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Teaser High-throughput screening of small molecules, which enables rapid hit identification and increases hit rate, is particularly helpful in the pursuit of ideal antifungal for ***Candida*** *infections.*

In pursuit of the ideal antifungal agent for *Candida* infections: high-throughput screening of small molecules

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Candida **infections have created a great burden on the public healthcare sector. The situation is worsened by recent epidemiological changes. Furthermore, the current arsenal of antifungal agents is limited and associated with undesirable drawbacks. Therefore, new antifungal agents that surpass the existing ones are urgently needed. High-throughput screening of small molecule libraries enables rapid hit identification and, possibly, increases hit rate. Moreover, the identified hits could be associated with unrecognized or multiple drug targets, which would provide novel insights into the biological processes of the pathogen. Hence, it is proposed that high-throughput screening of small molecules is particularly important in the pursuit of the ideal antifungal agents for** ***Candida*** **infections.**

Introduction

Candida, the major fungal pathogen in humans, is the fourth-most prevalent pathogen of nosocomial bloodstream infections surpassing most bacterial infections [1]. *Candida* infections are opportunistic and are, therefore, common among immunocompromised populations, such as neutropenic patients, patients under intensive care, organ-transplant recipients, patients with underlying malignancy, HIV patients and patients with uncontrolled diabetes. Invasive candidiasis is associated with significant mortality [2,3] and is, therefore, a serious threat to public health around the globe [4–6]. The recent shifting of the paradigm of *Candida* infections further complicates the situation and highlights the need for novel classes of antifungal agents, especially those with new mechanisms of action [7,8]. However, the progress of antifungal drug discovery has been lagging. The last first-in-class antifungal drug, caspofungin, was approved more than a decade ago in 2001 [9]. One of the reasons for the slow progress is the eukaryotic nature of fungi, which carry substantial similarities to human cells limiting the number of fungal-specific drug targets [10–12]. To accelerate the progress of antifungal drug discovery, the hit identification rate has to be significantly increased. High-throughput screening is a powerful tool that incorporates

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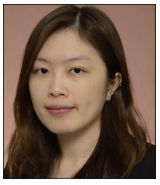

Sarah Sze Wah Wong obtained her BSc (Bioinformatics) and PhD from the University of Hong Kong (HKU). Her PhD project aimed at the discovery and development of novel antifungal for *Candida* infections through high-throughput screening of small molecule libraries. She is currently a post-doctoral fellow at HKU, where she continues her work on antifungal drug discovery and the biology of *Candida* species.

Lakshman Perera Samaranayake was previously the Dean of the Faculty of Dentistry, University of Hong Kong 2003–2014; and is currently serving as the Head and the Professor of Oral Microbiomics and Infection at the School of Dentistry, University of Queensland. With over 400 publications, he is a world-renowned expert in the research of *Candida*; in particular, oral candidal infection, oral microbiology and oral infections in immunocompromised populations. For his research, he has received a number of awards and honors including the Distinguished Scientist Award of the International Association for Dental Research, USA, and the King James IV Professorship of the Royal College of Surgeons of Edinburgh, UK.

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TABLE 1

The change in incidence of *Candida* bloodstream infections in various parts of the world from 1980 to 2009

Area	Publication year	Study period	Type of population	Trend or change in % incidence	Refs
Spain	2012	2000–2009	General hospital	Increased	[13]
Taiwan	2011	2000–2008	Tertiary medical center	Increased	[14]
Hong Kong	2009	1998–2006	Intensive care unit	+66%	[15]
Denmark	2008	2004–2006	Multiple general hospitals covering about 65% of Danish population	+17%	[16]
United States	2008	2000–2005	General populations	+52%	[17]
Switzerland	2003	1991–2000	General hospitals covering about 80% of Swiss population	Unchanged	[18]
Canada	2002	1992–1996	Three general hospitals	+155%	[19]
Iceland	2002	1980–1999	General populations	+250%	[20]
Norway	1998	1991–1996	General hospitals	Unchanged	[21]
Taiwan	1997	1981–1993	Single general hospital	Increased	[22]

synthetic chemistry and combinatorial chemistry to provide rich sources of small molecules of diverse structure to increase the hit rate for discovering novel antimicrobial lead compounds.

The need for novel antifungal agents

The recent changes in the epidemiology of *Candida* infections have pressured the healthcare sector and highlighted an urgent need for novel classes of antifungal agents with different chemical structures and cellular targets [7,8]. These issues include the increased incidence of invasive candidiasis, the shifting species distribution of *Candida* infections, the emergence of antifungal resistance and the limitation of the current arsenal of antifungal agents.

Increased incidence of invasive candidiasis

The secular trends of incidence of *Candida* infections, in particular *Candida* bloodstream infections, have been increasing over the past few decades across the globe [13–22] (Table 1). This could be attributed to the increased number of immunocompromised patients due to the growing widespread use of medical procedures, for instance the use of immunosuppressive drugs and broad-spectrum antibiotics, as well as invasive surgical procedures such as solid organ transplantation [23].

Shifting species distribution of Candida *infections*

Candida albicans, the predominant disease-causing *Candida* species, possesses various virulence factors that render it the most pathogenic of all the *Candida* species. Recently, the continued increase in invasive candidiasis caused by non-*albicans Candida* (NAC), such as *Candida dubliniensis*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei* and *Candida parapsilosis*, has been recognized [5,24–28]. This could be partly caused by the improvement in the sensitivity of species identification methods, as well as the indiscriminate use of antifungals [29]. Emergence of NAC raised a concern because they are often associated with antifungal resistance and higher mortality [30,31]. For instance, *C. glabrata* and *C. krusei* are intrinsically less susceptible to fluconazole [28], and lower susceptibility for amphotericin B and 5-fluorocytosine has also been observed in *C. krusei* [32].

Emergence of antifungal resistance

The emergence of antifungal resistance, which is one of the major reasons for antifungal treatment failure, has been regarded as a significant clinical problem [33]. The increase in the numbers of high-risk populations has raised the frequency of prophylactic treatment. Prolonged exposure to the existing antifungals increases the selection pressure and, as a result, drug resistance has become increasingly common from originally susceptible species [34,35]. This phenomenon further restricts the available choice of treatment from the limited arsenal of antifungal agents.

Current antifungal agents and their limitations

Up until 2012, existing antifungal agents for systemic candidiasis were mainly divided into four classes: polyenes, azoles, echinocandins and pyrimidines [8] (Table 2). The classes of antifungal agents refer to their distinct mode of action. In addition to the limited number of available antifungal agents, there exist limitations for each antifungal class.

Polyenes. The first antifungal, nystatin, isolated from *Streptomyces noursei*, was discovered in 1950 through screening various cultures of actinomycetes from soil for antifungal activity [36]. However, owing to its toxicity when injected intravenously and the lack of oral bioavailability, nystatin remains a topical antifungal agent [37]. Amphotericin B was developed in 1953 from a screening of *Streptomyces* cultures for antifungal activity [38]. Amphotericin B binds directly to ergosterol, the component of the fungal plasma membrane, and thereby causes the leakage of intracellular potassium and magnesium [39]. It is by far the most potent antifungal agent for systemic candidiasis, and has been regarded as the 'gold standard' [40]. Amphotericin B has a broad spectrum and fast onset of activity [41,42]. However, it is associated with adverse nephrotoxicity that is cumulative and might not be reversible [43]. Enhanced versions of amphotericin B have been developed by lipid formulations to allow various administration routes and reduced toxicity [44,45].

Pyrimidines. Flucytosine (or 5-fluorocytosine) is a synthetic compound, which was originally synthesized in 1957 as a potential antitumor drug; however, its antifungal activity was later discovered and it was used to treat candidiasis from 1968

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