

#RESEARCHNEVERSTOPS

Evotec Gene Therapy

Adding value to our partners' research



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Collaborative model for efficiency in drug discovery

17 Sites with platforms & technologies for more precision and efficiency

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

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

Toulouse (FR)

Campus Curie – Oncology

of excellence; integrated

& immuno-oncology centre

drug discovery; 2nd J.POD®

Verona (IT)

Hamburg (GER – HQ)

for leading end-to-end iPSC platform

Campus Levi-Montalcini Integrated drug discovery & development

Vienna (AU) Dedicated to gene therapy

Modena (IT) Cell therapy manufacturing

Manfred Eigen Campus – A major hub for integrated drug discovery including variety of HTS screening activities; home of neuroscience experts & the basis

Munich (GER) Dedicated to unrivalled proteomics and bioinformatics; unique mass spectrometrybased "omics" 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



Evotec GT¹ – 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



Success in Research, Development & Partnerships

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



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

Early de-risking through addressing the translational gap

Unlocking the promise of gene therapy



Augmented EVT-GT services

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





- 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



Evotec GT Non-viral LNP Capabilities

Integrated preclinical drug development platform

Formulation & payloads



Production platforms & principles

Continuous Solvent-Antisolvent Precipitation



In vitro & in vivo testing





In vitro potency testing

In vivo PoC, kinetics, efficacy & biodistribution testing

Analytics & QC





DLS characterization Bioanalyzer platform (size distribution, PDI) (payload integrity & stability)







RNAse contamination

Encapsulation efficacy % API concentration

6 Endotoxin (LAL) assay



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



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

Areas of gene therapy expertise at Evotec GT

Innovative and flexible solutions from target identification to IND



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



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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 CRISPR CRISPRi **CRISPRa** (knock-out) (knock-in) (interference) (activation) transcription transcription Homology inhibitor activator directed repair dCas9 gRNA dCas₉ Cas9 gRNA Cas₉ gRNA gRNA Π ТΠ П ORF ORF promotor ORF promotor promotor promotor ORF $T \rightarrow T$ mRNA level



Non-viral gene therapy – Lipid-Nanoparticles

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



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.