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Emerging Trends in Gene Therapy and Associated Challenges in Research Ethics and Research Compliance

Presented by:

Daniel Eisenman, PhD, RBP, SM(NRCM), CBSP

Executive Director, Biosafety Services, Advarra

Daniel.Eisenman@advarra.com

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Daniel Eisenman
PhD, RBP, SM(NRCM), CBSP

Executive Director,
Biosafety Services,
Advarra

- Leads Advarra's IBC service, focusing on review of research involving engineered genetic materials,
  - Including genetic vaccines, gene modified cellular therapies, and gene therapies
- Over a decade of experience in biosafety program management
  - Previously served as biosafety officer at UNC Chapel Hill and the Medical University of South Carolina
- Experienced educator, author, and presenter in biological safety, genetic engineering, immunology, and infectious diseases
- PhD in molecular biology and immunology from Augusta University
- Certified Biological Safety Professional, American Biological Safety Association
- Specialist Microbiologist in Biological Safety, National Registry of Certified Microbiologists, American Society for Microbiology
- Regulators Affairs Pharmaceuticals Certificate (RAPS)

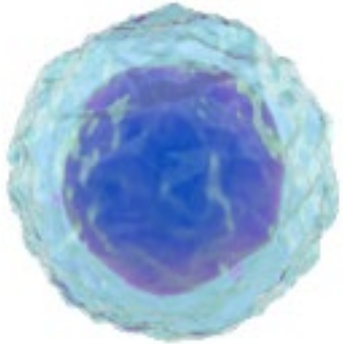
Agenda

- The current state of gene therapy research
- Intro to the science of gene therapy
- Risks
- Collaboration between the IRB and IBC
- Considerations for research ethics
  - FDA guidance on integrating vectors, gene editing and long term follow up
  - FDA guidance on decentralized clinical trials

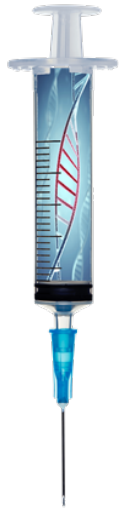
The Current State of Gene Therapy Research

Types of Gene Therapy Approaches

Gene Modified Cellular Therapy

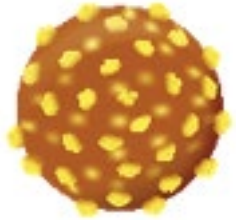


Genetic Vaccines

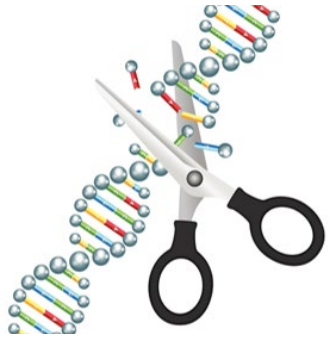


Gene Transfer

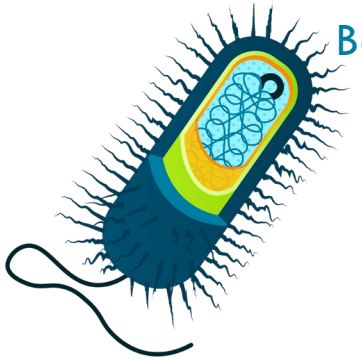
Oncolytics: Reprogramming viruses to kill cancer

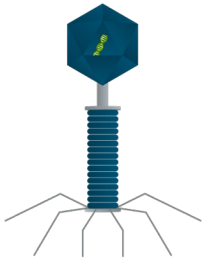


Gene Editing



Gene Modified Bacteria or Phages

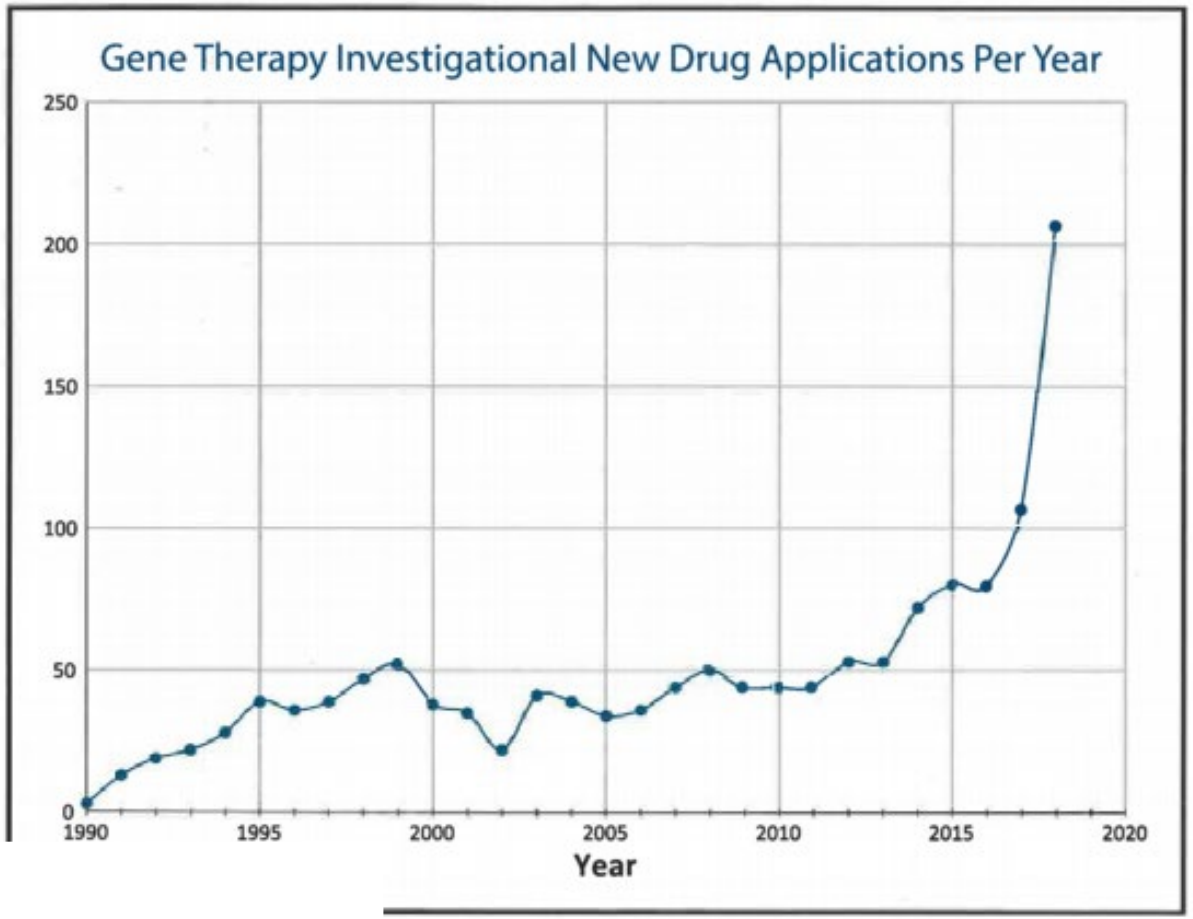




Sources: istockphoto.com/vector/shapes-of-viruses-gm507687357-45561846; Sarah Bowman

Applied Biosafety

www.absa.org Volume 24, Number 3, September 2019



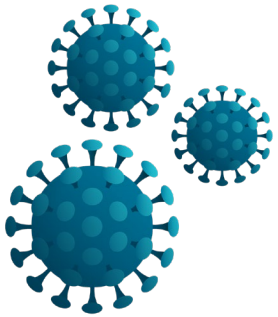
Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER)

Source: Eisenman, *Applied Biosafety,* 2019

Recent FDA Approvals: Gene Therapy Is No Longer Science Fiction

FDA approved products containing recombinant or synthetic nucleic acids

Oncology
8



Infectious Disease
***8**

Rare Disease
11

*1 Emergency Use Authorization for a COVID-19 Vaccine
Includes Moderna RSV vaccine, May 2024

FDA Approved Products Comprised of Viral Vectors

Name	Manufacturer	Indication	Recombinant DNA	Approval Date
IMLYGIC	Amgen	Melanoma	**Herpes simplex virus 1** based oncolytic therapy, expressing GM-CSF	October 2015
LUXTURNA	Spark Therapeutics	Retinitis Pigmentosa	**Adeno associated virus (AAV)** vector delivering RPE65	December 2017
DENGVAXIA	Sanofi Pasteur	Dengue serotypes 1-4	**Yellow fever 17D204 vaccine strain** encoding pre- membrane (prM) and envelope (E) proteins from dengue 1-4	May 2019
ZOLGENSMA	Novartis	Spinal Muscular Atrophy	**Adeno associated virus (AAV)** vector delivering the *SMN1* gene	May 2019
ERVEBO	Merck	Ebola vaccine	**Vesicular stomatitis virus (VSV)** based vector, Ebola Zaire glycoprotein (rVSVΔG-ZEBOV-GP)	December 2019
*Janssen COVID-19 Vaccine	Janssen Vaccines (Johnson & Johnson)	COVID-19	**Replication deficient adenovirus** encoding SARS-CoV-2 spike protein	*February 2021
HEMGENIX	CSL Behring LLC	Hemophilia B	**Adeno associated virus (AAV)** vector delivering Factor IX	November 2022
Adstiladrin	Ferring	High-risk (BCG)-unresponsive non-muscle-invasive bladder cancer	**Replication deficient adenovirus** encoding IFN-α2b	December 2022
Vyjuvek	Krystal Biotech	Dystrophic epidermolysis bullosa (DEB)	**Herpes simplex virus 1** based vector, collagen type VII alpha 1 chain (COL7A1) gene.	May 2023
Roctavian	BioMarin Pharmaceutical	Hemophilia A	**Adeno associated virus (AAV)** vector delivering Factor VIII	June 2023
Elevidys	Sarepta	Duchene Muscular Dystrophy	**Adeno associated virus (AAV)** vector delivering micro-dystrophin	June 2023
Lyfgenia	Bluebird Bio Inc.	Sickle cell disease	**Lentivirus** based transduction of blood stem cells to produce HbAT87Q, a gene-therapy derived hemoglobin that functions similarly to hemoglobin A	December 2023
BEQVEZ	Pfizer	Hemophilia B	**Adeno associated virus (AAV)** vector delivering Factor IX	April 2024

*Emergency Use Authorization for COVID-19 Vaccine

FDA NEWS RELEASE

FDA Launches Pilot Program to Help Further Accelerate Development of Rare Disease Therapies

For Immediate Release: September 29, 2023

Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program

Source: https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-further-accelerate-development-rare-disease-therapies

FDA's Operation Warp Speed for Rare Disease

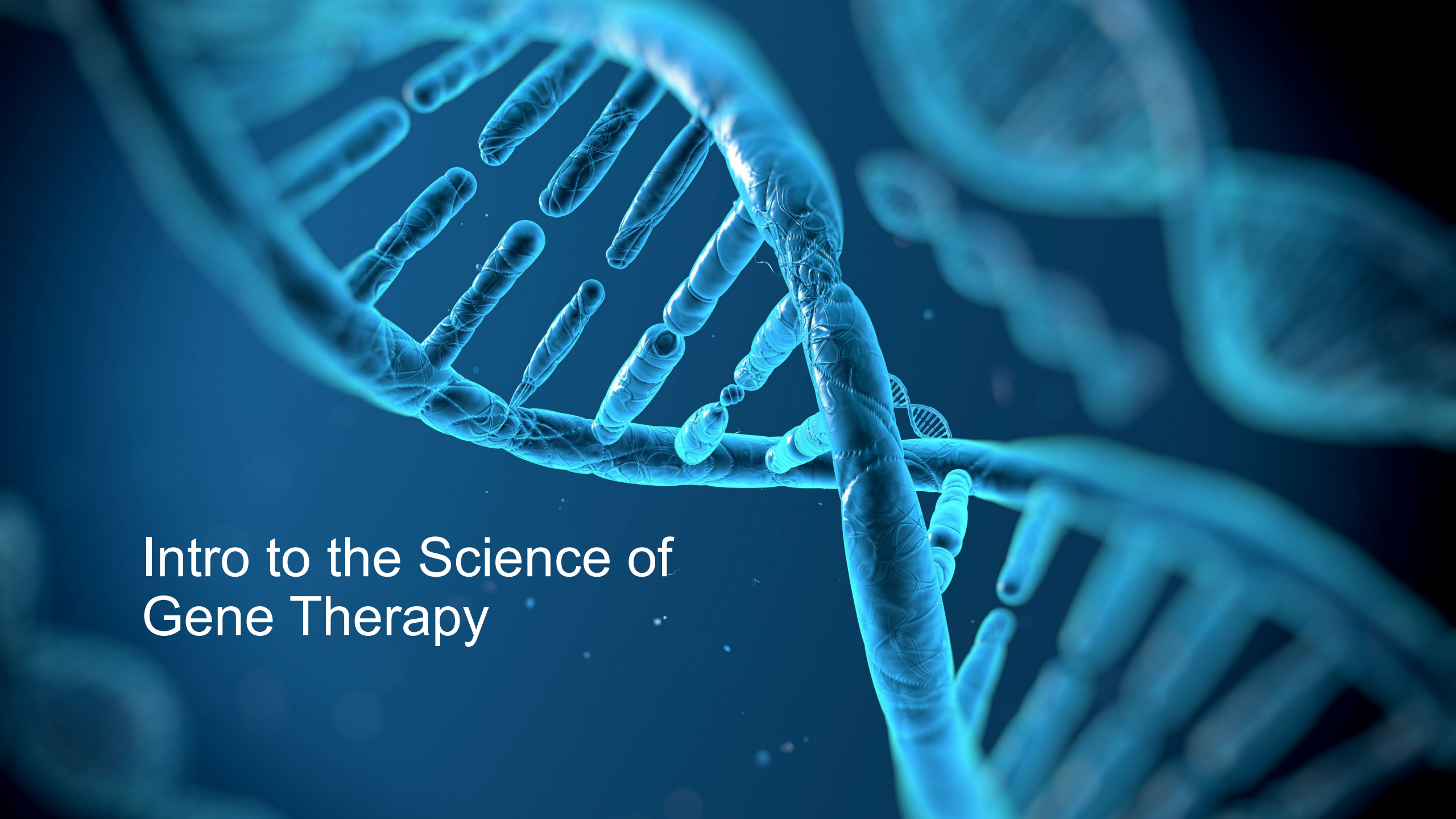
- Guidance and accelerated approval pathways
- Bespoke model

"I think it would be a shame if all we manage to do, every year in the next few years, is approve another two or three gene therapies—that's a failure," he said.
"Success would be that we start to watch what should be, if not exponential, at least some logarithmic progression here toward more and more gene therapies being approved."

Peter Marks
Director, FDA Center for Biologics Evaluation and Research (CBER)

https://www.biospace.com/article/cber-to-launch-operation-warp-speed-for-rare-diseases-by-year-s-end/

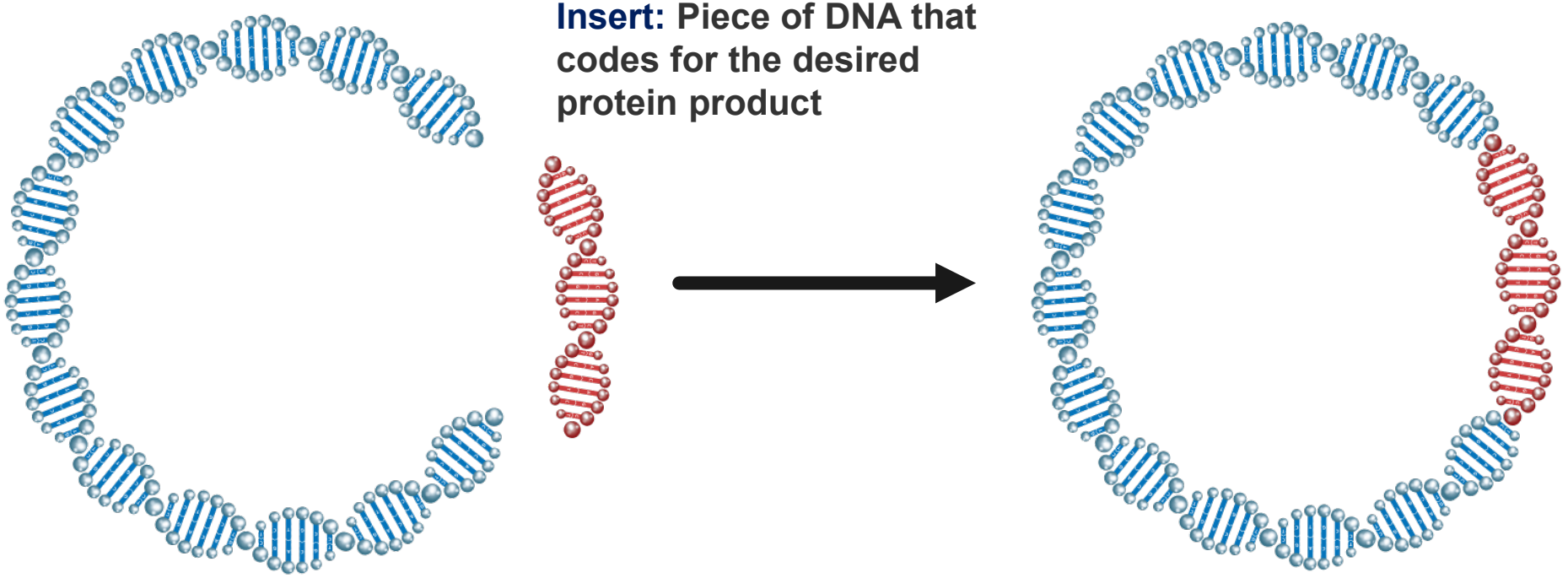
Source: Phillip Pessar via Wikimedia Commons/Creative Commons



Intro to the Science of Gene Therapy

Definition of Recombinant Nucleic Acid Molecules

(i) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids;

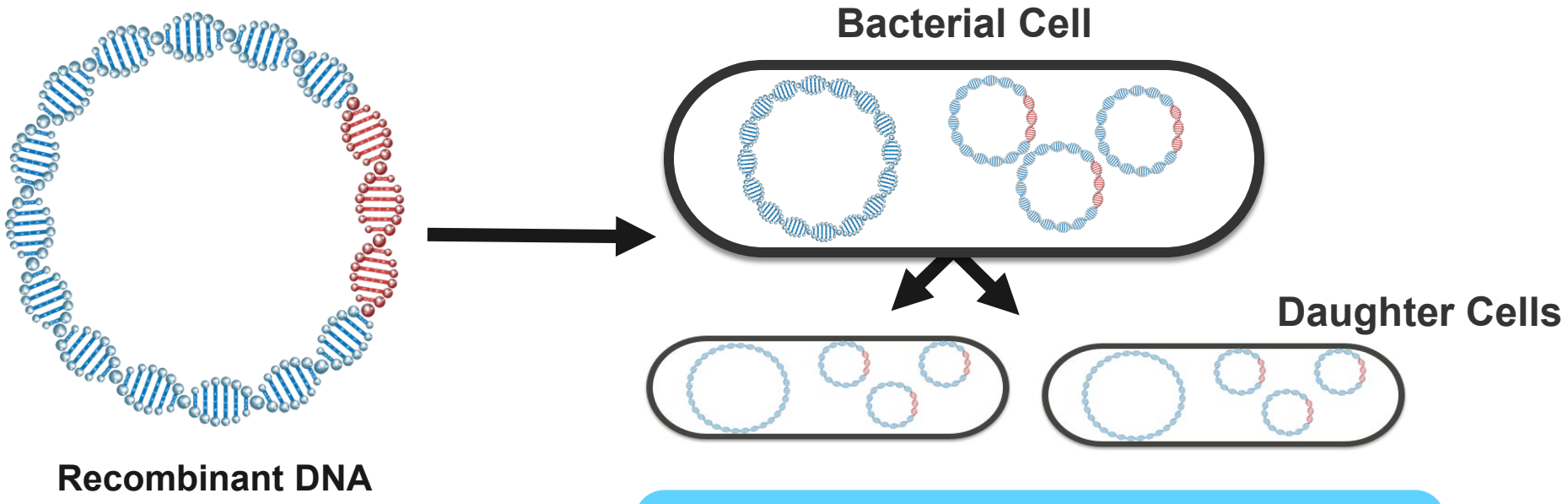


Insert: **Piece of DNA that codes for the desired protein product**

Vector
Vehicle for delivering DNA to cells

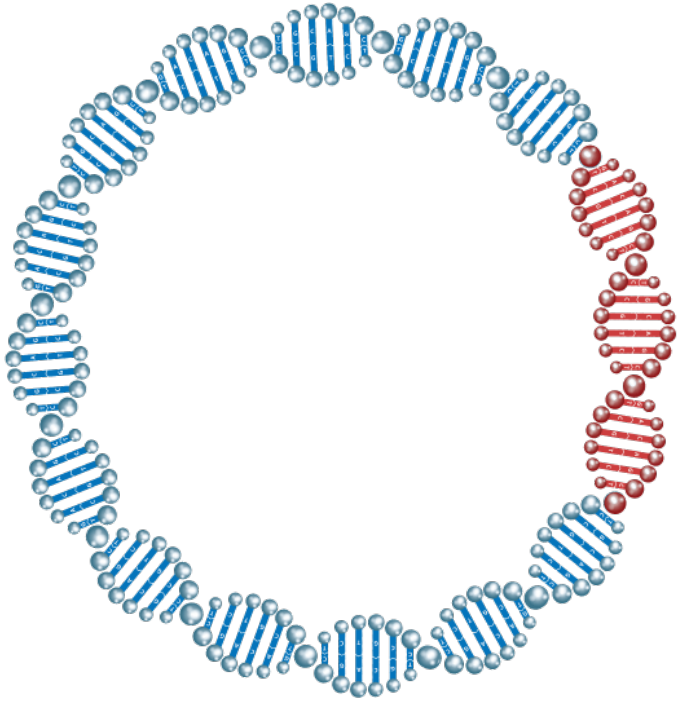
Recombinant DNA

Recombinant DNA Replicates Once Inside Living Organisms



New copies of the Recombinant DNA from the Parent Cell are inherited by the Bacterial Clones' "Daughter Cells"

Looking to Nature for Better DNA Delivery Vehicles



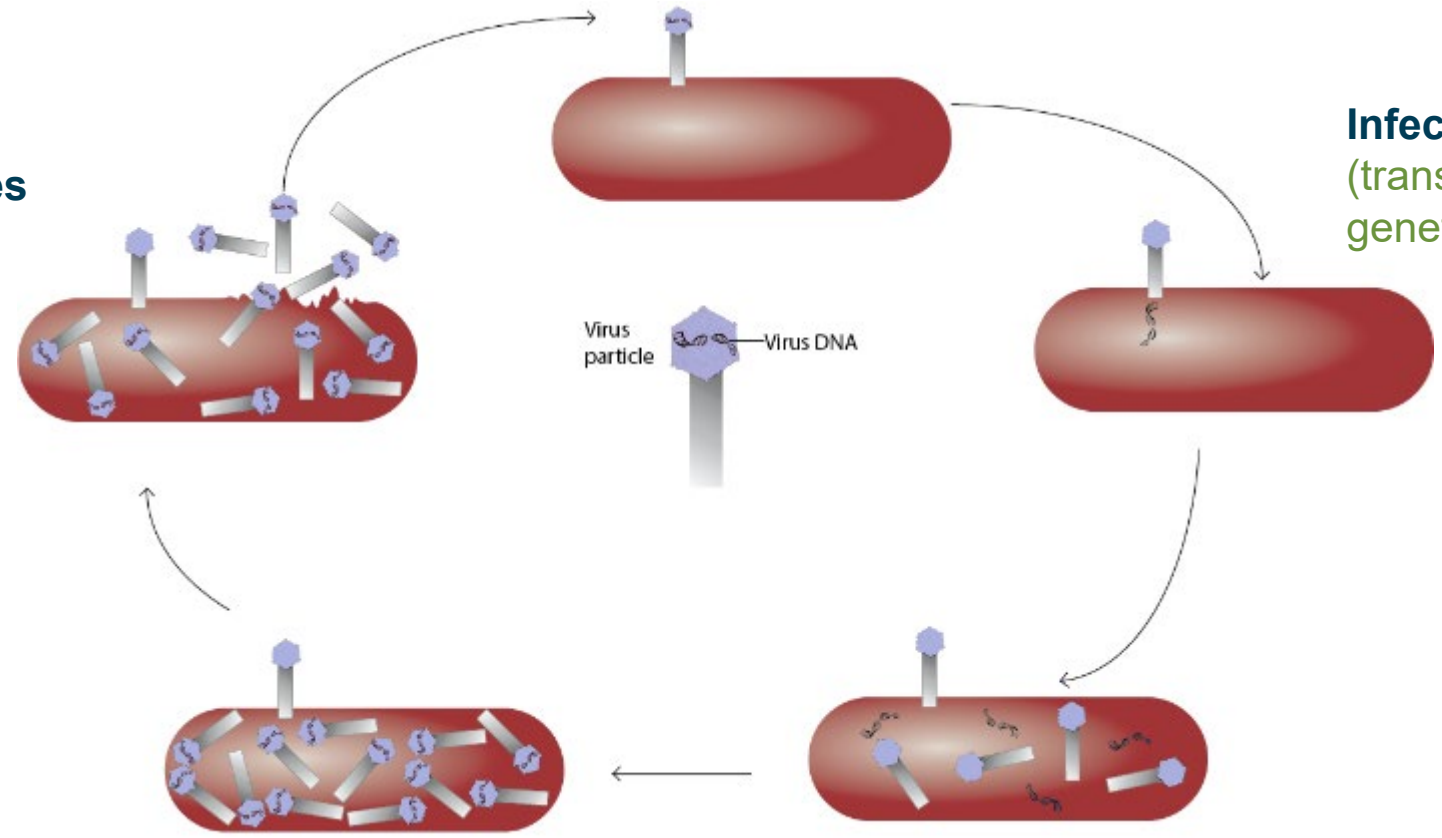
Recombinant DNA

Viral Life Cycle

Attachment

Release of Viral Particles (cell death)

Infection (transmission of genetic material)



Assembly of Viral Particles

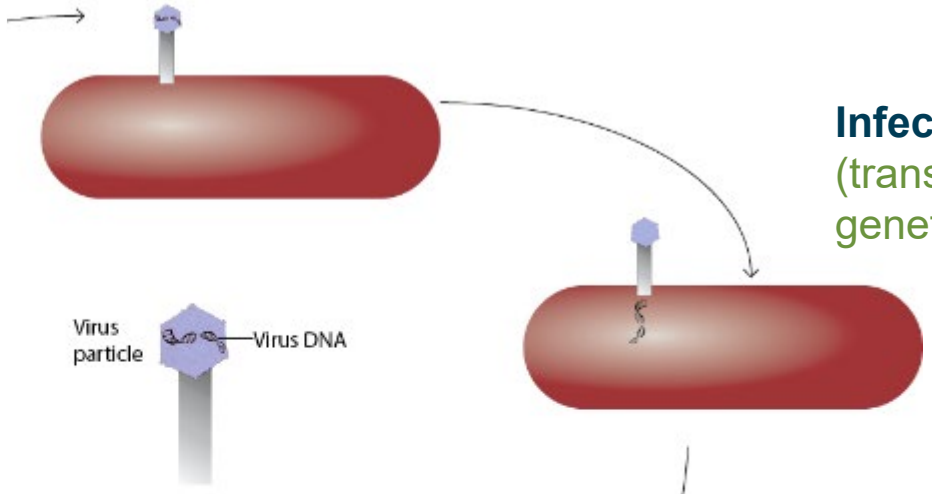
Production of Viral Components

Sources: istock.com/Rtimages; istock.com/Rost-9D

Viral Life Cycle

DNA loaded syringe

Attachment

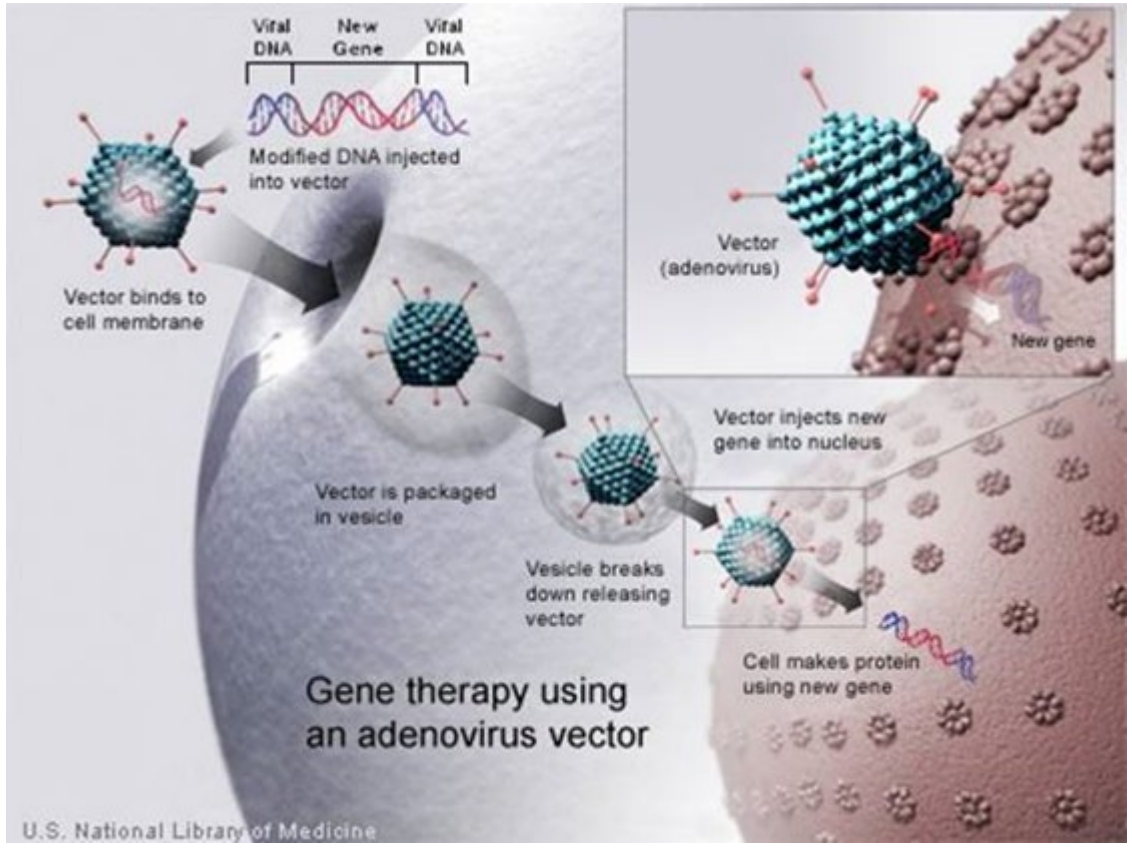


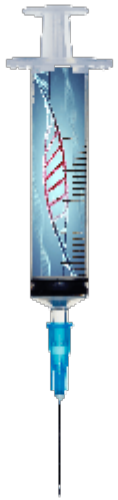
Infection
(transmission of genetic material)

Sources: istock.com/Rtimages; istock.com/Rost-9D

Viral Vectors: A Genetic “Syringe”

Virus vectors easily introduce genetic material into target cells during infection. Disease-causing genes are removed and replaced with genes of interest.





DNA loaded syringe

Sources: istock.com/Rtimages; istock.com/Rost-9D

Viruses Are Diverse!

Animal virus families possess varying properties as well as potential uses and risks

RNA

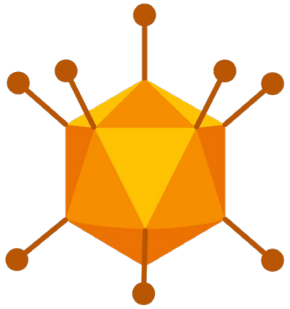
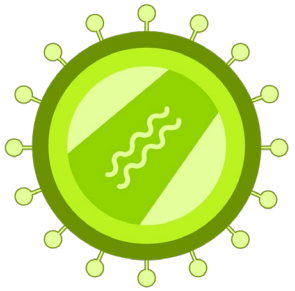
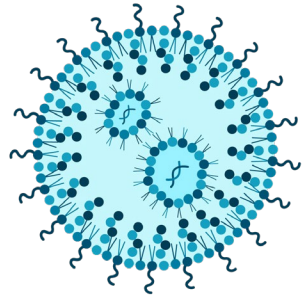
Symmetry of capsid	Naked or enveloped	Genome architecture	Baltimore class	Image	Family name	Virion polymerase	Virion diameter (nm)	Genome size (total in kb)
Icosahedral	Naked	ds 10-18 seg.	III		Reo	(+)	60-80	22-27
		ds 2 seg.	III		Birna	(+)	60	7
		(+) ss cont.	IV		Calci	(-)	35-40	8
		(+) ss cont.	IV		Picorna	(-)	28-30	7.2-8.4
	Enveloped	(+) ss cont.	IV		Flavi	(-)	40-50	10
		(+) ss cont.	IV		Toga	(-)	60-70	12
		(+) ss cont.	IV		Retro	(+)	80-130	3.5-9
Helical	Enveloped	(+) ss cont.	IV		Corona	(-)	80-160	16-21
		(-) ss cont.	V		Filo	(+)	80 x 790-14,000	12.7
		(-) ss cont.	V		Rhabdo	(+)	70-85 x 130-380	13-16
		(-) ss 3 seg.	V		Bunya	(+)	90-120	13.5-21
		(-) ss 8 seg.	V		Ortho-myxo	(+)	90-120	13.6
		(-) ss cont.	V		Para-myxo	(+)	150-300	16-20
		(-) ss 2 seg.	V		Arena	(+)	50-300	10-14

DNA

Symmetry of capsid	Naked or enveloped	Genome architecture	Baltimore class	Image	Family name	Virion polymerase	Virion diameter (nm)	Genome size (total in kb)
Icosahedral	Naked	ss linear (+) or (-)	II		Parvo	(-)	18-26	5
		ds circular	I		Papova	(-)	45-55	5-8
		ds linear	I		Adeno	(-)	70-90	36-38
	Enveloped	ds circle gapped	I		Hepadna	(+)	42	3.2
		ds linear	I		Herpes	(-)	150-200	120-200
	Naked/Env. (cytoplasmic)	ds linear	I		Irido	(-)	125-300	150-350
Helical	Enveloped	ds circular	I		Baculo	(-)	60 x 300	100
Complex	Enveloped (Cytoplasmic)	ds linear (x linked)	I		Pox	(+)	170-200 x 300-450	130-280

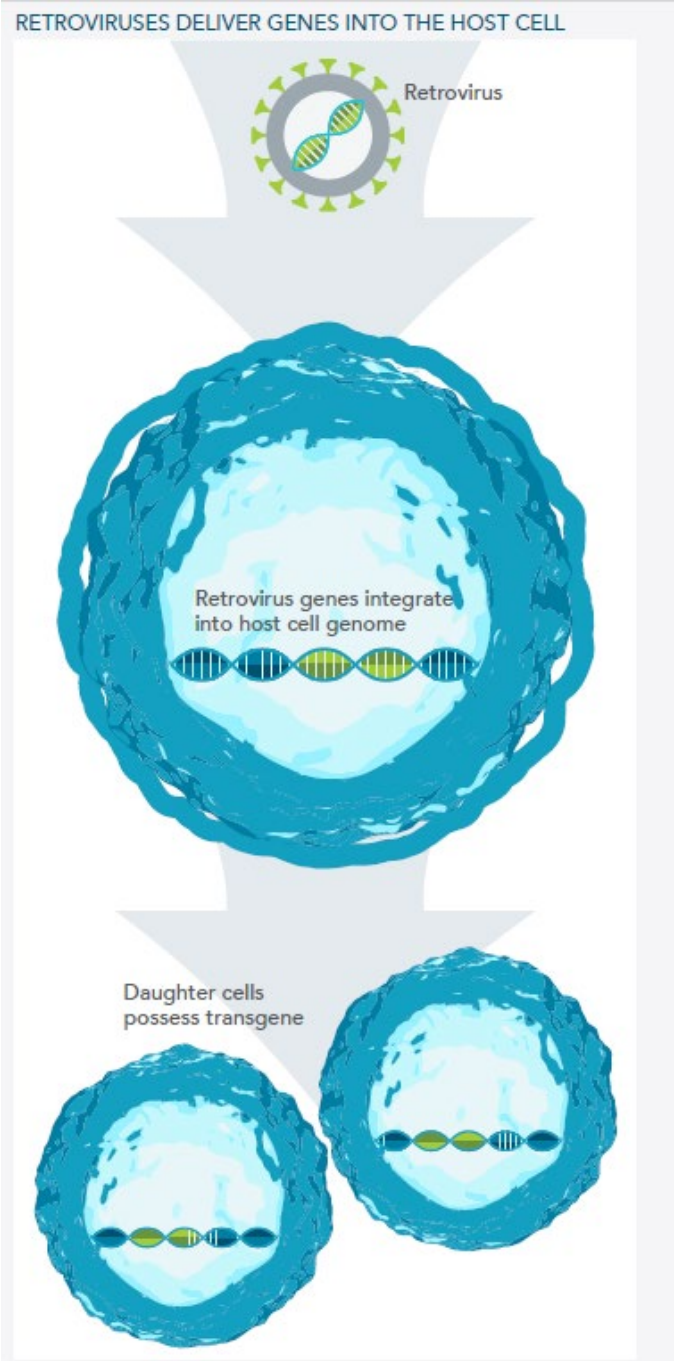
Diverse risks lead to diverse possibilities for toxicities

Overview of Common Vectors

		Adenovirus (Ad)	Adeno-associated virus (AAV)	Retrovirus (RV)	Lipid Nanoparticle (LNP)
					
1	Integrates into cellular DNA?	No genomic integration	No genomic integration	**Genomic integration**	No genomic integration
2	Expression diluted in dividing cells?	Yes	Yes	**No**	Degrades within a few hours
3	Immunogenicity	**High Immunogenicity**	Moderate Immunogenicity	Moderate Immunogenicity	Low Immunogenicity
	Clinical Trial	Yes	Yes	Ex Vivo	Yes

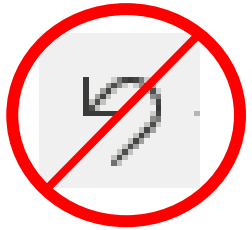
Benefits of Genomic Integration

- Permanently inserted into cellular DNA
- The transgene is passed on during cellular growth
- Beneficial for cells that require proliferation (e.g. CAR T cells and stem cells.)



Shown: Retrovirus genomes permanently integrating into a host cell's DNA and being transferred into future generations.

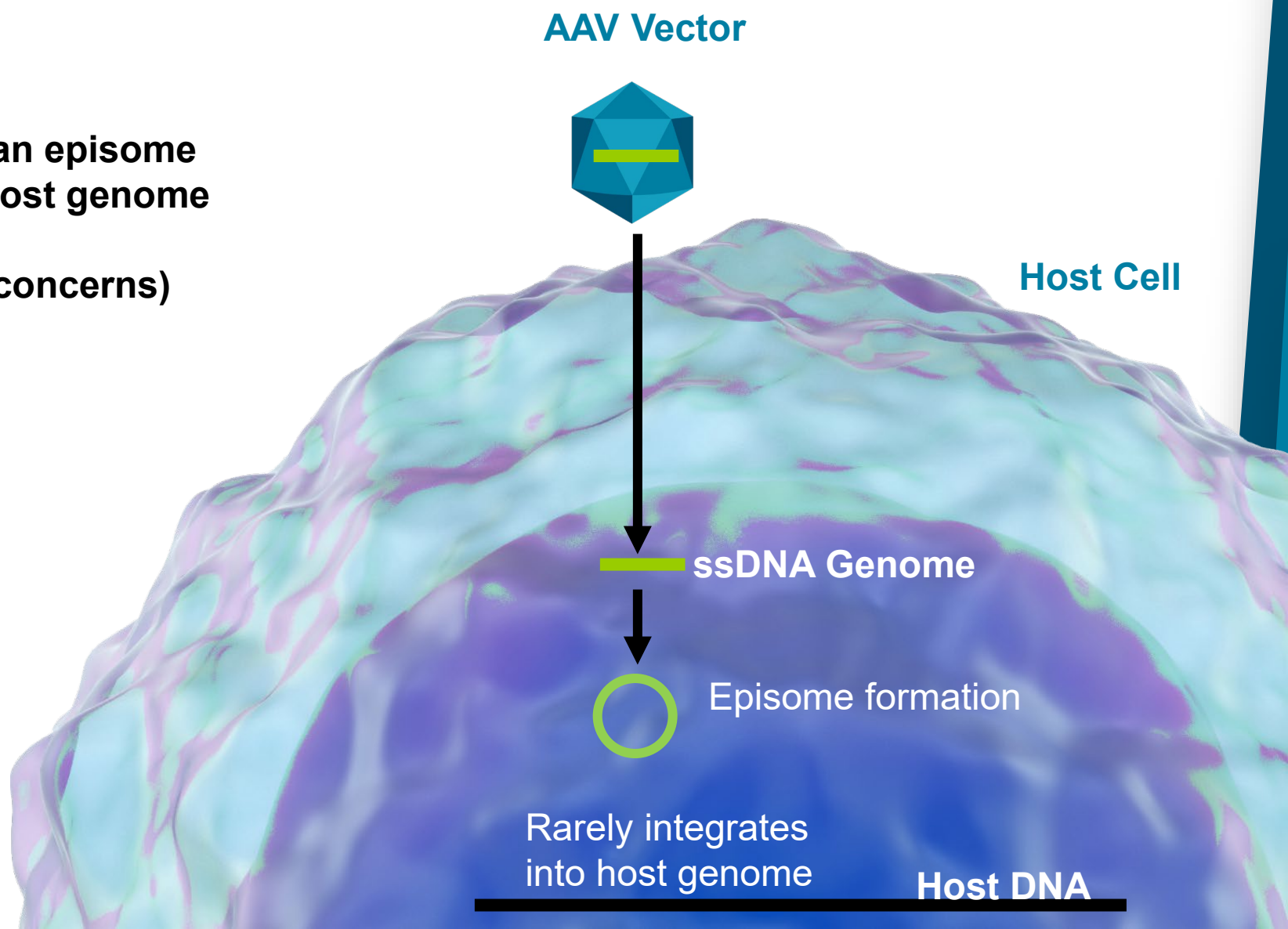
Risks of Genomic Integration

- Permanent (No Undo button) 
- Random insertion into cellular DNA
- Insertion into gene sequences can cause mutation or increase cancer risk
- Requires Long term follow up

Essentials of Adeno-Associated Virus (AAV) Vectors

- Considered Risk Group 1 (safest)
- Upon infection, the viral DNA forms an episome (circle), which rarely integrates into host genome
- Moderately immunogenic (redosing concerns)
- Commonly used for gene therapy

- Can be concentrated and administered at ultra-high doses (e.g. 10^{14} vector genomes / kg)
- Toxicities reported at high doses in subjects with pre-existing conditions.



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Essentials of Adeno-Associated Virus (AAV) Vectors

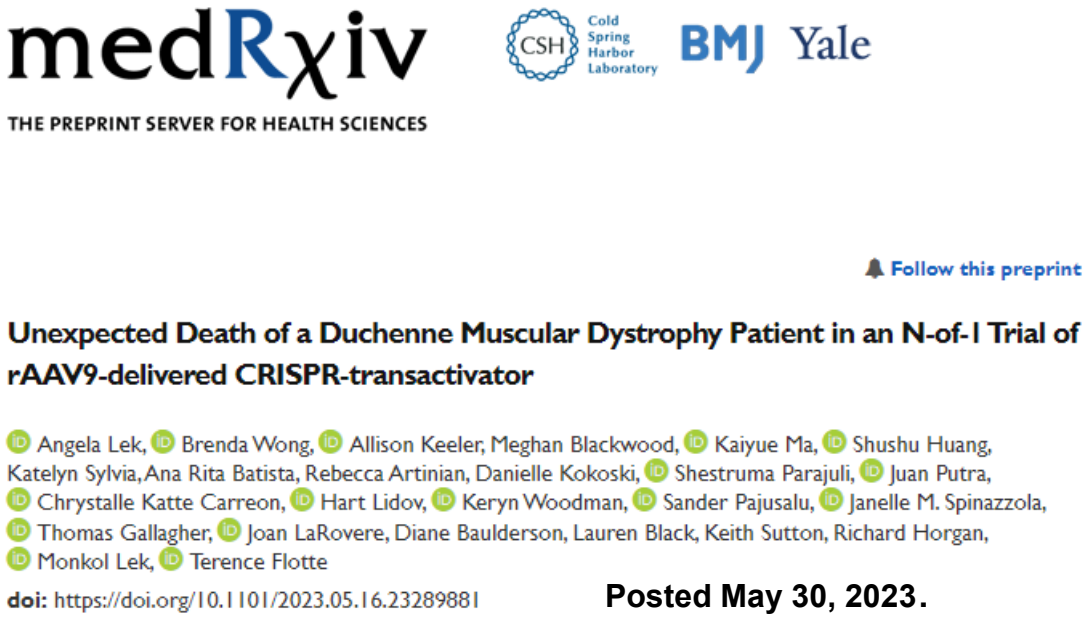
- **Can be concentrated and administered at ultra-high doses (e.g. 10^{14} vector genomes / kg)**
- **Toxicities reported at high doses in subjects with pre-existing conditions.**

After gene therapy deaths, Astellas brings in potentially safer treatment for muscle disorder

Astellas Pharma said Thursday it will license and develop a new gene therapy for a devastating muscle disorder, after four boys died in a clinical trial testing an earlier treatment.

The hope is that the new therapy will allow researchers to treat the disease, known as X-linked myotubular myopathy, or XLMTM, with much lower doses of the viruses used to shuttle genes into patients' cells. In theory that should minimize the risk of severe side effects.

https://www.statnews.com/2023/06/08/xlmtm-gene-therapy-astellas-pharma/



Posted May 30, 2023.

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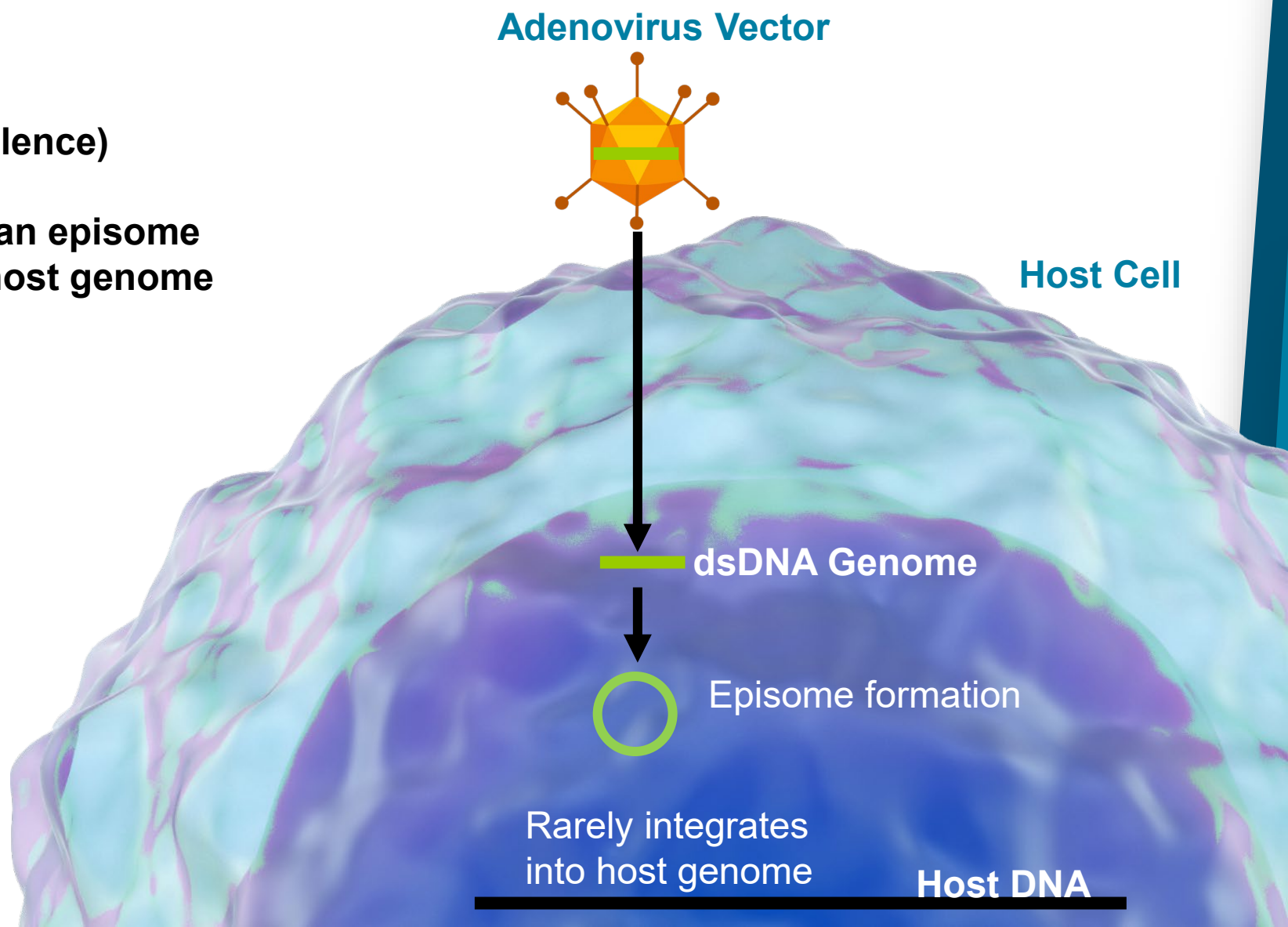
Essentials of Adenovirus Vectors

- Considered Risk Group 2 (some virulence)
- Upon infection, the viral DNA forms an episome (circle), which rarely integrates into host genome
- Adenovirus is highly immunogenic



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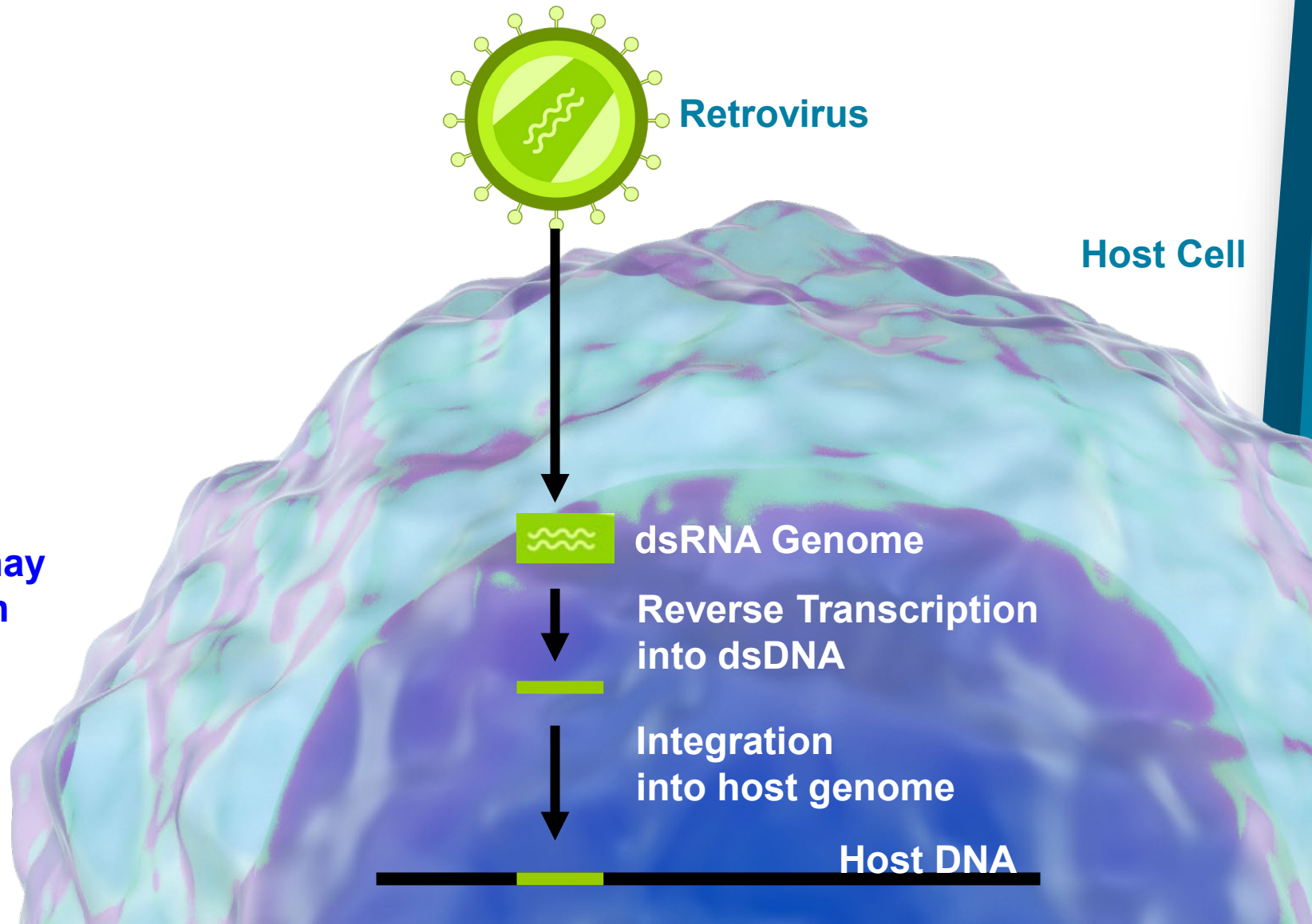
Essential Information for Retroviruses and Associated Vectors

- **Considered Risk Group 2 (some virulence)**
- **Genomic integration**
- **Stable transmission to all future cellular progeny**
- **Frequently used for *ex vivo* gene transfer to manufacture cellular therapies (e.g. CAR T cells)**

Random integration of viral genome may disrupt host genes. Of special concern Is disruption of genes involved in cell growth, which can lead to increased cancer risk.



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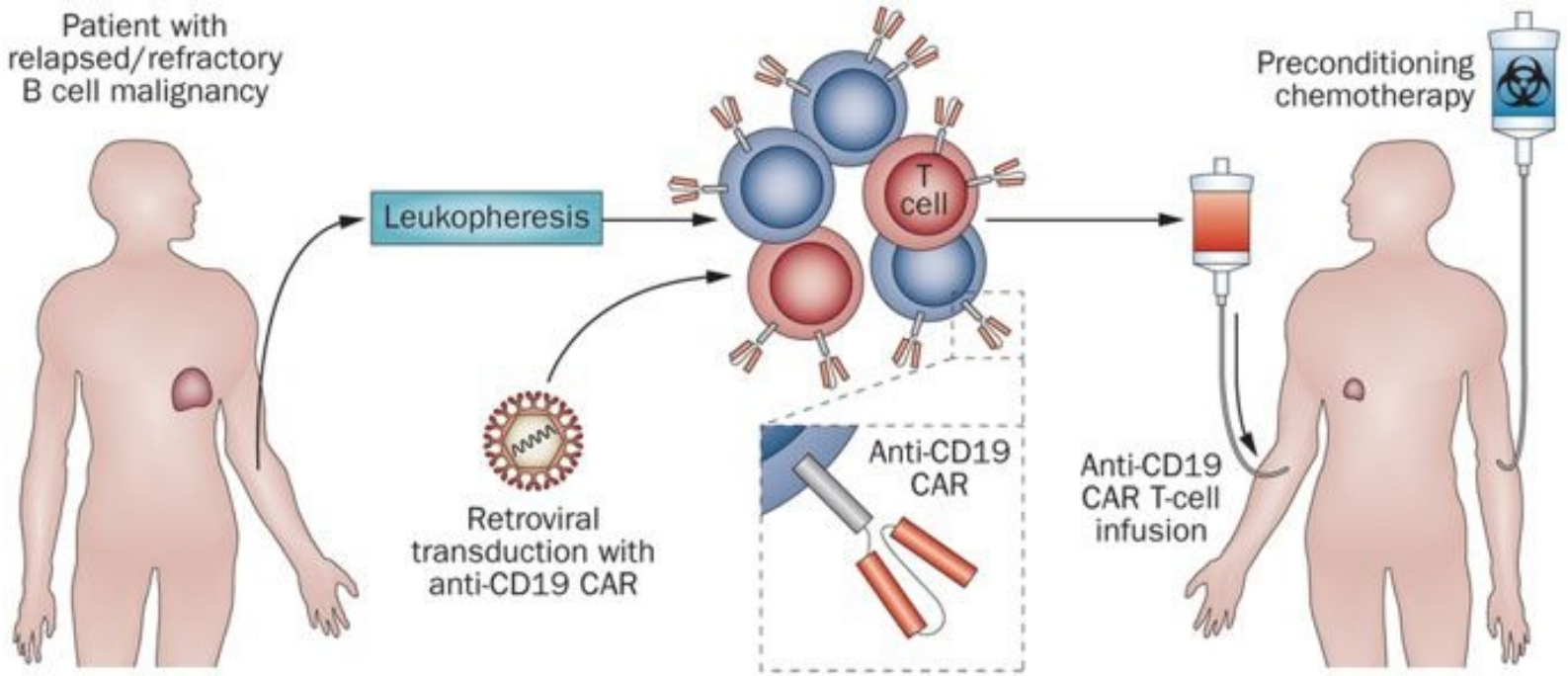
Approval of gene therapies for two blood cancers led to an 'explosion of interest' in 2017

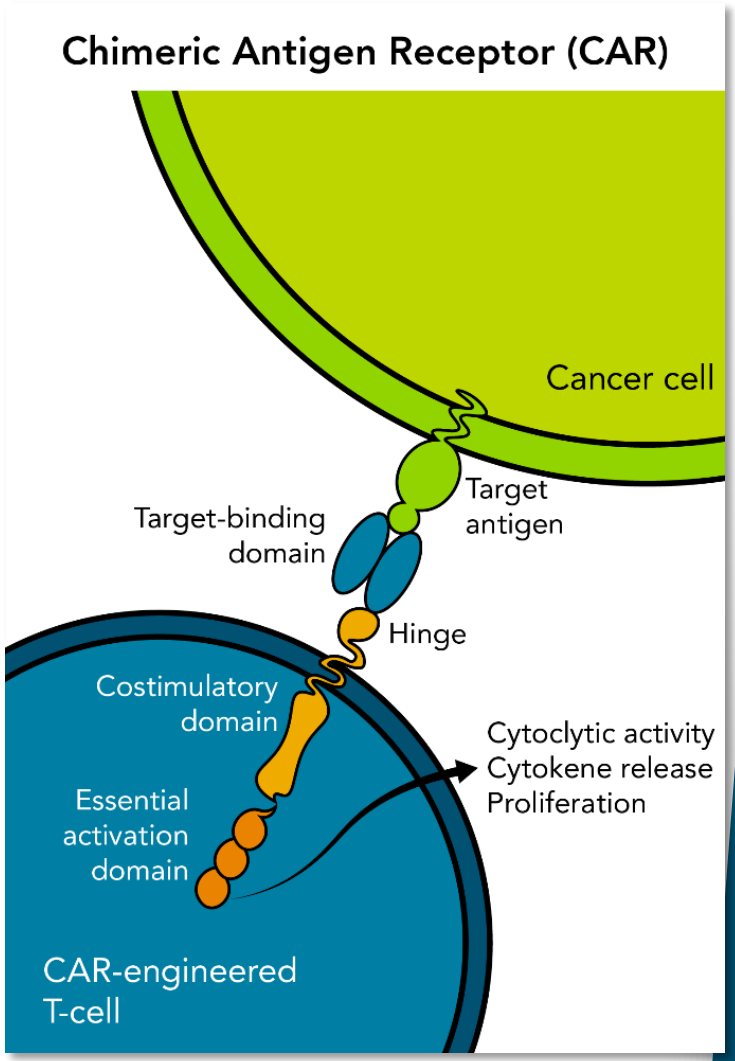
CAR-T cell therapy treats patients for whom other therapies haven't worked

BY LAUREL HAMERS 8:27AM, DECEMBER 13, 2017

https://www.sciencenews.org/article/car-t-cell-gene-therapy-top-science-stories-2017-yir



Nature Reviews Clinical Oncology **volume 11**, pages 685–686 (2014)



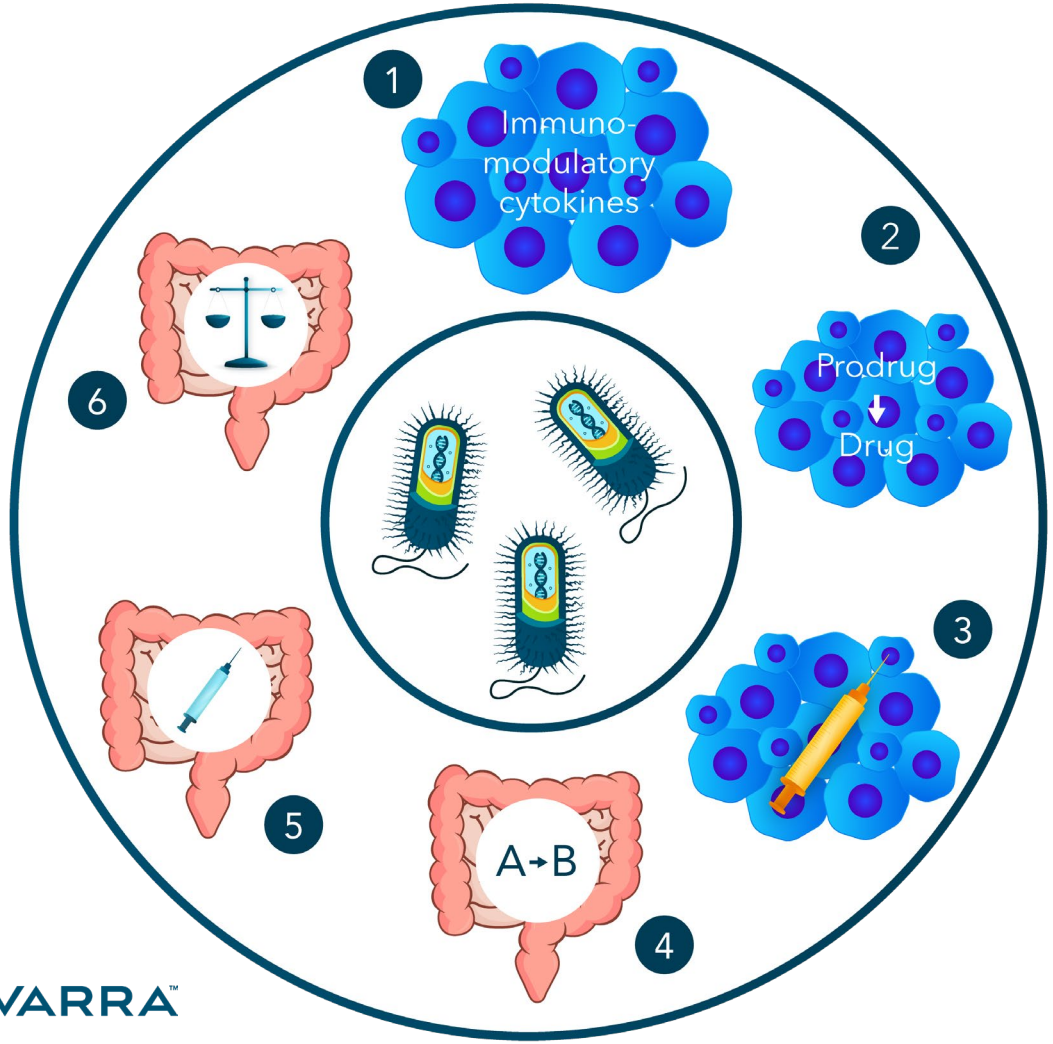
Applied Biosafety > Ahead of Print

Review Article | OPEN ACCESS | Published Online: 8 May 2024

A Review of Clinical Trials Involving Genetically Modified Bacteria, Bacteriophages and Their Associated Risk Assessments

Authors: Paul Gulig, Scott Swindle, Mark Fields, and Daniel Eisenman | AUTHORS INFO & AFFILIATIONS

Publication: Applied Biosafety • https://doi.org/10.1089/apb.2024.0002



In Tumors

1. Production of immune modulatory cytokines
2. Conversion of prodrugs to active drugs
3. Production of tumor antigens

In GI Tract

4. Expression of enzymes
5. Expressing antigens in the gut
6. Correcting microbial imbalance (dysbiosis)

Publication: Applied Biosafety
https://doi.org/10.1089/apb.2024.0002

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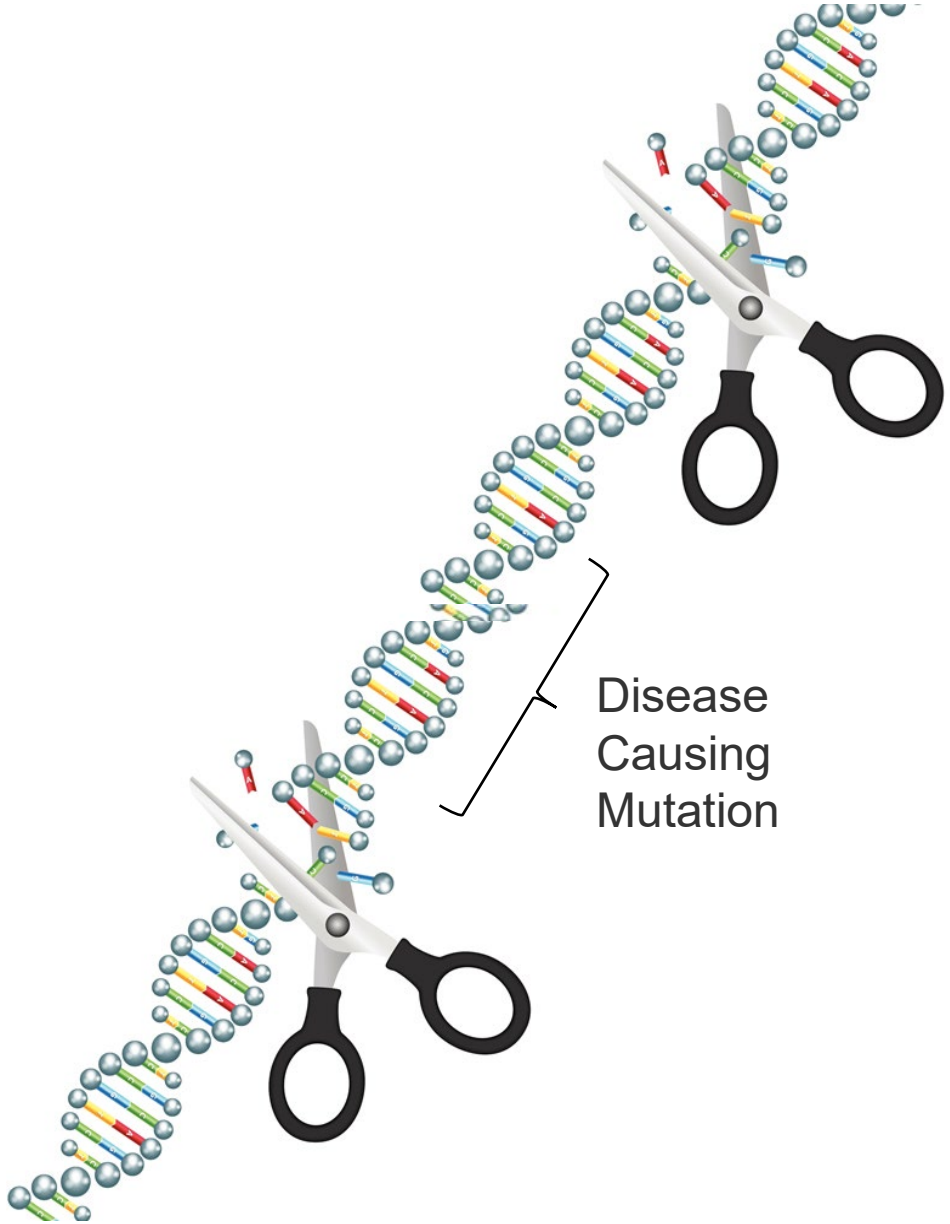
Gene Editing

Chemically Synthesized

Bind to genetic material or reproduce

Common uses include **genome editing technology** in viral vectors (e.g., TALEN, ZFN, CRISPR)



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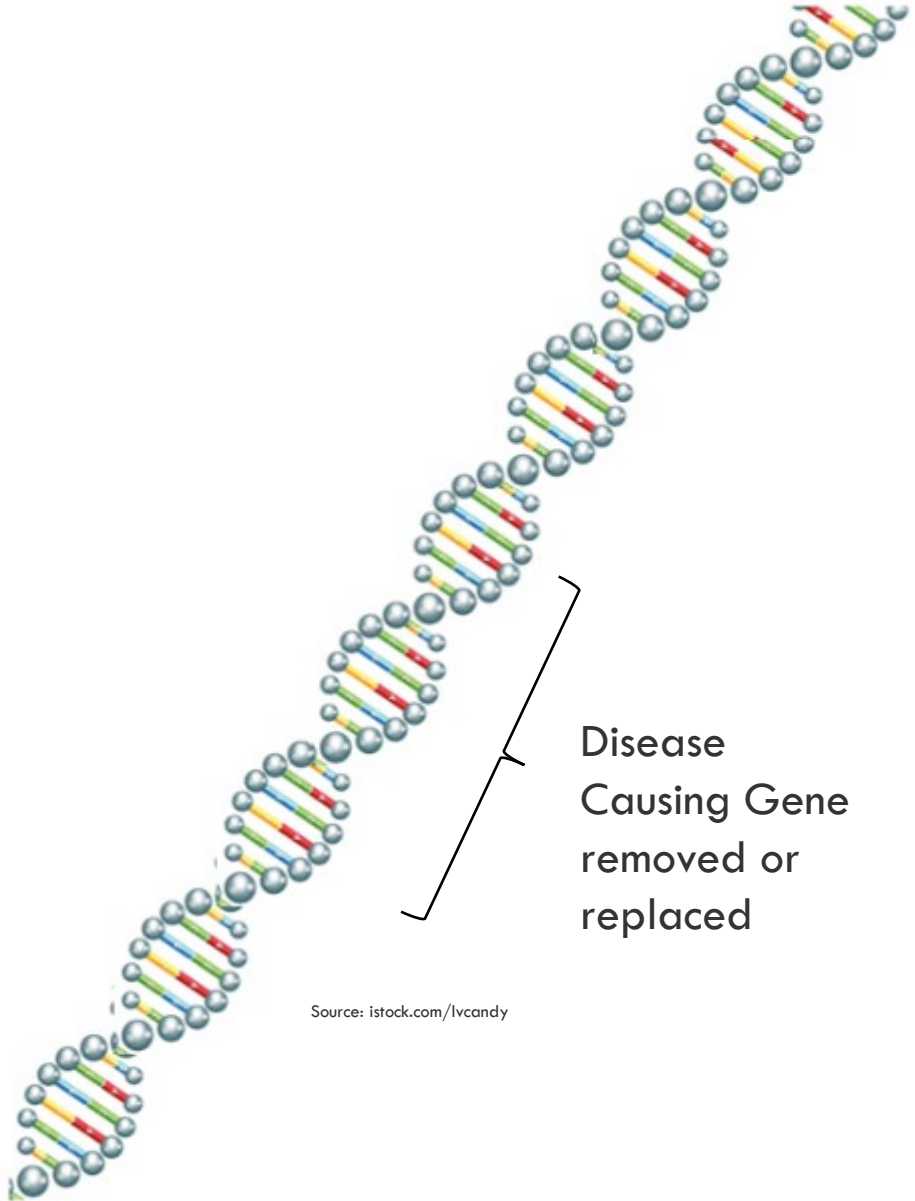

Source: istock.com/Ivcandy

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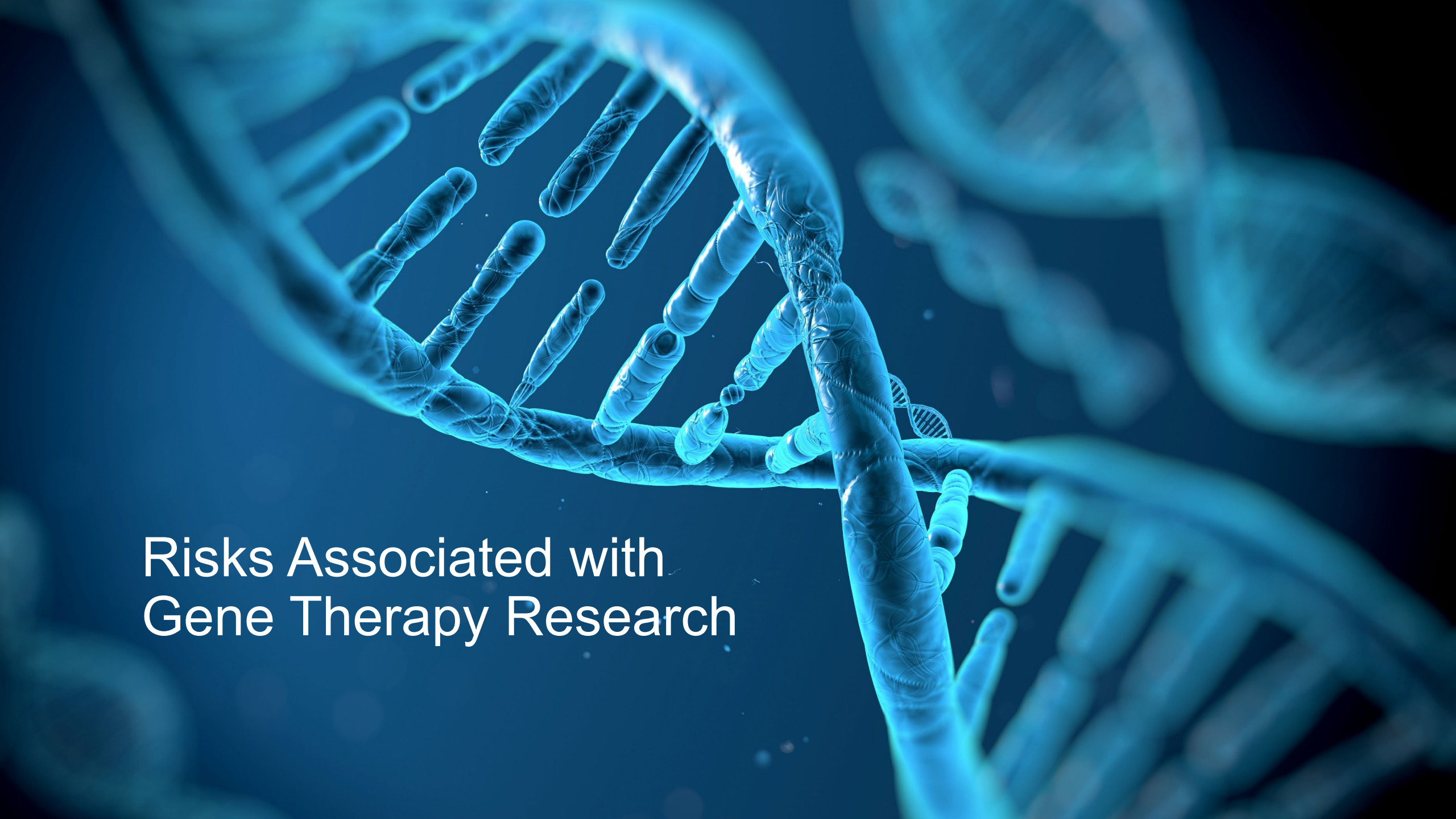


Risks Associated with Gene Therapy Research

Applied Biosafety

www.absa.org Volume 24, Number 3, September 2019

The Biotech Death of Jesse Gelsinger

By SHERYL GAY STOLBERG NOV. 28, 1999 The New York Times Magazine

Gene Therapy Death Prompts Review of Adenovirus Vector

Eliot Marshall

+ See all authors and affiliations

Science 17 Dec 1999:
Vol. 286, Issue 5448, pp. 2244-2245
DOI: 10.1126/science.286.5448.2244

nal New D

FDA halts gene therapy trials after leukaemia case in France

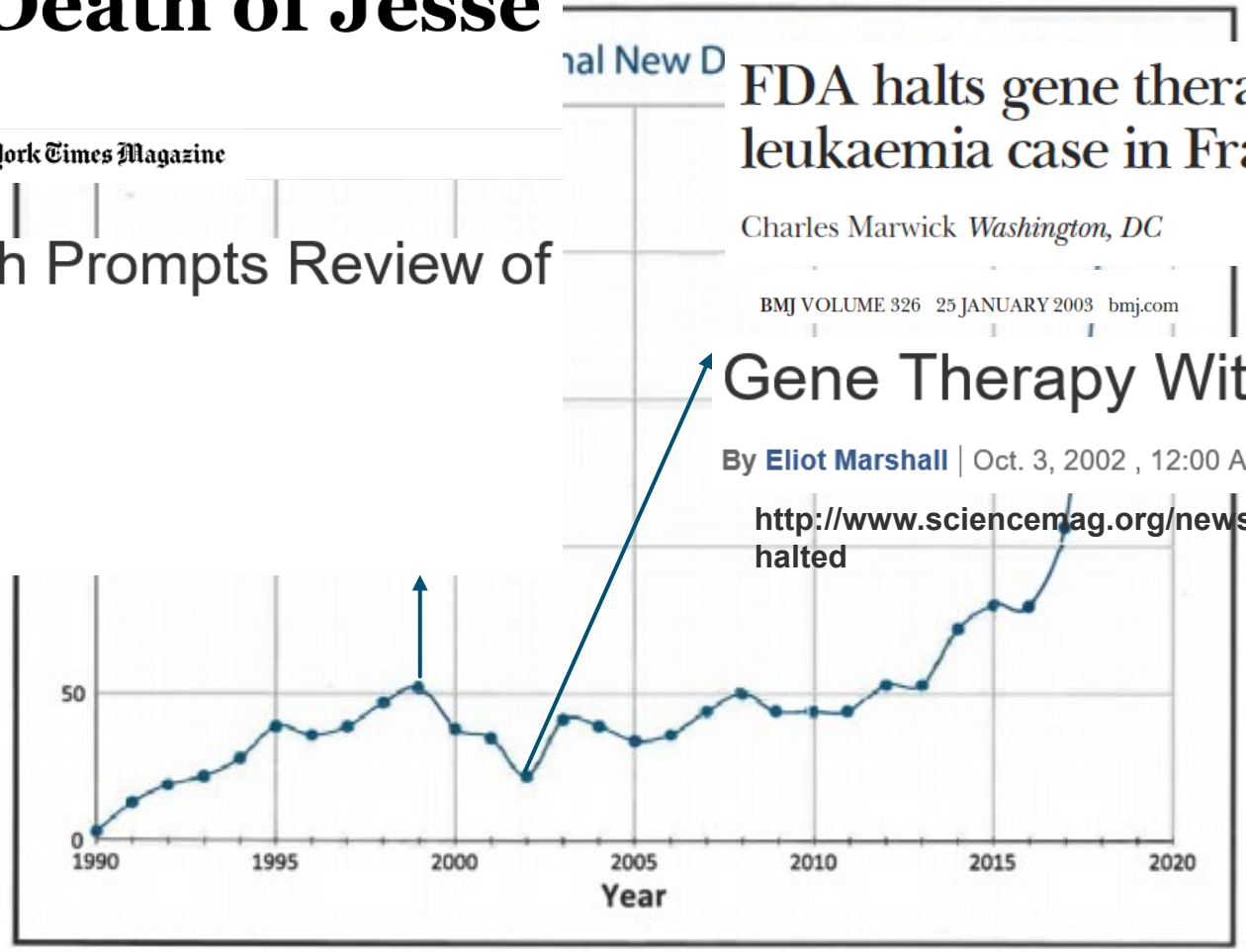
Charles Marwick *Washington, DC*

BMJ VOLUME 326 25 JANUARY 2003 bmj.com

Gene Therapy With Retroviruses Halted

By **Eliot Marshall** | Oct. 3, 2002 , 12:00 AM

http://www.sciencemag.org/news/2002/10/gene-therapy-retroviruses-halted



Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER)

Source: Eisenman, *Applied Biosafety,* 2019

Food and Drug Administration Guidance on Design of Clinical Trials for Gene Therapy Products with Potential for Genome Integration or Genome Editing and Associated Long-Term Follow-Up of Research Subjects

Daniel Eisenman* and Scott Swindle

Table 1. Clonal proliferation and malignancies resulting from retroviral insertional mutagenesis

Transduced cell type	*Disease under study*	*Transgene*	*Mechanism*	*Affected gene(s)*	*Serious adverse event*	*Research subjects*	
						No. of SAE	*Total subjects*
HSC	X-linked SCID	IL2Rγ	Gene activation[a]	*LMO2, CCND2, BMI1*	Leukemia[5]	4	9
HSC	X-linked SCID	IL2Rγ	Gene activation[a]	*LMO2*	Leukemia[6]	1	10
HSC	Wiskott–Aldrich Syndrome	WAS	Gene activation[a]	*LMO2*	Leukemia[7]	9	10
HSC	Chronic granulomatous disease	GP91^{phox}	Gene activation[a]	*EVI1*	Myelodysplasia[8]	2	2
CAR T	Chronic lymphocytic leukemia	CD19 CAR	Gene disruption[b]	*TET2*	Clonal proliferation[9]	1	26
HSC	β-thalassemia	β-globin	Gene disruption[c]	*HMGA2*	Clonal proliferation[10]	1	2

The clinical trials listed involved ex vivo transduction of either HSCs or were used to manufacture CAR T cells. The table lists the diseases under the study and the number of research subjects experiencing the serious adverse event listed. Genes affected by insertional mutagenesis are listed as well as the mechanism by which they were affected.

[a]The transcriptional enhancer in the LTRs of the integrated retrovirus activated expression of a nearby proto-oncogene.

[b]Retroviral integration into an intron of the *TET2* gene resulted in expression of a truncated mRNA and inactive form of TET2, a regulator of cellular transcription and proliferation.

[c]Disruption of a microRNA recognition element in the *HMGA2* 3' UTR resulted in expression of a stable mRNA and enhanced HMGA2 expression.

CAR, chimeric antigen receptor; HSC, hematopoietic stem cells; LTR, long terminal repeat; SAE, serious adverse event; SCID, severe combined immunodeficiency.

Appl Biosaf. December 2022; 27(4): 201–209.

U.S. FOOD & DRUG ADMINISTRATION

FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

November 28, 2023

FDA Requires Boxed Warning for Secondary Cancers on CAR-T Therapies

Published: Apr 19, 2024 | By Tristan Manalac

Pictured: FDA signage at its headquarters in Maryland/iStock, ***hapabapa***

The FDA announced on Thursday that it will **officially require an update** to the boxed warnings of CAR-T cell therapies, which should now also alert patients and prescribers to a heightened risk of developing secondary T cell malignancies.

All six commercially available CAR-T therapies will be affected, including Bristol Myers Squibb's Abecma (idecabtagene vicleucel) and Breyanzi (lisocabtagene maraleucel), Johnson & Johnson's Carvykti (ciltacabtagene autoleucel), Novartis' Kymriah (tisagenlecleucel), as well as Gilead's Tecartus (brexucabtagene autoleucel) and Yecarta (axicabtagene ciloleucel).

The FDA will also mandate amendments to other sections of their labels, including the warnings and precautions, postmarketing experience, patient counseling information and medication guide sections.

Patients and clinical trial participants being given these products should also be followed "life-long" for the potential development of secondary T cell cancers, according to the regulator's announcement.

The FDA **first revealed** that it was looking into the potential safety issues of BCMA- or CD19-directed autologous CAR-T therapies in November 2023, noting at the time that it had flagged a "serious risk" of secondary T cell malignancies "in patients treated with several products in the class." These cases were detected from both clinical trials and postmarket reporting.

In January 2024, the regulator **called on CAR-T manufacturers** to implement a class-wide boxed warning to their products, reflecting the increased risk of secondary malignancies. In its letter to the companies, the FDA did not explicitly cite a causal link between the products and the adverse event, though it did note that the secondary cancers could lead to "serious outcomes, including hospitalization and death."

A few days later, two FDA officials **published a perspective piece** in *The New England Journal of Medicine*, revealing more details from its safety probe. The officials revealed they found the CAR transgene in three cases of secondary malignancies, indicating that "the CAR-T product was most likely involved in the development of the T-cell cancer."

The FDA's boxed warning announcement on Thursday comes as CAR-T cell therapies continue to break new ground, demonstrating their potential in more treatment settings and new indications.

https://www.biospace.com/article/fda-requires-boxed-warning-for-secondary-cancers-on-car-t-therapies/

7 children developed blood cancer after Bluebird Bio gene therapy for rare neurological disease

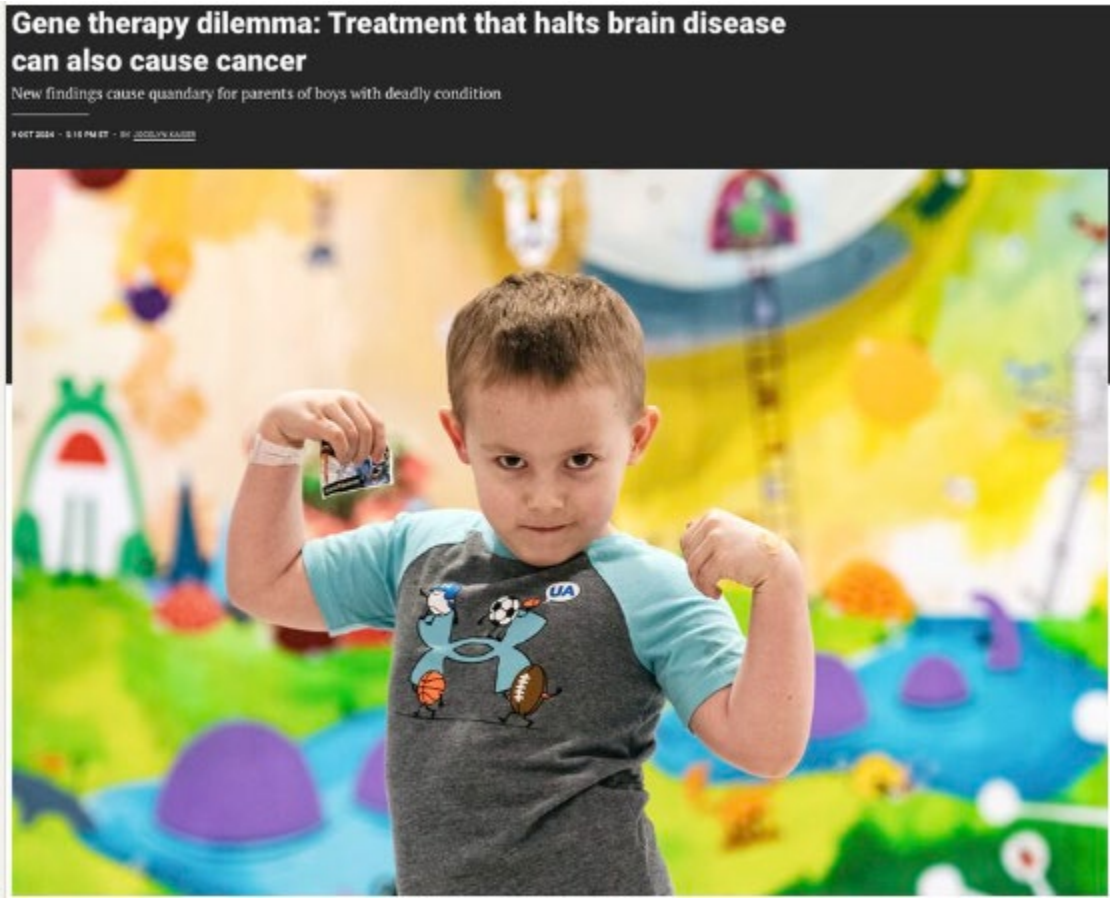
There are few alternative treatments for devastating neurological disorder

https://www.statnews.com/2024/10/09/bluebird-bio-gene-therapy-blood-cancer-children

Out of 67 patients
7 developed blood cancers
1 died

More could develop similar SAEs over time.

"Exactly why Skysona leads to such a profound risk of cancer remains unclear. But it appears to be linked to the particular design of the lentivirus. To ensure the new gene was produced at high levels in several key cells, for example, the lentivirus included instructional elements similar to the older technology that led to leukemia"



https://www.science.org/content/article/gene-therapy-dilemma-treatment-halts-brain-disease-can-also-cause-cancer

FDA News Release

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mu… specific gene

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release December 19, 2017

YEAR IN REVIEW CANCER, IMMUNE SCIENCE, 2017 TOP 10

Approval of gene therapies f… two blood cancers led to an 'explosion of interest' in 2017

CAR-T cell therapy treats patients for whom other therapies haven't worked

BY LAUREL HAMERS 8:27AM, DECEMBER 13, 2017

https://www.sciencenews.org/article/car-t-cell-gene-therapy-top-science-stories-2017-yir

FDA Approves First Oncolytic Virus Therapy

Imlygic for Melanoma

Oncology Times: December 10, 2015 - Volume 37 - Issue 23 - p 36
doi: 10.1097/01.COT.0000475724.97729.9e
FDA Updates

iosafety

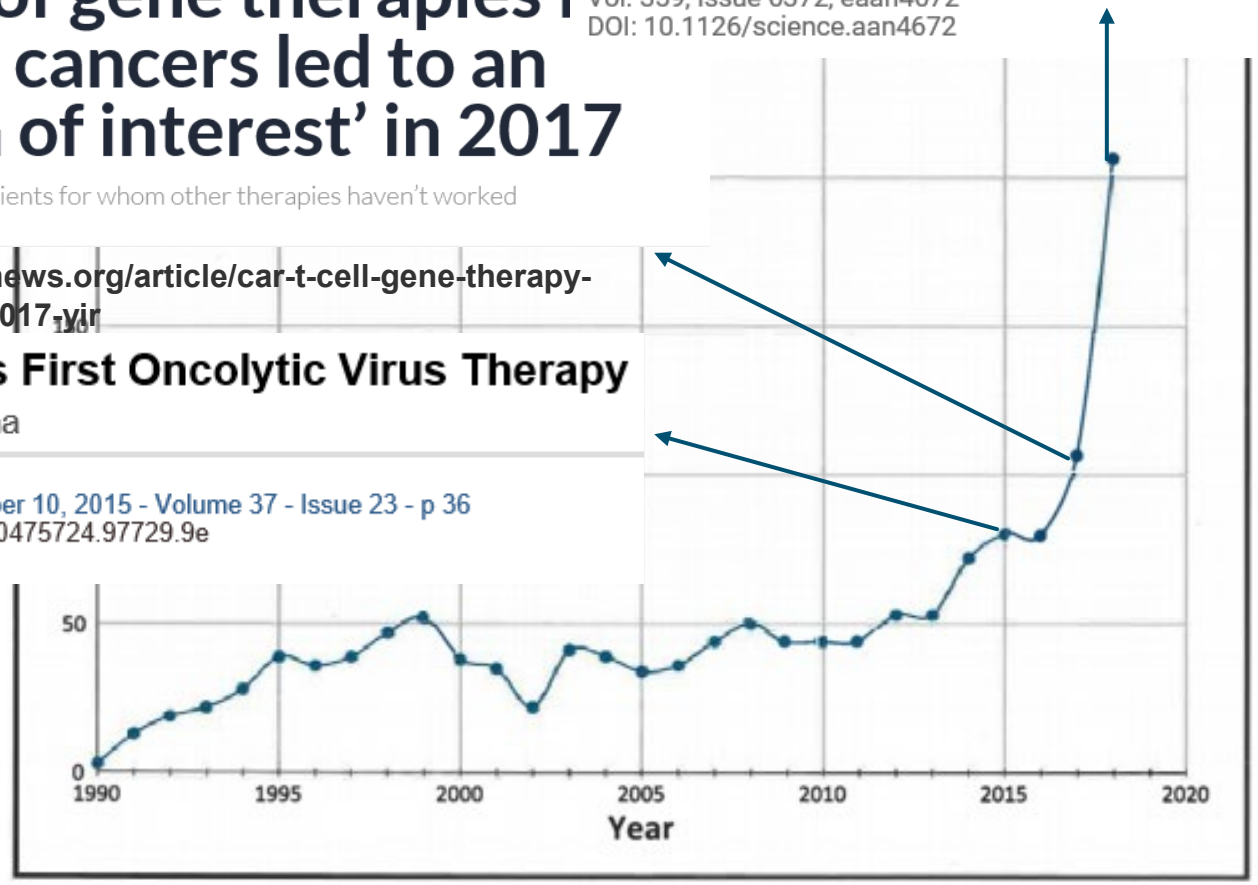
REVIEWS | REVIEW

Gene therapy comes of age

Cynthia E. Dunbar[1,*], Katherine A. High[2], J. Keith Joung[3], Donald B. Kohn[4], Keiya Ozawa[5], Michel Sadelain[6,*]

+ See all authors and affiliations

Science 12 Jan 2018:
Vol. 359, Issue 6372, eaan4672
DOI: 10.1126/science.aan4672



Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER)

Source: Eisenman, *Applied Biosafety,* 2019

FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa

"Today, the U.S. Food and Drug Administration approved Vyjuvek, a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy, for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.

"DEB is a genetic disorder that affects the connective tissue in the skin and nails and results from mutation(s) in the COL7A1 gene. This gene encodes type VII collagen (COL7), which is an essential protein that helps strengthen and stabilize the outer and middle layers of the skin. When COL7A1 is deficient, skin layers can separate, causing painful and debilitating blisters and wounds."

Sources: https://www.fda.gov/news-events/press-announcements/fda-approves-first-topical-gene-therapy-treatment-wounds-patients-dystrophic-epidermolysis-bullosa; https://med.stanford.edu/news/all-news/2022/12/epidermolysisbullosa-gel.html

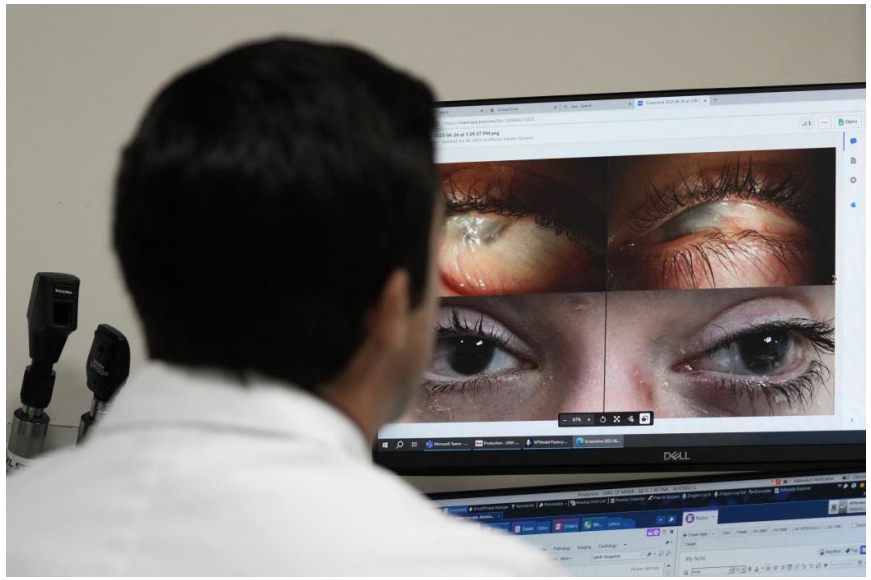
Five-year-old Rowan Millner has dystrophic epidermolysis bullosa.
Courtesy of the Millner family

FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa

“Patients or caregivers should take the following precautions during treatment with Vyjuvek:

- **Avoid direct contact with treated wounds** (e.g., touching and scratching) and dressings of treated wounds for approximately 24 hours following Vyjuvek application. In the event of accidental exposure, patients and exposed individuals should clean the affected area.
- **Wash hands and wear protective gloves when changing wound dressings.**
- **Disinfect bandages from the first dressing change following Vyjuvek treatment with a virucidal agent**, such as 70% isopropyl alcohol, 6% hydrogen peroxide, or <0.4% ammonium chloride, and dispose of the disinfected bandages in a separate sealed plastic bag in household waste. **Dispose of the subsequent used dressings and cleaning materials into a sealed plastic bag and dispose in household waste.**”

Sources: https://www.fda.gov/news-events/press-announcements/fda-approves-first-topical-gene-therapy-treatment-wounds-patients-dystrophic-epidermolysis-bullosa



JULY 24, 2023

Gene therapy eyedrops restored a boy's sight. Similar treatments could help millions

by LAURA UNGAR and FREIDA FRISARO

Source: https://medicalxpress.com/news/2023-07-gene-therapy-eyedrops-boy-sight.html

Risk Assessment Components: Shedding

Review > J Gene Med. 2007 Oct;9(10):910-21. doi: 10.1002/jgm.1096.

An inventory of shedding data from clinical gene therapy trials

Ellen A M Schenk-Braat [1], Marjolein M K B van Mierlo, Gerard Wagemaker, Chris H Bangma, Leonie C M Kaptein

- Reviewed 100 publications
  - Data from 1619 patients
  - Studies utilizing the most common viral vectors (retro/lentivirus, Ad, AAV, and poxviruses)
- **The authors found only 39% of publications included shedding data, highlighting the lack of emphasis placed on this concern**

Source: https://pubmed.ncbi.nlm.nih.gov/17880045/

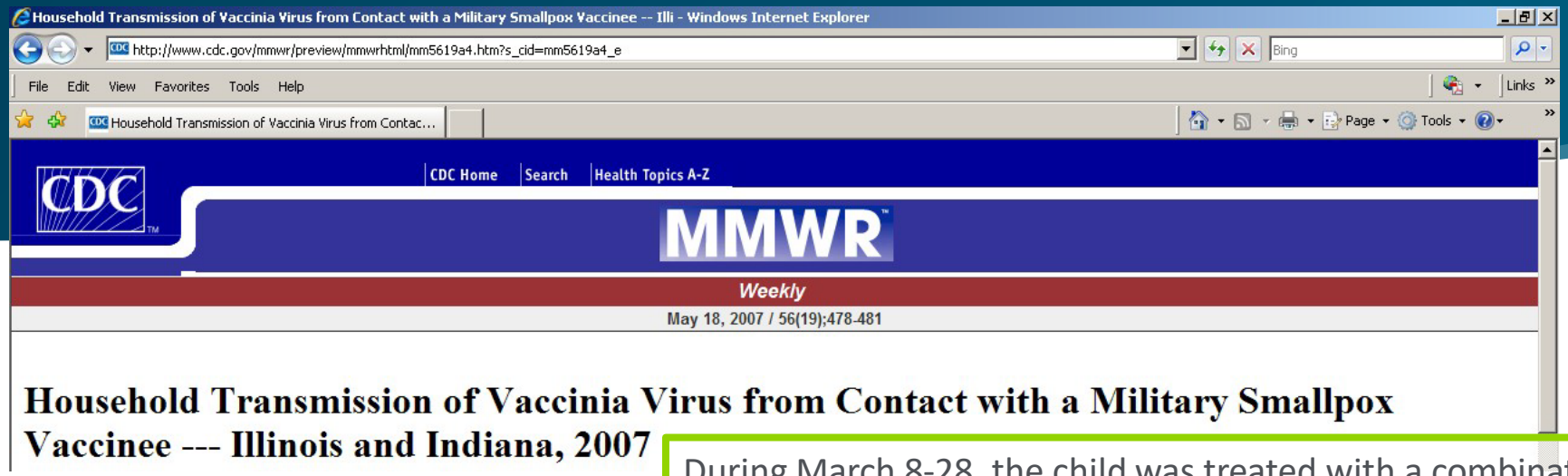
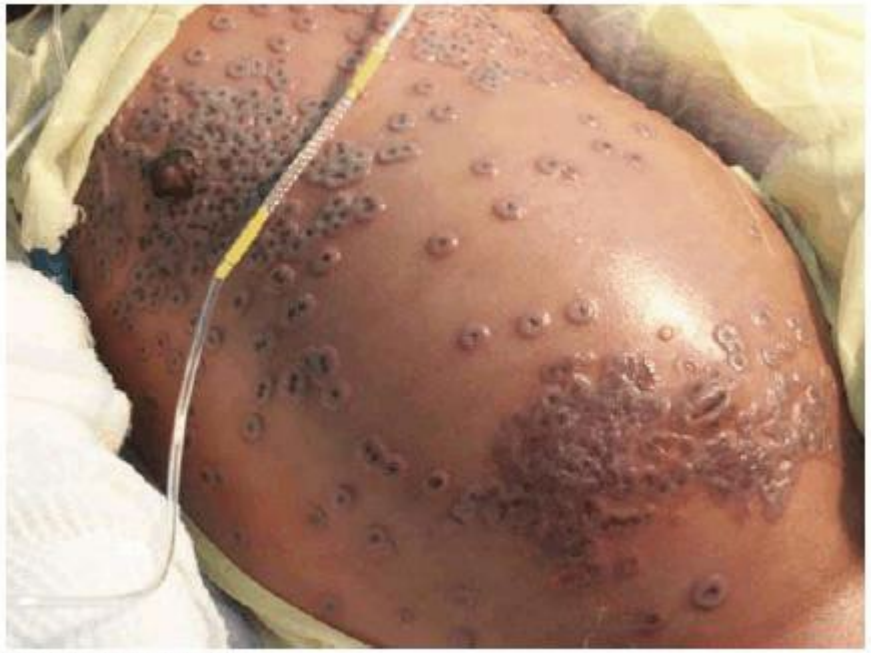


FIGURE. Abdomen and chest of a boy aged 28 months with a rash of umbilicated lesions caused by eczema vaccinatum — United States, 2007



Photo/John Marcinak

During March 8-28, the child was treated with a combination of immunotherapy and antivirals targeting vaccinia virus. The initial treatment included **Vaccinia Immune Globulin Intravenous** (Human) (VIGIV); supportive care included sedation, intubation, and mechanical ventilation. Despite these interventions, on March 10, the child's illness had progressed to hypothermia and hemodynamic instability requiring vasopressor support. **Antiviral therapies with cidofovir** and an investigational drug, ST-246 (SIGA Technologies, Corvallis, Oregon) under an Emergency Investigational Drug application, were initiated sequentially,* and additional infusions of VIGIV were administered. After approximately 1 week of interventions, the child began to improve. **On April 19, the child was discharged home after 48 days of hospitalization; he has no known sequelae other than possible scarring of the skin.**

Source: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5619a4.htm

Risk Assessment Components: Shedding

FDA Guidance on Shedding and Environmental Impact in Clinical Trials Involving Gene Therapy Products

Daniel Eisenman* and Scott Swindle

Daniel Eisenman and Scott Swindle, *Applied Biosafety*
Published Online: 28 Jul 2022
https://doi.org/10.1089/apb.2022.0020

Open camera or QR reader and scan code to access this article and other resources online.

First in Human Investigational Products Frequently Exempted from Environmental Assessment at IND

Environmental Assessment typically not required by FDA until considering final marketing approval

Exempted from Environmental Assessment at IND Unless:

The threshold for ‘‘significantly’’ affecting the quality of the environment is defined under 40 CFR 1508.27 as:

- The degree to which the effects of the gene therapy viral vector on the quality of the environment are likely to be highly controversial (40 CFR 1508.27(b)(4)).

- The degree to which the possible effects of the gene therapy viral vector on the human environment are highly uncertain or involve unique or unknown risks (40 CFR 1508.27(b)(5)).

- The degree to which the gene therapy viral vector may adversely affect an endangered or threatened species or its habitat that has been determined to be critical under the Endangered Species Act of 1973 (40 CFR 1508.27(b)(9)).

- Whether the effects of the gene therapy viral vector on the environment threaten a violation of Federal, State, or local law or requirements imposed for the protection of the environment (40 CFR 1508.27(b)(10)).

Research Highlights | Published: 19 December 2012

Environmental science

Rivers' antibiotic resistance threat

Nature **492**, 314(2012) | Cite this article

Synthetic antibiotic-resistant genes have found their way into microorganisms in Chinese rivers.

The team warns that this plasmid-containing lab waste could be a source of animal and human antibiotic resistance.

Collaboration Between the IRB and IBC

Origins of NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Abbreviated as “NIH Guidelines”

Framework created at a 1975 Asilomar academic conference by researchers in response to concerns over:

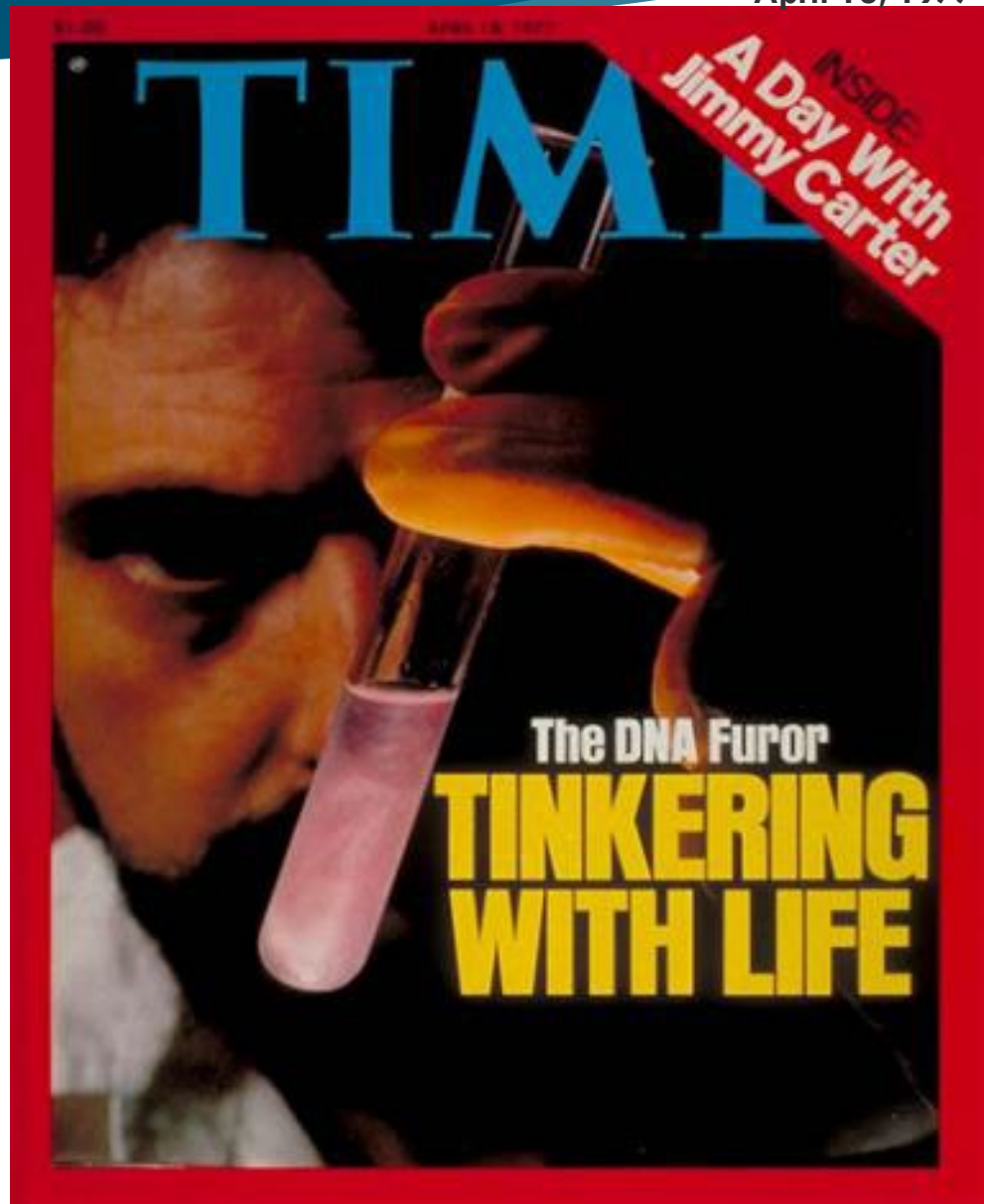
- **creation of “super bugs”**
- **gene therapy**

The guidelines were later adopted and implemented by the NIH.

Promulgated by the Office of Science Policy (OSP)

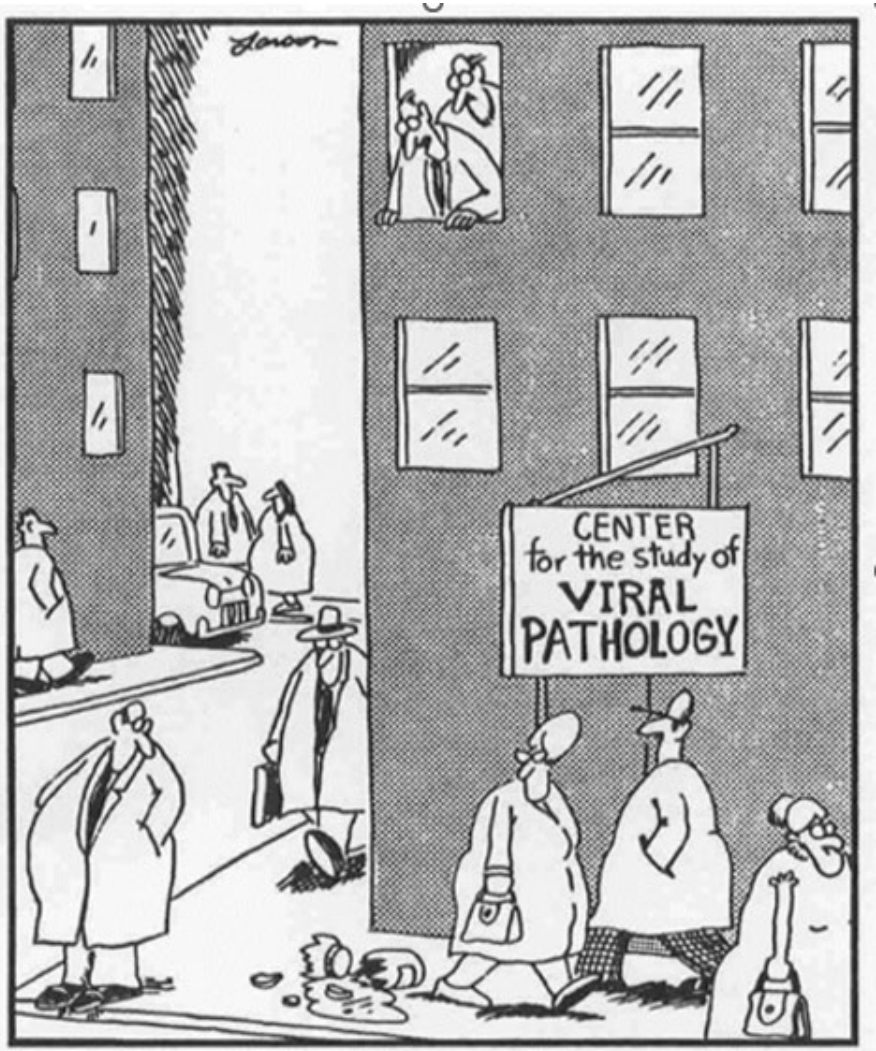
- **Most recently revised in April 2024**

The guidelines require institutions receiving NIH support to self police through IBCs that report to the NIH.



NIH Guidelines: Mandating Risk Assessment

- Ensure adequate risk assessment for the proposed research
- Containment levels specified in NIH Guidelines, elaborated on in Biosafety in Microbiological and Biomedical Laboratories (BMBL)
- Adequacy of:
  - Facilities,
  - Safety equipment
  - Personal protective equipment (PPE)
  - SOPs
  - Training
  - Waste Disposal Practices
  - Incident response plans
- Lab Inspection
- Periodic Rereview of the research



"Uh-oh."

When Is IBC Review Necessary?

- NIH Guidelines require IBC review when research involving recombinant DNA (genetic engineering or gene therapy research) is:

- Even if there are truly zero NIH funds involved, IBC review is a best practice
  - NIH Guidelines state that "[i]ndividuals, corporations, and institutions not otherwise covered by the NIH Guidelines are encouraged to adhere to the standards and procedures set forth" in the Guidelines (Section IV-D-1)

IRB vs IBC

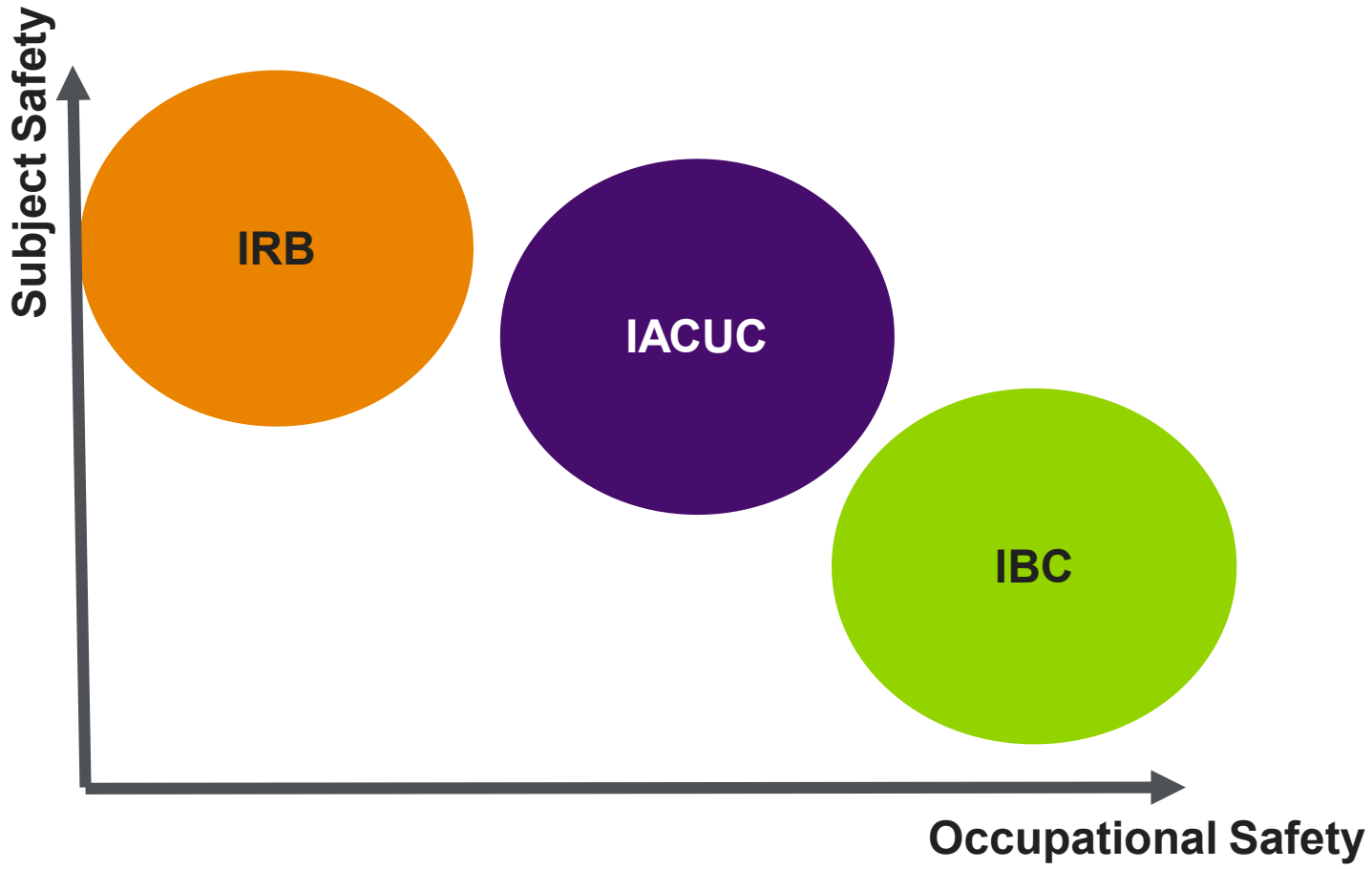
IRB

- Assures compliance with **FDA** Guidelines
- Focus on human research subjects
- Assesses safety of study design
- Assures:
  - Subjects are properly informed
  - Subjects are not coerced

IBC

- Assures compliance with **NIH** Guidelines
- Focus on research staff
  - Assesses risks posed by genetically modified materials
  - SOP for safe handling of IP
- Assures proper containment within facility
- Assesses risk to environment

Oversight Committees and Focus on Occupational Safety vs Subject Safety



ADVARRA™

Assessing Risk for Gene Therapies

Organism
Virulence
Mode of Transmission
Availability of Vaccines / Therapeutics
Quantities / Volumes
Procedures
Host Range / Susceptibility of Hosts
+ Genetic Modifications

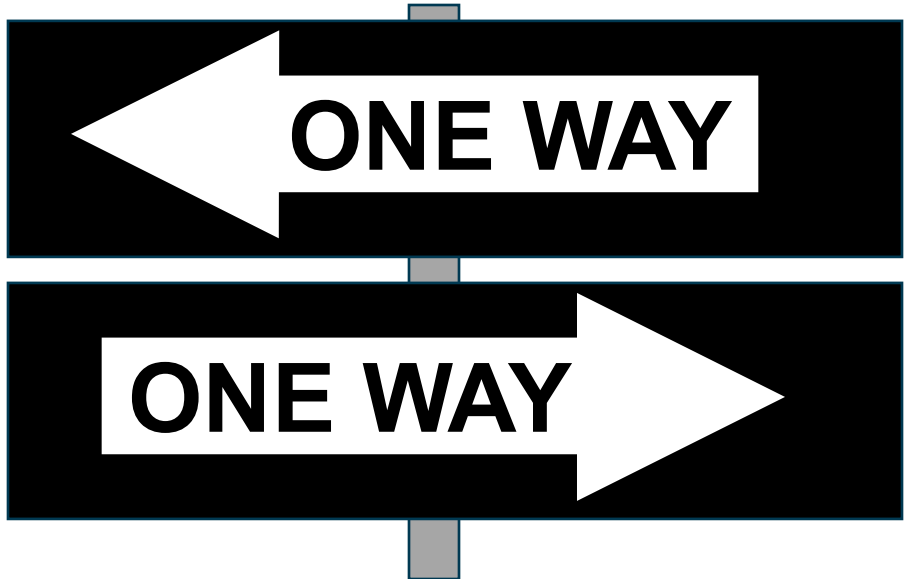
Overlap & Communication Between IBC & IRB: Informed Consent

- The IBC may request changes to the informed consent
- The informed consent should reference:
  - The investigational product contains engineered genetic material, may be a GMO
  - **Short and long term risks** pertaining to the engineered genetic material (cells, vector, genes, etc.)
  - Biodistribution, caring for the inoculation site and risks to others
    - Casual contacts
    - Sexual partners (Reproductive considerations)
    - Immune compromised individuals
    - Children

Strategies for Handling Federally Funded Multi-Site HGT Studies

How do we accommodate?

- NIH Single IRB policy and the upcoming changes to the Common Rule requiring multi-site studies to utilize **single IRBs**?
- NIH Guidelines' focus on **local IBC oversight**?



Strategies for Handling Federally Funded Multi-Site Gene Therapy Studies

1. **Utilize a single IRB from an institution with the bandwidth to service additional sites**
   - Creation of a consortium of IRBs
   - This approach minimizes or eliminates crosstalk between the additional sites' IBCs and the single IRB
   - Some sites may lack IBCs or the expertise to review gene therapy studies

2. **Utilize a commercial IRB with an associated IBC service**
   - Standardization of IBC forms, policies and procedures across sites/institutions to minimize turnaround times
   - Gene therapy research expertise readily available for all sites
   - Maintains crosstalk between the single IRB and all sites utilizing the IBC service

Considerations for Research Ethics

Considerations for Short and Long Term Risks

Protocol

- If the IP is specific to a given mutation, ensure the inclusion criteria require testing for that mutation.
- Testing for neutralizing antibodies against the viral vector
- Considerations for immune suppressive treatments to avoid inflammatory response against the IP
- CAR T cells typically require pre-conditioning chemotherapy
- Do inclusion / exclusion criteria minimize risks of SAEs or death from exposure to the IP?
- Considerations for co-morbidities and immune competency

Considerations for Short and Long Term Risks

Informed Consent

- Is the nature of the IP adequately described? Is it just “an investigational drug”?
- If a microorganism (viruses, bacteria, etc.) is that mentioned?
- Are the genetic modifications described along with associated risks?
- Potential for genotoxicity or cancer?
- Long term follow up?
- Reproductive considerations:

Abstaining from sexual intercourse and sperm / egg donation until a certain amount of time after dosing?
Exclusion of women of child bearing potential
Use of at least two medically effective methods of contraception including condoms
Can the treatment affect future reproductive potential?

RARE DISEASES > GENETIC DISORDERS

What Is Gene Therapy for Sickle Cell Disease?

Promising Therapy Undergoing Clinical Trials

By Ruth Jessen Hickman, MD | Updated on September 26, 2024

GUIDANCE DOCUMENT

Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

Guidance for Industry

JANUARY 2020

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testing-retroviral-vector-based-human-gene-therapy-products-replication-competent-retrovirus-during

GUIDANCE DOCUMENT

Human Gene Therapy Products Incorporating Human Genome Editing

Guidance for Industry

JANUARY 2024

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing

Food and Drug Administration Guidance on Design of Clinical Trials for Gene Therapy Products with Potential for Genome Integration or Genome Editing and Associated Long-Term Follow-Up of Research Subjects

Daniel Eisenman* and Scott Swindle

Appl Biosaf. December 2022; 27(4): 201–209.

GUIDANCE DOCUMENT

Human Gene Therapy Products Incorporating Human Genome Editing

Guidance for Industry

JANUARY 2024

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing

Risks Associated with Gene Editing

Delivery Risks
Delivery to proper cells (in vivo)
Can control with mode of delivery, vector tropism, and tissue specific promoters
Need reliable animal models and preclinical safety data
What if the gene sequence is different between the animal model and humans?

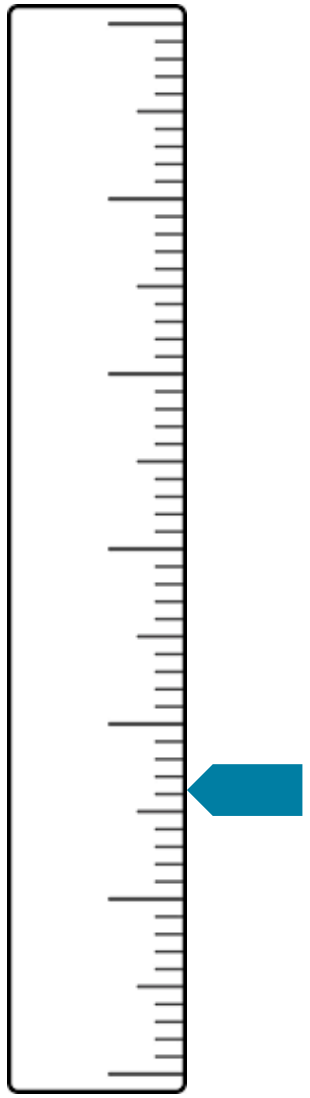
Gene Editing Risks
Greatest risk when introducing double stranded DNA breaks.
Indels (insertions and deletions)
Chromosomal rearrangements
On target and off target effects
Require thorough and reproducible testing
Requires long term follow up

Much lower risk with base editing technology (no double stranded DNA breaks).

ADVARRA

Decentralized Clinical Trials Involving Biologics

What Types of Facilities May Be Involved in DCTs?



- Traditional clinical research sites
- Local healthcare facilities
- Local pharmacies
- Local clinical laboratories
- Mobile units
- At subjects' homes
- Visit by healthcare professionals (site personnel or third party)
- Self-dosing subjects
- Monitoring by:
  - Telehealth
  - Digital health technologies

F. Investigational Products:

Drugs and Biologics

Consider the nature of the IP when determining whether administration outside of a clinical trial site in a DCT is appropriate

IPs may need in-person supervision by the investigator at the trial site if they:

- Involve complex administrative procedures
- Have a high-risk safety profile, especially in the immediate post-administration

Considerations for Use of Biologics in DCTs

Appropriateness and feasibility:

- Shipping
- Storage
- Dispensing
- Administration
- Waste disposal
- Return/Disposal of IP
- Shedding
- Training
- Facility
- Equipment and supplies (including PPE)

THE WALL STREET JOURNAL.

BUSINESS

Dry Ice Demand Swells as Covid-19 Vaccines Prepare for Deployment

Coronavirus shots requiring ultracold temperatures, coupled with holiday food shipments, kick off 'mad scramble' for solid carbon dioxide

Few pharmaceutical products before Pfizer and Moderna's coronavirus vaccines have required the low temperatures that dry ice is needed to maintain. WHITNEY CURTIS FOR THE WALL STREET JOURNAL

By Jesse Newman Follow | *Photographs by Whitney Curtis for The Wall Street Journal*
Dec. 3, 2020 9:52 am ET

Share Resize Listen (6 min)

Covid-19 vaccines awaiting regulatory approval will require ultracold temperatures for shipping and storage, and makers of dry ice are bracing for a surge in demand.

Source: https://www.wsj.com/articles/covid-19-vaccines-start-a-frenzy-for-dry-ice-its-like-a-herd-of-mustangs-11607007166

HEALTH

'We're being left behind': Rural hospitals can't afford ultra-cold freezers to store the leading Covid-19 vaccine

By Olivia Goldhill Nov. 11, 2020 Reprints

Frozen RNA samples are displayed in an ultra-cold freezer, chilled to -80 degrees Celsius, like the ones hospitals are buying to store the Pfizer-BioNTech Covid-19 vaccine.
ANDREW BURTON/GETTY IMAGES

Large urban hospitals across the U.S. are rushing to buy expensive ultra-cold freezers to store what's likely to be the first approved Covid-19 vaccine. But most rural hospitals can't afford these high-end units, meaning health workers and residents in those communities may have difficulty getting the shots.

Source: https://www.statnews.com/2020/11/11/rural-hospitals-cant-afford-freezers-to-store-pfizer-covid19-vaccine

THE WALL STREET JOURNAL.

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LOGISTICS REPORT

Supply-Chain Obstacles Led to Last Month's Cut to Pfizer's Covid-19 Vaccine-Rollout Target

Pharma giant found raw materials in early production didn't meet its standards

By Costas Paris Follow

Updated Dec. 3, 2020 6:58 pm ET

Share Resize

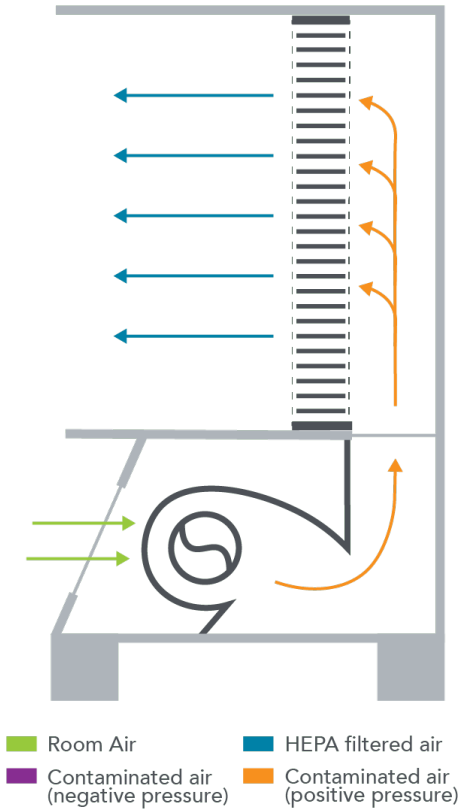
Source: https://www.wsj.com/articles/pfizer-slashed-its-covid-19-vaccine-rollout-target-after-facing-supply-chain-obstacles-11607027787

Clean Bench vs Biosafety Cabinet:

What's the Difference?

- Only protects IP
- Not intended for hazardous substances
- Increases risk of occupational exposure

Airflow Within a Clean Bench



Source: https://www.lorderan.com/products/horizontal-laminar-flow-cabinet

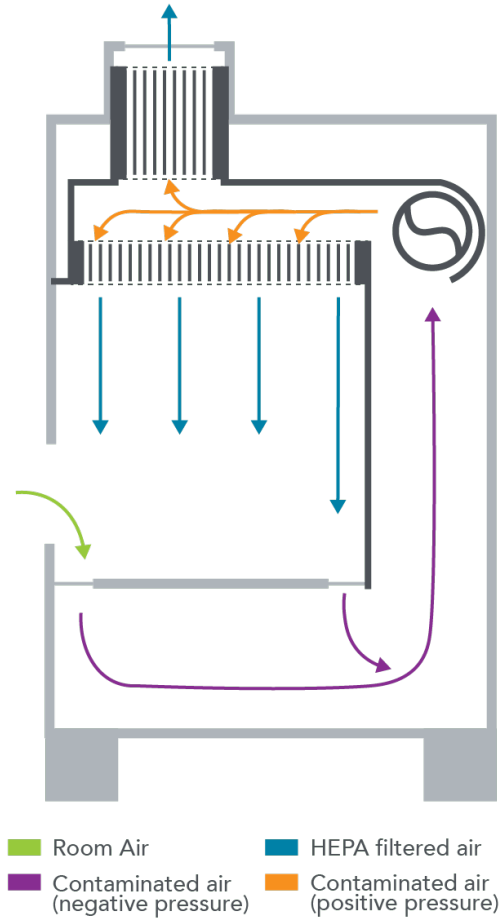
Learn more: https://www.advarra.com/blog/clean-bench-vs-biosafety-cabinet-whats-the-difference/

Clean Bench vs Biosafety Cabinet:

What's the Difference?

- Protects product, worker, and environment

Airflow within a biosafety cabinet



Source: https://www.fishersci.com/shop/products/purifier-logic-class-ii-a2-biosafety-cabinets-us-models-32/302610101

Learn more: https://www.advarra.com/blog/clean-bench-vs-biosafety-cabinet-whats-the-difference/

Challenges With At-home Use of Biologics

Storage

- Refrigeration/freezer?
- Comingling with food?

Adequacy of facilities

- Flooring/carpeting
- Impermeable furniture
- Restricting access
- Airflow

- Spill cleanup/disinfection
- Hand hygiene
- Waste disposal

Precautions for research involving biologics outlined in
CDC Biosafety in Microbiological and Biomedical Laboratories (BMBL)

Facility Challenges

Thank you

Dan Eisenman, PhD, RBP, SM(NRCM), CBSP
Executive Director of Biosafety Services
Advarra
Daniel.Eisenman@advarra.com

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