Bases Moléculaires des thérapies ciblées pour les cancers broncho-pulmonaires

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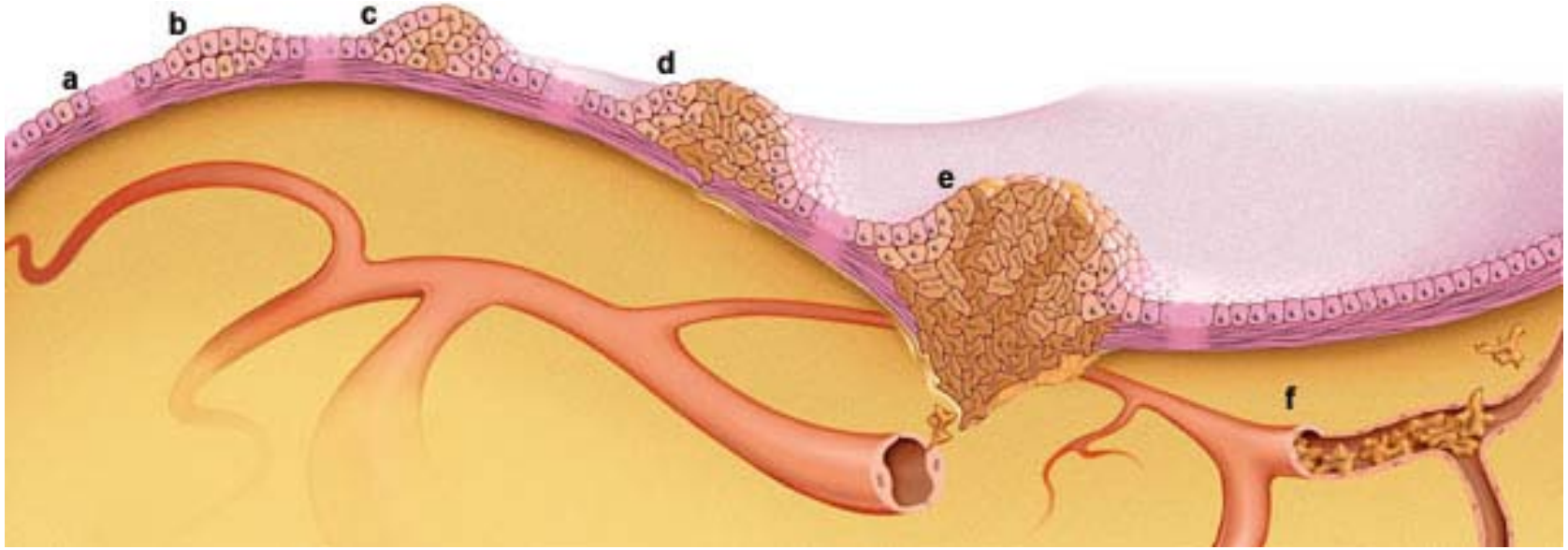
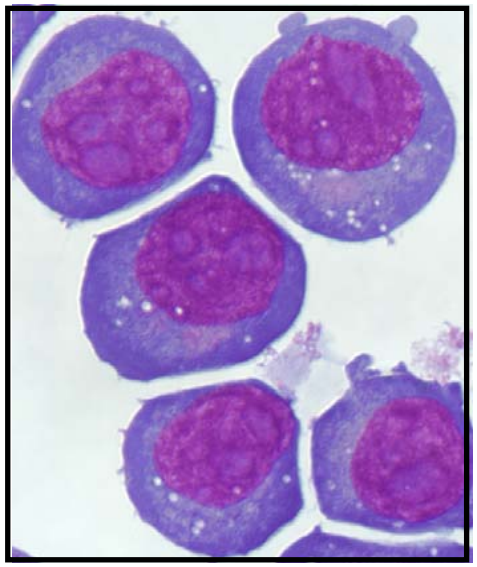
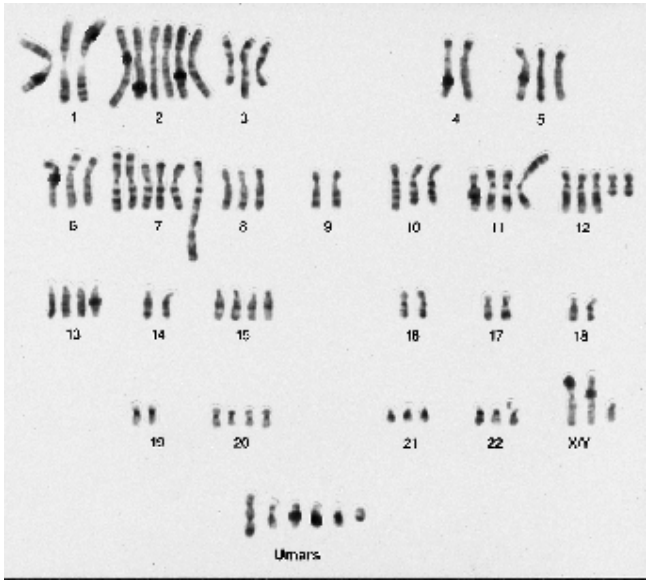
International Agency for Research on Cancer

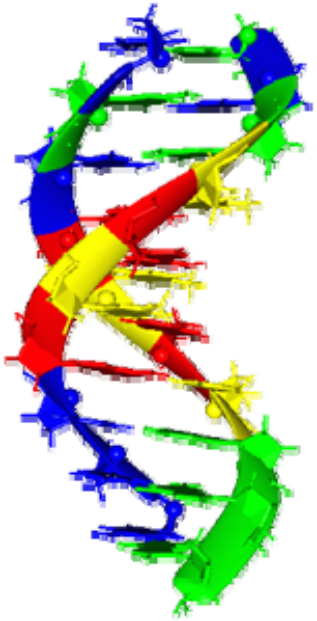
Cancer Progression



Cancer: A Disease of the Genome







Challenge in Treating Cancer:

- **Every tumour is different**
- **Every cancer patient is different**

Critical steps in carcinogenesis

Activate HaRas oncogene

Self-sufficiency for growth

Evading apoptosis

Produce IGF
Survival factors

Produce V-EGF inducers

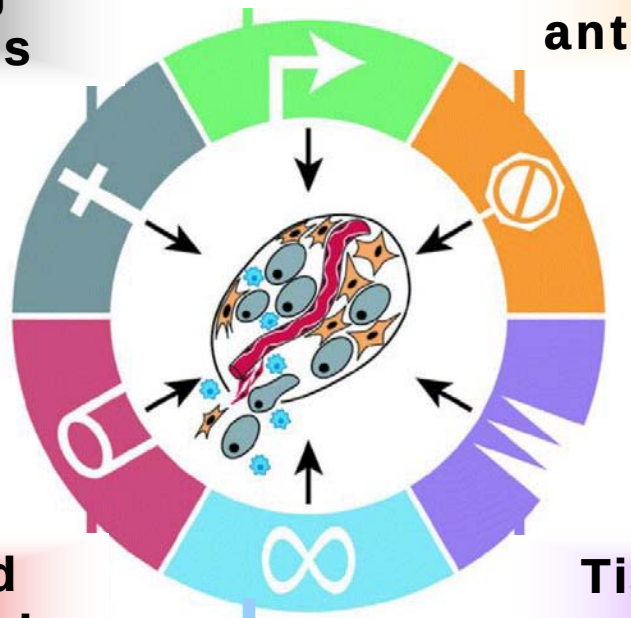
Sustained angiogenesis

Insensitivity to anti-growth signals

Loose TP53 and RB suppressors

Inactivate E-cadherin

Tissue invasion and metastasis



Unlimited replicative potential

Turn on telomerase

Adapted from Hanahan and Weinberg, 2000

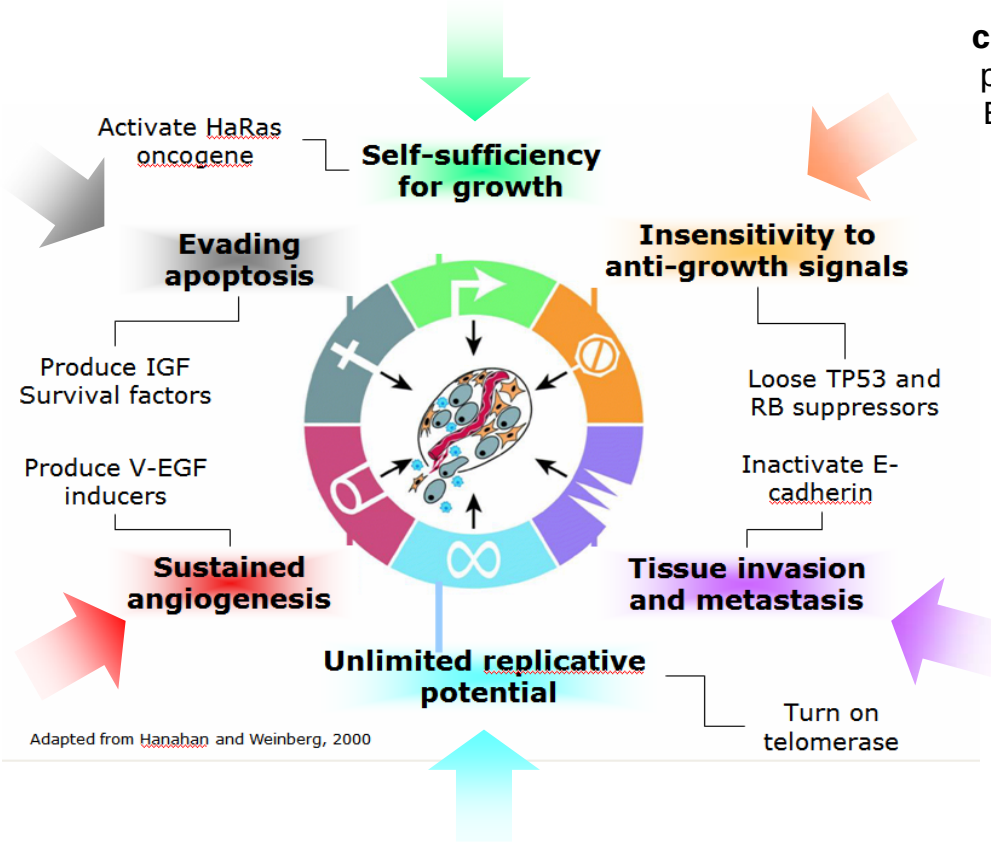
Targets for Therapy

Specifically inhibit activated oncogenes
e.g. EGFR, HER2, KRAS, betaCatenin

Inhibit survival factors
e.g. bcl2
Cox-2
Anti-hormone therapy

Stimulate Pro-apoptotic pathways, e.g. FAS, Killer DR5

Restore critical suppresor checkpoints, e.g. p53, p14arf, p16, Block E2F factors
Block DNA metabolism

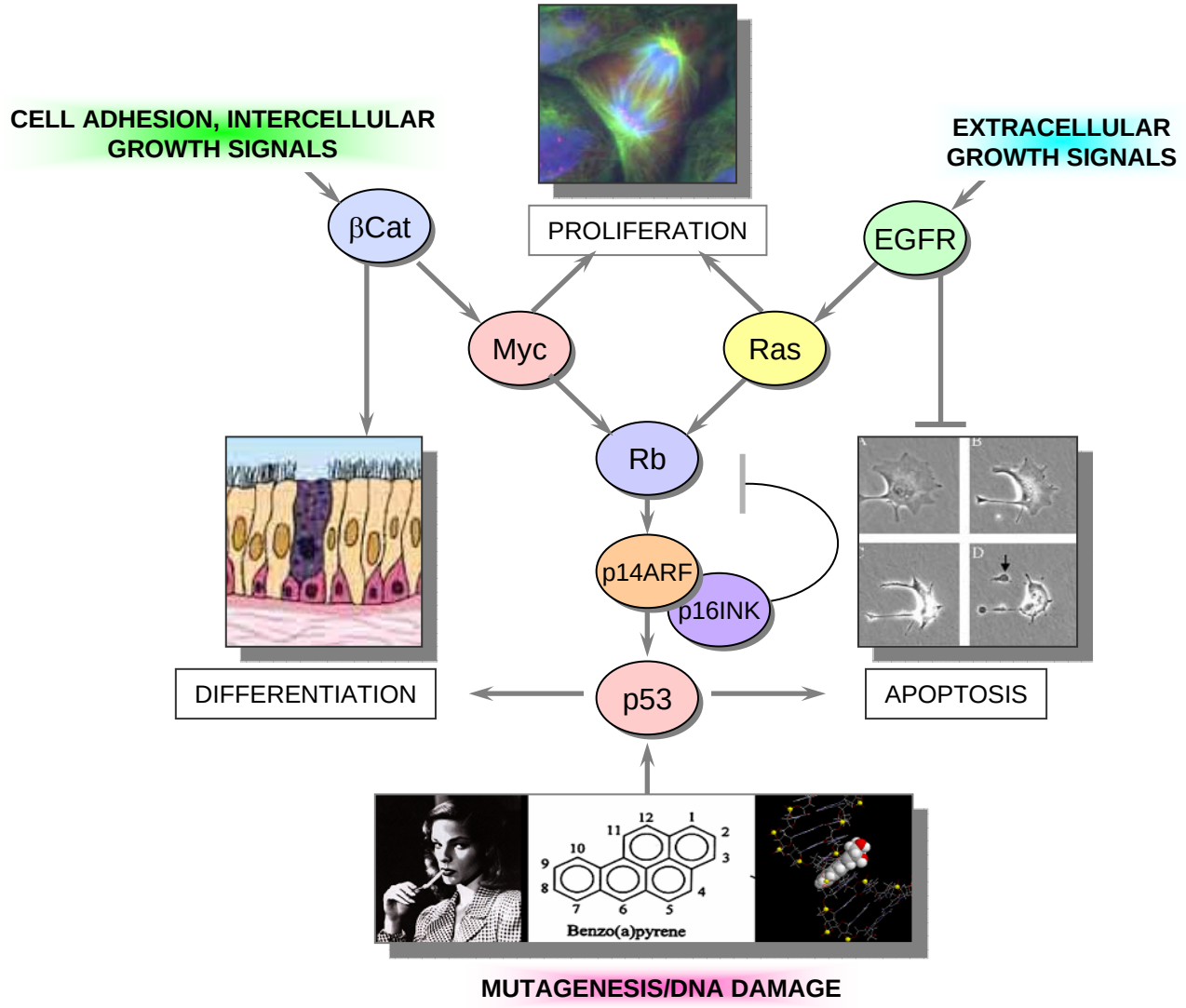


Block angiogenesis

Block invasion-related proteases
Immunotherapy
Adhesion moelcules

Inhibit telomerases

Cancer signaling “crossroad”



Thérapies Ciblées

Type de traitement qui vise à prévenir la croissance tumorale en intervenant avec une cible moléculaire spécifique, telle que par exemple un facteur de croissance indispensable à la prolifération cellulaire.

L'adressage d'un traitement sur une cible moléculaire précise sous-entend à la fois une plus grande efficacité à des doses pharmacologiques faibles, et une toxicité limitée, et la possibilité d'individualiser le traitement selon le profil pathologique et moléculaire du patient.

Targeted Therapy for Solid Tumors

Signal Transduction/Cell-Cycle Inhibitors

- Farnesyl transferase
- Retinoids
- UCN-101

Gene Therapy

- GM-CSF
- Wild-type p53
- Defective adenoviruses
- Antisense/RNA interference
  - c-*myc*

Vaccines

- Tumor cells
- Peptides
- Dendritic cells
- Viral vaccines

Angiogenesis Inhibitors

- SU5416/SU6668
- Anti-VEGF antibodies
- Interferon-a/b
- Marimastat
- ZD6474
- LY317615
- TNP-470
- Endostatin/angiostatin

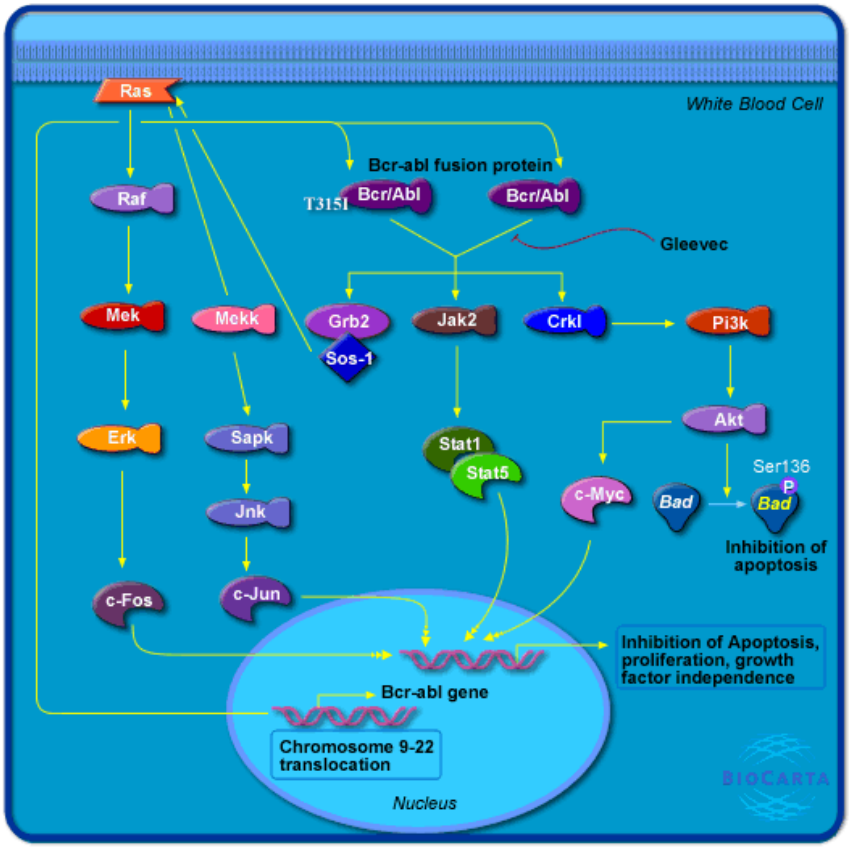
Receptor-Targeted Therapy

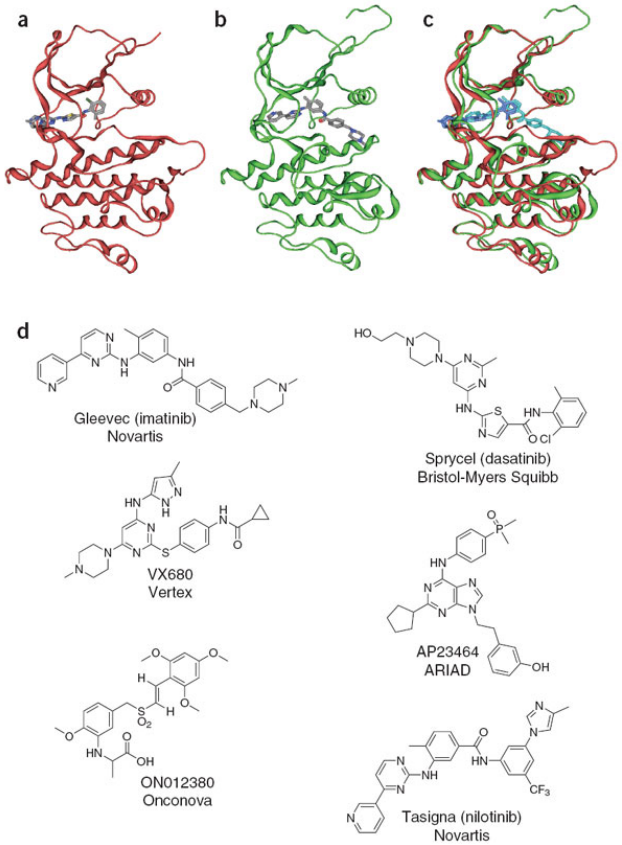
- Trastuzumab
- Anti-EGFR
  - ZD1839
  - C225
  - OSI-774

Nibs and Mabs

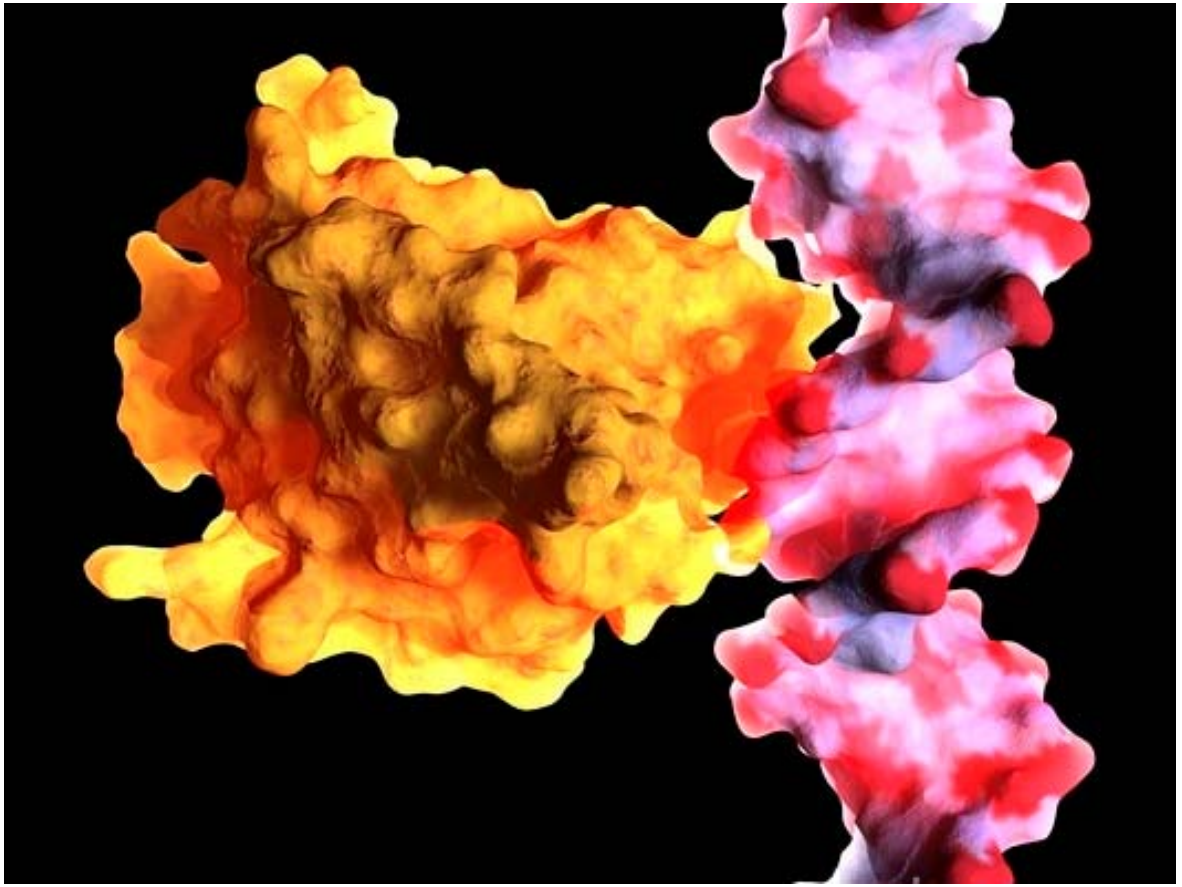
Target	« Nib »	« Mab »
EGFR	Gefinitib (Iressa) Erlotinib (Tarceva)	Cetuximab (Erbitux)
HER2	Lapatinib	Traztuzumab (Herceptin)
VEGFR	Sorafenib	
VEGFa		Bevacizumab (Avastin)
Bcr-Abl	Imanitib mesylate (Gleevec)	

Gleevec: inhibition of bcr/Abl

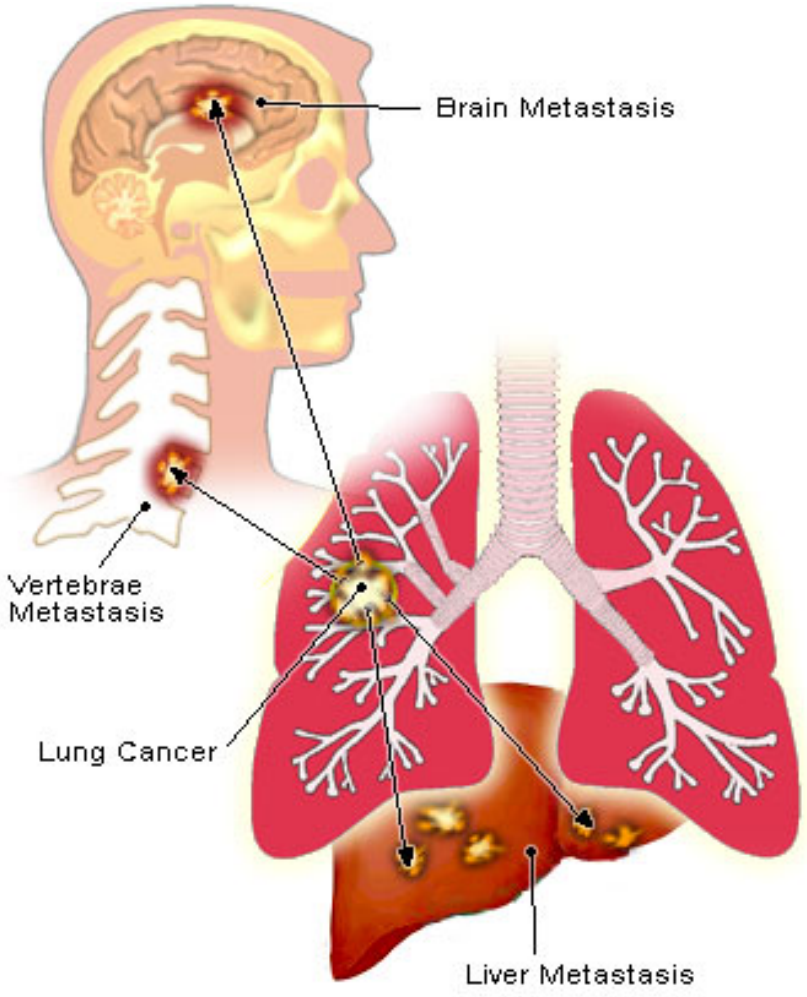




P53: suppresseur de tumeurs

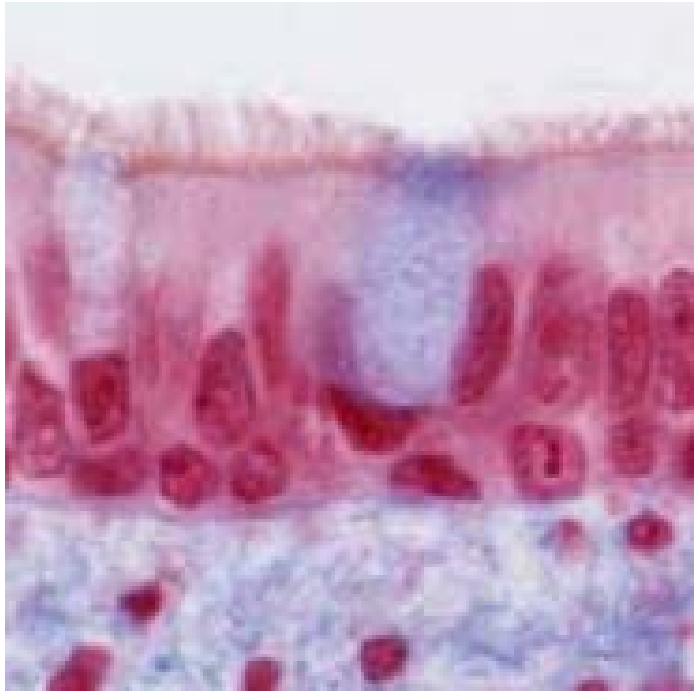


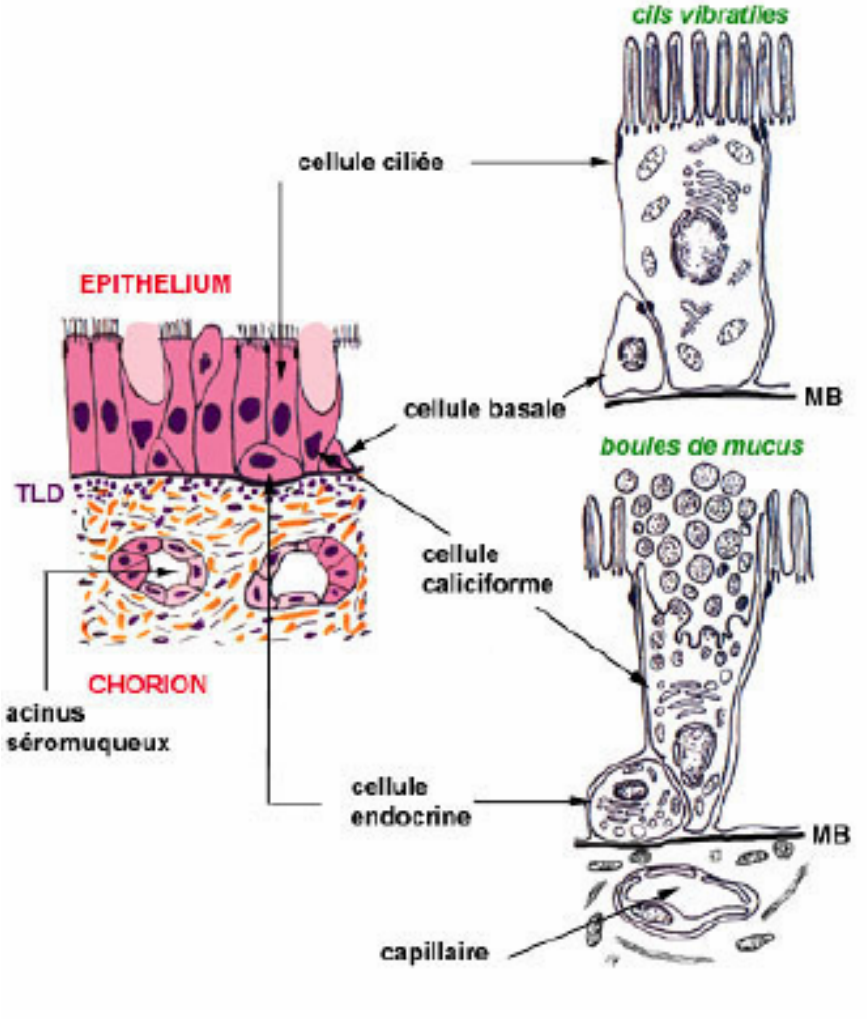
Lung Cancer



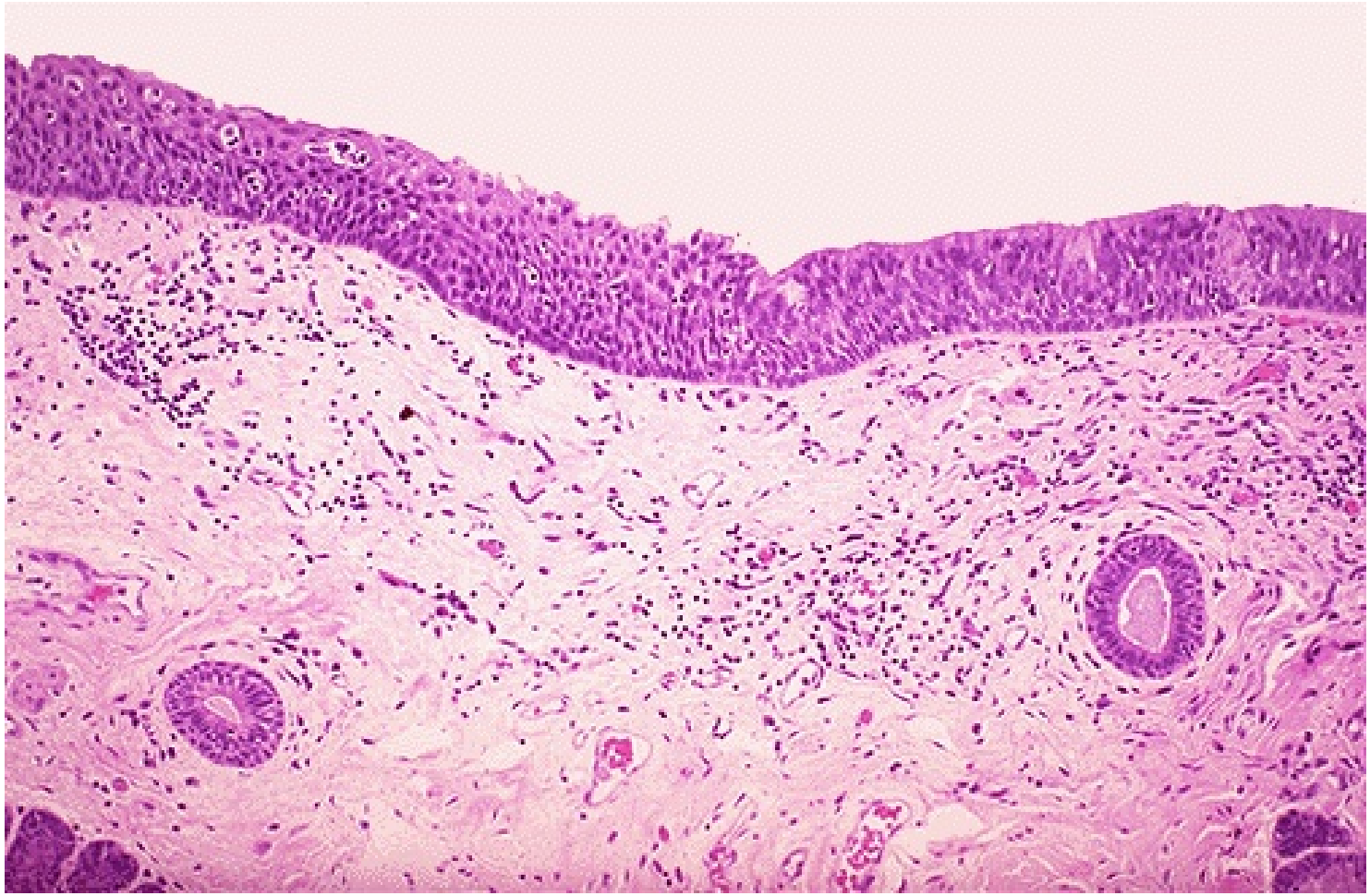
- Over 1,300,000 cases annually
- Untreated patients have a median survival of ~4 - 5 months
- CisPlatin-based Cx after surgery:
  - 5 yrs survival ~ 40%
  - Benefit over palcebo: 4-5%

Pseudo stratified epithelium

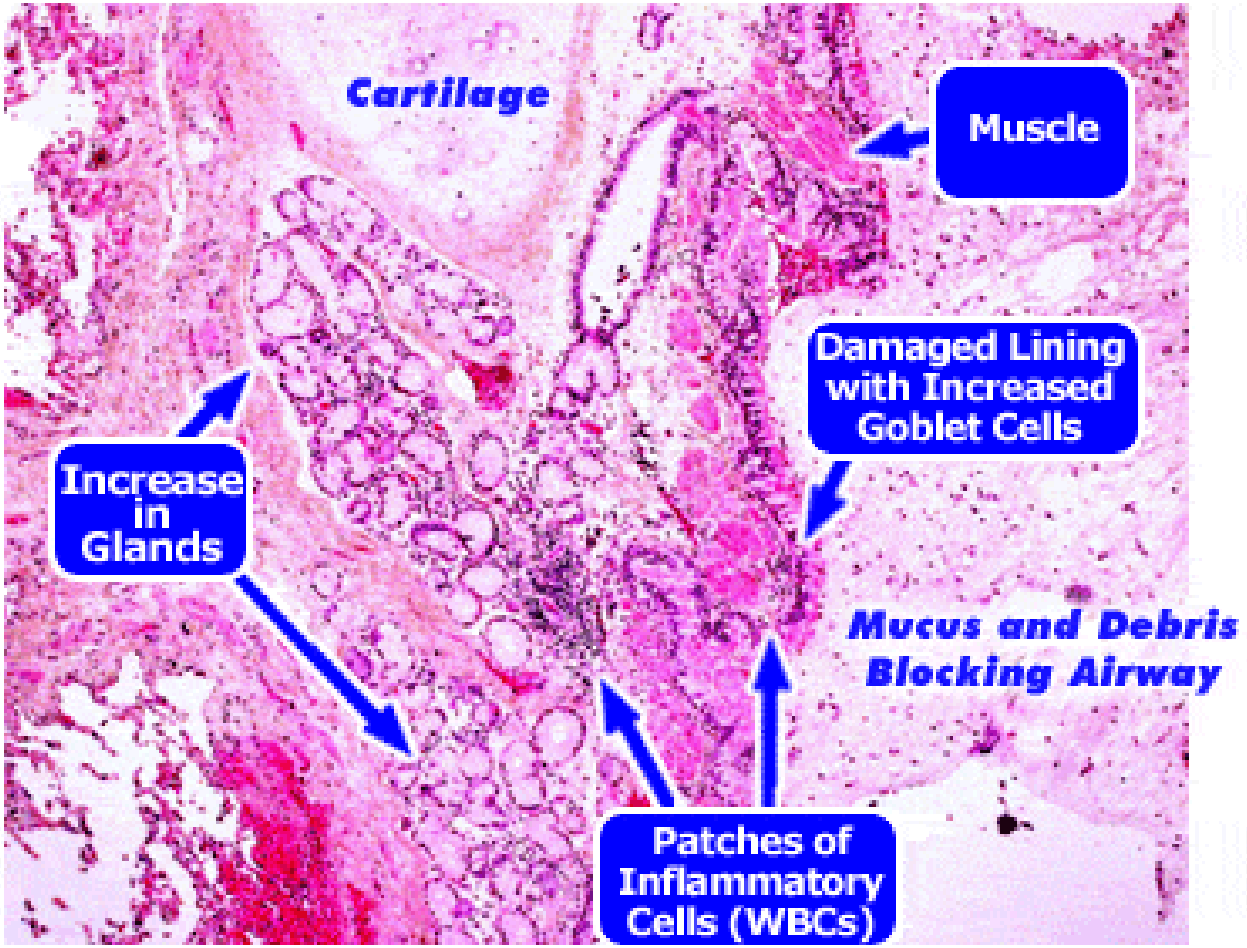




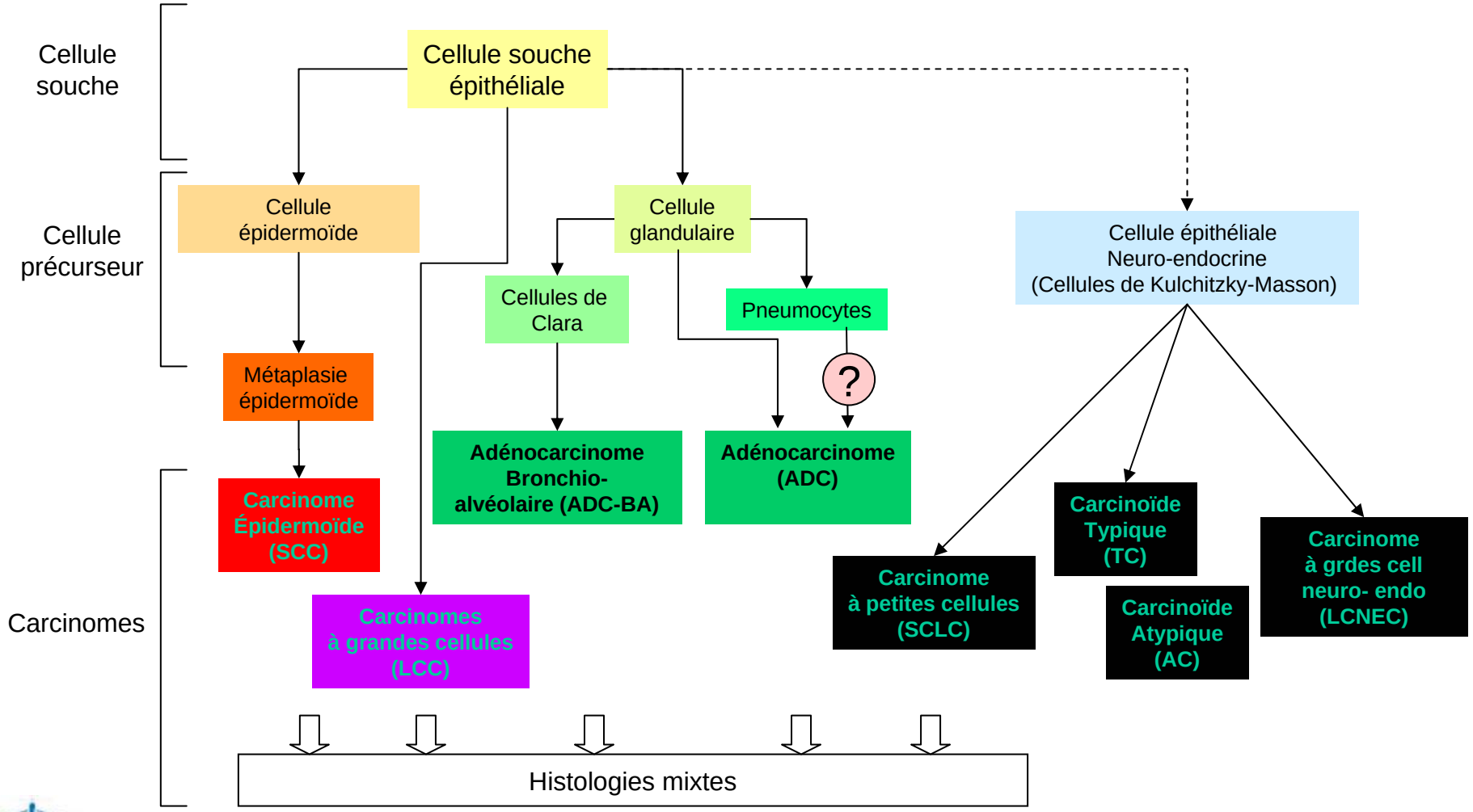
Tissue remodelling: Squamous metaplasia



Tissue remodelling: glandular cells in COPD

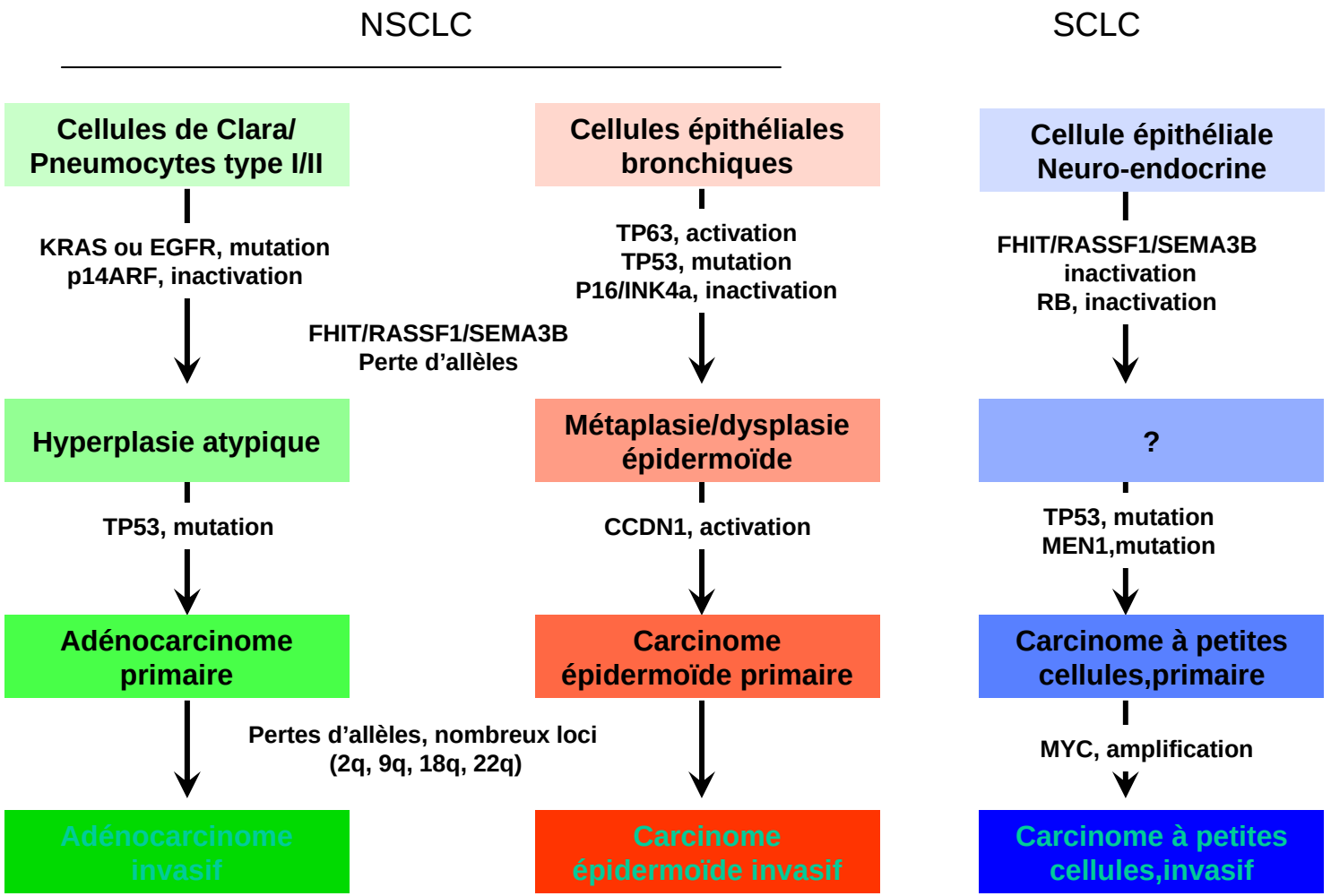


Histopathogenesis of lung cancers



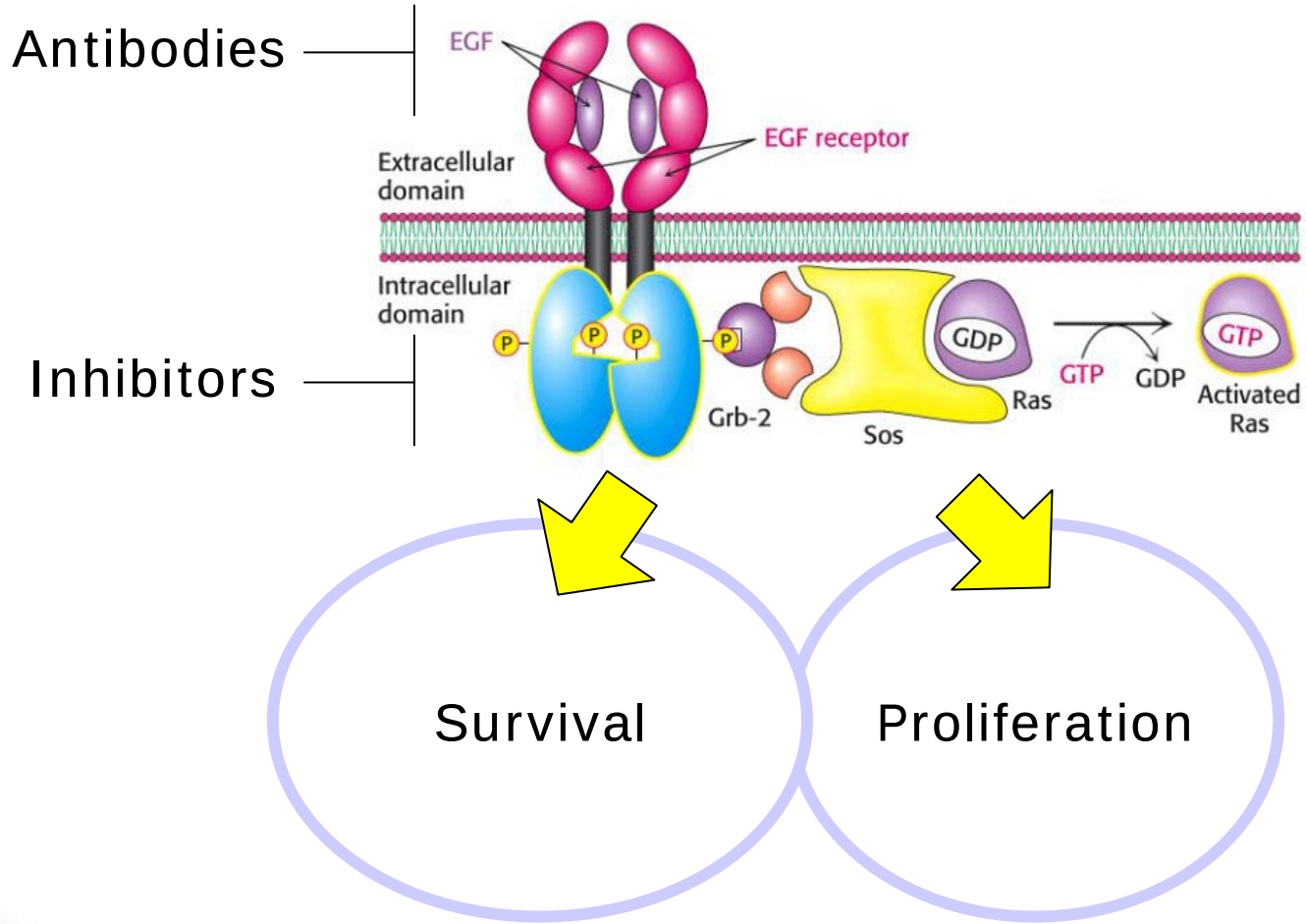
Monunawar et Hainaut Figure 1

Altérations génétiques

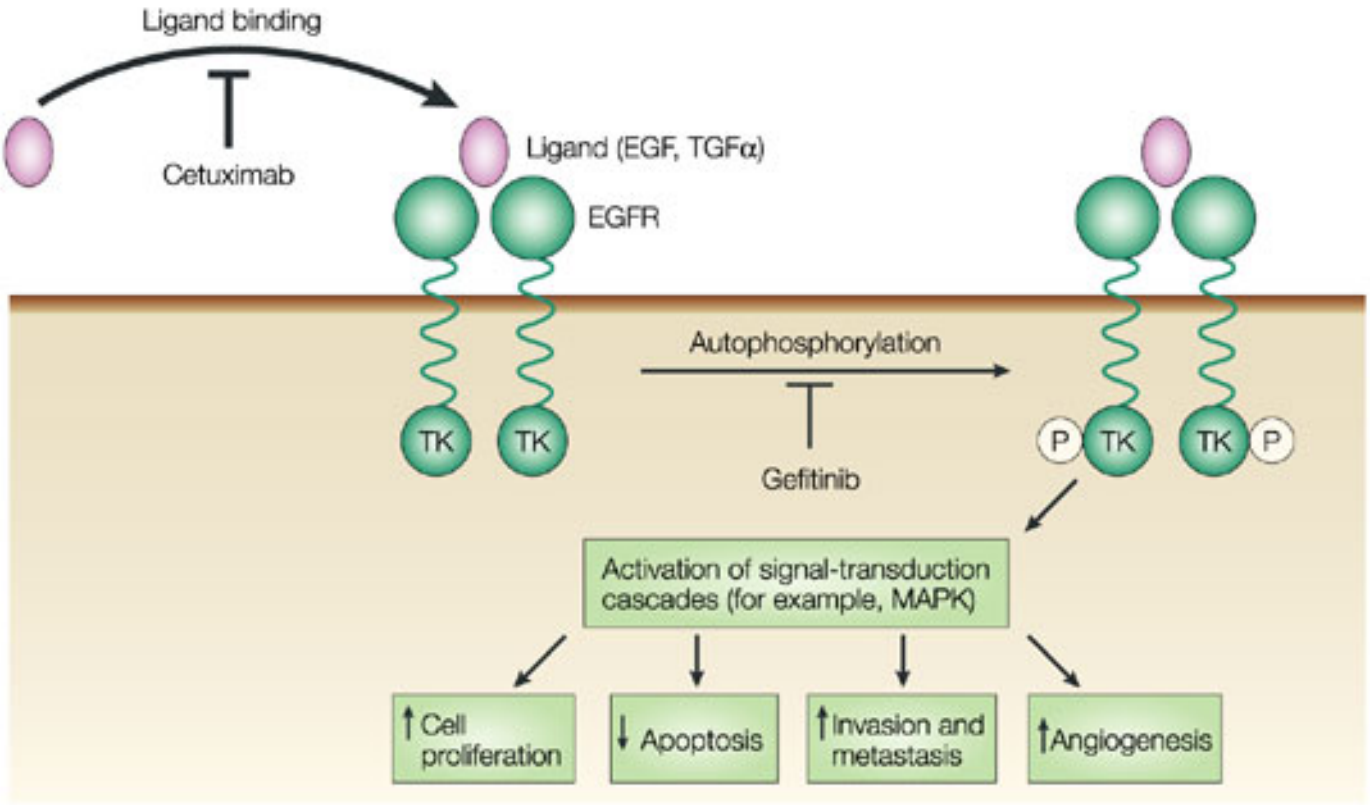


Mounawar et Hainaut Figure 2

EGFR/ Ras signalling pathway



Targeted therapies in the EGFR pathway



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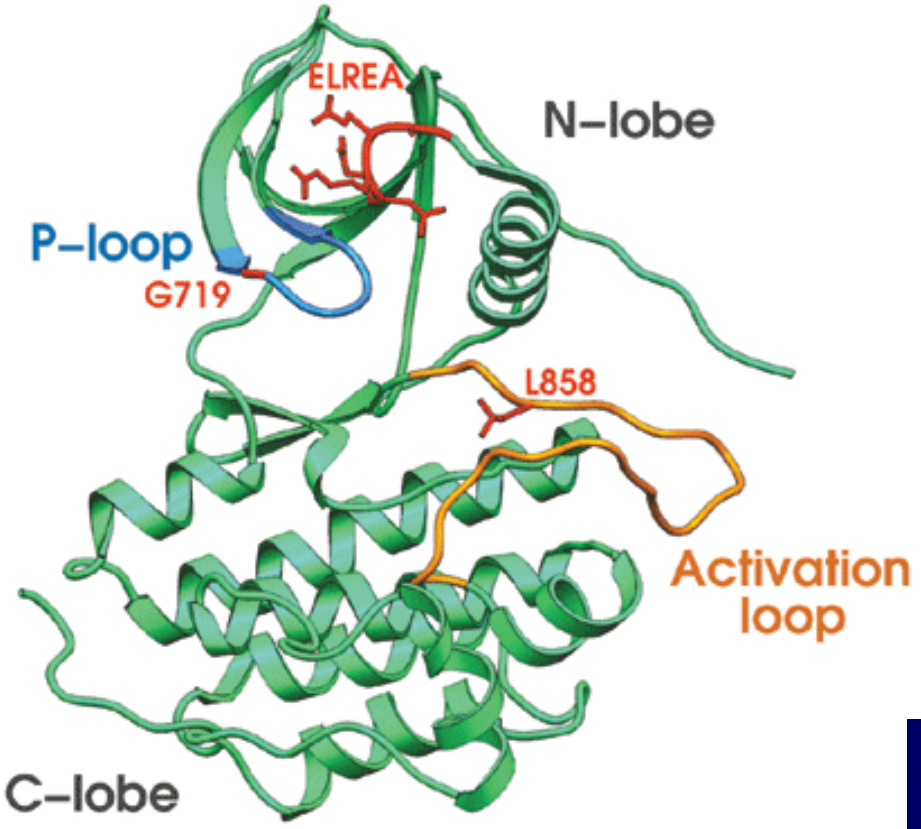
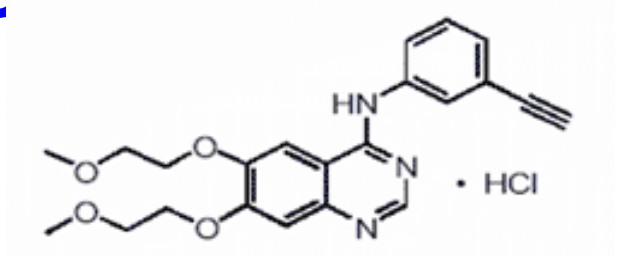
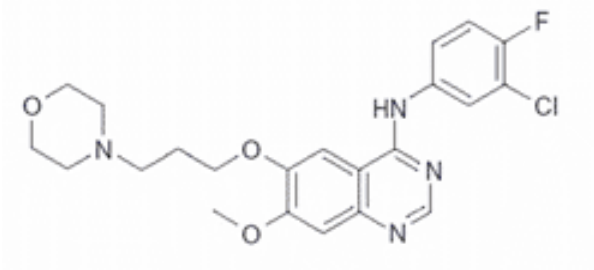
Inhibition of EGFR with small drugs





Gefintib, Iressa

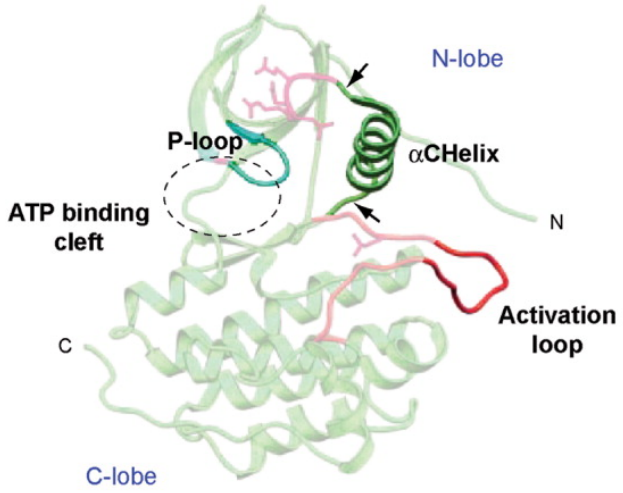


Erlotinib, Tarceva

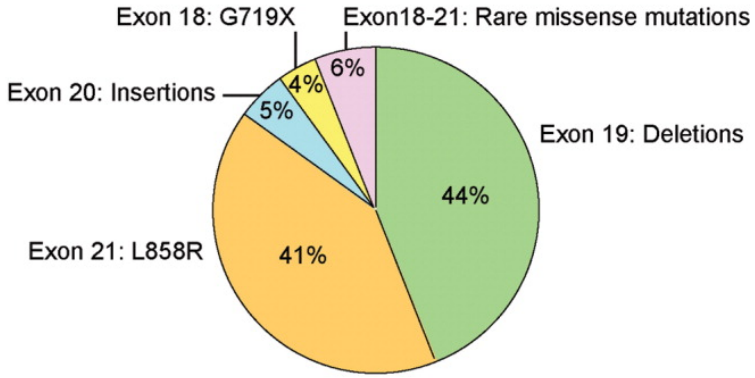
- EGFR IC_{50} = 0.023 µM
- erbB2 IC_{50} = 1.2-3.7 µM

EGFR mutations: never smokers

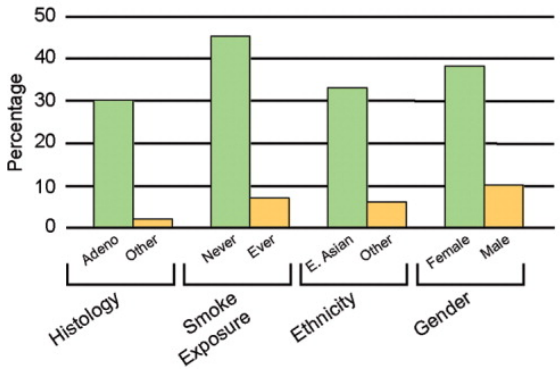
a Location of mutations in tyrosine kinase domain of EGFR gene.



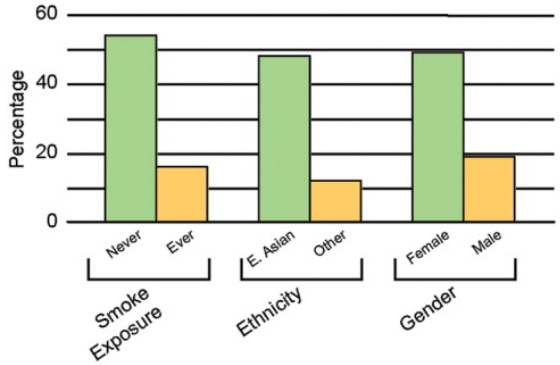
b Frequencies of EGFR mutational types (n = 477).



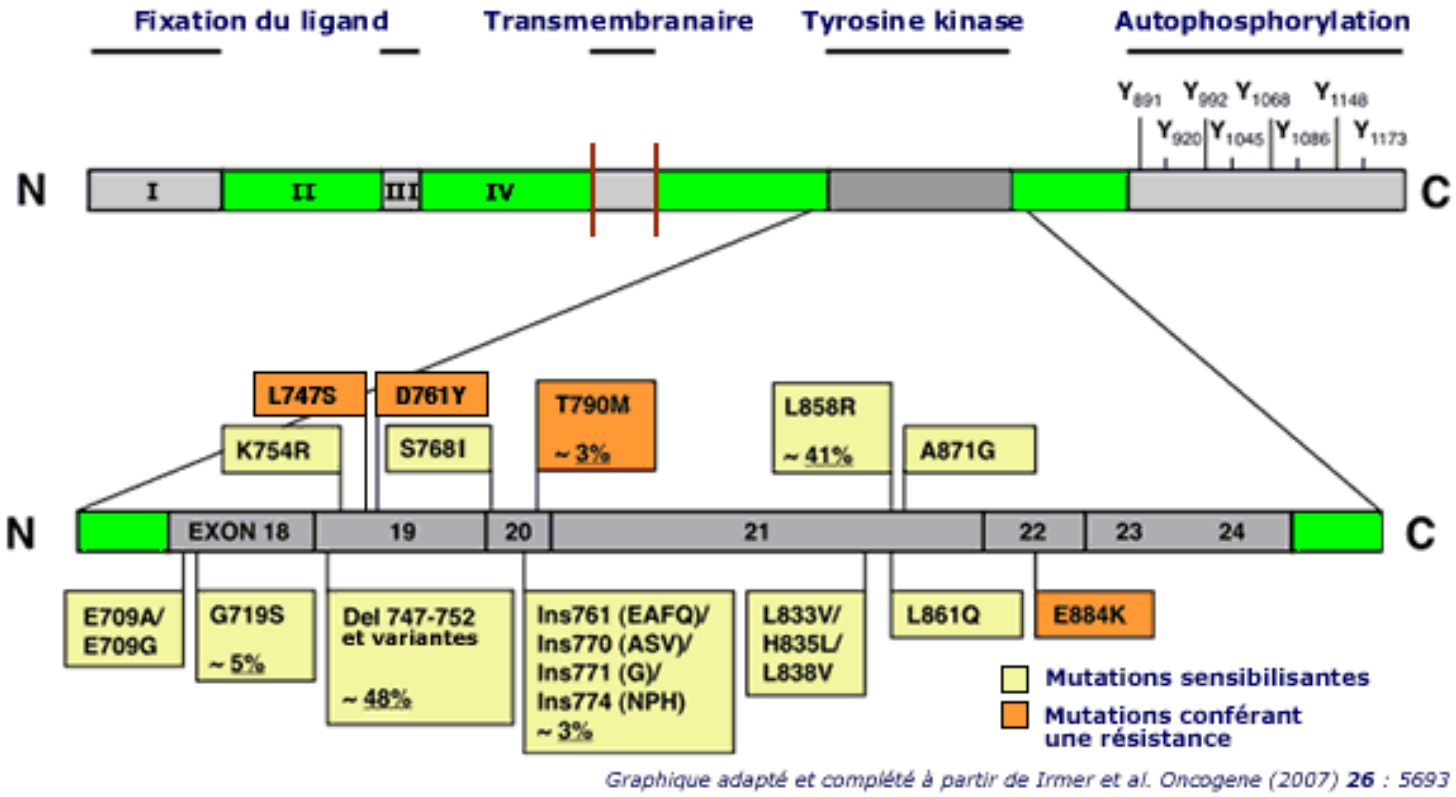
c EGFR mutations in NSCLC (n > 2000).



d EGFR mutations in Adenocarcinomas (n = 1082).



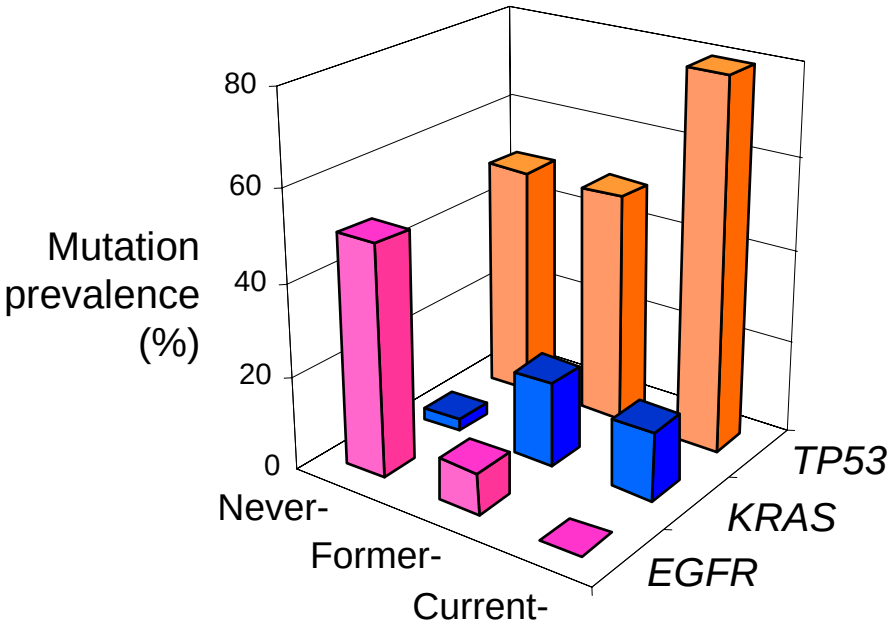
Mutations de l'EGFR: signification clinique

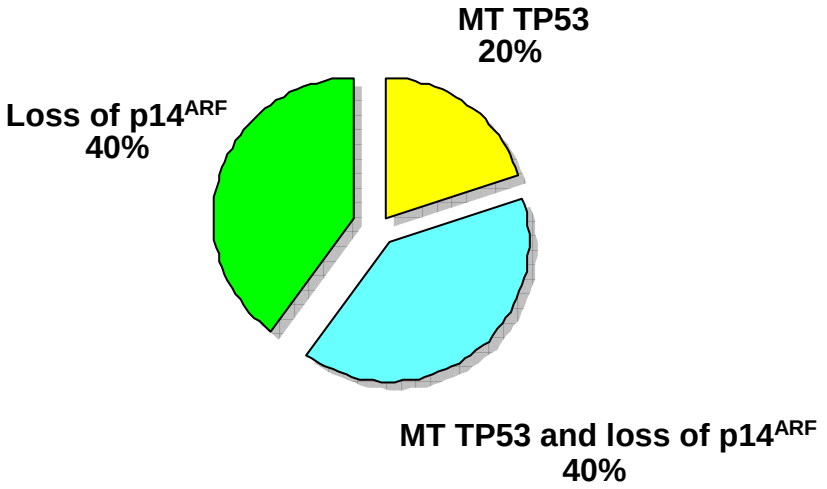


Graphique adapté et complété à partir de Irmer et al. Oncogene (2007) ***26*** *: 5693*

http://www.avernes.fr/Oncologie/rubrique.php3?id_rubrique=263

Mutations patterns in lung cancers

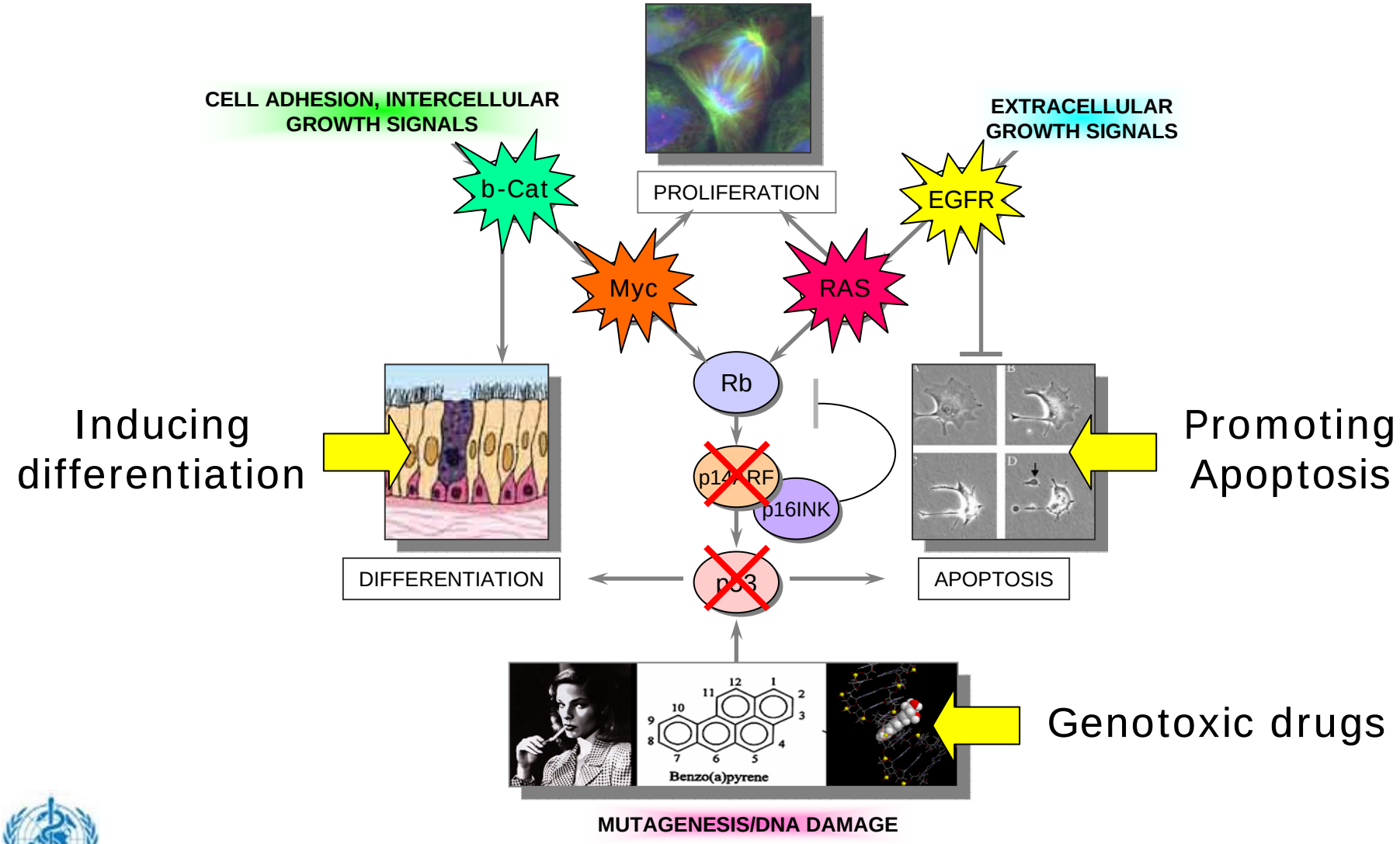




Never Smokers with EGFR mutations

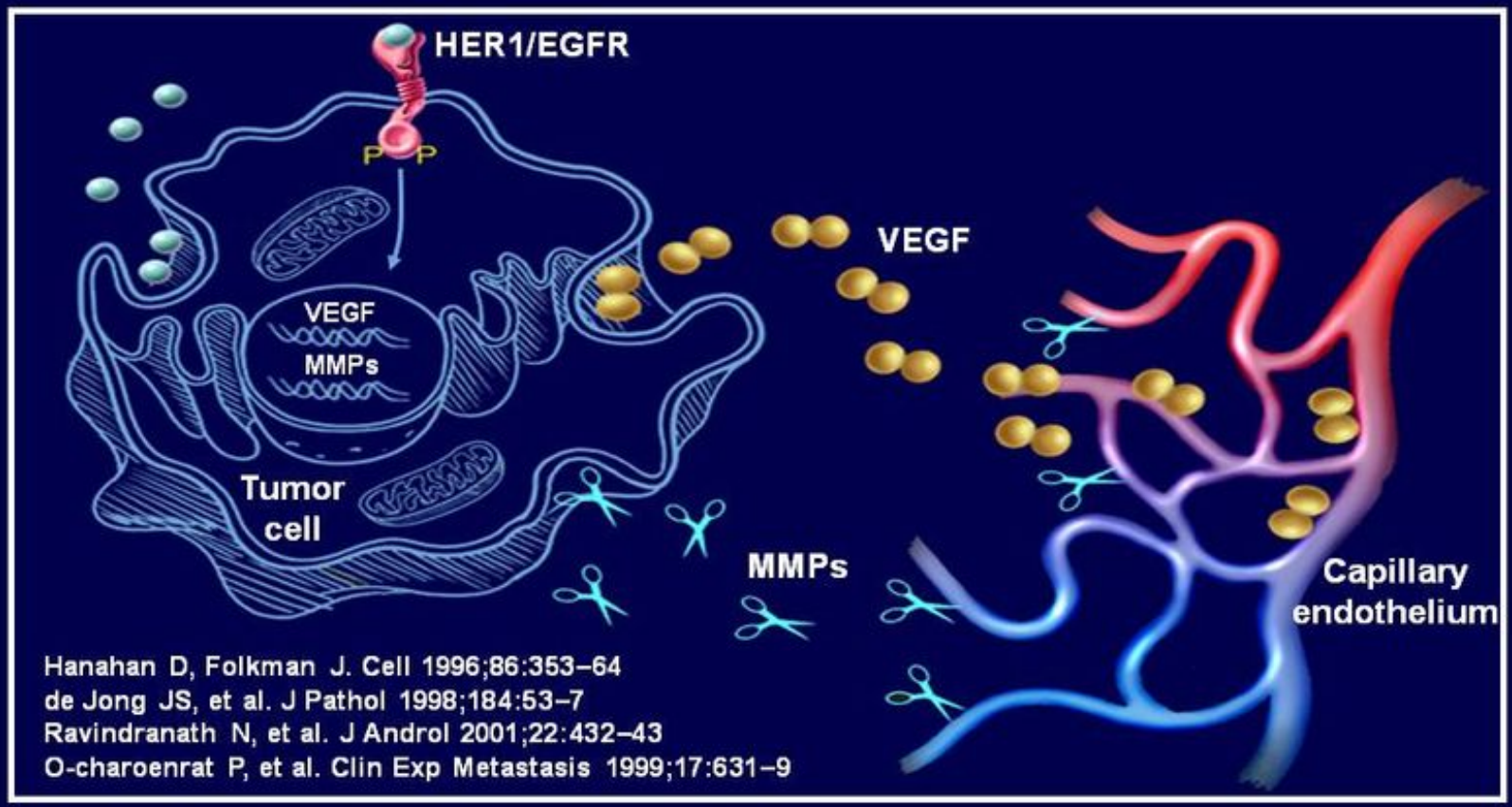
116 cases of lung cancers, Eastern European Case-control Study
Mounia Mounawar, Alexis Cortot
RayJean Hung, Paul Brennan, Paolo Boffetta
Anush Mukeria, David Zaridze

Cancer signaling “crossroad”



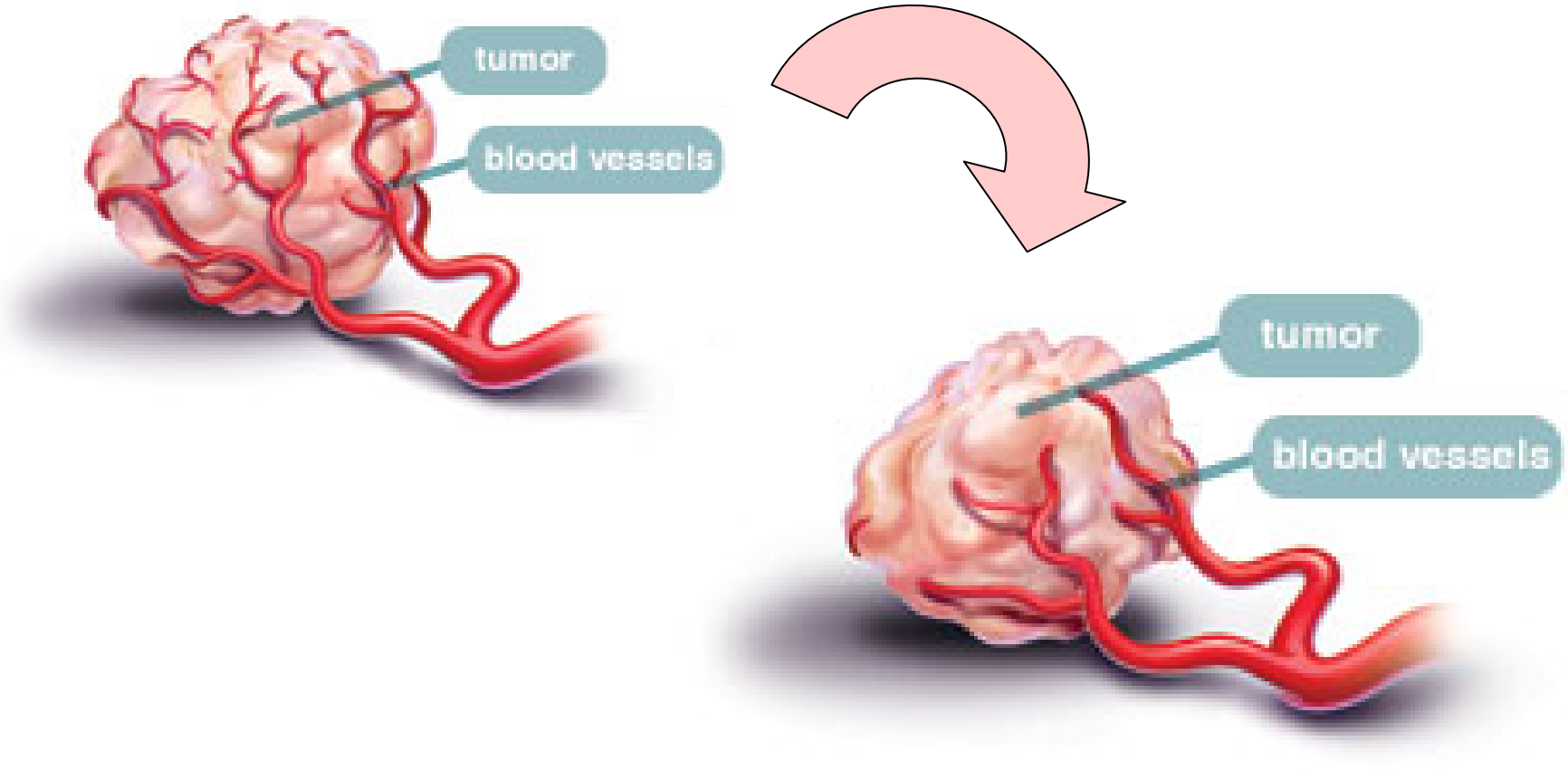
EGFR and Angiogenesis

- HER1/EGFR signaling increases vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP) levels

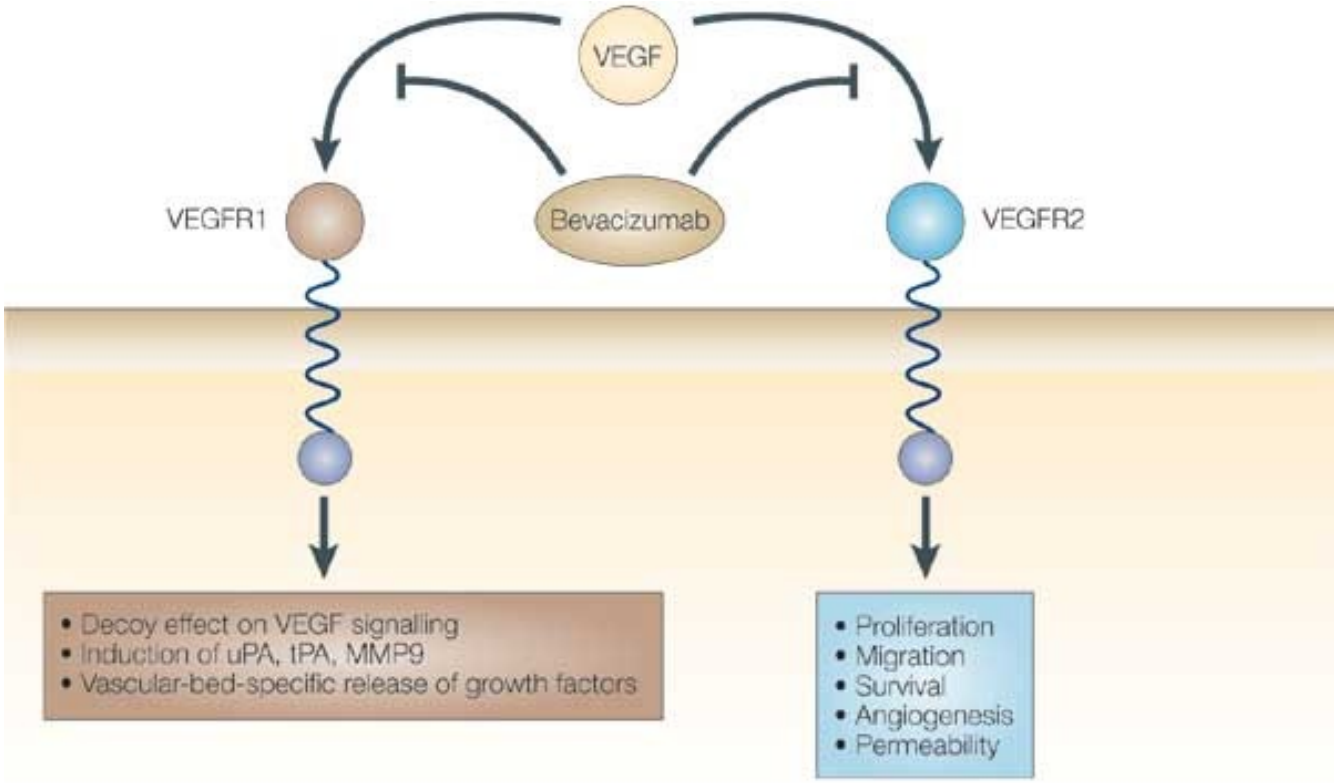


Hanahan D, Folkman J. Cell 1996;86:353–64
de Jong JS, et al. J Pathol 1998;184:53–7
Ravindranath N, et al. J Androl 2001;22:432–43
O-charoenrat P, et al. Clin Exp Metastasis 1999;17:631–9

Anti-angiogenic treatment



Bevacizumab (avastin)



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Resistance/escape

- Mutations in other genes of the EGFR pathway that overcome the role of the receptor
- Compensatory mutations in EGFR

Combination therapy is mandatory

« médecine individualisée? »

- Tests de détection fiables pour identifier les patients « répondeurs »
- Stratégies thérapeutiques à long-terme pour le contrôle des patients répondeurs
- Méthodes d'accompagnement et de conseil génétique/thérapeutique

Merci

Pour obtenir une copie de ces diapositives:

hainaut@iarc.fr

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Institut National du Cancer (INCa)