therapy and surgery with low success rates, resulting often in amputation and social sigma. To improve the current therapeutic success rates a novel drug is needed. Due to the lack of interest in the pharmaceutical industry, an open-source drug discovery program for mycetoma was established called MycetOS.

In total 1360 compounds were screened for *in vitro* activity against *M. mycetomatis*, and many more are currently being screened. Compounds that were able to inhibit growth at 100 μM, 25 μM, and had an IC50 <8 μM were selected for studying the *in vivo* efficacy in an *M. mycetomatis* grain model in the invertebrate *Galleria mellonella*.

Out of the 1360 compounds screened against *M. mycetomatis*, 302 were able to inhibit growth at 100 μM, and 23 of those met all criteria to be screened *in vivo*. Of these 23, nine did prolong larval survival. These included 3/7 azoles tested, olorofim, fenbendazole, MMV006357, MMV022478, MMV675968, and MMV1782387. Based on these results, 6 compound series were selected for further studying, these included the *fenarimols* (series 1), the *aminothiazoles* (series 2), the *phenotiazines* (series 3), *dihydrofolate reductase inhibitors* (series 4), *benzimidazoles* (series 5) and the *ketoximines* (series 6). For series 1 in total 185 additional compounds were screened. By analyzing the *in vitro* activity and *in vivo* efficacy in relation to the chemical properties of the molecules it appears that the LogD value of a compound was important for penetrating into the mycetoma grain.

In conclusion, using an open source drug discovery approach for mycetoma we were able to identify novel lead compounds. Some of these compounds were highly active against *M. mycetomatis* only (*fenarimols*, *aminothiazoles*, *phenotiazines*, and *ketoximines*), while other compounds such as the benzimidazoles also were active against other causative agents as well. Screening more analogs of identified compounds allowed us also to identify chemical properties which are favorable for grain penetration *in vivo*. This will allow us to chemically design more active compounds for this difficult to treat infection.

S6.5d

Molecular identification of mycetoma causative agents from patients in ahospital setting in Senegal

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S6.5 Efforts of improving the management of mycetoma: working towards the 2030 goals, September 22, 2022, 4:45 PM - 6:15 PM

Background: Mycetoma is a chronic granulomatous inflammatory disease that is caused either by bacteria or fungi. The diagnosis of species is important to guide the therapeutic management of patients particularly for white and yellow grains. However, the identification of the causative agents using mycological and histological techniques is a real problem in our countries. This study aims to identify etiologic agents using molecular techniques in Senegal.

Methods: A prospective study was carried out to compare mycological and histological techniques with molecular methods in patients attending hospital settings. Biopsy specimens and/or grains obtained from these patients were examined by PCR targeting the ITS (fungal agents) and 16S (actinomycosis agents) genes. Sequencing with the SANGER method allowed us to identify the species.

Results: Preliminary results were obtained from 30 patients. The grains collected were black (38%), red (4.7%), white (47.6%), and yellow (9.5%). Discriminative PCR ITS vs 16S identified 5 actinomycosis agents including white and yellow grains and 1 fungal agent. The fungal agent was identified after sequencing as *Microsporum langeronii*.

Conclusion: The preliminary results of this study show the importance of discriminative PCR to guide the therapeutic choice of clinicians. Its widespread use could improve the detection and management of mycetoma cases in Senegal.

S7.1d

Reliability of bedside point-of-care tests for *Candida neoformans* , *M. tuberculosis* and *S. pneumoniae* in adults living with HIV presenting with suspected central nervous system infection (CNS) in low- and middle-income settings: Preliminary results from the DREAMM study

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S7.1 Update in management of fungal infection in adult hematology, September 23, 2022, 10:30 AM - 12:00 PM

Background: Bedside point-of-care (POC) testing, with parallel laboratory testing, represents a unique opportunity to improve and speed up the diagnostic workup of people living with HIV with suspected CNS infection in resource-limited settings.

Objectives: To assess the agreement between POC tests for *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, and *Streptococcus pneumoniae* performed at the bedside and in the routine laboratory, in African low- and middle-income countries (LMICs).

Methods: From January 2018 to March 2021, the following POC tests were performed in parallel at the bedside and in the routine laboratory: Cryptococcal antigen lateral flow assay (CrAg LFA, Immy) in blood and cerebrospinal fluid (CSF), tuberculosis lipoarabinomannan (TB-LAM, Alere) in urine, and, where indicated, pneumococcal antigen (Streptococcus pneumoniae (SP), Biosynex) in CSF.

Participants: HIV-infected adults (>18 years old) suspected of CNS infection.

Setting: The prospective multicenter DREAMM project (Driving Reduced AIDS Meningo-Encephalitis Mortality) in five hospital sites in Cameroon, Malawi, and Tanzania.

Primary outcome: Cohen's kappa statistic of agreement between the results of POC tests obtained at the bedside and the routine laboratory.

Results: The study included 356 consecutive participants (mean age 39.5 +/- 10 years; 68.7% ART-experienced; 46.3% male; median CD4 count 75/mm3; abnormal mental status 75%). In total, 148/355 (41.7%) participants had positive bedside CrAg in blood, 140/315 (44.4%) positive bedside CrAg in CSF, 64/339 (18.9%) positive bedside TB-LAM in urine, and 10/175 (5.7%) positive bedside SP in CSF. Kappa statistics evaluating agreement between bedside and laboratory test results were: 0.98 [95% confidence interval (CI) 0.96-1.00; $n = 347$] for blood CrAg, 0.99 (95%CI, 0.98-1.00; $n = 307$) for CSF CrAg, 0.92 (95% CI, 0.87-0.98; $n = 330$) for urinary TB-LAM, and 0.68 (95%CI, 0.40-0.96; $n = 34$) for CSF SP.

Conclusions: Bedside POC tests for *Cryptococcus* spp. are highly reliable and can be safely performed in parallel to laboratory testing to expedite targeted treatment in people living with HIV with suspected CNS infection in African LMICs. Other bedside POC tests need further evaluation before large-scale implementation.

S7.2d

Divergent EGFR/MAPK-mediated immune responses to clinical *Candida* pathogens in vulvovaginal candidiasis

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S7.2 More than just candidemia: clinical aspects, diagnosis and treatment, and pathogenesis of deep-seated candidiasis, September 23, 2022, 10:30 AM - 12:00 PM

Objectives: Vulvovaginal candidiasis (VVC) is characterized by symptomatic inflammatory responses in the vagina caused by *Candida albicans* and non-*albicans Candida* (NAC) species. The epidermal growth factor receptor (EGFR) -mitogen-activated protein kinase (MAPK) signaling pathway has been linked to immune responses of oral epithelial cells upon *C. albicans* exposure, but whether this pathway plays a similar response in vaginal epithelial cells is not determined.

Methods: The activation of EGFR and MAPK signaling pathways in vaginal epithelial cells infected with *C. albicans* was determined by RNA sequencing and Western blot. The relationship between EGFR and MAPK signaling was verified via inhibition of EGFR and construction of EGFR-overexpressing cells. Enzyme-linked immunosorbent assay (ELISA) and Real Time Cellular Analysis (RTCA) techniques were used to detect the effect of EGFR-MAPK signaling pathway on regulating the secretion of inflammatory cytokines and cell damage induced by *C. albicans*. The mouse model of VVC infected by *C. albicans* was constructed, and the role of EGFR signaling pathway in regulating fungal burden, vaginal inflammation, and epithelial damage was determined by Periodic Acid-Schiff stain and immunofluorescence.

Results: We observed that phosphorylation of EGFR and p38 was continuously activated in vaginal epithelial cells by *C. albicans* strain SC5314. The response is not in a biphasic manner that is critical for oral epithelial cells to discriminate the morphology of *C. albicans*. When compared with SC5314, a highly azole-resistant *C. albicans* isolate 1052 can induce a stronger phosphorylated signal of EGFR and p38, while clinically-isolated NAC strains including *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. auris* triggered higher levels of phosphorylated ERK1/2 and c-Fos than *C. albicans*. Consistently, inhibition of EGFR significantly reduced inflammatory response and epithelial damage induced by *C. albicans in vitro* and *in vivo*, while inhibition of p38 led to great loss of epithelial damage triggered by both *C. albicans* and NAC species.

Conclusion: These results confirm the importance of the EGFR-MAPK signaling in VVC pathogenesis and highlight the remarkable immunogenic differences between *C. albicans* and NAC species in host-microbe interactions.