

# TARGET IDENTIFICATION AND VALIDATION



**Mark Slack**  
Vice President In vitro  
Pharmacology

### OFFERING

Evotec has established a world-leading platform to support the discovery and validation of innovative disease-modifying targets across different therapeutic areas as well as aid target deconvolution following a phenotypic screen. Our offering comprises:

- ▶ Differential expression studies followed by bioinformatics-driven data mining and hypothesis building

- ▶ 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 transcriptomics 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

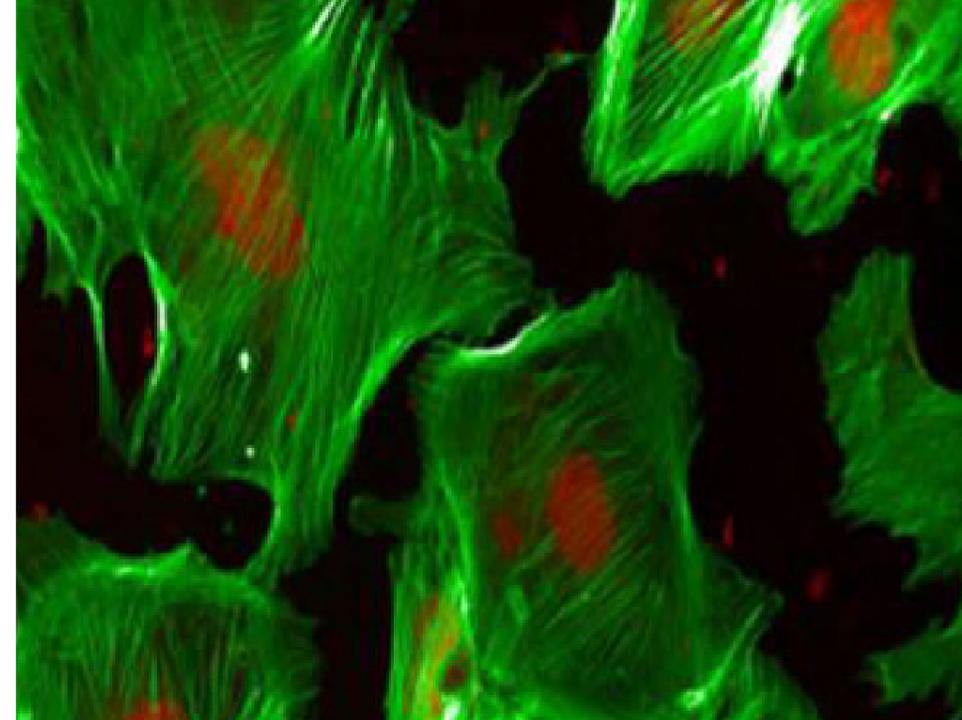
- ▶ Virus-based target *in vivo* knock-down and over-expression techniques

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, behavioural 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.



Identification of new mechanisms to treat kidney disease: Phenotypic screening of conditionally immortalised human podocytes

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

### High-Content Screening

Evotec has a world-class high-content screening platform that is increasingly used for hit identification through phenotypic screening

- ▶ >15 years know-how in the design and implementation of phenotypic assays using cell lines but also including complex cellular systems utilising primary cells and stem cells in the area of neurodegeneration, inflammation, metabolic disease and oncology
- ▶ Small molecule compound libraries: Evotec collection (400K com-

pounds) and Sanofi collection (800K compounds)

### Proteomics-based target deconvolution

Evotec has established a mass spectrometry-based approach to experimentally determine the binding partner(s) of a lead compound in a relevant cellular context:

- ▶ Metabolic or chemical labelling
- ▶ Optimised linker chemistry capabilities
- ▶ Determination of  $K^d$  values for each putative binding partner
- ▶ Combine with post-translational events to understand global cellular effects

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

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