

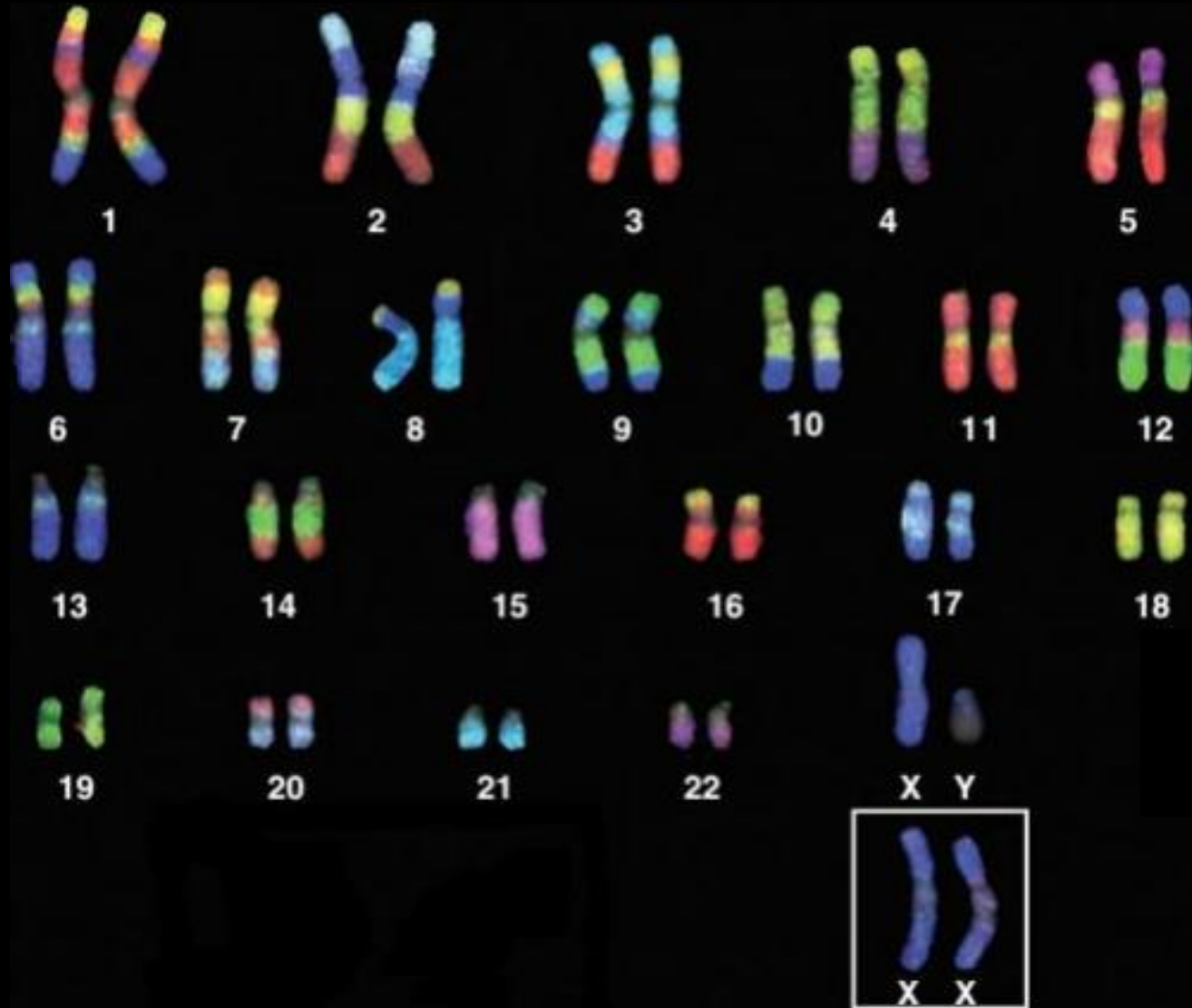
# Le chromosome X dans tous ses états

[claire.rougeulle@u-paris.fr](mailto:claire.rougeulle@u-paris.fr)

Image from Carolyn Brown, University of British Columbia

# Les chromosomes sexuels

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# Les chromosomes sexuels

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*Le Monde*  
SCIENCES · BIOLOGIE

## Le chromosome Y enfin déchiffré et toujours si intrigant

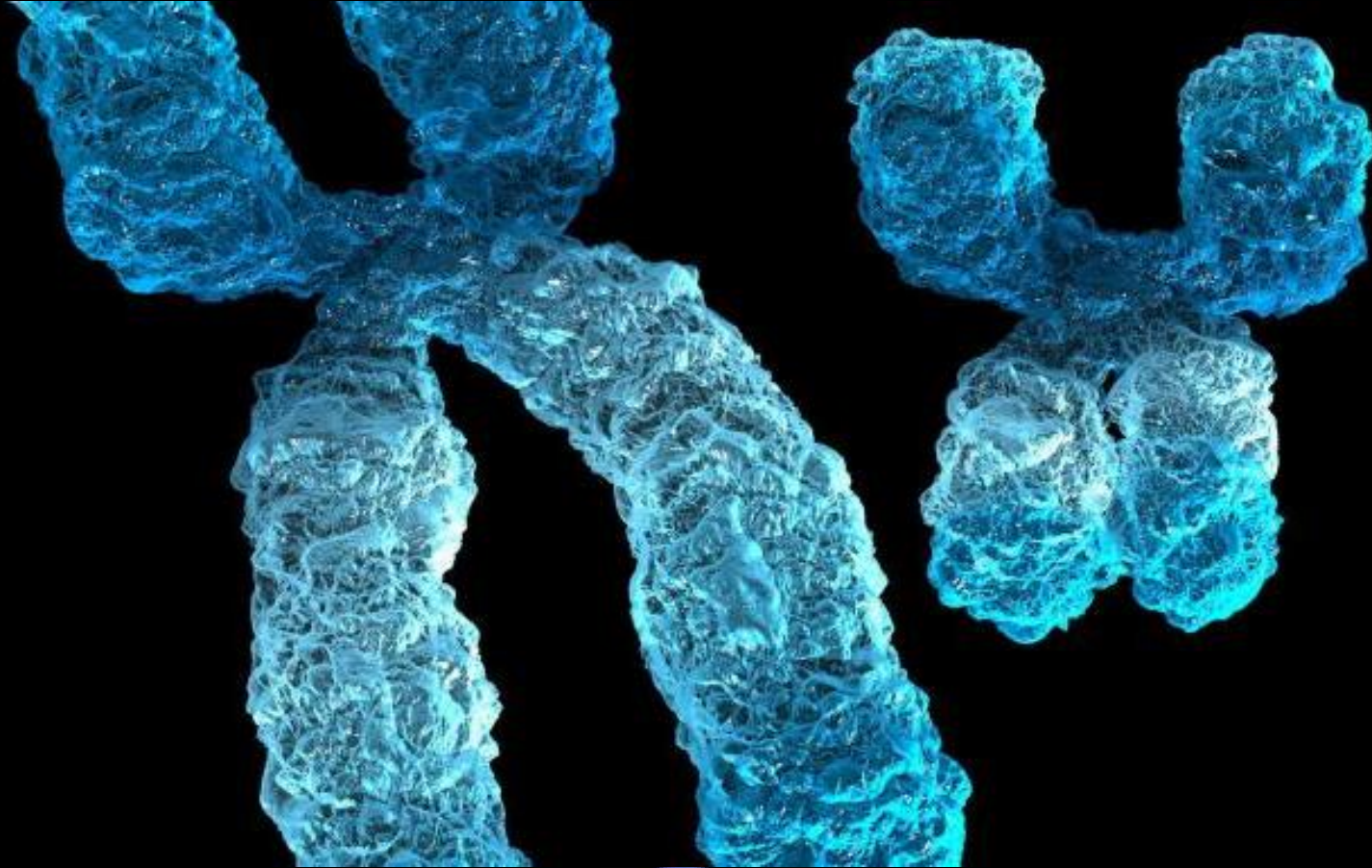
Par Florence Rosier

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



# Les chromosomes sexuels

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X Y

# Evolution des chromosomes sexuels

# X

153 million base pairs

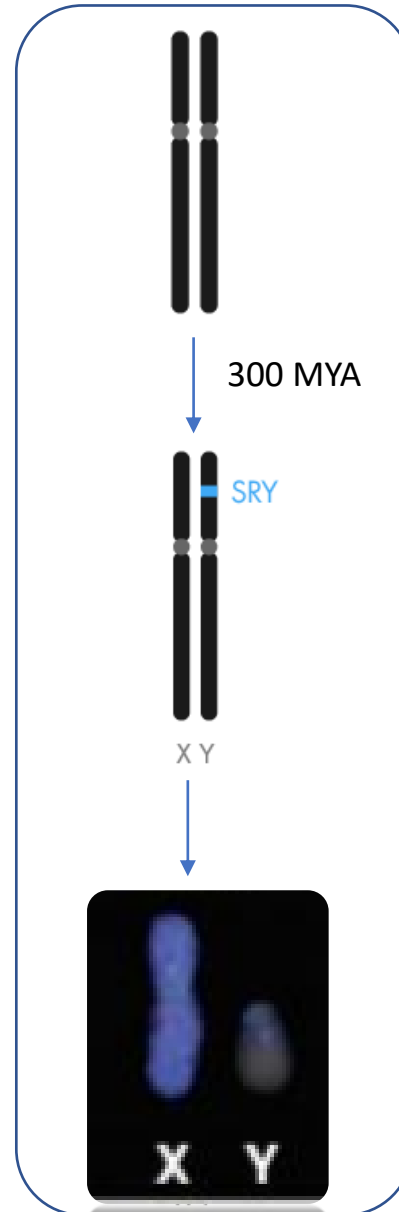
~ 867 gènes codants



# Y

50 million base pairs

~ 106 gènes codants



## Legend

- Regions reflecting the unique patterns of light and dark bands seen on human chromosomes 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 hétéromorphes

# X

153 million base pairs



~867 gènes codants

- Short stature, idiopathic familial
- Leri-Weill dyschondrosteosis
- Langer mesomelic dysplasia
- Kernia, acute myeloid, M2 type
- Chondrodysplasia punctata
- Albinism syndrome
- Kettleship-Falls type
- Acial-digital syndrome
- Nance-Horan cataract-dental syndrome
- Heterocellular hereditary persistence of fetal hemoglobin
- Pyruvate dehydrogenase deficiency
- Glycogen storage disease
- Coffin-Lowry syndrome
- Mental retardation
- Spondyloepiphyseal dysplasia tarda
- Paroxysmal nocturnal hemoglobinuria
- Infantile spasms syndrome
- Aicardi syndrome
- Deafness, sensorineural
- Simpson-Golabi-Behmel syndrome, type 2
- Adrenal hypoplasia, congenital
- Dosage-sensitive sex reversal
- Deafness, congenital sensorineural
- Retinitis pigmentosa
- Wilson-Turner syndrome
- Cone dystrophy
- Aland island eye disease (ocular albinism)
- Optic atrophy
- Night blindness, congenital stationary, type 1
- Erythroid-potentiating activity
- Arthrogyposis multiplex congenita
- Night blindness, congenital stationary, type 2
- Brunner syndrome
- Wiskott-Aldrich syndrome
- Thrombocytopenia
- Dent disease
- Nephrolithiasis, type I
- Hypophosphatemia, type III
- Proteinuria
- Anemia, sideroblastic/hypochromic
- Cerebellar ataxia
- Renal cell carcinoma, papillary
- Diabetes mellitus, insulin-dependent
- Sutherland-Haas syndrome
- Cognitive function, social
- Mental retardation, nonspecific
- Menkes disease
- Occipital horn syndrome
- Curtis laxa, neonatal
- FG syndrome
- Immunodeficiency, moderate and severe
- Miles-Carpenter syndrome
- Charcot-Marie-Tooth neuropathy, dominant
- Mental retardation
- X-inactivation center
- Premature ovarian failure
- Arts syndrome
- Cleft palate and/or ankyloglossia
- Megalocornea
- Epilepsy (Juberg-Hellman syndrome)
- Pelizaeus-Merzbacher disease
- Spastic paraplegia
- Alport syndrome
- Cowchock syndrome
- Hypertrichosis, congenital generalized
- Prosis, hereditary congenital
- Apoptosis inhibitor
- Panhypopituitarism
- Thoracoabdominal syndrome
- Simpson-Golabi-Behmel syndrome, type 1
- Split hand/foot malformation, type 2
- Hypoparathyroidism
- Mental retardation, Shashi type
- Lesch-Nyhan syndrome
- HPII-related gut
- Lowie syndrome
- Borjeson-Forsman-Lehmann syndrome
- Testicular germ cell tumor
- Hemophilia B
- Warfarin sensitivity
- Osseous dysplasia (male lethal), digital
- Adrenoleukodystrophy
- Adrenomyeloneuropathy
- Colorblindness, blue monochromatic
- Cardiac valvular dysplasia
- Emery-Dreifuss muscular dystrophy
- Heterotopia, periventricular
- Favism
- Hemolytic anemia
- Colorblindness, green cone pigment
- Incontinentia pigmenti, type II
- Hydrocephalus
- MASA syndrome
- Spastic paraplegia
- Rett syndrome
- Mature T-cell proliferation
- Myopia (Bornholm eye disease)
- Mental retardation with psychosis
- Endocardial fibroelastosis

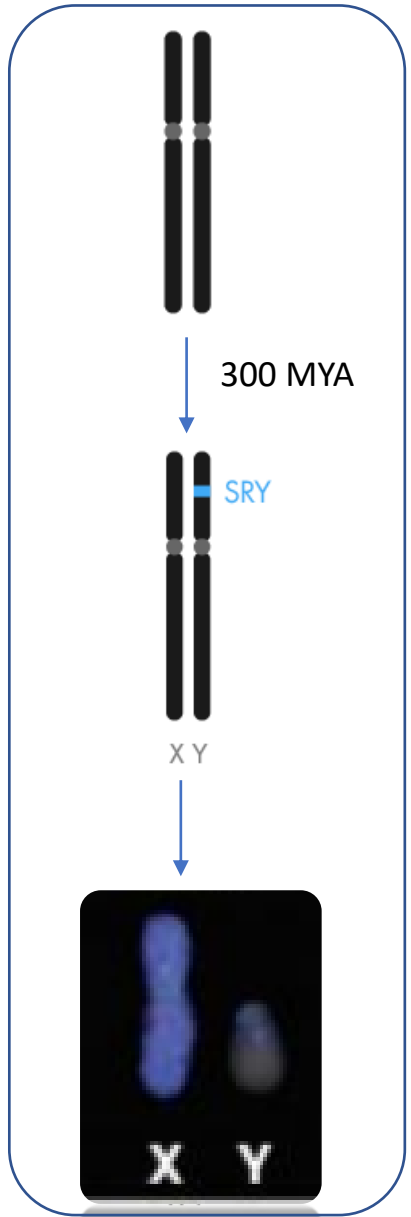
- Hodgkin disease susceptibility, pseudoautosomal
- Ichthyosis
- Microphthalmia, dermal aplasia, and sclerocornea
- Episodic muscle weakness
- Mental retardation
- Ocular albinism and sensorineural deafness
- ~867 gènes codants
- Charcot-Marie-Tooth disease
- Keratosulcus, bilateral, spinulosa
- Hypophosphatemia, hereditary
- Partington syndrome
- Retinosis
- Gonadal dysgenesis, XY female type
- Mental retardation, non-dysmorphic
- Agammaglobulinemia, type 2
- Craniofrontonasal dysplasia
- Opitz G syndrome, type I
- Pigment disorder, reticulate
- Melanoma
- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Cardiomyopathy, dilated
- Chronic granulomatous disease
- Snyder-Robinson mental retardation
- Noxie disease
- Exudative vitreoretinopathy
- Coats disease
- Renpenning syndrome
- Retinitis pigmentosa, recessive
- Mental retardation, nonspecific and syndromic
- Dyserythropoietic anemia with thrombocytopenia
- Chondrodysplasia punctata, dominant
- Autoimmunity-immunodeficiency syndrome
- Renal cell carcinoma, papillary
- Facio-genital dysplasia (Aarskog-Scott syndrome)
- Chorioathetosis with mental retardation
- Sarcoma, synovial
- Prieto syndrome
- Spinal muscular atrophy, lethal infantile
- Migraine, familial typical
- Androgen insensitivity
- Spinal and bulbar muscular atrophy
- Prostate cancer
- Perineal hypospadias
- Breast cancer, male, with Reiterstein syndrome
- Ectodermal dysplasia, anhidrotic
- Alpha-thalassemia/mental retardation
- Juberg-Marsidi syndrome
- Sutherland-Haas syndrome
- Smith-Fineman-Myers syndrome
- Hemolytic anemia
- Myoglobinuria/hemolysis
- Wickauer-Wolff syndrome
- Torsion dystonia-parkinsonism, Filipino type
- Leukemia, myeloid/lymphoid or mixed-lineage
- Anemia, sideroblastic, with ataxia
- Allan-Herndon syndrome
- Deafness
- Choroideremia
- Agammaglobulinemia
- Fabry disease
- Mohr-Tranebjerg syndrome
- Jensen syndrome
- Lissencephaly
- Baxex syndrome
- Mental retardation with growth hormone deficiency
- Mental retardation, South African type
- Lymphoproliferative syndrome
- X inactivation, familial skewed
- Petrigew syndrome
- Gustafson mental retardation syndrome
- Immunodeficiency, with hyper-IgM
- Retinitis pigmentosa
- Wood neuroimmunologic syndrome
- Heterotaxy, visceral
- Albinism-deafness syndrome
- Cone dystrophy, progressive
- Prostate cancer susceptibility
- Fragile X mental retardation
- Epidermolysis bullosa, macular type
- Diabetes insipidus, nephrogenic
- Cancer/testis antigen
- Dyskeratosis
- Hemophilia A
- Hunter syndrome
- Mucopolysaccharidosis
- Intestinal pseudoobstruction, neuronal
- Melanoma antigens
- Mental retardation-skeletal dysplasia
- Myotubular myopathy
- Otopalatodigital syndrome, type I
- Colorblindness, red cone pigment
- Goemanne TKCR syndrome
- Waisman parkinsonism-mental retardation
- Barth syndrome
- Cardiomyopathy, dilated
- Noncompaction of left ventricular myocardium
- Von Hippel-Lindau binding protein

# Y

50 million base pairs



~ 106 gènes codants



## Legend

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# Déséquilibre de dose

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# L'inactivation du chromosome X

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

372

NATURE

April 22, 1961 VOL. 190

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 *L. holstani*.

From *L. holstani* the isolate has so far been transmitted to tobacco (varieties White Burley and Samsun) and to *Petunia*, by sap and by *Myzodas persicae*; to *Nicotiana glutinosa*, *Datura stramonium*, *Vigna sinensis* and *L. 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 *L. holstani*, is higher than in the transmission from *L. 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.

<sup>1</sup> 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<sup>1</sup> 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 heteropyknotic 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<sup>2</sup> 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<sup>3,4</sup>, brindled<sup>5</sup>, tortoiseshell<sup>6</sup>, dappled<sup>6</sup>, and 26K<sup>7</sup>. 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<sup>8,9</sup>.

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<sup>9</sup> reported that the black regions of the coat of heterozygotes had a hair structure resembling that of the *Ta* homozygotes 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*<sup>10</sup>, may fit into this category, having 95 per cent penetrance and variable expression in heterozygotes. Jumpy, *jp*, is recessive, suggesting that the presence of some normal cells is enough to ensure a normal phenotype, but Phillips<sup>11</sup> reported one anomalous female which showed the jumpy 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 jumpy 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<sup>12,13</sup>. 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*<sup>14</sup>, and in the opossum, *Didelphis virginiana*<sup>15</sup>. 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



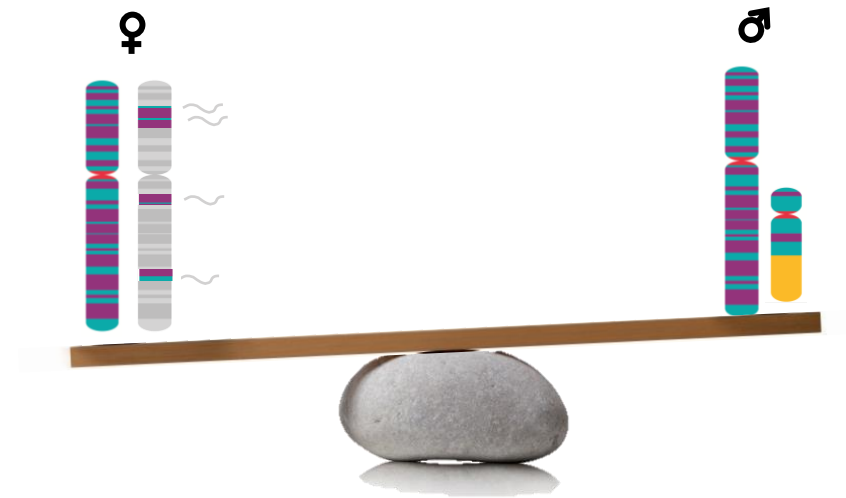
Mary F. Lyon (1925-2014)



# Des gènes « échappent » à l'inactivation

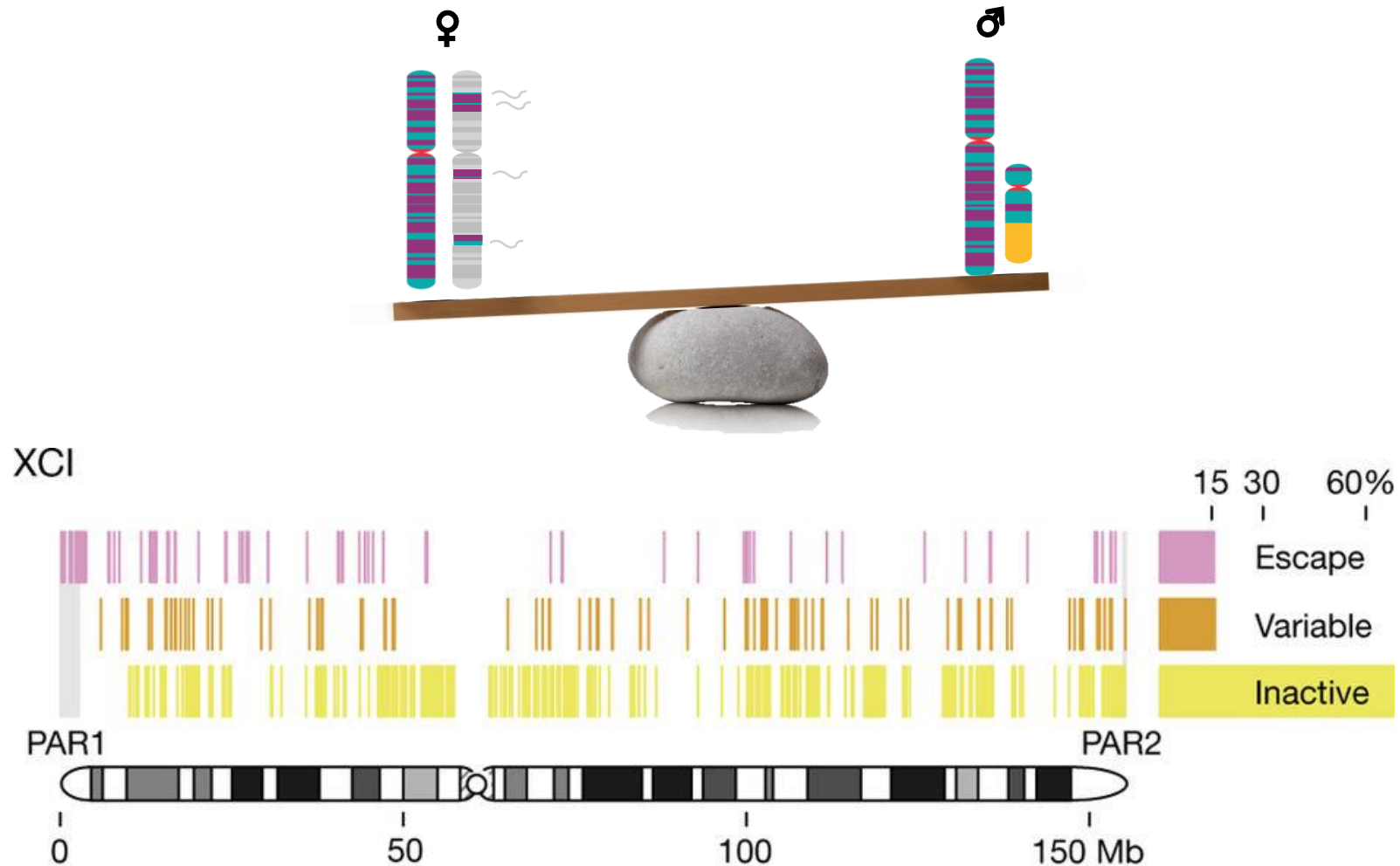
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Un des deux chromosomes X des femelles est majoritairement inactif



# Des gènes « échappent » à l'inactivation

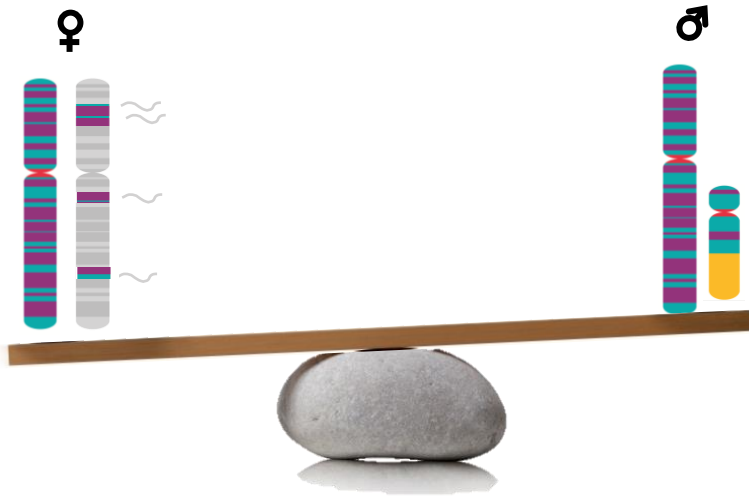
Chez l'humain, ~23% des gènes du chromosome X échappent à l'inactivation



# Un dosage inégal

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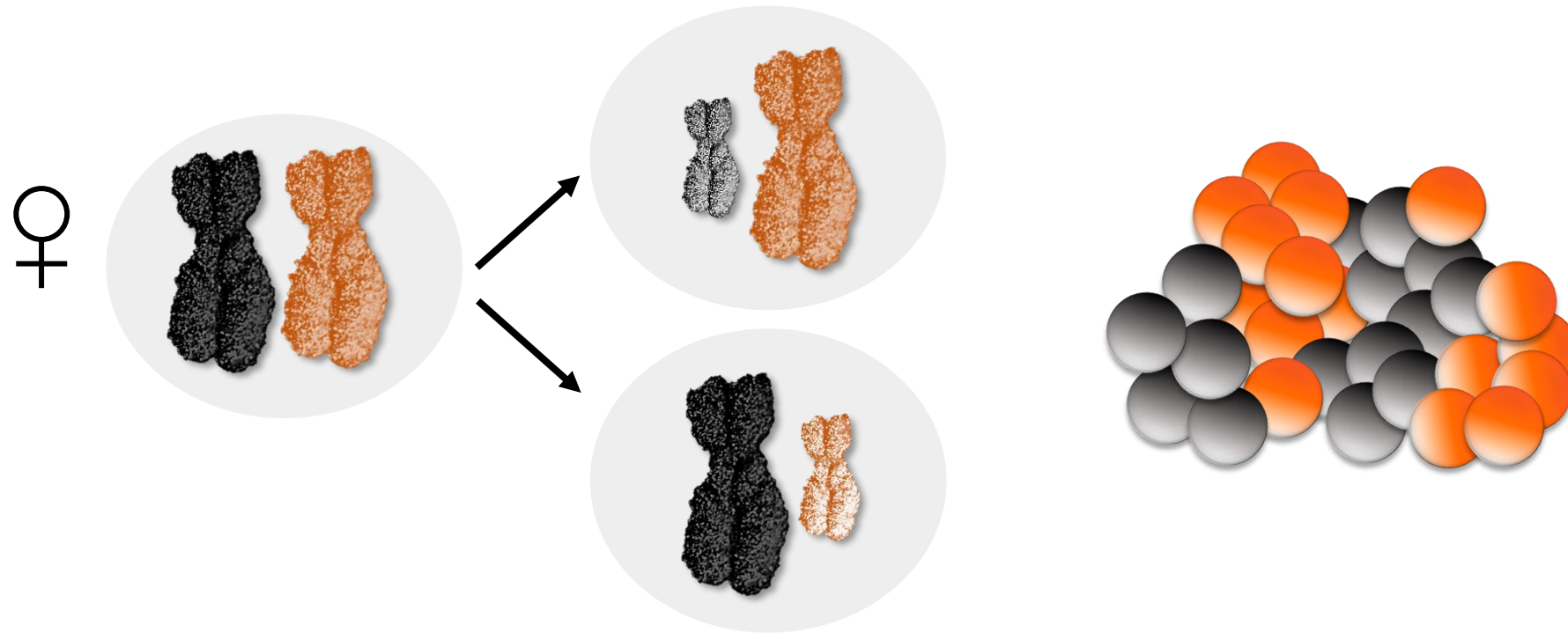
Chez l'humain, ~23% des gènes du chromosome X échappent à l'inactivation



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...

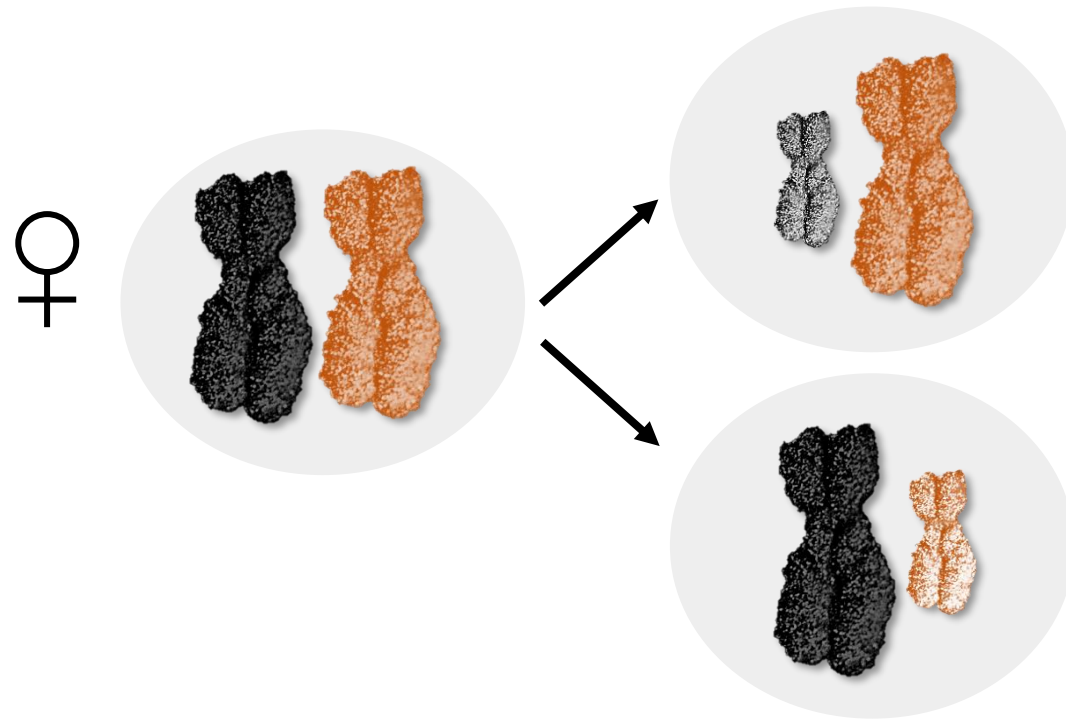
... en fonction du type de cellules, du stade de développement, ...

# L'inactivation touche aléatoirement un X ou l'autre



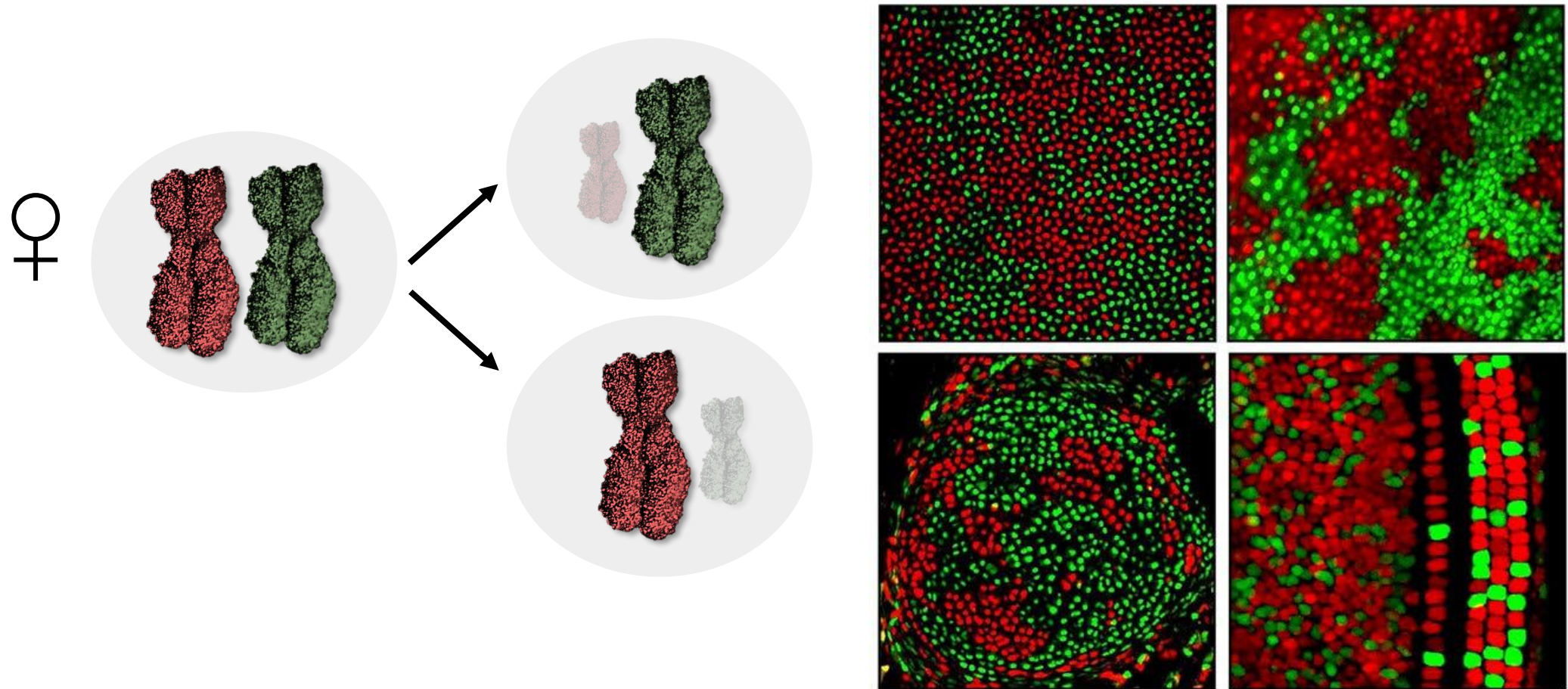


# L'inactivation touche aléatoirement un X ou l'autre



→ Les femelles sont des individus mosaïques

# L'inactivation touche aléatoirement un X ou l'autre

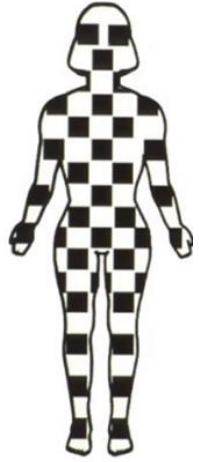


*Wu et al. Neuron 2014*

→ Les femelles sont des individus mosaïques

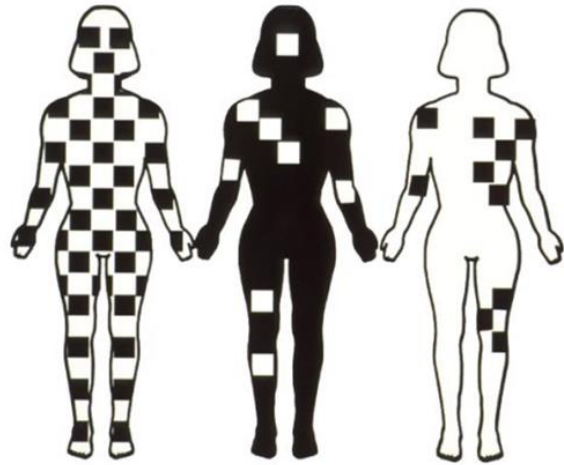
# Mosaïcisme et biais d'inactivation du X

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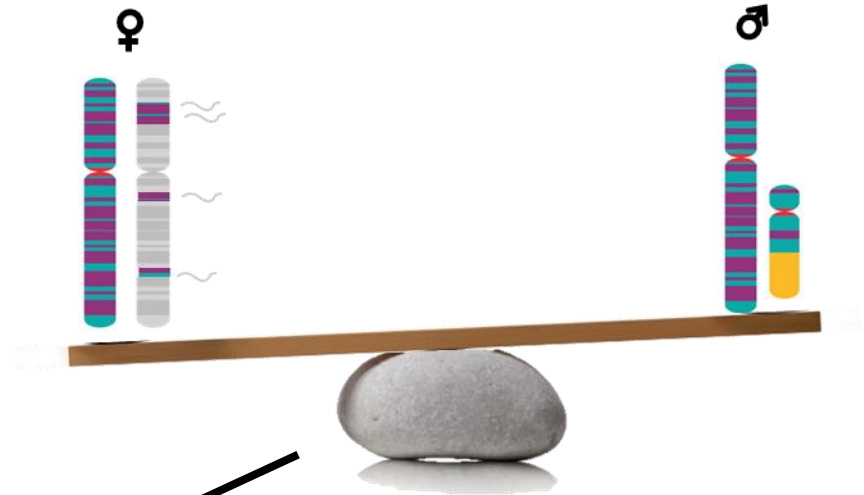
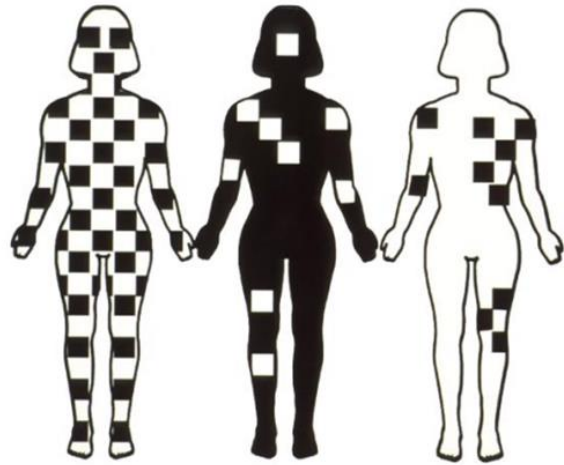
# Mosaicisme et biais d'inactivation du X

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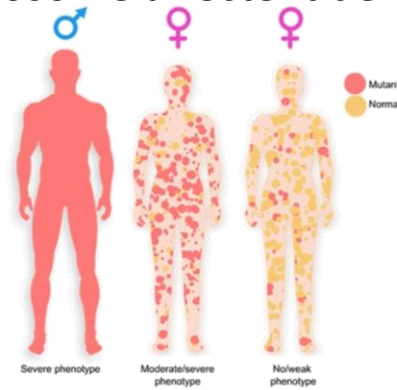




# Inactivation du X et pathologies



Dimorphismes sexuels dans la susceptibilité à différentes pathologies  
> 533 maladies liées au chromosome affectent de manière plus sévère les mâles



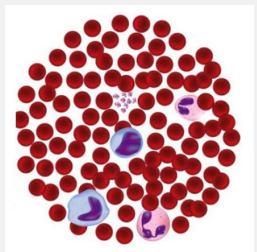
# Femmes et hommes ne sont pas égaux devant les maladies



XX

XY

Autoimmunité	Inflammation chronique	Infection
Maladie de Graves	Arthrite	Ebola
Thyroïdite de Hashimoto	Athérosclérose	Hépatite B
Sclérose en plaques		Tuberculose
Polyarthrite rhumatoïde		Amebiasis
Lupus érythémateux disséminé		Aspergillose
Diabète de type 1		COVID
		...



Neurodegenerative	Neuropsychiatrique	Neurodegenerative	Neuropsychiatrique
Alzheimer	Dépression	Parkinson	TDAH
Démence fronto-temporale	Anxiété	Maladies des motoneurones	Syndrome de Tourette
			Autisme



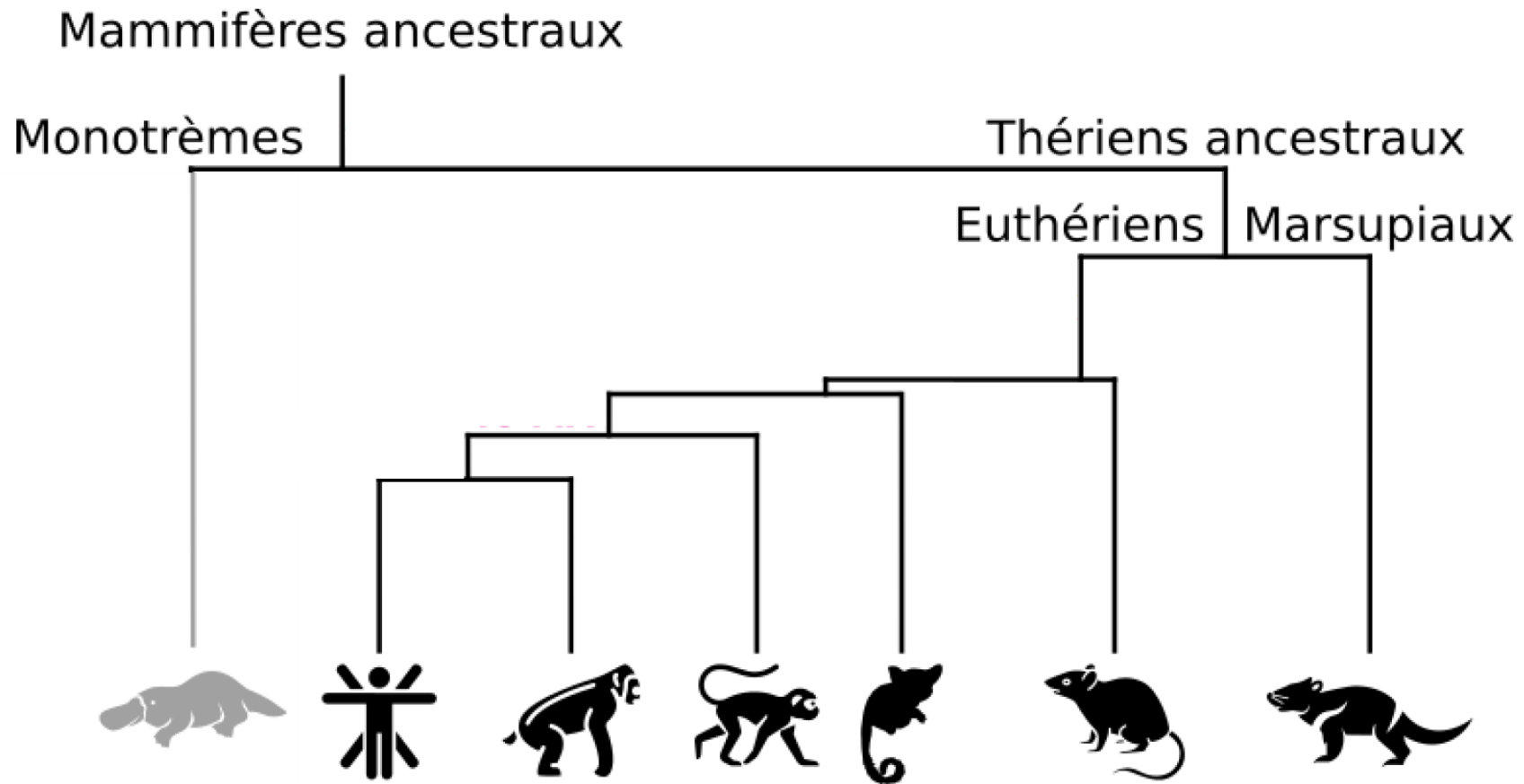
Cancers non liés à la reproduction





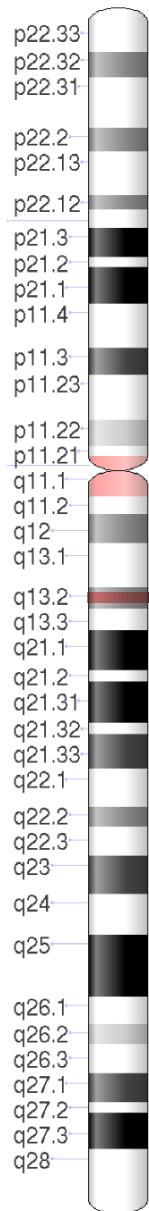
# L'inactivation du X concerne tous les mammifères

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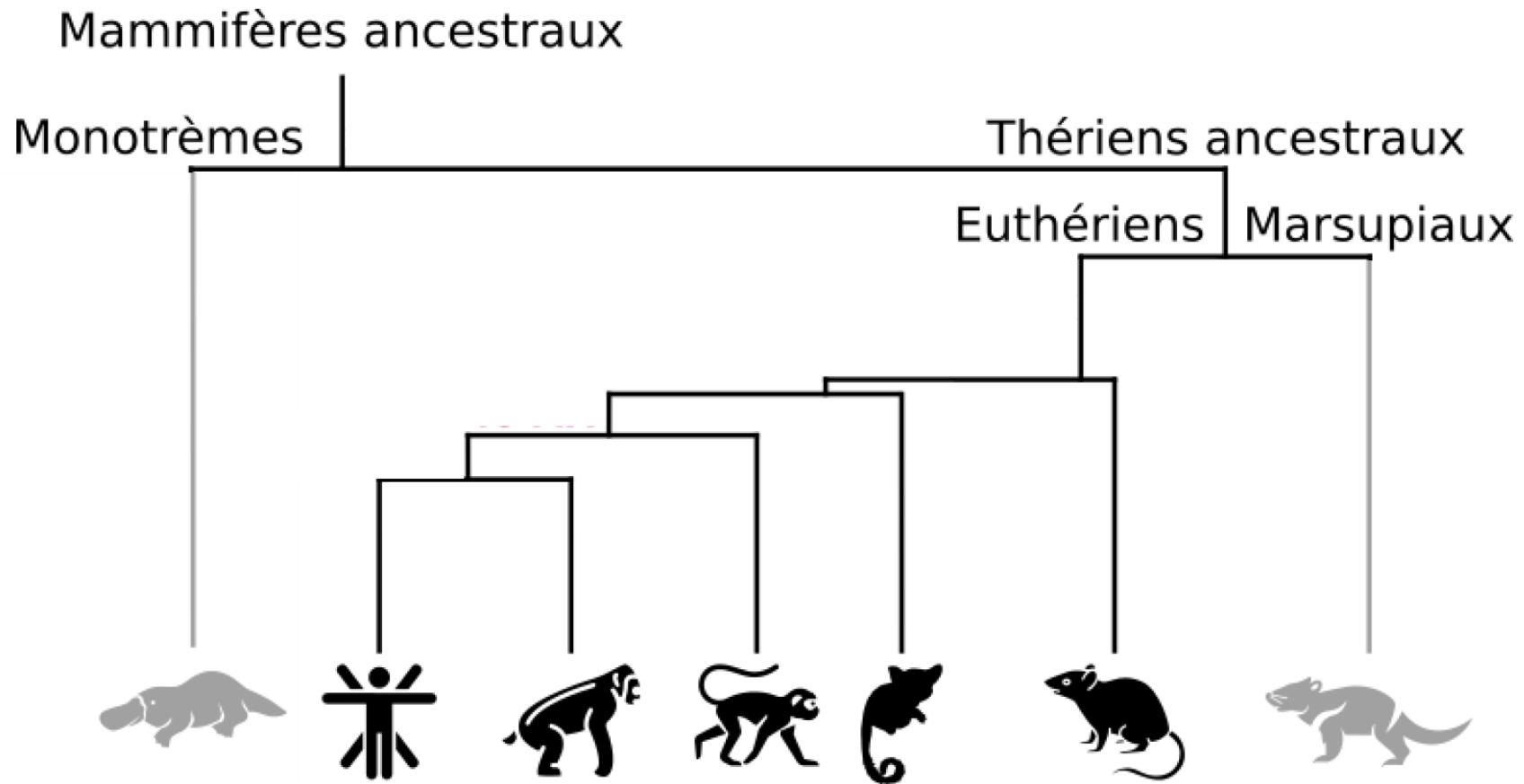




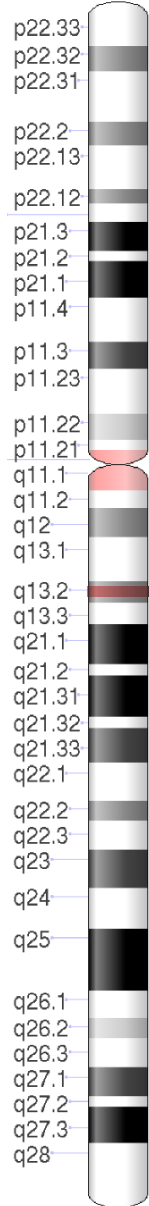
# L'ARN XIST déclenche l'inactivation du X



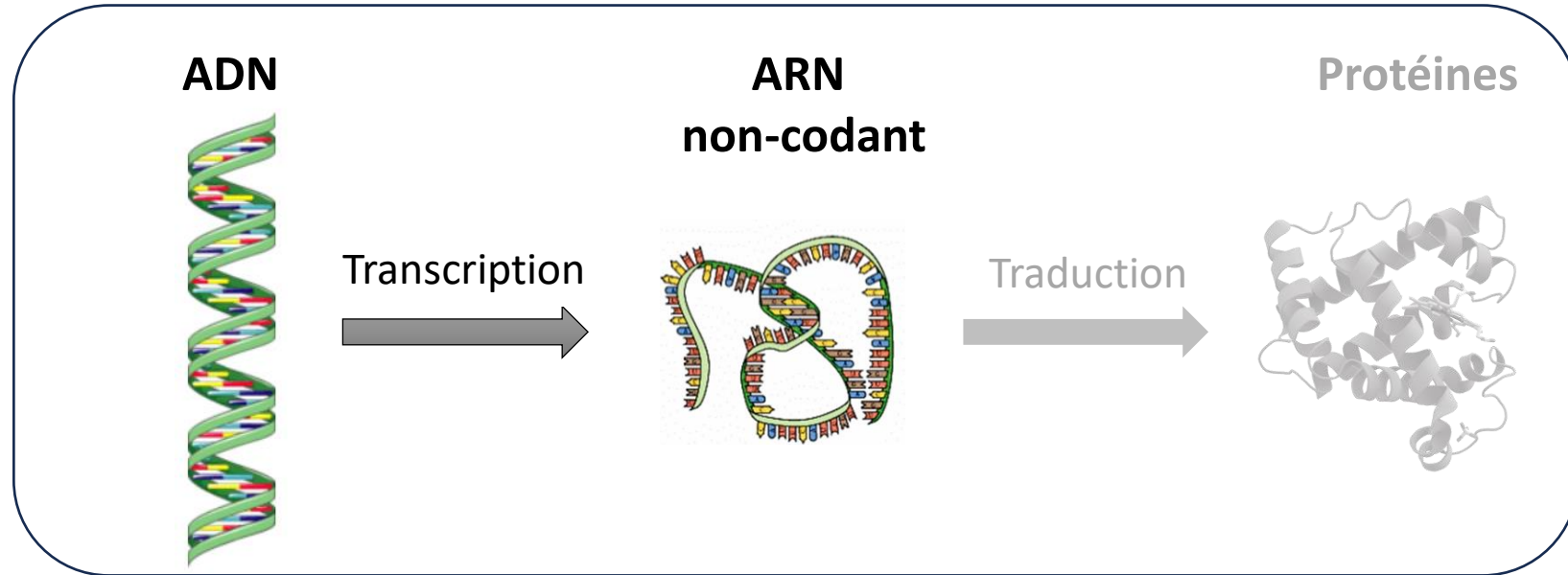
XIST



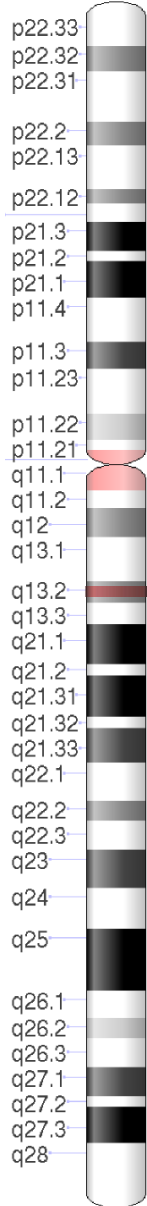
# XIST est un ARN non-codant



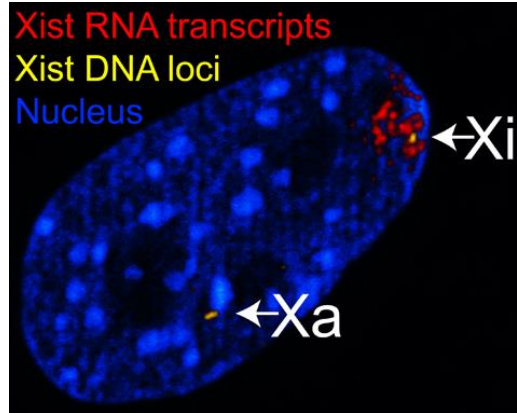
XIST



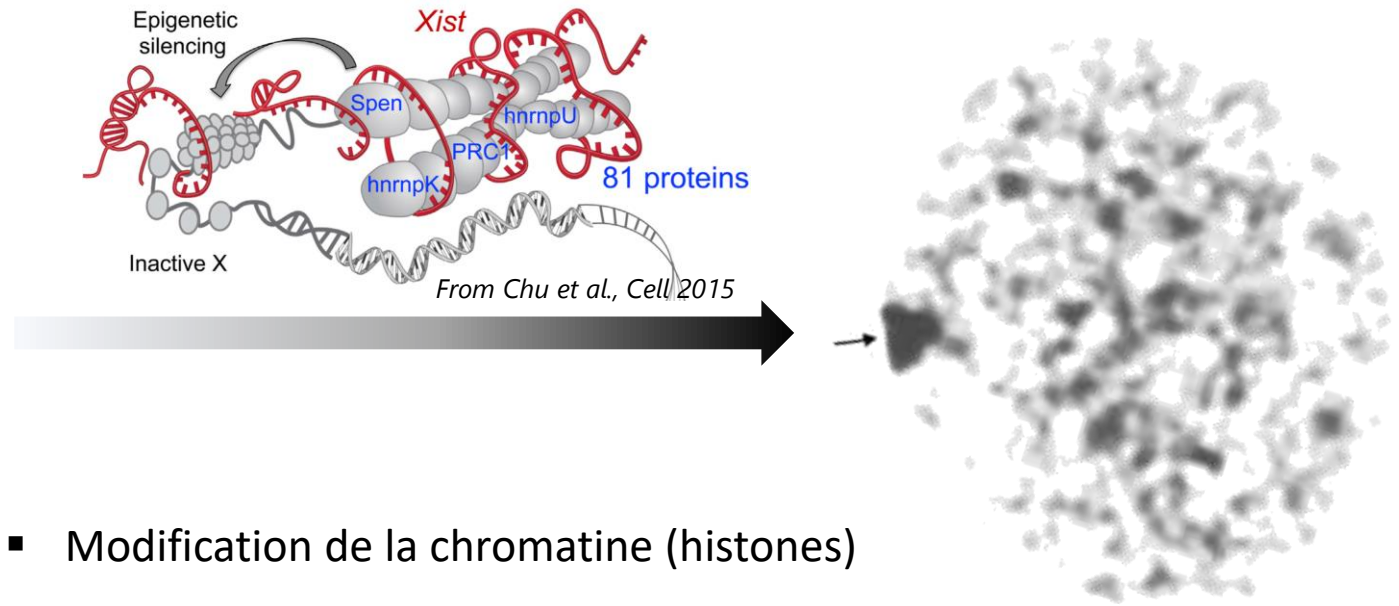
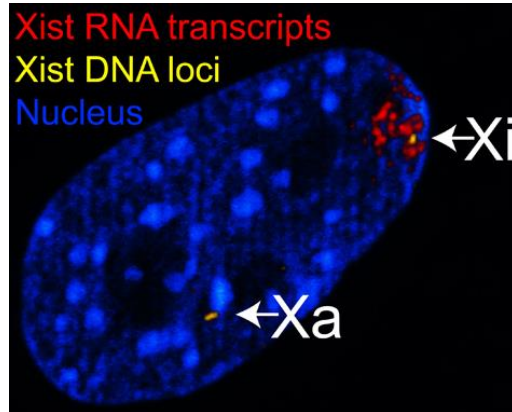
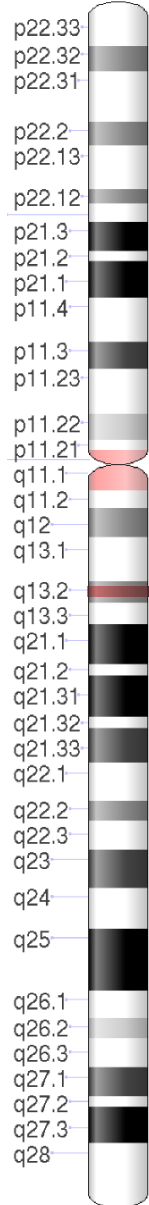
# L'ARN XIST s'accumule autour du chromosome X...



XIST



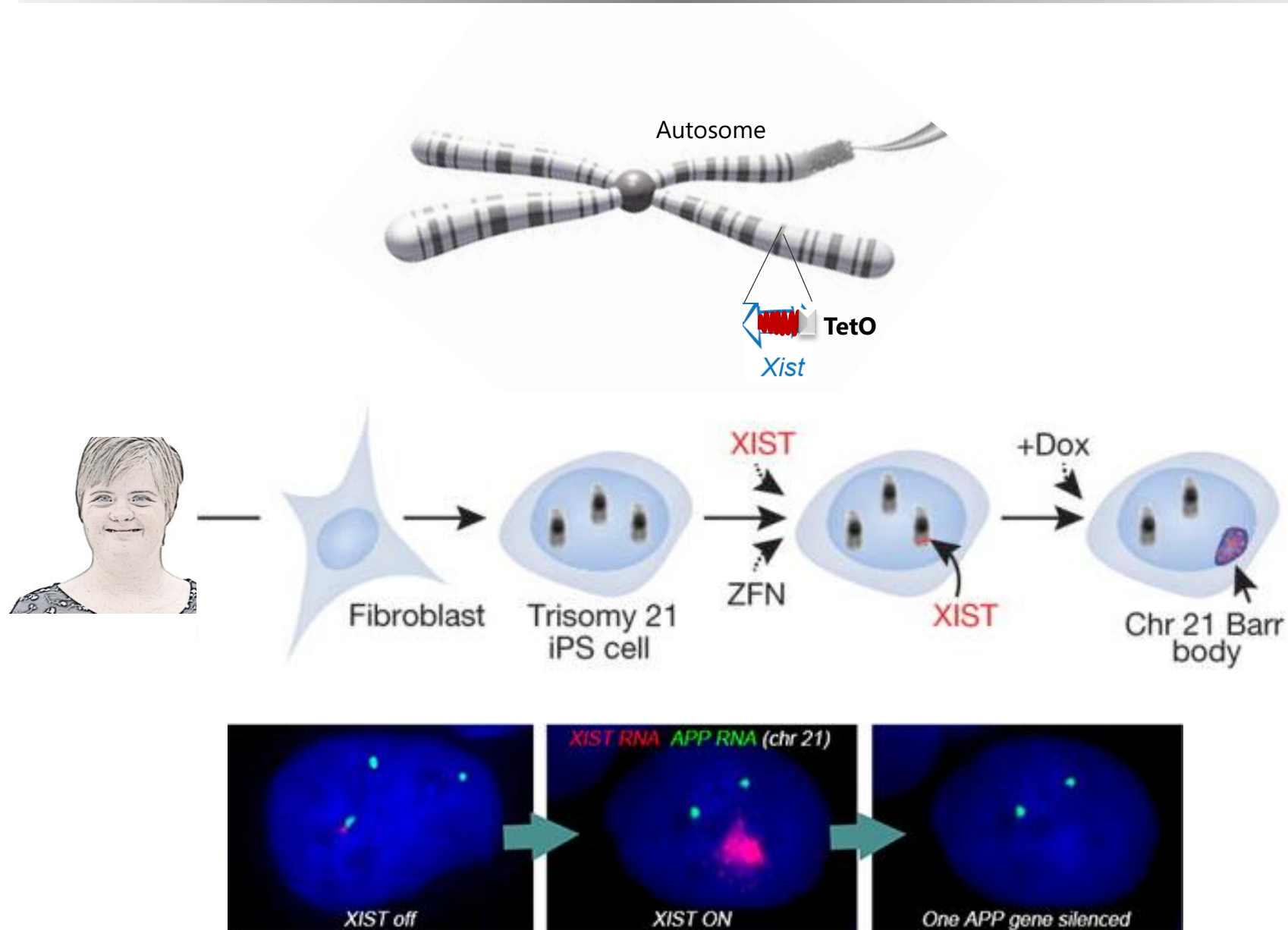
# ... et recrute de multiples facteurs



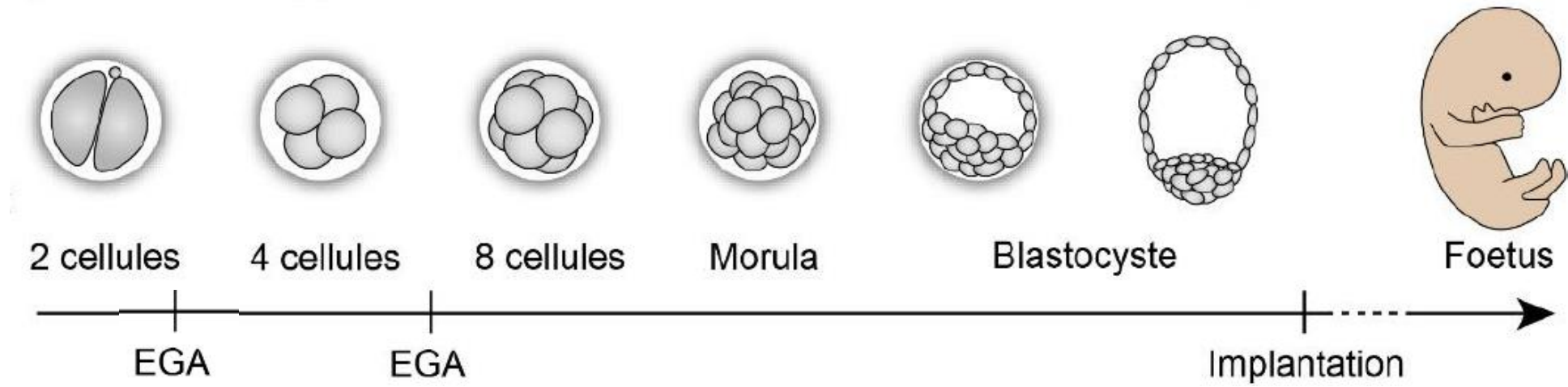
From Chu et al., Cell 2015

- 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



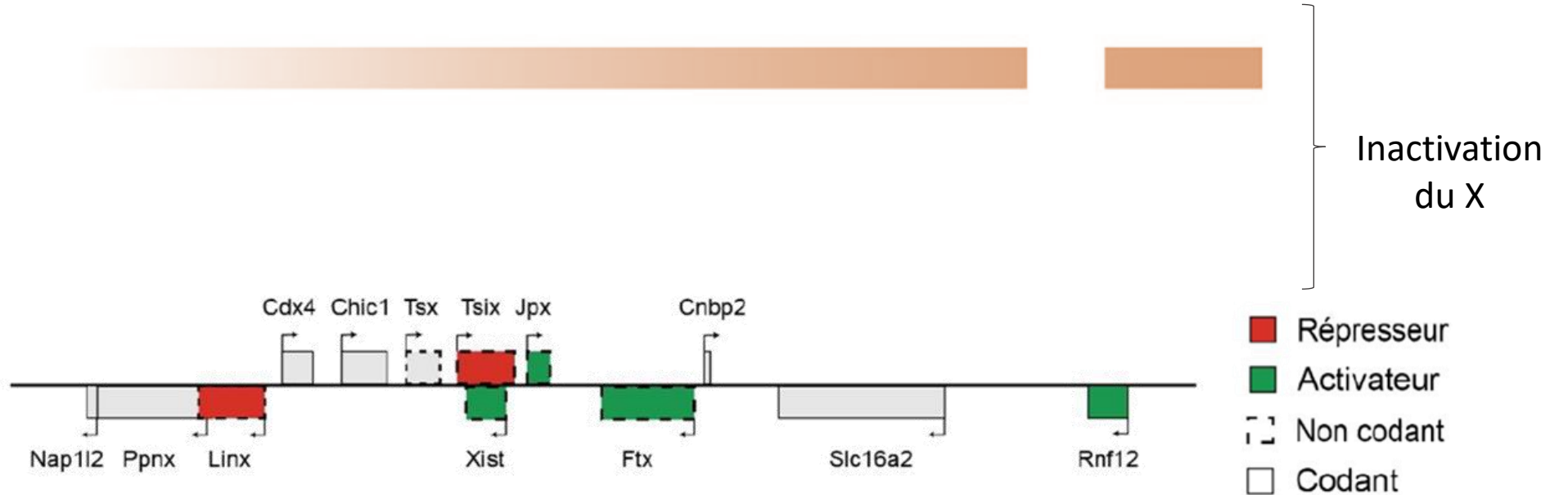
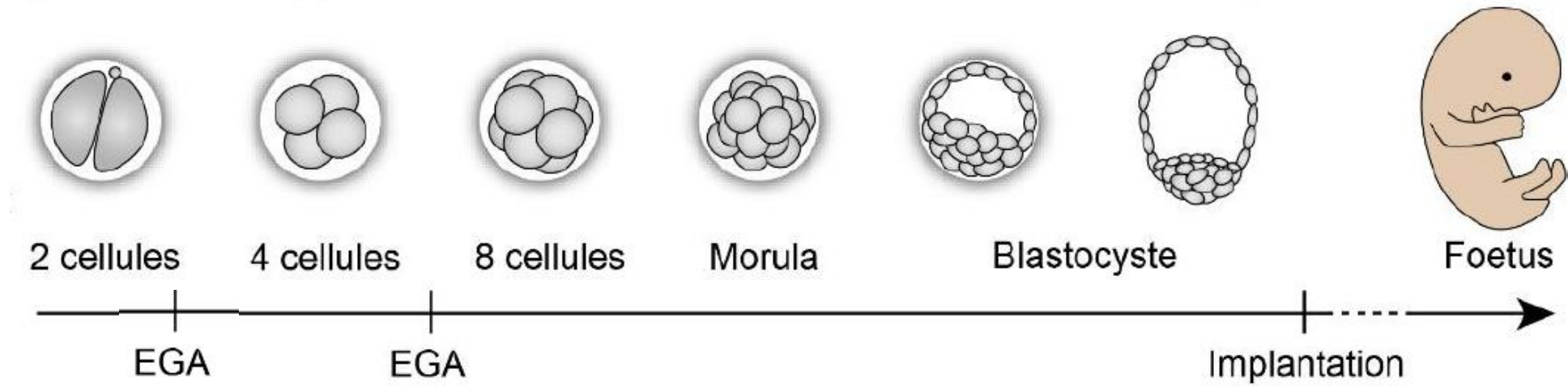
# Inactivation du X et développement embryonnaire



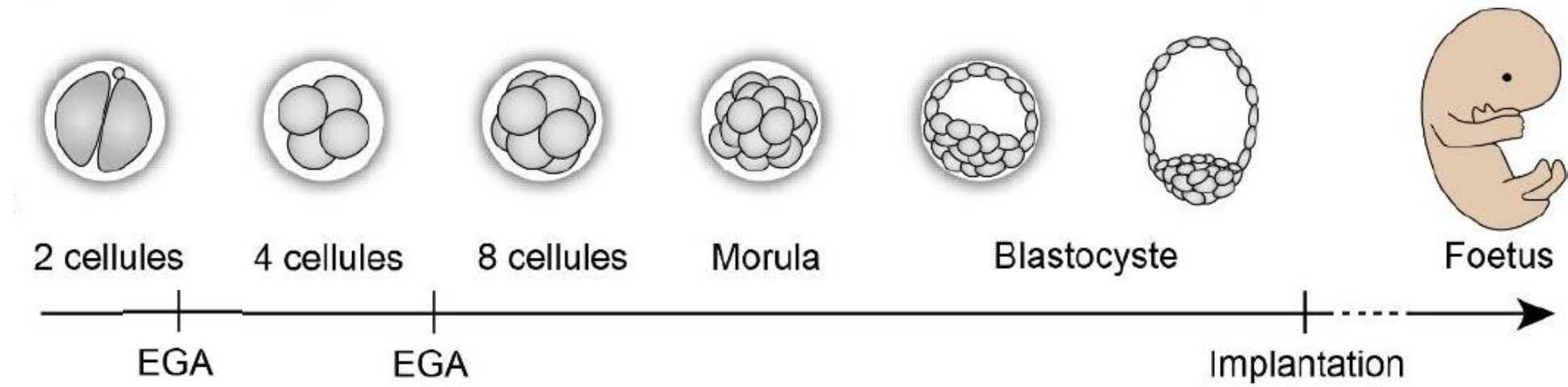
Inactivation  
du X



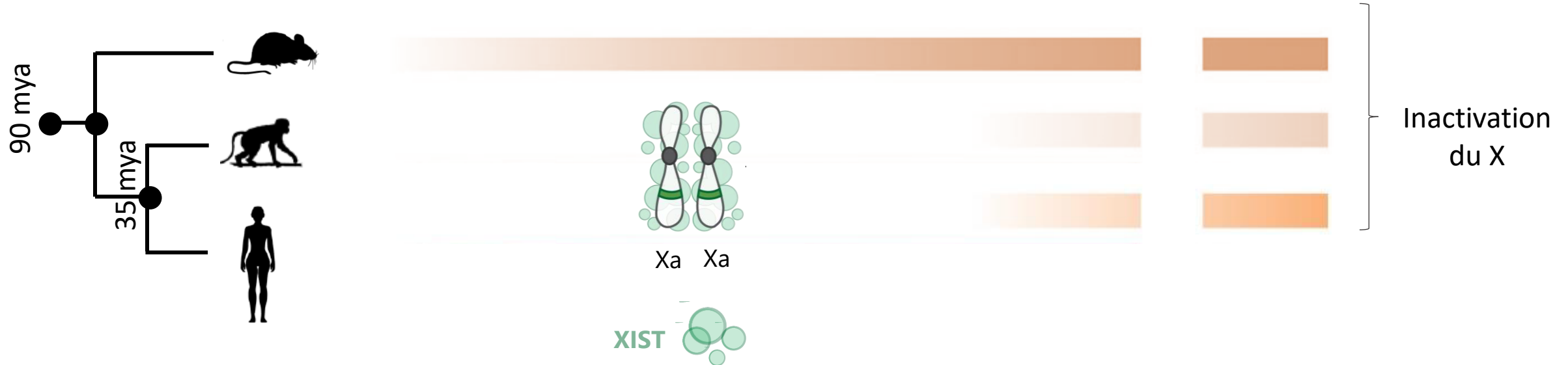
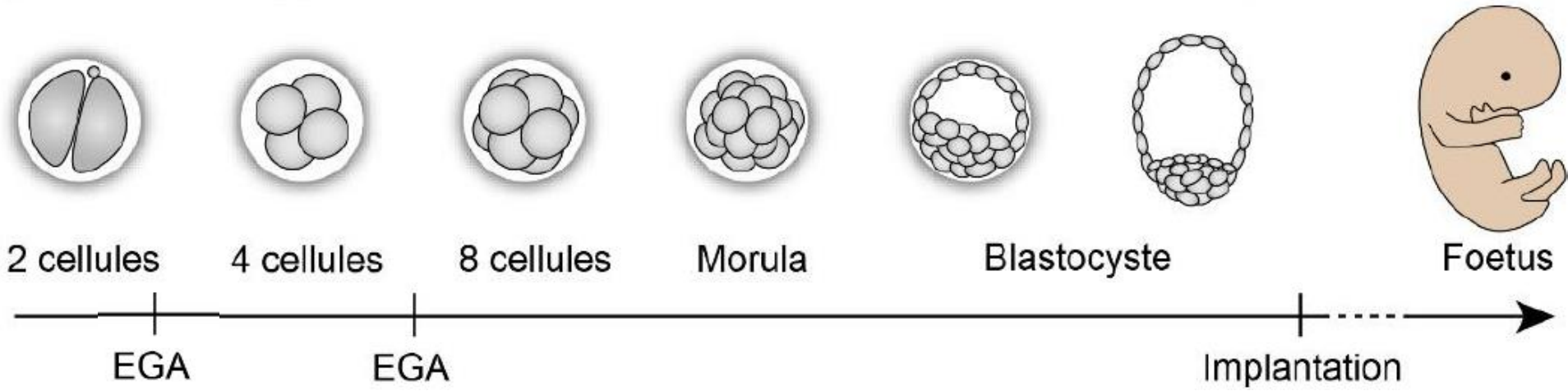
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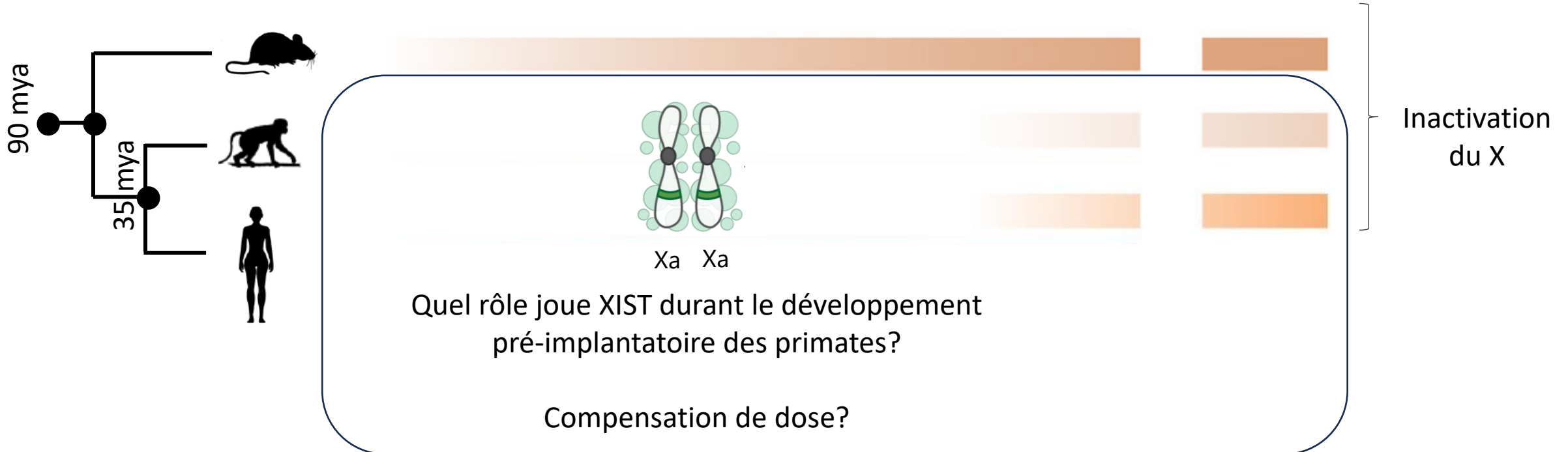
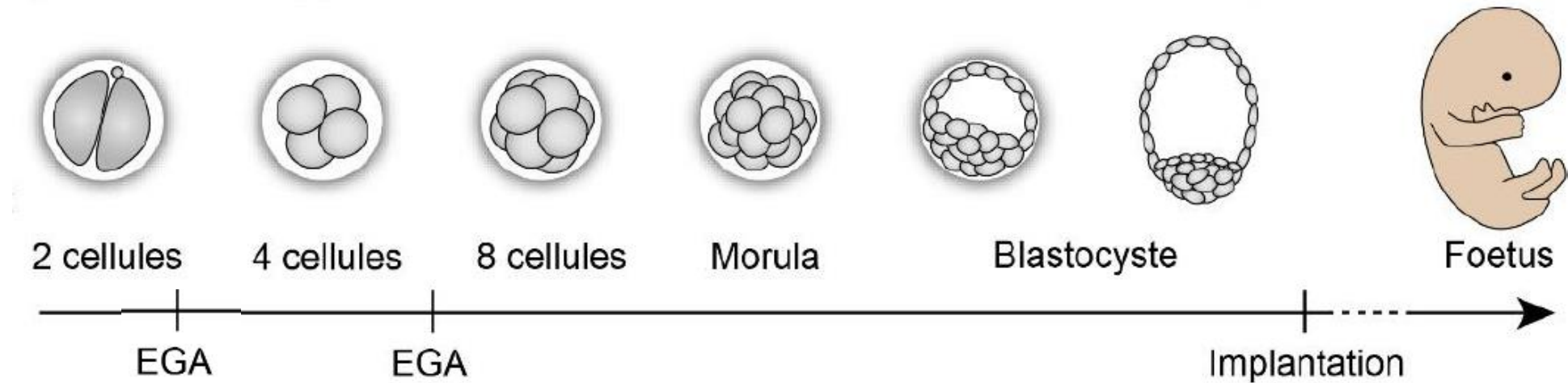
# Inactivation du X et développement embryonnaire



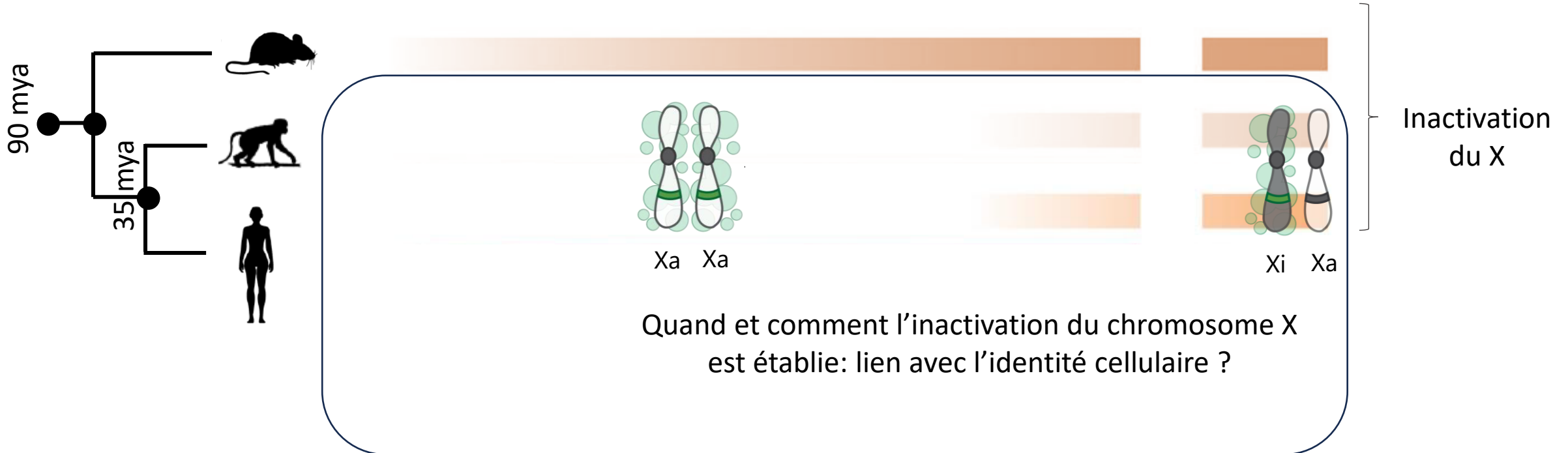
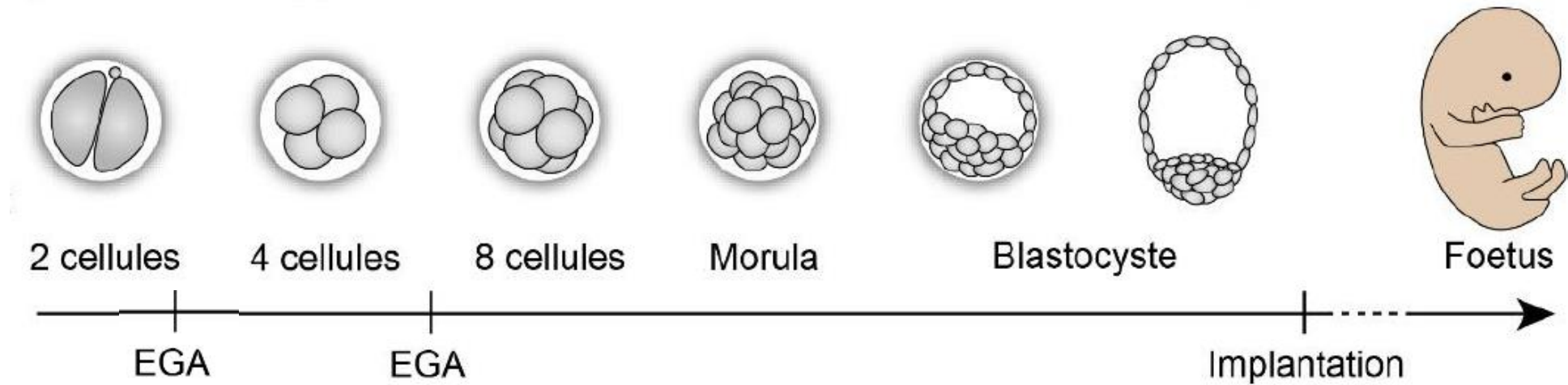
# Inactivation du X et développement embryonnaire



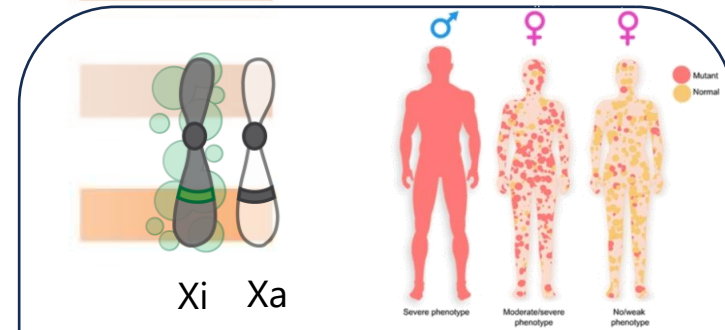
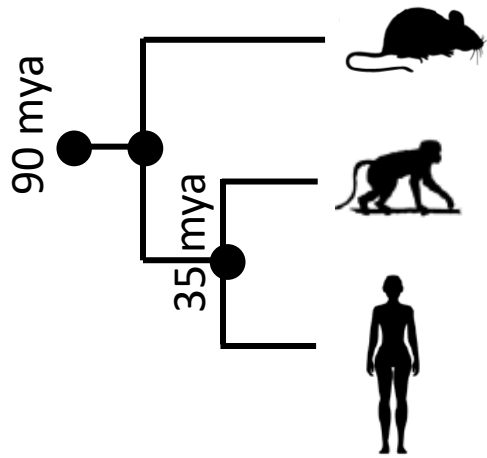
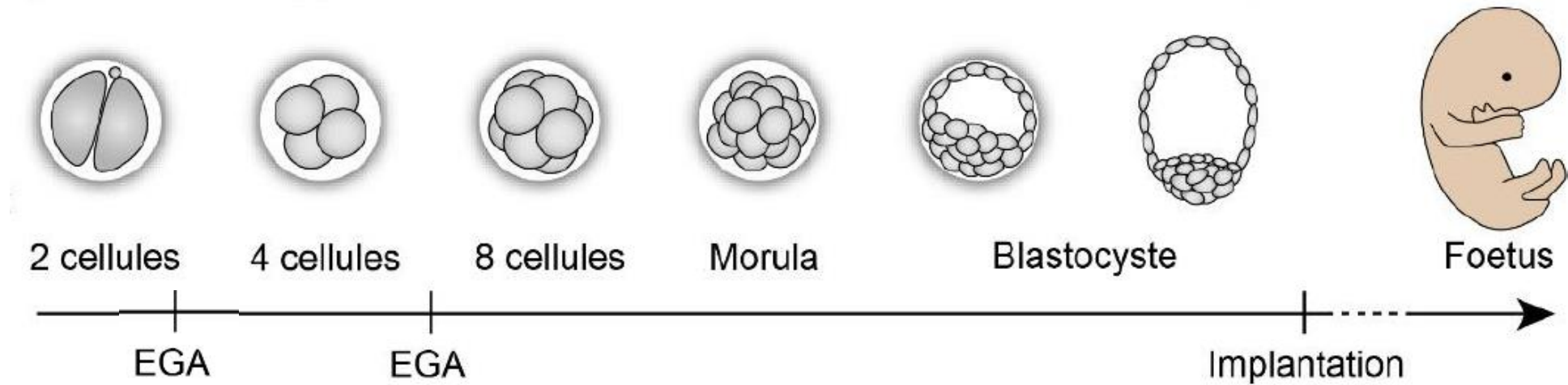
# Inactivation du X et développement embryonnaire



# Inactivation du X et développement embryonnaire



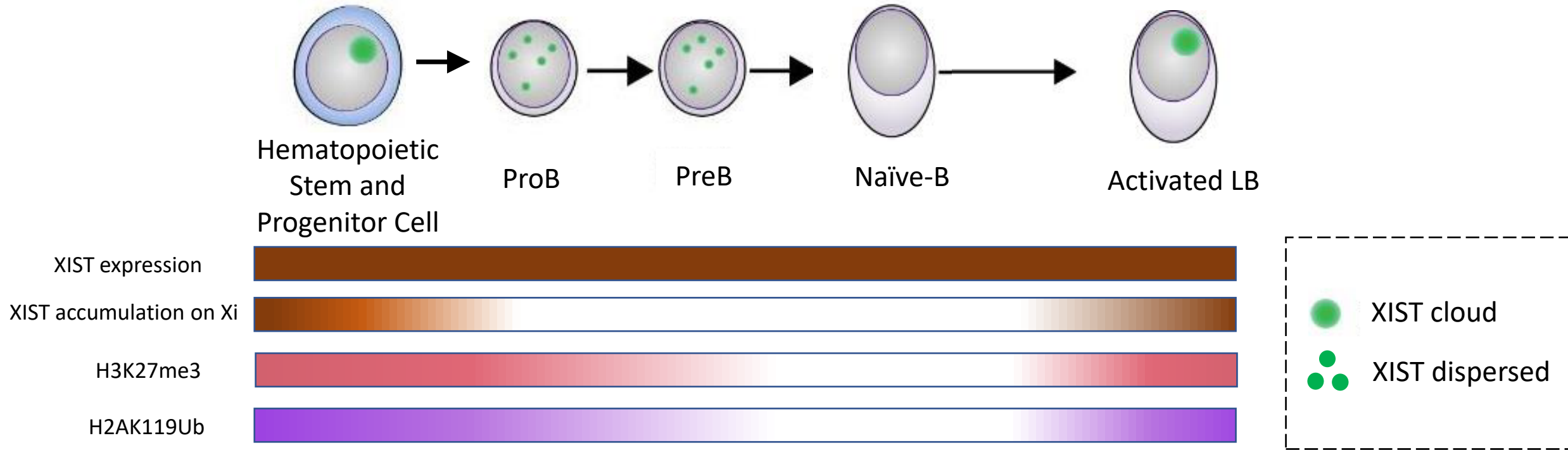
# Inactivation du X et développement embryonnaire



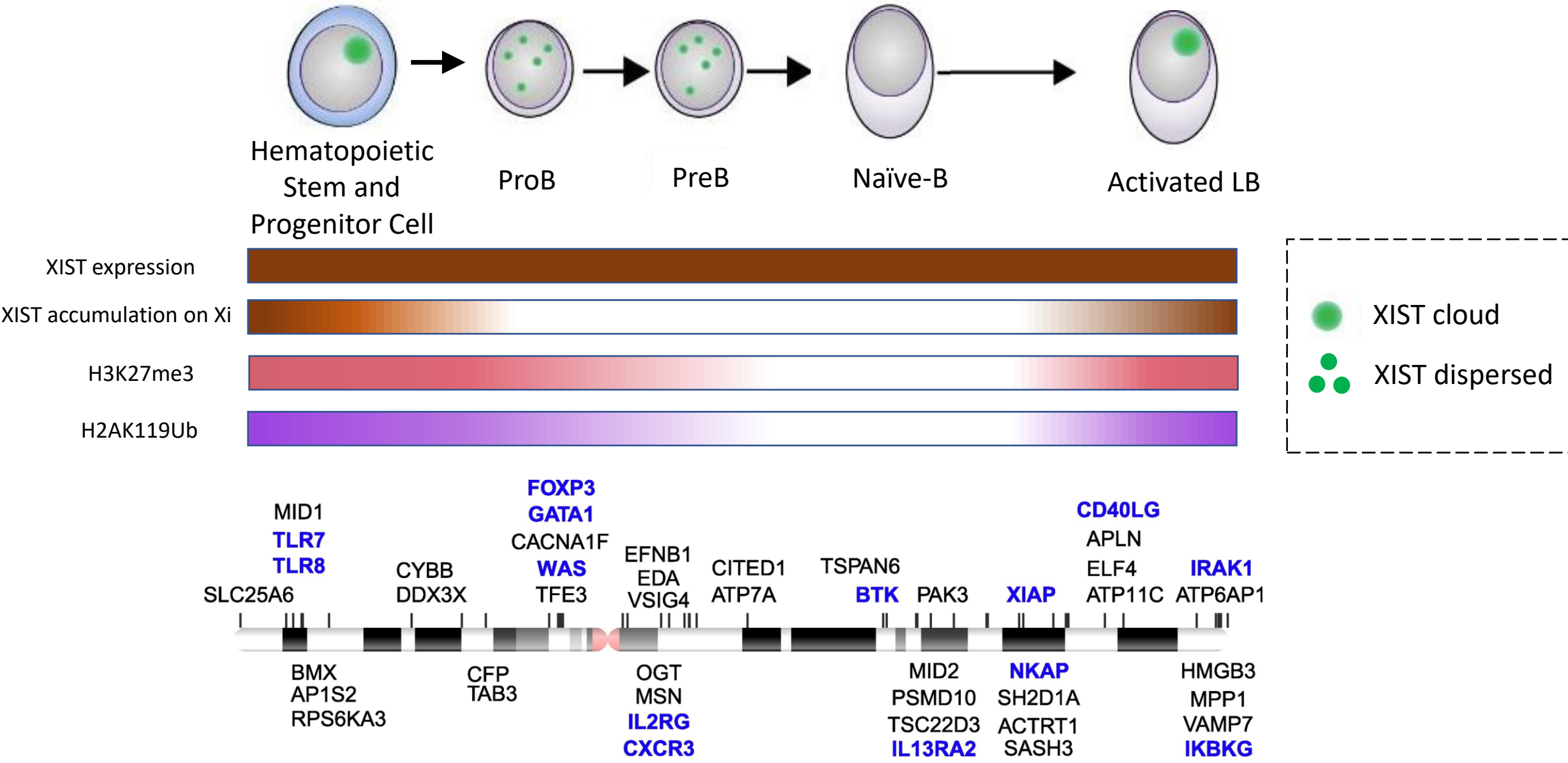
Maintien de l'inactivation dans les différents tissus: dimorphisme sexuel au niveau physiologique et pathologique



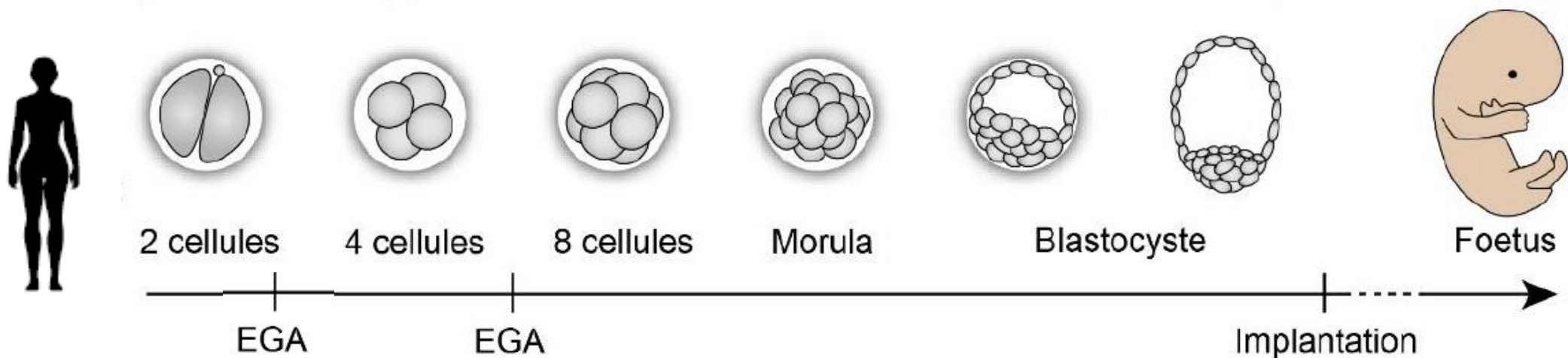
# L'inactivation du X dans le lignage hématopoïétique



# L'inactivation du X dans le lignage hémotopoïétique

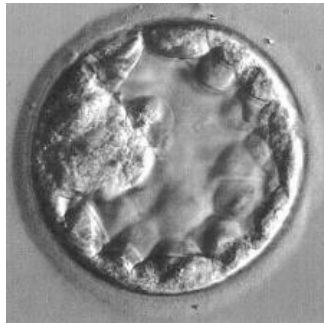
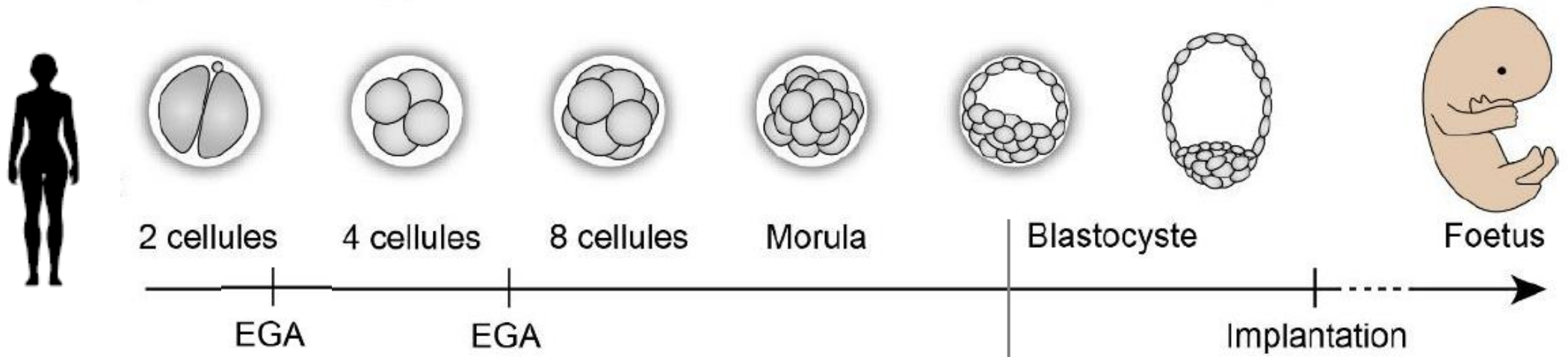


# Les modèles d'étude

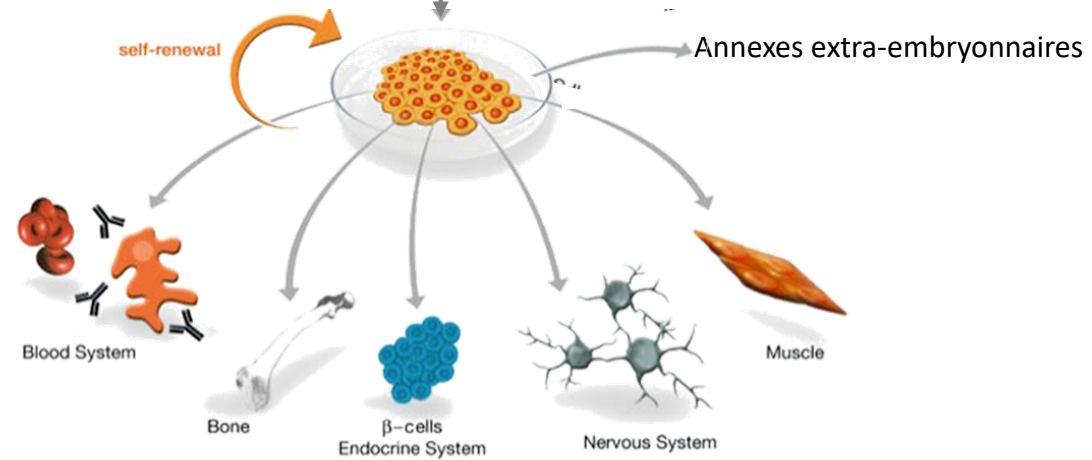


Embryons issus de fécondation *in vitro*  
Donnés à la recherche

# Les modèles d'étude

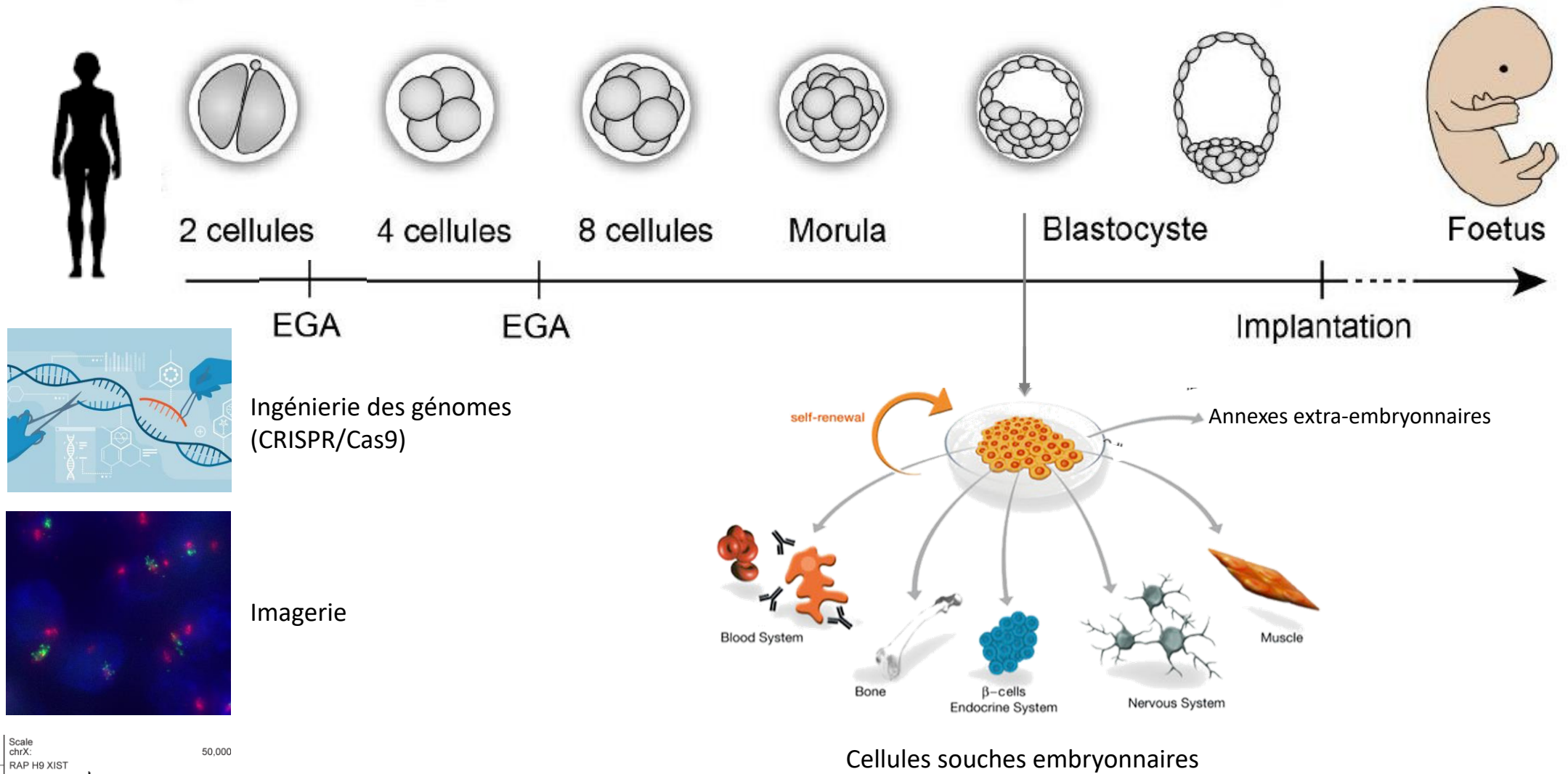


Embryons issus de fécondation *in vitro*  
Donnés à la recherche

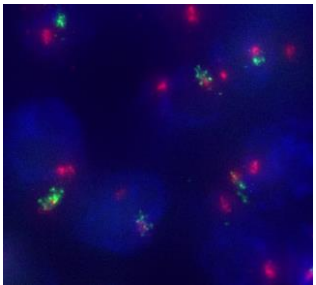


Cellules souches embryonnaires

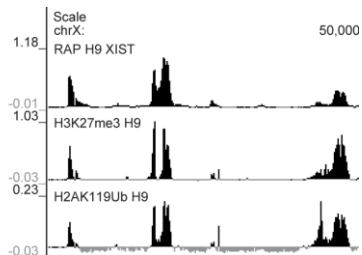
# Les outils et approches



Ingénierie des génomes  
(CRISPR/Cas9)



Imagerie

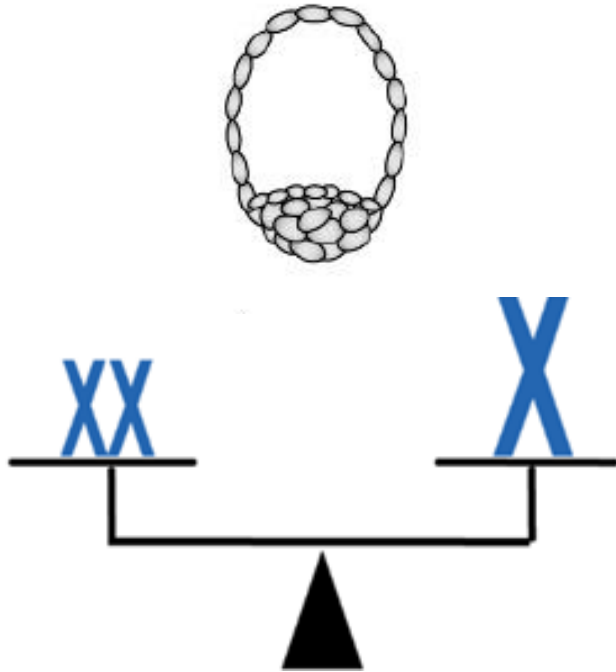


Approches « omiques »

# Nos résultats récents

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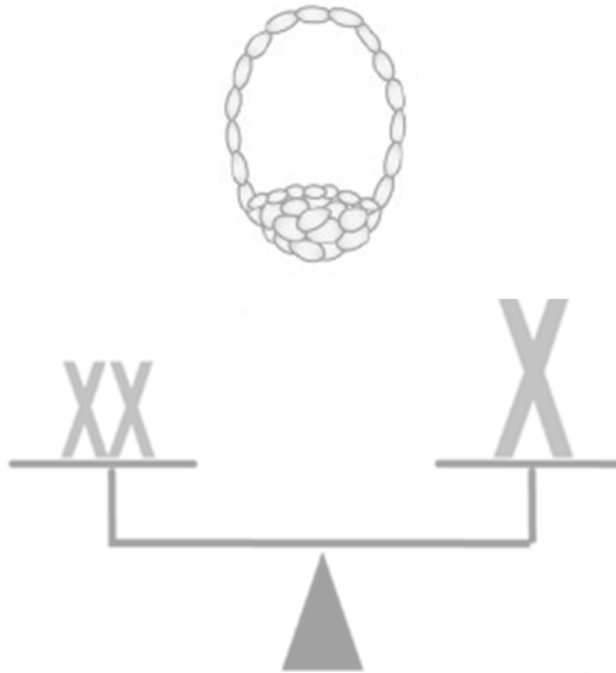
XIST réduit l'expression des 2 chromosomes Xs pendant le développement pré-implantatoire



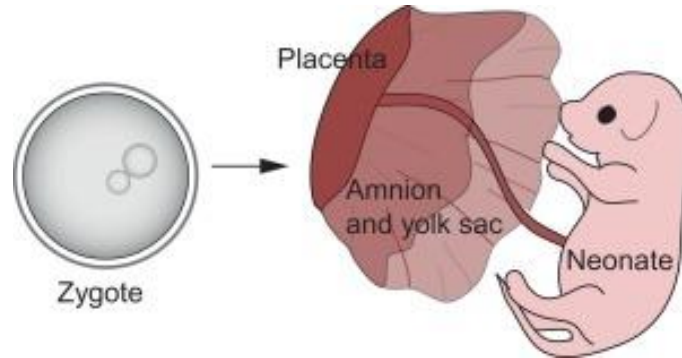


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XIST réduit l'expression des 2 chromosomes Xs pendant le développement pré-implantatoire

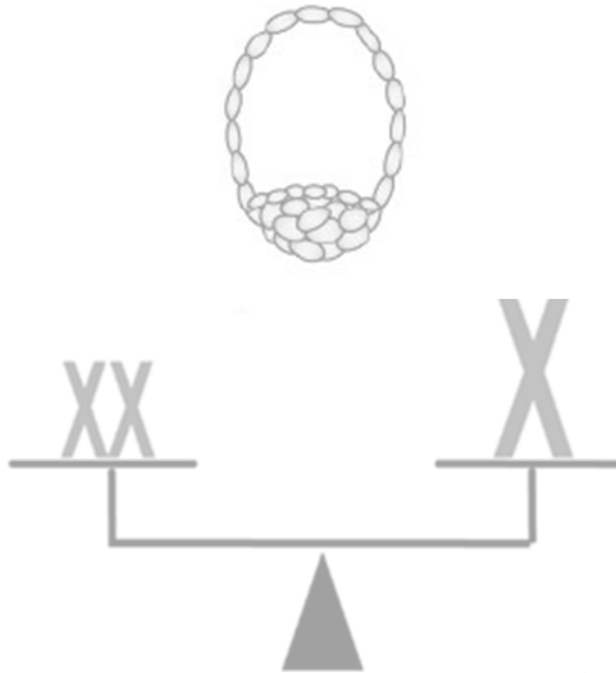


Un des deux chromosomes X doit être inactivé pour que les annexes extra-embryonnaires se développent



# Nos résultats récents

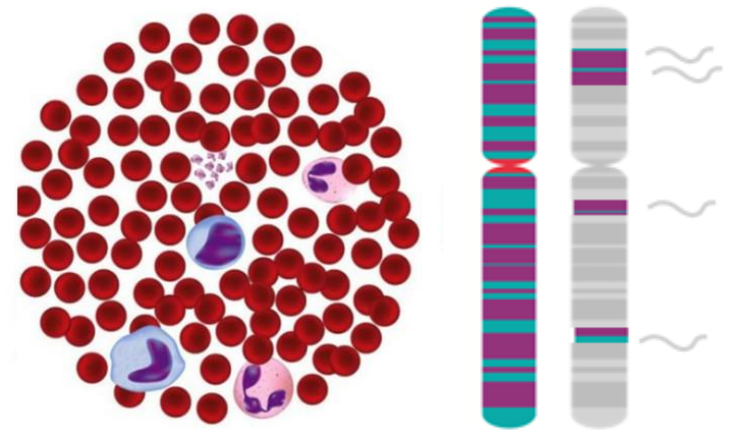
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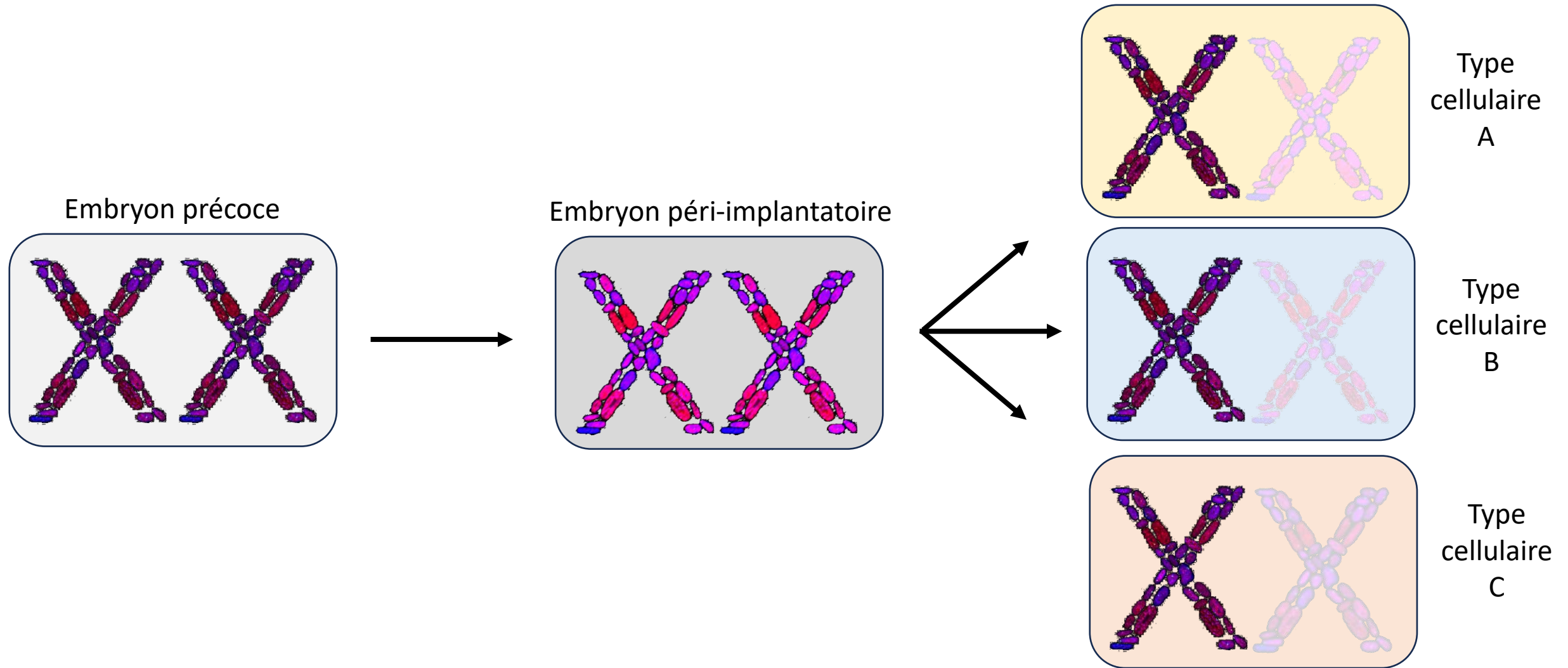
Un des deux chromosomes X doit être inactivé pour que les annexes extra-embryonnaires se développent



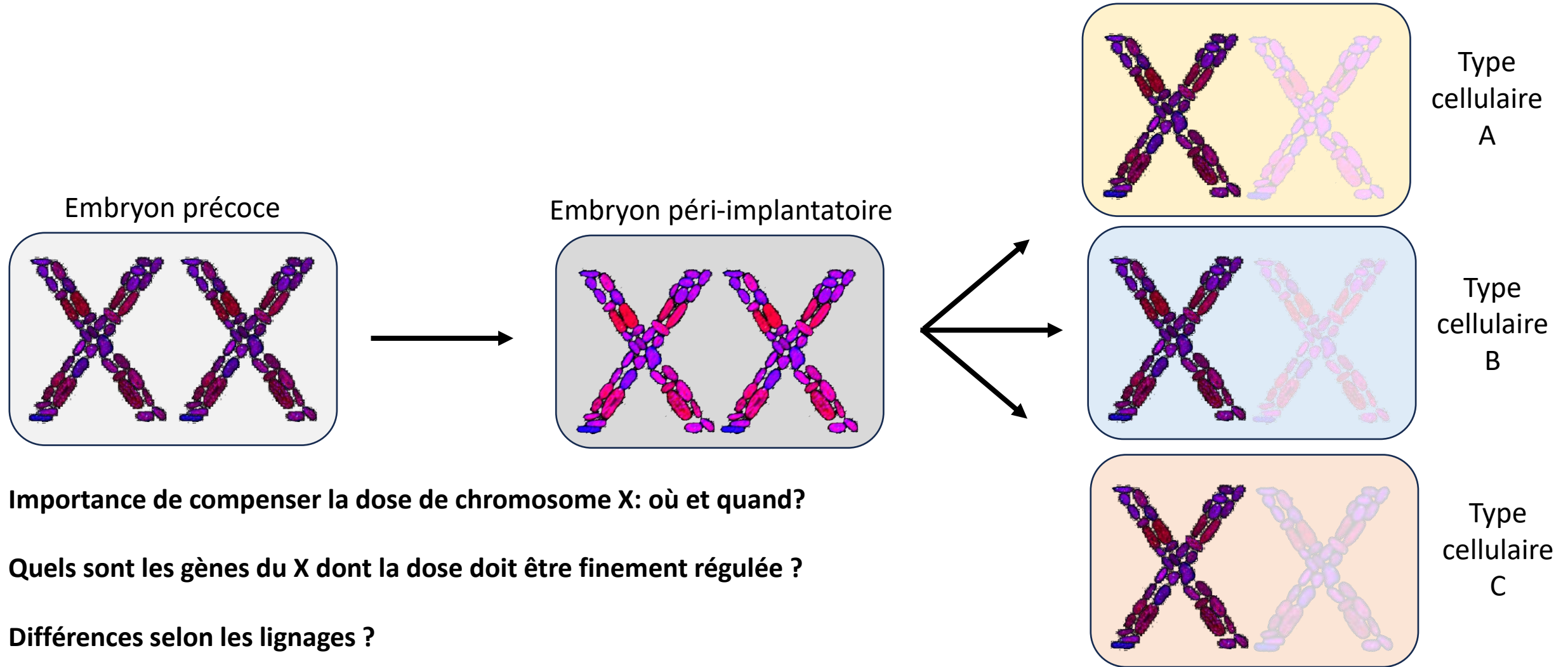
Perturber légèrement l'inactivation du X entraîne l'apparition de signes d'autoimmunité (modèle animal)



# Conclusions



# Les enjeux



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

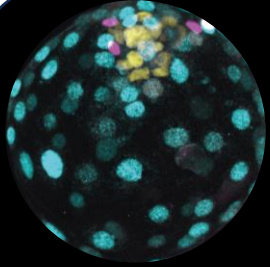
**Quels sont les gènes du X dont la dose doit être finement régulée ?**

**Différences selon les lignages ?**

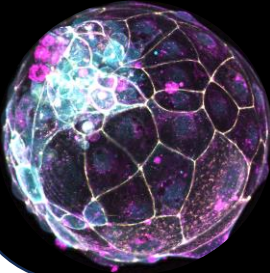
**Dans quelle mesure des variations dans l'activité résiduelle du Xi (physiologique ou pathologique, vieillissement etc) peuvent affecter l'homéostasie cellulaire et tissulaire ?**

# Les enjeux

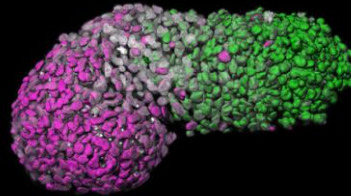
## Modèles d'embryons basés sur les cellules souches



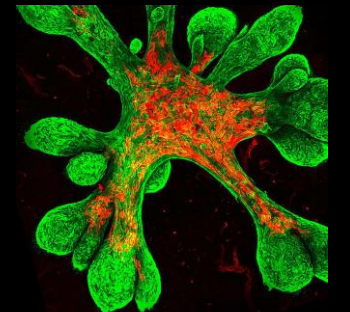
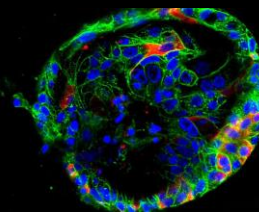
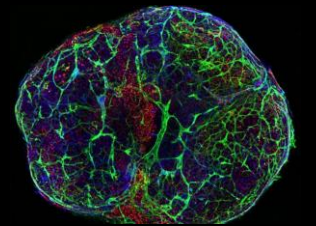
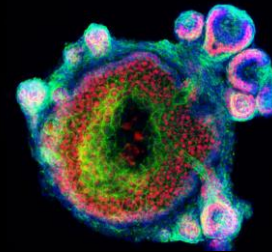
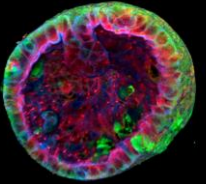
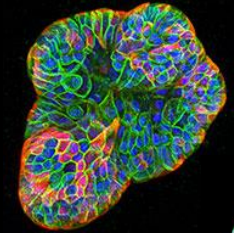
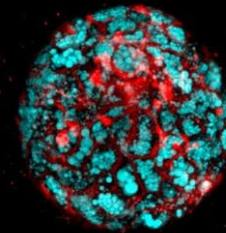
- blastoïdes



- gastruloïdes



## Organoides



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 ?





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Madeleine **MOSCATELLI**

**PLATFORMS**

**EPI2:** Epifluorescence microscopy  
**BiBs:** Bioinformatics and Biostatistics

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