results between the immune and non-immune groups were demonstrated in Table. In the logistic regression analysis, only patients’ age was found statistically significant predictor for immunity against tethanos (OR: 1.114 95% CI: 1.047–1.185).

**Conclusion.** We found that elderly patients with DFH have very low rate of immunization against tethanos. Therefore, tethanos vaccination should be given particularly to the elderly patients with DFH without any serological control.

| Characteristics                              | Immune patients (n = 26) | None-immune patients (n = 65) | P       |
|----------------------------------------------|--------------------------|-------------------------------|---------|
| Age (year) (Mean ± SD)                       | 53.3 ± 12.1              | 65.1 ± 8.6                    | 0.0001  |
| Age of diabetes (year) (Mean ± SD)           | 12.6 ± 8.1               | 16.4 ± 8.1                    | 0.042   |
| GEND ER                                      | Male, n (%)              | 21 (31.8)                     | 45 (68.2)| 0.265  |
|                                              | Female, n (%)            | 5 (20)                        | 20 (60) |         |
|                                              | Residency status         |                               |         |         |
|                                              | Urban, n (%)             | 24 (34.3)                     | 46 (65.7)| 0.028  |
|                                              | Rural, n (%)             | 2 (9.5)                       | 19 (90.5)|         |
|                                              | Educational status       |                               |         |         |
|                                              | Primary–Secondary School, n (%) | 20 (24.7) | 61 (75.3)| 0.029  |
|                                              | High School-University, n (%) | 6 (60)                   | 4 (40)  |         |
| Knowledge about vaccination history          | Full covered, n (%)      | 3 (50)                        | 3 (50)  | 0.461  |
|                                              | Not covered, n (%)       | 4 (30.8)                      | 9 (69.2) |         |
|                                              | Unknown, n (%)           | 19 (26.4)                     | 53 (73.6)|         |

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**271. Development of a Clinically Relevant Murine Model of Fungal (Aspergillus) Endophthalmitis**

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**Background.** Aspergillus fumigatus (AF) is the leading cause of exogenous endophthalmitis following traumatic injury to the eye, especially in tropical regions of the world. Delays in the identification and treatment of fungal endophthalmitis can result in significant vision loss. The aim of this study is to develop a mouse model of AFendophthalmitis and investigate the pathophysiology.

**Methods.** Endophthalmitis was induced in wild-type, C57BL/6, mice by intravitreal injections of varying doses of A. fumigatus spores. Disease progression was monitored by assessing corneal and vitreous haze and opacity, the fungal burden, and retinal tissue damage. Eye examination was performed using the slit-lamp and retinal fundus imaging at the desired time points post fungal infection. Fungal burden (CFU/eye) was determined from the whole-eye lysates using a standard plate count method. qRT PCR and ELISA were used to assess the level of inflammatory cytokines/chemokines. Flow cytometry and Immunostaining were used to assess PMN infiltration. Histological analysis was used to assess retinal tissue damage.

**Results.** In immunocompetent B6 mice, AF caused reproducible endophthalmitis only at the higher dose, i.e., ~10,000 spores/eye. Time-course study revealed increased corneal haze and opacity within 2 day post infection (dpi). The fungal burden in infected eyes peaked significantly (P < 0.5) at 2 dpi and declined thereafter up to 9 days. AF-infected eyes exhibited increased PMN infiltration as well as elevated levels of inflammatory mediators (TNFa, IL-1β, and IL6), both at mRNA as well as protein levels. Histological analysis revealed heavy cellular infiltrates in vitreous cavity as well as disruption of normal retinal architecture/histology, increased cell death (TUNEL positivity) as compared with uninfected control eyes. AF-infected neuroretina exhibited upregulation of pathogen recognizing receptors such as Toll-like receptors (TLRs).

**Conclusion.** Here, we describe the first immunocompetent murine model of Aspergillus endophthalmitis. This model can be utilized to study the pathogenesis of exogenous fungal endophthalmitis and to potentially evaluate the therapeutic efficacy of existing and newer antifungal agents in the eye.

**Disclosures.** All authors: No reported disclosures.

**272. De novo STAT3 Mutation in a Patient with Fatal, Treatment-Refractory Sino-orbital Aspergillosis**

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**Background.** Pa and AF are pathogens frequently found together in airways of immunocompromised patients and patients with cystic fibrosis (CF). Hence, interactions of Pa and AF require understanding. Both Pa and AF are crucially dependent on the availability of iron, and therefore are competitors in their microenvironment. We have shown, using deletion mutants of Pa, that the Pa siderophore pyoverdine, the dominant Pa inhibitor of AF, interferes with AF biofilms by iron chelation, and denial of iron to the fungus.

**Methods.** Protective compounds in AF supernatants were evaluated using assays for the quantification of AF biofilm metabolism by XTT measurement, spectrometric pyoverdine measurement, as well as Chrome Azoreol S (CAS) assay for the determination of siderophore production.

**Results.** Here we provide evidence that whereas iron usage by AF promotes pyoverdine production by Pa, AF has developed a defense mechanism against anti-fungal pyoverdine effects. The ability of AF to produce hydroxamate siderophores, and shed these into the surrounding medium, where they sequester and transport iron, is a key factor for AF self-defense against Pa. Under low iron conditions, such as in the presence of high amounts of the Pa siderophore pyoverdine, siderophore-bound iron is then led to AF, protecting the fungus from iron starvation. AF with a deletion mutation in sidA, a gene essential for the production of hydroxamate siderophores, was significantly more sensitive to Pa supernatants, as well as pure pyoverdine, than wild-type AF. AF supernatants, produced in the presence of celastrol, an inhibitor of SidA-generated biosynthesis of siderophores, or produced by the sidA mutant, were not able to protect AF from iron starvation.

**Conclusion.** Interference with the iron-dependent AF self-defense mechanism might represent a new approach for therapy against aspergillosis.

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posaconazole 0.25, terbinafine 0.06, and voriconazole 0.25. The patient underwent multiple surgical debridements and was treated over time with various antifungals (amphotericin B, micafungin, terbinafine, voriconazole, posaconazole), adjunct cytokines (IFN-γ, GM-CSF), and hyperbaric oxygen. However, the infection progressed into the right middle cranial fossa and meninges and the patient died 1 year after symptoms began. Post-mortem histology revealed a de novo spore-site mutation in STAT3 (c.1140 C>G). CDNA sequencing showed nonsense mediated decay of the affected allele. No mutations in CARD9 or NDP52 oxidase subunits were found; a DHRR test was normal. The patient had normal blood myeloid cell subsets. Serum IgE level was elevated at 833 IU/ml, serological tests for C. albicans were positive, and the patient’s memory CD4+ T cells and CD1c+ myeloid cells had reduced pSTAT3 levels compared with control cells. Cellular analysis of SOCS3, a STAT3-dependent downstream target, is underway to evaluate for functional STAT3 haploinsufficiency.

**Conclusion.** A novel de novo STAT3 splice site mutation results in impaired pSTAT3, and is associated with elevated IgE, eosinophilic esophagitis, and sino- orbital aspergillosis without other common features of Job’s syndrome.

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273. C5ar1-dependent phagocyte effector functions protect against systemic candidiasis  

Igjar V. Desai, PhD; Claudia Kemper, PhD; Jörg Köhl, MD; and Michail Lionakis, MD, ScD; Fungal Pathogenesis Unit, Laboratory of Clinical Infectious Diseases, NIAID, NIH, Bethesda, Maryland, Laboratory of Complement and Inflammation Research, NHLBI/NIH, Bethesda, Maryland, Inst. for Systemic Inflammation Research University of Lübeck, Lübeck, Germany, Mountains, not dendritic cells, express C5ar1 in the infected kidney; phagocyte C5ar1 expression was essential for survival we found that neutrophils, monocytes and macrophages, not dendritic cells, are critical for protection; yet, the molecular basis of phagocyte-mediated neutrophil recruitment in the infected kidney, but mediates neutrophil and macrophage fungal killing. The myeloid cell-type independent of the FCY2-FCY1-FUR1 pathway.

**Results.** C5ar1 and C5ar2 transcripts and their ligand C5a were induced post-infection in WT mouse kidney. C5ar1 KO mice showed dramatically increased susceptibility as compared with WT mice (100% mortality vs. 40%; P < 0.0001). Significantly greater fungal burden and tissue injury were observed in C5ar1 KO, but not in C5ar2 KO kidneys. BM radiation chimera experiments showed that hematopoietic, not stromal, C5ar1 expression promotes protection. Using GFP-C5ar1 reporter mice, we found that macrophages and neutrophils express C5ar1 in the infected kidney; phagocyte C5ar1 expression was essential for survival, with AAV-Cre/GFP-C5ar1tg mice succumbing to infection similar to C5ar1 KO mice. Mechanically, C5ar1 does not mediate phagocyte recruitment in the infected kidney, but mediates neutrophil and macrophage fungal killing. The reproducible cell-type specific contribution is under investigation using S100a8-Cre/GFP-C5ar1tg and Cxcr1-Cre/GFP-C5ar1tg mice as are the molecular mechanisms that promote C5ar1-dependent effector function.

**Conclusion.** C5ar1 is required for host survival during systemic candidiasis via regulating the antifungal effector function of phagocytes.

**Disclosures.** All authors: No reported disclosures.

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274. VT-1598 Inhibits the in vitro Growth of Mucosal Candida Isolates and Protects Against Oropharyngeal Candidiasis in IL-17 Deficient Mice  

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**Background.** Systemic candidiasis, the most common nosocomial human fungal infection, leads to mortality of >40% despite antifungal therapy. Myeloid phagocytes, not lymphocytes, are critical for protection; yet, the molecular basis of phagocyte-mediated neutrophil recruitment in the infected kidney, but mediates neutrophil and macrophage fungal killing. The myeloid cell-type independent of the FCY2-FCY1-FUR1 pathway.

**Results.** In vivo, VT-1598 significantly more effective, with compared with FLC, against FLC-susceptible and -resistant C. albicans, and led to elimination of fungal growth even at the lowest tested dose (3.2 mg/kg). After a 10-day washout period from the last dose, mice treated with VT-1598 did not have mucosal fungal growth, while mice treated with FLC had fungal loads similar to vehicle control.

**Conclusion.** VT-1598 shows in vitro activity against mucosally derived Candida, including FLC-resistant strains. In vivo, VT-1598 achieves high plasma concentrations and is orally bioavailable. C. albicans infection and once-daily oral treatment for 4 days with 25 mg/kg FLC or 3.2, and 20 mg/kg VT-1598 starting 18 hours post-infection.

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275. Replicative Aging in Candida auris Has an Effect on Antifungal Resistance  

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**Background.** Candida auris can colonize patients for a prolonged time causing life-threatening systemic infections. Replicative aging is the result of asymmetric division which cause phenotypic changes between mother and daughter cells. We have previously published that older Cryptococcus neoformans and C. albbrata cells exhibit enhanced resistance to antifungals including fluconazole (FLC), five fluocytosine (SFC), and sub-therapeutic amphotericin B (AMB). Additionally, they are more resistant to macrophage and neutrophil killing. This is relevant because older candidal cells accumulate in chronic infections. We hypothesized that older C. auris cells would also exhibit enhanced resistance to phagocytic cells and can alter drug resistance.

**Methods.** Magnetically labeled cells were grown for 10 generations (Gen) and then were seeded from dash 0 Gen and 4 Gen. After 4Gen, cells were treated with dexamethasone and macrophages were treated with R6G, whereas the three FLC sensitive isolates showed low efflux of R6G. Using these methods, we observed significant (1.5 to 2.0 fold, P < 0.05) increase in efflux activity of older cells would also exhibit enhanced resistance to phagocytic cells and can alter drug resistance.

**Results.** In C. auris, 10 Gen old cells are larger than younger cells (0–3 Gen) and exhibit a thicker cell wall on TEM. The older cells are significantly more resistant to neutrophil killing (24.5% vs. 51.6%, P < 0.05 by paired t-test)). Eleven distinct isolates manifest variable virulence in the Galleria infection model. Minimum inhibitory concentration to the antifungals was performed by CSLI methods. Rhodamine 6G (R6G), which is a fluorescent substrate for ABC-transporters, was used to measure efflux.

**Conclusion.** In C. auris, 10 Gen old cells are larger than younger cells (0–3 Gen) and exhibit a thicker cell wall on TEM. The older cells are significantly more resistant to neutrophil killing (24.5% vs. 51.6%, P < 0.05 by paired t-test)). Eleven distinct isolates manifest variable virulence in the Galleria infection model. Minimum inhibitory concentration to the antifungals was performed by CSLI methods. Rhodamine 6G (R6G), which is a fluorescent substrate for ABC-transporters, was used to measure efflux.

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276. Mechanisms of Fluocytosine Resistance in Cryptococcus gattii May Be Independent of the FCY2-FCY1-FUR1 Pathway  

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