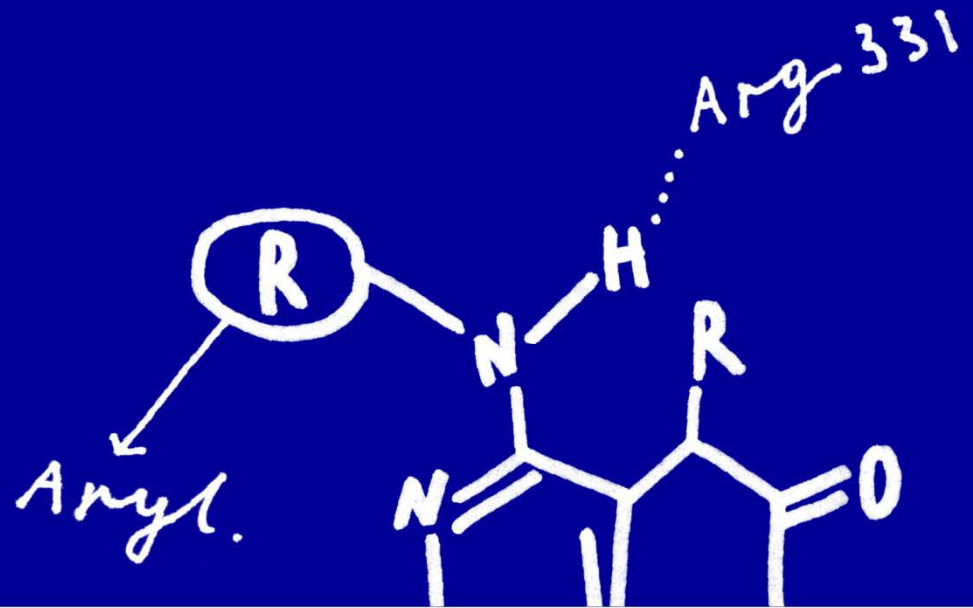


Oncology drug discovery at Evotec





Evotec, an ideal partner in oncology drug discovery

The different ways to work with us

On a specific target or programme

Access to Evotec drug discovery expertise & capabilities to support your programme

Starting from a phenotypic assay concept

Access to Evotec phenotypic screening expertise followed by target deconvolution leading into a drug discovery programme

On an existing Evotec programme

Sponsor an established theme such as epigenetics, cancer immunotherapy or cancer initiating cells

***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

1 Experienced Oncology Research team of **~100 FTEs**

2 Unique expertise in growth factor modulation, cancer metabolism, immuno-oncology and resistance to SoC ¹⁾ therapies

3 Multidisciplinary project teams working on over 12 active projects in the area of Cancer Metabolics, Immune evasion, Tumor suppressor biology and DNA damage repair

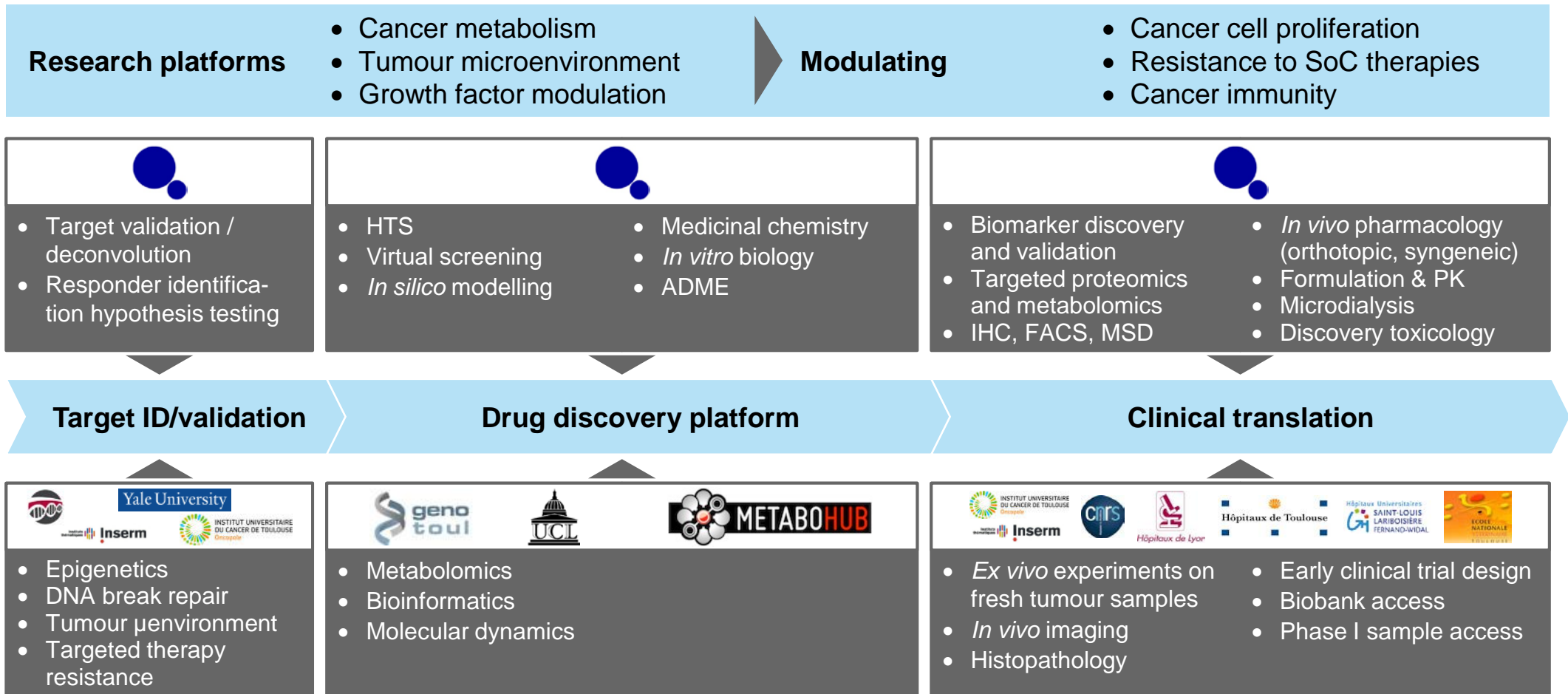
4 **Extensive portfolio of drug discovery capabilities:**

- 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

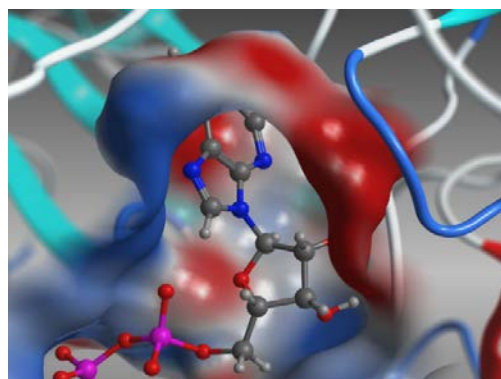
Supporting all activities from Target ID to clinical translation through a fully integrated platform

Evotec France (Toulouse) – Centre for integrated oncology research



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

1

Effective delivery of clients' objectives

Over 30 pre-clinical candidates nominated and 20 compounds approved for clinical trials across all therapeutic areas

2

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

Molecular Biology	Biochemistry	Cellular 2D models	Integrated 3D models	<i>Ex-vivo</i> analysis
<p>Cloning</p> <ul style="list-style-type: none"> • Plasmid construction • Ecotropic retroviral production (mouse) • transfection, transduction (plasmid, shRNA, siRNA) <p>Gene expression</p> <ul style="list-style-type: none"> • PCR, RT-qPCR, qPCR • TLDA <p>Analysis</p> <ul style="list-style-type: none"> • DNA (plasmid, genomic, mitochondrial) • mRNA 	<p>Enzymatic activity</p> <ul style="list-style-type: none"> • e.g. Kinase, protease and metabolic • Kinetic profiling • HTRF, FP, RF/MS etc. <p>Ligand/receptor binding</p> <p>Protein or peptide release</p> <p>Protein expression & signalling</p> <ul style="list-style-type: none"> • WB, BioDot, ELISA, cell-based ELISA, proteome array, MSD, • Immunoprecipitation <p>Second messenger</p> <ul style="list-style-type: none"> • Ca²⁺, cAMP 	<p>Incucyte Assays</p> <ul style="list-style-type: none"> • Proliferation • Apoptosis • Cytotoxicity <p>Migration/invasion</p> <p>High Content Assays and IF</p> <ul style="list-style-type: none"> • Localisation etc. <p>Flow Cytometry</p> <p>Bioassays</p> <ul style="list-style-type: none"> • RLU/RFU/abs <p>Metabolism</p> <ul style="list-style-type: none"> • SeaHorse • Oxphography • Hypoxia • Glycolytic/OXPHOS ATP • Metabolite consumption/production 	<p>Mimic hypoxia and substrate gradients in a 3D spheroid culture</p> <p>Characterization of spheroids</p> <ul style="list-style-type: none"> • Proliferation rate • Apoptosis • Protein expression (cytometry, WB) • mRNA patterns • Metabolic patterns (ATP, metabolites) • Gradient expression (IHC) <p>Evaluation of compound effects</p>	<p>Flow Cytometry</p> <ul style="list-style-type: none"> • 9 colour cytometry • Cell to platelet analysis • Cell sorter <p>Metabolism</p> <p>Validation with fresh patient tumour material</p> <ul style="list-style-type: none"> • Connection with translational group & clinics • Validate biomarkers and inhibitors developed <i>in vitro</i> on fresh patient samples

Providing a unique clinical translation for our partners

Tailored pharmacology and biomarker solutions

Animal welfare

- Trained veterinary staff
- State-of-the-art animal facilities, AAALAC accredited
 - 3,000 m² for animal husbandry, housing and experimentation
- Early toxicity assessments
- Rodent species focused

Biomarker discovery & target identification

- MS-based proteomics and metabolomics
- Target discovery and selectivity profiling
- Biomarker validation

In vivo pharmacology

- Skilled surgeons
- Development of bespoke models to understand
 - Tumour biology and new therapeutic mechanisms
 - PK/PD relationships
 - Efficacy / dose dependency
- *In vivo* models with high translational value

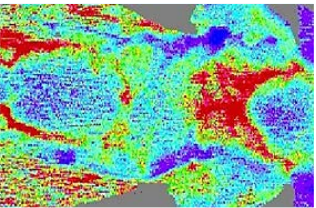

Clinical translation

- Processing of animal & human samples for *ex vivo* & biomarker analyses
- Established relationship with clinicians at the Toulouse Oncopole
- Target expression on human samples
- Prevalence determination as a function of pathology
- Assistance in the patient stratification process
- Proposal for Phase 1 clinical trial

Breakthrough scientific expertise & integrated teams to support translational biology activities

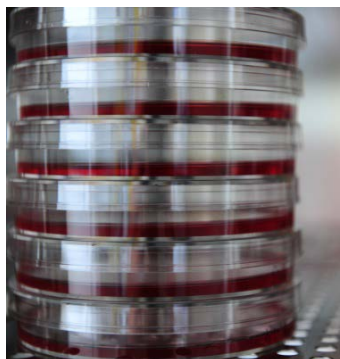
In vivo models exhibit high translational value

The right model for the right drug

Tumour models	Subcutaneous	Orthotopic	Transgenic animals	PDX models	<i>PDX(s) orthotopic</i>	
	<p>Tumour phenotype and tumour microenvironment modulations</p> <ul style="list-style-type: none"> • Syngeneic and xenograft models (immune response) • Subcutaneous and orthotopically localised (cross-talk with stroma cells) 					
<p>Bioanalysis and formulation</p>	<ul style="list-style-type: none"> • Plasma and tumour exposure after single or repeated doses administration • Formulation and administration route expertise (including aerosolized) 					
<p>Biomarker identification</p>	<ul style="list-style-type: none"> • Exploration of circulating (cells, proteins) and tumour parameters • Multi-level analysis of tumour modulation: genes, mRNA, proteins, metabolites 					
<p>Small animal imaging</p>	<p>Preclinical rodent imaging</p> <ul style="list-style-type: none"> • 2D/3D bioluminescence imaging • Laser Doppler blood flow analysis • X-ray radiography of bone and soft tissues • ¹⁸FDG PET/CT scan (in collaboration with IUC-T) 				<p>Clinical supply</p> <ul style="list-style-type: none"> • Patient biopsies • Imaging technologies • Translational biomarkers 	

Supporting oncology projects in epigenetics, immunotherapy, metabolics 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

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



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

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



Metabolomics

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

- Targeted analysis in cells, tissues, body fluids or *in vivo*

Oncology at Evotec, current and future areas of focus

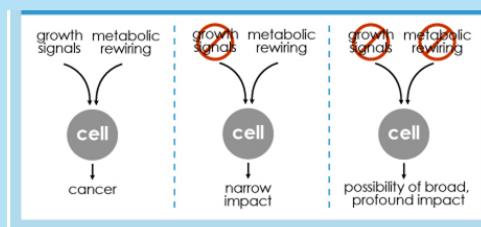
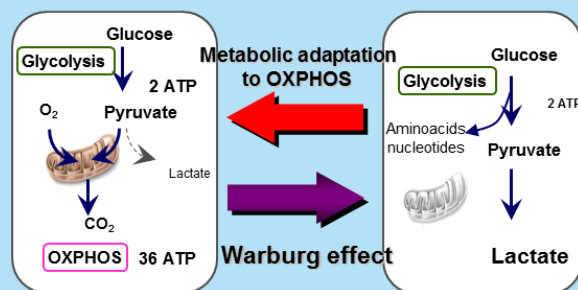
Evotec oncology themes

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

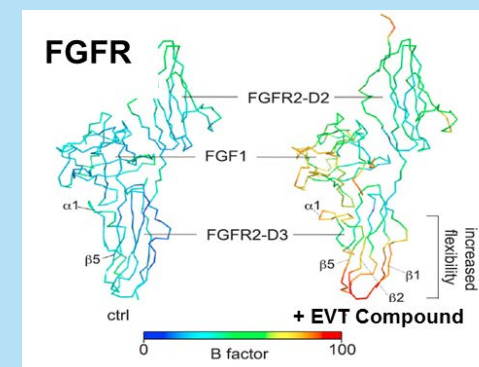
- Target metabolic adaptation mechanisms (phenotypic screening)



- 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)



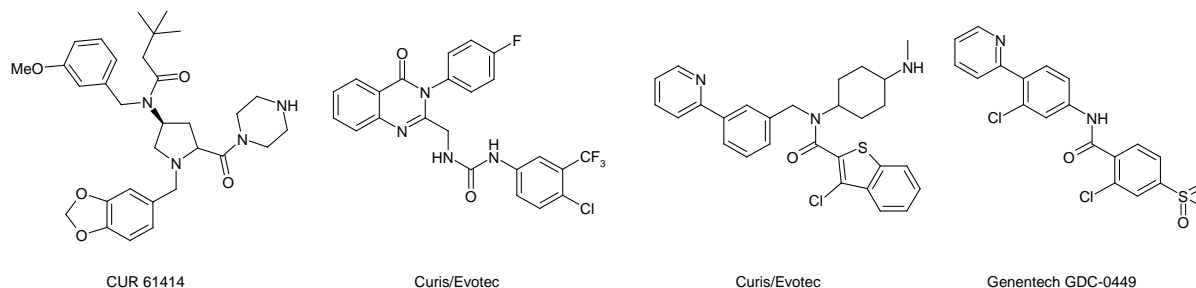
- For replacement of current targeted therapies (specific kinase inhibitors)

Case Study: Hedgehog signaling pathway inhibitors

Screen to development candidate by cellular assay

Partners	Programme	Target	Starting point	Outcome
	H2L & LO	Hedgehog Pathway	HCS Hit (EVT)	Clinical studies

- 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

Partners	Programme	Target	Starting point	Outcome
Institut Universitaire du Cancer (Toulouse)	Undisclosed	FGFR	<i>In vivo</i> validation	Biomarker

Validation of the antibody specificity

300-19 cells transfected

Negative control

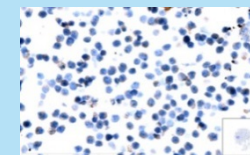
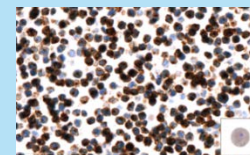
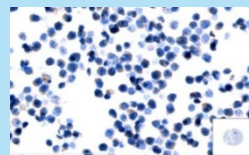
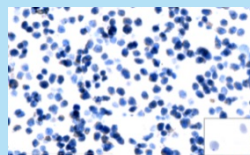
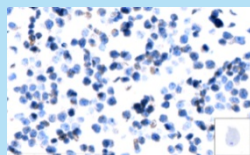
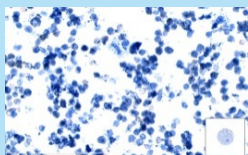
300-19 cells WT

with Receptor 1

with Receptor 2

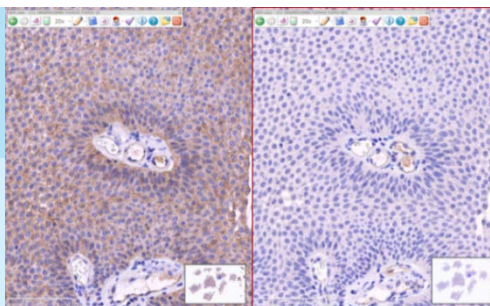
with Receptor 3

with Receptor 4



Target identification on human samples

Sample of human bladder Tumor (Sample from IUCT)

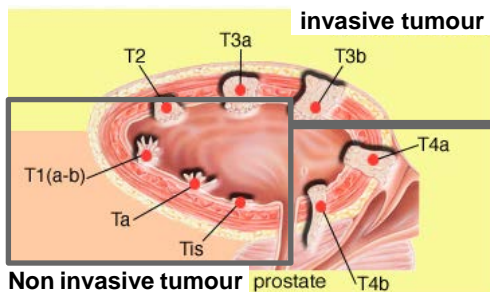


- Validation of antibody specificity
- Identification of the target on human samples coming from healthy patients
- Identification of the target on human tumor samples adapted to the target
- Set up of a protocol for an automated process (Ventana)

Case study: Evaluation on *ex-vivo* explant

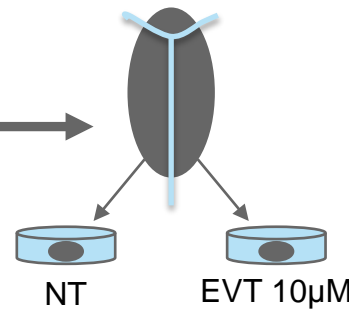
Research of biomarker on human non invasive bladder tumour (T1a-b)

Partners	Programme	Target	Starting point	Outcome
Institut Universitaire du Cancer (Toulouse)	Biomarker identification	FGFR	Clinical data	Biomarker identification



Monobloc Exeresse (~20–500mg)

Washing and cultivation of tumour samples



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

Protein expression on supernactant

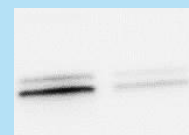
Dot plot



NT EVT

pErk expression on tumor sample

Western blot



NT EVT

Protein expression on tumor sample

Immunohistochemistry



Potential to develop this approach on other easily accessible tumour samples (head & neck, skin or colorectal cancer ...)

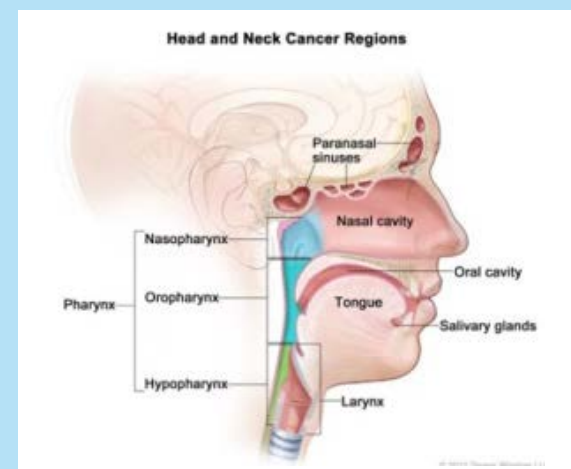
Case study: Approach targeting tumour micro environment

MoA targeting cells involved in tumor-promoting immunosuppression

Partners	Programme	Target	Starting point	Outcome
Internal project	Support to clinic – Proof on concept	VEGFR3	DC	Support PhI

- Integrated project involving Evotec *in vitro* biology, chemistry, *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
- Lymphangiogenesis

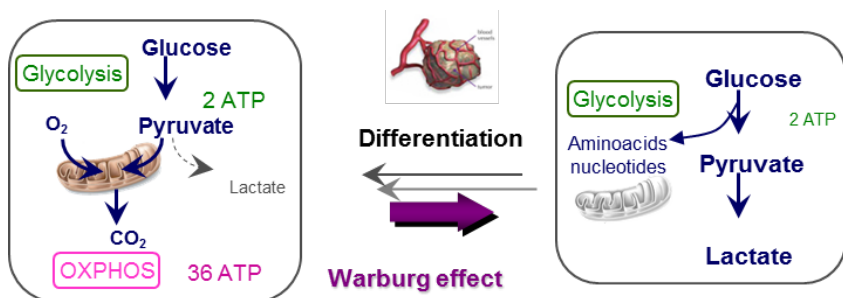


1 Pre-clinical development candidate identified: promising efficacy and safety for 2 major indications with POC in relevant *in vivo* tumor models (SCC, HNSCLC), and access to human patients samples

Case study: Phenotypic approach for cell metabolism

MoA addressing OXPHOS tumours & targeted therapy resistance

Partners	Programme	Target	Starting point	Outcome
Internal project	Target Validation to development candidate	MC1	Active metabolism modulator	PhI



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

- 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

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**

Your contact:

info@evotec.com

