Université Paris Sud - M1 parcours Physique Médicale

Physique de la Cellule & des Tissus

Nicolas Chevalier
Chargé de Recherche au CNRS
Laboratoire Matière & Systèmes Complexes, Université Paris Diderot

nicolas.chevalier@univ-paris-diderot.fr

Programme du cours

Intro et fil directeur: **le cancer, une instabilité physico-biologique**

Aujourd'hui

Domaine de la physique		**Effets « macro » physiologiques**
- **Energétique**: métabolisme, glycolyse, respiration	→	Respiration, chaleur, métabolisme
- **Hydro**: pression osmotiques, hydrauliques	→	Ecoulement sang, perméabilité membranaire, tissulaire

18 dec. 2020

- **Mécanique**: propriétés mécanique, contractilité, adhésivité	→	Migration cellulaire, génération de force
- **Électrique**: potentiel transmembranaire	→	Influx nerveux, contraction musculaire

+ exposés sur articles par binômes (format 12min + 5 min questions)

Importance de la physique pour aborder le vivant

- **Phénoménologie** très riche du vivant: « bazar de l'évolution »

- Mais **la vie est nécessairement physique**: elle est « contrainte » par ses lois, et elle s'appuie dessus

- **Concepts structurant** pour la compréhension du vivant: qu'est ce qui est physique et/ou biochimique/génétique ?

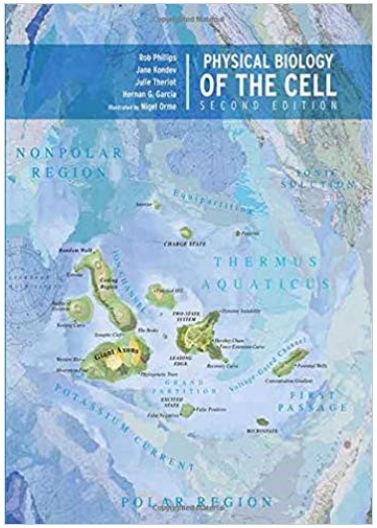
- Son **efficacité thérapeutique**: rayons X, protonthérapie, prothèses, massage, ultrasons, optique (e.g.endoscopie), lasers, cryogénie etc.

- **Buts du cours**:

  - Introduction aux **concepts physiques importants**, équations, et développement dans la recherche récente en bio/médecine.

  - **Culture biologique**, structure, anatomie / histologie, méthodes

Réferences de cours

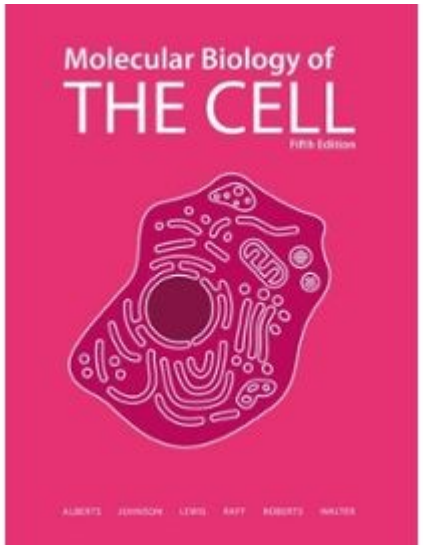


Physical Biology of the Cell 2nd Edition by Rob Phillips et al.

Tous les ordres de grandeur importants:

CELL BIOLOGY BY THE NUMBERS

http://book.bionumbers.org/



Molecular Biology Of The Cell
- **Bruce Alberts**

+ articles de recherche
→ Pubmed
→ SciHub

Cancer phenomenology

Some statistics
Proliferation
Apoptosis
Cell morphology
Migration
Neo-vascularization
Metastasis

Incidence of cancer in different organs

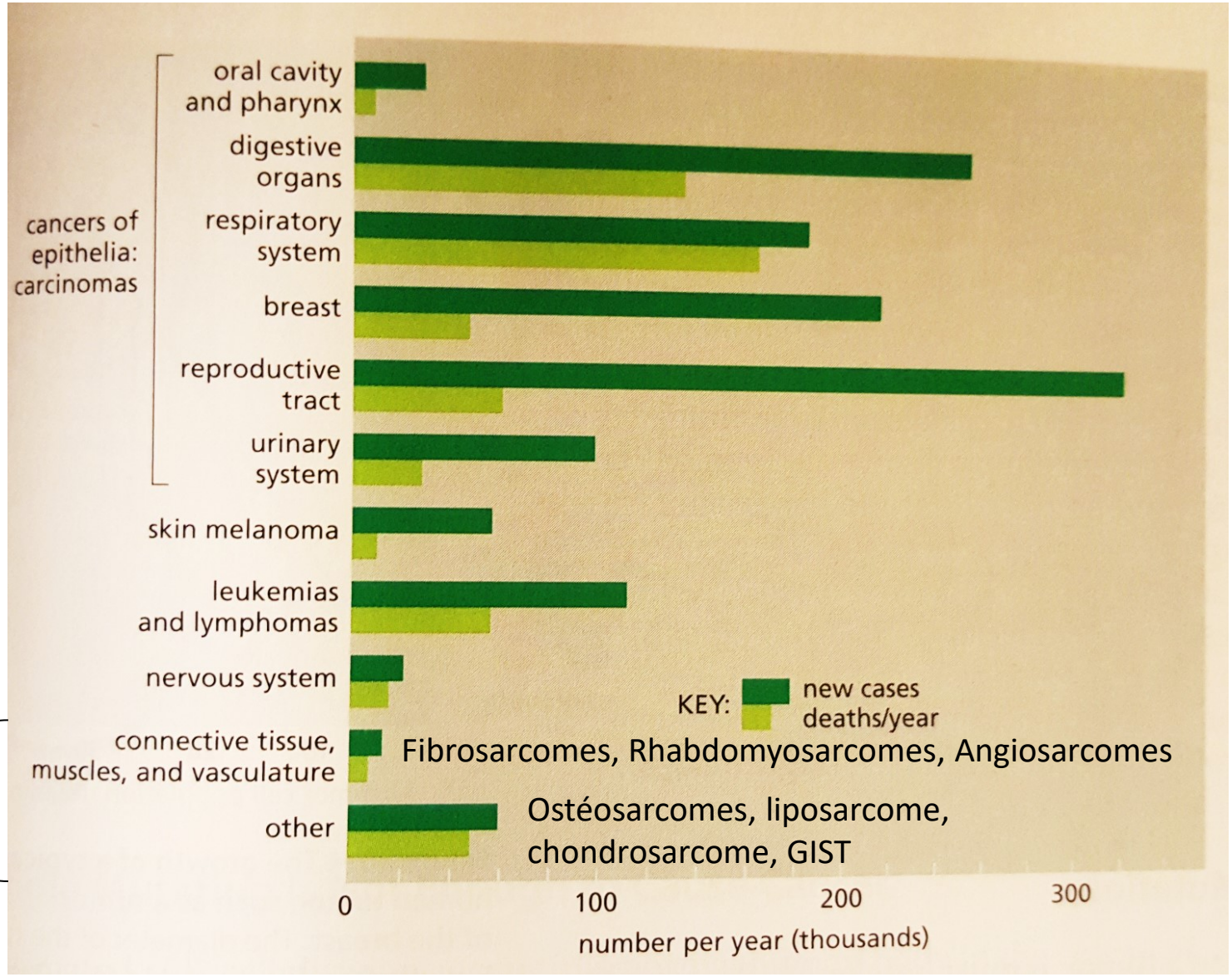
Carcinome

Melanomes

Leucémie & lymphomes

Gliome

Sarcomes



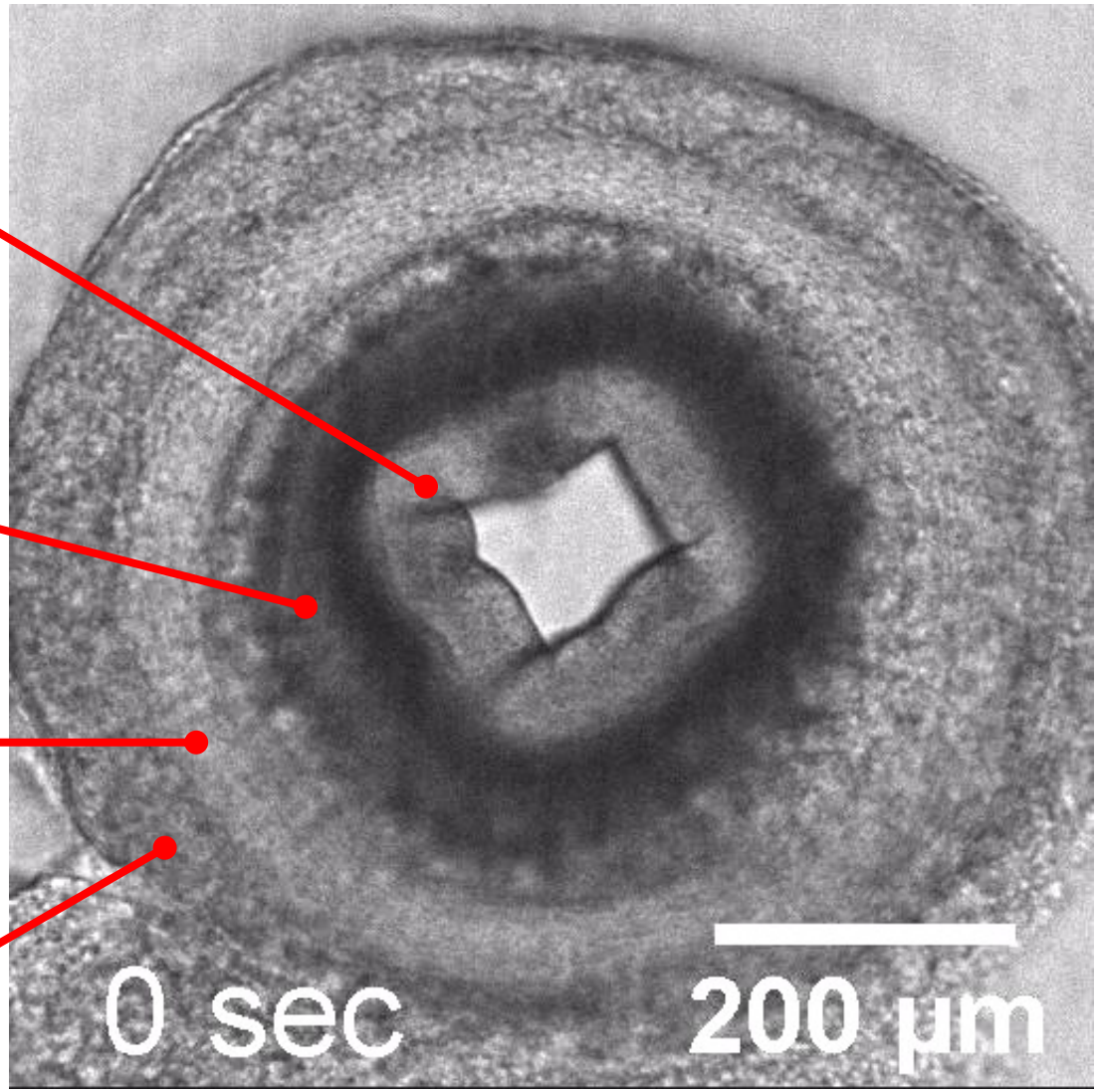
Epithelium, tissus conjonctif ... késako ?

epithelium

tissu conjonctif:
muqueuse,
vaisseaux sanguins

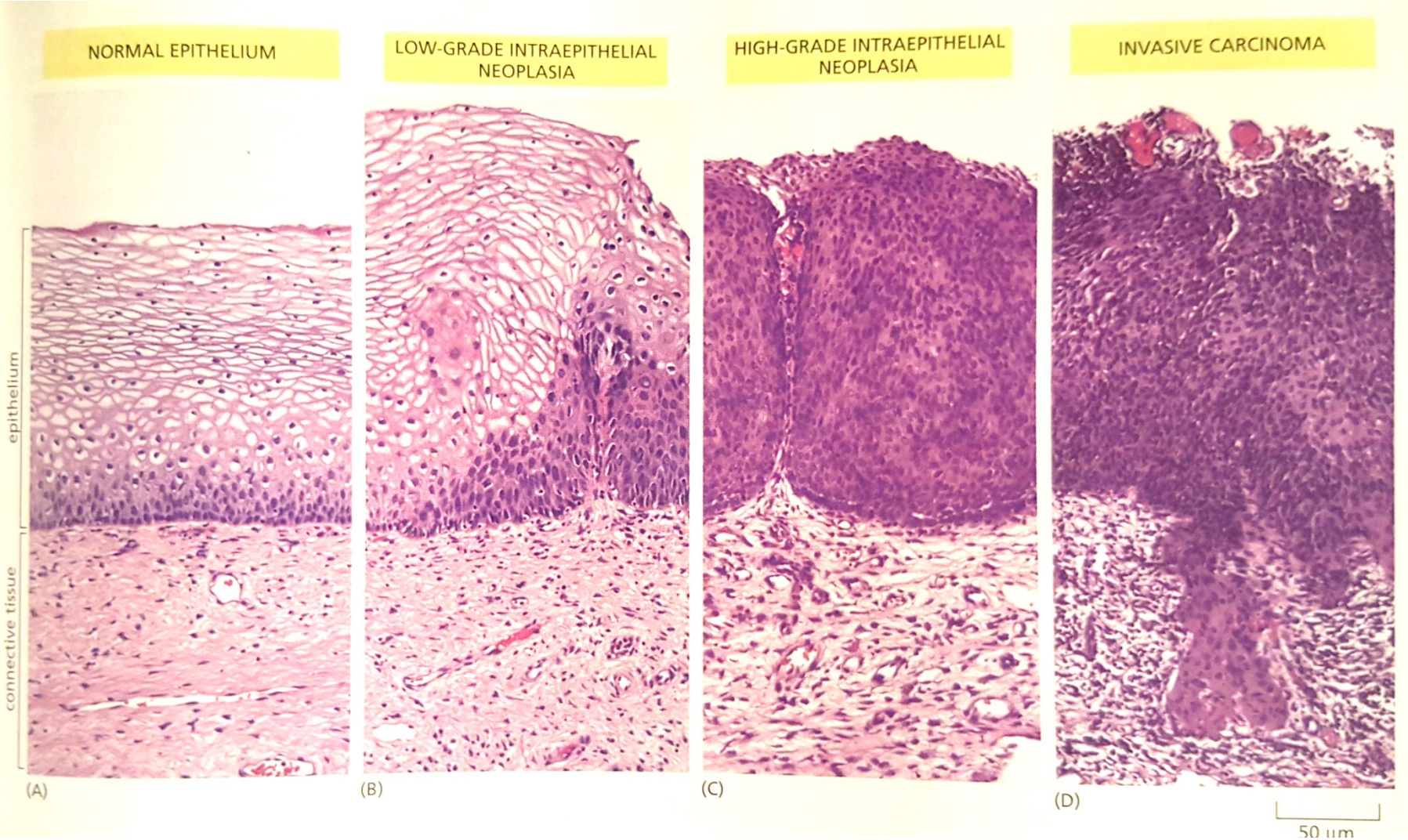
muscle lisse
circulaire

muscle lisse
longitudinal
et neurones

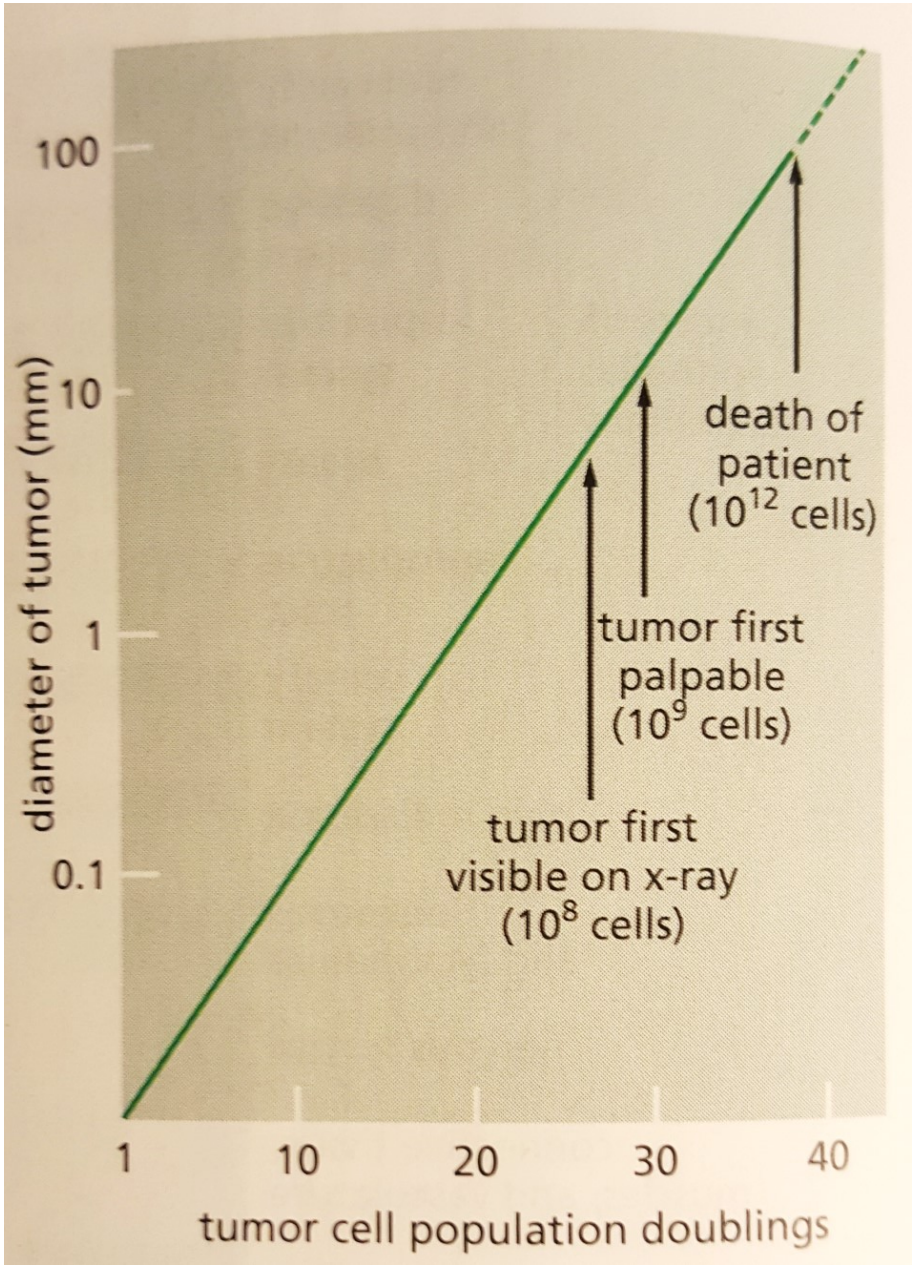


Exemple de l'intestin

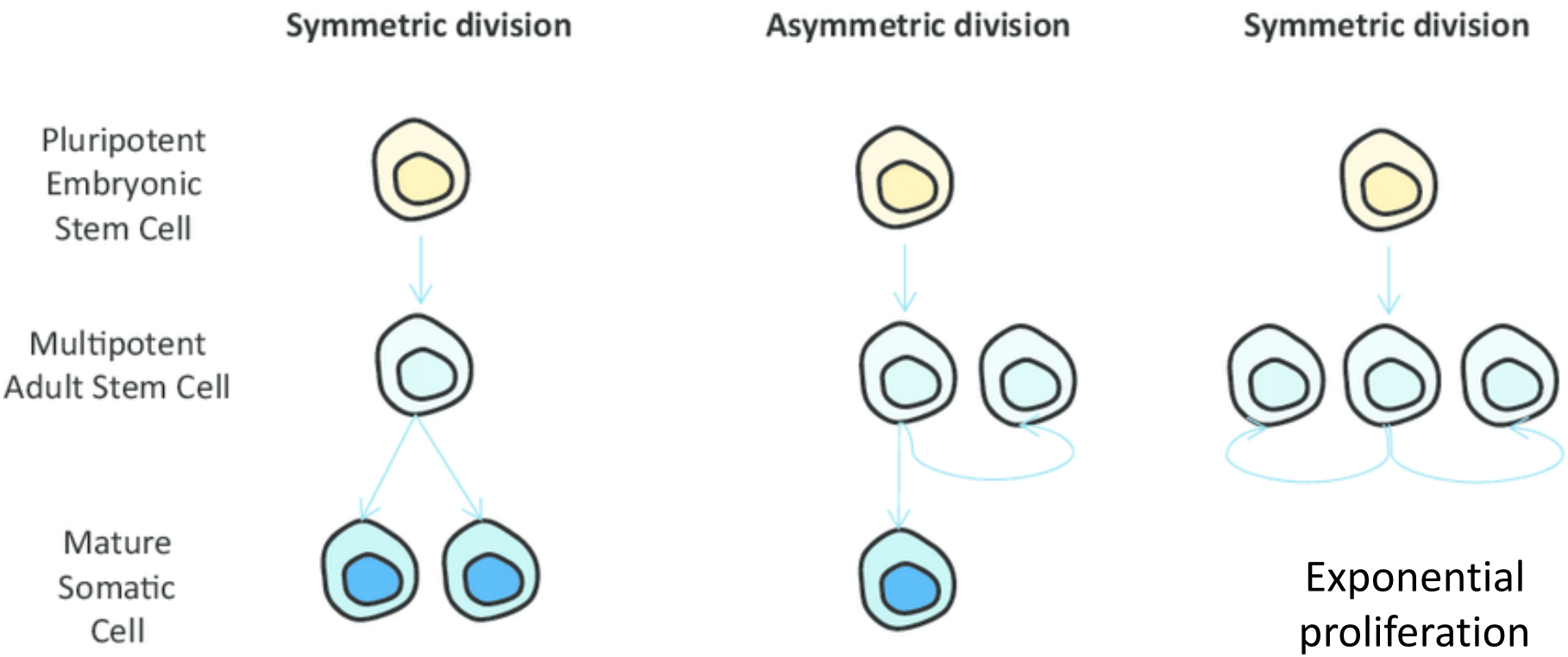
Cancer is characterized by aberrant cell proliferation



Without treatment, tumor growth is exponential



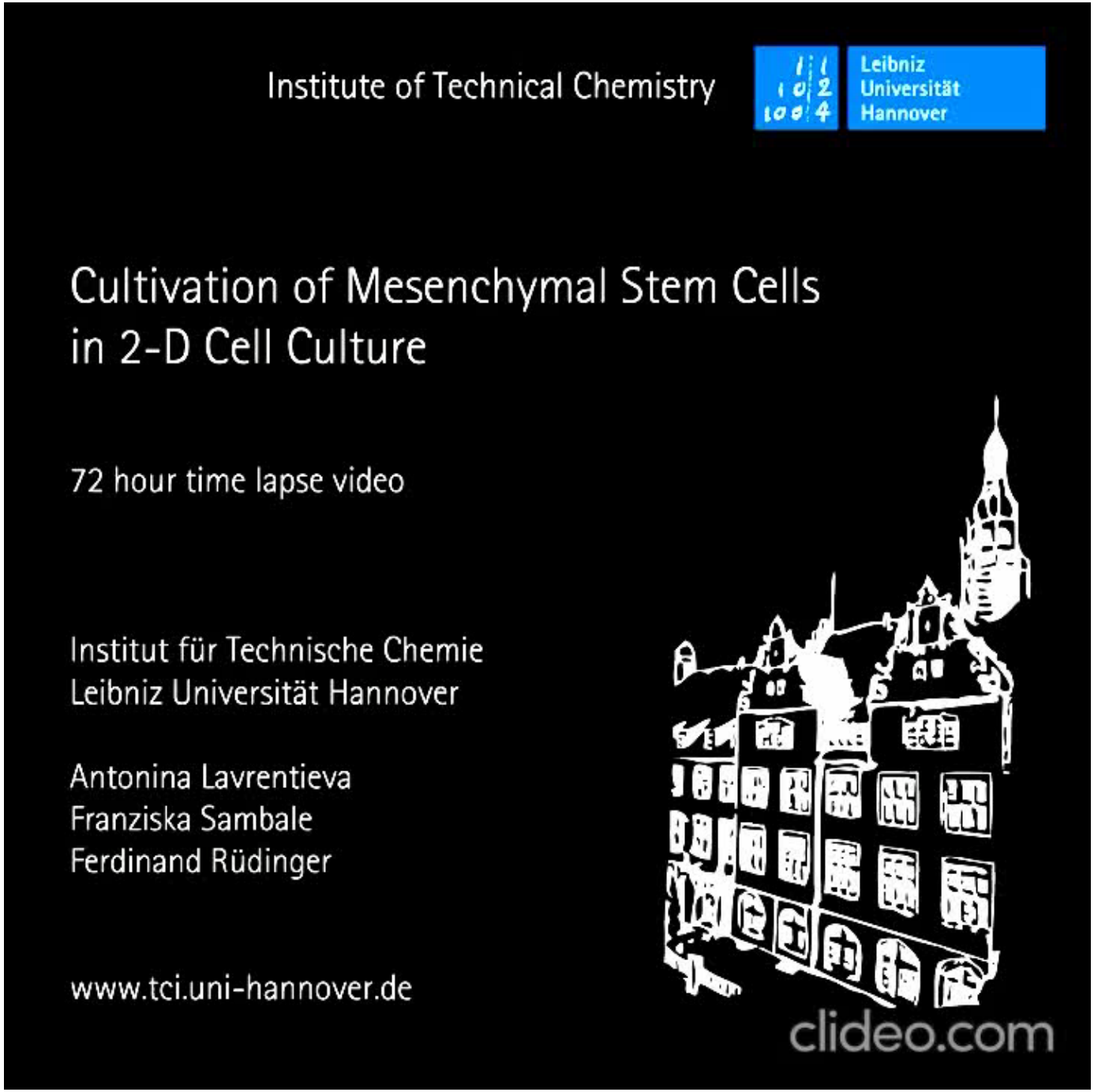
Cancer cells proliferate like stem cells



→ Differentiated cells do not proliferate !

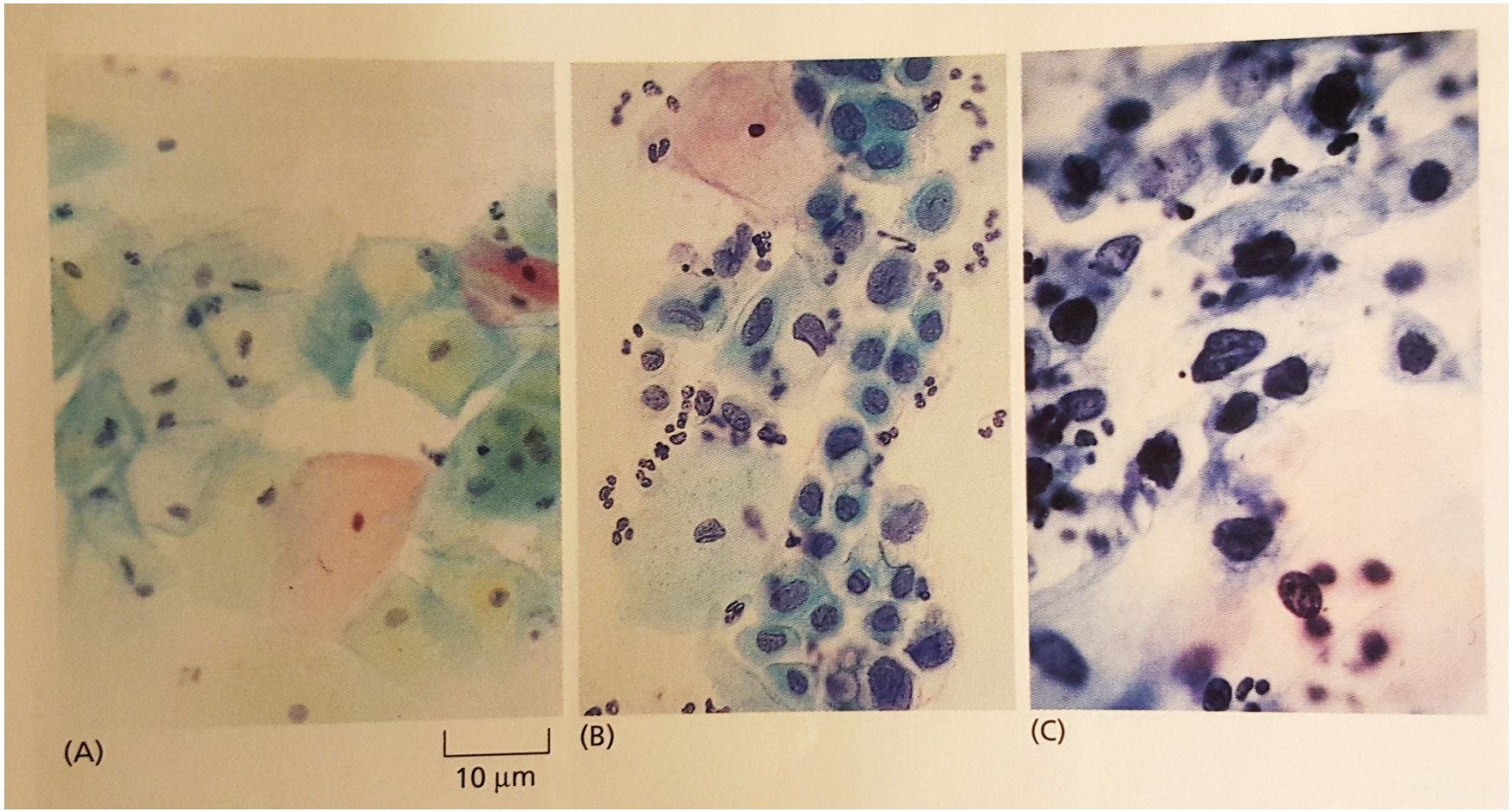
Linear proliferation

Video mesenchymal stem cell culture



Video single-cell division

Cancer cells present a bigger nucleus than normal cells



Normal | Pre-cancerous | Invasive Carcinoma

Nucleus to cytoplasm area ratio of in embryonic, normal and cancer cell

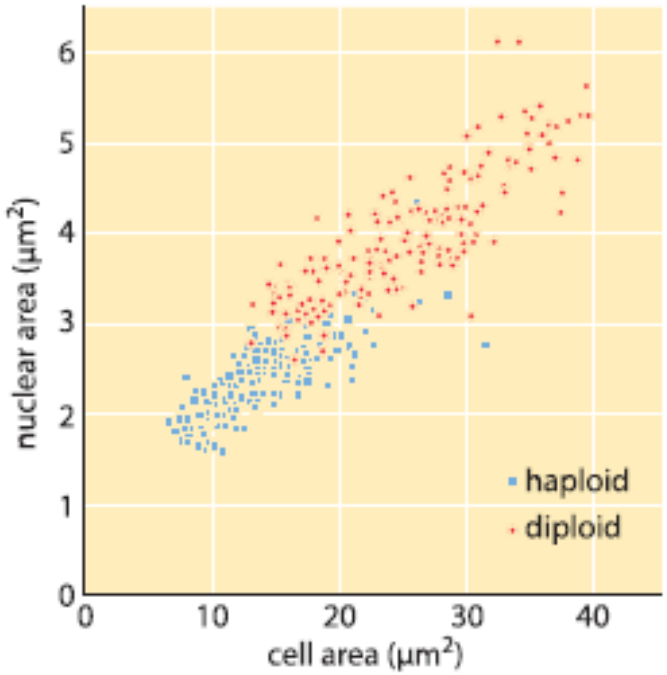
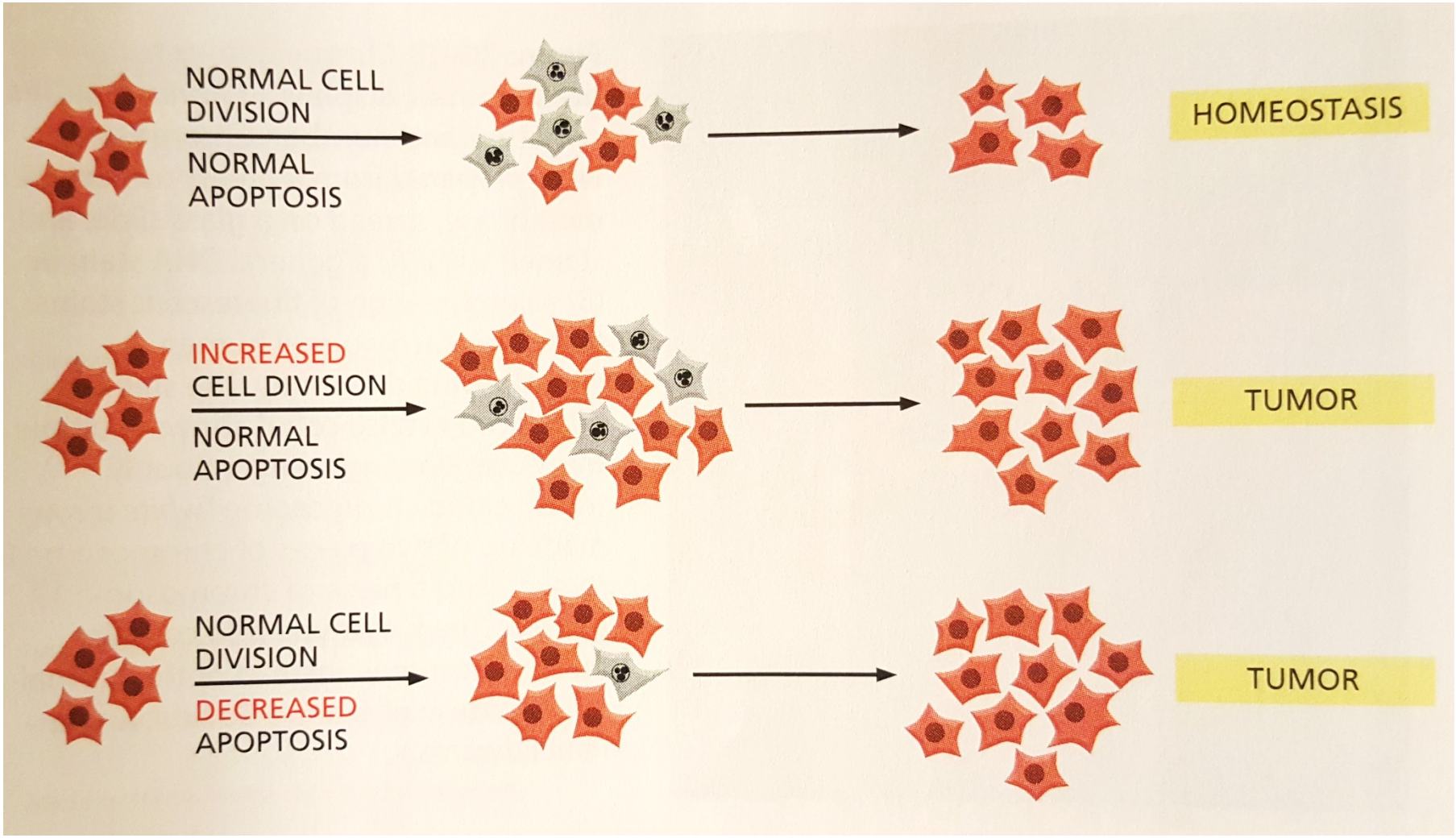


Figure 2: Nuclear size for haploid and diploid yeast cells. The cross sectional area of the nuclei are plotted as a function of the cross sectional area of the cells themselves. (Adapted from P. Jorgensen et al., Molecular Biology of the Cell, 18:3523, 2007.)

Cell type	Nucleus : Cytoplasm Area Ratio
Embryonic	1 : 4
Carcinoma	1 : 4.5
Neonate	1 : 6
Adult	1 : 12

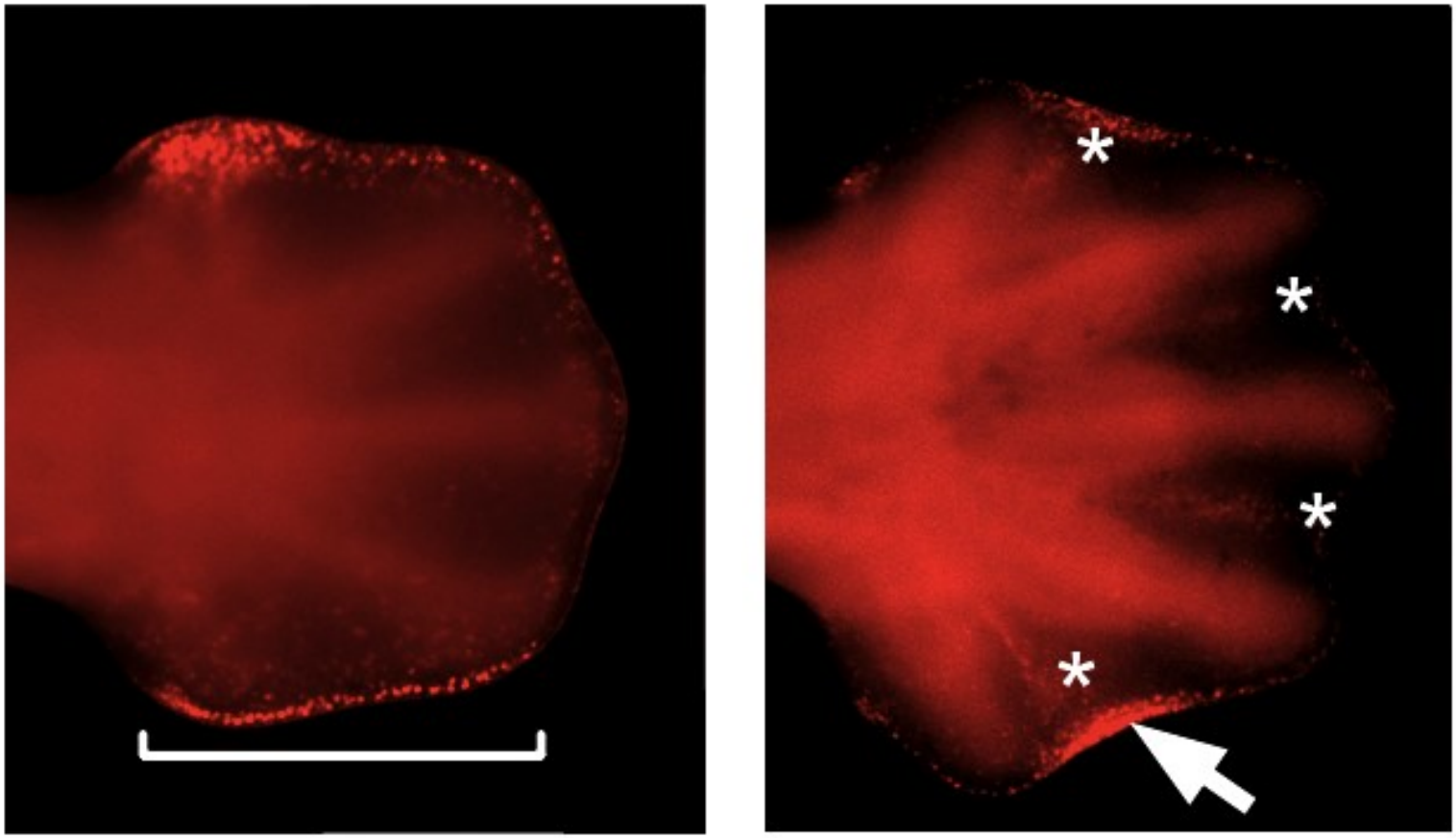
Cancer cells short-circuit regulation by apoptosis



Apoptosis (video)

Apoptosis occurs naturally during finger formation

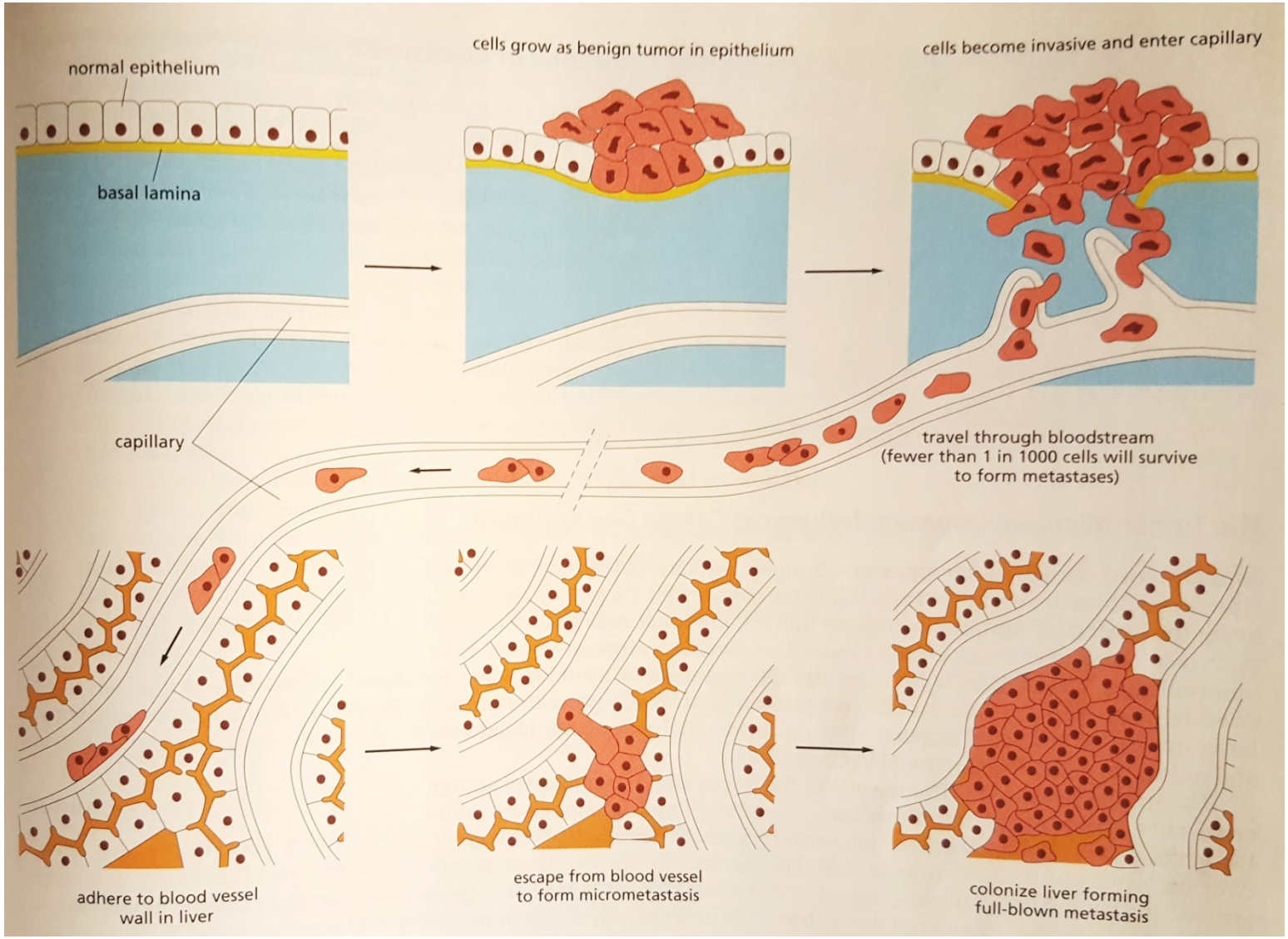
Red dots show cells undergoing apoptosis



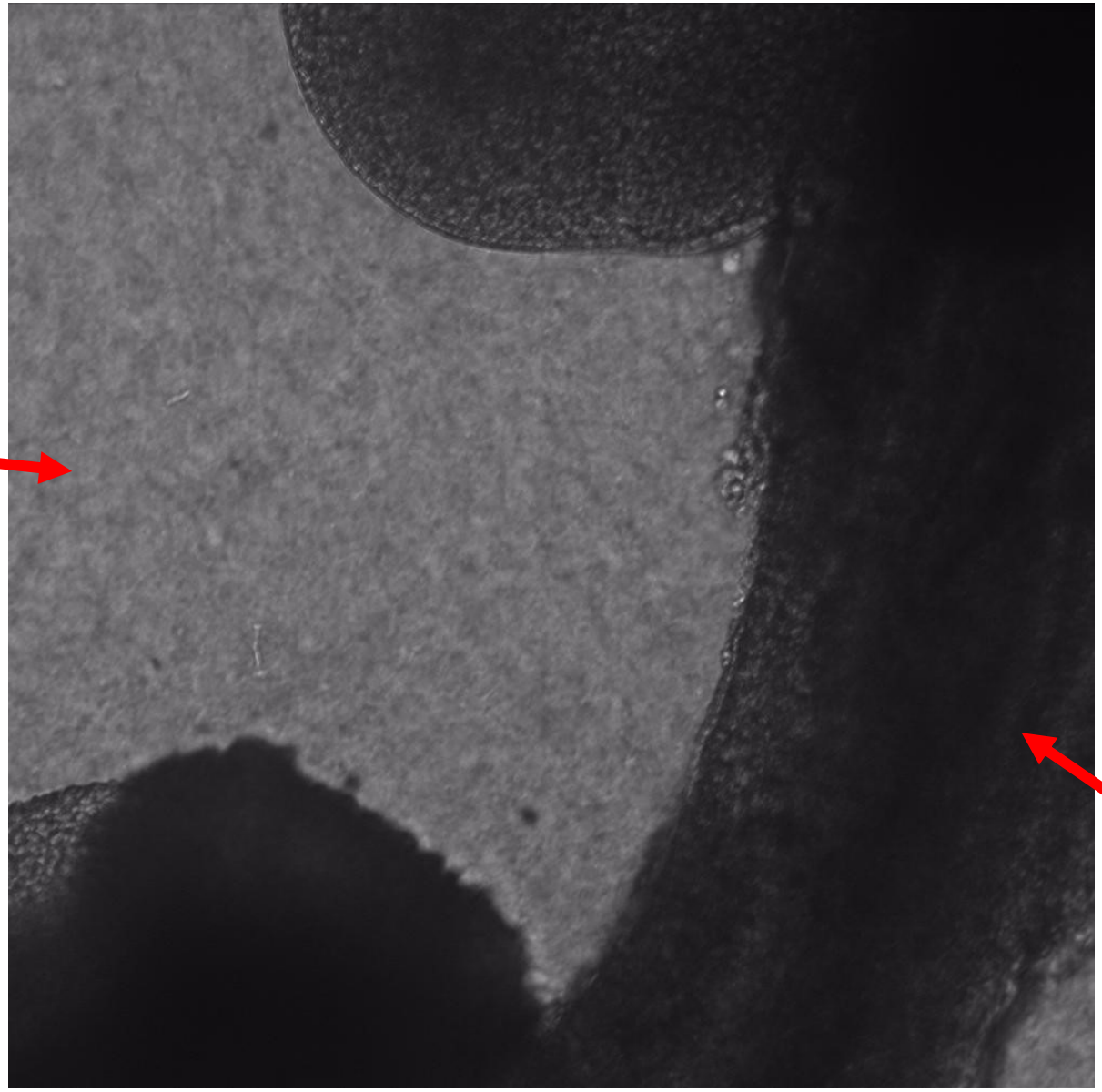
Developing mouse paw, embryonic day 12.5

Developing mouse paw, embryonic day 13.5

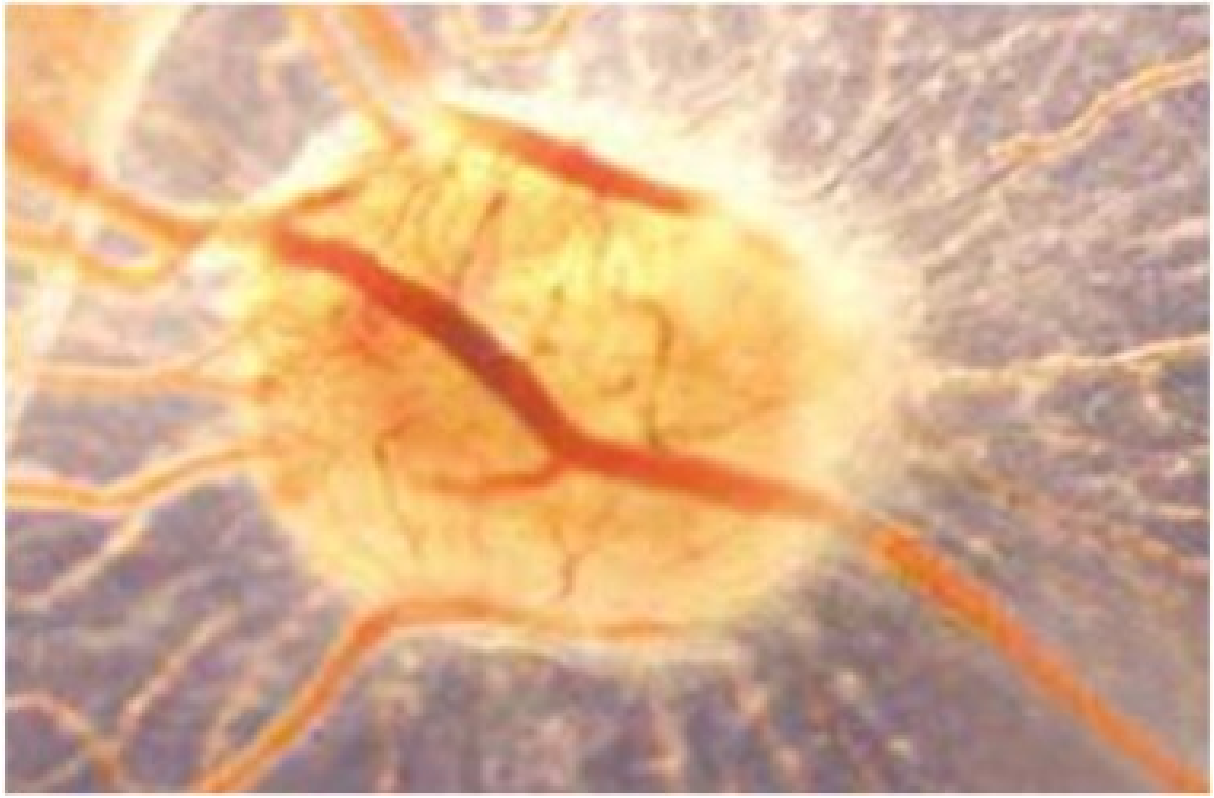
Cancer cells undergo epithelial – mesenchymal transition (EMT) to migrate out of tumor and metastase



Example of highly migratory cells in the embryo: neural crest cells



Tumors induce their own vascularization: neo-angiogenesis



A 12-day-old CAM incubated on day 8 for 4 days with bioptic specimen of a tumor xenograft, showing numerous host vessels around and inside the graft.

Tumors induce their own innervation: neo-neurogenesis

"Progenitors from the central nervous system drive neurogenesis in cancer"

new paper 2019 for someone

The causes of cancer

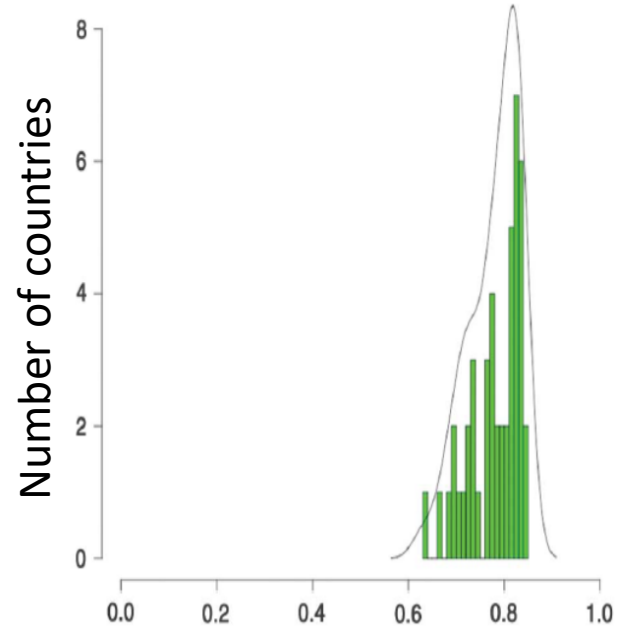
Cell turn-over, replicative error
Oncogenes
Viruses
Hallmarks of cancer and … embryogenesis

Cell turnover rate in different regions of the body and cancer risk

cell type	turnover time	BNID
small intestine epithelium	2-4 days	107812, 1
stomach	2-9 days	101940
blood Neutrophils	1-5 days	1019
white blood cells Eosinophils	2-5 days	10
gastrointestinal colon crypt cells	3-4 days	1
cervix	6 days	110321
lungs alveoli	8 days	101940
tongue taste buds	10 days	111427
platelets	10 days	111407,
bone osteoclasts	2 weeks	109906
intestine Paneth cells	20 days	107812
skin epidermis cells	10-30 days	109214,
pancreas beta cells (mouse)	20-50 days	109228
blood B cells (mouse)	4-7 weeks	107910
trachea	1-2 months	101940
hematopoietic stem cells	2 months	109232
sperm (male gametes)	2 months	110319, 1
bone osteoblasts	3 months	109907
red blood cells	4 months	101706, 1
liver hepatocyte cells	0.5-1 year	109233
fat cells	8 years	103455
cardiomyocytes	0.5-10% per year	107076, 10 107078
central nervous system	life time	101940
skeleton	10% per year	109908
lens cells	life time	109840
oocytes (female gametes)	life time	111451

Cancer risk

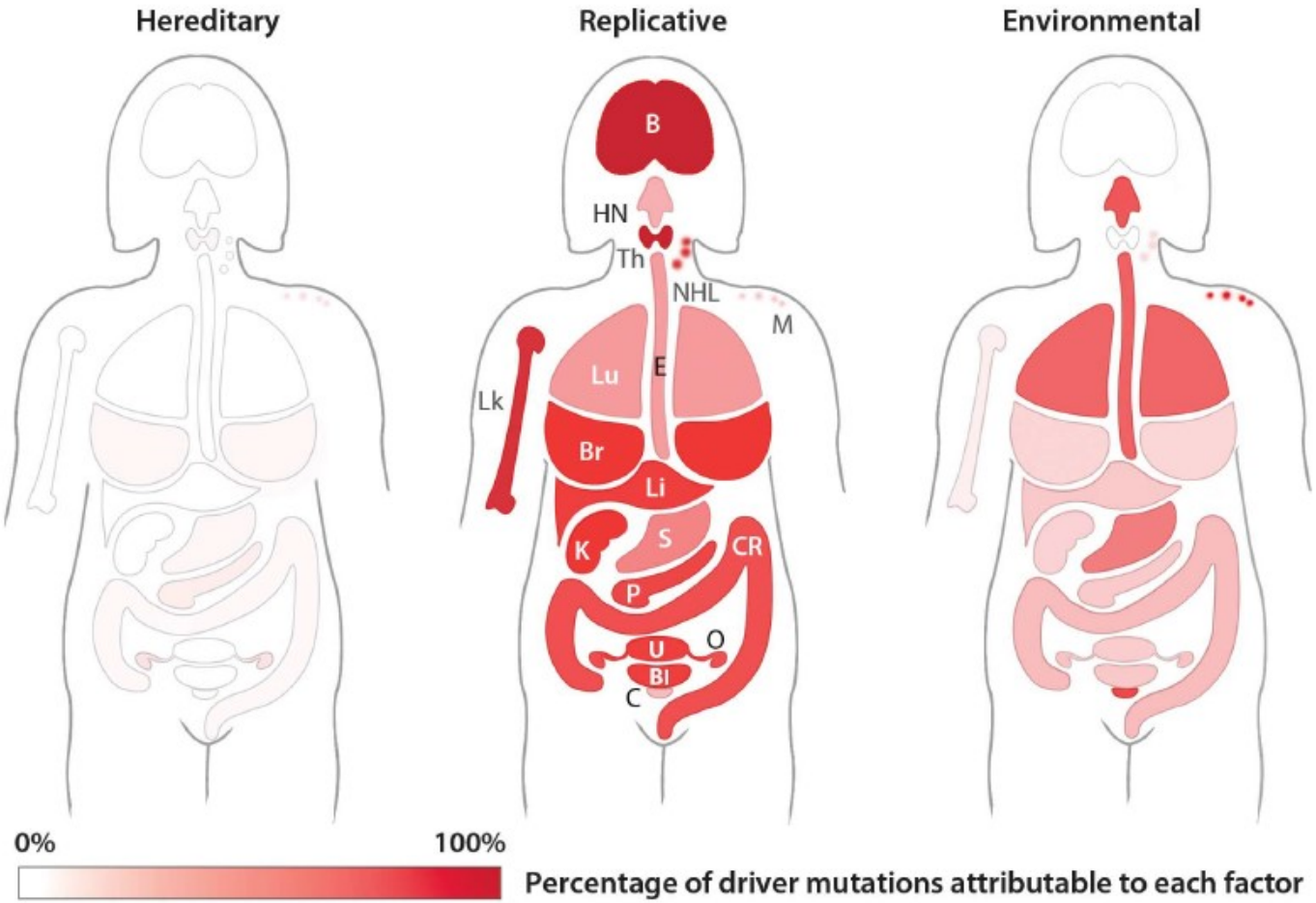
Because random erros in DNA duplication



Pearson's correlation coeff. between division number in tissue & cancer incidence rate

"Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention", Tomasetti et al. Science, 2017

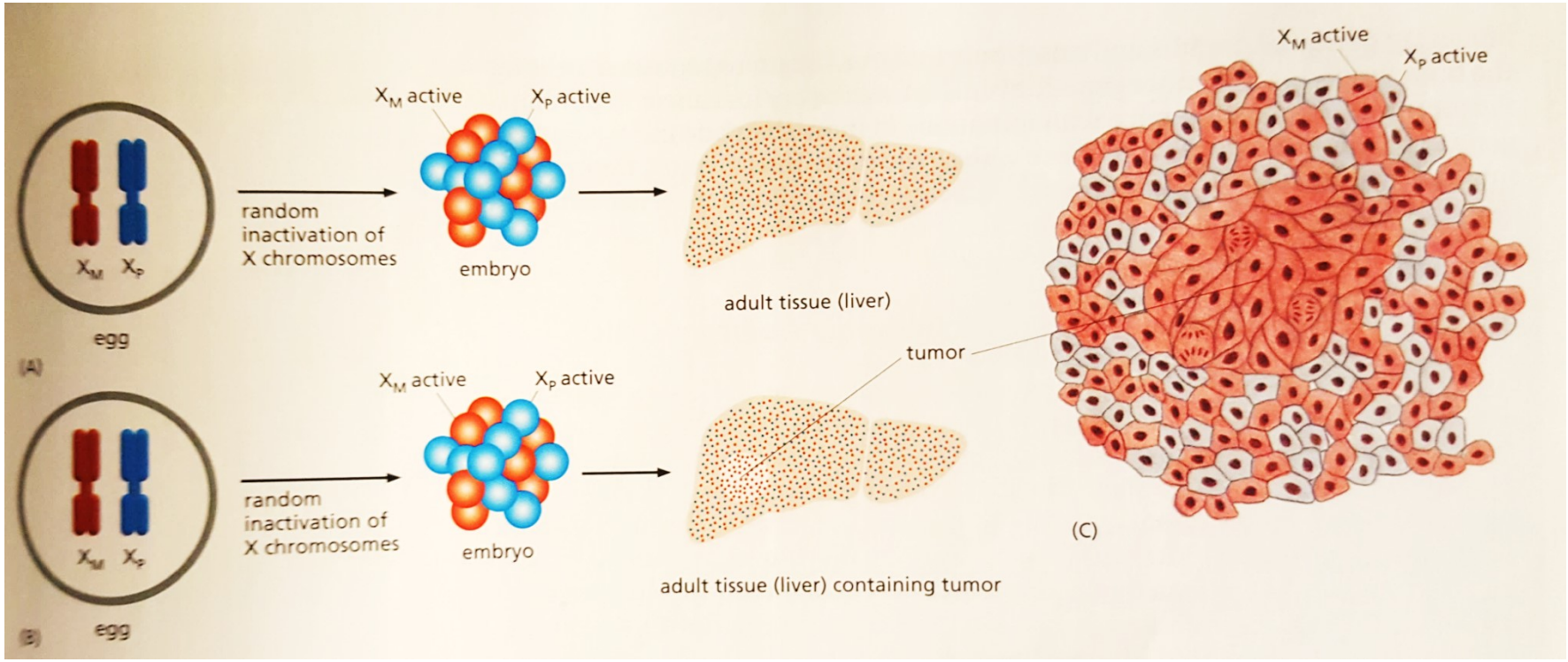
Most cancers are due to « bad luck »: replicative error



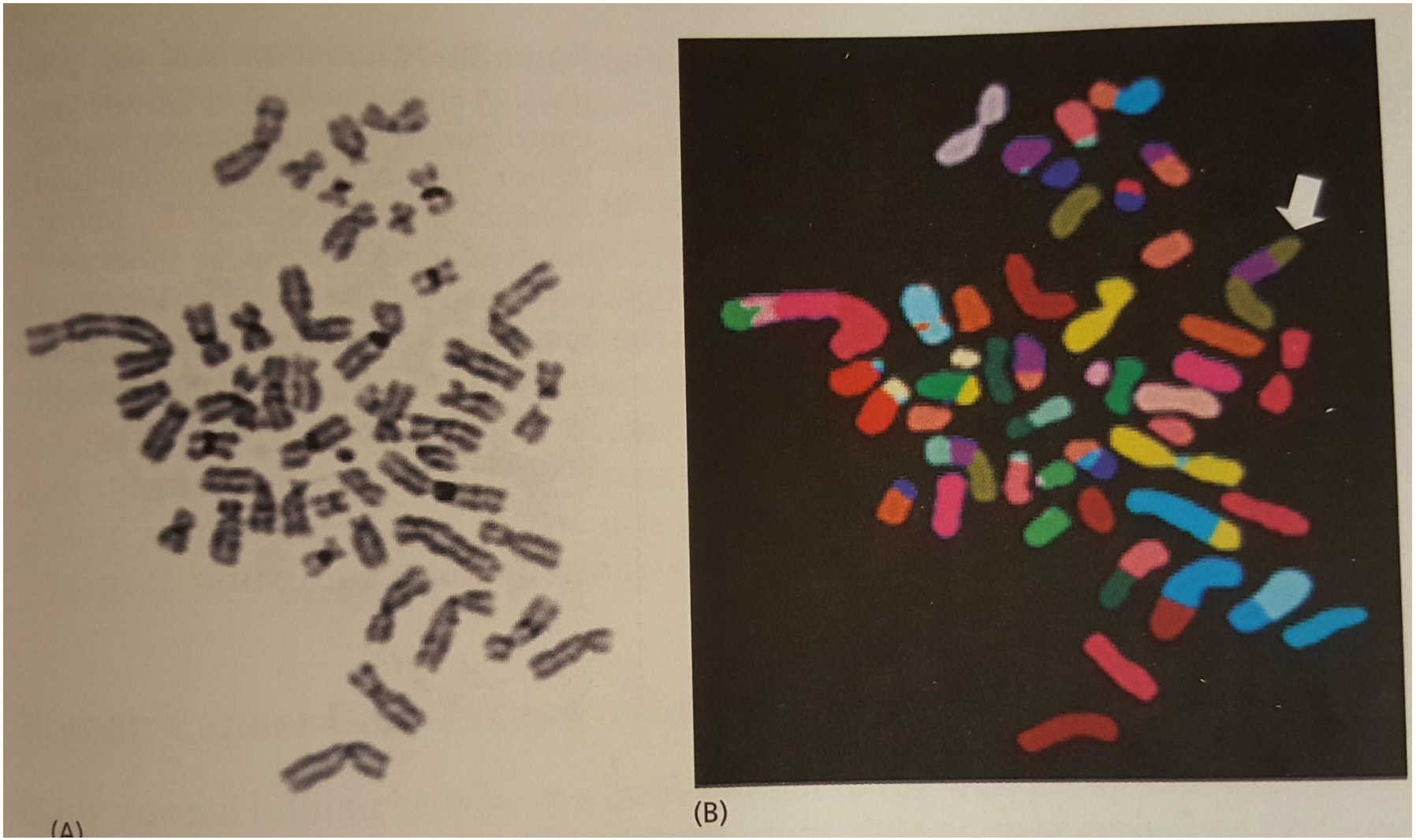
Tomasetti et al. Science, 2017

	Hereditary	Replicative	Environmental
All organ average:	5%	66%	29%
Lung or skin:			60%

The causes of cancer: tumours develop from cancer stem cells

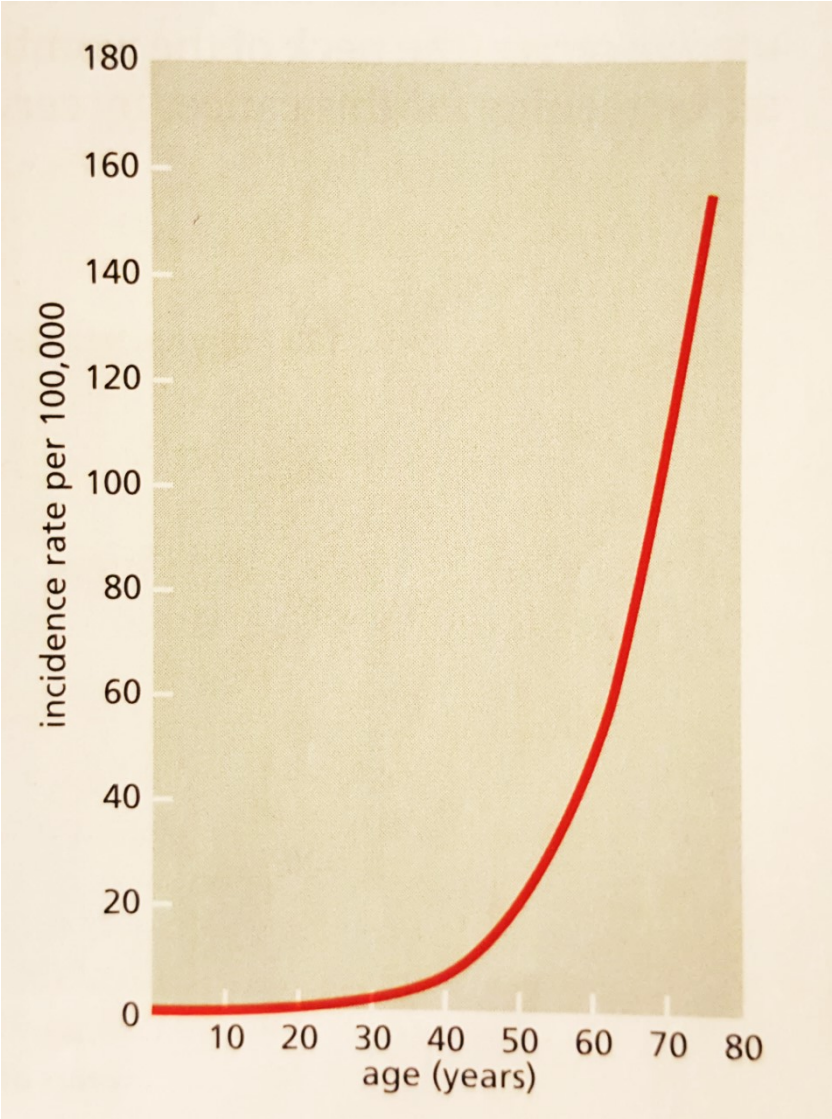


Cancer cells are genetically abnormal

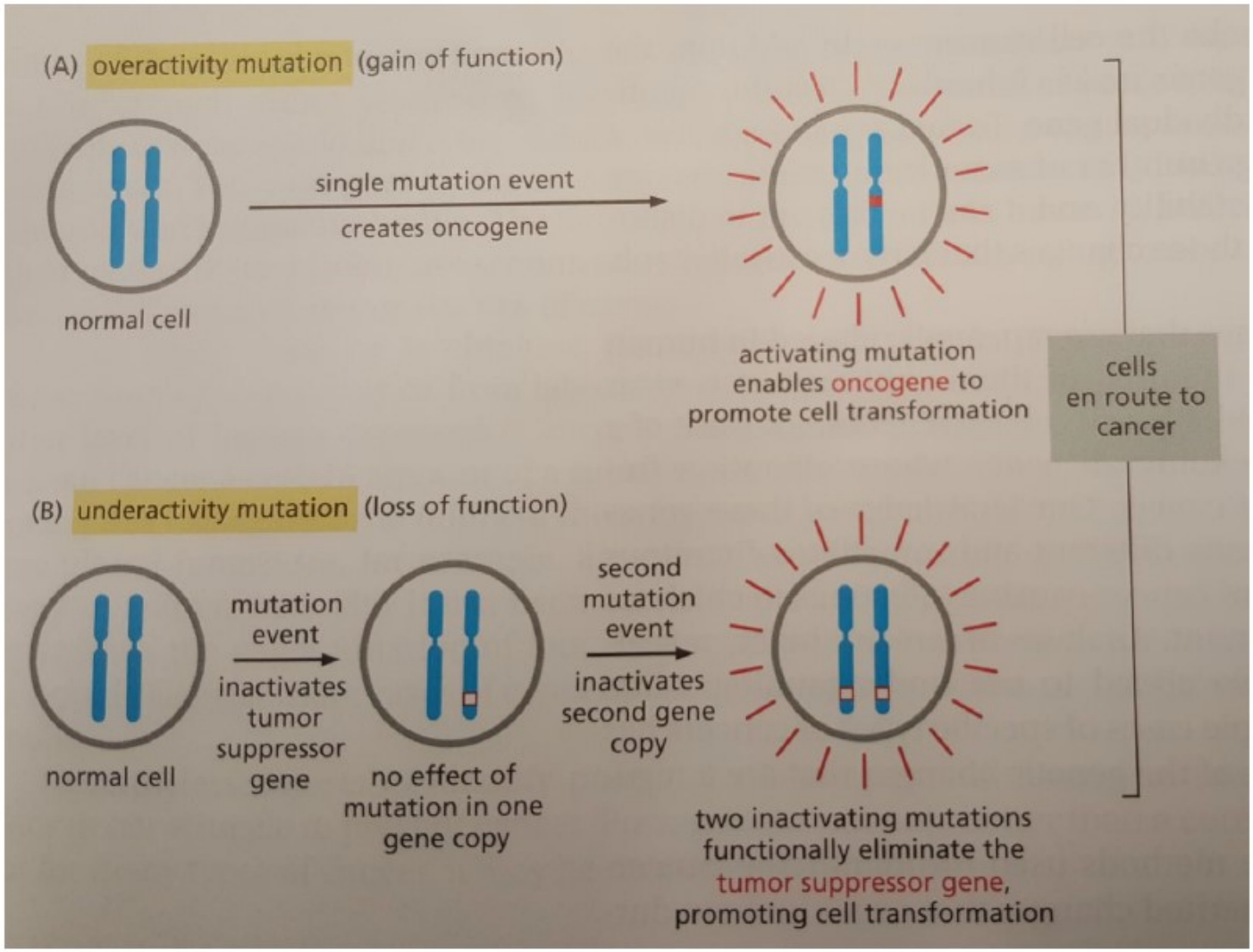


Caryotype: multicolored chromosomes indicate aberrant cross-over !

Multiple mutations are required to provoke cancer



Oncogenes



Mol. Biol. of the Cell, B. Alberts et al., 5th edition, Chap. 20

Example:

Ras, mutated in 1 out of 5 cancers

Example:

Rb tumor suppresor gene

Cancer can be caused by viruses

Table 20–1 Viruses Associated with Human Cancers

VIRUS	ASSOCIATED CANCER	AREAS OF HIGH INCIDENCE
DNA viruses		
Papovavirus family		
Papillomavirus (many distinct strains)	warts (benign)	worldwide
	carcinoma of the uterine cervix	worldwide
Hepadnavirus family		
Hepatitis-B virus	liver cancer (hepatocellular carcinoma)	Southeast Asia, tropical Africa
Hepatitis-C virus	liver cancer (hepatocellular carcinoma)	worldwide
Herpesvirus family		
Epstein–Barr virus	Burkitt's lymphoma (cancer of B lymphocytes)	West Africa, Papua New Guinea
	nasopharyngeal carcinoma	Southern China, Greenland
RNA viruses		
Retrovirus family		
Human T-cell leukemia virus type I (HTLV-1)	adult T-cell leukemia/lymphoma	Japan, West Indies
Human immunodeficiency virus (HIV, the AIDS virus)	Kaposi's sarcoma	Central and Southern Africa

Le cancer: une instabilité de la vie

Chromatine (gènes) ouverte, caryotype aberrant

Biologique

- Gros noyau
- Indifférencié (~cellule souche)
- Prolifération importante
- Non-apoptotique
- Migratoire

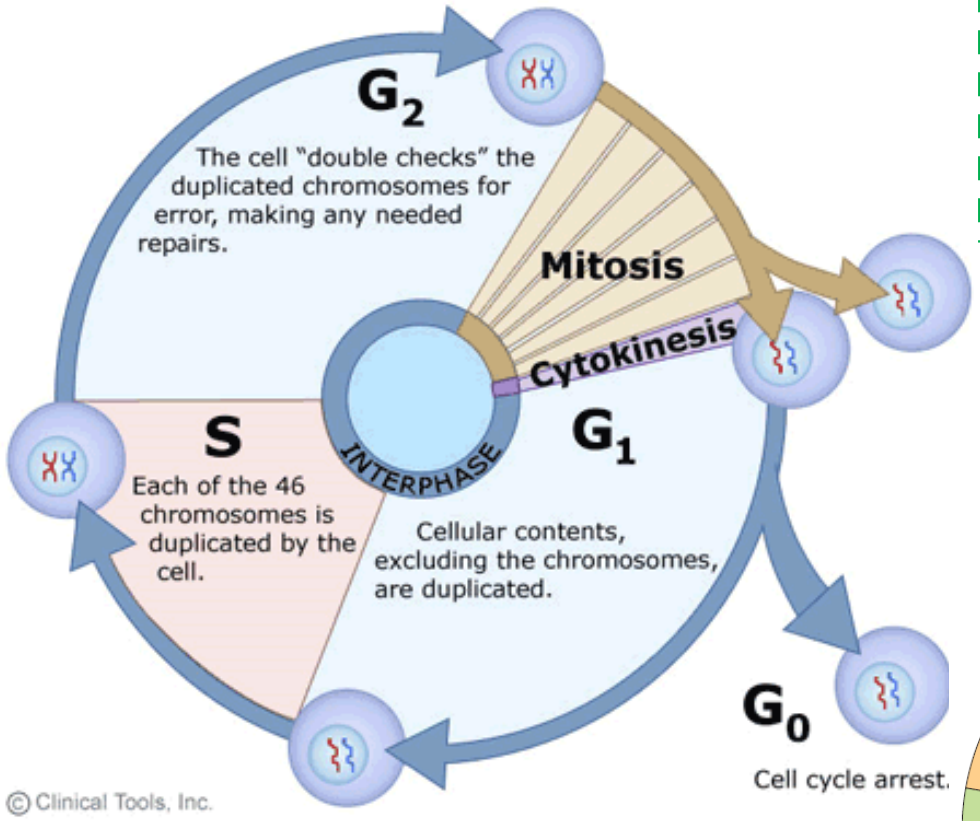
Biophysique

- Métabolisme: glycolyse, pH intracellulaire acide
- Néo-angiogénèse
- Cellules mécaniquement molles
- Membrane dépolarisée électriquement

Comme dans un embryon

Parenthèse technique: mesurer le cycle cellulaire

How long does it take a cell to divide ? The cell cycle:

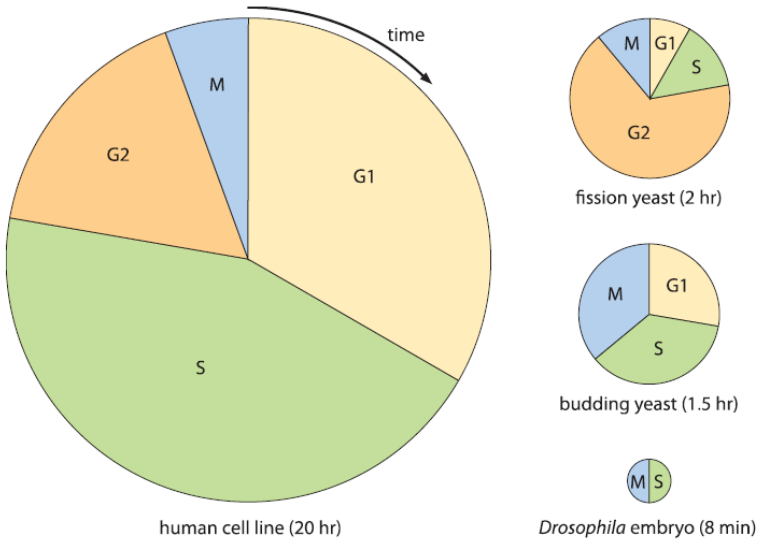


Exercice

Human cell-cycle: ~20h

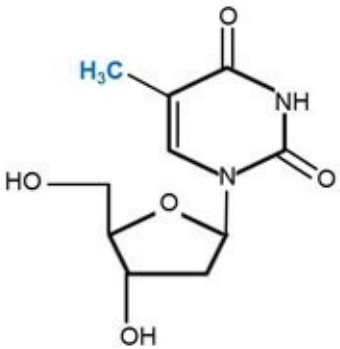
Compute how many cells in our body ?

How long does it take to get to this number by exponential mitotic growth ?



How to measure cell proliferation ?

Acide nucléïque



Thymidine

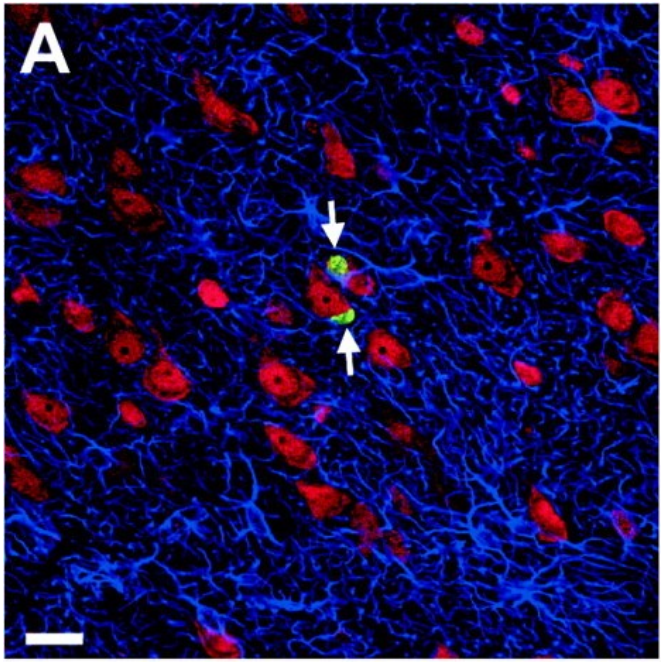
5'-bromo-2'-deoxyuridine (BrdU)

BrdU

↓

En excès: **incorporé à la place** de la thymidine lors de la phase S

Add **BrdU fluorescent antibody** to detect proliferating cells (S phase)

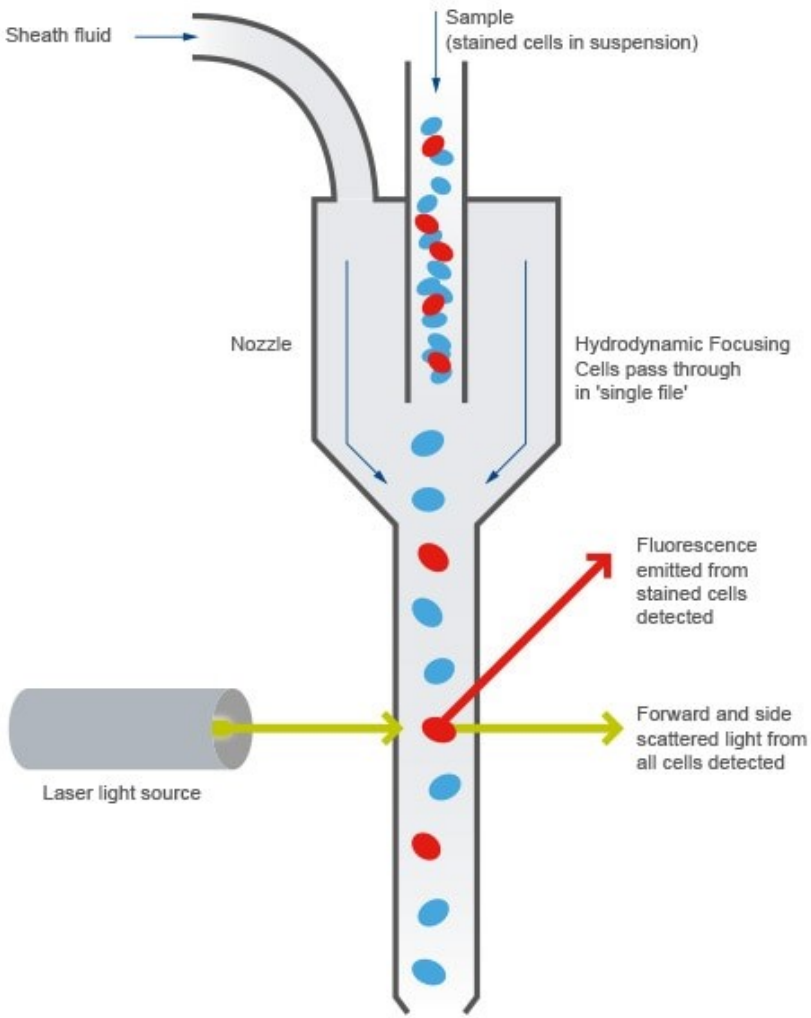


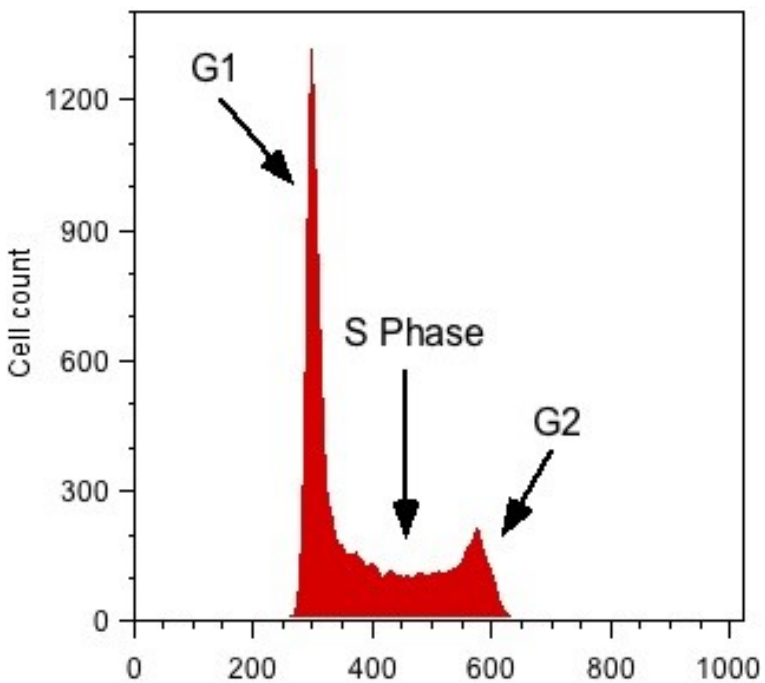
Example: Proliferation in thin section of cortex

→ Good to compare relative prolif. rate in diff. tissues, or same tissue in diff. conditions

How to measure cell cycle length ?

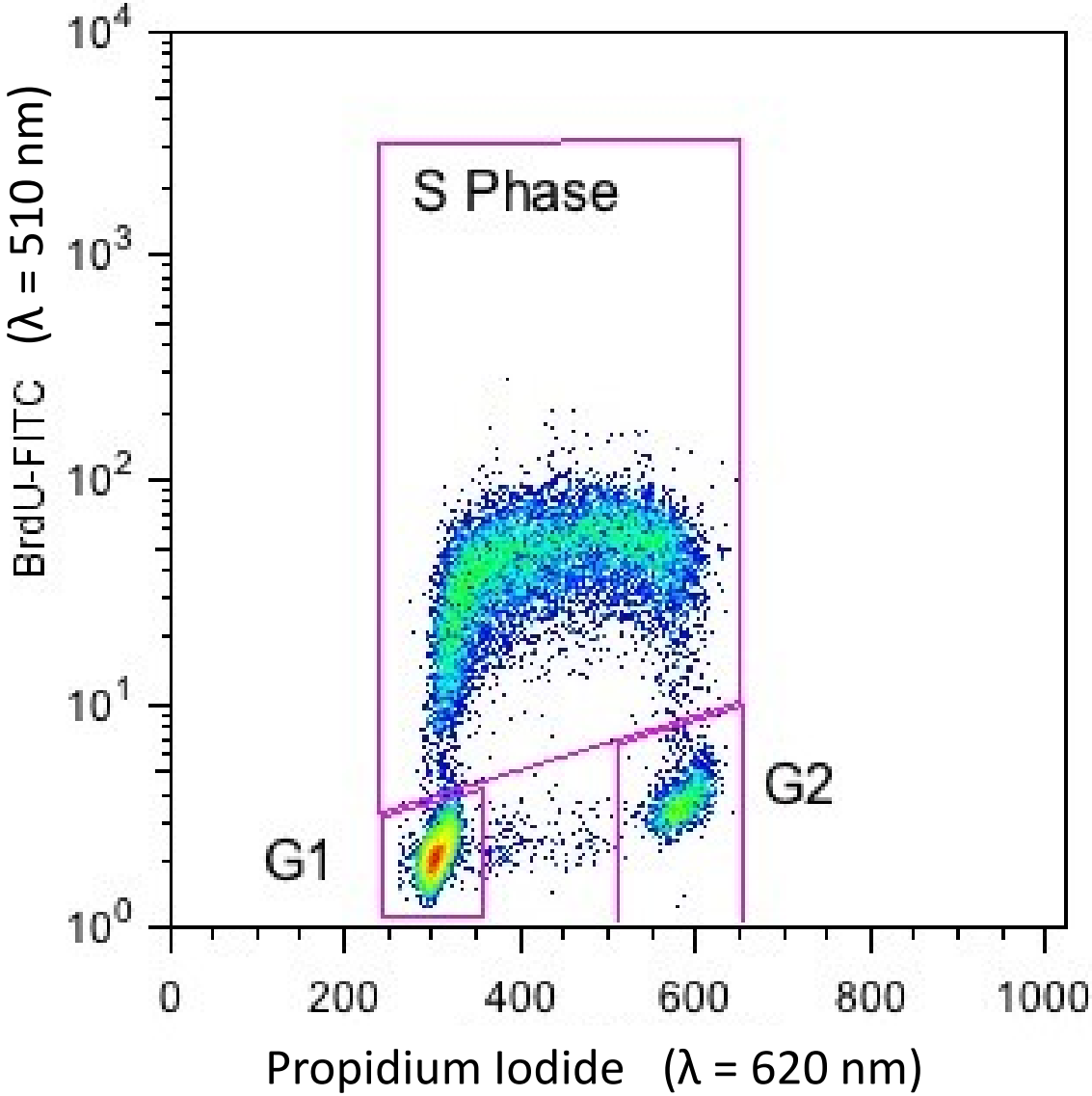
Flow cytometry





Propidium Iodide
Fluorescence intensity
(proportional to DNA content)

Cytométrie en flux à deux couleurs BrDU + propidium iodide



Nombre de points dans chaque phase
α durée du cycle

mais …

<u>Exercice :</u>

Proposer un protocole pour trouver la durée absolue de tout le cycle d'un type cellulaire en suspension ? Sur une tranche de tissu ?