evotec

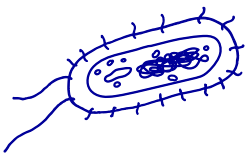
#RESEARCHNEVERSTOPS

Anti-Infective Drug Discovery & Development

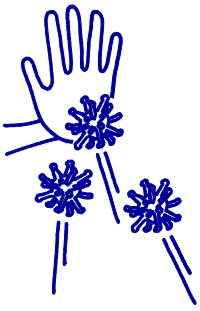
- More than 200 high calibre scientists supporting the Global Infectious Disease platform
- State-of-the-art, multimodality anti-infective discovery platform and world-leading expertise
- Efficient integration of knowledge, innovation and dedicated platforms – all under one roof
- Deep understanding of financing landscape for anti-infective discovery and development
- Proven track record in supporting a broad range of projects from HTS and discovery biology through to fully integrated drug discovery
- Seamless transition from Drug Discovery to IND: INDiGO, the fastest, most efficient and proven platform to select, de-risk and speed your drug through IND and beyond

Areas of expertise

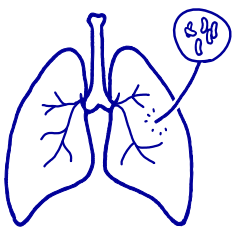
Anti-microbial resistance (AMR)



Viral Infections



Global Health
TB / Malaria



Contact our experts

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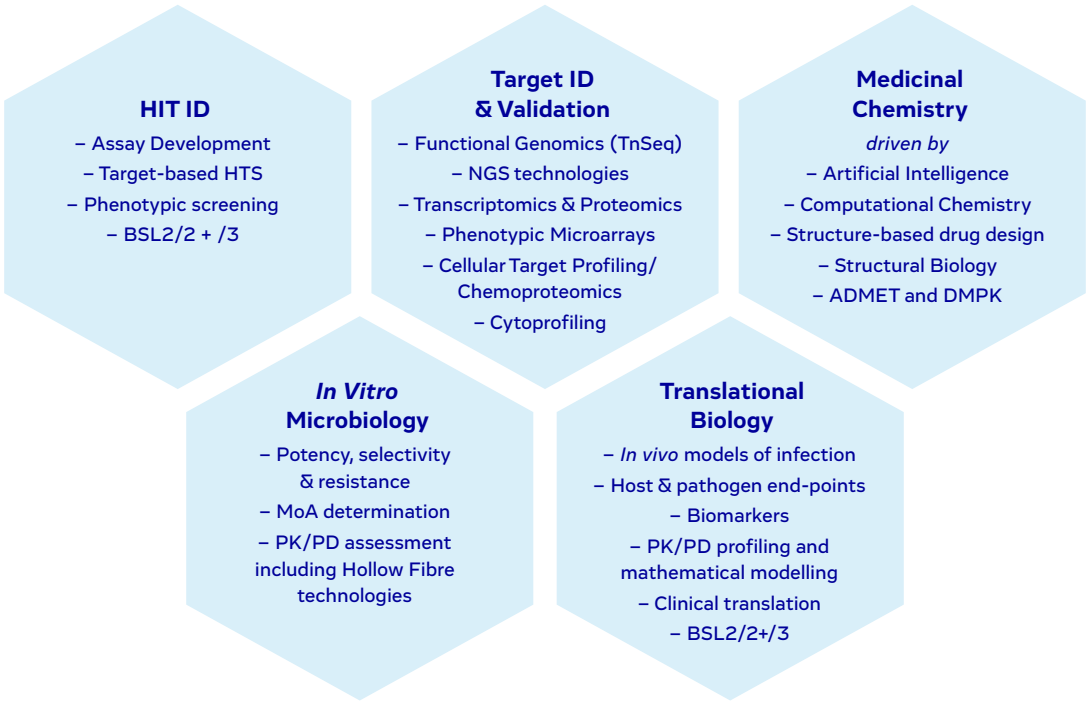
Evotec provides bespoke research and development services in the anti-infective disease area, ranging from concept to IND and into the clinic.

We have established a leading-edge platform enabling the discovery and development of new therapeutic approaches to treat and prevent serious and life-threatening infections. Integration, innovation and efficiency are the core tenets of Evotec's approach, coupled with deep experience and expertise.

We reach beyond conventional anti-microbial agents into multiple other modalities such as virulence attributes, specific pathogen antibodies, combination therapies, antimicrobial peptides (AMPs), and phage technologies.

Our anti-infective discovery teams have proven experience on multiple agent classes including small molecules, natural products, biologics, peptides, antibodies, combinations (including beta-lactam/beta-lactamase inhibitors) and biocides. They are carefully evaluating and adopting the most efficient and optimal drug discovery approaches from phenotypic screening to target- based discovery, fully supported by computational chemistry and state-of-the-art AI/ML platforms.



AMR – Anti-microbial resistance

Antibacterial, Anti-fungal

- Strategic partnerships discovering novel anti-biotics (Forge, GNA-NOW, COMBINE, IMI ENABLE, WTF AMR, AMR Industry Alliance, Novo REPAIR, ...)
- CARB-X funding for development of a novel broad spectrum antibiotic project
- Alliance with Liverpool School of Tropical Medicine (LSTM): IICON, organoids and PK/PD

MTS and HTS for drug discovery

- State-of-the-art robotic platforms
- Phenotypic and target based screening
- Screening against BSL 2/BSL 3 biological agents: human cells & micro-organisms
- Assay development and miniaturisation, HTS in 384 and 1536 well format
- Multiple compound collections including Natural Products that can be adapted to the targets or approaches (25K to 900K)
- Characterisation of active compounds and hits: diverse range of secondary assays
- Diverse readouts: fluorescence, luminescence, optical density, SPR, HCS

EvostrAIn™: a dedicated resource for AMR programs

- ~ 10,000 strains from the clinic and culture collections – Constantly evolving
- High degree of phenotypic and genotypic characterisation
- Isogenic mutant strains and mutant libraries Rapidly build bespoke selective panels for guiding SAR, validate TPP, MoA and MoR investigation, translational experiments

MoA and molecular profiling

- Target-based *in vitro* assays using a variety of technology platforms
- Whole-cell based assay such as MMS, Label-free quantification of compounds by mass spectrometry, Fluorescence Microscopy, Cytometry and Phenotypic microarray
- WGS, RNAseq, TnSeq for antibiotic MoA, MoR, compound profiling and translatability of *in vitro* models
- State-of-the-art molecular biology, including CRISPi
- Vivo Mimetic Media (VMM) for discovering novel Gram-negative antibacterials

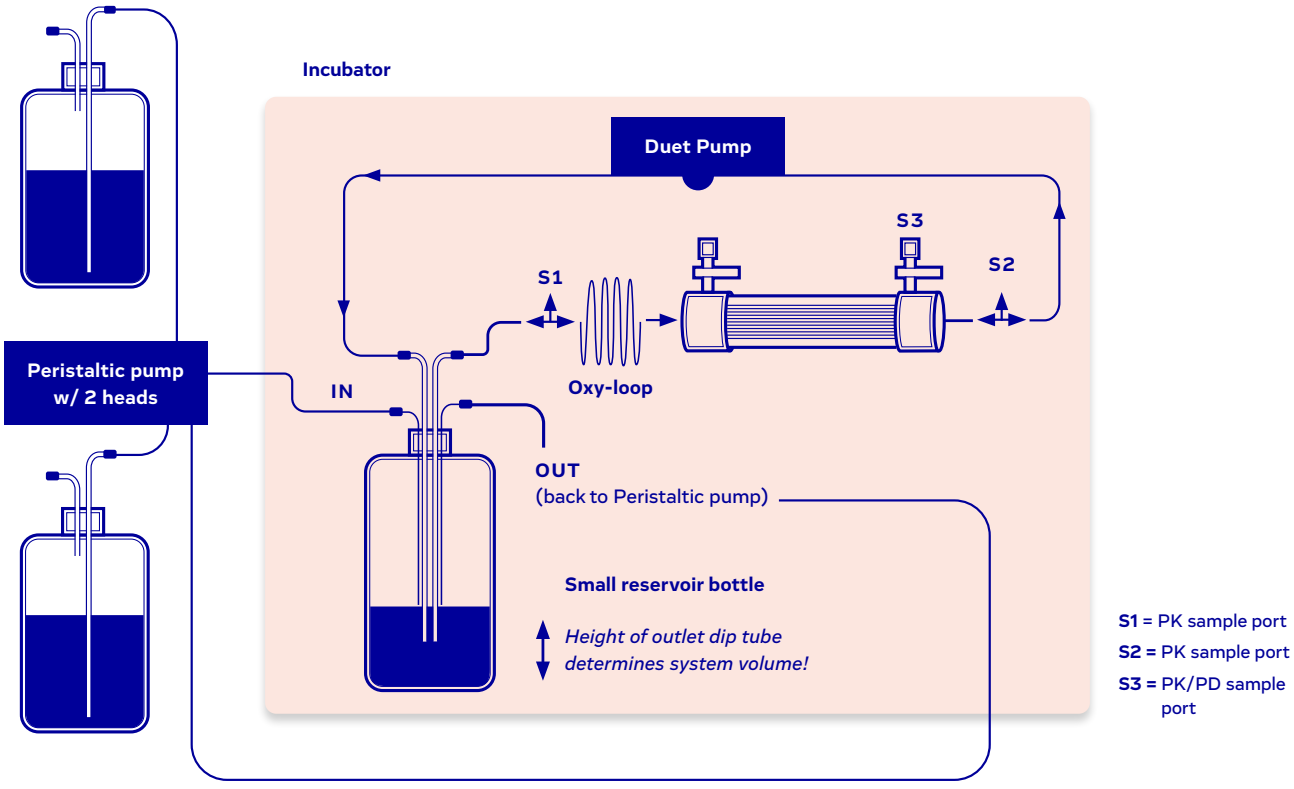
Translational Microbiology and PK/PD to deliver rapid PoC

- Standard and specialised PK studies in multiple rodent species
- Variety of sampling types (jugular vein cannulation, cardiac puncture, tail vein microsampling) and matrices (blood, plasma, CSF, BALF, whole tissues, bile, urine, faeces, GI specific)
- State-of-the-art bioanalytics
- Biomarker quantification: pathogen/infection specific and host response
- Comprehensive and growing portfolio of disease models to support AMR programmes using different rodent species, immuno-competent and neutropenic animals, acute and chronic infections, and evaluating several readouts
- Real time imaging of microbes with a range of validated readouts – IVIS, MRI, CAT, PET
- Evaluation of humanised dosing by infusion or dose fractionation

Hollow Fibre Infection Model (HFIM)

- Rapidly expanding facilities for *in vitro* PK/PD analysis in the Hollow Fibre Infection Model
  - Dedicated HFIM laboratory space at BSL2 with five tall double incubators, CO_2 incubator and 52 pumps
  - Up to 34 cartridges (depending on model type and duration) can be run in parallel for different organisms, variable drug infusion and clearance rates with study duration from hours to 6 weeks
  - State-of-the-art bioanalystics facilities for LC-MS analysis of PK samples
  - A dedicated PK/PD modelling team
- Can be adapted to range of organisms including strains that cannot be used for *in vivo* studies
  - *Mycobacterium tuberculosis H37Ra*
  - *Acinetobacter baumannii*
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Aspergillus fumigatus*
- Significant experience in establishing models and performing studies
  - Development of new infection models using reference or clinical isolates of different bacterial and fungal species
  - Mathematical modelling to establish experimental parameters required to mirror human or animal PK profiles in single- and multi-drug studies
  - Combination studies with up to four individual compounds
  - Dose-response and dose-fractionation studies to determine pharmacodynamic driver and magnitude of effect
  - Resistance generation studies/mutant prevention window identification and mechanism of resistance

Read our white paper:
Faster Development of Anti-Infective Therapies (PDF)



Viral Infections

- **Focus on human respiratory viruses:** Rapidly expanding capabilities supporting coronavirus research (including SARS-CoV2) e.g. biochemical screening assays, cell based assays with several coronavirus strains under BSL2 and BSL3 containment using a range of read-outs, VSV-pseudovirus entry assay
- **Significant collection** of SARS-CoV2 strains including all variants of concern
- **Expanding portfolio** e.g. Respiratory Syncytial virus (RSV), Human Rhinovirus (HRV), Human parainfluenza virus, influenza virus
- **Significant experience** with HBV and HDV
- **Culture of virus and compound testing** in cell lines and primary cells; e.g. culture of HBV/HDV in primary hepatocytes
- **Screening assays** in 96 and 384-well format; cytotoxicity testing of compounds can be performed in parallel
- **Additional endpoints plaque assays, RT-qPCR**
- **Immunology read-out** (ELISA, neutralisation assay, immunofluorescence)
- **Selection of resistant virus**
- **Infection and survival models** in suitable animal hosts; endpoints include viral load (culture/qPCR etc), biomarkers, cytokines, antibody response; pathogen associated and host response

Viral *in vitro* assays	
Viral ToxGlo™ Screening Assay ▸ Single step assay measuring metabolic activity ▸ Increase in luminescence signal by inhibition of virus ▸ Also suitable for cytotoxicity counter screens ▸ Adaptable to range of cell lines ▸ Evaluation of a range of viral isolates	**Plaque Assay** ▸ Quantification and validation of viral stocks for animal challenge assays ▸ Quantification of viral burden in tissue, e.g. as read-out for *in vivo* studies ▸ Generation of resistant virus ▸ Mechanistic studies
Microneutralisation Assay ▸ Quantification of virus specific neutralising antibodies from infected animals	**ELISA** ▸ Quantification of virus in infected cell culture ▸ Quantification of virus specific antibodies from infected animals

Viral animal models: RSV cotton rat and mouse model

- Cotton rat as gold standard model for RSV inhibitors, mouse for quicker access and availability of more biological tools
- Model validated endpoints
  - Viral load in nasal tissue and lung tissue by plaque staining assay
  - Antibody titre via ELISA
  - Neutralising antibodies in neutralisation assay
  - Immunohistochemistry
  - qPCR for viral load
- Viral burden measured 4 days post intranasal infection in nose and lung tissue (in cotton rat only)
- Improved tissue extraction method for quicker processing
- High levels of RSV specific antibodies throughout course of infection
- Model has been used for vaccination and treatment studies

HBV mouse model

- Immune competent animals transduced with HBV via AAV carrier
- Persistent viral products over time Protocol for treatment tailored for specific applications (direct antivirals or host-targeting agents)
- Readouts
  - Circulating viral DNA, RNA
  - HBeAg, HBsAg, HBcAg
  - AST/ALT
  - Anti-HBcAg antibodies
  - Activated immune cells
  - Liver viral DNA, RNA and cccDNA
  - Immuno-Histology of liver tissue:
    - Quantification of HBc
    - Histomorphometry
    - Immune infiltrate

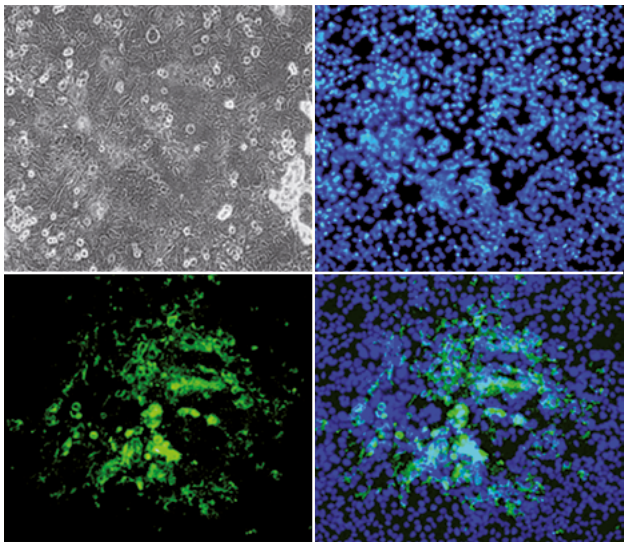
SARS-CoV2 model

- Hamster infection model
- Protocol for treatment tailored for specific applications (direct antivirals or host-targeting agents)
- Readouts
  - Body weight
  - Viral titre in tissues and oral swabs by plaque assay and RT-qPCR
  - Histopathology and Immuno-Histology of lung tissue:
    - Immune response (cytokines …)
    - Transmission between cage mates

Virology Platform: Screening to PD Assessment

- Antiviral HTS experience from reporter based replicon read-outs to infected cell assays handled in BSL2+ / BSL3
- Medium throughput screening in 96- and 384-well format, in infected cell assays with metabolic or enzyme read-out
- SAR screening for integrated programmes – antiviral potency vs. cytotoxicity
- MoA work e.g. resistant virus generation, order of addition effects, cell and virus strain specificity
- Target identification e.g. PhotoAffinity Labelling Mass Spectrometry (PALMS) studies, which can be performed in infected and uninfected cells
- Routine PK in mouse and rat, other rodent hosts are possible
- Development and performance of relevant rodent models

HEp2 cell infected with RSV-A2 | Stained with DAPI (nucleus)



Stained with anti-RSV-F | Stained with anti-RSV-F (green) and DAPI (blue)

Global Health – TB

The Anti-TB Autobahn – from Discovery Biology to Clinic

Supporting a wide range of R&D in TB therapeutics:

Small molecules against replicating/non-replicating *mycobacterium tuberculosis (M.tb)*

- BLS3 HTS for cell-based approaches in *M.tb*
- Gold standard and innovative *in vitro M.tb* assays
- Murine *M.tb* models for each stage of discovery/development

Host-directed approaches

- Assays in support of vaccines, oligonucleotides, antibody drug conjugates, therapeutic antibodies, natural products and more.
- *M.tb* intra-macrophage and whole blood assays
- Complex infection assays to assess host and bactericidal effects
- Functional assays to support vaccine development
- Murine *M.tb* models with immune marker readouts

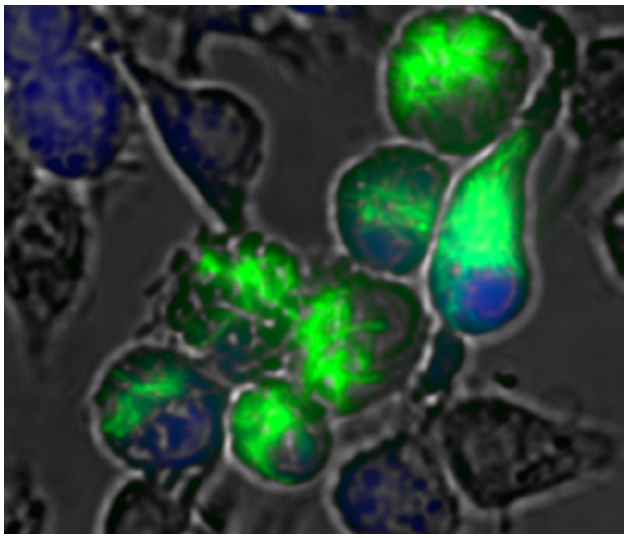
Regimen discovery/development

- *In vitro* combination studies, including hollow fibre
- *In vivo* combinations – relapsing mouse model

Custom assay-development or adaptation, to support individual project needs

Anti-TB *in vitro* platforms – Broad Capabilities, from HTS to Hollow Fiber System

- BSL3 screening capabilities for MTS/HTS
  - Assay development and miniaturization
  - Support for back-screening and hit expansion
- *In vitro* activity testing, anti-*M.tb* profiling
  - Virulent and attenuated *M.tb* – handled under BSL3 or BSL2
  - MICs to support SAR – replicating, non-replicating and intracellular *M.tb*
  - Readouts – CFU, absorbance, luminescence, fluorescence
  - MBCs, time kill curves, inoculum/serum effect for in-depth profiling
  - MoA studies and Mode of resistance studies including mutant generation and characterisation
  - Bespoke assay development or assay transfer
- Hollow Fibre Infection System for TB – H37Ra
  - Single drug or drug combination PK/PD; resistance studies (up to 4 drugs combined)
  - Evaluation against replicating, semi-dormant *M.tb*
  - Intracellular system under development



Pre-clinical *in vivo* Pharmacology – Tuberculosis

- Propose the most suitable *in vivo* models for POC studies, PK/PD studies or efficacy studies
- Tailored approach for your drug discovery project including:
  - Formulation of the drug in accordance with route of administration
  - PK studies in rodent species (infected or not)
  - Selection or tailoring of PK/PD models in accordance with *in vitro* assays and identification of pharmacodynamics biomarkers
  - Efficacy studies with optimised dosing regimen and suitable study endpoints (bacteria burden, survival, relapse, biomarkers)
- Process of continuous and interactive exchanges for flexibility, decision making to optimised timelines and process
- Sampling to support analysis for complete evaluation of drug
  - Blood micro-sampling, Organ collection (lung and spleen)
- Broad range of sample analysis
  - Gene/mRNA, Flow cytometry, Histology/IHC
  - Mass spectrometry (DMPK and metabolite follow up)
- Custom assay development
  - Protein analysis, (ELISA or MSD assay)

Murine *M. tb in vivo* Models (BSL3)

- BALB/c models of TB:
  - Highly Acute *M.tb* model (early PoC)
  - Acute *M.tb* model (confirmation)
  - 14-day *M.tb* model with kinetics analysis
  - 14-day *M.tb* model with/or without relapse
  - Chronic *M.tb* model: non necrotic granuloma
- Kramnik *M.tb* model: necrotic granuloma

Learn more about our commitment to Tuberculosis research