GENE / ADVANCED THERAPIES

EURORDIS OPEN ACADEMY TRAINING

4 JUNE 2025

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AFM-TÉLÉTHON

RARE ?

AFMTÉLÉTHON
CURE THROUGH INNOVATION

RARE ?

- Rare Diseases : ~8000
- 1 out of 20 people affected
- > 350 millions worldwide
- 80% of genetic origin
- Severe (50% fatales)
- Chronic, incapacitating (1/2)
- 2/3 appears before age 2
- Affects more people than diabetes and infectious diseases combined
- 1/3 childs death

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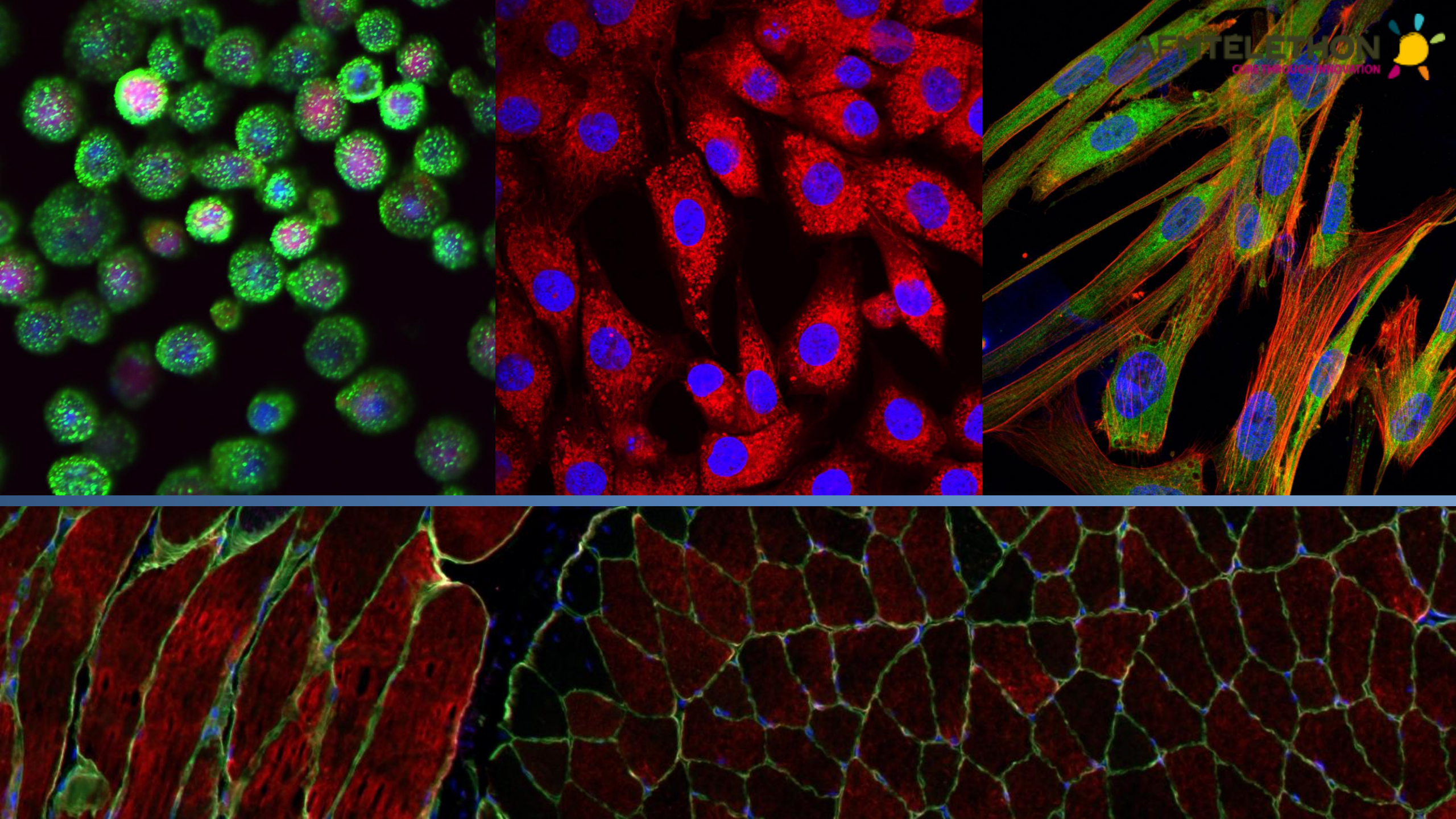
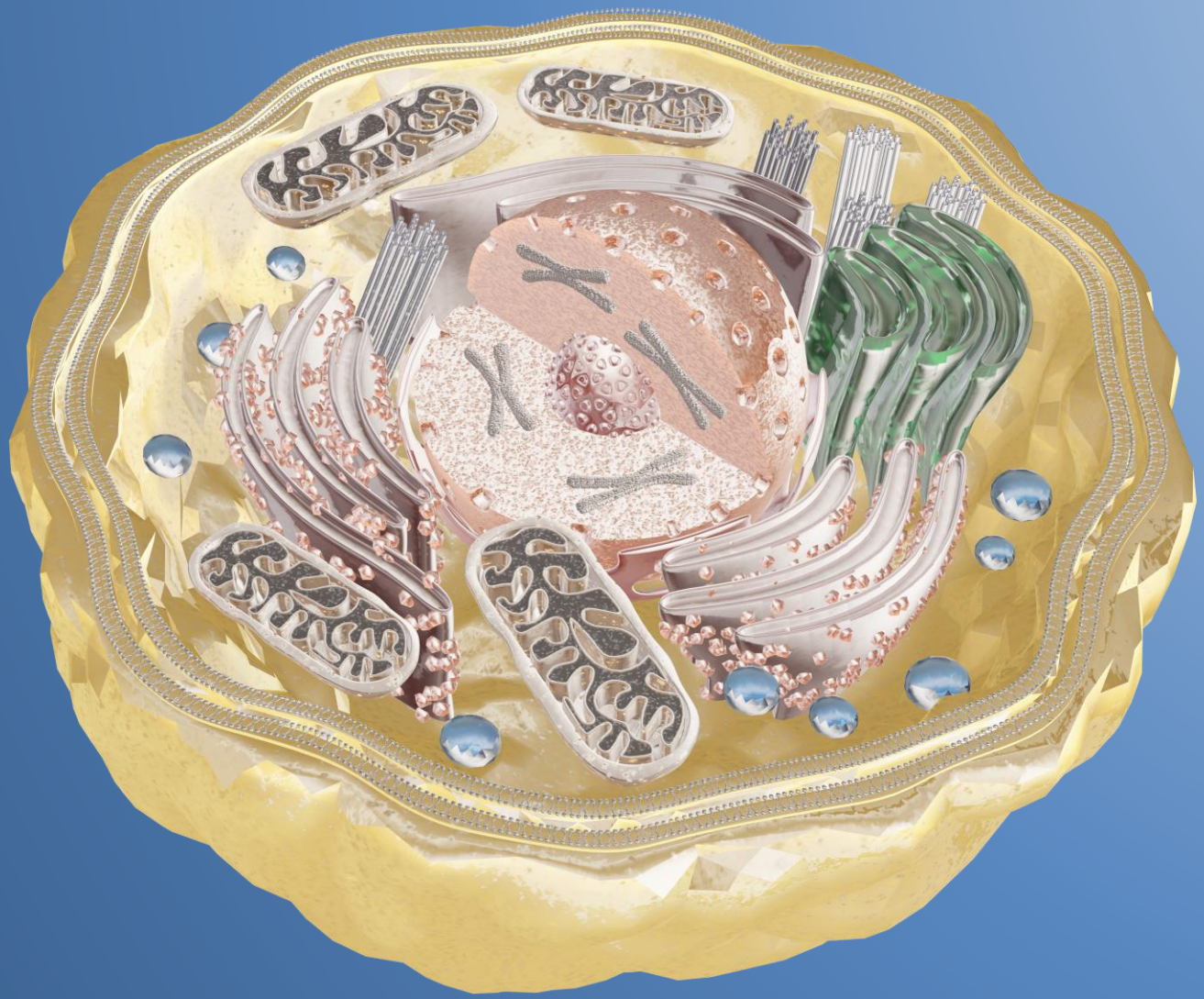
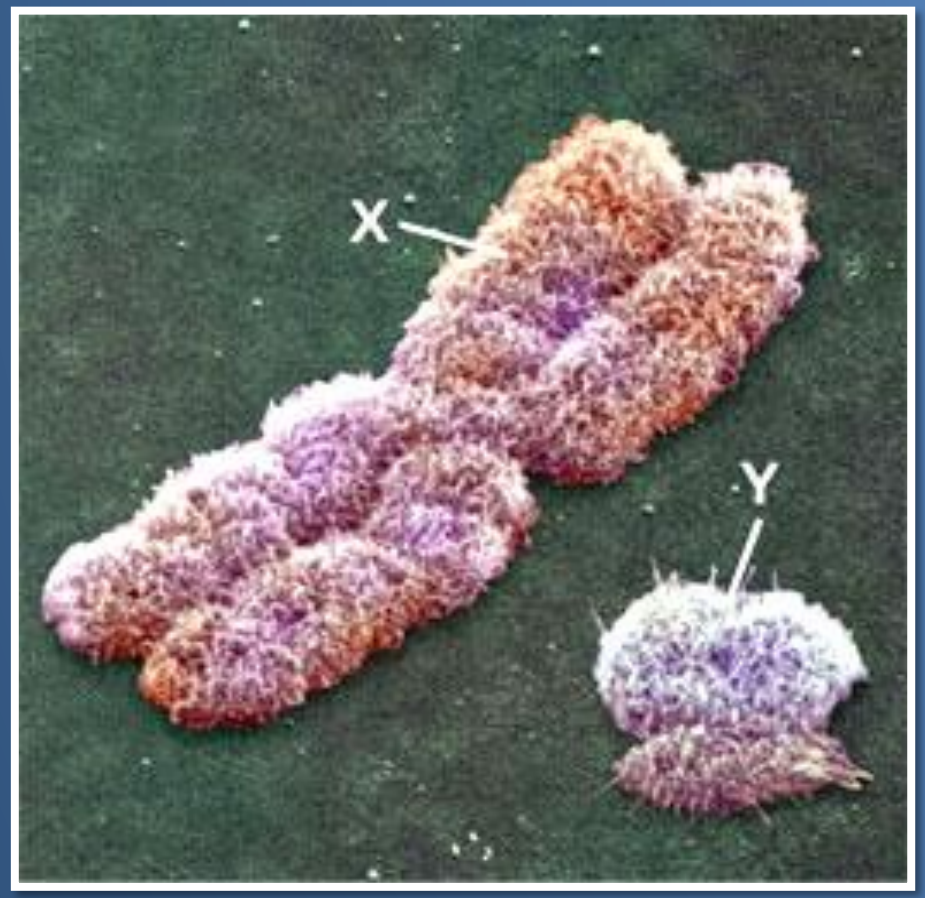
CURE THROUGH INNOVATION

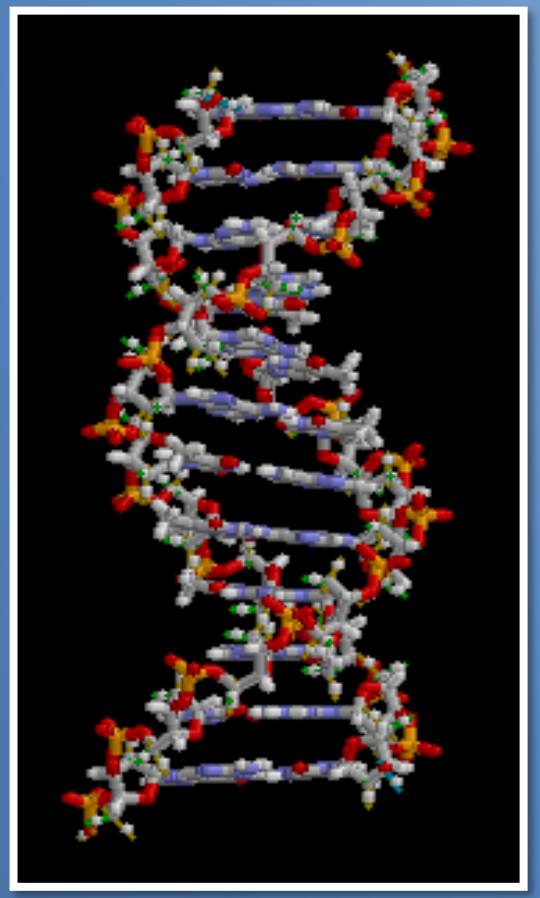
Studies on rare diseases starts with the study of our DNA


AFMTELETHON
CURE THROUGH INNOVATION

AFMTELETHON
CURE THROUGH INNOVATION







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CGAGCTCCGTCGACAAGCTTGCGGCCGCACTCGA
GCACCACCACCACCACCACTGAGATCCGGCTGCT
ACCAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTG
CCACCGCTGAGCAATATCTAGCATATCCCCGTTT
GAGGGGTTTTTTGCTGAAAGGAGGAACTATATCC
GGATTGGCGAATGGGACGCGCCCTGTAGCGGCGC
ATTAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGC
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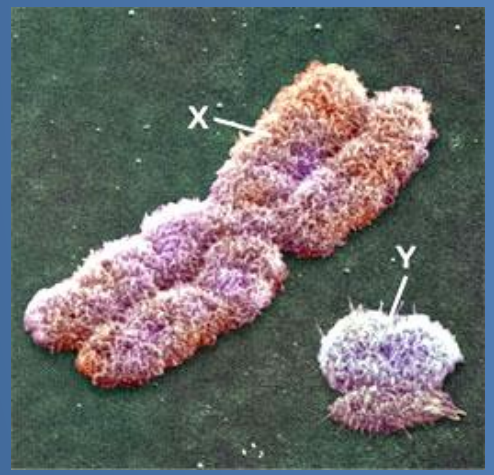
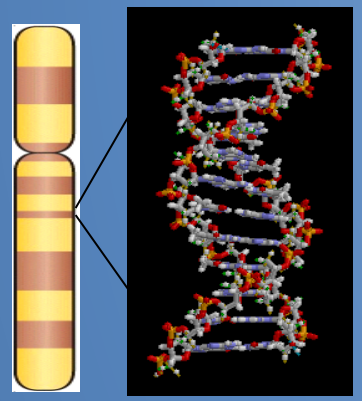
...





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CAGATGCTGAATTCGAGCTCCGTCGACAAGCTTGCGGCCGC
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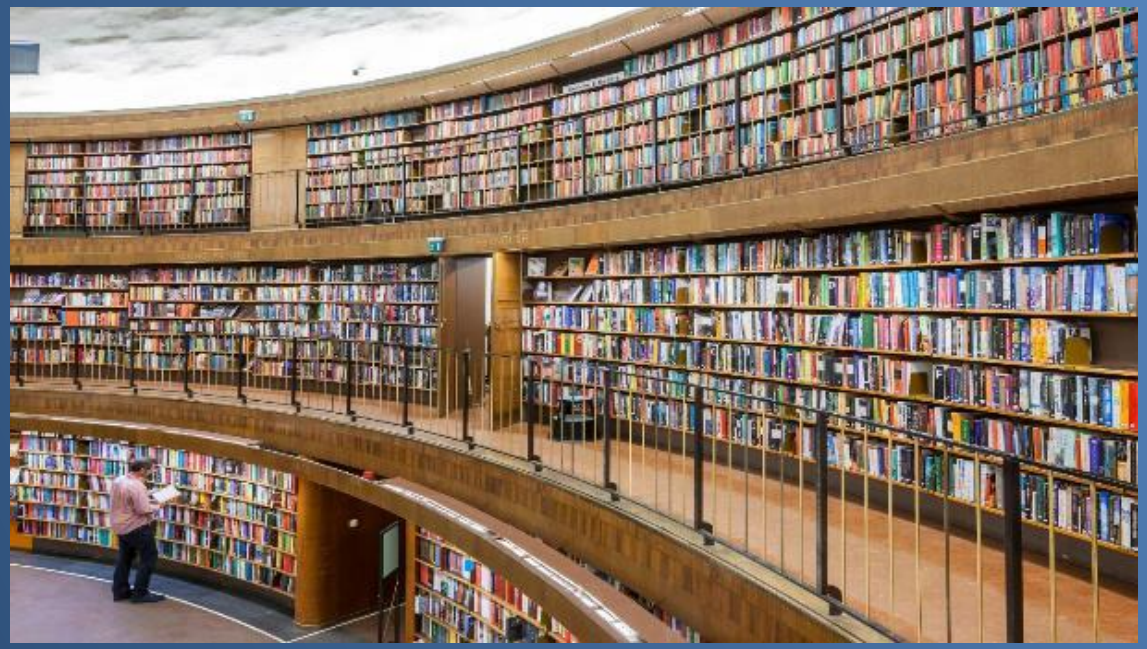

5 300 books !

How many letters in our genetic code?

6 400 000 000

GENOMICS REVOLUTION

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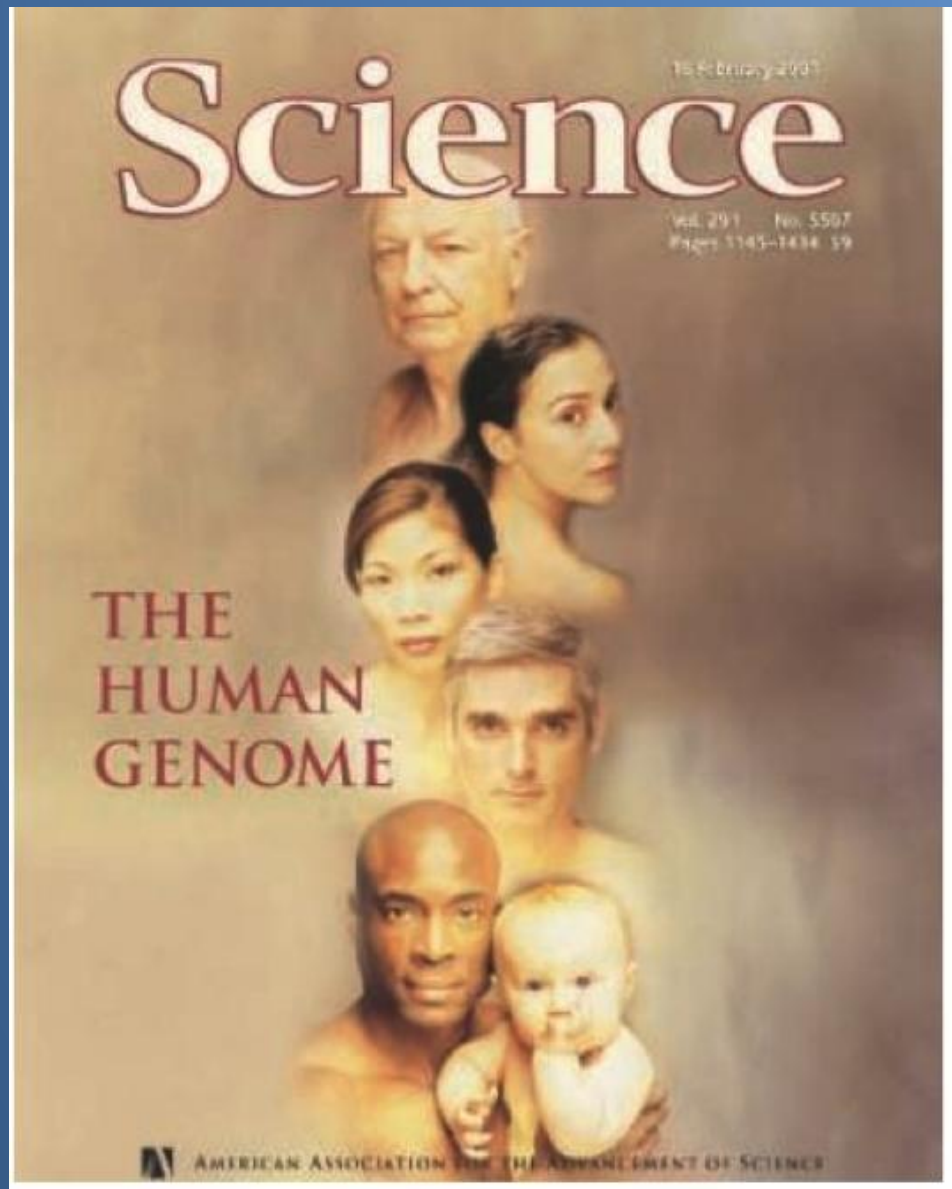
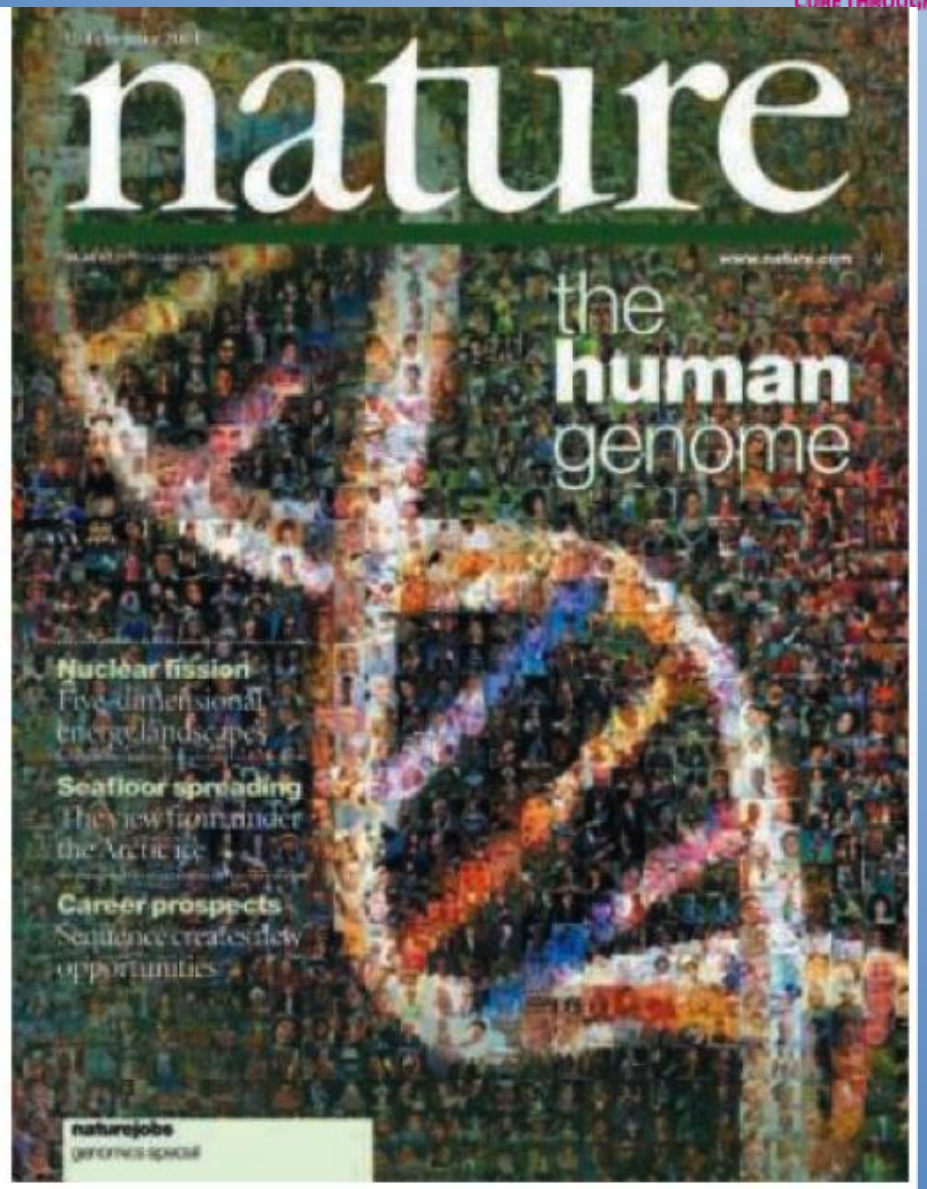
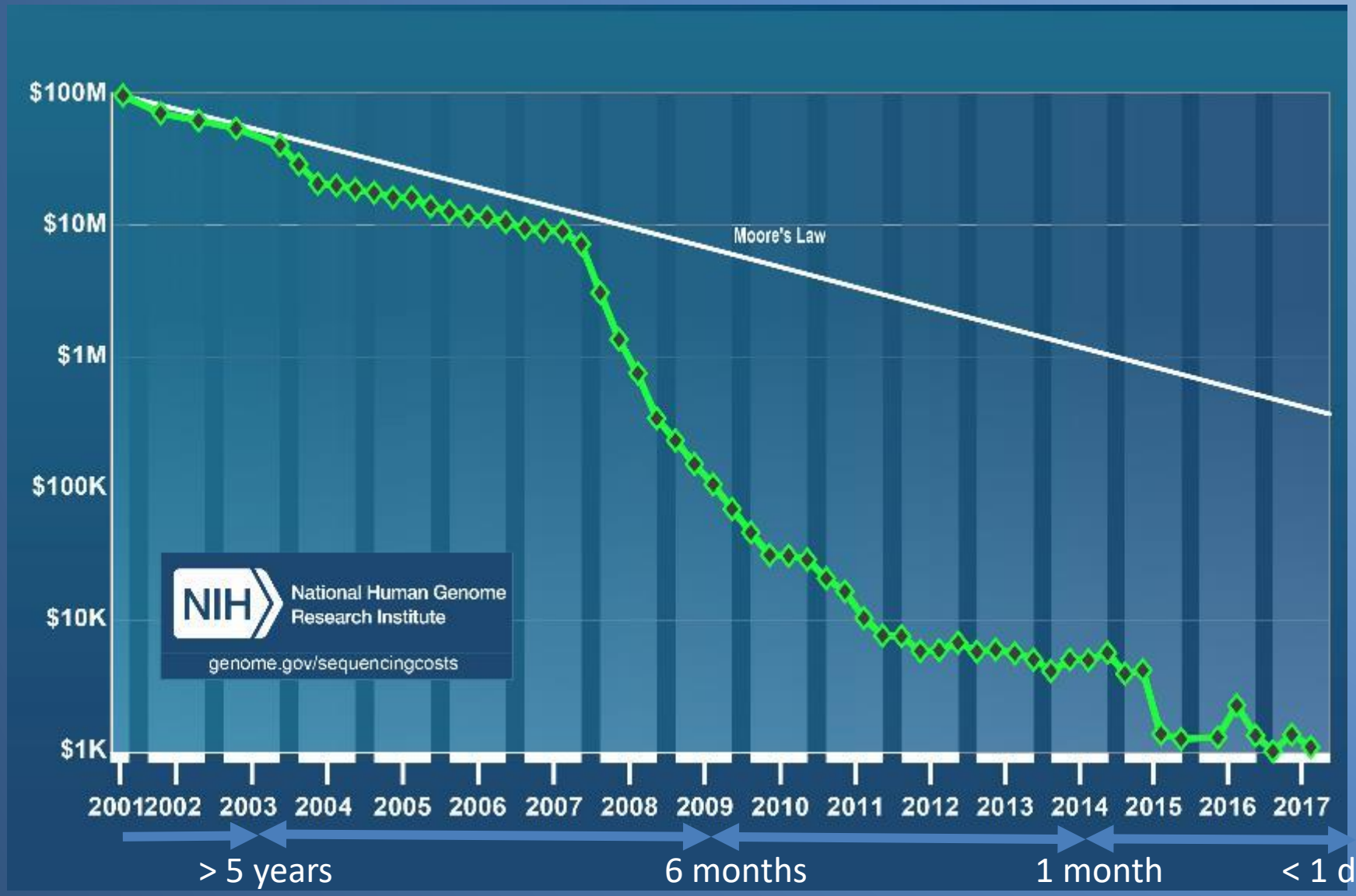
CURE THROUGH INNOVATION



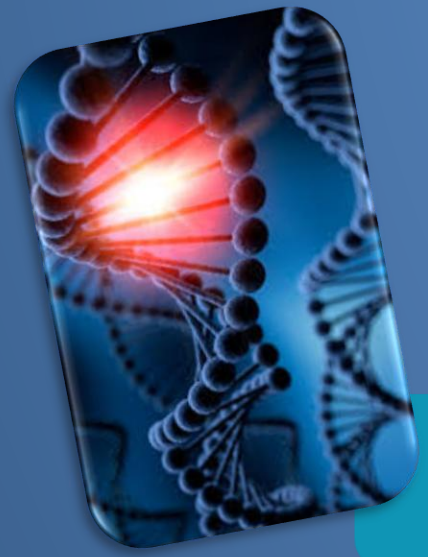


AND HIGH THROUGHPUT SEQUENCING BOOM

AFMTELETHON
CURE THROUGH INNOVATION



WHAT IS THE IMPACT OF A MUTATION IN THE GENOME ?



DNA

An error in the sequence

Missing or abnormal protein

Lost or altered information

Genetic disease

LEARN FROM THE RARE

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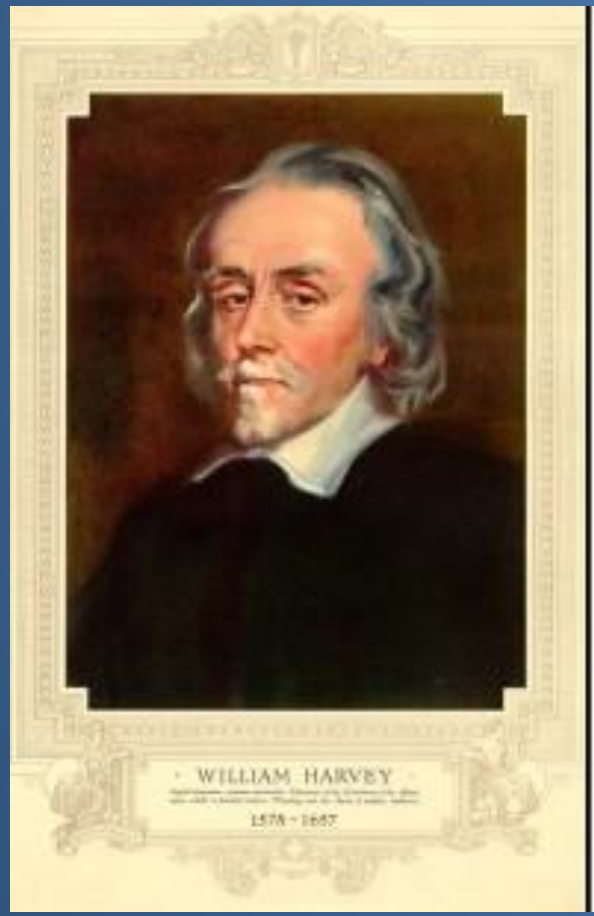
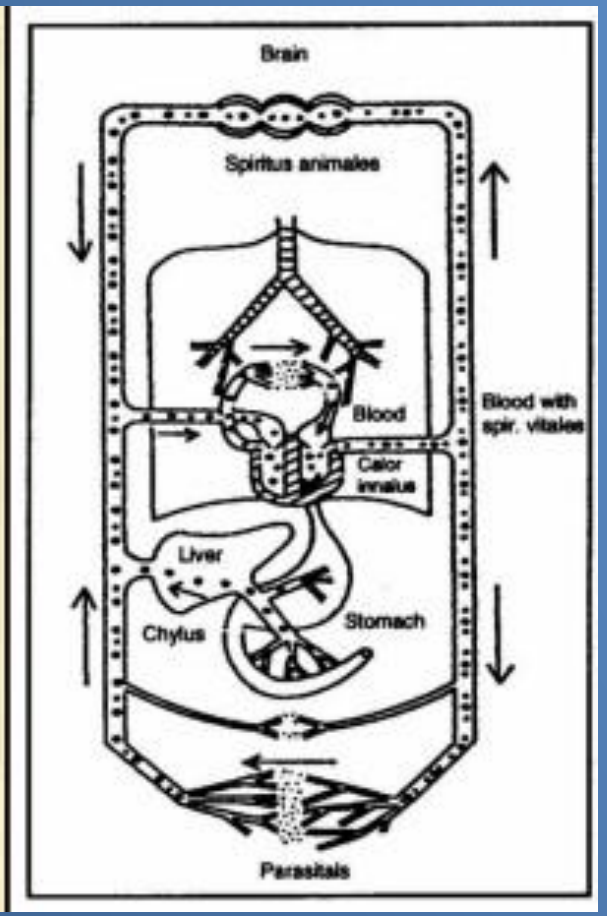
CURE THROUGH INNOVATION





« Learn from the rare » , William HARVEY, 1657:

"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path;

nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by the careful investigation of cases of rarer forms of disease.

For it has been found in almost all things, that what they contain of useful or of applicable nature, is hardly perceived unless we are deprived of them, or they become deranged in some way. ».

William Harvey (1578–1657) was the first to describe correctly the systemic circulation of blood pumped to the brain and body by the heart

AN EXAMPLE

Familial hypercholesterolemia

Link hypercholesterolemia and cardiovascular diseases (1930's)

↓

Research on familial hypercholesterolemia rare disease (1 /1,000,000)

↓

Identification of LDLR gene and its deficiencies

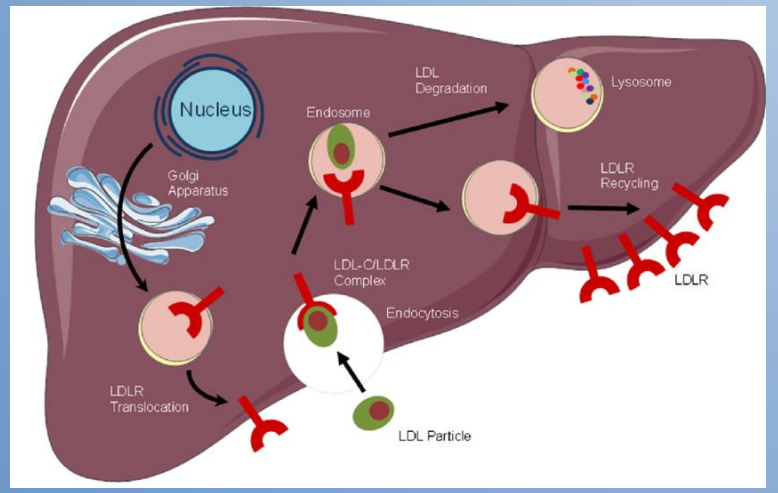
↓

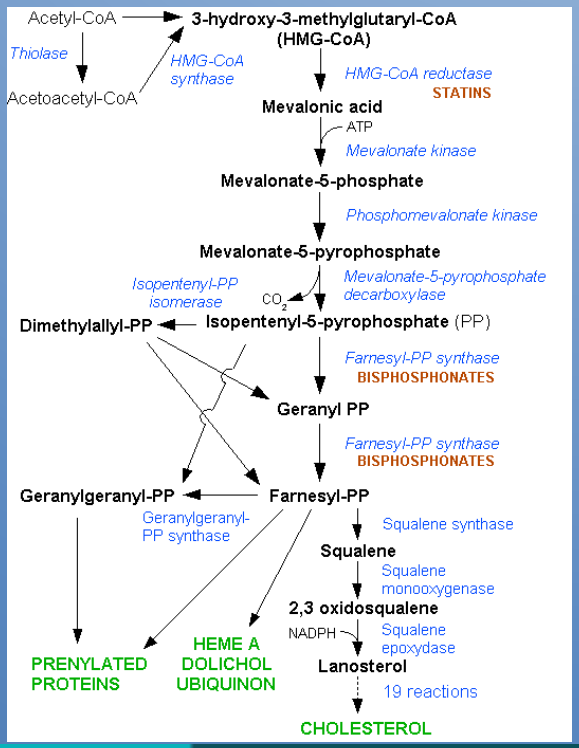
Characterisation of cholesterol biosynthesis pathway

↓

Development of statins

Medecine Nobel Price for Joseph Goldstein and Michael Brown on LDL receptors in 1985





TO CURE THOSE GENETIC DISEASES WE EXPLORE ALL THERAPEUTIC POSSIBILITIES

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CURE THROUGH INNOVATION

GENE THERAPY

CELL THERAPY

Advanced Therapy Medicinal Product (ATMP)

ANTIBODY THERAPIES

ENZYME REPLACEMENT THERAPY

SMALL NUCLEIC ACID DRUGS

TARGETED PROTEIN DEGRADERS

PHARMACOLOGY

TO CURE THOSE GENETIC DISEASES WE EXPLORE ALL THERAPEUTIC POSSIBILITIES

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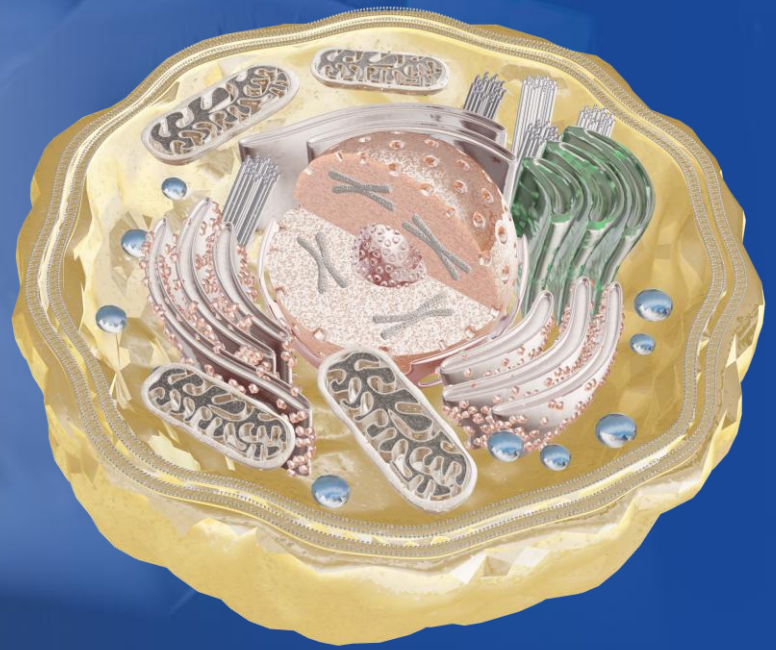
GENE THERAPY

How to deliver a therapeutic gene in each cell ?

How possible to act on abnormal genetic function in the cells ?

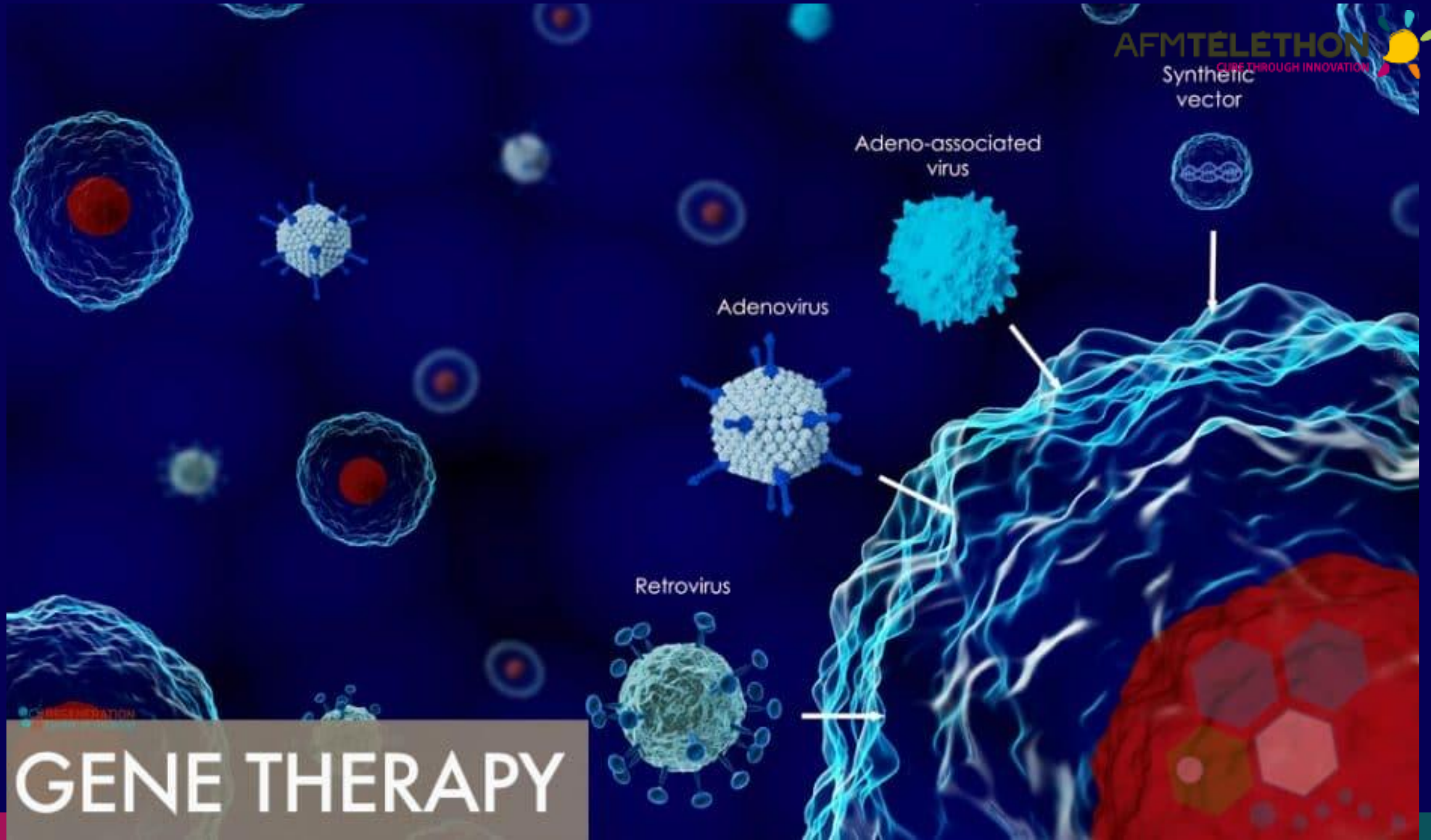
Electroporation

Shotgun



Micro injection

Chemical transfection



GENE THERAPY

GENE THERAPY CONCEPT

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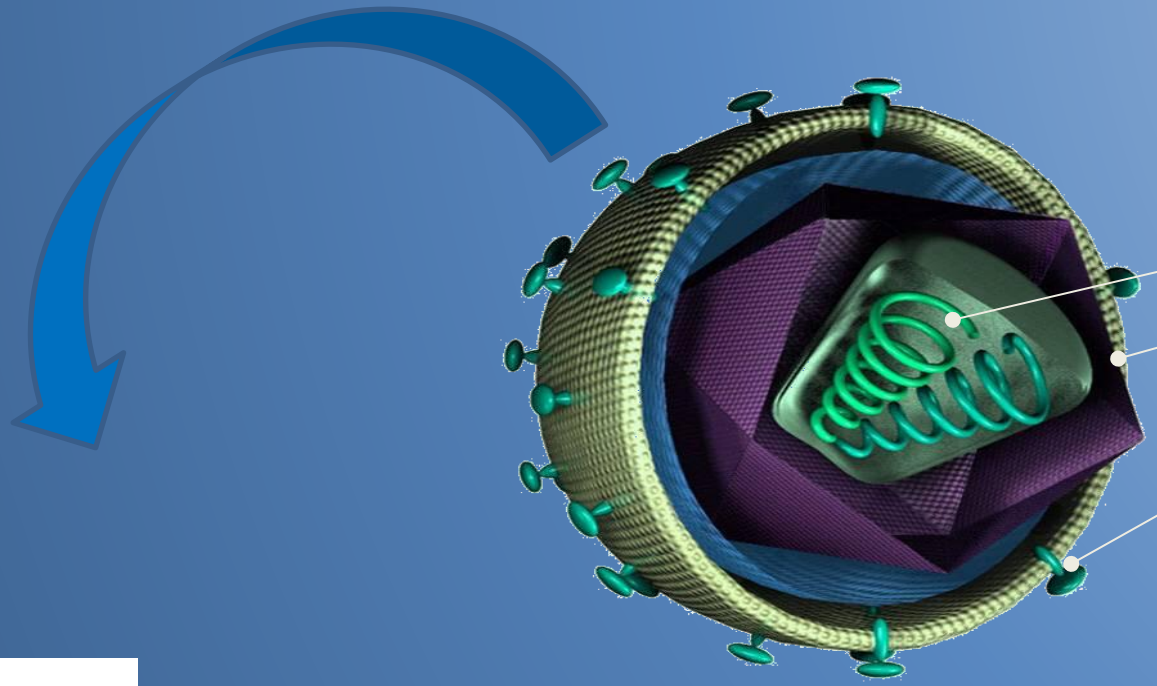
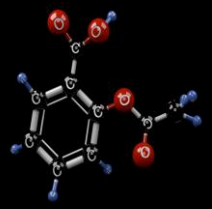
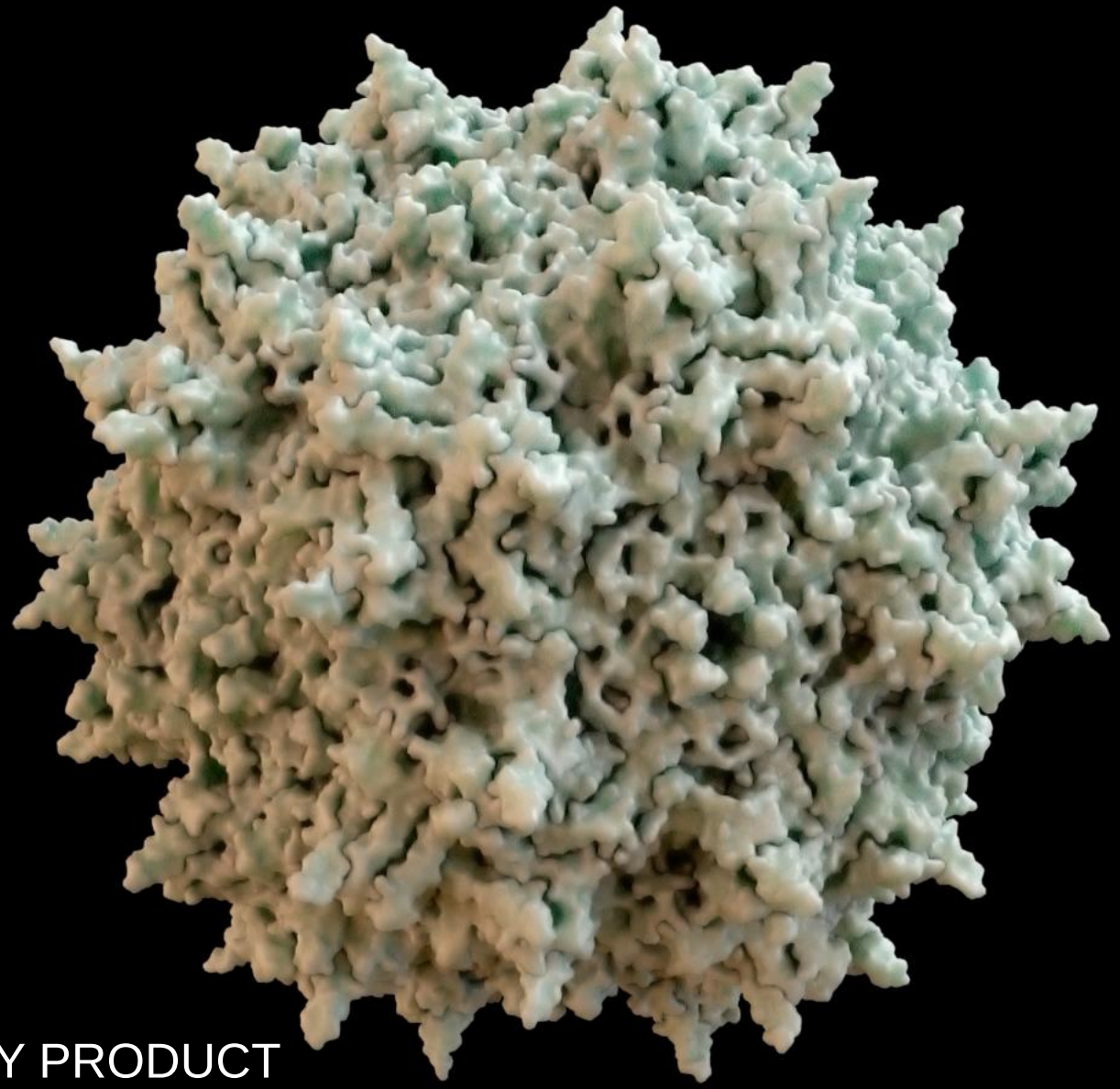


A viral vector is a modified virus that will bring the curative gene into the cell

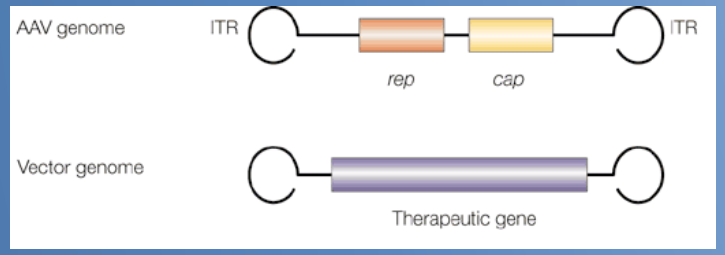


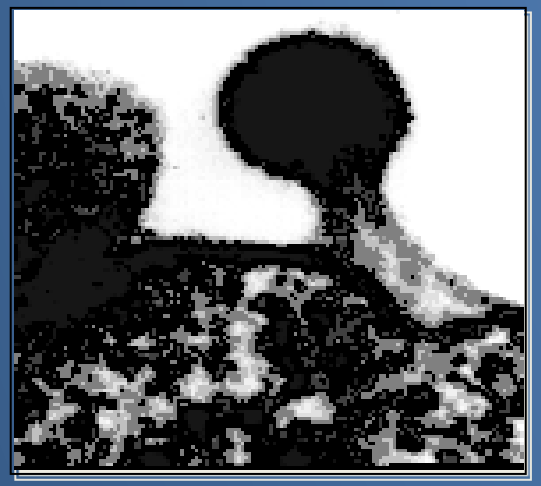
ASPIRINE MOLECULE



GENE THERAPY PRODUCT

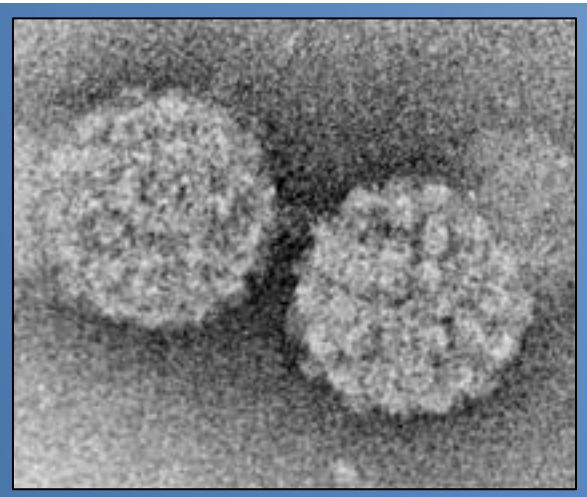
Examples of vectors





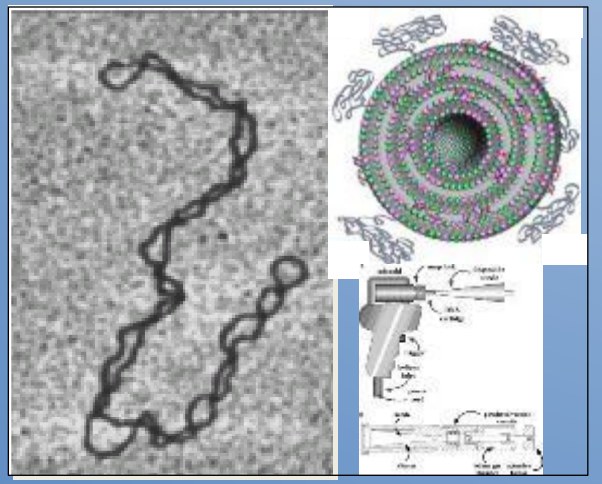
Retrovirus / Lentivirus

- Integrates
- Efficient
- Immunogenic
- Size limitation
- Large scale production



Adeno-associated virus

- Long term (episomal)
- Does not integrate (?)
- Efficient
- Immunogenic
- Size limitation
- Large-scale production



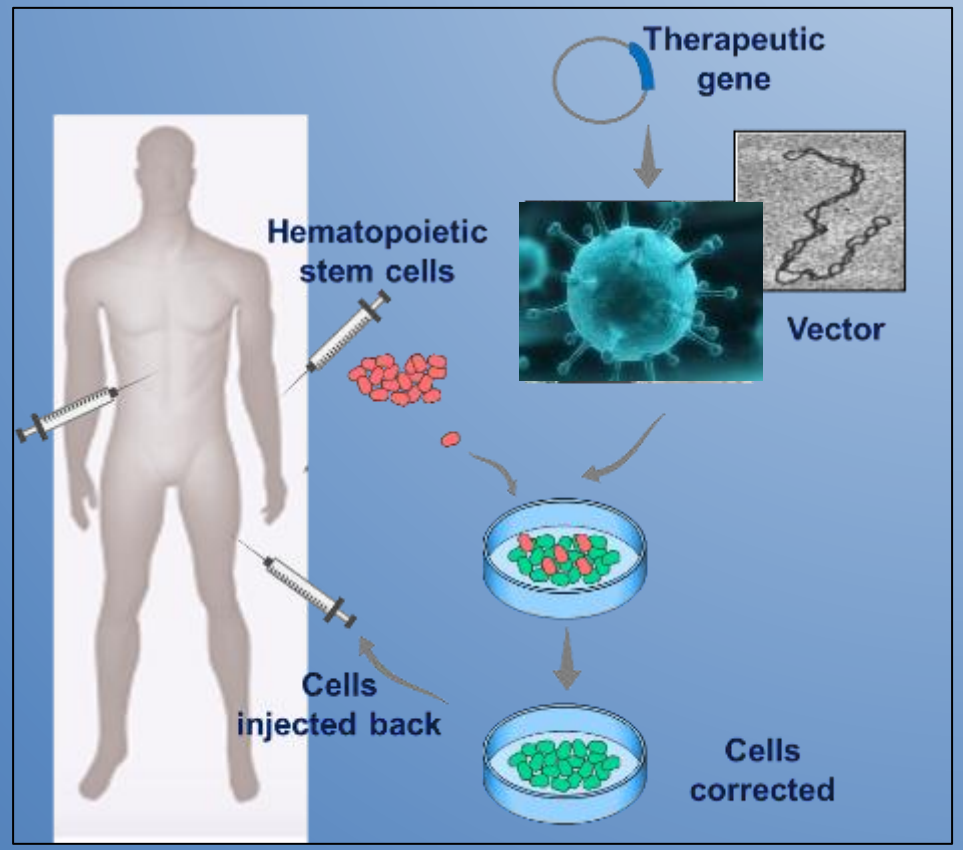
Non-viral

- May be long term
- Does not integrate (?)
- Poorly efficient
- Non-immunogenic
- Large transgenes
- Large-scale production

First gene therapy attempts in humans

1980: Martin Cline (UCLA), β-thalassemia
- 2 patients
- β-globin-HSVtk plasmid

Scientific, procedure, ethical controversy
→ recommandations & specific regulations



1990: William French Anderson (NIH)
- 1 ADA-SCID immunodeficient patient
- Retrovirus-ADA

First Wave : Proof of concepts amenable to a number of pathologies

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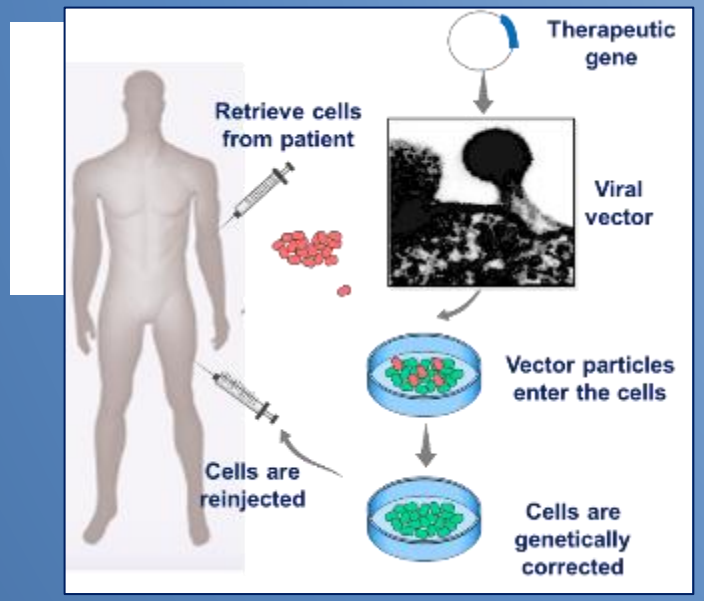
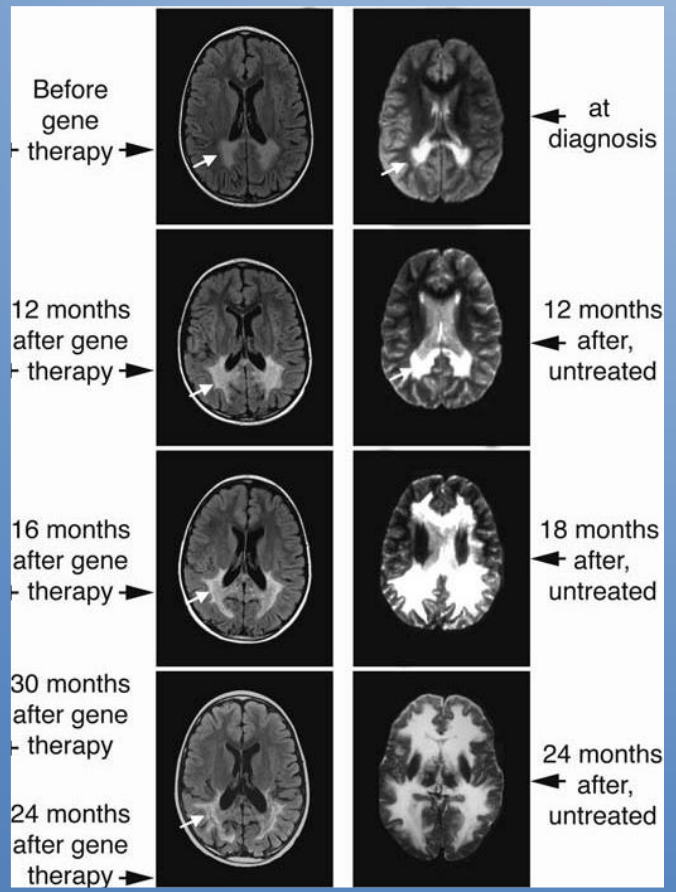
X-SCID

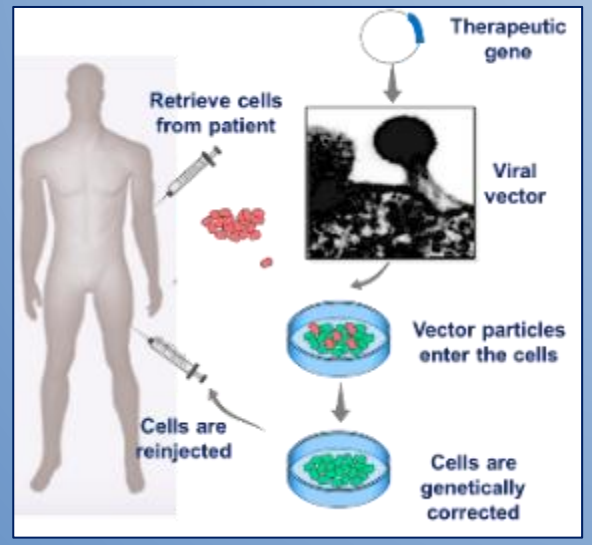


- Immunodeficiencies
- Blood diseases
- Bone diseases
- Adrenoleukodystrophy
- Cancer immunotherapy



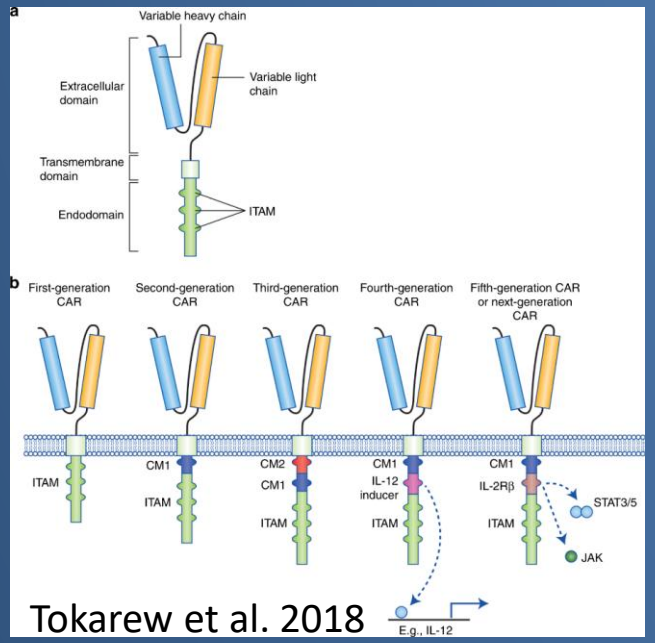
Cartier et al., Science 2009

From ex vivo gene therapy of immunodeficiencies…

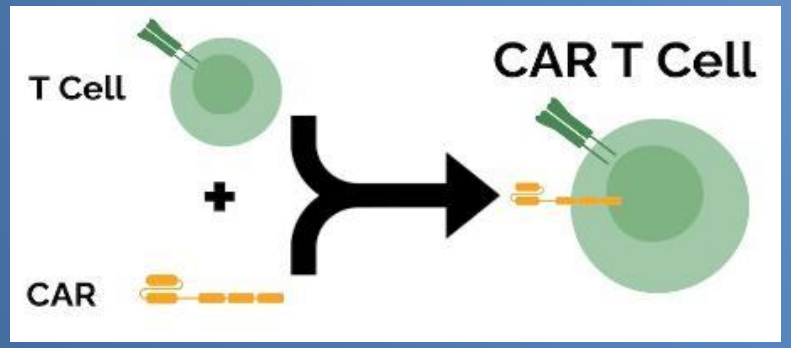


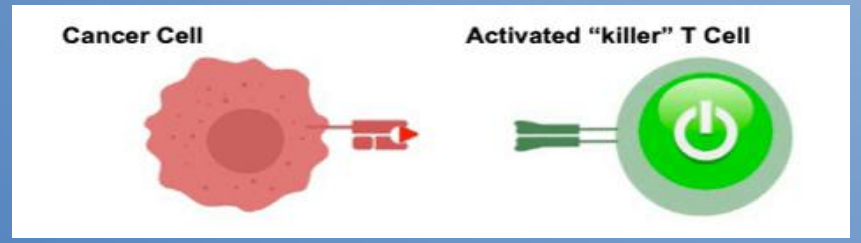
to CAR-T cell therapy in cancer…

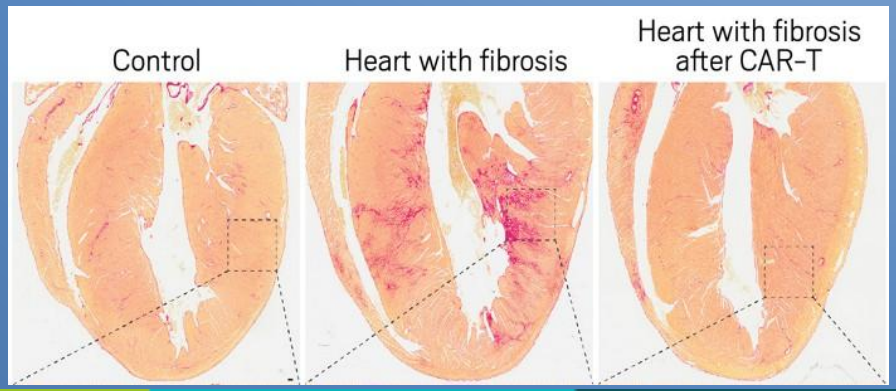
Chimeric Antigen Receptor (CAR) T Cells



Tokarew et al. 2018





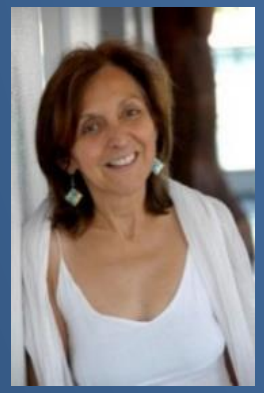


and back to rare diseases ?

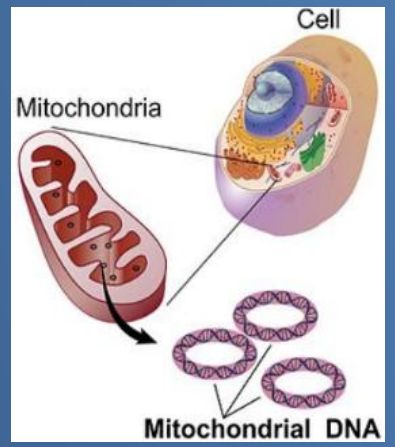
Second wave: local delivery

Leber Hereditary Optic Neuropathy

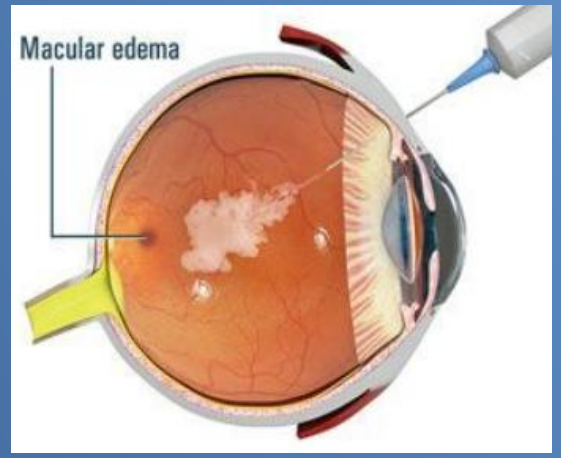
From Research on Mitochondria (1990)



Dr. Marisol Corral Debrinski



… To a gene therapy trial (2014)



Pr. José Alain Sahel

Third wave: systemic gene therapy

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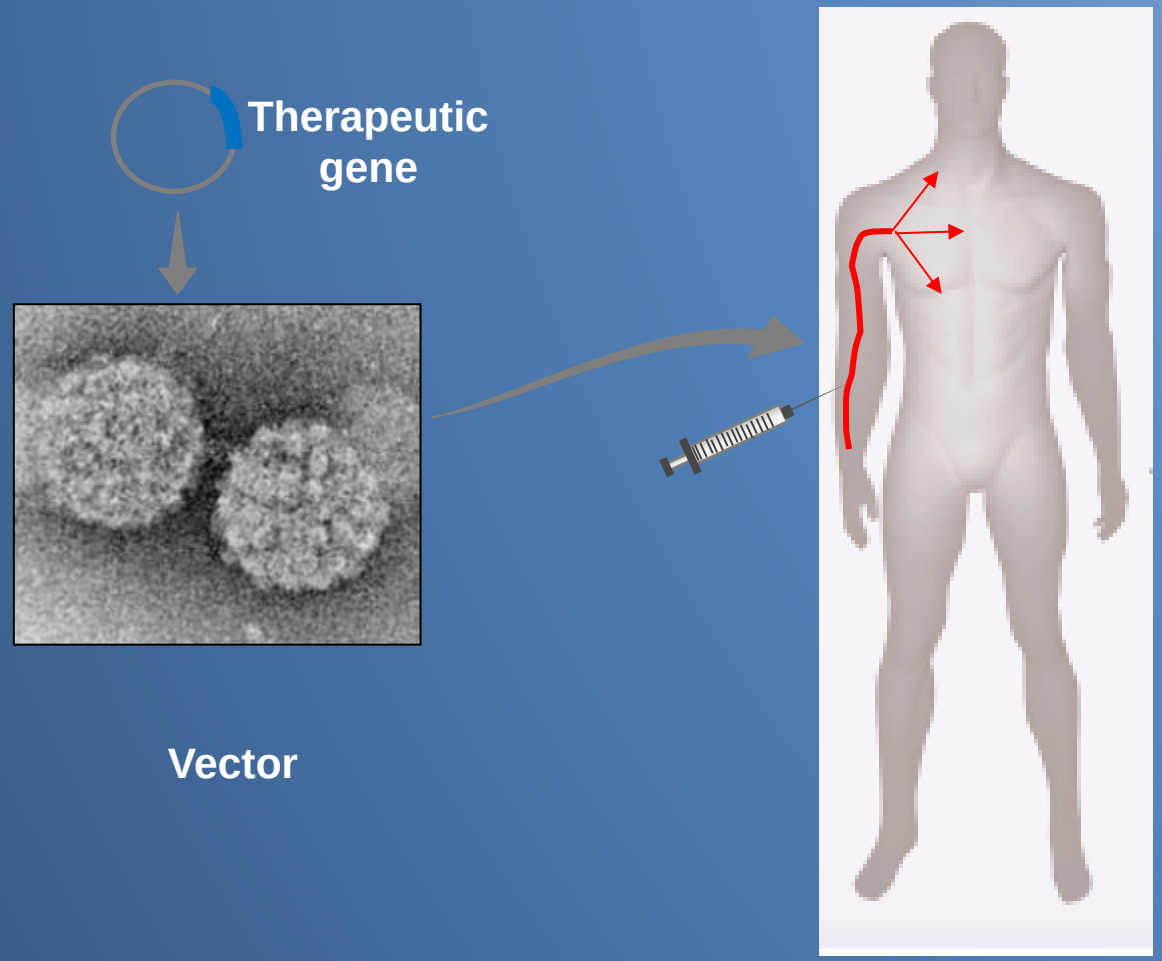
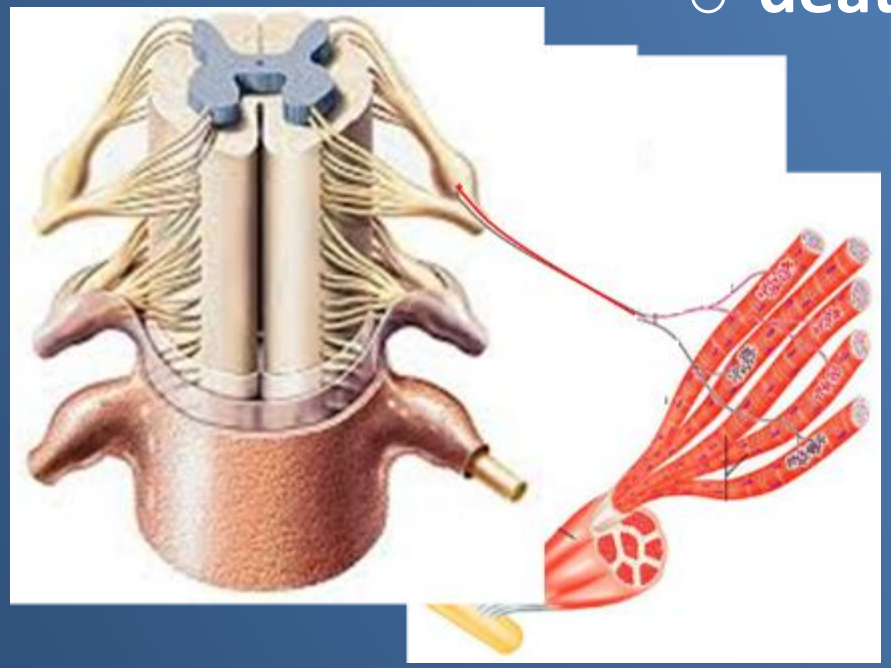


Spinal muscular atrophy

- 1/6000 – 1/10000
- 50% type I :
  - inability to maintain his head, sit, stand, walk, breath
  - death before age 2



The epic of SMA gene therapy

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- 1987: The day after the first Telethon, 150 SMA families start first **DNA collection**

- 1992: first **human genomic mapping** at Genethon

- 1995: identification of the SMN **gene responsible** for SMA by Judith Melki
- 2004: Martine Barkats POC of **gene therapy for SMA**
- 2019: **Zolgensma approved**

Martine Barkats

Brian Kaspar

zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

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A MEDICAL REVOLUTION IS ONGOING

MORE THAT 4000 PATIENTS TREATED IN THE WORLD

Available treatments do not correct all

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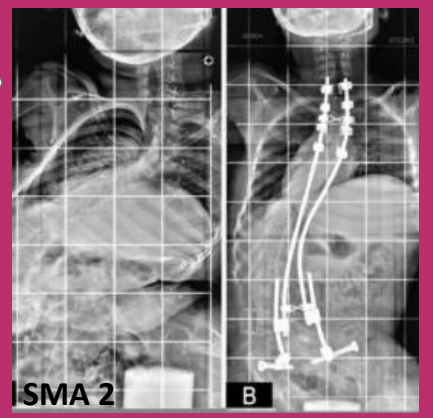
SMN-restoring therapies:

1) ZOLGENSMA (AAV9-SMN1) NOVARTIS

2) SPINRAZA (Nursinersen ASO) Biogen

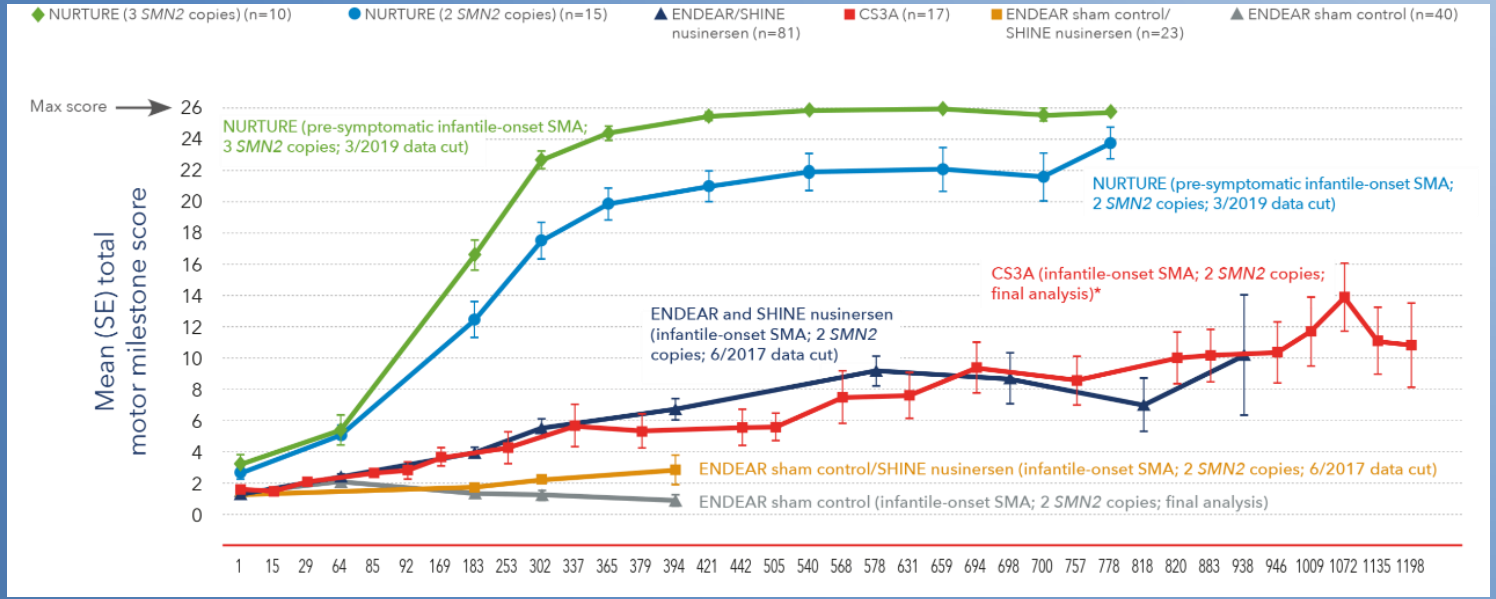
3) EVRYSDI (Risdiplam) Roche



- ☑ Ventilation-free survival
- ☑ Improved locomotion
- ☐ Scoliosis restoration
- ☐ Normal muscle function

- ➢ Role of epigenetics ?
- ➢ Need to combine therapies ?

AN EARLY DIAGNOSIS IS CRUCIAL



TREATING ALL THE MUSCLES POSSIBLE ?

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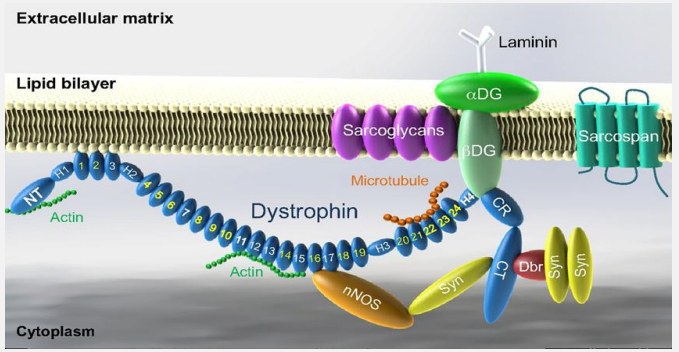
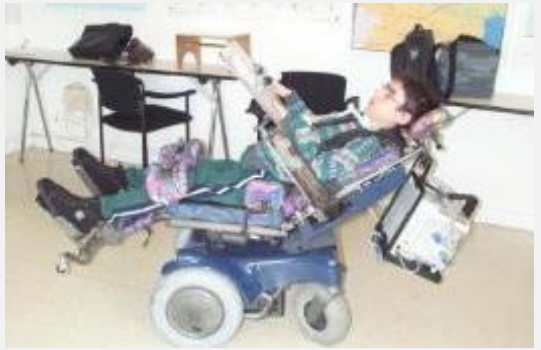
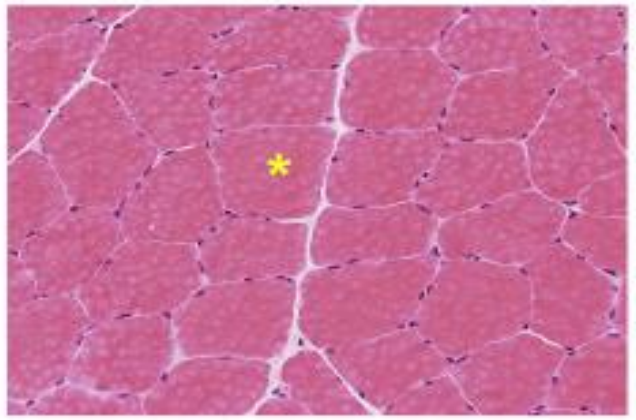
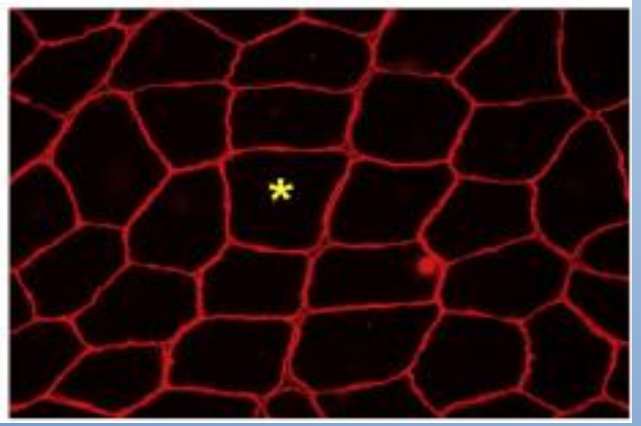
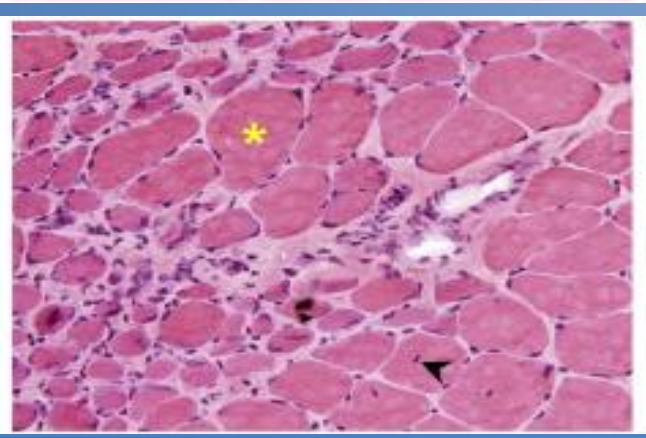
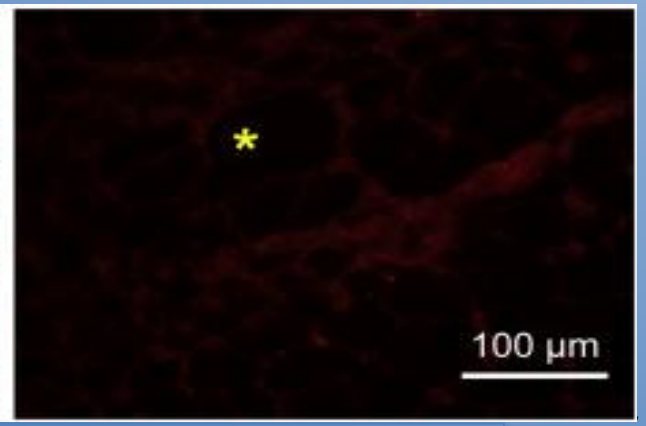




	H&E	Dystrophin
Healthy		
Duchenne Affected		

2020

KEY FIGURES

1/5,000 Males
~25K patients
in US &EU

Diagnosis
between
16 months
and 6 years

Loss of Ambulation
before 12
years

Need
respiratory assistance
before 20 years

Death
between
20 and 40
years

DYSTROPHIN GENE IS TOO LARGE FOR THE GENE THERAPY VECTORS !

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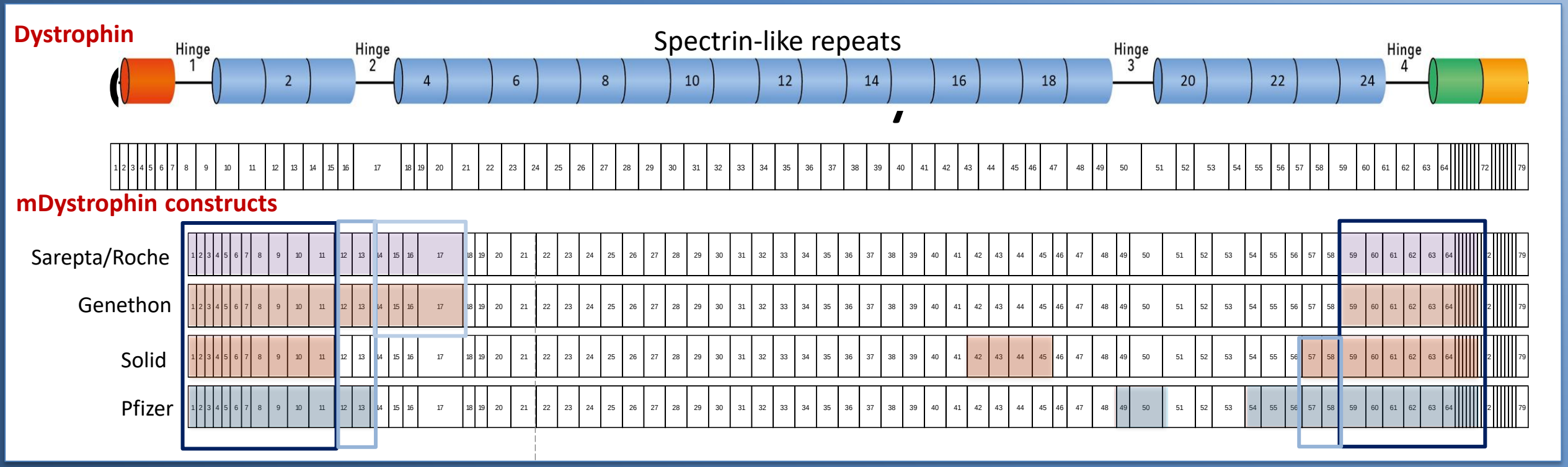

An Integrated example : GNT-0004

+ Spc5.12 Promoter +

Study Plan

Natural history/Baseline (GNT-014 study)

6-36 Month Follow-up
77 Patient Reservoir

Clinical trial (GNT-016 study)

GNT0004

Cohort 1 (n = 2)
$1x10^{13}$vg/kg

Cohort 2 (n = 3)
$3x10^{13}$vg/kg

Current status

S2-2025

With Selected Dose

Part 3:
Long Term Follow-up
(5 years post-treatment)

Main Eligibility Criteria

- Ambulant DMD boys aged 6 to 10 y.
- > 6 months natural history/baseline follow-up
- Stable or progressing disease
- No neutralizing anti-AAV8 antibodies

Primary endpoint

- Change from baseline of NSAA at week 52

Main measurements

- Muscle strength and function, mobility
- Safety
- Biomarkers (microdystrophin expression, CK, MRI,...)
- Patient reported outcomes

PERSISTENT FUNCTIONAL RECOVERY

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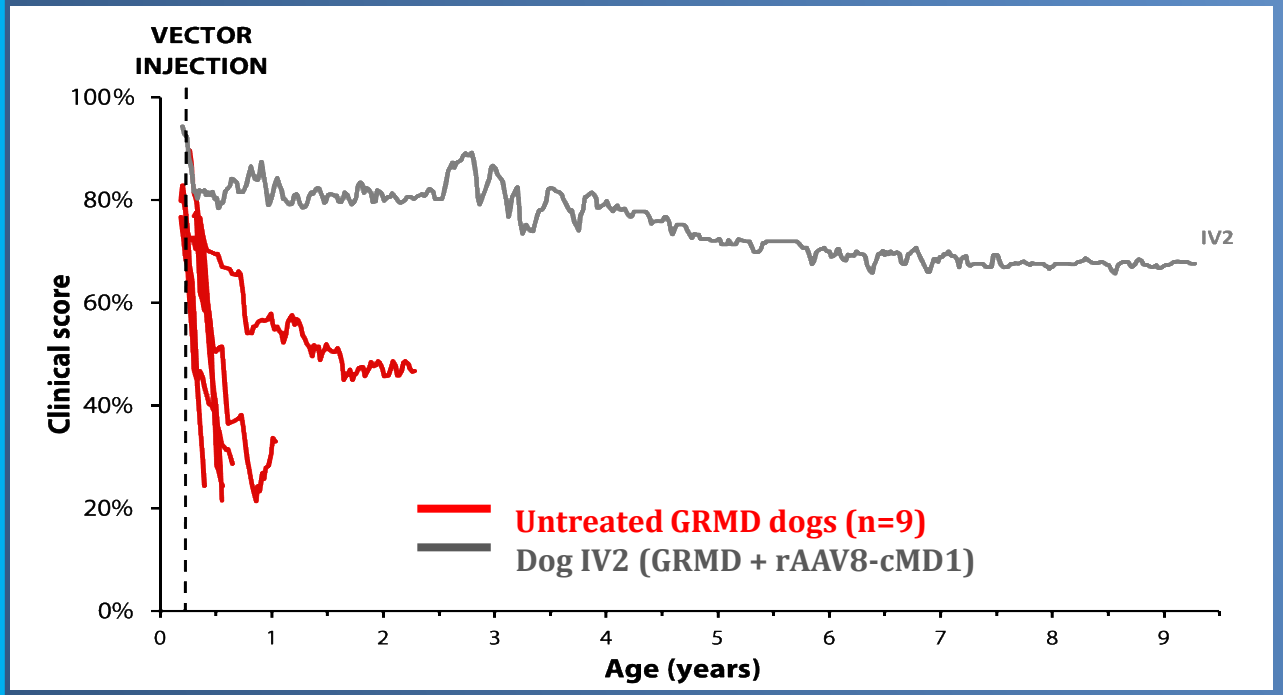
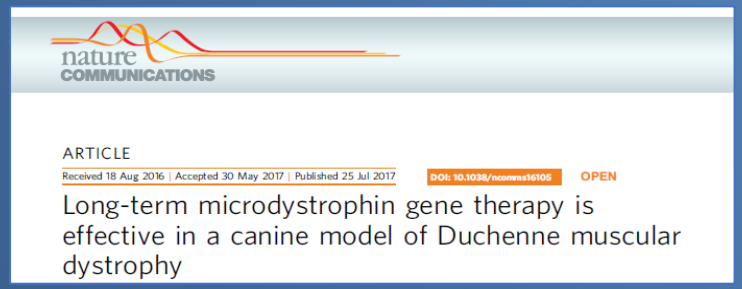
10 YEARS AFTER SINGLE I.V. ADMINISTRATION



*Scoring of different criteria : breathing, muscular firmness...

Le Guiner et al., Nature Com , July 2017


nature COMMUNICATIONS

ARTICLE

Received 18 Aug 2016 | Accepted 30 May 2017 | Published 25 Jul 2017 DOI: 10.1038/ncomms16105 OPEN

Long-term microdystrophin gene therapy is effective in a canine model of Duchenne muscular dystrophy

6 month-old GRMD dog

Untreated

10 years old

GNT-0004 : KEY RESULTS

- **Course of the disease stopped** (NSAA* score) 3 patients at dose 2 show a mean NSAA difference of 4.7 compared to non-treated patients in the Natural History
- **Rapid and up to 90% drop (mean 71% and maintaining)** of CK injury muscle biomarker
- **Other markers improved** like 6MWT, 10mWT, RFF, Stride velovity
- **Up to 85% microdystrophin-positive fibers** (immunostaining), mean 53.8%, with a mean vector copy number/nucleus: 1.2
- **Product well tolerated,** 4 mild, 1 serious event in the 1st patient due to immune rejection of microdystrophin => revised inclusion criteria + prophylactic immunosuppressive regimen

GNT0004: TREATING A DEVASTATING DISEASE

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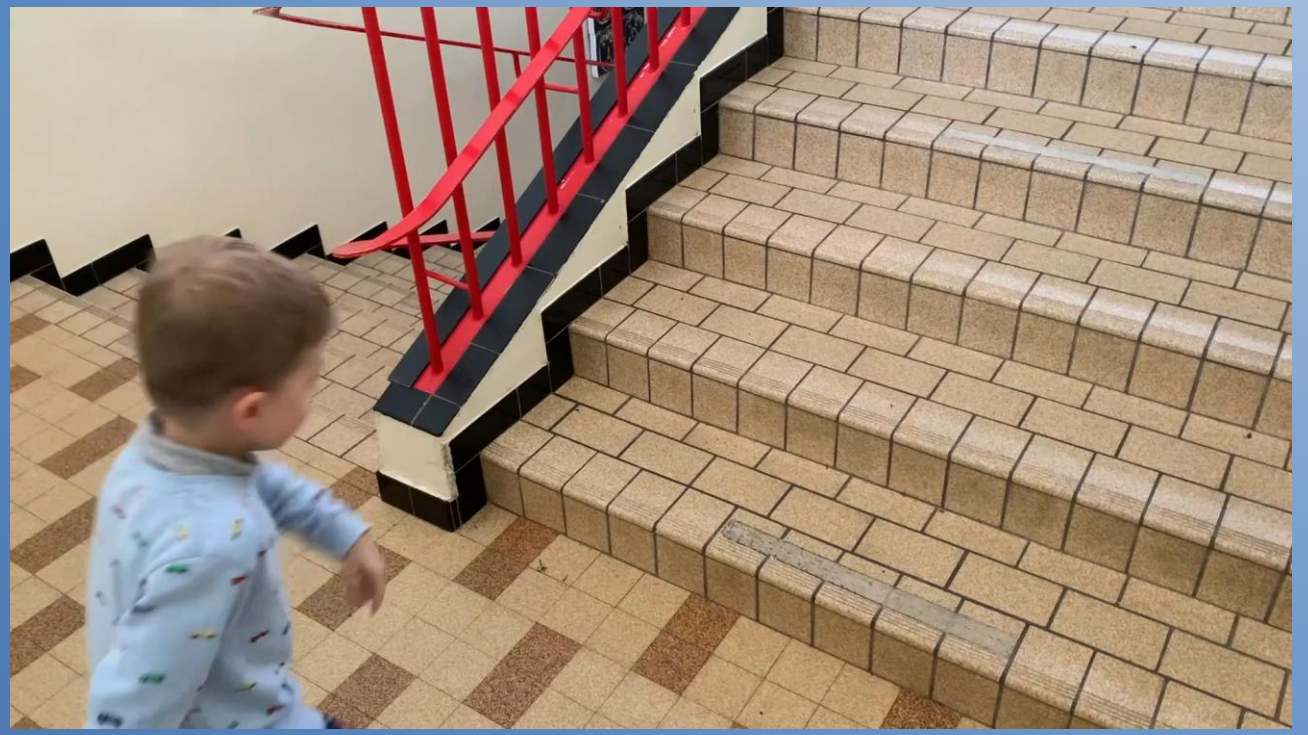
Patient without treatment

First patient treated at the pivotal dose (18 months post-treatment)



NEED FOR NEW PRODUCTION PROCESSES

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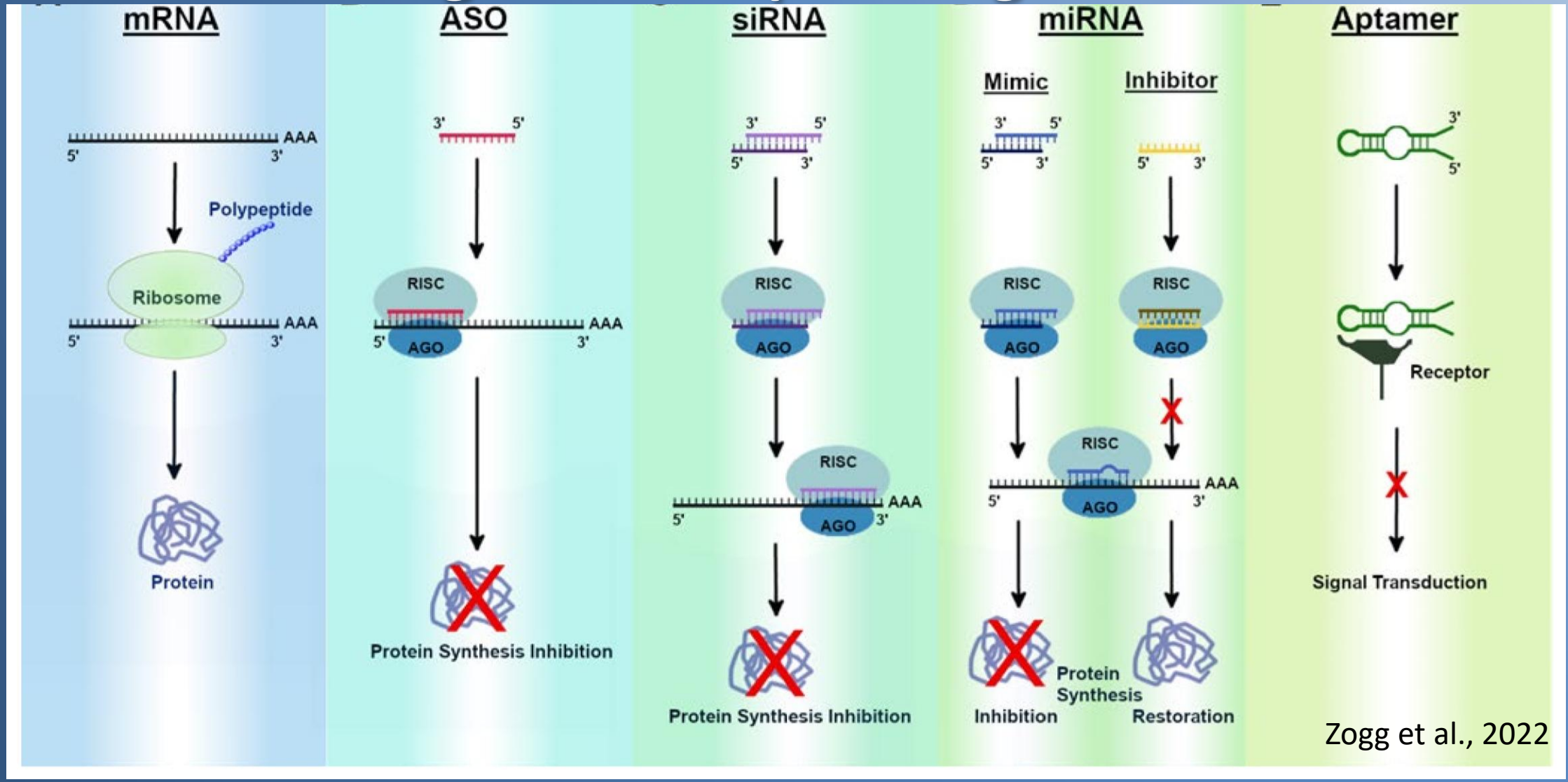
• **Vaccines:**	10^6 viral particles /dose
• **Leber Amaurosis:**	10^{11} viral particles /patient
• **Duchenne Muscular Dystrophy:**	10^{15} - 10^{16} viral particles /patient 1-10 million L / 15 000 patients
• **Sickle cell disease:**	1 lentivirus batch → 5 patients 150 millions patients

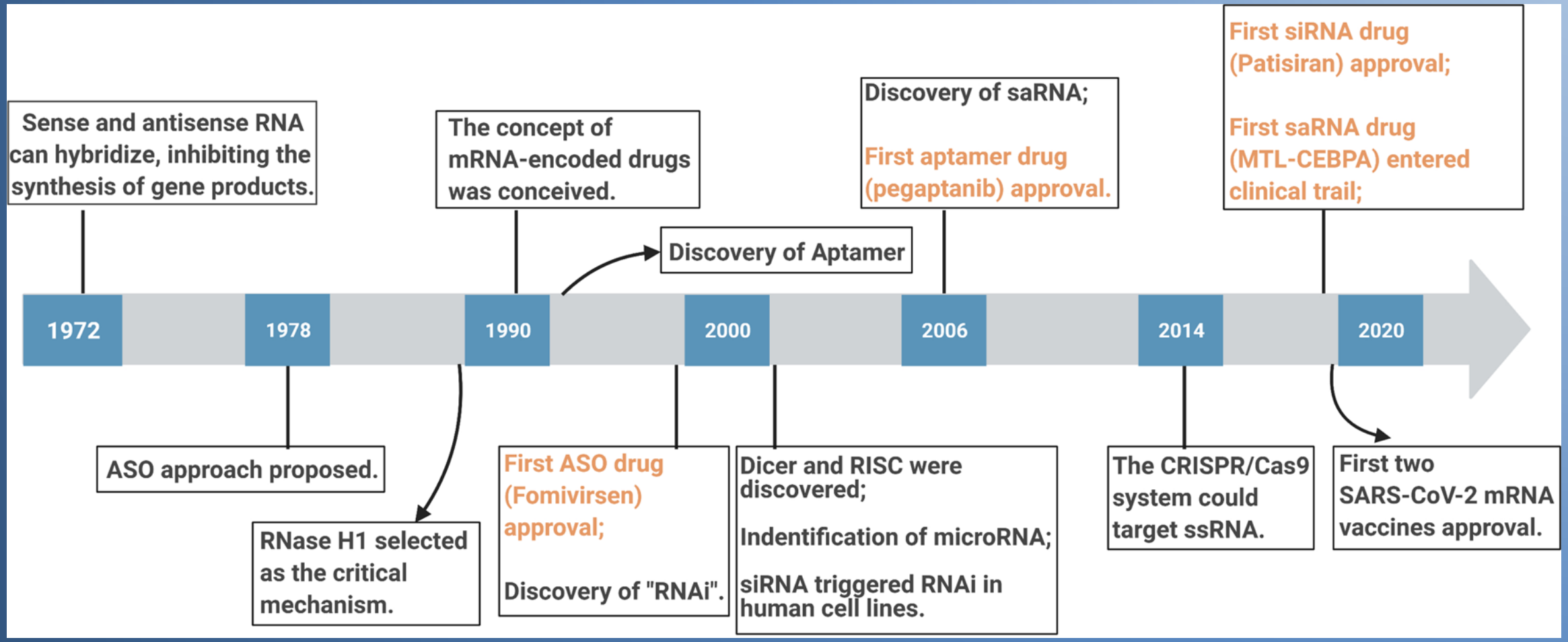
- ✓ **Need to increase the production capacities**
- ✓ **Need for breakthrough innovations in bioprocess**

What about the RNA ?

As a target or therapeutic agent



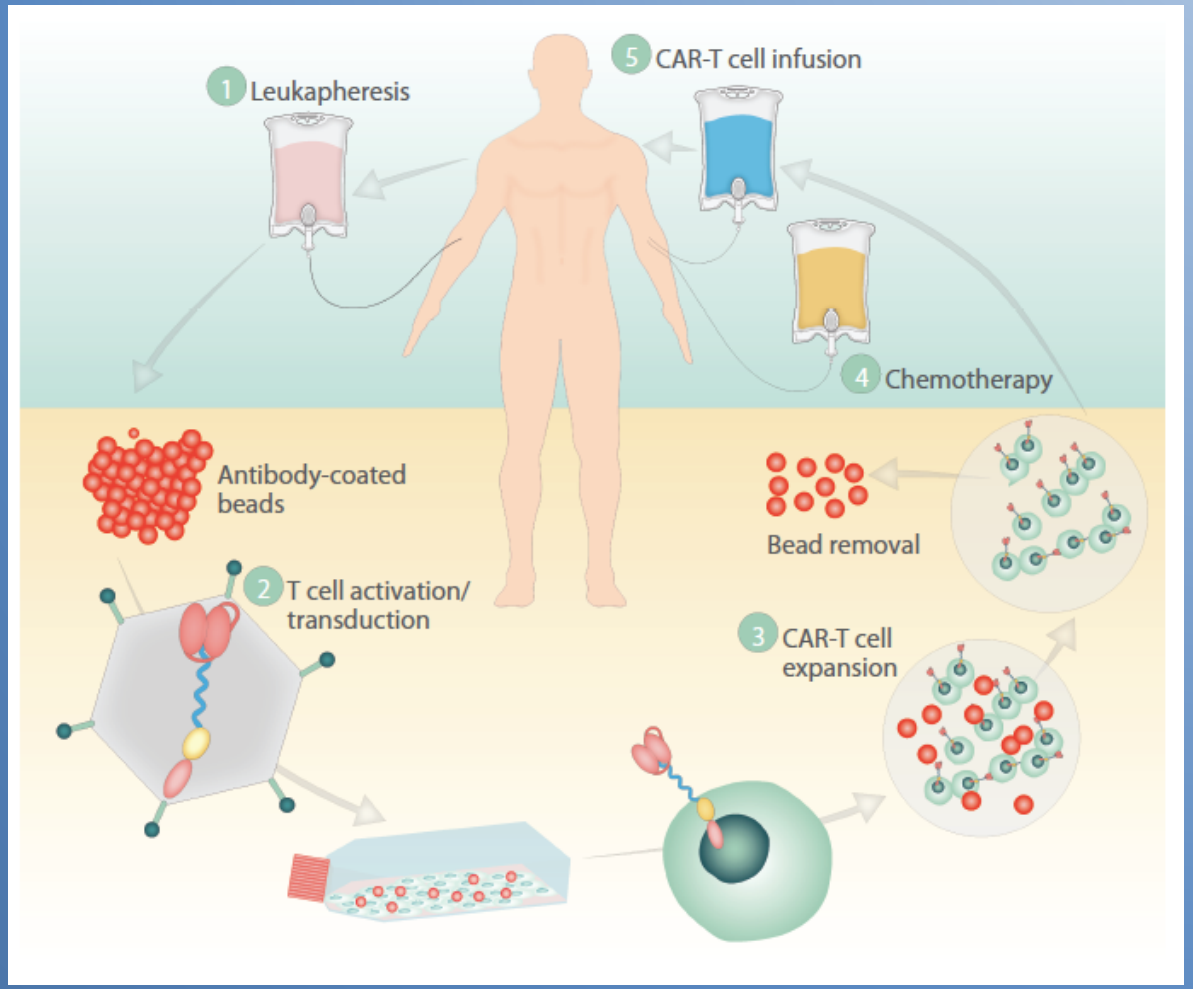
Zogg et al., 2022



Zhu *et al*. Nature 2022

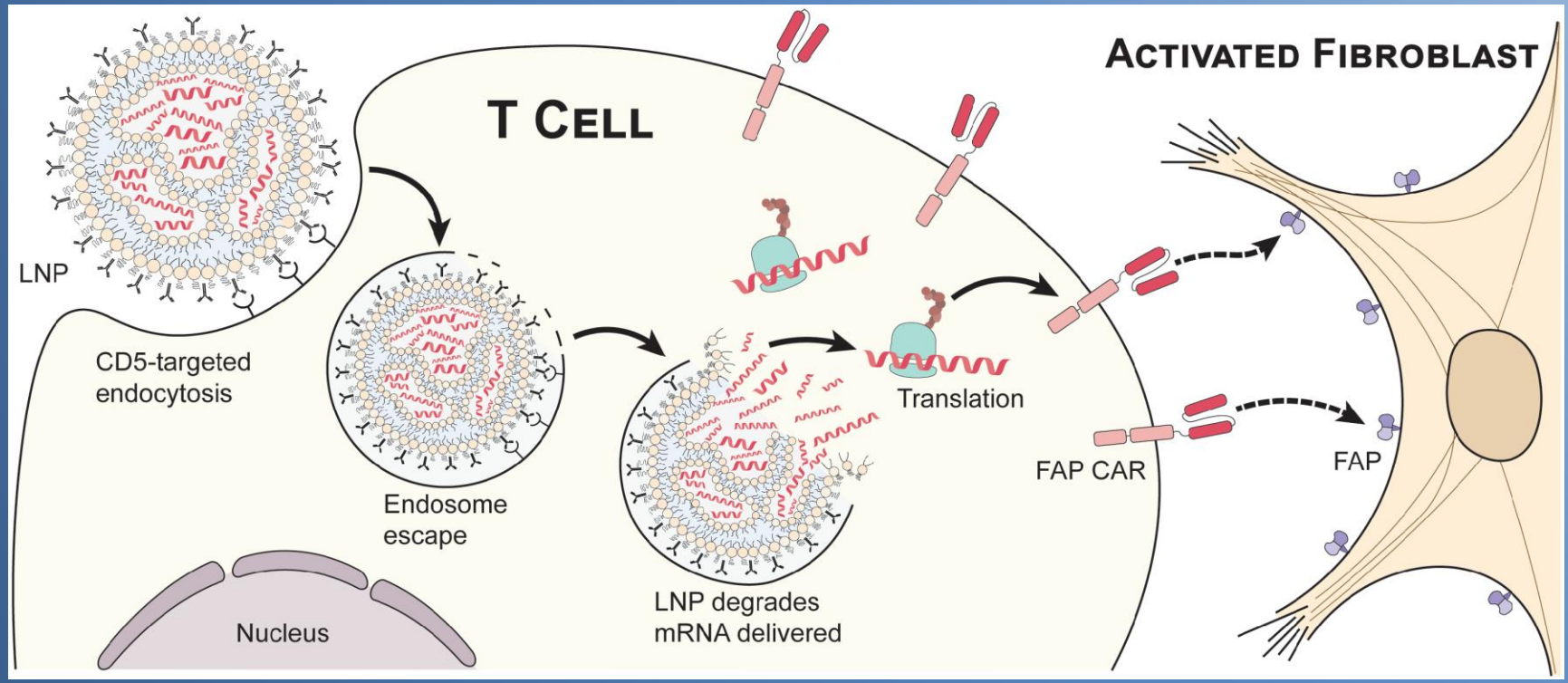
Current chimeric antigen receptor (CAR)-T cell therapy

- T cells are removed from the patient's blood
- Engineered to express a chimeric antigen receptor
- Reprograms T cells to target tumor cells



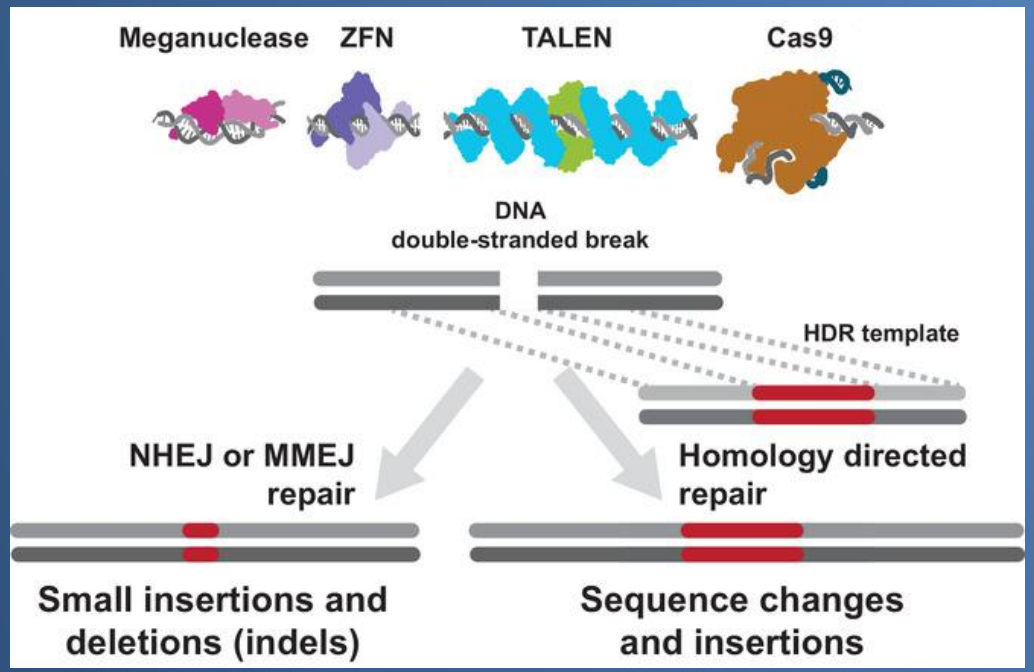
Citation: Buechner J, Kersten MJ, Fuchs M, Salmon F, Jäger U. Chimeric Antigen Receptor-T Cell Therapy: Practical Considerations for Implementation in Europe. *HemaSphere*, 2018;2:1. http://dx.doi.org/10.1097/HS9.0000000000000018

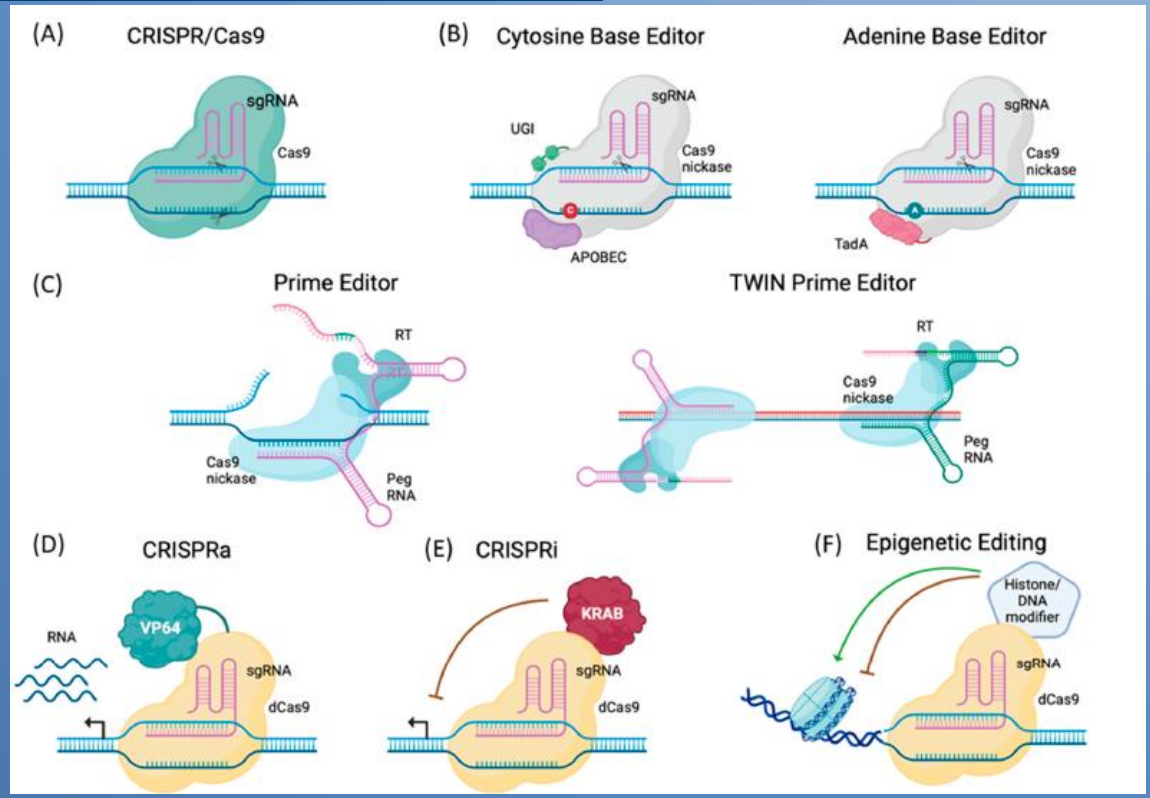
In vivo CAR T cell therapy



Science. 2022 Jan 7;375(6576):91-96. doi: 10.1126/science.abm0594.

GENOME EDITING





Laurent et al, 2024

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U.S. FOOD & DRUG ADMINISTRATION

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

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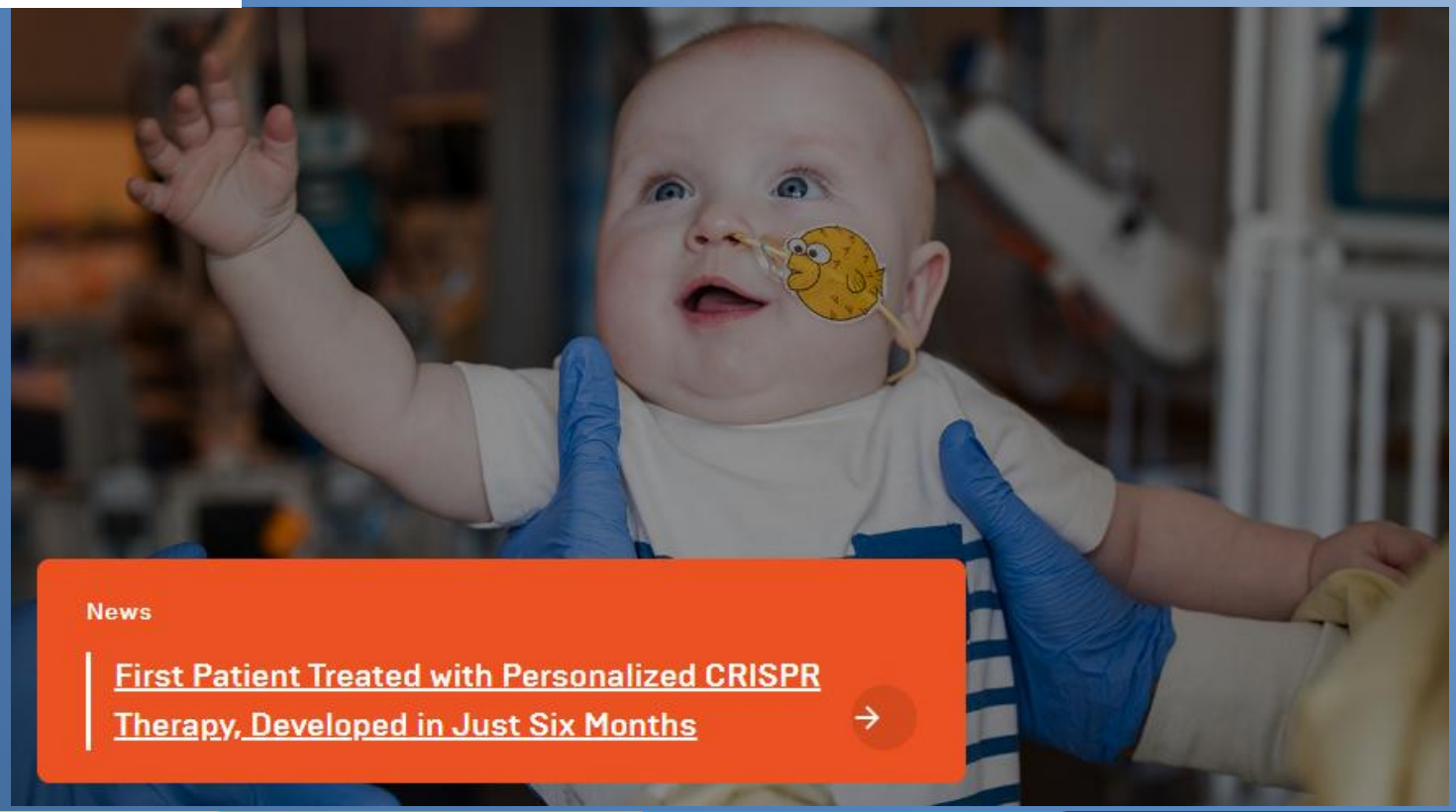

The question around AI

OMICS flood

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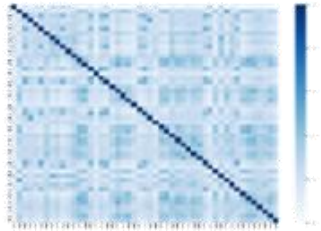

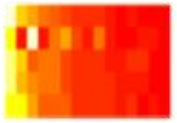

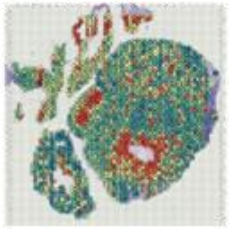

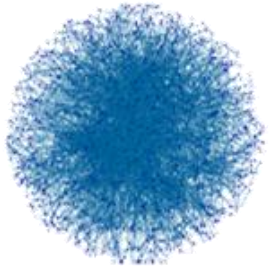

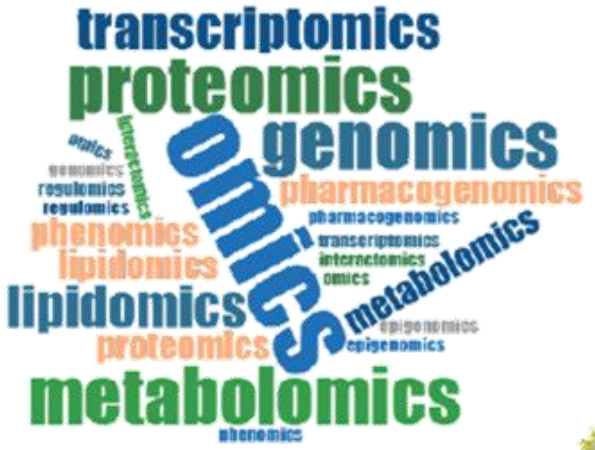

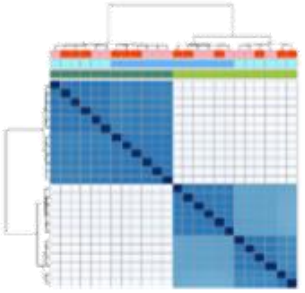

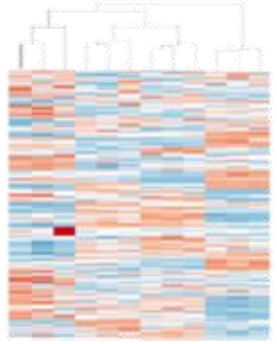

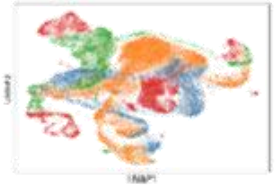

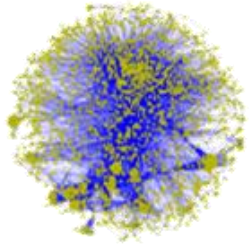

AI to sort out key networks

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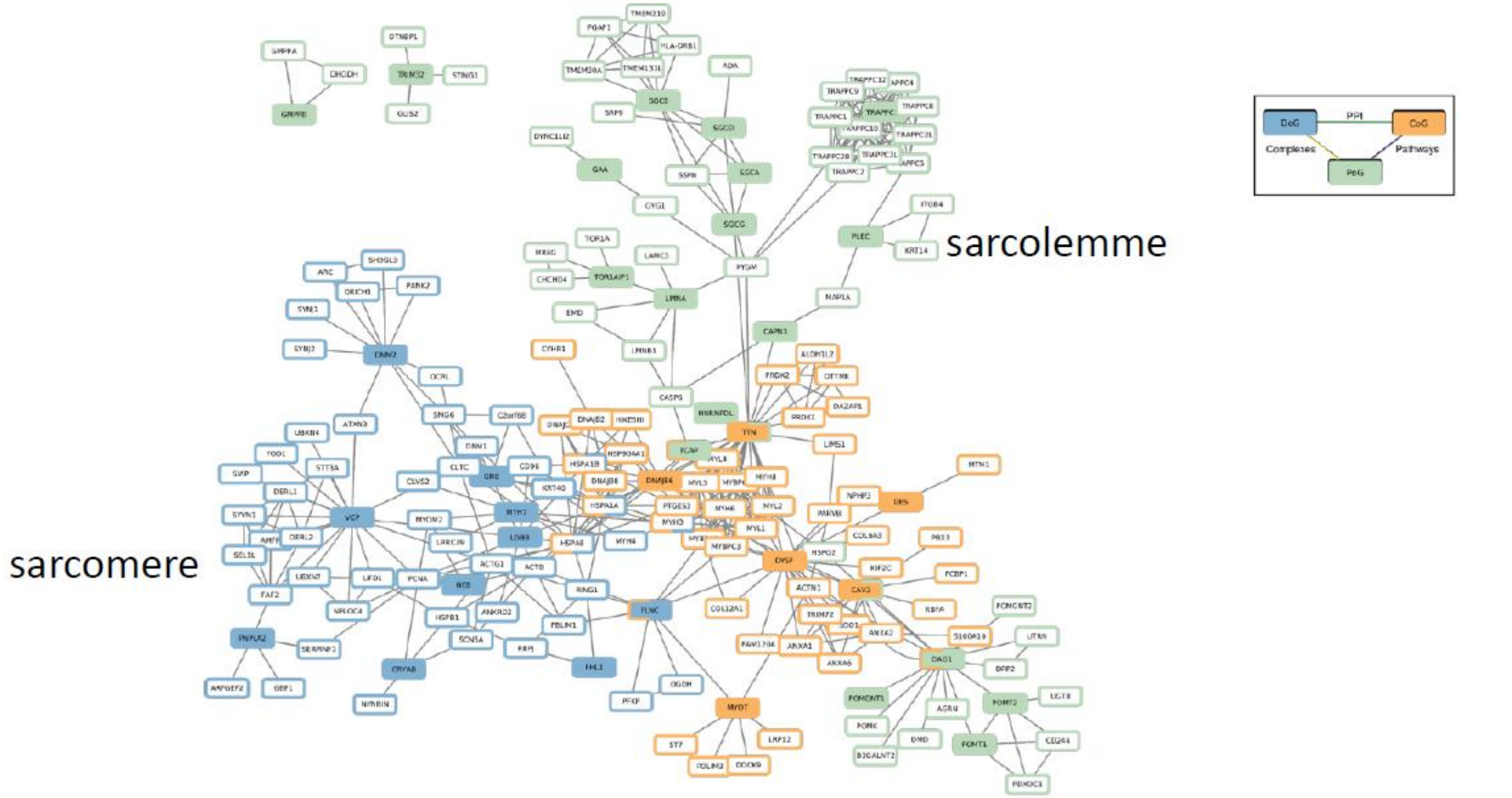

From Ozisik et al. BioRxic (2024) « Muscular Dystrophy »

BUT AI is also widely used in :

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- New Gene therapy capsids design
- Image analysis
- Drug optimisation
- Pathways identification
- Drug target identification

But of course human brain still needs to confirm and validate

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THANK YOU