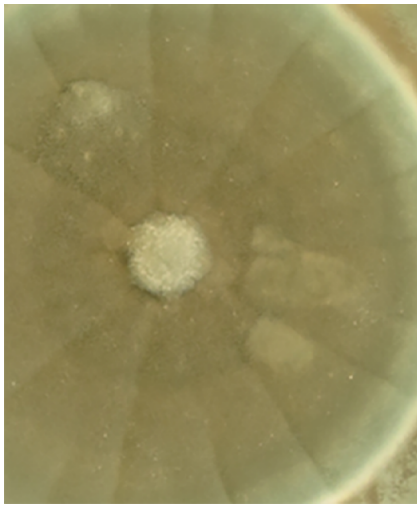
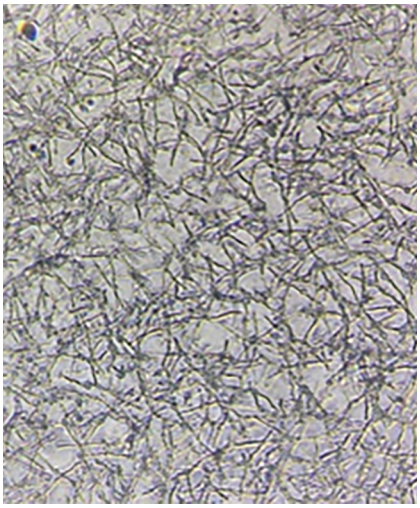
evotec

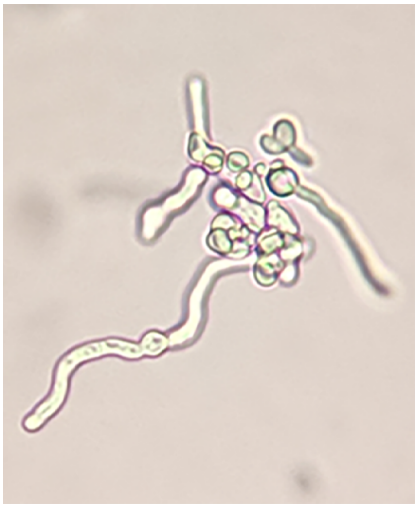
#RESEARCHNEVERSTOPS

Antifungal Drug Discovery

- Focus on WHO and CDC priority human pathogens; *Aspergillus fumigatus, Candida spp and Cryptococcus neoformans* and a proven track record in Evotec's contribution to new antifungals in late stage drug discovery.
- A breadth of established *in vivo* models of fungal infection allowing rapid progress and continuity from *in vitro* to *in vivo* models of disease.
- Containment Level 2, AAALAC-I accredited animal facility.
- Areas of expertise
  - *In vitro* compound characterization
  - Invasive and localised *in vivo* fungal infection models
  - PK/PD mathematical modelling
  - Custom assay development/*in vivo* model development to support individual project needs







Antifungal hit profiling

In vitro Microbiology

- Antifungal susceptibility testing (AFST):
  - Performed to industry standards; CLSI, EUCAST
  - MIC/MEC, MFC
  - Combination AFST to determine synergy or antagonism (FICI)
  - Multiple modalities
- *In vitro* PK/PD:
  - Time-kill kinetics (TKK)
  - Post-antifungal effect (PAE) studies
- MoA determination, resistance studies
- ELISA – whole cell
- Bespoke/sophisticated systems:
  - Designed in collaboration with clients
  - Galleria waxmoth insect model
  - Hollow fibre infection model (HFIM)
  - Biofilm formation and eradication

In vivo POC to lead optimization and beyond

- Tailored approach to POC, PK/PD and clinically relevant efficacy studies
- Multiple administration routes:
  - Standard; IV,PO,SC
  - Specialized; IN, IT, JVC and aerosolized administration
- Breadth of validated endpoints:
  - Fungal load in blood/tissue; CFU culture, qPCR
  - Biomarker; galactomannan ELISA, flow cytometry
  - Clinical observation; survival, body weight, condition
  - Histopathology
- Compound formulation, tolerability testing
- *In vivo* PK/PD:
  - Multiple rodent species PK
  - Dose-response and dose-fractionation studies to determine pharmacodynamic (PD) driver
  - Mathematical modelling to establish experimental parameters required to mirror human or animal PK profiles

EvostrAIn™

- >350 fungal strains from the clinic and culture collections – Constantly evolving
- Rapidly build bespoke selective panels for guiding SAR, validate TPP, MoA and MoR investigation, translational experiments
- Includes representatives from the WHO fungal critical priority pathogen list and the CDC antibiotic resistance threats report
  - *Candida* spp. (Including *C. auris, C. albicans* and *C. tropicalis*)
  - *Cryptococcus neoformans*
  - *Aspergillus spp.* (including *A. fumigatus*[1] and *A. flavus*)

  In addition to rarer moulds and dermatophytes such as
  - *Mucorales, Fusarium spp., Scedosporium spp., Malassezia spp*
  - Dermatophytes *(Epidermophyton floccosum, Trichophyton rubrum and T. mentagrophytes)*

Strain Characterization

The EvostrAIn™ collection of isolates has broad geographical, temporal, genotypic and phenotypic diversity. Bespoke fungal panels can be selected to drive your drug discovery program forwards.

Fungal isolates can be characterized using a combination of:

- Whole-genome sequencing, 18SrRNA sequencing
- Biochemical testing using the Vitek® 2 Compact and standard laboratory microscopy and culture techniques
- AFST using both CLSI and EUCAST guidelines as well as bespoke methods developed in conjunction with clients and collaborators

Translational Microbiology and PK/PD to deliver rapid PoC

- Standard and specialized 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 clinically relevant rodent fungal disease models to support drug discovery programmes using, 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 humanized dosing by infusion or dose fractionation

Rodent models of fungal infection

- A breadth of clinically relevant *in vivo* models of fungal infection are available to determine efficacy of novel antifungal therapeutics;
  - Acute models e.g. disseminated candidiasis or aspergillosis, multiple species including *C. albicans, C. glabrata, C. auris, A. fumigatus, A. flavus, A. terreus*
  - Chronic models e.g. immunocompetent disseminated candidiasis (7d model) and cryptococcal meningitis model
  - Disseminated models e.g. invasive pulmonary aspergillosis (5d model) with extended duration survival option (14d model)
  - Localised models e.g. dermatophyte skin infection, GI tract, vulvovaginal candidiasis (VVC)
  - Multiple rodent species; mouse, rat, guinea pig
  - Multiple standard of care comparators validated