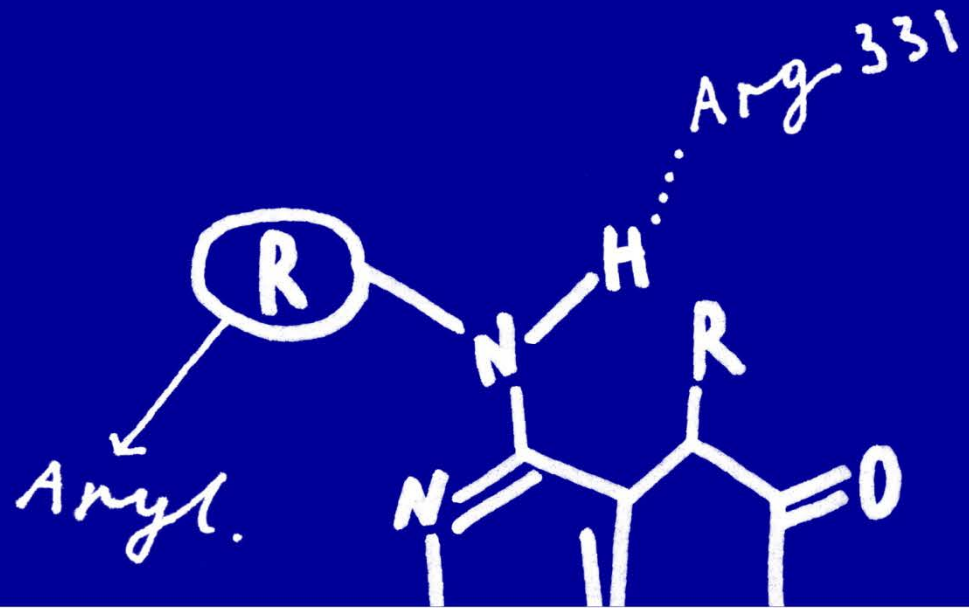


Immunology & Inflammation Drug Discovery at Evotec





Evotec, an ideal partner in Immunology & Inflammation drug discovery

The different ways to work with us

On your specific target or programme

Access to Evotec drug discovery expertise and 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 in the areas of immunology or inflammation

***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***

Integrated Immunology & Inflammation drug discovery platform to accelerate our partners' projects

Delivering excellence in Immunology & Inflammation research

1 Experienced Immunology & Inflammation team with **>30 FTEs**

2 10 active projects from target ID to PDC ¹⁾ in the area of autoimmune disorders, pain, endometriosis, inflammation and cancer immunotherapy

3 Expertise in many different target classes including enzymes, kinases, GPCRs, ion channels and PPI & Large tool kit of functional and translational assays using primary human lymphocytes or whole blood assays

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

- Phenotypic screening & target deconvolution
- Medicinal chemistry and structure-based drug design
- Hit finding & library screening
- *In vitro* & *in vivo* pharmacology
- Translational biology

Proven track record in Immunology & Inflammation drug discovery; Contribution to the discovery and development of multiple pre-clinical and clinical candidates

In depth expertise across all phases of Immunology and Inflammation drug discovery

Pipeline overview – Partnered projects

Molecule(s)	Indication (mechanism)	Partner	Status	Next milestone	Commercials
EVT401	Inflammation (P2X7 inhibitor)	 康恩贝集团 CONBA GROUP	Phase I/II	Phase II start	Up to € 60 m milestones, royalties
Various	Endometriosis	 BAYER	Pre-clinical	Pre-clinical candidate	€ 12 m upfront, up to approx. € 580 m milestones, royalties
Various	Various	 Boehringer Ingelheim	Pre-clinical	Phase I start	Undisclosed upfront, research payments, milestones, royalties
Not disclosed	Various	 NOVARTIS	Pre-clinical	Successful PoC ¹⁾	Research payments, milestones, royalties
Various	Inflammation	 ucb	Discovery	Pre-clinical	Research payments, up to € 183 m milestones/product, significant royalties
Not disclosed	Inflammatory pain	 Convergence PHARMACEUTICALS	Discovery	Pre-clinical	Milestones, significant royalties
Not disclosed	Cancer immunotherapy	 APEIRON BIOLOGICS  SANOFI	Discovery	Pre-clinical	Research payments, up to € 200 m milestones/product, significant royalties

Experience with key target classes and mechanisms

In vitro biology: validated assays for screening

1

**High quality screening libraries: HTS 400K
Fragments: 21K**

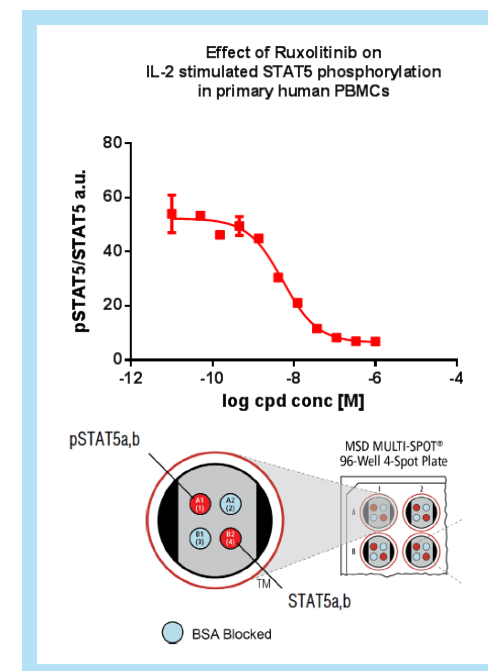
2

Extensive portfolio of biochemical and biophysical assay systems

3

State-of-the-art cellular assay systems with high content readouts

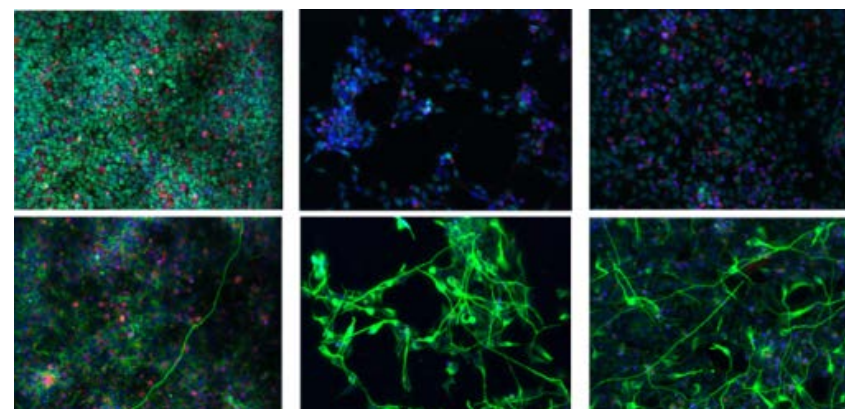
Target class	Indication	Biology contribution
Ion channels	Immunomodulation	HTS: membrane potential, YOPRO, calcium flux Automated & manual patch clamp Translational assays, animal models
Kinases	RA, SLE, asthma, sepsis	Biochemical FP/FRET, Cellular: MSD Translational assays: MSD, phenotypic, high content
Transporter	Anaemia in chronic inflammation	Phenotypic screen + SAR Translational assays Animal models
Cytokine PPI	RA, SLE	Biochemical FP/FRET Biophysical SPR, NMR, thermal shift Cellular reporter assay, translational assay
GPCRs	Pain & inflammation IBD	Cellular assay: HTS, H2L, moa Translational: migration assay, animal models
Enzyme	Neuroinflammation	Biochemical LC/MS LC/MS + primary μ Glia



State-of-the art platform to explore disease relevant phenotypes

Phenotypic assays & High content screening

- Access complex cellular environments (co-cultures) that mimic the pathophysiological state
- Utilise primary cells and tissue including stem cells to achieve tissue specific cellular models
- >Ten years of expertise in the development of the OPERA flows into Evotec's HCS drug discovery platform
- Assay platform routinely used to support both HTS & H2L/LO programs for established & orphan receptors
- Multifactorial data analysis integrated into SAR analysis delivering more informative data at earlier stages
- Integrated into Evotec's MS-based proteomic platform to aid target identification



Excellence in primary & stem cells science for hit identification and translational assays

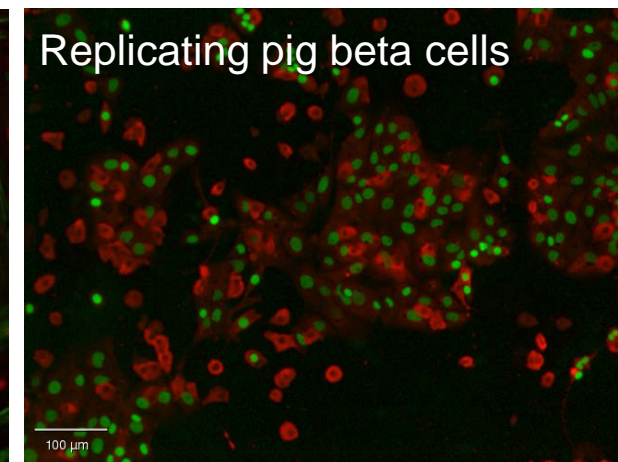
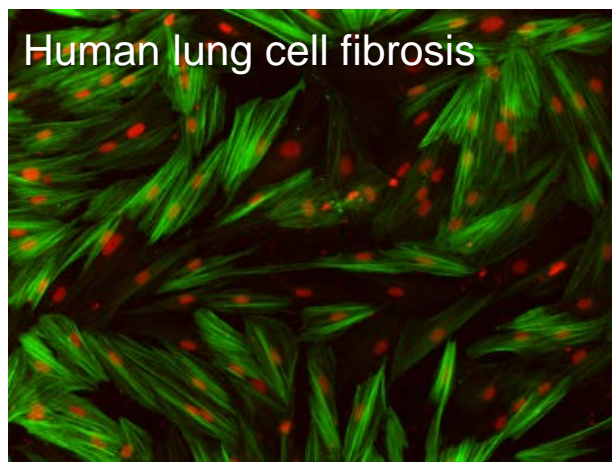
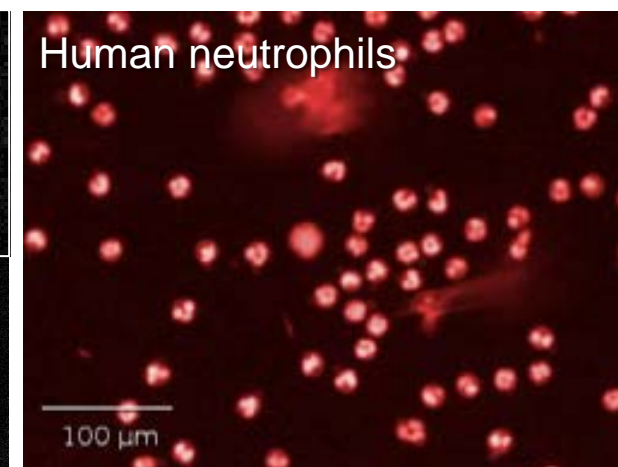
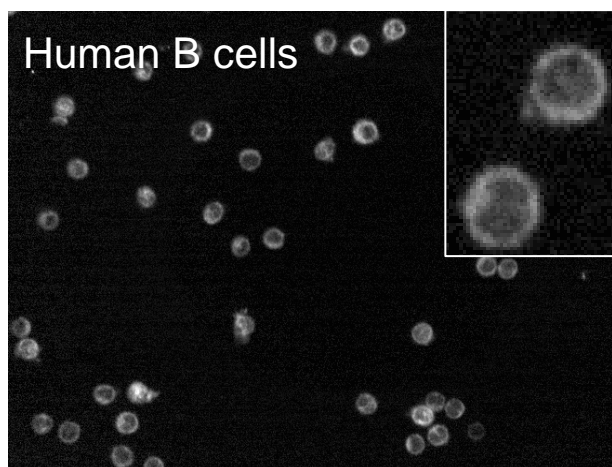
HCS as core technology

Isolation, cultivation and manipulation of primary cells:

- **Brain/PNS:** neurons (CNS, DRGs, motoneurons), astrocytes, microglia including co-cultures
- **Blood:** PBMCs, T_H1/T_H2 populations, B cells, neutrophils, spleenocytes, monocytes, macrophages, whole blood assays
- **Pancreas:** islets, beta cells
- **Kidney:** podocytes, fibroblasts
- **Stem cells:** murine, human, iPS

Assay read-outs:

- Cell density, degeneration, regeneration, survival
- Cytokine secretion
- Transcriptional activity
- Protein phosphorylation



World-class ion channel electrophysiology to successfully drive H2L, LO and safety pharmacology projects

Ion channel drug discovery platform



- Ion channel biology team: 15 FTEs with industrial drug discovery background such as GSK, Roche, Merck, GENION, Millipore
- High-throughput fluorescence-based and IonWorks® Quattro assays for hit identification campaigns
- Multiple automated and manual patch clamp systems offer maximal assay development and throughput options
- Track record of success with multiple ion channel classes: voltage-gated (K, Ca, Na), ligand-gated (P2X, Glu, Trp) and others
- In-depth expertise in ion channel disease biology, medicinal chemistry, pharmacology and drug discovery
 - Successfully prosecuted numerous H2L and LO programmes

Strong expertise in Immunology and Inflammation targets

Synthesis & medicinal chemistry



- Medicinal chemistry expertise for many inflammation and immunology targets e.g. ion channel, Kinase, GPCR, PPI, etc.
 - Rapid synthetic execution & ability to address difficult chemistry
- Outstanding computational chemistry and structural biology
- Strong expertise in SBDD of kinase inhibitors and optimisation of phenotypic screening hits
- Largest chemistry group in the UK (>150 synthetic, medicinal and computational chemists), >35% of our scientists have >8 years experience at major pharmaceutical and biotech companies prior to joining Evotec



1

Delivers on clients' needs with over 30 pre-clinical candidates nominated and 20 compounds approved for clinical trials

2

Adds value as demonstrated by Evotec medicinal chemists being named inventors on >200 client patents covering all major target and therapeutic areas

A mix of *in vivo* proprietary assets and validated assays in Immunology & Inflammation

In vivo pharmacology

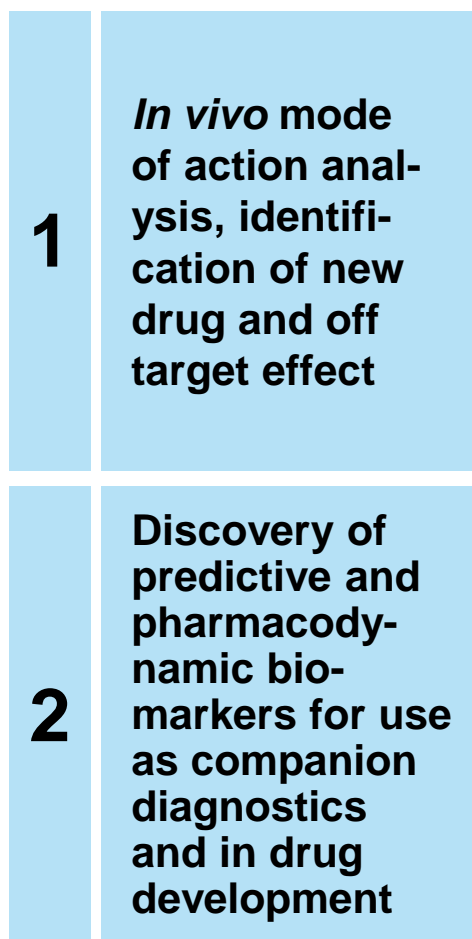
<p><i>In vitro</i> ADME <i>In vivo</i> PK</p>	<ul style="list-style-type: none"> • A comprehensive portfolio of <i>in vitro</i> ADMET assays • Distribution in tissues and fluids • Bioavailability study (p.o., s.c., i.v., i.m.; i.p.; intra cerebrospinal) • Bioanalytics (WinNonlin®)
<p>Pharmacodynamic assays – PK/PD</p>	<ul style="list-style-type: none"> • IL-1β/desArg9 Bradykinin paw oedema, • α,β-me-ATP flinching, • (R)-α-methylhistamine induced dipsogenia, • Anti-CD3 induced T-cell activation
<p>Animal (disease) models</p>	<ul style="list-style-type: none"> • Pain/Inflammation: Visceral pain (Colorectal distension), Collagen Antibody-Induced Arthritis; Inflammation induced by Peptidoglycan-Polysaccharid & Complete Freund`s Adjuvants • Neuroinflammation / Huntington: Q175 (mouse); BACHD (mouse and rat) • Anemia: Peptidoglycan-Polysaccharide-induced Anemia, Adenine-kidney insufficiency
<p>Preclinical imaging</p>	<ul style="list-style-type: none"> • High content histology including automated image analysis

Unbiased and comprehensive analysis by high-end proteomics

Phosphoproteomics, biomarker discovery & Mode-of-Action studies



- Quantitative unbiased analysis of protein modification & expression on a proteome-wide scale
 - Identification & quantification of 10,000+ phosphorylation sites, 1,000+ acetylation sites or 6,000+ proteins, e.g. upon drug treatment
- High-end quantitative mass spectrometry for comprehensive analysis in cultured cells, animal models and patient samples
- Expertise in autoimmune disease targets
 - Comprehensive investigation of signaling pathways and their response to drugs
 - Elucidation of off-target effect
 - Identification of pharmacodynamic read-outs and (comparative) mode of action analysis of kinase-selective drugs



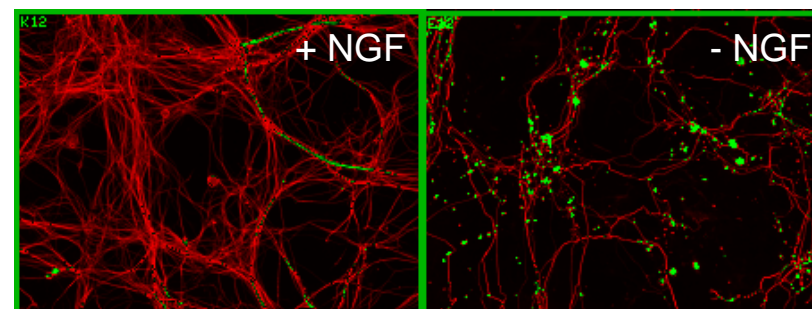
Case study: Integrated Multi-project collaboration

HTS to candidate

Partners	Programme	Therapeutic area	Starting point	Recent milestone
Major US biotech	Hit finding to candidate	Autoimmune disorders, CNS/PNS	Assays & hits	Approval for FIM study

- 15 FTEs, flexible allocation
- Supporting integrated drug discovery projects with *in vitro* profiling: potency, selectivity, mechanism, *ex vivo* assays
- Targets/indication:
 - Kinase: SLE
 - Kinase: asthma
 - Ion channel: psychiatric
 - Ion channel: pain
 - Kinase: ALS, neurodegeneration
- Activities:
 - Routine compound profiling
 - High-content screening
 - Electrophysiology
 - Stem cell research
 - Proteomics
 - Structural biology
 - Cytotox profiling
 - Assay development

Neuroprotection assay in rat DRGs: translational cellular assay



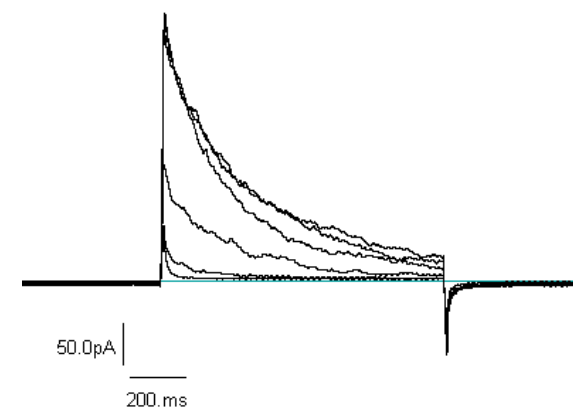
Case study: Kv1.3 antagonists identification & development

Hit ID and follow up

Partners	Programme	Therapeutic area	Starting point	Outcome
Not disclosed	HTS – H2L	AID, target Kv1.3	Assay development	Lead candidates


- Hits identified by HTS cell based assay using a membrane potential sensitive dye
- Screening of ~1 Mio compounds
- Kv1.3 selectivity assays (Kv1.1, Kv1.2, Kv1.4, Kv1.5, hERG)
- Automated electrophysiology for routine SAR generation on hKv1.3, rKv1.3
- *In vitro* Ephys assay, Kv1.3
 - KV1.3 CHO cell line Primary human T-cells
- *In vitro* functional assays
 - Cytokine production in relevant primary human T cell subpopulations

Human primary T lymphocytes (CD4+ labeled): MgTX titration



Case study: TargetImmuniT partnership with Sanofi and Apeiron

HTS to Candidate in cancer immunotherapy

Partners	Programme	Target	Starting point	Outcome
	HTS – LO	Phenotypic	Assay development	Advanced lead

- Collaboration with Apeiron and Sanofi on phenotypic campaign for cancer immunotherapy
- Optimization of chemical series, DMPK, *in vitro* pharmacology, *in vitro* phenotyping
- Target deconvolution, RNA seek ongoing
- PD models

NEWS RELEASE

10 August 2015


info@evotec.com | www.evotec.com

Evotec, Apeiron Biologics and Sanofi jointly develop novel small molecule-based cancer immunotherapies

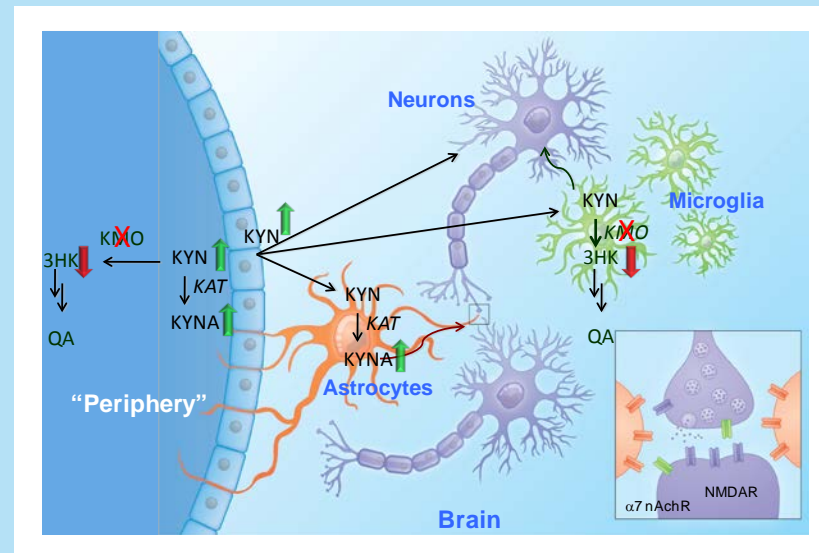
Hamburg, Germany – 10 August 2015: Evotec AG (Frankfurt Stock Exchange: EVT, TecDAX, ISIN: DE0005664809) and Apeiron Biologics AG, a biotech company with a focus on immunological approaches to treat cancer, today announced a strategic collaboration with Sanofi to develop novel small molecule-based cancer immunotherapies.

Case study: Neuroinflammation; KMO inhibitors

Huntington's disease

Partners	Evotec contribut.	Target	Starting point	Outcome
	<i>In vitro</i> , MedChem, DMPK	Kynurenine mono-oxygenase (KMO)	Assay development, HTS, rational design	1 pre-clinical candidate selected, back-up activities ongoing

- Novel, highly potent & selective inhibitor series and profiled using biochemical and cellular assays, addressing not only specificity and selectivity of the compounds but also mode of action studies using endogenous expression systems
- Development of a brain penetrant back-up series ongoing
- 2 articles published ¹⁾, 1 submitted and numerous patents filed
- Multi-FTE program of ~15 FTEs with flexible allocations



Why us?

Evotec – The right partner in Immunology & Inflammation 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

