CAPABILITIES INCLUDE
Integrated Services
Target Identification & Validation
Hit Identification
Compound Management
Research Informatics
Chemistry
DMPK
Proteomics & Metabolomics
Biomarker Discovery
Cell & Protein production
*In vivo & in vitro* pharmacology
Drug development is a high-reward but high-risk process, with as few as one in 10,000 new molecular entities making the successful but costly and lengthy journey from discovery to market. The pharmaceutical industry is struggling with the fall in R&D productivity and increasing demands from the regulatory authorities who demand first- and best-in-class therapies rather than me-tos.

Evotec’s drug discovery platform was established to deliver an industrialised, cutting-edge, comprehensive and unbiased infrastructure to meet the industry’s need for innovation in drug discovery. Using a strategic outsourcing partner like Evotec to drive Innovation Efficiency, reduces the risk and increases the chance of success in drug discovery without the need for the industry to invest in fixed cost structures.

Evotec’s portfolio of capabilities includes target identification and validation, compound management, screening, hit-to-lead and lead optimisation medicinal chemistry, in vivo and in vitro pharmacology, proteomics and biomarker science, protein production and early CMC activities. Working with Evotec, our partners gain access to an industry-leading team of scientists with years of experience in the Pharma and biotech industry. This experience effectively marries target and disease biology expertise with a world-class technology infrastructure. These scientists have successfully delivered clinical candidates in their past careers but more importantly they continue to do so at Evotec for our clients. The intellectual input of Evotec’s scientists is one of the pillar’s supporting Evotec’s business model. The most visible sign of our scientist’s ability to deliver innovative solutions is the number of customer patents on which Evotec scientists are named inventors. This number grows yearly and currently exceeds 200 and covers many therapeutic areas and target classes. Evotec is the partner of choice for standalone services which are charged on a purely fee-for-service basis. Alternatively, we can offer holistic, fully integrated drug discovery solutions through a variety of commercial structures. Our aim is to meet your requirements for the drug discovery solution you are seeking both scientifically and commercially. Our track record is second to none as testified by the number of projects that have moved through to the clinic and the strong portfolio of satisfied partners we have worked with through the years.

Evotec has been involved in more than 250 partnerships since its inception in 1993 and has delivered more than 30 pre-clinical candidates and 20 clinical candidates both in partnerships and within its own proprietary drug discovery efforts. This document showcases the state-of-the-art offerings of Evotec to address the challenges of Innovation Efficiency within our industry. In particular with this Drug Discovery Services update we introduce you to our new and expanded capabilities since the strategic alliance with Sanofi and the acquisition of an integrated drug discovery operation in Toulouse, France. This transaction gives us access to much needed capacity and some new capabilities including our state-of-the-art compound management facility – a first for us in Europe – as well as a ground breaking, innovation led access to the Sanofi compound library made available to our partners for screening. Of course the key addition is almost 200 first class scientists with significant experience in drug discovery bursting to collaborate with new and existing partners. This addition cements our place as the leading drug discovery partner in the world.

Please use this document to define how we can help you and contact us for the most innovation- and cost-efficient solution to your drug discovery requirements.

Yours sincerely

Mario Polywka
INTEGRATED SERVICES

In the next sections of this document, we have laid out a selection of the key technical capabilities and technologies which we have on offer at Evotec, and these capabilities can be accessed as stand-alone services on demand. In addition, through our extensive drug discovery know-how and experience and expert project management, we bring seamlessly integrated drug discovery capabilities to bear on our collaborations. We understand that each partner has different needs, internal capabilities and capacities, so through in-depth understanding of the project goals and your specific needs, we develop a coherent plan which enables you to leverage the benefits of our large, flexible, high-quality organisation as a one-stop, cost-effective solution, no matter where the project lies on the gene-to-candidate continuum.

Each collaboration has its own individual challenges so at Evotec “we start with the end in mind”, meaning that we consider the intended indication, frequency and route of administration, safety and efficacy demands, early development strategy etc as part of the product profile which in turn impacts directly on the project plan. Our scientists work with our partner’s scientists to select and execute the most promising strategy and technologies to deliver on the project goals. We also build into our processes key decision points that will guide us through the project and continually measure our progress against these. Using this approach, we provide innovative and efficient solutions that are always focused on the needs of our partners whilst minimising waste. Furthermore, by using Evotec as a single provider of integrated services, you can spend more time thinking about the science and less time managing the interfaces between multiple service providers.

Every single day, Evotec scientists are striving to solve drug discovery problems for their clients. Our scientists have made significant contributions to cutting-edge science throughout their careers and are drawn from a variety of backgrounds. They have been successful in all major therapeutic areas and target classes. Their ideas, inspiration, creativity, innovation and insightful analysis are all key elements of Evotec’s value proposition, and are critical contributions to successful and productive integrated collaborations. In addition, the conduct of such science is heavily dependent on being able to carry out the practical work smoothly, quickly, and without delays, problems, and frustration. Our client’s satisfaction, and our performance, is dependent on being able to carry out the conduct of such science is heavily dependent on being able to carry out the practical work smoothly, quickly, and without delays, problems, and frustration. Our client’s satisfaction, and our performance, is dependent on being able to carry out the practical work smoothly, quickly, and without delays, problems, and frustration.

As a result of this unique combination of depth, breadth, knowledge and experience of drug discovery with operational excellence, Evotec has established a successful track record in assisting academic institutions, not-for-profit foundations, biotech and pharmaceutical companies in developing novel therapeutics.
Evotec has a world-class high-content screening platform that is increasingly used for hit identification through phenotypic screening.

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.

Phenotypic screening and target deconvolution

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

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 Kd 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
**HIT IDENTIFICATION**

**HIGH-THROUGHPUT SCREENING**

Evotec has a long history in high-throughput screening (“HTS”) utilising large client compound collections and also our own 400,000 compound collection together with the exclusive access to the Sanofi library of 700,000 molecules. Evotec’s screening platform allows for assay miniaturisation and use of multiple read-out parameters to enable the assay read-out parameters to enable the assay miniaturisation and use of multi-ple read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay read-out parameters to enable the assay 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Evotec’s data analysis platform, Aplus, is suited to support all screening processes from HTS including multivariate analysis for HCS to SPR. This software facilitates the integration of all techniques into one analysis platform and streamlines the process flows.

Evotec’s screening library is differentiated through its quality, diversity and novelty and has a successful track record of delivering potent and attractive compounds as starting points for medicinal chemistry optimisation.

Evotec screens customer libraries of any size, virtual screening derived hits and also smaller, more target-directed libraries.

**SCREENING PROCESS**

The integration and connection of the different stages of the screening process from assay development to automation to compound management/tracking and finally data processing are essential. The Evotec screening team manages this complexity on a daily basis to deliver high-quality data on time to our clients.

In Evotec’s view the success of a screening project is determined by:

- Target selection
- Right strategy for target expression to address specific sites of interest
- Robust and sensitive assay system
- Well-selected compound collection for screening
- Reliable screening process
- Careful characterisation of screening hits in orthogonal test systems

Evotec’s screening library is also made available to our partners for screening. This creates one of the largest and most valuable sources of starting points for drug discovery with approx. 700,000 compounds physically available to screen which ultimately represent 2,000,000 molecules.

Evotec is flexible to meet customer needs in data formats for upload in different environments.

**THE OPTIMUM SCREENING COLLECTION**

Our library contains 400,000 compounds consisting of 70,000 proprietary Evotec compounds, a set of 330,000 maximally diverse "islands" and 20,000 natural products from Analyticon.

Evotec screens customer libraries of any size, virtual screening derived hits and also smaller, more target-directed libraries.

**DATA HANDLING**

Evotec’s data analysis platform, Aplus, is suited to support all screening processes from HTS including multivariate analysis for HCS to SPR and also HTMS. This software facilitates the integration of all techniques into one analysis platform and streamlines the process flows. For customer reporting, Evotec is flexible to meet customer needs in data formats for upload in different environments.
Evotec’s HCS expertise is built around the OPERA® platform where an essential understanding of the mechanics and image analysis tools, gathered over a period of more than 15 years in the development of the platform, flows into the hit identification process. Additional platforms include the Operetta® and ArrayScan™ to fulfill different requirements in resolution and throughput. The platform is completed with a powerful data management system and powerful data analysis tools including multi-factorial analysis. Based on this expertise, Evotec has performed many high-throughput screens of up to 400,000 compounds and developed over 30 assays to study mode of action of compounds and targets in a multitude of cellular backgrounds.

**PHENOTYPIC DRUG DISCOVERY**

The nature of HCS describes primarily a target agnostic approach measuring phenotypic/morphological changes associated with target engagement. The use of phenotypic screening provides Evotec’s clients with a whole new realm of drug discovery opportunities that otherwise could not be addressed. This includes experienced multi-disciplinary teams that build strategies for hit follow up towards identifying the molecular mechanism of action of a potential drug.

Accessing Evotec’s HCS platform offers a road to novel target space achieved via an array of disease-related secondary models post-HTS coupled to target deconvolution via the application of bioinformatics, genetic tools and finally mass spectrometry based proteomic approaches.

**Examples of track record**

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**DISEASE AREA EXPERTISE**

HCS at Evotec is now a common element in many drug discovery programmes across a variety of therapeutic areas. At present, the main focus of HCS is in the area of oncology, kidney disease, diabetes, pain, inflammation and neurodegeneration. Here the strengths of HCS are combined with regenerative medicine concepts to probe and discover new treatment paradigms such as beta cell regeneration for diabetes and podocyte protection for diabetic nephropathy. Applying stem cell technology in phenotypic and high-content screening is also an area of active research at Evotec where we are committed to delivering new treatment paradigms for ALS and other degenerative diseases.
HIT IDENTIFICATION
STRUCTURE-BASED DRUG DESIGN (SBDD)

Guided by high-quality data, SBDD at Evotec distills information into hypothesis-driven medicinal chemistry. By minimising unnecessary and wasteful compound synthesis, productivity is increased and chemistry teams are able to focus on an efficient path to the final drug.

Evotec has a comprehensive SBDD platform comprising state-of-the-art tools:
- Computational chemistry
- Protein engineering
- X-ray crystallography
- Biophysical screening tools such as NMR, SPR, MS and ITC

Evotec has developed a comprehensive fragment-based drug discovery (“FBDD”) platform. Sensitivities and efficacies of hit compounds are monitored by orthogonal assays and technologies, providing a robust foundation for rational design. The team is actively engaged with a newly established crystal soaking facility for medium-throughput fragment screening by X-ray crystallography, hosted at Diamond Light Source. The system brings together a host of advanced automation technologies centered on acoustic liquid handling and high-efficiency synchrotron data collection. As mentioned above, Evotec has developed a 3d-enriched library with the option to run in a cocktail mode designed by genetic algorithm methods for maximum diversity of target complexes.

FRAGMENT COLLECTIONS
We employ our collection of 20,000 fragments for biochemical, high concentration and SPR screening, a 3,000 fragment set for NMR screening and a 3d enriched 340 fragment set for crystal soaking. All sets are optimally designed for quality, diversity and solubility at high concentrations to provide tractable starting points for optimisation within SBDD projects. The collection integrity is maintained following validated processes used in our HTS collection to maintain quality, diversity and novelty.

NMR SCREENING AND HIT QUALIFICATION
NMR screening as part of the Evotec FBDD platform is an alternative option for the identification of new starting points for SBDD programmes. Evotec offers both protein-observed NMR assays monitoring chemical shift perturbations (SAR-by-NMR) as well as ligand-detected NMR assays (Saturation Transfer Difference (“STD”)) NMR and Water LOGSY) for hit identification. Hence, a broad range of target proteins amenable to NMR screening technique can be covered.

SURFACE PLASMON RESONANCE (“SPR”) SCREENING AND HIT QUALIFICATION
Another powerful tool for studying biomolecular interactions in a sensitive and label-free manner in real-time is SPR. While commonly used at later stages of drug discovery projects to qualify hit compounds with regards to binding kinetics, the instrumentation available at Evotec also allows for primary screening of fragments. Direct binding assays run on the Biacore™4000 screening device enable the identification of fragments interacting with immobilised target proteins. As the throughput is sufficiently high, we are able to screen both fragment sets thus increasing the chance to find bona fide binders of the target.

Independent of the primary screening strategy applied the assay techniques available at Evotec allow qualification of hits using alternative read-outs. Here we typically combine the above mentioned approaches with orthogonal assays and technologies like Isothermal Titration Calorimetry (“ITC”), Differential Scanning Fluorimetry (“DSF”) and Microscale Thermophoresis (“MST”). MST is applied in two modes available, the label free as well as the labelled version of the technology. This allows for maximal flexibility on a broad variety of targets in conjunction with low affinity fragment like compounds.

STRUCTURAL BIOLOGY
Evotec is located within a few miles of the UK’s third generation synchrotron and coupled with our own in-house X-ray source offers the ideal infrastructure for rapid cycle times in X-ray crystallography. The Structural biology team provides solutions to novel structure elucidation of drug targets and optimisation of crystal systems to support industrialisation of protein.ligand complex crystallography. Delivery of protein complexes is fine-tuned across a project’s lifetime to maintain the highest possible resolution while meeting the demanding cycle times of modern discovery. Experience covers the major target families with recent focus on crystallography of membrane proteins.

The team is co-located with the medicinal chemistry and computational chemistry teams to maximise interaction across integrated discovery programmes. The use of 3D virtual reality has provided the chemical teams with the ideal environment to understand and effectively mine structural information to focus synthetic strategies and rapidly progress optimisation. Working with innovative computational scoring techniques, Evotec is experienced in maximising the value of structural information, providing a robust foundation for rational design. The team is actively engaged with a newly established crystal soaking facility for medium-throughput fragment screening by X-ray crystallography, hosted at Diamond Light Source. The system brings together a host of advanced automation technologies centered on acoustic liquid handling and high-efficiency synchrotron data collection. As mentioned above, Evotec has developed a 3d-enriched library with the option to run in a cocktail mode designed by genetic algorithm methods for maximum diversity and high experimental efficiency. The capability of screening many hundreds of diverse fragments is achievable within a matter of weeks, delivering immediate structures to guide hypothesis-driven medicinal chemistry optimisation.
COMPOUND MANAGEMENT

OFFERING
Evotec is uniquely qualified in delivering its customers small and large molecule library management needs through over a decade of being the world’s leading compound management operation. Evotec expanded its operational presence in 2013 and again in 2015 by adding capacity and capabilities in Branford Connecticut and Toulouse France. These facilities are strategically positioned to support the strong presence of Evotec’s drug discovery services along the east coast of the U.S. and across Europe. Our service offering includes:

- Cost effective compound identification, selection, and procurement
- High-throughput compound analysis
- Multi-format plating and reformatting
- Inert or dry atmosphere and low temperature storage and processing
- Fast order fulfilment and worldwide delivery
- Multi-site disaster recovery and business continuity
- “In-sourcing” of Evotec sample management staff to client sites
- Access to compound collections of some of its partners through an open innovation strategy

Evotec has a broad range of compound management expertise across many sectors including large Pharma, biotechs, foundations and governmental organisations; which results in a deep understanding of its customers’ needs and deadlines. Each client has a dedicated Project Manager who provides a single point of contact to insure an open line of communication is always maintained.

COMPOUND IDENTIFICATION, SELECTION, AND PROCUREMENT
Evotec has extensive experience in the identification, selection and procurement of small molecule compounds possessing very specific (including commercial, physico-chemical or bioactivity-related) properties. Evotec has the capability to apply compound identification tools as required by the client.

Once compounds are identified for purchase, our Project Management group consults with selected suppliers to negotiate terms on behalf of our client requirements, e.g. price, purity and format. Evotec purchases tens of thousands of compounds on a regular basis for a number of clients; therefore, the client can benefit from our vendor relations and volume discounts.

COMPOUND QUALITY CONTROL
Evotec typically uses a three-part process comprised of weight, solubility and LC-MS purity and identity to ensure that all collections start with high-quality compounds. Systems include a Waters 8-channel LC-MS system, with digital UV, ELSD and an LCT Premier mass spectrometer, and two Waters LCT Premier XE uPLC systems featuring positive and negative ESI and UV and ELSD detection. Evotec also utilises a Xevo G2 Q-TOF system for quantitative determination and high resolution of compounds in DMSO solution.

COMPOUND STORAGE
Evotec has invested in industry-leading automated storage systems and supporting informatics. Storage capabilities support vials, tubes, plates and bulk materials at controlled temperatures of -80°C, -20°C (inert or humidity controlled atmosphere) and ambient. Actual storage conditions are dictated by sample type, containers and length of storage. Automated tube, vial and plate storage systems are equipped with high-speed pickers for fast arraying of tubes, plates and vials to support large plating, weighing and screening campaigns and rapid follow-up. Evotec can also prepare a disaster recovery set of the client’s collection for storage at one of our other compound management facilities. This set can be readily accessed and processed for distribution at the client’s request.

COMPOUND DISPENSATION AND reformATTING
DMSO solutions
Evotec has the capability for automated arraying of large numbers of compounds in DMSO or in water between a large variety of containers suitable for distribution or storage. Our extensive liquid handling resources cover the widest range of possible volumes.

- High-volume systems include the Beckman and Agilent plate replicators (formerly VPrep and Bravo) that can dispense from 1 ul to 2 mL and from 96, 384 and 1536 SB5 format arrays
- Low-volume systems include the LabCyd Echo S50 and S55 that acoustically dispenses volumes below 1 ul using multiples of 2.5 nL drops of solution, and the TTP Mosquito, which dispense volumes between 50 nL and 1.2 mL

Neat compound dispensation
Evotec has the capability to transfer neat samples via manual weighing, Volatile Solvent Transfer (“VST”) or Solvent Transfer methods, and using automation (Flexiweigh and XPert dose technologies). Range for automatic distribution goes from sub-milligram (0.2mg to 30mg).
SECTION 4

COMPOUND SHIPMENT
Our team has extensive experience in shipping chemicals, research compounds, controlled substances and reagents. Evotec delivers and receives compounds in all formats, both domestically and overseas (including, but not limited to, North America, Europe and Asia). We are well-versed in documentation requirements, tariff classification and import/export customs requirements. We have the ability to facilitate the import/export processes through the use of brokers as required by the have client.

DATA MANAGEMENT
Evotec currently uses both a proprietary Compound Inventory and Tracking (“ComIT”) software system and the industry leading commercial application (Titian Mosaic) to manage, record and report all manipulations of client samples. These systems operate independent of each other at different sites but both deliver end-to-end functionality and traceability.

QUALITY MANAGEMENT
Evotec operates under the ISO 9001:2008 Quality Management and internal auditing principles but is not formally ISO 9000 certified. We have well-defined and documented procedures to monitor and ensure the consistency of our output. Our process enables us to find defects early in the process and our procedures ensure corrective action is taken whenever a defect occurs, with the goal being to implement corrections with minimal impact to our final deliverables.

IN-SOURCING AND CONSULTING SERVICES
If a prospective client decides to retain compound management services within their operation then Evotec also offers both in-sourcing and/or consulting services. In these instances, Evotec reviews requirements with our clients and design solutions including need identification, process design, facility layout, process workflow, vendor qualification and selection, and even complete staffing and management of onsite services. Our in-sourcing programme provides scientific staffing specifically designed to give clients the “flexible” workforce needed for anywhere from one year to multiyear partnerships. We hire, train and manage our employees to perform analytical scientific programmes at client sites, using their quality systems. This advanced staffing model provides a non-permanent, long-term and cost-effective way to meet compound management staffing needs.
RESEARCH INFORMATICS & IN-SILICO DRUG DESIGN

OFFERING
The huge quantity of data that drug discovery generates both externally and internally requires that data informatics is at the heart of any modern research organisation. At Evotec the research informatics department smoothly integrates the disciplines of computational chemistry, bioinformatics, systems integration, data management and support informatics. The team empowers the discovery scientists to deliver data-driven design hypothesis using commercial, proprietary and bespoke software offerings. In short, the department delivers in-silico drug discovery and can be engaged in a standalone capacity or fully integrated with our discovery partners.

TARGET IDENTIFICATION
Evotec uses industry standard target interaction databases which combined with other ‘omics’ data can be used to construct target interaction maps. These networks can be significantly enhanced using our predictive pharmacology tools. >200M bioasay datapoints are currently sourced for model building. Pathway analysis can be used to identify new and novel targets proposed to modulate a disease hypothesis. Such approaches are fundamental in target deconvolution and drug repurposing.

DRUGABILITY ASSESSMENT
Structure-based assessment for novel targets gives an additional read on drugability when no/few drug-like compounds are known. New 2D sequence based “switchability” calculations projected onto 3D structures have successfully been used for predicting allosteric sites for modulation, surfaces for PPIs and mAb binding.

HIT IDENTIFICATION
For virtual screening Evotec uses multiple methods using the best-of-breed commercial software. A number of compound collections are available for screening:
- EvoSource (34M)
- Evotec Diversity (400K),
- Sanofi HTS (1.4M),
- Fragments (21K),
- Diverse Phenotype Library (20K)
- Annotated Druglike Library (6K)

Chemogenomics and ortholog approaches also provide a good starting point for identifying novel actives. Evotec has licensed LeadIT and Spark for scaffold hopping but also has a number of in-house tools using structure merging and vector placement algorithms.

HIT EXPANSION
The hits identified from screening require expansion to provide evidence of SAR. This is traditionally based upon chemical similarity and involves searching databases for ‘like’ molecules. Evotec also uses predictive pharmacology so that molecules that possess a similar target pathway signature can be identified. Library design, statistical analysis and virtual chemistry tools can be used to design the most information rich set of molecules for synthesis.

MULTI-OBJECTIVE DESIGN
The Evotec ELN reaction transform library can be used to perform virtual chemistry and grow fragments within the active site of protein.

2D fingerprinting and 2D/3D fingerprinting can be used for both structure-based and ligand-based design. Ideas generated can be scored across a range of objectives such as an ADMET profile (Evotec has its own proprietary ADMET models), target QSARs, off-target QSARs. The method can be used for both structure-based and ligand based design.

LIGAND OPTIMISATION
Evotec possesses significant expertise in QM guided SBDD using the fragment molecular orbital (FMO) approach. FMO calculates the strength of interaction between protein residues and ligand atoms to accurately pinpoint the drivers of molecular affinity. Molecular simulation (WaterScout) and ΔG (Nautlius) approaches can be applied to identify happy and unhappy waters. Evotec’s large internal HPC (high performance computing) capacity, employing multiple Intel and GPU clusters, ensures that these approaches are routinely applied.

Evotec has developed a number of statistical analysis tools for matched-molecular-pair analysis (MMPA) and Free-Wilson approaches. These can be used in combination with predictive modelling tools Q SAR, QSIPR to enable effective experimental design. PK/PD modelling is done in collaboration with the ADMET group.

THE RESEARCH INFORMATICS TEAM
The infrastructure of research informatics at Evotec is supported by a strong team of data managers who organise and securely store data from across the globe. The systems integration group maintains the computing environment and includes the software developers who build and maintain the proprietary software tools. The support informatics (training and education) and business operations teams provide the softer interface to the department and ensure the smooth operation of internal and external client relationships.

Mike Bodkin, Vice President Research Informatics
We understand that each partner has different needs, internal capabilities and capacities. Evotec prides itself in being able to provide flexible, innovative and efficient solutions. Evotec’s experienced scientists can support your aspirations in a variety of ways. The capabilities listed below can be accessed individually where required or brought together to form complete project solutions:

- Cutting-edge molecular design
- Rapid synthetic execution
- Expert advice on overall project strategy
- Developing strategy for and securing IP protection
- Scale-up chemistry
- Preparative chromatography
- Project management

SYNTHESIS

At the foundation of Evotec’s medicinal chemistry group is a talented and industry-experienced team of >175 synthetic organic chemists. Their skills are utilised during medicinal chemistry-driven projects, focused-library preparation, scale-up synthesis and when preparing chemical building blocks or literature compounds. Synthetic execution is one of the most cost- and time-consuming parts of the early discovery process. We understand that where synthesis is concerned, speed is paramount. The faster our teams can deliver molecules into bioassays, the faster the project teams can obtain new knowledge.

Our approach is to employ, educate and retain talented chemists and to enable them with the latest technology and equipment.

- More than 60% of our chemists are educated to PhD level
- >40% of our chemists have >8 years’ experience at major pharmaceutical and biotech companies prior to joining Evotec
- Our chemists utilise state-of-the-art equipment known to accelerate productivity: microwave reactors, automated purification systems, parallel synthesisers

These facets enable Evotec to provide superior synthetic chemistry and problem-solving capabilities to our partners and to efficiently deliver compounds in a shorter timeframe than our competitors.

Good molecular design often leads to complex syntheses (e.g. densely functionalised heterocycles, multiple chiral centres). Projects are successfully executed at Evotec that involve highly challenging syntheses and isolation procedures, for example:

- Natural products
- Steroids
- Macrocycles
- Nucleosides
- Carbohydrates
- Peptidomimetics

The origin of the chemistry department in Abingdon was in asymmetric synthesis and Evotec routinely develops enantioselective synthetic methods and has a full range of chiral separation technologies including SFC to deliver single isomers.

MEDICINAL CHEMISTRY

Evotec has a powerful core of experienced, industry-seasoned drug hunters who drive the molecular design process. Our teams in Abingdon, UK and Toulouse, France have co-located group of medicinal chemists, computational chemists, structural biologists and DMPK scientists that have made significant contributions to discovery projects throughout their careers:

- >100 development candidates
- Named inventors and authors on >860 patents and publications

Our scientists are drawn from a variety of backgrounds and have been successful in all major therapeutic areas and target classes. We have a particularly strong track record in prosecuting ion channel modulators, enzyme inhibitors and protein-protein interaction inhibitors, with several compounds progressing to pre-clinical development and beyond.

Our teams are fluent and expert in both protein structure-guided and ligand-based design, utilising internal knowledge and experience as well as a wealth of supporting computational models.

An example of multiparameter optimisation. Evotec’s design teams simultaneously improve physicochemical properties as well as biological activity. The plot above (-logp(LLE) versus calculated LogD) highlights three different chemotypes from the same project. Over 2 iterations, the arrows indicate the improvements made to each series as seen from the improved Lipophilic Ligand Efficiency (LLE) scores.
The focus of our medicinal chemistry teams is on high-quality design and crisp decision making. The process at Evotec is enabled by widespread availability of visualisation, analysis and design software tools. Our medicinal chemists target analogues within defined property space to answer specific structure-property and structure-activity questions – the emphasis is always on making the right compounds with optimisation of biological activity and properties in parallel. We firmly believe that the co-location and interaction of synthetic and medicinal chemistry, computational science, structural biology and DMPK enhances the overall design, analysis and communication process.

We continually review our internal processes (analysis, compound management, registration, dispatch etc.) to ensure that our discovery teams is on high-quality design and crisp decision making. We have implemented a companywide electronic lab notebook system and internal LIMS system for compound submissions. In addition we have project specific databases and workflows to enable rapid data sharing within teams and with our clients.

Our focus is to ensure the shortest possible “design-make-test-analyse” cycle with typically one complete cycle per month. With this in place we can achieve:
- Key project decision points in a shorter timeframe
- Increased knowledge and experience due to more learning cycles per time unit
- Better quality output/product
- Less waste due to more informed decisions
- Effective, efficient teams

**SCALE-UP CHEMISTRY**
Evotec can supply large quantities of molecules of interest through a team of very experienced chemists originating from chemical development that has contributed to:
- Late development synthesis of > 20 pre-clinical and clinical candidates
- Large scale synthesis of > 140 compounds for advanced pharmaceutical profiling

Their expertise allows them to cover areas such as:
- Large scale synthesis of API, intermediates (up to 100-200g)
- Route scouting for IND process
- Optimisation of synthetic routes
- Crystalline Salt selections
- Full technical package for transfer to larger scales for GMP batches synthesis

We ensure that synthetic processes match the safety requirements of large scale synthesis by using state-of-the-art equipments for calorimetric studies and in-process controls.

**PREPARATIVE CHROMATOGRAPHY**
Evotec has established a high quality preparative chromatography service catering from milligram to kilogram scales. The highly experienced group utilises complementary analytical and preparative HPLC and SFC separation techniques to provide:
- Separation of chiral compounds at the preparative scale (intermediates or final compounds)
- Successful purifications when higher resolution techniques are needed (peptides, vitamins, steroids, macrolides, amino-acid derivatives)
- Impurity isolation for structural identification
- Chiral analysis for asymmetric synthesis follow-up
- Evaluation of chiral stability of final molecules or development candidates

The group has also developed unique biomimetic oxidation models mimicking P450 monoxygenases for the synthesis, purification and structural identification of real and putative metabolites of active compounds.

**EVOTEC TRACK RECORD**
- Over the last 15 years, Evotec chemists have supported >125 hit-to-lead and/or lead optimisation projects
- Evotec scientists are named inventors on >200 client patents and have helped identify >30 pre-clinical candidates
- Our project teams have made major contributions to the identification of >20 compounds that have been approved for clinical trials
DRUG METABOLISM & PHARMACOKINETICS („DMPK“)

OFFERING

Over the past 20 years, Evotec has developed expertise in numerous therapeutic areas including diseases of the central nervous system („CNS“), pain, oncology, diabetes and metabolic diseases, inflammation and anti-infectives.

This collective experience has consolidated the view that successful small molecule drug discovery requires a deep understanding of biological context coupled with knowledge and experience of the property space required to deliver safe, efficacious drugs. DMPK continues to be a key player in this success since the major sources of attrition – clinical efficacy and safety – are clearly linked to exposure in key tissues either on- or off-target.

We understand that each partner has different needs, internal capabilities and capacities and Evotec prides itself in being able to provide flexible, innovative and efficient solutions.

Evotec’s experienced scientists can support your aspirations in a variety of ways, providing mechanistic interpretation as well as timely delivery of quality data. We firmly believe that the co-location and interaction of disciplines (e.g. DMPK, synthetic and medicinal chemistry, computational science and structural biology) enhances the overall design, analysis and communication process: More learning cycles per unit time = more knowledge and experience = better quality output. More, better-informed decisions = less waste.

Collectively, this group of experienced scientists has made significant contributions to discovery projects throughout their careers:

- >90 development candidates
- Named inventors and authors on >750 patents and publications

Evotec offers a comprehensive and flexible range of in vitro and in vivo DMPK studies designed to cover the majority of activities in the screen-to-candidate phase. The scientific expertise and processes are accessed in a variety of ways by our partners and project teams.

IN VITRO COMPOUND SCREENING AND PROFILING

Routine compound testing (e.g. weekly cycle times)

Evotec’s combination of routine in vitro assays and our flexibility to address your individual requirements enables us to offer a truly bespoke, differentiated service: Experienced DMPK scientists delivering data of excellent quality coupled with validated, cost efficient and highly automated processes. Interpretation of data and consultation is provided by our DMPK experts within integrated project teams.

For integrated projects, a range of physico-chemical assays are available together with analysis of permeability (PAMPA, Caco-2, MDCK II), metabolic stability (plasma, microsomes and hepatocytes for a range of species), plasma protein binding (multiple species) and drug-drug interaction (DDI) potential (cytochrome P450, CYP, inhibition). Recent additions to our portfolio include human transporter assays (e.g. OATP1B1) and CYP induction analysis (PXR receptor, HepaRG cells or cryopreserved human hepatocytes). Additional bespoke studies are often accommodated to troubleshoot emerging challenges within projects.

Estimation of human pharmacokinetic parameters, dose and exposure provide a contemporary framework for multi-parameter optimisation.

Working with multiple partners across a variety of sectors provides Evotec with unique insight in several areas.

STAND-ALONE SCREENING

- Automated, high-throughput assays allows for profiling of several hundreds of compounds per week against a broad panel of DMPK assays
- Tailored packages designed to address a specific problem associated with a compound, or more frequently, a series of compounds

In the pharmaceutical industry, early assessment of liabilities of potential drug candidates is an important element to decrease the high attrition rate in the drug discovery and development process. One of the key challenges is optimising the balance between drug efficacy and potential adverse effects at the earliest possible point in time for de-risking cost-intensive activities, especially during late-stage clinical development.
Once key liabilities are identified, DMPK assays can be applied to rapidly design out such properties, sometimes making use of quantitative structure-activity (Q SAR) analysis. To meet this demand, Evotec has established an industrialised high-throughput profiling platform for routine compound screening against a panel of the most critical targets:

- Potential DDIs can be determined by using our panel of cytochrome P450 ("CYP") reversible inhibition ("RI") assays for the major CYP isoforms.
- Assays for the four most highly relevant CYP isoforms are established on our high-throughput RapidFire/MS platform.
- Medium-throughput LC/MS/MS based assays are provided for CYP1A2 and 2C19.
- For CYP3A4, analysis of time-dependent inhibition ("TDI") and induction are also provided.

In support of discovery chemistry programmes, externalisation of such activities is providing a unique business opportunity for some partners to reserve internal capacity for core research activities, expand their assay portfolio and to mitigate risk.

Pharmacological sensitivity and statistical robustness of the DMPK assays is routinely monitored by a range of reference compound DMPK assays performed according to validated SOPs and provide 8-point IC50/EC50 for test compounds.

Examples of capacity for our higher throughput assays

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>CAPACITY (_WEEKLY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma protein binding (multiple species)</td>
<td>100</td>
</tr>
<tr>
<td>Permeability (e.g. MDCKII)</td>
<td>144</td>
</tr>
<tr>
<td>Microsomal stability (multiple species)</td>
<td>200</td>
</tr>
<tr>
<td>Hepatocyte stability (multiple species)</td>
<td>100</td>
</tr>
<tr>
<td>CYP inhibition (reversible)</td>
<td>200–800 (CYP-dependent)</td>
</tr>
<tr>
<td>CYP inhibition (time-dependent, CYP3A4 IC50 shift)</td>
<td>700</td>
</tr>
<tr>
<td>CYP Induction (hPXR)</td>
<td>800</td>
</tr>
</tbody>
</table>

**TECHNOLOGY PLATFORM AND EXPERT KNOWLEDGE**

Within many collaborations with major pharmaceutical and biotech companies, Evotec has successfully provided expert knowledge in development and integration of complex processes for our collaborator’s drug discovery programmes including:

- Support logistics of compound shipments in close interaction with global carriers.
- Management of large libraries and regularly shipped smaller compound batches for DMPK or SAR profiling.
- Broad expertise in development and validation of > 500 biochemical, biophysical and cell-based assays.
- Compound profiling using bench-top and fully automated screening platforms.
- State-of-the-art bioanalytical readout technologies including e.g. RapidFire/MS, FLIPR, SPR, fluorescence, radiometric, high-content imaging.
- Flexible data analysis to provide customised formats enabling rapid data uploads to internal or external data bases.
- Professional project management with experienced leads.

**IN VIVO Pharmacokinetics & PKPD support**

Obtaining pharmacokinetic data is a key requirement in the evaluation of new chemical entities providing validation of any in vitro-in vivo extrapolations and an understanding of ADME processes in pre-clinical species which can provide confidence in translation to Man and/or high-light key risks. As part of Evotec’s integrated drug discovery platform, in vivo pharmacology studies are also further supported by DMPK and histology.

Evotec offers:

- Various administration routes: intravenous (incl. infusion), per os (PO), intraperitoneal, subcutaneous, intra-cerebrospinal and intramuscular.
- Cassette PK screening of up to 10 compounds simultaneously.
- Different sampling routes:
  - Jugular vein cannulation, cardiac puncture, tail vein microsampling.
  - Different matrices: blood, plasma, cerebrospinal fluid, tissues, bile, urine and faeces.
- Data generated with the latest version of Phoenix® WinNonlin®6.3 software, analysis performed using rigorous acceptance criteria.
- Solid state evaluation, salt screening and enhanced formulation for problematic compounds.
- Biomarker development and application within projects.

DMPK also provide analysis and interpretation of pharmacokinetic-pharmacodynamic (PKPD) relationships in support of PD and/or disease models conducted by our colleagues in Biology. It is important to emphasise here the need to study concentration-time and response–time profiles since the temporal relationship between these varies with different targets and the position of a target in a biological pathway. Hence the time to equilibrium between the plasma and target tissue can be very rapid (e.g. anti-thrombotic agent) or delayed (e.g. anti-psychotic).

Simulations from early PK data assist study design and relationships between response, concentration and time based on exposure (often in target tissues) support translation to Man and early assessments of clinical dose and associated exposure.

Analysis of biomarkers can greatly enhance this process. Integration of such information in static or ideally dynamic (physiologically-based pharmacodynamic, PBPK) models forms the foundation for DDI and safety risk assessment.
PROTEOMICS

METABOLOMICS

AND BIOMARKER DISCOVERY

OFFERING
Evotec offers unique proteomics and metabolomics services to address key issues in drug and biomarker discovery. We continuously advance our capabilities in mass spectrometry-based proteomics and metabolomics to ensure unrivalled comprehensiveness and data quality when analysing cells, animal models and patient samples.

PROTEOMICS
Evotec’s proteomics platform encompasses:

- Highly optimised experimental strategies tailored to different proteomics applications and project needs
- Industry-leading capabilities in high-end quantitative mass spectrometry
- Experience and infrastructure to analyse the enormous amounts of data generated in large-scale proteomics projects
- Advanced statistics and bio-informatics for systems-wide data analysis
- In-depth data interpretation to extract relevant drug target and mode-of-action information from proteomics experiments
- Extensive track record to deliver high-quality results within agreed timelines

Evotec's chemical proteomics methods such as Evotec Cellular Target Profiling™ reveal cellular drug targets and selectivity in an unbiased manner. Other Evotec proteomics technologies record protein modification and expression on a proteome-wide scale for drug mode-of-action analysis or biomarker discovery efforts. Thus, our platform offers highly innovative solutions that can be leveraged across the entire drug discovery and development pipeline.

QUANTITATIVE CHEMICAL PROTEOMICS
Evotec scientists have pioneered chemical proteomics applications for the identification of cellular small molecule targets. The basic concept involves functional immobilisation of an appropriate linker derivative of a drug, followed by affinity purification of target proteins from cell or tissue extracts and finally their identification by MS analysis. Unlike other competitor technologies, our Evotec Cellular Target Profiling™ technology captures target specificity and affinity information by quantifying target binding across defined sets of affinity purification and drug competition experiments.

Evotec Cellular Target Profiling™
- Reveals and verifies specific cellular targets of a drug by quantitative mass spectrometry
- Determines target-specific dissociation constants for the compound studied, ranking targets according to their likely physiological relevance
- Performs selectivity analysis on a proteome-wide scale against native, post-translationally modified proteins in the pre-sence of cellular co-factors and complex partners
- Has an extensive, non-target class restricted track record in successful profiling of diverse small molecule compounds

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Selective data about cellular on- and off-target liabilities is particularly useful to inform decisions at various stages of drug development, for example in the lead optimisation phase or in the pre-clinical candidate selection process. Moreover, chemical proteomics enables target deconvolution of bioactive compounds identified in phenotypic screens. Cellular target identification is the crucial step to enable further drug optimisation and development. Evotec Cellular Target Profiling™ perfectly complements Evotec’s medicinal chemistry and high-content screening capabilities to deliver new drugs and targets across many therapeutic areas.

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Numerous small molecule kinase inhibitors are currently being developed for treatment of cancer, inflammation or autoimmune diseases. However, drug discovery faces significant challenges, particularly due to unacceptable safety pharmacology profiles caused by an inhibitor’s lack of selectivity. Undesirable off-target kinase profiles frequently induce toxicity that might halt the development of candidate drugs. To decrease the high attrition rate the design of selective as well as multi-specific inhibitors is becoming increasingly important.
**PhosphoScout® Workflow**

1. **Isotope labelling**
2. **Protein isolation**
3. **LC-MS analysis**
4. **Peptide enrichment**
5. **Protein isolation**
6. **Labeling**
7. **Protein capture**
8. **Spectrum analysis**
9. **Profiled proteins**

**Figure:** Activity-based protein profiling (ABPP) uses active site-directed chemical probes to broadly assay the functional state of enzymes across enzyme families. These probes consist of a reactive group and a reporter group, generally fluorescent or affinity tags for imaging and purification purposes, respectively. In gel-based ABPP, native proteins are reacted with the probe and proteins are separated by SDS-PAGE and visualised by fluorescent scanning. Competitive ABPP assesses the potency and selectivity of small molecules to bind enzymes, by competing with the ability of the probe to bind. Enzyme inhibition is indicated by a loss of fluorescent intensity by gel or by a loss of spectral changes by MS-MS-based ABPP, which facilitates the identification and quantification of enzyme activities following elution from, on-lead tryptic digest, and resolution by label-free quantitative mass spectrometry.

**GLOBAL PROTEOME PROFILING AND BIOMARKER DISCOVERY**

Evotec offers industry-leading platforms for comprehensive protein expression profiling allowing unbiased, proteome-wide target and activity in different biological contexts. These approaches allow specific profiling of modification-specific sub-proteomes including N- and O-GlcNAc-modified glycoproteins, sialic acid-modified proteins, fucosylated glycoproteins, palmitoylated or myristoylated proteins and iso-prenylated proteins.

Such studies may be performed in cells, tissues or patient samples. Accurate quantification is enabled by differential isotope labelling and label-free approaches, while highly optimised peptide enrichment and analysis on fast, sensitive and accurate mass spectrometers ensure highest coverage. Evotec’s platform provides highly reliable results, both for in-depth bioinformatics involving enrichment, cluster, network and motif analysis, as well as for expert data interpretation on the level of site-specific changes.

Our quantitative phosphoproteomics (PhosphoScout®) enables the unbiased and comprehensive investigation of large-scale proteomic surrogates to delineate the cellular modes of action for kinase inhibitors. Typical applications include:

- Identification of specific pharmacodynamic read-outs for therapeutic kinase inhibition
- Selection of lead compounds or development of combination therapeutic strategies based on non-native, non-perturbing chemical handles
- Identification of potential off-target activity
- Monitoring phosphoproteome regulation in different biological models to shed light on factors underlying differential biological activity of lead compounds or pre-clinical candidates

In addition to PhosphoScout®, Evotec’s acetylomics and ubiquitinomics platforms offer high-throughput, unbiased proteomics for HDAC and E3 ligase and methyltransferase inhibitors using highly optimised workflows with regard to sensitivity and selectivity. As a result, these technology platforms enable comprehensive mode of action studies in the biologically relevant context.

**KinAffinity** is Evotec’s hit-to-lead compatible approach for rapid target identification of kinase inhibitors in cell and tissue samples. Unlike traditional biochemical kinase panel screening, the inhibitor’s target affinities are determined simultaneously for a large number of native kinases within their physiological cellular environment, thereby complementing traditional biochemical assays that use only recombinant proteins.

KinAffinity® employs a ready-to-use affinity matrix comprising well-characterised broad-spectrum kinase inhibitors to enrich the subproteome of endogenously expressed kinases of cells or tissues. This enables rapid determination of kinase target Kd values for free kinase inhibitors without needing to immobilise the inhibitor. Evotec’s third chemical proteomics platform makes use of reactive drug conjugates for covalent target capture, enabling applications such as activity-based protein profiling (ABPP) of a wide range of enzyme classes including serine hydrolases, metalloproteases, oxidoreductases, histone deacetylases, and glutathione S-transferases. ABPP visualises only the active forms of particular enzymes using reactive chemical probes directed to the active site of a particular target protein (or protein family).

Besides the monitoring specific enzymatic activities, ABPP can also be used to identify and characterise (unknown) protein functions, to study up- and down-regulation of enzymatic activity in various disease states, to discover and evaluate putative new enzyme inhibitors, and to identify the protein targets of covalently binding natural products.

Evotec has also developed Photo-Affinity Labeling combined with Mass Spectrometry (PALMS), a powerful technology to identify the target(s) of a drug, to determine the affinity and selectivity of drug-target interaction, to determine drug-target stoichiometry, and to identify ligand binding sites. PALMS uses an analog of a biologically active ligand (small-molecule, peptide), known as a photoaffinity probe, that bears photo-reactive and reporter functional groups, to identify protein binding partners. During PALMS, the photoaffinity probe binds proteins through reversible affinity interaction.

UV-irradiation of reversible complexes generates a covalent bond between the photoaffinity probe and target proteins. Photo-crosslinked protein targets can be visualised by the reporter group using conventional imaging and identified using affinity purification combined with quantitative mass spectrometry.

**GLOBAL ANALYSIS OF PROTEIN MODIFICATIONS**

Evotec’s proteomics platform for global protein modification analysis permits the identification and quantification of about 15,000 phosphorylation sites, more than 5,000 ubiquitination sites, or several hundred arginine methylations sites in a single experiment. Moreover, Evotec has established bioorthogonal chemical reporter strategies based on non-native, non-perturbing chemical handles that can be modified in living systems through highly selective reactions with exogenously delivered probes. These approaches allow specific profiling of modification-specific sub-proteomes including N- and O-GlcNAc-modified glycoproteins, sialic acid-modified proteins, fucosylated glycoproteins, palmitoylated or myristoylated proteins and iso-prenylated proteins.

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Such studies may be performed in cells, tissues or patient samples. Accurate quantification is enabled by differential isotope labelling and label-free approaches, while highly optimised peptide enrichment and analysis on fast, sensitive and accurate mass spectrometers ensure highest coverage. Evotec’s platform provides highly reliable results, both for in-depth bioinformatics involving enrichment, cluster, network and motif analysis, as well as for expert data interpretation on the level of site-specific changes.

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are available: tailored proteome analysis workflows application and required throughput, protein level. Depending on the biomarker discovery on the functional protein level. On the application and required throughput, tailored proteome analysis workflows are available:

- Deep proteome profiling for detection of up to 10,000 proteins from cell or tissue samples upon efficient peptide pre-fractionation
- Single-shot proteome profiling to a depth of 5,000 proteins in cell or tissue lysate, enabling comparative proteome analysis across 100+ samples
- Comprehensive analysis of any type of biological material, including formalin-fixed paraffin-embedded (FFPE) solid tumour samples and body fluids such as plasma and CSF.
- Targeted mass spectrometry analysis by Multiple Reaction Monitoring (“MRM”) and Parallel Reaction Monitoring (“PRM”) fully established at Evotec for follow-up validation experiments

Both the expertise and the data processing infrastructure are in place for accurate quantification across many different samples, such as whole panels of cell lines, xenograft models or patient tissue and body fluid samples. Such data, together with drug response information, provides a unique basis for the discovery of predictive protein biomarkers, arguably one of the most exciting proteomics applications in future medicine.

**EVOTEC’S THREE-TIER STRATEGY TO SUPPORT ONCOLOGY BIOMARKER DISCOVERY**

Evotec technologies cover the entire biomarker discovery phase including elaborate bioinformatics for the identification and verification of predictive multivariate markers, so-called protein signatures. These capabilities have been demonstrated in various cancer-related projects, delivering response prediction signatures in lung cancer cell lines, mouse xenograft models and leukemia patients.

In conclusion, Evotec offers an integrated and unique platform of innovative proteomics technologies for drug and biomarker discovery. Moreover, Evotec is constantly investing in R&D activities dedicated to advance its high-end proteomics capabilities and maintain industry leadership in the years to come.

**METABOLOMICS**

Metabolomics can be defined as the quantitative assessment of the metabolic responses of a biological system (cell, tissue, organ or biological fluids) at a particular time and to measure the changes in the metabolic response when exposed to any pathophysiological stimuli and/or genetic alterations. Metabolomics have a potential role in the pharmaceutical research and development (R&D), starting from drug discovery to clinical development and even beyond.

Evotec has established expertise and state-of-the-art methodologies in targeted-metabolomics for the functional analysis of metabolic networks with applications in health, biotechnology and microbiology. Evotec offers unique metabolomics services to address key issues in biomarker discovery and/or validation in various therapeutic areas including cancer, metabolic syndrome, diabetes, CNS and cardiovascular diseases. Applications of metabolomics include pre-clinical biomarker identification, disease mechanism and validation of animal models for disease, and the discovery of biomarkers for patient stratification as well as clinical safety and efficacy assessment.

Our targeted metabolomics approach focuses on the analysis of specific group of metabolites related to certain metabolic pathways or a class of compounds including endogenous metabolites, eicosanoids, corticosteroids, neurosteroids, oxysterols, nucleotides free fatty acids, and nicotinamide metabolome.

A detailed list of all compounds which have been measured and quantified so far is available upon request. Due to its sensitivity and specificity, our approach allows absolute quantitation of metabolites using selected reaction monitoring (SRM), with detection limits of ng/mL, in sample matrices (e.g., biofluids, cells, organs) and also in-vivo on awake or anaesthetised animals using microdialysis coupled with XLC-MS/MS.

**IN-VITRO/EX-VIVO TARGETED METABOLOMICS (CHRONIC STUDIES)**

Absolute quantification of metabolites is performed in complex matrices including animal body fluids and tissues (brain, adipose tissue, liver, intestine, muscle, tumours, plasma, blood, serum, urine, CSF), human body fluids and tissues (plasma, serum, blood, CSF, adipose tissue, brain), and cell lines (cells and culture medium), enabling comparative metabolome analysis across 100+ samples. Measurements in further matrices can be established upon request.

**IN VIVO TARGETED METABOLOMICS (ACUTE STUDIES)**

Relative quantification of metabolites is performed directly in awake (1 probe) or anaesthetised (2 probes) animals. Microdialysis can be performed in many tissues including brain skeletal muscles, adipose tissues, liver, tumours. In kinetic studies, animals can be monitored continuously for 24 to 48 hours with a time-point generally every 30 min.
Evotec's wealth of expertise covers all principles including cell line generation, small- or large-scale transient transfection, frozen cell technologies and protein expression from small-scale proof-of-concept studies through batch production for HTS, counter screening activities as well as structural biology applications. For clients looking to outsource the management and supply of their own cell collections, Evotec offers a cell bank management scheme, establishing, propagating and distributing thousands of cell lines between various locations.

In 2015 the offering for reagents has undergone a rapid expansion with new facilities opening in Princeton, NJ, on the East Coast of the US, to serve the North American market, and the acquisition of the Sanofi site in Toulouse, France. In Princeton, the team offers rapid cycle times of the highest quality in cell and protein production with a focus on membrane proteins. In Toulouse, the team brings new capabilities in large scale microorganism or cell culture processes as well as the relevant purification steps to provide larger amounts of high grade quality proteins batches. It also incorporates scientists with research, development and industrial expertise in the biotherapeutics field (from recombinant hormones, enzymes to antibody production). The team is expert in adapting laboratory scale results to large scale equipment including 20L to 100L wave system for mammalian or insect cells and all the related separation techniques in a controlled environment. Relevant in-process and final controls are elaborated and run to document quality prior to batch release.

CELL LINE GENERATION AND BANKING

From recombinant cells which have been either generated by stable transfection or viral transduction, monoclonal cell lines are isolated and screened for their functional expression of the target protein. After a first broad screening on expression level using immunofluorescence labelling, Western blot, or RT-PCR, usually a secondary screening of selected clones by a cell-based assay is applied.

There are numerous reasons why a target may not be stably expressed in mammalian cells and a transient approach may be more appropriate for cell-based screening. To address this problem, Evotec routinely uses a variety of transfection technologies from lipid based to viral mediated delivery to achieve transient expression.

Particularly the MaxCyte electroporation platform offers access to large batches of up to 10 billion cells, a cost-effective and efficient transfection process. Transiently transfected or virus transduced cells can be provided as assay-ready frozen instant cells, which are functionally expressing the target instantly after thawing.

The availability of cells is a critical bottleneck in screening campaigns. Frozen instant cells, which can be assayed without prior cultivation have become a valid and frequently used alternative to cells from a continuous growing culture.

Evotec’s cell culture unit was one of the first suppliers of frozen instant cells for global pharmaceutical research. Cells are:

- Expanded under controlled culture conditions to large bulk quantities
- Harvested applying a gentle method which does not affect surface receptors
- Prepared to a density which corresponds to the requirements of your assay, the cells are dispensed into vials using an automated filling device. This fast processing of the cells significantly decreases the time from harvest, which is critical for maintaining the quality of frozen instant cells
- Frozen in a controlled rate freezer and stored in the vapour phase of a N2 tank until they are shipped.

For your ligand binding assays or in vitro transporter activity assays, we offer cell membranes in bulk in two different purity grades. All batches of cells and cell-based products are carefully controlled for their quality before they are shipped to you. Frozen instant cells are checked not only for viability but also for their ability to adhere shortly after thawing. A good “fitness” of the cells is often correlated with fully functional response. Finally, the assay performance of the frozen cells is compared to cells from a continuous growing culture considering Z’ S/B and EC_{50}.
Evotec offers professional management and maintenance of client cell banks encompassing the addition of new cell lines and shipment of assay ready cells and vials to the client’s research centres. A dedicated team with access to the necessary bioinformatics, quality control processes and infrastructure can additionally provide support in the sourcing and maintenance of disease relevant cell banks such as oncology. The databases covering all aspects of the respective cell line such as growth rates, morphology and genetic confirmation are available over a web-based client portal providing clients with the essential access to all necessary information.

RECOMBINANT PROTEIN PRODUCTION

Protein production lies at the heart of drug discovery. Evotec’s recombinant protein production facilities provide comprehensive coverage of expression hosts, purification techniques and analysis tools and delivers a unique solution for the efficient delivery of proteins in a timely fashion. Our capabilities can be accessed flexibly, either as standalone units or as part of an integrated drug discovery programme. All proteins are prepared with end use in mind, including the delivery of high-quality proteins for bio-assay and biophysical applications.

- Labelled proteins for NMR and Mass Spectroscopy
- Biotinylated proteins for Surface Plasmon Resonance
- Yields and quality suitable for Isothermal Calorimetry, Differential Scanning Fluorimetry and Microscale Thermophoresis
- High-throughput protein purification and construct triage to deliver crystal grade material for macromolecular X-ray crystallography

The experienced team of scientists will determine optimal host for expression and yield and develop suitable protocols for purification using a suite of techniques, including semi-automated expression analysis and purification.

Specific expertise in the team covers the common protein families and also extends into the more demanding areas of macromolecular complexes (protein:protein and protein:DNA) and membrane proteins.

The team has unparalleled experience in labelling of proteins for NMR work including ubiquitous 15N, 13C and 2H in E. coli and yeast and side chain specific labelling in insect expression hosts.

In addition to purification of proteins by SOPs or according to literature precedents, Evotec has extended methods commonly employed in structural genomic facilities so that the team can perform high-throughput (“HTP”) expression screening in E. coli, insect and mammalian hosts to determine optimal conditions for production ahead of parallel purification or large scale production runs. Large scale expressions can be carried out in parallel, either in shake flasks or in WAVE cellbag bioreactors.

### Uses of protein

- **NMR** 47%
- **Assays** 33%
- **Other** 6%
- **Mammalian** 14%
- **E. coli** 68.3%
- **Insect cells** 27.5%
- **Pichia pastoris** 0.7%
- **Other** 6%

### Expression hosts in 2014, >550 production runs completed

- **E. coli**
  - up to 295 L/week + 450 L fermentation vessel
  - Tags: no tag, His (N- or C- terminal), GST, MBP, Trx
  - Strains: BL21 (DE3);pLysS, ArcticExpress, BL21-AI
  - Secretion signal peptide (if needed): pelB

- **Pichia pastoris**
  - up to 40 L/week
  - Tags: no tag or C- terminal His-tag
  - Strain: X-33
  - Secretion signal: α-Factor

- **Insect cells** (Baculovirus)
  - up to 160 L/week + 100 L wave system
  - Tags: no tag, His (N- or C- terminal), GST, MBP
  - Strains: Sf21, Sf9, T. ni
  - Secretion signals (if needed): gp67, honeybee melittin, wild type

- **Mammalian cells**
  - up to 80 L/week + 100 L wave system
  - Tags: no tag, His (N- or C- terminal), GST, MBP
  - Strains: CHO, HEK293, CAP-T, EXPi293
  - Secretion signals (if needed): wild type, Igk
Evotec offers labelling of biological relevant molecules and reagents for use in ELISA, FACS, FCS, plate readers and other fluorescence based detection systems. Our service helps clients to improve their research results in all areas of biological and pharmacological assays, as well as clinical diagnostics and analytics. Our expertise covers the labelling of the following:

- Small organic molecules e.g. hormones, neurotransmitters
- Peptides and chemokines (as enzyme substrates, GPCR ligands, etc.)
- Proteins including antibodies
- Site-specific mutagenesis of proteins (for site-specific labelling)
- Glycoproteins
- Carbohydrates
- Lipids (for membrane studies)
- Beads and surfaces

Evotec’s labelling chemistry team has acquired a comprehensive expertise having successfully designed and labelled components for more than 150 different assays representing a broad range of assay classes. For labelling we use the optimally suited dyes and tags for your application, such as:

- Proprietary dyes (EVOblue™ family)
- Commercially available fluorescent dyes and the in-licensed MR121 dye
- Non-fluorescent markers and probes like affinity tags, biotin, reporter enzymes, etc.

With a range of ÄKTA purification modules (from Purifiers to Pilots) and HTP methods suitable for cost-effective parallelisation, Evotec has the capacity to deliver significant quantities of proteins in parallel using a variety of purification schemes (see figure above).

All proteins pass stringent in-process quality controls, including Mass Spectroscopy, Dynamic Light Scattering, Differential Scanning Fluorimetry, Activity Testing and NMR, before final release to the end user. In summary, by tailoring the purification schemes to the problem to be solved and using appropriate input from scientists on the projects, Evotec delivers the target protein optimised for the end use.
IN VITRO
PHARMACOLOGY, MICROBIOLOGY & TRANSLATIONAL SCIENCE

In addition to its extensive capabilities in mammalian biological systems, Evotec has in depth in vitro microbiology expertise spanning a broad range of pathogens from bacteria to fungi and viruses.

Typical activities include:
- Development of biochemical and functional assays
- Secondary and tertiary characterisation of screening hits
- Compound profiling as part of hit-to-lead and lead optimisation programmes:
  - Design and implementation of target-relevant assays (screening cascades)
  - Potency and selectivity testing
  - Mode of action studies (e.g. competitive versus allosteric mechanisms, reversibility, use-dependent mechanisms for ion channel modulators)
- Translational cellular assays to bridge the gap between in vitro and in vivo studies: testing of compound potency and mechanism using disease-relevant primary cells from rodents, primates or human
- Translational biomarkers: building assays in the discovery phase that allow measuring target engagement in patients and thus de-risking of clinical projects

Such activities are part of Evotec’s integrated lead finding and optimisation projects but are also frequently used to support medicinal chemistry projects that are executed in the labs of Evotec’s partners.

AVAILABLE READ-OUT AND ASSAY TECHNOLOGIES
Evotec has access to a wealth of assay technologies that can be used to assess compound activity. Appropriate technologies and expert teams are selected to answer key project questions and to ensure project advancement. Beyond standard and established read-out technologies for biochemical and cellular assays, Evotec has built key expertise in a number of technological areas that have shown to be drivers for the success of our partner’s projects. These include:
- The use of stem cells to derive neurons and primary neuronal cultures to build disease-relevant cellular models and to identify and characterise new compounds with disease-modifying properties
- An extensive knowledge of high-content screening and a state-of-the-art hardware platform to run complex and disease-relevant imaging assays, e.g. using primary neuronal cultures, kidney cells, muscle cells as well as rodent and human beta cells
- A world-leading ion channel discovery platform including fluorescence-based assays, automated and manual patch clamp methods
- An excellent suite of biophysical methods including SPR and NMR that are utilised as part of our structure-based drug design projects but also LC-MS-based methods that are utilised to assess difficult-to-assay enzyme targets
- In the oncology area, the setup of integrated assays based on tumour cells, fibroblasts, macrophages, endothelial cells, or adipocytes in 2D, co-culture or 3D culture to recapitulate tumour and microenvironment conditions
- The use of extensive read-outs, from signalling to metabolic pathway engagement, to develop new ways to address pathologies and overcome resistance to treatments

Studying compounds modulating beta cell proliferation

Read-out technologies

CELL-BASED ASSAY TECHNOLOGIES
- Fluorescence read-outs
  - HTRF, standard dyes, ligand binding
  - Second messengers (Ca2+; cAMP, IP3)
  - Membrane potential (GPRs, ion channels and transporters)
- Manual and automated patch clamp
- Reporter gene assays
- ELISA (standard and Mesoscope)
- Imaging (HCS)
  - OPERA®, Operetta, Zeiss and ArrayScan
- Radioactive binding and uptake
- Flow cytometry and cell sorting
- Migration and invasion assays
- Whole cell blood assays
- Metabolic analysis (seahorse, metabolomics, mitochondrial OXPHOS function)
- Primary cell culture
- Stem cells
- Established cell lines
  - Co-culture
  - 3D culture

BIOCHEMICAL ASSAY TECHNOLOGIES
- FCS + plus
- Fluorescence polarisation
- Fluorescence intensity
- HTRF/Delfia
- AlphaScreen
- ELISA
- Mesoscale electrochemiluminescence
- Single/C single protein molecule counting
- Luminescence
- LC/MS

BIOPHYSICAL READ-OUT TECHNOLOGIES
- Surface Plasmon Resonance (SPR)
- Mass Spectrometry (LC-MS)
- Nuclear Magnetic Resonance (NMR)
- Radiometric
- Thermal Shift
OVERVIEW TARGET CLASSES

Our in-depth experience in the biology and pharmacology of disease-relevant target classes is what our partners come to us for. This expertise is a key driver to the successful and rapid execution of lead finding and optimisation processes. Evotec’s in vitro pharmacology team has gained expertise across a wide area of disease targets. Beyond a large number of projects that have successfully been run in the classical target areas such as GPCRs, ion channel and kinases, we have also worked on a large diversity of other target areas such as transporters, protein-protein interactions and multiple enzyme families, including novel target classes such as epigenetic regulators and immune and metabolic pathways modulators.

DISEASE EXPERTISE, TRANSLATIONAL ASSAYS AND BIOMARKERS

Evotec’s core expertise includes areas such as CNS, neurodegeneration, pain, inflammation, metabolic disease, oncology and immunology. Our scientific expertise and understanding of disease mechanisms combined with our track record in setting up relevant in vitro models and translational biomarker assays for pre-clinical and clinical use are a key factor in our success when working with our partners.

Setting up complex in vitro assays utilising rodent or human primary cells to confirm the potency and mechanism of lead compounds is a prerequisite to build confidence in the translatability of any mechanism. We build these assays early in the drug discovery process to gather disease-relevant data before assessing compound efficacy in vivo. Such assays are also utilised to identify read-outs for in vivo target engagement. We routinely utilise various neuronal and stem cell cultures, pancreas and beta cells, kidney cells and various immune cells, tumour cells, endothelial cells, fibroblasts, adipocytes and muscle cells to assess bespoke read-outs and mechanisms, including cell health and survival, metabolism, apoptosis, differentiation, de-/regeneration; neurite outgrowth, retraction and synaptic density; cellular signalling and secretion.

A key challenge for bringing a new therapy to the market is to provide proof of efficacy in the clinic and to reduce the risk of a failed trial due to inadequate clinical read-outs. Robust and objective biomarker read-outs that are applicable to clinical samples are therefore needed to stratify patient populations, quantify disease progression and to demonstrate target engagement and dosing response. Together with our partners, we utilise state-of-the-art single molecule counting Singulex technology to routinely develop, validate and apply ultra-sensitive protein biomarker quantification read-outs for clinical samples such as human blood, plasma and CSF.

Extensive expertise with translational cellular assays using primary cells and tissues to investigate compound potency and mechanism
EvostrAIn™: A collection of highly characterised clinical isolates available to establish a detailed activity profile of lead compounds, both in vitro and in vivo models of infection

<table>
<thead>
<tr>
<th>BACTERIA: Gram positive pathogens</th>
<th>BACTERIA: Gram negative pathogens</th>
<th>FUNGI</th>
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<tbody>
<tr>
<td>Staphylococcus aureus including MRSA, VISA and VRSA strains</td>
<td>Klebsiella pneumoniae Carbenapenemase producing strains (KPCs &amp; MDR)</td>
<td>Candida spp. (including strains resistant to azoles, polynes and echinocandins with known mechanisms of resistance)</td>
</tr>
<tr>
<td>β-Haemolytic streptococci groups A, B, C and G</td>
<td>Acinetobacter baumannii including MDRAB</td>
<td>Mucorales</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (including penicillin, macrolide, fluoroquinolone, cephalosporin and MDRSP resistant strains)</td>
<td>Pseudomonas spp. including multi-resistant strains</td>
<td>Cryptococcus</td>
</tr>
<tr>
<td>Vancomycin Resistant Enterococci (VRE)</td>
<td>Haemophilus influenzae</td>
<td>Dermatophytes including Malassezia spp and Trichophyton spp</td>
</tr>
<tr>
<td>Bacillus species</td>
<td></td>
<td>Fusarium</td>
</tr>
<tr>
<td>Listeria species</td>
<td>Bacteroides spp.</td>
<td>Protozoa</td>
</tr>
<tr>
<td>Corynebacterium and Propionibacterium species</td>
<td>Neisseria gonorrhoeae and N. meningitidis</td>
<td>Acanthamoeba spp</td>
</tr>
<tr>
<td>Clostridium difficile (multiple ribotypes including 012, 027 and 078)</td>
<td>Intestinal pathogens: Vibrio spp, Campylobacter spp, Salmonella spp, Shigella spp, Yersinia spp</td>
<td></td>
</tr>
<tr>
<td>Other Clostridia (including C. perfringens)</td>
<td>Legionella spp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycobacterium</td>
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</tbody>
</table>

MICROBIOLOGY
Evotec’s specialist group in the infectious disease therapeutic area boasts state-of-the-art microbiology facilities including a unique and highly characterised strain bank, EvostrAIn™. Our team provides bespoke anti-infective drug discovery and development services to a growing number of global partners and has an established track record in collaborating to discover and develop new therapies and vaccines to treat and prevent serious and life-threatening infections resulting from multi-drug resistant pathogens including Gram positive and Gram negative bacteria, including the ESKAPE organisms, fungi, and viruses.

The group’s offering is fully integrated with the wider discovery platform at Evotec enabling either a standalone microbiology service or a fully integrated anti-infective drug discovery capability. Core strengths of Evotec’s microbiology group fall into the four areas of EvostrAIn™. Microbiology, Pharmacology and ADME/PK/PD as follows:

EvostrAIn™ is a highly valuable collection of clinical isolates that can be used to establish the activity profile of lead compounds and candidates. A key feature is that the isolates are highly characterised and, in many cases, mechanisms of resistance defined. EvostrAIn™ contains an extensive range of geographically diverse human bacterial and fungal pathogens that cover isolates susceptible and resistant to current antimicrobial drugs.

We employ industry-standard methods such as CLSI, EUCAST and BSAC to test compounds for antimicrobial activity against strains and clinical isolates from EvostrAIn™ or strains provided by our collaborators. This includes the ability to conduct whole-cell screening for antimicrobial activity for hit identification in an HTS format, MIC, MBC/MFC, time-kill and PAE studies using single or combinations of agents, hollow fibre PK/PD or bioreactor human cell systems for detailed profiling for characterisation of novel anti-infective agents, and compound/drug combination studies for assessment of synergistic, antagonistic and additive effects. Bespoke methods for susceptibility profiling can be developed for testing novel agents where standardised methods may not be appropriate. In parallel, mechanism of action determination studies and resistance frequency assays can be performed.
ION CHANNELS

OFFERING
Evotec’s world-class ion channel platform combines industry-driven expertise with state-of-the-art instrumentation. In routine use are multiple setups for manual patch clamp studies and all of the most popular automated patch clamp instruments. The automated patch clamps or FLIPRs can be used as entry points for HTS, and the manual and automated patch clamps enable on-going support of medicinal chemistry programs progressing from HTS through hit expansion, hit-to-lead, lead optimisation but are also utilised for safety pharmacology.

We now offer brain and spinal cord slice electrophysiology to measure the effects of test substances or manipulation of CNS targets on synaptic function.

Stephen Hess
Research Leader Ion Channels

OVERVIEW OF ION CHANNEL SCREENING AT EVOTEC
Evotec has a strong background in running hit identification campaigns against ion channel targets. On average more than 235,000 compounds per target are screened in singlicate at a fixed compound concentration. Campaigns resulted in “primary” hit rates in the range of 1% and confirmation rates are generally good (>50%), underlining robust assay performance. Secondary assays using electrophysiology to confirm compound activity is part of the routine HTS follow-up and are key to the successful identification of relevant starting points for medicinal chemistry projects.

 люди мы будем работать над нейрологическими каналами.

The electrophysiology platforms in place at Evotec

<table>
<thead>
<tr>
<th>PLATFORM</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>SynchroPatch384PE</td>
<td>384-well</td>
<td>4,000-10,000</td>
<td>High-throughput screening, hit-to-lead</td>
<td></td>
</tr>
<tr>
<td>IonWorks® Quattro™</td>
<td>384-well</td>
<td>4,000-10,000</td>
<td>High-throughput screening, hit-to-lead</td>
<td></td>
</tr>
<tr>
<td>Q-patch HTX®</td>
<td>48-well</td>
<td>150-450</td>
<td>Hit-to-lead, lead optimisation and early safety assessment</td>
<td></td>
</tr>
<tr>
<td>PatchLiner®</td>
<td>16-well</td>
<td>75-150</td>
<td>Hit-to-lead, lead optimisation and early safety assessment</td>
<td></td>
</tr>
<tr>
<td>Port-A-Patch®</td>
<td>1-well</td>
<td>25-50</td>
<td>Hit-to-Lead, Lead optimisation</td>
<td></td>
</tr>
<tr>
<td>Manual Electrophysiology (Dynaflow®/TM optional)</td>
<td>1-well</td>
<td>1-25</td>
<td>Lead optimisation, safety pharmacology</td>
<td></td>
</tr>
<tr>
<td>Slice Electrophysiology</td>
<td>1-well</td>
<td>Varies with assay</td>
<td>Detailed MOA studies on brain &amp; spinal cord synaptic function</td>
<td></td>
</tr>
</tbody>
</table>

Electrophysiological recordings from primary cells provide additional mechanistic insight beyond that possible using recombinant cells. In this case we used neurons isolated from dorsal root and nodose ganglia. On the right is an example taken from our efforts using mouse nodose ganglion neurons:

- Voltage-gated sodium channels (NaV) are expressed in neurons
- The selective NaV blocker, TTX (300nM) inhibited NaV signal in big diameter cells (arrows)
IN VIVO PHARMACOLOGY

Evotec offers a range of acute and chronic pain models in rodents with different read-outs depending on the model of interest. Importantly, our scientists are fully blinded to reduce the potential for operator bias.

Pain Models
Spinal Nerve Ligature model (SNL); Visceral pain: colorectal distension-induced visceromotor reflex; CFA-induced inflammatory pain: Formalin induced nocifensive behavior, mustard-oil induced neurogenic inflammation

Evotec will work with you to identify the most appropriate in vivo pharmacology solution for your drug discovery programme; whether that’s an off-the-shelf standard protocol or developing bespoke assays / read-outs for your specific requirements. We utilise a plethora of acute, mechanistic, pharmacodynamic models relevant to the target biology to assess target engagement and establish PK / PD relationships. Our efficacy models are used to assess biological effects on pathophysiology’s relevant to the disease of interest and are validated with appropriate standards of care and supported by rigorous statistical methods. At Evotec we are continually striving to develop in vivo models and endpoints with greater translational relevance to the clinic and all our models can be supported by relevant pharmacokinetic measurements to determine exposure to effect relationship. Importantly, Evotec’s in vivo pharmacology functions are typically co-localised with our in vitro pharmacology units and this complementarity leads to disease biology platforms with a stronger disease focus and breadth of expertise.

Evotec has developed considerable in vivo pharmacology expertise in our key therapeutic areas of CNS, metabolic disease and complications, oncology and infectious disease. Our in vivo pharmacology team (> 70 staff), consisting of highly experienced scientists with extensive biopharmaceutical and drug hunting expertise, supports in vivo studies from early target validation through to candidate selection. Furthermore, we have the flexibility to support defined stand-alone studies in addition to in vivo work conducted as part of larger integrated drug discovery programmes. All experimental procedures involving animals are carried out to the highest standards of animal welfare in state-of-the-art facilities and approved according to European Union and national regulations.

Evotec’s IN VIVO PHARMACOLOGY supports target identification. Our expert team of highly experienced scientists with extensive biopharmaceutical and drug hunting expertise, supports in vivo studies from early target validation through to candidate selection. Furthermore, we have the flexibility to support defined stand-alone studies in addition to in vivo work conducted as part of larger integrated drug discovery programmes. All experimental procedures involving animals are carried out to the highest standards of animal welfare in state-of-the-art facilities and approved according to European Union and national regulations.

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CENTRAL NERVOUS SYSTEM (CNS)

Acute/Chronic Pain
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Key Read-outs
- Pain models: Spinal Nerve Ligature (SNL); Visceral pain: colorectal distension-induced visceromotor reflex; CFA-induced inflammatory pain: Formalin induced nocifensive behavior, mustard-oil induced neurogenic inflammation
- Pharmacodynamic models: Acute/chronic pain
- Thermal sensitivity: Hargreaves test, hot plate, tail flick
- Mechanical sensitivity: Von Frey test, pressure application measurement device, dynamic weight bearing
- Lasics automated recording for formalin paw and locomotor activity
- Visceral motor reflex-EMG activity

Neurodegenerative Disease
Evotec offers phenotypic screening in a variety of models of neurodegeneration, primarily in transgenic animals for Chorea Huntington and for Alzheimer’s disease.

Key Read-outs
- Behavioral assays, histology and immuno-histochemistry (IHC), morphometric analysis
- High-content IHC analysis
- Biomarkers (e.g. cytokines using Mesoscale)

Oncology
Evotec offers a range of rodent models, spanning xenograft, syngeneic and orthotopic models coupled with the possibility of a broad range of efficacy and biomarker read-outs. In addition, we have access to a range of relevant human tumour tissue samples via the Institut Universitaire du Cancer Toulouse Biobank which can be utilised for biomarker studies or ex vivo evaluations including compound treatment.

Oncology Models
- Subcutaneous human xenograft models. Syngeneic models suitable for the evaluation of immuno-oncology therapies Orthotopic models including: Bladder, brain, breast, colon, kidney, liver, lung, ovary, skin. Suitable for metastasis studies. Angiogenesis models (in mice and rats), with Laser Doppler

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Adjacent sections (20 μm), male Sprague Dawley rat, 8 weeks old

1 nM 3H-naloxone

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Adjacent sections (20 μm), male Sprague Dawley rat, 8 weeks old

1 nM 3H-naloxone
Key Read-outs

Efficacy evaluation by tumour volume and/or Bioluminescence (IVIS Spectrum) imaging for 3D tomography and metastasis.
- Full Hematological analysis including FACS analysis
- Bioanalysis for associated pharmacokinetic studies (PK/PD)
- Tissue sampling for:
  - Genomics studies including: RT-PCR, Taqman, TLDA
  - Protein analysis (total and phosphorylated protein profiling)
  - ELISA, Western Blotting, dot-blotting, histology, immunohistochemistry
  - Quantitative image analysis (Definiens technology)
- Mitochondrial metabolism:
  - Cellular ATP generation: Glycolytic vs mitochondrial pathways
  - Oxygen Consumption Rate (OCR) and Extracellular acidification rate (ECAR)
- Oxphorygraph: a way to analyse the isolated mitochondrial function
- Mitochondrial membrane potential, respiration rate, phosphorylation rate
- Metabolite analysis for quantification of lactate, glucose, glutamine, glutamate
- Microdialysis
  - Detection of metabolites and/or drug levels by ex vivo microdialysis in tumour, brain, adipose tissue or biological fluids

METABOLIC AND DIABETIC COMPLICATION

Metabolic diseases like Diabetes mellitus, obesity or the metabolic syndrome belong to the major chronic diseases in the world. Long term Diabetes mellitus results in a number of severe diabetic complications impairing kidney, eyes, heart and peripheral nerve function.

Animal models of metabolic diseases include genetic models (ie. ZDF rats, Ins2 Akita mice), diet-induced models using different diets, chemically-induced models with Streptozotocin (STZ) or Alloxan as well as a humanised beta-cell model where human islets are transplanted into STZ-treated diabetic NOD-SCID mice.

Chronic kidney disease (CKD) is a progressive loss in renal function over a period of months or years resulting from e.g. Diabetes mellitus or genetic predisposition. In order to identify new therapeutic options clinically relevant animal models for acute and chronic kidney disease have been developed which include surgery models (e.g. Acute and Chronic Ischemia Reperfusion Injury models (IRI, CRI), Unilateral Ureter Obstruction model (UUO), genetic models of Diabetes mellitus (ie. BTBRob/ob mice on different diets, Ins2-Akita mice) and models of chemically induced Diabetes mellitus with STZ and combinations thereof.

Relevant animal models of eye disease for proliferative and diabetic retinopathy have been developed and validated. These include models of chemically induced diabetes (ie. STZ) as well as a model of Oxygen Induced Retinopathy (OIR).
All metabolic and diabetic complication animal models are run under standardised conditions and profiled with a variety of supporting read-outs:

- **Standart Read-outs**
  - Standard clinical and metabolic read-outs including functional glucose/insulin tolerance test, ex vivo read-outs including RT-PCR, biochemical assays, hormonal status and histology.

Advanced Read-outs

Hyperinsulinemic euglycemic clamp, food intake profiles, pairfeeding, body composition analysis by Nuclear Magnetic Resonance (NMR) spectroscopy, morphometric analysis with customised algorithms e.g. with pancreas and adipose tissue, blood pressure analysis, assessment of Glomerular Filtration Rate (GFR).

**Biomarker approaches**

Plasma and tissue analysis (e.g. ELISA, quantitative RT-PCR), high-content tissue imaging for bright as well as immune histochemistry, single and multiplexing on the Mesoscale platform, e.g. cytokines, mass spectrometry (ie. LC-MS/MS).

**INFECTIOUS DISEASE**

Etvotec specialises in assessing the efficacy of lead and candidate compounds in highly relevant and validated models of infection. Our extensive range of established models are well-suited to the development of multiple classes of agent including small molecules, natural products, peptides, antibodies, other biologics and vaccines. We provide a highly bespoke service, customising studies to meet the exact requirements based on programme needs and parameters / endpoints of interest.

**Models of Infection**

For efficacy assessment against bacterial and fungal infections, our models address different sites of infection (localised and systemic) and pathogens by Gram-positive (including Staphylococcus aureus, Streptococcus pneumoniae, and others), Gram-negative (including Pseudomonas aeruginosa, Escherichia coli, Acinetobacter baumannii and others), anaerobes (including Clostridium difficile) or fungal species (including Candida sp., Aspergillus sp., Mucorales, Malassezia sp.).

In particular, Evotec specialises in PK/PD profiling and modelling of antimicrobial agents in multiple disease models in order to understand the key drivers for efficacy and translation of data into clinical trial design.

**Key Read-outs**

Efficacy evaluation by:
- Burden at site of infection and in multiple biological matrices including quantitative culture, QPCR and biomarkers
- Microbiome analysis and sequencing
- Bioluminescence (IVIS Spectrum) imaging.
- Host response endpoints including ELISA, Western Blotting, dot-blotting, histology, immunohistochemistry, cytokine profiling and cytometry

**HISTOLOGY, IMMUNOHISTOCHEMISTRY AND MORMOPHOMETRIC ANALYSIS PLATFORM**

The combination of in vivo pharmacology with histology techniques offers a powerful tool to further analyse disease relevant biomarkers. Whereas histology and IHC helps to identify disease and target relevant changes, automated morphometric analysis can yield unbiased quantitative information amenable to statistical analysis, which adds significant value to the customer’s drug discovery effort. Furthermore, histopathology on critical organ systems will allow early risk assessment.

**Infectious Disease**

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EVOMAB
ANTIBODY GENERATION AND SELECTION

OFFERING
Antibody identification including B-cell cloning and high-throughput expression platform is embedded in Evotec’s pre-clinical development expertise.

As a partner in antibody drug development, Evotec offers high-throughput antibody cloning and expression which can be combined with all standard immunisation and selection technologies.

The offering includes reformatting antibody pools from phage display selections or animal immunisations into suitable screening formats. Evotec’s own ‘AbExpress’ technology combines specific B-cell enrichment with high-throughput cloning and expression of antibodies in mammalian cells. We provide optimal cell-based HTS/HCS screening formats supporting fast development cycles. Evotec offers a turnkey solution for antibody development up to the production of mg quantities necessary for testing in animal models.

CAPABILITIES AND PLATFORM
Evotec has established its antibody screening platform EVOMAb to incorporate functional screening early in the antibody discovery and selection process. Attractive targets such as transmembrane proteins need to be altered in their activity in order to achieve a meaningful pharmacological effect. The most critical challenge in functional screening is the availability of sufficient antibody in assay compatible media or buffers. AbExpress combines high-throughput cloning with high parallel expression and purification strategies. Isolating antibodies directly from single B cell lineages overrides hybridoma technologies due to efficiency in isolating rare functional clones. The limiting factor in high parallel expression of antibodies is the cost of cloning and handling thousands of individual sequences while preserving cognate pairs of heavy and light chain during the primary screening process. In our pool cloning and expression strategy each heavy chain is co-expressed with a limited, pool of light chains including its cognate partner during screening. This primary expression step yields several hundred microgram of antibody. Following the primary screen, interesting heavy chains are paired with their cognate light chains using sequence information obtained from primary plates.

The EVOMAb workflow maximises the rapid capture of a diverse set of antibody clones and enables primary functional screening with recombinant antibodies.

Arnd Steuernagel
Senior Vice President Biologics

GENERATE ANTIBODY POOLS by immunisation, phage display, yeast display. Various platforms available, either in-house, through collaborations or from customer
Typical output is thousands of clones (B-cells, Hybridomas, Yeast cells) expressing no or low amounts of soluble antibody

Efficient recovery from B-cells
Massive parallel expression
High-Throughput Screening

Proprietary antibody discovery platform
Hundreds of recombinant antibodies at high microgram yield
Early screen for functional activity

AbExpress High parallel expression of antibodies

Cell based screening platforms
Established at Evotec in combination with target know-how and tools

Antibodies

> > 10,000 clones

1,000 to

Cell Lines

- Ion Channels
- GPCRs
- Integrins
- Receptors
- Cytokines

Cell Based Assays

- Automated electrophysiology
- GPCR
- Ca²⁺ flux
- cAMP/Arrestin
- Signalling cascades
- Phenotypic changes
- Translocation
- Differentiation

Equipment

- FLIPR384
- FLIPR Tetra
- Tecan Safire II
- Perkin Elmer EnVision
- TopCount
- Opera
- SKL BIND
- IonWorks® Quattro™
- Q-patht® HTX™
- PatchLab™

Ion Channels
GPCRs
Integrins
Receptors
Cytokines
Evotec, with its broad expertise and services, its repeat business and strategic alliances, is perfectly positioned to be your drug discovery services provider of choice. We are aware of the fact that it takes much more than just the highest quality services to develop new drugs, but nevertheless this is the most important starting point. Evotec delivers an industrialised, high-tech, and comprehensive infrastructure to our partners.

Evotec has a broad client base ranging from venture capital firms to virtual biotechs to large pharmaceutical companies. We are a truly global company with clients in the United States, Europe and Japan. We have a loyal client base with many long-term agreements as well as regular repeat clients that keep coming back with project after project as Evotec delivers the drug discovery solutions and value they need to drive their discovery programmes forward.

Evotec is one of the few drug discovery businesses that can execute a comprehensive outsourcing strategy. In significant large-scale, multi-target deals, Evotec’s customers work with our scientists to progress discovery programmes from target through to lead optimisation using the Company’s integrated drug discovery platform.

Evotec’s knowledge in Alzheimer’s disease greatly enabled this collaboration

«Evotec is the ideal partner to provide the resource bandwidth and drug-hunting expertise»

«Our new collaboration with Evotec will perfectly complement our activities in this field of high unmet medical need»

«We are impressed by Evotec’s breadth of drug discovery expertise»

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