Unlocking the potential of gene therapy in health

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Gene therapy definition

Gene therapy medicines contain genes that lead to a therapeutic, prophylactic or diagnostic effect.

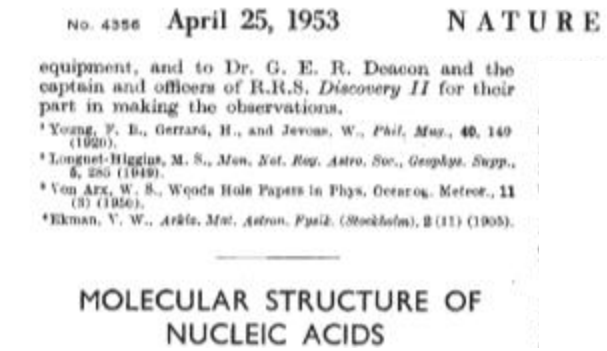
They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

a) Contains an active substance which is **a recombinant nucleic acid**
b) to regulate, repare, replace, add or suppress a genetic sequence
c) Therapeutic, prophylactic or diagnostic effect.

1953 : Molecular structure of DNA

Double helix
(Watson & Crick)

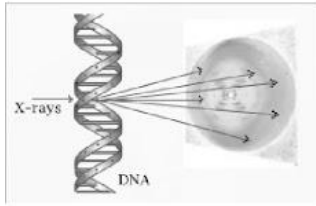
1866 1906 1909 1911 1932 1944 1947 1953 years 60-70

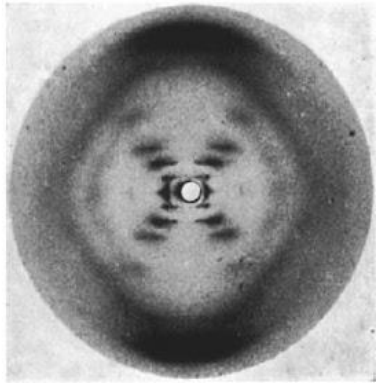

No. 4356 April 25, 1953 NATURE

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

¹ Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
² Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
³ Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1956).
⁴ Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS





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Transferring genetic information: an old concept

Principles of inheritance
(G. Mendel)

« Genetic engineering »
(6th International Congress of Genetics)

1866 1906 1909 1911 1932 1944 1947 1953 years 60-70

« Gene therapy »
(C.E. Keeler; *J Hered.*)

Genes transferred by nucleic acid : « genetic correction »
(O. Avery)

« Genetics »
(W. Bateson)

« Genes »
(W. Johannsen)

Genes on chromosomes
(T. Morgan)

STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES

INDUCTION OF TRANSFORMATION BY A DESOXYRIBONUCLEIC ACID FRACTION ISOLATED FROM PNEUMOCOCCUS TYPE III

BY OSWALD T. AVERY, M.D., COLIN M. MACLEOD, M.D., AND MACLYN MCCARTY,* M.D.

(From the Hospital of The Rockefeller Institute for Medical Research)

PLATE 1

(Received for publication, November 1, 1943)

Today, Tomorrow, Together for Public Health

… requiring molecular biology advances


SCIENCE

Gene Therapy for Human Genetic Disease?

Double helix
(Watson & Crick)

1866 1906 1909 1911 1932 1944 1947 1953 years 60-70


Joshua Lederberg (1963)


Paul Berg
Recomb. DNA
Nobel 1980

Etablishment of the bases of molecular biology :

- Genetic code
- Segregation, conception, synthesis and transfer of genes in
  bacteria, then animal and human cells
- Recombinant DNA technology with selection systems

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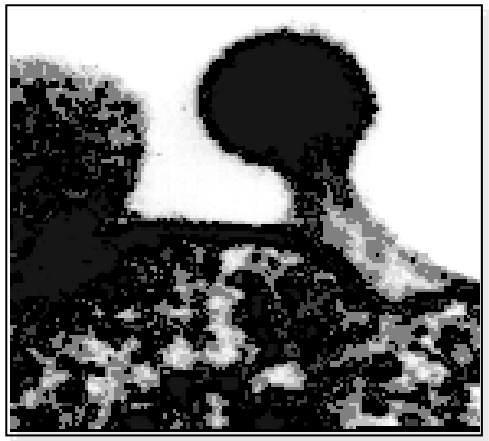
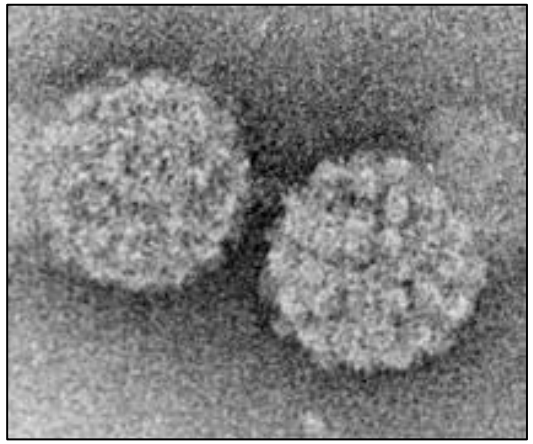
Example of vectors



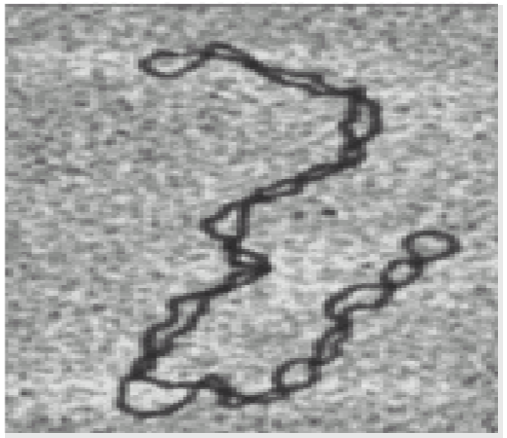
Retrovirus / Lentivirus

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



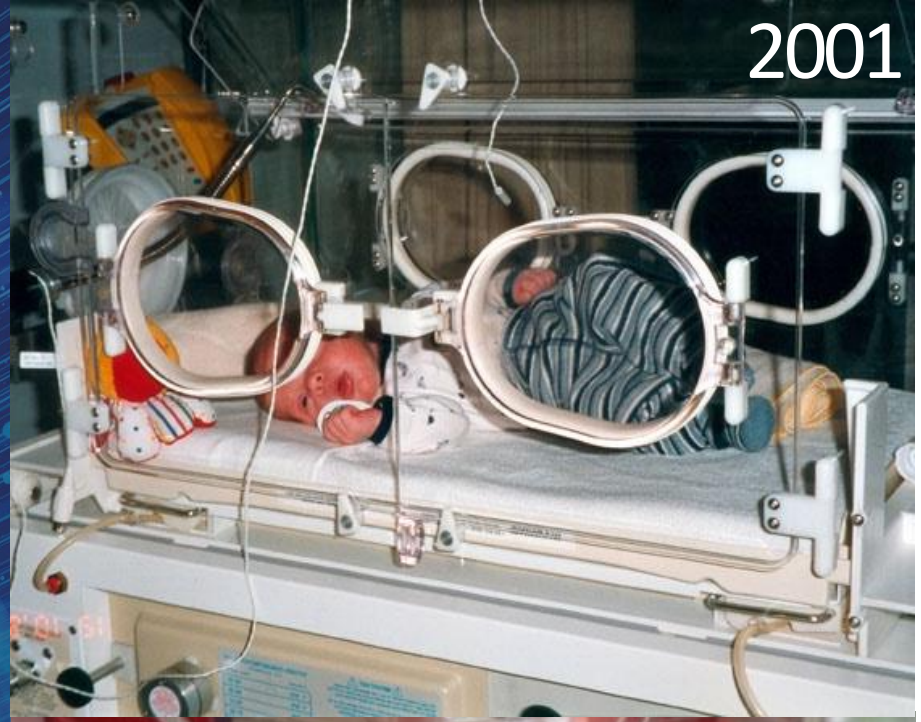
Adeno-associated virus

- 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 cure

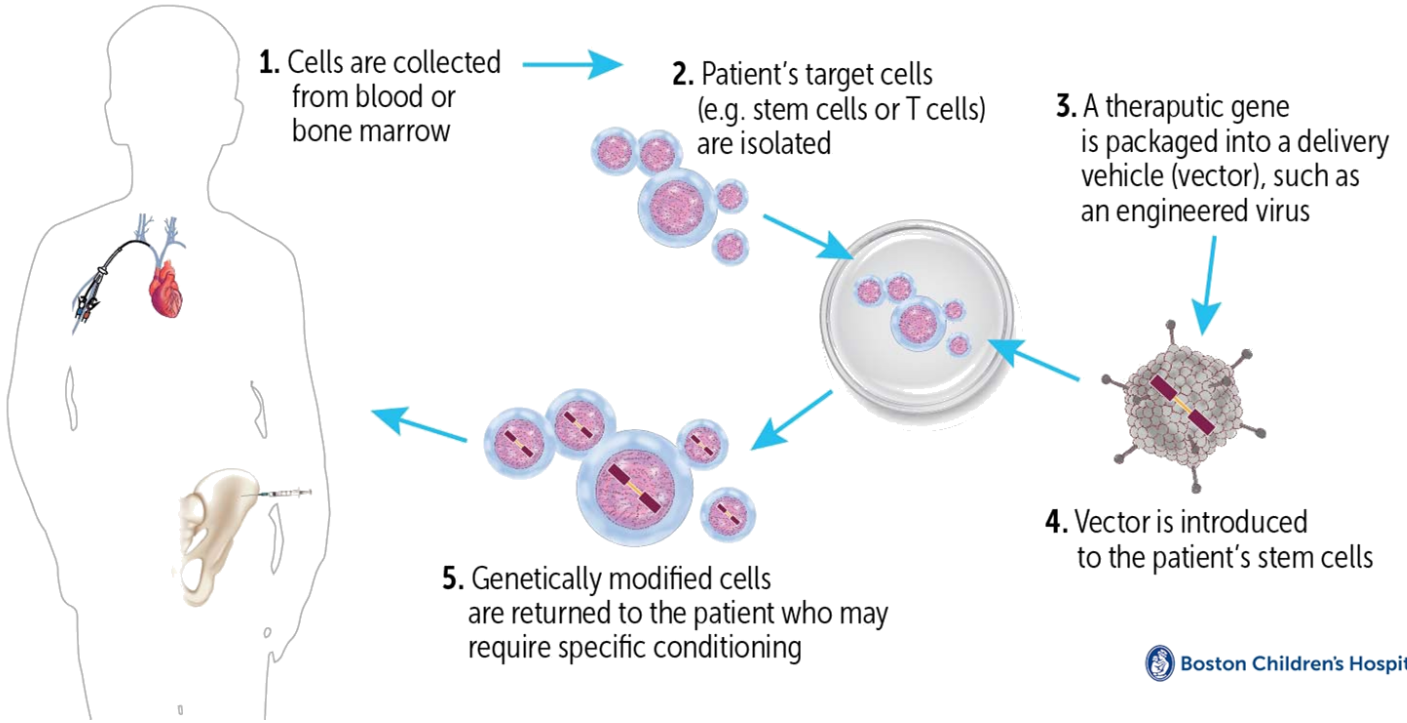


Illustration: David Chrisom, Boston Children's Hospital

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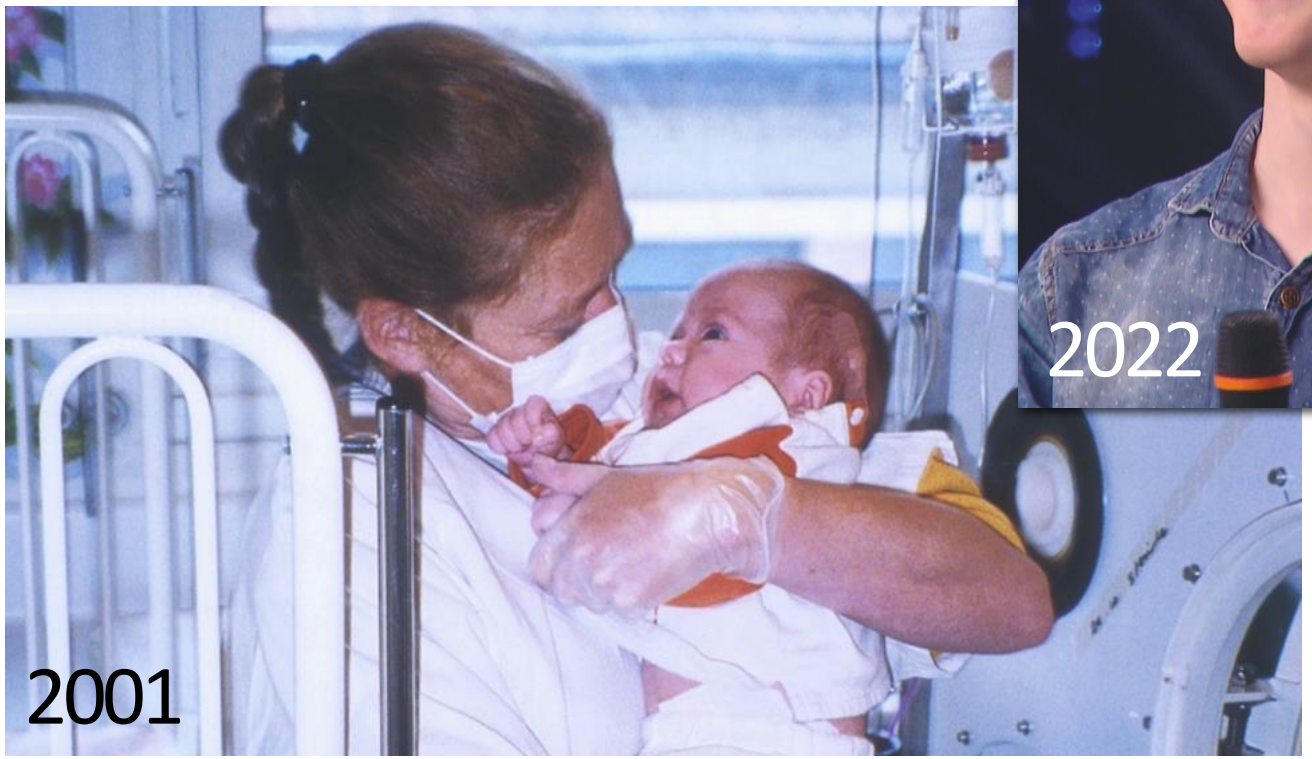
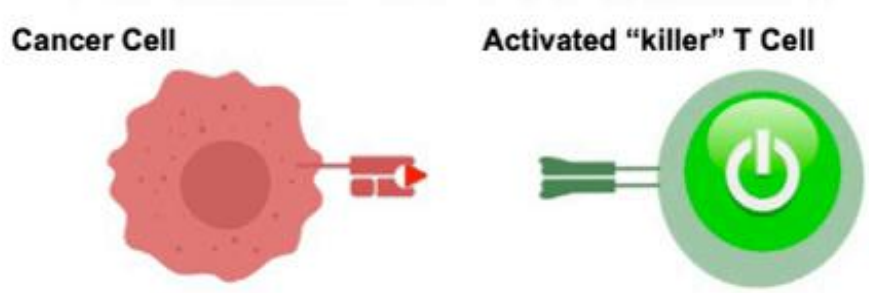
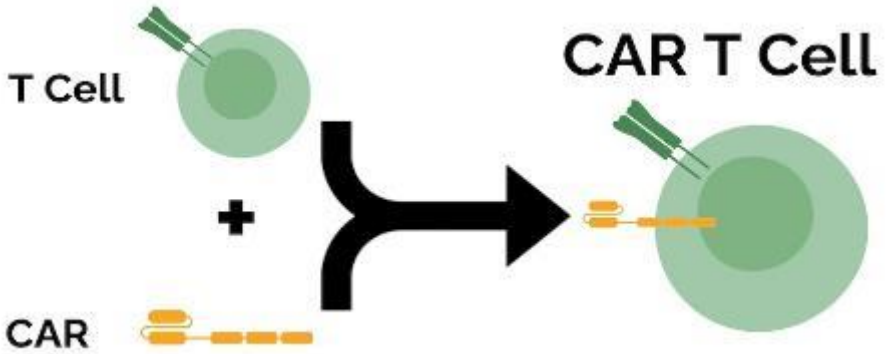
A proof of concept amenable to a number of pathologies



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

From *ex vivo* gene therapy… to CAR-T cells



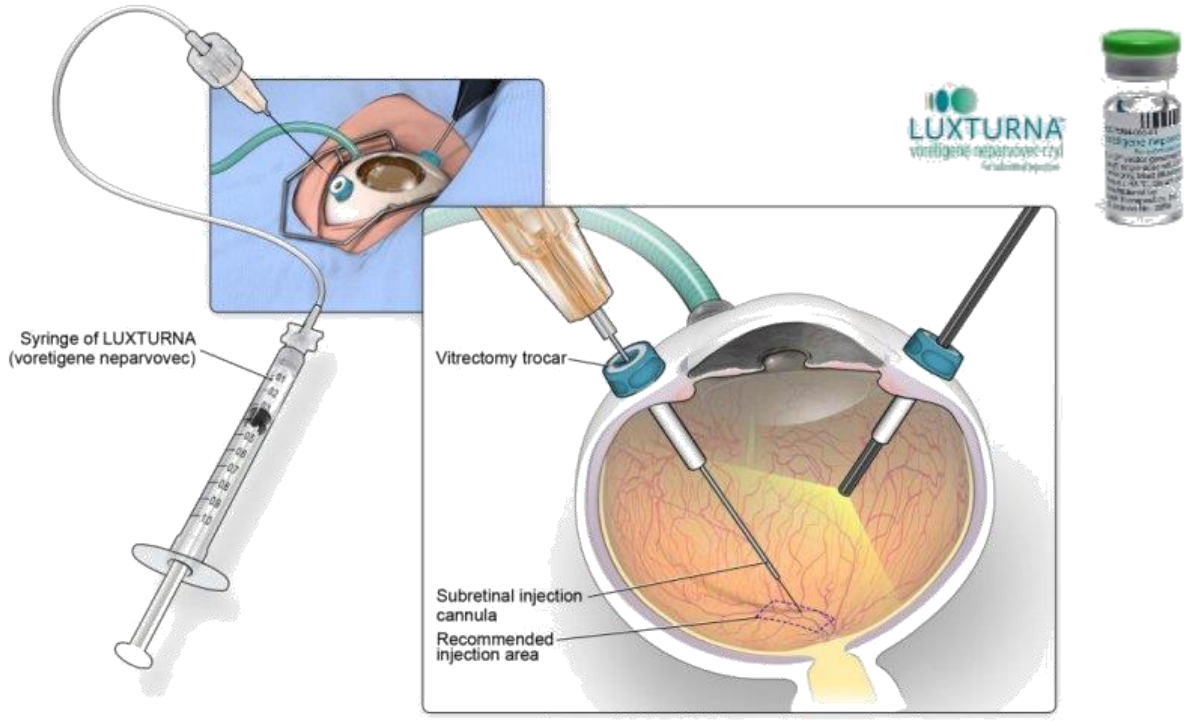


- **Axicabtagene ciloleucel** (YescartaTM): CD19; lymphoma
- **Brexucabtagene autoleucel** (TecartusTM): CD19; leukemia and lymphoma
- **Idecabtagene vicleucel** (AbecmaTM): targets B lymphocyte maturation antigen, multiple myeloma
- **Lisocabtagene maraleucel** (BreyanziTM): CD19, lymphoma
- **Ciltacabtagene autoleucel** (CarvyktiTM): BCMA, multiple myeloma

- Zevorcabtagene Autoleucel (Zevor-Cel, CT053): CAR-T, multiple myeloma

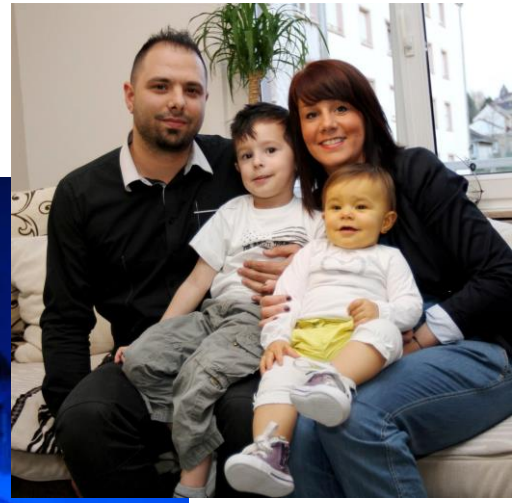
From *ex vivo* gene therapy … to local delivery

2011



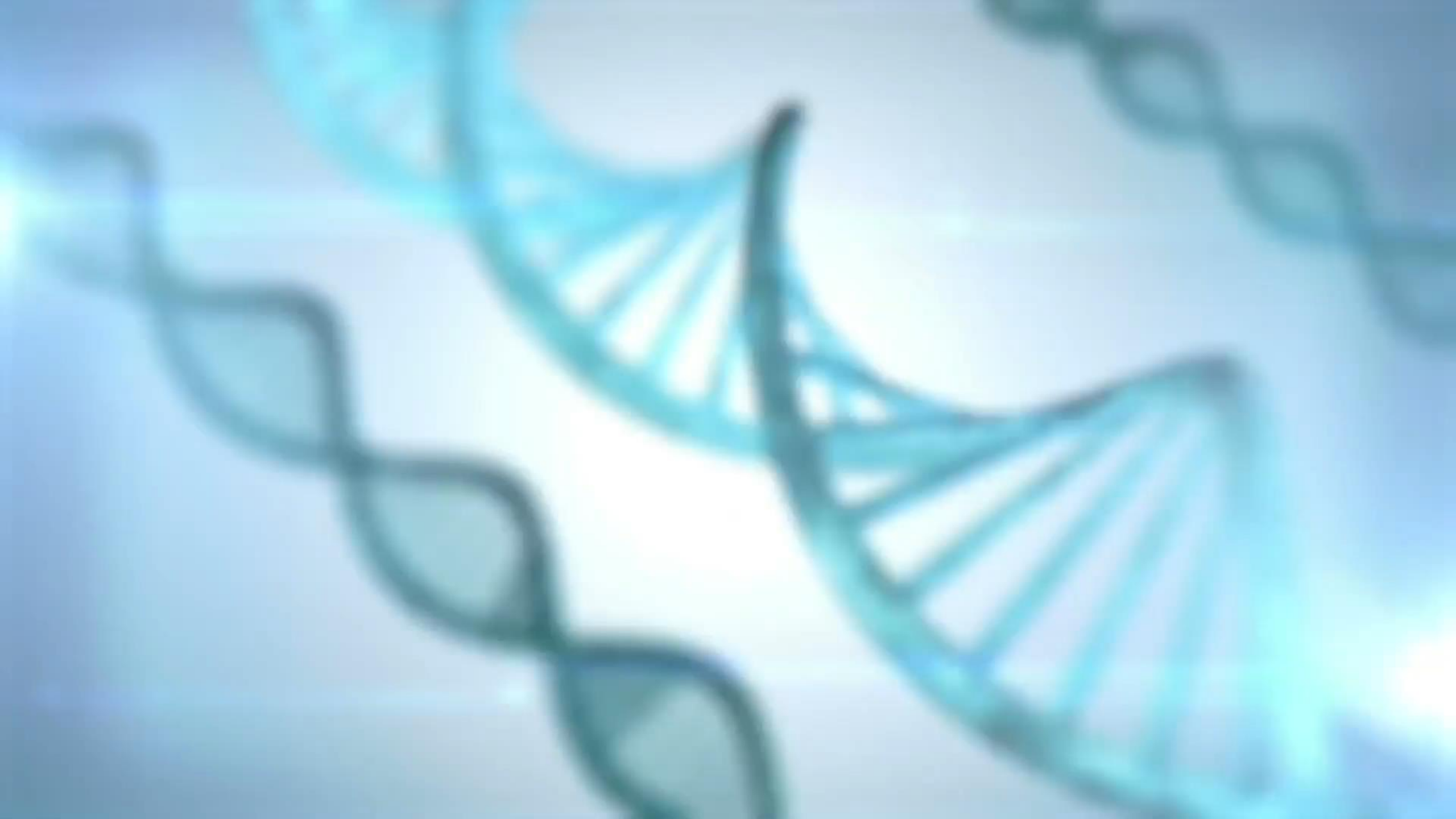
Leber's Congenital Amaurosis

From local delivery … to systemic delivery



Crigler-Najjar syndrome is a rare and serious disease caused by a deficiency of the liver-specific enzyme UDP-glycosyltransferase 1 polypeptide A1 (UGT1A1), leading to a potentially fatal accumulation of unconjugated bilirubin in serum and all body tissues, which becomes toxic in the brain.

Currently, the only treatment is phototherapy.



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From mobilizing families…

to identifying the gene

1988
Families comes together

1990
SMA gene is located

1995
SMA gene is identified

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From gene therapy development…

to clinical trial

2004/2012

Proof of efficiency of SMA gene therapy

2015

Clinical trial

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2019

Market authorization in USA and access in France and Europe

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

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A crucial need for genetic diagnosis and new born screening

For a large number of diseases, the earlier the treatment is applied, the more effective it will be.

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In vivo gene therapy SAE overview

Type of disease	Immune-related adverse events observed	Other SAE that may involve immune reactions	Gene therapy drug
Duchenne dystrophy	Myocarditis/Myositis	Mid transaminitis Mid transaminitis	PF-06939926 SRPT9001 GNT0004
	Atypical Hemolytic Uremic syndrome (aHUS)	Mid transaminitis	SGT-001 PF-06939926
SMA	Thrombotic microangiopathy (TMA*) Hemophagocytic lymphohistiocytosis (HLH)	Mid transaminitis	ZolgenSMA®
Myotubular myopathy		Fatal hepatotoxicity	AT132
CNS disorders	_	DRG toxicity	ALS and GAN AAV GT
Blood/coagulation disorders		Mid transaminitis	Almost all

Immune reactions
Innate reactions
(i.e. complement activation)

↓

Preexisting Ab → ineligible patients
Loss of efficacy, prevent redosing

The need for innovation in gene therapy manufacturing

- **Vaccine:** **10^7 viral particles/dose**
- **Leber's Congenital Amaurosis:** **10^{11} vg/patient**
- **Duchenne / SMA :** **10^{15} to 10^{16} vg/patient**

treating only incident patients in Europe with the current technologies would require >500 AAV lots of 200 L per year.
Each batch € 0,5 M to € 1M worth.

Forecast: Annual viral vector bioreactor needs for gene therapy

	Annual demand (clinical+commercial)
Liters bioreactor capacity needed (LV+AAV)	**285,000,000**
Number of 10, 20 and 50L bioreactors required	**5,200,000**
Number of 2000L bioreactors required	**1,500**

Adapted from: GlobalData, Pharma Intelligence Center Clinical trials (2019)

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The economic burden of gene therapy

Bugatti Veyron – 1.2 M€

Bugatti Chiron – 2 M€

Bugatti Veyron Super Sport – 2.8 M€

Bugatti Chiron Diamond Edition - 3.5 M€

zynteglo™
(autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene)

uniQure

HEMGENIX

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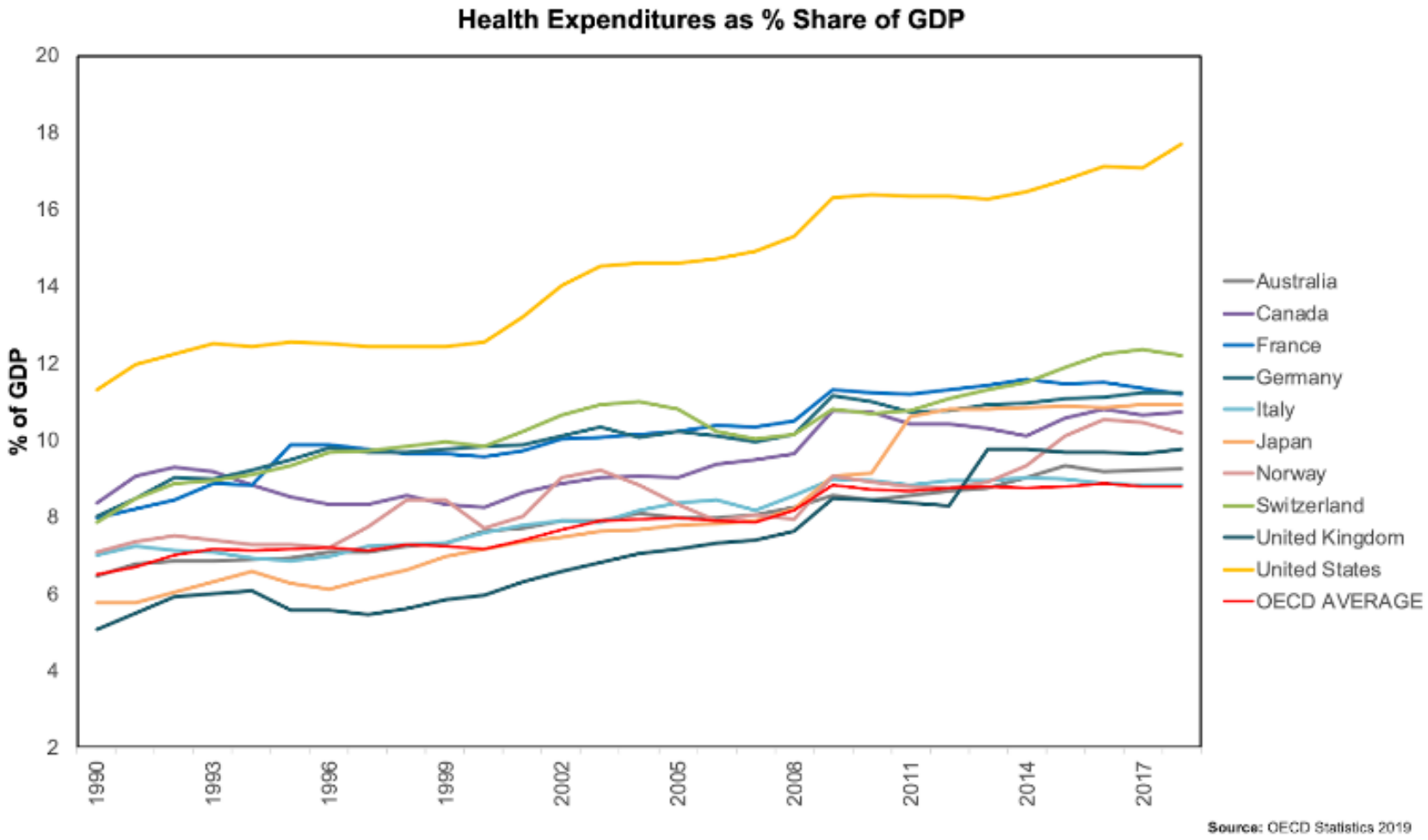
The economic burden of gene therapy



Source: OECD Statistics 2019

DRUG MARKET ($ B)

CURRENT		WITH GENE THERAPY
1400	→	4800

Goldman Sachs

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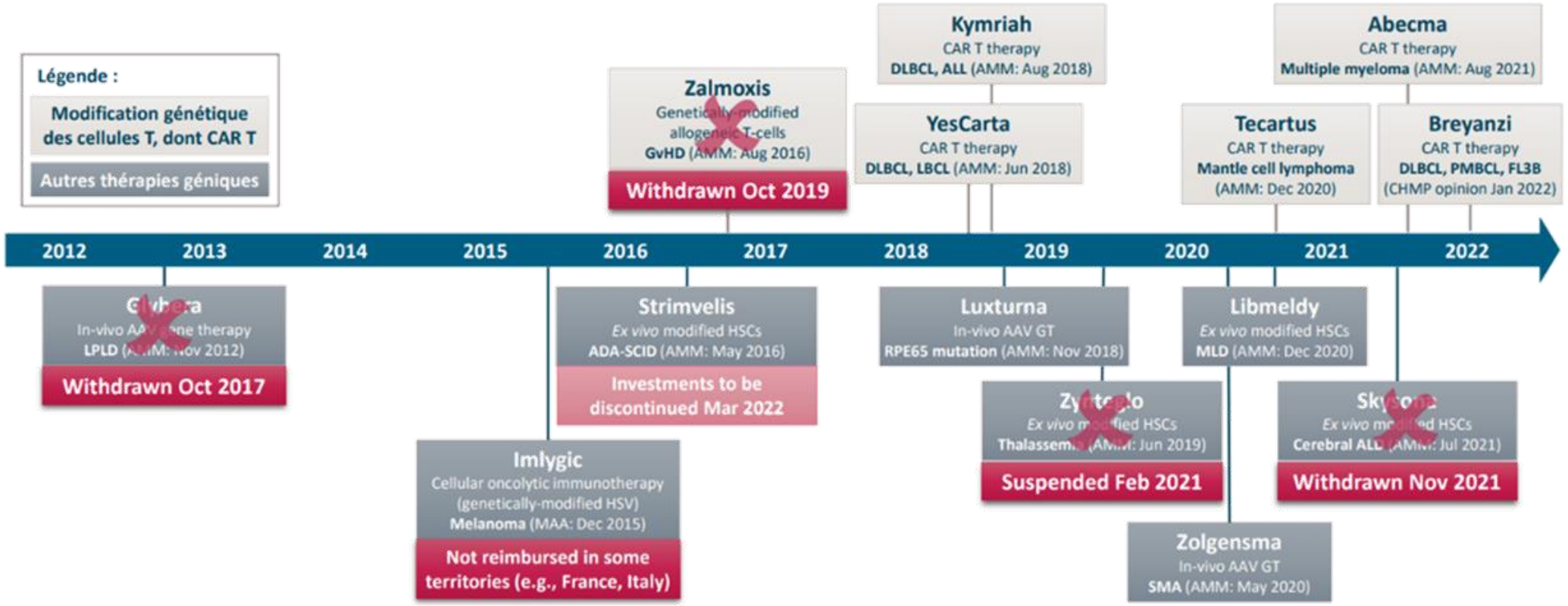
Gene therapy commercialisation

A significant number of EMA-approved gene therapies are not accessible to patients



MAA: Marketing Authorization Approval by the European Medicines Agency (EMA)
Glybera withdrawal: https://www.ema.europa.eu/en/medicines/human/EPAR/glybera ; also refer to: https://pharmaphorum.com/news/glybera-expensive-drug-world-withdrawn-commercial-flop/
Zalmoxis withdrawal: https://www.ema.europa.eu/documents/public-statement/public-statement-zalmoxis-withdrawal-marketing-authorisation-european-union_en.pdf
Zynteglo marketing suspension: https://www.ema.europa.eu/en/news/precautionary-marketing-suspension-thalassaemia-medicine-zynteglo
Skysona withdrawal: https://ec.europa.eu/health/documents/community-register/html/h1563.h
Strimvelis : discontinuation : https://ir.orchard-tx.com/

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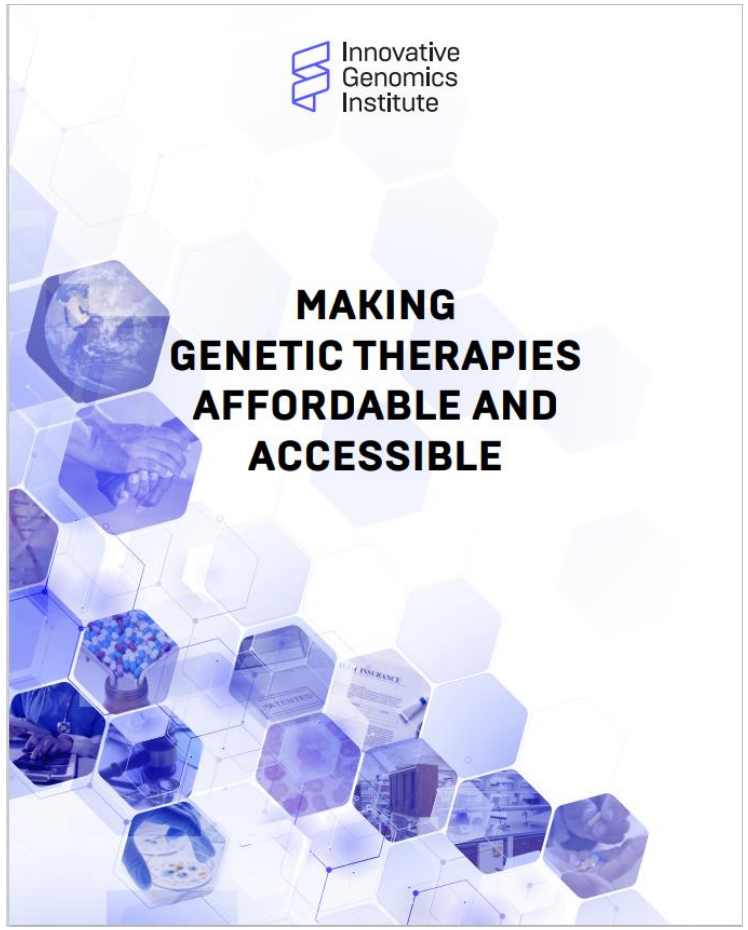

"Now we are at an inflection point (...) While the therapeutic potential of genetic therapies is immense, their real-world impact will be limited if we do not secure access for everyone who stands to benefit."

Jennifer Doudna

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Thank You!

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