

Le développement des cancers

Pr. Boris BARDOT

Institut Curie – Centre de Recherche

Bâtiment 110

boris.bardot@curie.fr

ETYMOLOGY

- **Tumorigenesis** *Latin : tumere (to swell)*
- **Oncogenesis** *Grec : oncos (swelling)* **Galien (130-200 ap. J.C.)**
- **Carcinogenesis** *Grec : crab* **Hippocrates (460-370 av. J.C.)**

CANCERS

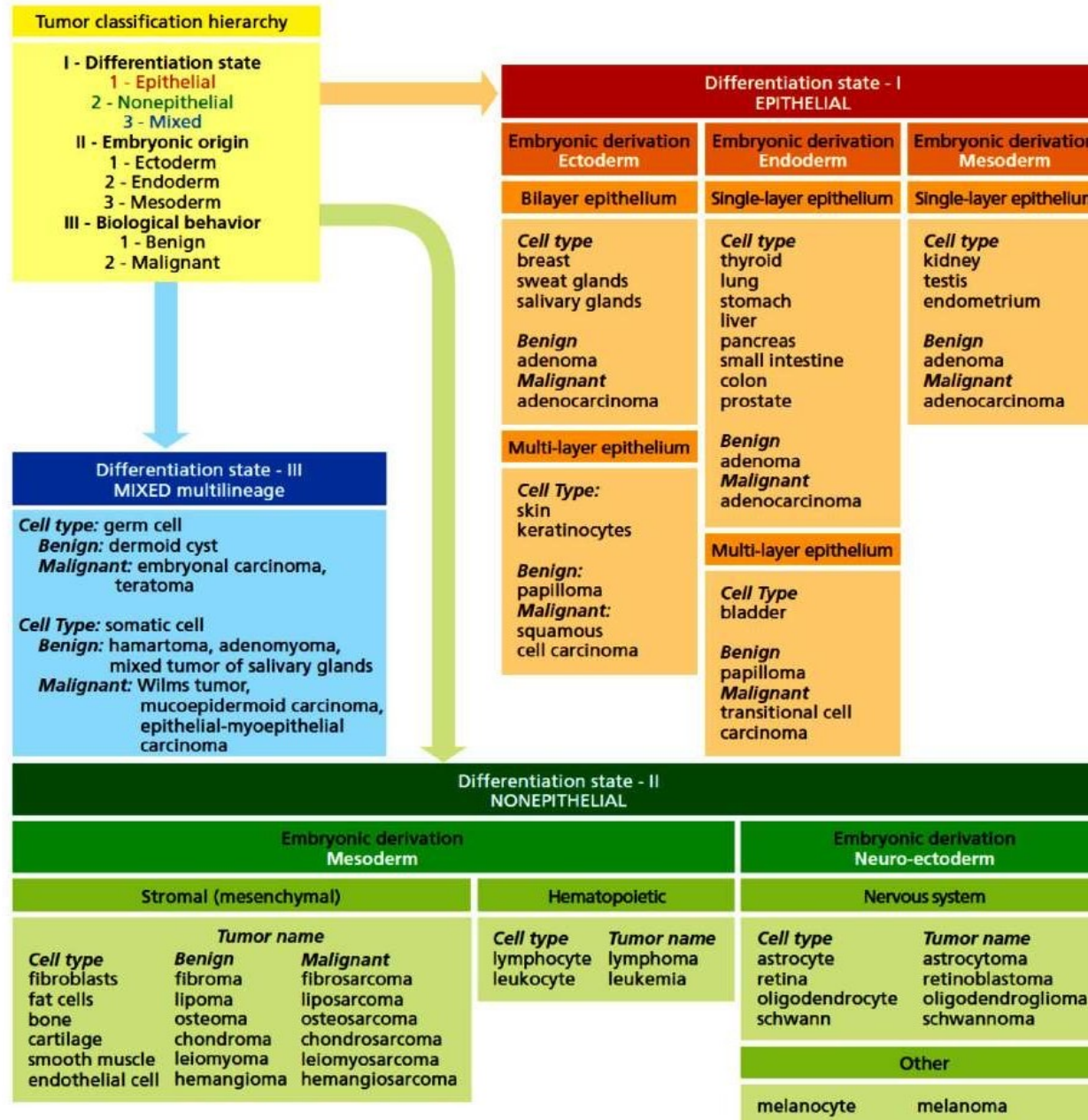


Fig.2.18 The Biology of Cancer, 2014

I –Origin and evolution of cancers : A progressive cell disease

Hyperplasia

Cells divide more rapidly than normal

Dysplasia

Altered cells with increased growth potential

In situ cancer

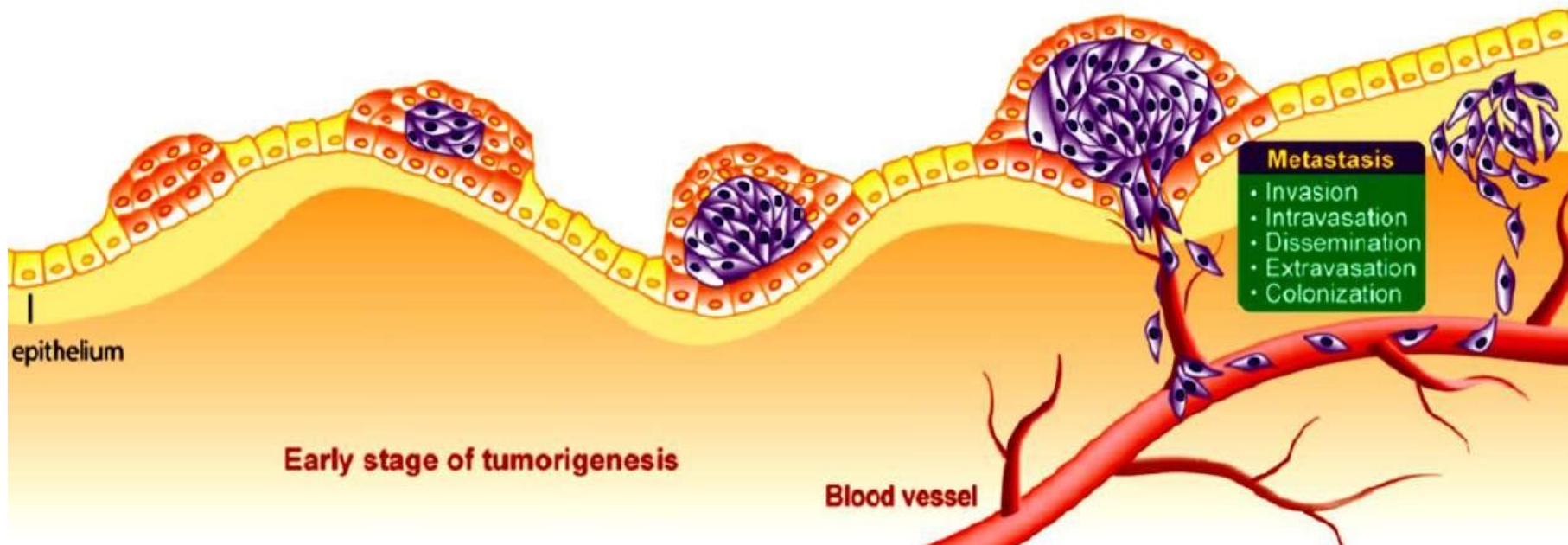
Cells rapidly grow and stay in one place

Invasive cancer

Cells invade normal tissue and enter blood and lymph

Metastasis

Metastases form at distant sites



Une maladie cellulaire progressive

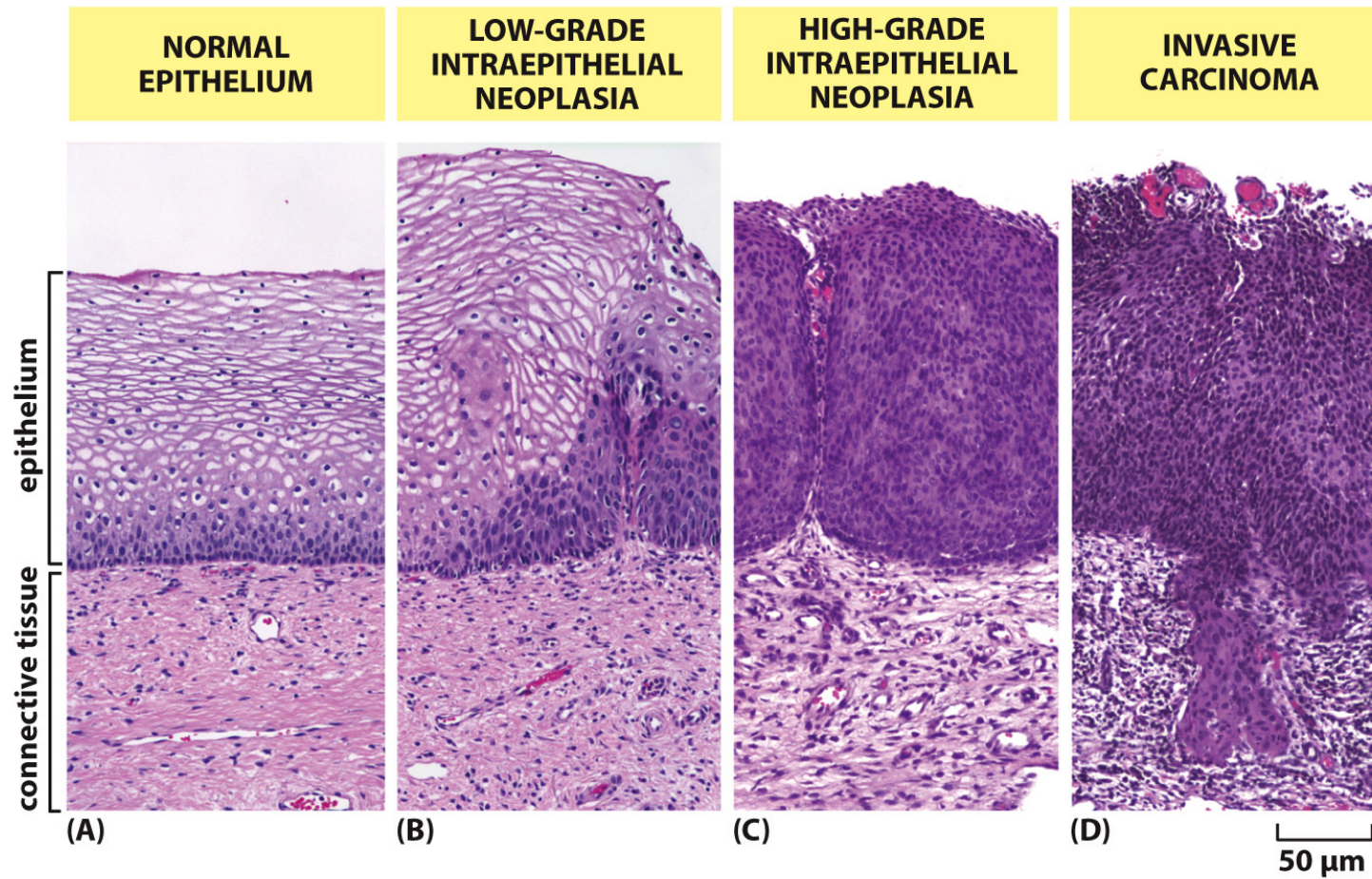
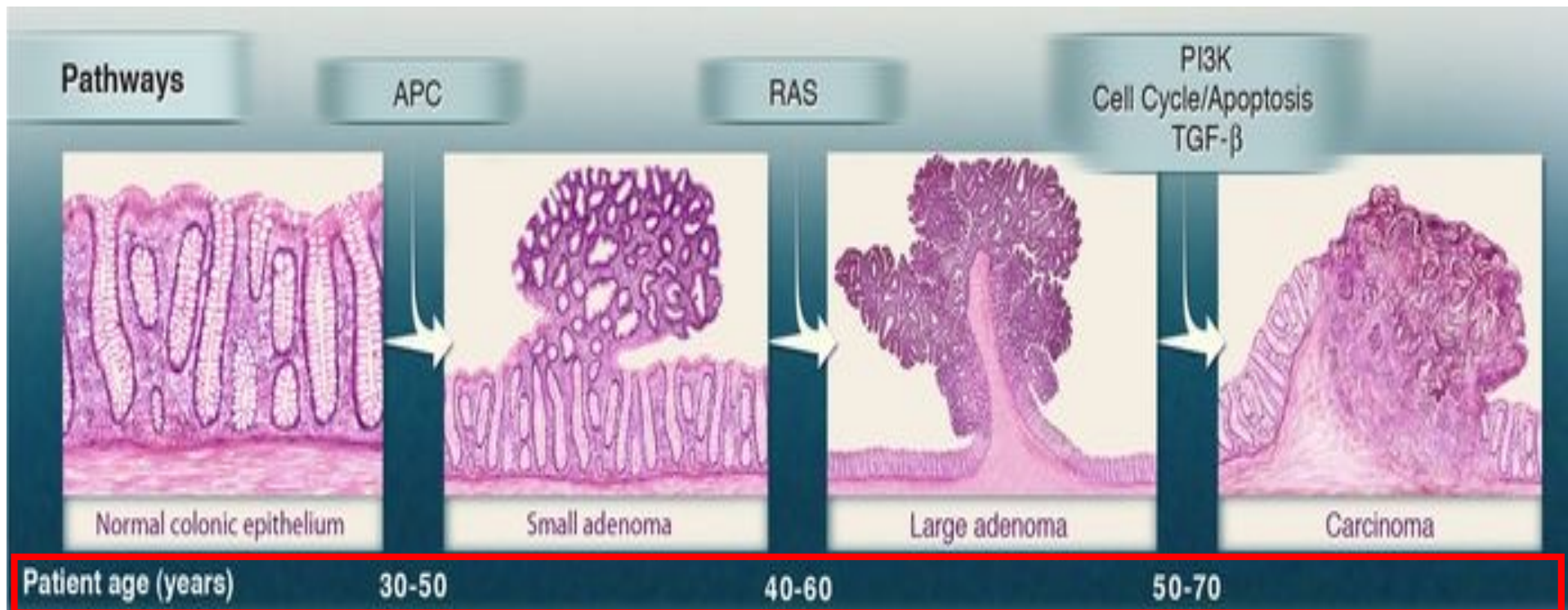


Figure 20-8 Molecular Biology of the Cell 6e (© Garland Science 2015)

Une maladie causée par des altérations génétiques

The accumulation of genome alterations occurs over the evolution of pre-cancerous lesions



4-10 driver mutations to come to a carcinoma

I –Origin and evolution of cancers : genetic aspects

A –Tumors are of monoclonal origin....

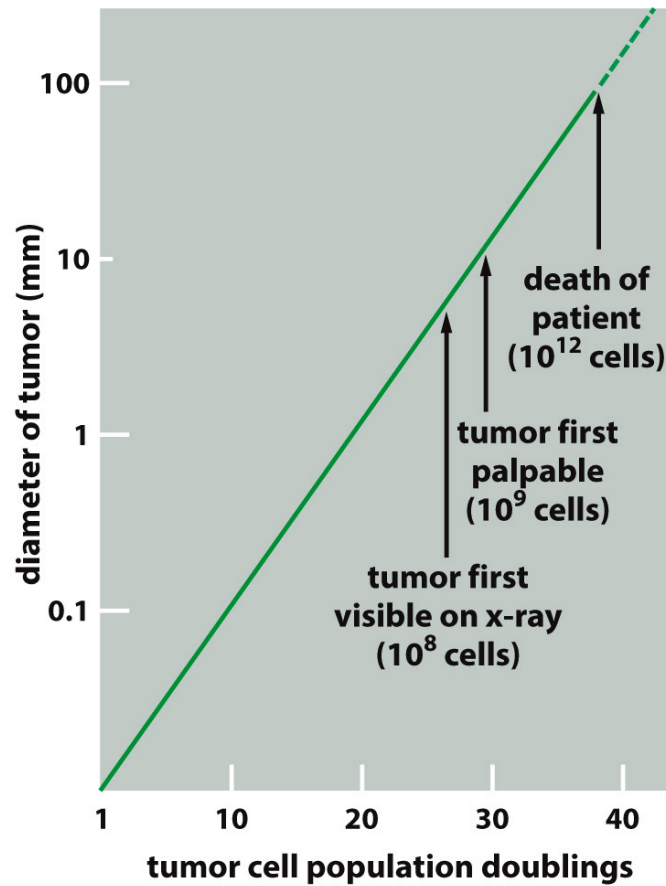


Figure 20-4 Molecular Biology of the Cell 6e (© Garland Science 2015)

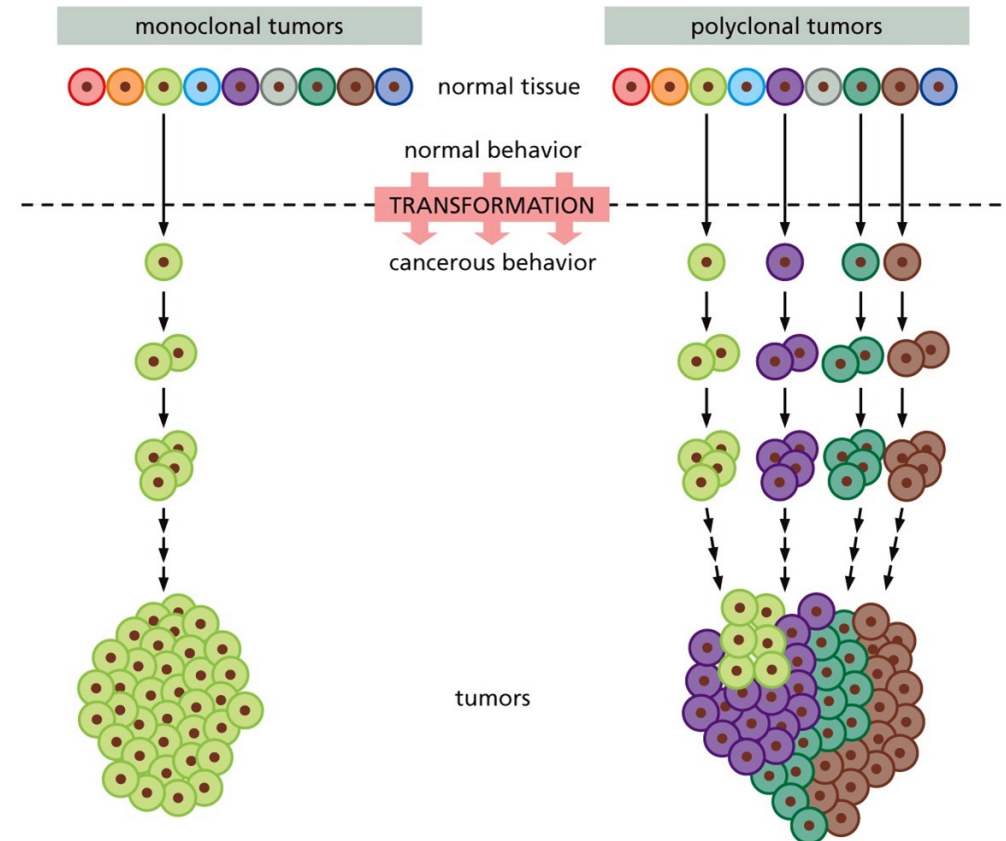


Figure 2.19 The Biology of Cancer (© Garland Science 2014)

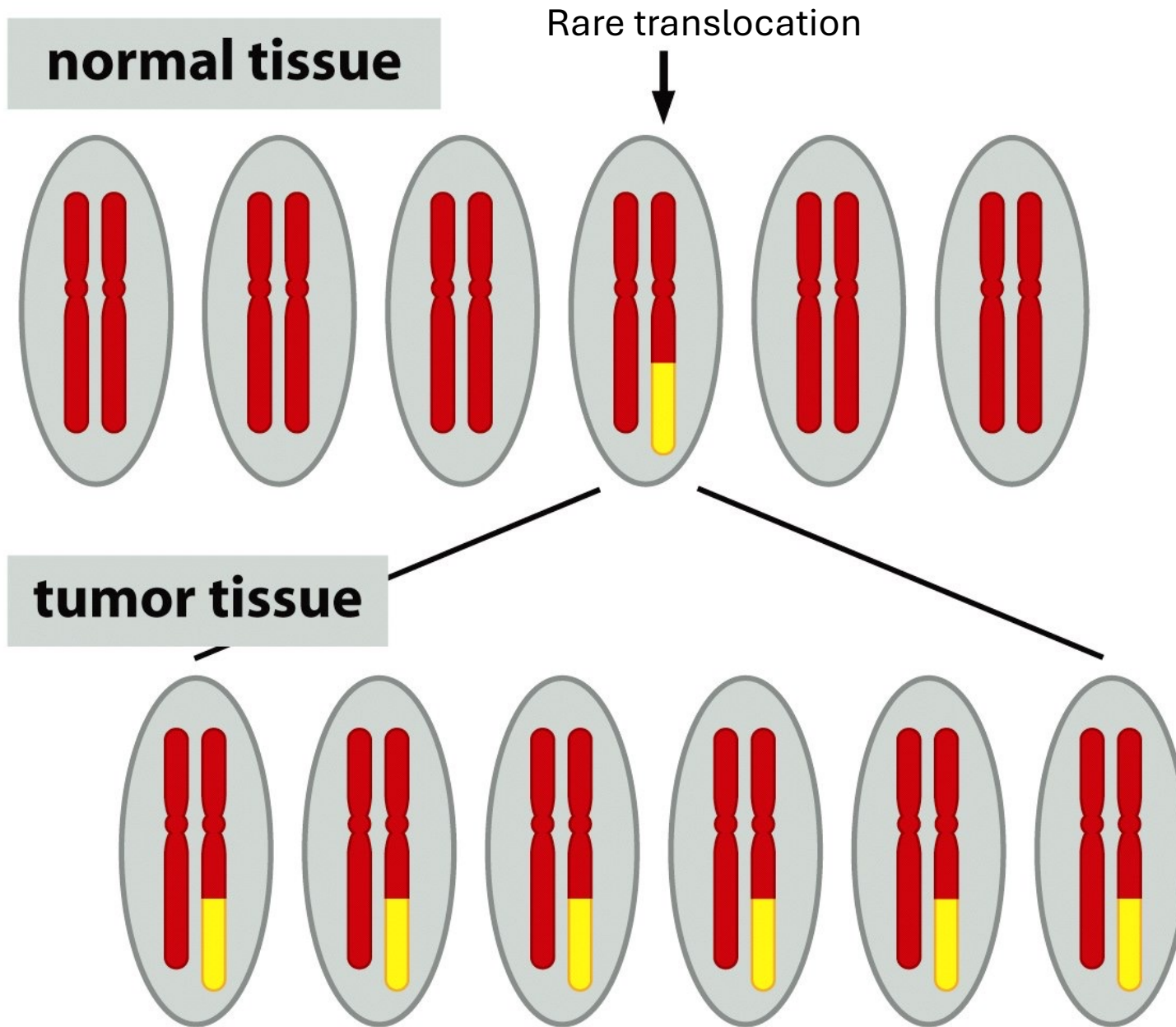
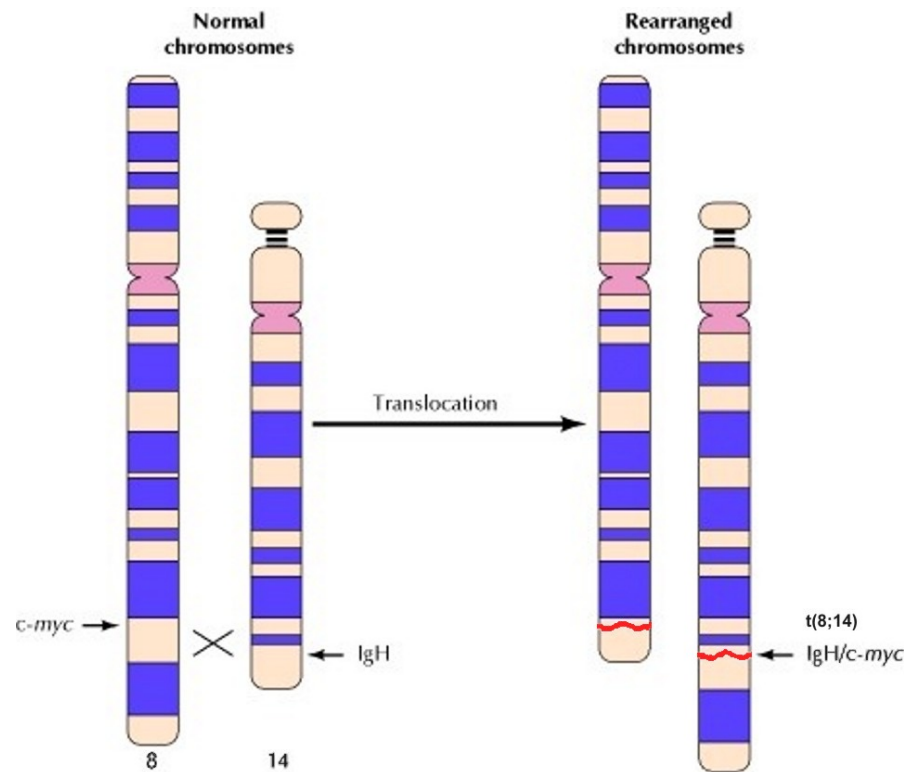


Figure 2.19b *The Biology of Cancer* (© Garland Science 2007)

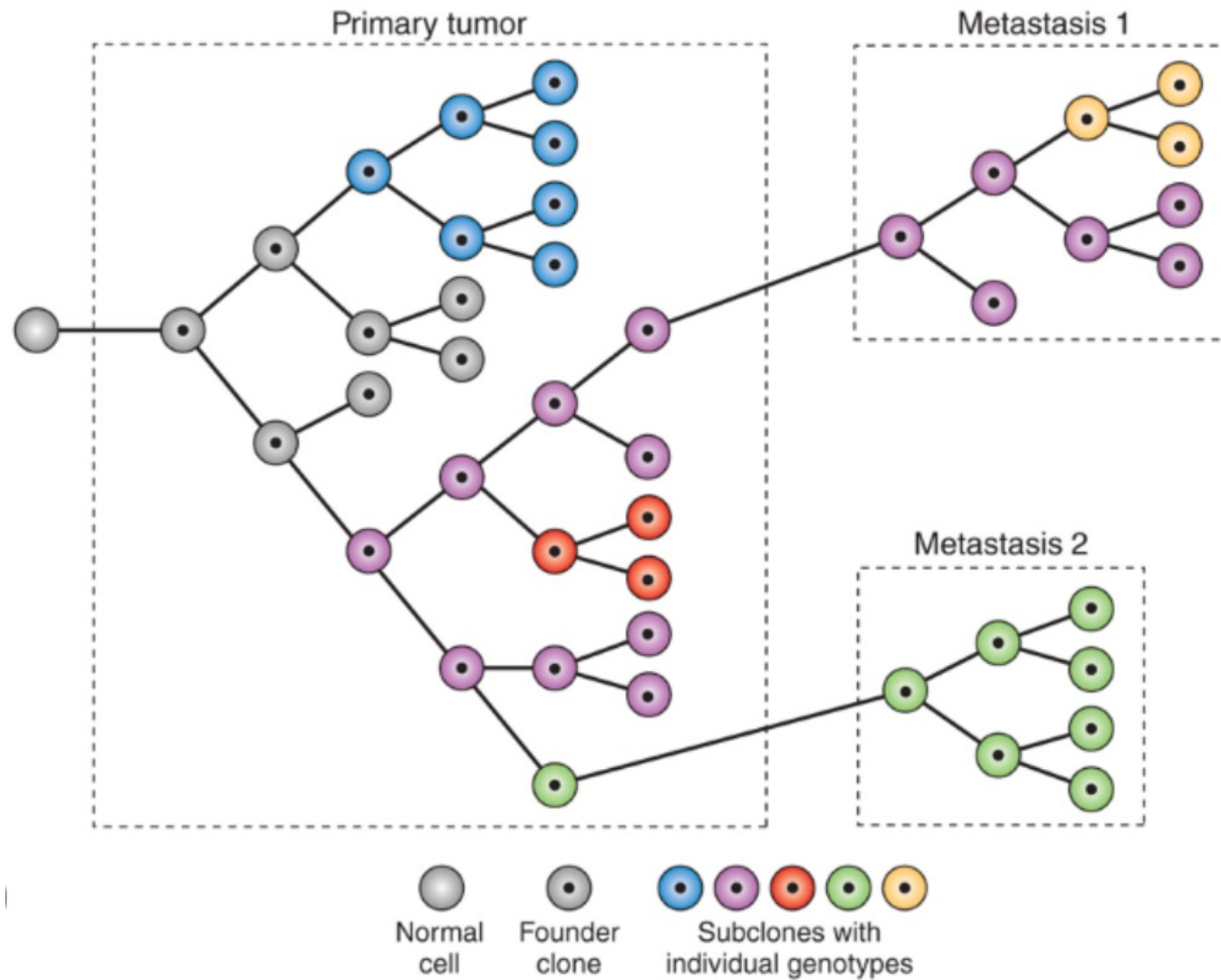
EXEMPLE: TRANSLOCATIONS CHROMOSOMIQUES IMPLIQUANT L'ONCOGENE C-MYC

Translocations chromosomiques impliquant c-MYC et les gènes des immunoglobulines dans les lymphomes de Burkitt (lymphome B)

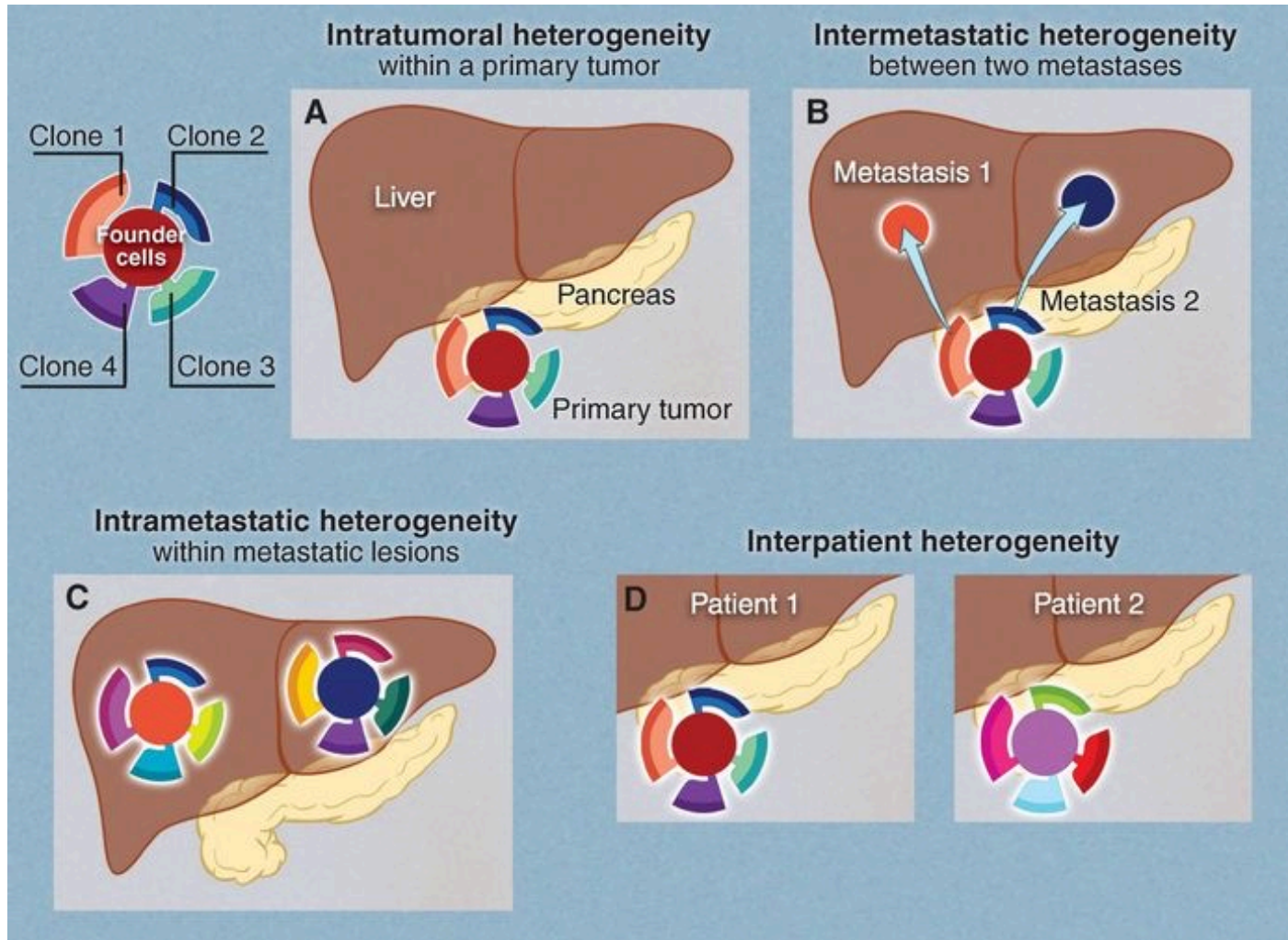


t(8,14)(q24;q32)	c-myc (8q24) IgH (14q32)	80%
t(8,22)(q24;q11)	c-myc (8q24) Igλ (22q11)	15%
t(2,8)(p12;q24)	c-myc (8q24) Igκ (2p12)	5%

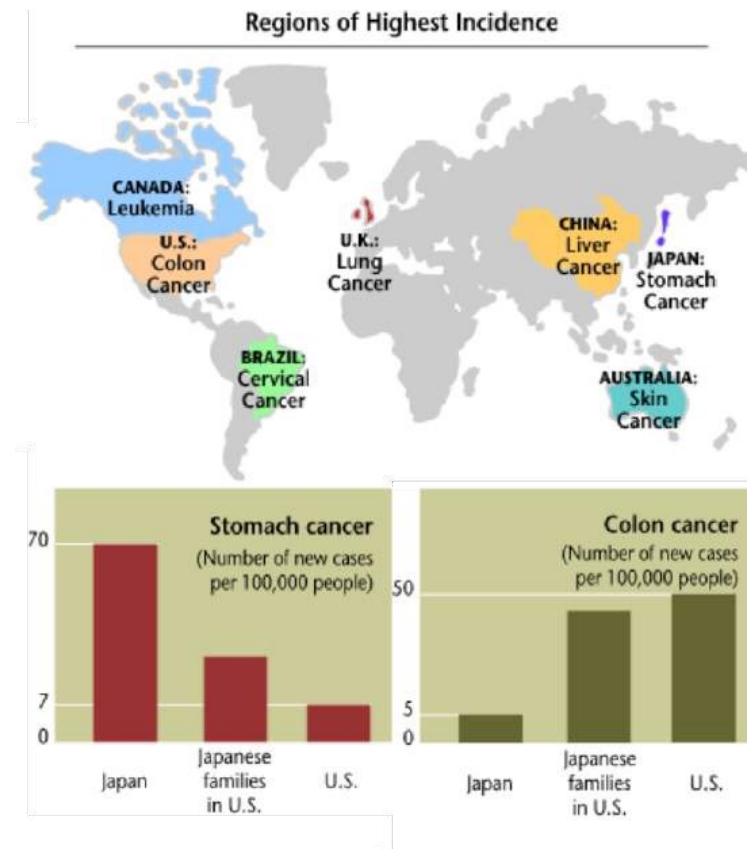
Le séquençage à haut-débit et en cellules uniques révèle l'évolution clonale des cancers



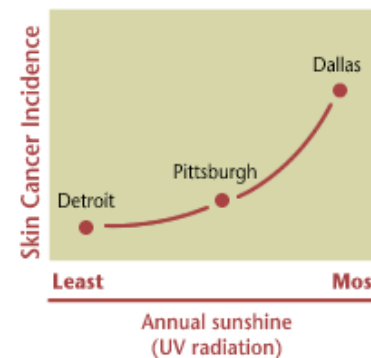
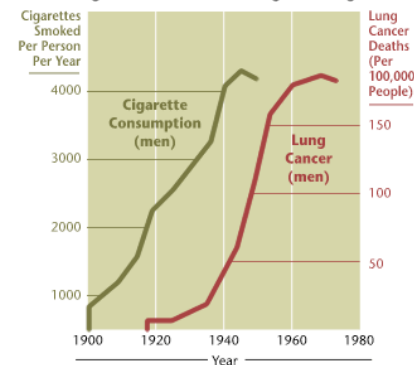
B -....but at the time they are diagnosed, they have become heterogenous from a genomic point of view



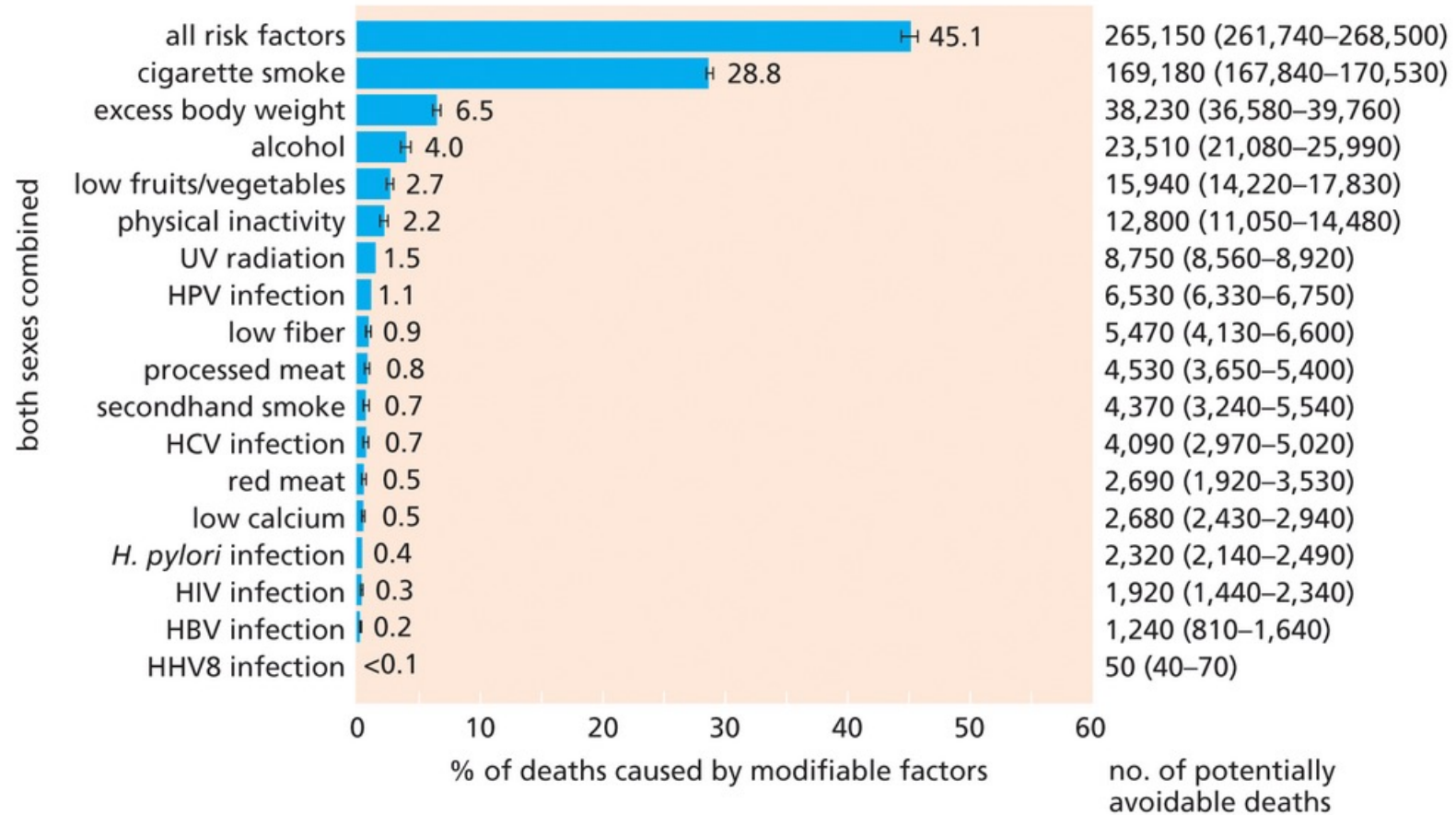
I –Origin and evolution of cancers : environmental aspects



20-Year Lag Time Between Smoking and Lung Cancer

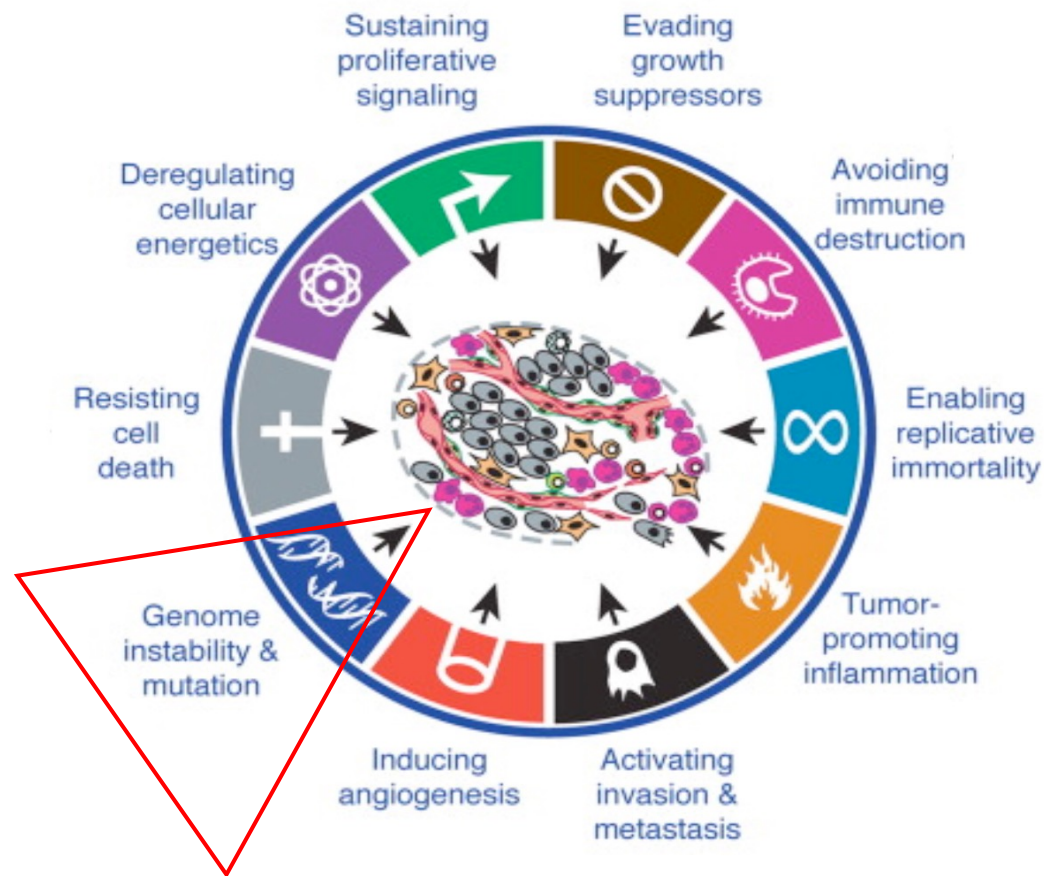


Percentage of avoidable cancers (in the US)



II –Genomic instability is both a hallmark of cancer cells AND an enabling characteristic

The Hallmarks of Cancer



Le cancer: une maladie du génome

- Le cancer résulte d'une cascade d'altérations (mutations) du génome des cellules ayant pour conséquence l'altération du fonctionnement de gènes essentiels pour le contrôle de la prolifération.
- Ces mutations sont majoritairement les conséquences accidentelles des effets génotoxiques d'agents auxquels sont exposées les cellules dans leur environnement.

Le cancer: une maladie génétique

- Certaines mutations sont transmises **héréditairement** et initient la cascade de mutations = **prédisposition au cancers**.
- Il existe des formes héréditaires de la plupart des cancers: sein , colon, peau....

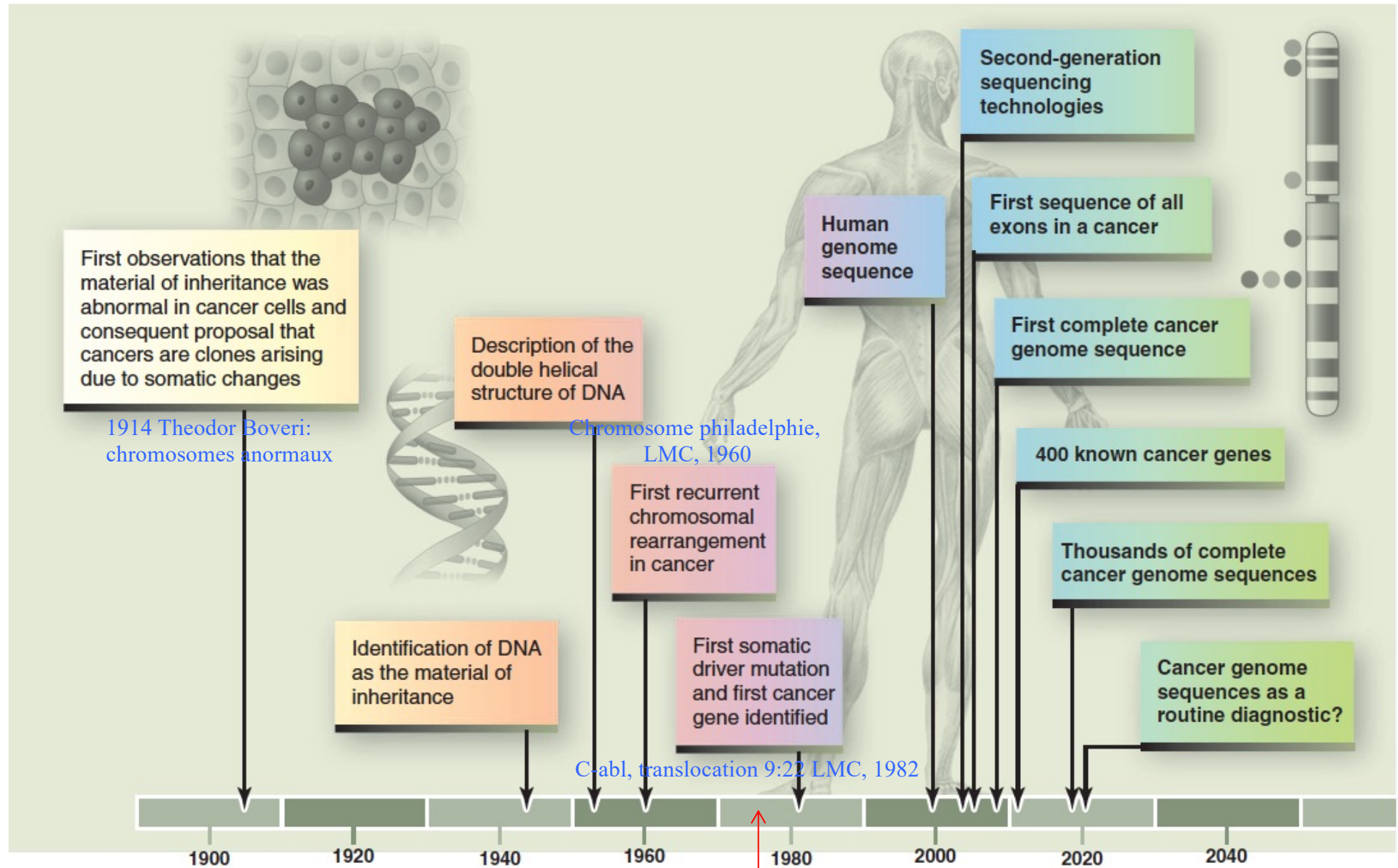
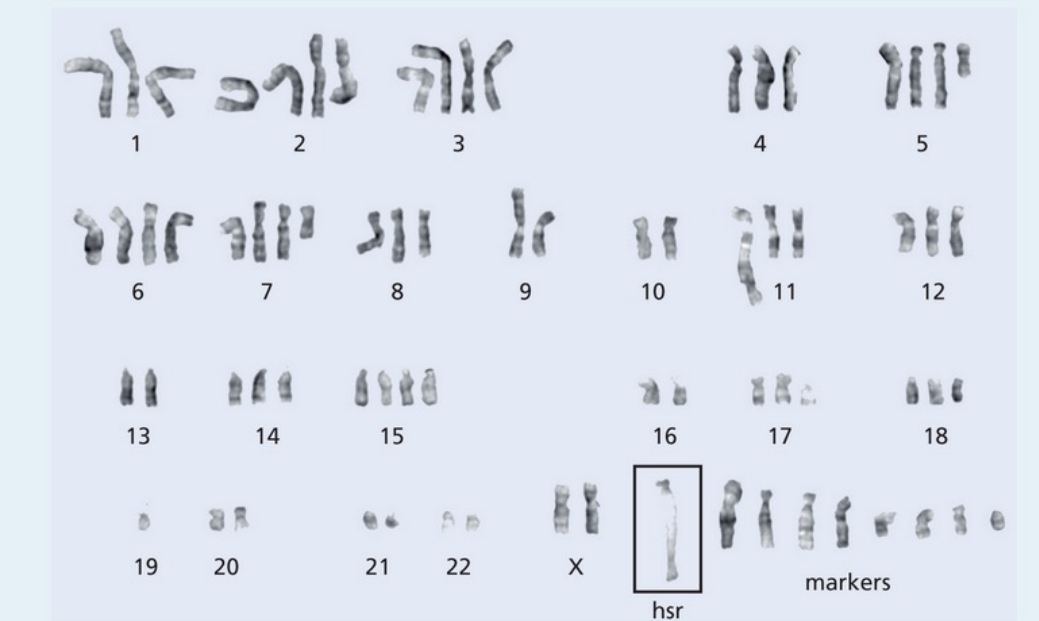


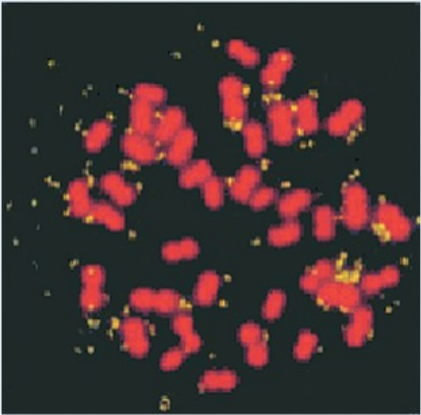
Fig. 1. Time line showing key events in the investigation of the cancer genome.

Src, first oncogene discovered

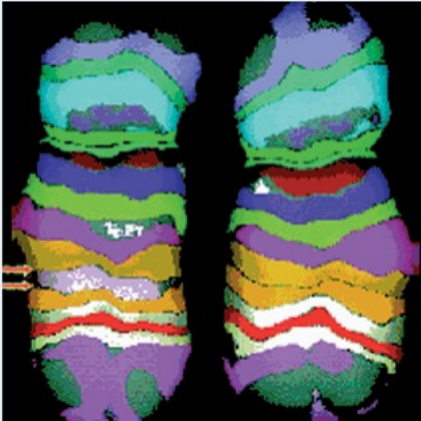
Les chromosomes sont altérés dans la plupart des cellules cancéreuses



(A)

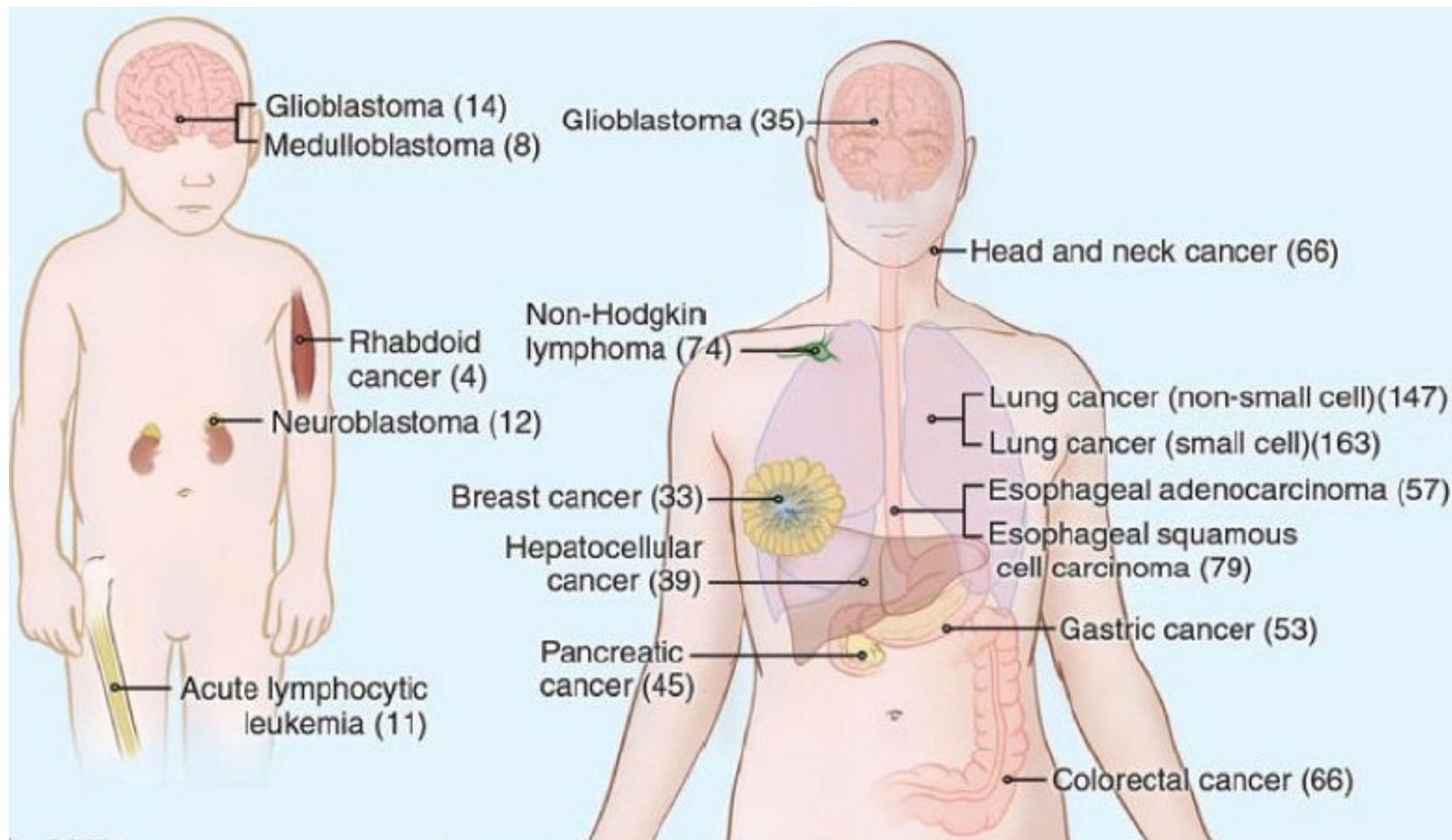


(B)



(C)

Fig. 1. Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies



Science. 2013 March 29; 339(6127): 1546–1558.

Mutations germinales/somatiques

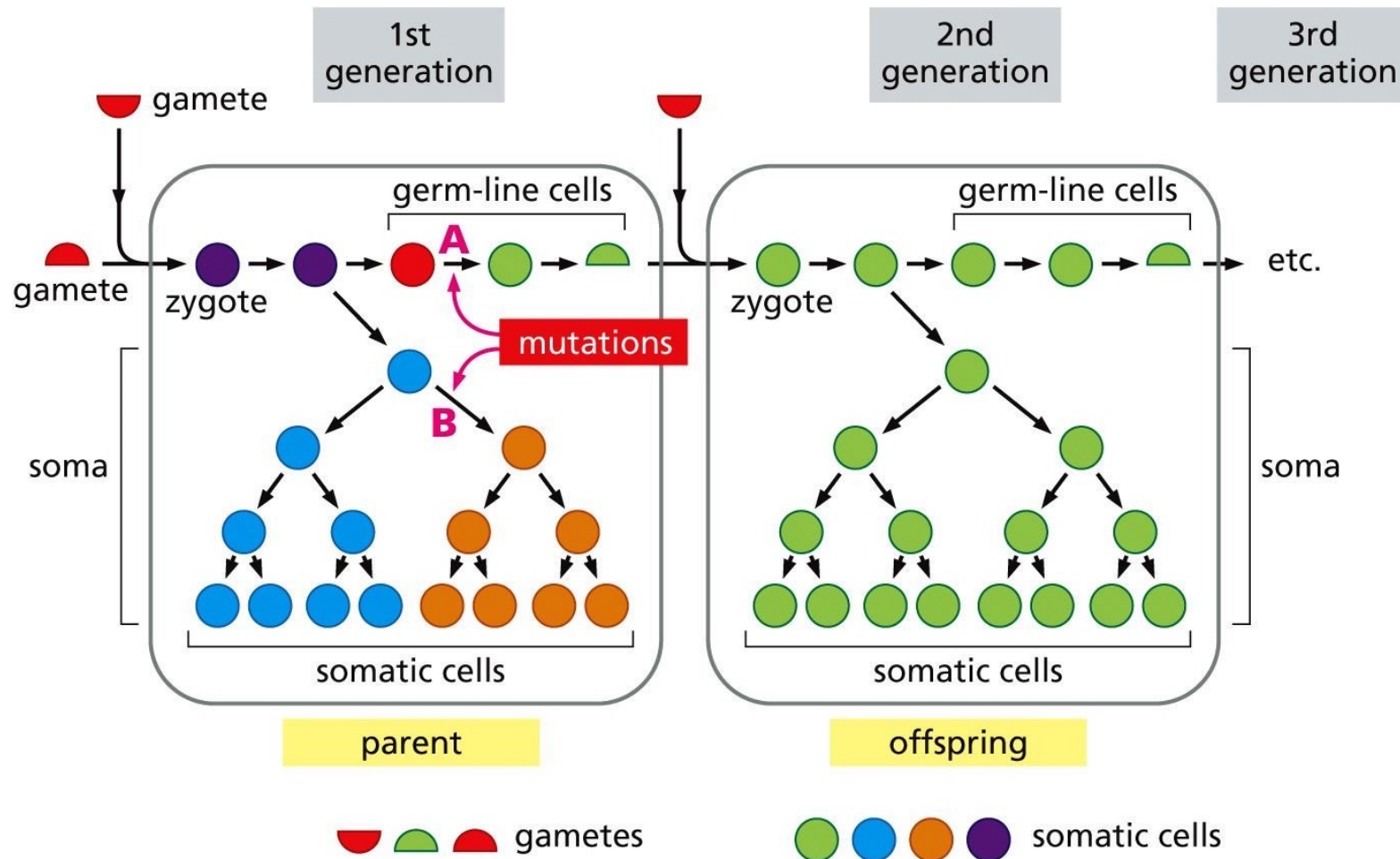
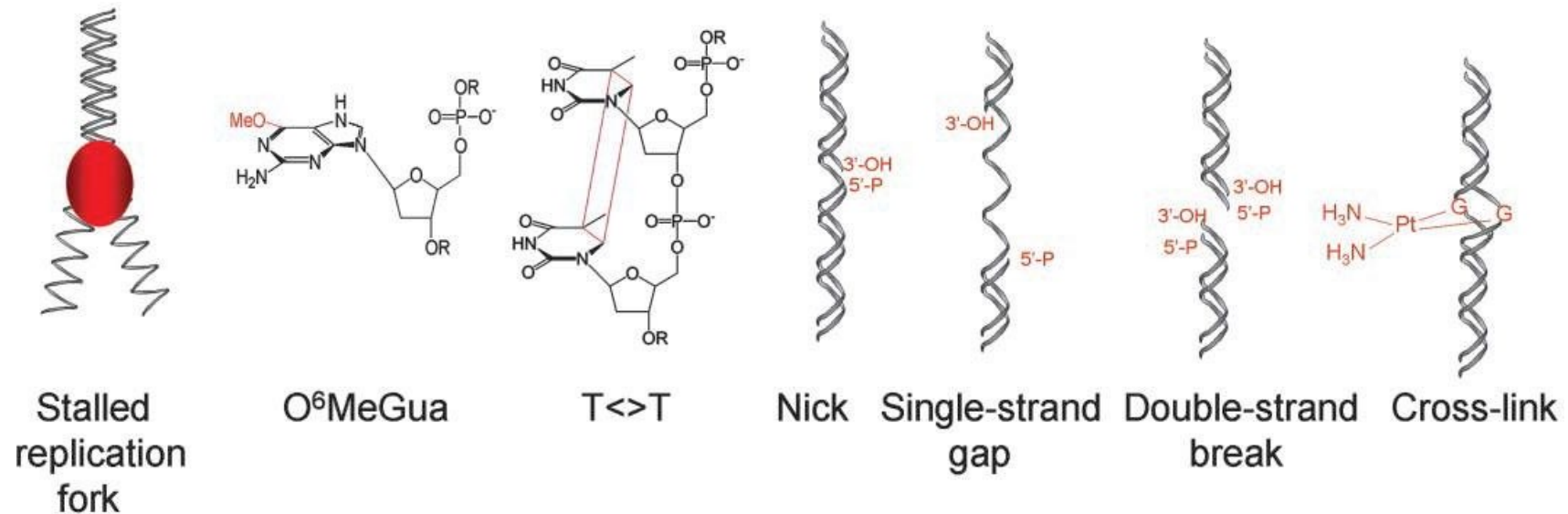


Figure 1.10 The Biology of Cancer (© Garland Science 2014)

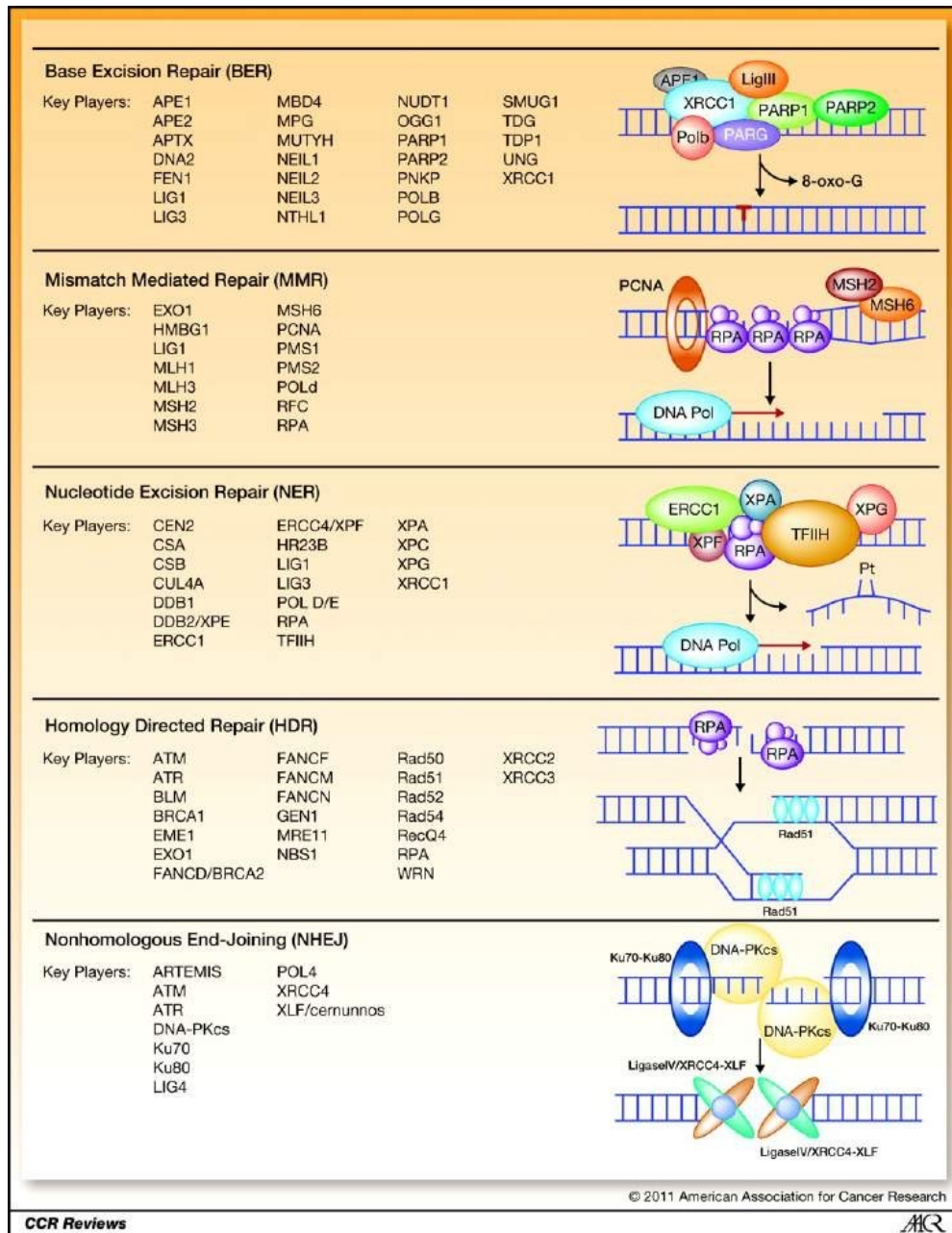
At the origin of genetic instability: the DNA lesions



... but the lesions do not generate
« directly » mutations

At the origin of genetic instability: DNA repair abnormalities

Shadia Jalal et al. Clin Cancer Res 2011;17:6973-6984



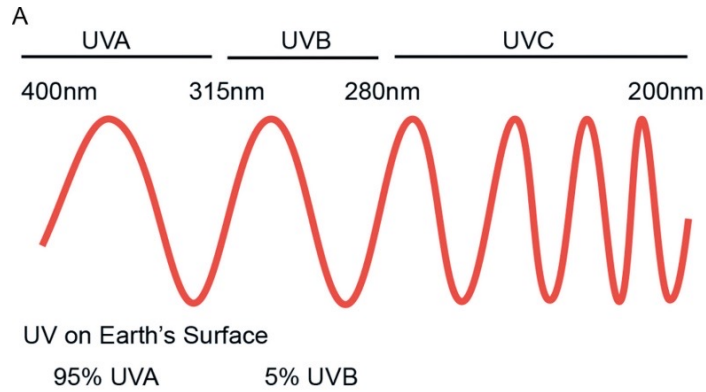
Saving the gene sequence

Saving the gene sequence, and chromosome structure, and ploidy.

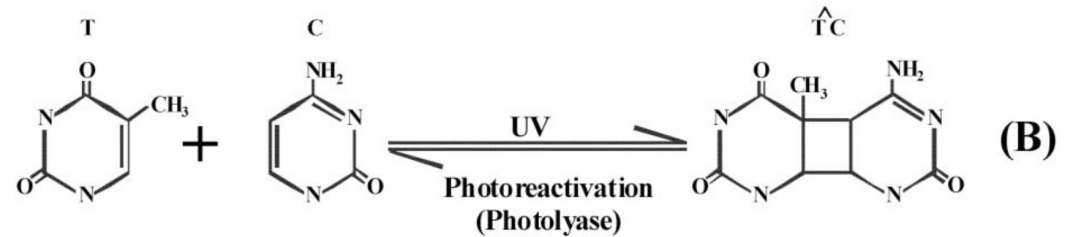
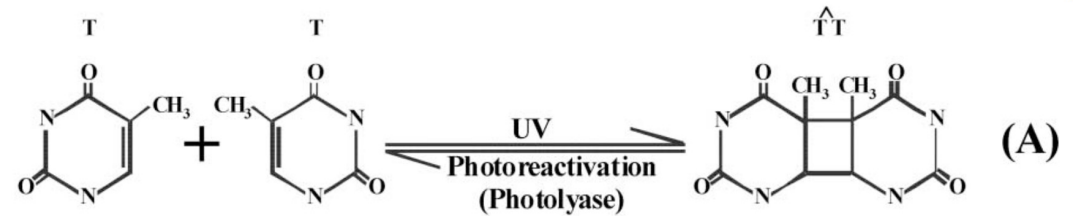
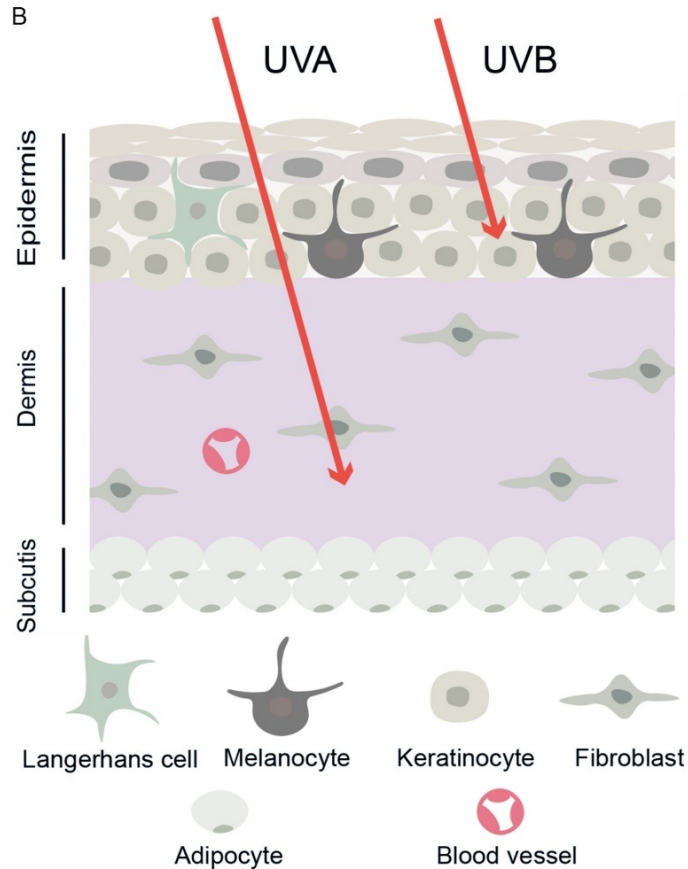
SOURCE DES MUTATIONS

- Source exogène
(ex: exposition aux UV ou à des carcinogènes)
- Source endogène
(ex: déamination ou oxydation naturelle des bases, mutation dans les gènes de réparation)

Example of UV-induced DNA damages



The UVR signature : formation of cyclobutane pyrimidine dimers...



Bouclier anti-UV par la mélanine stockée dans les kératinocytes

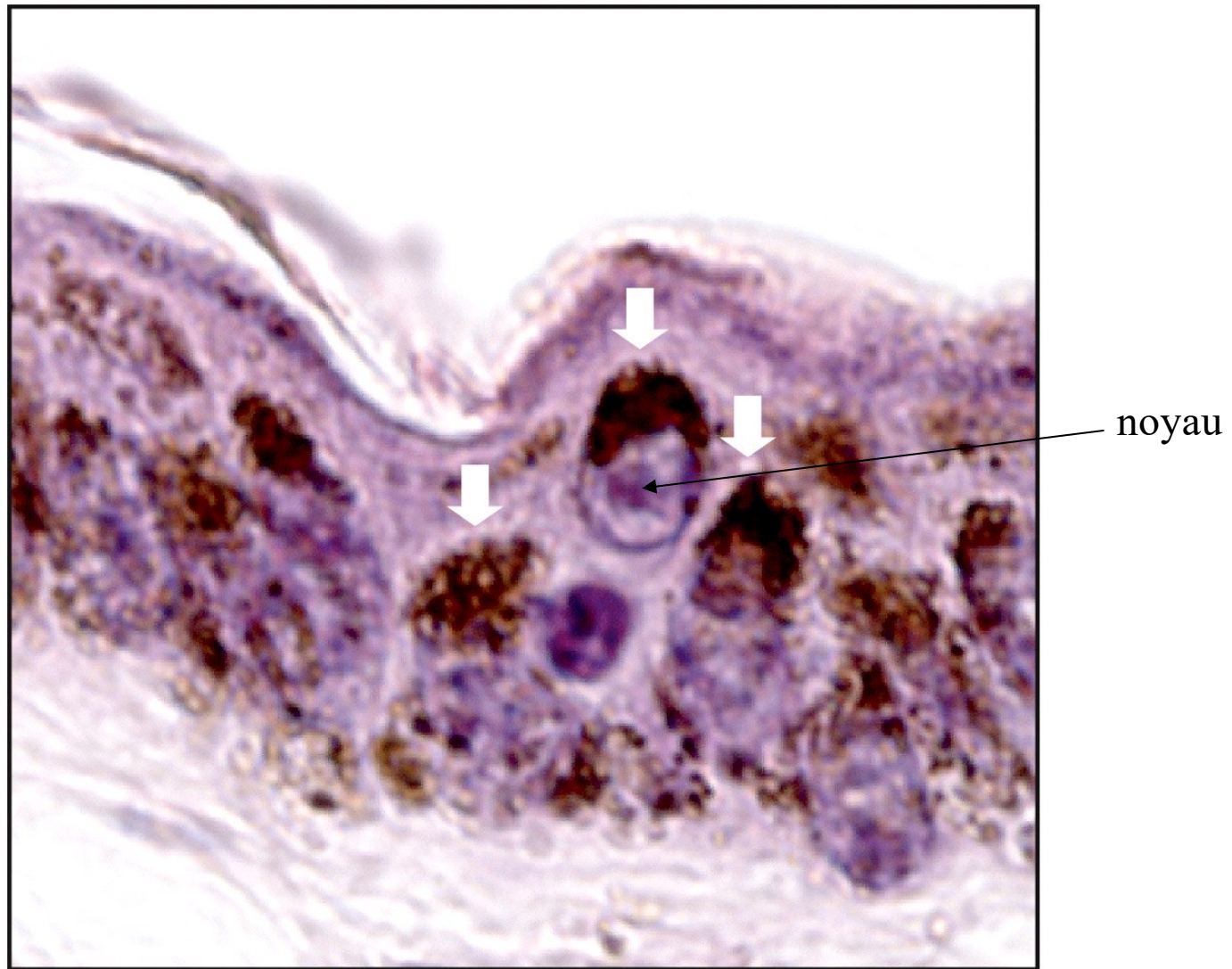
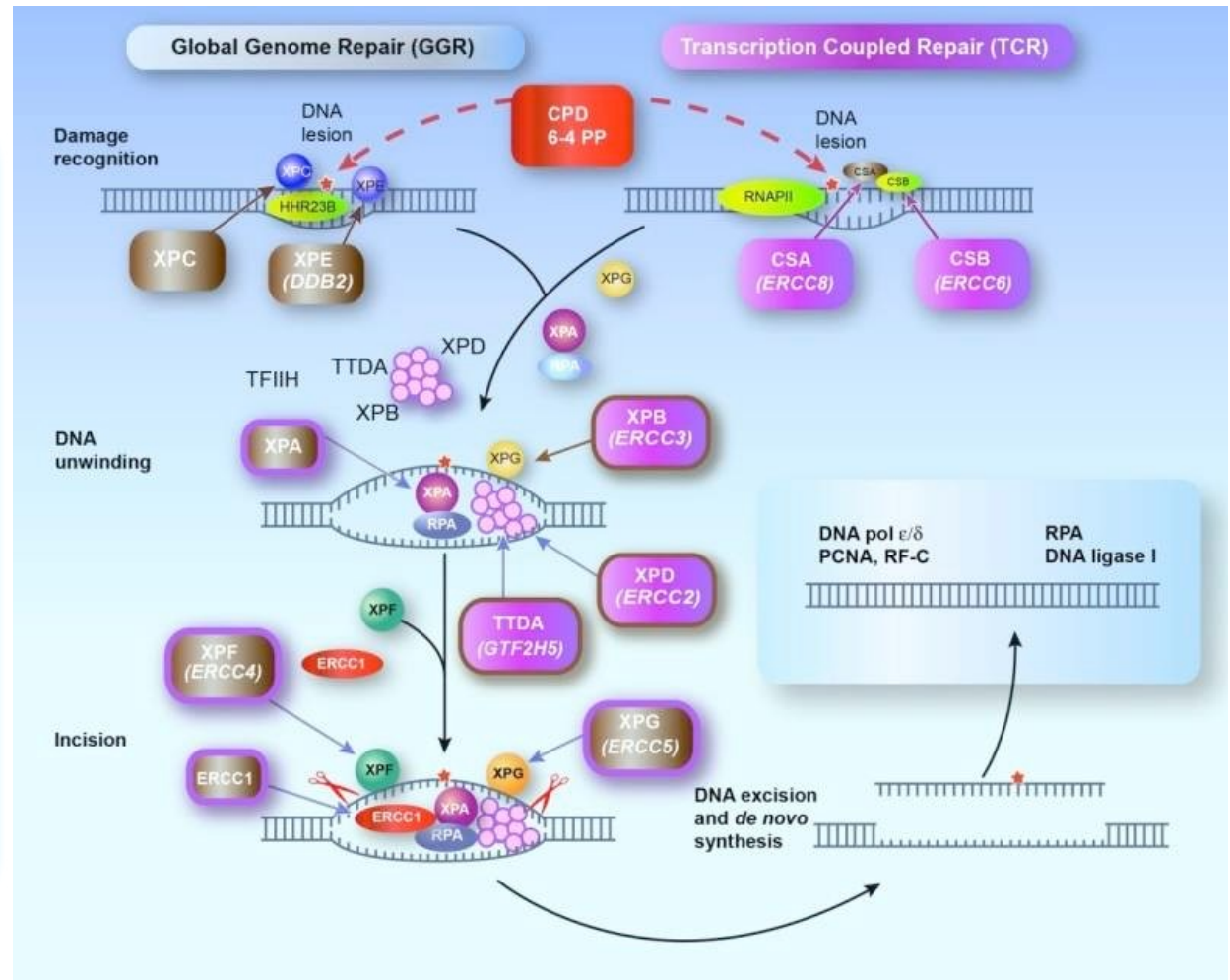
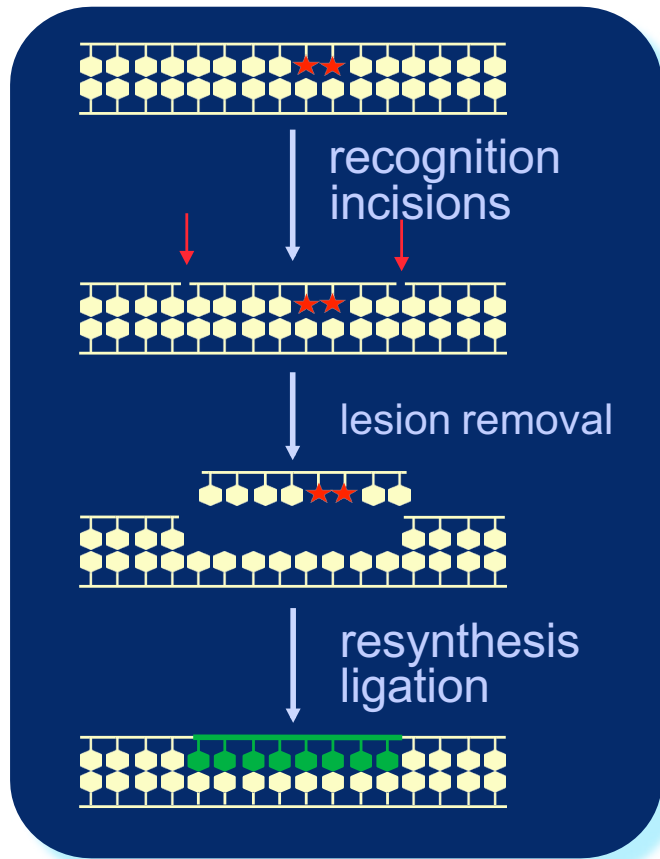


Figure 12.20 *The Biology of Cancer* (© Garland Science 2007)

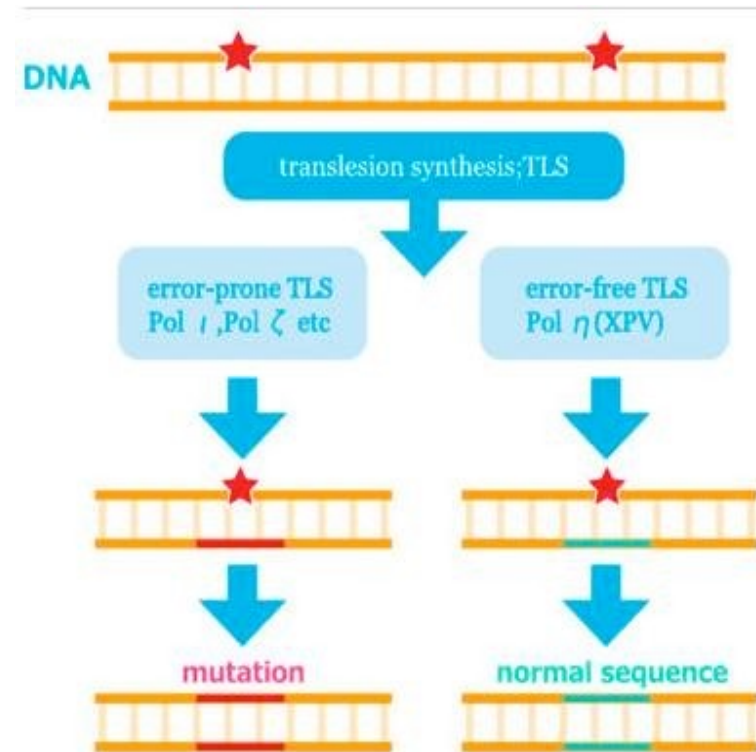
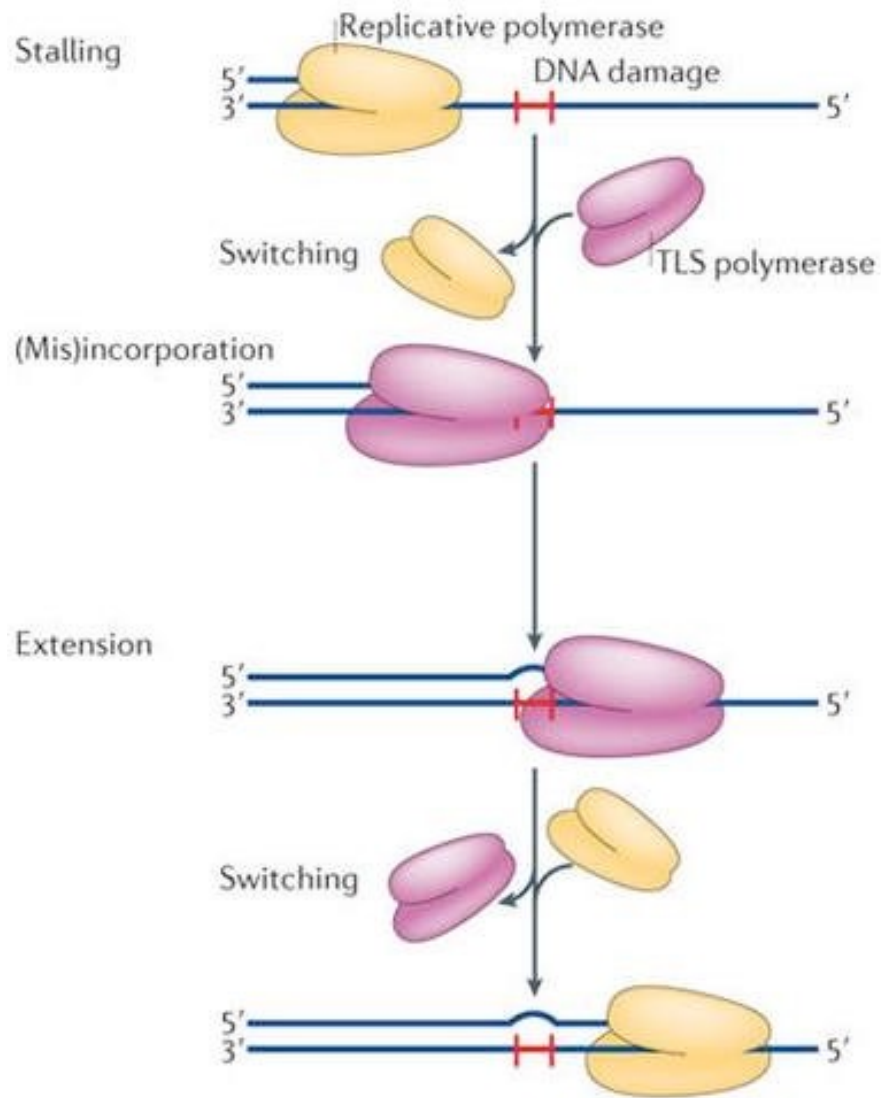


Cut & Fill pathways

DNA repair pathways: The Nucleotide excision repair pathway



...Formation of cyclobutane pyrimidine dimers can lead to C=>T or CC =>TT substitutions if error prone translesional synthesis occurs during S phase



XERODERMA PIGMENTOSUM

Rare, autosomal, recessive hereditary disease

Hypersensitivity to sunlight

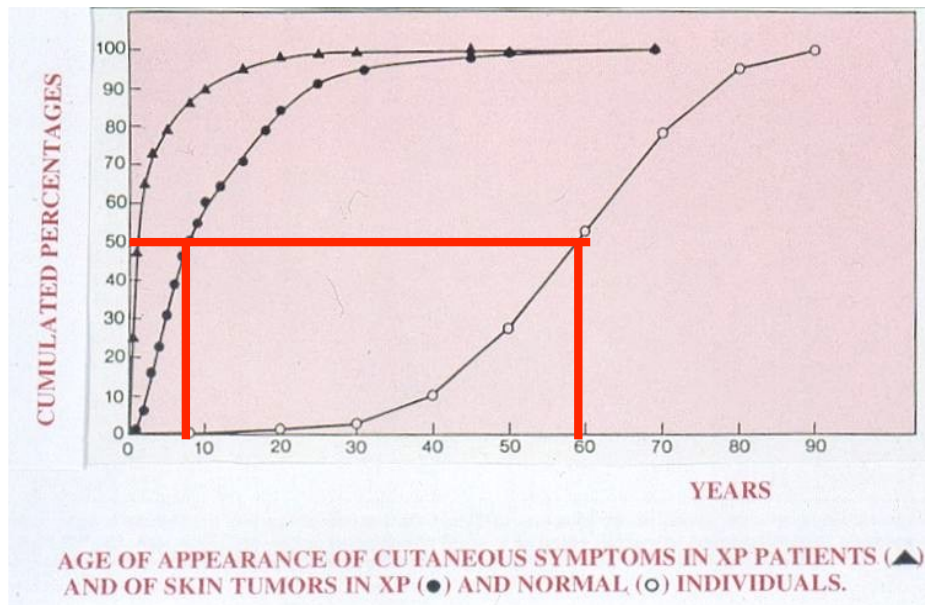
Sun-exposed skin tumours

Early (before the age of 20)

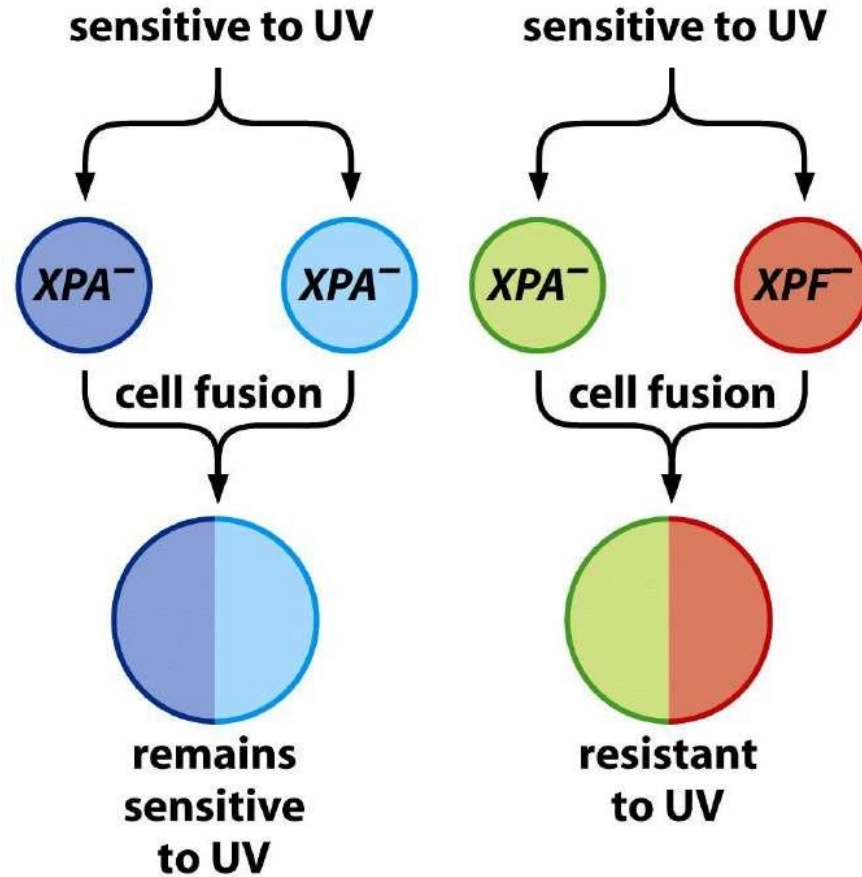
Classical XP :

Nucleotide excision repair deficiency

Genetic heterogeneity : 7 NER-XP genes



Xeroderma pigmentosum



8 Functional Complementation Groups

Xeroderma pigmentosum

Table 1 | **Genes affected in xeroderma pigmentosum**

Repair mechanism	Gene	Chromosome	Size (aa)	Residual levels of repair (%)	Function
Global genome repair	<i>XPE</i> (<i>DDB2</i>)	11p11-12	427	>50	Damage binding, E3 ligase
	<i>XPC</i>	3p25.1	940	5–20	Damage binding
Common pathway	<i>XPA</i>	9p34.1	273	2–5	Damage verification
	<i>XPB</i>	2q21	782	3–7	Helicase, 3'–5'
	<i>XPD</i>	19q13.2	760	25–50	Helicase, 5'–3'
	<i>XPG</i>	13q32-33	1186	<2	3' nuclease
	<i>XPF</i>	16p13.3	916	18	5' nuclease
Post-replication repair	<i>XPV</i> (Pol η)	6p21	713	100	Bypass polymerase

-> *Nucleotide Excision Repair*

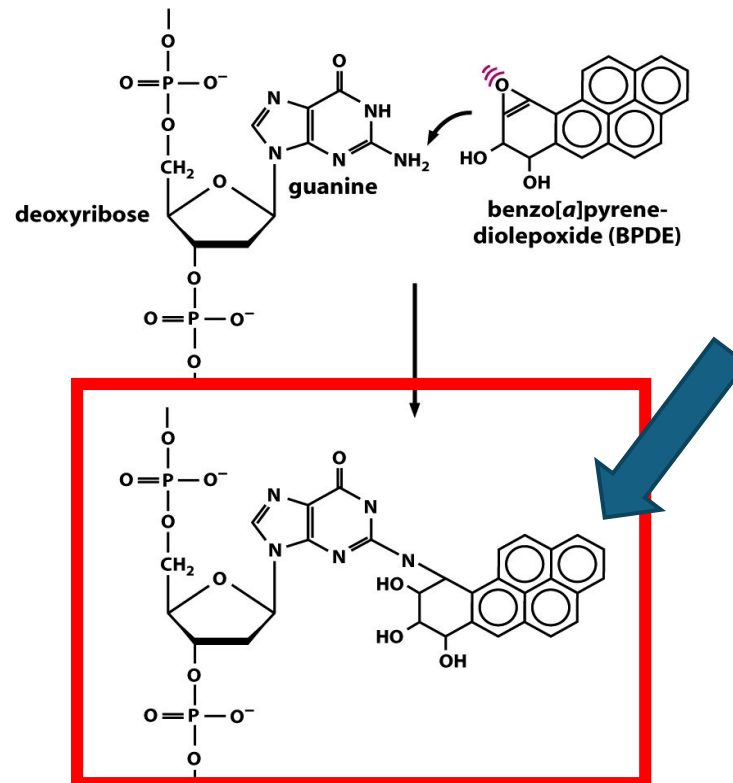
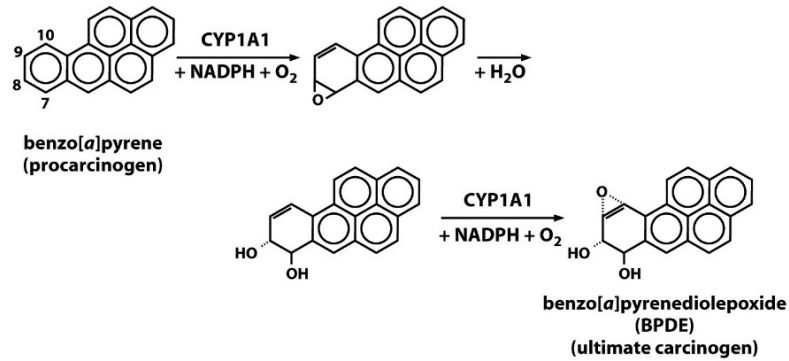
Exposure to chemical carcinogens

Since 1971, the International Agency for Research on Cancer published a list of almost 1000 substances recognized as carcinogens, probable carcinogens, or possible carcinogens.

These molecules, or their metabolites, often act by modifying cellular macromolecules, including DNA.

Some (very few) are of natural origin

Example : benzo(a)pyrene (cigarette smoke, exhaust gases from diesel engines, chimney smoke, ...)



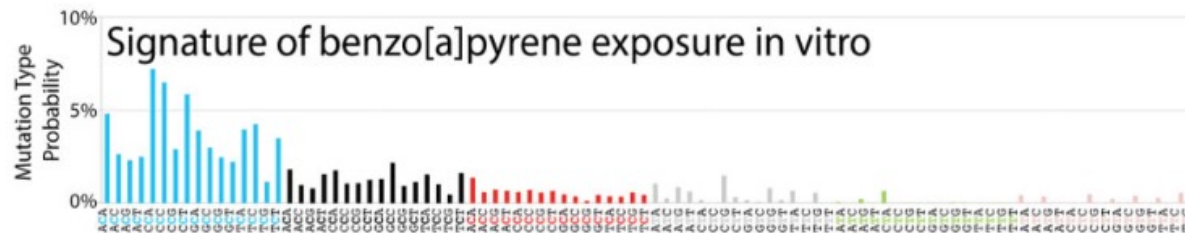
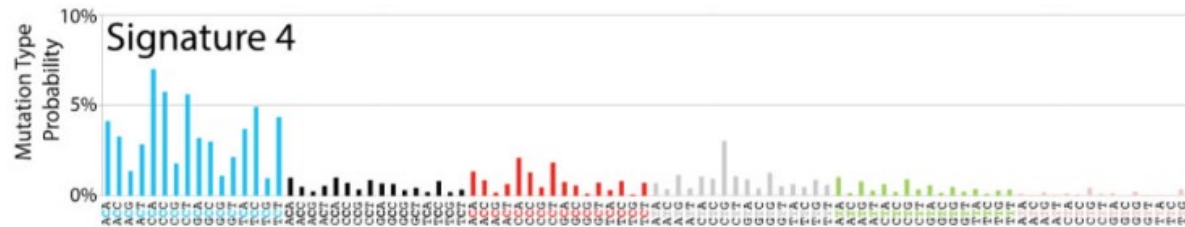
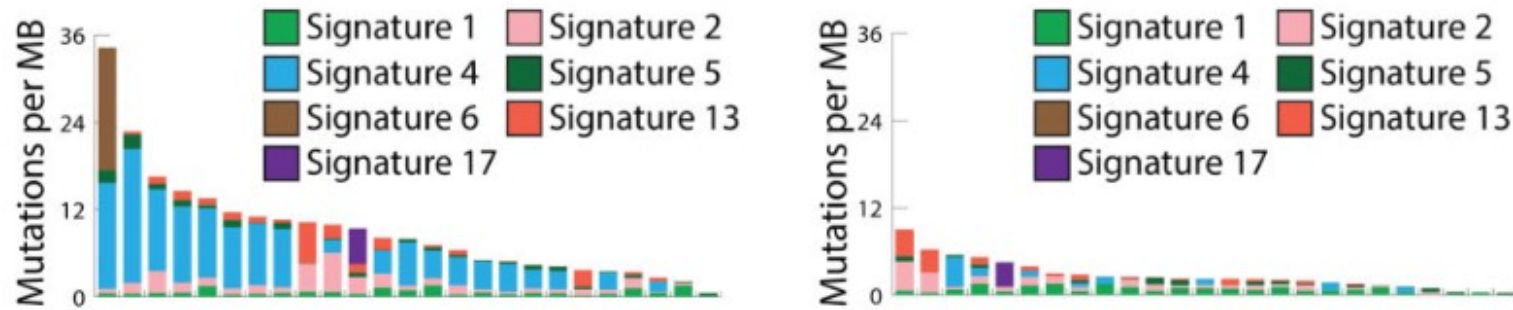
Mutational signatures associated with tobacco smoking in human lung cancer

A

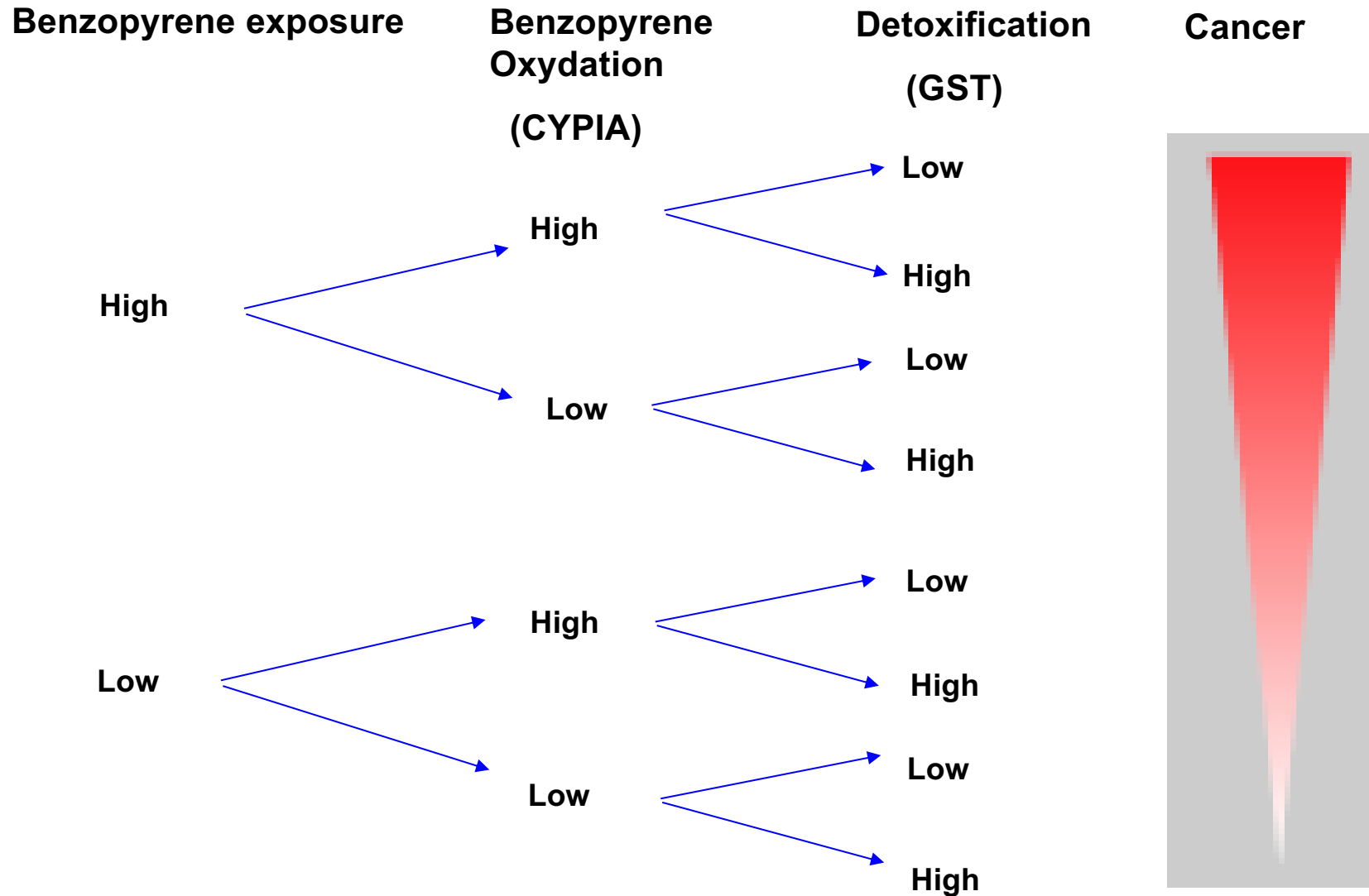
Lung Adeno

Tobacco Smokers

Non-Smokers



Polymorphisms in genes involved in Benzopyrene metabolism can alter cancer risk



Aflatoxine produite par les moisissures du grain

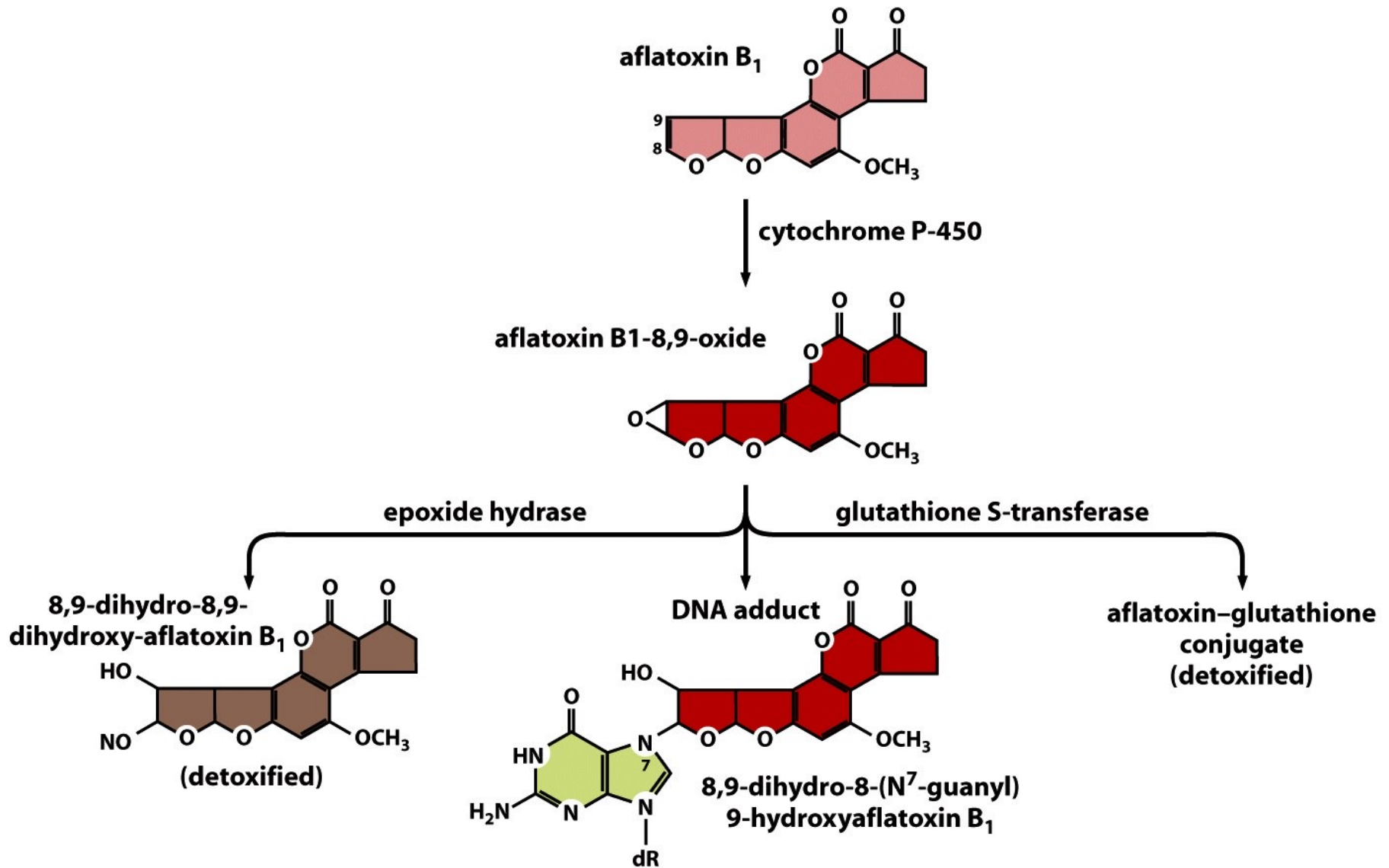


Figure 12.18b *The Biology of Cancer* (© Garland Science 2007)

Carte de l' incidence de cancer du foie: aflatoxine

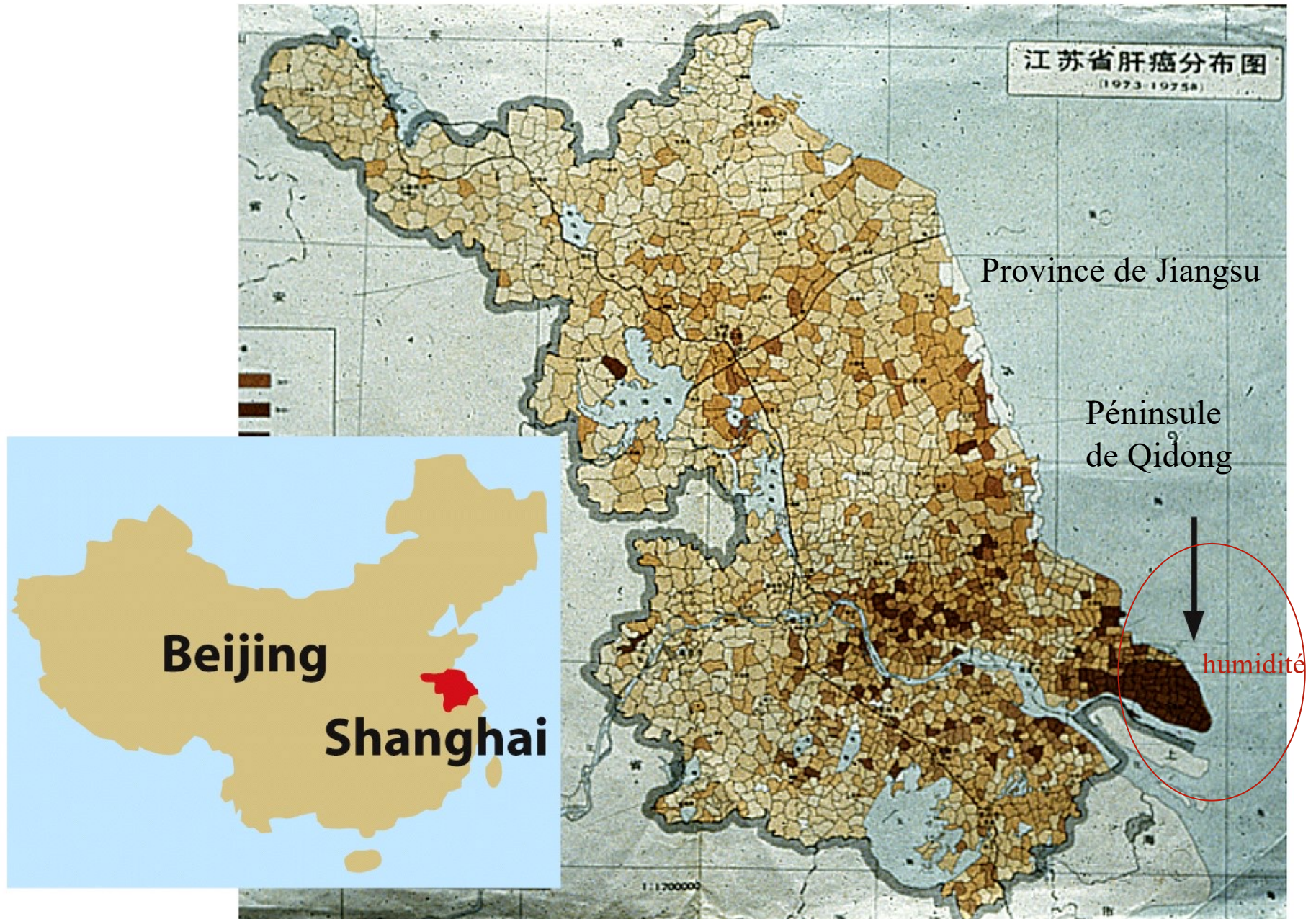
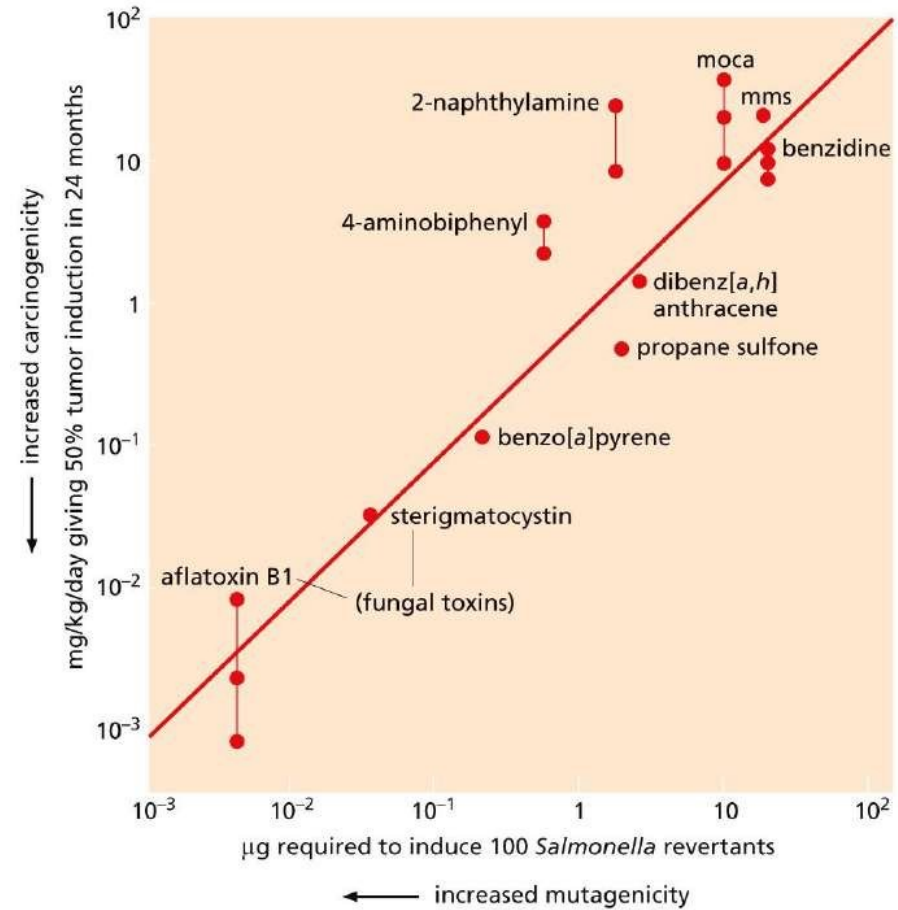
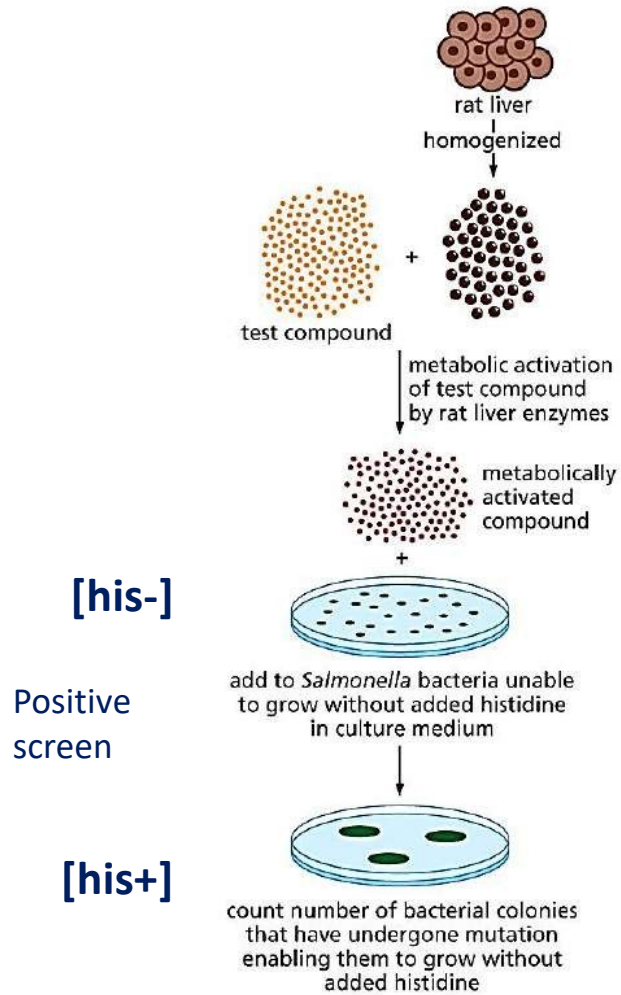


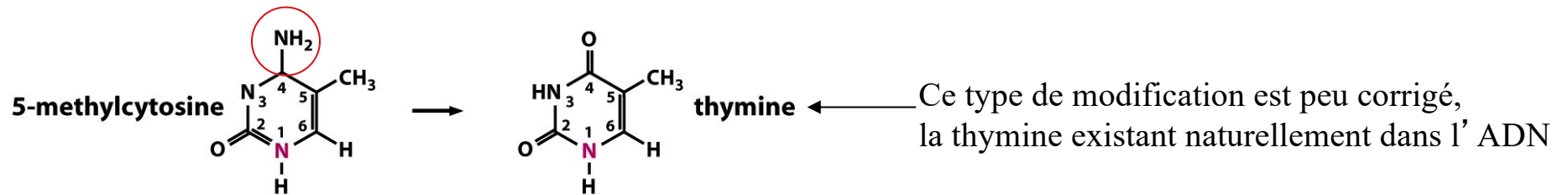
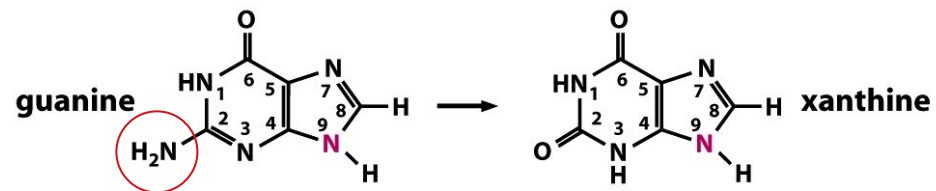
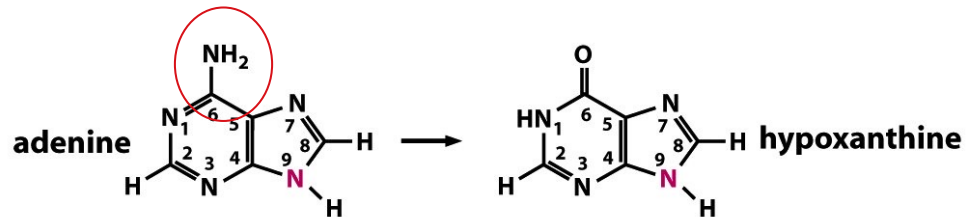
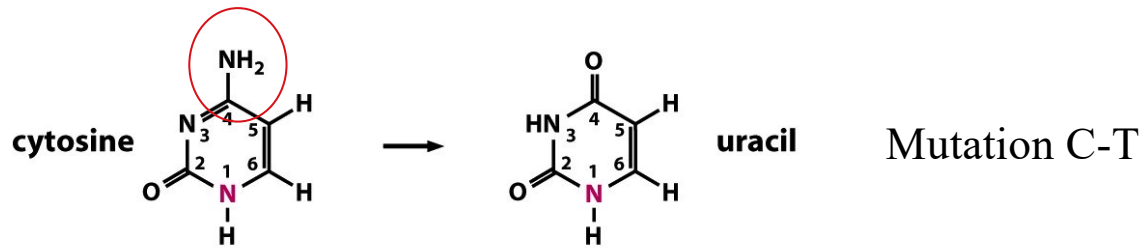
Figure 12.18a *The Biology of Cancer* (© Garland Science 2007)

Ames mutagenesis Test

❖ (1973) Ames Test

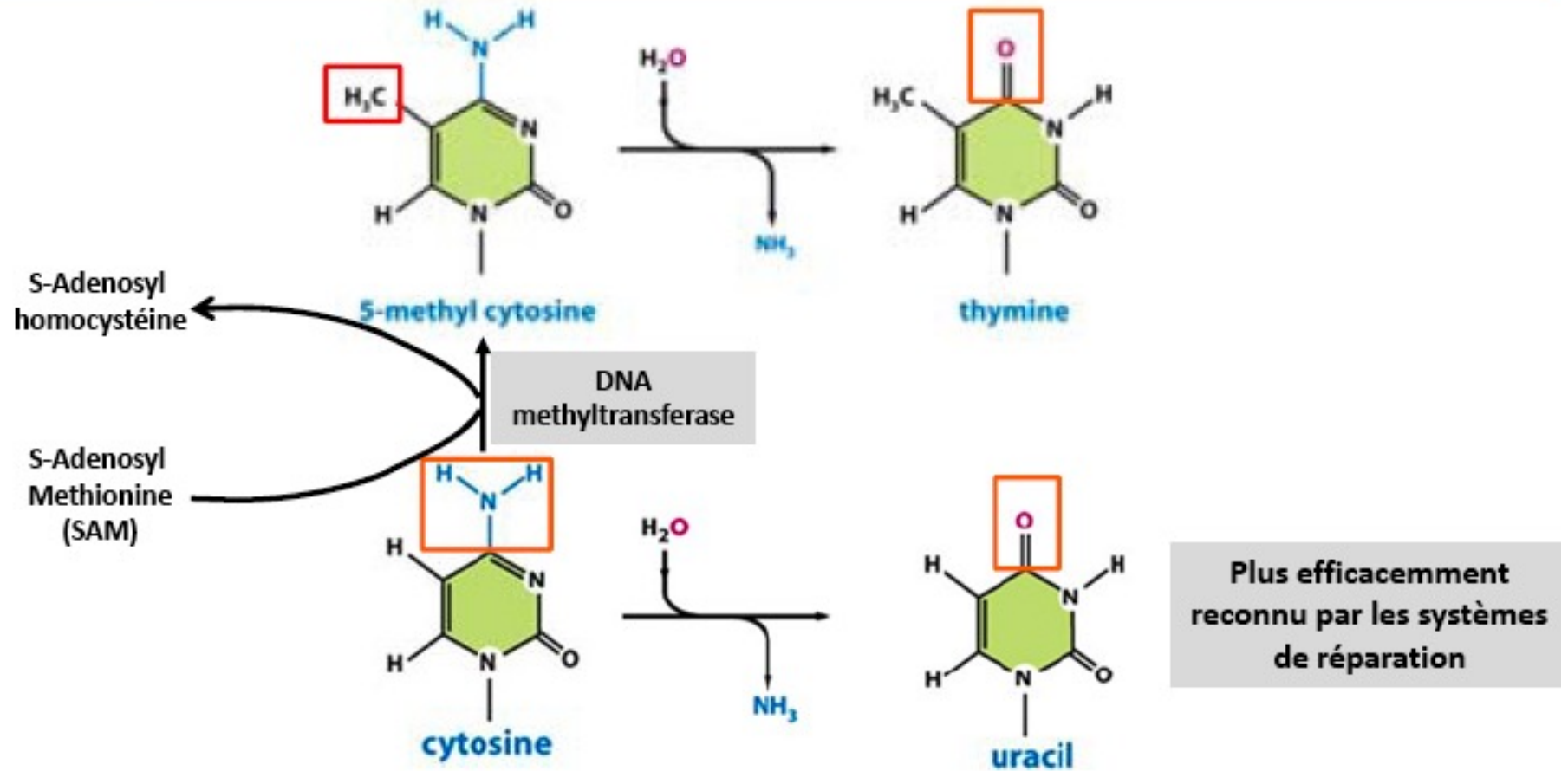


La déamination des bases: une source endogène de mutations (1/2)



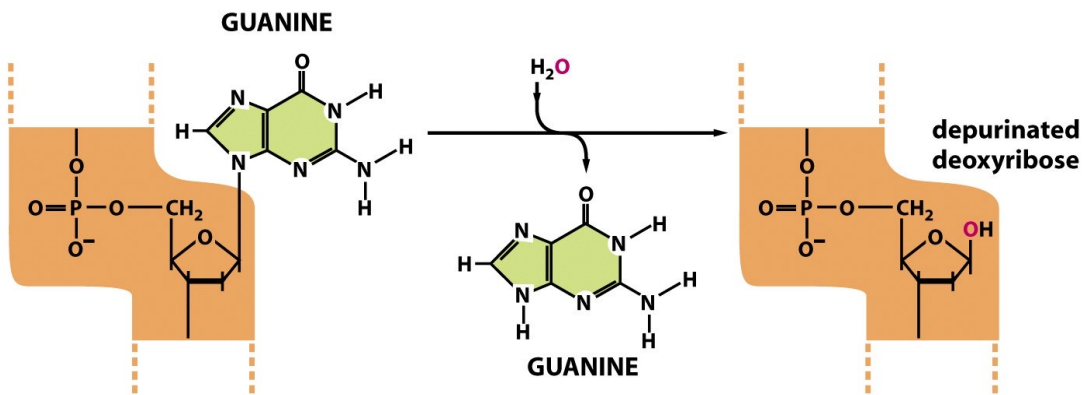
Déamination
des bases.
Phénomènes spontanés.

Désamination oxydative



- La 5-methyl cytosine représente ~1% des bases de l'ADN humain mais 30% des sites de mutations ponctuelles

La dépurination et la dépyrimidination des bases: une source endogène de mutations



Dépurination: 10^{17} /jour/génome;
Dépyrimidination: 10^{15} /jour/génome;
En taux de base entre 4000
et 50 000 nucléotides sans bases /génome

FORMATION DES RADICAUX LIBRES : LES PRINCIPALES SOURCES

Physique

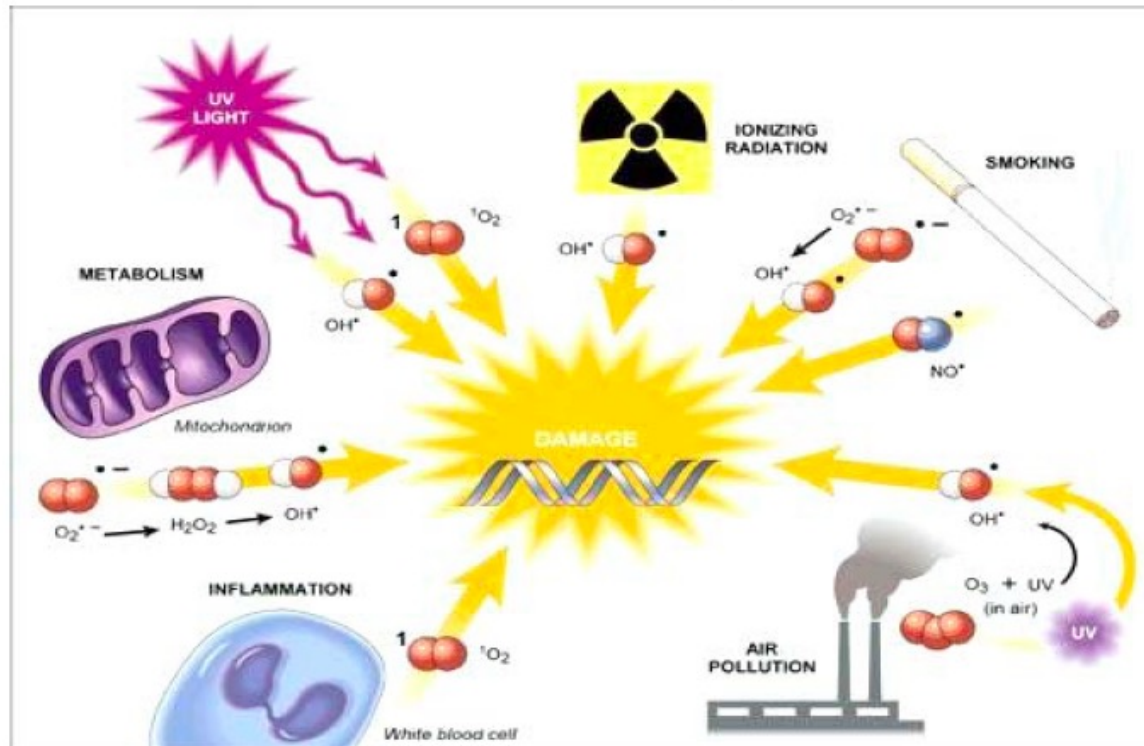
UV, radiations ionisantes

Chimique

polluants, drogues,
médicaments, pesticides

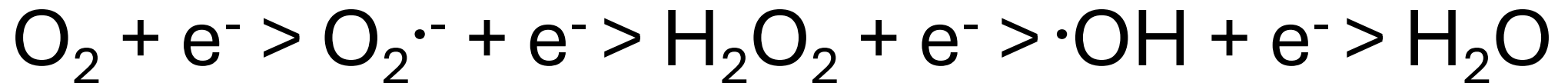
Biologique

virus, bactéries, réactions immunologiques, fuite
des électrons (métabolisme humain normal)



Les radicaux libres sont inévitablement produits lors des réactions physiologiques normales – les radicaux libres sont nécessaires à la vie mais ils sont aussi le fléau de notre existence

Les espèces réactives de l'oxygène (ROS)

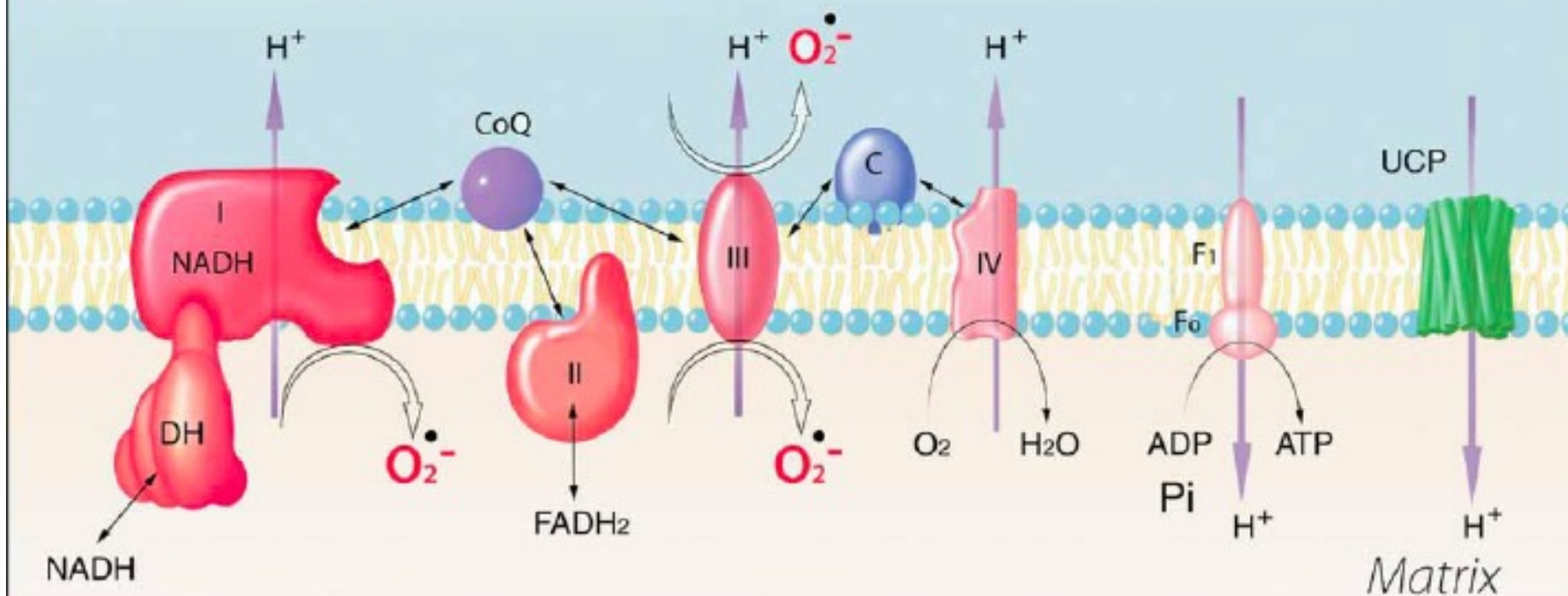


$\text{O}_2^{\cdot-}$: ion superoxyde

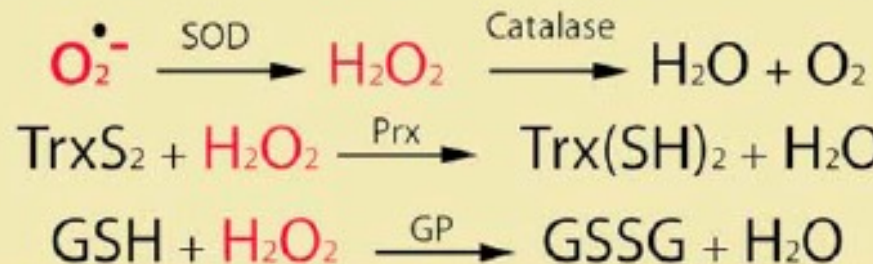
H_2O_2 : Peroxide d'hydrogen

$\cdot\text{OH}$: radical hydroxyl

Génèse de ROS dans la mitochondrie



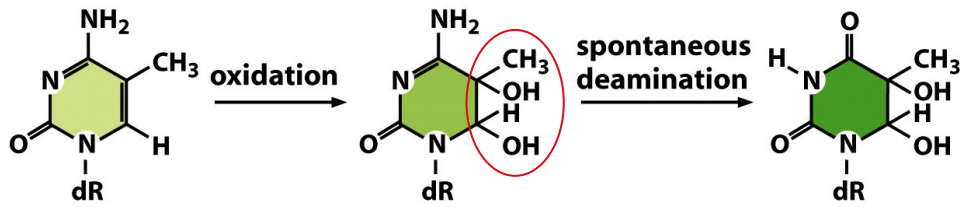
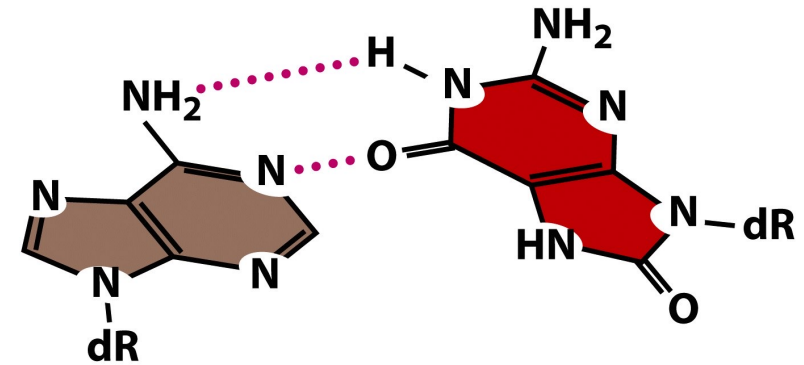
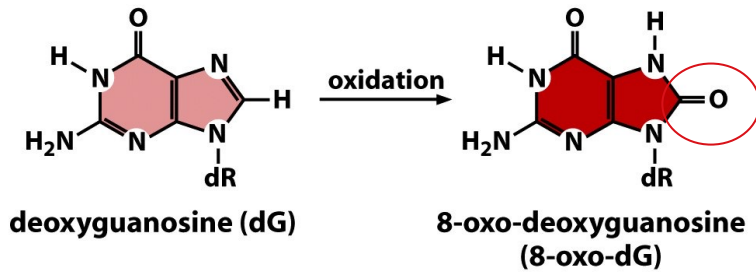
Antioxidant Scavenger Reactions:



peroxiredoxin (Prx),
superoxide dismutase (SOD),
and glutathione peroxidase (GP).

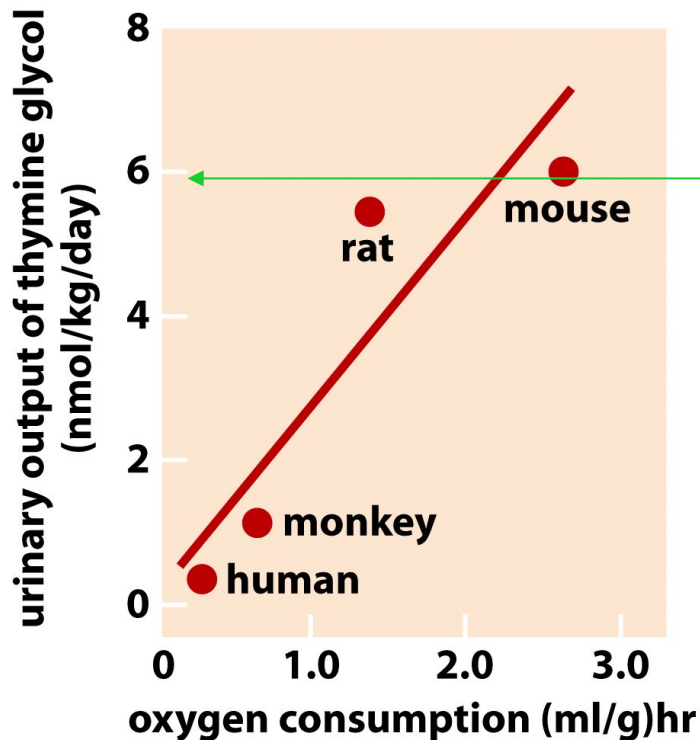
Oxydation des bases: effet des ROS

(MTH1 est chargé de son élimination; souris -/- : 4fois plus de tumeurs)



deoxy 5-methyl-cytosine (présent dans les îlots CpG) → deoxythymidine glycol (dTg)

(Bloque la réplication)

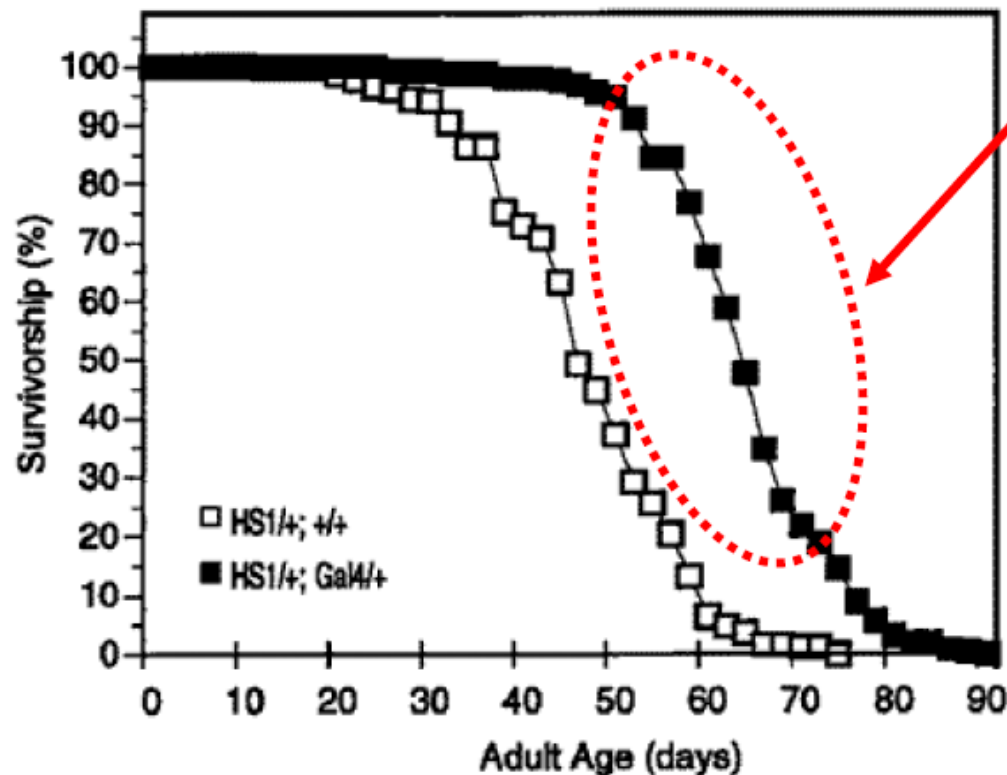


6nmol de deoxythymidine par kg et par jour excrété dans les urines (rat /souris) correspond à 3000 thymidine oxydées par jour et par cellules.

Consommation d' O2 inversement proportionnelle au poids: plus de ROS (reactive oxygene species) chez les rongeurs; les ROS sont également produits par les cellules du système immunitaire en cas d' infection (hélicobacter, HPV...)

EFFET POSITIF DE LA SUREPRESSION DES ENZYMES ANTIOXYDANTES SUR LA LONGEVITE

Les drosophiles surexprimant les enzymes qui détruisent ROS (catalase et superoxyde dismutase) vivent **30% plus longtemps que les animaux contrôles**



(Orr et sohal 1994) Cat + Cu-Zn SOD (=SOD1)
(Sun and Tower 1999) Cu-Zn SOD(=SOD3)

(Parkes et al. 1998) H- SOD1 dans motoneurones

• Cancer colorectal héréditaire

■ HNPCC

Incidence 2 à 5 / 10 000

Localisation majoritaire: Paroi du colon

Non lié à APC (Peltomaki et al.1992)

Etudes de liaison avec autres types tumoraux

2p16 (Peltomaki et al.1993; Aaltonen et al.1993; Green et al. 1994)

instabilité microsatellite : hypothèse des gènes du mismatch repair (Thibodeau et al. 1993; Ionov et al. 1993; Parson et al. 1993)

Clonage et mutations de hMSH2 2p16 (Fishel et al. 1993)

Recherche de mutations dans les autres gènes (Liu et al .1996)

E. coli	Human	Location in man	% of HNPCC
MutS	MSH2	2p16	50–60%
	GTBP (MSH6)	2p16	v. low
MutL	MLH1	3p21.3	30–40%
	PMS1	2q31-q33	v. low
	PMS2	7p22	v. low

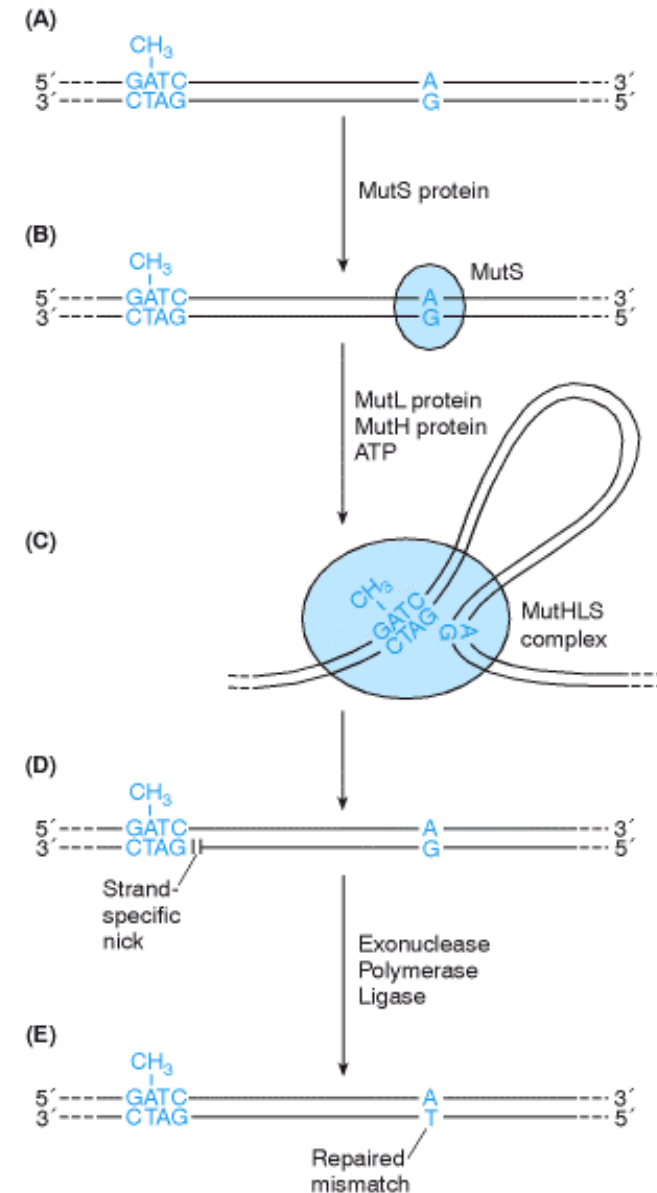


Table 12.2 Genes and proteins that have been inactivated in human cancer cell genomes because of mismatch repair defects

Gene	Function of encoded protein	Wild-type coding sequence	Colon	Stomach	Endometrium
<i>ACTR11</i>	GF receptor	A ₈	X		
<i>AIM2</i>	interferon-inducible	A ₁₀	X		
<i>APAF1</i>	pro-apoptotic factor	A ₈	X	X	
<i>AXIN-2</i>	Wnt signaling	A ₆ , G ₇ , C ₆	X		
<i>BAX</i>	pro-apoptotic factor	G ₈	X	X	X
<i>BCL-10</i>	pro-apoptotic factor	A ₈	X	X	X
<i>BLM</i>	DNA damage response	A ₉	X	X	X
<i>Caspase-5</i>	pro-apoptotic factor	A ₁₀	X	X	X
<i>CDX2</i>	homeobox TF	G ₇	X		
<i>CHK1</i>	DNA damage response	A ₉	X		X
<i>FAS</i>	pro-apoptotic factor	T ₇	X		X
<i>GRB-14</i>	signal transduction	A ₉	X	X	
<i>hG4-1</i>	cell cycle	A ₈	X		
<i>IFRIIR</i>	decoy GF receptor	G ₈	X	X	X
<i>KIAA097</i>	unknown	T ₉	X		
<i>MLH3</i>	MMR	A ₉	X		X
<i>MSH3</i>	MMR	A ₈	X	X	X
<i>MSH6</i>	MMR	C ₈	X	X	X
<i>NADH-UO8</i>	electron transport	T ₉	X		
<i>OGT</i>	glycosylation	T ₁₀	X		
<i>PTEN</i>	pro-apoptotic	A ₆	X		X
<i>RAD50</i>	DNA damage response	A ₉	X	X	
<i>RHAMM</i>	cell motility	A ₉	X		
<i>RIZ</i>	pro-apoptotic factor	A ₈ , A ₉	X	X	X
<i>SEC63</i>	protein translocation into endoplasmic reticulum	A ₁₀ , A ₉	X		
<i>SLC23A1</i>	transporter	C ₉	X		
<i>TCF-4</i>	transcription factor	A ₁₀	X	X	X
<i>TGF-βRII</i>	TGF-β receptor	A ₁₀	X	X	X
<i>WISP-3</i>	growth factor	A ₉	X		

From A. Duval and R. Hamelin, *Cancer Res.* 62:2447–2454, 2002.

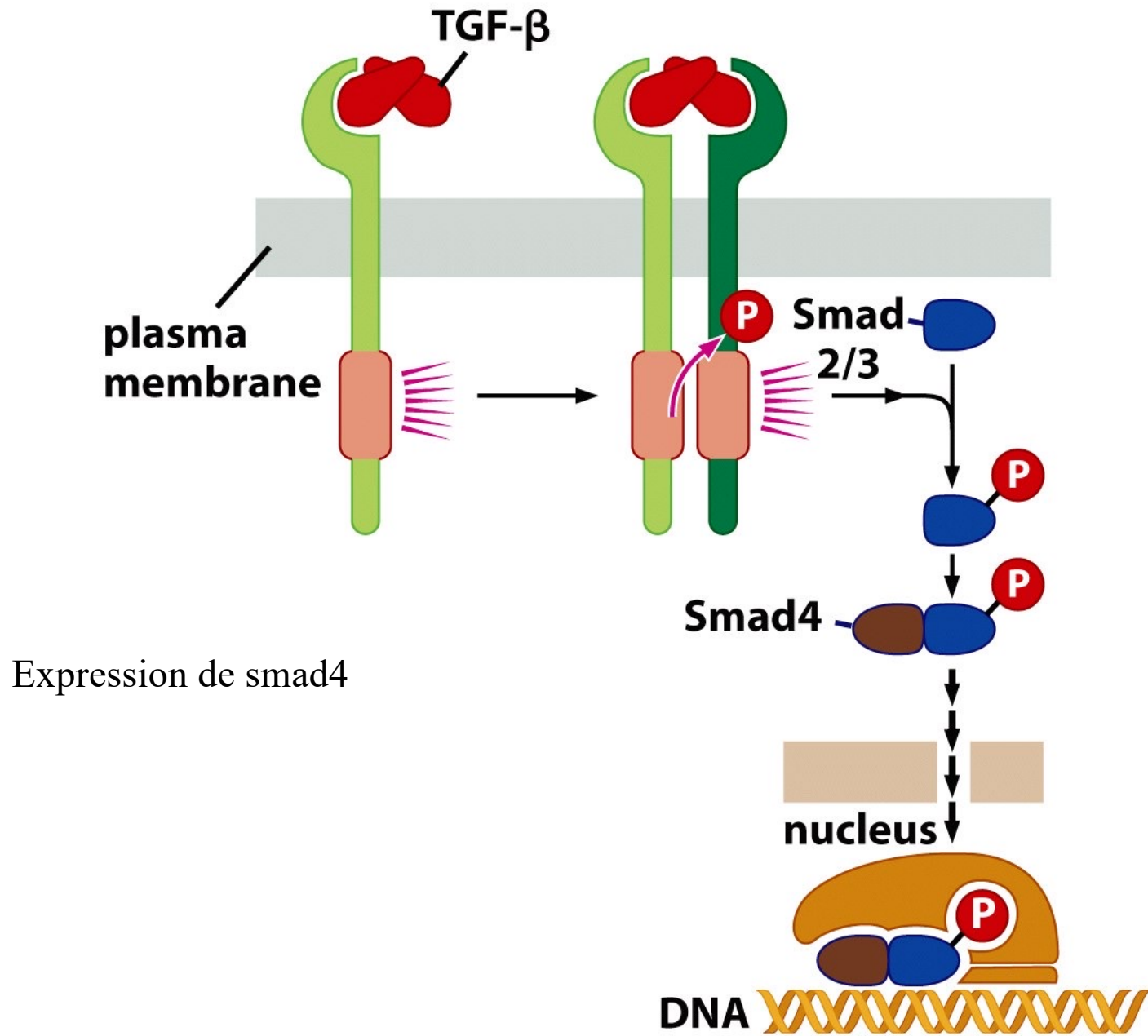


Figure 6.29d *The Biology of Cancer* (© Garland Science 2007)

Contrôle négatif de la progression du cycle cellulaire par le TGFbeta et induction des CDKN

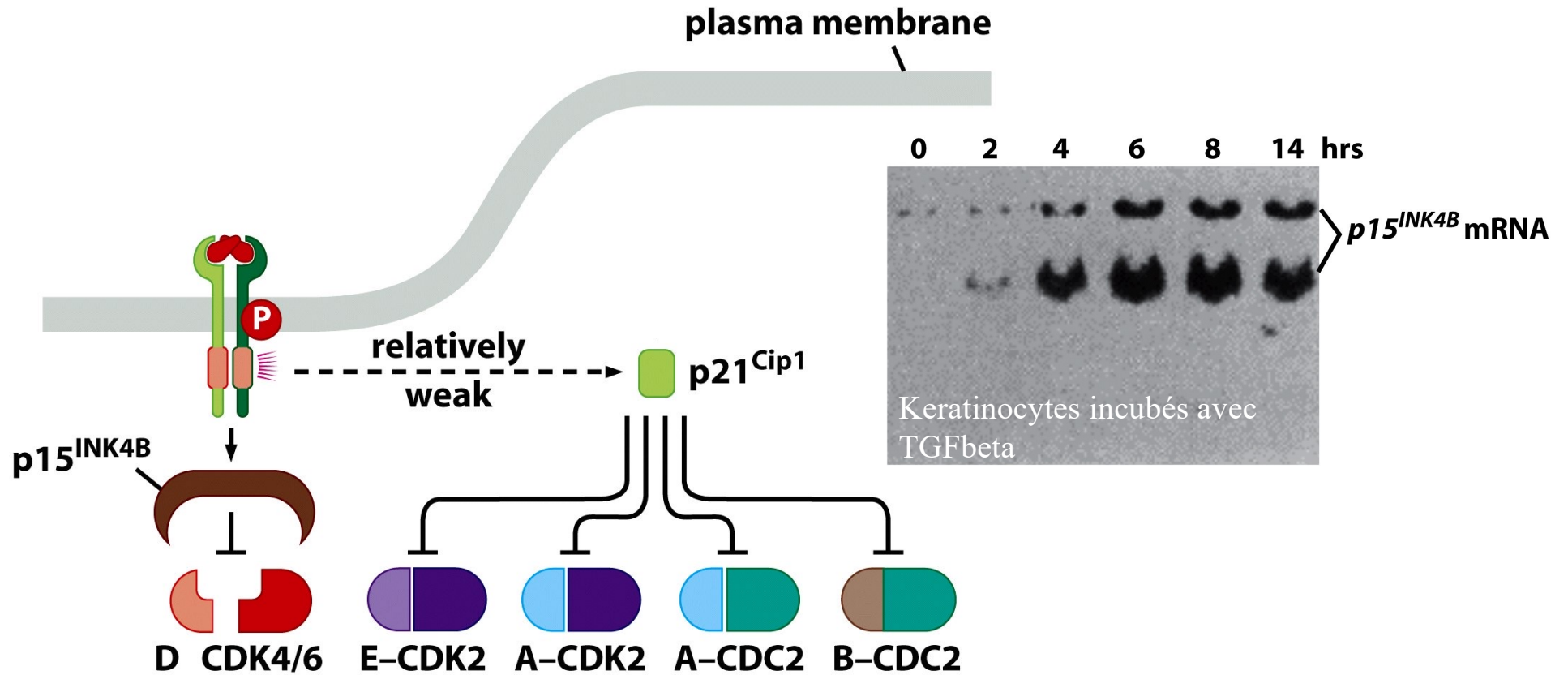


Figure 8.14a *The Biology of Cancer* (© Garland Science 2007)

Conséquence d'un déficit dans les gènes codant les enzymes MMR (réparation des misappariements)

Expansion ou raccourcissement des microsatellites. Dans le cas du TGFbetaIR, arrêt du cadre de lecture. Les cellules deviennent insensibles à l'effet antiprolifératif du TGFbeta; observé dans 100/110 carcinomes du colon (HNPCC, hereditary no polyposis colon carcinomas, 4% de ces carcinomes).

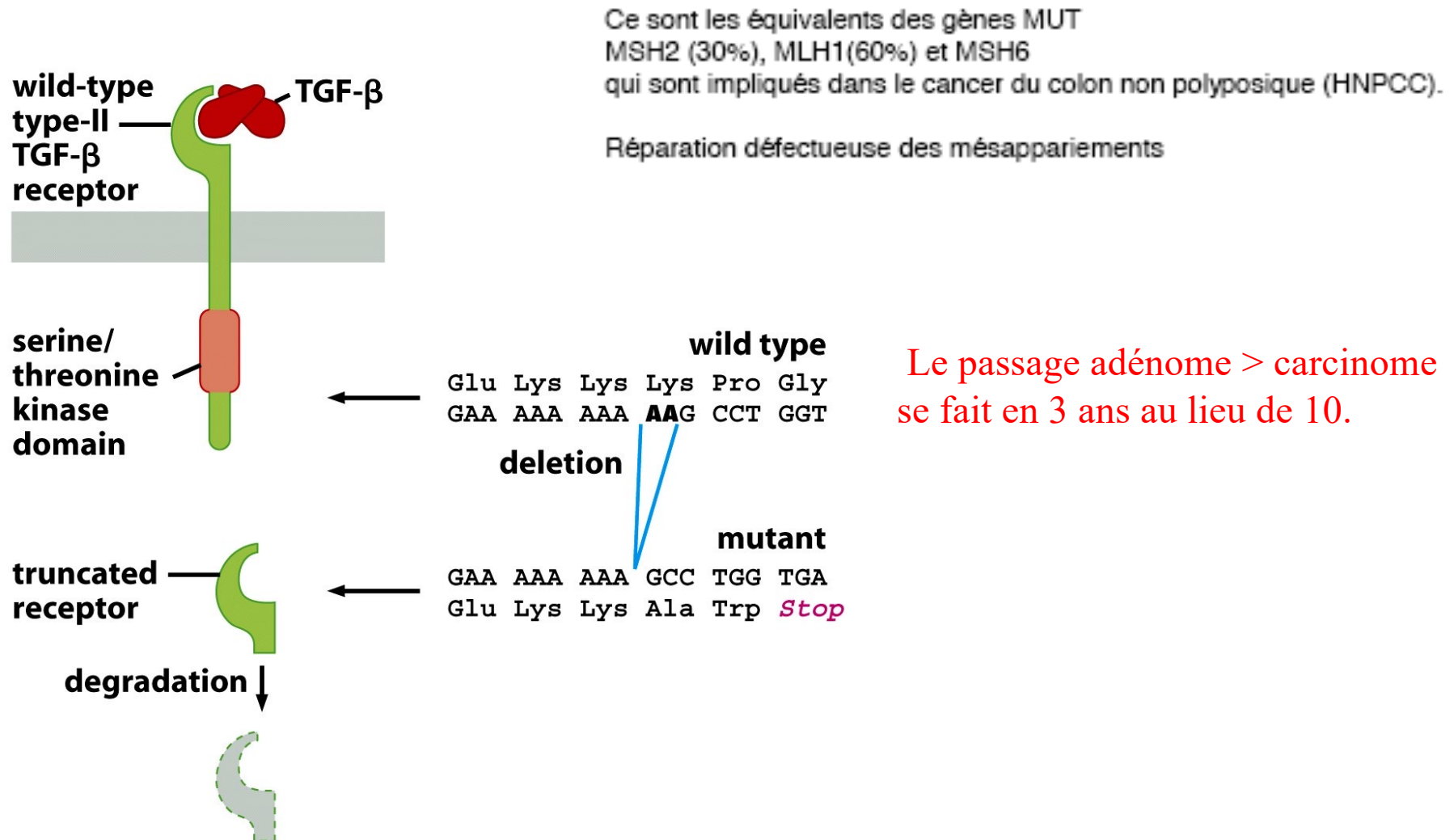


Figure 12.28 *The Biology of Cancer* (© Garland Science 2007)

III –Cancer as an infectious disease?

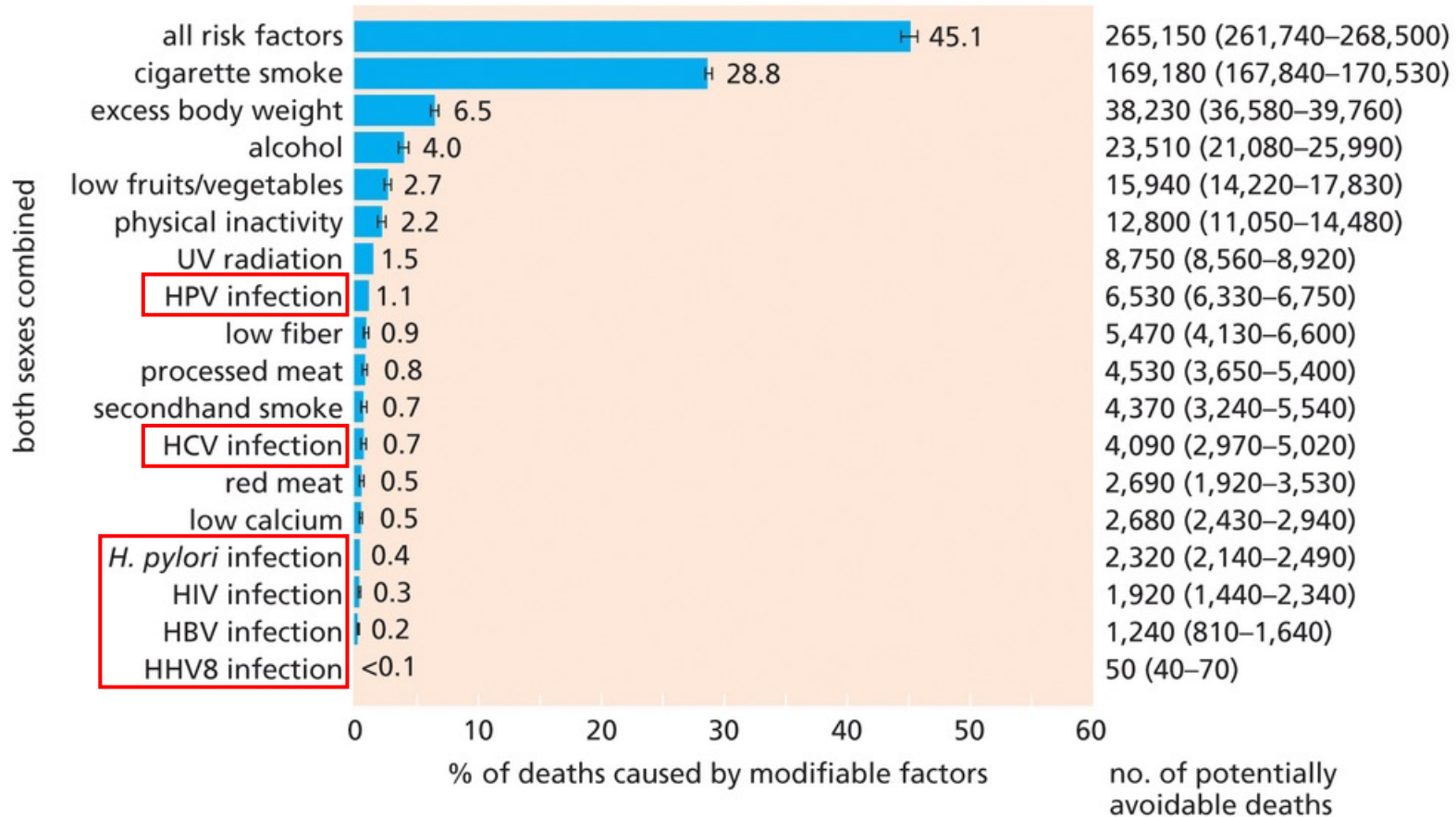


Table 2.2.1. Estimated numbers of new cancer cases in 2018 attributable to infectious agents

Infectious agent	Cancer types for which there is sufficient evidence of causality	Number of new cancer cases
<i>Helicobacter pylori</i>	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma	810 000
Human papillomavirus	Carcinomas of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil	690 000
Hepatitis B virus (chronic infection)	Hepatocellular carcinoma	360 000
Hepatitis C virus	Hepatocellular carcinoma, non-Hodgkin lymphoma	160 000
Epstein–Barr virus	Nasopharyngeal carcinoma, Burkitt lymphoma, immunosuppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma	160 000
Kaposi sarcoma-associated herpesvirus	Kaposi sarcoma, primary effusion lymphoma	42 000
Human T-cell lymphotropic virus type 1	Adult T-cell leukaemia/lymphoma	3 600
HIV-1	Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, cervical cancer, anal cancer, conjunctival cancer	— ^a
<i>Schistosoma haematobium</i>	Bladder cancer	6 000
<i>Opisthorchis viverrini</i> <i>Clonorchis sinensis</i>	Cholangiocarcinoma	3 600

^a Cancers attributable to HIV are included with the underlying causal infections.

FUNDAMENTALS

- Eleven infectious agents, or groups of related agents, are established human carcinogens, including one bacterium, seven viruses, and three macroparasites.
- About 13% of cancers worldwide, or 2.2 million cases per year, are caused by chronic infections. This proportion varies by geographical region and World Bank income group; it is highest in the lowest-income regions, especially for cervical cancers caused by human papillomaviruses. In sub-Saharan Africa, at least one third of cancer cases are of infectious origin, and the proportion may be significantly underestimated, because there is limited cancer registration in many countries in this region.
- Four agents – *Helicobacter pylori*, human papillomaviruses, hepatitis B virus, and hepatitis C virus – contribute most to the burden of cancer caused by infections globally. Several carcinogenic infectious agents, including *H. pylori*, hepatitis B virus, hepatitis C virus, Epstein–Barr virus, HIV, and macroparasites, also cause substantial morbidity and mortality from non-malignant diseases.

Tumor virus groups and associated cancers

Taxonomic group

- RNA viruses

Retroviruses

- DNA viruses

Hepadnaviruses (3Kb)

Polyomaviruses (5Kb)

Papillomaviruses (8Kb)

Adenoviruses (35Kb)

Herpesviruses (120Kb)

Poxviruses (150Kb)

Associated cancers

Hematopoietic cancers involving lymphoid, myeloid, or erythroid cells; various sarcoma and carcinoma

Hepatocellular carcinoma

Various solid tumors

papilloma and carcinoma

Various solid tumors

lymphoma and carcinoma

Myxoma and fibroma

Les virus tumoraux induisent plusieurs types de phénotypes cellulaires, incluant l'acquisition de la tumorigénicité

Altered morphology (rounded shape, refractile in phase-contrast microscope)

Loss of contact inhibition (ability to grow over one another)

Ability to grow without attachment to solid substrate (anchorage independence)

Ability to proliferate indefinitely (immortalization)

Reduced requirement for mitogenic growth factors

High saturation density (ability to accumulate large numbers of cells in culture dish)

Inability to halt proliferation in response to deprivation of growth factors

Increased transport of glucose

Tumorigenicity

Adapted in part from S.J. Flint, L.W. Enquist, R.M. Krug et al., Principles of Virology. Washington, DC: ASM Press, 2000.
Table 3.2 The Biology of Cancer (© Garland Science 2014)

Croissance dans un milieu semi-solide

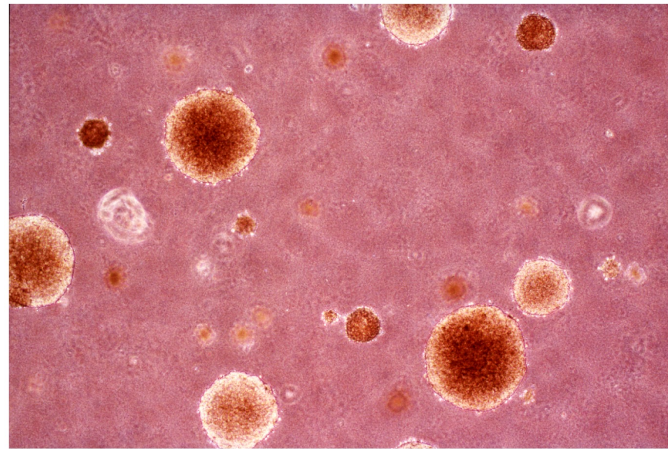


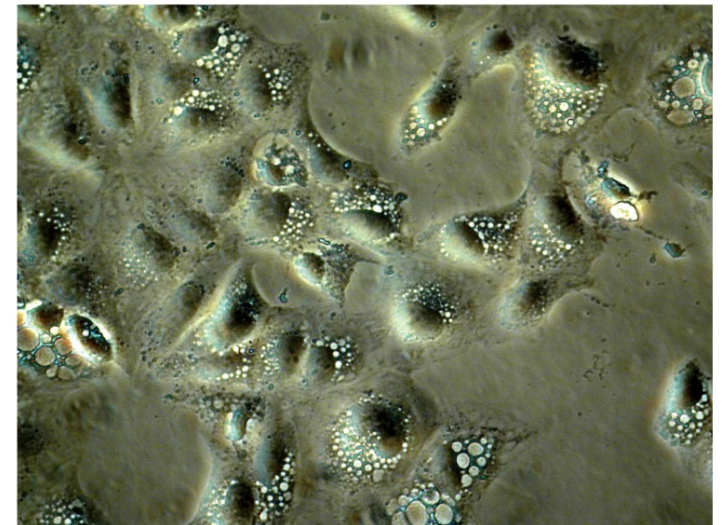
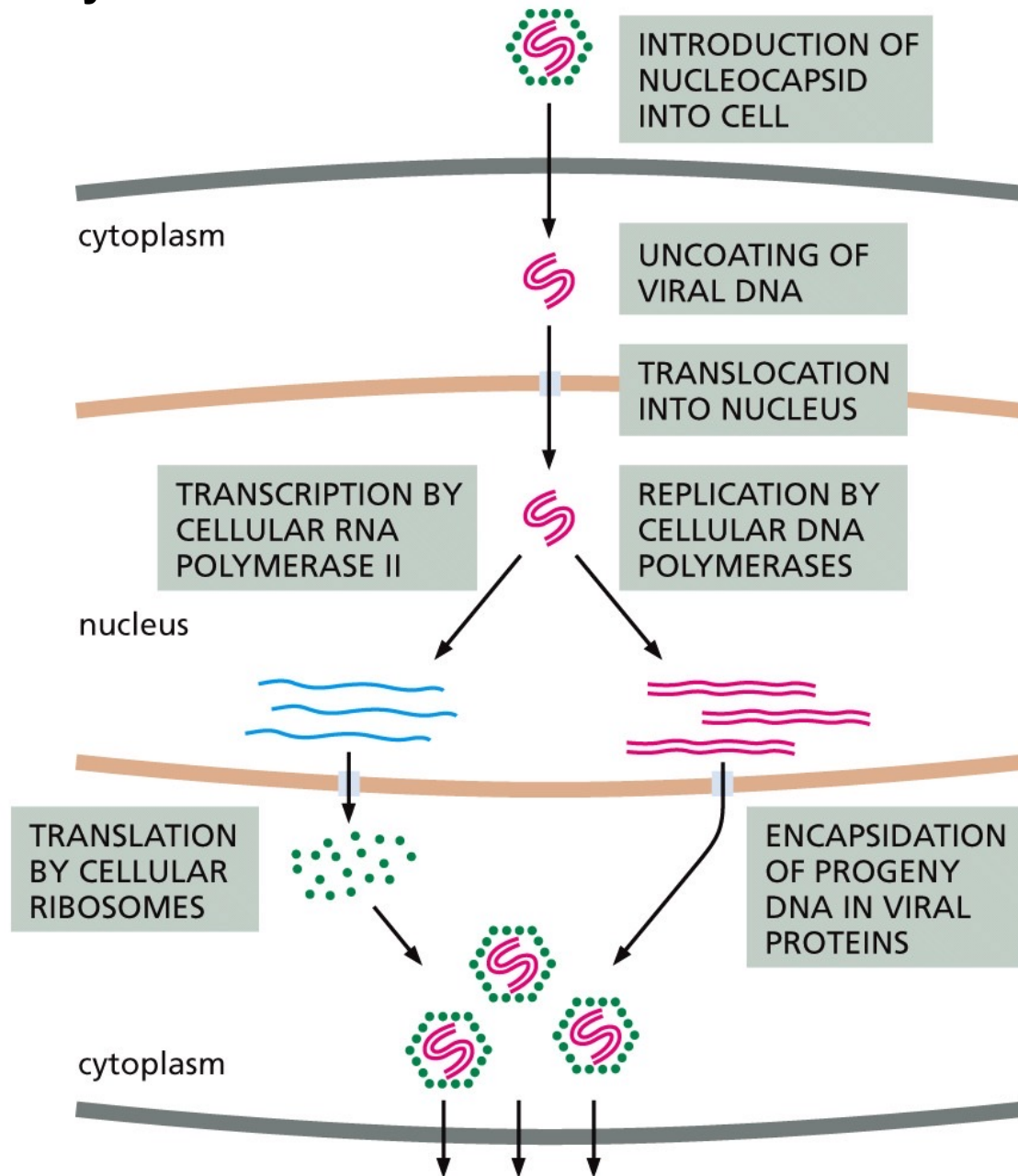
Figure 3.12 The Biology of Cancer (© Garland Science 2014)

Test de tumorigénicité dans des souris Nude



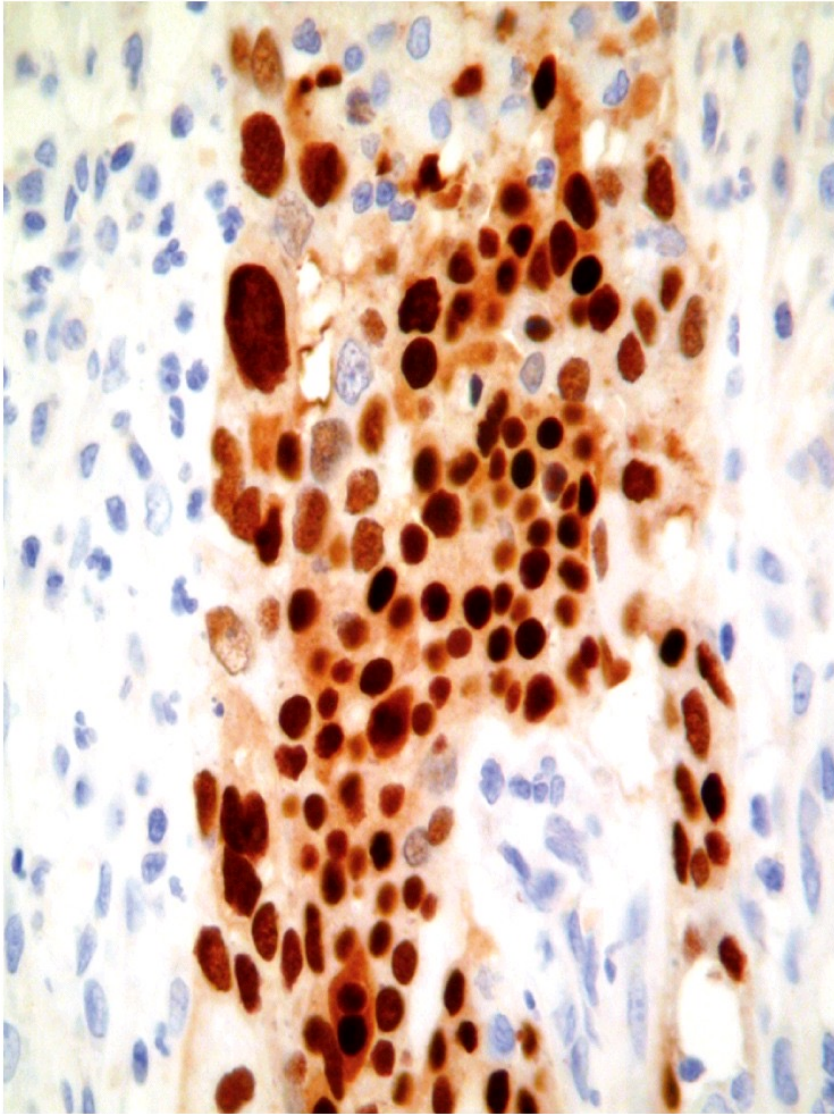
Figure 3.13 The Biology of Cancer (© Garland Science 2014)

Cycle de « vie » de virus à ADN double brin



Cycle lytique dans des cellules de reins de singe (→ formation de vacuoles) induit la mort de la cellule ≠ rétrovirus

Le génome des virus tumoraux peut s'intégrer dans le génome des cellules infectées



Carcinome de la vessie.

Présence de l'antigène T d'un virus proche de SV40 (virus BK)

Le génome des virus tumoraux peut s'intégrer dans le génome des cellules infectées

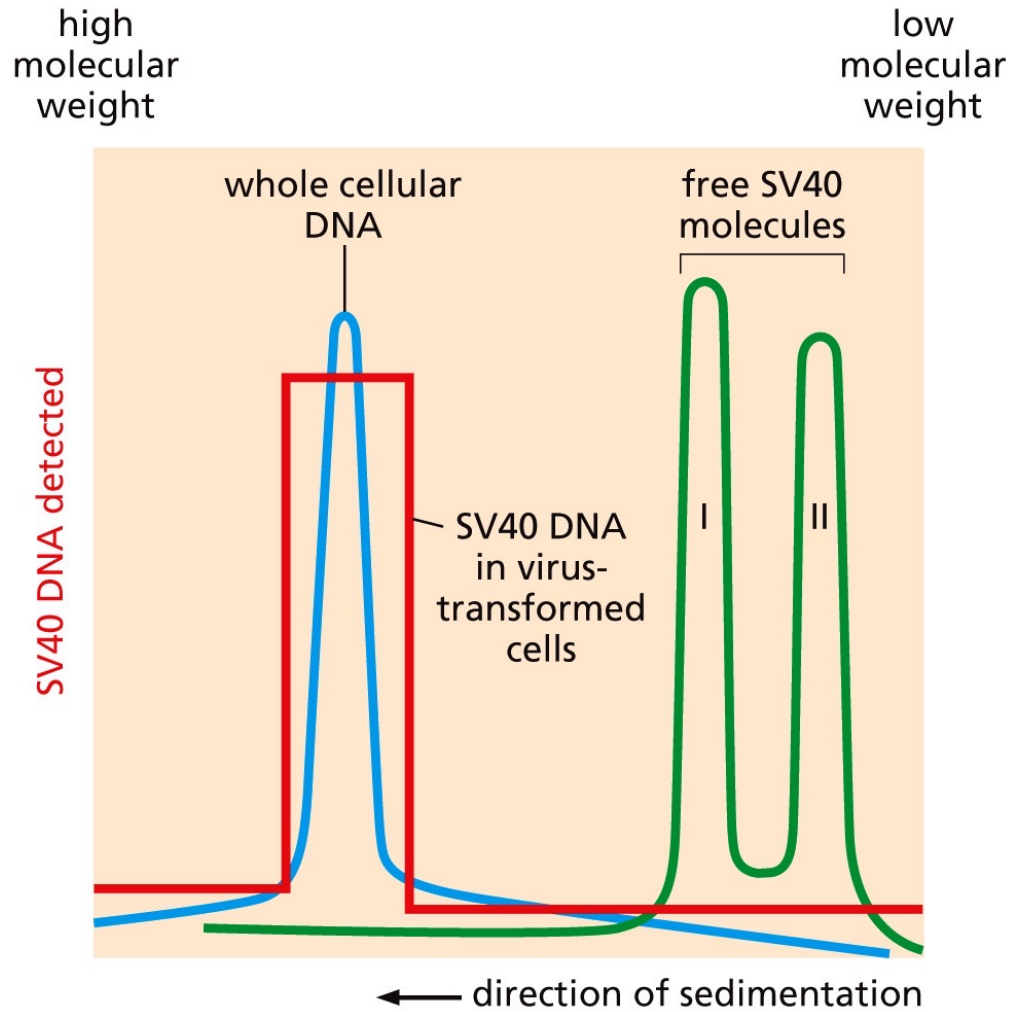


Figure 3.15 The Biology of Cancer (© Garland Science 2014)



Figure 3.11 The Biology of Cancer (© Garland Science 2014)

Génome de SV40

→ Co-sédimentation du génome de SV40 avec le génome cellulaire

Le génome des virus tumoraux peut s'intégrer dans le génome des cellules infectées

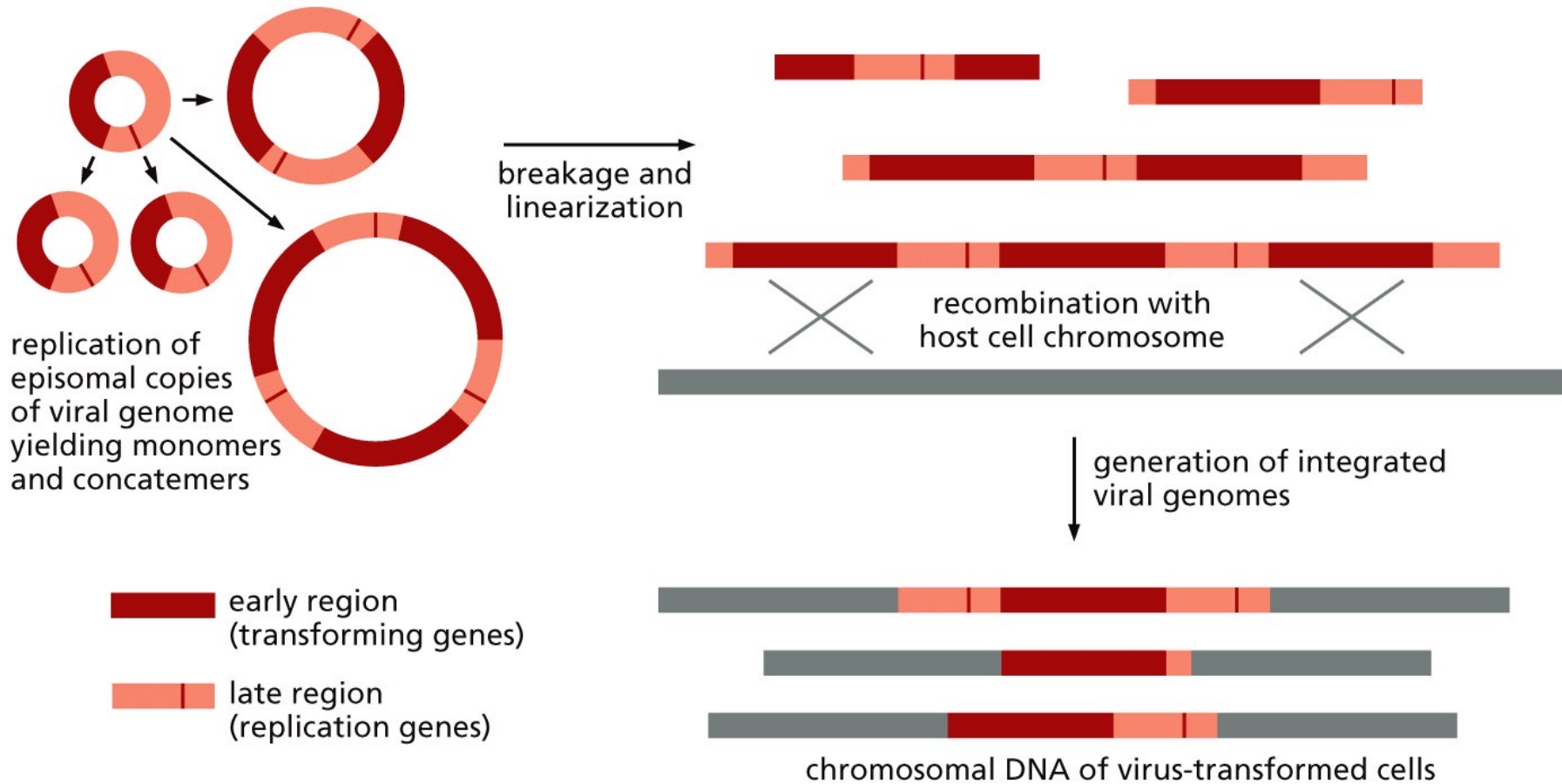
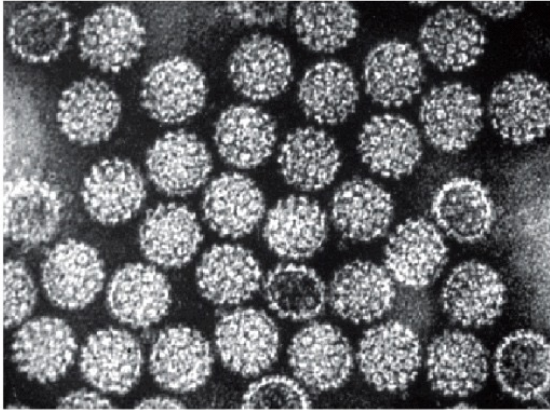


Figure 3.16 The Biology of Cancer (© Garland Science 2014)

**Mécanisme moléculaire sous-jacents à l'intégration du génome de SV40
→ Recombinaison non-homologue à des sites aléatoires**

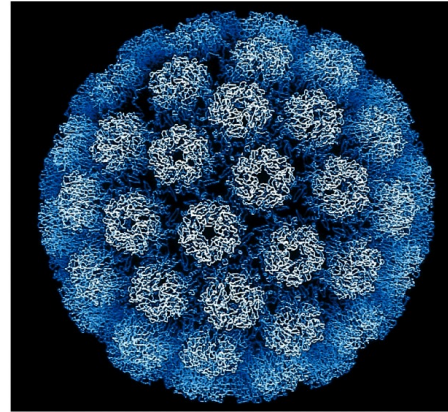
Des Virus à ADN peuvent induire des cancers (oncovirus)

Virus du papillome humain

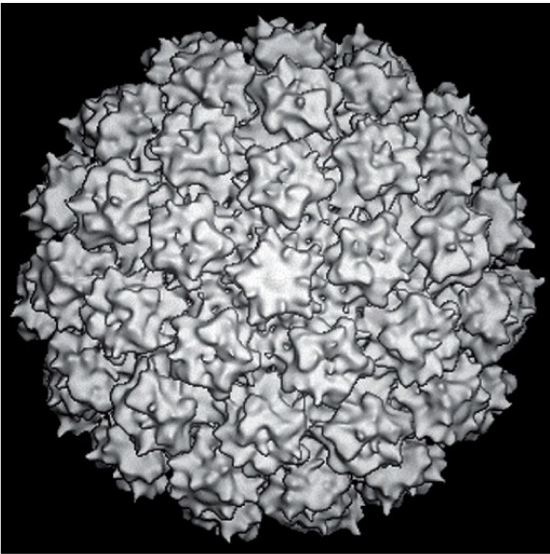


(A)

SV40 (Simian Virus N°40)



3 protéines qui s'assemblent en pentamères et en hexamères donnant une symétrie icosaédrique



(B)

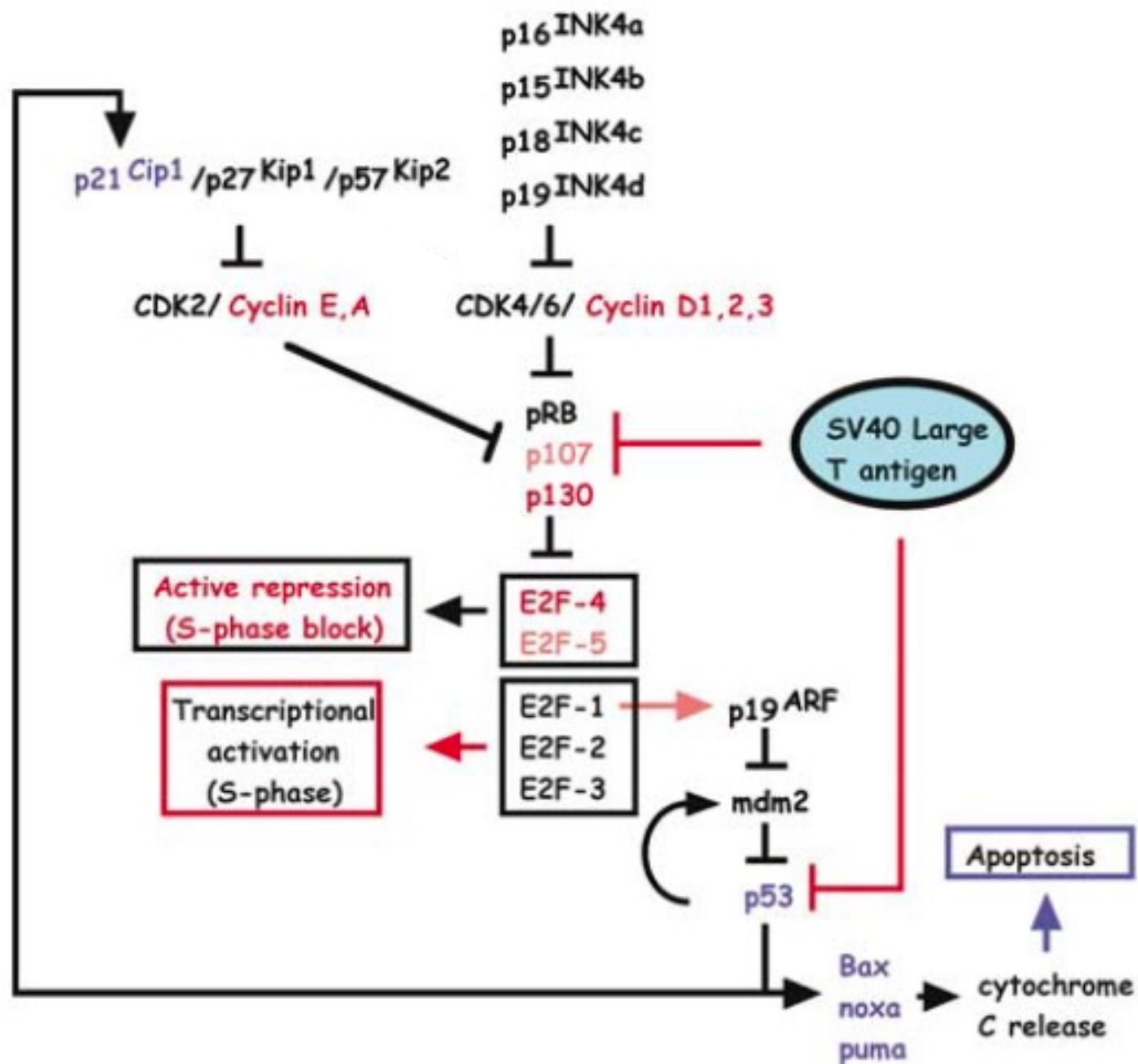
Les fonctions des antigènes de tumeur du polyomavirus murin

Antigène LT essentiel pour l'immortalisation in vitro

- Initiation de la synthèse de l'ADN viral
- Régulation de la transcription
- Fixation de pRb et promotion de la transition G1→S
- Fixation de p300/CBP
- Fixation de p53
- Domaine chaperone

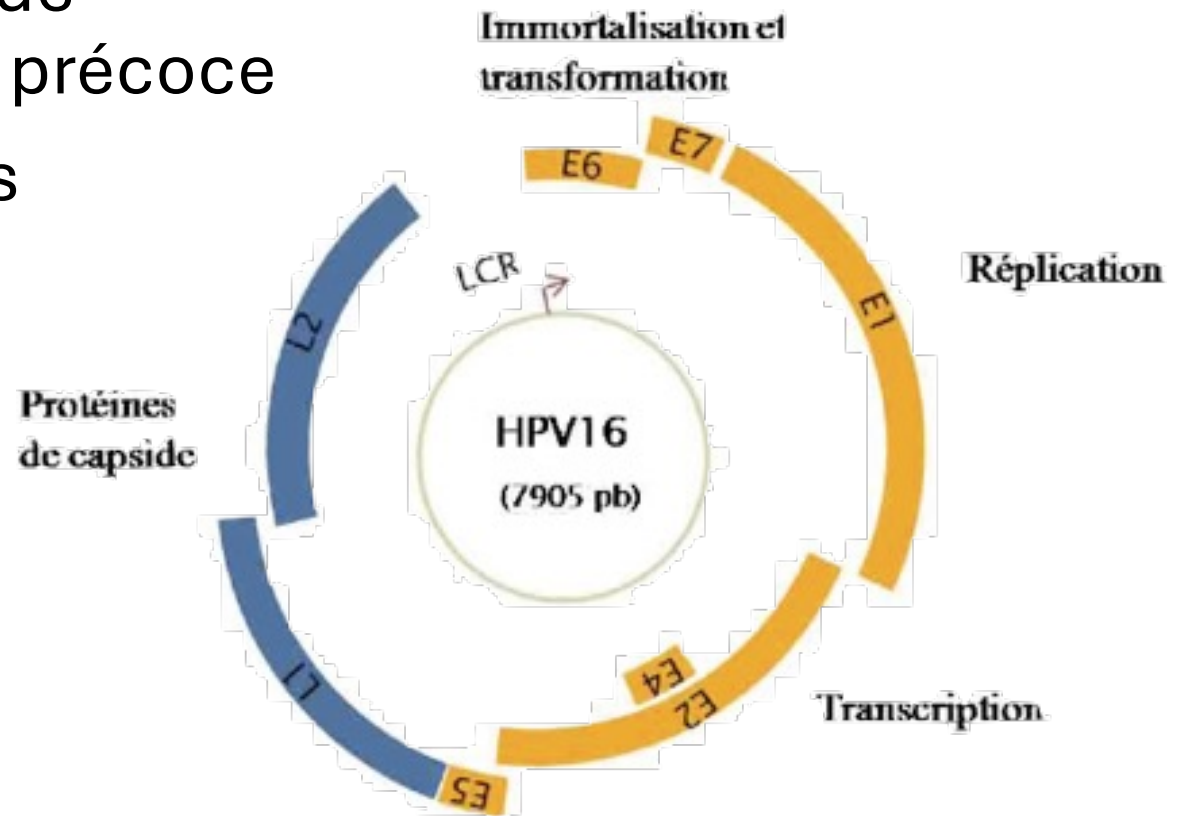
Antigène sT essentiel pour la transformation in vitro

- Fixe et inhibe PP2A
- Active la voie MAP kinase
- Transactive les promoteurs de cyclines

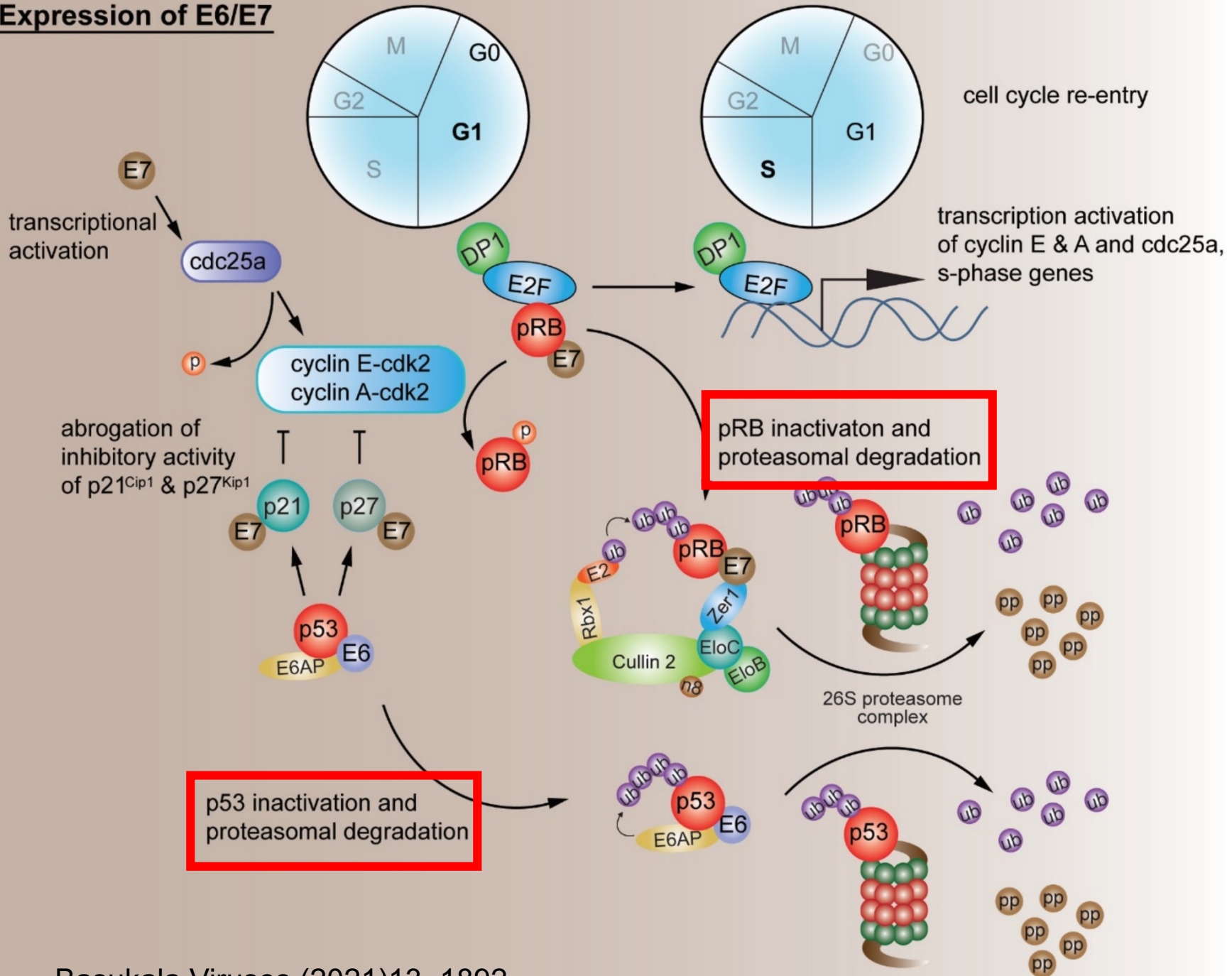


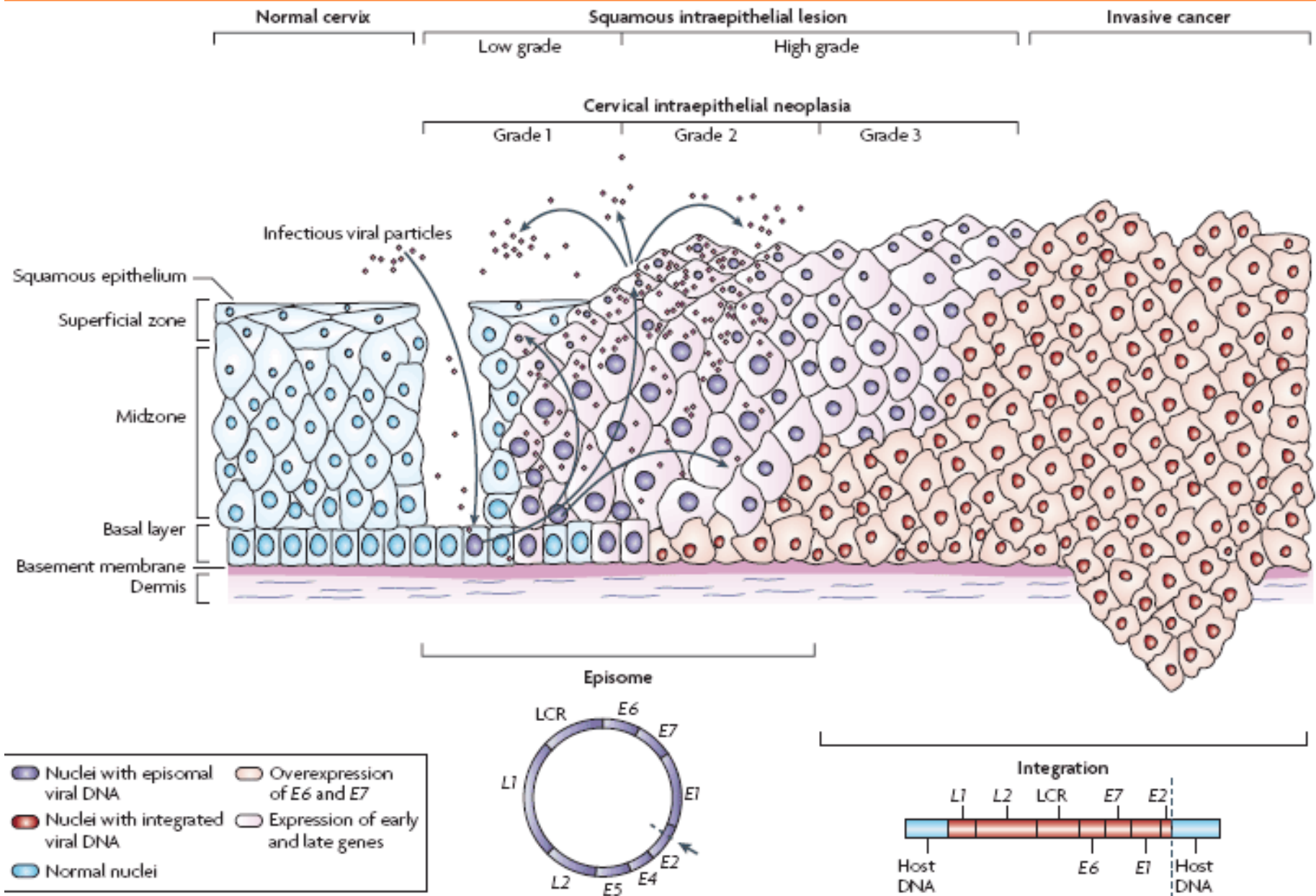
Structure HPV (Papillomavirus humain)

- 6 phases ouvertes de lecture d'expression précoce
- E6 et E7 oncogènes

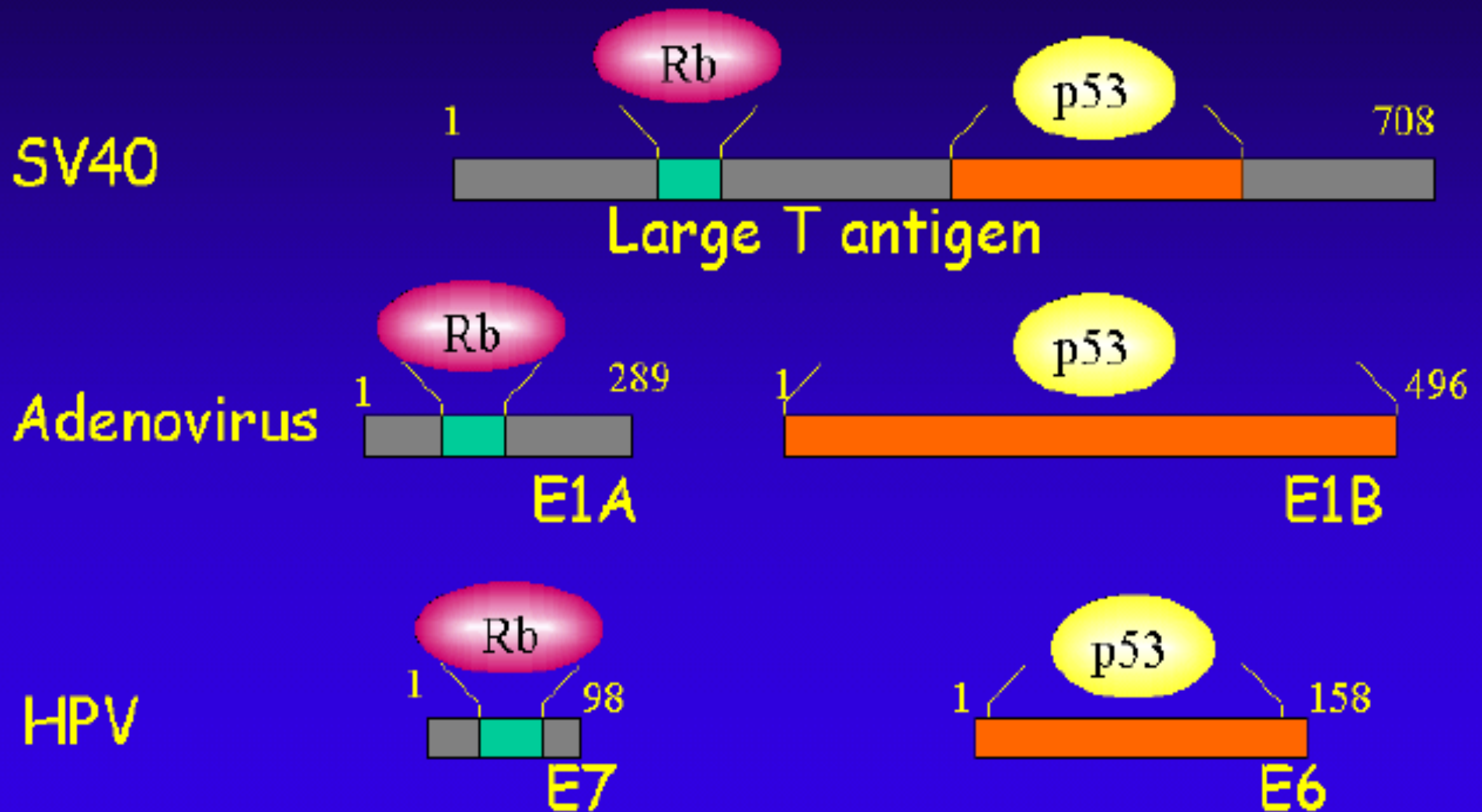


Expression of E6/E7





DNA tumor viruses bind multiple cellular proteins



Les Rétrovirus (virus à ARN)

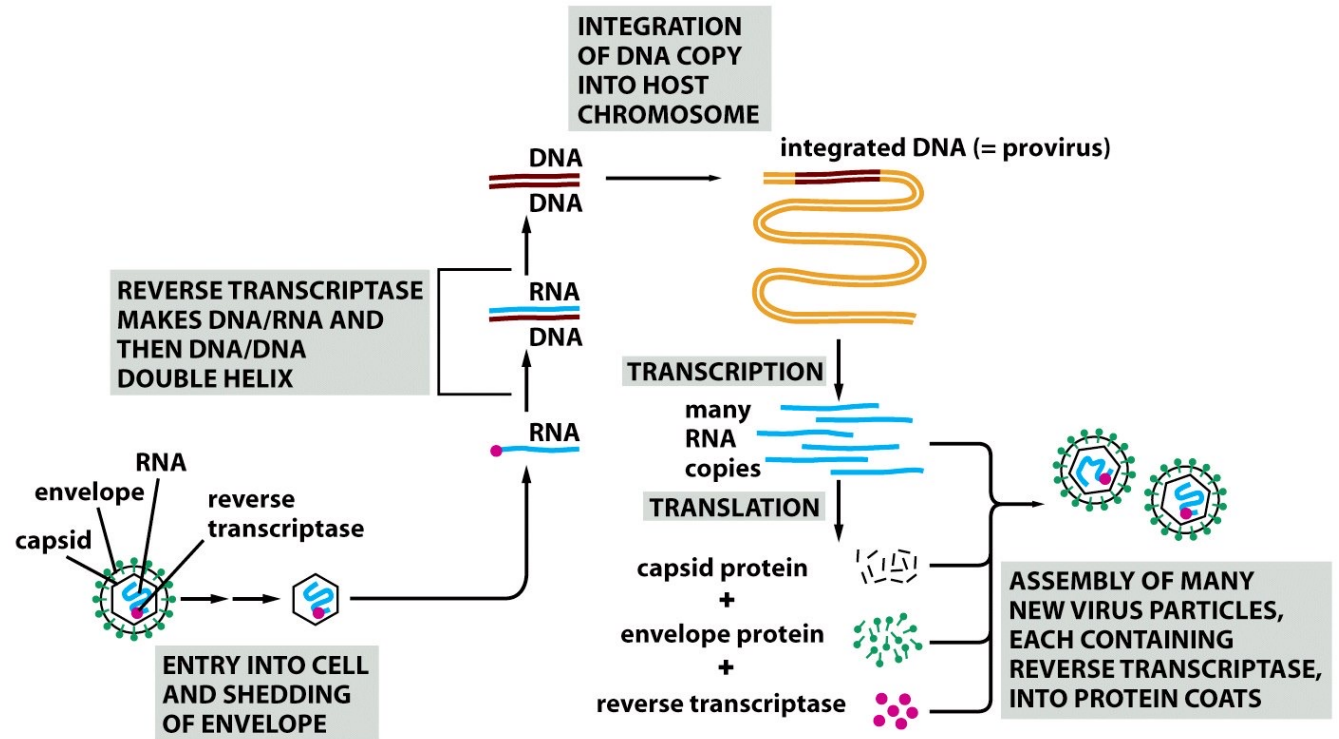
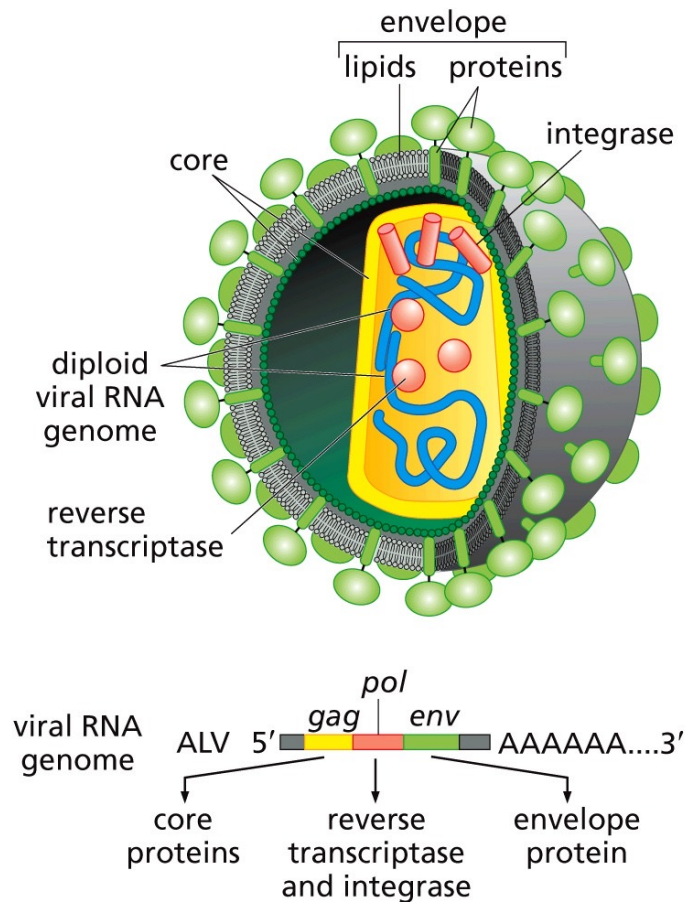


Figure 3.4a The Biology of Cancer (© Garland Science 2014)

Structure et Génome d'un Rétrovirus

Cycle de vie d'un rétrovirus

Des rétrovirus dépourvus d'oncogène peuvent transformer des cellules par mutagenèse insertionnelle

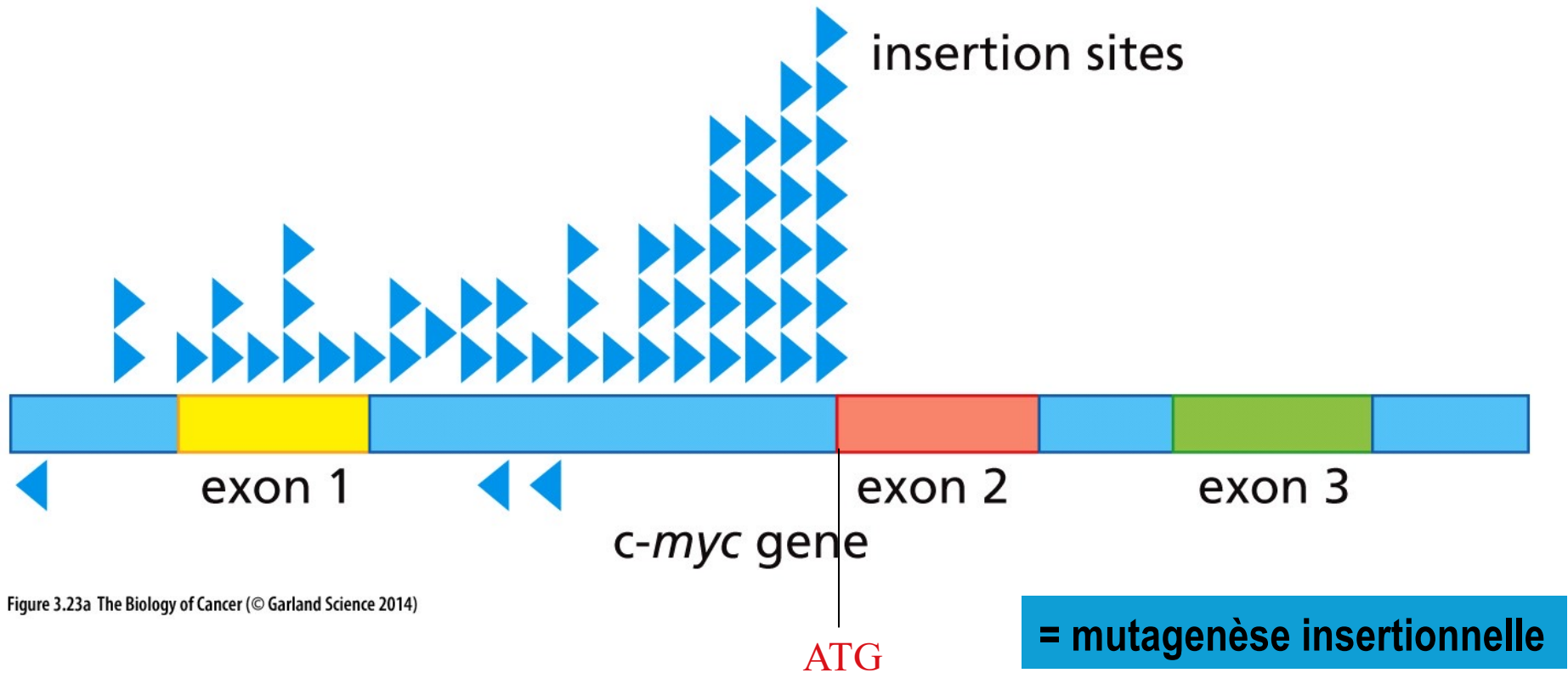


Figure 3.23a The Biology of Cancer (© Garland Science 2014)

Le virus ALV insère son génome de façon (*a priori*) aléatoire chez l'hôte, mais dans les cellules transformées (leucémie) on le retrouve essentiellement dans les séquences régulatrices du gène *c-myc*

→ sur-expression ... avantage sélectif lié à une prolifération accrue et incontrôlée

Table 3.4 Examples of cellular genes found to be activated by insertional mutagenesis

Gene	Insertional mutagen	Tumor type	Species	Type of oncoprotein
<i>myc</i>	ALV	B-cell lymphoma	chicken	transcription factor
<i>myc</i>	ALV, FeLV	T-cell lymphoma	chicken, cat	transcription factor
<i>nov</i>	ALV	nephroblastoma	chicken	growth factor
<i>erbB</i>	ALV	erythroblastosis	chicken	receptor TK
<i>mos</i>	IAP	plasmacytoma	mouse	ser/thr kinase
<i>int-1^a</i>	MMTV	mammary carcinoma	mouse	growth factor
<i>int-2^b</i>	MMTV	mammary carcinoma	mouse	growth factor
<i>int-3</i>	MMTV	mammary carcinoma	mouse	receptor ^c
<i>int-H/int-5</i>	MMTV	mammary carcinoma	mouse	enzyme ^d
<i>pim-1</i>	Mo-MLV	T-cell lymphoma	mouse	ser/thr kinase
<i>pim-2</i>	Mo-MLV	B-cell lymphoma	mouse	ser/thr kinase
<i>bmi-1</i>	Mo-MLV	T-cell lymphoma	mouse	transcription repressor
<i>tpl-2</i>	Mo-MLV	T-cell lymphoma	mouse	non-receptor TK
<i>lck</i>	Mo-MLV	T-cell lymphoma	mouse	non-receptor TK
<i>p53</i>	Mo-MLV	T-cell lymphoma	mouse	transcription factor
<i>GM-CSF</i>	IAP	myelomonocytic leukemia	mouse	growth factor
<i>IL2</i>	GaLV	T-cell lymphoma	gibbon ape	cytokine ^e
<i>IL3</i>	IAP	T-cell lymphoma	mouse	cytokine
<i>K-ras</i>	F-MLV	T-cell lymphoma	mouse	small G protein
<i>CycD1</i>	F-MLV	T-cell lymphoma	mouse	G1 cyclin
<i>CycD2</i>	Mo-MLV	T-cell lymphoma	mouse	G1 cyclin

^aSubsequently renamed *Wnt-1*.

^bSubsequently identified as a gene encoding a fibroblast growth factor (FGF).

^cRelated to notch receptors.

^dEnzyme that converts androgens to estrogens.

^eCytokines are GFs that largely regulate various types of hematopoietic cells.

Abbreviations: ALV, avian leukosis virus; FeLV, feline leukemia virus; F-MLV, Friend murine leukemia virus; GaLV, gibbon ape leukemia virus; GF, growth factor; IAP, intracisternal A particle (a retrovirus-like genome that is endogenous to cells); Mo-MLV, Moloney murine leukemia virus; MMTV, mouse mammary tumor virus; ser/thr, serine/threonine; TK, tyrosine kinase.

Adapted in part from J. Butel, *Viral carcinogenesis: Revelation of molecular mechanisms and etiology of human disease*, *Carcinogenesis* 21:405–426, 2000; and from N. Rosenberg and P. Jolicoeur, *Retroviral pathogenesis*, in J.M. Coffin, S.H. Hughes and H.E. Varmus (eds.), *Retroviruses*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1997. Also in part from G.M. Cooper, *Oncogenes*, 2nd ed. Boston: Jones and Bartlett Publishers, 1995.

Peyton Rous (1879-1970) prix Nobel 1966, isole le virus du sarcome de Rous (RSV) en 1910

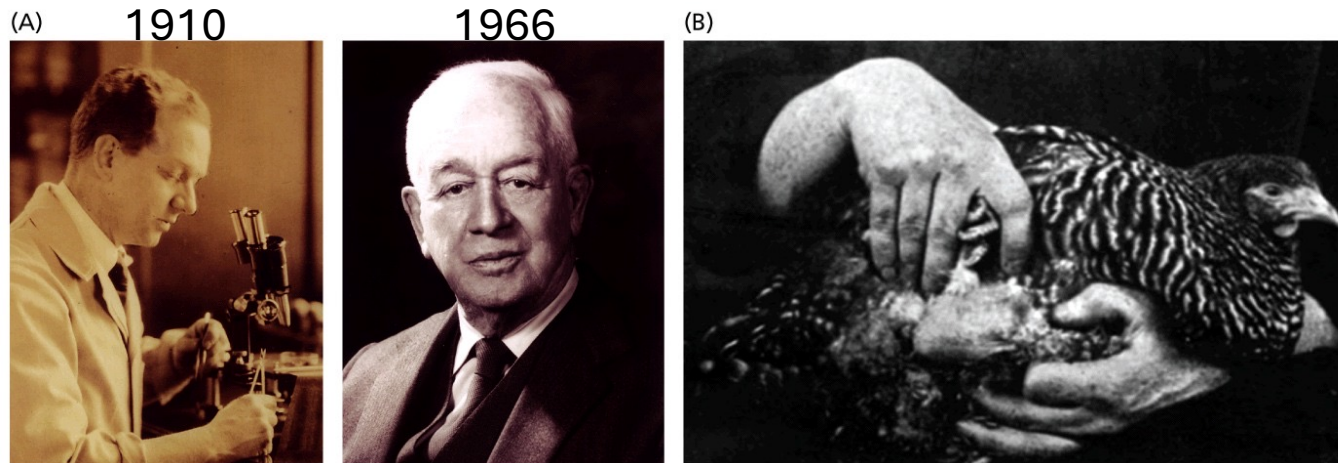


Figure 3.1 The Biology of Cancer (© Garland Science 2014)

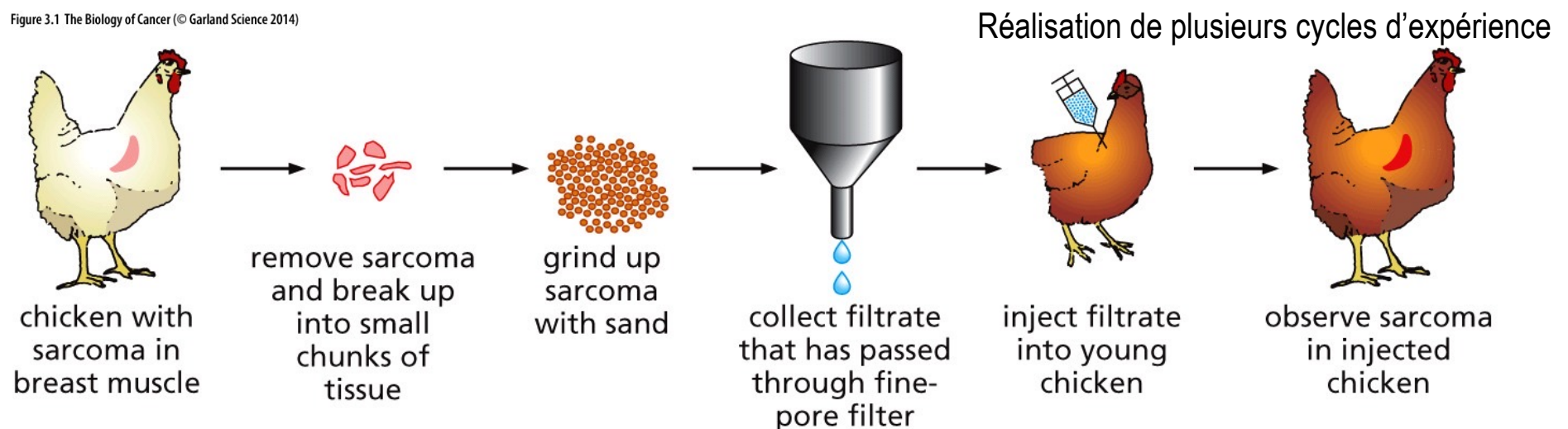


Figure 3.2 The Biology of Cancer (© Garland Science 2014)

- Présence d'un « petit » agent carcinogène infectieux = RSV
- Cet agent (le RSV) est capable de se multiplier dans le tissu de l'hôte
 → le cancer serait-il une maladie infectieuse ?

RSV transforme des cellules infectées en culture

Harry Rubin (Post-Doc) et Howard Temin (étudiant) dans le laboratoire de Rénato Dubelcco au California Institute of Technology, à Pasadena, introduisent des stocks de RSV dans des boîtes de Petri contenant des fibroblastes de Poule.



Howard Temin
(Nobel en 1975)

→ Les cellules sont comme « parasitées » par le RSV et se mettent à produire de grandes quantités de RSV.

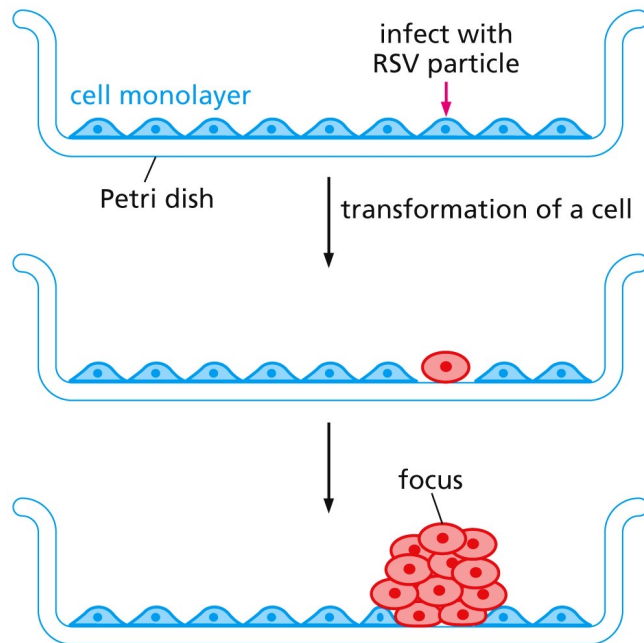


Figure 3.7a The Biology of Cancer (© Garland Science 2014)

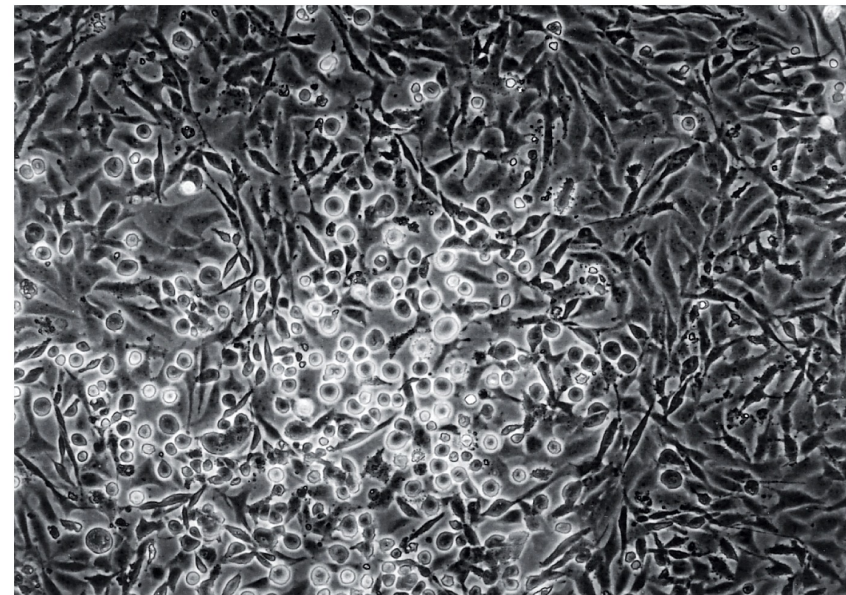
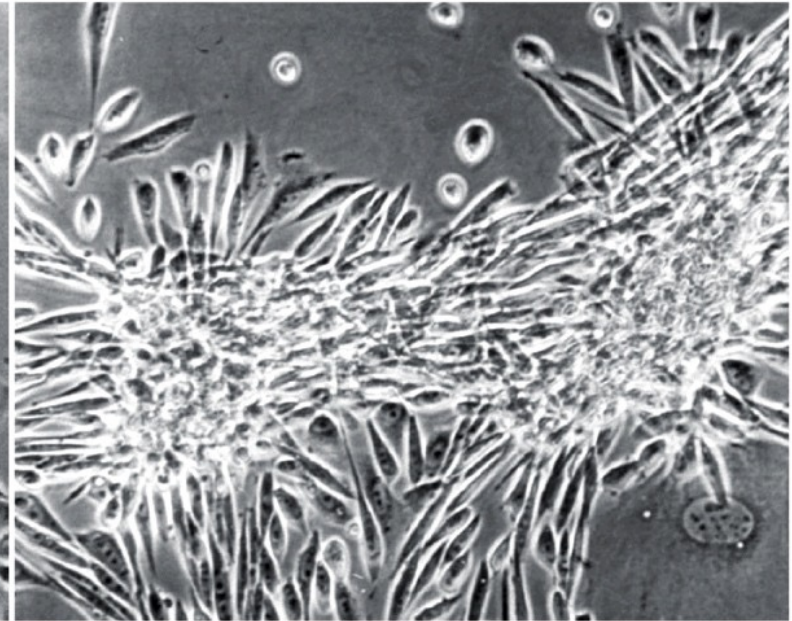
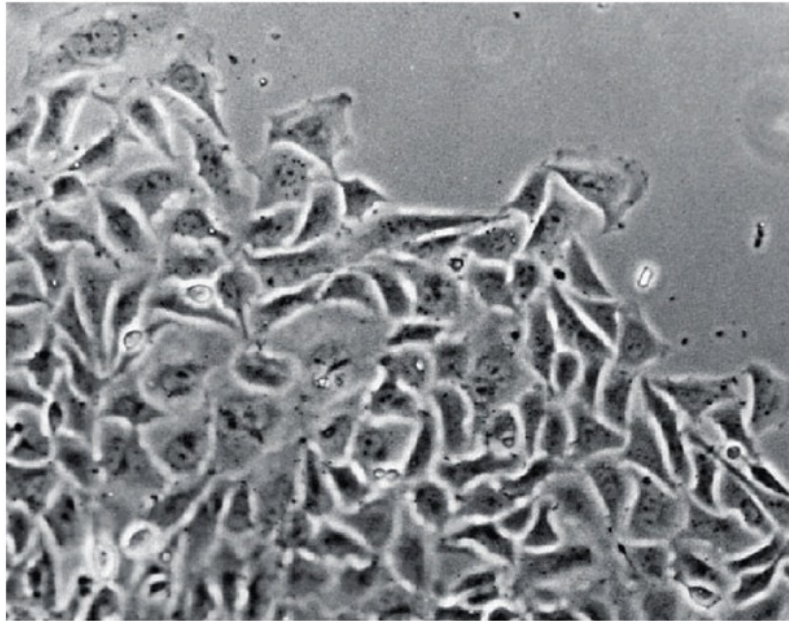


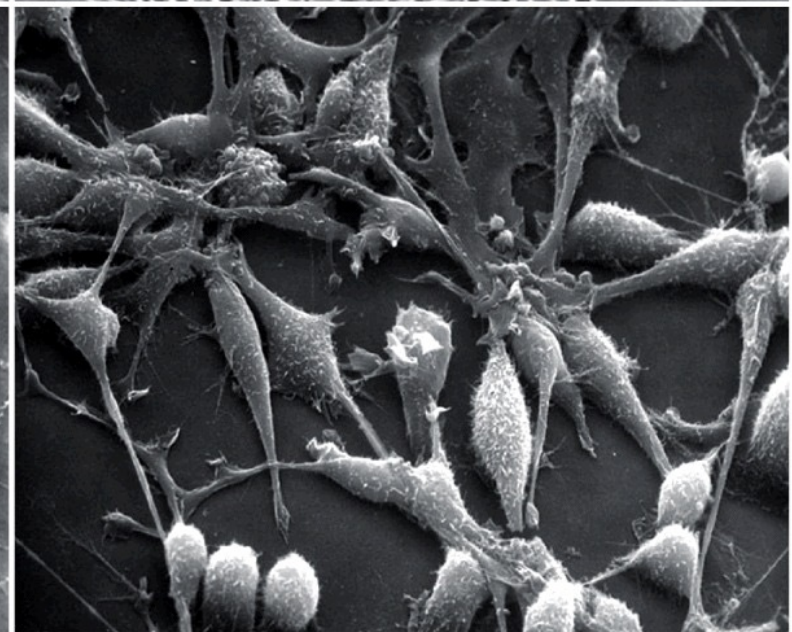
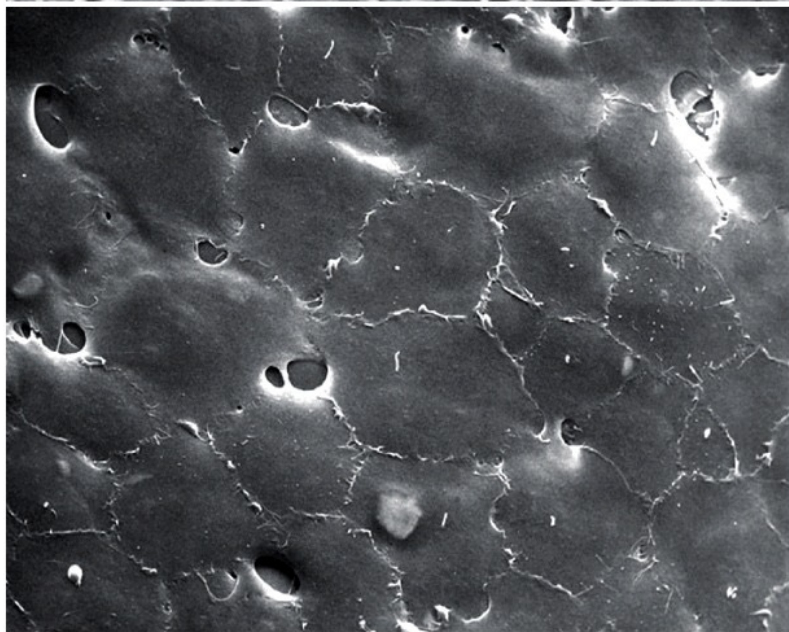
Figure 3.5 The Biology of Cancer (© Garland Science 2014)

→ Formation de foci de cellules transformées *in vitro*
→ Survie des cellules « apparemment » indéfiniment

Contraste
de phase



MEB



Cellules contrôle

Cellules transformées par le RSV

La présence du génome de RSV est nécessaire pour maintenir la transformation

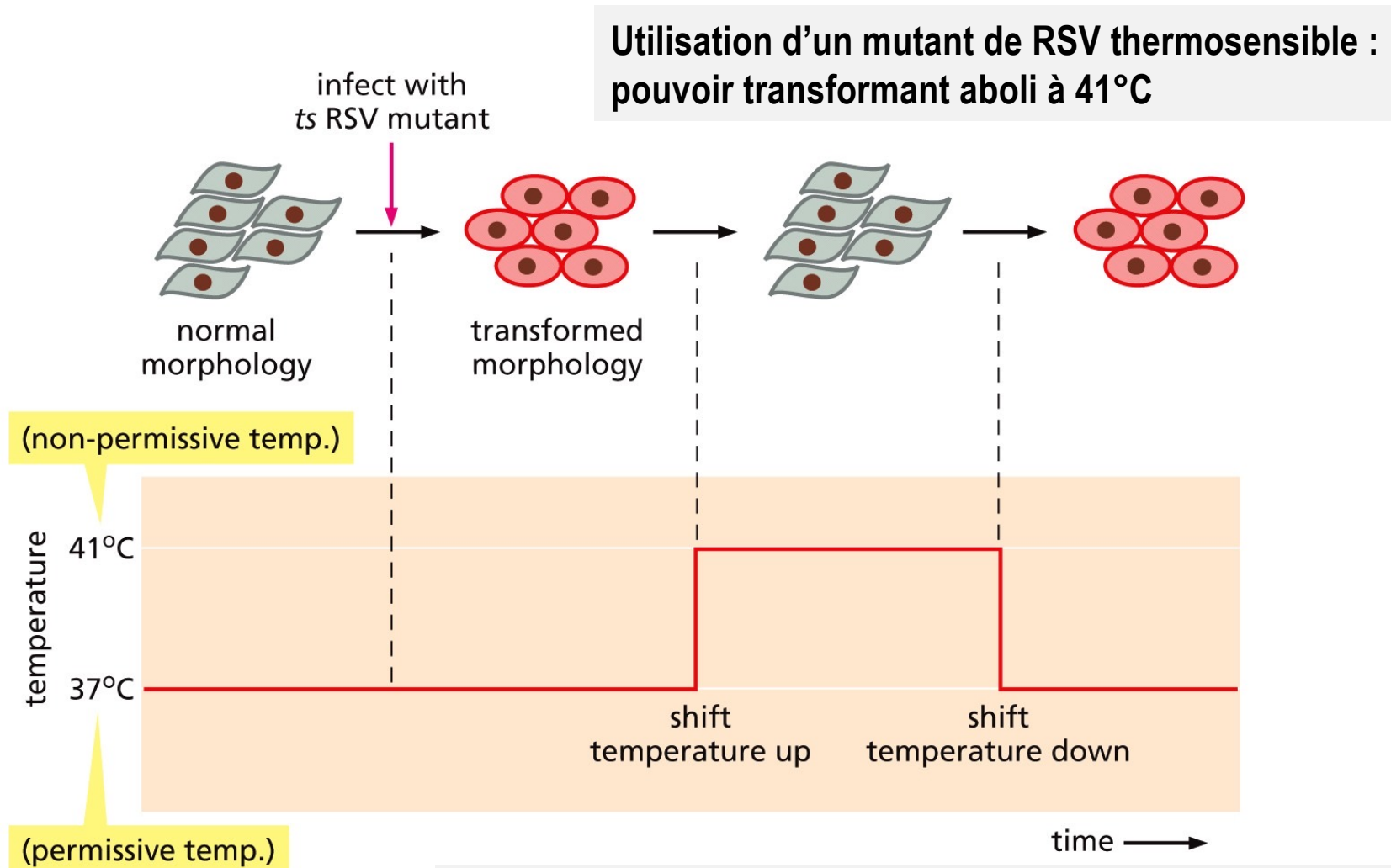


Figure 3.8 The Biology of Cancer (© Garland Science 2014)

Remarque : pas de virus dans le milieu après la 1^{ère} infection, fonctionne avec un RSV incapable de se répliquer. La ré-infection ne peut pas expliquer la transmission stable du génome RSV sur de nombreux cycles de division

La présence du génome de RSV est nécessaire pour maintenir la transformation

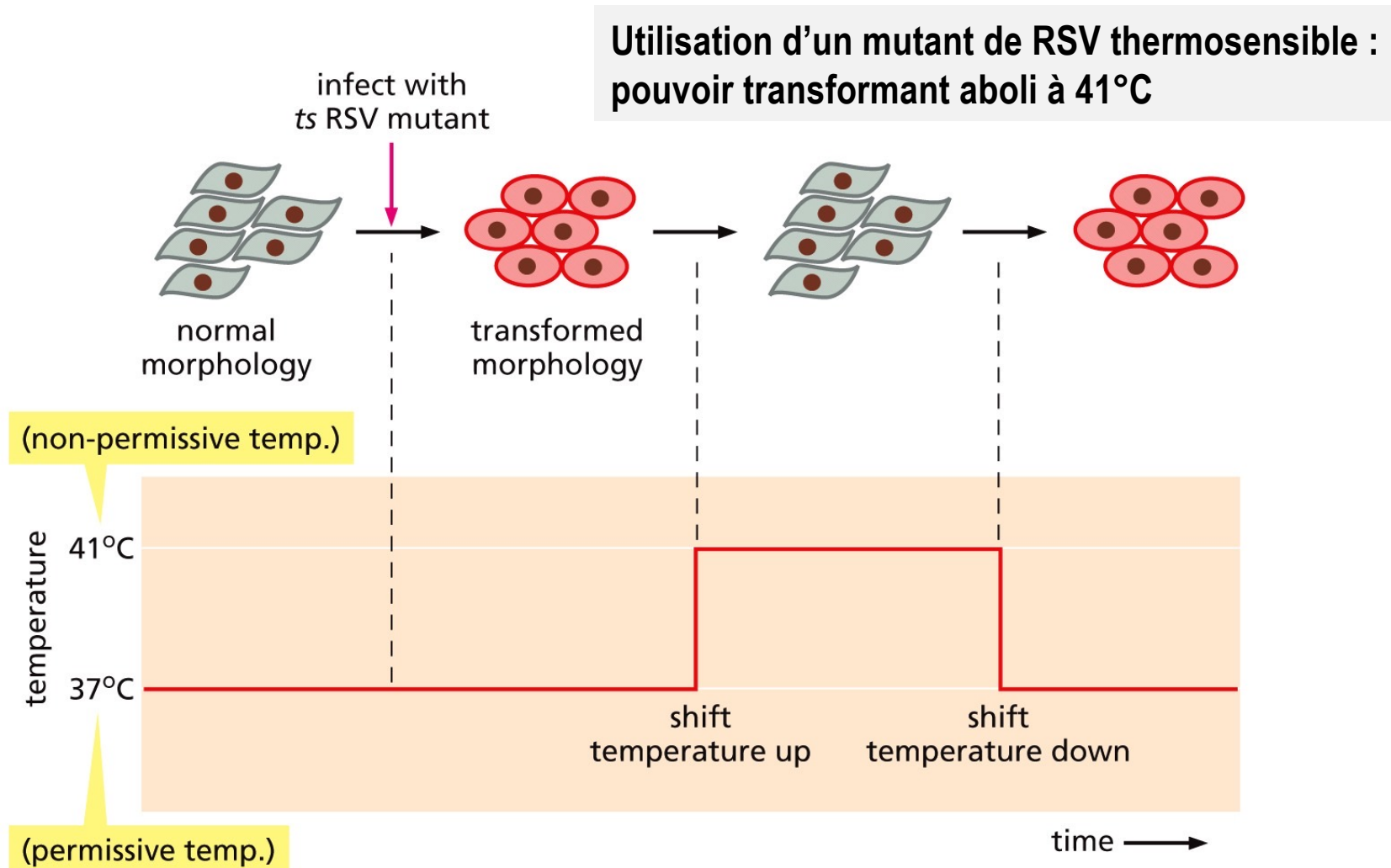


Figure 3.8 The Biology of Cancer (© Garland Science 2014)

- Réversibilité du processus de transformation
- Génome du RSV maintenu dans les cellules transformées

Le génome des virus tumoraux s'intègre dans le génome des cellules infectées

Mais, le RSV a un un génome à ARN. Comment concevoir son intégration dans le génome de l'hôte ?

→ La solution de Howard Temin : RSV fabriquerait, après l'infection, des ADN double brin (dsDNA) copies de leur génome ARN
= **Transcription Inverse**

Le dsDNA pourrait alors s'intégrer = **provirus**

→ **Hypothèse très fortement soutenue par la découverte de la Transcriptase Inverse dans le RSV par Howard Temin et David Baltimore (en //)**

Nobel en 1975

Activité découverte dans d'autres virus, nommés collectivement Rétrovirus

Le génome des virus tumoraux s'intègre dans le génome des cellules infectées

Les rétrovirus intègrent leur génome dans le génome de l'hôte pour transmettre ses gènes.

L'intégration est une étape essentielle du cycle de réplication chez le rétrovirus ≠ des virus à ADN (<< 1 pour 1000 chez les virus tumoraux à ADN)

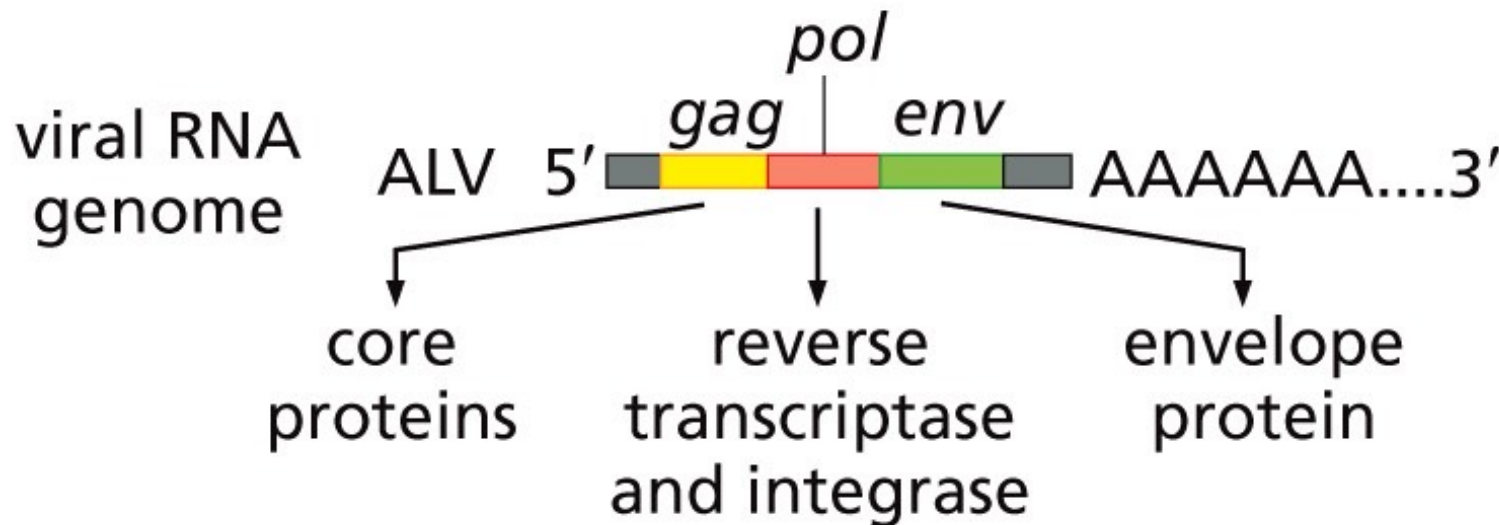


Figure 3.4a The Biology of Cancer (© Garland Science 2014)

« Pol » code une Intégrase et la Transcriptase Inverse

Cycle rétroviral

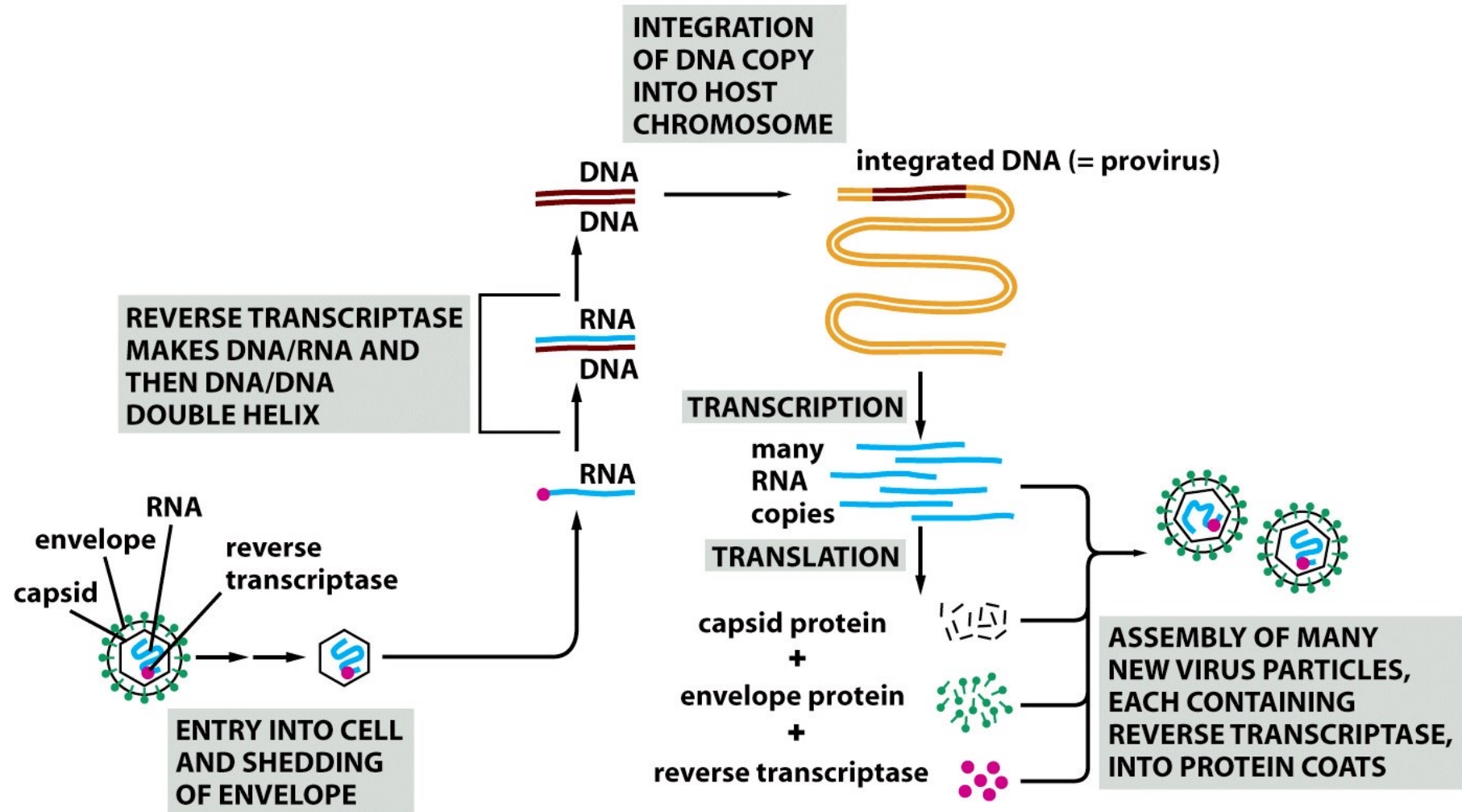


Figure 3.17 *The Biology of Cancer* (© Garland Science 2007)

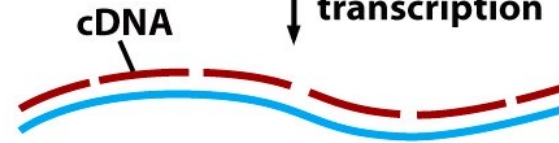
Isolement de la séquence src (D. Stehelin, 1976)



wild-type viral RNA



reverse transcription



RNA is destroyed



hybridized to viral RNA of td mutant



ds RNA:DNA hybrids discarded
(src gene missing)

src-specific probe

used to detect src sequences in other DNAs



DNAs to be tested for presence of src sequences

Td mutant 5' gag pol env AAAAAA...3'

(P. Vogt)

RSV 5' gag pol env src AAAAAA...3'

Chromatographie sur colonne d'hydroxylapatite

Figure 3.20 *The Biology of Cancer* (© Garland Science 2007)

La séquence src est présente dans les cellules non infectées

La sonde met en évidence la présence de src dans le génome de la poule (2 copies).

Séquence retrouvée chez d'autres oiseaux et chez les mammifères

→ Donc présent depuis des millions d'années,

→ un gène cellulaire normal, donc...

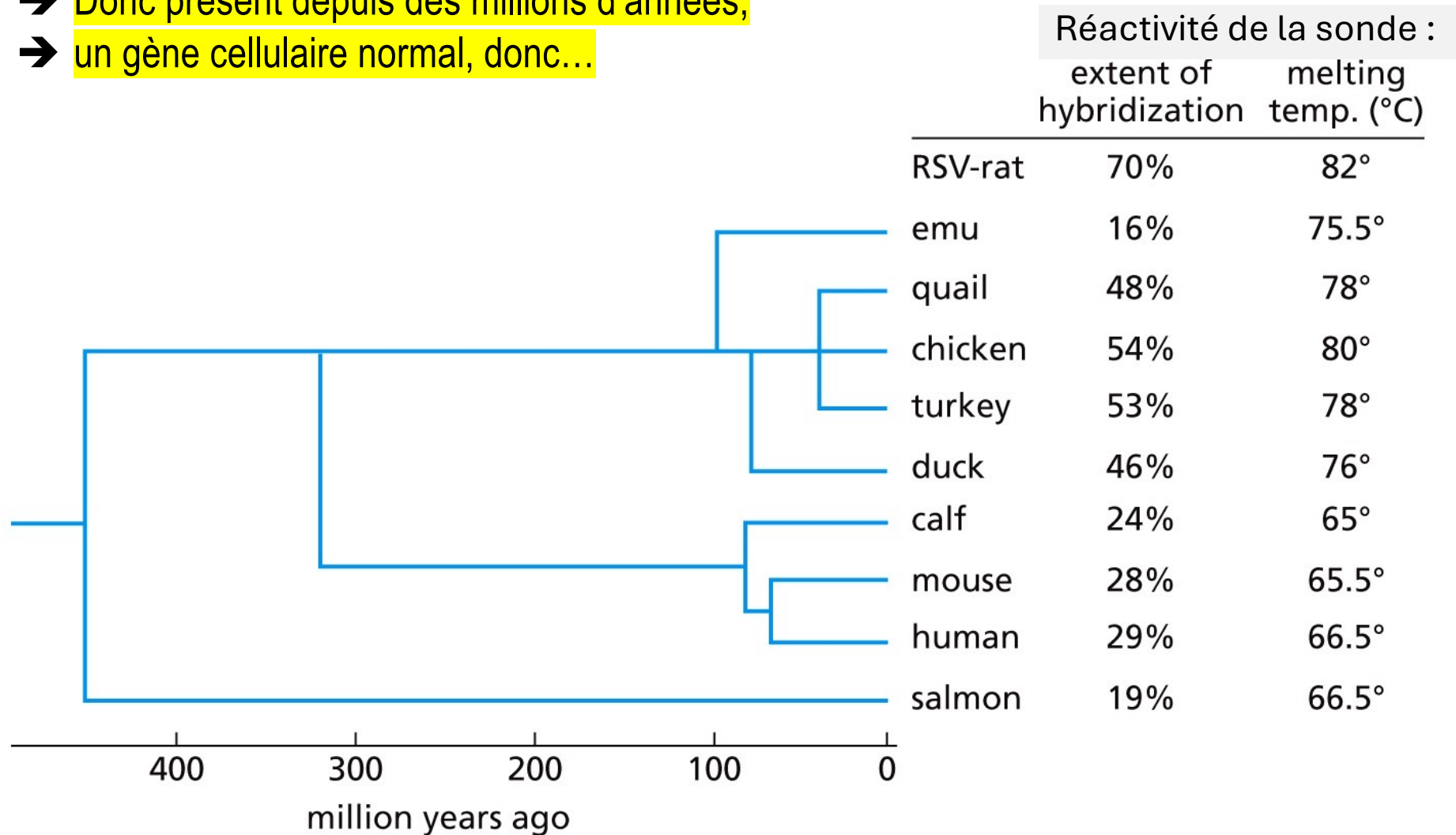
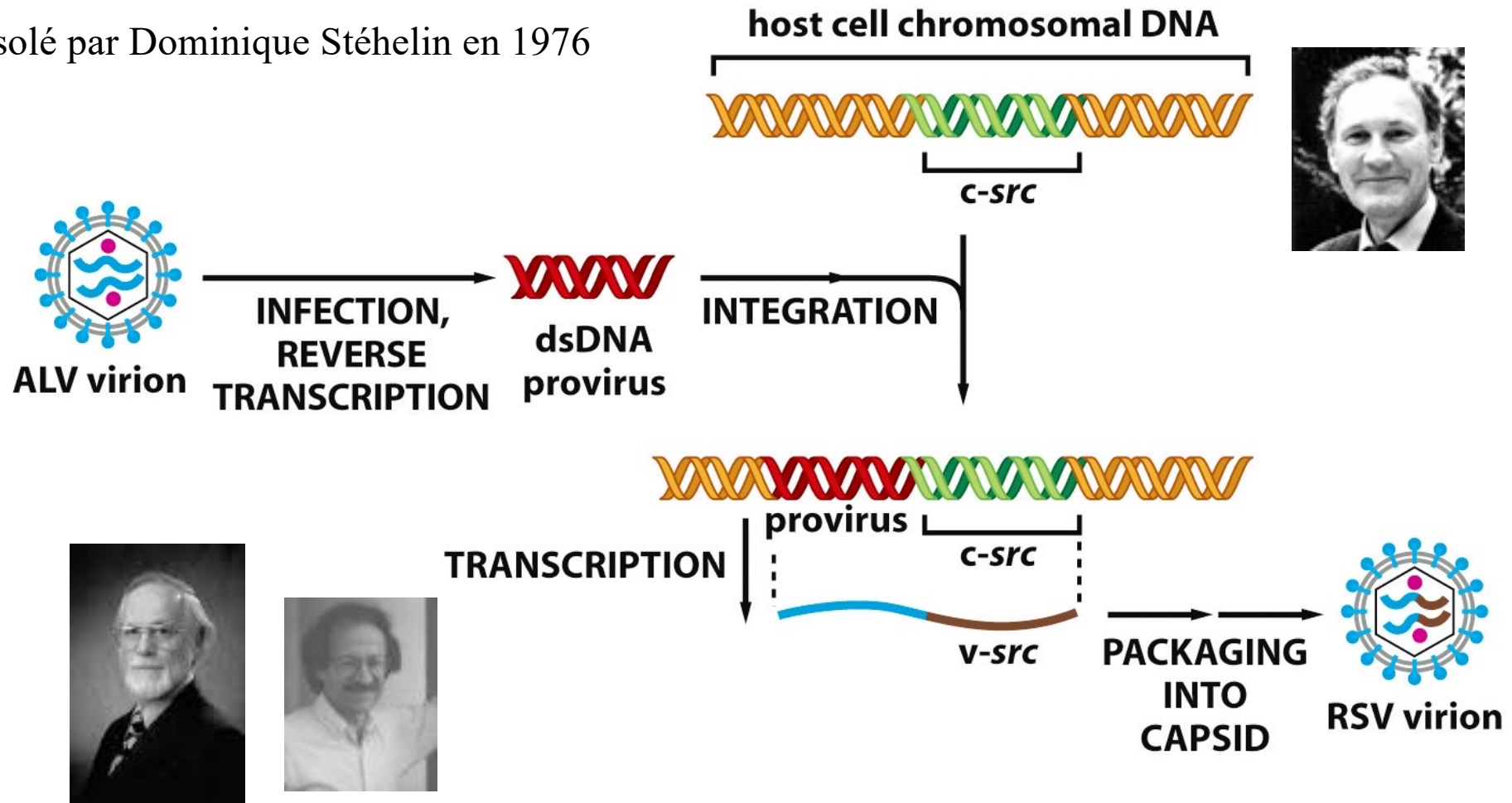


Figure 3.21 The Biology of Cancer (© Garland Science 2014)

Les gènes viraux transformants sont d'origine cellulaire (oncogènes)

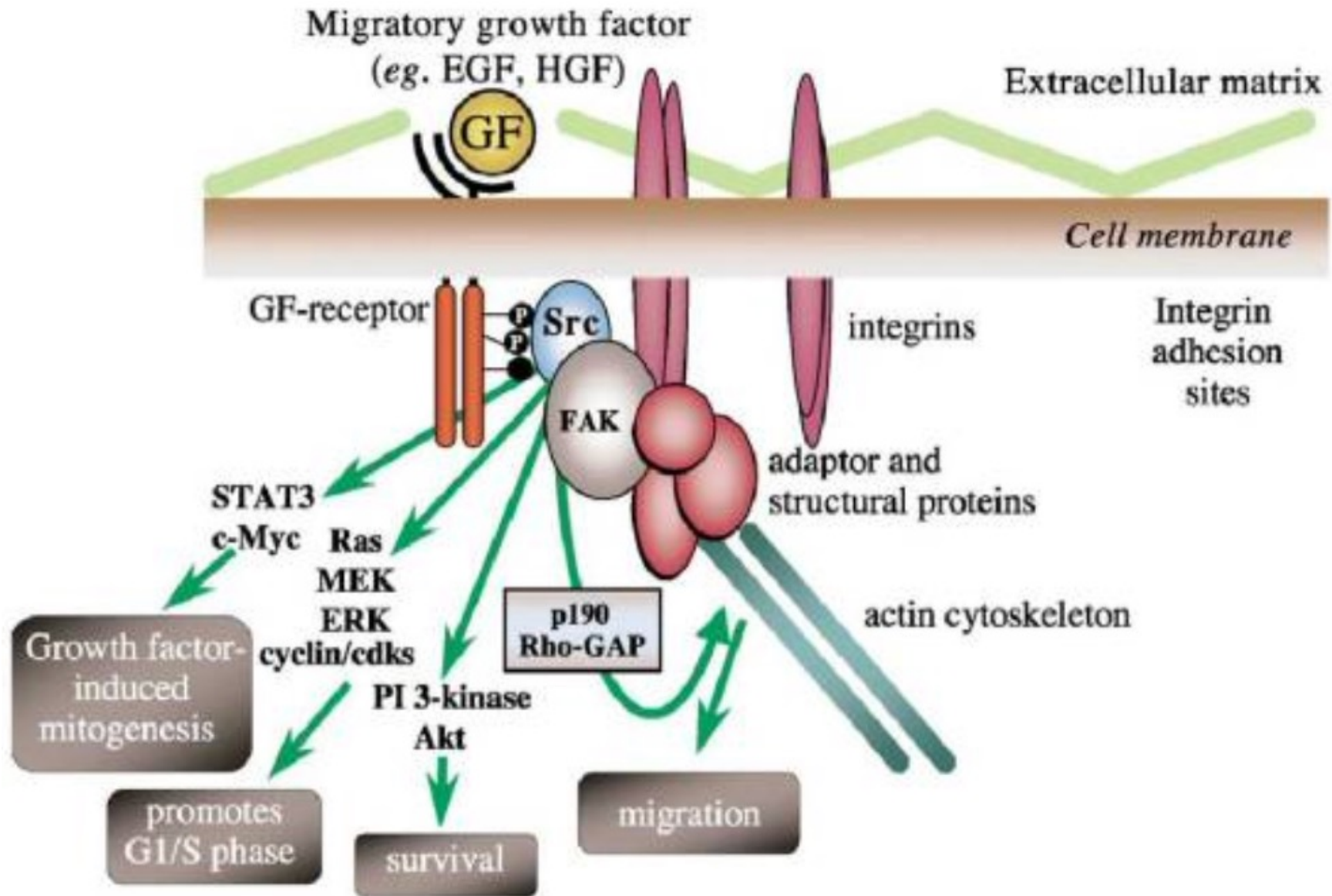
Cibles des produits mutagènes (mutations activatrices)

Isolé par Dominique Stéhelin en 1976

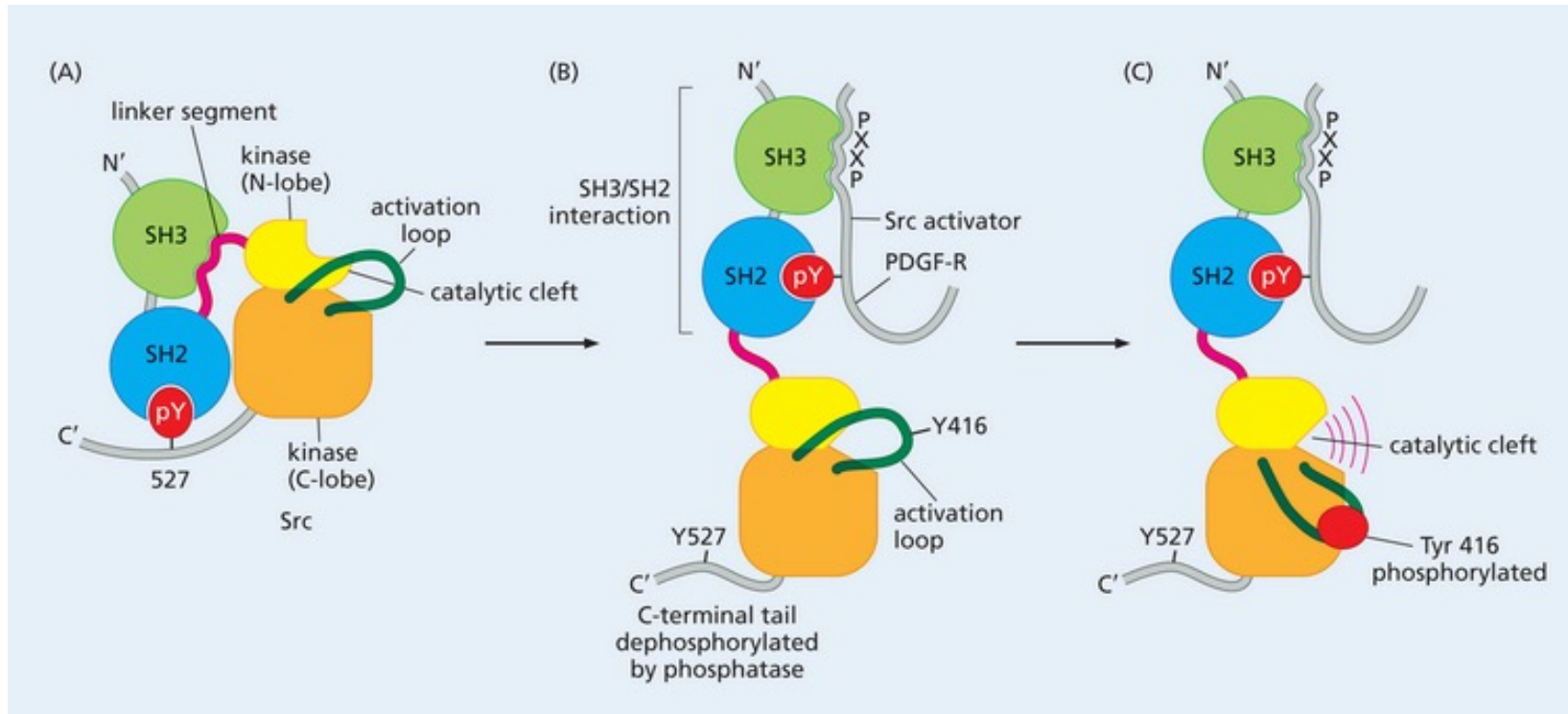


C-src: prix Nobel de médecine Mike Bishop/Harold Varmus, 1989

c-Src est une kinase qui régule plusieurs voies de signalisation



Structure et mécanisme d'activation de c-Src



Remarque: v-Src est rendue hyperactive suite à une mutation faux-sens du résidu Y527

Table 3.3 Acutely transforming retroviruses and the oncogenes that they have acquired^a

Name of virus	Viral oncogene	Species	Major disease	Nature of oncoprotein
Rous sarcoma	<i>src</i>	chicken	sarcoma	non-receptor TK
Y73/Esh sarcoma	<i>yes</i>	chicken	sarcoma	non-receptor TK
Fujinami sarcoma	<i>fps</i> ^b	chicken	sarcoma	non-receptor TK
UR2	<i>ros</i>	chicken	sarcoma	RTK; unknown ligand
Myelocytomatosis 29	<i>myc</i>	chicken	myeloid leukemia ^c	transcription factor
Mill Hill virus 2	<i>mil</i> ^d	chicken	myeloid leukemia	ser/thr kinase
Avian myeloblastosis E26	<i>myb</i>	chicken	myeloid leukemia	transcription factor
Avian myeloblastosis E26	<i>ets</i>	chicken	myeloid leukemia	transcription factor
Avian erythroblastosis ES4	<i>erbA</i>	chicken	erythroleukemia	thyroid hormone receptor
Avian erythroblastosis ES4	<i>erbB</i>	chicken	erythroleukemia	EGF RTK
3611 murine sarcoma	<i>raf</i> ^e	mouse	sarcoma	ser/thr kinase
SKV770	<i>ski</i>	chicken	endothelioma (?)	transcription factor
Reticuloendotheliosis	<i>rel</i>	turkey	immature B-cell lymphoma	transcription factor
Abelson murine leukemia	<i>abl</i>	mouse	pre-B-cell lymphoma	non-receptor TK
Moloney murine sarcoma	<i>mos</i>	mouse	sarcoma, erythroleukemia	ser/thr kinase
Harvey murine sarcoma	H- <i>ras</i>	rat, mouse	sarcoma	small G protein
Kirsten murine sarcoma	K- <i>ras</i>	mouse	sarcoma	small G protein
FBJ murine sarcoma	<i>fos</i>	mouse	osteosarcoma	transcription factor
Snyder–Theilen feline sarcoma	<i>fes</i> ^f	cat	sarcoma	non-receptor TK
McDonough feline sarcoma	<i>fms</i>	cat	sarcoma	CSF-1 RTK
Gardner–Rasheed feline sarcoma	<i>fgr</i>	cat	sarcoma	non-receptor TK
Hardy–Zuckerman feline sarcoma	<i>kit</i>	cat	sarcoma	steel factor RTK
Simian sarcoma	<i>sis</i>	woolly monkey	sarcoma	PDGF
AKT8	<i>akt</i>	mouse	lymphoma	ser/thr kinase
Avian virus S13	<i>sea</i>	chicken	erythroblastic leukemia ^g	RTK; unknown ligand
Myeloproliferative leukemia	<i>mpl</i>	mouse	myeloproliferation	TPO receptor
Regional Poultry Lab v. 30	<i>eyk</i>	chicken	sarcoma	RTK; unknown ligand
Avian sarcoma virus CT10	<i>crk</i>	chicken	sarcoma	SH2/SH3 adaptor
Avian sarcoma virus 17	<i>jun</i>	chicken	sarcoma	transcription factor
Avian sarcoma virus 31	<i>qin</i>	chicken	sarcoma	transcription factor ^h
AS42 sarcoma virus	<i>maf</i>	chicken	sarcoma	transcription factor
Cas NS-1 virus	<i>cbl</i>	mouse	lymphoma	SH2-dependent ubiquitylation factor

Abbreviations: CSF, colony-stimulating factor; EGF, epidermal growth factor; G, GTP-binding; PDGF, platelet-derived growth factor; RTK, receptor tyrosine kinase; ser/thr, serine/threonine; SH, src-homology segment; TK, tyrosine kinase; TPO, thrombopoietin.

^aNot all viruses that have yielded these oncogenes are indicated here.

^bOrtholog of the mammalian *fes* oncogene.

^cAlso causes carcinomas and endotheliomas.

^dOrtholog of the mammalian *raf* oncogene.

^eOrtholog of the avian *mil* oncogene.

^fOrtholog of the avian *fps* oncogene.

^gAlso causes granulocytic leukemias and sarcomas.

^hFunctions as a transcriptional repressor.

Adapted in part from S.J. Flint, L.W. Enquist, R.M. Krug et al., Principles of Virology. Washington, DC: ASM Press, 2000. Also in part from G.M. Cooper, Oncogenes. Boston: Jones and Bartlett Publishers, 1995.

Table 3.3 *The Biology of Cancer* (© Garland Science 2007)

»Tumors destroy man in a unique and appalling way, as flesh of his own flesh which has somehow been rendered proliferative, rampant predatory and ungovernable. They are the most concrete and formidable of human maladies, yet despite more than 70 years of experimental study they remain the least understood. »

Francis Peyton Rous, tumor virologist, Nobel lecture, 1966

»The viral origin of the majority of all malignant tumors... has now been documented beyond any reasonable doubt. It... would be rather difficult to assume a fundamentally different etiology for human tumors »

Ludwik Gross, tumor virologist, 1970

L'origine virale des tumeurs est loin d'être généralisable

Chez l'humain, dans les années 70, seul deux types de tumeurs étaient imputables à des agent viraux : Hépatomes et tumeurs du col de l'utérus

Hypothèse 1, les cancers humains sont principalement dus à des gènes du génome humain

Hypothèse 2, des causes chimiques et/ou physiques pourraient activer des virus en dormance dans le génome

C'est l'hypothèse 1 qui a fini par prévaloir !

(Même s'il y a des cas connus d'activation de virus « dormants »)