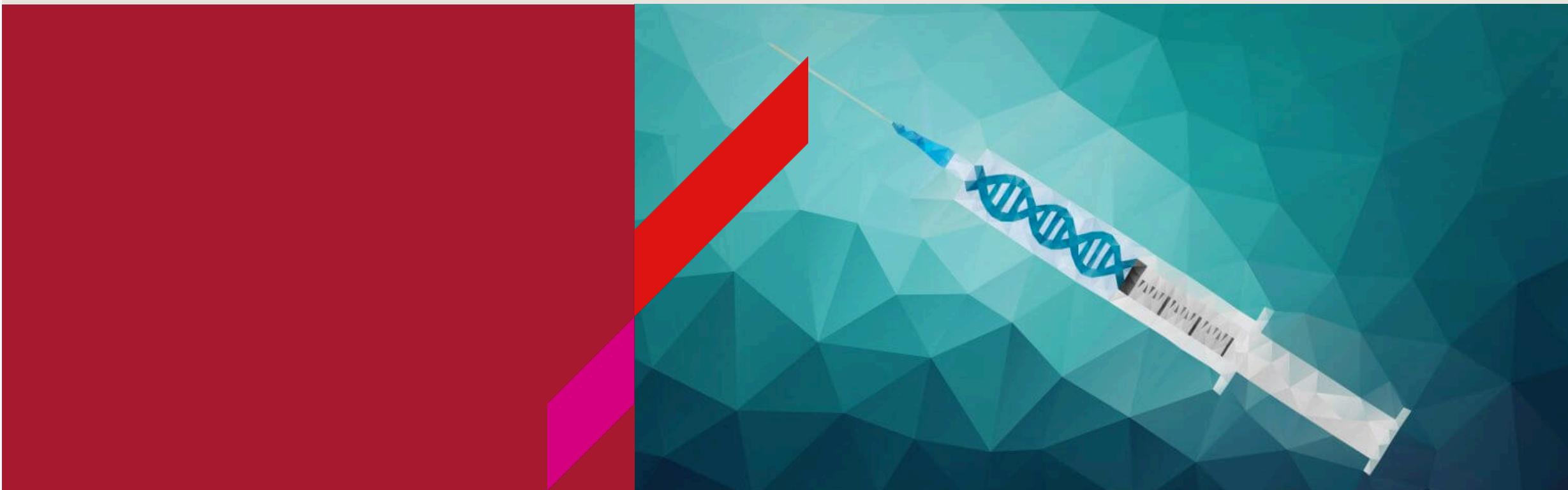


# BIOL3120: Human genetics and evolutionary medicine

## LECTURE 13: TREATMENT FOR GENETIC CONDITIONS





- Medication for genetic conditions
- Gene therapy
  - In vivo
  - Ex vivo

## Learning outcomes

- Discuss medication use for genetic conditions, linking the mechanism / details of the disease with treatment
- Discuss approaches to gene therapy with examples of their current uses

# Some genetic conditions are mild, or easily treatable

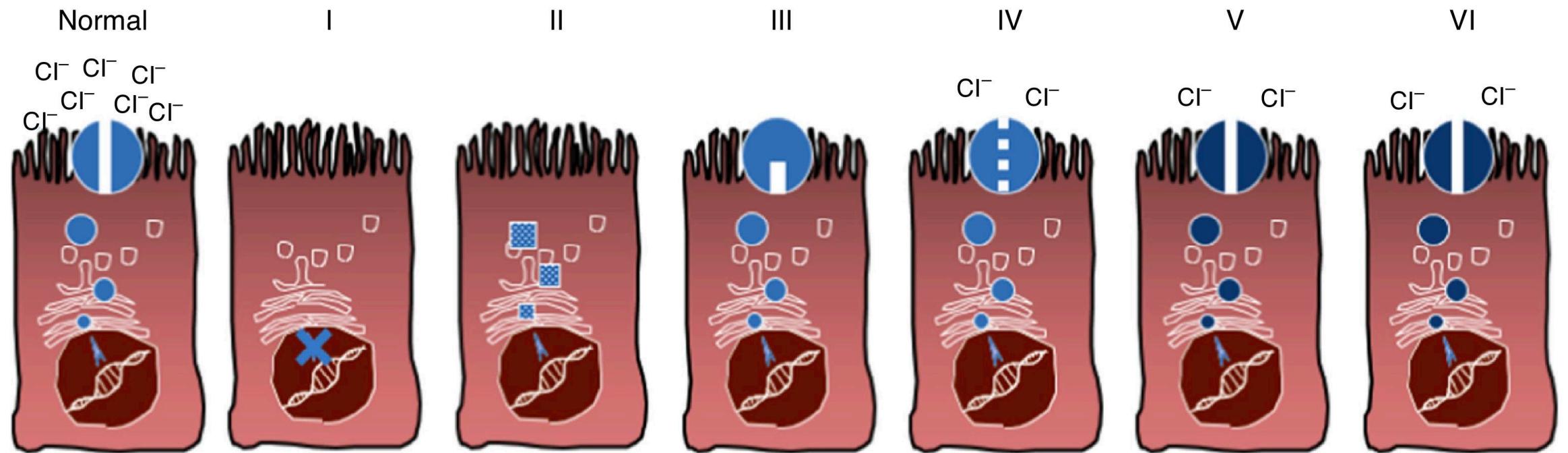
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- Haemochromatosis -> regular blood donation
- Phenylketonuria (PKU) -> low protein diet, phenylalanine restricted diet, aspartame restricted diet
- Cancer / cardiac predisposition -> make lifestyle changes, increased surveillance
- But mostly after a diagnosis:
  - Surveillance
  - Management of symptoms
  - .. Not much

# Classic medication for genetic conditions



### Class of mutation

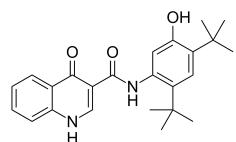


Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Main mutations	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

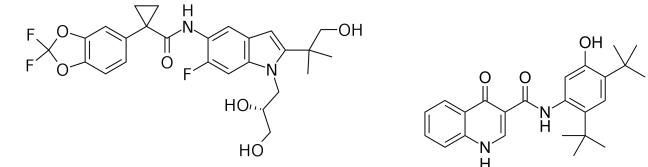
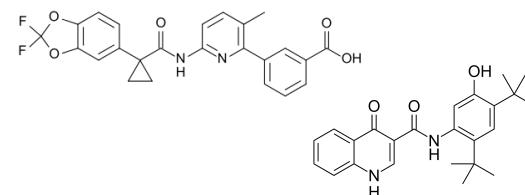
# Three treatments for cystic fibrosis



(ivacaftor) tablets 150 mg  
oral granules 25·50·75 mg

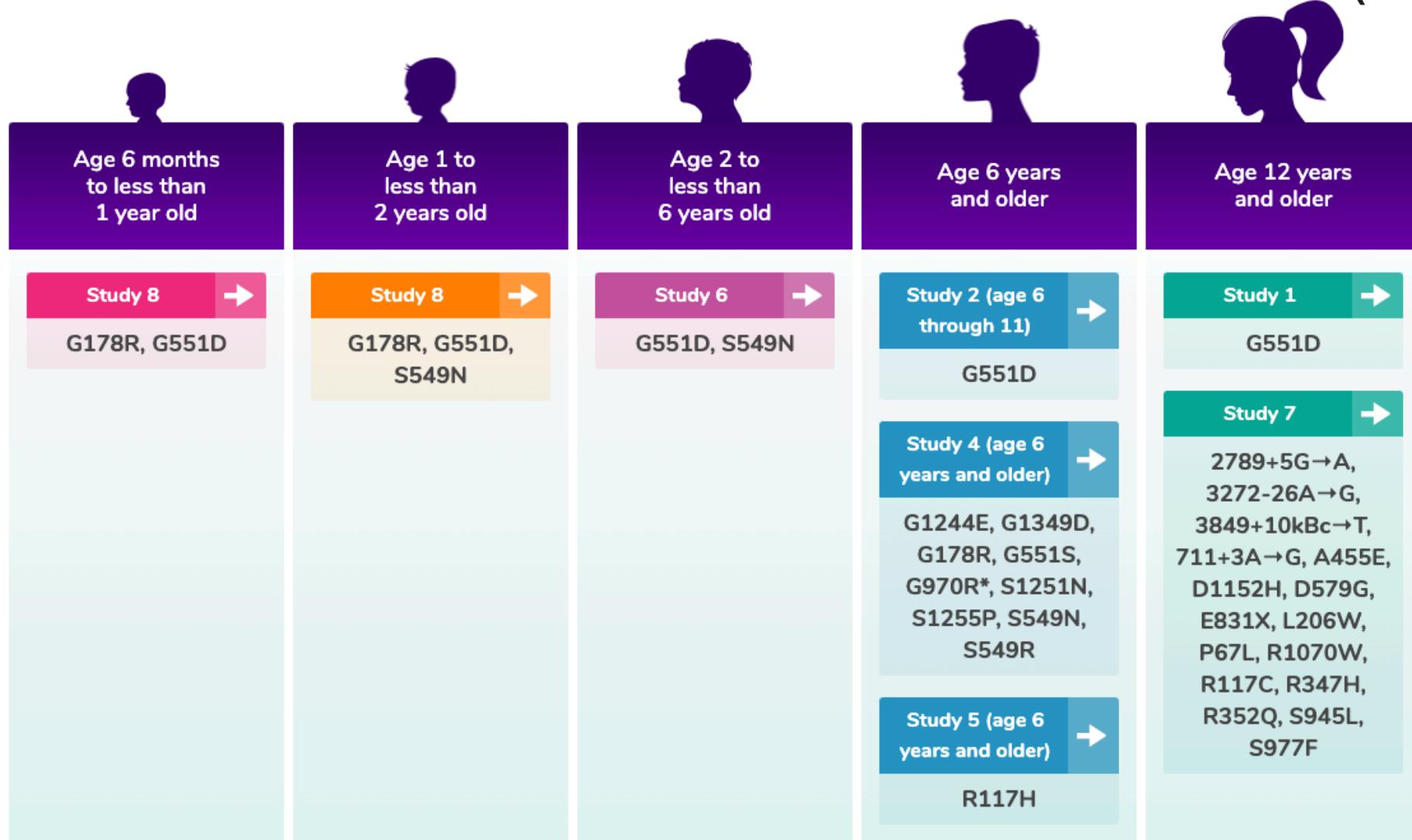


Ivacaftor = helps CFTR channels stay open



Lumacaftor and tezacaftor = helps bring more CFTR proteins to cell surface

# Kalydeco treats a range of CF mutations



# Orkambi

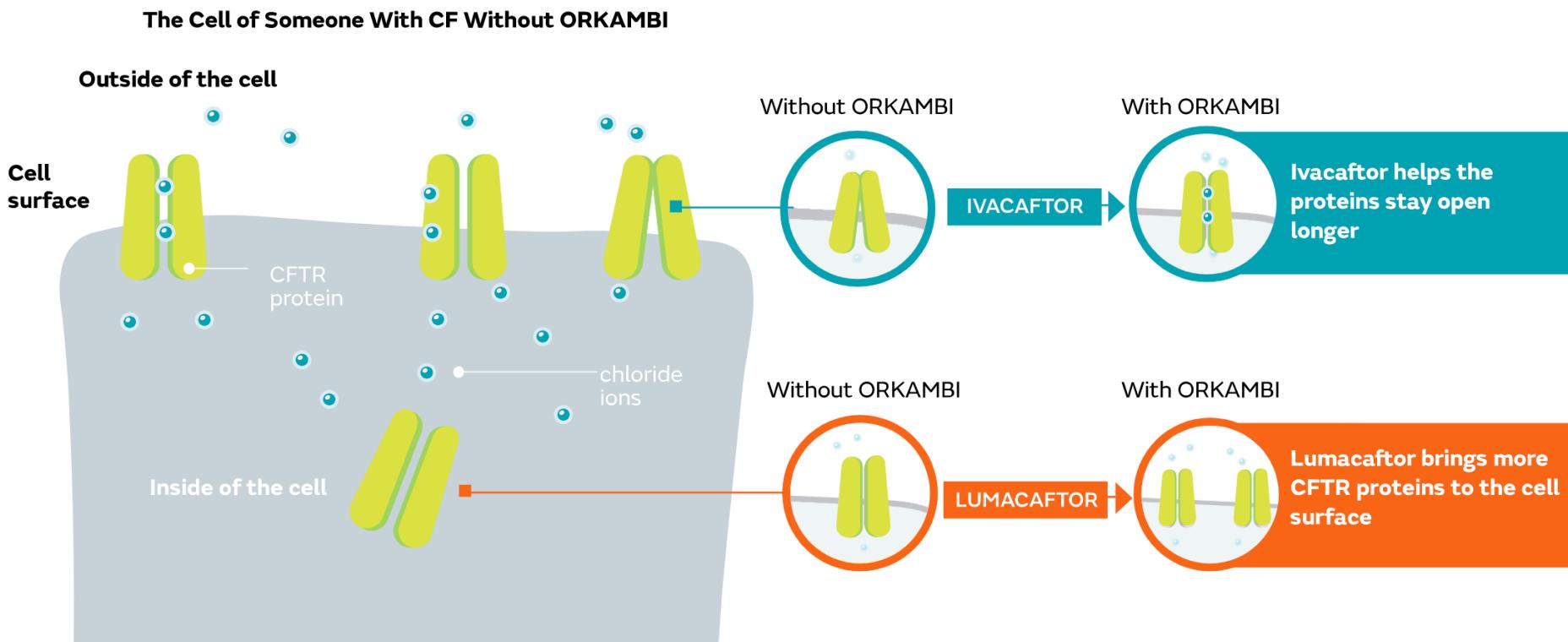


**ORKAMBI®**  
(lumacaftor/ivacaftor)

200 / 125 mg • 100 / 125 mg tablets

100 / 125 mg • 150 / 188 mg oral granules

- **Orkambi** works for patients with the **F508del** mutation in both copies of the CFTR gene – 75-80% of CF patients



# Symdeko treats..



## **CFTR Mutations That Produce CFTR Protein Responsive to SYMDEKO<sup>1-3\*</sup>**

<b>F508del/F508del*</b> c.1521_1523delCTT	<b>E56K</b> c.166G>A	<b>R347H</b> c.1040G>A
<b>A1067T</b> c.3199G>A	<b>E831X</b> c.2491G>T	<b>R352Q</b> c.1055G>A
<b>A455E</b> c.1364C>A	<b>F1052V</b> c.3154T>G	<b>R74W</b> c.220C>T
<b>D110E</b> c.330C>A	<b>F1074L</b> c.3222T>A	<b>S945L</b> c.2834C>T
<b>D110H</b> c.328G>C	<b>K1060T</b> c.3179A>C	<b>S977F</b> c.2930C>T
<b>D1152H</b> c.3454G>C	<b>L206W</b> c.617T>G	<b>2789+5G&gt;A</b> c.2657+5G>A
<b>D1270N</b> c.3808G>A	<b>P67L</b> c.200C>T	<b>3272-26A&gt;G</b> c.3140-26A>G
<b>D579G</b> c.1736A>G	<b>R1070W</b> c.3208C>T	<b>3849+10kbC&gt;T</b> c.3718-2477C>T
<b>E193K</b> c.577G>A	<b>R117C</b> c.349C>T	<b>711+3A&gt;G</b> c.579+3A>G

\*A patient must have 2 copies of the F508del mutation or at least one copy of a responsive mutation listed above in this table to be indicated.

# Orkambi - Does it work? 2-6 year olds

## SAFETY



The safety in this study was similar to what was observed in studies of ORKAMBI® in older patients. [See the possible side effects of ORKAMBI on the next page.](#)

During the study, 3 children taking ORKAMBI stopped permanently because of high liver enzymes.

## SWEAT CHLORIDE



Sweat Chloride



At Week 24:

**Decreased 31.7 mmol/L on average**

(average mmol/L at beginning of study was 105.8)



At Week 26, after ORKAMBI was stopped for 2 weeks:

**Increased 33.0 mmol/L on average**

- Less than or equal to 29 mmol/L  
= CF is unlikely regardless of age
- Between 30 - 59 mmol/L  
= CF is possible and additional testing is needed
- Greater than or equal to 60 mmol/L  
= CF is likely to be diagnosed

# Orkambi - Does it work? 12+ years old

**STUDY**

No one in the Long-Term Study took placebo for comparison.

**Results from 2 Short-Term Studies compared to placebo**

**CF Re**

**Study 1 ↑ 1.5**

Based on statistical analysis of the 24-week study results.

**From a separate analysis combining the results of the 2 Short-Term Studies**

 **↓ 56% less likely to have a pulmonary exacerbation that requires intravenous antibiotics**

 **↓ 61% less likely to have a pulmonary exacerbation that requires hospitalization**

**This analysis was not planned as part of the original study, nor is it included in the full Prescribing Information. It cannot be determined if the observed changes were due to ORKAMBI.**

**Measured Over Time**

**BMI Increase**

**Study 1 ↑ 0.1 kg/m<sup>2</sup>**

For example:  
+0.7 pounds for a person 5'4" and weighs 110 lbs

Based on statistical analysis of the 24-week study results.

**Results from 2 Short-Term Studies compared to placebo**

**BMI Increase**

**Study 1 ↑ 0.1 kg/m<sup>2</sup>**

For example:  
+0.7 pounds for a person 5'4" and weighs 110 lbs

Based on statistical analysis of the 24-week study results.

**Results from 2 Short-Term Studies compared to placebo**

**BMI Increase**

**Study 1 ↑ 0.1 kg/m<sup>2</sup>**

For example:  
+0.7 pounds for a person 5'4" and weighs 110 lbs

Based on statistical analysis of the 24-week study results.

# Does it work? 12+ years old

**ORKAMBI can cause serious side effects, including:**



**Worsening of liver function** in people with severe liver disease. The worsening of liver function can be serious or cause death. Talk to your child's doctor if you have been told that he or she has liver disease as your child's doctor may need to adjust the dose of ORKAMBI

**High liver enzymes in the blood**, which can be a sign of liver injury in people receiving ORKAMBI. Your child's doctor will do blood tests to check your child's liver:

- before starting ORKAMBI
- every 3 months during the first year of taking ORKAMBI
- every year while taking ORKAMBI



Call your child's doctor right away if he or she has any of the following symptoms of liver problems:

- |   |  |
|---|--|
| <ul style="list-style-type: none"><li>▪ pain or discomfort in the upper right stomach (abdominal) area</li><li>▪ yellowing of the skin or the white part of the eyes</li><li>▪ loss of appetite</li></ul> | <ul style="list-style-type: none"><li>▪ nausea or vomiting</li><li>▪ dark, amber-colored urine</li><li>▪ confusion</li></ul> |
|---|--|



**Breathing problems** such as shortness of breath or chest tightness in patients when starting ORKAMBI, especially in patients who have poor lung function. If your child has poor lung function, your child's doctor may monitor him or her more closely when starting ORKAMBI



**An increase in blood pressure** in some people receiving ORKAMBI. Your child's doctor should monitor your child's blood pressure during treatment with ORKAMBI



**Abnormality of the eye lens (cataract)** in some children and adolescents receiving ORKAMBI. Your child's doctor should perform eye examinations before and during treatment with ORKAMBI to look for cataracts

# From a CF patient trying Orkambi:

---

“I have days where I lay in bed at night, hear the silence of my effortless breathing, and realize that I am feeling so good. Like, “Man, I felt great today!” I don’t have symptomless days by any means, but I have days where I feel like I’m not as much of a sick person. Where I may have gone the day without thinking much about my CF. Which is a huge improvement from before. And because of that, I am thankful to say that Orkambi has simply changed my life”.

- Blog entry on <http://cysticfibrosis.com/orkambi-experience/>

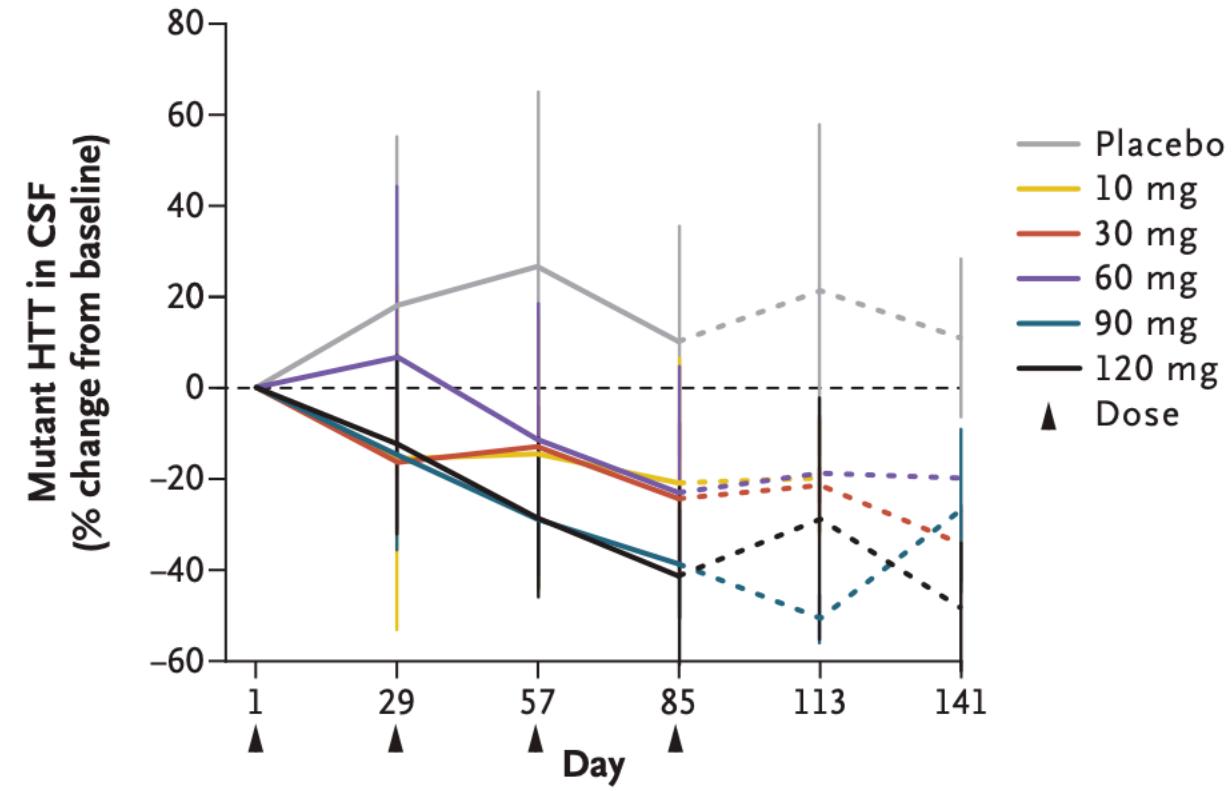
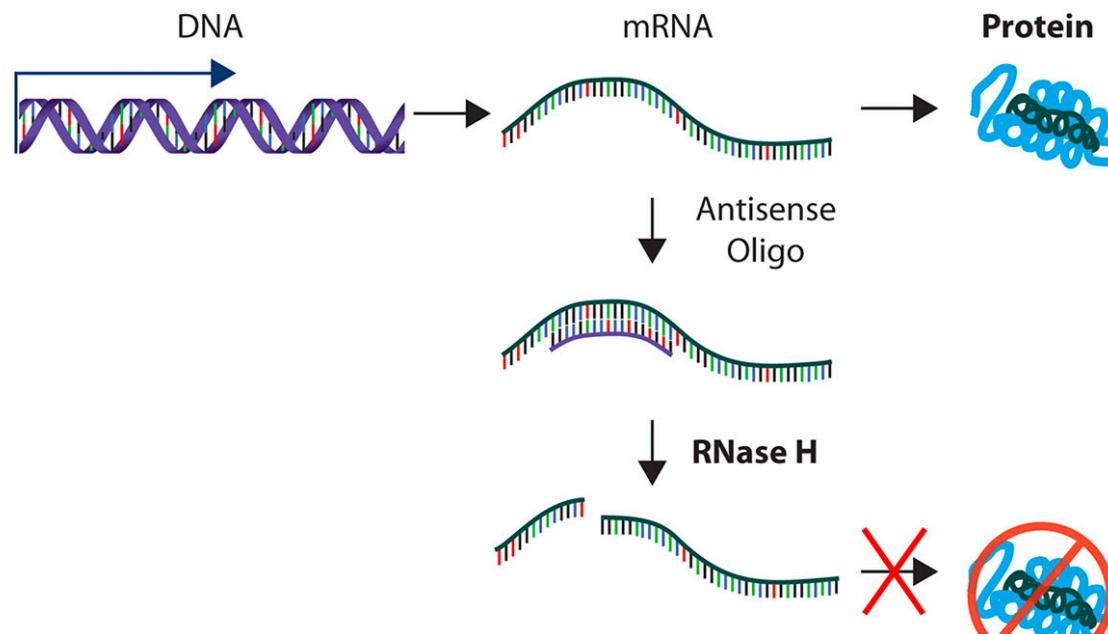
# Price...

- 
- Orkambi = \$272,000 per year
  - Kalydeco = \$311,000 / year
  - Symdeko = \$~32,000 / month
  - Now all on PBS -> ~\$40/month

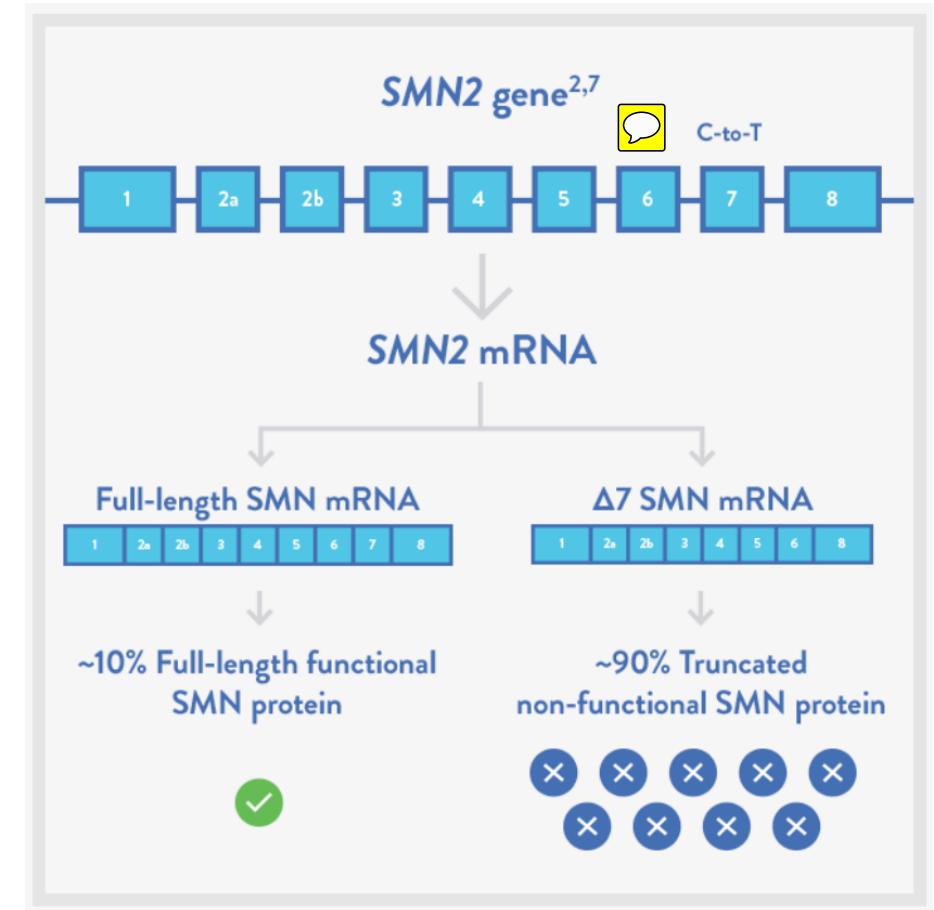
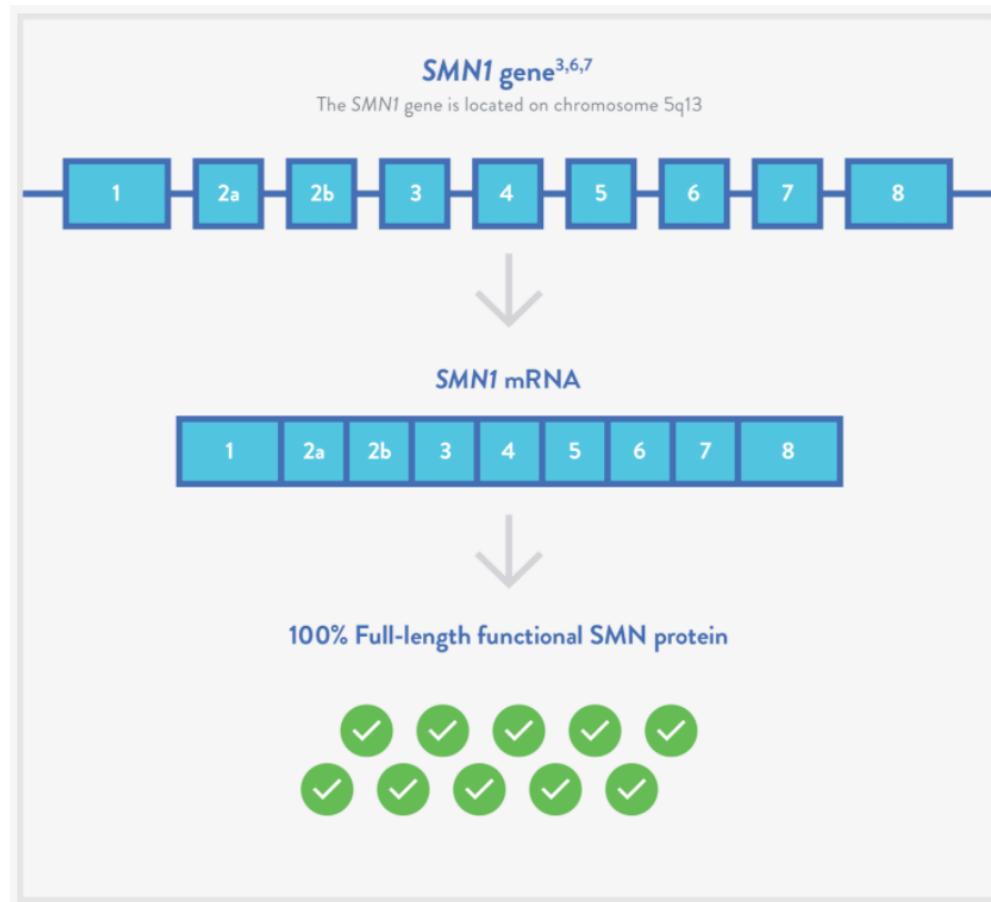
# Nucleic acids as medication for genetic conditions



# Huntington's disease treatment: antisense oligonucleotide gene silencing



# Spinal muscular atrophy (SMA) – Autosomal recessive



# Spinal muscular atrophy (SMA) – Autosomal recessive

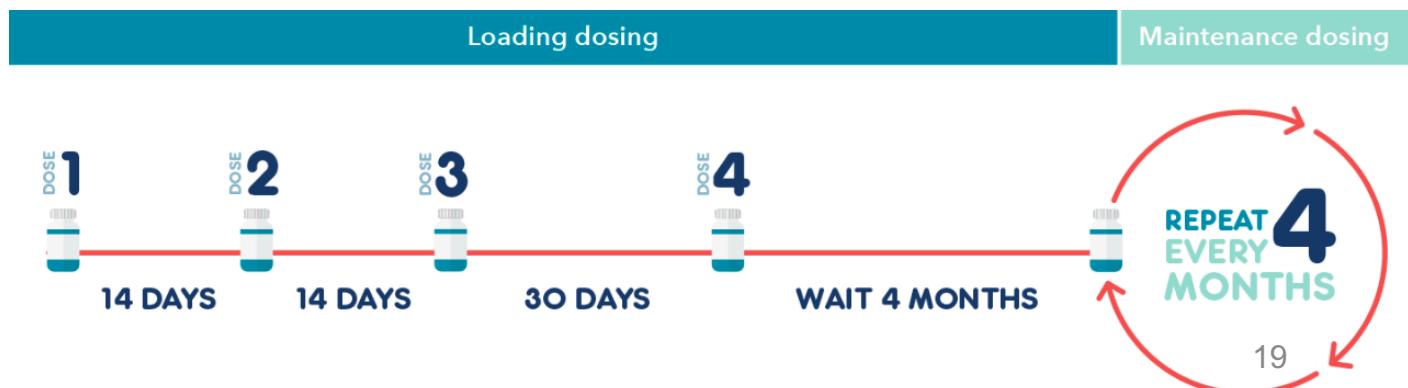
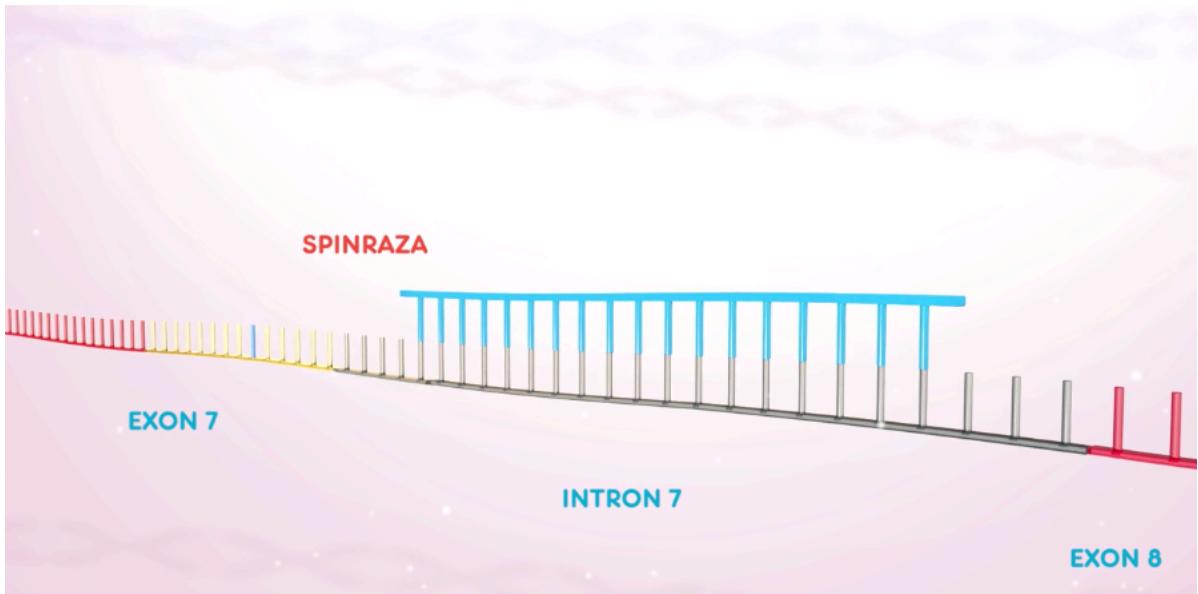
Phenotype	Age of Onset	Life Span <sup>1</sup>
<b>SMA 0</b>	Prenatal	A few weeks, <6 mos
<b>SMA I</b>	<6 mos	Median survival 8-10 mos
<b>SMA II</b>	6-18 mos	70% alive at age 25 yrs
<b>SMA III</b>	>18 mos	Normal
<b>SMA IV</b>	Adulthood	Normal

- More than 95% of individuals with spinal muscular atrophy retain at least 1 copy of the *SMN2* gene
- About 80% of individuals with Type I spinal muscular atrophy have 1 or 2 copies of the *SMN2* gene
- About 82% of individuals with Type II spinal muscular atrophy have 3 copies of the *SMN2* gene
- About 96% of individuals with Type III spinal muscular atrophy have 3 or 4 copies of the *SMN2* gene

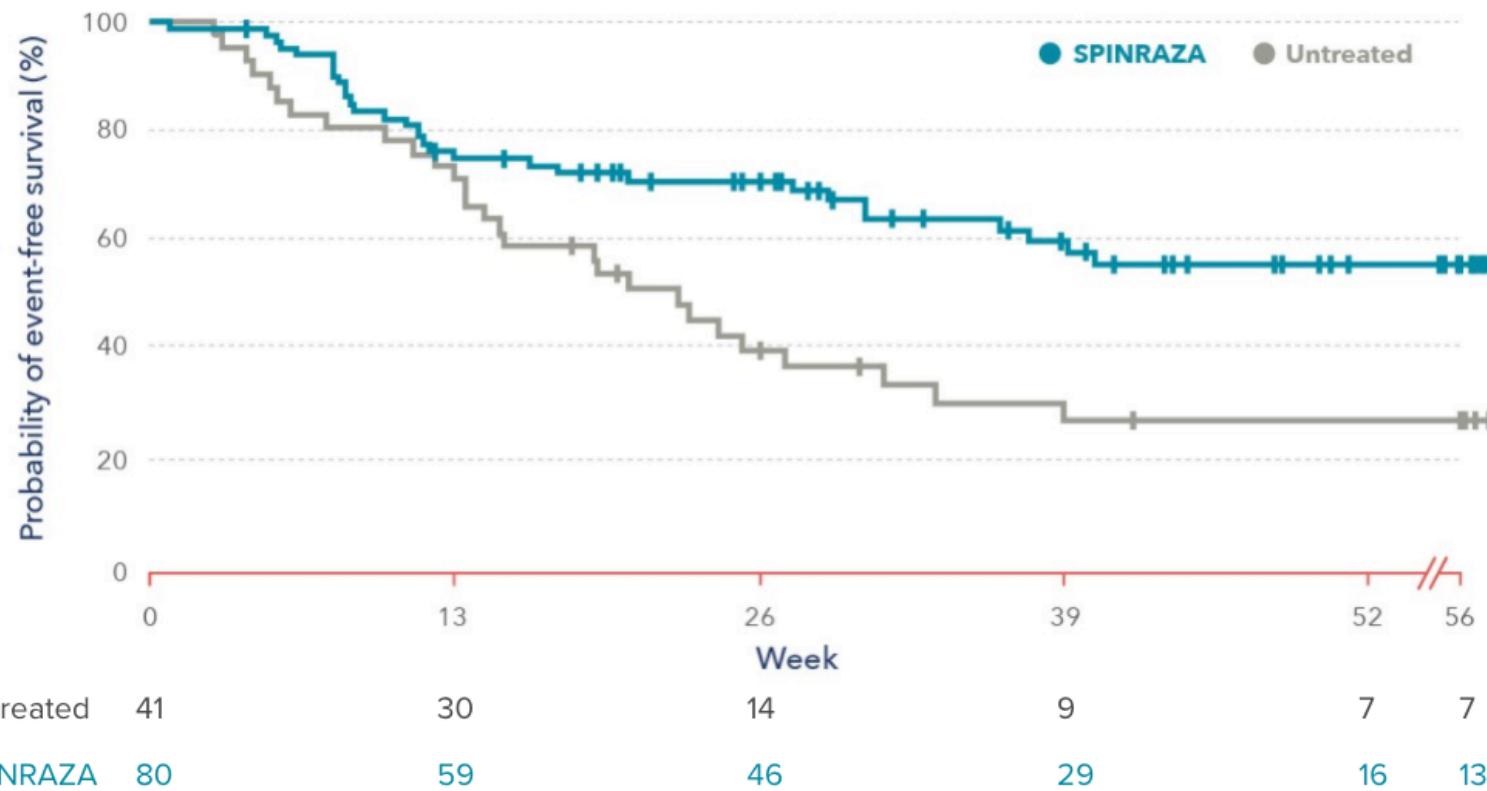
# SMA treatment



- Antisense oligonucleotide anneals to intron 7
- Intron 7 still spliced out, but exon 7 remains
- = functioning SMN protein



# SMA treatment



**47%**

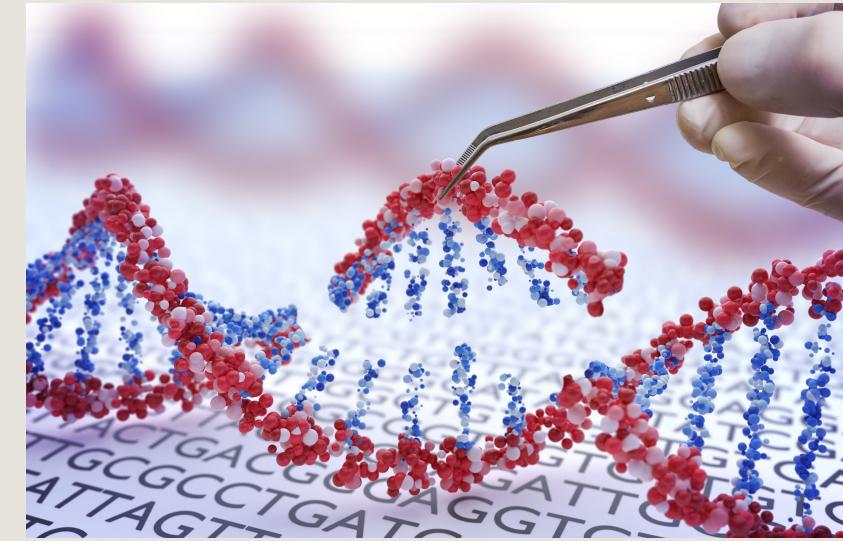
reduction in risk of death or  
permanent ventilation  
(HR=0.53; P=0.005)<sup>1</sup>

Medicare  
Pharmaceutical Benefits  
Scheme (PBS)

\$375,000 annually - >  
\$40/month

\*Event-free survival defined as time to death or permanent assisted ventilation (tracheostomy or ≥16 hours of ventilatory support per day for >21 continuous days in the absence of an acute reversible event).<sup>1</sup>

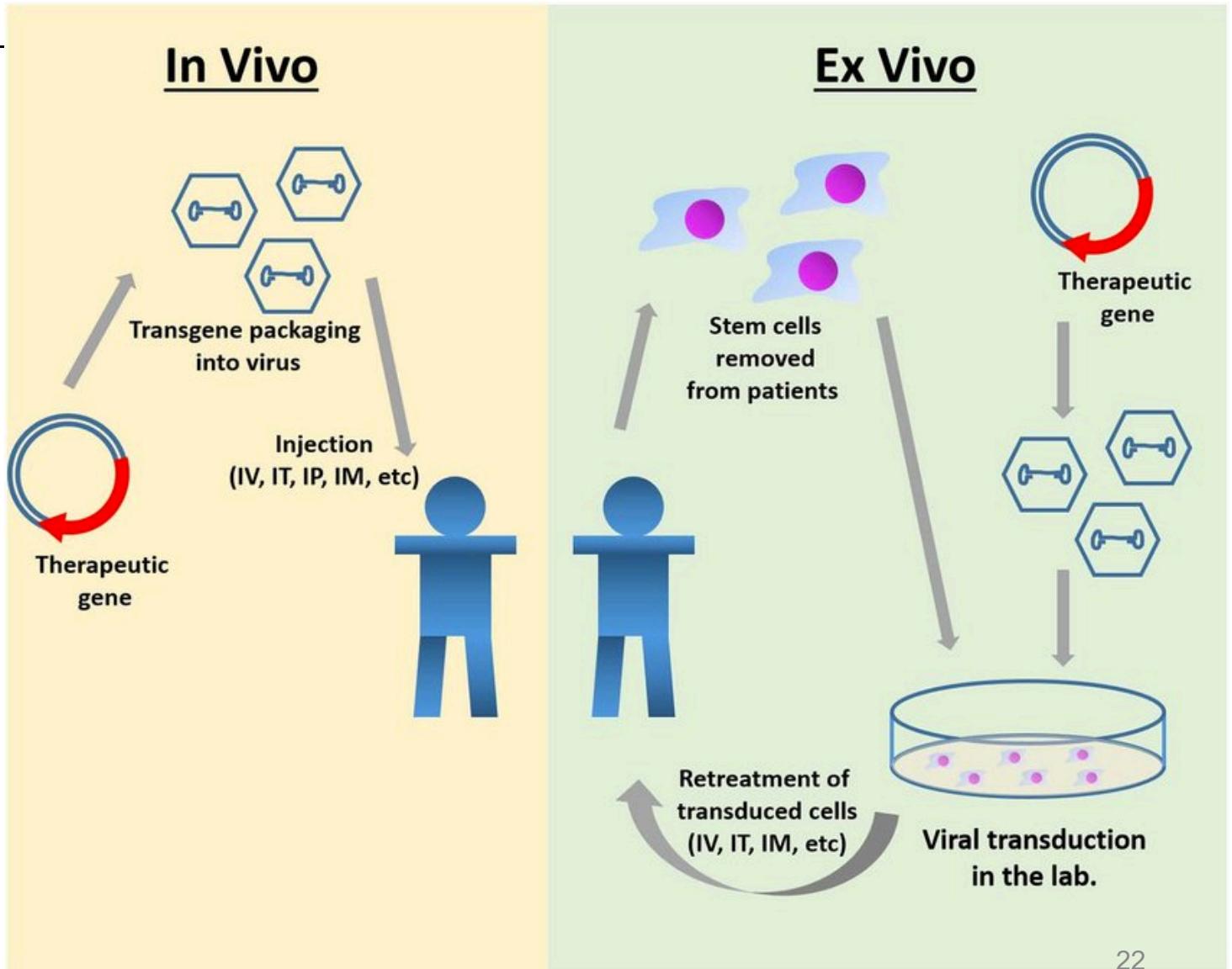
# Gene therapy for genetic conditions



# Gene therapy

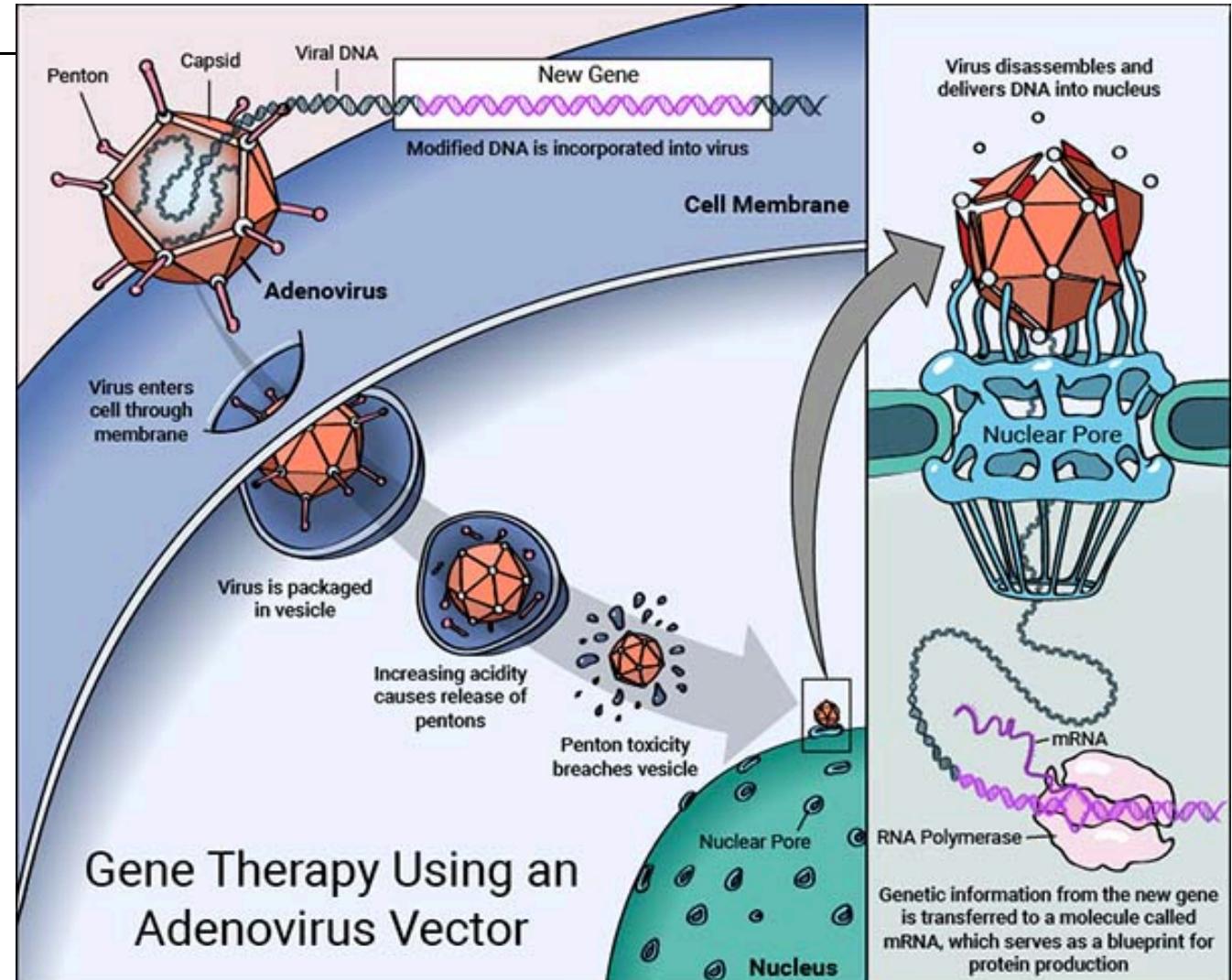
Challenges of gene therapy:

- Gene delivery
- Immune response  
(Jesse Gelsinger)
- Off target effects
- Cost / feasibility

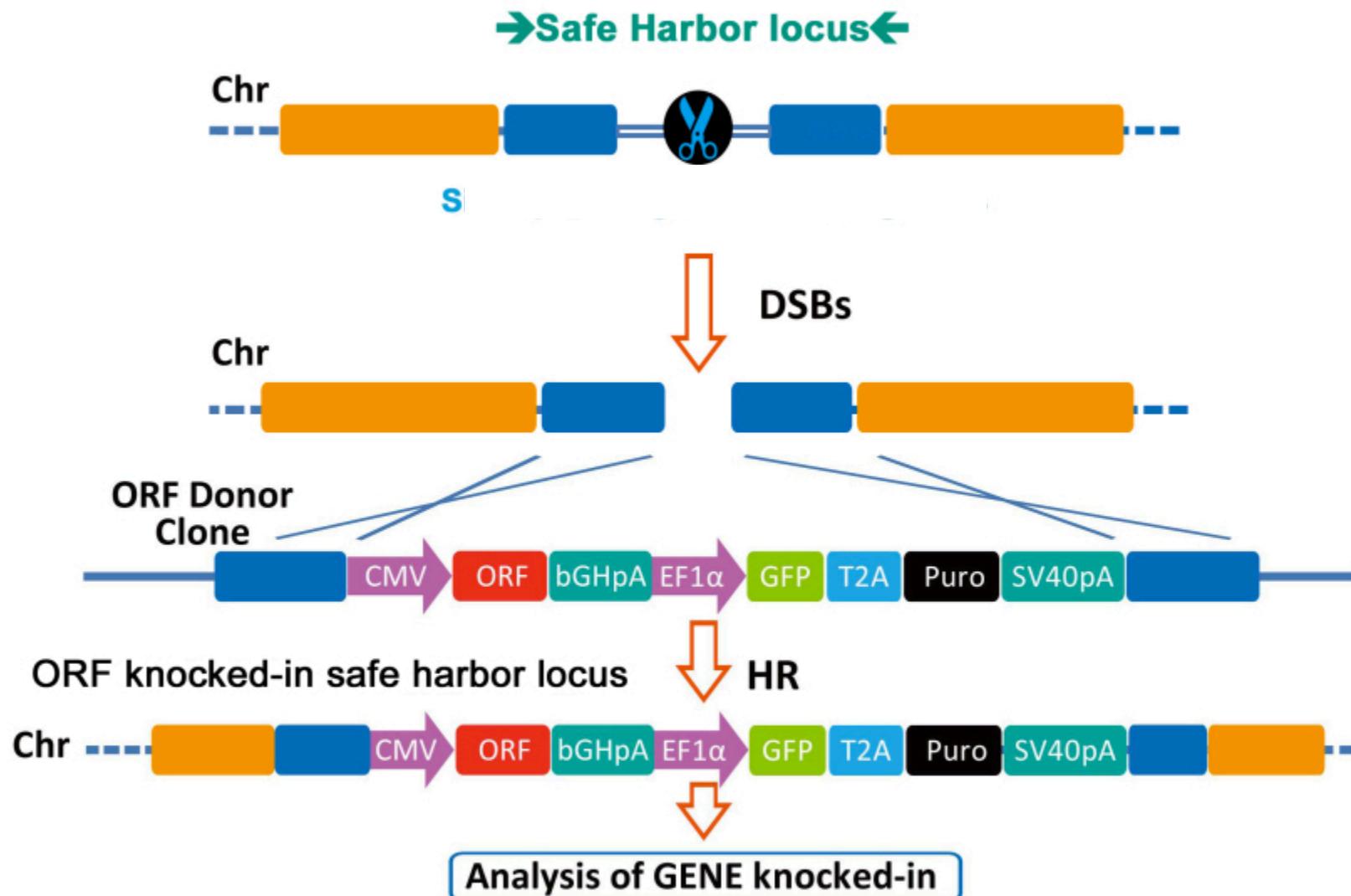


# Virus as a vector

- Adenovirus
- Transports DNA into cell and expresses
- DNA can integrate if desired
- Virus disabled (does not replicate and spread)

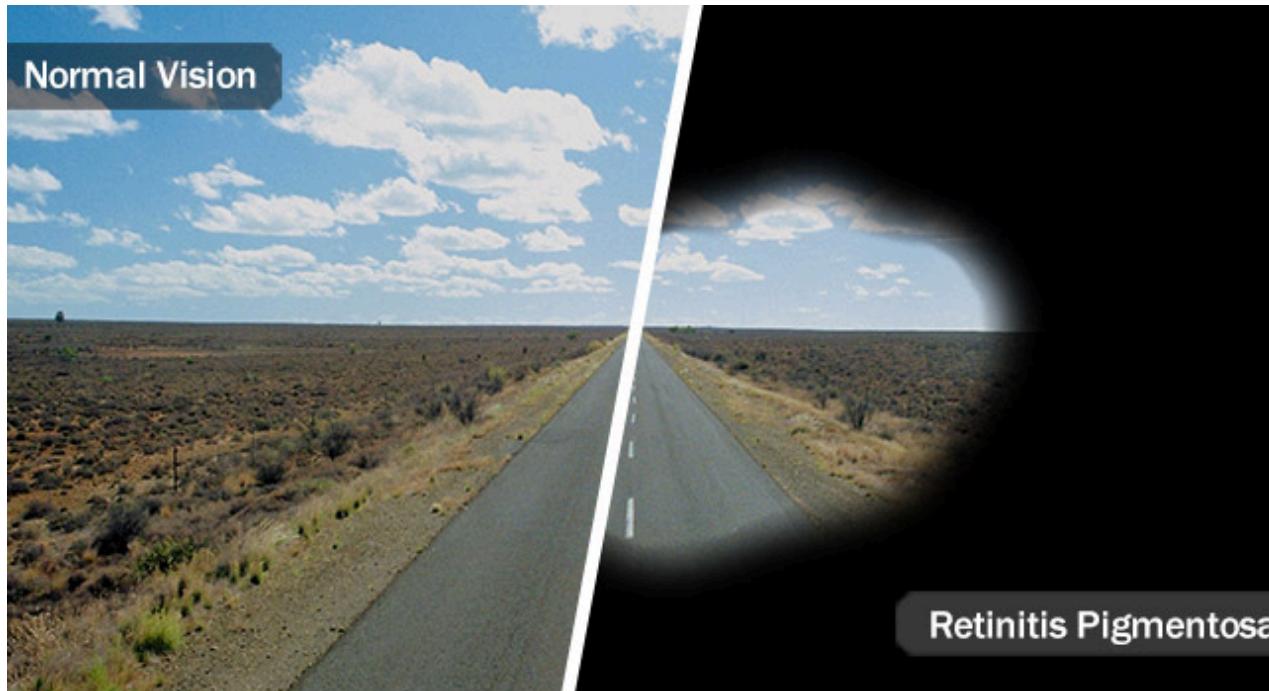


# AAV1 ‘safe harbor’ site



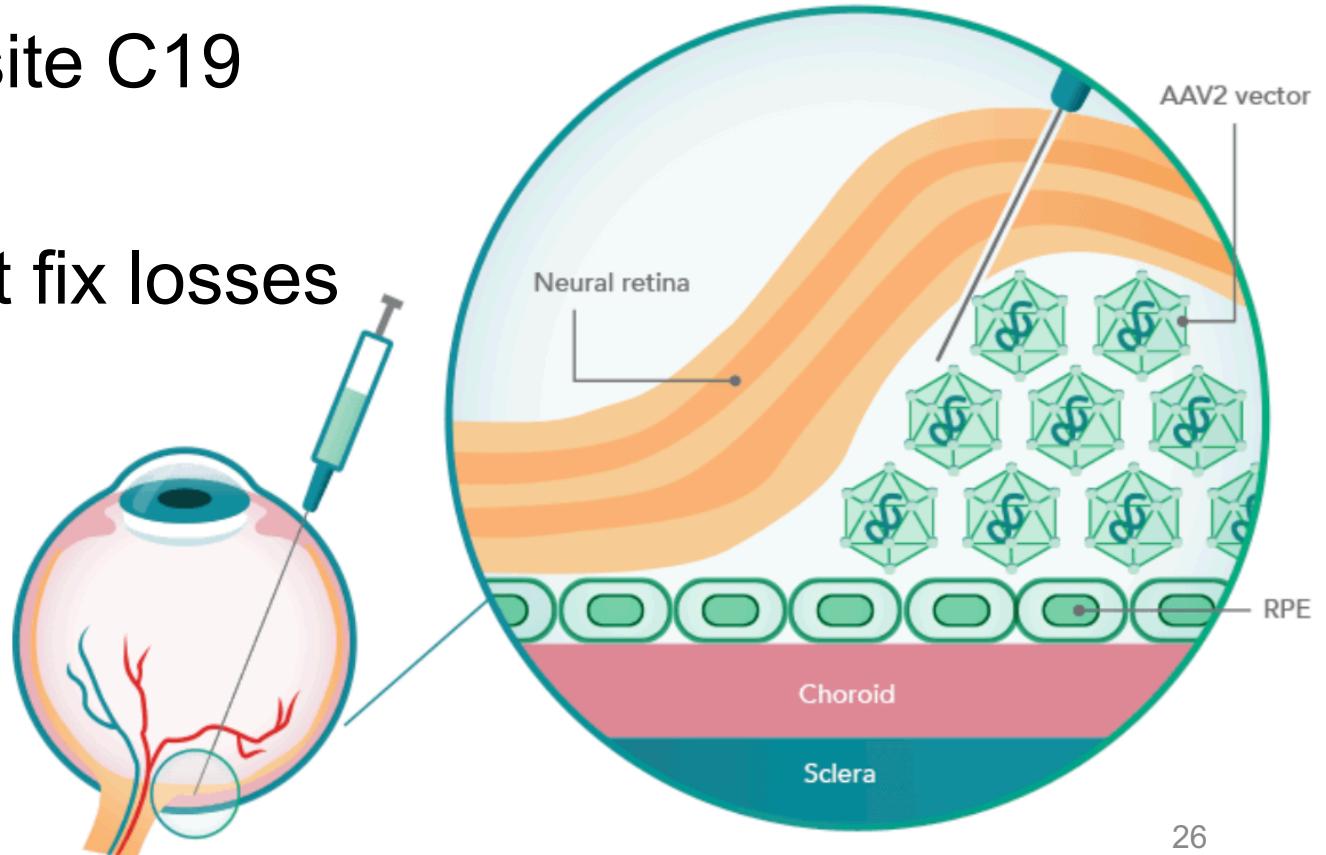
# Examples of gene therapy: Luxturna uses adeno-associated virus

- Multiple diseases caused by lack of functioning RPE65 including retinitis pigmentosa
- RPE65 involved in translating light into electrical signals
- Progressive loss of vision, especially night vision



# Examples of gene therapy: Luxturna uses adeno-associated virus

- Delivers working copy of RPE65 gene
- Integrates into genome AAV site C19
- Stops progression but doesn't fix losses already sustained
- \$425,000 per eye



# Examples of gene therapy: Zolgensma SMA gene therapy

- Single injection earlier than 2 years of age
- AAV insertion of working SMN1 gene
- Cost: \$2.1 million USD



Motor Milestones Achieved, n (%)	
Head control	11 (92)
Rolls from back to sides	9 (75)
Sitting with assistance	11 (92)
Sitting without assistance	
≥5 seconds <sup>b</sup>	11 (92)
≥30 seconds <sup>c,d</sup>	9 (75)
Standing with assistance	2 (17)
Walking alone	2 (17)

# Other in vivo gene therapies



**Table 2. Clinical and product development landmarks for in vivo gene therapies.**

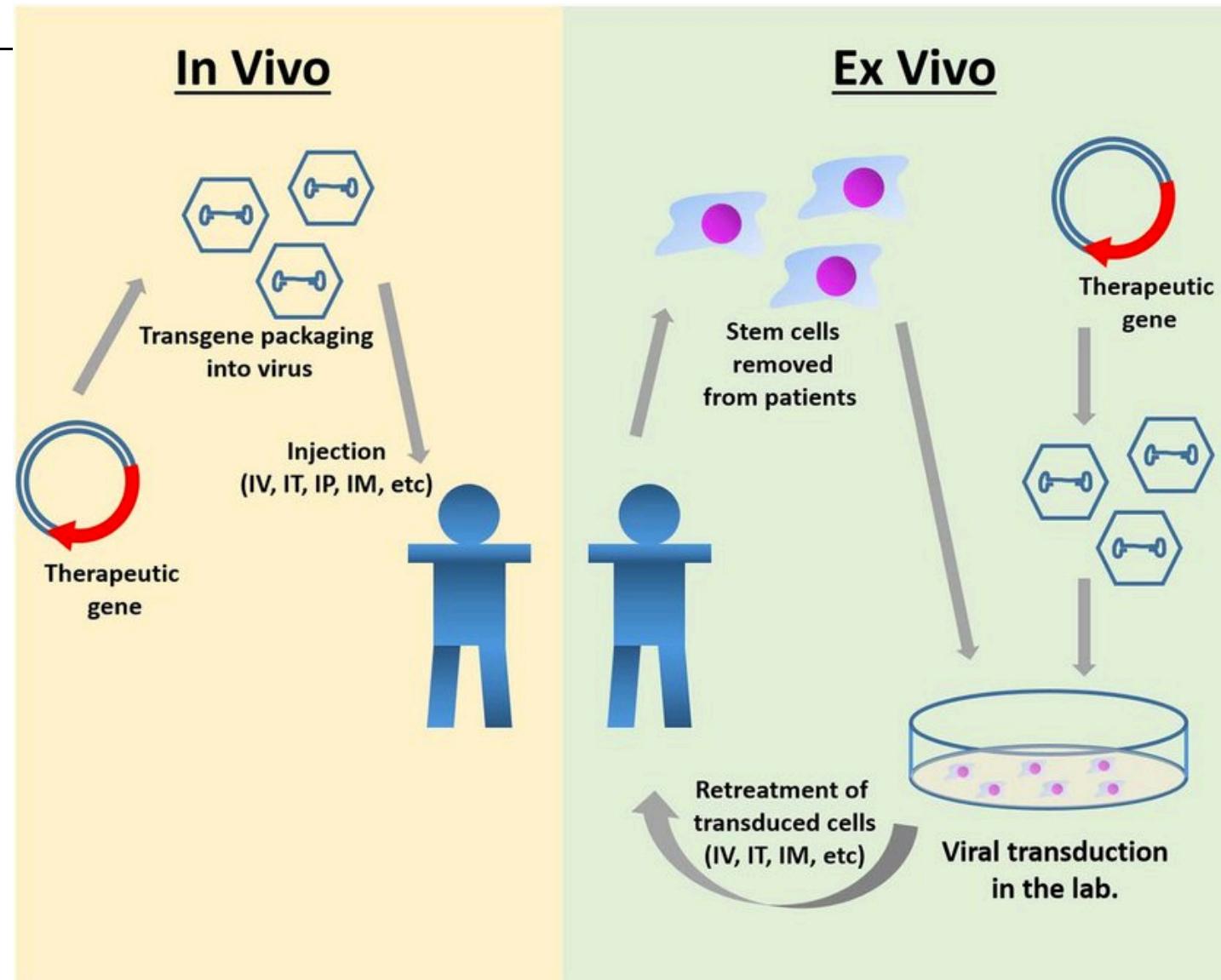
Cell type	Disease	Vector/transgene	Key publication(s) or clinicaltrials.gov no.	Institutional and/or industry partners	FDA breakthrough/EMA* PRIME designation or product approval
CNS	Parkinson's disease	AAV2-AADC	(101, 102)	Jichi Medical University/UCSF/Voyager	
	Aromatic L-amino acid decarboxylase deficiency	AAV2-AADC	(105)	Jichi Medical University/National Taiwan University	
	Spinal muscular atrophy	AAV9-SMN	(107)	Nationwide Children's Hospital/AveXis	FDA 2016; EMA 2017
Liver	Hemophilia B	AAV8-Factor IX	(86, 87)	Royal Free Hospital/St. Jude	FDA 2014; EMA 2017
		AAV100-FIX Padua	(88)	Spark Therapeutics	FDA 2016; EMA 2017
		AAV5-Factor IX	NCT02396342	uniQure	FDA 2017; EMA 2017
		AAV2/6-Factor IX and ZFNs	NCT02695160	Sangamo Therapeutics	FDA 2017
	Hemophilia A	AAV5-Factor VIII	NCT02576795	Multiple academic sites/Biomarin	EMA 2017
		AAV200-Factor VIII	NCT03003533	Spark Therapeutics	
		AAV2/6-B domain-deleted Factor VIII and ZFNs	NCT03061201	Sangamo Therapeutics	
Muscle	Mucopolysaccharidosis type II (Hunter's syndrome)	AAV2/6-IDA and ZFNs	NCT03041324	Sangamo Therapeutics	
	Lipoprotein lipase deficiency	AAV1-LPL	(155)	uniQure	EMA 2012 approval of "Glybera", company will not renew license as of 2017
Retina	Inherited retinal dystrophy due to X-linked recessive mutations in RPE65	AAV2-RPE65	(93, 95, 99)	Children's Hospital of Philadelphia/Spark	FDA approval 2017
		AAV2-RPE65	(92, 97)	University College London/MeiraGTx	
		AAV2-RPE65	(94, 96)	University of Florida	

\*Abbreviations: CNS, central nervous system; FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; AAV, adeno-associated virus; AADC, amino acid decarboxylase; ZFNs, zinc finger nucleases; IDA, iduronate-2-sulfatase.

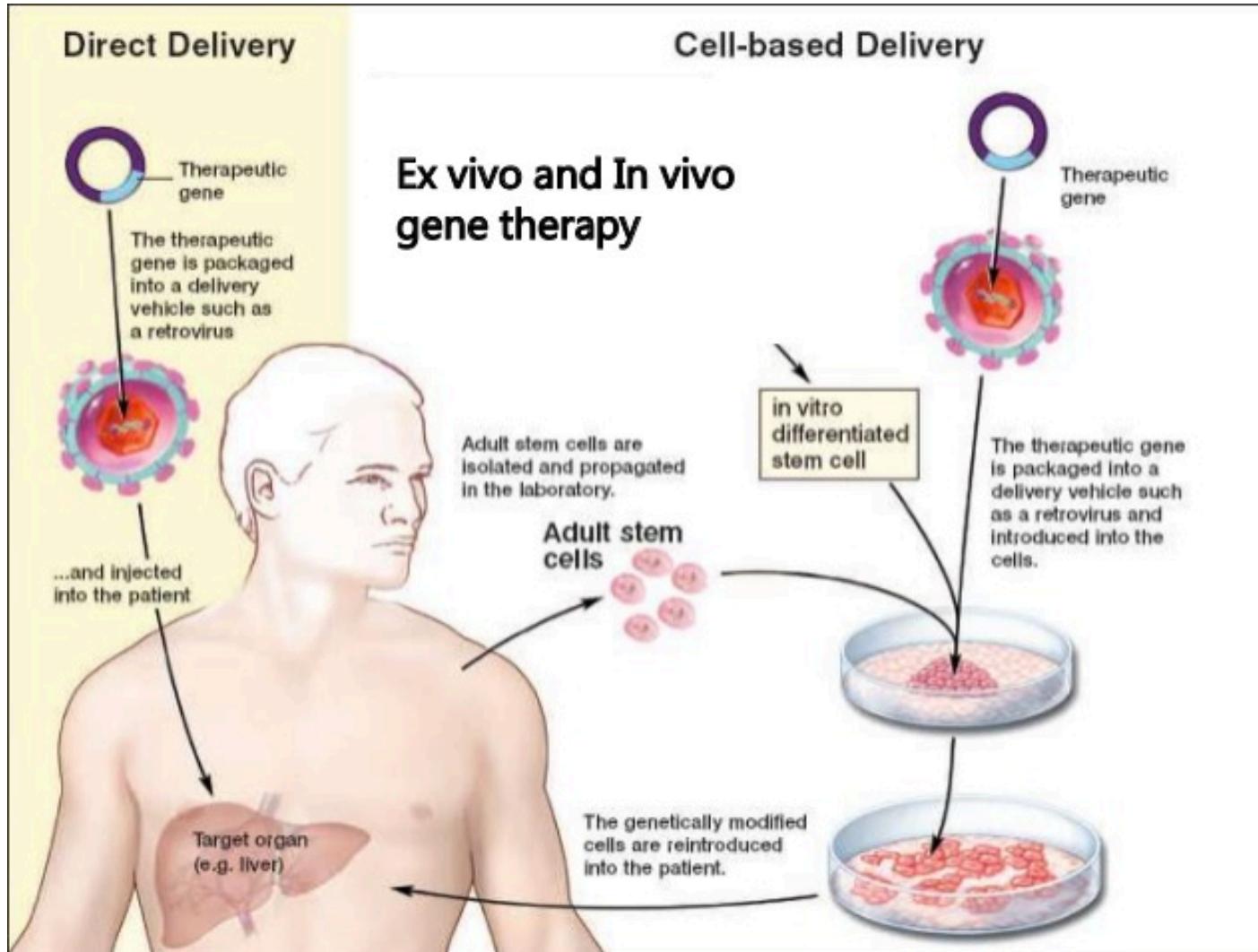
Liver in vivo example:

<https://www.ucalgary.ca/news/new-clinical-trial-unit-performs-canadas-first-gene-therapy-urea-cycle-disorder>

# 'In vivo' vs 'ex vivo' gene therapy



# Ex vivo gene therapy overview



# Ex vivo example: Strimvelis

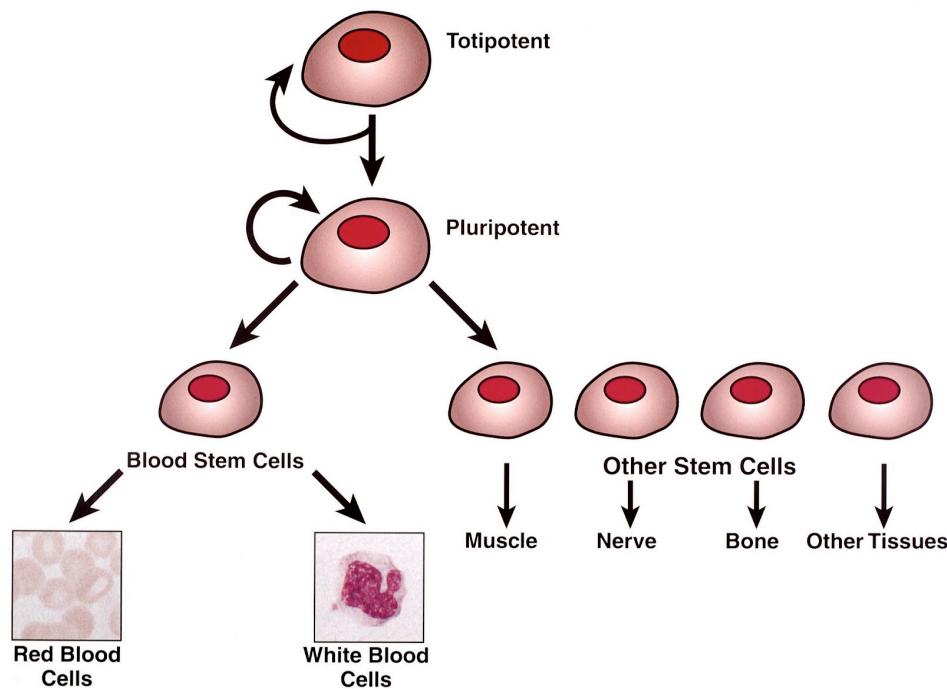
- 
- Treats Adenosine deaminase deficiency – severe combined immunodeficiency (SCID) – Autosomal recessive. 15 people born per year in Europe with condition
  - Retrovirus used to insert working ADA gene into hematopoietic stem cell (HSC), and then transplanted into bone marrow
  - 75% of treated people no longer need enzyme replacement therapy
  - 594,000 euros for treatment vs enzyme replacement therapy requires weekly injections and costs about \$4.25 million for one patient over 10 years.

# Ex vivo therapies

VIRUS					
HSPCs	β-Thalassemia	LV anti-sickling β-hemoglobin	(120) NCT01745120 NCT02151526 NCT03207009	Hopitaux de Paris/academic centers worldwide/Bluebird Bio	FDA 2015; EMA 2016
Sickle cell anemia	LV β-hemoglobin	NCT02453477	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	Memorial Sloan Kettering Cancer Center	
	LV anti-sickling β-hemoglobin	NCT01639690 (121) NCT02151526, NCT02140554	Hopitaux de Paris/US academic sites/ Bluebird Bio		
	LV anti-sickling β-hemoglobin	NCT02247843	UCLA/California Institute of Regenerative Medicine		
Wiskott-Aldrich syndrome	LV WAS	(114)	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline		
	LV WAS	(152)	Hopital Necker-Enfants/ University College/Genethon		
Adenosine deaminase deficiency	γRV ADA	(116)	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	EMA 2016 approved "Strimvelis"	
	LV ADA	NCT02999984	University College/UCLA/ Orchard Therapeutics	FDA 2015	
IL2Rγ-deficient X-SCID	γRV SIN IL2Rγ	(115)	Hopital Necker-Enfants/Great Ormond Street		
	LV IL2Rγ	(153)	National Institute of Allergy and Infectious Diseases		
Adrenoleukodystrophy	LV ABCD1	(118)	St. Vincent de Paul, Paris		
	LV ABCD1	(119)	Multiple academic sites/Bluebird Bio		
Metachromatic leukodystrophy	LV ARSA	(117, 154)	San Raffaele Telethon Institute of Gene Therapy/GlaxoSmithKline	EU Orphan Drug 2007	
Human Immunodeficiency virus	ZFN CCR5 electroporation	NCT02500849	City of Hope/Sangamo		

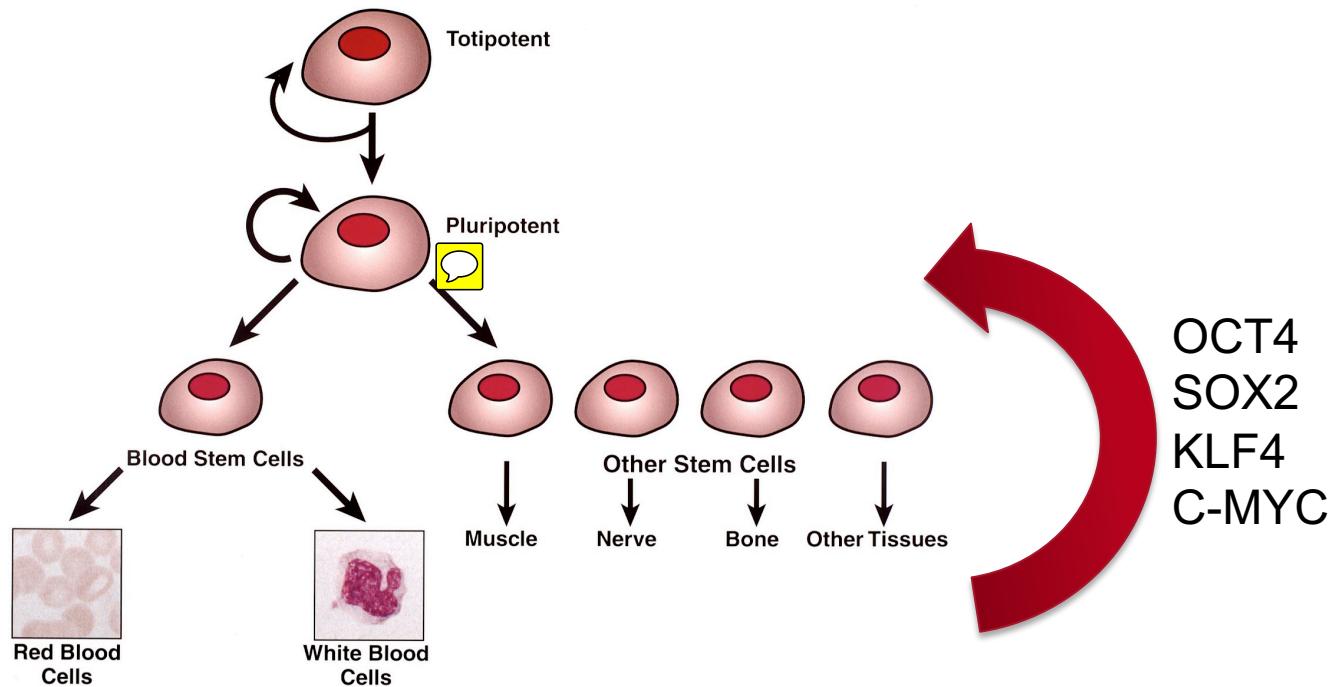
\*Abbreviations: FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; γRV, murine γ-retrovirus; LV, lentivirus; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; HSPC, hematopoietic stem and progenitor cells; X-SCID, X-linked severe combined immunodeficiency; ZFN, zinc finger nuclease; BCMA, B cell maturation antigen; ARSA, arylsulfatase A; ABCD1, transporter gene mutated in adrenoleukodystrophy.

# Stem cells in nature



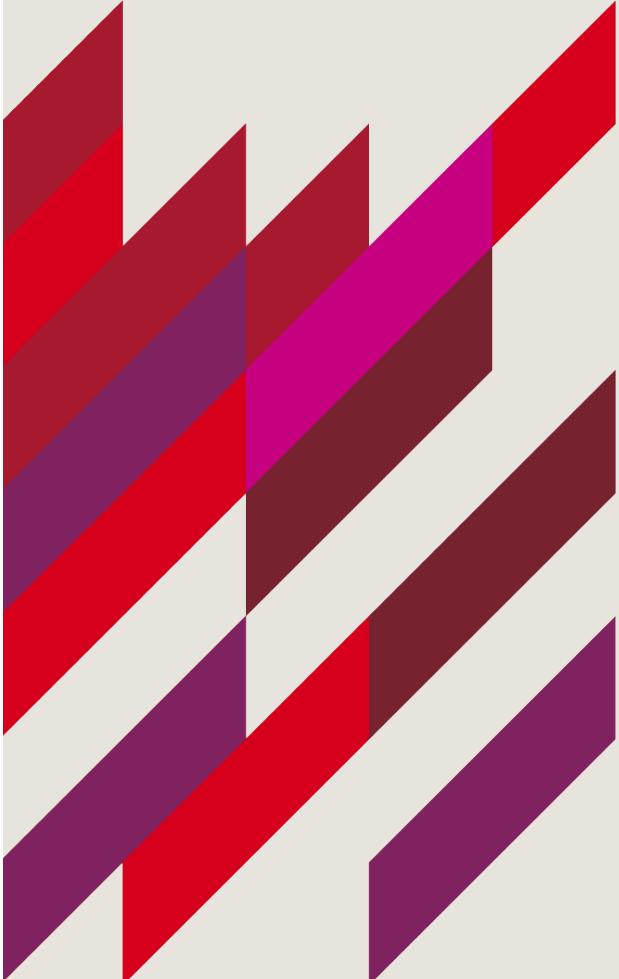
# Induced pluripotent stem cells (iPSCs)

- We can now take any type of cell and turn it back into a stem cell 
- We can direct stem cells to grow into any other type of cell (differentiation)



Shinya Yamanaka

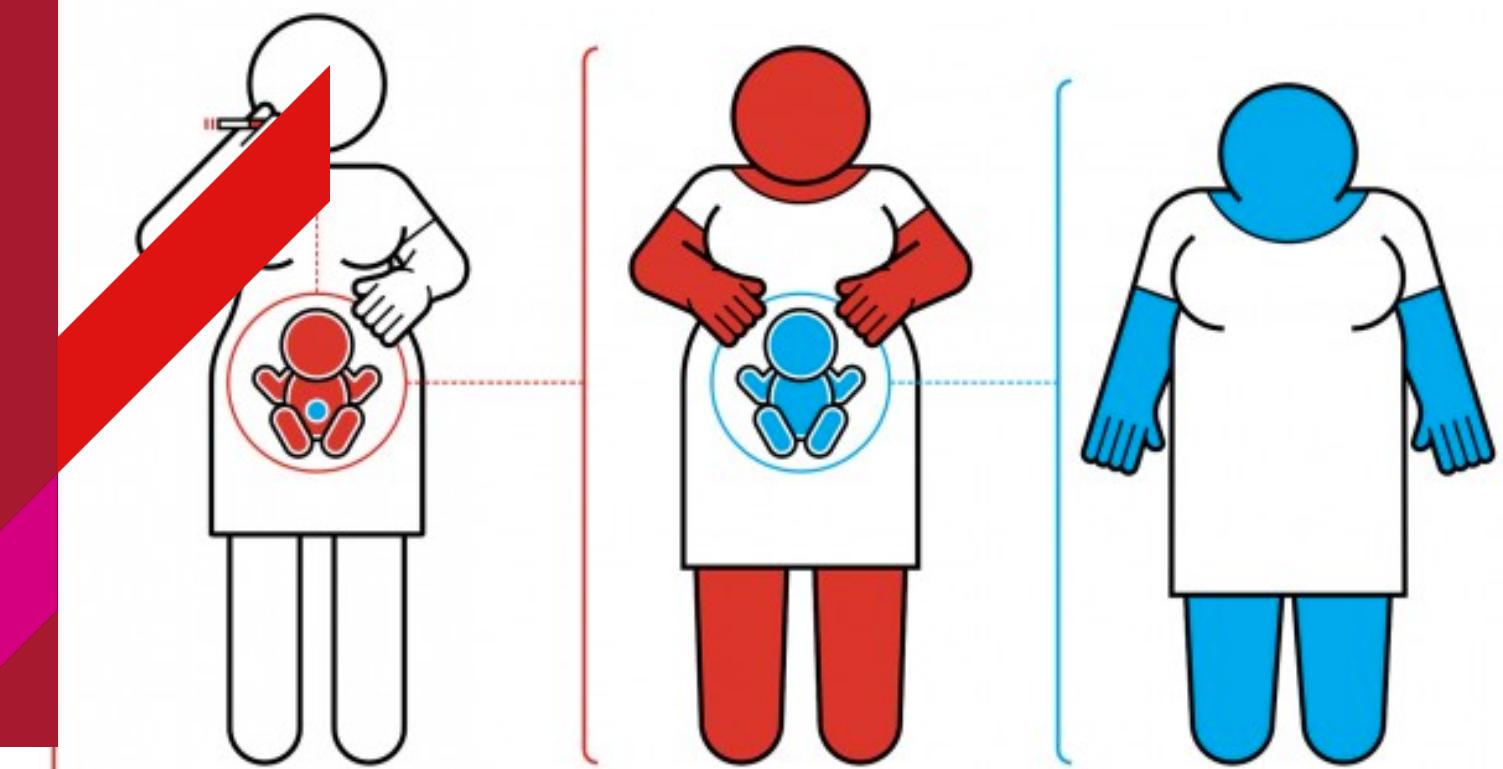
# What you should be able to do

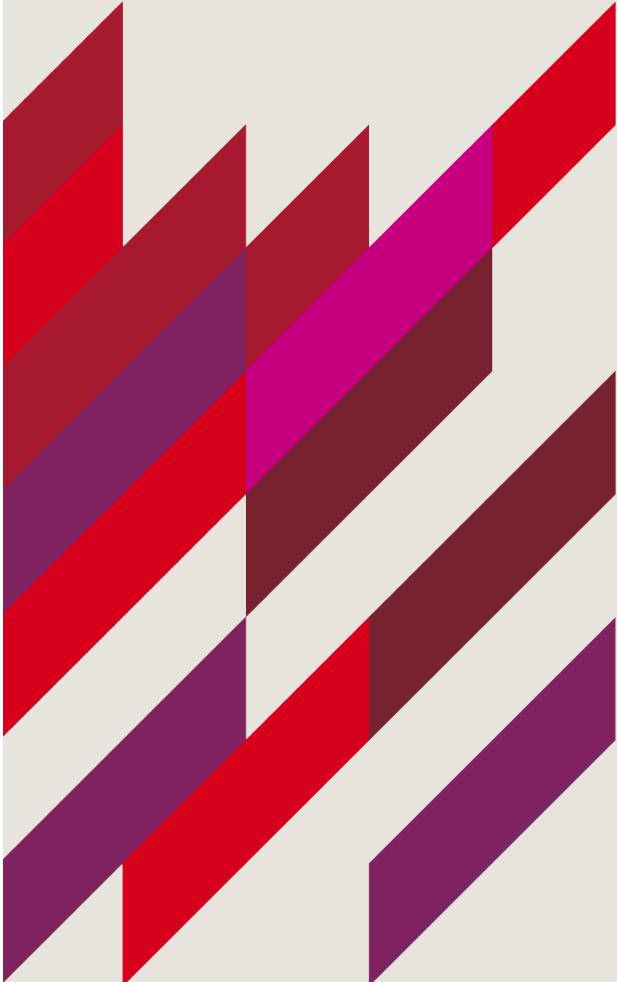


- Discuss medication use for genetic conditions, linking the mechanism / details of the disease with treatment
- Discuss approaches to gene therapy with examples of their current uses

# BIOL3120: Human genetics and evolutionary medicine

## LECTURE 14: EPIGENETICS AND IMPRINTING





## 1. Epigenetics

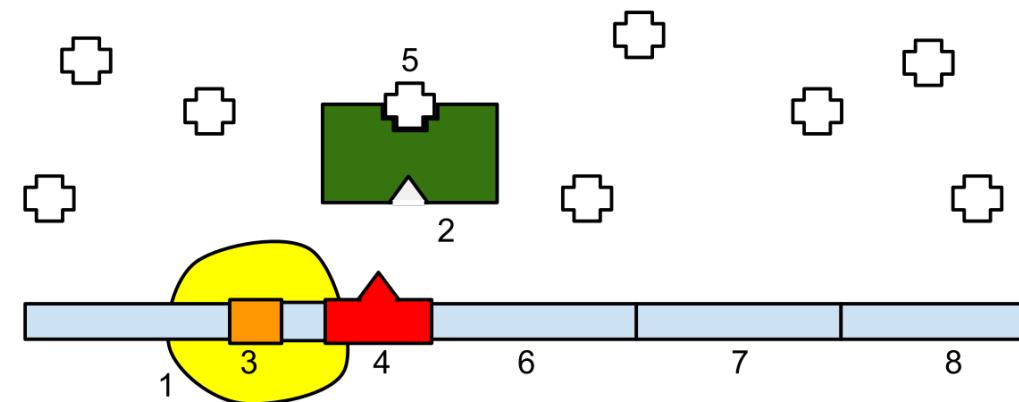
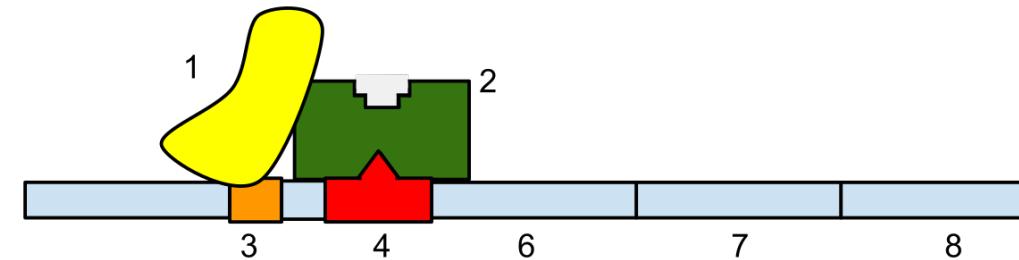
**Objective:** Describe the importance of epigenetic processes in human health and disease

## 2. Imprinting

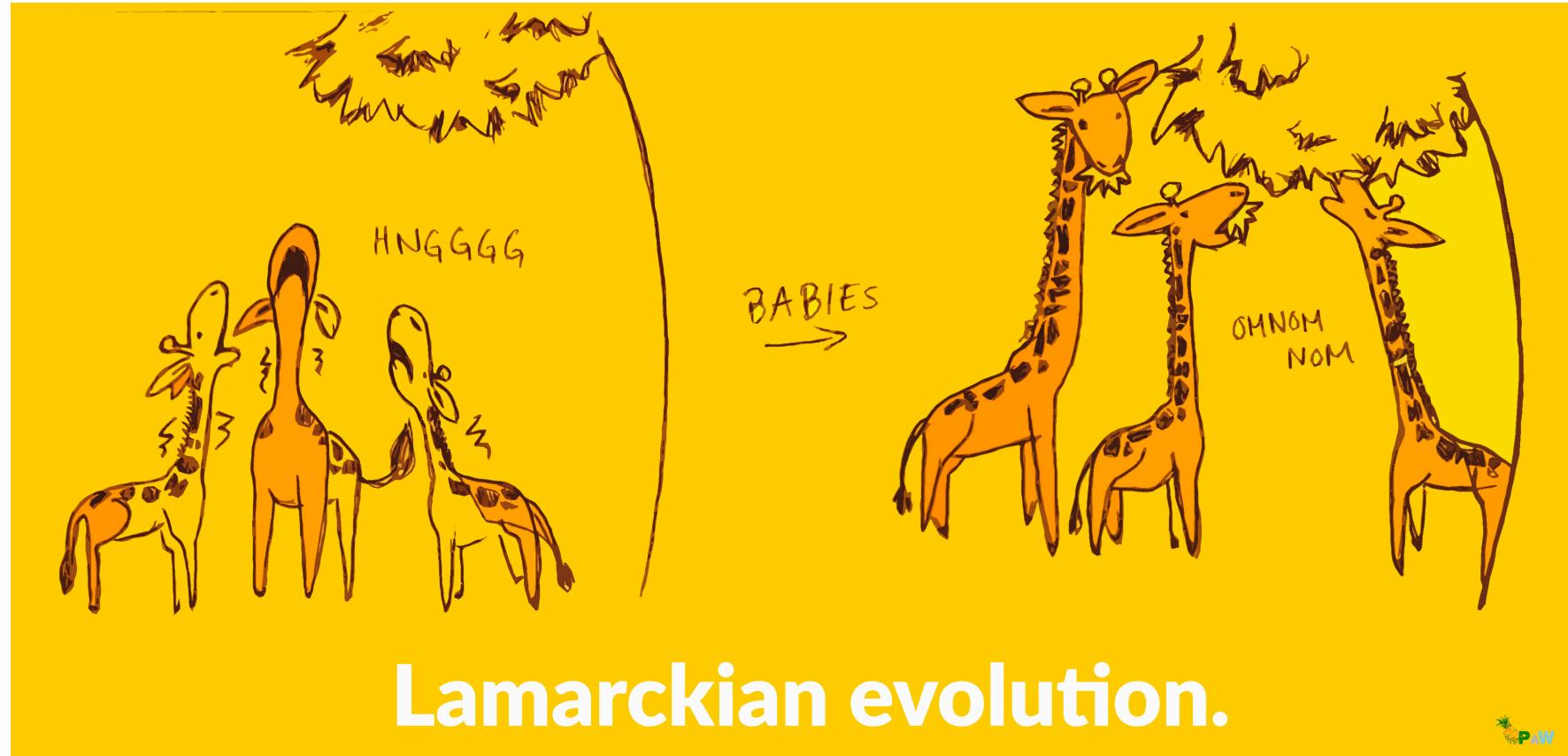
**Objective:** Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases

# What epigenetics is not..

- Genes expressed under certain conditions,   
consider a very basic example, the lac operon: 

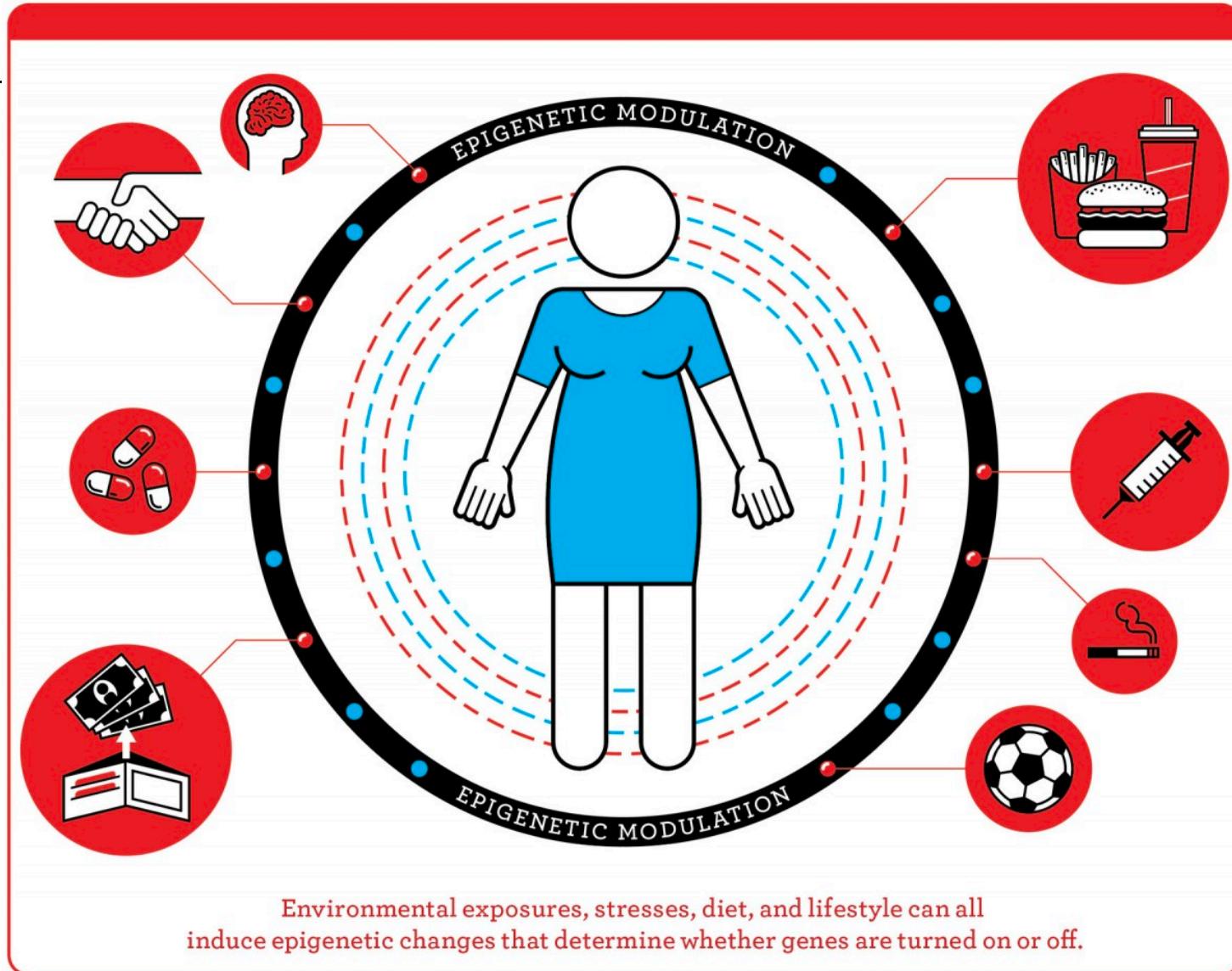


# What epigenetics is not..

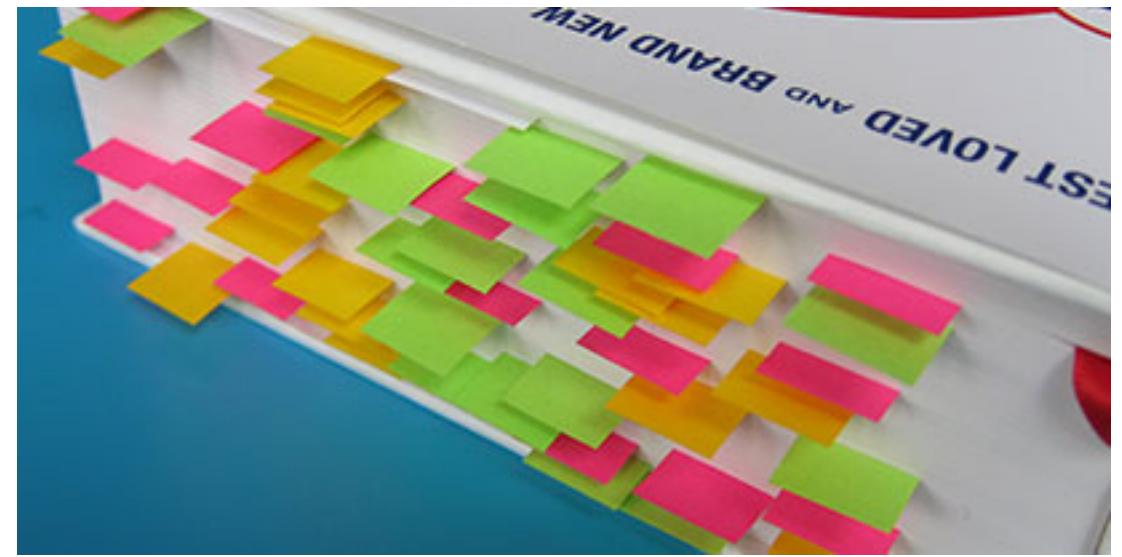
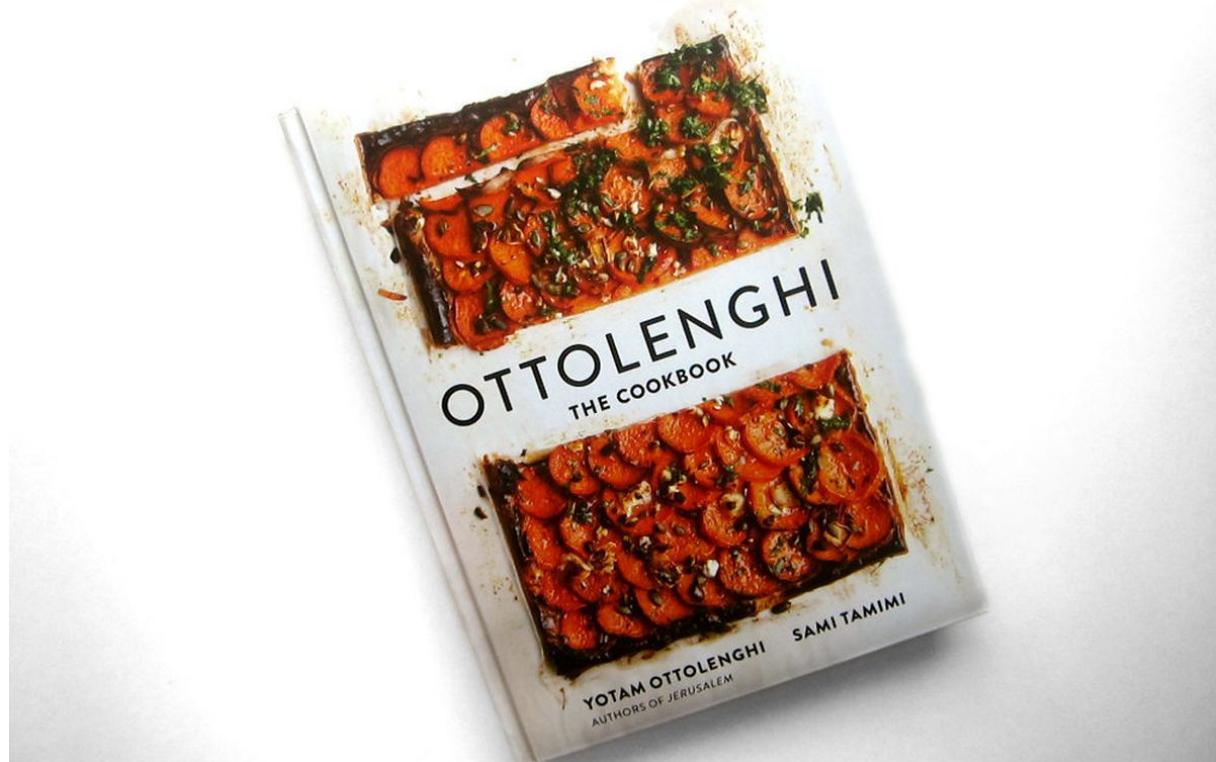


# Epigenetics

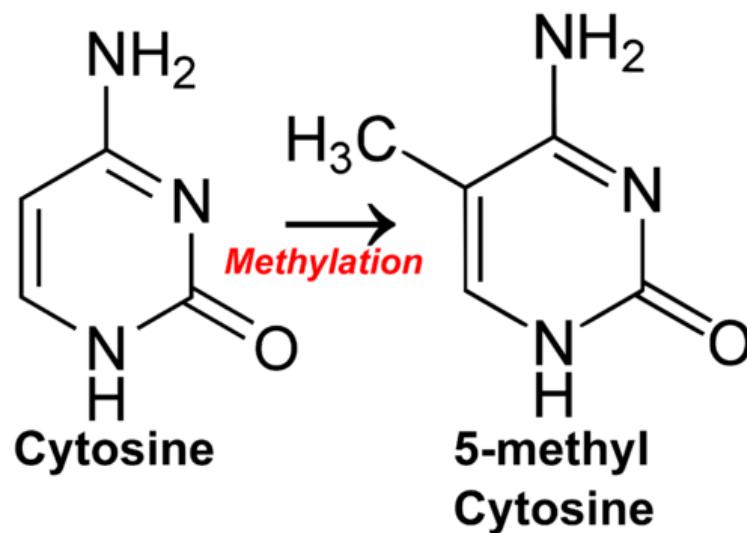
- Epi = over or upon
- Changes in gene expression that do not involve changes in DNA sequence
  - **But can be inherited**
- Changes due to our environment/experiences, that are "inherited" through cell division
- Mechanisms
  - Methylation on DNA at 'CpG islands'
  - Histone modifications / chromatin changes
  - microRNAs (associated with CpG islands)
  - more



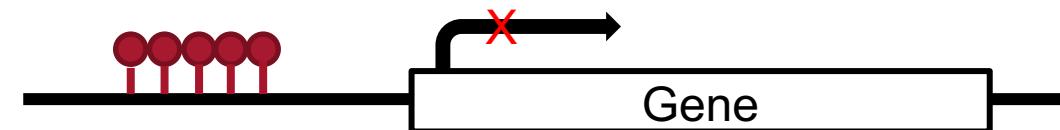
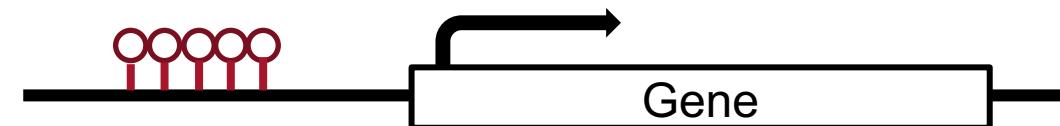
# Epigenetics analogy



# Methylation



○ Unmethylated  
● Methylated

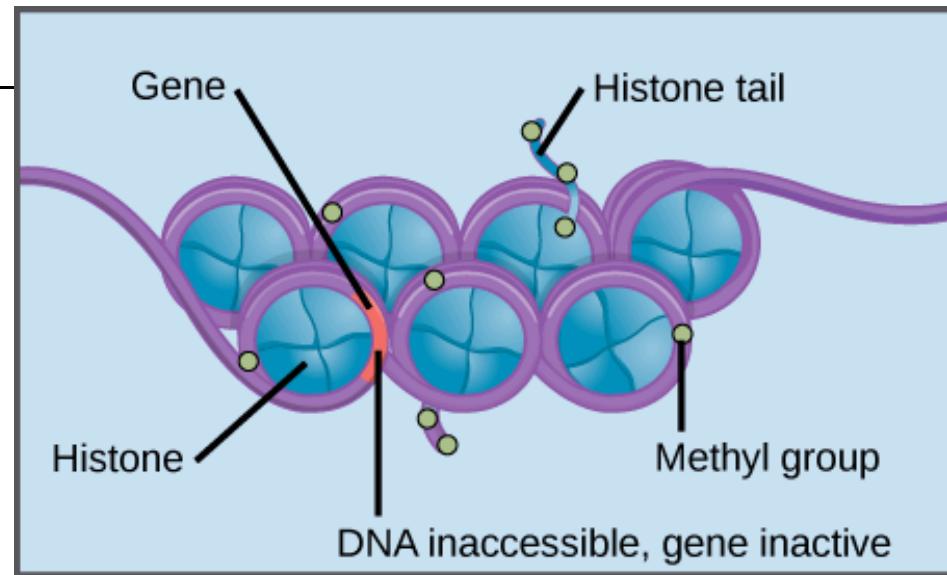


# CpG sites & Islands

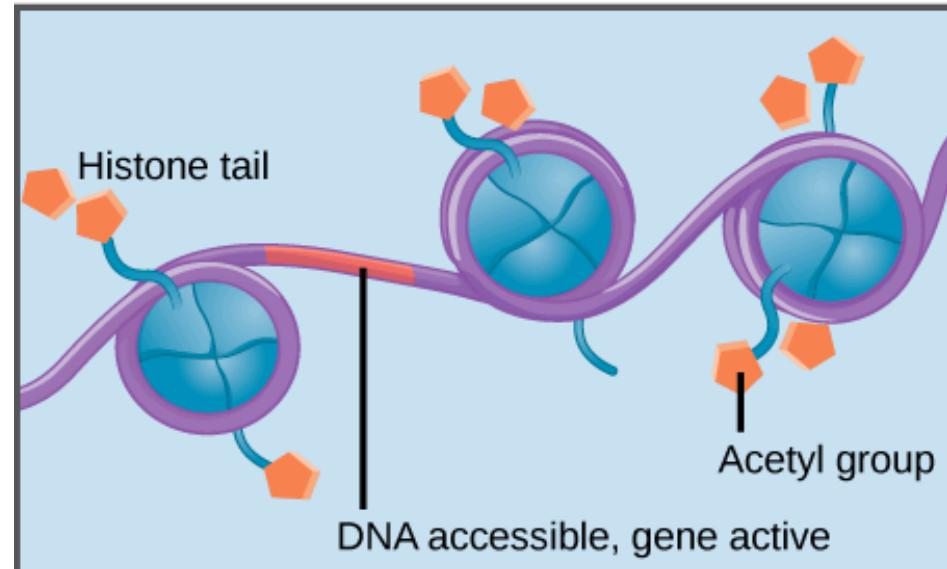


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CTCACCGCTTCTCACCC CGCCGCAGCTCC CGCGCAGCGCTGGG  
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GTGGGCGAGACCAGCTCA CGCCCTCCCTCAGCG CGCAAGGCCCGGCC  
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FTGTTCTGGGCCACATGAAACCAATTACACAGCGGGAGAACCGAGCTAA  
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# Histone modification



Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.

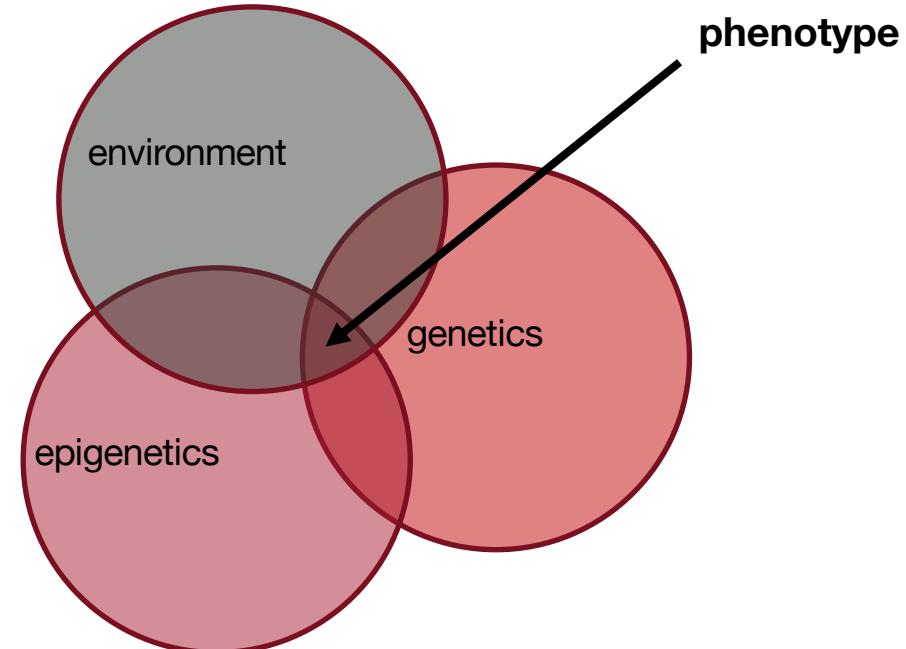


Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.

# Epigenetics

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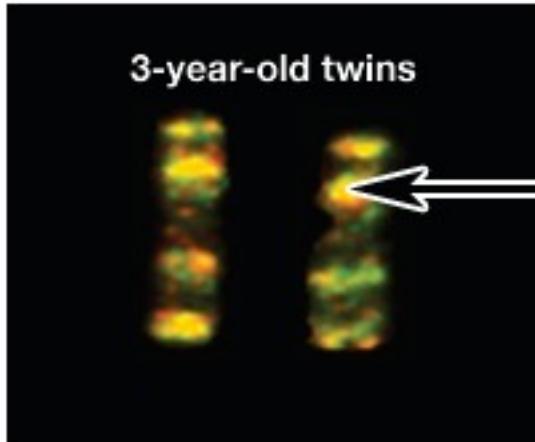
The term ‘epigenetics’ now used to explain phenotypic variation among individuals



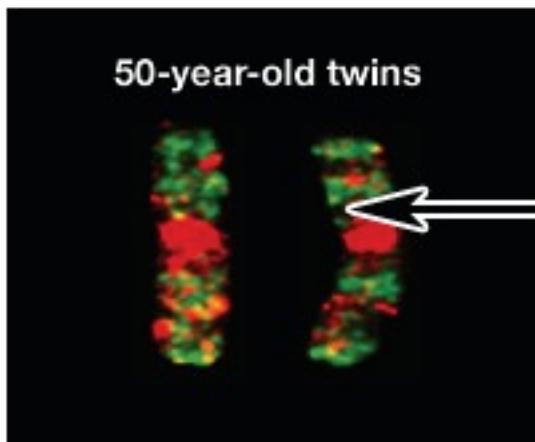
# Environmentally induced epigenetics modifications

## Chromosome 3 Pairs

3-year old twins vs. 50-year-old twins



Yellow shows where the twins have epigenetic tags in the same place.



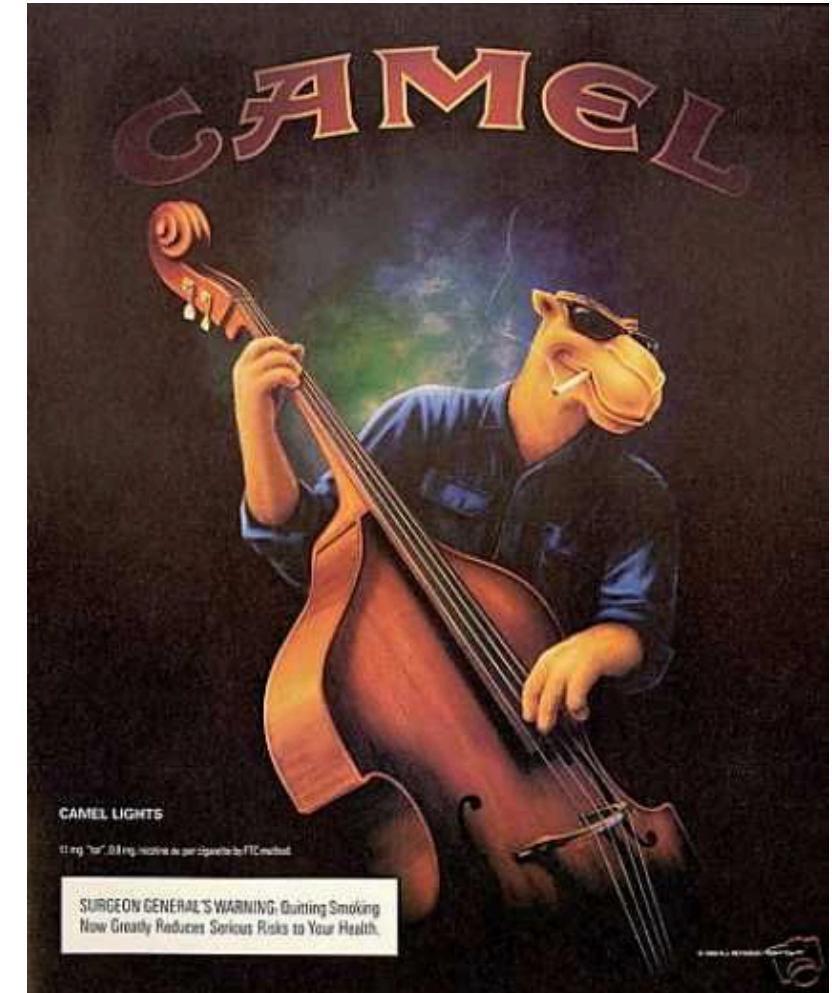
Red and green show where the twins have epigenetic tags in different places.



# Epigenetic signatures of cigarette smoking

Joehanes et al., 2016 compared DNA methylation of:

- 2,433 current smokers
- 6,518 former smokers
- 6,956 never smokers
- Comparing current to never smokers: 2,623 significantly different methylation sites linked to 1,405 genes.
- These genes more likely to be linked to pulmonary function, cancer, inflammatory disease, heart disease 
- Comparing former vs. never smokers, 185 of these remained significantly different = “persistent altered methylation” 



# Epigenetics in space?

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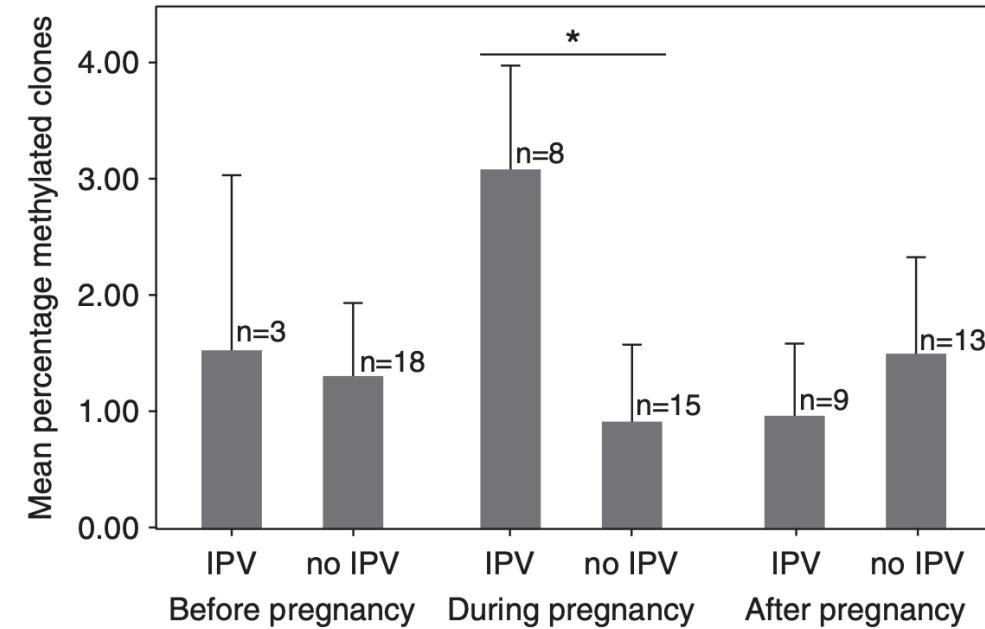
## ISS environment for one year:

- Telomeres significantly lengthened, returned to normal 2 days after landing
- Many genes differently expressed, 93% returned to normal postflight, subset of several hundred “space genes” still disrupted after return to Earth.
- Methylation changes to areas near telomere regulating gene and collagen gene



# Transgenerational epigenetics? Violence during pregnancy

- Analysed methylation of children 10-19 years whose mothers experienced intimate partner before, during, or after pregnancy
- Methylation of glucocorticoid receptor (GR) gene – linked to response to stress, higher likelihood of anxiety



**Figure 2** Gestational effects of IPV on methylation of the *GR* promoter in the children. Mean  $\pm$  s.e.m. of percentage of methylated clones for the children of women exposed to IPV. IPV only associates with increased methylation, if maternal exposure occurred during pregnancy. The percentage of methylated clones was calculated as the number of clones containing at least one methylated CpG site divided by the total number of clones. \* $P < 0.05$ ; IPV, intimate partner violence.

# Transgenerational: The Dutch Hongerwinter

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1944 - 1945

Food supplies in Nazi-occupied Holland became increasingly limited

A harsh winter froze canals, cutting off supply

Rations ~500 calories per day

## The Dutch Famine Birth Cohort Study

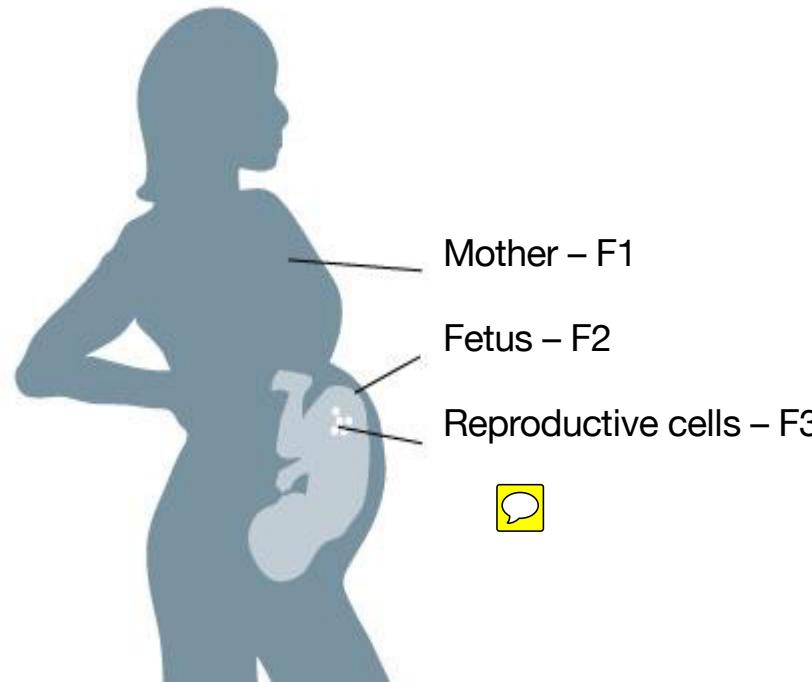
Found that the **children and the grandchildren** of pregnant women exposed to famine were more susceptible to obesity, diabetes, cardiovascular disease and other health problems.

The children who were affected in the second trimester of their mother's pregnancy had an increased incidence of schizophrenia in these children.

## In utero influences

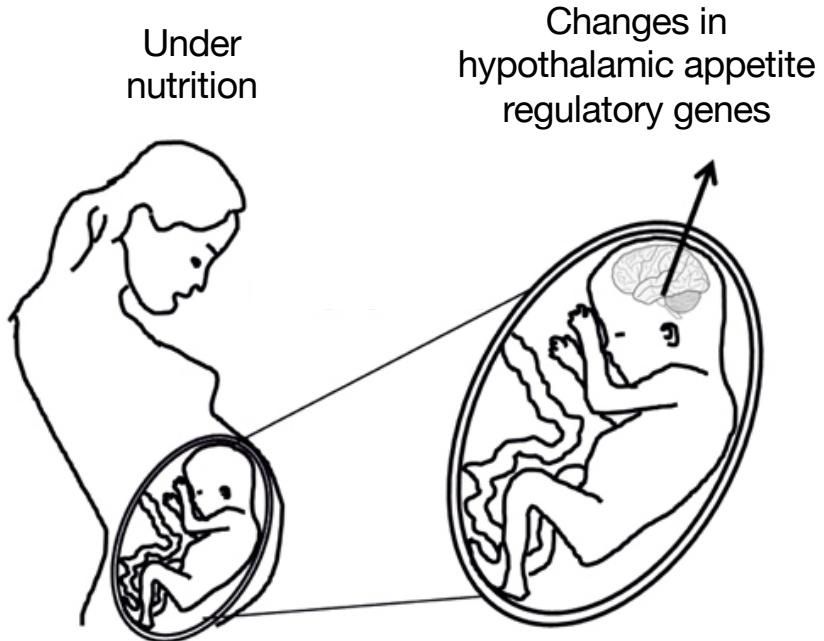
e.g. maternal nutrition, smoking, depression,  
etc.

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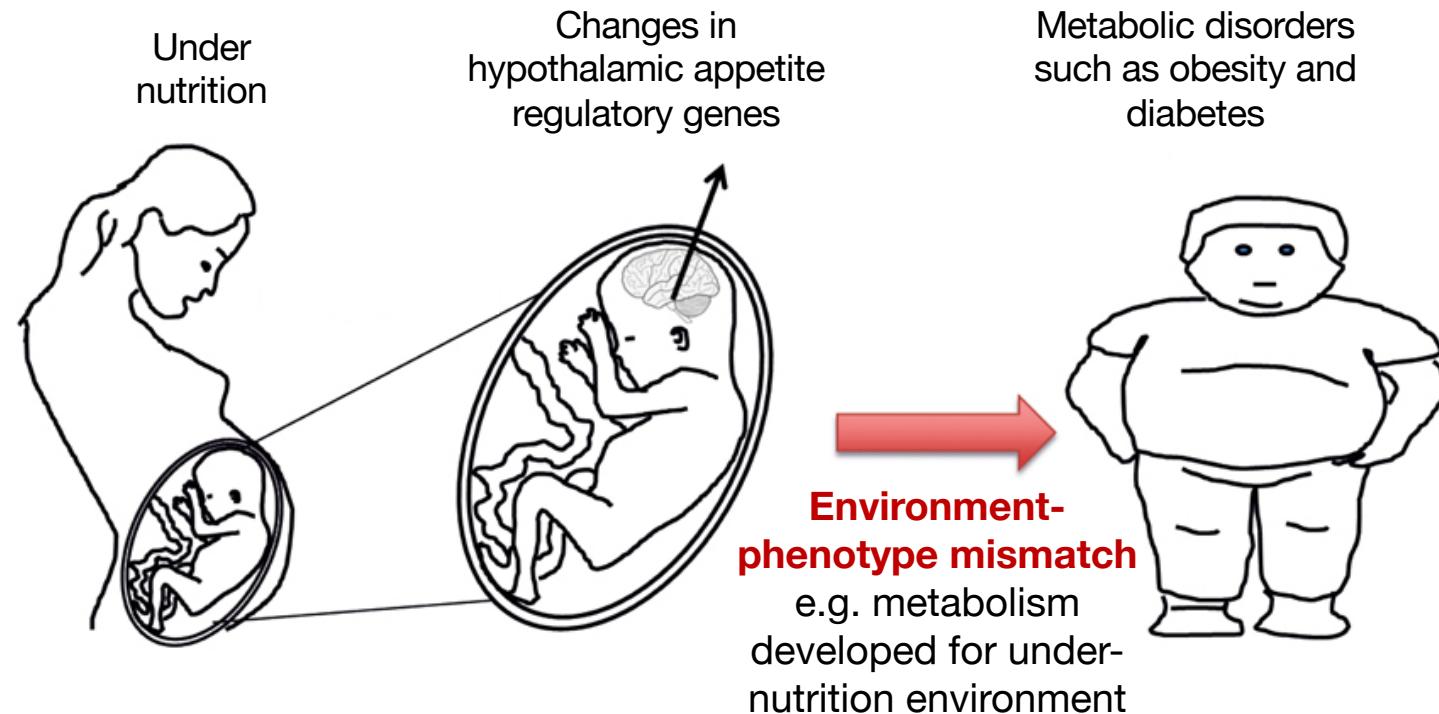


# Transgenerational Phenotypic Effects

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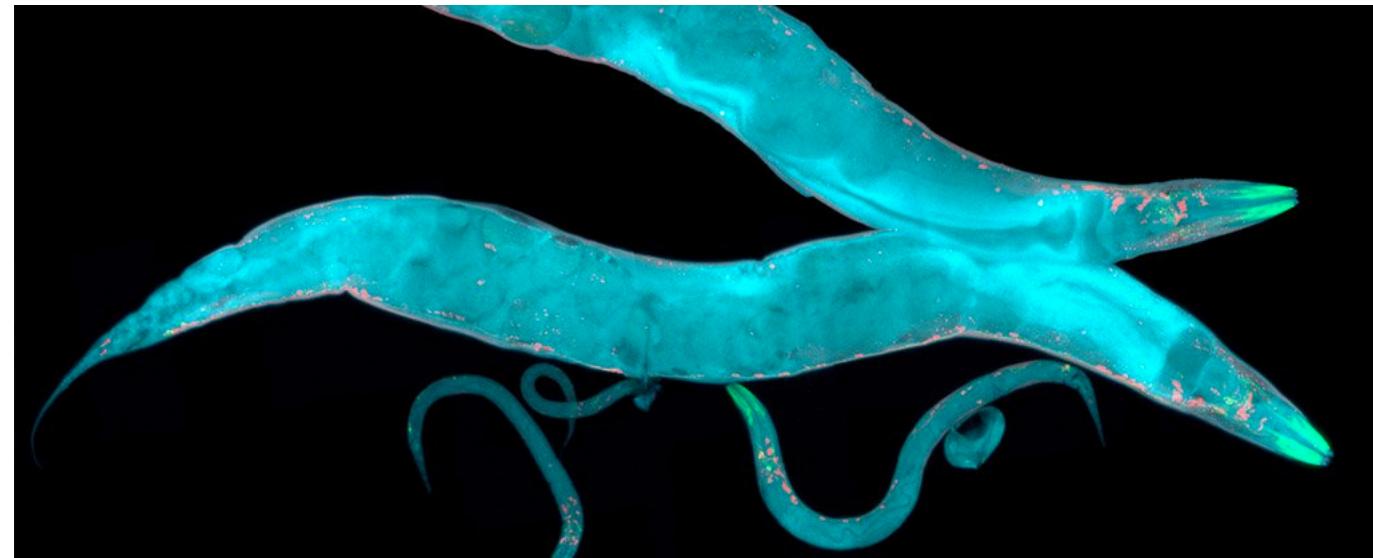


# Transgenerational Phenotypic Effects



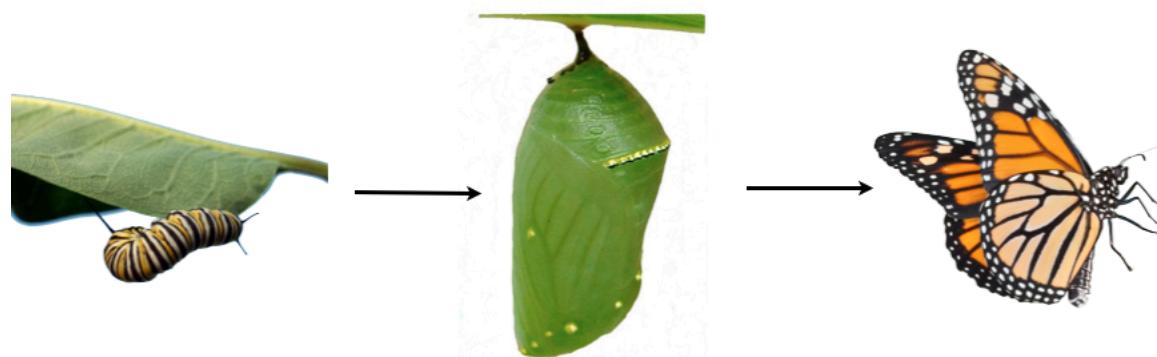
# Transgenerational epigenetics? Worm studies

- *C. elegans* kept in 25°C show increase expression in heat tolerance gene HSP90 (HSP90 promoter: fluorescence expression)
- Exposure to 25°C for 1 generation, increased expression for 7 generations
- Exposed to 25°C for 5 generations, Increased expression for 14 generations
- Histone modifications apparent cause

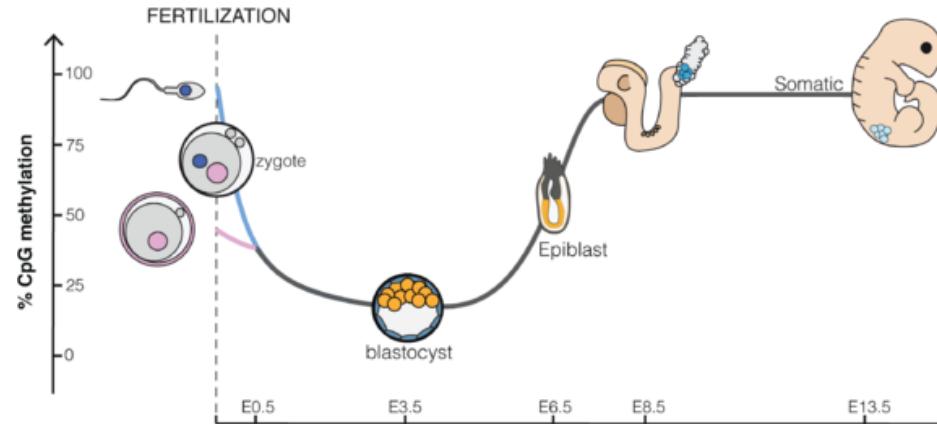


# Epigenetics and phenotypic plasticity

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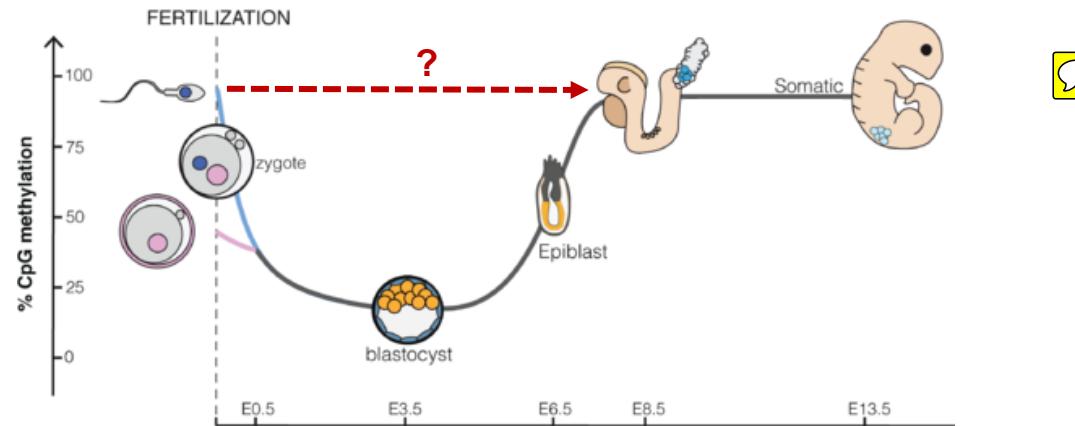
# Epigenetic Reprogramming



For inheritance of DNA Methylation patterns, some cells must escape epigenetic reprogramming during development

Only epigenetic modifications in the germ line will be passed on → are epigenetic modifications maintained during meiosis?

# Epigenetic Reprogramming



For inheritance of DNA Methylation patterns, some cells must escape epigenetic reprogramming during development

Only epigenetic modifications in the germ line will be passed on → are epigenetic modifications maintained during meiosis?



## Human Epigenome Pilot Project

The Human Epigenome Consortium is a public/private collaboration that aims to identify and catalogue Methylation Variable Positions (MVPs) in the human genome. As a prelude to the full-scale Human Epigenome Project (HEP), we have recently completed a pilot study of the methylation patterns within the Major Histocompatibility Complex (MHC) - a region of chromosome 6 that is associated with more diseases than any other region in the human genome.

We have identified MVPs in the vicinity of the promoter and other relevant regions of approximately 150 loci within the MHC in tissues from a range of individuals. This will provide an unprecedented insight into the complex relationship between genetics and epigenetics that underlies both normal cellular homeostasis and disease states, in particular autoimmune diseases.

For the pilot project, we developed an integrated genomics-based technology platform. The pipeline involves the automated bisulphite treatment of DNA from minute tissue biopsies, gene-specific bisulphite PCR and large-scale sequencing of PCR amplicons. Analysis and quantification of methylation patterns is achieved by mass spectrometric and microarray assays.

- Consortium
- Human Epigenome Pilot Project
  - Data Analysis
  - Epigenotyping
- Human Epigenome Project
- Data
- Data Release Policy
- Publications
- Home



## 1. Epigenetics

**Objective:** Describe the importance of epigenetic processes in human health and disease

## 2. Imprinting

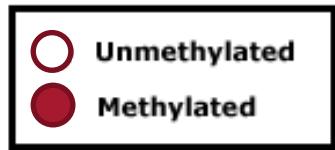


**Objective:** Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases

# Genomic Imprinting

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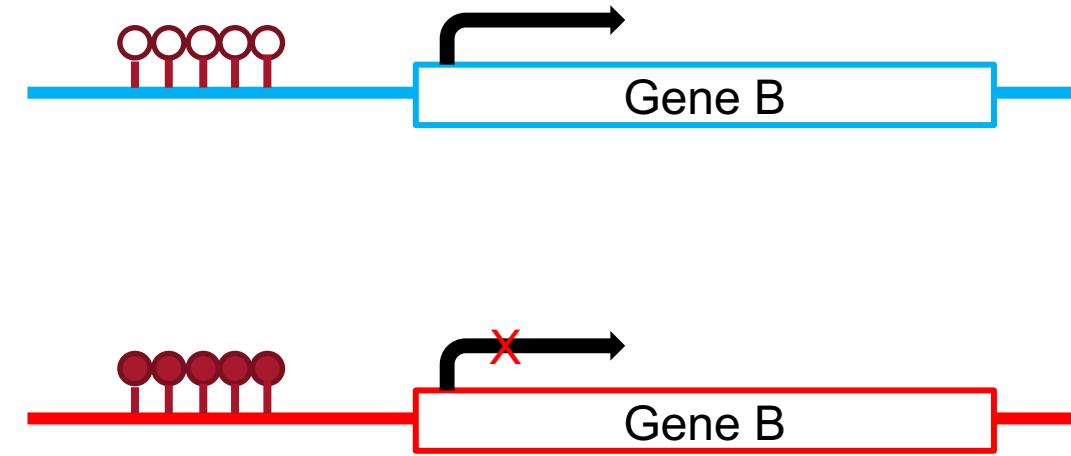
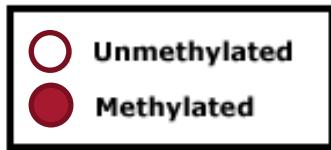
The unequal expression of the maternal and paternal alleles of a gene



# Genomic Imprinting

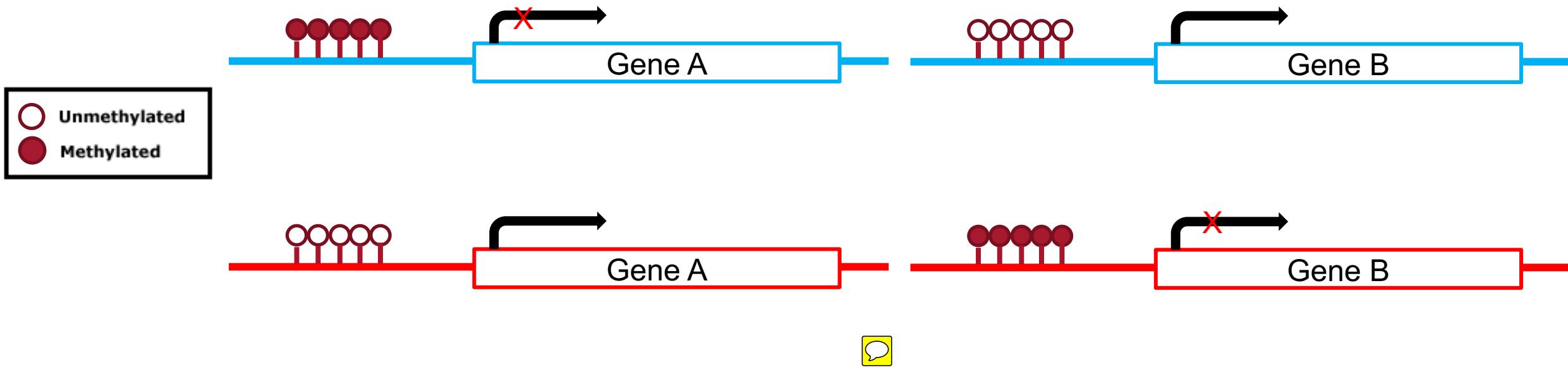
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The unequal expression of the maternal and paternal alleles of a gene



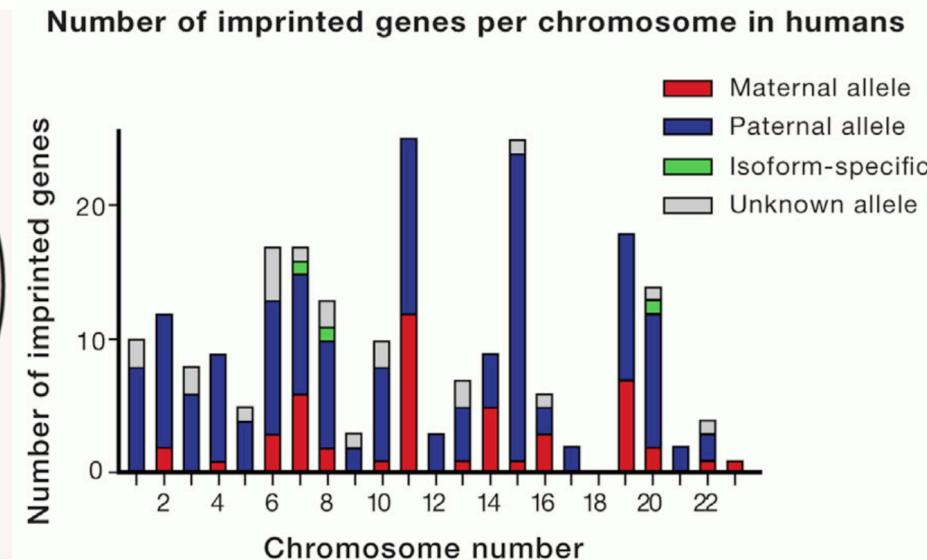
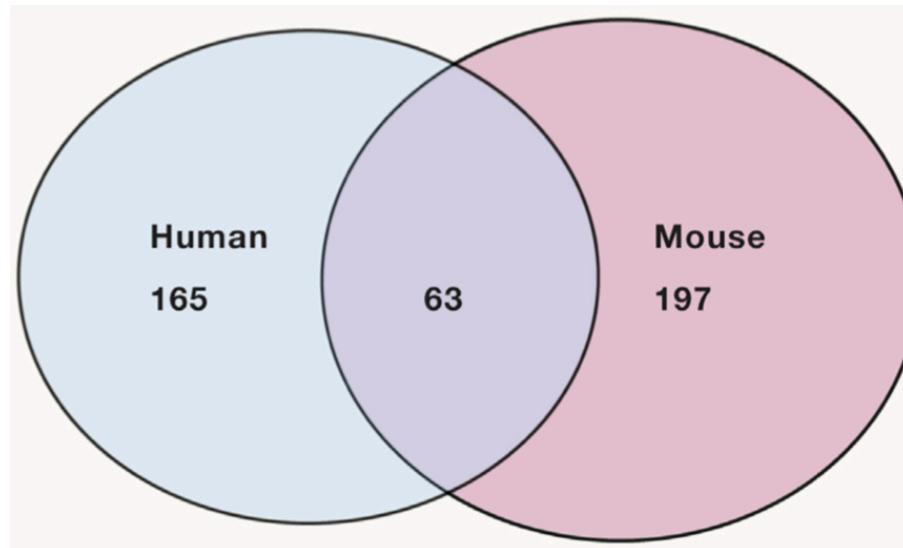
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The unequal expression of the maternal and paternal alleles of a gene

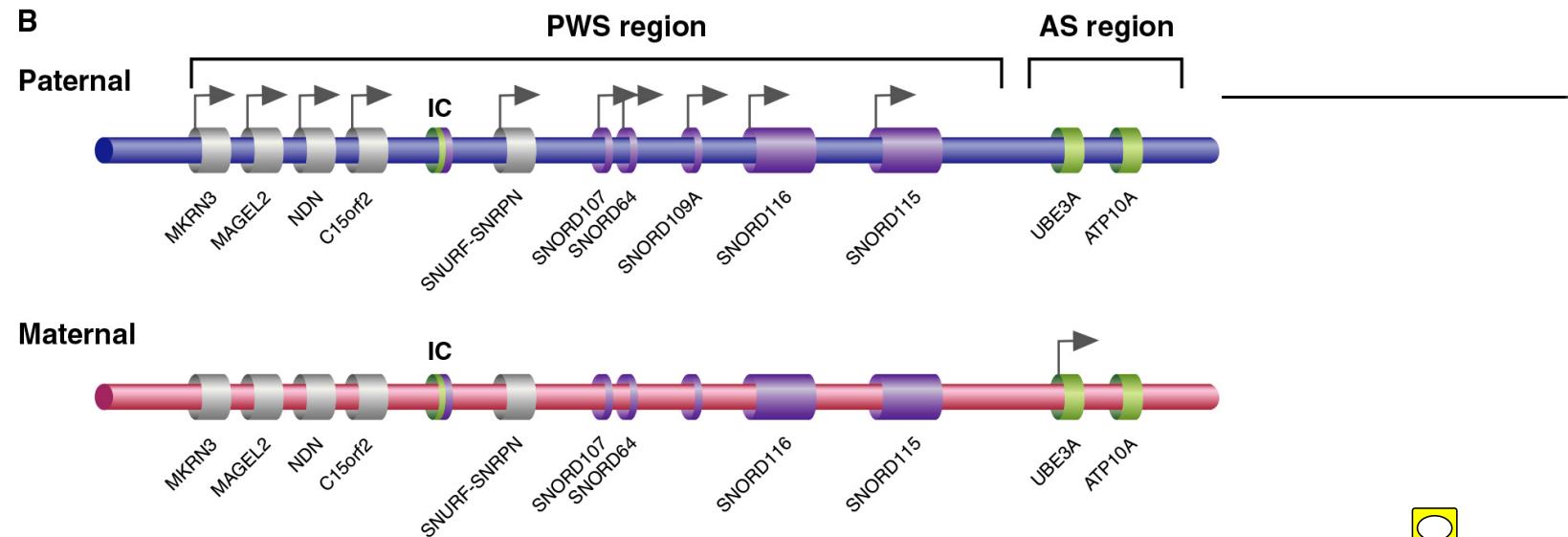


# Genomic Imprinting - humans

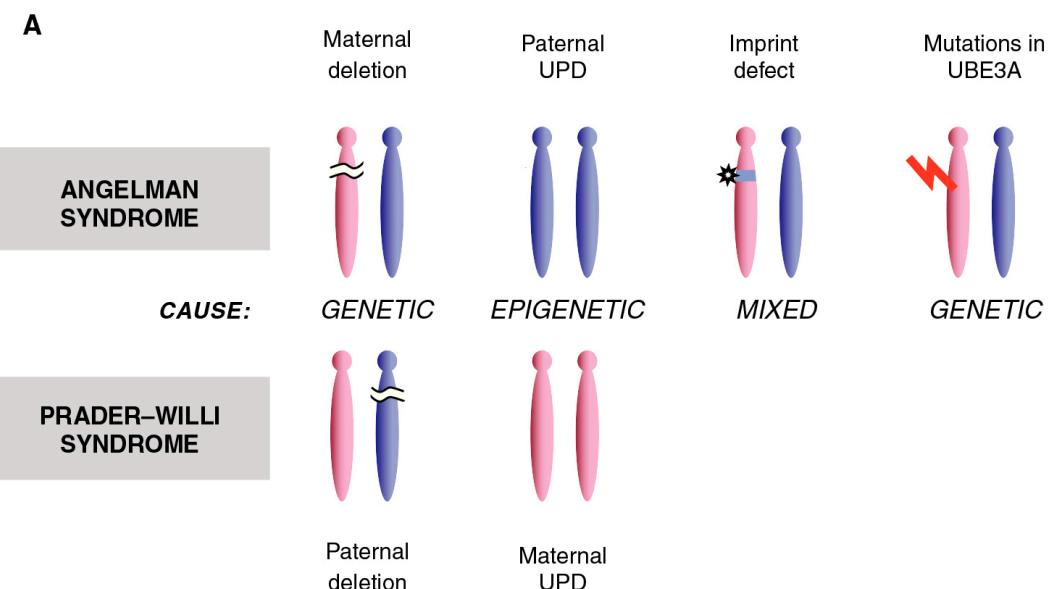
- 
- Fetal growth
  - Placental biology
  - Homeostasis
  - Nervous system
  - Half of all imprinted genes are expressed in brain



# Diseases associated with imprinting: 15q11-13 region

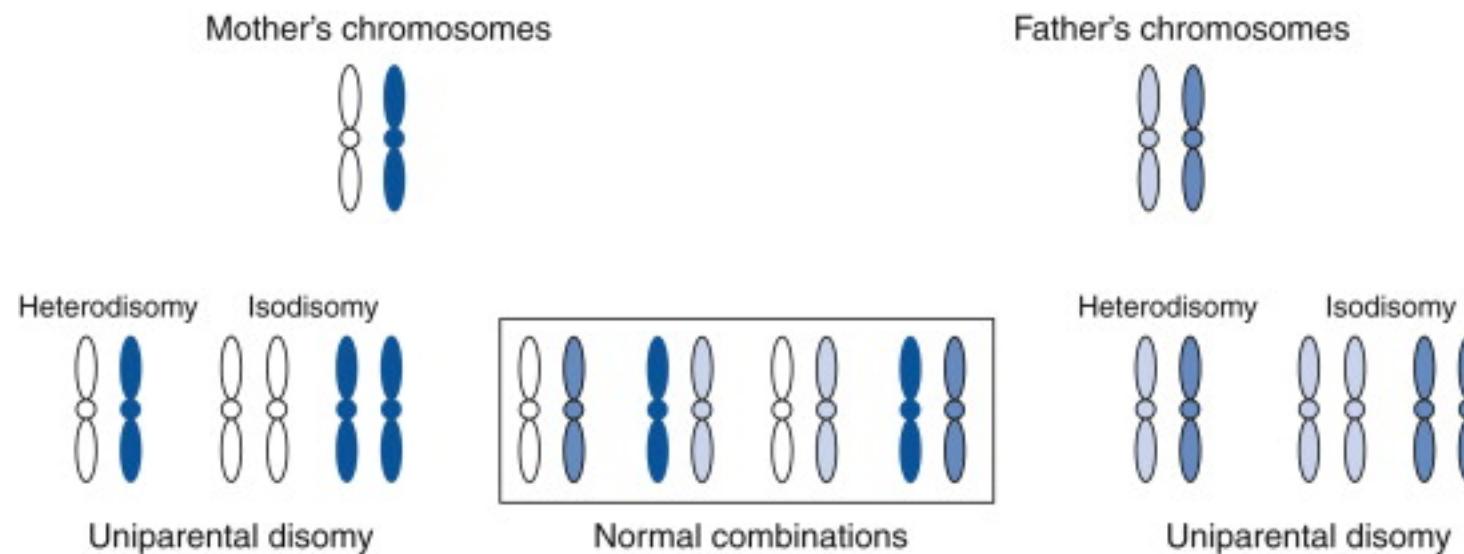


- Loss of paternal expression of 11 genes = **Prader-Willi syndrome**
- Loss of maternal expression of UBE3A = **Angelman syndrome**



# Uniparental disomy (from previous lectures)

- When two copies of a chromosome are inherited from the same parent
- **Heterodisomy** = inherited both of one parent's chromosomes
  - Error in meiosis I
- **Isodisomy** = inherited two identical copies of a chromosome from one parent
  - Error in meiosis II



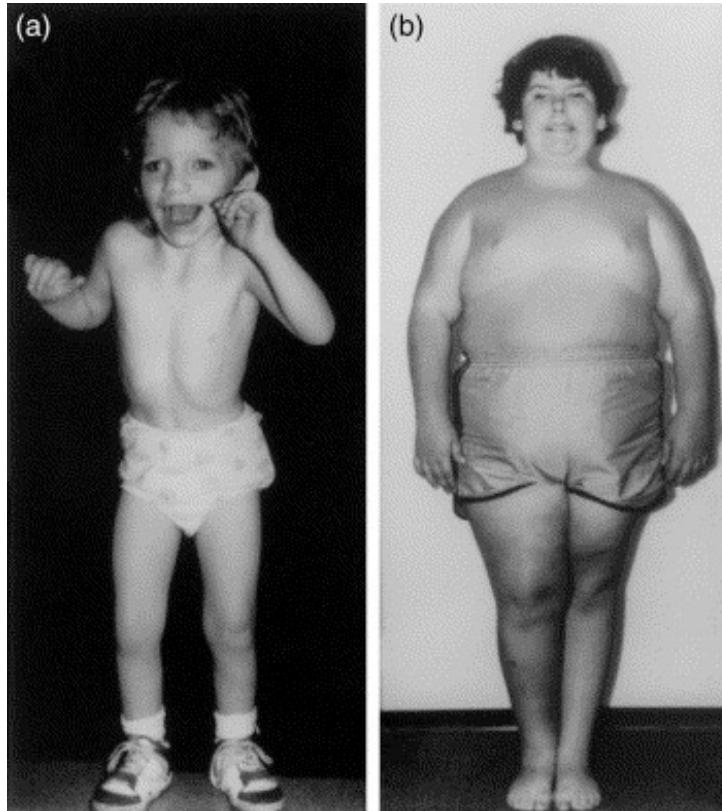
# Angelman / Prader-Willi syndromes

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Chromosome 15

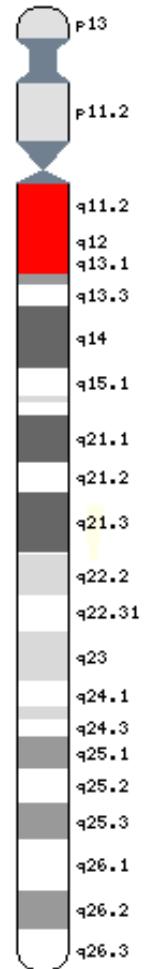
**a) Angelman Syndrome (AS)**

- jerky movements
- severe mental retardation
- growth retardation
- inappropriate laughter



**b) Prader-Willi Syndrome (PWS)**

- hypotonia (floppy baby)
- moderate mental retardation
- obesity beginning in childhood  
(caused by insatiable appetite)



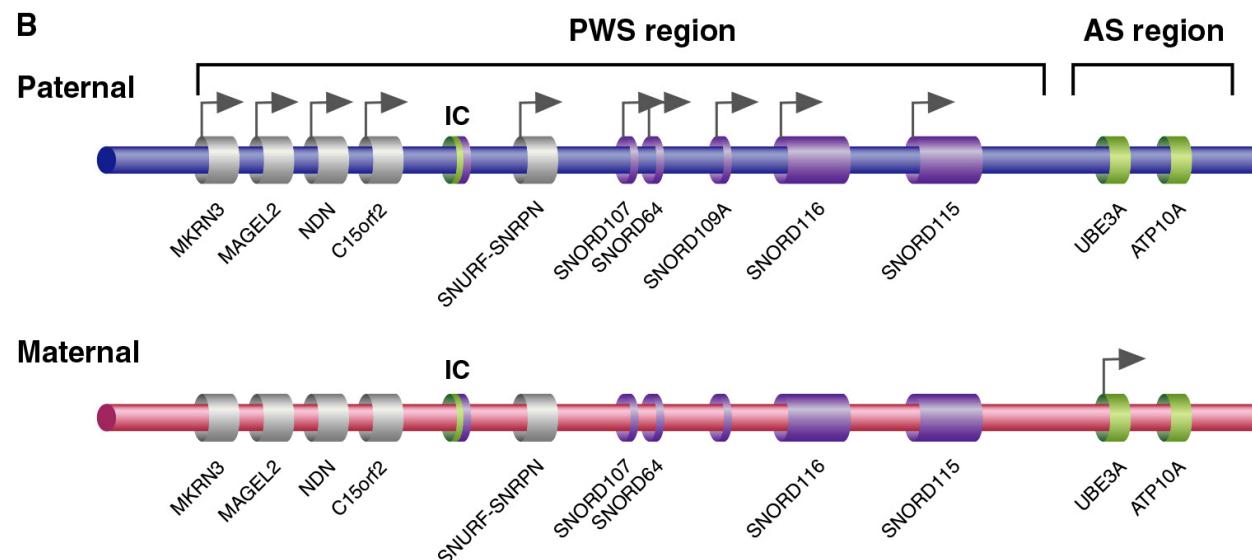
# What do these genes do?

## Angelman genes:

- **UBE3A** important for regulation of protein synthesis at synapses (junctions between nerve cells)
  - only imprinted in brain – both copies expressed in most other body tissues

## PWS genes:

- SNORD genes small nucleolar RNA – modify other RNAs
- SNORD116 most responsible for PWS symptoms?



# Other imprinting regions/conditions

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## 11p15.5

- maternal expression problems or paternal UPD = Beckwith-Wiedemann syndrome
- Paternal expression problems or maternal UPD = Silver-Russell syndrome

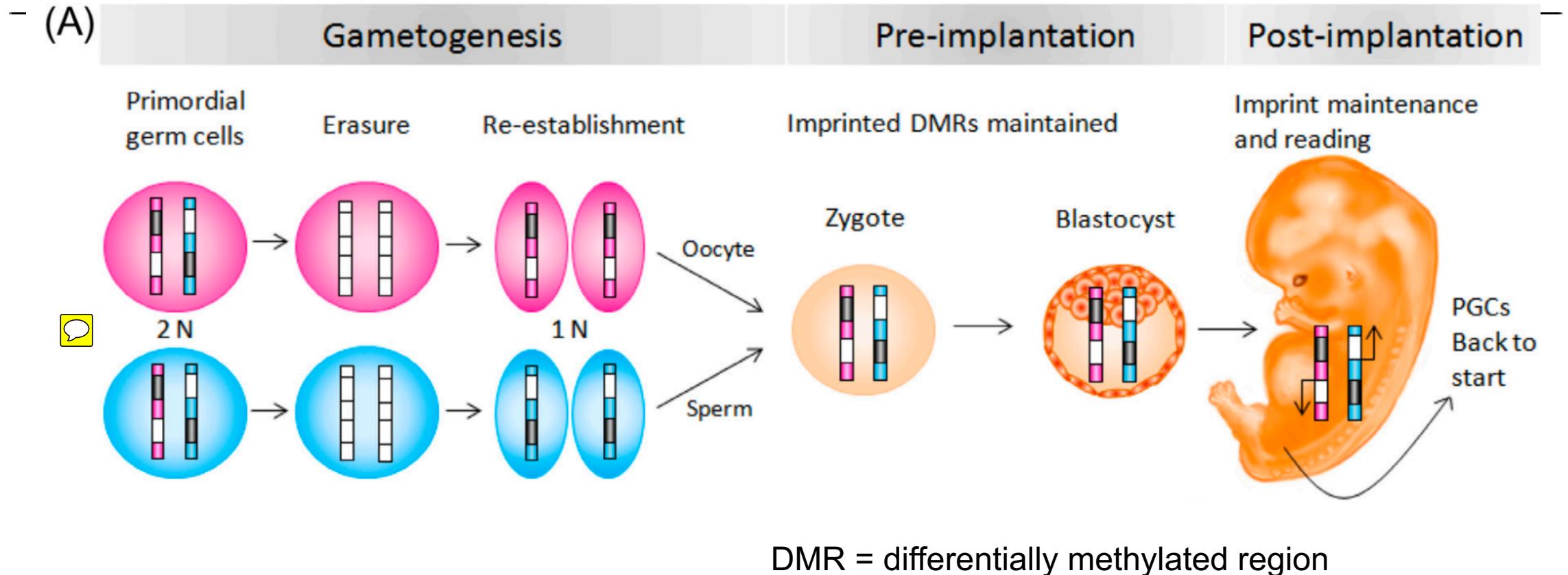
## 14q32

- MatUPD14 syndrome
- PatUPD14 syndrome

## 20q13.3

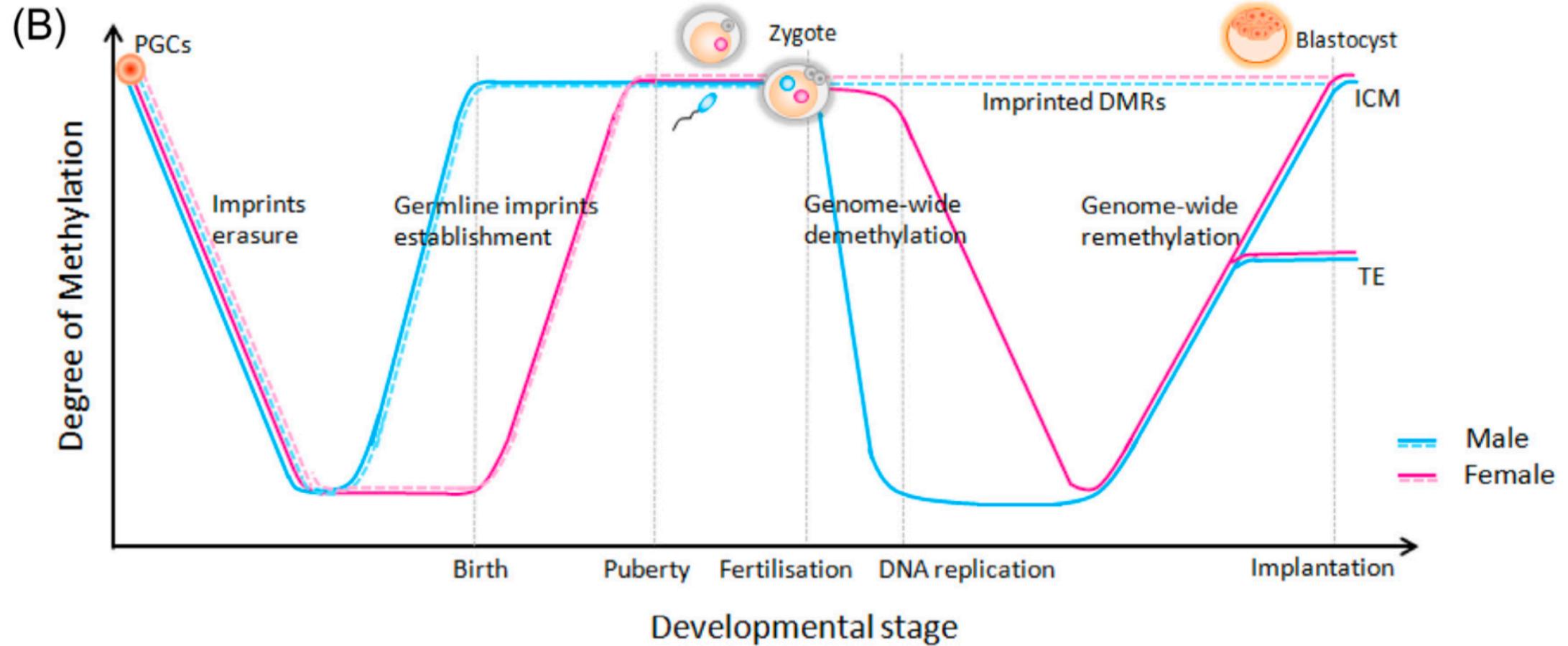
- Pseudo-hypoparathyroidism types 1a and 1b

# How does imprinting work?



PGC = primordial germ cell

# How does imprinting work?



DMR = differentially methylated region

ICM = inner cell mass, goes on to become fetus

TE = trophectoderm , goes on to become <sup>25</sup> placenta

# Why does imprinting exist?

## Evolutionary explanation - “kinship theory”



The inequality between parental genomes due to imprinting is a result of the differing interests of each parent



David Haig  
Harvard University

**Father:** greater fitness success of offspring at the expense of the mother; future babies might not have father's alleles → paternally expressed genes are growth-promoting

**Mother:** conserve resources for her own survival while providing sufficient nourishment to current and subsequent offspring → maternally expressed genes are growth-limiting

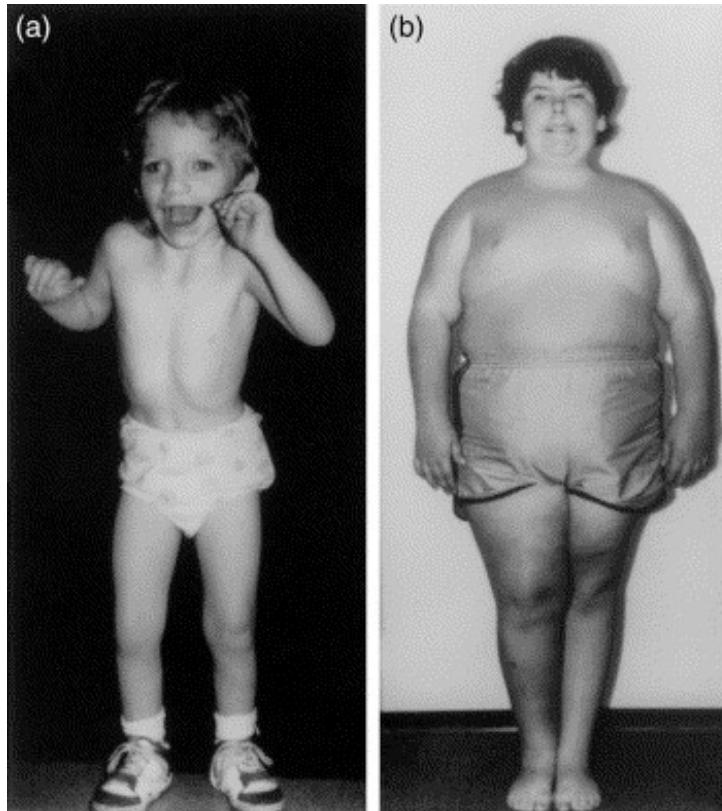
# Angelman / Prader-Willi syndromes

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Chromosome 15

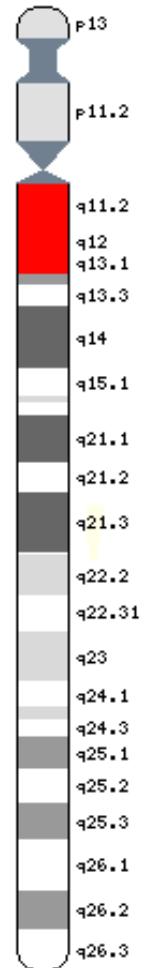
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- obesity beginning in childhood  
(caused by insatiable appetite)





## 1. Epigenetics

- Subtle layer of gene regulation
- Can persist over time/generations

**Objective:** Describe the importance of epigenetic processes in human health and disease

## 2. Imprinting

- Differential expression of genes based on parent of origin
- methylation of CpG islands
- Angelman / Pader Willi syndromes as example conditions

**Objective:** Explain the concept and mechanism of genomic imprinting, and its significance in specific human diseases