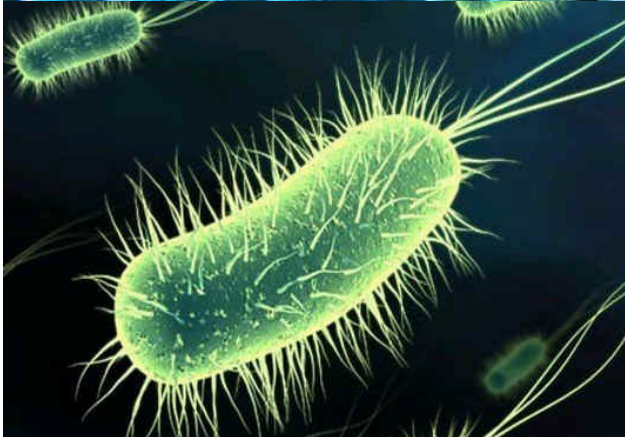
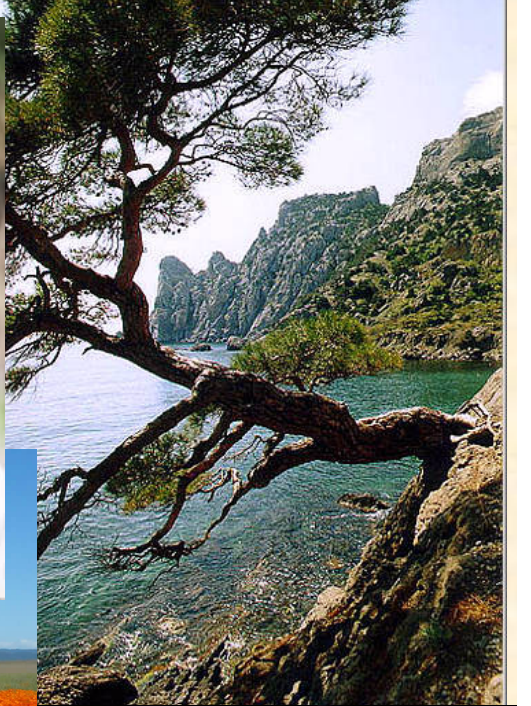


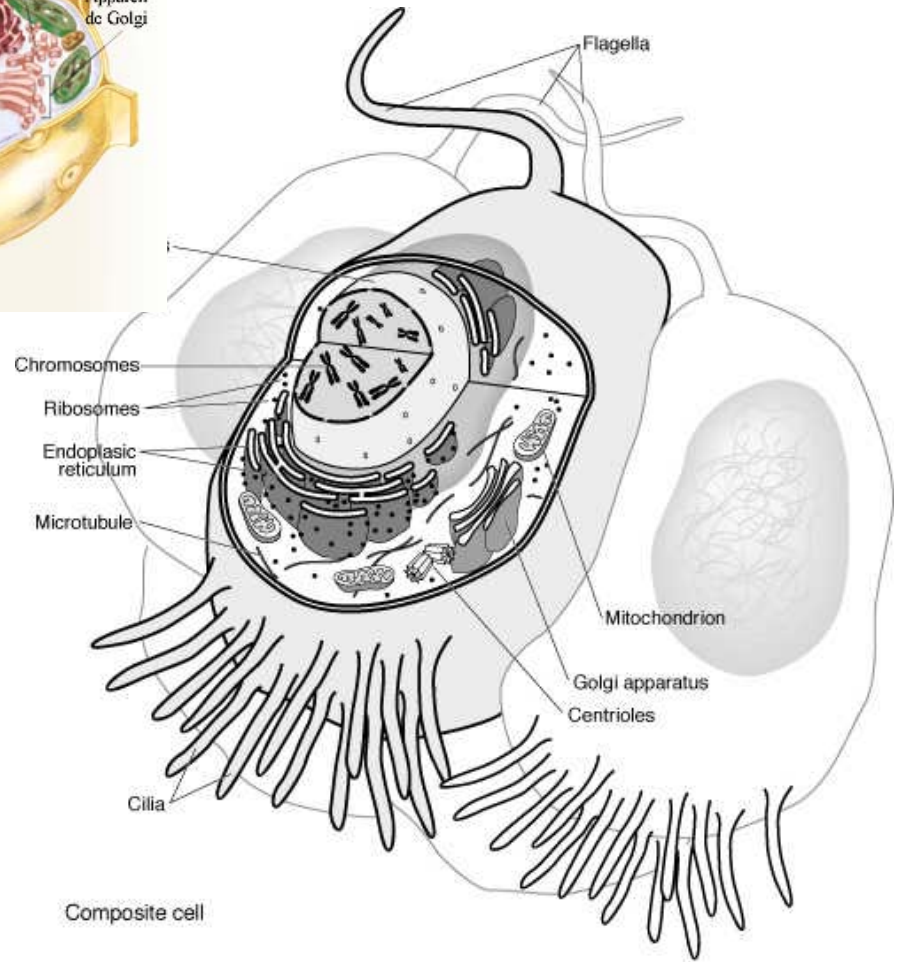
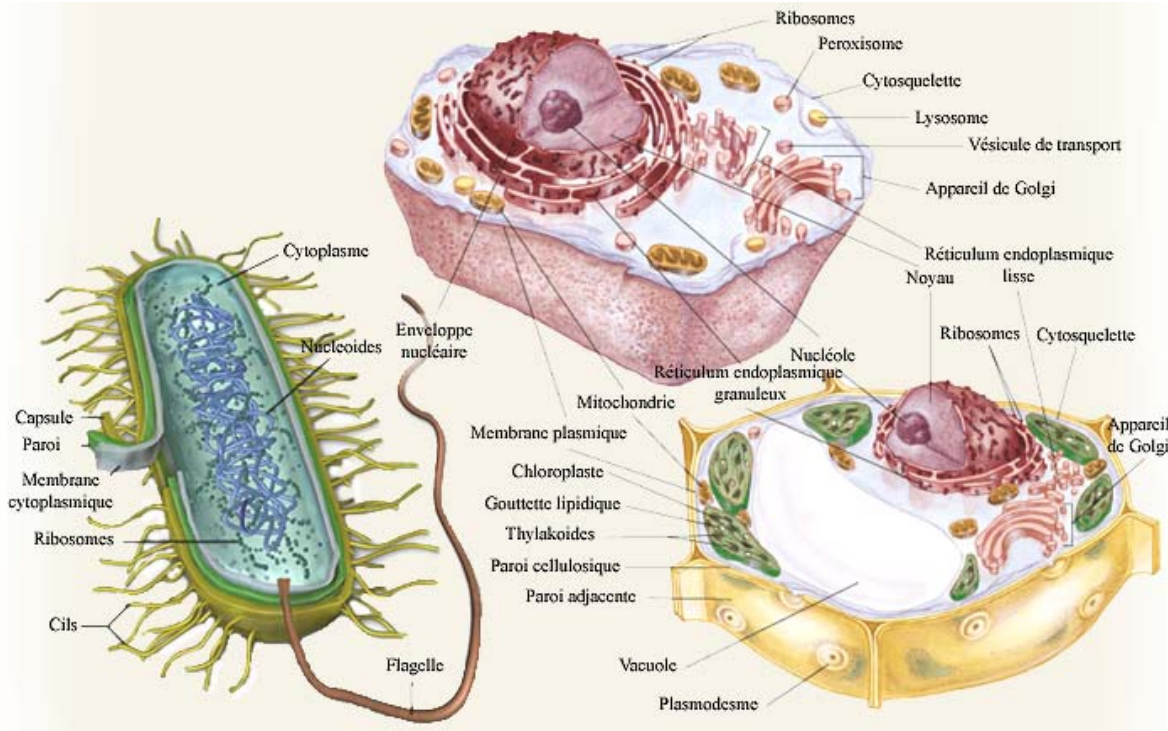
# La Génomique et l'Après-Génome: Promesses et Défis

Jean-Philippe Vert

**Inserm**  
●

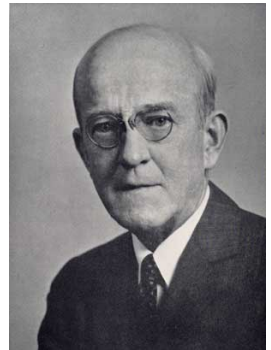
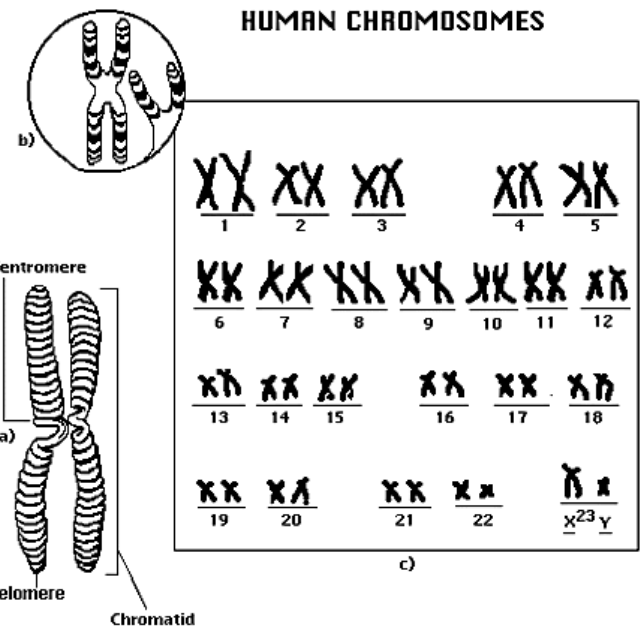
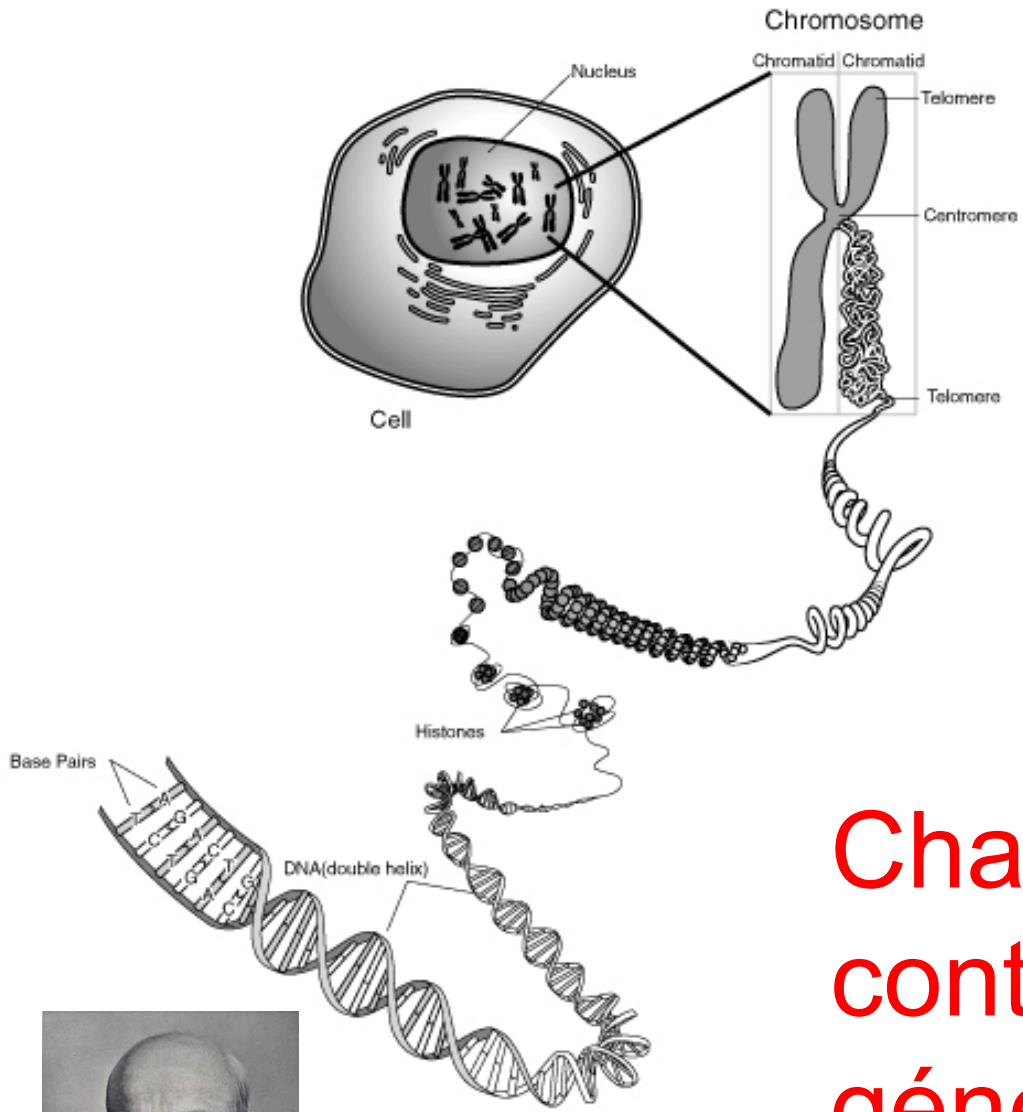






Tous les êtres vivants sont faits de cellules

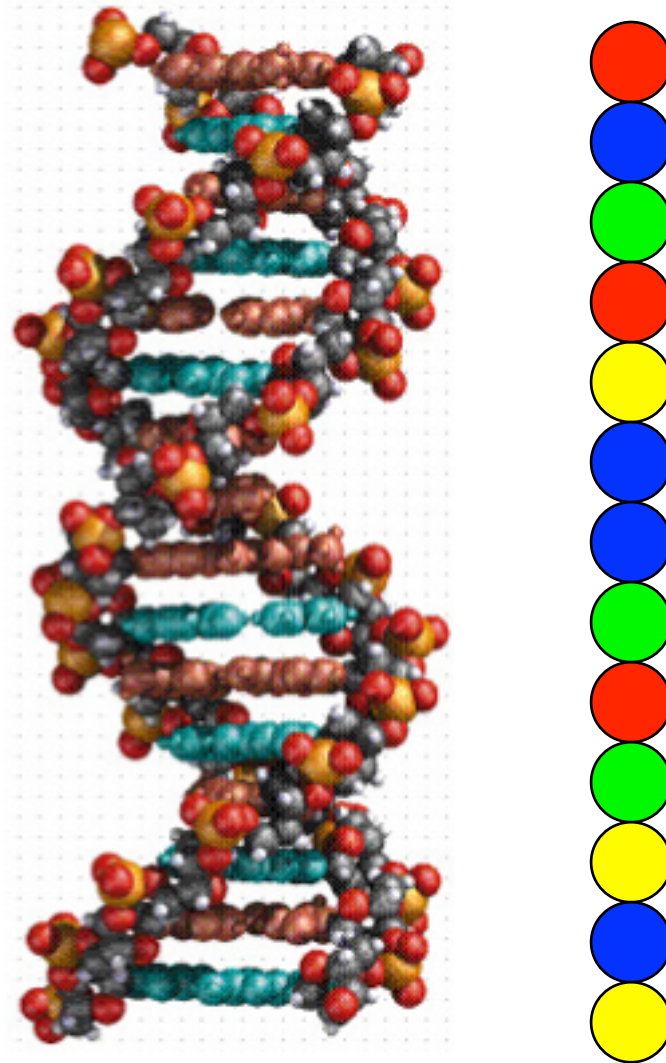
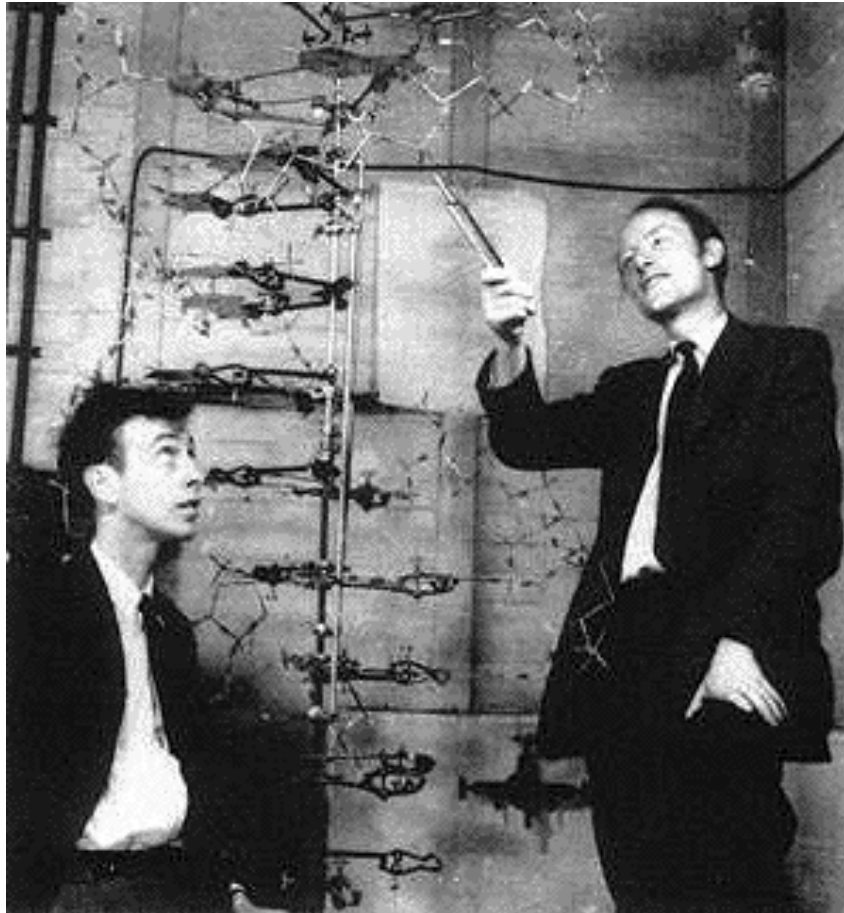
Composite cell



*(Avery, 1944)*







Chaque cellule contient le patrimoine génétique de l'individu sous forme d'ADN

# Structure de l'ADN

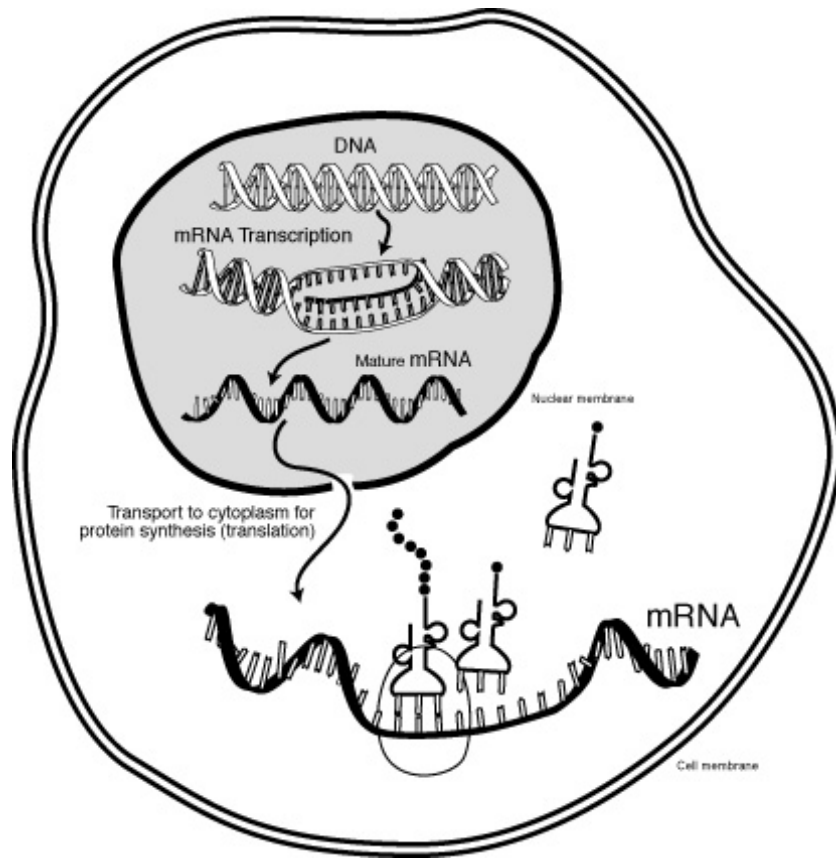


J.D. Watson & F.H.C. Crick (1953) Molecular structure of Nucleic Acids. *Nature*, **171**:737-738.

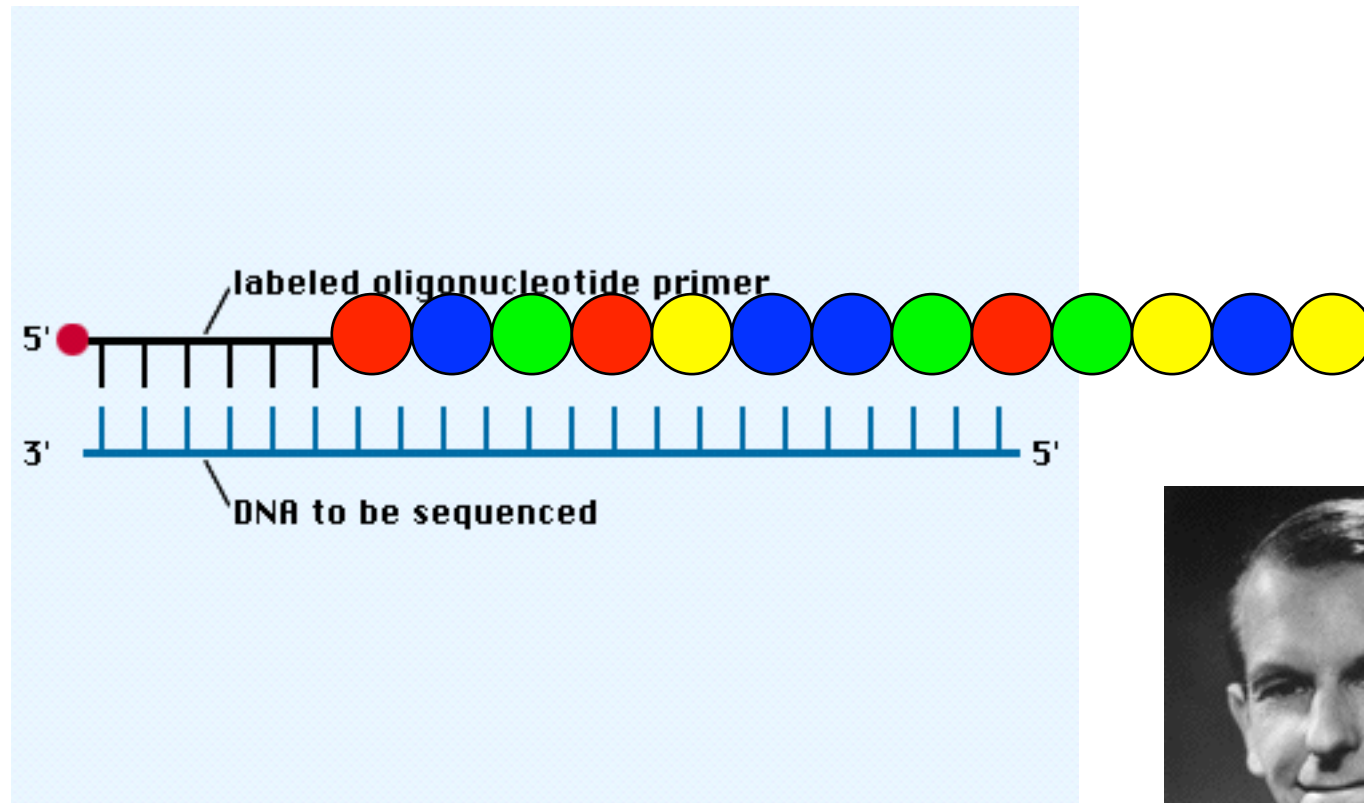


Organisme	Chromosomes	Taille du génome	
 Bactéries	1	400,000 à 10,000,000	$< 1$
 <i>La recherche du temps perdu...</i>	7	9,609,000	1
 Levure	12	14,000,000	1,5
 Mouche	4	300,000,000	30
 Homme	46	6,000,000,000	600
 Tulipe	60	30,000,000,000	3,000

# L'ADN est le «programme» de la cellule



# Séquençage de génome = lire le programme

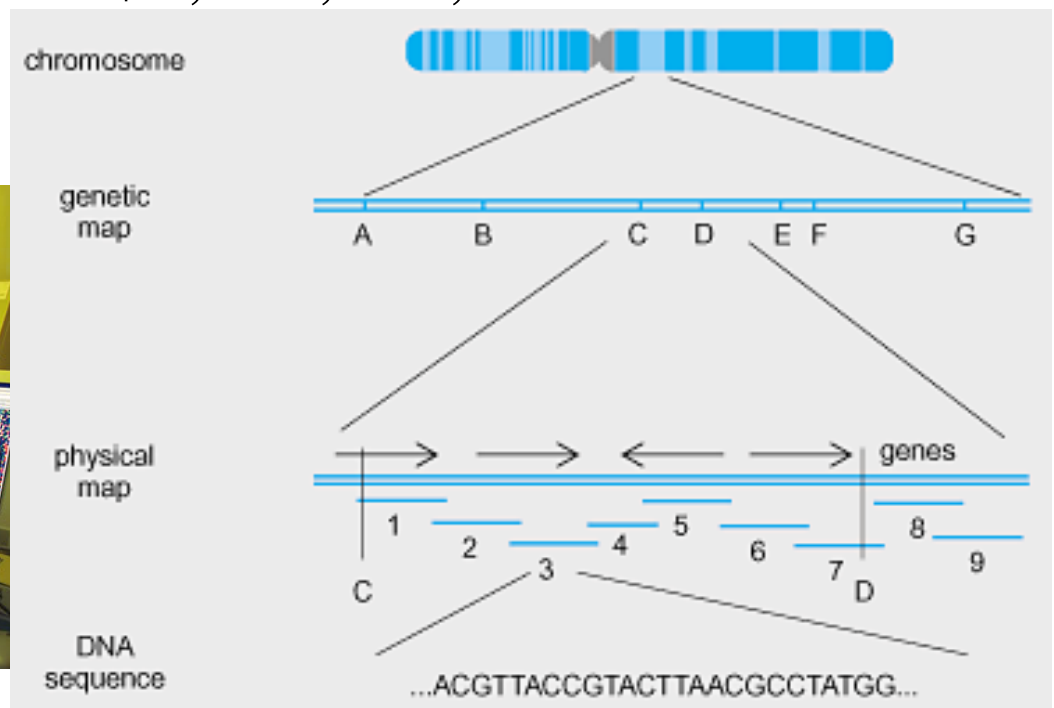


*Frederick Sanger, Nobel 1958/1980*



# Projet Génome Humain (1990-2003)

- But : séquencer les 3,000,000,000 de bases du génome humain
- Consortium de 20 laboratoires, 6 pays
- Coût : environ \$3,000,000,000



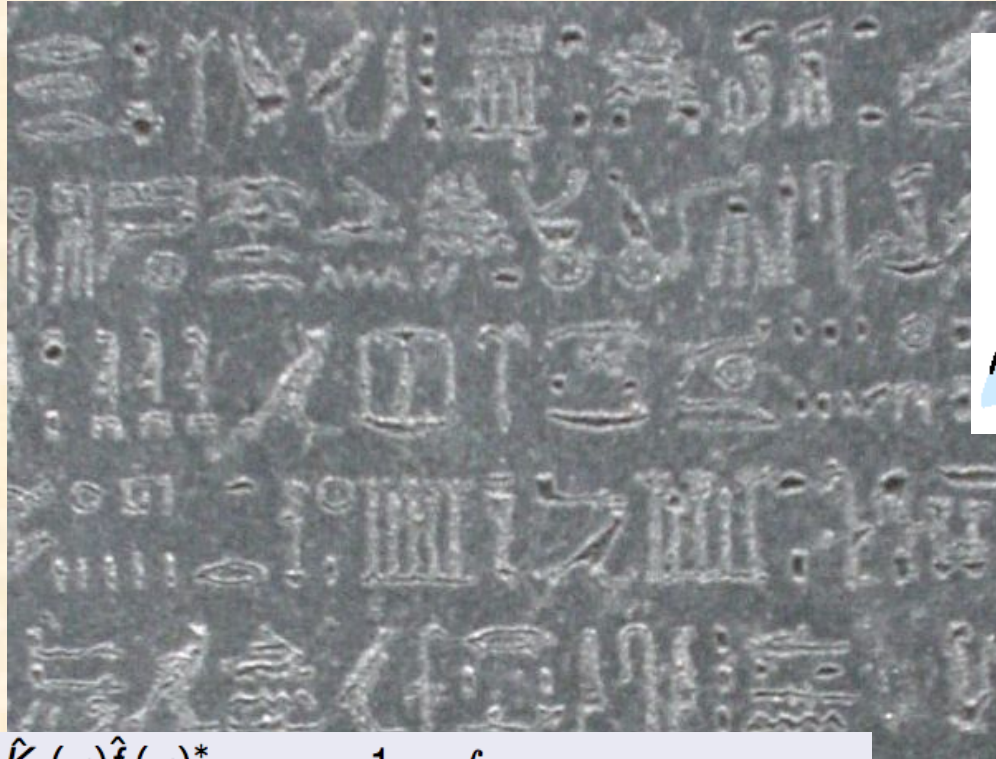
# Février 2001 : Ebauches du génome humain



Avril 2003: Version finale!

**50** Years of DNA: *From Double Helix to Health*  
A Celebration of the Genome

# Le « décryptage » du génome

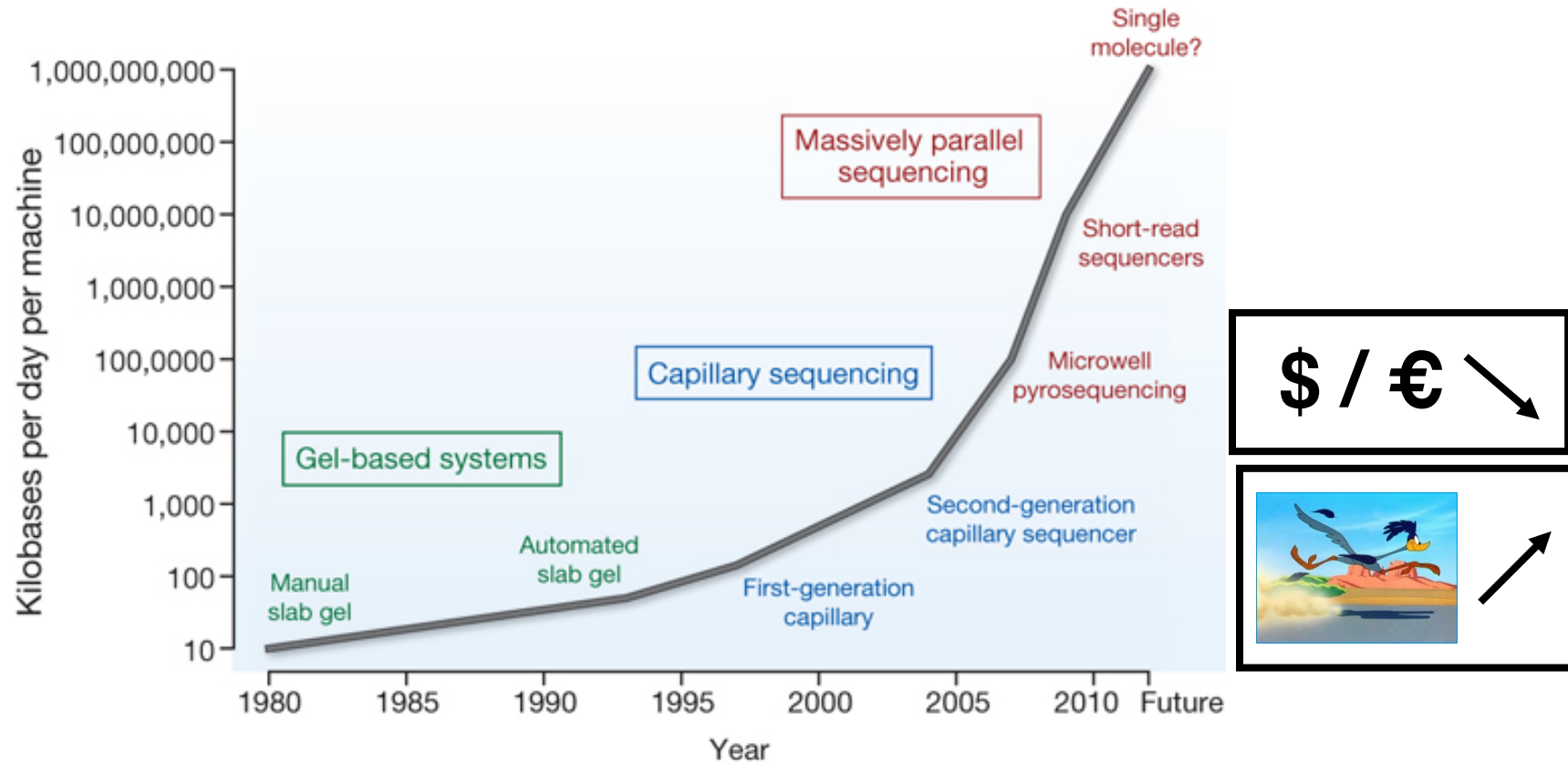


$$\langle f, K_x \rangle_{\mathcal{H}} = \frac{1}{(2\pi)^d} \int_{\mathbb{R}^d} \frac{\hat{K}_x(\omega) \hat{f}(\omega)^*}{\hat{k}(\omega)} d\omega = \frac{1}{(2\pi)^d} \int_{\mathbb{R}^d} \hat{f}(\omega)^* e^{-i\omega \cdot x} = f(x)$$

$$K(\mathbf{x}, \mathbf{y}) = \sum_{k=1}^{\infty} \lambda_k \psi_k(\mathbf{x}) \psi_k(\mathbf{y}) = \langle \Phi(\mathbf{x}), \Phi(\mathbf{y}) \rangle_{\ell^2}$$

- Peu de gènes (20~25,000)
- On ignore le rôle de 97% de l'ADN

# Les progrès continuent...



# Variations génomiques

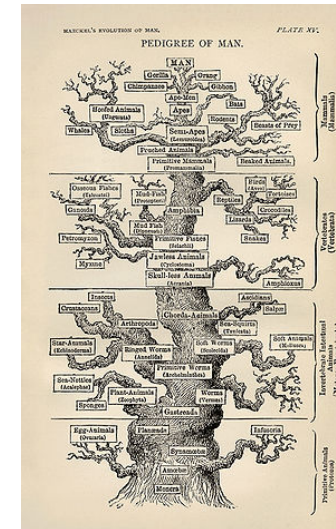
- Entre **espèces**
  - *> 1 lettre / ligne*



- Entre **individus**
  - *1 lettre / page*

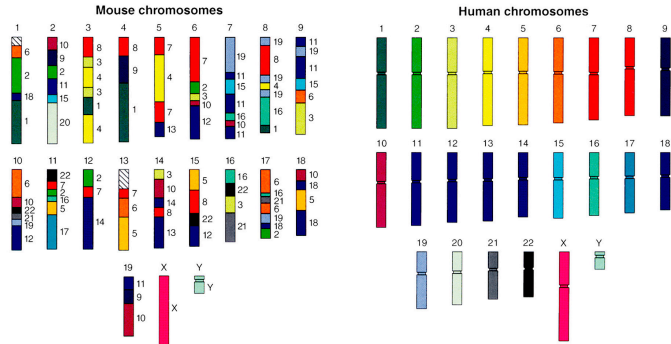


- Entres **cellules**
  - *< 1 lettre / livre*



# Variations entre espèces

## Mouse and Human Genetic Similarities



Courtesy Lisa Stubbs  
Oak Ridge National Laboratory



YGA 98-075R2

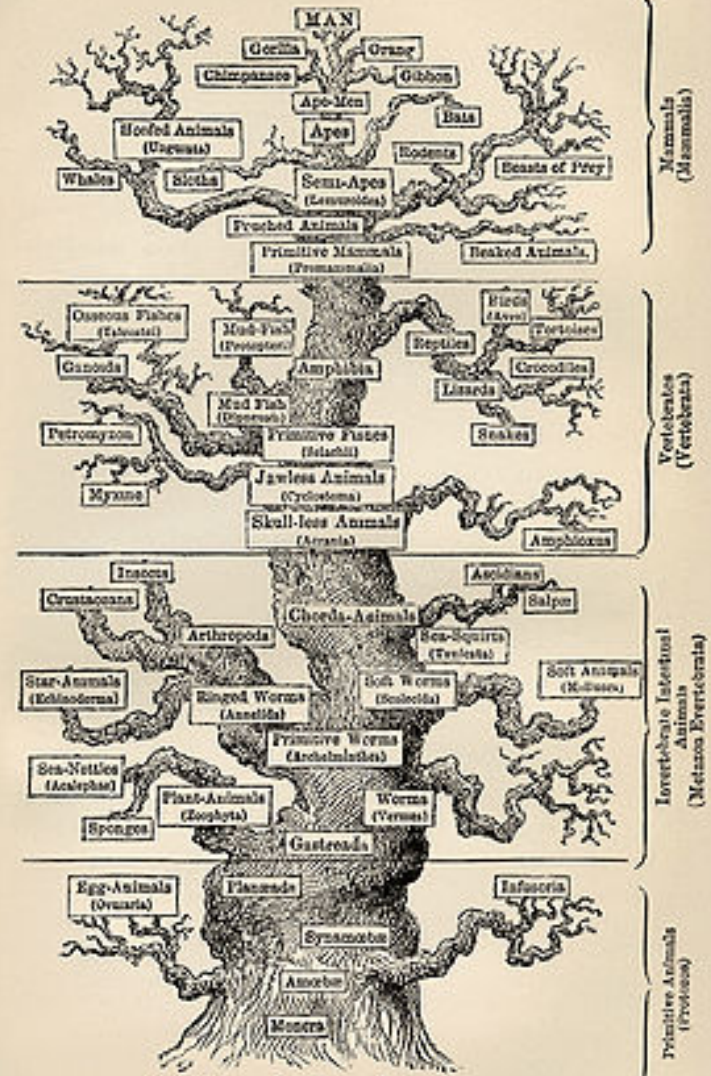
Souris TAAGCAGTGGCAGGGC--CAG-GCTGAGCTTATCAGTCTCCAGCCAGCCCTGCCCACACATAT  
 Lapin GGAGCAGTGACTAGGC--CCA-GCTGGGCTTATCAGCCTCACAGCCAGCCCTGCTGGAGCATAA  
 Ho AA  
 Po AA



HAECKEL'S EVOLUTION OF MAN.

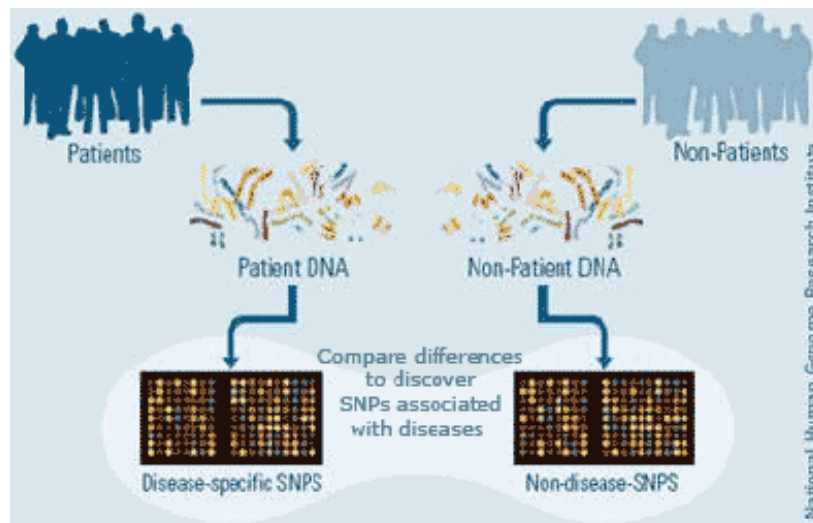
PLATE XVI.

## PEDIGREE OF MAN.

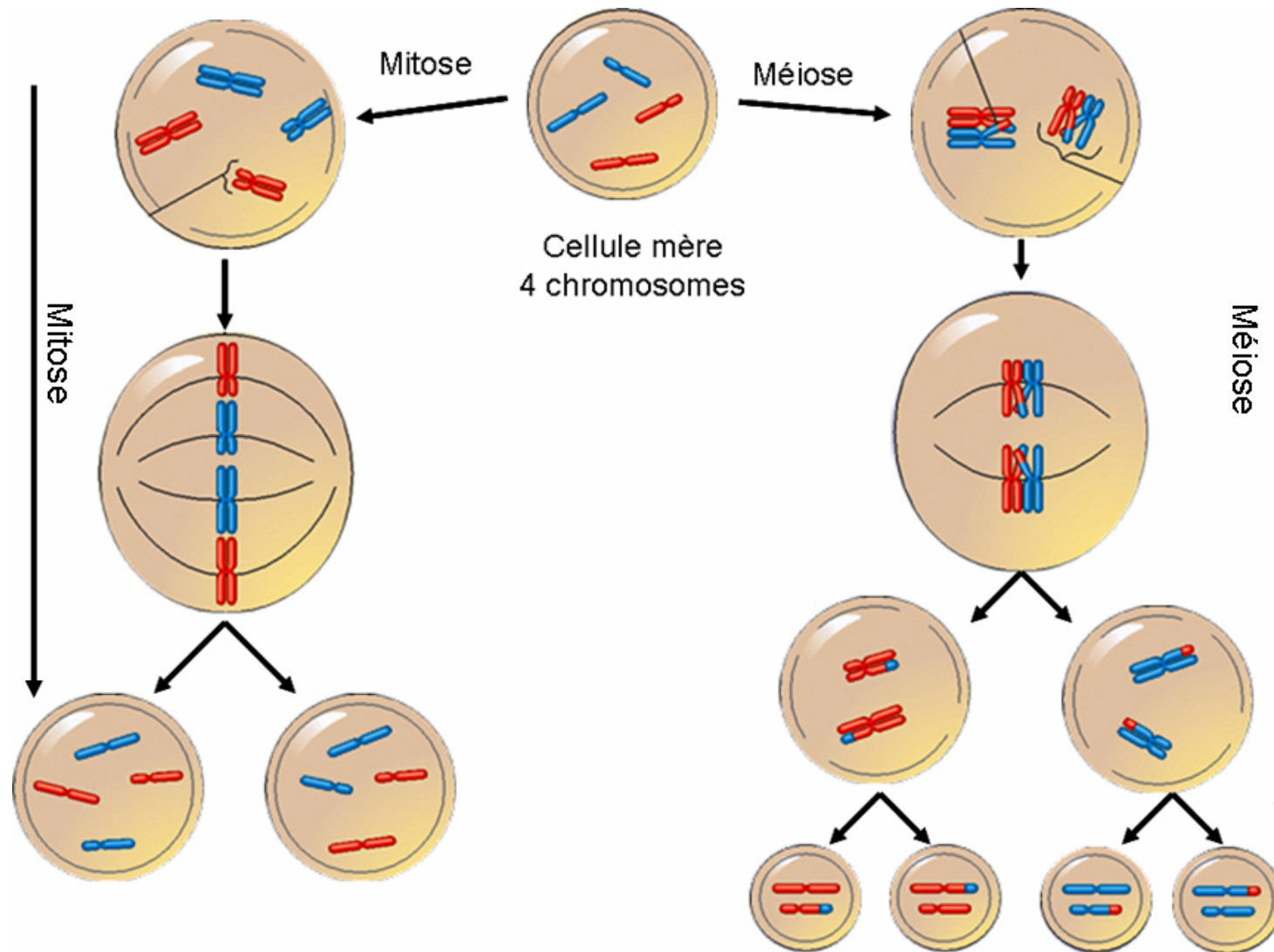


# Variations entre individus

- Prédisposition génétique à des maladies
- Médecine personnalisée (« pharmacogénomique »)
- Identification (sécurité, paternité, criminalité...)

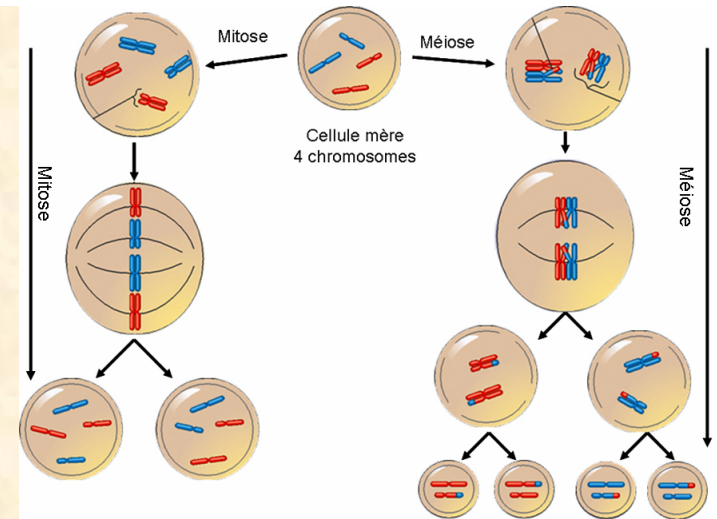


# La division cellulaire





# Variations entre cellules



- Une dizaine d'erreurs de copies par division cellulaire en temps normal
- Le taux d'erreur augmente sous l'effet d'agents mutagènes



tabac

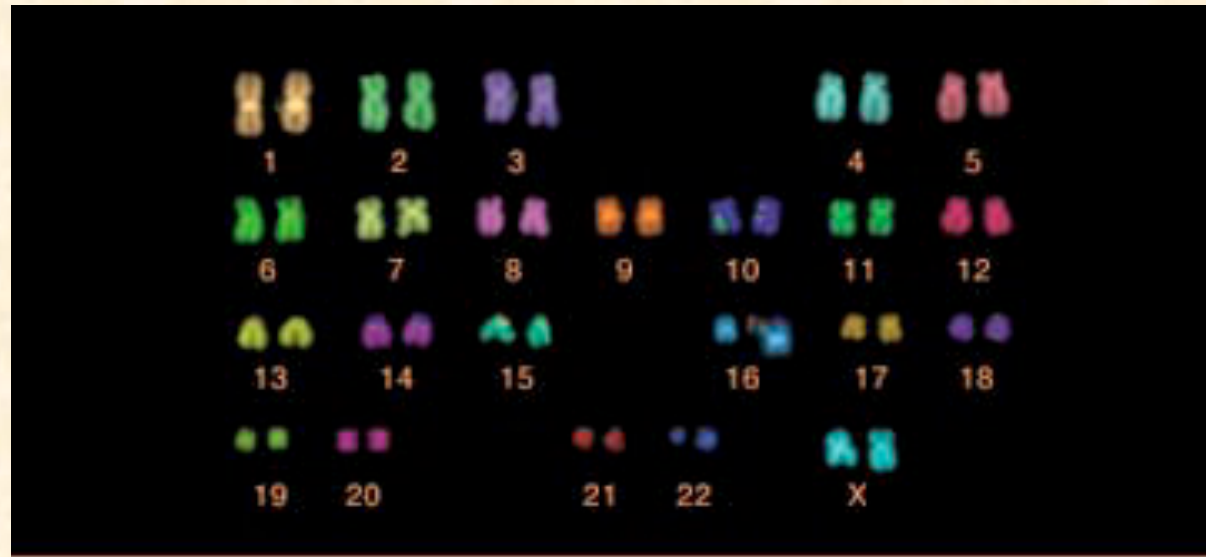


aflatoxine

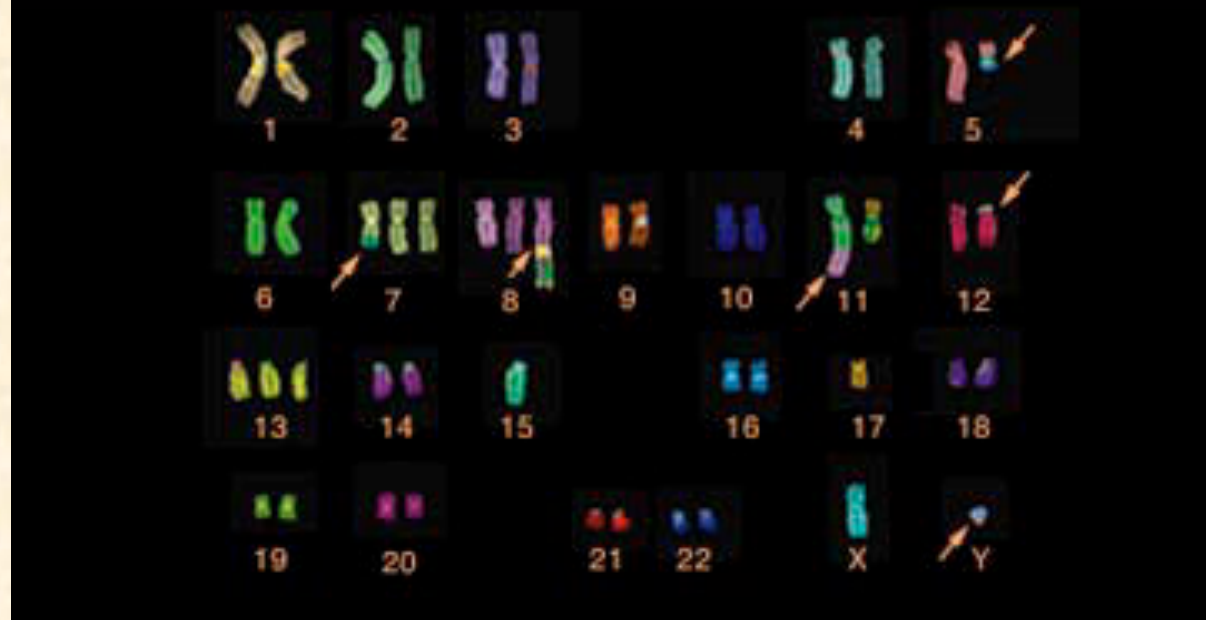


Radiations ionisantes

Normal

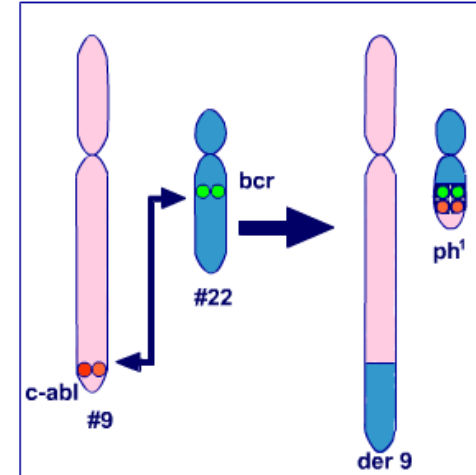


Cancer



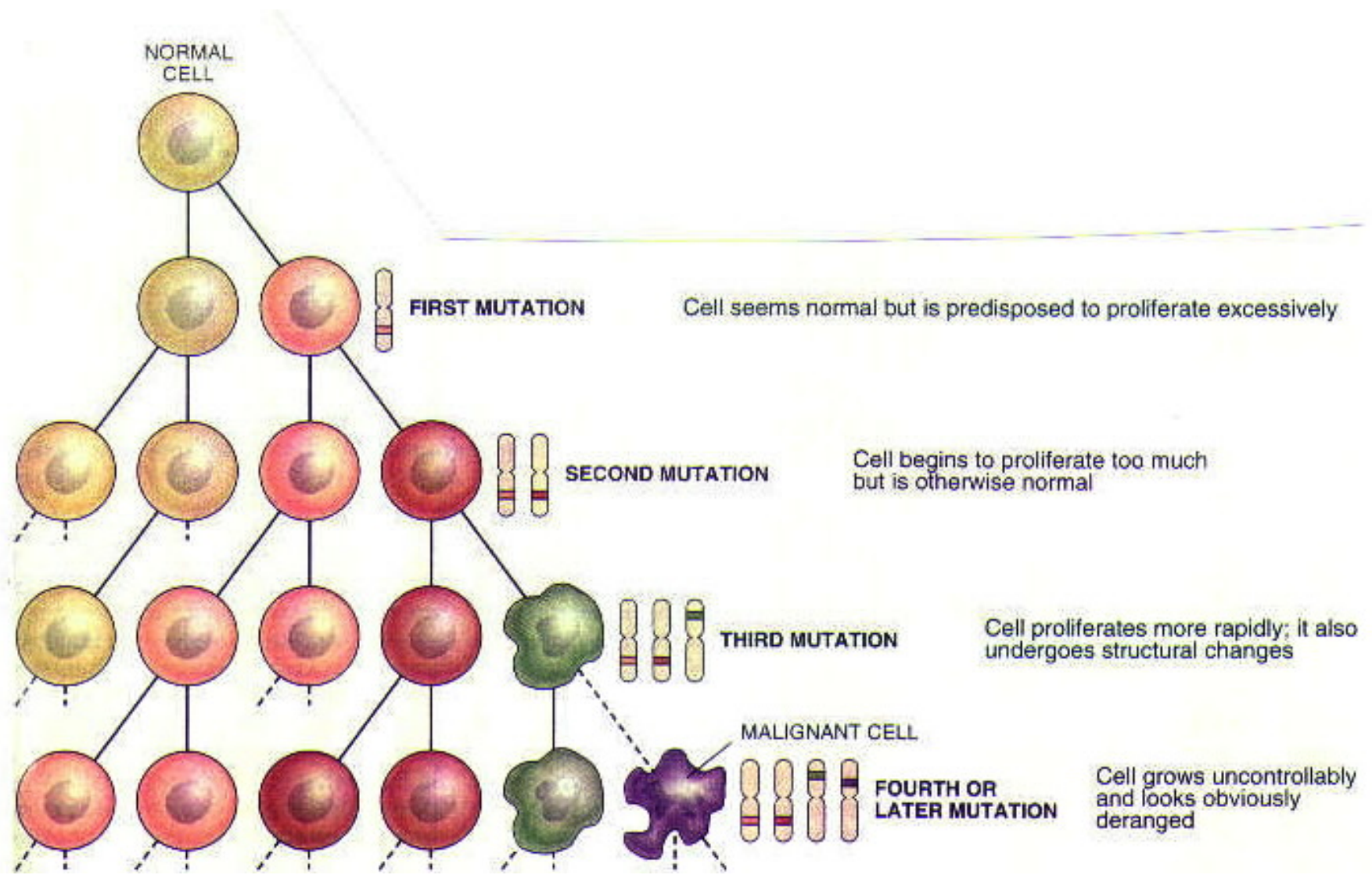
# Le cancer est une maladie « génétique »?

- ~1900: von Hansemann, Boveri voient des anomalies chromosomiques au microscope
- 1973: translocation de Philadelphie dans 95% des CML

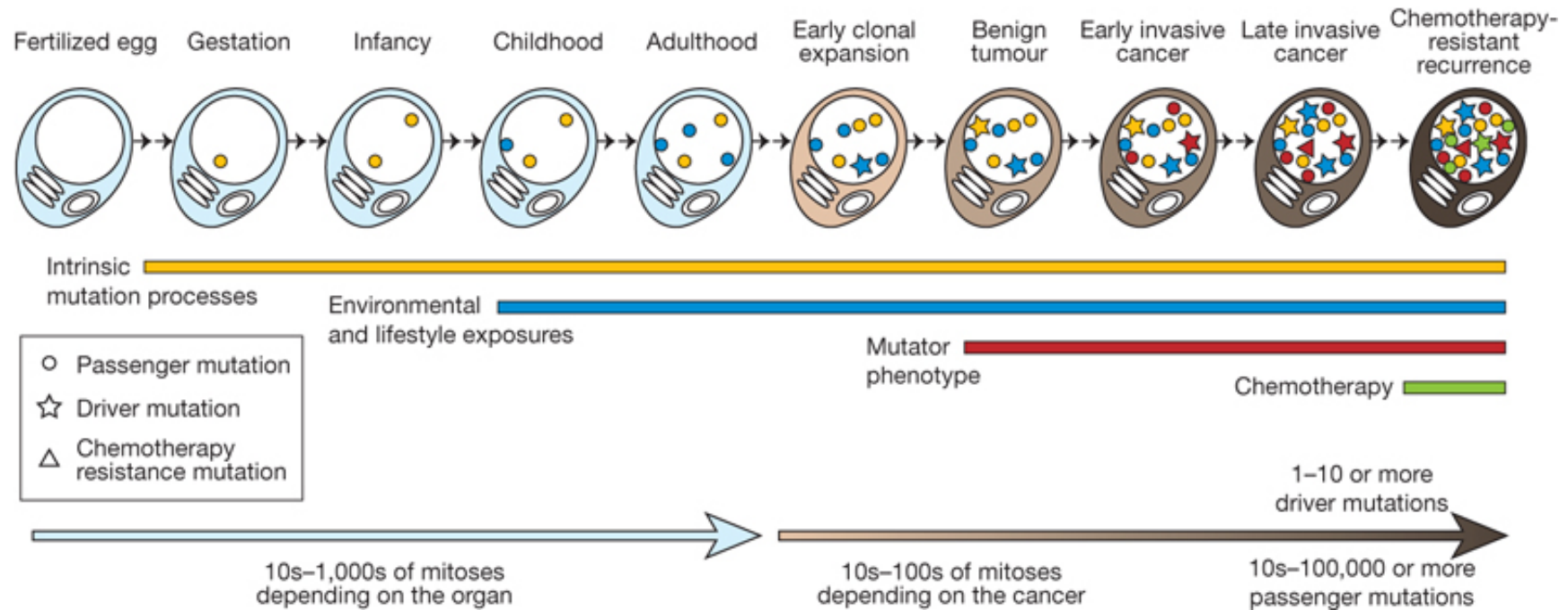


- 1982: mutation HRAS
- Depuis 1982: des centaines de « gènes du cancer »

# Mutations et compétition entre cellules

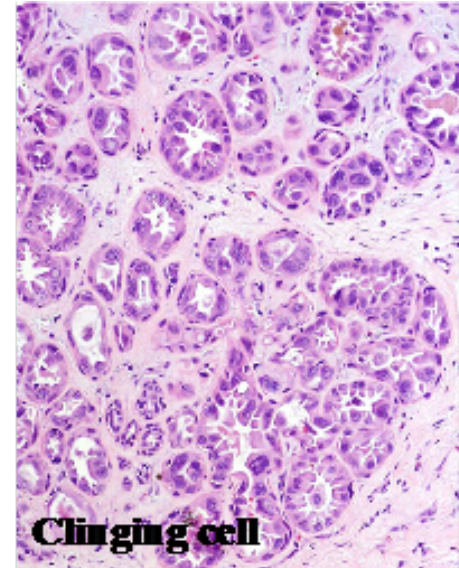
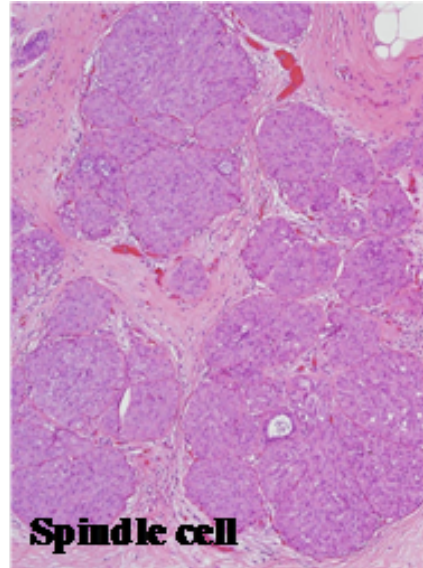
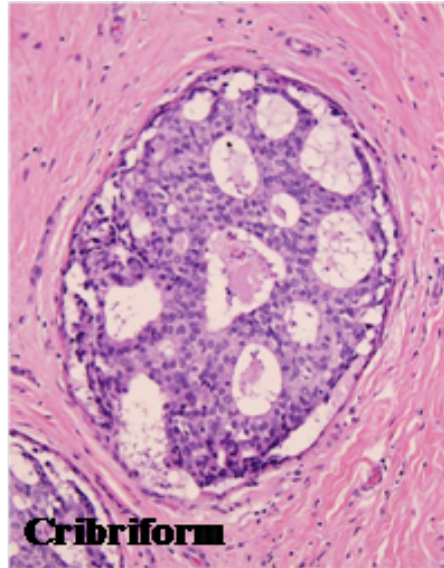
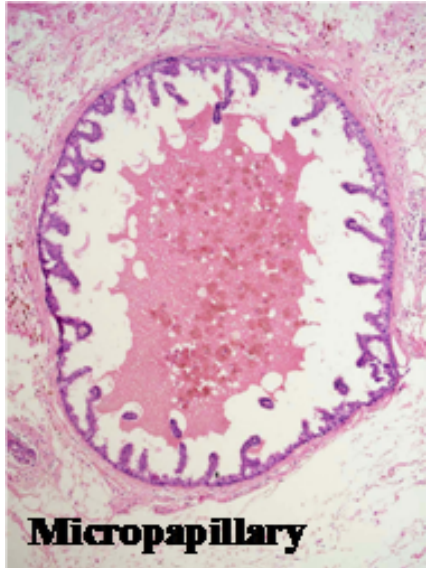


# Les mutations s'accumulent au cours de la vie



MR Stratton *et al. Nature* **458**, 719-724 (2009) doi:10.1038/nature07943

# Hétérogénéité des cancers



- Différences macroscopiques
- Différences dans la réponse aux traitements
- Différences de risques
- **Différences moléculaires**

# Le « génome du cancer »



International Cancer Genome Consortium

http://www.icgc.org/

International Cancer Genome Consortium

Overview | Cancer Genome Projects | Committees | Policies and Guidelines | Media | Contacts

## International Cancer Genome Consortium

Bladder Cancer United States

Blood Cancer United States

Bone Cancer United Kingdom

Brain Cancer United States

Breast Cancer European Union / United Kingdom

Breast Cancer France

Breast Cancer United Kingdom

Breast Cancer United States

Cervical Cancer United States

Chronic Lymphocytic Leukemia Spain

Chronic Myeloid Disorders United Kingdom

Colon Cancer United States

Endometrial Cancer United States

Gastric Cancer

[Show]

will facilitate communication among the members and provide a forum for coordination with the objective of maximizing efficiency among the scientists working to understand, treat, and prevent these diseases.

**Announcements:**

25/Nov/2010 - The ICGC Data Coordination Center (DCC) is pleased to announce the release of version 3 of the ICGC data portal. This release includes data from 22 different cancer projects and recent updates from the ICGC projects in Canada, Australia and the UK. In addition to open access data, ICGC controlled data can now be retrieved securely by users who have been authorized by the Data Access Compliance Office (DACO).

International network of cancer genome projects. Nature 464, 993-998 (15 April 2010)

[HTML](#)

Liver Cancer Japan

Liver Cancer United States

Lung Cancer United States

Malignant Lymphoma Germany

Oral Cancer India

Ovarian Cancer Australia

Ovarian Cancer United States

Pancreatic Cancer Australia

Pancreatic Cancer Canada

Pediatric Brain Tumors Germany

Prostate Cancer Germany

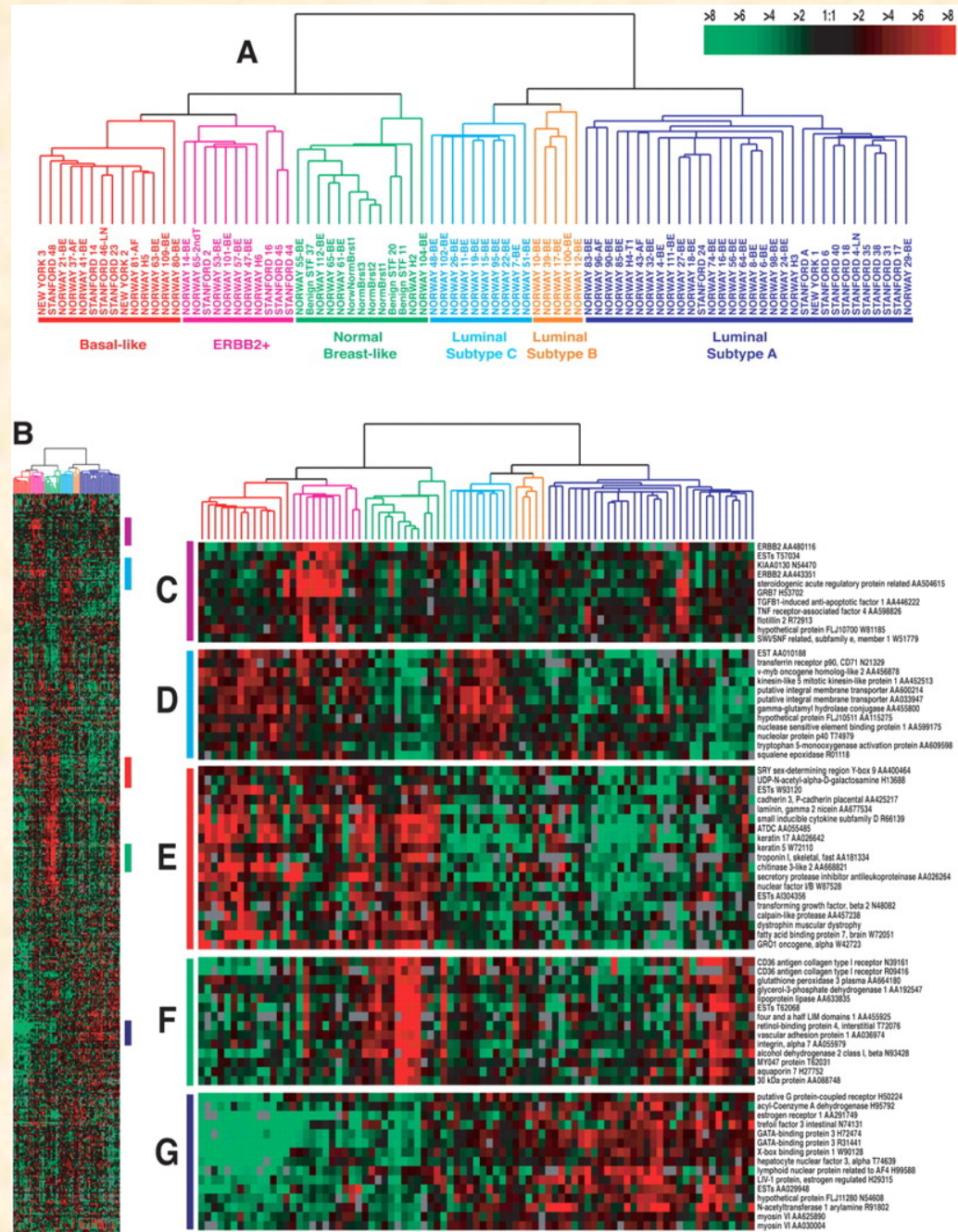
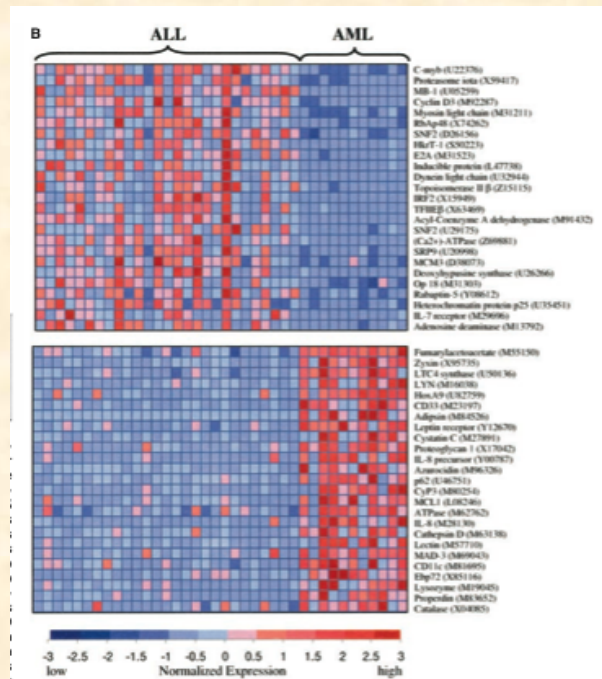
Prostate Cancer United States

Prostate Cancer Canada

Rare Pancreatic Tumors

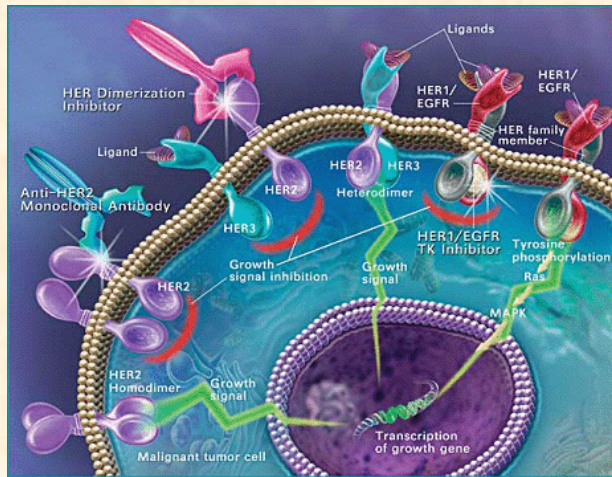
Ouvrir « <http://www.icgc.org/icgc/cgp/68/427/1221> »

# Nouvelles classifications des tumeurs





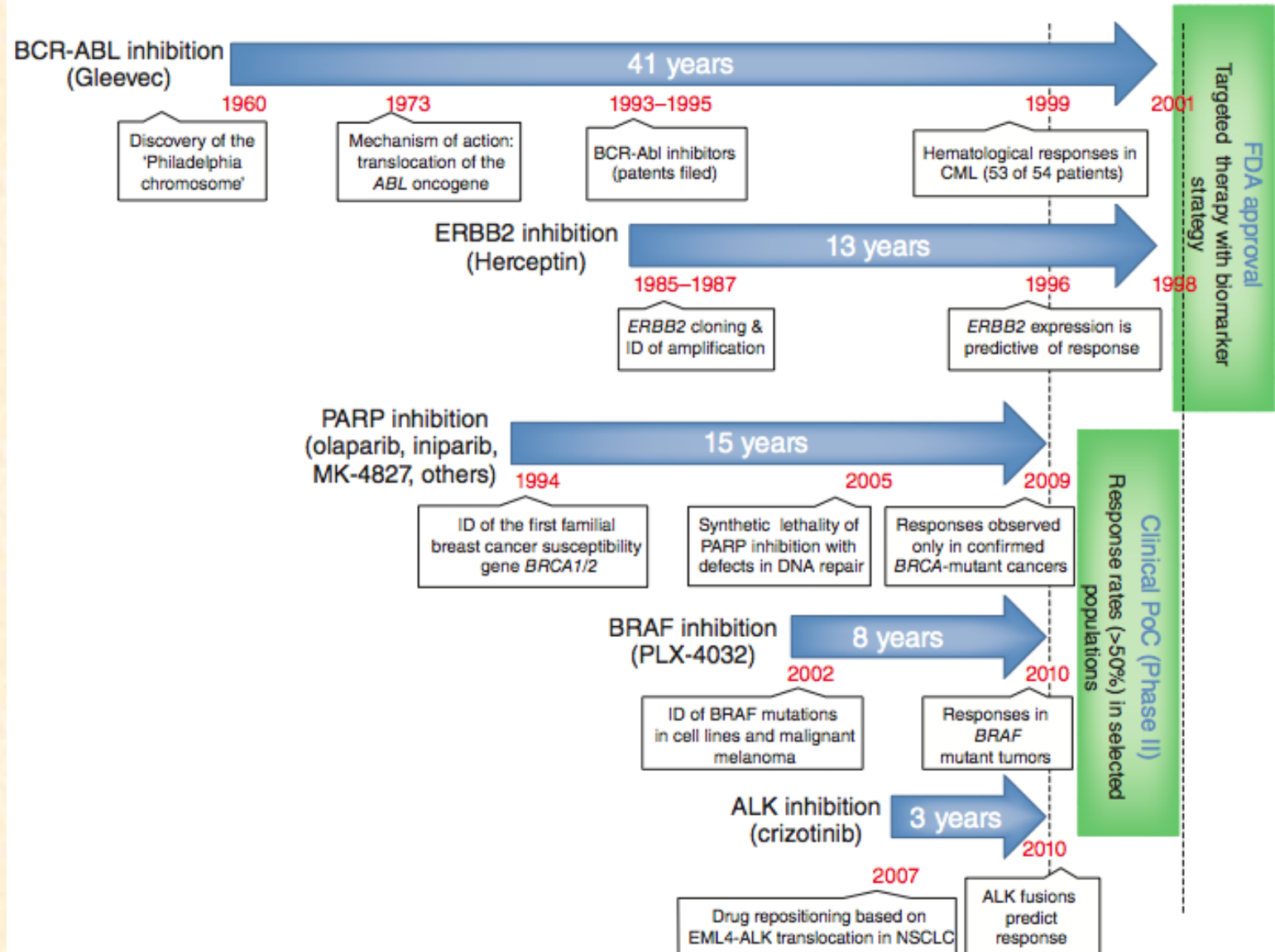
# Nouvelles thérapies ciblées



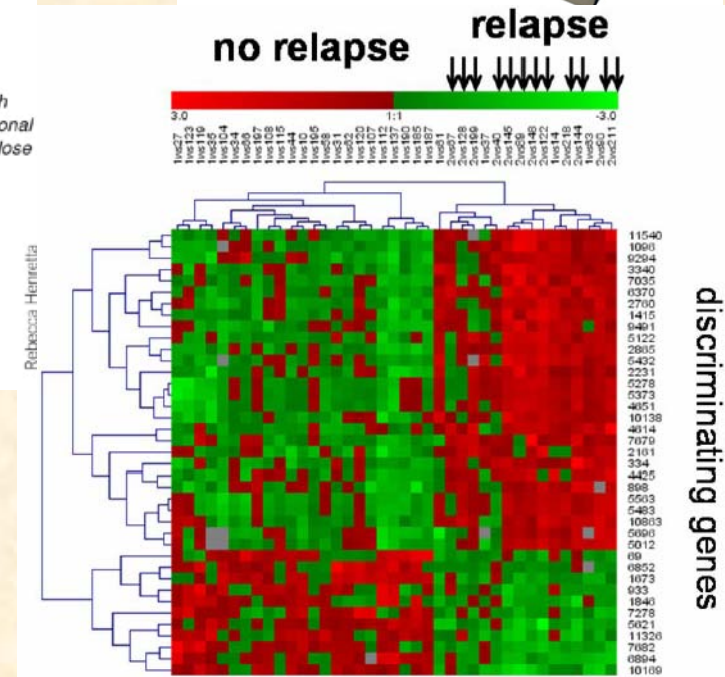
**TIME**  
THERE IS NEW AMMUNITION  
IN THE WAR AGAINST  
**CANCER.**  
THESE ARE THE BULLETS.  
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

A pile of yellow, oblong capsules, likely representing the targeted therapy mentioned in the advertisement.

# Découvertes de nouveaux traitements ciblés



# Nouveaux tests pour optimiser le choix du traitement

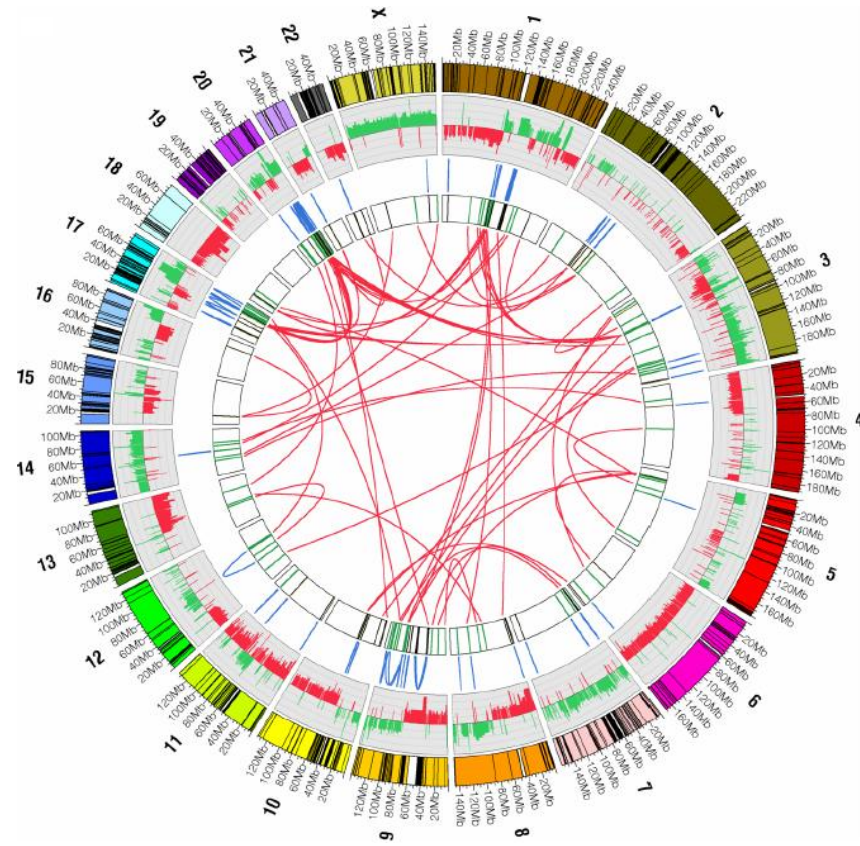
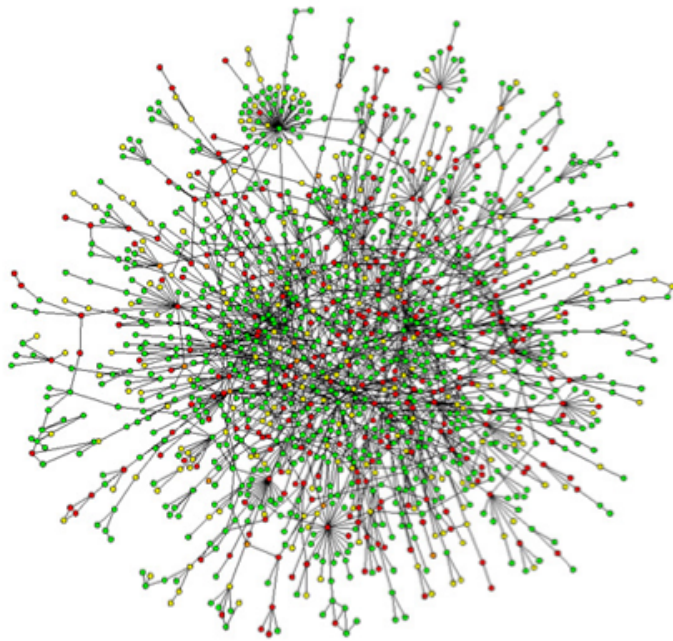


# « Médecine personnalisée »



# De nouveaux défis...

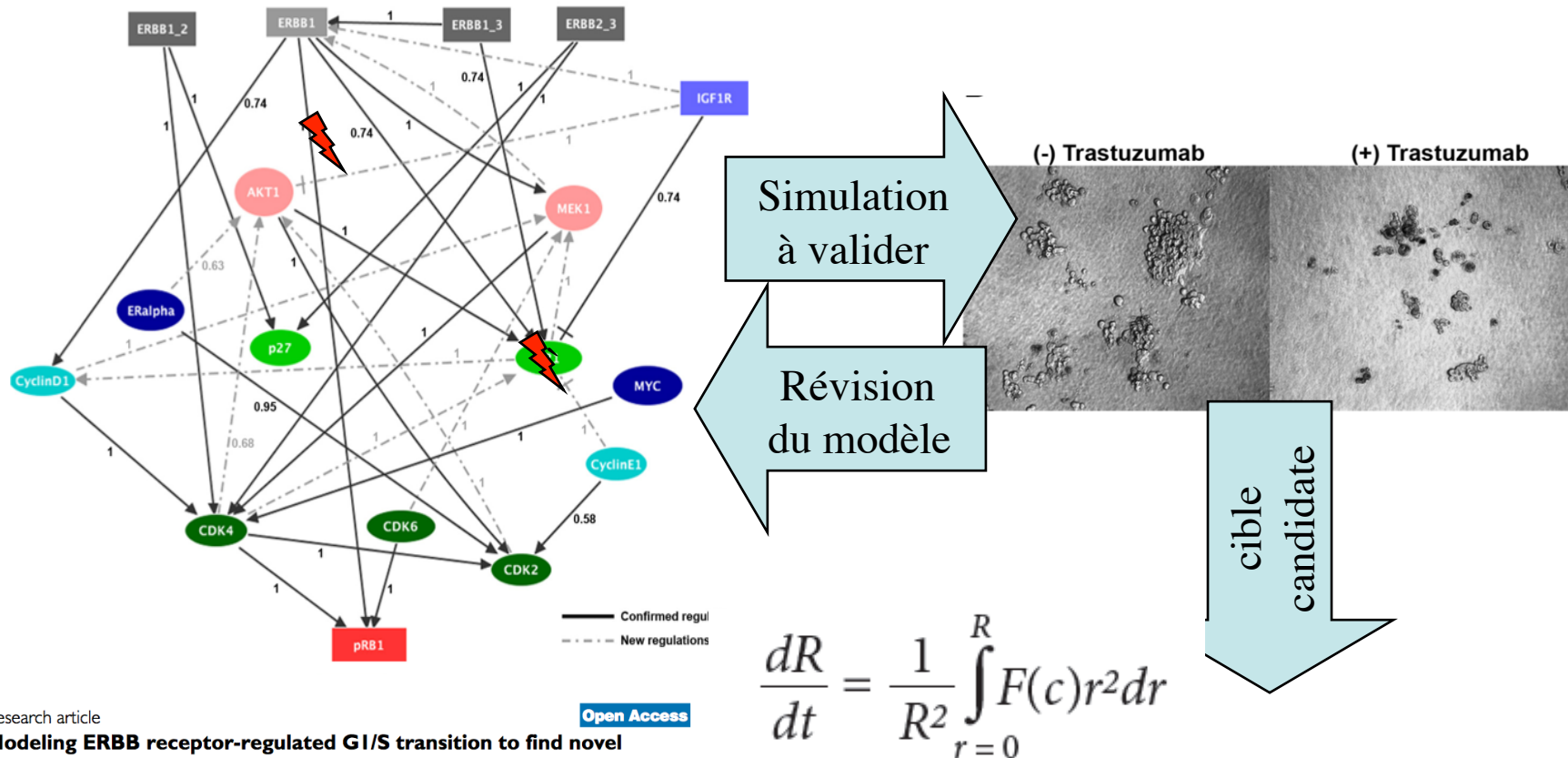
## Appréhender la complexité du vivant



# De nouveaux défis...

## Modéliser et prédire

- Modéliser la réponse de la cellule au trastuzumab
- Proposer des cibles thérapeutiques pour les tumeurs résistantes



Research article

Open Access

**Modeling ERBB receptor-regulated G1/S transition to find novel targets for de novo trastuzumab resistance**

Özgür Sahin\*<sup>1</sup>, Holger Fröhlich<sup>1</sup>, Christian Löbke<sup>1,2</sup>, Ulrike Korf<sup>1</sup>, Sara Burmester<sup>1</sup>, Meher Majety<sup>1,3</sup>, Jens Mattem<sup>1</sup>, Ingo Schupp<sup>1</sup>, Claudine Chaouiya<sup>4</sup>, Denis Thieffry<sup>4</sup>, Annemarie Poustka<sup>1</sup>, Stefan Wiemann<sup>1</sup>, Tim Beissbarth<sup>1</sup> and Dorit Arlt\*<sup>1</sup>

# Des enjeux économiques de taille



- Marchés en très forte croissance!
- De nombreuses applications
  - **Santé**: nouveaux traitements, médecine personnalisée...
  - **Agro-alimentaire**: OGM, optimisation des processus de production...
  - **Energie/environnement**: biofuels, détection de polluant, remédiation environnementale, séquestration de carbone...

# Des questions éthiques et sociétales à ne pas oublier!

- Bioéthique
- Brevetabilité du vivant
- Clonage
- Eugénisme
- Ingénierie du vivant, OGM...

**MERCI !**

