evotec

#RESEARCHNEVERSTOPS

Evotec Anti-infectives

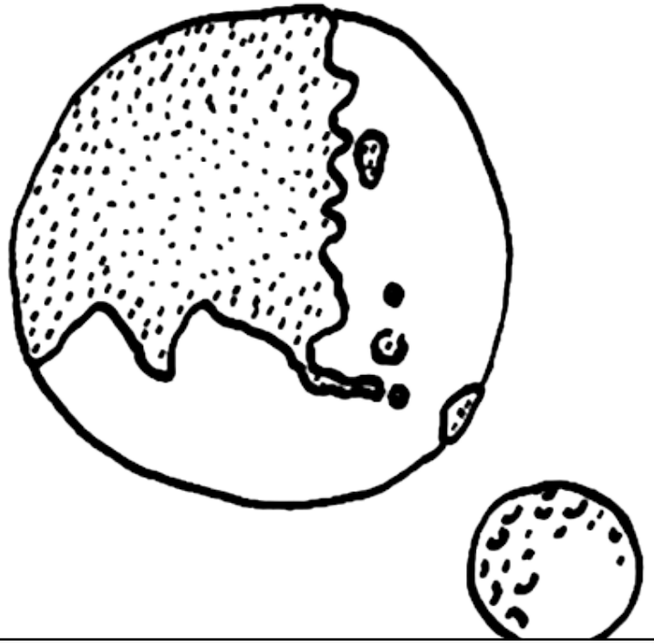
Screening Capabilities

Agenda

Working with us

Screening Expertise

In Vitro and *In Vivo* Studies



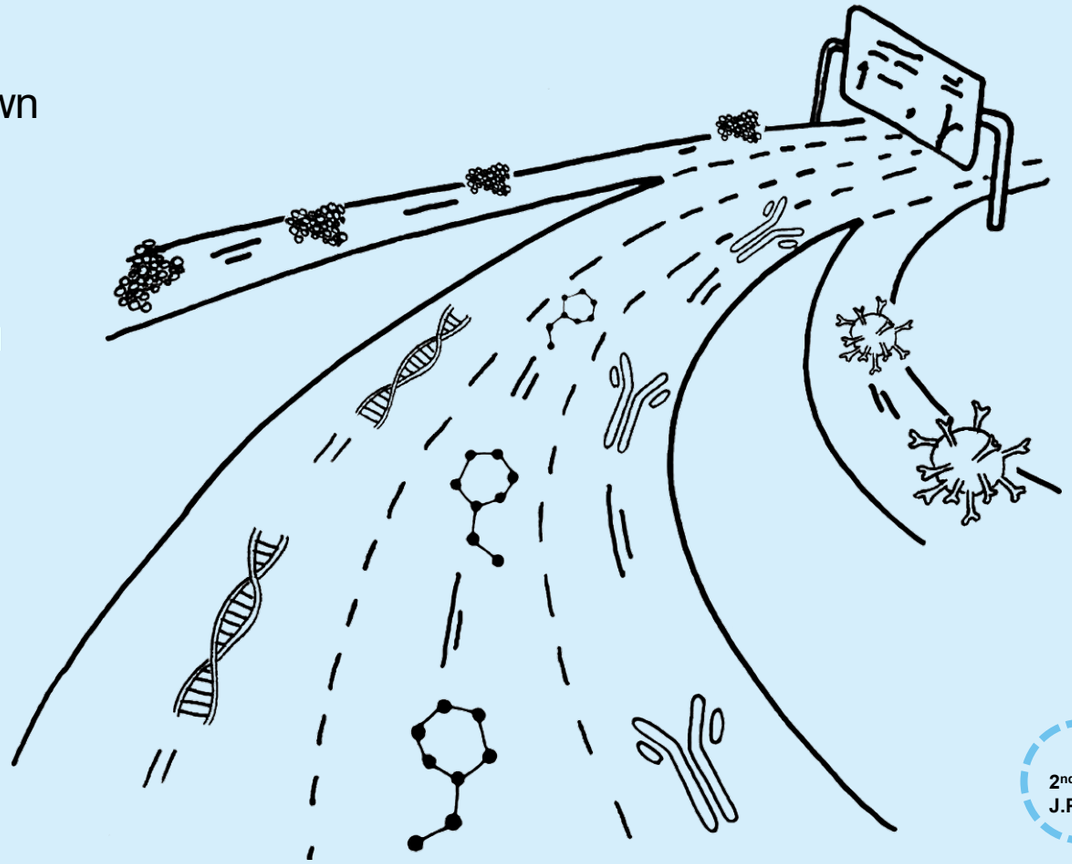
One platform – more efficiency, better precision, higher speed

Evotec today – 14 Sites & close to 4,000 employees

Princeton, Seattle, Branford, Watertown
~400 FTE

Orth an der Donau
~35 FTE

Verona (Campus Levi-Montalcini)
~700 FTE



Hamburg (HQ), Goettingen (Manfred Eigen Campus) Cologne, Munich,
~900 FTE

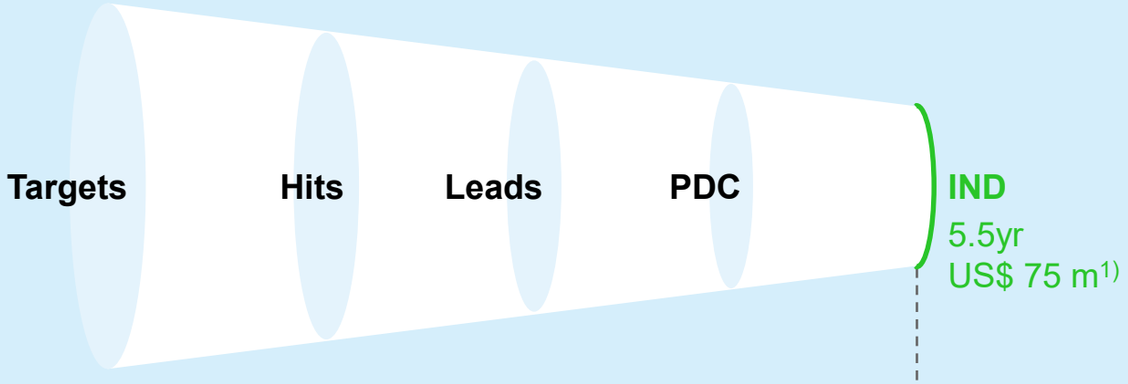
Abingdon (Dorothy Crowfoot Hodgkin), Alderley Park
~850 FTE

Lyon, Toulouse (Campus Curie)
~800 FTE

High degree of integration creates speed and value

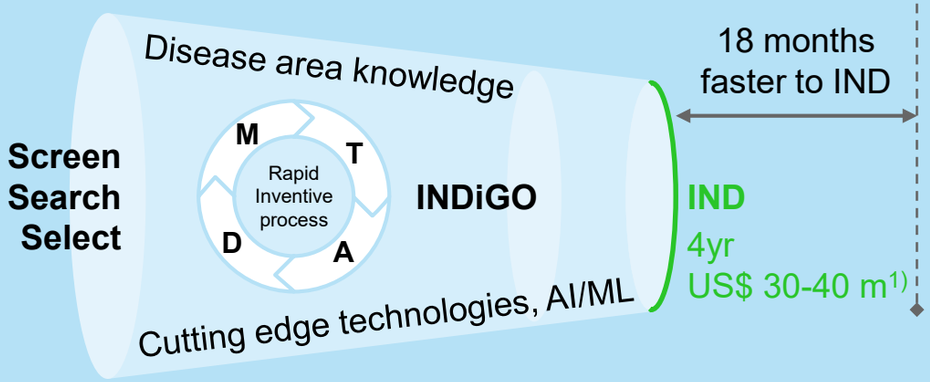
Key performance Indicators (**EVO***iR&D*)

Industry



- Benchmarks for speed and cost are not improving in last 10 years
- Attrition getting even worse, i.e. because of more complex targets/biology

Evotec



- Integrated processes create speed and early prioritisation in experimental cascades
- Expertise solves problems, creates inventive steps, faster and at lower costs

1) Including attrition; DMTA = Design Make Test Analyse

Comprehensive integrated research and development

Illustrative functional capabilities along Evotec value chain (**EVO***iR&D*)[1)]

Sourcing novel ideas	Target ID/ Validation	Hit-Identification	Lead Optimisation	Pre-clinical development	Phase I	Phase II	Phase III	Approval	Market
• Exploratory biology • Hit-finding technologies • Chemistry • DMPK • Sample Management	• Disease area expertise • Biology, translational biology • Design/Chemistry • DMPK • PK:PD	• Translational biology • Design/Chemistry • DMPK/physical chem • Formulation, PK/PD & ADME • Safety • Biomarkers • Clinical planning and project management	• Translational biology • API process development and manufacturing • Formulation & drug product for clinical testing • Safety / Safety prediction	• Commercial API and drug product manufacturing					

EVO*iR&D*

- Focused, inter-disciplinary teams
- Comprehensive “under ONE” roof offering of technologies, experience, and expertise
- Operational excellence and AI/ML-driven predictive science driving rapid progress and successful outcomes

[1)] Illustrative for small molecules, but in full build-up also for biologics as well as cell therapy processes

Evotec is confronting the renewed challenge in Infectious Diseases

Innovation and operational excellence

INNOVATION
Innovative thinking
Creativity
Novel approaches

INTEGRATION
Infrastructure
Knowledge

EFFICIENCY
Dedicated platforms
Expertise and
operational excellence

~200 Scientists dedicated to ID across multiple functions

Bringing together an experienced team for expert project design, execution and outcomes

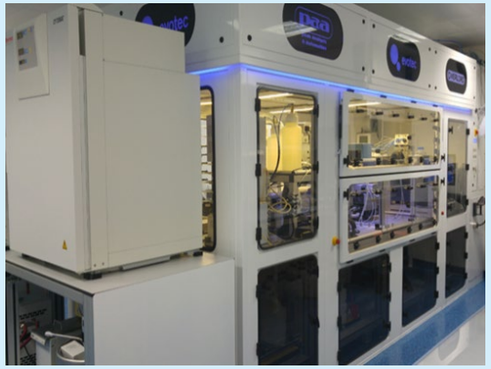
World leading expertise

								
Florian Von Groote Bidlingmaier	**Anna Upton**	**Pia Thommes**	**Francesca Bernardini**	**Antoine Alam**	**Eric Bacque**	**Gilbert Lassalle**	**Guillaume Mondésert**	**Mike Bodkin**
EVP, Head Global Health & Clinical Dev	SVP R&D Tuberculosis, TB TA Lead	VP Anti-infectives, Virology TA Lead	VP, *in vitro* biology, Anti-infectives, AMR TA Lead	VP Head of Virology Research	Head of Chemistry	Head of Chemistry	Head of Screening Group	SVP, Global Head of Comp Chem & Informatics Innovation
>10 years Pharma & clinical	>13 years Not-for-profit	>20 years Pharma & Biotech	>19 years Pharma & Biotech	>20 years Pharma	>20 years Pharma	>25 years Pharma	>15 years Pharma	>20 years Pharma
TASK Applied Science	TB Alliance	Euprotec, Astra Zeneca KuDOS, GSK	Arpida, Polyphor, Debiopharm,	Sanofi	Rhone-Poulenc Rorer, Sanofi	Sanofi Synthelabo	Microcide, Sanofi	Lilly

Screening platforms for Anti-Infectives including TB

HTS & MTS – BSL2 & BSL3 capabilities

BSL2⁺

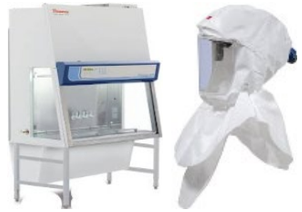


- >15 years screening expertise, from assay development to hit finding & hit profiling, in the anti-infective space
- Assay development and miniaturization
- BSL2/BSL2⁺ screening capabilities for HTS
  - 1 HTS BSL2/BSL2⁺ platform, 1 HTS BSL2 platform
  - 1 MTS BSL2 platform (Agilent workstation)
- BSL3 screening capabilities for MTS/HTS
  - BSL3 facilities (~200 m^2) including autoclave and H_2O_2 SAS for waste handling
  - 6 BSL3-trained FTE
  - Automation equipment under safety cabinet
    - Dispenser/washer (ELX406, Biotek) for cell/reagent dispensing/washing
    - Pipetor (Cybiwell, Cybio) for compound addition
    - Multimode plate reader (PheraStar)
- Support for back screening and hit expansion
- Secondary assays for hit characterization
- Genedata Screener for data analysis,
- Dotmatics for data register
- Access to Evotec and Aptuit compound collections
- Close interaction with Sample Management for plate preparation

BSL3

BSL3 pathogen screening capabilities

Generic assay workflow



BSL3
pathogen preparation

Day 1

Dispensing Station

BSL3 pathogen addition in 384-w ARP[1)] plates

Detection reagent addition

Plates sealing

Day 1

Day 4/7

Reading station

Reading

Day 5/8

Data analysis

Genedata

Screener

Incubation
3-6 days, 37°C

Incubation
24 hours, 37°C

HTS Throughput

- up to 400k
- up to 200 plates/week

[1)] ARP: Assay Ready Plate

BSL2+ screening capabilities

Primary cells infected by wild-type HBV

Day -1
Cell seeding in 384-w plates

Incubation
1 day, 37°C

Day 0
HBV addition

Incubation
3 days, 37°C

Day 3
Compound treatment

Incubation
4 days, 37°C

Day 7
HTRF reagent addition
Reading

- Mitsubishi RV-2FL robotic arm
- Barcode scanner
- Plate labeller
- Plate peeler
- Plate sealer
- Centrifuge
- V-prep pipetting station
- ELX-406 washers x3
- Multiflo dispenser
- Multidrop Combi dispenser
- 4°C and 37°C cytomats
- Spark multimode reader

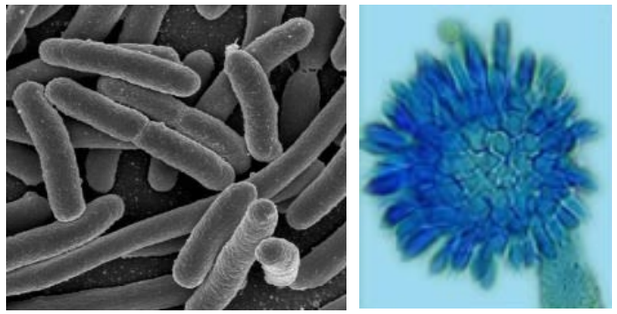
- HTS Throughput
- up to 400K samples
- up to 200 plates/week

EvostrAIn™: A dedicated resource for ID programs

Evotec's collection of characterised strains and clinical isolates

A constantly evolving resource of thousands of primary clinical isolates and reference strains

EvostrAIn™



- Broad collection of bacteria, fungi, viruses & parasites
  - ~10,000 strains from the clinic and culture collections
  - Global, recent sources with continual refreshment
  - High degree of characterisation (susceptibility profiles, mechanisms of resistance and *in vivo* drug response, genome sequences available)
  - Includes isogenic mutant strains and mutant libraries
- Used to establish spectrum of activity and potential clinical use of new antimicrobials
- Rapidly build bespoke panels
  - Guide SAR
  - MoA / MoR (target validation & identification)
  - TPP validation
  - Translational activities

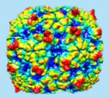
SAR: Structural activity relationship, MoA: Mechanism of action, MoR: Mechanism of resistance, TPP: Target product profile

Continuous development of viral disease *in vitro* biology capability and expertise

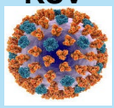
Investment in bolstering the platform for respiratory viruses as well as for HBV and HDV

Respiratory viruses

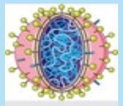
HRV



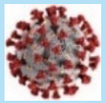
RSV



IFV

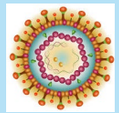


Coronaviruses*

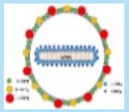


Hepatic viruses

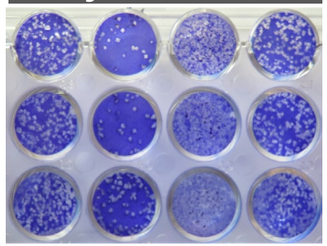
HBV



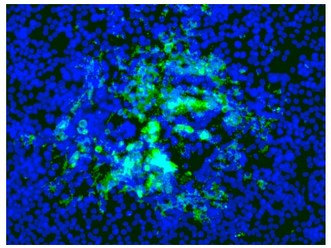
HDV



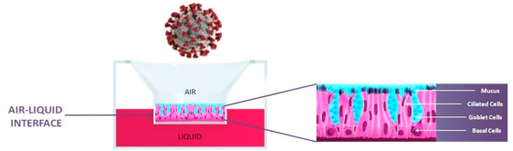
Plaque forming assay

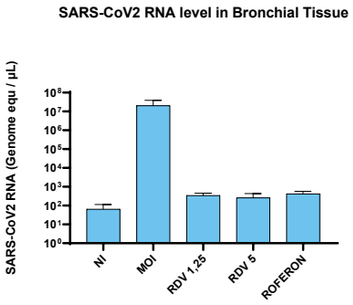


Immuno-fluorescence

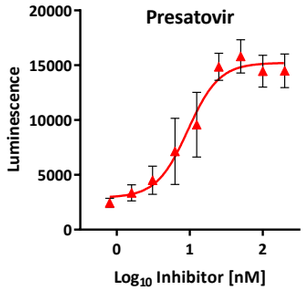


Human airway epithelial assay***

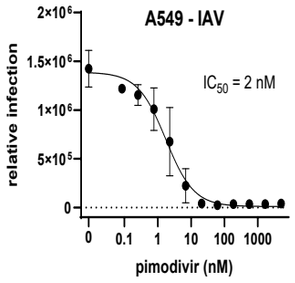




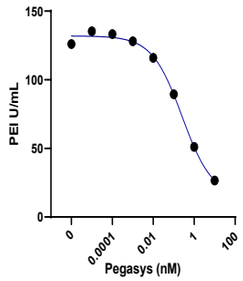
Viral ToxGlo™



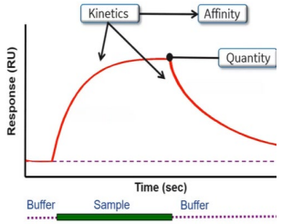
Enzymatic assays**



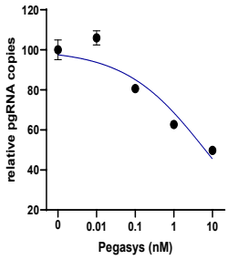
ELISA / multiplex



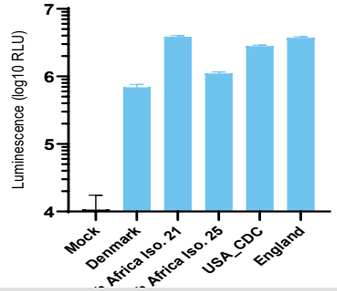
Biochemical Biacore



RT-PCR / ddPCR



Pseudoviruses neutralisation assays



Additional endpoints include host biomarkers, cytokines, antibody response

* 229E, OC43, SARS-CoV-2 (several variants)

** include protease, polymerase, neuraminidase, endonuclease, minigenome assays…

***Schematic representation of MucilAirTM. (adapted from http://www.epithelix.com/products/mucilair)

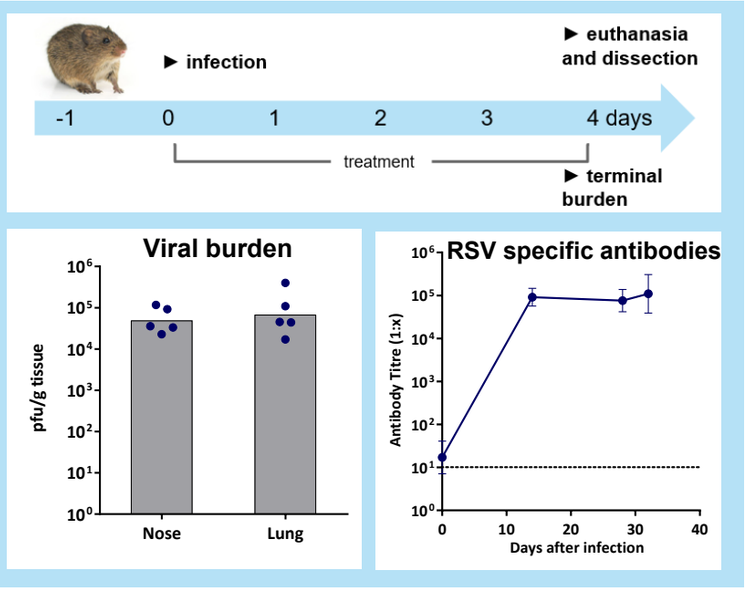
In vivo virology assessment

Gold standard assays

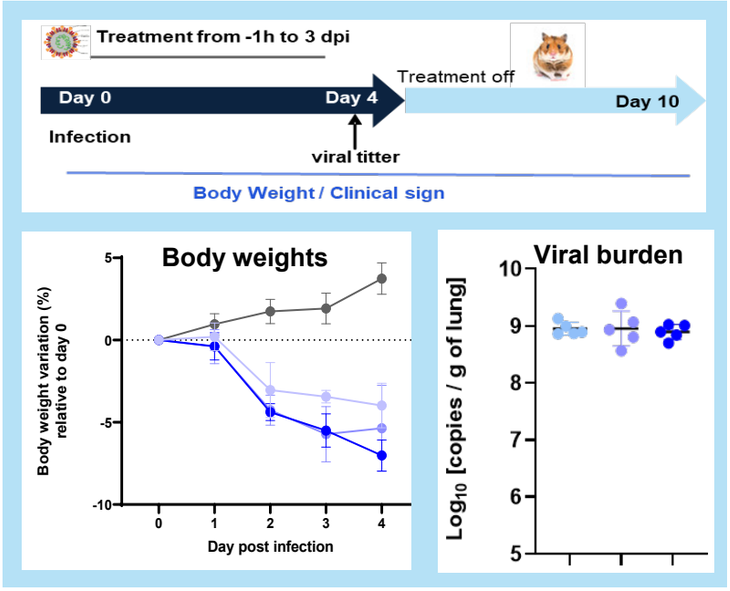
- **Respiratory virus capabilities:**
  - **SARS-CoV-2** Hamster Model (intranasal Infection with SARS-CoV-2)
  - **RSV** infection model in cotton rat and mouse
  - **Coxsackie virus** neonate model (surrogate model) for HRV in CD1 mice

- **HBV mouse model:** Immune competent animals transduced with HBV via AAV carrier
  - **Viral readouts**: HBs, Hbe, HBV DNA, pgRNA, cccDNA
  - **Host readouts**: immunoprofiling, cytokines, liver enzymes

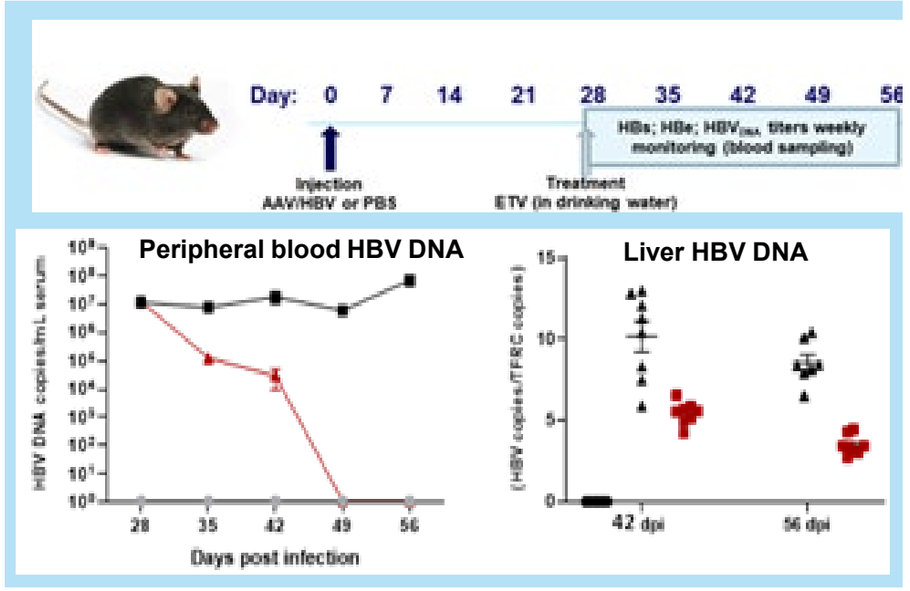
RSV mouse model



SARS-CoV-2 Hamster model



HBV mouse model



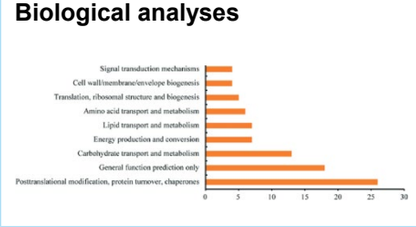
Utilising the power of genomics & transcriptomics in AMR

Next Generation Sequencing (NGS) for MoA, MoR and Translation

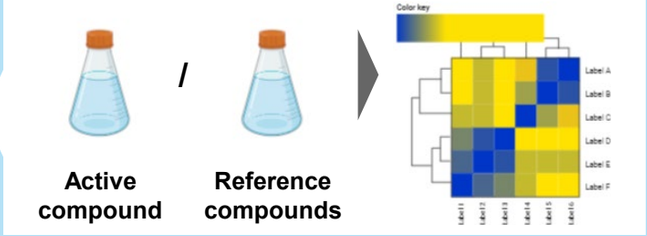
Antibiotic MoA / MoR / Cpd profiling (SAR)

WGS (high throughput)
Characterise resistance-associated mutations

RNAseq (high throughput)
Identify bacterial pathways regulated by active compounds



TnSeq (low throughput) – *E.coli*, *K.pneumoniae*
Comparing gene fitness in presence of sub-lethal (for MoA) or lethal (for MoR) concentrations of antibiotics and clustering by fitness profile vs. reference compounds.



Active compound **Reference compounds**

Translatability of *in vitro* models

TnSeq: use genome-wide transposon mutagenesis to link genotype to phenotype & compare *in vitro* vs *in vivo* models

RNASeq: compare gene expression levels in *in vitro* vs *in vivo* models

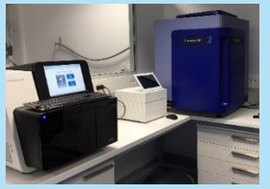
Define gene fitness & essentiality *in vitro* and *in vivo* models

Clusterise by fitness

Genomic sequence collection

Search engine / GWAS approach in development

Applications	WGS	TnSeq	RNASeq
Target ID	X	X	–
MoA	–	X	X
MoR	X	X	–
Translation	–	X	X
SAR	–	X	–



Collection of TnSeq reference compound profiles

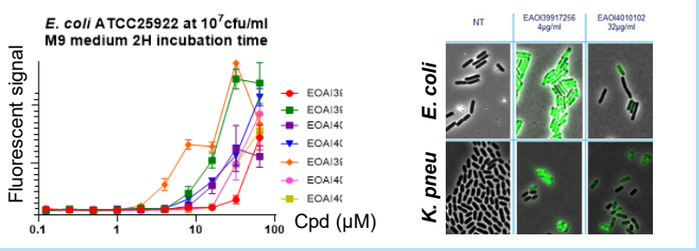
Full support from dedicated Bioinformatics team

Deep knowledge from MoA signature to MoA phenotyping

Multiscale phenotypic approach by microscopy-cytometry-plate reader

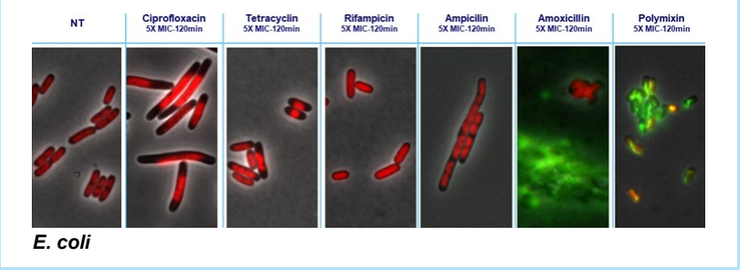
MoA guided screen / counterscreen / validation assay

- Fluorescent-based assay for any relevant pathway (specific reporter): e.g. permeabilisation of membranes, SOS response, RNA transcription
- Assay development on demand: e.g. Alon library (GFP transcriptional fusions)



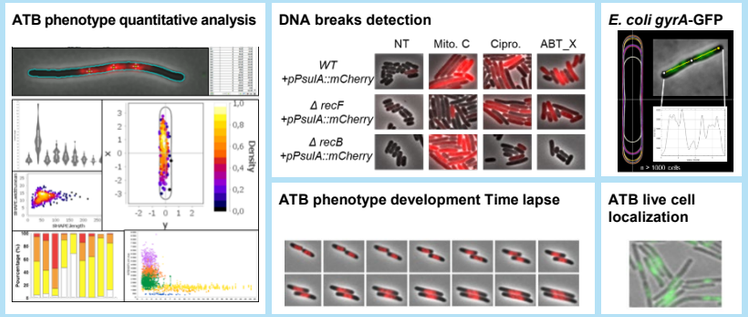
Hit selection and MoA profiling

- Bacterial Cytological Profiling (BCP)
- Reporter specific BCP (rsBCP)
- Qualitative or quantitative MoA profile attribution
- Family / subfamily MoA studies
- Reference panel comparison on demand

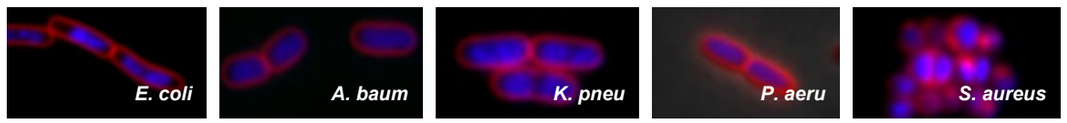


Specific MoA studies and target validation

- MoA specific reporters and assays
- Qualitative/quantitative analysis
- Compound live cell localisation
- Target live cell localisation
- Space and time resolution



- In rich/poor media or *in vivo mimetic media* – In WT, tolC or any background (combination with e.g. KEIO – CRISPr)
- Developed for *E. coli*, on-going development with ESKAPE spectrum



Overview of *in vivo* bacterial infection models (BSL2)

Gram-positive and Gram-negative sensitive or resistant strains (a growing list)

Model	**Pathogen**	**Immune System** (Rodent species, gender)	**Number of strains validated/species**
IP Sepsis	*A. baumannii, E.coli, K. pneumoniae, P. aeruginosa, E. cloacae, S. aureus, S. pneumoniae, E. faecalis*	Competent & Neutropenic (some *E. coli* strains)	1 to 27
IV Sepsis	*A. baumannii, E. coli, P. aeruginosa, S. aureus, S. pneumoniae*	Competent or Neutropenic	1 to 6
Thigh infection	*A. baumannii, E.coli, K. pneumoniae, P. aeruginosa, P. mirabilis, P. stuartii, E. cloacae, C. freundii, S. aureus, S. pneumoniae, E. faecalis, E. faecium, S. pyogenes*	Neutropenic (mouse or rat)	2 to 32
Lung infection	*A. baumannii, K. pneumoniae, P. aeruginosa (acute or chronic), H. influenza, S. pneumoniae, S. aureus (nasal colonisation in cotton rat)*	Competent or Neutropenic	2 to 26
UTI	*A. baumannii, E.coli, K. pneumoniae, P. aeruginosa, P. mirabilis*	Competent (mouse or rat, male or female)	1 to 9
Skin/foreign body/endo-carditis/Osteomyelitis	*S. aureus, P. aeruginosa, P. acnes, S. epidermidis*	Competent (mouse, rat guinea pig, rabbit)	1 to 5
Gastrointestinal infection	*C. difficile, V. cholerae, S. enterica, E. coli*	Competent (mouse or hamster)	1 to 4

A range of BSL3 assays for Tuberculosis discovery

Accessing the full anti-*Mtb* profile, to better predict performance as a novel therapeutic

In Vitro models

Virulent and attenuated M.tb – handled under BSL3 or BSL2

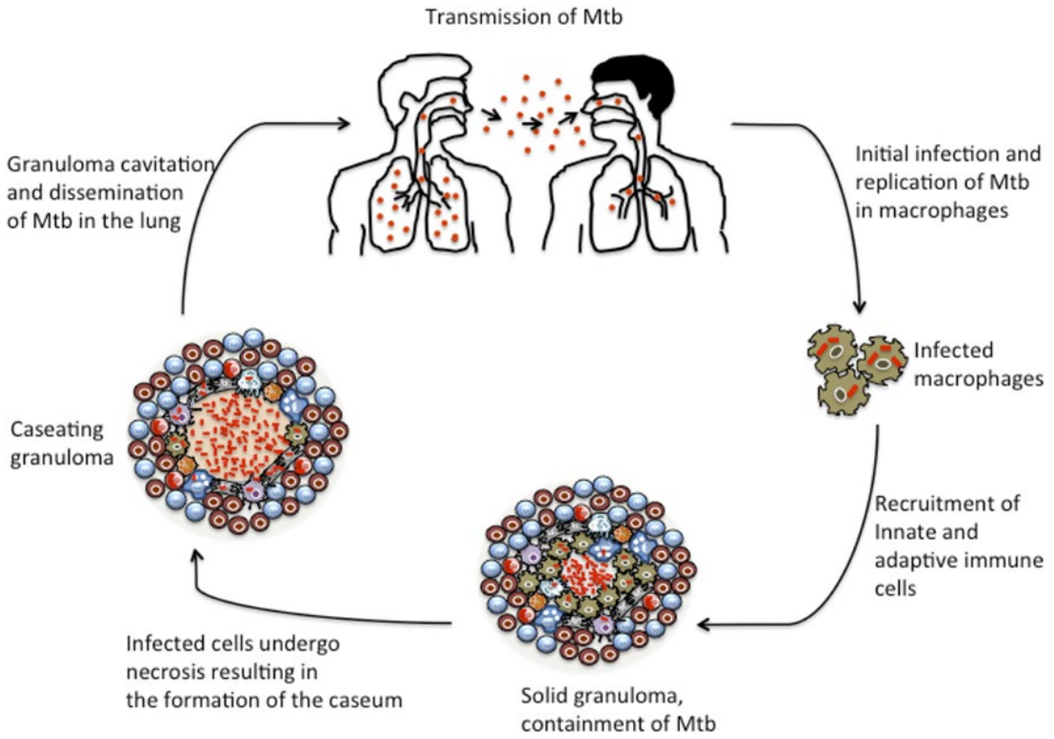
MICs to support SAR replicating, non-replicating and intracellular M.tb

Readouts – CFU, absorbance, luminescence, fluorescence

MBCs, time kill curves, inoculum /serum effect for in-depth profiling

MoA / MoR studies including mutant generation and characterisation

Hollow Fibre Infection System for TB-H37Ra



In Vivo models

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 granulom

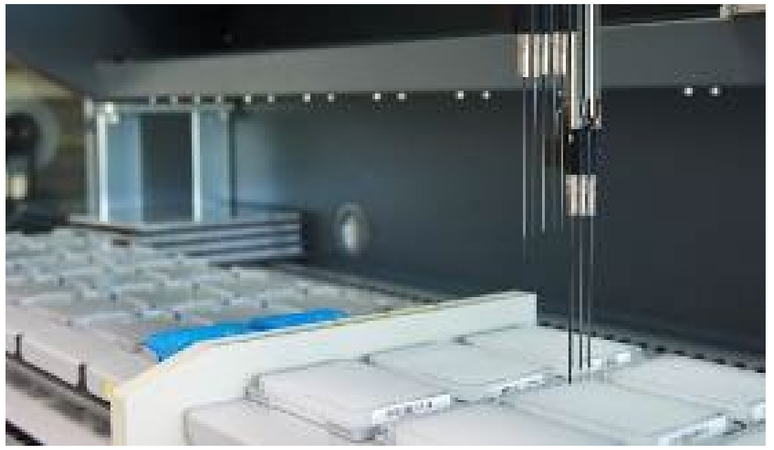
Kramnik TB model: necrotic granuloma

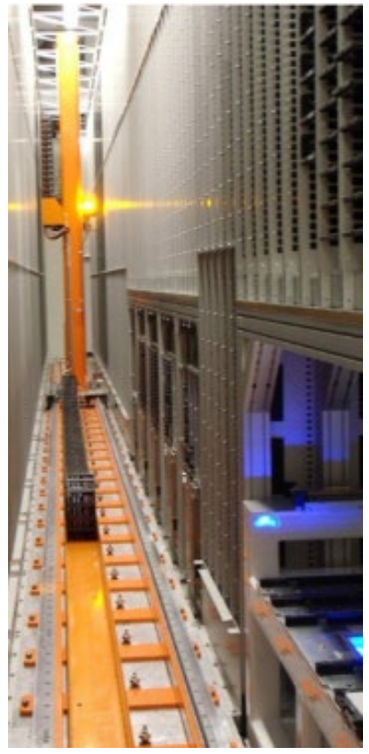
Reference (Figure): Cambier, C.J., et al. Cell. 2014; doi:10.1016/j.cell.2014.11.024

A center of excellence for compound and Sample Management

Based on best practices from the storage up to the delivery driven by experts

Scalable, flexible service provider supporting small molecule and biologics compound management





Scalable & flexible platform to meet all your sample management needs

Four critical pillars

Informatics / Data Management

- Web based access built on industry standard techno-logies (Oracle and Java)
- Industry leading Sample Management software: Mosaic Titian
- Flexible data and reporting capabilities; end-to-end tracking

Quality Control

- High throughput capabilities
- Purity and Identity confirmation (LC/MS)
- Concentration determination (LC/MS)
- Solubility analysis

Plating & Vial Processing

- Nano liter to 1,000µL transfer volumes
- High throughput dissolution and replication
- DMSO & DCE:MeOH or ACN/MeOH transfers
- Manual neat sample transfers; 150 to 200 transfers / day / technician

Storage and Handling

- Modular and scalable; automated storage capacity of 11 million samples, e.g. Brooks, TTP
- Vials, microtubes, micro-plates and oversize containers
- Advanced automation capable of more than 48,000 picks per day

Sample & Data Integrity

evotec

#RESEARCHNEVERSTOPS

Your contact:

Business Development
114 Innovation Drive, Milton Park, Abingdon
Oxfordshire OX14 4RZ, UK

T: +44.(0)1235.86 15 61
F: +44.(0)1235.86 31 39
info@evotec.com