Le chromosome X dans tous ses états

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Image from Carolyn Brown, University of British Columbia

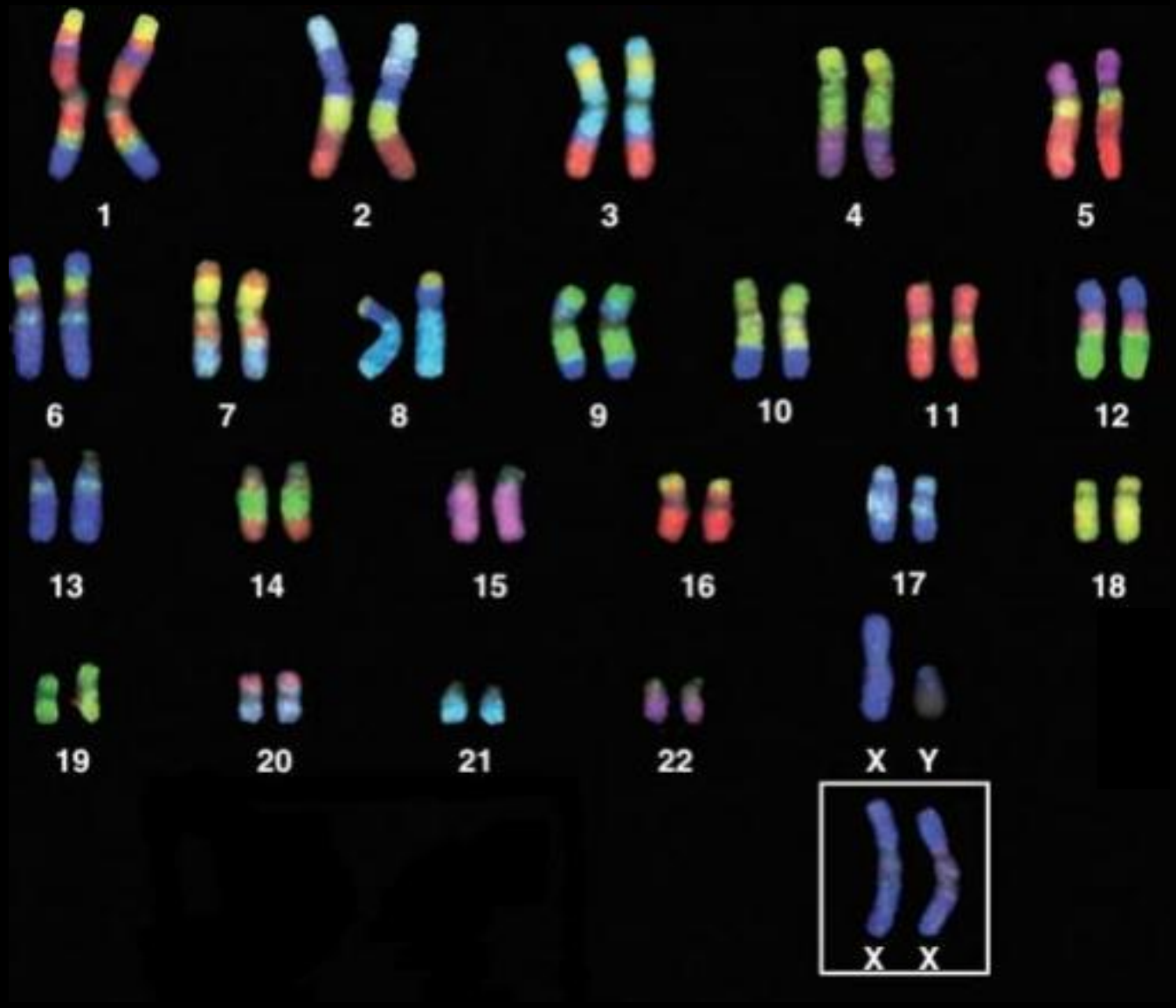
Université Paris Cité

UMR 7216 Epigenetics & Cell Fate

labex who am I?

cnrs dépasser les frontières

Les chromosomes sexuels



Les chromosomes sexuels

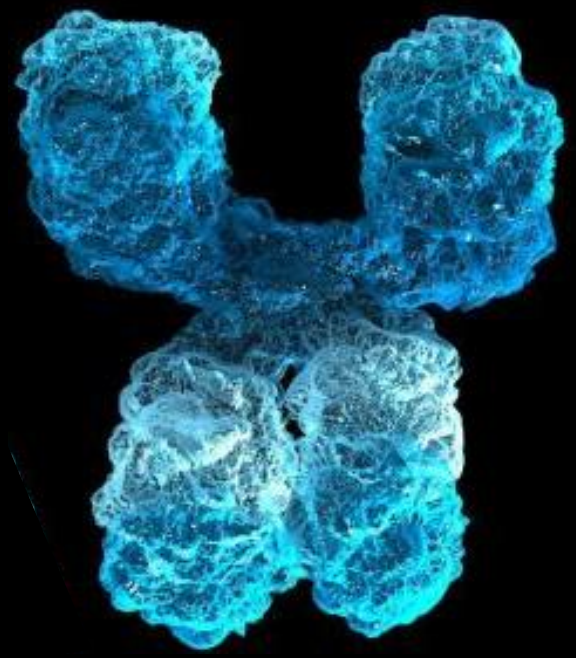
Le Monde

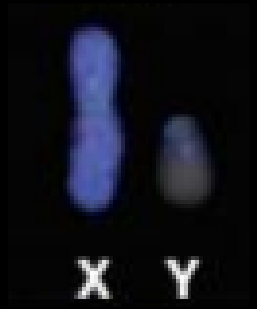
SCIENCES • BIOLOGIE

Le chromosome Y enfin déchiffré et toujours si intrigant

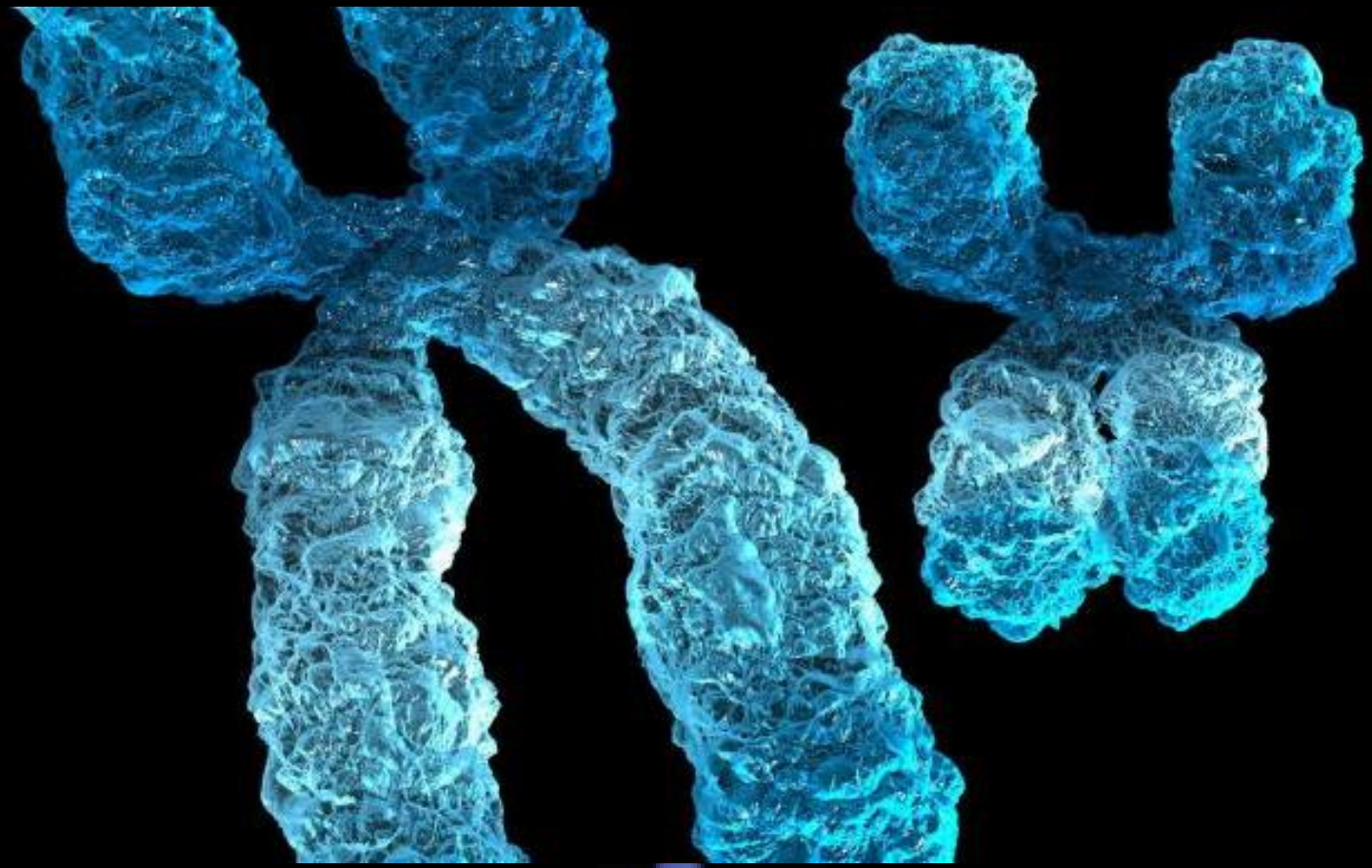
Par Florence Rosier

Publié le 28 août 2023 à 18h15, modifié le 29 août 2023 à 05h48





Les chromosomes sexuels

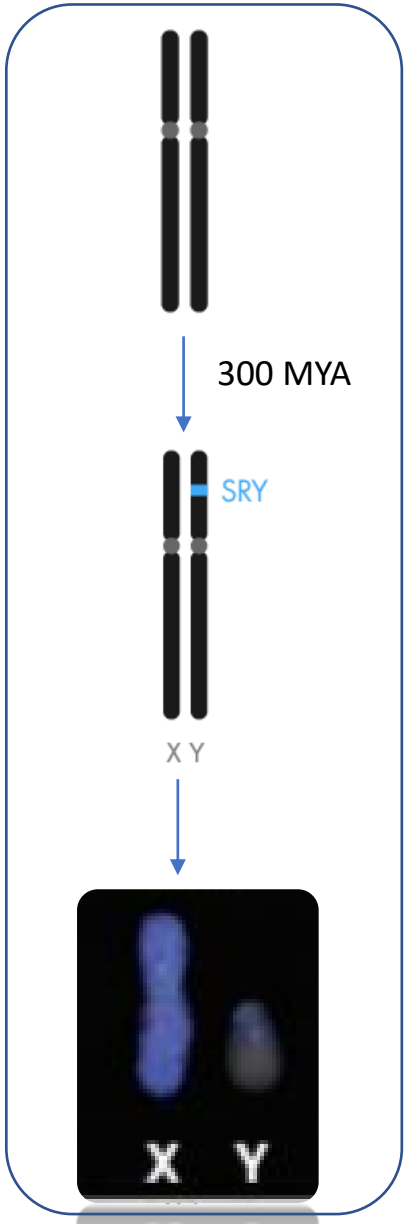


Evolution des chromosomes sexuels

X

153 million base pairs

~ 867 gènes codants



Y

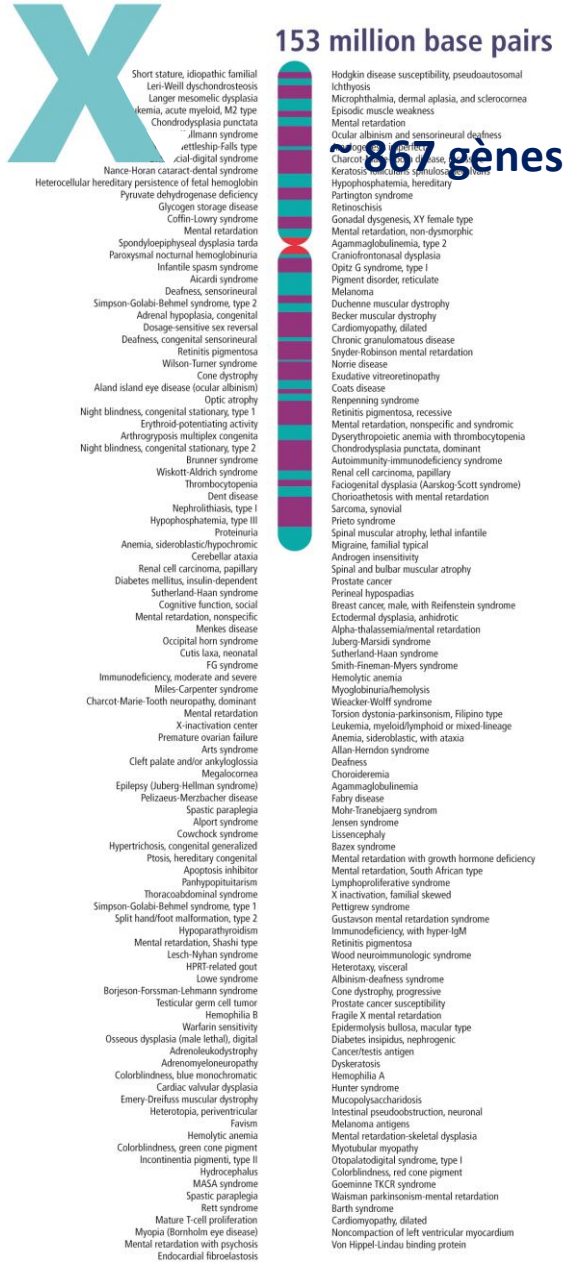
50 million base pairs

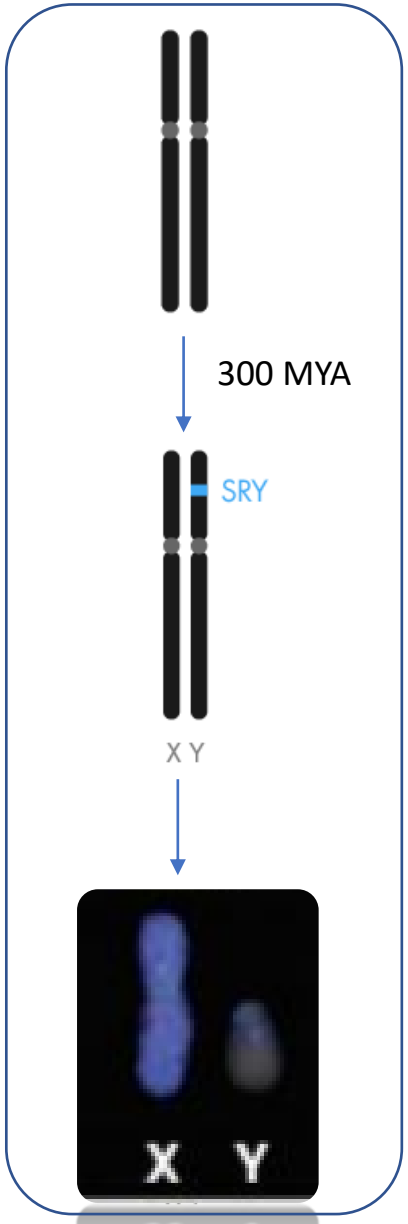
~ 106 gènes codants

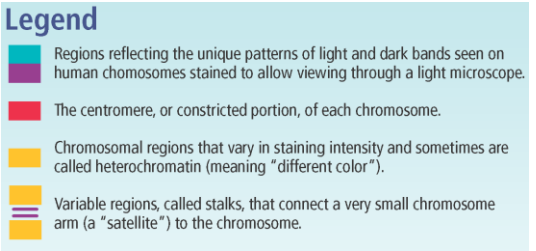
Legend

- Regions reflecting the unique patterns of light and dark bands seen on human chomosomes stained to allow viewing through a light microscope.
- The centromere, or constricted portion, of each chromosome.
- Chromosomal regions that vary in staining intensity and sometimes are called heterochromatin (meaning "different color").
- Variable regions, called stalks, that connect a very small chromosome arm (a "satellite") to the chromosome.

Les chromosomes sexuels sont hétéromophes







Déséquilibre de dose

L'inactivation du chromosome X

Un des deux chromosomes X des femelles est (majoritairement) inactif

of the year gave the same symptoms; (e) on *L. esculentum* × *L. pimpinellifolium* the symptoms were identical both in the inoculation from the vine and from diseased *I. holstani*.

From *I. holstani* the isolate has so far been transmitted to tobacco (varieties White Burley and Samsun) and to *Petunia*, by sap and by *Myzodes persicae*; to *Nicotiana glutinosa*, *Datura stramonium*, *Vigna sinensis* and *I. holstani* by sap. The percentage infection in the transmission from these species to the same species or to the other species that gave positive results in the inoculation from *I. holstani*, is higher than in the transmission from *I. holstani*.

We are trying to transmit the isolates from the herbaceous plants to grape vine. For this work we use symptomless grape vines, selected during three years and belonging to varieties that appeared to be very receptive to the 'infectious degeneration' in previous experiments on transmission by grafting from vine to vine.

Other work in progress is the identification of the isolates.

No rod-shaped virus particles were seen in a series of observations, using the electron microscope, with exudates obtained by Johnson's method and with drops prepared with Brandes's dipping method both with diseased grape vines (leaves, shoots and roots) and with infected herbaceous plants.

E. Baldacci
A. Amici
P. Bonola
E. Betto
G. Fogliani
E. Refatti

Istituto di Patologia vegetale,
Università di Milano.

[1] Amici, A., Baldacci, E., and Refatti, E., *Ann. Facoltà Agraria Milano* (N.S.), 7, 41 (1958).

GENETICS

Gene Action in the *X*-chromosome of the Mouse (*Mus musculus* L.)

Ohno and Hauschka[1] showed that in female mice one chromosome of mammary carcinoma cells and of normal diploid cells of the ovary, mammary gland and liver was heteropyknotic. They interpreted this chromosome as an *X*-chromosome and suggested that the so-called sex chromatin was composed of one heteropyknotic *X*-chromosome. They left open the question whether the heteropyknosis was shown by the paternal *X*-chromosome only, or the chromosome from either parent indifferently.

The present communication suggests that the evidence of mouse genetics indicates: (1) that the heteropyknotic *X*-chromosome can be either paternal or maternal in origin, in different cells of the same animal; (2) that it is genetically inactivated.

The evidence has two main parts. First, the normal phenotype of *XO* females in the mouse[2] shows that only one active *X*-chromosome is necessary for normal development, including sexual development. The second piece of evidence concerns the mosaic phenotype of female mice heterozygous for some sex-linked mutants. All sex-linked mutants so far known affecting coat colour cause a 'mottled' or 'dappled' phenotype, with patches of normal and mutant colour, in females heterozygous for them. At least six mutations to genes of this type have been reported, under the names mottled[3,4], brindled[3], tortoiseshell[5], dappled[6], and 26*K* [2]. They have been thought to be allelic with one another, but since no fertile males can be obtained from any except, in rare cases, brindled, direct tests of allelism have usually not been possible. In addition, a similar phenotype, described as 'variegated', is seen in females heterozygous for coat colour mutants translocated on to the *X*-chromosome[7,8].

It is here suggested that this mosaic phenotype is due to the inactivation of one or other *X*-chromosome early in embryonic development. If this is true, pigment cells descended from cells in which the chromosome carrying the mutant gene was inactivated will give rise to a normal-coloured patch and those in which the chromosome carrying the normal gene was inactivated will give rise to a mutant-coloured patch. There may be patches of intermediate colour due to cell-mingling in development. The stripes of the coat of female mice heterozygous for the gene tabby, *Ta*, which affects hair structure, would have a similar type of origin. Falconer[9] reported that the black regions of the coat of heterozygotes had a hair structure resembling that of the *Ta* hemizygotes and homozygotes, while the agouti regions had a normal structure.

Thus this hypothesis predicts that for all sex-linked genes of the mouse in which the phenotype is due to localized gene action the heterozygote will have a mosaic appearance, and that there will be a similar effect when autosomal genes are translocated to the *X*-chromosome. When the phenotype is not due to localized gene action various types of result are possible. Unless the gene action is restricted to the descendants of a very small number of cells at the time of inactivation, these original cells will, except in very rare instances, include both types. Therefore, the phenotype may be intermediate between the normal and hemizygote types, or the presence of any normal cells may be enough to ensure a normal phenotype, or the observed expression may vary as the proportion of normal and mutant cells varies, leading to incomplete penetrance in heterozygotes. The gene bent-tail, *Bn* [10], may fit into this category, having 95 per cent penetrance and variable expression in heterozygotes. Jimpy, *jp*, is recessive, suggesting that the presence of some normal cells is enough to ensure a normal phenotype, but Phillips[11] reported one anomalous female which showed the jimpy phenotype. Since it showed the heterozygous phenotype for *Ta* this animal cannot be interpreted as an *XO* female; it is possible that it represents an example of the rare instance when by chance all the cells responsible for the jimpy phenotype had the normal gene inactivated.

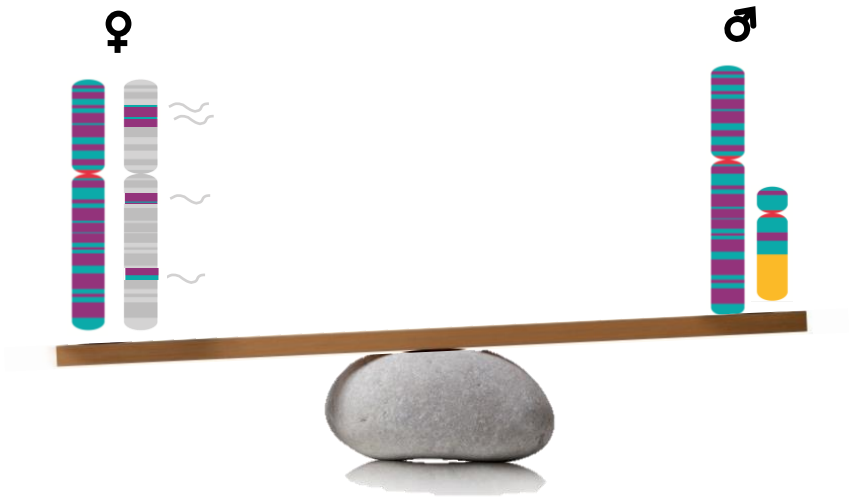
The genetic evidence does not indicate at what stage of embryonic development the inactivation of one *X*-chromosome occurs. In embryos of the cat, monkey and man sex-chromatin is first found in nuclei of the late blastocyst stage[12,13]. Inactivation of one *X* at a similar stage of the mouse embryo would be compatible with the observations. Since an *XO* female is normally fertile it is not necessary to postulate that both *X*-chromosomes remain functional until the formation of the gonads.

The sex-chromatin is thought to be formed from one *X*-chromosome also in the rat, *Rattus norvegicus*[14], and in the opossum, *Didelphis virginiana*[15]. If this should prove to be the case in all mammals, then all female mammals heterozygous for sex-linked mutant genes would be expected to show the same phenomena

Mary F. Lyon (1925-2014)

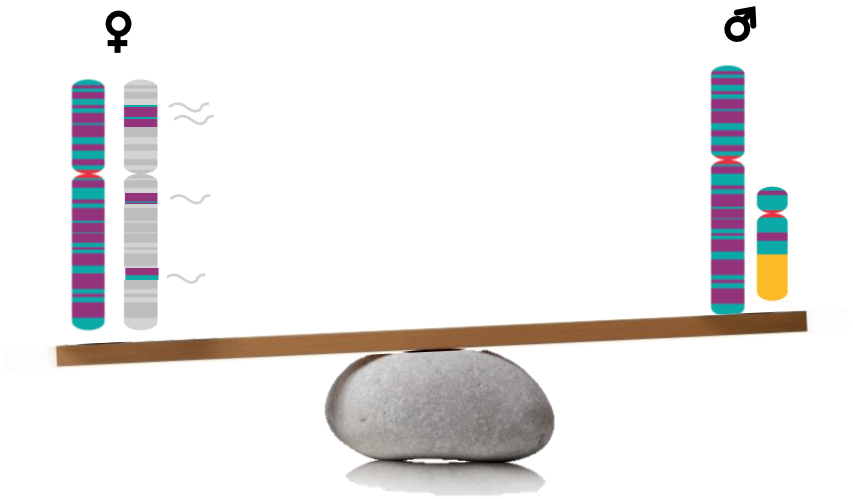
Des gènes « échappent » à l'inactivation

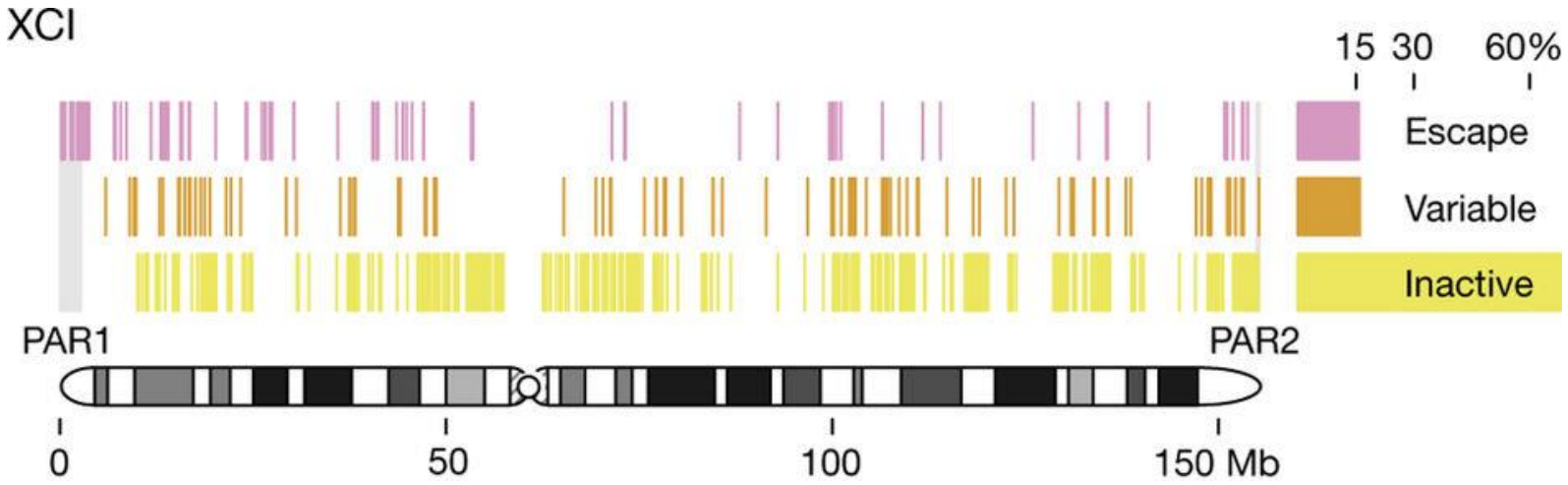
Un des deux chromosomes X des femelles est <u>majoritairement</u> inactif



Des gènes « échappent » à l'inactivation

Chez l'humain, ~23% des gènes du chromosome X échappent à l'inactivation

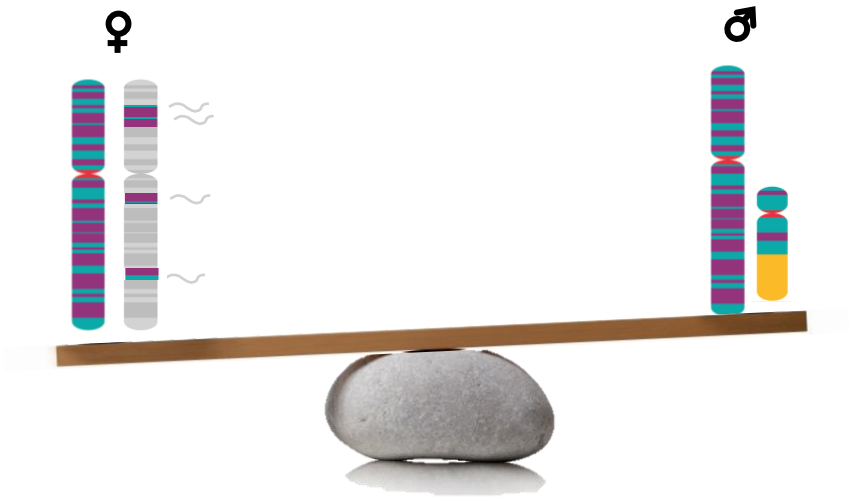




Tukiainen et al. Nature 2017

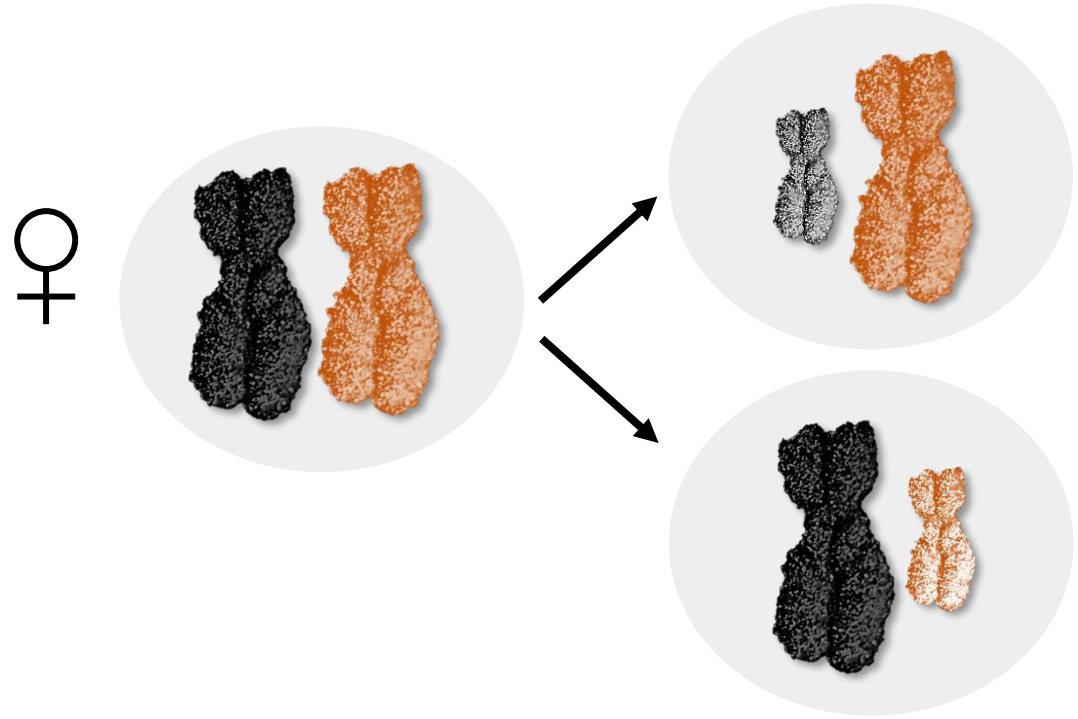
Un dosage inégal

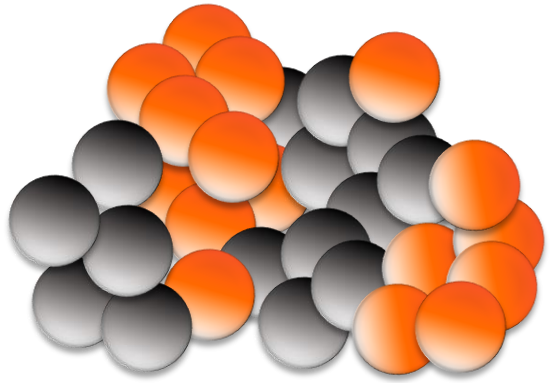
Chez l'humain, ~23% des gènes du chromosome X échappent à l'inactivation



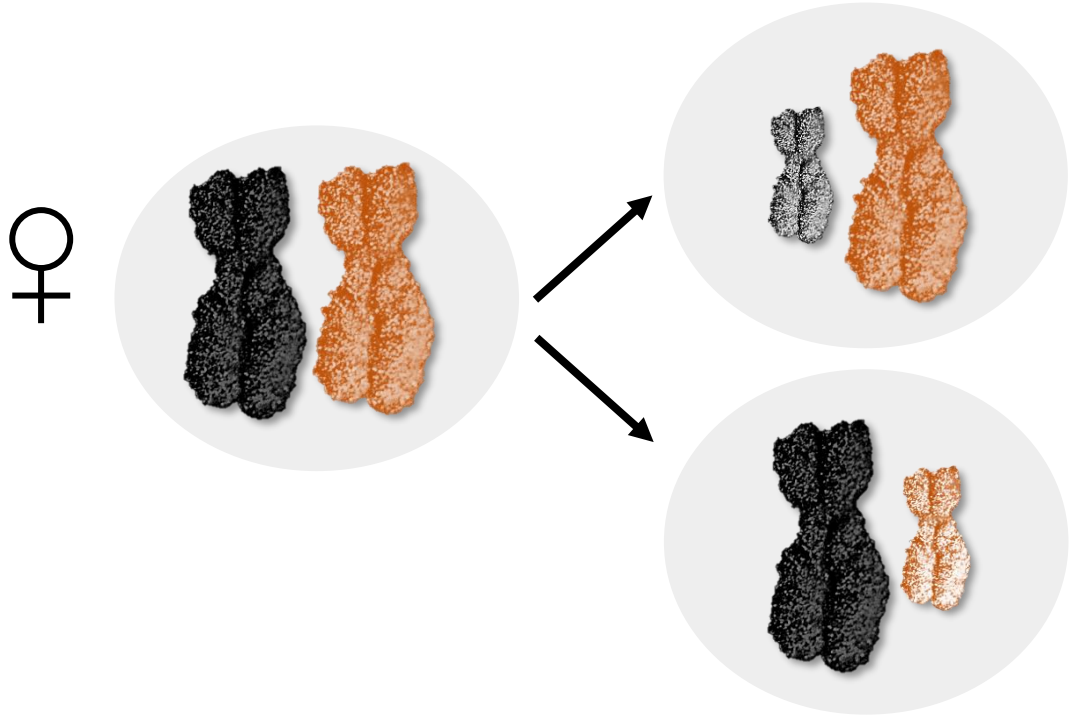
Malgré l'inactivation d'un des deux chromosomes X chez les femelles, des différences persistent dans les niveaux d'expression de gènes du X entre mâles et femelles…
… en fonction du type de cellules, du stade de développement, …

L’inactivation touche aléatoirement un X ou l’autre



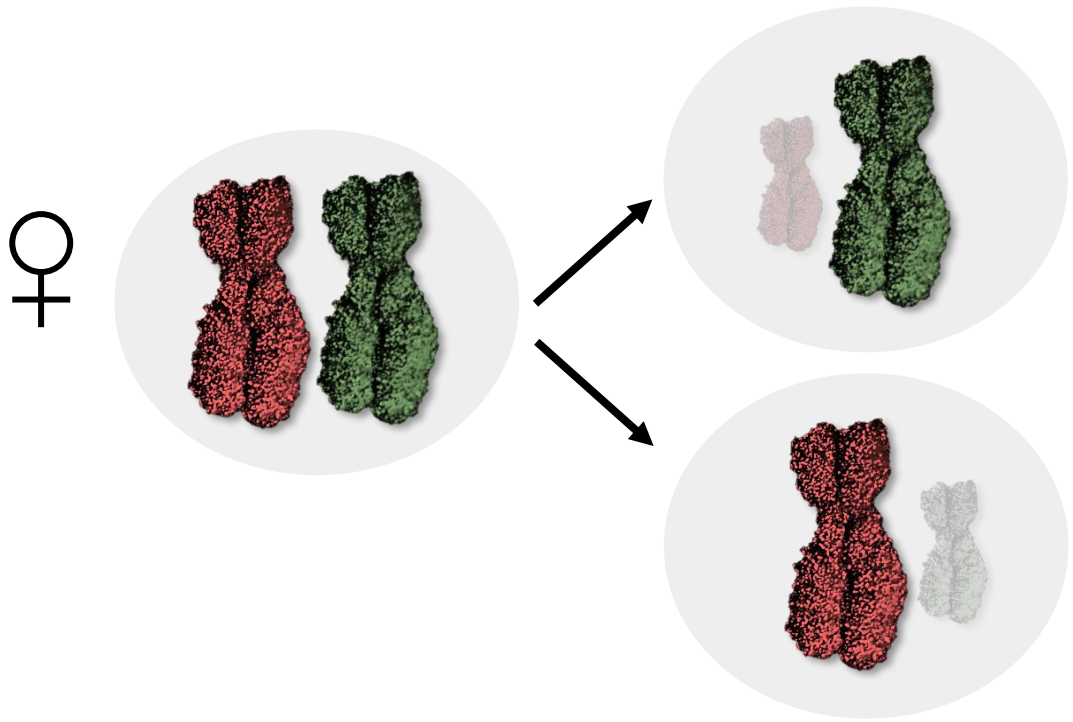


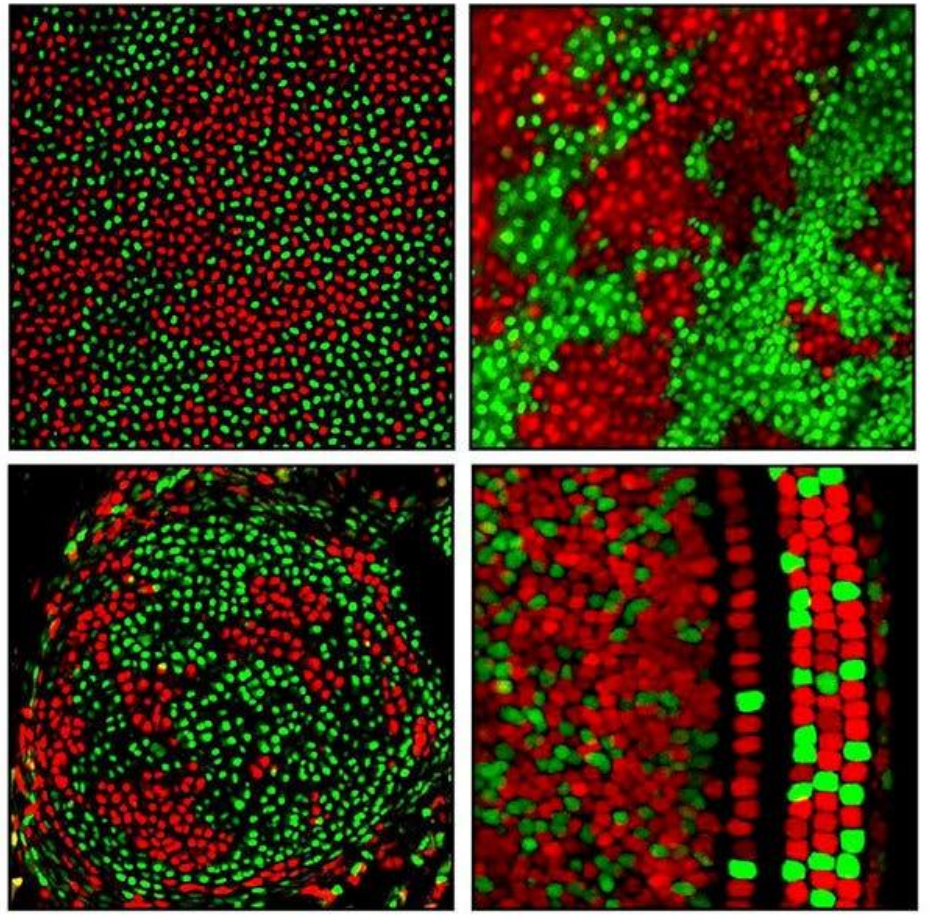
L’inactivation touche aléatoirement un X ou l’autre



→ Les femelles sont des individus mosaiques

L’inactivation touche aléatoirement un X ou l’autre

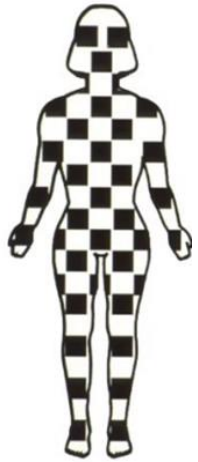




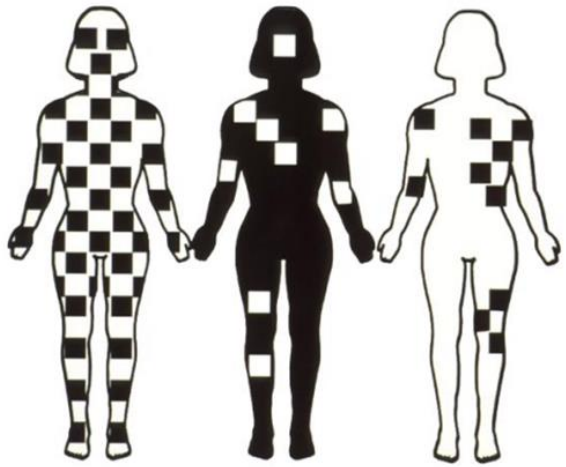
Wu et al. Neuron 2014

→ Les femelles sont des individus mosaiques

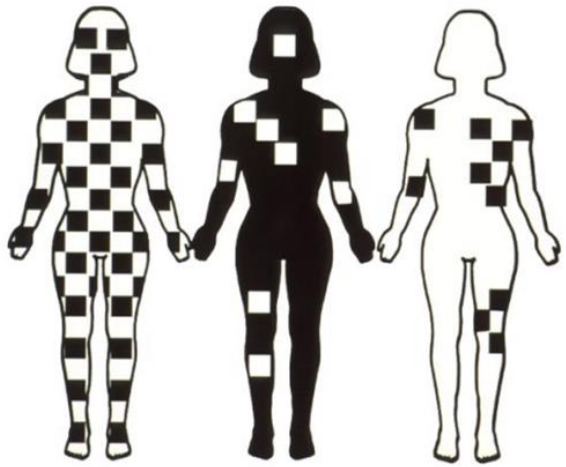
Mosaicisme et biais d’inactivation du X

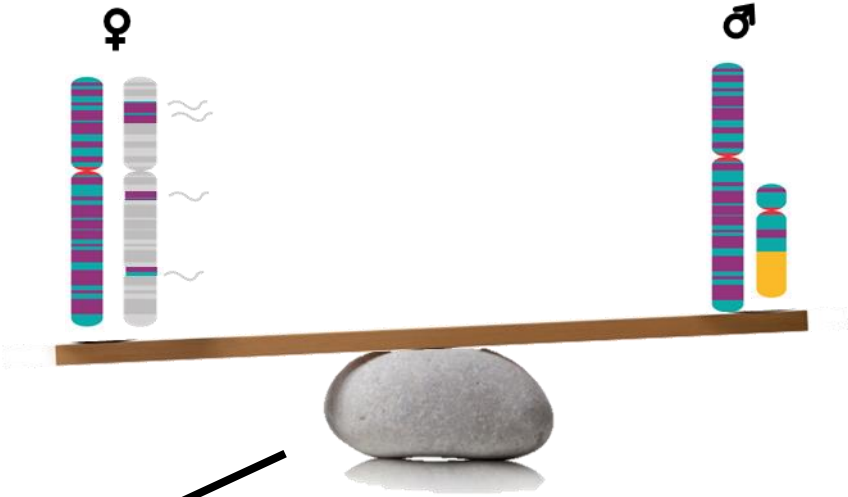


Mosaicisme et biais d’inactivation du X



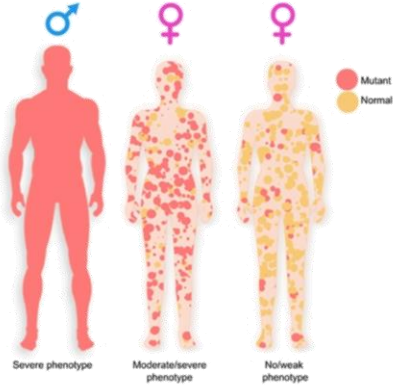
Inactivation du X et pathologies





Dimorphismes sexuels dans la susceptibilité à différentes pathologies

> 533 maladies liées au chromosome affectent de manière plus sévère les mâles



Femmes et hommes ne sont pas égaux devant les maladies

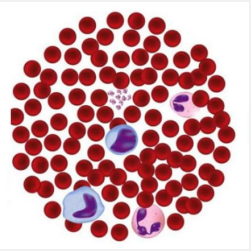
♀ ♂

XX XY

Autoimmunité
Maladie de Graves
Thyroïdite de Hashimoto
Sclérose en plaques
Polyarthrite rhumatoïde
Lupus érythémateux disséminé
Diabète de type 1

Inflammation chronique
Arthrite
Athérosclerose

Infection
Ebola
Hepatite B
Tuberculose
Amebiasis
Aspergillose
COVID
…



Neurodegenerative
Alzheimer
Démence fronto-temporale

Neuropsychiatrique
Dépression
Anxieté

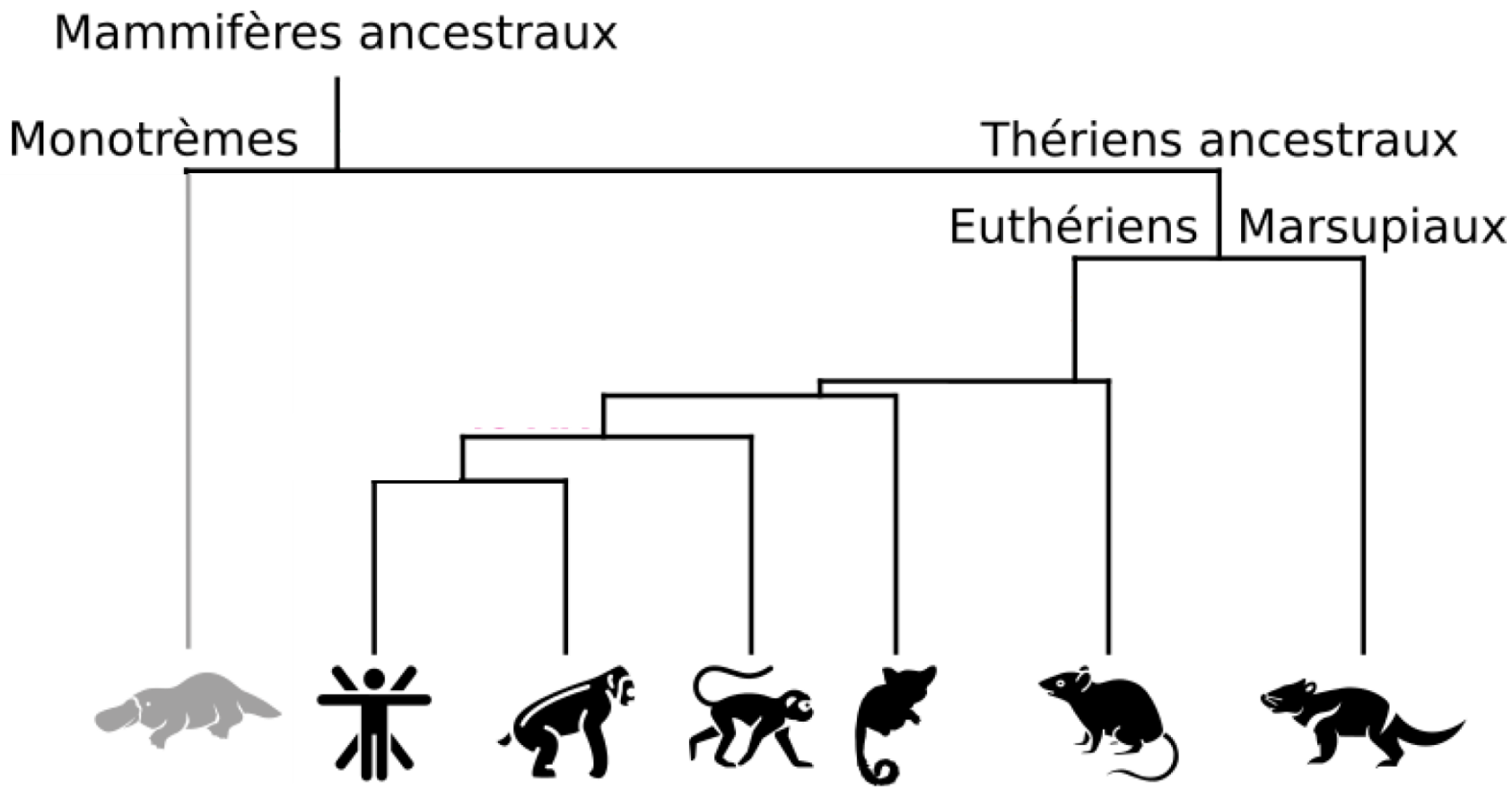
Neurodegenerative
Parkinson
Maladies des motoneurones

Neuropsychiatrique
TDAH
Syndrome de Tourette
Autisme

Cancers non liés à la reproduction

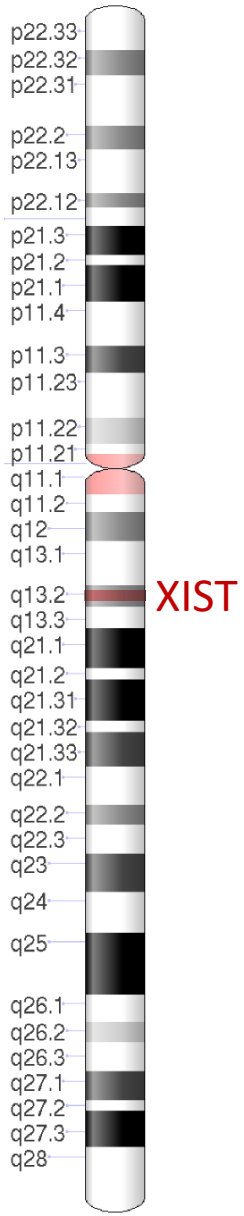
Importance de prendre en compte le sexe et le genre dans les études biomédicales

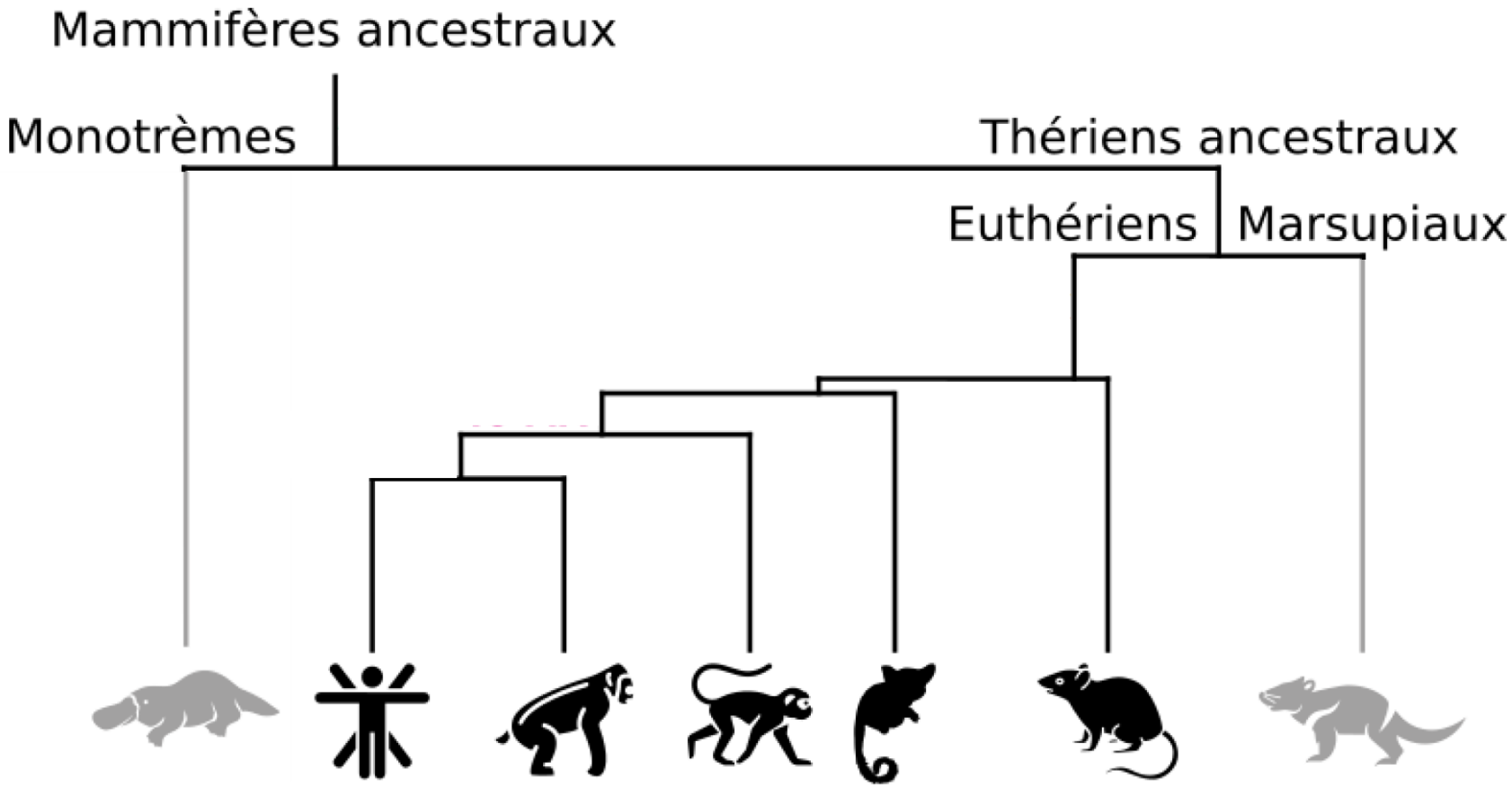
L’inactivation du X concerne tous les mammifères



Illustrations: Louis Chauviere

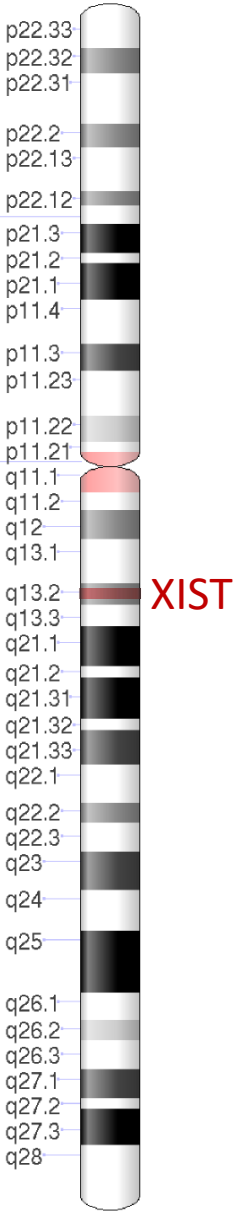
L'ARN XIST déclenche l'inactivation du X

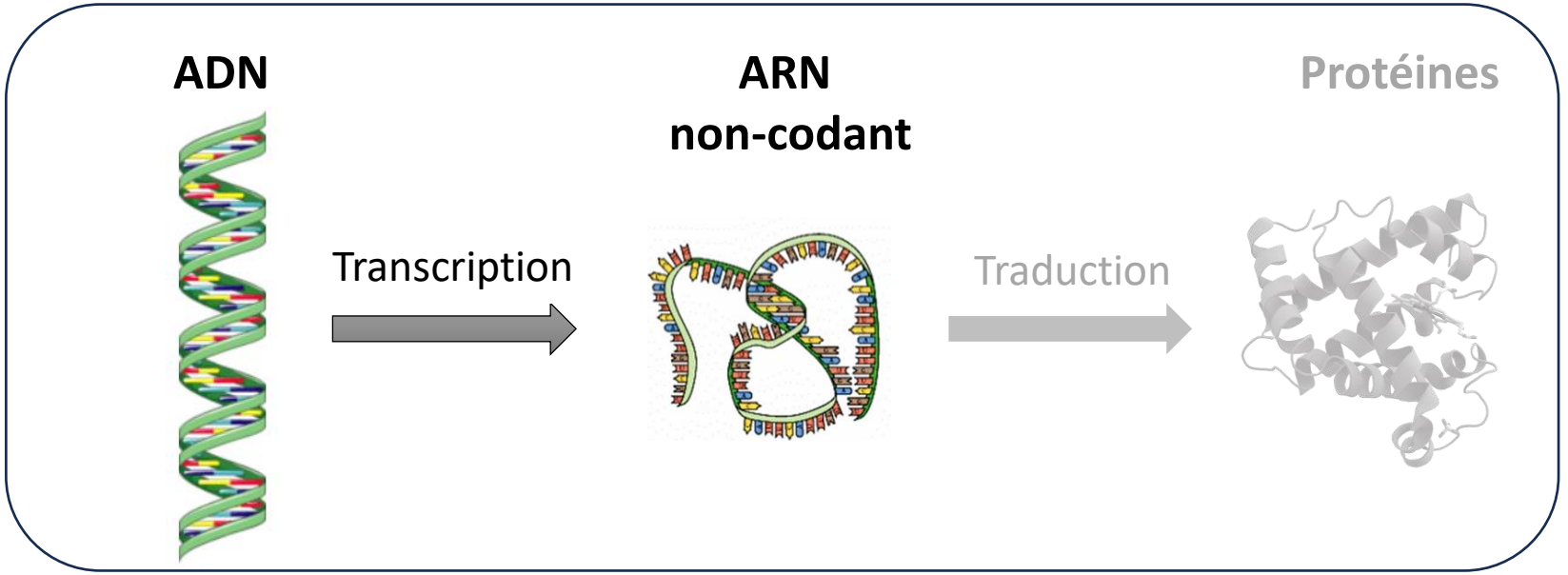




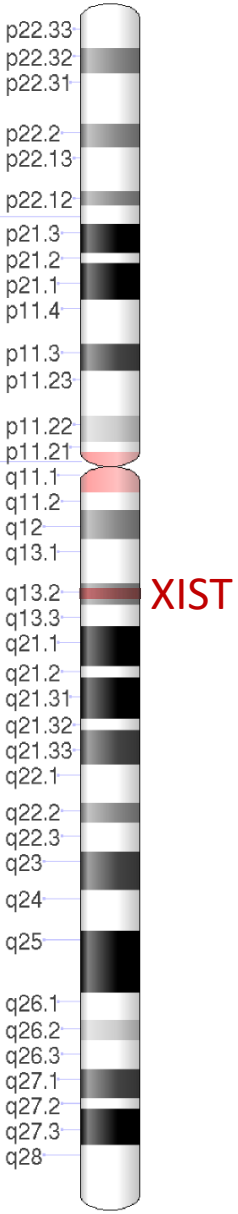
Illustrations: Louis Chauviere

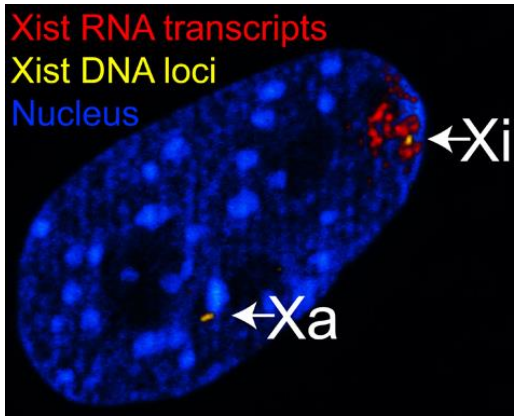
XIST est un ARN non-codant



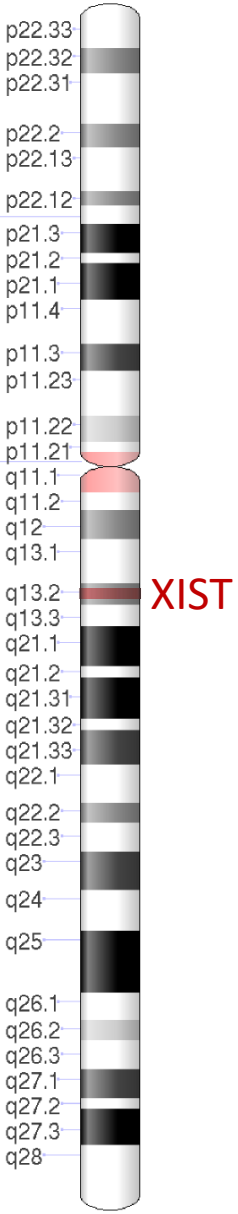


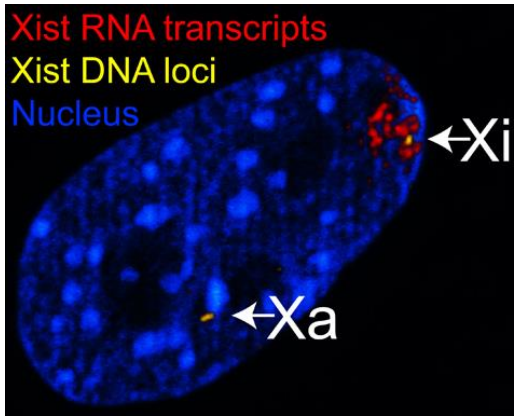
L’ARN XIST s’accumule autour du chromosome X…

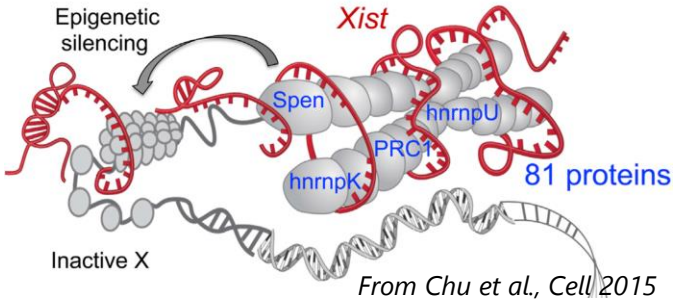


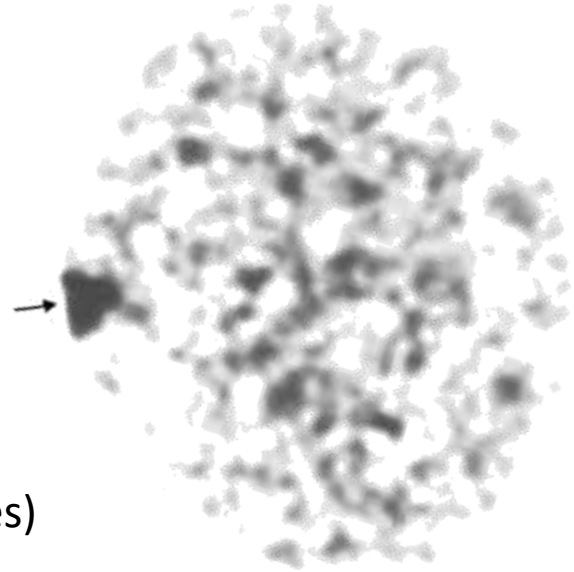


… et recrute de multiples facteurs



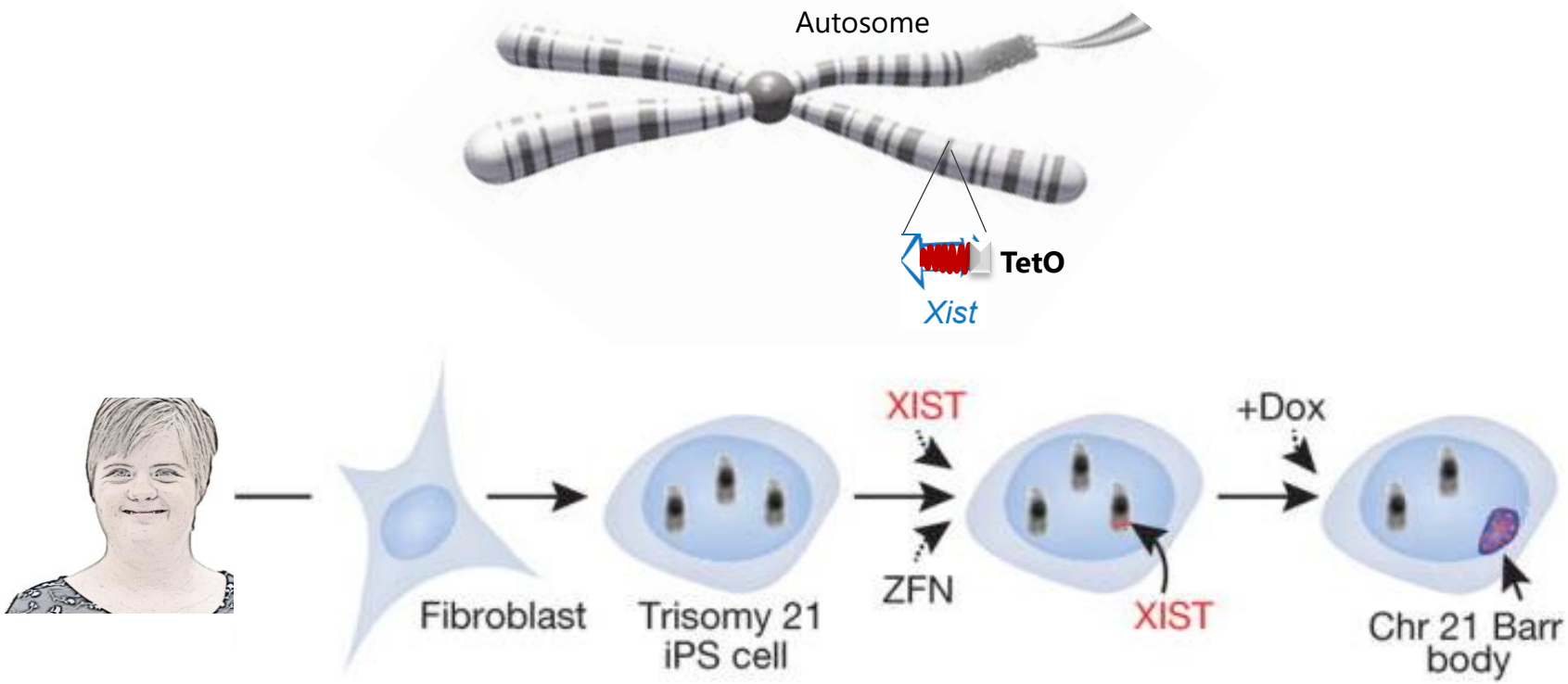


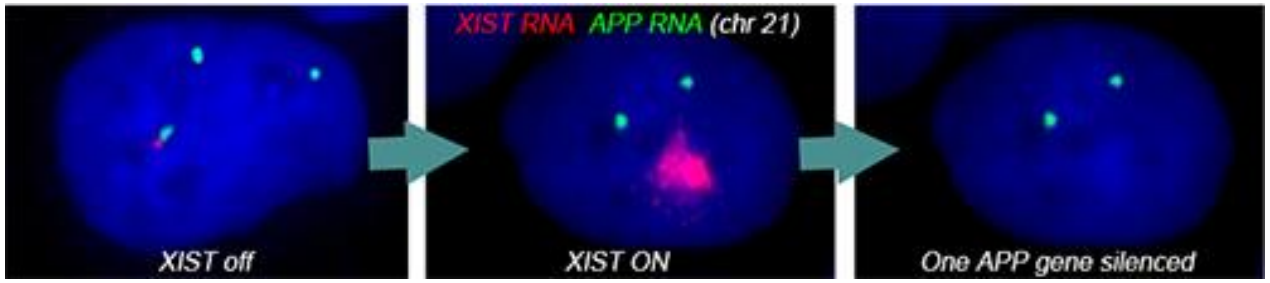




- Modification de la chromatine (histones)
- Exclusion de la machinerie de transcription
- Réorganisation tri-dimensionnelle du chromosome

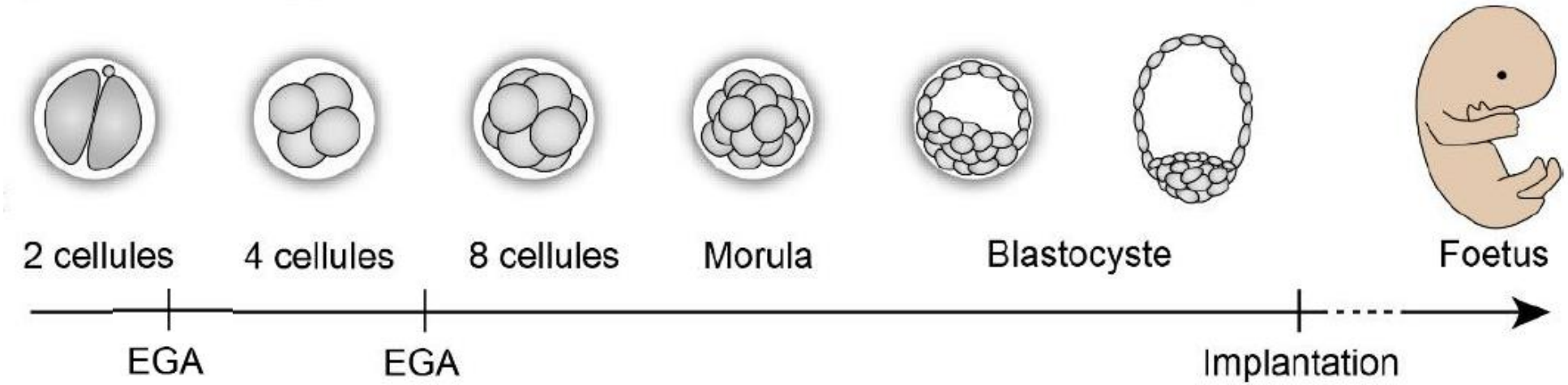
Inactivation d'un chr21 par XIST dans des cellules trisomiques





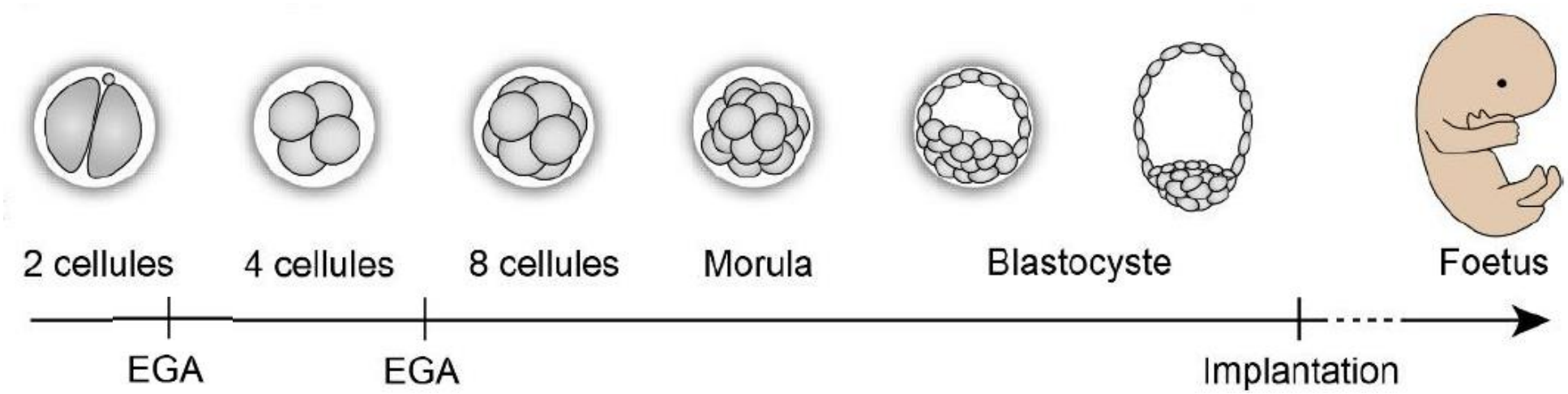
Jiang et al. Nature 2013

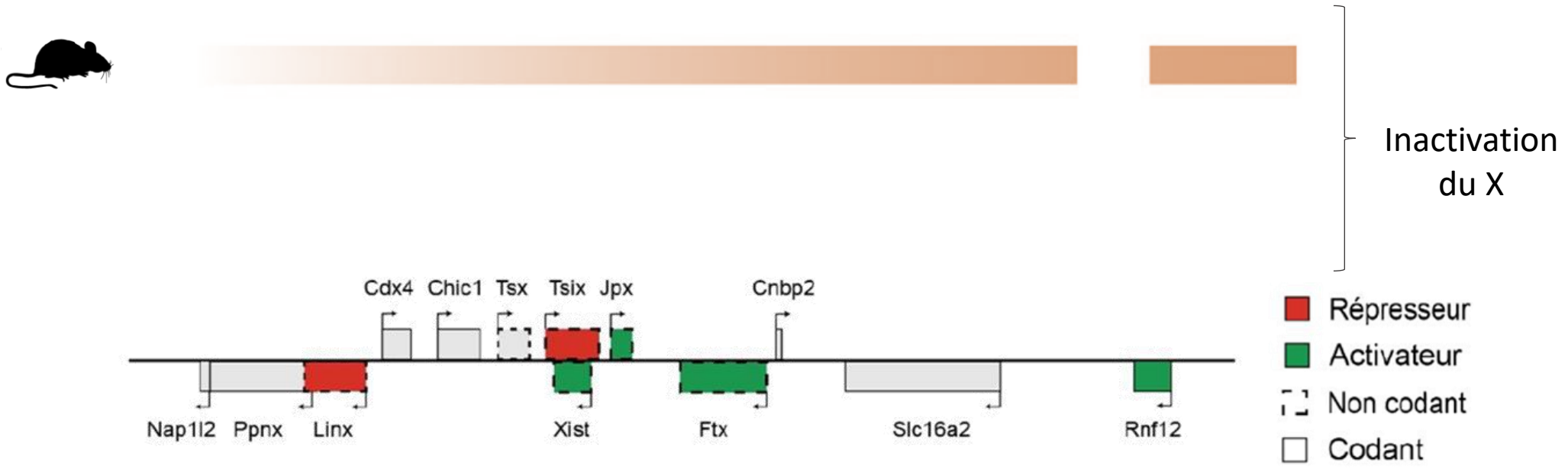
Inactivation du X et développement embryonnaire



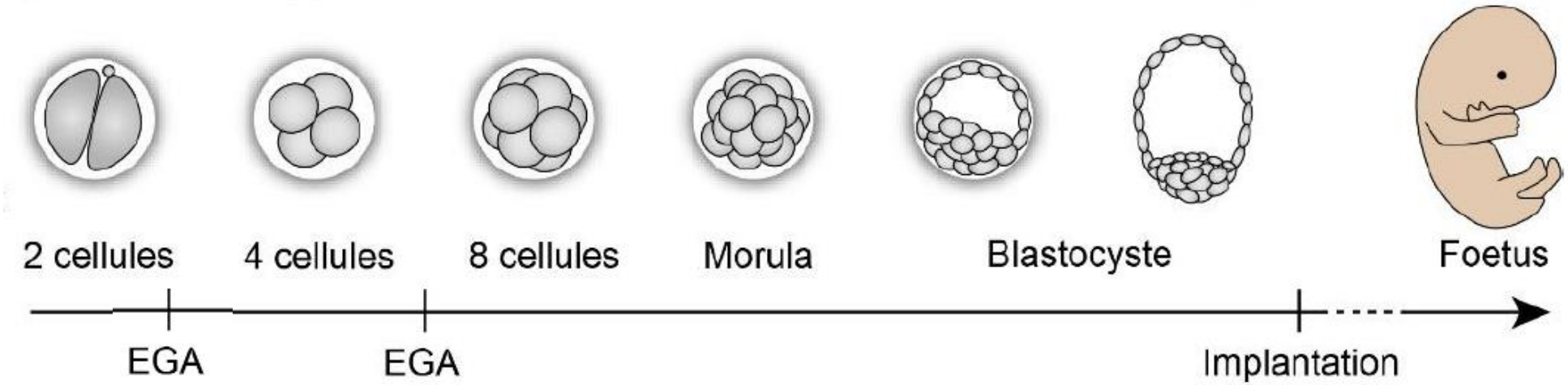
Illustrations: Madeleine Moscatelli

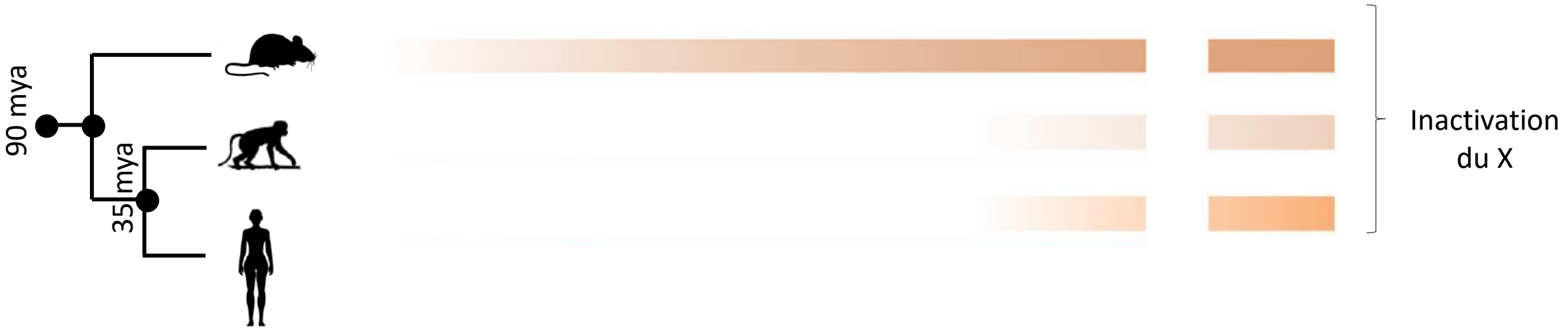
Inactivation du X et développement embryonnaire





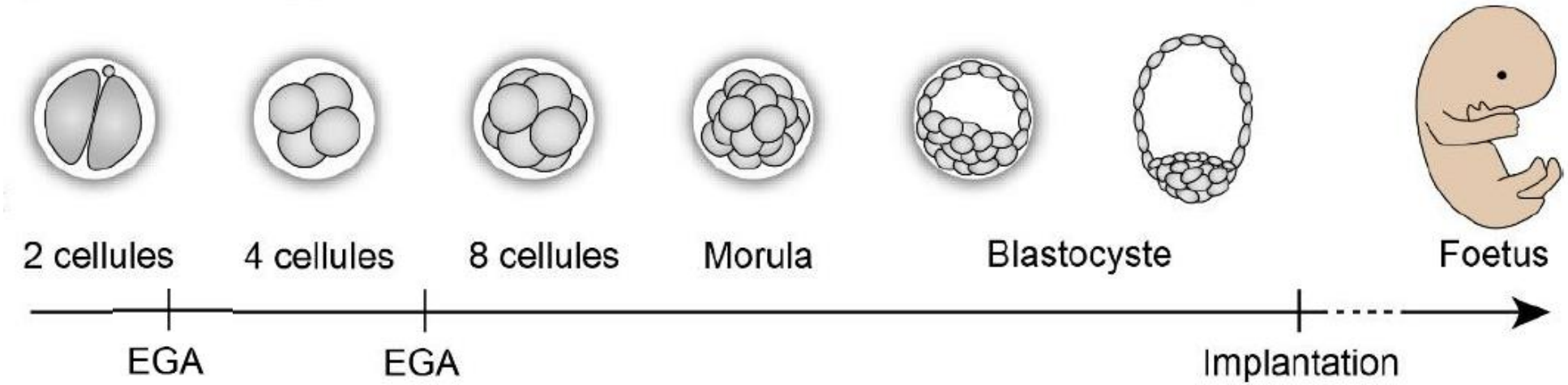
Inactivation du X et développement embryonnaire

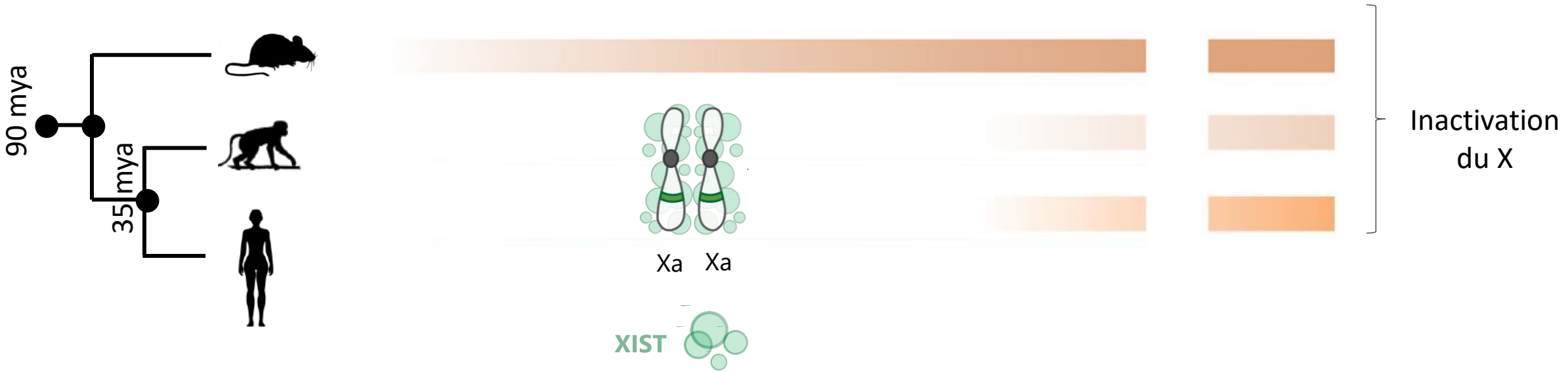




(Okamato et al. 2011; Okamoto et al. 2021)

Inactivation du X et développement embryonnaire





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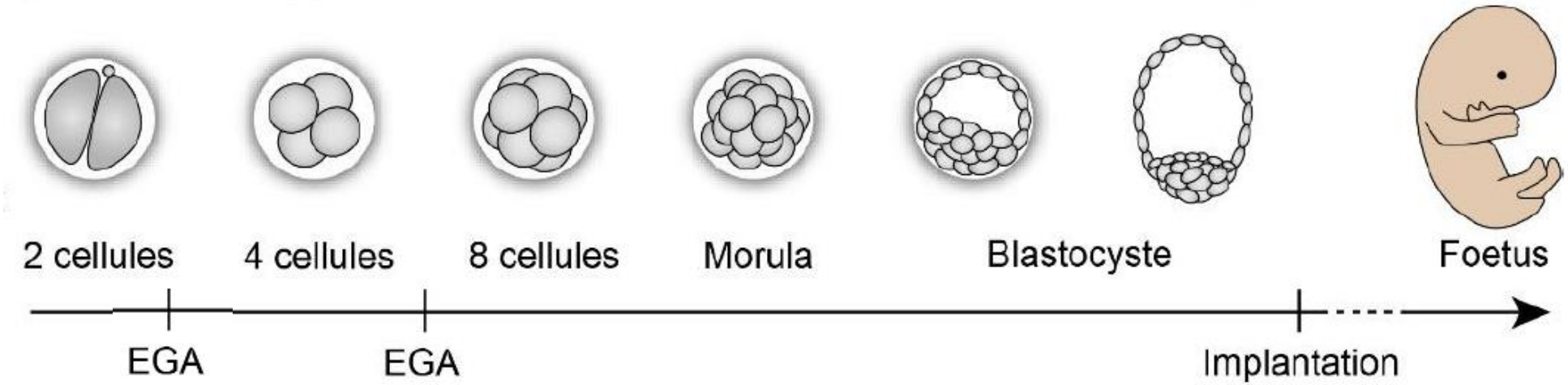
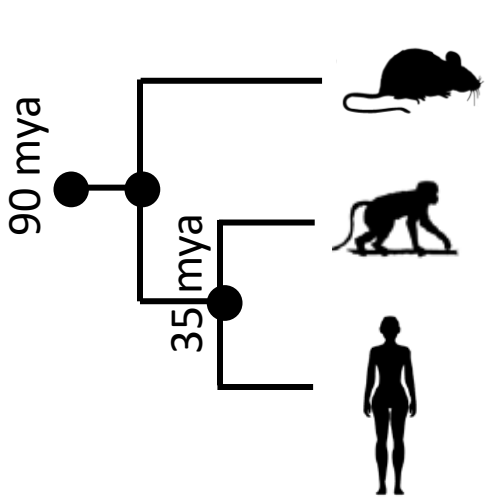




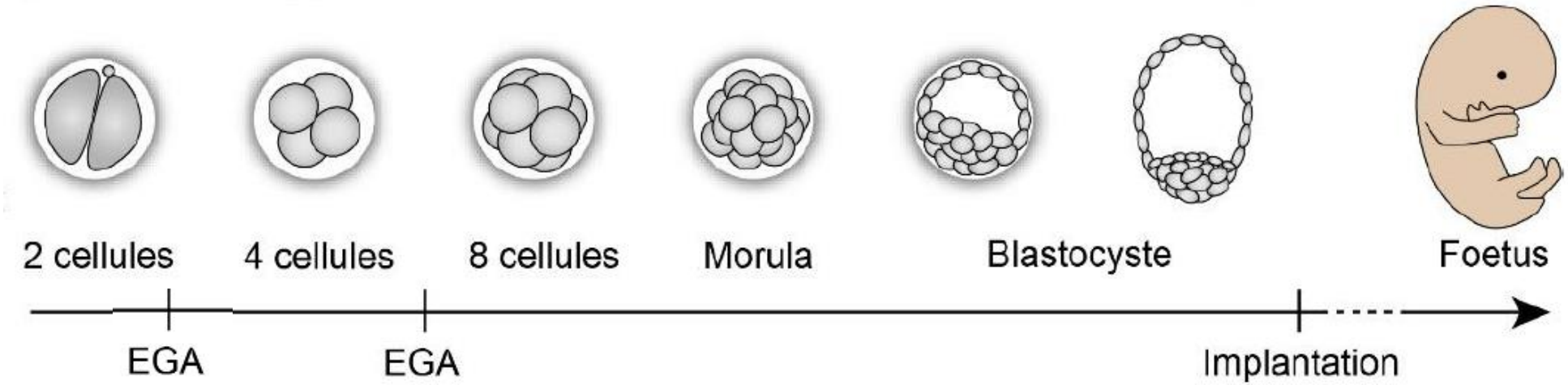
Inactivation du X

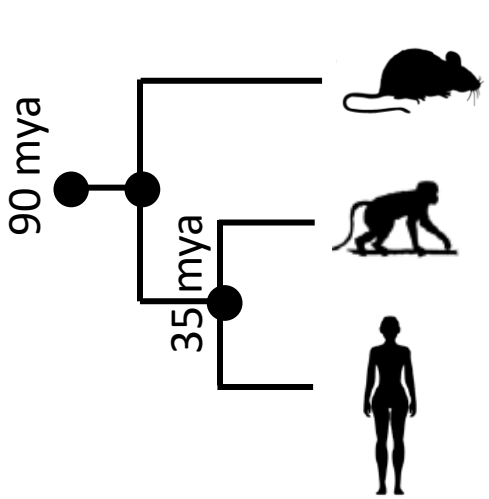
Xa Xa

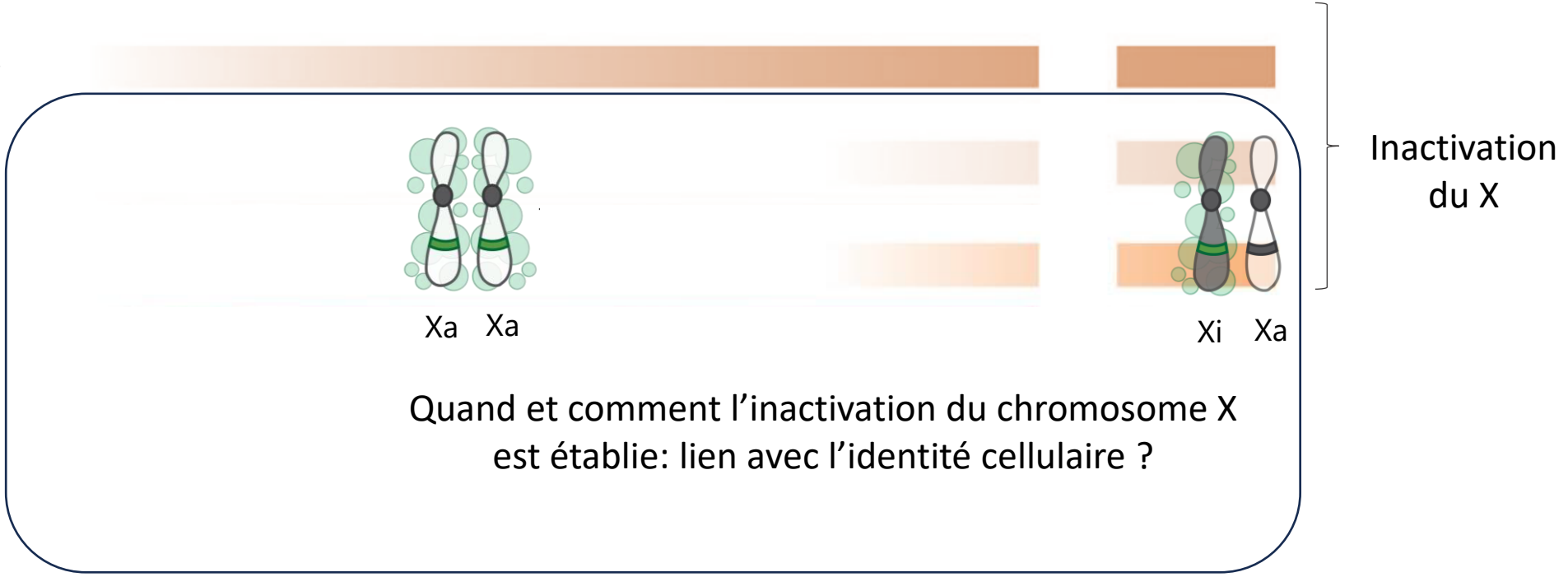
Quel rôle joue XIST durant le développement pré-implantatoire des primates?

Compensation de dose?

Inactivation du X et développement embryonnaire







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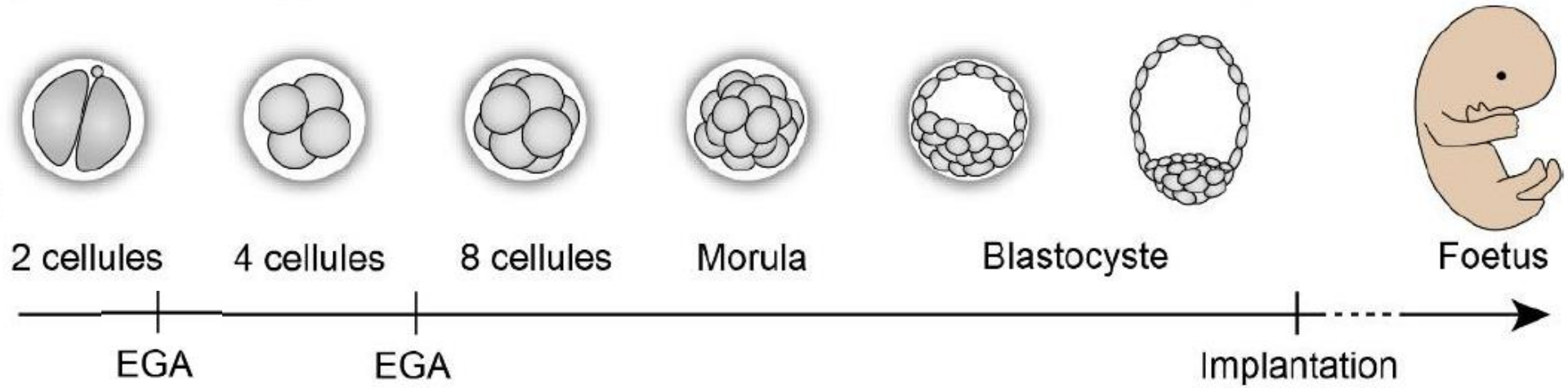
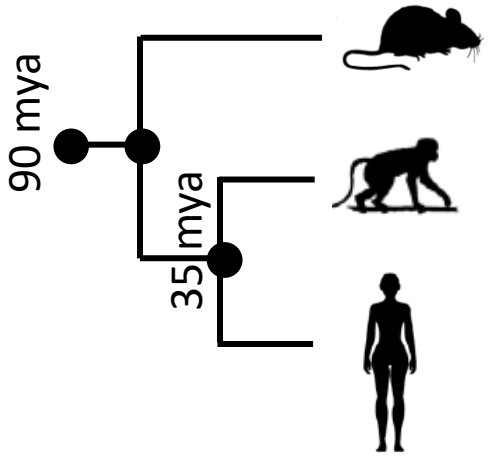
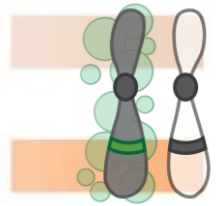
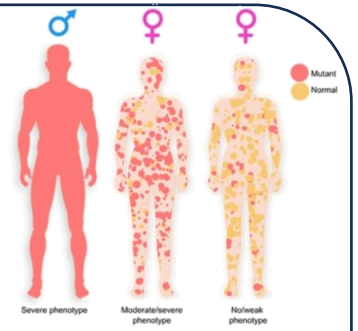


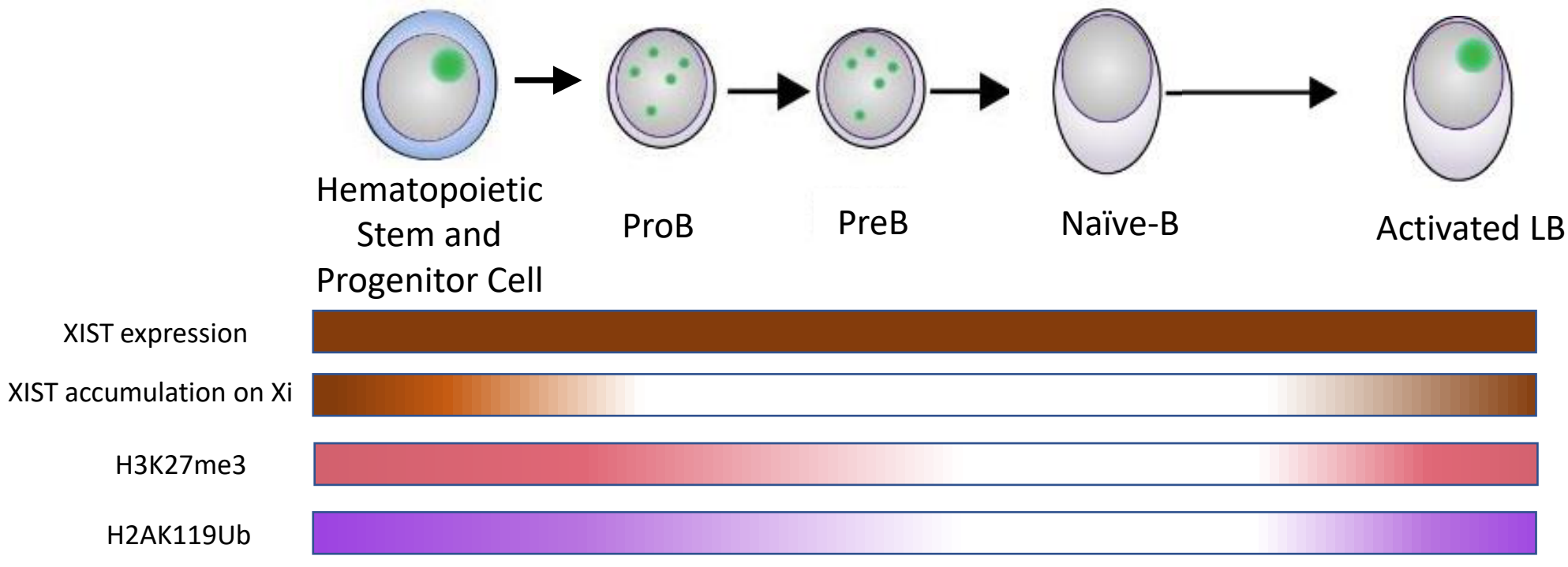






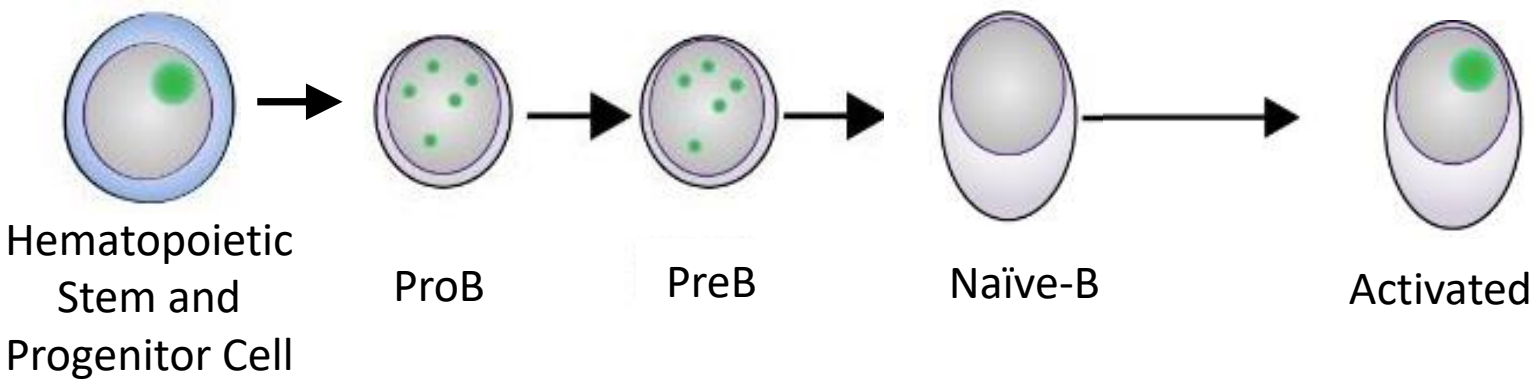
Maintien de l'inactivation dans les différents tissus: dimorphisme sexuel au niveau physiologique et pathologique

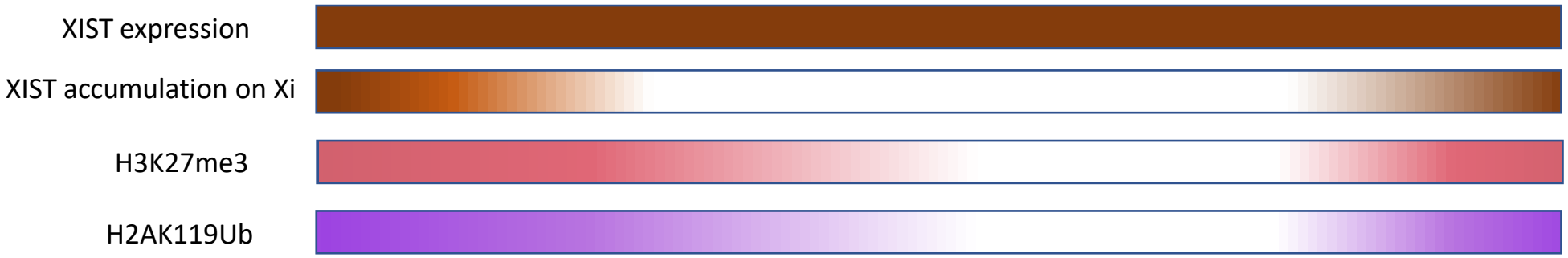
L’inactivation du X dans le lignage hématopoïétique

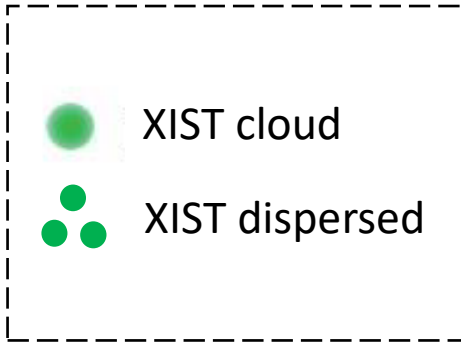


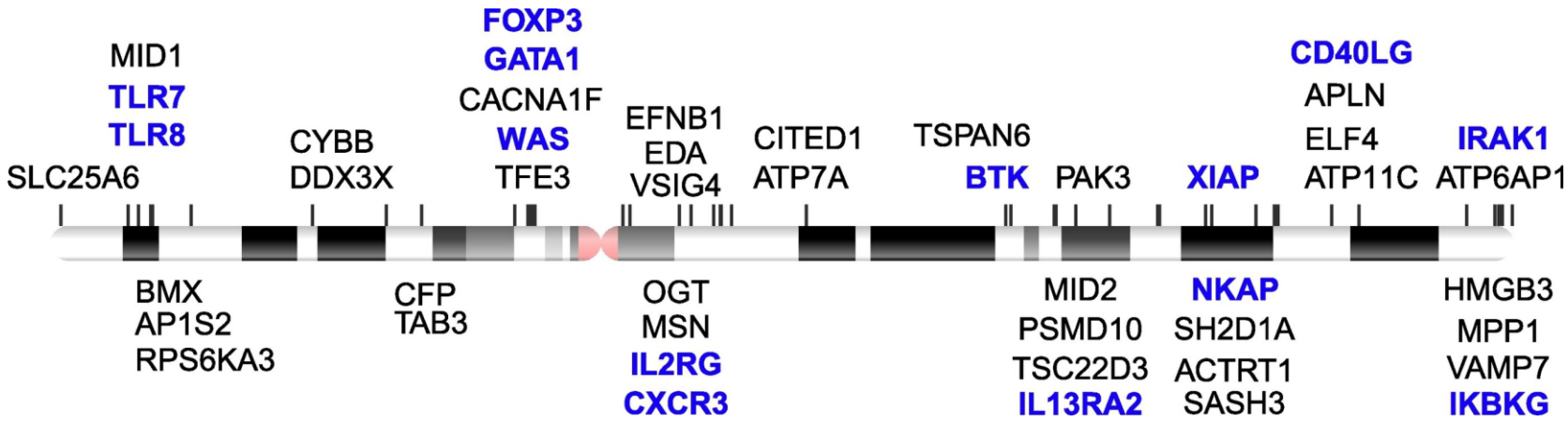
Wang et al. 2016

L'inactivation du X dans le lignage hémotopoïétique



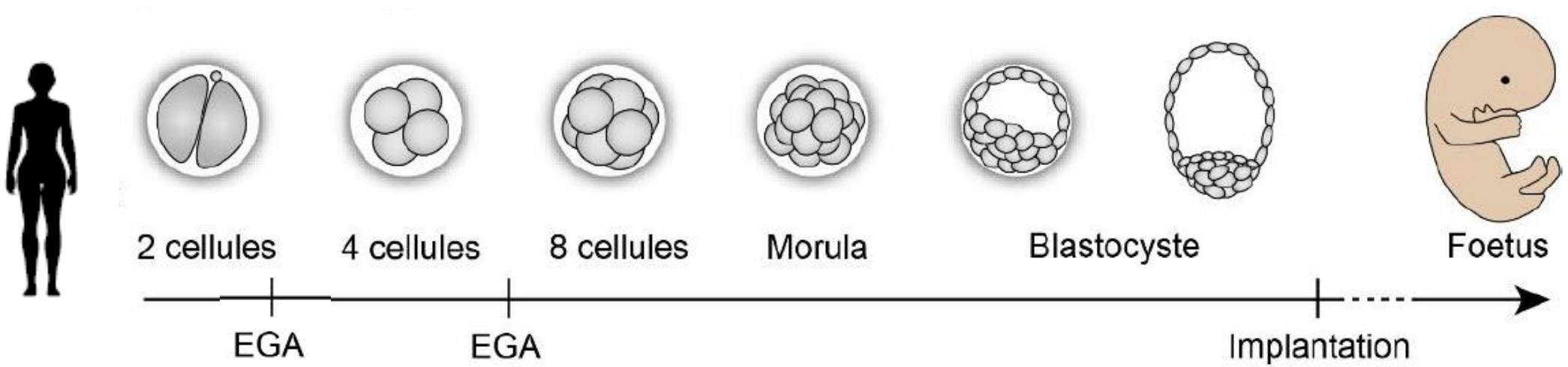


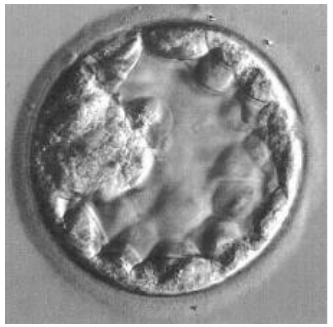




Wang et al. 2016

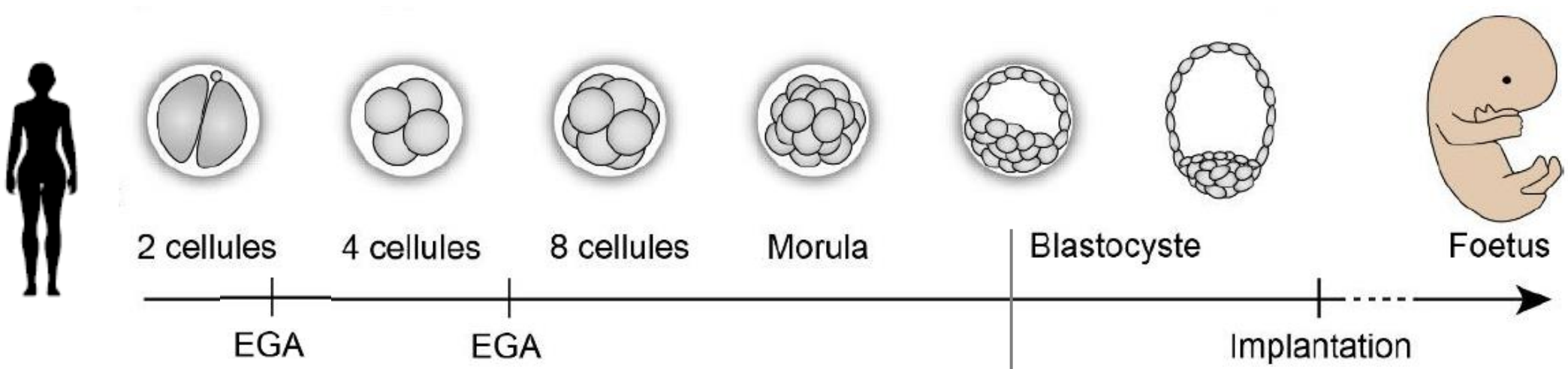
Les modèles d'étude

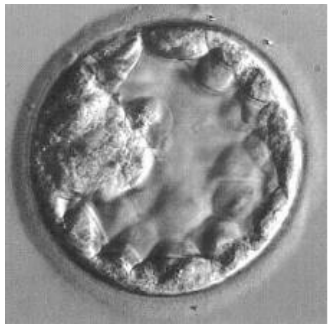




Embryons issus de fécondation *in vitro*
Donnés à la recherche

Les modèles d'étude





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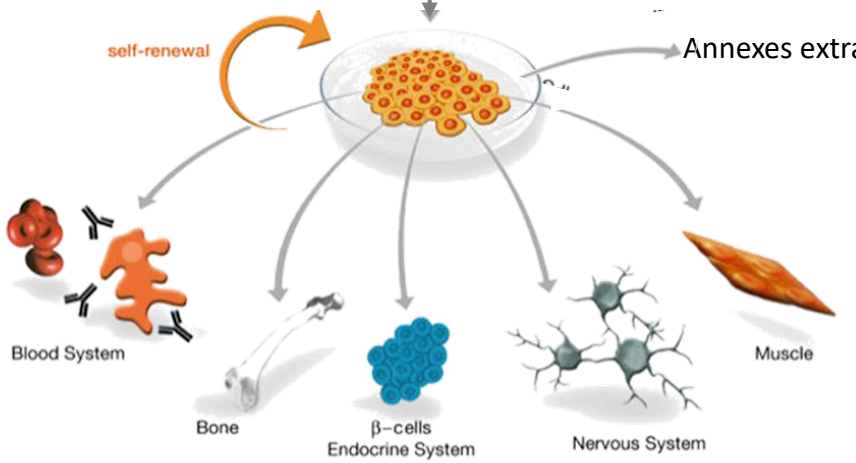
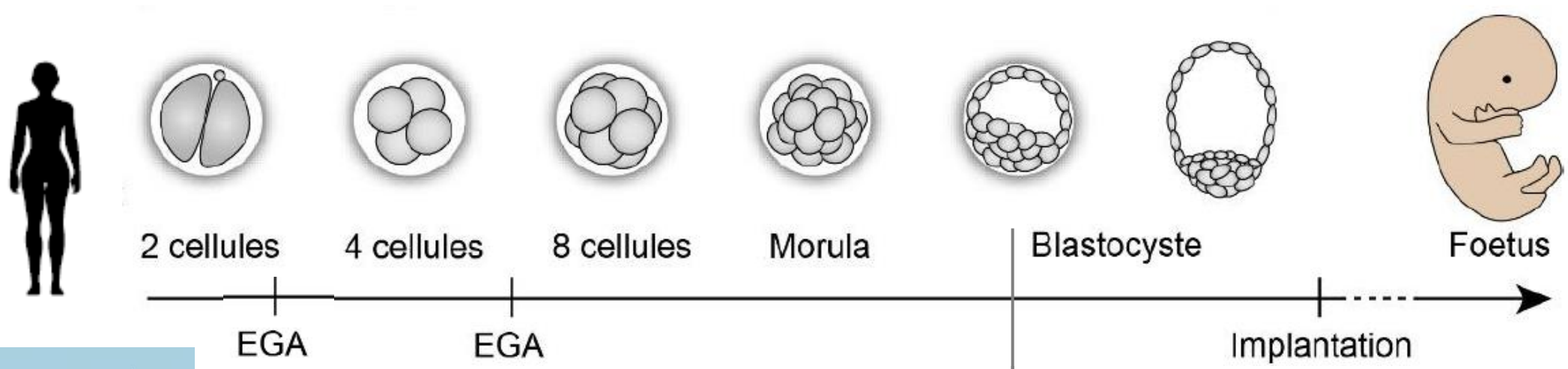
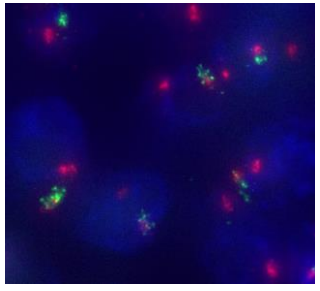


Cellules souches embryonnaires

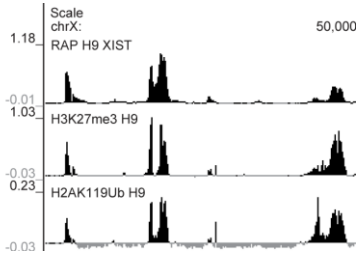
Les outils et approches



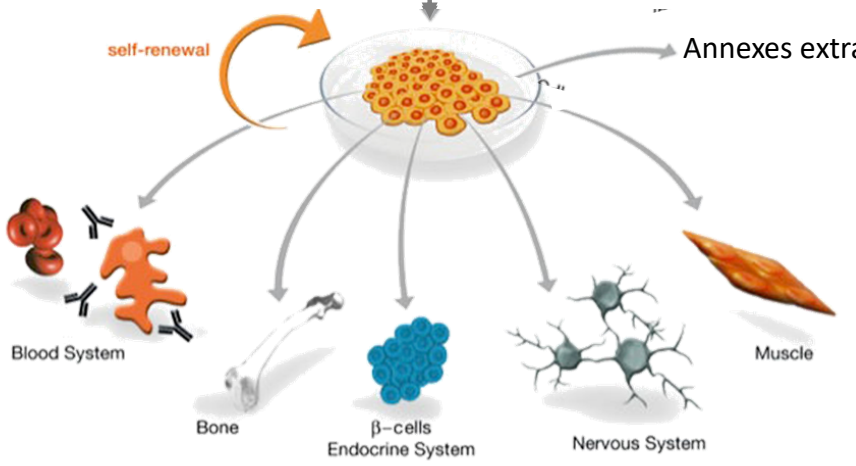
Ingénierie des génomes (CRISPR/Cas9)



Imagerie



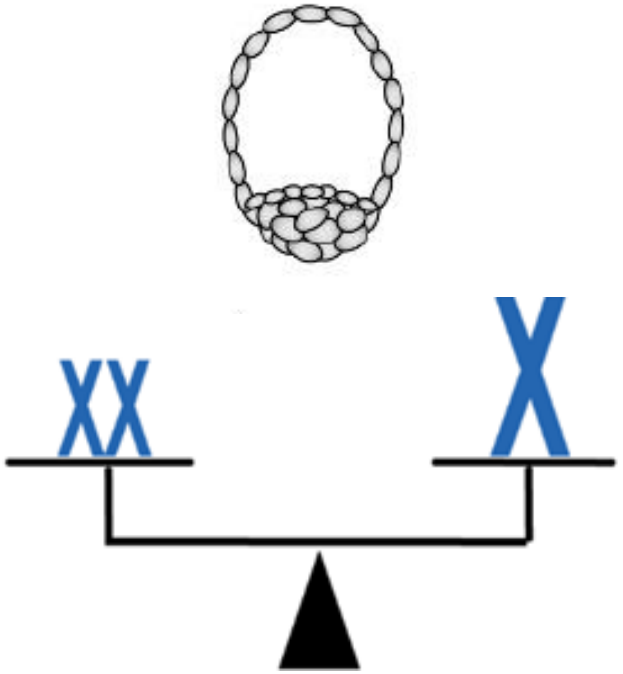
Approches « omiques »



Cellules souches embryonnaires

Nos résultats récents

XIST réduit l'expression des 2 chromosomes Xs pendant le développement pré-implantatoire



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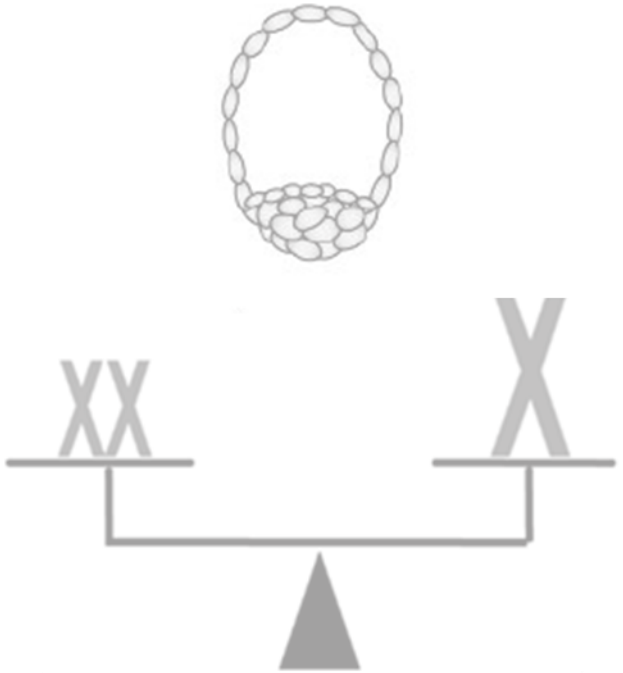
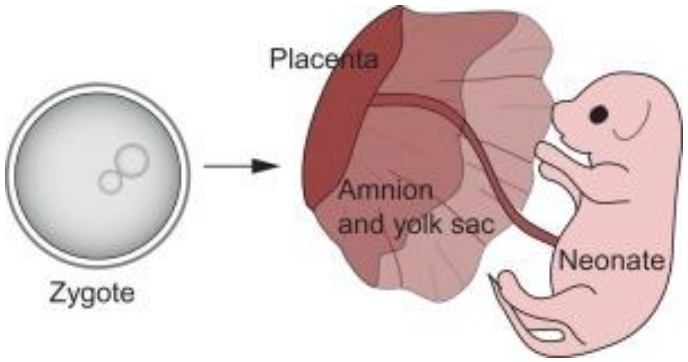


Un des deux chromosomes X doit être inactivé pour que les annexes extra-embryonnaires se développent



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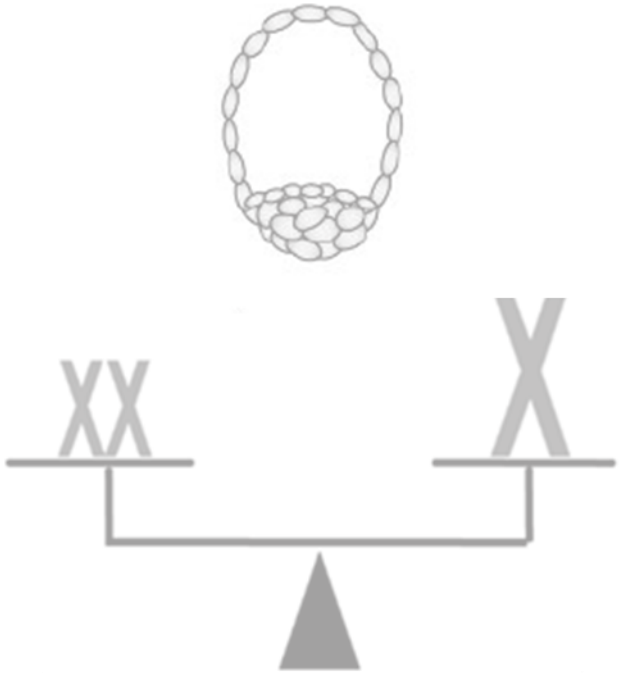

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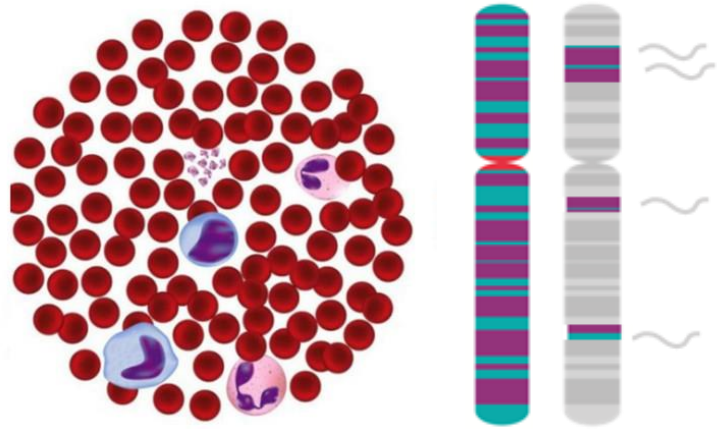
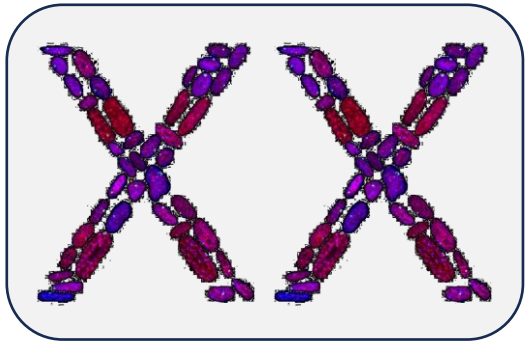
Perturber légèrement l'inactivation du X entraine l'apparition de signes d'autoimmunité (modèle animal)

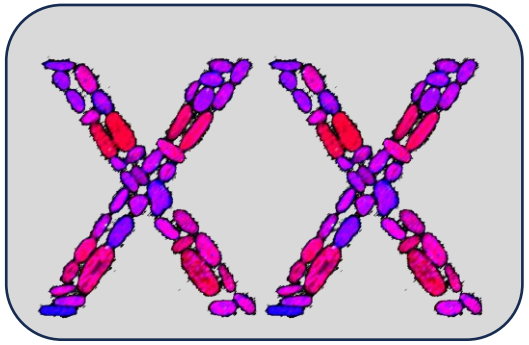


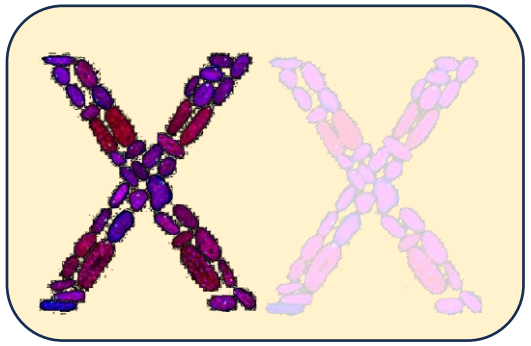
Conclusions

Embryon précoce

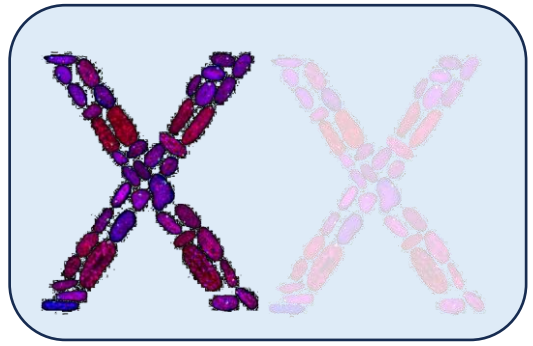


Embryon péri-implantatoire

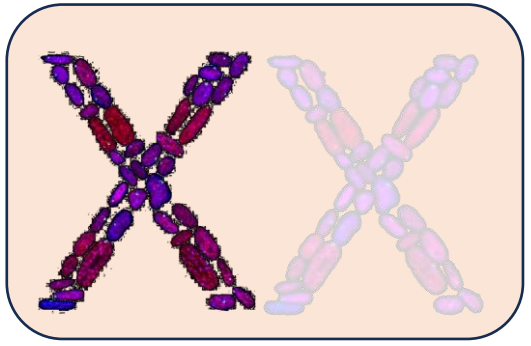




Type cellulaire A

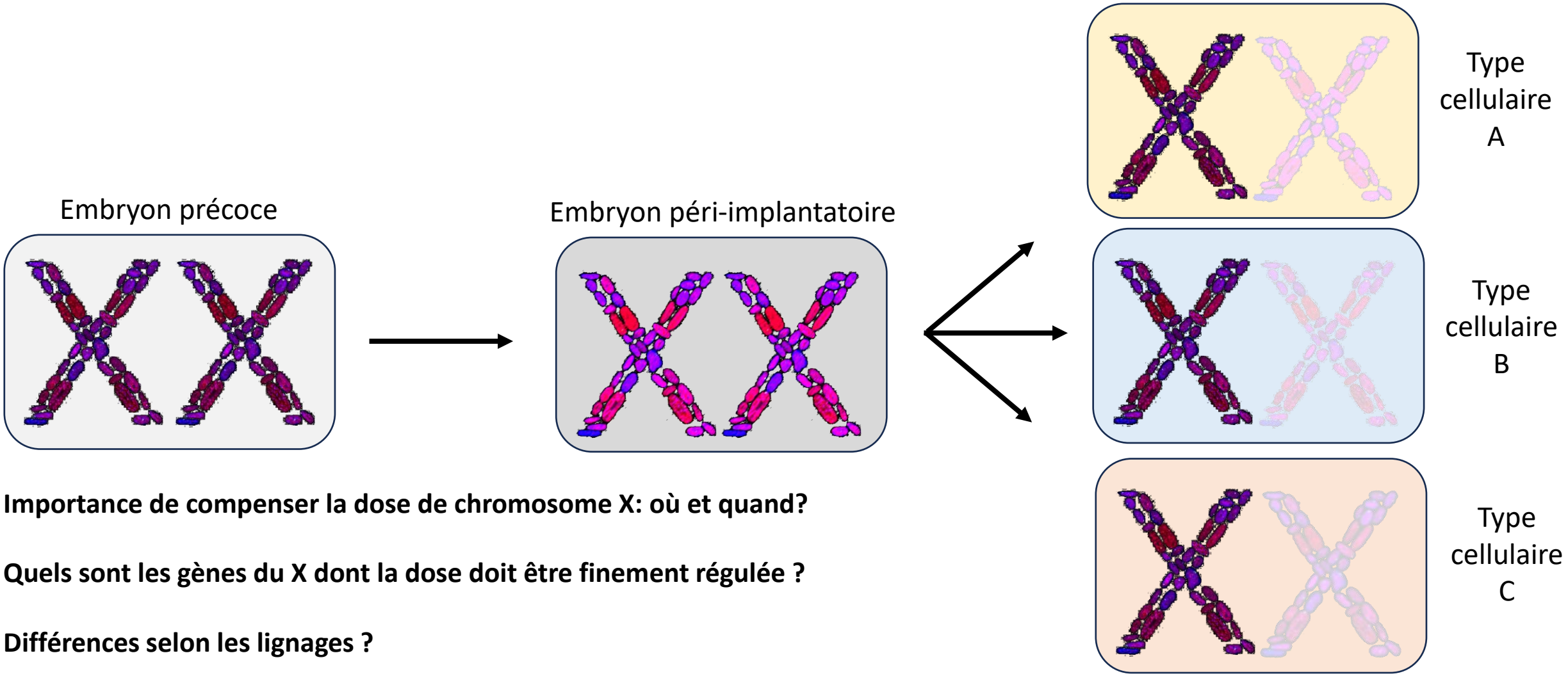


Type cellulaire B



Type cellulaire C

Les enjeux



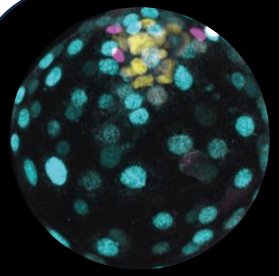
Importance de compenser la dose de chromosome X: où et quand?

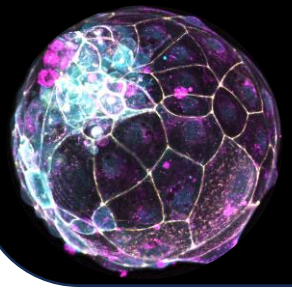
Quels sont les gènes du X dont la dose doit être finement régulée ?

Différences selon les lignages ?

Dans quelle mesure des variations dans l'activité résiduelle du Xi (physiologique ou pathologique, vieillissement etc) peuvent affecter l'homéostasie cellulaire et tissulaire ?

Les enjeux

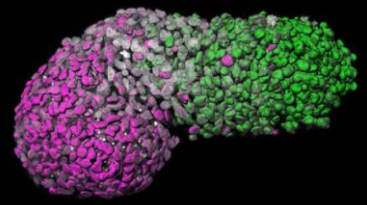




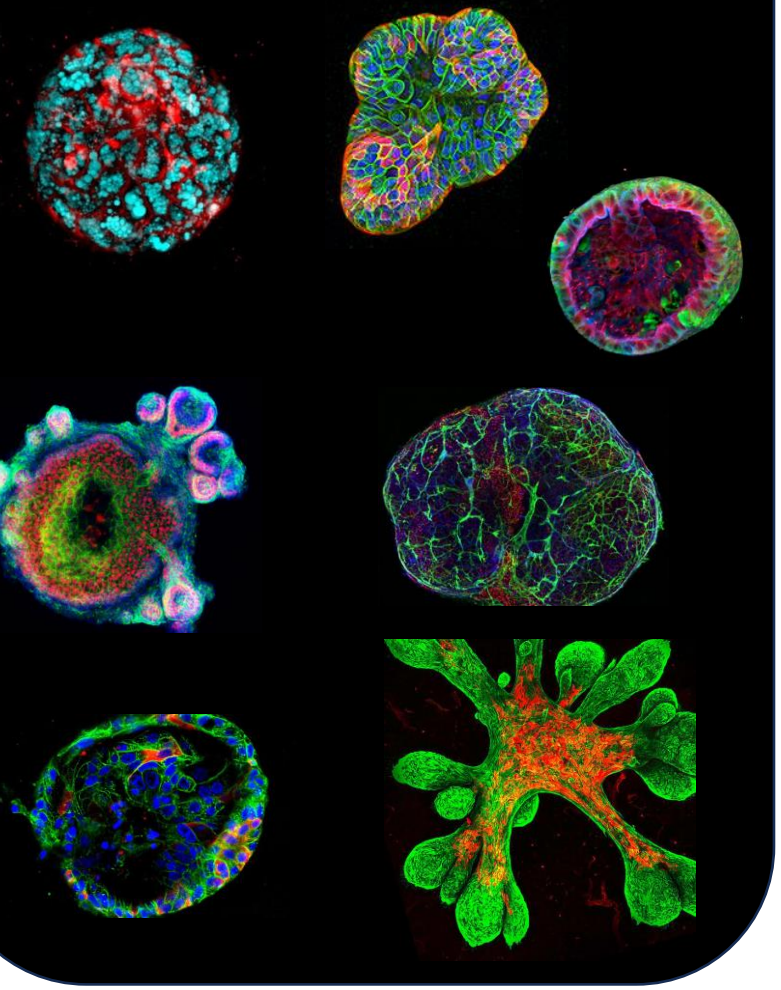
Modèles d'embryons basés sur les cellules souches

- blastoides

- gastruloides



Organoides



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UMR 7216 Epigenetics & Cell Fate

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BiBs: Bioinformatics and Biostatistics

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Pierre **SAVATIER**
Irene **ASKOI**
Cloé **ROGNARD**

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