Brigham and Women's Hospital
Founding Member, Mass General Brigham

Gene and stem cell therapy in pulmonary medicine

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Clinical focus: Pulmonary Genetics

DISCLOSURES

Genetics Section Editor for UpToDate, Inc.

Consultant for General Medicines, Inc. (a gene therapy company, no related content)

Spouse consultant for CRO as blinded interpreter of clinical trial data in hematology (unrelated)

OBJECTIVES

By the end of this session, participants will be able to:

1. **Describe** the principles and classes of gene therapeutics and the challenges specific to lung delivery.

2. **Compare** the advantages and disadvantages of major gene-therapeutic strategies in the context of pulmonary disease.

3. **Identify** at least two gene- or cell-based therapies currently in clinical development for a pulmonary genetic disease relevant to clinical practice.

Why This Matters Now

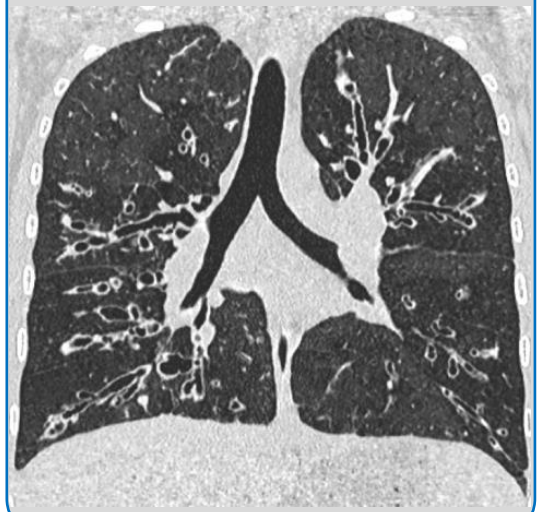
Why This Matters Now: > 60 monogenic lung disorders

Bronchiectasis

Cystic Fibrosis (CFTR)

Primary Ciliary Dyskinesia (> 40 genes)

Immune deficiency (>100 genes)

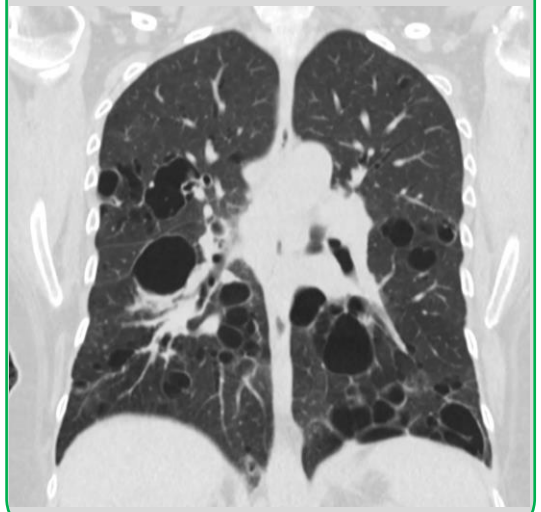


Cystic Lung Disease

Alpha-1-antitrypsin deficiency (SERPINA1)

Birt-Hogg-Dubé (FLCN)

LAM (TSC1/TSC2)

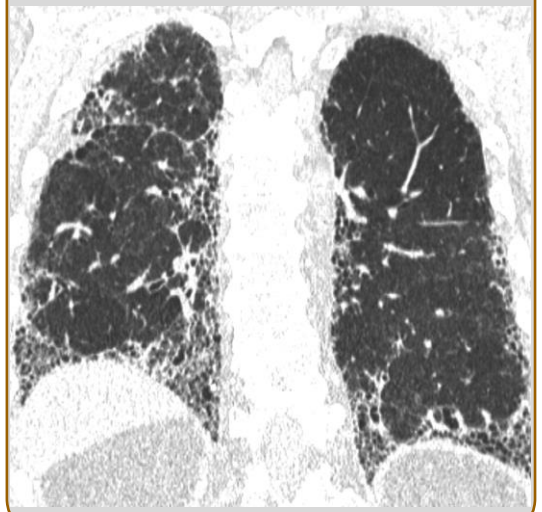


Interstitial Lung Disease

Telomere (TERT, TERC, RTEL1, PARN)

Surfactant (SFTPB, SFTPC)

Alveolar Proteinosis (CSF2RA or CSF2RB)



Pulmonary Vascular Disease

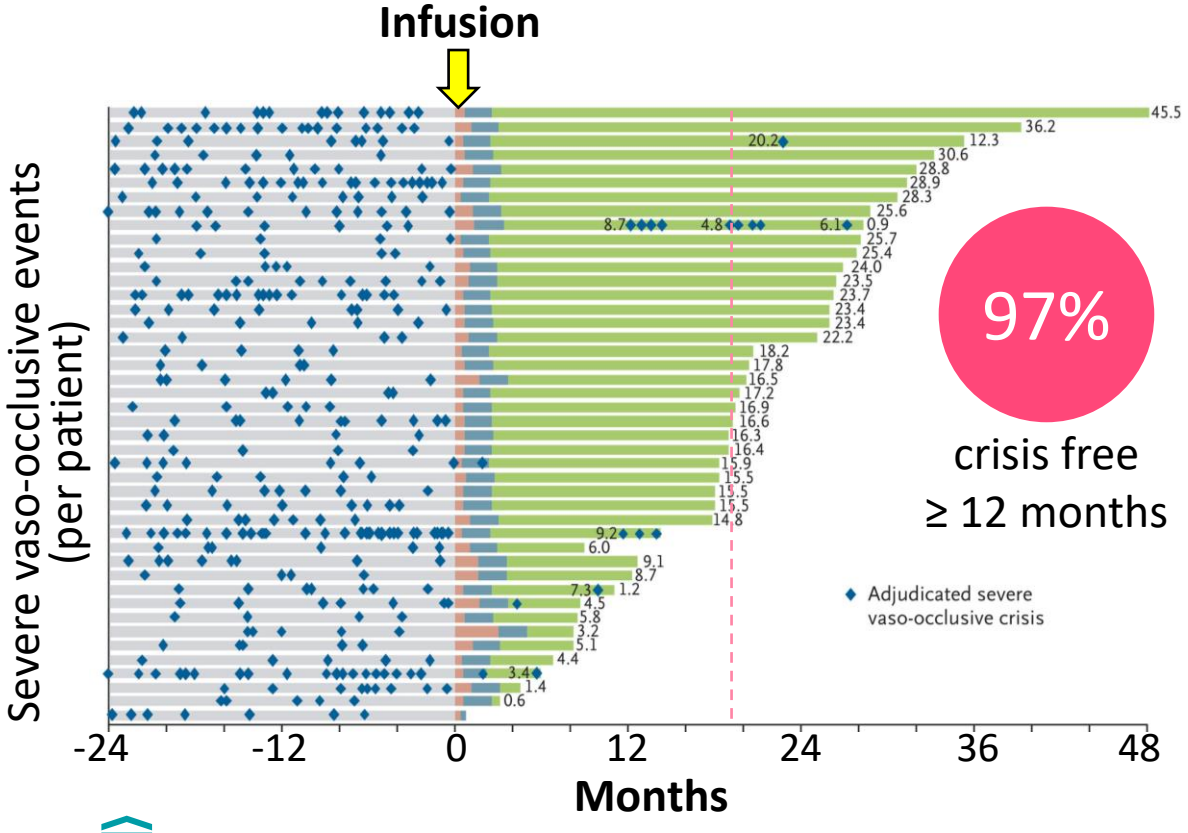
Pulmonary Hypertension (BMPR2, TBX4, KDR…)

Hereditary hemorrhagic telangiectasia (ENG, ACVRL, SMAD4)

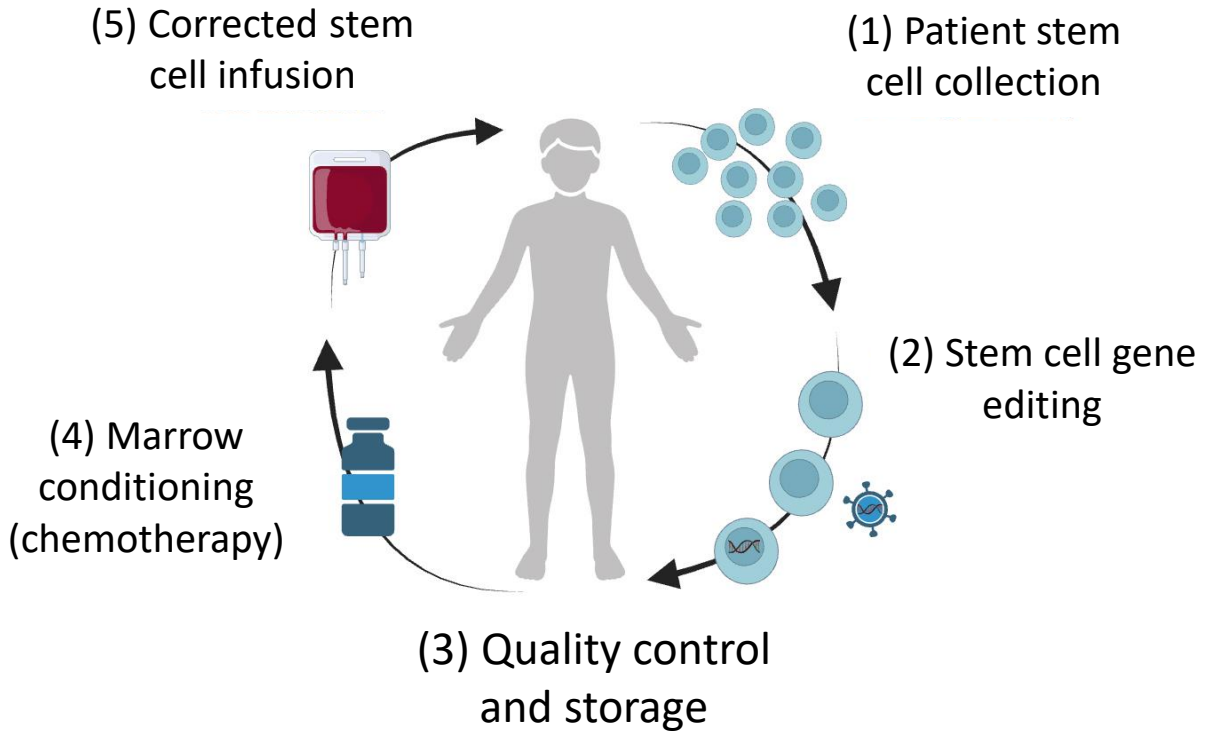
Why This Matters Now: FDA-approved therapies for Sickle Cell Disease (December 2023)

Exagamglogene autotemcel (gene editor):

Permanent editing the erythroid-specific BCL11A enhancer to increase circulating fetal hemoglobin



Ex-vivo gene editing in hematologic disease



Frangoul et al. N Engl J Med 2024;390:1649-1662

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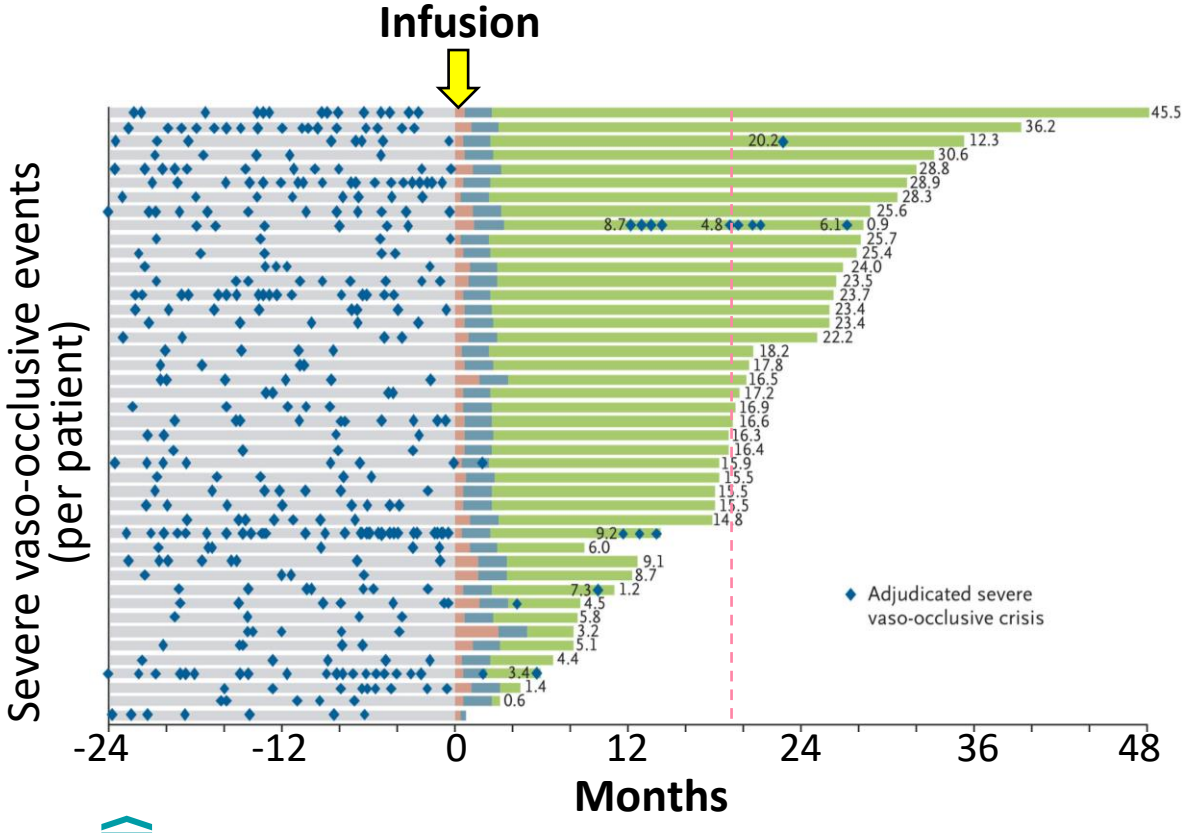
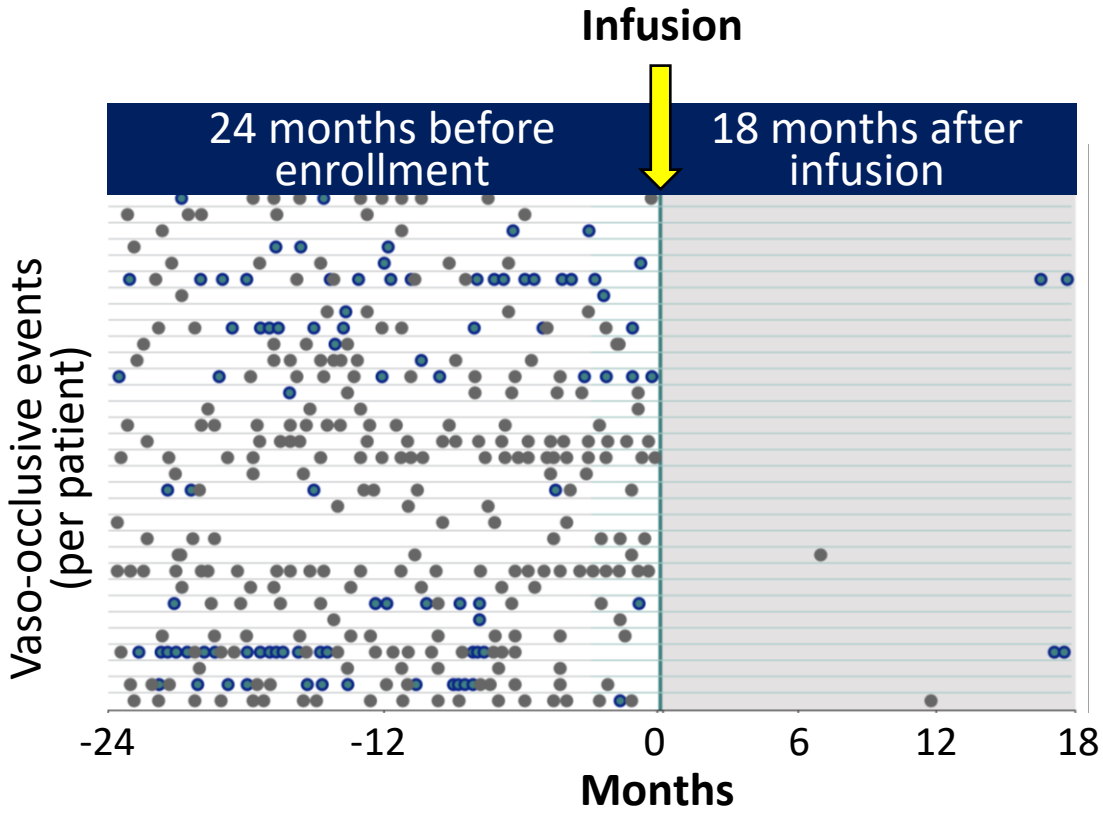
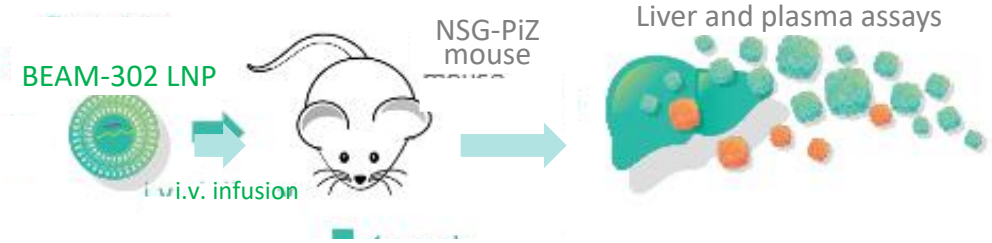


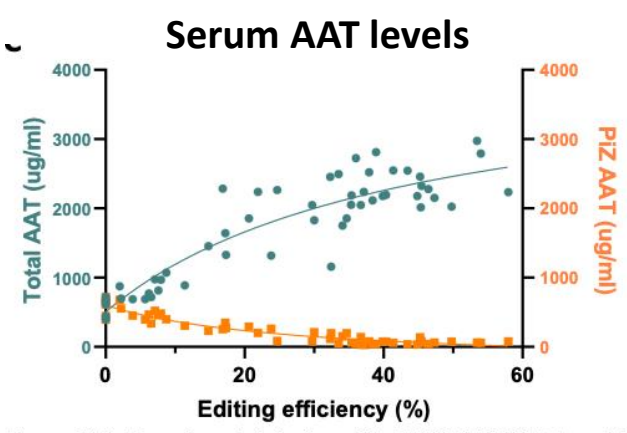
Lovotibeglogene autotemcel (transgene):

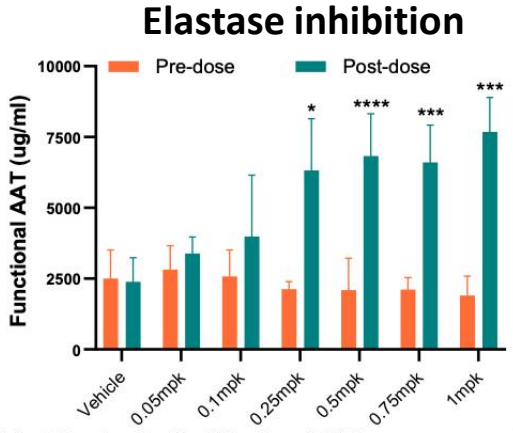
Lentiviral-mediated insert of a functional beta-globin gene

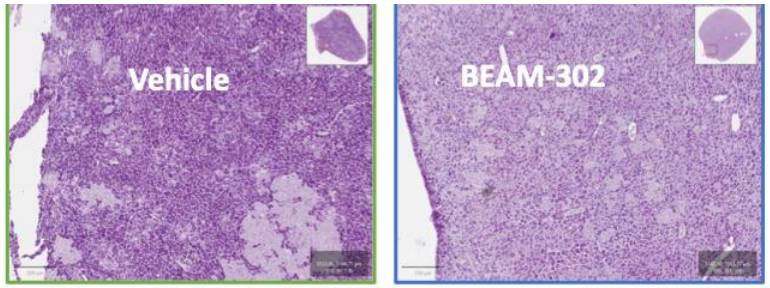


Why This Matters Now: In vivo gene editing for A1ATD









BEAM Therapeutics – BEAM-302
Phase I/II human data (29 patients, March 2026)

Results to date	March 25, 2026
Total AAT plasma levels, mean	16.5 µM
% normal protein structure (day 84)	95%
% reduction of Z allele (day 84)	80%
Toxicity	No severe adverse events No dose limiting effects
FDA approval status	Pursuing accelerated approval

YolTech Therapeutics - YOLT-202
Phase I data (2 patients, March 2026)

Results to date	March 15, 2026
AAT level ≥ 11 µM	2 of 2
% normal protein structure	95%
% reduction of Z allele (day 84)	NR
Toxicity	NR
FDA approval status	IND approval for Phase 2/3

Mouse data: Banerjee et al. Am Thoracic Society International Conference, 2026
Human data: **BEAM press release** – March 24, 2026 at investors.beamtx.com/news-releases/news-release-details/beam-therapeutics-announces-compelling-updated-clinical-data/
YolTech press release – March 15, 2026 at https://www.biospace.com/press-releases/yoltech-therapeutics-receives-fda-clearance-to-initiate-phase-2-3-study-of-in-vivo-gene-editing-therapy-yolt-202-in-alpha-1-antitrypsin-deficiency-aatd

What Is Gene Therapy Trying to Achieve?

What Is Gene Therapy Trying to Achieve?

Goal	Description	Indications
Gene silencing	**Silence** a toxic gain-of-function transcript	Gain-of-function variants Duplications
Gene addition	**Replace or add** a missing or non-functional gene	Loss-of-function variants Gene deletions
Gene correction	**Correct** the DNA or RNA sequence directly	All variants
Cell replacement	**Replace** the target cell population itself	Accessible cell types and tissues

Fix the message, fix the messenger, or fix the cell

Molecular genetics: the central dogma and its therapeutic targets

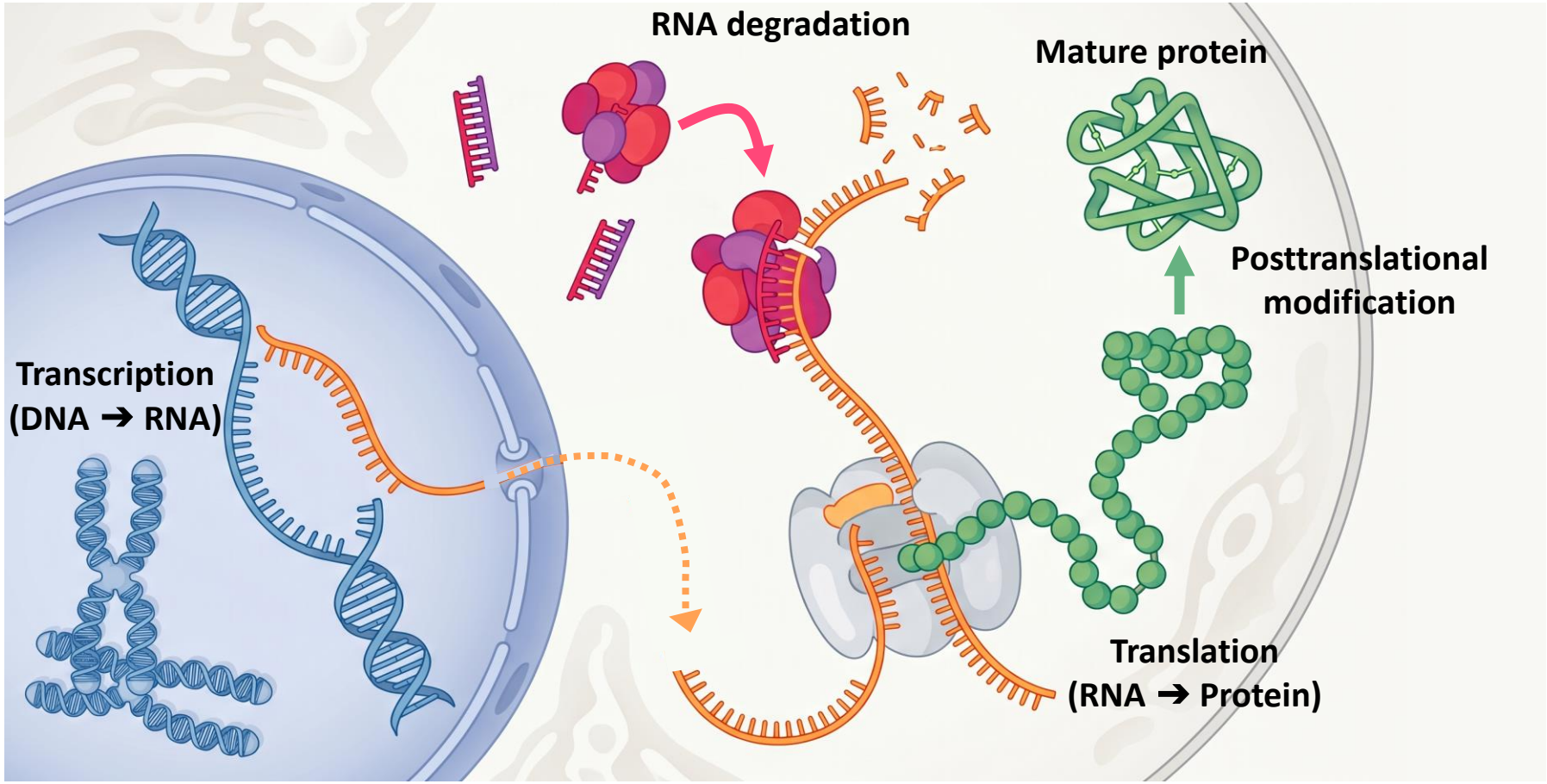


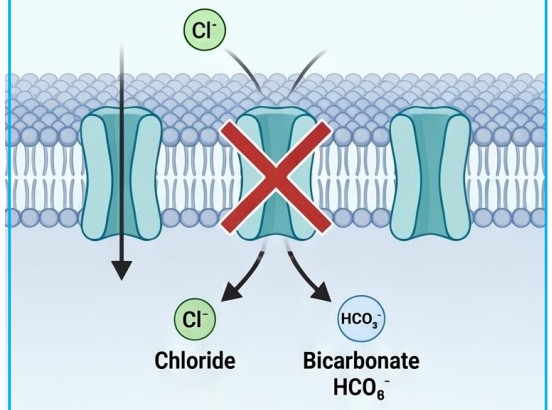
Image generated by Notebook LM, modified by presenter

Loss-of-function and Gain-of-function variants

LOSS-OF-FUNCTION (LOF)

Example: CFTR

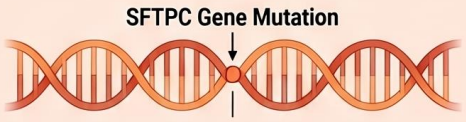
Prevents protein localization to cell surface



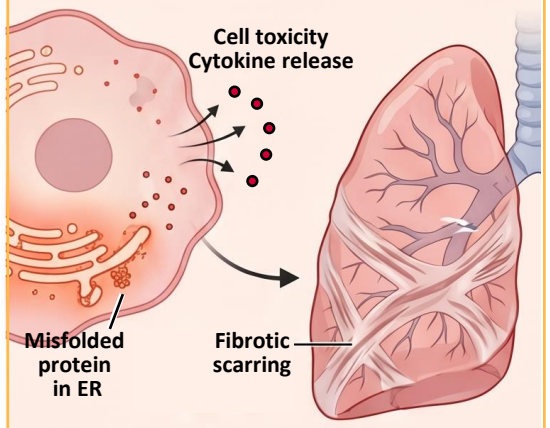
Lack of transepithelial ion transport

GAIN-OF-FUNCTION (GOF)

Example: SFTPC



Promotes accumulation of protein in ER (toxic)



Cellular toxicity and lung fibrosis

LOSS-OF-FUNCTION (LOF)

Destroy protein completely
Severely reduce expression of protein
Disrupt functional segment of protein
Prevent protein activation
Weaken a physical property (solubility, scaffolding…)
Disrupt transport of protein to correct cellular location
Prevent secretion of protein from cell
…

GAIN-OF-FUNCTION (GOF)

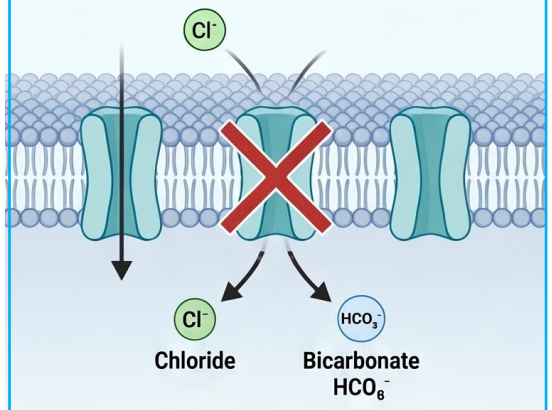
Excessive protein production
Ectopic protein production
Impaired protein clearance
Prevent protein deactivation / silencing
Augmented function (i.e., excessive signaling)
Novel gene function
Novel inhibitory function (dominant negative)

Loss-of-function and Gain-of-function variants

LOSS-OF-FUNCTION (LOF)

Example: CFTR

Prevents protein localization to cell surface



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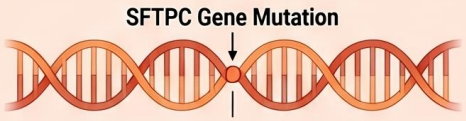

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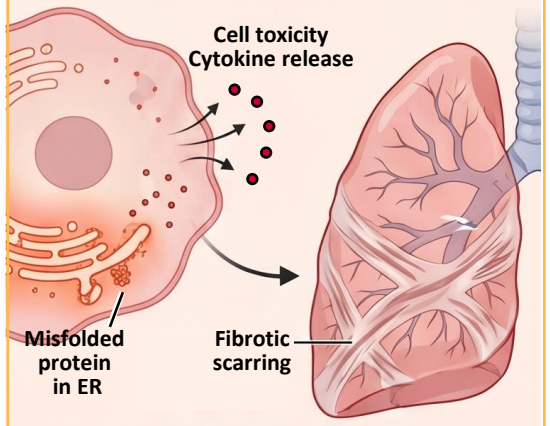
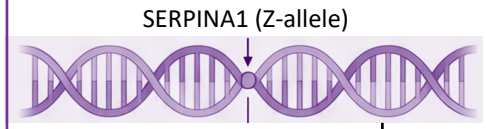


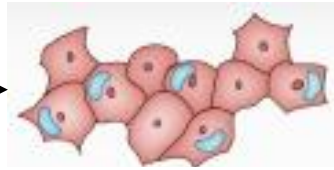
Cellular toxicity and lung fibrosis

BOTH LOSS- AND GAIN-OF-FUNCTION

Example: Alpha-1-antitrypsin deficiency



Mutation prevents secretion of A1AT protein



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Fix the message, fix the messenger, or fix the cell

The major gene therapy classes

A taxonomy of gene- and cell-based therapies

Goal	Technique	Target level
Gene silencing	**siRNA (small interfering RNA)** **ASO (Antisense Oligonucleotides)**	**Message inhibition** **Message inhibition**
Gene addition	**Gene Transfection** Adeno-associated virus (AAV) Lentivirus (LV)	**Message addition** Non-integrating Integrating
Gene correction	**CRISPR-based editing** Gene editing Base-editing	**DNA (integrating)** Long sequence Single base / several bases
Cell replacement / Cell therapy	**Cell engineering / reprogramming** Ex-vivo gene repair CART-T systems	**Cell populations** Tissue (i.e. Bone marrow) Cell type (i.e. T-cell)

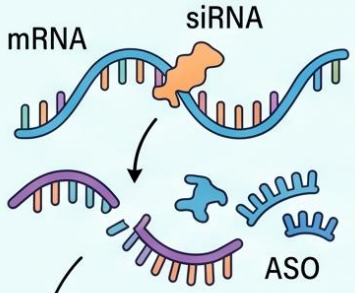
A taxonomy of gene- and cell-based therapies

Goal	Technique	Target	Integrating
Gene silencing	**siRNA (small interfering RNA)** **Patisiran:** hereditary transthyretin amyloidosis	**RNA**	**No**
	ASO (Antisense Oligonucleotides) **Nusinersen:** Spinal Muscular Atrophy	**RNA**	**No**
Gene addition	**AAV-based** **Voretigene neparvovec :** Inherited retinal disease **Onasemnogene abeparvovec:** SMA type 1	**RNA** **RNA**	**RNA** **RNA**
Gene correction	No in vivo correction yet FDA approved Pending: **BEAM-302:** Alpha-1-antitrypsin (ZZ)	**DNA**	**Yes**
Cell replacement / cell therapy	**Tisagenlecleucel:** B-cell ALL (CART-T) **Axicabtagene ciloleucel:** B-cell lymphoma (CART-T) **Exagamglogene autotemcel:** Sickle cell	**DNA** **DNA** **DNA**	**Yes** **Yes** **Yes**

A taxonomy of gene- and cell-based therapies

MOLECULAR-LEVEL GENE MODULATION

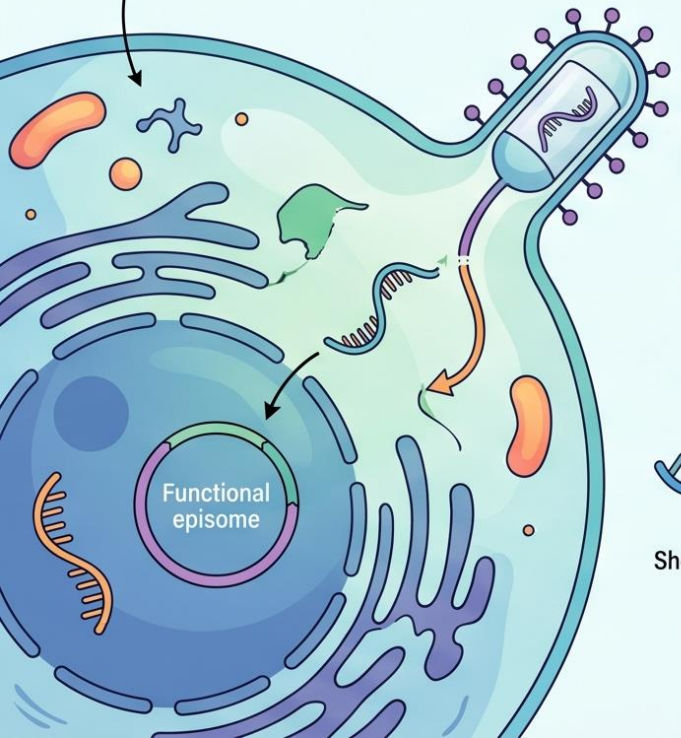
RNA-Targeting (Gene Silencing)



Modulates protein translation by targeting mRNA without altering the underlying DNA sequence.

Examples of FDA-approved therapies for molecular modulation

siRNA	Patisiran	Hereditary transthyretin amyloidosis
ASO	Nusinersen	Spinal Muscular Atrophy (SMA)
Gene Replacement	Luxturna	Inherited retinal disease



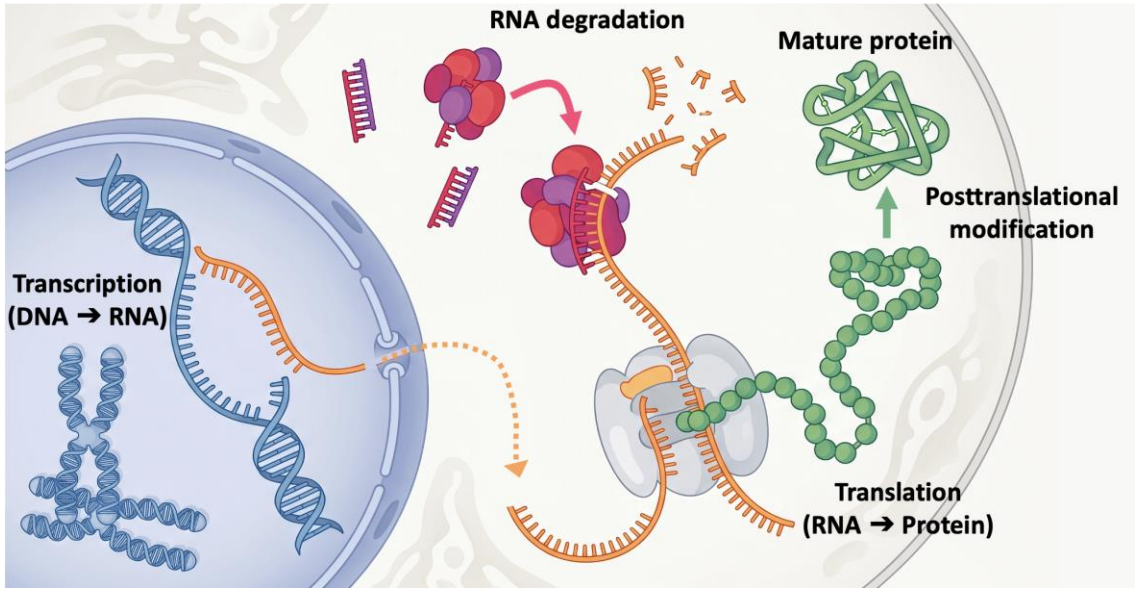
Gene Replacement (Augmentation)

Delivers functional gene copies via viral vectors (AAV or Lentivirus) to restore missing functions.

Transient vs. Episomal Delivery

RNA therapies

Gene replacements



A taxonomy of gene- and cell-based therapies

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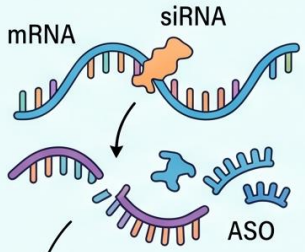

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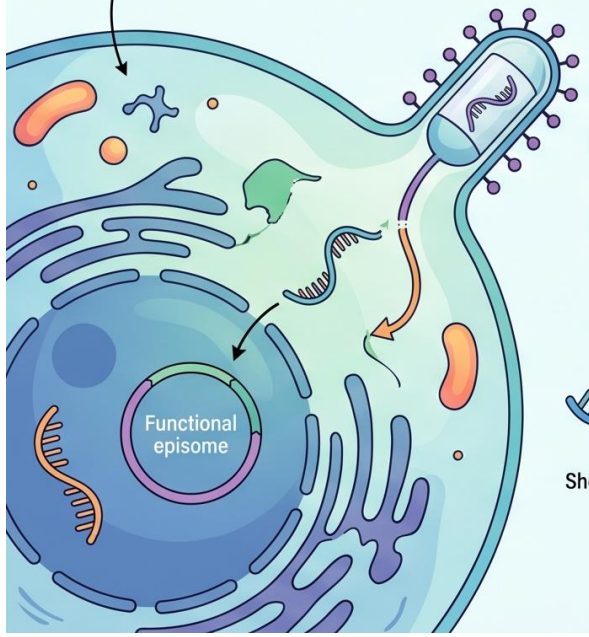

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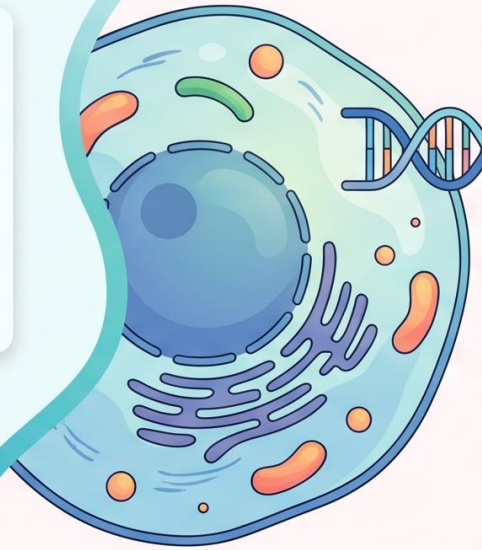
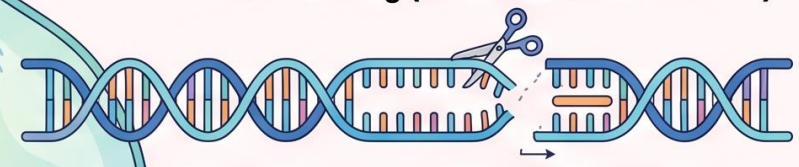
STRUCTURAL ENGINEERING & CELL DELIVERY



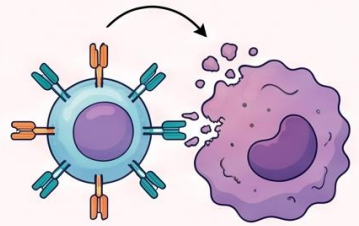
Genome Editing (Permanent Modification)



Uses "molecular scissors" like CRISPR or TALENs to permanently knockout or repair DNA.

Cell-Based Therapy

Injects engineered living cells, such as CAR-T cells, to replace or repair damaged tissue.

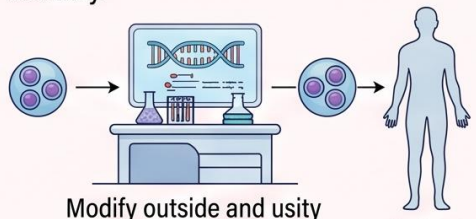


Advanced therapeutic approaches currently in human testing or approved

CRISPR-Cas9	CTX001	In Human Testing (Sickle-cell)
CAR-T Cell	Kymriah	FDA Approved (B-cell ALL)
TALENs	UCART19	In Human Testing (Leukemia)

Ex Vivo Genetic Engineering

Many cell therapies involve genetically modifying a patient's own cells outside the body.



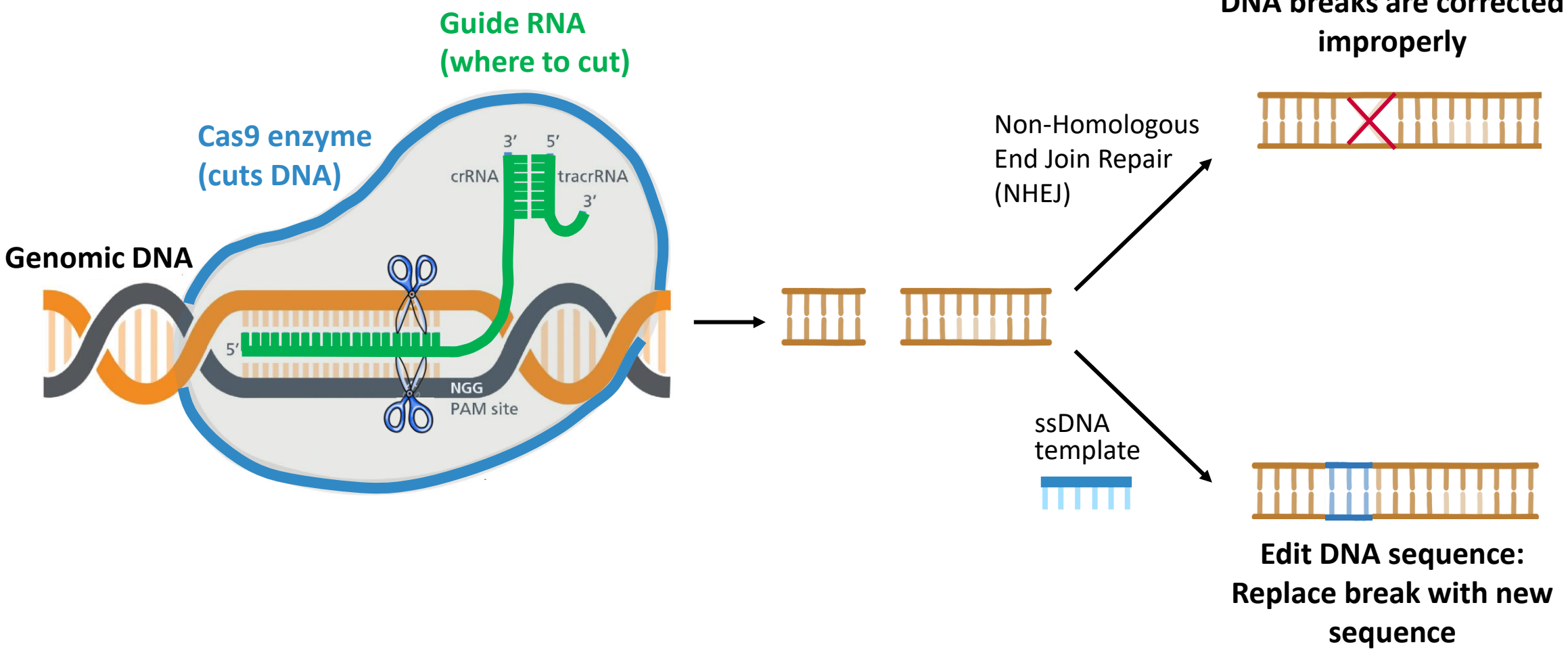
Modify outside and usity using genetic tools.

Patient

NotebookLM

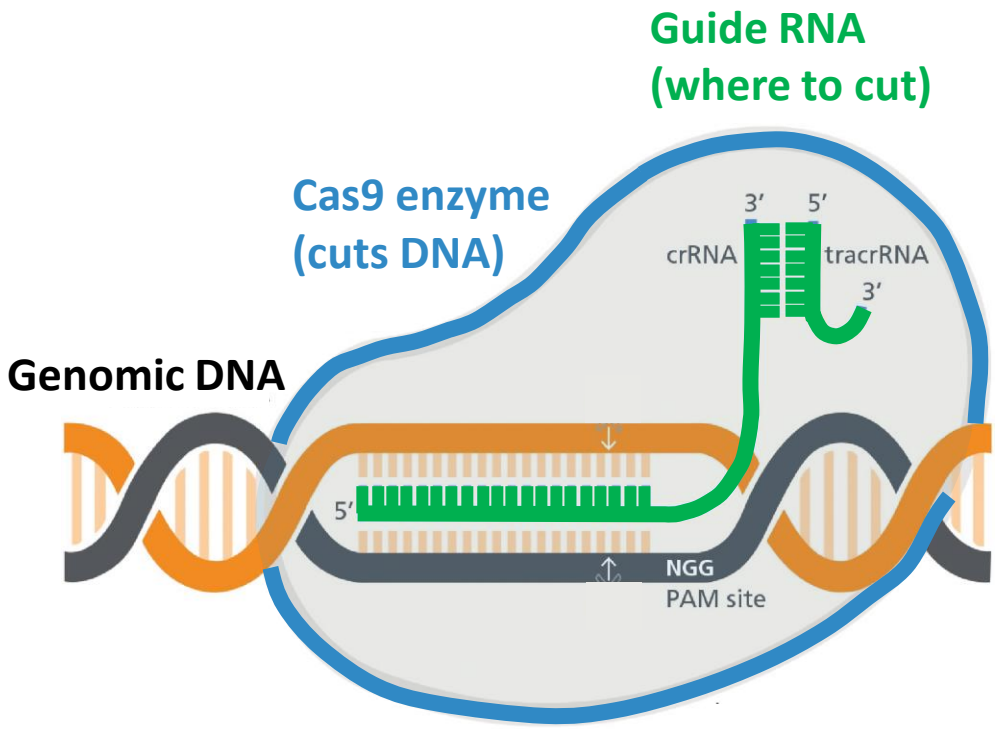
Gene editing

CRISPR-Cas9

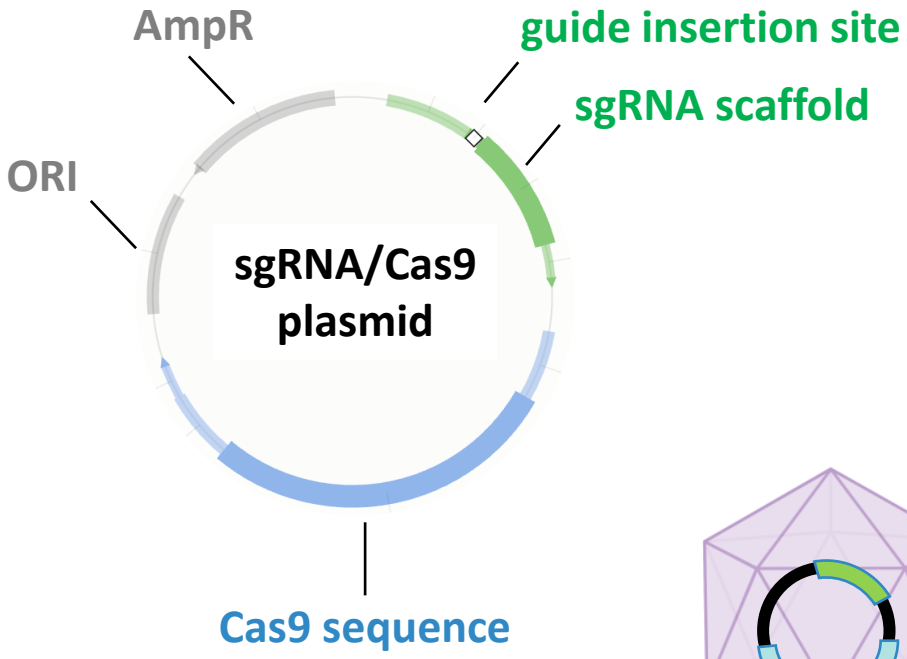


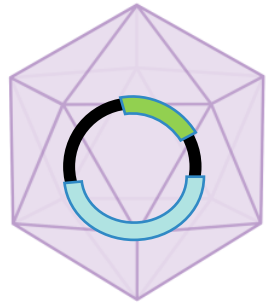
Gene editing

CRISPR-Cas9



CRISPR-Cas9 plasmid





Plasmid in AAV

Major Strategies & Their Trade-Offs

Strategy	Mechanism	Advantages	Disadvantages
Viral gene addition • AAV episomal • lentiviral integrating	Deliver a functional gene copy	• Durable (one-time dosing) • Established manufacturing	• Limited cargo size (AAV ~4.7 kb) • Pre-existing immunity (limits redosing) • Insertional mutagenesis risk • Can't fix toxic GoF variants
RNA-based • siRNA • ASO • mRNA replacement	• Transcript silencing • Transient gene replacement	• Treats GoF variants • Transient/reversible • No integration • Quicker development	• Requires repeat dosing • Delivery to airway epithelium is difficult
Gene editing • CRISPR/Cas9 • base editing • prime editing	• Directly correct the causal DNA sequence	• One-time, permanent correction (potentially) • Treats dominant GoF alleles	• Off-target editing risk; • Delivery challenges • Mutation-specific (expensive) • cells (not yet feasible in lung • True *in vivo* editing not yet in clinic
Cell-based therapy • transplant of ex vivo corrected or iPSC-derived cells	• Replace the dysfunctional cell population	• Autologous options avoid immunosuppression	• Manufacturing complexity • Engraftment durability uncertain • Tumorigenicity risk • Delivery logistics

Technical issues and barriers

Delivery

Packaging capacity

Tissue tropism

Transfection efficiency

Durability

Transient vs. permanent change

Product stability

Toxicity

AAV toxicity (Immunogenicity)

Transgene toxicity:

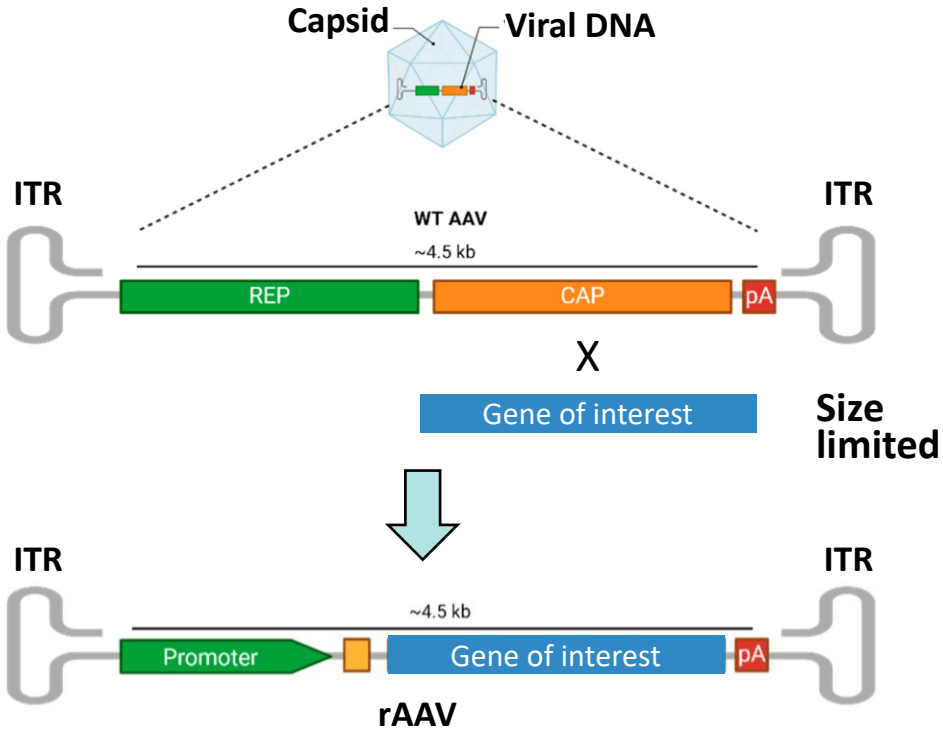
Immunogenicity

Off-target effects

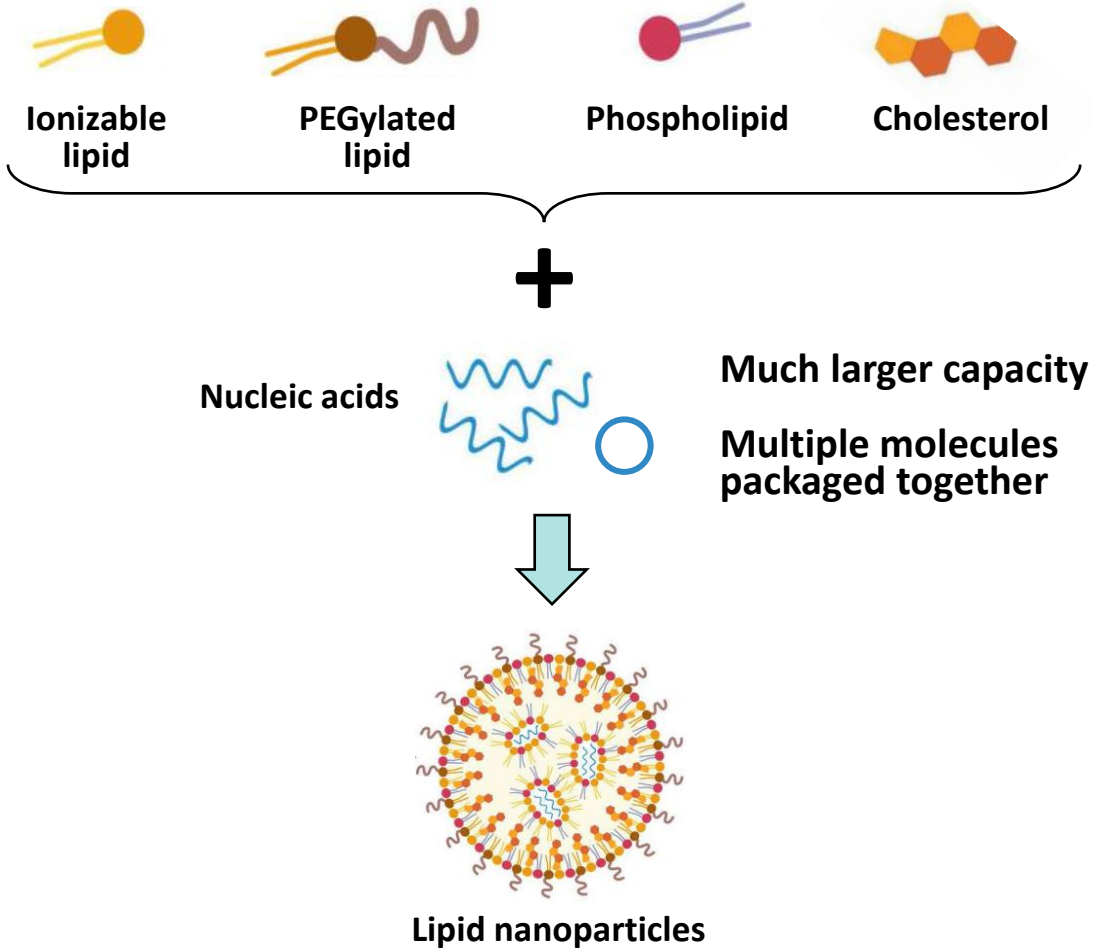
Oncogenicity

Packaging: AAVs vs. LNP

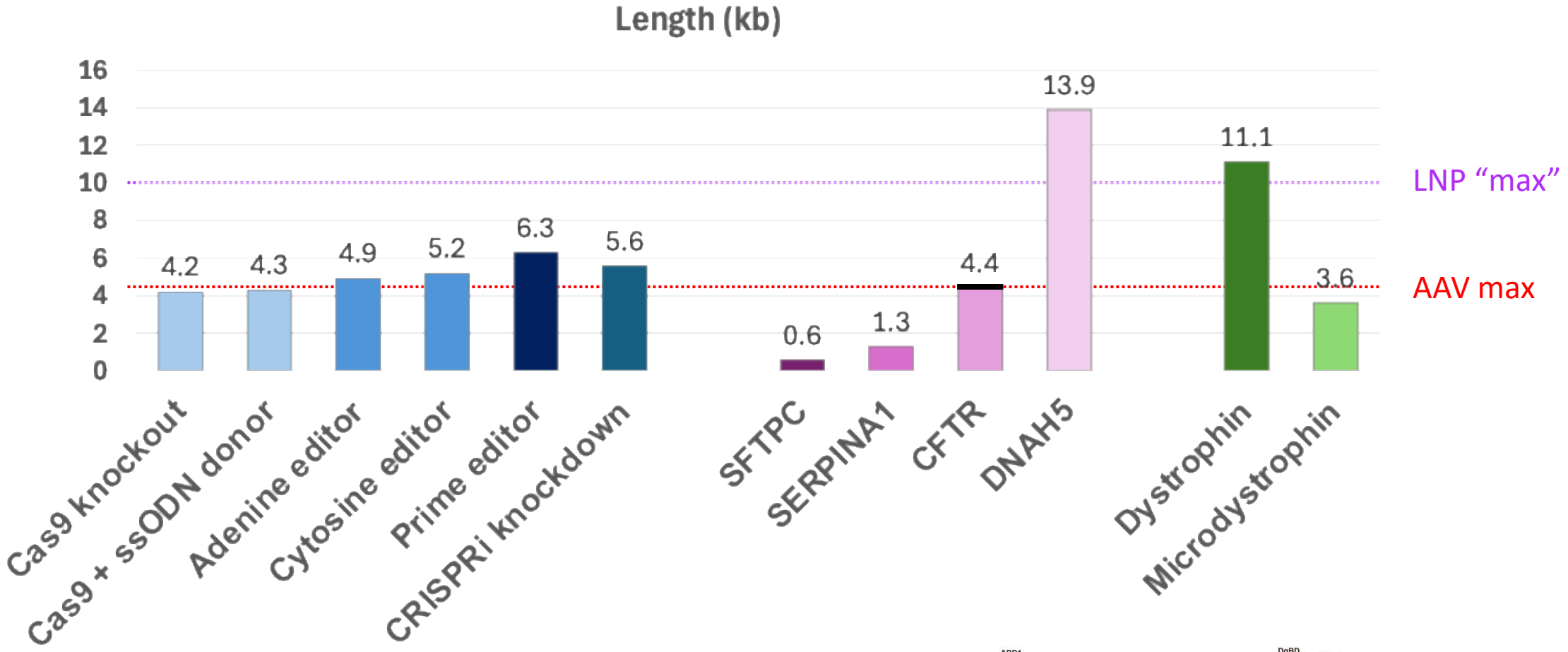
Adeno-associated virus

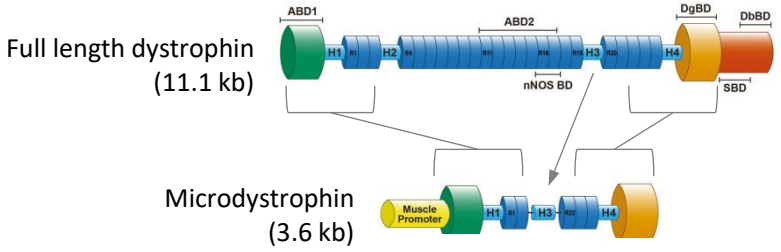


Lipid nanoparticles

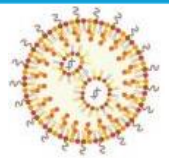


Packaging: Package size determines vector suitability

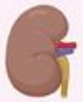




Packaging: Other considerations

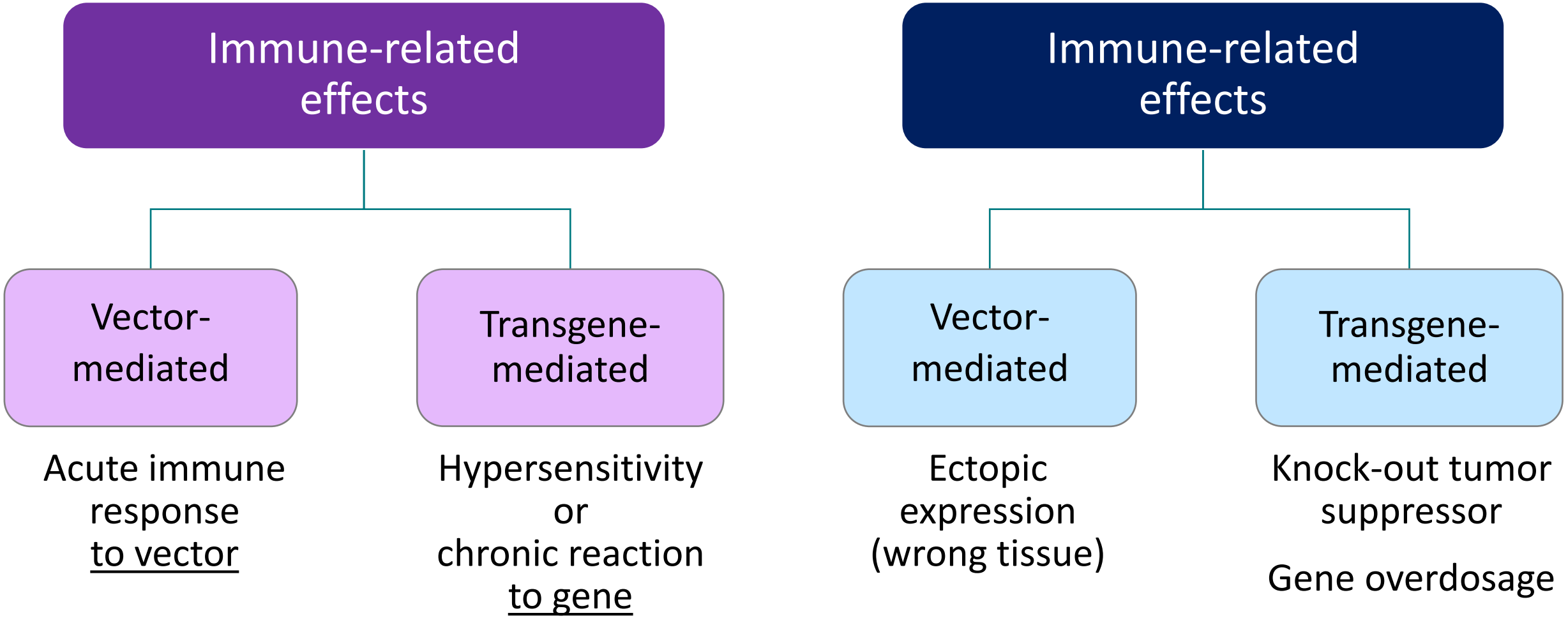
	AAV	LNP
		
Structure	Protein Capsid	Polymers / lipid particles
Cargo type	RNA / DNA	**Peptides, proteins, nucleic acids**
Capacity	4.7 kb	**~10 kb (and multiple constructs)**
Tissue tropism	Serotype-based	**Engineered**
Transduction	**High efficiency (all cell states)**	Low efficiency (dividing cells only)
Durability	**Long effect**	Short effect
Immunogenicity	Strong (viral proteins)	**Weaker (synthetic materials)**
Safety	Risk of integration	Hypersensitivity and long-term toxicities
Cost	$$$$$	**$$**
Scalability	Cell-based (lower)	**Synthetic (high)**
Clinical track record	Modest	Low (Moderna vaccines)

AAV Tissue Tropism

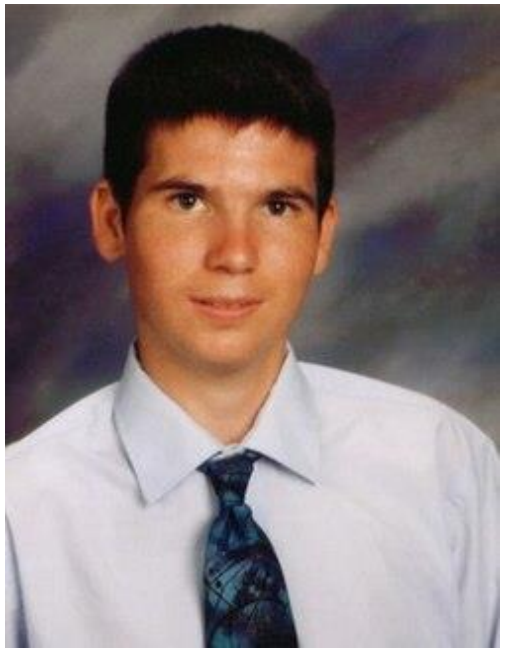
Vector	Muscle (8)	CNS (7)	Retina (5)	Liver (5)	Lung (4)	Heart (3)	Pancreas (3)	 Kidney (2)	Intestine (1)	Glycan Receptor	Co-receptor / Other	Source
AAV1	X	X	X		X		X			N-linked SA	?	Primate
AAV2	X	X		X				X	X	HSPG	FGFR1, HGFR, LamR, ++	Human
AAV3	X									HSPG	FGFR1, HGFR, LamR	Primate
AAV4		X	X							O-linked SA	?	Primate
AAV5	X	X	X	X	X					N-linked SA	PDGFR	Human
AAV6	X				X	X				N-linked SA HSPG	EGFR	Human
AAV7	X	X	X							?	?	Primate
AAV8	X	X	X	X		X	X			?	LamR	Primate
AAV9	X	X		X	X	X	X	X		N-linked galactose	LamR	Primate
AAV10				X						?	?	Primate

SA = sialic acid HSPG = Heparan sulfate proteoglycans

Toxicity


Immune-related effects
Vector-mediated
Transgene-mediated
Acute immune response to vector
Hypersensitivity or chronic reaction to gene
Immune-related effects
Vector-mediated
Transgene-mediated
Ectopic expression (wrong tissue)
Knock-out tumor suppressor
Gene overdosage

Gene therapy related deaths – majority immune-related



Jesse Gelsinger
1981 – 1999

- Intrahepatic injection of adenoviral gene Rx for ornithine transcarbamylase deficiency
- Injected Sept 13th, died Sept 17th.
- Suffered massive immune response to vector → MSOF → brain death

Major protocol violations

- Recent febrile illness
- High ammonia level at screening
- Poor informed consent

Additional consequences:

- Suspension of gene therapy trials for a decade
- Gene Therapy Clinical Trial Monitoring Plan
- Gene Transfer Safety Symposia

Active trials on hold

Sarepta Therapeutics (AAVrh74 vector):

- Elevidys for Duchene's Muscular Dystrophy
- 3 patient deaths (acute liver failure)

Capsida Biotherapeutics:

- CAP-002 (STXBP1) for encephalopathy
- First participant died → voluntary halt to trial

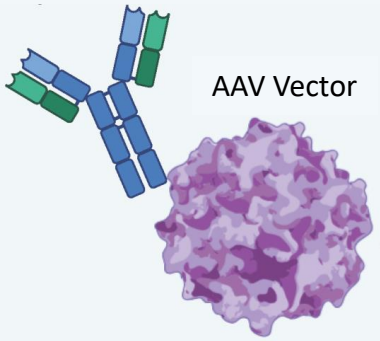
IMPORTANT SAFETY INFORMATION

BOXED WARNING: Serious Liver Injury

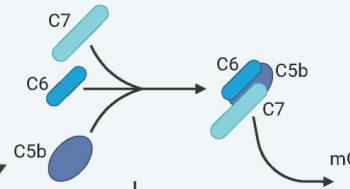
Acute serious liver injury can occur with ITVISMA. Hepatotoxicity, with elevated alanine transaminase (ALT) and/or aspartate transaminase (AST) levels, has occurred with ITVISMA. Patients with

Toxicity: Immunogenicity

Preexisting neutralizing antibodies

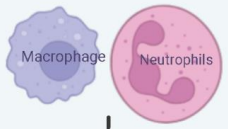


Complement pathway activation

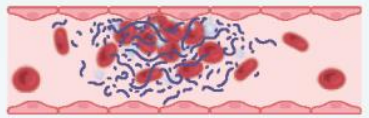


Membrane attack complex (MAC)

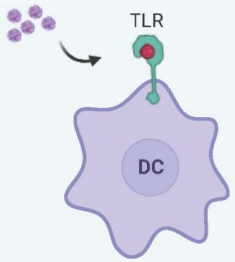
C3a/C5b recruits



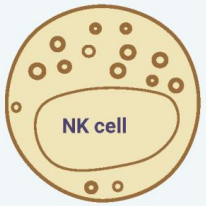
Endothelial injury



PAMPs



activates



Immature dendritic cell activation

NK cell activation

Cytokine storm (IL-6, IL-1B, TNFa)

Early response (1-3 weeks)

Sepsis / MSOF

Thrombotic Microangiopathy

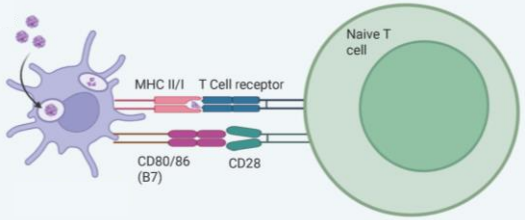
Acute toxicity (1–2 weeks post-dosing): overwhelming innate immune response

Delayed response (later)

Hepatotoxicity
Cardiotoxicity
Neurotoxicity

Subacute toxicity (1–3 months): acquired response to either the viral capsid or the new transgene protein

Antigen



APC

Naïve T-cell

Activated CD4+ T-cell

Toxicity: many potential targets

Primary toxicity

Immune reactions

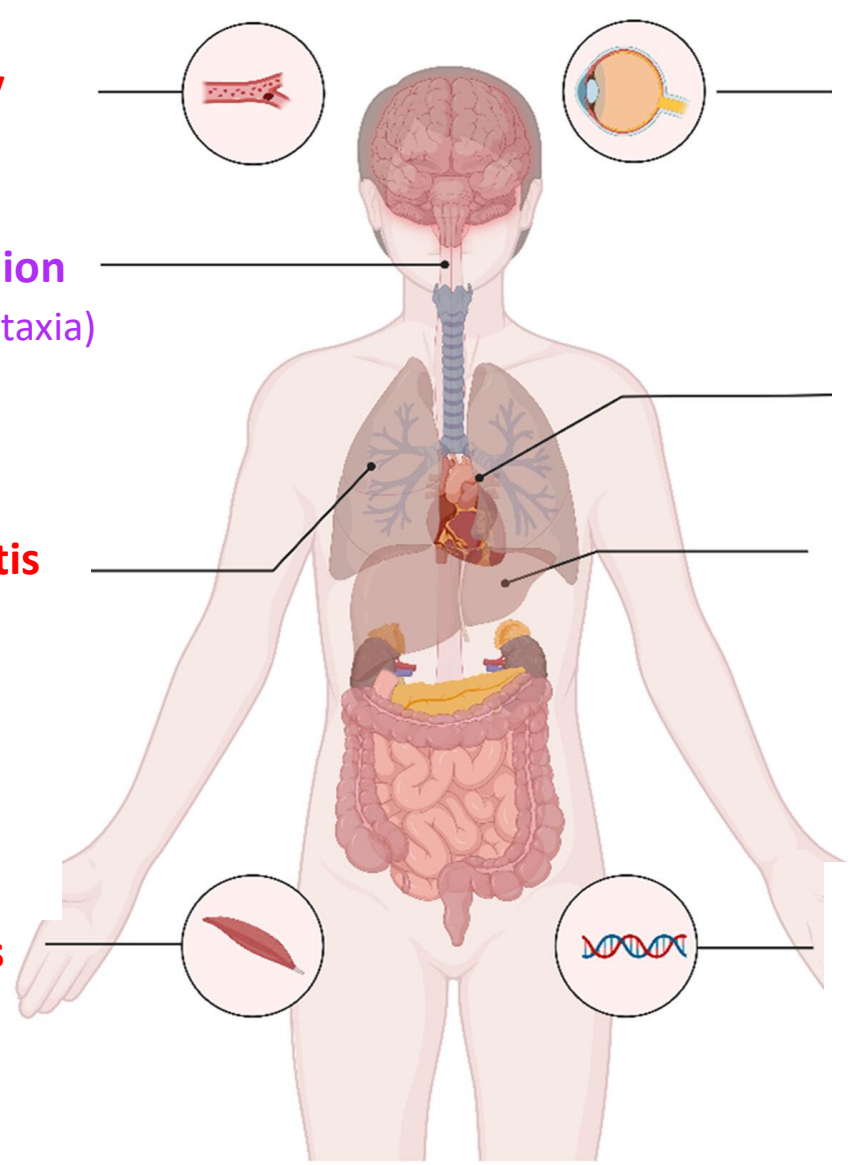
Overexpression or

Ectopic expression

Stochastic toxicity

Off-target effects

Oncogenicity



Gene therapies in the clinic

FDA-Approved DNA & RNA Therapies (Non-Pulmonary)

- **RNA-based** — 6 FDA-approved drugs:
  - **antisense oligonucleotides:** nusinersen (2016, spinal muscular atrophy)
  - **siRNA: patisiran** (2018, hereditary ATTR amyloidosis, first-ever siRNA approval)

- **AAV gene addition** —
  - Zolgensma (SMA)
  - Luxturna (RPE65 inherited retinal disease)
  - Hemgenix/Roctavian (hemophilia B/A).

- **Ex vivo CRISPR editing** —
  - Casgevy (Dec 2023): first CRISPR-Cas9 approval (sickle cell disease and β-thalassemia.

- **In vivo CRISPR editing** —
  - None FDA approved (yet)

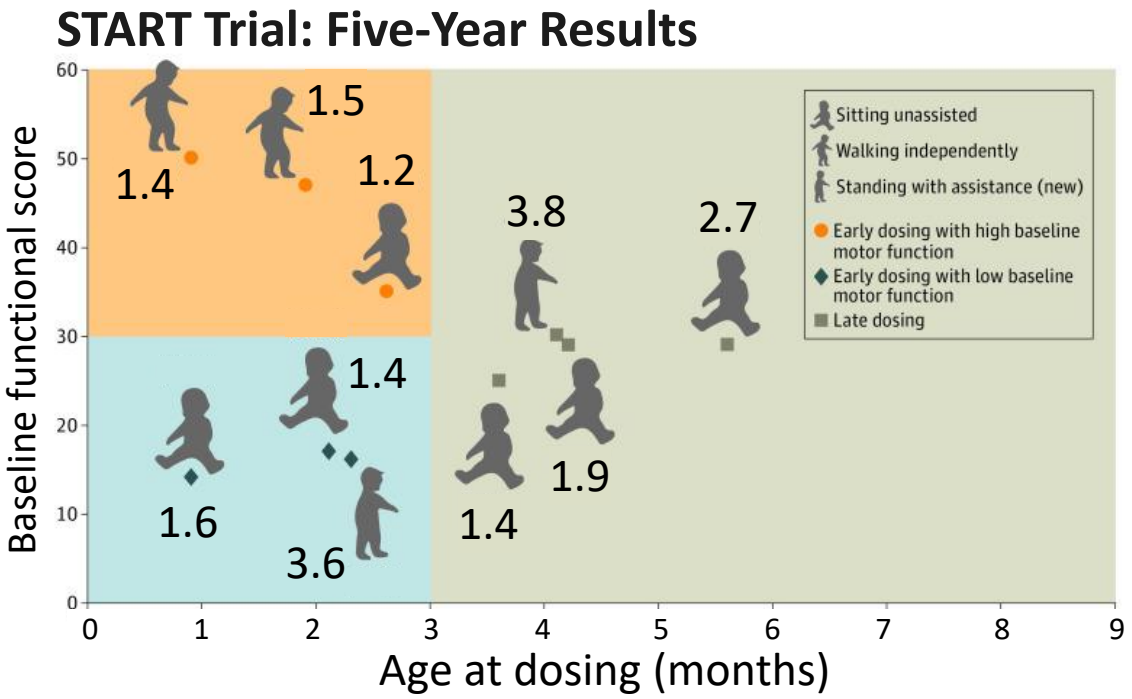
Gene replacement therapy for spinal muscular atrophy (SNM1)

SMA type 1

- Weakness onset by 6 months of age
- Never able to sit independently
- Death or permanent ventilation by 2 years
- Median survival: 6 to 8 months

Onasemnogene Abeparvovec: cDNA replacement

- 13 patients treated (10 at therapeutic dose)
- All 10 patients:
  - were alive
  - without the need for permanent ventilation
  - maintained previously acquired motor milestones
- 2 patients attained new milestone of “standing with assistance”



Mendell JR et al. JAMA Neurol. 2021 PMID: 33999158

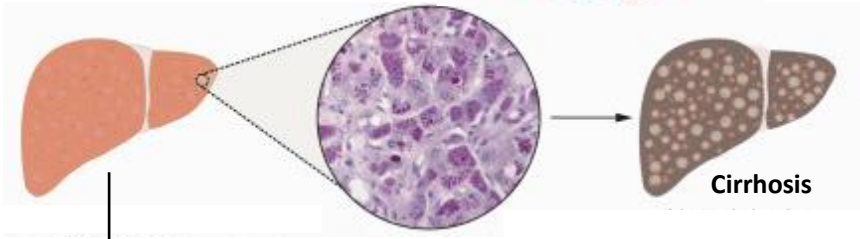
In vivo gene editing

Alpha-1-antitrypsin deficiency

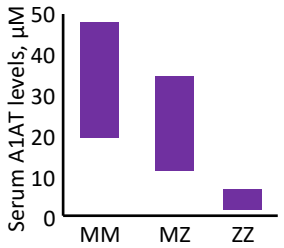
BOTH LOSS- AND GAIN-OF-FUNCTION

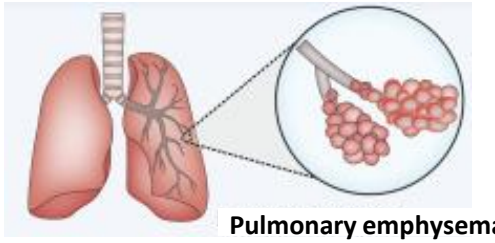
Mutation prevents secretion of A1AT protein

Gain of Function: Toxic accumulation in hepatocytes

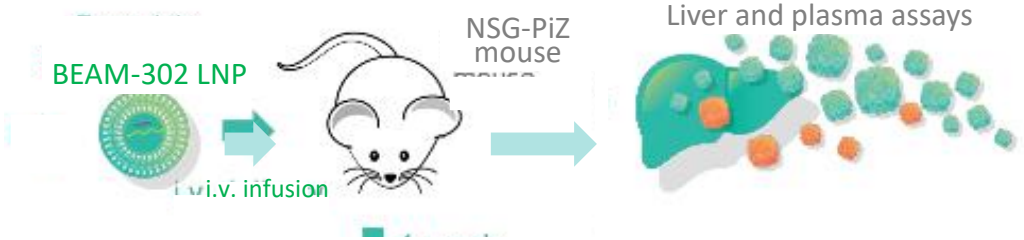


Loss of Function: reduced circulating A1AT levels

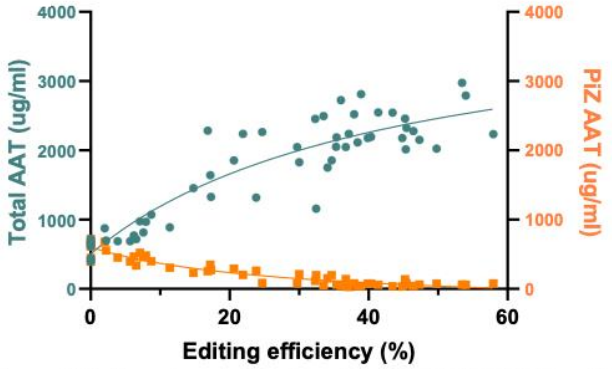




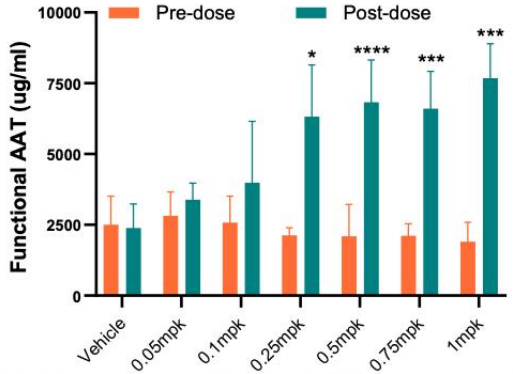
In vivo gene editing for Alpha-1 Antitrypsin deficiency Phase I/II human data (29 patients, March 2026)



Serum AAT levels



Elastase inhibition



BEAM Therapeutics – BEAM-302
Phase I/II human data (29 patients, March 2026)

YolTech Therapeutics - YOLT-202
Phase I data (2 patients, March 2026)

Banerjee et al. Am Thoracic Society International Conference, 2026
BEAM press release – March 24, 2026 at investors.beamtx.com/news-releases/news-release-details/beam-therapeutics-announces-compelling-updated-clinical-data/
YolTech press release – March 15, 2026 at https://www.biospace.com/press-releases/yoltech-therapeutics-receives-fda-clearance-to-initiate-phase-2-3-study-of-in-vivo-gene-editing-therapy-yolt-202-in-alpha-1-antitrypsin-deficiency-aatd

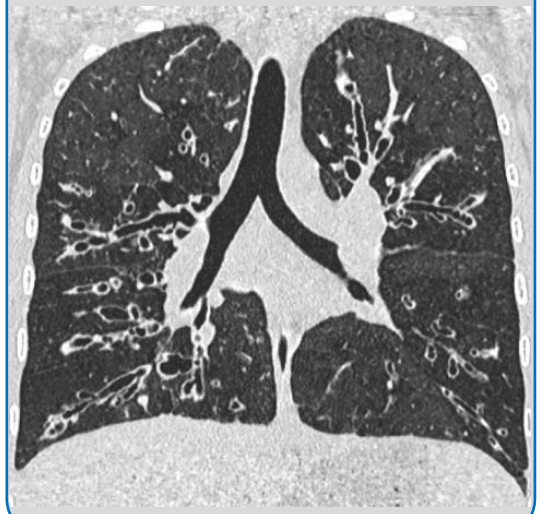
What about gene therapy targeting the lung?

Bronchiectasis

Cystic Fibrosis (CFTR)

Primary Ciliary Dyskinesia (> 40 genes)

Immune deficiency (>100 genes)

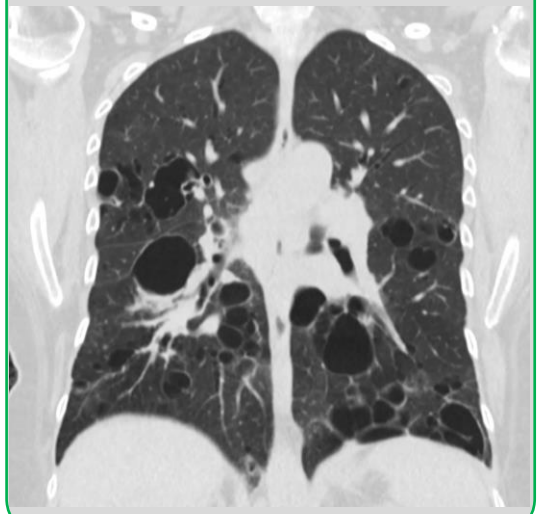


Cystic Lung Disease

Alpha-1-antitrypsin deficiency (SERPINA1)

Birt-Hogg-Dubé (FLCN)

LAM (TSC1/TSC2)

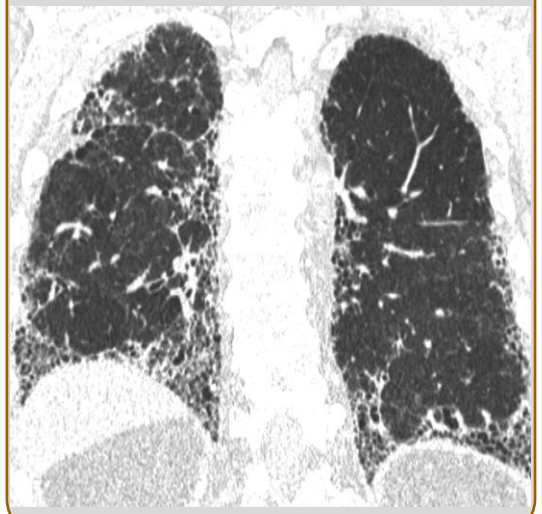


Interstitial Lung Disease

Telomere (TERT, TERC, RTEL1, PARN)

Surfactant (SFTPB, SFTPC)

Alveolar Proteinosis (CSF2RA or CSF2RB)



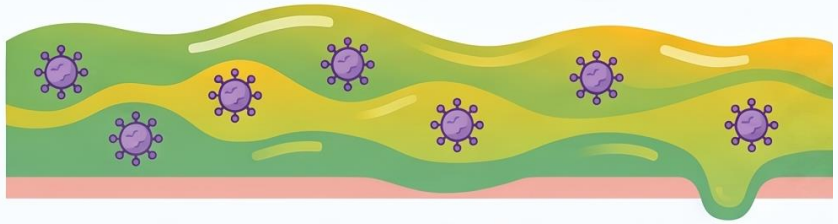
Pulmonary Vascular Disease

Pulmonary Hypertension (BMPR2, TBX4, KDR…)

Hereditary hemorrhagic telangiectasia (ENG, ACVRL, SMAD4)

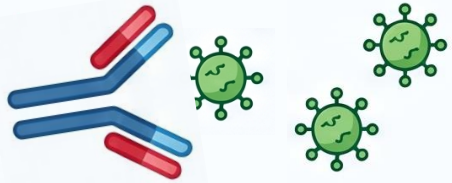
Why CF gene therapy has been an uphill battle

Mucus: The Viscoelastic Barrier



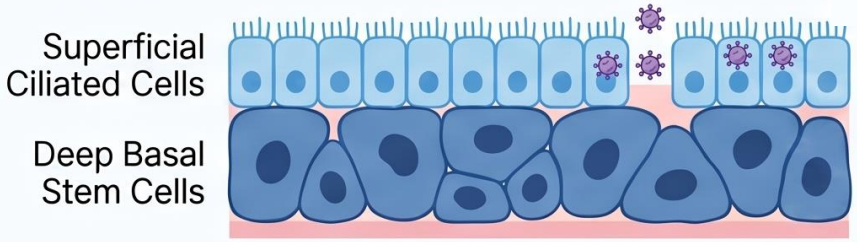
Abnormal, thick mucus in CF traps vectors before they reach the underlying epithelium.

Immune Shield Blocks Repeat Dosing



Pre-existing antibodies to vectors limit initial treatment and prevent necessary redosing.

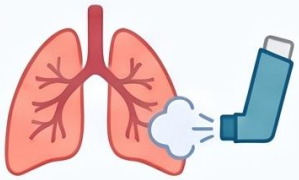
Accessing Deep Basal Stem Cells



Durable correction requires reaching deep stem cells, which are less accessible to inhaled vectors.

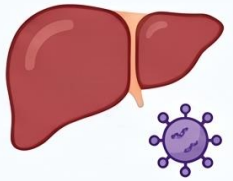
Local Delivery vs. Natural Tropism

Local Delivery



Inhalation multiplies delivery hurdles.

Natural Tropism



Benefits from natural organ attraction.

NotebookLM

CF Gene Therapy: 30 Year History, Success in Sight

4D-710 (4D Molecular Therapeutics)

- Engineered/evolved AAV capsid (A101)
- Codon-optimized CFTRΔR minigene
- Mutation-agnostic
- Delivered by aerosol

Phase 1/2 AEROW trial:

	Baseline		Change from baseline	
Participant	$ppFEV_1$ *(Impairment)*	QoL by CFQ-R-R	$ppFEV_1$ *(f/u)*	QoL by CFQ-R-R max *(f/u)*
1	83 (*Mild*)	72	0 (*Mo 12*)	**+11** (*Mo 12*)
2	69 (*Moderate*)	61	**+7** (*Mo 9*)	**+22** (*Mo 9*)
3	95 (*Normal*)	83	-2 (*Mo 6**)	**+6** (*Mo 6**)

Phase 1/2 AEROW trial:

Interim data (Dec 2025):
16 participants (4-24 months of follow-up)

Dose-dependent RNA levels at or above target levels

At one year:

- improved lung clearance ($LCI_{2.5}$)
- Improved lung function ($ppFEV_1$)
- quality of life (CFQ-R-R)

Lowest dose (2.5E14 vg) advancing to Phase 2

ir.4dmoleculartherapeutics.com/news-releases/news-release-details/4dmt-presents-positive-interim-data-aerosolized-4d-710-phase-12/
ir.4dmoleculartherapeutics.com/news-releases/news-release-details/4dmt-announces-positive-interim-clinical-data-4d-710-aerow-phase

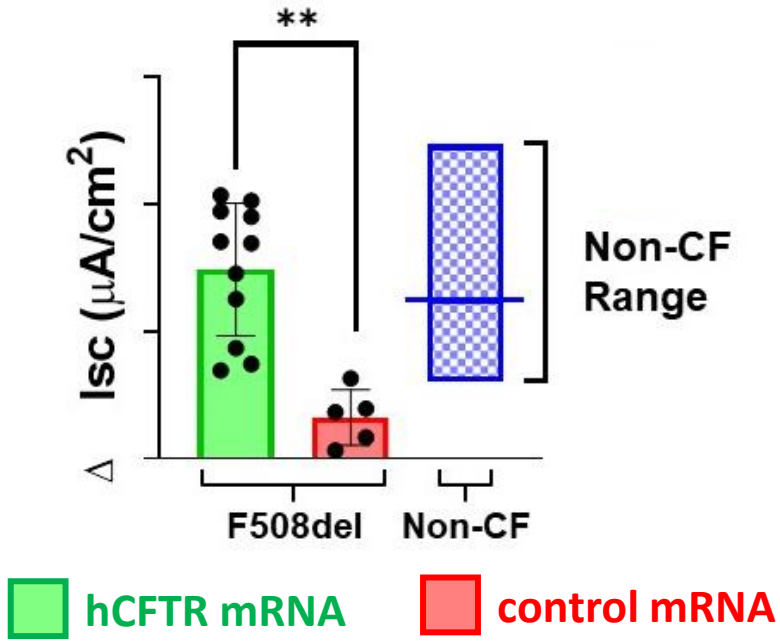
CF Gene Therapy: 30 Year History, Success in Sight

ARCT-032 (Arcturus / CF Foundation)

Inhaled mRNA-lipid nanoparticle (LUNAR platform)

Chloride gradient restoration

(Ussing chamber, n = 2 donors)



Interim results (Oct. 22, 2025)

(6 patients, Class I variants)

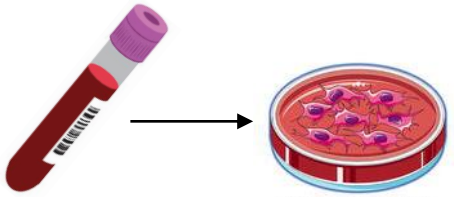
Subject	% Change (Day 28 from baseline) Mucus Plugs (Count)	Mucus Volume (ml)
1	25.60%	60.90%
2	-38.50%	-67.40%
3	23.80%	9.10%
4	-34.90%	-27.50%
5	-9.10%	-6.10%
6	-28.50%	-29.50%

No change in FEV1 from baseline at day 28

https://ir.arcturusrx.com/news-releases/news-release-details/arcturus-therapeutics-provides-interim-phase-2-data-cystic

Cell therapies for pulmonary medicine

Cell-Based Therapy: iPSCs, Reprogramming & Regenerative Medicine

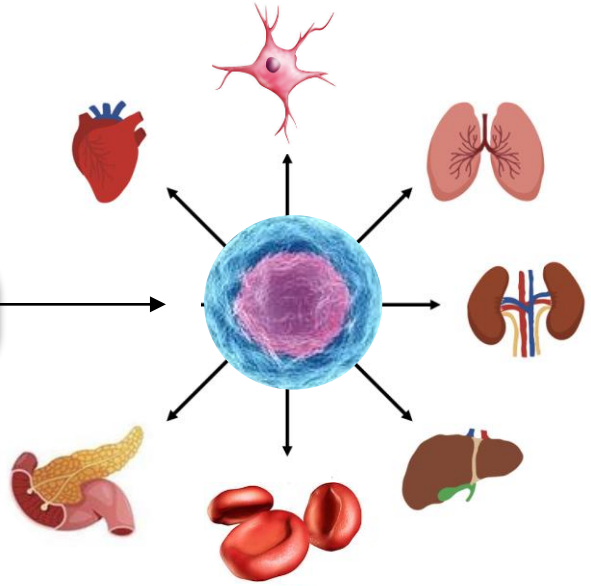


Peripheral blood mononuclear cells

Reprogramming Factors

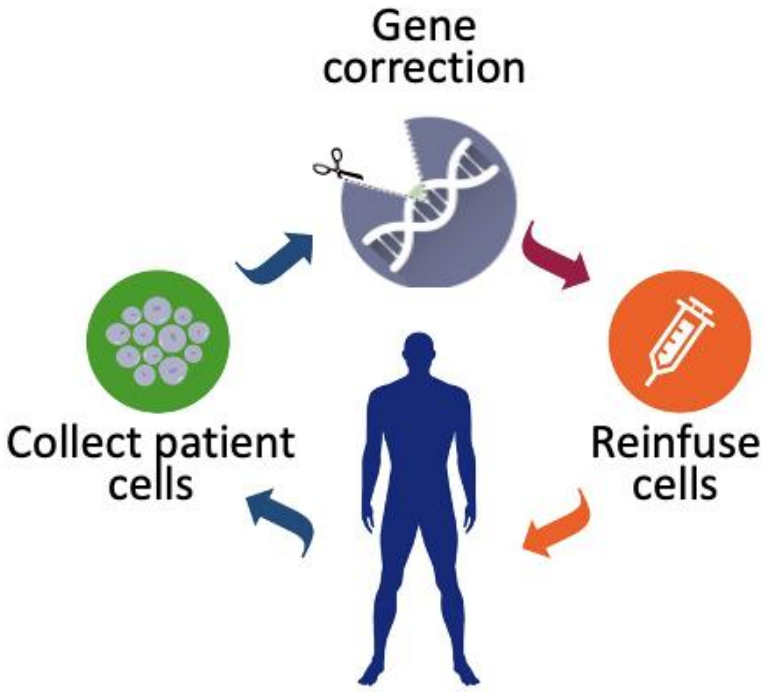
Oct-4 SOX4
c-Myc KLF4

Inducible Pluripotent Stem Cells



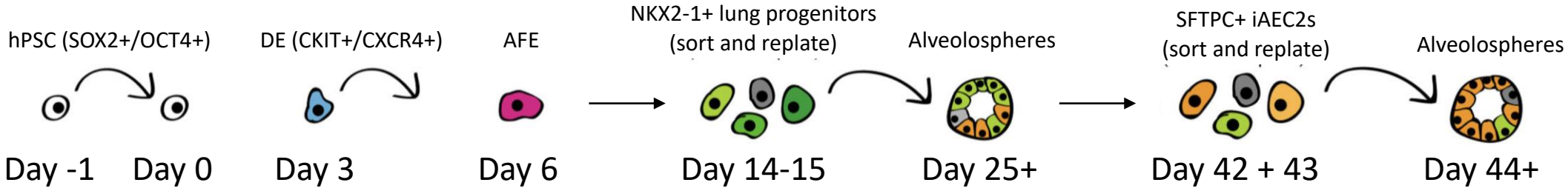
"Natural" cell type
Patient-specific
Renewable source

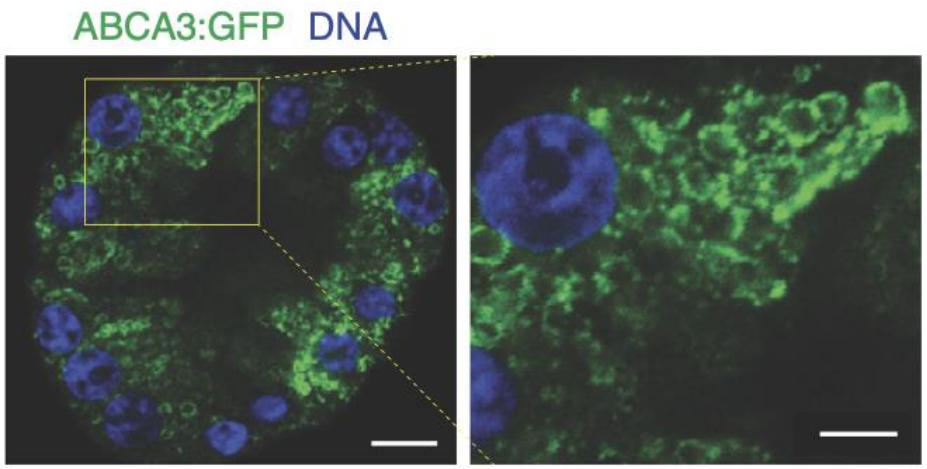
Ex vivo gene editing



iPSC-Derived Alveolar Epithelial Cells

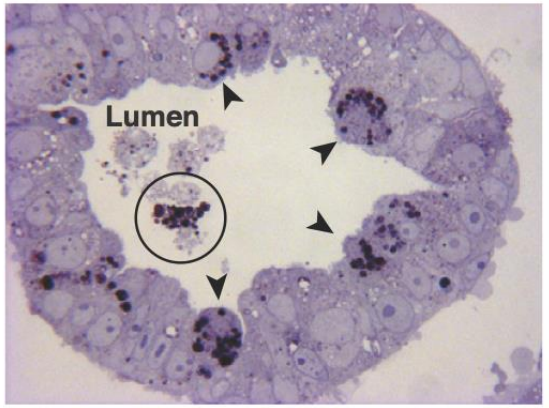
Type II Alveolar Epithelium



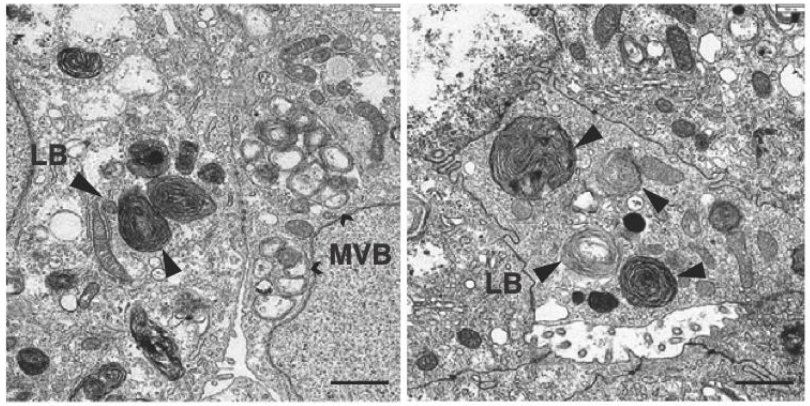


Sun YL et al. Am J Respir Cell Mol Biol. 2021 (PMID: 34101541)

Alveolosphere

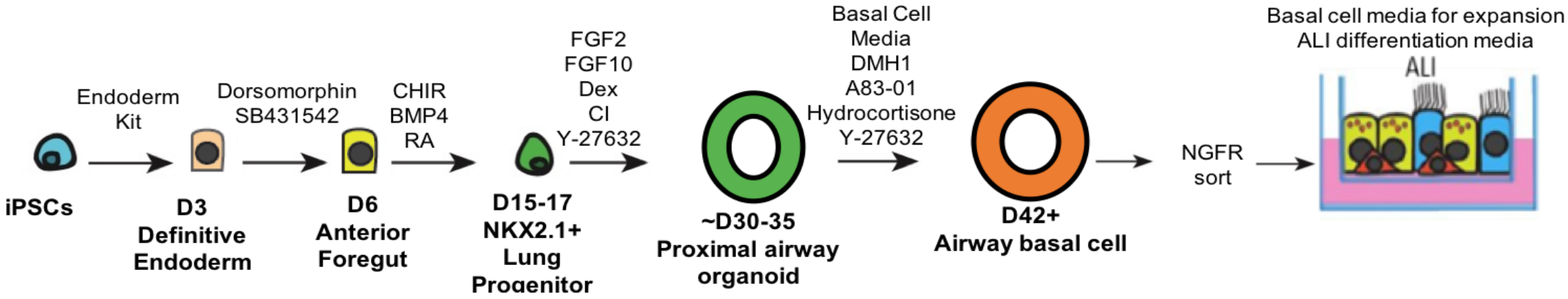


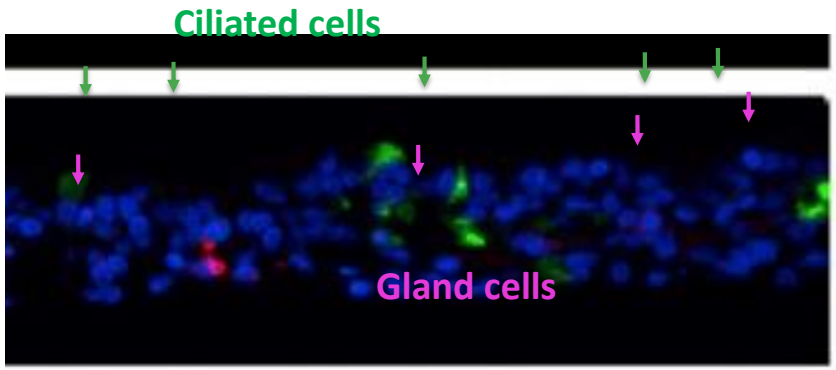
Alveolosphere EM: lamellar bodies

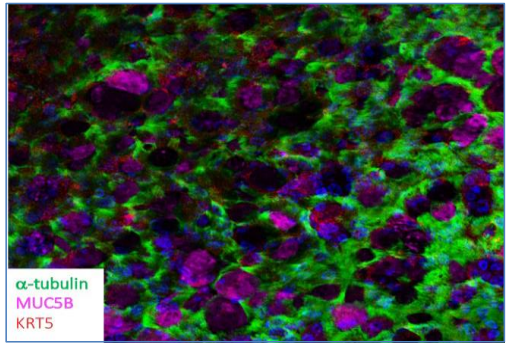


Burgess CL et al. Generation of human alveolar epithelial type I cells from pluripotent stem cells. Cell Stem Cell. 2024 (PMID: 38642558)
Burgess CL et al. STAR Protoc. (PMID: 40048418)
Herriges MJ et al. Durable alveolar engraftment of PSC-derived lung epithelial cells into immunocompetent mice. Cell Stem Cell. 2023 (PMID: 37625412)

iPSC-Derived Airway Epithelium



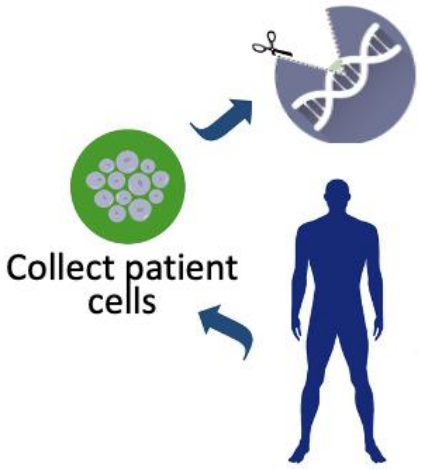


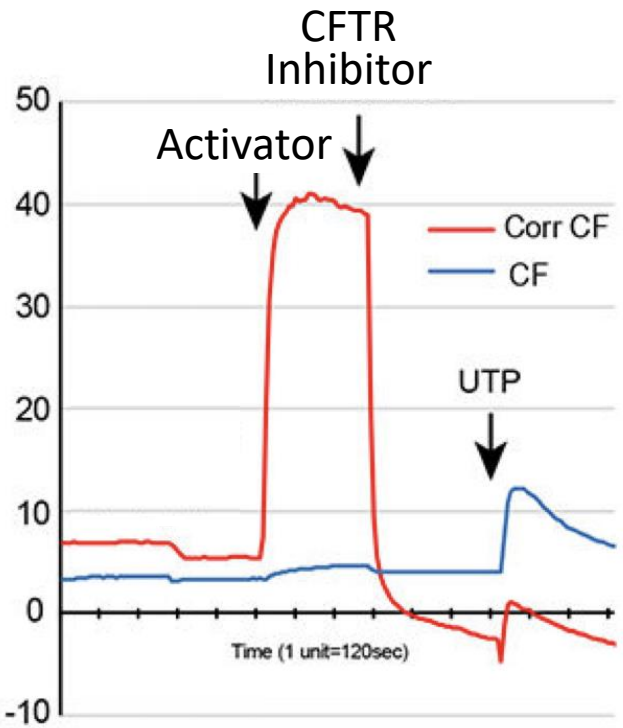


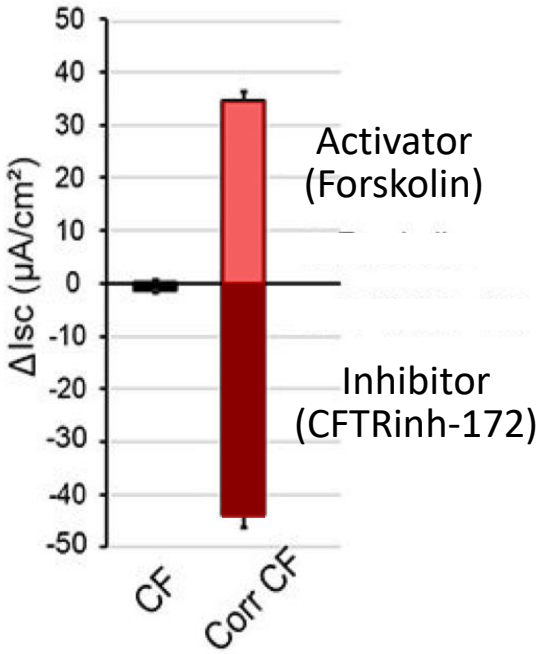
Hawkins et al, CSC, 2021

Towards cellular therapy for CF

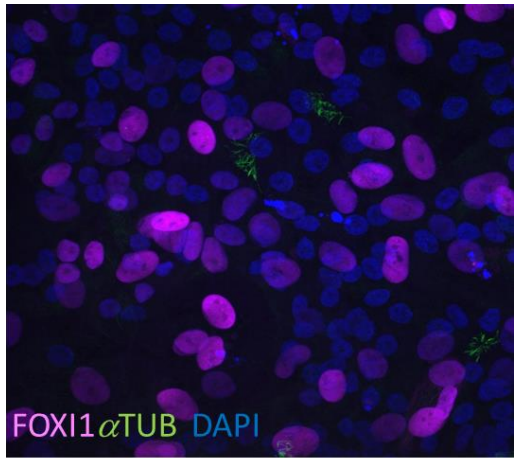
Ex vivo CF gene repair

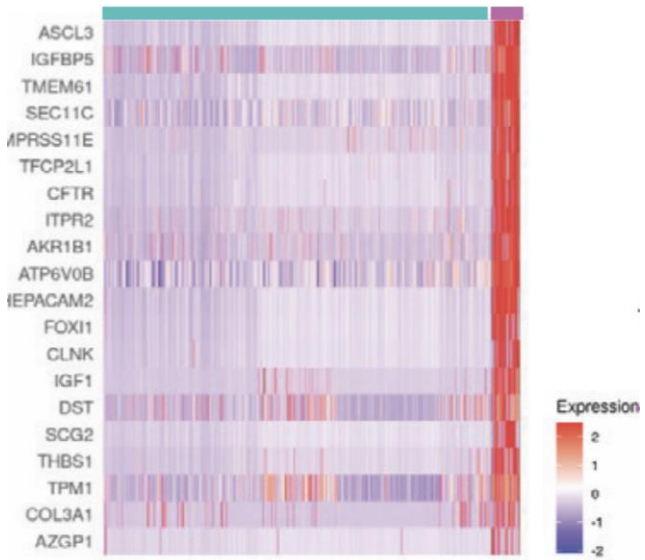






Mass produce ionocytes





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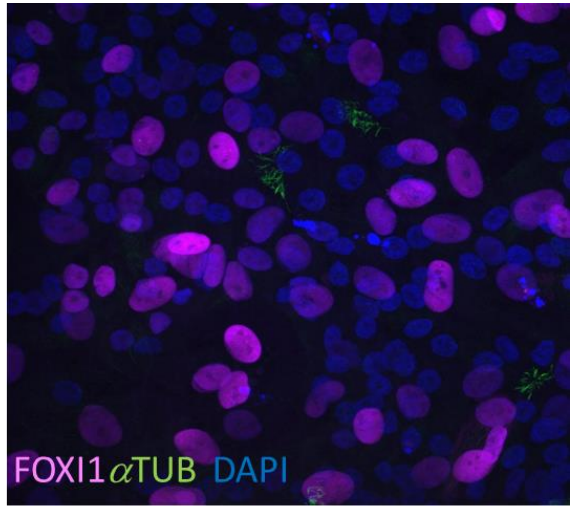
Wang R et al. Am J Respir Crit Care Med. 2023; 207(9):1249-1253. PMID: 36857488.

Towards cellular therapy for CF

Mass produce cells

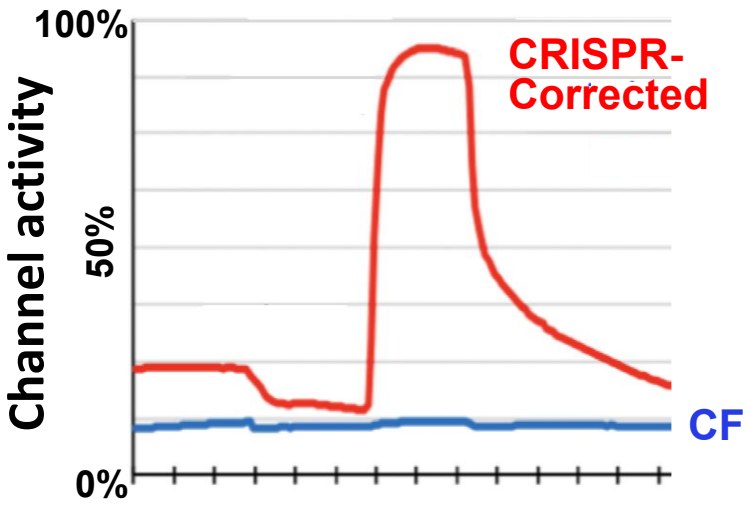
Wang et al. AJRCCM 2023



Ionocytes

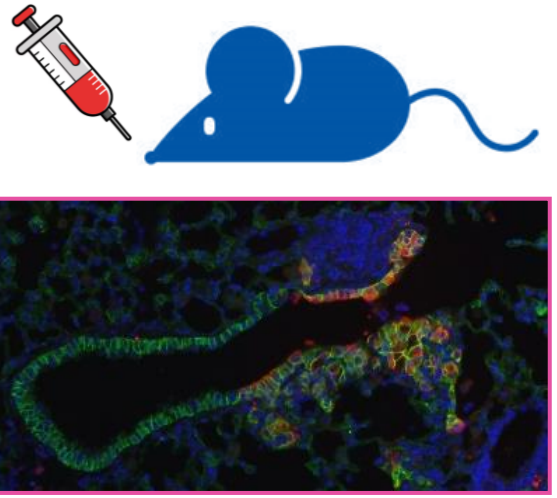
CF gene repair

Hawkins et al. Cell Stem Cell 2021



CF gene activity restored

Implantation



Derived cells implant and survive

Ruby Wang

Stuart Rollins

Carla Kim

Barriers for pulmonary cellular therapies

Engraftment efficiency

in vivo durability (remains low relative to native regeneration)

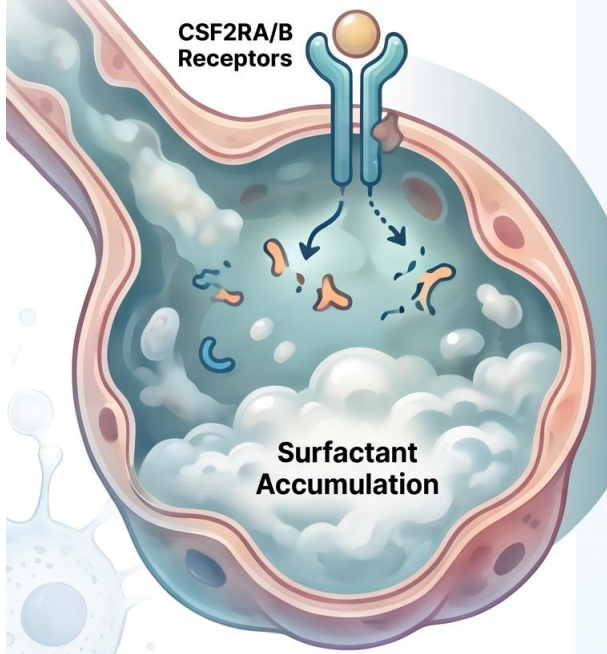
Risk of residual undifferentiated pluripotent cells (tumorigenicity);

Manufacturing scale and cost for clinical-grade cell products

Pulmonary Macrophage Transplantation for Hereditary PAP

The Driver: GM-CSF Dysfunction

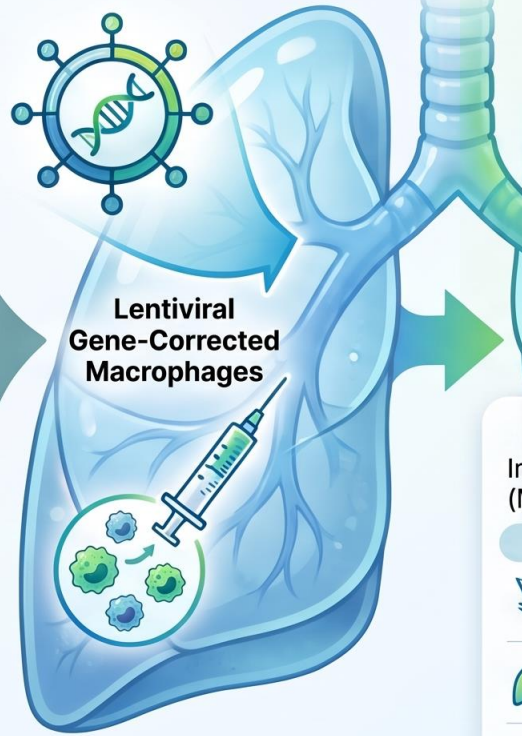
Mutations in CSF2RA/B receptors cause surfactant to accumulate, leading to respiratory failure.

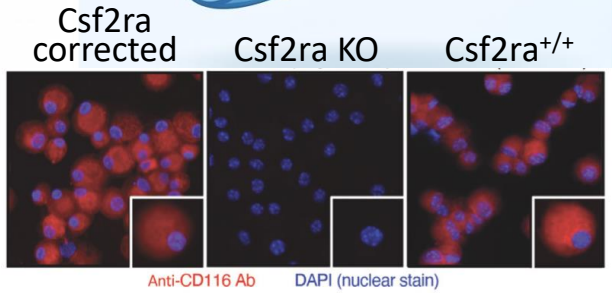


Surfactant accumulates in the lungs due to GM-CSF signaling failure.

Gene-Corrected Macrophage Delivery

Lentiviral gene-corrected macrophages are transplanted directly into the lungs to restore function.





Long-Term Efficacy Without Myeloablation

A single administration provides therapeutic benefits that persist for at least 12 months.

Impact of PMT vs. Disease State (Murine Models)

Metric	Impact of PMT
Surfactant Burden	Significant Reduction
Lung Weight	Normalized
Duration of Benefit	12+ Months

Clinical Evidence & Transition

Effective Target Dose

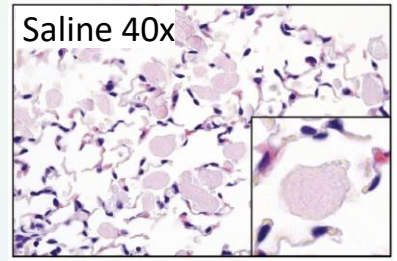
500,000 Cells

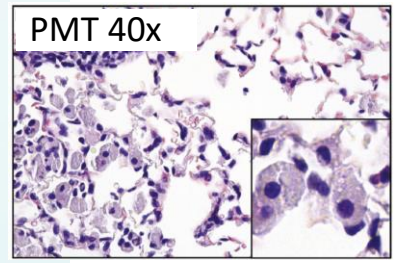
Toxicology studies confirmed this dose reduces surfactant burden and pulmonary lung weight.

Significant Biomarker Reduction

SP-D GM-CSF M-CSF MCP-1

Treatment successfully lowers levels of SP-D, GM-CSF, M-CSF, and MCP-1.





First-in-Human Trial (NCT05761899)

Transitioning to GMP-compliant human trials following successful safety and scale-up validation.

NotebookLM

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SUMMARY STATEMENT

1. Medicine has entered the gene/cell therapy era:
   - The underlying platforms (RNA-based, AAV, base-editing, iPSC) are all clinically validated.

2. Pulmonary medicine is entering the era:
   - Pulmonary has lagged roughly a decade behind liver- and blood-directed programs.
   - The lung is a harder delivery target (mucus, immunity, and local-access constraints)

3. Three leading indications in clinical trials:
   4D-710 (CF, entering Phase 2),
   BEAM-302 (AATD, entering pivotal development), and
   pulmonary macrophage transplantation for hereditary PAP (Phase 1/2, first-in-human).

4. For clinical practice today: CFTR modulators remain first-line for eligible CF patients; gene therapy targets the modulator-ineligible/intolerant residual population. **No gene or cell therapy is yet FDA-approved for any primary pulmonary disease.**

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