



HEALTH RESEARCH  
I N C O R P O R A T E D

## Antifungal Target and Method to Screen for Specific Inhibitors (CaESS1)

### Background:

Drug resistance is an escalating problem especially in immunocompromised patients susceptible to pathogens. ESS1 is a peptidyl prolyl *cis/trans* isomerase (PPIase) that is required for the virulence of the pathogenic fungi *Candida albicans* and *Cryptococcus neoformans*. Since CaEss1 encoded PPIase enzyme is essential for viability, cells cannot become resistant by this mechanism. The human homolog of ESS1, called Pin1, has been implicated in a wide range of diseases, including cancer and Alzheimer's disease. Differences in interdomain interactions and linker flexibility have been observed in crystallographic and NMR states of the substrate binding domain in Pin1 and the alpha-helix structure in ESS1. These marked differences in conformation between the human and fungal enzymes provide a structural basis for therapeutic targeting of ESS1. Therefore, we propose the use of CaEss1 to be developed as an anti-fungal drug.

### Applications:

- Antifungal drug target
- Combination therapeutic for immunosuppression

### Advantages:

- *C. albicans*, ESS1 encoded PPIase enzyme is essential for viability and cannot become resistant to drugs.
- ESS1 is highly conserved in other pathogenic fungi suggesting that anti-ESS1 inhibitors should have a broad spectrum use.

### State of Development:

- X-ray crystallographic and NMR studies have been completed on the structural components of ESS1 and Pin1, the human homolog.
- ESS1 genes have been cloned and characterized from *Candida albicans* and *Cryptococcus neoformans*. "Knock-out" strains and expression systems are available.
- Animal models demonstrated importance of ESS1 products to virulence.

### Patents:

- USPTO 7,217,538 CaESS1: A *Candida albicans* gene, methods for making and using and targeting it or its expression products for antifungal applications.
- USPTO 6,537,753 CaESS1: A *Candida albicans* gene, methods for making and using and targeting it or its expression products for antifungal applications.

### Licensing Potential:

Health Research, Inc. is seeking commercial partners for licensing.

### Inventors:



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### Publications:

McNaughton, L., Li, Z., Van Roey, P., Hanes, S.D., and LeMaster, D. (2010). Restricted domain mobility in the *Candida albicans* Ess1 prolyl isomerase. ***Biochim. Biophys. Acta*** 12 March 2010.

Singh, N., Ma, Z., Gemmill, T., Wu, X., Rossettini, A., Rabeler, C., Beane, O., DeFiglio, H., Palumbo, M., Morse, R. and Hanes, S. D. (2009). The Ess1 prolyl isomerase is required for transcription termination of small non-coding regulatory RNAs via the Nrd1 pathway. ***Mol. Cell*** 36: 255-266. Selected for Faculty of 1000 Biology



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**Publications:**

M.A. Pfaller MA, Chaturvedi V, Diekema DJ, Ghannoum MA, Holliday NM, Killian SB, C.C. Knapp CC, Messer SA, Miskov A, and Ramani R. 2008. Clinical evaluation of the Sensititre YeastOne colorimetric antifungal plate for antifungal susceptibility testing of the echinocandins Anidulafungin, Caspofungin, and Micafungin. *Journal of Clinical Microbiology*. doi:10.1128/JCM.00493-08.

Chaturvedi V, Ramani R, Ghannoum MA, Killian SB, Holliday N, Knapp C, Ostrosky-Zeichner, Messer SA, Pfaller MA, Iqbal NJ, Arthington-Skaggs BA, Vazquez JA, Sein T, Rex JH, Walsh TJ. 2008 Multilaboratory testing of antifungal combinations against a quality control isolate of *Candida krusei*. *Antimicrobial Agents Chemotherapy*. 52:1500-1502.

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