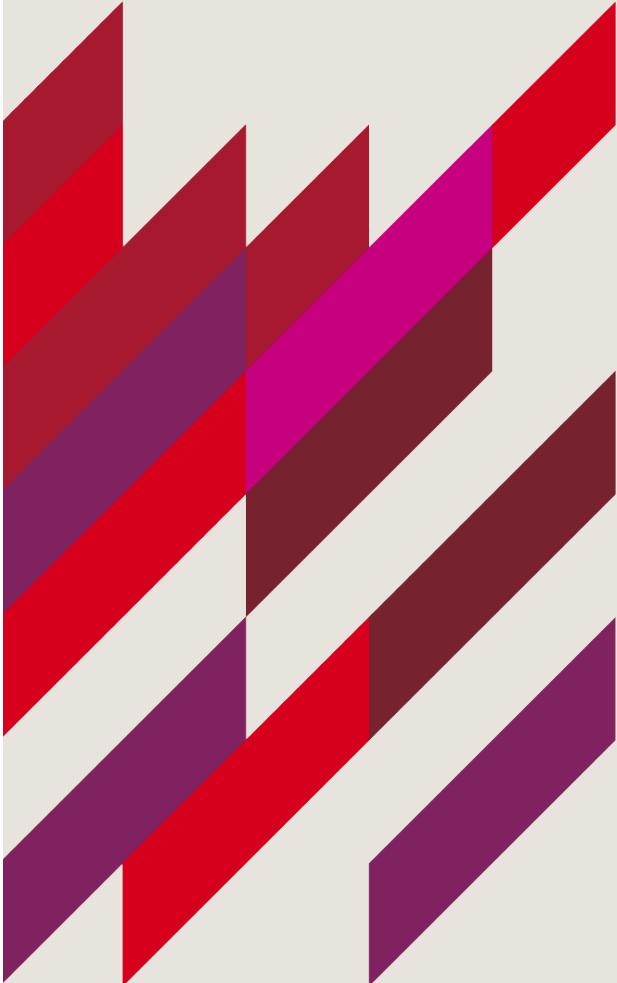


# BIOL3120: Human genetics and evolutionary medicine

## 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

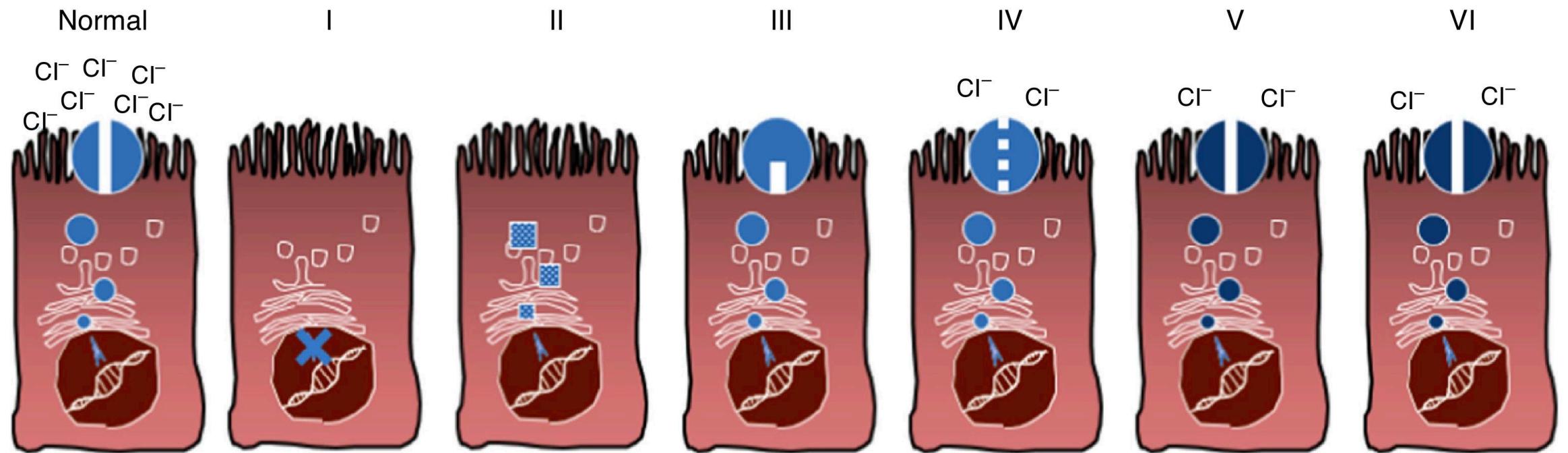
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- Haemochromatosis -> regular blood donation
- Phenylketonuria (PKU) -> low protein diet, phenylalanine restricted diet, aspartame restricted diet
- Cancer / cardiac predisposition -> make lifestyle changes, increased surveillance
- But mostly after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

# Classic medication for genetic conditions



### Class of mutation

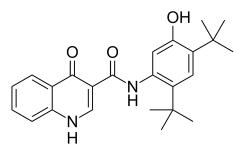


Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Main 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

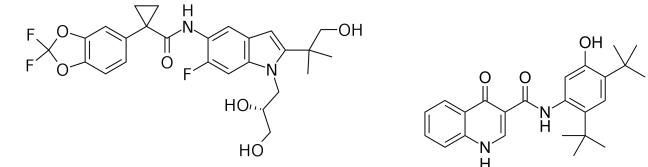
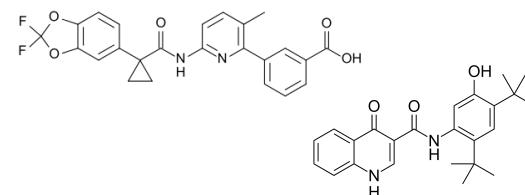
# Three treatments for cystic fibrosis



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

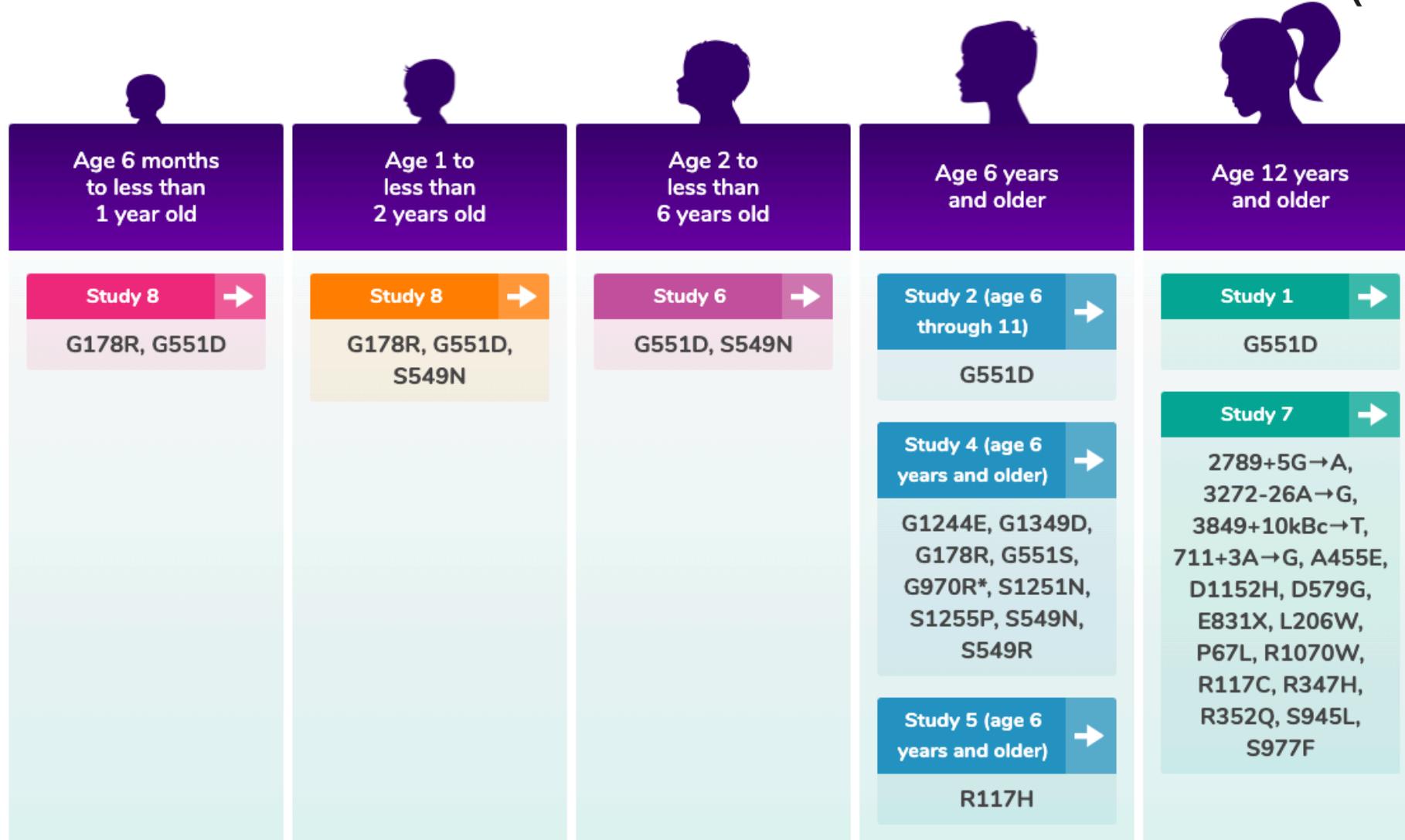


Ivacaftor = helps CFTR channels stay open



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

# Kalydeco treats a range of CF mutations



# Orkambi

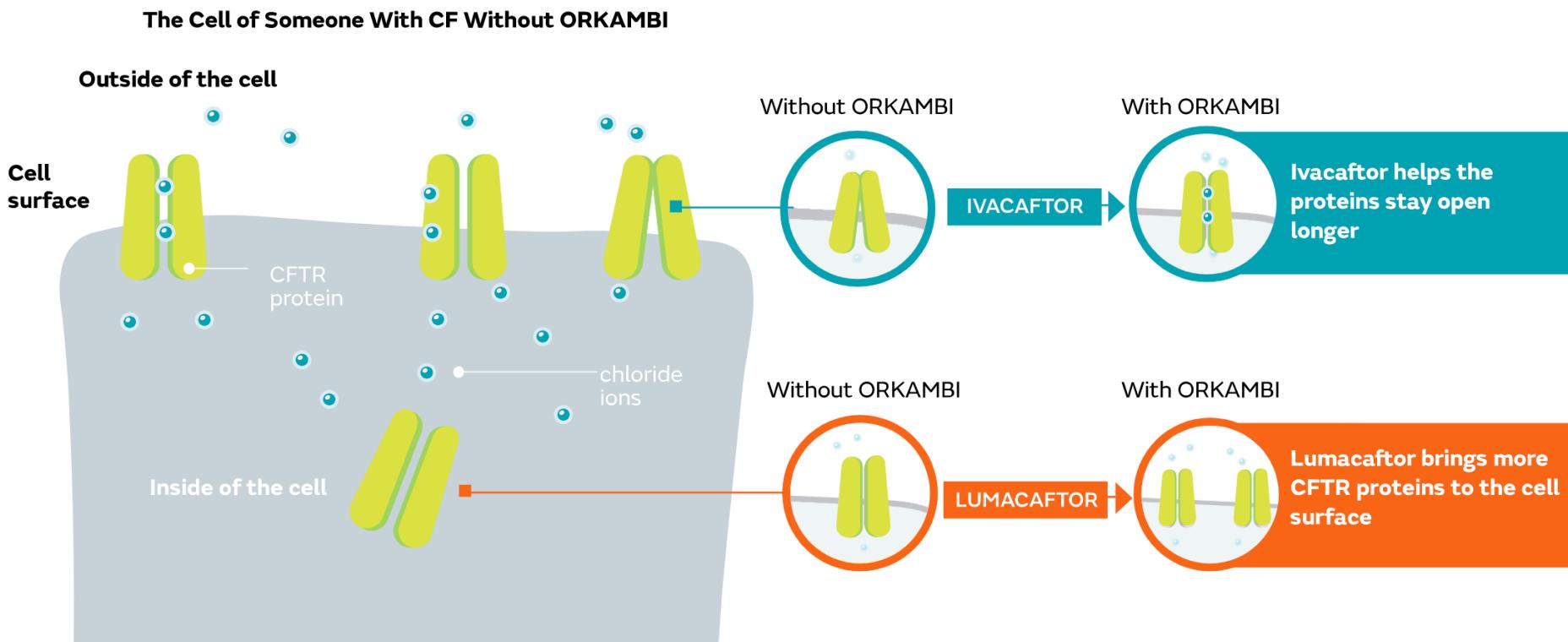


**ORKAMBI®**  
(lumacaftor/ivacaftor)

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

\*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 In**

**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 In**

**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 In**

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

# 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:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of the skin or the white part of the eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine
- confusion



**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/>

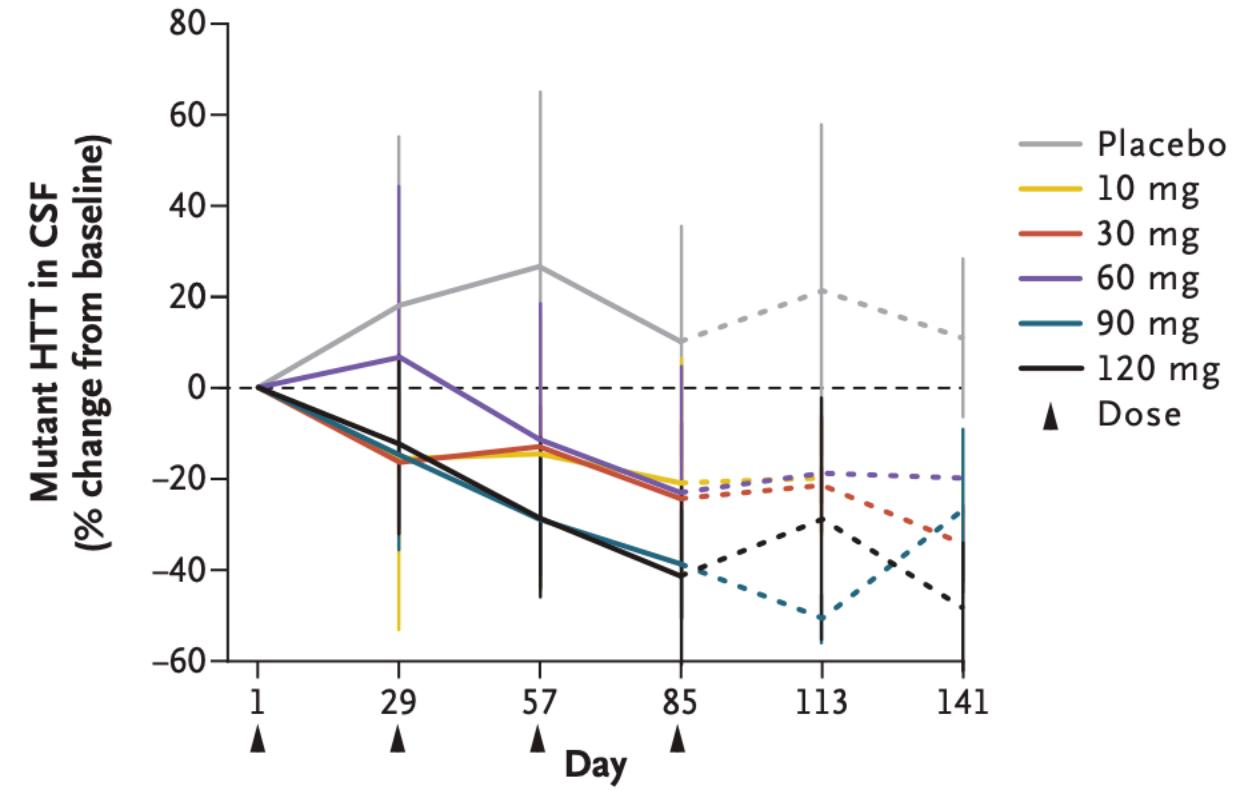
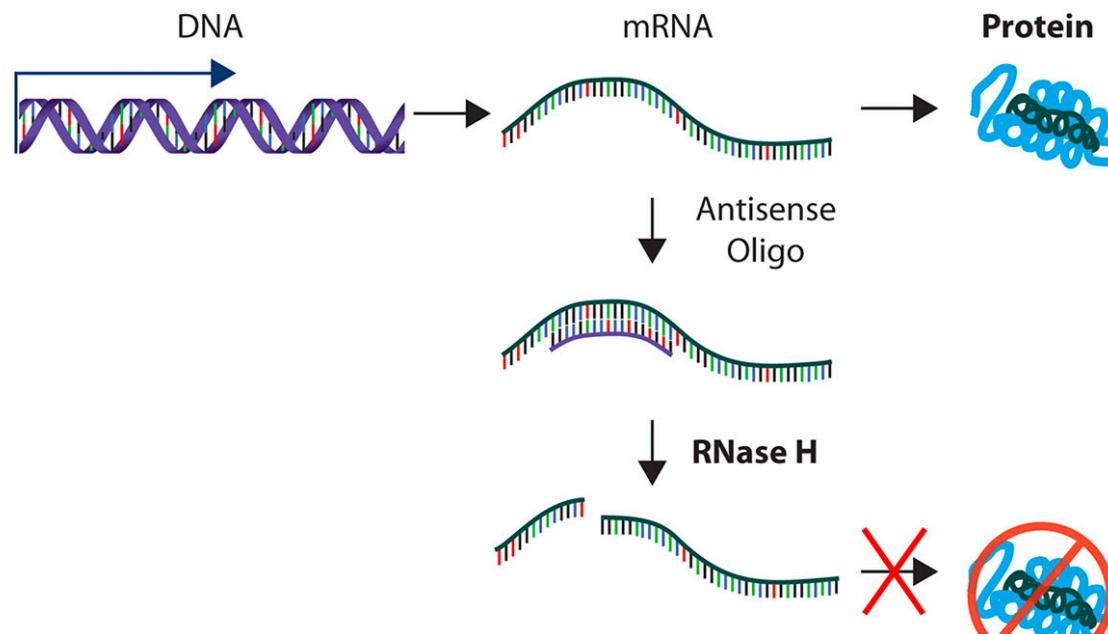
# Price...

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

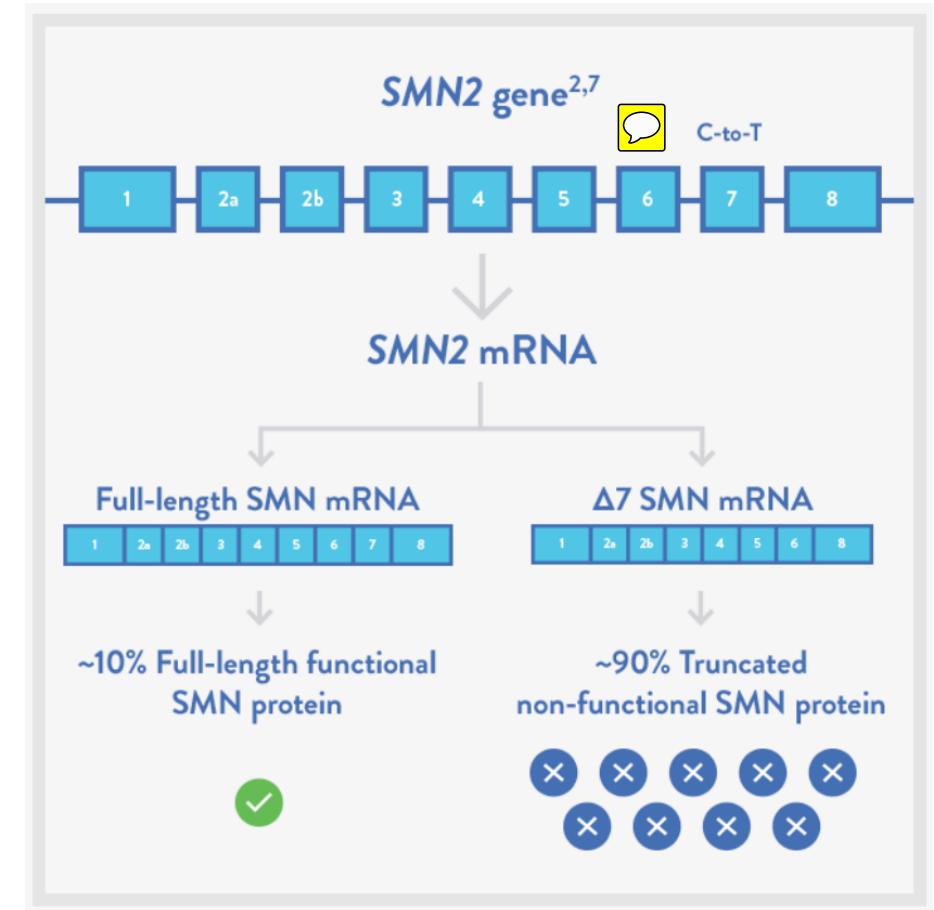
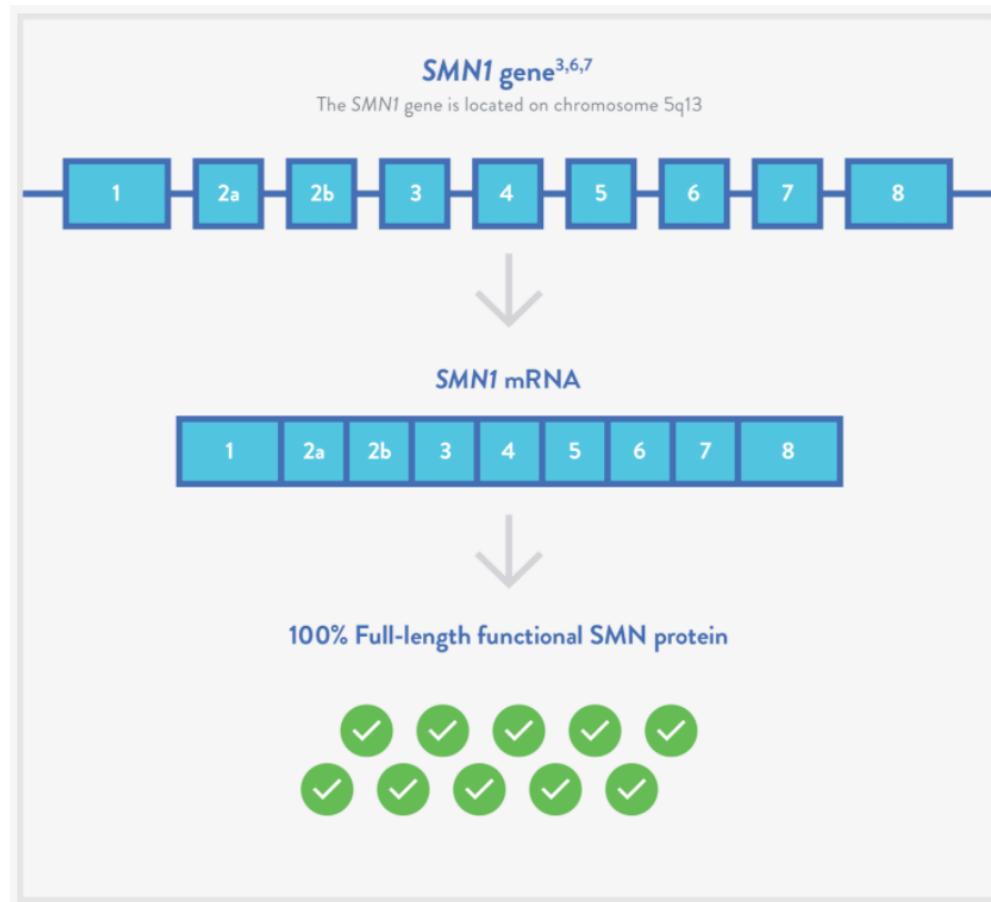
# Nucleic acids as medication for genetic conditions



# Huntington's disease treatment: antisense oligonucleotide gene silencing



# Spinal muscular atrophy (SMA) – Autosomal recessive



# Spinal muscular atrophy (SMA) – Autosomal recessive

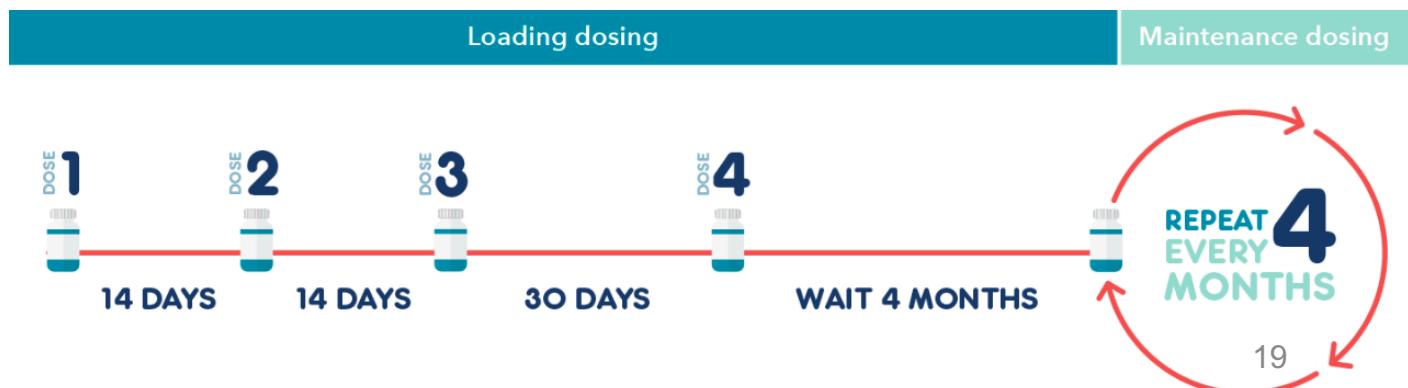
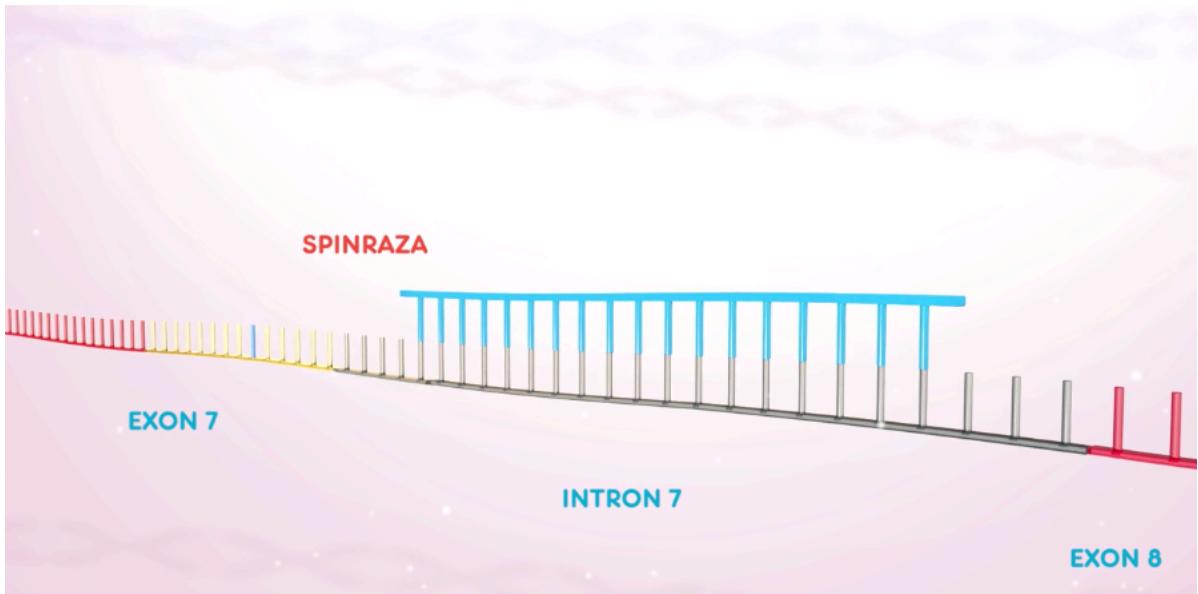
Phenotype	Age of Onset	Life Span <sup>1</sup>
<b>SMA 0</b>	Prenatal	A few weeks, <6 mos
<b>SMA I</b>	<6 mos	Median survival 8-10 mos
<b>SMA II</b>	6-18 mos	70% alive at age 25 yrs
<b>SMA III</b>	>18 mos	Normal
<b>SMA IV</b>	Adulthood	Normal

- 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

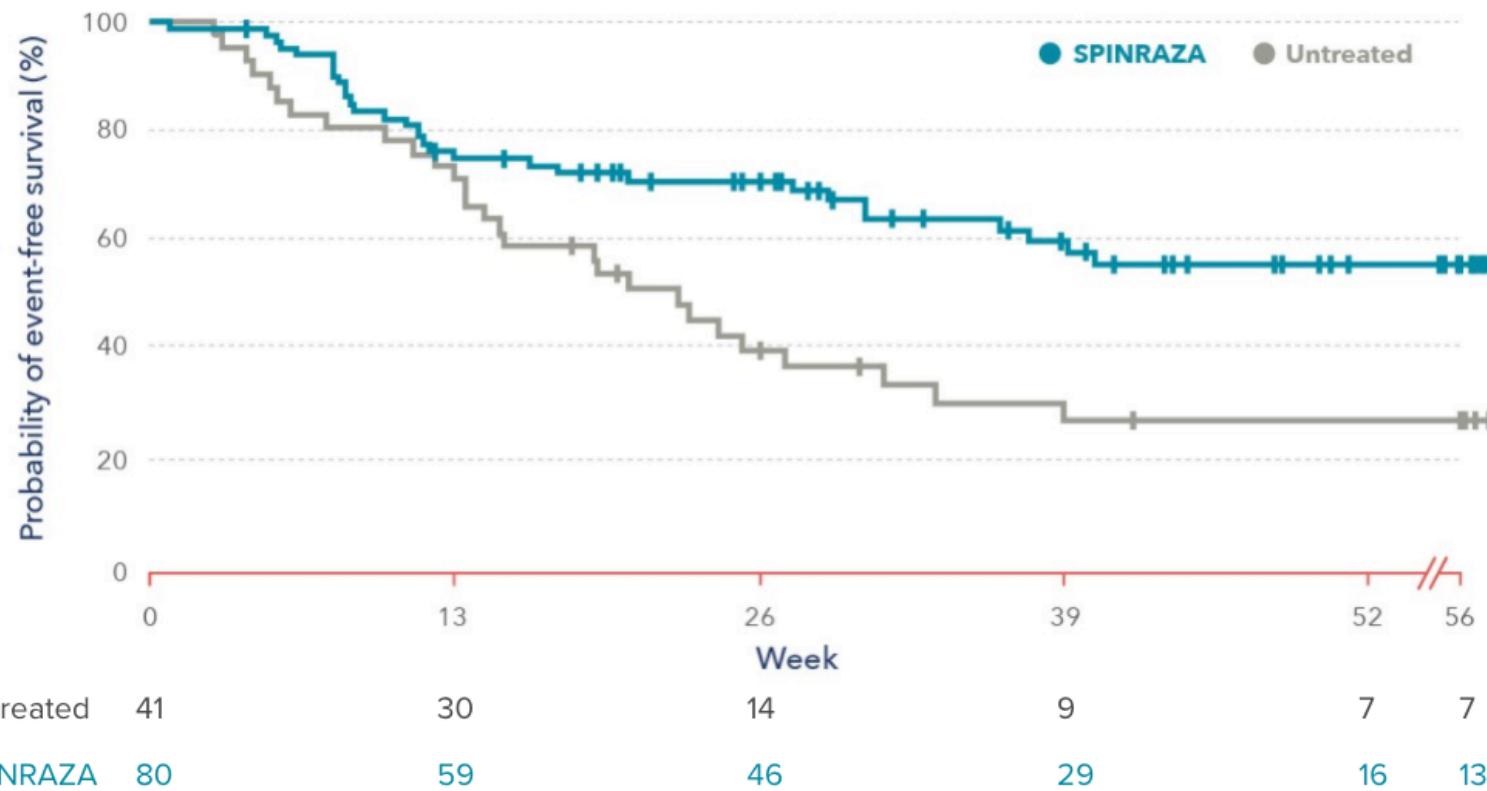
# SMA treatment



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



# SMA treatment



**47%**

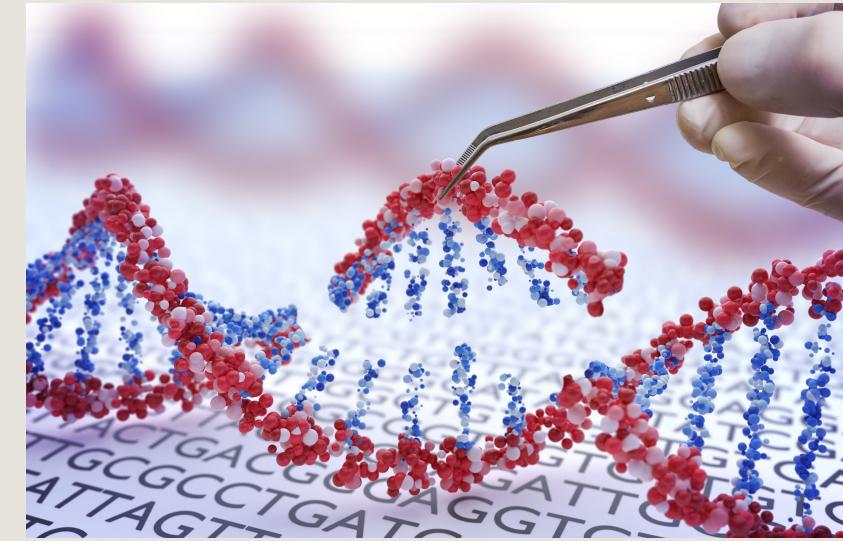
reduction in risk of death or  
permanent ventilation  
(HR=0.53; P=0.005)<sup>1</sup>

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>

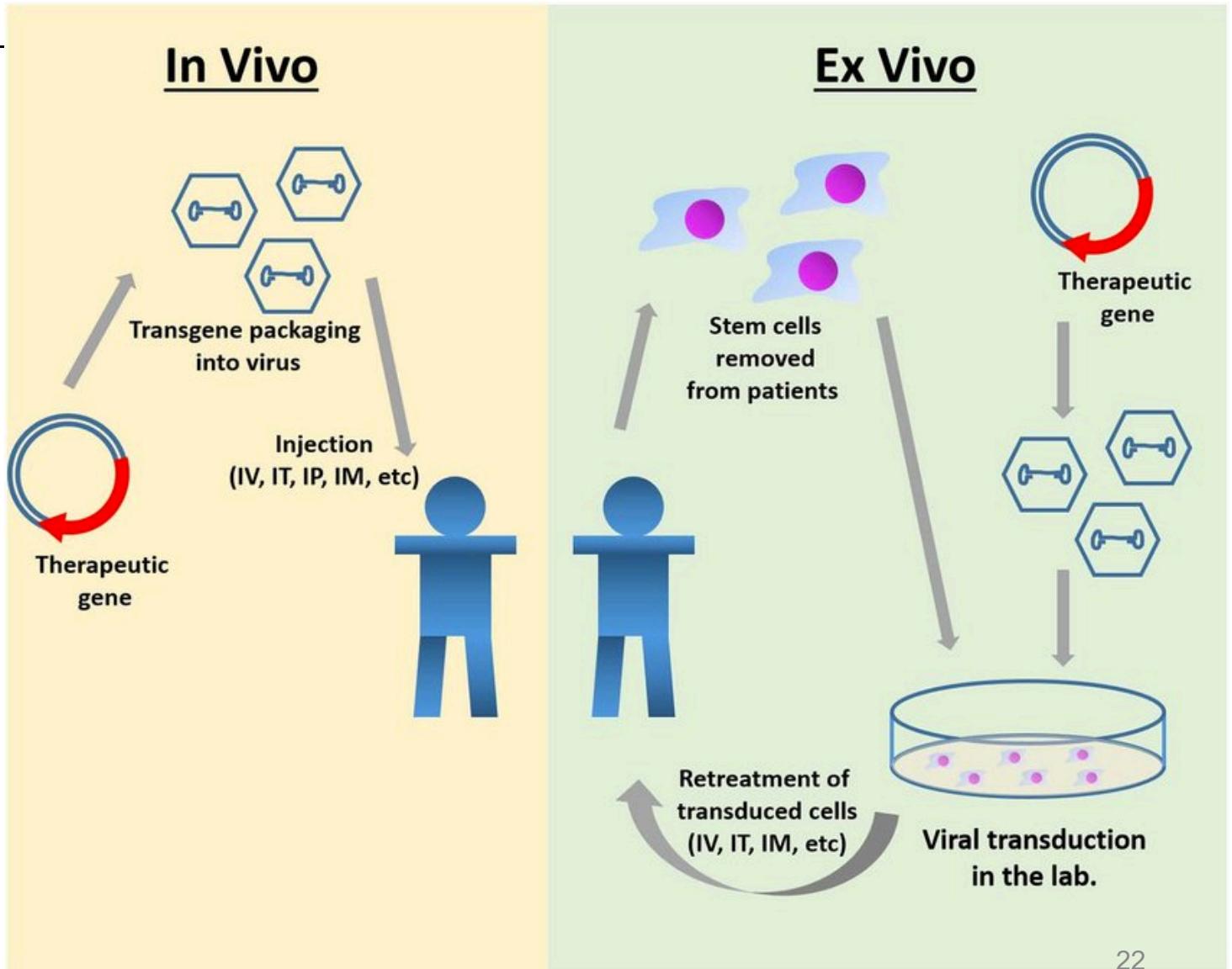
# Gene therapy for genetic conditions



# Gene therapy

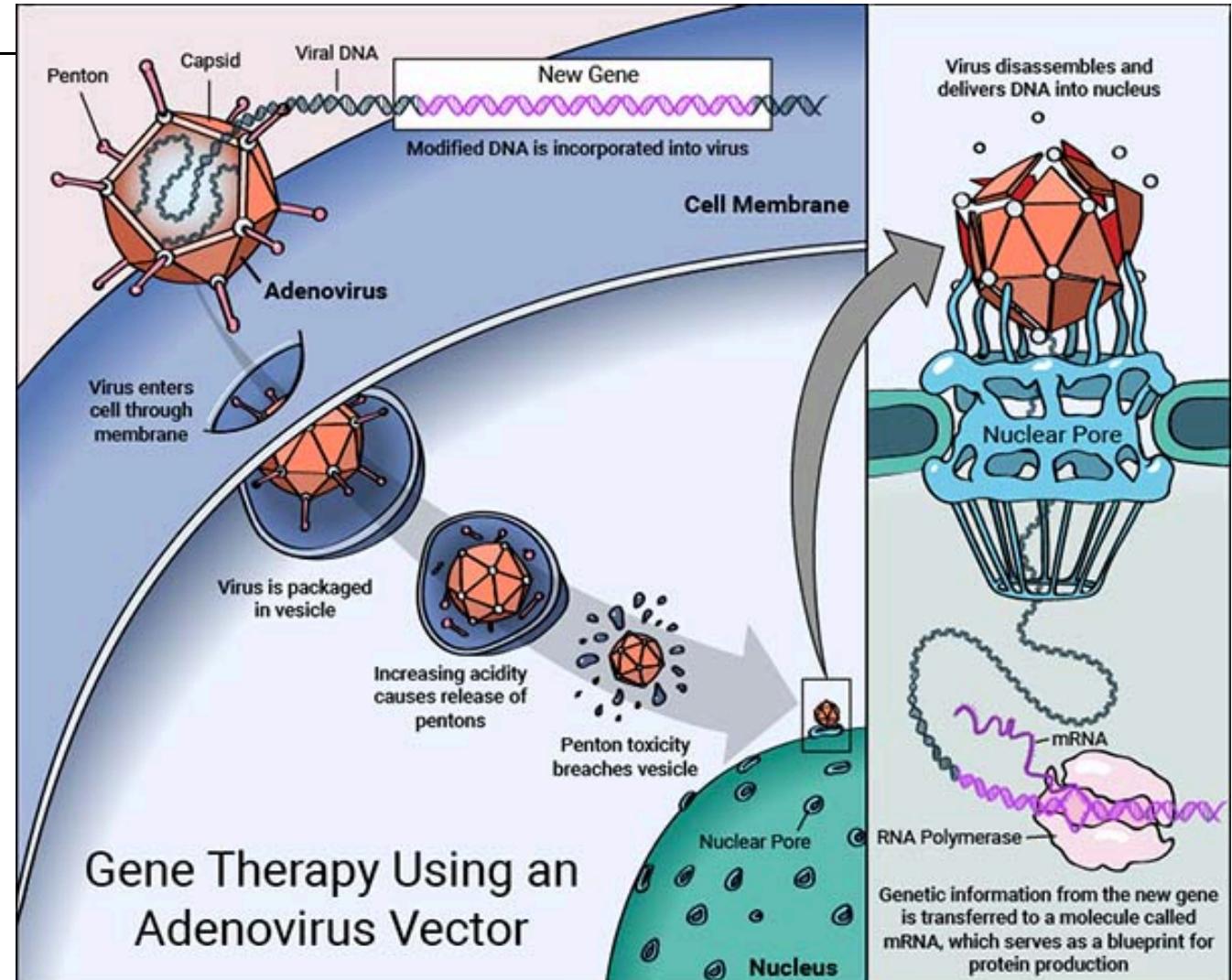
Challenges of gene therapy:

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

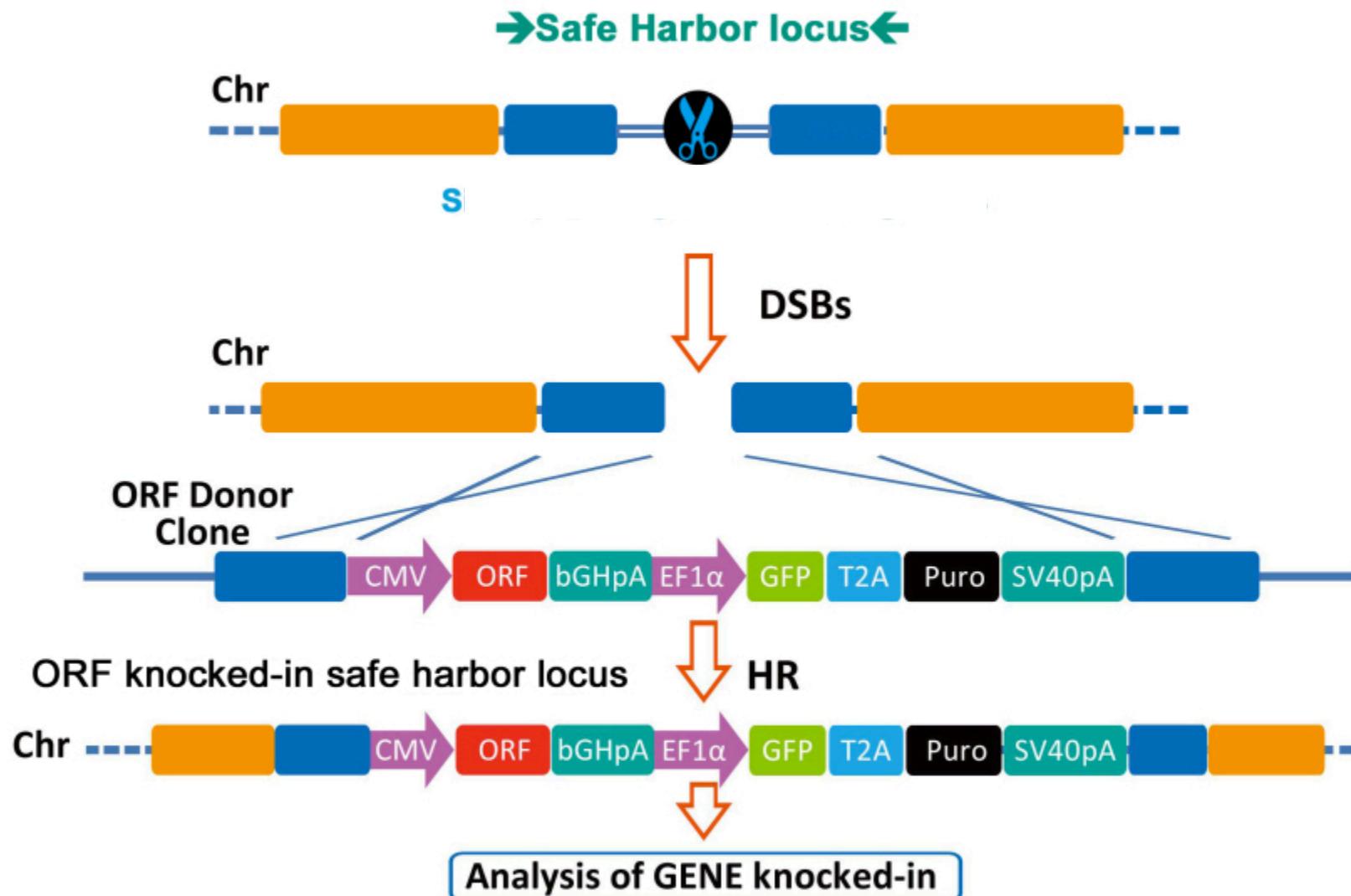


# Virus as a vector

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

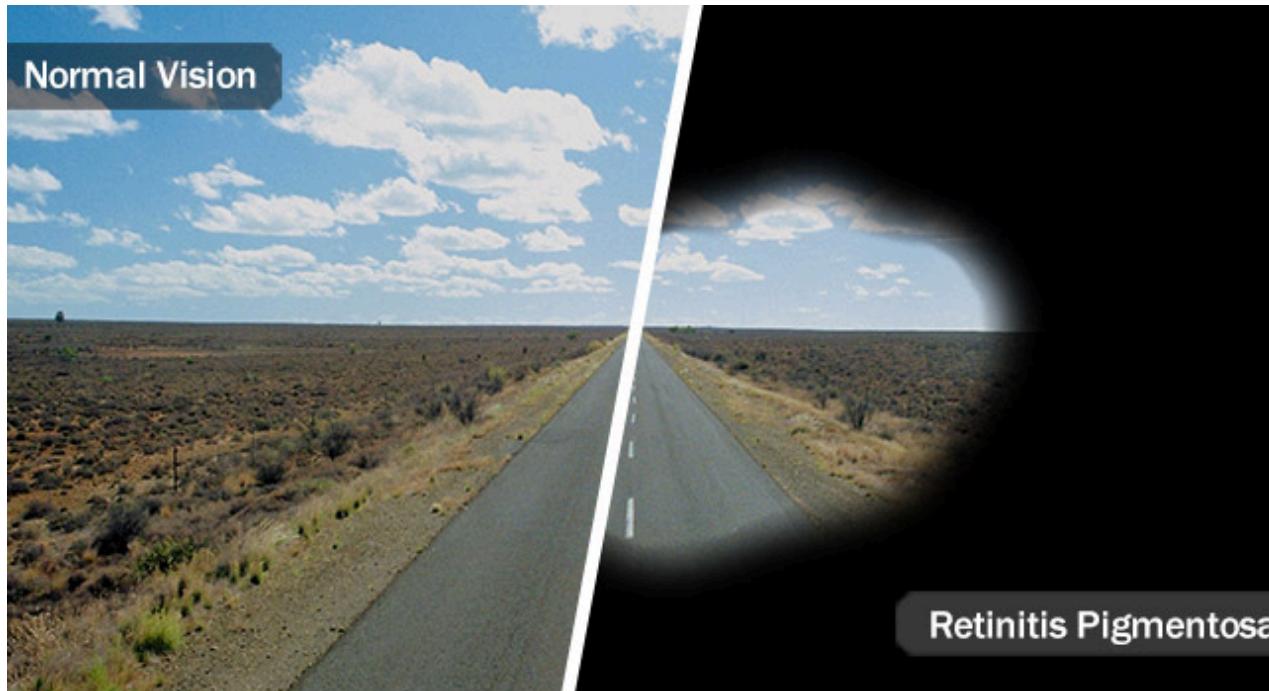


# AAV1 ‘safe harbor’ site



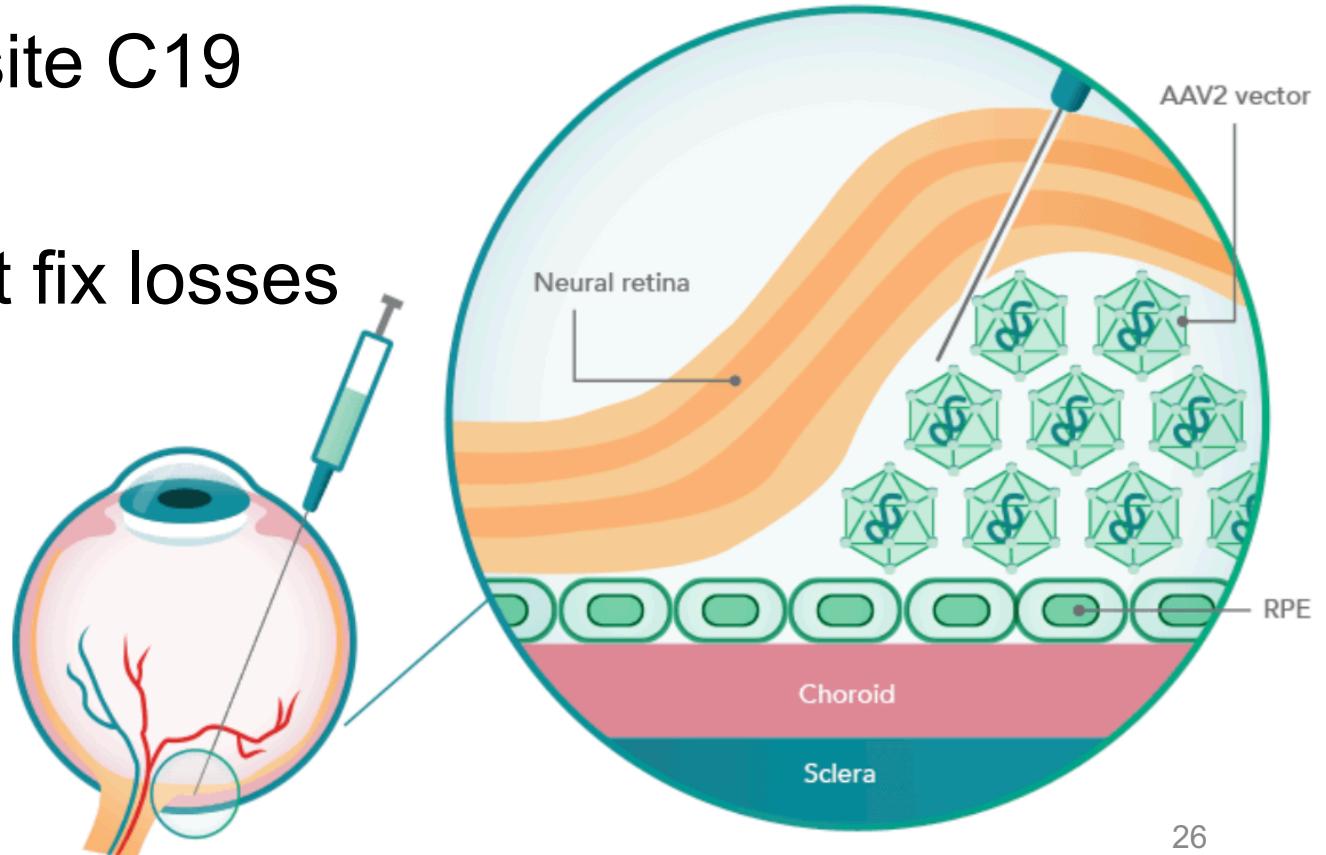
# Examples of gene therapy: Luxturna uses adeno-associated virus

- 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

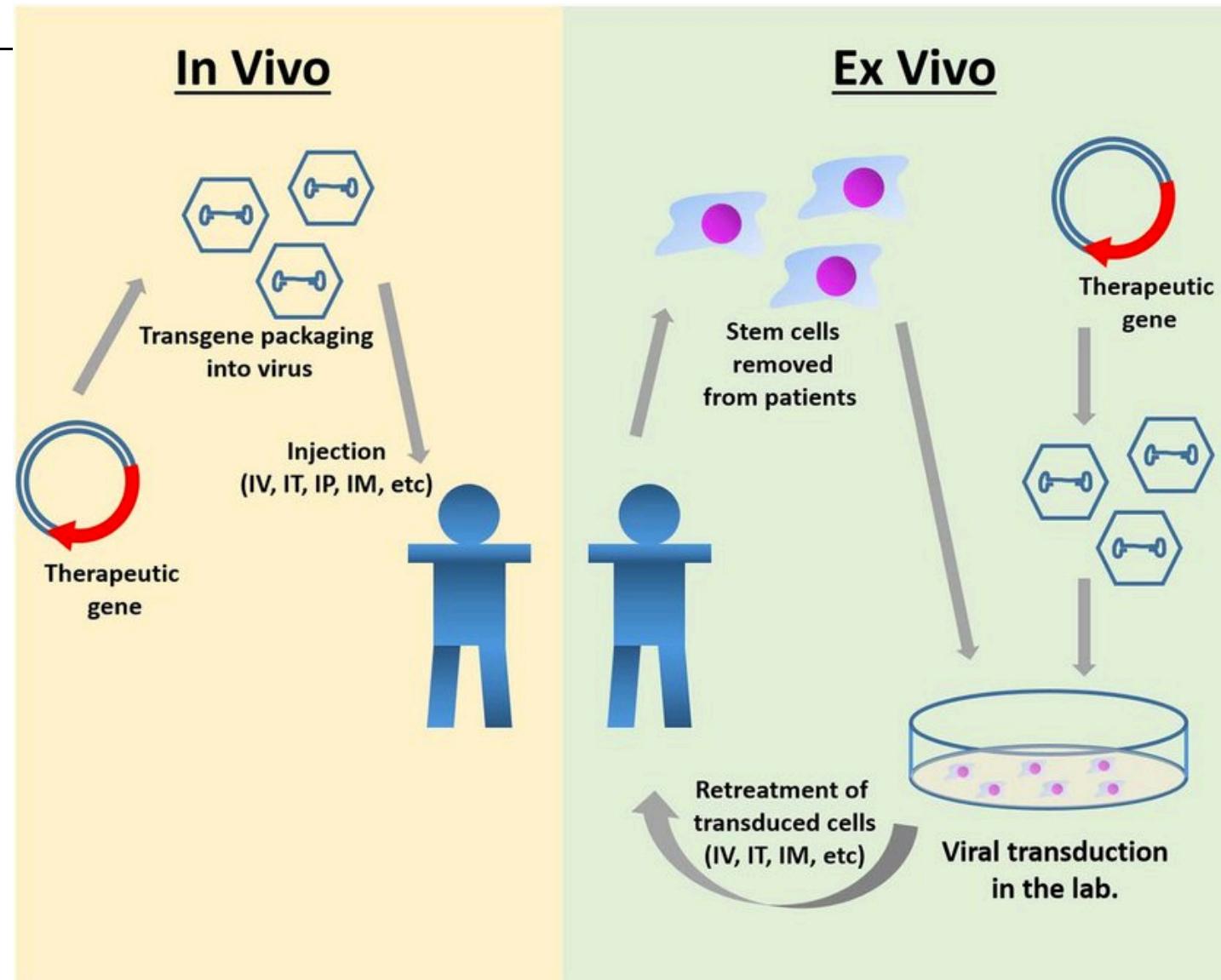
- Single injection earlier than 2 years of age
- AAV insertion of working SMN1 gene
- Cost: \$2.1 million USD



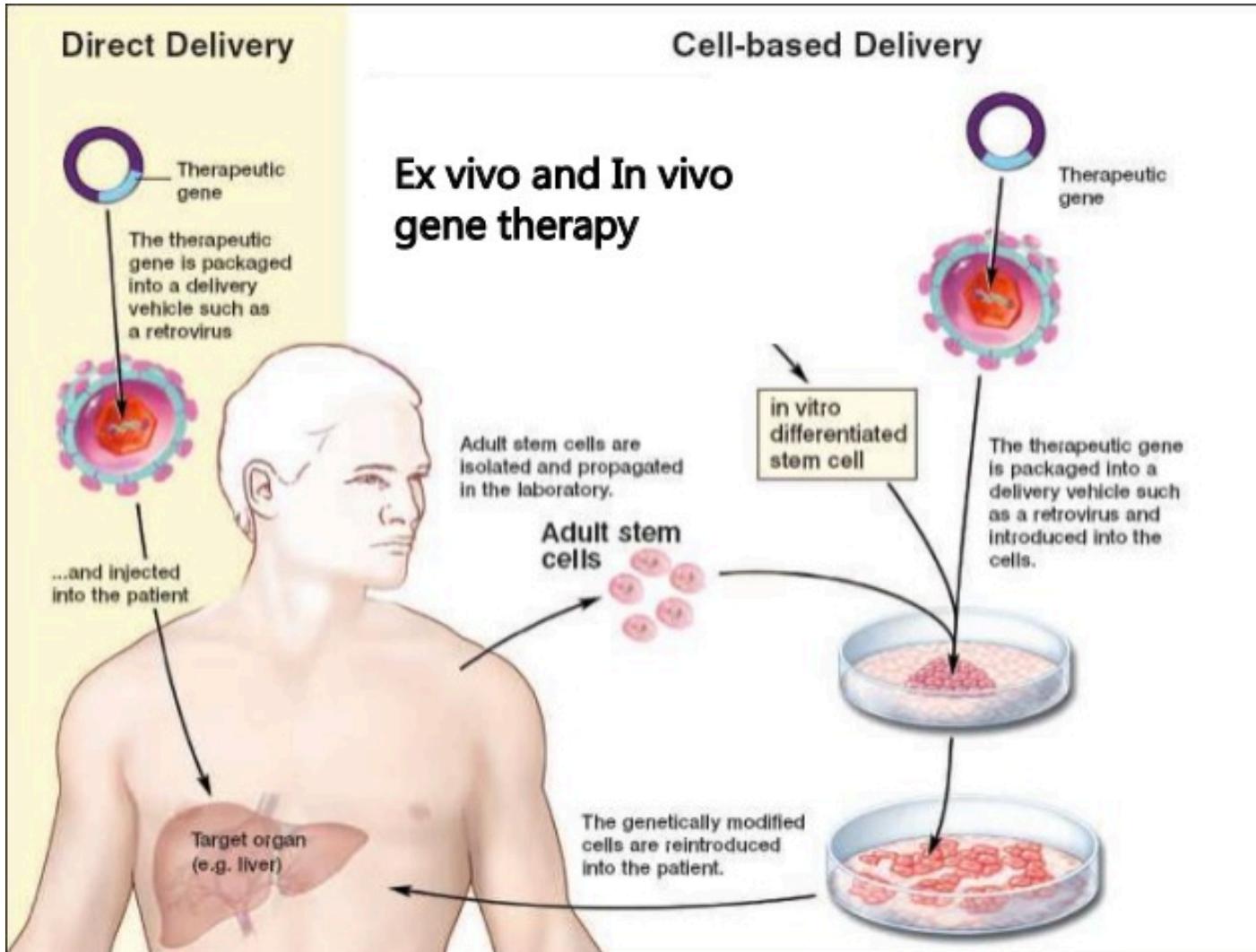
Motor Milestones Achieved, n (%)	
Head control	11 (92)
Rolls from back to sides	9 (75)
Sitting with assistance	11 (92)
Sitting without assistance	
≥5 seconds <sup>b</sup>	11 (92)
≥30 seconds <sup>c,d</sup>	9 (75)
Standing with assistance	2 (17)
Walking alone	2 (17)



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



# Ex vivo gene therapy overview



# Ex vivo example: Strimvelis

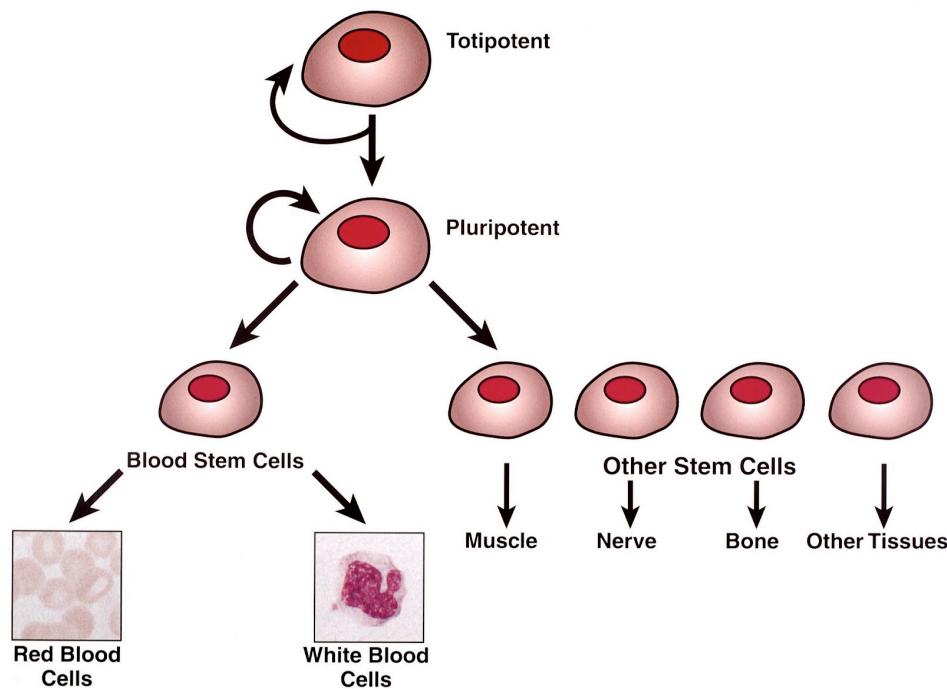
- 
- Treats Adenosine deaminase deficiency – severe combined immunodeficiency (SCID) – Autosomal recessive. 15 people born per year in Europe with condition
  - Retrovirus used to insert working ADA gene into hematopoietic stem cell (HSC), and then transplanted into bone marrow
  - 75% of treated people 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		

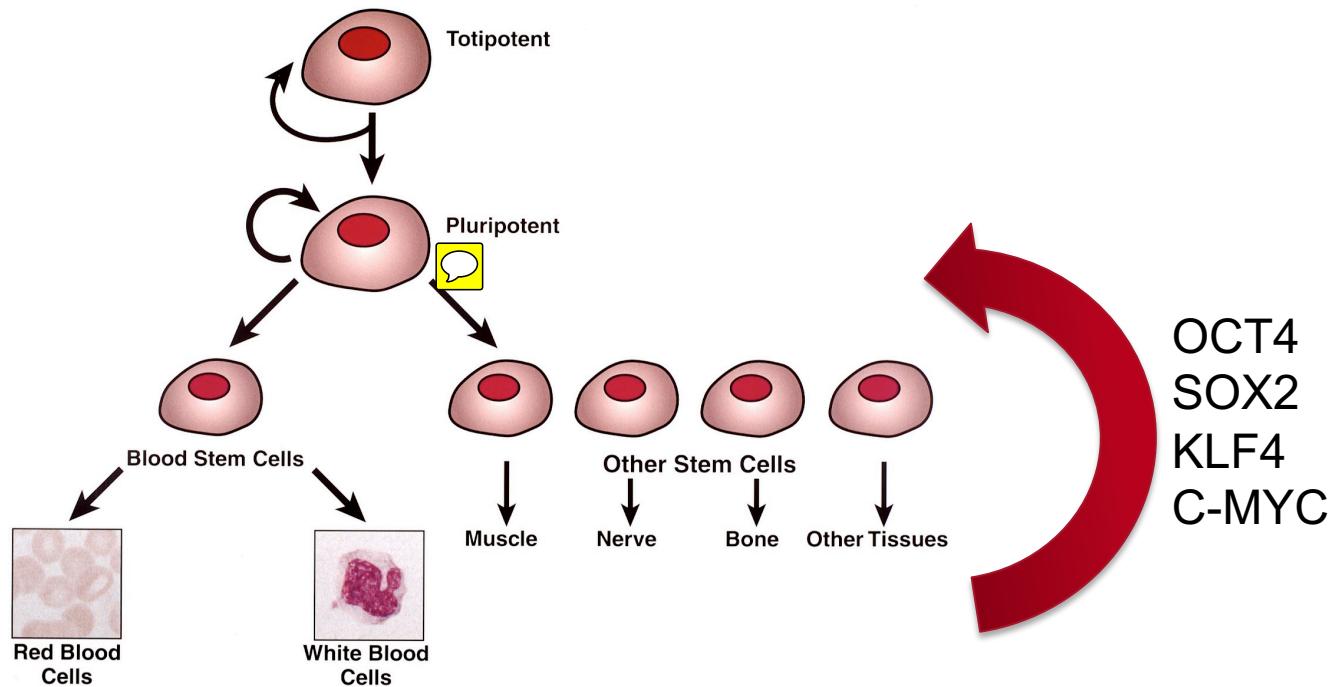
\*Abbreviations: FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; γRV, murine γ-retrovirus; LV, lentivirus; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; HSPC, hematopoietic stem and progenitor cells; X-SCID, X-linked severe combined immunodeficiency; ZFN,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

# Stem cells in nature



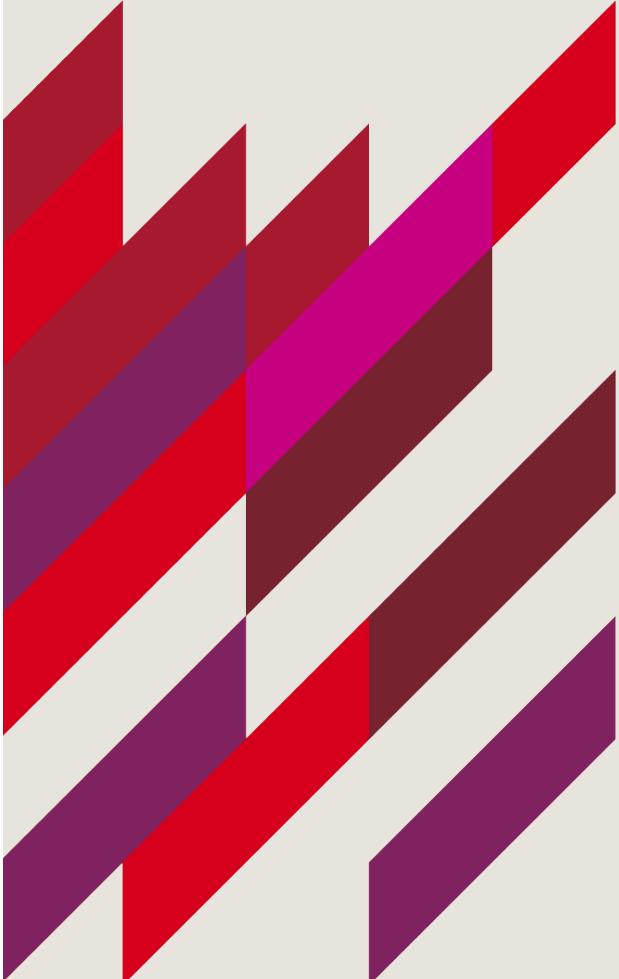
# Induced pluripotent stem cells (iPSCs)

- 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