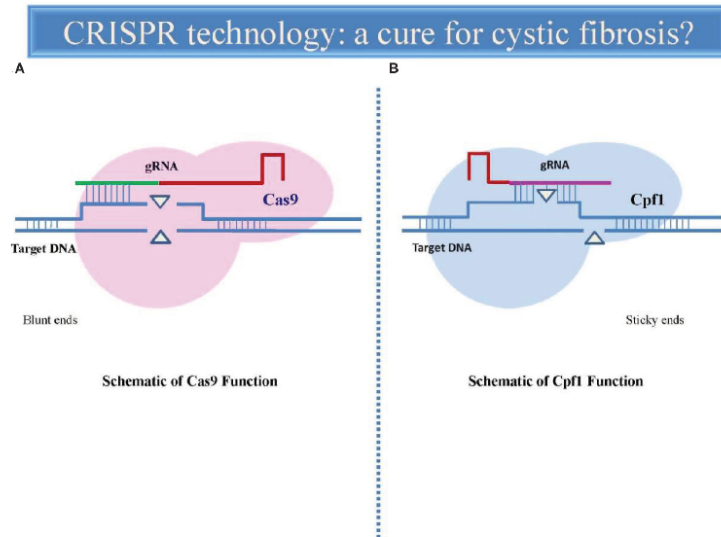
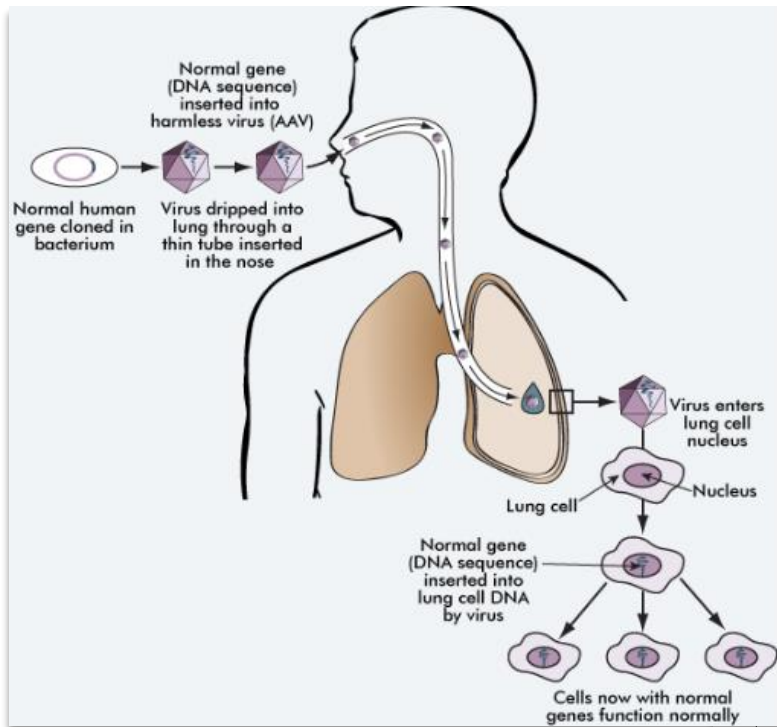


***Genová terapie  
a cílená farmakoterapie:  
na modelu personalizované léčby  
cystické fibrózy***

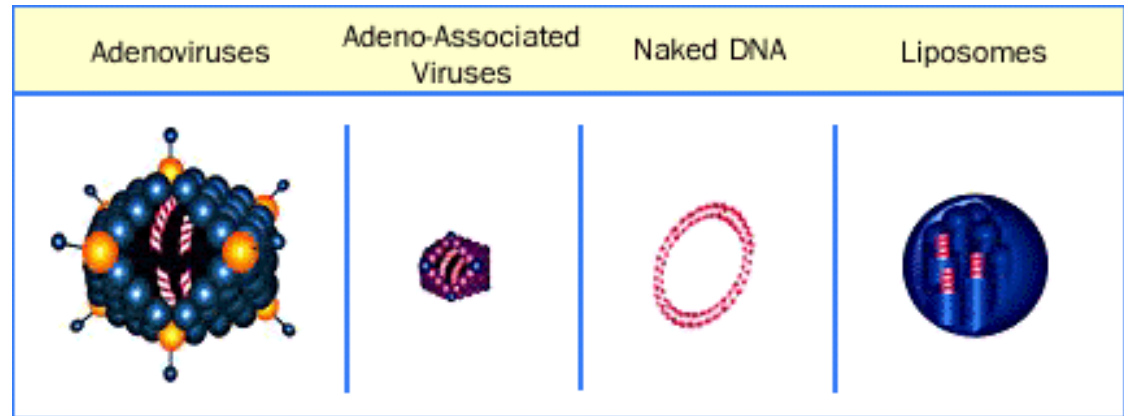
**Prof. Milan Macek M.D., PhD.**

# Genová terapie 1.0 versus Genová terapie 2.0



**FIGURE 1 |** Comparative representation of CRISPR-Cas9 and CRISPR-Cpf1-mediated genome editing. The gRNA directs endonuclease Cas9 (**A**) to the target DNA sequence (blue) where it induces a double-strand break, leading to a sequence deletion. Cas9 uses a structural region of gRNA as a handle (red) and a variable targeting region (green) which identifies the target sequence to match and cleave. Cas9 can be specifically directed to the any target site of genome simply by modifying the sequence of the gRNA. Cpf1 endonuclease (**B**) contains a shorter and single identified nuclease domain (CRISPR-RNA), in contrast to the two nuclease domains present in Cas9. Cpf1-crRNA efficiently cleaves target DNA without the requirement for any additional RNA species. Cpf1 generates a staggered cut, in contrast to the blunt ends generated by Cas9. In both cases, the DSBs are subsequently repaired by two major cellular mechanisms, non-homologous end joining (NHEJ) and homology-directed repair (HDR).

# GT1 vektory



Retroviry

Lentiviry

Adenoviry

Adeno-associované viry (AAV)

Ostatní virové vektory

Vaccinia– Hepatitis virus

Herpes virus – Polio virus

Papilloma virus– Sindbis and other RNA viruses

Nevirové metody

Ligand-DNA conjugates – Adenovirus- ligand-DNA

Lipofection – Direct DNA injection

CaPO<sub>4</sub> precipitation – Ribozymes

chimeric oligo/gene correction

# Obecné problémy

Jak dodat DNA ?

Dosažení žádoucí exprese?

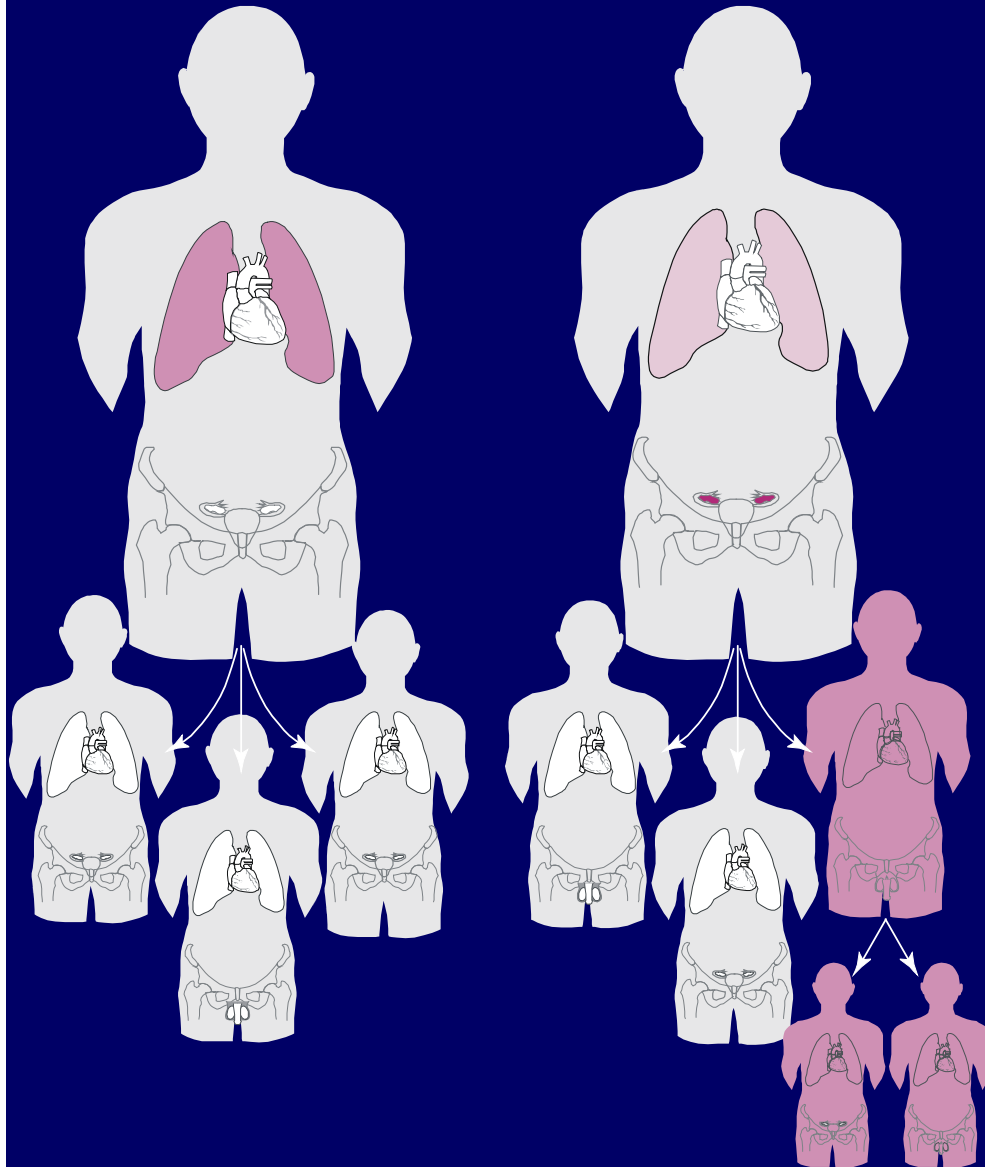
Udržení žádoucí exprese?

Tkáňová specifčnost

*in vivo* regulace?

Co když budou nežádoucí účinky?

## SOMATIC GENE THERAPY    GERMLINE GENE THERAPY

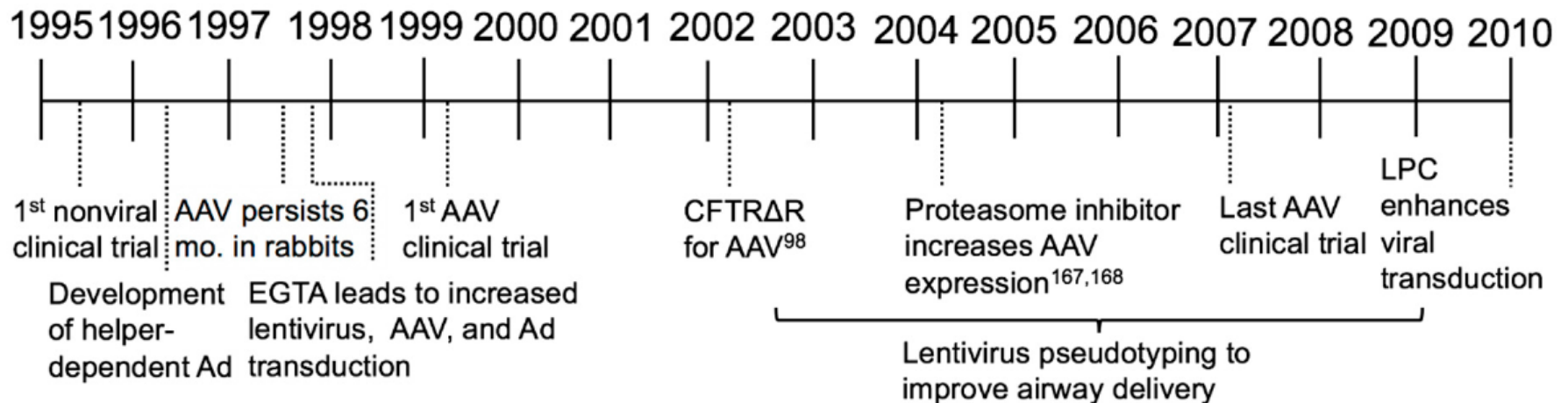
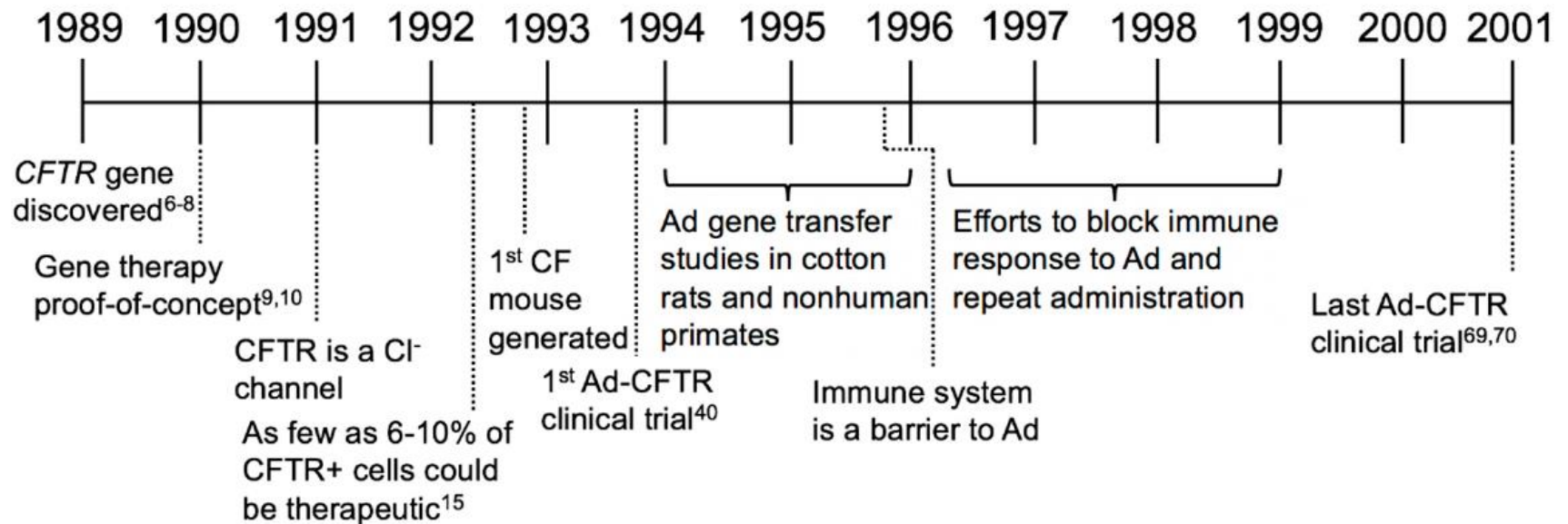


TD Gelehrter, FS Collins, D Ginsburg.  
**Principles of Medical Genetics.** 1997.

# Plus a minusy virových vektorů

| Vector                       | Advantages   | Disadvantages  |
|------------------------------|--|--|
| Retrovirus                   | High efficiency transduction of appropriate target cells.<br>Long-term expression-integration into chromosomal DNA).                     | Potential for insertional mutagenesis.<br>Requires dividing cells.<br>Limited size of DNA insert.      |
| Adenovirus                   | High transduction efficiency.<br>Broad range of target cells.<br>Does not require cell division.<br>Low risk of insertional mutagenesis. | Transient expression.<br>Immunogenicity.<br>Direct cytopathic effects of virus.                        |
| Adeno-associated virus (AAV) | Does not require cell division.<br>? Site specific integration.  | Potential for insertional mutagenesis if integration not site-specific.<br>Limited size of DNA insert. |
| Non-viral vectors            | No infectious risk.<br>Completely synthetic.<br>No limitation on insert size.  | Low efficiency.<br>Limited target cell range.<br>Transient expression.                                 |

# Vývoj genové terapie u CF (1989-2010)



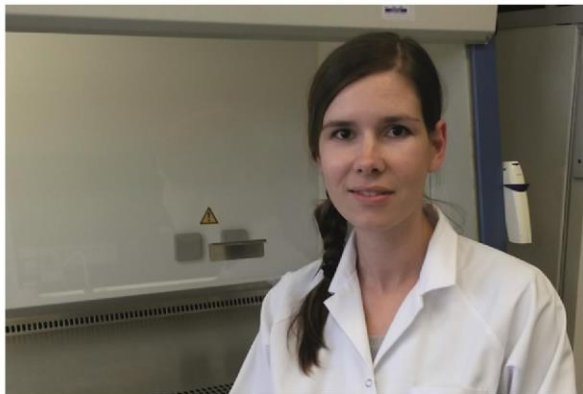


# Vývoj genové terapie u CF (2008-2022)



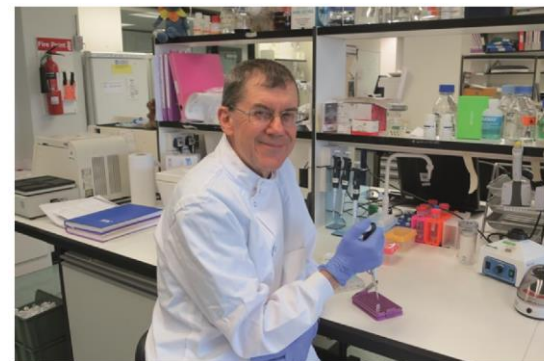
Source: Eric Alton

Eric Alton, professor of gene therapy and respiratory medicine at Imperial College London, is coordinator of the UK Cystic Fibrosis Gene Therapy Consortium



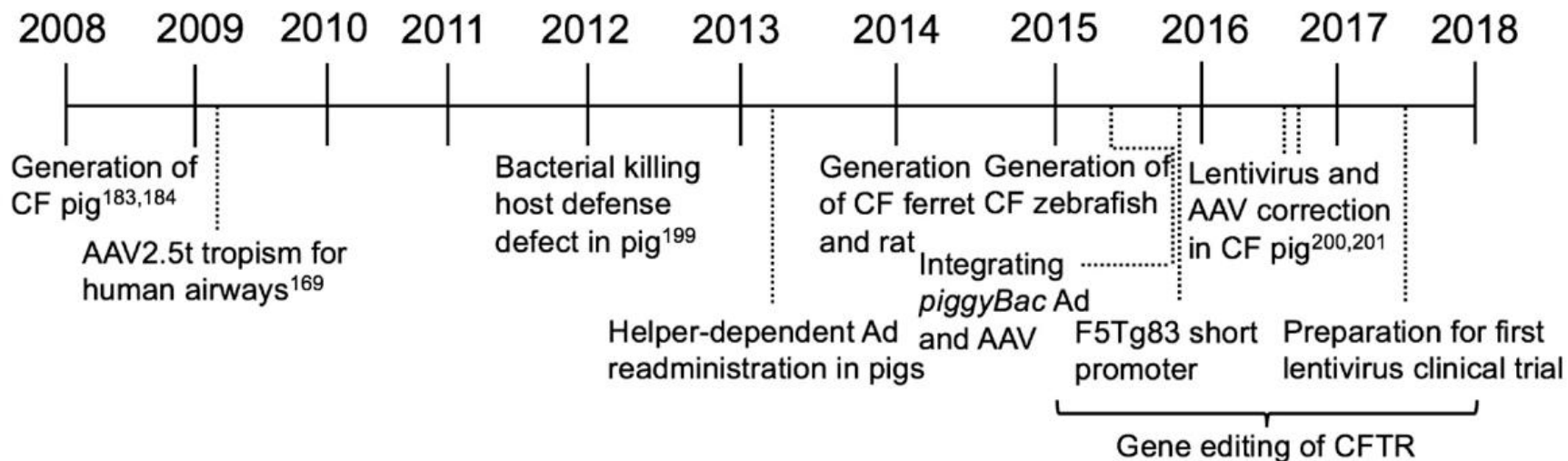
Source: Marianne Carlon

Marianne Carlon, a gene therapy researcher at Catholic University in Leuven, Belgium, says liposomes are not very efficient at getting their genetic cargo into the host nucleus



Source: Chris Boyd

Chris Boyd, a medical geneticist at the University of Edinburgh and a member of the UK Cystic Fibrosis Gene Therapy Consortium, says the cells lining the airways perceive gene therapy delivery systems as alien invaders, and do their best to keep them out





# UK – klinické protokoly (2015-2018)

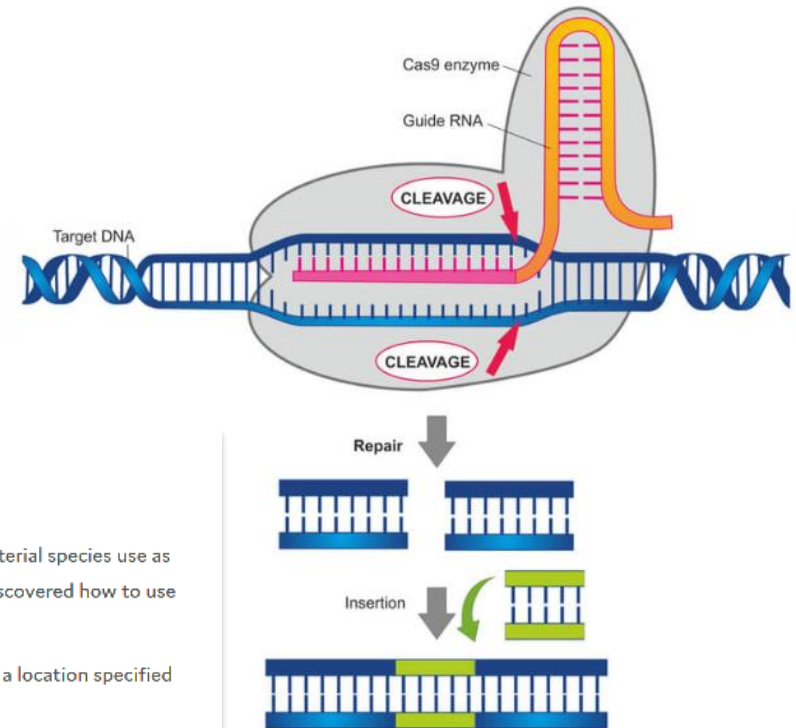
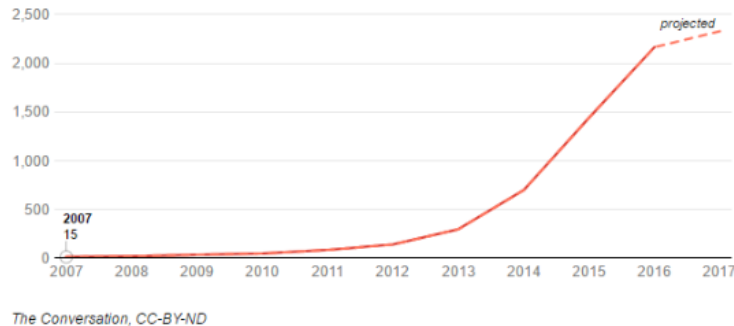


| <i>Phase</i>  | <i>Objectives</i>   | <i>Progression criteria</i>   |
|---|---|---|
| Preclinical selection and development of a GTA suitable for repeated administration to patients with CF | Selection of pGM169/GL67A   | <ol style="list-style-type: none"> <li>1. Transfection of AECs</li> <li>2. Low toxicity</li> <li>3. Repeat administration feasible</li> <li>4. Stability in nebulizer</li> <li>5. GMP production feasible</li> </ol>            |
| Tracking study  | Validation of putative end-point assays in patients undergoing exacerbations  | Selection of end points that respond to conventional treatment  |
| Single-dose phase I/IIa pilot trial   | <ol style="list-style-type: none"> <li>1. Selection of suitable dose for MDT</li> <li>2. Confirmation of dosing interval in patients with CF</li> </ol>                           | <ol style="list-style-type: none"> <li>1. Suitable dose: 5 ml of pGM169/GL67A per dose</li> <li>2. Dosing interval: Monthly for 12 months</li> </ol>  |
| Run-in study  | <ol style="list-style-type: none"> <li>1. Selection of primary and secondary end points</li> <li>2. Characterization of most suitable patient population for MDT trial</li> </ol> | <ol style="list-style-type: none"> <li>1. Primary end point: Percent change in relative FEV<sub>1</sub> from baseline</li> <li>2. Inclusion of patients &gt; 12 years and with baseline FEV<sub>1</sub> of 50 to 90%</li> </ol> |
| Multidose murine and ovine regulatory-compliant toxicology studies                                      | Prove safety in animal models   | <ol style="list-style-type: none"> <li>1. No chronic inflammation</li> <li>2. No remodeling of lung</li> <li>3. No extrapulmonary effects</li> </ol>  |
| Multidose, double-blinded, placebo-controlled phase IIb trial   | Significant difference in primary end point comparing active and placebo groups   | Depending on outcome of trial   |

AECs, airway epithelial cells; CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in the first second; GMP, Good Manufacturing Process; GTA, gene transfer agent; MDT, multidose trial.

# GeneTherapy 2.0: CRISPR-Cas9

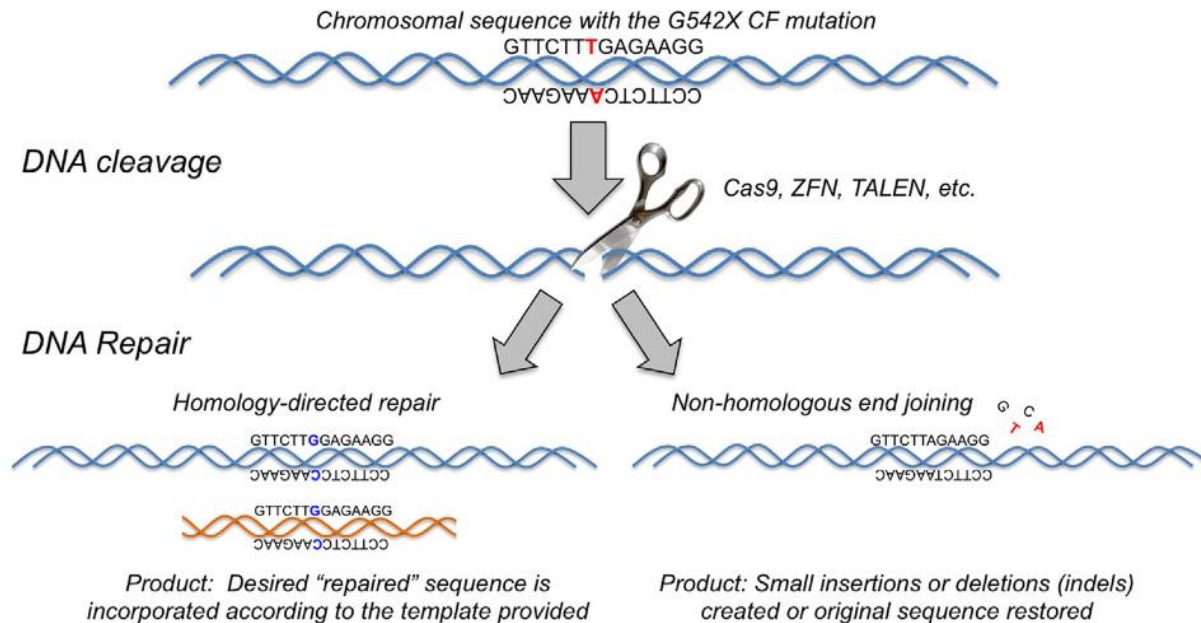
CRISPR research publications



## CRISPR Lexicon

- **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats of genetic information that some bacterial species use as part of an antiviral system. A group of scientists, including our co-founder Dr. Emmanuelle Charpentier, discovered how to use this system as a gene-editing tool (Jinek, *et al.* Science 2012)
- **Cas9:** a CRISPR-associated (Cas) endonuclease, or enzyme, that acts as "molecular scissors" to cut DNA at a location specified by a guide RNA
- **Deoxyribonucleic acid (DNA):** the molecule that most organisms use to store genetic information, which contains the "instructions for life"
- **Ribonucleic acid (RNA):** a molecule related to DNA that living things use for a number of purposes, including transporting and reading the DNA "instructions"
- **Guide RNA (gRNA):** a type of RNA molecule that binds to Cas9 and specifies, based on the sequence of the gRNA, the location at which Cas9 will cut DNA

# Genová editace u CF- základní principy



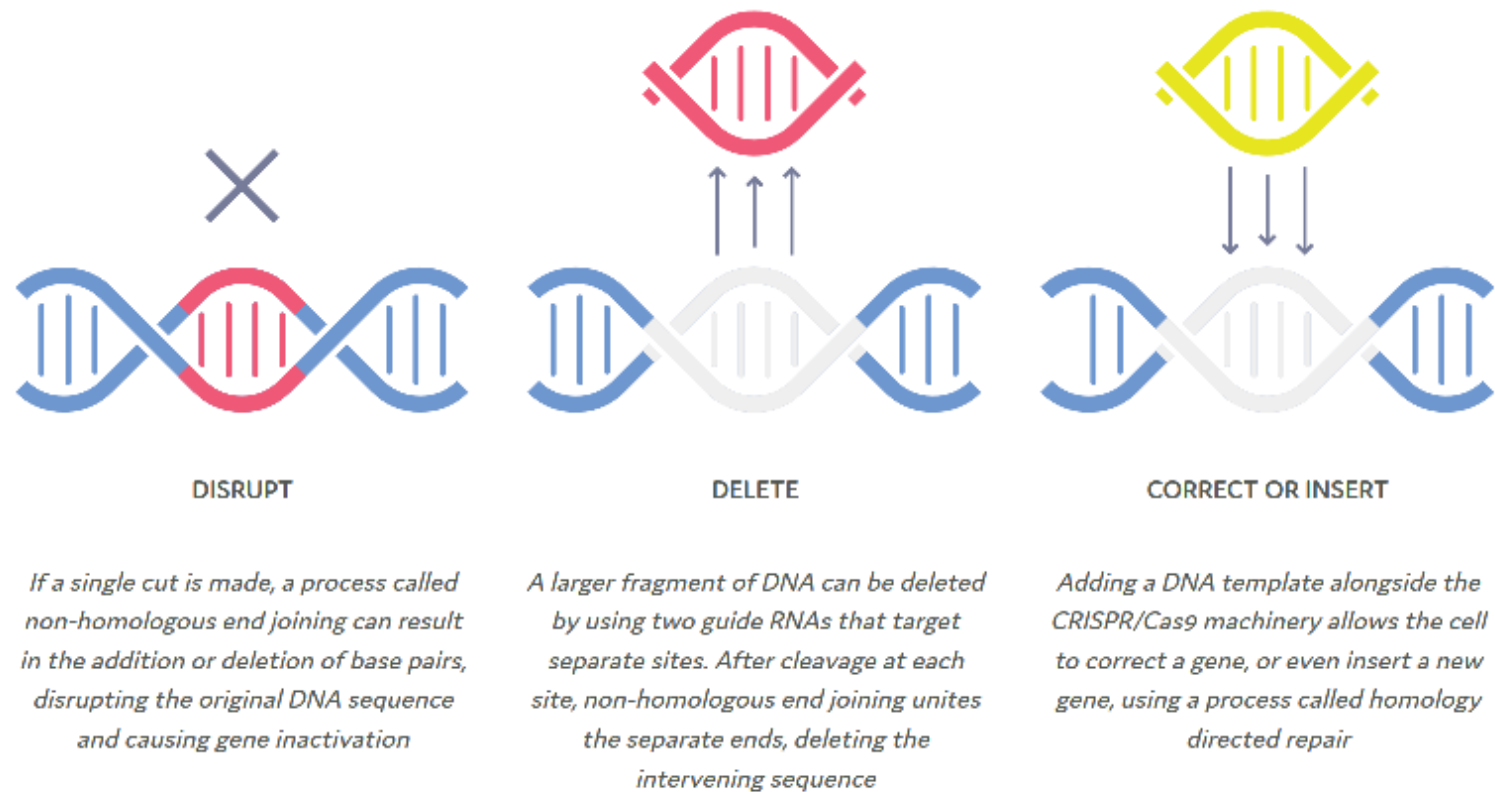
**FIGURE 1** The gene editing process. Gene editing takes advantage of a cell's ability to repair DNA damage. A DNA break can be induced at a position of choice, such as a disease causing mutation like G542X, by any number of methods (CRISPR/Cas9, ZFNs, TALENs), and the broken ends may be reconnected by a process called nonhomologous end-joining (at right) that often results in a small number of nucleotides being lost or inserted during the repair. If a template is available (in orange), DNA polymerase can use the homology between the template and the breakage site during repair to incorporate the template's sequences, in this case an arrangement that would repair the G542X stop codon mutation

# CRISPR Therapeutics 1.



Three main categories of genetic edits can be performed with CRISPR/Cas9:

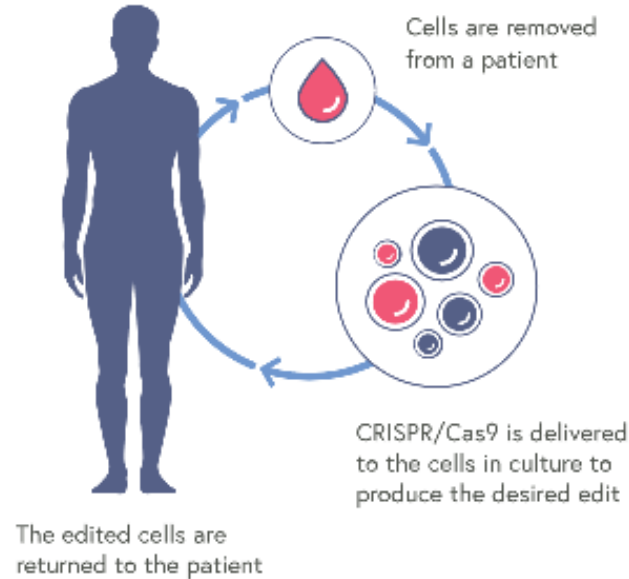
## CRISPR/Cas9 Gene Editing



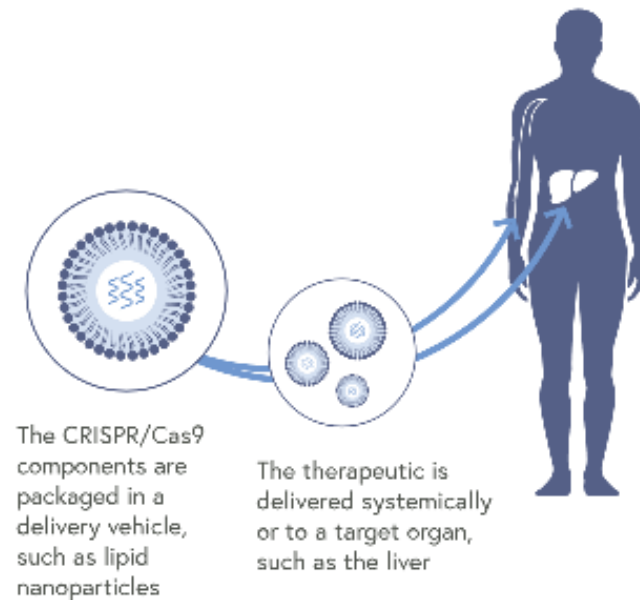
# CRISPR Therapeutics 2.



## *Ex vivo*

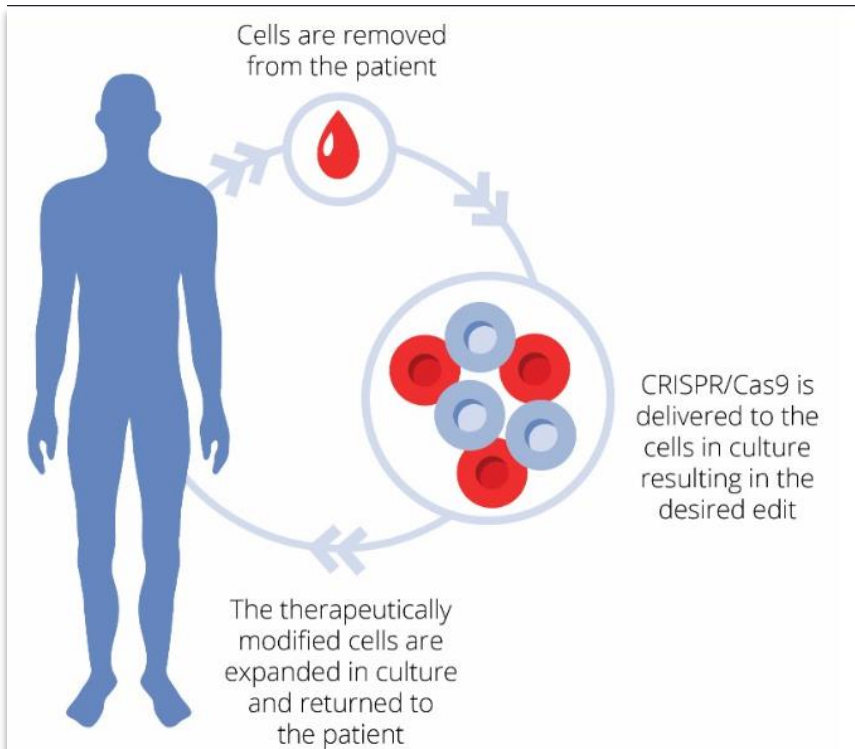


## *In vivo*



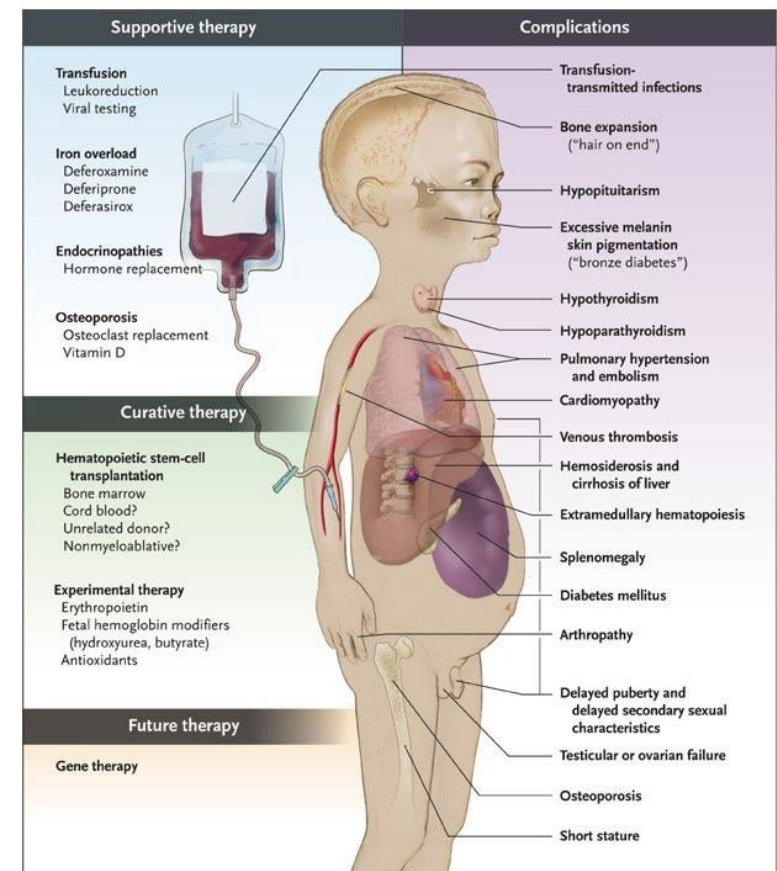


# Thalassemie – ex vivo therapie (2018)

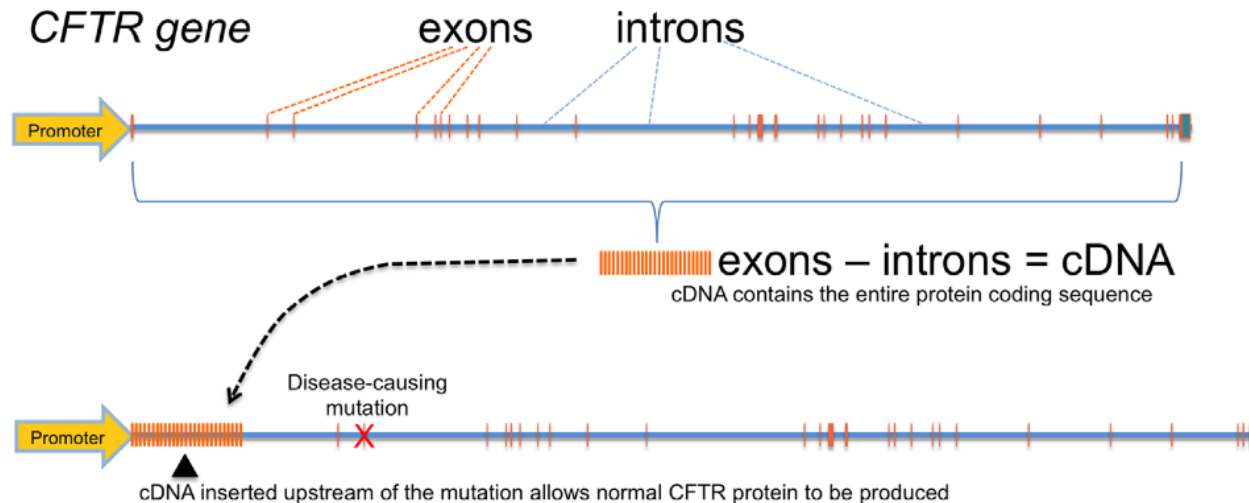


CRISPR Therapeutics and Vertex presented [preclinical data](#) supporting the efficacy of the therapy last weekend at ASH 2017. The researchers showed that they were able to consistently edit over **80%** of human hematopoietic stem cells using CTX001 and that their infusion into mice models resulted in an increased production of fetal hemoglobin. The team is now ready to test if these results are consistent in humans.

If the EMA approves the application, CRISPR Therapeutics will be the first to run a clinical trial in humans with CRISPR/Cas9 genome editing technology in Europe. The gene editing company, based in Basel, Switzerland, and co-founded by CRISPR/Cas9 co-inventor **Emmanuelle Charpentier**, is one of the most advanced players in the development of human therapeutics



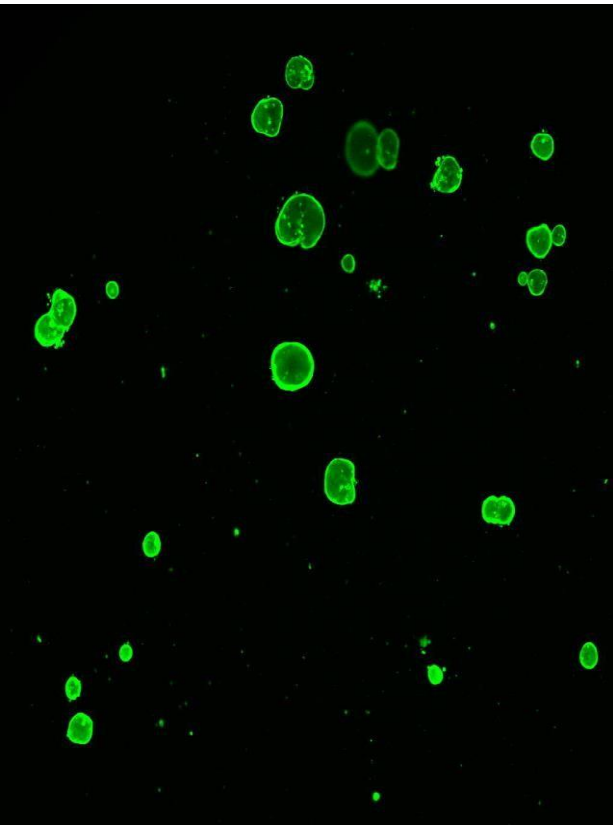
# „One – size – fits“ strategie CRISPR-Cas9 u CF



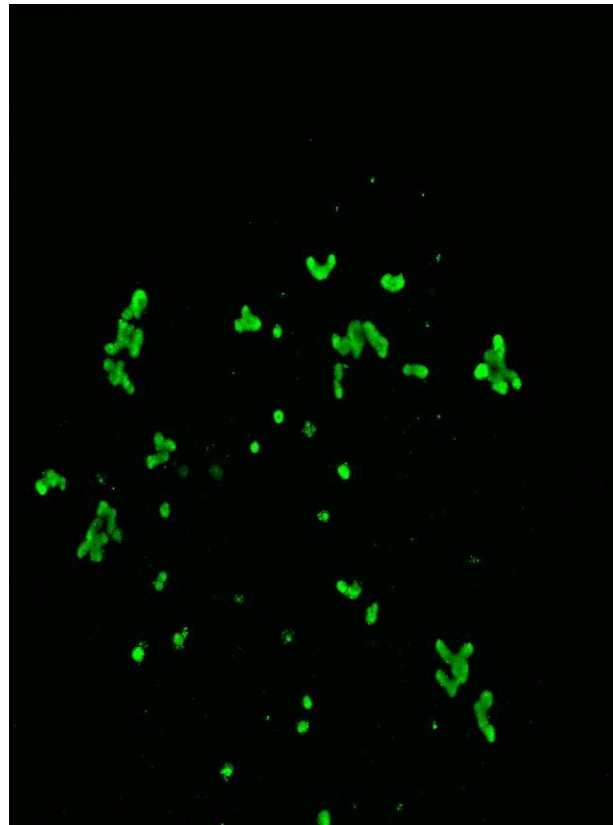
**FIGURE 2** One strategy to circumvent all mutations. A DNA break provides an opportunity to insert sequences of choice into a specified position. One strategy being explored to accommodate almost any mutation is to insert the protein-coding sequence of *CFTR* (a cDNA) upstream of the mutations so that the modified gene would produce functional *CFTR* before it reached mutations, regardless of their location in the gene, yet still maintaining endogenous regulation of the gene



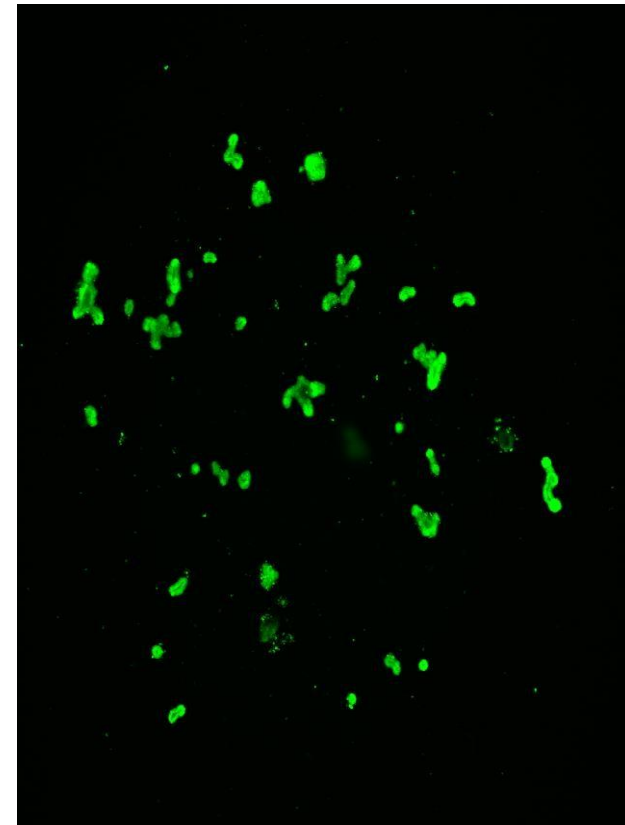
# Organoidy jako *ex vivo* CFTR biomarkers („CF Avataři“)



Non-CF



CF - F508del/F508del



CF - F508del/F508del  
Ivacaftor+lumacaftor

# Hlavní problémy CRISPR-Cas9 (nejenom u CF)

Jak dodat komponenty in vitro ?

Jak dodat komponenty in vivo ?

Co přesně aplikovat ?

Kdy editovat ?

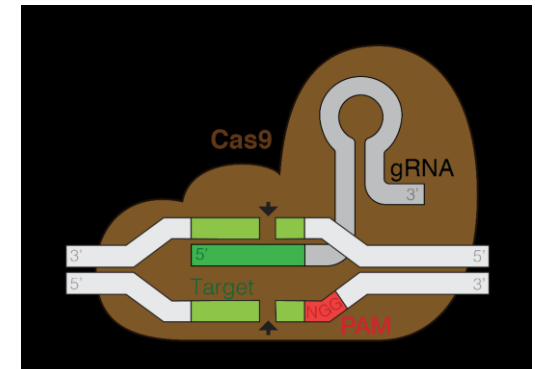
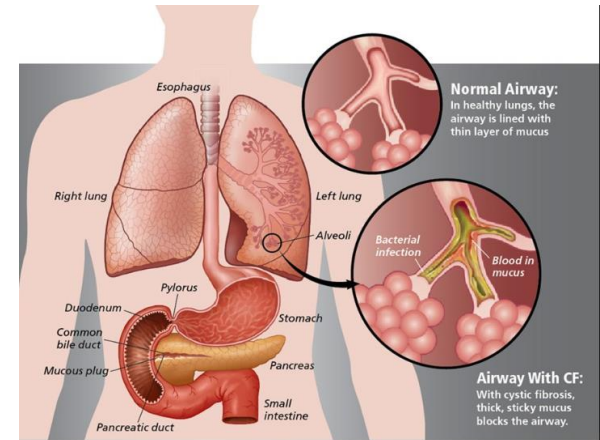
Jaké buňky editovat ?

Jako dlouho editace vydrží?

Imunologická odpověď ?

Off target editace a jak ji zjistíme?

A co když budou nežádoucí účinky  
(genová terapie je „navždy“)?



# Dopad na pacienty- SMA

Například pacientům se spinální svalovou atrofií (SMA) jsou dnes díky novele zákona standardně hrazeny už dvě varianty inovativní léčby

⇒ lepší dostupnost péče

⇒ odpadá nutnost žádat o schválení léku na § 16



## Nejdražší léčba jediného pacienta stála VZP 63 milionů korun

28.8.2023 | Tiskové zprávy



Nejnákladnější léčba jediného pacienta stála VZP vloni 62,88 milionu korun. Jednalo se o dvouletou dívku se spinální svalovou atrofií. Za léčbu dvaceti nejnákladnějších pacientů VZP v součtu uhradila 718 milionů korun.

V devíti případech se jednalo právě o SMA (spinální svalovou atrofií), kterým pojišťovna hradila léčbu přípravkem Zolgensma za více než půl miliardy korun (521,14 mil. Kč). K dalším onemocněním s nejnákladnější léčbou patřily také poruchy srážlivosti krve či různé typy poruch metabolismu. U nejdražších pacientů výdaje na léčivé přípravky tvoří 96 % všech nákladů.

„Nejnákladnější léčbu jsme hradili ve všech koutech republiky. Nejmladší pacient z těchto dvaceti ještě ani neoslavil první narozeniny, naopak tomu nejstaršímu bylo 81 let. Rovnoměrně jsou zde zastoupeni muži i ženy. Z dat vyplývá, že VZP hradí nejmodernější dostupnou léčbu všem klientům, kteří ji potřebují,“ vysvětluje ředitel VZP Zdeněk Kabátek a dodává: „To bychom si mohli jen těžko dovolit bez aktivní lékové politiky, kdy v podstatě bez ustání vedeme s dodavateli jednání o cenách těchto nejmodernějších, a tedy i nejdražších léčivých přípravků. Česko se tak díky tomu po právu řadí mezi země s nejlepší dostupností inovativních léčiv.“

### Náklady VZP na nejdražší pojištěnce za posledních 5 let

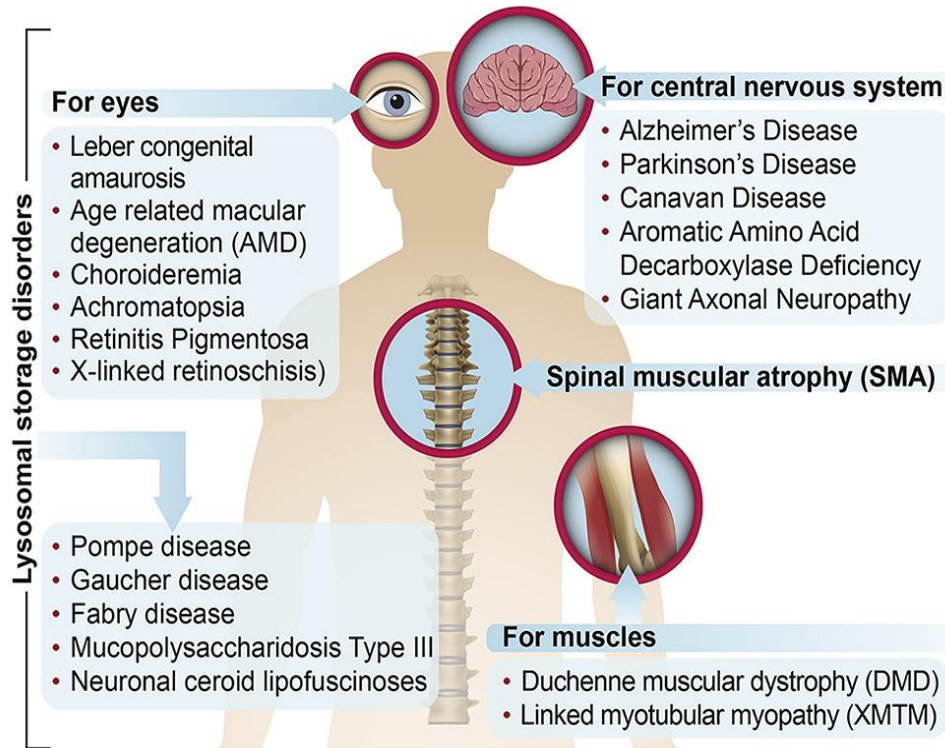
|                             | Rok 2018  | Rok 2019  | Rok 2020                                     | Rok 2021                              | Rok 2022                              |
|-----------------------------|-----------|-----------|--|---------------------------------------|---------------------------------------|
| TOP 20 celkem v mil. Kč     | 347,73    | 282,6     | 493,89                                       | 1036,84                               | 718,1                                 |
| Nejdražší pacient v mil. Kč | 74,12     | 25,85     | 57,32  | 64,67                                 | 62,88                                 |
| Pohlaví                     | muž       | Muž       | Muž  | muž                                   | žena                                  |
| Diagnóza                    | hemofilie | Hemofilie | infantilní spinální svalová atrofie I. typ * | jiná vrozená spinální svalová atrofie | jiná vrozená spinální svalová atrofie |

\* Werdnigova-Hoffmannova nemoc

### TOP 20 nejdražších klientů VZP v roce 2022

| Pořadí | Pohlaví | Diagnóza  | Náklady na léčbu v Kč |
|--------|---------|---|-----------------------|
| 1.     | Z       | Jiná vrozená spinální svalová atrofie                               | 62 883 265            |
| 2.     | M       | Infantilní spinální svalová atrofie I. typ (Werdnigova-Hoffmannova) | 58 300 615            |
| 3.     | M       | Infantilní spinální svalová atrofie I. typ (Werdnigova-Hoffmannova) | 57 408 830            |
| 4.     | Z       | Jiná vrozená spinální svalová atrofie                               | 57 157 158            |
| 5.     | Z       | Jiná vrozená spinální svalová atrofie                               | 57 143 594            |
| 6.     | M       | Jiná vrozená spinální svalová atrofie                               | 57 131 404            |
| 7.     | Z       | Jiná vrozená spinální svalová atrofie                               | 57 071 260            |
| 8.     | Z       | Jiná vrozená spinální svalová atrofie                               | 57 064 227            |
| 9.     | Z       | Jiná vrozená spinální svalová atrofie                               | 56 983 750            |
| 10.    | Z       | Porucha koagulace NS  | 27 037 515            |
| 11.    | M       | Poruchy metabolismu plazmatických bílkovin NJ                       | 21 706 427            |
| 12.    | M       | Svalová dystrofie   | 18 357 499            |
| 13.    | Z       | Neuronální ceroidní lipofuscinóza (NCL)                             | 17 845 330            |
| 14.    | M       | Mukopolysacharidóza, typ II   | 17 127 011            |
| 15.    | M       | Hemofilie   | 17 062 352            |
| 16.    | Z       | Poruchy metabolismu plazmatických bílkovin NJ                       | 16 152 063            |
| 17.    | M       | Poruchy metabolismu plazmatických bílkovin NJ                       | 16 133 843            |
| 18.    | M       | Porucha metabolismu lipoproteinů NS                                 | 15 456 881            |
| 19.    | Z       | Neuronální ceroidní lipofuscinóza (NCL)                             | 15 301 506            |
| 20.    | M       | Svalová dystrofie   | 14 777 076            |

## In vivo Gene Therapy with AAVs



# Gene Therapy Net .com

The startpoint for all your information about gene therapy

HOME BREAKING NEWS PATIENT INFORMATION CONFERENCES PUBLICATIONS VIRAL VECTORS CLINICAL TRIALS BOOKS JOBS QUIZ

News Articles Conferences Clinical Trials

### Gene Therapy Products on the Market

China was the first country in the world that has approved commercial gene therapy products. The first product was called Gendicine. In the western world the first approved gene therapy product was Glybera in 2012. Below is a summary of gene therapy products that are world wide on the market. Please note that the list is not exhaustive.

In Europe, gene therapy products have to be approved by the European Medicines Agency (EMA) which is the European agency for the evaluation of medicinal products, including gene therapy medicinal products. Gene therapy products are regarded as advanced therapy medicinal products (ATMPs). In the end, the gene therapy products need to be approved by the European Commission.

In the United States, gene therapy products need approval by the U.S. Food and Drug Administration (FDA).

Overview of approved cellular and gene therapy products:

- In the US by the FDA
- In Europe by the EMA en EC

### Gene Therapy Products

- Gendicine
- Onconine
- Glybera
- Imlygic
- Zalmonix
- Strimvelis
- Luxturna
- Kymriah
- Yescarta
- Zoligenma
- Zynteglo

### Patient Information

Historic Overview of Gene Therapy

Ethical and Social Issues in

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

### Final draft guidance

## Eladocagene exuparvec for treating aromatic L-amino acid decarboxylase deficiency

### 1 Recommendations

1.1 Eladocagene exuparvec is recommended, within its marketing authorisation, as an option for treating aromatic L-amino acid decarboxylase (AADC) deficiency in people 18 months and over with a clinical, molecular and genetically confirmed diagnosis of AADC deficiency with a severe phenotype. Eladocagene exuparvec is only recommended if the company provides it according to the commercial arrangement (see section 2).

Doi:10.1016/j.ymthe.2020.12.007; <https://www.genetherapynet.com/gene-therapy-products-on-the-market.html>



REVIEW

Open Access



## Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency

Tessa Wassenberg<sup>1</sup>, Marta Molero-Luis<sup>2</sup>, Kathrin Jeltsch<sup>3</sup>, Georg F. Hoffmann<sup>3</sup>, Birgit Assmann<sup>4</sup>, Nenad Blau<sup>4</sup>, Angeles Garcia-Cazorla<sup>5</sup>, Rafael Artuch<sup>6</sup>, Roser Pons<sup>6</sup>, Toni S. Pearson<sup>7</sup>, Vincenzo Leuzzi<sup>8</sup>, Mario Mastrangelo<sup>8</sup>, Phillip L. Pearl<sup>9</sup>, Wang Tso Lee<sup>10</sup>, Manju A. Kurian<sup>11</sup>, Simon Heales<sup>12</sup>, Lisa Flint<sup>13</sup>, Marcel Verbeek<sup>1,14</sup>, Michiel Willemsen<sup>1</sup> and Thomas Opladen<sup>3\*</sup>

### Abstract

Aromatic L-amino acid decarboxylase deficiency (AADC) is a rare, autosomal recessive neurometabolic disorder that leads to a severe combined deficiency of serotonin, dopamine, norepinephrine and epinephrine. Onset is early in life, and key clinical symptoms are hypotonia, movement disorders (oculogyric crisis, dystonia, and hypokinesia), developmental delay, and autonomic symptoms. In this consensus guideline, representatives of the International Working Group on Neurotransmitter Related Disorders (INTD) and patient representatives evaluated all available evidence for diagnosis and treatment of AADC and made recommendations using SIGN and GRADE methodology. In the face of limited definitive evidence, we constructed practical recommendations on clinical diagnosis, laboratory diagnosis, imaging and electroencephalography, medical treatments and non-medical treatments. Furthermore, we identified topics for further research. We believe this guideline will improve the care for AADC patients around the world whilst promoting general awareness of this rare disease.

**Keywords:** Aromatic L-amino acid decarboxylase deficiency, AADC deficiency, Neurotransmitter, Dopamine, Serotonin, Guideline, Infantile dystonia-parkinsonism, SIGN, GRADE

### German abstract

Der Aromatische L-Aminosäuren Decarboxylase Mangel (AADC) ist eine seltene autosomal rezessive neurometabolische Störung, die zu einem schweren kombinierten Mangel an Serotonin, Dopamin, Norepinephrin und Epinephrin führt. Die Symptome setzen in einer frühen Phase des Lebens ein. Die klinischen Hauptsymptome sind muskuläre Hypotonie, Bewegungsstörungen (Oculogyrie Krisen, Dystonie und Hypokinesie), Entwicklungsverzögerung und autonome Symptome.

In diesen Konsensus basierten Leitlinien haben Mitglieder der "International Working Group on Neurotransmitter Related Disorders (INTD)" sowie Patientenvertreter die verfügbare Evidenz für die Diagnose und Behandlung von AADC ausgewertet und evidenzbasierte Empfehlungen nach den Methoden von SIGN und GRADE formuliert. Stets im Bewusstsein der limitierten Evidenz haben wir praktische Empfehlungen für die klinische Diagnose, Labordiagnostik, Bildgebung und EEG, medizinische und nicht medizinische Behandlung formuliert. Des Weiteren haben wir Themen identifiziert, die der weiteren Forschung bedürfen. Wir glauben, dass diese Leitlinie die Behandlung von Patienten mit AADC verbessert und gleichzeitig das Bewusstsein für diese seltene Erkrankung schärft wird.

\* Correspondence: Thomas.Opladen@med.uni-heidelberg.de  
<sup>3</sup>Department of Child Neurology and Metabolic Disorders, University Children's Hospital, Heidelberg, Germany  
Full list of author information is available at the end of the article



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1:9000

# Genová terapie-Upstaza

CENTOGENE  
THE RARE DISEASE COMPANY

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## CENTOGENE Signs New Collaboration with PTC Therapeutics for Global Diagnostic Testing Program

18 Nov, 2019

Cambridge, MA, USA & Rostock, Berlin, GERMANY, 18 November 2019 – Centogene N.V. (NASDAQ: CNTG), a commercial-stage company focused on rare diseases that transforms real-world clinical and genetic data into actionable information for patients, physicians and pharmaceutical companies, announced that it has signed an agreement with PTC Therapeutics, Inc. (PTC) for a global diagnostic program for aromatic L-amino acid decarboxylase (AADC) deficiency.

The testing program for AADC deficiency will provide physicians with much needed analysis of 3-O-Methyldopa (3OMD), a powerful metabolic biomarker measured by mass spectrometry. When indicated by abnormal 3OMD levels, next generation sequencing (NGS) of the dopa decarboxylase (DDC) gene and variant analysis – providing 100% coverage – will be conducted. Eventually, deletion/duplication analysis will then be run if no mutation is identified via NGS.

Analysis will be performed using CentoCard® – CENTOGENE's CE-marked dried blood spot collection kit – that will be directly shipped to physicians. CENTOGENE also is in the process of validating DDC enzyme activity from

způsob podání – efektivita – (auto)imunita – vyhasínání – vypnutí-úhrady

<https://www.centogene.com/news-events/news/newsdetails/centogene-signs-new-collaboration-with-ptc-therapeutics-for-global-diagnostic-testing-program>

# Voxzogo



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NEWS FEATURE | 30 August 2023

## Is a boost to height a boost to health? Dwarfism therapies spark controversy

Emerging treatments for achondroplasia pose difficult choices for parents. Proponents say they are changing lives. Others fear they will feed stigma and erase identity.

[Cassandra Willyard](#)

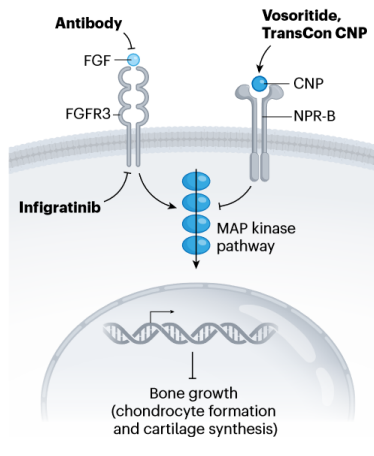


## Výška versus kvalita života ?

<https://www.nature.com/articles/d41586-023-02647-w>

### THERAPEUTIC MECHANISMS

Achondroplasia occurs when a cell-surface protein called fibroblast growth factor receptor 3 (FGFR3) is overactive and turns on a signalling pathway that restricts bone growth. Vosoritide and some emerging drugs simulate C-type natriuretic peptide (CNP), which turns that pathway off through a different cell-surface protein, natriuretic peptide receptor B (NPR-B). Other therapies in testing (in bold) include an antibody and a cancer therapeutic that acts directly on FGFR3.



BioMarin Receives Positive CHMP Opinion in Europe to Expand Use of VOXZOGO® (vosoritide) to Treat Children Aged 4 Months and Older with Achondroplasia



Sep 15, 2023

European Commission Approval Decision Expected Q4 2023

Opinion Based on Positive Results from Global Phase 2 and Ongoing Extension Study

U.S. Food and Drug Administration PDUFA Target Action Date for Supplemental New Drug Application for VOXZOGO for Children Under 5 is Oct. 21, 2023

SAN RAFAEL, Calif., Sept. 15, 2023 /PRNewswire/ – BioMarin Pharmaceutical Inc. (Nasdaq: BMRN), a global biotechnology



Four-year-old Liberty Anderson has a form of dwarfism called achondroplasia, which affects about 250,000 people worldwide.



HOHE PREISE FÜR MEDIKAMENTE

## TK-Chef will Pharma-Gewinne deckeln

Der Chef der größten deutschen Krankenkasse fordert drastische Mittel gegen steigende Arzneimittelpreise. Die Pharmabranche reagiert entsetzt – und droht mit Konsequenzen.



Jürgen Klöckner

01.07.2023 - 13:05 Uhr • 2 x geteilt



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## These are the first 10 drugs subject to Medicare price negotiations



By Tami Luhby, CNN

Updated 3:32 PM EDT, Tue August 29, 2023



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## Mají „obscénní zisky.“ Největší německá zdravotní pojišťovna požaduje zastropování zisků farmaceutických společností

Drahé léky



Jens Baas, šéf největší německé zdravotní pojišťovny Techniker-Krankenkasse (TK) požaduje razantní opatření proti růstu cen léků. Foto: wikimedia commons, © Superbass / CC-BY-SA-4.0

<https://www.handelsblatt.com/politik/deutschland/hohe-preise-fuer-medikamente-tk-chef-will-pharma-gewinne-deckeln/29229034.html>; <https://echo24.cz/a/Hh4jf/zpravy-ekonomika-leky-nemecko-zdravotni-pojistovna-zastropovani-zisky-farmaceuticke-spolecnosti-baas>

