Oral Presentations

Genomics and metagenomics of Madurella mycetomatis

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Mycetoma is a debilitating disease recognized as a neglected tropical disease by the World Health Organization. The etiology of mycetoma is poorly understood; ~60% of cases are caused by fungi and the rest are bacterial, although this varies by region. The pathogenic fungus, Madurella mycetomatis, is most frequently identified in mycetoma cases. Here, we present a high-quality genome assembly of M. mycetomatis and the results of the whole genome sequence analysis of 25 isolates from Sudan. We demonstrate evidence of at least seven genetically diverse lineages and extreme clonality among isolates within these lineages. Shotgun metagenomic analysis of DNA from mycetoma grains confirmed that M. mycetomatis was the predominant causative agent of mycetoma Sudan; however, 10% of grains also contained bacterial reads suggestive of secondary infections. A thorough understanding of the genetic structure and diversity of fungi causing mycetoma is essential for the development of new diagnostic methods and for identifying potential drug targets.

MycetOS: identifying drugs which can penetrate the mycetoma grain

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Mycetoma is a neglected tropical disease characterized by large subcutaneous swellings and the formation of grains. Madurella mycetomatis is the most common causative agent. Currently, mycetoma is treated with a combination of imidazoles...
therapy and surgery with low success rates, resulting often in aspiration and social stigma. To improve the current therapeutic success rates in patients suffering from disease, a new drug may be introduced to improve outcomes for people with significant interest in the pathophysiology of infection. A novel drug discovery approach for mycetoma was established called MycoSOS.

In total, 1560 compounds were screened for in vitro activity against M. mycetomatis, and many more were currently being screened. The new drug that was able to inhibit growth at 100 μM, 25 μM, and had an IC50 of 8 μM were selected for studying the in vivo efficacy as it in M. mycetomatis model in the intradermal Gallium-67clod. One of the 1560 compounds screened for M. mycetomatis, 3202 was able to inhibit growth at 100 μM, 25 μM, and 23 of those most active were selected to be in vivo. Of these 23, none had any larval survival. These included 37% azoles tested, oloriflavin, benfotimod, MMV361357, MMV224475, MMV716948, and MMV1792387. Based on these results, 6 compounds were selected for further evaluation (note 7), and 4 were included for further evaluation (note 7), the amphotericin B (note 7), the Pneumocystis (note 7), the hidradenitacule inhibitors (note 7), the mycolactone (note 7), and the tachycardia (note 7). For 31 in total 187 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 LogP value of a compound was important for positioning into the mycetoma grain.

In conclusion, using an open source drug discovery approach for mycetoma we were able to identify novel lead compounds. Of these compounds were highly active against M. mycetomatis only (benzimidazole, antifungal, pharmaceutics, and ketoximines); while other compounds such as the hidradenitacules 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.

S5.6d Molar identification of mycetoma causative agents from patients in abiotropic setting in Senegal

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S5.6d Efforts of improving the management of mycetoma: working towards the 2030 goals, September 23, 2022, 4:45 PM - 6:15 PM

Background: Mycetoma is a chronic granulomatous infectious 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 etiological agents using molecular techniques in Senegal.

Methods: A retrospective 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 (actinomycota 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 white (15%), red (47%), white (47%), and yellow (9%). Discriminative PCR ITS vs 16S identified 7 actinomycota agents including white and yellow grains and fungal fungal agent was identified after sequencing in Microsporum langeroni.

Conclusion: The preliminary results of this study show the importance of discriminative PCR to guide the therapeutic choice of patients. 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 DREAM Study

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S7.1d 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, offers a unique opportunity to improve and speed up the diagnostic workup of people living with HIV who are suspected to have 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 (CAG-LFA, Immy) in blood and cerebrospinal fluid (CSF); Tuberculin liposome (TB-LAM, Alere) in urine, and, where indicated, pneumococcal antigen (Streptococcus pneumoniae SP, Buretox) in CSF.

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

Setting: The prospective multicenter DREAM project (Driving Redac’s H3D Meningo-Epidermal Mortality) in five hospital sites in Cameroun, Malawi, and Tanzania.

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

Results: The study included 316 consecutive participants (mean age 59.9 ± 17 years, 48.7% ART-experienced, 46.3% male, on ART (54.5%) and median CD4+ cell count 370 cells/mm3, abnormal mental status 78%). In total, 460535 (46.3%) participants had positive bedside CAG in blood, 145315 (44.4%) positive bedside CAG in CSF, 64379 (18.8%) positive bedside TB-LAM in urine, and 15171 (57.2%) positive bedside SP in CSF. Kappa statistics evaluating agreement between bedside and laboratory test results were 0.98 (95% confidence interval [CI] 0.97-0.99), 0.95 (95% CI 0.94-0.97), 0.98 (95% CI 0.96-1.00), and 0.98 (95% CI 0.97-0.99) for blood CAG, CAG in CSF, SP in CSF, and TB-LAM in urine, respectively.

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 needs further evaluation before large-scale implementation.