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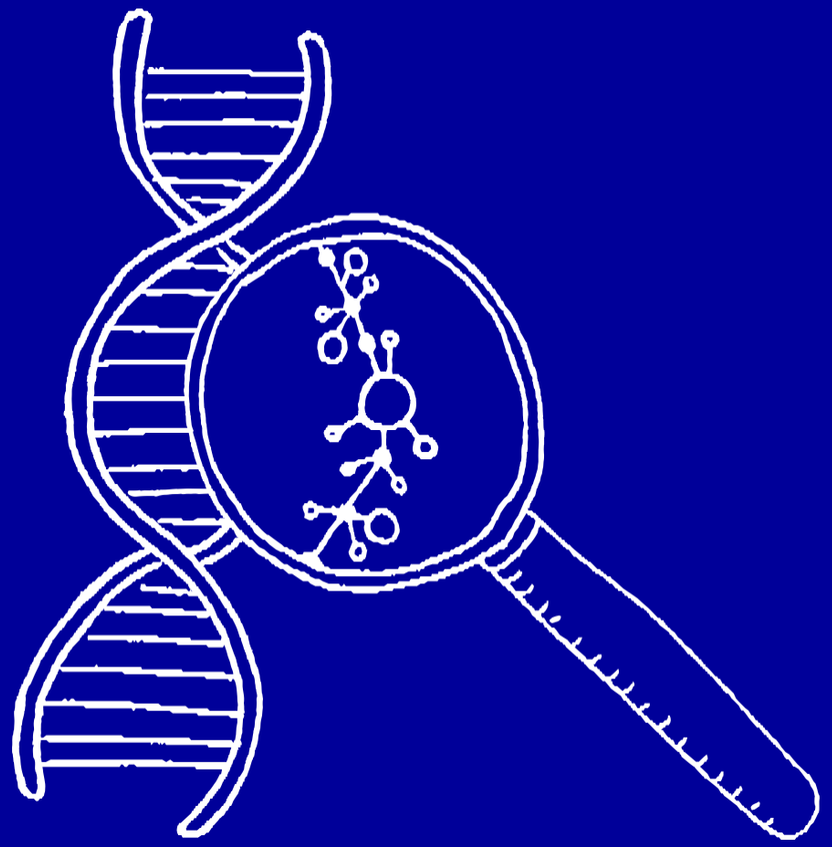
#RESEARCHNEVERSTOPS

Evotec Gene Therapy

Experienced team, novel capsids
and non-AAV viral platform



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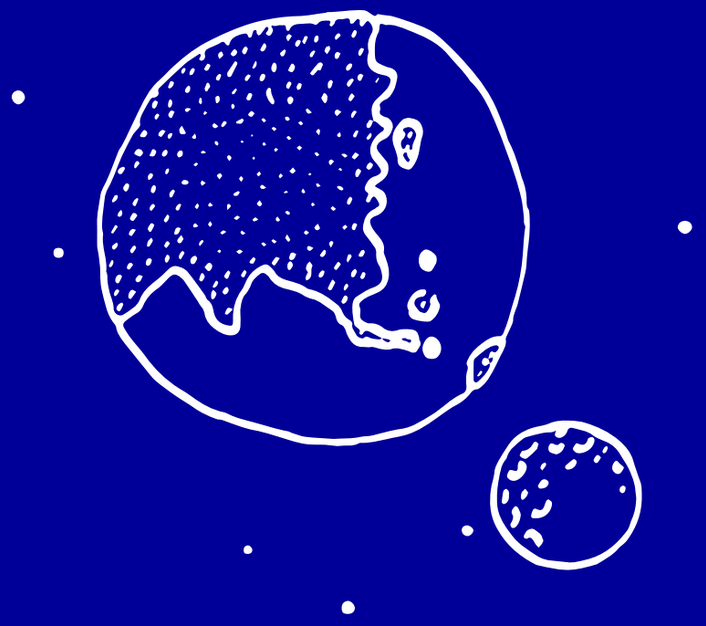
Executive Summary

EVO*genes* - Adding value to our partners' research

The Scope	• Applying clinically proven modalities with focus on developing novel and differentiated viral vector platforms for improving the applicability of genetic medicines • Open to entry within development partnerships, spin-off or service models
The Novel Platform	• Identification and engineering of novel vectors with attractive attributes i.e. increased therapeutic cargo size, tissue targeting; potential for redosing (tbd) • Multi-year collaboration with world-leading academic institution
AAV and Beyond	• Novel AAV vector identification through rational design and directed evolution in large animal species • AAV - swap technology: Innovative and novel approach leveraging defined capsid domains of selected serotypes. Unlocking the potential for combined best attributes in a novel proprietary capsid platform.
The Therapies	• *"Adapt the vector to the patient, and not the patient to the vector"* • Novel platform: Pursuing genetic medicines in diseases not fully addressable with other delivery system • AAV: Addressing unmet medical need in proven disease arena with trans-correction of enzyme deficiency
The Track-Record	• High performing teams with several decades of expertise across the GT development spectrum • Multiple development programs, patents and applications within biotech field • Three successful gene therapy IND submissions supporting clinical trial initiation

Agenda

1. General capabilities
2. Novel non AAV-viral platform
3. Novel AAV capsids
4. Viral Gene Therapy safety prediction
5. Therapeutic programs



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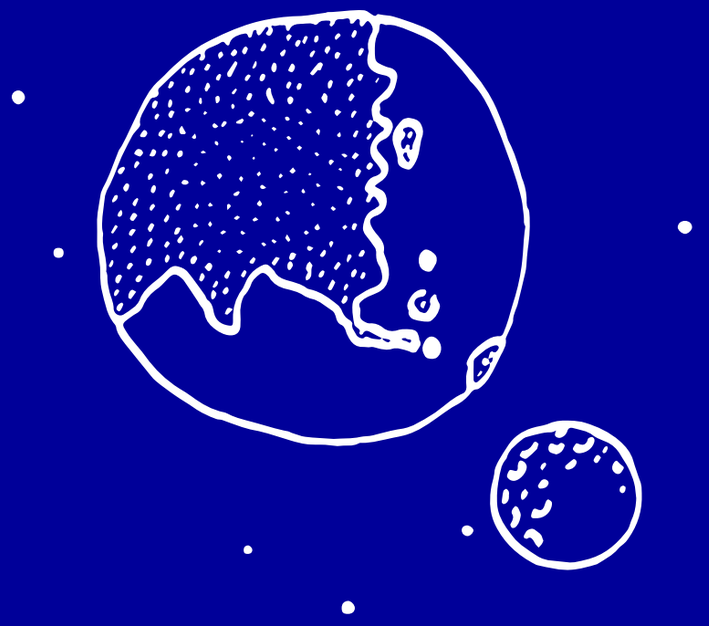

Leadership

A team of experts

Friedrich Scheiflinger

EVP, General Manager Gene Therapy

>30 years Academia and Pharma

Hematology, Immunology. Rare Diseases, Metabolic diseases, LSD's / IEM.

TSRI, Immuno AG, Baxter Int., Baxalta, Shire, Takeda

Hanspeter Rottensteiner

SVP, Head *In vitro* Gene therapy

>20 years Academia and Pharma

Gene expression and regulation, Cell Biology, Rare Diseases, Hematology

Baxter, Baxalta, Shire, Takeda

Werner Höllriegl

VP, Head *In vivo* Gene therapy

>20 years Pharma

In vivo Translational Research, Nonclinical Development, Rare Diseases

AstraZeneca, Novartis IBR, Baxter, Baxalta, Shire, Takeda

Georg Feichtinger

Lead Vectorology

>15 years Academia and Entrepreneurship

Synthetic biology, Gene expression & delivery, Musculoskeletal diseases, Regenerative medicine

Univ. of Leeds, UCL, Univ. of York, LBI Trauma, Phycosera

Barbara Plaimauer

Lead Biology

>20 years Pharma

Transgene Biology, Biochemical and cell-based assays, Rare diseases

Immuno AG, Baxter Int., Baxalta, Shire, Takeda

Vera Schoft

Sen. Res. Scientist Novel Technologies

>15 years Academia and Contract Research

Molecular Biology, Epigenetics, Genome editing

VBCF

Helmut Glantschnig

Lead *In vivo* Sciences

>20 years Pharma

Molecular Pharmacology, Preclinical Sciences, Musculoskeletal diseases

LBI, Merck & Co, Baxter, Shire, Takeda

Eva Mihailovska

Lead Novel Platform

>15 years Academia and Pharma

Molecular cell biology, Neuro-degenerative disease. Vaccine Dev. (non-clinical and clinical).

University of Vienna, Max Perutz Laboratories, AFFiRiS AG, Valneva SE

Strong Track-Record

- Highly experienced teams spanning decades of expertise in biologics, gene therapy & gene-editing development
- Numerous development programs, patents, and applications in the biotech field
- Successful submission of three gene therapy IND applications, paving the way for clinical trial initiation

Evotec Gene Therapy – Technical expertise

Covering viral and non-viral transduction technology

Technology cornerstones

AAV vector technology

Novel non-AAV vector technology

Non-viral delivery (LNP)

Genome editing

Functional *in vitro* and *in vivo* assays

CTA/IND-enabling packages

World-class drug discovery & development expertise

Access to research and preclinical specialists within Evotec network

Flexible deal structures for EVO*genes*: Integrated collaborations & stand-alone services

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AAV platform Novel viral platform[1] Non-viral platform	**Biology/ pathways Assay de-velopment**	**Integrated OMICS platforms**	**From PoC studies to lead candi-date identi-fication**	**Pre-clinical development & CMC**	**Clinical phase[2]**

Relative contribution of Evotec and the respective partner at each phase is mutually agreed on a project-by-project basis

Accelerate and maximize our partners' success

- mRNA
  - mRNA research grade expression
  - LNP delivery
- DNA transfection
  - LNP delivery

1 Under development

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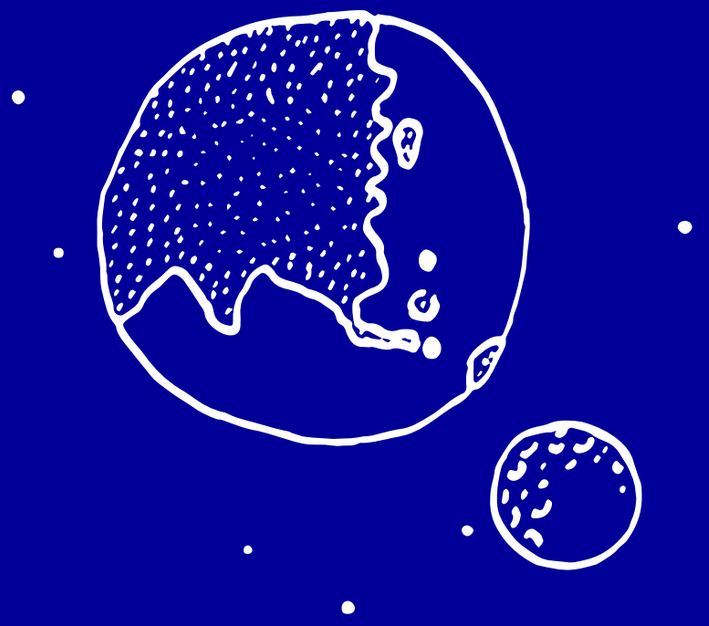


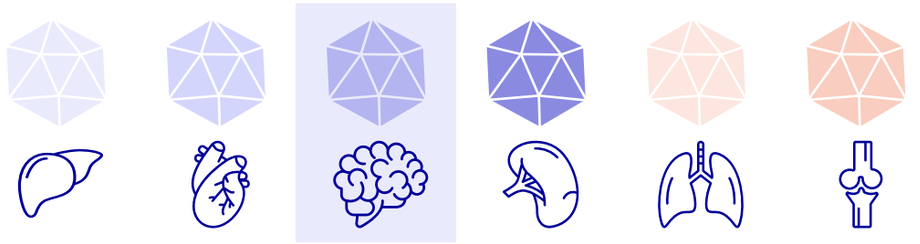
Novel capsid technology is in high demand

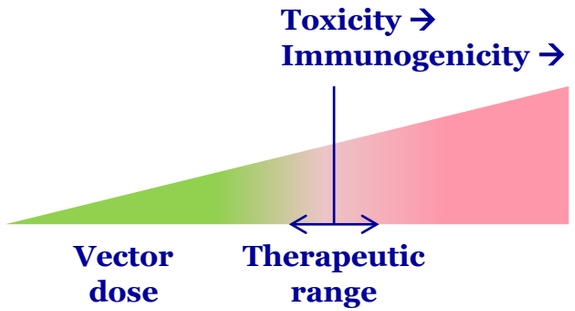
Clinical success is limited by high vector doses and insufficient tissue specificity

- Viral capsid sequences dictate *in vivo* cell type/tissue specificity, cell transduction efficiency and therapeutic vector dose
- High tissue specificity results in better targeted therapies and lower toxicity – hence driving a favourable benefit/risk profile
  - High capsid titres (infectious and empty particles) negatively impact the risk-benefit profile
  - Recent FDA Adcomm asks for increase of efforts to close translational gap[1]
- Industry invests heavily in the growing proprietary engineered capsid space – however, the associated IP space gets pretty crowded
  - Expensive license agreements
  - Sameness rules of FDA[2] increase pressure on available AAV technology
- Novel viral transduction systems other than AAV or Lentivirus are actively researched

The field is expanding from AAV to more innovative viral transduction and gene transfer technologies

Novel engineered virus capsids with tailored tropism





Challenges

- Tox prediction
- Precision Biomarker
- Immunogenicity & Immunotoxicity

The translational challenge: Gene Therapy is a highly tissue/cell type specific therapeutic modality

1 https://cowen.bluematrix.com/links2/doc/pdf/3b585dcb-4173-43e6-a417-5b3b34a41836?id=ZXJpbi5tY2NhbGxpc3RlckBjb3dlbi5jb206NA==
2 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interpreting-sameness-gene-therapy-products-under-orphan-drug-regulations
3 ITR: inverted terminal repeat

Novel platform: Addressing key challenges

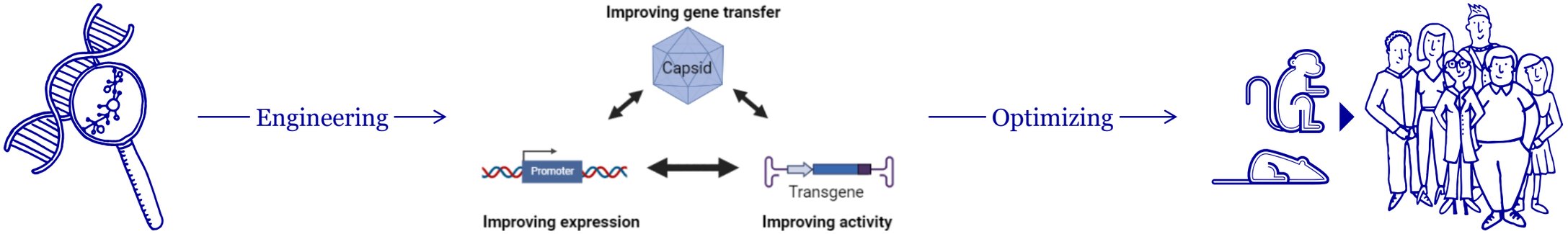
Designed to differentiate from AAV

Druggability: Cargo size, Tissue Tropism

- Extended payload capacity expands the design space, amplifies the potential for drug development and therapeutic interventions
  - Enables efficient gene editing
  - Allows packaging of genes too large for AAV
- Leveraging distinct tissue tropism compared to AAV can enhance therapeutic efficacy and target specific organs or tissues
- Leveraging high-throughput RNA sequencing for robust data acquisition
- Innovative scaffold designs are expected to be recognized as unique within FDA guidelines on drug similarity

Supportive technology platforms:

- Achieving superior pre-clinical safety profiles, through proteomics based **"safety prediction"** technology allowing to uncover potential development threats i.e. dose-related Drug-Induced Liver Injury (DILI)
- Utilizing proteomics and metabolomics for comprehensive analysis of differential protein **expression profiles** and **biomarker** expression
- Closing the translational gap by utilizing human **iPSC technology** in addition to NHP studies to efficiently bridge the preclinical to clinical stages of drug development



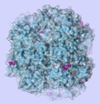
1 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interpreting-sameness-gene-therapy-products-under-orphan-drug-regulations

Novel vector platform development

Capsid engineering

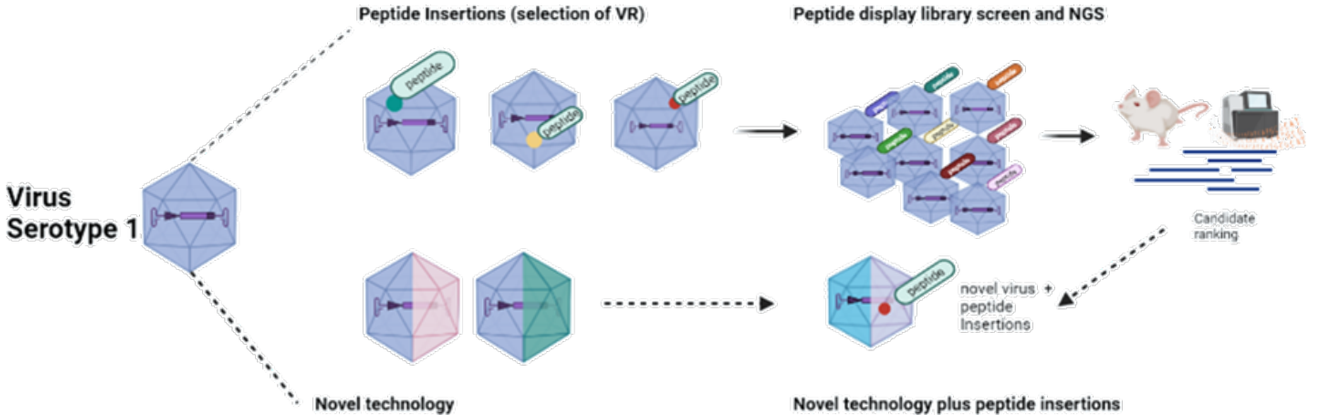
Capsid engineering

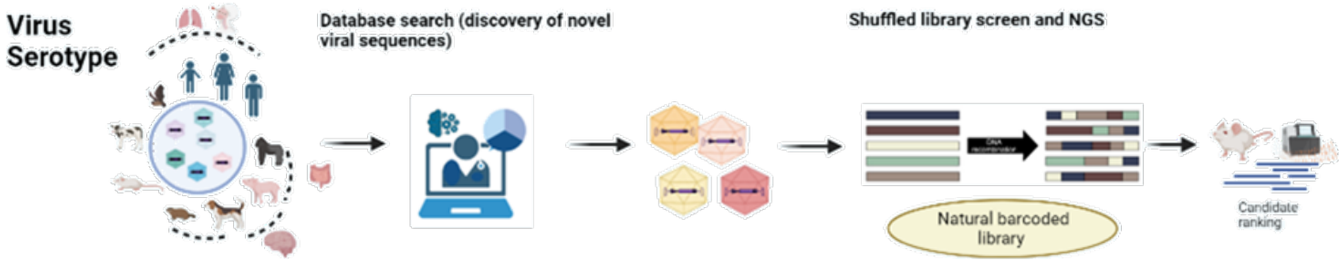
(A) Structural analysis & prediction of mutation target sites



(B) Shuffled capsid libraries (Academic collaboration)

- Design of barcoded mutant capsid gene libraries
- *In vivo* application and selection/persistence
- NGS[1] of organ samples and analysis of barcode frequencies
- Capsid candidate library (*In vitro* and *in vivo* screening)[2]





1 NGS: next generation sequencing
2 Tropism, improved transduction and expression efficacy

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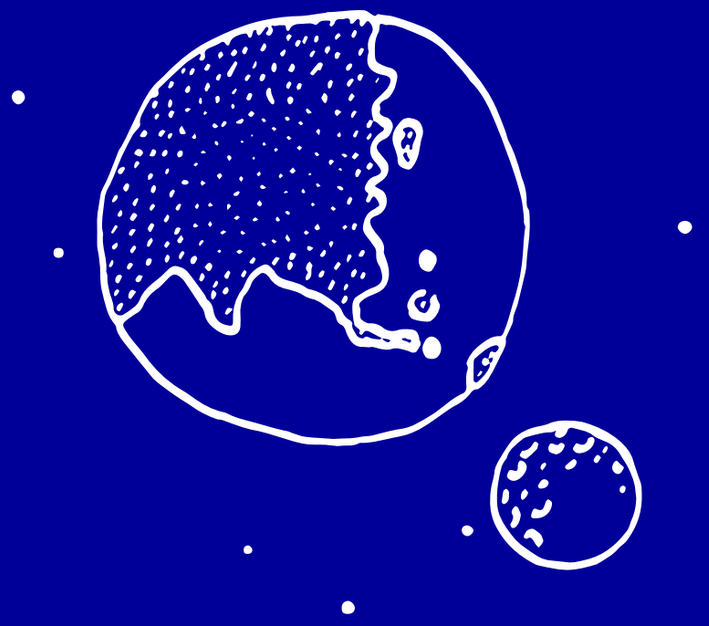


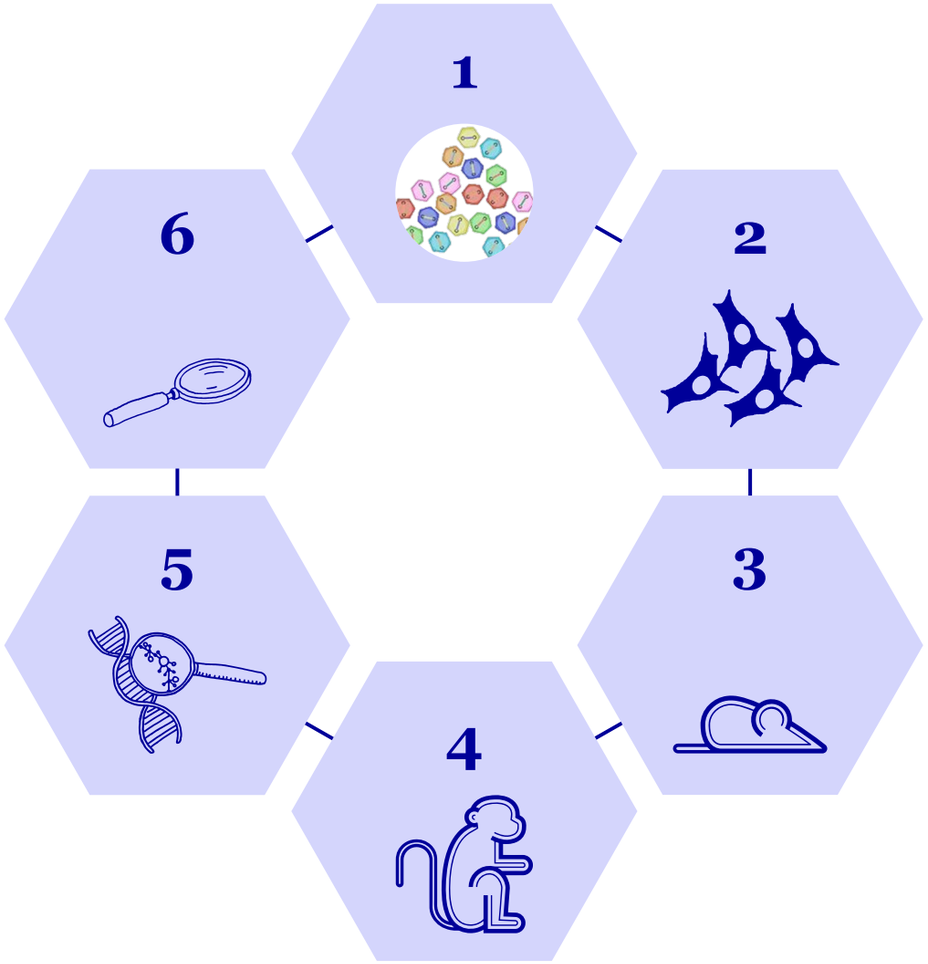
Novel and differentiated AAV Capsids

Evotec's cutting edge RNAseq/bioinformatics based *in vivo* capsid discovery

1 Customizible EVOlibrary[1]
- Flexible design space
- Engineered AAV serotypes
- Barcoded for comparative analyses

2 Functionality
- Transduction in human cells / organoids
- RNAseq and bioinformatics for *in vitro* transduction functional QC tests

3 *In vivo* testing
- Transduction in humanized mice
- Ranking by tissue- or single-nuclei RNAseq and bioinformatics
- Selection and/or decision to bioengineer



4 NHP
- Administration to NHPs
- Transduction in focused or broad multi-tissue approach according to customer needs

5 Capsid engineering
- Rational or random substitutions
  - Peptide display, chimera, shuffling
- Medium to high complexity libraries
- *In vitro* analytical and functional QC
- RNAseq-compatible library design

6 Validation
- Validate improved attributes of leads
- *In-vitro/in-vivo* prioritization

1 Example customized library. Highly complex peptide insertion library (AAV5).

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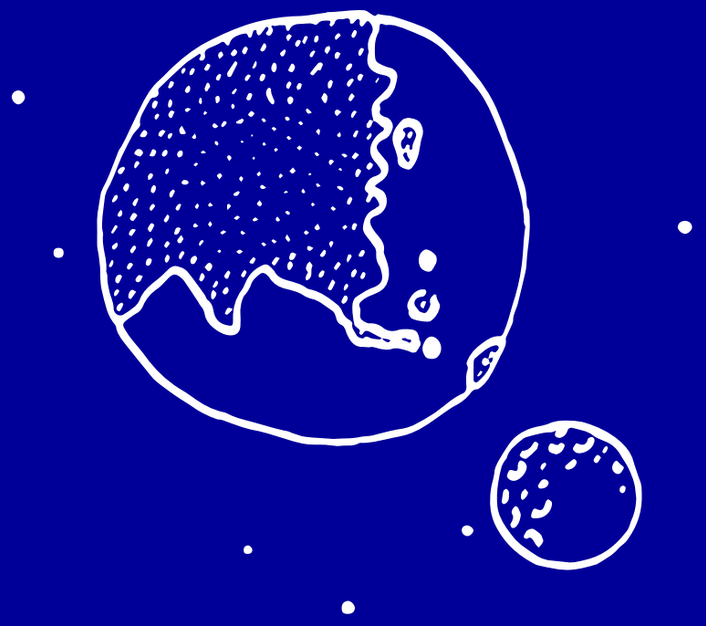
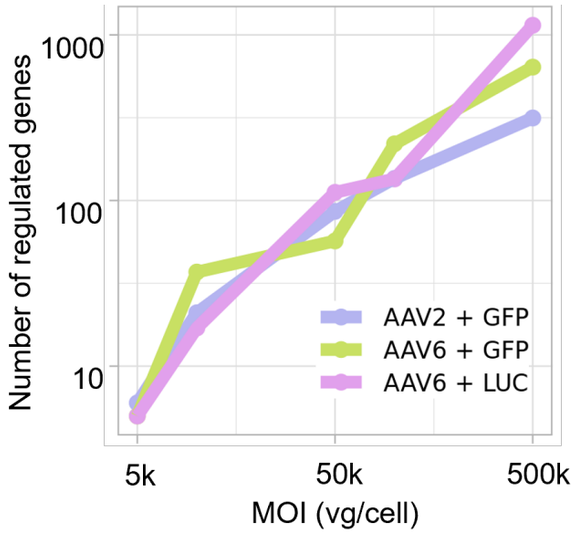
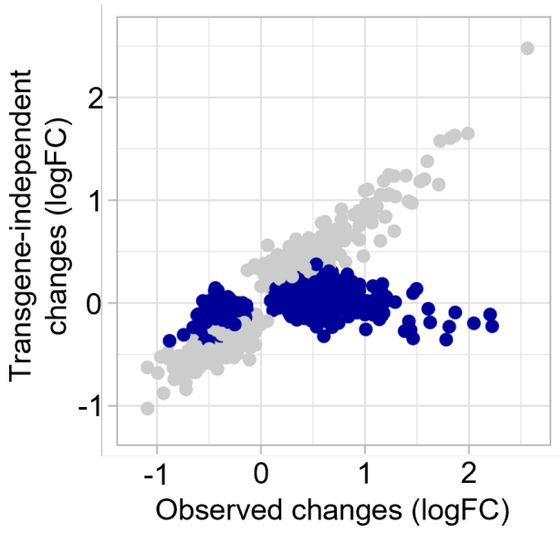


Towards Safety Prediction for AAV based gene therapy

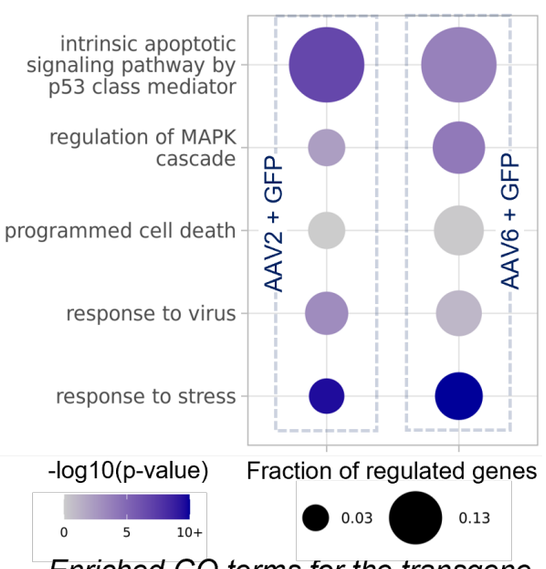
High-throughput method to quantify transduction efficiency and analyze transcriptomic response



Correlation between MOI and strength of transcriptomic response (quantified as the number of significantly regulated genes)



*Separation of transcriptomic response In **transgene-independent** and **transgene-specific** components*



Enriched GO terms for the transgene-independent response component.

Results

- ScreenSeq enables unbiased analysis of transcriptomic response to transduction
- The Pilot study showed that the transcriptomic response can be decomposed in **transgene-independent and transgene-specific components**

ScreenSeq is a powerful tool to analyze AAV in in vitro studies

logFC - log fold change; A.U. - arbitrary unit (here, a measure of fluorescence intensity); CPM - counts per million; GO - gene ontology; MOI - multiplicity of infection X/Y graph: Universal data interpretation shown.

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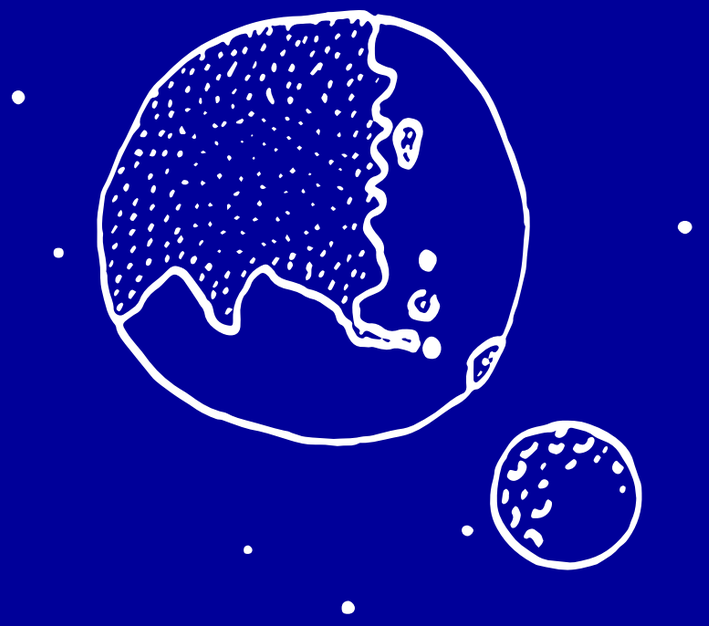
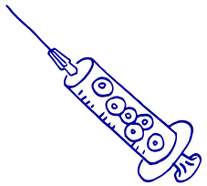


Gene Therapy for Hypophosphatasia (HPP)

Evotec's strong expertise in rare diseases and gene therapy solutions

- Rare monogenic disease – high mortality in untreated children[1]
- Defective skeletal mineralization, deformity and seizures[2]
- Effective ERT but burdensome, life-long treatment & high costs



High unmet medical need

Market attractiveness

- >1B USD market dominated by STRENSIQ[2] franchise without entry of competing therapies on the horizon
- GT dose curative and safe in mice
- No known clinical development

- AAV Lead is potent and durable
- Exquisite liver-specific expression and selectivity. Active suppression in non-target tissue feasible.
- Cross-correction of disease phenotypes in mouse model of HPP

Innovation platform

Partnership opportunity

- Precedence for path to IND and clinical development
- Potential to spin off asset in an external company
- Evotec GT to perform preclinical development work

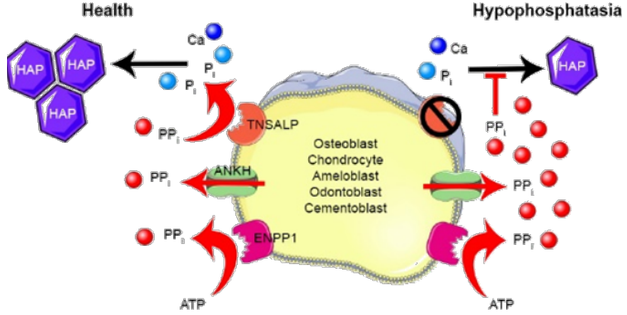
1 substitutions in TNAP gene (Alpl). Estimated prevalence for severe or moderate HPP is 1:300,000 or 1:6,370.respectively. Ann Hum Genet 75:439 (2011).
2 asfotase alpha subcutaneous injection, (Alexion/AstraZeneca).
HPP, Hypophosphatasia; ERT, Enzyme Replacement Therapy; TNAP, tissue non-specific alkaline phosphatase; GT, Gene therapy; IND, Investigational New Drug application; AAV, adeno-associated virus

Hypophosphatasia

Viral vector delivery of bone-targeted TNAP[1] has potential to treat HPP

Tissue nonspecific alkaline phosphatase (TNAP):

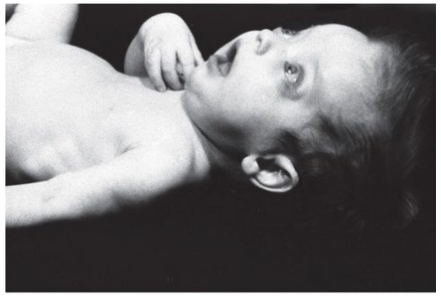
- TNAP hydrolyses pyro-phosphate, a mineralization inhibitor and pyridoxal 5`-phosphate (phospho-Vitamin-B6)
- Expressed in the skeleton, liver, kidney and other tissues



TNAP (TNSALP) regulates pyrophosphate (PPi) and phosphate (Pi) ratios in the mineralization of hydroxyapatite (HAP).

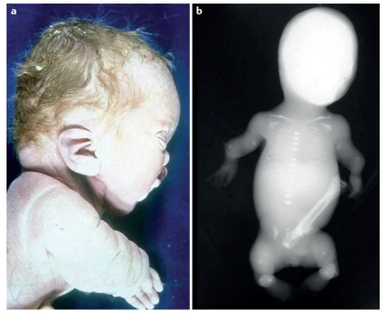
Genetics: >400 substitutions in TNAP gene *(Alpl)*. Estimated prevalence for severe or moderate HPP is 1:300,000 or 1:6,370, respectively[3].

Clinical presentation: Onset prenatal to adulthood correlates with residual TNAP activity. Defective skeletal mineralization, soft bones prone to fracture and deformity, pyridoxine-responsive seizures, hypercalcemia/calciuria, myopathy and dental manifestations.



Nature Reviews | Endocrinology

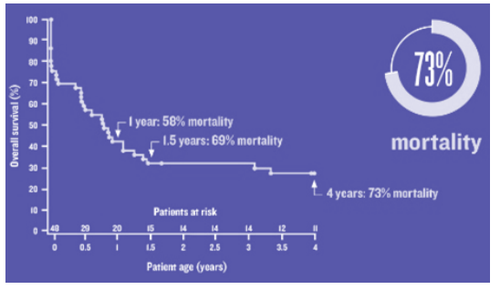
4-month-old girl has developed infantile HPP. Prominent fontanel, proptotic eyes, chest retraction, and rachitic changes[2].



Nature Reviews | Endocrinology

a) Stillborn neonate, b) Almost no mineralization of the skeleton by radiographic examination[2]

Mortality: 73% from birth to 5-years of age in untreated patients (hypophosphatasia.com)

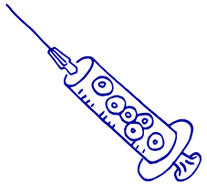


1 TNAP, tissue nonspecific alkaline phosphatase
2 Michael P. Whyte, Nature Reviews Endocrinology 12:233 (2016)
3 Mornet E, et al. Ann Hum Genet 75:439 (2011)
4 ERT, enzyme replacement therapy; asfotase alfa, Strensiq (Alexion)

Gene Therapy for cTTP (Upshaw-Schulman syndrome)

Evotec's strong synergistic core expertise in ADAMTS13/cTTP and gene therapy solutions

- Rare monogenic disease – high mortality if untreated with plasma infusion
- Disseminated microvascular thrombi, serious health problems
- Life-long intravenous ERT expected (candidate effective in Phase-3)



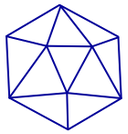
High unmet medical need

Market attractiveness

- Estimated total direct costs/patient undergoing regular transfusion $1.2M - $1.7M[2]
- No gene therapy candidate has entered the development space
- Potential therapeutic expansions

- AAV-based front-runner candidate
- Exquisite liver-specific expression and PoC in mouse model of cTTP
- Potential preclinical candidate selection 4Q23

Innovation platform



Partnership opportunity

- Precedence for path to IND and clinical development
- Evotec GT to perform AAV-therapeutic development work
- Potential to spin off asset in an external company

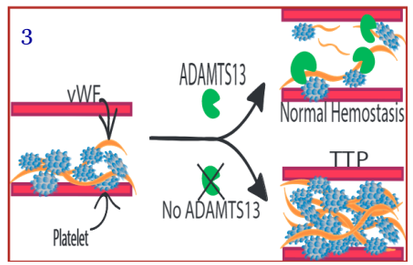
1 https://www.nature.com/articles/d42473-020-00432-1
2 Oladapo et al., ISTH Congress 2019, (life time costs) https://academy.isth.org/isth/2019/melbourne/264771/abiola.oladapo.cost.of.illness.28coi29.of.congenital.thrombotic.thrombocytopenic.html
cTTP, Congenital thrombotic thrombocytopenic purpura; ERT, Enzyme Replacement Therapy; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PoC, proof of concept; GT, Gene therapy; AAV, adeno-associated virus

Congenital TTP

Viral delivery of ADAMTS13 has potential to treat cTTP

ADAMTS13 function:

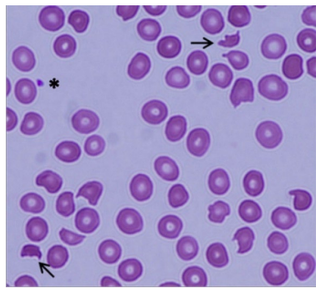
- the protease responsible for the cleavage of VWF
- expressed by liver stellate cells, to a lesser degree by endothelial cells
- severe deficiency at <10% of normal values
- >150 mutations in cTTP have been reported



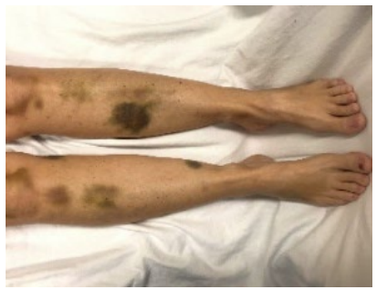
Genetics: Autosomal recessive trait with inactivating substitutions in ADAMTS13 gene. The prevalence and annual incidence is estimated at less than 1/1,000,000[1,2]. 600 prevalent cases of cTTP (and 5,401 cases of aTTP) in the US (2020).

Clinical presentation:

- Disseminated microvascular platelet rich-thrombi can block the flow of oxygen-rich blood to organs, such as the brain, kidneys, and heart
- Low platelet count and bleeding tendencies inside the body, underneath the skin, or from the surface of the skin. Injuries may bleed longer than normal.
- Occurs suddenly and lasts for days or weeks, or months, with frequent repeat episodes that need to be treated
- Consequently, serious health problems cause a significant burden on healthcare facilities. Approximately two thirds of patients have relapses every 2-3 weeks.



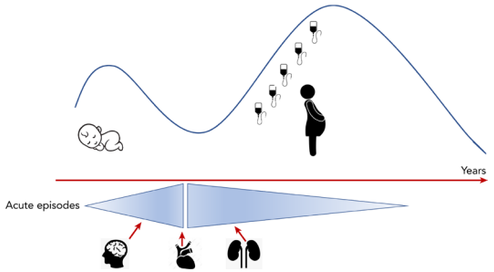
TTP: Peripheral blood smear showing schistocytes (arrows) and a marked decrease in platelet numbers.



Spontaneous bruising in a woman with critically low platelets

Mortality/Life expectancy:

- Rapidly fatal disease (> 90%) w/o treatment. Therapeutic plasma exchange/infusion has led to a decrease in the mortality rate (15%).
- Projected life expectancy for patients with cTTP (mean age; 19.1 years at diagnosis) 31.1 years, compared with 60.6 years in the general population[4]



Presentation and acuity of congenital TTP[6].

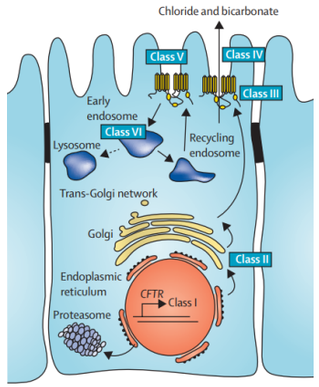
1 Orphanet https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=93583
2 JN George Congenital TTP: toward a turning point. 2019 (Blood 133:1615. https://www.sciencedirect.com/science/article/pii/S000649712042631X
3 https://www.tamingthesru.com/blog/annals-of-b-pod/b-pod-case/thrombotic-thrombocytopenic-purpura
4 Oladapo et al., ISTH Congress 2019, https://academy.isth.org/isth/2019/melbourne/264771/abiola.oladapo.cost.of.illness.28coi29.of.congenital.thrombotic.thrombocytopenic.html
5) Loirat et al., Pediatric Nephrology 24:19–29 (2009)
5 https://www.marketresearch.com/DelveInsight-v4028/Thrombotic-Thrombocytopenic-Purpura-TTP-Insight-30196545/
6 Scully M (2021) Congenital TTP, next stop acuity and therapy. Blood 137:3469
VWF, von Willebrand Factor; cTTP, congenital thrombotic thrombocytopenic purpura; aTTP, acquired thrombotic thrombocytopenic purpura

Cystic Fibrosis

Novel vector platform for *genotype-agnostic* CF gene therapy with full length CFTR

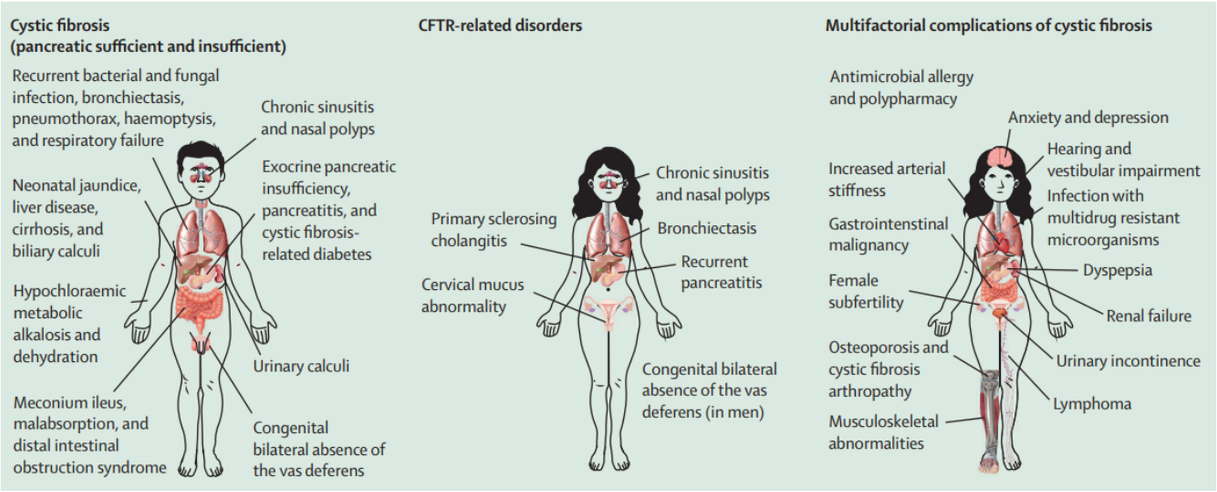
Cystic fibrosis trans-membrane conduc-tance regulator *(CFTR)* gene[1]

Encodes a chloride/ bicarbonate ion channel (1480 aa) expressed in epithelial cells of lung and other organs. Impaired Cl- transport leads to salt/ water imbalance and mucus build up on epithelial surfaces.



Genetics: >350 recognized recessive CF-causing mutations in the *CFTR* gene affect protein quantity (transcription/ translation, intracellular trafficking) or function, with variable phenotypes.

Clinical presentation: Affects all exocrine glands and damages the lung and digestive system. Pancreatic insufficiency and recurrent respiratory infections. The sweat chloride test confirms a CF diagnosis. Affects 30,000 patients in US and >70,000 globally.



Unmet need:

- Genotype-specific *CFTR-modulators* and other therapies, improve median predicted survival to about 50 years[2]. Long-term tolerability & compliance of new therapies are not known.
- World-wide estimate: only 64.9% are diagnosed and only 12% receive triple modulator combination therapy[3]
- 10% of patients are not eligible for *genotype-specific* modulator therapies

1 Images from Michal Shteinberg et al., Lancet 2021; 397: 2195 (2021)
2 Allen et al., Nature Comm 14:693 (2023)
3 Guo et al J Cystic Fibrosis 3:456 (2022)
CF, Cystic Fibrosis; CFTR, Cystic fibrosis trans-membrane conductance regulator; aa, aminoacids; Cl–, chloride ion.

Evotec GT: Summary

- Highly experienced gene therapy team
- Broad gene therapy related technical capabilities (viral and non-viral gene transfer)
- Development of a novel and potentially superior viral, but non-AAV, gene transfer platform
- Development of novel, highly tissue specific AAV capsids
- Development of a safety prediction methodology
- Support of gene therapy development programs through access to iPSC technology and biomarker discovery

evotec

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Business Development
114 Innovation Drive,
Milton Park, Abingdon
Oxfordshire OX14 4RZ, UK

T: +44.(0)1235.86 15 61
F: +44.(0)1235.86 31 39
info@evotec.com