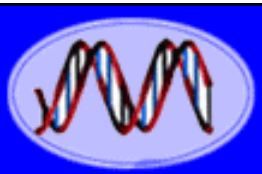
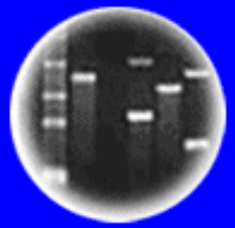


DNA
Genetic Code of Life

Entire Genetic Code
of a Bacteria



DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

HC70A, SAS70A, & PLSS059
Winter 2019
Genetic Engineering in Medicine, Agriculture, and Law

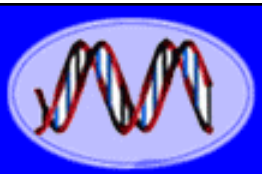
Professors Bob Goldberg, John Harada, & Channapatna Prakash

Lecture 8
Human Genetic Engineering and Gene Therapy

UCLA

TUSKEGEE UNIVERSITY

UCDAVIS UNIVERSITY OF CALIFORNIA



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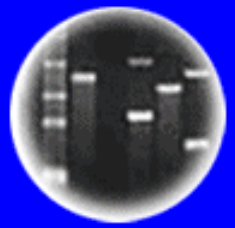

DNA Fingerprinting

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THEMES

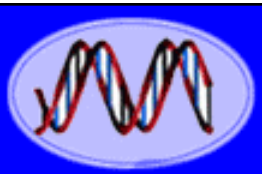
Human Genetic Engineering and Gene Therapy

1. What is Gene Therapy?
2. Case Study of Gene Therapy for Severe Combined Immunodeficiency (SCID)
    a. Types of Gene Therapy
    b. Vectors
    c. Some Problems and Improvements with Gene Therapy
3. Ex Vivo Gene Therapy for Cancer
4. *In Vivo* Gene Therapies
5. Regulation of Gene Therapy
6. Current Status of Gene Therapy
7. Issues Concerning Gene Therapy
8. Gene Editing & Human Gene Therapy

Genetically Engineered Organisms & Their Uses

DATE	HC70A/SAS70A LECTURE SCHEDULE
1/8	**Lecture 1:** *The Age of DNA: What is Genetic Engineering - Part One* **Experiment:** Isolating DNA
1/10	**Film:** *Race for the Double Helix (2 Hours)*
1/15	**Lecture 2:** *The Age of DNA: What is Genetic Engineering - Part Two* **Demonstration:** Genetic Engineering of Food Crops
1/17	**Film:** *The Gene Engineers (1 Hour); Playing God (1 Hour)*
1/22	**Lecture 3:** *What Are Genes & How Do They Work: Part One*
1/24	**Film:** *Extraordinary Measures (1.75 Hours)*
1/29	**Lecture 4:** *What Are Genes & How Do They Work: Part Two* **Tuskegee Students Visit UCLA**
1/31	**Lecture 5 –** *How Are Genes Cloned & Engineered: The Hemophilia Story* **TAKE-HOME EXAM QUESTIONS HANDED OUT** **All-Class Reception**
2/5	**Lecture 6 –** *A 21st Century Genetic Engineering Revolution*
2/7	**Film:** *Food Evolution (1.5 Hours)* **Speaker:** Channapatna Prakash, Ph.D.
2/12	**ALL-CLASS MIDTERM ORAL EXAM**
2/14	**Speaker: Harry Klann,** Supervising Criminologist, LAPD, Retired *DNA Forensics & The Law* **Experiment:** Making Your Own DNA Fingerprint!
2/19	**Lecture 7 –** *Age of Genomics: Three Parent Babies, Human Origins, & Race* **Short Film:** *Knowledge or Certainty*
2/21	**Speaker: Pei Yun Lee, PhD:** *Stem Cells: Promise, Reality, and Conflict* **All-Class Reception**
2/26	**Lecture 8 –Professor John Harada:** *Human Genetic Engineering* **FINAL ORAL EXAM QUESTIONS HANDED OUT**

1. Bacteria
   a. Drugs
2. Fungi
   a. Drugs
   b. Fermentation
3. Animals
   a. Mice-Human Gene Functions
   b. Farm Animals-Drugs
4. Plants
   a. Genetically Engineered Crops
   b. Feedstock for Biofuels
5. Humans



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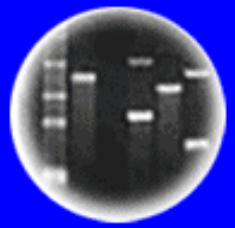

DNA Fingerprinting

Cloning: Ethical Issues
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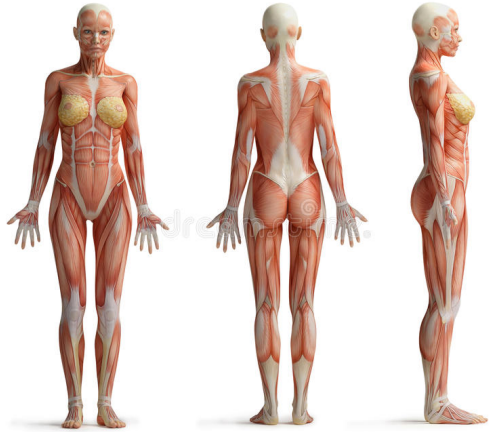
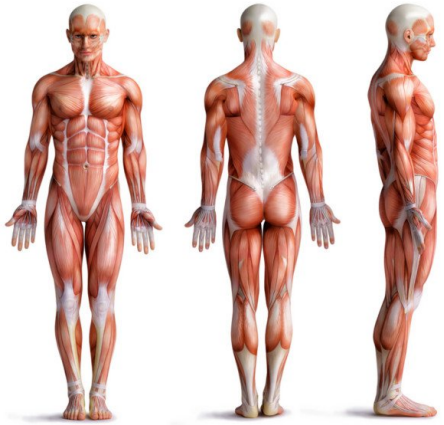
Plants of Tomorrow

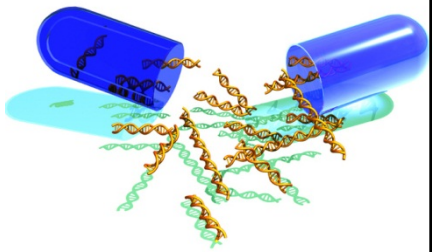
Human Genetic Engineering and Gene Therapy





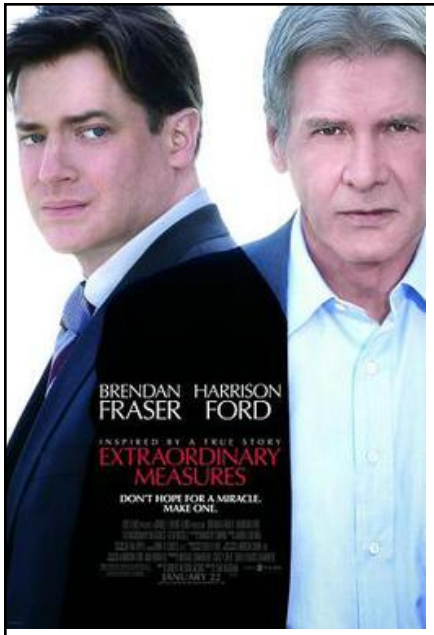
What is Gene Therapy?

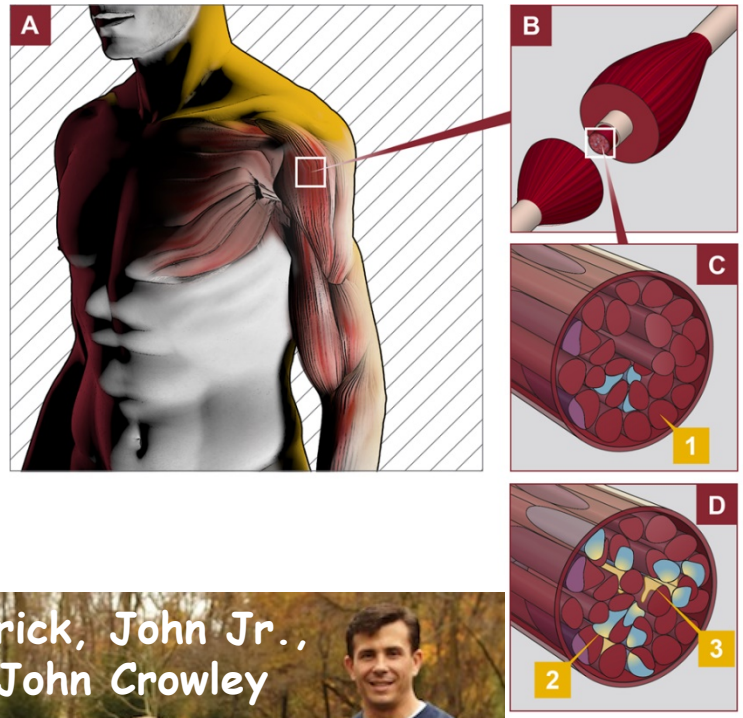
- The insertion of usually genetically altered genes into cells especially to replace defective genes in the treatment of genetic disorders or to provide a specialized disease-fighting function - *Merriam-Webster Dictionary*
- Experimental treatment of a genetic disorder by replacing, supplementing, or manipulating the expression of abnormal genes with normally functioning genes - *National Center for Biotechnology*
- It is an approach to treating disease by either modifying the expressions of an individual's genes or correction of abnormal genes - *American Society of Gene and Cell Therapy*
- Gene therapy is the use of DNA as a pharmaceutical agent to treat disease - *Wikipedia*



Humans Have Been Genetically Engineered to Cure Genetic Diseases

Pompe Disease



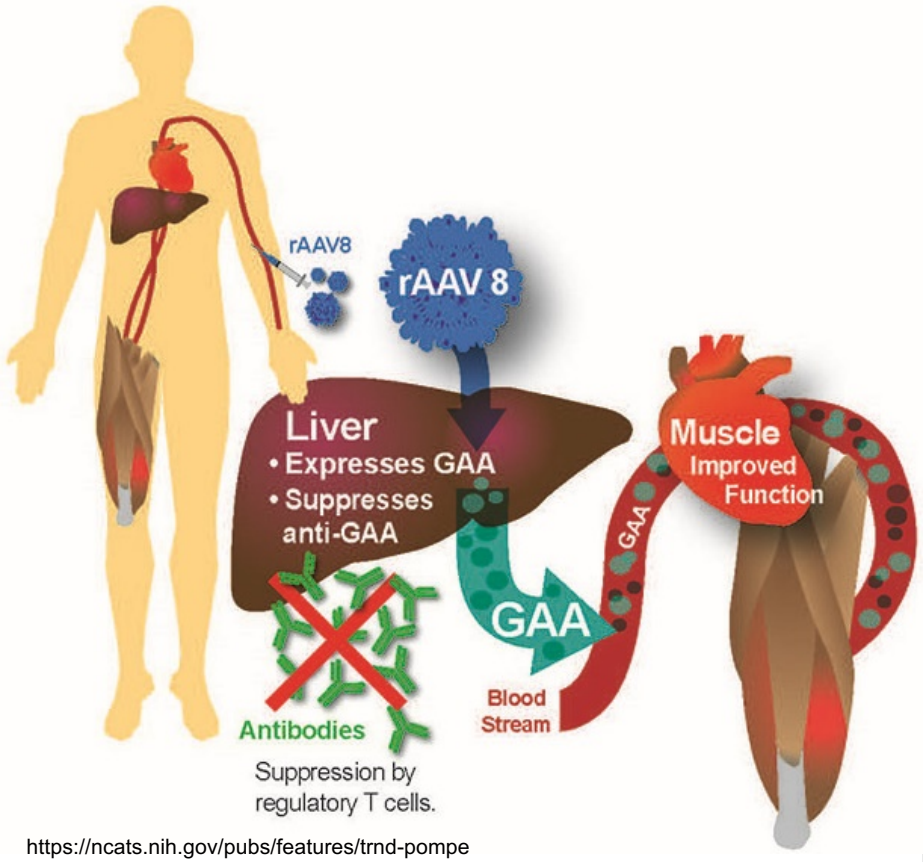


- **A** Skeletal muscle
- **B** Bundle of muscle fibers
- **C** Normal breakdown of glycogen by GAA in muscle cells
- **D** Harmful build-up of glycogen in the muscle cells due to lack of GAA

1. Glycogen is broken down in parts of each cell called lysosomes
2. In Pompe disease, glycogen builds up in the lysosomes, damaging the muscle cells
3. As the condition worsens, glycogen leaks out of the lysosomes, damaging the surrounding muscle cells and weakening the muscle

- Glycogen is stored in the lysosome, an organelle
- Acid alpha glucosidase (GAA) converts glycogen, a storage form of sugar, into glucose
- GAA is defective in individuals with Pompe disease. Glycogen over-accumulation damages muscle cells.
- Pompe disease occurs in 1 in 40,000 births

Gene Therapy for Pompe Disease with the Acid Alpha Glucosidase Gene



https://ncats.nih.gov/pubs/features/trnd-pompe

POMPE DISEASE NEWS

Actus Therapeutics

Phase 1/2 Trial Investigating ACTUS-101 Gene Therapy for Pompe Disease Doses First Patient

FEBRUARY 6, 2019 BY PATRICIA INACIO, PHD IN NEWS.

Hemophiliacs Have Mutations in Factor VIII, Factor IX, or Factor XI Genes

TABLE 13.2 Some Important Genetic Disorders

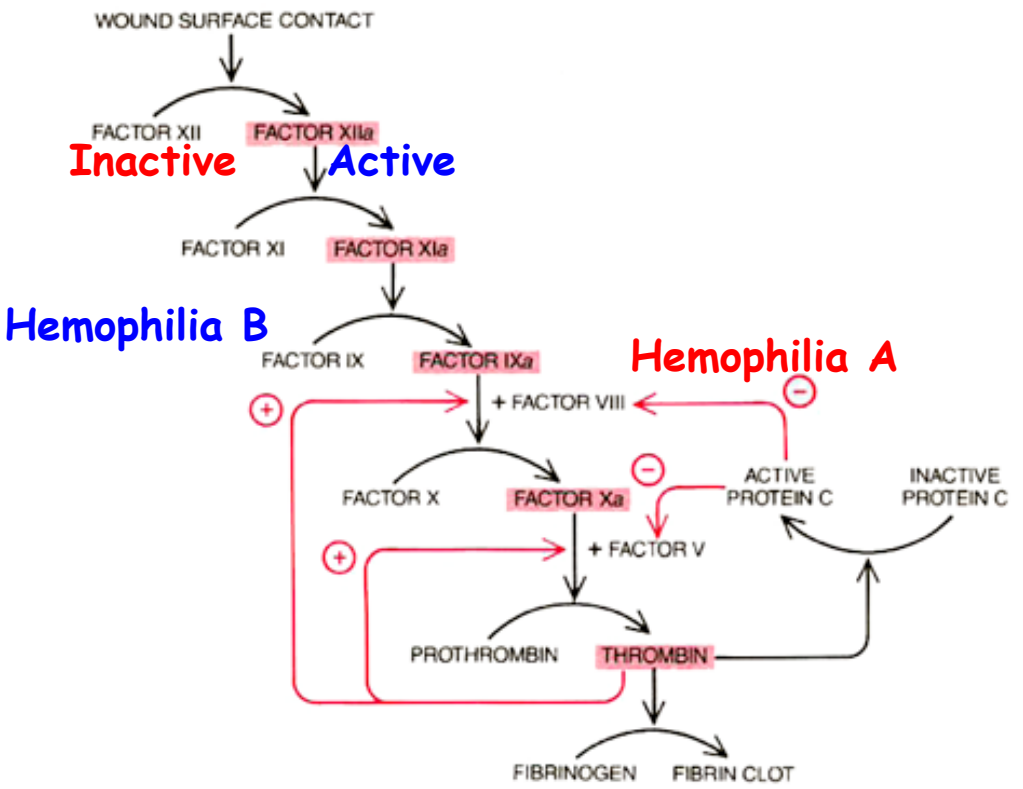
Disorder	Symptom	Defect	Dominant/ Recessive	Frequency Among Human Births
Cystic fibrosis	Mucus clogs lungs, liver, and pancreas	Failure of chloride ion transport mechanism	Recessive	1/2500 (Caucasians)
Sickle cell anemia	Blood circulation is poor	Abnormal hemoglobin molecules	Recessive	1/600 (African Americans)
Tay–Sachs disease	Central nervous system deteriorates in infancy	Defective enzyme (hexosaminidase A)	Recessive	1/3500 (Ashkenazi Jews)
Phenylketonuria	Brain fails to develop in infancy	Defective enzyme (phenylalanine hydroxylase)	Recessive	1/12,000
Hemophilia	Blood fails to clot	Defective blood-clotting factor VIII	X-linked recessive	1/10,000 (Caucasian males)
Huntington disease	Brain tissue gradually deteriorates in middle age	Production of an inhibitor of brain cell metabolism	Dominant	1/24,000
Muscular dystrophy (Duchenne)	Muscles waste away	Degradation of myelin coating of nerves stimulating muscles	X-linked recessive	1/3700 (males)
Hypercholesterolemia	Excessive cholesterol levels in blood lead to heart disease	Abnormal form of cholesterol cell surface receptor	Dominant	1/500

18,000 People in US Have Hemophilia & 400 Babies/Year Are Born With Disorder
Prior to 1960s – Average Life Span Was 11 Years

Hemophilia A	Defective Factor VIII Gene	1/10,000 males	80%
Hemophilia B	Defective Factor IX Gene	1/30,000 males	20%
Hemophilia C	Defective Factor XI Gene	Autosomal	<1%

Both Factor VIII & IX Genes on X-Chromosome (♀→♂'s)

Protein Factors in Blood Lead To Clotting



CLOTTING CASCADE begins when cell damage at a wound somehow activates the enzyme factor XII; it ends with the conversion of fibrinogen into fibrin by thrombin. At each step an inactive protein is converted into a protease, or protein-cutting enzyme (*color*), which activates the next protein. Some steps require cofactors such as factors VIII and V. The cascade includes positive- and negative-feedback loops (*colored arrows*). Thrombin activates factors VIII and V; it also deactivates them (by activating protein *C*), which helps to halt clotting. Some 85 percent of hemophiliacs lack factor VIII. The rest lack factor IX.

Eight Proteins/Genes Required:

1. Factor VII
2. Factor XI
3. Factor IX
4. Factor VIII
5. Factor X
6. Protein C
7. Prothrombin
8. Fibrinogen

What Happens If Any of These Proteins, or Genes, are Mutated?

↓

No Blood Clot!

Gene Therapies for Hemophilia A & B

blood® Review Series

blood® 31 JANUARY 2019 | VOLUME 133, NUMBER 5 407

NEW THERAPEUTICS FOR INHERITED AND ACQUIRED BLEEDING CONDITIONS

Update on clinical gene therapy for hemophilia

George Q. Perrin,[1] Roland W. Herzog,[1,2] and David M. Markusic[2]

[1]Department of Pediatrics, Division of Cellular and Molecular Therapy, University of Florida, Gainesville, FL; and [2]Department of Pediatrics, Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN

In contrast to other diverse therapies for the X-linked bleeding disorder hemophilia that are currently in clinical development, gene therapy holds the promise of a lasting cure with a single drug administration. Near-to-complete correction of hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) have now been achieved in patients by hepatic in vivo gene transfer. Adeno-associated viral vectors with different viral capsids that have been engineered to express high-level, and in some cases hyperactive, coagulation factors were employed. Patient data support that sustained endogenous production of clotting factor as a result of gene therapy eliminates the need for infusion of coagulation factors (or alternative drugs that promote coagulation), and may therefore ultimately also reduce treatment costs. However, mild liver toxicities have been observed in some patients receiving high vector doses. In some but not all instances, the toxicities correlated with a T-cell response directed against the viral capsid, prompting use of immune suppression. In addition, not all patients can be treated because of preexisting immunity to viral capsids. Nonetheless, studies in animal models of hemophilia suggest that the approach can also be used for immune tolerance induction to prevent or eliminate inhibitory antibodies against coagulation factors. These can form in traditional protein replacement therapy and represent a major complication of treatment. The current review provides a summary and update on advances in clinical gene therapies for hemophilia and its continued development. (*Blood*. 2019;133(5):407-414)

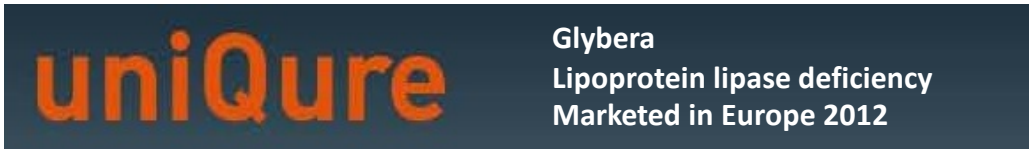
Companies sponsoring hemophilia gene therapy clinical trials

BIOMARIN CELEBRATING 20 YEARS · Pfizer · Sangamo THERAPEUTICS · SANOFI · Shire · Spark THERAPEUTICS · ultragenyx pharmaceutical · uniQure

The Future of Human Gene Therapy is Now!

Approved Gene Therapy Products

P53 tumor suppressor deficiency
Marketed in China 2004



Glybera
Lipoprotein lipase deficiency
Marketed in Europe 2012

ADA-SCID
European Medicines Agency
Approved in 2016

LCA Blindness
FDA Approved 2017

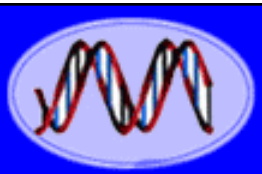
LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

CAR-T Therapy
FDA Approved 2017

YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

Hereditary Transthyretin Amyloidosis
FDA Approved 2018

onpattro™
(patisiran) lipid complex injection



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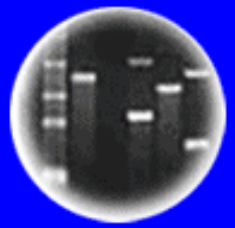


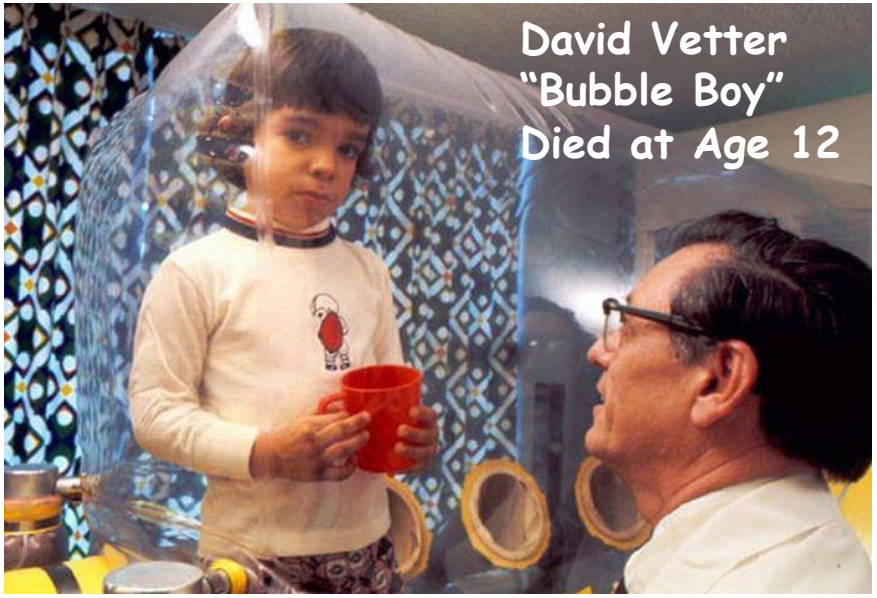
DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

Case Study of Gene Therapy for Severe Combined Immunodeficiency (SCID)

Severe Combined Immunodeficiency Diseases (SCID)

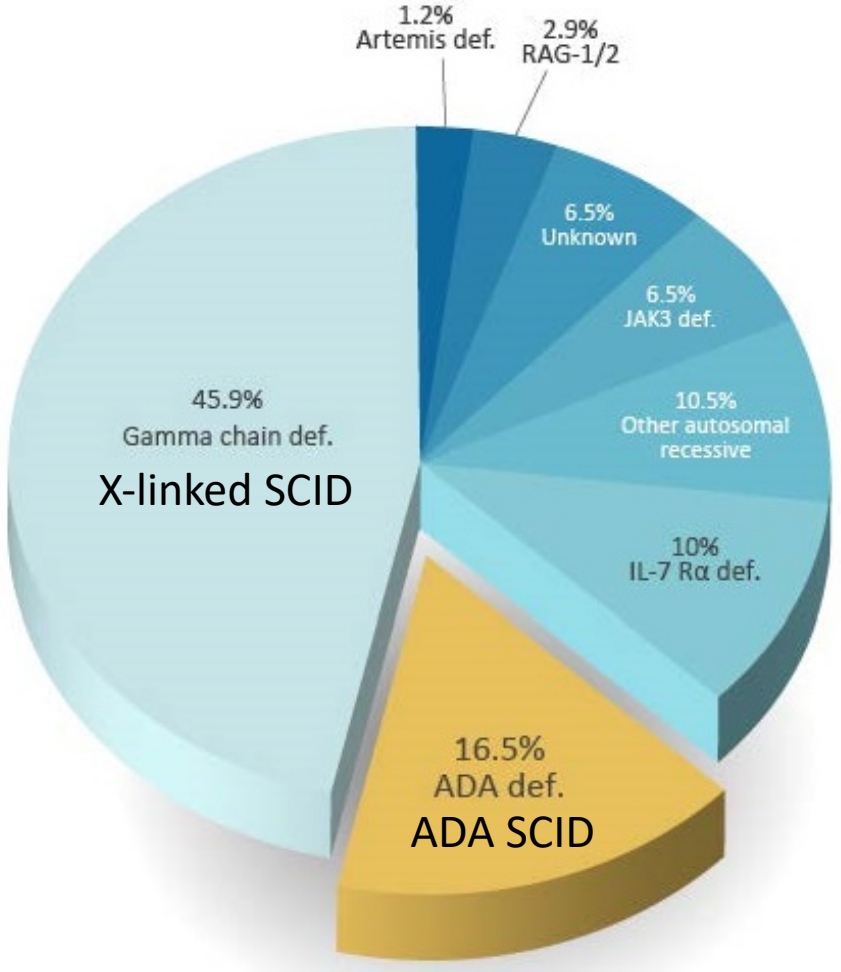


A group of rare, sometimes fatal, congenital disorders characterized by little or no immune response.

Types of SCIDs

- Adenosine deaminase deficiency
- X-linked severe combined immunodeficiency
- Purine nucleoside phosphorylase deficiency
- Reticular dysgenesis
- Omenn syndrome
- Bare lymphocyte syndrome
- JAK3
- Artemis/DCLRE1C

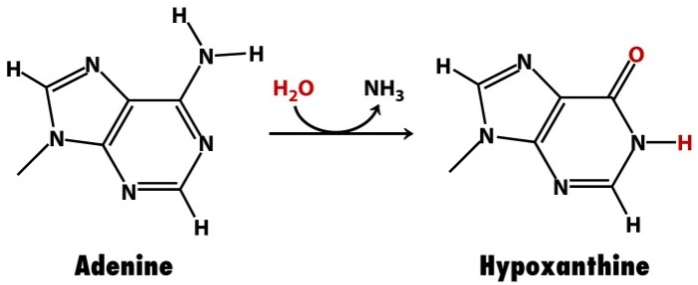
Relative Frequency of the Different Molecular Defects in SCID



Severe Combined Immunodeficiency Disease (SCID)
Adenosine Deaminase Gene (*ADA*) Deficiency

- ADA is an enzyme that metabolizes adenosine and deoxyadenosine
- ADA deficiency results in elevated adenosine and deoxyadenosine levels
- Abnormal levels impair lymphocyte development and function
- **The immune system is severely compromised or completely defective**
- ADA-SCID patients can be treated with PEG-ADA, a stabilized form of the enzyme

- 32,213 kb Gene
- Chromosome 20
- 12 Exons
- 1,092 kb mRNA
- 323 aa protein



Degradation of Adenosine

Treatments for ADA-SCID

	Bone Marrow Transplant (non-HLA identical sibling donor)	Gene Therapy	(PEG-ADA) Adagen
Type of therapy[5]	Replacement of host immune system by donor hematopoietic stem cells	Genetic modification of patient stem cells, autologous transplant	Enzyme replacement therapy
Goal[5,6]	Cure	Cure	Management
Patient selection[2,4,6]	Pts must be stabilized prior to transplant; higher success rate in younger pts	Pts must be stabilized prior to treatment	Pts can be treated within days of diagnosis

Severe Combined Immunodeficiency Disease (SCID)
Adenosine Deaminase Gene (*ADA*) Deficiency

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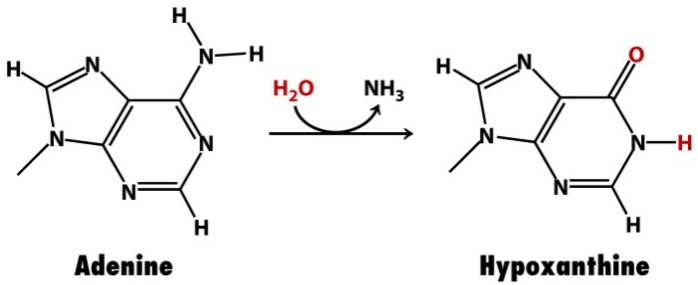


Degradation of Adenosine

Treatments for ADA-SCID

	(PEG-ADA) Adagen
Type of therapy[5]	Enzyme replacement therapy
Goal[5,6]	Management
Patient selection	Pts can be treated within days of diagnosis

What Information is Needed Before Initiating Development of a Gene Therapy?

1.
2.
3.
4.
5.

What Information is Needed Before Initiating Development of a Gene Therapy?

1. What is known about the biology of the disorder?
2. Does the condition result from a mutation of one or more genes?
3. Has the affected gene been cloned?
4. Will adding a normal copy of the gene fix the problem in the affected tissue?
5. Can you deliver the gene to cells of the affected tissue?

Gene Therapy for Human Genetic Disease?

3 March 1972, Volume 175, Number 4025

SCIENCE

Proposals for genetic manipulation in humans raise difficult scientific and ethical problems.

Theodore Friedmann and Richard Roblin

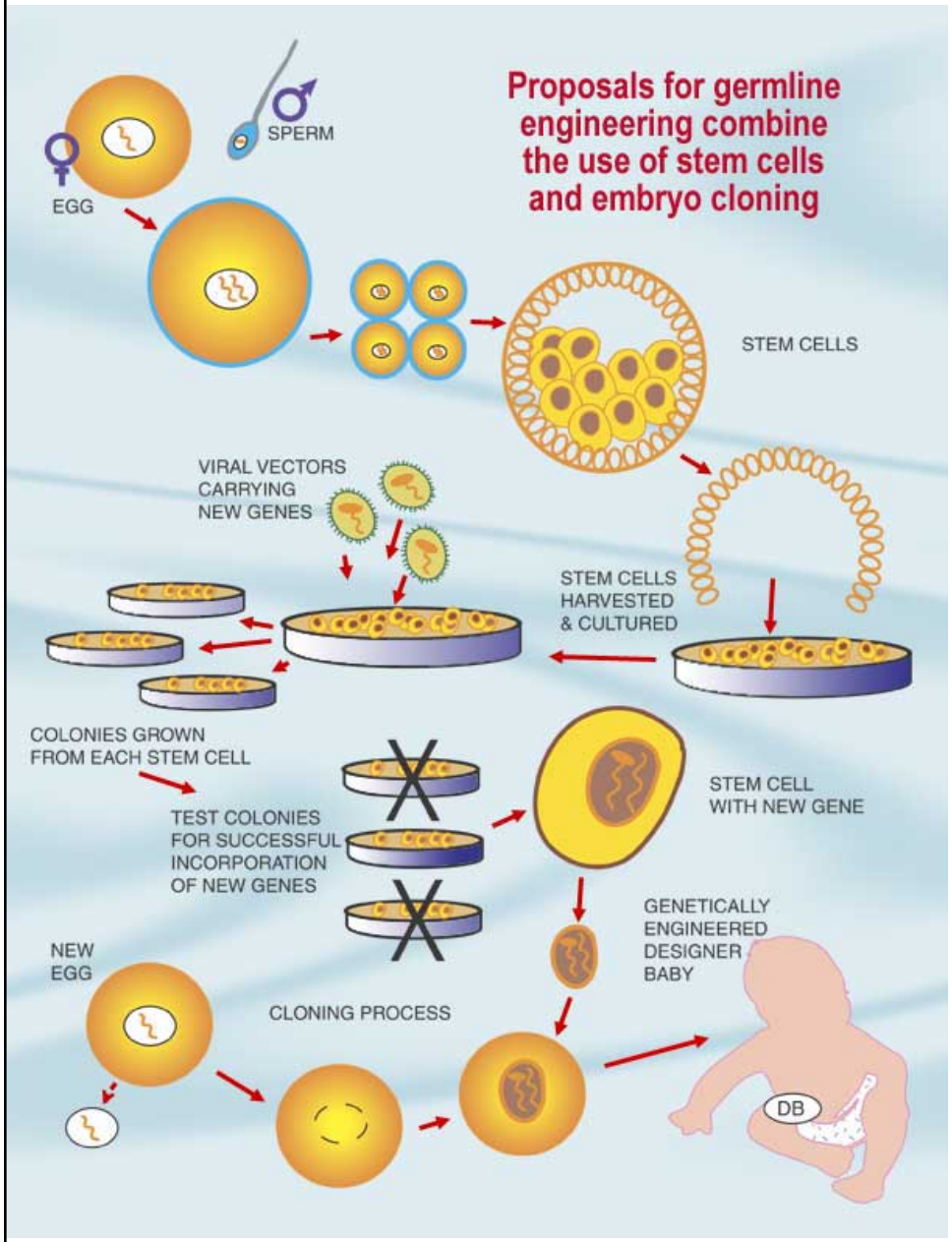
"We propose the following ethico-scientific criteria which any prospective techniques for gene therapy in human patients should satisfy:"

1. There should be adequate biochemical characterization of the prospective patient's genetic disorder.
2. There should be prior experience with untreated cases of what appears to be the same genetic defect
3. There must be an adequate characterization of the quality of the exogenous DNA vector.
4. There should be extensive studies in experimental animals to evaluate the therapeutic benefits and adverse side effects of the prospective techniques.
5. Where possible, determine whether the prospective gene therapy technique can restore enzyme function in the cells of the prospective patient

Types of Gene Therapy

- Germline gene therapy
- Somatic gene therapy

Germline Gene Therapy



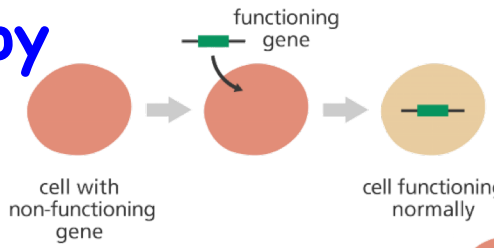
- Germline gene therapy is when DNA is transferred into the cells that produce reproductive cells, eggs or sperm, in the body. This type of therapy allows for the correction of disease-causing gene variants that are certain to be passed down from generation to generation
- It is NOT ILLEGAL to conduct human germline gene therapy in the US – however, experiments using federal funding must be approved by the Recombinant DNA Advisory Committee and use by public and private labs requires FDA approval.
- FDA cannot review applications for clinical trials that involve human embryos with heritable genetic modifications

Types of Gene Therapy

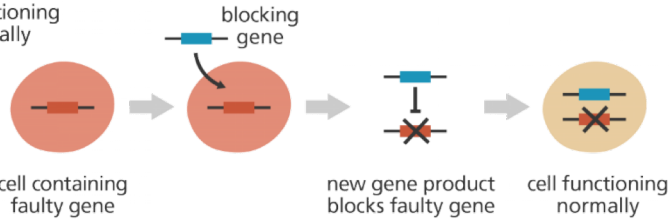
- **Germline gene therapy**

Somatic cell - any cell of a living organism other than the reproductive cells

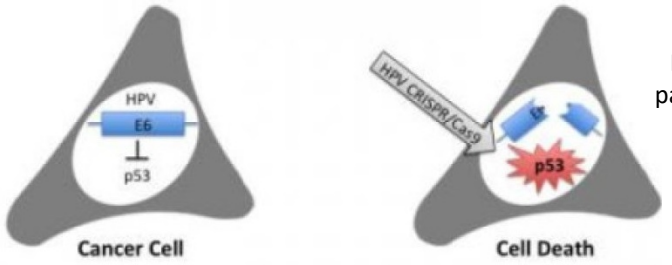
- **Somatic gene therapy**
  - Gene augmentation



  - Targeted silencing of gene expression

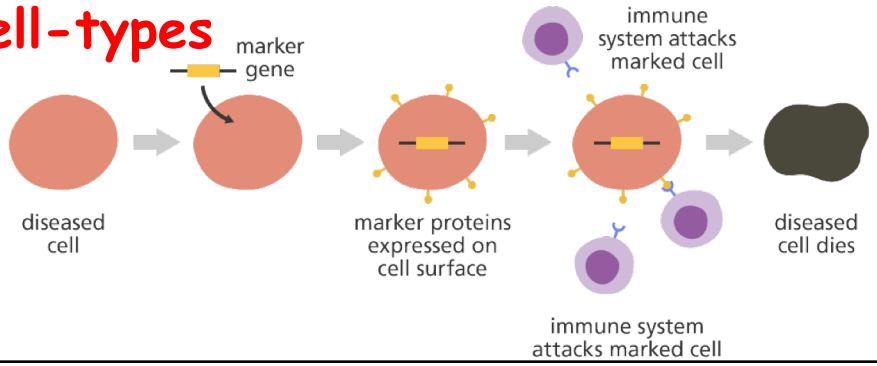


  - Gene alteration

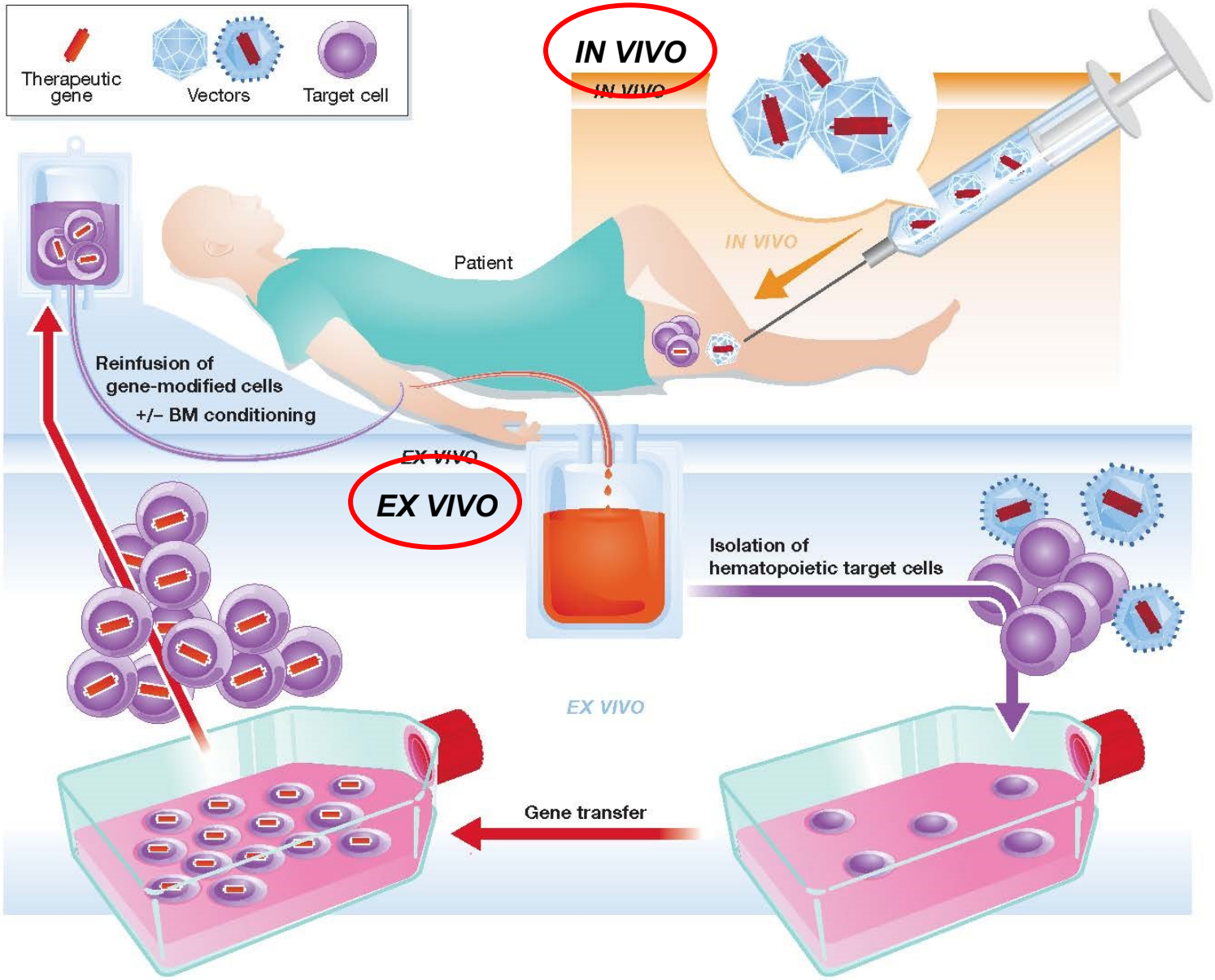


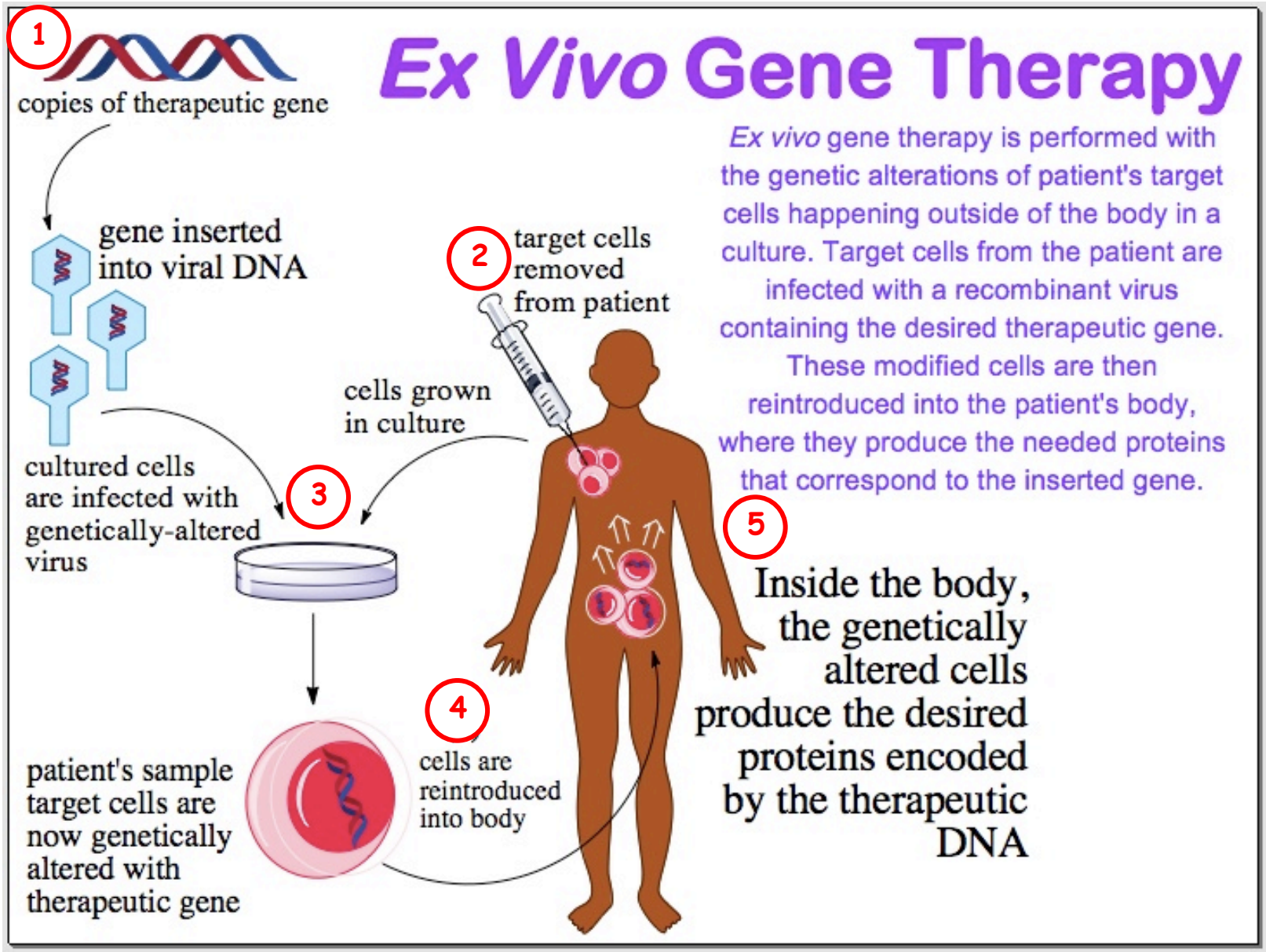
HPV (human papillomavirus) E6 gene ⊣ p53 tumor suppressor ⊣ CANCER

  - Gene replacement
  - Targeted killing of specific cell-types



Somatic Cell Gene Therapy – *In Vivo* and *Ex Vivo*



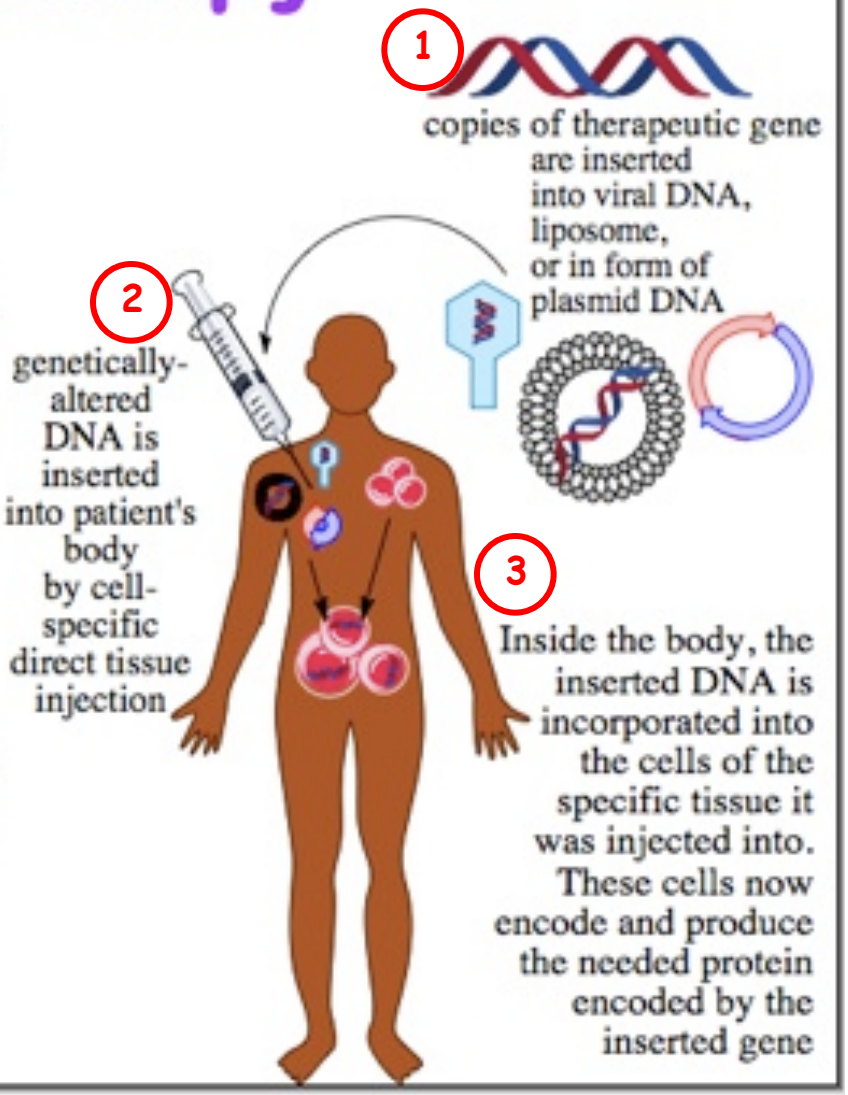


Ex Vivo Gene Therapy

Ex vivo gene therapy is performed with the genetic alterations of patient's target cells happening outside of the body in a culture. Target cells from the patient are infected with a recombinant virus containing the desired therapeutic gene. These modified cells are then reintroduced into the patient's body, where they produce the needed proteins that correspond to the inserted gene.

In Vivo Gene Therapy

In vivo gene therapy involves introduction of therapeutic DNA directly into the patient's body. The DNA is introduced by cell-specific direct injection into tissue in need. DNA in the form of a plasmid vector is introduced by a dermal vaccination. Modified liposomes are not currently used for gene therapy, but they will likely be the next advancement in therapeutic gene delivery as cell-specific receptor-mediated DNA carriers. Once inside the body and in contact with the specifically targeted cells, the inserted DNA is incorporated into the tissue's cells where it encodes the production of the needed protein.



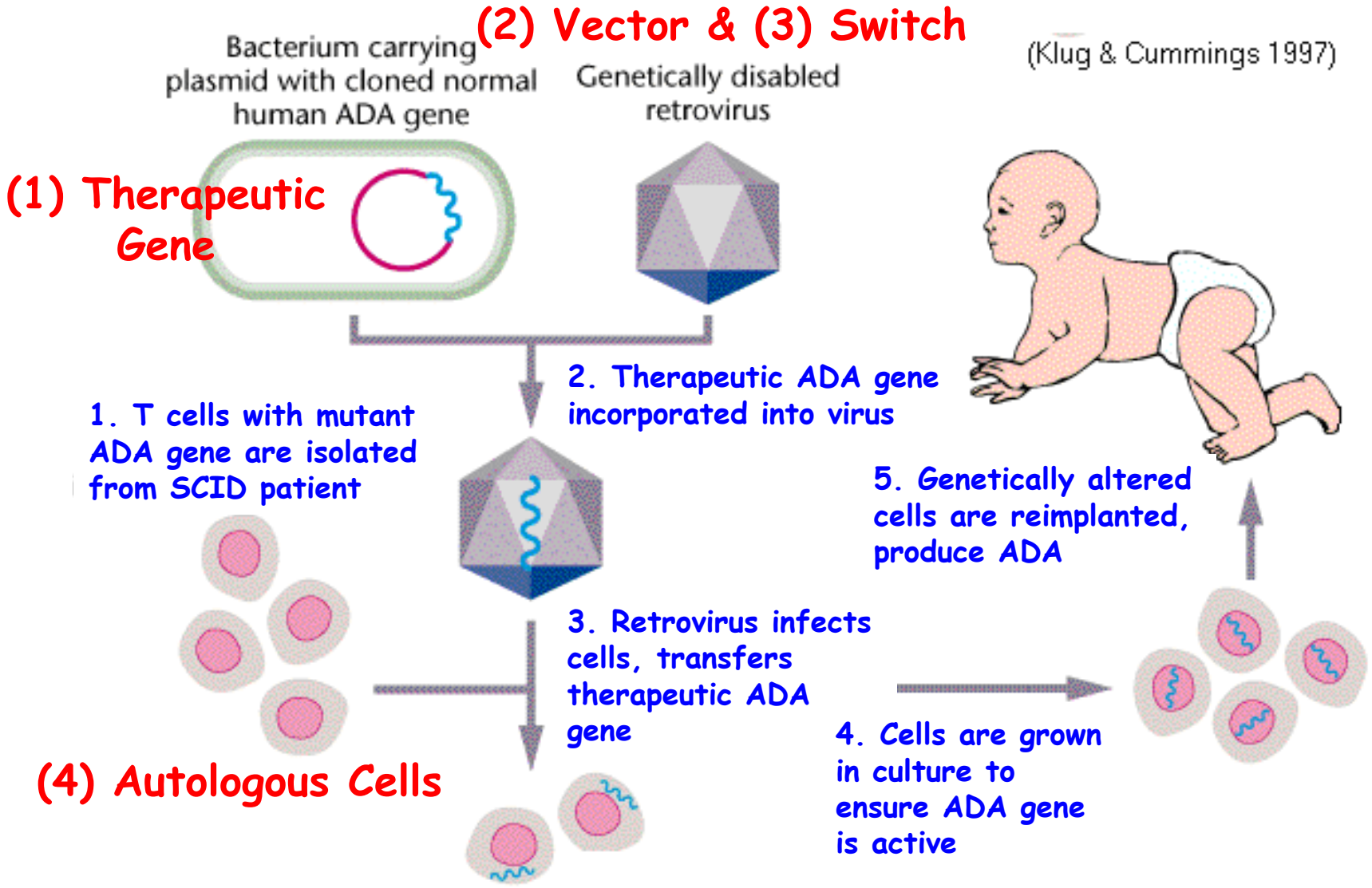
What "Tools" are Needed for Ex Vivo Somatic Cell Gene Therapy Protocols?

1.
2.
3.
4.

What "Tools" are Needed for Ex Vivo Somatic Cell Gene Therapy Protocols?

1. Cloned copy of the therapeutic gene
2. Appropriate switch - often a strong switch to drive high level expression of the gene
3. Vector to transfer the gene into the cells
4. Autologous cells (obtained from the same individual) or non-autologous cells

Ex Vivo Gene Therapy for ADA-Severe Combined Immunodeficiency (SCID)



ADA-SCID Clinical Trial Started in 1990

Vectors Target and Deliver Therapeutic Genes to Cells of Interest

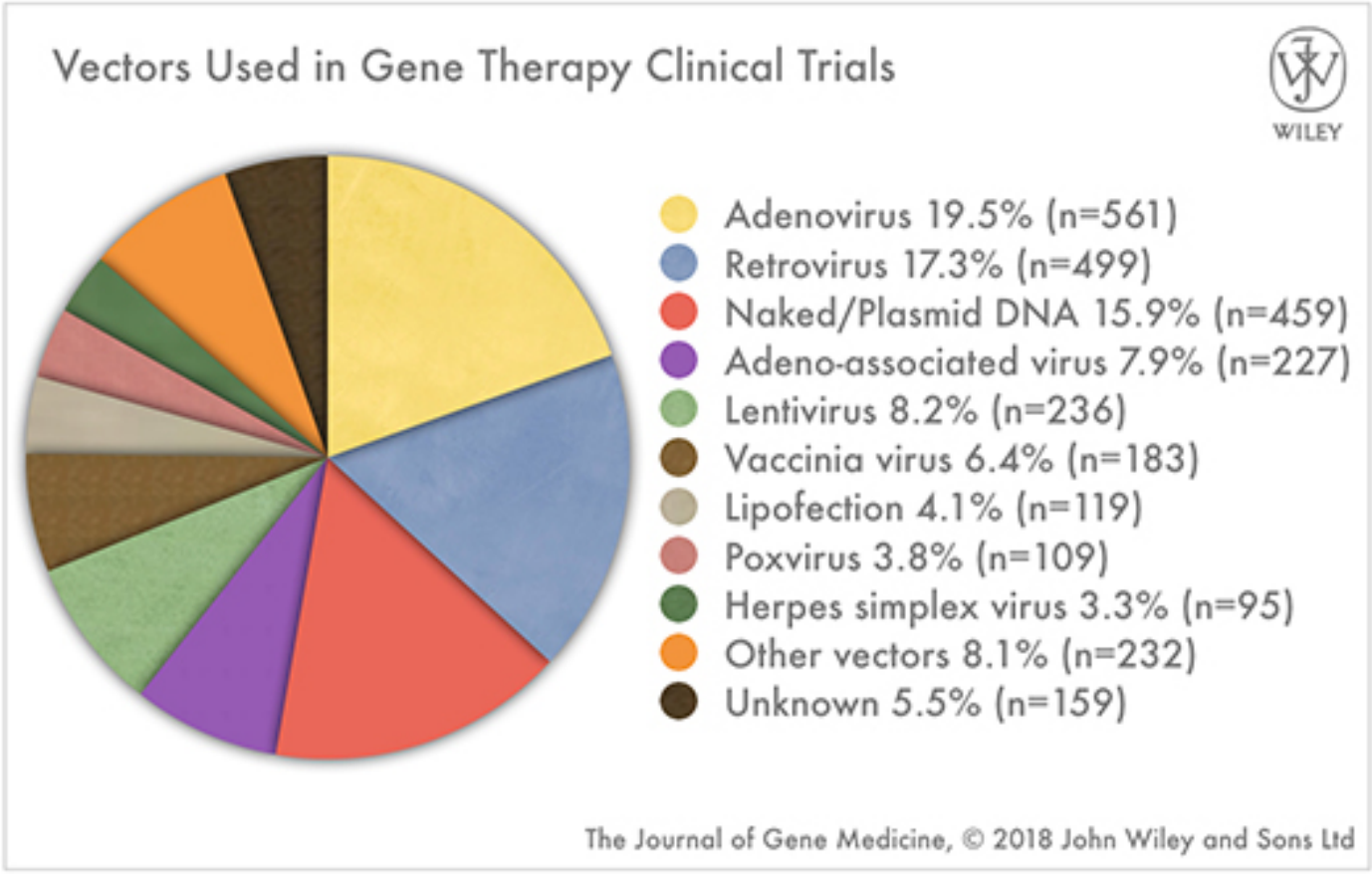
398 NATURE VOL. 233 OCTOBER 8 1971

Bacterial Virus Gene Expression in Human Cells

CARL R. MERRIL & MARK R. GEIER
Laboratory of General and Comparative Biochemistry, National Institute of Mental Health, Bethesda, Maryland 20014

JOHN C. PETRICCIANI
Laboratory of Pathology, Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland 20014

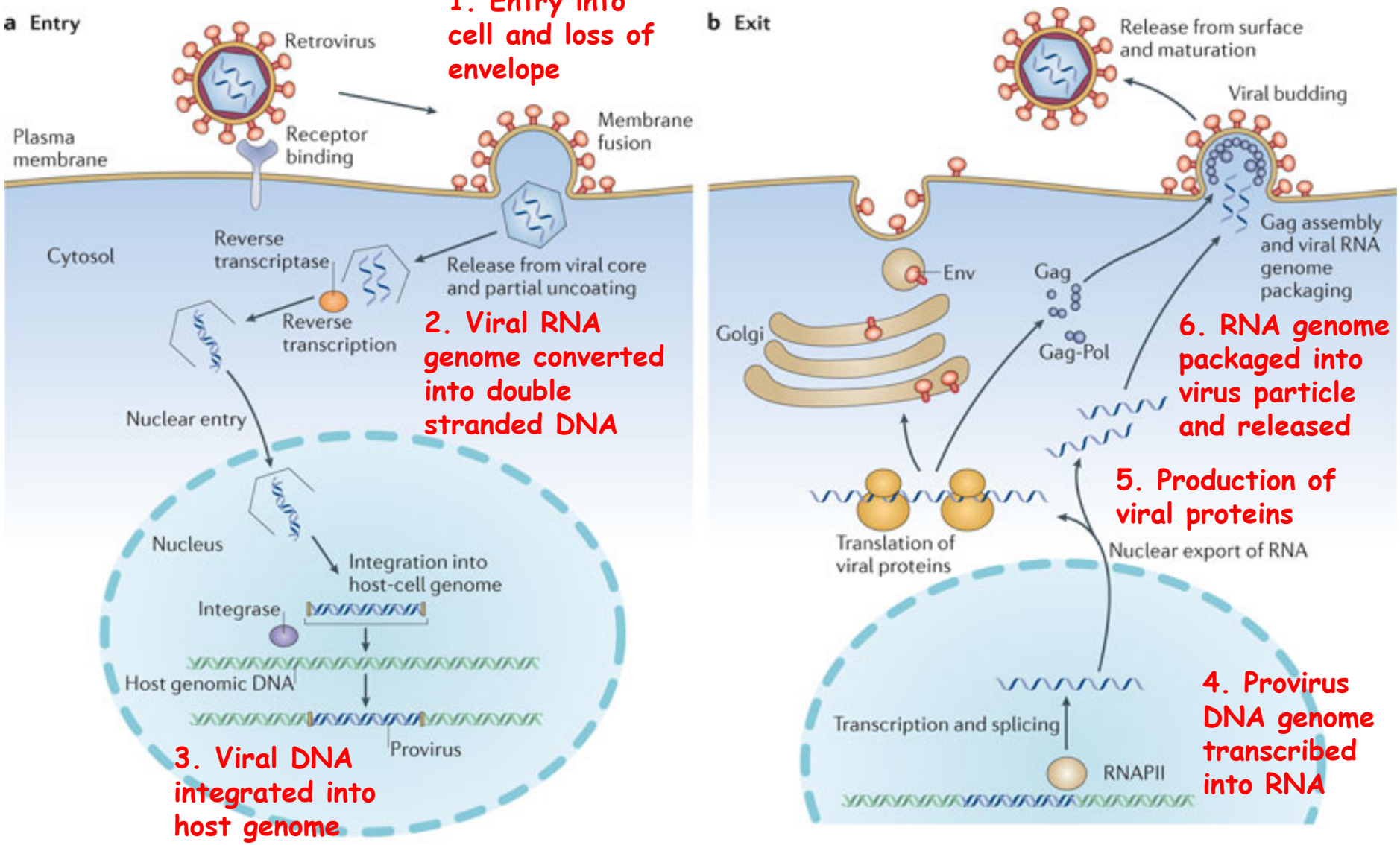
Human fibroblasts, from a patient with congenital lack of α-D-galactose-1-phosphate uridyl transferase activity, have been infected with transducing bacteriophage that harbours either wild type or defective transferase gene. Infection only by the former phage initiates transferase synthesis.



Vectors Used to Deliver Genes to Cells in Gene Therapy

Viral vector	Type	Advantages	Disadvantages
Retrovirus	Integrates with host chromatin	Effective over long periods Efficient transfection *ex vivo* Low immune response in host Transfects proliferating hosts	Small, max 8kb insert size Inefficient transfection *in vivo* Relies on target cell mitosis Safety concerns
Lentivirus	Integrates with host chromatin	Transfects proliferating and non-proliferating hosts and haemo stem cells New generations are self-inactivating for safety	Need active transport into cell Small, max 8kb insert size Technologically challenging Safety concerns, immunodeficiency origins
Adeno-Associated Virus	Either	Very good length of expression especially *in vivo* Efficient transfection *in vivo* Low immune response in host Transfects both types of hosts	Safety problems owing to potential insertional mutagenesis Small, max 4.5kb insert size High immuno response Technologically challenging
Adenovirus	Extra chromosomal DNA	Highly efficient transfection *in vivo* and *ex vivo* Transfects proliferating and non-proliferating hosts	Repeat treatments ineffective due to strong immune response Small, max 7.5kb insert size Technologically challenging Short expression duration
Herpes simplex virus	Extra chromosomal DNA	Very good length of expression especially *in vivo* Safe for use in immunocompromised patients Large insert size up to 30 kb Effective on many cell types	Difficult to produce in large quantities

Retrovirus Life Cycle



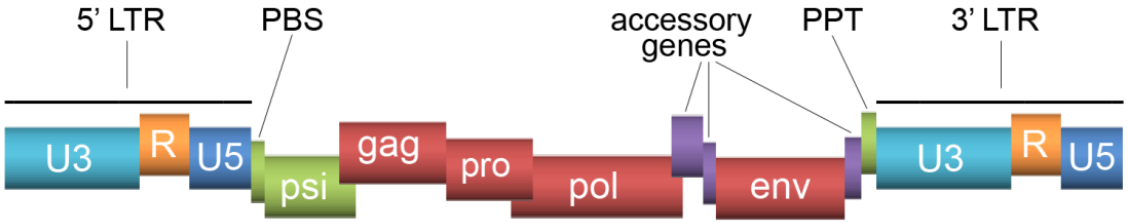
Nature Reviews | Microbiology

Retroviruses Replicate Using Reverse Transcriptase

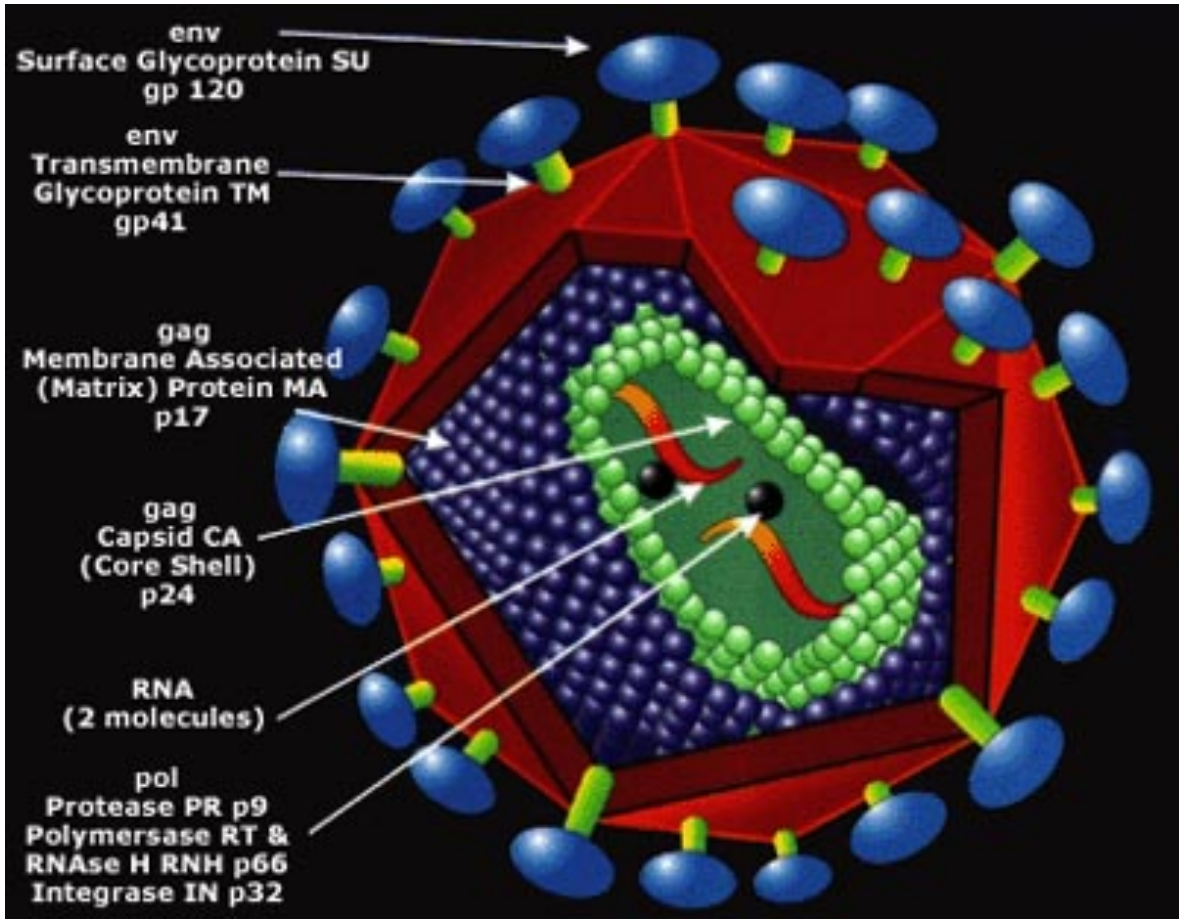
David Baltimore & Howard Temin-Nobel Prize 1975

Modification of the Central Dogma of Molecular Biology - RNA to DNA to RNA to Protein

Retrovirus Genome

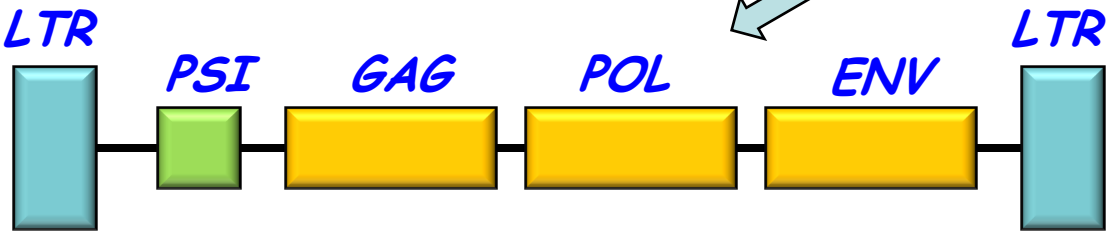


- 5' long terminal repeat (LTR) – strong switch & integration
- 3' LTR – strong switch, integration & transcriptional termination
- psi (Ψ) – packaging element needed to package the RNA genome into the viral particle
- gag – structural (coat) proteins
- pro – protease
- pol – reverse transcriptase
- env – envelope proteins

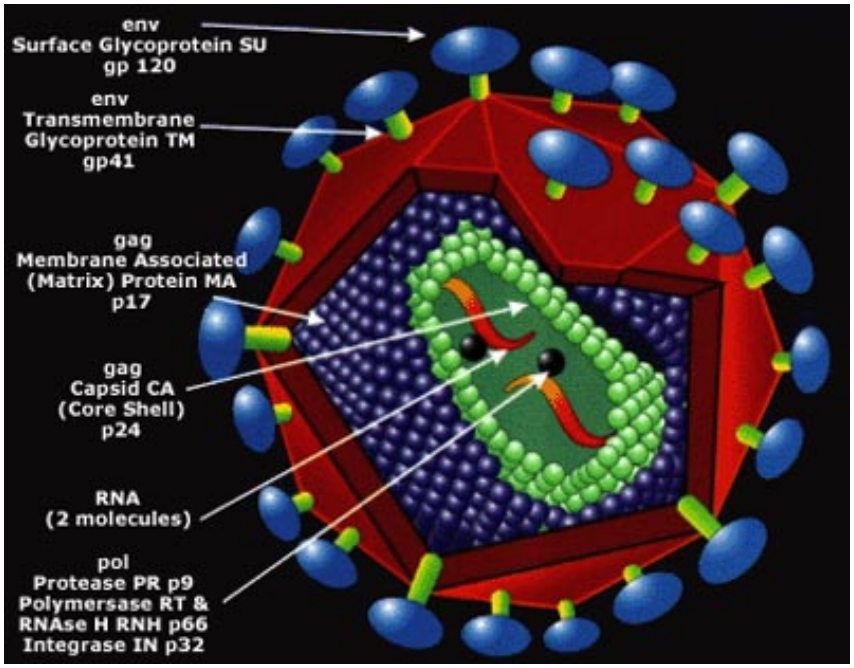


Retroviral Vector

THERAPEUTIC GENE

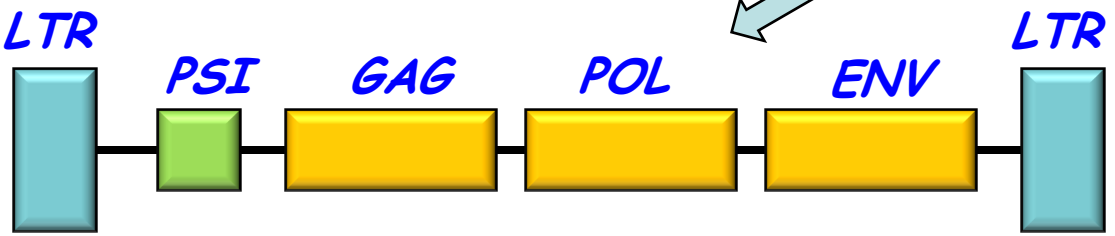


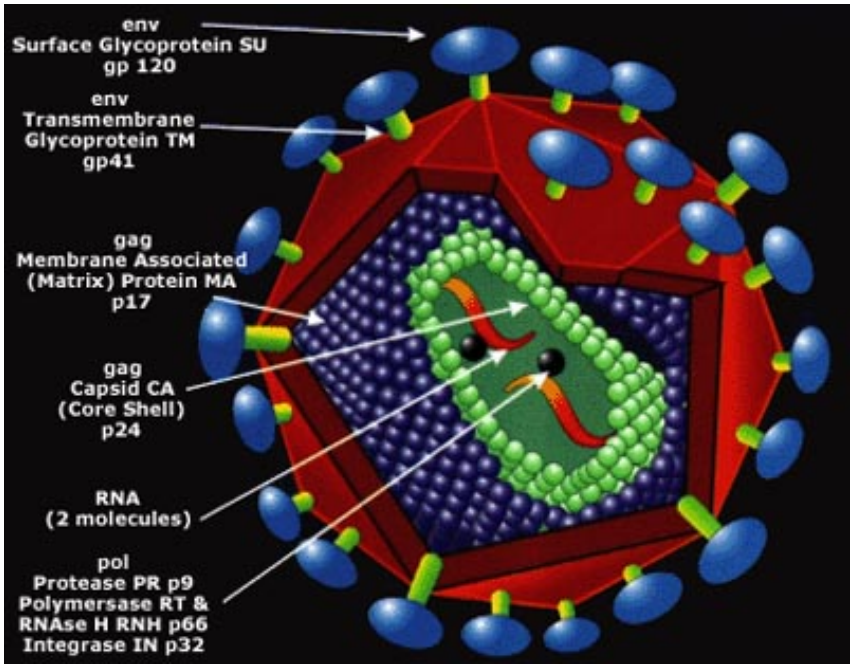
Retrovirus



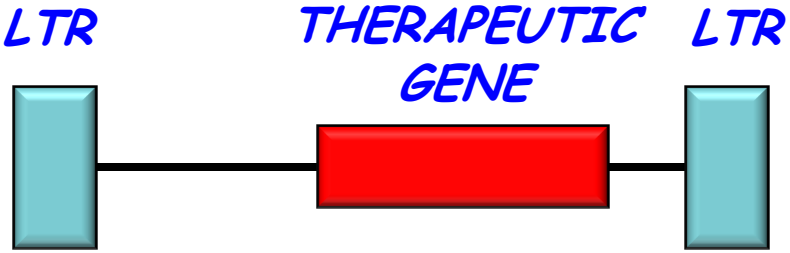
Retroviral Vector

Retrovirus





Retroviral Gene Therapy Vector

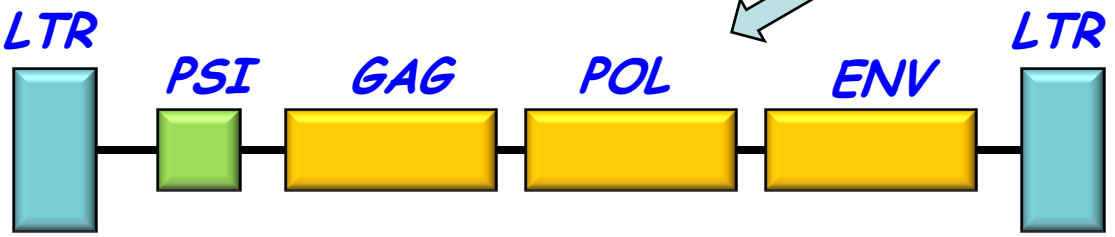


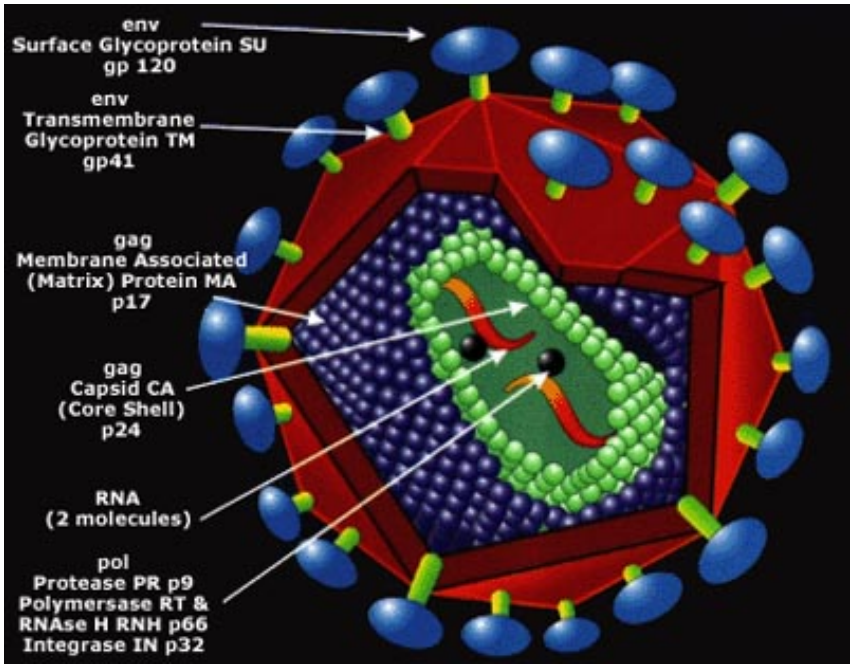
How is this RNA genome packaged into a virus particle?

Retroviral Vector

THERAPEUTIC GENE

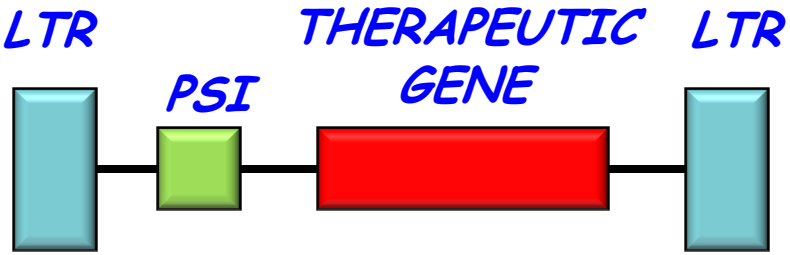
Retrovirus





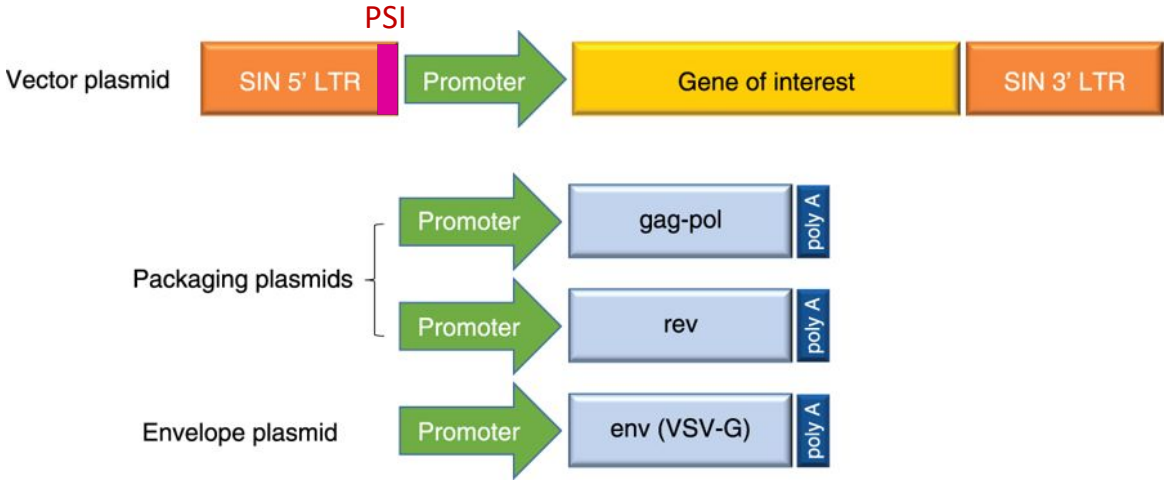
PSI is a packaging element – a RNA sequence that is required for the viral RNA to be packaged into the virus

Retroviral Gene Therapy Vector

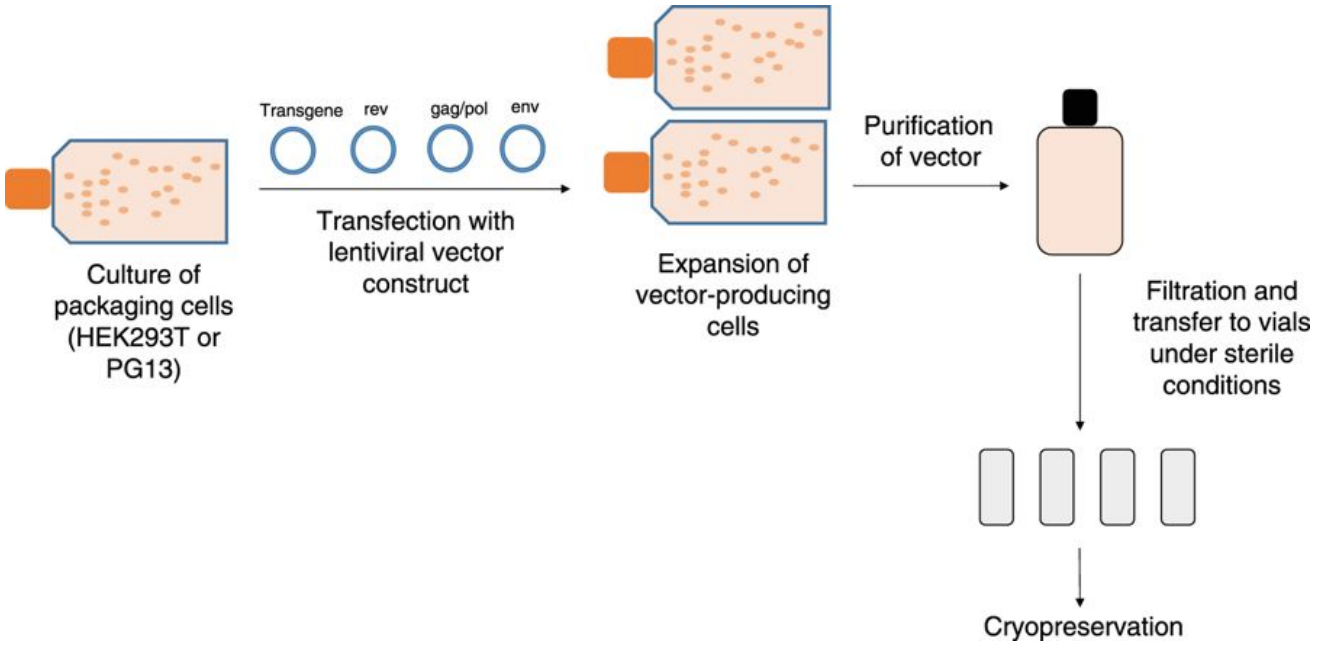


Packaging and Production of Retroviral Vectors for Gene Therapy

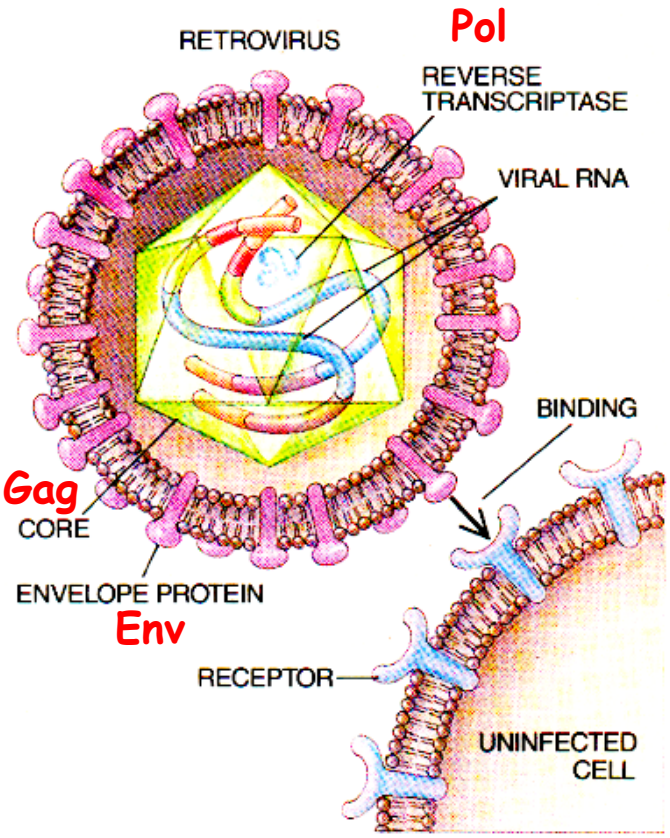
Plasmids used for packaging

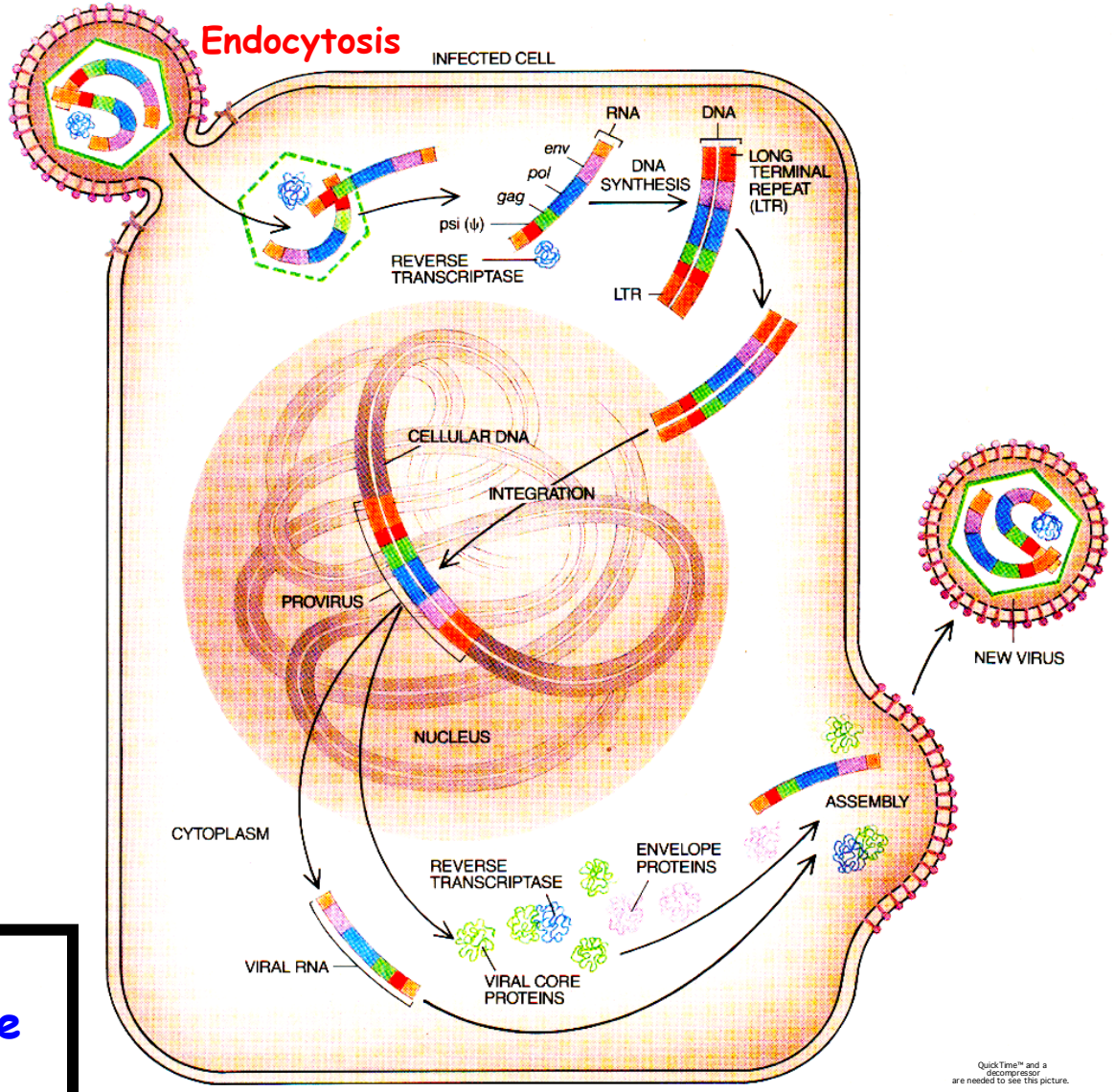


Vector Production



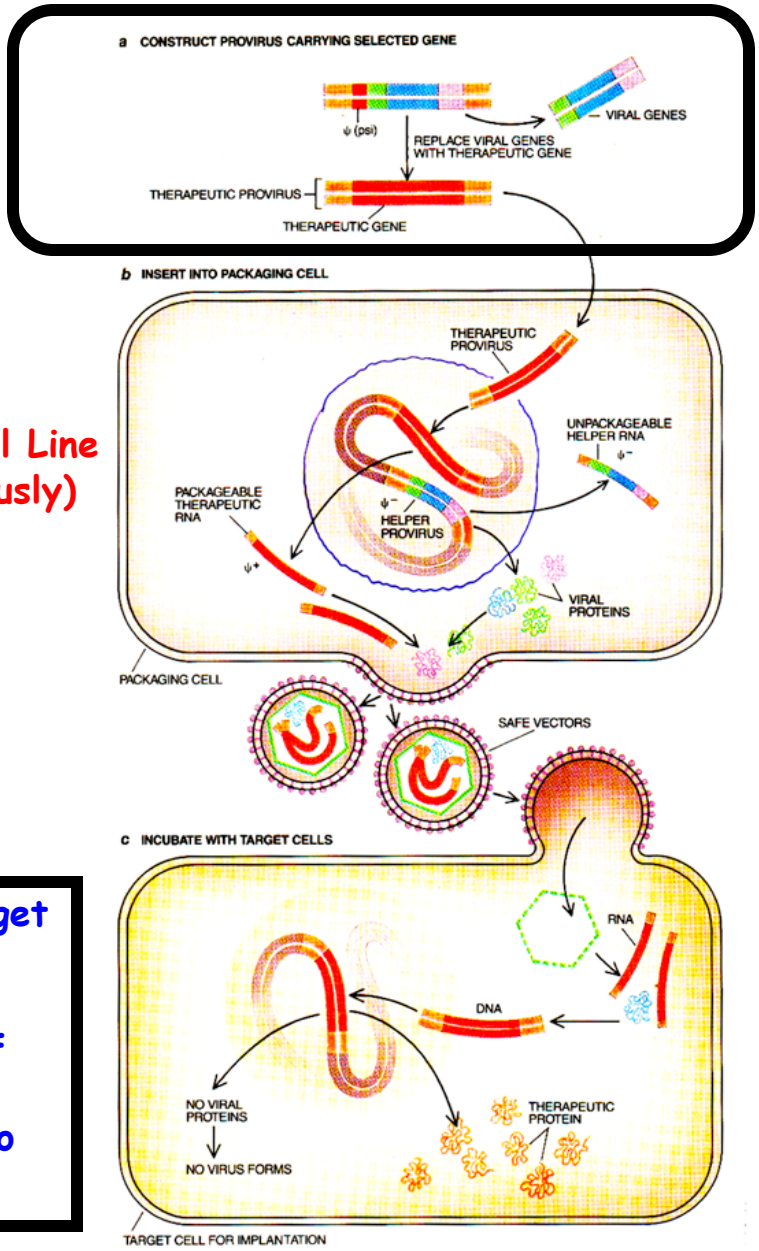
Using a Retrovirus as a Vector For Human Ex Vivo Gene Therapy





- Gag = Capid Protein
- Pol = Reverse Transcriptase
- Env = Envelope Protein
- Ψ (Psi) = Packaging Sequence

Using Retroviruses for Ex Vivo Gene Therapy



A.

1. Cloning in Bacteria
2. DNA Transformation into Packaging Cell

B.

1. Packaging Cells Makes Viral Proteins
2. Cannot Package (Provirus Minus Ψ)
3. Packages Therapeutic Transcript (RNA contains Ψ)

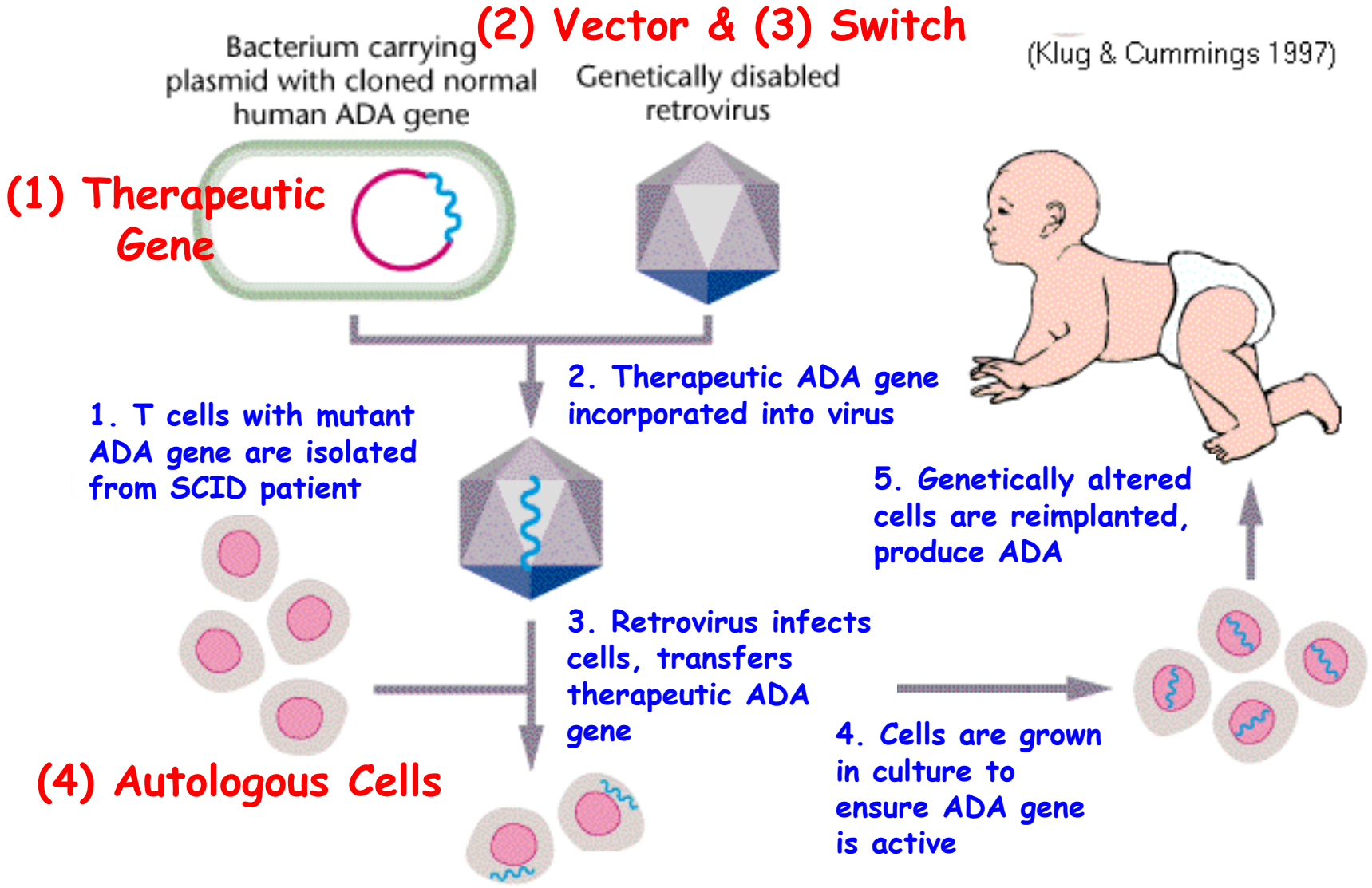
Packaging Cell Line (Made Previously)

C.

1. Infect Target Cells
2. Check For Presence of Gene
3. Transfer To Patient

RETROVIRAL VECTORS are assembled, or packaged, in cells designed to release only safe vectors. Investigators substitute a therapeutic gene for viral genes in a provirus (*a*) and insert that provirus into a packaging cell (*b*). The viral DNA directs the synthesis of viral RNA but, lacking viral genes, cannot give rise to the proteins needed to package the RNA into particles for delivery to other cells. The missing proteins are supplied by a "helper" provirus from which the psi region has been deleted. Psi is crucial to the inclusion of RNA in viral particles; without it, no virus carrying helper RNA can form. The particles that escape the cell, then, carry therapeutic RNA and no viral genes. They can enter other cells (*c*) and splice the therapeutic gene into cellular DNA, but they cannot reproduce.

Ex Vivo Gene Therapy for ADA-Severe Combined Immunodeficiency (SCID)



ADA-SCID Clinical Trial Started in 1990

Did the Gene Therapy Strategy Work?

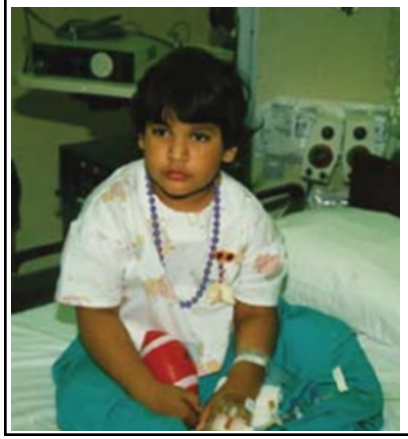
Science
AAAS

T Lymphocyte–Directed Gene Therapy for ADA$^-$ SCID: Initial Trial Results After 4 Years

R. Michael Blaese,* Kenneth W. Culver, A. Dusty Miller, Charles S. Carter, Thomas Fleisher, Mario Clerici,† Gene Shearer, Lauren Chang, Yawen Chiang, Paul Tolstoshev, Jay J. Greenblatt, Steven A. Rosenberg, Harvey Klein, Melvin Berger, Craig A. Mullen,‡ W. Jay Ramsey, Linda Muul, Richard A. Morgan, W. French Anderson§

In 1990, a clinical trial was started using retroviral-mediated transfer of the adenosine deaminase (ADA) gene into the T cells of two children with severe combined immunodeficiency (ADA$^-$ SCID). The number of blood T cells normalized as did many cellular and humoral immune responses. Gene treatment ended after 2 years, but integrated vector and ADA gene expression in T cells persisted. Although many components remain to be perfected, it is concluded here that gene therapy can be a safe and effective addition to treatment for some patients with this severe immunodeficiency disease.

- ADA gene expression in T cells persisted after four years
- But - patients remained on ADA enzyme replacement therapy throughout the gene therapy treatment



Ashanthi DeSilva
1992

Ashanthi DeSilva
2018

Setbacks for Gene Therapy

The New York Times 1999

The Biotech Death of Jesse Gelsinger

By Sheryl Gay Stolberg
Published: November 28, 1999

- Gelsinger had a mild form of ornithine transcarbamylase (OTC) deficiency – results in an inability to metabolize ammonia
- He volunteered for clinical trial of gene supplementation therapy and was injected with adenovirus vector containing OTC gene
- He died of systemic inflammatory response syndrome – immune reaction to adenovirus vector

The New York Times 2002

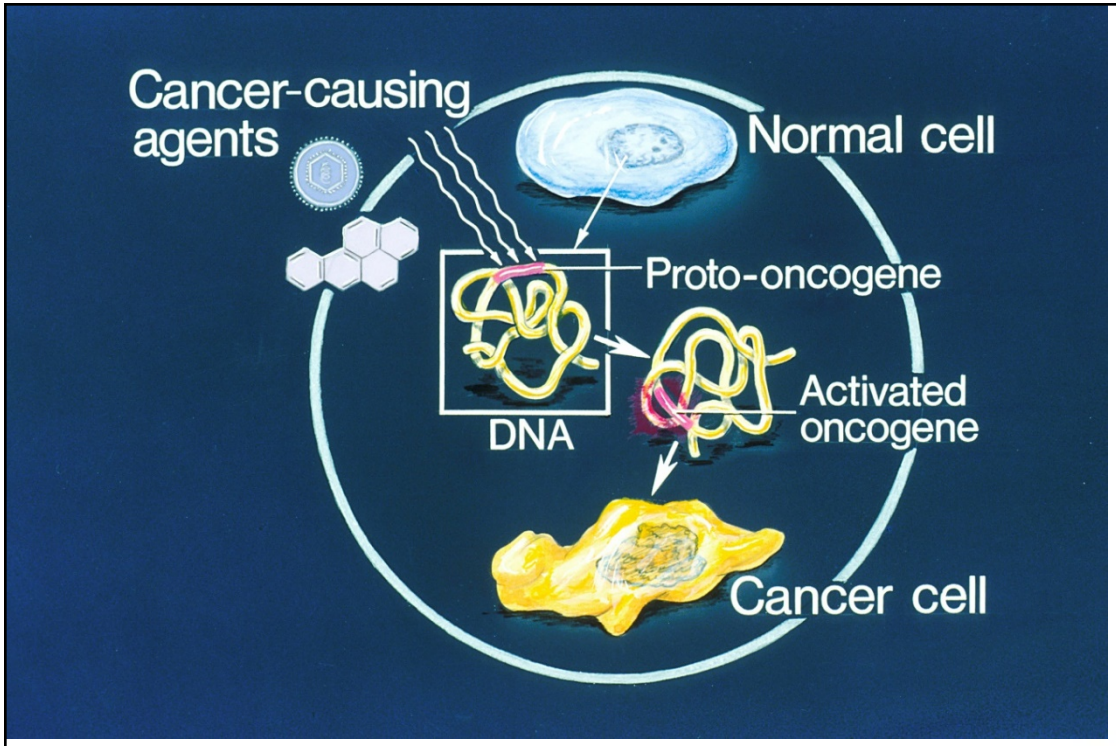
TRIALS ARE HALTED ON A GENE THERAPY

By SHERYL GAY STOLBERG
Published: October 4, 2002

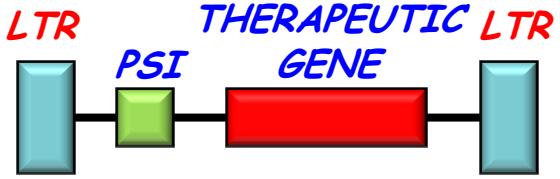
WASHINGTON, Oct. 3— Officials in the United States and France said today that they had suspended four gene therapy experiments because the treatment, which cured a 3-year-old boy of a fatal immune deficiency, may have given him an illness similar to leukemia.

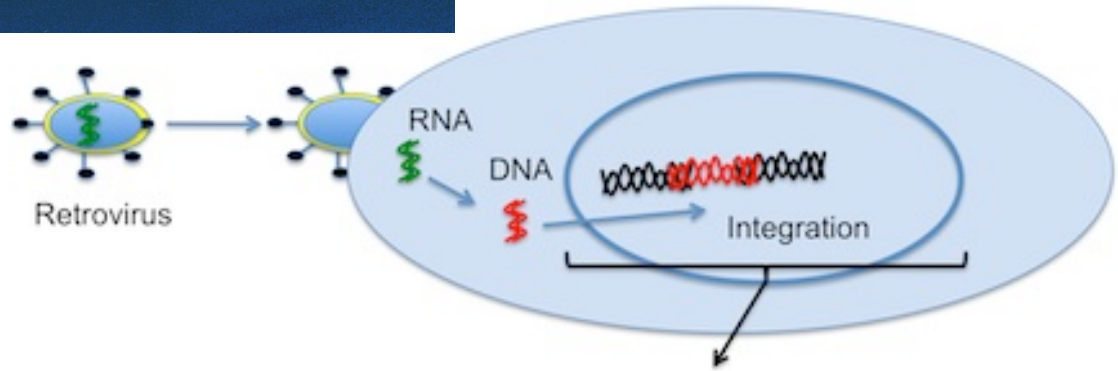
- 3 of 17 patients in clinical trial for X-SCID gene therapy developed clonal lymphoproliferative disorder – a leukemia
- The leukemia was caused by insertion of retrovirus near proto-oncogenes and activation of these proto-oncogenes by retroviral switches

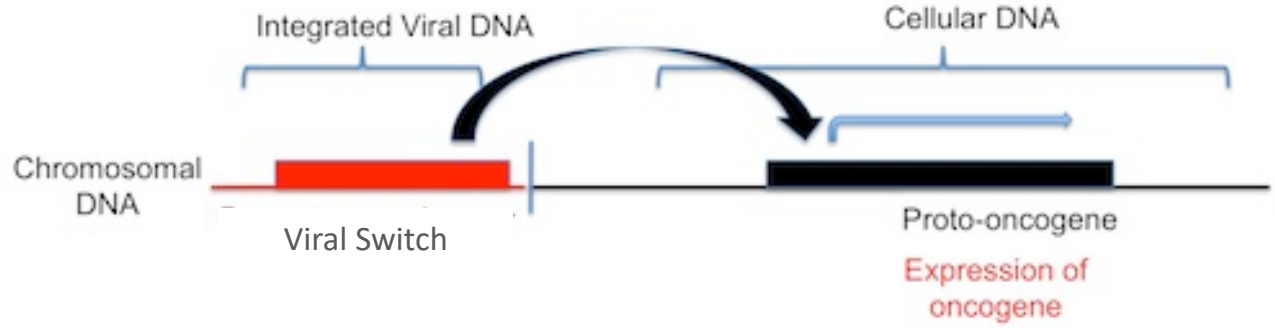
Retroviral Switches can Activate Proto-Oncogenes and Induce Cancers



A Typical Retrovirus Gene Therapy Vector







Some Early Problems with Human Gene Therapy

- Inefficient delivery of vector to target cells
- Low expression level of therapeutic gene
- Adverse immune reactions to vector
- Insertional mutagenesis causing other diseases (e.g., leukemia)
- Incomplete understanding of disease biology
- Human error - failure to adhere to strict NIH and IRB procedures (experimental therapies)

REPORT AND RECOMMENDATIONS OF THE PANEL TO ASSESS THE NIH INVESTMENT IN RESEARCH ON GENE THERAPY

Stuart H. Orkin, M.D. Arno G. Motulsky, M.D.
Co-chairs
December 7, 1995

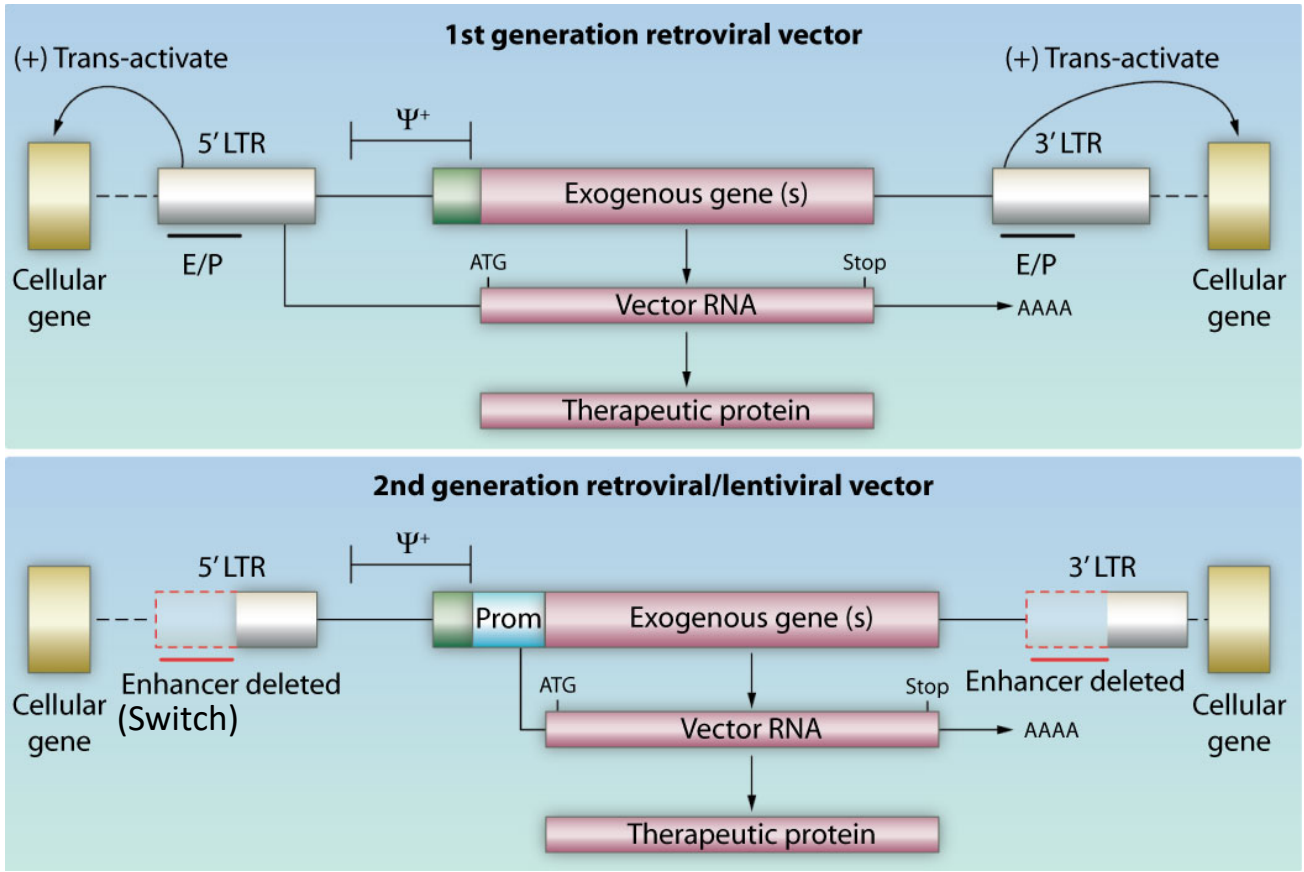
MAJOR RECOMMENDATIONS

- In order to confront the major outstanding obstacles to successful somatic gene therapy, greater focus on basic aspects of gene transfer, and gene expression within the context of gene transfer approaches, is required. Such efforts need to be applied to improving vectors for gene delivery, enhancing and maintaining high level expression of genes transferred to somatic cells, achieving tissue-specific and regulated expression of transferred genes, and directing gene transfer to specific cell types.
- To address important biological questions and provide a basis for the discovery of alternative treatment modalities, the Panel recommends increased emphasis on research dealing with the mechanisms of disease pathogenesis, further development of animal models of disease, enhanced use of preclinical gene therapy approaches in these models, and greater study of stem cell biology in diverse organ systems
- Strict adherence to high standards for excellence in clinical protocols must be demanded of investigators. Gene therapy protocols need to meet the same high standards required for all forms of translational (or clinical) research, whatever the enthusiasm for this (or any other) treatment approach.

Improvements in Gene Therapy

- Increases in efficiency of viral transduction
- Higher levels of therapeutic gene expression
- Development of self-inactivating vectors
- Coupling of gene therapy and stem cell technologies

Development of Self-Inactivating (SIN) Vectors



1. First generation vectors often caused leukemia because they inserted viral DNA next to proto oncogenes (cancer causing genes).

2. The 5′ LTR of the viral vector is a powerful switch that can activate proto oncogenes and cause cancers to form.

3. SIN vectors have transcriptionally disabled LTRs. They are less likely to activate adjacent genes.

Self-Inactivating (SIN) Vectors are Effective in Gene Therapy

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HEALTH PHYSICAL/TECH ENVIRONMENT SOCIETY/EDUCATION QUIRKY

Featured Research *from universities, journals, and other organizations*

X-linked severe combined immunodeficiency syndrome: Gene therapy trial shows promising early results

Date: December 8, 2013

Source: Dana-Farber/Boston Children's Cancer and Blood Disorders Center

Summary: Researchers reported promising outcomes data for the first group of boys with X-linked severe combined immunodeficiency syndrome, a fatal genetic immunodeficiency also known as "bubble boy" disease, who were treated as part of an international clinical study of a new form of gene therapy. Its delivery mechanism was designed to prevent the leukemia that arose a decade ago in a similar trial in Europe.

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"Eight of the nine boys registered to date in the new trial are alive and well, with functioning immune systems and free of infections associated with SCID-X1, between nine and 36 months following treatment".

Fischer et al. 2015

Table 1. PID diseases and gene therapy

	First-generation γRV vectors	Second-generation SIN vectors	
	Effective	Effective	Planned
SCID X1	+[a]	+	
ADA deficiency	+	+	
WAS	+[b]	+	
SCID Rag-1			+
SCID Artemis			+
X-linked chronic granulomatous disease	+[b]		+
Leukocyte adhesion deficiency			+
HLH perforin deficiency			+[c]
HLH Munc13-4 deficiency			+[c]
XLP1			+[c]
IPEX (FoxP3 deficiency)			+[c]

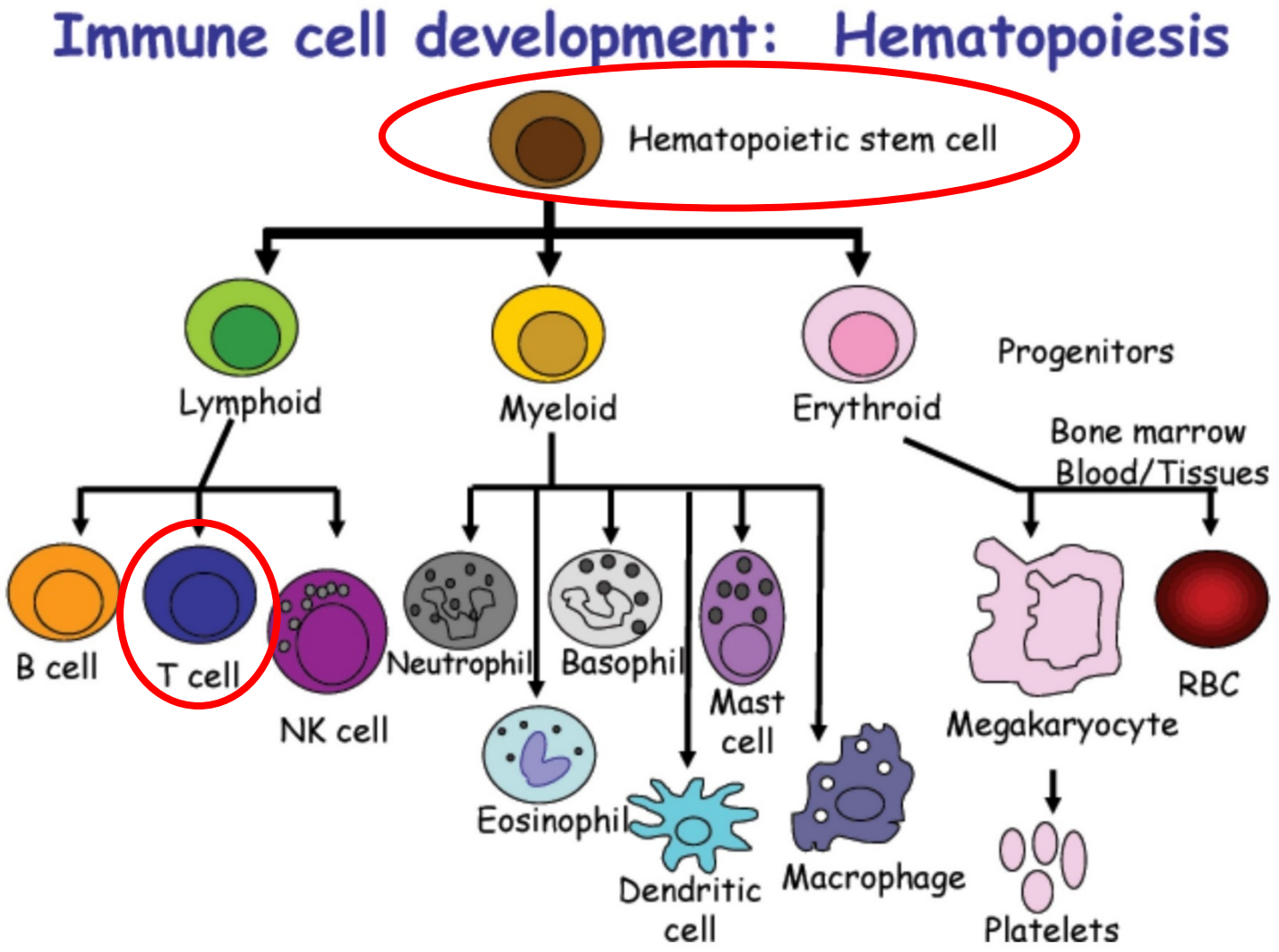
ADA, adenosine deaminase; HLH, hemophagocytic lymphohistiocytosis; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PID, primary immunodeficiencies; SAEs, serious adverse events; SCID, severe combined immunodeficiencies; SIN, self-inactivating; WAS, Wiskott–Aldrich syndrome.

[a]Associated with high frequency of SAEs (5 out of 19).

[b]Associated with very high frequency of SAEs (seven out of nine for WAS, and four out of four for CGD).

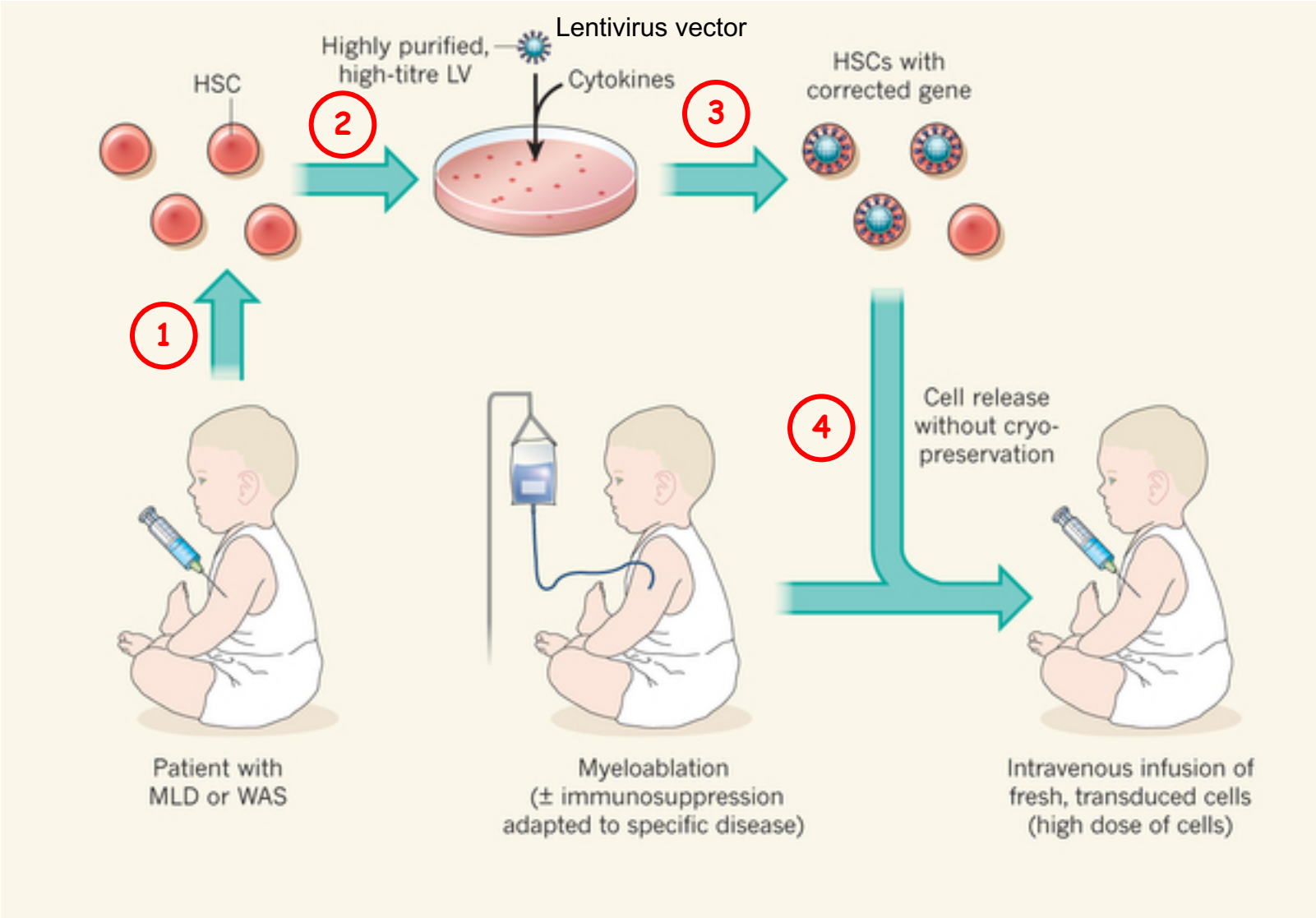
[c]CD34 and T cell strategy are both envisaged.

Using Stem Cells in *Ex Vivo* Gene Therapy



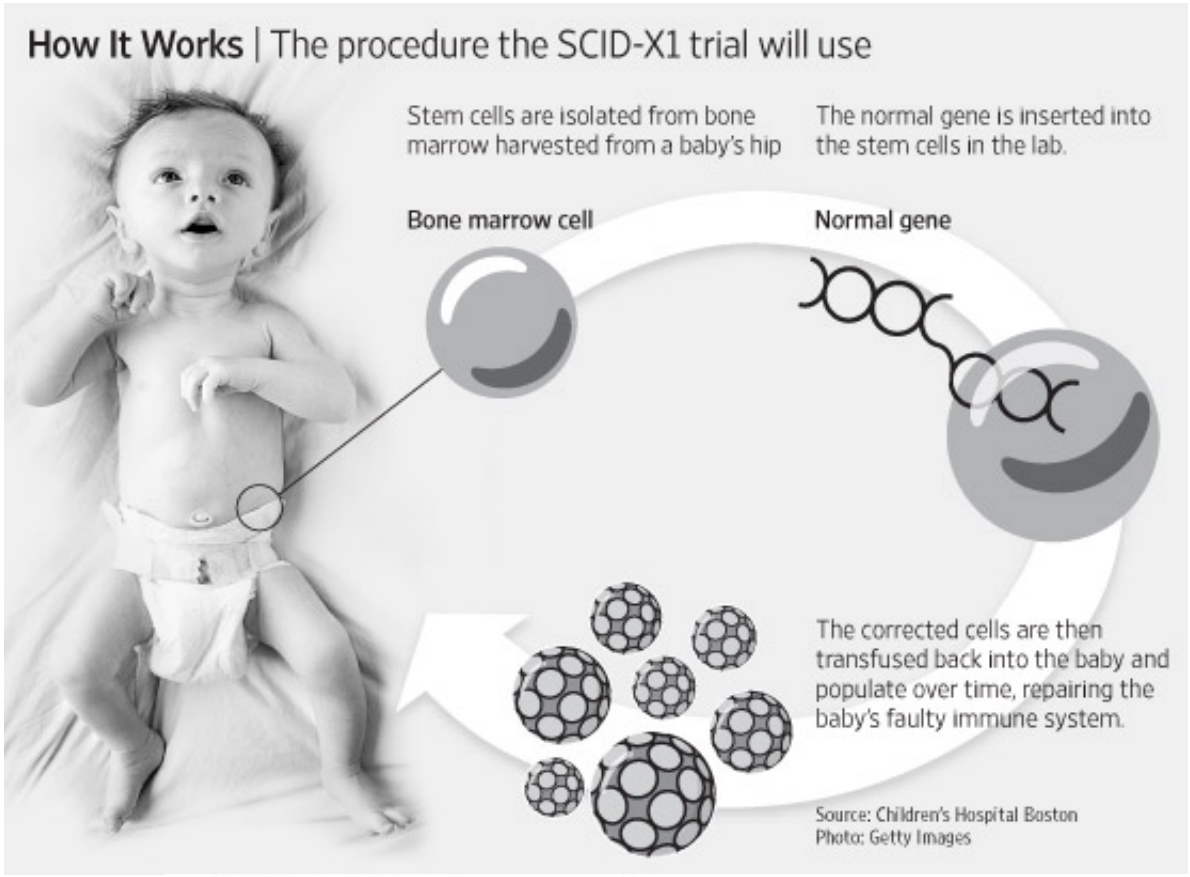
Dr. Pei-Yun Lee

General Strategy for Use of Hematopoietic Stem Cells in Gene Therapy



Updated Ex Vivo Gene Therapy for ADA-SCID & SCID-X1

- **SCID-X1**
  - Most common form of SCID
  - Results from mutations in the common gamma chain gene required for interleukin receptors
  - Patients are immune deficient
- **Gene Therapy Improvements**
  - Used hematopoietic stem cells
  - Improved retroviral vectors with higher titers



UCLA researcher pioneers gene therapy cure for 'Bubble Baby' disease

Game-changing stem cell treatment to be tested for sickle cell disease next

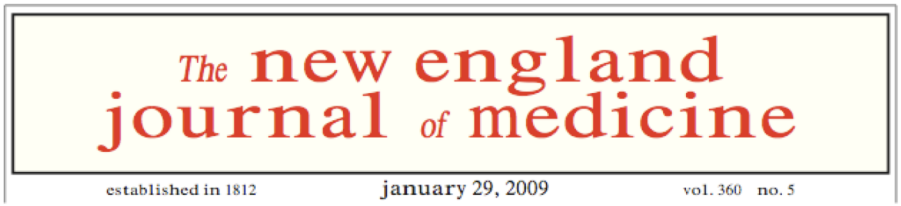
Peter Bracke | November 20, 2014

UCLA

It Works!

Gene therapy cures 'bubble boy disease'

31 Jan 2009, 1128 hrs IST, AP



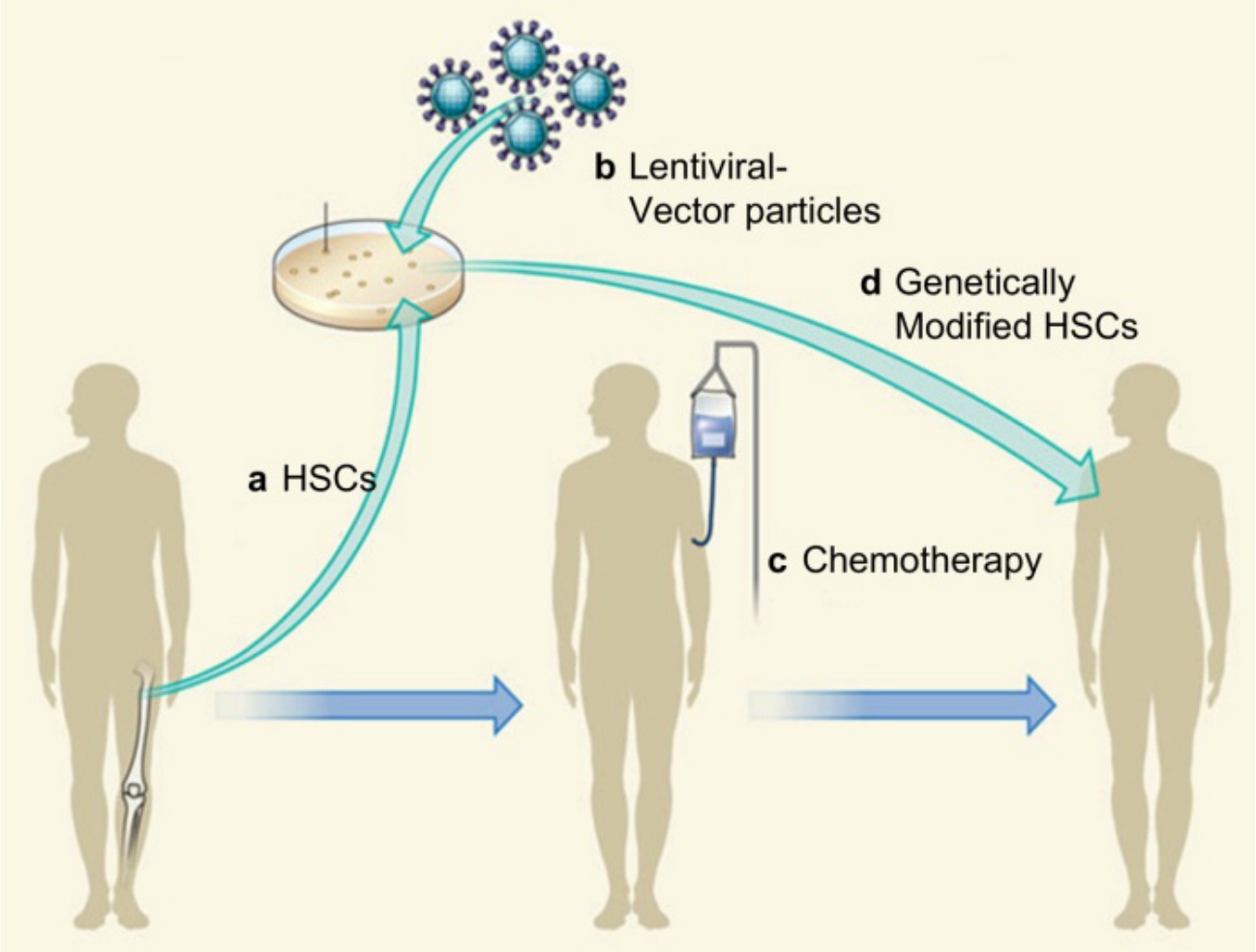
Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Results after 10 years

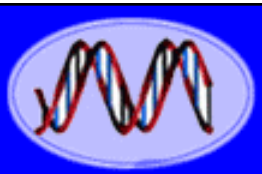
- ADA-SCID – 4 of 6 children experienced immune reconstitution
- SCID-X1 – 9 of 10 children experienced normal T-cell number
- But - 5 of 20 SCID-X1 subjects experienced leukemia-like T lymphoproliferation in another study

- ADA-SCID gene therapy product named Strimvelis from GlaxoSmithKline (sold to Orchard Therapeutics)
- Approved for use in Europe in May 2016, first used March 2017
- One time treatment costs $714,000, with money-back guarantee

Other Diseases that are Being Targeted Using Ex Vivo Gene Therapy with Hematopoietic Stem Cells

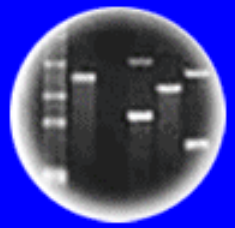


- SCID Artemis
- SCID Rag-1
- Sickle cell disease
- -thalassaemia
- Chronic granulomatous disease
- Leucocyte adhesion deficiency
- Wiskott Aldrich Syndrome
- X-linked lymphoproliferative syndrome



DNA
Genetic Code of Life

Entire Genetic Code
of a Bacteria



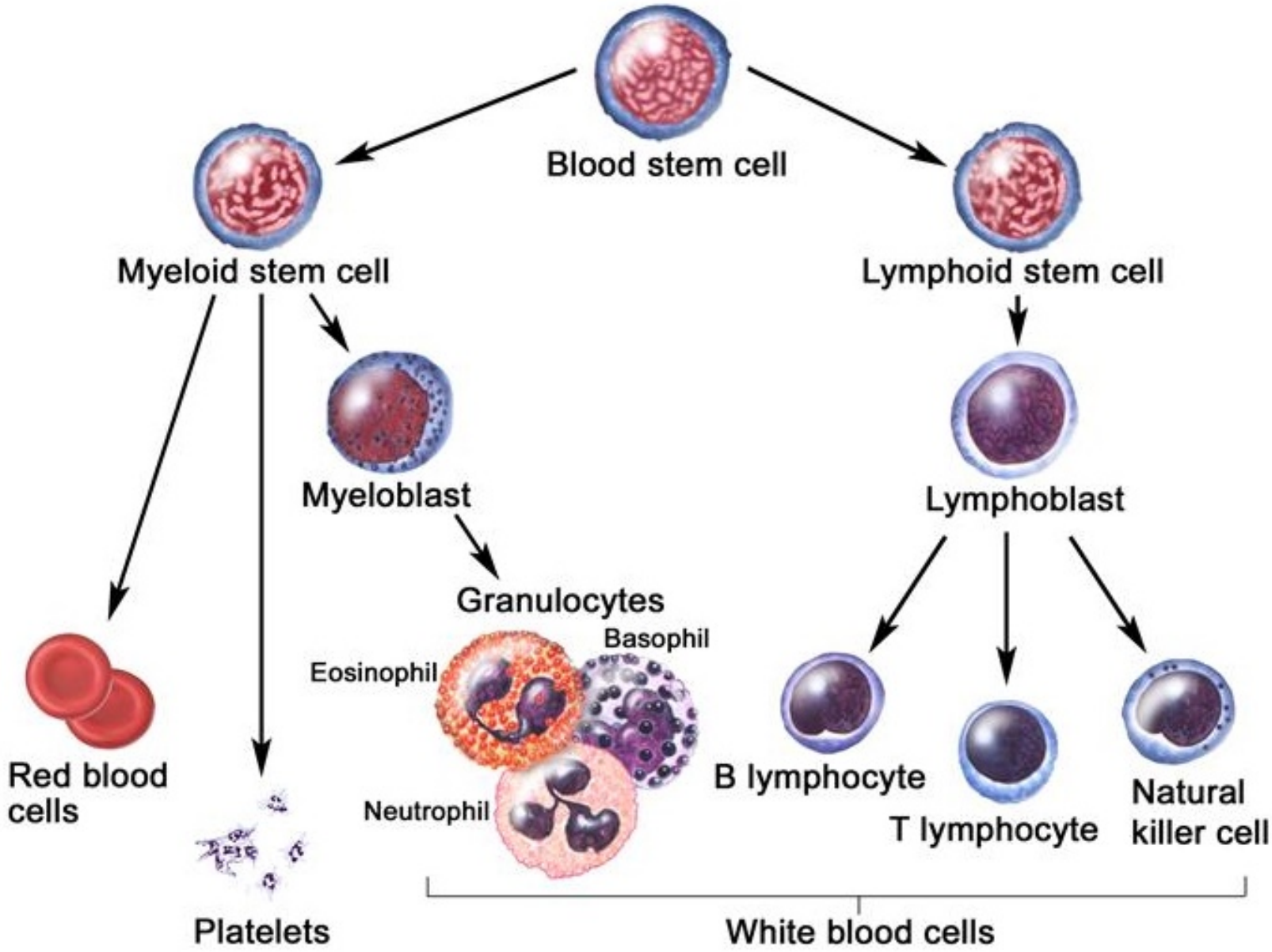
DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

Ex Vivo Gene Therapy to Control Cancers

Normal Blood Cell Development



The New York Times

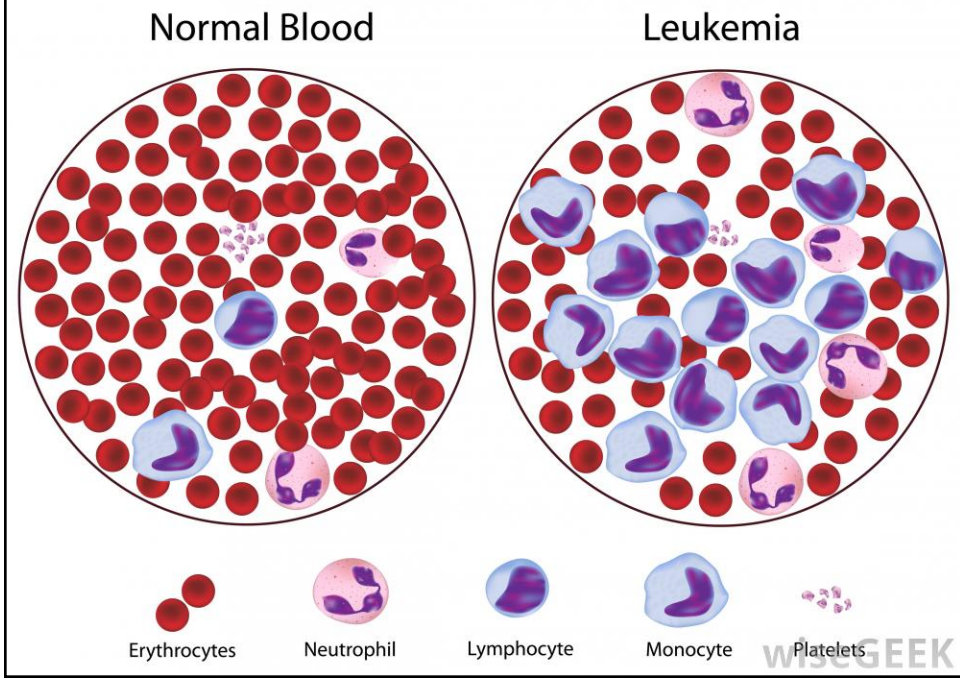
December 9, 2012

2013

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY

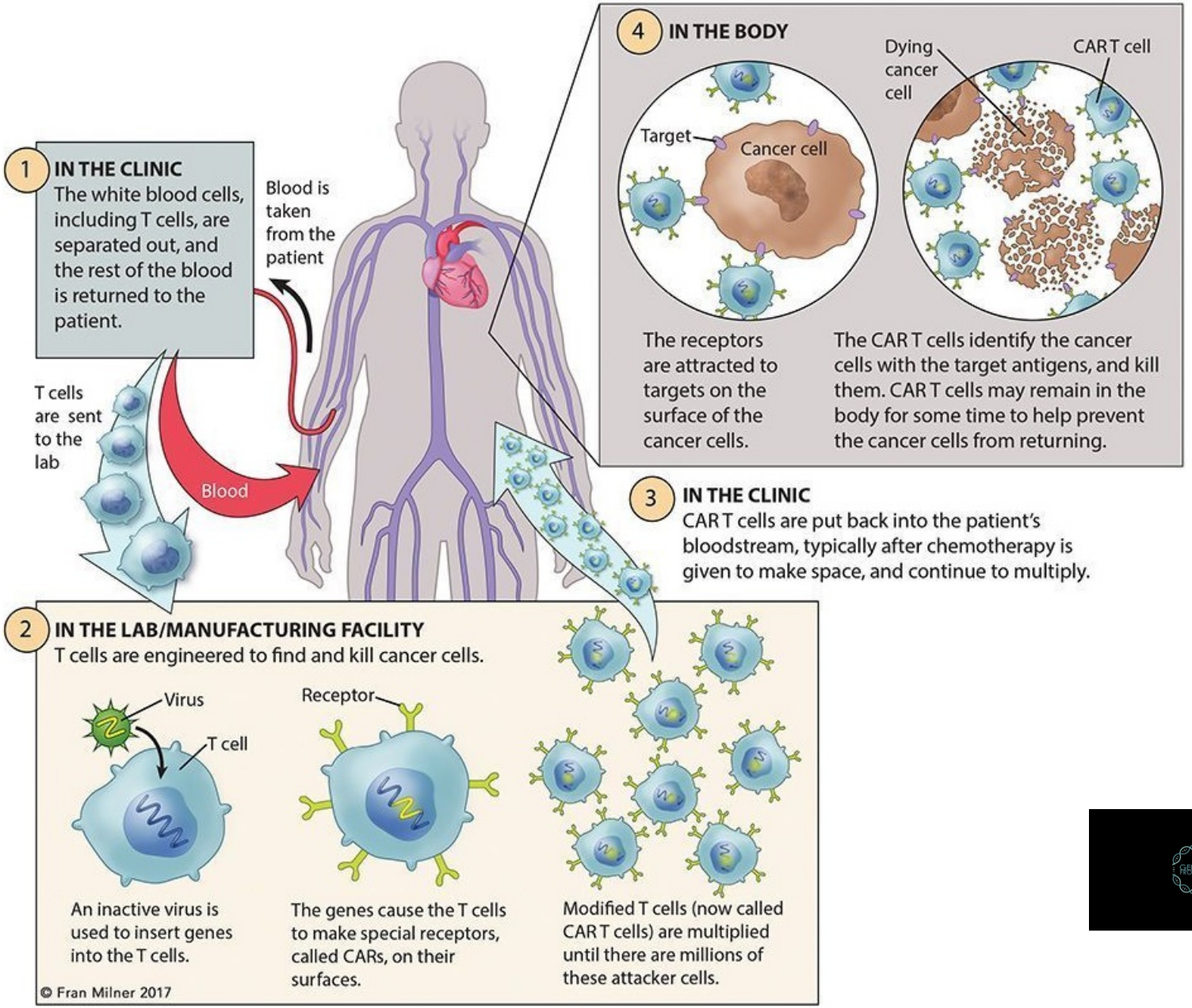
Leukemia is cancer of the blood, that results in an increase in immature white blood cells. Chronic lymphoid leukemia affects B cell lymphocytes



Emily Whitehead, 7, was the first child to receive gene therapy for leukemia at CHOP. (Photo courtesy of The Children's Hospital of Philadelphia)

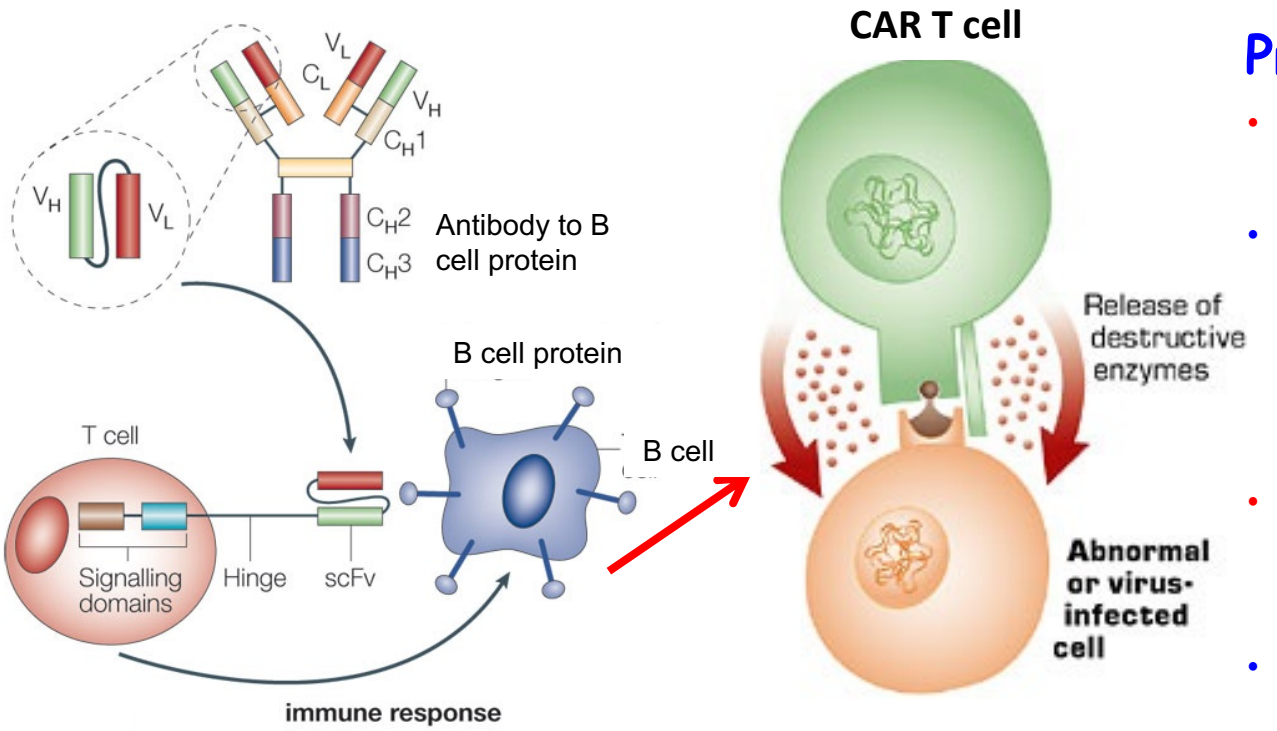
Emily Whitehead, alive at age 7 because of a novel gene therapy strategy

Chimeric Antigen Receptor (CAR) T Cell Strategy



Ex-vivo Gene Therapy for Lymphocytic Leukemia

Science Translational Medicine
AAAS



Protocol

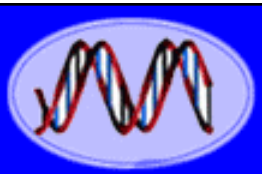
- Removed T cells from patients
- Created gene encoding Chimeric Antigen Receptor (CAR) that recognize a protein on the surface of B cells
- Transferred CAR gene into T cells to allow them to target B cells
- Infused CAR T cells back into patients

- **Results**
  - CAR T cells expanded more than 1,000 fold and persisted more than six months
  - Estimated that each CAR T cell killed more than 1,000 cancer cells
  - In one trial, 19 of 22 children who had exhausted all drug treatment and bone-marrow transplant options for leukemia went into remission after receiving CART-19
  - 45 of 75 leukemia patients saw complete regressions with CARs

Two CAR-T Cell Treatments were the First FDA Approved Gene Therapies - 2017

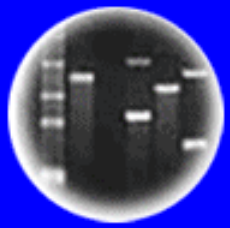
- Treatment for B-cell acute lymphoblastic leukemia
- Approved August 30, 2017
- $475,000 per treatment course

- Treatment for non-Hodgkin lymphoma
- Approved October 18, 2017
- $373,000 per treatment course



DNA
Genetic Code of Life

Entire Genetic Code
of a Bacteria

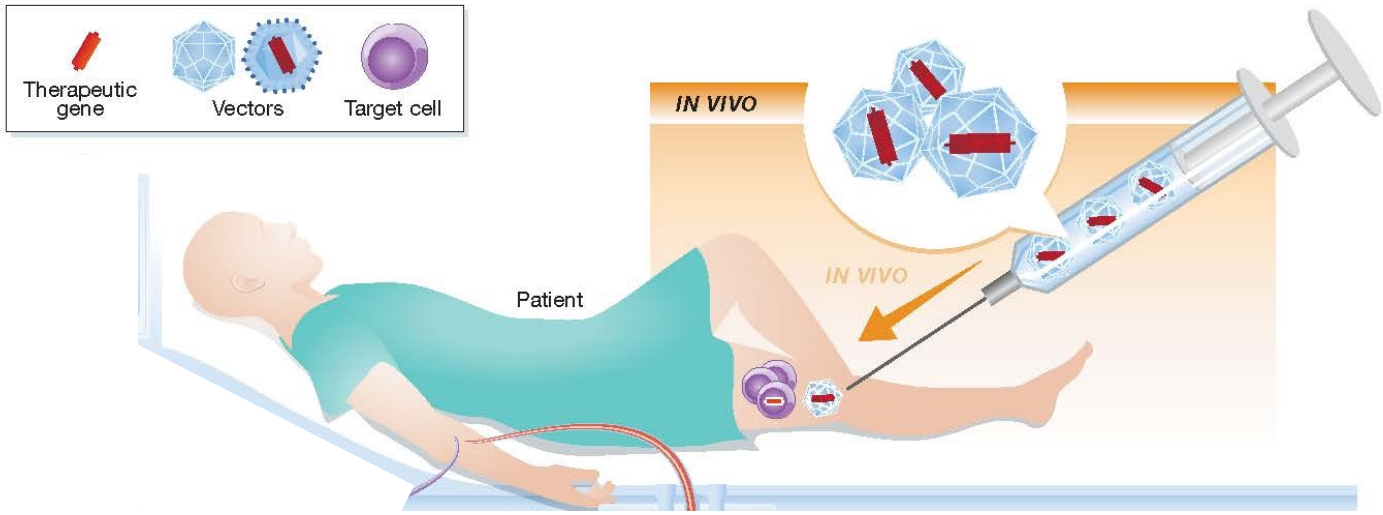


DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

In Vivo Gene Therapy



What "Tools" are Needed for In Vivo Somatic Cell Gene Therapy Procedures?

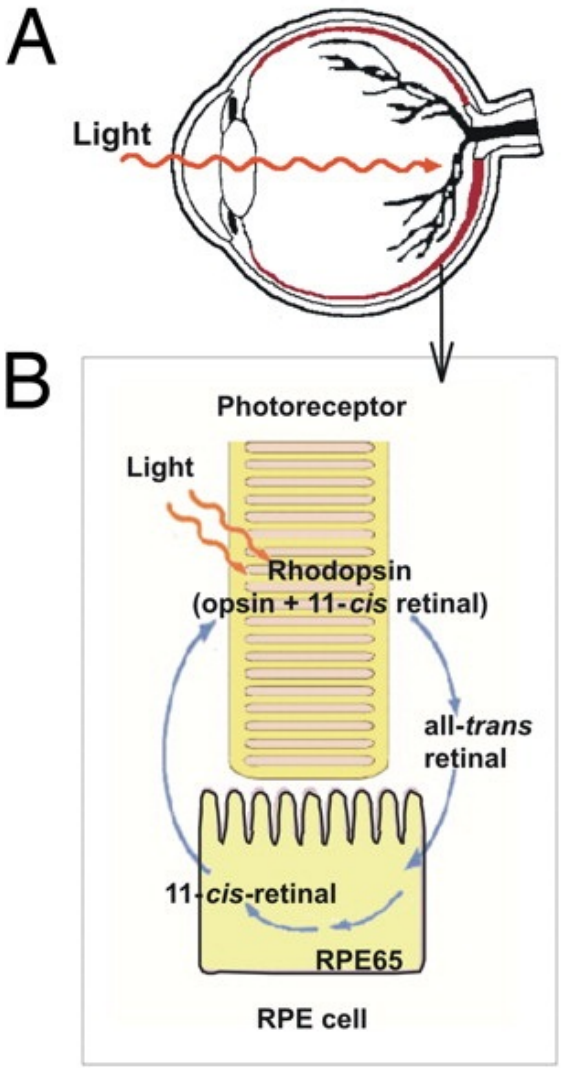
1.
2.
3.
4.

What "Tools" are Needed for In Vivo Somatic Cell Gene Therapy Procedures?

1. Cloned copy of the therapeutic gene
2. Appropriate switch, often high expression level
3. Vector to transfer the gene into the cells
4. *Ability to target the vector to desired cells*

Blindness - Leber Congenital Amaurosis (LCA)

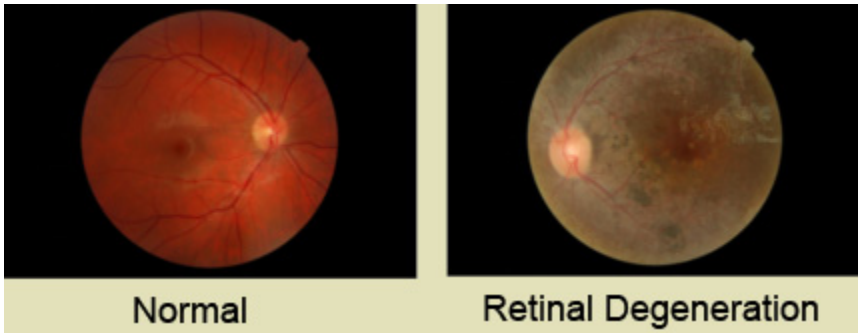
How We See



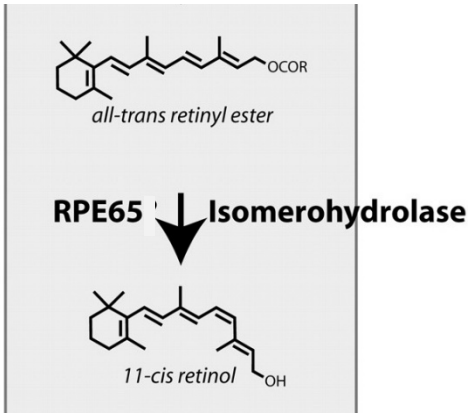
Cideciyan et al. PNAS 2008;105:15112

- Degenerative disease of the retina
- The most common cause of congenital blindness in children

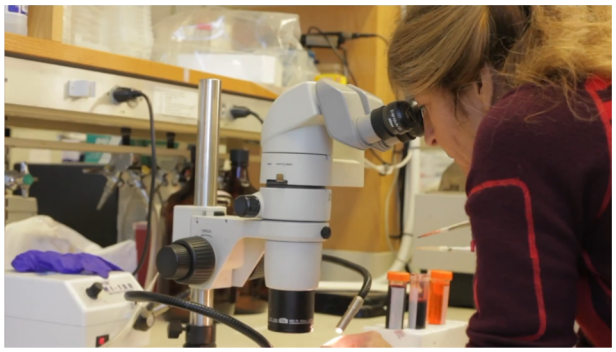
Normal retina **LCA retina**



Type 2 LCA is caused by recessive mutations in the RPE65 isomerase gene



A Gene Therapy for LCA



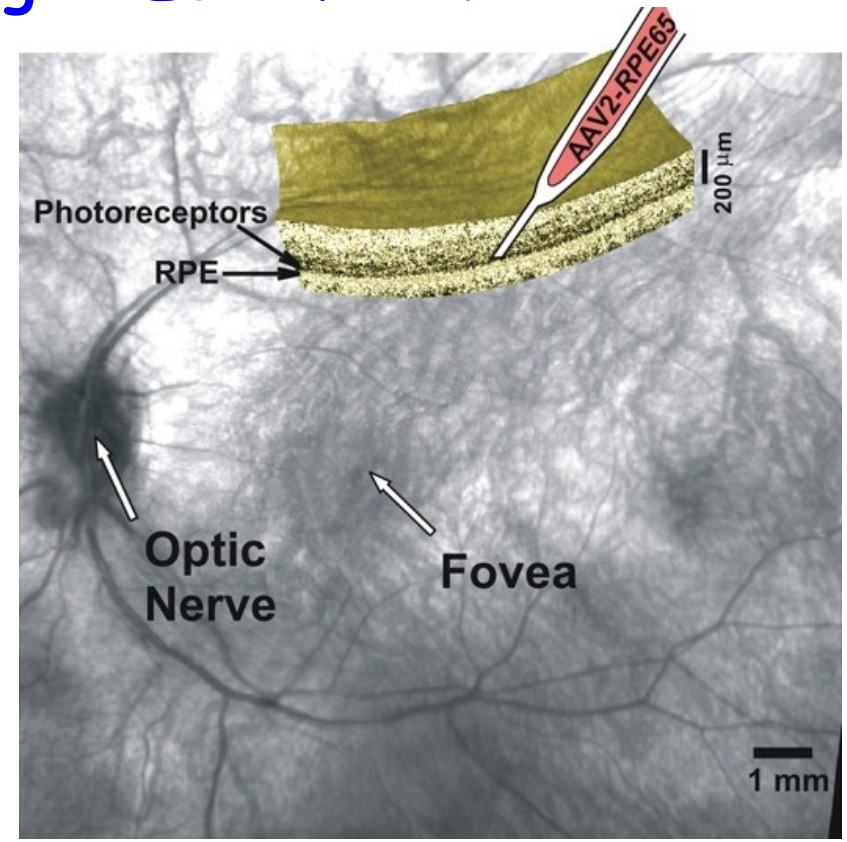
LCA Gene Therapy Using RPE65 & AAV2

Protocol

- Subretinal injection of adeno-associated viruses (AAV2) with RPE65 gene. AAVs…
  - do not generally provoke antibody formation
  - infects nondividing cells of many different tissues
  - has little or no integration of viral DNA into the host genome

Results

- Patients showed statistically significant improvement in vision in Phase 3 clinical trials, with 65% showing maximum possible improvement
- Improvements maintained up to three years



LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

NOW A REALITY: THE FIRST FDA-APPROVED GENE THERAPY FOR A GENETIC DISEASE

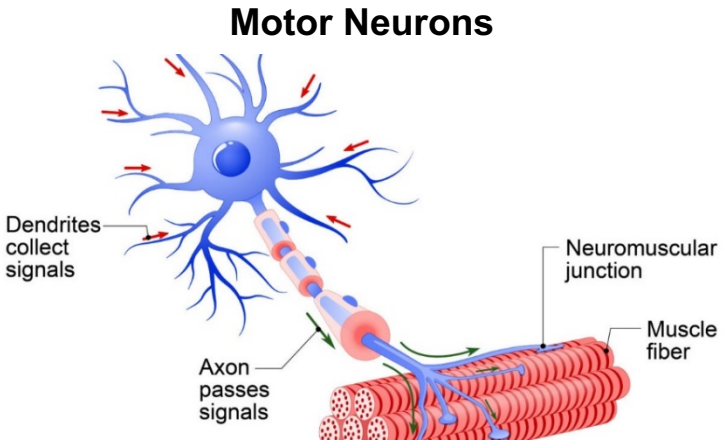
LUXTURNA is a prescription gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the *RPE65* gene, which can only be confirmed through genetic testing. You must also have enough remaining cells in your retina (the thin layer of tissue in the back of your eyes) as determined by your healthcare professional.

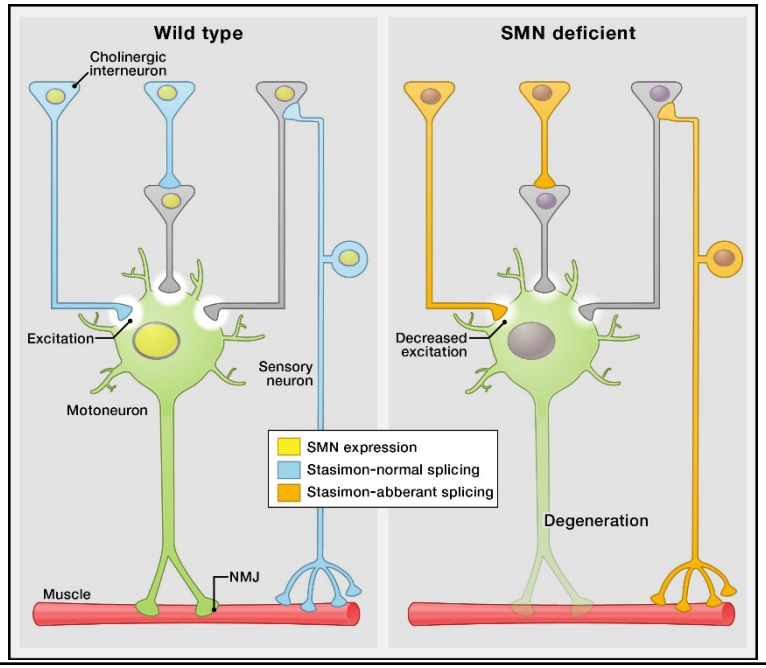
LEARN MORE ABOUT LUXTURNA | TAKE THE FIRST STEP TOWARD TREATMENT | REGISTER FOR UPDATES ON LUXTURNA

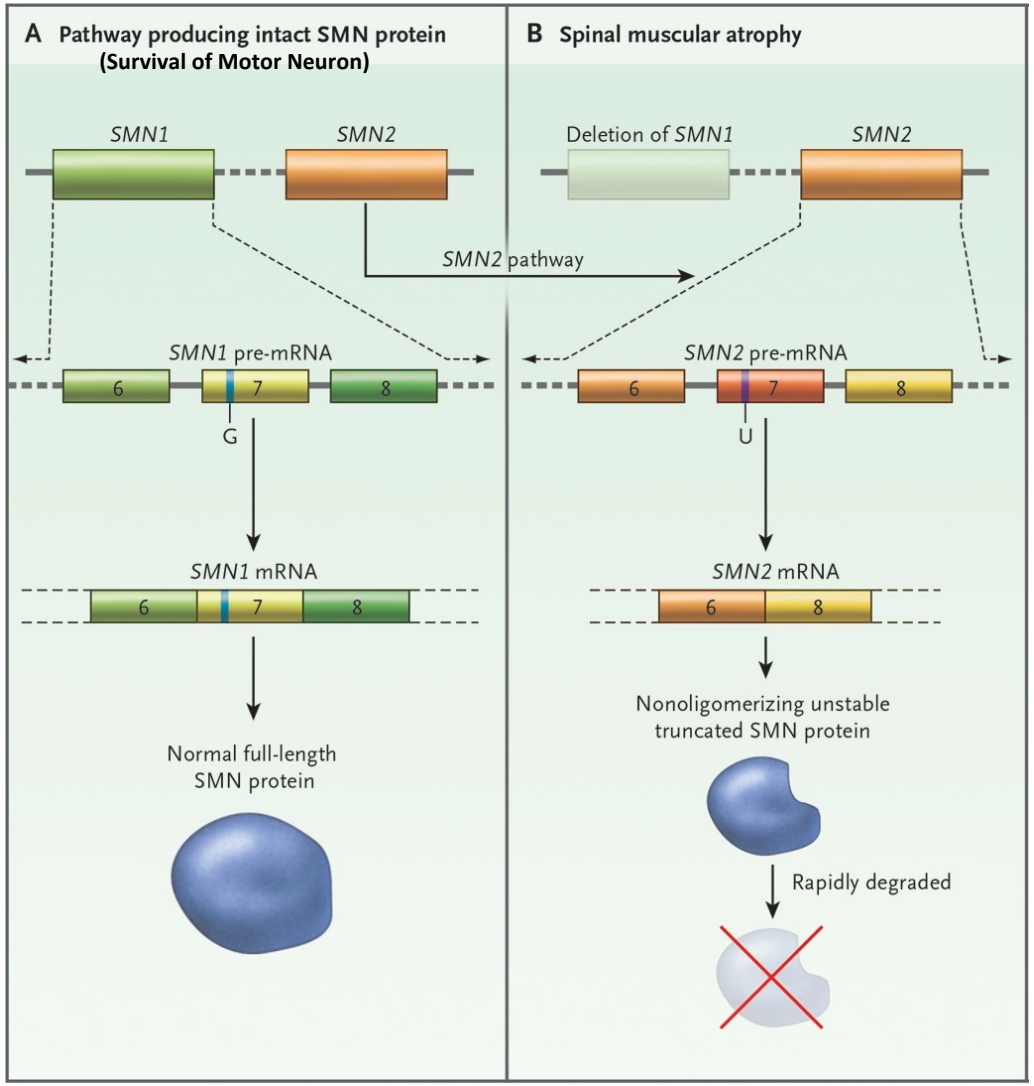
- Approved December 19, 2017
- $425,000 per eye
- Money-back guarantee

Spinal Muscular Atrophy (SMA)

- Spinal Muscular Atrophy is an autosomal recessive neurodegenerative disease
- Number one genetic cause of infant mortality, with life expectancy of <2 years
- Characterized by progressive muscle weakness caused by a loss of specialized nerve cells (motor neurons) in the spinal cord and brainstem







In-vivo Gene Therapy for SMA Type 1

Protocol for Phase 1 Clinical Trial

- Transferred the SMN gene into the AAV9 vector
  - AAV9 when infused into a vein can move across the blood-brain barrier to the central nervous system
- Patients were given a single of intravenous AAV9-SMN treatment – 3 at a low dose and 12 at a high dose

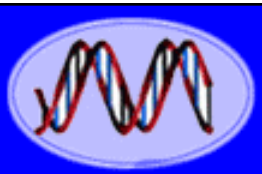
Results

- All 15 children treated were alive at 20 months or older and did not require ventilation
  - Other studies show that only 8% of untreated children survive to 20 months without ventilation
- Of 12 patients given the high dose, 11 sat unassisted, 9 rolled over, 11 fed orally and could speak, and 2 walked independently

Evelyn Villarreal

AveXis Files for FDA Approval of Gene Therapy for Spinal Muscular Atrophy Type I

BY CURE SMA | PUBLISHED ON OCTOBER 18, 2018



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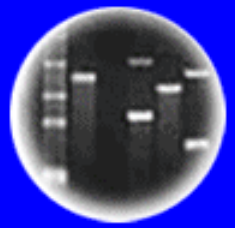

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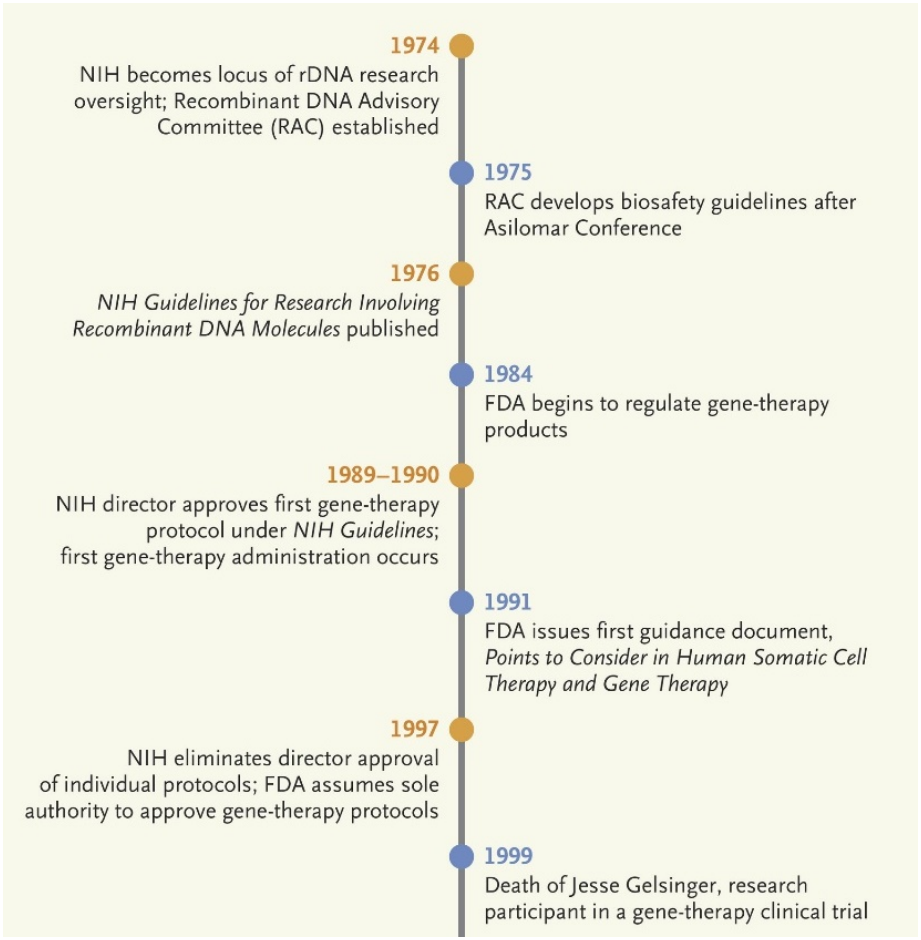
Regulation of Gene Therapy

Timeline of Regulatory Authority for Gene Therapy in the USA



US Regulatory Authority for Gene Therapy

- Department of Health and Human Services (DHHS) has been charged with oversight of clinical trials
  - Office for Human Research Protections
    - All research involving human subjects undergo Institutional Review Board review
  - U.S. Food and Drug Administration
    - Center for Biologics Evaluation and Research regulates human gene therapies. Manufacturers of gene therapy products must test their products extensively and meet FDA requirements for safety, purity and potency before they can be sold in the United States
    - FDA cannot review applications for clinical trials that involve human embryos with heritable genetic modifications
- National Institutes of Health (NIH), oversees the conduct of federally funded clinical trials
  - Recombinant DNA Advisory Committee review human gene transfer research on behalf of the NIH through the Office of Biotechnology Activities

http://www.genetherapynet.com/united-states-of-america.html

Gene Therapy Comes of Age

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 11, 2018

The Next Phase of Human Gene-Therapy Oversight

Francis S. Collins, M.D., Ph.D., and Scott Gottlieb, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health (NIH) Office of Science Policy (OSP) Recombinant or Synthetic Nucleic Acid Research: Proposed Changes to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) seeks public comment on its proposal to amend the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* to streamline oversight for human gene transfer clinical research protocols and reduce duplicative reporting requirements already captured within the existing regulatory framework. Specifically, NIH proposes amendments to: Delete the NIH protocol registration submission and reporting requirements under Appendix M of the *NIH Guidelines*, and modify the roles and responsibilities of entities that involve human gene transfer or the Recombinant DNA Advisory Committee (RAC).

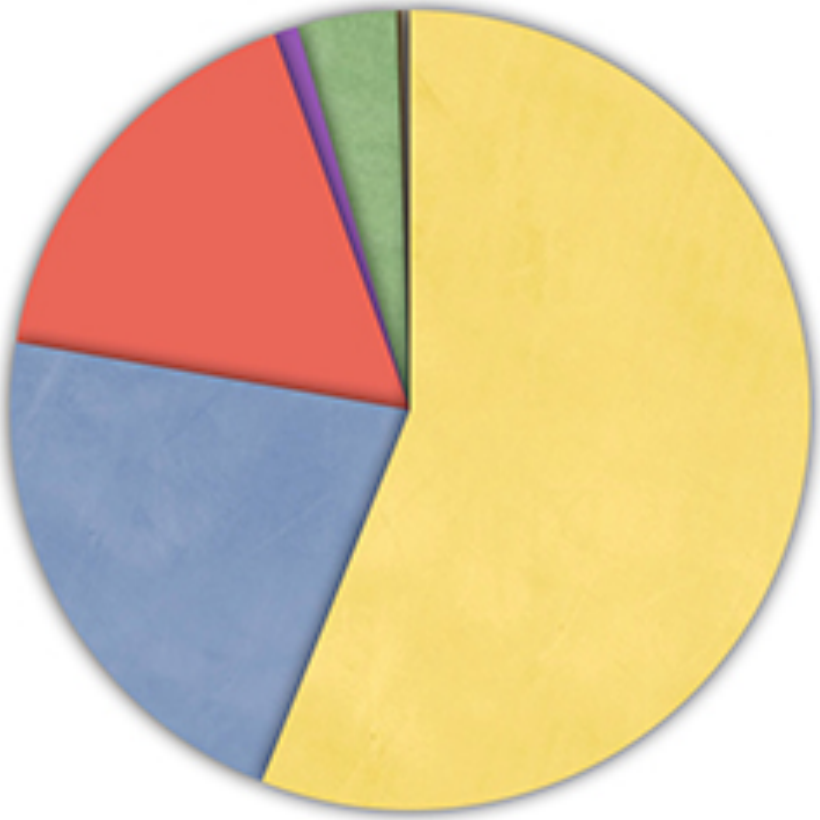
DATES: To ensure consideration, comments must be submitted in writing by October 16, 2018.

In changes proposed on August 17, 2018, in the *Federal Register*, the NIH and the FDA seek to reduce the duplicative oversight burden by further limiting the role of the NIH and RAC in assessing gene-therapy protocols and reviewing their safety information. Specifically, these proposals will eliminate RAC review and reporting requirements to the NIH for human gene-therapy protocols. They will also revise the responsibilities of institutional Biosafety Committees, which have local oversight for this research, making their review of human gene-therapy protocols consistent with review of other research subject to the *NIH Guidelines*. Such streamlining will also appropriately place the focus of the *NIH Guidelines* squarely back on laboratory biosafety.

Clinical Trials

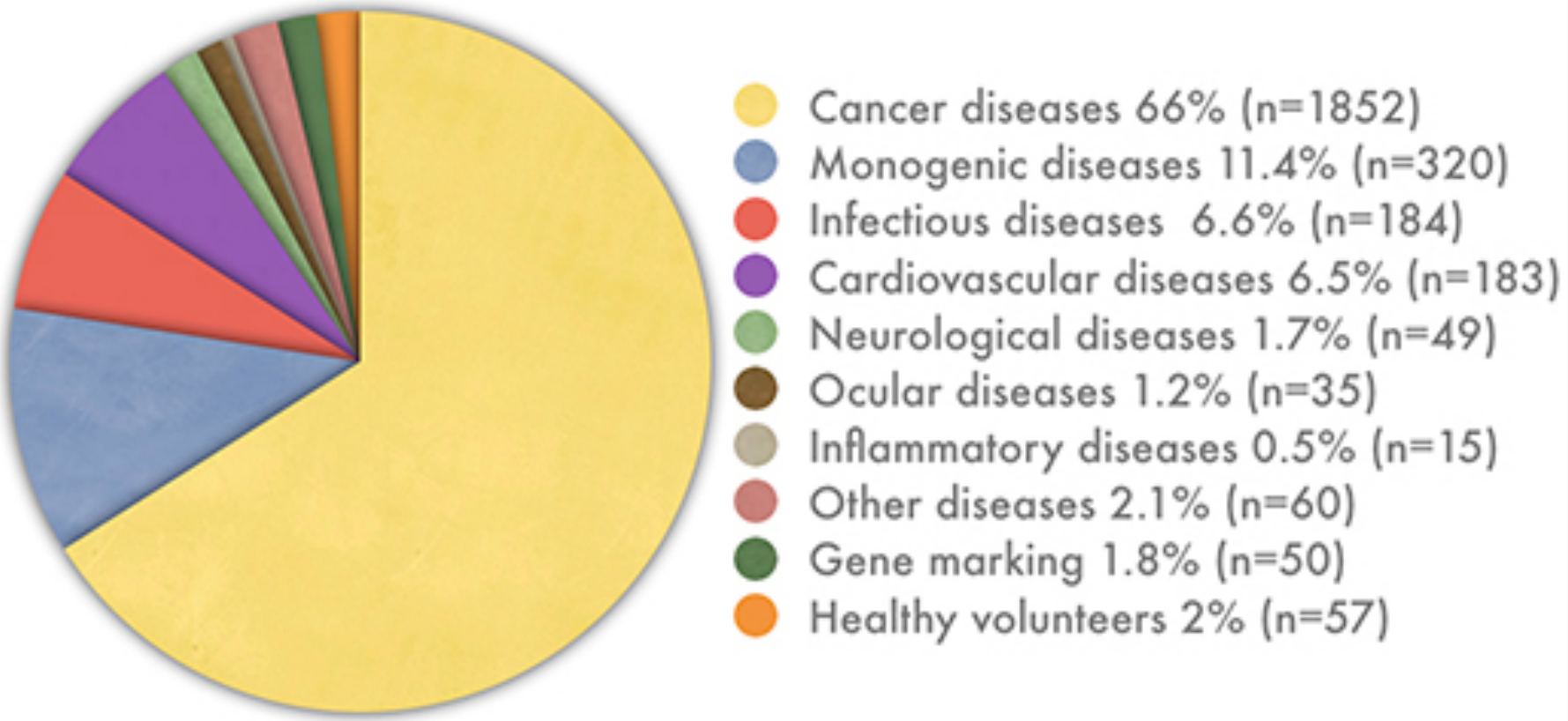
Phase I	Phase II	Phase III	Phase IV
20-80 participants	**100-300 participants**	**1,000-3,000 participants**	**Thousands of participants**
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

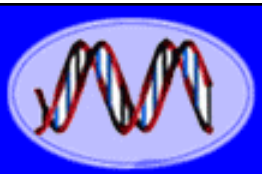
Phases of Gene Therapy Clinical Trials



- Phase I 56% (n=1572)
- Phase I/II 21.7% (n=608)
- Phase II 16.8% (n=470)
- Phase II/III 1% (n=27)
- Phase III 4% (n=113)
- Phase IV 0.2% (n=5)
- Single subject 0.4% (n=10)

Indications Addressed by Gene Therapy Clinical Trials





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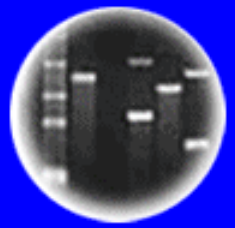

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Current Status of Gene Therapy

Approved Gene Therapy Products Worldwide

赛百诺 SIBIONO

P53 tumor suppressor deficiency
Marketed in China 2004

~~uniQure~~

~~**Glybera**~~
~~**Lipoprotein lipase deficiency**~~
~~**Marketed in Europe 2012**~~

Strimvelis

ADA-SCID
European Medicines Agency
Approved in 2016

LCA Blindness
FDA Approved 2017

LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

NOW APPROVED

CAR-T Therapy
FDA Approved 2017

YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

Hereditary Transthyretin Amyloidosis
FDA Approved 2018

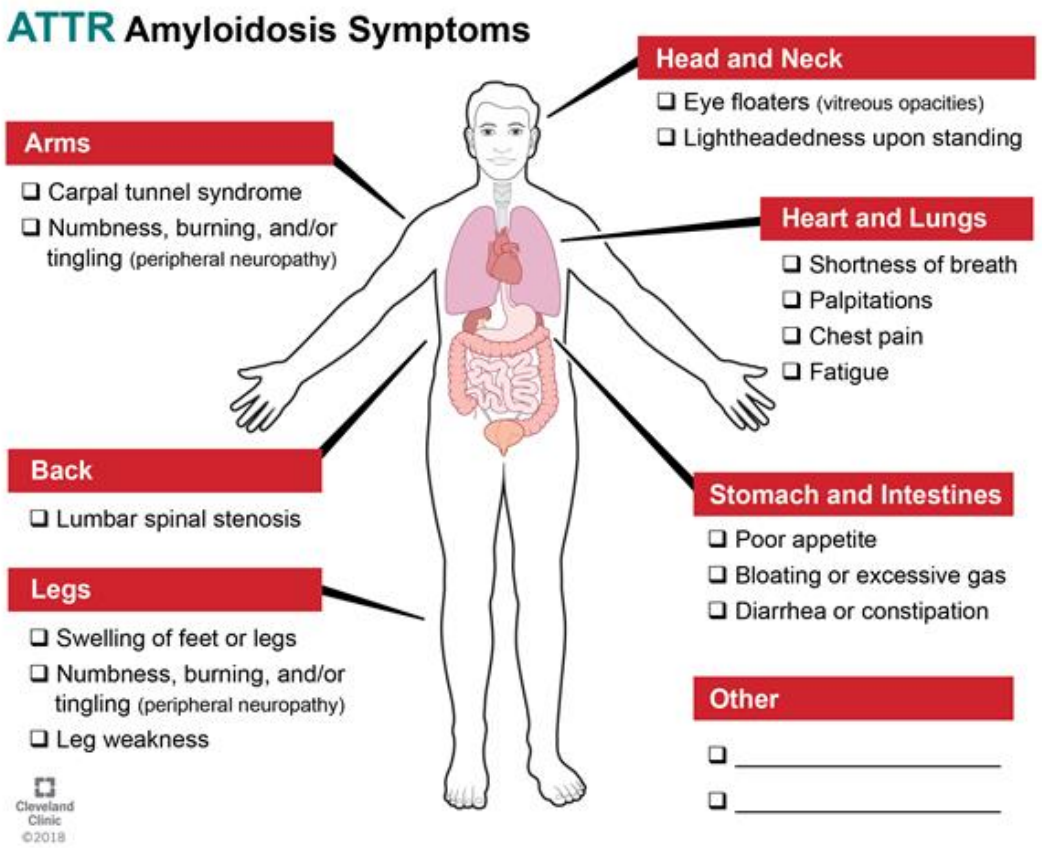
onpattro™
(patisiran) lipid complex injection

2017
Introducing the first
FDA-approved CAR-T cell therapy:
CTL019 is now

KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion

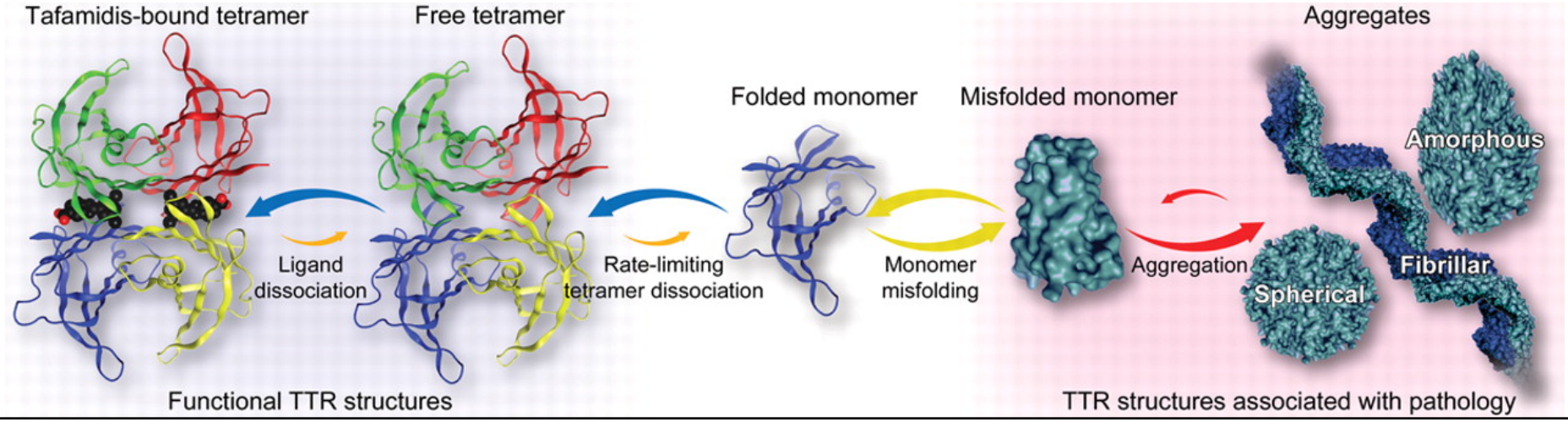
AVXS-101
avexis

Spinal Muscular Atrophy
Anticipated FDA Approval in 2019



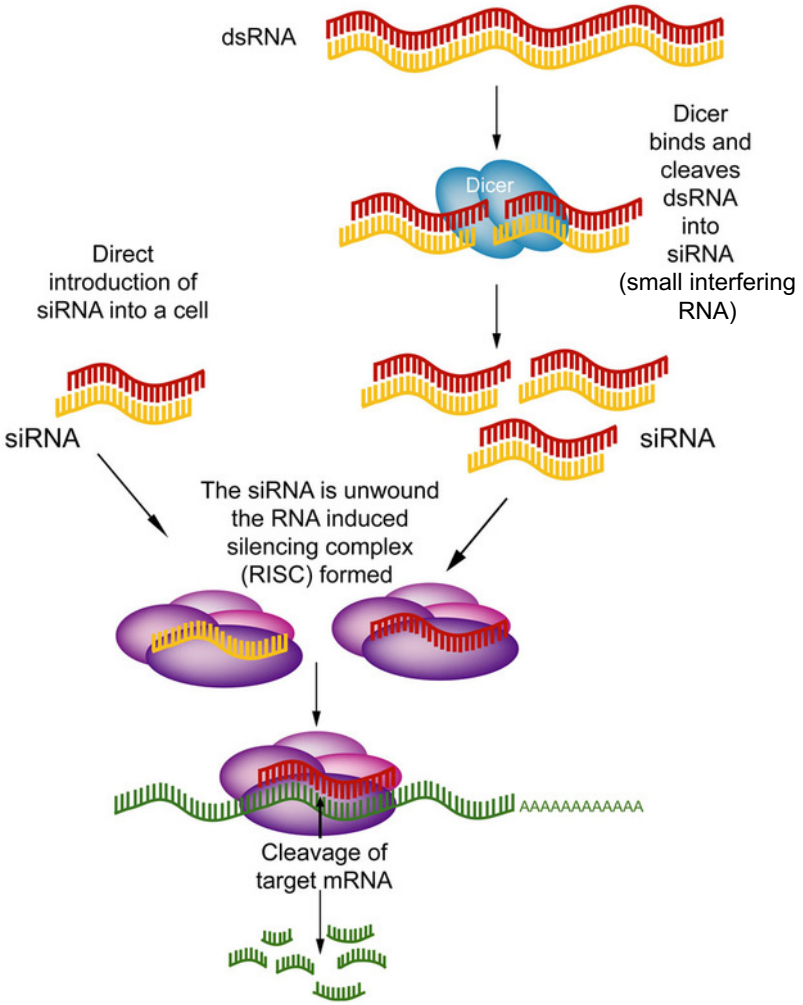
Hereditary Transthyretin (hATTR) Amyloidosis

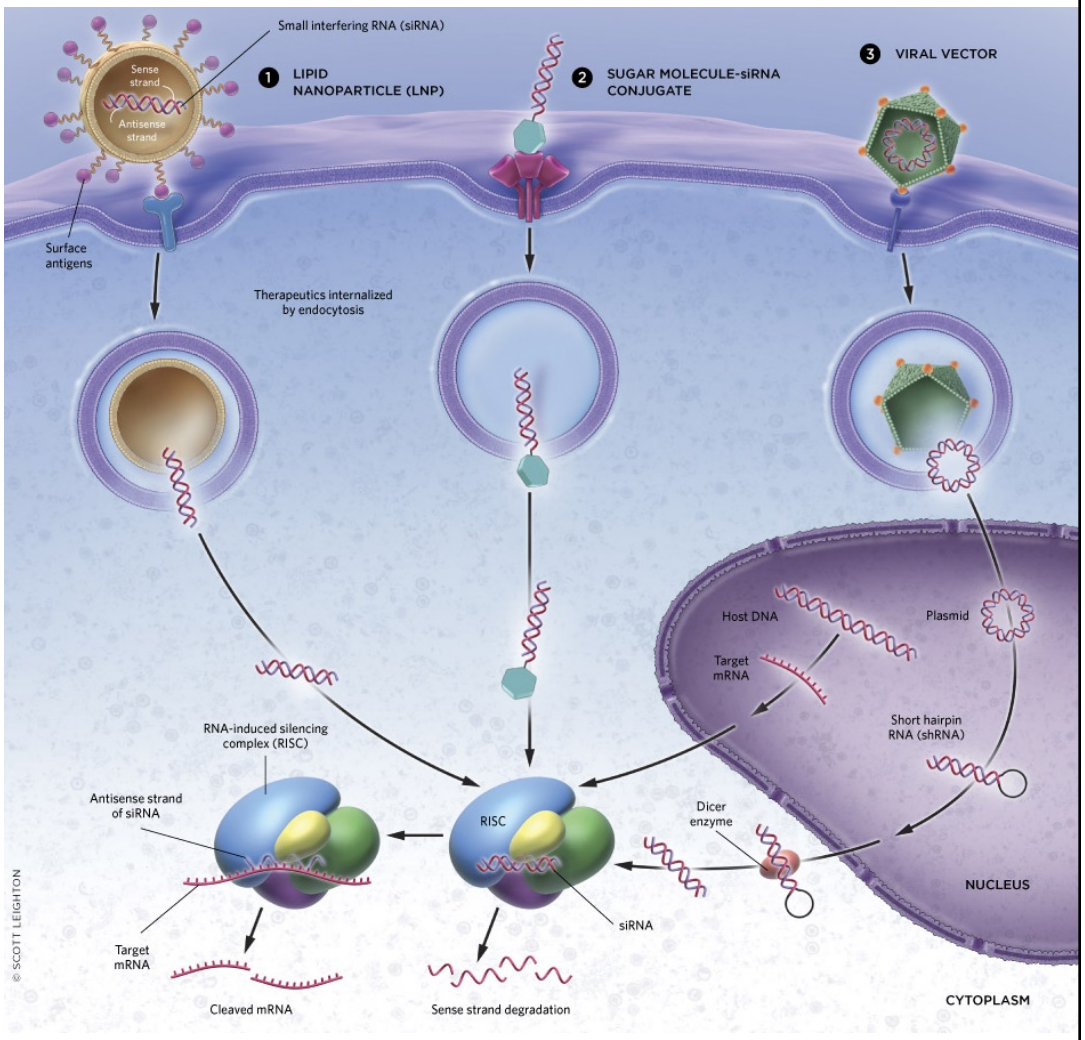
- Transthyretin (TTR) is a tetrameric transport protein synthesized in the liver
- Missense mutations in *TTR* results in protein misfolding and amyloid (protein aggregate) formation and amyloidosis
- Reduction in TTR levels decreases amyloid production



RNA Interference

Silencing Genes Through mRNA Degradation





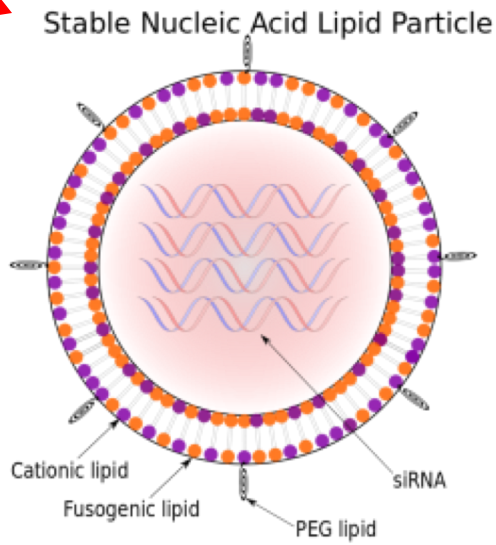
DNA → ~~mRNA~~ → ~~Protein~~

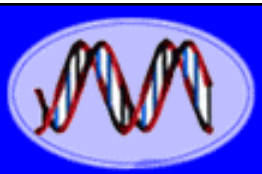
RNAi Gene Therapy for Transthyretin-mediated Amyloidosis

- **Protocol**
  - Create a small interfering RNA (siRNA) against transthyretin (TTR) mRNA with a modified phosphodiester RNA backbone
  - Encapsulate siRNA in lipid nanocarriers
  - Deliver the drug intravenously
- **Results**
  - Observed a 82 – 87% mean reduction in TTR levels
  - Efficiency of TTR knockdown supports monthly or bimonthly dosing
  - No adverse effects observed

Alnylam PHARMACEUTICALS

onpattro™ (patisiran) lipid complex injection





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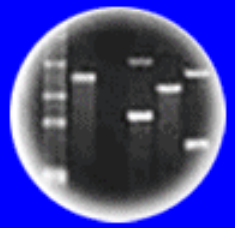

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Issues Concerning Gene Therapy

Some Issues With Human Gene Therapy

- More Information is Needed
- Availability for Everyone
- Eugenics & the "Slippery Slope" Towards Enhancement
- Consent
- Germline Gene Therapy

More Information is Needed About the Safety and Effectiveness of Gene Therapy Protocols

IN DEPTH | BIOMEDICINE

Gene therapy field hit by fresh safety concern

Jocelyn Kaiser
+ See all authors and affiliations

Science 09 Feb 2018:
Vol. 359, Issue 6376, pp. 621
DOI: 10.1126/science.359.6376.621

Human Gene Therapy, Vol. 29, No. 3 | Research Articles

Full Access

Severe Toxicity in Nonhuman Primates and Piglets Following High-Dose Intravenous Administration of an Adeno-Associated Virus Vector Expressing Human SMN

Christian Hinderer, Nathan Katz, Elizabeth L. Buza, Cecilia Dyer, Tamara Goode, Peter Bell, Laura K. Richman, and James M. Wilson

Published Online: 1 Mar 2018 | https://doi.org/10.1089/hum.2018.015

GEN Genetic Engineering & Biotechnology News

Gene Therapy May Not Be a Viable Option for Many Patients

By **Christina Bennett** - January 30, 2018 0

A Large Portion of Patients Have Pre-Existing Antibodies Against AAV

News | Cancer | Leukemia | Blood Disorders | Companies | Hematologic Conditions | Industry News

After 2 Patient Deaths, FDA Imposes Partial Clinical Hold on Trial of Xencor Blood Cancer Antibody XmAb14045

February 20, 2019 0

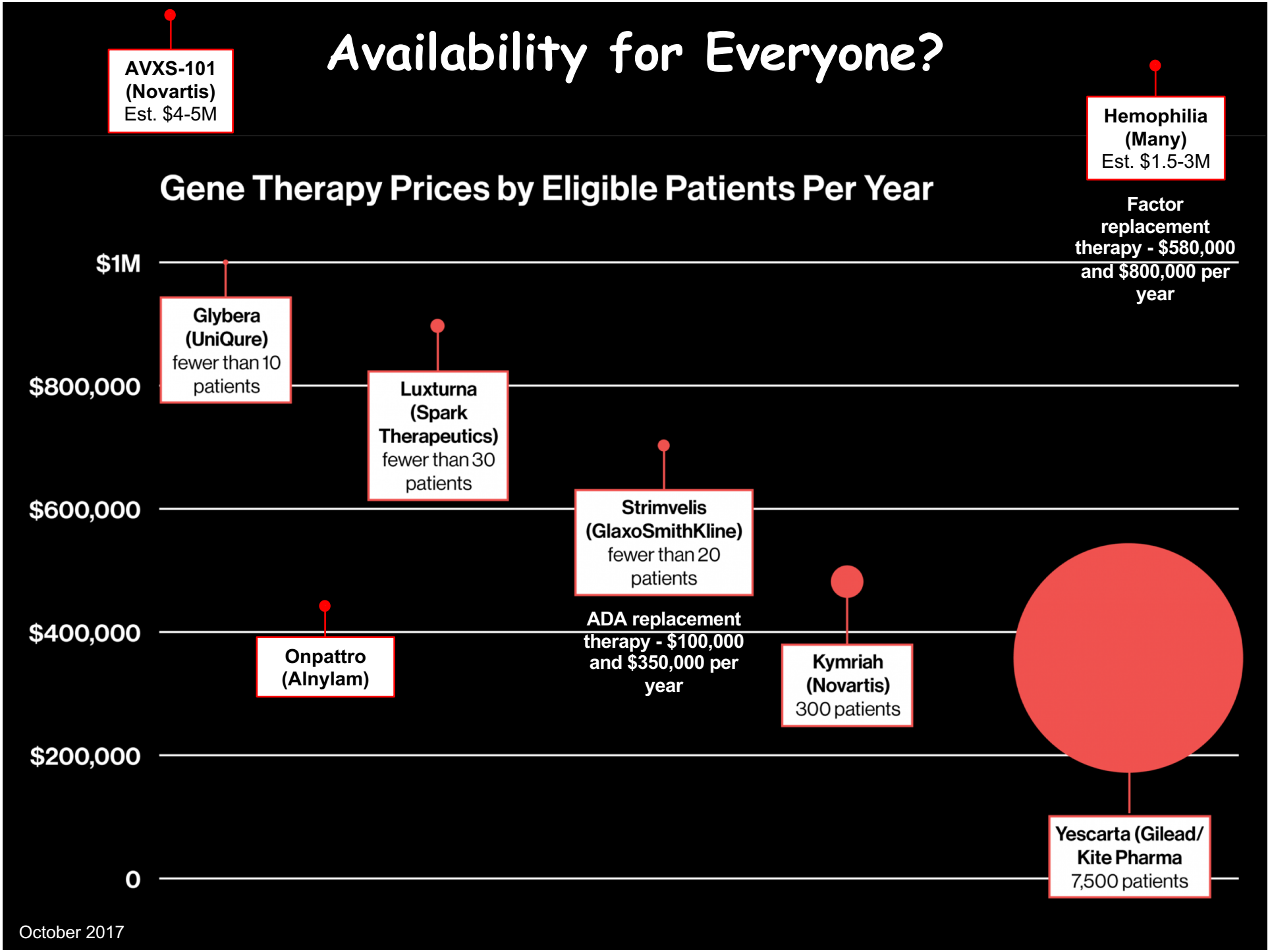
FierceBiotech

Biotech

Sangamo sinks as genome editing flunks early clinical test

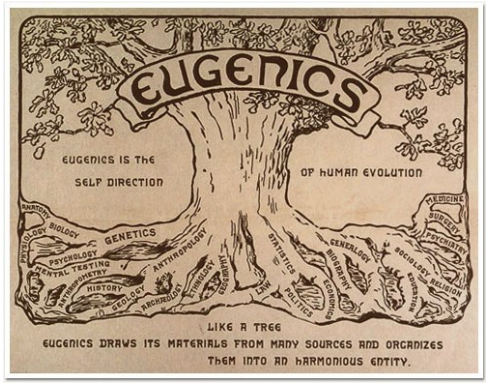
by Nick Paul Taylor | Feb 8, 2019 9:22am

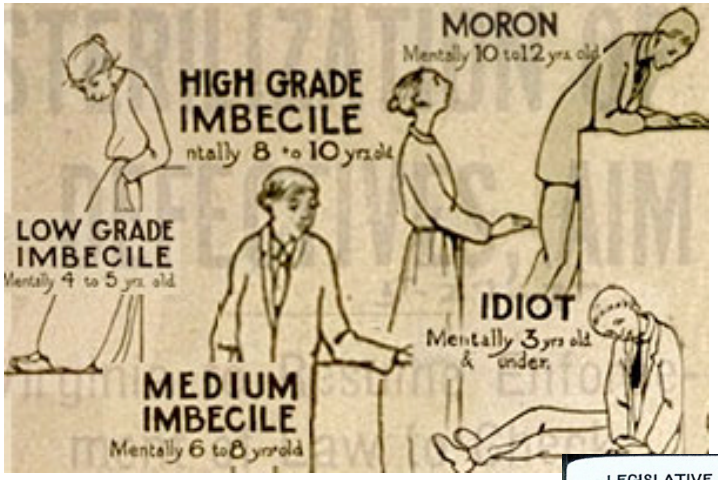
Availability for Everyone?



October 2017

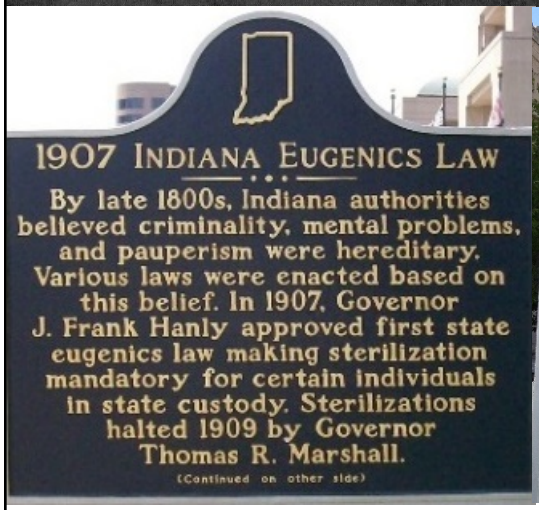
Eugenics: The study of or belief in the possibility of improving the qualities of the human species or a human population, especially by such means as discouraging reproduction by persons having genetic defects or presumed to have inheritable undesirable traits (negative eugenics) or encouraging reproduction by persons presumed to have inheritable desirable traits (positive eugenics) – dictionary.com

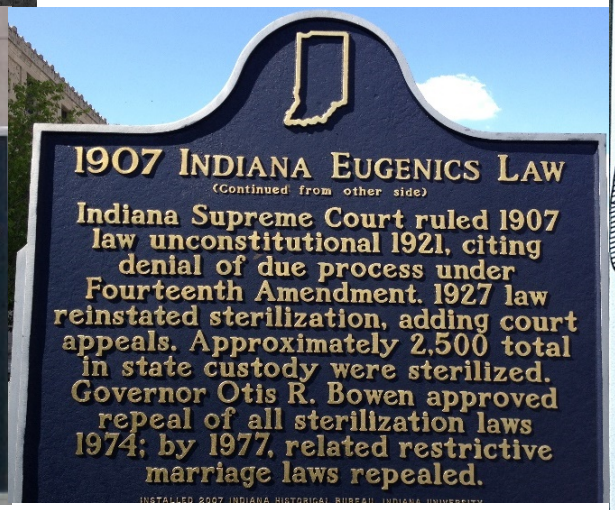


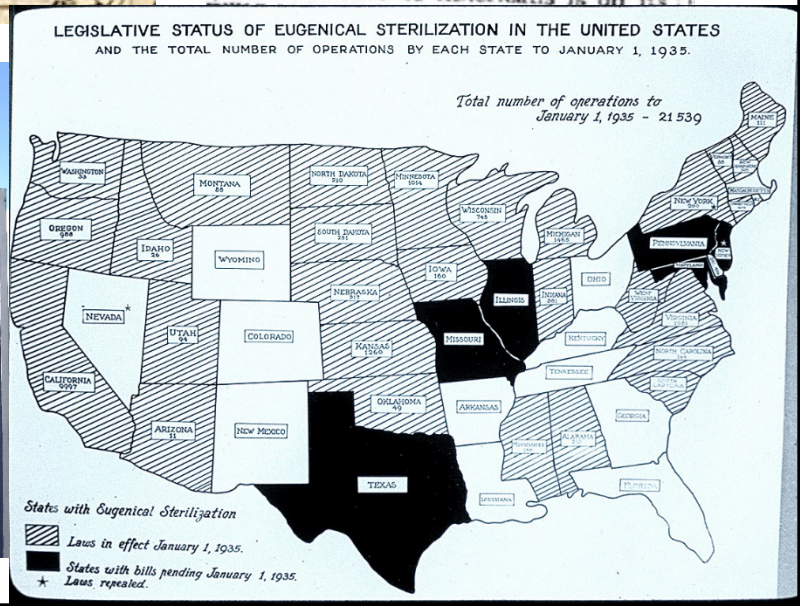



DECISION HELD
STEP TOWARD
A SUPER-RACE
Health Official Praise Court in Upholding Sterilization Law
WASHINGTON, May 5.—(INS)—An improved race of Americans is on its

Some people are born to be a burden on the rest.


1907 INDIANA EUGENICS LAW
By late 1800s, Indiana authorities believed criminality, mental problems, and pauperism were hereditary. Various laws were enacted based on this belief. In 1907, Governor J. Frank Hanly approved first state eugenics law making sterilization mandatory for certain individuals in state custody. Sterilizations halted 1909 by Governor Thomas R. Marshall.
(Continued on other side)


1907 INDIANA EUGENICS LAW
(Continued from other side)
Indiana Supreme Court ruled 1907 law unconstitutional 1921, citing denial of due process under Fourteenth Amendment. 1927 law reinstated sterilization, adding court appeals. Approximately 2,500 total in state custody were sterilized. Governor Otis R. Bowen approved repeal of all sterilization laws 1974; by 1977, related restrictive marriage laws repealed.



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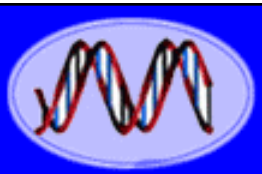

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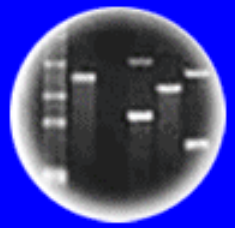
Entire Genetic Code
of a Bacteria



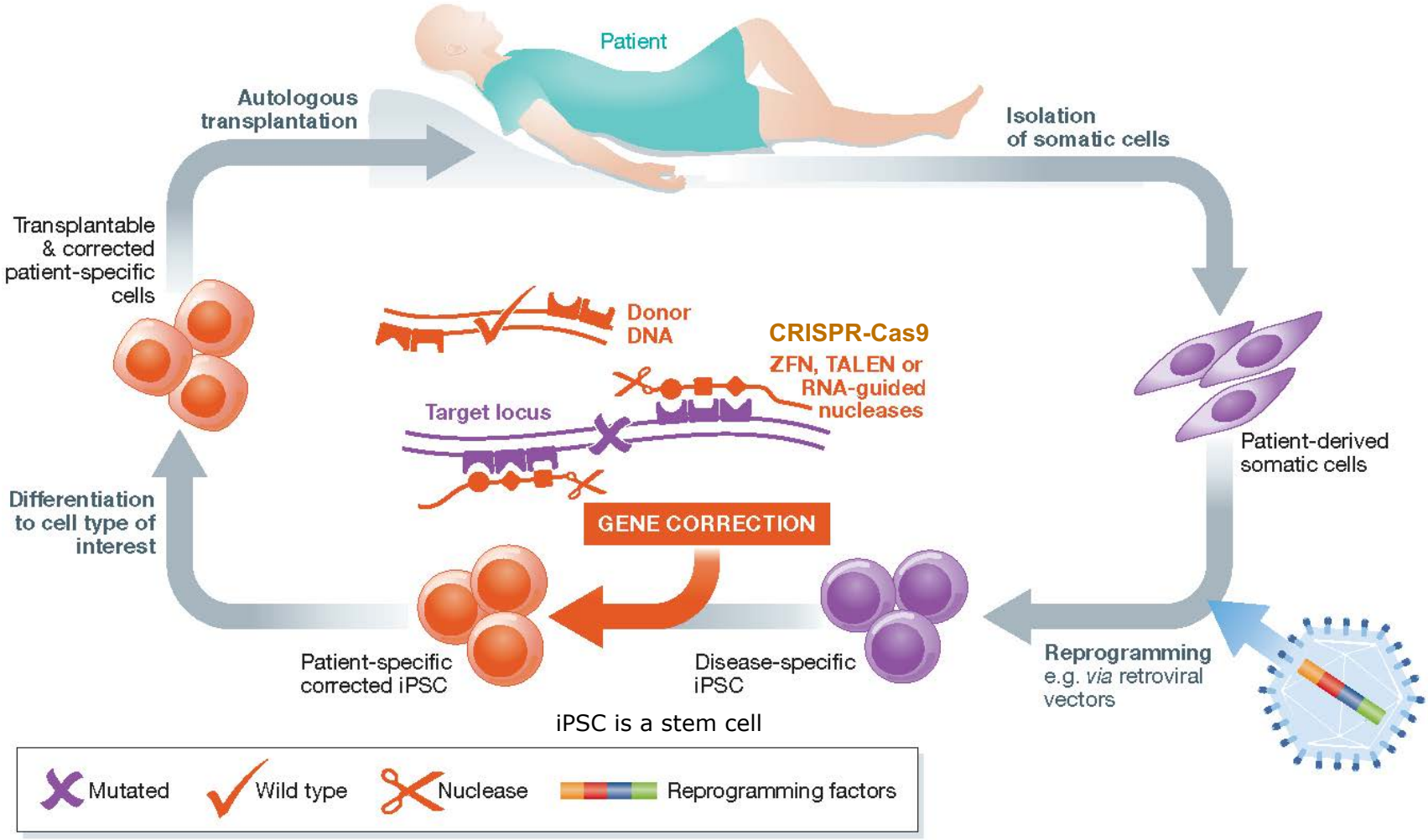
DNA Fingerprinting

Cloning: Ethical Issues
and Future Consequences

Plants of Tomorrow

Gene Editing & Human Gene Therapy

Human Genome Editing Therapy



Uses of Genome Editing

- Correct monogenic disorders – germline and somatic cells
  - Induce precise sequence changes to correct mutations
- Engineering pathogen DNA to combat infectious disease
  - Mutate integrated proviral DNA in host cells
- Induce therapeutic or protective mutations
  - Introduce mutations that cause resistance to HIV infection

Xiao-Jie et al. 2015

Gene Editing Therapy Phase 1/2 Clinical Trials

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

Sangamo Reports Positive Preliminary Data from Hemophilia Gene Therapy Trial

August 9, 2018

Gene Therapy for Hunter's Syndrome

TheScientist
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Preliminary Results Point to Success of In Vivo Gene Editing

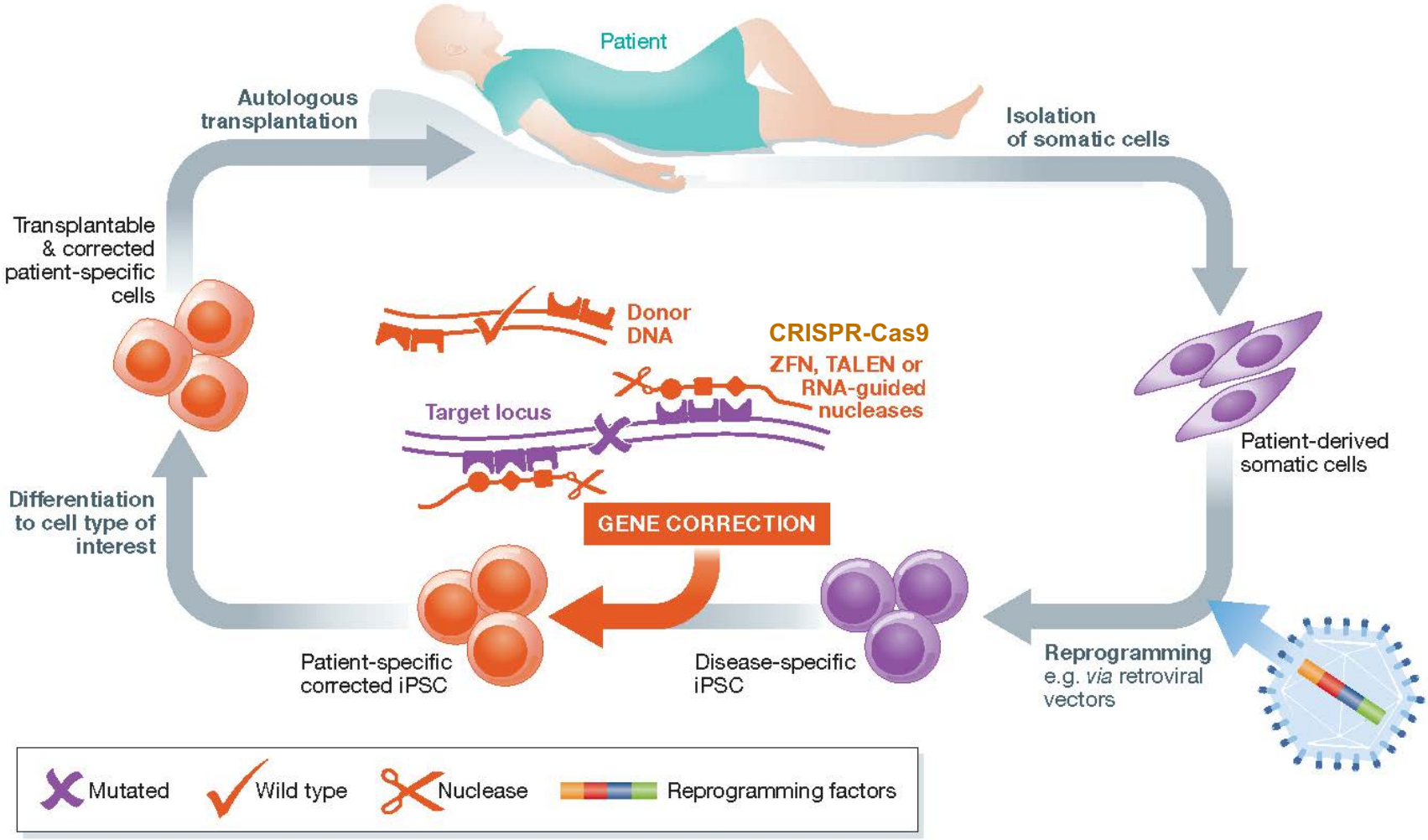
Two studies show signs that the introduced DNA is functioning, but it's too early to know if patients actually benefit.

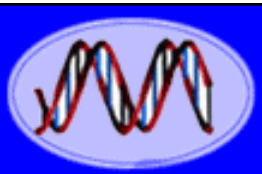
Feb 12, 2019
CAROLYN WILKE

387 1 44

Brian Madeux – first human gene editing therapy patient - 2018

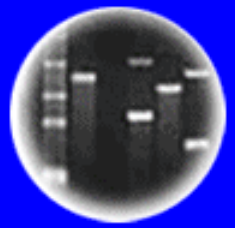
Human Genome Editing Therapy





DNA
Genetic Code of Life

Entire Genetic Code
of a Bacteria



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The End!!

HC70A/SAS70A/PLSS059 Lectures on the History, Science, and Applications of Genomics & Genetic Engineering