Oncology drug discovery at Evotec
Evotec, an ideal partner in oncology drug discovery

The different ways to work with us

<table>
<thead>
<tr>
<th>On a specific target or programme</th>
<th>Starting from a phenotypic assay concept</th>
<th>On an existing Evotec programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to Evotec drug discovery expertise &amp; capabilities to support your programme</td>
<td>Access to Evotec phenotypic screening expertise followed by target deconvolution leading into a drug discovery programme</td>
<td>Sponsor an established theme such as epigenetics, cancer immunotherapy or cancer initiating cells</td>
</tr>
</tbody>
</table>

Flexible commercial solutions: multiple business models available to suit our partners

Access to expert discovery platform as *stand-alone activities* or as part of *integrated drug discovery programmes*
A leading platform for rapid progress and increased success of your programme

Evotec oncology platform

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Experienced Oncology Research team of ~100 FTEs</td>
</tr>
<tr>
<td>2</td>
<td>Unique expertise in growth factor modulation, cancer metabolism, immuno-oncology and resistance to SoC (^1) therapies</td>
</tr>
<tr>
<td>3</td>
<td>Multidisciplinary project teams working on over 12 active projects in the area of Cancer Metabolics, Immune evasion, Tumor suppressor biology and DNA damage repair</td>
</tr>
</tbody>
</table>
| 4 | Extensive portfolio of drug discovery capabilities:  
  - Structure-based drug design-driven medicinal chemistry  
  - Target identification and validation  
  - *In vitro* and *in vivo* pharmacology  
  - Proteomic and metabolomics platform  
  - Translational biology |

Significant track record achieving numerous oncology milestones including 8 PDCs \(^2\) and 14 clinical drugs and 1 marketed drug

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1. SoC: Standard Of Care
2. PDC: Preclinical Drug Candidate
Supporting all activities from Target ID to clinical translation through a fully integrated platform

Evotec France (Toulouse) – Centre for integrated oncology research

**Research platforms**
- Cancer metabolism
- Tumour microenvironment
- Growth factor modulation

**Modulating**
- Cancer cell proliferation
- Resistance to SoC therapies
- Cancer immunity

**Target ID/validation**
- Target validation / deconvolution
- Responder identification hypothesis testing

**Drug discovery platform**
- HTS
- Virtual screening
- *In silico* modelling
- Medicinal chemistry
- *In vitro* biology
- ADME

**Clinical translation**
- Biomarker discovery and validation
- Targeted proteomics and metabolomics
- IHC, FACS, MSD

- *In vivo* pharmacology (orthotopic, syngeneic)
- Formulation & PK
- Microdialysis
- Discovery toxicology

- Epigenetics
- DNA break repair
- Tumour microenvironment
- Targeted therapy resistance

- Metabolomics
- Bioinformatics
- Molecular dynamics

- *Ex vivo* experiments on fresh tumour samples
- *In vivo* imaging
- Histopathology

- Early clinical trial design
- Biobank access
- Phase I sample access
Rapid cycle times to efficiently progress oncology programmes

Structure Based Drug Design-driven Medicinal chemistry

- Rapid synthetic execution & ability to address difficult chemistry and optimisation of phenotypic screening hits
- Strong expertise in SBDD by our outstanding computational chemistry and structural biology teams
- Very large chemistry group (>180) synthetic, medicinal and computational chemists, >35% of our scientists have >8 years prior experience at major Pharma and biotech companies

Effective delivery of clients’ objectives
Over 30 pre-clinical candidates nominated and 20 compounds approved for clinical trials across all therapeutic areas

Added value
Evotec medicinal chemists are named inventors on >275 client patents covering all major target and therapeutic areas
Supporting target characterisation, MoA studies & drug optimisation

State-of-the art in vitro oncology pharmacology platform

<table>
<thead>
<tr>
<th>Molecular Biology</th>
<th>Biochemistry</th>
<th>Cellular 2D models</th>
<th>Integrated 3D models</th>
<th>Ex-vivo analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cloning</strong></td>
<td><strong>Enzymatic activity</strong></td>
<td><strong>Incucyte Assays</strong></td>
<td><strong>Mimic hypoxia and substrate gradients in a 3D spheroid culture</strong></td>
<td><strong>Flow Cytometry</strong></td>
</tr>
<tr>
<td>• Plasmid construction</td>
<td>• e.g. Kinase, protease and metabolic</td>
<td>• Proliferation</td>
<td>• Characterization of spheroids</td>
<td>• 9 colour cytometry</td>
</tr>
<tr>
<td>• Ecotropic retroviral production (mouse)</td>
<td>• Kinetic profiling</td>
<td>• Apoptosis</td>
<td>• Proliferation rate</td>
<td>• Cell to platelet analysis</td>
</tr>
<tr>
<td>• transfection, transduction (plasmid, shRNA, siRNA)</td>
<td>• HTRF, FP, RF/MS etc.</td>
<td>• Cytotoxicity</td>
<td>• Apoptosis</td>
<td>• Cell sorter</td>
</tr>
<tr>
<td><strong>Gene expression</strong></td>
<td><strong>Ligand/receptor binding</strong></td>
<td><strong>Migration/invasion</strong></td>
<td><strong>Metabolism</strong></td>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td>• PCR, RT-qPCR, qPCR</td>
<td><strong>Protein or peptide release</strong></td>
<td><strong>High Content Assays and IF</strong></td>
<td>• SeaHorse</td>
<td><strong>Validation with fresh patient tumour material</strong></td>
</tr>
<tr>
<td>• TLDA</td>
<td><strong>Protein expression &amp; signalling</strong></td>
<td>• Localisation etc.</td>
<td>• Oxphography</td>
<td>• Connection with translational group &amp; clinics</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td></td>
<td></td>
<td>• Hypoxia</td>
<td>• Validate biomarkers and inhibitors developed in vitro on fresh patient samples</td>
</tr>
<tr>
<td>• DNA (plasmid, genomic, mitochondrial)</td>
<td><strong>Second messenger</strong></td>
<td></td>
<td>• Glycolytic/OXPHOS ATP</td>
<td></td>
</tr>
<tr>
<td>• mRNA</td>
<td>• Ca2+, cAMP</td>
<td></td>
<td>• Metabolite consumption/production</td>
<td></td>
</tr>
<tr>
<td><strong>Enzymatic activity</strong></td>
<td><strong>Incucyte Assays</strong></td>
<td><strong>Migration/invasion</strong></td>
<td><strong>Evaluation of compound effects</strong></td>
<td></td>
</tr>
</tbody>
</table>
Providing a unique clinical translation for our partners

Tailored pharmacology and biomarker solutions

<table>
<thead>
<tr>
<th>Animal welfare</th>
<th>Biomarker discovery &amp; target identification</th>
<th>In vivo pharmacology</th>
<th>Clinical translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trained veterinary staff</td>
<td>• MS-based proteomics and metabolomics</td>
<td>• Skilled surgeons</td>
<td>• Processing of animal &amp; human samples for ex vivo &amp; biomarker analyses</td>
</tr>
<tr>
<td>• State-of-the-art animal facilities, AAALAC accredited</td>
<td>• Target discovery and selectivity profiling</td>
<td>• Development of bespoke models to understand</td>
<td>• Established relationship with clinicians at the Toulouse Oncopole</td>
</tr>
<tr>
<td>- 3,000 m² for animal husbandry, housing and experimentation</td>
<td>• Biomarker validation</td>
<td>- Tumour biology and new therapeutic mechanisms</td>
<td>• Target expression on human samples</td>
</tr>
<tr>
<td>• Early toxicity assessments</td>
<td></td>
<td>- PK/PD relationships</td>
<td>• Prevalence determination as a function of pathology</td>
</tr>
<tr>
<td>• Rodent species focused</td>
<td></td>
<td>- Efficacy / dose dependency</td>
<td>• Assistance in the patient stratification process</td>
</tr>
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</table>

Breakthrough scientific expertise & integrated teams to support translational biology activities
**In vivo models exhibit high translational value**

The right model for the right drug

<table>
<thead>
<tr>
<th>Tumour models</th>
<th>Subcutaneous</th>
<th>Orthotopic</th>
<th>Transgenic animals</th>
<th>PDX models</th>
<th>PDX(s) orthotopic</th>
</tr>
</thead>
</table>
| Tumour phenotype and tumour microenvironment modulations | • Syngeneic and xenograft models (immune response)  
• Subcutaneous and orthotopically localised (cross-talk with stroma cells) |

| Bioanalysis and formulation | • Plasma and tumour exposure after single or repeated doses administration  
• **Formulation and administration route expertise** (including aerosolized) |

| Biomarker identification | • Exploration of **circulating** (cells, proteins) and **tumour parameters**  
• **Multi-level analysis of tumour modulation**: genes, mRNA, proteins, metabolites |

| Small animal imaging | Preclinical rodent imaging  
• 2D/3D bioluminescence imaging  
• Laser Doppler blood flow analysis  
• X-ray radiography of bone and soft tissues  
• $^{18}$FDG PET/CT scan (in collaboration with IUC-T) |

| Clinical supply | • Patient biopsies  
• Imaging technologies  
• Translational biomarkers |
Supporting oncology projects in epigenetics, immunotherapy, metabolomics etc. ...

Chemical proteomics, global proteomics and metabolomics

**Chemical proteomics**
- Evotec Cellular Target Profiling™ technology to both identify and quantify interactions with cellular compound targets
- Drug photoaffinity labelling and activity-based protein profiling for covalent target capture

**Global Proteomics Platforms**
- High-end quantitative mass spectrometry to monitor protein expression and glycosylation
- Interactome, secretome, surfacome analyses
- Targeted mass spectrometry assay development and deployment

**Metabolomics**
- *In vitro* and *in vivo* quantification of metabolites in complex samples using SPE-LC–MS/MS

- Cellular compound selectivity analysis in a native context
- Target de-convolution of hit compounds from phenotypic screens

- *In vivo* mode-of-action analysis in cells, tissues or patients
- Discovery & verification of biomarker candidates

- Targeted analysis in cells, tissues, body fluids or *in vivo*
Oncology at Evotec, current and future areas of focus

Evotec oncology themes

Cancer immunity & tumour microenvironment

- Target immune suppressive cells (MDSCs & M2 macrophages within the tumour microenvironment)
- Target tumour associated fibroblasts implicated in:
  - Cancer cell proliferation, invasion survival and epithelial mesenchymal transition
  - Regulation of extracellular matrix (ECM) remodelling, migration & angiogenesis, recruitment of stromal cells
  - Regulation of Tumour immunity
- For combination with SoC therapies and check point inhibitors

Cancer metabolism

- Target metabolic adaptation mechanisms (phenotypic screening)
- For combination with SoC therapies

Novel targeted therapies: Allosteric interaction

- Induce conformational change of receptors leading to their inactivation
- Application to well validated onco-targets (tyrosine kinase receptors)
- For replacement of current targeted therapies (specific kinase inhibitors)
Case Study: Hedgehog signaling pathway inhibitors

Screen to development candidate by cellular assay

<table>
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<tr>
<th>Partners</th>
<th>Programme</th>
<th>Target</th>
<th>Starting point</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Curis</td>
<td>H2L &amp; LO</td>
<td>Hedgehog Pathway</td>
<td>HCS Hit (EVT)</td>
<td>Clinical studies</td>
</tr>
</tbody>
</table>

- SAR developed via a high content assay: Agonist and antagonist focused programs
- Curis partnered programs with Wyeth and Genentech ($170M and $240M respectively)
- Compound from the Curis collaboration CUR 61414 progressed into Phase I clinical trials

Subsequent work at Genentech based on Evotec starting points led to discovery of vismodegib (Erivedge; GDC-0449), approved by FDA in January 2012 for treating basal cell carcinoma
## Case study: Target validation on human tissues

Target validation on human non-invasive bladder tumour

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</thead>
<tbody>
<tr>
<td>Institut Universitaire du Cancer (Toulouse)</td>
<td>Undisclosed</td>
<td>FGFR</td>
<td><em>In vivo</em> validation</td>
<td>Biomarker</td>
</tr>
</tbody>
</table>

### Validation of the antibody specificity

<table>
<thead>
<tr>
<th>Validation of the antibody specificity</th>
<th>300-19 cells transfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control</td>
<td>300-19 cells WT</td>
</tr>
<tr>
<td>with Receptor 1</td>
<td>with Receptor 2</td>
</tr>
<tr>
<td>with Receptor 3</td>
<td>with Receptor 4</td>
</tr>
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</table>

### Target identification on human samples

- Sample of human bladder Tumor (Sample from IUCT)

- Validation of antibody specificity
- Identification of the target on human samples coming from healthy patients
- Identification of the target on human tumor samples adapted to the target
- Set up of a protocol for an automated process (Ventana)
## Case study: Evaluation on ex-vivo explant

Research of biomarker on human non invasive bladder tumour (T1a-b)

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<tr>
<td>Institut Universitaire du Cancer (Toulouse)</td>
<td>Biomarker identification</td>
<td>FGFR</td>
<td>Clinical data</td>
<td>Biomarker identification</td>
</tr>
</tbody>
</table>

- Samples collected directly from the surgeon
- Dot blot with supernatants
- Formalin fixation for IHC
- Nitroxide freezing for WB
- Possibility to obtain patient urine sample

### Monobloc Exerese (~20–500mg)

- Washing and cultivation of tumour samples

### Protein expression on supernatant

- Dot plot

### pErk expression on tumor sample

- Western blot

### Protein expression on tumor sample

- Immunohistochemistry

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Potential to develop this approach on other easily accessible tumour samples (head & neck, skin or colorectal cancer …)
Case study: Approach targeting tumour micro environment

MoA targeting cells involved in tumor-promoting immunosuppression

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<tbody>
<tr>
<td>Internal project</td>
<td>Support to clinic – Proof on concept</td>
<td>VEGFR3</td>
<td>DC</td>
<td>Support PhI</td>
</tr>
</tbody>
</table>

- Integrated project involving Evotec *in vitro* biology, *in vivo* pharmacology, DMPK and chemical development platforms
- Collaboration with histopathology department of the Toulouse Oncopole for patient stratification
- In house development of *in vitro, in vivo* models and biomarkers to stratify patients, and follow compound efficacy
- Contract with clinicians to leverage translational biology and challenge clinical positioning

- Tumor cells expressing the target
- Tumor-promoting immunosuppression
- Angiogenesis
- Lymphangioiogenesis

1 Pre-clinical development candidate identified: promising efficacy and safety for 2 major indications with POC in relevant *in vivo* tumor models (SCC, HNSCLC), and access to human patients samples
Case study: Phenotypic approach for cell metabolism

MoA addressing OXPHOS tumours & targeted therapy resistance

- Integrated project involving Evotec HTS, in vitro biology, chemistry, in vivo pharmacology, DMPK and chemical development platforms
- Chemical optimisation from natural product (22 steps chemical synthesis, chiral purification, ADME issues)
- Deorphaning based on metabolomic approach (collaboration with an academic platform)
- In house development in vitro, in vivo models and biomarker to stratify patients, and follow compound efficacy
- Contract with clinicians to leverage translational biology and challenge clinical positioning

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<tbody>
<tr>
<td>Internal project</td>
<td>Target Validation to development candidate</td>
<td>MC1</td>
<td>Active metabolism modulator</td>
<td>Phi</td>
</tr>
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</table>

1 Preclinical development candidate identified with promising efficacy & safety for 2 major indications with POC in relevant in vivo orthotopic tumour models (NSCLC, DLBCL), and human patients samples
Why us?

Evotec – The right partner in oncology drug discovery

- A track record of success means that we consistently deliver on our clients’ needs
- State-of-the-art capabilities and scientific excellence will maximise your chances of success
- Fully integrated drug discovery platform and project management expertise will accelerate your drug discovery programme
- Evotec is a low-risk outsourcing partner who is continually investing in its platform to the benefit of the customer

Flexible commercial solutions:
multiple business models available to suit our partners