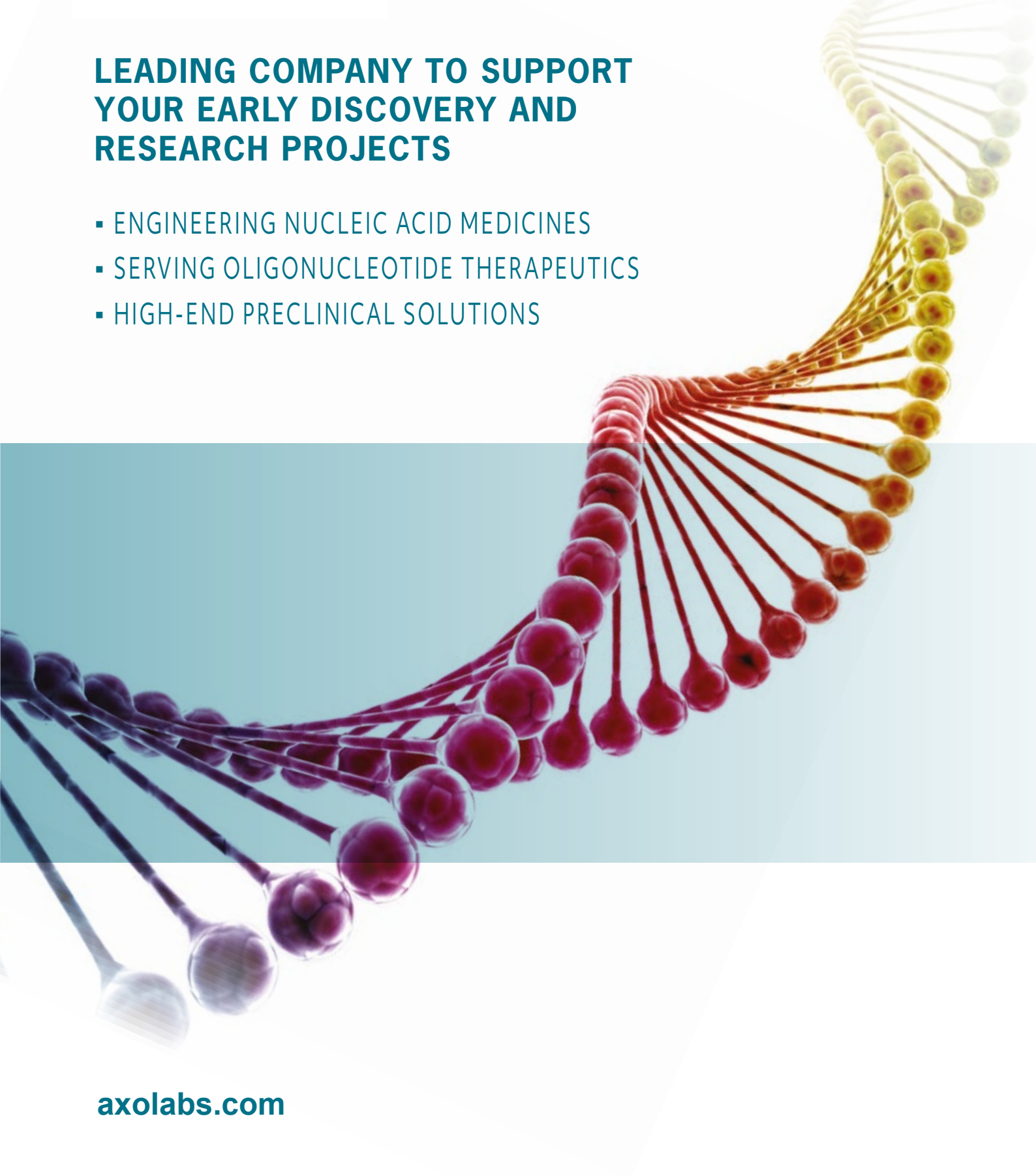
AXOLABS

Nucleic Acid Therapeutics by LGC

LEADING COMPANY TO SUPPORT YOUR EARLY DISCOVERY AND RESEARCH PROJECTS

- ENGINEERING NUCLEIC ACID MEDICINES
- SERVING OLIGONUCLEOTIDE THERAPEUTICS
- HIGH-END PRECLINICAL SOLUTIONS



axolabs.com

Axolabs is the leading custom research organisation providing high-end solutions and consultancy in the field of oligonucleotide therapeutics and nucleic acid medicines.

Scientific excellence

We leverage 20+ years of expertise in oligonucleotide research and drug development for the benefit of our customers.

Flexible and effective interaction with clients

Our custom-tailored blend of project management, scientific input and technological know-now facilitates optimal advancement of your projects

From target to clinic

As a one-stop-shop we provide efficient and validated services towards the successful development of oligonucleotide-based therapeutics.

Services across multiple disciplines

We deliver integrated solutions for preclinical research and clinical development covering chemistry, biology, bio-analytics as well as analytics and manufacturing of nucleic acid therapeutics.

High quality services and products

Axolabs' unique combination of a dedicated team with state-of-the-art equipment and well established processes ensures highest quality of our services and products.

Commercial and late clinical phase

We also offer contract development and manufacturing services at our sites in Berlin, Germany and Petaluma, USA.
For more information visit axolabs.com

Oligonucleotide Synthesis

» Oligonucleotide drug design
- Bioinformatics for in silico sequence pre-selection
- Rational oligonucleotide design tailored for specific delivery systems

» Chemically modified oligonucleotides and conjugates using:
- Wide range of chemically modified building blocks
- Fluorescent labels
- Small molecule, lipid, peptide and carbohydrate conjugates (e.g. GalNAc clusters)
- Various conjugation strategies and chemistries available

» Long RNA/DNA
- Single guide RNAs for CRISPR/Cas applications
- Aptamers

» Potency and stability improvement of oligonucleotide-based therapeutics by optimisation of sequence, structure and chemistry

» Custom-tailored manufacturing process optimisation to maximise yield and quality

» High quality oligonucleotides
- High throughput synthesis for lead identification and lead optimisation
- Oligonucleotide synthesis up to multiple 100 gram quantities
- Synthesis of drug substance for GLP toxicology studies
- Synthesis of reference material and drug substance-related impurity markers

» Lipid synthesis
- For clinically verified LNP formulation of oligonucleotides
- Set of proprietary lipids available

Gene Editing Therapeutics

Accelerating CRISPR-based drug development

» Solid phase synthesis of therapeutic sgRNAs
- Variety of chemical modifications
- Scalable manufacturing process
- Unprecedented purity

» Superior biological editing efficiency

» Advanced analytics
- Release by uHPLC with high resolution ESI-MS
- Sequence tailored LC-MS/MS based sequencing methods
- 5'-specific sequence failure analysis
- Thermodynamic characterisation
- Micro Scale Thermophoresis (MST) analysis of binding interaction with Cas-protein

» We offer guidance, beyond manufacturing, through the entire drug development process

- Bioanalysis of sgRNA and Cas9 mRNA in blood and tissue (under GLP/GCP)
- Support of delivery/formulation
- Editing analysis

Biology & Pharmacology

» State-of-the-art facilities
- Safety level 1 facility
- Safety level 2 cell culture laboratories

» Safety and toxicology analysis
- PBMC assays to measure oligonucleotide-induced cytokine response
- Clinical chemistry; analysis of 36 different parameters from biological fluids like serum, plasma or urine (COBAS Integra®)

» Ligand-receptor interaction and uptake studies/histology
- Confocal microscopy (Zeiss) for analysis with up to four channels in parallel
- Fluorescence microscopy (Apotome, Zeiss)

» Nucleic acid analysis and quantification of mRNA
- Quantigene™ Singleplex (branched DNA) assay
- Quantitative RT-PCR (QuantStudio™)
- Tape Station electrophoresis
- Next generation sequencing using Illumina based RNA-Seq analysis for coding transcriptome analysis and Oxford Nanopore sequencing for direct RNA sequencing

» *In vivo* monitoring of cell number and cell viability via xCelligence System
- Preparation (magnetic beads) and differentiation of specific cell types
- Standard cytotoxicity and apoptosis assays

» Custom-tailored preclinical services

» CRISPR/Cas-related technologies
- Activity testing of sgRNAs
- Determination of genome editing efficiency by T7 endonuclease I + TIDE assay

» Lead identification and characterisation

» Monitor cell type-specific oligonucleotide drug delivery to multiple tissues *in vivo*

» Analysis in primary cells such as hepatocytes from various species

» Protein analysis
- Quantification of multiple proteins from the same sample, as e.g. cytokine panels, by Luminex® Multiplex Reader or Meso Quickplex
- Classical ELISA and MSD-ELISA
- WES Simple Western

» Flow cytometry

Lead Identification

Well established and proven process including:

» Bioinformatics assessment for *in silico* sequence pre-selection
- Considering species cross-reactivity
- Proprietary algorithm for selection of specific oligonucleotide (avoiding off-targets)

» Oligonucleotide design (structure and chemistry) and synthesis

» Lead identification by high throughput *in vitro* screening
- Assay development for monitoring of mRNA, protein or phenotype by technologies including Quantigene®, (q-) PCR, ELISA and cell based assays
- Efficacy screening in established cell lines or primary cells by transfection and/or direct incubation
- More than 200 cell lines on stock
- Primary cell cultures from various species

» Iterative process for lead characterisation and optimisation
- Determination of IC_{50} values
- Analysis of immuno-stimulatory properties (PBMC assay)
- Oligonucleotide safety
  In vitro specificity and off-target analysis (e.g. by RNA-Seq)
  In vitro monitoring of toxicity (e.g. xCELLigence system)
- Stability analysis in biological matrices
- Informed chemical modification

» *In vivo* efficacy and early safety assessment of oligonucleotide-based therapeutics in wild type mice

Bioanalytics of Oligonucleotides and mRNA

» Axolabs has a unique and proprietary assay system platforms (PNA-HPLC Assay and LC-MS/MS) for the sensitive detection of oligonucleotides from biological matrices for the analysis and characterisation of DMPK and ADME properties of oligonucleotide-based therapeutics

- Sensitive detection of single- and double-stranded oligonucleotides down to 0.1 ng/mL
- Assays are compatible with conjugates and different oligonucleotide chemistries
- Assays are suitable for all therapeutic entities such as siRNAs, miRNAs, ASOs, Aptamers, complex oligonucleotide structures with > 90nt and others
- Assays allow simultaneous detection of multiple analytes employing an extraction-free and robust procedure
- Downstream mass spectrometric identification of oligonucleotide metabolites
- Calculation of PK parameter by WinNonLin analysis

» Quantitative detection of mRNA therapeutics including PK/TK of mRNA therapeutics from various biological matrices by:

- qRT-PCR using SYBR Green or TaqMan
- Quantigene™ Singleplex branched DNA assay
  - Sensitive and extraction-free (no mRNA extraction necessary)
  - Parallel quantitative detection of oligonucleotide and target mRNA from a single sample

GLP-/GCP-Compliant Analytical Testing

» Dedicated GLP/GCP laboratories separated from the non-GLP laboratory space

» Established quality management system compliant with the OECD principles of GLP and with the ICH guideline for GCP

» Method validations in conformance with the:

- EMA Guideline on bioanalytical method validation
- US FDA Guidance for Industry for Bioanalytical Method Validation

» Storage stability testing of test items in biological matrix

» PK and TK analyses of study samples from GLP-toxicology studies and from clinical trials:

- Unique and proprietary assay system for the sensitive detection of oligonucleotides
- Quantigene branched DNA assay for the quantitative detection of mRNA

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Oligonucleotide Drug Substance and Drug Product Analytics (non-GMP/GMP)

» Development and validation of analytical test packages required for the release of oligonucleotide Drug Substances and Drug Products
  • Including mRNAs and LNP formulations
» Characterisation of single-stranded and double-stranded oligonucleotides by state-of-the-art high resolution mass spectrometry and uHPLC techniques
  • uHPLC and LC/MS method development
  • Development of specific sequencing methods including Tandem-MS up to 45mers
  • Proven technology transfer processes from and to third party CDMOs
» Full characterisation of oligonucleotide reference standards
» Forced degradation studies on Drug Substance and Drug Product including photo-stability
» ICH-compliant stability studies
» Physicochemical and thermodynamic characterisation of oligonucleotides by differential scanning calorimetry (DSC), temperature controlled UV- Flourescence or CD spectroscopy
» Determination of molar extinction coefficient

Analytical equipment:

- uHPLC systems equipped with UV-, FL- or CA-Detector
- High resolution ESI-MS (Q-Tof and OrbiTrap)
- Temperature-controlled UV- and CD- and Fluorescence Spectrophotometer
- FT-IR
- DSC
- Malvern Particle Sizer
- Coulometric Karl-Fischer instrument
- Flame Photometer for sodium determination
- Endosafe nexgen-MCS Endotoxin testing instrument
- Osmometer
- Stability chambers for ICH-compliant stability studies
- Micro Scale Thermophoresis (MST) instrument

Analytics of mRNA Therapeutics

Characterisation of mRNA Drug Substance (non-GMP/GMP):

» Analysis of mRNA size and purity/integrity by uHPLC (IP-RP or SEC)
» Identity confirmation by mRNA fingerprinting and Nanopore sequencing
» Determination of poly(A) tail length and polydispersity by uHPLC with UV and ESI-MS
» Analysis of capping structure and capping efficiency by uHPLC with UV and with ESI-MS
» Determination of residual NTPs, plasmid or protein
» Base composition analysis
» Thermodynamic analysis by UV, CD or DSC
» Determination of dsRNA impurities by ELISA

Characterisation of mRNA-LNP Drug Product (non-GMP/GMP):

» Determination of mRNA label claim by uHPLC
» Determination of mRNA encapsulation
» Analysis of lipid content and composition
» Analysis of particle size, polydispersity and zeta-potential by DLS
» mRNA and mRNA-LNP bioanalysis
» PK and biodistribution of mRNA (GLP/GCP)

mRNA pharmacology

» Proof-of-concept studies in mice
» *In vitro* and *in vivo* safety analysis
» Cell-based assays to study mRNA therapeutics
» Target expression/function (ELISA, Luminex and MSD platforms, cell viability, flow cytometry)

Functional delivery of oligonucleotides *in vitro* and *in vivo*

» Preparation of lipid nanoparticle formulations (LNPs) composed of commercial or proprietary lipids

» Monitor cell type-specific oligonucleotide drug delivery to multiple tissues *in vivo*

» Rational oligonucleotide design tailored for specific delivery systems

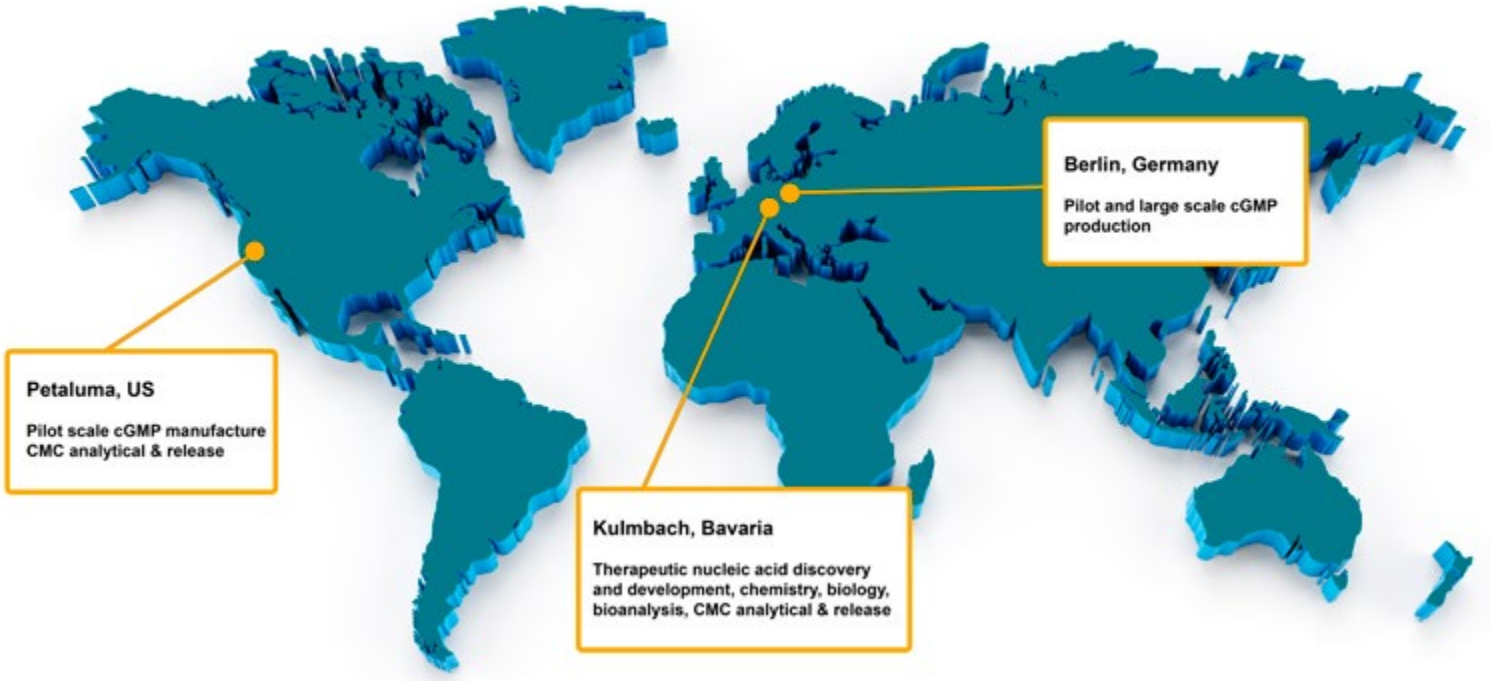
» *In vitro* functional analysis of oligonucleotides by monitoring mRNA, protein or phenotype

» Established delivery to hepatocytes, Stellate and Kupffer cells, endothelial cells and others, based on our proprietary platform of LNPs

Consultancy

With our experience and specific know-how across oligonucleotide drug discovery and preclinical development we consult customers and partners from the pharmaceutical and Biotechnology industry, academic research institutes and venture capital firms.

LOCATION



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