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Genome wide Essential Gene Identification in *Candida albicans* and Applications to Antifungal Drug Discovery

Status	Past
Competition	Competition II
Sector	Health
Genome Centre	Genome Quebec
Project Leaders	Terry Roemer & Bo Jiang

Project Description

Fungal infections, such as systemic *Candidiasis* and invasive *Aspergillosis*, are major causes of mortality among immuno-compromised patients. Over the past several decades, the at-risk population – such as AIDS patients, cancer patients, and organ transplant recipients – has increased significantly.

Despite the prevalence of these life-threatening fungal infections, treatments are restricted to a relatively few antifungal drugs whose use is increasingly challenged by the emergence of drug-resistant fungi and by serious problems of toxicity. An urgent need exists for a new generation of antifungal drugs with superior safety and efficacy against a broad fungal spectrum.

Our project's overall objectives were to screen and identify novel antifungal drug targets based on their demonstrated requirement for cell growth. A large-scale screen for essential genes in *Candida albicans* was performed using a gene replacement and conditional expression (GRACE) strain construction strategy (Roemer et al 2003). Resulting from our continued target validation efforts, we have identified several highly attractive antifungal targets with corresponding inhibitory compounds (Rodriguez-Suarez et al 2007; Jiang et al 2008).

Antifungal compounds resulting from this project are currently at various stages of development, ranging from microbiological inhibitory spectrum and mechanism-of-action studies, to medicinal chemistry exploration. Target validation data provides critical information to prioritize these antifungal compounds for their potential downstream development.

Safer and more effective antifungal drugs will reduce health care costs, while increasing life expectancy and quality of life for patients. Our project addressed the need for antifungal agents in a manner, and on a scale, which will be of social benefit internationally and which is poised to bring significant economic returns to Canada.

We have continued to make progress towards our commitment for strain release and knowledge dissemination to the general research community. Dissemination of the knowledge gained and technologies developed from this project will offer new tools and insights to Canadian and

international academic researchers, which will facilitate basic scientific research and provide international recognition of the high quality genomic research being conducted in Canada.

Fast Facts

<i>Highlighted outcome:</i>	identification of several highly attractive antifungal drug targets and cognate inhibitory compounds, which are currently at various stages of development, ranging from microbiological inhibitory spectrum and mechanism-of-action studies to medicinal chemistry explorations
<i>Number of research personnel employed by the project:</i>	14
<i>Resources generated:</i>	deposit of Merck & Co.'s proprietary, whole-genome sequence of the <i>Aspergillus fumigatus</i> CEA10 strain in GenBank (Hu et al 2007; Fenorova et al 2008), making these sequences freely available to the general research community
<i>Number of patents in process or obtained:</i>	3 patents issued – “A Dominant Selectable Marker for Gene Transformation and Gene Disruption in Yeast”; “Gene Disruption Methodologies for Drug Target Discovery”; and “Identification of <i>Candida albicans</i> Essential Fungal Specific Genes and Use Thereof in Antifungal Drug Discovery”
<i>Co-funders:</i>	Merck & Co.