the car analogy, a defective repair gene is much like having a bad mechanic. Examples are nucleotide-excision- repair genes and mismatch-repair genes, whose inactivation leads to susceptibility to skin and colon tumours, respectively.

Ataxia-telangiectasia (also Louis–Bar syndrome)

Ataxia is a neurological sign consisting of lack of voluntary coordination of muscle movements.

Telangiectasia denotes the presence of small dilated blood vessels near the surface of the skin or mucous membranes, measuring between 0.5 and 1 millimeter in diameter.

A-T is caused by a defect in the ATM gene which is responsible for managing the cell's response to multiple forms of stress including double-strand breaks in DNA.

In simple terms, the protein produced by the ATM gene recognizes that there is a break in DNA, recruits other proteins to fix the break, and stops the cell from making new DNA until the repair is complete

A-T matters because it shows us what happens when the DNA repair system is malfunctioning, and therefore it mimics the accumulation of heavy DNA damage in normal individuals.

There is substantial variability in the severity of features of A-T between affected individuals, and at different ages. The following symptoms or problems are either common or important features of A-T:

- Ataxia (difficulty with control of movement) that is apparent early but worsens in school to pre-teen years
- Oculomotor apraxia (difficulty with coordination of head and eye movement when shifting gaze from one place to the next)
- Involuntary movements
- Telangiectasia (dilated blood vessels) over the white (sclera) of the eyes, making them appear bloodshot. Telangiectasia may also appear on sun-exposed areas of skin.
- Problems with infections, especially of the ears, sinuses and lungs
- Increased incidence of cancer (primarily, but not exclusively, lymphomas and leukemias)
- Delayed onset or incomplete pubertal development, and very early menopause
- Slowed rate of growth (weight and/or height)
- Drooling particularly in young children when they are tired or concentrating on activities
- Dysarthria (slurred, slow, or distorted speech sounds)
- Diabetes in adolescence or later
- Premature changes in hair and skin

Note: homeostasis in cells

Homeostasis is the property of a system in which variables are regulated so that internal conditions remain stable and relatively constant.

Examples of homeostasis include the regulation of temperature and the balance between acidity and alkalinity (pH). It is a process that maintains the stability of the human body's internal environment in response to changes in external conditions.

Example: the levels of many enzymes are regulated homeostatically by the equilibrium between production and destruction

rate of change of substance S

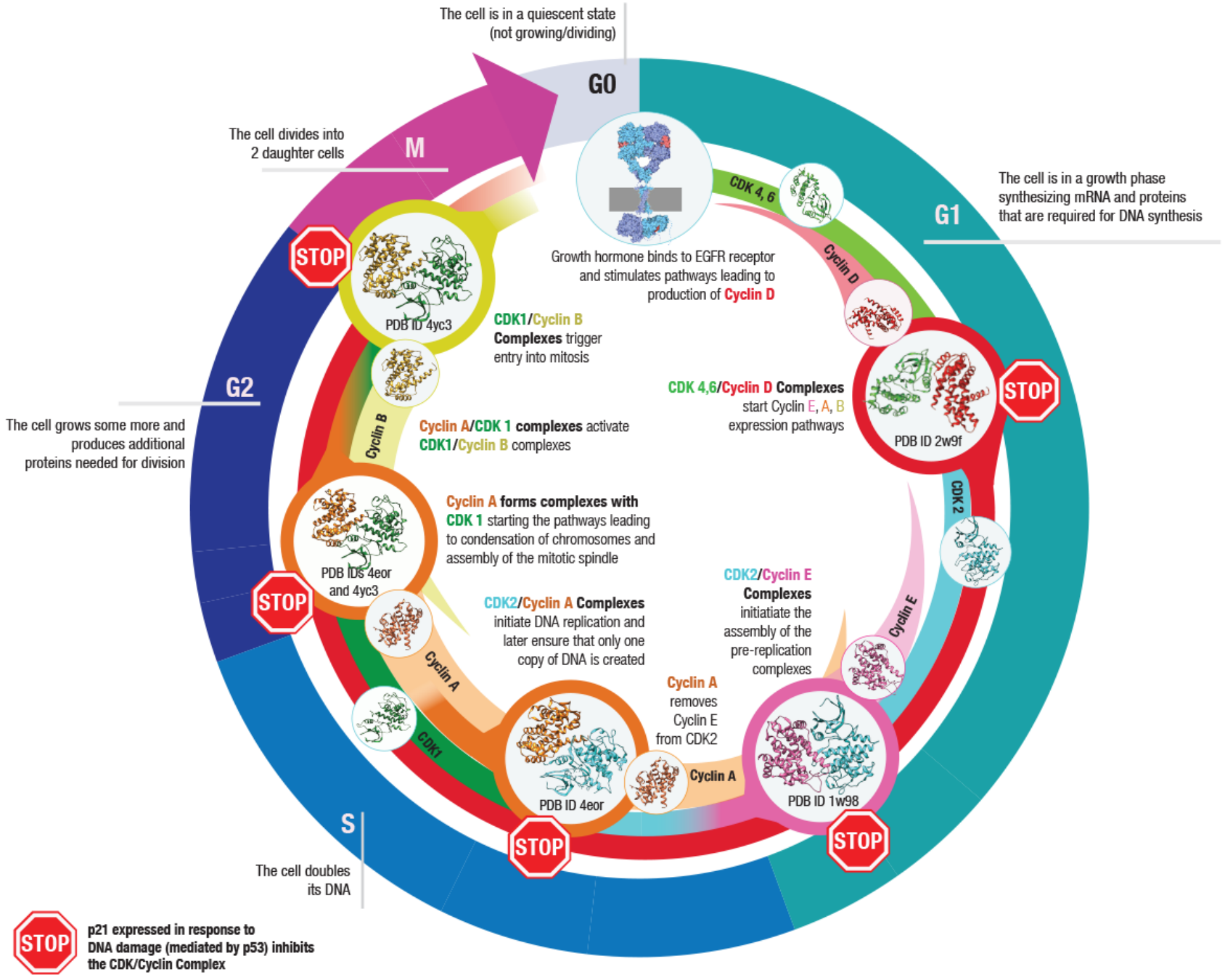
destruction rate proportional to amount of substance

$$\frac{dS}{dt} = \alpha - \beta S$$

fixed production rate

at equilibrium the total rate of change vanishes, and the amount of substance is dynamically fixed

$$S_{eq} = \frac{\alpha}{\beta}$$


The cell is in a quiescent state (not growing/dividing)
G0
The cell is in a growth phase synthesizing mRNA and proteins that are required for DNA synthesis
G1
The cell doubles its DNA
S
The cell grows some more and produces additional proteins needed for division
G2
The cell divides into 2 daughter cells
M
Growth hormone binds to EGFR receptor and stimulates pathways leading to production of Cyclin D
CDK 4, 6
Cyclin D
CDK 4,6/Cyclin D Complexes start Cyclin E, A, B expression pathways
PDB ID 2w9f
CDK 2
Cyclin E
CDK2/Cyclin E Complexes initiatiate the assembly of the pre-replication complexes
PDB ID 1w98
Cyclin A removes Cyclin E from CDK2
Cyclin A
CDK2/Cyclin A Complexes initiate DNA replication and later ensure that only one copy of DNA is created
PDB ID 4eor
CDK1
Cyclin A forms complexes with CDK 1 starting the pathways leading to condensation of chromosomes and assembly of the mitotic spindle
PDB IDs 4eor and 4yc3
Cyclin A
Cyclin A/CDK 1 complexes activate CDK1/Cyclin B complexes
Cyclin B
CDK1/Cyclin B Complexes trigger entry into mitosis
PDB ID 4yc3
STOP
STOP
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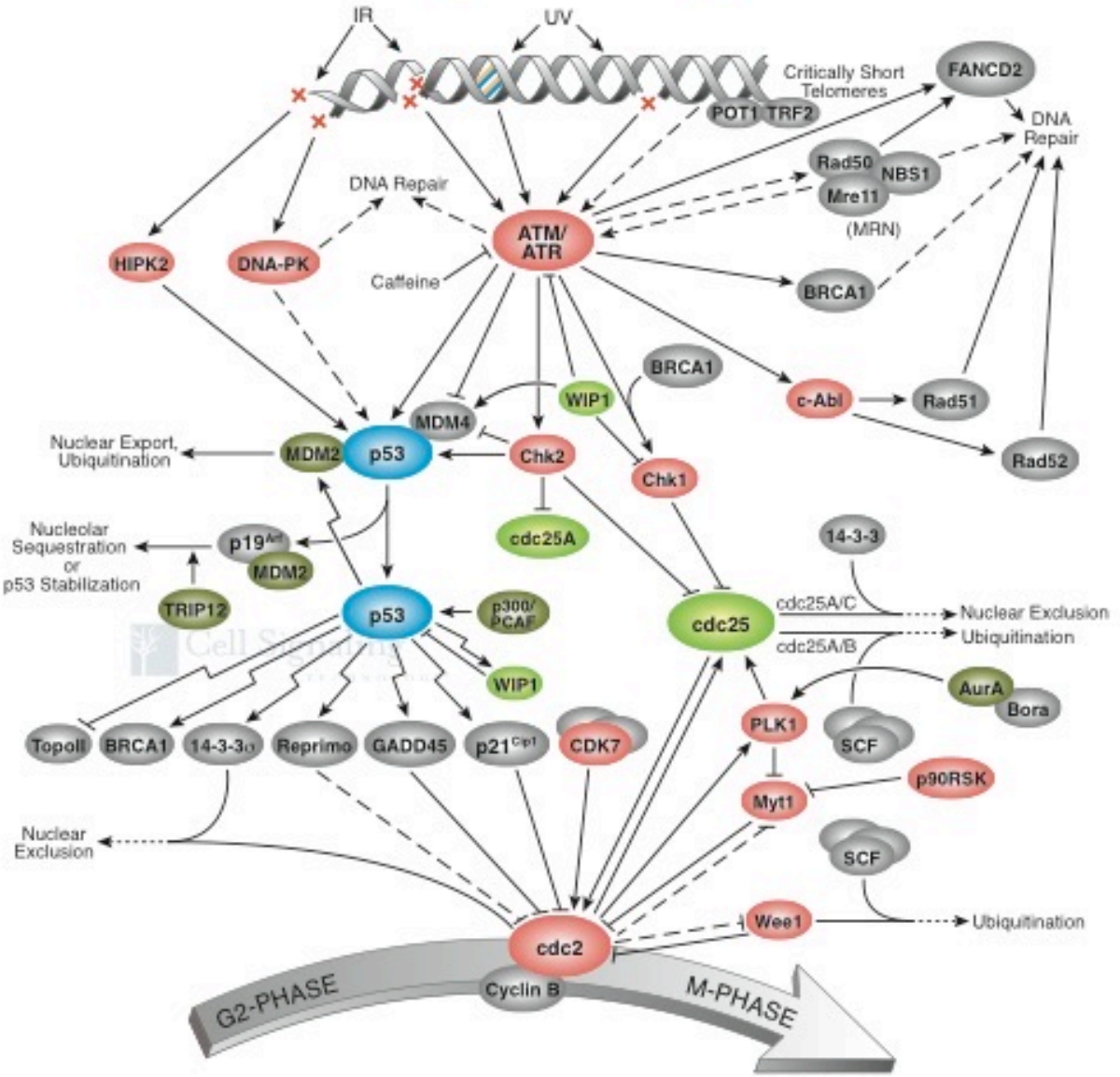
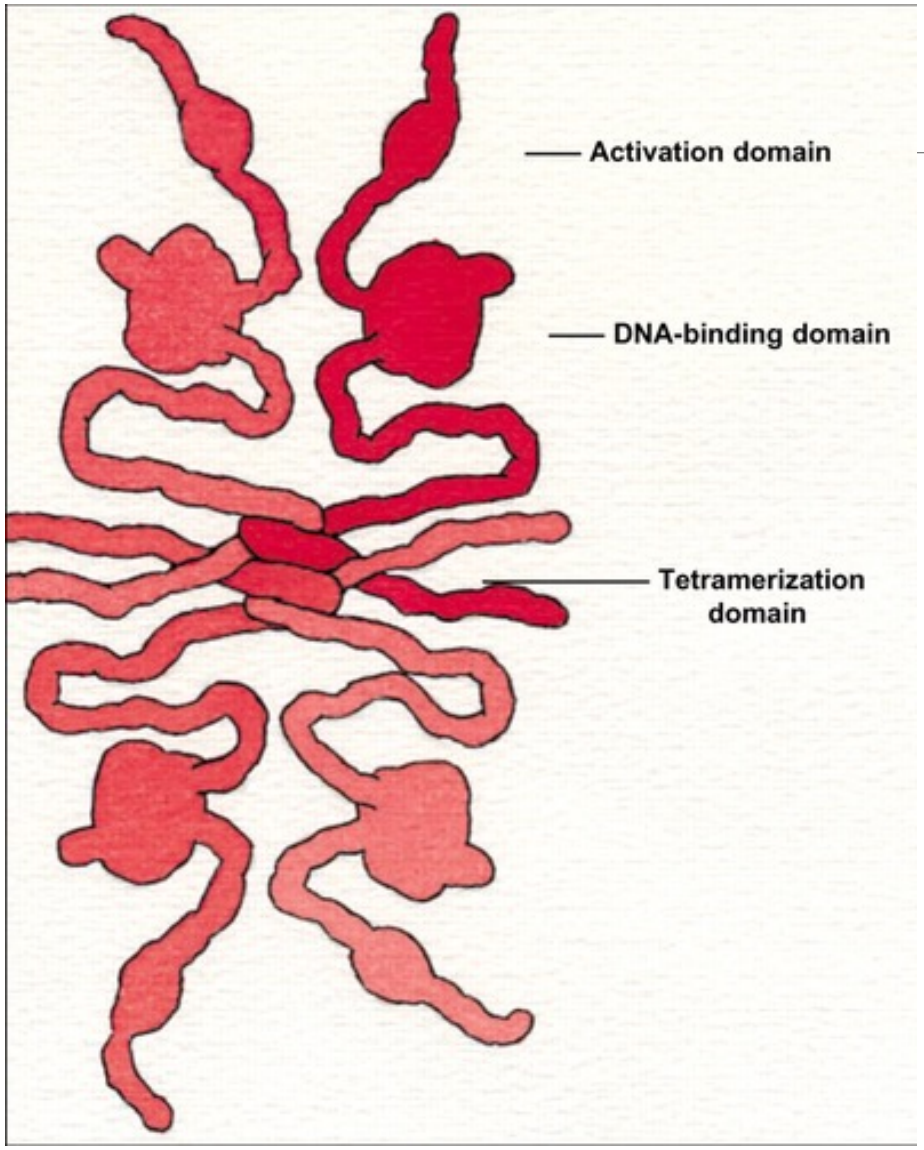
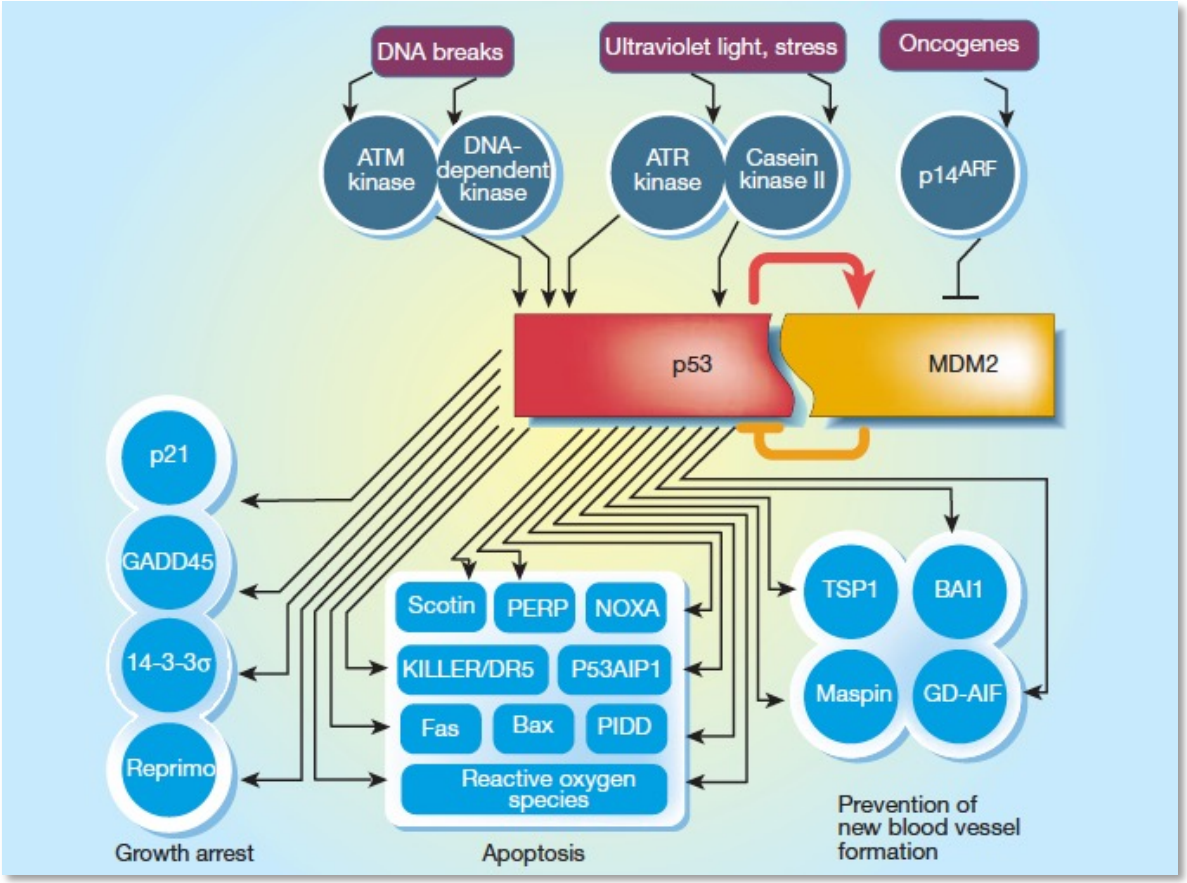
STOP
p21 expressed in response to DNA damage (mediated by p53) inhibits the CDK/Cyclin Complex

Cell Cycle Control:
G2/M DNA Damage Checkpoint





p53 tumor suppressor. *For those who think of proteins as uniformly compact and globular, the structure of p53 will come as a surprise. It is composed of four identical chains, bound together to form a flexible, four-armed starfish. Each chain folds into three structured domains, connected by long, flexible linkers. At the tip of each arm is an activation domain, which binds to the transcriptional machinery and activates gene expression. This domain also binds to the regulatory protein MDM2. At the center of each arm is the largest domain, the globular DNA-binding domain that binds specifically to the target DNA site. These DNA-binding domains are the sites of most of the cancer-causing mutations observed in p53. At the center of the tetramer, the four chains interlock, forming a strong Celtic knot that ties the molecule together.*



The p53 network. Activation of the network (by stresses such as DNA damage, ultraviolet light and oncogenes) stimulates enzymatic activities that modify p53 and its negative regulator, MDM2. This results in increased levels of activated p53 protein. The expression of several target genes is then activated by binding of the activated p53 to their regulatory regions. These genes are involved in processes that slow down the development of tumours. For example, some genes inhibit cell-cycle progression or the development of blood vessels to feed a growing tumour; others increase cell death (apoptosis). **A negative feedback loop between MDM2 and p53 restrains this network.** Many other components of this network, not shown here, have been identified. Similarly, p53 activation results in a variety of other effects, including the maintenance of genetic stability, induction of cellular differentiation, and production of extracellular matrix, cytoskeleton and secreted proteins. The components of the network, and its inputs and outputs, vary according to cell type. p53 is a highly connected 'node' in this network. It is therefore unsurprising that the loss of p53 function is so damaging, and that such loss occurs in nearly all human cancers. (adapted from Vogelstein et al., Nature **408** (2000) 307)

p53 – a tumour suppressor – is an important player in the ATM/ATR network; what happens when it is inactivated?

malfunctioning of the homeostatic regulation of p53

Mechanism of inactivating p53	Effect of inactivation	Typical tumours
Amino-acid-changing mutation in the DNA-binding domain	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes	Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus and many others
Deletion of the carboxy- terminal domain	Prevents the formation of tetramers of p53	Occasional tumours at many different sites
Multiplication of the MDM2 gene in the genome	Extra MDM2 stimulates the degradation of p53	Sarcomas, brain
Viral infection	Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation	Cervix, liver, lymphomas
Deletion of the $p14^{ARF}$ gene	Failure to inhibit MDM2 and keep p53 degradation under control	Breast, brain, lung and others, expecially when p53 itself is not mutated
Mislocalization of p53 to the cytoplasm, outside the nucleus	Lack of p53 function (p53 functions only in the nucleus)	Breast, neuroblastomas

(adapted from Vogelstein et al., Nature **408** (2000) 307)

The tumor microenvironment

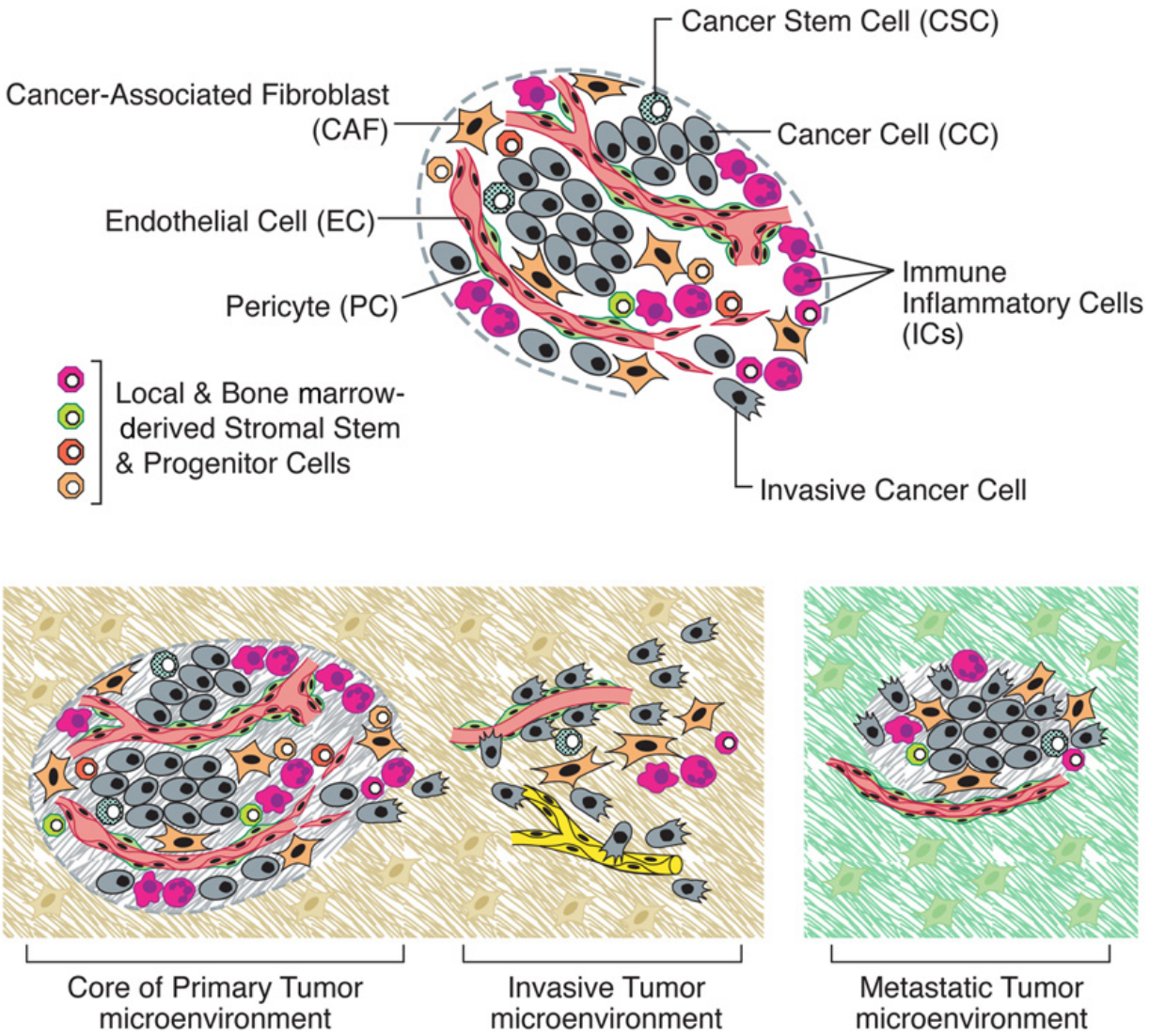
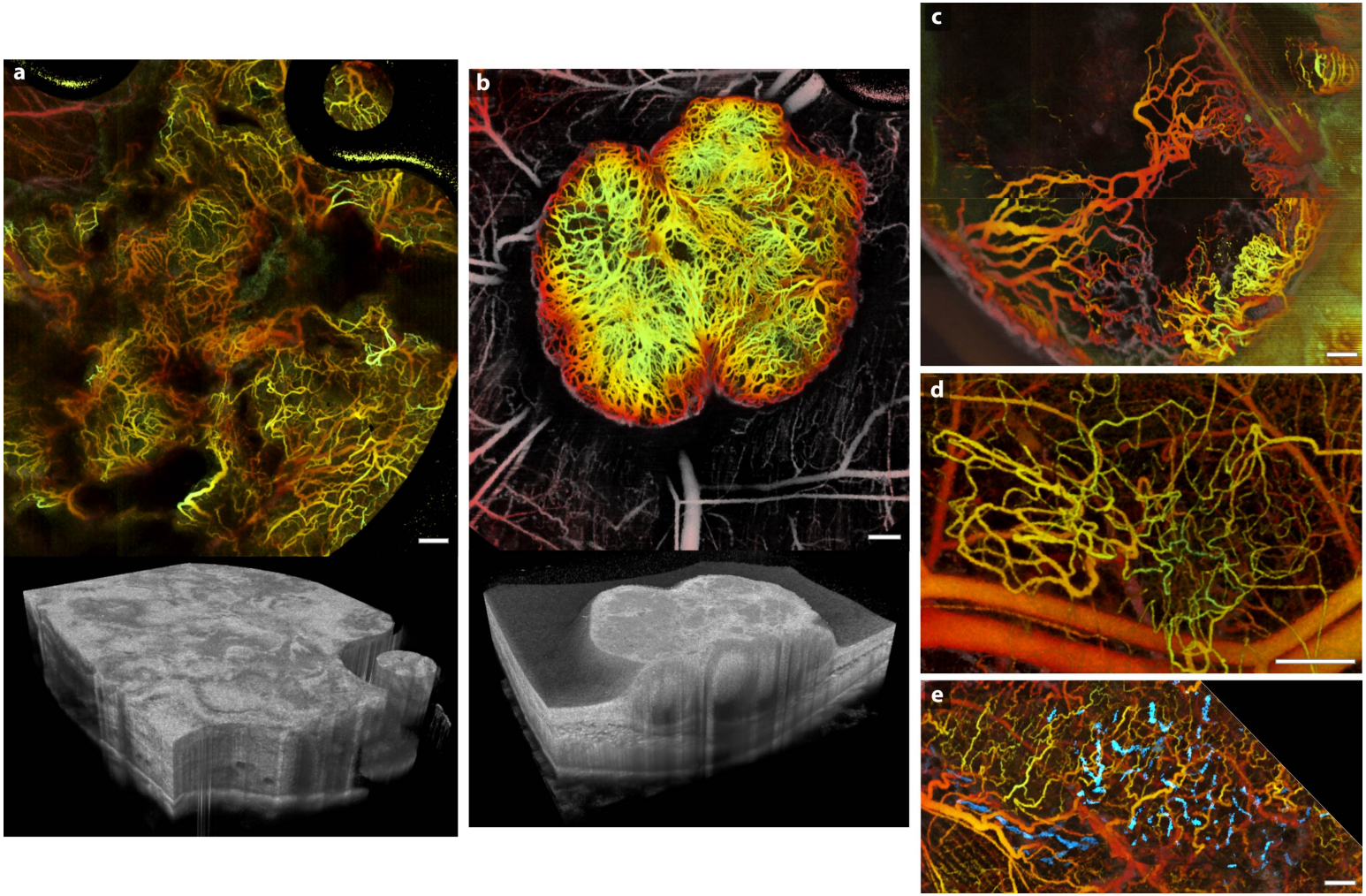


Figure 4. The Cells of the Tumor Microenvironment

(Upper) An assemblage of distinct cell types constitutes most solid tumors. Both the parenchyma and stroma of tumors contain distinct cell types and subtypes that collectively enable tumor growth and progression. Notably, the immune inflammatory cells present in tumors can include both tumor-promoting as well as tumor-killing subclasses.

(Lower) The distinctive microenvironments of tumors. The multiple stromal cell types create a succession of tumor microenvironments that change as tumors invade normal tissue and thereafter seed and colonize distant tissues. The abundance, histologic organization, and phenotypic characteristics of the stromal cell types, as well as of the extracellular matrix (hatched background), evolve during progression, thereby enabling primary, invasive, and then metastatic growth. The surrounding normal cells of the primary and metastatic sites, shown only schematically, likely also affect the character of the various neoplastic microenvironments. (Not shown are the premalignant stages in tumorigenesis, which also have distinctive microenvironments that are created by the abundance and characteristics of the assembled cells.)

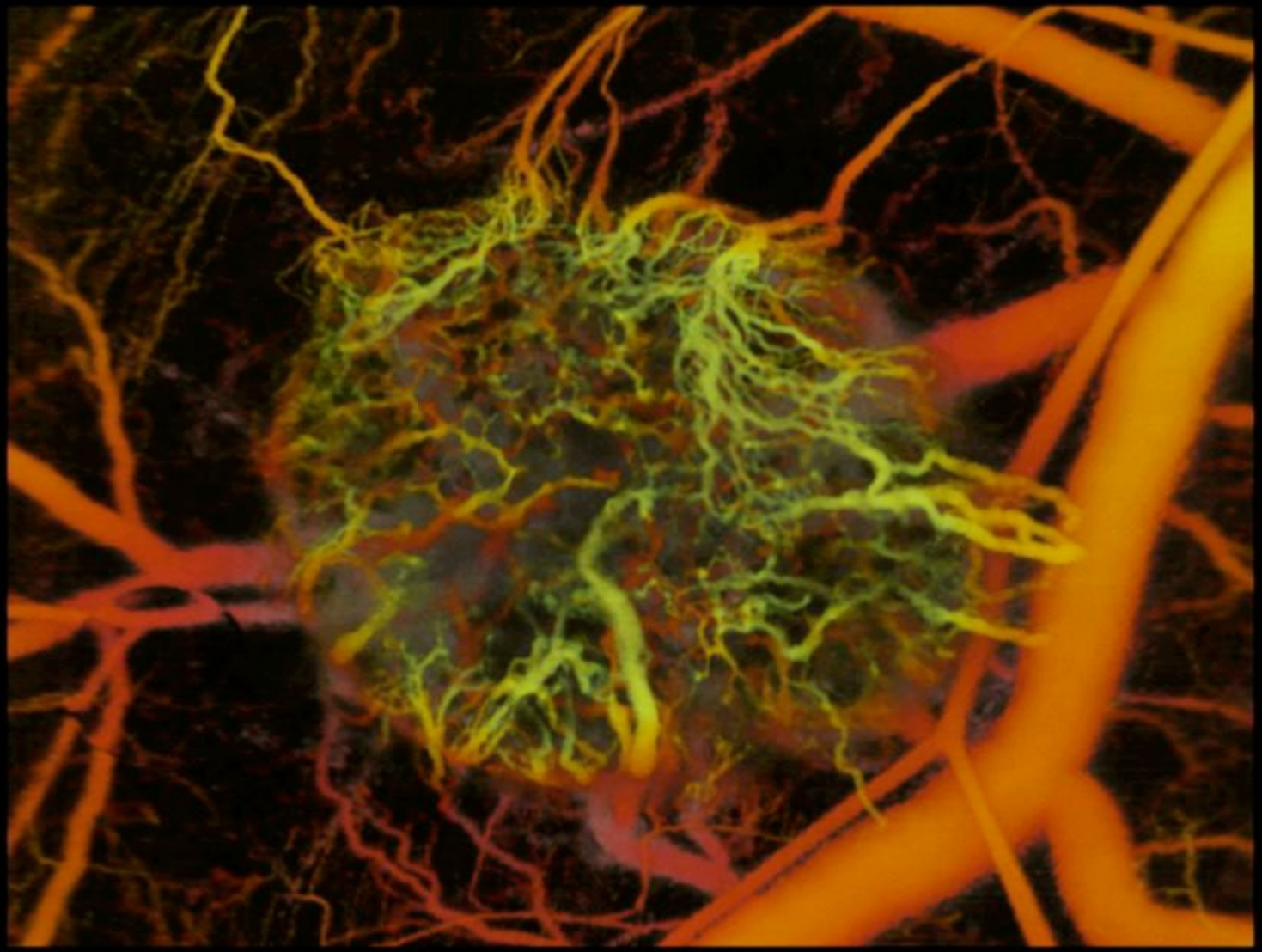


Supplementary Figure 3. OFDI angiography across tumor types and sites. (**a**) A human breast cancer cell line (MDA-MB-361HK) growing in the mammary fat pad window chamber model of a female SCID mouse. Large avascular regions are notable in the vascular image (*top*) and reflected in the topographically diffuse tumor microstructure (*bottom*). (**b**) Tumor vasculature of a human colorectal adenocarcinoma (LS174T) implanted in the dorsal skinfold chamber of a SCID mouse (*top*). Non-viable tissue is evident within the tumor nodules on cross-section (lighter regions) in the tissue scattering intensity image (*bottom*). (**c**) Angiography of a subcutaneous orthotopic human breast tumor xenograft (MDA-MD-231BR) imaged by the skin flap preparation. (**d**) Limited vasculature of the human soft-tissue sarcoma (HSTS-26T) growing orthotopically in the dorsal skinfold chamber. (**e**) Simultaneous vascular and lymphatic imaging of a tumor and nearby normal tissue in the ear of a nude mouse, a commonly utilized model in the study of tumor-associated lymphatics. Scale bars, 500 μm.

from Vakoc et al., Nature Medicine **15** (2009) 1219

Doppler OFDI reveals the kinetic response to VEGFR-2 blockade (DC101) in a murine mammary carcinoma (MCaIV) tumor

Time (relative to DC101, hrs) : -8
Tumor Volume (mm^3) : 3.60
Intratumoral Mean Vessel Diameter (μm) : 55.2



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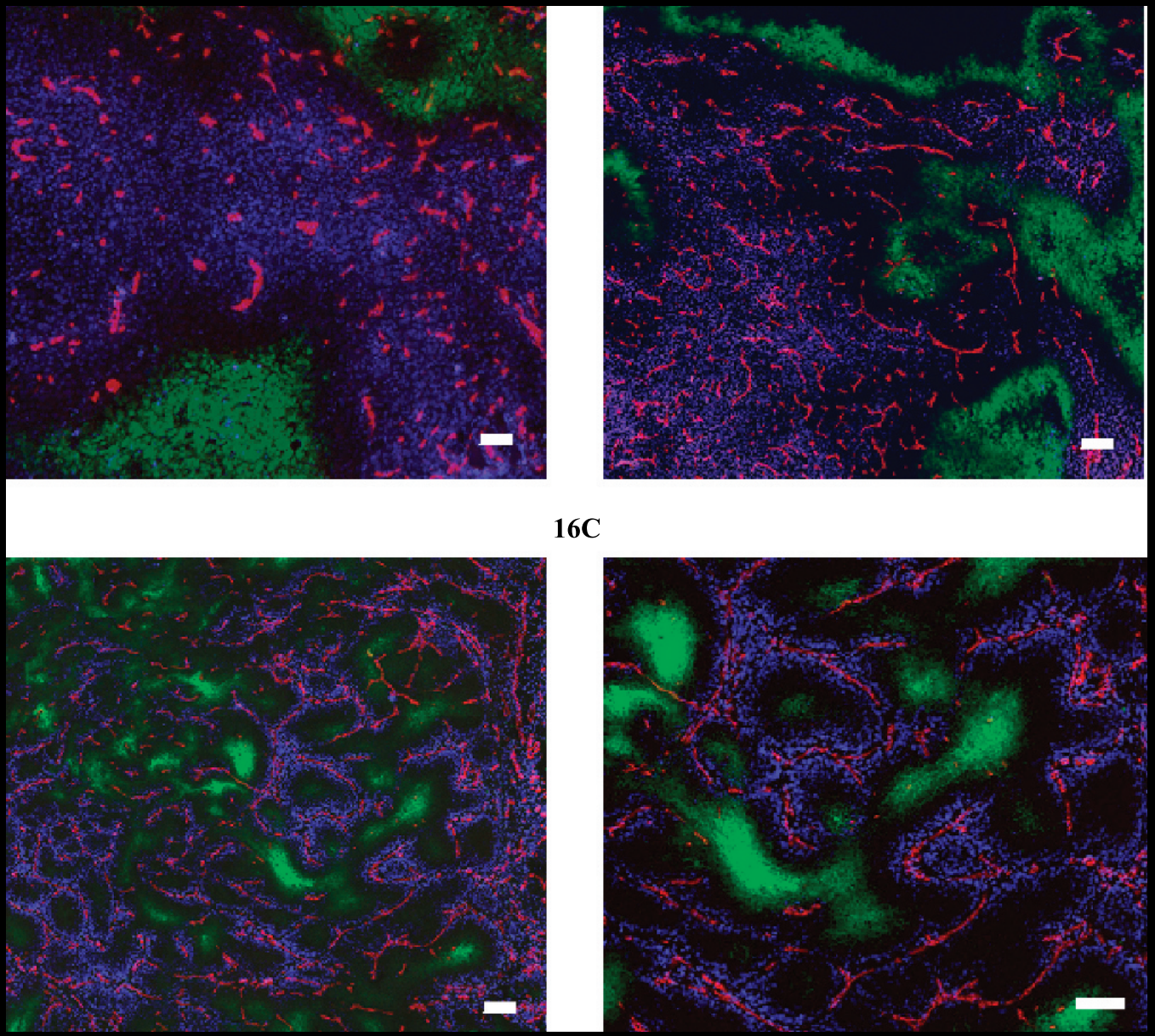
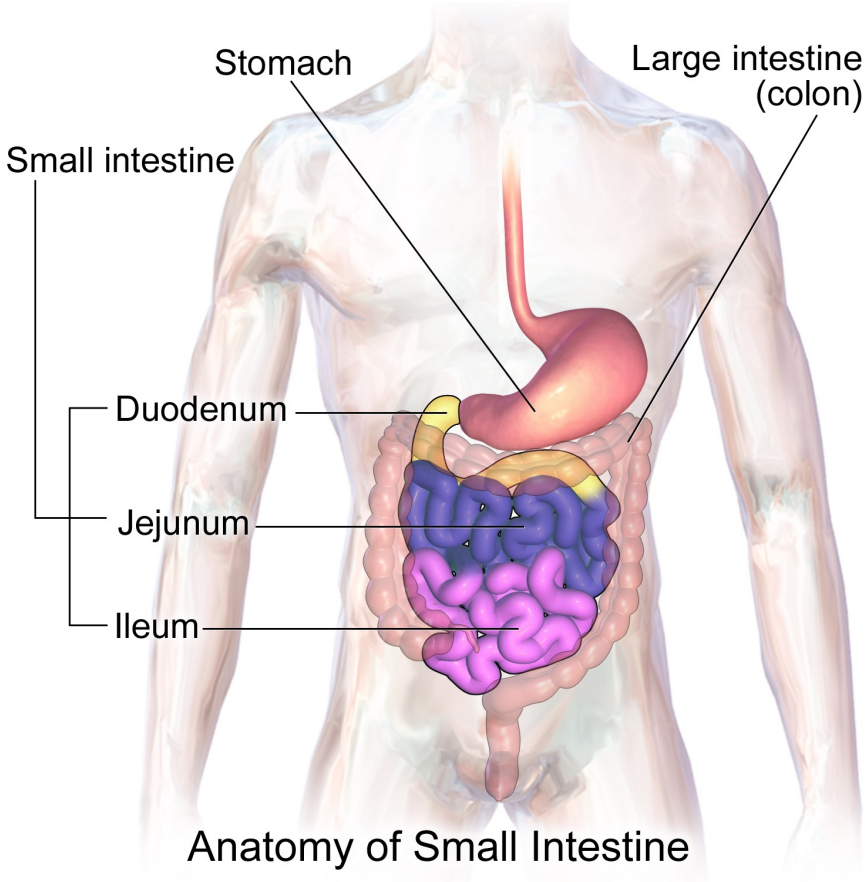


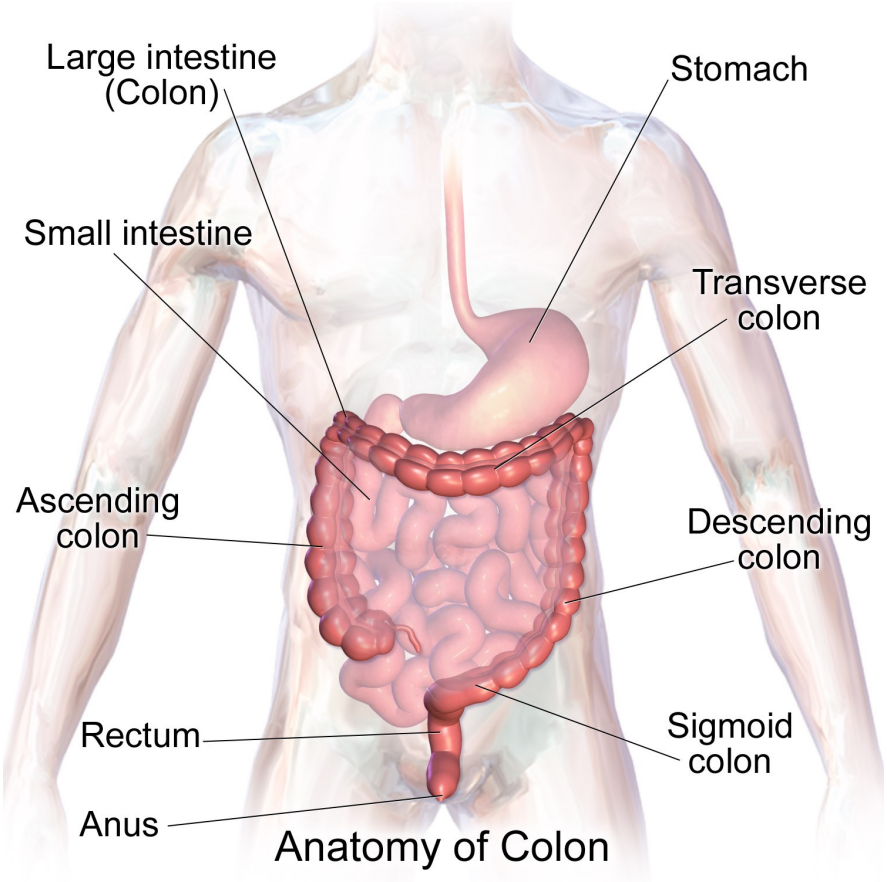
Representative three-color composite images showing the perivascular distribution of doxorubicin (blue) in relation to blood vessels (red) and hypoxic regions (green) in tissue sections from PC-3, 16C, and EMT6 tumors. Bar, 100 μm.

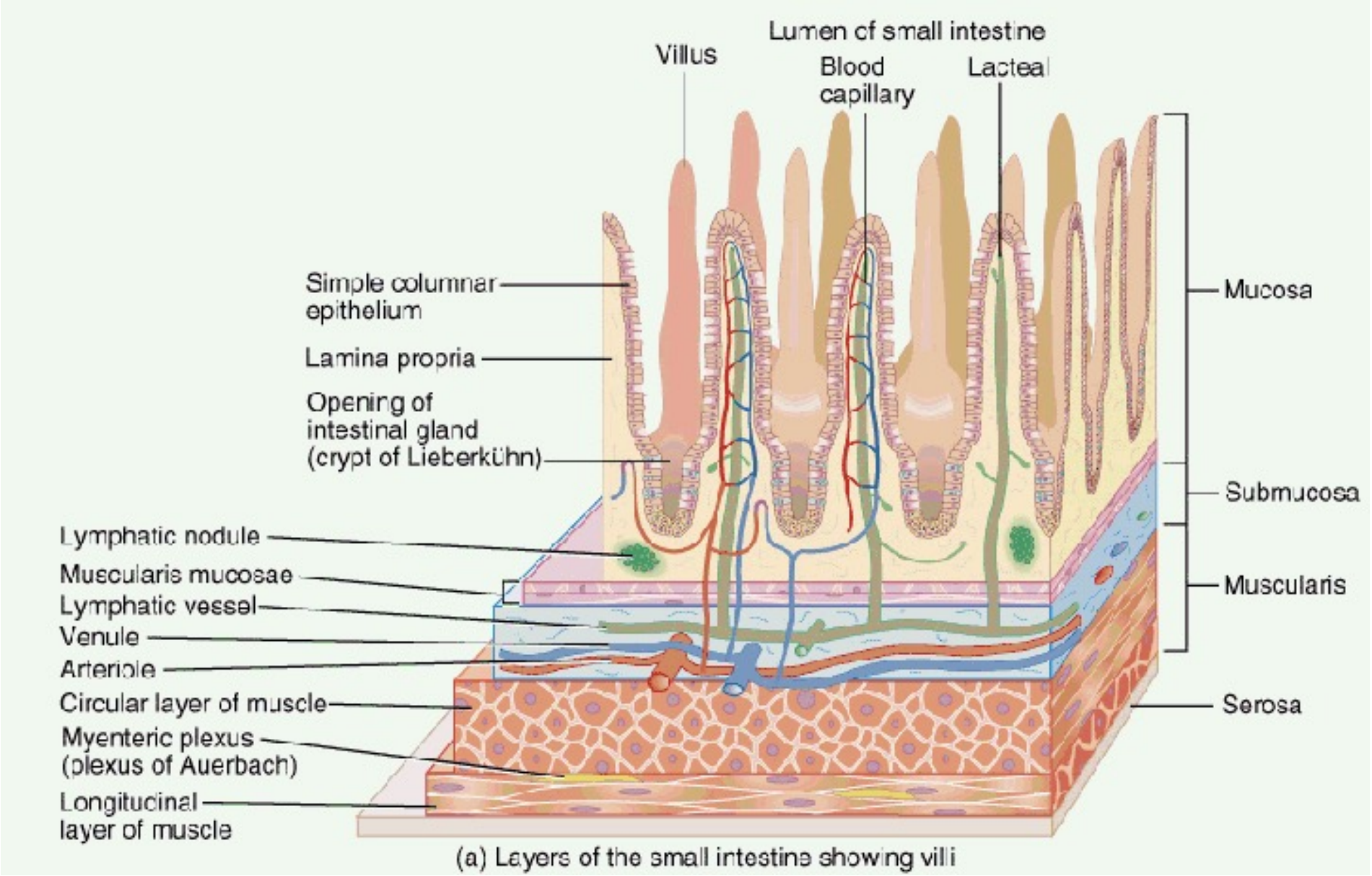
from Primeau et al, Clin Cancer Res **11** (2005) 8782

Mulstistage model of colorectal cancer

The human intestine







(a) Layers of the small intestine showing villi

Mulstistage model of colorectal cancer

A simple mathematical model

$$p(\text{onset of illness at age } a) \approx b\,a^{k}$$

this constant incorporates all the biological parameters

number of stages

In the epidemiology of colorectal cancer, $k \approx 5$ or 6

Normal mutation rate is low, ~ 10^{-9} per base, per division.

This means that in a 1000 base-long gene, the mutation rate is $u \approx 10^{-6}$ per division.

Then the probability that in *d* divisions the gene is not mutated, is

$$p(\text{no mutation in gene}) \approx (1-u)^d$$

and therefore, the probability that it is mutated is

$$p(\text{gene is mutated})$$

$$= p(\text{at least one mutation in gene}) \approx 1-(1-u)^d$$

Then, if there are *N* compartments with *m* cells each that are at risk of reaching the critical mutation level, the probability that no cell reaches this critical level is

$$p\left(\begin{array}{l}\text{no cell in the } N \text{ compartments}\\ \text{reaches the critical level}\\ \text{of mutations}\end{array}\right)=\left\{1-\left[1-(1-u)^{d}\right]^{k}\right\}^{Nm}$$

and finally, the probability of the onset of illness is

$$p\left(\text{onset of illness after } d \text{ divisions}\right)=$$

$$=p\left(\begin{array}{l}\text{at least one cell in the } N\\ \text{compartments reaches the}\\ \text{critical level of mutations}\end{array}\right)=1-\left\{1-\left[1-(1-u)^{d}\right]^{k}\right\}^{Nm}$$

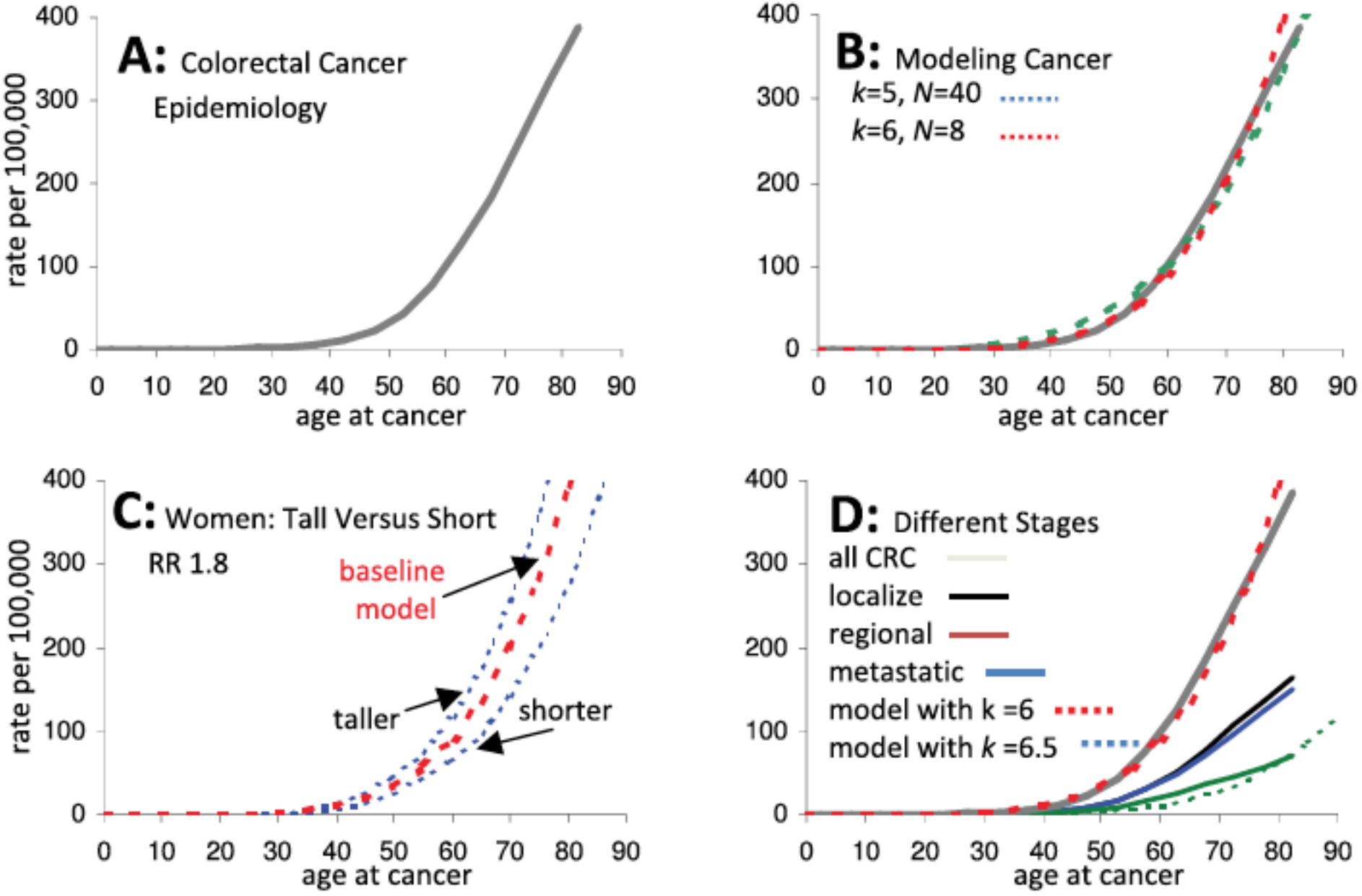
$$p\left(\text{onset of illness after } d \text{ divisions}\right) = 1 - \left\{1 - \left[1 - \left(1-u\right)^{d}\right]^{k}\right\}^{Nm}$$

$$\approx 1 - \left\{1 - \left[du\right]^{k}\right\}^{Nm}$$

$$\approx Nm\left(du\right)^{k}$$

Since $d \approx a/T$ (where T is the duplication time)

$$p\left(\text{onset of illness at age } a\right) \approx Nm\left(\frac{a}{T}u\right)^{k} = \left(\frac{Nmu^{k}}{T^{k}}\right)a^{k} = ba^{k}$$



from P .Calabrese and D. Shibata, "A simple algebraic cancer equation: calculating how cancers may arise with normal mutation rates", BMC Cancer **10** (2010) 3

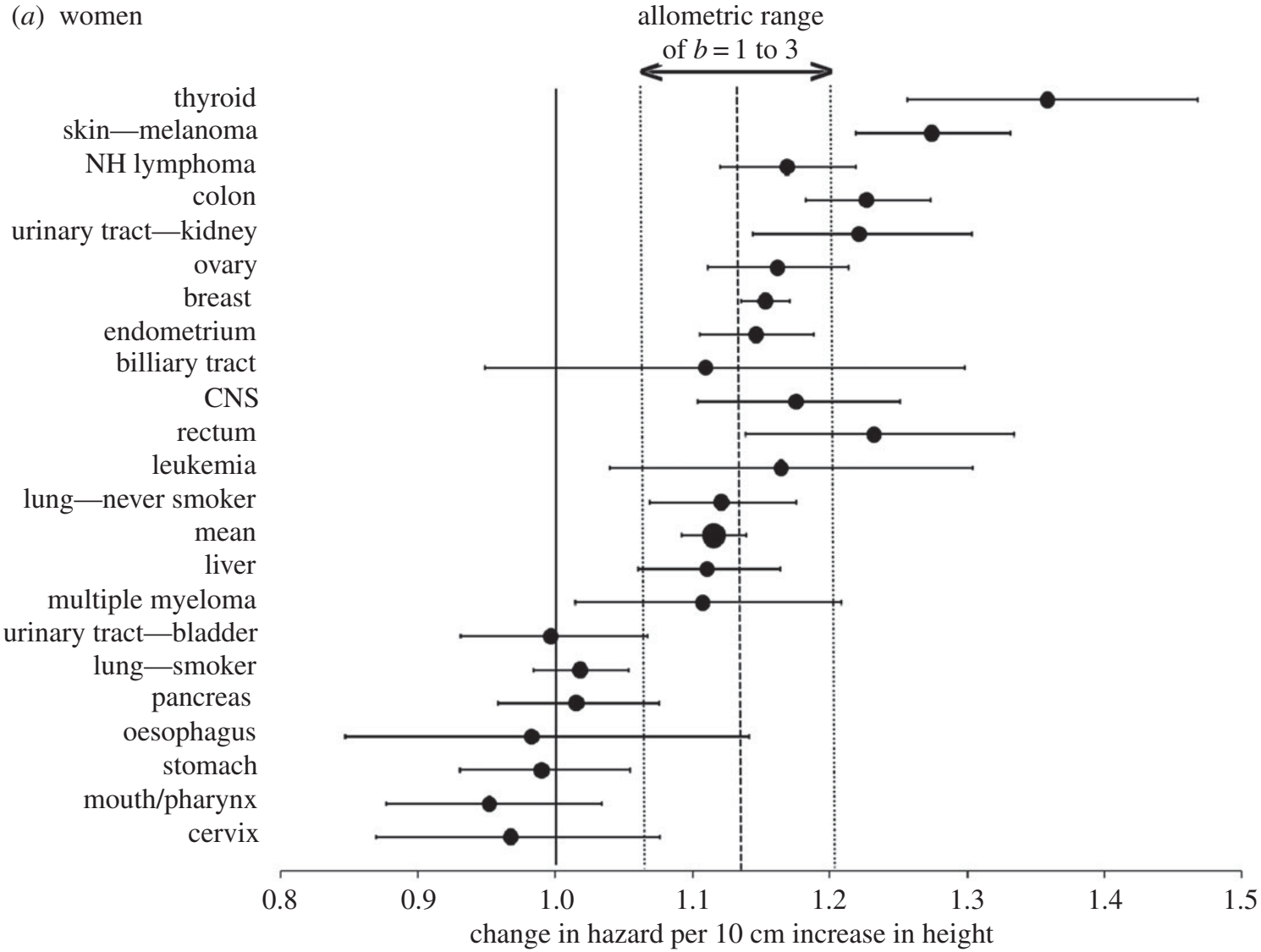
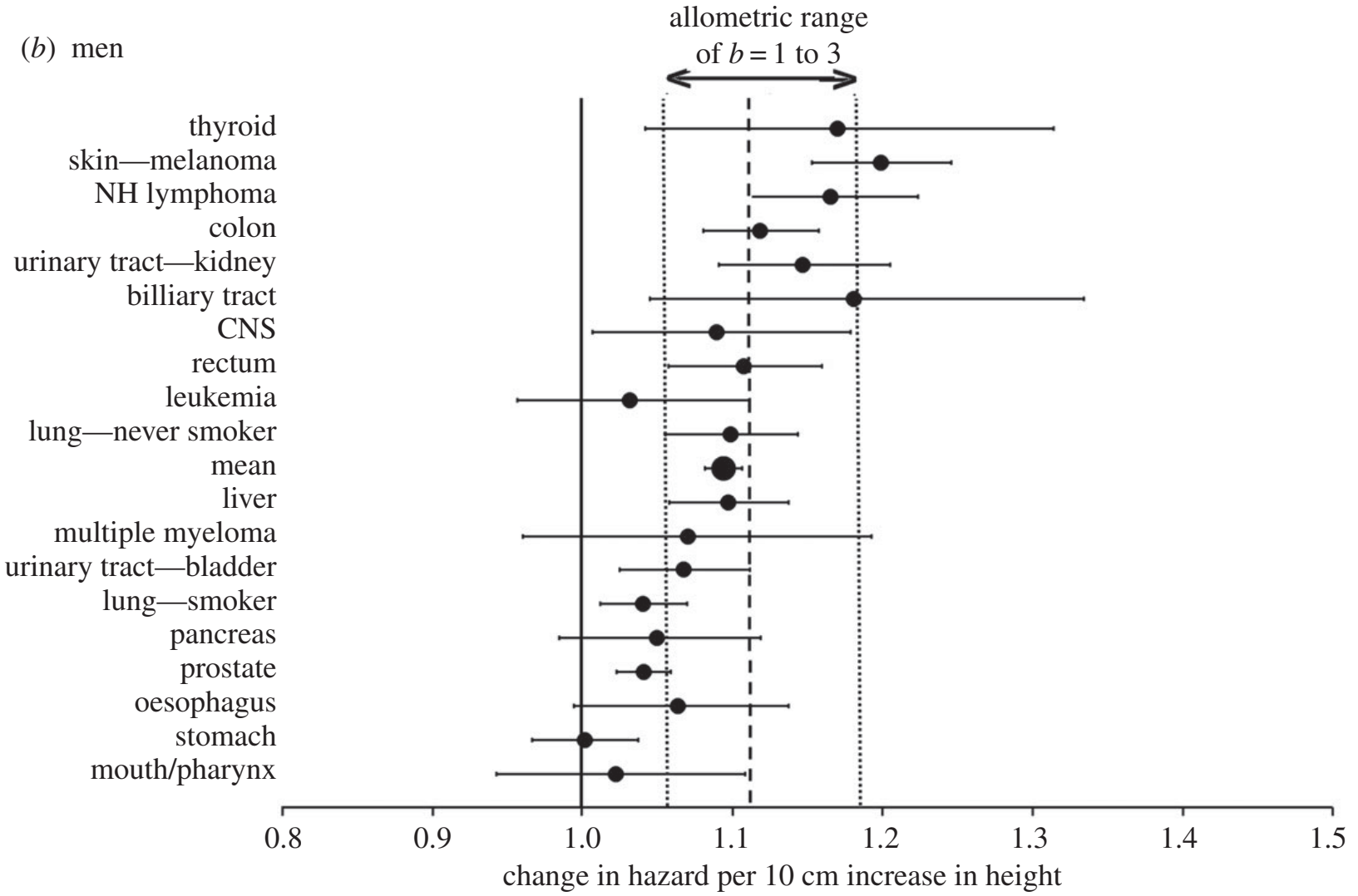


Figure 2. A comparison of the observed and predicted effect of height on the risk of specific cancers: the observed hazard ratio (HR_{10}) and 95% confidence interval linking a 10 cm increase in height to the increased risk of specific cancers, showing only cancers included in at least two of the target studies (for women [22–25]; for men [23–25]). The vertical lines illustrate: no effect of height ($HR_{10} = 1.00$; solid line); the average HR_{10} predicted from the multistage model based on the allometry of human height to overall body mass, which is used as a proxy for cell number (dashed line); and (3) the predicted effect based on the expected extremes of organ cell number allometry to height: linear, $b = 1$ (lower dotted line); and volumetric, $b = 3$ (upper dotted line). For data sources, see electronic supplementary material, table S1.



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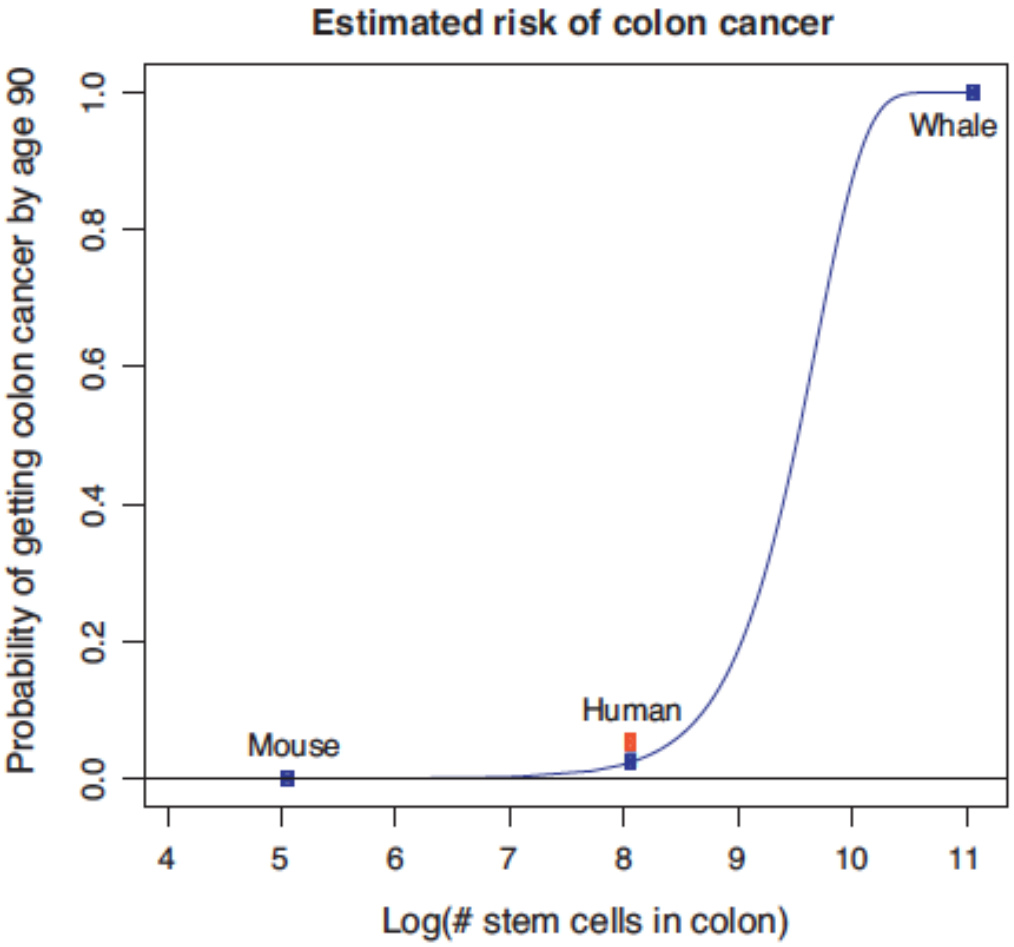
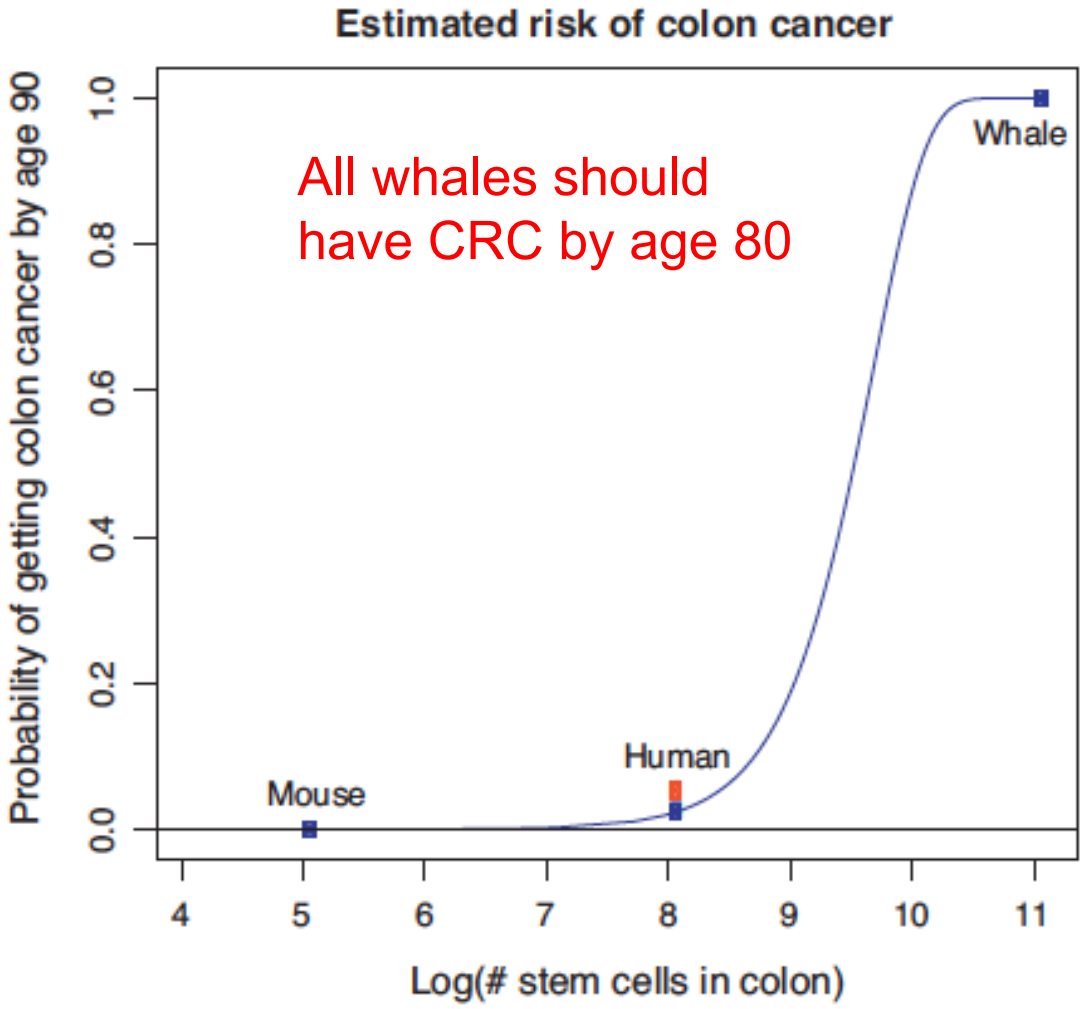
If the probability of colon cancer risk grows with the number of cells, i.e., with body size, how large is the risk for a whale?



Assuming all other parameters are equal, larger animals should have a greater lifetime risk of developing cancer compared with smaller organisms.

Blue dots for mouse, human and whale indicate the estimated risk of CRC occurring within 90 years of life, given the approximate number of cells in a human colon, 1000 times fewer cells to represent the mouse and 1000 times more cells to represent the whale.

The red dot indicates the lifetime risk of colon cancer according to the American Cancer Society, which is approximately 5.3% for men and women averaged together.



A. F. Caulin and C. C. Maley, "Peto's Paradox: evolution's prescription for cancer prevention", Trends in Ecology and Evolution **26** (2011) 175

Parameter	Value*	Meaning
u	3×10^{-6}	Mutations per gene per cell division
d	8212.5	Divisions after 90 years, at a rate of one division every 4 days
k	6	Rate-limiting mutations needed to get cancer
N	8	Effective stem cells per crypt
m	$[1.5 \times 10^{3}–1.5 \times 10^{10}]$	Crypts in the colon

However, whales *are not* more cancer-prone than humans ...

Why cancer is not actually more frequent in large animals?

More cells means higher rate of potentially dangerous mutation events.

The near-constancy of tumor rate in animals is called Peto's Paradox.

Cancer deaths on total of all deaths

- mice in lab conditions: 46%
- dogs: 20%
- humans: 25%
- beluga whale: 18%

Although the number of cells differs by orders of magnitude and the lifespan also differs, there are no big differences between these values.

A list of possible answers to Peto's paradox

- Lower mutation rates in large animals (better error correction mechanisms)
- Redundancy of tumor suppressor genes
- Lower selective advantage of mutant cells
- More efficient immune system
- More sensitive or efficient apoptotic processes
- Increased contact inhibition
- Shorter telomeres
- ...

At least one solution to Peto's paradox may have been found. Elephants have 20 copies of a gene called *p53* (or, more properly, *TP53*), in their genome, where humans and other mammals have only one. The gene is known as a tumour suppressor, and it snaps to action when cells suffer DNA damage, churning out copies of its associated p53 protein and either repairing the damage or killing off the cell.

It was found that elephants produce extra copies of the p53 protein, and that elephant blood cells seem exquisitely sensitive to DNA damage from ionizing radiation. The animals' cells carry out apoptosis in response to DNA damage at much higher rates than do human cells. Instead of repairing the DNA damage, compromised elephant cells seem to have evolved to kill themselves to nip nascent tumours in the bud.

(from Nature News, Oct. 8th 2015, see also https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-017-0401-7 and https://www.pnas.org/content/116/6/1825)

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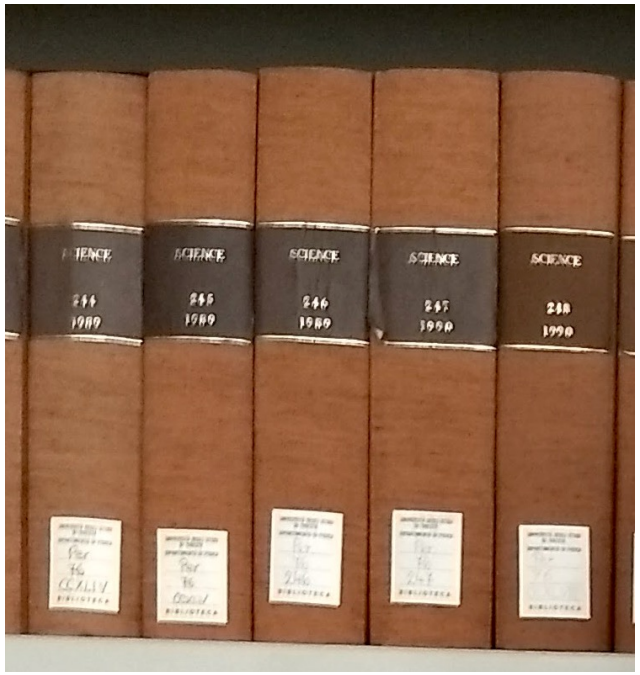

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http://sbcrowe.net/lists/journals/

https://academic.oup.com/oncolo

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Stephanie D Small, Kelcey A Bland, Julia N Rickard, Amy A Kirkham

The Oncologist, Volume 27, Issue 1, January 2022, Pages 1–3,
https://doi.org/10.1093/oncolo/oyab009

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Clinical Implication of Simultaneous Intensity-modulated Radiotherapy Boost to Tumor Bed for Cervical Cancer with Full-thickness Stromal Invasion

Zongkai Zhang, Long Jiang, Rui Bi, Xiaohua Wu, Jun Zhu, Guihao Ke Author Notes

The Oncologist, Volume 27, Issue 1, January 2022, Pages e53–e63,
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Abstract

Objective

The objective of this study was to retrospectively explore the clinical implications of simultaneous intensity-modulated radiotherapy (IMRT) boost to the tumor bed in cervical cancer with full-thickness stromal invasion (FTSI).

Patients and Methods

Patients diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB and IIA cervical cancer with confirmed FTSI were included. Patients received pelvic IMRT from a dose of 50.4 Gy in 28 fractions with (or without) a simultaneous integrated boost (SIB) to 58.8 Gy in 28 fractions for the tumor bed. The progression-free survival (PFS), overall survival (OS), and pelvic-PFS (p-PFS) were analyzed using the Kaplan–Meier method, and independent prognostic factors were explored by Cox regression analyses.

The Molecular Perspective: Cisplatin

David S. Goodsell

The Oncologist, Volume 11, Issue 3, March 2006, Pages 316–317,
https://doi.org/10.1634/theoncologist.11-3-316
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After completing this course, the reader will be able to:

1. Describe the structure and action of cisplatin.

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