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REVIEW

Sixty Years from Segretain's Description: What Have We Learned and Should Learn About the Basic Mycology of *Talaromyces marneffei*?

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Abstract The fungus *Talaromyces marneffei* was described by Professor Gabriel Segretain in 1959, originally as a member of the genus *Penicillium*. As early as 60 years ago, its peculiarity in exhibiting temperature-dependent morphological dimorphism, its characteristic ability to secrete diffusing red pigment during the mycelial phase and its pathogenicity have already been recognised. Six decades have passed, and our understanding on this intriguing fungus has improved. Apart from the clinical aspect, we have gained a glimpse on its taxonomy, animal or environmental source(s), mechanism of thermal dimorphism, molecular genetics, virulence as well as pathogenesis. However, we are still on our way to get out of the talaromycosis mist. A lot more collective endeavour on *T. marneffei* research is needed to solve the jigsaw puzzle.

Keywords *Talaromyces marneffei* · Segretain · Sixty years · Anniversary

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This year marks the 60th anniversary of the official description of the thermally dimorphic fungus, *Talaromyces marneffei* (previously called *Penicillium marneffei*), which is an important fungal pathogen endemic in Southeast Asia especially to HIV-positive patients, by Professor Gabriel Segretain [1]. This fungus was first isolated in 1955 by Capponi and Sureau from laboratory Chinese bamboo rats (*Rhizomys sinensis*), which are native in the Central Highlands of Vietnam, at Institut Pasteur de Dalat [2], where it caused fatal spontaneous disseminated infection involving the reticuloendothelial system in three of the rats. The pathogenicity of *T. marneffei* was further demonstrated by Segretain, Capponi and Sureau in various animal models, including mice, rats, hamsters and guinea pigs [2, 3].

Six decades have passed since the discovery of *T. marneffei*; however, our understanding on this peculiar fungus is still poor despite its clinical significance. Such a lack of knowledge could be reflected by the fact that up to the end of August 2019, there are only ~730 published articles about *T. marneffei* indexed in PubMed. This figure significantly lags behind those

for *Aspergillus fumigatus* (~11,480 articles) as well as other thermally dimorphic pathogenic fungi such as *Histoplasma capsulatum* (~4050 articles) and *Coccidioides immitis*/*C. posadasii* (~2020 articles), and it is only slightly more than two times than that for the notorious, recently emerged multidrug-resistant yeast, *Candida auris*, discovered in 2009 (~300 articles). *Mycopathologia*, as a journal dedicated to the understanding of human and animal fungal diseases with over 80 years of history [4], has long supported research on *T. marneffei*. Notably, around 4% of the ~730 *T. marneffei* articles were published in *Mycopathologia* [3, 5–34], including one of the initial works by Segretain [3].

Since the first discovery of *T. marneffei*, its taxonomy had remained stable until early 2010s. The original description by Segretain depicted *T. marneffei* as a *Penicillium*-like fungus (and so it was first named as '*P. marneffei*'), and this fungus was classified in *Penicillium* section *Biverticillium* following Biourge's taxonomy or section *Asymmetrica* subsection *Divaricata* following Raper's and Thom's taxonomy [1]. At room temperature, its morphology was found to partly resemble *P. janthinellum* and *P. citrinum*, with bluish light grey–green colonies and diffusing red pigment (Fig. 1a, b). However, at 37 °C '*P. marneffei*' exhibited a very different morphology. Colonies were bacterial-like, hairless, colourless, matt smooth at first and later pleated cerebriform, with no diffusing pigment. Instead of hyphal filaments, the fungus was composed of separate arthroconidia at this temperature, which were divided by transverse partitioning (fission) [1] but not budding [2]. In mature culture, the cells were almost spherical in shape and this was similar to the morphology of the fungus in vivo [3] (Fig. 1c–e). The affiliation of the fungus to the genus *Penicillium*, based on phenotypic characteristics, had lasted for over 50 years. In 2011, based on phylogenetic analyses inferred from the RNA polymerase II largest subunit gene (*RPB1*) and internal transcribed spacer (ITS) region as well as extrolite profiling, '*P. marneffei*' was transferred to the genus *Talaromyces* together with other members of *Penicillium* subgenus *Biverticillium*. As a result, the fungus attained its present name '*T. marneffei*' [35]. Such transfer was also supported by phylogenetic analysis based on mitochondrial genomes [36]. Currently *T. marneffei* is the only member of the genus recognised to cause invasive infections in humans and animals.

Given the high mortality rate of *T. marneffei* infection in untreated patients, especially in immunocompromised patients, it is important to identify the possible sources of talaromycosis. In particular, the fact that HIV patients who have travel histories to endemic areas could also become infected by *T. marneffei* implies that short-term exposure to the source(s) of the fungus is sufficient to trigger infection and that the infection source(s) should originate from an environment contacted by tourists [37]. Studies beginning from the 1980s identified a number of bamboo rats species, including Chinese bamboo rats, hoary bamboo rats (*R. pruinosus*), large bamboo rats (*R. sumatrensis*) and lesser bamboo rats (*Cannomys badius*), as the natural carriers of *T. marneffei* in southern China, central and northern Thailand as well as India [9, 19, 38–45]. The fungus could also be recovered from the faeces of bamboo rats as well as soils from their burrows [40, 43, 45, 46]. Apart from bamboo rats and their associated soil samples, recently the fungus has been detected from nasal swabs of outdoor dogs in Chiang Mai, Thailand, as well, although fungal culture was not successful [37]. A case-control study in 1997 demonstrated that exposure to or consumption of bamboo rats did not constitute a risk factor for talaromycosis [47]. There was also no significant association between exposure to bamboo thickets or forests, where the rodents reside, to *T. marneffei* infection [47]. Instead, it was shown that recent occupational exposure to animals or plants, probably involving soil, was associated with talaromycosis [47]. Indeed, a previous environmental study detected *T. marneffei* from soil samples collected outside the habitats of bamboo rats, including a bat cave, an elephant camp and surroundings of a Buddhist Temple using molecular methods [48]. Unfortunately, viable culture of the fungus could still not be obtained from these positive soil samples [48]. These findings suggested that an environmental reservoir, likely soil, should exist for *T. marneffei* and humans and bamboo rats, and possibly dogs, may acquire the infection from this common environmental source. Interestingly, although earlier studies in Thailand and Vietnam showed that the incidence of *T. marneffei* infection increased during rainy season [49, 50], a later study in Vietnam found that humidity, but not rainfall, temperature nor wind, was the environmental predictor of *T. marneffei* hospital admission [51]. It was suspected that humidity may

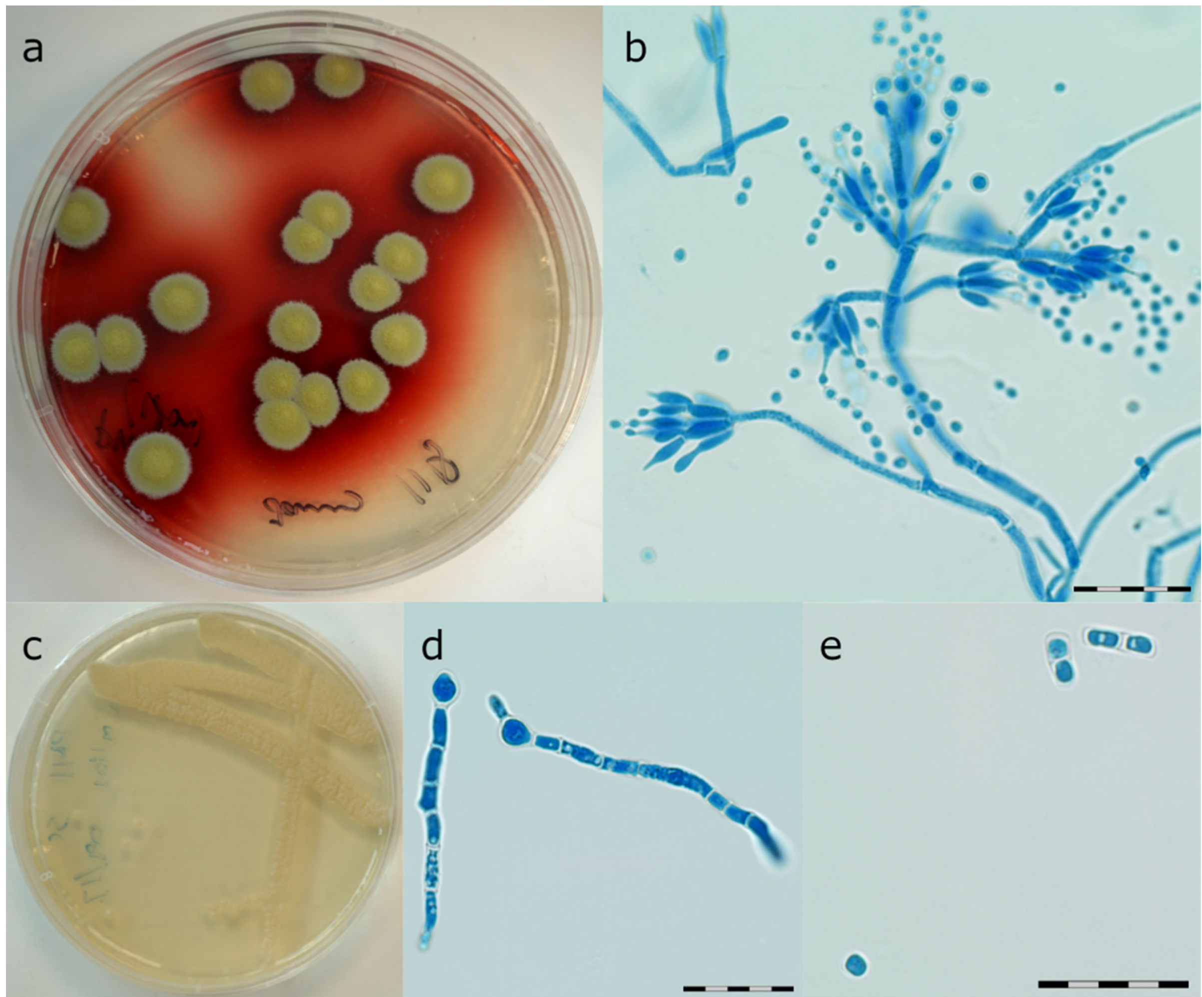

Fig. 1 Morphology of *Talaromyces marneffei*. **a** On Sabouraud glucose agar, after 6 days of incubation at room temperature, colonies are yellowish green with diffusing red pigment. **b** The conidiophores are usually biverticillate. Oval, smooth-walled conidia are produced in chains. Scale bar = 20 µm. **c** On Sabouraud glucose agar, after 6 days of incubation at 37 °C, colonies are yeast-like and creamy. Diffusing red pigment is no longer observed. **d** In Sabouraud glucose broth, after 3 days of incubation at 37 °C with shaking at 250 rpm, the fungus grows as short hyphae composed of undissociated arthroconidia. Scale bar = 20 µm. **e** In yeast nitrogen base supplemented with 1% mycological peptone [118], after 3 days of incubation at 37 °C with shaking at 250 rpm, arthroconidiation is not observed. Instead, the fungus grows as individual yeast-like cells and divides by fission and this mode of growth resembles the in vivo situation. Scale bar = 20 µm

facilitate the environmental reservoir of *T. marneffei* to expand, favour fungal growth or aid in conidia release into the environment [51]. Further efforts are in need to determine the environmental source(s) of this fungus and to connect this/these environmental reservoir(s) with the animal hosts and humans such that the route of infection acquisition can be identified or confirmed.

Temperature-dependent morphological dimorphism is one of the characteristics of *T. marneffei*. Indeed, this fungus is the only known *Talaromyces* species exhibiting such a feature. Although the change in morphology has been well studied during phase transition [52], the underlying molecular mechanism still warrants much further investigation. From 2000 onwards, a number of genes have been identified to be involved in morphogenesis and during phase transition, including *abaA* [53], *brlA* [54], *cflA* [55], *cflB* [56], *drkA* [57], *gasA* [58], *gasC* [59], *hgrA* [60], *madsA* [61, 62], *myoB* [63], *pakA* [64], *pakB* [65],

PmHHK1 [66], *rasA* [67], *rfxA* [68], *rttA* [69], *sadA* [70], *sakA* [71, 72], *slnA* [57], *sskA* [73], *stuA* [74], *tupA* [54] and *yakA* [75], by loss-of-function studies. The majority of these genes are related to transcriptional regulation [53, 54, 60, 62, 68, 74] or G-protein signalling [55, 56, 58, 59, 67] or encode kinases [57, 64–66, 71, 72, 75]; the functions of these genes were recently thoroughly reviewed by Andrianopoulos and his colleagues [76, 77]. Other than these genes, differentially expressed gene analyses by suppression subtractive hybridisation [78], microarray [79, 80] or RNA-sequencing [61, 81] identified groups of genes that are signature to phase transition. In addition to protein-coding genes, small RNA-sequencing also revealed 24 microRNA-like small RNA (milRNA) candidates which were more abundantly expressed during the hyphal stage than the yeast phase [82]. However, further functional studies are needed to authenticate the participations of these genes in dimorphic switching. Moreover, how *T. marneffei* detects the temperature stimulus and transduces the environmental signals to effect morphological change is still unclear. Elucidation of the molecular mechanism for this could help reveal potential drug targets for stopping dimorphic switching to the yeast phase in vivo so as to prevent the fungus from evading host immune response by hiding intracellularly.

The advancement of various omics technologies in the twenty-first century has allowed more in-depth and sophisticated characterisation of the mycology of *T. marneffei*. The first draft genome of the fungus, based on the original ex-type strain ATCC 18224^{T} isolated by Capponi and Sureau, was sequenced using the Sanger strategy. It was around 28 Mb in length and was released online in 2007 [83]. A few years later, using a similar approach the draft genome for a second strain (PM1), isolated in Hong Kong, was published [84]. Subsequent second- and third-generation sequencing technologies further improved this draft genome [61]. Earlier this year, the genome of *T. marneffei*, based on a Chinese clinical strain TM4, was completed with the help of optical mapping; it was revealed that the *T. marneffei* genome consisted of eight chromosomes [85]. The availability of the whole genome sequences of *T. marneffei* has boosted further research on this fungus, especially in the past decade; knowledge generated from the fungal genomes as well as additional transcriptomic, proteomic and metabolomic studies was discussed in detail in a recent review [86]. One example was that the pigmentation phenomenon observed for *T. marneffei* could now be explained, with the molecular identities of the various pigments uncovered [87–90].

While there is accumulating information about the basic mycology of *T. marneffei*, it is equally important to understand what makes this special fungus a successful pathogen to humans and animals. Thermal dimorphism, as discussed above, is one of the more well-studied properties of the fungus which aids in causing infection. Apart from this, a number of virulence factors of *T. marneffei* have been identified. These virulence mechanisms include the production of melanin [87, 91, 92], mitorubrinol and mitorubrinic acid (yellow pigment) [88], aspartyl protease [93], catalase–peroxidase [94], laccases [95] and superoxide dismutase [96], induction of the glyoxylate cycle at host's body temperature [97–99], utilisation of non-preferred nitrogen sources in host's environment [100], utilisation of the methylcitrate cycle for detoxification of propionyl-CoA [101] as well as sequestration of host's proinflammatory lipids [102–105]. Interestingly, a study last year found that *T. marneffei* infected with the mycovirus *Talaromyces marneffei partitivirus*-1 exhibited hypervirulence in a murine model [106], although the underlying mechanism still awaits additional investigation. In addition to the intrinsic virulent properties of *T. marneffei*, how it interacts with the human/animal hosts may also contribute to pathogenicity. Although the infection route for talaromycosis is still unclear as discussed above, it is generally believed that patients acquire pathogenic conidia through inhalation. After entering the host's airway, conidia bind to the extracellular matrices [107–110], which is mediated by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [110], and adhere to the host bronchoalveolar epithelium. There, the fungus interacts with epithelial cells [111, 112] and is phagocytosed by pulmonary macrophages. Our limited understanding on macrophage immunity against *T. marneffei* and the fungal adaptation response was summarised in three review articles [52, 77, 113]. Yet, the ability of *T. marneffei* to survive inside macrophages might also help them evade host immunity [52, 77]. In addition to macrophage response, CD4^{+} T cells were also shown to be key mediators in anti-*T. marneffei* response [114, 115]. It is of note that there have been an

increasing number of talaromycosis cases in patients with non-HIV-related immunodeficiency in recent years [116] and whether the pathologies in these patients are the same or similar to those observed in HIV-positive patients requires further research. A number of experimental infection models, including nematode (*Caenorhabditis elegans*), greater wax moth (*Galleria mellonella*), zebrafish (*Danio rerio*), mouse (*Mus musculus*) and human primary monocyte-derived macrophages, have been established for *T. marneffei*, and their pros and cons were reviewed in a recent article by Weerasinghe et al. [77]. More studies are needed to verify how representative these infection models are for the in vivo conditions during *T. marneffei* infections in humans.

Following 60 years of effort, the mist of *T. marneffei* has somehow faded away. We have gained some knowledge on its taxonomy, source(s), underlying mechanism of thermal dimorphism, molecular genetics, virulence and pathogenesis. However, the jigsaw puzzle is still far from completion. Continuous collective endeavour is needed to uncover the *T. marneffei* mystery so that this fungus, currently recognised as one of the ten most feared fungi in the world [117], no longer poses threats to humanity.

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Compliance with Ethical Standards

Conflict of interest Patrick C. Y. Woo has provided scientific advisory/laboratory services for Gilead Sciences, Incorporated, International Health Management Associates, Incorporated, Merck & Corporation, Incorporated, and Pfizer, Incorporated. The other authors report no conflicts of interest. The funding sources had no role in study design, data collection, analysis, interpretation or writing of the report. The authors alone are responsible for the content and the writing of the manuscript.

References

1. Segretain G. Description d'une nouvelle espèce de *Penicillium*: *Penicillium marneffei* n.sp. Bull Soc Mycol Fr. 1959;75:412–6.
2. Capponi M, Sureau P, Segretain G. Pénicilliose de *Rhizomys sinensis*. Bull Soc Pathol Exot. 1956;49:418–21.
3. Segretain G. *Penicillium marneffei* n. sp., agent d'une mycose du système réticulo-endothélial. Mycopathol Mycol Appl. 1959;11(4):327–53.
4. Chaturvedi V, Bouchara J-P, Hagen F, Alastruey-Izquierdo A, Badali H, Bocca AL, et al. Eighty years of *Mycopathologia*: a retrospective analysis of progress made in understanding human and animal fungal pathogens. Mycopathologia. 2018;183(6):859–77.
5. Sekhon AS, Li JSK, Garg AK. *Penicillosis marneffei*: serological and exoantigen studies. Mycopathologia. 1982;77(1):51–7.
6. Kaufman L, Standard P, Padhye AA. Exoantigen tests for the immunoidentification of fungal cultures. Mycopathologia. 1983;82(1):3–12.
7. Imwidthaya P. Update of penicillosis marneffei in Thailand. Mycopathologia. 1994;127(3):135–7.
8. Sekhon AS, Stein L, Garg AK, Black WA, Glezos JD, Wong C. Pulmonary penicillosis marneffei: report of the first imported case in Canada. Mycopathologia. 1994;128(1):3–7.
9. Ajello L, Padhye AA, Sukroongreung S, Nilakul CH, Tantimavanic S. Occurrence of *Penicillium marneffei* infections among wild bamboo rats in Thailand. Mycopathologia. 1995;131(1):1–8.
10. Ajello L, Padhye AA, Sukroongreung S, Nilakul CH, Tantimavanic S. Erratum to: Occurrence of *Penicillium marneffei* infections among wild bamboo rats in Thailand. Mycopathologia. 1996;135(3):195.
11. Imwidthaya P, Sekhon AS, Mastro TD, Garg AK, Ambrosie E. Usefulness of a microimmunodiffusion test for the detection of *Penicillium marneffei* antigenemia, antibodies, and exoantigens. Mycopathologia. 1997;138(2):51–5.
12. Kaufman L. *Penicilliosis marneffei* and pythiosis: emerging tropical diseases. Mycopathologia. 1998;143(1):3–7.
13. Imwidthaya P, Thipsuvan K, Chaiprasert A, Danchaivijitra S, Sutthent R, Jearanaisilavong J. *Penicillium marneffei*: types and drug susceptibility. Mycopathologia. 2001;149(3):109–15.
14. Liyan X, Changming L, Xianyi Z, Luxia W, Suisheng X. Fifteen cases of penicilliosis in Guangdong, China. Mycopathologia. 2004;158(2):151–5.
15. Cao C, Liu W, Li R. *Penicillium marneffei* SKN7, a novel gene, could complement the hypersensitivity of *S. cerevisiae skn7* disruptant strain to oxidative stress. Mycopathologia. 2009;168(1):23–30.
16. Zeng H, Li X, Chen X, Zhang J, Sun J, Xie Z, et al. Identification of *Penicillium marneffei* in paraffin-embedded tissue using nested PCR. Mycopathologia. 2009;168(1):31–5.
17. Cao C, Bulmer G, Li J, Liang L, Lin Y, Xu Y, et al. Indigenous case of disseminated histoplasmosis from the *Penicillium marneffei* endemic area of China. Mycopathologia. 2010;170(1):47–50.
18. Luo D-Q, Chen M-C, Liu J-H, Li Z, Li H-T. Disseminated *Penicillium marneffei* infection in an SLE patient: a case report and literature review. Mycopathologia. 2011;171(3):191–6.

19. Li X, Yang Y, Zhang X, Zhou X, Lu S, Ma L, et al. Isolation of *Penicillium marneffei* from soil and wild rodents in Guangdong, SE China. Mycopathologia. 2011;172(6):447–51.
20. Hu Y, Zhang J, Li X, Yang Y, Zhang Y, Ma J, et al. *Penicillium marneffei* infection: an emerging disease in mainland China. Mycopathologia. 2013;175(1):57–67.
21. Lu S, Hu Y, Lu C, Zhang J, Li X, Xi L. Development of in vitro macrophage system to evaluate phagocytosis and intracellular fate of *Penicillium marneffei* conidia. Mycopathologia. 2013;176(1–2):11–22.
22. Zhou F, Bi X, Zou X, Xu Z, Zhang T. Retrospective analysis of 15 cases of *Penicilliosis marneffei* in a Southern China hospital. Mycopathologia. 2014;177(5):271–9.
23. Mo D, Li X, Wei L, Sun C, Liang H, Cao C. In vitro interactions of calcineurin inhibitors with conventional antifungal agents against the yeast form of *Penicillium marneffei*. Mycopathologia. 2014;178(3):217–20.
24. Bordoloi P, Nath R, Borgohain M, Huda MM, Barua S, Dutta D, et al. Subcutaneous mycoses: an aetiological study of 15 cases in a tertiary care hospital at Dibrugarh, Assam, Northeast India. Mycopathologia. 2015;179(5):425–35.
25. Huang X, Li D, Xi L, Mylonakis E. *Galleria mellonella* larvae as an infection model for *Penicillium marneffei*. Mycopathologia. 2015;180(3):159–64.
26. Qiu Y, Lu D, Zhang J, Zhong X, Liu G, Li B. Treatment of disseminated *Talaromyces marneffei* with tracheal infection: two case reports. Mycopathologia. 2015;180(3):245–9.
27. Ouyang Y, Cai S, Liang H, Cao C. Administration of voriconazole in disseminated *Talaromyces* (*Penicillium*) *marneffei* infection: a retrospective study. Mycopathologia. 2017;182(5):569–75.
28. Mohsin J, Khalili SA, van den Ende AHGG, Khamis F, Petersen E, de Hoog GS, et al. Imported talaromycosis in Oman in advanced HIV: a diagnostic challenge outside the endemic areas. Mycopathologia. 2017;182(7):739–45.
29. Wang P, Chen Y, Xu H, Ding L, Wu Z, Xu Z, et al. Acute disseminated *Talaromyces marneffei* in an immunocompetent patient. Mycopathologia. 2017;182(7):751–4.
30. Wang Y, Cheng J, Ding H, Lin X, Chen G, Zhou M, et al. Study on the clinical features and prognosis of *Penicilliosis marneffei* without human immunodeficiency virus infection. Mycopathologia. 2018;183(3):551–8.
31. Wong SCY, Sridhar S, Ngan AHY, Chen JHK, Poon RWS, Lau SKP, et al. Fatal *Talaromyces marneffei* infection in a patient with autoimmune hepatitis. Mycopathologia. 2018;183(3):615–8.
32. Han X, Su D, Yi J, Zou Y, Shi Y. A literature review of blood-disseminated *P. marneffei* infection and a case study of this infection in an HIV-negative child with comorbid eosinophilia. Mycopathologia. 2019;184(1):129–39.
33. Luo H, Pan K, Luo X, Zheng D, Andrianopoulos A, Wen L, et al. In vitro susceptibility of berberine combined with antifungal agents against the yeast form of *Talaromyces marneffei*. Mycopathologia. 2019;184(2):295–301.
34. Guo J, Li B-K, Li T-M, Wei F-L, Fu Y-J, Zheng Y-Q, et al. Characteristics and prognosis of *Talaromyces marneffei* infection in non-HIV-infected children in southern China. Mycopathologia. 2019. https://doi.org/10.1007/s11046-019-00373-4.
35. Samson RA, Yilmaz N, Houbraken J, Spierenburg H, Seifert KA, Peterson SW, et al. Phylogeny and nomenclature of the genus *Talaromyces* and taxa accommodated in *Penicillium* subgenus *Biverticillium*. Stud Mycol. 2011;70(1):159–83.
36. Tam EWT, Tsang C-C, Lau SKP, Woo PCY. Comparative mitogenomic and phylogenetic characterization on the complete mitogenomes of *Talaromyces* (*Penicillium*) *marneffei*. Mitochondrial DNA B Resour. 2016;1(1):941–2.
37. Chaiwun B, Vanittanakom N, Jiviriyawat Y, Rojanasthien S, Thorner P. Investigation of dogs as a reservoir of *Penicillium marneffei* in northern Thailand. Int J Infect Dis. 2011;15(4):e236–9.
38. Deng Z, Yun M, Ajello L. Human penicilliosis marneffei and its relation to the bamboo rat (*Rhizomys pruinosus*). J Med Vet Mycol. 1986;24(5):383–9.
39. Wei XG, Ling YM, Li C, Zhang FS. Study of 179 bamboo rats carrying *Penicillium marneffei*. Chin J Zoonoses. 1987;3:34–5.
40. Deng Z, Ribas JL, Gibson DW, Connor DH. Infections caused by *Penicillium marneffei* in China and Southeast Asia: review of eighteen published cases and report of four more chinese cases. Rev Infect Dis. 1988;10(3):640–52.
41. Li JC, Pan LQ, Wu SX. Mycologic investigation on *Rhizomys pruinous* senex in Guangxi as natural carrier with *Penicillium marneffei*. Chin Med J (Engl). 1989;102(6):477–85.
42. Sukroongreung S, Nilakul C, Tantimavanic S, Ajello L. Natural carrier of *Penicillium marneffei*. Mahidol Univ Annu Res Abstr Bibliogr Non-Formal Publ. 1992;19:43.
43. Chariyalertsak S, Vanittanakom P, Nelson KE, Sirisanthana T, Vanittanakom N. *Rhizomys sumatrensis* and *Cannomys badius*, new natural animal hosts of *Penicillium marneffei*. J Med Vet Mycol. 1996;34(2):105–10.
44. Gugnani H, Fisher MC, Paliwal-Johsi A, Vanittanakom N, Singh I, Yadav PS. Role of *Cannomys badius* as a natural animal host of *Penicillium marneffei* in India. J Clin Microbiol. 2004;42(11):5070–5.
45. Huang X, He G, Lu S, Liang Y, Xi L. Role of *Rhizomys pruinosus* as a natural animal host of *Penicillium marneffei* in Guangdong. China Microbial Biotechnology. 2015;8(4):659–64.
46. Deng ZL, Yie QY, Li S, Ma Y. *Penicillium marneffei* isolated from the feces of bamboo rats using the "biological filtration"method. J Guangxi Med Coll. 1986;3(3):1–3.
47. Chariyalertsak S, Sirisanthana T, Khuanchai S, Praparattanapan J, Nelson KE. Case-control study of risk factors for *Penicillium marneffei* infection in human immunodeficiency virus-infected patients in northern Thailand. Clin Infect Dis. 1997;24(6):1080–6.
48. Pryce-Miller E, Aanensen D, Vanittanakom N, Fisher MC. Environmental detection of *Penicillium marneffei* and growth in soil microcosms in competition with *Talaromyces stipitatus*. Fungal Ecology. 2008;1(1):49–56.
49. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE. Seasonal variation of disseminated *Penicillium*

marneffei infections in northern Thailand: a clue to the reservoir? J Infect Dis. 1996;173(6):1490–3.

50. Le T, Wolbers M, Chi NH, Quang VM, Chinh NT, Huong Lan NP, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated *Penicillium marneffei* infection in Ho Chi Minh City, Viet Nam. Clin Infect Dis. 2011;52(7):945–52.
51. Bulterys PL, Le T, Quang VM, Nelson KE, Lloyd-Smith JO. Environmental predictors and incubation period of AIDS-associated *Penicillium marneffei* infection in Ho Chi Minh City, Vietnam. Clin Infect Dis. 2013;56(9):1273–9.
52. Vanittanakom N, Cooper CR Jr, Fisher MC, Sirisanthana T. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. Clin Microbiol Rev. 2006;19(1):95–110.
53. Borneman AR, Hynes MJ, Andrianopoulos A. The *abaA* homologue of *Penicillium marneffei* participates in two developmental programmes: conidiation and dimorphic growth. Mol Microbiol. 2000;38(5):1034–47.
54. Todd RB, Greenhalgh JR, Hynes MJ, Andrianopoulos A. TupA, the *Penicillium marneffei* Tup1p homologue, represses both yeast and spore development. Mol Microbiol. 2003;48(1):85–94.
55. Boyce KJ, Hynes MJ, Andrianopoulos A. The *CDC42* homolog of the dimorphic fungus *Penicillium marneffei* Is required for correct cell polarization during growth but not development. J Bacteriol. 2001;183(11):3447–57.
56. Boyce KJ, Hynes MJ, Andrianopoulos A. Control of morphogenesis and actin localization by the *Penicillium marneffei RAC* homolog. J Cell Sci. 2003;116(7):1249–60.
57. Boyce KJ, Schreider L, Kirszenblat L, Andrianopoulos A. The two-component histidine kinases DrkA and SlnA are required for in vivo growth in the human pathogen *Penicillium marneffei*. Mol Microbiol. 2011;82(5):1164–84.
58. Zuber S, Hynes MJ, Andrianopoulos A. G-protein signaling mediates asexual development at 25 °C but has no effect on yeast-like growth at 37 °C in the dimorphic fungus *Penicillium marneffei*. Eukaryot Cell. 2002;1(3):440–7.
59. Zuber S, Hynes MJ, Andrianopoulos A. The G-protein α-subunit GasC plays a major role in germination in the dimorphic fungus *Penicillium marneffei*. Genetics. 2003;164(2):487–99.
60. Bugeja HE, Hynes MJ, Andrianopoulos A. HgrA is necessary and sufficient to drive hyphal growth in the dimorphic pathogen *Penicillium marneffei*. Mol Microbiol. 2013;88(5):998–1014.
61. Yang E, Chow W-N, Wang G, Woo PCY, Lau SKP, Yuen K-Y, et al. Signature gene expression reveals novel clues to the molecular mechanisms of dimorphic transition in *Penicillium marneffei*. PLoS Genet. 2014;10(10):e1004662.
62. Wang Q, Du M, Wang S, Liu L, Xiao L, Wang L, et al. MADS-box transcription factor *madsA* regulates dimorphic transition, conidiation, and germination of *Talaromyces marneffei*. Front Microbiol. 2018;9:1781.
63. Cánovas D, Boyce KJ, Andrianopoulos A. The fungal type II myosin in *Penicillium marneffei,* MyoB, is essential for chitin deposition at nascent septation sites but not actin localization. Eukaryot Cell. 2011;10(3):302–12.
64. Boyce KJ, Andrianopoulos A. A p21-activated kinase is required for conidial germination in *Penicillium marneffei*. PLoS Pathog. 2007;3(11):e162.
65. Boyce KJ, Schreider L, Andrianopoulos A. In vivo yeast cell morphogenesis is regulated by a p21-activated kinase in the human pathogen *Penicillium marneffei*. PLoS Pathog. 2009;5(11):e1000678.
66. Wang F, Tao J, Qian Z, You S, Dong H, Shen H, et al. A histidine kinase *PmHHK1* regulates polar growth, sporulation and cell wall composition in the dimorphic fungus *Penicillium marneffei*. Mycol Res. 2009;113(9):915–23.
67. Boyce KJ, Hynes MJ, Andrianopoulos A. The Ras and Rho GTPases genetically interact to co-ordinately regulate cell polarity during development in *Penicillium marneffei*. Mol Microbiol. 2005;55(5):1487–501.
68. Bugeja HE, Hynes MJ, Andrianopoulos A. The RFX protein RfxA is an essential regulator of growth and morphogenesis in *Penicillium marneffei*. Eukaryot Cell. 2010;9(4):578–91.
69. Suwunnakorn S, Cooper CR Jr, Kummasook A, Pongpom M, Vanittanakom P, Vanittanakom N. Role of the *rttA* gene in morphogenesis, stress response, and virulence in the human pathogenic fungus *Penicillium marneffei*. Med Mycol. 2014;53(2):119–31.
70. Kummasook A, Cooper CR Jr, Sakamoto A, Terui Y, Kashiwagi K, Vanittanakom N. Spermidine is required for morphogenesis in the human pathogenic fungus *Penicillium marneffei*. Fungal Genet Biol. 2013;58–59:25–322.
71. Nimmanee P, Woo PCY, Kummasook A, Vanittanakom N. Characterization of *sakA* gene from pathogenic dimorphic fungus *Penicillium marneffei*. Int J Med Microbiol. 2015;305(1):65–74.
72. Nimmanee P, Tam EWT, Woo PCY, Vanittanakom P, Vanittanakom N. Role of the *Talaromyces marneffei* (*Penicillium marneffei*) *sakA* gene in nitrosative stress response, conidiation and red pigment production. FEMS Microbiol Lett. 2016;364(8):fnw292.
73. Boyce KJ, Cao C, Andrianopoulos A. Two-component signaling regulates osmotic stress adaptation via SskA and the high-osmolarity glycerol MAPK pathway in the human pathogen *Talaromyces marneffei*. mSphere. 2016;1(1):e00086-15.
74. Borneman AR, Hynes MJ, Andrianopoulos A. A basic helix–loop–helix protein with similarity to the fungal morphological regulators, Phd1p, Efg1p and StuA, controls conidiation but not dimorphic growth in *Penicillium marneffei*. Mol Microbiol. 2002;44(3):621–31.
75. Suwunnakorn S, Cooper CR Jr, Kummasook A, Vanittanakom N. Role of the *yakA* gene in morphogenesis and stress response in *Penicillium marneffei*. Microbiology. 2014;160(9):1929–39.
76. Boyce KJ, Andrianopoulos A. Morphogenetic circuitry regulating growth and development in the dimorphic pathogen *Penicillium marneffei*. Eukaryot Cell. 2013;12(2):154–60.
77. Weerasinghe H, Payne M, Beard S, Andrianopoulos A. Organism-wide studies into pathogenicity and morphogenesis in *Talaromyces marneffei*. Future Microbiol. 2016;11(4):511–26.
78. Liu H, Xi L, Zhang J, Li X, Liu X, Lu C, et al. Identifying differentially expressed genes in the dimorphic fungus

Penicillium marneffei by suppression subtractive hybridization. FEMS Microbiol Lett. 2007;270(1):97–103.
79. Lin X, Ran Y, Gou L, He F, Zhang R, Wang P, et al. Comprehensive transcription analysis of human pathogenic fungus *Penicillium marneffei* in mycelial and yeast cells. Med Mycol. 2012;50(8):835–42.
80. Pasricha S, Payne M, Canovas D, Pase L, Ngaosuwankul N, Beard S, et al. Cell-type–specific transcriptional profiles of the dimorphic pathogen *Penicillium marneffei* reflect distinct reproductive, morphological, and environmental demands. G3 (Bethesda). 2013;3(11):1997–2014.
81. Yang E, Wang G, Woo PCY, Lau SKP, Chow W-N, Chong KTK, et al. Unraveling the molecular basis of temperature-dependent genetic regulation in *Penicillium marneffei*. Eukaryot Cell. 2013;12(9):1214–24.
82. Lau SKP, Chow W-N, Wong AYP, Yeung JMY, Bao J, Zhang N, et al. Identification of microRNA-like RNAs in mycelial and yeast phases of the thermal dimorphic fungus *Penicillium marneffei*. PLoS Negl Trop Dis. 2013;7(8):e2398.
83. Nierman WC, Fedorova-Abrams ND, Andrianopoulos A. Genome sequence of the AIDS-associated pathogen *Penicillium marneffei* (ATCC18224) and its near taxonomic relative *Talaromyces stipitatus* (ATCC10500). Genome Announc. 2015;3(1):e01559-14.
84. Woo PCY, Lau SKP, Liu B, Cai JJ, Chong KTK, Tse H, et al. Draft genome sequence of *Penicillium marneffei* strain PM1. Eukaryot Cell. 2011;10(12):1740–1.
85. Li Y, Luo H, Fan J, Lan X, Liu G, Zhang J, et al. Genomic analysis provides insights into the transmission and pathogenicity of *Talaromyces marneffei*. Fungal Genet Biol. 2019;130:54–61.
86. Lau SKP, Tsang C-C, Woo PCY. *Talaromyces marneffei* genomic, transcriptomic, proteomic and metabolomic studies reveal mechanisms for environmental adaptations and virulence. Toxins. 2017;9(6):192.
87. Woo PCY, Tam EWT, Chong KTK, Cai JJ, Tung ETK, Ngan AHY, et al. High diversity of polyketide synthase genes and the melanin biosynthesis gene cluster in *Penicillium marneffei*. FEBS J. 2010;277(18):3750–8.
88. Woo PCY, Lam C-W, Tam EWT, Leung CKF, Wong SSY, Lau SKP, et al. First discovery of two polyketide synthase genes for mitorubrinic acid and mitorubrinol yellow pigment biosynthesis and implications in virulence of *Penicillium marneffei*. PLoS Negl Trop Dis. 2012;6(10):e1871.
89. Woo PCY, Lam C-W, Tam EWT, Lee K-C, Yung KKY, Leung CKF, et al. The biosynthetic pathway for a thousand-year-old natural food colorant and citrinin in *Penicillium marneffei*. Sci Rep. 2014;4:6728.
90. Tam EWT, Tsang C-C, Lau SKP, Woo PCY. Polyketides, toxins and pigments in *Penicillium marneffei*. Toxins. 2015;7(11):4421–36.
91. Youngchim S, Hay RJ, Hamilton AJ. Melanization of *Penicillium marneffei* in vitro and in vivo. Microbiology. 2005;151(1):291–9.
92. Liu D, Wei L, Guo T, Tan W. Detection of DOPA-melanin in the dimorphic fungal pathogen *Penicillium marneffei* and its effect on macrophage phagocytosis in vitro. PLoS ONE. 2014;9(3):e92610.
93. Payne M, Weerasinghe H, Tedja I, Andrianopoulos A. A unique aspartyl protease gene expansion in *Talaromyces marneffei* plays a role in growth inside host phagocytes. Virulence. 2019;10(1):277–91.
94. Pongpom P, Cooper CR Jr, Vanittanakom N. Isolation and characterization of a catalase-peroxidase gene from the pathogenic fungus *Penicillium marneffei*. Med Mycol. 2005;43(5):403–11.
95. Sapmak A, Kaewmalakul J, Nosanchuk JD, Vanittanakom N, Andrianopoulos A, Pruksaphon K, et al. *Talaromyces marneffei* laccase modifies THP-1 macrophage responses. Virulence. 2016;7(6):702–17.
96. Thirach S, Cooper CR Jr, Vanittanakom P, Vanittanakom N. The copper, zinc superoxide dismutase gene of *Penicillium marneffei*: cloning, characterization, and differential expression during phase transition and macrophage infection. Med Mycol. 2007;45(5):409–17.
97. Cánovas D, Andrianopoulos A. Developmental regulation of the glyoxylate cycle in the human pathogen *Penicillium marneffei*. Mol Microbiol. 2006;62(6):1725–38.
98. Sun J, Li X, Feng P, Zhang J, Xie Z, Song E, et al. RNAi-mediated silencing of fungal *acuD* gene attenuates the virulence of *Penicillium marneffei*. Med Mycol. 2014;52(2):167–78.
99. Feng J, Chen Z, He L, Xiao X, Chen C, Chu J, et al. *AcuD* gene knockout attenuates the virulence of *Talaromyces marneffei* in a zebrafish model. Mycobiology. 2019;47(2):207–16.
100. Bugeja HE, Hynes MJ, Andrianopoulos A. AreA controls nitrogen source utilisation during both growth programs of the dimorphic fungus *Penicillium marneffei*. Fungal Biol. 2012;116(1):145–54.
101. Feng J, He L, Xiao X, Chen Z, Chen C, Chu J, et al. Methylcitrate cycle gene MCD is essential for the virulence of *Talaromyces marneffei*. Med Mycol. 2019. https://doi.org/10.1093/mmy/myz063.
102. Liao S, Tung ETK, Zheng W, Chong K, Xu Y, Dai P, et al. Crystal structure of the Mp1p ligand binding domain 2 reveals its function as a fatty acid-binding protein. J Biol Chem. 2010;285(12):9211–20.
103. Woo PCY, Lau SKP, Lau CCY, Tung ETK, Chong KTK, Yang F, et al. Mp1p is a virulence factor in *Talaromyces* (*Penicillium*) *marneffei*. PLoS Negl Trop Dis. 2016;10(8):e0004907.
104. Sze K-H, Lam W-H, Zhang H, Ke Y-H, Tse M-K, Woo PCY, et al. *Talaromyces marneffei* Mp1p is a virulence factor that binds and sequesters a key proinflammatory lipid to dampen host innate immune response. Cell Chem Biol. 2017;24(2):182–94.
105. Lam W-H, Sze K-H, Ke Y, Tse M-K, Zhang H, Woo PCY, et al. *Talaromyces marneffei* Mp1 protein, a novel virulence factor, carries two arachidonic acid-binding domains to suppress inflammatory responses in hosts. Infect Immun. 2019;87(4):e00679-18.
106. Lau SKP, Lo GCS, Chow FWN, Fan RYY, Cai JJ, Yuen K-Y, et al. Novel partitivirus enhances virulence of and causes aberrant gene expression in *Talaromyces marneffei*. MBio. 2018;9(3):e00947-18.
107. Hamilton AJ, Jeavons L, Youngchim S, Vanittanakom N, Hay RJ. Sialic acid-dependent recognition of laminin by

Penicillium marneffei conidia. Infect Immun. 1998;66(12):6024–6.

108. Hamilton AJ, Jeavons L, Youngchim S, Vanittanakom N. Recognition of fibronectin by *Penicillium marneffei* conidia via a sialic acid-dependent process and its relationship to the interaction between conidia and laminin. Infect Immun. 1999;67(10):5200–5.
109. Srinoulprasert Y, Kongtawelert P, Chaiyaroj SC. Chondroitin sulfate B and heparin mediate adhesion of *Penicillium marneffei* conidia to host extracellular matrices. Microb Pathog. 2006;40(3):126–32.
110. Lau SKP, Tse H, Chan JSY, Zhou AC, Curreem SOT, Lau CCY, et al. Proteome profiling of the dimorphic fungus *Penicillium marneffei* extracellular proteins and identification of glyceraldehyde-3-phosphate dehydrogenase as an important adhesion factor for conidial attachment. FEBS J. 2013;280(24):6613–26.
111. Li Y, Li M, Luo H, Bai J, Zhang J, Zhong X, et al. Expression profile of lncRNA in human bronchial epithelial cells response to *Talaromyces marneffei* infection: a microarray analysis. Microb Pathog. 2017;104:155–60.
112. Li Y, Liu G, Zhang J, Zhong X, He Z. Identification of key genes in human airway epithelial cells in response to respiratory pathogens using microarray analysis. BMC Microbiol. 2018;18(1):58.
113. Pongpom M, Vanittanakom P, Nimmanee P, Cooper CR Jr, Vanittanakom N. Adaptation to macrophage killing by *Talaromyces marneffei*. Future Sci OA. 2017;3(3):FSO215.
114. Kudeken N, Kawakami K, Kusano N, Saito A. Cell-mediated immunity in host resistance against infection caused by *Penicillium marneffei*. J Med Vet Mycol. 1996;34(6):371–8.
115. Kudeken N, Kawakami K, Saito A. $CD4^{+}$ T cell-mediated fatal hyperinflammatory reactions in mice infected with *Penicillium marneffei*. Clin Exp Immunol. 1997;107(3):468–73.
116. Chan JFW, Lau SKP, Yuen K-Y, Woo PCY. *Talaromyces* (*Penicillium*) *marneffei* infection in non-HIV-infected patients. Emerg Microbes Infect. 2016;5:e19.
117. Hyde KD, Al-Hatmi AMS, Andersen B, Boekhout T, Buzina W, Dawson TL, et al. The world's ten most feared fungi. Fungal Divers. 2018;93(1):161–94.
118. Tongchusak S, Pongtanalert P, Pongsunk S, Chawengkirttikul R, Chaiyaroj SC. Distinct immunologic properties of *Penicillium marneffei* yeasts obtained from different *in vitro* growth conditions. Asian Pac J Allergy Immunol. 2004;22(4):229–35.

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