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# Antifungal Prophylaxis with CD101 in Immunosuppressed Mouse Models of Candidiasis, Aspergillosis, and Pneumocystis Pneumonia (PCP)


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## INTRODUCTION

Fungal infections cause significant morbidity and mortality. Disease- and treatment-related immunosuppression in patients with hematological diseases increase the risk of opportunistic infection caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis* spp.

Antifungal prophylaxis is an important consideration for this population. For example, lack of adequate prophylaxis increased risk of *Pneumocystis* pneumonia (PCP) to 15%-45%, and mortality rates due to PCP are high (48% to 70%) among HSCT recipients.[1]

Safety and tolerability, drug-drug interactions, and variable pharmacokinetics are among the complications encountered with antifungals currently used for prophylaxis, such as azoles for *Candida* spp. and *Aspergillus* spp. and trimethoprim/sulfamethoxazole (TMP/SMX) for PCP.[2,3] Evidence of emerging resistance to TMP/SMX is also a concern.[4-5] Unmet needs in antifungal prophylaxis remain.[3]

CD101, a novel echinocandin in phase 2 development, has demonstrated preclinical safety and efficacy in studies of invasive fungal infection. Whereas currently approved echinocandins are limited to once-daily IV dosing, CD101 stability and long half-life enable once-weekly IV dosing and subcutaneous (SC) administration,[6-7] suggesting a potential for prophylaxis.

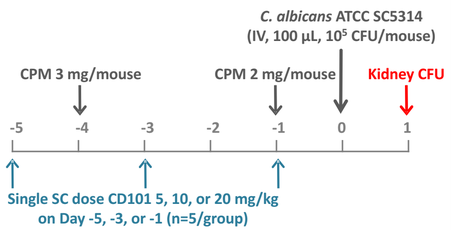
## OBJECTIVES

To evaluate CD101 as antifungal prophylaxis in neutropenic mouse models of candidiasis, aspergillosis, and PCP, respectively.

## MATERIALS & METHODS

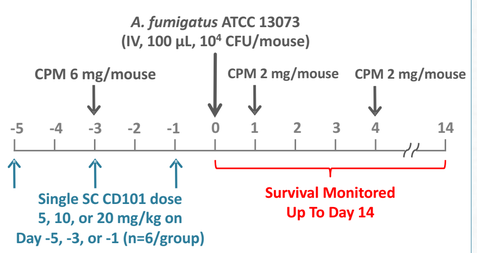
### Candidiasis model

ICR mice were rendered neutropenic by cyclophosphamide on days -4 and -1, and challenged with *Candida albicans* on day 0.




### Aspergillosis model

ICR mice were rendered neutropenic by cpm on days -3, +1, and +4, then challenged with *Aspergillus fumigatus* on day 0.




In both the candidiasis and aspergillosis models, a single SC dose of CD101 5, 10, or 20 mg/kg was given on Day -5, -3, or -1.

### PCP model

Immunosuppressed (dexamethasone 4 mg/L) C3H/HeN mice were inoculated with *Pneumocystis murina* (intranasally, 2 x $10^6$/50 µL). CD101 was given intraperitoneally (IP) at time of inoculation and weekly for 6 wks (Table). TMP/SMX was the positive control. At 6 wks, lungs were processed for counts of both trophic and asci (cyst) forms.

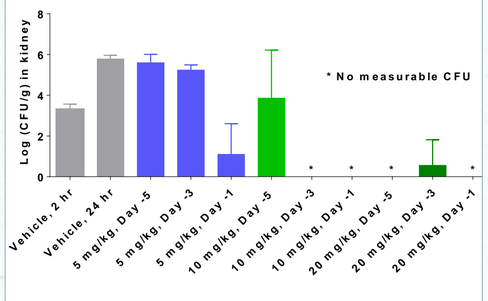
**Treatment Groups in the PCP Model (n=10/group)**

| Drug | CD101 (mg/kg) | | | | | | TMP/SMX |
|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | 20 | 20 | 2 | 2 | 0.2 | 0.2 | 50/250 |
| Freq/wk | 3x | 1x | 3x | 1x | 3x | 1x | 3x |

## RESULTS

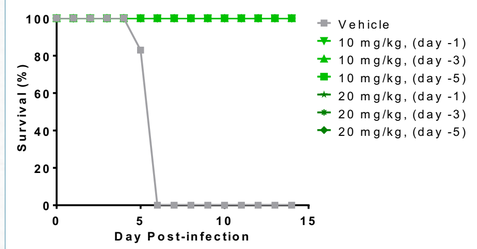
### Candidiasis (MIC=0.03 µg/mL) – Kidney CFU

CFU burden was completely cleared in all animals given 20 mg/kg except one (prophylaxis on day -3). No measurable CFU were seen in the groups given 10 mg/kg on day -3 or -1. Significant decreases in CFU were seen with 5 mg/kg given on day -3 or -1.

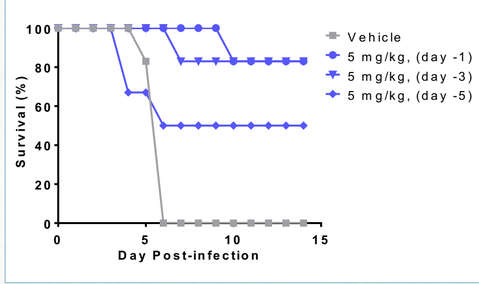



### Aspergillosis (MEC=0.0078 µg/mL) – Survival

All animals in the 10 and 20 mg/kg groups survived regardless of prophylaxis day.




Survival in the 5 mg/kg group improved with prophylaxis given closer to the day of challenge.

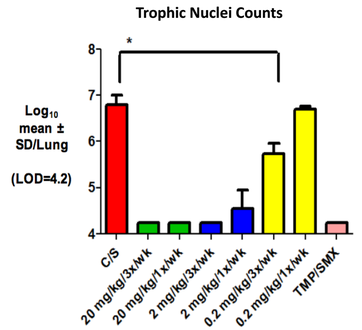



## RESULTS (cont'd)

### PCP – Trophic Nuclei Counts

Clearance of trophic forms with CD101 was comparable to the active control TMP/SMX (ie, no nuclei detected) in the groups given CD101 20 mg/kg 1x or 3x/wk and 2 mg/kg 3x/wk.

Trophic nuclei counts were significantly reduced in all CD101-treated groups (except 0.2 mg/kg 1x/wk) compared with the vehicle control.

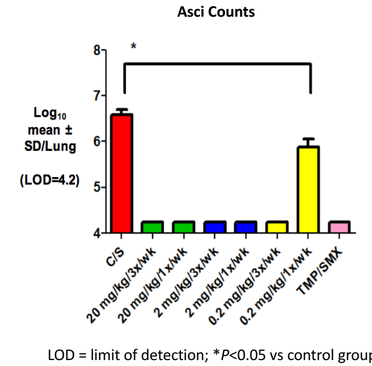



LOD = limit of detection; *$P$<0.05 vs control group.

### PCP – Asci/cyst Counts

Efficacy with CD101 was comparable to TMP/SMX in all but the lowest dose group (0.2 mg/kg 1x/wk), with no detectable asci.

Asci counts were significantly reduced in all CD101 groups compared with vehicle.




LOD = limit of detection; *$P$<0.05 vs control group.

## CONCLUSIONS

CD101, a novel echinocandin, was protective against fungal challenge in immunosuppressed mouse models of candidiasis, aspergillosis, and PCP.

Single SC doses of CD101 ≥10 mg/kg in mice protected against candidiasis and improved survival in aspergillosis when administered at up to 5 days prior to infection challenge.

Once-weekly and intermittent (3x/wk) doses of CD101 IP were comparable to TMP/SMX in reducing both trophic and asci/cyst forms of *Pneumocystis*.

These data suggest that CD101 may provide benefit to antifungal prophylaxis for patients with hematological diseases at risk for infection.

The efficacy of SC-administered CD101 demonstrated in the candidiasis and aspergillosis models also suggests potential utility of CD101 in the outpatient setting for treatment or prophylaxis.

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