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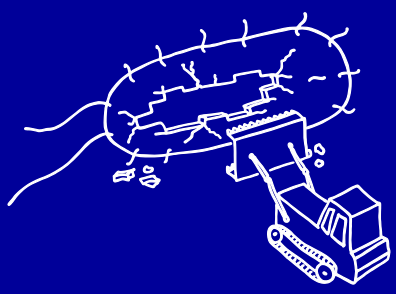
ANTI-INFECTIVE DRUG DISCOVERY & DEVELOPMENT

- More than 200 high calibre scientist 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
- Seamless transition from Drug Discovery to IND: INDiGO, the fastest path to the clinic

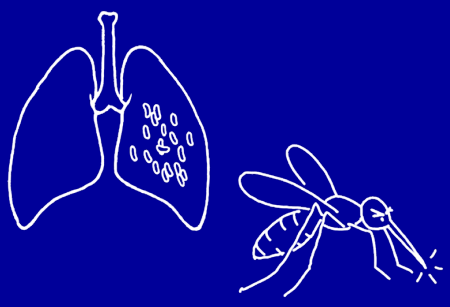
AREAS OF EXPERTISE

ANTI-MICROBIAL RESISTANCE (AMR)



VIRAL INFECTIONS

GLOBAL HEALTH TB / MALARIA



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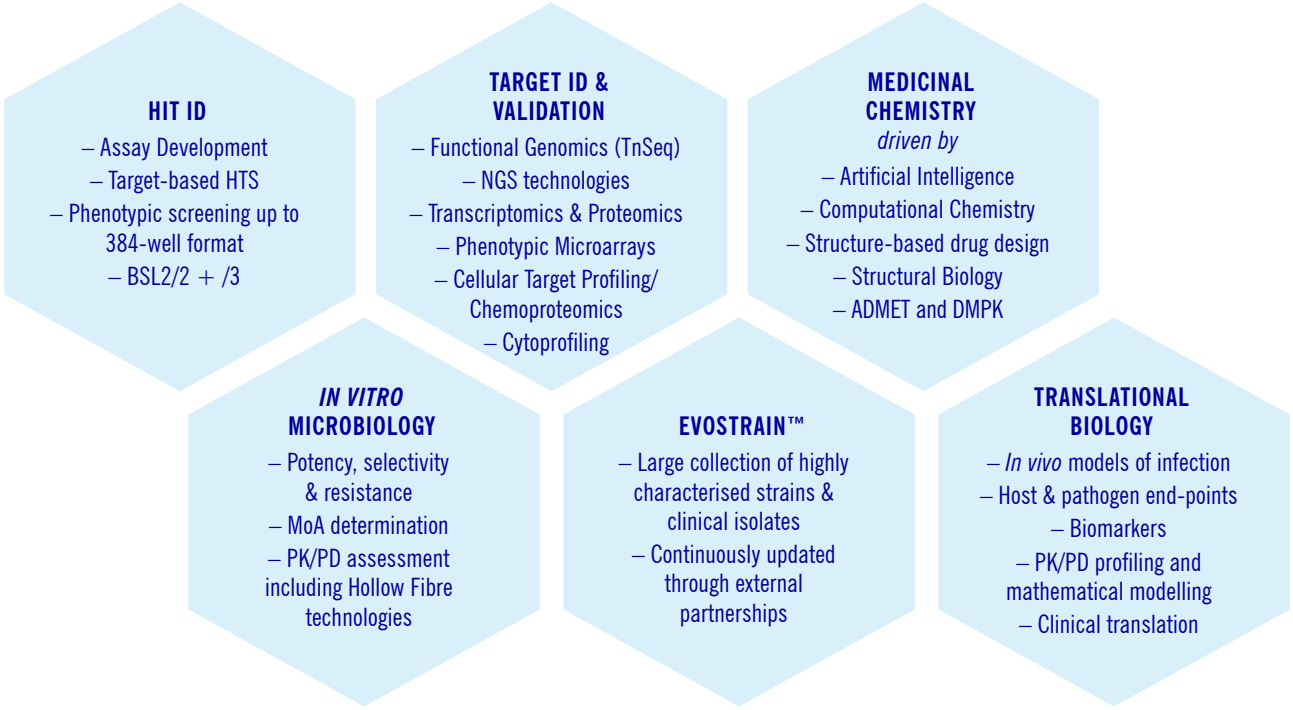
Evotec provides bespoke research and development services in the anti-infective disease area, ranging from target ID to the Clinic.

We have established a leading-edge platform enabling the discovery and development of new therapies and therapeutic approaches to treat and prevent serious and life-threatening infections. Integration, innovation and efficiency are the main elements characterising Evotec's expertise. This also reaches beyond conventional antimicrobial agents into multiple alternative modalities such as targeting virulence attributes, specific pathogen antibodies, combination therapies, antimicrobial peptides (AMPs), and phage technologies.

Our anti-infective discovery team of more than 200 scientists has proven experience on multiple agent classes including small molecules, natural products, biologics, peptides, antibodies, combinations (including beta-lactam / beta-lactamase inhibitors), biocides and vaccines. They are carefully evaluating and adopting the most efficient and optimal drug discovery approaches from phenotypic screening to target-based discovery.



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AMR – ANTI-MICROBIAL RESISTANCE

Antibacterial, Anti-fungal, Anti-parasitic IDD

- **Strategic partnerships discovering novel anti-biotics (GARDP, 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 genetics, including CRISPi
- Vivo Mimetic Media (VMM) for discovering novel Gram-negative antibacterials

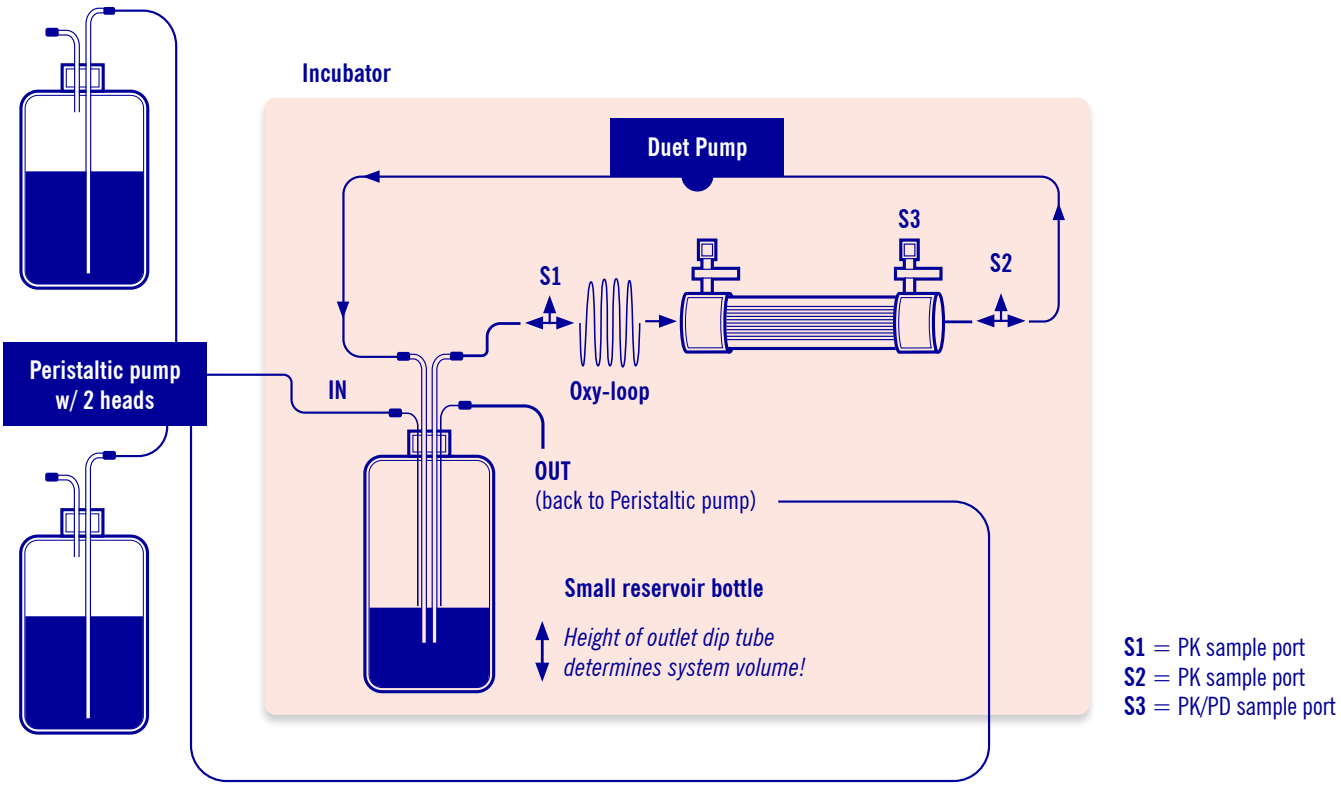
Translational Microbiology and PK/PD to deliver rapid PoC

- 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 programs 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
  - A team of scientists trained in setting up and running the system
  - Full microbiology support
  - BioA facilities for LC-MS analysis of PK samples
  - A dedicated PK/PD modelling team
- Significant experience in establishing models and performing studies
  - Development of new infection models using reference or clinical isolates of different bacterial and fungal species
  - Performance of HFIM using *Mycobacterium tuberculosis* non-virulent strain
  - 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)



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VIRAL INFECTIONS

- Focus on human respiratory viruses: Respiratory Syncytial virus (RSV), Human Rhinovirus (HRV), influenza virus, coronavirus
- Rapidly expanding capabilities supporting coronavirus research 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 experience with HBV
- Culture of virus and compound testing in cell lines and primary cells; e.g. culture of HBV 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 by plaque assay
  - Viral load in lung homogenate by plaque assay
  - Antibody titre via ELISA
  - Neutralising antibodies in neutralisation assay
  - Immunohistochemistry
  - qPCR for viral load under development
- 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

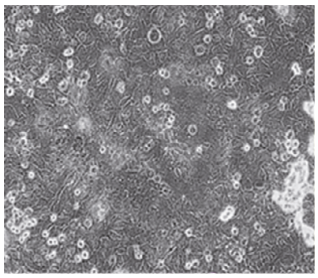
HBV mouse model

- 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

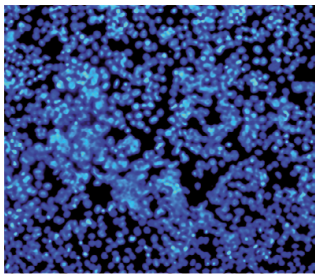
Virology Platform: Screening to PD Assessment

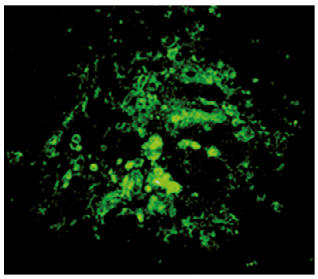
- Antiviral HTS experience from reporter based replicon read-outs to infected cell assays handled in BSL2+ / BSL3
- Medium throughput screening in 96- and 384-well format, in infected cell assays with metabolic or enzyme read-out
- SAR screening for integrated programmes – antiviral potency vs. cytotoxicity
- 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

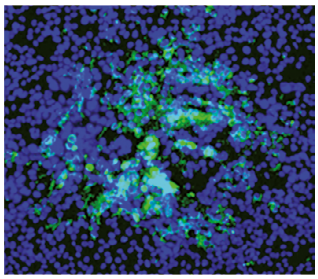


Stained with DAPI (nucleus)





Stained with anti-RSV-F



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

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GLOBAL HEALTH – TB

The Anti-TB Autobahn – from Discovery Biology to Clinic

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

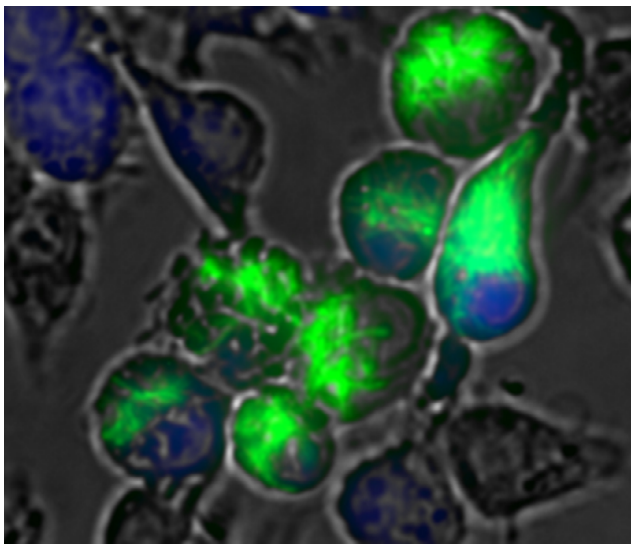
SMALL MOLECULES AGAINST REPLICATING/ NON-REPLICATING *MYCOBACTERIUM TUBERCULOSIS* (M.TB)
- BLS3 HTS for cell-based approaches in M.tb
- Gold standard and innovative *in vitro* M.tb assays
- Murine TB models for each stage of discovery/development

HOST-DIRECTED APPROACHES
- M.tb intra-macrophage assays, binding assays
- Murine 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
  - Evaluation against replicating, semi-dormant M.tb
  - Intracellular system under development



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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 TB *in vivo* Models (BSL3)

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

Learn more about our commitment to Tuberculosis research