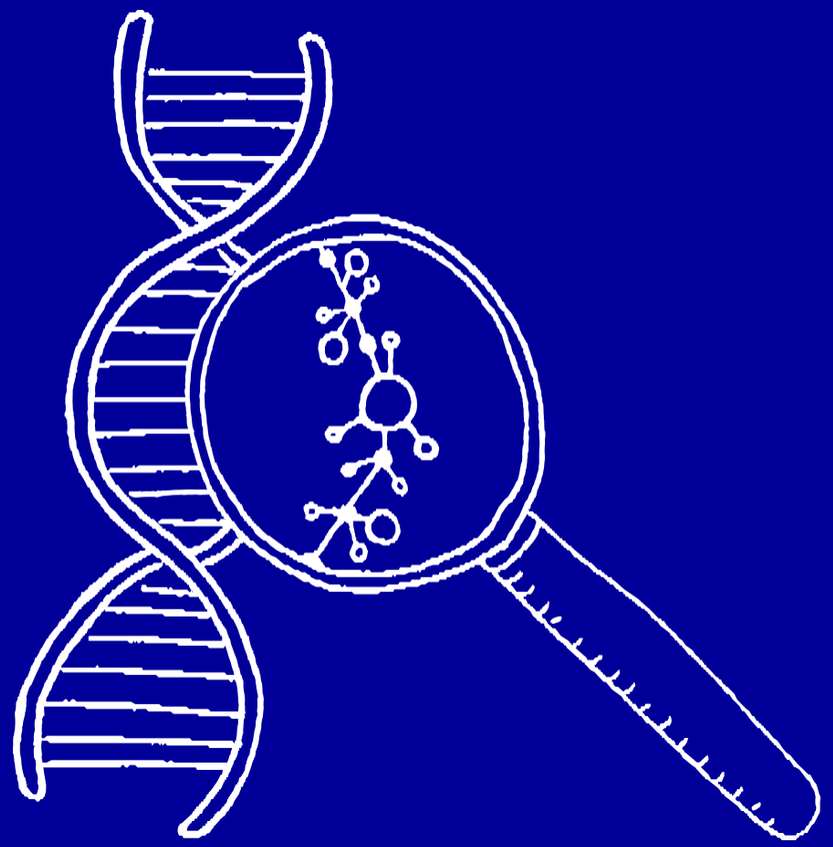
evotec

#RESEARCHNEVERSTOPS

Evotec Gene Therapy

Adding value to our partners’ research



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“Adapt the vector to the patient, and not the patient to the vector”

A multidisciplinary, strong translational approach to gene therapy at Evotec

At Evotec basic gene therapy experience i.e. viral and non-viral transduction technology is coupled with ample pre-clinical and clinical translational capabilities[1]

We have the capability to couple insights in genetic vector design with biomarker discovery that predict the clinical response and potential adverse effects[2,3]

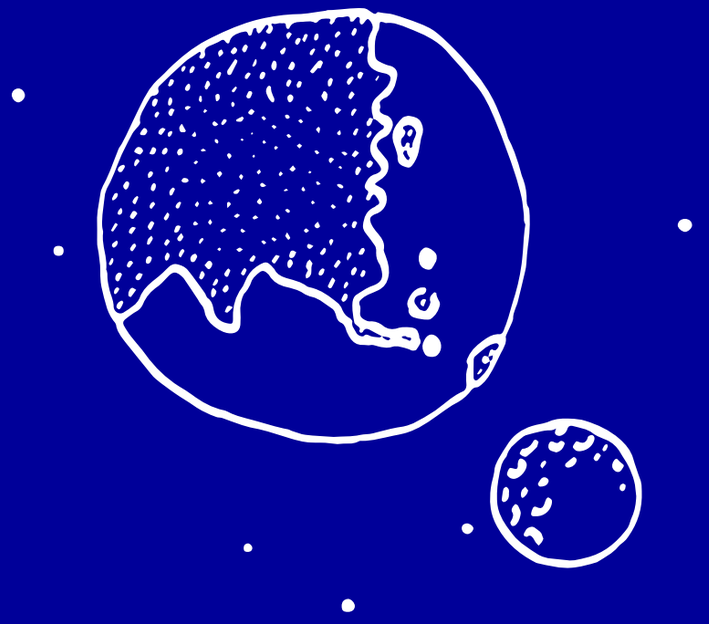
This involves a range of preclinical work, such as investigating where vectors end up in the body, comparing candidate vectors and overseeing animal studies

By integrating Evotec’s broader technologies and deep biology expertise, we not only develop new vectors, but also look more broadly at whether the vector is likely to succeed

1 https://www.nature.com/articles/d42473-020-00432-1
2 Ronzitti et al., Front. Immunol. (2020). https://doi.org/10.3389/fimmu.2020.00670
3 Nair et al., Blood (2014). https://ashpublications.org/blood/article/123/20/3195/32715/Computationally-designed-liver-specific

Agenda

1. A Dedicated Gene Therapy Center within Evotec
2. Expertise & Overview
3. Novel platforms

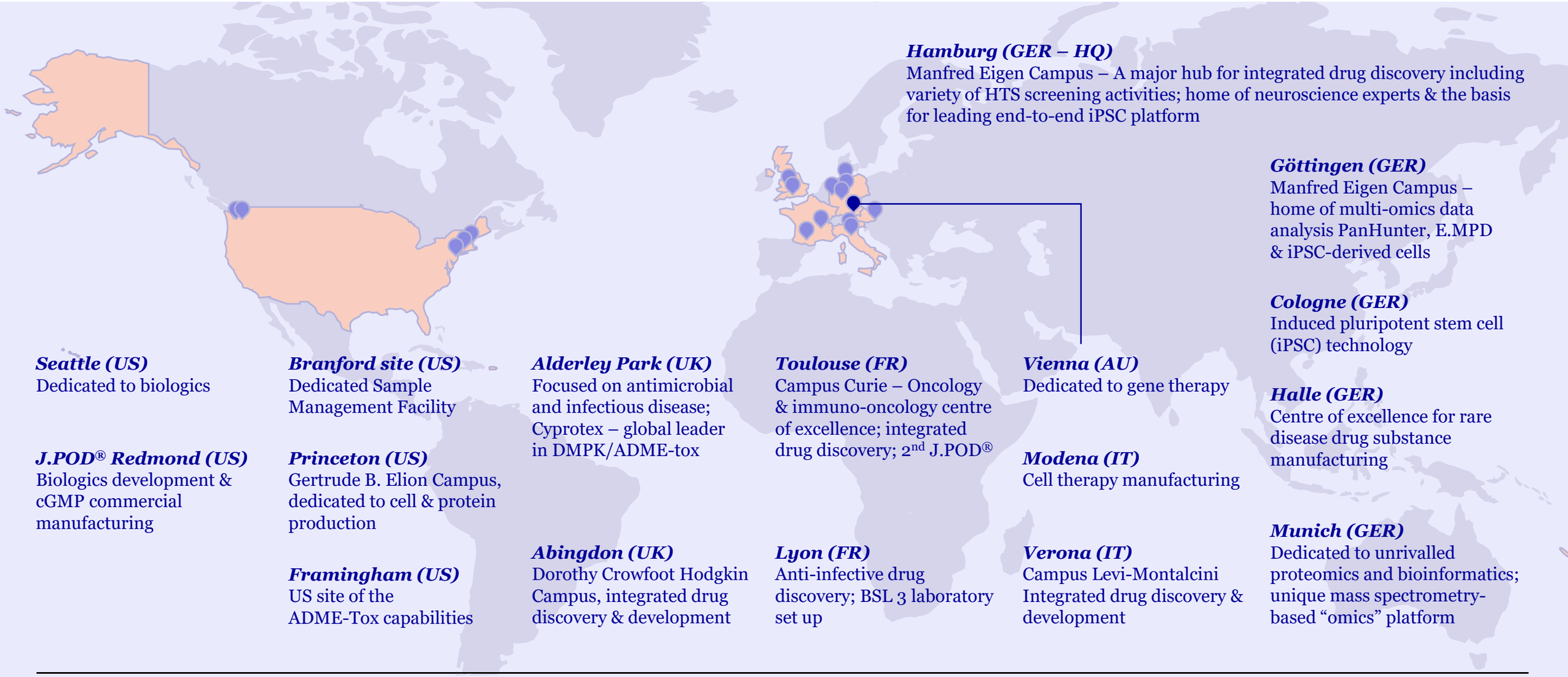


Agenda

1. A Dedicated Gene Therapy Center within Evotec
2. Expertise & Overview
3. Novel platforms

Collaborative model for efficiency in drug discovery

17 Sites with platforms & technologies for more precision and efficiency



Hamburg (GER – HQ)
Manfred Eigen Campus – A major hub for integrated drug discovery including variety of HTS screening activities; home of neuroscience experts & the basis for leading end-to-end iPSC platform

Göttingen (GER)
Manfred Eigen Campus – home of multi-omics data analysis PanHunter, E.MPD & iPSC-derived cells

Cologne (GER)
Induced pluripotent stem cell (iPSC) technology

Halle (GER)
Centre of excellence for rare disease drug substance manufacturing

Munich (GER)
Dedicated to unrivalled proteomics and bioinformatics; unique mass spectrometry-based “omics” platform

Seattle (US)
Dedicated to biologics

J.POD® Redmond (US)
Biologics development & cGMP commercial manufacturing

Branford site (US)
Dedicated Sample Management Facility

Princeton (US)
Gertrude B. Elion Campus, dedicated to cell & protein production

Framingham (US)
US site of the ADME-Tox capabilities

Alderley Park (UK)
Focused on antimicrobial and infectious disease; Cyprotex – global leader in DMPK/ADME-tox

Abingdon (UK)
Dorothy Crowfoot Hodgkin Campus, integrated drug discovery & development

Toulouse (FR)
Campus Curie – Oncology & immuno-oncology centre of excellence; integrated drug discovery; 2nd J.POD®

Lyon (FR)
Anti-infective drug discovery; BSL 3 laboratory set up

Vienna (AU)
Dedicated to gene therapy

Modena (IT)
Cell therapy manufacturing

Verona (IT)
Campus Levi-Montalcini Integrated drug discovery & development

Evotec GT[1] – Adding value to our partners' research

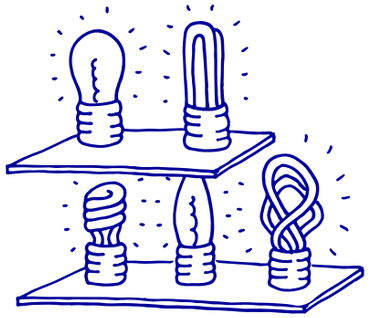
Innovative and flexible solutions from target identification to clinical candidates

The people

- Outstanding scientists
- Strong experience in gene therapy and drug development for rare diseases
- Poised to progress pipeline assets into clinic

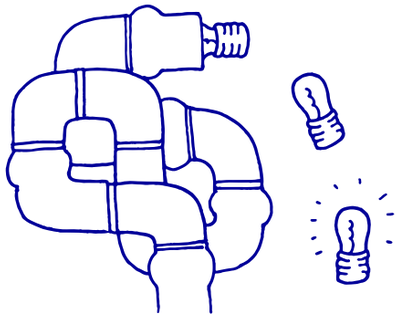
Therapeutic area expertise

- Team leverages therapeutic area insights from years of industry experience and across Evotec



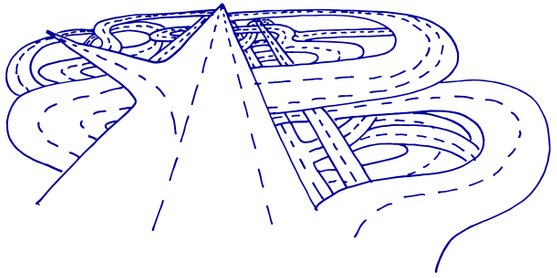
Integrated drug discovery & development

- State-of-the-art capabilities
- Best-in-class technology platforms



Flexible deal structures

- Integrated collaborations and stand-alone services



A gene therapy platform combined with world-class drug discovery & development expertise to accelerate and maximize our partners' success

1 GT = Gene Therapy

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

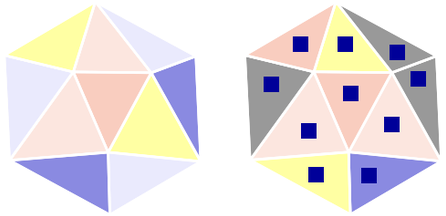
Strong Track-Record

- 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

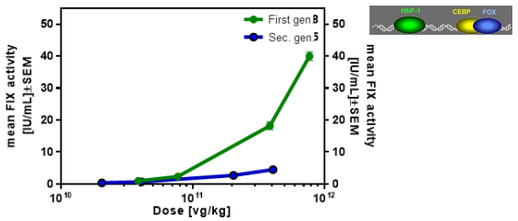
Success in Research, Development & Partnerships

A proven track record covering all phases of preclinical gene therapy development

Capsid Engineering: Increasing Transduction Efficiency[1]

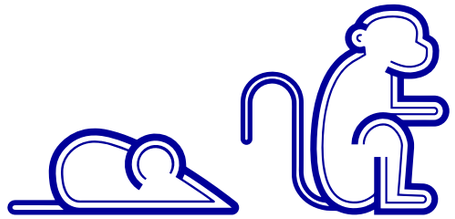


Promoter Engineering: Boosting Liver-specific Expression by a Molecular Turbocharger[3]



Establishing predictive models for transduction efficiency in humans[6]

Bridging the gap between mouse & man

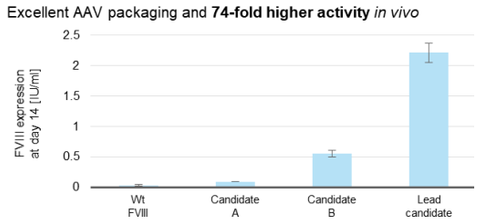


11 INDs filed & approved

- 3 gene therapies
- 8 biotherapeutics

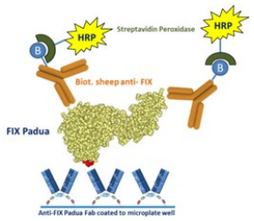
Lead Identification — *Lead Optimization* — *Preclinic & Translation* — *IND-enabling* — *Clinic*

Vector Optimisation to Achieve Efficient Transgene Expression[2]

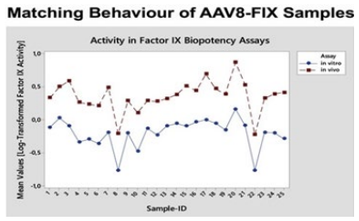


Analytical method development[4]

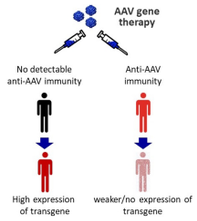
Selective measure-ment of a trans-gene variant with a single aminoacid change



IVIVC of bio-potency tests[5]



AAV8 gene therapy for patients with anti-AAV8 immunity[7]



1 Strategic Partnership (external partner)
2 Rottensteiner, H. (ISTH 2017), Baxalta
3 Weiller et al. (ASGCT 2018), Partnership with academic partner (VUB)
4 Weber et al. (2018) Mol Ther Meth. Clin Dev. 10:29-37
5 Lengler et al. (2020) Mol Ther Meth. Clin Dev. 17:581-88
6 Weiller et al., (ISTH 2019)
7 Kruzik et al. (ASH 2019); Industry Partnership (Miltenyi Biotech) IVIVC, InVitroInVivo Correlation; IND, Investigational New Drug Application

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

evotec

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**

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

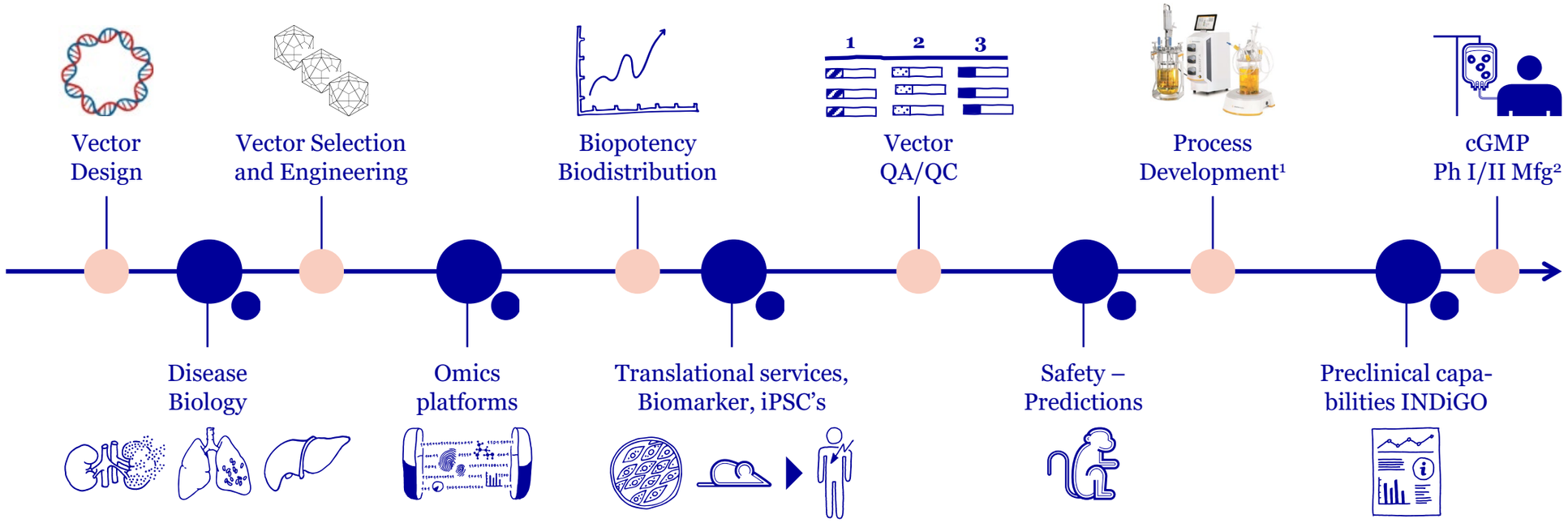
- mRNA
  - mRNA research grade expression
  - LNP delivery
- DNA transfection
  - LNP delivery

1 Under development

Early de-risking through addressing the translational gap

Unlocking the promise of gene therapy

Traditional GT services



Augmented EVT-GT services

„Competitive gene therapy development proposition, from program discovery up to entry into the clinic"

Standard viral in vivo gene therapy development technologies are strongly augmented by readily available, highly innovative, in-house capabilities

GT = Gene Therapy; IND = Investigational New Drug; Mfg = Manufacturing; OA/QC = Quality Assurance/Control
1 & 2 provided by external partner

Agenda

1. A Dedicated Gene Therapy Center within Evotec
2. Expertise & Overview
3. Novel platforms

End to End Solutions – Integrated Drug Discovery

We apply gene therapy expertise & capabilities through all stages of development

Vector Design

- Choice of approach
  - Viral (e.g. AAV)
  - Non-viral (e.g. LNP)
- Payload
  - Transgene
  - Antisense (e.g. shRNA, miRNA)
  - Gene editing

Lead Identification

Vector Optimization

- Proprietary capsids (off-the-shelf & co-develop.)
- Codon optimization
- Engineered improved payload variants
- Constitutive and tissue specific promoter / enhancer elements
- Introns, poly A, others

Lead Optimization

Lead Characterization

- *In vitro* biopotencies & pharmacodynamics
- Translational pharma-cology – Disease area expertise
- Vector biodistribution to target & off-target organs

Preclinic & Translation

Analytics

- Vector quantification and characterisation
- Payload specific functional assays
- *In vivo* imaging
- Combined pharmacology & safety studies
- Immunological assays

IND-enabling

Pre-IND

- Vector shedding study
- Immunogenicity assessment
- IND-enabling Pharm / Tox packages
- *In vivo* biopotency screening of gene therapy candidate

Clinic

Safety predictions and Biomarker identification/validation

- Target specific & proprietary tox prediction tools applying pan-omics & bioinformatics
- Safety/Efficacy Biomarker identification in small and large animal species

Gene Editing

Overview of core activities

End to end integrated discovery

Selection of suitable editing tools (ZFN, TALEN, CRISPR) and designs, and delivery systems that fit project needs

- Transfection, electroporation, AAV, Plasmids, RNA, RNP formats

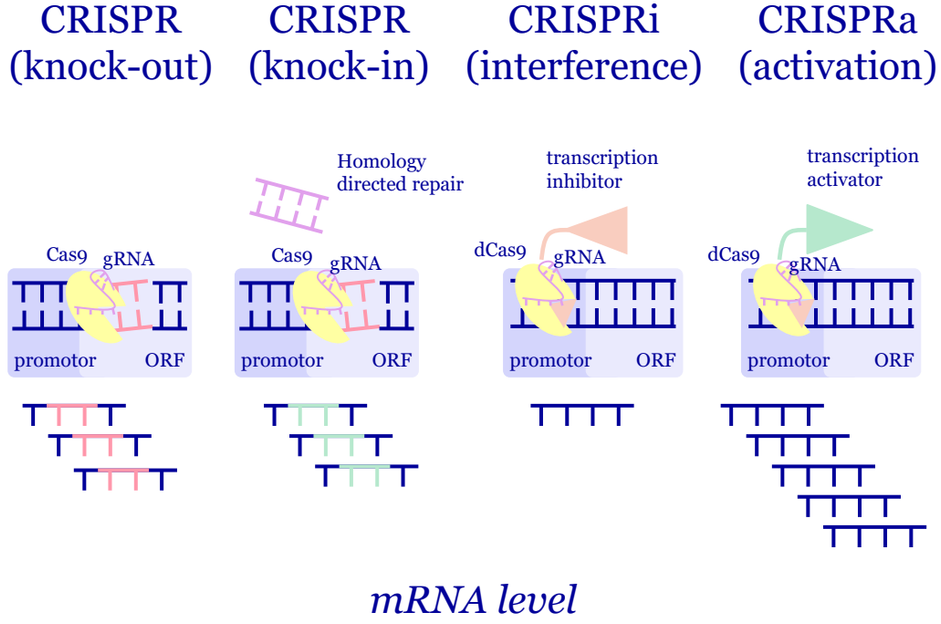
Optimization of editing components and efficiency in various cellular assays tailored to project needs

- Evaluation of on- and off-targets
- Applying specialized technology as needed (e.g. MS, proteomics, RNAseq)

Integration of *in vitro* and *in vivo* areas of expertise

- Optimization of transduction & editing efficiencies
- On/Off target editing analyses
- Assessment of gene editing efficacy in animal models of disease

CRISPR toolbox for genetic approaches

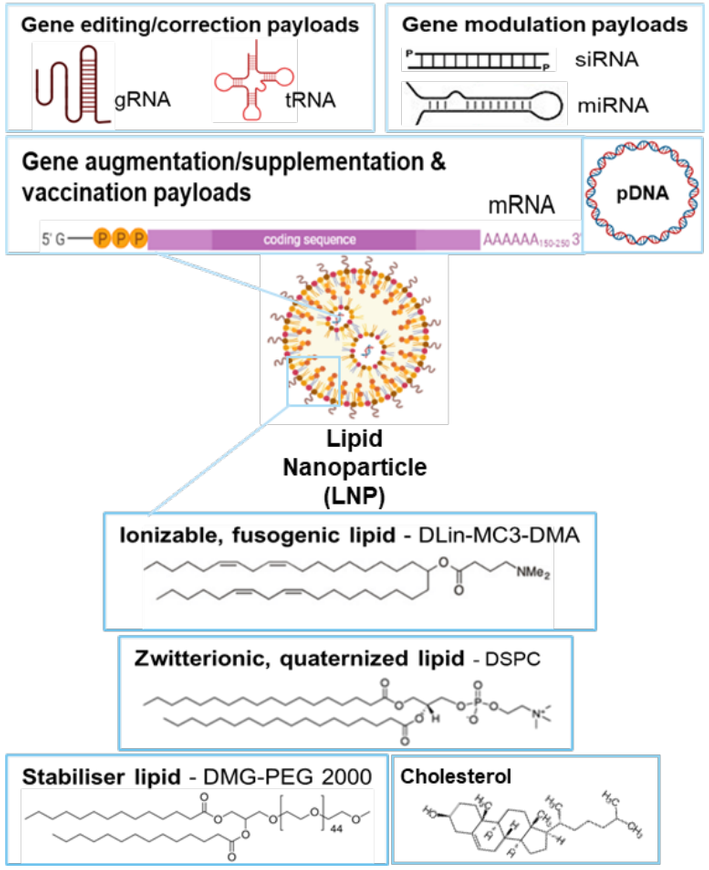


CRISPR, clustered regularly interspaced short palindromic repeats; ZFN, Zinc finger nuclease; TALEN, Transcription activator-like effector nuclease; MS, Mass spectrometry.

Evotec GT Non-viral LNP Capabilities

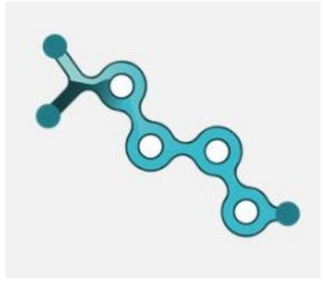
Integrated preclinical drug development platform

Formulation & payloads



Production platforms & principles

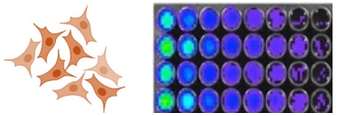
Continuous Solvent-Antisolvent Precipitation



Microfluidics
Laminar mixing

Laminar flow platform

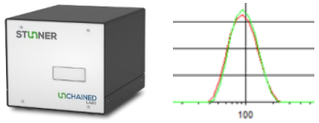
In vitro & *in vivo* testing



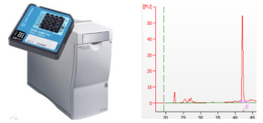
In vitro potency testing

In vivo PoC, kinetics, efficacy & biodistribution testing

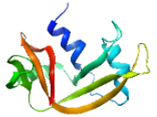
Analytics & QC



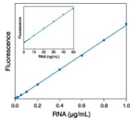
DLS characterization (size distribution, PDI)



Bioanalyzer platform (payload integrity & stability)



RNAse contamination



Encapsulation efficacy % API concentration

Endotoxin (LAL) assay

Areas of gene therapy expertise at Evotec GT

Innovative and flexible solutions from target identification to IND

Gene Therapy & Gene Editing

Capsid
- Common natural serotypes
- Research licenses for engineered capsids
- Developing proprietary capsids: internal research & co-partnerships

Promoter Regulatory elements
- Constitutive and tissue-specific promoter / enhancers
- Ongoing development effort towards proprietary synthetic promoters

Analytics
- Vector quantification and characterisation
- *In vitro* assays: infectivity & *in vitro* biopotency
- Payload specific functional assays
- Immunological assays

Payload
- Codon-optimized transgenes
- Vectorized antibodies
- Antisense approaches (e.g., shRNA, miRNA)
- Genome editing: *in vivo* models to be built

CMC
- Research material (<10^{14} vg)
- Based on HEK293 cell lines (suspension & adherent)

Translation & Nonclinical Dev.
- Pharmacology & biodistribution in humanized or disease models
- Safety pharmacology (integration & off-target analyses)
- Behavioural and functional phenotyping (cognition, physical tests)

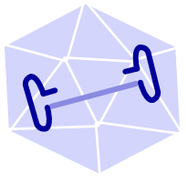
Evotec GT stands at the forefront of gene therapy innovation with robust capabilities.

In vitro Sciences

Full bandwidth of vector design and characterizations

Vector design

- Payload
  - Transgenes
  - Antisense approaches (e.g. shRNA, miRNA)
  - Vectorized antibodies
- Codon-optimization
- Capsids
  - Natural serotypes
  - Engineered capsids
- Genome editing
- Non-viral GT



Vector production

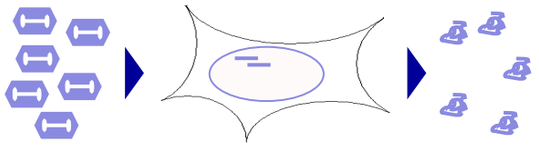
- Lab scale transfection & vector harvest
  - 1 to 5L benchtop bioreactor transfections
- Chromatography Systems (Äkta platform)
  - Affinity chromatography
  - Ion exchange chromatography
- Ultracentrifugation
- TFF

Vector characterization

- Vector quantification
  - Real time qPCR, ddPCR
  - Fluorometry
  - ELISA capsid protein
- Vector integrity
  - Agarose gel
  - DNA Sequencing
  - SDS-PAGE and Immunoblot
- Full to empty capsid particle ratio

Functional assays

- Cell-based assays
  - Celigo S – analysis platform
  - FACS analysis and (single) cell sorting
- Transgene expression assays
- Biopotency assays
  - Enzymatic assays
  - Functional ELISA and other biochemical assays



We cover within Evotec the entire value chain of preclinical drug discovery and development, from early discovery to lead candidate identification and preclinical development candidate characterization

Non-Clinical Sciences

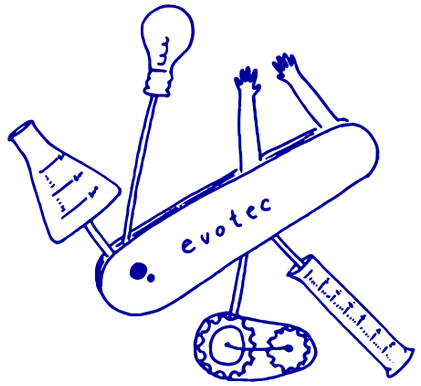
We cover a broad range of preclinical work under one roof with clear line of sight

Discovery Sciences

- Target biology / pathway: *in vivo* proof of concept studies
- Available mouse models or customized disease models
- On-site capacity: 5,000 rodents (IVC housed); AAALAC

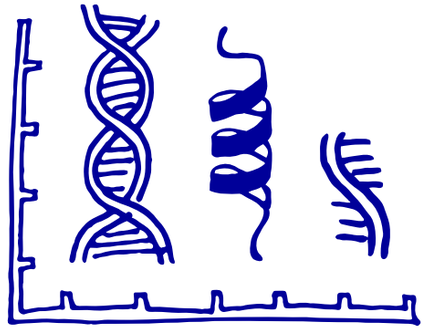
GT Pharmacology

- Biopotency and pharmocodynamic readouts
- Translational pharmacology
- Immunohistochemistry and histology
- Small and large animal species



Biodistribution / Safety

- Vector biodistribution to target and off-target organs
- *In vivo* imaging
- Combined pharmacology and safety studies
- Safety & Efficacy Biomarker ID



Seamless Road to Clinic

- Vector shedding study
- Immunogenicity assessment
- IND-enabling Pharm / Tox packages
- *In vivo* biopotency screening of gene therapy candidates

We integrate a multitude of complementary best-in-class technology platforms within Evotec's scientific network such as large animal models, biomarker discovery, single nuclei RNA sequencing and Evotec's computational bioinformatic powerhouse.

Gene therapy – Translational Sciences

We offer unique synergies with therapeutic area expertise at Evotec

Gene Therapy Translational Value

Oncology
- Human xenograft / Syngeneic mouse models
- Immunization models
- *Ex vivo* T-cell / TCR assay

Metabolic Disorders
- Diabetes / Obesity / Insulin Resistance
- Diet-induced NASH
- Kidney Disease / Fibrosis
- Polycystic ovary syndrome

Rare Diseases
- Muscular dystrophies
- Lysosomal storage disease
- Bleeding disorders
- Neuronal diseases

Neuro-sciences
- Pain / Inflammation
- Huntington & Alzheimer Disease
- Behavior / Cognition
- Translational approaches

Respiratory
- Lung infection acute / chronic
- Pulmonary Inflammation
- Allergic Asthma
- Pulmonary fibrosis

Immunology Inflammation
- Induced Arthritis models
- Vascular inflammation
- Dermal and Neuroinflammation

Broad translational sciences & pre-clinical expertise in multiple disease areas

Agenda

1. A Dedicated Gene Therapy Center within Evotec
2. Expertise & Overview
3. Novel platforms

Novel platform: Addressing key challenges

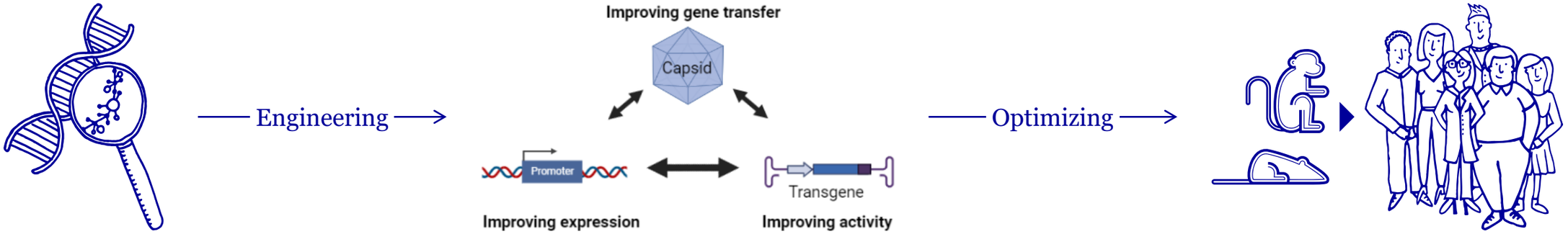
Designed to differentiate from AAV

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



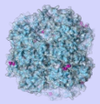
1 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interpreting-sameness-gene-therapy-products-under-orphan-drug-regulations

Novel vector platform development

Capsid engineering

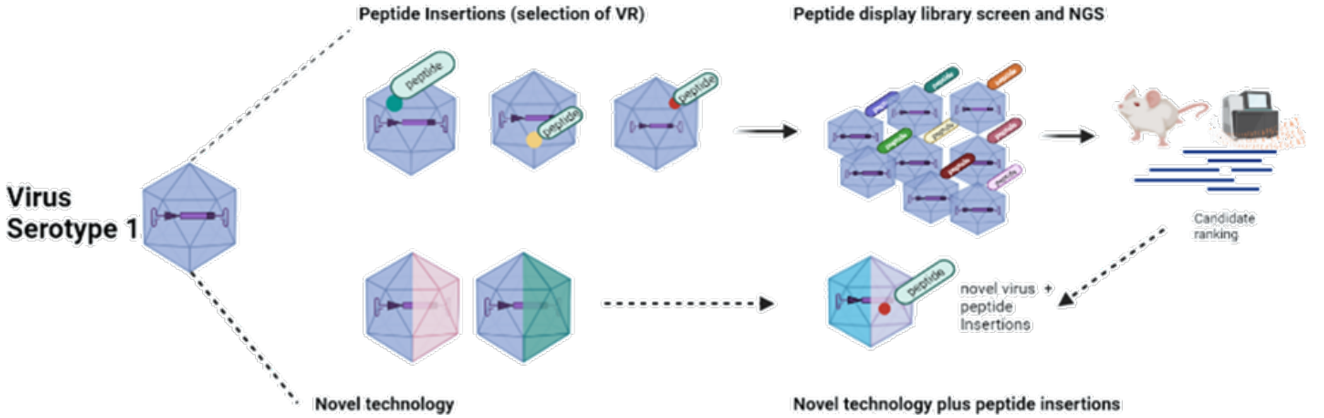
Capsid engineering

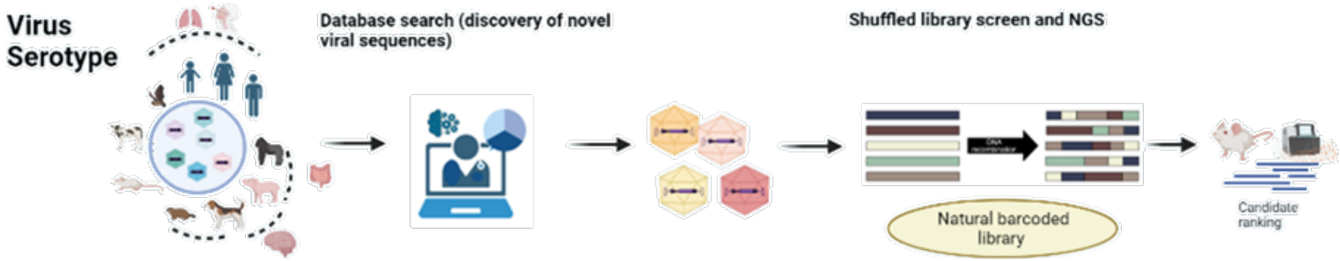
(A) Structural analysis & prediction of mutation target sites



(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

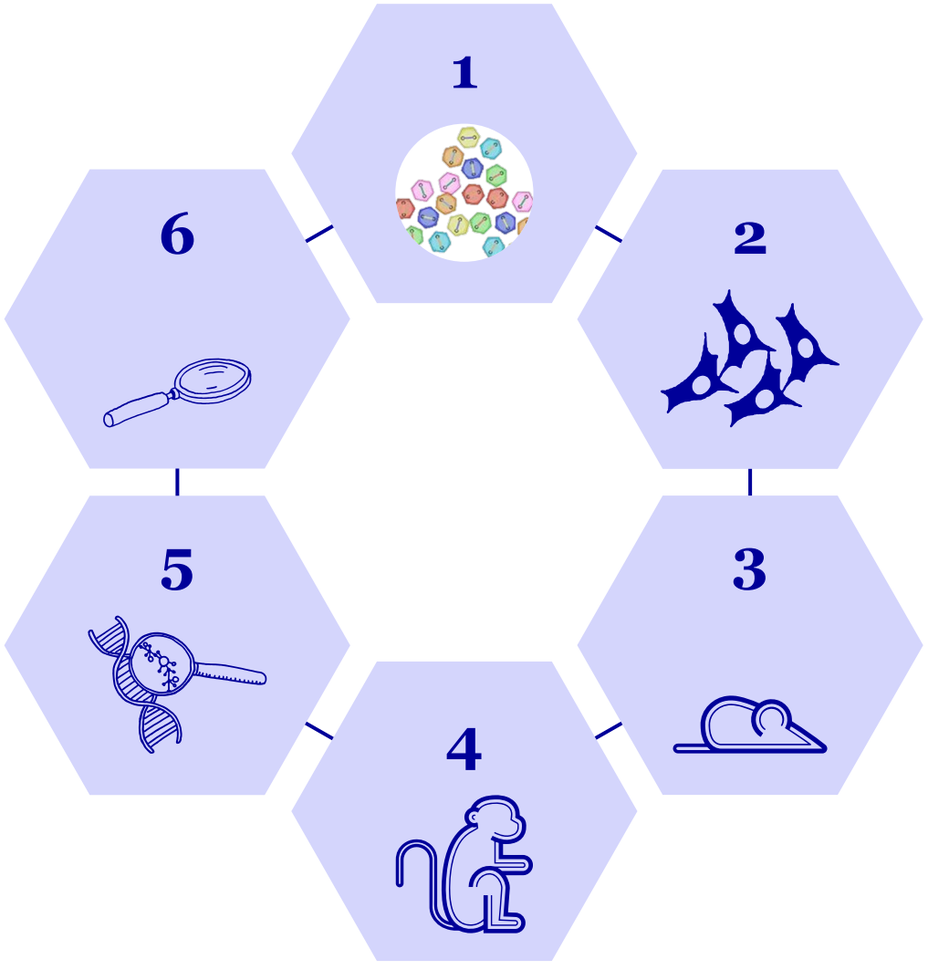
Novel and differentiated AAV Capsids

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

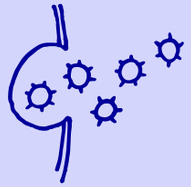
1 Example customized library. Highly complex peptide insertion library (AAV5).

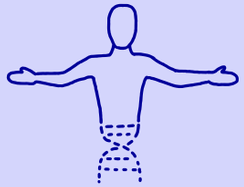
Predictive Toxicology for Gene Therapy

Evotec strives towards implementing AAV safety/tox signatures in gene therapy development

AAV safety

Multifactorial AAV-toxicities are emerging in the pre-clinic/clinic, but mechanisms remain largely opaque. Raise concerns with HCPs and Regulators.



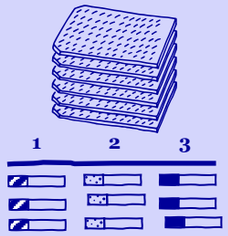


Adverse events

Hepatotoxicity/DILI: With or without an evidence of a cellular immune response. TMA: Thrombocytopenia, hemolytic anemia, AKI. Neurotoxicities: DRG neuronal loss.

Omics tox predictions

Omics has entered mainstream toxicology. Evotec is building an industry leading DILI database. ML/AI-DILI probability and MoA predictions in EVOpanHunter. Modality agnostic. Also in areas such as cardiac- or nephrotoxicity.



HT RNAseq – AAV transduction

Broad array of liver *in vitro* tox assays established in HepaRG, PHH (2D). Expand into co-culture (innate immune) and 3D human liver microtissues, hepatobiliary organoids (cholestatic liver injury). RNAseq scalable to >100k samples, 10-20k genes/sample.

Building AAV reference profiles

Multiple AAV serotypes/transgenes, full/empty and MOIs. Target-tissue specific readouts, cell-tox liability parameters, like UPR response, immuno- and metabolic markers, transgene-related interaction networks.

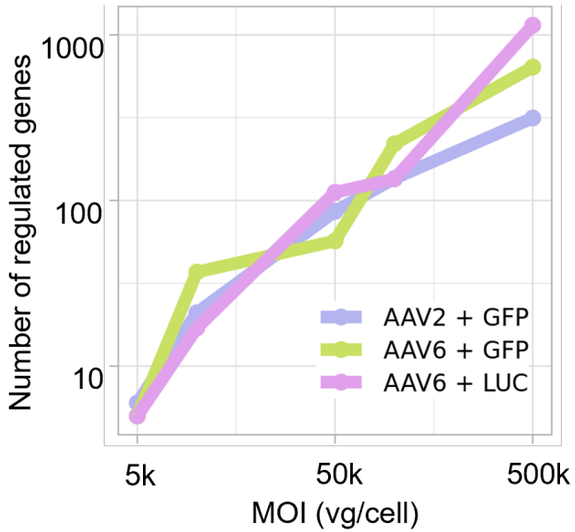
Value aspiration

Inform AAV vector selections and vector-design modifications to mitigate potential risks. Validated by translational assessments *in-vivo*.

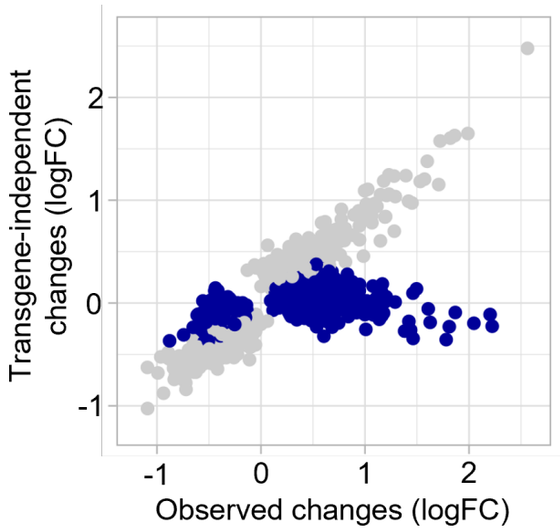
AI, artificial intelligence; AKI, acute kidney injury; DRG, dorsal root ganglion; DILI, dru induced liver injury; HCP, health care provider; HT RNAseq, high throughput RNA sequencing; ML, machine learning; MoA, mechanism of action; TMA, thrombotic microangiopathy; PHH, primary human hepatocytes;

Towards Safety Prediction for AAV based gene therapy

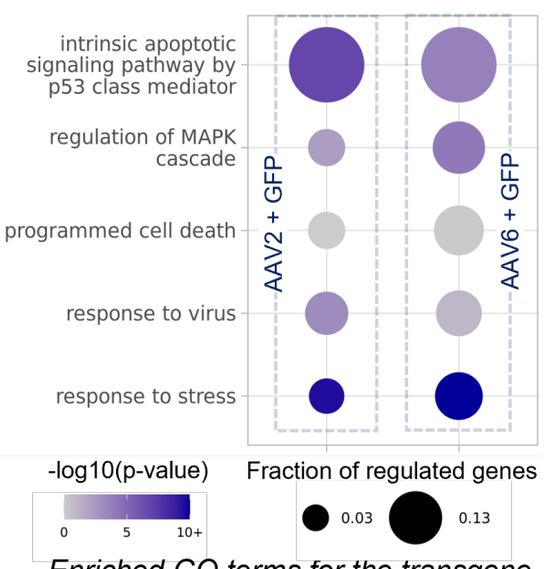
High-throughput method to quantify transduction efficiency and analyze transcriptomic response



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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