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[1)]

At Evotec basic gene therapy experience (viral and non-viral transduction technology) is coupled with strong pre-clinical and clinical translational capabilities

Insights in genetic vector design need to be coupled with biomarkers 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

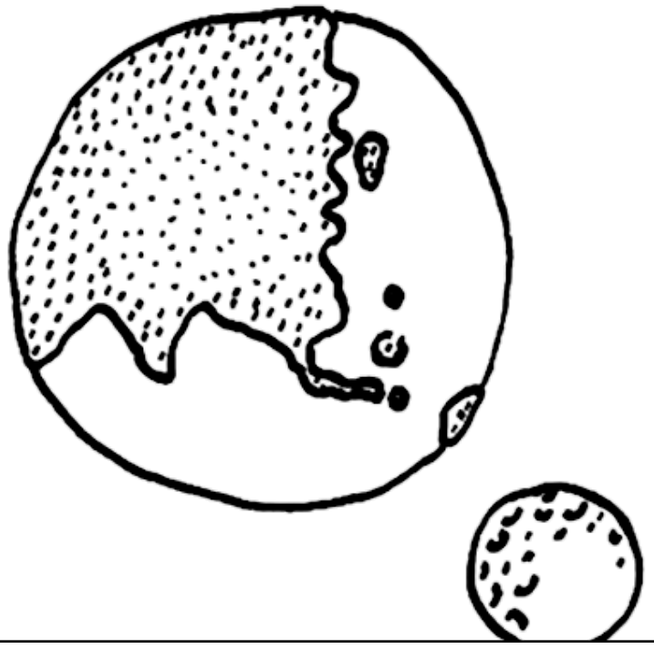
By integrating Evotec’s broader technologies and deep biology expertise, we not only develop new vectors, but also look more broadly at whether the vector is likely to succeed

[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

A Dedicated Gene Therapy Center within Evotec

Expertise & Overview



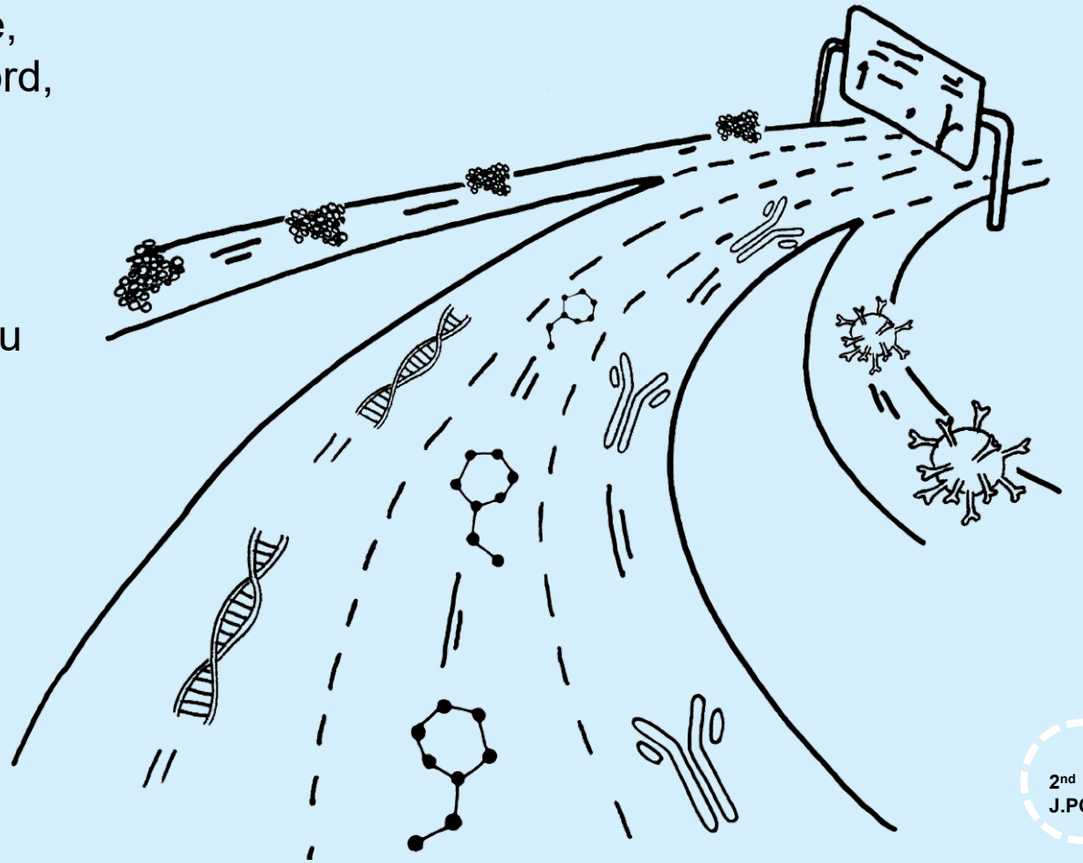
Platforms & technologies for more precision and efficiency

Evotec today – 16 Sites & more than 4,400 employees

Princeton, Seattle, Redmond, Branford, Watertown
~500 FTE

Orth an der Donau
~40 FTE

Verona (Campus Levi-Montalcini), Modena
~850 FTE



Hamburg (HQ), Goettingen (Manfred Eigen Campus) Cologne, Munich,
~1,050 FTE

Abingdon (Dorothy Crowfoot Hodgkin), Alderley Park
~950 FTE

Lyon, Toulouse (Campus Curie)
~950 FTE

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

Innovative and flexible solutions from target identification to clinical candidates

The people

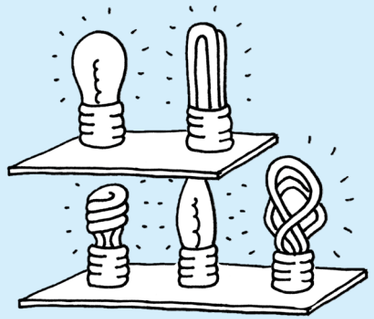
Outstanding scientists

Strong experience in gene therapy and drug development for rare diseases

Poised to progress pipeline assets into clinic

Therapeutic area expertise

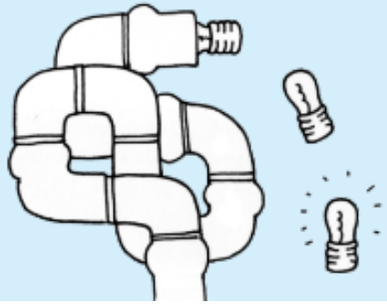
Team leverages therapeutic area insights from years of industry experience and across Evotec.



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

The Gene Therapy Leadership Team

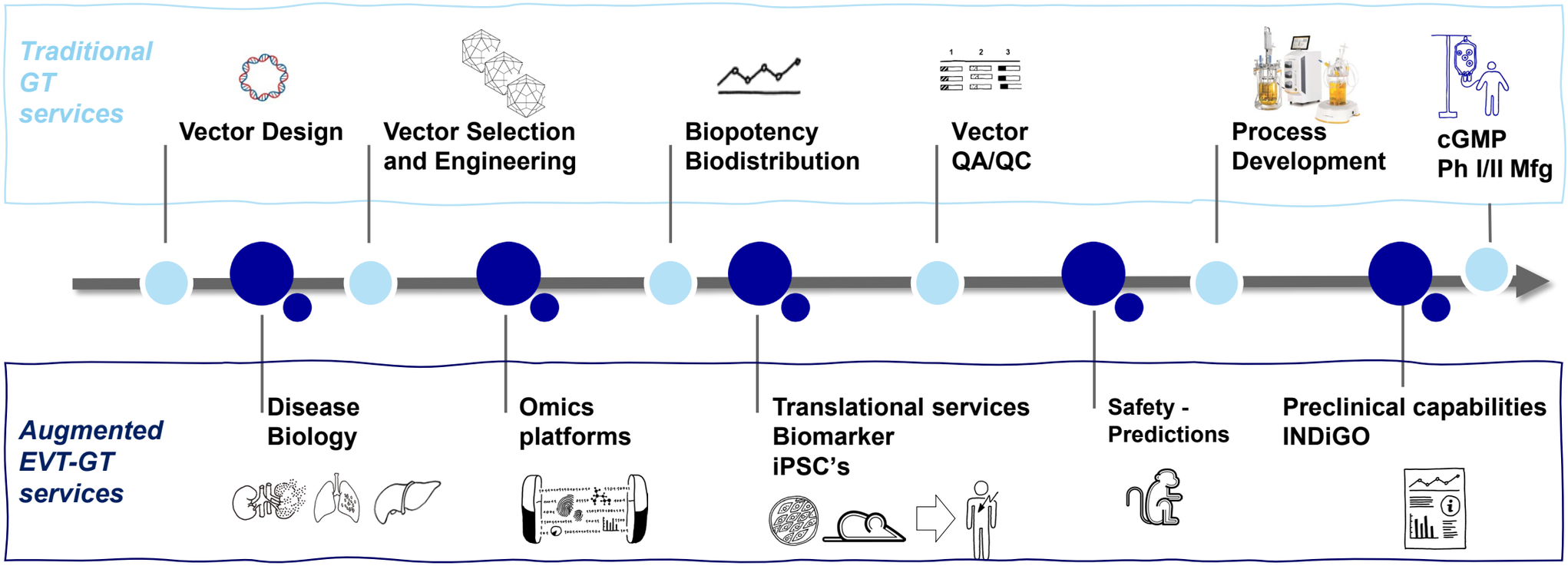
Longstanding experience in Biologics product development

							
Friedrich Scheiflinger	**Hanspeter Rottensteiner**	**Werner Höllriegl**	**Georg Feichtinger**	**Bartosz Muszynski**	**Vera Schoft**	**Helmut Glantschnig**	**Eva Mihailovska**
EVP General Manager Gene Therapy	VP Head of *In vitro* Gene therapy	VP Head of *In vivo* Gene therapy	Lead GT Vectorology	Sen. Res. Scientist Vector Process Development	Sen. Res. Scientist Novel Technologies	Lead GT *In vivo* Sciences	Lead GT Novel Platform
• TSRI • Immuno AG • Baxter Int. • Baxalta • Shire • Takeda >30 years Academia and Pharma	• Baxter • Baxalta • Shire • Takeda >20 years Academia and Pharma	• AstraZeneca • Novartis IBR • Baxter • Baxalta • Shire • Takeda >20 years Pharma	• Univ. of Leeds • UCL • Univ. of York • LBI Trauma • Phycosera >15 years Academia and Entrepreneurship	• SNS Pisa • Danish Tech. Univ. • OxfordBiomedica • Adaptimmune • Shire • Takeda >15 years Academia and Pharma	• VBCF >15 years Academia and Contract Research	• LBI • Merck & Co • Baxter • Shire • Takeda >20 years Pharma	• University of Vienna • Max F. Perutz Laboratories • AFFiRiS AG • Valneva SE >12 years Academia and Pharma
• Hematology • Immunology • Rare Diseases • Metabolic diseases LSD's / IEM	• Gene expression and regulation • Cell Biology • Rare Diseases • Hematology	• *In vivo* Translational Research • Nonclinical Development • Rare Diseases	• Synthetic biology • Gene expression • Gene delivery • Musculoskeletal diseases & Reg. medicine	• Virology • Gene and cell therapy • Vector design, production and characterization	• Molecular Biology • Epigenetics • Genome editing	• Molecular Pharmacology • Preclinical Sciences • Musculoskeletal diseases	• Molecular, cell, and mouse biology • Neurodegenerative disease • Vaccine Dev. (non-clinical and clinical)

TSRI: The Scripps Research Institute; LSD: lysosomal storage disease; IEM: Inborne Error of Metabolism
UCL: University College London; VBCF: Vienna BioCenter Core Facilities; LBI: Ludwig Boltzmann Institute

Early de-risking of gene therapy programs through addressing the translational gap

Unlocking the promise of gene therapy



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

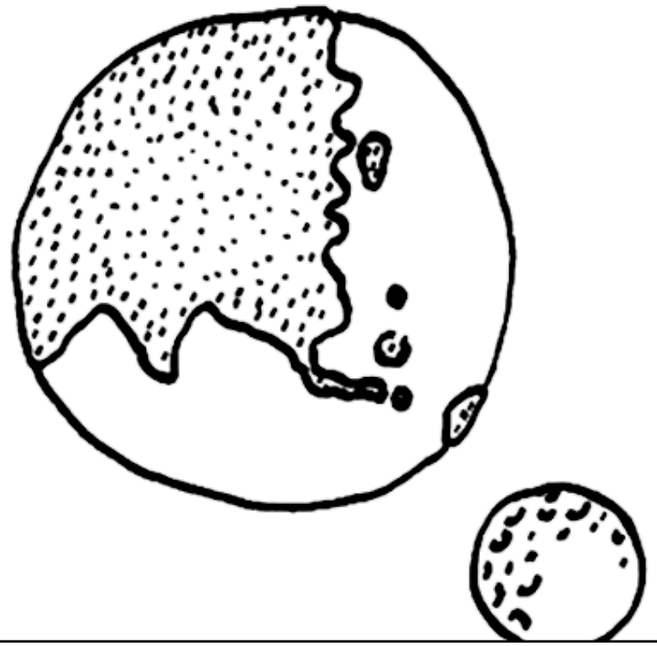
Standard viral *in vivo* gene therapy development technologies are strongly augmented by readily available, highly innovative, in-house capabilities

GT, Gene Therapy; IND, Investigational New Drug; Mfg, Manufacturing; OA/QC, Ouality Assurance/Control;

Agenda

A Dedicated Gene Therapy Center within Evotec

Expertise & Overview



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

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

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

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

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

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

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

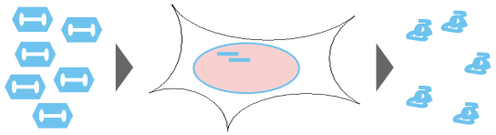
- Lab scale transfection & vector harvest
  - 1 to 5L benchtop bioreactor transfections
- Chromatography Systems (Äkta platform)
  - Affinity chromatography
  - Ion exchange chromatography
- Ultracentrifugation
- TFF

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



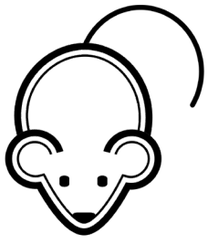
We cover within Evotec the entire value chain of preclinical drug discovery and development, from early discovery to lead candidate identification and preclinical development candidate characterization

Non-Clinical Sciences

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

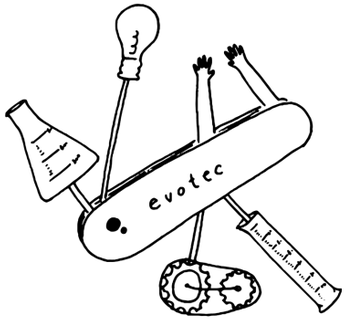
Discovery Sciences

- 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



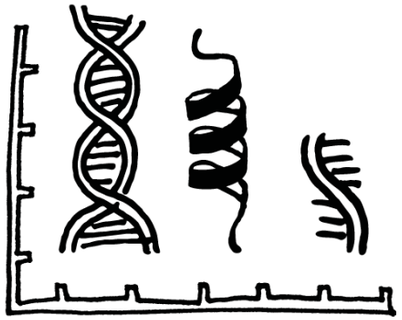
GT Pharmacology

- 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 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

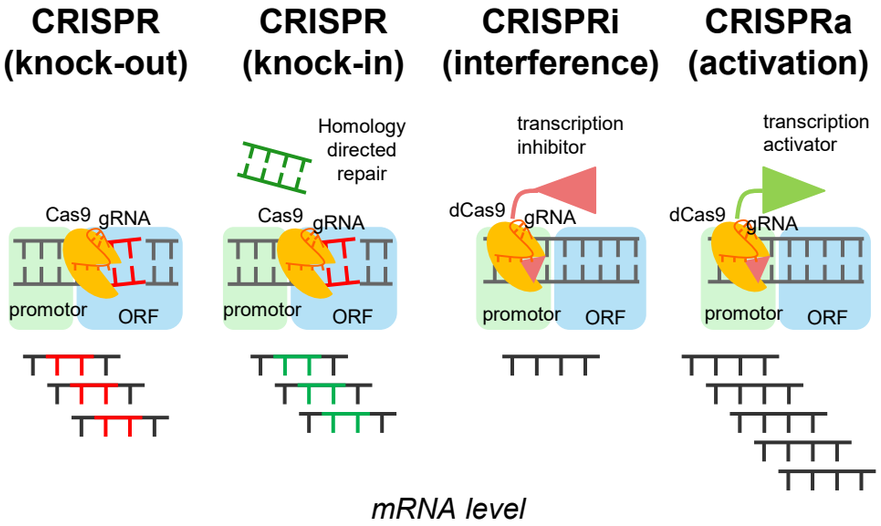
Optimization of editing components and efficiency in various cellular assays tailored to project needs

- 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

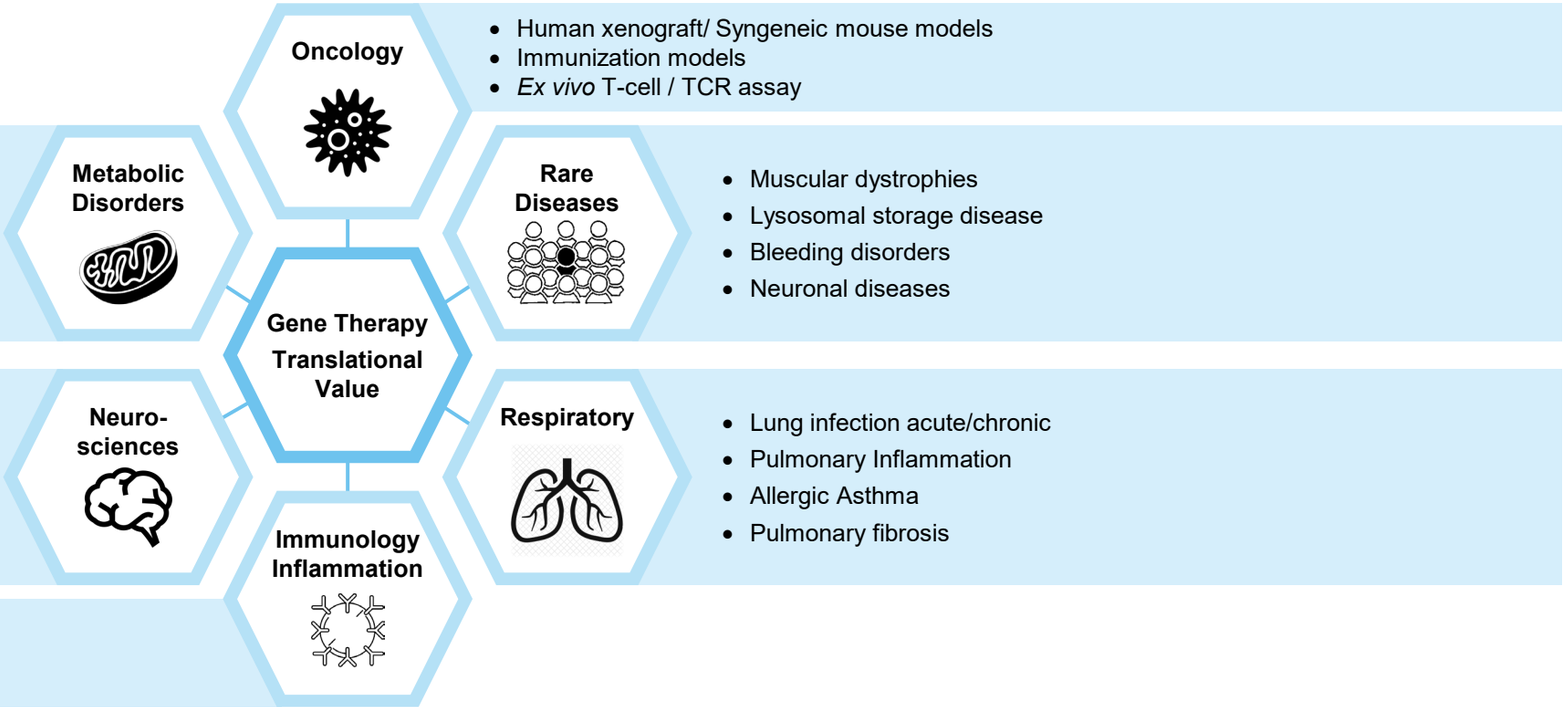
CRISPR toolbox for genetic approaches



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

Gene therapy – Translational Sciences

We offer unique synergies with therapeutic area expertise at Evotec



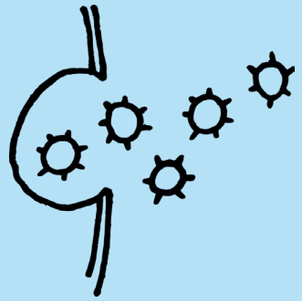
Broad translational sciences & pre-clinical expertise in multiple disease areas

Selection of gene therapy delivery platforms

Evotec's modality-agnostic gene therapy discovery platform

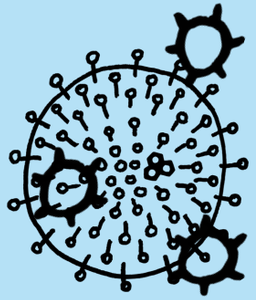
Viral gene delivery

- Natural AAV serotypes
- Engineered AAV capsids
- Capsid Library screening



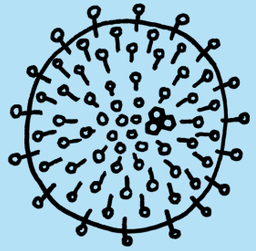
Combination of viral vector & lipids

- LNPs
- Exosomes (exo-AAV)
- Liposomes



Non-viral gene delivery

- Lipid nanoparticles



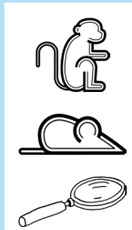
Guided by your project's specific needs and integrating Evotec's broader technologies and deep biology expertise, we not only develop new vectors, but also look more broadly at whether the vector is likely to succeed.

AAV, adeno-associated virus; LNP, lipid-nanoparticle

High complexity peptide display library

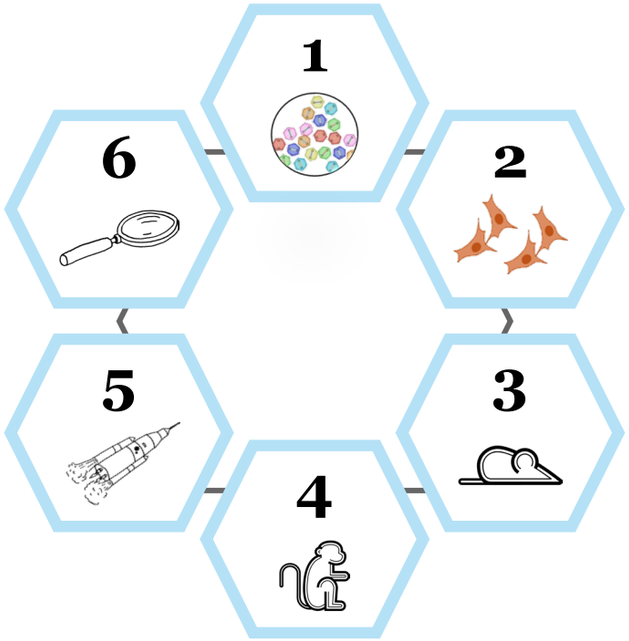
Evotec's cutting edge RNAseq/bioinformatics based *in vivo* capsid discovery

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



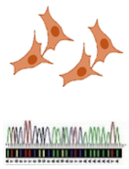
5 Consecutive libraries
- Generation of high-complexity engineered library (Library B)
- *In vitro*/*In vivo* NGS screen of consecutive sublibraries

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



1 High complexity peptide display library[1)]
- Flexible design space
- Peptide insertion in AAV5 backbone (> $1*10^9$)
- Barcoded for comparative analyses

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



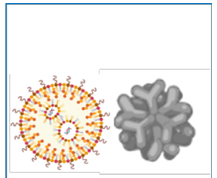
3 *In vivo* testing
- Transduction in humanized mice
- Ranking by tissue- or single-nuclei RNAseq and bioinformatics
- Selection and/or decision to bioengineer

[1)] 1e9, AAV5 backbone

Non-viral gene therapy – Lipid-Nanoparticles

We leverage substantial LNP expertise in-house and across the Evotec network

Customizable LNPs for versatile gene delivery



LNP & NANOPARTICLE GENE DELIVERY

Preclinical LNP production & characterisation

Phosphate-salt NPs

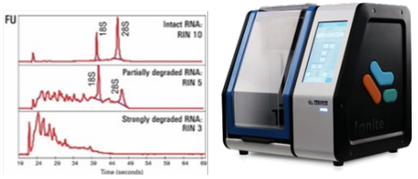
Biodistribution
Stability
Transfection-efficacy
Toxicity
[PD/PK]

JET Bioreactors for pre-clinical LNP production

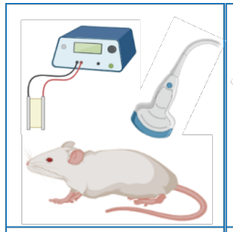
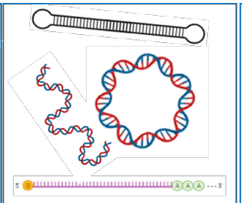
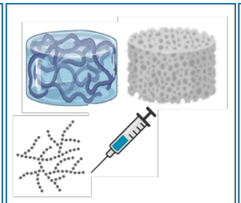
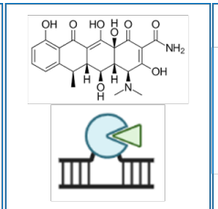
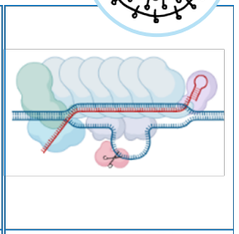
DLS instrumentation for characterization

Nucleic acid payload integrity & potency analytics

Encapsulation efficacy (EE%)



Inquire about our technology panel for co-development

TARGETED PHYSICAL IN VIVO GENE DELIVERY	NOVEL NON-VIRAL PAYLOADS	GENE-ACTIVATED MATERIALS (GAMS)	INDUCER-REGULATED GENE EXPRESSION	SAFE-HARBOR CRISPR/Cas9
				
Electroporation **Sonoporation** Intramuscular Hepatic Musculoskeletal CNS Longitudinal *in vivo* imaging - expression yields - localisation and kinetics	**ccDNA** **Synthetic mRNA** **Modified nucleic acids** Hairpin adapters Aptamers Preclinical-scale IVT Metabolic labelling (click-chemistry, phosphorothioates) Carrier-coupling	**Biomaterial-based gene delivery** **Regenerative gene therapy** Multi-phasic scaffold designs Stem-cell incorporation Musculoskeletal applications (e.g. OA)	**TetON/OFF** **Vitamin-regulated** *In vivo* regulation of localised transgene expression Temporally-regulated therapeutic transgene expression	**HDR-based KnockIn** **Cell-engineering** **Stable *in vivo* ntegration** AAVS1 (H. sapiens) ROSA26 (M. musculus) Multi-cistronic targeting constructs (>3 ORFs)

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

Designed using bioRender

Predicting Safety/Toxicology for Gene Therapies

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.

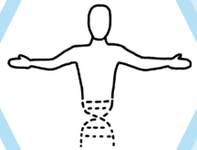
Omics tox predictions

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.

Building AAV reference profiles

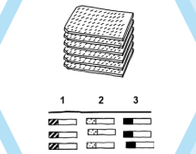
Multiple AAV serotypes/transgenes, full/empty and MOIs. Target-tissue specific readouts, cell-tox liability parameters, like UPR response, immuno- and metabolic markers, transgene-related interaction networks



Adverse events

Hepatotoxicity/DILI: W or w/o evidence of a cellular immune response.

TMA:Thrombocytopenia, hemolytic anemia, AKI. Neurotoxicities: DRG neuronal loss



HT RNAseq – AAV trans-duction

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

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 trhoughput RNA sequencing; ML, machine learning; MoA, mechanism of action; TMA, thrombotic microangiopathy; PHH, primary human hepatocytes

AAV Gene Therapy's translational efficacy gap

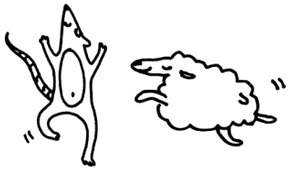
Dose predictions: from the preclinic to FIH clinical trials

Multiple species specific differences

capsid biodistribution, transduction efficiencies, protein expression & clearance, dose volumes (local)

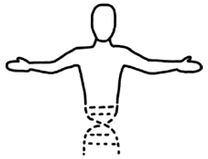
Disease model limitations

in mice/rodents or select large animal species. Some with poor dose translatability into humans.



Humanized models are useful

Mouse models with humanized target organ can help reducing the translational gap



Studies in NHP

Preferable for human dose prediction; Availability and pre-screens are challenging and add complexity

Modeling

Careful evaluation of preclinical data required to model accurate FIH dose to enter clinical phase

Critical clinical FIH dose information

- Starting dose must be effective (curative)
- Low safety doses considered unethical
- Dose escalation regimen considerations

NHP = non-human primate; FIH = first in human

Innovation in AAV GT development to close the translational gap

Utilizing predictive toxicology platform in AAV based gene therapies

Serious Adverse Events in AAV Vector Clinical Trials raise concerns with HCPs and Regulators

Multifactorial AAV-toxicities are emerging in the pre-clinic/clinic but ***mechanisms remain largely opaque*** *for most experimental therapies.*

We investigate molecular mechanisms of drug toxicities and potential safety liabilities

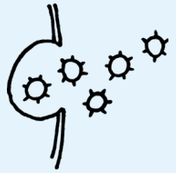
Omics has entered mainstream toxicology for Drug-Induced-Liver-Injury tox-predictions *but also in areas such as cardiac- or nephrotoxicity and others.*

A 21st century Omics service offering for vector safety liability profiling

We aim for an ***integrated pan-omics approach to help guide vector selections****, vector optimizations & dose finding strategies.*

2011-2021

- **Hepatotoxicity/DILI (& loss of pharmacology)**
  - Elevated liver enzymes, serious liver injury, liver failure
  - With or w/o evidence of a cellular immune response
  - Most common adverse event associated with intra-venous (systemic) administration of AAV vectors
- **Thrombotic microangiopathy (TMA)**
  - Thrombocytopenia, hemolytic anemia, acute kidney injury
- **Neurotoxicities**
  - Dorsal root ganglia (DRG) neuronal loss



Today

- **A robust & versatile high troughput environment**
  - Leading bioinformatics platforms for interactive multivariate data analysis
  - Applicable to pharmacology and exploratory toxicology studies with AAV vectors
    - *In vitro* in target cells (2D, 3D, organoids)
    - *In vivo* in (humanized) mice, rats and NHPs
- **Plan: Tissue- and/or Single-cell based correlations of AAV transduction with selected indicators of toxicities**
  - Target-tissue specific readouts, cell-tox liability para-meters, like UPR response, immuno- and metabolic markers, transgene-related interaction networks

Aim

- **Mechanistic insights in vector safety assessments aided by transcriptomic profiling**
  - Inform AAV vector selections and vector-design modifications to mitigate potential risks
  - **Vector-Toxicity finger prints aimed at identify-cation of differentiating safety attributes**

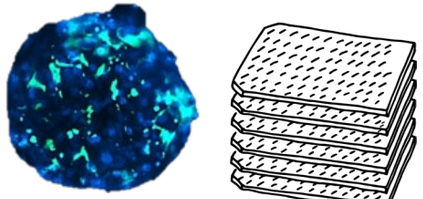
HCP = Health Care Provider; UPR = unfolded protein stress response; DILI = Drug induced liver injury

Liver adverse effects as a concern in Gene Therapy: Adopting molecular profiling tools from compounds

Evotec providing fully integrated PanOmics workflow for liver tox and beyond

Cell Biology

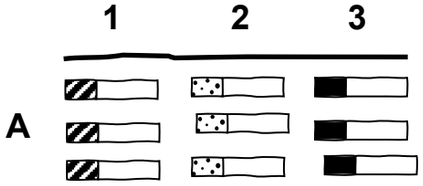
- High throughput – 384 well plates
- Broad array of liver *in vitro* tox assays
- HepaRG, PHH and Human liver microtissues



3D hLiMT

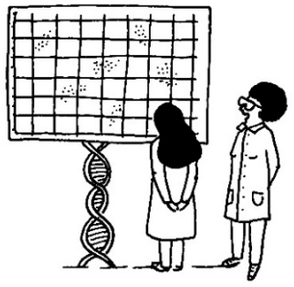
ScreenSeq™

- High throughput unbiased RNA-Seq
- Scalable to >100,000 samples
- 10,000-20,000 genes per sample



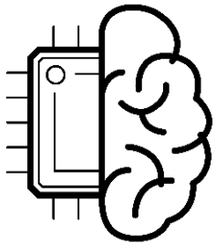
EVO*panHunter*

- Automated quality control
- Tox report
- Interactive platform



Data Interpretation

- Machine Learning / AI DILI prediction
- MoA prediction
- Expert data review and conclusion
- IVIVC in animal model



IVIVC, *In-vitro In-vivo* correlations

evotec

#RESEARCHNEVERSTOPS

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