Background. Cryptococcus is an opportunistic fungal infection caused by both Cryptococcus neoformans and its sibling species, Cryptococcus gattii. Flucytosine (5FC) is one of the most widely used antifungals against Cryptococcus spp., yet very few studies have looked at the molecular mechanisms responsible for 5FC resistance in this pathogen.

Methods. Eleven Cryptococcus gattii clinical isolates were selected based on different 5FC susceptibility. All isolates underwent whole-genome sequencing and genomic differences in key genes involved in flucytosine metabolism were examined. Heterologous expression of C1Y1 and spot sensitivity assays were performed to examine regions of interest based on genomic differences.

Results. Susceptibility assays and sequencing analysis revealed an association between a point mutation in cytochrome b (CITY1) and 5FC resistance in two C. gattii clinical isolates, B9322 and J55. This mutation results in the replacement of arginine for histidine at position 29 and occurs within an unconserved stretch of amino acids. Heterologous expression of CITY1 and spot sensitivity assays demonstrate that the point mutation did not have any effect on CITY1 activity and was not responsible for 5FC resistance. Comparative sequence analysis further showed that no amino acid changes were observed in either cytochrome peroxidase (PCY2-4) or uracil phosphoribosyltransferase (UPRTase, encoded by UR5) among 5FC resistant and 5FC susceptible C. gattii isolates.

Conclusion. Together, our work suggests that the mediator(s) of 5FC resistance in C. gattii is likely a nontraditional mechanism(s).

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277. Fungal Mechanobiology: High Shear Forces Increase Rhizopus Virulence
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Session: 48. Fungus Among Us: Basic Science
Thursday, October 5, 2017: 12:30 PM

Background. It has been observed in both civilian and military populations that high-energy events, such as tornadoes and blast injuries, have been associated with mucormycosis in otherwise immunocompetent patients. However, the effects of high shear force directly on fungal biology have not been explored. In order to elucidate the relationship between fungal mechanobiology and virulence, R. oryzae was exposed to high shear stress. Subsequent changes in virulence were measured in a validated fly model of mucormycosis. Finally, spores were simultaneously exposed to high shear forces and calcineurin inhibitors to determine whether this cellular stress pathway was involved in changes in virulence in response to shear force.

Methods. 10 or 100 spores/ml of R. oryzae in 100 ml saline were either: (1) grown in static culture (CNTRL); (2) subjected to stirring at 1100 RPMs for 30–45 minutes (HSS) (i.e. 5000 HU); (3) subjected to TFSC in the presence of the calcineurin inhibitor tacrolimus (TPSCS + TAC). Wild-type flies were subsequently infected with either conidia or hyphae from the calcineurin inhibitor tacrolimus (TPSCS + TAC). Wild-type flies were subsequently infected via dorsal thorax inoculation and monitored for survival over 7 days (n = 26 per group; performed in triplicate).

Results. Flies inoculated with R. oryzae exposed to high shear stress experienced significantly greater mortality compared with spores grown under static conditions (P < 0.001). Co-culture of spores grown under TFSC with tacrolimus (1 mg/ml) resulted in increased fly survival (P < 0.001). In fact, there was no significant difference between flies inoculated with spores subjected to high shear and TAC and spores grown under static conditions (P = 0.934).

Conclusion. Fungal exposure to high shear stress increases virulence. As calcineurin inhibition completely mitigated the effect of shear stress on Mucorales virulence, activation of the calcineurin stress response may play an important role in the mechanotransduction of shear stress to increased fungal virulence.

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278. Optimization of the CRISPR/Cas9 System to Manipulate Gene Function in Rhizopus delemar
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Session: 48. Fungus Among Us: Basic Science
Thursday, October 5, 2017: 12:30 PM

Background. The genus Rhizopus is the main cause of mucormycosis, a life-threatening infection that affects predominantly hosts with an impaired immune system. However, patients with severe trauma and burns, without prior immune deficiency, are also at increased risk of developing mucormycosis. Despite aggressive treatment, this often involves disfiguring surgery and antifungal therapy, mortality rates range from 50–90%. Recent developments on tip4p have been critical for identifying fungal targets to develop more effective therapies. However, Rhizopus genetics are challenging because of lack of dominant selection markers, low efficiency of transformation, and rarity of chromosomal integration. Here we attempted to adapt the CRISPR/Cas9 technology to disrupt genes in R. delemar.

Methods. We used the Gibson cloning strategy to assemble all necessary elements of the CRISPR/Cas9 system in one plasmid using the pyrF as a selection marker. The targeted gene for disruption was a toxin-encoding gene with similarity to ricin. This disruption cassette was transformed using biolistic delivery system into R. delemar pyrF strain (M16). Recombination events were studied by Southern blot analysis and gene expression by qRT-PCR. Furthermore, damage to alveolar epithelial cells (A549) and nasal epithelial cells (CCL30) was studied with Cr-release assay.

Results. Five stable transformants were obtained with the CRISPR/Cas9 construct. Southern blot analysis and gene expression confirmed a partial deletion of the ricin gene, in the region where the guide RNA was designed. Moreover, gene disruption was confirmed by abrogation of ricin expression in comparison to reference strains (wild-type or mutant with the CRISPR/Cas9 plasmid void of ricin gene sequence). Finally, ricin mutants showed significant reduction in damage to A549 cells and CCL30 cells when compared with the reference strains (20–30% reduction, P < 0.01 by t-test).

Conclusion. We have successfully adapted the CRISPR/Cas9 system to disrupt the ricin-like gene in R. delemar. This tool will enable us to better understand the phagocytosis of mucormycosis designing novel and more successful strategies to manage this lethal fungal infection.

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279. Studies of Pseudomonas aeruginosa Mutants Indicate Pyoverdine as the Central Factor in Inhibition of Aspergillus fumigatus Biofilm
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Session: 48. Fungus Among Us: Basic Science
Thursday, October 5, 2017: 12:30 PM

Background. Pseudomonas aeruginosa (Pa) and Aspergillus fumigatus (Af) are common opportunistic bacterial and fungal pathogens, respectively. They often co-exist in airways of immunocompromised patients and individuals with cystic fibrosis, where they form biofilms and cause acute and chronic illnesses. Hence, the interactions between these two pathogens have long been investigated, and known that Pa can inhibit Af in vitro.

Methods. We have approached the definition of the inhibitory Pa molecules by studying 24 Pa mutants, with various genes deleted, for their ability to inhibit Af biofilms. The ability of Pa cells, or their extracellular products produced during planktonic or biofilm growth, to affect Af biofilm formation, preformed Af biofilm, or planktonic Af was studied in agar and liquid assays with Pa cells or supernatants.

Results. Four mutants, pvdD/pvdE, pvdD, lasR- and hlbR were shown defective in the various assays. This suggested a central place for the siderophore pyoverdine as the key inhibitory molecule, although additional quorum sensing-regulated factors likely contribute to the deficiency of the latter two mutants. Studies of pure pyoverdine substantiated these results and restored inhibition by pyoverdine deletion mutants. Added iron or hemin reversed the inhibition by pyoverdine-producing Pa strains.

Conclusion. The key inhibitor for Af biofilms produced by Pa is pyoverdine. The inhibitory mechanism is chelation of iron, and denial of iron to Af.

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280. Aedes aegypti and Aedes albopictus Occurrences in Guatemala
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Session: 49. Global Health Potpourri
Thursday, October 5, 2017: 12:30 PM

Background. Recent emergence of zika and chikungunya along with the continuous prevalence of dengue in Guatemala has become a threat to public health resulting in high morbidity and mortality. According to national epidemiologic vigilance reports, the prevalence for dengue, chikungunya, and zika are 53.42, 30.96, and 19.02 per 100,000 inhabitants respectively. Despite cases of the diseases being reported worldwide, the regional occurrences of Aedes aegypti and Aedes albopictus are unknown, with some studies reporting the presence of the vectors in only four of 22 departments.

Methods. National active larval entomologic surveillance information was obtained and the results where validated through Geographical Information Systems tools to generate a map of occurrences of either Aedes aegypti or Aedes albopictus. The information compared with the reported occurrences of the dengue and chikungunya.
281. Efficacy of a Novel Nutritional Product in Acute Childhood Diarrhea in Guatemala: Secondary and Exploratory Analyses of a Randomized, Double Blind, Placebo Controlled Trial

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Session: 49. Global Health Potpourri
Thursday, October 5, 2017: 12:30 PM

Background. PTM202 is a nutritional intervention for acute diarrhea that combines bovine colostrum with egg produced by hens vaccinated with USDA approved vaccines to standardize the levels of pathogenic specific immunoglobulin-Y which target rotavirus, enterotoxigenic E. coli, shigatoxin + E. coli, and Salmonella. In a randomized, double-blind, placebo-controlled trial, PTM202 shortened acute non-bloody diarrhea in Guatemalan children who had ≥1 targeted organism in stool. To further define the clinical relevance of these findings, we conducted secondary and exploratory analyses of study outcomes.

Methods. From 3/2015 to 1/2016, 323 children 6–35 months with acute non-bloody diarrhea were randomized at three sites (1 rural, 2 urban) to one oral dose daily for 3 days of study product or placebo. Diarrheal pathogens on Day 1 were determined by multiplex PCR (FilmArray GI Panel, BiFireTech). Efficacy was measured by stool pathogen specific IgG. Efficacy was assessed by secondary targeted organisms.

Results. In urban patients with at least one targeted organism, statistically significant efficacy of the study product was noted in 1, 2, and 3 days (Table). No effect was demonstrated in analysis of all subjects, or in subjects with targeted organisms from the rural area (who had more targeted and non-targeted stool pathogens and poorer nutritional status). No impact of study treatment on 2 or 4 weeks weight gain was noted in overall or stratified analyses.

Conclusion. PTM202 appears to shorten diarrhea duration in children with targeted stool pathogens, and may add to the therapeutic armamentarium against one of the major global causes of pediatric morbidity. Exploratory analysis suggests that three doses may not be required for efficacy - which would be a tremendous advantage for taking this treatment to scale in low and middle income countries - and will form the basis of future clinical trials.

Table: Efficacy at days 1, 2, 3, and 7 after first study dose: urban children with ≥1 targeted pathogen

| % resolved diarrhea | Day | PTM202 | Placebo | Efficacy, % | P (2) |
|---------------------|-----|--------|---------|-----------|-----|
| 1                   | 56.0 | 25.0   | 41      | 0.021     |
| 2                   | 88.0 | 64.3   | 66      | 0.045     |
| 3                   | 96.0 | 71.4   | 86      | 0.026     |
| 7                   | 100.0| 89.3   | 100     | 0.002     |

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282. Endoscopic Characteristics Comparison of Helicobacter pylori and Orientia tsutsugamushi Infection

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Session: 49. Global Health Potpourri
Thursday, October 5, 2017: 12:30 PM

Background. Aside from Helicobacter pylori, another cause for the development or worsening of gastrointestinal ulcers is scrub typhus, an acute febrile disease caused by Orientia tsutsugamushi. We aimed to compare the endoscopic characteristics of peptic ulcers caused by these infectious agents.

Methods. This retrospective case–control study involved patients who underwent upper gastrointestinal endoscopy at Chosun University Hospital in Korea.

Results. In total, 141 patients with peptic ulcer were included in the study. Compared with patients with O. tsutsugamushi infection (n = 62; age, 63.8 ± 12.1 years; male sex, 42%), those with H. pylori infection (n = 79; age, 53.0 ± 14.8 years; male sex, 81%) were younger and more likely to be male (P < 0.001 for both). Patients with O. tsutsugamushi infection were more likely to have multiple lesions (40/62, 64.5% vs. 37/79, 46.8%; P = 0.042) and irregular-shaped lesions (27/62, 43.6% vs. 20/79, 25.3%; P = 0.031). Patients with H. pylori infection had higher incidence of hemorrhagic ulcers (28/79, 32.9% vs. 8/62, 12.9%; P = 0.007), and lesions occurred more often in the antrum (43.6%), followed by the antrum and body (33.9%), body (34.2%), and angle (12.7%) of the stomach. In patients with O. tsutsugamushi infection, lesions occurred most often in the antrum (70.9%) of the stomach. In both groups, gastric ulcer lesions occurred most often in the antrum, followed by the body and angle of the stomach (16.7% vs. 16.7% and 11.1% vs. 11.1%, respectively). Compared with H. pylori and O. tsutsugamushi infection, respectively. Patients with O. tsutsugamushi infection had significantly higher incidence of ulcers on the antrum (79.6% vs. 36.7%, P < 0.001) and the greater curvature (45.2% vs. 24.0%, P = 0.012). Finally, 38.5% of patients with gastric ulcer caused by scrub typhus also had duodenal ulcer.

Conclusion. This is the first study to compare endoscopic features of peptic ulcers caused by H. pylori and O. tsutsugamushi. Peptic ulcers in patients with H. pylori infection occurred predominantly in the antrum/body/lesser curvature and presented with irregular-shaped lesions. Patients with scrub typhus occurred predominantly in the antrum/greater curvature and presented with multiple, irregular lesions. Scrub typhus should be considered as a cause of duodenal ulcer in scrub typhus-endemic areas.

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283. Soil-Transmitted Helminths Prevalence in Refugees Arriving to Colorado in 2009–2012

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Session: 49. Global Health Potpourri
Thursday, October 5, 2017: 12:30 PM

Background. Refugees are at high risk for contracting soil-transmitted helminths (STH) infections. The CDC advises presumptive pre-departure albendazole treatment to reduce STH infection rate. We aimed to determine the rate and prevalence of STH infections among refugees arriving from countries providing presumptive pre-departure albendazole treatment.

Methods. We retrospectively examined CDPHE data, which included results of stool O&P studies on 3,870 newly arrived refugees to Colorado (2009–2012). We examined the rate of STH infection by country and pre-departure albendazole treatment status. We excluded children under the age of 1 for whom albendazole treatment is generally contraindicated.

Results. In total, 3,870 refugees underwent screening with stool O&P; 1,668 received treatment with albendazole while 2,202 did not. 478 of 3,870 (12.3%) were positive for pathogenic parasites. Of these, a majority were pathogenic STH (55, 11.5%). Thailand and Malaysia had the highest prevalence of stool samples positive for pathogenic STH (2.12% and 2.59%, respectively), followed by nepal with the lowest prevalence (0.39%). A lower proportion of albendazole-treated patients was positive for a pathogenic STH on stool O&P relative to untreated individuals (0.78% vs. 1.91%, P = 0.05).

Conclusion. Among newly arriving refugees to Colorado, more than 1 in 10 was positive for a pathogenic parasite; a smaller proportion was positive for a pathogenic STH infection. Although albendazole pretreatment appears to lower the rate of pathogenic STH positivity on stool O&P, the rate among untreated individuals was lower than prior estimates.

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284. High Prevalence of Parasitic Infections Among Recent Immigrants in Chicago

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Poster Abstracts • OFID 2017:4 (Suppl 1) • S117