Target Identification and Validation

Gene knock-out and over-expression studies both in vitro and in vivo as well as access to relevant in vivo disease models
World-class ex vivo imaging technology platform using tissue sections to study cellular and molecular events
Phenotypic screening of complex cellular systems for hit identification
Target deconvolution using proteomics

Gene Expression Profiling
Changes in gene expression, as result of a disease state or as a consequence of drug action, give invaluable insights into biological systems. From early target identification to mode of action studies and biomarker identification the analysis of gene expression data supports the drug discovery processes. Our capabilities include:
- Design and execution of transcriptional studies in vitro or in vivo including rigorous quality control
- Bioinformatics analysis to determine differential expression and generate annotated gene lists
- Cluster analysis to identify groups of regulated genes
- Data interpretation turning raw data into meaningful biological and pharmacological information

In Vitro Target Modulation Capabilities
The powerful combination of CRISPR and disease-related cellular models coupled with a variety of read-outs including high-content imaging are designed to provide an accelerated solution to target identification, validation and target deconvolution following a phenotypic screen. Our offering includes:
- Screening of shRNA and CRISPR libraries for target identification
- Validation of specific targets in various cellular models using disease-relevant read-outs

Additionally, expertise in working with nontraditional cellular models such as co-cultures and primary cell culture is available.

IN VIVO TARGET VALIDATION
Evotec has disease models in a number of areas such as diabetes, diabetic complications, kidney diseases, neurodegeneration, oncology, inflammation and pain that can be used for target validation. Approaches utilised include:
- Application of target-selective small molecules or biologics in acute or sub-chronic in vivo studies in rodents
- Virus-based target in vivo knock-down and over-expression techniques

A variety of read-outs have been established that allow the investigation of target modulation. Such studies are run on a routine basis and additional read-outs are developed on a continuous basis
- Classical pharmacodynamic and efficacy read-outs such as blood glucose and HbA1c for diabetes, behavourial read-outs for pain and neurodegeneration
- A world-class ex vivo histology and immunohistochemistry platform investigating cellular and molecular markers in tissue sections prepared from treated animals

Use of Phenotypic Assays to Identify New Disease Relevant Targets and Pathways
The ability to study compound effects in a disease-relevant cell type in a target-unbiased way offers enormous potential and has thus become increasingly popular in recent years, with more complex and disease-relevant cellular systems becoming available for higher throughput assays.

Evotec has in-depth expertise in the area of phenotypic screening and target deconvolution.

Overview of Evotec capabilities and expertise in target identification and validation across different disease areas

<table>
<thead>
<tr>
<th>METABOLIC DISEASE</th>
<th>ONCOLOGY</th>
<th>CNS, NEURODEGENERATION, PAIN</th>
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<tbody>
<tr>
<td>Differential gene expression</td>
<td>+++</td>
<td>n.a.</td>
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<tr>
<td>shRNA/CRISPR/overexpression</td>
<td>+</td>
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<td>Cellular/ex vivo tissue imaging</td>
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<td>In vivo efficacy studies</td>
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