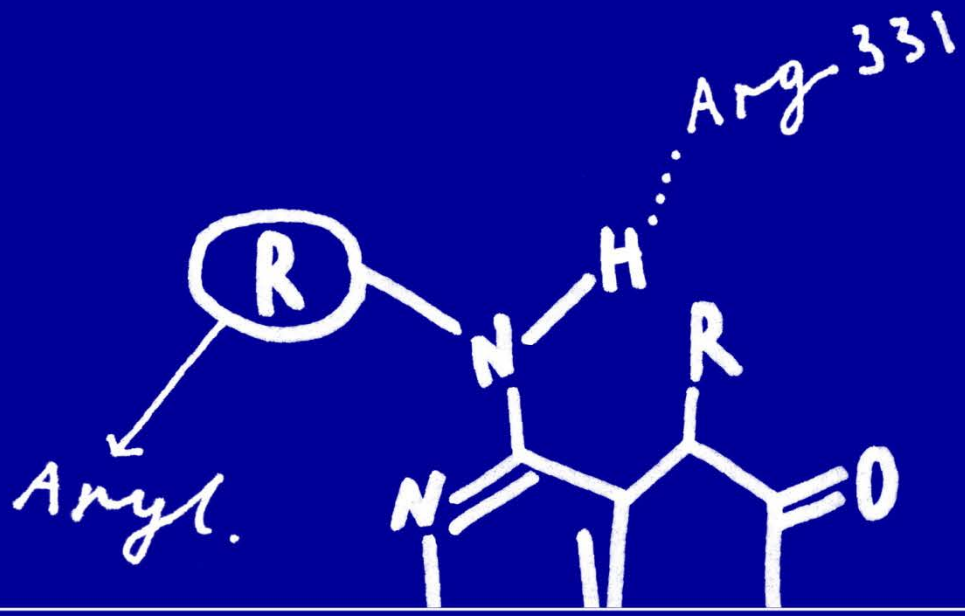
evotec

'RESEARCH NEVER STOPS'

Neuroscience drug discovery at Evotec



Evotec, an ideal partner in neuroscience drug discovery

The different ways to work with us

On a specific target or programme	**Starting from a phenotypic assay concept**	**On an existing Evotec programme**
Access to Evotec drug discovery expertise and capabilities to support your programme	Access to Evotec phenotypic screening expertise followed by target deconvolution leading into a drug discovery programme	Sponsor an established theme in the areas of ALS or neurodegeneration

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

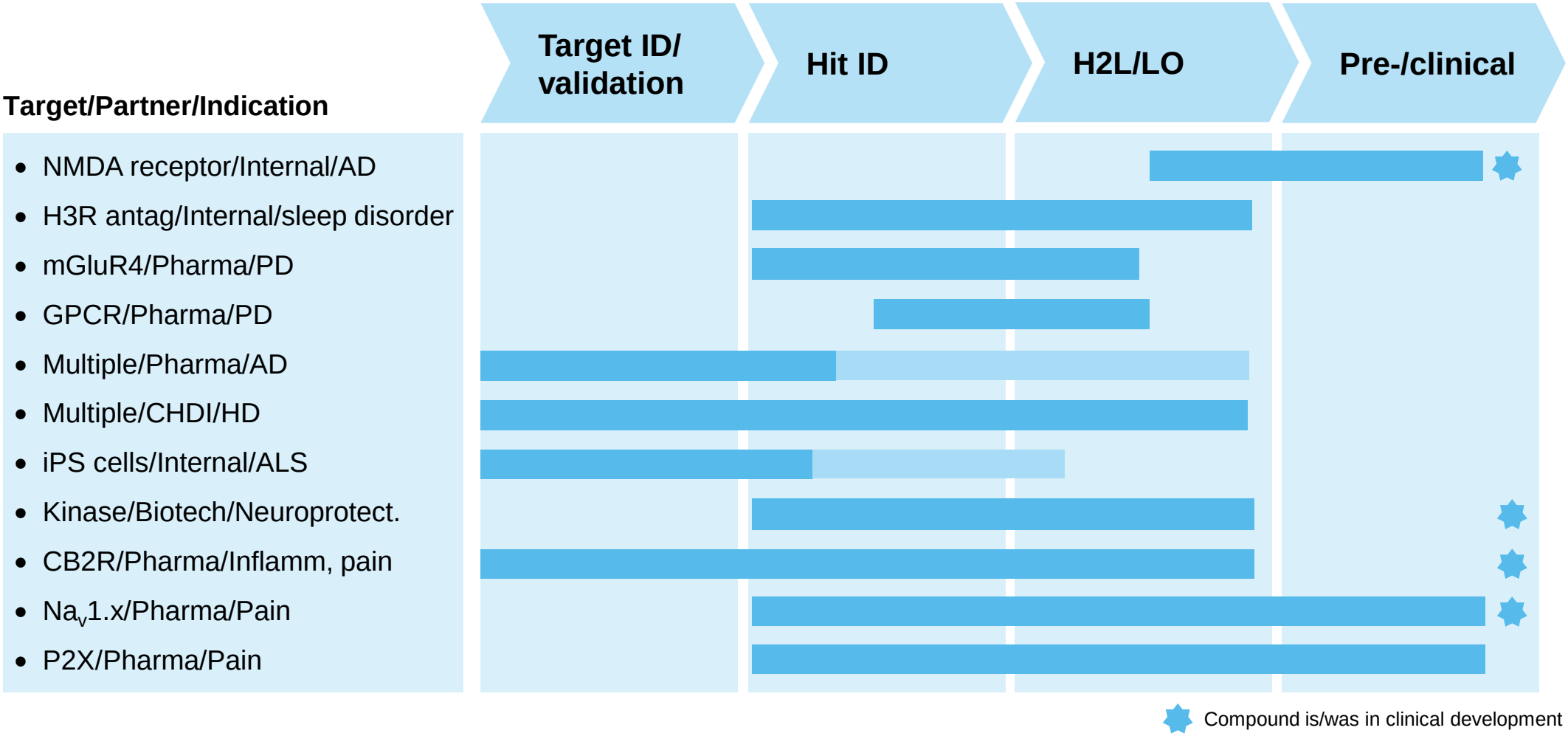
Evotec neuroscience platform state-of-the art capabilities & 20 years expertise

1	Dedicated Neuroscience drug discovery team with **>60 FTEs**
2	Experience and know-how in pursuing phenotypic/pathway paradigms to identify, validate and prosecute **disease-modifying approaches** *e.g.* AD, ALS, HD
3	Innovative technologies such as neuronal differentiation and disease modelling from human iPS cells, phenotypic screening and cellular high-content assays, AAV-based target validation and high-throughput histology
4	**Extensive portfolio of drug discovery capabilities:** • Medicinal chemistry and structure-based drug design • Target identification and validation • High Content Screening • *In vitro* biology, including world class ion channel platform • *In vivo* pharmacology • Translational biomarker assays

Proven track record in Neuroscience discovery with contri-bution to 19 candidates (including back-ups); 11 mechanisms and 9 com-pounds evaluated in humans

In-depth expertise across all phases of Neuroscience research

Overview on Evotec's past and present project success in Neuroscience



Experience with key target classes and mechanisms

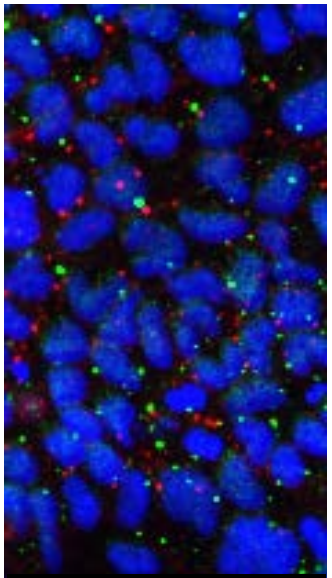
In vitro biology

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

2	Extensive portfolio of bio-chemical and biophysical assay systems

3	Disease-relevant cellular assay systems with high-content & other read-outs

	Targets
Sleep disorders	H3 receptor, Orexin 1&2, GABA-A
Psychatric/epilepsy	mGluR, dopamine receptor, NaV, KCNQ, CB2, KCNQ
Amino acid metabolism	KMO, serine racemase
Excitotoxicity	NMDA receptor, mGluR, DAAO
Neuroinflammation	P2X, KMO
Neurodegeneration	BACE, Neu, protein aggregation, HDAC, NRF2, SLC7A11, Asc-1
Cellular models	Primary neurons, microglia, astrocytes and co-cultures, stem cells
Readouts	Neuroprotection, spine morphology, synaptic density and function (electrophysiology & others)



Synaptophysin / PSD95

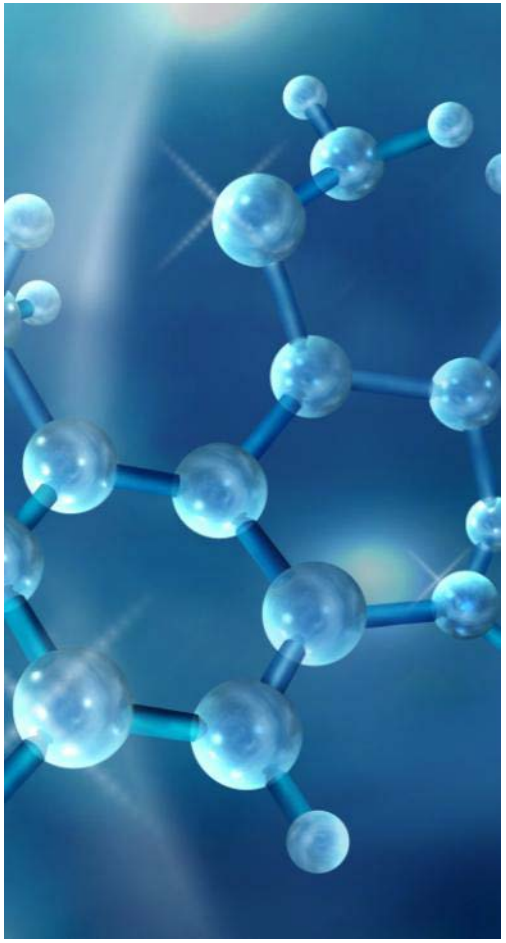
A mix of *in vivo* proprietary assets & validated assays

In vivo pharmacology

Pharmacodynamic assays – PK/PD	• IL-1β/desArg9 Bradykinin paw oedema, α,β-me-ATP flinching, (R)-α-methylhistamine induced dipsogenia
Animal (disease) models	• **Pain/Inflammation:** Spinal Nerve Ligation, Visceral pain, Collagen Antibody-Induced Arthritis; Inflammation induced by Peptidoglycan-Polysaccharid & Complete Freund's Adjuvants • **Huntington:** Q175 (mouse); BACHD (mouse and rat) • **Anemia:** Peptidoglycan-Polysaccharide-induced Anemia, Adenine-kidney insufficiency
Behavioural and side effect profiling	• Motor (Locomotor Activity, rotarod), Emotion (Elevated Zero Maze, fear conditioning), Cognition (Novel Object Recognition, spatial memory), Irwin test
Translational approaches	• Pre-pulse inhibition, Gait analysis, Novel Object Recognition, Visceral pain (ColoRectal Distension; CRD) model

Providing best-quality leads and development candidates

Medicinal Chemistry



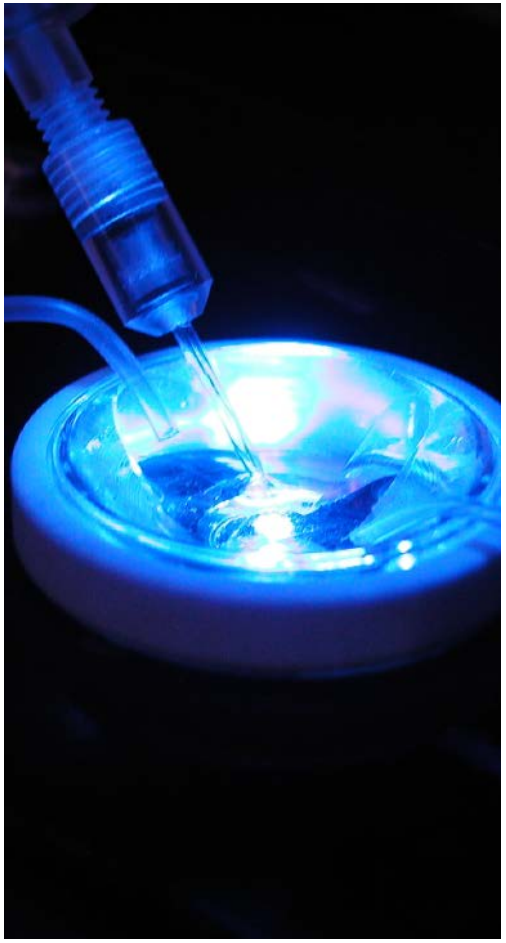
- Experienced drug hunters who understand the quality requirements of the development process and the major sources of attrition
- Expertise and success in all major target classes using both structure-based and ligand-based design
- Rapid synthetic execution & ability to address difficult chemistry
- Critical mass – the largest single chemistry department in the UK
- Expert understanding in the areas of data integrity, IP and patents
- Major contributors to >30 pre-clinical candidates and >20 compounds approved for clinical trials

Critical success factors

- Experienced personnel
- Project strategy, management and communication
- Analysis and design that address activity and properties
- Problem solving & ability to address difficult chemistry
- Short test-analyse cycles
- Experience of risk and attrition
- A track record of success

Electrophysiology and pharmacology expertise with most ion channel families

World-class platform for ion channel drug discovery

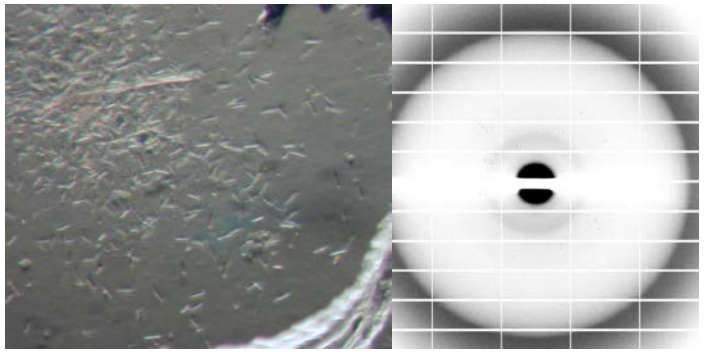


- Ion channel biology team: 15 FTEs with industrial drug discovery background such as GSK, Roche, Merck, GENION, Millipore
- Electrophysiology & Pharmacology expertise with
  - Transiently & stably expressing cell lines or cells from primary tissues (e.g. DRGs)
  - Ion channels from different families (voltage- and ligand-gated or K^+, Na^+, Ca^{2+}, Cl^-)
- Ion channel technology and screening expertise with automated and manual patch-clamp
  - IonWorks® Quattro™, PatchLiner©, QpatchHTX® , Qube®
  - Manual patch-clamp: Fast perfusion (Dynaflow®), Temperature control
- Project management in drug development programmes from Screen to PDC

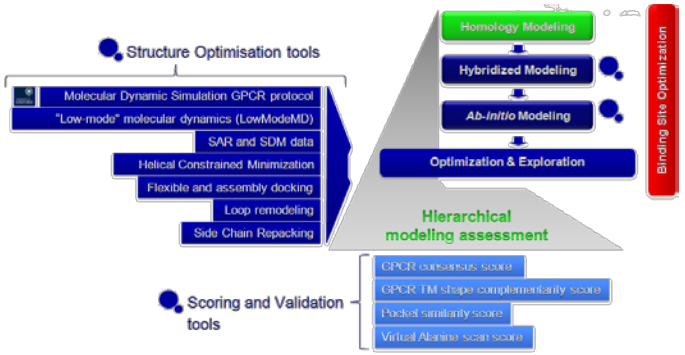
Access wide expertise in the GPCR arena

>15 years experience in GPCR pharmacology

- Expertise with Class A,B and C GPCRs
  - Access expertise in Hit ID through to LO
  - All assay platforms utilised to address around endogenous coupling
  - Receptor occupancy determination
  - Access pathway profiling/ Biased molecules
- Structural biology
  - Confirmed several published structures in house
  - Currently developing de-novo structures within client collaborations
- Cutting-edge GPCR Modelling expertise
  - Homology modelling successfully used to drive compound design
- Several HTS PAM screens run in last 5 years
  - Multiple assay formats to identify PAM activity and drive SAR

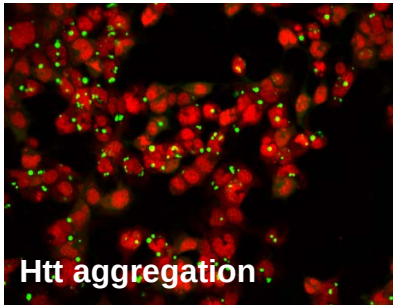


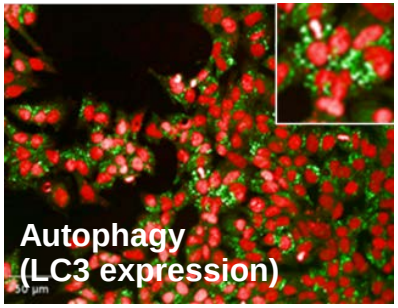
GPCR crystals in LCP

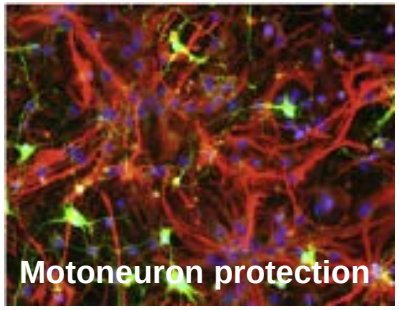


Combining complex disease-relevant cellular models and read-outs

High-content screening as enabling technology







Use imaging to access complex read-outs

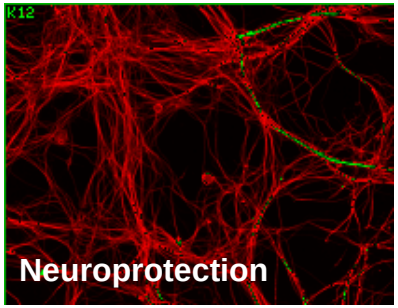
- Subcellular events: protein aggregation and localization, post-translational modification, protein levels, others
- Cell morphology: neurite outgrowth, synapse formation, spine morphology
- Cell survival: Apoptosis, ER stress, mitochondria function
- siRNA screening

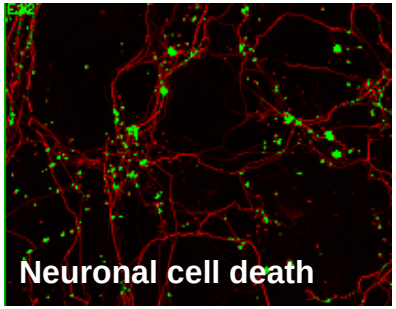
Utilise complex cellular models to mimic disease biology

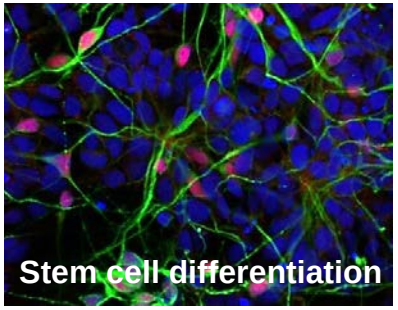
- Co-cultures: neurons & glia
- iPS/ES derived neuron populations

Combined with experience in primary cell culture

- DRG, neuronal and microglia, slice cultures







Accessing the complete stem cell-based value chain for neuroscience research

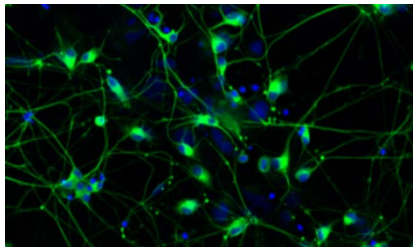
Drug discovery with stem cells at Evotec

Stem cell culture

- Experience with rodent and human stem cells
- Access to iPSC lines (wt, patient-derived)
- Expansion and banking of iPS cell lines
- Scale up of iPSC culture

In vitro differentiation

- Stem cell-derived disease-specific cell types i.e. cortical neurons, motor neurons
- Assay development and scale up for phenotypic screening

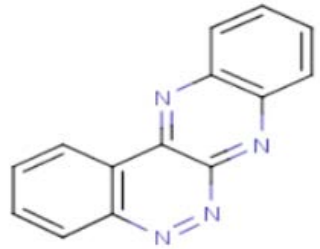


Hit identification

- High-content screen
  a) Cell morphology
  b) Disease-specific alterations
- Known drugs/ annotated or diverse libraries

H2L/LO

- Phenotypic assays
- Mechanism of action
- Electrophysiology
- Expression profil.
- Neuroprotection/ neurotoxicity



Discovery of molecular markers to advance target validation & efficacy studies

High-throughput histology: *ex vivo* experiments

AAV platform

- *In vivo* target modulation
- Focal and reproducible application of rAAVs to the desired brain regions
- Fast and long lasting manipulation of target abundance and function

High-throughput imaging platform

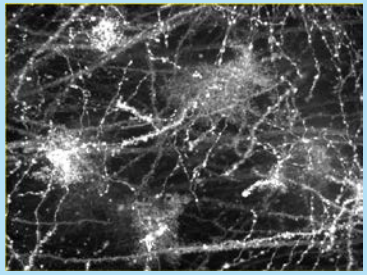
- Portfolio of validated antibodies and staining protocols
- Highly flexible and sophisticated imaging platform with expert image analysis process
- Semi-automated process

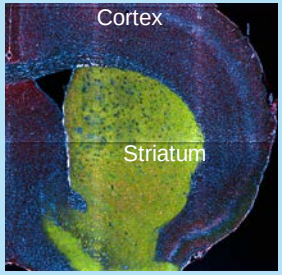
Target validation & efficacy studies

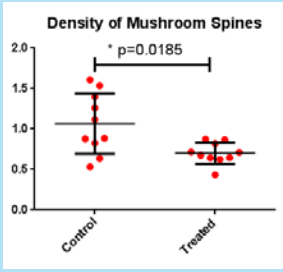
- Target modulation through AAV or small molecules
- Quantification of disease-relevant PD/biomarkers in disease models
- Correlation of *in vitro* and *in vivo* phenotypes

Disease relevant read-outs

- Cell types and morphology
- Synapse density
- Dendritic spines
- Intracellular markers: signalling, protein aggregation
- Secreted proteins





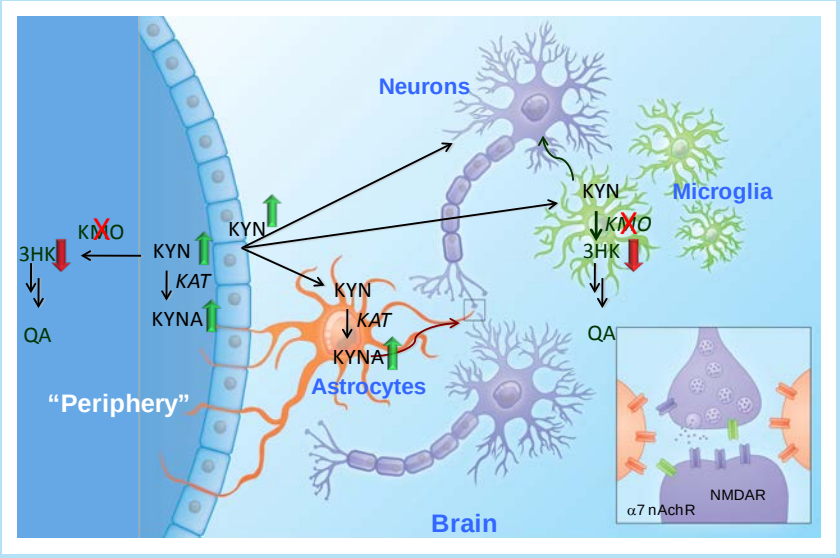


Case study: Multiple approaches targeting Huntington's Disease

Integrated drug discovery projects for multi CNS targets

Partners	Evotec contribut.	Target	Starting Point	Outcome
Huntington Disease Foundation	Biology, chemistry, DMPK, SBDD	Incl. KMO, TG2, Caspases, HDACs	HTS, rational design	Candidate selection (KMO)

- CHDI is a non-profit organisation pursuing biotech approach to rapidly discover and develop drugs that prevent or slow HD
- Multiple challenging targets progressed over a number of years
- Significant resource exploring target validation and systems biology approaches
- Kynurenine mono-oxygenase (KMO) most advanced project
  - Kyn pathway implicated in mechanism of neural cell loss
  - Novel, highly potent & selective inhibitor series identified by rational design
  - Lead compound currently in pre-clinical development

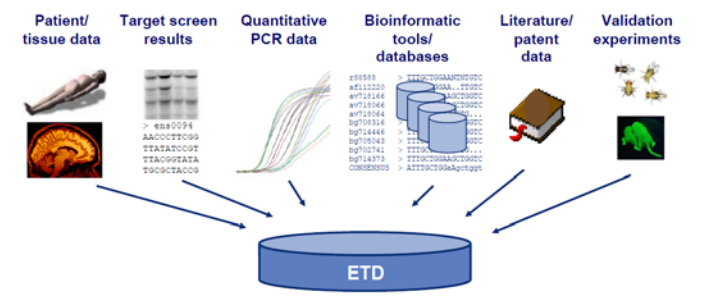


Case study: Identification of novel mechanisms in AD

From patient tissue to target validation

Partners	Programme	Target	Starting point	Outcome
janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson	Target validation & lead discovery	Various	Differentially regulated genes in human brain	Lead compounds

- The ETD [1)] consists of nearly 400 target candidates
  - Different validation state of distinct target candidates
- Valuable asset for driving early stage, innovative AD research but largely under-exploited for drug discovery



- Technical and scientific know-how to execute target ID campaign using patient tissue
- Neuroscience expertise to build relevant hypothesis combined with high-end technologies for target validation
- Drug discovery engine

1) Evotec Targets Database

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

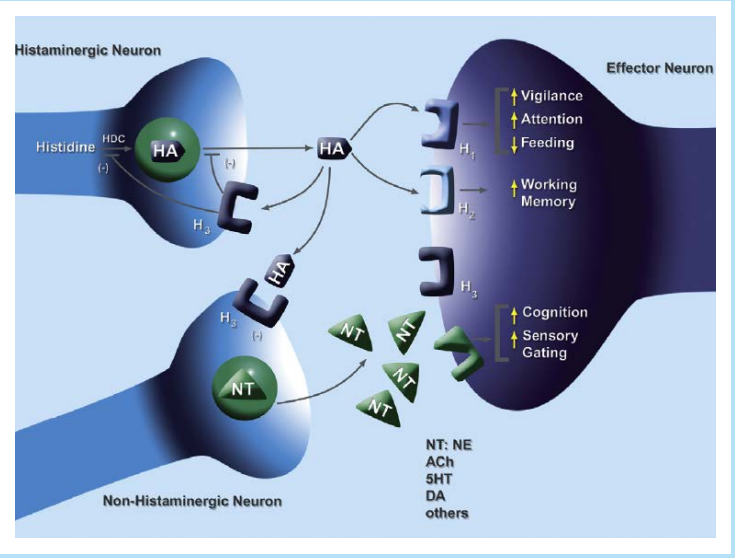
evotec

Case study: Histamine H3 antagonist development

From Hit identification to preclinical development

Partners	Programme	Target	Starting point	Outcome
n/a	Hit identification and optimisation	H3	HTS	PDC; IND-enabling studies ongoing

- 2.5 years from inception of programme to PDC
- Evotec carried out HTS, FBS and VS for hit identification as well as all activities in hit-to-candidate phase
- Several Early DCs identified across multiple chemical series
  - Clean profile demonstrated through extensive *in vitro* profiling
  - Appropriate PK in multiple species
- Evotec compounds have demonstrated robust *in vivo* activity
  - Cognition, wakefulness (EEG), neurotransmitter release
  - Clear PK/PD relationship
- Up to € 1.5 m BMBF research funding to advance the programme up to and through Phase I clinical studies
- **Current Status: IND-track PDC**



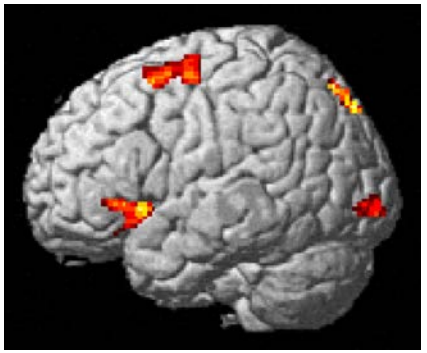
Case study: NR2B-selective NMDA antagonists

From lead optimisation to clinic

Partners	Programme	Target	Starting point	Outcome
janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson	Lead-to-clinic	Ion channel	Lead optimisation	2 molecules in the clinic – Clinical development ongoing

- Programme in-licensed from Janssen while molecules in lead optimisation
- Target validated in TRD, pain & Alzheimer's by non-selective antagonists, but these produce side effects due to blockade of all receptor subtypes
- NR2B-selective antagonists avoid side effects and provide potential for better efficacy through wider therapeutic window
  - Identification of orally active NR2B-selective antagonists suitable for clinical development has proved extremely challenging
- Evotec's most advance molecule has now progressed into Phase II (TRD)
  - Follow-on molecule has successfully completed Phase I

Rendered image of increase in activation of the retrieval network following 15mg EVT101



Why us?

Evotec – The right partner in neuroscience 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 man-agement 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

evotec

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